(*43 pages*)

Supporting Information For

Rh(III)-catalyzed and alcohol-involved carbenoid C–H insertion into *N*-phenoxyacetamides using α-diazomalonates

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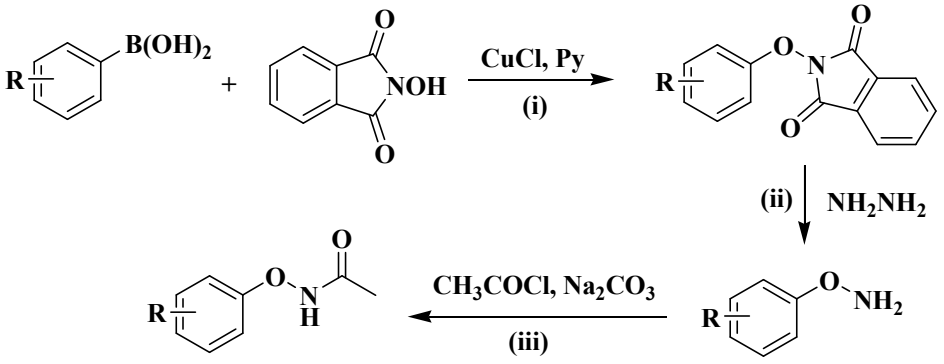
General methods and materials:

$[Cp^*RhCl_2]_2$ and $AgSbF_6$ were purchased from Aldrich and used without further purification. Catalysts $[Cp^*Rh(MeCN)_3][SbF_6]_2$[1] and $[Cp^*Rh(OAc)_2]_2$[2] and substrates *N*-phenoxyacetamides[3] and α-diazomalonates[4] were synthesized according to published procedures. Other chemicals were purchased from commercial suppliers and were dried and purified when necessary. The water used was re-distillated and ion-free. Melting points were determined on a WRS-1B digital instrument without correction. ^1H and ^{13}C NMR spectra were recorded on Varian Mercury-Plus 400 NMR (^1H 400 MHz; ^{13}C 100 MHz) in either $CDCl_3$ or DMSO-d_6. Abbreviations for data quoted are s, singlet; brs, broad singlet; d, doublet; t, triplet; dd, doublet of doublets; m, multiplet. Mass spectra and high-resolution mass spectra were measured on an agilent TOF-G6230B mass spectrometer and Thermo-DFS mass spectrometer. Thin-layer chromatographies were done on pre-coated silica gel 60 F254 plates (Merck). Silica gel 60H (200-300 mesh) manufactured by Qingdao Haiyang Chemical Group Co. (China) was used for general chromatography.

General procedure for the synthesis of *N*-phenoxyacetamides:



(**i**) *N*-aryloxyphthalimides were prepared following a published procedure reported by Kelly[3]: In a reaction flask, a mixture of *N*-hydroxyphthalimide (1.0 equiv), arylboronic acid (2.0 equiv), CuCl (1.0 equiv), freshly activated 4Å molecular sieves (250 mg/mmol) and pyridine (1.1 equiv) in 1,2-dichloroethane (DCE, 0.2 M) were stirred at room temperature. The reaction flask was open to atmosphere. After 24-48 h, the reaction mixture became green as the reaction proceeded. Silica gel was added to the flask and volatiles were evaporated under reduced pressure. The purification was performed by flash column chromatography on silica gel to afford desired *N*-aryloxyphthalimides.

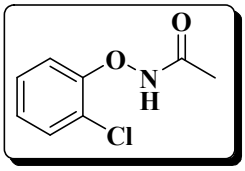
(**ii**) Hydrazine monohydrate (3.0 equiv) was added to the solution of the corresponding *N*-aryloxyphthalimide (1.0 equiv) in 10% MeOH in $CHCl_3$ (0.1 M). The reaction was allowed to stir at room temperature for 1 h. The precipitate was filtered off and washed with DCM. The filtrate was concentrated and the resulting oil was passed through a plug of silica gel washing with 30% EtOAc in Petrol ether. The solvent was then removed under reduce pressure to afford the corresponding *N*-aryloxyamines.

(**iii**) *N*-Aryloxyamine (1.0 equiv) was added to a biphasic mixture of Na_2CO_3 (1.2 equiv) in a 2:1 mixture of EtOAc: H_2O (0.6 M). The resulting solution was cooled to 0 ^oC followed by dropwise addition of acyl chloride (1.0 equiv). After stirring at 0 ^oC for 2 h, the reaction was quenched with sat. $NaHCO_3$ and diluted with EtOAc. The organic phase was washed twice with sat. $NaHCO_3$ after which it was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was

purified by recrystallization from EtOAc/PE to give the desired *N*-aryloxyacetamides as yellow crystals.

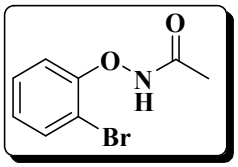
1a-i and **1l-m** are known compounds and all data were in agreement with those reported.[3,5,6,7,8]

_N_-(2-chlorophenoxy)acetamide (1j)



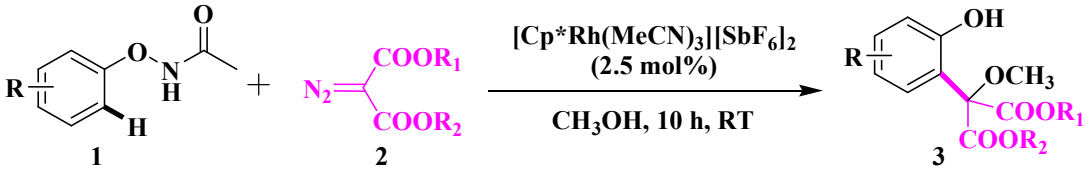
This compound was obtained in whole 45% yield as a white solid; Mp 111-112 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34 (m, 1H), 7.20 (m, 2H), 7.00 (m, 1H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.6, 128.4, 125.8, 122.0, 17.4; HRMS (ESI) calcd for 186.0322, 188.0292 ($[M+H]^+$), found 186.0320, 188.0288 ($[M+H]^+$).

_N_-(2-bromophenoxy)acetamide (1k)



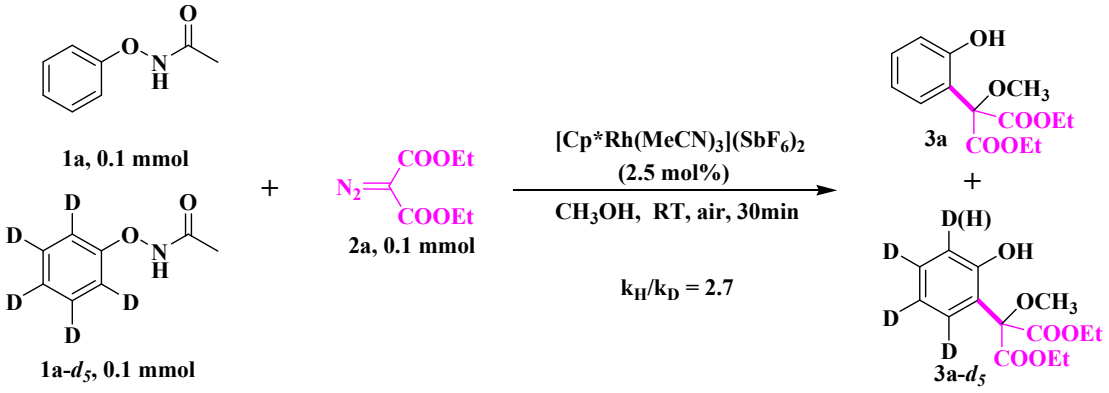
This compound was obtained in whole 62% yield as a white solid; Mp 123-124 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.51 (m, 1H), 7.25 (m, 2H), 6.93 (m, 1H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.4, 131.4, 126.6, 122.4, 17.4; HRMS (ESI) calcd for 229.9817, 231.9796 ($[M+H]^+$), found 229.9811, 231.9782 ($[M+H]^+$).

General procedure for C-H activation:

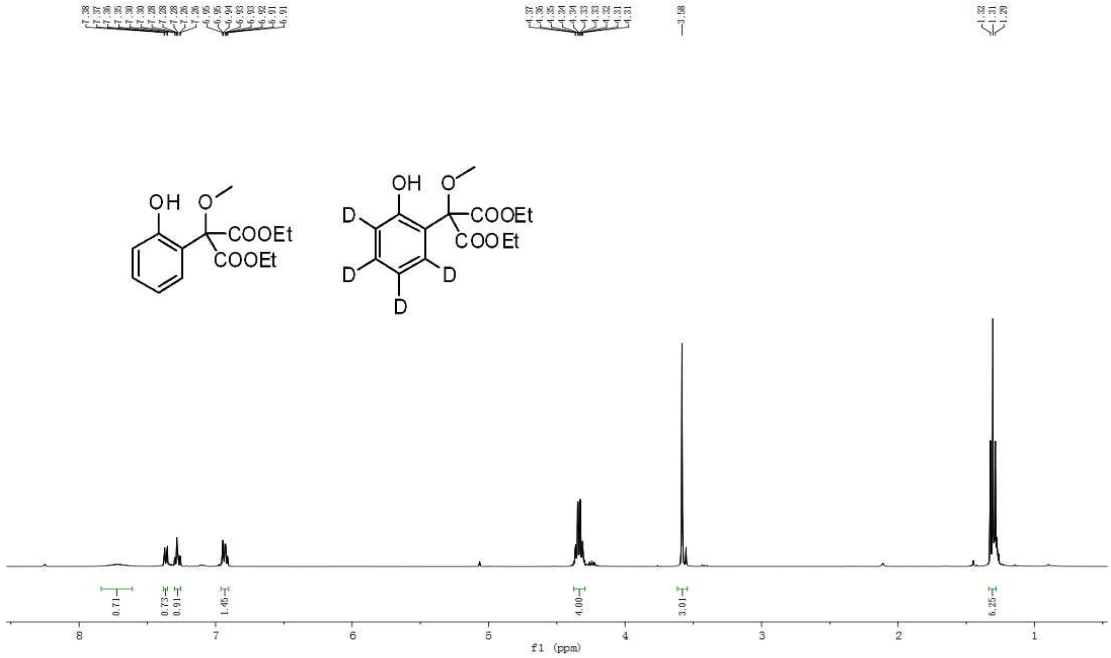


The mixture of $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (0.0025 mmol, 0.025 equiv), *N*-phenoxyacetamide **1** (0.10 mmol, 1.0 equiv), α-diazomalonate **2** (0.12 mmol, 1.2 equiv) and MeOH (1.0 mL) were stirred at room temperature for 10 h under air. The solvent was then removed under reduce pressure, purified by silica gel column directly to give the corresponding products **3**.

General procedure for estimation of the KIE:

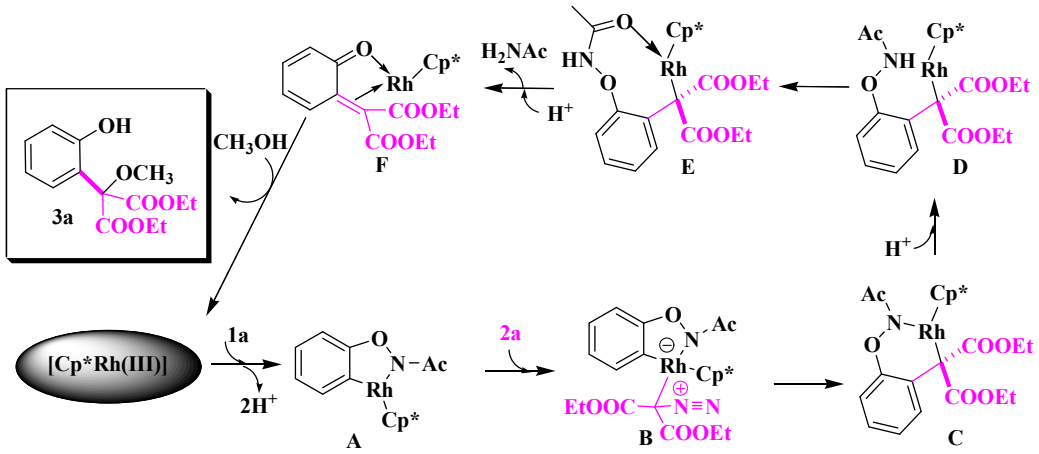


An equimolar mixture of **1a** and [D_5]-**1a** were allowed to react with **2a** (1:1:1 ratio) in MeOH (1 mL) in the presence of 2.5 mol% [$Cp^*Rh^{III}(MeCN)_3$](SbF_6)$_2$. The reaction was stopped after 30 min, and the product generated was isolated by using column chromatography and was analyzed by ^{1}H NMR spectroscopy ($CDCl_3$, 400 MHz). The two multiplets at d 7.69 (73%, 1H), 6.93 (72.5%, 2H) were used for calculation and an average value of k_H/k_D = 2.7 was obtained.



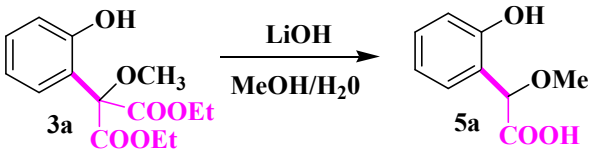
Proposed mechanism:

Taken together our obtained results and literature precedent, a plausible reaction mechanism is proposed as bellow:

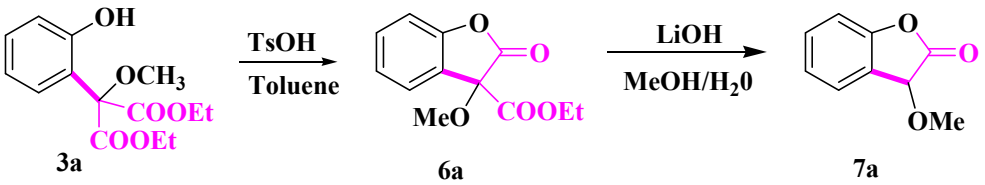


First, the coordination of *N*-phenoxyacetamide **1a** to a [Cp*Rh(III)] species is the key rate-determining step for the regioselective C−H bond cleavage to form a five-membered rhodacyclic intermediate **A**. Further coordination of **A** with **2a** affords the diazonium intermediate **B**. Subsequently, Rh(III)–carbene migratory insertion from **B** provids six-membered rhodacycle intermediate **C** with the emission of N_2. Protonolysis of **C** delivers the intermediate **D** *via* the Rh−N bond cleavage. Subsequently, the intramolecular coordination of intermediate **D** was occurs to form intermediate **E**, followed by α-H elimination/intramolecular rearrangement to afford intermediate **F** with extrusion of acetamide. Finally, intermediate **F** undergoes a similar 1,4-addition step by using MeOH as a reactant to give the desired product **3a** along with the regeneration of the rhodium(III) catalyst.

Procedure for derivatization of 3a:



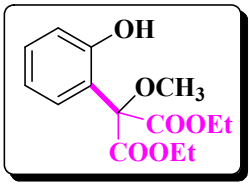
The mixture of **3a** (28 mg, 0.1 mmol), LiOH (0.4 mmol) and MeOH / H_2O (5:1, 1 mL) were stirred at room temperature for 5 h. The solvent was then removed under reduce pressure, acidified by 1M HCl, filtered and purified by silica gel column directly to give the desired product **5a**.



The mixture of **3a** (56 mg, 0.2 mmol), TsOH (5 mg) and toluene (2 mL) were stirred at 100 °C for 3 h, and then extracted by EtOAc, washed with $NaHCO_3$. The solvent was then removed under reduce pressure and purified by silica gel column directly to give the desired product **6a**, then followed by using the synthetic procedure of **6a** to afford the product **7a**.

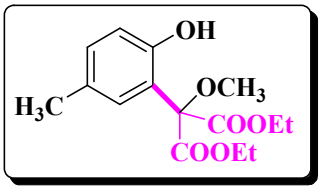
Characterizations of products:

Diethyl 2-(2-hydroxyphenyl)-2-methoxymalonate (3a)



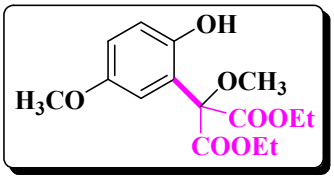
This compound was obtained in 81% yield as a white solid. Mp 62-63°C;^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.71 (brs, 1H), 7.37 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.31 – 7.25 (m, 1H), 6.98 – 6.89 (m, 2H), 4.34 (m, 4H), 3.59 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.4, 155.2, 130.4, 128.4, 120.6, 120.0, 118.2, 86.8, 62.6, 55.0, 14.0; HRMS (ESI) calcd for 281.1025 ($[M-H]^-$), found 281.1021 ($[M-H]^-$).

Diethyl 2-(2-hydroxy-5-methylphenyl)-2-methoxymalonate (3b)



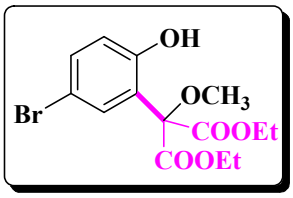
This compound was obtained in 78% yield as a white solid. Mp 74-75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.18 (d, *J* = 1.6 Hz, 1H), 7.08 (dd, *J* = 8.2, 1.6 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 4.42 – 4.16 (m, 4H), 3.58 (s, 3H), 2.30 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.6, 152.8, 131.2, 129.4, 128.4, 120.6, 118.0, 86.4, 62.6, 55.0, 20.8, 14.0; HRMS (ESI) calcd for 295.1182 ($[M-H]^-$), found 295.1180 ($[M-H]^-$).

Diethyl 2-(2-hydroxy-5-methoxyphenyl)-2-methoxymalonate (3c)



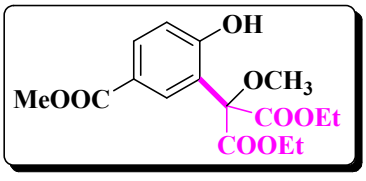
This compound was obtained in 83% yield as a white solid. Mp 60-61 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.01 (d, J = 2.8 Hz, 1H), 6.91 – 6.82 (m, 2H), 4.34 (q, J = 7.2 Hz, 4H), 3.78 (s, 3H), 3.58 (s, 3H), 1.32 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.6, 153.2, 148.8, 122.0, 119.10, 116.0, 113.4, 86.0, 62.6, 55.8, 56.0, 14.0. HRMS (ESI) calcd for 311.1131 ([M-H]$^{-}$), found 311.1130 ([M-H]$^{-}$).

Diethyl 2-(5-bromo-2-hydroxyphenyl)-2-methoxymalonate (3d)



This compound was obtained in 75% yield as a white solid; Mp 81-82 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.84 (brs, 1H), 7.58 (d, J = 2.4 Hz, 1H), 7.37 (dd, J = 8.8, 2.4 Hz, 1H), 6.83 (d, J = 8.8 Hz, 1H), 4.39 – 4.30 (m, 4H), 3.57 (s, 3H), 1.32 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.2, 154.4, 133.4, 130.8, 123.0, 120.2, 112.4, 85.8, 62.8, 55.2, 14.0; HRMS (ESI) calcd for 359.0130, 361.0110 ([M-H]$^{-}$), found 359.0128, 361.0107 ([M-H]$^{-}$).

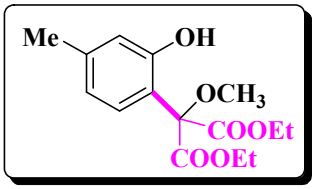
Diethyl 2-(2-hydroxy-5-(methoxycarbonyl) phenyl)-2-methoxymalonate (3e)



This compound was obtained in 66% yield as a white solid; Mp 59-60 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.34 (brs, 1H), 8.12 (d, J = 2.0 Hz, 1H), 7.95 (dd, J = 8.6, 2.0 Hz, 1H), 6.95 (d, J = 8.6 Hz, 1H), 4.41 – 4.29 (m, 4H), 3.88 (s, 3H), 3.58 (s, 3H), 1.29 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.0, 166.4, 159.6, 132.2, 130.8,

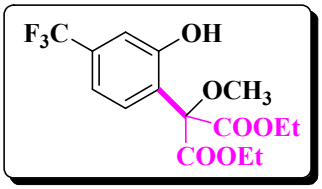
122.21, 120.4, 118.2, 86.4, 62.8, 55.2, 52.0, 14.0; HRMS (ESI) calcd for 339.1080 ([M-H]$^-$), found 339.1079 ([M-H]$^-$).

Diethyl 2-(2-hydroxy-4-methylphenyl)-2-methoxymalonate (3f)



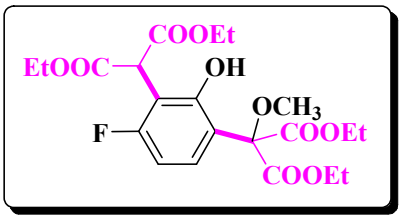
This compound was obtained in 73% yield as a white solid; Mp 67-68 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23 (t, J = 7.6 Hz, 1H), 6.75 – 6.74 (m, 2H), 4.38 – 4.28 (m, 4H), 3.56 (s, 3H), 2.31 (s, 3H), 1.31 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.4, 155.12, 140.8, 128.4, 121.0, 118.6, 117.4, 86.6, 62.4, 54.8, 21.0, 14.0; HRMS (ESI) calcd for 295.1182 ([M-H]$^-$), found 295.1179 ([M-H]$^-$).

Diethyl 2-(2-hydroxy-4-(trifluoromethyl)phenyl)-2-methoxymalonate (3g)



This compound was obtained in 58% yield as a yellow liquid; ^{1}H NMR (400 MHz, CDCl3) δ: 8.14 (brs, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.18 – 7.16 (m, 2H), 4.38 – 4.28 (m, 4H), 3.59 (s, 3H), 1.30 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.6, 155.1, 132.1 (q, J = 32.7 Hz), 128.6, 123.9, 123.1 (q, J = 272.5 Hz), 116.2 (q, J = 3.8 Hz), 115.1 (q, J = 3.8 Hz), 85.9, 62.5, 54.8, 13.5; HRMS (ESI) calcd for 349.0899 ([M-H]$^-$), found 349.0895 ([M-H]$^-$).

Diethyl 2-(3-(1,3-diethoxy-1,3-dioxopropan-2-yl)-4-fluoro-2-hydroxyphenyl)-2-methoxymalonate **(3h)**

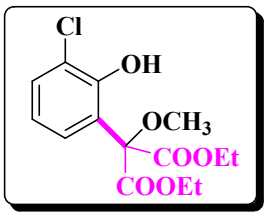


This compound was obtained in 61% yield as a yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ; 8.64 (s, 1H), 7.43 – 7.35 (dd, J = 9.0, 6.4 Hz, 1H), 6.72 (t, J = 9.0 Hz, 1H), 5.07 (s, 1H), 4.36 – 4.20 (m, 8H), 3.52 (s, 3H), 1.29 (m, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.2, 167.5, 161.7 (d, J = 249.5 Hz), 154.9 (d, J = 6.7 Hz), 129.5 (d, J = 11.1 Hz), 118.5 (d, J = 3.2 Hz), 111.2 (d, J = 16.7 Hz), 107.4 (d, J = 23.1 Hz), 85.7, 62.6, 62.1, 54.9, 47.6 (d, J = 2.4 Hz), 13.93, 13.90; HRMS (ESI) calcd for 457.1510 ($[M-H]^-$), found 457.1508 ($[M-H]^-$).

Diethyl 2-(2-hydroxy-4-methoxyphenyl)-2-methoxymalonate [3i(i)] and **diethyl 2-(3-(1,3-diethoxy-1,3-dioxopropan-2-yl)-2-hydroxy-4-methoxyphenyl)- 2-methoxymalonate [3i(ii)]**

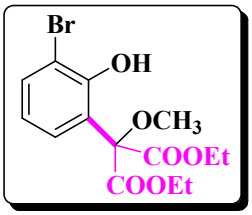
This compound was obtained in 73% yield [mixture of **(i)** and **(ii)** (3:1)] as a yellow liquid; **3i(i)** ^{1}H NMR (400 MHz, CDCl3) δ: 7.79 (s, 1H), 7.27 (d, J = 8.4 Hz, 1H), 6.50 – 6.42 (m, 2H), 4.34 – 4.27 (m, 4H), 3.77 (s, 3H), 3.53 (s, 3H), 1.30 – 1.24 (m, 6H). **3i (ii)** ^{1}H NMR (400 MHz, CDCl3) δ: 8.37 (s, 1H), 7.31 (d, J = 8.8 Hz, 1H), 6.52 (d, J = 8.8 Hz, 1H), 5.21 (s, 1H), 4.27 – 4.21 (m, 8H), 3.82 (s, 1H), 3.46 (s, 1H), 1.30 – 1.24 (m, 12H); **3i (i)** and **3i (ii)** ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.4, 167.8, 167.4, 161.4, 158.6, 156.8, 154.6, 129.4, 129.4, 115.6, 112.4, 111.6, 106.6, 103.0, 103.0, 86.4, 85.8, 62.4, 62.4, 61.8, 56.0, 55.2, 54.8, 54.4, 47.6, 14.0, 13.8; **3i (i)** HRMS (ESI) calcd for 311.1131 ($[M-H]^-$), found 311.1128 ($[M-H]^-$); **3i (ii)** HRMS (ESI) calcd for 469.1710 ($[M-H]^-$), found 469.1706 ($[M-H]^-$).

Diethyl 2-(3-chloro-2-hydroxyphenyl)-2-methoxymalonate (3j)



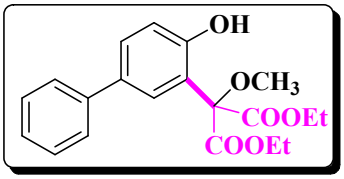
This compound was obtained in 78% yield as a yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.30 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.89 (t, *J* = 8.0 Hz, 1H), 4.38 – 4.28 (m, 4H), 3.55 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.2, 150.6, 130.6, 127.2, 122.8, 122.2, 120.4, 86.0, 62.8, 55.0, 14.0; HRMS (ESI) calcd for 315.0635, 317.0606 ($[M-H]^-$), found 315.0632, 317.0604($[M-H]^-$).

Diethyl 2-(3-bromo-2-hydroxyphenyl)-2-methoxymalonate (3k)



This compound was obtained in 72% yield as a yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.83 (s, 1H), 7.54 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.35 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.84 (t, *J* = 8.0 Hz, 1H), 4.39 – 4.29 (m, 4H), 3.57 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.2, 151.4, 133.8, 128.0, 122.4, 120.8, 112.0, 86.2, 62.8, 55.2, 14.0; HRMS (ESI) calcd for 359.0130, 361.0110 ($[M-H]^-$), found 359.0128, 361.0106 ($[M-H]^-$).

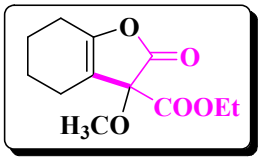
Diethyl 2-(4-hydroxy-[1,1'-biphenyl]-3-yl)-2-methoxymalonate (3l)



This compound was obtained in 82% yield as a white solid. Mp 77-78 ^{o}C; ^{1}H NMR (400 MHz,$CDCl_3$) δ: 7.82 (brs, 1H), 7.66 (d, *J* = 2.2 Hz, 1H), 7.58 – 7.51 (m, 3H),

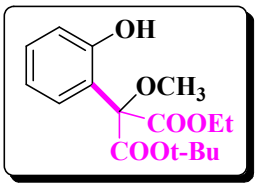
7.44 (t, J = 7.6 Hz, 2H), 7.33 (t, J = 7.3 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 4.41 – 4.32 (m, 4H), 3.62 (s, 3H), 1.32 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.4, 154.8, 140.6, 133.2, 129.2, 128.8, 127.2, 126.8, 126.8, 120.8, 118.6, 86.6, 62.8, 55.0, 14.0; HRMS (ESI) calcd for 357.1338 ($[M-H]^-$), found 357.1336 ($[M-H]^-$).

Ethyl 3-methoxy-2-oxo-2,3,4,5,6,7-hexahydrobenzofuran-3-carboxylate (3m)



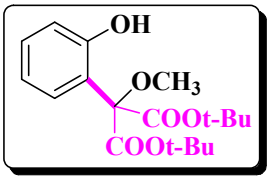
This compound was obtained in 55% yield as a yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.29 (q, J = 7.2 Hz, 2H), 3.50 – 3.42 (m, 1H), 3.12 (s, 3H), 2.48 – 2.46 (m, 1H), 2.20 (td, J = 13.2, 5.8 Hz, 1H), 2.06 – 2.03 (m, 1H), 1.70 – 1.63 (m, 2H), 1.50 – 1.35 (m, 2H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ: 175.8, 165.6, 160.8 , 118.8, 105.0, 61.4 , 50.4, 37.8, 27.4, 27.0, 21.6, 14.0; HRMS (ESI) calcd for 241.1076 ($[M+H]^+$), found 241.1073 ($[M+H]^+$).

1-*Tert*-butyl 3-ethyl 2-(2-hydroxyphenyl)-2-methoxymalonate (3n)



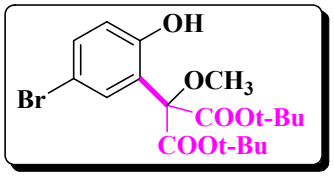
This compound was obtained in 78% yield as a white solid; Mp 74-75 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38 (dd, J = 8.4, 1.2 Hz, 1H), 7.26 (t, J = 8.4 Hz, 1H), 6.93 – 6.89 (t, J = 7.2 Hz, 2H), 4.32 (q, J = 7.1 Hz, 2H), 3.58 (s, 3H), 1.49 (s, 9H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.8, 166.2, 155.4, 130.4, 128.6, 120.7, 119.9, 118.0, 87.0, 84.0, 62.4, 54.8, 27.8, 14.0; HRMS (ESI) calcd for 309.1338 ($[M-H]^-$), found 309.1335 ($[M-H]^-$).

Di-*tert*-butyl 2-(2-hydroxyphenyl)-2-methoxymalonate (3o)



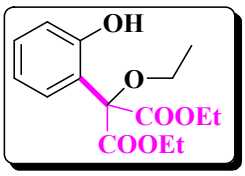
This compound was obtained in 72% yield as a white solid; Mp 58-59 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.91 (brs, 1H), 7.42 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.28 – 7.22 (m, 1H), 6.94 – 6.87 (m, 2H), 3.56 (s, 3H), 1.50 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.4, 155.6, 130.2, 129.0, 120.6, 119.8, 117.8, 87.0, 83.6, 54.4, 27.8; HRMS (ESI) calcd for 337.1651 ($[M-H]^-$), found 337.1646 ($[M-H]^-$).

Di-*tert*-butyl 2-(5-bromo-2-hydroxyphenyl)-2-methoxymalonate (3p)



This compound was obtained in 70% yield as a white solid; Mp 80-81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.04 (brs, 1H) 7.62 (d, *J* = 2.4 Hz, 1H), 7.34 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 1H), 3.56 (s, 3H), 1.51 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.2, 154.6, 133.0, 131.4, 123.2, 119.8, 111.87, 86.2, 84.2, 54.6, 27.8.HRMS (ESI) calcd for 415.0756, 417.0736 ($[M-H]^-$), found 415.0754, 417.0732($[M-H]^-$).

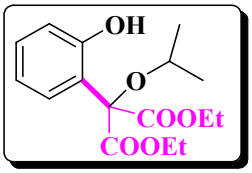
Diethyl 2-ethoxy-2-(2-hydroxyphenyl)malonate (3q)



This compound was obtained in 64% yield as a white solid; Mp 68-69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95 (s, 1H), 7.33 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.26 – 7.20 (m, 1H), 6.95 – 6.86 (m, 2H), 4.38 – 4.26 (m, 4H), 3.77 (q, *J* = 7.0 Hz, 2H), 1.37 (t, *J* = 7.0 Hz, 3H), 1.29 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.6, 155.4, 130.4,

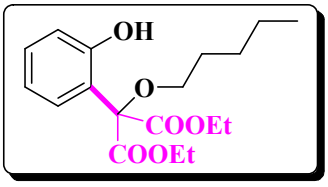
128.2, 120.8, 120.0, 118.2, 86.6, 63.8, 62.4, 15.4, 14.0; HRMS (ESI) calcd for 295.1182 ([M-H]$^-$), found 295.1178 ([M-H]$^-$).

Diethyl 2-(2-hydroxyphenyl)-2-isopropoxymalonate (3r)



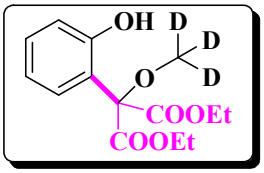
This compound was obtained in 51% yield as a white solid; Mp 78-79 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20 (brs, 1H), 7.35 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.27 – 7.19 (m, 1H), 6.98 – 6.83 (m, 2H), 4.38 – 4.20 (m, 5H), 1.34 – 1.27 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.4, 155.6, 130.2, 128.4, 121.6, 119.8, 118.2, 86.4, 72.4, 62.4, 23.4, 13.8. HRMS (ESI) calcd for 309.1338 ([M-H]$^-$), found 309.1335 ([M-H]$^-$).

Diethyl 2-(2-hydroxyphenyl)-2-(pentyloxy)malonate (3s)



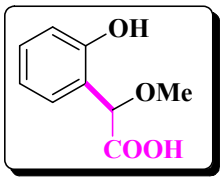
This compound was obtained in 57% yield as a white solid; Mp 50-51 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (brs, 1H), 7.34 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.28 – 7.23 (m, 1H), 6.93 – 6.89 (m, 2H), 4.35 – 4.27 (m, 4H), 3.71 (t, *J* = 6.8 Hz, 2H), 1.81 – 1.71 (m, 2H), 1.45 – 1.35 (m, 4H), 1.29 (t, *J* = 7.2 Hz, 6H), 0.93 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.8, 155.4, 130.2, 128.2, 121.0, 120.0, 118.2, 86.6, 68.0, 62.4, 29.4, 28.0, 22.4, 14.0; HRMS (ESI) calcd for 337.1651 ([M-H]$^-$), found 337.1650 ([M-H]$^-$)

Diethyl 2-(2-hydroxyphenyl)-2-(*d3*) methoxymalonate (3t)



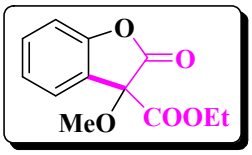
This compound was obtained in 76% yield as a white solid; Mp 65-66 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63 (brs, 1H), 7.27 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.21 – 7.15 (m, 1H), 6.89 – 6.79 (m, 2H), 4.29 – 4.20 (m, 4H), 1.21 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100MHz, $CDCl_3$) δ: 167.4, 155.2, 130.4, 128.4, 120.6, 120.0, 118.2, 86.8, 62.6, 14.0; HRMS (ESI) calcd for 284.1213 ($[M-H]^-$), found 284.1210 ($[M-H]^-$)

2-(2-Hydroxyphenyl)-2-methoxyacetic acid (6a)



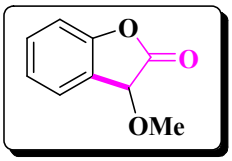
This compound was obtained in 83% yield as a white solid; Mp 122-123 ^{o}C; ^{1}H NMR (400 MHz, DMSO) δ: 7.11 – 6.99 (m, 2H), 6.76 – 6.64 (m, 2H), 4.91 (s, 1H), 3.16 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ: 170.4, 153.4, 127.8, 126.4, 122.0, 117.2, 113.8, 74.0, 55.2; HRMS (ESI) calcd for 181.0501($[M-H]^-$), found 181.0496 ($[M-H]^-$).

Ethyl 3-methoxy-2-oxo-2, 3-dihydrobenzofuran-3-carboxylate (7a)



This compound was obtained in 86% yield as a yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.51 – 7.41 (m, 2H), 7.30 – 7.24 (m, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 4.34 – 4.13 (m, 2H), 3.41 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.0, 165.6, 154.4, 132.0, 125.0, 124.8, 123.0, 111.8, 82.0, 62.8, 54.0, 14.0; HRMS (ESI) calcd for 237.0763($[M+H]^+$), found 237.0760 ($[M+H]^+$).

3-Methoxybenzofuran-2(3*H*)-one (8a)



This compound was obtained in 81% yield as a white solid; Mp 119-120 ^{o}C; ^{1}H NMR (400 MHz, DMSO) δ: 7.21 – 7.09 (m, 2H), 6.87 – 6.76 (m, 2H), 5.02 (s, 1H), 3.27 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ: 170.4, 153.4, 127.6, 126.4, 122.0, 117.2, 113.8, 74.0, 55.2; HRMS (EI) calcd for 164.0473 ($[M+H]^{+}$), found 164.0467 ($[M+H]^{+}$).

References:

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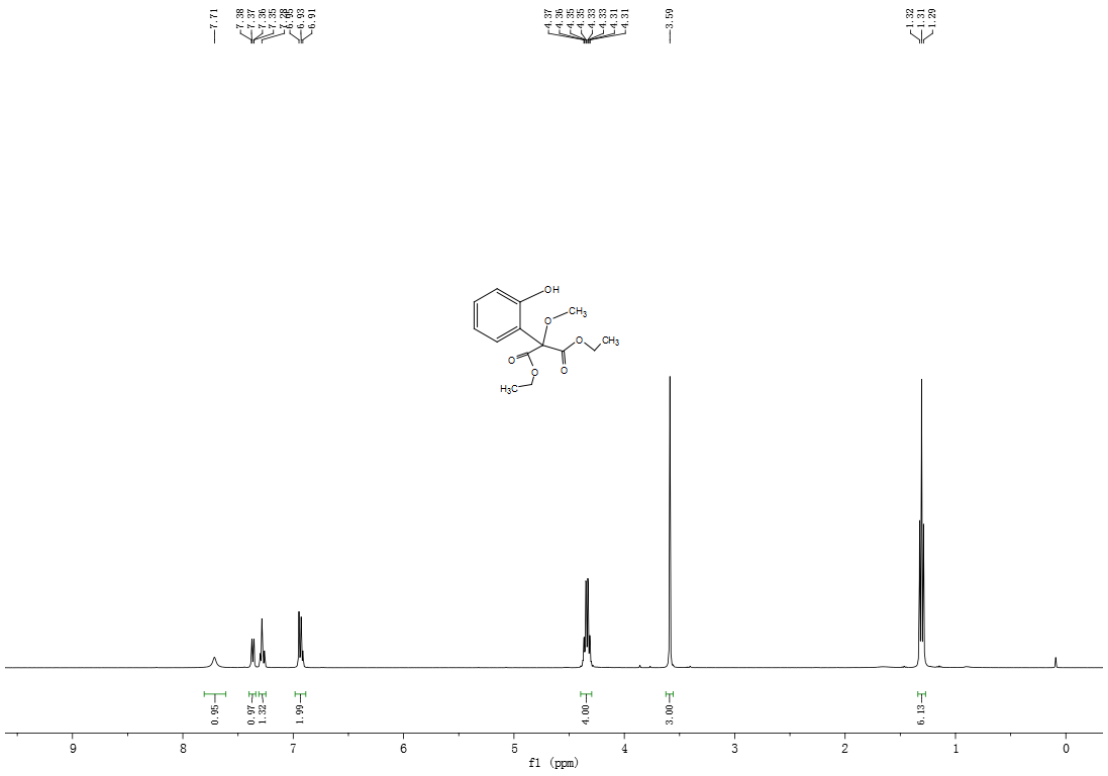
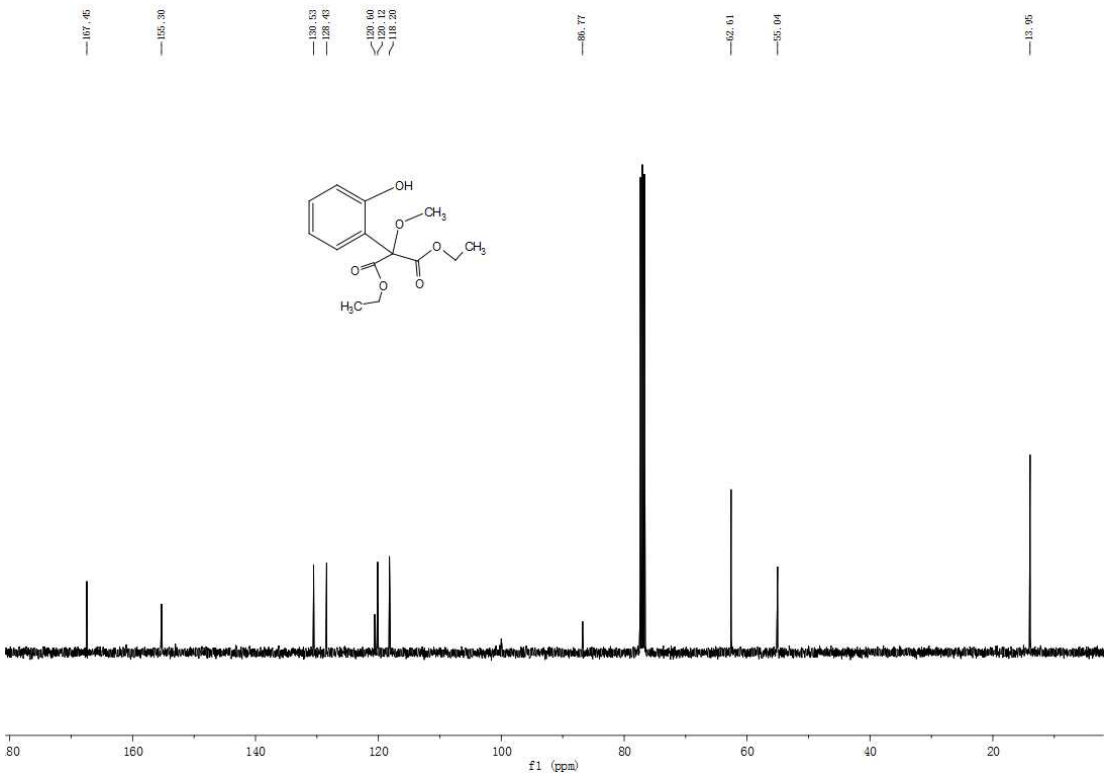
^{1}H and ^{13}C NMR spectra of products

3a

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128.43
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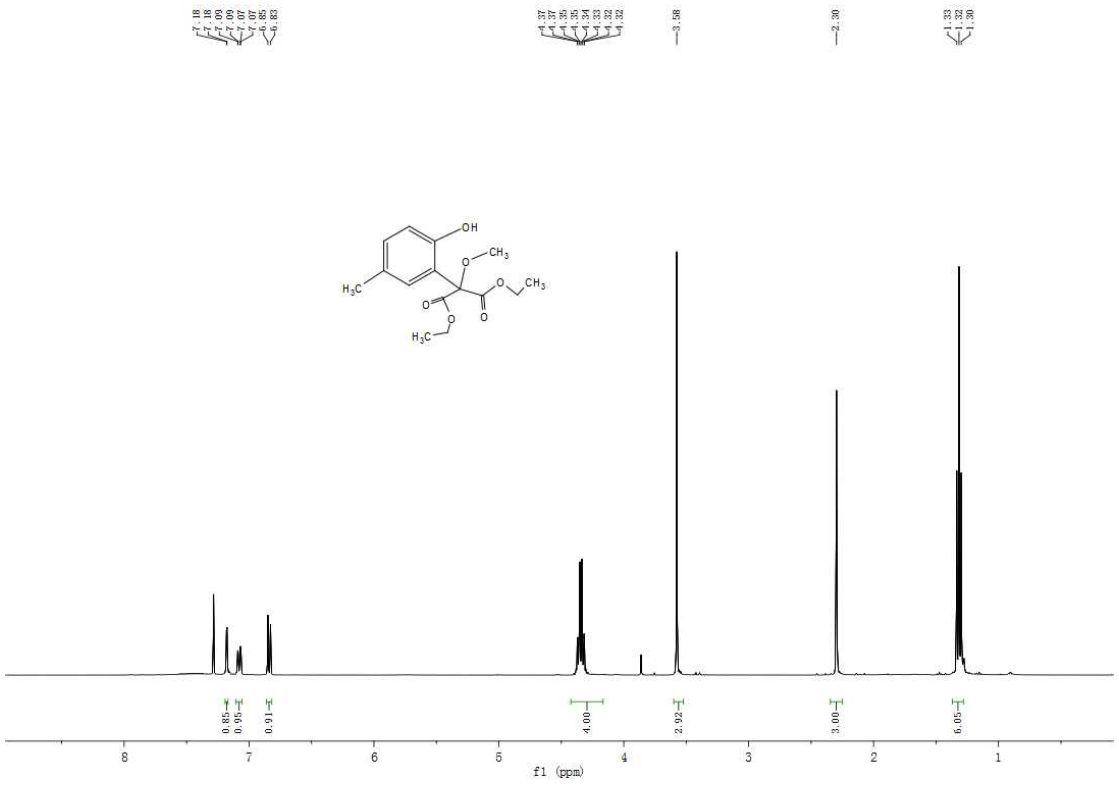
120.12
118.20
86.77
62.61
55.04
13.95
OH
CH3
O
CH3
O
O
O
O
H3C
80
160
140
120
100
80
60
40
20
f1 (ppm)

3b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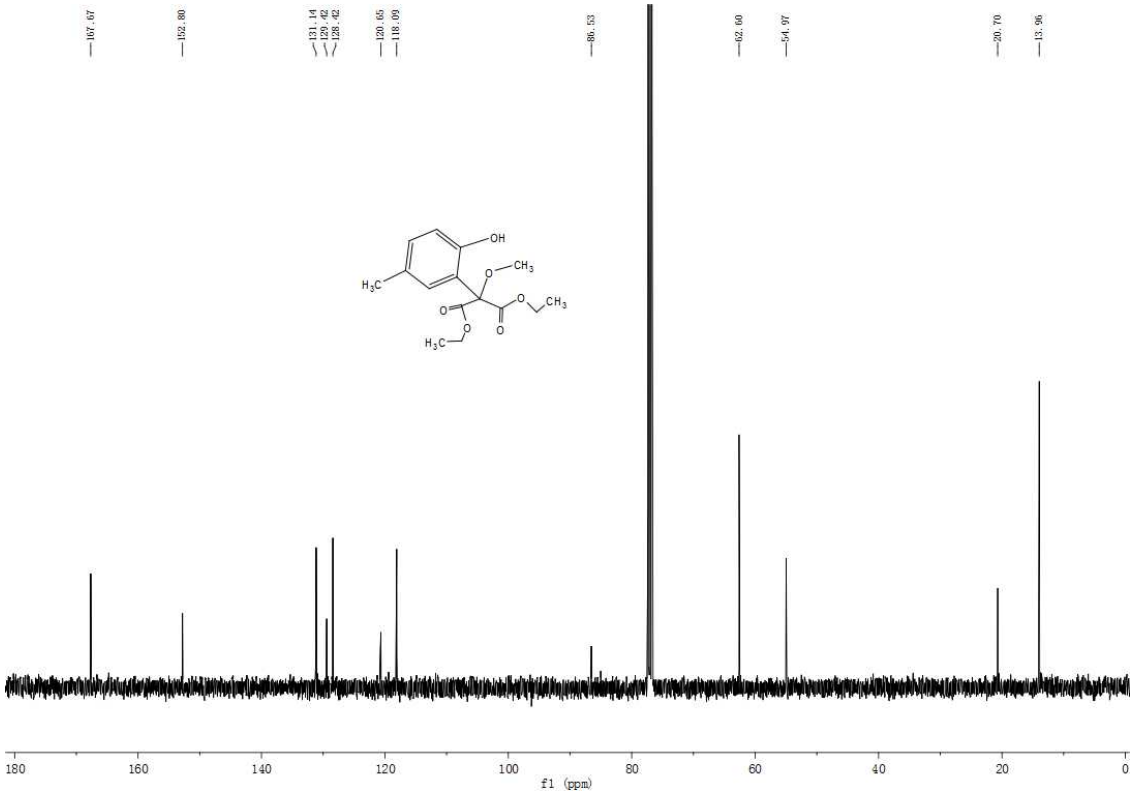
7.16
7.09
7.09
7.07
7.07
6.85
6.83
4.37
4.35
4.35
4.34
4.33
4.32
4.32
3.58
2.30
1.33
1.32
1.30
OH
CH3
O
CH3
O
O
O
O
H3C
0.85
0.93
0.91
4.00
2.92
3.00
6.05
8
7
6
5
4
3
2
1
f1 (ppm)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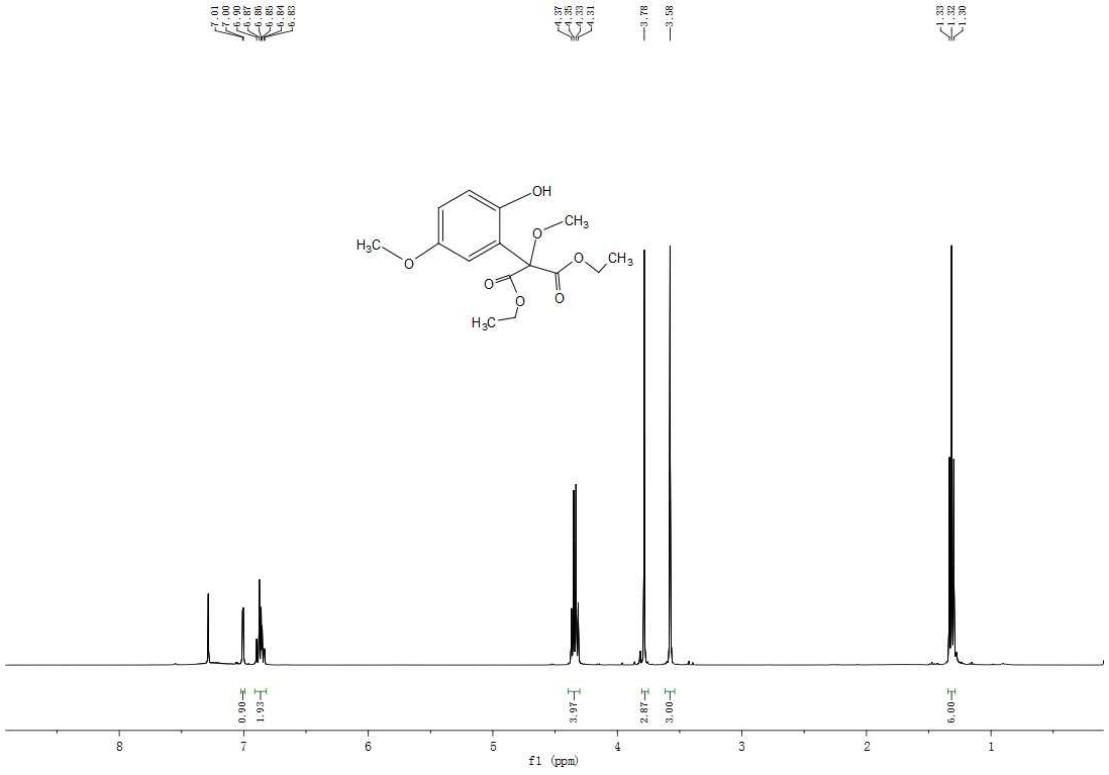
80.53
62.60
54.97
20.70
13.96
OH
CH3
H3C
O
CH3
O
O
O
H3C
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

3c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7.00
6.99
6.87
6.86
6.85
6.84
6.83
4.37
4.35
4.33
4.31
3.78
3.58
1.33
1.32
1.30
OH
CH3
H3C
O
CH3
O
O
O
H3C
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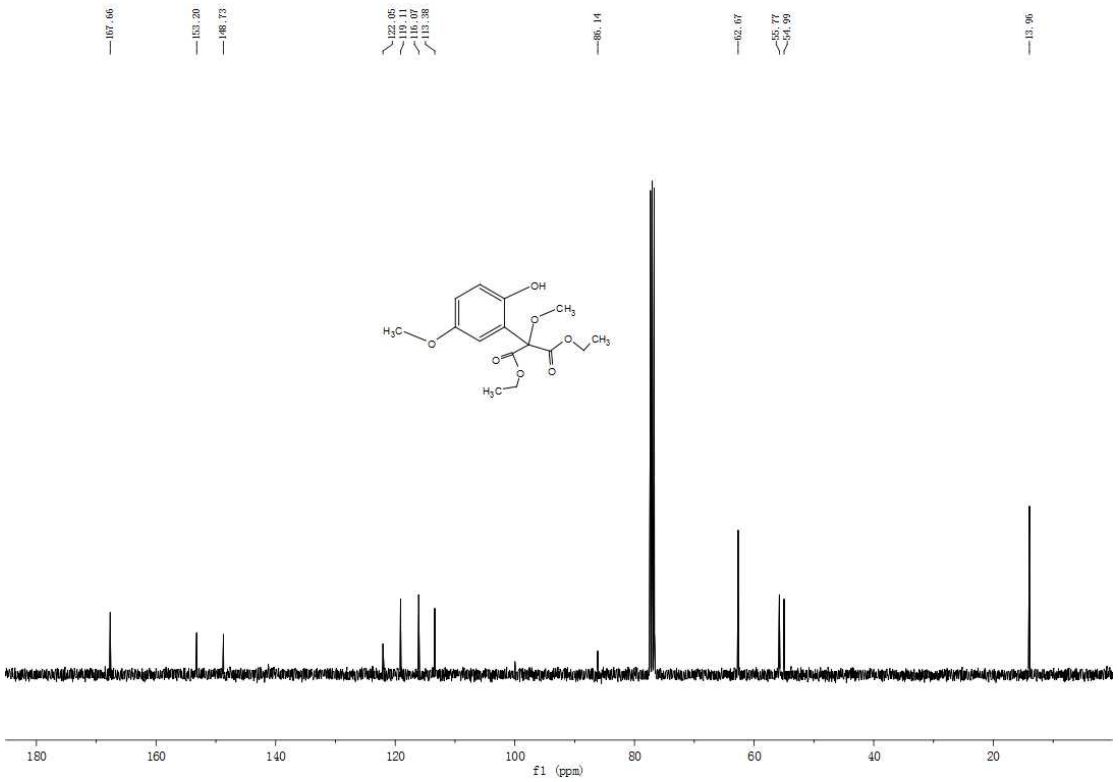
1.93
3.97
2.87
3.00
6.00
8
7
6
5
4
3
2
1
f1 (ppm)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122.65
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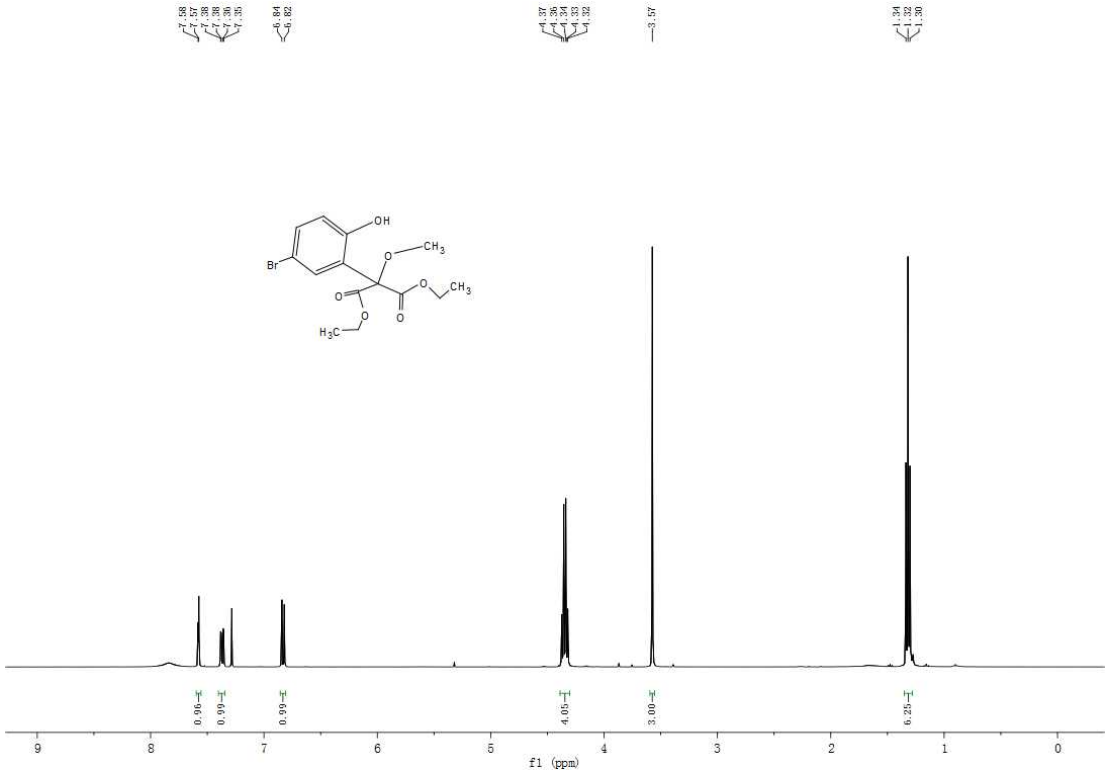
113.38
86.14
62.67
55.77
54.99
13.96
OH
H_3C
O
CH_3
O
CH_3
O
O
O
H_3C
180
160
140
120
100
80
60
40
20
f1 (ppm)

3d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7.36
7.35
6.84
6.82
4.37
4.36
4.34
4.33
4.32
3.57
1.34
1.32
1.30
OH
Br
O
CH_3
O
CH_3
O
O
O
H_3C
0.96
0.99
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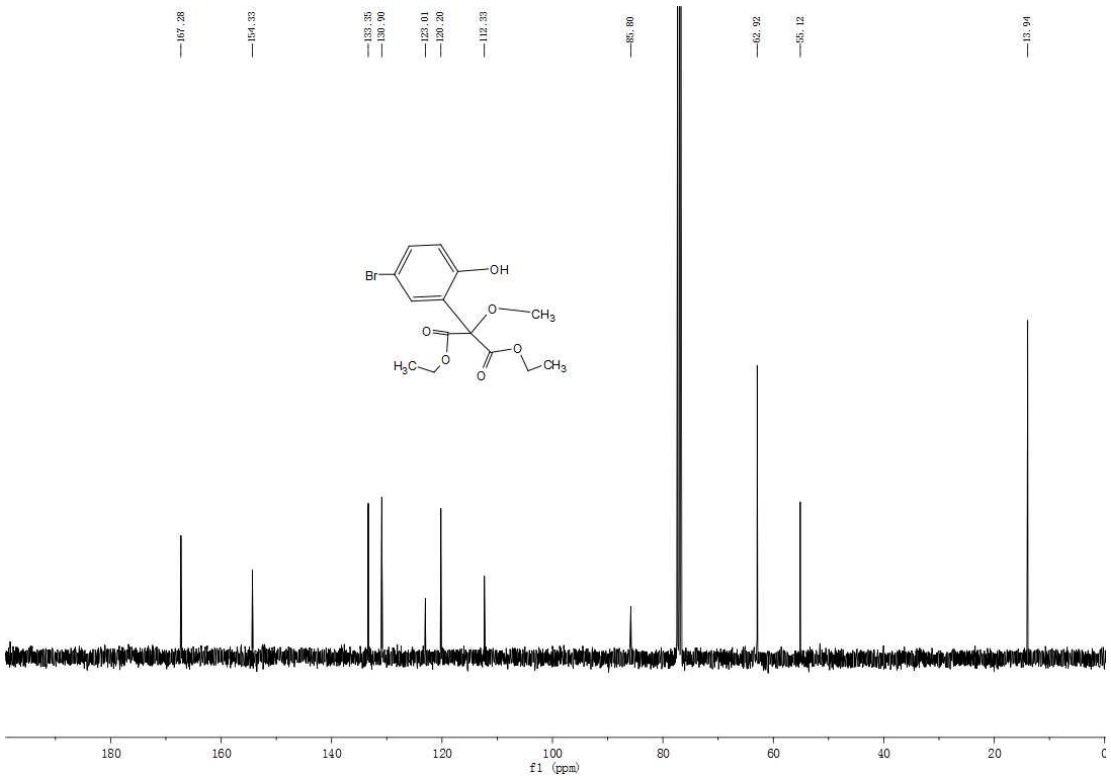
3.00
6.25
9
8
7
6
5
4
3
2
1
0
f1 (ppm)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123.01
120.20
112.33
85.80
62.92
55.12
13.94
Br
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CH3
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CH3
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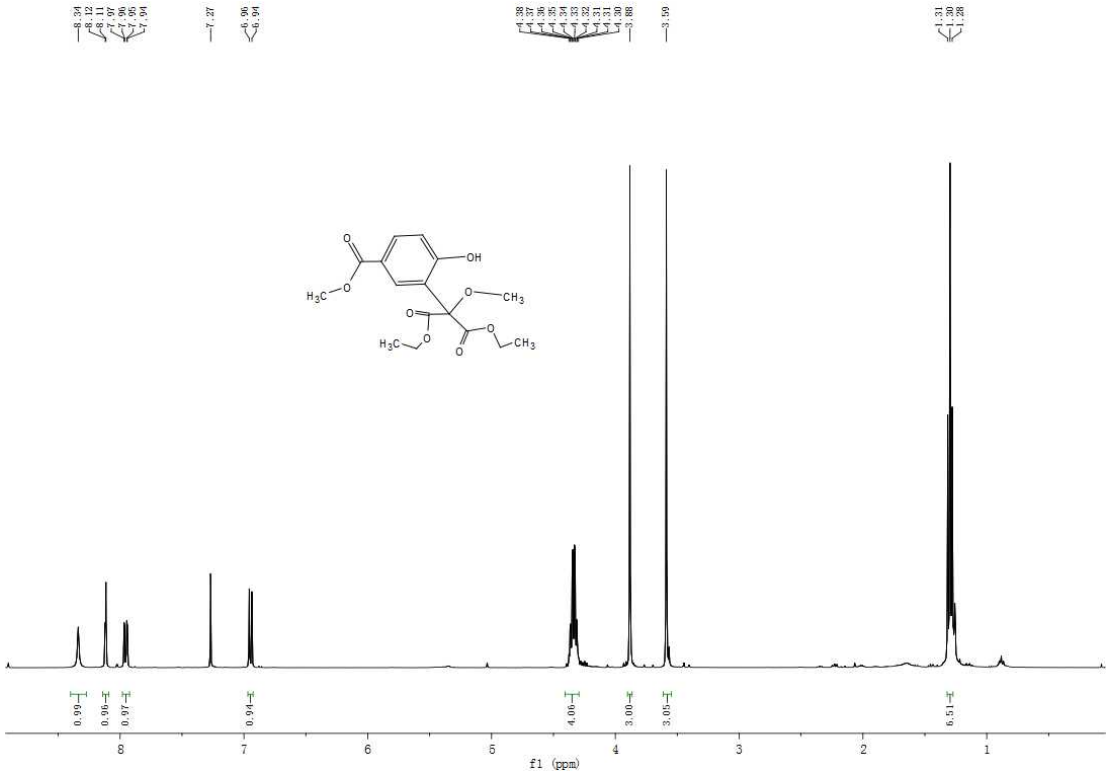
120
100
80
60
40
20
f1 (ppm)

3e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8.12
8.11
7.98
7.96
7.95
7.94
7.27
6.96
6.94
4.38
4.37
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4.35
4.34
4.33
4.32
4.31
4.30
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3.59
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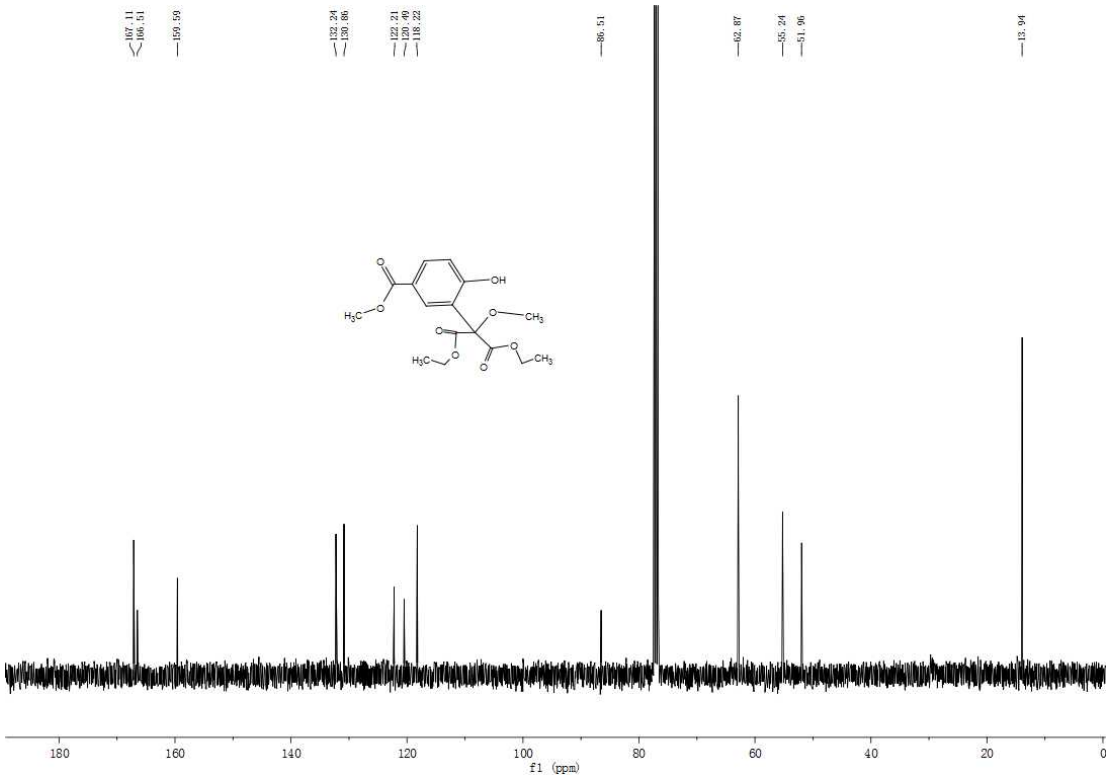
1.30
1.28
O
OH
H3C
O
O
CH3
O
H3C
O
O
CH3
0.99
0.96
0.97
0.94
4.06
3.00
3.05
6.51
8
7
6
5
4
3
2
1
f1 (ppm)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132.24
130.86
122.21
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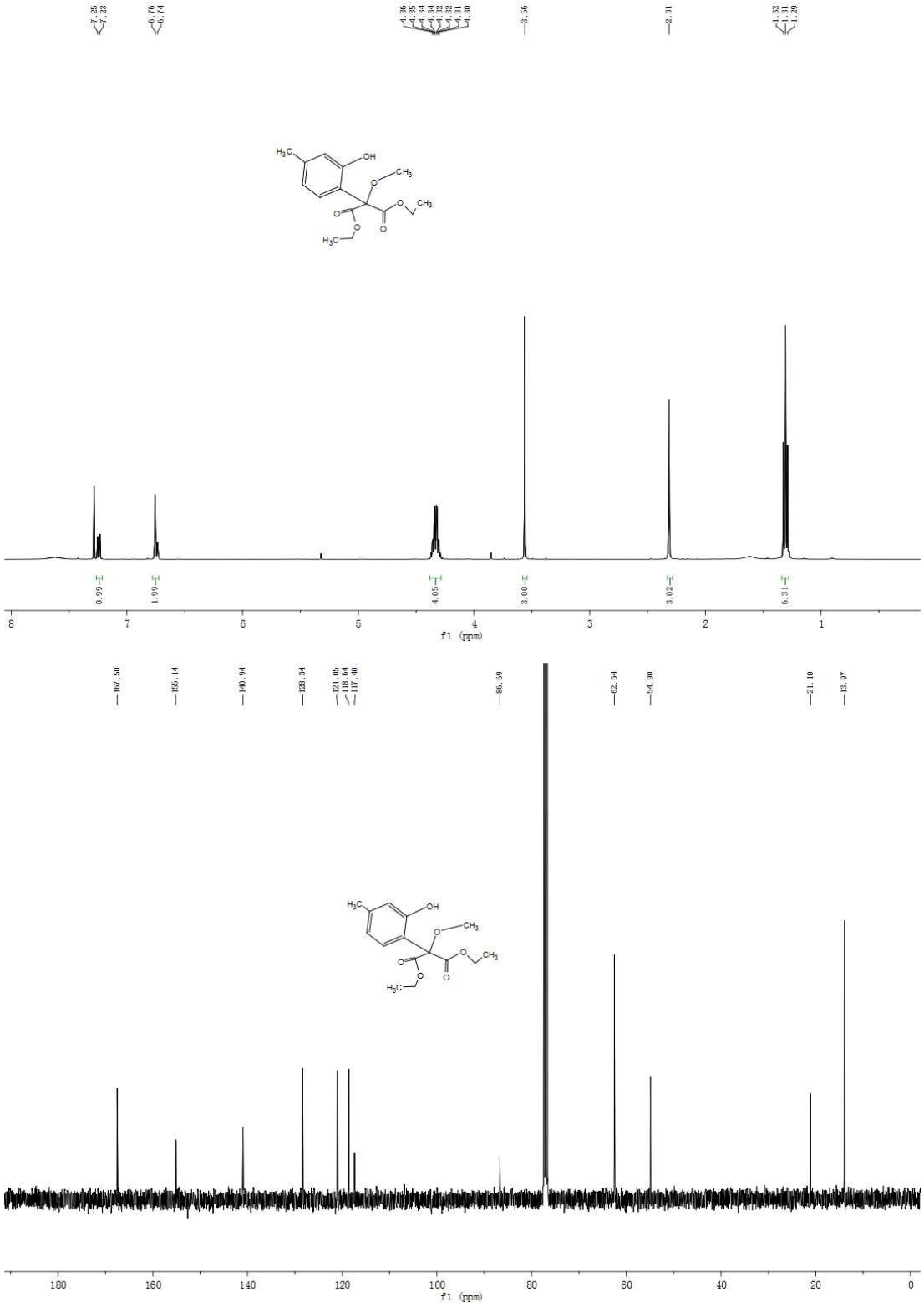
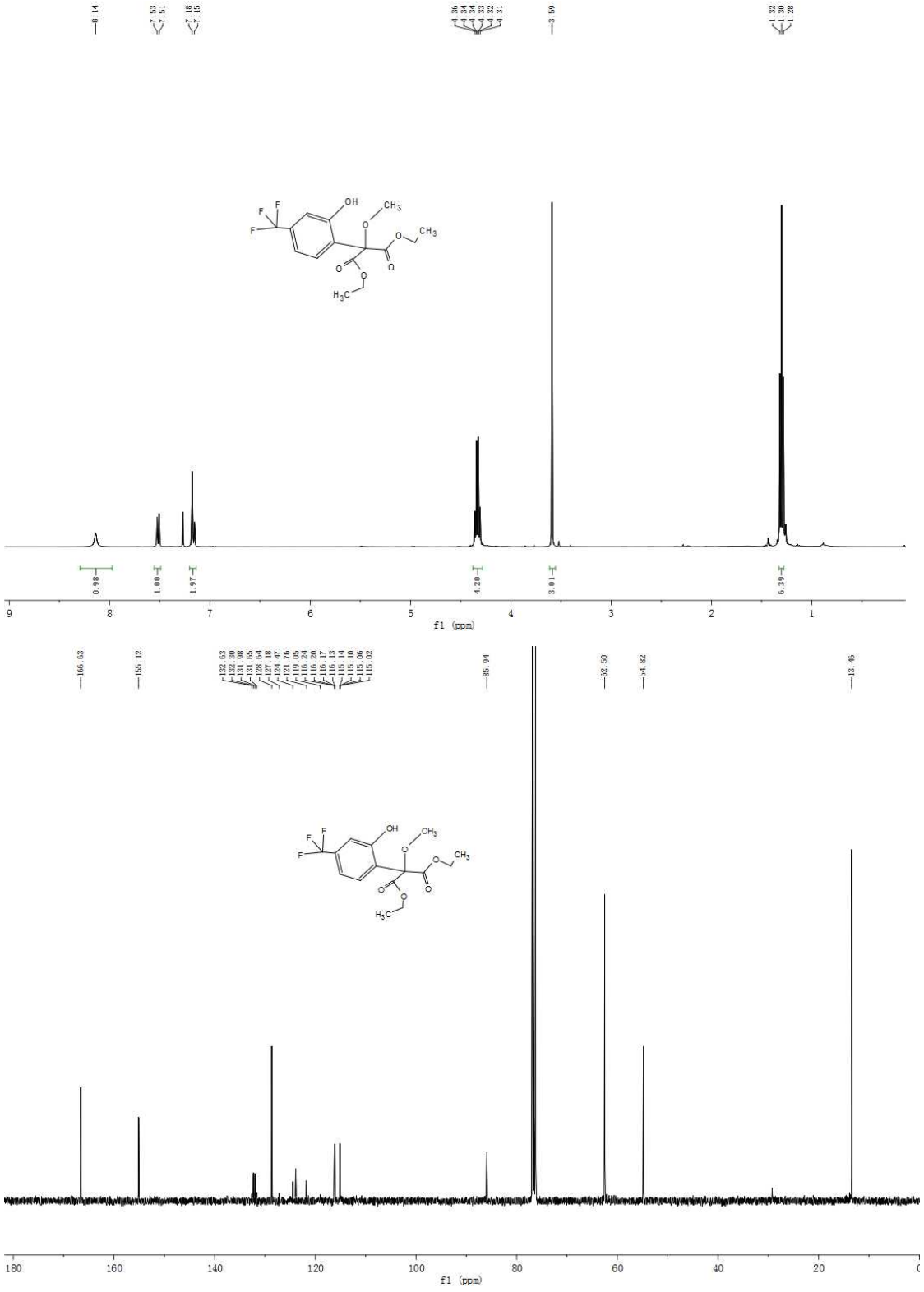
118.22
86.51
62.87
55.24
51.96
13.94
OH
H3C
CH3
H3C
CH3
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

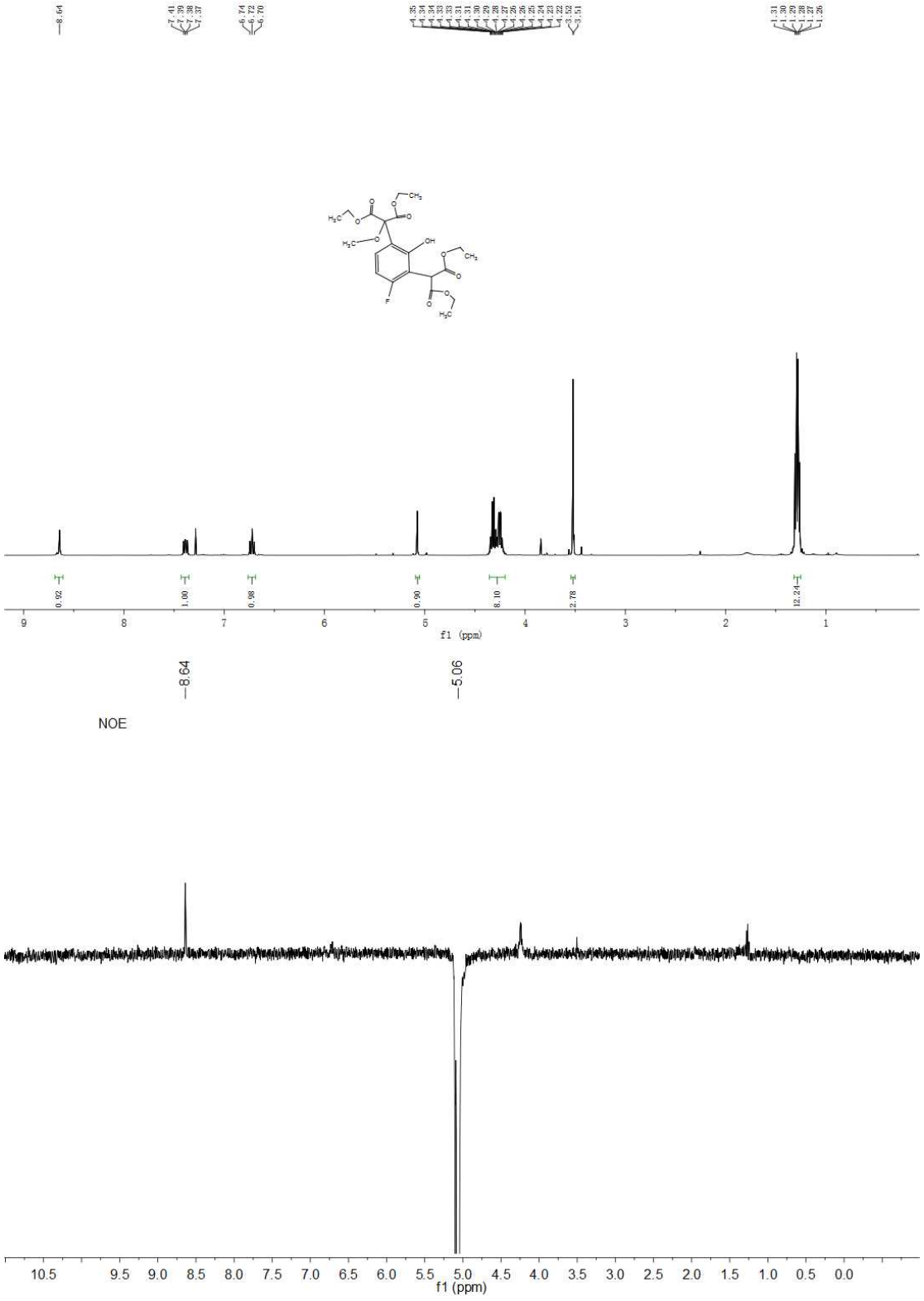
3f

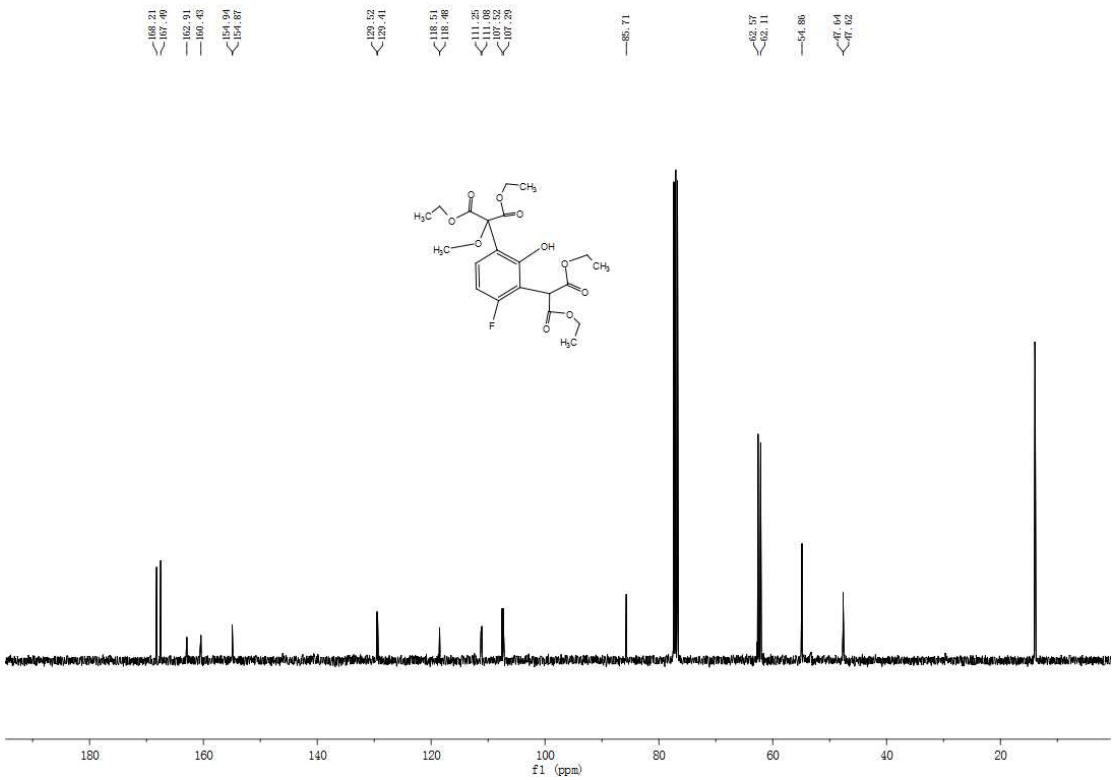

7.25
7.23
6.76
6.74
4.36
4.35
4.34
4.34
4.32
4.31
4.30
3.56
2.31
1.32
1.31
1.29
0.99
1.99
4.05
3.00
3.02
6.31
f1 (ppm)
167.50
155.14
140.94
128.34
121.05
118.64
117.90
86.69
62.54
54.90
21.10
13.97
f1 (ppm)

3g

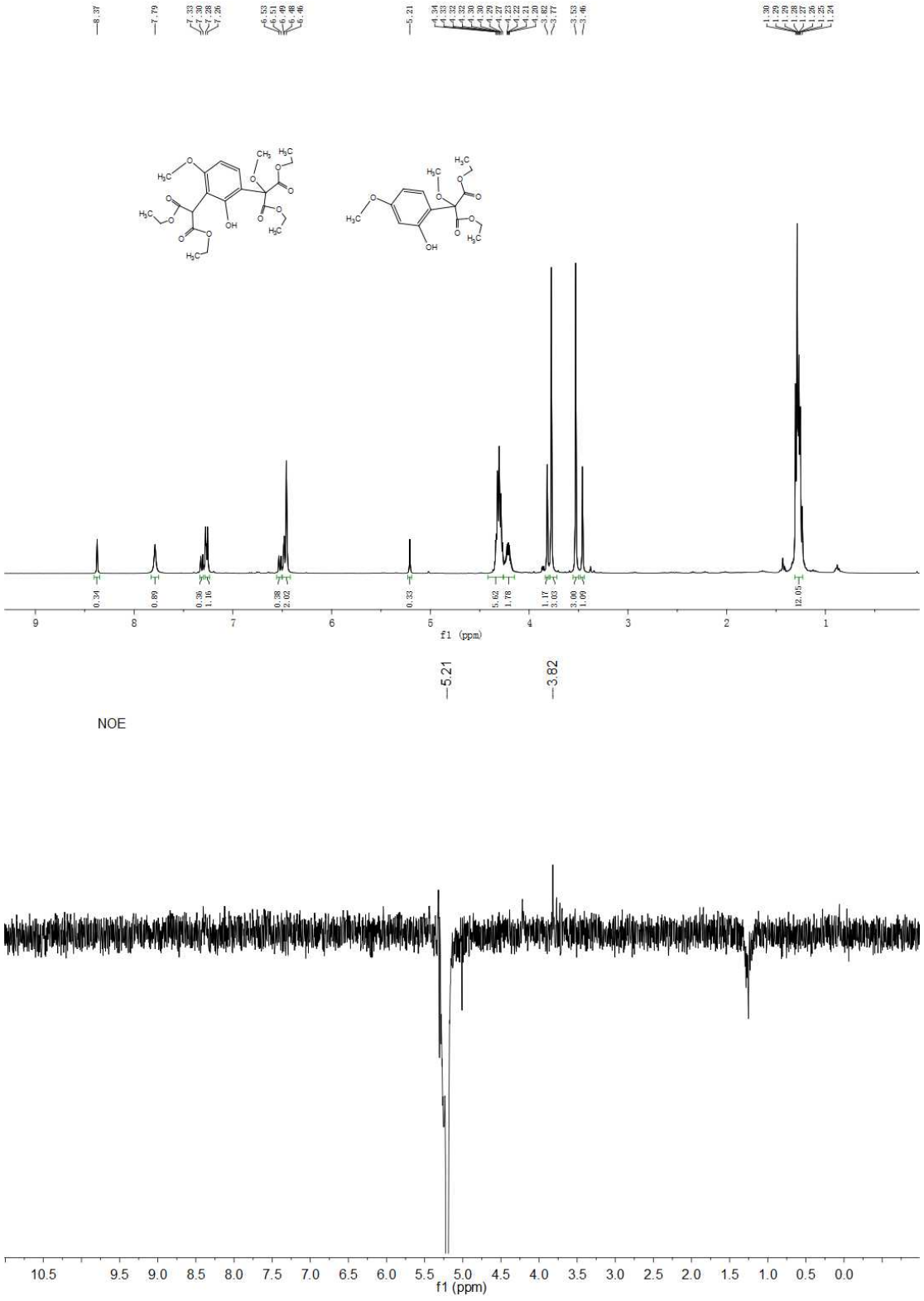

8.14
7.53
7.51
7.18
7.15
4.36
4.34
4.34
4.33
4.32
4.31
3.99
1.32
1.30
1.28
OH
CH3
O
O
CH3
O
O
O
H3C
F
F
F
0.98
1.00
1.97
4.20
3.01
6.39
f1 (ppm)
166.63
155.12
132.63
132.30
131.98
131.65
128.64
127.18
124.47
123.76
119.05
116.24
116.20
116.17
116.13
115.14
115.10
115.06
115.02
85.94
62.59
54.82
13.46
f1 (ppm)

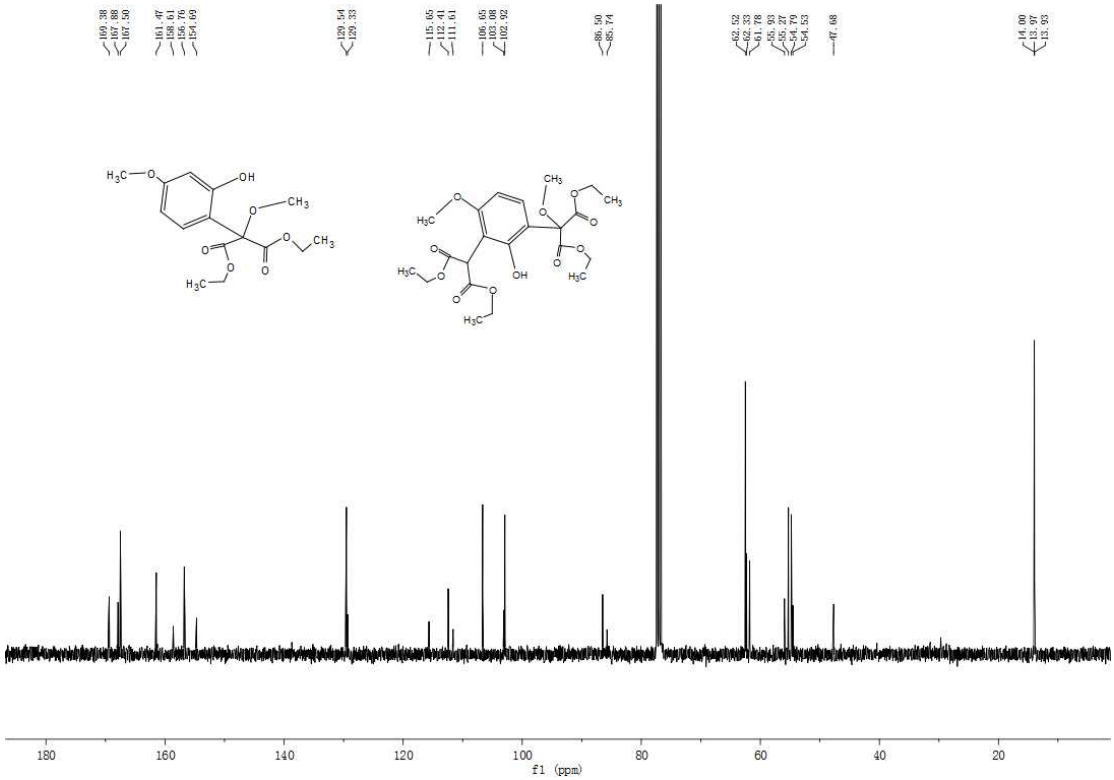
3h


8.64
7.41
7.39
7.38
7.37
6.74
6.72
6.70
4.35
4.34
4.34
4.33
4.33
4.31
4.30
4.29
4.28
4.27
4.26
4.26
4.25
4.24
4.23
4.22
3.52
3.51
1.31
1.30
1.29
1.28
1.27
1.26
0.92
1.00
0.98
0.90
8.10
2.78
12.24
f1 (ppm)
8.64
5.06
NOE
f1 (ppm)

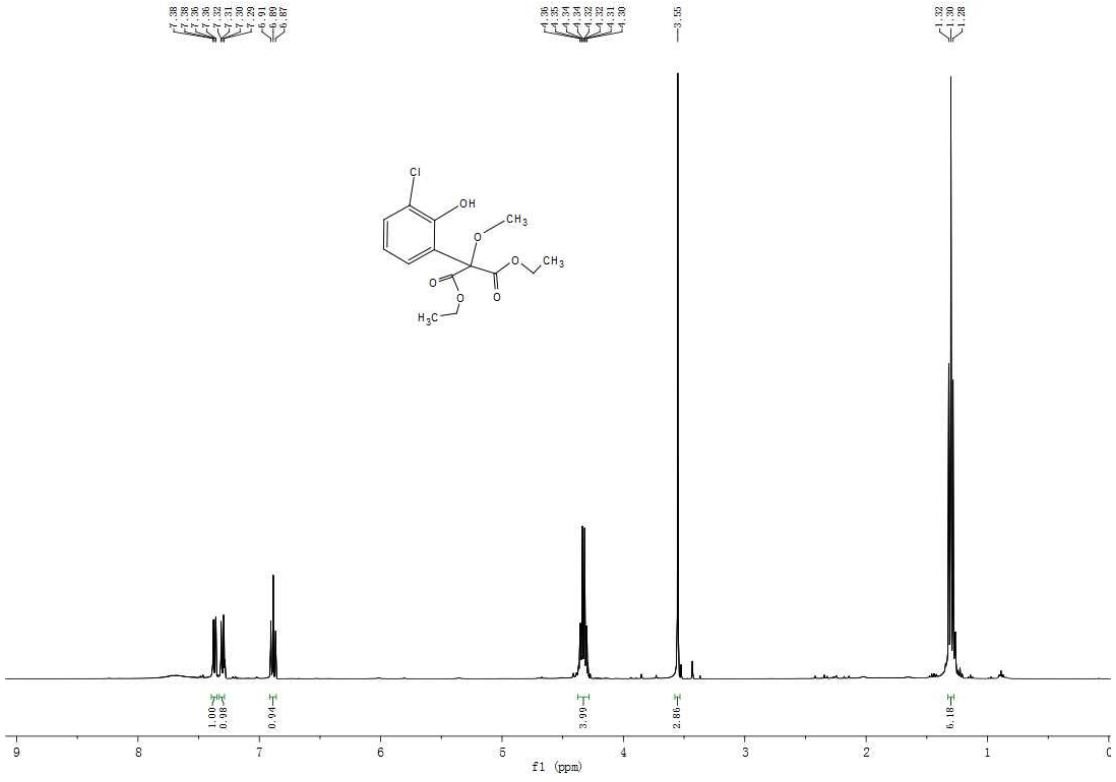

168.21
167.49
162.91
160.43
154.94
154.87
129.52
129.41
118.51
118.48
111.25
111.08
107.52
107.29
85.71
62.57
62.11
54.86
47.64
47.62
180
160
140
120
100
80
60
40
20
f1 (ppm)

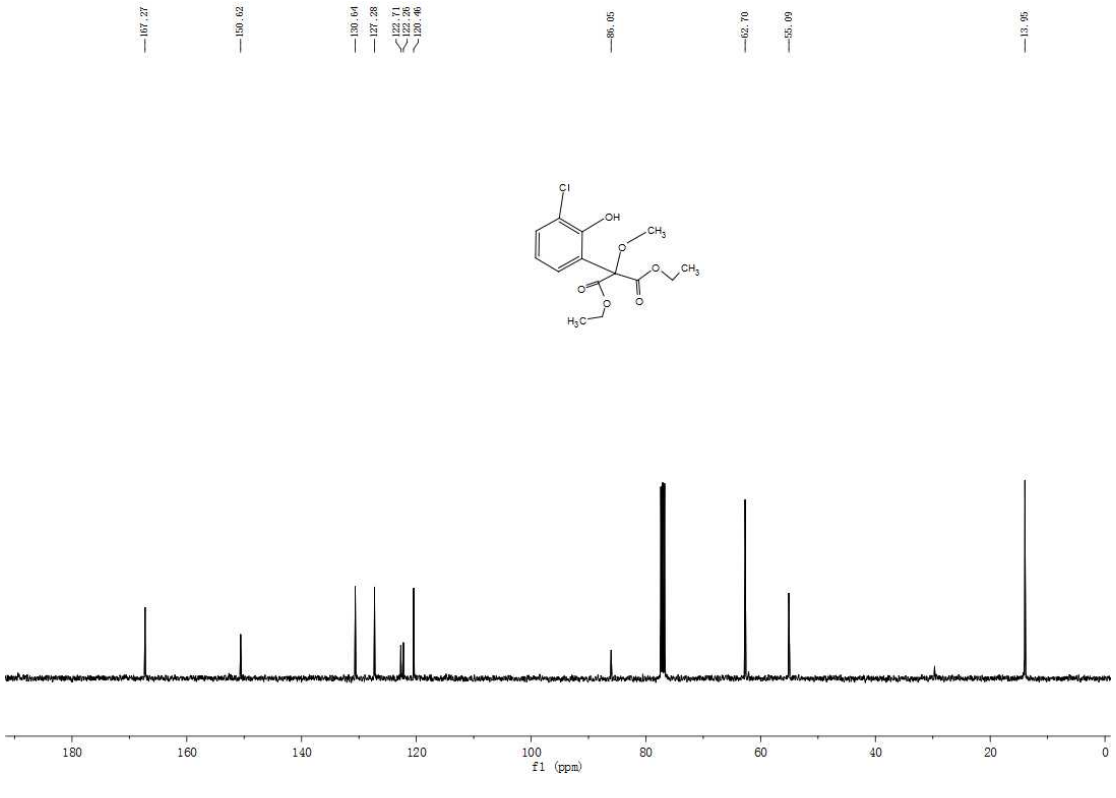
3i


8.37
7.79
7.33
7.30
7.28
7.26
6.53
6.51
6.49
6.48
6.46
5.21
4.34
4.33
4.32
4.32
4.30
4.29
4.27
4.23
4.22
4.21
4.20
3.82
3.77
3.53
3.46
1.30
1.29
1.29
1.28
1.27
1.26
1.25
1.24
0.34
0.89
0.36
1.16
0.38
2.02
0.33
5.62
1.78
1.17
3.03
3.00
1.00
12.05
f1 (ppm)
5.21
3.82
NOE
f1 (ppm)

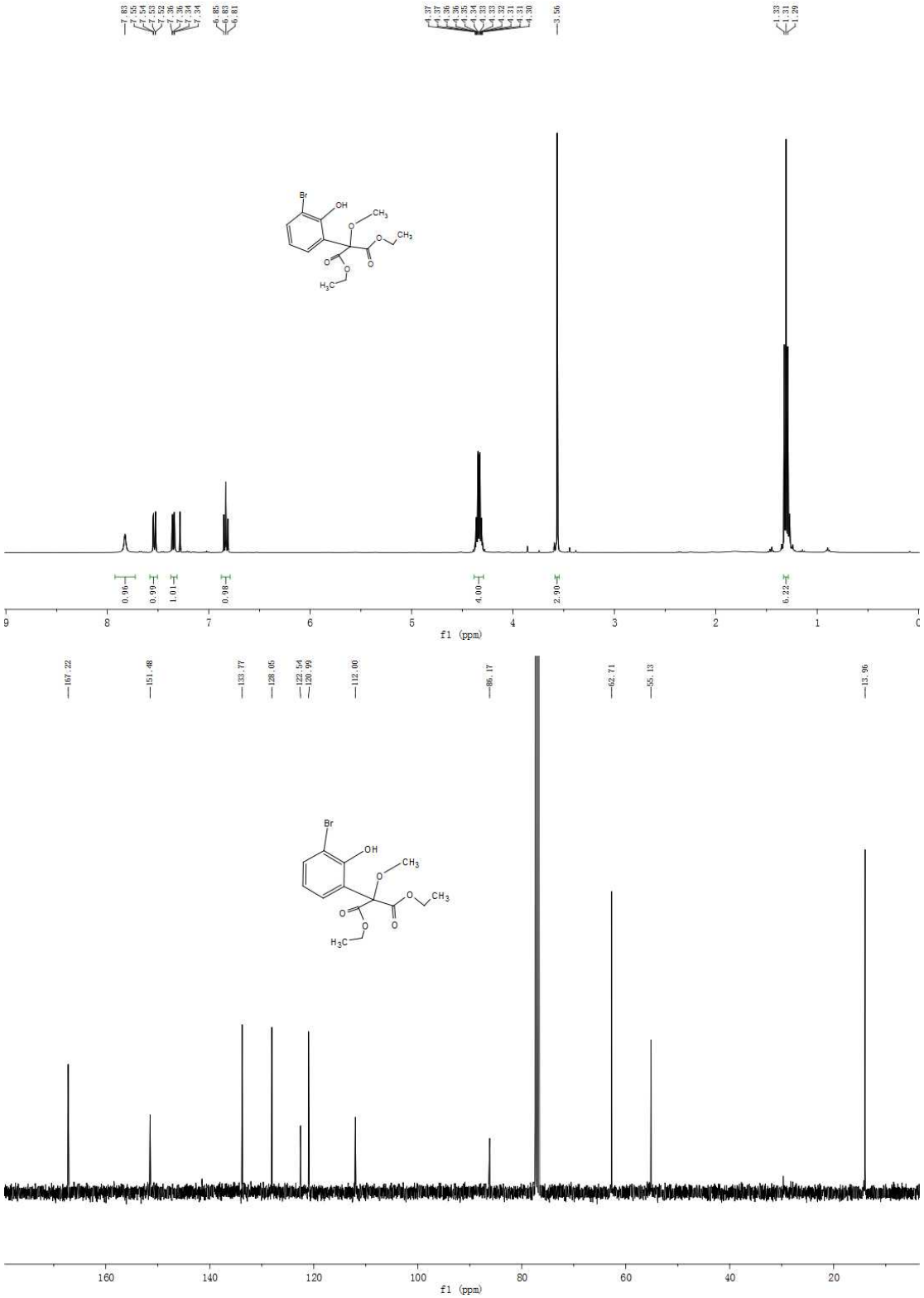

169.38
167.88
167.50
161.47
158.61
156.76
154.69
129.54
129.33
115.65
112.41
111.61
106.65
103.08
102.92
86.50
85.74
62.52
62.33
61.78
55.93
55.87
54.79
54.53
47.68
14.00
13.97
13.93
180
160
140
120
100
80
60
40
20
f1 (ppm)

3j

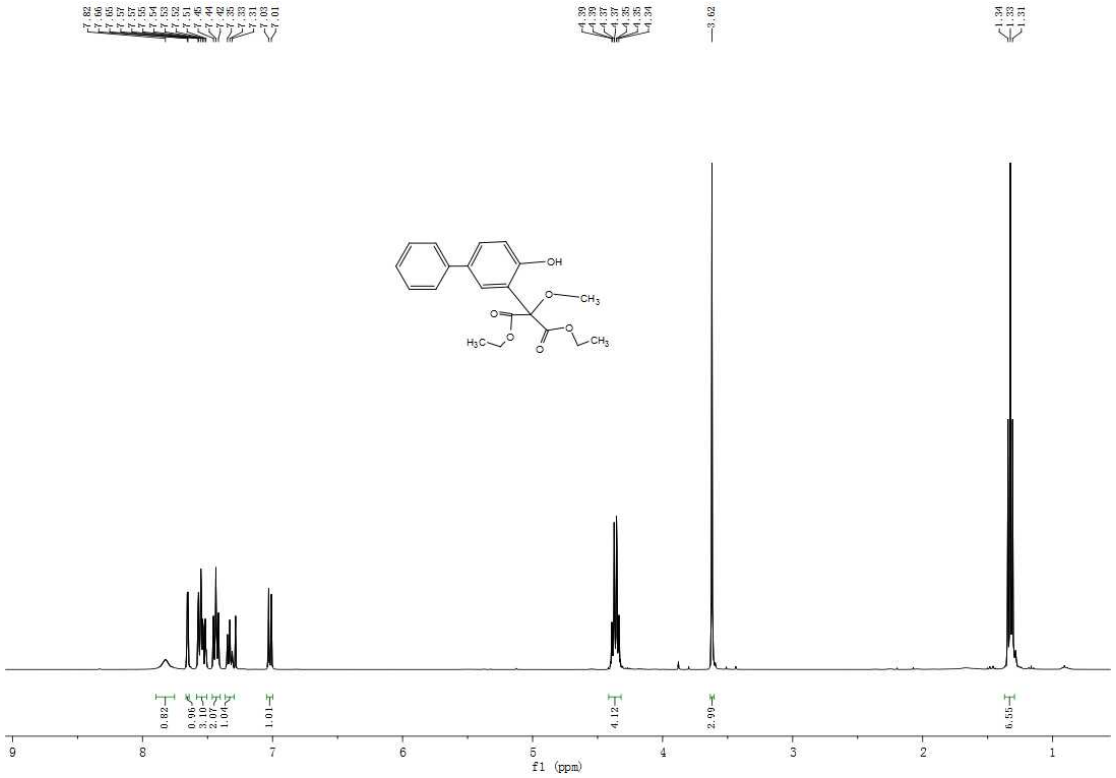

7.38
7.38
7.36
7.36
7.32
7.31
7.30
7.29
6.91
6.89
6.87
4.36
4.35
4.34
4.34
4.32
4.32
4.31
4.30
3.55
1.32
1.30
1.28
Cl
OH
CH3
O
O
CH3
O
O
O
H3C
1.00
0.98
0.94
3.99
2.86
6.18
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

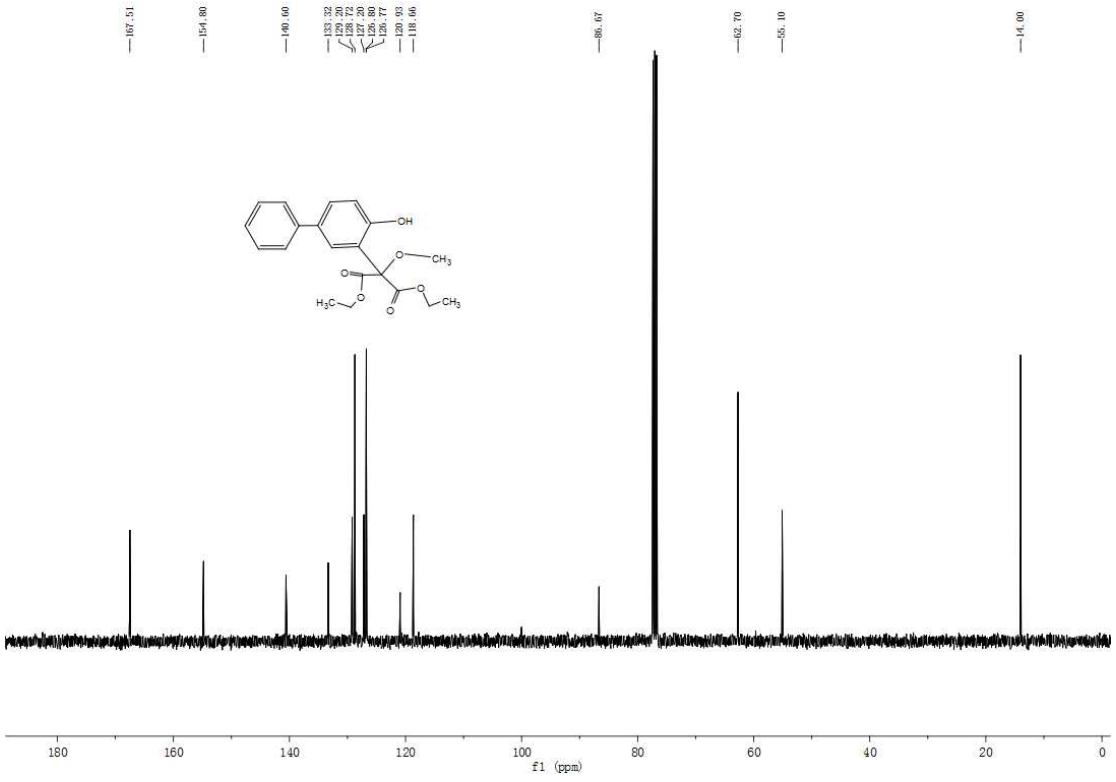

167.27
150.62
130.64
127.28
122.71
122.26
120.46
86.05
62.70
55.09
13.95
Cl
OH
CH3
O
O
CH3
O
O
O
H3C
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

3k

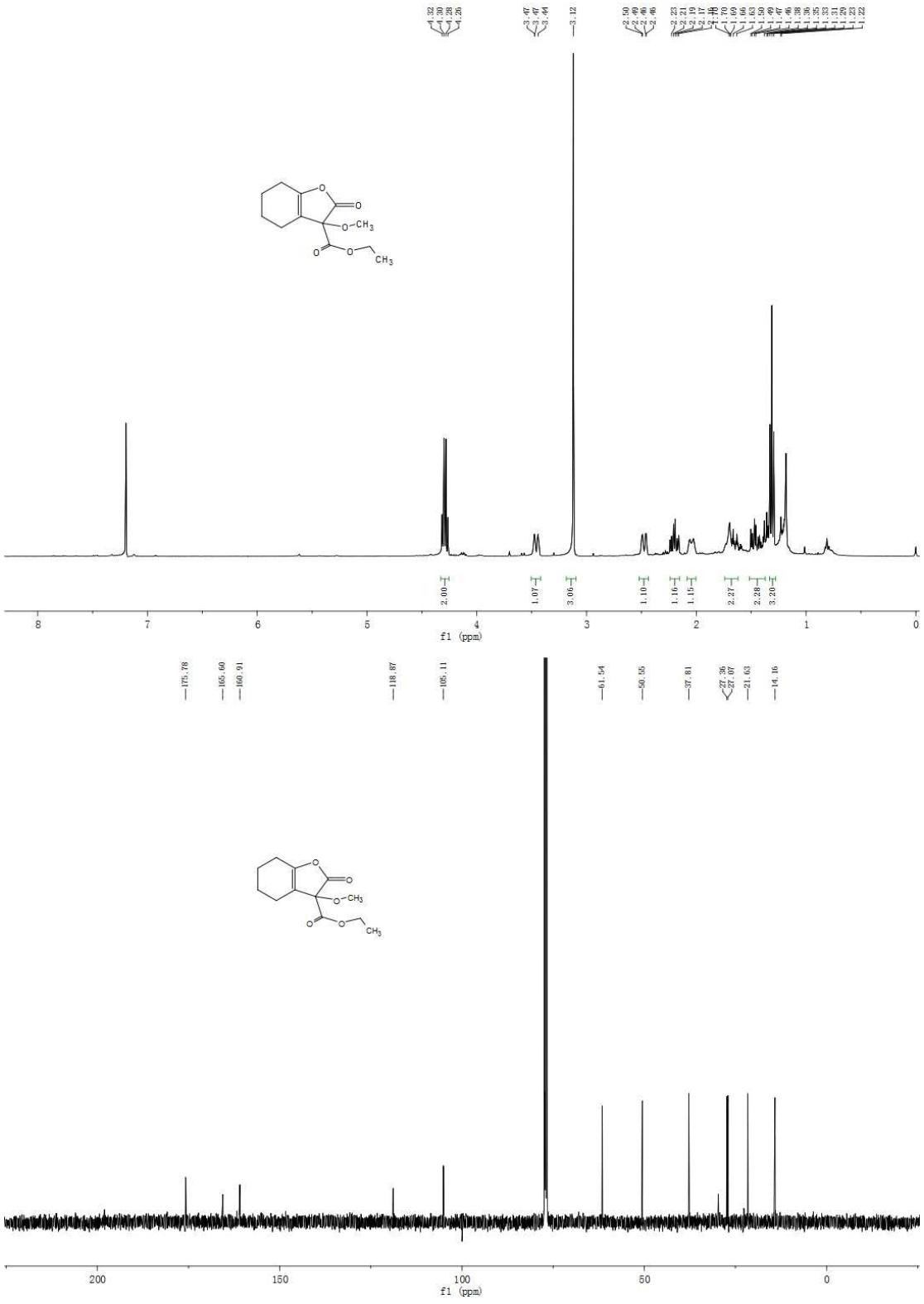

7.83
7.55
7.54
7.53
7.52
7.36
7.36
7.34
7.34
6.85
6.83
6.81
4.37
4.36
4.36
4.35
4.34
4.33
4.33
4.32
4.31
4.31
4.30
3.56
1.33
1.31
1.29
Br
OH
CH3
O
O
CH3
O
O
O
H3C
0.06
0.99
1.01
0.98
4.00
2.90
6.22
f1 (ppm)
167.22
151.48
133.77
128.05
122.54
120.99
112.00
86.17
62.71
55.13
13.96
Br
OH
CH3
O
O
CH3
O
O
O
H3C
f1 (ppm)

3l

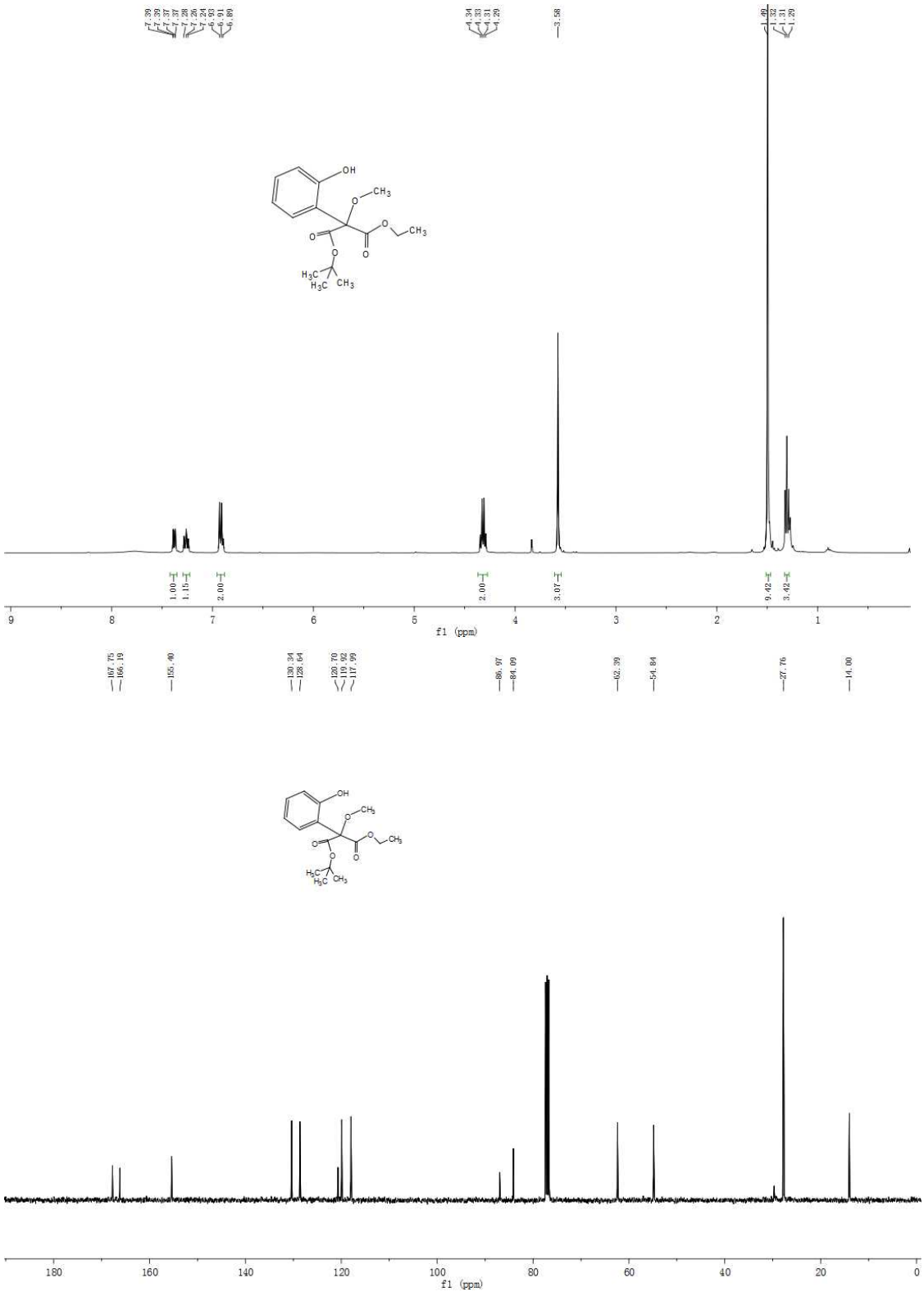

7.82
7.66
7.66
7.57
7.57
7.55
7.54
7.53
7.52
7.51
7.45
7.44
7.42
7.35
7.33
7.31
7.03
7.01
4.39
4.39
4.37
4.37
4.35
4.35
4.34
3.62
1.34
1.33
1.31
OH
O
CH3
O
H3C
O
O
O
CH3
0.82
0.96
3.10
2.07
1.04
1.01
4.12
2.99
6.55
9
8
7
6
5
4
3
2
1
f1 (ppm)


167.51
154.80
140.60
133.32
129.20
128.72
127.20
126.80
126.77
120.93
118.66
86.67
62.70
55.10
14.00
OH
O
CH3
O
H3C
O
O
O
CH3
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

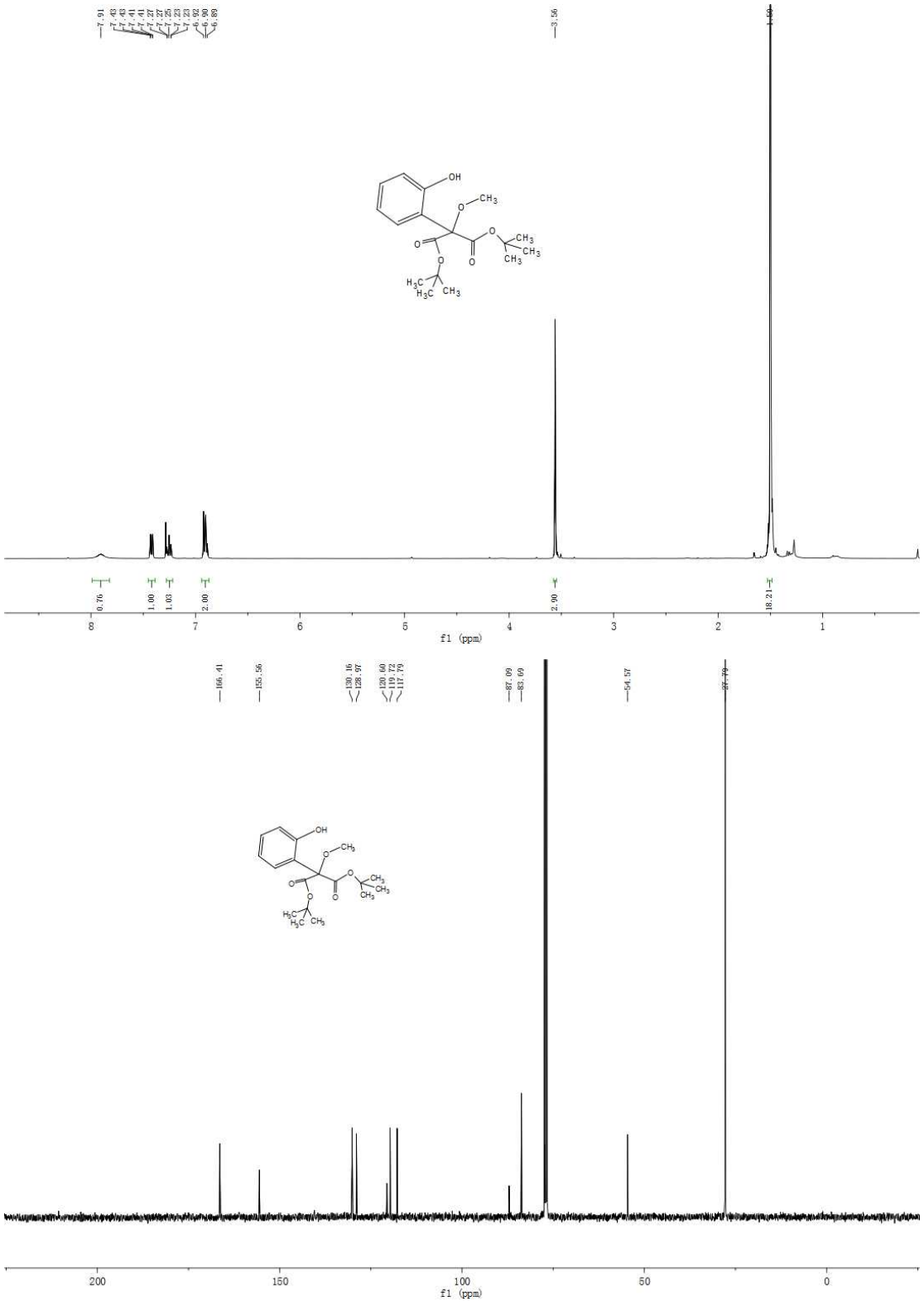
3m



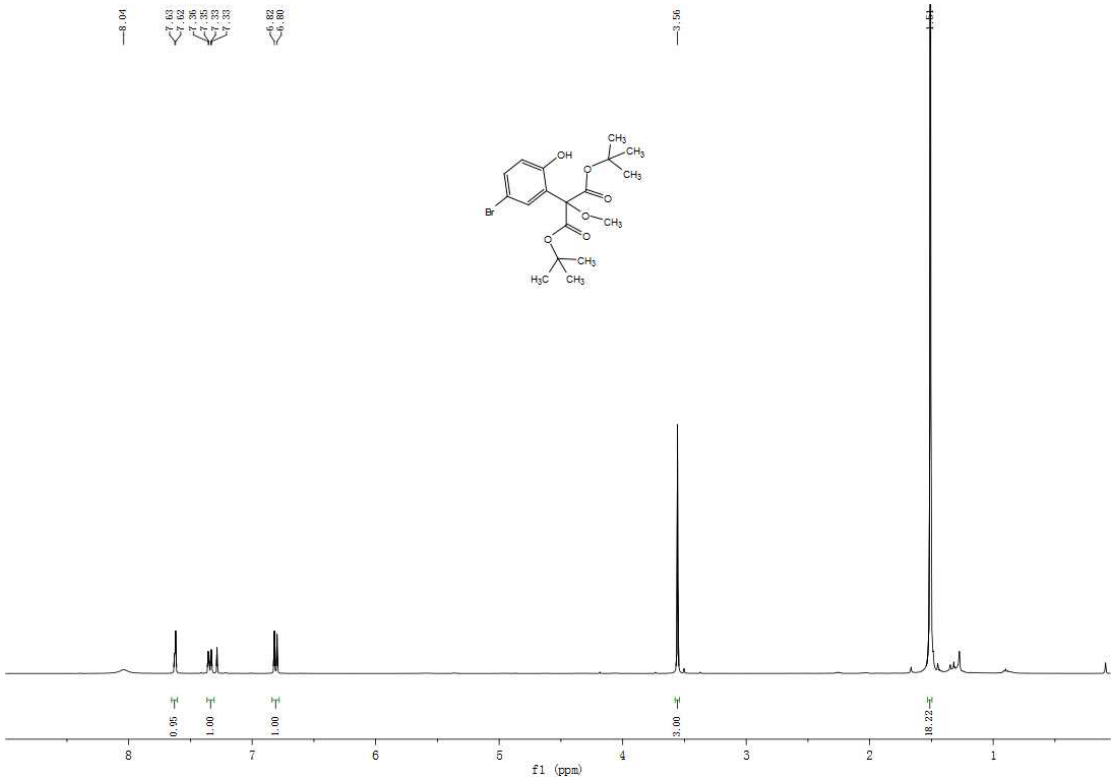
3n

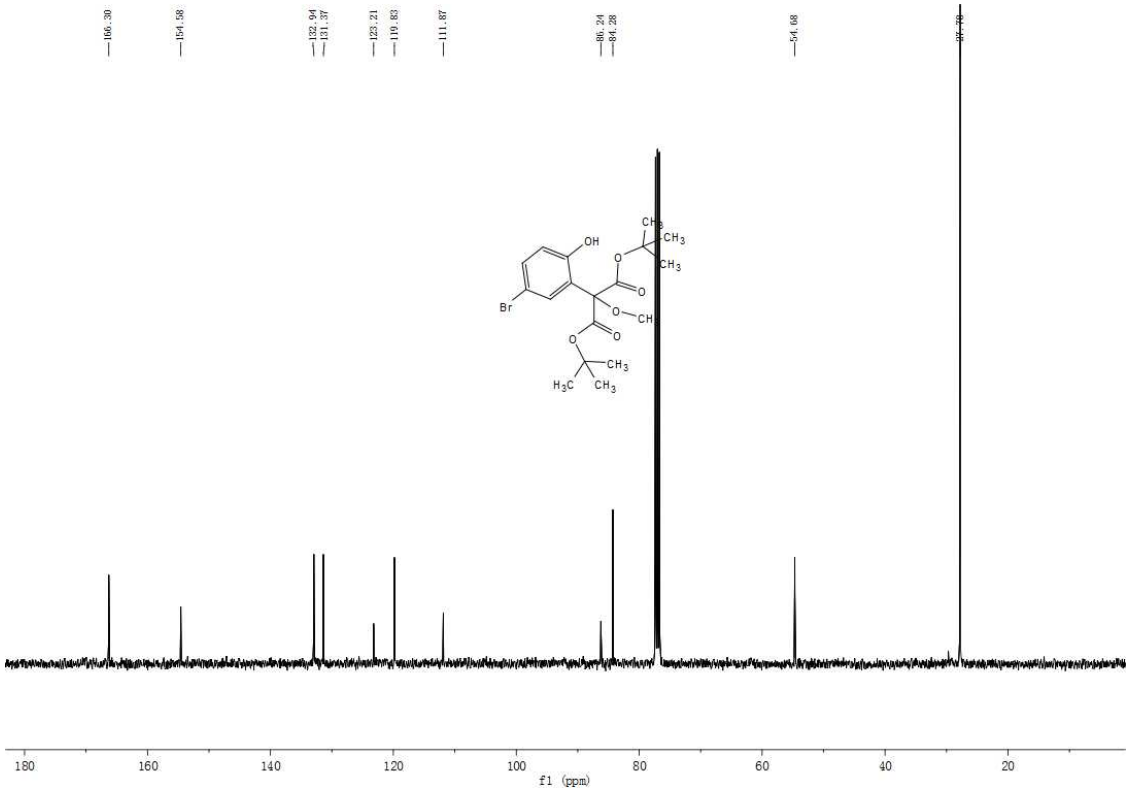

7.39
7.37
7.28
7.26
7.24
6.93
6.91
6.89
4.34
4.33
4.31
4.29
3.58
1.32
1.31
1.29
OH
CH3
O
O
CH3
O
O
H3C
H3C
CH3
1.00
1.15
2.00
2.00
3.07
9.42
3.42
f1 (ppm)
167.75
166.19
155.40
130.34
128.64
120.70
119.98
117.99
86.97
84.09
62.39
56.84
27.76
14.00
f1 (ppm)

3o

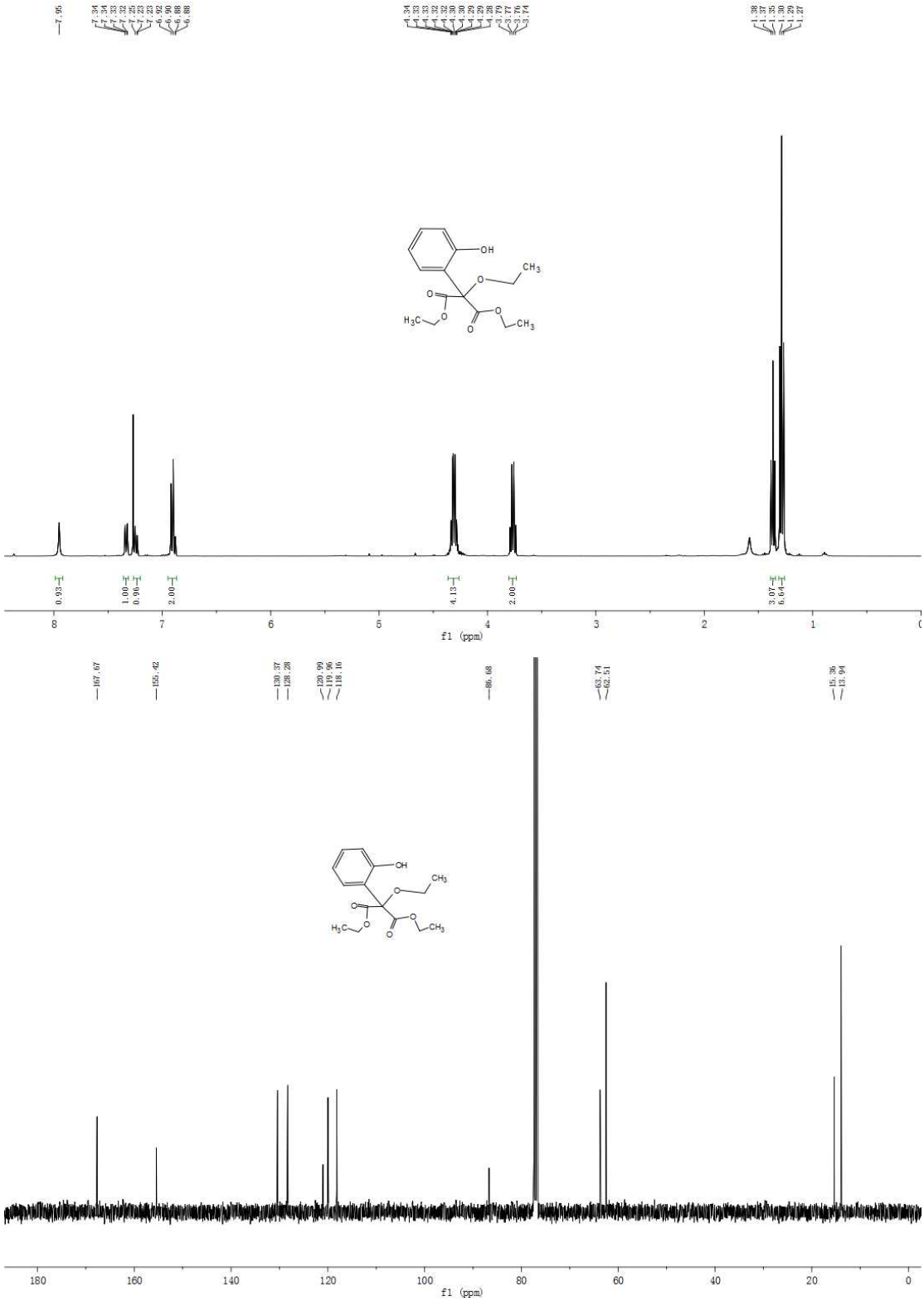

7.91
7.43
7.41
7.27
7.25
7.23
6.92
6.90
6.89
3.56
1.60
OH
CH3
O
O
O
O
CH3
CH3
CH3
H3C
H3C
CH3
0.76
1.00
1.03
2.00
2.90
18.21
8
7
6
5
4
3
2
1
f1 (ppm)
166.41
155.56
130.16
128.97
120.60
119.72
117.79
87.09
83.69
54.57
27.79
OH
CH3
O
O
O
O
CH3
CH3
CH3
H3C
H3C
CH3
200
150
100
50
0
f1 (ppm)

3p

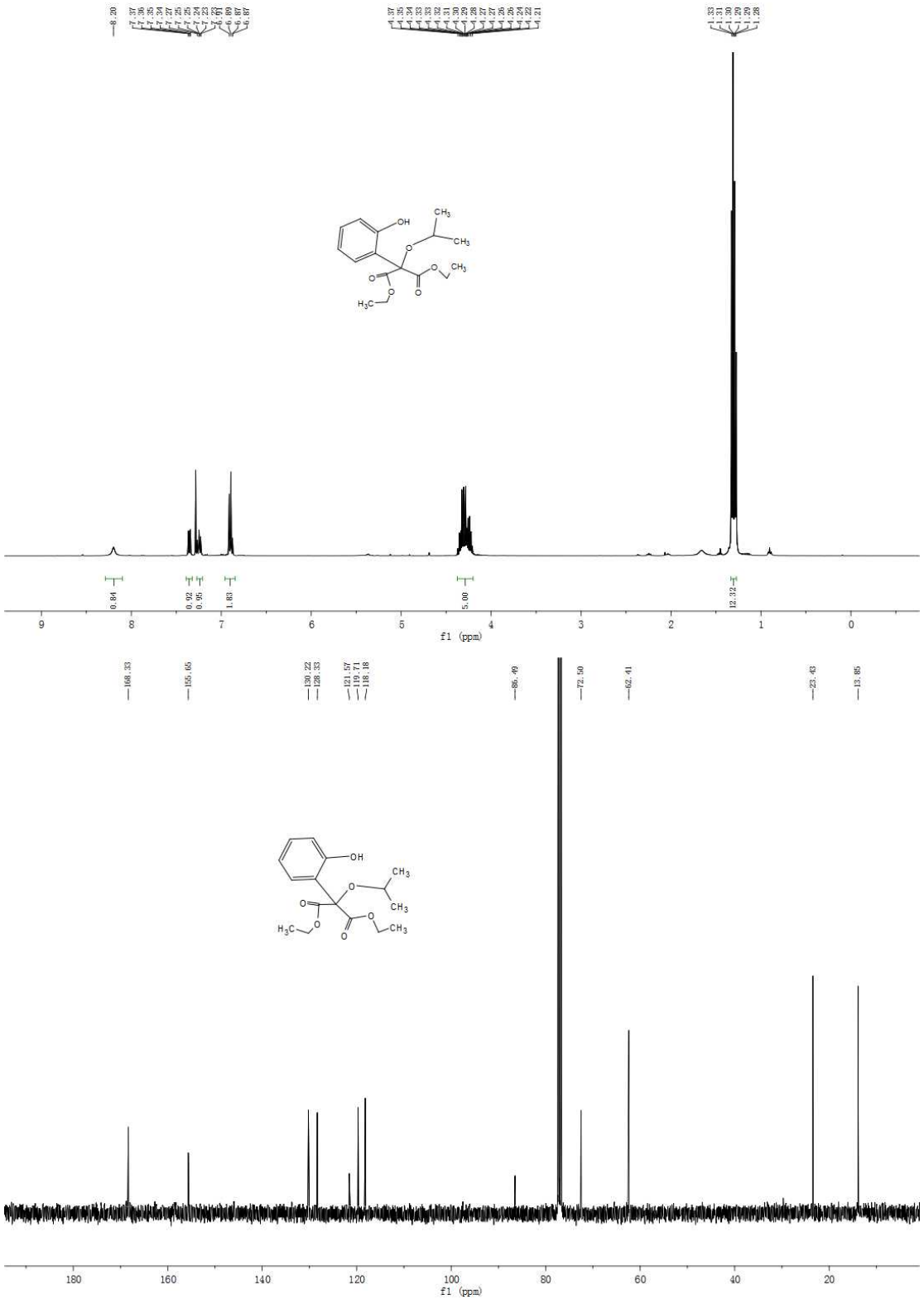

8.04
7.63
7.62
7.36
7.35
7.33
7.33
6.82
6.80
3.56
1.61
OH
Br
CH3
CH3
CH3
O
O
O
O
CH3
O
CH3
H3C
CH3
0.95
1.00
1.00
3.00
18.22
8
7
6
5
4
3
2
1
f1 (ppm)


166.30
154.58
132.94
131.37
123.21
119.83
111.87
86.24
84.28
54.68
27.78
OH
Br
CH3
CH3
CH3
O
O
O
O
CH3
O
CH3
H3C
CH3
180
160
140
120
100
80
60
40
20
f1 (ppm)

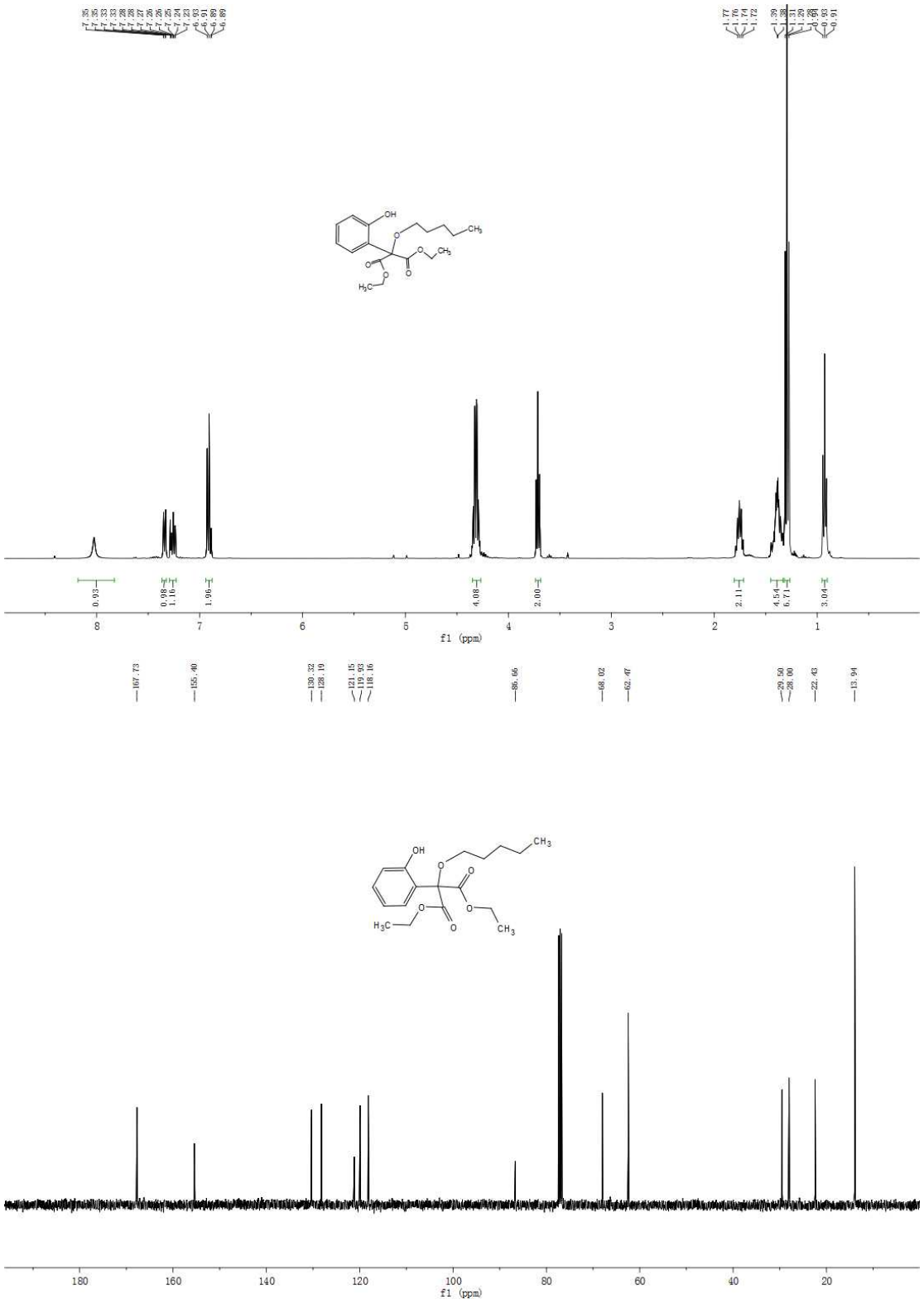
3q


7.95
7.34
7.34
7.33
7.32
7.25
7.23
7.23
6.92
6.90
6.88
6.88
4.34
4.33
4.33
4.32
4.32
4.30
4.29
4.29
4.28
4.28
3.79
3.77
3.76
3.74
1.38
1.37
1.35
1.30
1.29
1.27
OH
CH3
O
O
O
H3C
O
O
CH3
0.93
1.00
0.96
2.00
4.13
2.00
3.07
6.64
f1 (ppm)
167.67
155.42
130.37
128.28
120.99
119.96
118.16
86.68
63.74
62.51
15.36
13.94
OH
CH3
O
O
O
H3C
O
O
CH3
f1 (ppm)

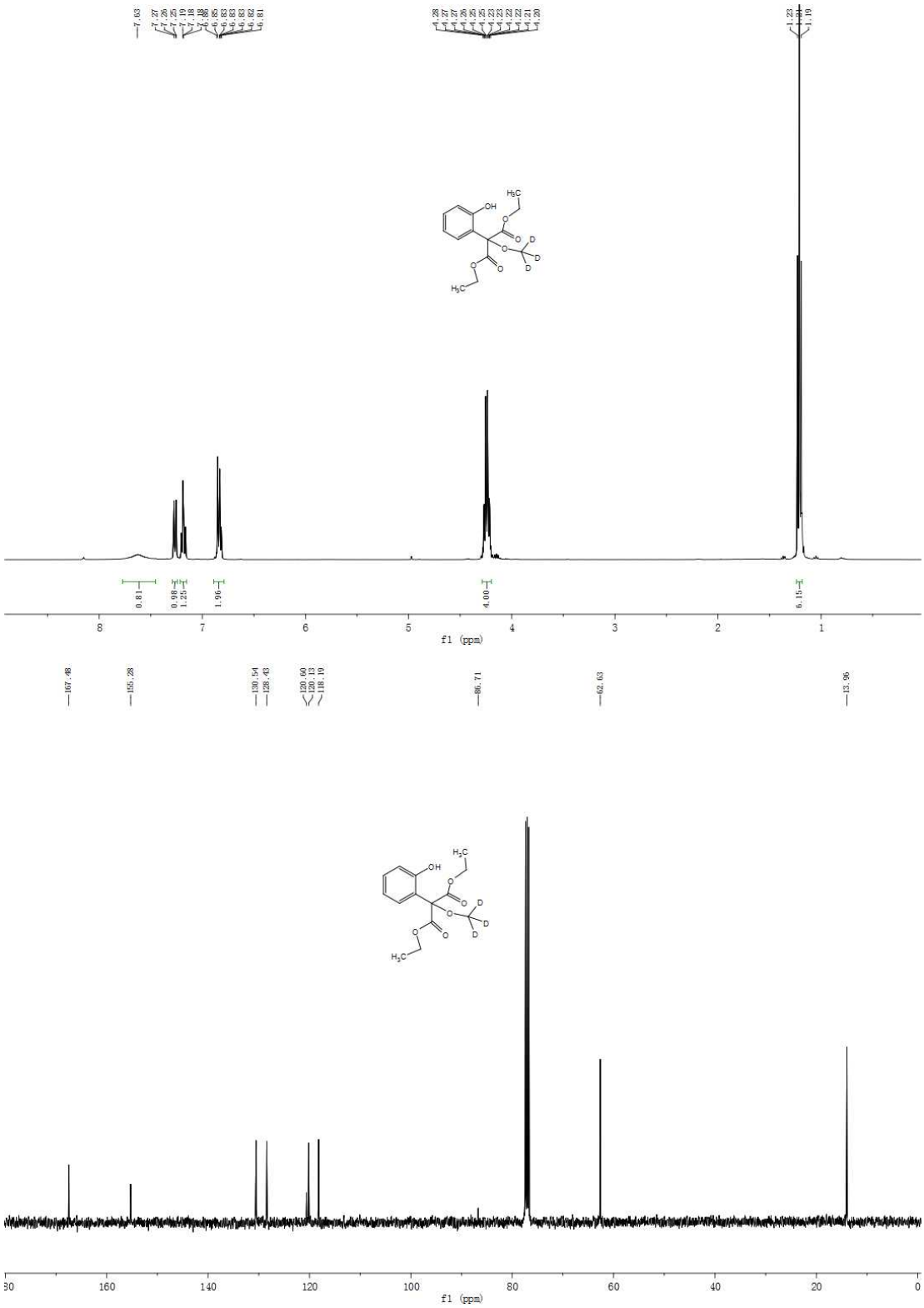
3r



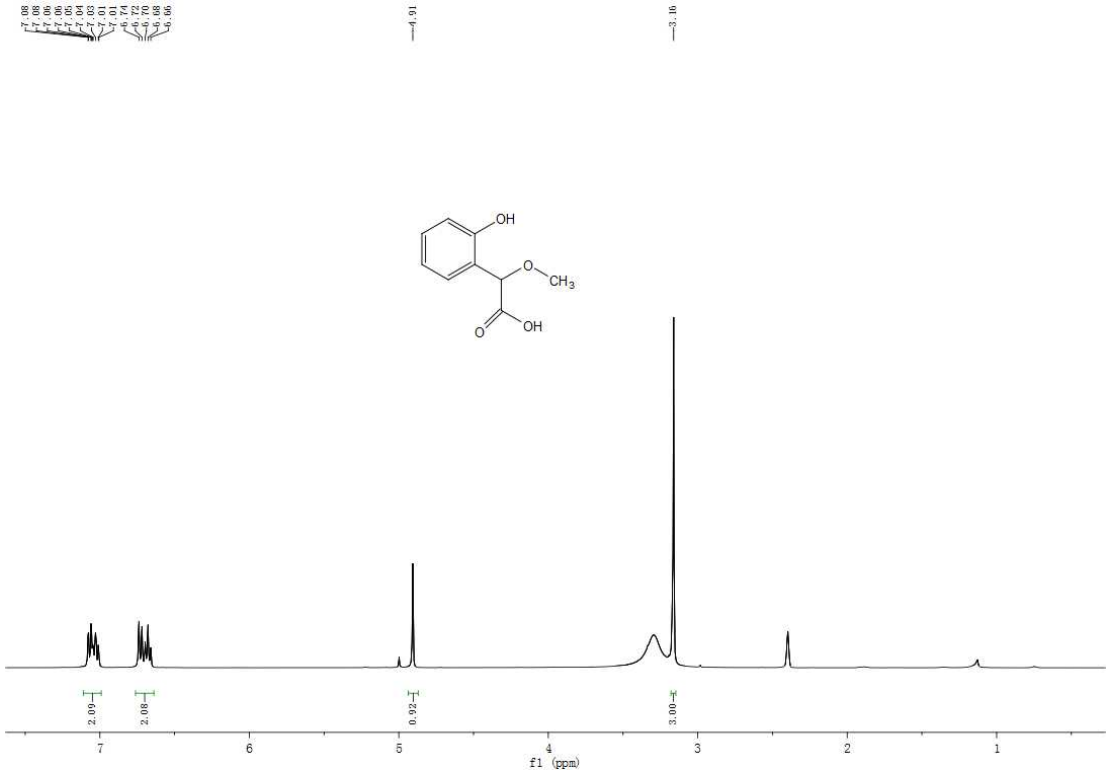
3s

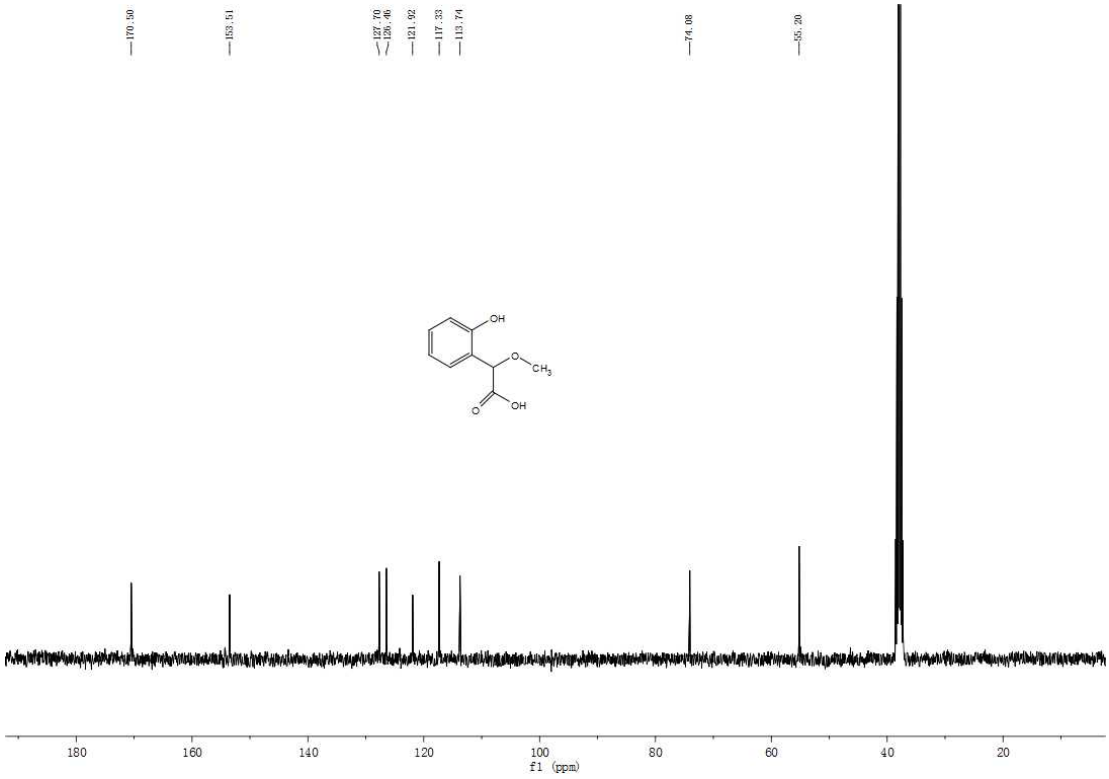


3t

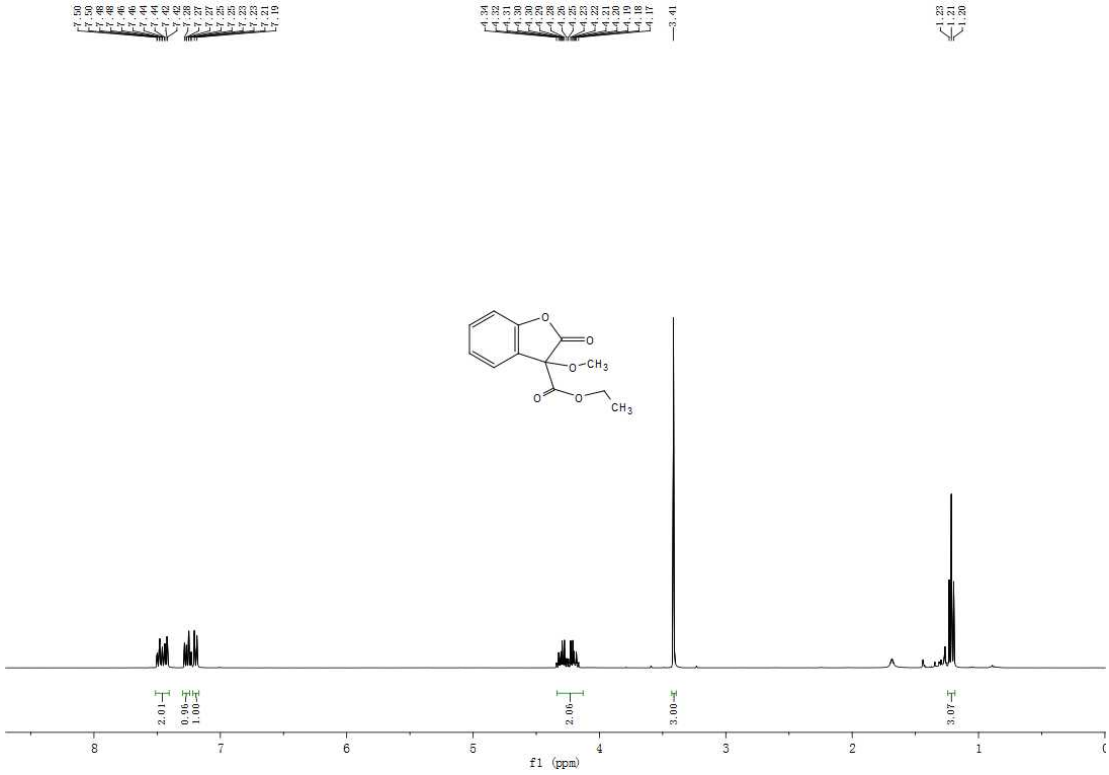


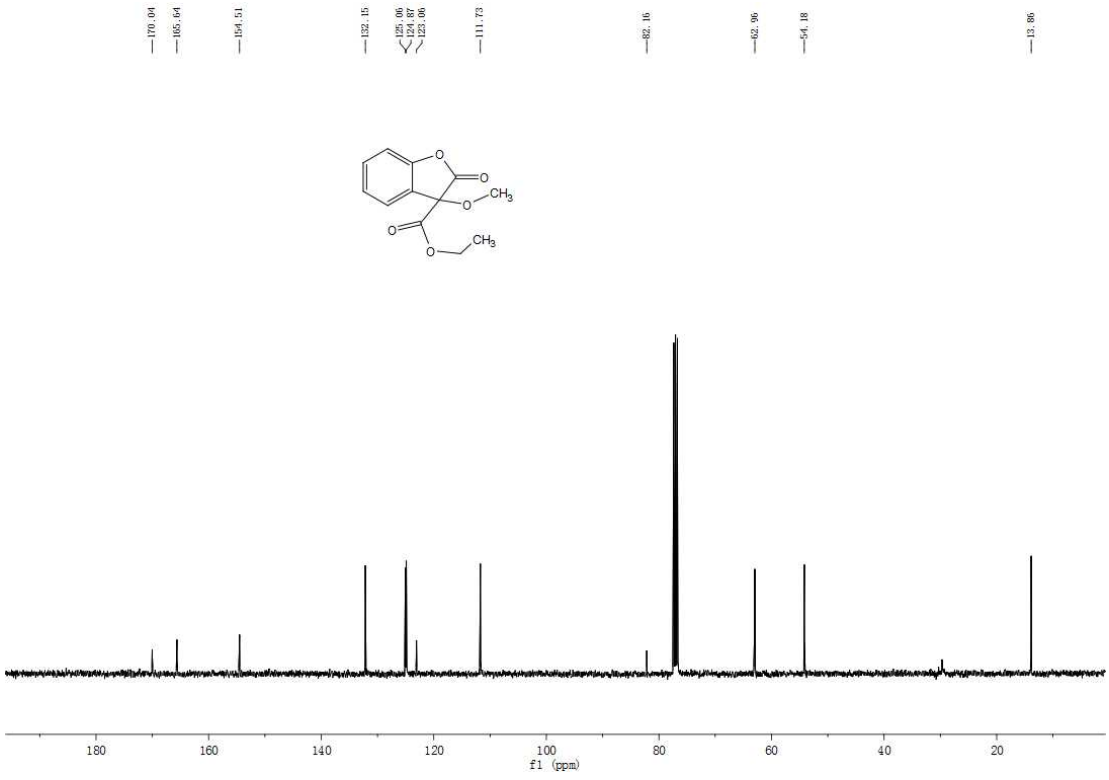
5a


7.08
7.08
7.06
7.06
7.05
7.04
7.03
7.01
7.01
6.74
6.72
6.70
6.68
6.66
4.91
3.16
OH
O
CH3
OH
2.09
2.08
0.92
3.00
7
6
5
4
3
2
1
f1 (ppm)

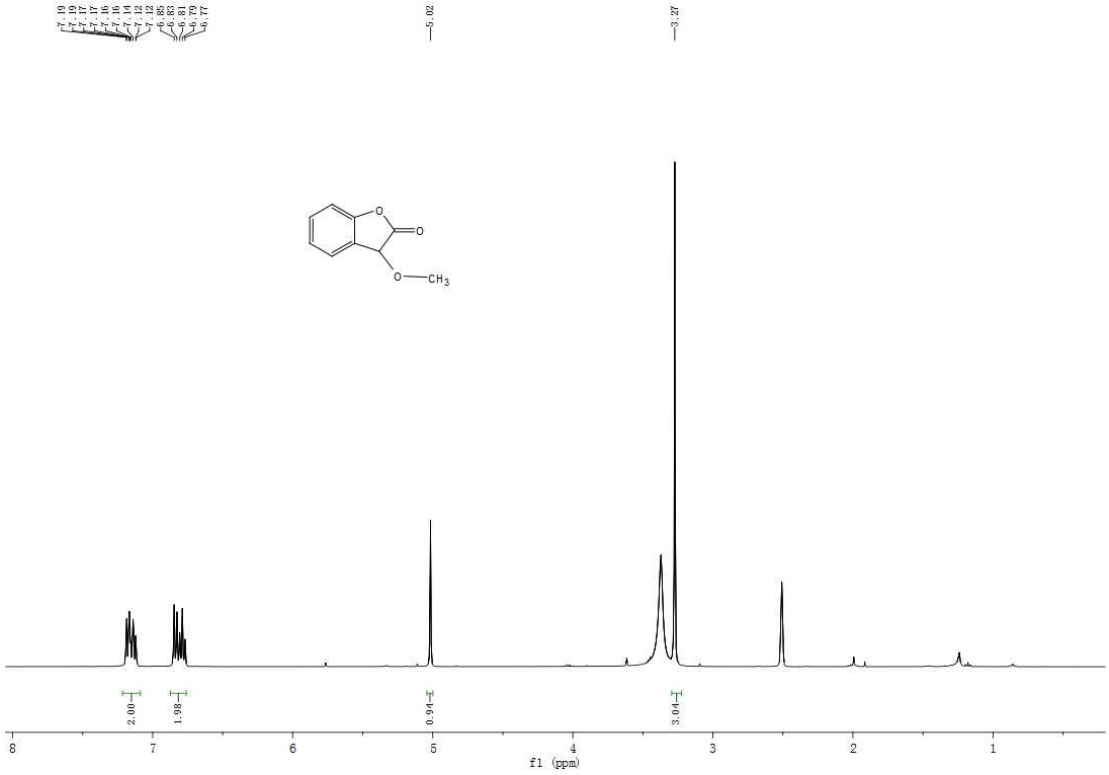

170.50
153.51
127.70
126.46
121.92
117.33
113.74
74.08
55.20
OH
O
CH3
OH
180
160
140
120
100
80
60
40
20
f1 (ppm)

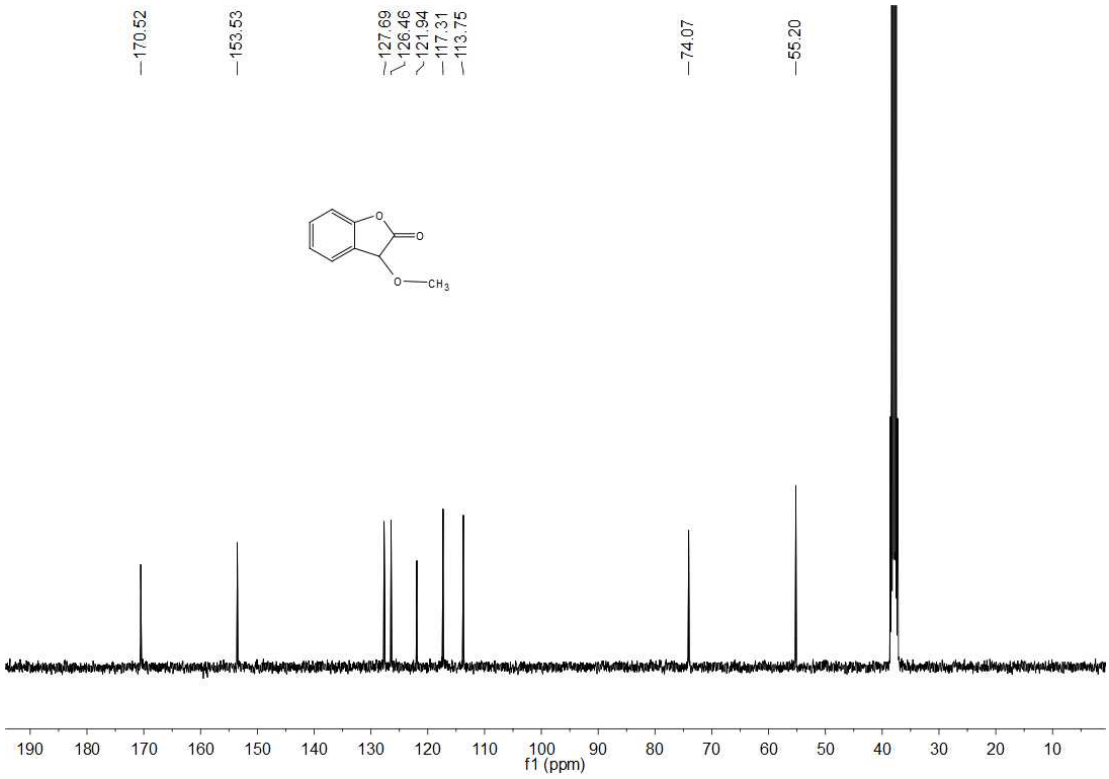
6a


7.50
7.48
7.46
7.44
7.42
7.28
7.27
7.25
7.23
7.21
7.19
4.34
4.32
4.31
4.30
4.29
4.28
4.26
4.25
4.23
4.22
4.21
4.20
4.19
4.18
4.17
3.41
1.23
1.21
1.20
2.01
0.96
1.00
2.06
3.00
3.07
f1 (ppm)


170.04
165.64
154.51
132.15
125.06
124.87
123.06
111.73
82.16
62.96
54.18
13.86
f1 (ppm)

7a


7.19
7.19
7.17
7.17
7.16
7.16
7.14
7.12
7.12
6.85
6.83
6.81
6.80
6.77
5.02
3.27
2.00
1.98
0.94
3.04
f1 (ppm)


170.52
153.53
127.69
126.46
121.94
117.31
113.75
74.07
55.20
f1 (ppm)