Electronic Supplementary Information

Enantiocomplementary Synthesis of Vicinal Fluoro Alcohols through Photo-bio Cascade Reactions

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1. Figure S1-S4

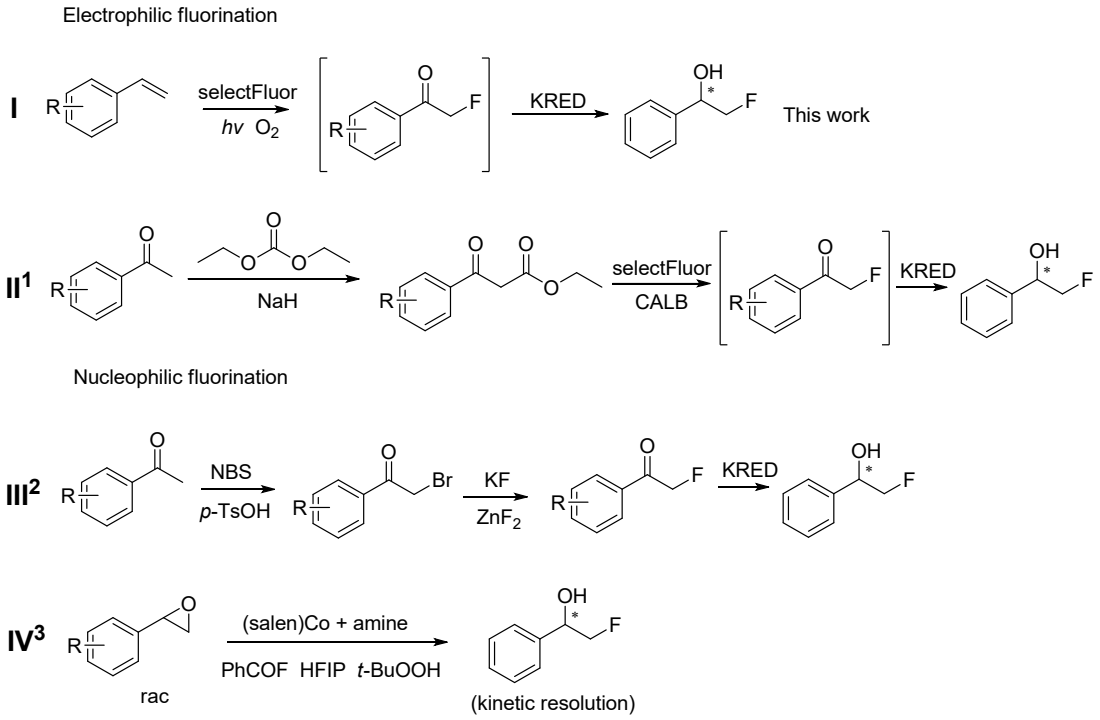


Figure S1 Methods to prepare chiral vicinal fluoro alcohols [1, 2, 3]

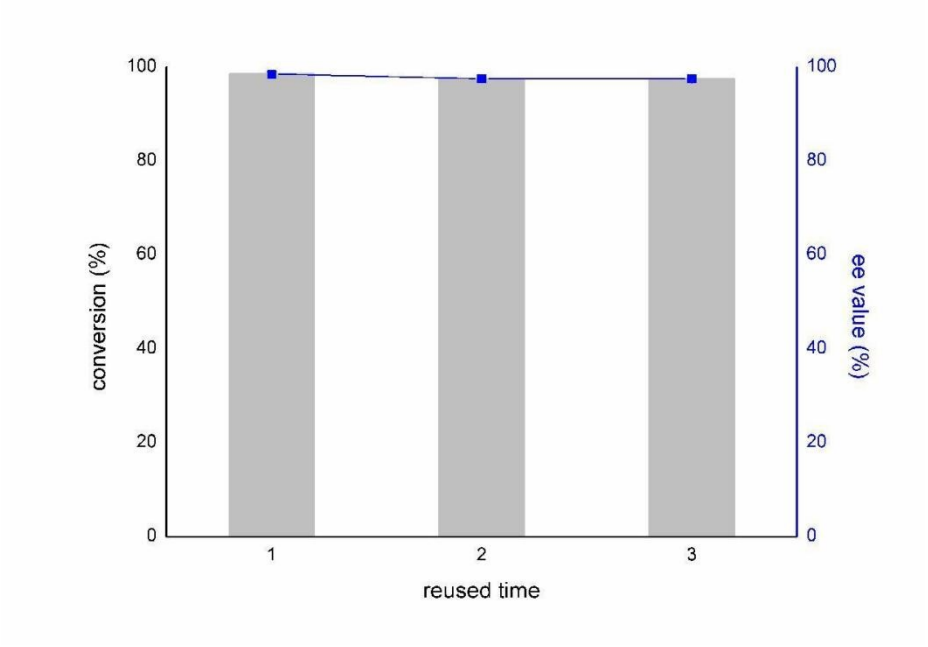


Figure S2 Catalytic activity and selectivity of the reused whole-cell system.

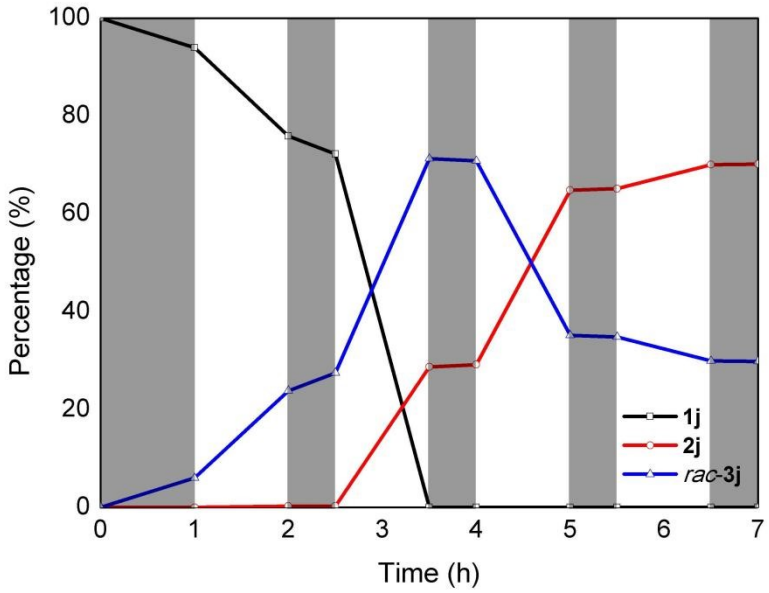


Figure S3 Contents of **1j**, **2j** and *rac*-**3j** during the light off/on experiment for photo-oxidation fluoridation.

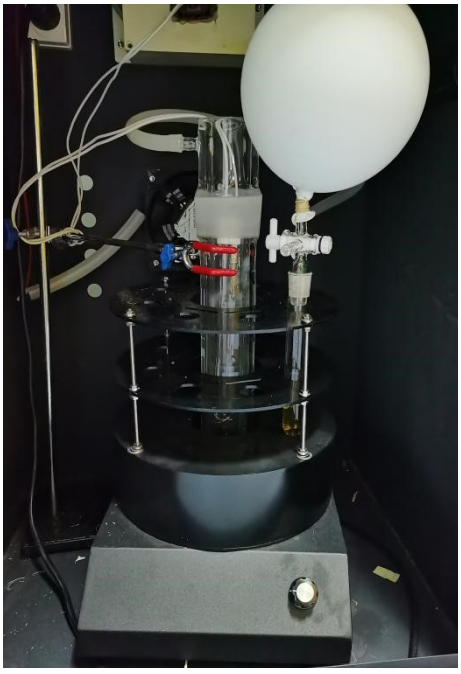


Figure S4 Picture of photochemical reaction apparatus.

2. General Information

All commercially available reagents are of analytical grade, and were purchased from Macklin, Aladdin. Unless otherwise noted, all the purchased reagents were used without further purification. Spectra of ^{1}H and ^{13}C NMR were recorded on a BRUKER 400 MHZ

spectrometer (400 MHz for ^{1}H and 101 MHz for ^{13}C) using TMS as an internal standard in $CDCl_3$. All known products were characterized by comparison of ^{1}H and ^{13}C NMR data with those reported in the literature. High resolution mass spectral analysis (HRMS) was performed on a Waters GCT PremierTM orthogonal acceleration time-of-flight (oa-TOF) mass spectrometry with an EI source. Gas chromatography (GC) was performed on a Shimadzu GC-2010 plus device (Shimadzu, Kyoto Japan) with a flame ionization detector (FID) and an Agilent CP-chirasil-Dex CB column (dimensions 30 m × 0.25 mm × 0.25 μm), carrier gas: Nitrogen, injection temperature 250 ˚C; detector temperature 310 ˚C. High performance liquid chromatography (HPLC) was performed on a Thermo U3000 device, equipped with a UV/Vis Detector (DAD-3000RS) and a Chiralpak OD-H column(250 mm × 4.6 mm, n-hexane/2-propanol as the mobile phase). The photosource was 100 W metal halide lamp with effective photon flux of 90 lm/W.

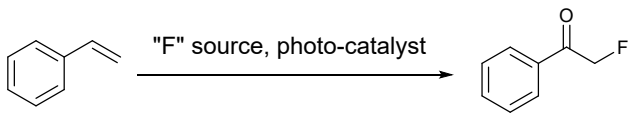
3. Experiments

2.1 Preparation of ketoreductase *Ras*ADH and KtCR

Glycerol stock of E. *coli* BL21 (DE3) harboring *Ras*ADH or KtCR expression plasmids was first incubated in 5 mL LB medium (1% tryptone, 0.5% yeast extract, 1% NaCl) with Kanamycin (50 μg/mL), shaking at a 37˚C incubator overnight. The precultures were used as the inoculum for a 500 mL culture in fresh LB medium with 50 μg/mL Kanamycin. The cultures were shaken at a 37˚C incubator until OD600 at 0.6 and cooled at 4˚C for 30 min, isopropyl β-thiogalactopyranoside (IPTG) was added to a final concentration of 0.5 mM to induce expression. Cultivation was continued at 25˚C and 200 rpm for 12 h.

Cell were harvested by centrifugation at 4000 rpm for 10 min, and the pellet was resuspended in 50 mL 100 mM PBS buffer at pH 6.5 for further whole cell reaction.

2.2 Reaction optimization for fluoridation and photo-oxidation



1a **2a**

0.2 mmol styrene (**1a**) was dissolved in 200 μL CH_3CN, and added in 800 μL solution of "F" source (0.22 mmol, Selectfluor or $EtN_3 \cdot 3HF$ solved in water, or NFSI solved in CH_3CN), and photo catalyst (0.02 mmol, SAS, $lr(ppy)_3$, $Ru(bpy)_3Cl_2$ or Riboflavin). The concentration of **1a** was 200 mM. With air blowing and magnetic stirring, the reaction was taken under the irradiation at room temperature. After 12h, the reaction was quenched by removing the irradiation. The solution was extracted with ethyl acetate for three times, and the yield was then determined by GC.

2.3 General procedure for the optimized fluoridation and photo-oxidation

1.0 mmol styrene (**1a**) was dissolved in 1mL CH_3CN, and added in 4 mL solution of Selectfluor (1.1 mmol) and SAS (0.1 mmol). The concentration of **1a** was 200 mM. With air blowing and magnetic stirring, the reaction was taken under the irradiation of at room temperature. After 12 h, the reaction was quenched by removing the irradiation. The reaction was monitored by TLC and GC. And the yield was then determined by GC.

2.4 Controlling experiments for the photo-oxidation fluoridation process

"F" source, photo catalyst and light irradiation were considered as the necessary factors for the photo-oxidation fluoridation process. The corresponding control experiments were done to prove it.

2.4.1 None light.

0.2 mmol styrene (**1a**) was dissolved in 200 μL CH_3CN, and added in 800 μL solution of Selectfluor (0.22 mmol) and SAS (0.02 mmol). With air blowing and magnetic stirring, the reaction was taken in dark at room temperature. After 12h, the solution was extracted with ethyl acetate for three times, and the yield was then determined by GC. The result was listed in **Table 1**, entry 7.

2.4.2 None photo catalyst

0.2 mmol styrene (**1a**) was dissolved in 200 μL CH_3CN, and added in 800 μL solution of Selectfluor (0.22 mmol). With air blowing and magnetic stirring, the reaction was taken under the irradiation at room temperature. After 12h, the reaction was quenched by removing the irradiation. The solution was extracted with ethyl acetate for three times, and the yield was then determined by GC. The result was listed in **Table 1**, entry 8.

2.4.3 None “F” source

0.2 mmol styrene (**1a**) was dissolved in 200 μL CH_3CN, and added in 800 μL solution of SAS (0.02 mmol). With air blowing and magnetic stirring, the reaction was taken under the irradiation at room temperature. After 12h, the reaction was quenched by removing the irradiation. The solution was extracted with ethyl acetate for three times, and the yield was then determined by GC. The result was listed in **Table 1**, entry 9.

2.5 Light off/on experiment for photo-oxidation fluoridation

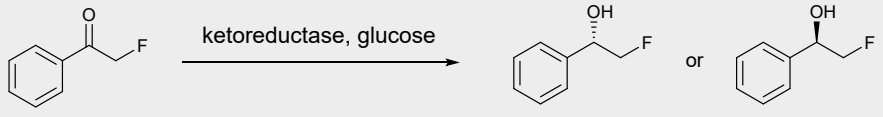
2.0 mmol **1j** was dissolved in 2mL CH_3CN, and added in 8 mL solution of Selectfluor (2.2 mmol) and SAS (0.2 mmol). The concentration of **1j** was 200 mM. With air blowing and magnetic stirring, the reaction was first taken in dark for 1 h, then, a process of 1 h irradiation

period preceded 0.5 h dark period was taken. After each period, the contents of **1j**, **2j** and *rac*-**3j** was monitored (see **figure S3**).

2.6 Reaction optimization for the enzymatic reduction

Whole-cell reaction system was applied for the enzymatic reduction process. 2 mL whole cell culture of ketoreductase (resuspended in 100 mM PBS buffer, pH 6.5) with glucose (100 mM) was mixed with the reaction solution of **2a**, and shaken at a 30°C incubator overnight. Different volume of **2a** reaction solution was screened to optimize the enzyme activity. The resulting solution was extracted with ethyl acetate, and the yield and ee value were then determined by chiral GC and listed in Table **S1**.

Table S1 optimization of material ratio for the enzymatic reduction



2a **(*S*)-3a** **(*R*)-3a**

Entry	ketoreductase	Volume of **2a** reaction solution	GC Yield (%)	Conversion (%)	ee %
1	*Ras*ADH (2 mL)	0.1 mL	73	99	99
2		0.2 mL	81	99	99
3		0.4 mL	95	99	98
4		0.8 mL	50	61	96
5	KtCR (2 mL)	0.1 mL	71	99	99
6		0.2 mL	82	99	99
7		0.4 mL	95	99	99
8		0.8 mL	40	53	94

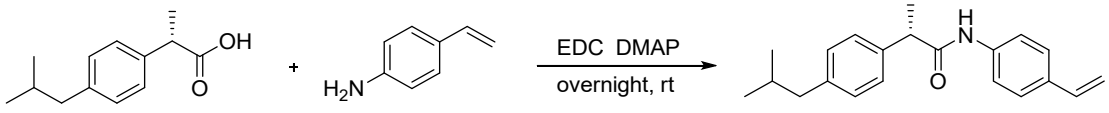
2.7 General procedure for scale-up one-pot reaction

1.0 mmol substrate (styrenes, **1a-1n**) was dissolved in 1mL CH_3CN, and added in 4 mL solution of Selectfluor (1.1 mmol) and SAS (0.1 mmol). With air blowing and magnetic stirring, the reaction was taken under the irradiation of at room temperature. After 8 h, 25 mL whole cell culture of ketoreductase (resuspended in 100 mM PBS buffer, pH 6.5) with glucose (100 mM) was added into the reaction solution, and stired overnight. The concentration of **1a-1n** was 33 mM. The resulting solution was extracted with ethyl acetate for three times, then the organic phase was dried over anhydrous sodium sulfate and concentrated in vacuum. The obtained crude product was further separated and purified by

using flash column chromatography. Yields were determined by GC, external standard method to get contents, and the recovery was 96%, ee values were determined by chiral GC or HPLC.

The absolute configurations of **3a-3m** were confirmed by comparison with literature values [1, 2], and absolute configuration of **3n** was confirmed based on Prelog's rule [4].

2.8 Preparation of styrene-derived (*S*)-Ibuprofen (1n)

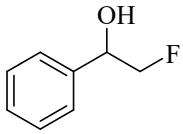


In a 50 mL round-bottom flask, (*S*)-Ibuprofen (412 mg, 2 mmol), DMAP (24 mg, 0.2 mmol), CH_2Cl_2 (20 mL), N,N'-diisopropylcarbodiimide (EDC, 766 mg, 4 mmol) and 4-vinylaniline (262 mg, 2.2 mmol) were successively added. The mixture was stirred at rt overnight. The reaction was quenched with H_2O (10 mL) and extracted with EtOAc (3 × 30 mL). The organics were combined, dried (Na_2SO_4), and the volatiles were removed under reduced pressure. After purification by flash column chromatography, **1n** was obtained as a white solid (402 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 35.9, 8.1 Hz, 4H), 7.19 (dd, *J* = 43.4, 6.8 Hz, 4H), 6.63 (dd, *J* = 17.5, 10.9 Hz, 1H), 5.64 (d, *J* = 17.6 Hz, 1H), 5.16 (d, *J* = 10.8 Hz, 1H), 3.68 (q, *J* = 6.7 Hz, 1H), 2.46 (d, *J* = 7.0 Hz, 2H), 1.93 – 1.78 (m, 1H), 1.57 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.62, 141.08, 138.01, 137.50, 136.08, 133.57, 129.84, 127.40, 126.70, 119.60, 112.90, 77.36, 77.04, 76.73, 47.70, 45.01, 30.18, 22.39, 18.53; HRMS (EI-TOF) m/z: [M]+ Calcd. for C21H25NO 307.1936, Found 307.1941.

2.9 Procedure of reuse experiments

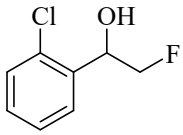
The reuse experiments were performed in photo-KtCR-catalyzed cascade reaction of 0.2 mmol **1j** (Entry 8, **Table 3**). After reaction, the resulting solution was extracted with ethyl acetate (5 mL X 3), and cells were harvested by centrifugation of aqueous phase. Then the pellet was resuspended in 5 mL 100 mM pH 6.5 PBS buffer, and added to another fluorination solution as biocatalyst. In the meantime, 72 mg glucose (0.4 mmol, 2 equiv), 50 U GDH and a solution of $NADP^+$ (100 μL of 80 mM stock, 0.04 equiv) were added, in order to eliminate the activity loss of NADPH regeneration system during the reaction, extraction and centrifugation process. After 2 h at rt, the ketone **2j** was transformed to (*S*)-**3j** completely, so the reaction time of bioreduction in the reuse experiments was 2 h. The conversion and ee value were determined by chiral GC.

4. Characterization data



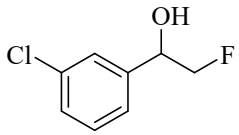
2-fluoro-1-phenylethan-1-ol (3a)

The crude residue was purified by flash column chromatography (petroleum ether : ethyl acetate =10:1 to 2:1) to get the target product as pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.30 (m, 5H), 5.03 (ddd, *J* = 9.3, 5.5, 2.4 Hz, 1H), 4.59 – 4.34 (m, 2H), 2.49 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.18 (d, *J* = 8.2 Hz), 128.67, 128.45, 126.36, 87.20 (d, *J* = 174.3 Hz), 72.99 (d, *J* = 19.7 Hz). HRMS (EI-TOF) m/z: $[M]^+$ Calcd. for C_8H_9FO 140.0637, Found 140.0637.



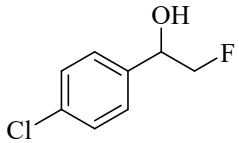
1-(2-chlorophenyl)-2-fluoroethan-1-ol (3b)

The crude residue was purified by flash column chromatography (petroleum ether : ethyl acetate =10:1 to 2:1) to get the target product as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.45 – 7.18 (m, 3H), 5.54 – 5.35 (m, 1H), 4.48 (dddd, *J* = 48.5, 17.6, 9.6, 5.4 Hz, 2H), 2.73 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.52 (d, *J* = 8.7 Hz), 132.05, 129.47, 129.44, 127.93, 127.28, 85.68 (d, *J* = 174.8 Hz), 69.85 (d, *J* = 20.5 Hz). HRMS (EI-TOF) m/z: $[M]^+$ Calcd. for C_8H_8ClFO 174.0248, Found 174.0248.



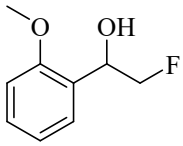
1-(3-chlorophenyl)-2-fluoroethan-1-ol (3c)

The crude residue was purified by flash column chromatography (petroleum ether : ethyl acetate =10:1 to 2:1) to get the target product as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.35 – 7.28 (m, 2H), 7.28 – 7.22 (m, 1H), 5.06 – 4.92 (m, 1H), 4.62 – 4.27 (m, 2H), 2.80 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.20 (d, *J* = 8.1 Hz), 134.63, 129.95, 128.58, 126.57, 124.49, 86.90 (d, *J* = 174.8 Hz), 72.33 (d, *J* = 20.1 Hz). HRMS (EI-TOF) m/z: $[M]^+$ Calcd. for C_8H_8ClFO 174.0248, Found 174.0247.



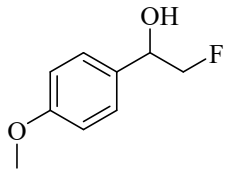
1-(4-chlorophenyl)-2-fluoroethan-1-ol (3d)

The crude residue was purified by flash column chromatography (petroleum ether : ethyl acetate =10:1 to 2:1) to get the target product as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.29 (m, 4H), 5.07 – 4.91 (m, 1H), 4.63 – 4.25 (m, 2H), 2.71 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.60 (d, *J* = 8.2 Hz), 134.24, 128.85, 127.73, 86.94 (d, *J* = 174.8 Hz), 72.31 (d, *J* = 20.0 Hz). HRMS (EI-TOF) m/z: $[M]^+$ Calcd. for C_8H_8ClFO 174.0248, Found 174.0249.



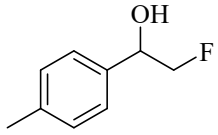
2-fluoro-1-(2-methoxyphenyl)ethan-1-ol (3e)

The crude residue was purified by flash column chromatography (petroleum ether : ethyl acetate =10:1 to 2:1) to get the target product as brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.34 – 7.23 (m, 1H), 6.99 (t, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 5.38 – 5.17 (m, 1H), 4.49 (dddd, *J* = 48.8, 17.3, 9.3, 5.6 Hz, 2H), 3.84 (s, 3H), 2.93 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.38, 129.23, 127.45, 126.29 (d, *J* = 8.3 Hz), 120.92, 110.36, 86.15 (d, *J* = 173.1 Hz), 69.12 (d, *J* = 20.5 Hz), 55.33. HRMS (EI-TOF) m/z: $[M]^+$ Calcd. for $C_9H_{11}FO_2$ 170.0743, Found 170.0743.



2-fluoro-1-(4-methoxyphenyl)ethan-1-ol (3g)

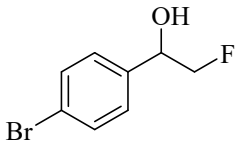
The crude residue was purified by flash column chromatography (petroleum ether : ethyl acetate =10:1 to 2:1) to get the target product as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 5.01 – 4.90 (m, 1H), 4.55 – 4.29 (m, 2H), 3.80 (s, 3H), 2.66 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.68, 130.28 (d, *J* = 8.4 Hz), 127.67, 114.07, 87.18 (d, *J* = 174.5 Hz), 72.55 (d, *J* = 19.8 Hz), 55.32. HRMS (EI-TOF) m/z: $[M]^+$ Calcd. For $C_9H_{11}FO_2$ 170.0743, Found 170.0742.



2-fluoro-1-(p-tolyl)ethan-1-ol (3h)

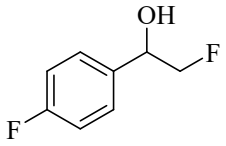
The crude residue was purified by flash column chromatography (petroleum ether : ethyl acetate =10:1 to 4:1) to get the target product as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 34.3, 8.0 Hz, 4H), 4.97 (ddd, *J* = 13.8, 8.3, 3.2 Hz, 1H), 4.44 (dddd, *J* = 34.1, 17.8, 9.6, 5.8 Hz, 2H), 2.35 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 138.26, 135.20 (d, *J* = 8.5 Hz), 129.35, 126.30, 87.21

(d, J = 174.3 Hz), 72.84 (d, J = 19.8 Hz), 21.16. HRMS (EI-TOF) m/z: $[M]^+$ Calcd. for $C_9H_{11}FO$ 154.0794, Found 154.0794.



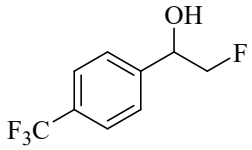
1-(4-bromophenyl)-2-fluoroethan-1-ol (3i)

The crude residue was purified by flash column chromatography (petroleum ether : ethyl acetate =10:1 to 3:1) to get the target product as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.10 (m, 4H), 5.09 – 4.85 (m, 1H), 4.60 – 4.23 (m, 2H), 2.72 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.12 (d, J = 8.2 Hz), 131.80, 128.06, 122.37, 86.87 (d, J = 174.9 Hz), 72.35 (d, J = 20.1 Hz). HRMS (EI-TOF) m/z: $[M]^+$ Calcd. for C_8H_8BrFO 217.9743, Found 217.9742.



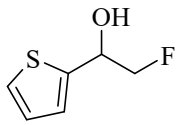
2-fluoro-1-(4-fluorophenyl)ethan-1-ol (3j)

The crude residue was purified by flash column chromatography (petroleum ether : ethyl acetate =10:1 to 3:1) to get the target product as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (ddd, J = 120.2, 13.0, 7.0 Hz, 4H), 5.09 – 4.90 (m, 1H), 4.58 – 4.26 (m, 2H), 2.82 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.70 (d, J = 246.8 Hz), 133.93 (dd, J = 8.2, 3.0 Hz), 128.11 (d, J = 8.2 Hz), 115.59 (d, J = 21.7 Hz), 87.04 (d, J = 174.6 Hz), 72.30 (d, J = 19.9 Hz). HRMS (EI-TOF) m/z: $[M]^+$ Calcd. for $C_8H_8F_2O$ 158.0543, Found 158.0542.



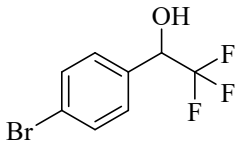
2-fluoro-1-(4-(trifluoromethyl)phenyl)ethan-1-ol (3k)

The crude residue was purified by flash column chromatography (petroleum ether : ethyl acetate =10:1 to 3:1) to get the target product as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, J = 47.7, 8.3 Hz, 4H), 5.08 (ddd, J = 14.3, 8.0, 3.2 Hz, 1H), 4.63 – 4.30 (m, 2H), 2.69 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.07 (d, J = 8.0 Hz), 130.64 (q, J = 32.6 Hz), 126.67 (s), 125.60 (q, J = 3.7 Hz), 122.63 (s), 86.83 (d, J = 175.0 Hz), 72.39 (d, J = 20.2 Hz). HRMS (EI-TOF) m/z: $[M]^+$ Calcd. for $C_9H_8F_4O$ 208.0511, Found 208.0509.



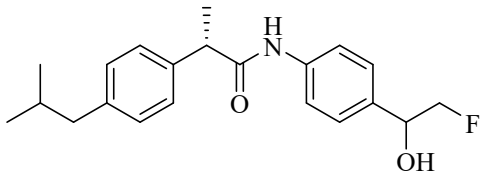
2-fluoro-1-(thiophen-2-yl)ethan-1-ol (3l)

The crude residue was purified by flash column chromatography (petroleum ether : ethyl acetate =10:1 to 3:1) to get the target product as light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.05 (dt, *J* = 4.9, 3.5 Hz, 2H), 5.27 (ddd, *J* = 14.3, 7.5, 3.5 Hz, 1H), 4.57 (dddd, *J* = 25.6, 17.0, 9.5, 5.6 Hz, 2H), 2.80 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.31 (d, *J* = 8.5 Hz), 126.98 (s), 125.62 (s), 125.03 (s), 86.61 (d, *J* = 175.3 Hz), 69.10 (d, *J* = 21.6 Hz). HRMS (EI-TOF) m/z: $[M]^+$ Calcd. for $C_9H_8F_4O$ 146.0202, Found 146.0200.



1-(4-bromophenyl)-2,2,2-trifluoroethan-1-ol (3m)

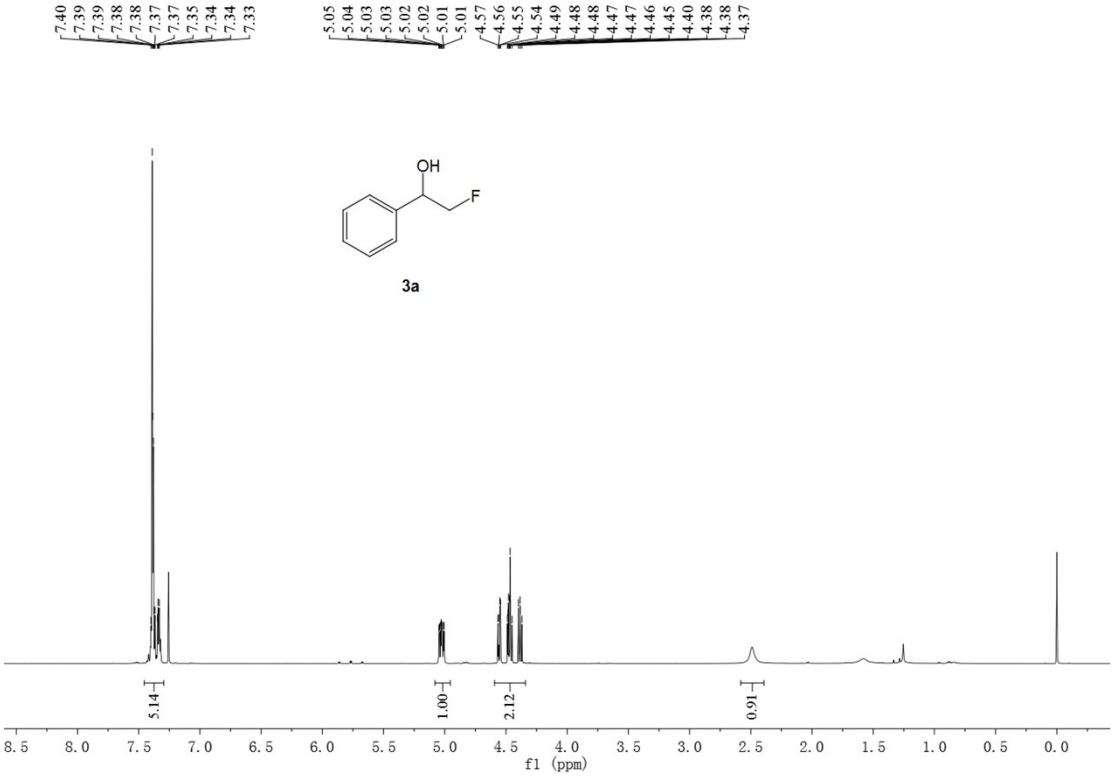
The crude residue was purified by flash column chromatography (petroleum ether : ethyl acetate =10:1 to 3:1) to get the target product as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.1 Hz, 2H), 7.35 (d, *J* = 7.7 Hz, 2H), 5.07 – 4.95 (m, 1H), 2.76 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.79, 131.78, 129.05, 128.12, 123.86 (t, *J* = 141.1 Hz), 72.17 (q, *J* = 32.1 Hz). HRMS (EI-TOF) m/z: $[M]^+$ Calcd. for $C_8H_6BrF_3O$ 253.9554, Found 253.9547.

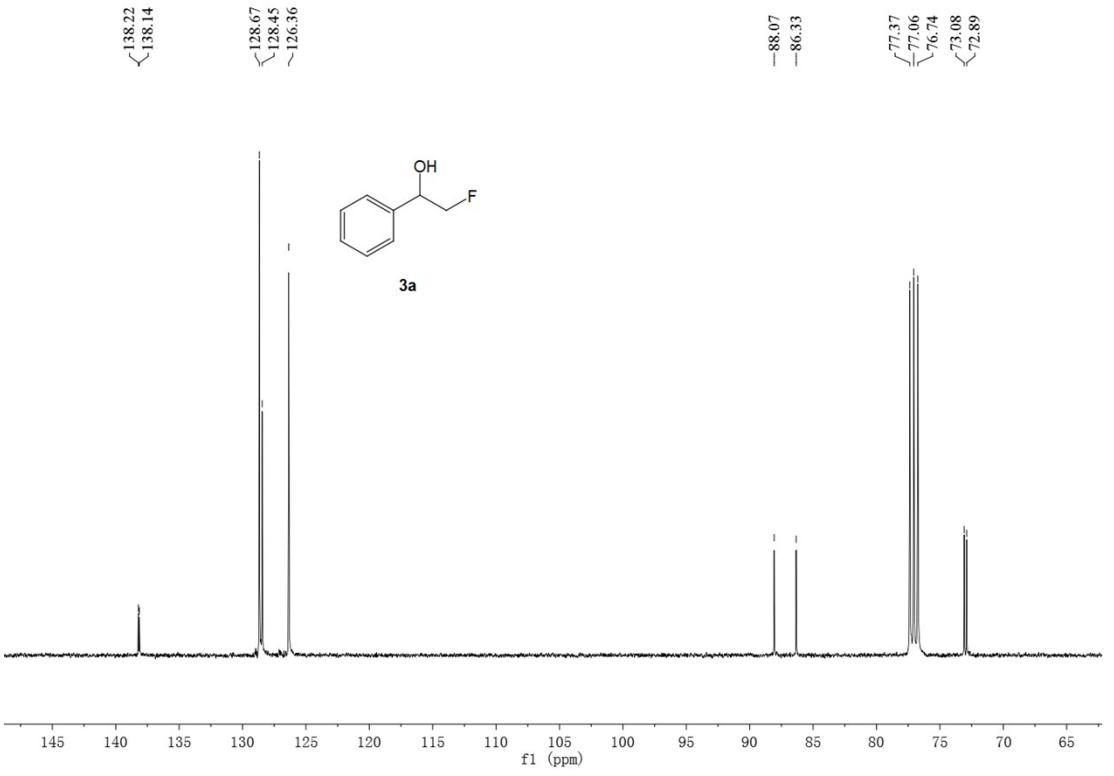


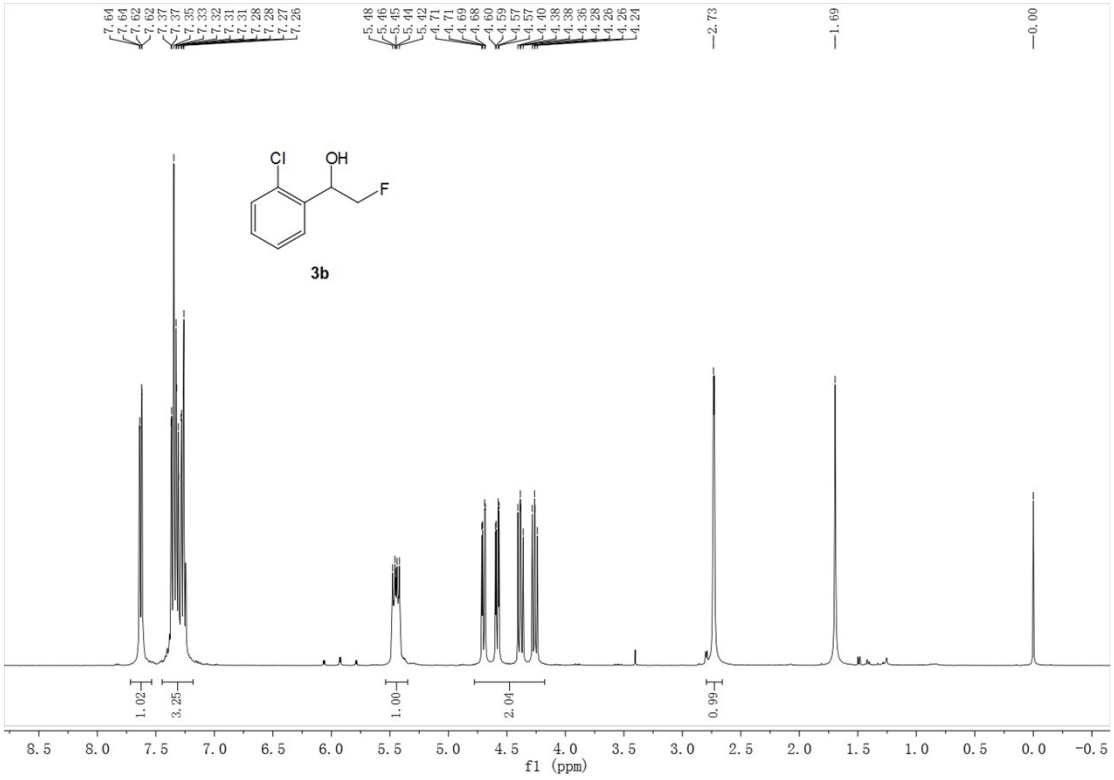
(2*S*)-*N*-(4-(2-fluoro-1-hydroxyethyl)phenyl)-2-(4-isobutylphenyl)propanamide (3n)

The crude residue was purified by flash column chromatography (petroleum ether : ethyl acetate =5:1 to 2:1) to get the target product as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 11.2 Hz, 1H), 7.44 – 7.23 (m, 4H), 7.16 (d, *J* = 21.0 Hz, 4H), 4.86 (s, 1H), 4.34 (dd, *J* = 47.6, 15.4 Hz, 2H), 3.70 (s, 1H), 2.46 (d, *J* = 5.3 Hz, 2H), 1.85 (s, 1H), 1.54 (s, 3H), 0.90 (d, *J* = 4.7 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.24, 140.98, 138.07, 137.85, 134.36, 129.74, 127.34, 126.88, 120.12, 86.91 (d, *J* = 175.1 Hz), 72.37 (d, *J* = 19.5 Hz), 47.41, 45.00, 30.17, 22.39, 18.55. ^{19}F NMR (376 MHz, $cdcl_3$) δ -219.39 (m, 1F). HRMS (EI-TOF) m/z: $[M]^+$ Calcd. for $C_{21}H_{26}FNO_2$ 343.1948, Found 343.1955.

5. ^{1}H, ^{13}C and ^{19}F NMR spectra



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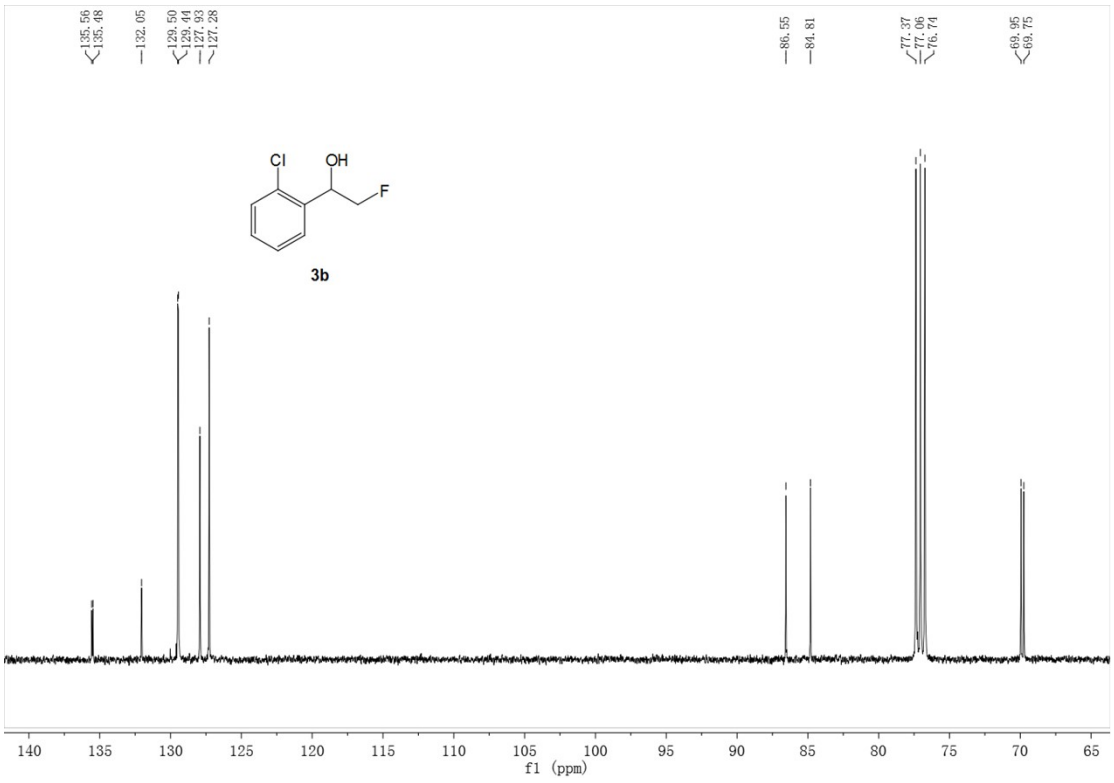
f1 (ppm)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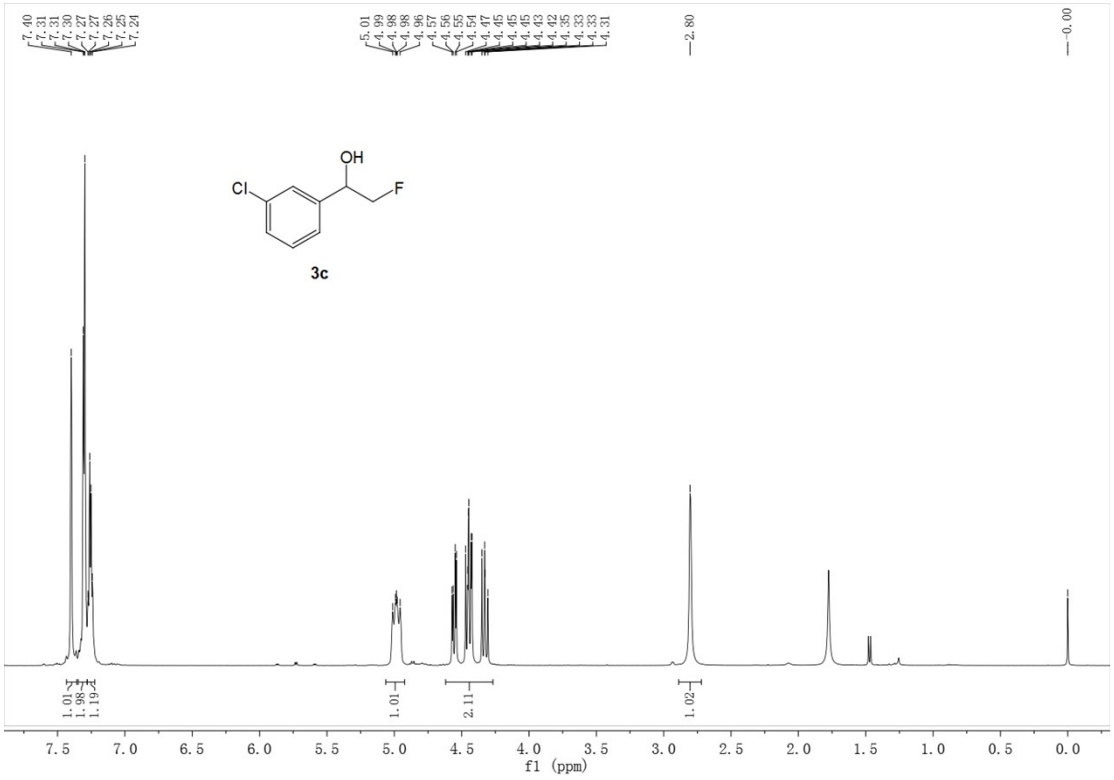
F
3b
f1 (ppm)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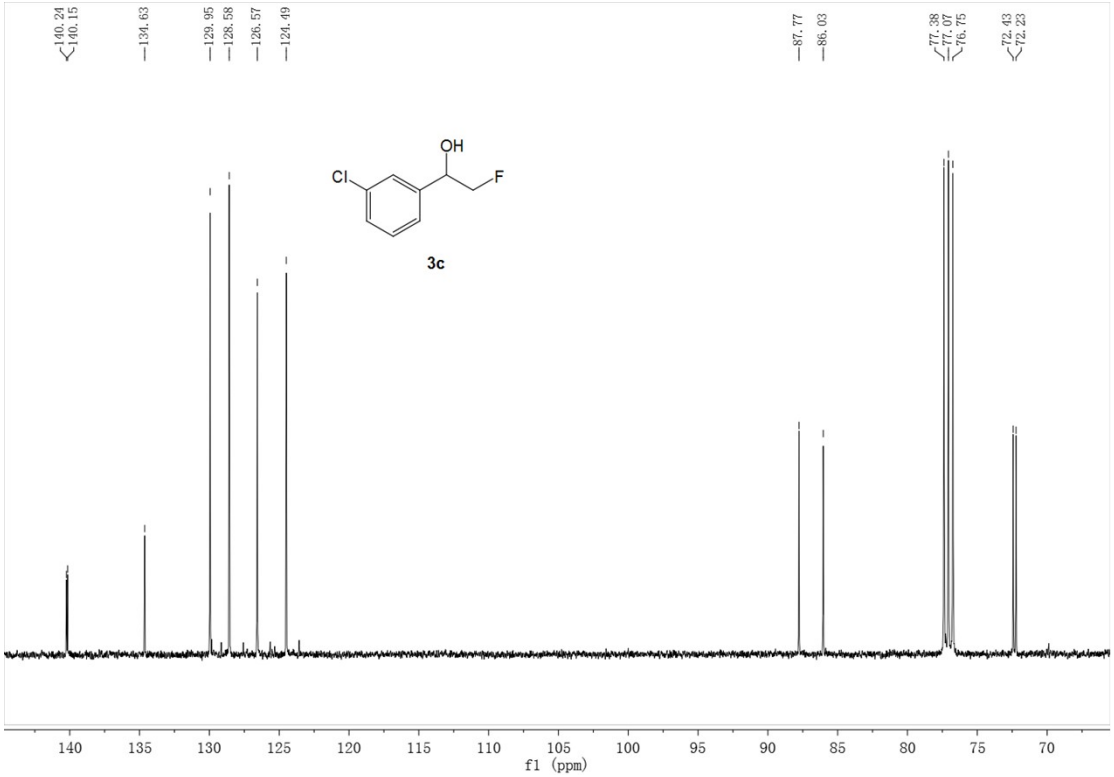
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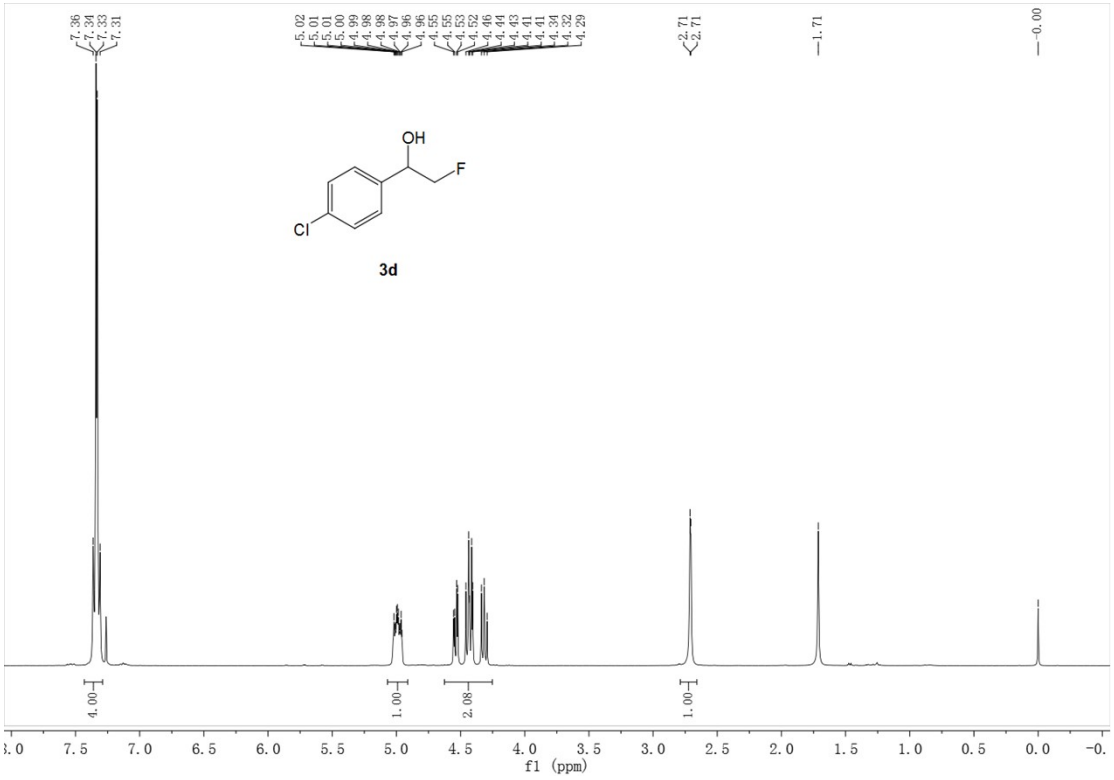
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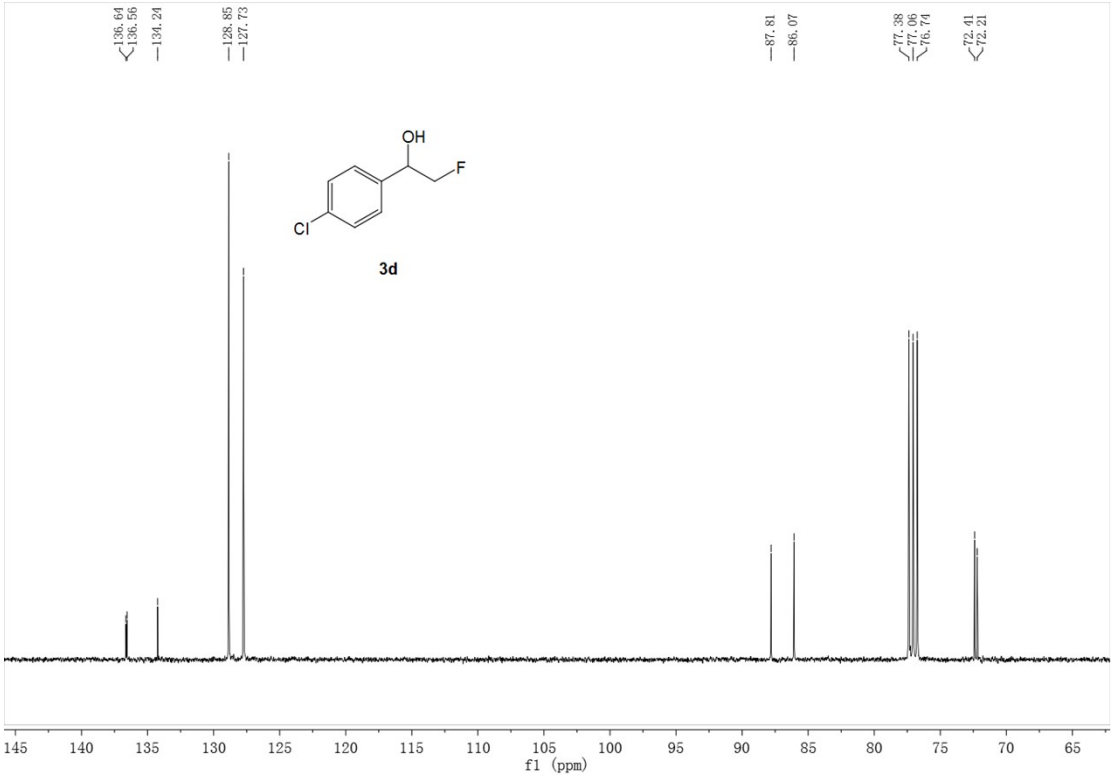
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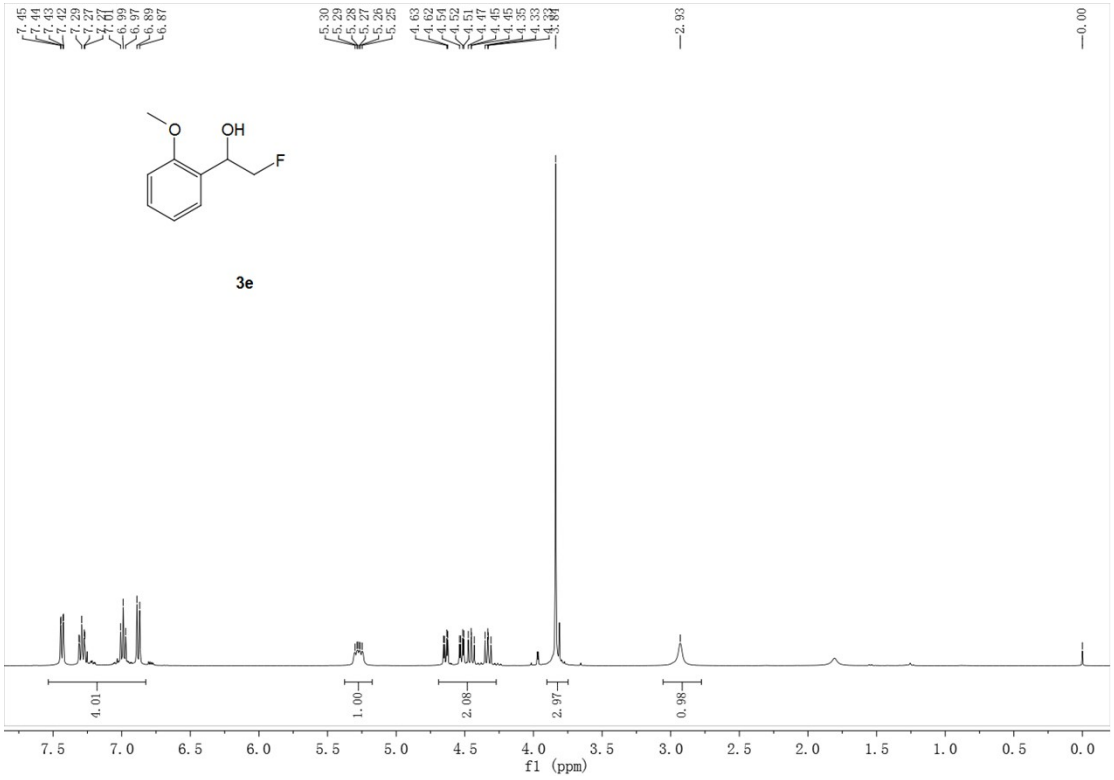
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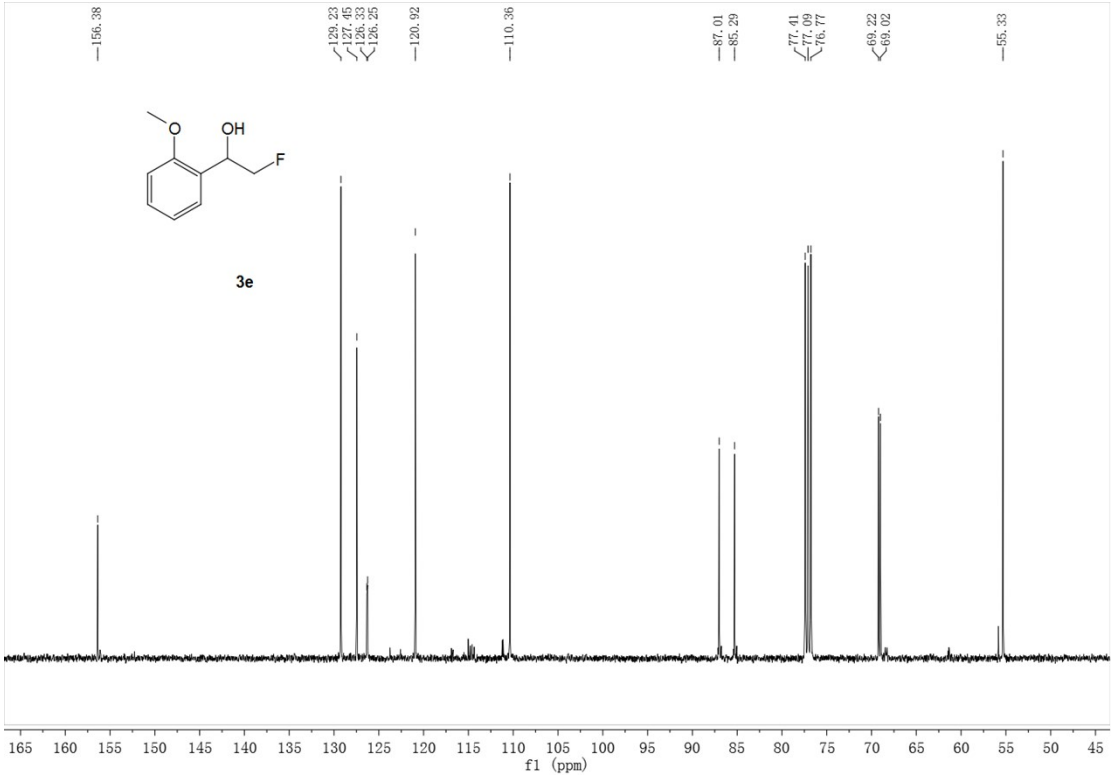
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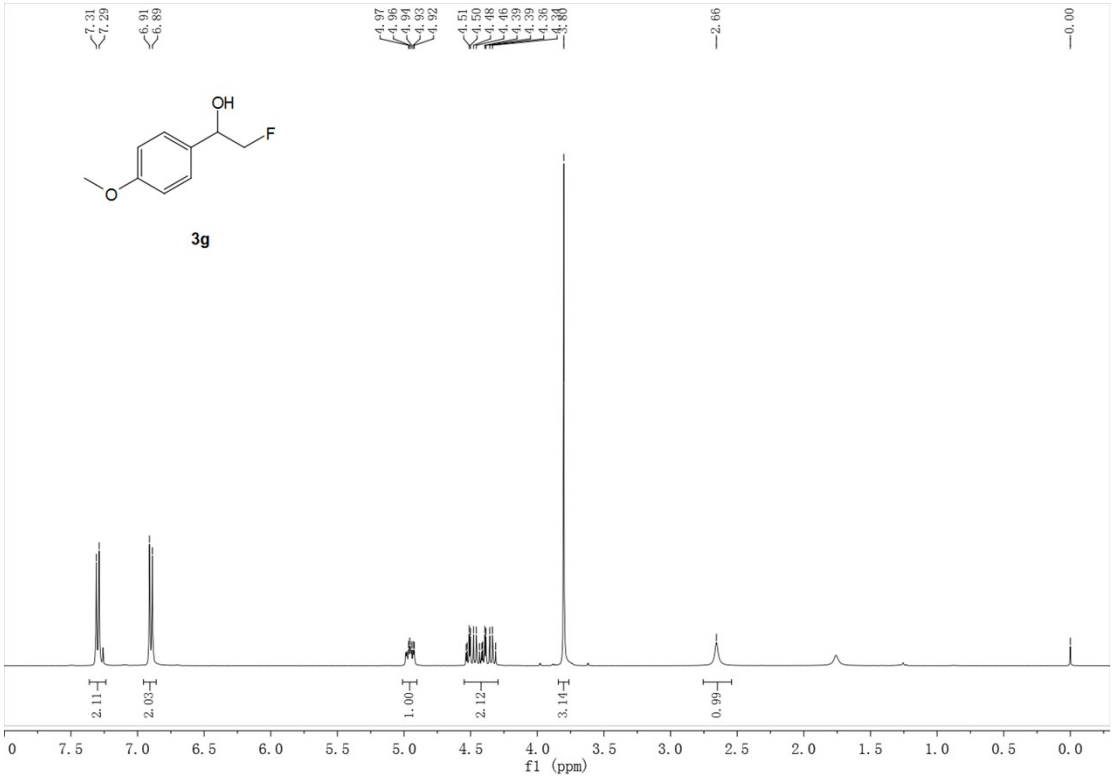
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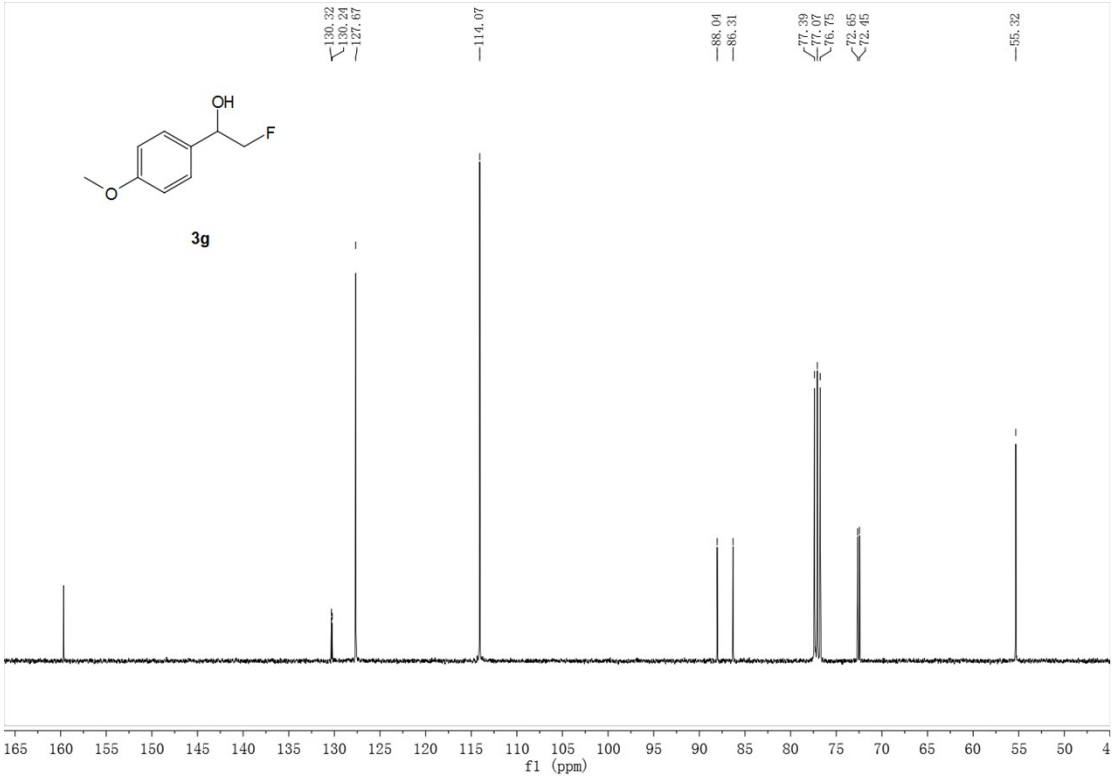
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O
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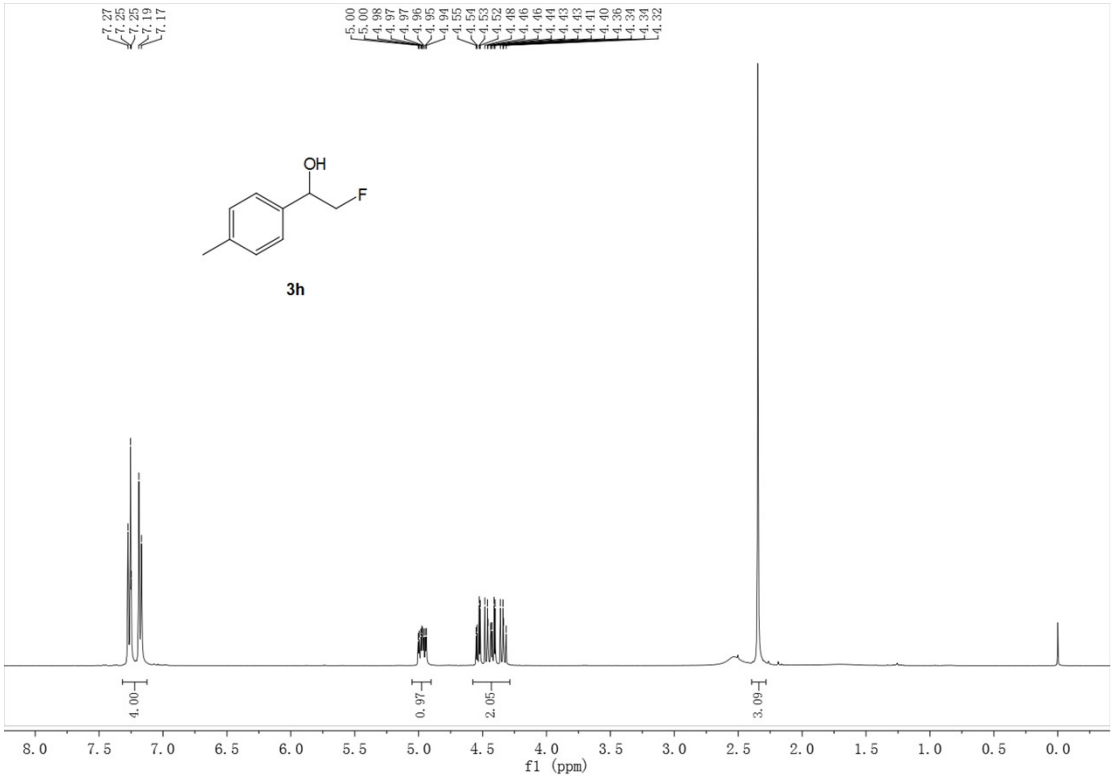
f1 (ppm)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3.09
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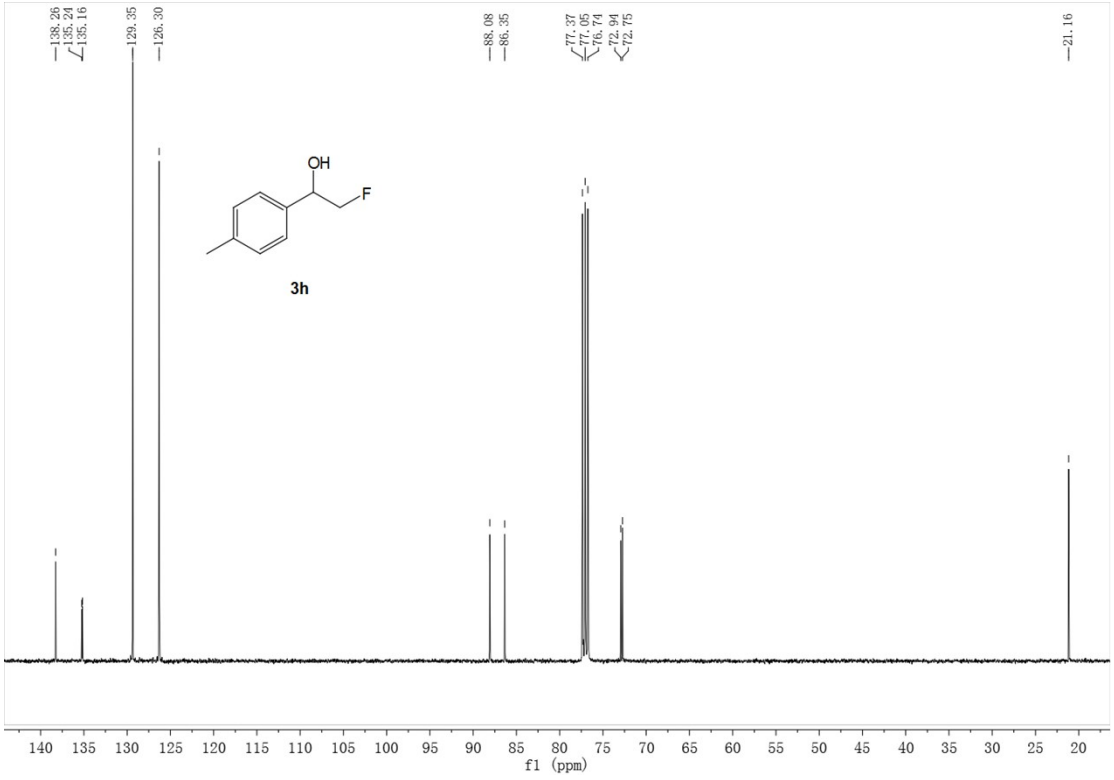
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3h
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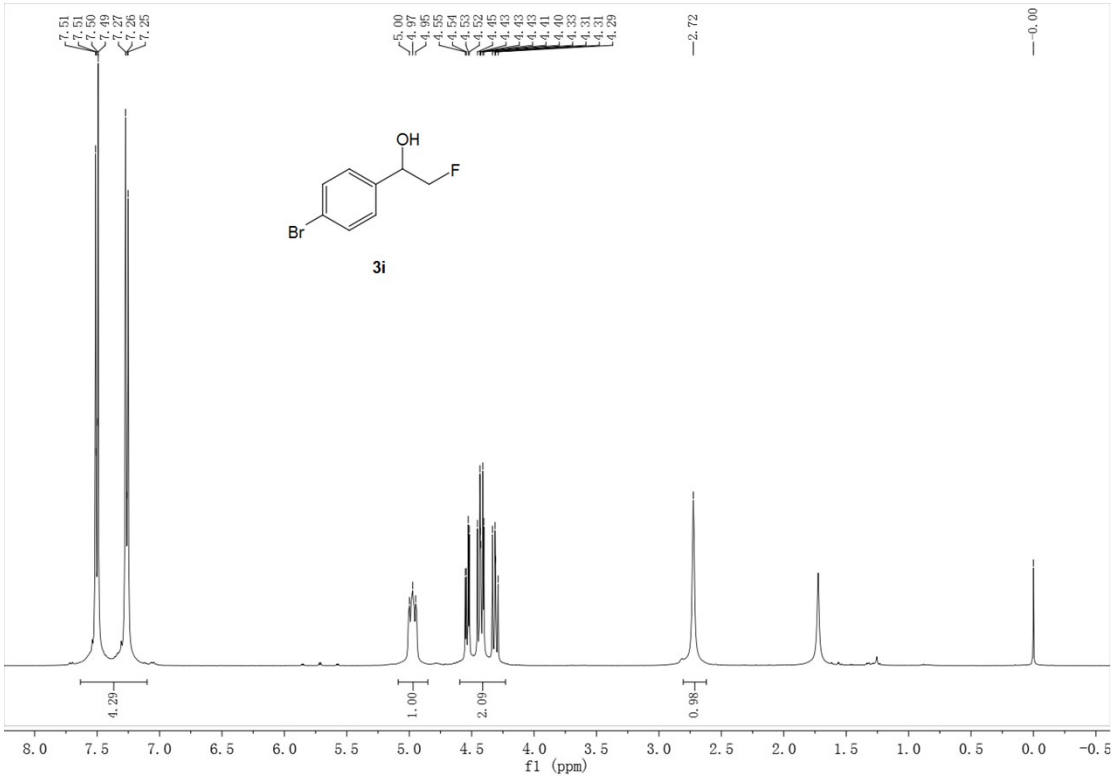
f1 (ppm)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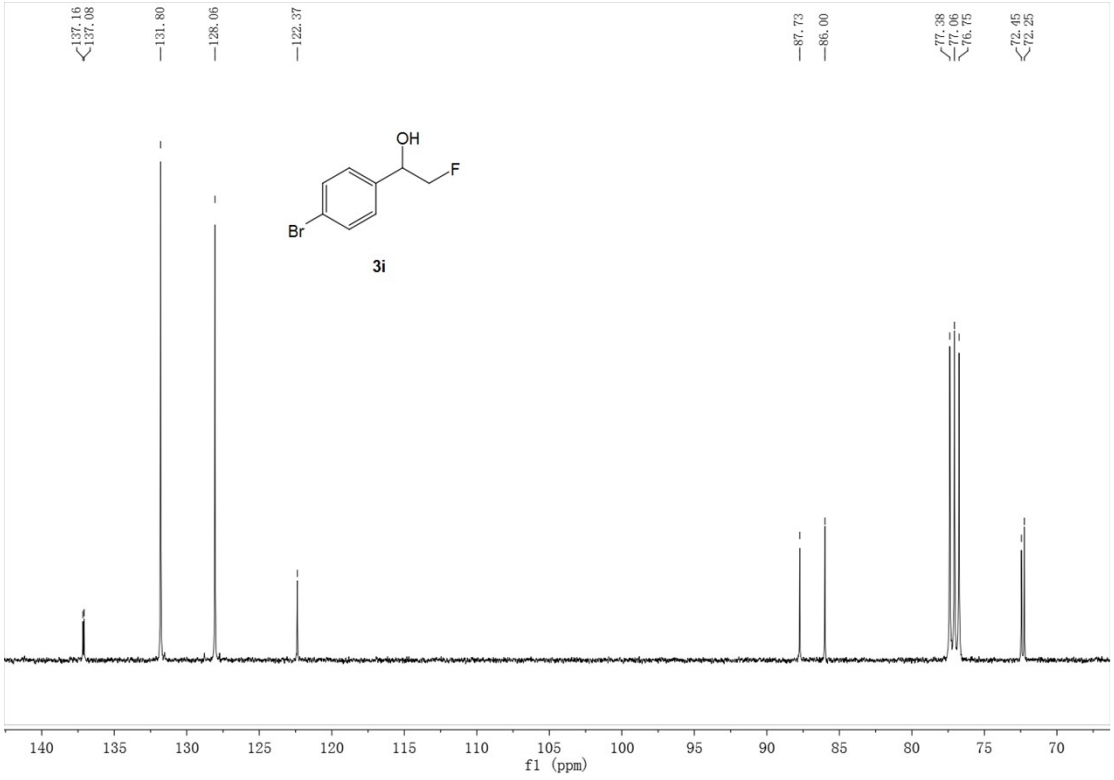
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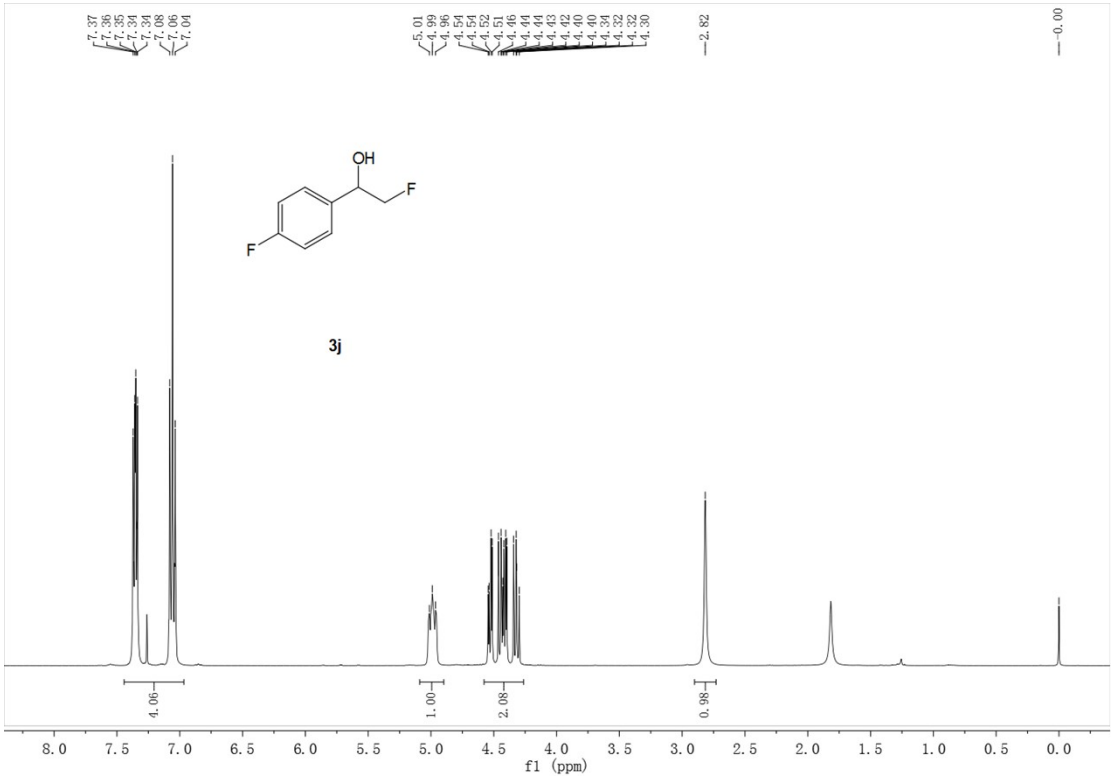
f1 (ppm)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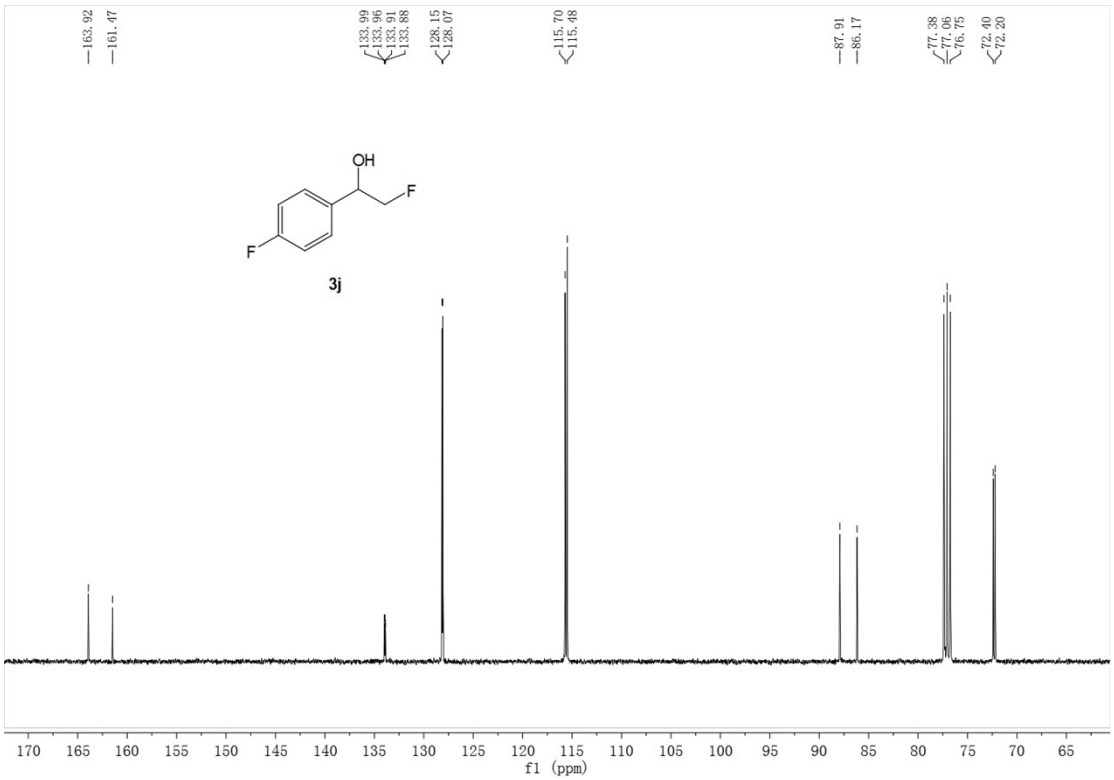
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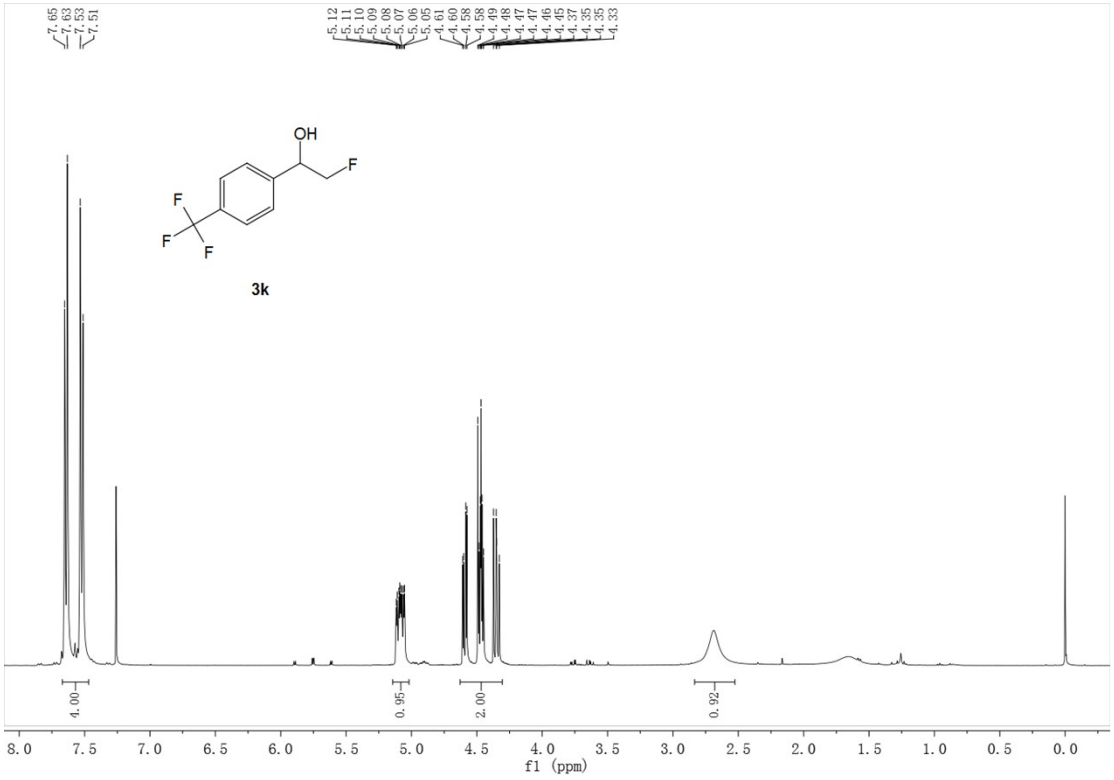
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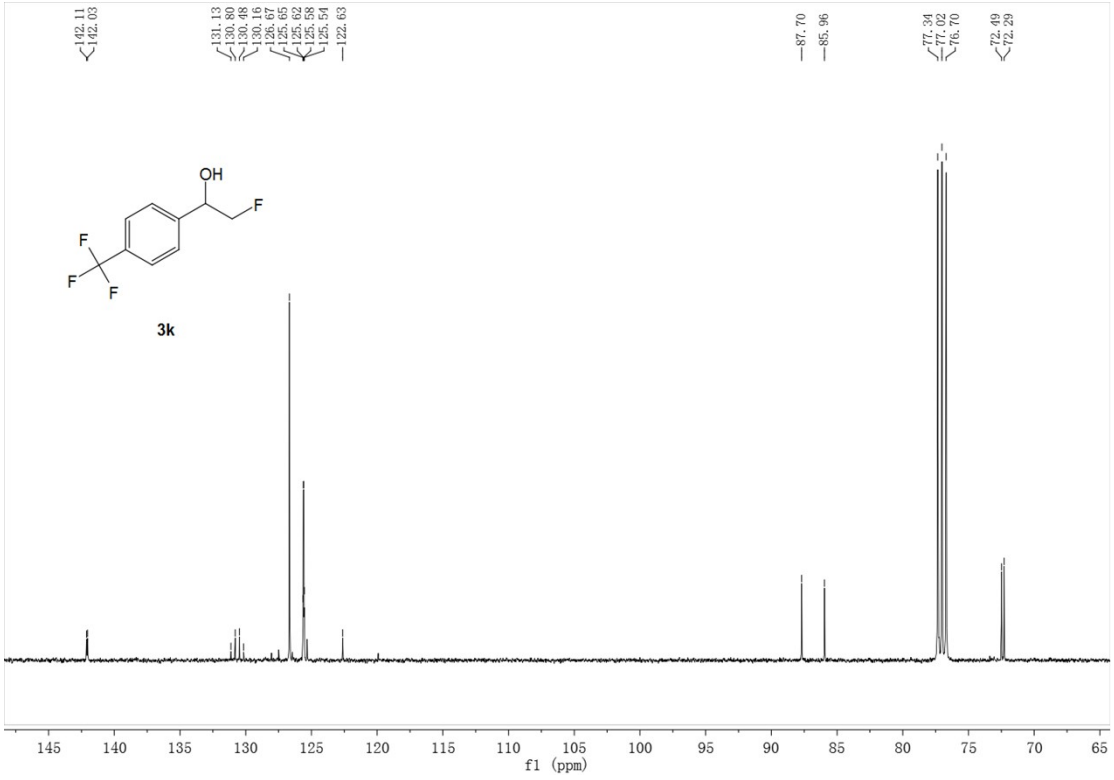
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F
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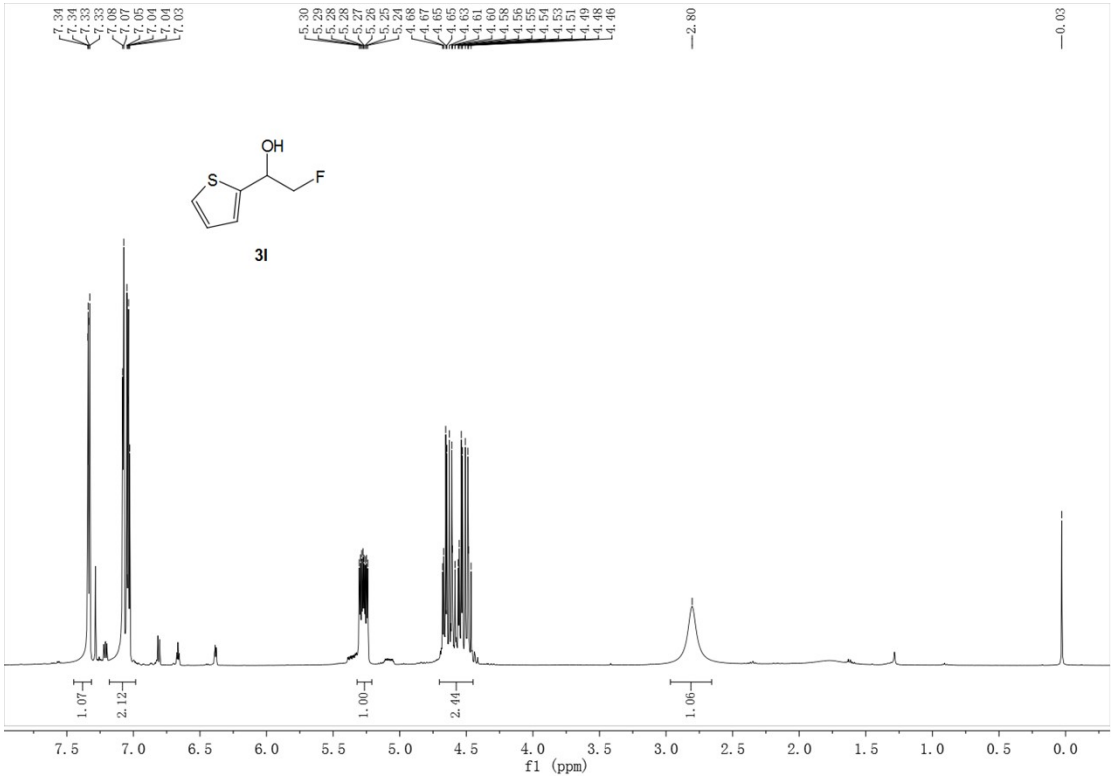
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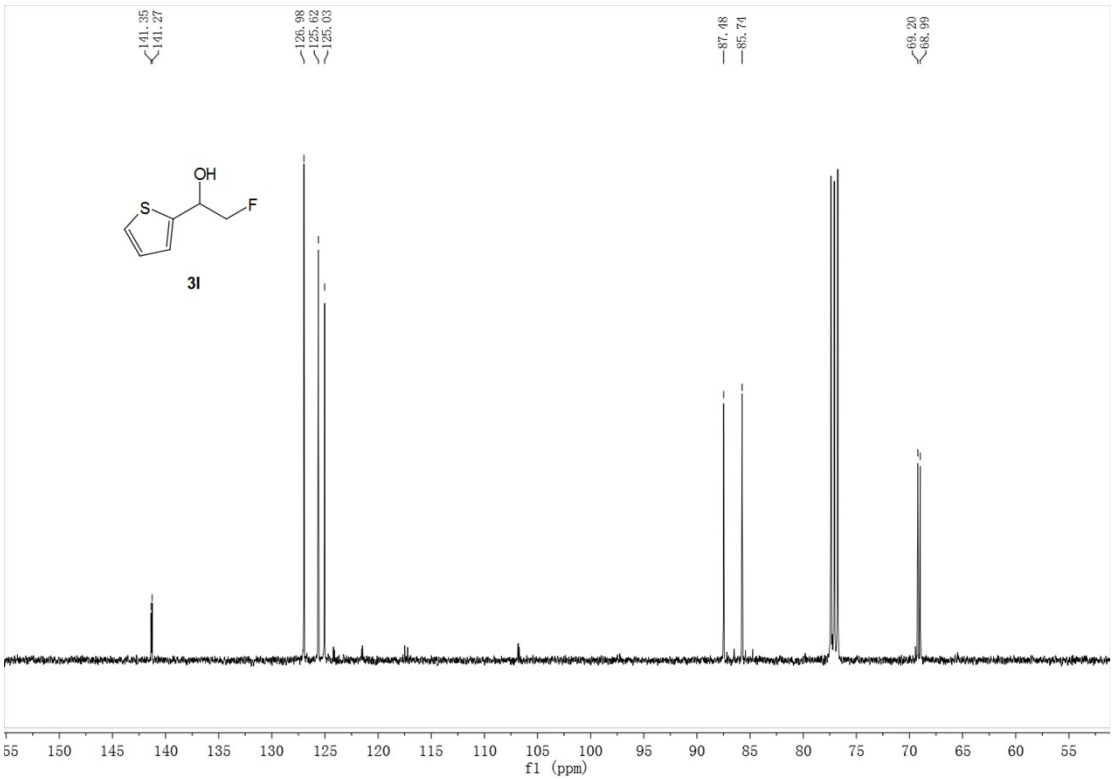
f1 (ppm)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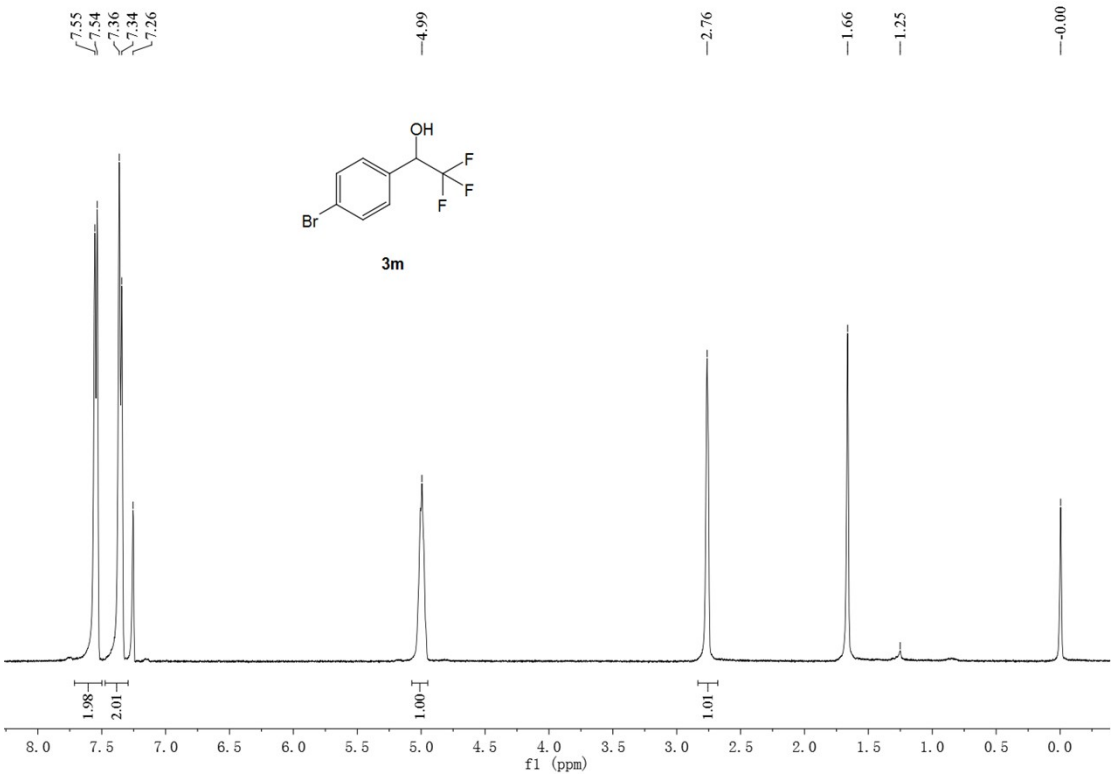
f1 (ppm)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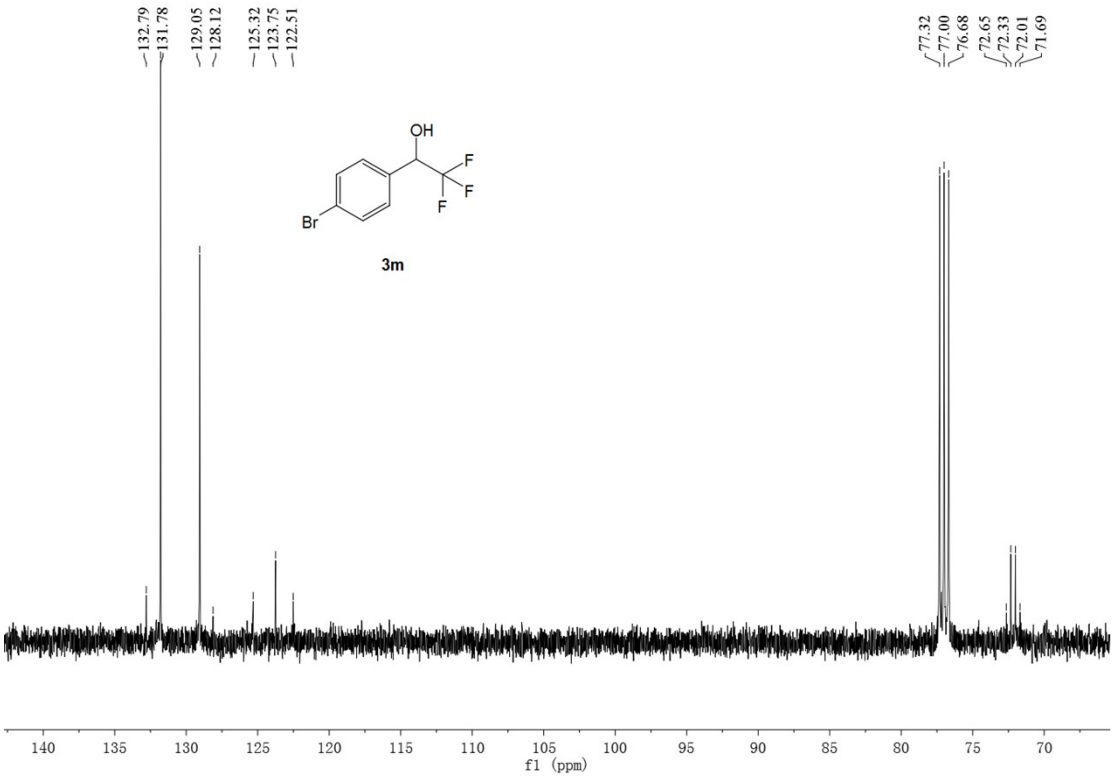
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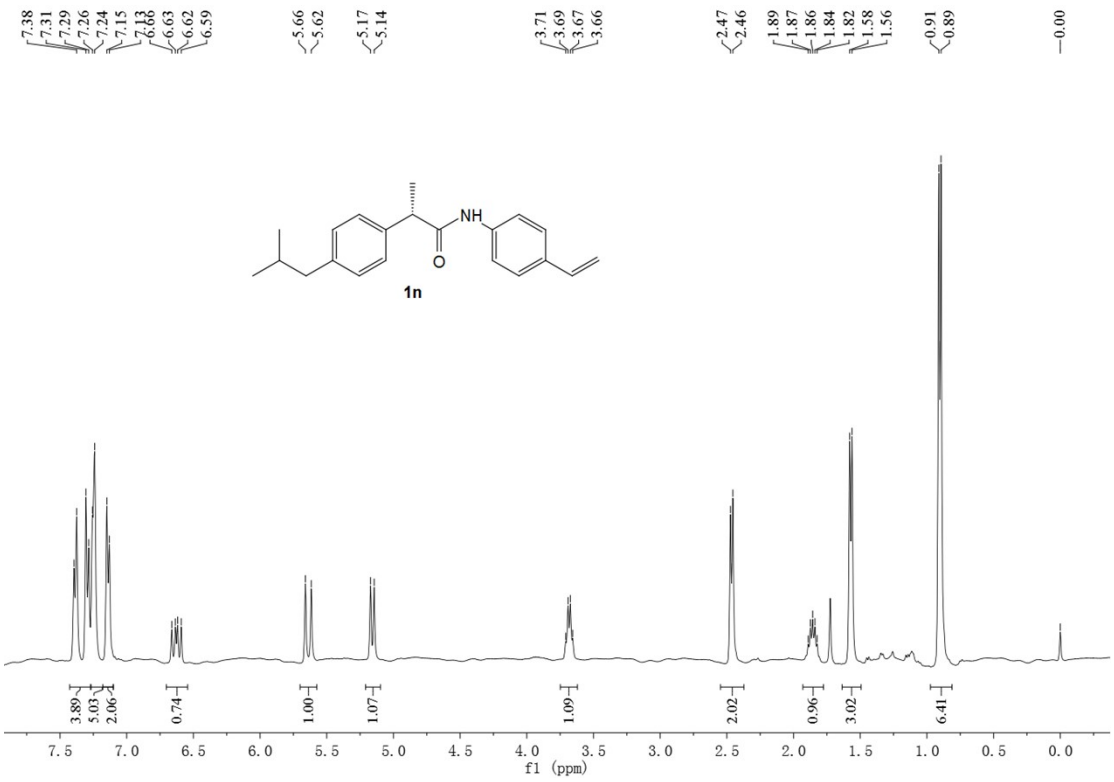
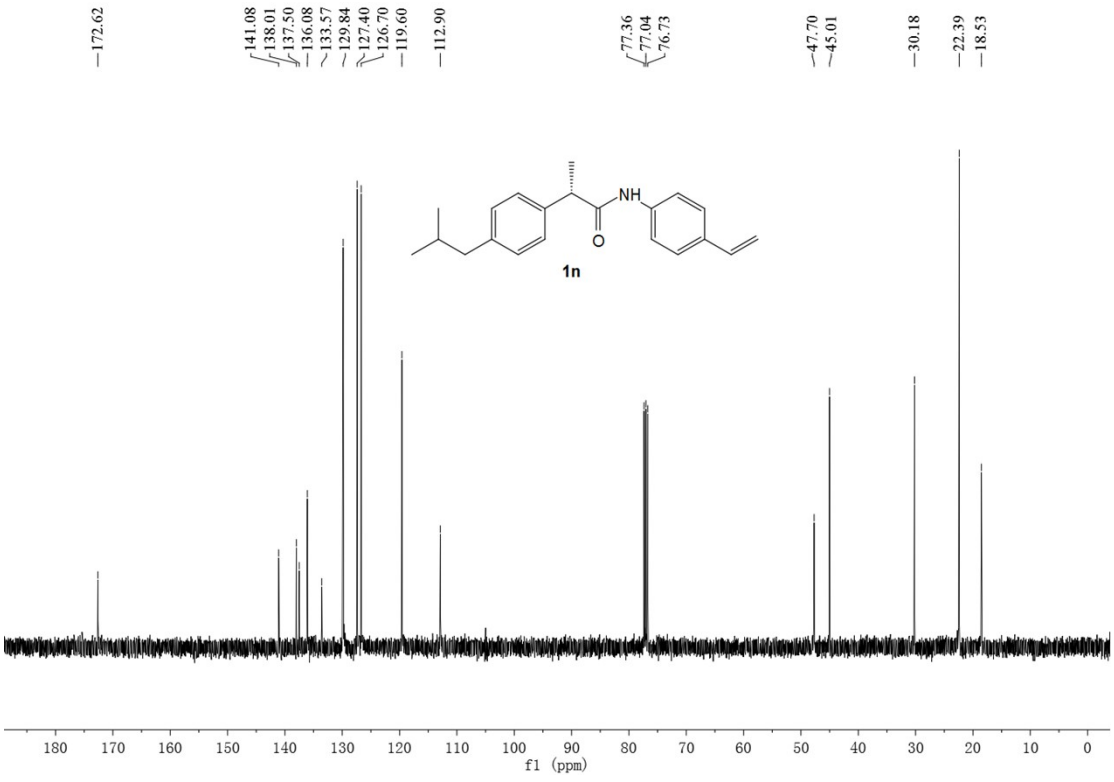
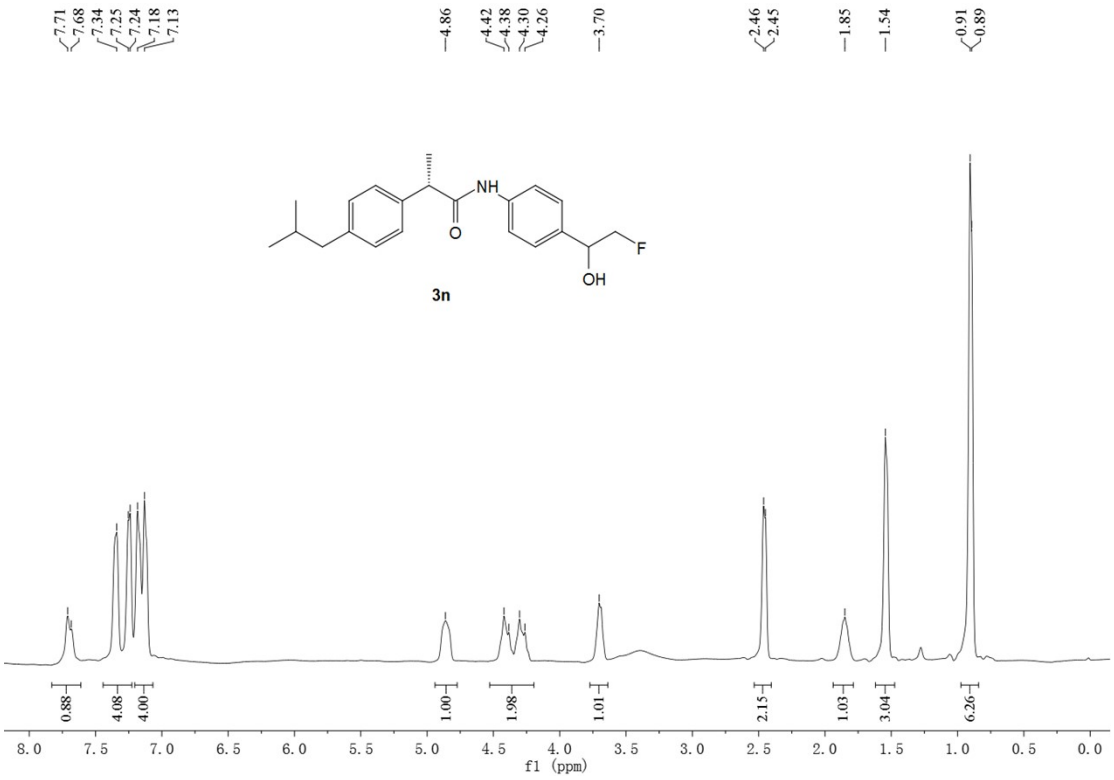
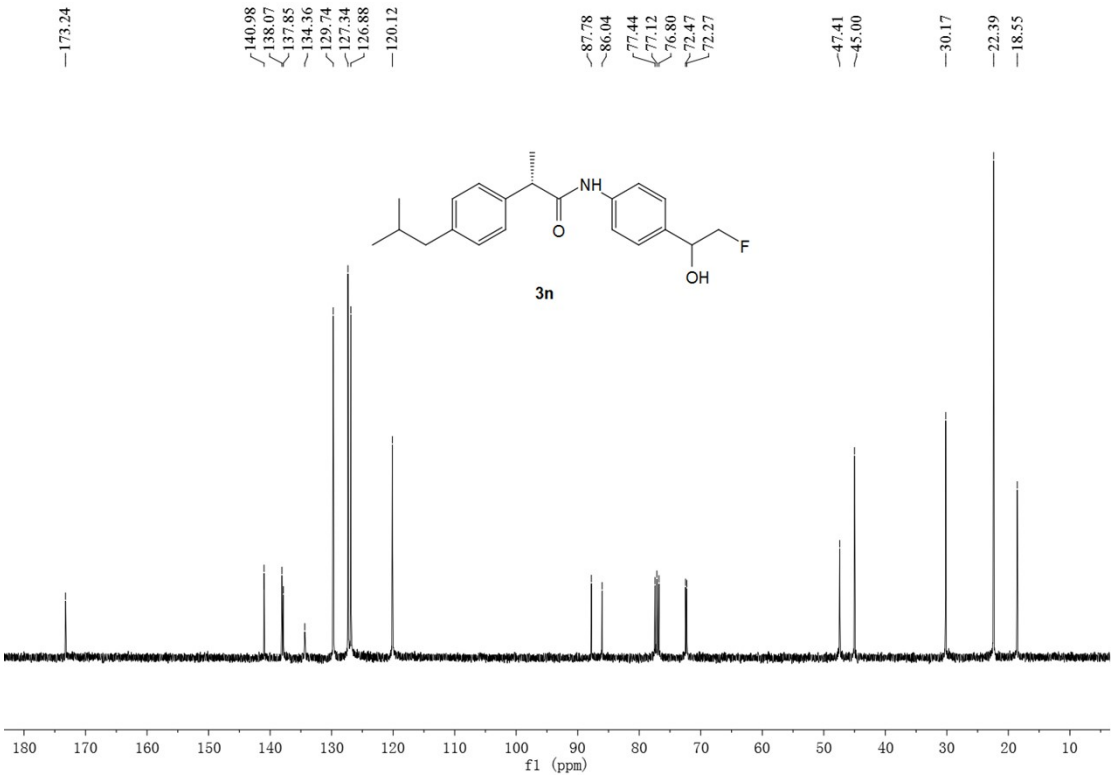
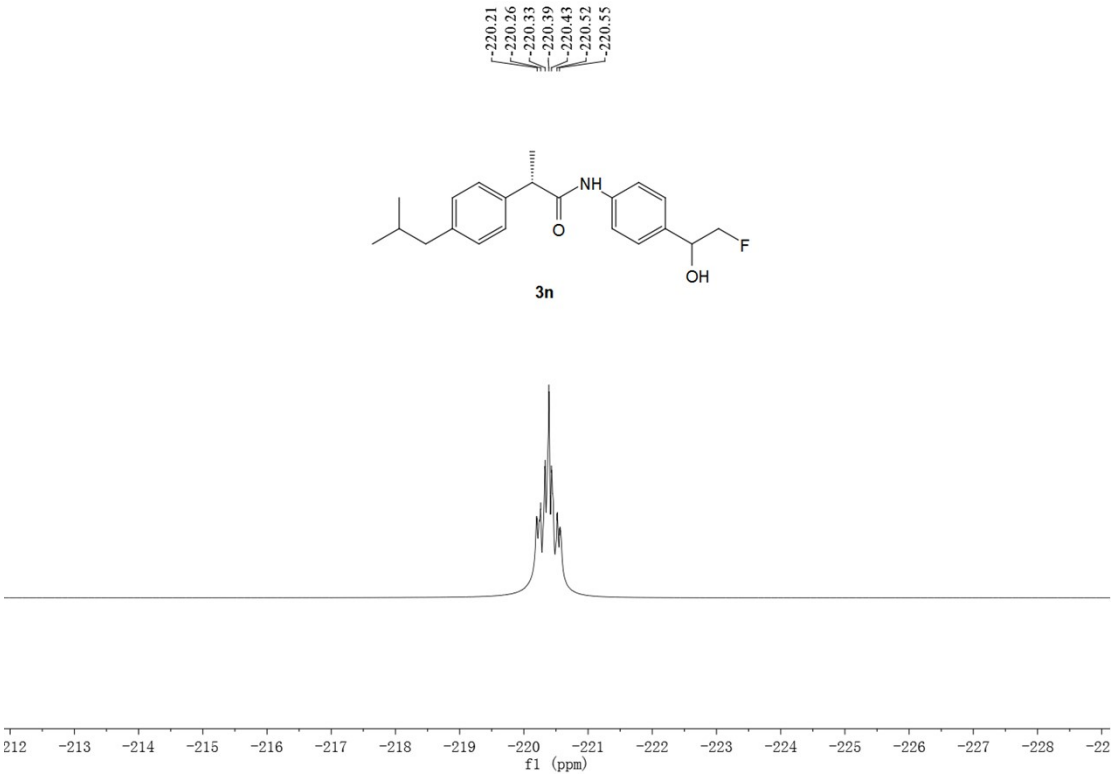
123.75
122.51
77.32
77.00
76.68
72.65
72.33
72.01
71.69
OH
F
F
F
Br
3m
f1 (ppm)


7.38
7.31
7.29
7.26
7.24
7.15
7.13
6.68
6.63
6.62
6.59
5.66
5.62
5.17
5.14
3.71
3.69
3.67
3.66
2.47
2.46
1.89
1.87
1.86
1.84
1.82
1.58
1.56
0.91
0.89
0.00
NH
O
1n
3.89
5.03
2.06
0.74
1.00
1.07
1.09
2.02
0.96
3.02
6.41
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)


172.62
141.08
138.01
137.50
136.08
133.57
129.84
127.40
126.70
119.60
112.90
77.36
77.04
76.73
47.70
45.01
30.18
22.39
18.53
NH
O
1n
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

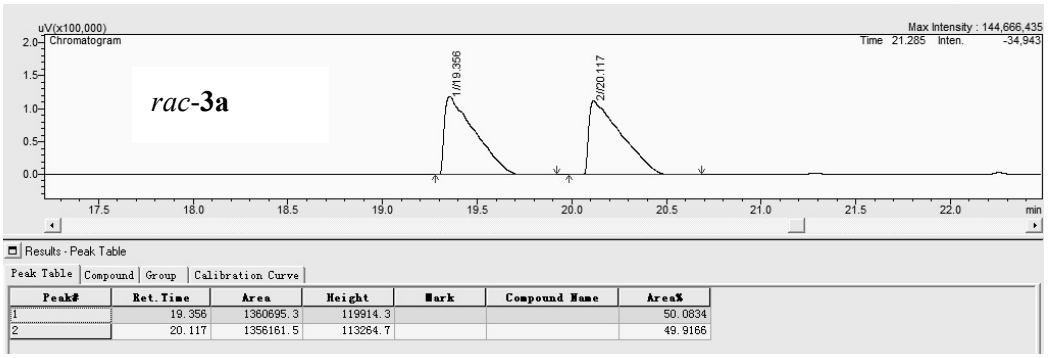

7.71
7.68
7.34
7.25
7.24
7.18
7.13
4.86
4.42
4.38
4.30
4.26
3.70
2.46
2.45
1.85
1.54
0.91
0.89
NH
O
F
OH
3n
0.88
4.08
4.00
1.00
1.98
1.01
2.15
1.03
3.04
6.26
f1 (ppm)


173.24
140.98
138.07
137.85
134.36
129.74
127.34
126.88
120.12
87.78
86.04
77.44
77.12
76.80
72.47
72.27
47.41
45.00
30.17
22.39
18.55
NH
O
F
OH
3n
f1 (ppm)


-220.21
-220.26
-220.33
-220.39
-220.43
-220.52
-220.55
NH
O
F
OH
3n
212
-213
-214
-215
-216
-217
-218
-219
-220
-221
-222
-223
-224
-225
-226
-227
-228
-22
f1 (ppm)

6. Chiral GC and HPLC data

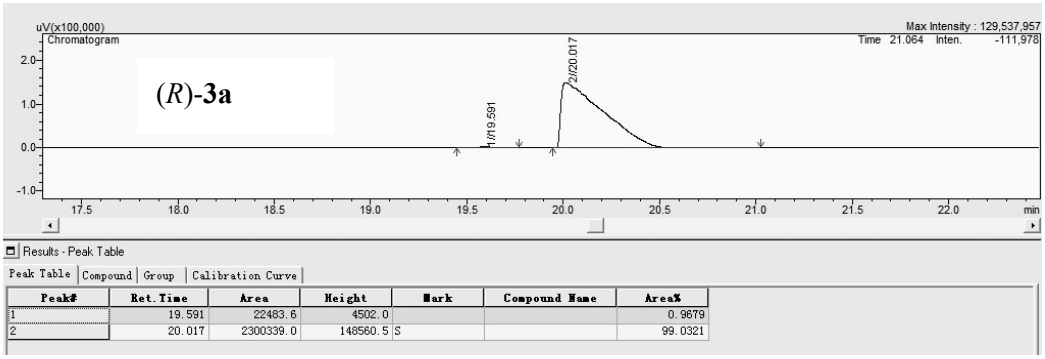
3a, chiral GC (Agilent CP-chirasil-Dex CB, T_S = 19.3 min, T_R = 20.1 min, Temperature conditions: initial temperature 100℃, 2℃/min to 150℃, then 40℃ /min to 180℃, holding 1 min).



Results - Peak Table

Peak Table | Compound | Group | Calibration Curve

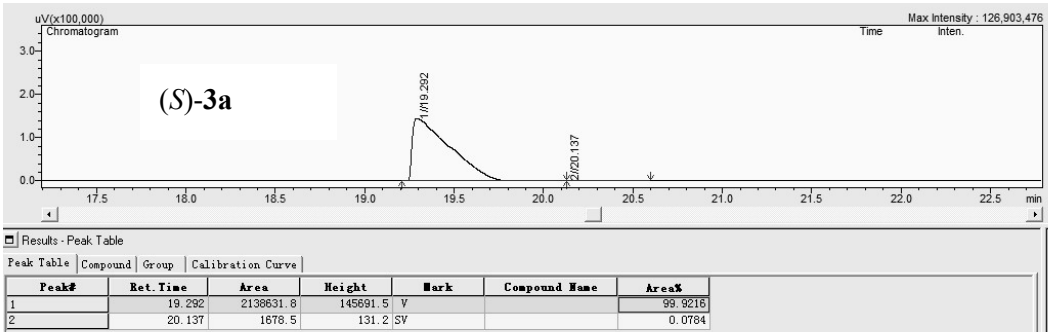
Peak#	Ret. Time	Area	Height	Mark	Compound Name	Area%
1	19.356	1360695.3	119914.3			50.0834
2	20.117	1356161.5	113264.7			49.9166



Results - Peak Table

Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Compound Name	Area%
1	19.591	22483.6	4502.0			0.9679
2	20.017	2300339.0	148560.5	S		99.0321

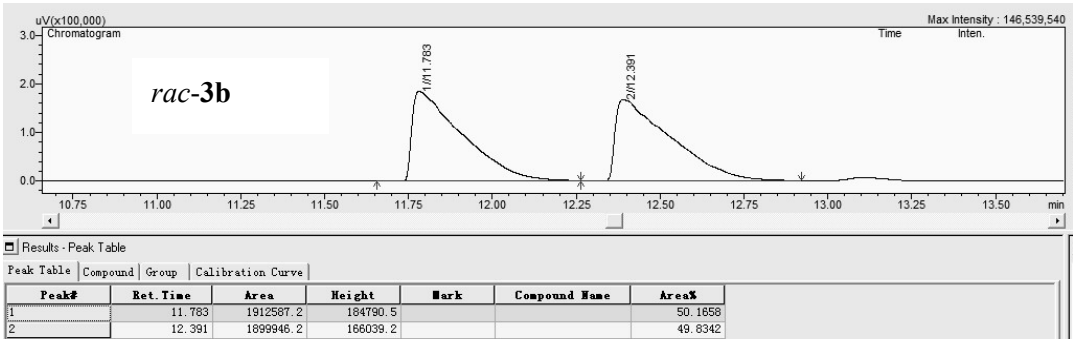


Results - Peak Table

Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Compound Name	Area%
1	19.292	2138631.8	145691.5	V		99.9216
2	20.137	1678.5	131.2	SV		0.0784

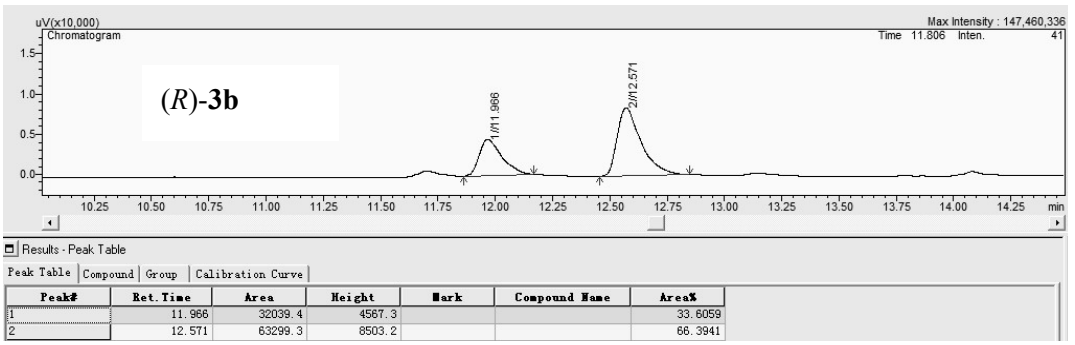
3b, chiral GC (Agilent CP-chirasil-Dex CB, T_S = 12.0 min, T_R = 12.6 min, Temperature conditions: initial temperature 140℃, 2℃ /min to 180℃ holding 1 min).



Results - Peak Table

Peak Table | Compound | Group | Calibration Curve

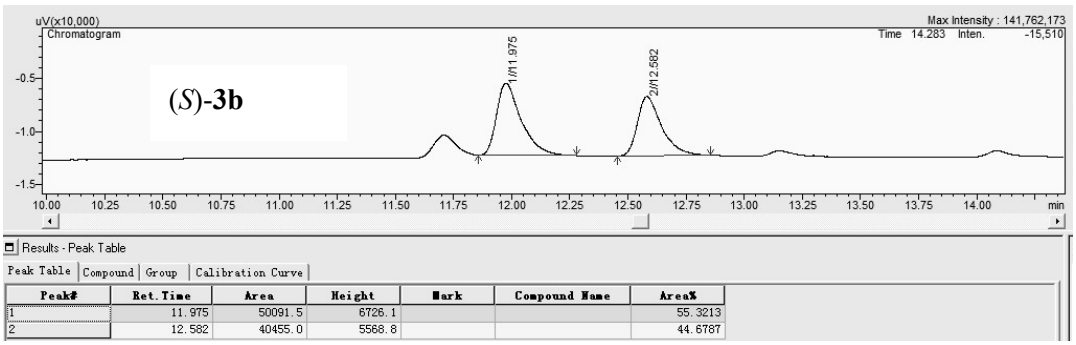
Peak#	Ret. Time	Area	Height	Mark	Compound Name	Area%
1	11.783	1912587.2	184790.5			50.1658
2	12.391	1899946.2	166039.2			49.8342



Results - Peak Table

Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Compound Name	Area%
1	11.966	32039.4	4567.3			33.6059
2	12.571	63299.3	8503.2			66.3941

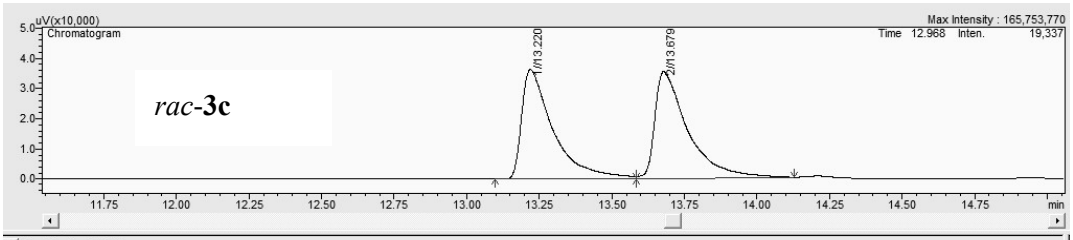


Results - Peak Table

Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Compound Name	Area%
1	11.975	50091.5	6726.1			55.3213
2	12.582	40455.0	5568.8			44.6787

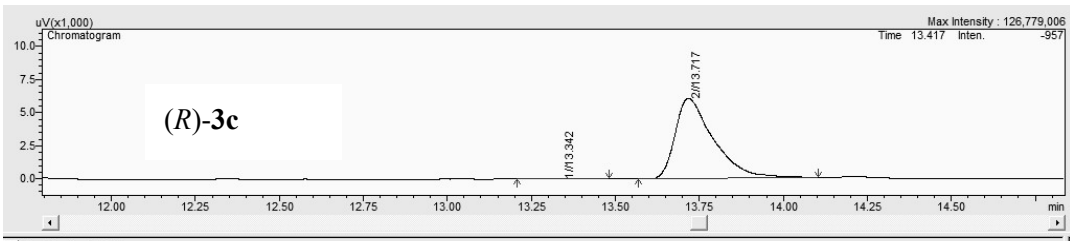
3c, chiral GC (Agilent CP-chirasil-Dex CB, T_S = 13.3 min, T_R = 13.7 min, Temperature conditions: initial temperature 140℃, 2℃/min to 180℃, holding 1 min).



Results - Peak Table

Peak Table | Compound | Group | Calibration Curve

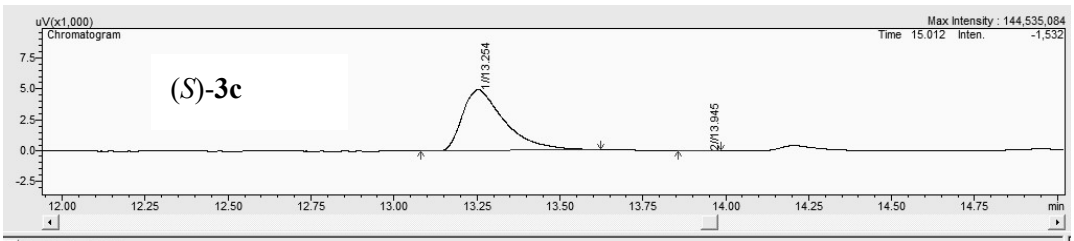
Peak#	Ret.Time	Area	Height	Mark	Compound Name	Area%
1	13.220	274362.5	36269.4			49.8187
2	13.679	276359.5	35253.1	V		50.1813



Results - Peak Table

Peak Table | Compound | Group | Calibration Curve

Peak#	Ret.Time	Area	Height	Mark	Compound Name	Area%
1	13.342	375.0	42.8			0.7611
2	13.717	48894.6	6088.5			99.2389

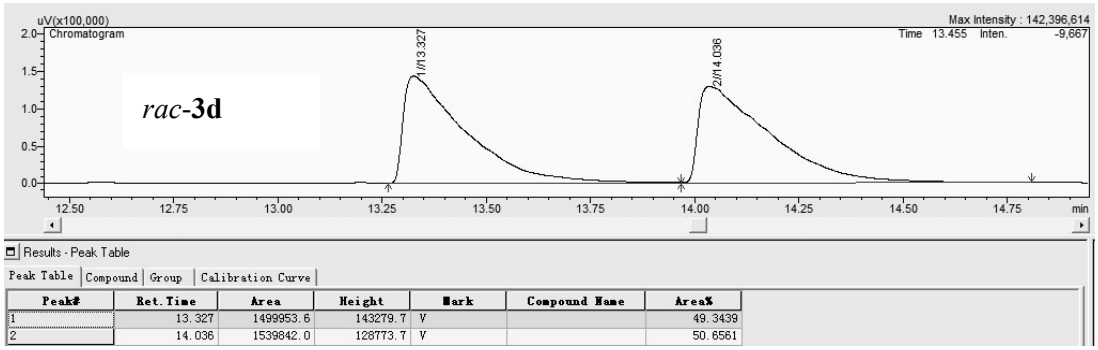


Results - Peak Table

Peak Table | Compound | Group | Calibration Curve

Peak#	Ret.Time	Area	Height	Mark	Compound Name	Area%
1	13.254	44100.0	4953.4			99.8681
2	13.945	58.2	16.5			0.1319

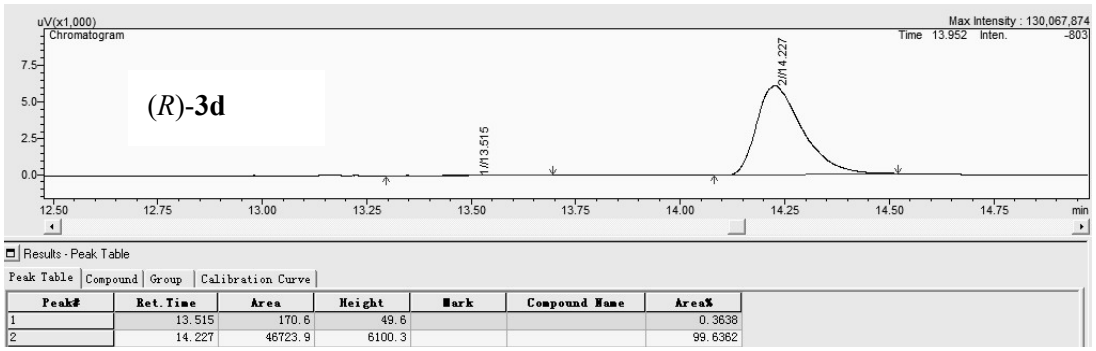
3d, chiral GC (Agilent CP-chirasil-Dex CB, T_S = 13.5 min, T_R = 14.2 min, Temperature conditions: initial temperature 140℃, 2℃/min to 180℃, holding 1 min).



Results - Peak Table

Peak Table | Compound | Group | Calibration Curve

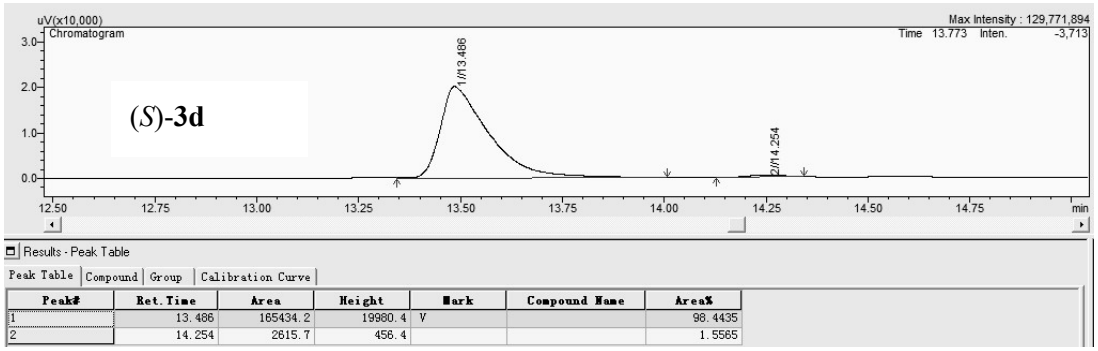
Peak#	Ret. Time	Area	Height	Mark	Compound Name	Area%
1	13.327	1499953.6	143279.7	V		49.3439
2	14.036	1539842.0	128773.7	V		50.6561



Results - Peak Table

Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Compound Name	Area%
1	13.515	170.6	49.6			0.3638
2	14.227	46723.9	6100.3			99.6362

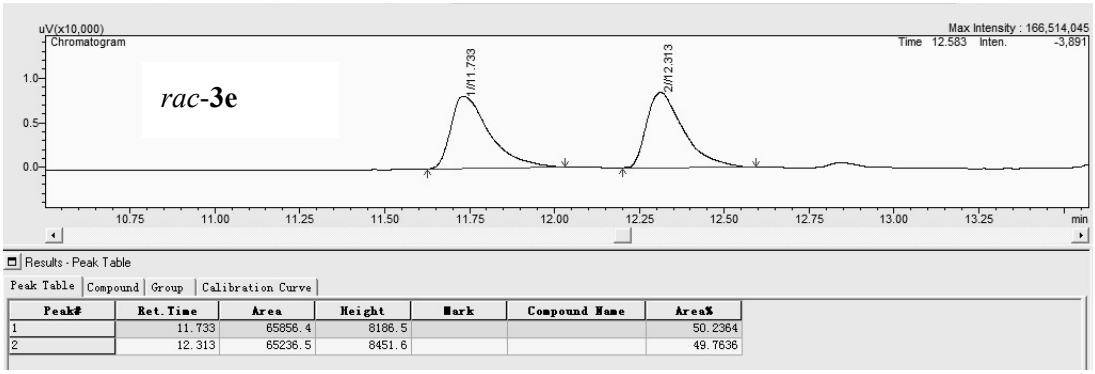


Results - Peak Table

Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Compound Name	Area%
1	13.486	165434.2	19980.4	V		98.4435
2	14.254	2615.7	456.4			1.5565

3e, chiral GC (Agilent CP-chirasil-Dex CB, T_S = 11.7 min, T_R = 12.3 min, Temperature conditions: initial temperature 140℃, 2℃/min to 180℃, holding 1 min).

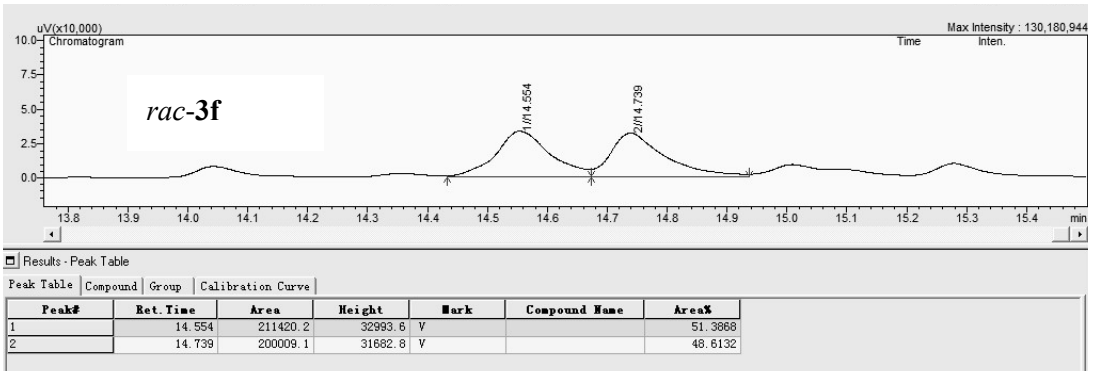


Results - Peak Table

Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Compound Name	Area%
1	11.733	65856.4	8186.5			50.2364
2	12.313	65236.5	8451.6			49.7636

3f, chiral GC (Agilent CP-chirasil-Dex CB, T_S = 14.6 min, T_R = 14.7 min, Temperature conditions: initial temperature 140℃, 2℃/min to 180℃, holding 1 min).

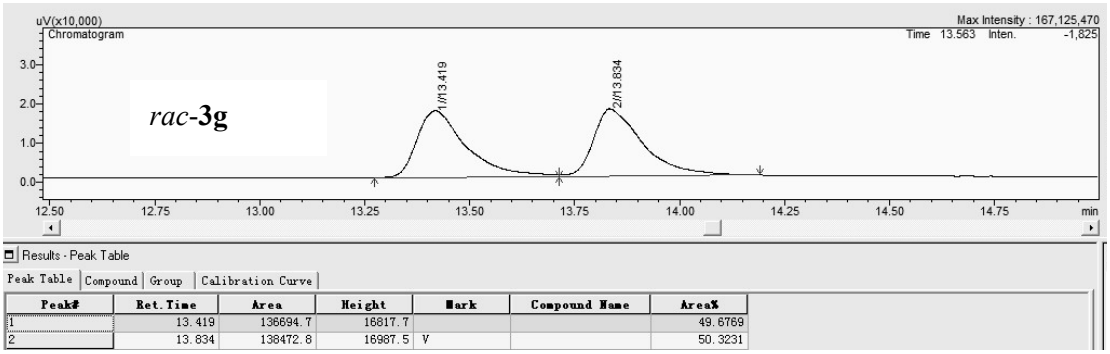


Results - Peak Table

Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Compound Name	Area%
1	14.554	211420.2	32993.6	V		51.3868
2	14.739	200009.1	31682.8	V		48.6132

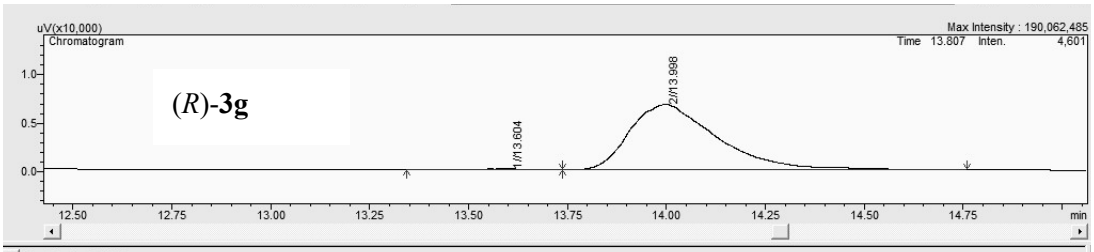
3g, chiral GC (Agilent CP-chirasil-Dex CB, T_S = 13.4 min, T_R = 13.9 min, Temperature conditions: initial temperature 140℃, 2℃/min to 180℃, holding 1 min).



Results - Peak Table

Peak Table | Compound | Group | Calibration Curve

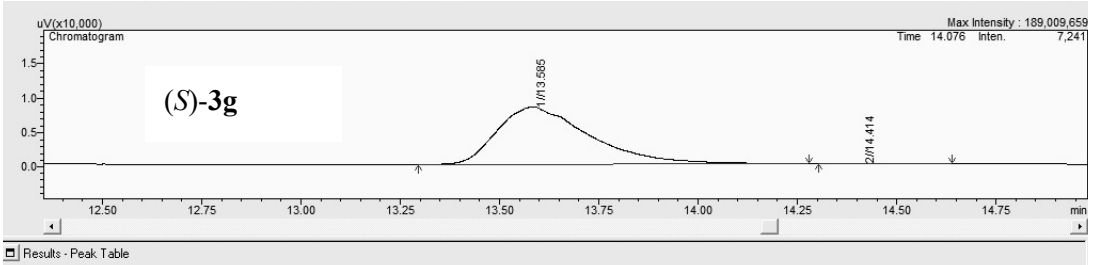
Peak#	Ret. Time	Area	Height	Mark	Compound Name	Area%
1	13.419	136694.7	16817.7			49.6769
2	13.834	138472.8	16987.5	V		50.3231



Results - Peak Table

Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Compound Name	Area%
1	13.604	1125.5	77.2			1.0900
2	13.998	102130.0	6695.4	V		98.9100

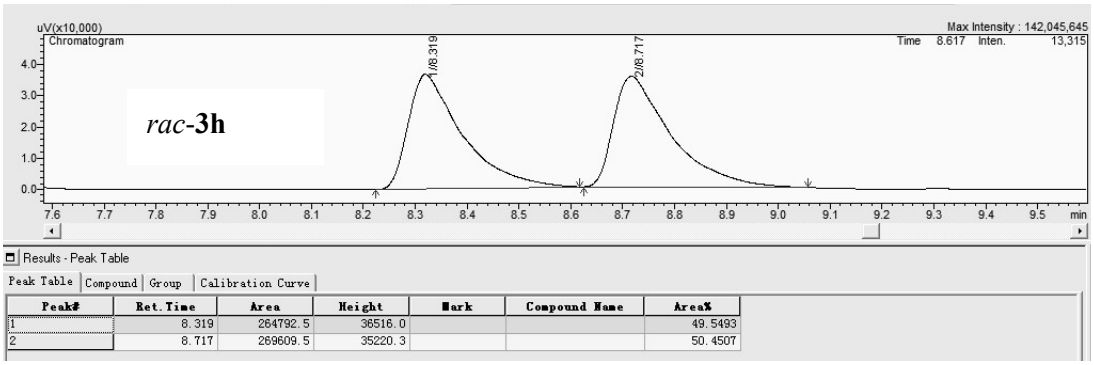


Results - Peak Table

Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Compound Name	Area%
1	13.585	134238.4	8319.9			99.3033
2	14.414	941.9	99.5			0.6967

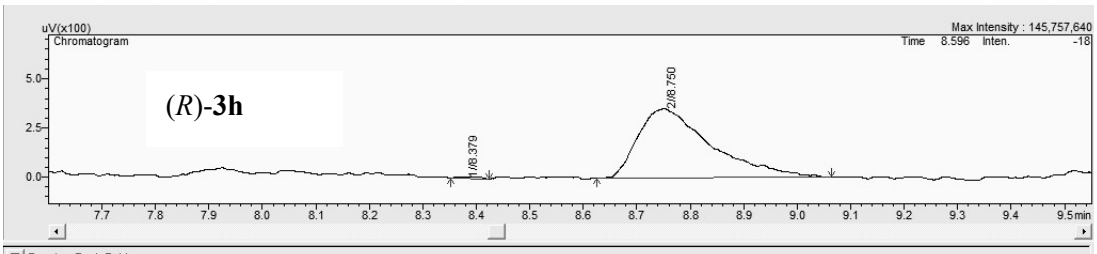
3h, chiral GC (Agilent CP-chirasil-Dex CB, T_S = 8.3 min, T_R = 8.7 min, Temperature conditions: initial temperature 140℃, 2℃/min to 180℃, holding 1 min).



Results - Peak Table

Peak Table | Compound | Group | Calibration Curve

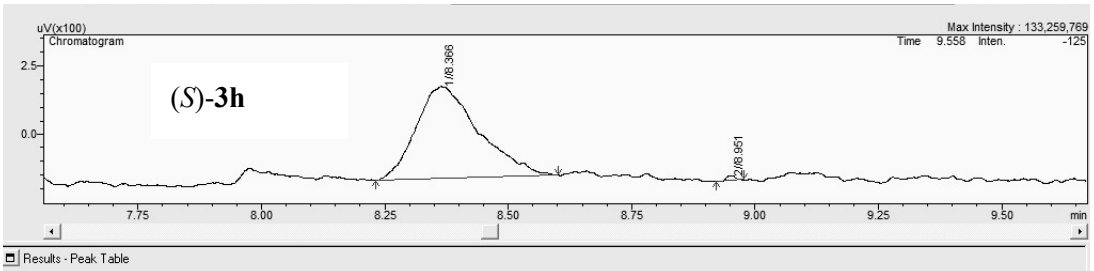
Peak#	Ret. Time	Area	Height	Mark	Compound Name	Area%
1	8.319	264792.5	36516.0			49.5493
2	8.717	269609.5	35220.3			50.4507



Results - Peak Table

Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Compound Name	Area%
1	8.379	33.0	14.2			0.9652
2	8.750	3388.5	353.2			99.0348

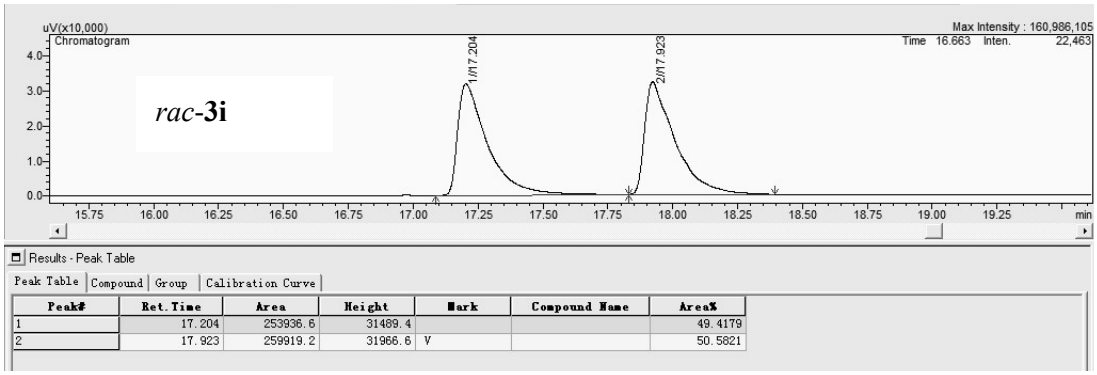


Results - Peak Table

Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Compound Name	Area%
1	8.366	2971.6	335.6			99.3729
2	8.951	18.8	15.4			0.6271

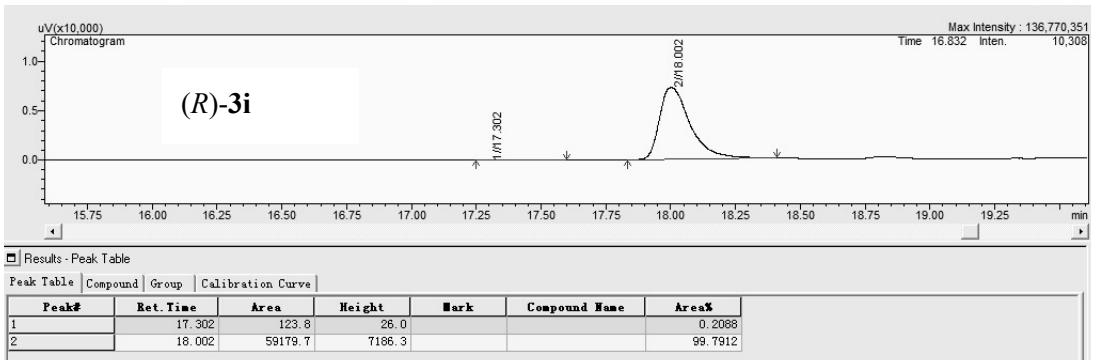
3i, chiral GC (Agilent CP-chirasil-Dex CB, T_S = 17.2 min, T_R = 17.9 min, Temperature conditions: initial temperature 140℃, 2℃/min to 180℃, holding 1 min).



Results - Peak Table

Peak Table | Compound | Group | Calibration Curve

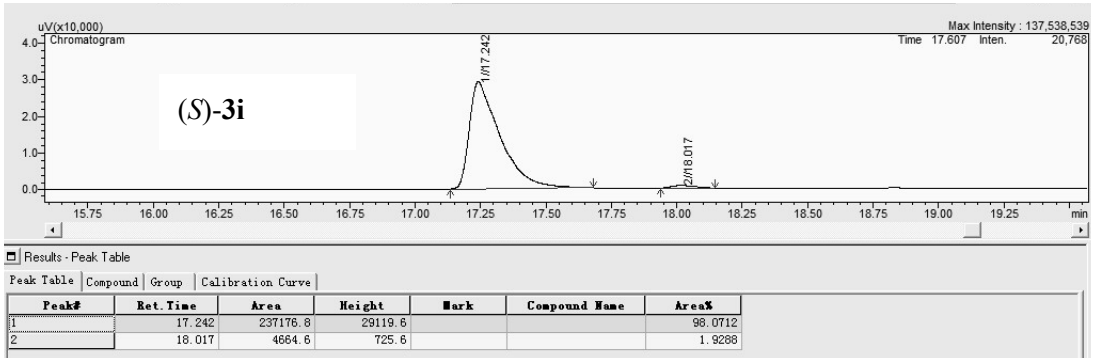
Peak#	Ret. Time	Area	Height	Mark	Compound Name	Area%
1	17.204	253936.6	31489.4			49.4179
2	17.923	259919.2	31966.6	V		50.5821



Results - Peak Table

Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Compound Name	Area%
1	17.302	123.8	26.0			0.2088
2	18.002	59179.7	7186.3			99.7912

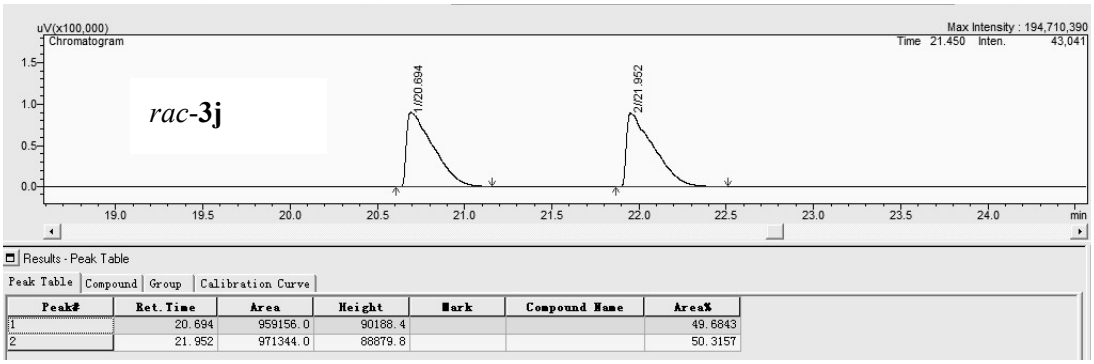


Results - Peak Table

Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Compound Name	Area%
1	17.242	237176.8	29119.6			98.0712
2	18.017	4664.6	725.6			1.9288

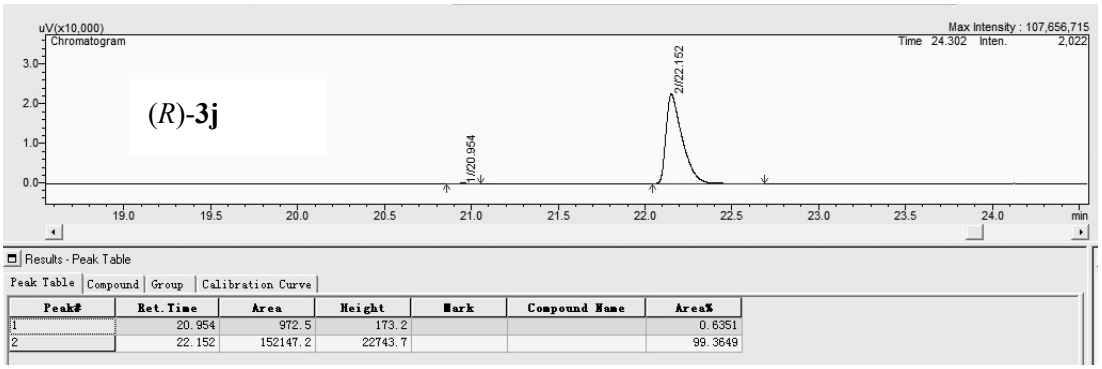
3j, chiral GC (Agilent CP-chirasil-Dex CB, T_S = 20.7 min, T_R = 22.0 min, Temperature conditions: initial temperature 100℃, 2℃/min to 150℃, then 40℃/min to 180℃, holding 1 min).



Results - Peak Table

Peak Table | Compound | Group | Calibration Curve

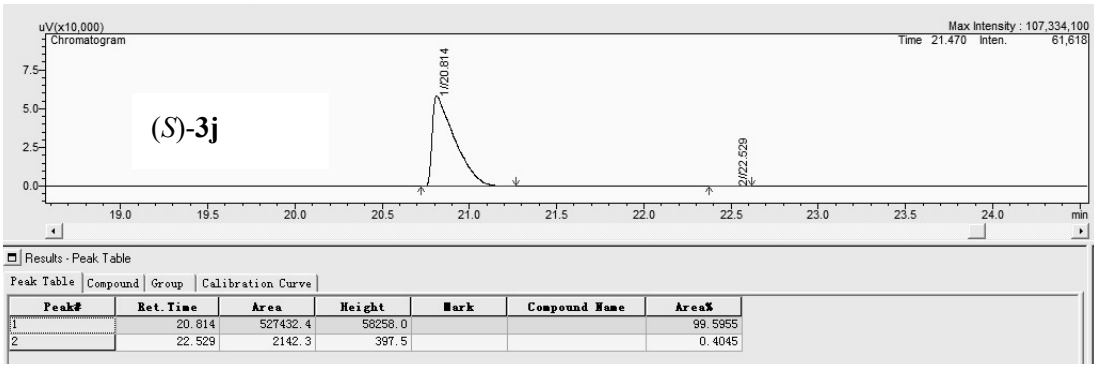
Peak#	Ret. Time	Area	Height	Mark	Compound Name	Area%
1	20.694	959156.0	90188.4			49.6843
2	21.952	971344.0	88879.8			50.3157



Results - Peak Table

Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Compound Name	Area%
1	20.954	972.5	173.2			0.6351
2	22.152	152147.2	22743.7			99.3649

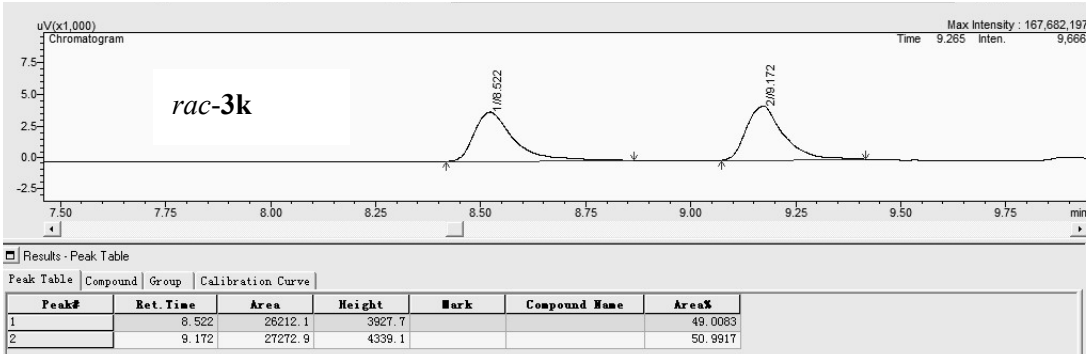


Results - Peak Table

Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Compound Name	Area%
1	20.814	527432.4	58258.0			99.5955
2	22.529	2142.3	397.5			0.4045

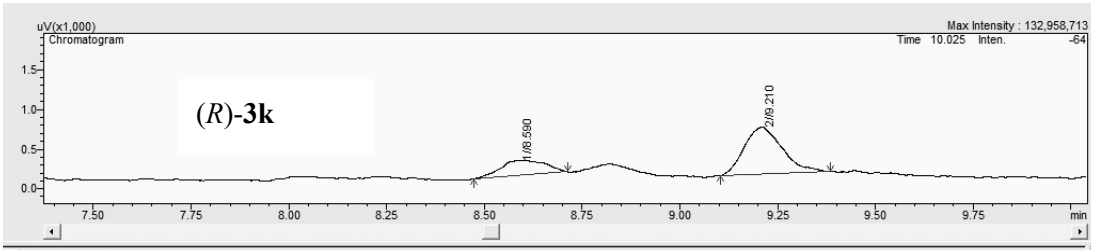
3k, chiral GC (Agilent CP-chirasil-Dex CB, T_S = 8.5 min, T_R = 9.2 min, Temperature conditions: initial temperature 140℃, 2℃/min to 180℃, holding 1 min).



Results - Peak Table

Peak Table | Compound | Group | Calibration Curve

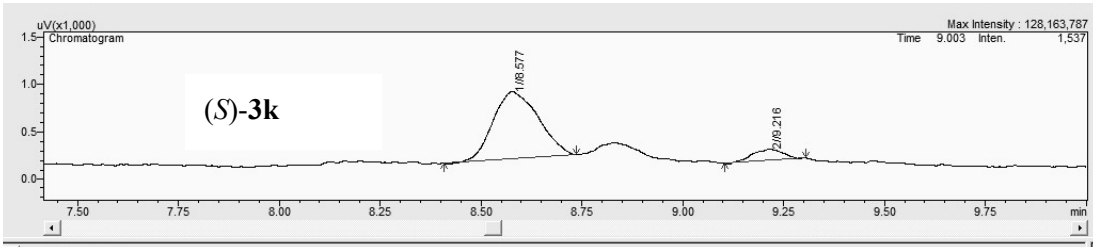
Peak#	Ret. Time	Area	Height	Mark	Compound Name	Area%
1	8.522	26212.1	3927.7			49.0083
2	9.172	27272.9	4339.1			50.9917



Results - Peak Table

Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Compound Name	Area%
1	8.590	1490.3	191.9			27.1680
2	9.210	3995.3	588.2			72.8320

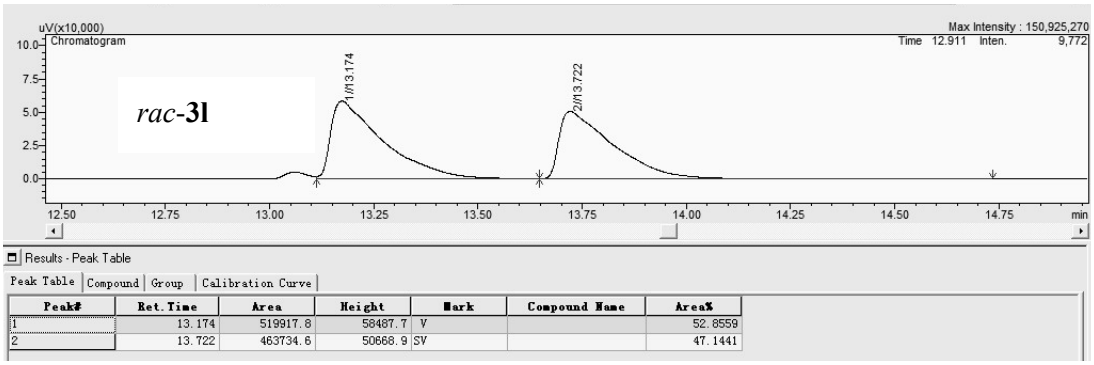


Results - Peak Table

Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Compound Name	Area%
1	8.577	5504.6	703.1			89.8784
2	9.216	619.9	114.7			10.1216

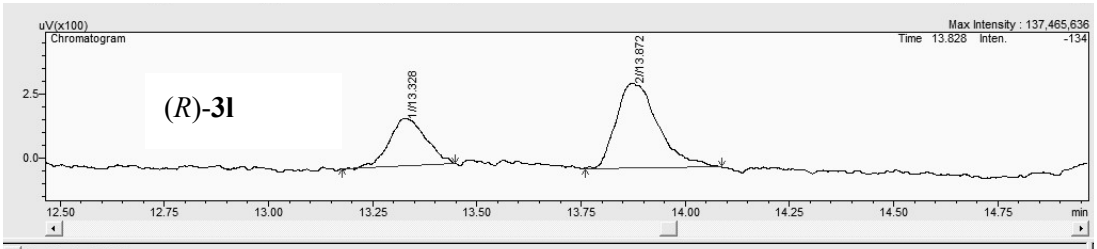
3l, chiral GC (Agilent CP-chirasil-Dex CB, T_S = 13.3 min, T_R = 13.8 min, Temperature conditions: initial temperature 140℃, 2℃/min to 180℃, holding 1 min).



Results - Peak Table

Peak Table | Compound | Group | Calibration Curve

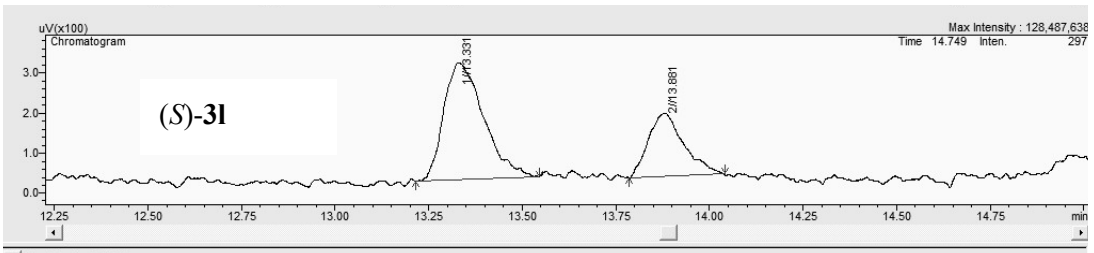
Peak#	Ret. Time	Area	Height	Mark	Compound Name	Area%
1	13.174	519917.8	58487.7	V		52.8559
2	13.722	463734.6	50668.9	SV		47.1441



Results - Peak Table

Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Compound Name	Area%
1	13.328	1174.8	187.7			33.3616
2	13.872	2346.6	332.4			66.6384

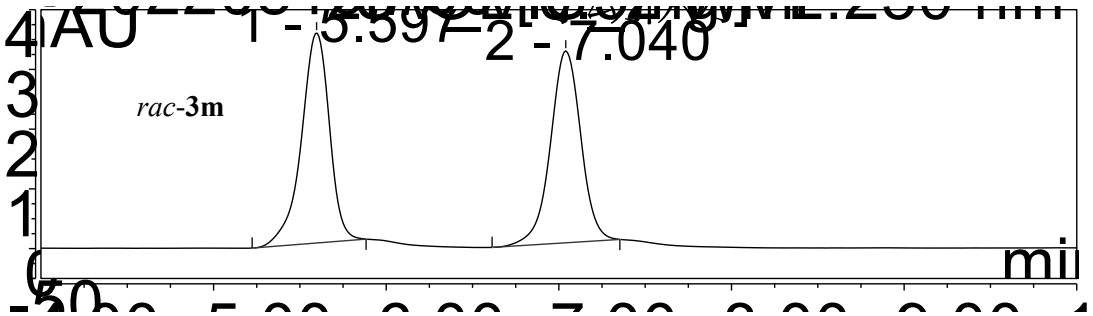


Results - Peak Table

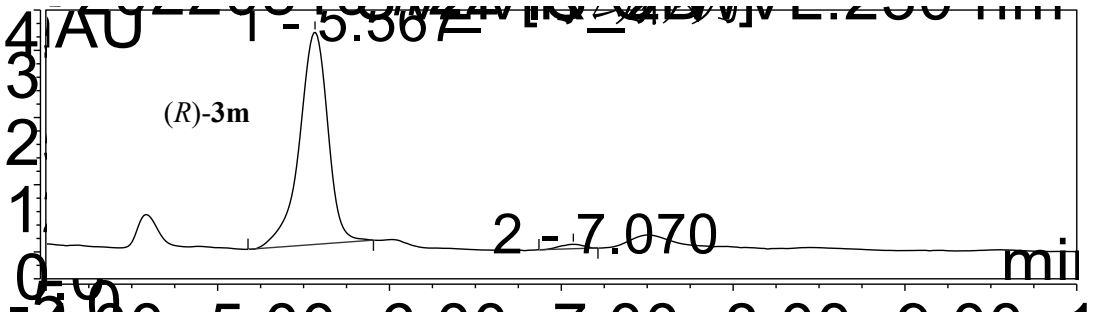
Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Compound Name	Area%
1	13.331	2143.9	290.0			67.6222
2	13.881	1026.5	155.6			32.3778

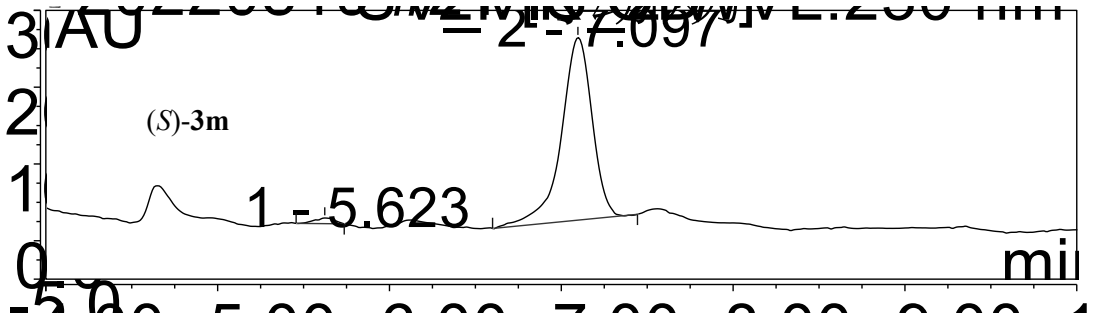
3m, chiral HPLC (Daicel, CHIRALCEL OD-H, T_R = 5.6 min, T_S = 7.0 min, mobile phase: n-Hexane/2-Propanol = 90/10 (v/v), flow rate: 1.0 mL/min, detection: UV 230 nm, temperature: 30 °C.)



Peak	Retention time (min)	Peak area (mAU*min)	Relative peak area (%)
1	5.597	66.310	50.23
2	7.040	65.711	49.77

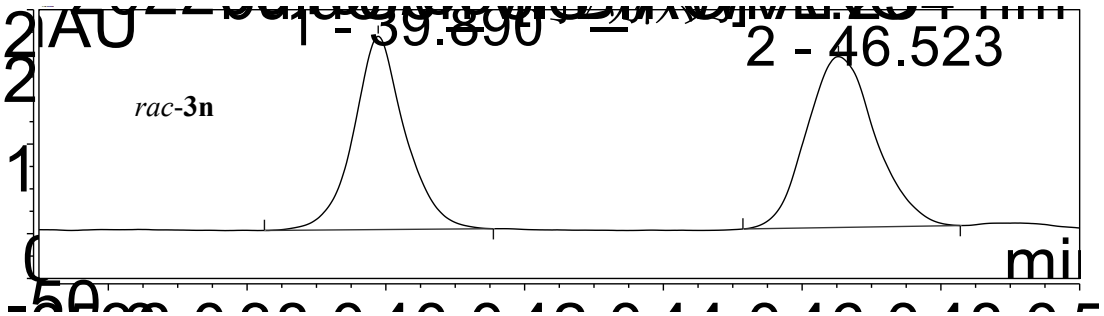


Peak	Retention time (min)	Peak area (mAU*min)	Relative peak area (%)
1	5.567	7.596	98.33
2	7.070	0.129	1.67

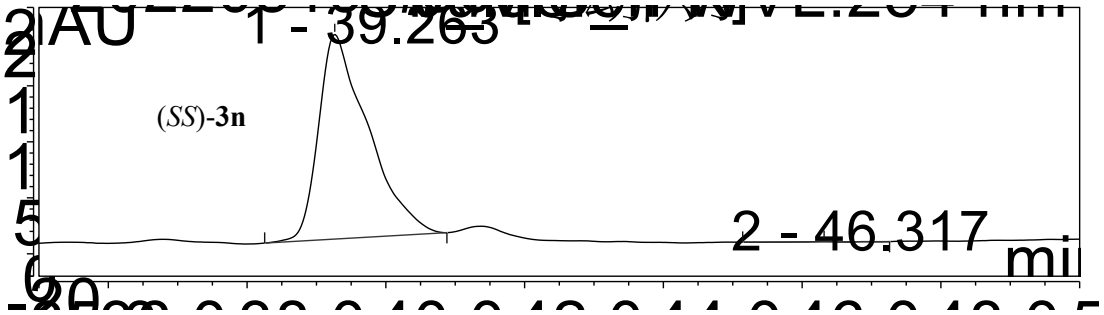


Peak	Retention time (min)	Peak area (mAU*min)	Relative peak area (%)
1	5.623	0.100	1.98
2	7.097	4.954	98.02

3n, chiral HPLC (Daicel, CHIRALCEL OD-H, T_R = 39.8 min, T_S = 46.5 min, mobile phase: n-Hexane/2-Propanol = 98/2(v/v) to 90/10 (v/v) in 30 min, holding 30 min, flow rate: 1.0 mL/min, detection: UV 254 nm, temperature: 30 °C.)



Peak	Retention time (min)	Peak area (mAU*min)	Relative peak area (%)
1	39.890	186.071	45.87
2	46.523	219.574	54.13



Peak	Retention time (min)	Peak area (mAU*min)	Relative peak area (%)
1	39.263	151.338	99.93
2	46.317	0.101	0.07

7. References

1. W. Borzecka, I. Lavandera and V. Gotor, *J. Org. Chem.*, 2013, **78**, 7312-7317.

2. J. Fan, Y. Peng, W. Xu, A. Wang, J. Xu, H. Yu, X. Lin and Q. Wu, *Org. Let.*, 2020, **22**, 5446-5450.

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