

Total synthesis of Sparstolonin B, a potent anti-inflammatory agent

Yongqiang Wang,^{a,b} Chao Wang,^{*a} Yuanxun Wang,^a Lijin Dong,^a and Jian Sun^{*a}

[†] Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu 610041, China

[‡] University of Chinese Academy of Sciences, Beijing 100049, China.

E-mail: sunjian@cib.ac.cn; wangchao@cib.ac.cn

Supporting Information

Contents

General information	1
Experimental procedures of the strategy 1	2-5
Experimental procedures of the strategy 2	5-11
Reference	12
NMR spectra	13-26

General information

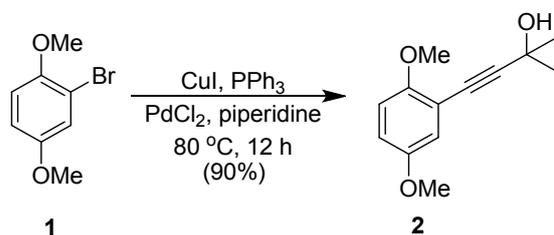
All reactions involving air- and moisture-sensitive reagents were carried out using oven dried glassware and standard syringe-septum cap techniques. TLC inspections were on silica gel GF254 plates. Column chromatography was performed on silica gel (200–300 mesh). All chemicals were purchased from commercial suppliers and used as received.

All solvents and reagents were used as supplied with following exceptions. Tetrahydrofuran (THF), toluene, mesitylene and diethyl ether were freshly distilled from Na metal/benzophenone under argon. N,N-Dimethylformamide (DMF), dimethyl sulfoxide (DMSO), CH₂Cl₂, MeCN, pyridine, N,N-Diisopropylamine (i-Pr₂NH) and triethylamine (Et₃N) were distilled from calcium hydride under argon. Acetone was distilled from phosphorus pentoxide under argon.

Melting points were taken on X-4 micro melting point apparatus and were uncorrected. ¹H and ¹³C NMR spectra were obtained on a Bruker Avance 400 (400 MHz), and tetramethylsilane (TMS) was used as internal standard. Data for ¹H were reported as follows: chemical shift (ppm), and multiplicity (S = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Data for ¹H NMR and ¹³C NMR were all reported as ppm. Coupling constants were reported in Hertz (Hz). All high resolution mass spectra were obtained on a micro TOF-QII 10203 spectrometer.

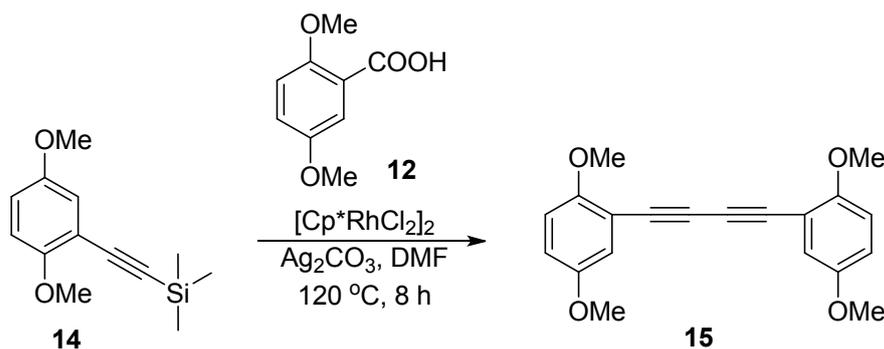
Experimental procedures of the strategy 1

4-(2,5-dimethoxyphenyl)-2-methylbut-3-yn-2-ol (**2**).



A mixture of **1** (2.17 g, 10 mmol), PdCl₂ (35.5 mg, 0.2 mmol), CuI (19.1 mg, 0.1 mmol), PPh₃ (78.7 mg, 0.3 mmol), 3-Methyl butynol (2.91 mL, 30 mmol) and piperidine (40 mL) in a 50 mL of sealed tube was heated at 80 °C for 12 h under nitrogen atmosphere. The reaction was monitored for completion by TLC. Upon completion, the reaction mixture was cooled to room temperature, piperidine was removed under reduced pressure and the reaction mixture was partitioned between EtOAc (2 × 100 mL) and water (2 × 50 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic fractions were washed with 3% aqueous HCl (100 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel (PE/EtOAc = 5/1) to yield the product **2** as a yellow oil (1.96 g, 90%). Spectroscopic data matched that previously reported.¹ ¹H NMR (400 MHz, CDCl₃) δ 6.95 (d, *J* = 2.9 Hz, 1H), 6.88 – 6.83 (m, 1H), 6.81 (d, *J* = 9.0 Hz, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 1.66 (s, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 154.4, 153.2, 118.2, 115.7, 112.5, 112.2, 98.1, 78.3, 65.6, 56.5, 55.8, 31.5. HRMS (ESI, TOF) (*m/z*): calcd for C₁₆H₁₆O₃, [M + Na]⁺ 243.0997, found: 243.0990.

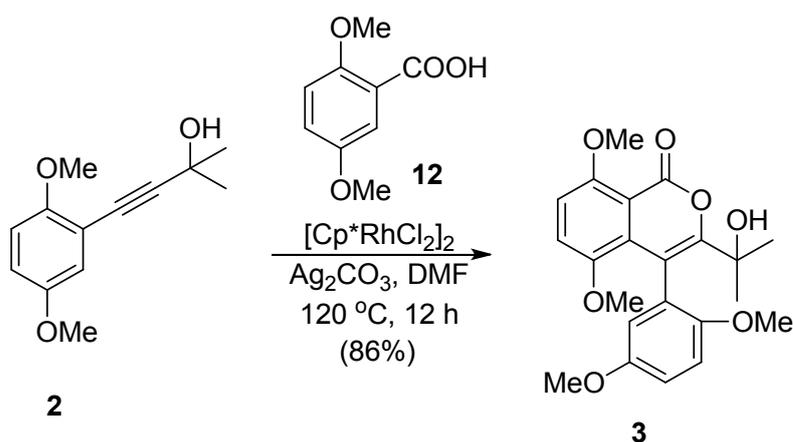
1,4-bis(2,5-dimethoxyphenyl)buta-1,3-diyne(**15**)



A mixture of **12** (36 mg, 0.2 mmol), **14** (52 mg, 0.22 mmol), [Cp*RhCl₂]₂ (1.24 mg, 0.002 mmol) Ag₂CO₃ (61 mg, 0.22 mmol) and DMF (2 mL) in a 25 mL of sealed tube was heated at 120 °C for 8 h under nitrogen atmosphere. The reaction was monitored for completion by TLC. Upon completion, the reaction mixture was cooled to room temperature and was partitioned between EtOAc (20 mL) and water (15 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic fractions were washed with brine (10 mL), dried

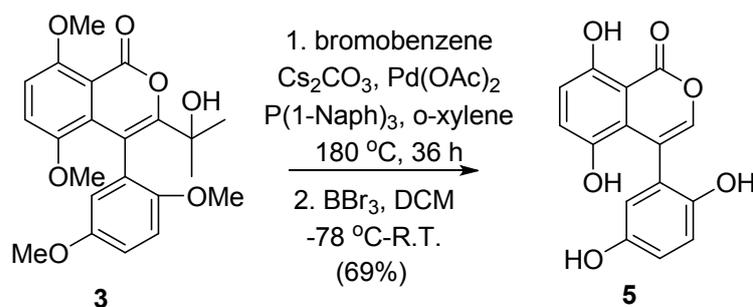
over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel (PE/EtOAc = 5/1) to yield the product **15** as a yellow oil (28 mg, 78 %). Spectroscopic data matched that previously reported.² ^1H NMR (400 MHz, CDCl_3) δ 7.04 (d, J = 3.1 Hz, 1H), 6.93 – 6.88 (m, 1H), 6.83 (d, J = 9.1 Hz, 1H), 3.88 (s, 3H), 3.79 (s, 3H).

4-(2,5-dimethoxyphenyl)-3-(2-hydroxypropan-2-yl)-5,8-dimethoxy-1H-isochromen-1-one (3).



A mixture of **12** (0.91 g, 5.0 mmol), **2** (1.32 g, 6.0 mmol), $[\text{Cp}^*\text{RhCl}_2]_2$ (31.0 mg, 0.05 mmol), Ag_2CO_3 (1.53 g, 5.5 mmol) and DMF (40 mL) in a 50 mL of sealed tube was heated at 120 °C for 12 h under nitrogen atmosphere. The reaction was monitored for completion by TLC. Upon completion, the reaction mixture was cooled to room temperature and was partitioned between EtOAc (2 × 100 mL), water (2 × 80 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic fractions were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel (PE/EtOAc = 2/1) to yield the product **3** as a yellow solid (1.76 g, 86 %), mp 114 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.10 (d, J = 9.1 Hz, 1H), 6.94 (d, J = 9.0 Hz, 1H), 6.84 (dd, J = 10.6, 5.7 Hz, 2H), 6.70 (d, J = 2.5 Hz, 1H), 3.99 (s, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 3.23 (s, 3H), 2.35 (s, 1H), 1.47 (s, 3H), 1.40 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 158.7, 158.1, 156.8, 156.0, 153.0, 152.5, 149.7, 130.9, 127.9, 121.0, 116.9, 112.8, 110.9, 110.5, 108.4, 73.7, 57.4, 56.8, 56.0, 55.8, 29.4. HRMS calcd for $\text{C}_{22}\text{H}_{24}\text{O}_7$, $[\text{M} + \text{Na}]^+$ 423.1420; Found: 423.1431.

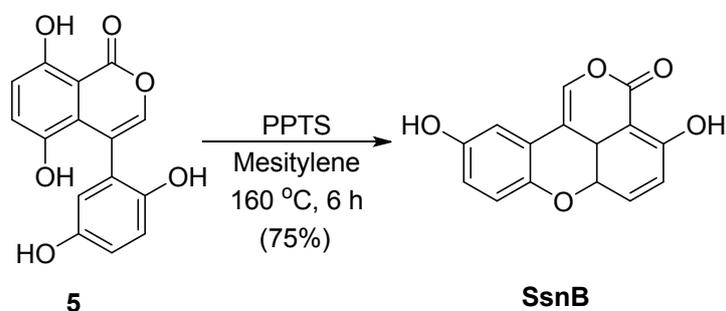
4-(2,5-dihydroxyphenyl)-5,8-dihydroxy-1H-isochromen-1-one (5).



A mixture of **3** (200 mg, 0.5 mmol), $\text{Pd}(\text{OAc})_2$ (11.2 mg, 0.05 mmol), Cs_2CO_3 (0.1 mmol,

32.6 mg), P(1-Naph)₃ (0.1 mmol, 41.3 mg), bromobenzene (0.1 mmol, 15.7 mg) and o-xylene (5 mL) in a 25 mL of sealed tube was heated at 180 °C for 36 h under nitrogen atmosphere. After completed, the reaction mixture was cooled to room temperature and was partitioned between EtOAc (2 × 50 mL) and water (2 × 20 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic fractions were washed with brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel (PE/EtOAc = 2/1) to yield the product directly used as the material of the next step. The product obtained (137 mg, 0.4 mmol) was dissolved in 5 mL of DCM in flask and cooled to -78 °C under argon atmosphere, BBr₃ (1.2 mL, 2.4 mmol, diluted with DCM, V_{BBr₃}/V_{DCM}=1/4) was dropwised slowly via a syringe. The reaction mixture was kept stirring for 3 h at -78 °C and then raised to room temperature until completed. The reaction mixture was quenched with water (40 mL) and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic fractions were washed with brine (30 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel (PE/EtOAc = 2/1) to yield the product as a yellow solid (0.10 g, 69% yield for two steps), mp 272 °C. ¹H NMR (400 MHz, DMSO) δ 10.89 (s, 1H), 9.08 (s, 1H), 8.66 (s, 1H), 8.42 (s, 1H), 7.17 (s, 1H), 7.08 (d, *J* = 8.9 Hz, 1H), 6.91 (d, *J* = 8.9 Hz, 1H), 6.68 – 6.48 (m, 3H). ¹³C NMR (101 MHz, DMSO) δ 166.6, 154.1, 149.4, 149.0, 146.3, 141.5, 125.5, 124.4, 123.0, 117.6, 117.4, 116.2, 115.3, 115.2, 106.5. HRMS calcd for C₁₅H₁₀O₆, [M + Na]⁺ 309.0375; Found: 309.0374.

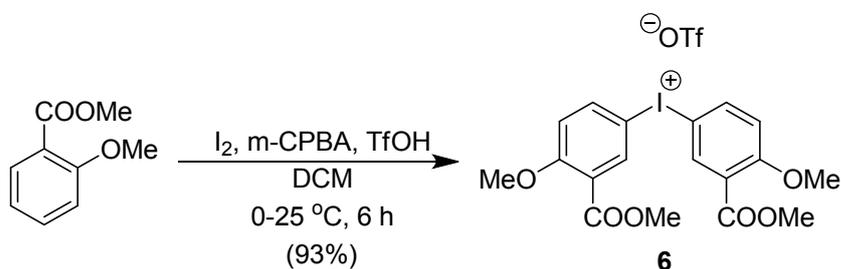
4,10-dihydroxy-3a1,6a-dihydro-3H-pyrano[3,4,5-kl]xanthen-3-one (SsnB).



The isocoumarin **5** (57.3 mg, 0.2 mmol) and Pyridinium toluene-4-sulphonate (50.0 mg, 2.0 mmol) were dissolved in 10 mL of mesitylene in flask under oxygen atmosphere, kept the reaction mixture stirring for 2.5 h at 160 °C. After completed, the mixture was cooled to room temperature, quenched with 1 N hydrochloric acid (10 mL) and diluted with DCM (150 mL). The organic layer was washed with brine (2 × 50 mL), water (30 mL), and dried over Mg₂SO₄. After evaporation of the solvent under vacuum, the crude residue was purified by flash chromatography over silica gel (PE/EtOAc = 2/1) to yield the product as a yellow solid, (40.6 mg, 75%). ¹H NMR (400 MHz, DMSO) δ 10.36 (s, 1H), 9.53 (s, 1H), 7.97 (s, 1H), 7.47 (d, *J* = 9.0 Hz, 1H), 7.09 (d, *J* = 2.7 Hz, 1H), 7.06 (d, *J* = 9.0 Hz, 1H), 7.02 (d, *J* = 8.9 Hz, 1H), 6.82 (dd, *J* = 8.9, 2.7 Hz, 1H). ¹³C NMR (101 MHz, DMSO) δ 164.3, 155.4, 154.2, 143.1, 140.9, 135.3, 123.9, 120.2, 118.6, 118.5, 117.6, 115.0, 109.9, 108.0, 105.0.

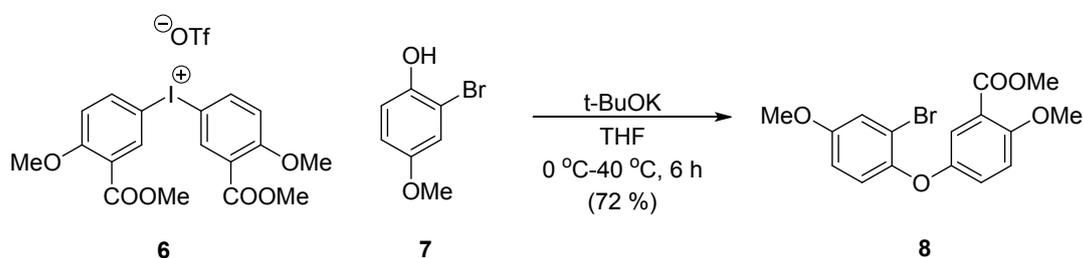
Experimental procedures the strategy 2

Bis(4-methoxy-3-(methoxycarbonyl)phenyl)iodonium trifluoromethanesulfonate salt (6).



The similar procedure of Berit Olofsson's work³ was followed. Iodine (2.54 g, 10.0 mmol) was added into 100 mL of DCM in one portion, stirred at room temperature until the iodine was dissolved, m-CPBA (6.36 g, 30.0 mmol) was added and the purple solution was stirred for 10 minutes. The reaction mixture was cooled to 0 °C and then methyl 2-methoxybenzoate (3.32 g, 20.0 mmol) was added in one portion, kept stirring for an additional 10 minutes. Trifluoromethanesulfonic acid (TfOH, 3.52 mL, 40.0 mmol) was slowly added via a funnel. The reaction mixture was kept stirring for 3 h and then raised to room temperature slowly, stirring for additional 3 h at room temperature before the reaction completed. Transferred the reaction mixture to a separatory funnel, diluted with DCM (300 mL), washed with H₂O (2 × 100 mL). The organic layers were concentrated in vacuo and the crude product was obtained. Diethyl ether (100 mL) was added to the crude product, stirred at 0 °C for 20 minutes causing precipitation of the product. The solid was collected by suction filtration and washed with diethyl ether (3 × 80 mL) obtained pure product **6** as white solid (12.6 g, 92%), mp 96 °C. ¹H NMR (400 MHz, DMSO) δ 8.53 (d, *J* = 2.0 Hz, 2H), 8.42 (dd, *J* = 9.0, 1.9 Hz, 2H), 7.32 (d, *J* = 9.1 Hz, 2H), 3.88 (s, 6H), 3.83 (s, 6H). ¹³C NMR (101 MHz, DMSO) δ 165.0, 160.9, 140.8, 137.9, 123.1, 116.5, 106.0, 57.0, 53.0 (s).

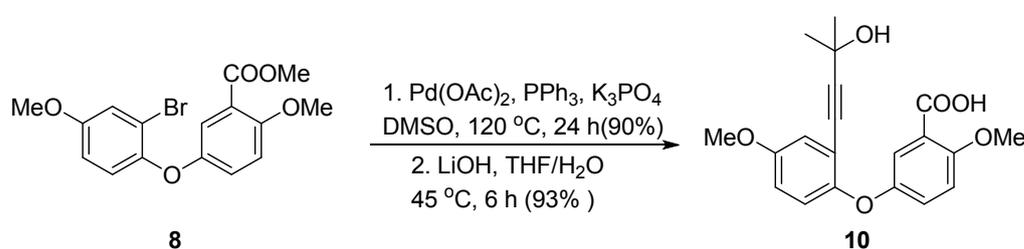
Methyl-5-(2-bromo-4-methoxyphenoxy)-2-methoxybenzoate (8).



The similar procedure of Berit Olofsson's work⁴ was followed. The 2-bromo-4-methoxyphenol **7** (1.00 g, 5.0 mmol) was added to a suspension of t-BuOK (0.67 g, 6.0 mmol) in THF (40 mL) at 0 °C and the reaction mixture was stirred for 15 minutes. Diaryliodonium salt **6** (3.64 g, 6.0 mmol) was added in one portion and the reaction

was stirred at 40 °C until TLC indicated complete consumption of phenol. The solvent of THF was removed in vacuo, and the residue mixture was diluted with EtOAc (200 mL), washed with H₂O (2 × 80 mL). The aqueous layer was extracted with EtOAc (100 mL). Combined the organic phases, dried over Na₂SO₄ and concentrated in vacuo. The crude material was purified by flash chromatography over silica gel (PE/EtOAc = 5/1) to yield the product as a yellow solid (1.0 g, 72%), mp 72 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.38 (d, *J* = 3.1 Hz, 1H), 7.18 (d, *J* = 2.9 Hz, 1H), 7.07 (dd, *J* = 9.0, 3.1 Hz, 1H), 6.94 (dd, *J* = 9.0, 6.2 Hz, 2H), 6.84 (dd, *J* = 8.9, 2.9 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.82 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 166.1, 156.4, 154.9, 150.7, 147.2, 122.4, 121.6, 120.8, 120.3, 118.6, 115.4, 114.6, 113.5, 56.6, 55.9, 52.2. HRMS calcd for C₁₆ H₁₅BrO₅, [M + Na]⁺ 389.0001; Found: 388.9990.

5-(2-(3-hydroxy-3-methylbut-1-yn-1-yl)-4-methoxyphenoxy)-2-methoxybenzoic acid (10).

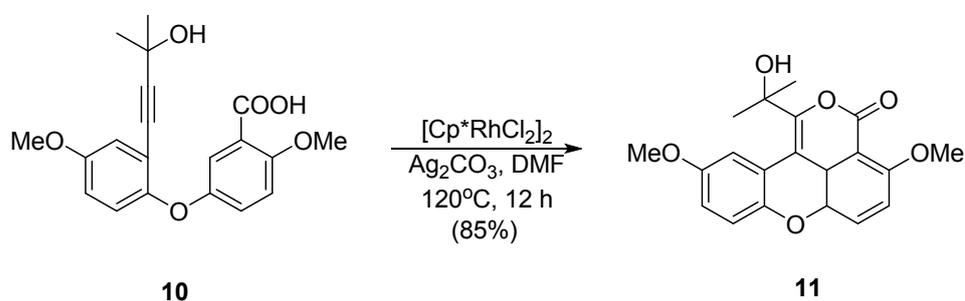


A mixture of **8** (0.92 g, 2.5 mmol), Pd(OAc)₂ (5.6 mg, 0.025 mmol), PPh₃ (13.1mg, 0.05 mmol), K₃PO₄ (1.59 g, 7.5 mmol), 3-Methyl butynol (0.61 mL, 6.3 mmol) and DMSO (30 mL) in a 50 mL of sealed tube was heated at 120 °C for 24 h under nitrogen atmosphere. The reaction was monitored for completion by TLC. Upon completion, the reaction mixture was cooled to room temperature and the reaction mixture was partitioned between DCM (2 × 150 mL) and water (2 × 100 mL). The organic layer was separated, and the aqueous layer was extracted with DCM (100 mL). The combined organic fractions were washed with brine (100 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel (PE/EtOAc = 2/1) to yield the product directly used for the next step.

The product obtained (0.74 g, 2 mmol) was dissolved in THF (30 mL), and aqueous LiOH (0.24 g, 10 mmol, dissolved in 15 mL of H₂O) was added in one portion. The reaction mixture was kept stirring at 45 °C for 6 h until completed. THF was removed under reduced pressure. The residue mixture was diluted with H₂O (100 mL), neutralized with 3 N HCl until PH < 3. The aqueous layer was extracted with DCM (3 × 100 mL). The combined organic fractions were washed with brine (100 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Flash chromatography of the residue on silica gel column (PE/EtOAc = 1/1) afforded the target product **10** as yellow oil (0.75 g, 84% yield for two steps). ¹H NMR (400 MHz, CDCl₃) δ 7.68 (d, *J* = 3.0 Hz, 1H), 7.19 (dd, *J* = 9.0, 3.1 Hz, 1H), 7.02 (d, *J* = 9.0 Hz, 1H), 6.97 (dd, *J* = 5.9, 2.8 Hz, 2H), 6.88 (dd, *J* = 9.0, 2.8 Hz, 1H), 4.06 (s, 3H), 3.82 (s, 3H), 1.43 (s, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 165.0, 156.1, 153.3, 153.2, 149.9, 77.6, 65.5,

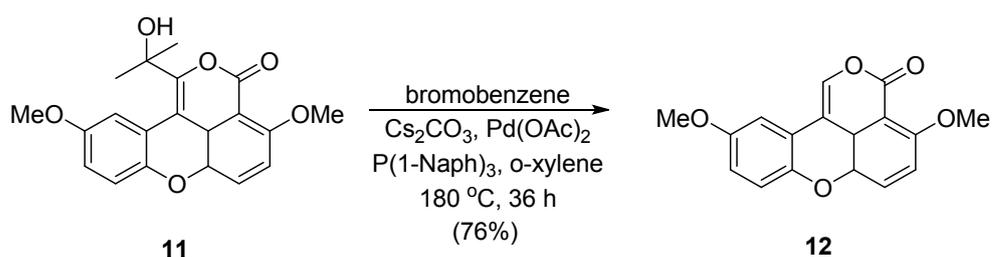
57.3, 55.8, 31.1. HRMS calcd for C₂₀H₂₀O₆ [M + Na]⁺ 379.1158; Found: 379.1195.

1-(2-hydroxypropan-2-yl)-4,10-dimethoxy-3a1,6a-dihydro-3H-pyrano[3,4,5-kl]xanthen-3-one(11).



A mixture of **10** (0.71 g, 2.0 mmol), [Cp*RhCl₂]₂ (12.4 mg, 0.02 mmol), Ag₂CO₃ (0.61 g, 2.2 mmol) and DMF (20 mL) in a 25 mL of sealed tube was heated at 120 °C for 12 h under nitrogen atmosphere. The reaction was monitored for completion by TLC. Upon completion, the reaction mixture was cooled to room temperature and the reaction mixture was partitioned between DCM (2 × 100 mL) and water (2 × 100 mL). The organic layer was separated, and the aqueous layer was extracted with DCM (100 mL). The combined organic fractions were washed with brine (100 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel (PE/EtOAc = 2/1) to yield the product **11** as a yellow solid (0.6 g, 85%), mp 108 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.78 (d, *J* = 2.6 Hz, 1H), 7.29 (s, 1H), 6.94 (dd, *J* = 13.3, 9.0 Hz, 2H), 6.86 (dd, *J* = 8.9, 2.7 Hz, 1H), 3.96 (s, 4H), 3.85 (s, 3H), 1.76 (s, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 157.5, 155.7, 154.6, 153.5, 146.1, 142.8, 126.5, 121.2, 117.0, 116.9, 116.4, 115.4, 111.1, 108.2, 106.2, 73.7, 56.6, 55.9, 29.4. HRMS calcd for C₂₀ H₁₈O₆ [M + Na]⁺ 377.1001; Found: 377.0985.

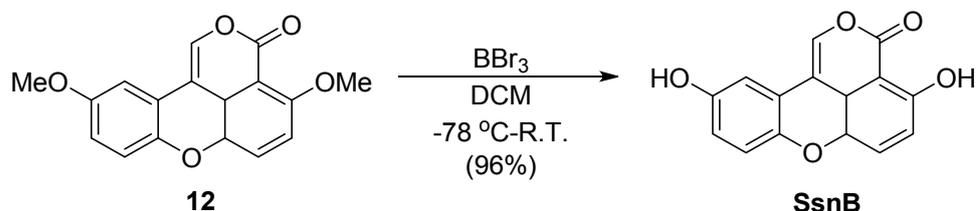
4,10-dimethoxy-3a1,6a-dihydro-3H-pyrano[3,4,5-kl]xanthen-3-one(12).



A mixture of **11** (178.0 mg, 0.5 mmol), Pd(OAc)₂ (11.2 mg, 0.05 mmol), Cs₂CO₃ (0.1 mmol, 32.6 mg), P(1-Naph)₃ (0.1 mmol, 41.3 mg), bromobenzene (0.1 mmol, 15.7 mg) and o-xylene (10 mL) in a 25 mL of sealed tube was heated at 180 °C for 36 h under nitrogen atmosphere. The reaction was monitored for completion by TLC. Upon completion, the reaction mixture was cooled to room temperature and the reaction mixture was partitioned between DCM (2 × 50 mL) and water (2 × 50 mL). The organic layer was separated, and the aqueous layer was extracted with DCM (2 × 50 mL). The combined organic fractions were washed with brine (50 mL), dried over anhydrous Mg₂SO₄ and concentrated under reduced pressure. The crude residue

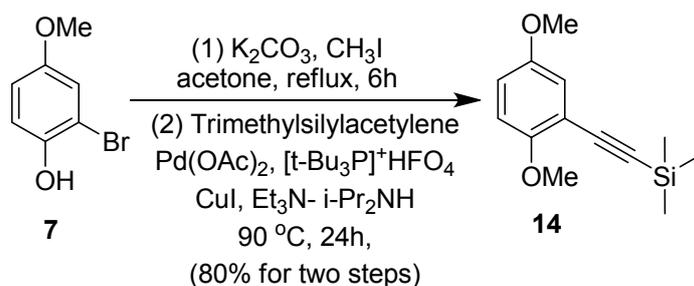
was purified by flash chromatography over silica gel (PE/EtOAc = 2/1) to yield the product **12** as a yellow solid (113 mg, 76%), mp 185°C. ¹³C NMR (101 MHz, CDCl₃) δ 158.1, 156.3, 155.8, 144.1, 142.1, 134.6, 122.9, 121.7, 118.3, 116.6, 115.0, 112.3, 108.7, 108.4, 105.0, 77.3, 77.0, 76.7, 56.6, 55.8, 29.7. HRMS calcd for C₁₄H₁₄O₅ [M + Na]⁺ 321.0739; Found: 321.1131.

4,10-dihydroxy-3a1,6a-dihydro-3H-pyrano[3,4,5-kl]xanthen-3-one (SsnB).



The start material of **12** (119 mg, 0.4 mmol) was dissolved in 3 mL of DCM in flask and cooled to -78°C under argon atmosphere. BBr₃ (0.58 mL, 1.2 mmol, diluted with DCM, V_{BBr₃}/V_{DCM} = 1/4) was dropwised slowly via a syringe, and then raised to room temperature until TLC indicated complete consumption of **12**. The reaction mixture was quenched with H₂O (50 mL), extracted with DCM (2 × 60 mL) and then dried over Mg₂SO₄. After evaporation of the solvent under vacuum, the crude residue was purified by flash chromatography over silica gel (PE/EtOAc = 2/1) to yield the product of SsnB as a yellow solid (103 mg, 96%yield). ¹H NMR (400 MHz, DMSO) δ 10.36 (s, 1H), 9.53 (s, 1H), 7.97 (s, 1H), 7.47 (d, *J* = 9.0 Hz, 1H), 7.09 (d, *J* = 2.7 Hz, 1H), 7.06 (d, *J* = 9.0 Hz, 1H), 7.02 (d, *J* = 8.9 Hz, 1H), 6.82 (dd, *J* = 8.9, 2.7 Hz, 1H). ¹³C NMR (101 MHz, DMSO) δ 164.3, 155.4, 154.2, 143.1, 140.9, 135.3, 123.9, 120.2, 118.6, 118.5, 117.6, 115.0, 109.9, 108.0, 105.0.

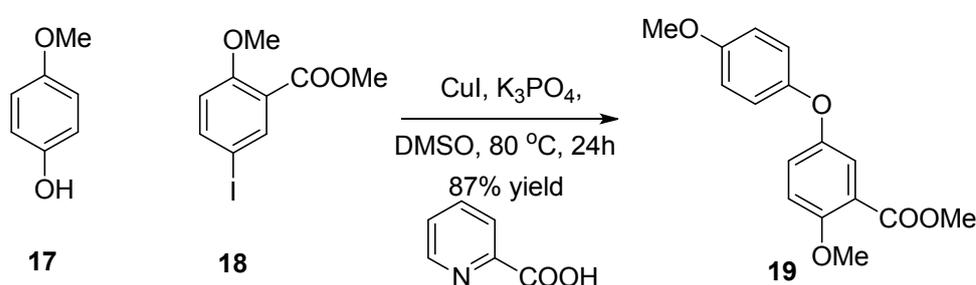
[(2,5-dimethoxyphenyl)ethynyl]trimethylsilane(14)



The 2-bromo-4-methoxyphenol **7** (0.42 g, 2.1 mmol) was dissolved in 30mL of acetone. K₂CO₃ (0.57 g, 4.2 mmol) was added in one portion. After stirring for 10 minutes at room temperature, CH₃I (0.38mL, 6.3mmol) was added. The reaction mixture was kept stirring for 6 h at 60 °C. After the TLC indicated complete consumption of phenol, K₂CO₃ was filtered. The residue was washed with 60 mL of EtOAc. After evaporated of the solvent under vacuum, the product obtained was directly used in the subsequent step without further purification. The product obtained (0.43 g, 2.0 mmol), Pd(OAc)₂ (28 mg, 0.10 mmol), [t-Bu₃P]⁺HFO₄⁻ (35 mg, 0.12 mmol), CuI (7.6 mg, 0.04 mmol), Trimethylsilylacetylene (0.57 mL, 4 mmol), Et₃N (15 mL) and i-Pr₂NH (15 mL) in a 50 mL of sealed tube was heated at 90 °C for

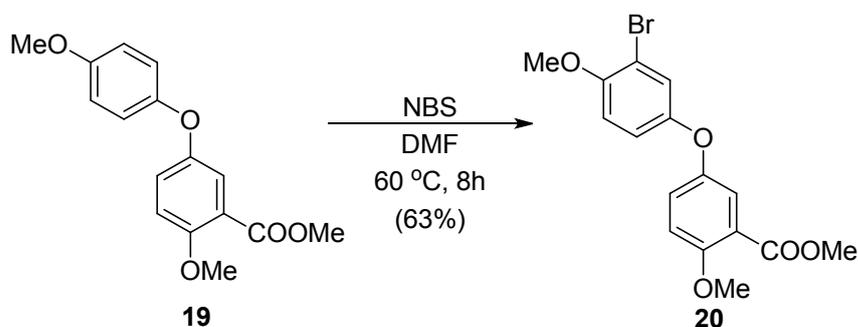
24 h under nitrogen atmosphere. After the reaction completed, the tube was cooled to room temperature and the solvent was removed under reduced pressure. The reaction mixture was partitioned between EtOAc (2 × 100 mL) and water (2 × 80 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic fractions were washed with 3% aqueous HCl (100 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel (PE/EtOAc = 10/1) to yield the product **14** as yellow solid (0.39 g, 80% yield for two steps). Spectroscopic data matched that previously reported.⁵ ¹H NMR (400 MHz, CDCl₃) δ 7.00 (d, *J* = 3.0 Hz, 1H), 6.89 – 6.83 (m, 1H), 6.80 (d, *J* = 9.0 Hz, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 0.29 (s, 10H).

methyl 2-methoxy-5-(4-methoxyphenoxy)benzoate(**19**)



A mixture of **17** (0.51 g, 4.1 mmol), **18** (1.1 g, 3.8 mmol), CuI (36 mg, 0.19 mmol), K₃PO₄ (1.6 g, 7.5 mmol), picolinic acid (46 mg, 0.38 mmol) and DMSO (30 mL) in a 50 mL of sealed tube was heated at 80 °C for 24 h under nitrogen atmosphere. After completed, the reaction mixture was cooled to room temperature and the reaction mixture was partitioned between EtOAc (2 × 100 mL) and water (2 × 100 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (100 mL). The combined organic fractions were washed with brine (100 mL), dried over anhydrous Mg₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel (PE/EtOAc = 5/1) to yield the product **19** as yellow oil (0.95 g, 87% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.43 (d, *J* = 3.0 Hz, 1H), 7.12 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.95 (d, *J* = 9.6 Hz, 3H), 6.89 (d, *J* = 9.1 Hz, 2H), 3.91 (s, 4H), 3.88 (s, 3H), 3.82 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 166.1, 155.7, 154.9, 151.0, 150.9, 123.4, 121.3, 120.8, 119.8, 114.9, 113.5, 56.6, 55.7, 52.2.

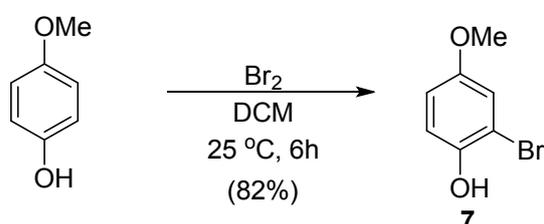
methyl 5-(3-bromo-4-methoxyphenoxy)-2-methoxybenzoate(**20**)



To a solution of diaryl ether **19** (57.6 mg, 0.2 mmol) in DMF (1 mL) was added

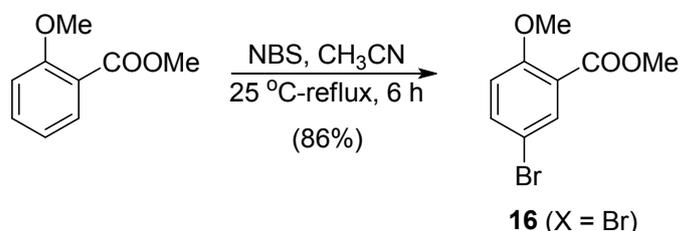
dropwise a solution of N-Bromosuccinimide (39.2 mg, 0.24 mmol dissolved in an additional 1.0 mL of DMF) at room temperature, the resulting bright yellow solution was stirred for 30 minutes, and then raised to 60 °C, stirring for 8h. Upon completion, the reaction mixture was quenched with H₂O (15 mL), extracted with EtOAc (2 × 10 mL). The combined organic fractions were dried over anhydrous Mg₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel (PE/EtOAc = 10/1) to yield the product as yellow oil (46 mg, 63% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.44 (d, *J* = 3.1 Hz, 1H), 7.21 (d, *J* = 2.8 Hz, 1H), 7.13 (dd, *J* = 9.0, 3.1 Hz, 1H), 6.97 (d, *J* = 9.0 Hz, 1H), 6.93 (dd, *J* = 8.9, 2.8 Hz, 1H), 6.87 (d, *J* = 8.9 Hz, 1H), 3.91 (s, 3H), 3.89 (d, *J* = 1.9 Hz, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 166.0, 155.3, 152.1, 151.5, 150.2, 123.9, 123.7, 121.8, 121.0 (s), 118.3, 113.6, 112.6, 112.0, 56.7, 56.6, 52.2.

2-bromo-4-methoxyphenol (**7**)



To a stirred solution of 4-methoxyphenol (3.0 g, 24.2 mmol) in DCM (100 mL) was slowly added a solution of bromine (1.37 mL, 26.6 mmol, dissolved in 20 mL of DCM) at room temperature. After completed, stirring at room temperature until TLC indicated complete consumption of phenol. The reaction mixture was treated with saturated aqueous Na₂SO₃ solution until the violet color disappeared. The mixture was partitioned between DCM (2 × 150 mL) and water (2 × 100 mL). The organic phase was separated, washed with brine (80 mL) and then dried over Mg₂SO₄. The organic layer was concentrated in vacuo and the crude residue was purified by flash chromatography over silica gel (PE/EtOAc = 5/1) to yield the product **7** as a brown solid, (4.0 g, 82%). Spectroscopic data matched that previously reported.⁶ ¹H NMR (400 MHz, CDCl₃) δ 7.04 (d, *J* = 2.9 Hz, 1H), 6.96 (d, *J* = 8.9 Hz, 1H), 6.82 (dd, *J* = 8.9, 2.9 Hz, 1H), 5.24 (s, 1H), 3.77 (s, 3H).

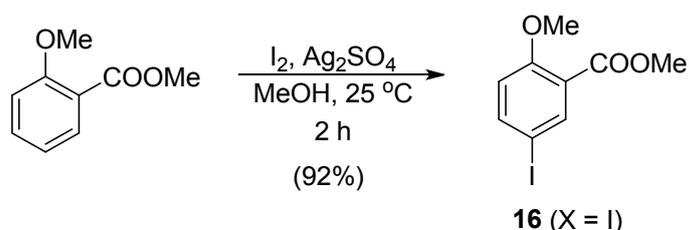
methyl 5-bromo-2-methoxybenzoate



To a stirred solution of methyl 2-methoxybenzoate (0.83 g, 5.0 mmol) in CH₃CN (20 mL) was slowly added a solution of N-Bromosuccinimide (0.98 g, 5.5 mmol, dissolved in additional 20 mL of CH₃CN) at room temperature. The reaction mixture was raised to 60 °C and stirring until TLC indicating the complete consumption of methyl 2-methoxybenzoate. After evaporated of the solvent under vacuum, the residue

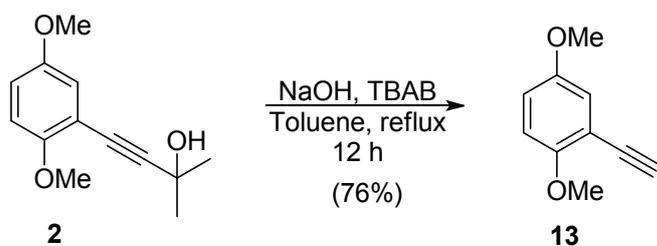
mixture was diluted with H₂O (120 mL), extracted with EtOAc (2 × 100 mL), the organic phase was combined, dried over Mg₂SO₄, evaporated under vacuum. The crude residue was purified by flash chromatography over silica gel (PE/EtOAc = 10/1) to yield the product as white solid, (1.05 g, 86%). Spectroscopic data matched that previously reported.⁷ ¹H NMR (400 MHz, CDCl₃) δ 7.92 (d, *J* = 2.6 Hz, 1H), 7.57 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.88 (d, *J* = 8.9 Hz, 1H), 3.91 (s, 6H).

methyl 5-iodo-2-methoxybenzoate



A suspension of methyl 2-methoxybenzoate (1.1 g, 7.0 mmol), iodine (2.03 g, 8.0 mmol) and Ag₂SO₄ (2.8 g, 9.0 mmol) in methanol was stirred at room temperature for 2 h and then the solid was filtrated off. The filtrate was treated with saturated aqueous Na₂SO₃ solution until the violet color disappeared and then concentrated under reduced pressure. The resulting residue was diluted with EtOAc (150 mL). The organic phase was washed with water (2 × 50 mL) and brine (30 mL), dried over Na₂SO₄. Upon removal of the solvent under reduced pressure, the crude residue was purified by flash chromatography over silica gel (PE/EtOAc = 10/1) to yield the product as a brown solid (1.78 g, 92%). Spectroscopic data matched that previously reported.⁸ ¹H NMR (400 MHz, CDCl₃) δ 7.92 (d, *J* = 2.6 Hz, 1H), 7.57 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.88 (d, *J* = 8.9 Hz, 1H), 3.91 (s, 6H).

2-ethynyl-1,4-dimethoxybenzene(13)



A suspension of **2** (1.0 g, 4.5 mmol), NaOH (0.55 g, 1.4 mmol) and TBAB (tetrabutyl ammonium bromide, 30 mg, 0.1 mmol) in 20 mL of toluene was stirred at 120 °C for 6 h. The reaction was monitored for completion by TLC. Upon completion the reaction mixture was cooled to room temperature and partitioned between EtOAc (2 × 80 mL) and water (2 × 50 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 80 mL). The combined organic fractions were washed with brine, dried over anhydrous Mg₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel (PE/EtOAc = 10/1) to yield the product **13** as white solid (0.56 g, 76%). Spectroscopic data matched that previously reported.⁹ ¹H NMR (400 MHz, CDCl₃) δ 7.03 (d, *J* = 3.0 Hz, 1H), 6.90 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.84 (d, *J* = 9.0 Hz, 1H), 3.89 (s, 3H), 3.79 (s, 3H),

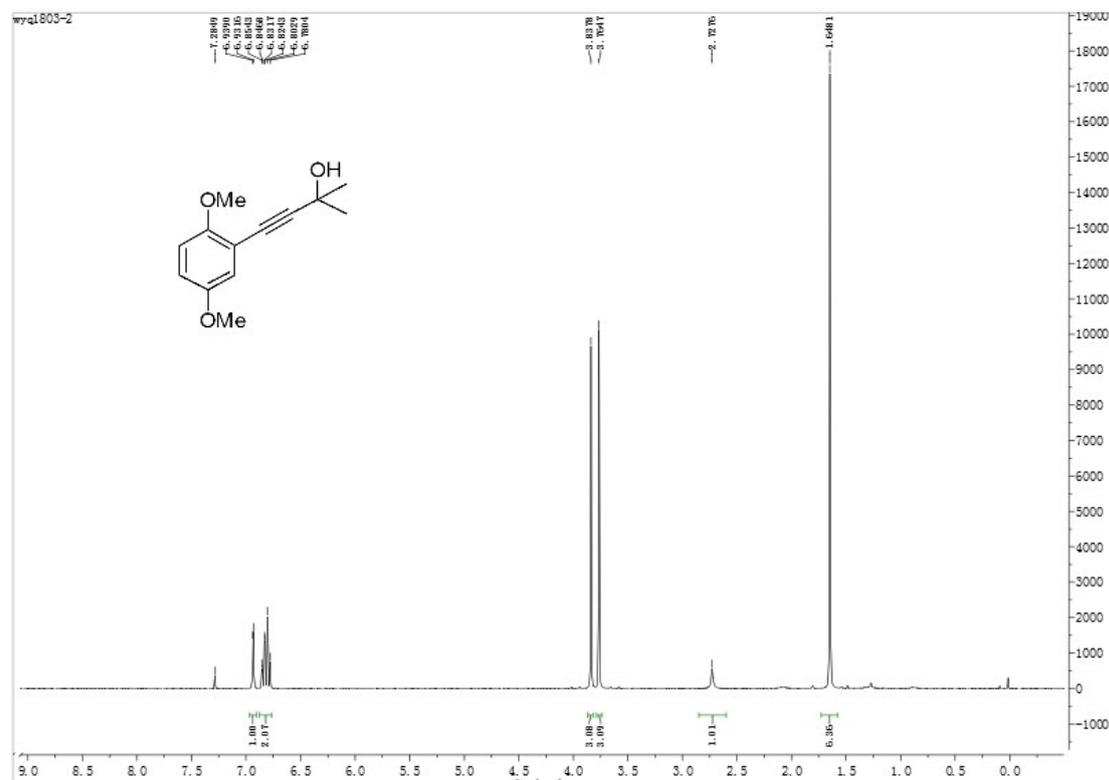
3.33 (s, 1H).

Reference

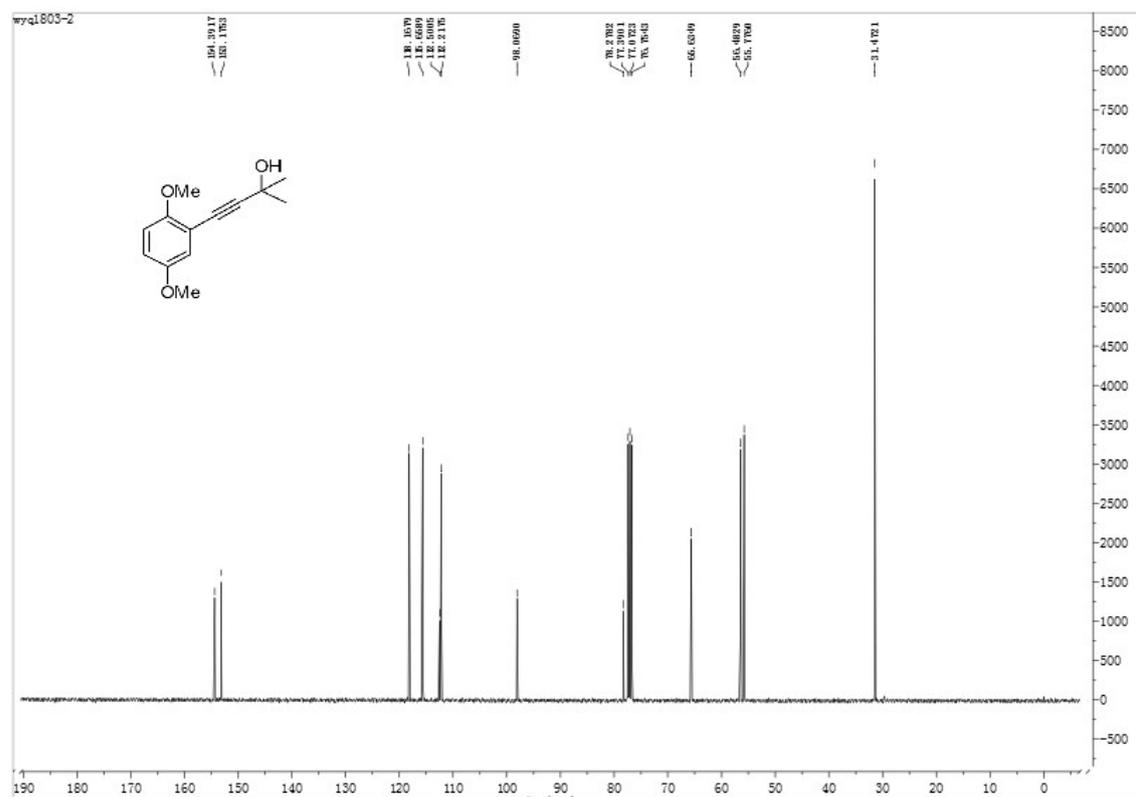
1. Manarin, F.; Roehrs, J. A.; Gay, R. M.; Brandao, R.; Menezes, P. H.; Nogueira, C. W.; Zeni, G., *J. Org. Chem.* **2009**, *74*, 2153-2162.
2. Esser, B.; Swager, T. M., *Angew. Chem.Int. Ed.* **2010**, *49*, 8872-8875.
3. Marcin, B.; Olofsson, B., *Org. Synth.* **2009**, *86*, 308.
4. Jalalian, N.; Petersen, T. B.; Olofsson, B., *Chem. Eur. J.* **2012**, *18*, 14140-14149.
5. Elicio, P. D.; Chao, M. N.; Galizzi, M.; Li, C.; Szajnman, S. H.; Docampo, R.; Moreno, S. N.; Rodriguez, J. B., *Eur. J. Med. Chem.* **2013**, *69*, 480-9.
6. Ting, C.-M.; Hsu, Y.-L.; Liu, R.-S., *Chem. Commun.* **2012**, *48*, 6577-6579.
7. Mo, F.; Yan, J. M.; Qiu, D.; Li, F.; Zhang, Y.; Wang, J., *Angew. Chem.Int. Ed.* **2010**, *49*, 2028-2032.
8. Wang, L.; Xiao, Z.-Y.; Hou, J.-L.; Wang, G.-T.; Jiang, X.-K.; Li, Z.-T., *Tetrahedron* **2009**, *65*, 10544-10551.
9. Flavia, M.; Juliano, A. R.; Rafaela, M.; ozzaquatro, G.; Ricardo, B.; Gilson, Z., *J. Org. Chem.* **2009**, *74*, 2153-2162.

NMR spectra.

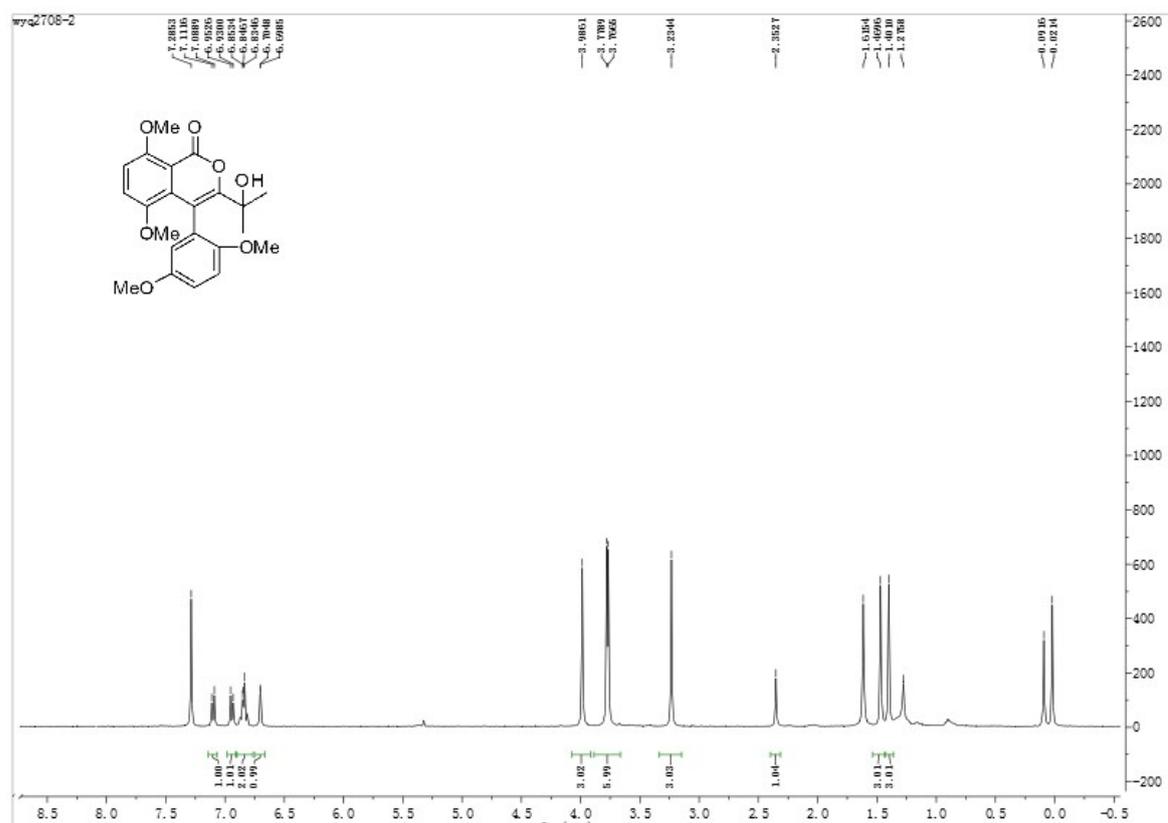
¹H NMR of 2



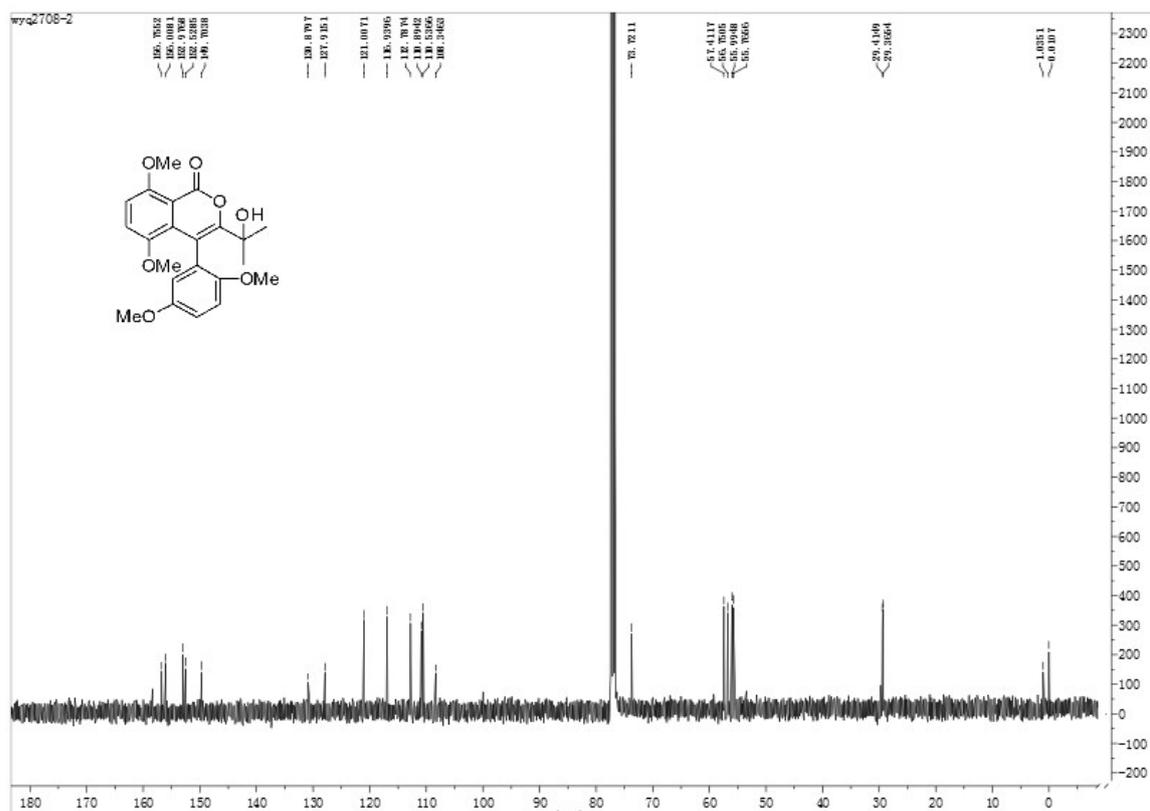
¹³C NMR of 2



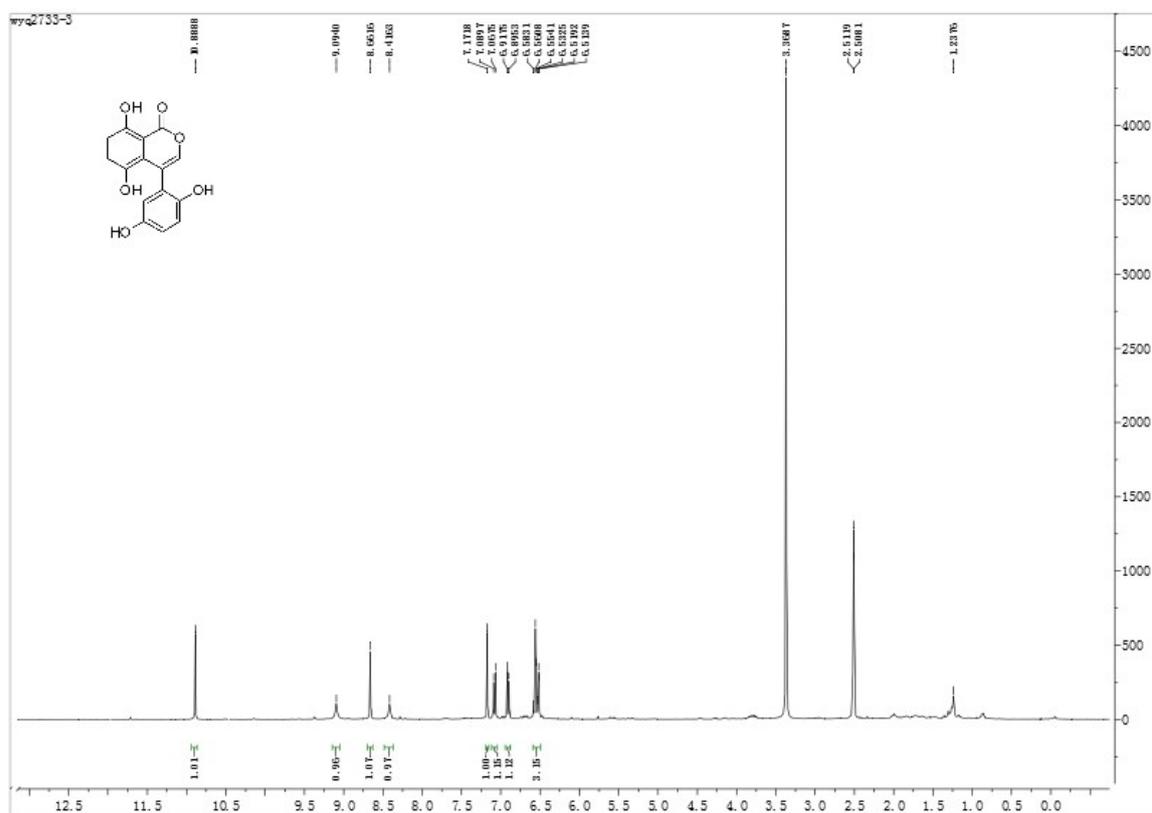
¹H NMR of 3



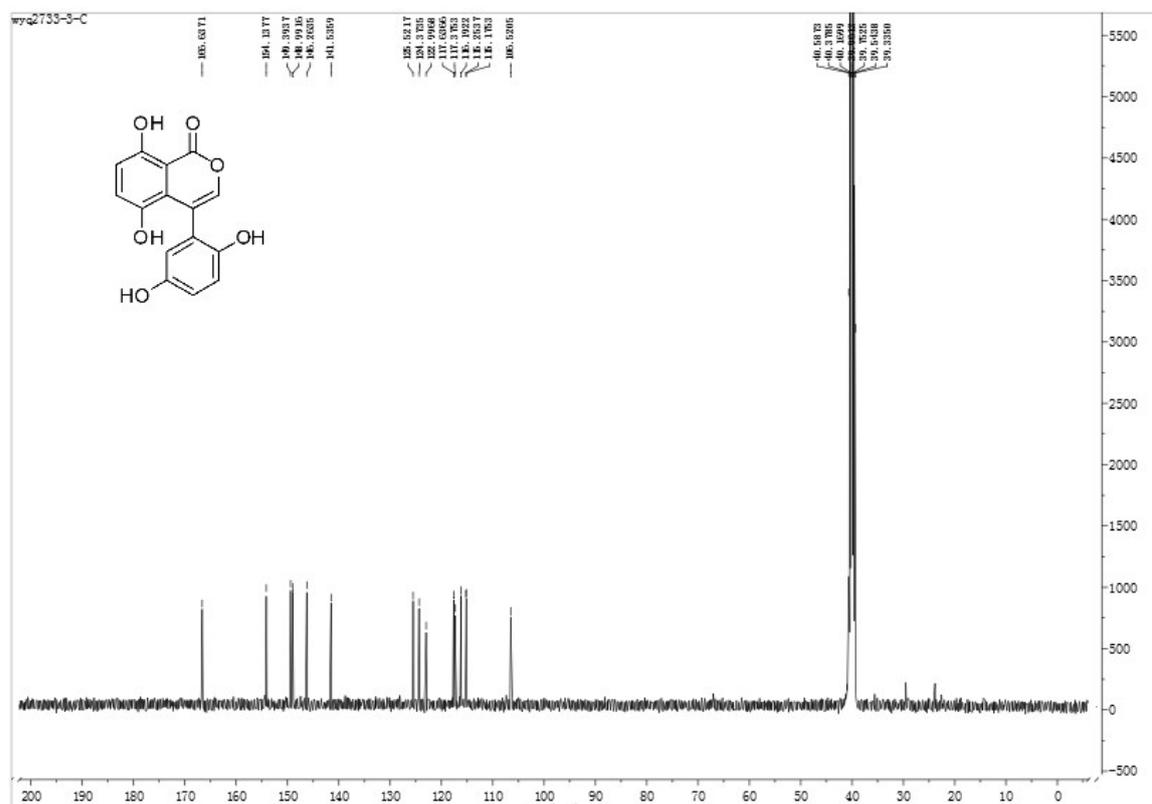
¹³C NMR of 3



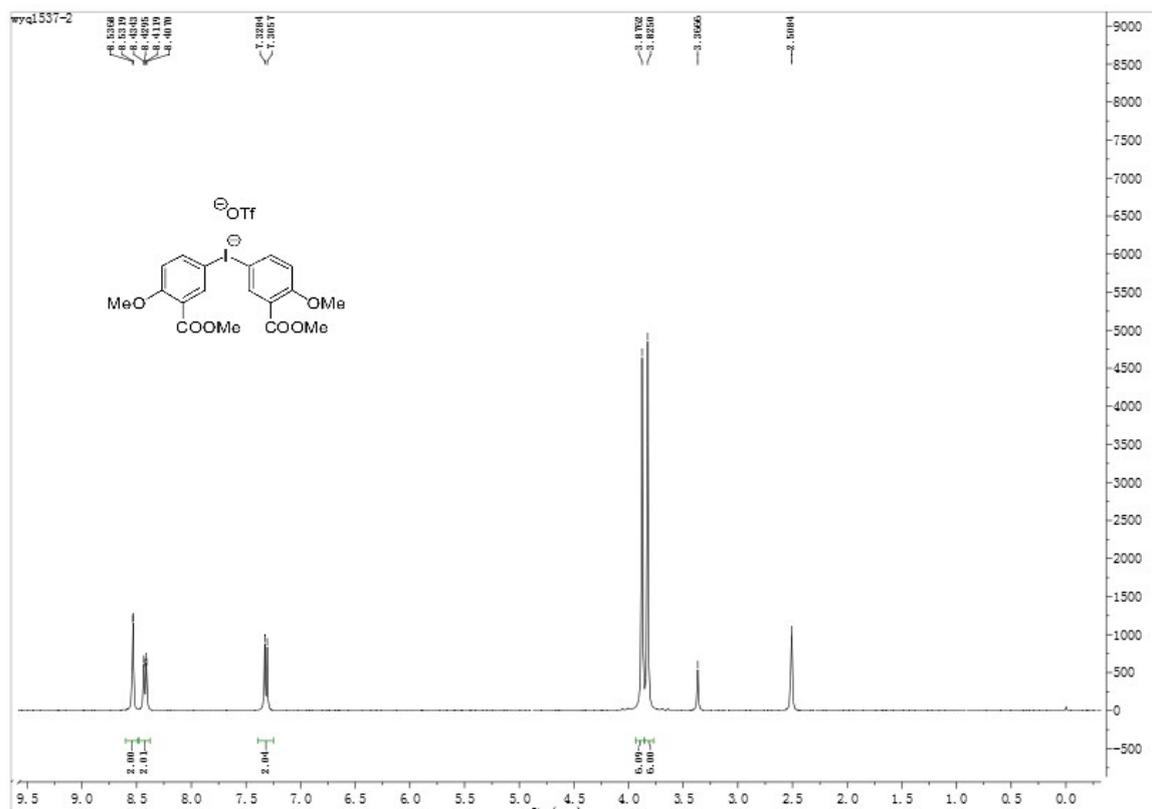
¹H NMR of 5



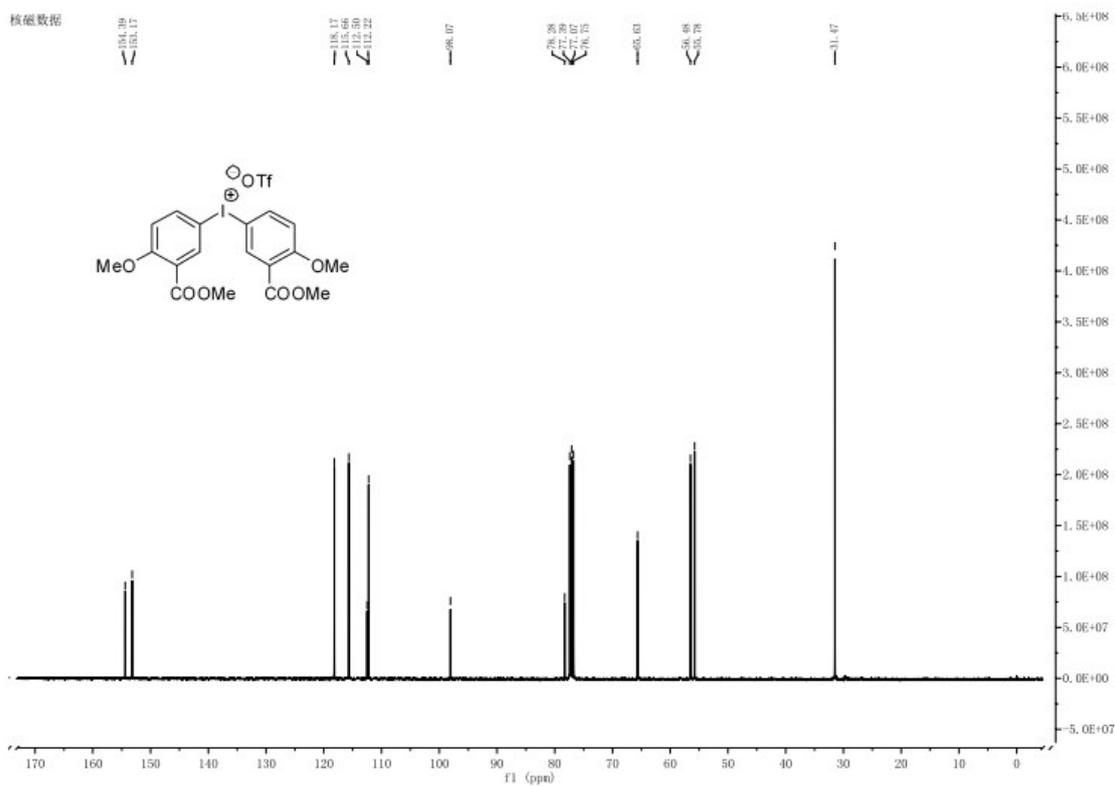
¹³C NMR of 5



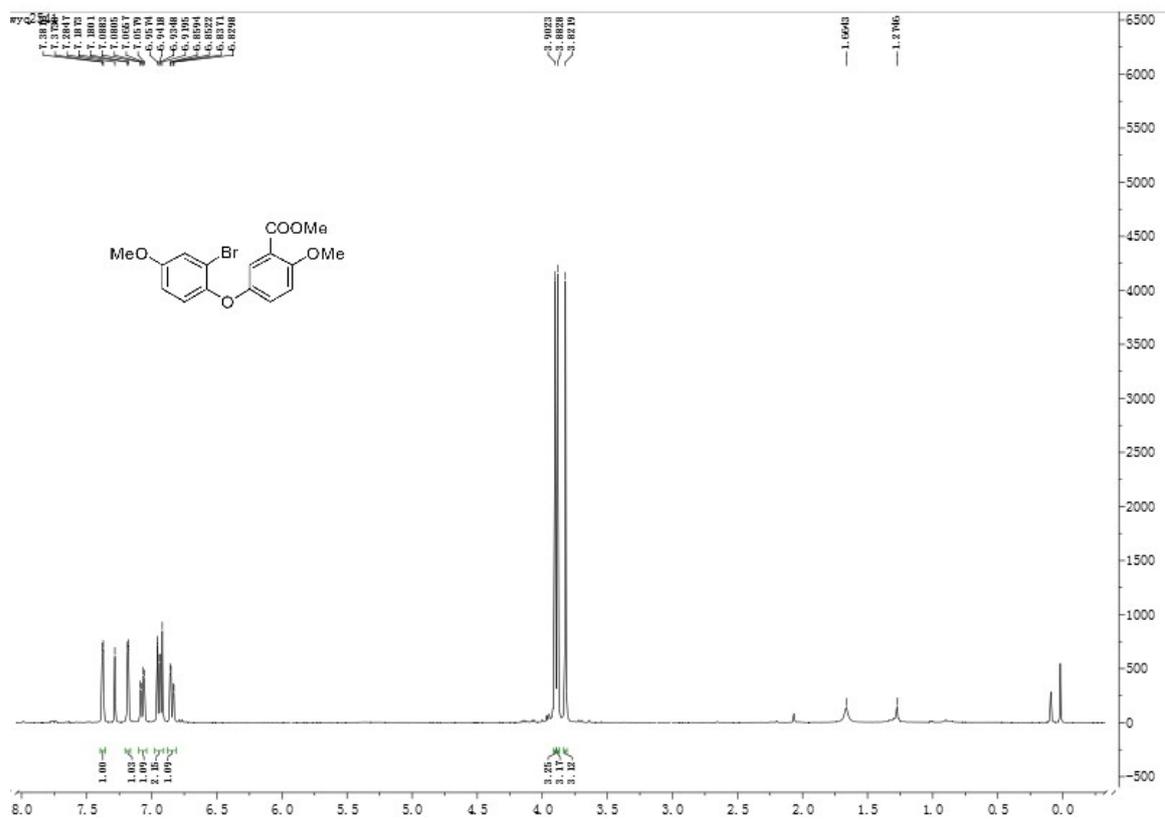
¹H NMR of 6



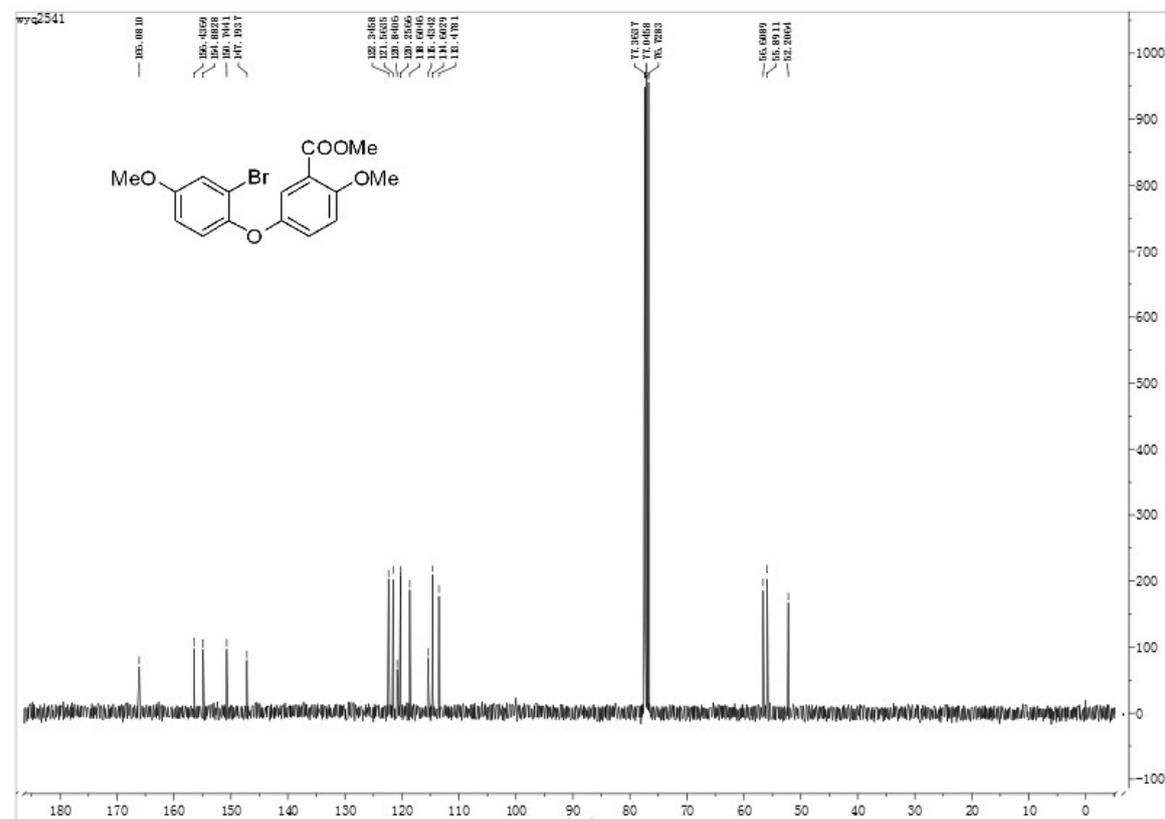
¹³C NMR of 6



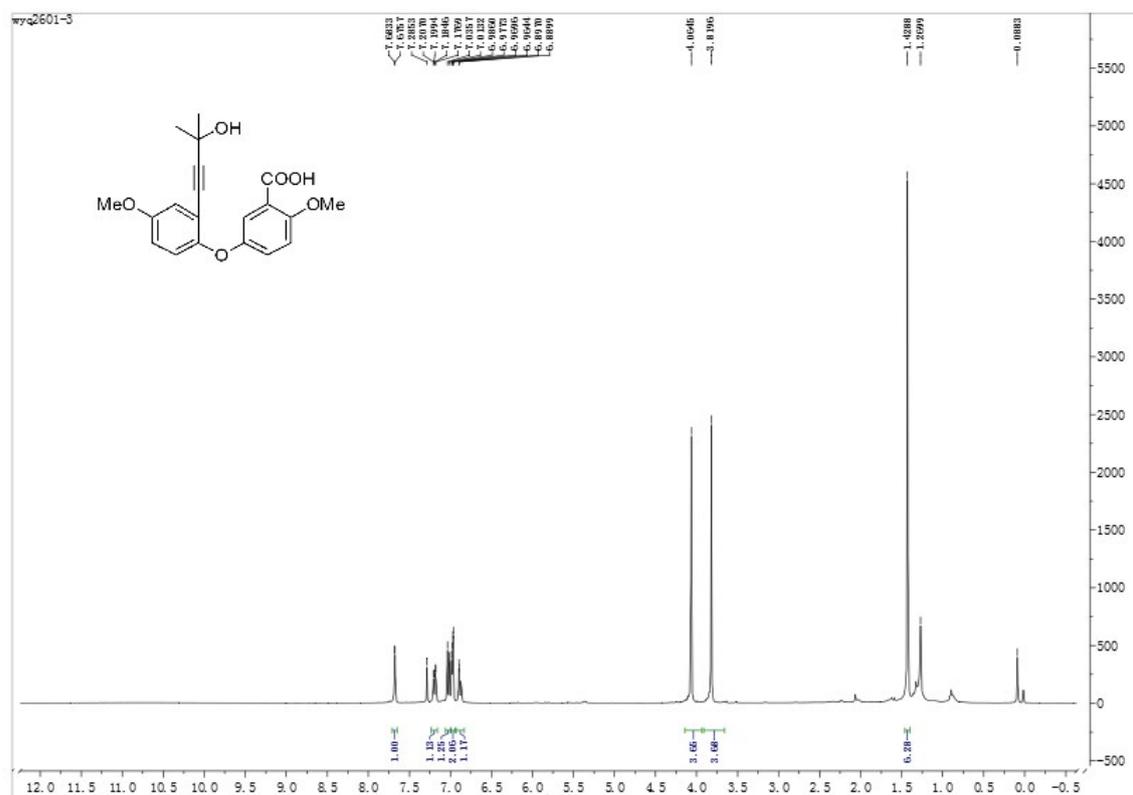
¹H NMR of 8



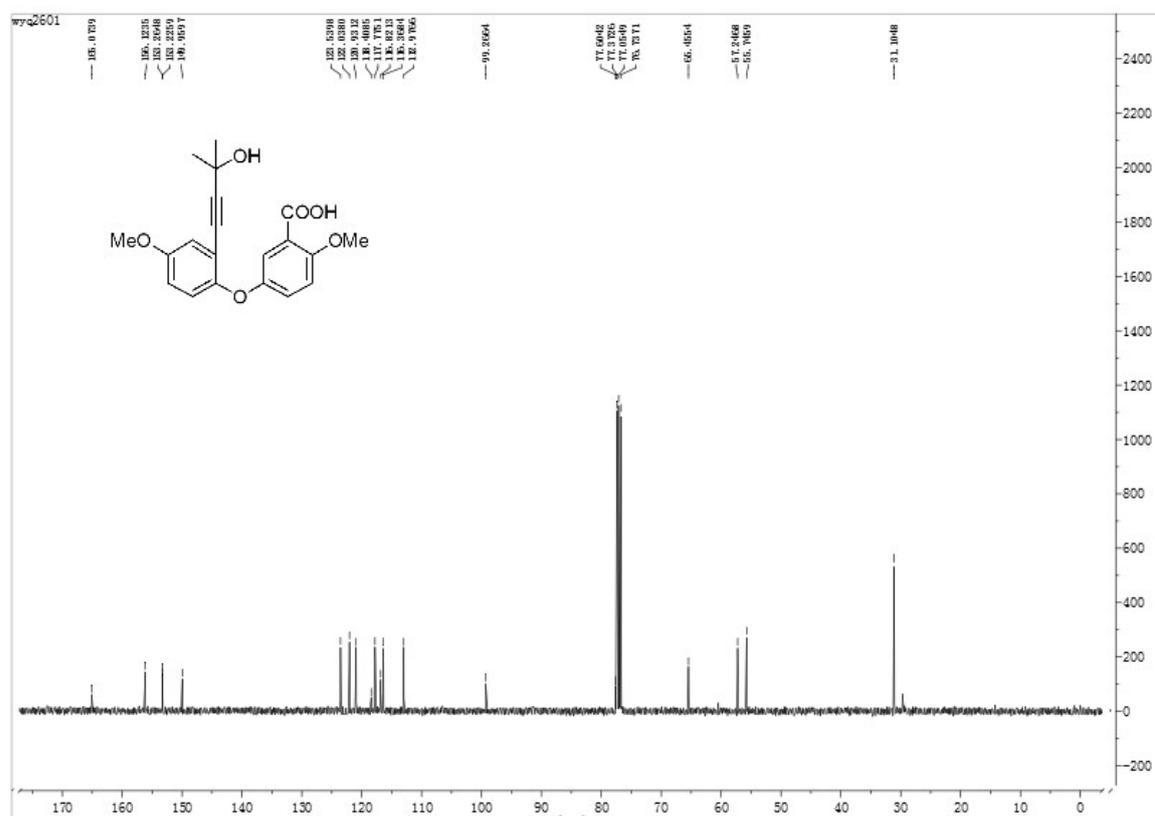
¹³C NMR of 8



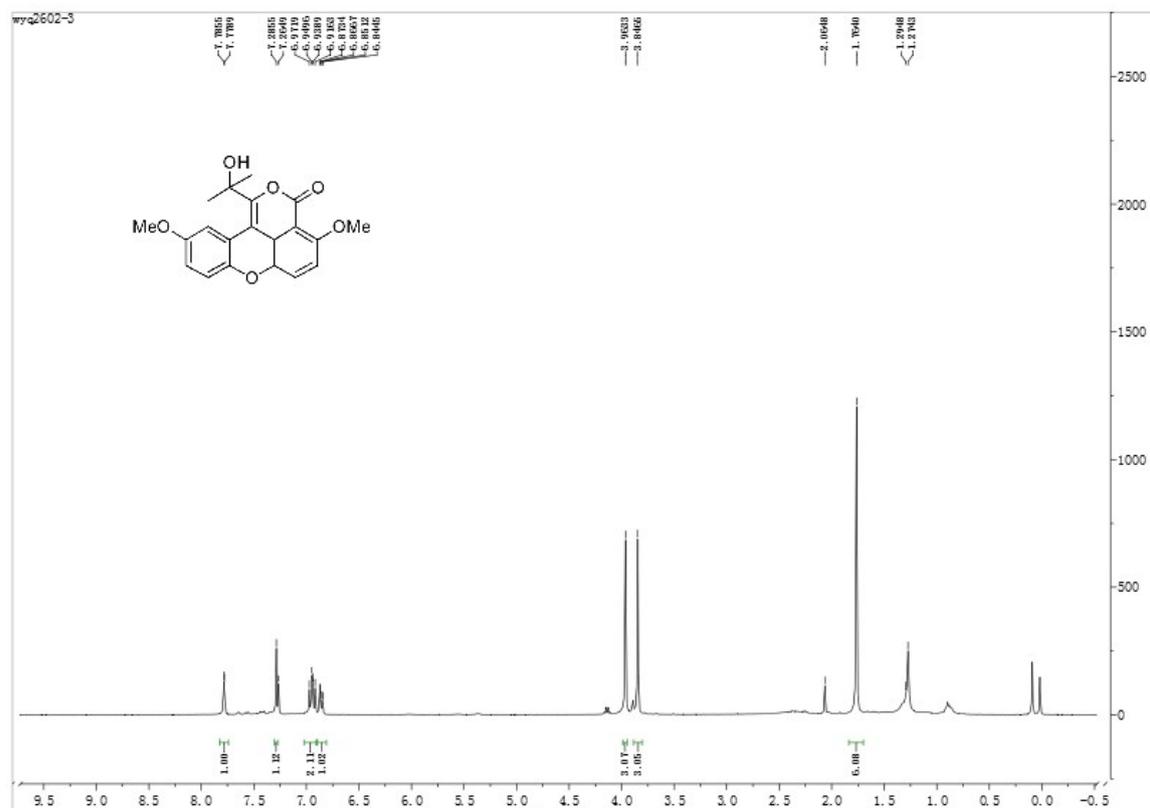
¹H NMR of 10



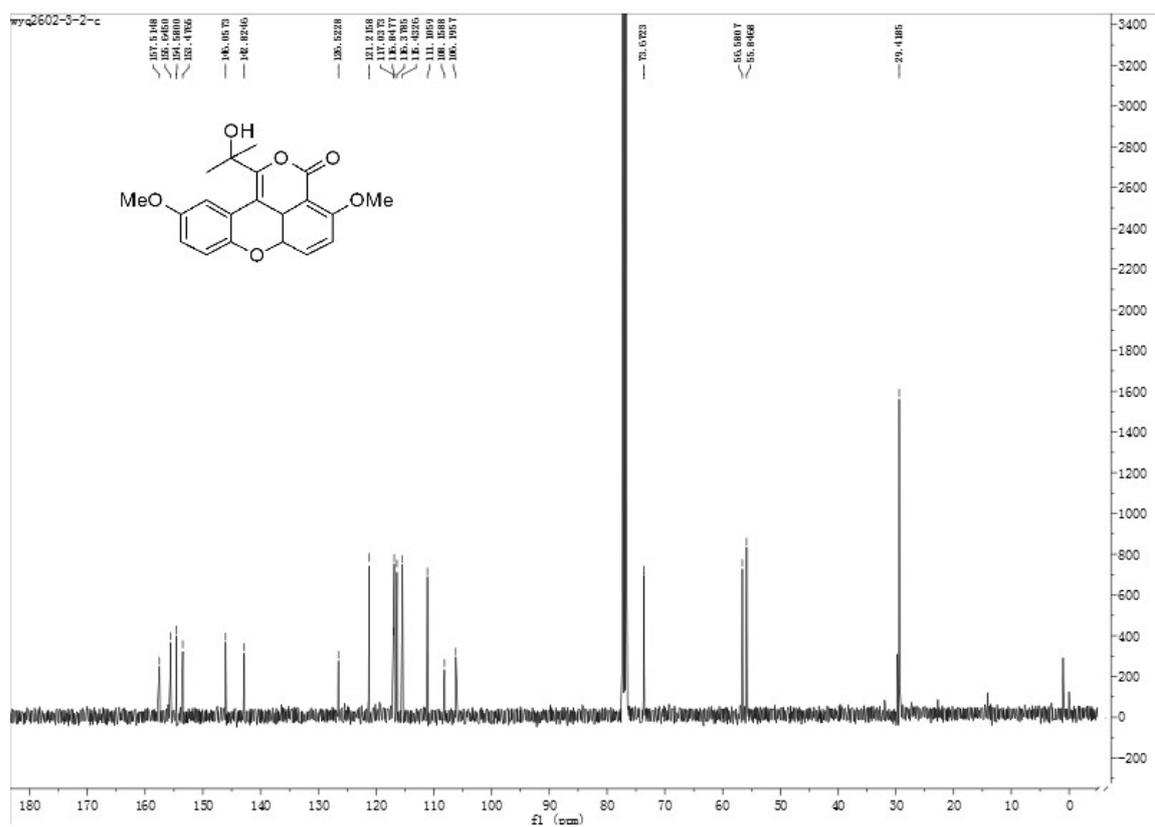
¹³C NMR of 10



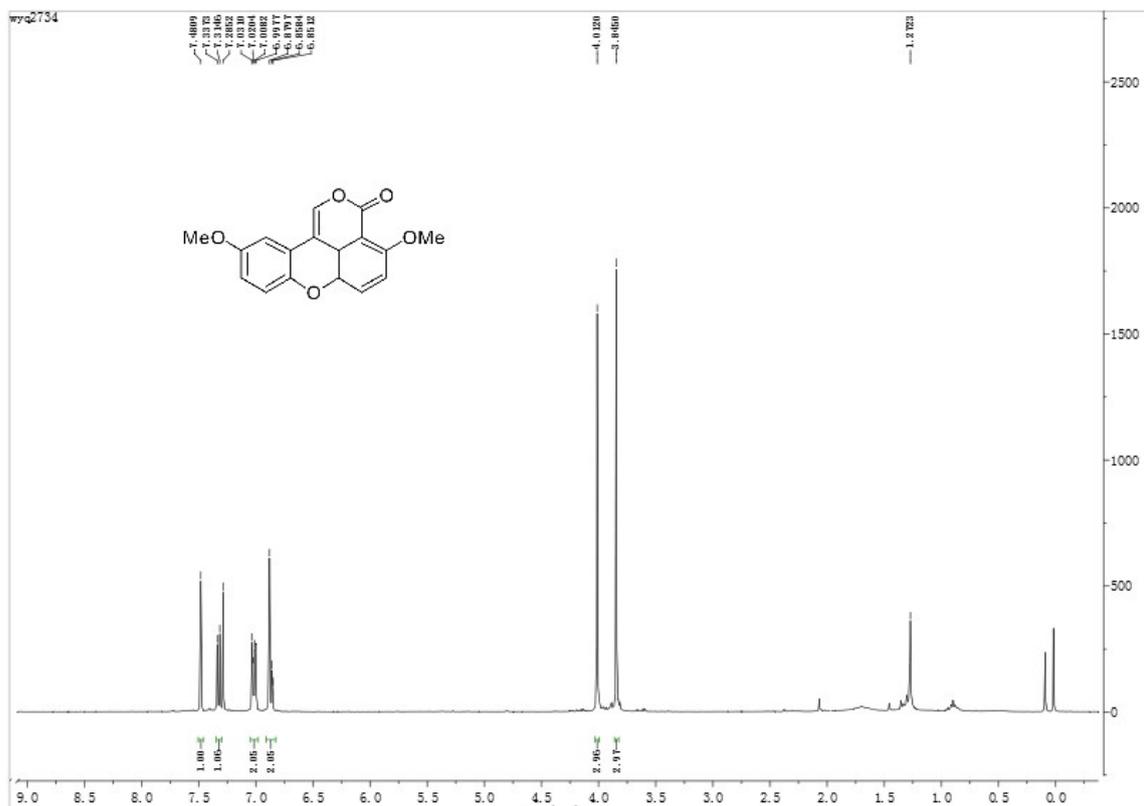
¹H NMR of 11



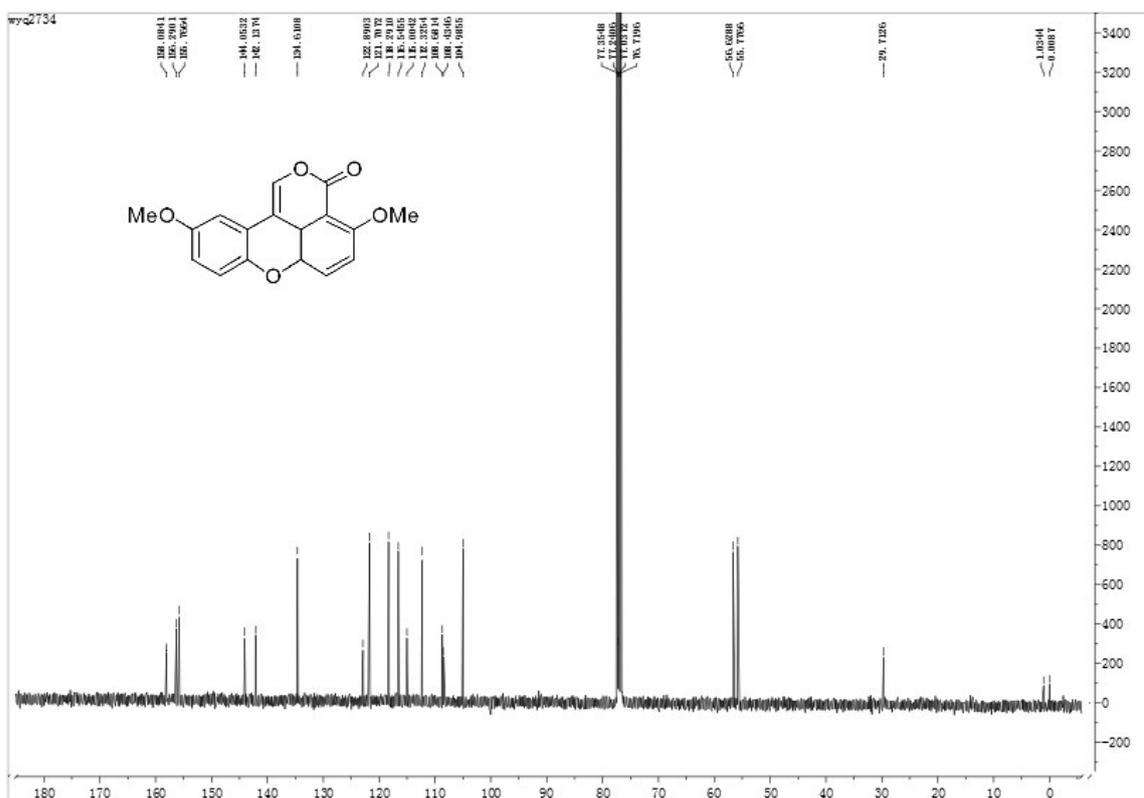
¹³C NMR of 11



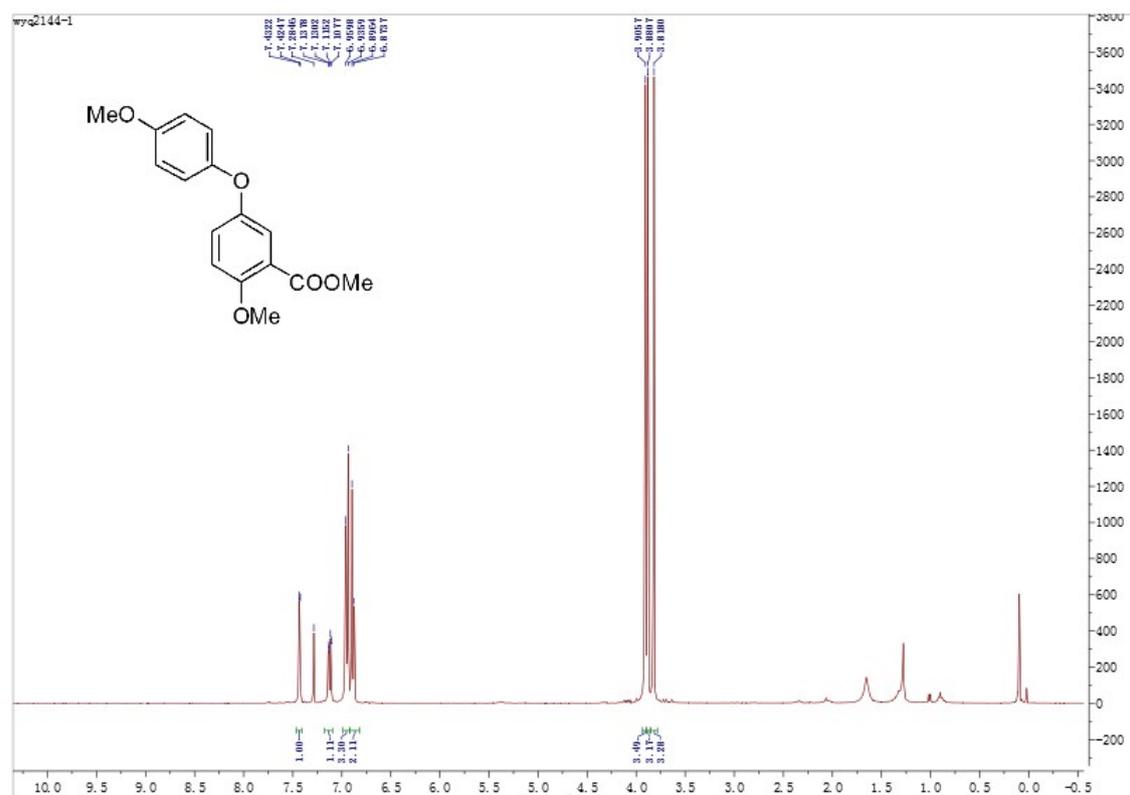
¹H NMR of 12



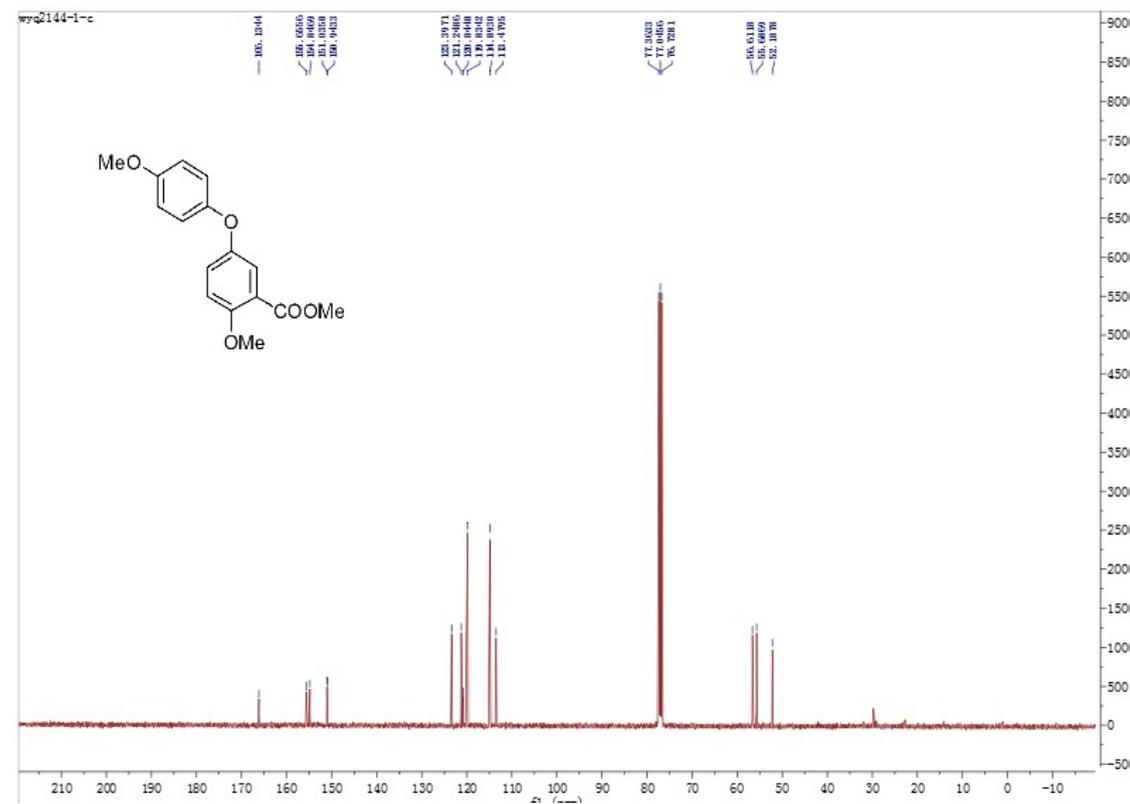
¹³C NMR of 12



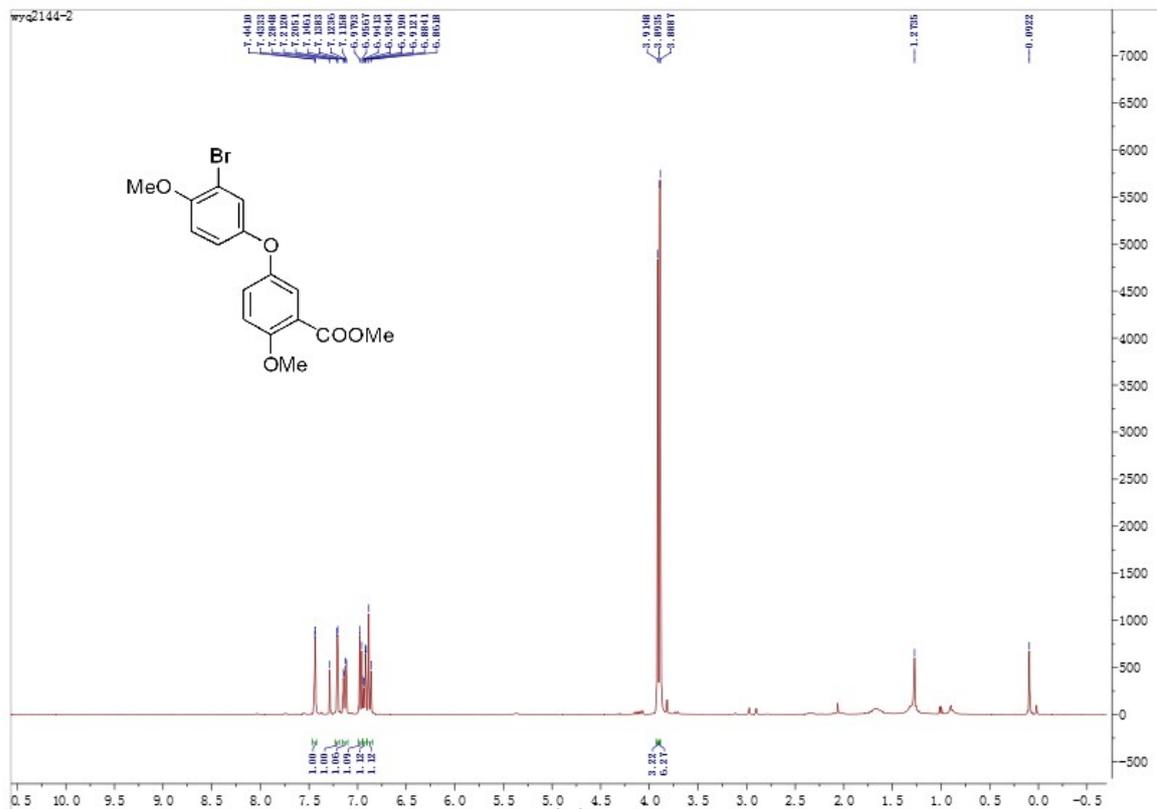
¹H NMR of 19



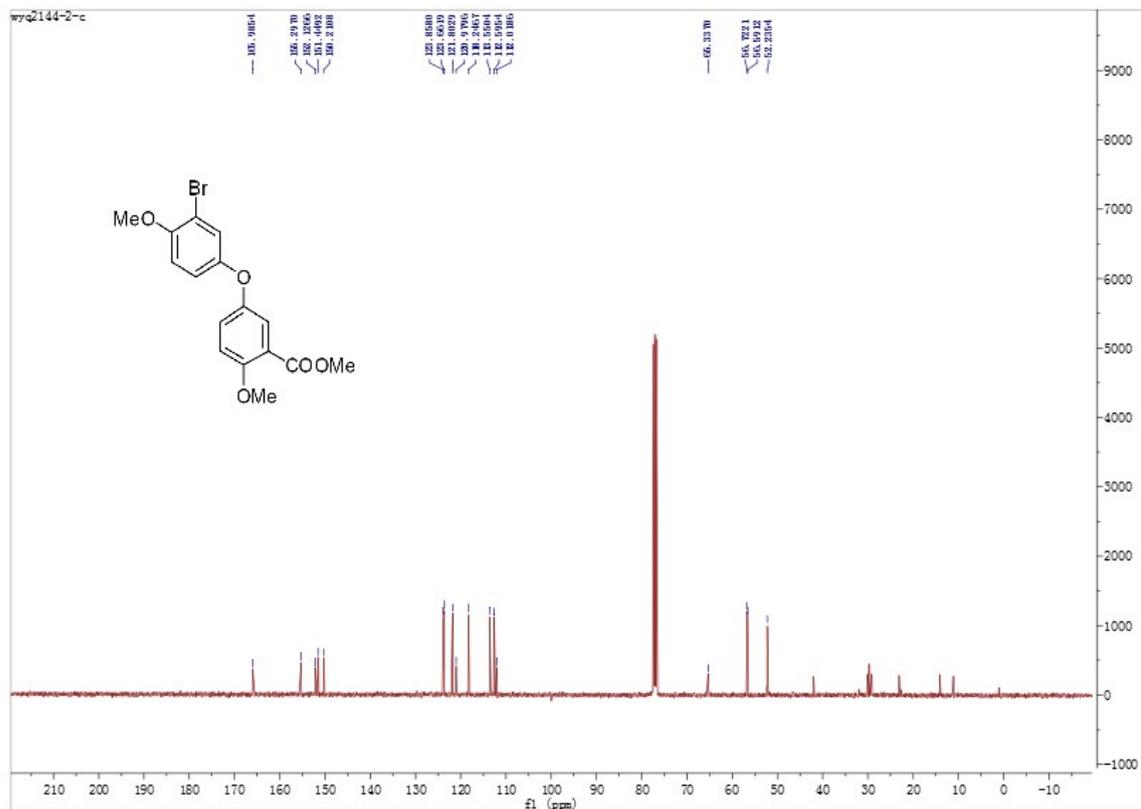
¹³C NMR of 19



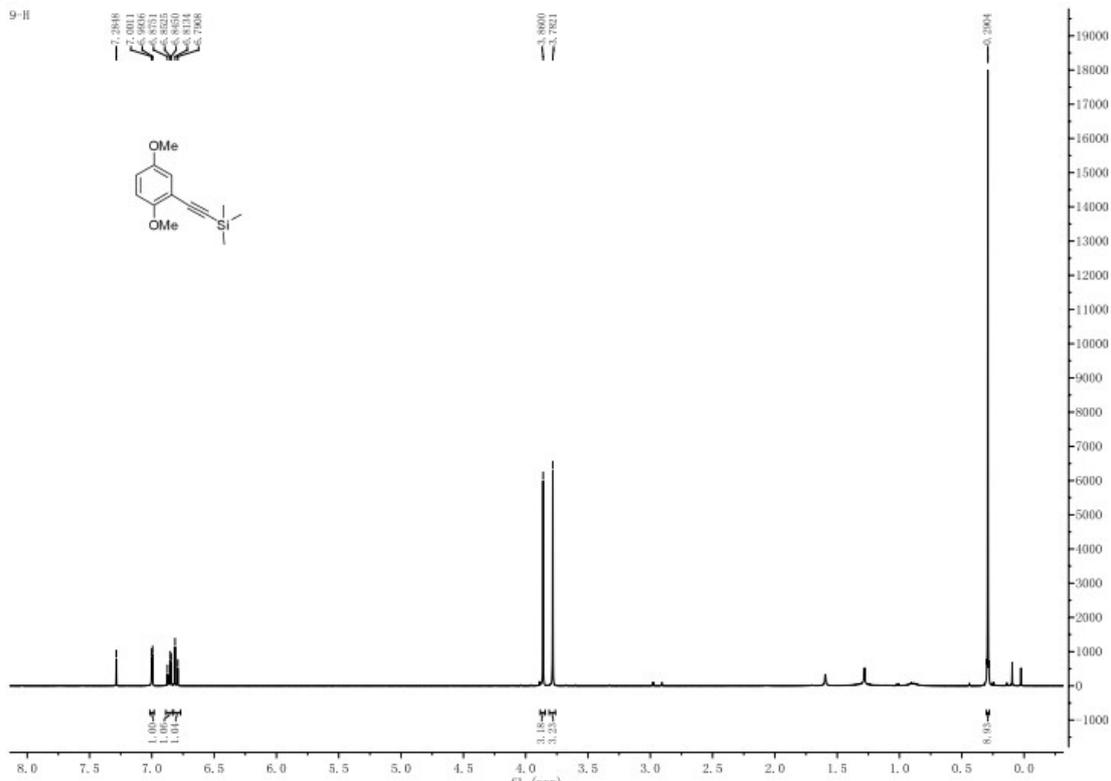
¹H NMR of 20



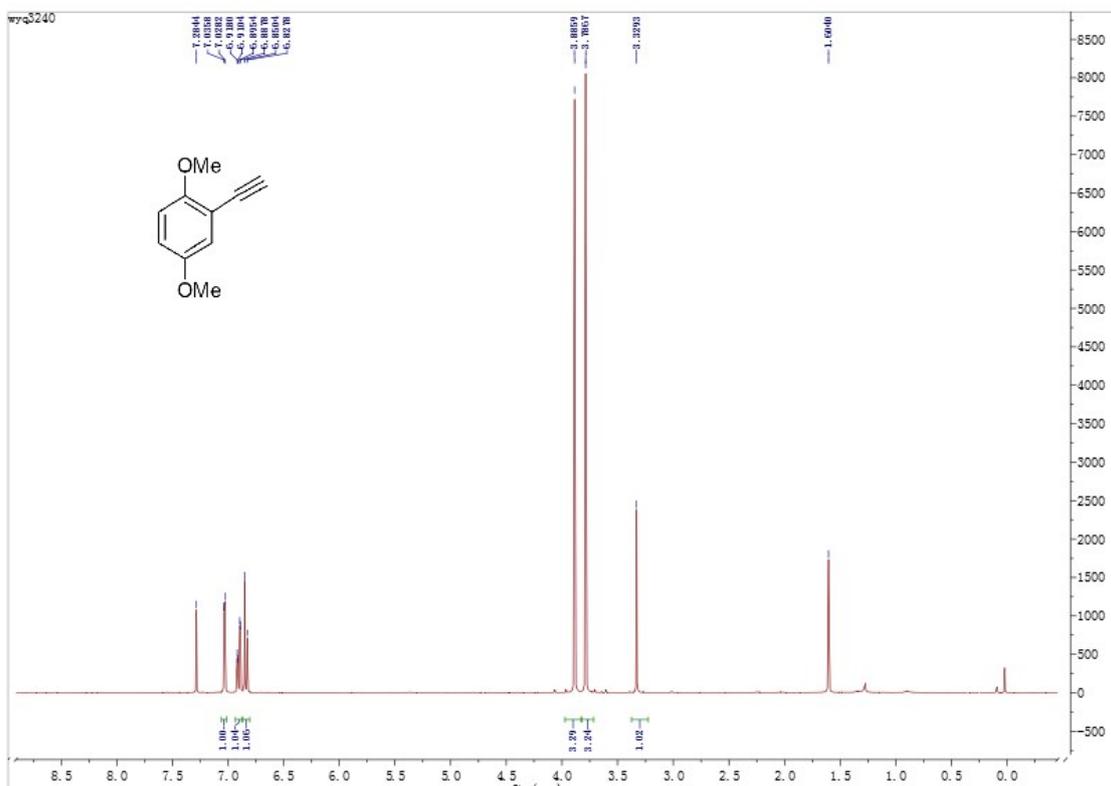
¹³C NMR of 20



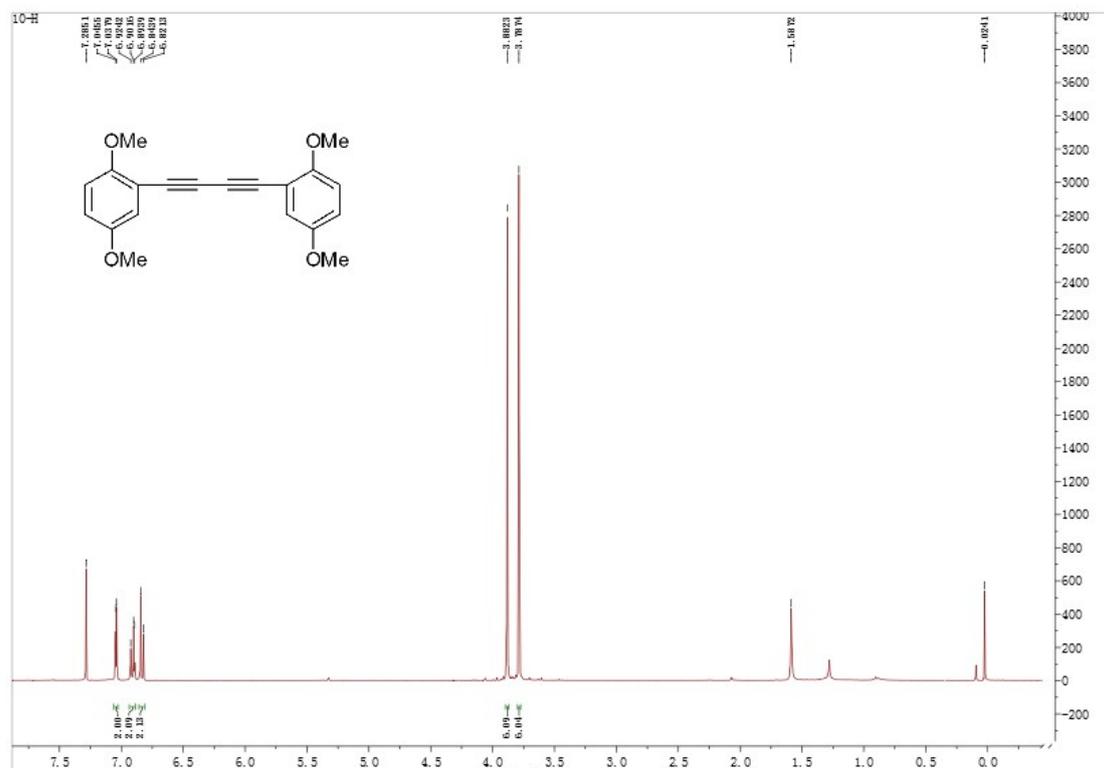
¹H NMR of 14



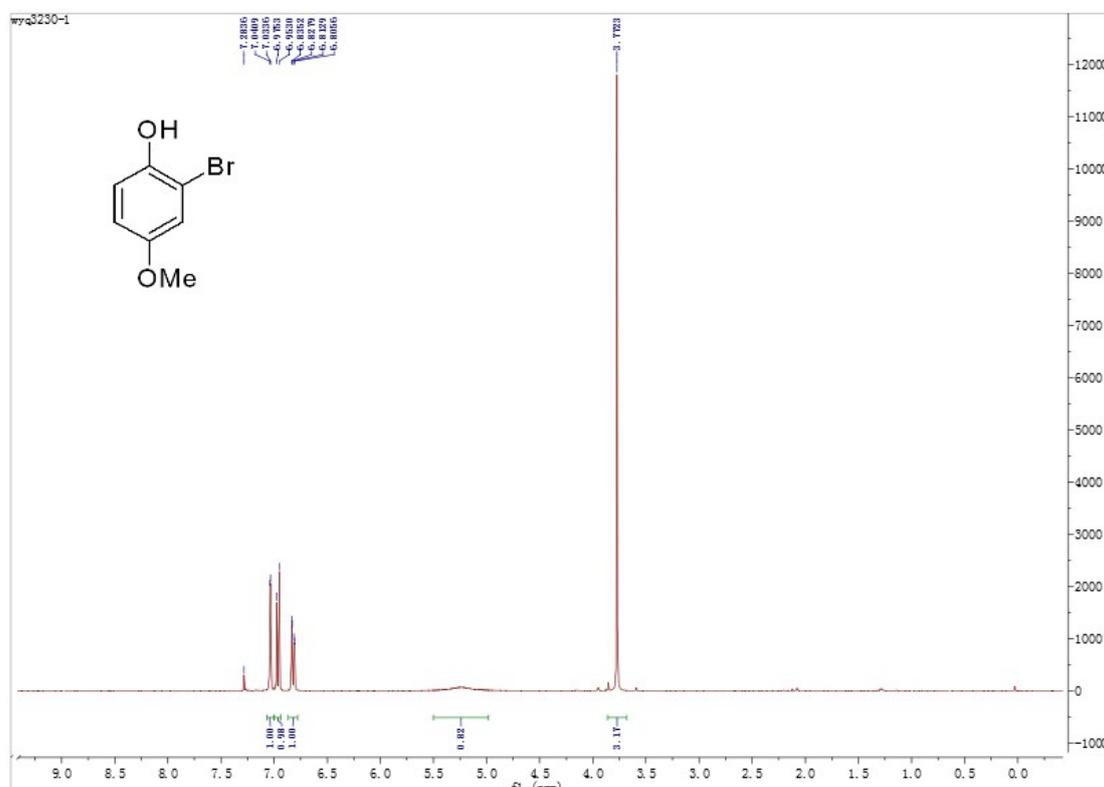
¹H NMR of 13



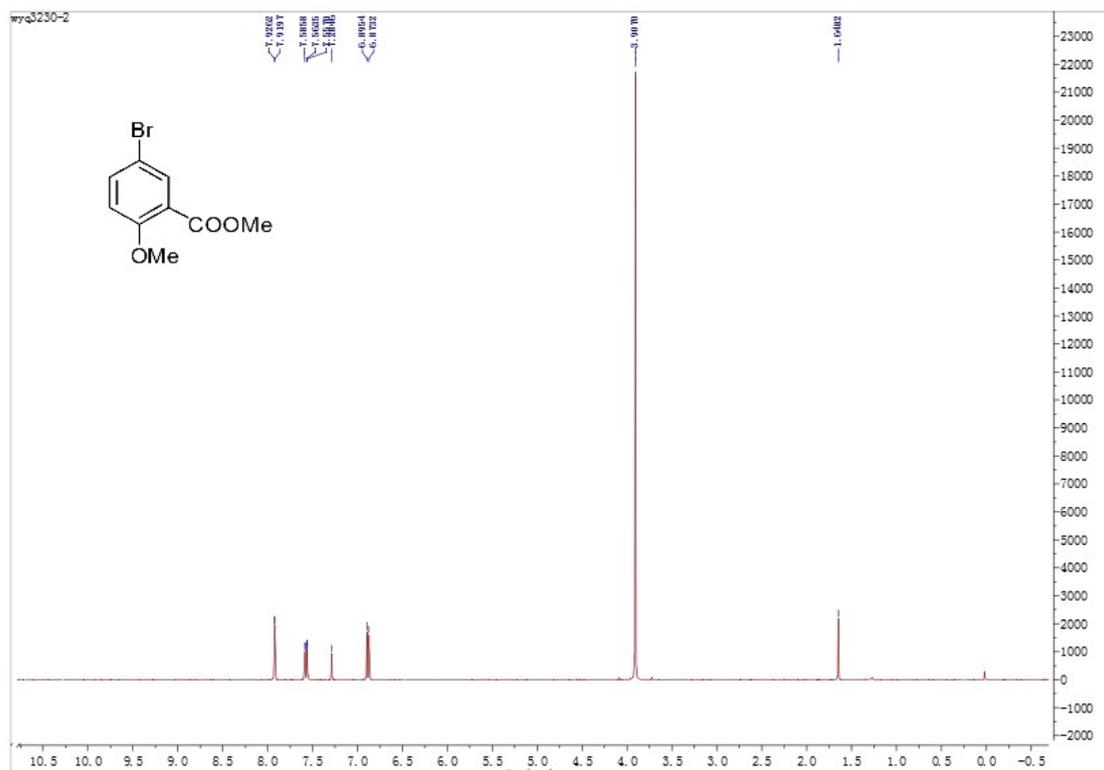
¹H NMR of 15



¹H NMR of 1



^1H NMR of 16a



^1H NMR of 16b

