Supporting Information

Biocatalytic asymmetric reduction of fluoroalkyl ketones to access enantiopure fluoroalkyl secondary alcohols

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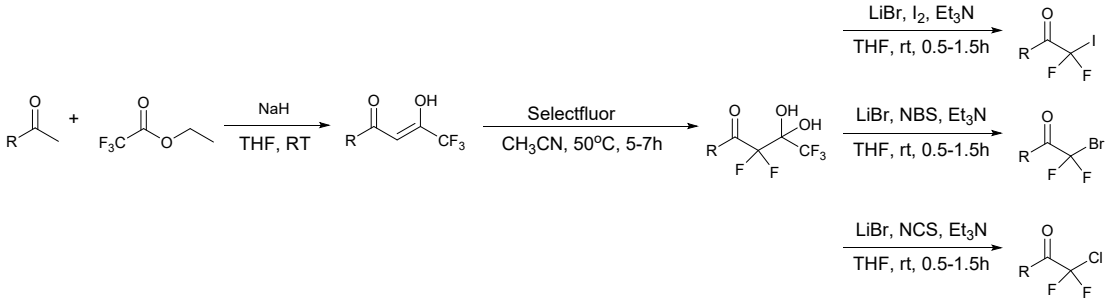
1. General Information

All reagents were commercially available and used without further purification unless indicated otherwise. Ketoreductases were obtained from Syncozymes. Reactions were monitored by thin layer chromatorgraphy (TLC) carried out on GF254 plates (0.25 mm layer thickness) using UV light as visualizing agent. ^{1}H NMR spectra were recorded on Bruker 400 MHz and 500 MHz spectrometers, ^{13}C NMR spectra were obtained using a Bruker 100 MHz and 125 MHz spectrometers. The samples were dissolved in 0.6 mL $CDCl_3$ (99.8% D. TMS). The ^{19}F NMR spectra were obtained using a Bruker 470 MHz and 375MHz using trifluorotoluene as external standard. The chemical shifts (δ) are given in ppm and the coupling constants (J) in hertz (Hz). ESI and EI-TOF for HRMS(samples was dissolved in CH3OH).

2. Experimental section

2.1 General procedure for the synthesis of ketone 1a-1u

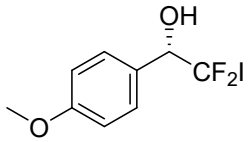


The 2-halo-2,2-difluoroacetophenone **1a-1u** were prepared according to the reported procedures[1]. As shown above, the intermediates enols were obtained from the reaction of ethyl 2,2,2-trifluoroacetate and ketones. The enols reacted with Selectfluor® to form fluorinated gem-diols, which then reacted with I_2 to afford 2-iodo-2,2- difluoroacetophenones **1a-1n** (reacted with NCS (2.0 equiv.) to afford 2-chloro-2,2- difluoroacetophenones **1s** and reacted with NBS (2.0 equiv.) to afford 2-bromo-2,2- difluoroacetophenones **1t,1u**) using the trifluoroacetate release conditions. The **1r** is commercially available.

2.2 General procedure for the synthesis of 2a-2u

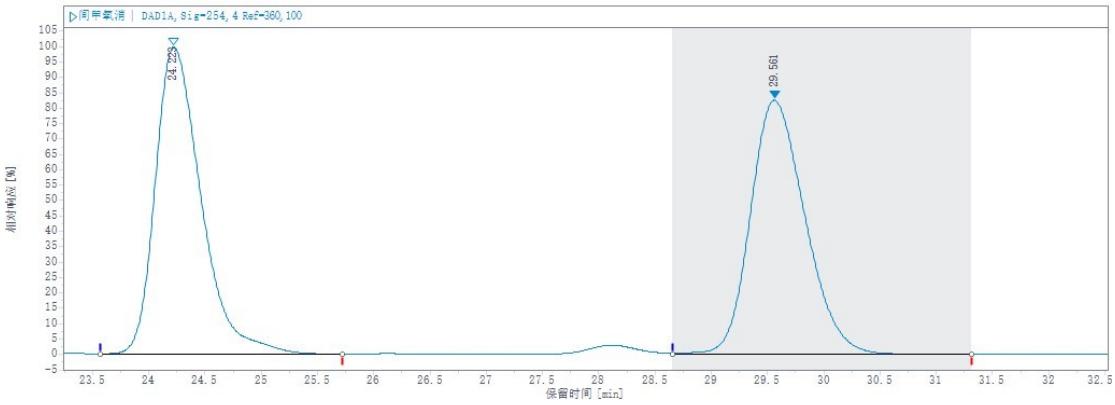
In a 1.5 mL Eppendorf vial, KRED (12 g/L) and NADP (0.08 g/L) were added in water (0.5 mL) and mixed with 2-propanol (0.5 mL) and the corresponding ketone **1** (100 g/L). The reaction was

shaken at 30 °C and 1000 rpm for 12 h and stopped by extraction with EtOAc (3 × 0.5 mL), and the combined organic phases washed with water (0.5 mL), dried over Na_2SO_4. Conversions and e.e. of the corresponding alcohols were determined by HPLC.

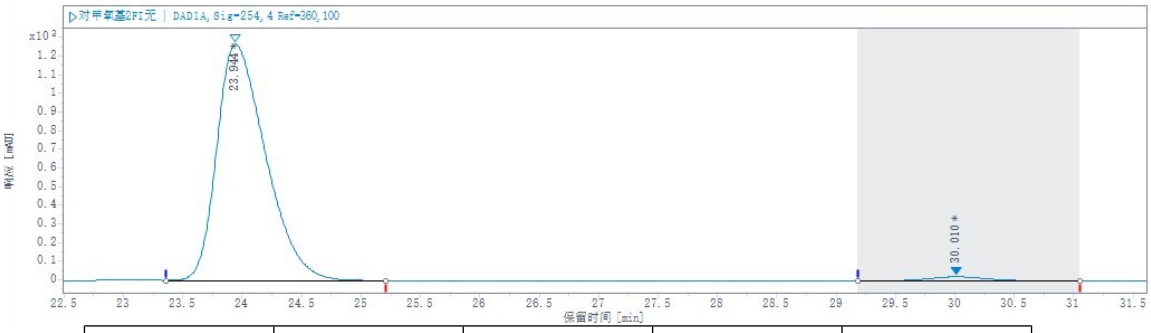


(S)-2,2-difluoro-2-iodo-1-(4-methoxyphenyl)ethanol (2a)： Light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 10.0 Hz, 2H), 6.91 (d, *J* = 10.0 Hz, 2H), 4.63 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.82 (s, 3H), 2.65 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2, 129.4, 128.7, 113.9, 108.5 (t, *J* = 316.3 Hz), 79.6 (t, *J* = 22.5 Hz), 55.5. ^{19}F NMR (470 MHz, $CDCl_3$) δ -48.40 (d, *J* = 178.6 Hz, 1F), -52.96 (d, *J* =178.6 Hz, 1F). HRMS (ESI) calcd for $C_9H_9F_2IO_2Na$([M+Na]$^+$) 336.9508; found, 336.9507. [α]20 D= +9.300 (c 1, EtOH), e.e. 96.1%(S).

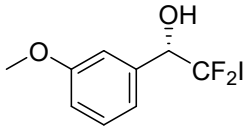
HPLC analysis: Chiralpak OD-H, hexane/isopropanol = 95/5, flow 0.6 mL/min, detection at 254 nm.



Peak	Ret. Time(min)	Area	Height	Con. (%)
1	24.223	24992.214	883.656	50.308
2	29.561	24686.216	730.539	49.692

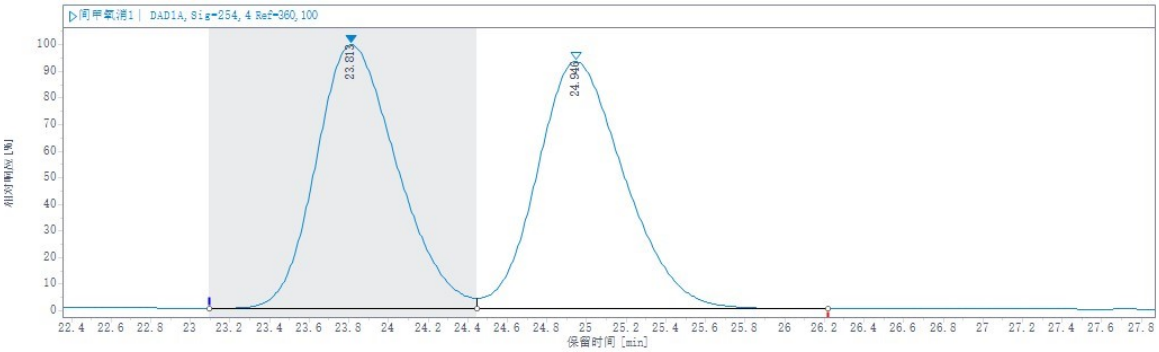


Peak	Ret. Time(min)	Area	Height	Con. (%)
1	23.944	36217.848	1266.945	98.070
2	30.010	712.891	21.414	1.930

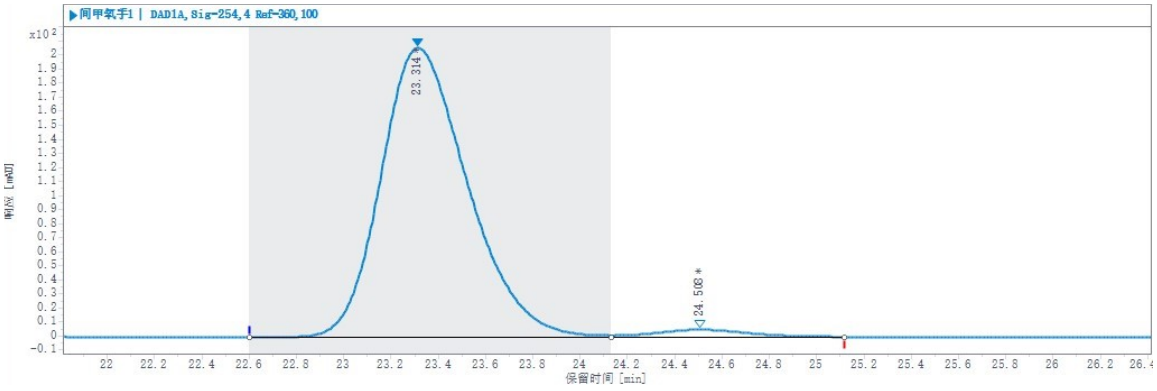


(S)-2,2-difluoro-2-iodo-1-(3-methoxyphenyl)ethanol (2b): Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, *J* = 8.0 Hz, 1H), 7.08 – 7.01 (m, 2H), 6.99 – 6.92 (m, 1H), 4.65 (dd, *J* = 10.6, 7.7 Hz, 1H), 3.83 (s, 3H), 2.83 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 135.1, 128.4, 119.3, 114.0, 112.6, 106.5 (t, J = 318.0 Hz), 78.9 (t, J = 23.0 Hz), 54.3. ^{19}F NMR (375 MHz, $CDCl_3$) δ -47.87 (d, *J* = 181.0 Hz, 1F), -52.62 (d, *J* = 181.0 Hz, 1F). HRMS (EI-TOF) calcd for $C_9H_{10}F_2IO_2$ ([M+H]$^+$) 314.9694, found 314.9701. [α]20 D= +0.733 (c 1, $CHCl_3$), e.e. 94.8%(S).

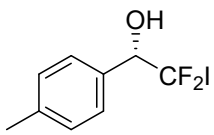
HPLC analysis: Chiralpak OD-H, hexane/isopropanol = 95/5, flow 0.6 mL/min, detection at 254 nm.



Peak	Ret. Time(min)	Area	Height	Con. (%)
1	23.813	1640.403	57.592	49.808
2	24.946	1653.048	54.009	50.192



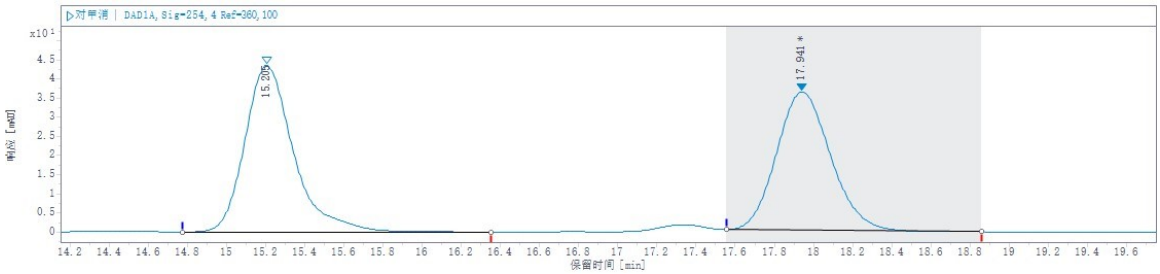
Peak	Ret. Time(min)	Area	Height	Con. (%)
1	23.314	5254.911	205.825	97.418
2	24.508	139.282	5.158	2.582



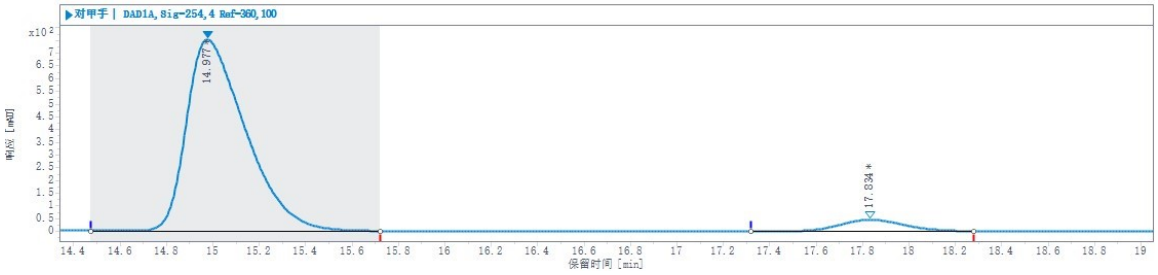
(S)-2,2-difluoro-2-iodo-1-(4-methylphenyl)ethanol (2c)： Light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* =5.0 Hz, 2H), 7.19 (d, *J* =10.0 Hz, 2H), 4.62 (dd, *J* =15.0, 5.0 Hz, 1H), 2.72 (s, 1H),

2.35 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.5, 131.7 (d, *J* =2.5 Hz), 129.2, 127.9, 108.1 (t, *J* =316.3 Hz), 79.9 (t, *J* =22.5 Hz), 21.4. ^{19}F NMR (470 MHz, $CDCl_3$) δ -48.15 (d, *J* =178.6 Hz, 1F), -52.82 (d, *J* =178.6 Hz, 1F). HRMS (EI-TOF) calcd for $C_9H_9F_2IONa$ ([M+Na]$^+$) 320.9564, found 320.9572. [α]20 D= +7.633 (c 1, $CHCl_3$), e.e. 87.6%(S).

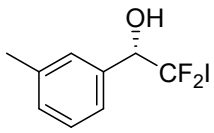
HPLC analysis: Chiralpak OD-H, hexane/isopropanol = 95/5, flow 0.6 mL/min, detection at 254 nm.



Peak	Ret. Time(min)	Area	Height	Con. (%)
1	15.205	751.925	43.450	51.971
2	17.941	694.889	36.145	48.029

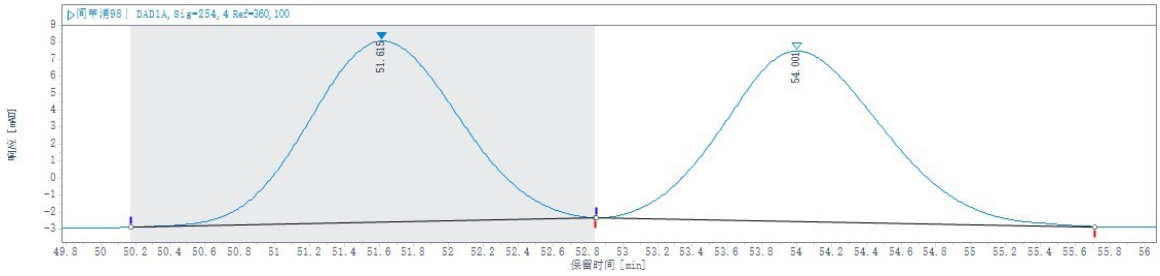


Peak	Ret. Time(min)	Area	Height	Con. (%)
1	14.977	13366.676	752.024	93.825
2	17.834	879.696	45.543	6.175

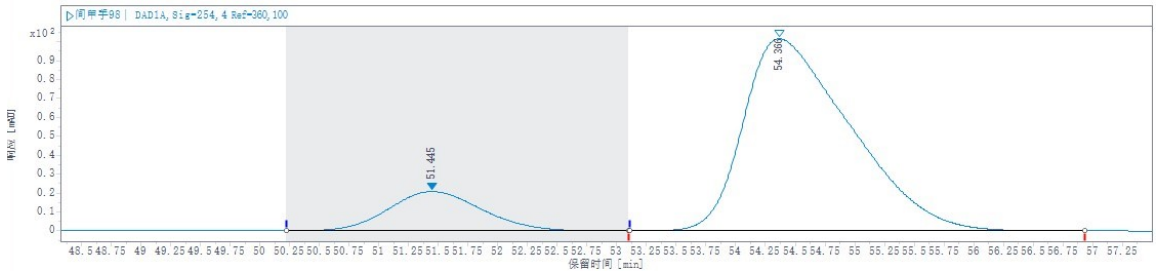


(S)-2,2-difluoro-2-iodo-1-(3-methylphenyl)ethanol (2d)： Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 3H), 7.25 – 7.21 (m, 1H), 4.67 (dd, *J* = 8, 4 Hz, 1H), 2.80 (s, 1H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 133.4 (d, *J* =2.5 Hz), 129.2, 127.5, 127.3, 124.0, 106.8 (t, *J* =316 Hz), 79.2 (t, *J* =23 Hz), 20.4. ^{19}F NMR (375 MHz, $CDCl_3$) δ -47.95 (d, *J* = 180.3 Hz), -52.77 (d, *J* = 180.3 Hz). HRMS (EI-TOF) calcd for $C_9H_9F_2IONa$ ([M+Na]+) 320.9564, found 320.9571. [α]20 D= +3.267 (c 1, $CHCl_3$), e.e. 69.8%(S).

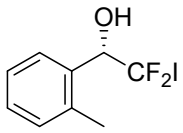
HPLC analysis: Chiralpak OD-H, hexane/isopropanol = 98/2, flow 0.6 mL/min, detection at 254 nm.



Peak	Ret. Time(min)	Area	Height	Con. (%)
1	51.615	638.891	10.654	50.055
2	54.001	637.487	10.009	49.945

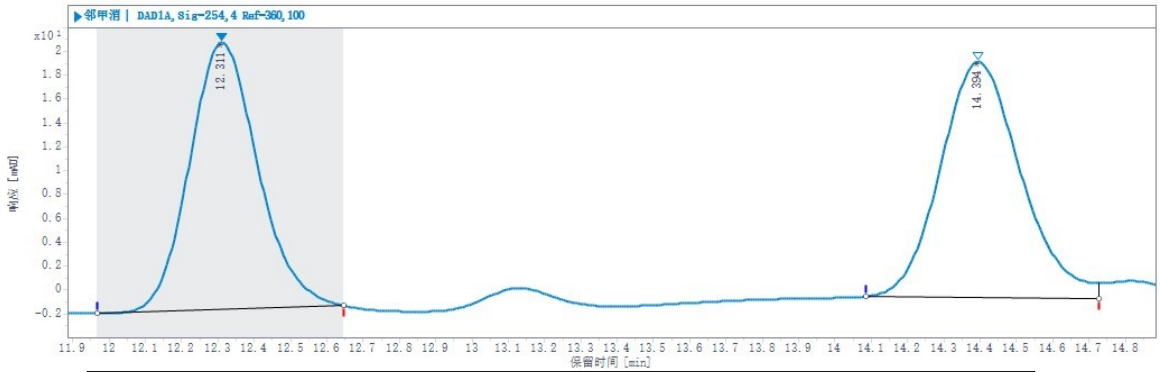


Peak	Ret. Time(min)	Area	Height	Con. (%)
1	51.445	1125.801	20.703	15.089
2	54.366	6335.104	84.911	84.911



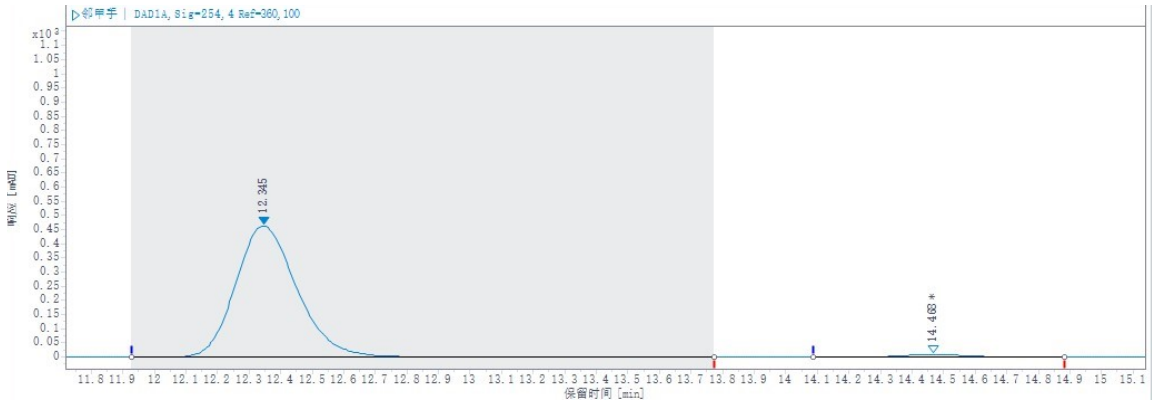
(S)-2,2-difluoro-2-iodo-1-(2-methylphenyl)ethanol (2e)： Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.0 Hz, 1H), 7.25 – 7.17 (m, 2H), 7.15 – 7.10 (m, 1H), 4.98 (dd, *J* = 8.0, 4.0 Hz, 1H), 2.80 (s, 1H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 132.9, 130.6, 129.3, 127.7, 126.2, 107.6 (t, *J* =316.0 Hz), 76.4 (t, *J* =22.0 Hz), 19.7. ^{19}F NMR (375 MHz, $CDCl_3$) δ -47.68 (d, *J* = 179.8 Hz, 1F), -51.82 (d, *J* = 179.8 Hz, 1F). HRMS (ESI) calcd for $C_9H_9F_2IONa$([M+Na]$^+$) 320.9558, found 320.9558. [α]20 D= +8.733 (c 1, $CHCl_3$), e.e. 95.2%(S).

HPLC analysis: Chiralpak OD-H, hexane/isopropanol = 95/5, flow 0.6 mL/min, detection at 254 nm.

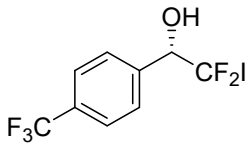


Peak	Ret. Time(min)	Area	Height	Con. (%)
1	12.311	292.944	22.385	48.310

2	14.394	313.440	19.763	51.690

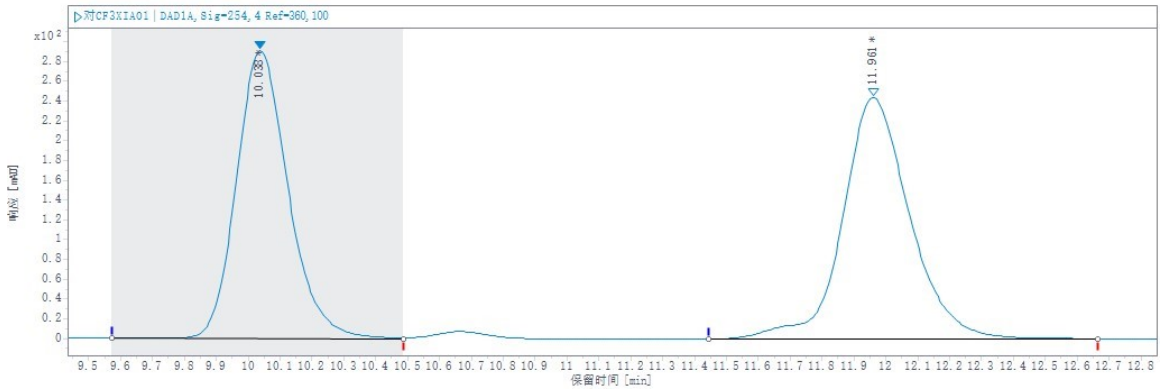


Peak	Ret. Time(min)	Area	Height	Con. (%)
1	12.345	6321.097	464.764	97.611
2	14.468	154.701	10.037	2.389

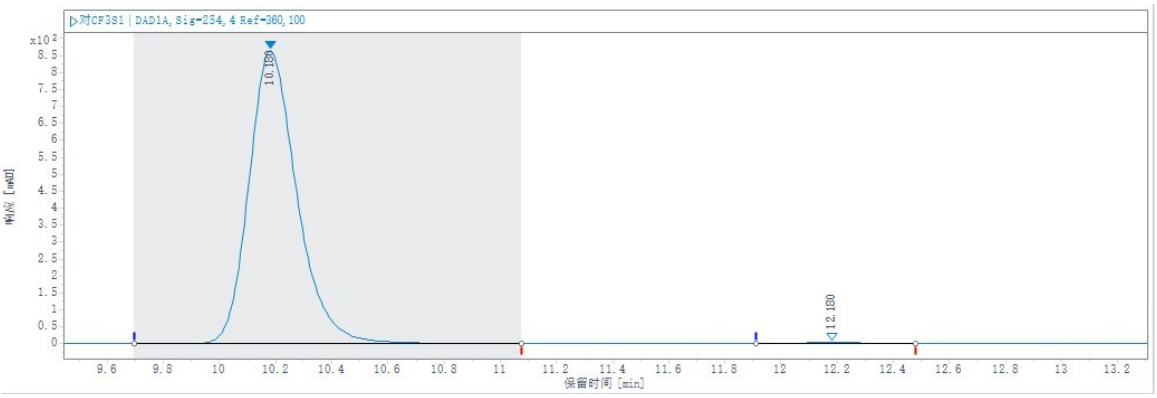


(S)-2,2-difluoro-2-iodo-1-(4-trifluoromethylphenyl)ethanol(2f): Light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 10 Hz, 2H), 7.62 (d, *J* = 10 Hz, 2H), 4.74 (t, *J* = 10 Hz, 1H), 3.17 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.7 (t, *J* =27.5 Hz), 130.2, 128.9, 128.4, 128.3, 127.1 (q, *J* =133.3 Hz), 114.2 (t, *J* =238.8 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ -48.28 (d, *J* = 183.3 Hz, 1F), -53.52 (d, *J* = 183.3 Hz, 1F), -62.76(s, 3F). HRMS (EI-TOF) calcd for $C_9H_6F_5IONa$ ([M+Na]$^+$) 374.9281，found 374.9287. [α]20 D= +2.200 (c 1, $CHCl_3$), e.e. >99%(S).

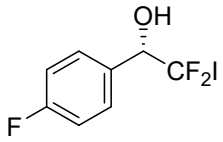
HPLC analysis: Chiralpak OD-H, hexane/isopropanol = 95/5, flow 0.6 mL/min, detection at 254 nm.



Peak	Ret. Time(min)	Area	Height	Con. (%)
1	10.038	3299.626	291.045	48.094
2	11.961	3561.101	243.913	51.906

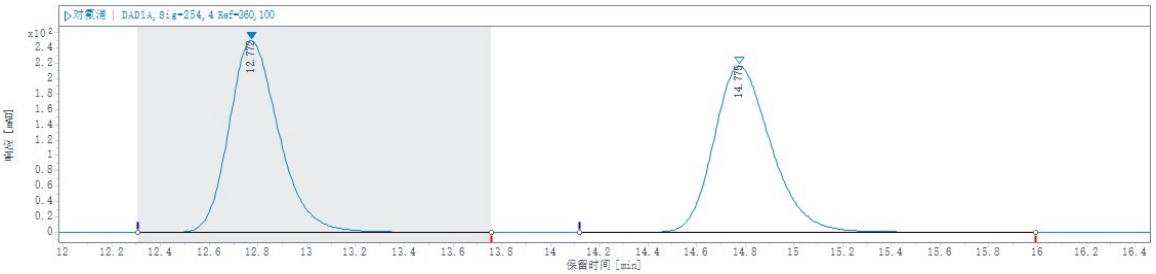


Peak	Ret. Time(min)	Area	Height	Con. (%)
1	10.180	10285.319	863.278	99.556
2	12.180	45.862	3.428	0.444

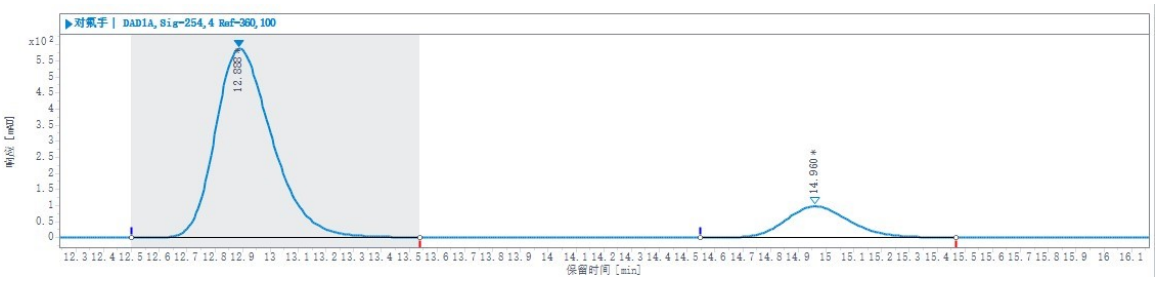


(S)-2,2-difluoro-2-iodo-1-(4-fluorophenyl)ethanol (2g): Light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (t, *J* =5.0 Hz, 2H), 7.09 (t, *J* =10.0 Hz, 2H), 4.67 (dd, *J* =10.0, 5.0 Hz, 1H), 2.94 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3 (d, *J*=258.8 Hz), 129.8 (d, *J*=8.8 Hz), 115.4 (d, *J*=21.3 Hz), 107.8 (t, *J* =316.3 Hz), 79.3 (t, *J* =23.8 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ -48.53 (d, *J* =183.3 Hz, 1F), -53.41 (d, *J* =183.3 Hz, 1F), -111.8 (s, 1F). HRMS (EI-TOF) calcd for $C_8H_6F_3IONa$([M+Na]$^+$) 324.9313, found 324.9314. [α]20 D= +0.833 (c 1, $CHCl_3$), e.e. 68.3%(S).

HPLC analysis: Chiralpak OD-H, hexane/isopropanol = 95/5, flow 0.6 mL/min, detection at 254 nm.

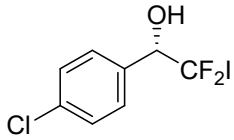


Peak	Ret. Time(min)	Area	Height	Con. (%)
1	12.772	3553.308	249.401	49.994
2	14.775	3554.114	216.841	50.006



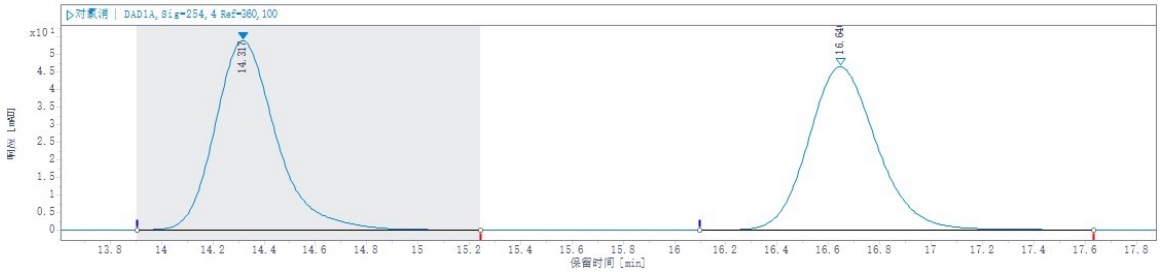
Peak	Ret. Time(min)	Area	Height	Con. (%)

1	12.888	8374.681	588.052	84.180
2	14.960	1573.898	97.911	15.820

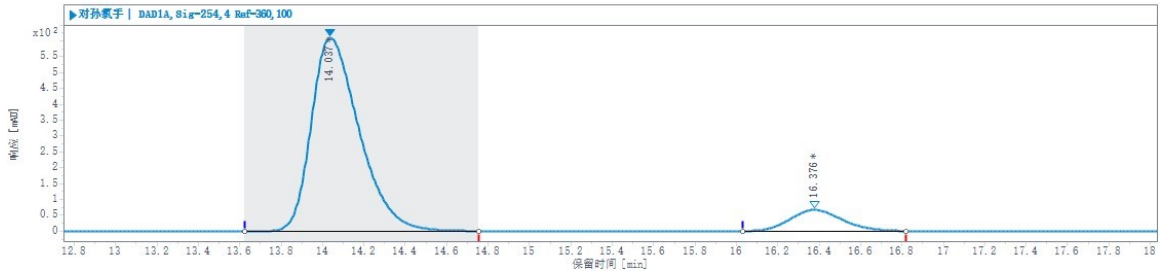


(S)-2,2-difluoro-2-iodo-1-(4-chlorophenyl)ethanol (2h)： Light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (dd, *J* =20.0, 10.0 Hz, 4H), 4.65 (dd, *J* =10.0, 8.0 Hz, 1H), 2.58 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.5, 133.1, 129.4, 128. 7, 107.4 (t, *J* =316.3 Hz), 79.3 (t, *J* =23.8 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ -48.39 (d, *J* =183.3 Hz, 1F), -53.40 (d, *J* =183.4 Hz, 1F). HRMS (EI-TOF) calcd for $C_8H_7ClF_2IO$([M+H]$^+$) 318.9198, found 318.9191. [α]20 D= +4.500 (c 1, EtOH), e.e. 78.5%(S).

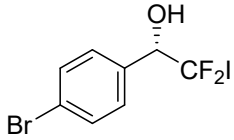
HPLC analysis: Chiralpak OD-H, hexane/isopropanol = 95/5, flow 0.6 mL/min, detection at 254 nm.



Peak	Ret. Time(min)	Area	Height	Con. (%)
1	14.317	891.554	53.853	50.894
2	16.646	860.230	46.500	49.106



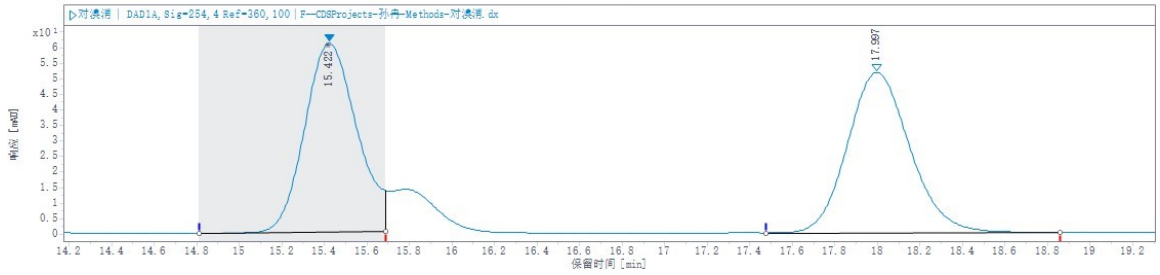
Peak	Ret. Time(min)	Area	Height	Con. (%)
1	14.037	9804.906	609.317	89.283
2	16.376	1176.954	66.594	10.717



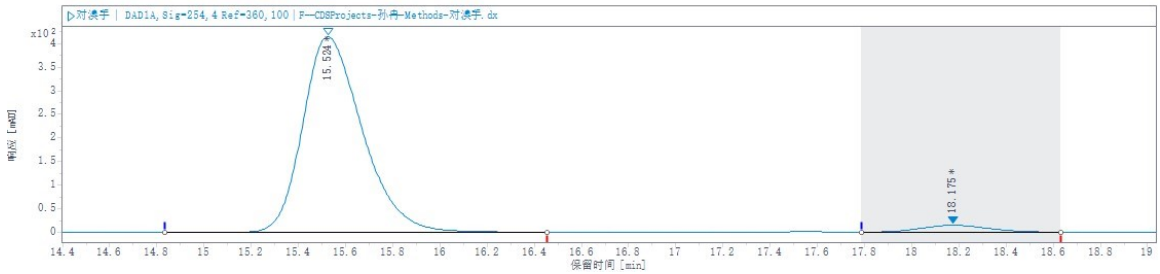
(S)-2,2-difluoro-2-iodo-1-(4-bromophenyl)ethanol (2i)： Light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* =5.0 Hz, 2H), 7.36 (d, *J* =10.0 Hz, 2H), 4.64 (dd, *J* =10.0, 5.0 Hz, 1H), 2.92 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.61, 133.24, 131.60, 129.64, 107.30 (t, *J* =317.5 Hz), 79.31 (t, *J*=23.8 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ -48.35 (d, *J* =183.4 Hz, 1F), -53.43 (d, *J* =178.7 Hz, 1F). HRMS (EI-TOF) calcd for $C_8H_6BrF_2IONa$([M+Na]$^+$) 384.8512, found 384.8508. [α]20 D= +4.567 (c 1,

EtOH), e.e. 92.3%(S).

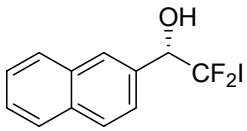
HPLC analysis: Chiralpak OD-H, hexane/isopropanol = 95/5, flow 0.6 mL/min, detection at 254 nm.



Peak	Ret. Time(min)	Area	Height	Con. (%)
1	15.422	1034.107	60.810	49.647
2	17.997	1048.812	51.515	50.353

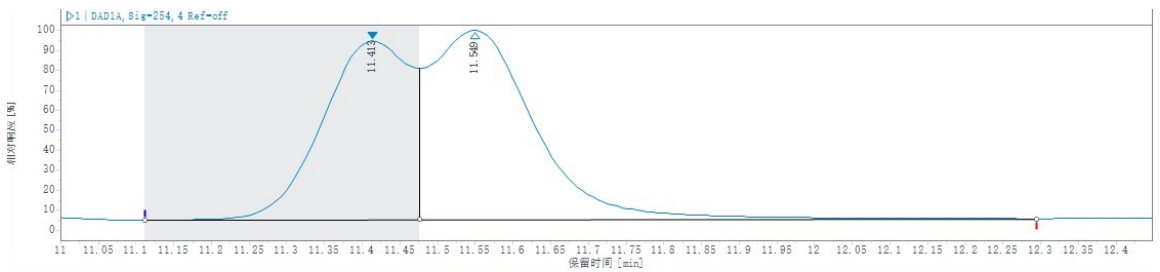


Peak	Ret. Time(min)	Area	Height	Con. (%)
1	15.524	7262.935	414.015	96.182
2	18.175	288.334	14.532	3.818



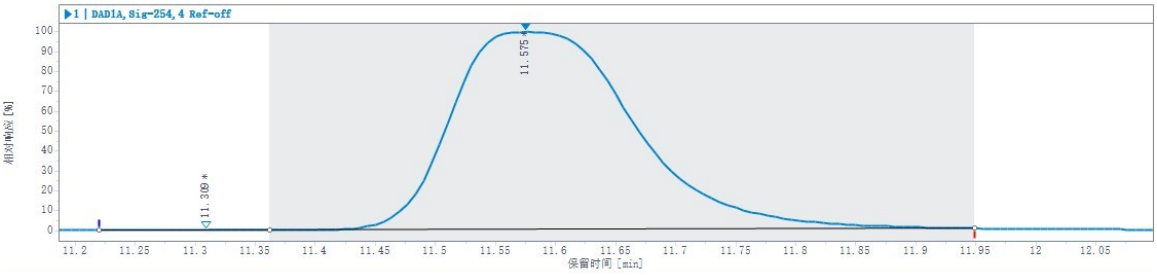
(S)-2,2-difluoro-2-iodo-2-naphthylethanol (2k): Light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.88 (t, *J* =10.0 Hz, 3H), 7.59 – 7.50 (m, 3H), 4.85 (dd, *J* =10.0, 5.0 Hz, 1H), 2.75 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.6, 131.8, 131.0 (d, *J* =2.5 Hz), 127.3, 127.1, 126.8, 126.7, 125.8, 125.4, 123.8, 106.9 (t, *J* =316.9 Hz), 79.1 (t, *J*=23.1 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ -47.78 (d, *J* =178.6, 1F), -52.58 (d, *J* =178.6, 1F). HRMS (ESI) calcd for $C_{12}H_9F_2IONa$ ([M + Na]+) 356.9558, found 356.9565. [α]20 D= +2.400 (c 1, $CHCl_3$), e.e. >99%(S).

HPLC analysis: Chiralpak OD-H, hexane/isopropanol = 95/5, flow 0.6 mL/min, detection at 254 nm.

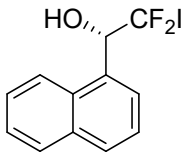


Peak	Ret. Time(min)	Area	Height	Con. (%)

1	11.413	1497.393	185.503	44.271
2	11.549	1884.926	196.358	55.729

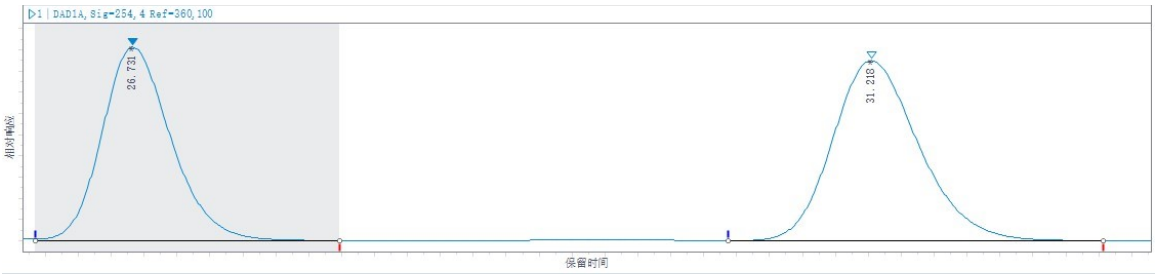


Peak	Ret. Time(min)	Area	Height	Con. (%)
1	11.309	16.014	1.190	0.044
2	11.575	36370.683	3451.665	99.956

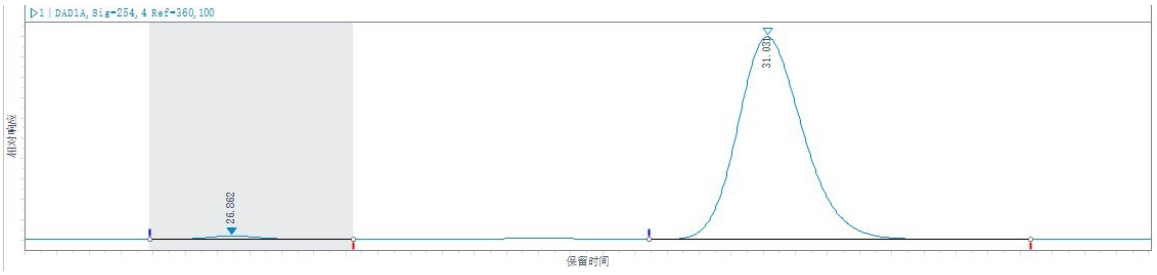


(S)-2,2-difluoro-2-iodo-1-naphthylethanol (2l): Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.0 Hz, 1H), 7.95 – 7.78 (m, 3H), 7.61 – 7.44 (m, 3H), 5.60 (dd, *J* = 8.0, 4.0 Hz, 1H), 2.99 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.6, 131.3, 130.4 (d, *J* =2.0 Hz), 130.2, 129.0, 126.7, 126.6, 125.9, 125.1, 123.1, 108.0 (t, *J* =318.0 Hz), 76.1 (t, *J* =24.0 Hz). ^{19}F NMR (375 MHz, $CDCl_3$) δ -45.80 (d, *J* = 179.9 Hz, 1F), -50.57 (d, *J* = 179.9 Hz, 1F). HRMS (EI-TOF) calcd for $C_{12}H_9F_2IONa$ ($[M+Na]^+$) 356.9564, found 356.9555. [α]20 D= +29.733 (c 1, $CHCl_3$), e.e. 97.0%(S).

HPLC analysis: Chiralpak OD-H, hexane/isopropanol = 95/5, flow 0.6 mL/min, detection at 254 nm.

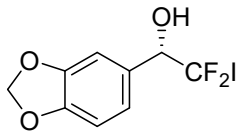


Peak	Ret. Time(min)	Area	Height	Con. (%)
1	26.731	7611.893	260.251	46.220
2	31.218	8856.813	242.189	53.780



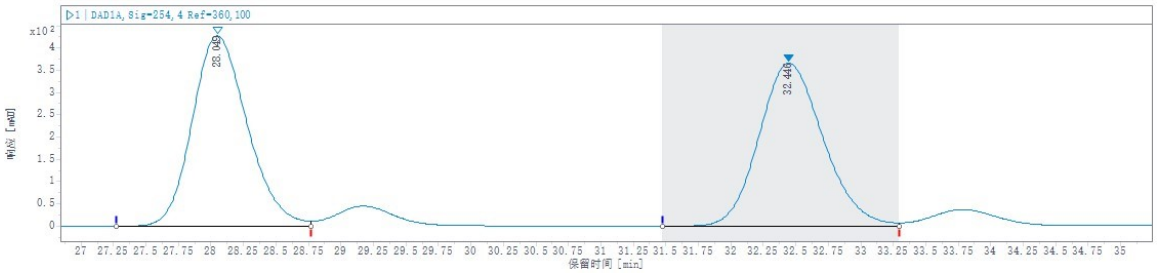
Peak	Ret. Time(min)	Area	Height	Con. (%)
1	26.862	129.257	4.336	1.468

2	31.031	8675.779	244.299	98.532

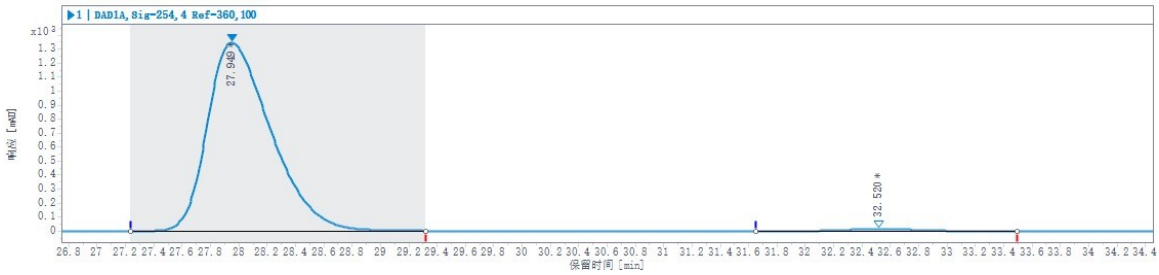


(S)-2,2-difluoro-2-iodo-1-((1,3-Benzodioxol-5-yl))ethanol (2m): Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (s, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 5.99 (s, 2H), 4.60 (dd, *J* = 8.0, 4.0 Hz, 1H), 2.92 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 147.7, 128.2, 122.1, 108.2, 108.1, 107.9 (t, *J* =318.0 Hz), 101.4, 79.8(t, *J* =24.0 Hz). ^{19}F NMR (375 MHz, $CDCl_3$) δ -48.40 (d, *J* = 180.5 Hz, 1F), -52.90 (d, *J* = 180.5 Hz, 1F). HRMS (ESI) calcd for $C_9H_7F_2IO_3Na$ ([M+Na]$^+$) 350.9300, found: 350.9298. [α]20 D= +1.000 (c 1, EtOH), e.e. 97.5%(S).

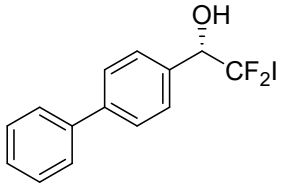
HPLC analysis: Chiralpak OD-H, hexane/isopropanol = 95/5, flow 0.6 mL/min, detection at 254 nm.



Peak	Ret. Time(min)	Area	Height	Con. (%)
1	28.049	12585.252	427.651	50.041
2	32.446	12564.418	366.508	49.959



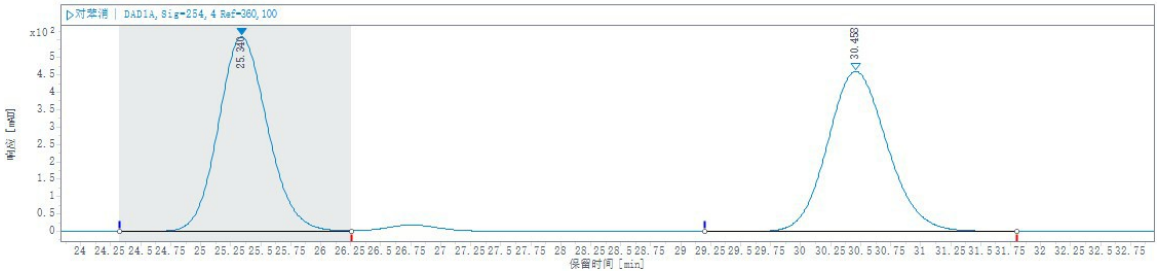
Peak	Ret. Time(min)	Area	Height	Con. (%)
1	27.949	42018.719	1346.274	98.792
2	32.520	513.655	14.985	1.208



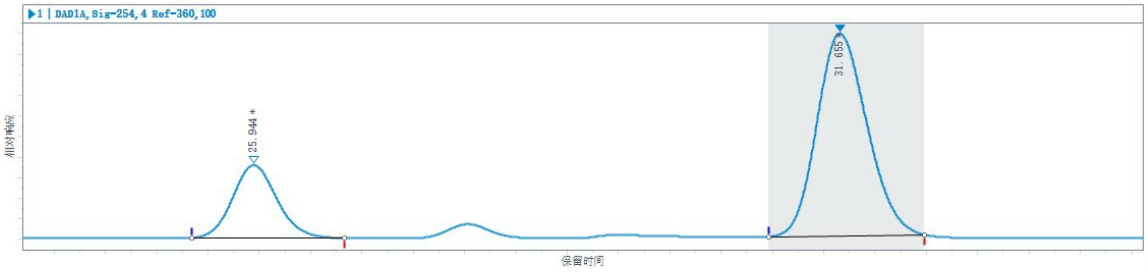
(S)-1-([1,1'-biphenyl]-4-yl)-2,2-difluoro-2-iodo-1-ol (2n): Light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 – 7.62 (m, 4H), 7.58 (dd, *J* =10.0, 5.0 Hz, 2H), 7.49 (t, *J* =5.0 Hz, 2H), 7.42 (t, *J* =10.0 Hz, 1H), 4.90 (dt, *J* =165.0, 10.0 Hz, 1H), 3.64 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.3 (d, *J* =12.5 Hz), 140.4 (d, *J* =2.5 Hz), 133.6 (d, *J* =38.8 Hz) , 129.0, 128.5 (d, *J* =8.8 Hz), 127.8 (d, *J* =1.3

Hz), 127.2 (d, *J* =2.5 Hz), 127.1 (d, *J* =6.3 Hz), 79.8 (t, *J* =23.8 Hz), 78.3 (t, *J*=25.0 Hz). ^{19}F NMR (375 MHz, $CDCl_3$) δ -47.9 (dd, *J* =181.0, 7.7 Hz, 1F), -55.67 (dd, *J* =162.4, 6.8 Hz, 1F). HRMS (ESI) calcd for $C_{14}H_{11}F_2IONa$([M + Na]+) 382.9715, found: 382.9697. [α]20 D= +4.200 (c 1, EtOH), e.e. 51.5%(S).

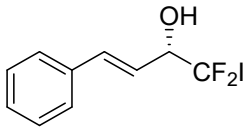
HPLC analysis: Chiralpak OD-H, hexane/isopropanol = 95/5, flow 0.6 mL/min, detection at 254 nm.



Peak	Ret. Time(min)	Area	Height	Con. (%)
1	25.340	15946.511	559.362	50.138
2	30.458	15858.424	460.081	49.862

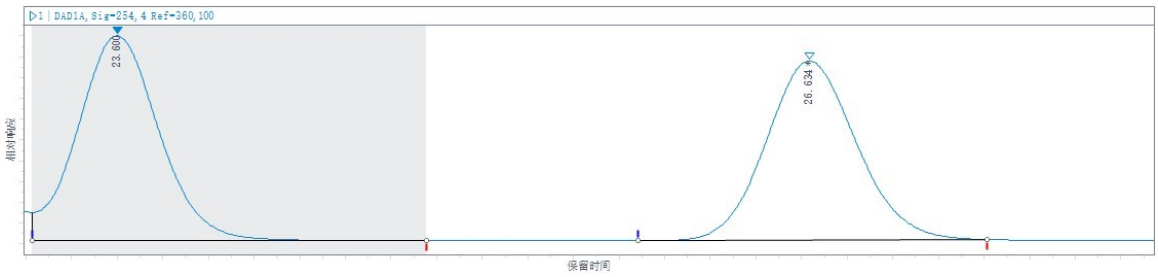


Peak	Ret. Time(min)	Area	Height	Con. (%)
1	25.944	15434.802	514.173	24.204
2	31.655	48334.078	1425.808	75.796

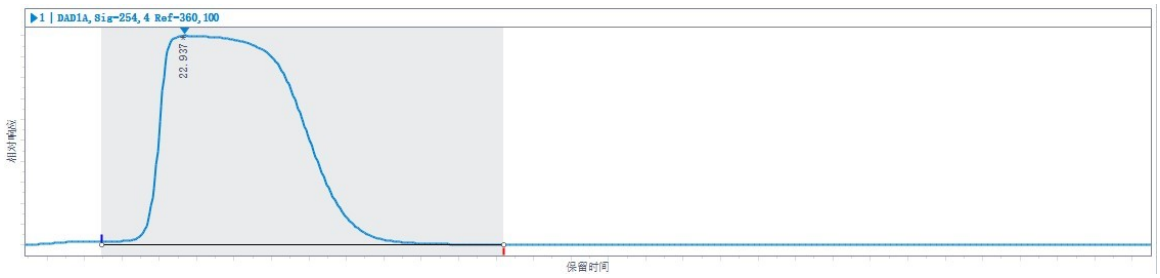


(S, E)-1,1-difluoro-1-iodo-4-phenylbut-3-en-2-ol (2o): colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* =10.0, 2H), 7.35-7.28 (m, 3H), 6.34 (dd, *J* =15.0, 5.0 Hz, 1H), 6.16 (ddd, *J* =27.5, 15.9, 6.1 Hz, 1H), 4.17-4.11 (m, 1H), 2.96 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.1, 135.6, 128.8, 128.7, 127.0, 122.6, 108.2 (t, *J* = 316.3 Hz), 78.6 (t, *J* = 23.8 Hz). ^{19}F NMR (375 MHz, $CDCl_3$) δ -48.8 (dd, *J* = 179.8, 8.6 Hz, 1F), -52.9 (dd, *J* = 179.9, 7.6 Hz, 1F). HRMS (EI-TOF) calcd for $C_{10}H_{10}F_2IO$([M+H]$^+$) 309.9666, found 309.9661. [α]20 D= +21.067 (c 1, $CHCl_3$), e.e. >99%(S).

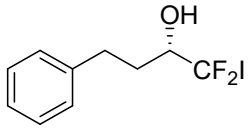
HPLC analysis: Chiralpak OD-H, hexane/isopropanol = 95/5, flow 0.6 mL/min, detection at 254 nm.



Peak	Ret. Time(min)	Area	Height	Con. (%)
1	23.600	2110.382	84.805	50.825
2	26.634	2041.858	74.180	49.175

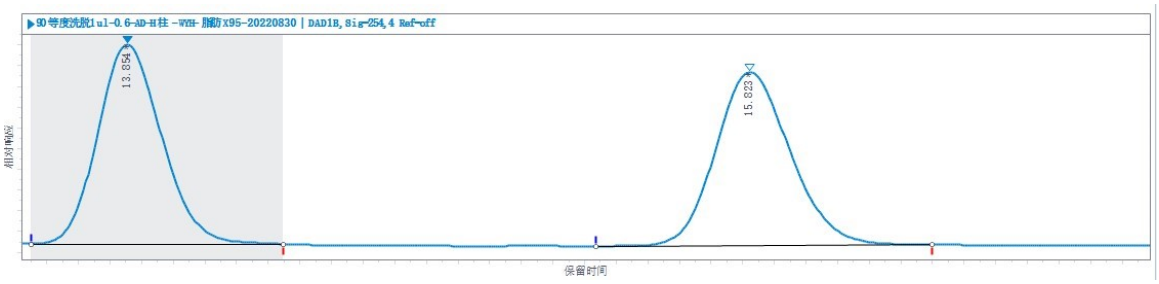


Peak	Ret. Time(min)	Area	Height	Con. (%)
1	22.937	165319.596	3346.664	100

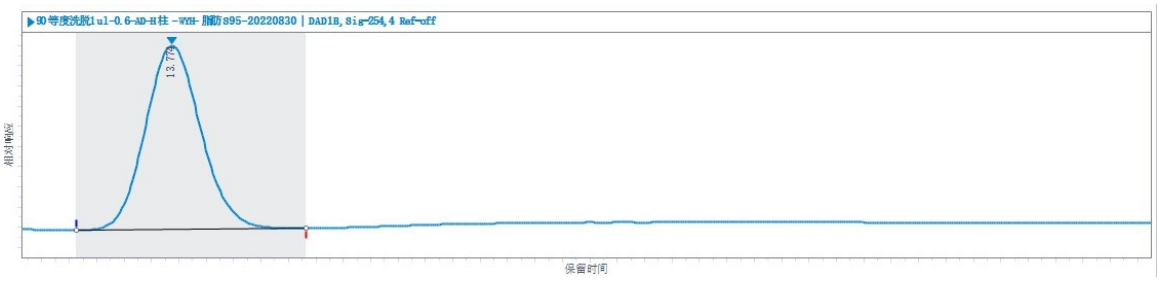


(S)-1,1-difluoro-1-iodo-4-phenylbutan-2-ol (2p): Light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, *J* =15.0 Hz, 2H), 7.28 (d, *J* =10.0 Hz, 3H), 3.40 (s, 1H), 3.03-2.97 (m, 1H), 2.85-2.77 (m, 2H), 2.20-2.10 (m, 1H), 2.03-1.88 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) 140.9, 128.9, 128.8, 126.7, 109.9 (t, *J* =316.3 Hz), 77.5 (t, *J* =23.8 Hz), 33.6, 31.2. ^{19}F NMR (470 MHz, $CDCl_3$) -47.8 (dd, *J* =225.6, 9.4 Hz, 1F), -52.2 (dd, *J* =225.6, 9.4 Hz, 1F). HRMS (EI-TOF) calcd for $C_{10}H_{12}F_2IO$([M+H]+) 311.9823, found 311.9824. [α]20 D= -16.000 (c 1, EtOH), e.e. >99%(S).

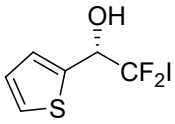
HPLC analysis: Chiralpak OD-H, hexane/isopropanol = 95/5, flow 0.6 mL/min, detection at 254 nm.



Peak	Ret. Time(min)	Area	Height	Con. (%)
1	13.854	1257.250	89.021	49.805
2	15.823	1267.109	77.130	50.195

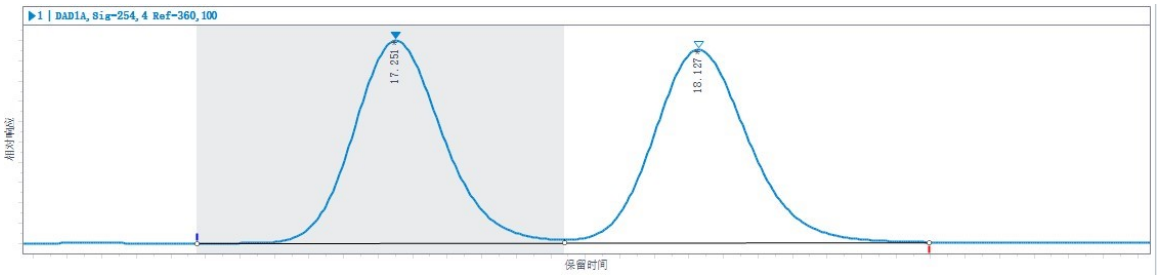


Peak	Ret. Time(min)	Area	Height	Con. (%)
1	13.774	277.046	19.661	100

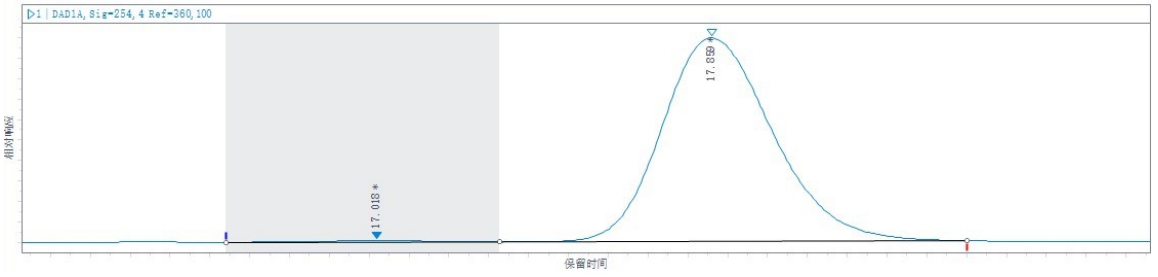


(S)-2,2-difluoro-2-iodo-1-thiopheneethanol (2q): yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (dd, *J* =10.0, 5.0 Hz, 1H), 7.20 (d, *J* =5.0 Hz, 1H), 7.05 (dd, *J* =10.0, 5.0 Hz, 1H), 4.91 (t, *J* =10.0 Hz, 1H), 2.78 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3, 127.5 (d, *J* =91.4 Hz), 106.9 (t, *J* =316.4 Hz), 77.1 (t, *J* =26.3 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ -49.6 (d, *J* =183.3 Hz, 1F), -53.3 (d, *J* =183.3 Hz, 1F). HRMS (EI-TOF) calcd for $C_6H_6F_2IOS$ ([M+H]$^+$) 290.9152, found 290.9157. [α]20 D= +0.700 (c 1, $CHCl_3$), e.e. >99%(S).

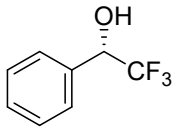
HPLC analysis: Chiralpak OD-H, hexane/isopropanol = 95/5, flow 0.6 mL/min, detection at 254 nm.



Peak	Ret. Time(min)	Area	Height	Con. (%)
1	17.251	6021.021	334.195	49.687
2	18.127	6096.968	318.334	50.313

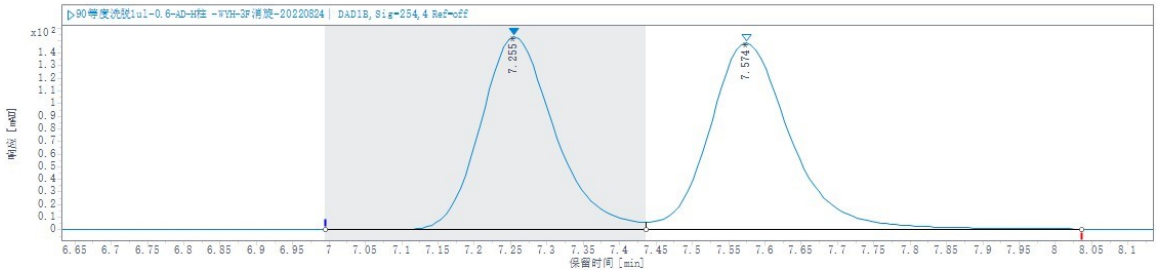


Peak	Ret. Time(min)	Area	Height	Con. (%)
1	17.018	206.744	13.852	0.495
2	17.859	41537.412	2149.976	99.505

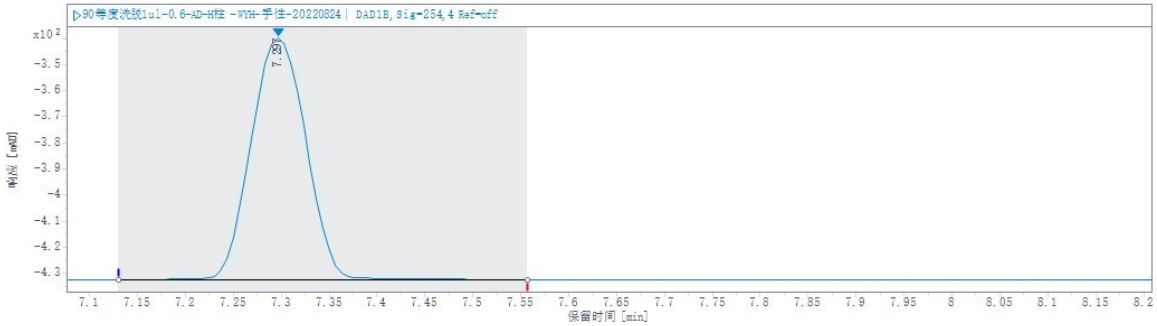


(S)-1-Phenyl-2,2,2-trifluoroethanol (2r): Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 3.1 Hz, 2H), 7.42 (d, *J* = 3.0 Hz, 2H), 7.41 (s, 1H), 5.01 (q, *J* = 12 Hz, 1H), 2.86 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.0, 129.6, 128.6, 127.4, 124.3(q, *J* = 280.3 Hz), 72.9(q, *J* = 31.7 Hz). ^{19}F NMR (375 MHz, $CDCl_3$) δ -78.33(s, 3F). [α]20 D= +7.500 (c 0.5, $CHCl_3$), e.e. >99%(S) (Lit[2]: [α]25 D= +8.33 (c 0.5, $CHCl_3$), e.e. >51%(S)).

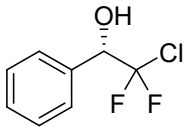
HPLC analysis: Chiralpak OD-H, hexane/isopropanol = 98/2, flow 0.6 mL/min, detection at 254 nm.



Peak	Ret. Time(min)	Area	Height	Con. (%)
1	7.255	1087.442	152.906	48.718
2	7.574	1144.681	147.960	51.282

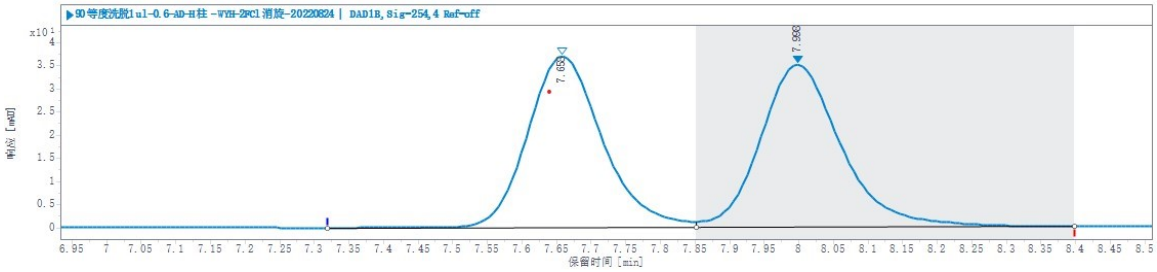


Peak	Ret. Time(min)	Area	Height	Con. (%)
1	7.297	366.636	92.786	100

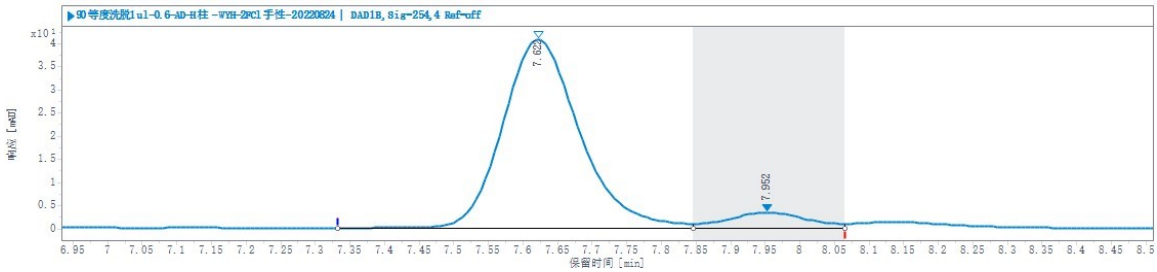


(S)-2-chloro-2,2-difluoro-1-phenylethan-1-ol (2s): Light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (dd, *J* =10.0, 5.0 Hz, 2H), 7.42-7.37 (m, 3H), 5.22 (d, *J* =5.0 Hz, 1H), 3.38 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.1, 129.8, 129.5, 128.1, 103.4, 84.8 (d, *J* =1.3 Hz). ^{19}F NMR (375 MHz, $CDCl_3$) δ -62.9 (dd, *J* =165.0, 7.4 Hz, 1F), -64.7 (dd, *J* =165.0, 8.5 Hz, 1F). [α]20 D= +3.200 (c 0.5, EtOH), e.e. 84%(S) (lit[3]: [α]25 D = +23.1 (c 0.46, EtOH), e.e. 93%(S)).

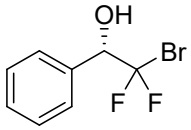
HPLC analysis: Chiralpak OD-H, hexane/isopropanol = 98/2, flow 0.6 mL/min, detection at 254 nm.



Peak	Ret. Time(min)	Area	Height	Con. (%)
1	7.658	278.126	37.029	49.439
2	7.998	284.438	35.085	50.561

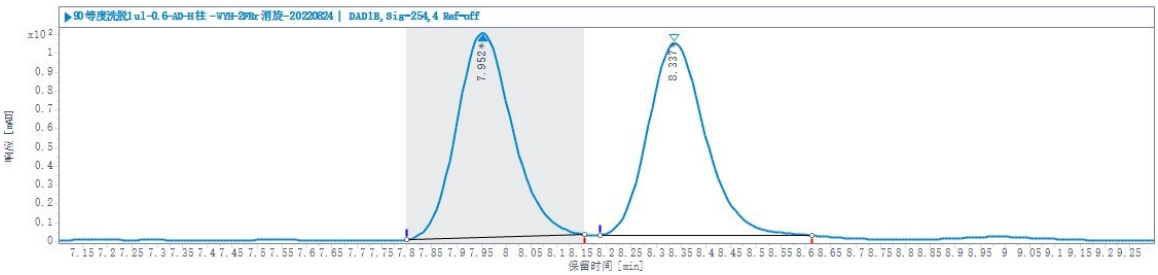


Peak	Ret. Time(min)	Area	Height	Con. (%)
1	7.622	316.445	40.780	91.875
2	7.952	27.985	3.454	8.125

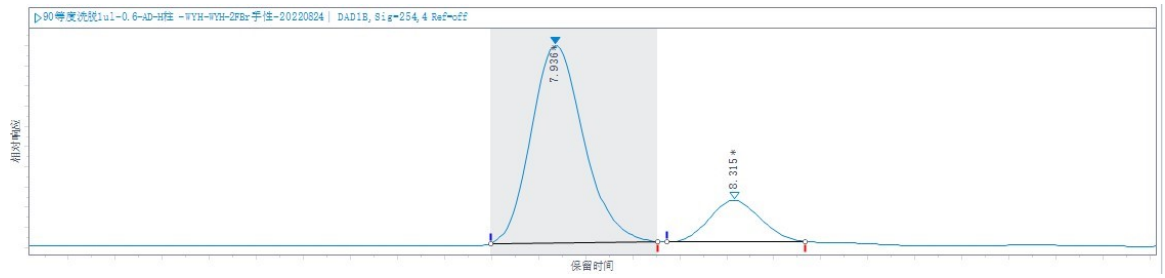


(S)-2-bromo-2,2-difluoro-1-phenylethan-1-ol (2t): Light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (t, *J* =10.0 Hz, 2H), 7.41-7.38 (m, 3H), 5.15 (dd, *J* =20.0, 10.0 Hz, 1H), 2.89 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.6, 129.8, 128.7, 128.2, 124.5 (t, *J* =307.5 Hz), 78.8 (t, *J*=25.0 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ -55.8(dd, *J* =202.1, 9.4 Hz, 1F), -59.2(dd, *J* =202.1, 9.4 Hz, 1F). HRMS (EI-TOF) calcd for $C_8H_7BrF_2ONa$([M+Na]$^+$) 258.9546, found 258.9551. [α]20 D= +8.800 (c 1, EtOH), e.e. 66.1%(S).

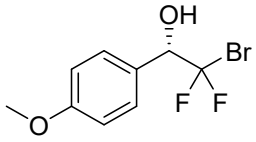
HPLC analysis: Chiralpak OD-H, hexane/isopropanol = 98/2, flow 0.6 mL/min, detection at 254 nm.



Peak	Ret. Time(min)	Area	Height	Con. (%)
1	7.952	844.781	108.841	50.916
2	8.337	814.386	102.151	49.084

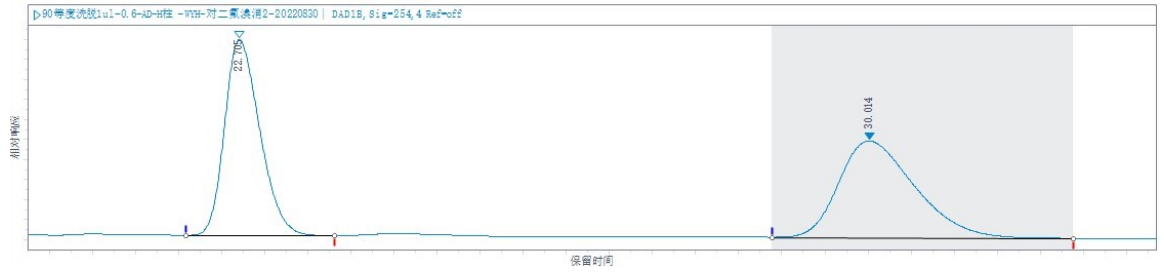


Peak	Ret. Time(min)	Area	Height	Con. (%)
1	7.936	745.210	96.272	83.057
2	8.315	152.017	20.276	16.943

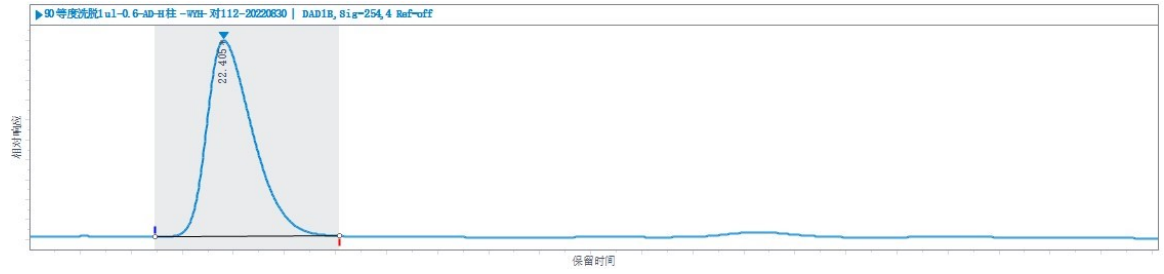


(S)-2,2-difluoro-2- bromo -1-(4-methoxyphenyl)ethanol (2u): Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.0 Hz, 2H), 6.92 (d, *J* = 8.0 Hz, 2H), 4.96 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.82 (s, 3H), 2.99 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 129.2, 126.4, 124.4 (t, *J* = 309.0 Hz), 113.9, 78.3 (t, *J* = 25.0 Hz), 55.3. ^{19}F NMR (375 MHz, $CDCl_3$) δ -56.12 (d, *J* = 161.3 Hz, 1F), -59.19 (d, *J* = 161.3 Hz, 1F). HRMS (EI-TOF) calcd for $C_9H_9BrF_2O_2Na$([M+Na]$^+$) 288.9652, found 288.9654. [α]20 D= +17.900 (c 1, $CHCl_3$), e.e.>99%(S).

HPLC analysis: Chiralpak OD-H, hexane/isopropanol = 95/5, flow 0.6 mL/min, detection at 254 nm.



Peak	Ret. Time(min)	Area	Height	Con. (%)
1	22.705	2974.167	104.775	48.504
2	30.014	3157.671	51.496	51.496

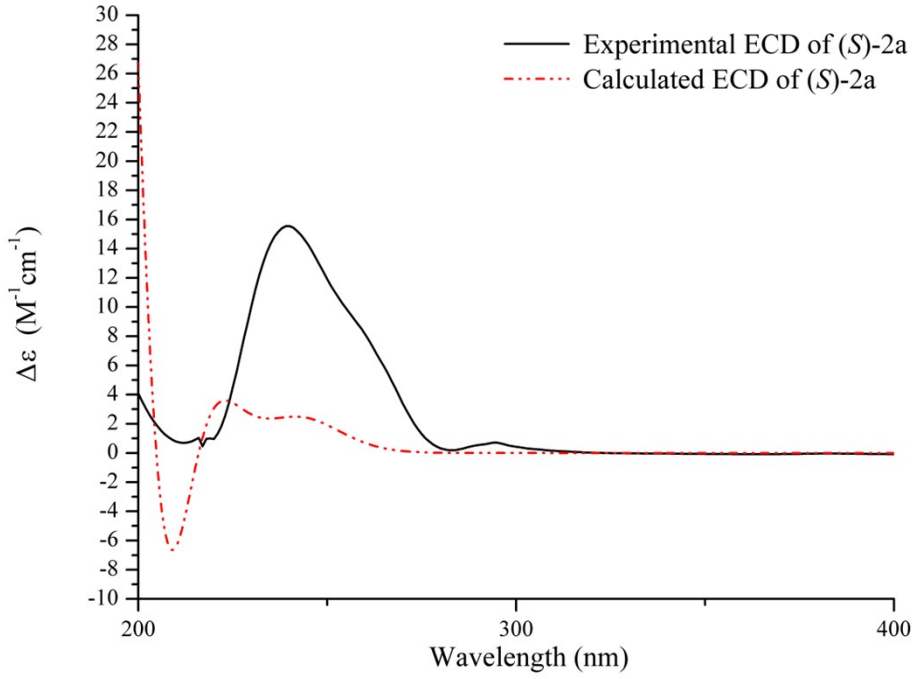


Peak	Ret. Time(min)	Area	Height	Con. (%)
1	22.405	5329.183	170.718	100

2.3 Enzymatic reduction using K234 in the absence of the nicotinamide cofactor.

In a 1.5 mL Eppendorf vial, K234 (12 g/L) was added in water (0.5 mL) and mixed with 2-propanol (0.5 mL) and the corresponding ketone **1** (100 g/L). The reaction was shaken at 30 °C and 1000 rpm for 12 h and stopped by extraction with EtOAc (3 × 0.5 mL), and the combined organic phases washed with water (0.5 mL), dried over Na2SO4. Conversions and e.e. of the corresponding alcohols were determined by HPLC.

2.4 Experimental ECD and calculated ECD of 2a.



3. References

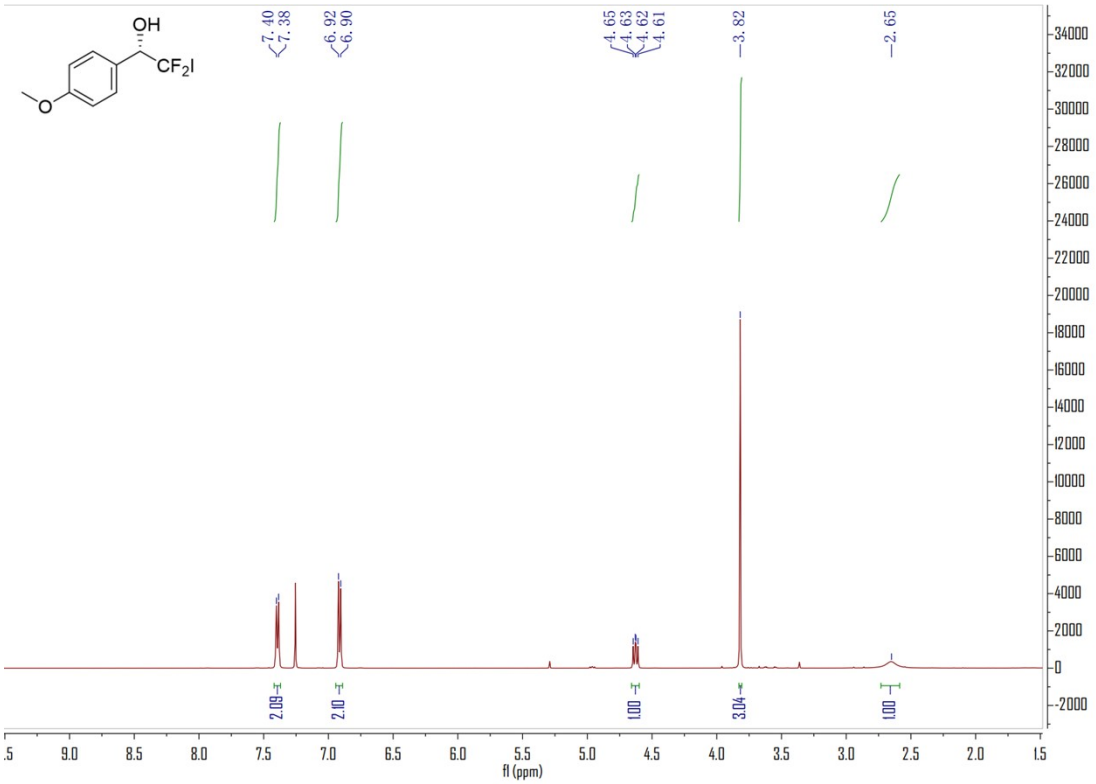
[1] H. Chen, J. Wang, J. Wu, Y. Kuang, F. Wu, Journal of Fluorine Chemistry 2017, **200**, 41-46.

[2] R. Hodgkinson, V. Jurcik, A. Zanotti-Gerosa, H.G.n. Nedden, A. Blackaby, G.J. Clarkson and M. Wills, Organometallics, 2014, 33, 5517-5524.

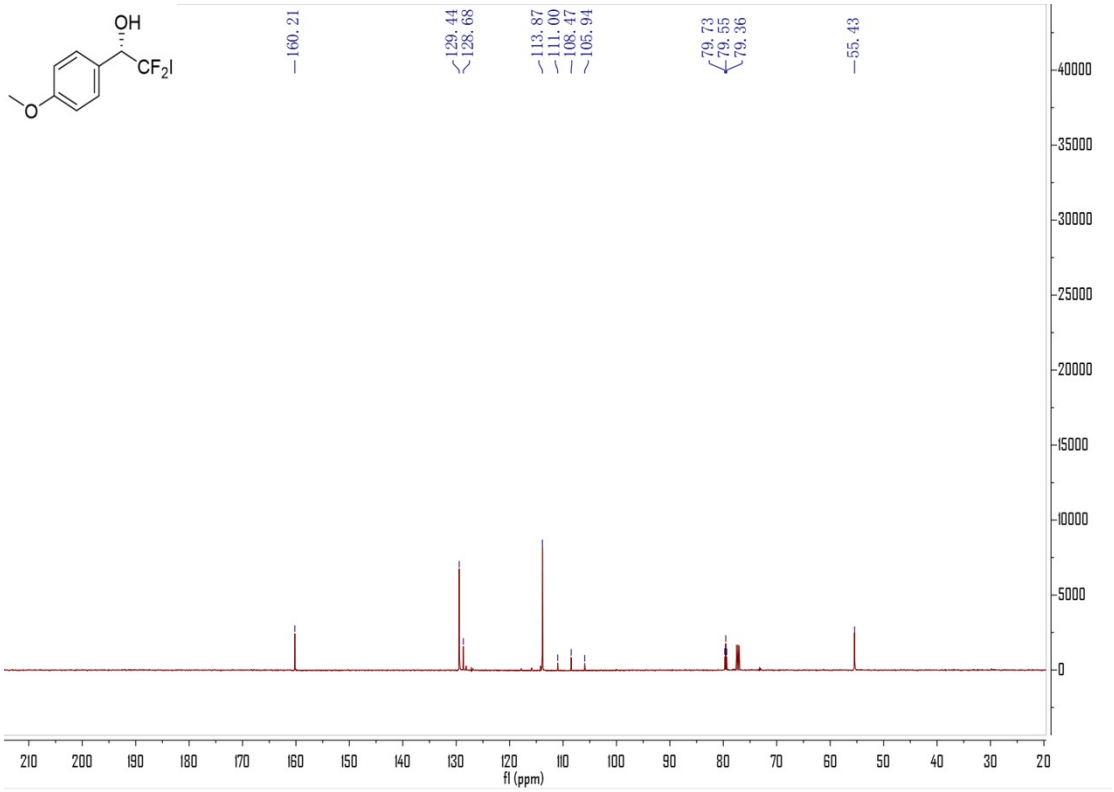
[3] F. Brüning, H. Nagae, D. Käch, K. Mashima and A. Togni, Chem.–A Eur. J., 2019, 25, 10818-10822.

4. Spectral data

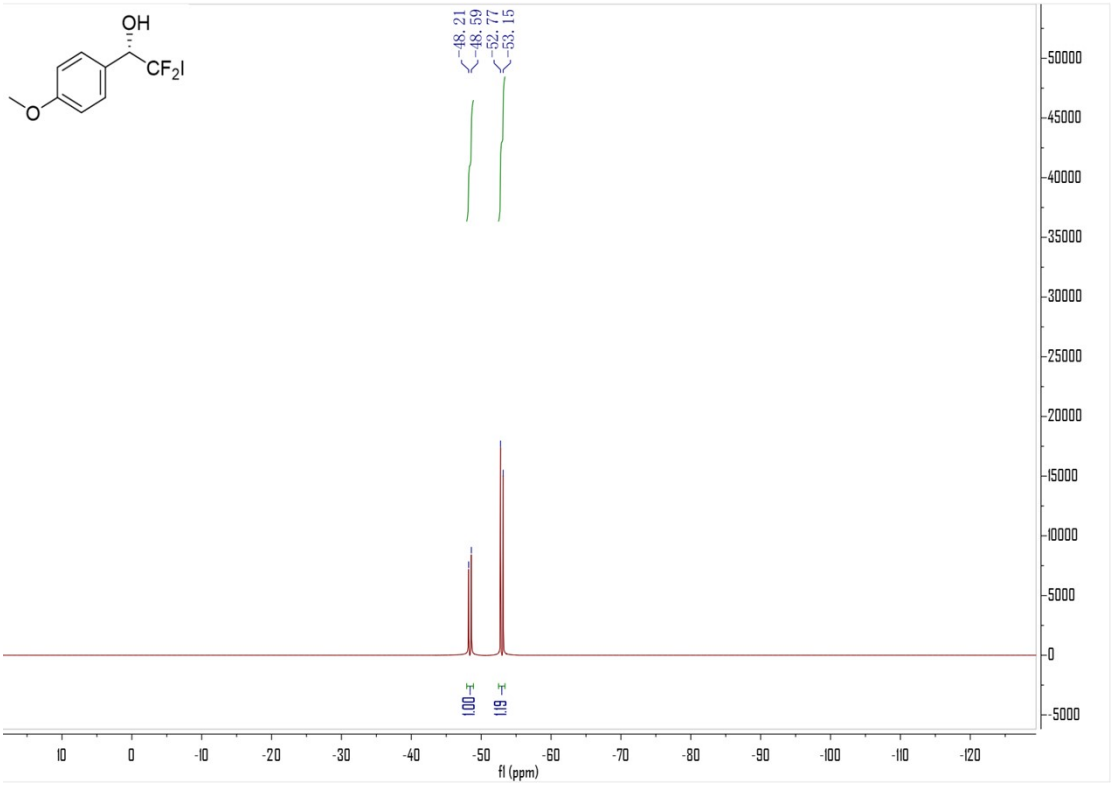
2a ^{1}H NMR



2a ^{13}C NMR



2a ^{19}F NMR



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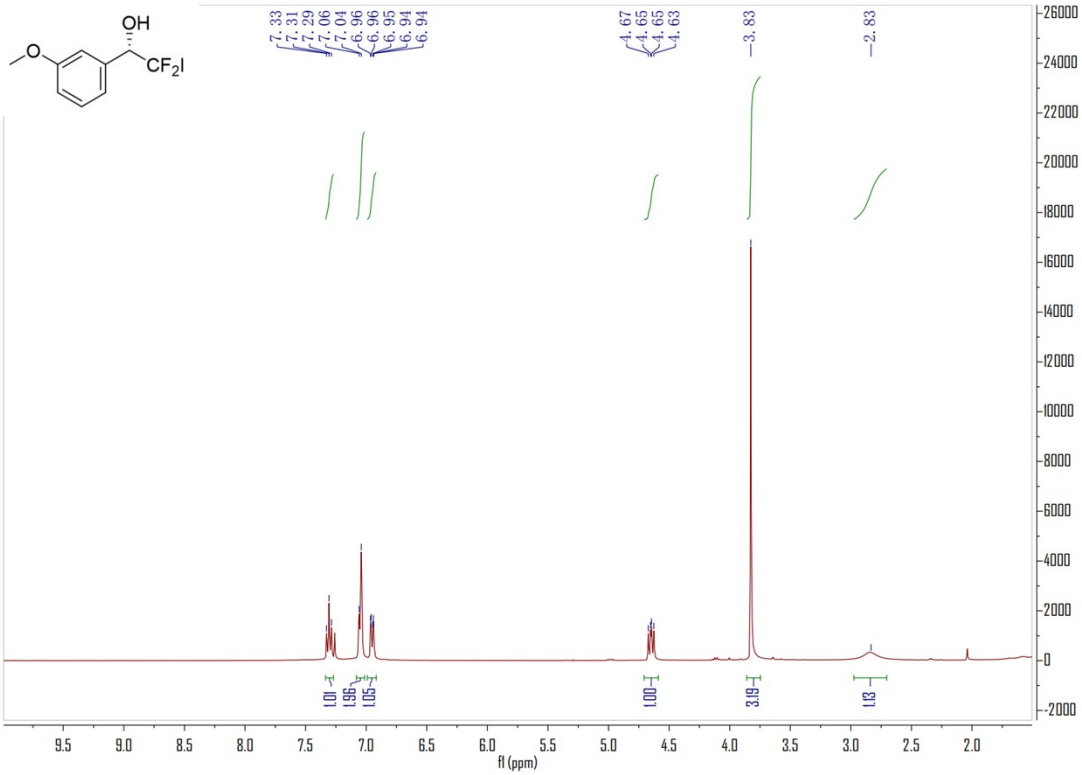

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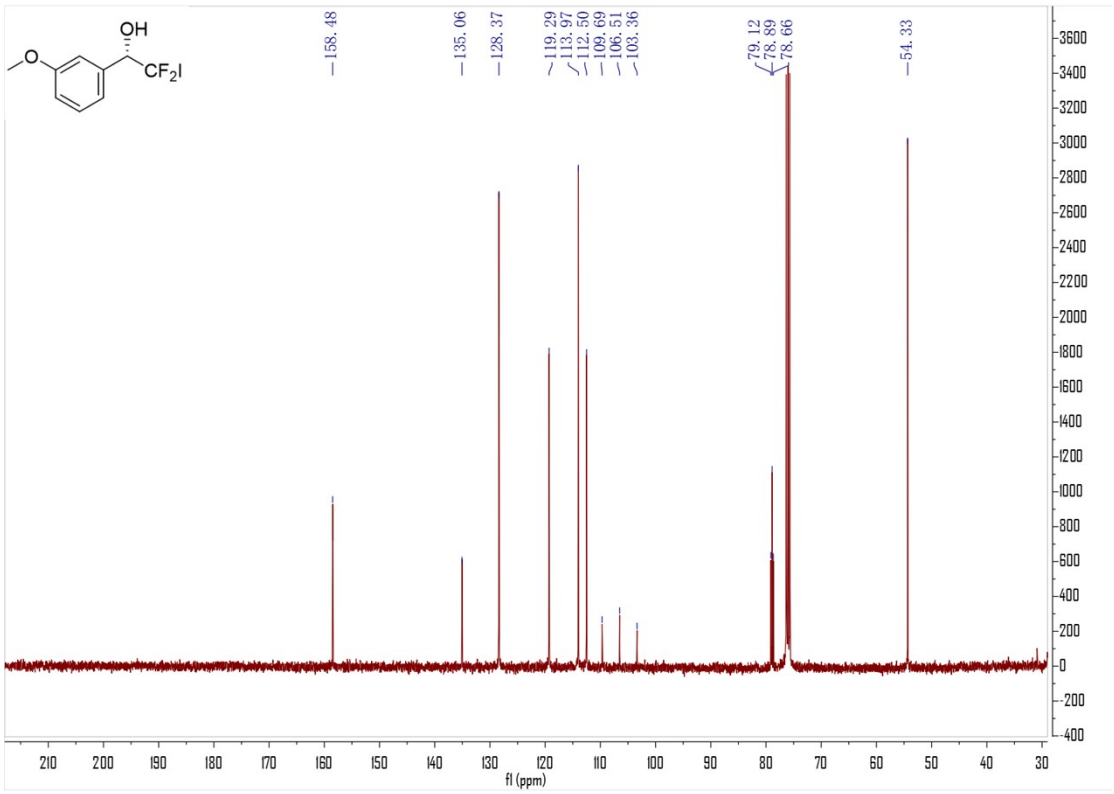

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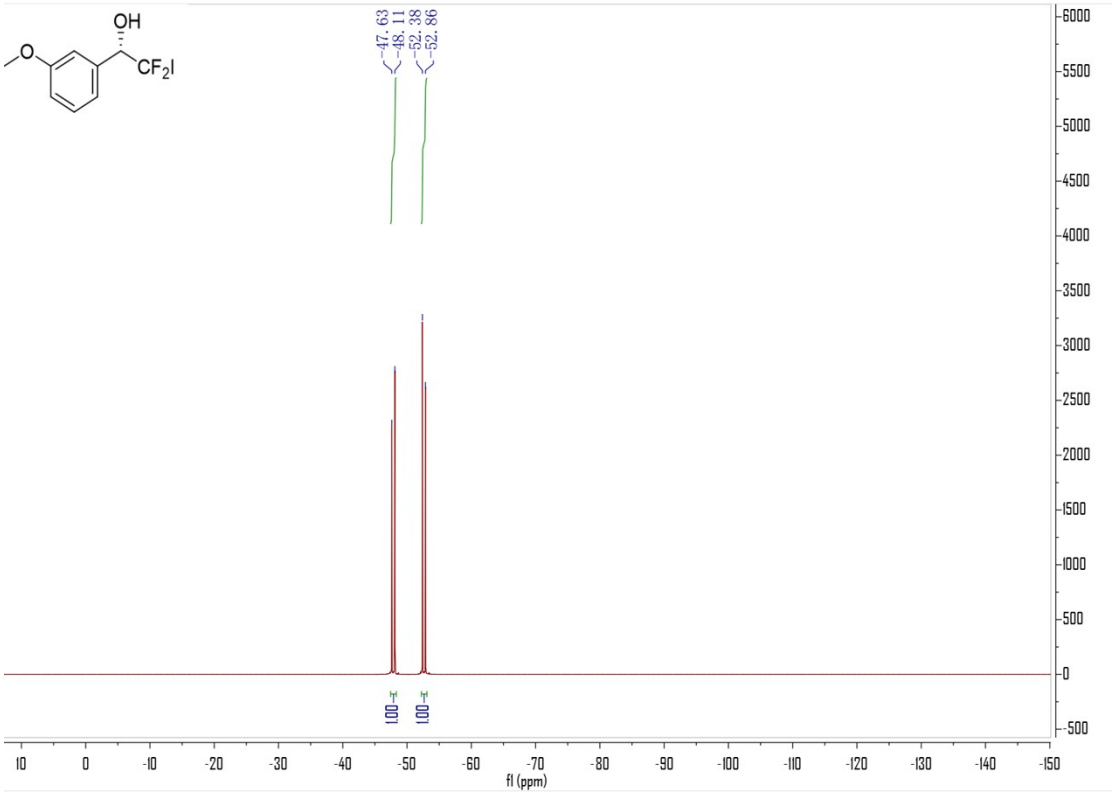

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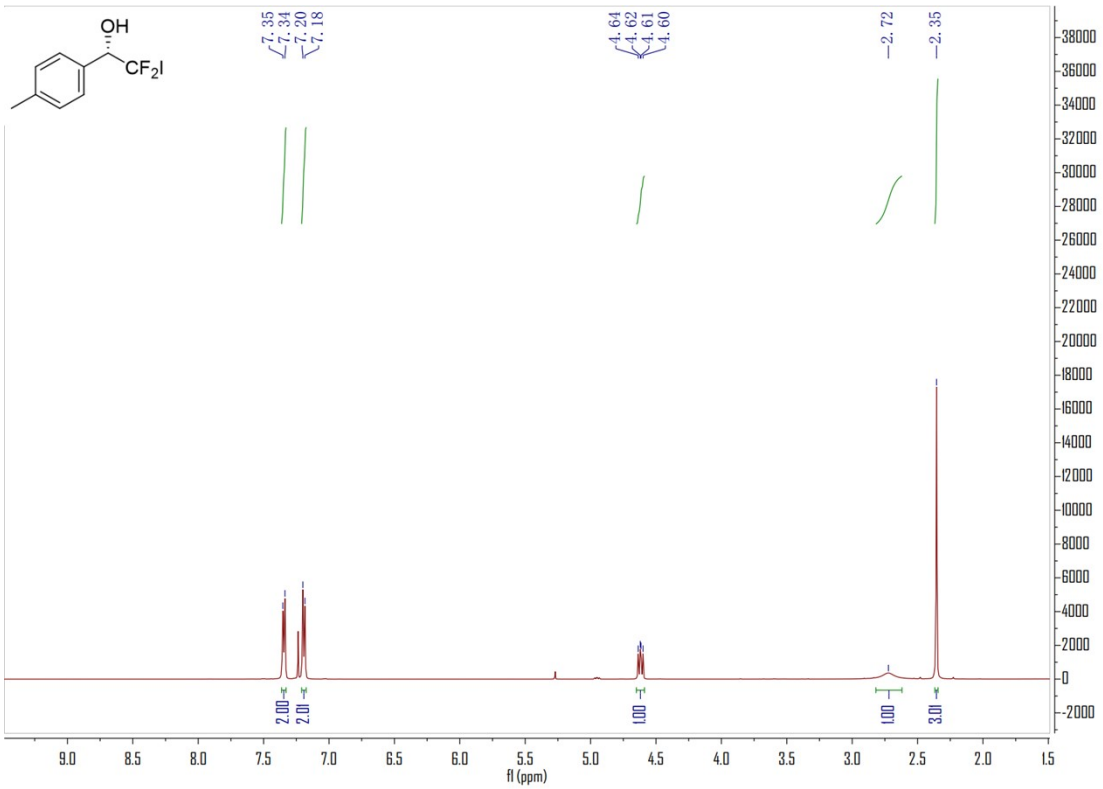

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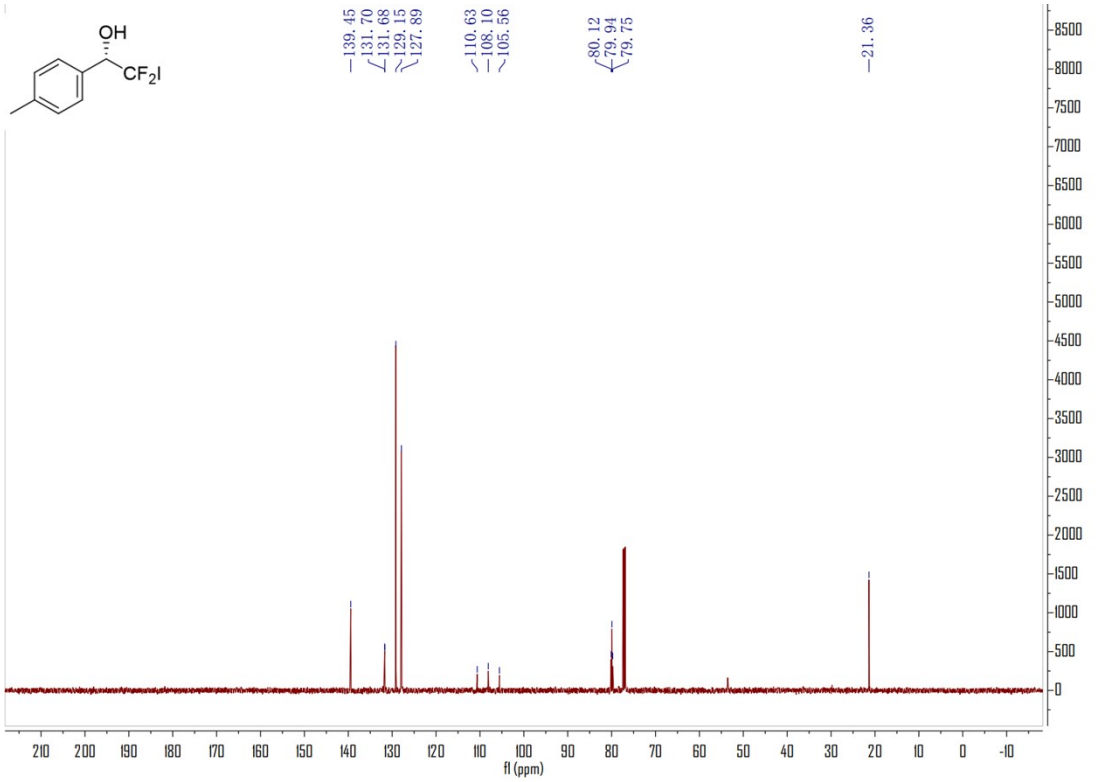

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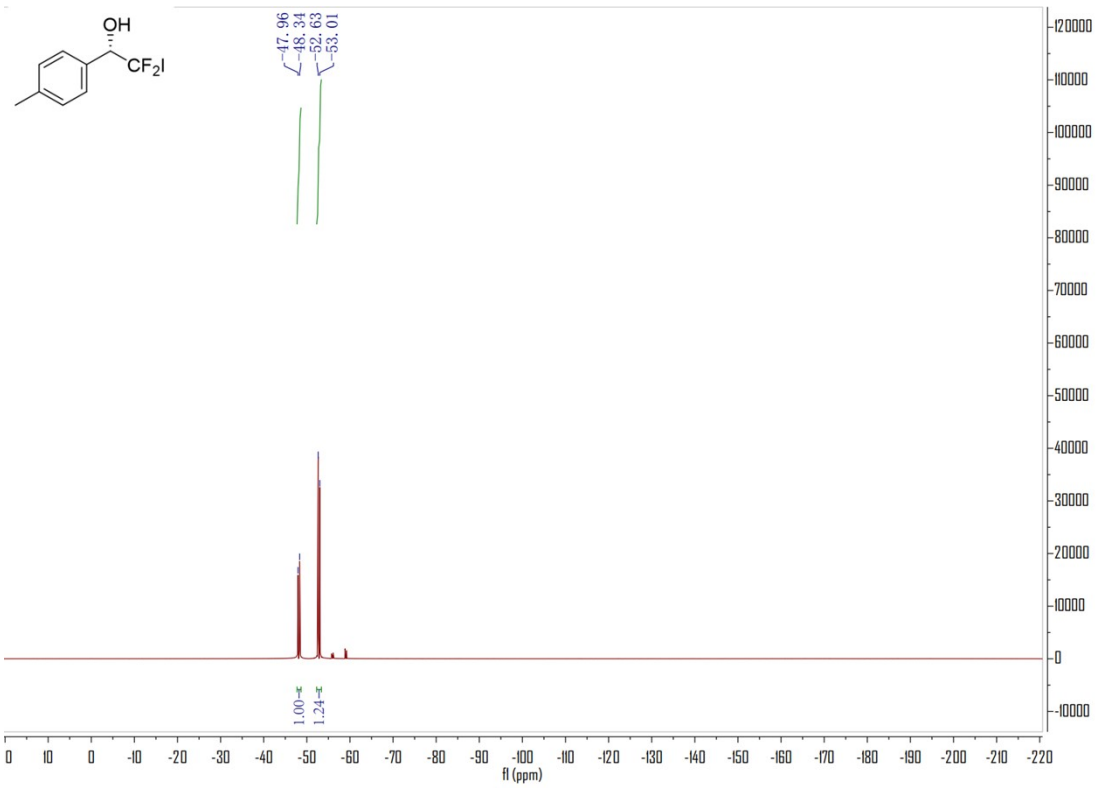
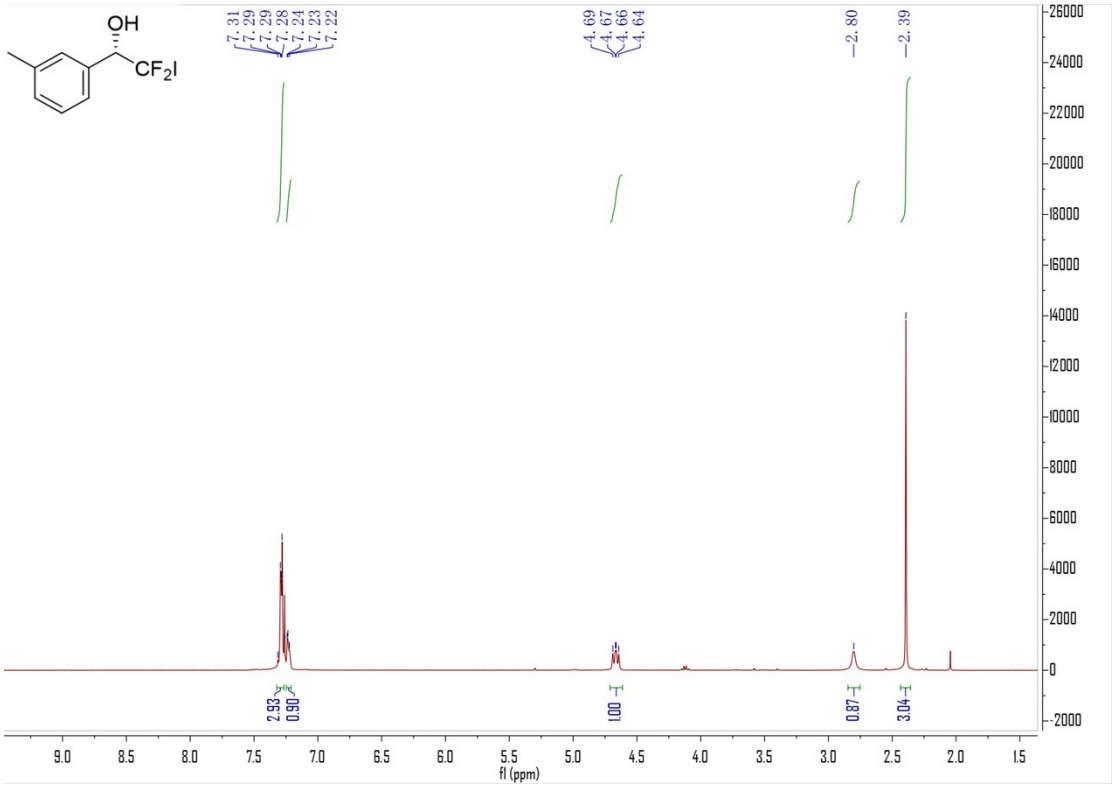


2d ^{1}H NMR



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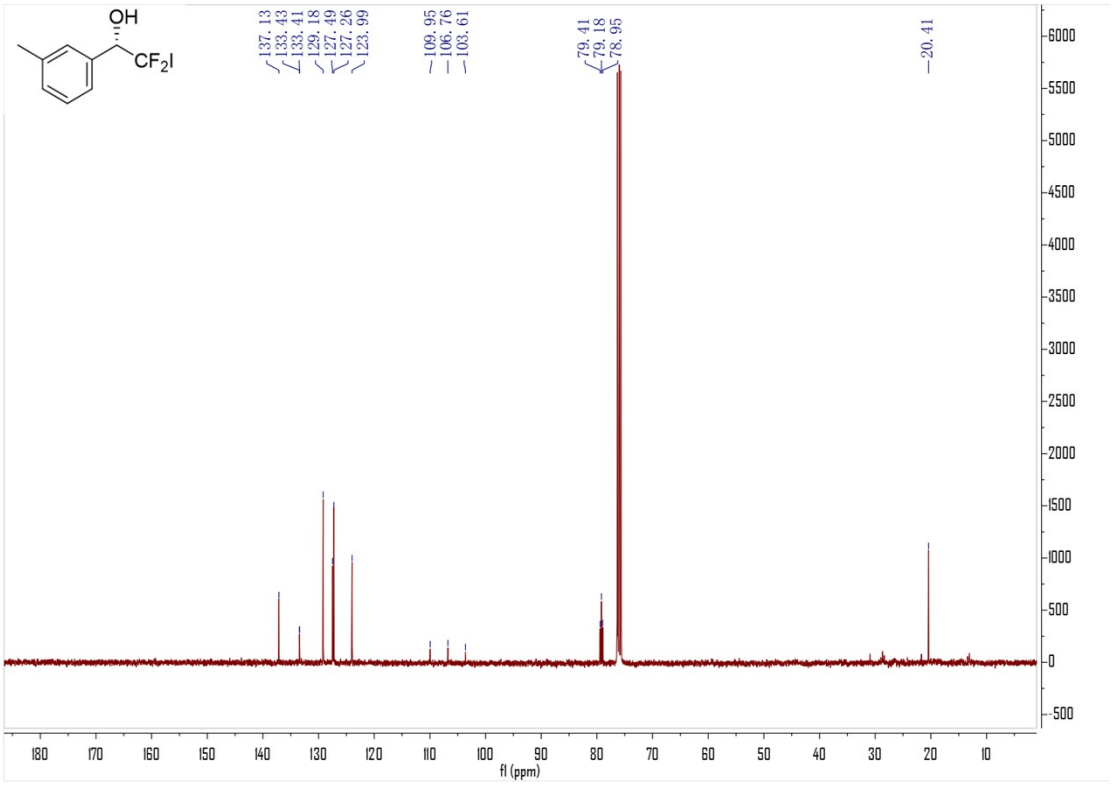

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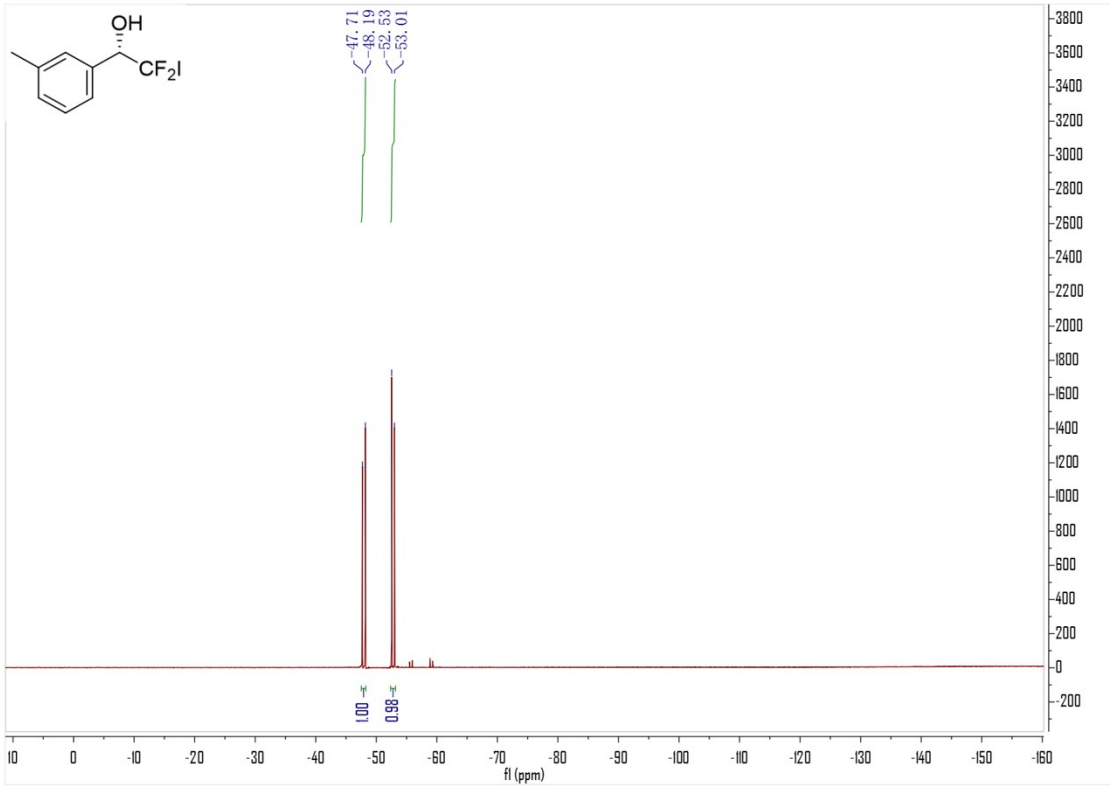

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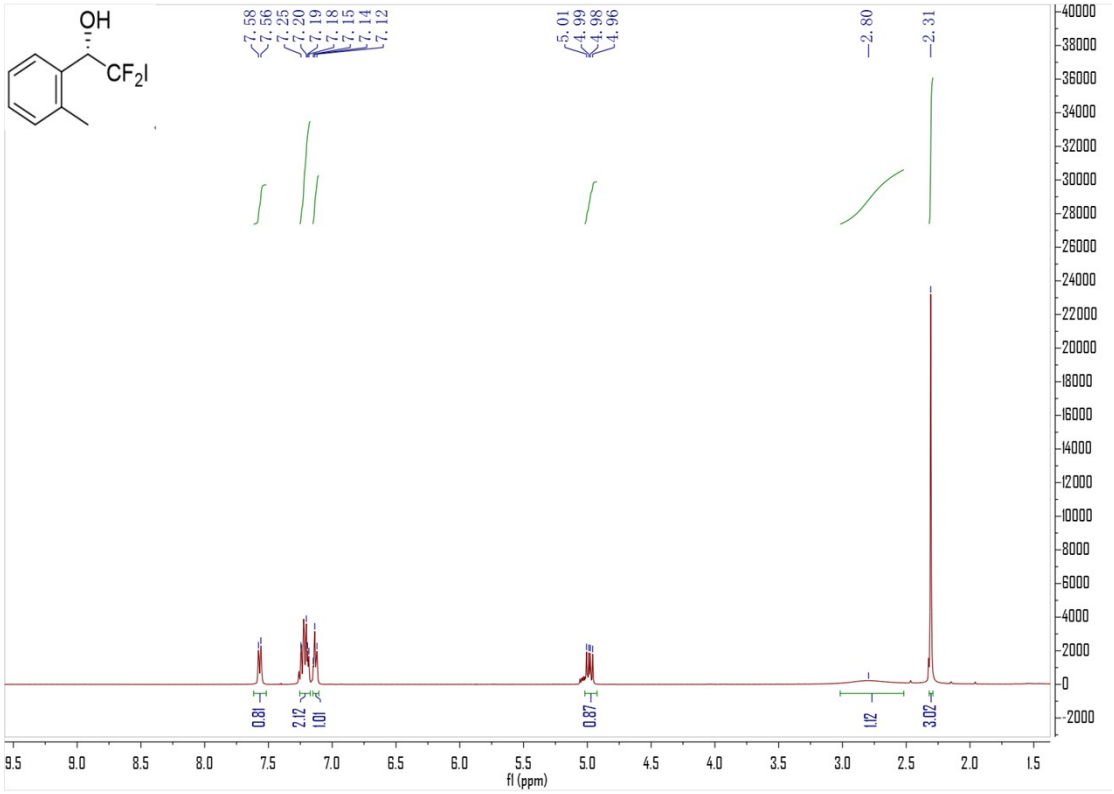

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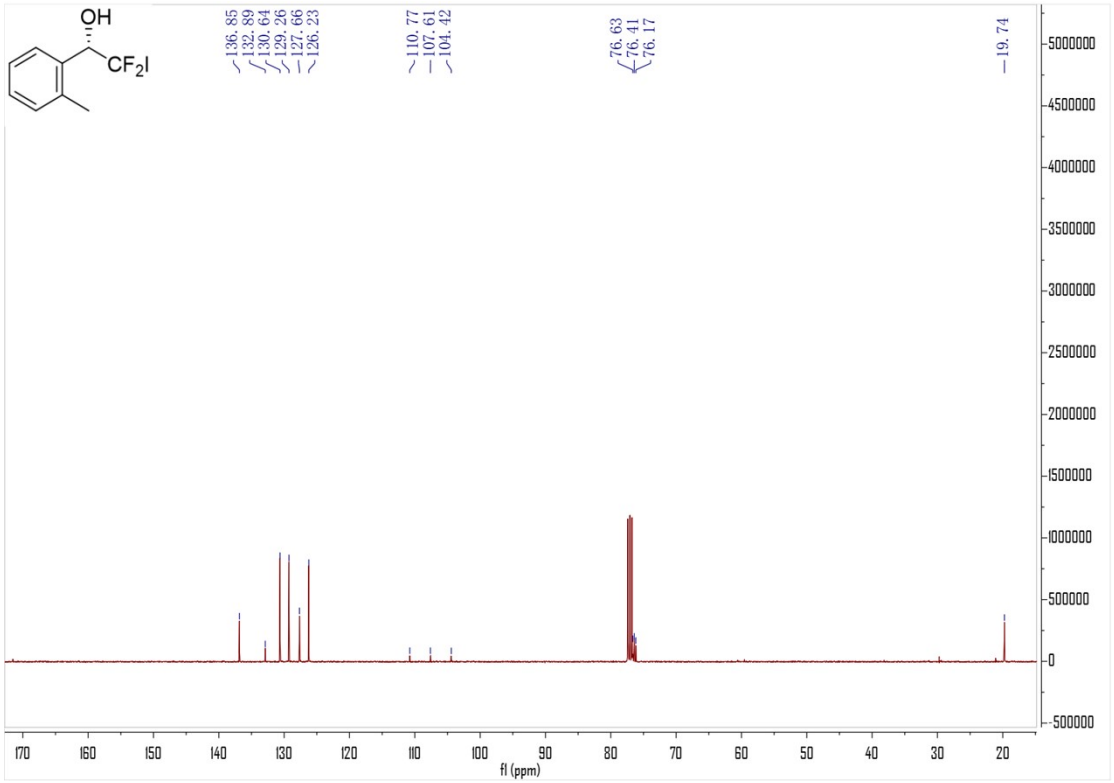

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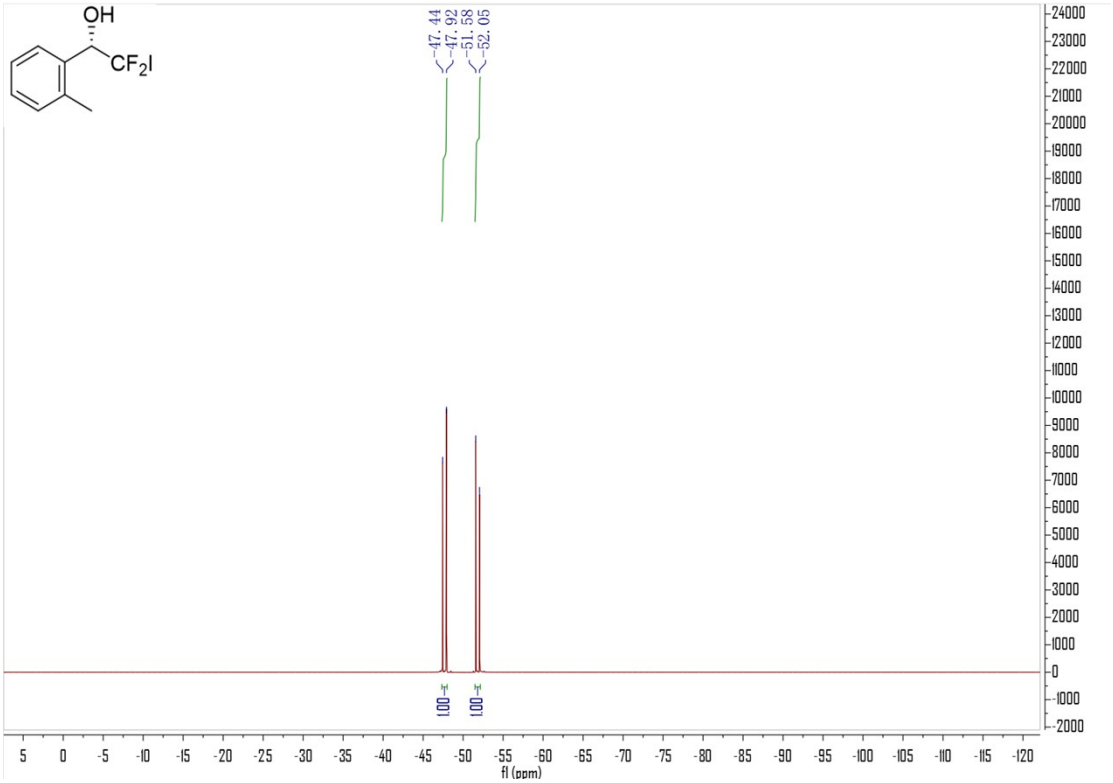

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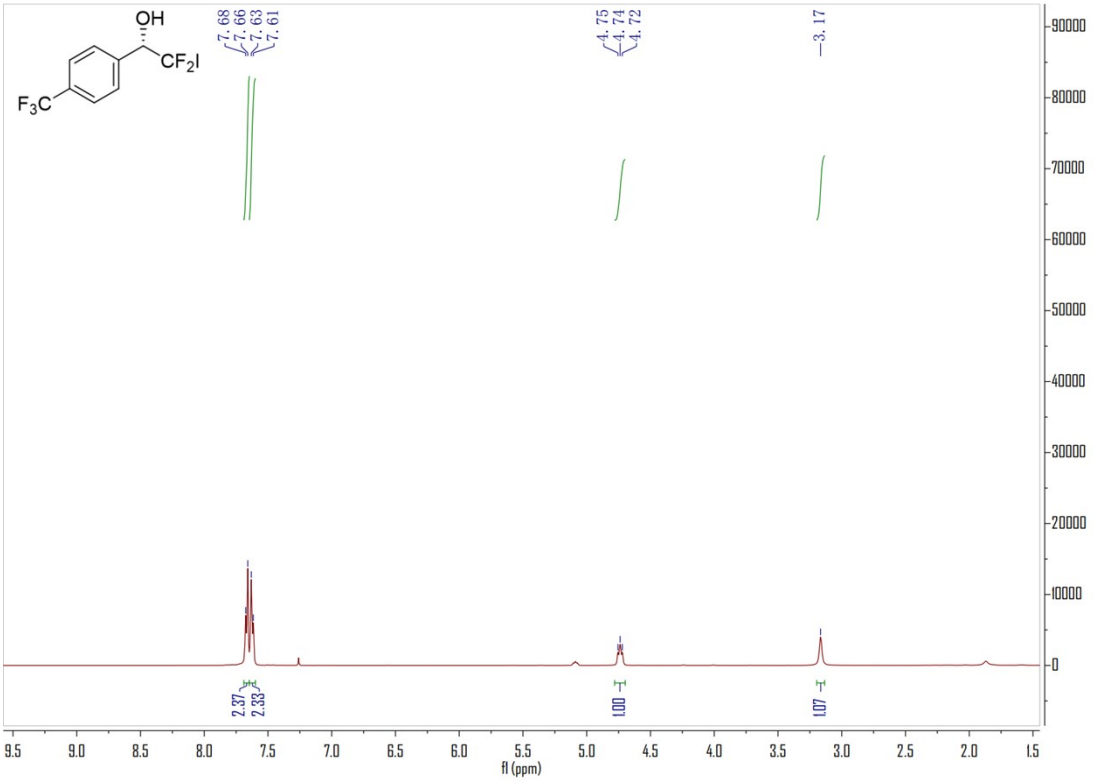

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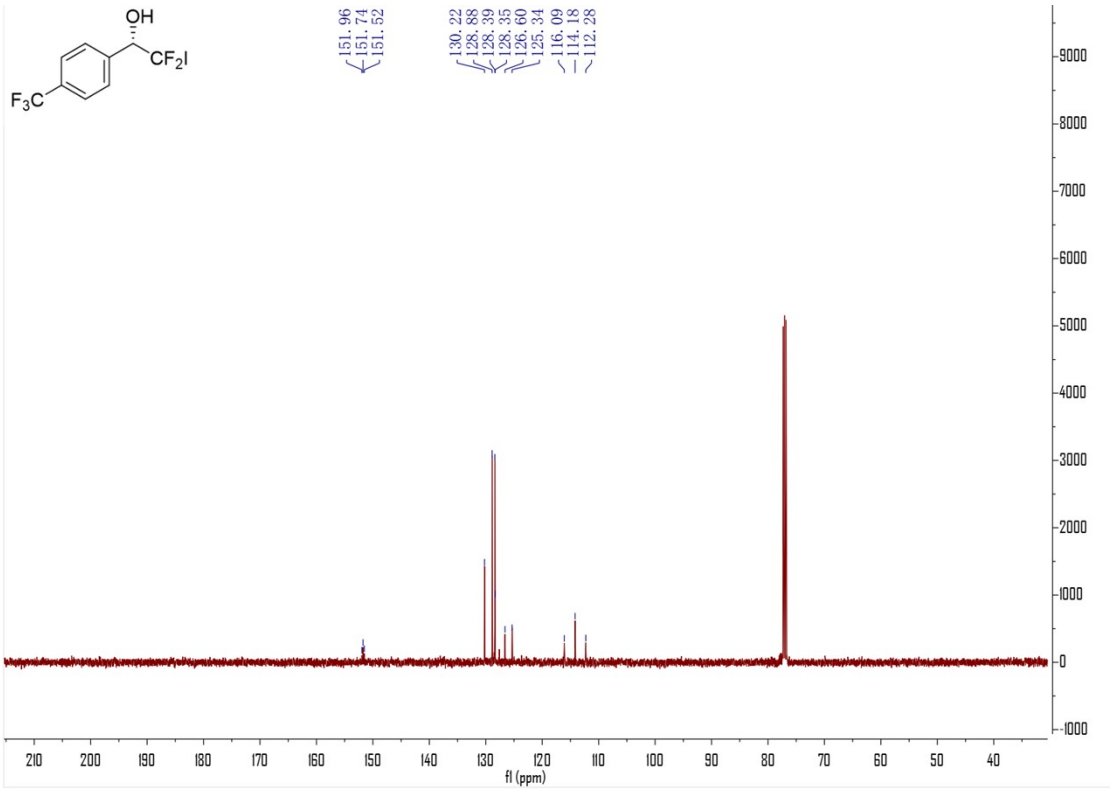

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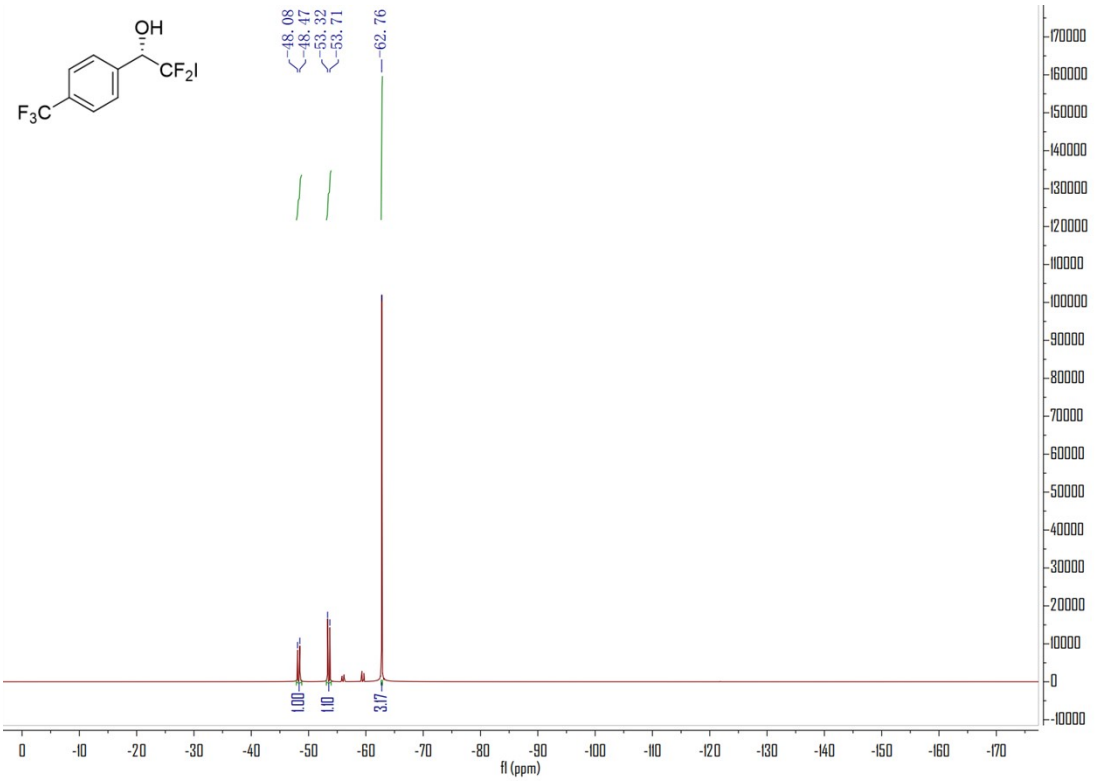

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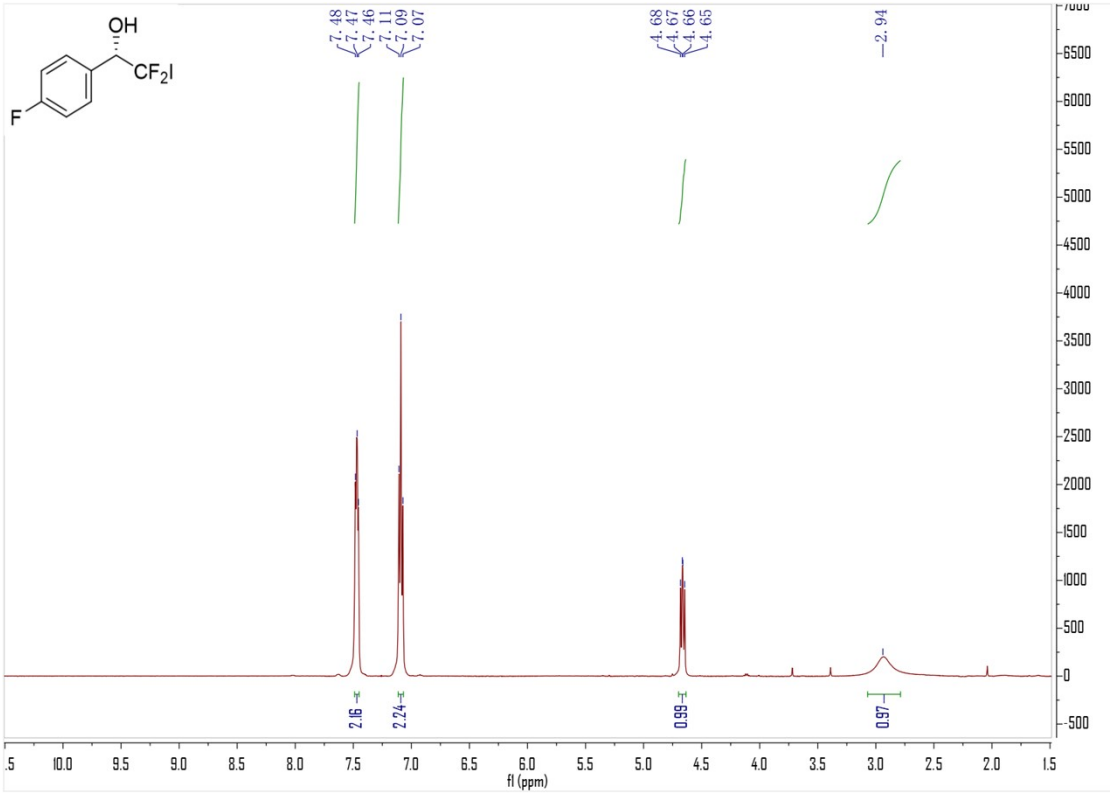

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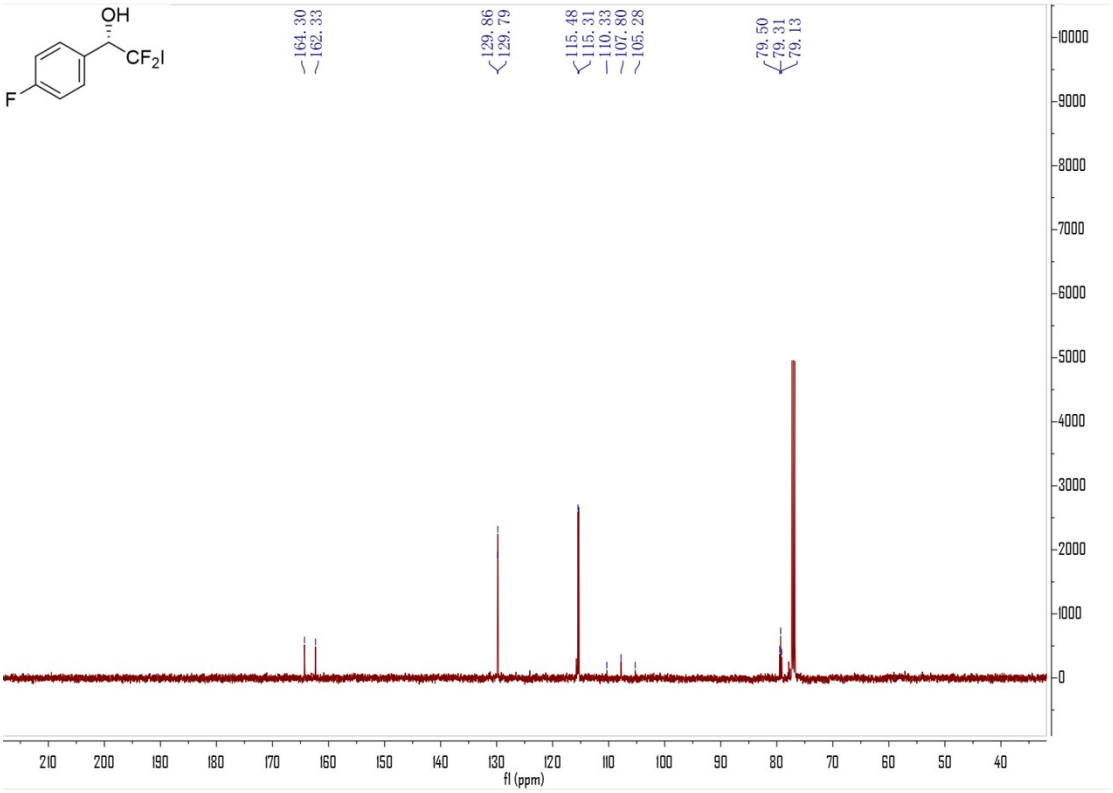

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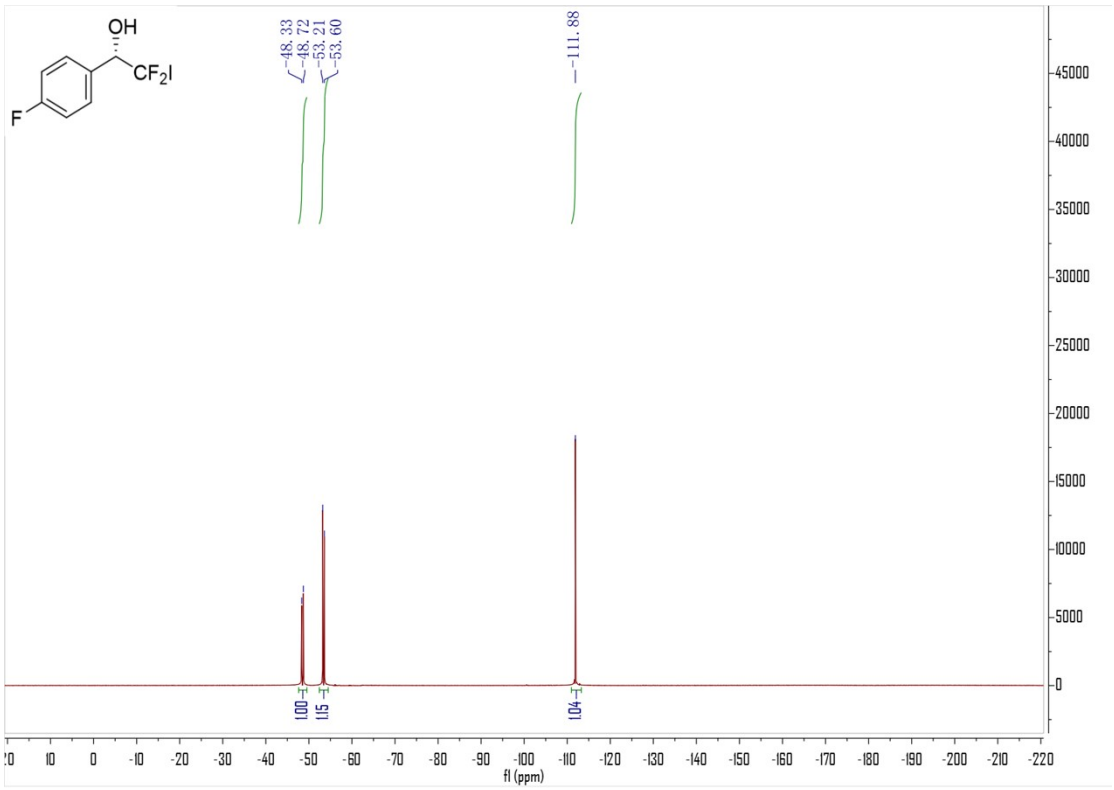

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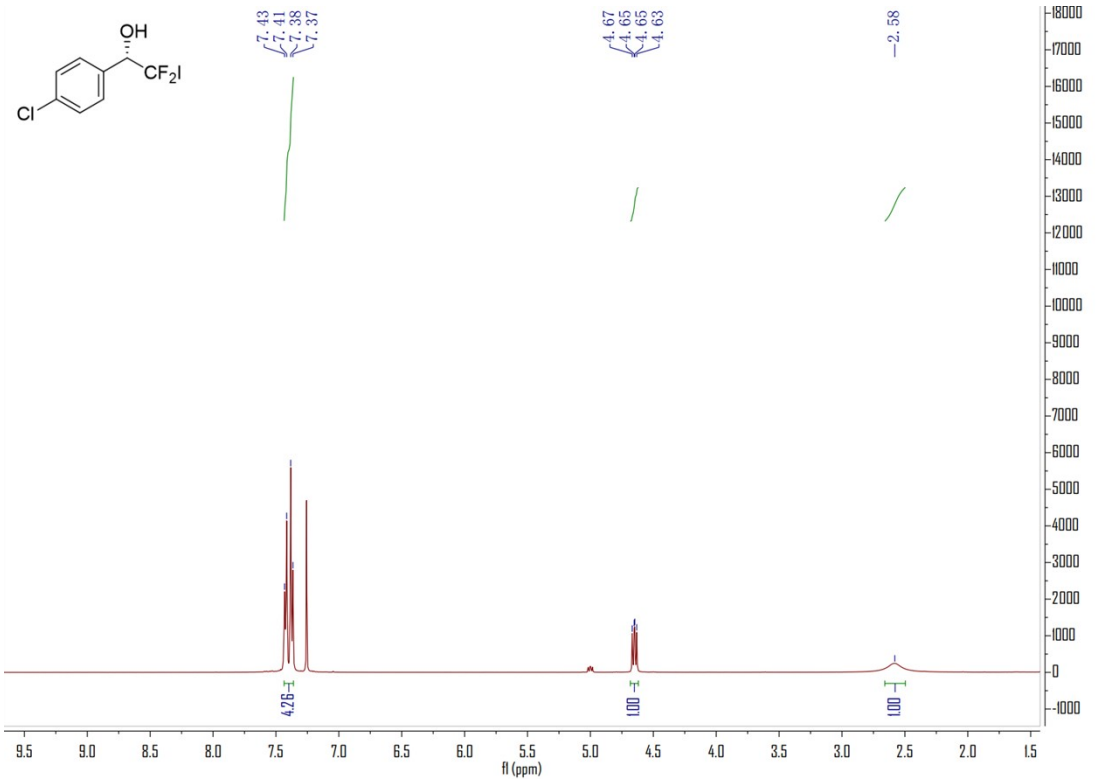

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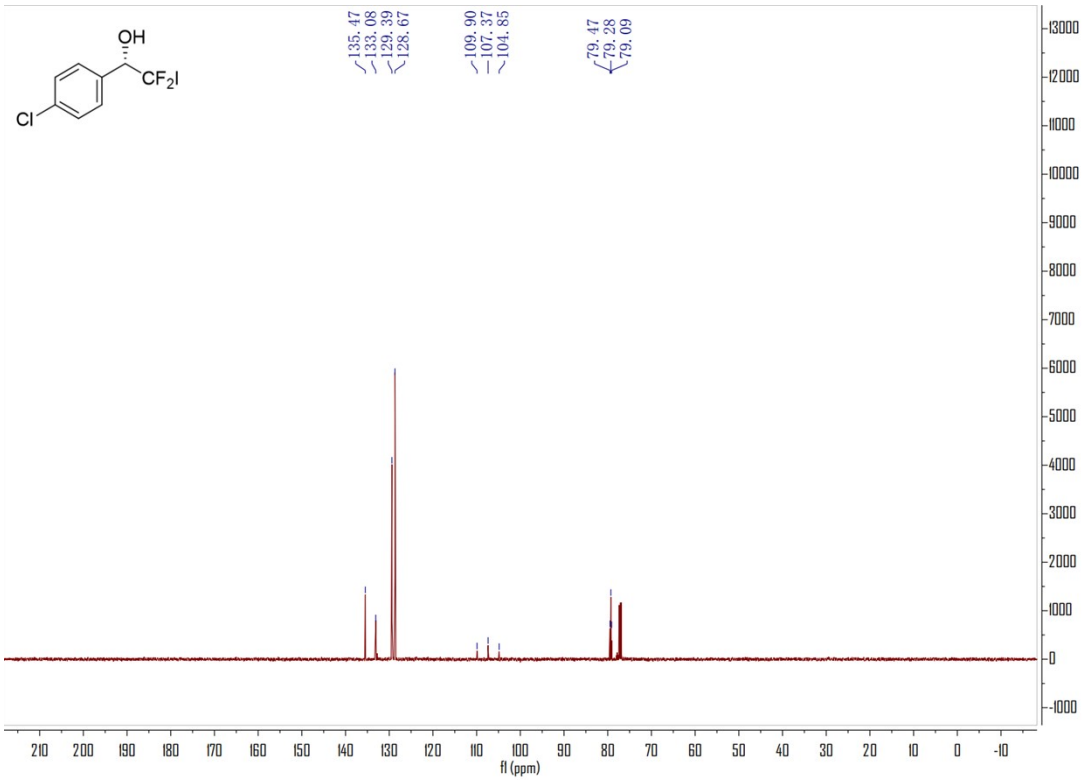

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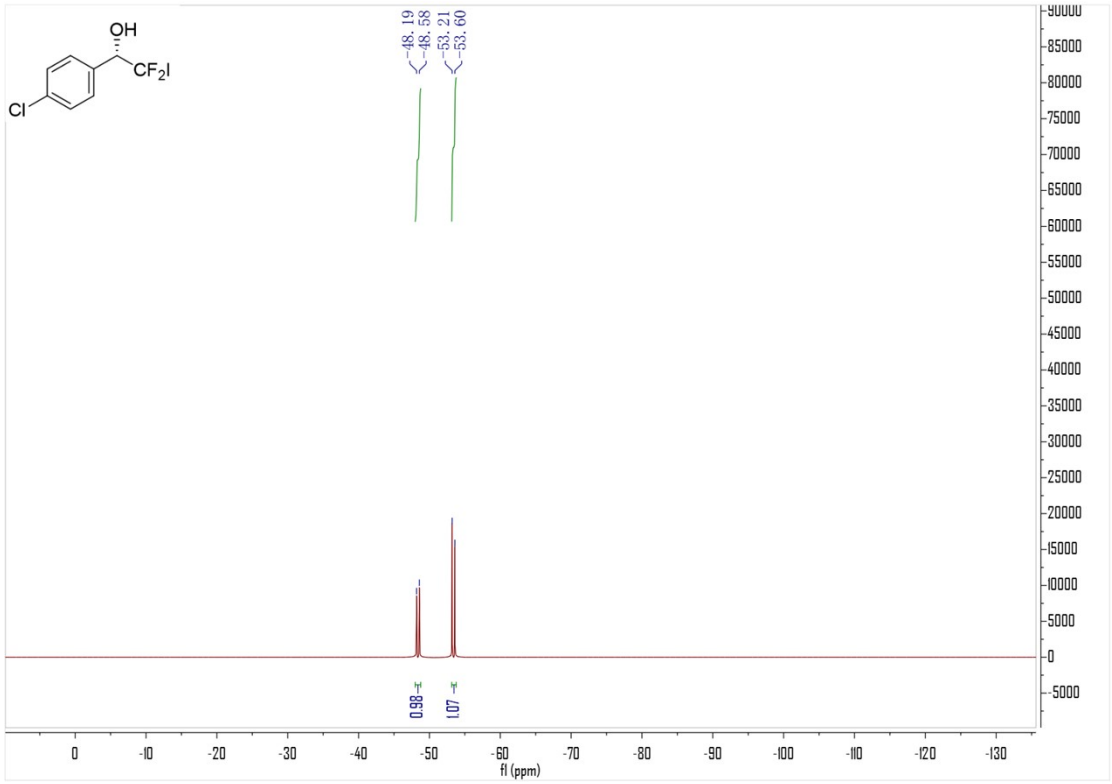

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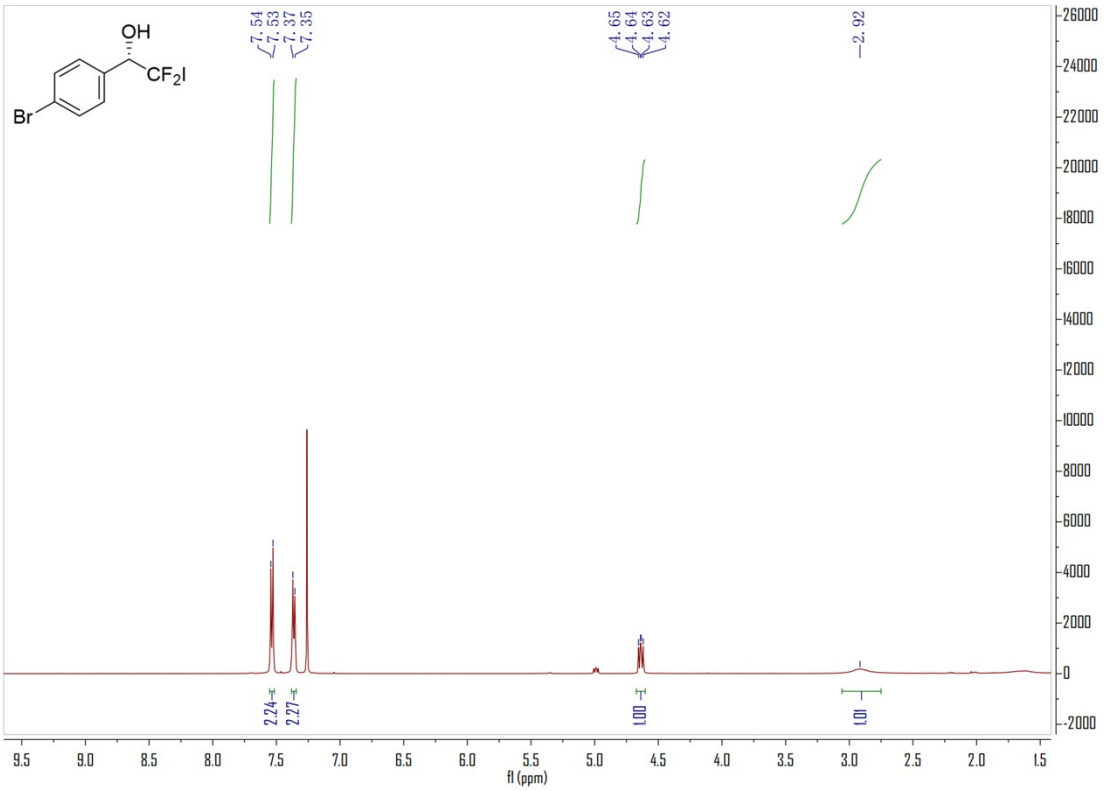

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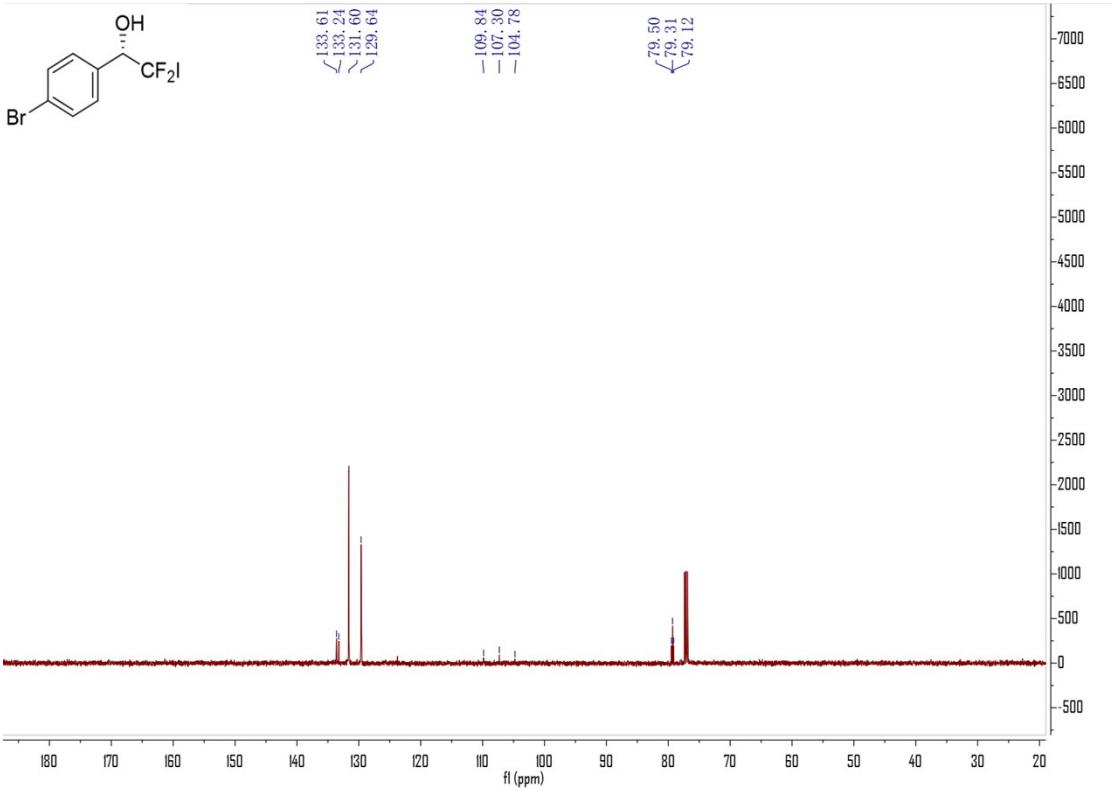

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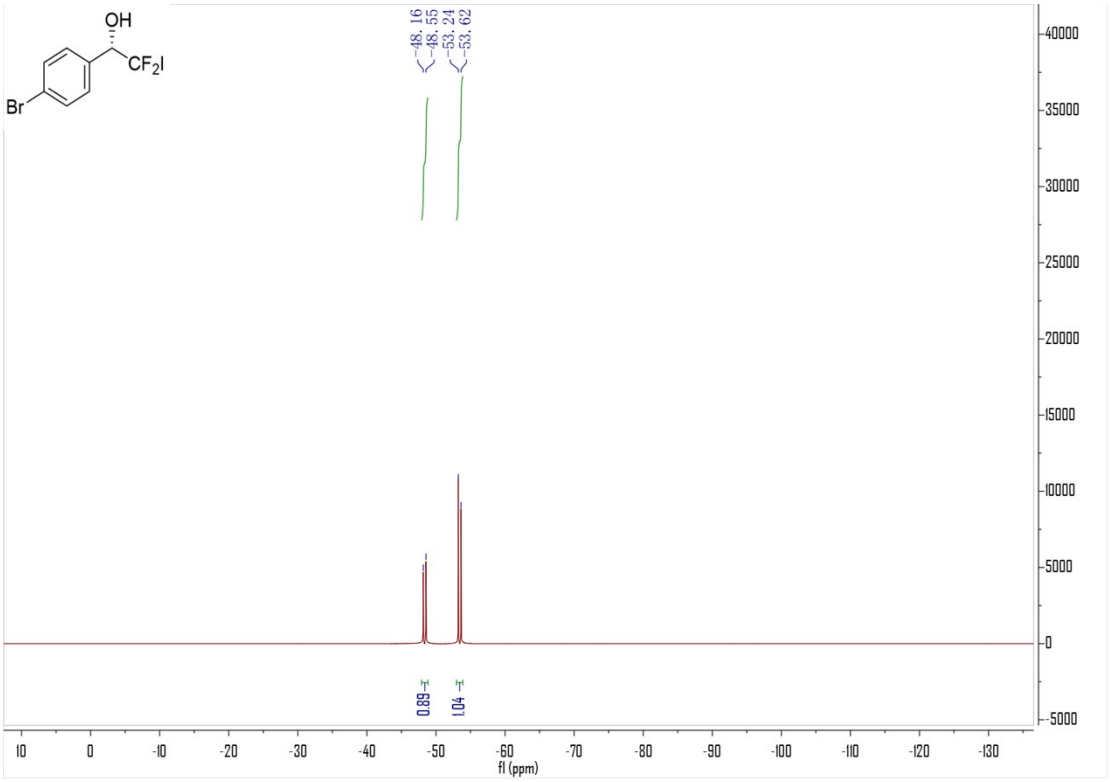

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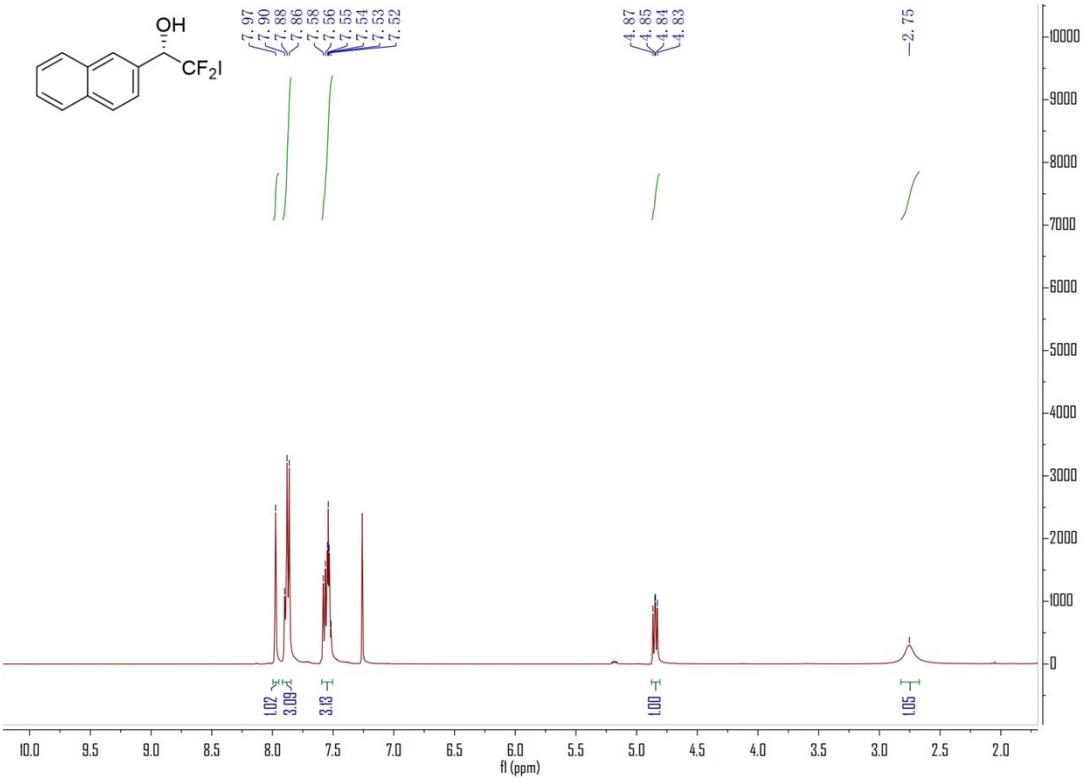

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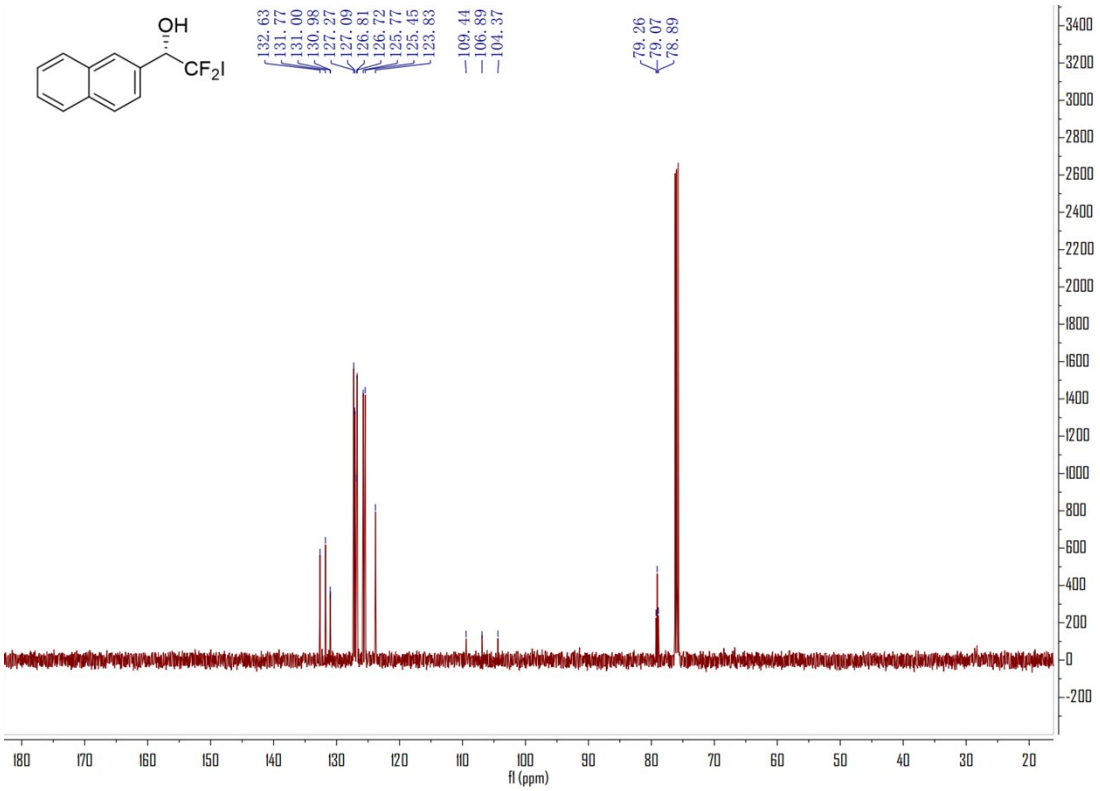

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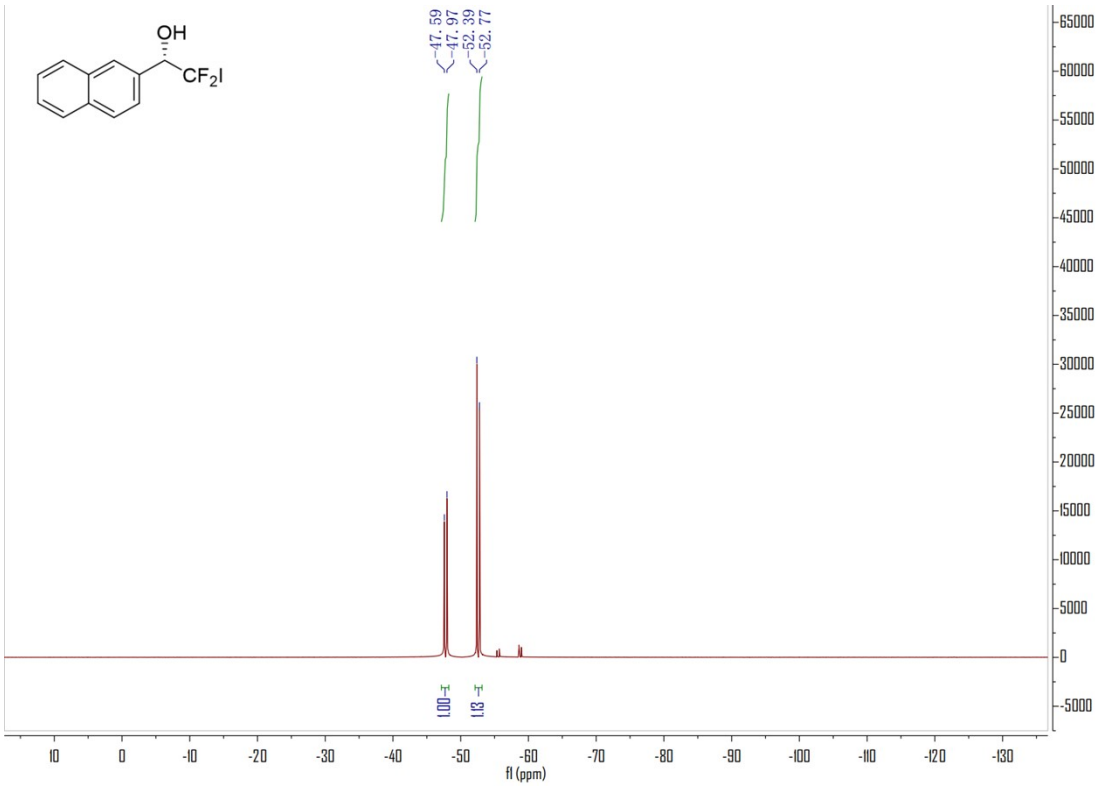

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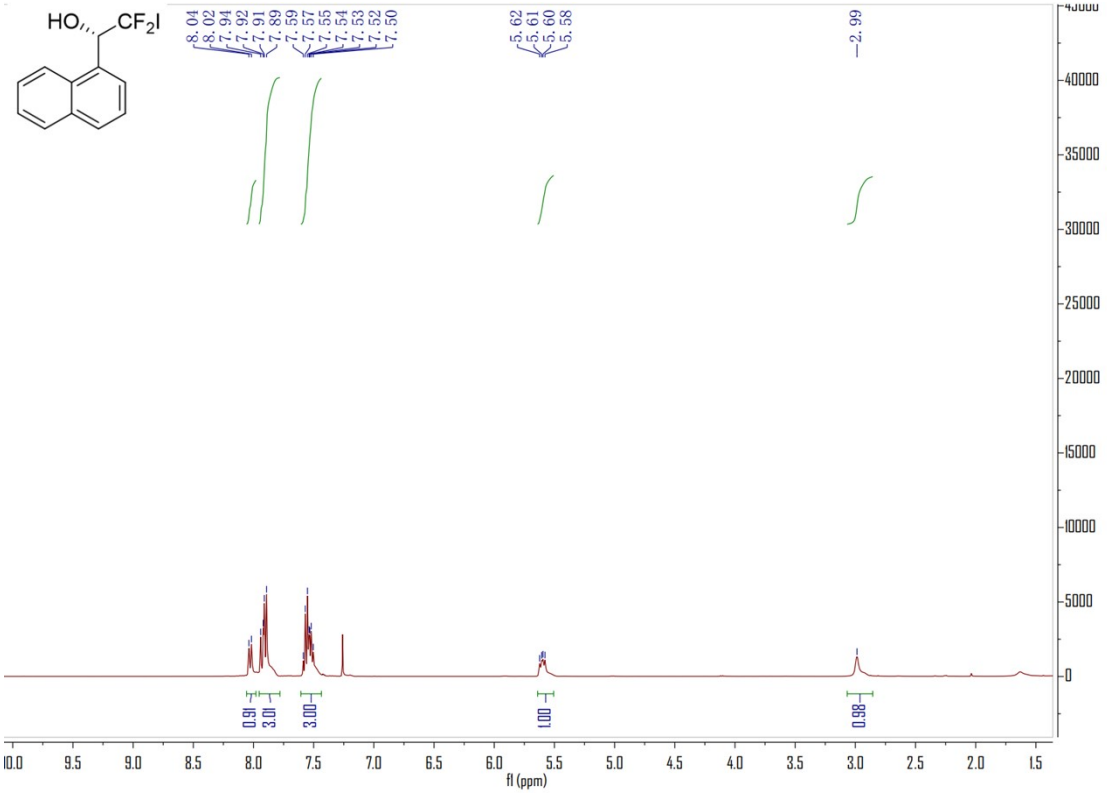

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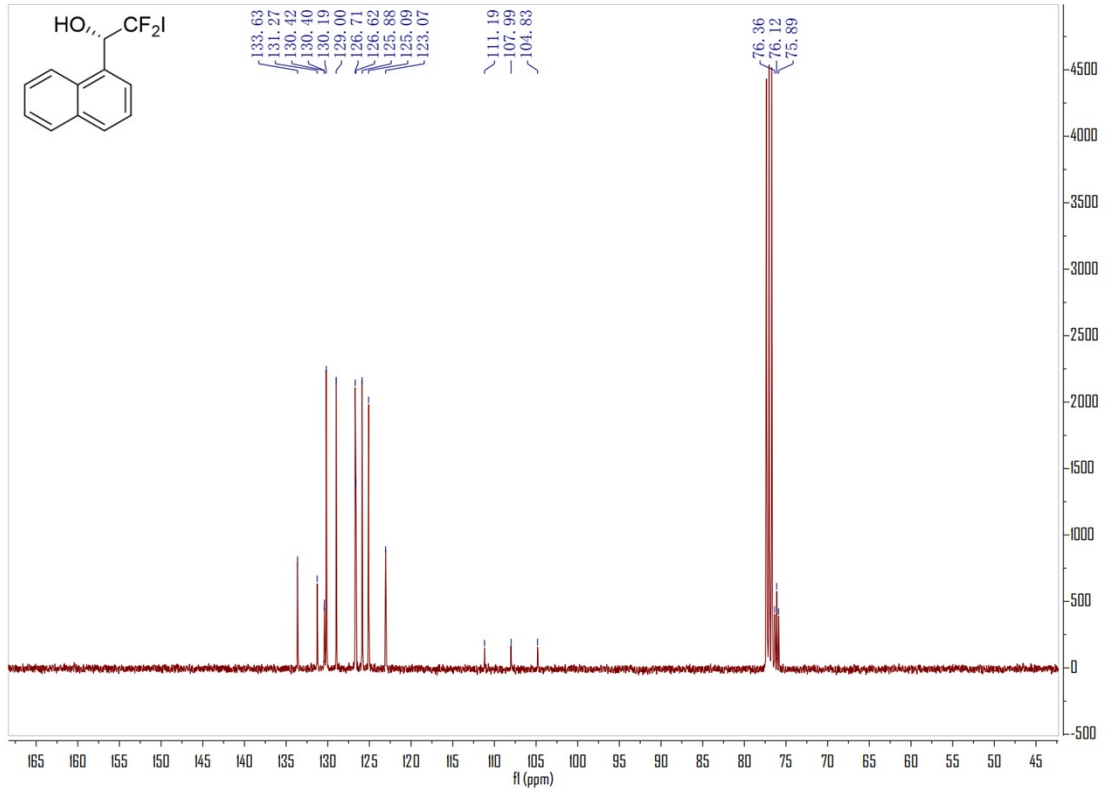

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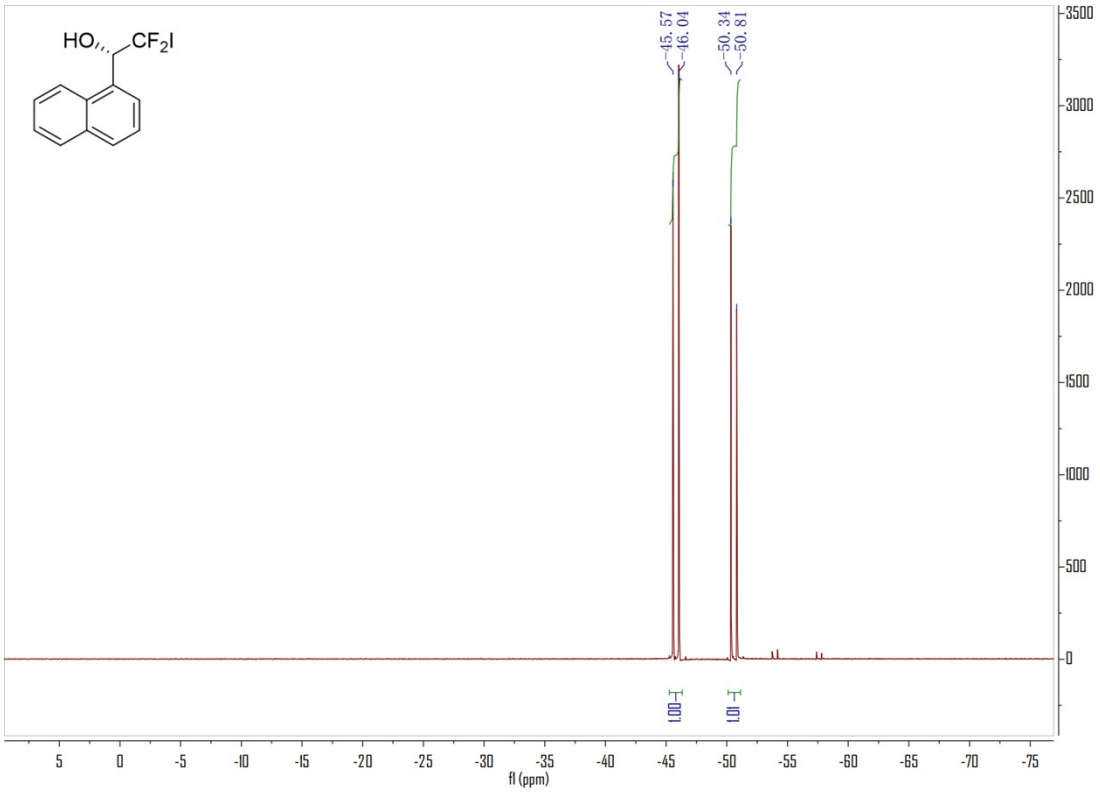

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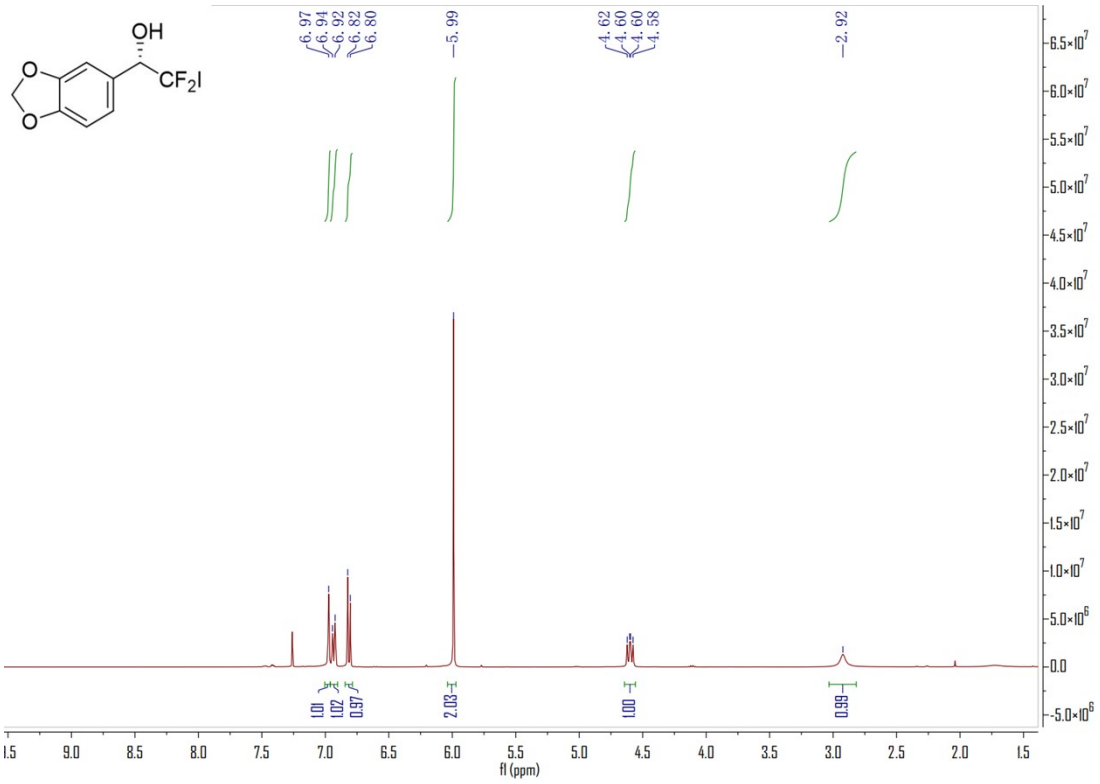

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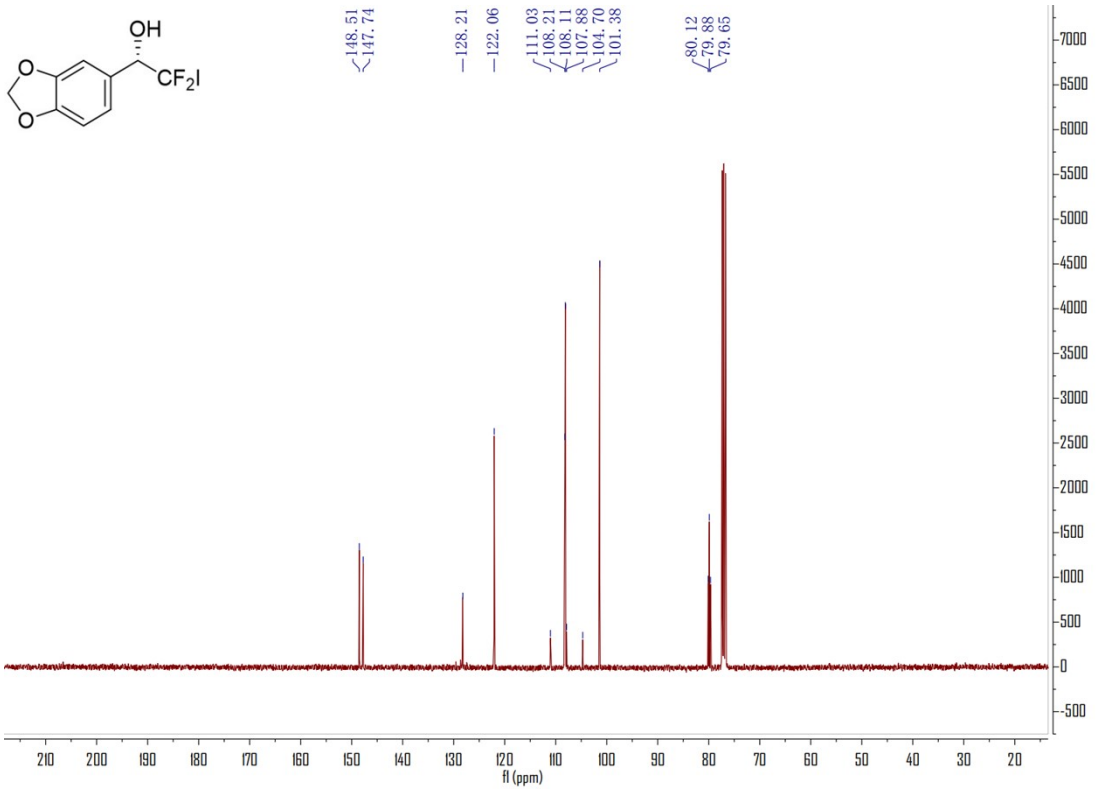

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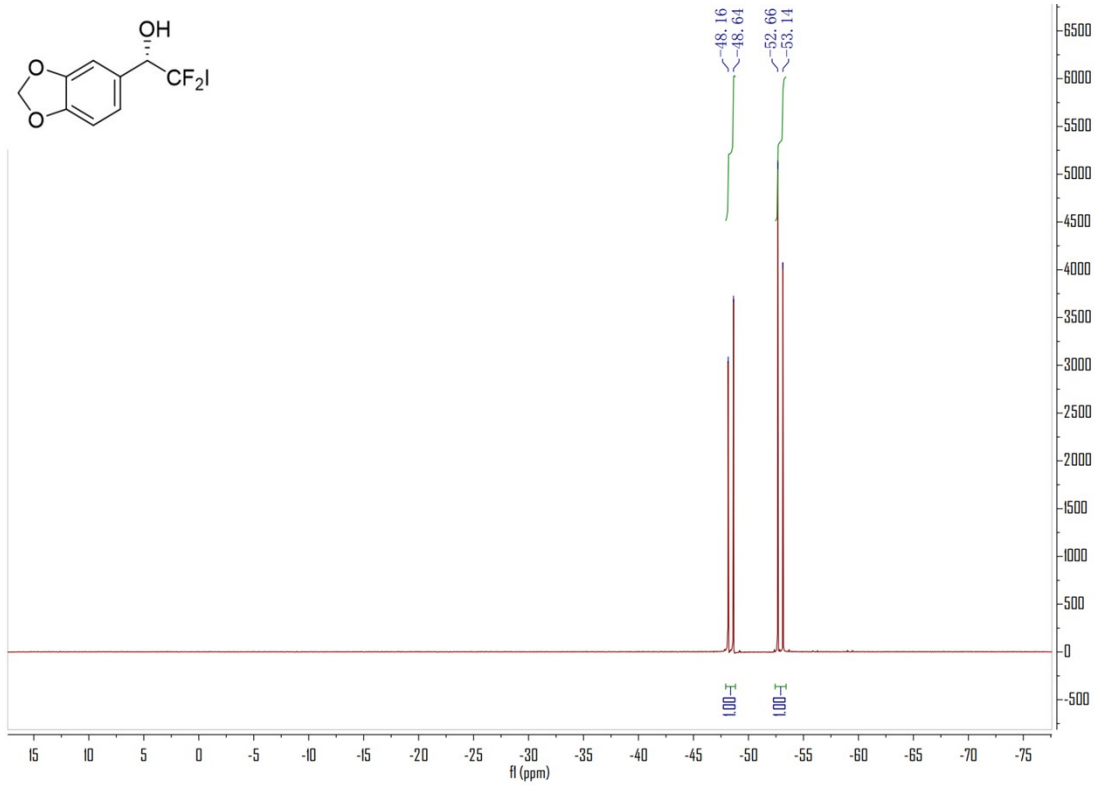
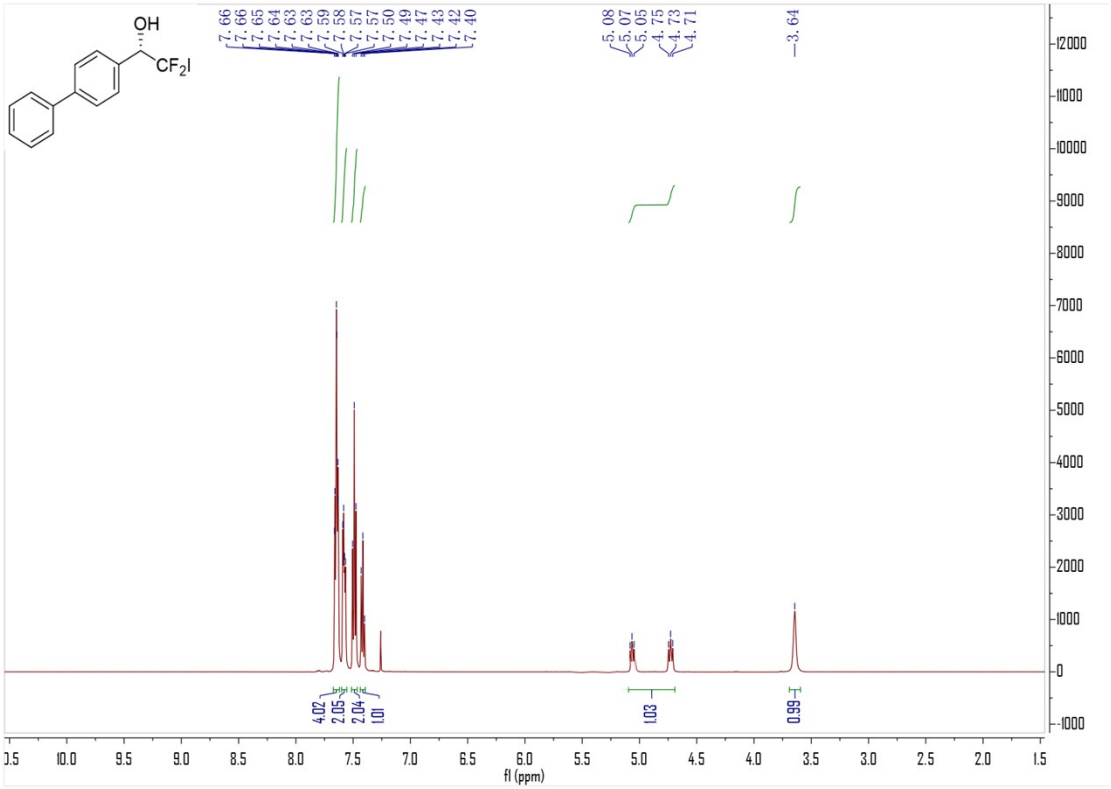
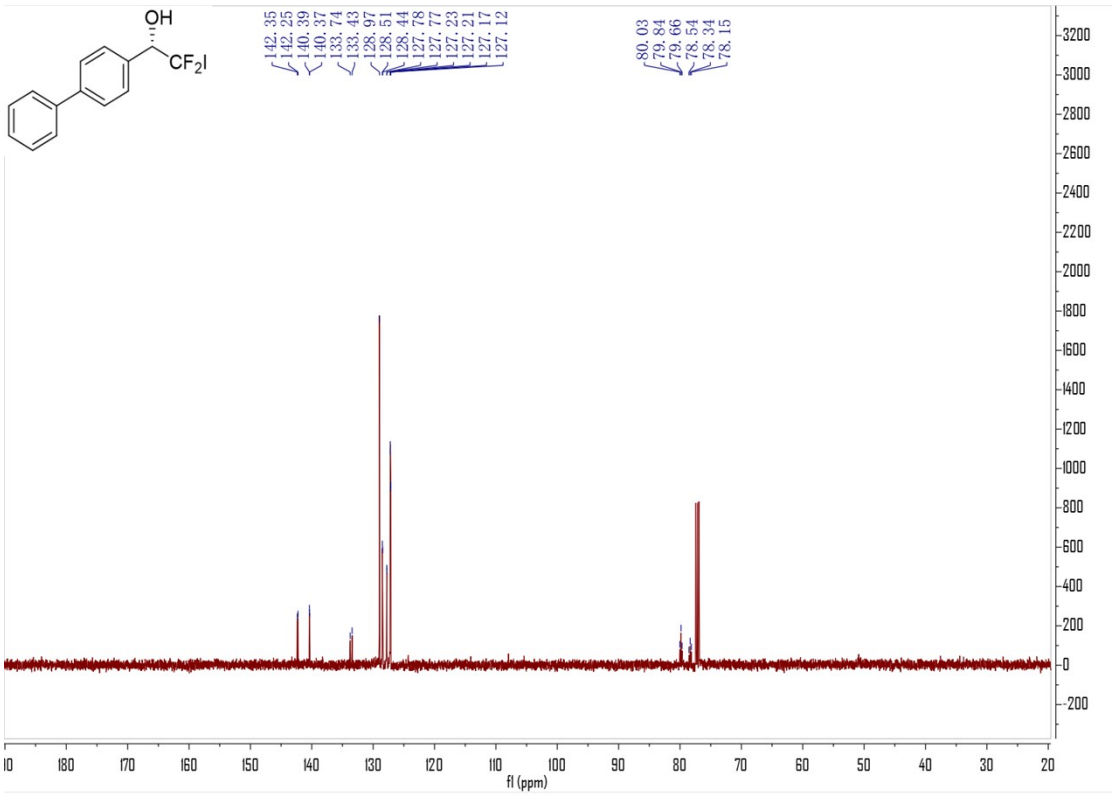


2n ^{1}H NMR



2n ^{13}C NMR



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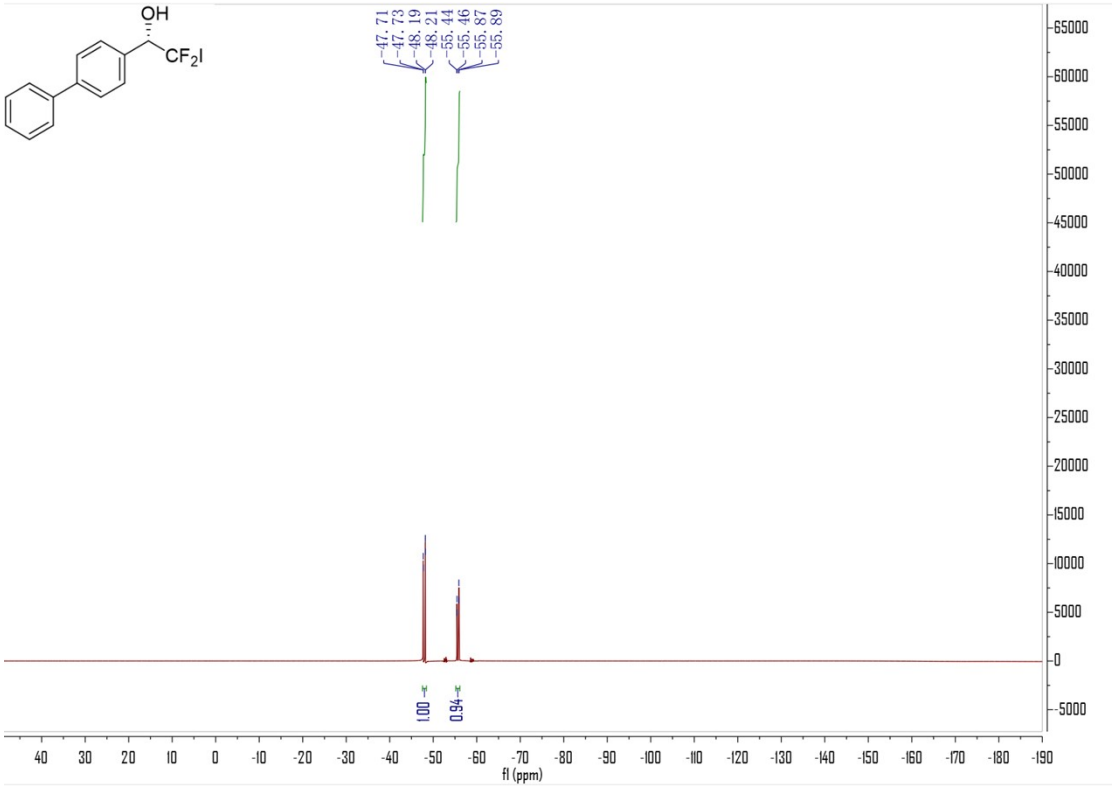

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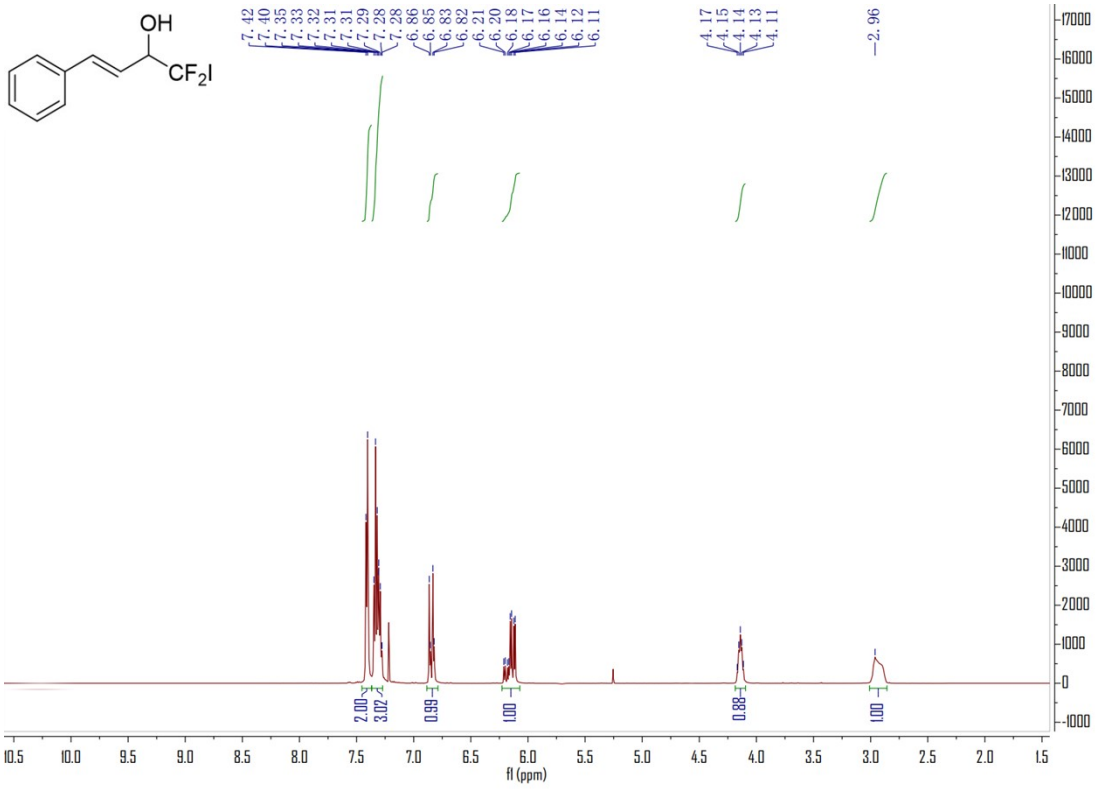

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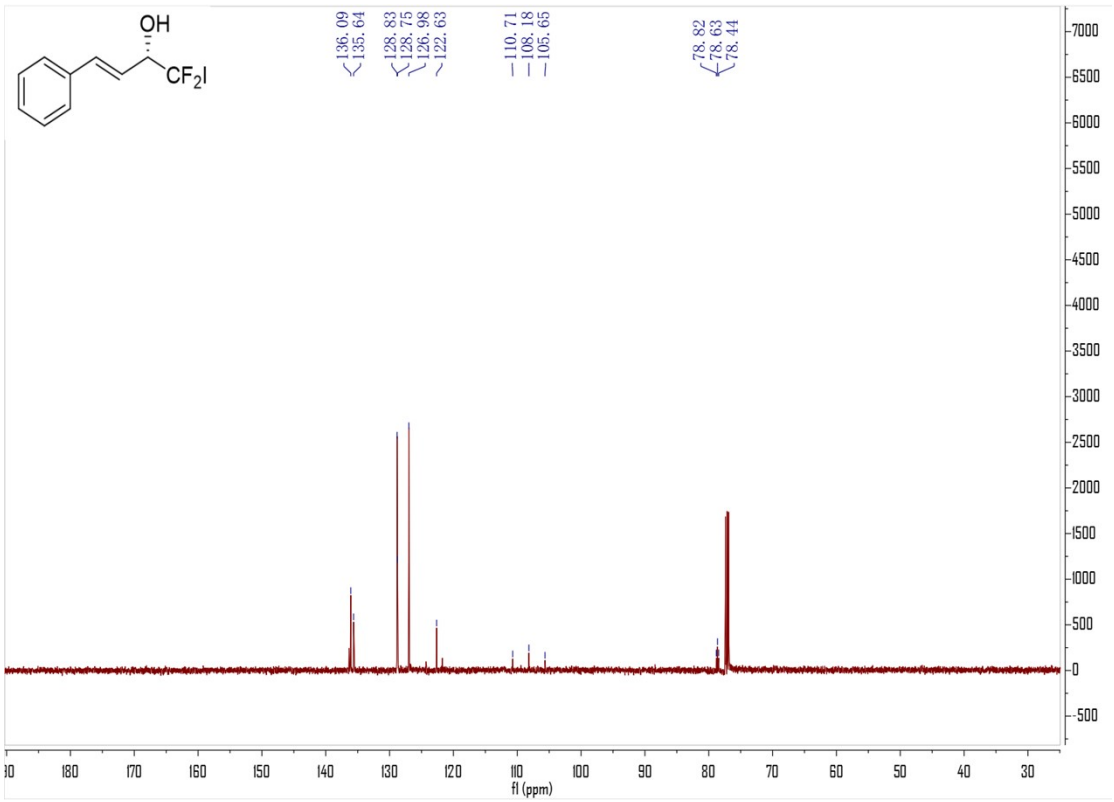

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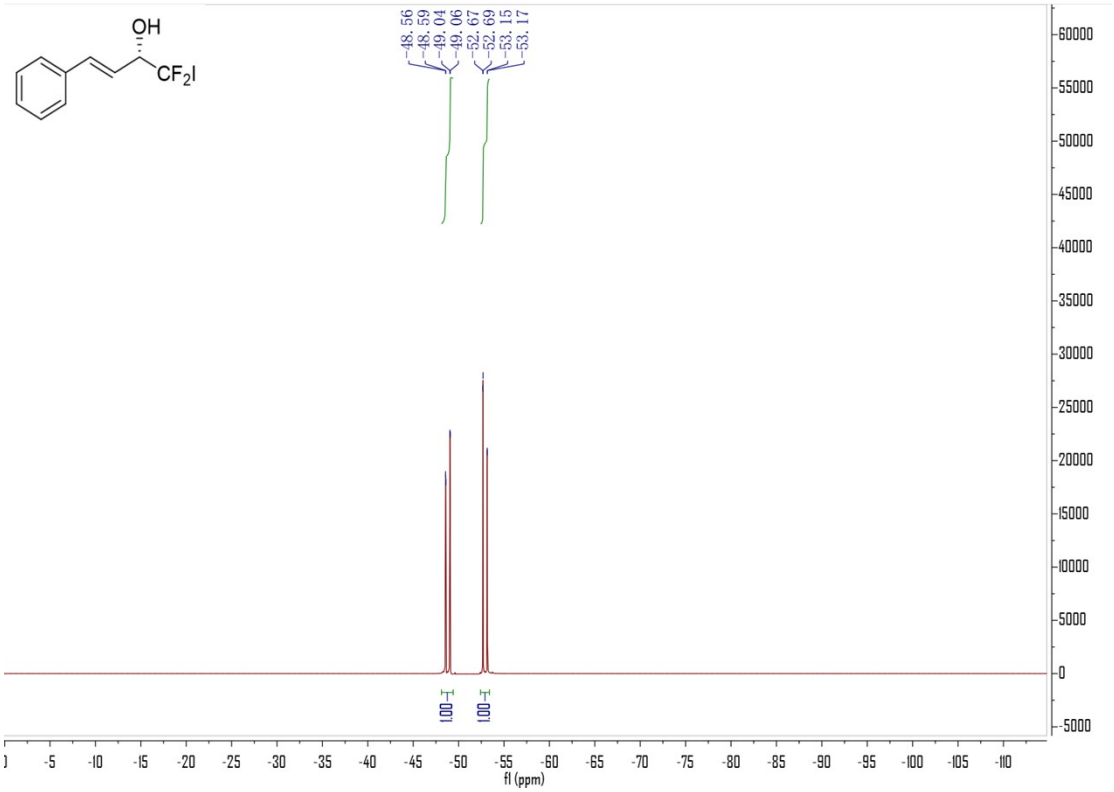

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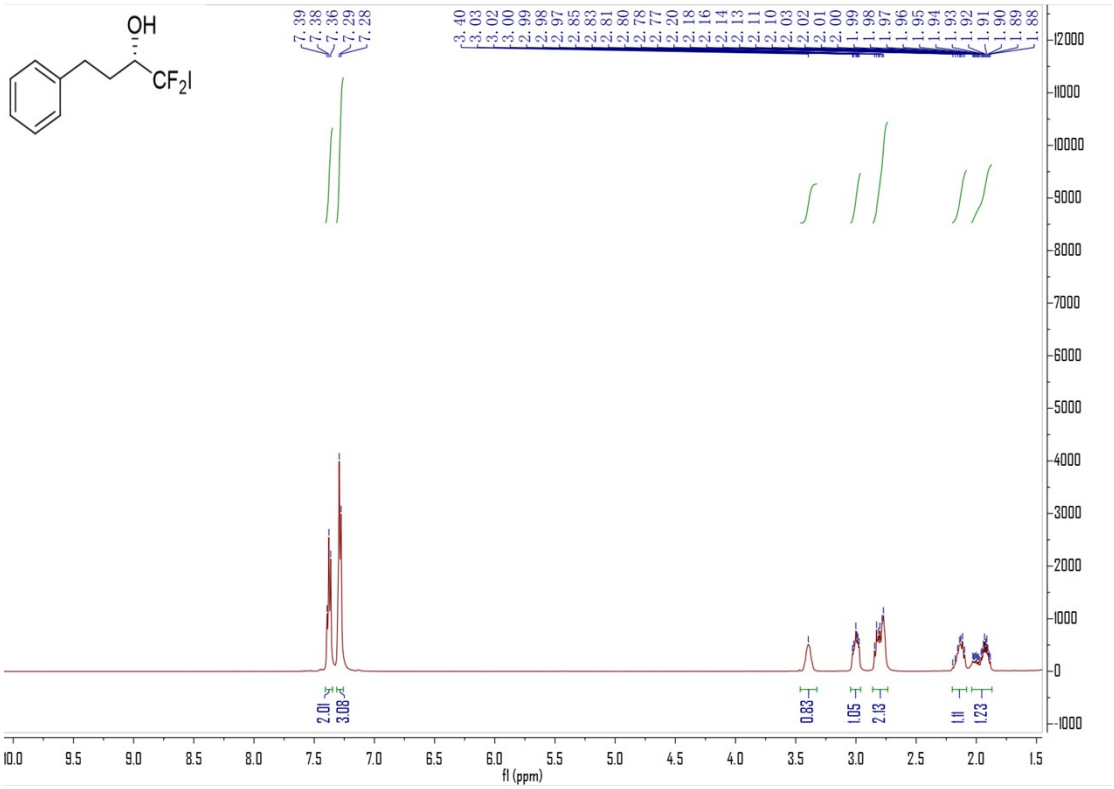
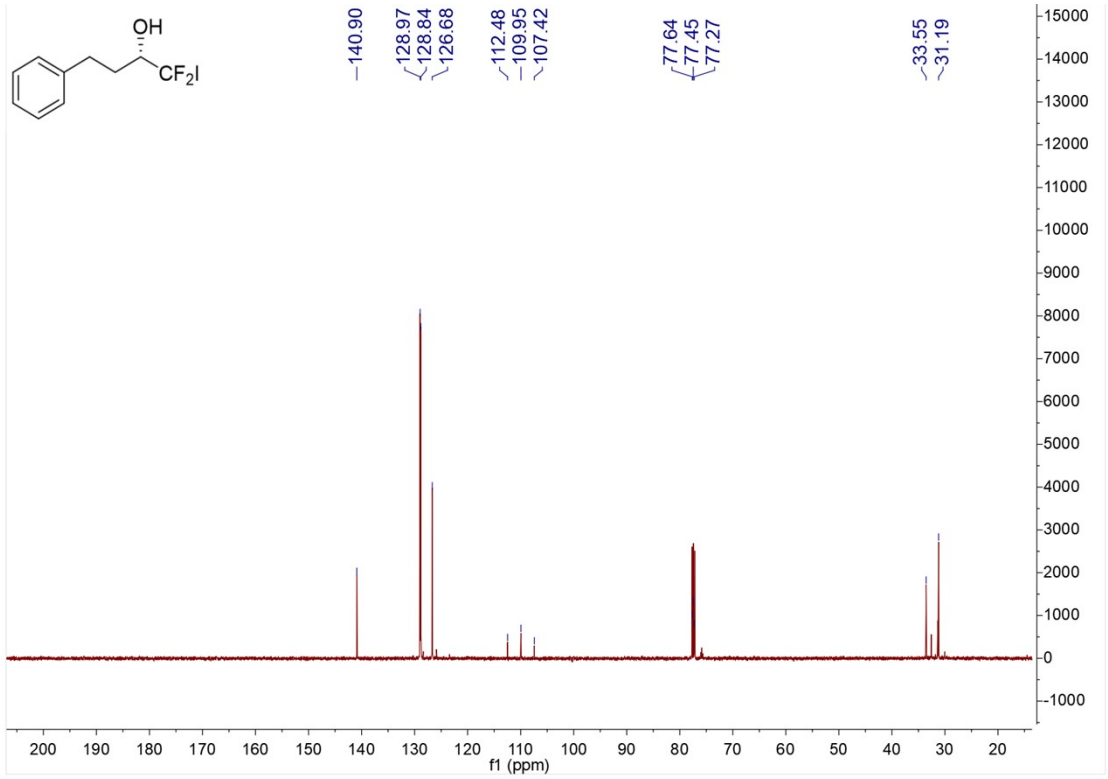


2P ^{13}C NMR



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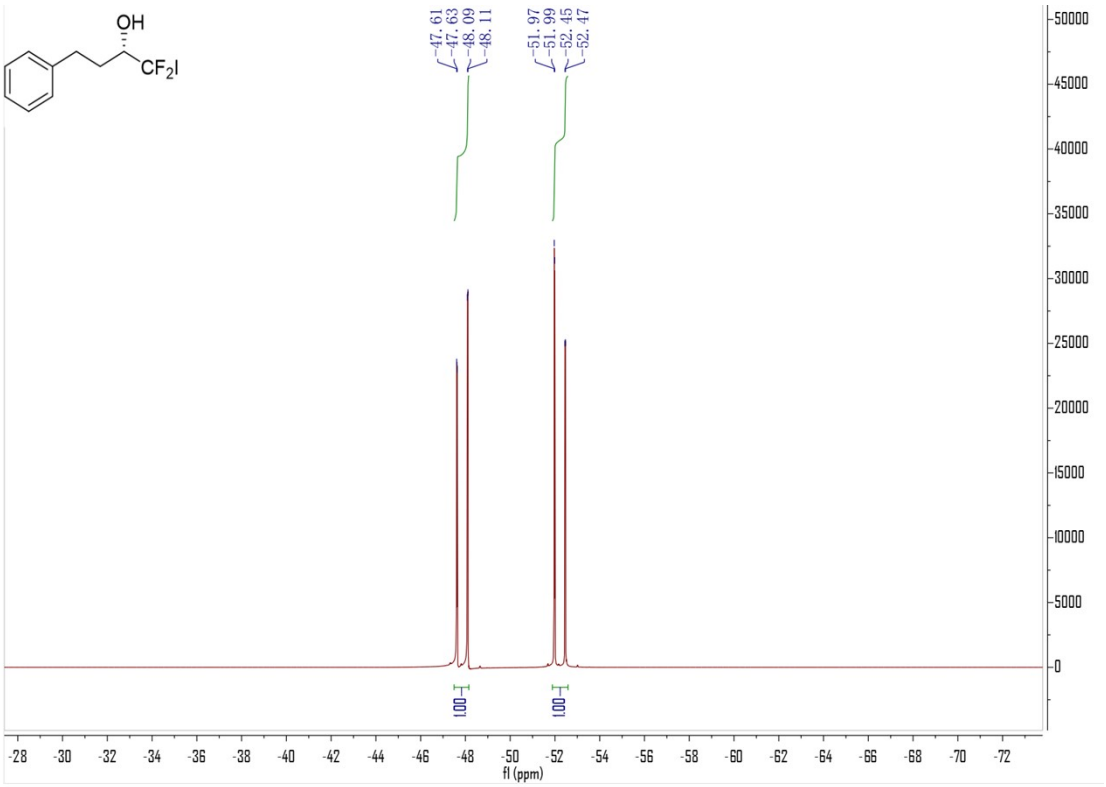

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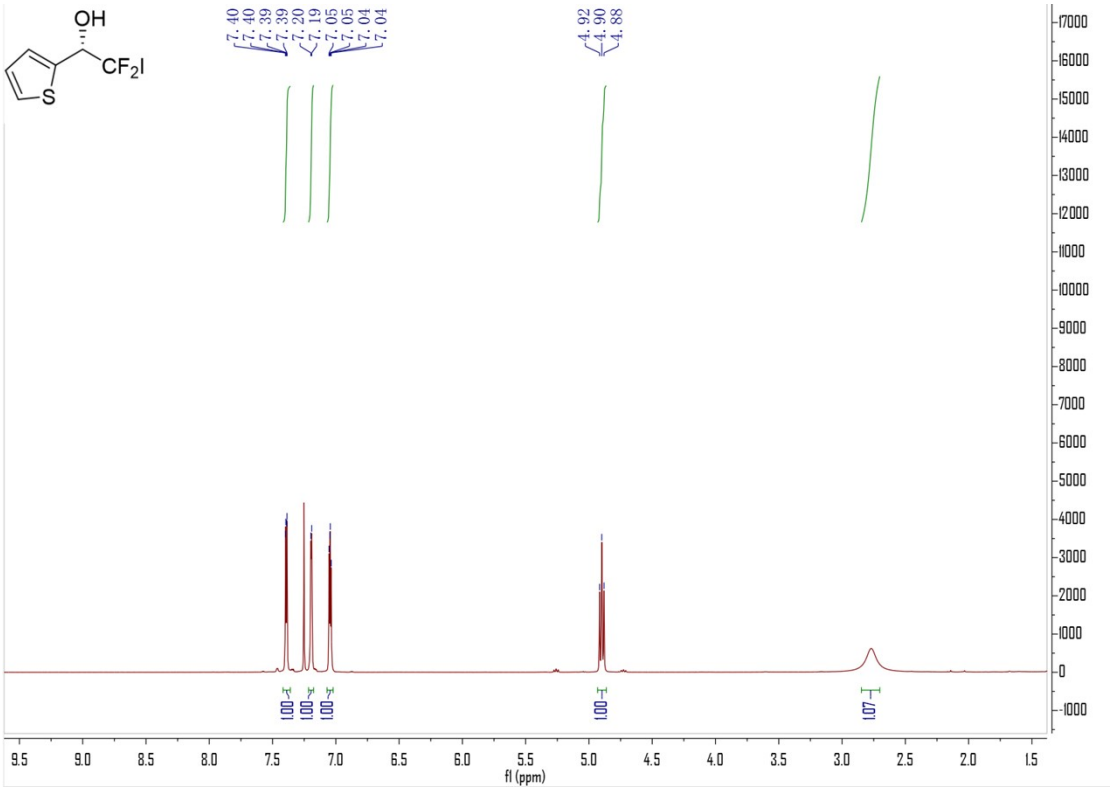

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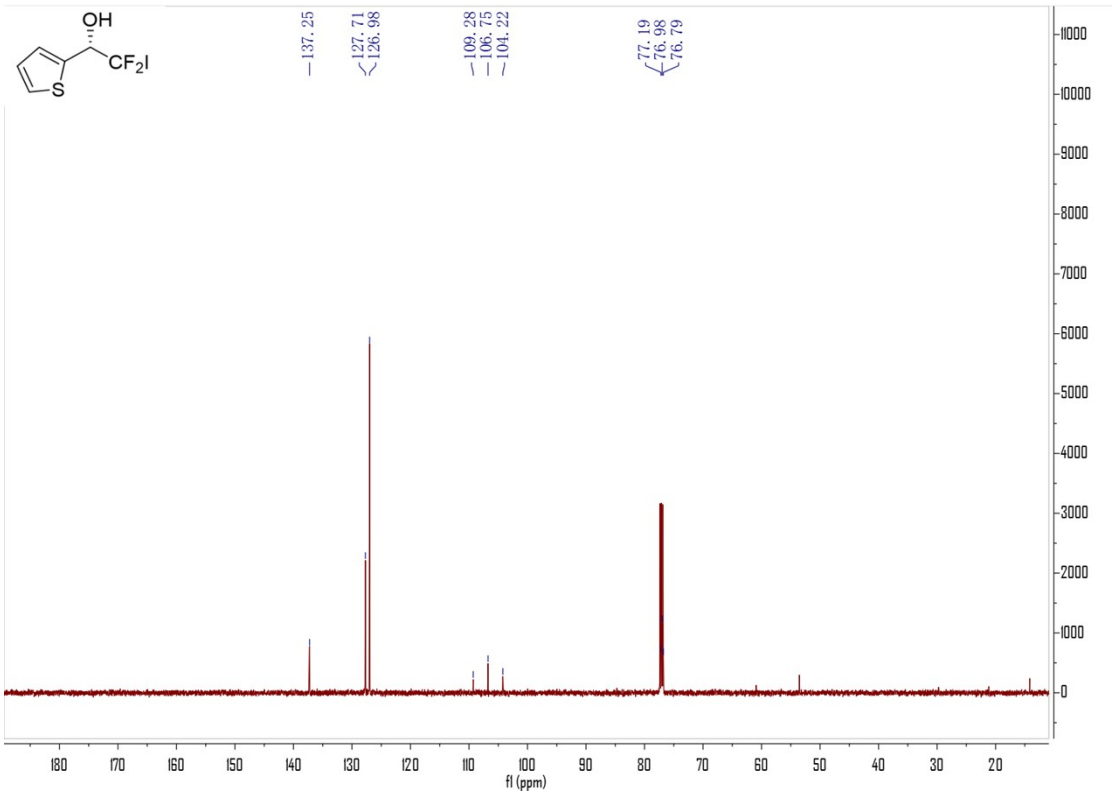

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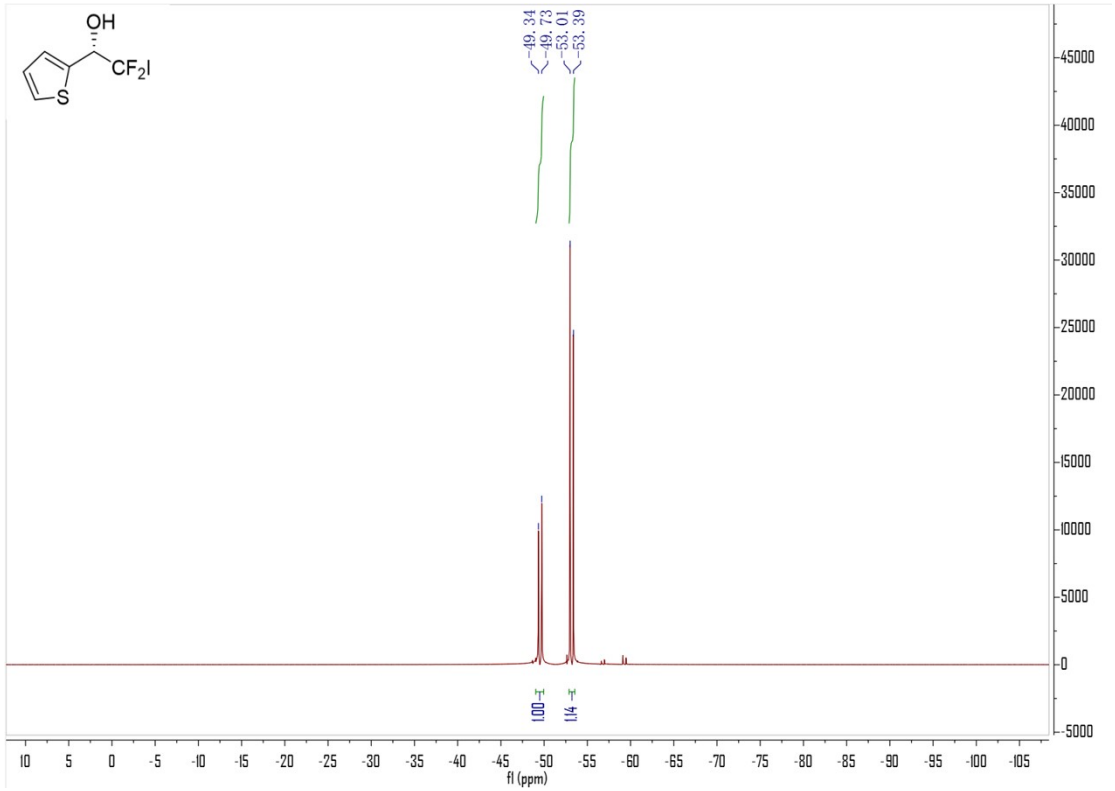

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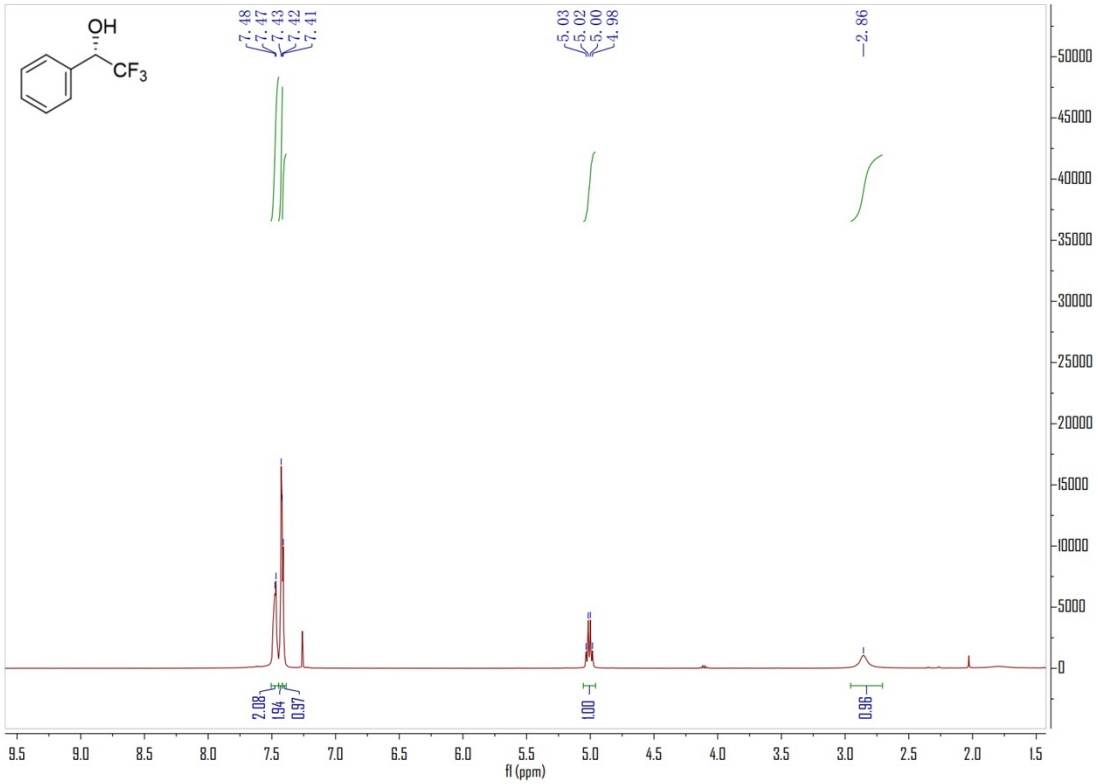

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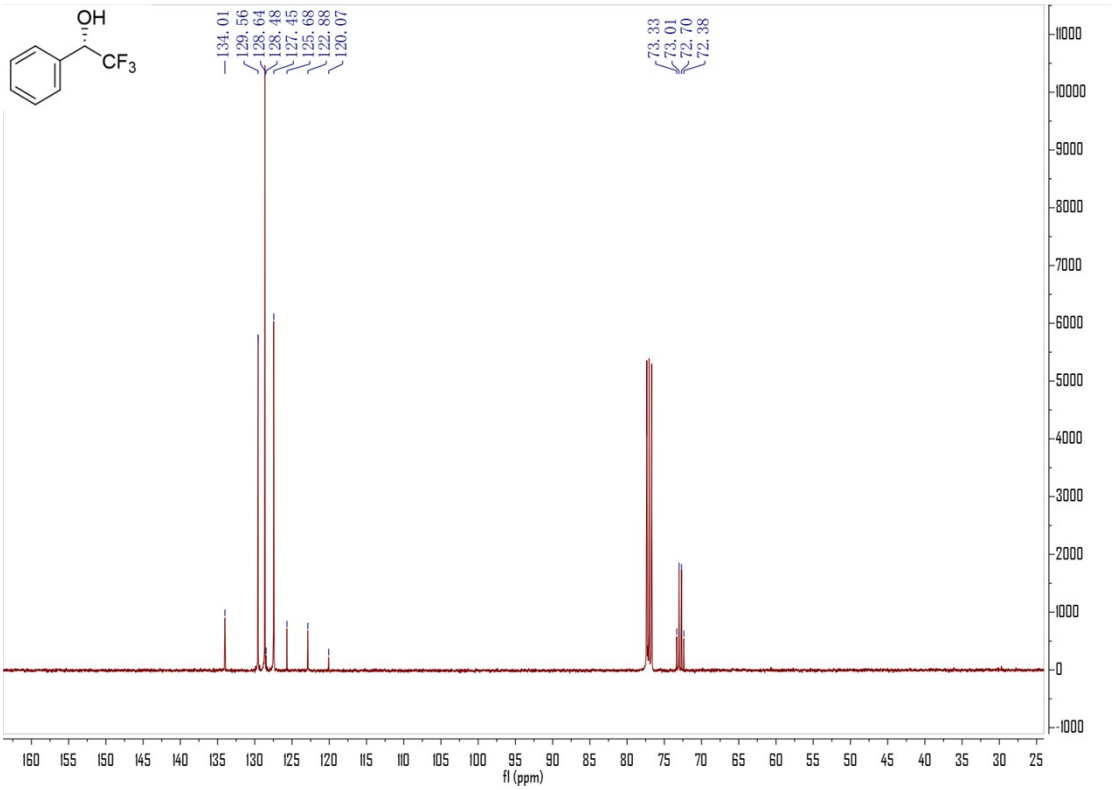

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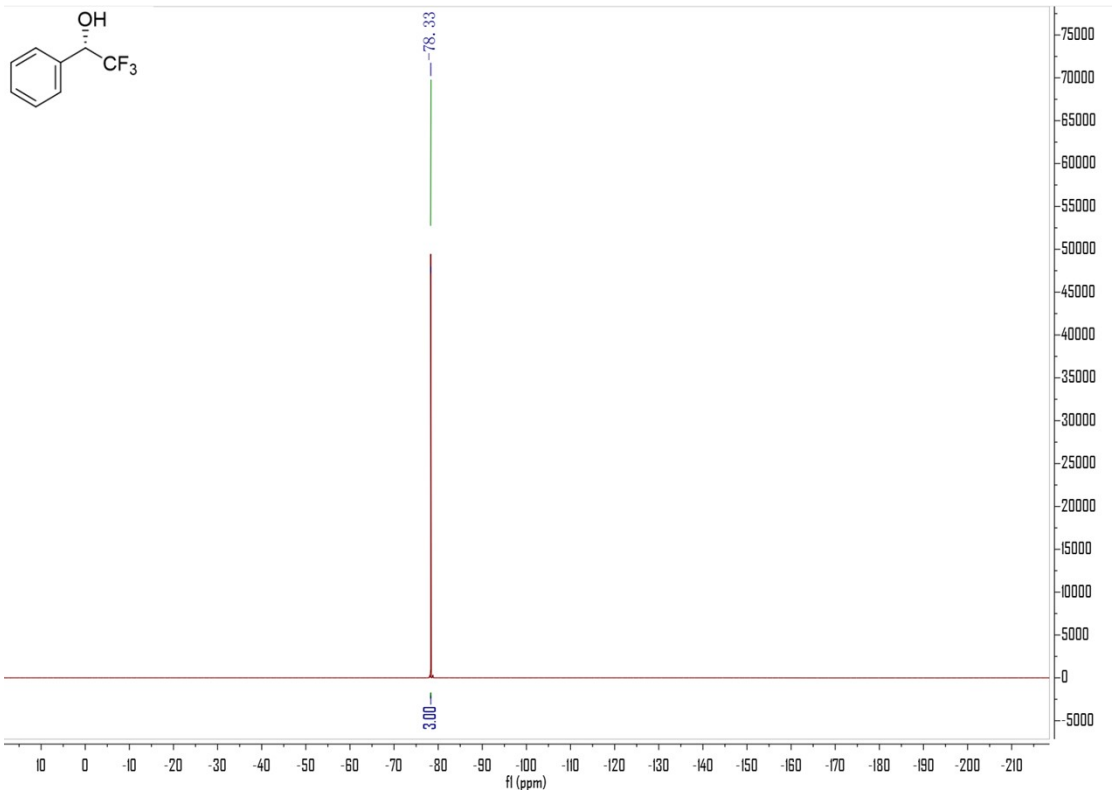
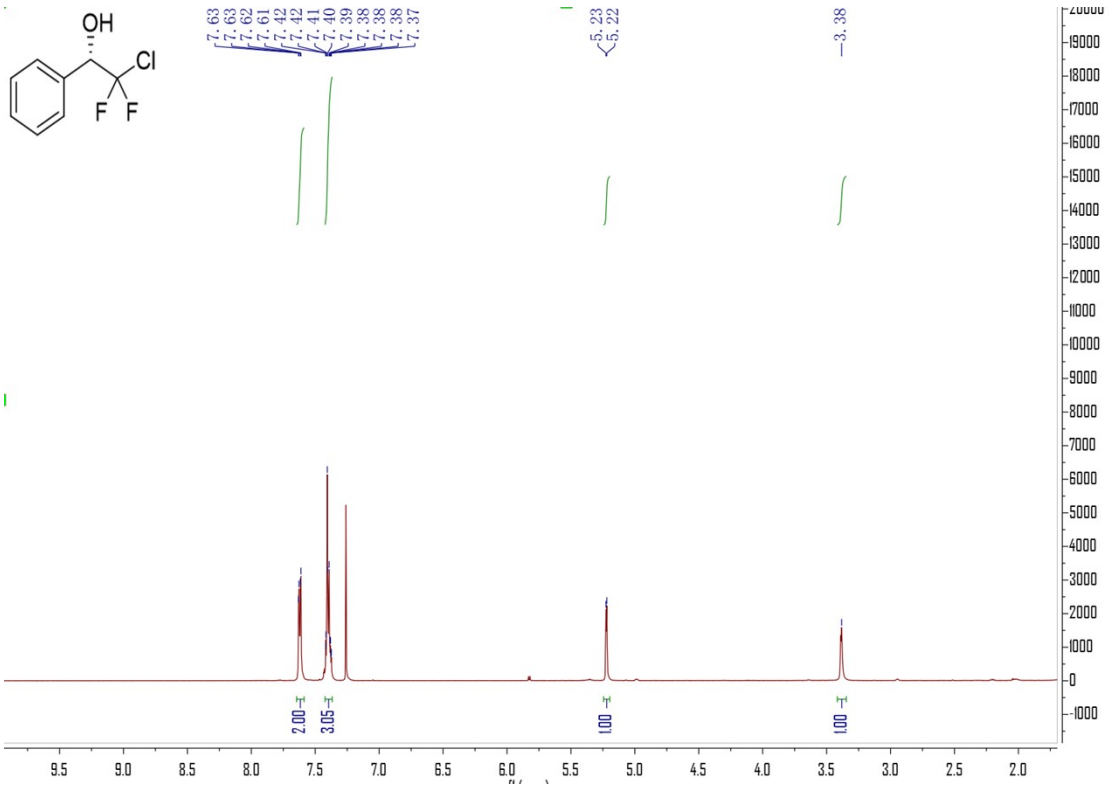


2s ^{1}H NMR



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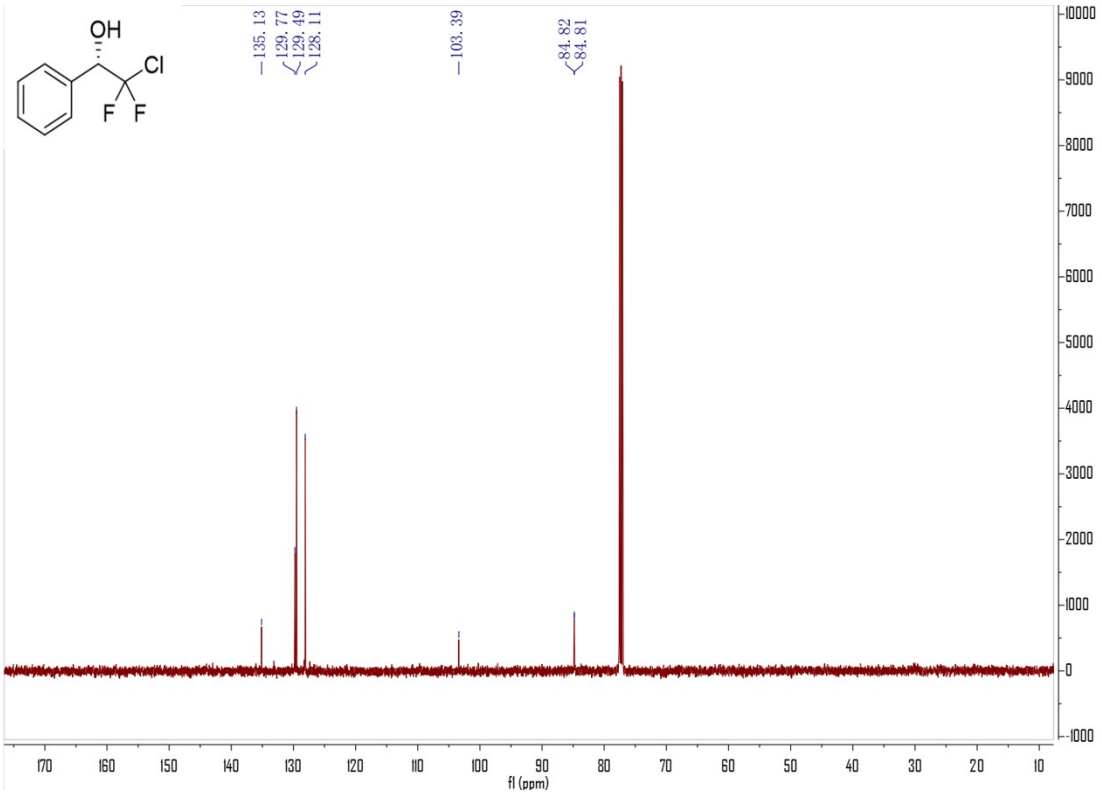

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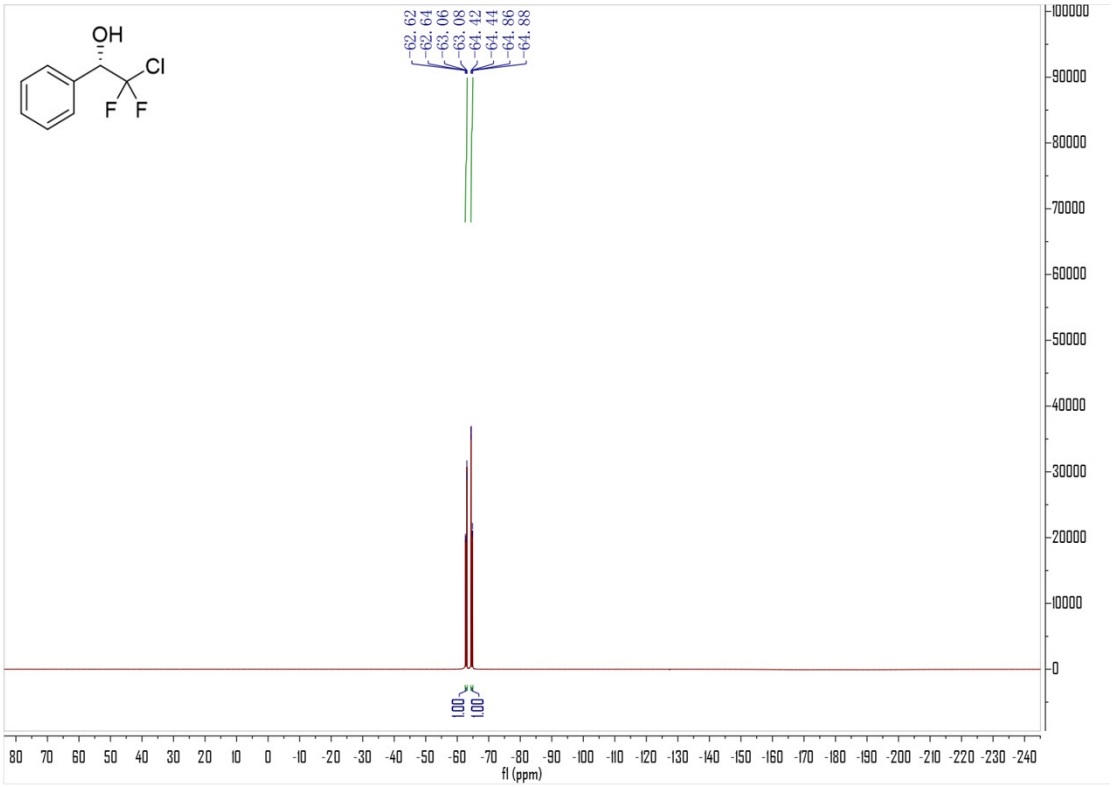
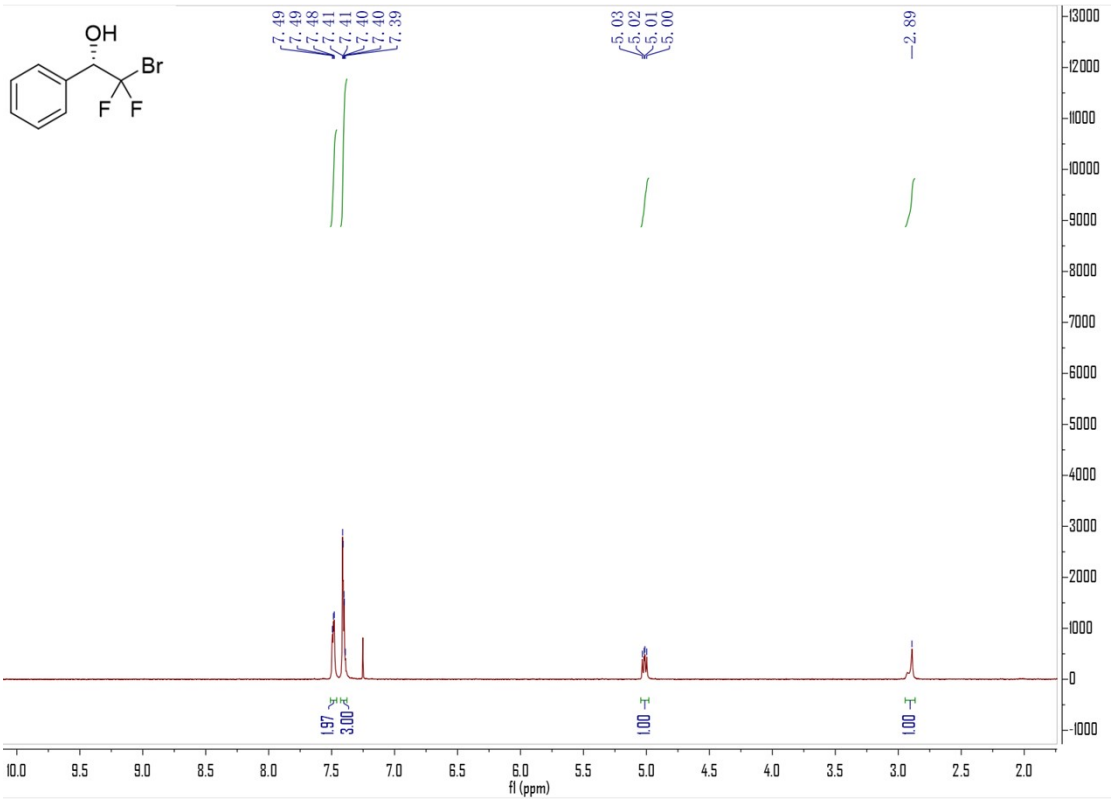


2t ^{1}H NMR



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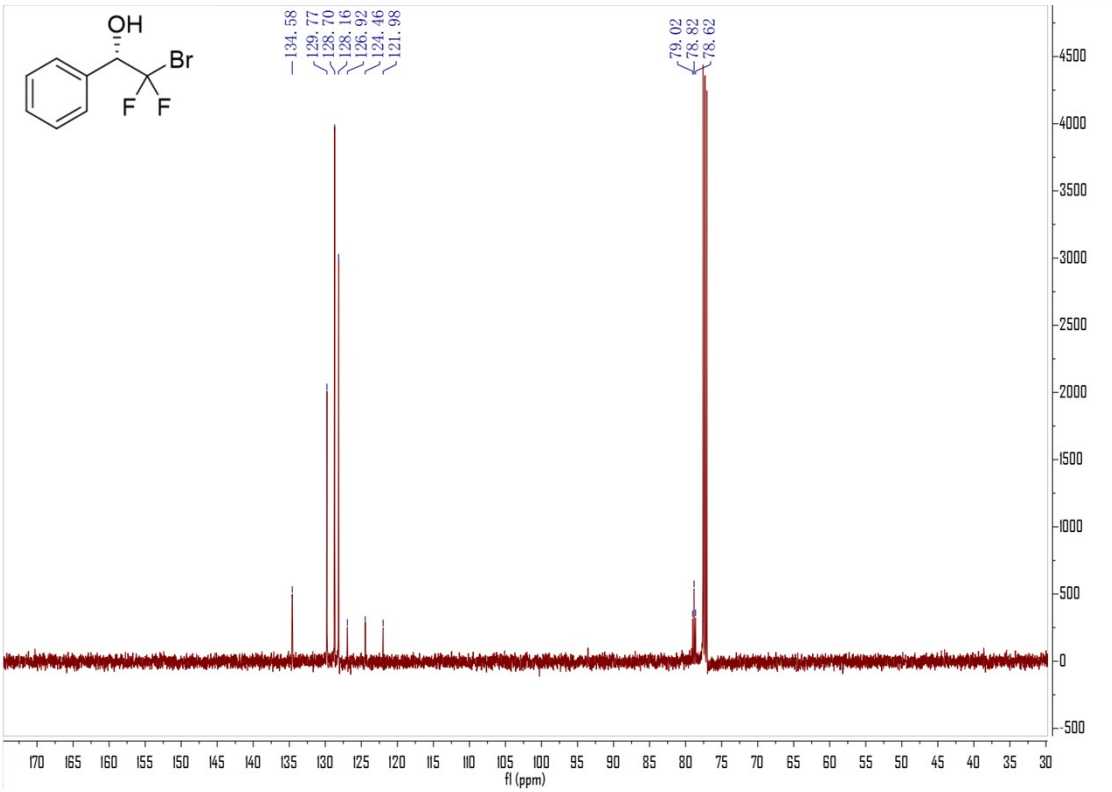

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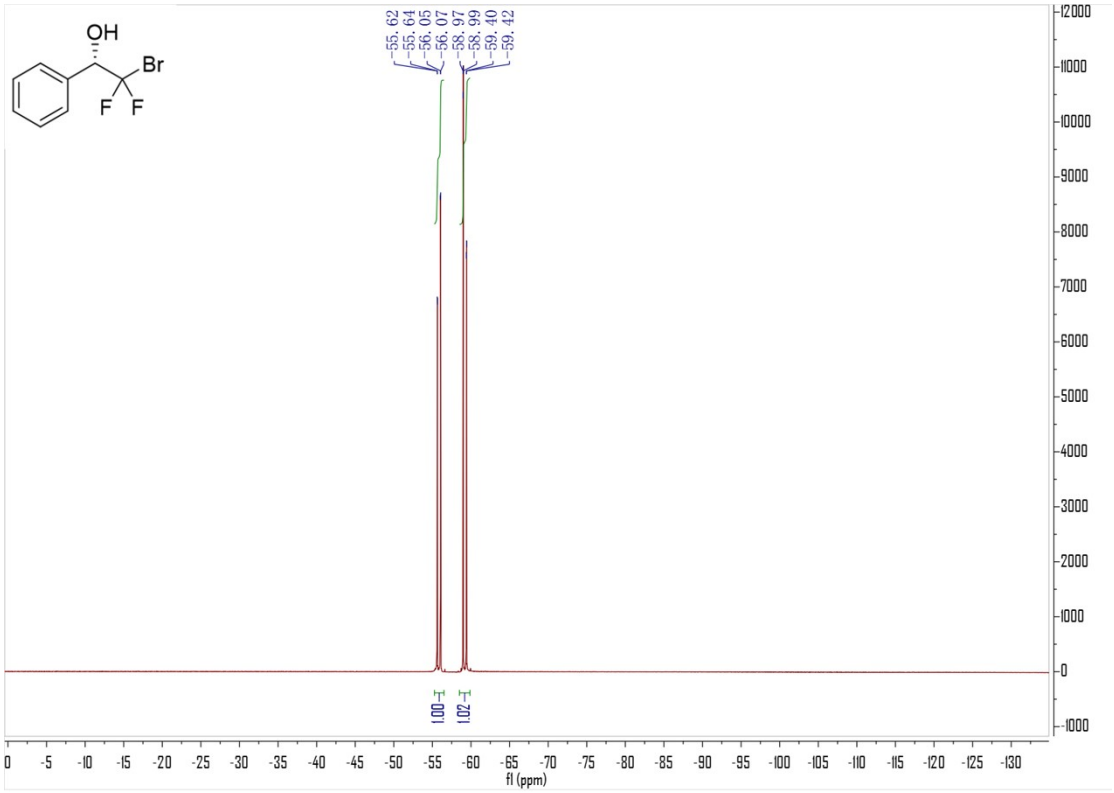
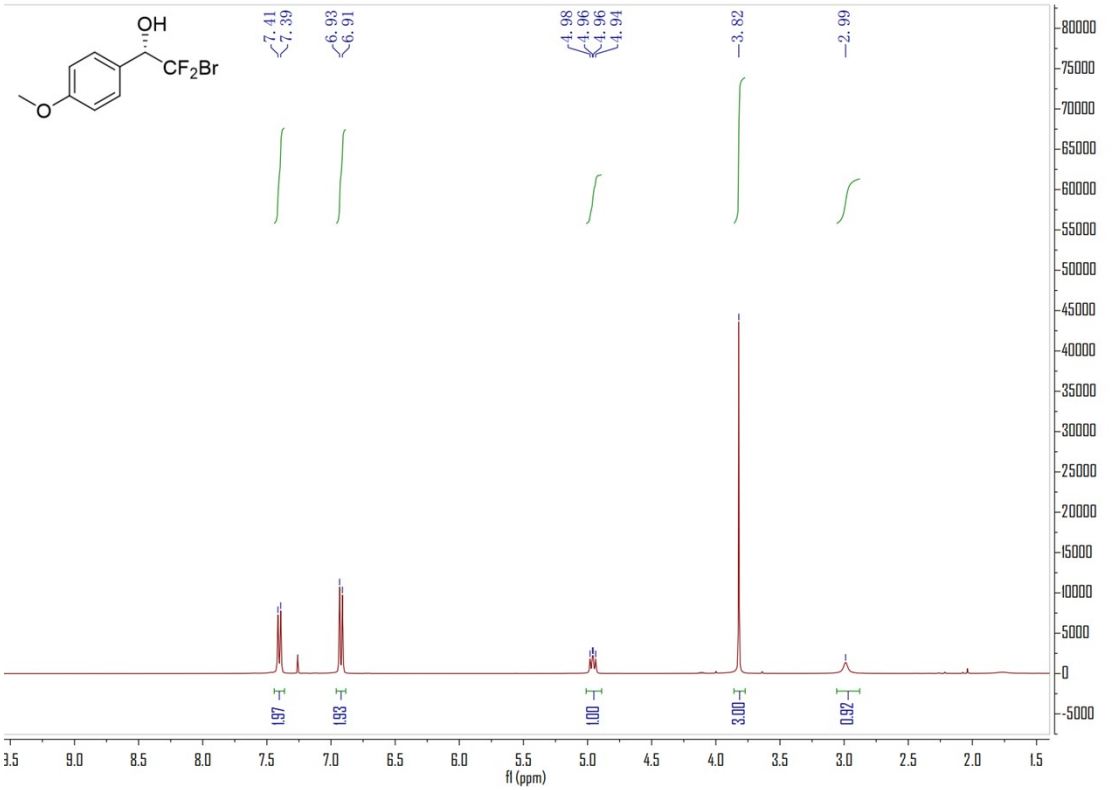
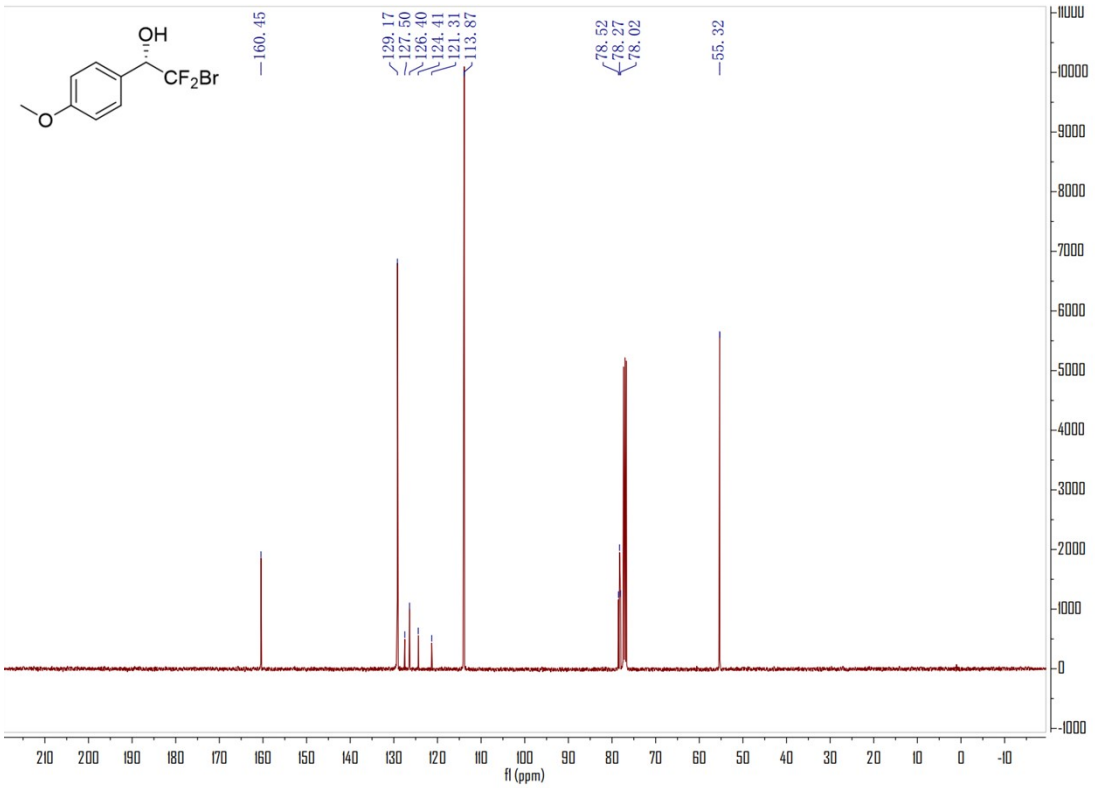


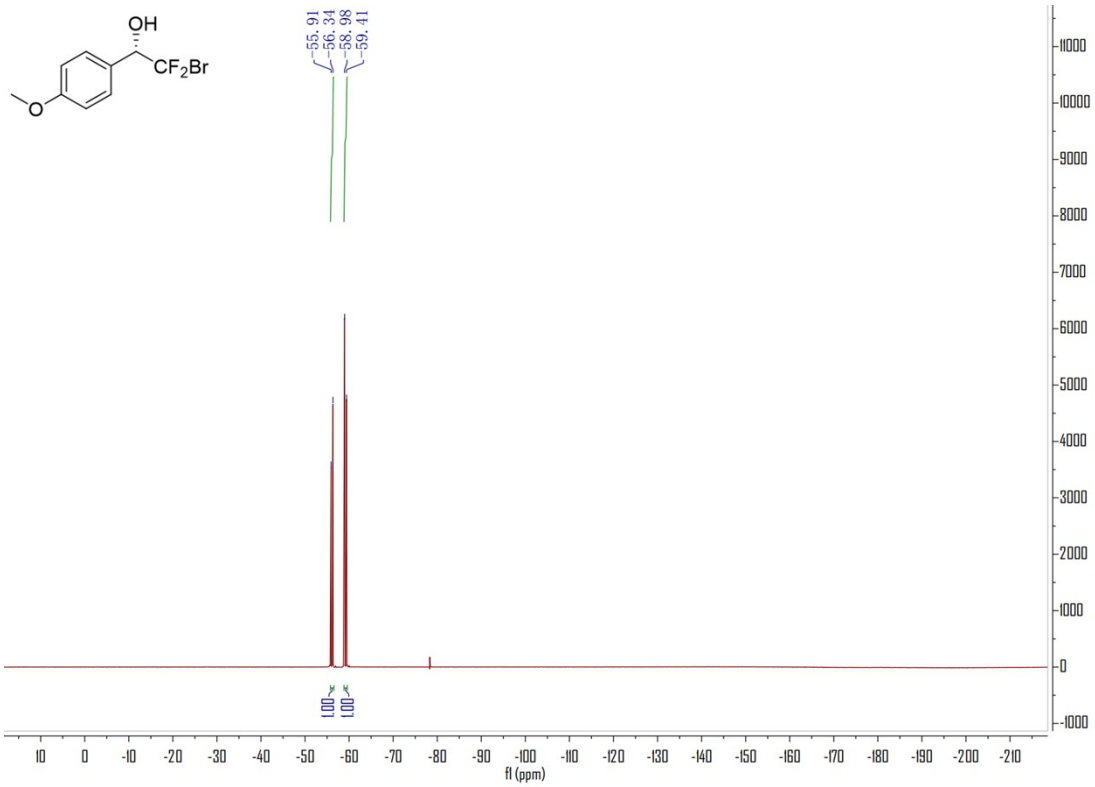
2u ^{1}H NMR



2u ^{13}C NMR


OH
CF2Br
O
160.45
129.17
127.50
126.40
124.41
121.31
113.87
78.52
78.27
78.02
55.32
f1 (ppm)

2u ^{19}F NMR


OH
CF2Br
O
-55.91
-56.34
-58.98
-59.41
1.00
1.00
f1 (ppm)