

Enantiocomplementary Decarboxylative Hydroxylation Combining Photocatalysis and Whole-Cell Biocatalysis in One-pot Cascade Process

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Experimental procedures

General information

All reagents were obtained commercially unless otherwise noted. The ^1H and ^{13}C NMR spectra were recorded with a Bruker AMX400 MHz spectrometer using TMS as an internal standard. Chiral GC was performed with Agilent CP-chirasil-Dex CB using dodecane or pentadecane as internal standard. Chiral HPLC was performed with a Chiralpak OB-H, OJ-H column (250 mm \times 4.6 mm, n-hexane/2-propanol as the mobile phase) and a UV detector (220 or 254 nm). All known products were characterized by comparison of ^1H and ^{13}C NMR data with those reported in the literature. Absolute configuration confirmed by comparison with literature values. The power of the LEDs is 8W.

Preparation of ketoreductases¹ (KtCR and YueD)

100 μL Stored bacteria was first incubated in 5 mL LB media with Kanamycin (50 $\mu\text{g}/\text{mL}$) and then shaken at 37 $^\circ\text{C}$ overnight. A fresh 200 mL of LB medium with 50 $\mu\text{g}/\text{mL}$ Kanamycin was inoculated from 5 mL preculture. The cultures were allowed to grow at 37 $^\circ\text{C}$ until OD_{600} at 0.6. After cooling at 4 $^\circ\text{C}$ for 30 min, isopropyl β -thiogalactopyranoside (IPTG) was added to a final concentration of 0.5 mM to induce ketoreductases expression at 25 $^\circ\text{C}$ (OD_{600} at 6, when using for whole-cell reaction system). Cells were harvested by centrifugation, and resuspended in buffer (50 mM sodium phosphate buffer, pH 6.5 for KtCR and pH 7.4 for YueD), then repeated freezing and thawing for 3 times, and released the target proteins by sonication. The cell lysate was removed by centrifugation. The supernatant was concentrated by freeze drying and stored in $-20\text{ }^\circ\text{C}$ for next reaction.

Preparation of racemic alcohols

The given ketone (2 mmol) was added into a stirred solution of NaBH_4 (5 mmol) in methanol (10 mL) at room temperature (20 $^\circ\text{C}$). The clear solution was stirred until the complete disappearance of ketone substrate indicated by TLC. The crude product was evaporated in vacuo and diluted in dichloromethane (20 mL), and then washed with water (10 mL). The organic phase was separated and dried over anhydrous magnesium sulfate, and then evaporated in vacuo.

General procedure for decarboxylative hydroxylation

SAS (3 mM, 10% mol) was dissolved in 2 mL water containing **1a** (30 mM). After irradiation with Blue LEDs for 18 hours (the reaction time could be extended to ensure no residual alcohols), 10 mL whole-cell culture medium of ketoreductase ($\text{OD}_{600}=6$) with glucose (0.3 mmol) was added into the photocatalytic mixture and shaken at 30 $^\circ\text{C}$ over night. The solution was extracted with equal volume of ethyl acetate for three times, and the stereoselectivity was then determined by chiral GC or HPLC.

Scaling-up one-pot decarboxylative hydroxylation catalyzed by photocatalyst and ketoreductase.

The scale-up reaction was performed as follows: A solution of SAS (0.3 mmol, 20 mol%) in 50 mL water with **1a** (1.5 mmol, dissolved in 500 μL acetonitrile). The reaction mixture was irradiated with Blue LEDs for 18 hours (the reaction time could be extended to ensure no residual alcohols). 150 mL whole-cell culture medium of ketoreductase ($\text{OD}_{600}=6$) with glucose (8 mmol) was added into the photocatalytic mixture and shaken at 30 $^\circ\text{C}$ over night. The reaction 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.

Table S1 Semi-quantitative comparison of existing decarboxylative carbonylation methods

Entry	Conditions	Substrate	Product	Yield (%)	Expense (\$/mg) ^a	Ref
1	Catalyst: 10%SAS, solvent: H ₂ O, <i>hν</i>	1a	2a	98	0.025	This work
2	Catalyst: 10%SAS, solvent: H ₂ O, <i>hν</i>	1j	2j	80	0.013	This work
3	Catalyst: 2eq K ₂ S ₂ O ₈ , solvent: H ₂ O, 90 °C	1j	2j	89	0.08	2
4	Solvent:CH ₃ CN, <i>hν</i>	1a	2a	27	0.91	3
5	Catalyst: FSM-16, solvent: Hexane, <i>hν</i>	1a	2a	47	0.39 ^b	4
6	Catalyst: HgO, solvent: CH ₃ CN/CH ₃ OH, <i>hν</i>	1a	2a	77	0.09	5
7	Catalyst: HgF ₂ , solvent: CH ₃ CN, <i>hν</i>	1a	2a	94	0.25	6
8	Catalyst: 4eq K ₅ Co ^{III} W ₁₂ O ₄₀ , solvent: CH ₃ CN/H ₂ O, <i>hν</i>	1a	2a	95	0.09 ^b	7
9	Catalyst : 10% Cu(OAC) ₂ , solvent: DMSO, 120 °C	1j	2j	31	0.11	8
10	Catalyst: NaIO ₄ /Mn(salophen), solvent: CH ₃ CN/H ₂ O	1a	2a	93	0.09 ^b	9

^a The rough estimation of reaction expenses is based on the price of commercial reagents in Sigma-Aldrich, the consumption of electricity was considered. ^b The expense calculated in entries 5, 8, 10 did not include FSM-16, K₅Co^{III}W₁₂O₄₀ and Mn(salophen), respectively.

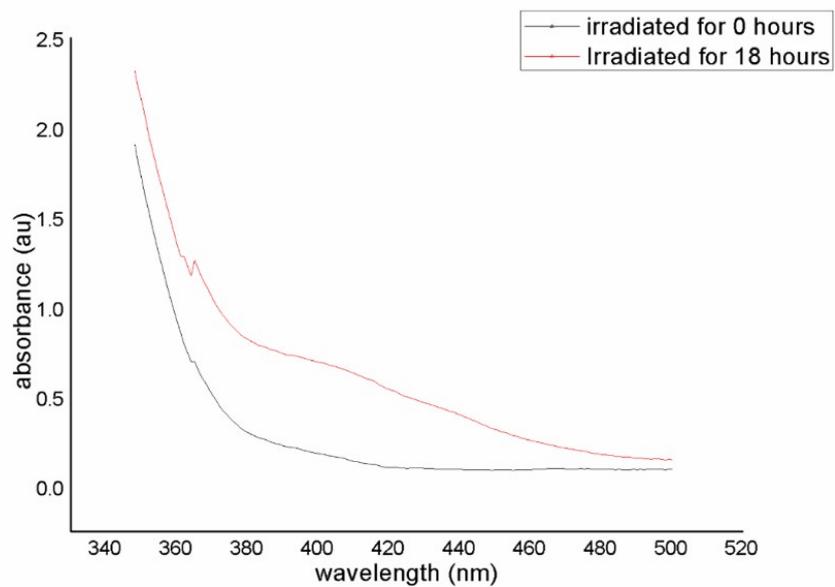


Figure S1. Ultraviolet-visible spectrum of SAS

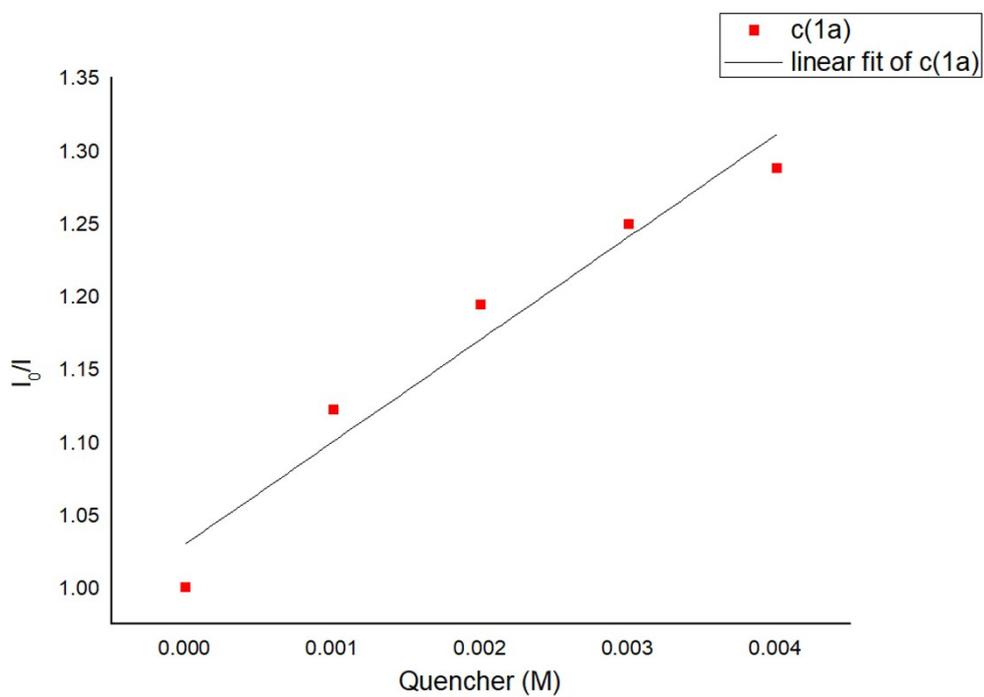
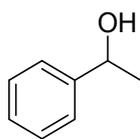


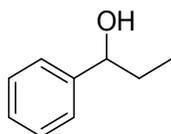
Figure S2. Stern-Volmer plot for the decarboxylation reaction

Characterization data



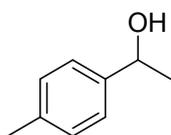
1-phenylethanol (3a)

^1H NMR (500 MHz, CDCl_3): δ 7.39–7.32 (m, 4H), 7.30–7.24 (m, 1H), 4.88 (q, J = 6.3 Hz, 1H), 1.48 (d, J = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3): δ 145.83, 128.51, 127.48, 125.41, 70.42, 25.17.



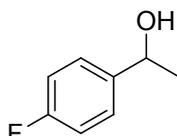
1-phenylpropan-1-ol (3b)

^1H NMR (400 MHz, CDCl_3): δ 7.37–7.25 (m, 5H), 4.58 (t, 1H), 1.92–1.65 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3): δ 144.59, 128.42, 127.52, 126.00, 76.04, 31.89, 10.18.



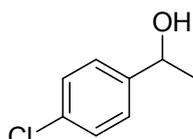
1-(p-tolyl)ethanol (3c)

^1H NMR (400 MHz, CDCl_3): δ 7.19 (d, J = 7.8 Hz, 2H), 7.09 (d, J = 7.9 Hz, 2H), 4.79 (q, J = 6.3 Hz, 1H), 2.27 (s, 3H), 1.41 (d, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3): δ 141.82, 136.15, 128.14, 124.33, 69.24, 24.04, 20.07.



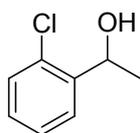
1-(4-fluorophenyl)ethanol (3d)

^1H NMR (400 MHz, CDCl_3): δ 7.37–7.30 (m, 2H), 7.06–6.99 (m, 2H), 4.88 (q, J = 6.3 Hz, 1H), 1.47 (d, J = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3): δ 163.33, 160.90, 141.52, 141.49, 127.09, 127.01, 115.37, 115.16, 69.79, 25.29.



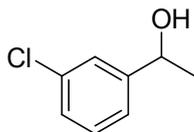
1-(4-chlorophenyl)ethanol (3e)

^1H NMR (400 MHz, CDCl_3): δ 7.43–7.16 (m, 4H), 4.86 (qd, J = 6.4, 3.1 Hz, 1H), 1.46 (d, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3): δ 144.25, 133.06, 128.61, 126.81, 69.74, 25.27.



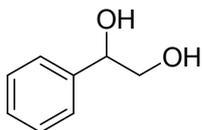
1-(2-chlorophenyl)ethanol (3f)

^1H NMR (400 MHz, CDCl_3): δ 7.60 (dd, J = 7.7, 1.6 Hz, 1H), 7.31 (ddd, J = 14.5, 7.8, 1.1 Hz, 2H), 7.20 (td, J = 7.6, 1.7 Hz, 1H), 5.30 (qd, J = 6.4, 3.6 Hz, 1H), 1.50 (d, J = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3): δ 143.04, 131.66, 129.42, 128.43, 127.23, 126.41, 67.00, 23.52.



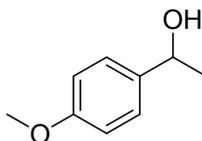
1-(3-chlorophenyl)ethanol (3g)

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.37 (s, 1H), 7.30 – 7.21 (m, 3H), 4.87 (q, $J = 6.0$ Hz, 1H), 1.48 (d, $J = 6.5$ Hz, 3H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 147.86, 134.37, 129.81, 127.54, 125.64, 123.55, 69.81, 25.25.



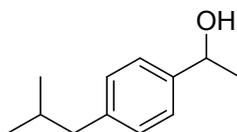
1-phenylethane-1,2-diol (3h)

$^1\text{H NMR}$ (500 MHz, CDCl_3): δ 7.39–7.28 (m, 5H), 4.82 (dd, $J = 8.2, 3.4$ Hz, 1H), 3.76 (dd, $J = 11.3, 3.3$ Hz, 1H), 3.66 (dd, $J = 11.3, 8.3$ Hz, 1H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3): δ 140.51, 128.57, 128.04, 126.08, 74.70, 68.10.



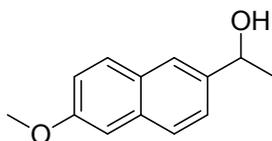
1-(4-methoxyphenyl)ethanol (3i)

$^1\text{H NMR}$ (500 MHz, CDCl_3): δ 7.29 (d, $J = 8.6$ Hz, 2H), 6.88 (d, $J = 8.7$ Hz, 2H), 4.84 (q, $J = 6.4$ Hz, 1H), 3.80 (s, 3H), 1.47 (d, $J = 6.5$ Hz, 3H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3): δ 158.98, 138.03, 126.68, 113.86, 69.98, 55.31, 25.02.



1-(4-isobutylphenyl)ethanol (3j)

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.28 (d, $J = 8.0$ Hz, 2H), 7.13 (d, $J = 8.1$ Hz, 2H), 4.87 (q, $J = 6.4$ Hz, 1H), 2.46 (d, $J = 7.2$ Hz, 2H), 1.88–1.84 (m, 1H), 1.49 (d, $J = 6.5$ Hz, 3H), 0.90 (d, $J = 6.6$ Hz, 6H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 143.05, 141.03, 125.21, 70.33, 45.09, 30.25, 25.02, 22.38.

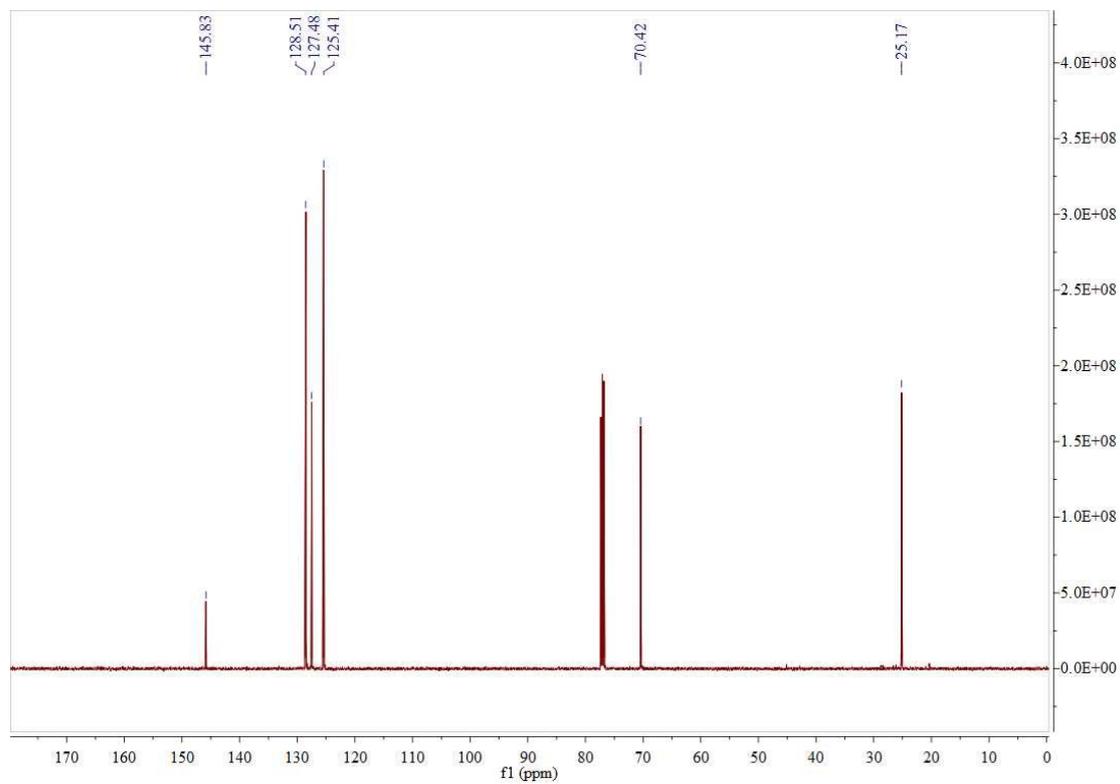
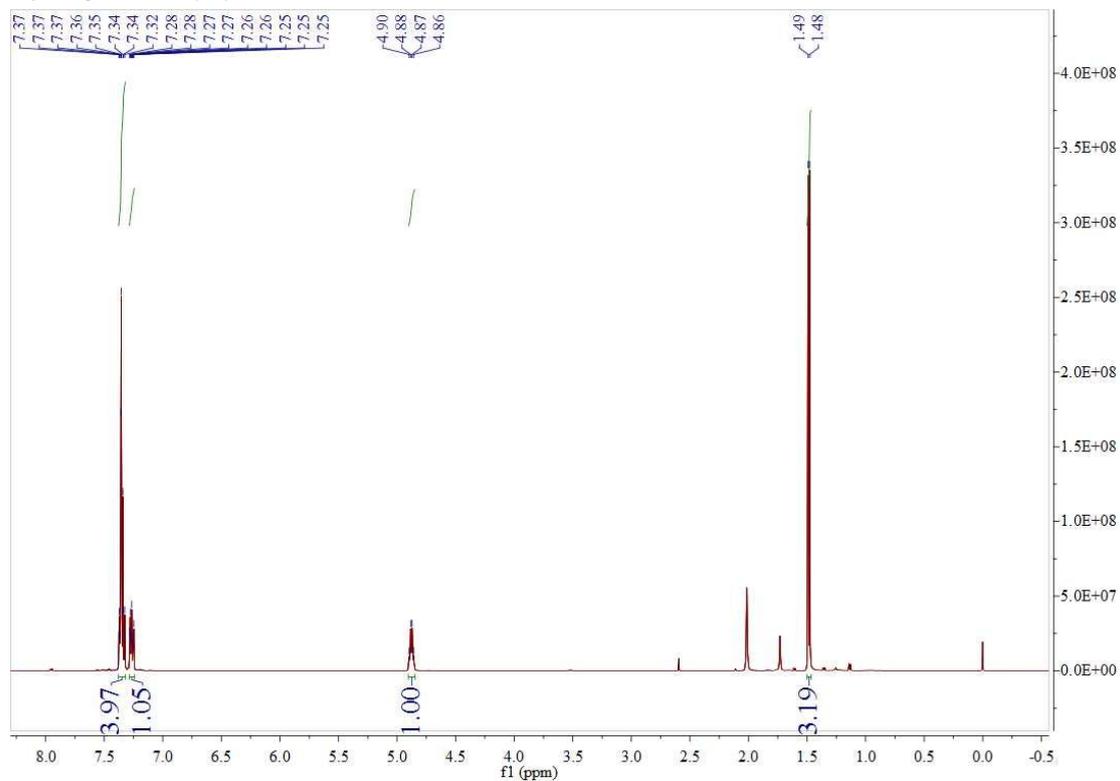


1-(6-methoxynaphthalen-2-yl)ethanol (3k)

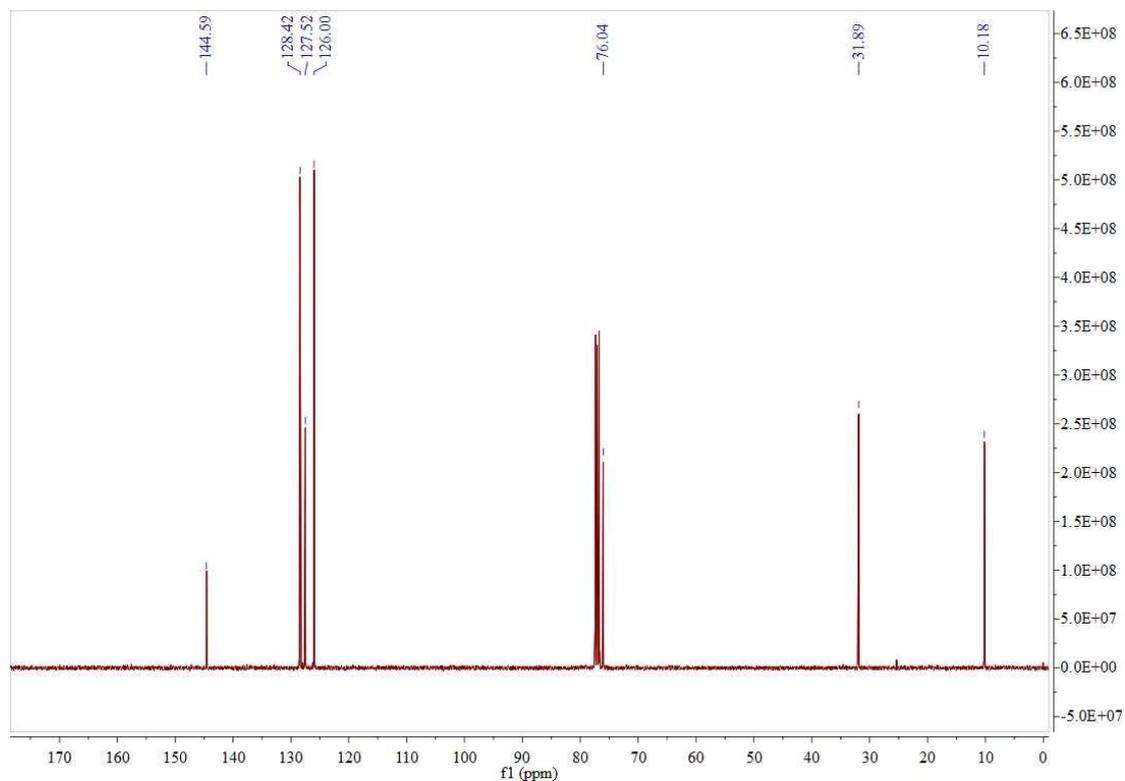
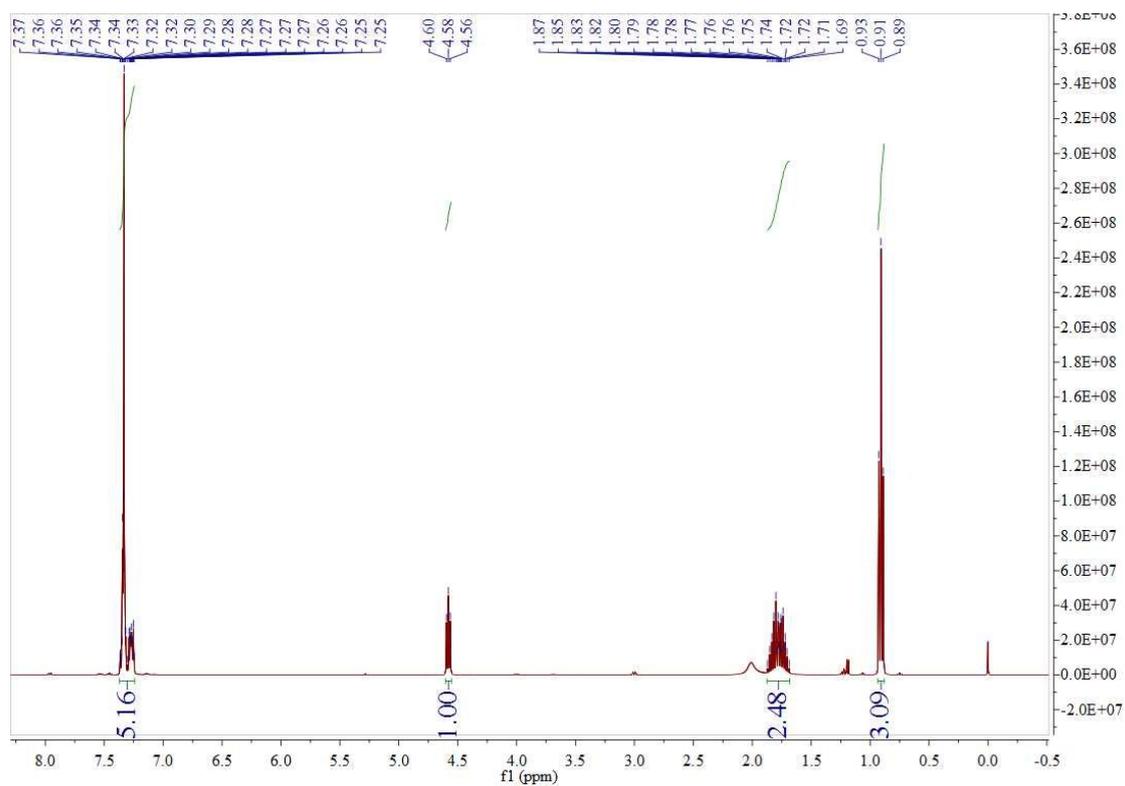
$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.77–7.69 (m, 3H), 7.51–7.41 (m, 1H), 7.19–7.07 (m, 2H), 5.28–4.86 (m, 1H), 3.92 (s, 3H), 1.57 (d, 3H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 129.41, 127.19, 124.37, 123.79, 118.98, 105.69, 70.55, 55.32, 25.08.

NMR spectra

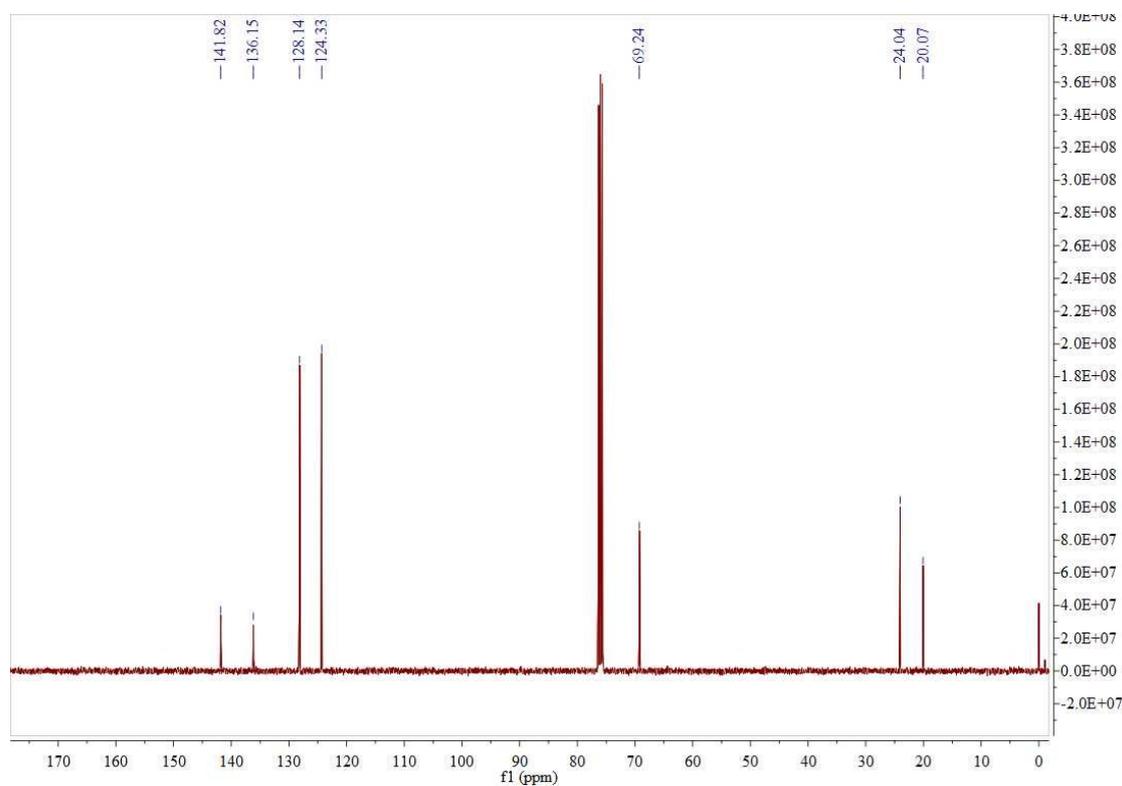
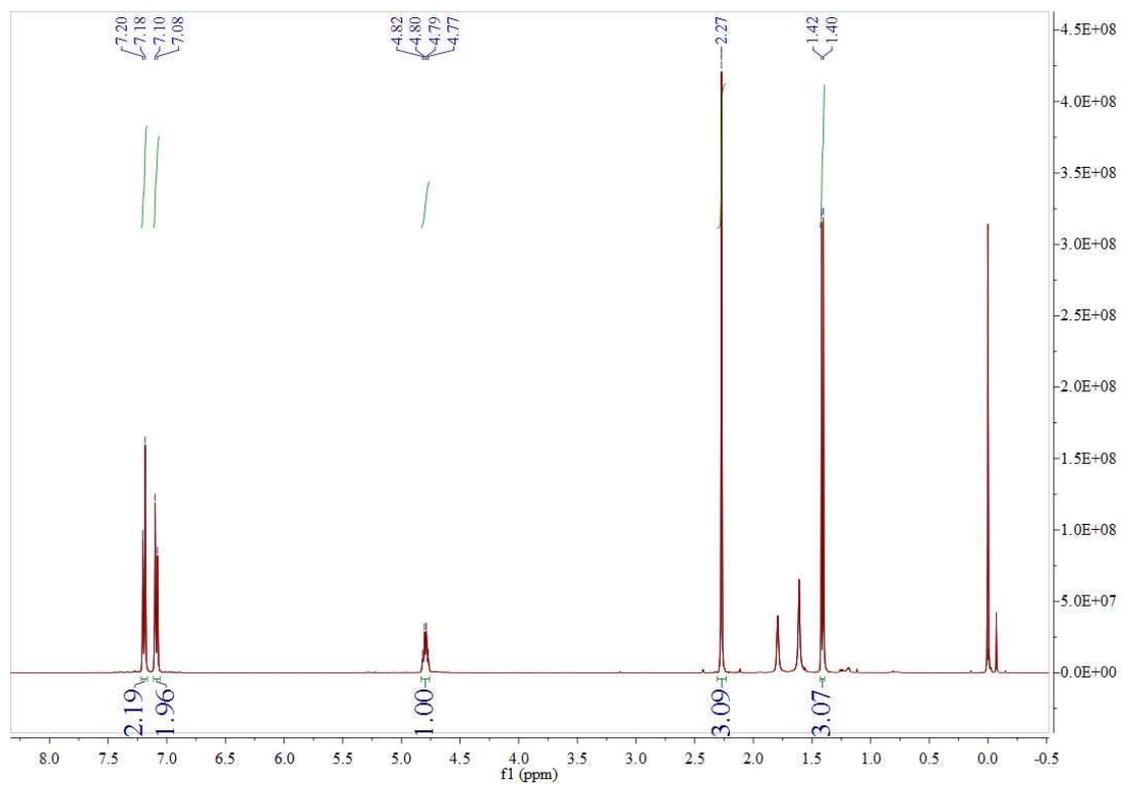
1-phenylethanol (3a)



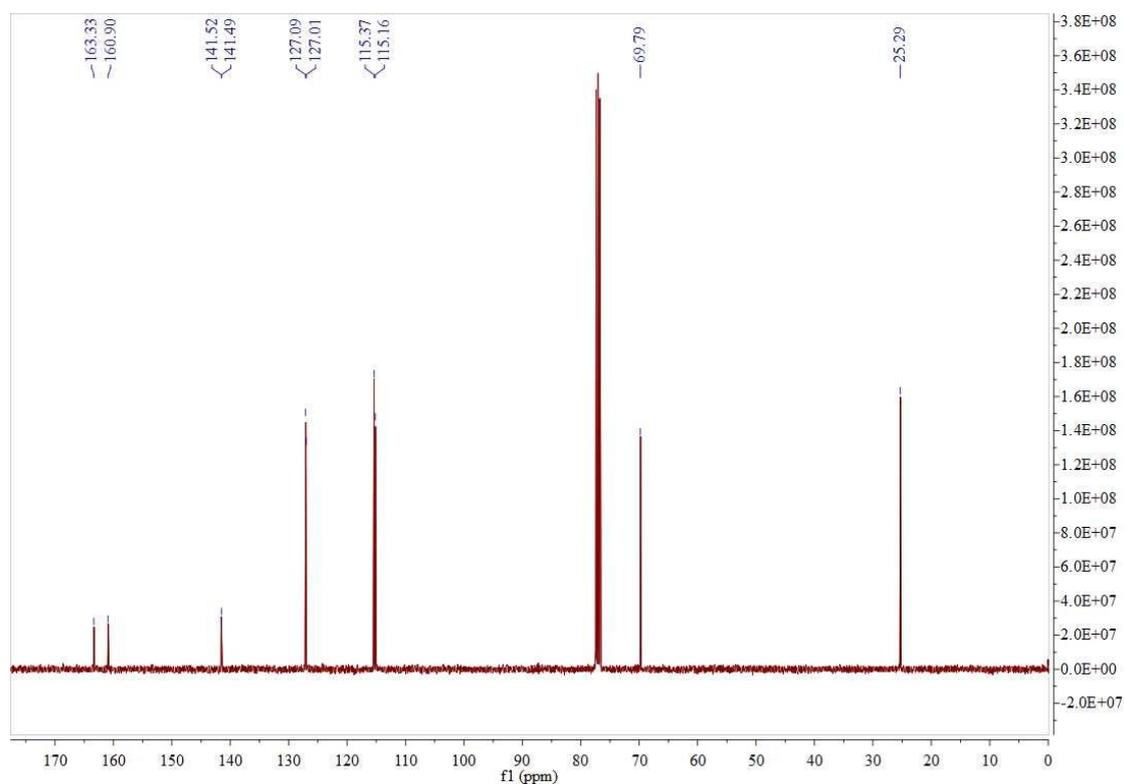
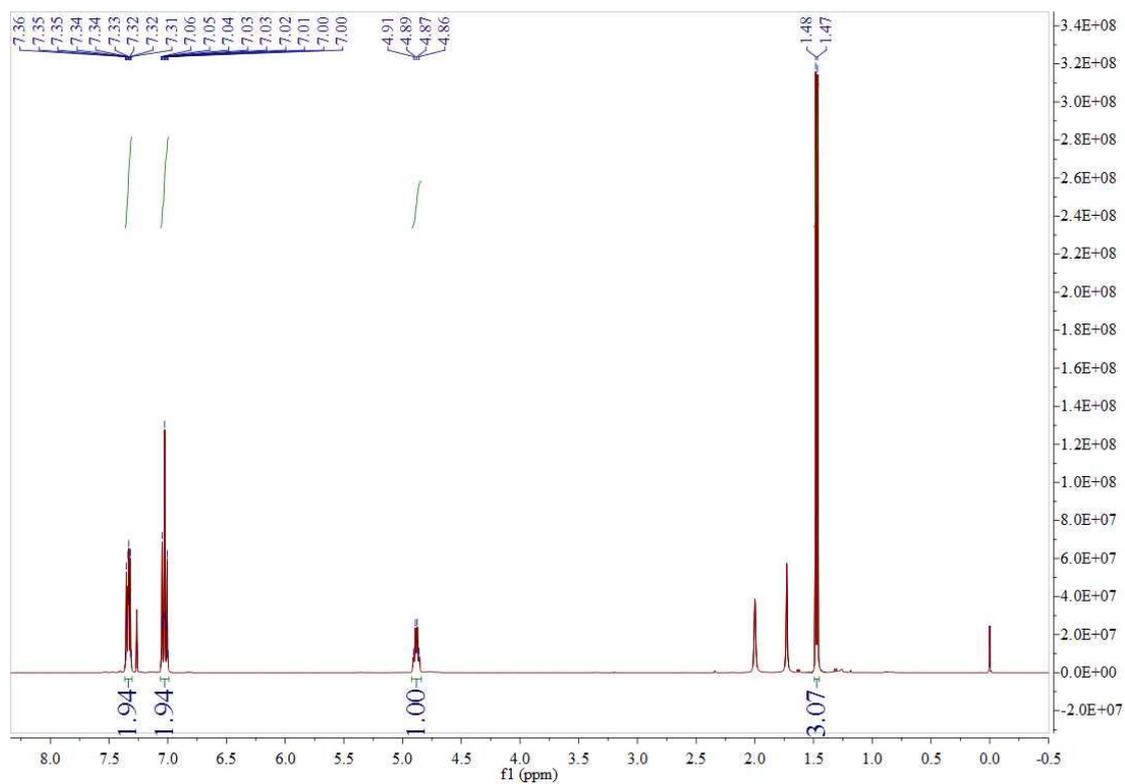
1-phenylpropan-1-ol (3b)



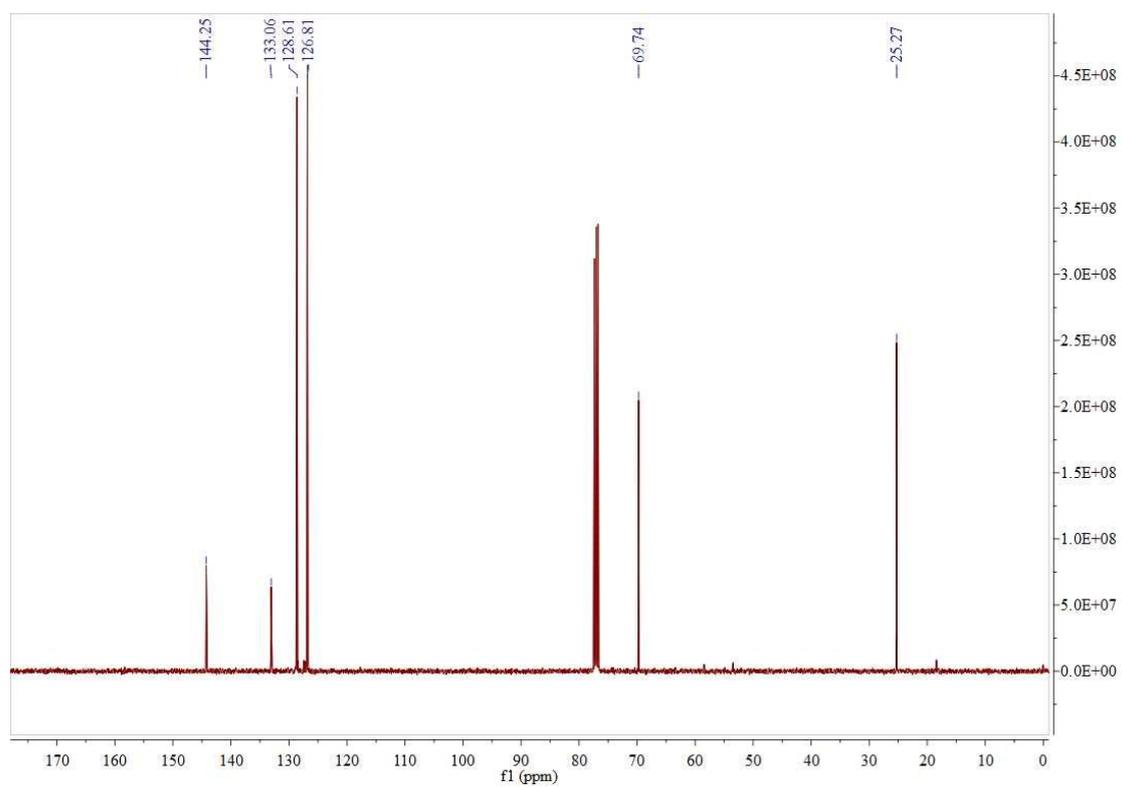
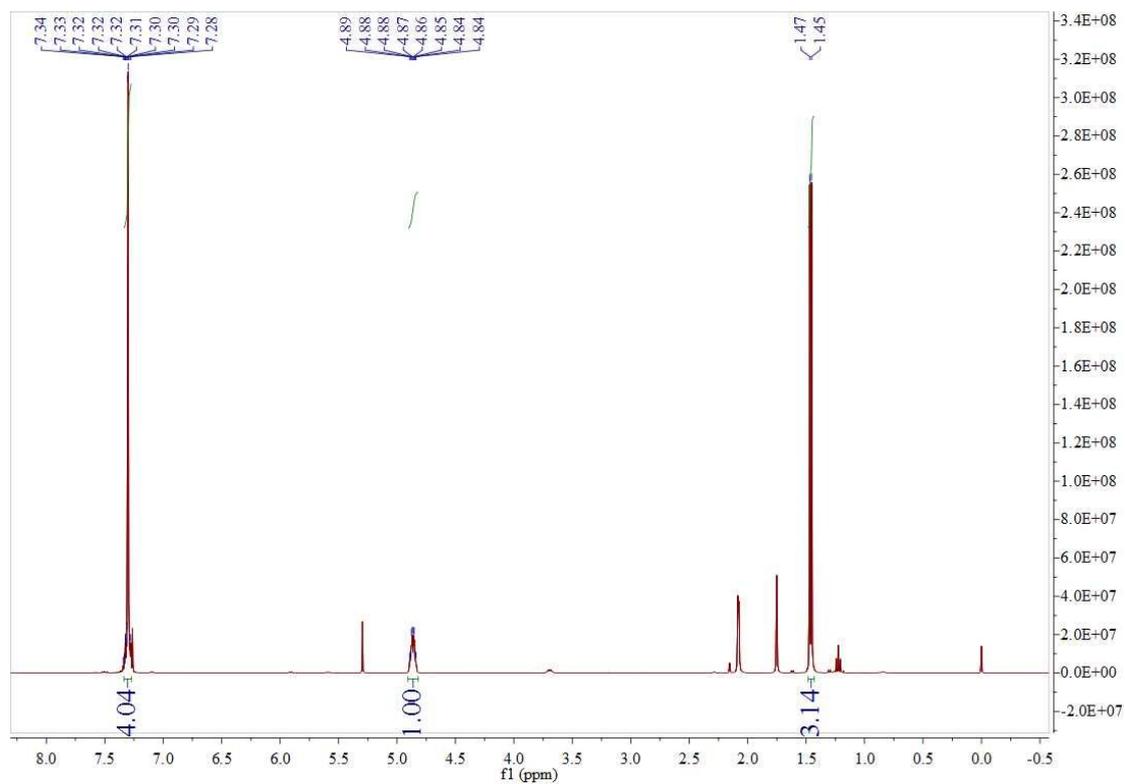
1-(p-tolyl)ethanol (3c)



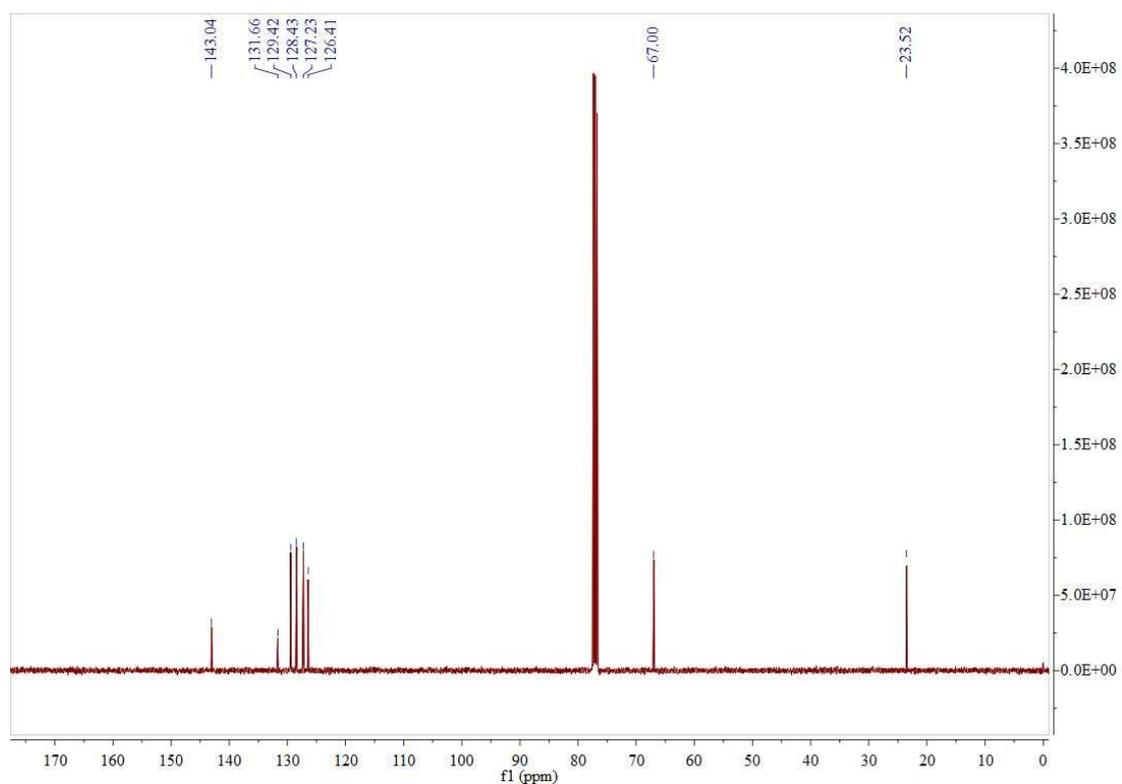
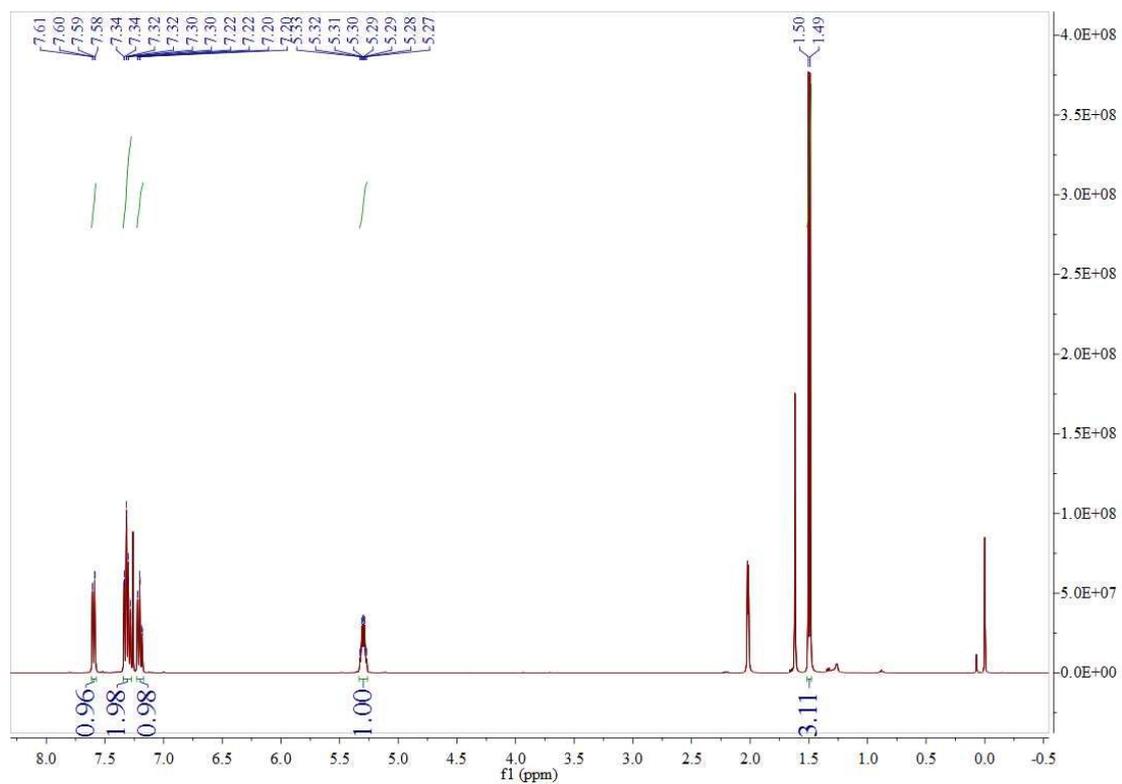
1-(4-fluorophenyl)ethanol (3d)



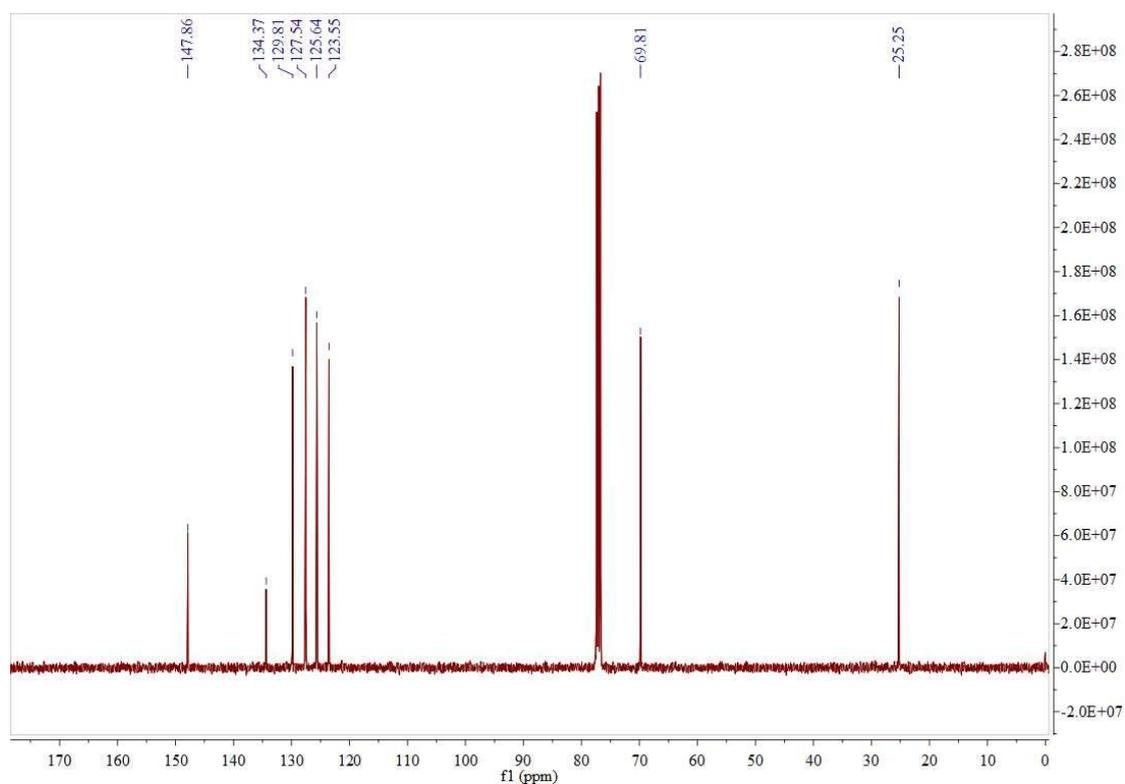
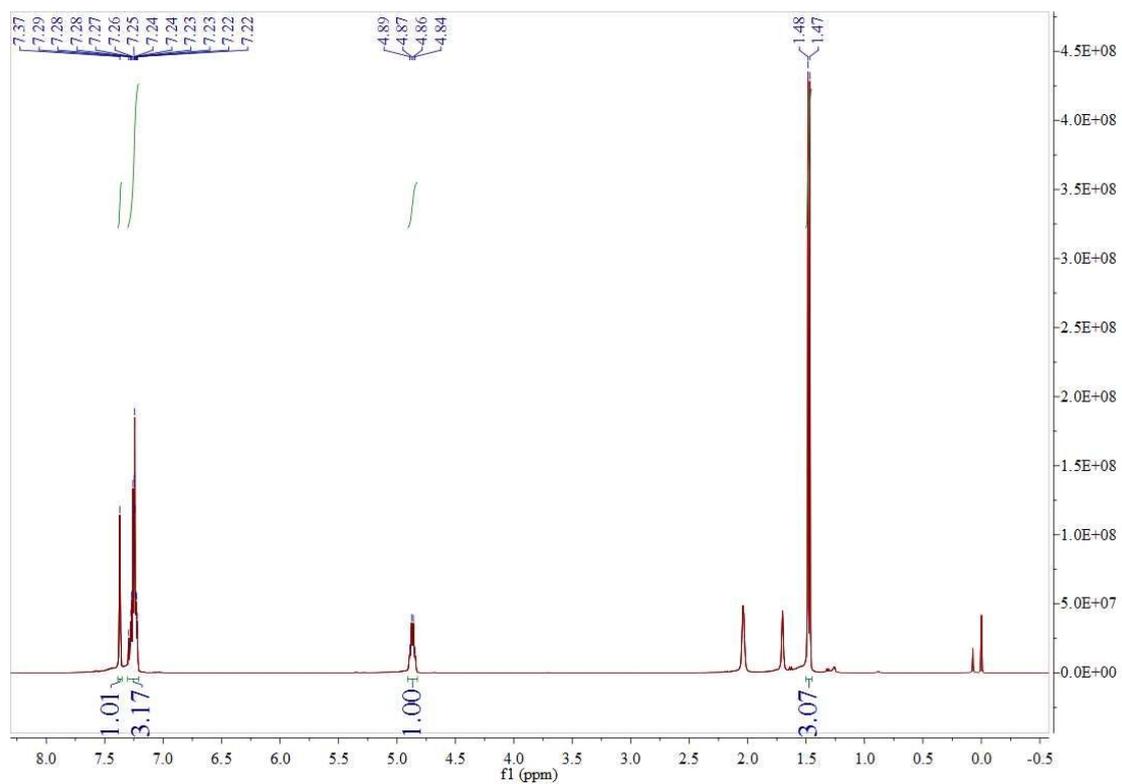
1-(4-chlorophenyl)ethanol (3e)



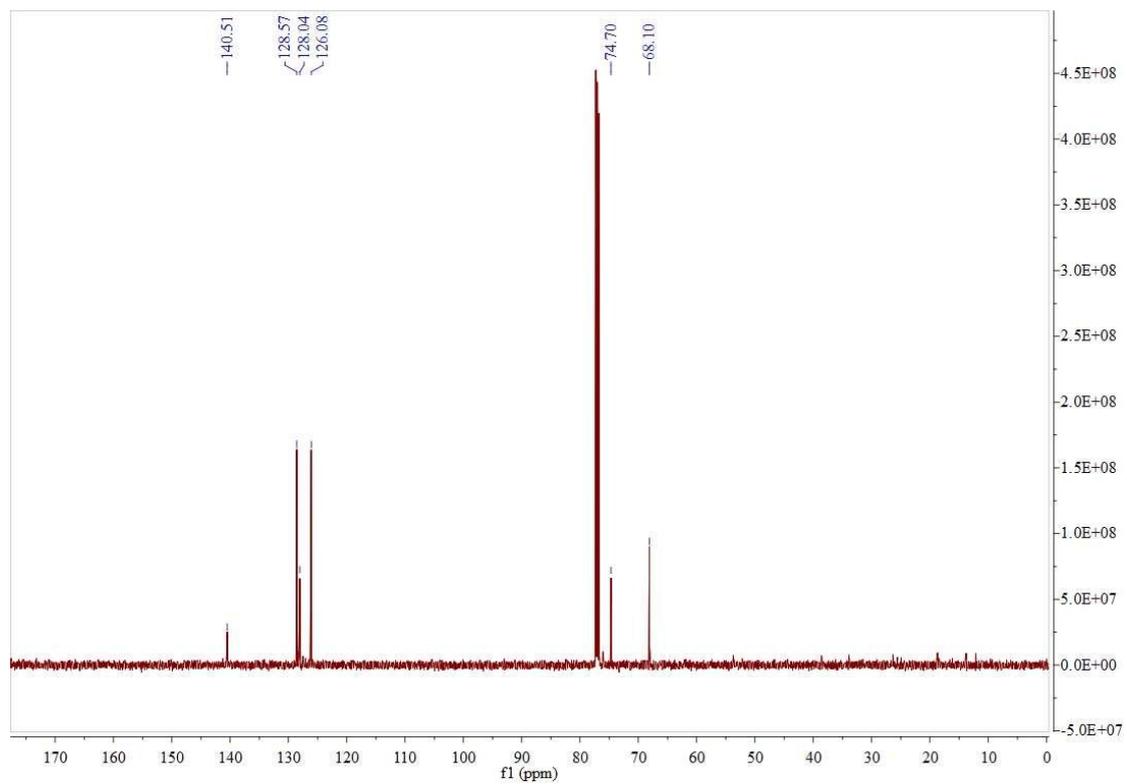
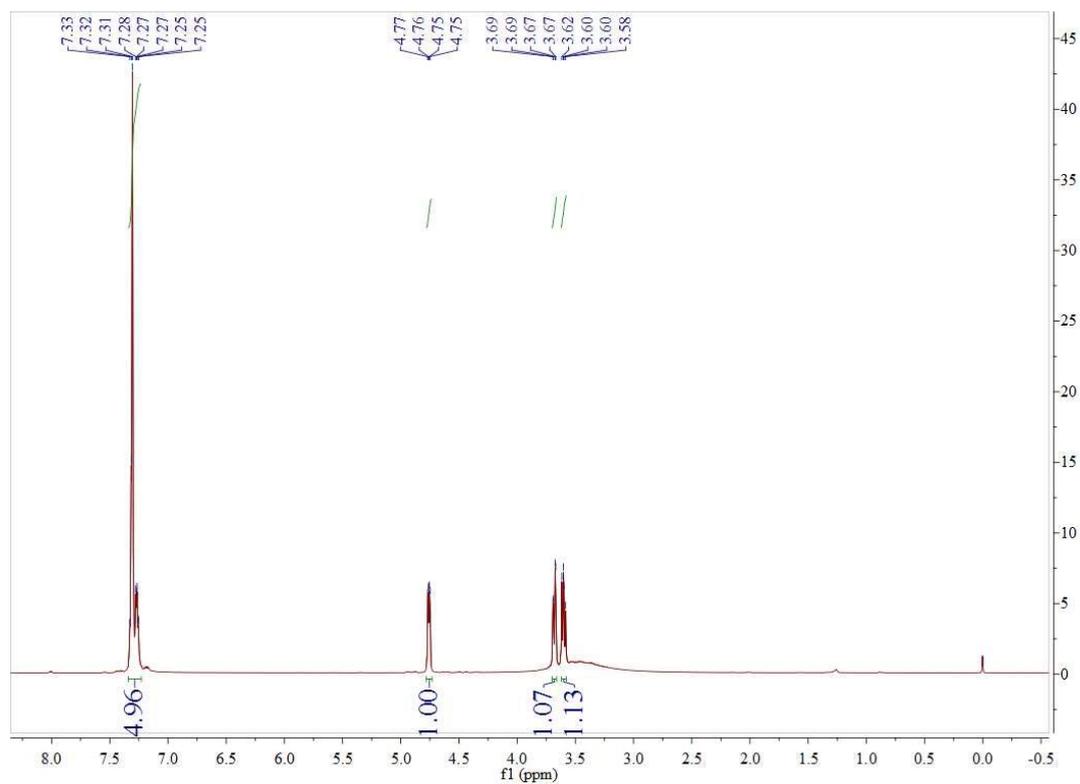
1-(2-chlorophenyl)ethanol (3f)



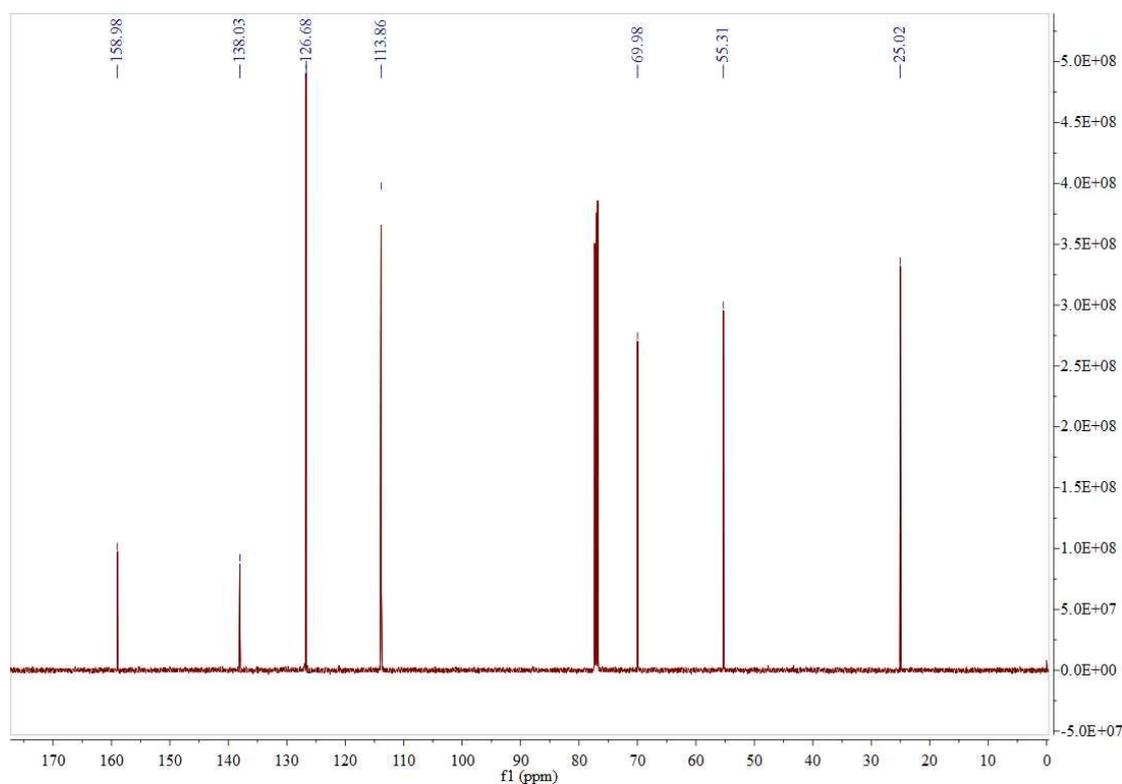
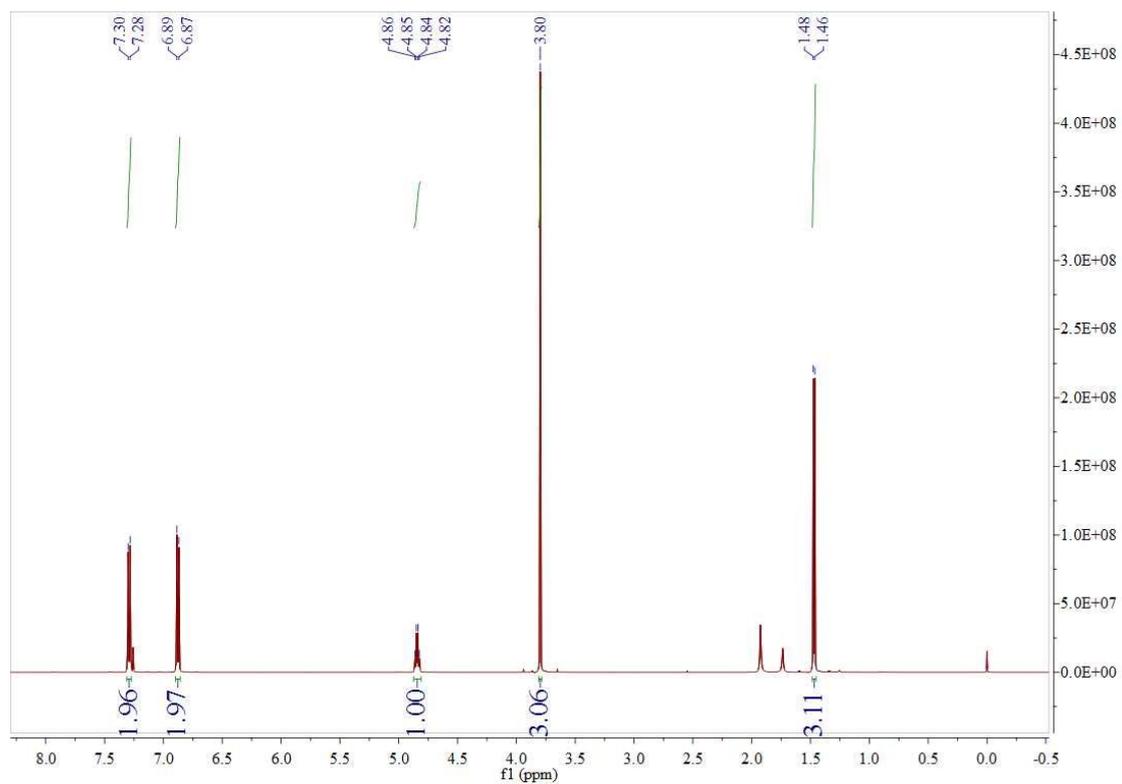
1-(3-chlorophenyl)ethanol (3g)



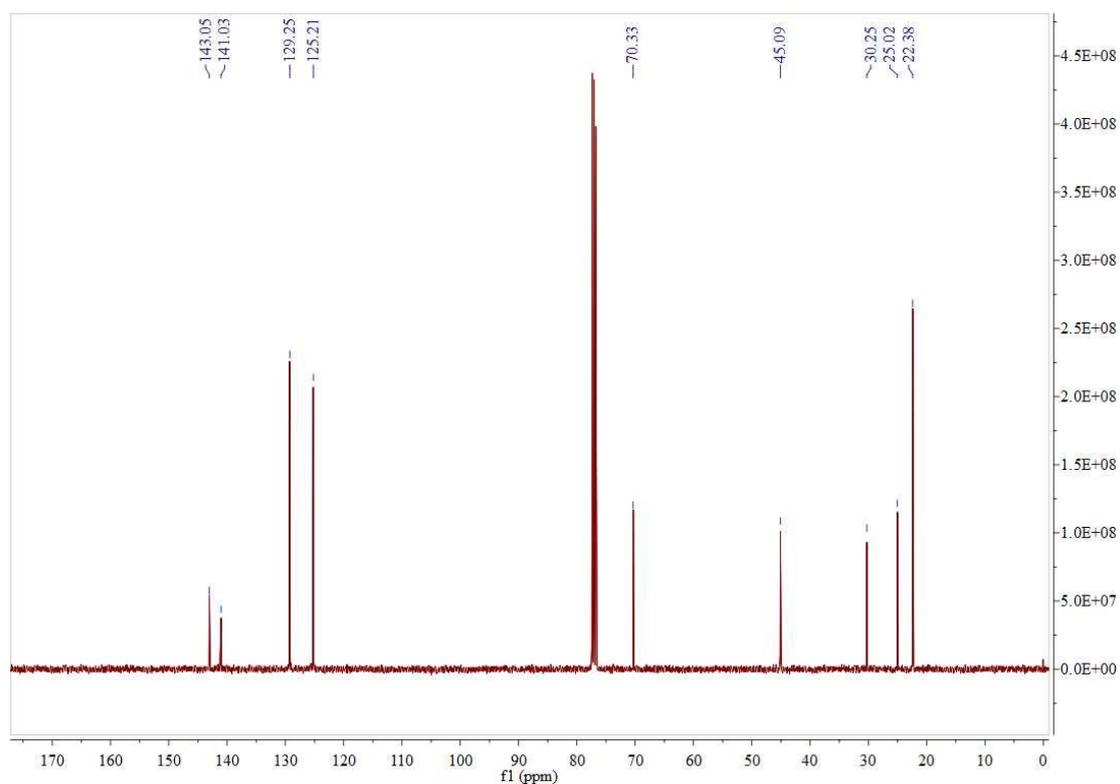
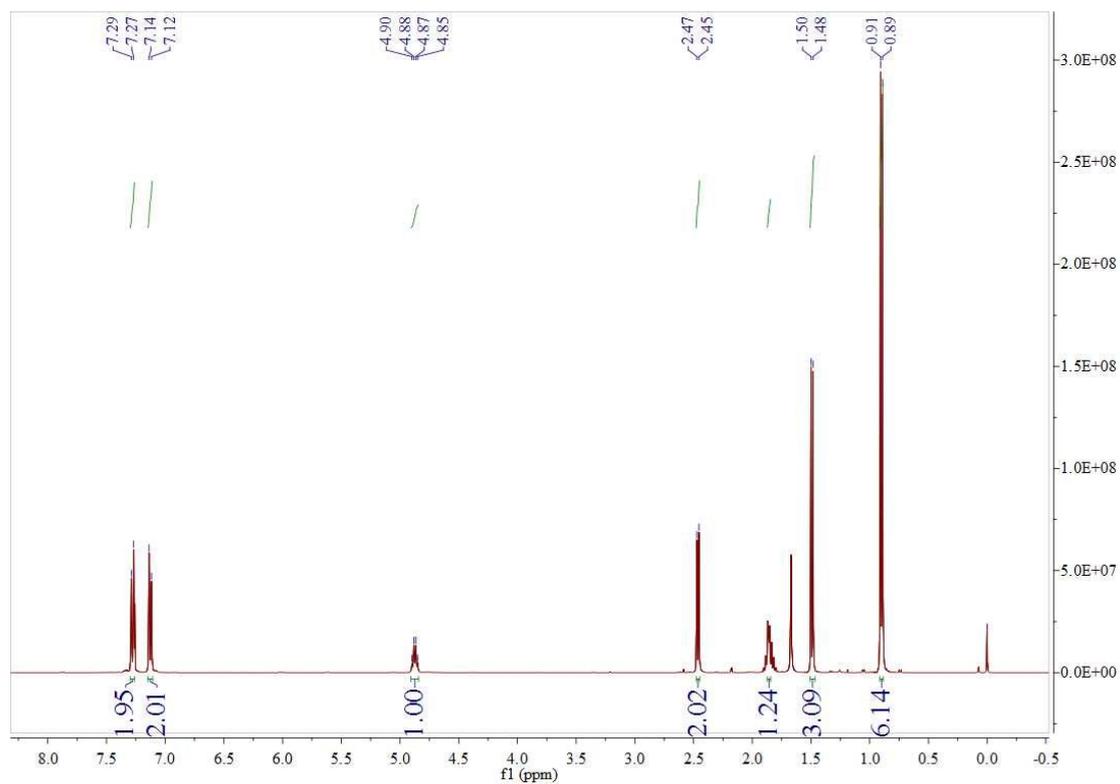
1-phenylethane-1,2-diol (3h)



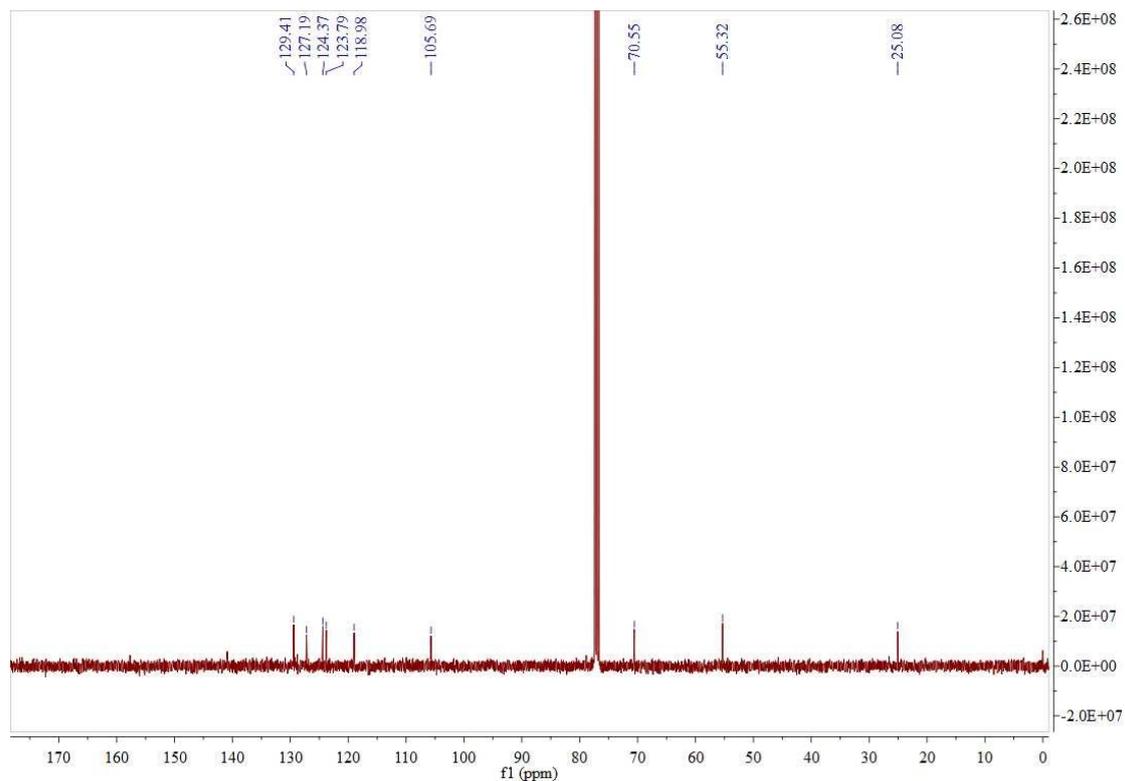
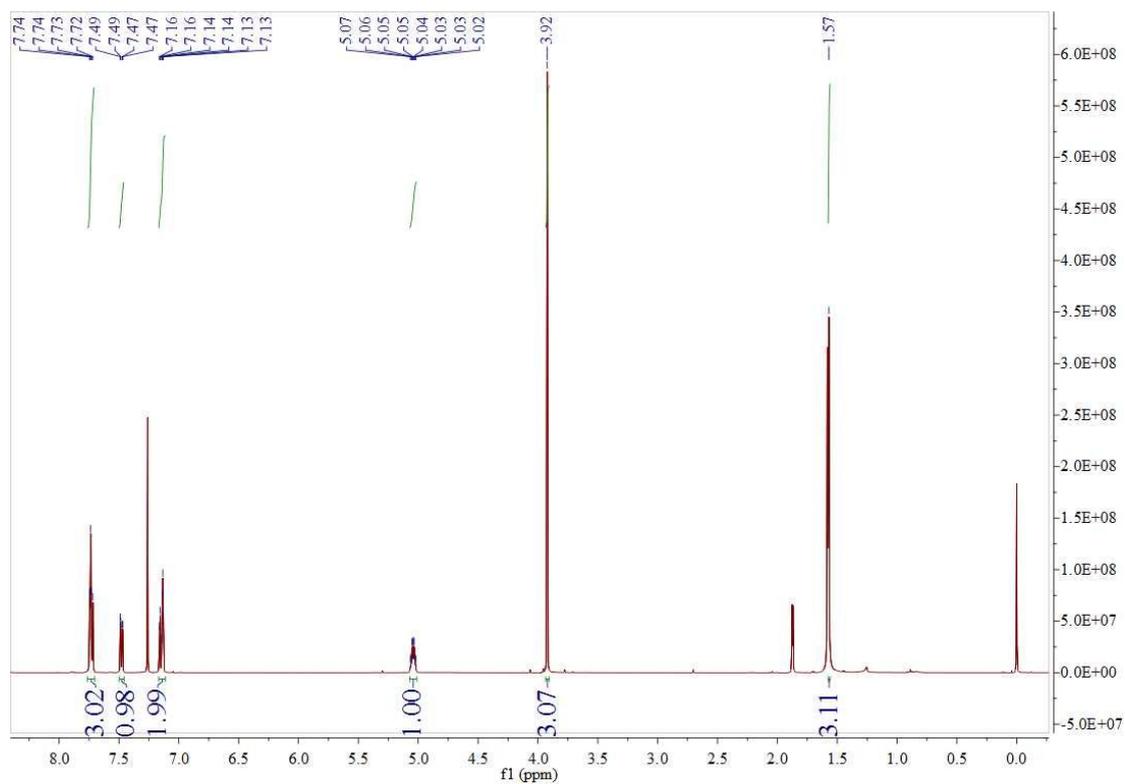
1-(4-methoxyphenyl)ethanol (3i)



1-(4-isobutylphenyl)ethanol (3j)

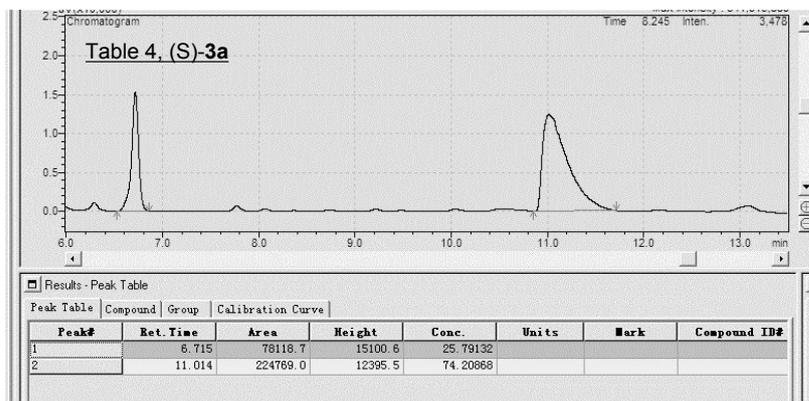
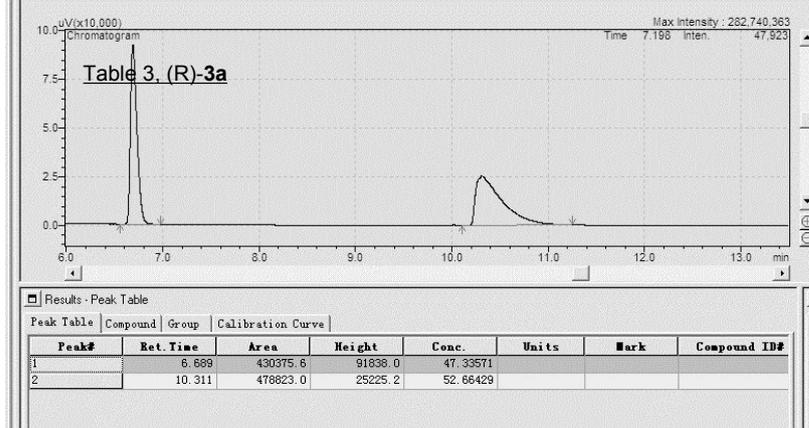
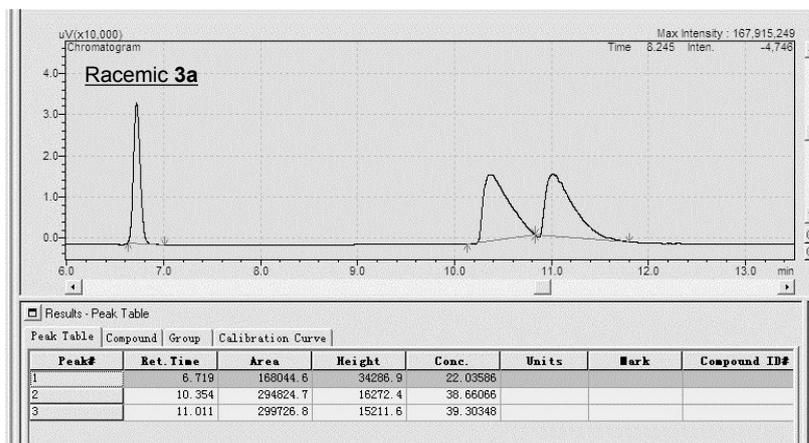


1-(6-methoxynaphthalen-2-yl)ethanol (3k)

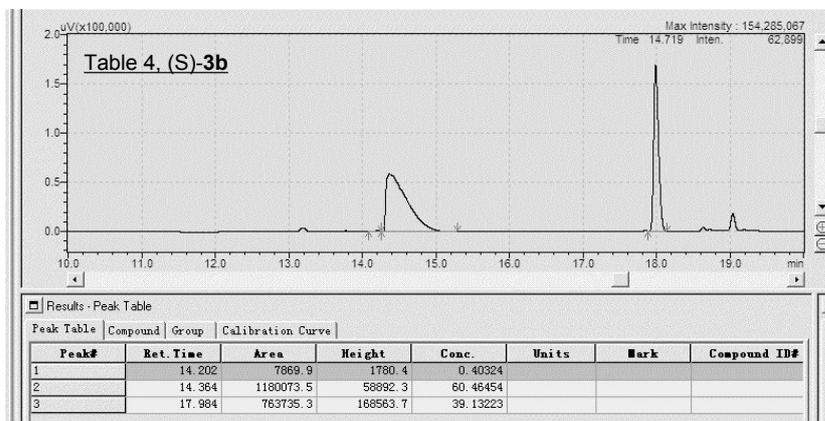
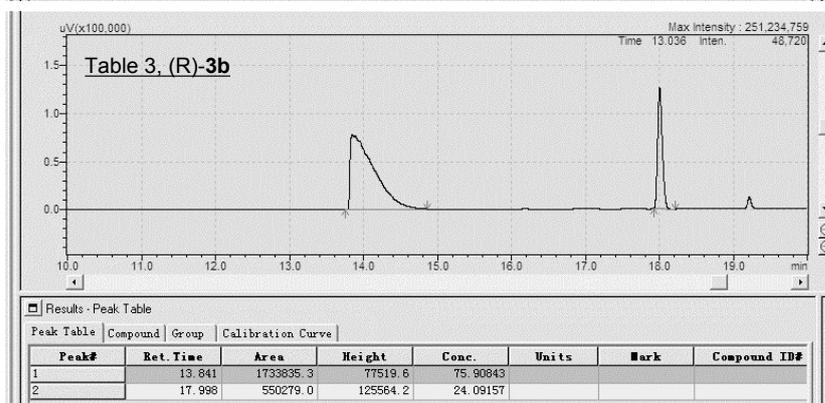
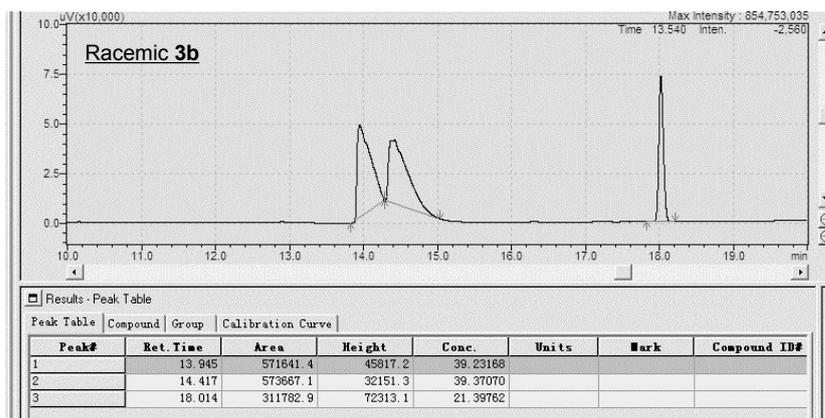


GC or HPLC data

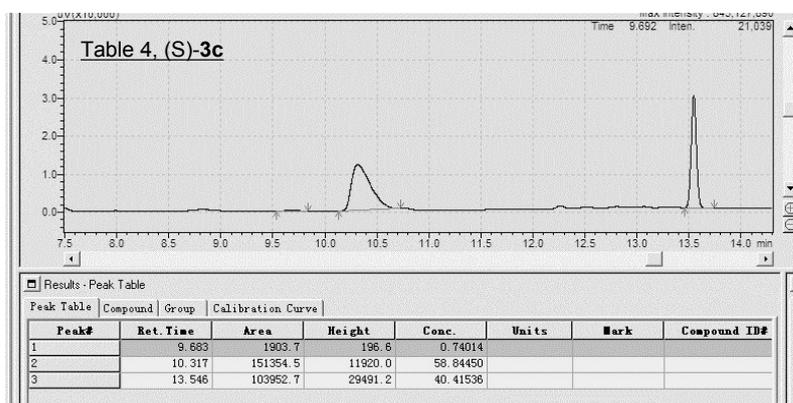
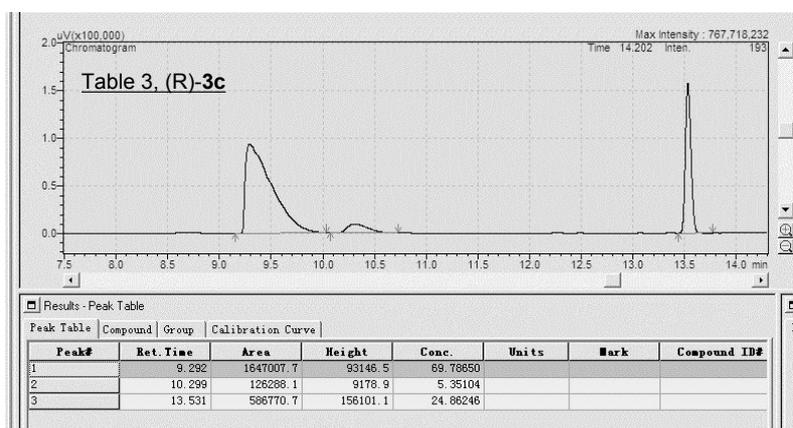
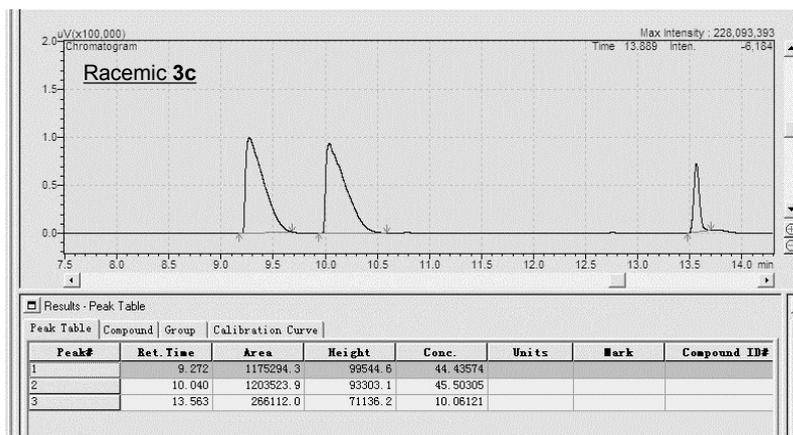
3a, chiral GC (Agilent CP-chirasil-Dex CB, T_{Internal Standard} = 6.7 min, T_R = 10.3 min, T_S = 11.0 min, Temperature conditions: initial temperature 100 °C, 2 °C/min to 126 °C, then 40 °C/min to 200 °C, holding 1min).



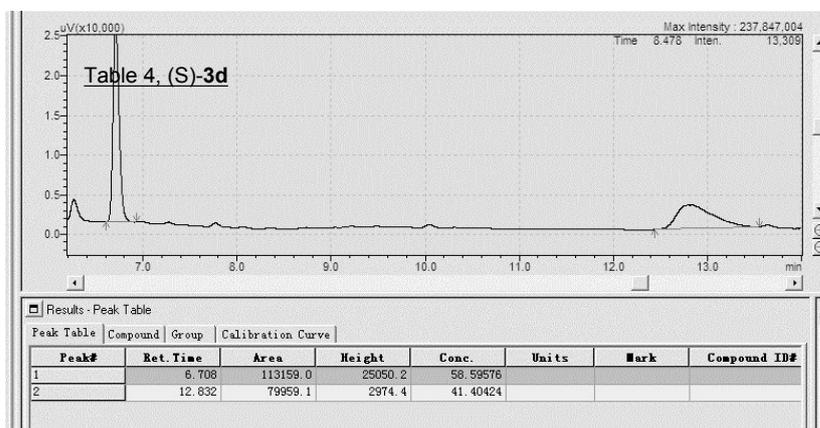
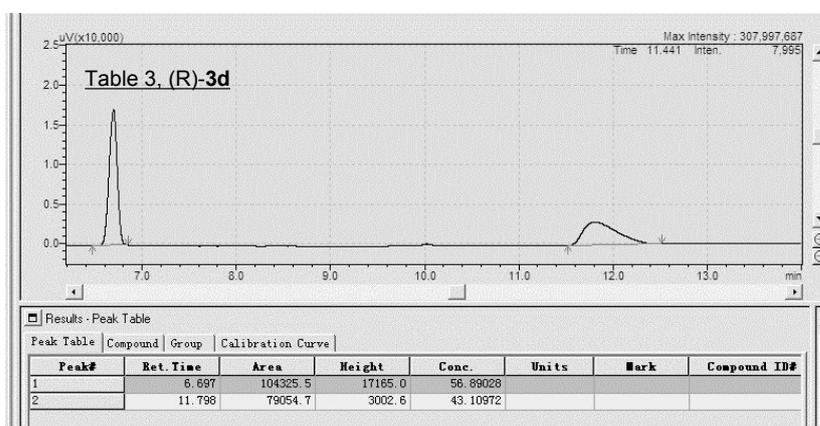
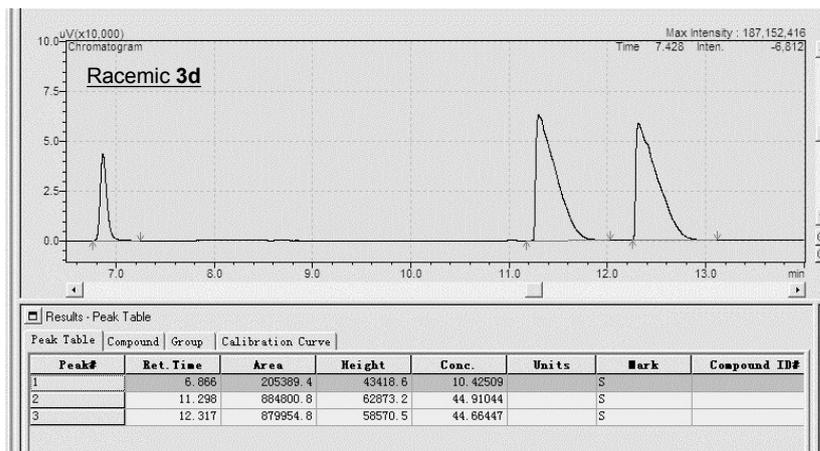
3b, chiral GC (Agilent CP-chirasil-Dex CB, $T_{\text{Internal Standard}} = 18.0$ min, $T_R = 13.9$ min, $T_S = 14.4$ min, Temperature conditions: initial temperature 100 °C, 2 °C/min to 132 °C, then 10 °C/min to 200 °C, holding 1min).



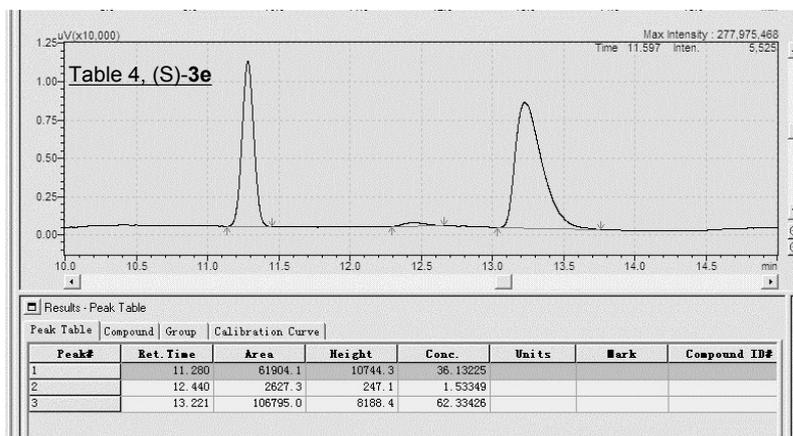
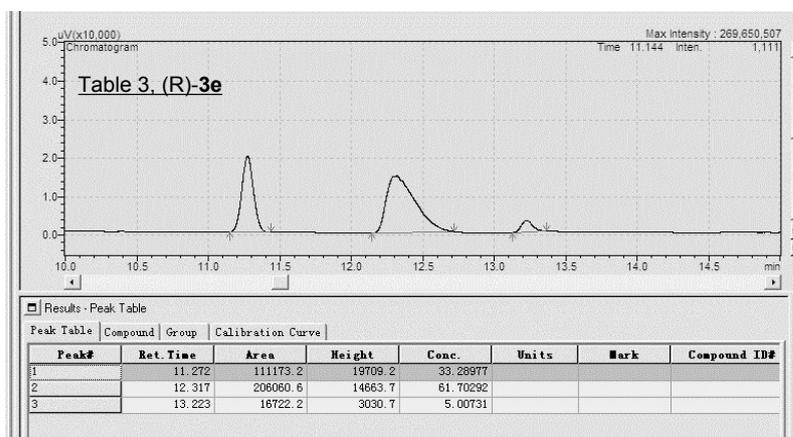
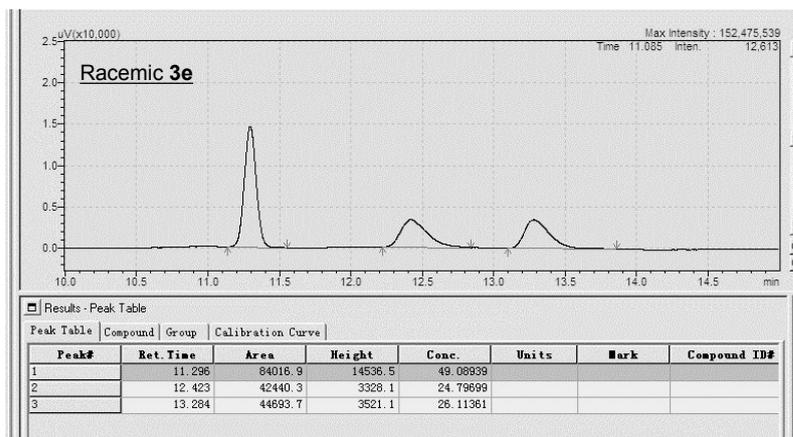
3c, chiral GC (Agilent CP-chirasil-Dex CB, T_{Internal Standard} = 13.5 min, T_R = 9.3 min, T_S = 10.0 min, Temperature conditions: initial temperature 110 °C, 2 °C/min to 140 °C, then 40 °C/min to 200 °C, holding 1min).



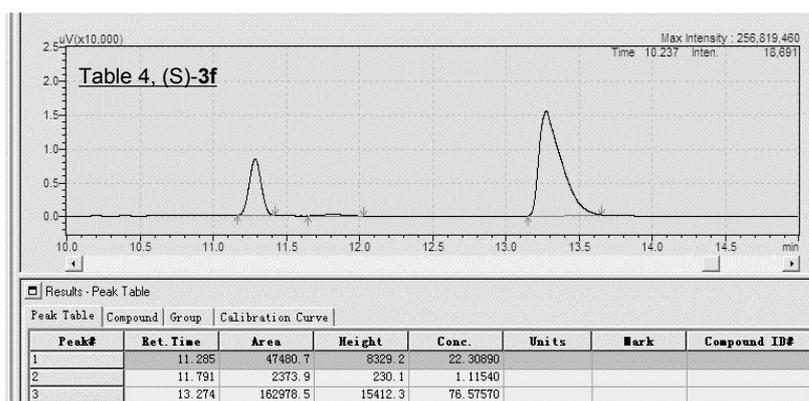
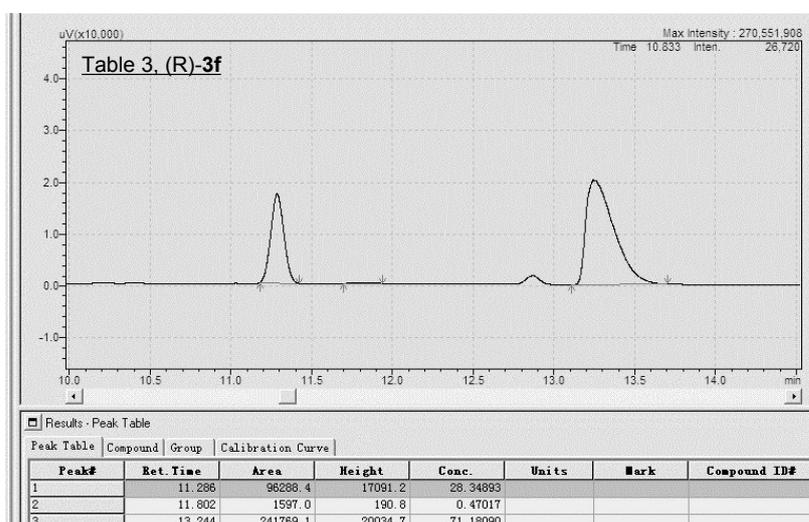
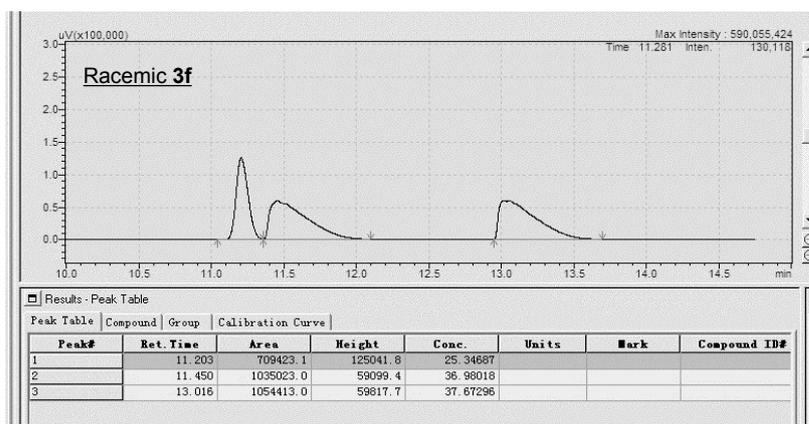
3d, chiral GC (Agilent CP-chirasil-Dex CB, $T_{\text{Internal Standard}} = 6.9$ min, $T_{\text{R}} = 11.8$ min, $T_{\text{S}} = 12.8$ min, Temperature conditions: initial temperature 100 °C, 2 °C/min to 130 °C, then 40 °C/min to 200 °C, holding 1min).



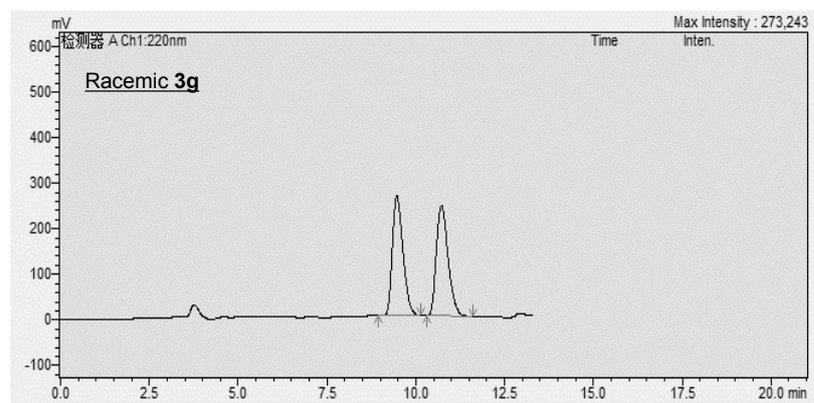
3e, chiral GC (Agilent CP-chirasil-Dex CB, $T_{\text{Internal Standard}} = 11.3$ min, $T_R = 12.4$ min, $T_S = 13.2$ min, Temperature conditions: initial temperature 120 °C, 2 °C/min to 150 °C, then 40 °C/min to 200 °C, holding 1min).



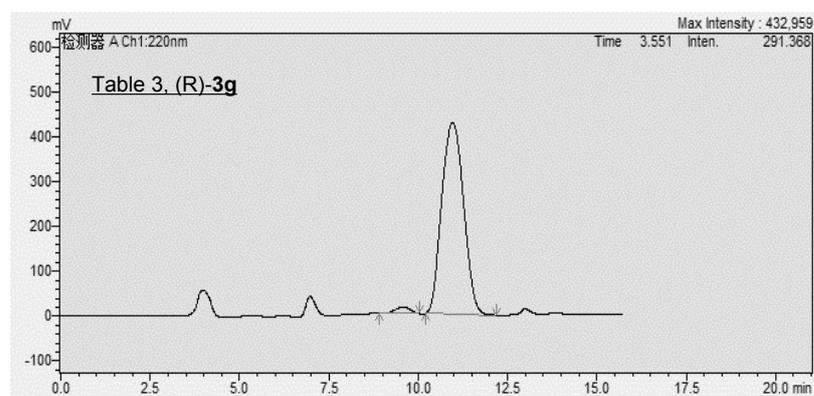
3f, chiral GC (Agilent CP-chirasil-Dex CB, $T_{\text{Internal Standard}} = 11.2$ min, $T_S = 11.4$ min, $T_R = 13.0$ min, Temperature conditions: initial temperature 120 °C, 2 °C/min to 150 °C, then 40 °C/min to 200 °C, holding 1 min).



3g, chiral HPLC (OJ-H, hexane: iopropanol=95: 5, $\lambda=220$ nm, 1 ml/min, $T_S = 9.5$ min, $T_R = 10.9$ min).

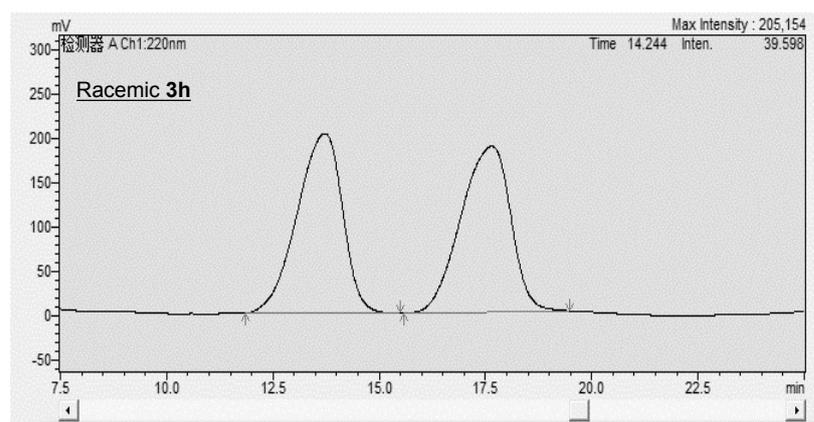


Peak#	ID#	Name	Ret. Time	Conc.	Area	Height	Mark
1			9.464	0.00000	5496139	263759	
2			10.719	0.00000	5606975	243147	

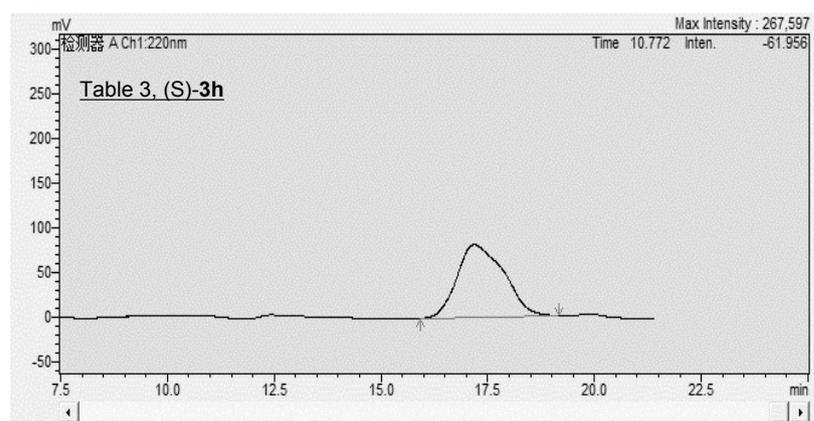


Peak#	ID#	Name	Ret. Time	Conc.	Area	Height	Mark
1			9.587	0.00000	424957	13957	
2			10.961	0.00000	18288304	428272	

3h, chiral HPLC (OB-H, hexane: iopropanol=95: 5, $\lambda=220$ nm, 1 ml/min, $T_S = 13.7$ min, $T_R = 17.6$ min).

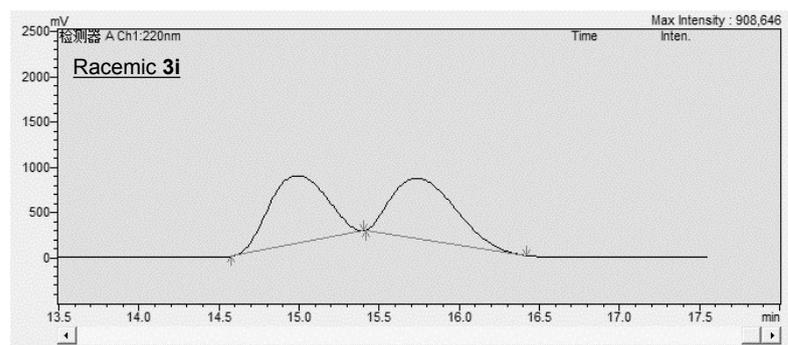


Peak#	ID#	Name	Ret. Time	Conc.	Area	Height	Mark
1			13.720	0.00000	15110778	202570	
2			17.638	0.00000	15288885	186910	

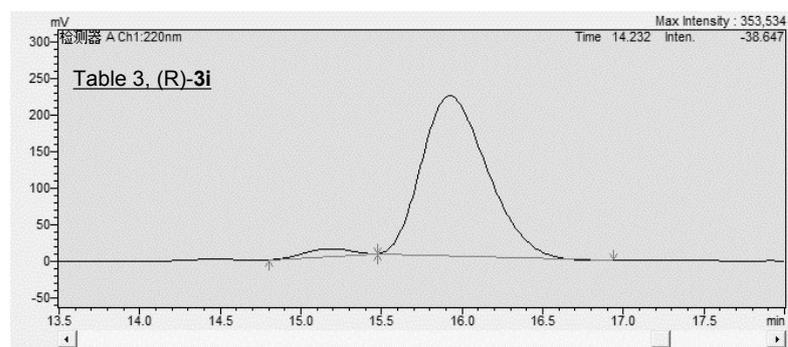


Peak#	ID#	Name	Ret. Time	Conc.	Area	Height	Mark
1			17.184	0.00000	6220942	81545	

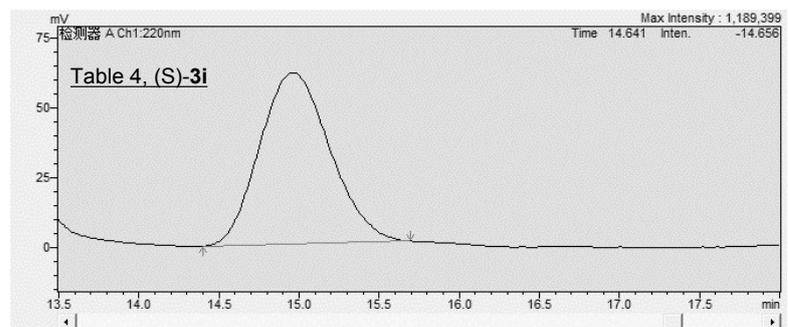
3i, chiral HPLC (OJ-H, hexane: iopropanol=90: 10, $\lambda=220$ nm, 1 ml/min, $T_S = 15.0$ min, $T_R = 15.7$ min).



Peak#	ID#	Name	Ret. Time	Conc.	Area	Height	Mark
1			14.985	0.00000	18660530	751547	
2			15.732	0.00000	18365034	662279	

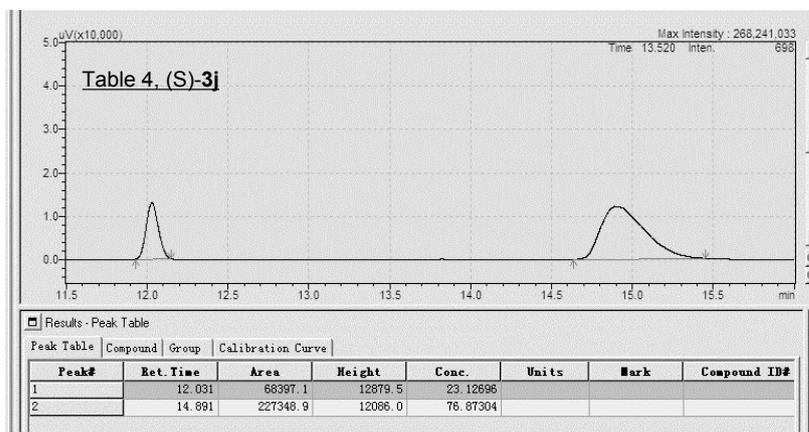
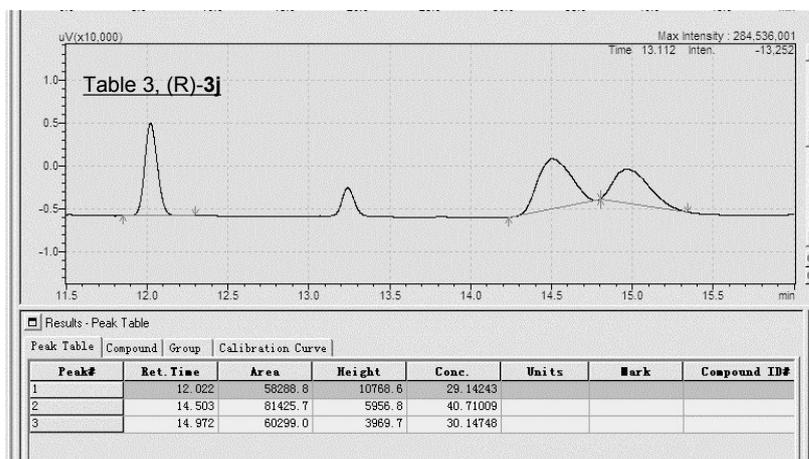
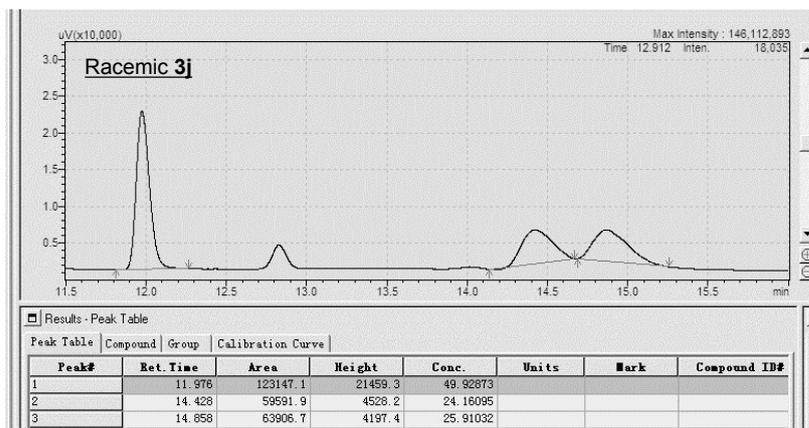


Peak#	ID#	Name	Ret. Time	Conc.	Area	Height	Mark
1			15.181	0.00000	206979	10495	
2			15.920	0.00000	6167567	218467	

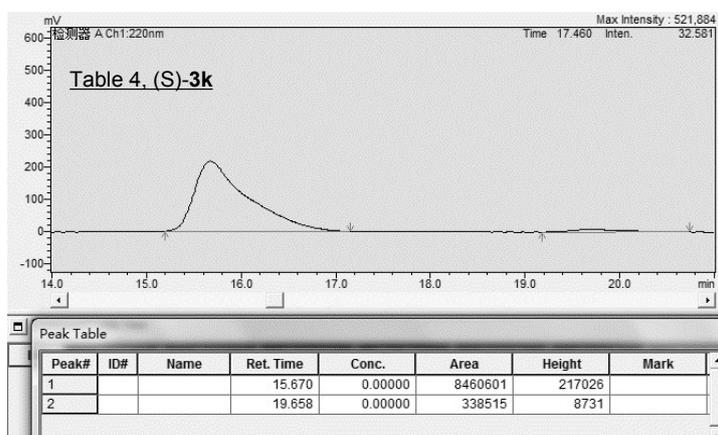
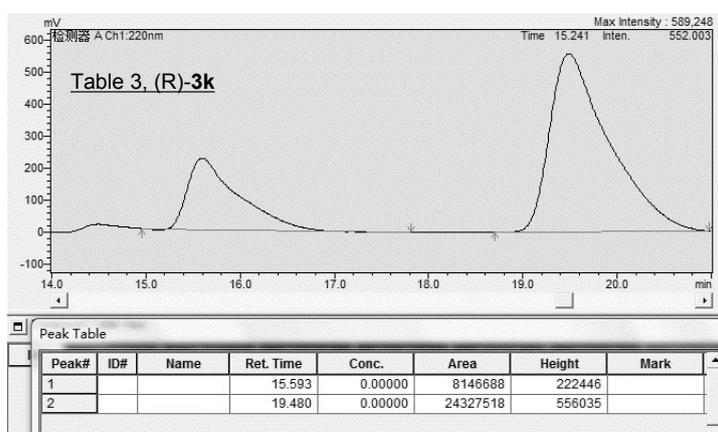
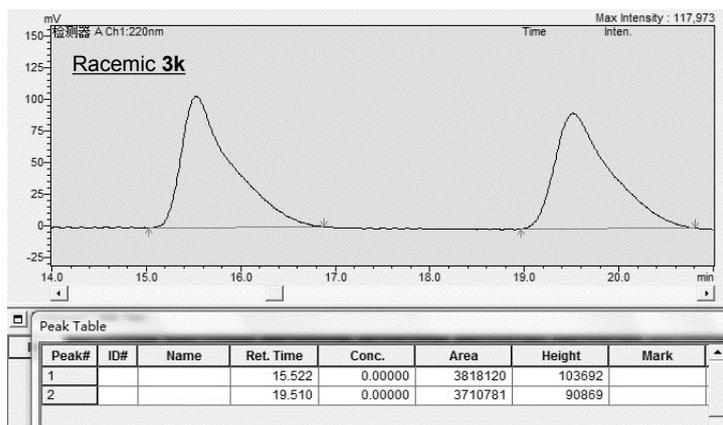


Peak#	ID#	Name	Ret. Time	Conc.	Area	Height	Mark
1			14.958	0.00000	1870459	61356	

3j, chiral GC (Agilent CP-chirasil-Dex CB, T_{Internal Standard} = 12.0min, T_R = 14.4 min, T_S = 14.9 min, Temperature conditions: initial temperature: 120 °C, 2 °C/min to 160 °C, then 40 °C/min to 200 °C, holding 1min).



3k, chiral HPLC (OJ-H, hexane: isopropanol=50: 50, $\lambda=220$ nm, 0.7 ml/min, $T_S = 15.5$ min, $T_R = 19.5$ min).



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