

H₂O₂ promoted C-C bond oxidative cleavage of β-O-4 lignin models to benzanilides using water as solvent under metal-free conditions

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1. General Experimental Methods

1.1 Materials

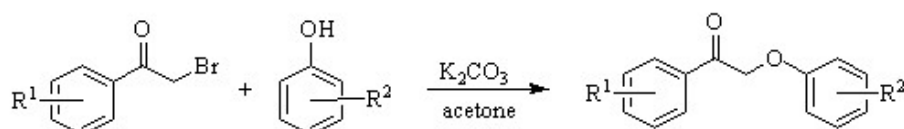
All reagents and solvents were purchased from Accela, Adamas, Innochem, Psaitong and Aladdin. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. All the reactions were carried out under an air atmosphere.

1.2 Instrumentation

Products were purified by flashchromatography on silica gel. Analysis of crude reaction mixture was performed on an Agilent 7820A GC System with a HP-INNOWAX capillary column (30 m×0.25 mm×0.32 μm) and an FID detector. The following GC temperature program was used: 40°C is maintained for 0 minutes, then rises to 150 °C at 30 °C/min, and finally rises to 300 °C at a rate of 20 °C/min, and hold for 4 minutes.

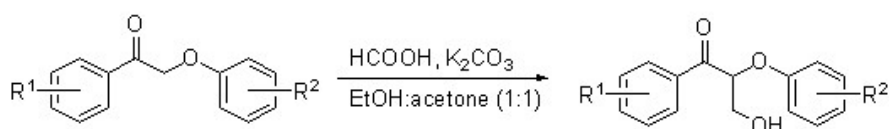
Nitrogen was used as a carrier gas. The injector temperature was held at 250 °C. GC-MS analysis was carried out on a SHIMADZU GCMS-QP2010 with a DB-5 capillary column (30 m×0.25 mm×0.32 μm). ¹H NMR spectra were recorded in CDCl₃ or DMSO using internal reference (the residue proton peaks of CDCl₃ at 7.26 ppm and DMSO at 2.5 ppm) on Bruker 400 spectrometer. Liquid ¹³C NMR was recorded at 100.6 MHz in CDCl₃ using residual CDCl₃ as internal reference (the residue proton peaks of CDCl₃ at 77.02 ppm and DMSO at 40.03 ppm).

2.Synthesis of lignin models



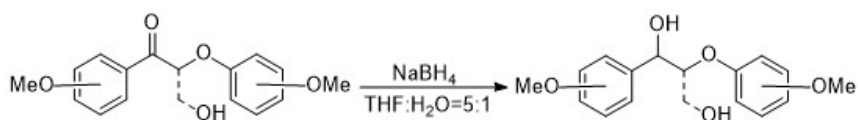
Scheme S1 synthetic ketone lignin model

The synthesis reaction was carried out in a 150 mL round glass flask containing a condenser. 2-phenoxyacetophenone were synthesized by the reaction of the corresponding phenol with 2-bromoacetophenone according to the reported procedure.¹ Typically, 2-bromoacetophenone (5 mmol) is dissolved in a solution of K₂CO₃ (7.5 mmol, 1.036 g) and phenol (5 mmol) in acetone (50 mL) and loaded in a reactor. The reaction mixture is then stirred at reflux temperature for 5 hours, filtered and vacuumized. The residue was purified by column chromatography with hexane:ethyl acetate a stirring. For the other methoxy substituted 2-phenoxy-1-phenylethanone, the preparation procedure is the same as described above, except of using different starting materials.



Scheme S2 synthetic 3-hydroxy-2-phenoxy-1-phenylpropan-1-one

To a stirring suspension of K₂CO₃ (0.6 g, 4.3 mmol) in ethanol/acetone (v/v = 1/1, 20 mL) and 2-phenoxyacetophenones (0.78 g, 4 mmol) at rt., a water solution of formaldehyde (36.5~38 wt %, 0.6 mL, 7.3 mmol) was added. After 4 h, the reaction mixture was filtered to remove K₂CO₃ and concentrated in vacuo to get a solid product. The crude product was purified with petroleum ether: ethyl acetate (3:1) to obtain the required 2-phenoxyacetophenone, on silica gel to obtain 3-hydroxy-1,2-diphenylpropan-1-one in 90% yield.

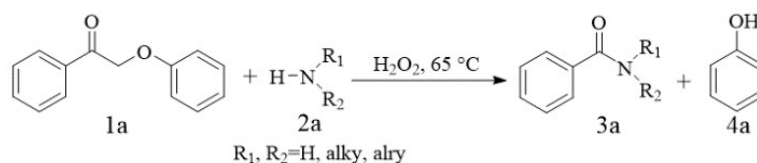


Scheme S3 synthetic alcohol lignin model compound

The resulting compound (3.5 mmol, 0.847 g) was dissolved in the mixture of THF:H₂O (5:1) (25 mL), and sodium borohydride (7 mmol, 0.26 g) was added portion wise to maintain a gentle evolution of gas. Then, the mixture was stirred for 6 h at room temperature. The reaction mixture was quenched with saturated aqueous NH₄Cl (50 mL) and diluted with 30 mL water. The aqueous portion was extracted with ethyl acetate (3×30 mL). The organic parts were combined, dried over MgSO₄, filtered and concentrated under vacuum. The residue was purified by column chromatography with hexane:ethyl acetate (2:1).

3. Additional Screening of Reaction Conditions

3.1 Synthesis of aromatic amides

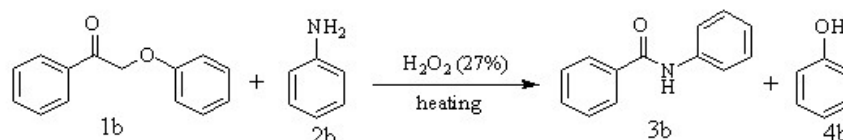


Scheme S4 Synthesis of aromatic amides

The synthesis was carried out in a 5 mL reaction tube. Taking the synthesis of benzanilide as an example, the reaction steps are as follows. 2-phenoxyacetophenone (0.5 mmol), aniline (1.5 mmol), H₂O (1.5 mL), and H₂O₂ (0.5 mL) were loaded into the reaction. Transfer the tube to an oil bath at a specified temperature (e.g., 65 °C) and maintain the required reaction time at that temperature. The reaction solution is then treated to separate the unreacted reactants and products. First, an aqueous solution of hydrochloric acid (10 mL) was added to the reaction mixture, followed by 10 mL dichloromethane to extract the organic compounds. The composition of the reaction solution was determined by gas chromatography using n-dodecane as the internal standard. The organic phase was further purified by silica gel column chromatography to obtain the desired product (eluent: petroleum ether/ethyl acetate=50/1), thus obtaining the isolated yield of the product.

3.2 Optimization of reaction conditions

Table S1 Optimization of reaction conditions



A

Entry	amounts of aniline (x eq)	Yield(%)		Conversion (%)
		3b	4b	
1	1	30	33	42
2	2	58	64	76
3	3	82	86	94
4	4	83	87	93
5	5	82	87	95

B

Entry	temperatures (°C)	Yield(%)		Conversion (%)
		3b	4b	
1	35	27	29	33
2	45	39	47	56
3	55	58	62	74
4	65	82	86	90
5	75	78	84	94
6	85	78	80	95

C

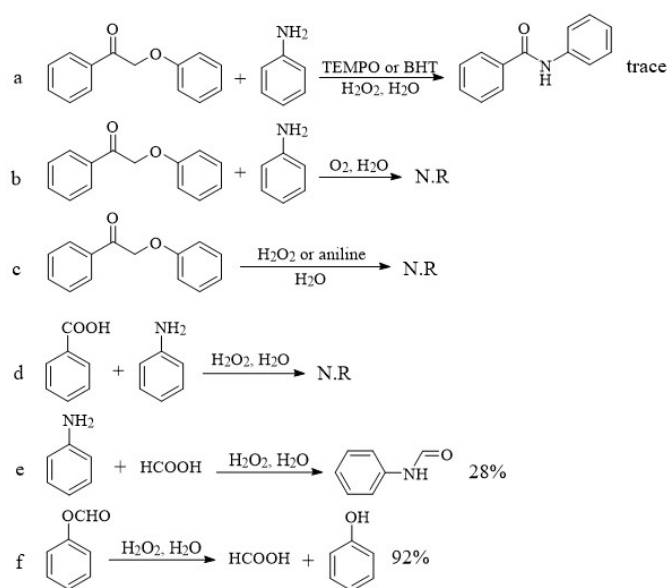
Entry	times (h)	Yield(%)		Conversion (%)
		3b	4b	
1	5	42	47	52
2	6	54	56	60
3	7	66	68	79
4	8	82	86	89
5	9	81	88	96
6	10	83	87	97

D

Entry	amounts of H ₂ O ₂ (mL)	Yield(%)		Conversion (%)
		3b	4b	
1	0.1	42	45	60
2	0.25	60	68	79
3	0.5	82	86	90
4	0.75	81	86	92
5	1	82	85	93

Oxidative amidation of lignin model compound. General reaction conditions: 1b (0.5 mmol), H₂O₂ (27 wt.% 0.5 mL), H₂O (1.5 mL) and aniline (1.5 mmol) at 65 °C for 8 h. A) Different amounts of aniline. B) Different reaction temperatures. C.) Different reaction times. D) Different amounts of H₂O₂.

4. Control experiments



Scheme S5. Reaction conditions: substrate (0.5 mmol), H₂O₂ (27 wt.% 0.5 mL), H₂O (1.5 mL), aniline (1.5 mmol) and formic acid (1 mmol) at 65 °C for 8 h.

5. Detection by GC

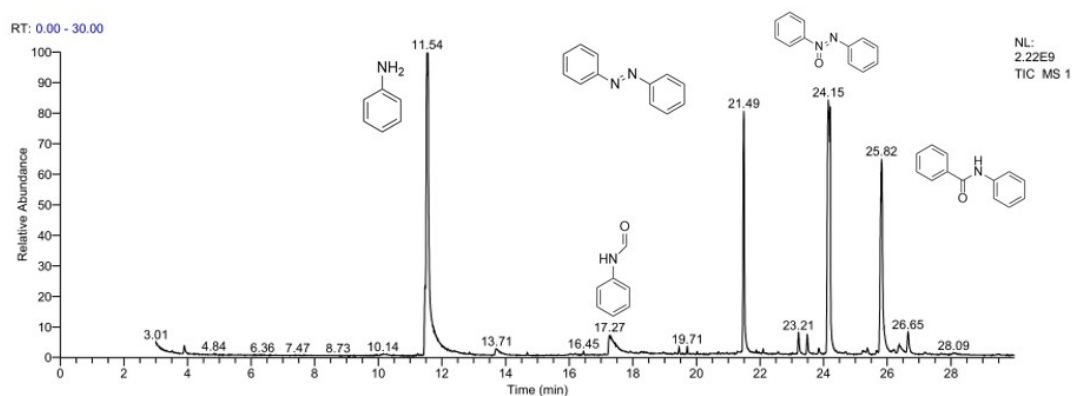


Figure S1 GC-MS of the reaction solution. Conditions: 1 (0.5 mmol), H₂O₂ (27 wt.% 0.5 mL), H₂O (1.5 mL) and aniline(3 mmol) at 65 °C for 8 h.

Some by-products are affected by the reaction system. When we add aniline in batches, it can effectively reduce the reaction of aniline itself. In addition, we also found the final product formanilide by GC-MS, which further proved the reaction mechanism.

6.¹H NMR and ¹³C NMR spectra of compounds

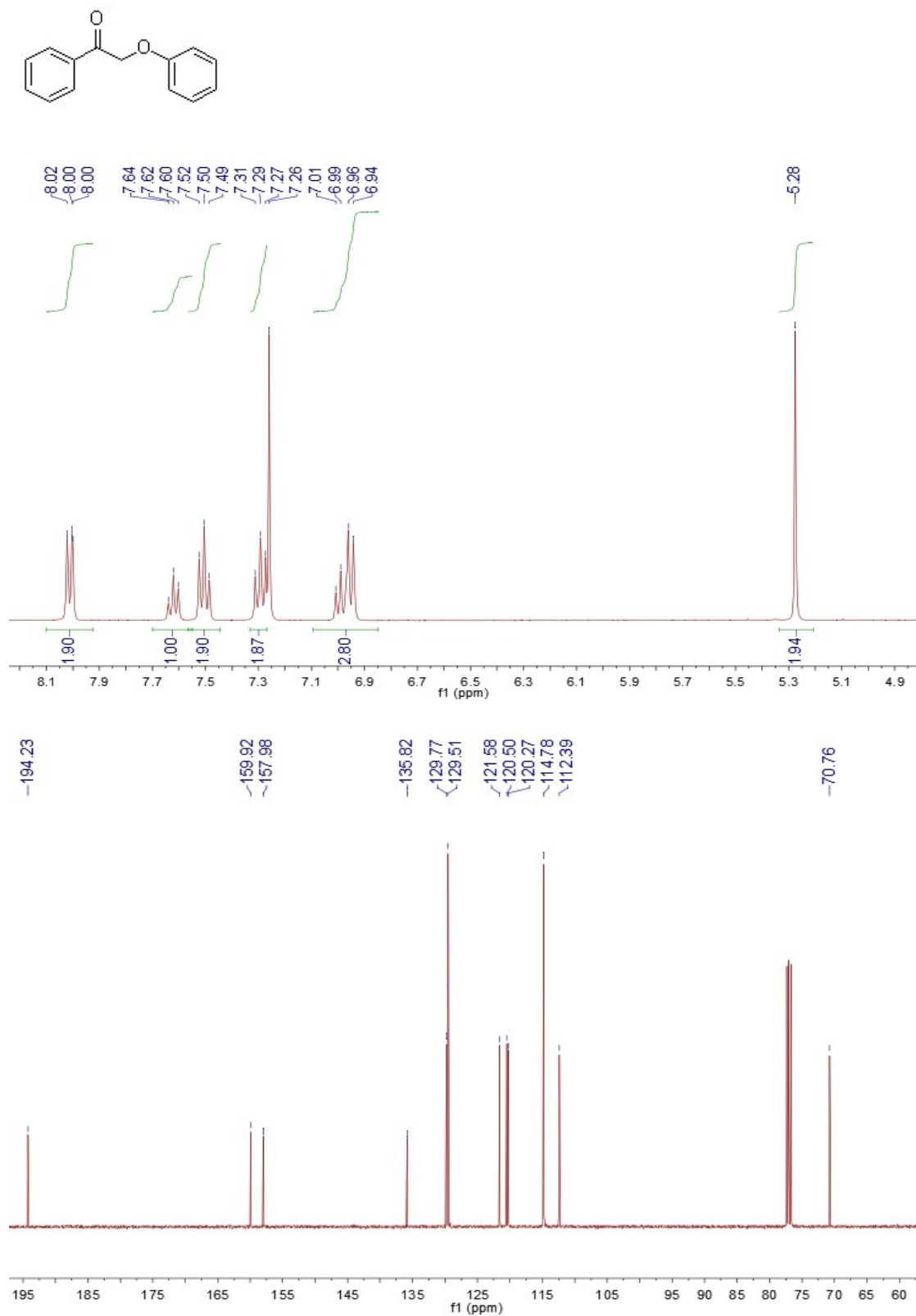


Figure S2 ¹H (top) and ¹³C (bottom) NMR spectra of 2-phenyloxy-acetophenone

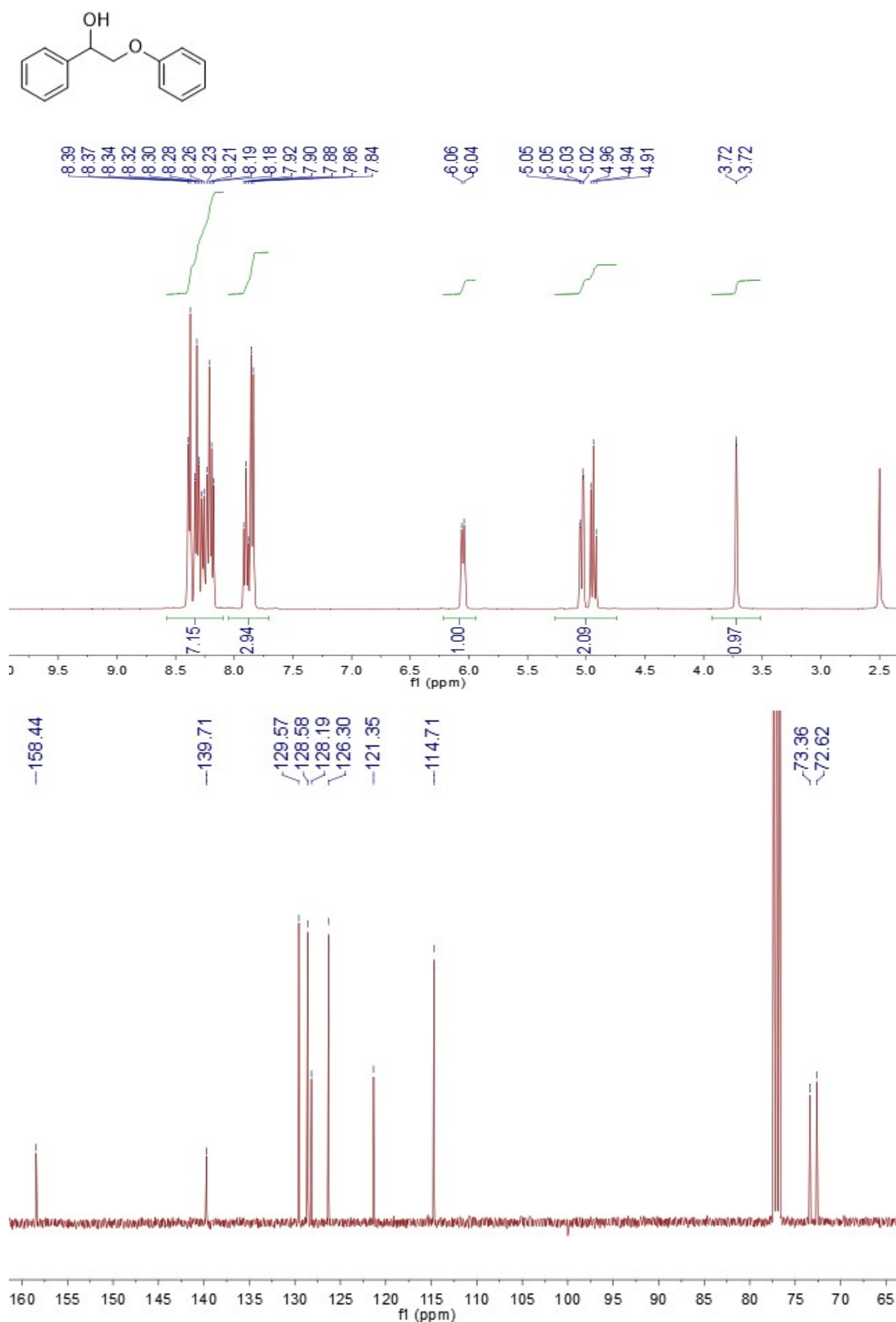


Figure S3 ¹H (top) and ¹³C (bottom) NMR spectra of 2-Phenoxy-1-phenyl-ethanol

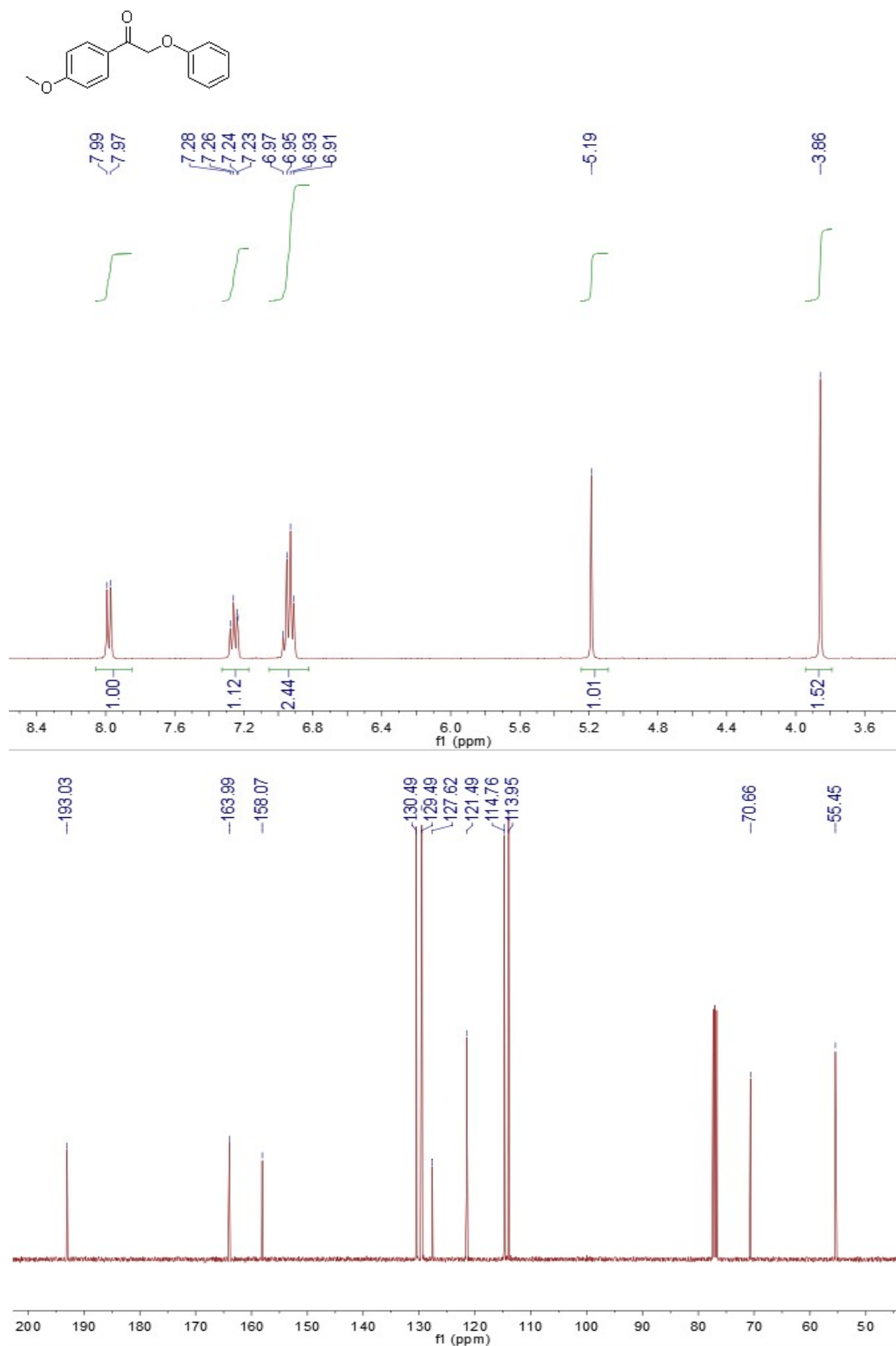


Figure S4 ¹H (top) and ¹³C (bottom) NMR spectra of 1-(4-methoxyphenyl)-2-phenoxyethan-1-one

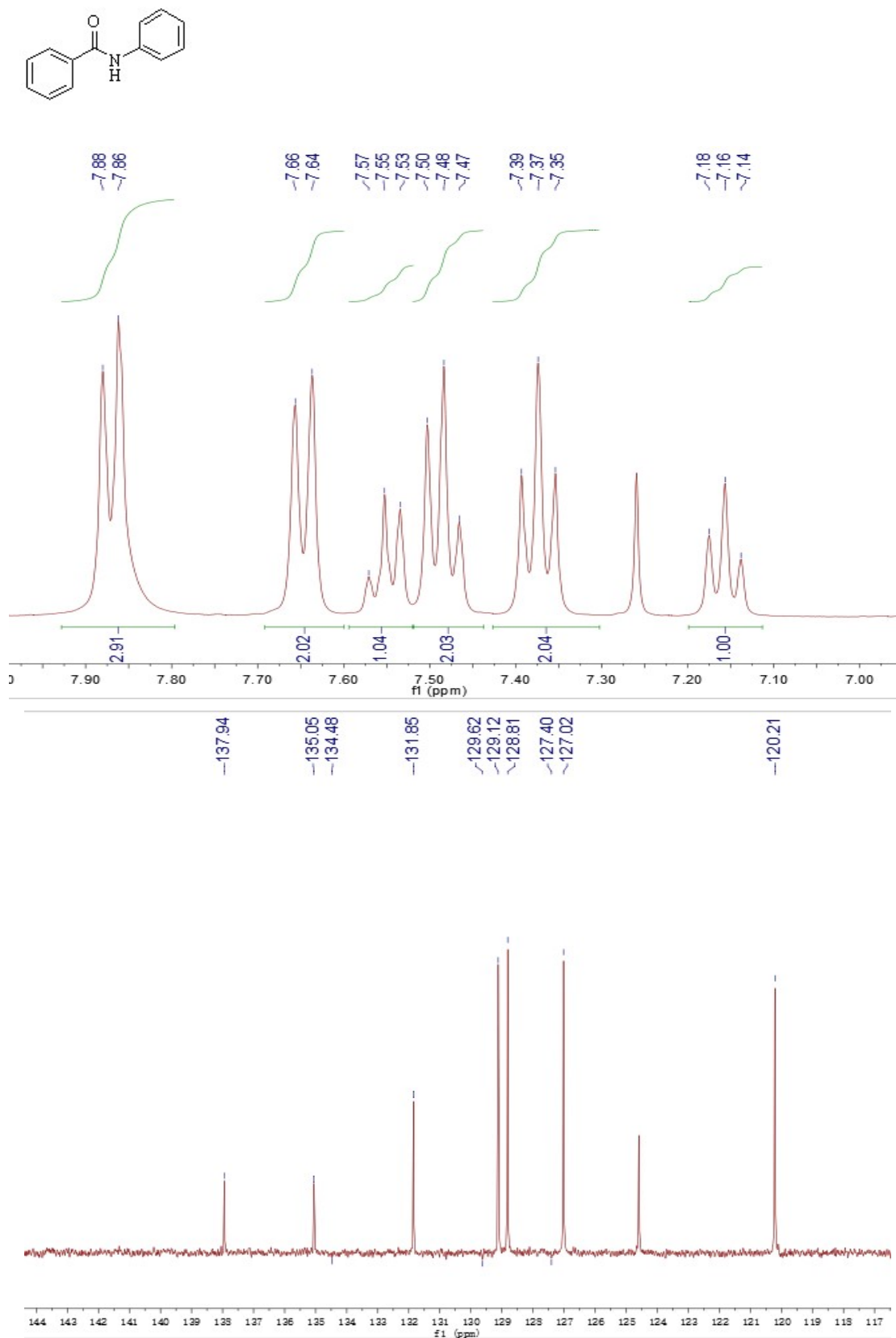


Figure S5 ¹H (top) and ¹³C (bottom) NMR spectra of N-phenylbenzamide

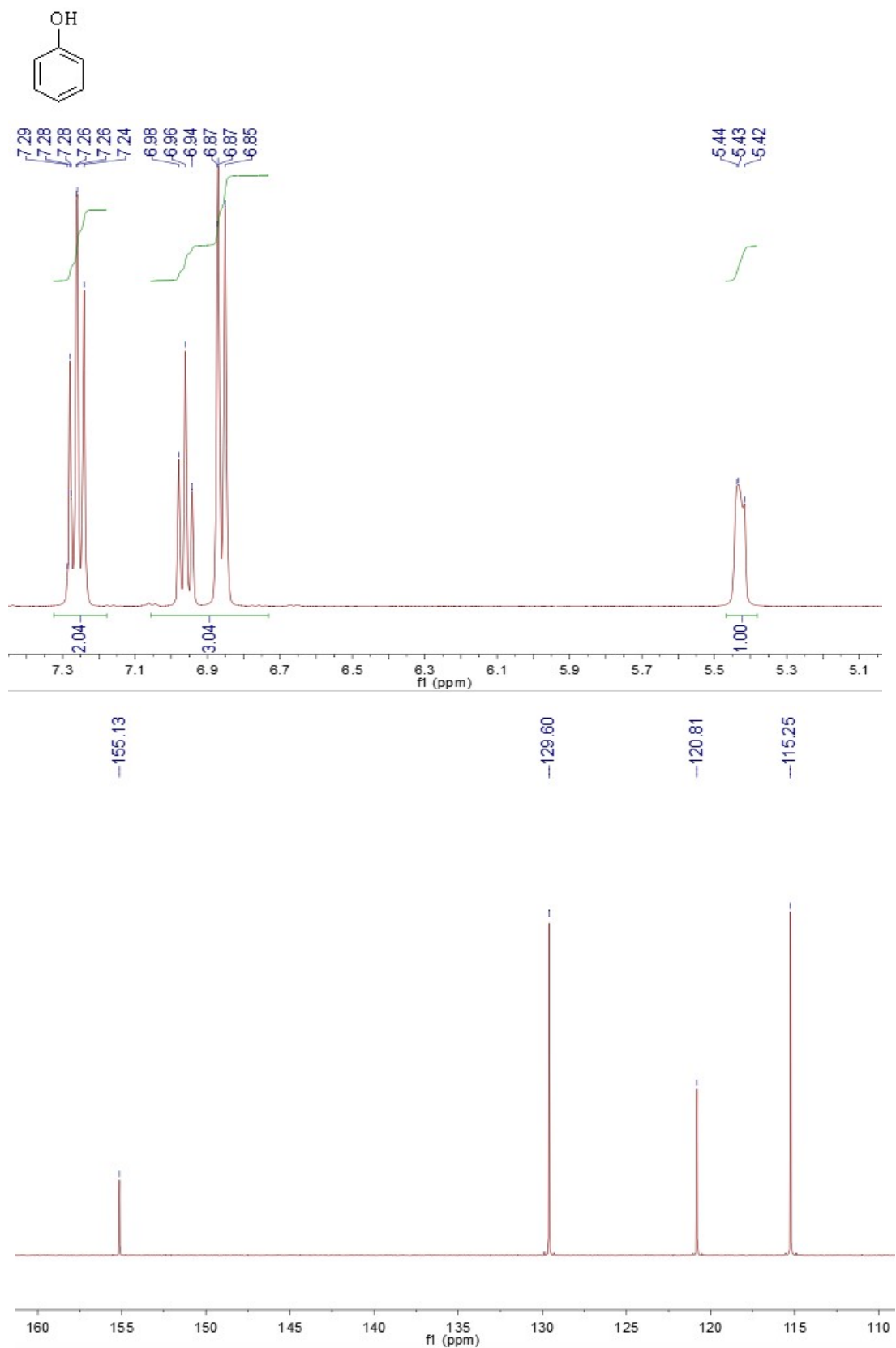


Figure S6 ^1H (top) and ^{13}C (bottom) NMR spectra of phenol

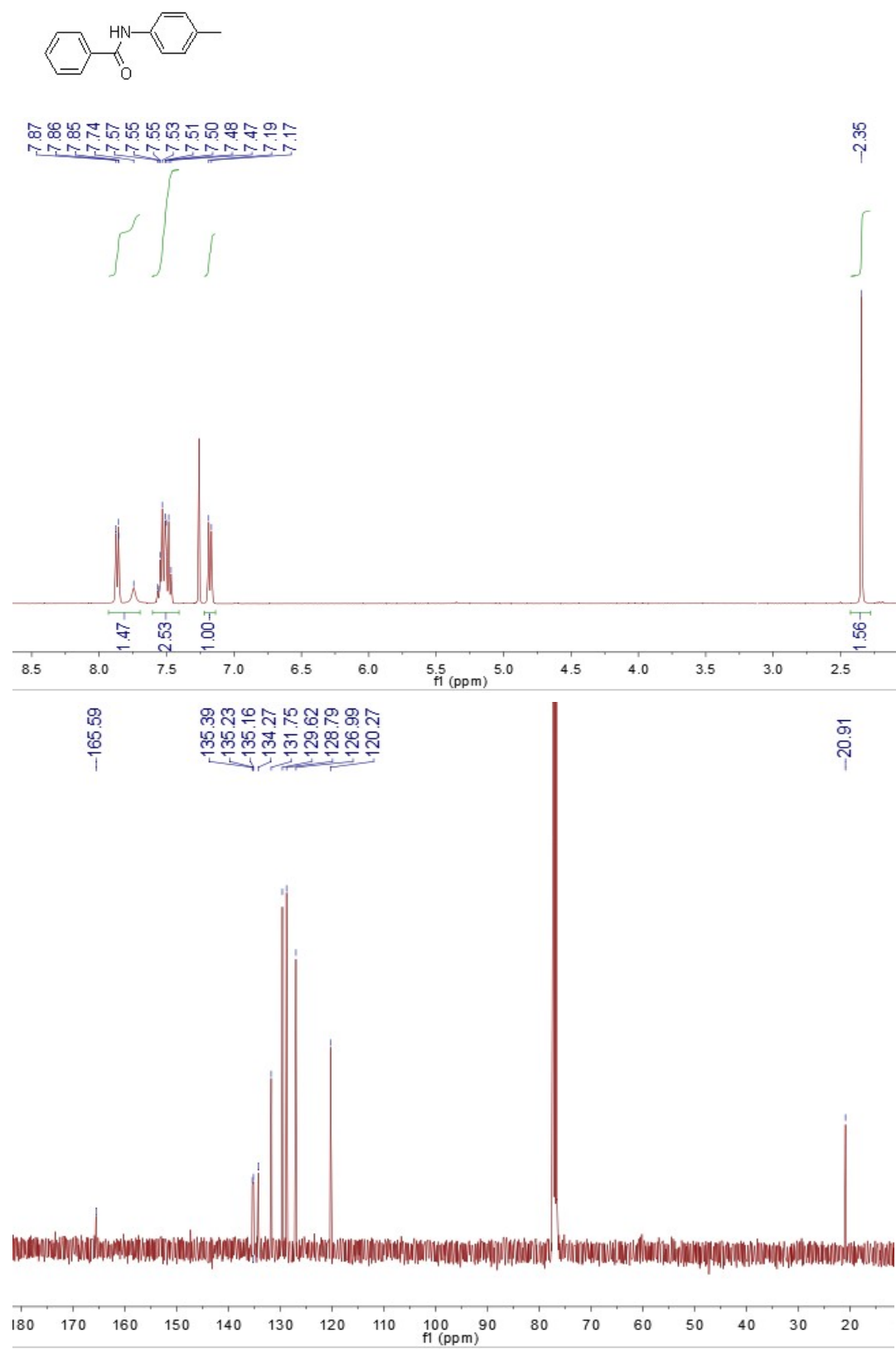


Figure S7 ¹H (top) and ¹³C (bottom) NMR spectra of N-(p-tolyl)benzamide

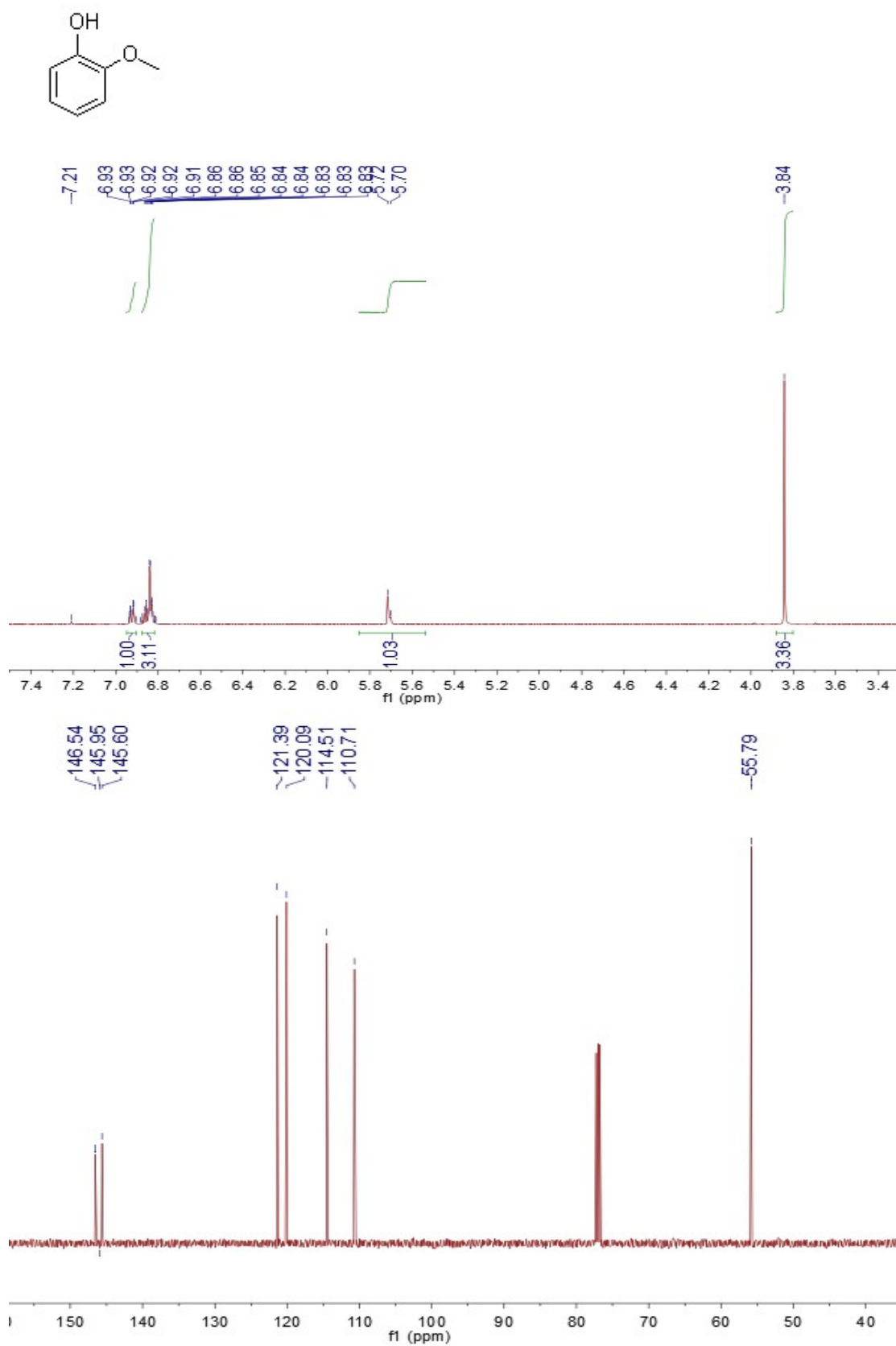


Figure S8 ¹H (top) and ¹³C (bottom) NMR spectra of 2-methoxyphenol

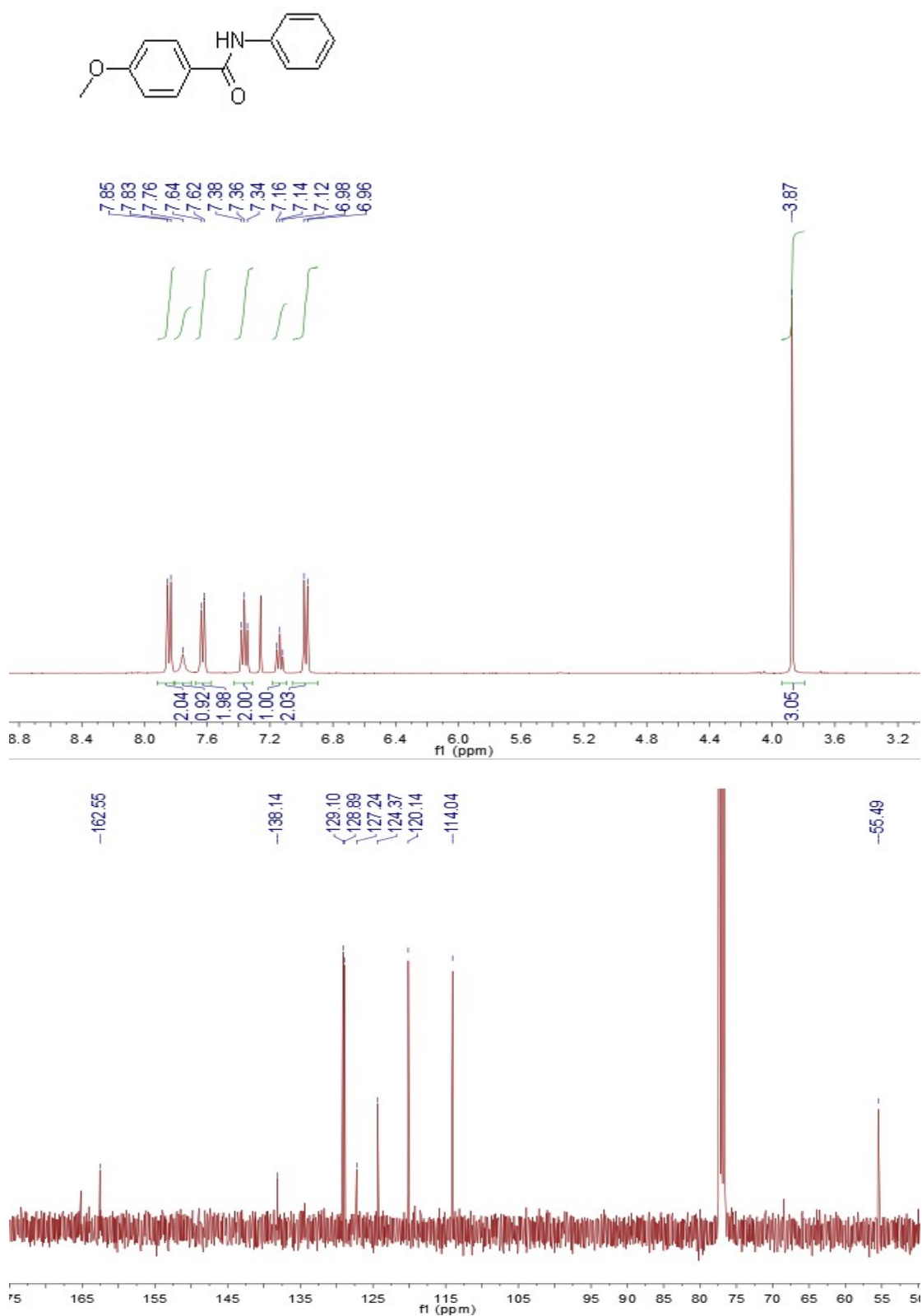


Figure S9 ¹H (top) and ¹³C (bottom) NMR spectra of 4-methoxy-N-phenylbenzamide

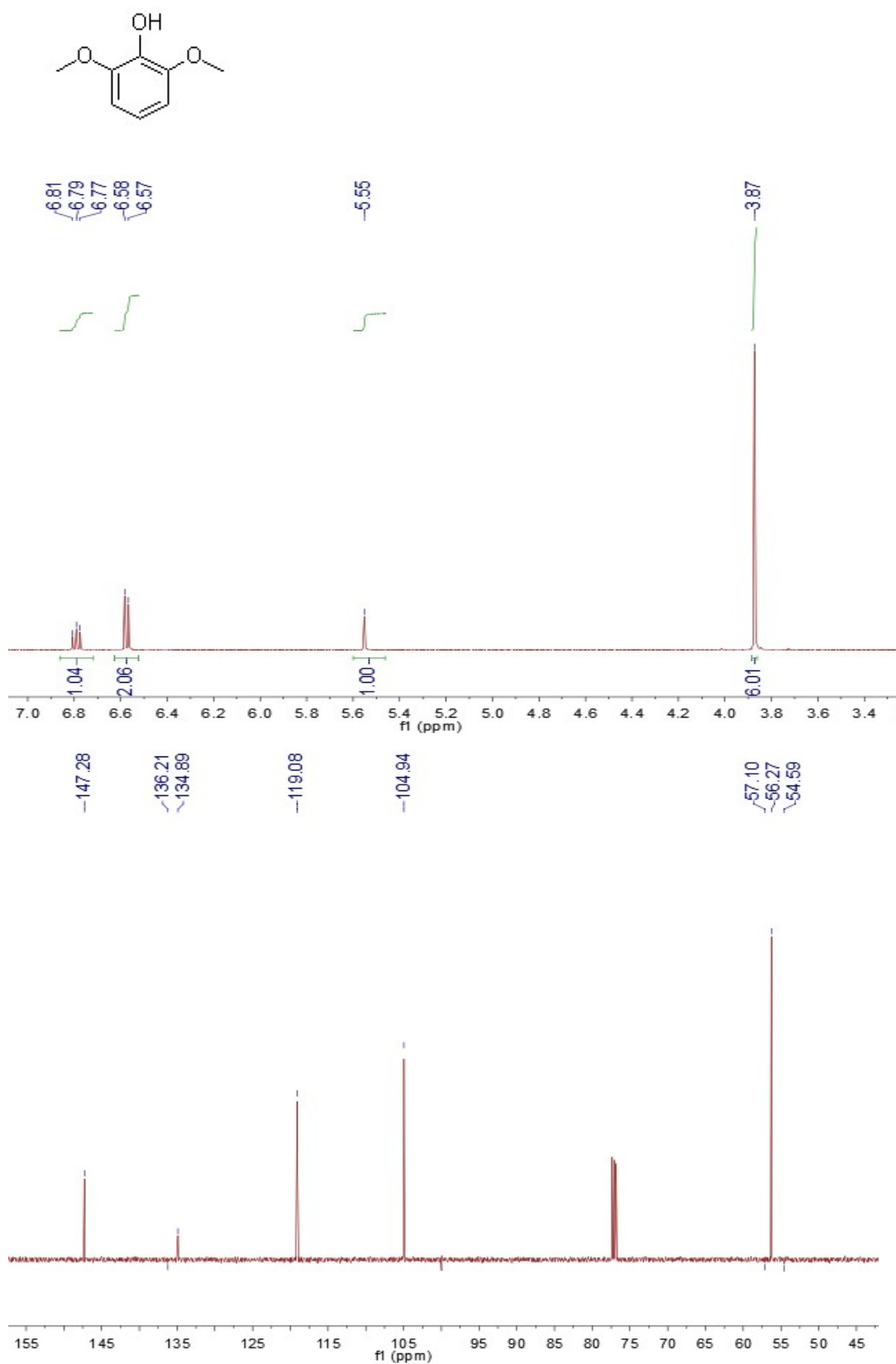


Figure S10 ¹H (top) and ¹³C (bottom) NMR spectra of 2,6-dimethoxyphenol

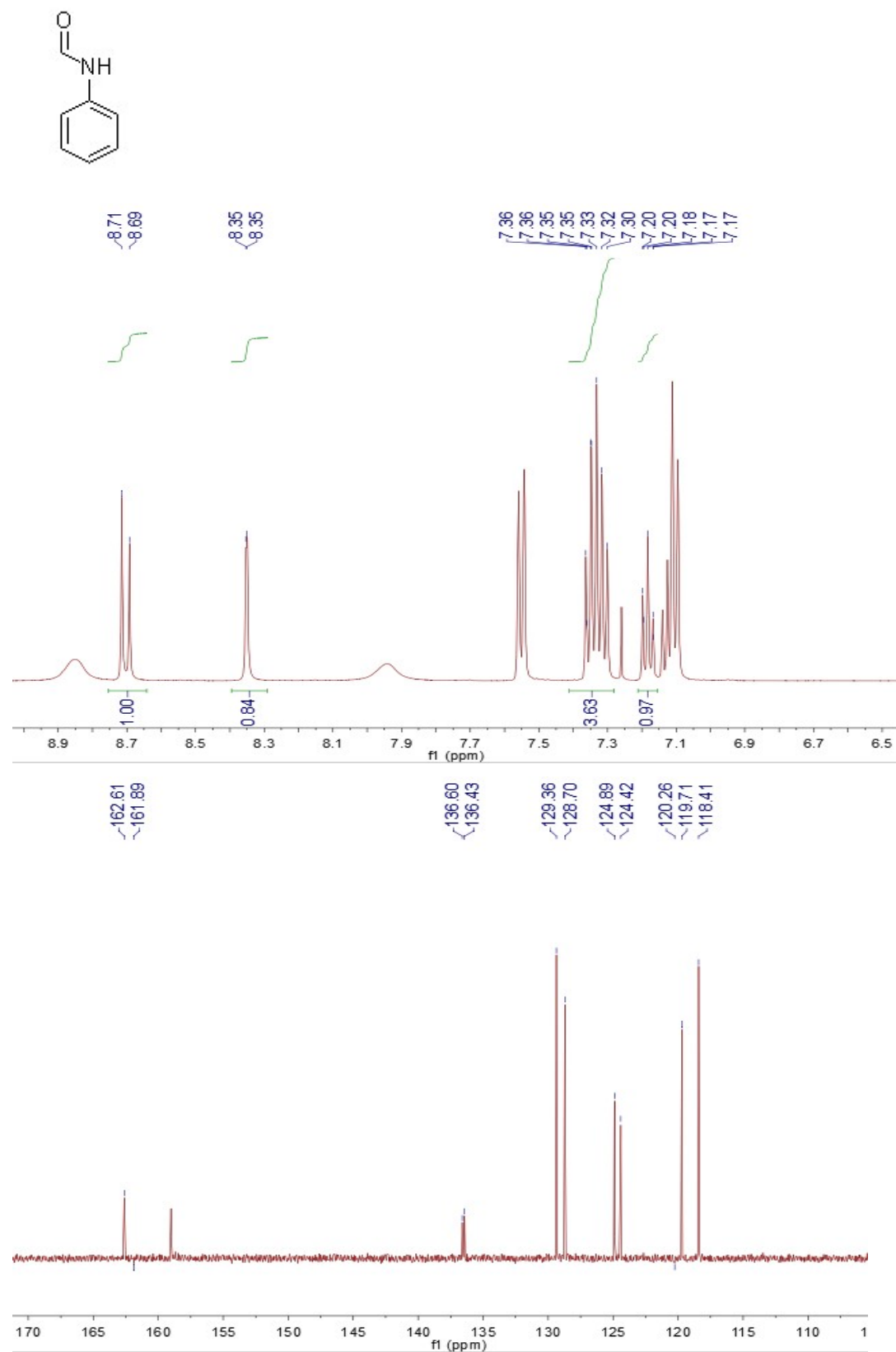


Figure S11 ¹H (top) and ¹³C (bottom) NMR spectra of N-phenylformamide

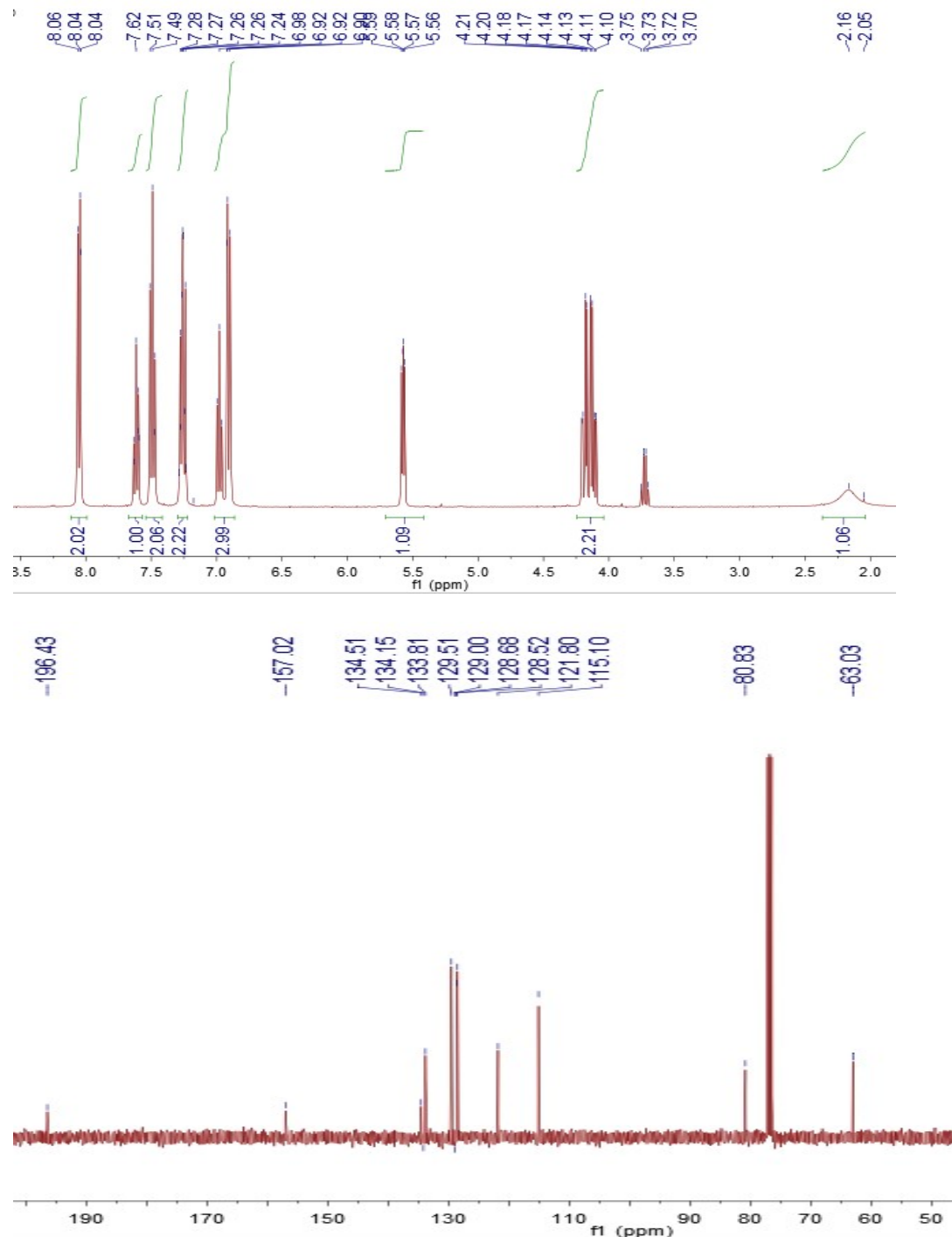
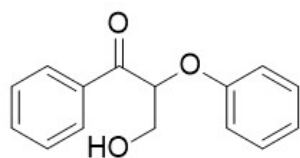


Figure S12 ¹H (top) and ¹³C (bottom) NMR spectra of 2-(cyclohexa-1,5-dien-1-yloxy)-3-hydroxy-1-phenylpropan-1-one

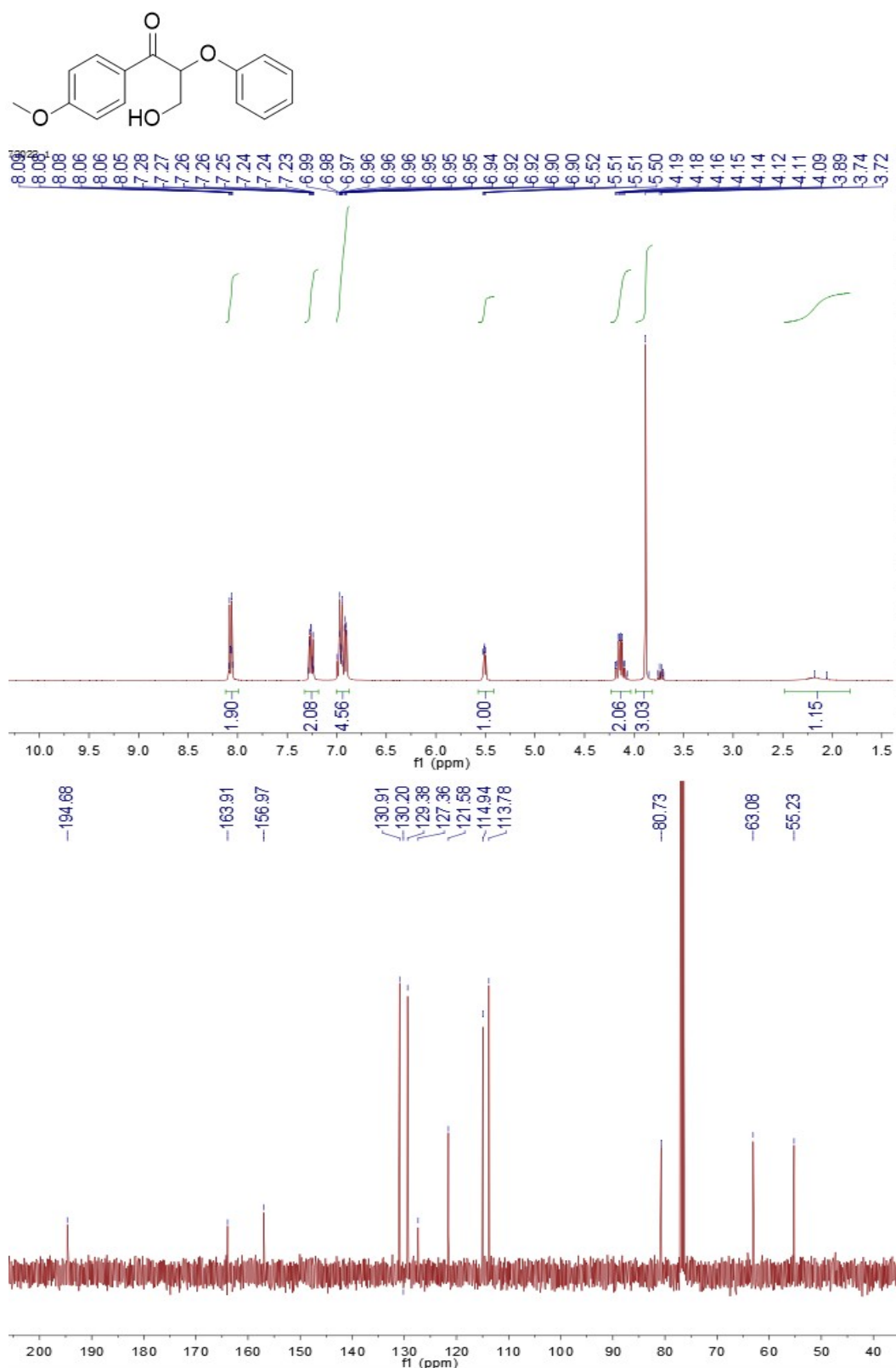


Figure S13 ¹H (top) and ¹³C (bottom) NMR spectra of 2-(cyclohexa-1,5-dien-1-yloxy)-3-hydroxy-1-(4-methoxyphenyl)propan-1-one

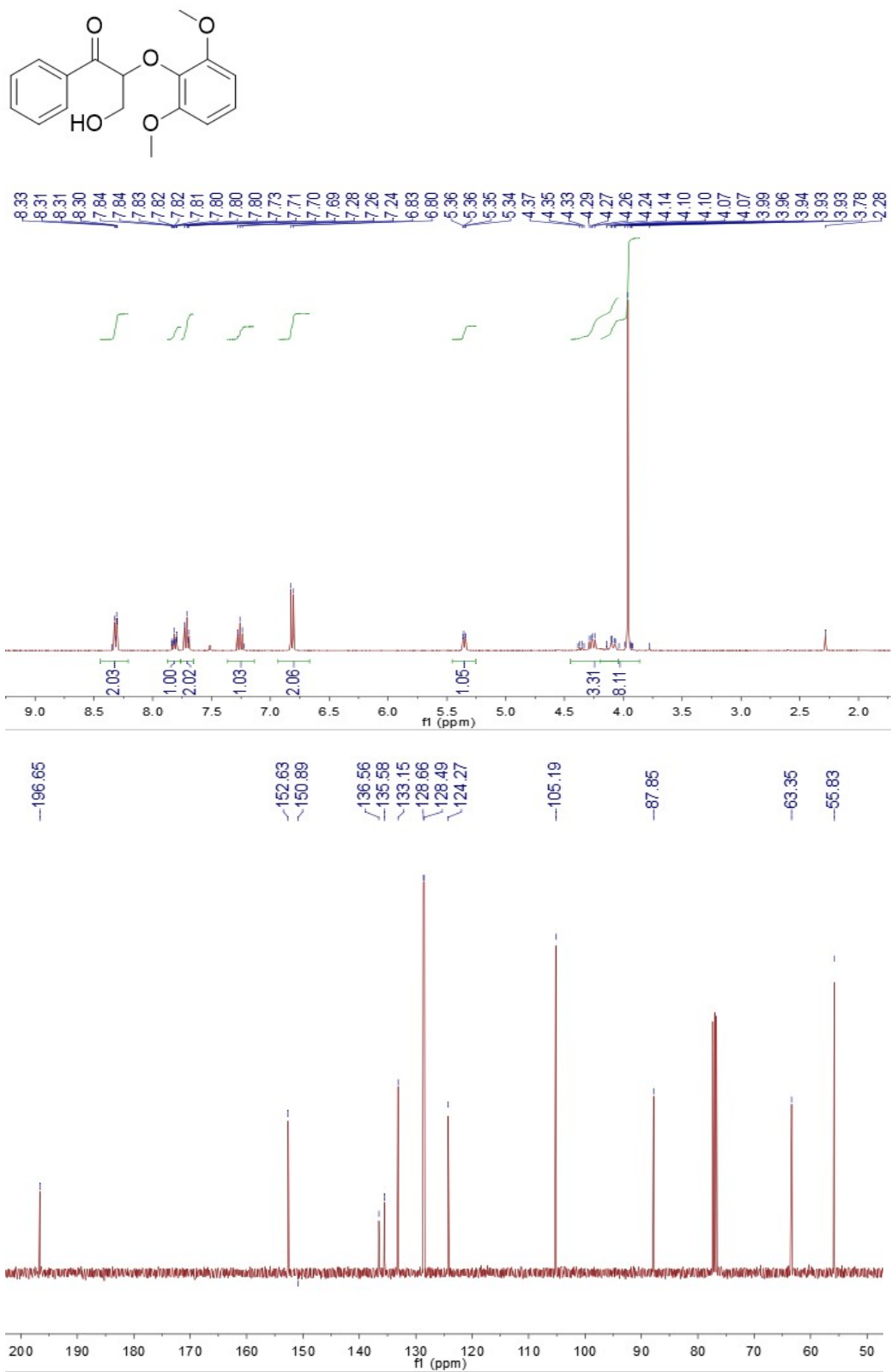


Figure S14 ¹H (top) and ¹³C (bottom) NMR spectra of 2-((2,6-dimethoxycyclohexa-1,5-dien-1-yl)oxy)-3-hydroxy-1-phenylpropan-1-one

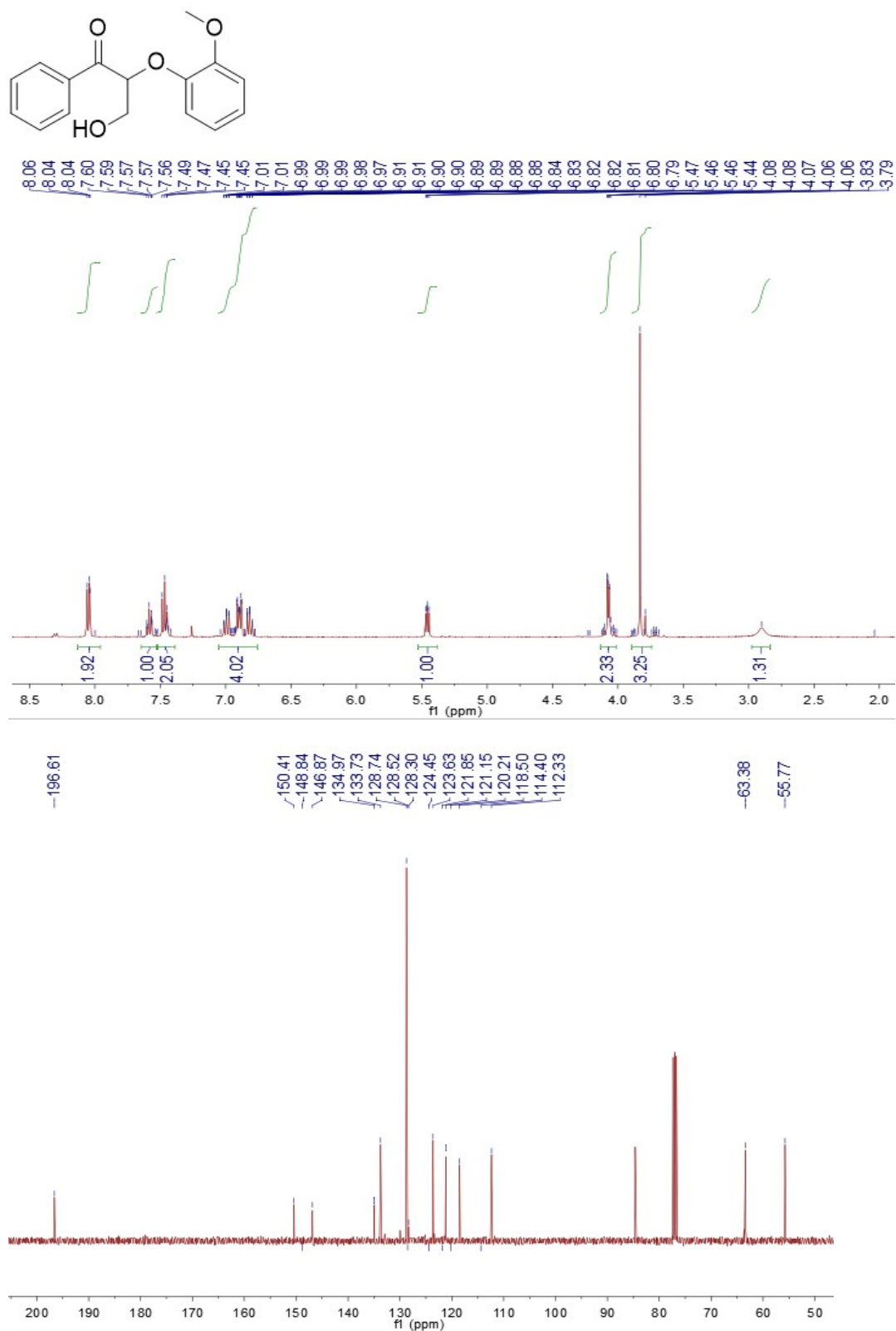


Figure S15 ¹H (top) and ¹³C (bottom) NMR spectra of 3-hydroxy-2-((6-methoxycyclohexa-1,5-dien-1-yl)oxy)-1-phenylpropan-1-one

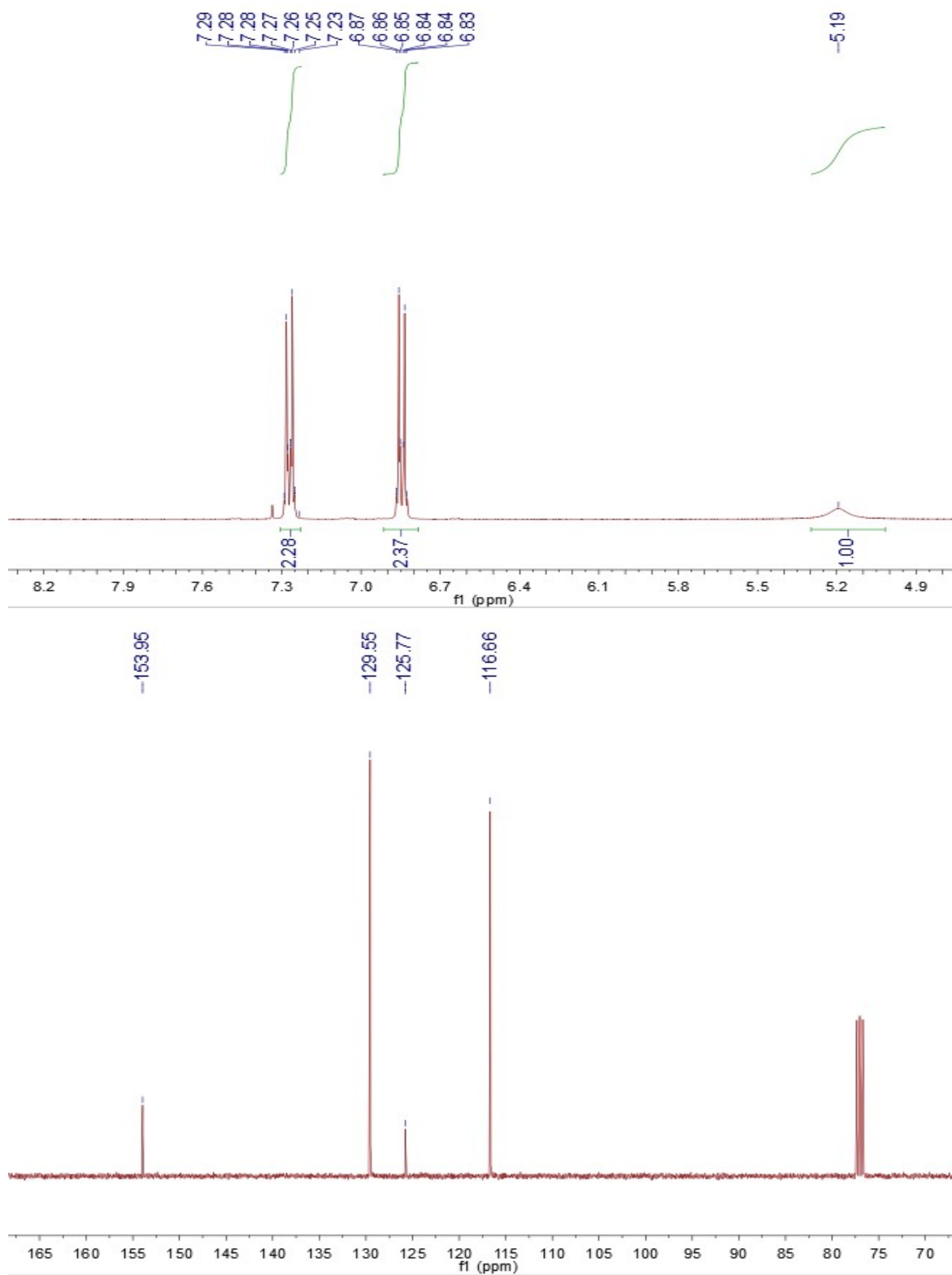
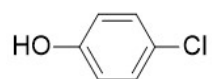


Figure S16 ¹H (top) and ¹³C (bottom) NMR spectra of 4-chlorophenol

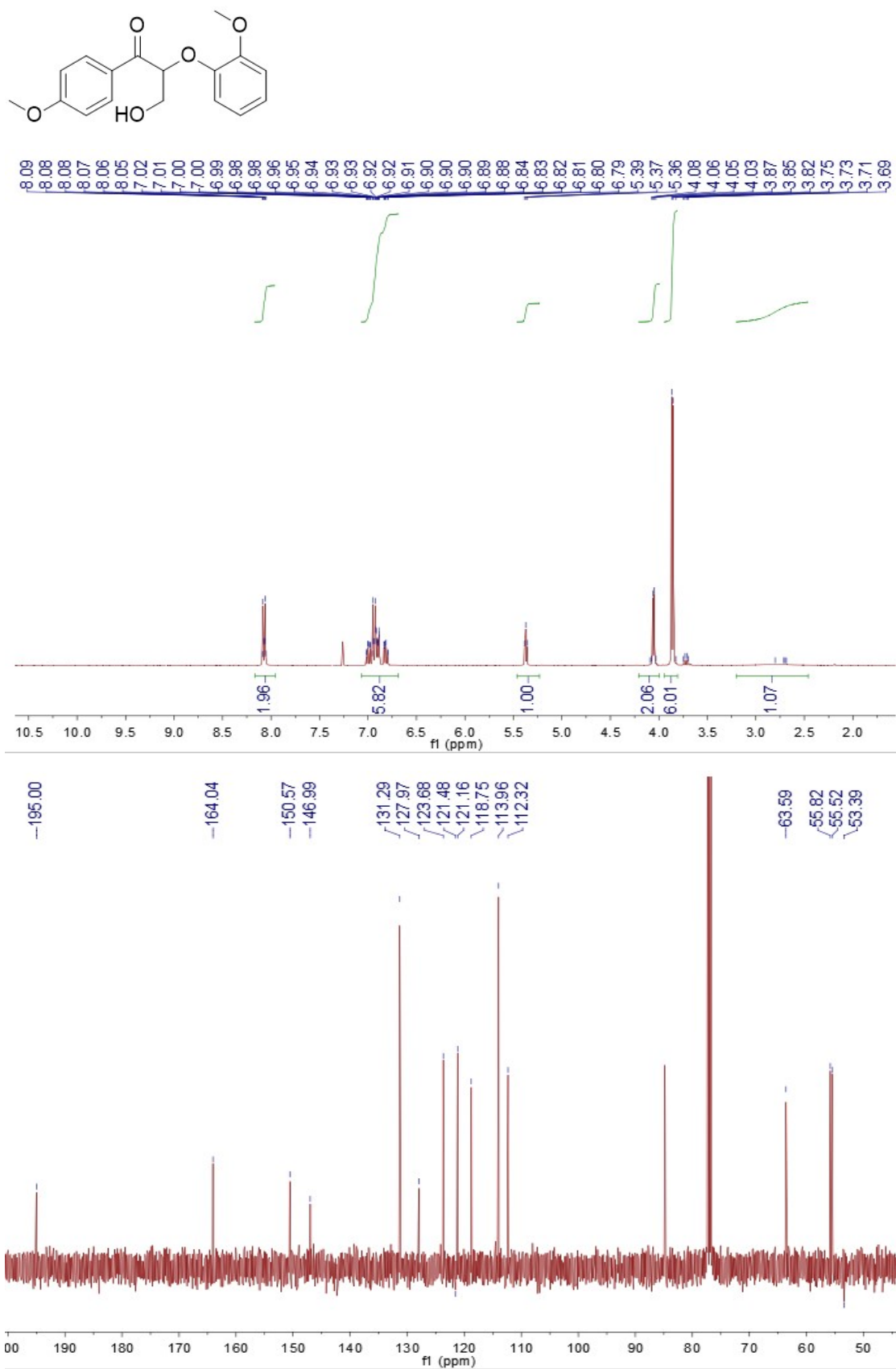


Figure S17 ¹H (top) and ¹³C (bottom) NMR spectra of 3-hydroxy-2-((6-methoxycyclohexa-1,5-dien-1-yl)oxy)-1-(4-methoxyphenyl)propan-1-one

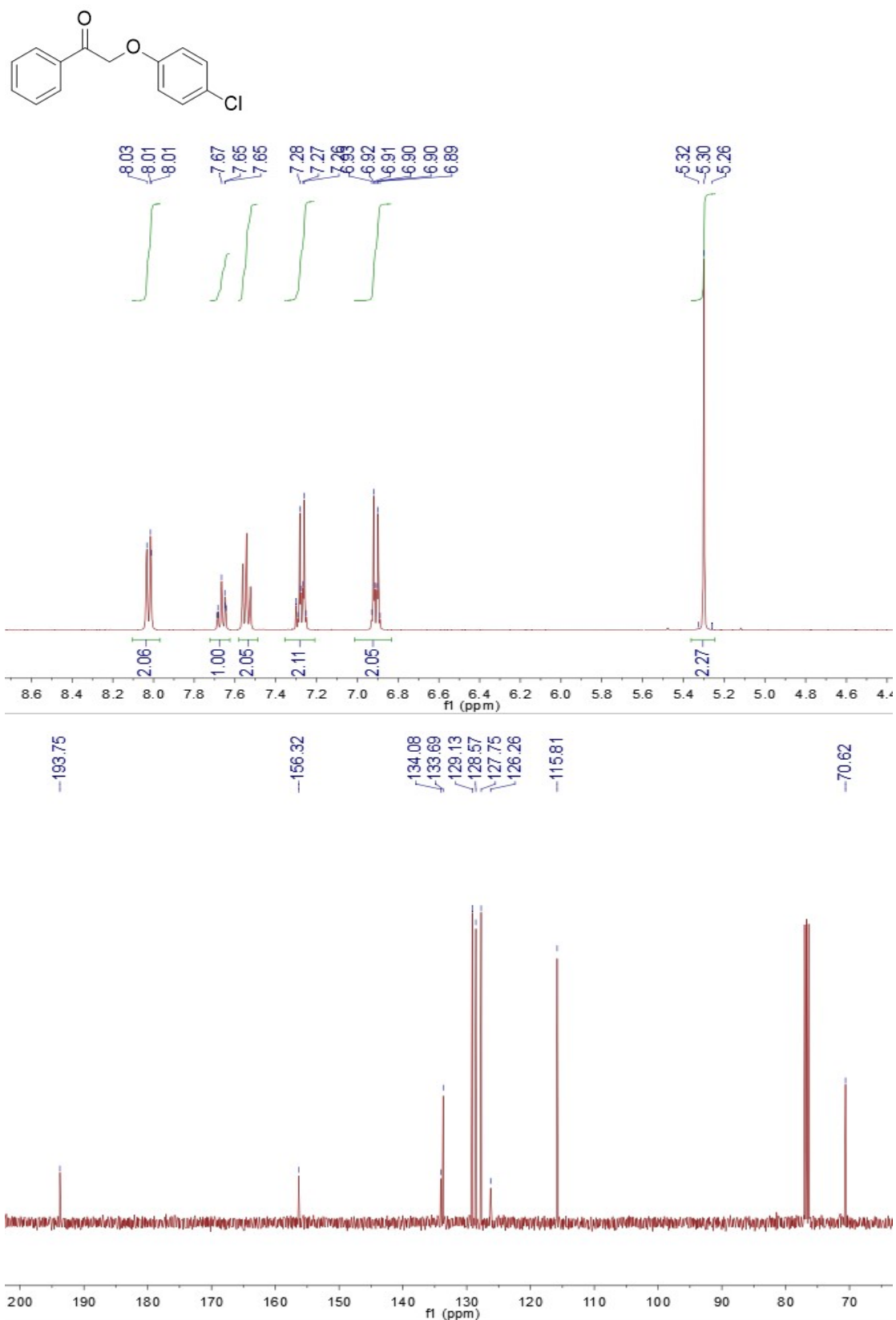


Figure S18 ¹H (top) and ¹³C (bottom) NMR spectra of 2-((4-chlorocyclohexa-1,5-dien-1-yl)oxy)-1-phenylethan-1-one

7. References

S1. Kim, S. A.; Kim, S. E.; Kim, Y. K.; Jang, H. Y. Copper-Catalyzed Oxidative Cleavage of the C-C Bonds of β -Alkoxy Alcohols and β -1 Compounds. *ACS Omega* 2020, **5**, 31684-31691.