

Supporting information

Synthesis of All Four Stereoisomers of Reboxetine via Diastereoselective Henry Reaction

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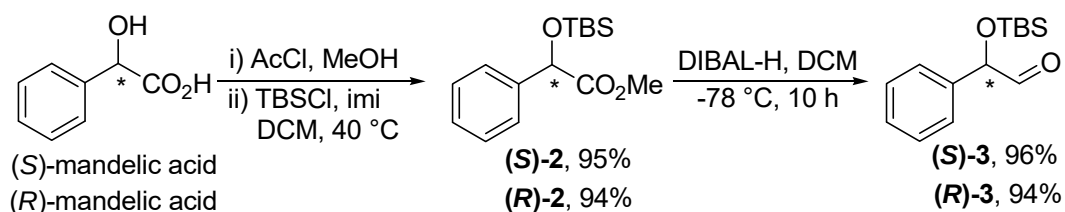
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Xiamen 361005, P. R. China. E-mail: hbchan@xmu.edu.cn

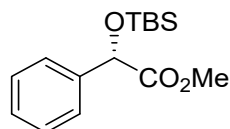
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I. Preparations of aldehydes (*S*)- and (*R*)-3

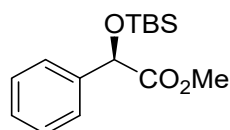


Methyl (*S*)-2-(*tert*-butyldimethylsilyloxy)-2-phenylacetate [(*S*)-2]



To a solution of (*S*)-mandelic acid (30.40 g, 200 mmol) in dry methanol (150 mL) was added 1.4 mL of acetyl chloride (20 mmol) via syringe. The mixture was stirred at room temperature overnight and then concentrated under reduced pressure. The residue was diluted with ethyl acetate (200 mL), washed with water (60 mL), saturated aqueous sodium bicarbonate (30 mL) and brine (30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was dissolved in dry DCM (200 mL), and then sequentially added imidazole (20.40 g, 300 mmol) and *tert*-butyldimethylsilyl chloride (36.40 g, 240 mmol). The reaction mixture was stirred at 40 °C for 5 hours (as monitored by TLC), quenched with saturated ammonium chloride and extracted with DCM (2 × 100 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate (50:1, v/v), which afforded the product as a colorless liquid (53.24 g, 95% yield). $[\alpha]_{\text{D}}^{20} +50.0$ (*c* 1.0 in CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 7.49-7.45 (m, 2H), 7.36-7.26 (m, 3H), 5.24 (s, 1H), 3.68 (s, 3H), 0.92 (s, 9H), 0.11 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (CDCl_3 , 126 MHz) δ 172.6, 139.2, 128.4, 128.1, 126.4, 74.4, 52.2, 25.7, 18.4, -5.0(8), -5.1(4); HRMS (ESI): *m/z* calcd for $\text{C}_{15}\text{H}_{24}\text{O}_3\text{Si}$ $[\text{M}+\text{Na}]^+$ 303.1392, found 303.1397.

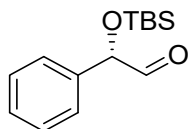
(*R*)-Methyl 2-(*tert*-butyldimethylsilyloxy)-2-phenylacetate [(*R*)-2]



Following the same procedure for (*S*)-2, the title product was obtained starting from (*R*)-mandelic acid in 93% yield. $[\alpha]_{\text{D}}^{20} -51.2$ (*c* 1.0 in CHCl_3); ^1H and ^{13}C NMR data are

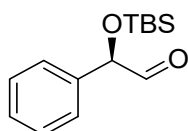
identical to that of **(S)-2**.

(S)-2-(tert-butyldimethylsilyloxy)-2-phenylacetaldehyde [(S)-3]



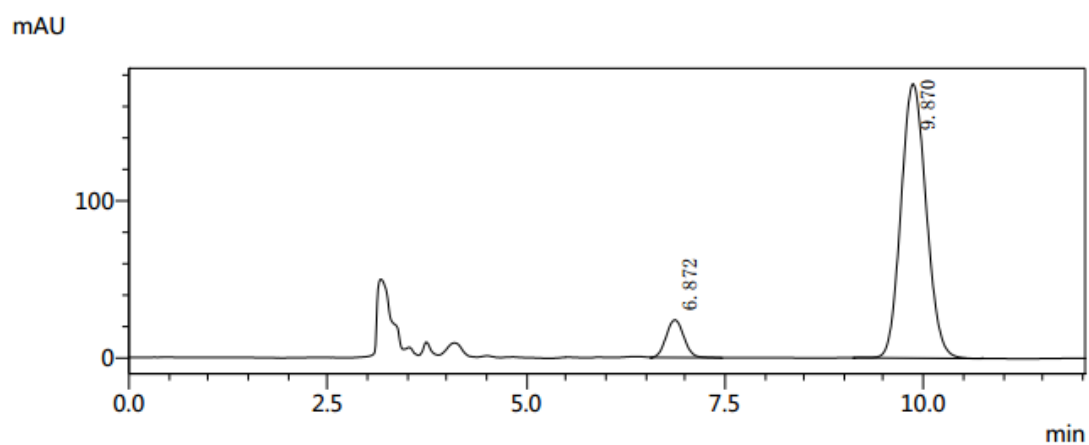
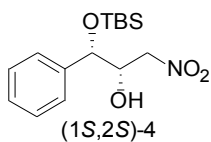
To a solution of **(S)-2** (22.40 g, 80.0 mmol) in dry DCM (240 mL) was dropwise added a solution of DIBAL-H in hexane (1M, 88 mL, 88 mmol) at -78 °C under nitrogen. The reaction mixture was stirred at -78 °C for additional 10 hours before being quenched with MeOH (10 mL). A saturated Rochelle salt solution (30 mL) was then added to the reaction, stirred rapidly at room temperature for 30 min and then extracted with DCM (3 × 50 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. Flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate (50:1, v/v) afforded the product as a colorless liquid (19.21 g, 76.8 mmol, 96%). $[\alpha]_{\text{D}}^{20}$ -14.2 (*c* 1.0, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 9.51 (d, *J* = 2.15 Hz, 1H), 7.41-7.36 (m, 4H), 7.34-7.30 (m, 1H), 5.00(d, *J* = 2.07 Hz, 1H), 0.95 (s, 9H), 0.12 (s, 3H), 0.04 (s, 3H); ¹³C NMR (CDCl₃, 126 MHz) δ 199.6, 136.6, 128.7, 128.4, 126.4, 80.0, 25.8, 18.3, -4.8; HRMS (ESI): *m/z* calcd for C₁₄H₂₂O₂Si [M+Na]⁺ 273.1287, found 273.1285.

(R)-2-(tert-butyldimethylsilyloxy)-2-phenylacetaldehyde [(R)-3]



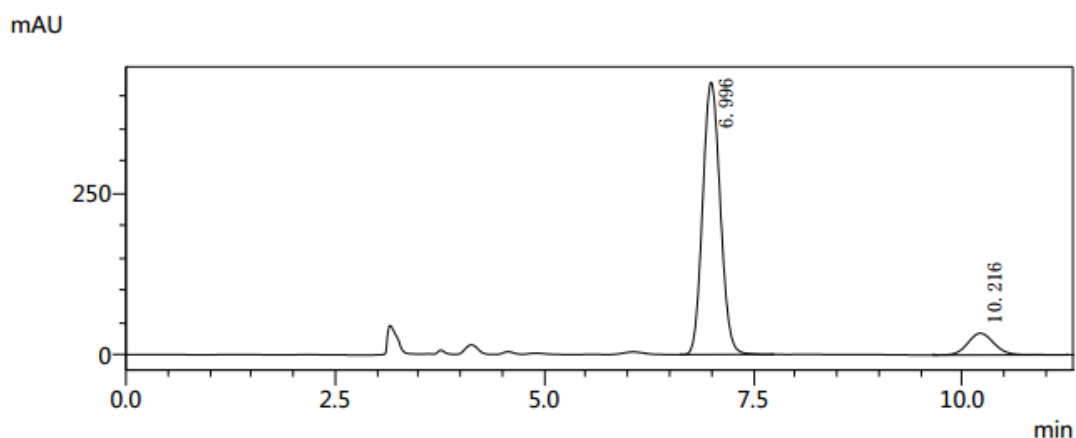
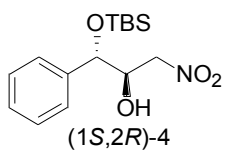
Following the same procedure for **(S)-3**, the title product was obtained starting from (*R*)-mandelic acid in 94% yield. $[\alpha]_{\text{D}}^{20}$ +10.6 (*c* 1.0 in CHCl₃); ¹H and ¹³C NMR data are identical to that of **(S)-3**.

Column:Chiralpak OD-H+G
 Mobile Phase:Hex/iPrOH=95/5(v/v)
 Flow Rate: 1.0mL/min
 CT:20°C
 Sample Name: (1S,2S)-4



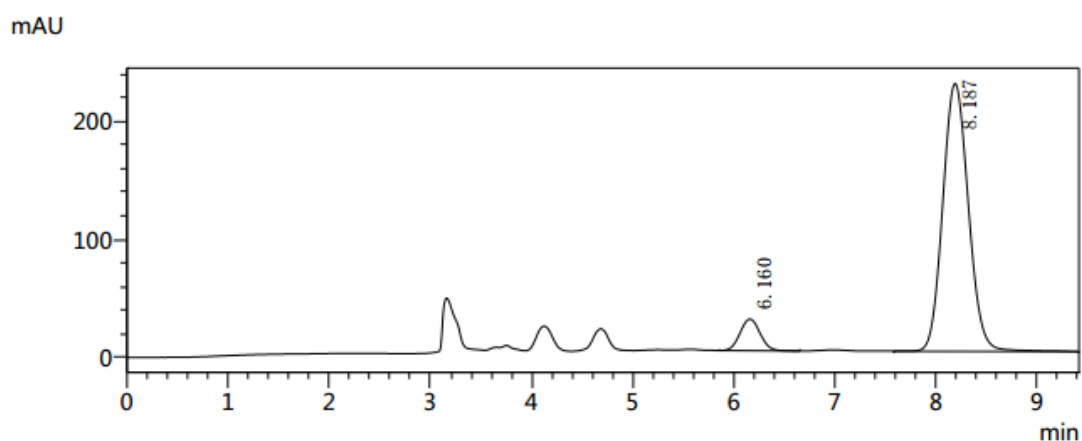
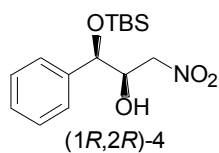
PDA Ch1 208nm			
Peak#	Retention Time	Area	Area Percent
1	6.872	369935	8.767
2	9.870	3849545	91.233
Totals		4219480	100.000

Column:Chiralpak OD-H+G
 Mobile Phase:Hex/iPrOH=95/5(v/v)
 Flow Rate: 1.0mL/min
 CT:20°C
 Sample Name: (1*S*,2*R*)-4



PDA Ch1 208nm			
Peak#	Retention Time	Area	Area Percent
1	6.996	6165934	89.405
2	10.216	730715	10.595
Totals		6896649	100.000

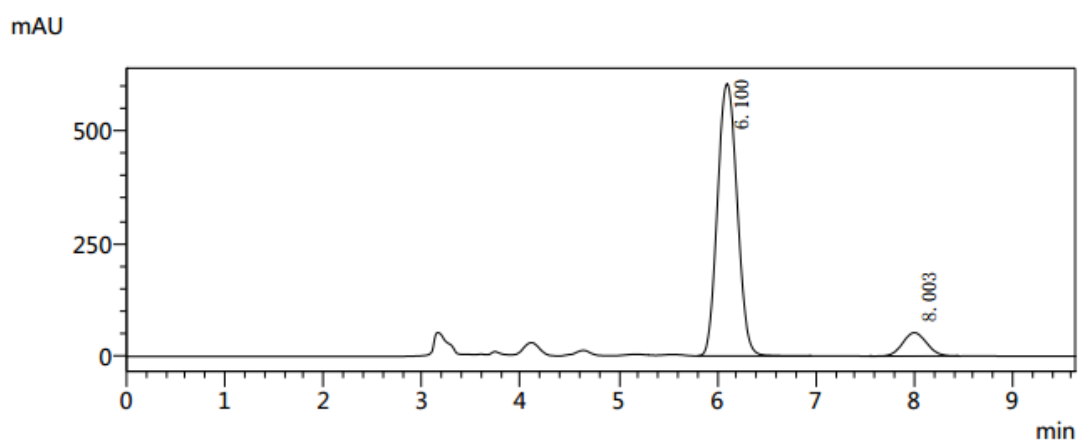
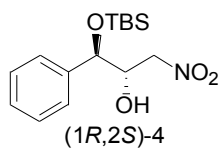
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 Mobile Phase:Hex/iPrOH=95/5(v/v)
 Flow Rate: 1.0mL/min
 CT:20°C
 Sample Name: (1*R*,2*R*)-4



PDA Ch1 208nm

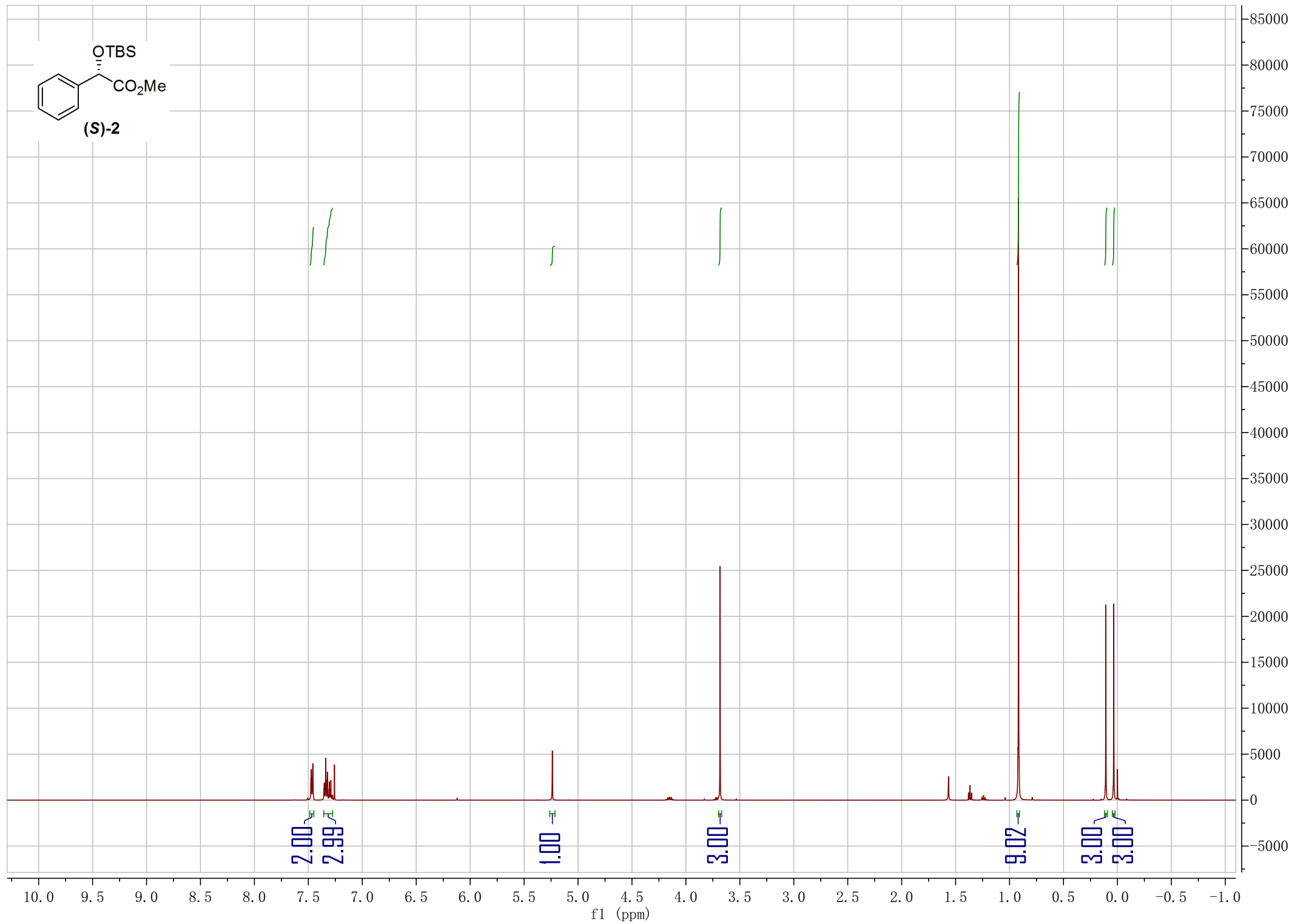
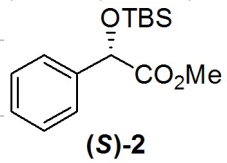
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2	8.187	4007391	91.648
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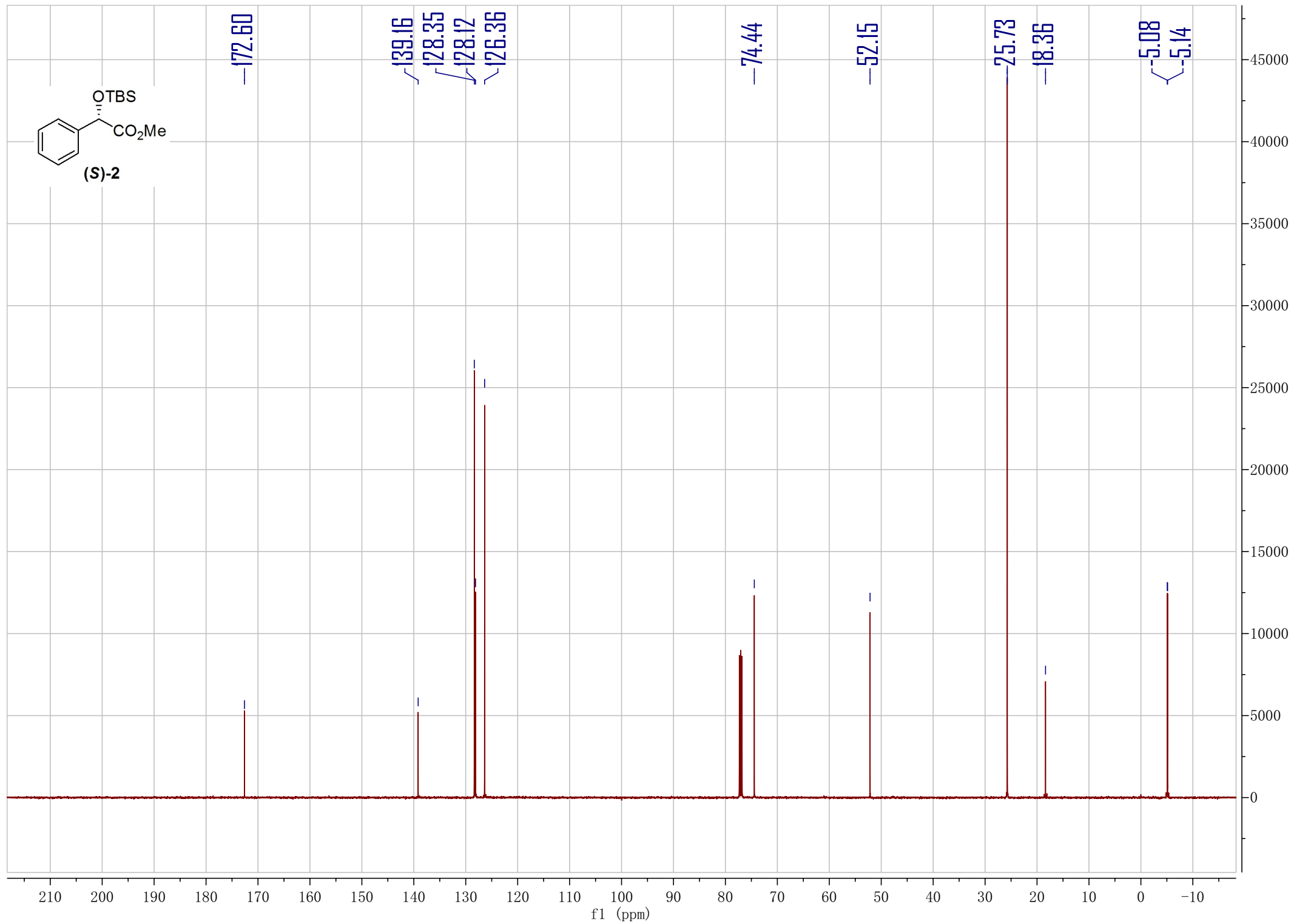
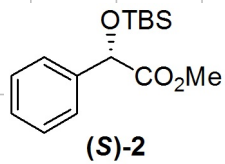
Column:Chiralpak OD-H+G
 Mobile Phase:Hex/iPrOH=95/5(v/v)
 Flow Rate: 1.0mL/min
 CT:20°C
 Sample Name: (1*R*,2*S*)-4

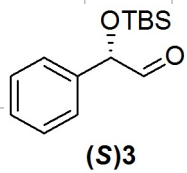


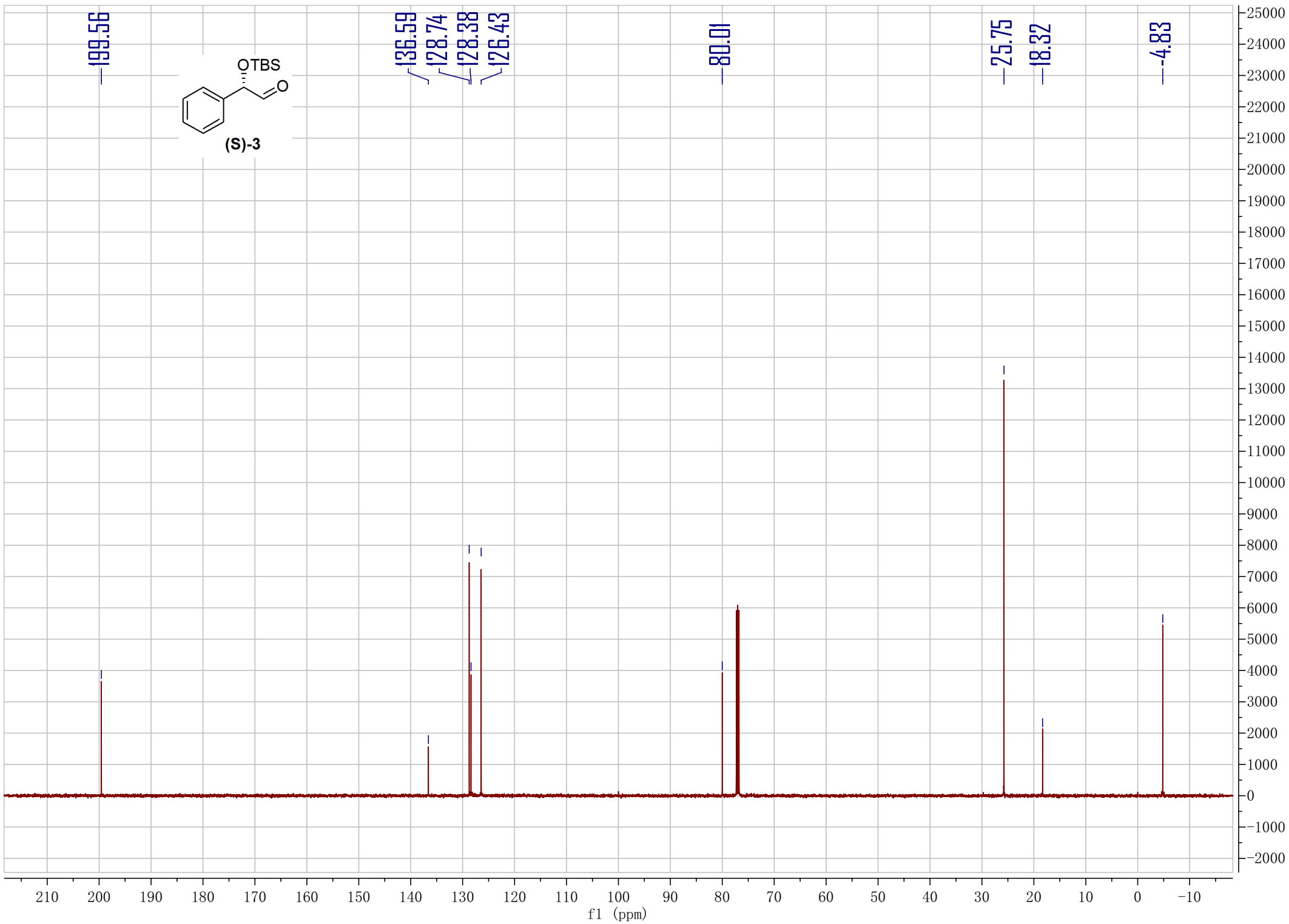
PDA Ch1 208nm

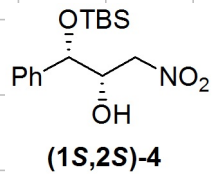
Peak#	Retention Time	Area	Area Percent
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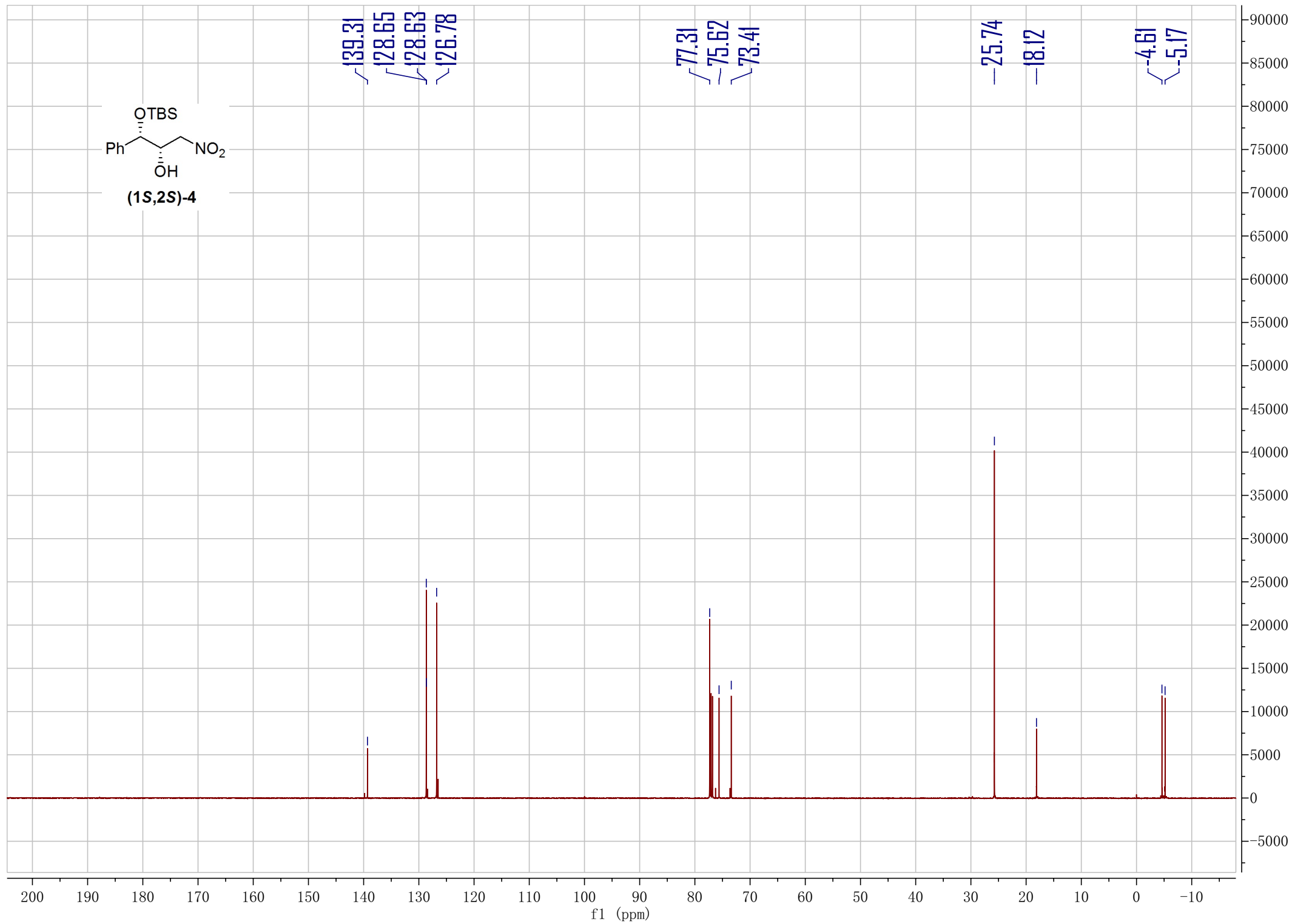
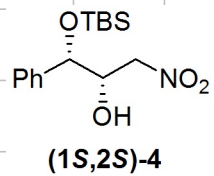


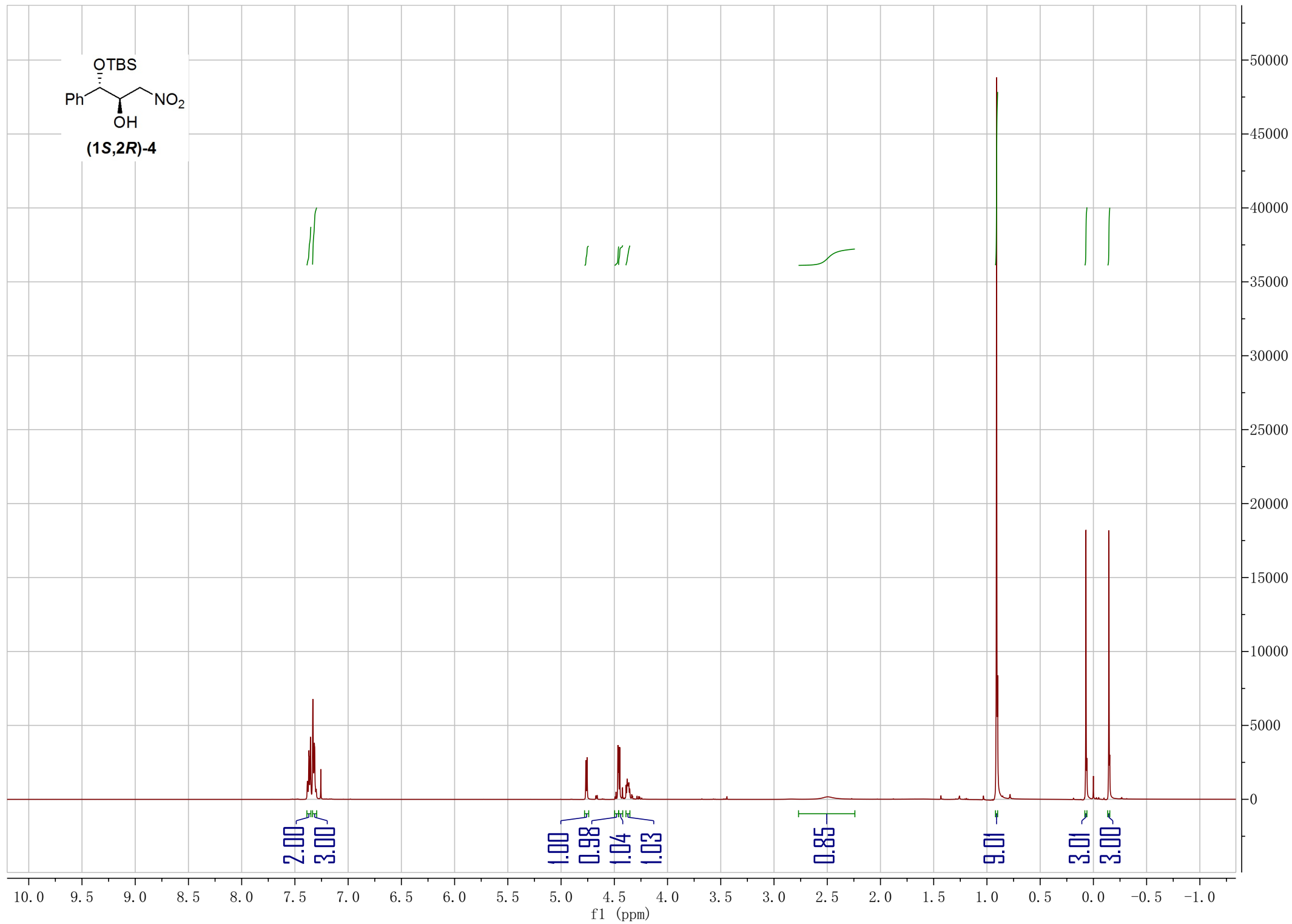
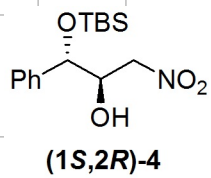


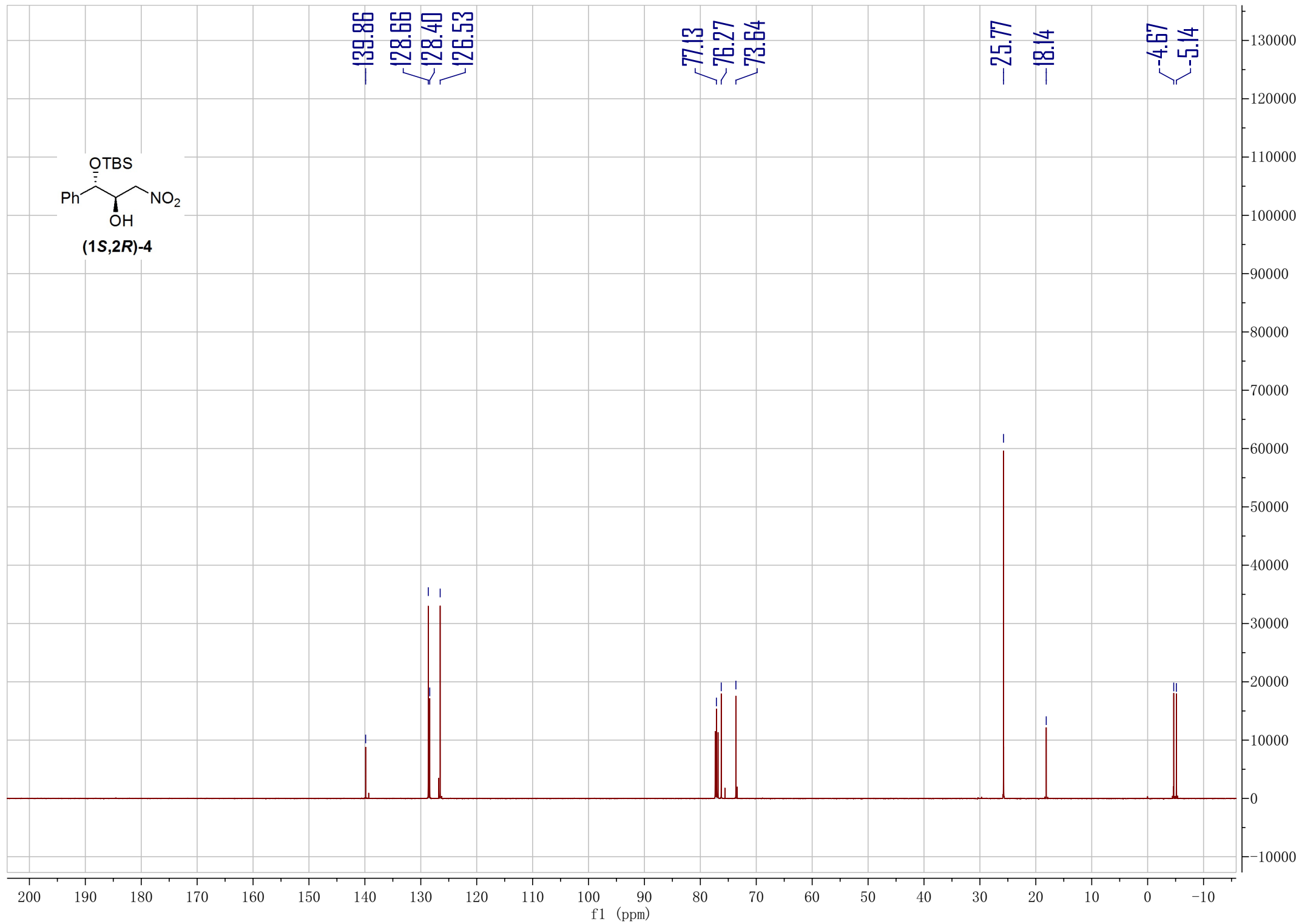
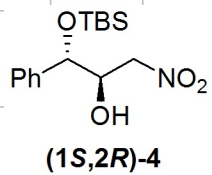


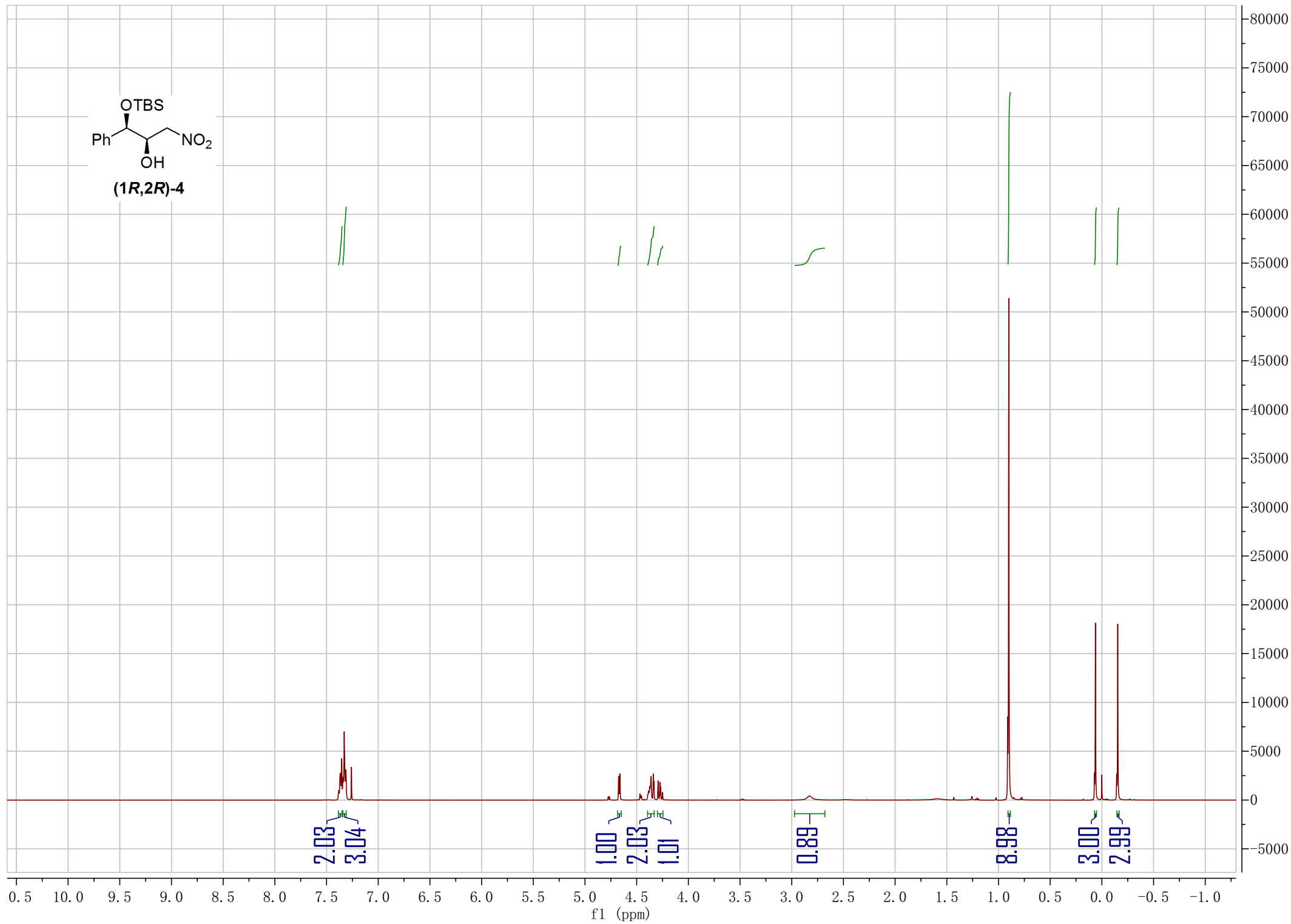
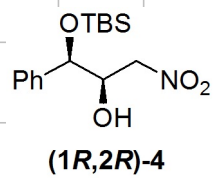


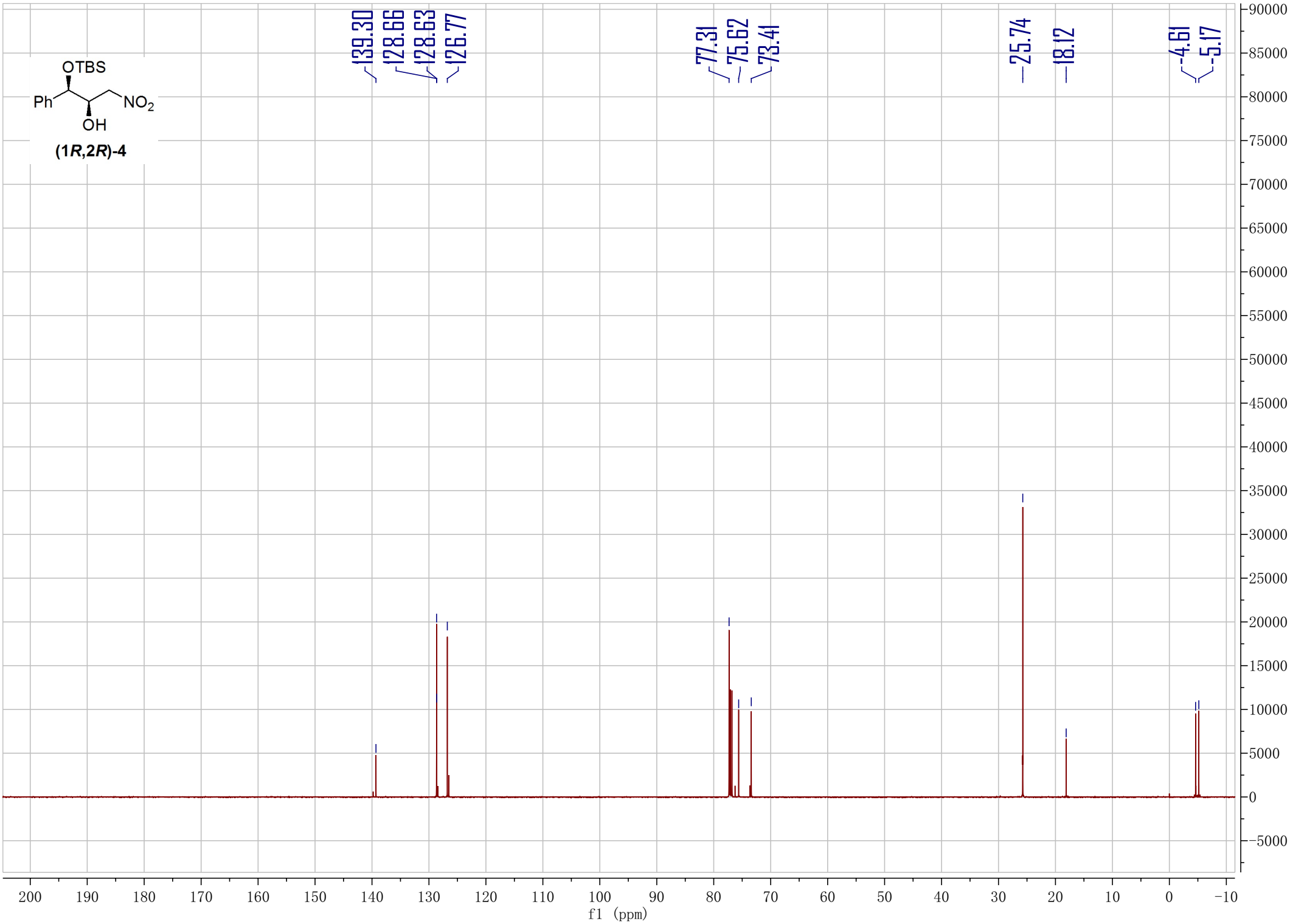


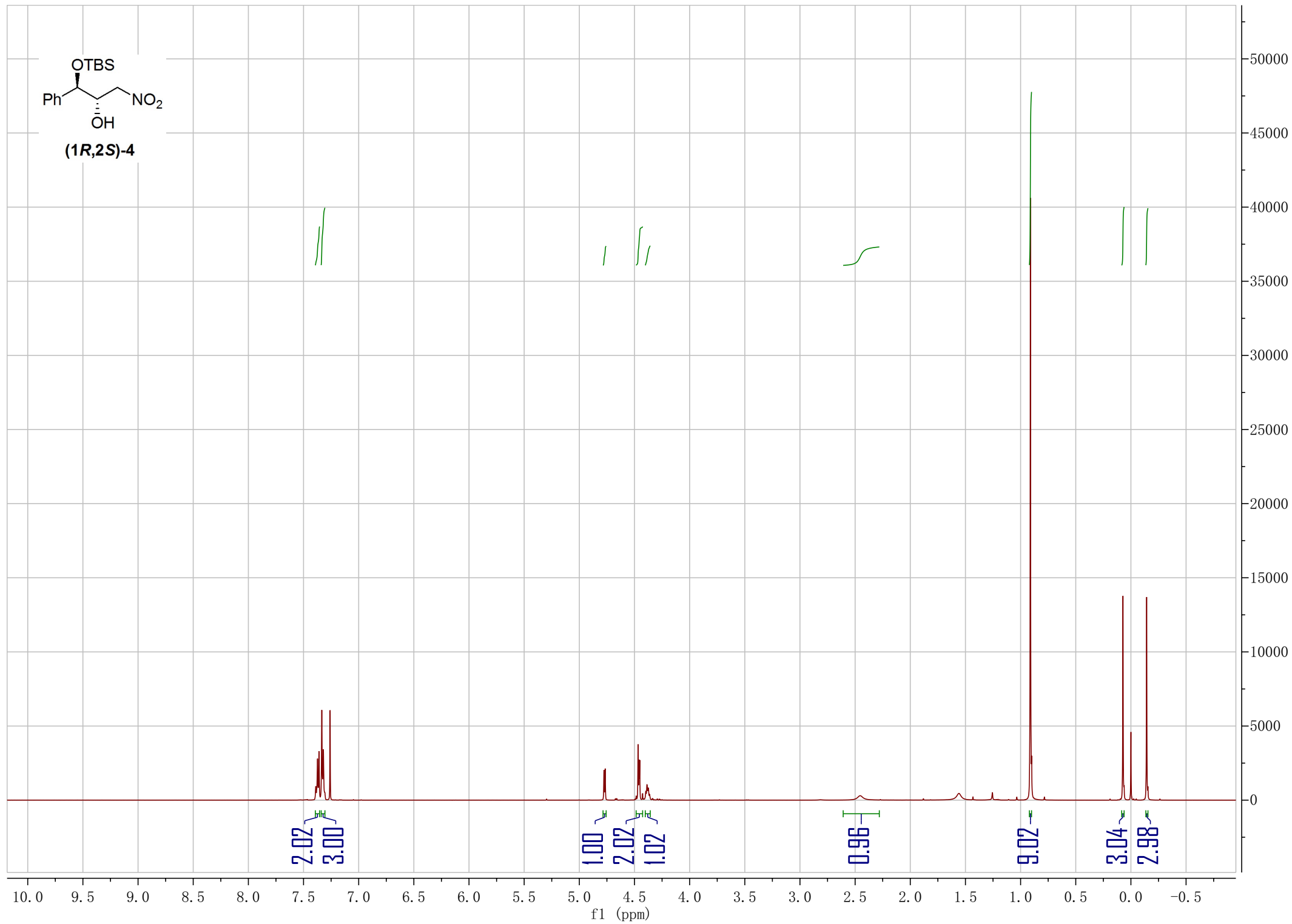
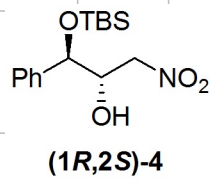


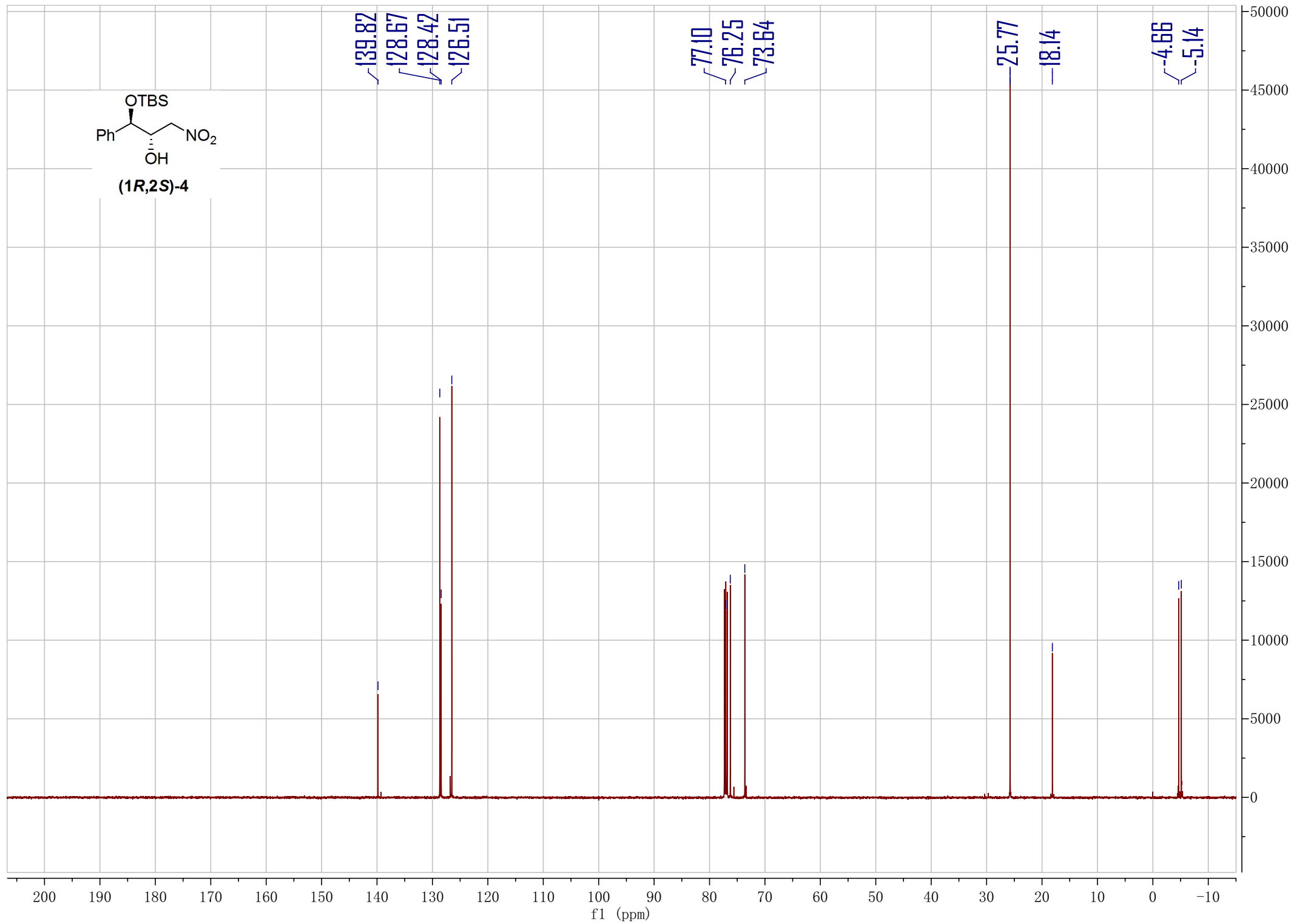
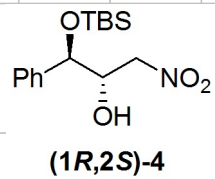


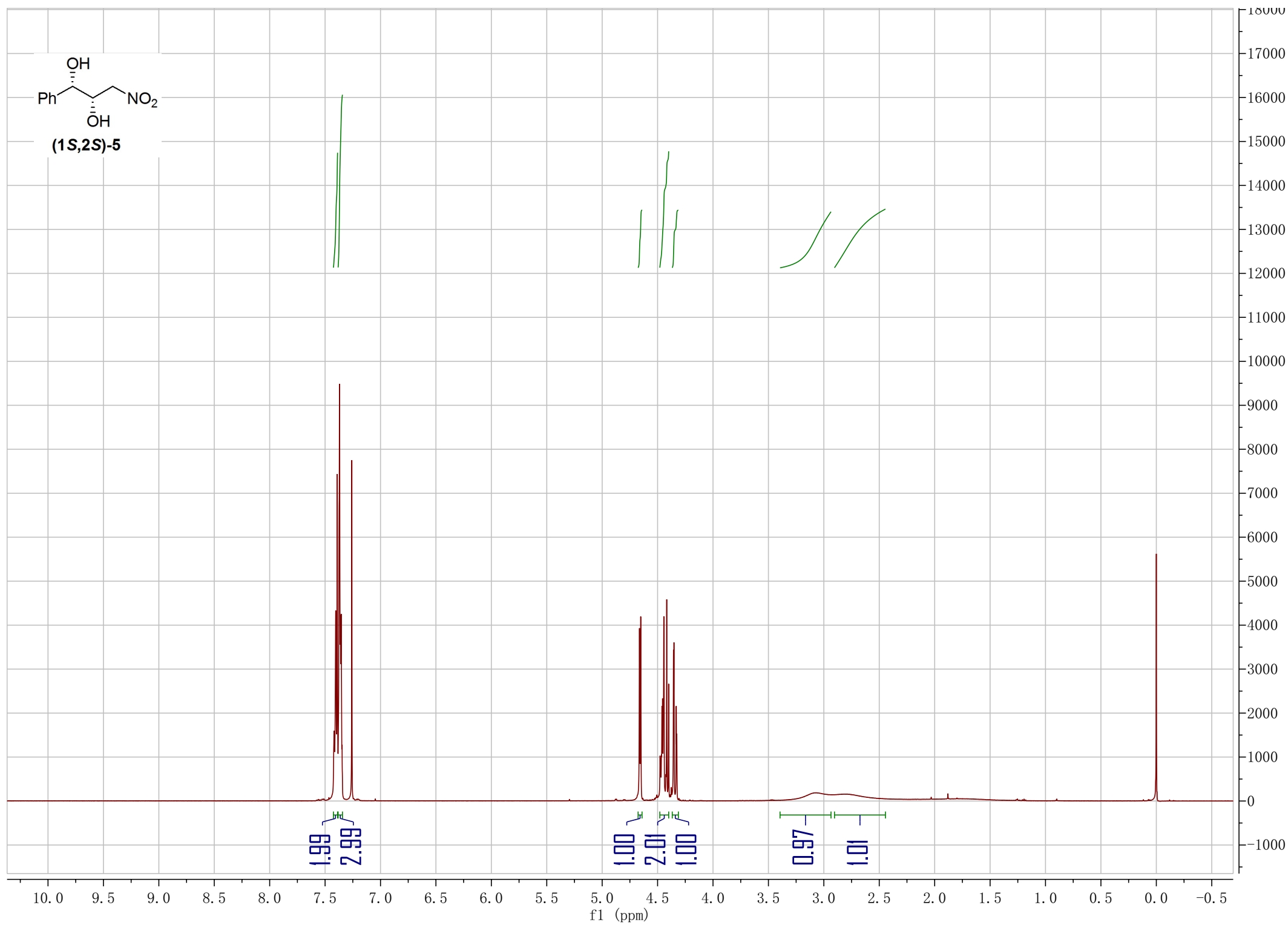
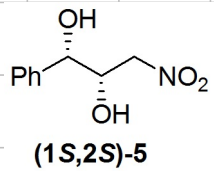


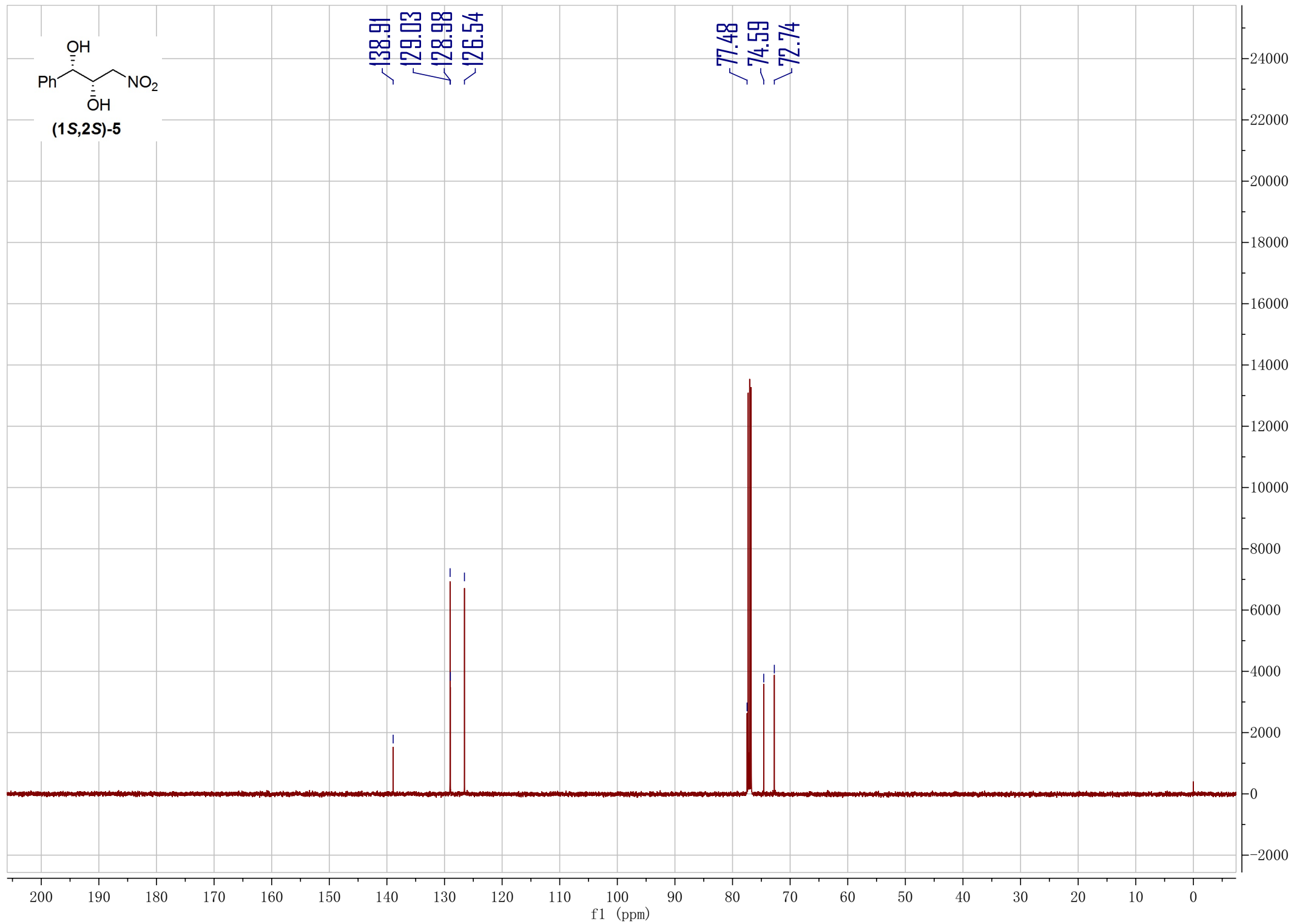
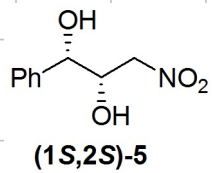


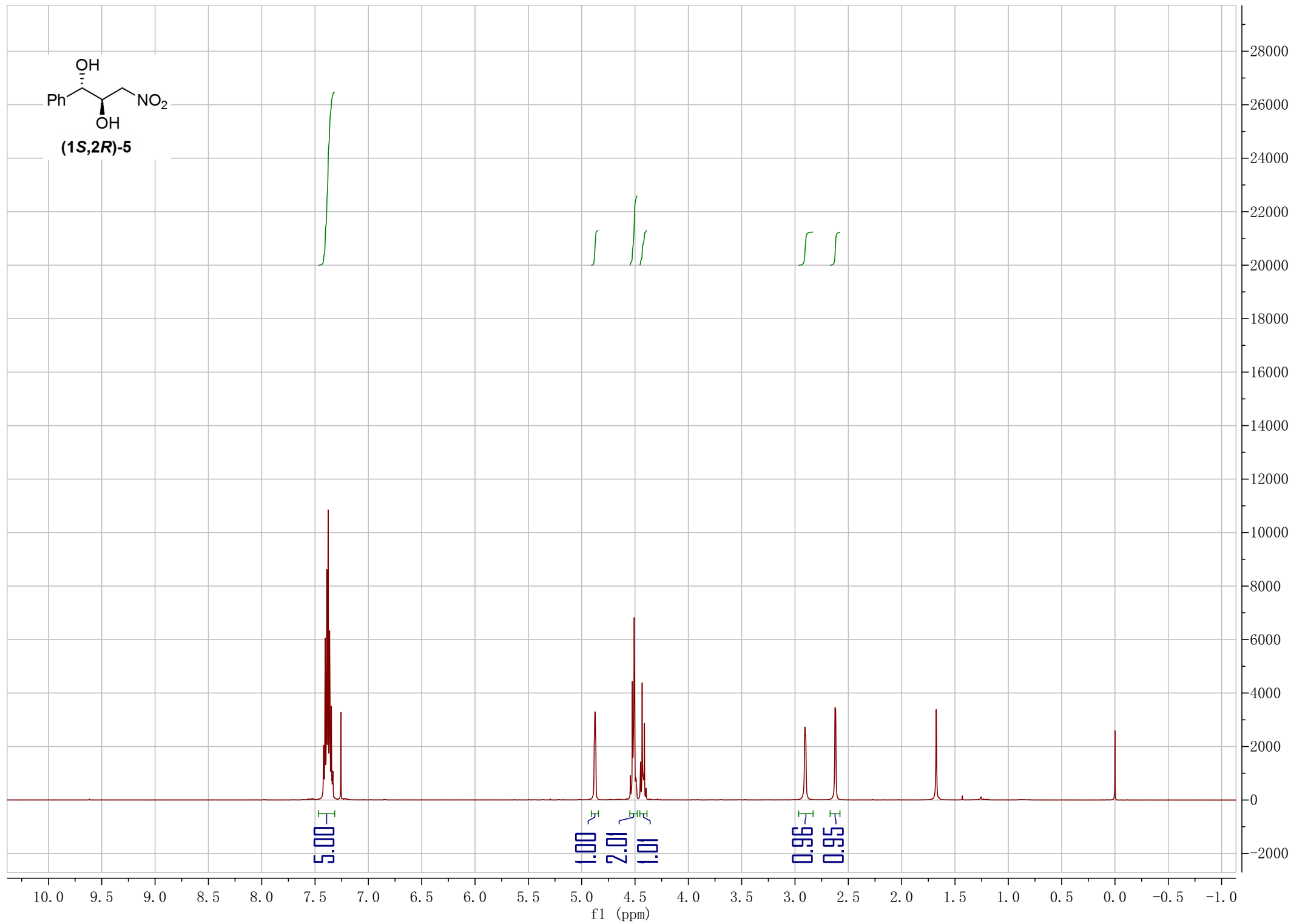
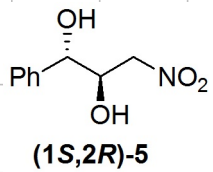


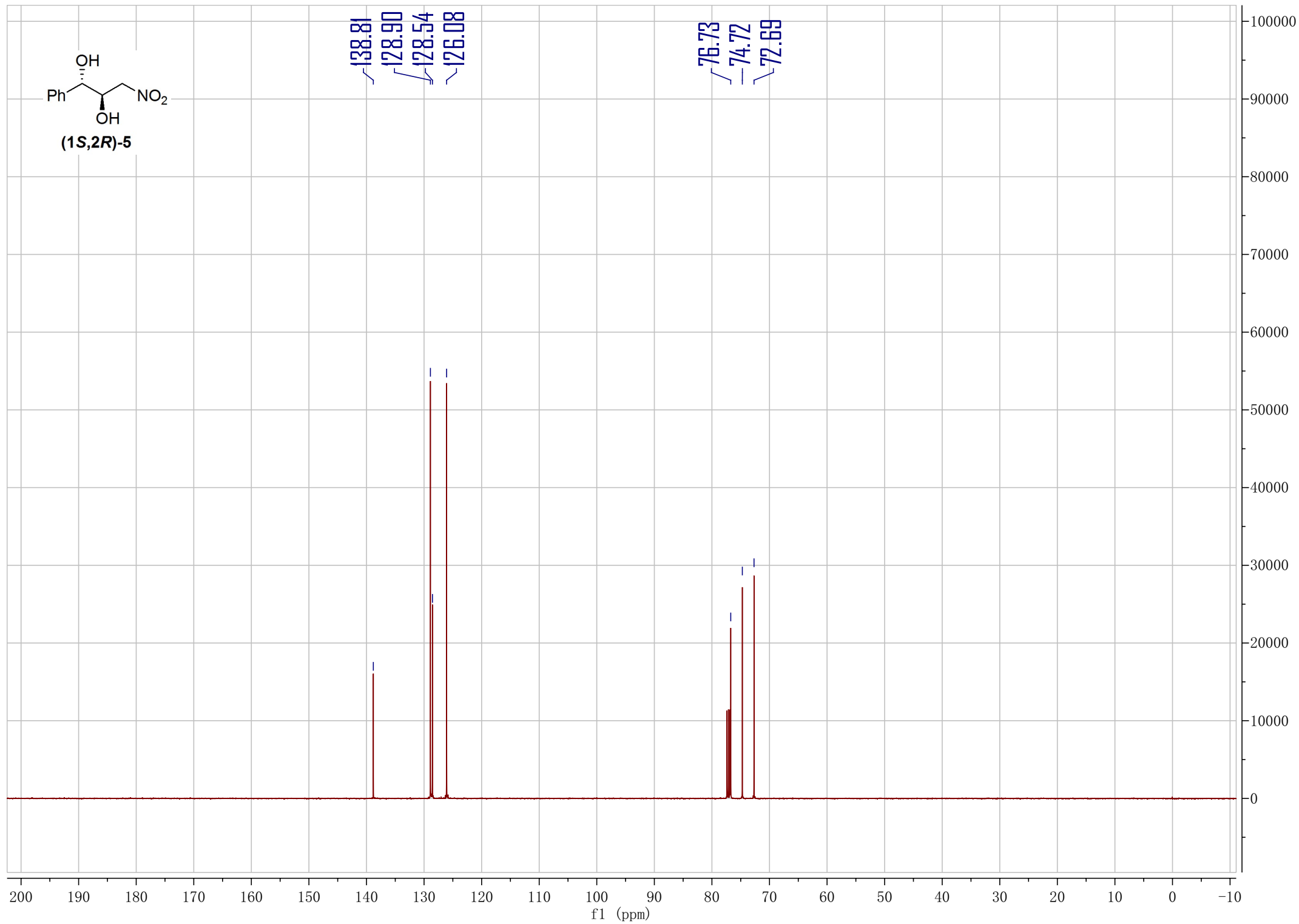
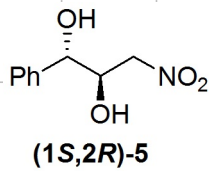


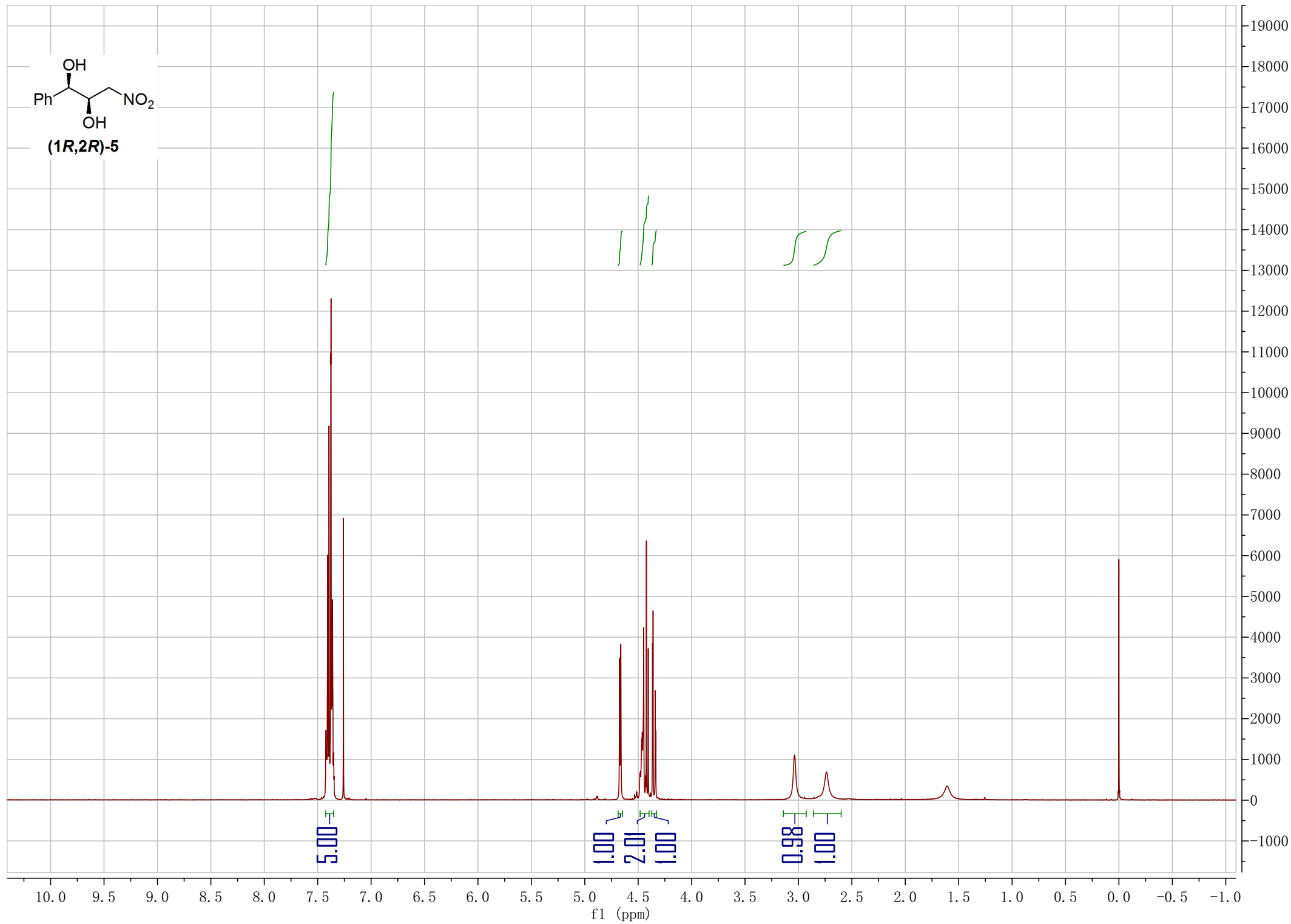
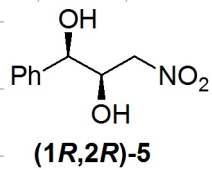


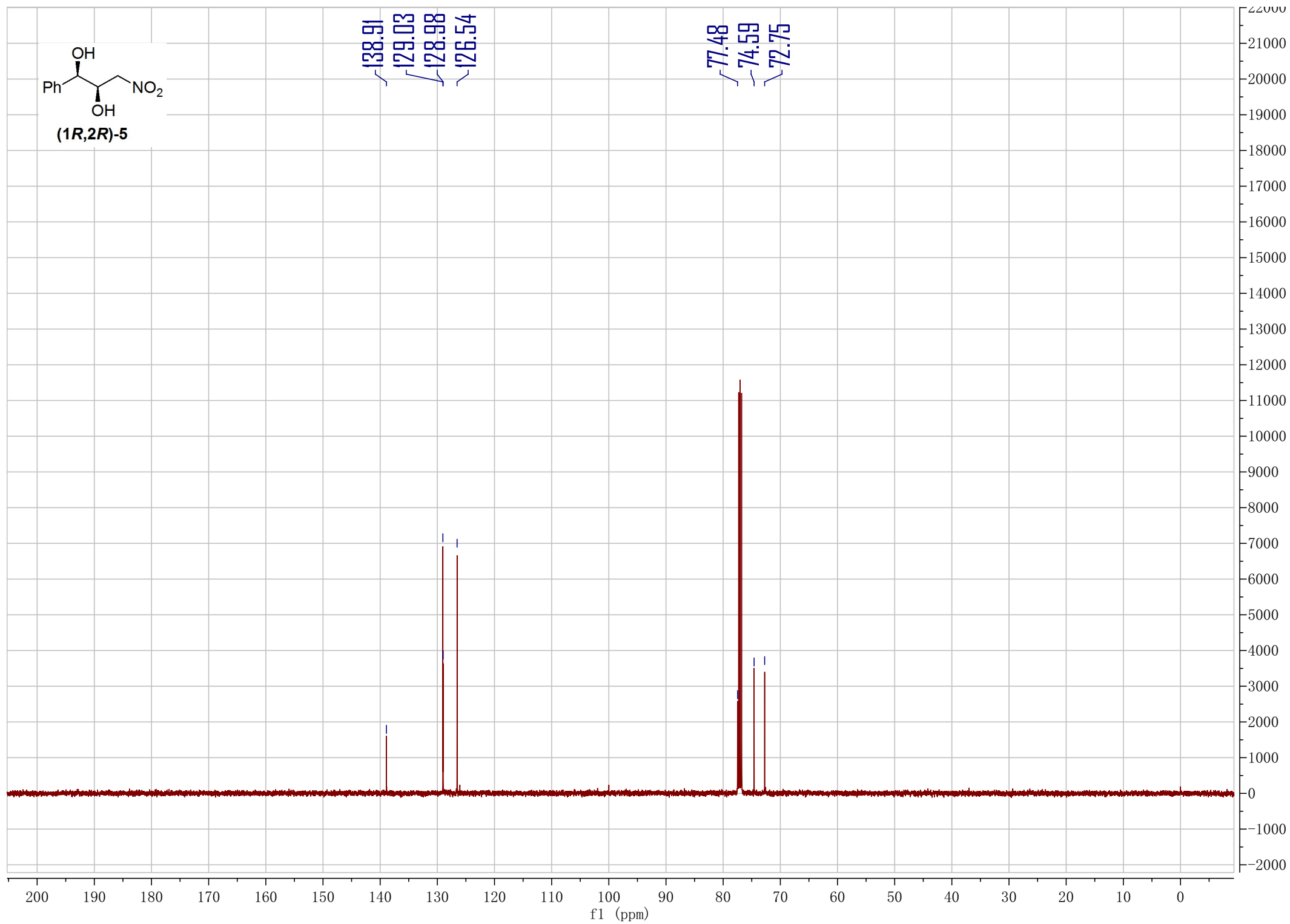
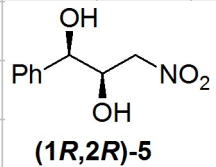


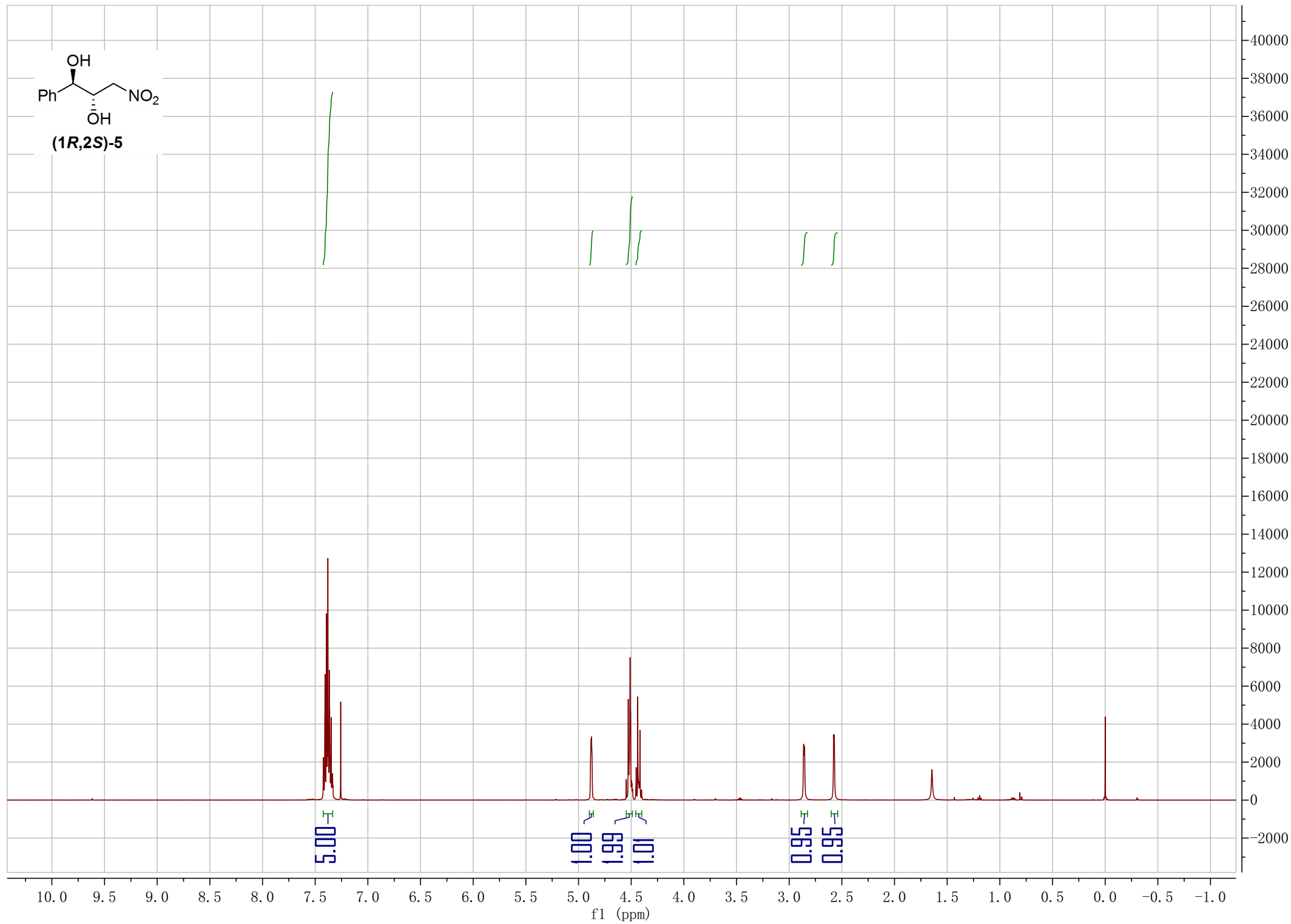
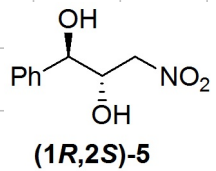


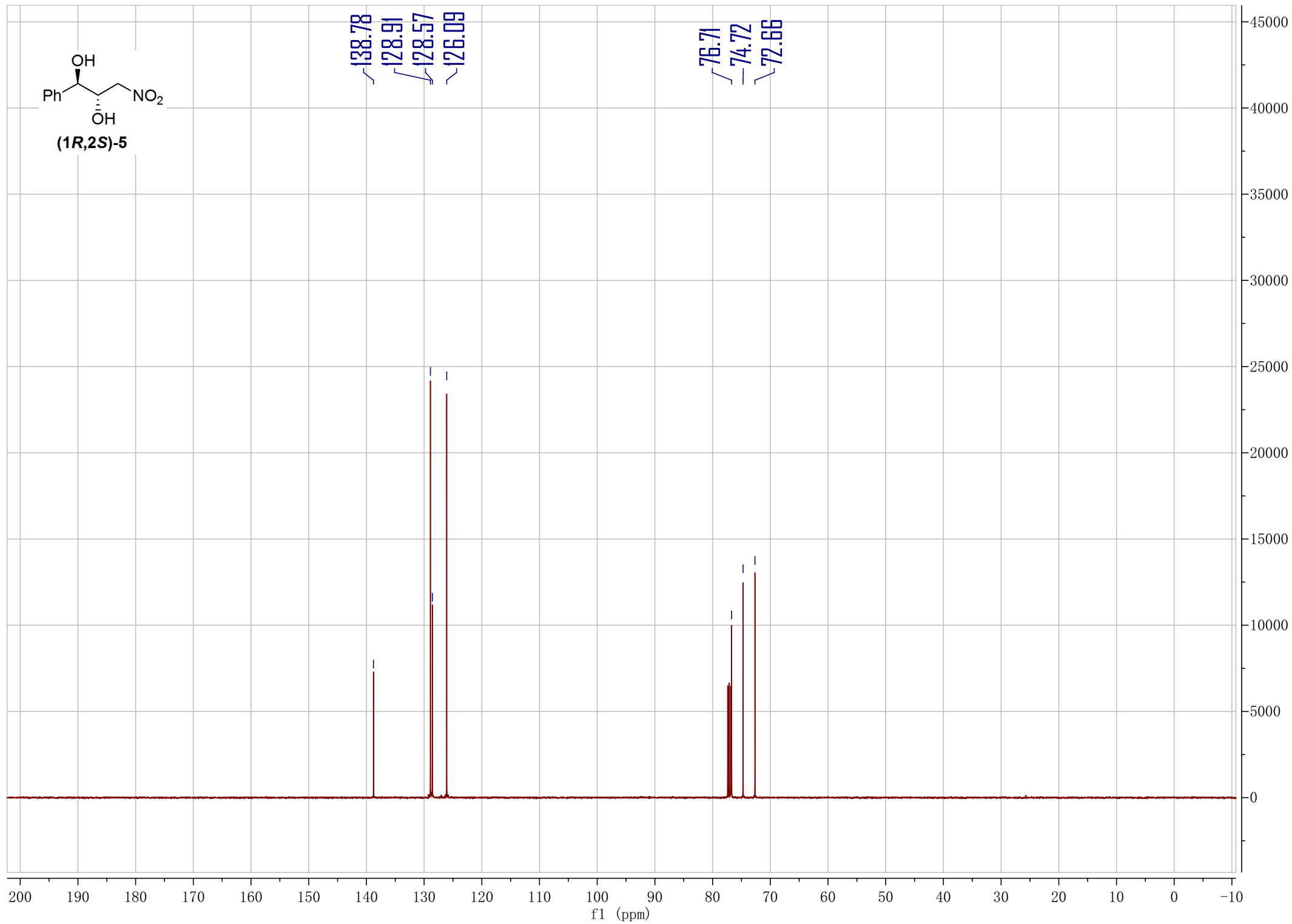
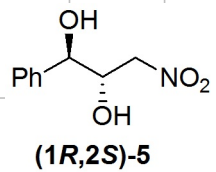


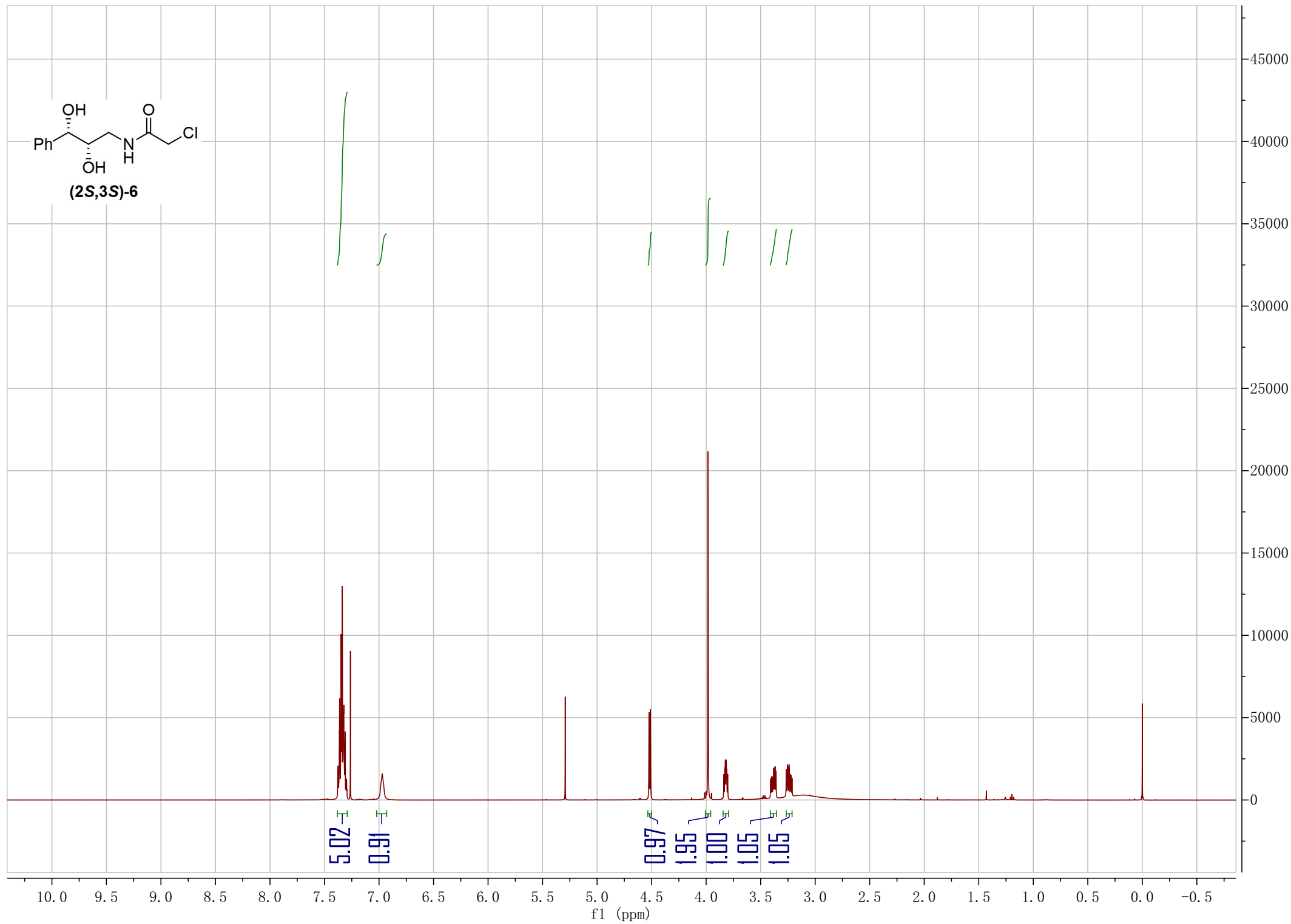
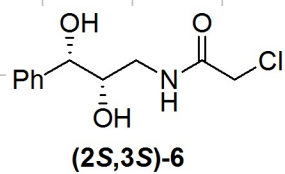


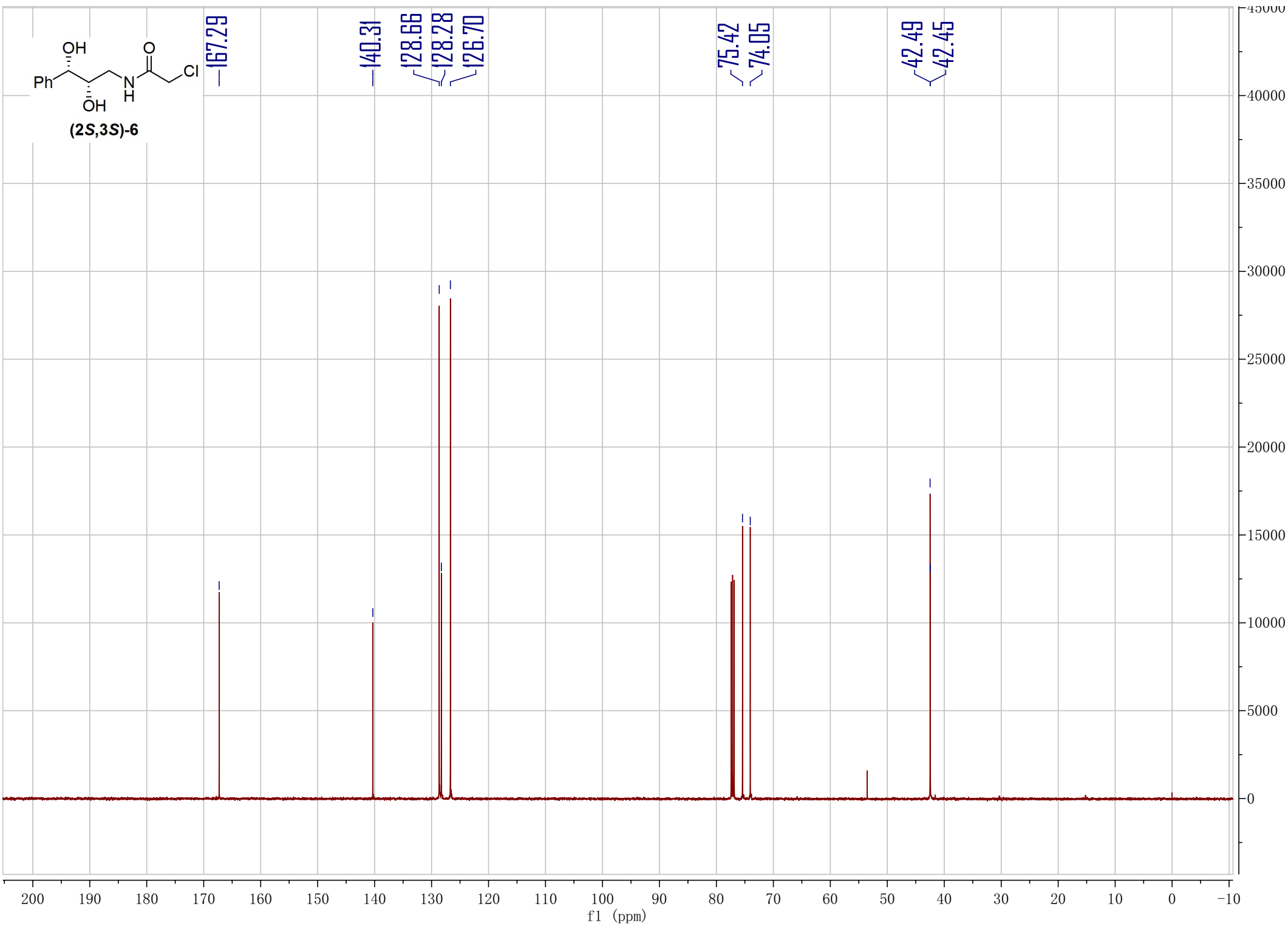
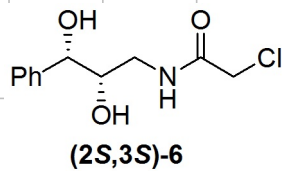


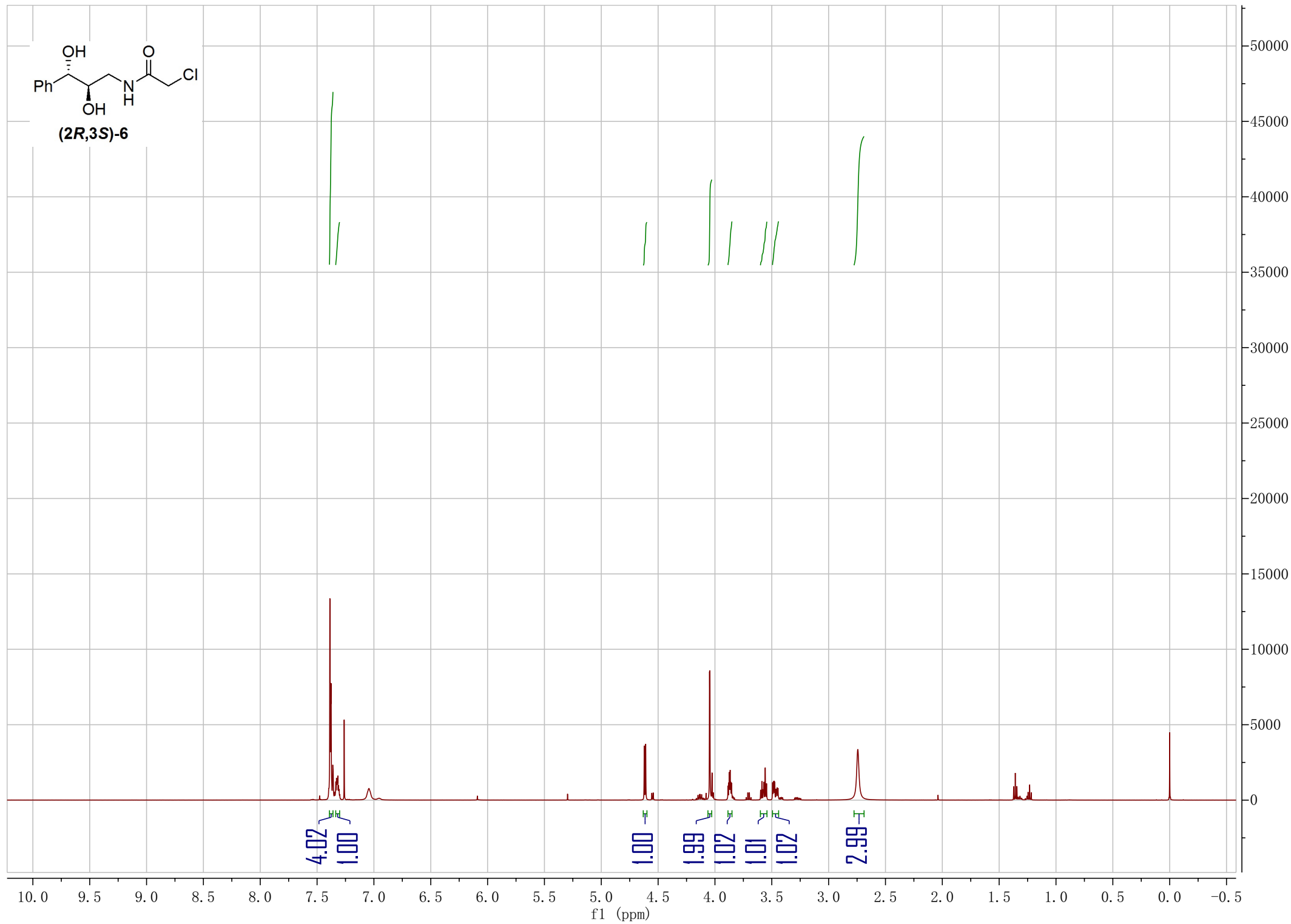
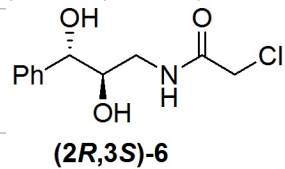


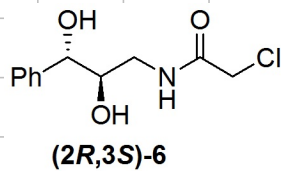












167.77

140.10

128.62

128.11

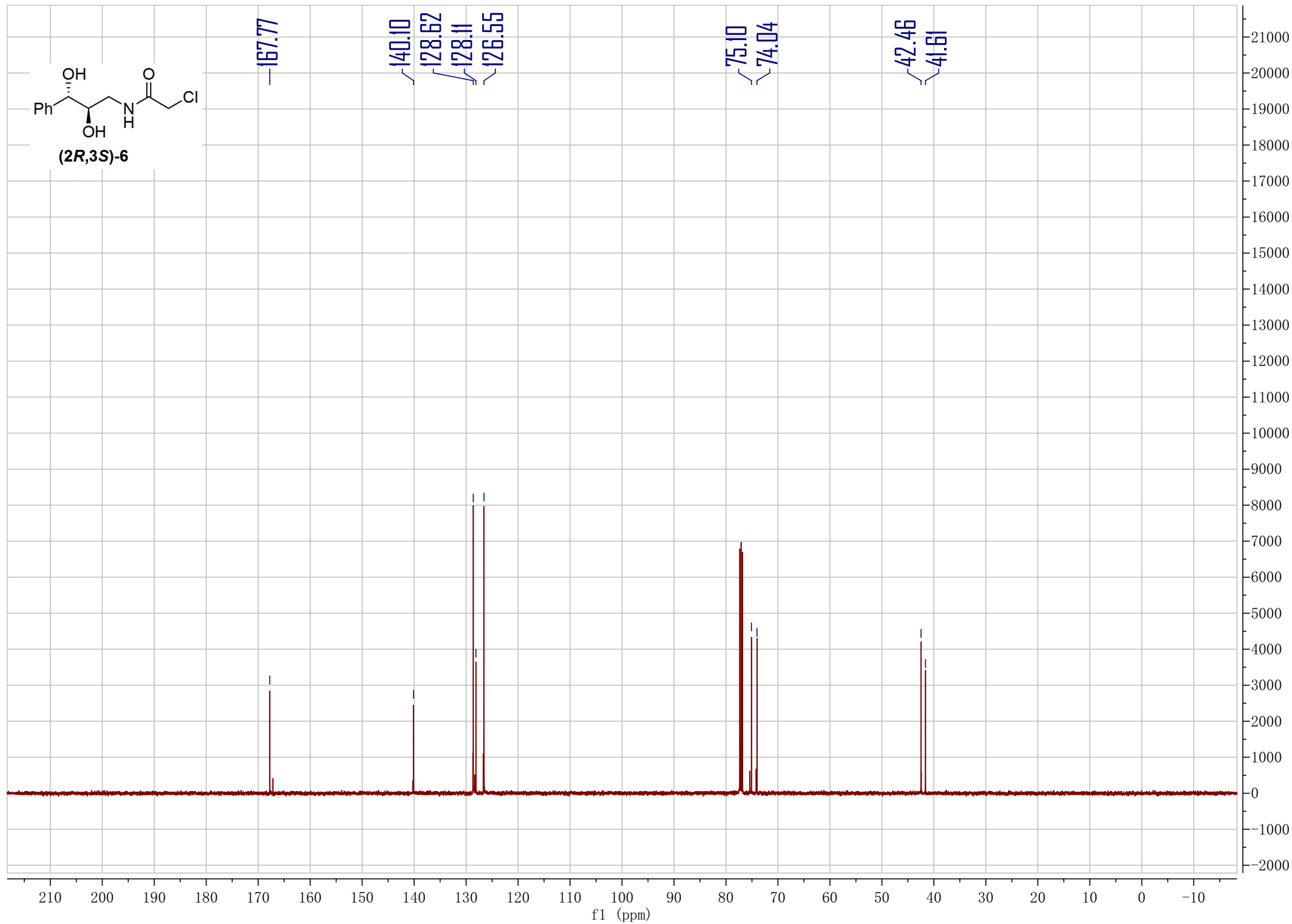
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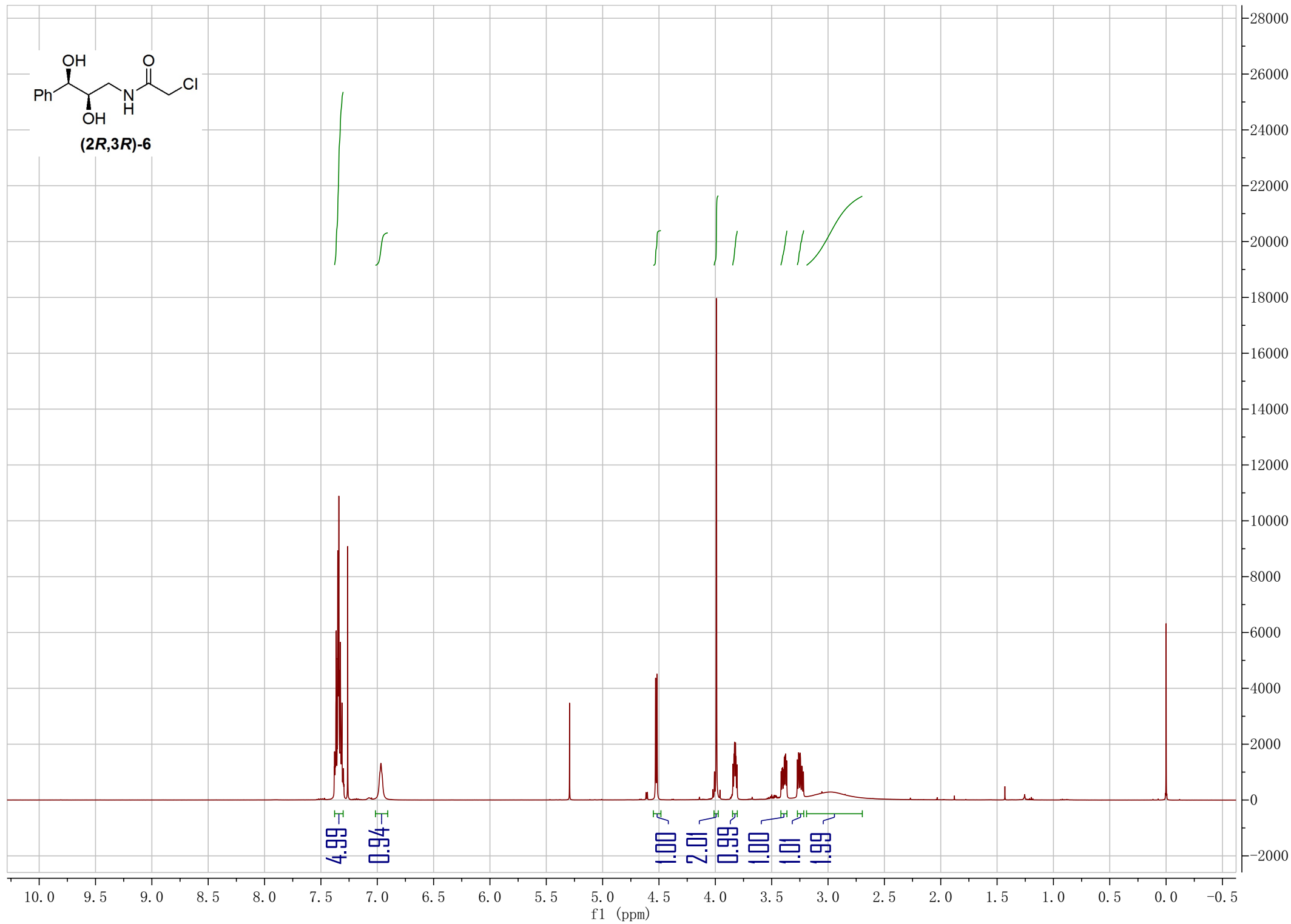
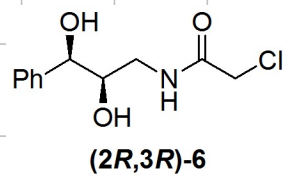
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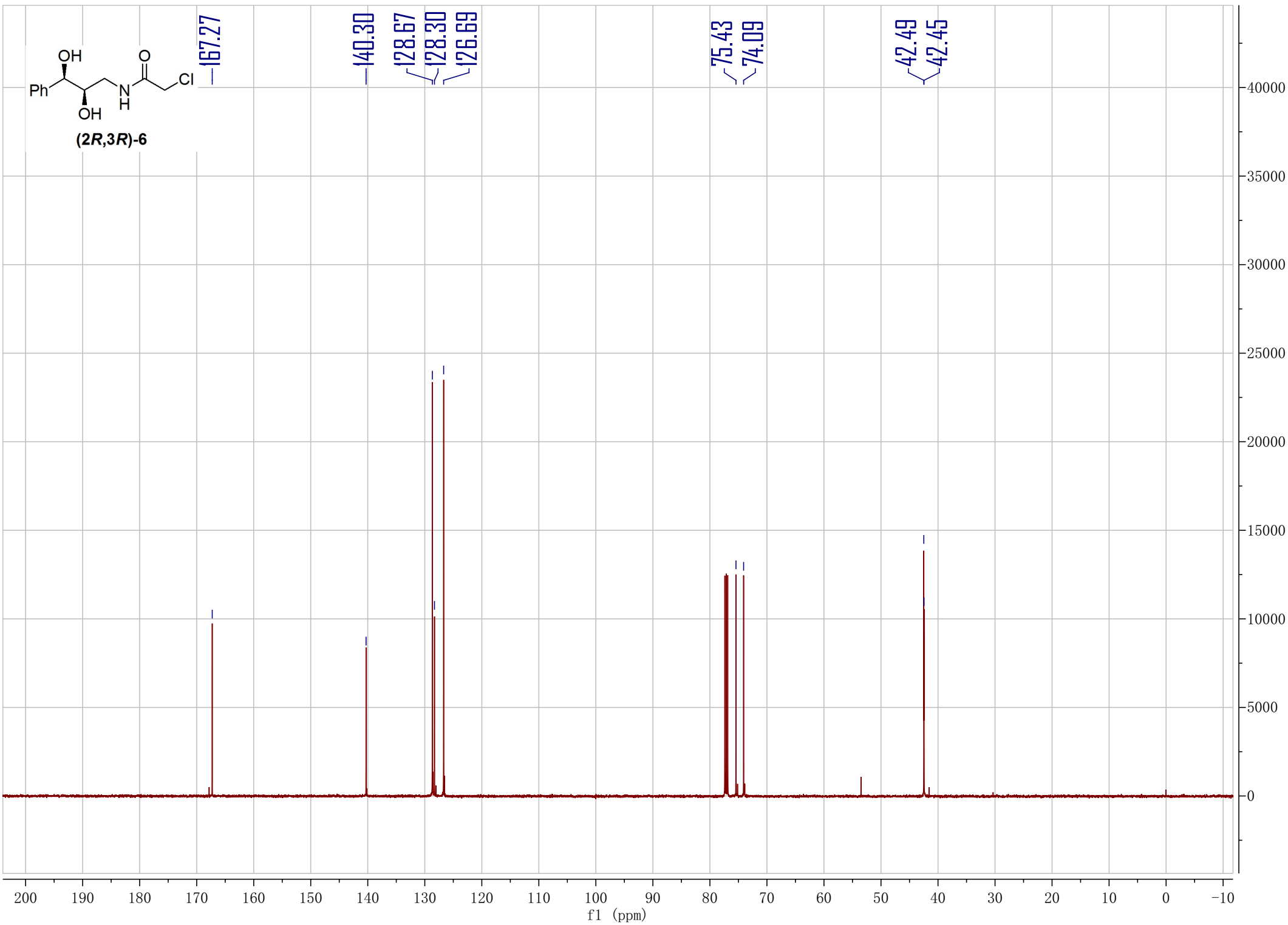
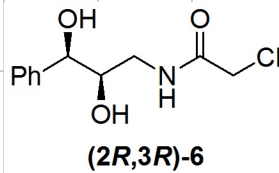
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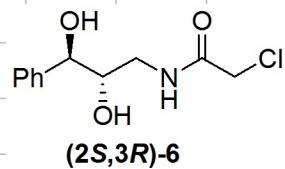
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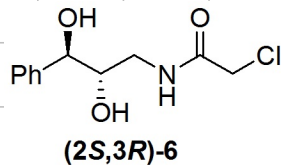
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140.13

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128.09

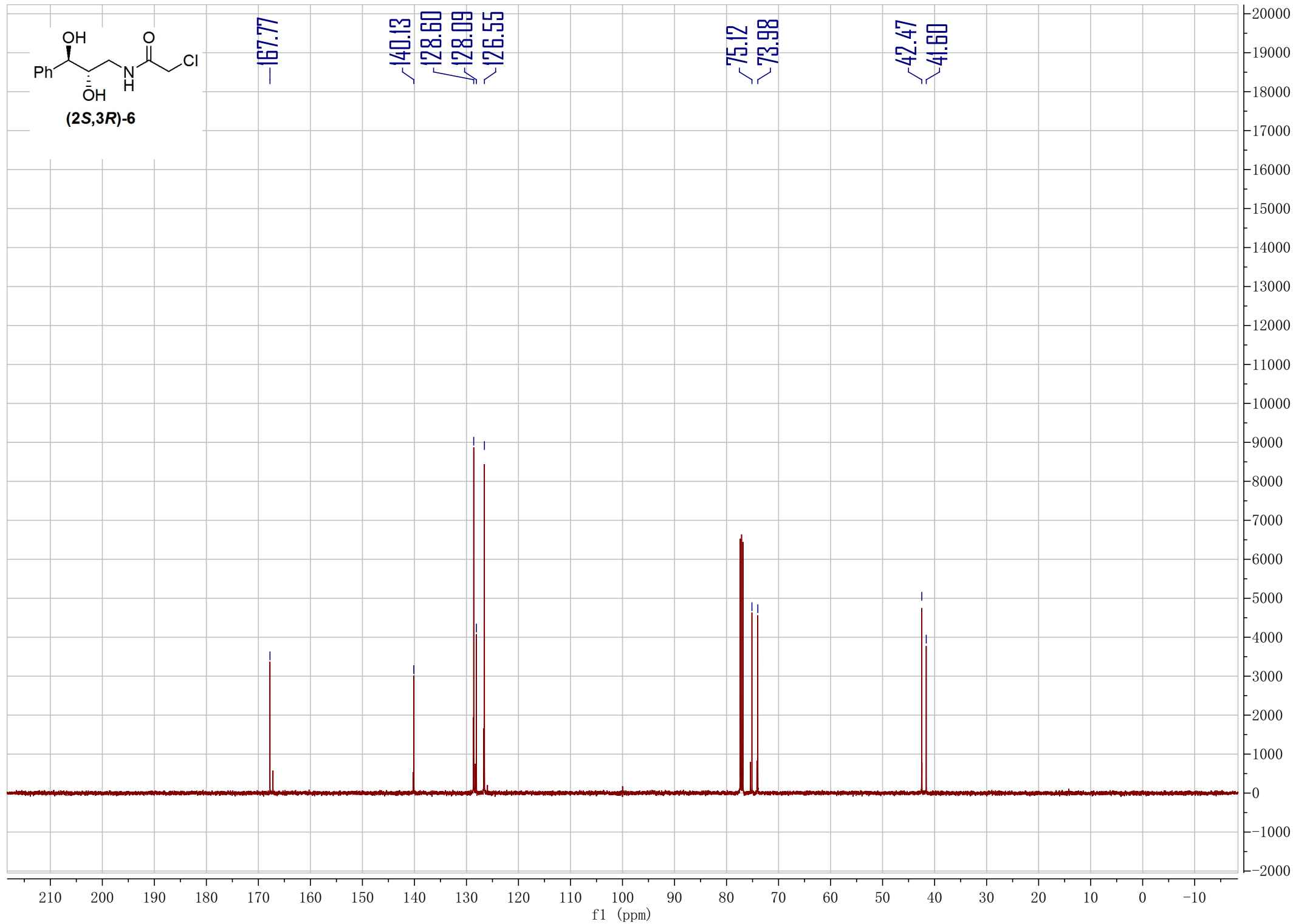
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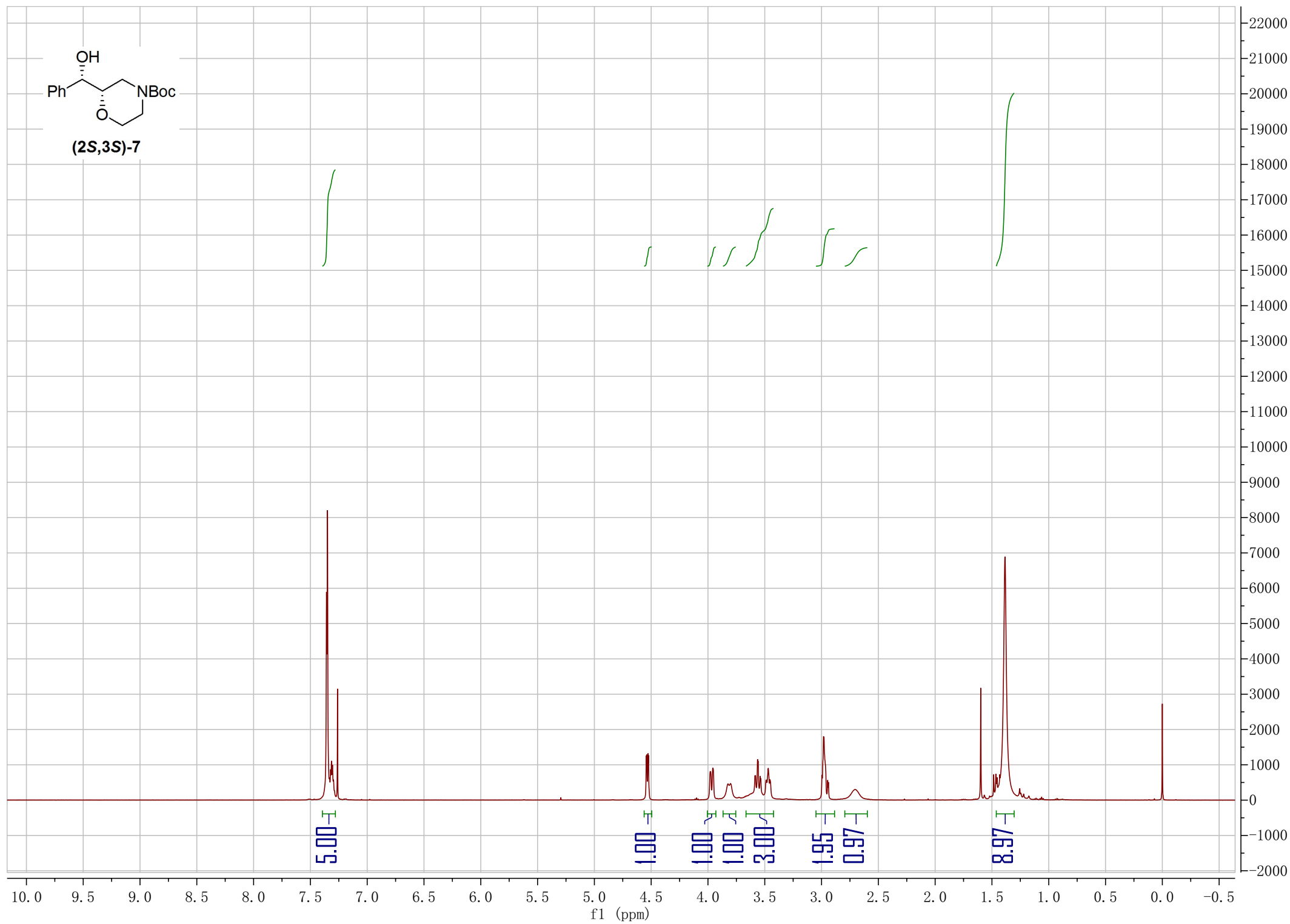
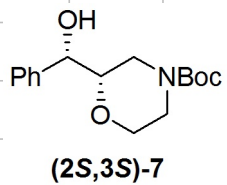
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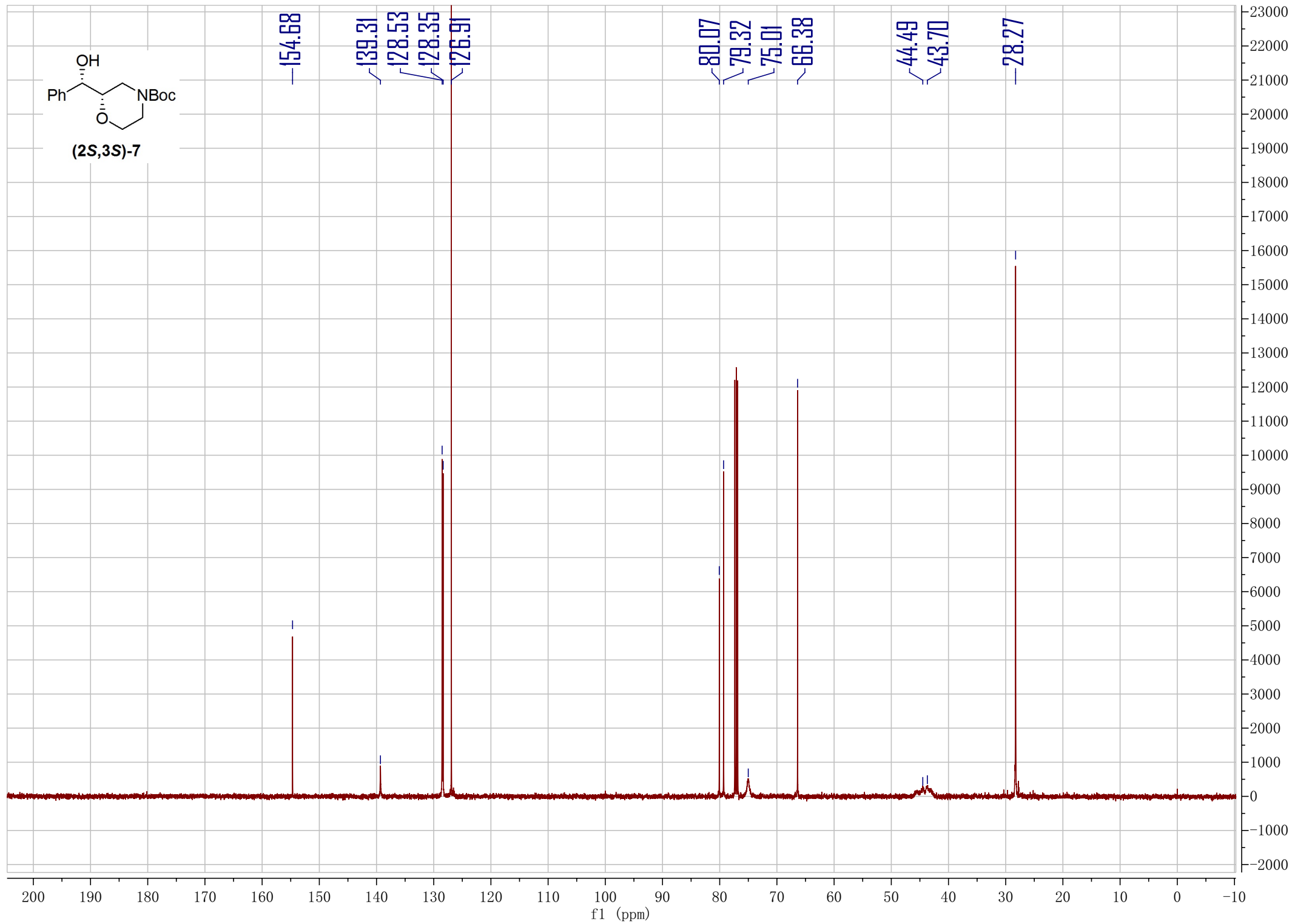
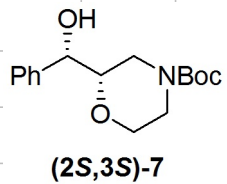
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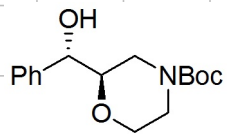
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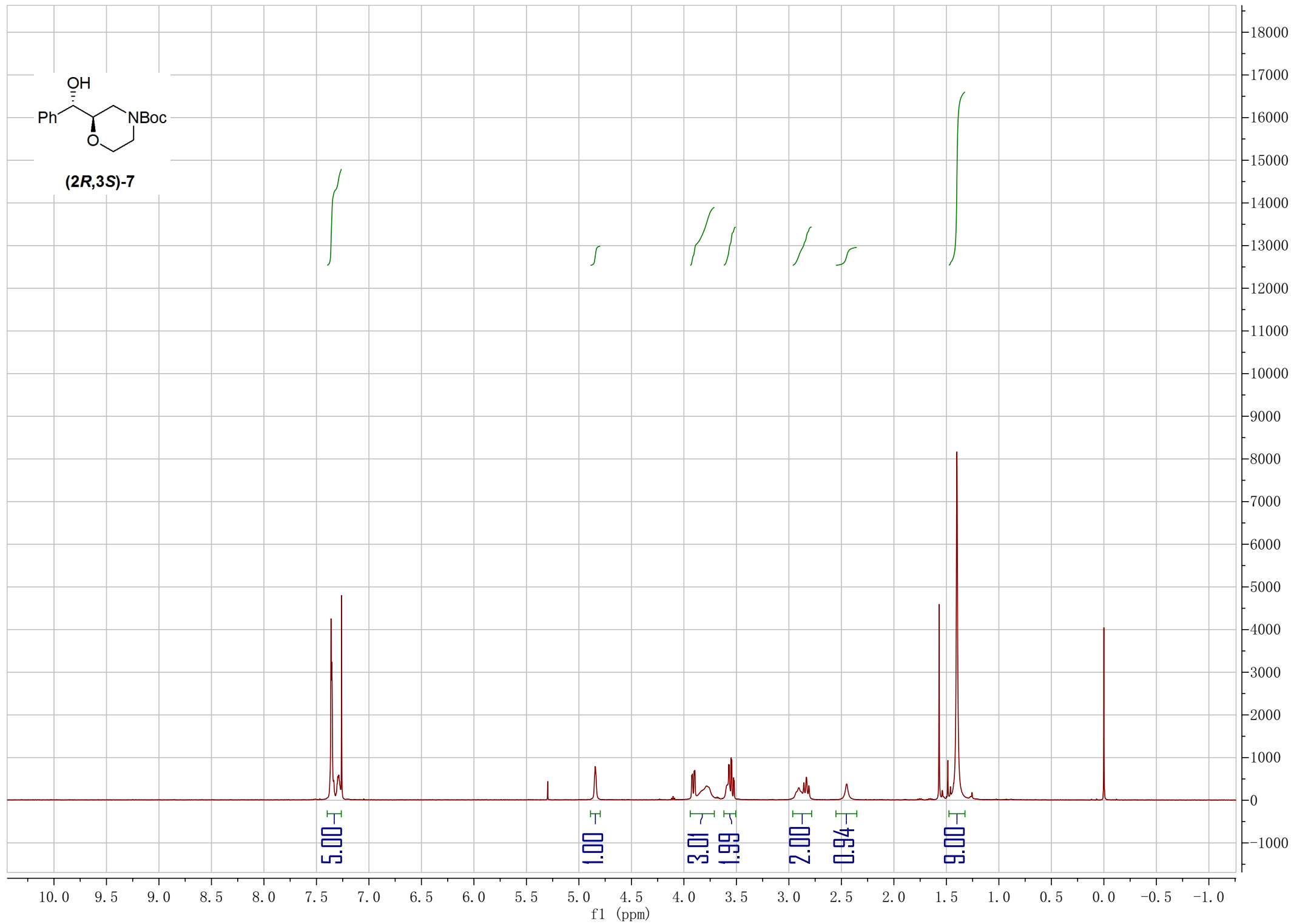


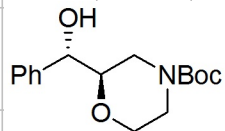




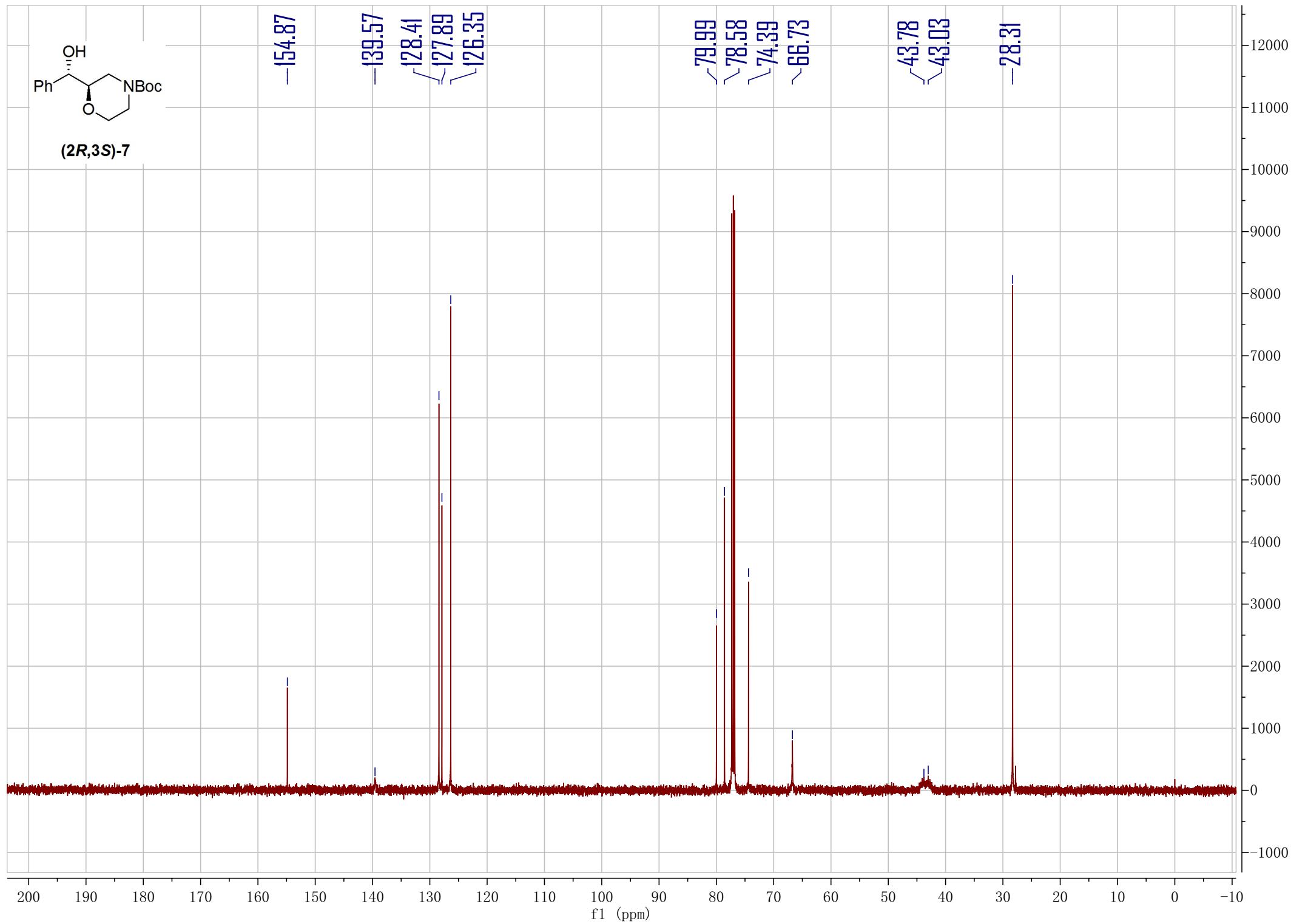


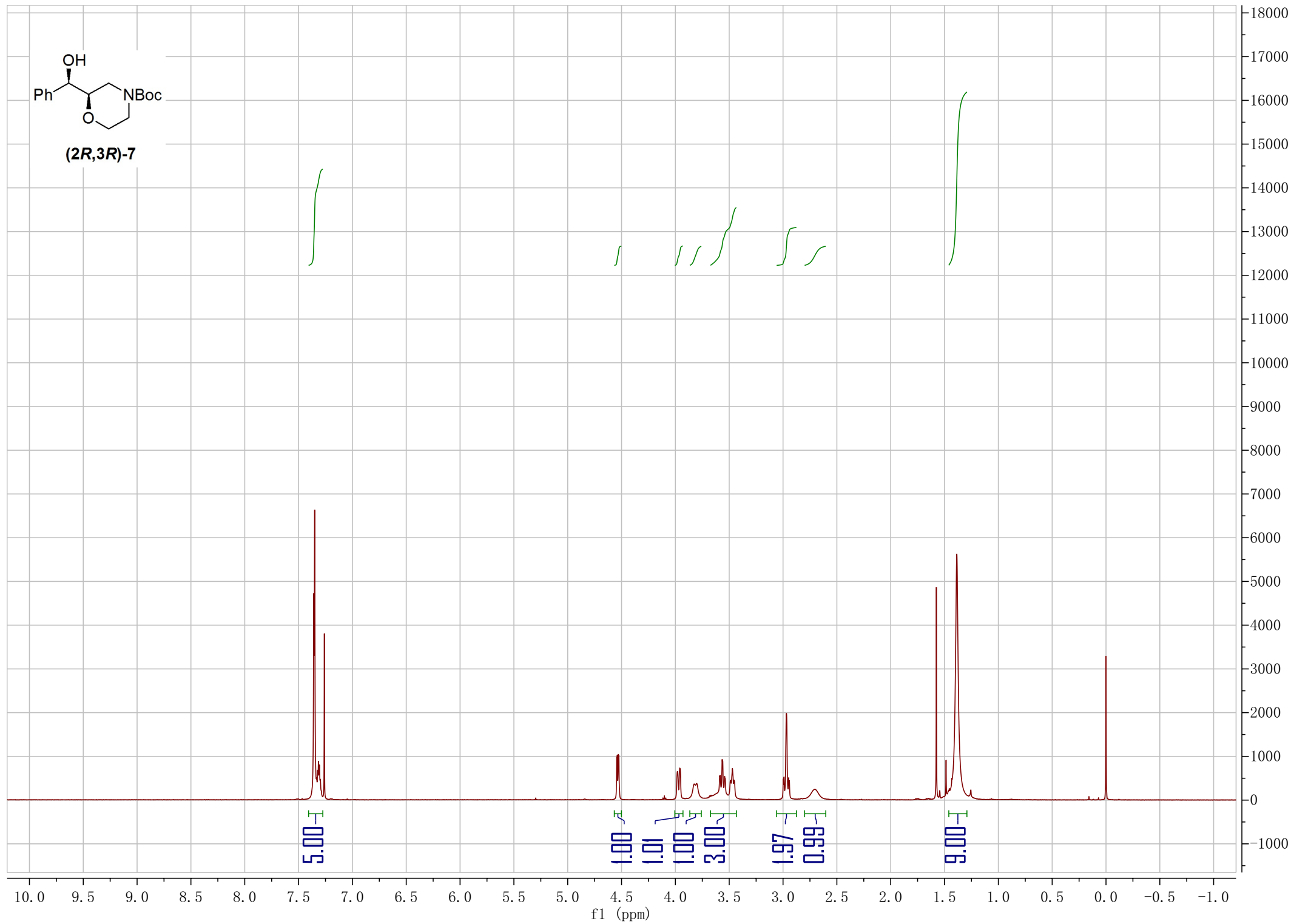
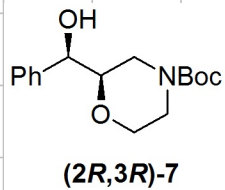
(2*R*,3*S*)-7

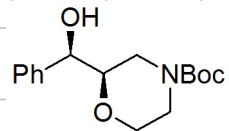
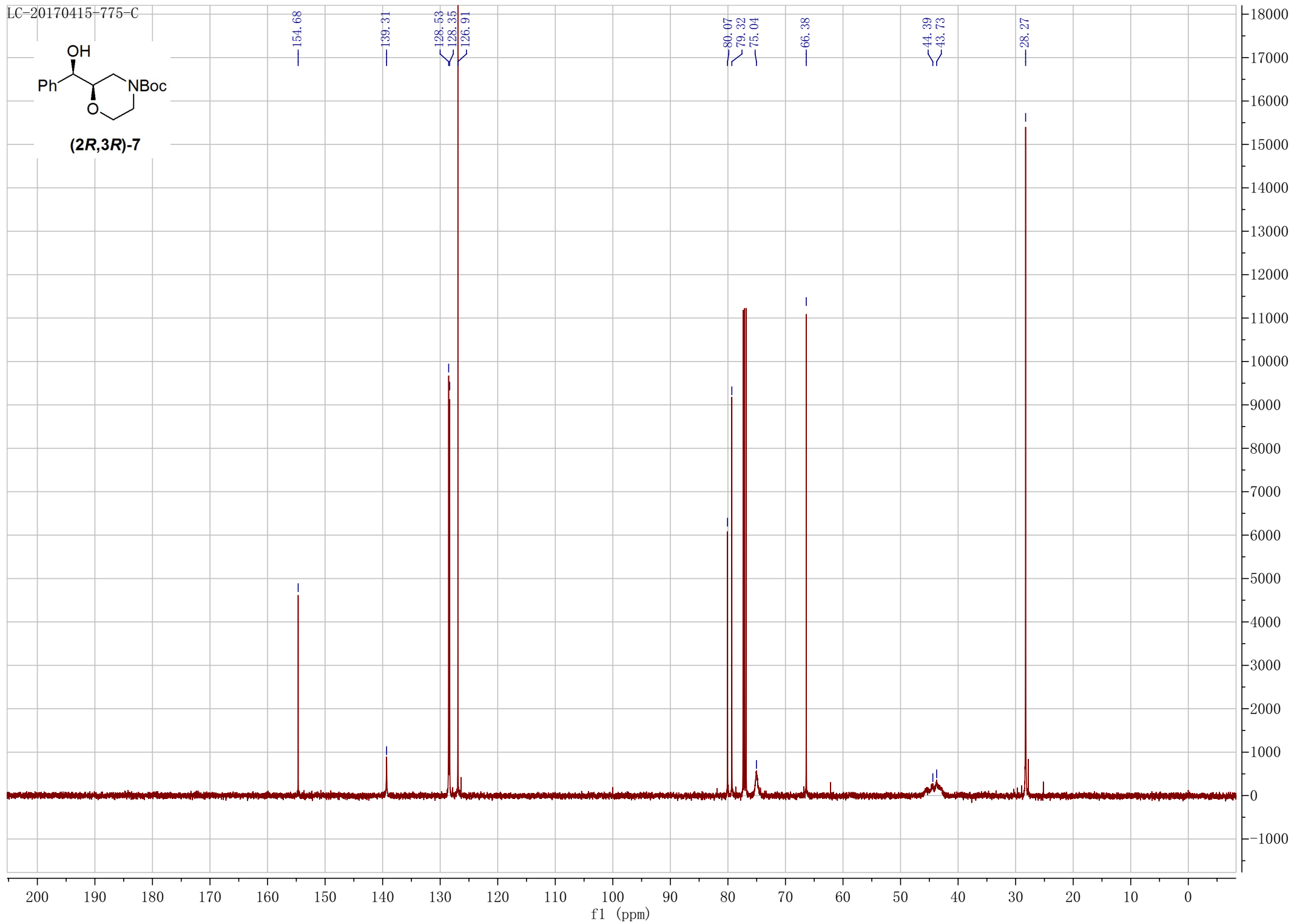


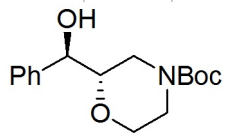


(2*R*,3*S*)-7

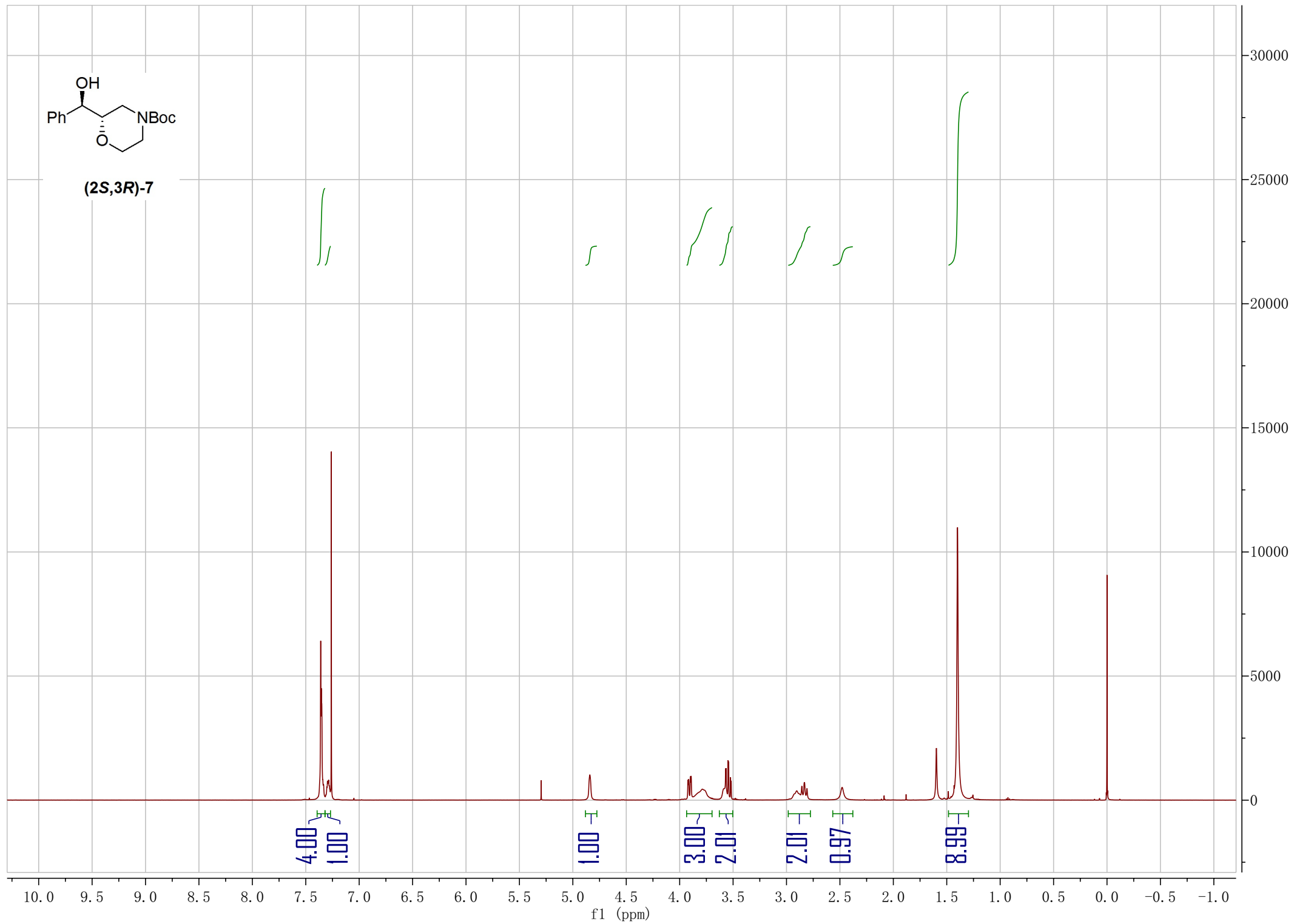


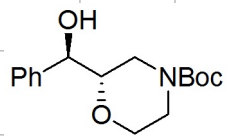


**(2R,3R)-7**

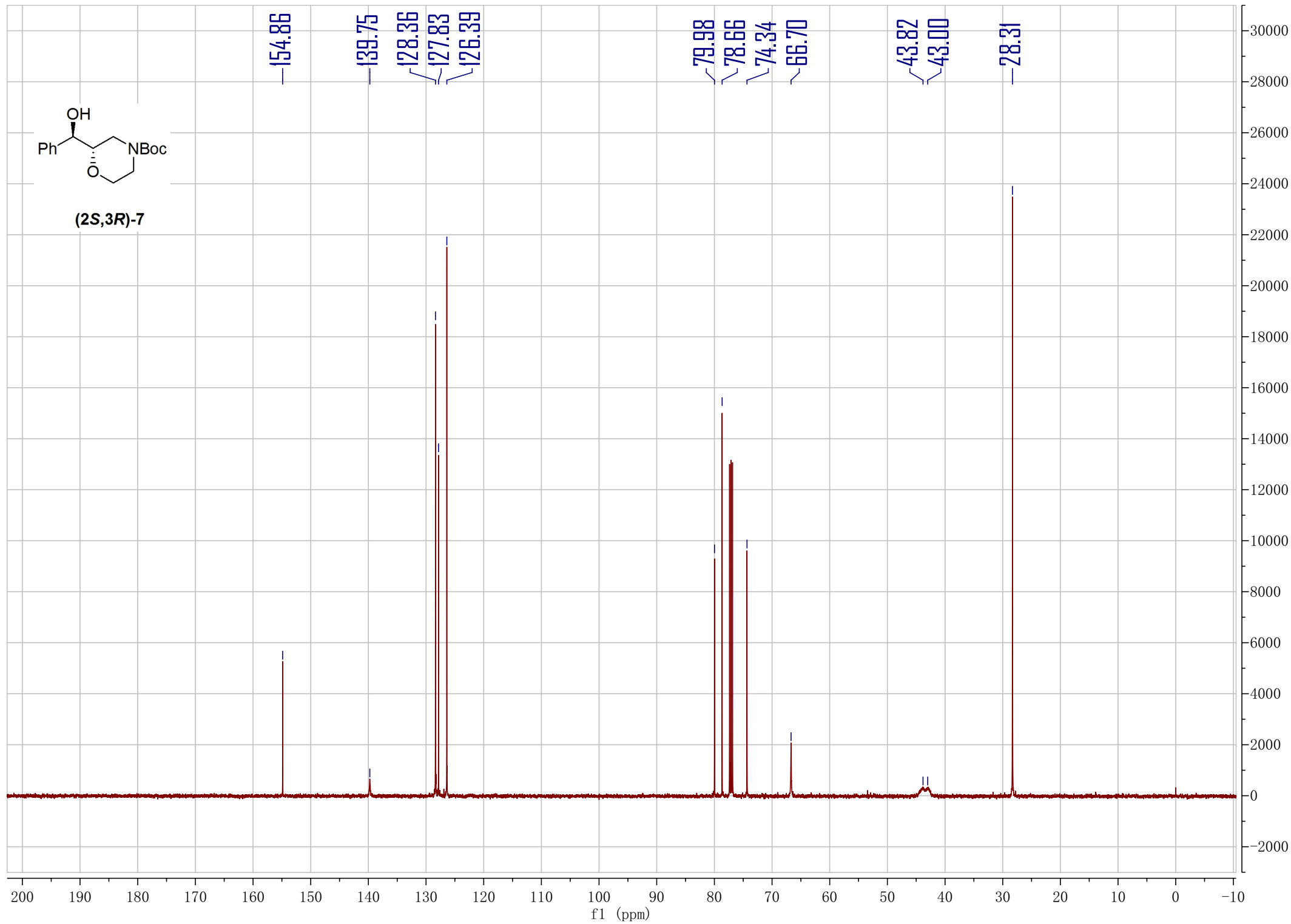


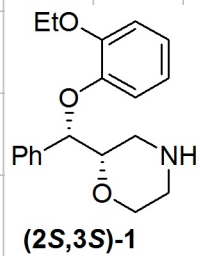
(2*S*,3*R*)-7

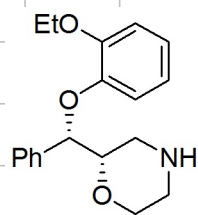




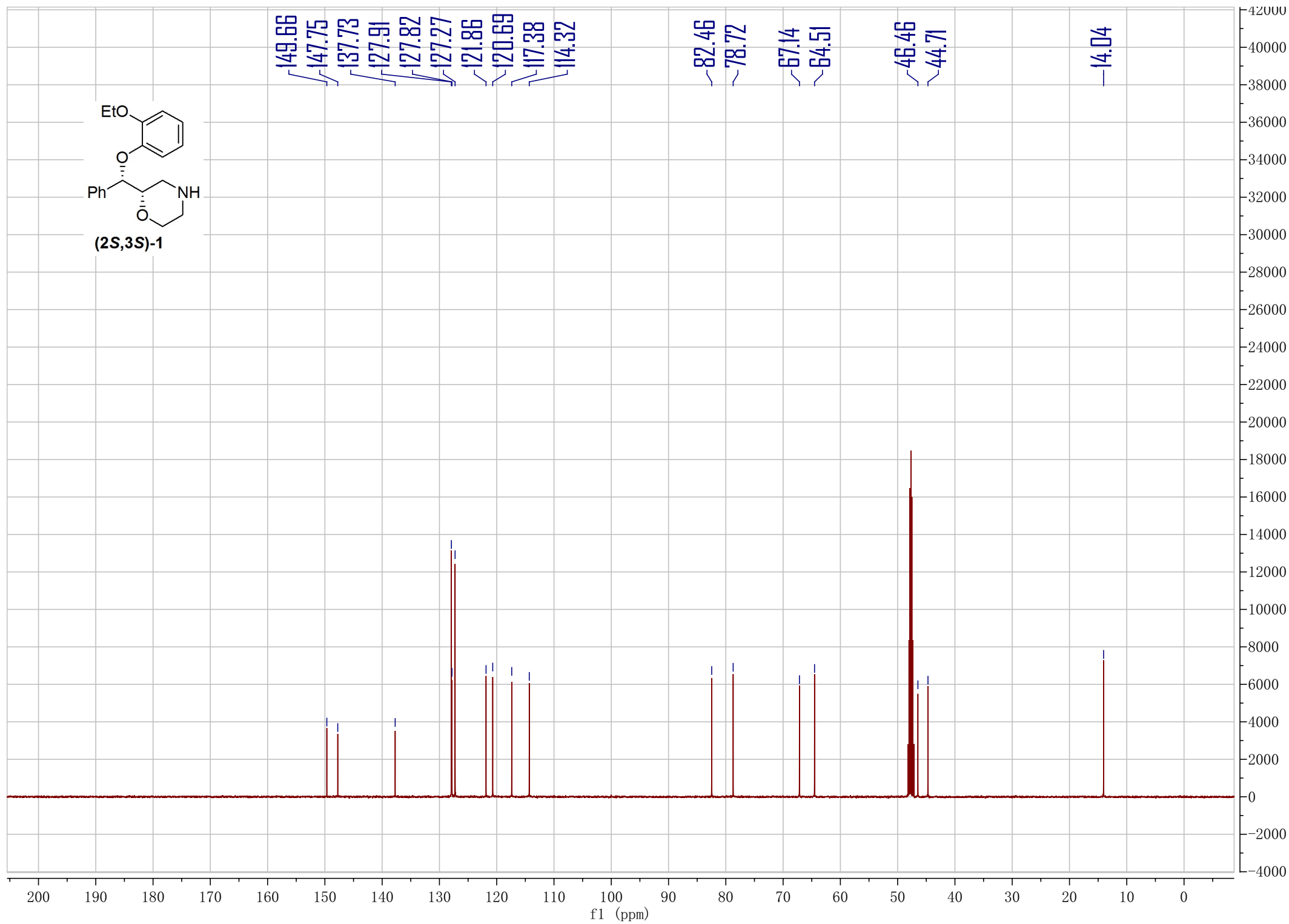
(2*S*,3*R*)-7

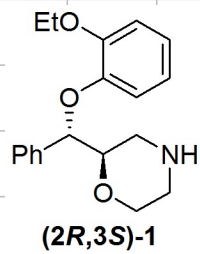


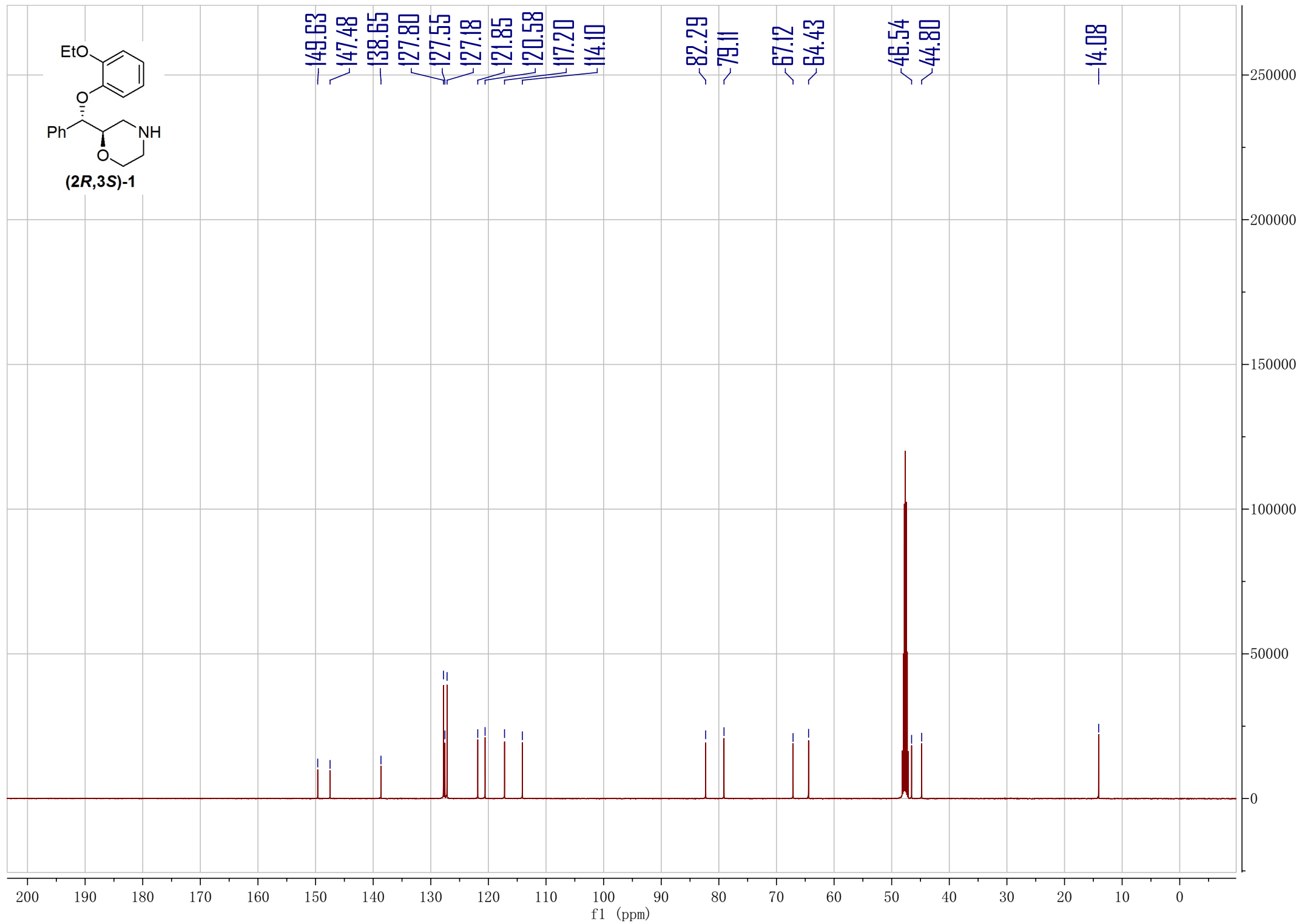
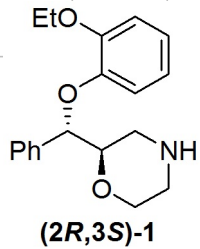


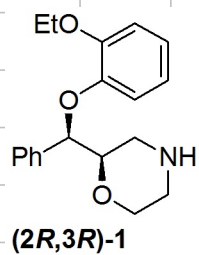


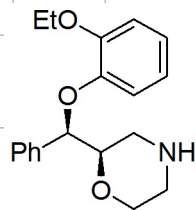
(2S,3S)-1











(2*R*,3*R*)-1

