Electronic Supplementary Material (ESI) for Green Chemistry.

Supporting Information

Hydrogen bonding network enabled Brønsted acid catalyzed Friedel-Crafts reactions: A green approach to access unsymmetrical diaryl- and triarylmethanes

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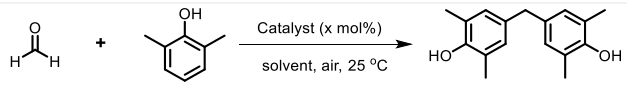
1. General Information:

All reagents and solvents were of pure analytical grade. Analytical thin-layer chromatography (TLC) was carried out using 0.2 mm commercial silica gel plates (silica gel 60, F254, EMD Chemical). The vials (Wheaton® Standard Scintillation Vials, 1 dram, 15x45 mm with PTFE lined cap attached) were purchased from DAIHAN and dried in an oven overnight. High-resolution mass spectra (HRMS) were recorded on a mass spectrometer using electrospray ionization-time of-flight (ESITOF) reflectron experiments. Aldehydes, *p*TSA•H_2O, and hexafluoroisopropanol were purchased from Sigma-Aldrich, TCI, (or) Alfa Aesar. All reactions were run in flame- (or) oven-dried glassware under an atmosphere of N_2 gas with dry solvents unless otherwise stated. ^{1}H-NMR and ^{13}C-NMR were recorded on 400 MHz, and 500 MHz spectrometers, using $CDCl_3$ (or) DMSO-d_6 solution, the chemical shifts are reported as parts per million (ppm) referenced to residual protium (or) carbon of the solvents; $CDCl_3$ δ H (7.26 ppm) or DMSO-d_6 δ H (2.50 ppm) and $CDCl_3$ δ C (77.16 ppm) (or) DMSO-d_6 δ C (39.52 ppm). Coupling constants are reported in Hertz (Hz). Data for ^{1}H NMR spectra are reported as follows: chemical shift (ppm, referenced to protium; s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sext = sextet, dd = doublet of doublets, td = triplet of doublets, ddd = doublet of doublet of doublets, m = multiplet, coupling constant (Hz), and integration).

2. Optimization studies:

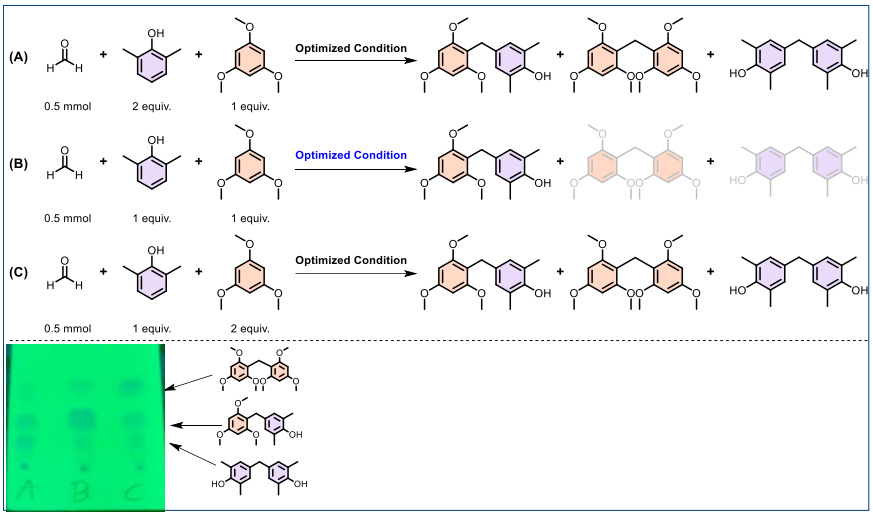
Table S1: Optimization of reaction conditions.



E. no	Catalyst	Catalyst (X mol%)	Solvent	Yield (%)[a]
1	BF_3•OEt_2	10	$CHCl_3$	70
2	I_2	10	$CHCl_3$	52
3	(*L*)-Proline	10	$CHCl_3$	NR
4	TFA	10	$CHCl_3$	48
5	*p*TSA•H_2O	10	$CHCl_3$	81
6	*p*TSA•H_2O	5	$CHCl_3$	78
7	*p*TSA•H_2O	5	-	30
8	*p*TSA•H_2O	5	H_2O	trace
9	*p*TSA•H_2O	5	MeOH	trace
10	*p*TSA•H_2O	5	Ethanol	trace
11	*p*TSA•H_2O	5	CF_3CH_2OH	72
12	*p*TSA•H_2O	5	HFIP	98%
13	-	-	HFIP	trace

Reaction Conditions: Formaldehyde (0.5 mmol), 2,6-dimethylphenol (2.1 equiv.) in 0.5 ml solvent at 25 °C for 12-14 h.

Scheme S1. Variation of stoichiometry of arene nucleophiles.

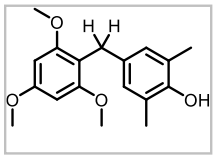


3. General procedure for synthesis of unsymmetrical triarylmethanes/diarylmethanes (GP1): To a 5 ml round bottom flask equipped with a magnetic stir bar was sequentially added the two different aryl nucleophiles (0.55 mmol, 1.1 equiv. each), aldehyde (0.5 mmol, 1.0 equiv.) and *p*TSA•H_2O (5 mol%, 4.75 mg), the in 0.5 ml HFIP solvent at room temperature (25 ^{0}C). Further the reaction mixture was stirred at room temperature for 10-12 h. The completion of the reaction was monitored by a TLC plate in 20% EtOAc in hexane. The solvent was removed under reduced pressure to get the crude product. Further, column chromatography was carried out over silica gel (100-200) mesh using mixture of hexane and ethyl acetate to purify the crude product. The product was characterized and identified by analysing spectral data (^{1}H, ^{13}C, ^{19}F-NMR, and HRMS).

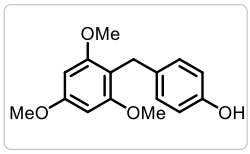
4. General procedure for Intra & inter-molecular Friedel-Crafts arylation products (GP2): To a 5 ml round bottom flask equipped with a magnetic stir bar was sequentially added the aldehyde (0.5 mmol, 1.0 equiv.), *p*TSA•H_2O (5 mol%, 4.75 mg), the aryl nucleophiles (0.55 mmol, 1.1 equiv. each) in 0.5 ml HFIP solvent at room temperature (25 ^{0}C). Further the reaction mixture was stirred at room temperature for 10-12 h. The completion of the reaction was monitored by a TLC plate in 20% EtOAc in hexane. The solvent was removed under reduced pressure to get the crude product. Further, column chromatography was carried out over silica gel (100-200) mesh using mixture of hexane and ethyl acetate to purify the crude product. The product was characterized and identified by analyzing spectral data (^{1}H, ^{13}C, ^{19}F-NMR, and HRMS).

5. Analytical data of synthesized unsymmetrical TRAMs (1-36):

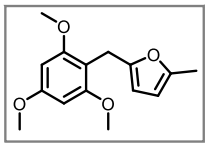
2,6-Dimethyl-4-(2,4,6-trimethoxybenzyl)phenol (1)[1] Prepared according to the general procedure (GP1); Yellow solid; m.p = 165 °C; 120.4 mg, 81%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.87 (s, 2H), 6.20 (s, 2H), 4.46 (s, 1H), 3.85 (s, 5H), 3.83 (s, 6H), 2.21 (s, 6H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 159.3, 158.7, 149.8, 133.5, 128.3, 122.4, 110.6, 90.6, 55.6, 55.1, 27.2, 15.8.



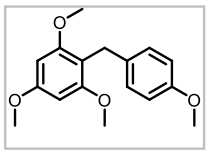
4-(2,4,6-Trimethoxybenzyl)phenol (2) Prepared according to the general procedure (GP1); Colourless liquid, 101.5mg, 74%; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.10 (d, 2H), 6.70 (d, 2H), 6.11 (s, 2H), 4.70 (s, 1H), 3.80 (s, 2H), 3.75 (s, 3H), 3.74 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 159.5, 158.8, 153.2, 134.5, 129.5, 114.8, 110.7, 90.7, 55.8, 55.4, 27.4; Calculated for **HRMS** (ESI): $C_{16}H_{18}O_4Na$ $[M+Na]^+$: 297.1097, Found: 297.1103.



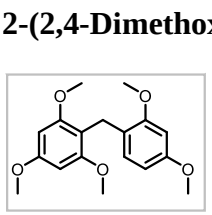
2-Methyl-5-(2,4,6-trimethoxybenzyl)furan (3)[2] Prepared according to the general procedure (GP1); Sticky oil, 102.3 mg, 78%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.17 (s, 1H), 6.11 (s, 1H), 5.79 (s, 1H), 5.63 (s, 1H), 3.89 (s, 2H), 3.83 (s, 3H), 3.80 (s, 6H), 2.25 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 159.9, 159.1, 153.8, 149.7, 107.4, 105.9, 105.0, 90.8, 55.9, 55.3, 21.6, 13.6.



1,3,5-Trimethoxy-2-(4-methoxybenzyl) benzene (4) Prepared according to the general procedure (GP1); White solid, 109.5 mg, 76%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.07 (d, *J* = 8.6 Hz, 2H), 6.68 (d, *J* = 8.6 Hz, 2H), 6.06 (s, 2H), 3.78 (s, 2H), 3.72 (s, 3H), 3.71 (s, 6H), 3.67 (s, 3H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 159.6, 158.8, 157.4, 134.5, 129.3, 113.4, 110.7, 90.6, 55.7, 55.3, 55.2, 27.4; Calculated for **HRMS** (ESI): $C_{16}H_{18}O_2Na$ $[M+Na]^+$: 265.1199, Found: 265.1197.



2-(2,4-Dimethoxybenzyl)-1,3,5-trimethoxybenzene (5) Prepared according to the general procedure (GP1); Colourless liquid, 114.5 mg, 72%; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.40 (d, 1H), 6.30 (d, 1H), 6.18 (dd, 1H), 6.08 (s, 2H), 3.72 (s, 2H), 3.70 (s, 6H), 3.64 (m, 9H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ = 159.7, 159.4, 158.6, 158.2, 127.9, 122.2, 108.9, 103.5, 98.2, 90.7, 55.8, 55.4, 55.3, 55.2, 21.5



4-Hydroxy-3-(2,4,6-trimethoxybenzyl)-2*H*-chromen-2-one (6) Prepared according to the general procedure (GP1); Sticky oil, 152.3 mg, 89%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.85 (s, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.35 (dd, *J* = 11.3, 4.1 Hz, 1H), 7.15 (d, *J* = 8.3 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.10 (s, 2H), 3.83 (d, *J* = 3.1 Hz, 8H), 3.70 (s, 3H), 1.34 (s, 1H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 163.27, 160.68, 160.31, 158.08, 152.37, 131.23, 123.41, 123.04, 116.24, 116.12, 107.25, 104.06, 91.15, 56.07, 55.41, 16.85.

4-(2,4-Dimethoxybenzyl)-2,6-dimethylphenol (7) Prepared according to the general procedure (GP1); Pale yellow liquid, 107.5 mg, 79%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.82 (s, 1H), 6.81 (s, 2H), 6.45 (s, 2H), 4.47 (s, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.75 (s, 2H), 2.20 (s, 6H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 156.5, 156.0, 150.1, 133.3, 132.2, 128.9, 122.7, 121.7, 117.9, 95.5, 56.1, 55.4, 34.0, 16.3, 15.1.

4-(4-Methoxybenzyl)-2,6-dimethylphenol (8) Prepared according to the general procedure (GP1); Yellow liquid, 93.3 mg, 77%; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.98 (d, 2H), 6.74 (d, 2H), 6.68 (s, 2H), 4.45 (s, 1H), 3.67 (m, 5H), 2.10 (s, 6H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 157.9, 150.5, 134.0, 133.2, 129.7, 129.0, 123.0, 113.9, 55.3, 40.2, 16.0.

4-Hydroxy-3-(4-hydroxy-3,5-dimethylbenzyl)-2*H*-chromen-2-one (9) Prepared according to the general procedure (GP1); Colourless liquid, 130.3 mg, 88%; δ **^{1}H NMR** (500 MHz, DMSO-d_6) δ 7.87 (d, *J* = 7.9 Hz, 1H), 7.58 – 7.51 (m, 1H), 7.29 (dd, *J* = 14.8, 7.8 Hz, 2H), 6.72 (s, 2H), 3.64 (s, 2H), 2.02 (s, 6H); **^{13}C{^{1}H} NMR** (126 MHz, DMSO-d_6) δ 170.3, 161.2, 152.1, 151.3, 132.4, 130.7, 128.3, 124.7, 124.5, 123.6, 116.7, 105.4, 85.8, 28.4, 16.7.

2,6-Di-*tert*-butyl-4-(4-methoxybenzyl)phenol (10) Prepared according to the general procedure (GP1); Pale yellow solid; m.p = 122 °C; 122.4 mg, 79%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.6 Hz, 2H), 6.97 (s, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 5.04 (s, 1H), 3.84 (s, 2H), 3.77 (s, 3H), 1.40 (s, 18H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 157.8, 152.0, 135.8, 134.0, 132.1, 129.8, 125.4, 113.8, 55.3, 41.0, 34.4, 30.4.

2,6-Dimethyl-4-(2,4,5-trimethoxybenzyl)phenol (11) Prepared according to the general procedure (GP1); Pale yellow liquid ; 114.9 mg, 76%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.82 (s, 8H), 6.67 (s, 4H), 6.57 (s, 5H), 4.57 (s, 4H), 3.91 (s, 13H), 3.82 (s, 11H), 3.81 (s, 7H), 3.80 (s, 11H), 2.22 (s, 24H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 151.5, 150.3, 147.9, 143.0, 132.9, 128.8, 122.8, 121.8, 114.7, 98.1, 56.7, 56.6, 56.2, 34.3, 16.0.

5-Methoxy-3-((1-methyl-1*H*-indol-3-yl)methyl)-1*H*-indole (12)[2] Prepared according to the general procedure (GP1); Colourless liquid; 116.1 mg, 80%; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 1H), 7.22 (dd, *J* = 9.3, 5.9 Hz, 2H), 7.08 (dd, *J* = 14.8, 7.7 Hz, 2H), 6.91 (s, 1H), 6.85 (d, *J* = 7.7 Hz, 1H), 6.76 (s, 1H), 4.19 (s, 2H), 3.81 (s, 3H), 3.69 (s, 3H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 153.9, 137.2, 131.6, 128.0, 127.9, 127.0, 123.1, 121.4, 119.3, 118.6, 115.6, 114.1, 112.1, 111.7, 109.1, 101.1, 56.0, 32.6, 21.1.

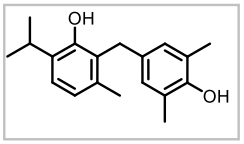
2,6-Dimethyl-4-((2-phenyl-3a,7a-dihydro-1*H*-indol-3-yl)methyl)phenol (13)[1] Prepared according to the general procedure (GP1); Colourless liquid; 115.3 mg, 70%; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.51 – 7.46 (m, 2H), 7.42 – 7.27 (m, 5H), 7.18 – 7.11 (m, 1H), 7.01 (t, 1H), 6.78 (m, 2H), 4.42 (s, 1H), 4.10 (s, 2H), 2.10 (s, 6H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 150, 136, 135, 133, 129, 128.9, 128.4, 127.9, 127.8, 123.1, 122.4, 119.9, 111.8, 110.9, 29.7, 16.1.

1-(4-Hydroxy-3,5-dimethylbenzyl)naphthalen-2-ol (14) Prepared according to the general procedure (GP1); Colourless oil; 104.4 mg, 75%; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.70 (s, 1H), 7.95 (s, 1H), 7.88 (d, 1H), 7.79 (d, 1H), 7.71 (d, 1H), 7.41 (t, 1H), 7.32 - 7.20 (m, 2H), 6.81 (s, 2H), 4.24 (s, 2H), 2.10 (s, 6H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 153.0, 151.5, 133.2, 132.1, 128.0, 128.8, 128.4, 128.1, 126.5, 124.1, 123.2, 122.0, 119.1, 118.1, 29.4, 17.0.

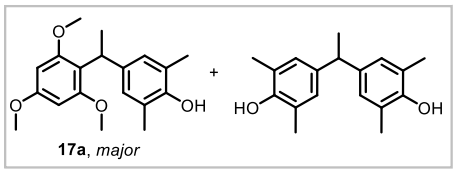
1-(4-Methoxybenzyl)naphthalen-2-ol (15) Prepared according to the general procedure (GP1); Pale yellow solid; m.p = 122 °C; 95.04 mg, 72%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.6 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 1H), 7.47 – 7.43 (m, 1H), 7.36 – 7.32 (m, 1H), 7.15 – 7.12 (m, 2H), 6.83 – 6.75 (m, 2H), 5.12 (s, 1H), 4.39 (s, 2H), 3.75 (s, 3H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 158.0, 151.3,

133.7, 132.0, 131.9, 129.8, 129.5, 129.2, 128.6, 128.4, 126.7, 123.3, 123.2, 118.5, 118.0, 114.1, 55.3, 29.8.

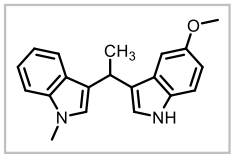
2-(4-Hydroxy-3,5-dimethylbenzyl)-6-isopropyl-3-methylphenol (16) Prepared according to the general procedure (GP1); Colourless liquid; 108.1 mg, 76%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.02 (d, *J* = 7.8 Hz, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 6.77 (s, 2H), 4.78 (s, 1H), 4.54 (s, 1H), 3.91 (s, 2H), 3.20 – 3.09 (m, 1H), 2.30 (s, 3H), 2.17 (s, 6H), 1.22 (d, *J* = 6.9 Hz, 6H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 151.6, 150.8, 135.1, 132.5, 130.4, 128.2, 125.1, 123.8, 123.5, 122.4, 31.8, 27.0, 22.8, 20.0, 16.0.



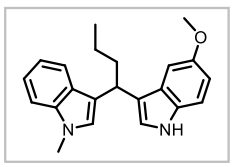
2,6-Dimethyl-4-(2,4,6-trimethoxybenzyl)phenol (17) Prepared according to the general procedure (GP1); Pale yellow liquid; 123.2 mg, 78%; (*3:1*); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.87 (s, 2H), 6.12 (s, 2H), 4.62 (q, *J* = 7.3 Hz, 1H), 3.78 (s, 3H), 3.70 (s, 6H), 2.17 (s, 6H), 1.59 (d, *J* = 7.3 Hz, 3H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 159.2, 159.0, 149.6, 138.2, 127.6, 127.5, 122.7, 121.9, 116.1, 91.6, 55.8, 55.2, 32.3, 18.4, 16.1, 16.0.



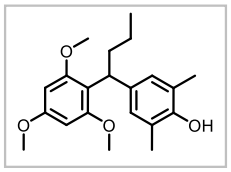
5-Methoxy-3-(1-(1-methyl-1*H*-indol-3-yl)ethyl)-1*H*-indole (18)[2] Prepared according to the general procedure (GP1); Brown solid; m.p = 149 °C; 127.1 mg, 83%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 1H), 7.14 – 7.08 (m, 2H), 6.97 – 6.92 (m, 2H), 6.78 (d, *J* = 1.4 Hz, 1H), 6.74 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.66 (s, 1H), 4.53 (q, *J* = 7.0 Hz, 1H), 3.67 (s, 3H), 3.58 (s, 3H), 1.70 (d, *J* = 7.1 Hz, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 153.7, 137.4, 131.9, 127.3, 126.1, 122.1, 121.6, 121.3, 120.1, 119.8, 118.5, 111.8, 111.7, 109. 101.9, 56.0, 32.6, 28.1, 21.9.



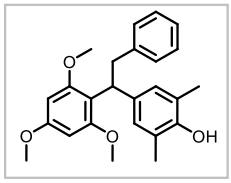
5-Methoxy-3-(1-(1-methyl-1*H*-indol-3-yl)butyl)-1*H*-indole (19) Prepared according to the general procedure (GP1); Brown sticky liquid; 120.4 mg, 72%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.22 – 7.14 (m, 2H), 7.11 (dd, *J* = 14.5, 8.1 Hz, 2H), 6.98 – 6.94 (m, 2H), 6.90 (s, 1H), 6.75 (s, 2H), 4.36 (t, *J* = 7.1 Hz, 1H), 3.69 (s, 3H), 3.62 (s, 3H), 2.10 (dd, *J* = 7.0, 3.6 Hz, 2H), 1.35 (dd, *J* = 14.6, 7.1 Hz, 2H), 0.88 (t, *J* = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 153.6, 137.3, 131.8, 127.7, 127.6, 126.2, 122.2, 121.3, 120.5, 119.7, 119.0, 118.4, 111.6, 111.6, 109.1, 102.0, 77.3, 77.0, 76.8, 56.0, 38.3, 33.6, 32.6, 21.4, 14.2.



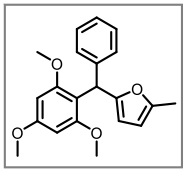
2,6-Dimethyl-4-(1-(2,4,6-trimethoxyphenyl)butyl)phenol (20) Prepared according to the general procedure (GP1); Pale yellow liquid; 132.6 mg, 77%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.92 (s, 2H), 6.87 (s, 1H), 6.11 (s, 2H), 4.48 – 4.43 (t, 2H), 3.77 (s, 3H), 3.73 (d, *J* = 10.8 Hz, 6H), 2.17 (s, 6H), 1.99 (ddd, *J* = 9.3, 7.6, 4.6 Hz, 1H), 1.96 – 1.85 (m, 1H), 1.25 – 1.17 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 159.2, 149.7, 137.7, 128.2, 127.8, 122.8, 121.9, 91.5, 55.8, 55.2, 38.4, 34.9, 21.7, 16.1, 14.3; Calculated for **HRMS** (ESI): $C_{21}H_{28}O_4Na$ $[M+Na]^+$: 367.1880, Found: 367.1886.



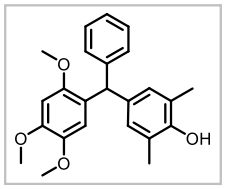
2,6-Dimethyl-4-(2-phenyl-1-(2,4,6-trimethoxyphenyl)ethyl)phenol (21) Prepared according to the general procedure (GP1); Pale yellow sticky oil; 147.2 mg, 75%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.14 – 7.07 (m, 2H), 7.03 (d, *J* = 6.0 Hz, 3H), 6.96 (s, 2H), 6.05 (s, 2H), 4.85 (s, 1H), 4.42 (s, 1H), 3.73 (s, 3H), 3.57 (s, 6H), 3.54 (d, 1H), 3.36 (d, *J* = 12.7, 1H), 2.18 (s, 6H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 159.3, 149.9, 142.2, 136.9, 129.0, 128.2, 128.0, 127.7, 125.3, 122.0, 113.9, 91.6, 55.9, 55.2, 40.4, 38.7, 16.1; Calculated for **HRMS** (ESI): $C_{25}H_{28}O_4Na$ $[M+Na]^+$: 415.1880, Found: 415.1871.



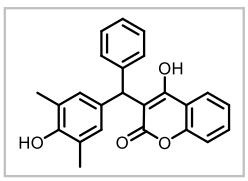
2-Methyl-5-(phenyl(2,4,6-trimethoxyphenyl)methyl)furan (22) Prepared according to the general procedure (GP1); Radish oil; 142.1 mg, 84%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.17 (dd, *J* = 31.1, 4.1 Hz, 5H), 6.14 (s, 2H), 5.94 (s, 1H), 5.85 (s, 1H), 5.78 (s, 1H), 3.80 (s, 3H), 3.64 (s, 6H), 2.24 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 160.2, 159.1, 155.3, 150.0, 143.1, 128.4, 127.6, 125.6, 112.0, 107.3, 105.9, 91.6, 55.9, 55.3, 39.6, 13.7. Calculated for **HRMS** (ESI): $C_{21}H_{22}O_4Na$ $[M+Na]^+$: 361.1416, Found: 361.1426.



2,6-Dimethyl-4-(phenyl(2,4,5-trimethoxyphenyl)methyl)phenol (23) Prepared according to the general procedure (GP1); Pale yellow oil; 145.7 mg, 77%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 9.3, 5.6 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.13 (d, *J* = 7.3 Hz, 2H), 6.73 (s, 2H), 6.58 (s, 1H), 6.51 (s, 1H), 5.79 (s, 1H), 4.66 (s, 1H), 3.92 (s, 3H), 3.72 (s, 3H), 3.69 (s, 3H), 2.20 (s, 6H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 151.46, 150.47, 148.11, 144.72, 142.79, 135.51, 129.46, 129.28, 128.07, 125.89, 124.93, 122.67, 114.99, 98.20, 56.95, 56.76, 56.12, 48.33, 16.06.

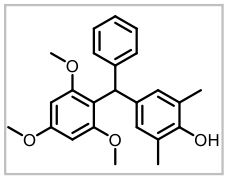


4-Hydroxy-3-((4-hydroxy-3,5-dimethylphenyl)(phenyl)methyl)-2*H*-chromen-2-one (24) Prepared according to the general procedure (GP1); White solid; m.p = 170-172 °C; 162.9 mg, 88%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.56 – 7.51 (m, 1H), 7.37 (t, *J* = 7.3

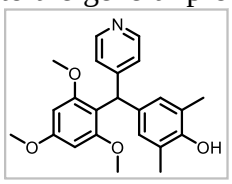


Hz, 2H), 7.32 (dd, *J* = 7.8, 2.8 Hz, 2H), 7.28 – 7.26 (m, 2H), 6.84 (s, 2H), 6.50 (s, 1H), 5.82 (s, 1H), 4.83 (s, 1H), 2.19 (s, 6H); **$^{13}C\{^{1}H\}$ NMR** (126 MHz, $CDCl_3$) δ 163.3, 160.8, 152.6, 152.0, 140.2, 132.0, 131.3, 129.2, 128.9, 128.8, 127.6, 124.4, 123.9, 123.2, 116.5, 116.1, 107.9, 46.7, 16.10

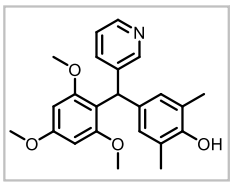
4,4'-(Phenylmethylene)bis(2,6-dimethylphenol) (25) Prepared according to the general procedure (GP1); Pale yellow solid; m.p = 122 °C; 162.7 mg, 86%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22 – 7.08 (m, 5H), 6.83 (s, 2H), 6.15 (s, 2H), 5.92 (s, 1H), 4.43 (s, 1H), 3.79 (s, 3H), 3.58 (s, 6H), 2.17 (s, 6H); **$^{13}C\{^{1}H\}$ NMR** (126 MHz, $CDCl_3$) δ 160.1, 159.4, 150.3, 145.3, 135.4, 129.7, 129.1, 127.6, 125.3, 122.4, 114.4, 92.1, 56.0, 55.4, 44.6, 16.3. Calculated for **HRMS** (ESI): $C_{24}H_{27}O_4$ $[M+H]^+$: 379.1904, Found: 379.1904.



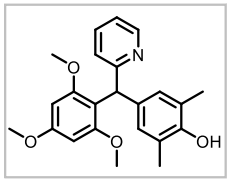
2,6-Dimethyl-4-(pyridin-4-yl(2,4,6-trimethoxyphenyl)methyl)phenol (26) Prepared according to the general procedure (GP1); Sticky oil; m.p = 122 °C; 136.6 mg, 72%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.59 (d, *J* = 6.6 Hz, 2H), 7.79 (d, *J* = 8.1 Hz, 2H), 7.49 (d, *J* = 6.0 Hz, 2H), 7.12 (d, *J* = 7.9 Hz, 2H), 6.74 (s, 2H), 6.13 (s, 2H), 5.91 (s, 1H), 4.47 (s, 1H), 3.80 (s, 3H), 3.60 (s, 6H), 2.15 (s, 6H); **$^{13}C\{^{1}H\}$ NMR** (126 MHz, $CDCl_3$) δ 168.9, 161.2, 158.4, 152.1, 141.8, 140.2, 139.9, 129.2, 128.8, 126.0, 124.0, 109.8, 91.3, 55.5, 45.4, 21.3, 16.5. Calculated for **HRMS** (ESI): $C_{24}H_{27}O_4$ $[M+H]^+$: 379.1904, Found: 379.1904.



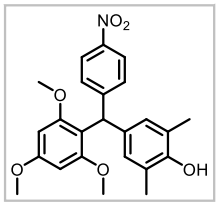
2,6-Dimethyl-4-(pyridin-3-yl(2,4,6-trimethoxyphenyl)methyl)phenol (27) Prepared according to the general procedure (GP1); Colourless liquid; 147.9 mg, 78%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.41 (s, 1H), 8.38 (d, *J* = 4.1 Hz, 1H), 7.49 (d, *J* = 7.9 Hz, 1H), 7.16 (dd, *J* = 7.8, 4.8 Hz, 1H), 6.81 (s, 2H), 6.17 (s, 2H), 5.94 (s, 1H), 3.83 (s, 3H), 3.72 (s, 1H), 3.64 (s, 6H), 2.20 (s, 6H); **$^{13}C\{^{1}H\}$ NMR** (126 MHz, $CDCl_3$) δ 160.2, 158.9, 150.5, 150.2, 146.0, 141.8, 140.8, 139.4, 136.6, 133.4, 129.1, 122.5, 91.5, 55.6, 55.3, 42.1, 16.2; Calculated for **HRMS** (ESI): $C_{23}H_{26}O_4Na$ $[M+Na]^+$: 380.1856, Found: 380.1861.



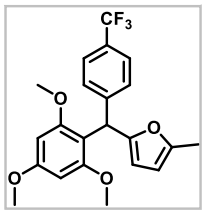
2,6-Dimethyl-4-(pyridin-2-yl(2,4,6-trimethoxyphenyl)methyl)phenol (28) Prepared according to the general procedure (GP1); Colourless sticky oil; 132.7 mg, 70%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.52 (d, *J* = 4.1 Hz, 1H), 7.50 (t, *J* = 7.1 Hz, 1H), 7.28 (s, 1H), 7.02 (t, *J* = 8.9 Hz, 2H), 6.88 (s, 2H), 6.16 (s, 2H), 6.00 (s, 1H), 3.80 (s, 3H), 3.58 (s, 6H), 2.20 (s, 6H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 165.6, 160.0, 158.9, 150.5, 148.3, 135.3, 133.6, 129.7, 123.1, 122.5, 120.0, 113.4, 91.7, 55.7, 55.3, 47.8, 16.2.



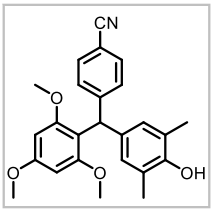
2,6-Dimethyl-4-((4-nitrophenyl)(2,4,6-trimethoxyphenyl)methyl)phenol (29) Prepared according to the general procedure (GP1); Pale yellow solid; m.p = 157 °C; 184.2 mg, 87%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 8.03 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.82 (s, 2H), 6.15 (s, 2H), 5.95 (s, 1H), 3.81 (s, 3H), 3.60 (s, 6H), 2.18 (s, 6H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.4, 158.7, 154.1, 150.5, 145.5, 133.2, 129.4, 129.2, 122.7, 122.6, 112.4, 91.5, 55.5, 55.3, 44.4, 16.2.



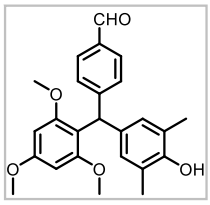
2-Methyl-5-((4-(trifluoromethyl)phenyl)(2,4,6-trimethoxyphenyl)methyl)furan (**30**) Prepared according to the general procedure (GP1); Colourless sticky oil; 154.4 mg, 76%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 6.18 (s, 2H), 6.02 (s, 1H), 5.91 (s, 1H), 5.85 (s, 1H), 3.84 (s, 3H), 3.68 (s, 6H), 2.29 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.45, 158.97, 153.91, 150.28, 147.49, 147.47, 128.60, 124.52, 124.48, 124.44, 124.41, 110.97, 107.86, 106.04, 91.48, 55.74, 55.27, 39.38, 13.65; **^{19}F NMR** (471 MHz, $CDCl_3$) δ -63.1.



4-((4-Hydroxy-3,5-dimethylphenyl)(2,4,6-trimethoxyphenyl)methyl)benzonitrile (31) Prepared according to the general procedure (GP1); Pale yellow sticky liquid; 169.4 mg, 84%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.2 Hz, 2H), 7.20 (d, *J* = 7.7 Hz, 2H), 6.80 (s, 2H), 6.14 (s, 2H), 5.91 (s, 1H), 4.58 (s, 1H), 3.80 (s, 3H), 3.59 (s, 6H), 2.18 (s, 6H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 160.4, 159.0, 151.8, 150.6, 133.4, 131.3, 129.5, 122.6, 119.7, 112.7, 108.6, 91.7, 55.7, 55.4, 44.8, 16.2.

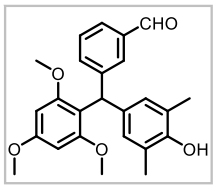


4-((4-Hydroxy-3,5-dimethylphenyl)(2,4,6-trimethoxyphenyl)methyl)benzaldehyde (32)



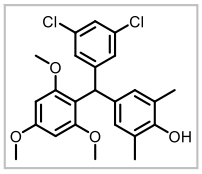
Prepared according to the general procedure (GP1); Pale yellow oil; 164.6 mg, 81%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.94 (s, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 6.83 (s, 2H), 6.15 (s, 2H), 5.95 (s, 1H), 4.60 (s, 1H), 3.81 (s, 3H), 3.59 (s, 6H), 2.19 (s, 6H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 193.3, 161.1, 159.8, 154.5, 151.4, 134.6, 130.4, 130.2, 130.0, 123.3, 113.9, 92.5, 56.5, 56.2, 45.7, 17.0.

3-((4-Hydroxy-3,5-dimethylphenyl)(2,4,6-trimethoxyphenyl)methyl)benzaldehyde (33)



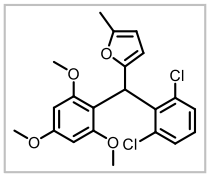
Prepared according to the general procedure (GP1); Pale yellow solid; m.p = 139 - 140 °C; 152.4 mg, 75%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.92 (s, 1H), 7.65 (s, 2H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 6.81 (s, 2H), 6.15 (s, 2H), 5.98 (s, 1H), 4.48 (s, 1H), 3.81 (s, 3H), 3.60 (s, 6H), 2.18 (s, 6H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 194.0, 161.1, 159.9, 151.3, 147.6, 136.8, 136.2, 135.0, 131.7, 130.3, 128.9, 127.2, 123.2, 114.0, 92.6, 56.6, 56.2, 45.1, 17.0.

4-((3,5-Dichlorophenyl)(2,4,6-trimethoxyphenyl)methyl)-2,6-dimethylphenol (34) Prepared



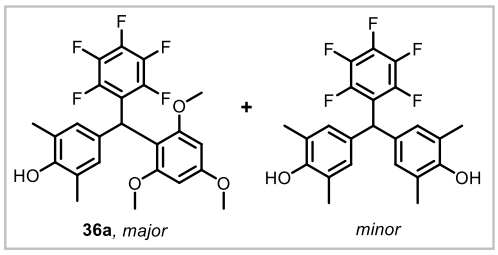
according to the general procedure (GP1); Pale yellow sticky solid; 187.8 mg, 84%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.15 (s, 1H), 7.04 (s, 2H), 6.83 (s, 2H), 6.18 (s, 2H), 5.86 (s, 1H), 4.55 (s, 1H), 3.85 (s, 3H), 3.66 (s, 6H), 2.22 (s, 6H); **^{13}C{^{1}H} NMR (**101 MHz, $CDCl_3$) δ 160.3, 158.9, 150.5, 149.3, 133.8, 133.4, 129.4, 127.4, 125.2, 122.4, 112.5, 91.7, 55.7, 55.3, 44.1, 16.1.

2-((2,6-Dichlorophenyl)(2,4,6-trimethoxyphenyl)methyl)-5-methylfuran (35) Prepared



according to the general procedure (GP1); Colourless sticky oil; 177.2 mg, 87%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.0 Hz, 2H), 7.01 (t, *J* = 8.0 Hz, 1H), 6.23 (s, 1H), 6.12 (s, 2H), 5.82 (d, *J* = 1.7 Hz, 1H), 5.53 (d, *J* = 1.7 Hz, 1H), 3.80 (s, 3H), 3.63 (s, 6H), 2.27 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 160.6, 158.9, 153.1, 150.5, 146.9, 133.9, 127.0, 125.8, 110.3, 108.2, 106.1, 91.4, 55.7, 55.3, 39.0, 13.7.

2,6-Dimethyl-4-((perfluorophenyl)(2,4,6-trimethoxyphenyl)methyl)phenol (36) Prepared



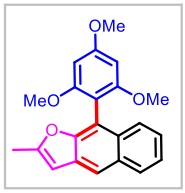
36a, *major* *minor*

according to the general procedure (GP1); Sticky oil; mixed 90% (2:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.83 (s, 2H), 6.74 (s, 2H), 6.24 (s, 1H), 6.22 (s, 2H), 4.72 (s, 1H), 3.88 (s, 3H), 3.73 (s, 6H), 2.22 (s, 6H); **^{13}C{^{1}H} NMR**

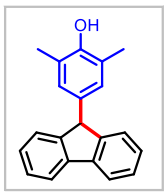
(126 MHz, $CDCl_3$) δ 160.7, 160.6, 159.2, 159.1, 151.2, 150.6, 128.7, 127.9, 123.1, 122.5, 91.2, 91.1, 55.7, 55.7, 55.3, 55.3, 16.1, 16.0, 15.9.

6. Intra & inter-molecular Friedel-Crafts arylation products (37-42):

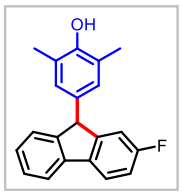
2-Methyl-9-(2,4,6-trimethoxyphenyl)naphtho[2,3-b]furan (37) Prepared according to the general procedure (**GP1**); Sticky solid; 135.7 mg, 78%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.94 – 7.79 (m, 2H), 7.56 (d, *J* = 8.5 Hz, 1H), 7.39 – 7.31 (m, 1H), 7.27 (ddd, *J* = 8.1, 6.7, 1.2 Hz, 1H), 6.45 (s, 1H), 6.34 (s, 2H), 3.90 (s, 3H), 3.59 (s, 6H), 2.40 (s, 3H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 161.6, 159.6, 158.0, 152.5, 130.7, 130.2, 130.0, 128.1, 125.8, 123.8, 123.3, 116.9, 112.2, 104.8, 102.3, 91.2, 77.3, 77.1, 76.8, 56.0, 55.4, 14.6; Calculated for **HRMS** (ESI): $C_{22}H_{20}O_4Na$ $[M+Na]^+$: 371.1253, Found: 371.1242.



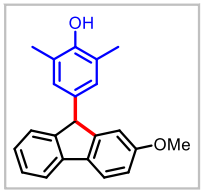
4-(9*H*-fluoren-9-yl)-2,6-dimethylphenol (38) Prepared according to the general procedure (**GP2**); Sticky solid; Yellow sticky liquid; 124.5 mg, 87%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.6 Hz, 2H), 7.28 (t, *J* = 7.4 Hz, 2H), 7.23 (d, *J* = 7.4 Hz, 2H), 7.16 (t, *J* = 7.3 Hz, 2H), 6.60 (s, 2H), 4.82 (s, 1H), 4.44 (s, 1H), 2.07 (s, 6H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 151.1, 148.4, 140.9, 133.0, 128.4, 127.3, 127.2, 125.3, 123.2, 119.8, 53.8, 16.0.



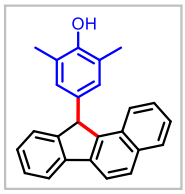
4-(2-Fluoro-9*H*-fluoren-9-yl)-2,6-dimethylphenol (39)[xx] Prepared according to the general procedure (**GP2**); Pale yellow sticky oil; 98.9 mg, 65%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 – 7.63 (m, 2H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.18 (s, 1H), 7.17 – 7.10 (m, 2H), 7.01 (td, *J* = 8.5, 1.9 Hz, 1H), 6.94 (s, 1H), 6.89 – 6.80 (m, 1H), 6.59 (s, 1H), 5.38 (s, 1H), 2.58 (s, 3H), 2.22 (s, 3H); **^{19}F NMR** (471 MHz, $CDCl_3$) δ = -75.6.



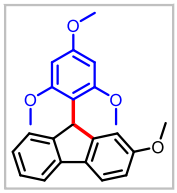
4-(2-Methoxy-9*H*-fluoren-9-yl)-2,6-dimethylphenol (40) Prepared according to the general procedure (**GP2**); Colourless sticky oil; 143.9 mg, 91%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 – 7.58 (m, 2H), 7.26 (t, *J* = 7.4 Hz, 1H), 7.19 (d, *J* = 6.3 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 6.85 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.78 (d, *J* = 1.9 Hz, 1H), 6.62 (s, 2H), 4.79 (s, 1H), 4.42 (s, 1H), 3.72 (s, 3H), 2.10 (s, 6H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 159.6, 151.1, 150.2, 148.0, 140.8, 133.9, 133.0, 128.4, 127.1, 126.1, 125.1, 123.2, 120.5, 119.0, 113.4, 110.7, 55.5, 53.8, 16.0.



4-(11*H*-Benzo[a]fluoren-11-yl)-2,6-dimethylphenol (41) Prepared according to the general procedure (GP2); Pale yellow sticky liquid; 137.9 mg, 82%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.96 (dt, *J* = 15.8, 8.2 Hz, 3H), 7.86 (d, *J* = 7.5 Hz, 1H), 7.78 (s, 1H), 7.40 (ddd, *J* = 20.4, 9.9, 4.3 Hz, 4H), 7.32 – 7.24 (m, 1H), 6.75 (s, 2H), 5.24 (s, 1H), 4.54 (s, 1H), 2.16 (s, 6H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 151.0, 149.7, 143.0, 140.8, 139.1, 133.5, 133.0, 130.6, 128.9, 128.7, 128.1, 127.0, 127.0, 126.3, 125.1, 124.9, 124.8, 123.4, 119.5, 118.5, 53.5, 16.0.

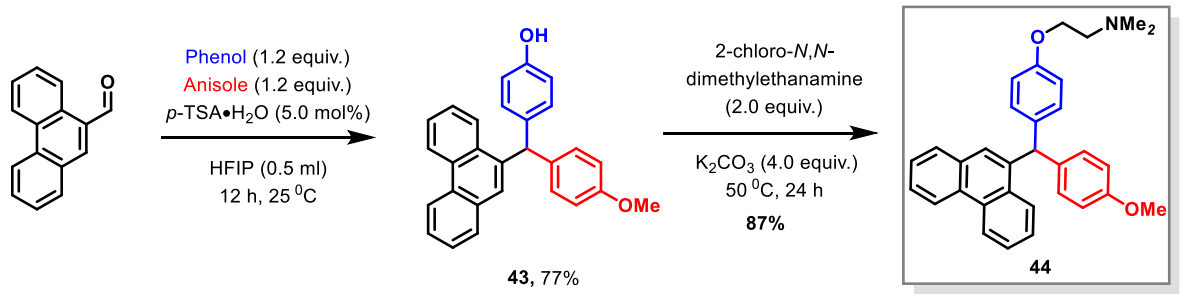


2-Methoxy-9-(2,4,6-trimethoxyphenyl)-9*H*-fluorene (42) Prepared according to the general procedure (**GP2**); Colourless sticky liquid; 159.4 mg, 88%; **^{1}H NMR** (500 MHz, DMSO-d_6) δ 7.76 (t, *J* = 7.4 Hz, 2H), 7.27 (t, *J* = 7.4 Hz, 1H), 7.11 (t, *J* = 7.3 Hz, 1H), 7.04 (d, *J* = 7.4 Hz, 1H), 6.90 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.62 (d, *J* = 1.1 Hz, 1H), 6.42 (d, *J* = 2.0 Hz, 1H), 6.05 (d, *J* = 1.9 Hz, 1H), 5.41 (s, 1H), 3.96 (s, 3H), 3.77 (s, 3H), 3.72 (s, 3H), 2.95 (s, 3H); **^{13}C{^{1}H} NMR** (126 MHz, DMSO-d_6) δ 160.4, 159.8, 159.4, 159.4, 150.6, 148., 140.9, 126.6, 125.9, 123.5, 119.3, 112.7, 109.5, 109.2, 93.0, 91.7, 56.9, 55.9, 55.7, 55.6, 43.7.

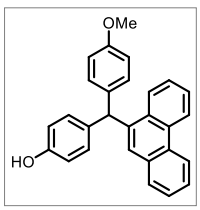


7. Applications (43-47):

Total synthesis of phenantharene based anti-breast cancer agent (44)

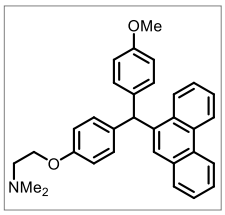


4-((4-Methoxyphenyl)(phenanthren-9-yl)methyl)phenol (43)[2] To a 5 ml round bottom flask equipped with a magnetic stir bar was sequentially added the phenanthrene-9-carbaldehyde (0.5 mmol, 1.0 equiv.), *p*TSA•H_2O (5.0 mol%, 4.75 mg), followed by the addition of phenol (0.55 mmol, 1.1 equiv.) and anisole (0.55 mmol, 1.1 equiv.) aryl nucleophiles together in 0.5 ml HFIP solvent at room temperature (25 °C). Further the reaction mixture was stirred at room temperature for 12 h. The completion of the reaction was monitored by a TLC plate in 30% EtOAc in hexane. The solvent was removed under reduced pressure to get the crude product. Further, column chromatography



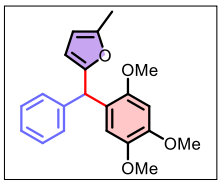
was carried out over silica gel (100-200) mesh using mixture of hexane and ethyl acetate to purify the crude product to afford the **43** as pale-yellow oil; 148.3 mg, 76%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.66 (d, *J* = 8.2 Hz, 2H), 8.00 (d, *J* = 8.3 Hz, 1H), 7.61 – 7.41 (m, 5H), 7.15 (s, 1H), 7.08 – 7.01 (m, 4H), 6.82 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 6.14 (s, 1H), 4.10 (d, 1H), 3.81 (s, 3H).

2-(4-((4-Methoxyphenyl)(phenanthren-9-yl)methyl)phenoxy)-*N*,*N*-dimethylethan-1-amine (44)[2] The above-obtained product **43** (100.0 mg, 0.25 mmol) was mixed with 2-chloro-*N*,*N*-



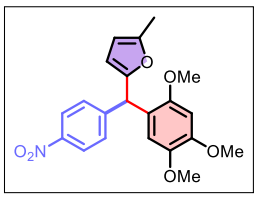
dimethylethan-1-amine hydrochloride (0.51 mmol, 2.0 equiv.), K_2CO_3 (1.0 mmol, 4.0 equiv.) in acetone (3 mL). The reaction mixture was refluxed for 5-6 h and then acetone was removed under reduced pressure. Water (6-7 mL) was added and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the desired *anti-breast*-cancer agent (**44**) Waxy oil; 100.2 mg, 87%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.73 (dd, *J* = 30.5, 8.1 Hz, 2H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 7.7 Hz, 1H), 7.63 (t, *J* = 7.4 Hz, 2H), 7.54 (dd, *J* = 15.6, 7.8 Hz, 2H), 7.23 (t, *J* = 7.1 Hz, 1H), 7.17 (s, 1H), 7.11 (d, *J* = 7.8 Hz, 2H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 4H), 6.58 (s, 1H), 4.00 (d, *J* = 4.8 Hz, 2H), 3.81 (s, 3H), 2.44 (d, *J* = 2.9 Hz, 2H), 2.08 (s, 6H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 159.0, 156.2, 138.9, 135.1, 133.0, 131.6, 131.4, 130.8, 130.7, 130.5, 129.8, 128.6, 127.7, 127.6, 126.6, 126.5, 126.2, 126.0, 125.2, 122.9, 122.4, 120.6, 113.7, 112.0, 67.0, 58.1, 55.2, 45.8, 45.6.

2-Methyl-5-(phenyl(2,4,5-trimethoxyphenyl)methyl)furan (45) Prepared according to the



general procedure (**GP1**); Pale yellow sticky oil; 135.3 mg, 80%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.27 – 7.22 (m, 2H), 7.20 (d, *J* = 7.0 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 2H), 6.60 (s, 1H), 6.53 (s, 1H), 5.85 (s, 1H), 5.77 (s, 1H), 5.72 (d, *J* = 2.5 Hz, 1H), 3.87 (s, 3H), 3.73 (s, 3H), 3.71 (s, 3H), 2.24 (s, 3H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 155.08, 151.24, 151.20, 148.47, 142.98, 142.34, 128.60, 128.16, 126.31, 122.31, 114.05, 108.84, 105.84, 98.09, 56.84, 56.67, 56.14, 43.10, 13.67.

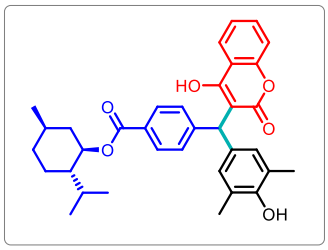
2-Methyl-5-((4-nitrophenyl)(2,4,5-trimethoxyphenyl)methyl)furan (46) Prepared according to



the general procedure (**GP1**); Pale yellow sticky oil; 164.8 mg, 86%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.7 Hz, 2H), 7.33 (d, *J* = 8.6 Hz, 2H), 6.58 (d, *J* = 18.6 Hz, 2H), 5.92 (d, *J* = 2.0 Hz, 1H), 5.85 (s, 1H), 5.80 (d, *J* = 2.9 Hz, 1H), 3.91 (s, 3H), 3.75 (d, *J* = 5.2 Hz, 6H), 2.28 (s, 3H);

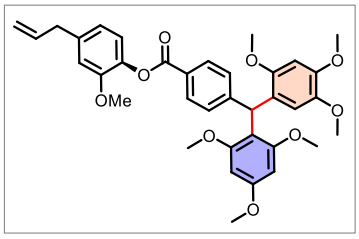
$^{13}C\{^1H\}$ (126 MHz, $CDCl_3$) δ 153.17, 151.90, 151.14, 150.22, 149.08, 143.12, 129.38, 123.46, 120.52, 113.77, 109.44, 106.10, 97.75, 56.77, 56.51, 56.15, 43.21, 13.63.

(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl-4-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)(4-hydroxy-3,5-dimethylphenyl)methyl)benzoate (47) Prepared according to the general procedure



(GP1); Colourless sticky oil; 78.7 mg, 71%; **^1H NMR** (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.1 Hz, 20H), 7.77 (d, *J* = 7.8 Hz, 10H), 7.57 (s, 11H), 7.38 (d, *J* = 8.0 Hz, 20H), 7.34 (d, *J* = 8.3 Hz, 10H), 7.33 – 7.26 (m, 15H), 6.84 (s, 19H), 5.88 (s, 9H), 4.95 (d, *J* = 4.1 Hz, 18H), 2.22 (s, 60H), 2.15 (d, *J* = 12.0 Hz, 12H), 1.98 (d, *J* = 6.8 Hz, 12H), 1.75 (d, *J* = 11.2 Hz, 24H), 1.57 (d, *J* = 9.6 Hz, 24H), 1.13 (dd, *J* = 19.4, 11.0 Hz, 25H), 0.97 – 0.87 (m, 82H), 0.81 (d, *J* = 6.7 Hz, 31H); **$^{13}C\{^1H\}$ NMR** (126 MHz, $CDCl_3$) δ 166.0, 163.2, 160.9, 152.9, 152.0, 144.9, 131.8, 130.6, 129.7, 128.8, 124.6, 124.0, 123.2, 116.8, 115.5, 107.6, 75.3, 47.3, 46.5, 40.8, 34.5, 31.4, 29.8, 26.7, 23.5, 21.8, 20.8, 16.5, 16.1, 14.0; Calculated for **HRMS** (ESI): $C_{35}H3_8O_6Na$ $[M+Na]^+$: 577.2566, Found: 577.2558.

4-Allyl-2-methoxyphenyl-4-((2,4,5-trimethoxyphenyl)(2,4,6-trimethoxyphenyl)methyl)benzoate (48) Prepared according to the general procedure (GP1);



Pale yellow sticky oil; 100.8 mg, 82%; **^1H NMR** (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.3 Hz, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.88 – 6.71 (m, 2H), 6.56 (s, 2H), 6.44 (s, 2H), 6.13 (s, 1H), 6.06 – 5.88 (m, 1H), 5.19 – 4.97 (m, 2H), 3.90 (s, 6H), 3.80 (s, 3H), 3.68 (s, 6H), 3.66 (s, 6H), 3.40 (d, *J* = 6.7 Hz, 2H); **$^{13}C\{^1H\}$ NMR** (126 MHz, $CDCl_3$) δ 161.10, 151.62, 151.18, 150.86, 150.30, 149.61, 148.37, 142.79, 138.96, 138.26, 137.14, 131.23, 130.08, 129.11, 127.77, 127.04, 123.34, 122.71, 120.78, 116.13, 114.57, 112.88, 98.22, 58.30, 56.85, 56.77, 56.75, 56.11, 55.92, 42.90, 40.13.

8. Mechanistic studies - reaction profile and mechanism

^1H NMR titration Studies with PhCHO and HFIP with gradual addition of *p*TSA•H_2O

In a NMR tube, HFIP (0.5 mmol., 52 µL) was added in $CDCl_3$ and **NMR-1** was recorded. In NMR tubes (2-8) benzaldehyde (0.5 mmol , 51µL) was dissolved in HFIP (1equiv., 53 µL) and stock solutions (2-8) were prepared. In these stock solutions subsequently, *p*TSA•H_2O was added incrementally (5 to 100 mol%) and recorded the respective NMR.

In 2nd NMR tube having stock solution of PhCHO and HFIP (0.5 mmol each) 5 mol% *p*TSA.H_2O (4.8 mg), 0.4 ml of $CDCl_3$ was added and **NMR 2** was recorded immediately.

In 3rd NMR tube having stock solution of PhCHO and HFIP (0.5 mmol each) 10 mol% *p*TSA•H_2O (9.5 mg), 0.4 ml of $CDCl_3$ was added and **NMR 3** was recorded immediately.

In 4th NMR tube having stock solution of PhCHO and HFIP (0.5 mmol each) 20 mol% *p*TSA.H_2O (19.0 mg), 0.4 ml of $CDCl_3$ was added and **NMR 4** was recorded immediately.

In 5th NMR tube having stock solution of PhCHO and HFIP (0.5 mmol each) 30 mol% *p*TSA.H_2O (28.5 mg), 0.4 ml of $CDCl_3$ was added and **NMR 5** was recorded immediately.

In 6th NMR tube having stock solution of PhCHO and HFIP (0.5 mmol each) 40 mol% *p*TSA.H_2O (38.1 mg), 0.4 ml of $CDCl_3$ was added and **NMR 6** was recorded immediately.

In 7th NMR tube having stock solution of PhCHO and HFIP (0.5 mmol each) 50 mol% *p*TSA.H_2O (47.6 mg), 0.4 ml of $CDCl_3$ was added and **NMR 7** was recorded immediately.

In 8th NMR tube having stock solution of PhCHO and HFIP (0.5 mmol each) 100 mol% *p*TSA.H_2O (95 mg), 0.4 ml of $CDCl_3$ was added and **NMR 8** was recorded immediately.

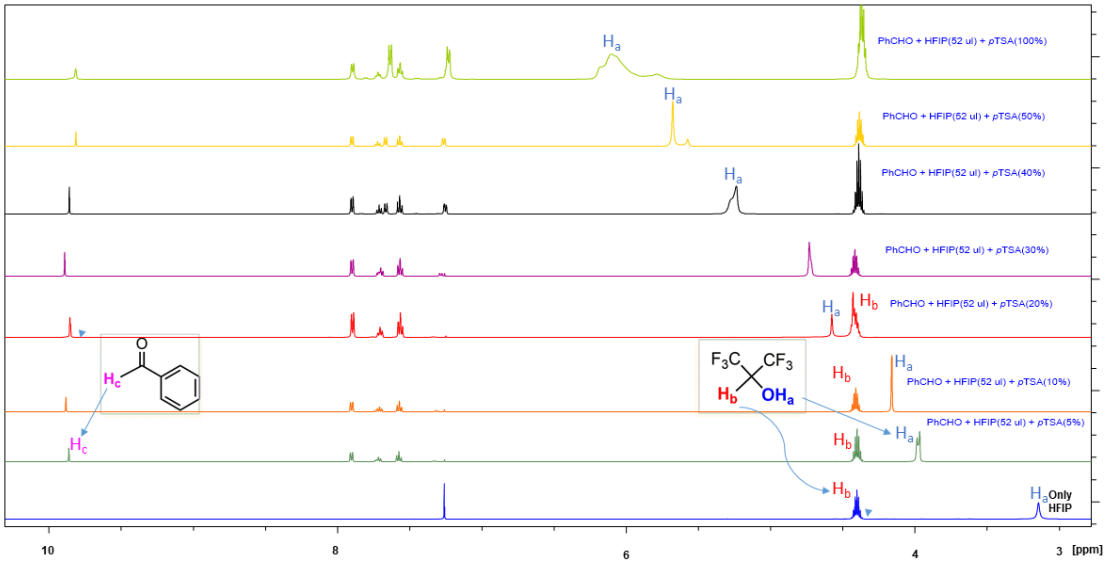
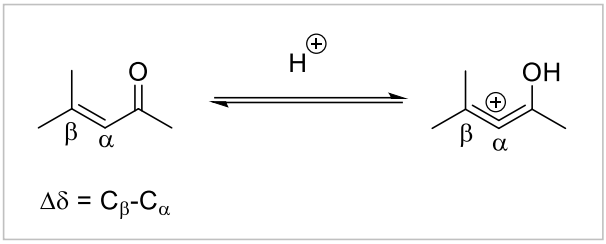


Figure 1 Real time NMR studies showing the activation of the *p*TSA•H_2O with HFIP.

^{13}C NMR study of the mixture of *p*-toluenesulphonic acid and HFIP[3,4]

For the acidity calculation of the mixture of *p*TSA•H_2O and HFIP we used the mesityl oxide method as reported by Farcasiu and co-workers and also by Song and co-workers.

The determination of the acid strength H_0 is based on the protonation equilibrium shown below wherein the presence of strong acid the oxygen atom of the ketone (mesityl oxide) is protonated thereby causing a relative shift in the 13C NMR spectra before and after addition of the proton.



In a NMR tube, mesityl oxide (0.5 mmol., 57.2 μL) was added in 0.5 ml CD_3OD and **NMR -1** was recorded. In NMR tube (2-5) mesityl oxide (0.5 mmol., 57.2 μL) and *p*TSA•H_2O (50 mol%; 0.25mmol; 47.6 mg) was added and a stock solution was prepared in CD_3OD. In NMR tubes (3-5) to the stock solution, HFIP (50 mol%, 100 mol% and 300 mol%) were added and respective NMR (3-5) were recorded.

In 2nd NMR tube having stock solution of mesityl oxide (0.5 mmol., 57.2 μL), *p*TSA•H_2O (50 mol%; 0.25mmol; 47.5mg), 0.4 ml of CD_3OD was added and **NMR 2** was recorded immediately.

In 3rd NMR tube having stock solution of mesityl oxide (0.5 mmol., 57.2 μL), *p*TSA•H_2O (50 mol%; 0.25mmol; 47.5mg), HFIP (50 mol%, 27.0 μL) , 0.4 ml of CD_3OD was added and **NMR 3** was recorded immediately.

In 4th NMR tube having stock solution of mesityl oxide (0.5 mmol., 57.2 μL), *p*TSA•H_2O (50 mol%; 0.25mmol; 47.5mg), HFIP (100 mol%, 53.0 μL) ,~0.4 ml of CD_3OD was added and **NMR 4** was recorded immediately.

In 5th NMR tube having stock solution of mesityl oxide (0.5 mmol., 57.2 μL), *p*TSA•H_2O (50 mol%; 0.25mmol; 47.5mg), HFIP (300 mol%, 160 μL) , ~0.35 ml of CD_3OD was added and **NMR 5** was recorded immediately.

	C=O (in ppm)	C_β (in ppm)	C_α (in ppm)	$\Delta\delta = C_\beta - C_\alpha$ (in ppm)
Set-1 {mesityl oxide (0.5 mmol., 57.2 μL) + 0.5 ml CD_3OD}	201.00	157.17	124.99	32.18
Set-2 {mesityl oxide (0.5 mmol., 57.2 μL) + *p*TSA.H_2O (50 mol%; 0.25mmol; 47.6 mg) + 0.4 ml CD_3OD}	201.11, 201.06	157.12	124.94	32.18
Set-3 {mesityl oxide (0.5 mmol., 57.2 μL) + *p*TSA.H_2O (50 mol%; 0.25mmol; 47.6 mg) + HFIP (50 mol%, 27.0 μL)+ 0.4 ml CD_3OD}	201.32, 201.27	157.32	124.94 124.70	32.62
Set-4 {mesityl oxide (0.5 mmol., 57.2 μL) + *p*TSA.H_2O (50 mol%; 0.25mmol; 47.6 mg) + HFIP	201.37	157.42	124.67	32.75

(100 mol%, 53.0 µL)+ 0.4 ml CD_3OD}				
Set-5 {mesityl oxide (0.5 mmol., 57.2 µL) + *p*TSA.H_2O (50 mol%; 0.25mmol; 47.6 mg) + HFIP (300 mol%, 160 µL)+ 0.35 ml CD_3OD}	202.16	158.30	124.51	33.79

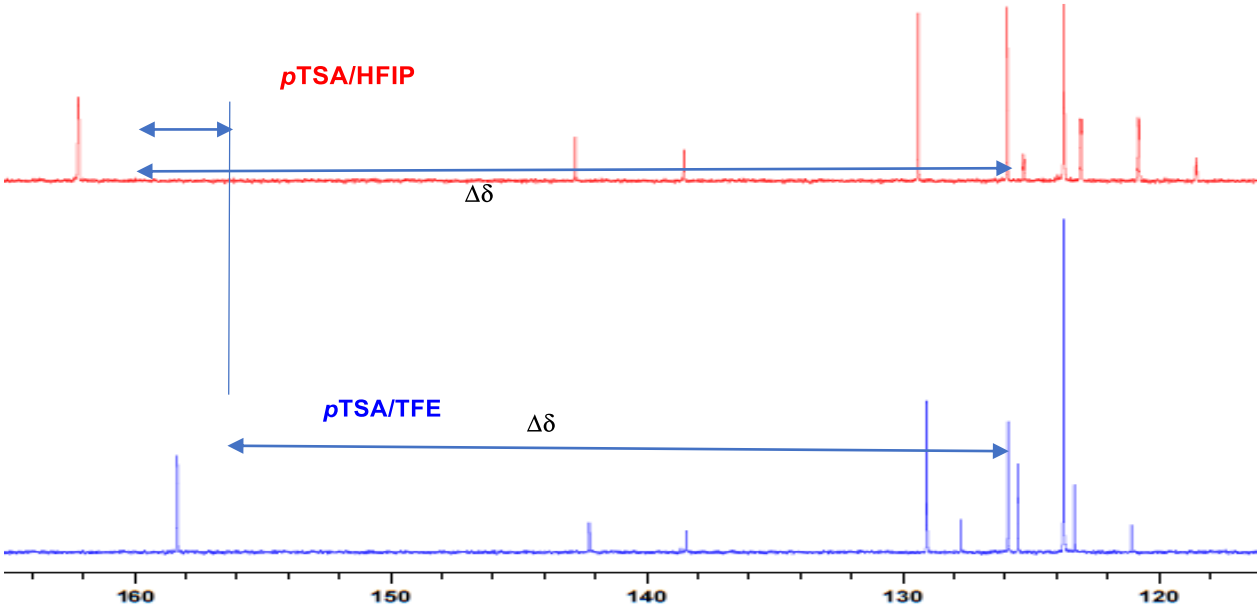


Figure 2A pKa comparison of *p*TSA•H_2O in two different fluoroalcohol solvents (a) HFIP and (b) TFE using mesityl oxide as the probe.

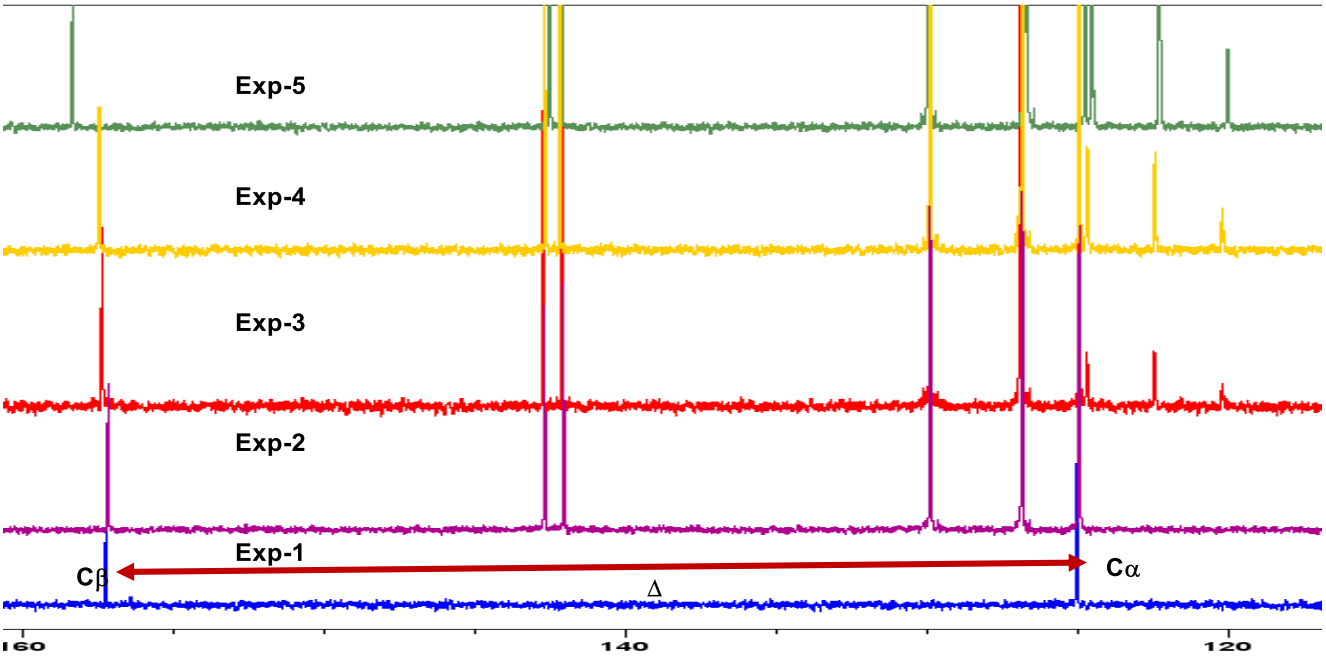
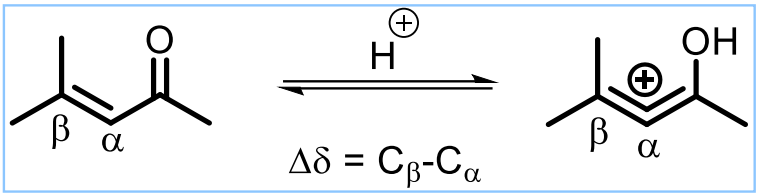


Figure 2B Exp-1 ^{13}C-NMR of pure mesityl oxide (0.5 mmol); **Exp-2** ^{13}C-NMR mesityl oxide (0.5 mmol) + *p*TSA•H_2O (0.25 mmol); **Exp-3 ^{13}C-NMR** mesityl oxide (0.5 mmol) + *p*TSA•H_2O (0.25 mmol) + HFIP (0.25 mmol); **Exp-4 ^{13}C-NMR** mesityl oxide (0.5 mmol) + *p*TSA•H_2O (0.25 mmol) + HFIP (0.5 mmol); **Exp-5 ^{13}C-NMR** mesityl oxide (0.5 mmol) + *p*TSA•H_2O (0.25 mmol) + HFIP (1.5 mmol); in CD_3OD.



9. Recycle and reusability of HFIP solvent[5]

Initial reaction:

To a 50 ml round bottom flask added 1,3,5-trimethoxybenzene (1.1 equvi., 21 mmol) and 2,6-dimethylphenol (1.1 equvi., 21 mmol) and paraformaldehyde (0.60 g, 20 mmol, 1.0 equiv.) and *p*TSA•H_2O (5 mol%) in 20 ml of HFIP. The resultant mixture was stirred at room temperature for 12 h. The HFIP solvent was recovered by distillation directly from the reaction pot (60–70 ˚C) (18.0 mL, 90%). The remaining product was purified by column chromatography using EtOAc/hexanes (20:80) to afforded **1** (4.5g, 75%) as a white solid. 2nd reaction, using recovered HFIP solvent. To a solution of 1,3,5-trimethoxybenzene (1.1 equiv., 11 mmol) and 2,6-dimethylphenol (1.1 equvi., 11 mmol) and paraformaldehyde (0.30 g, 10 mmol, 1.0 equiv.), *p*TSA•H_2O (5 mol%) in HFIP (10.0 mL) solvent obtained by distillation from previous reaction was added. The resultant mixture was stirred at room temperature for 12 h. Further, HFIP solvent was recovered by distillation as discussed in initial reaction (9.0 mL, 90%). The remaining product was purified by column chromatography using EtOAc/hexanes (20:80) to afforded **1** (2.3 g, 77%) as a white solid.

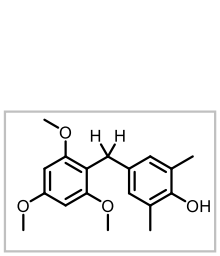
3rd reaction, using 2-times recovered HFIP solvent

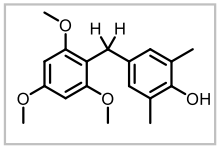
To a solution of 1,3,5-trimethoxybenzene (1.1 equiv., 5.5 mmol) and 2,6-dimethylphenol (1.1 equiv., 5.5 mmol) and paraformaldehyde (0.150 g, 5 mmol, 1.0 equiv.), *p*TSA•H_2O (5 mol%) in HFIP (5.0 mL) solvent obtained by distillation from previous reaction was added. The resultant mixture was stirred at room temperature for 12 h. HFIP solvent was recovered by distillation as discussed in initial reaction (4.0 mL, 80%). The remaining product was purified by column chromatography using EtOAc/hexanes (20:80) to afforded **1** (1.2 g, 80%) as a white solid.

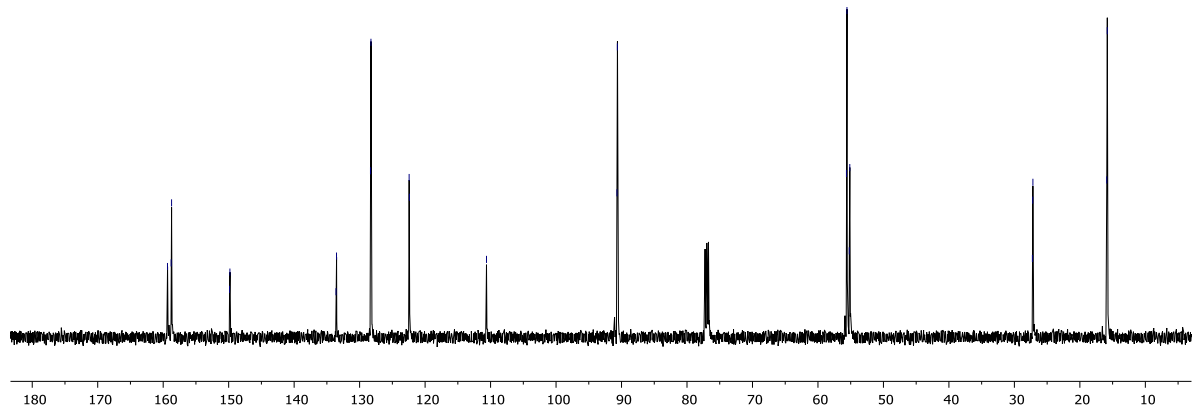
10. Copies of ^{1}H, ^{13}C {^{1}H} and ^{19}F-NMR spectra of products

2,6-Dimethyl-4-(2,4,6-trimethoxybenzyl)phenol (1)

^{1}H (400 MHz) and $^{13}C\{^{1}H\}$ (126 MHz) NMR spectra of **1** in $CDCl_3$

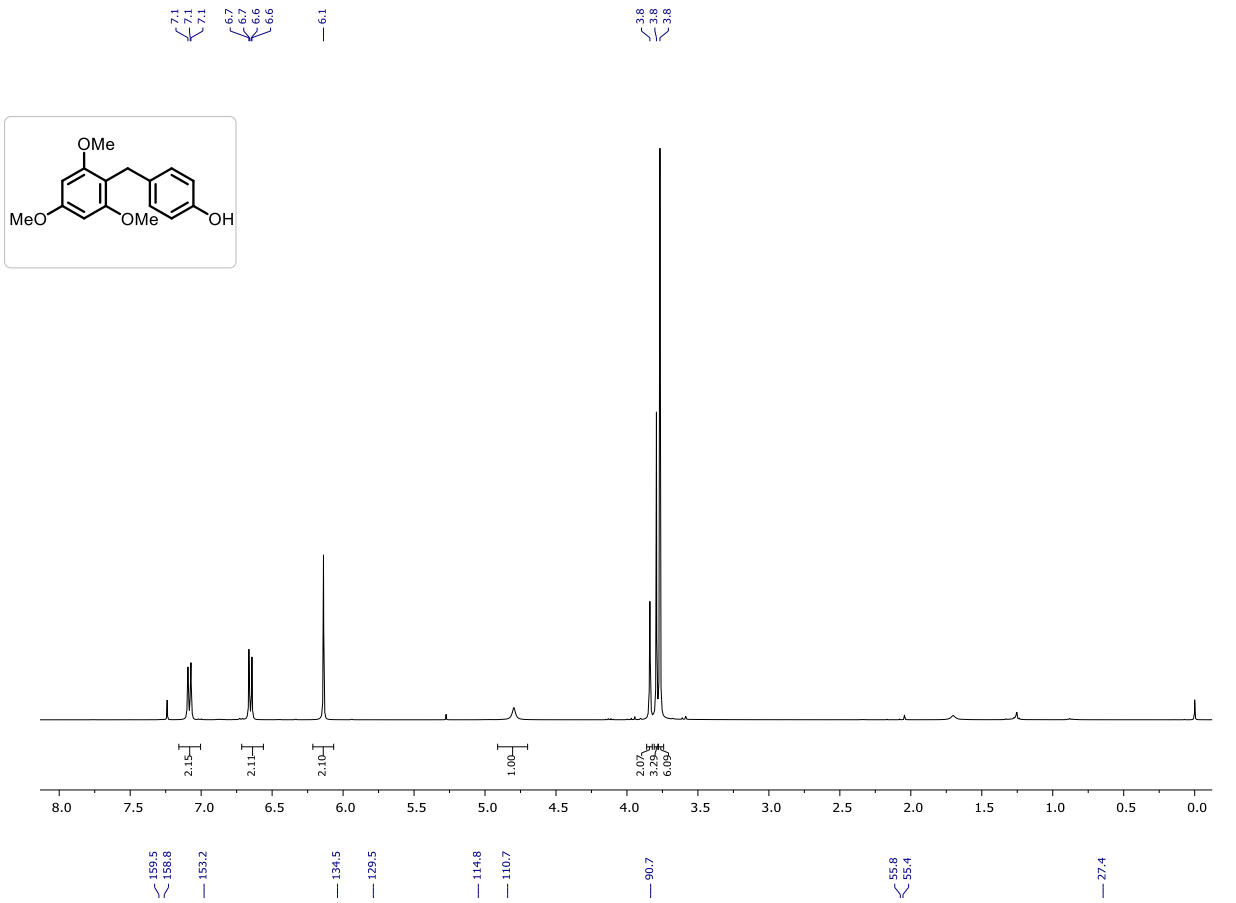


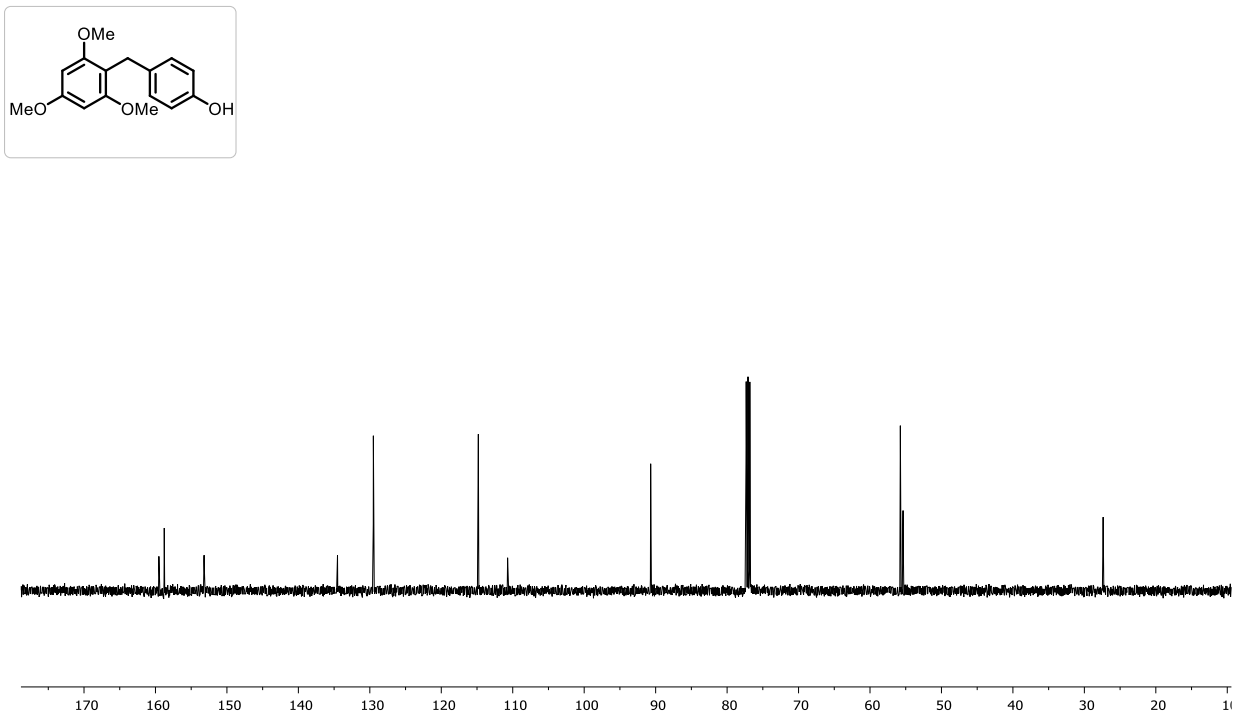




4-(2,4,6-Trimethoxybenzyl)phenol (2)

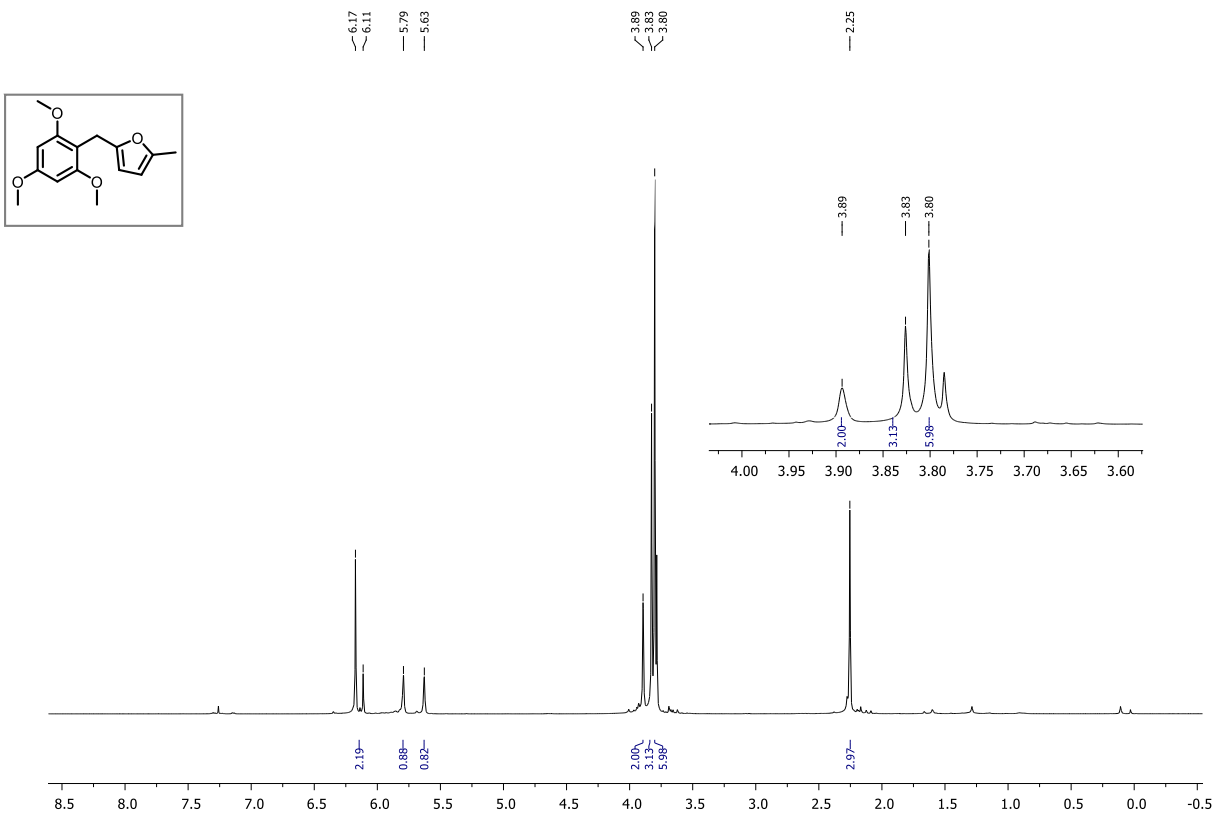
^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (126 MHz) NMR spectra of **2** in $CDCl_3$

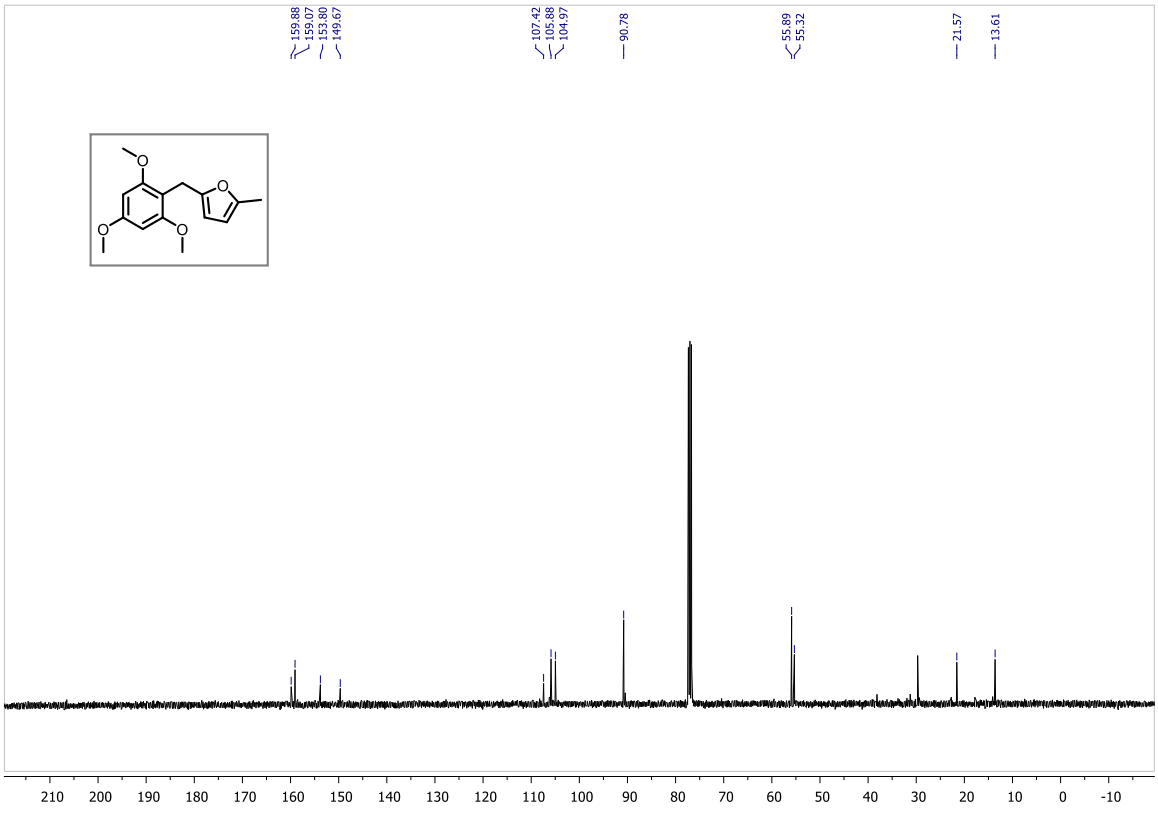




2-Methyl-5-(2,4,6-trimethoxybenzyl)furan (3)

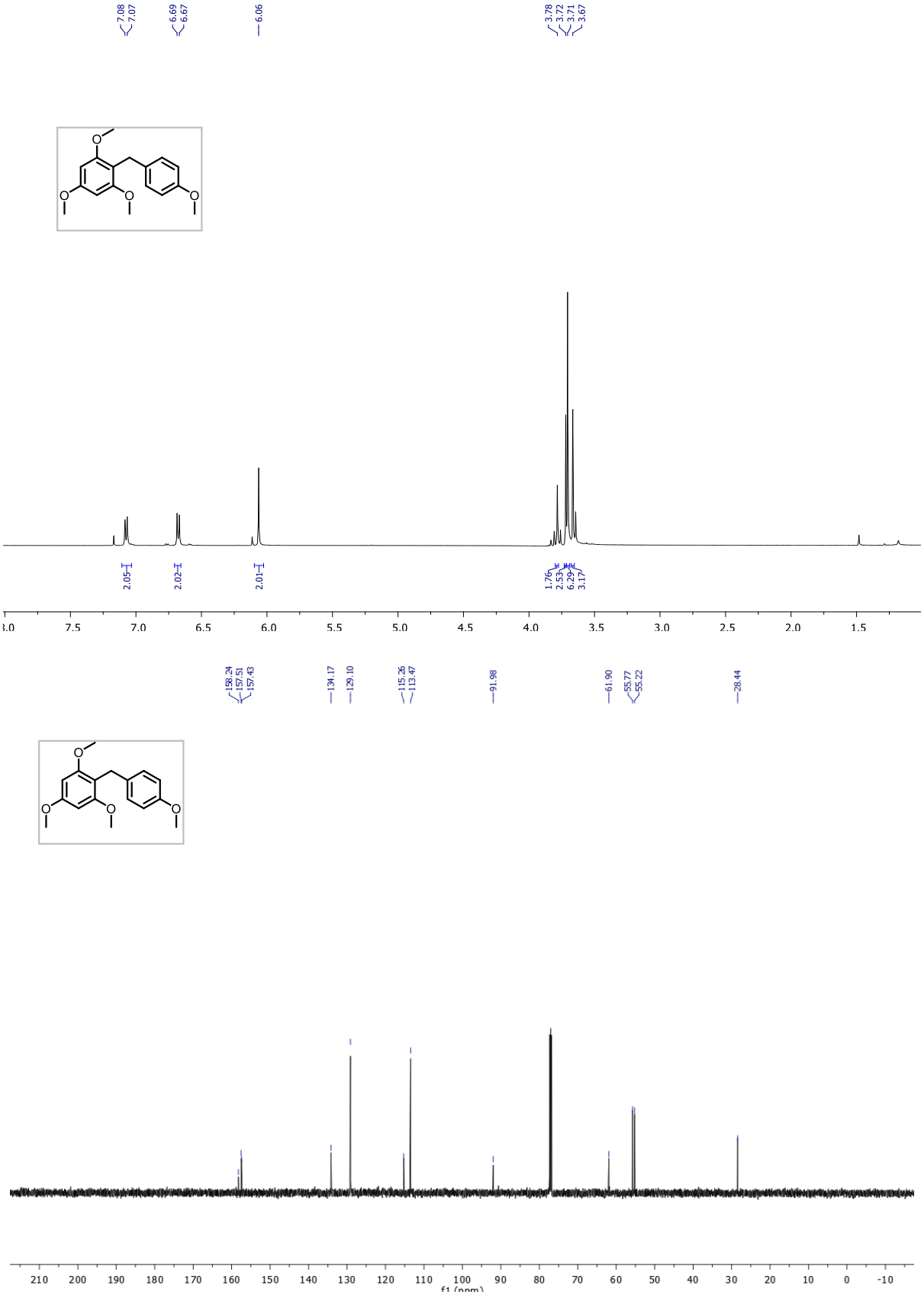
^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (101 MHz) NMR spectra of **3** in $CDCl_3$





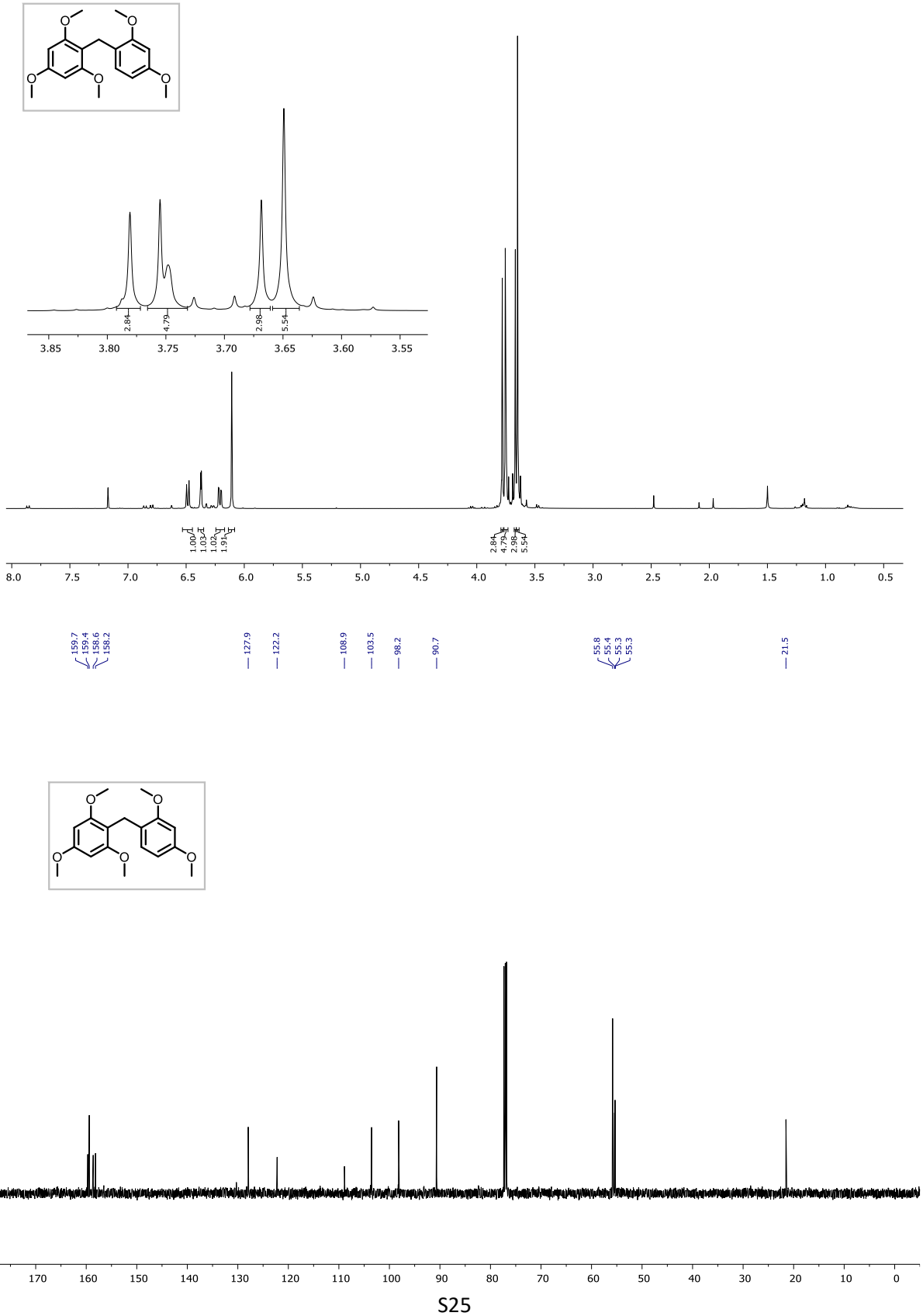
1,3,5-Trimethoxy-2-(4-methoxybenzyl) benzene (4)

^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (121 MHz) NMR spectra of **4** in $CDCl_3$



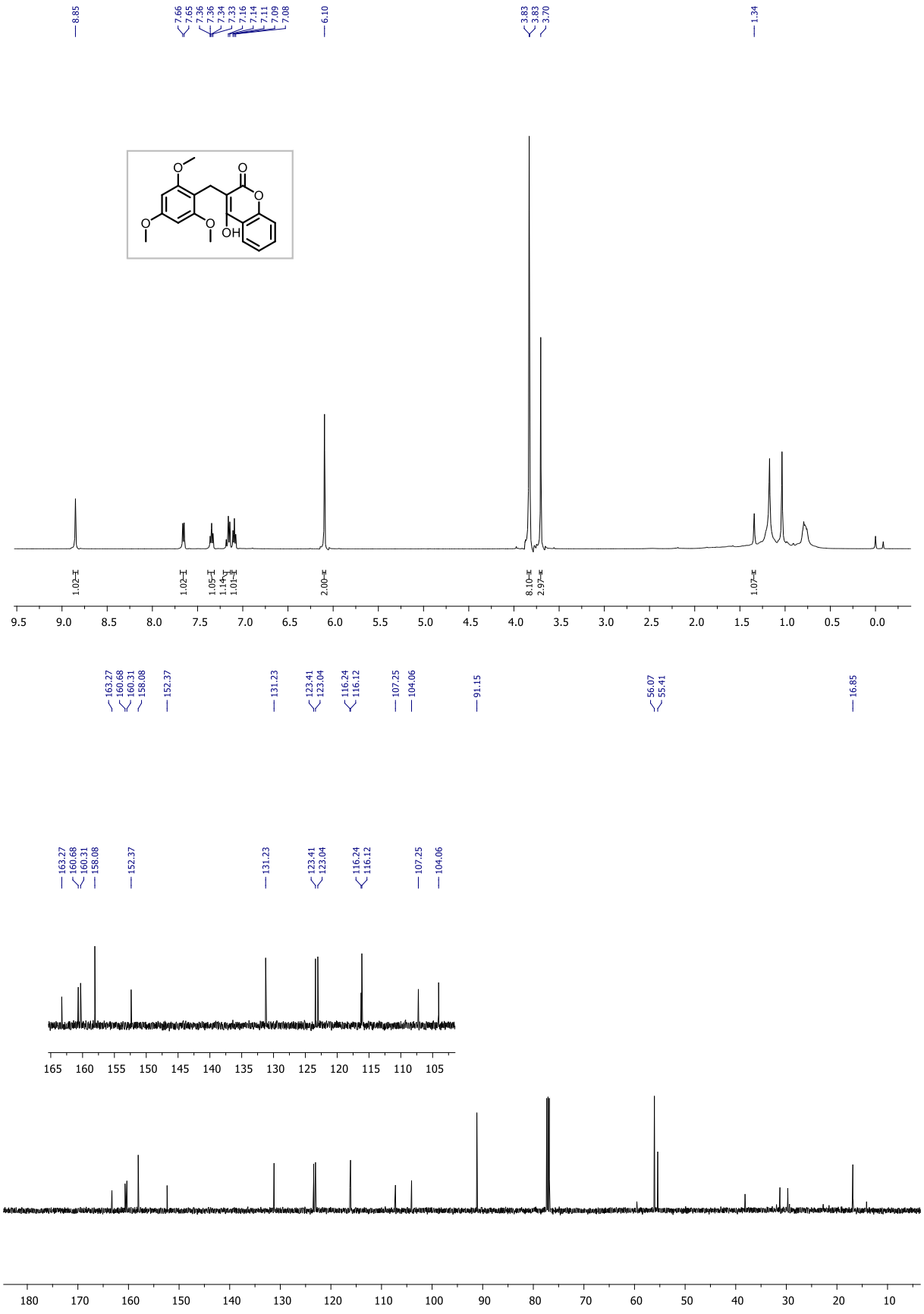
2-(2,4-Dimethoxybenzyl)-1,3,5-trimethoxybenzene (5)

^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (126 MHz) NMR spectra of **5** in $CDCl_3$



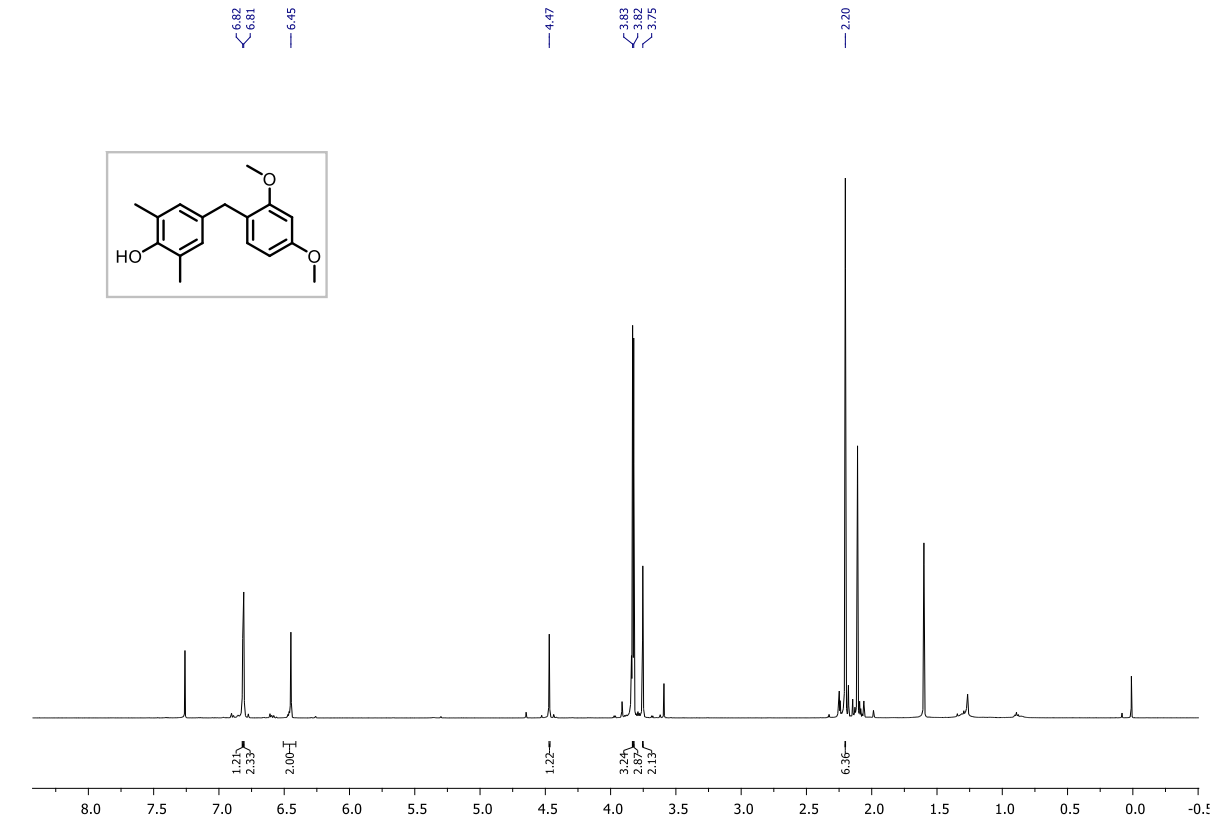
4-Hydroxy-3-(2,4,6-trimethoxybenzyl)-2*H*-chromen-2-one (6)

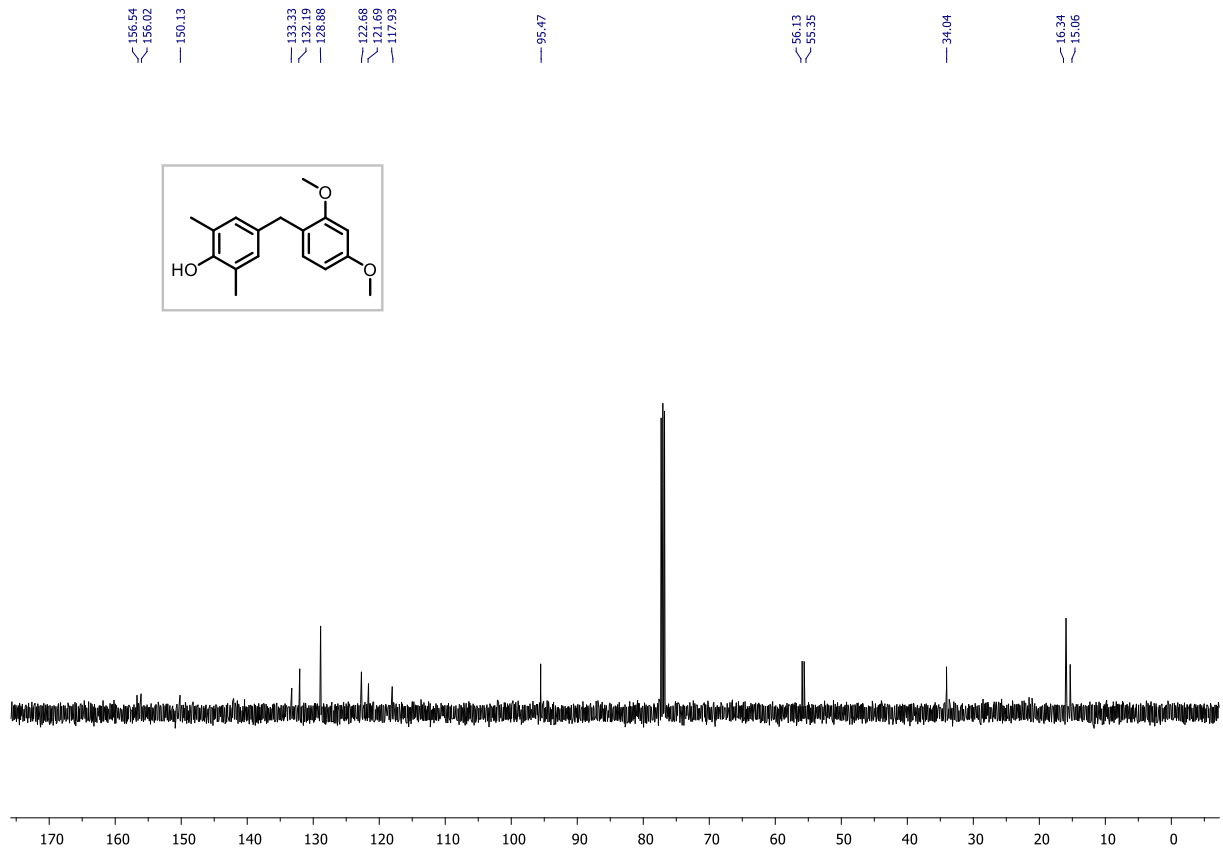
^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (126 MHz) NMR spectra of **6** in $CDCl_3$



4-(2,4-Dimethoxybenzyl)-2,6-dimethylphenol (7)

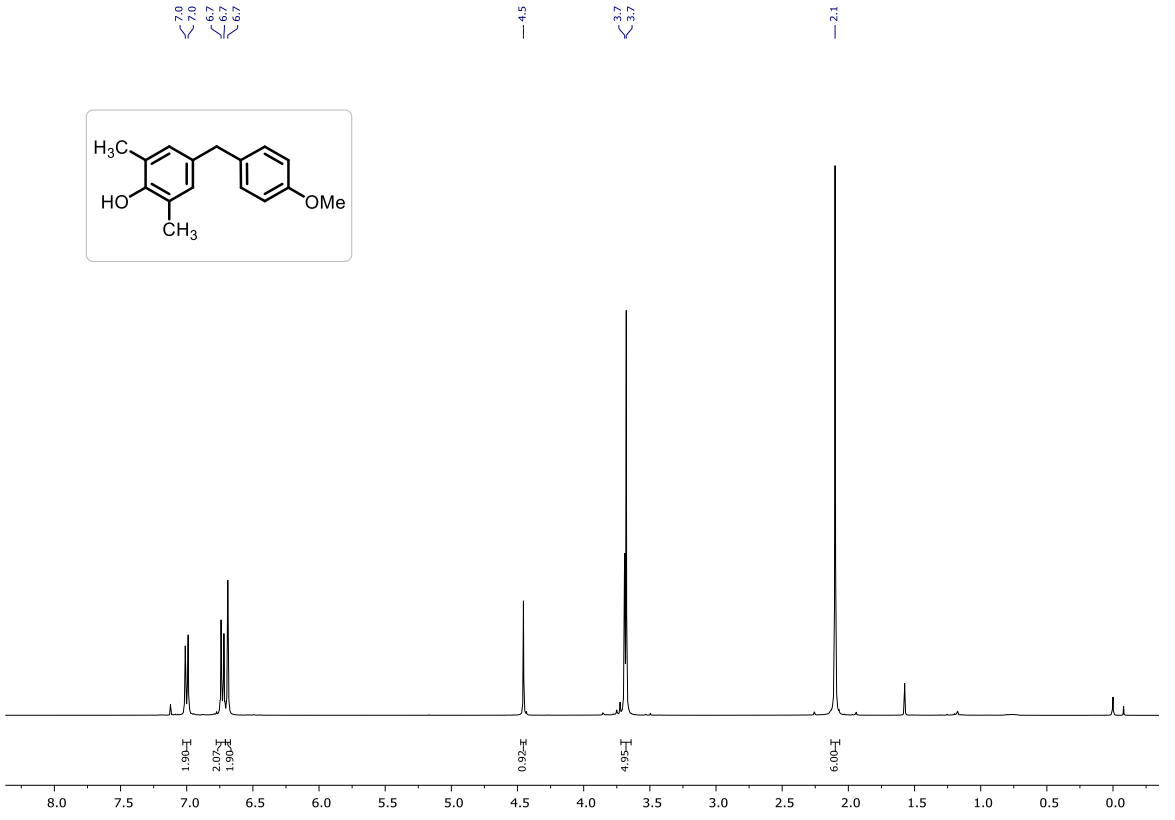
^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (126 MHz) NMR spectra of **7** in $CDCl_3$

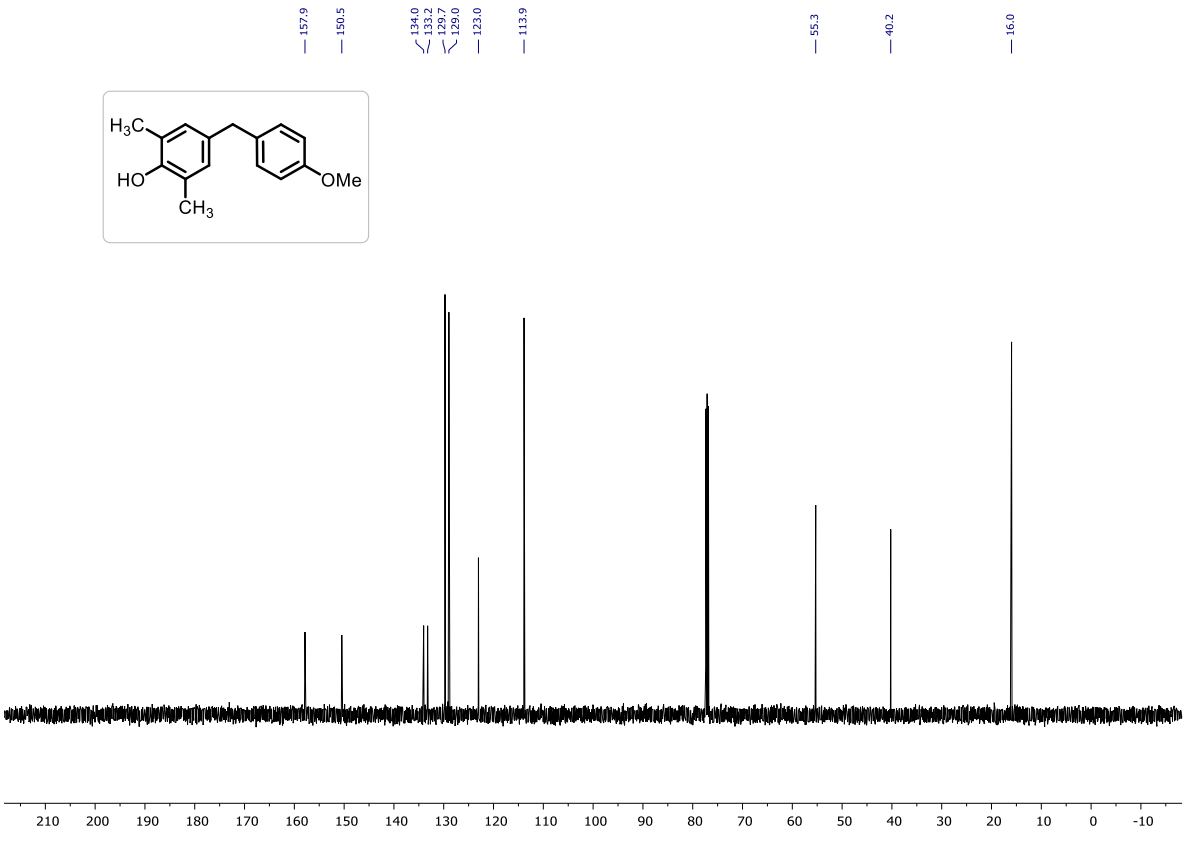




4-(4-Methoxybenzyl)-2,6-dimethylphenol (8)

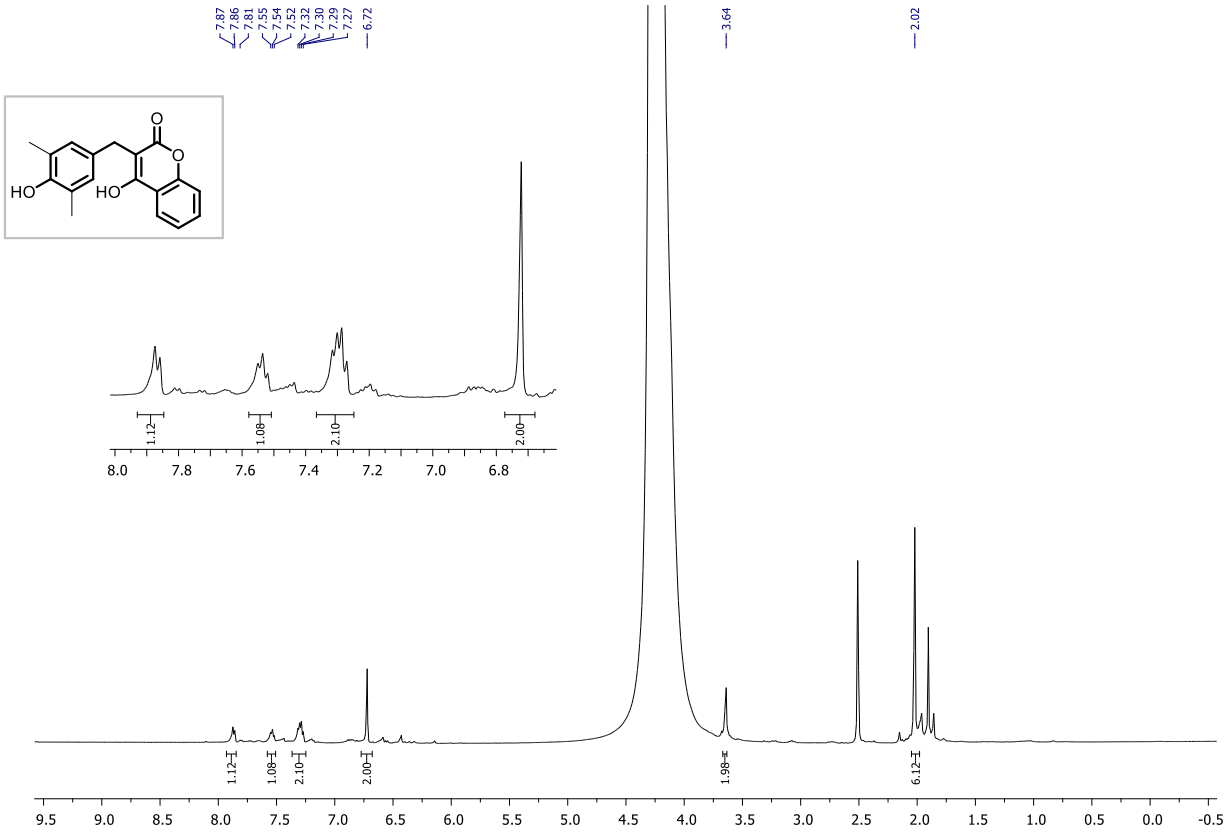
^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (126 MHz) NMR spectra of **8** in $CDCl_3$

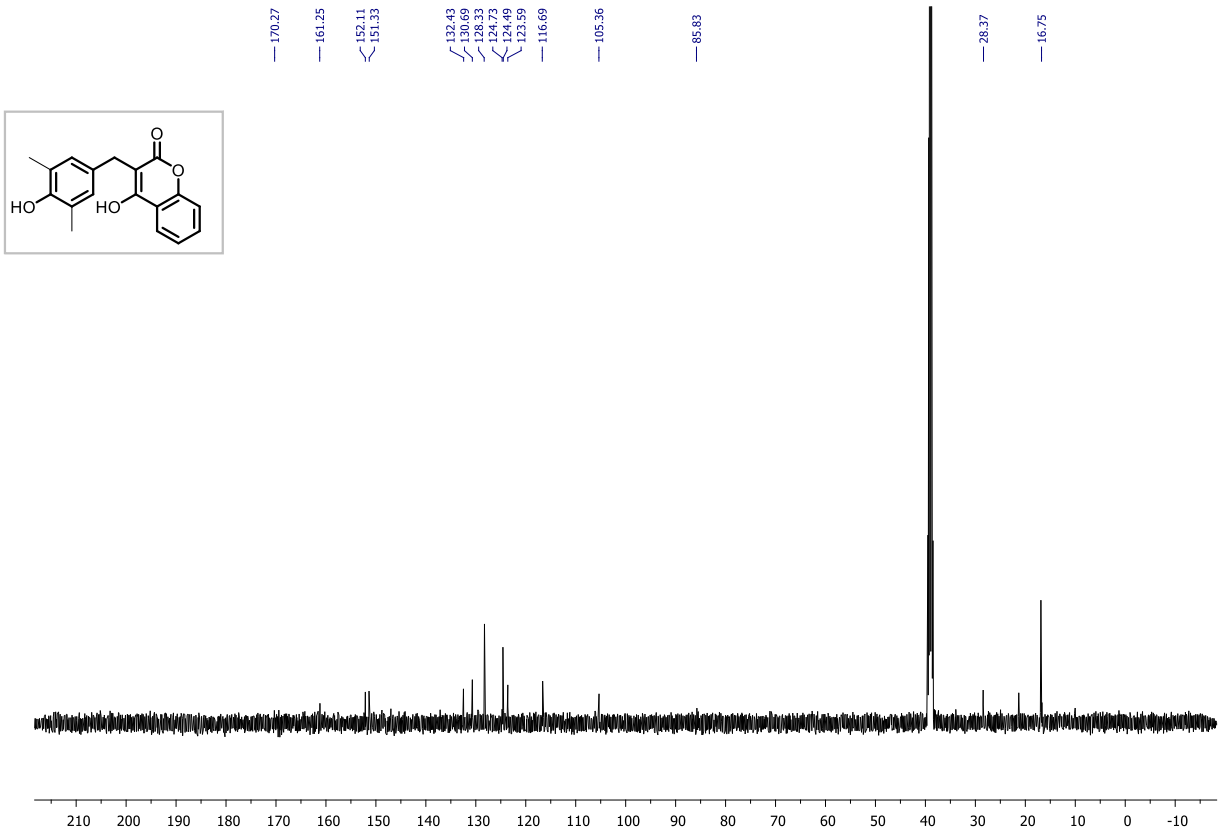




4-Hydroxy-3-(4-hydroxy-3,5-dimethylbenzyl)-2*H*-chromen-2-one (9)

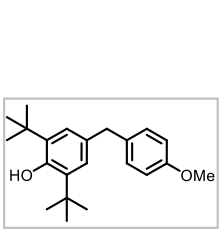
^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (126 MHz) NMR spectra of **9** in DMSO-d_6

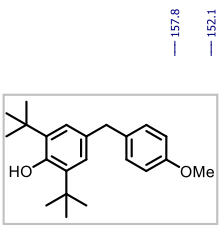




2,6-Di-*tert*-butyl-4-(4-methoxybenzyl)phenol (10)

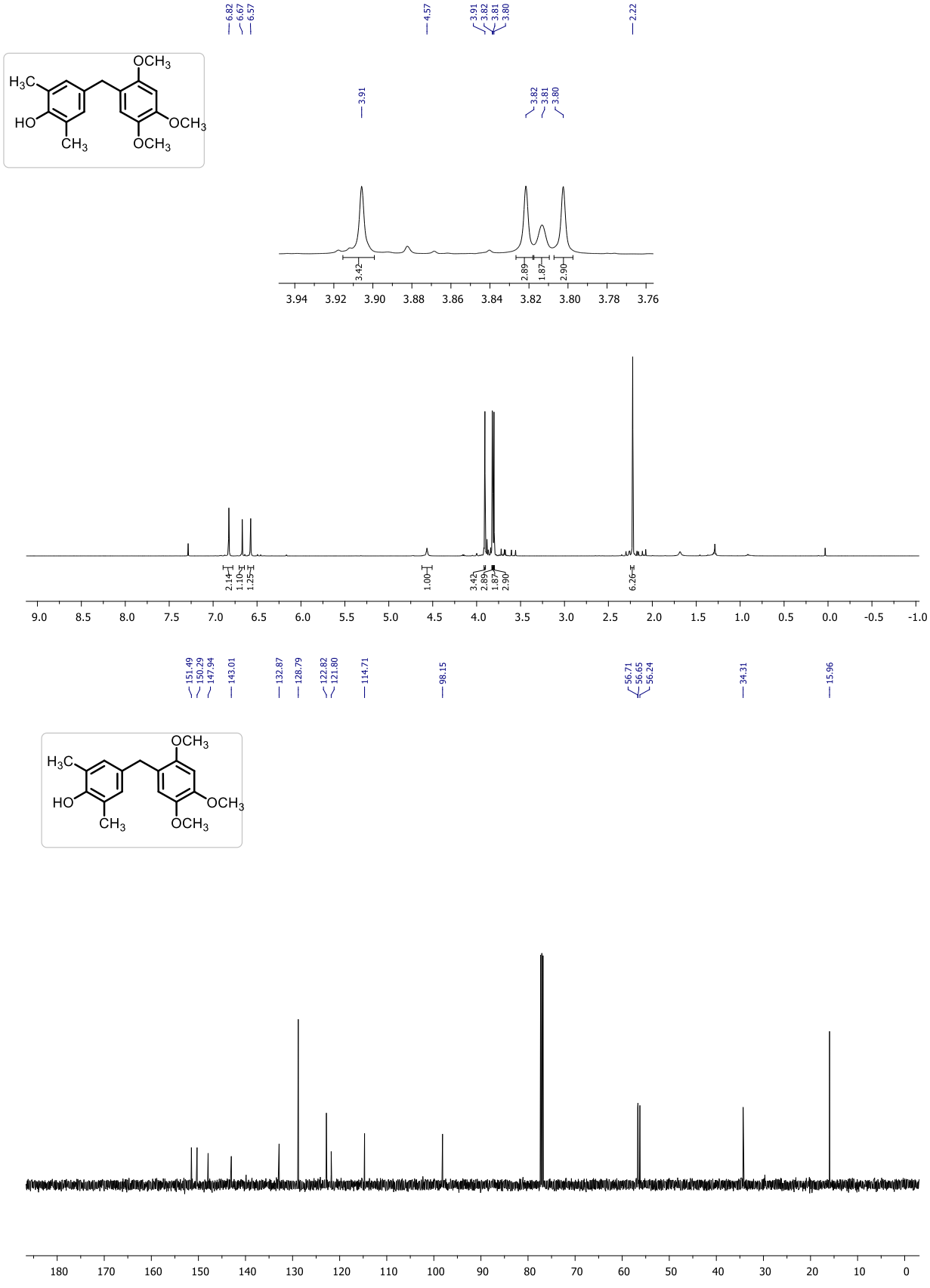
^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (126 MHz) NMR spectra of **10** in $CDCl_3$





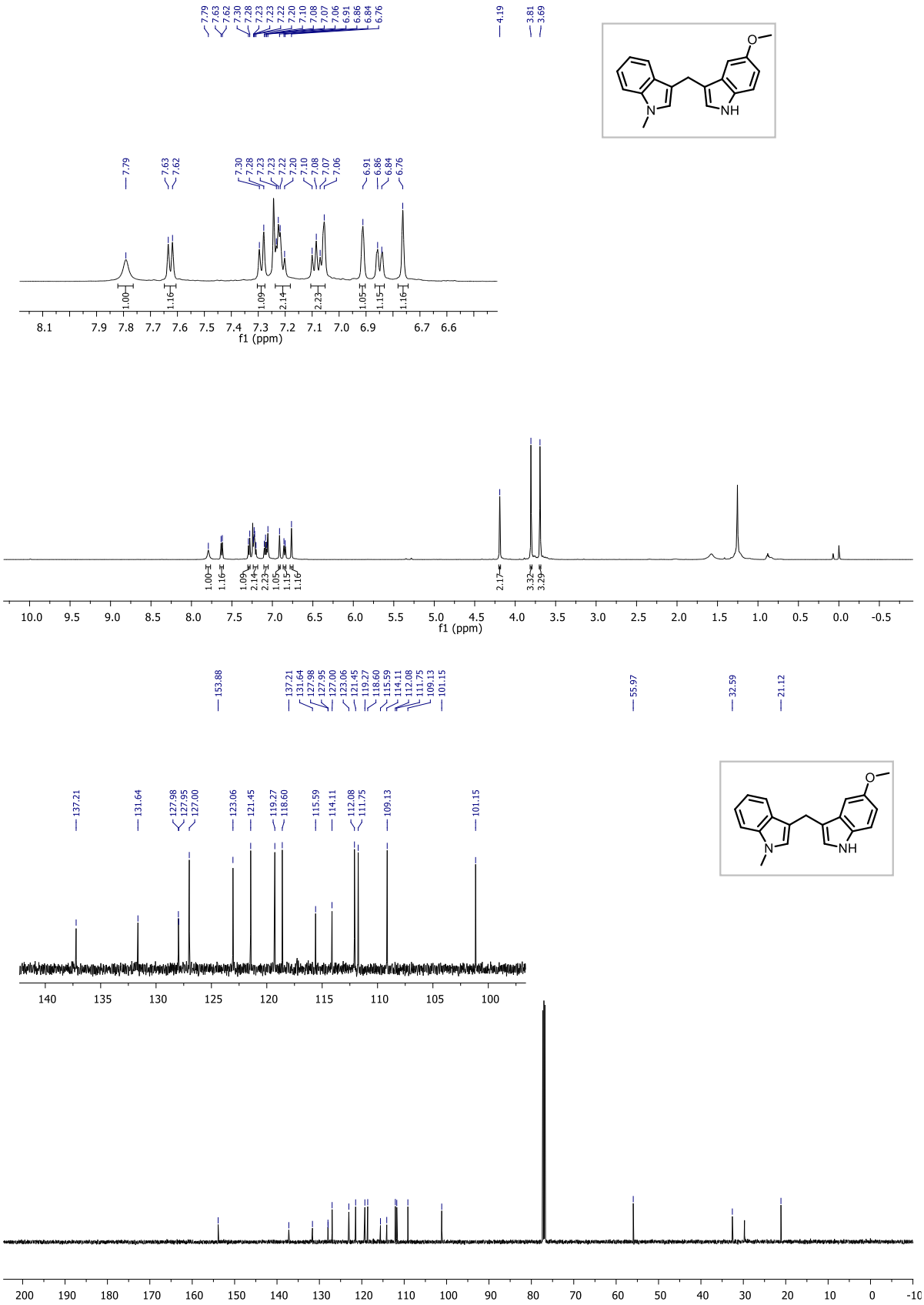
2,6-Dimethyl-4-(2,4,5-trimethoxybenzyl)phenol (11)

^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (126 MHz) NMR spectra of **11** in $CDCl_3$



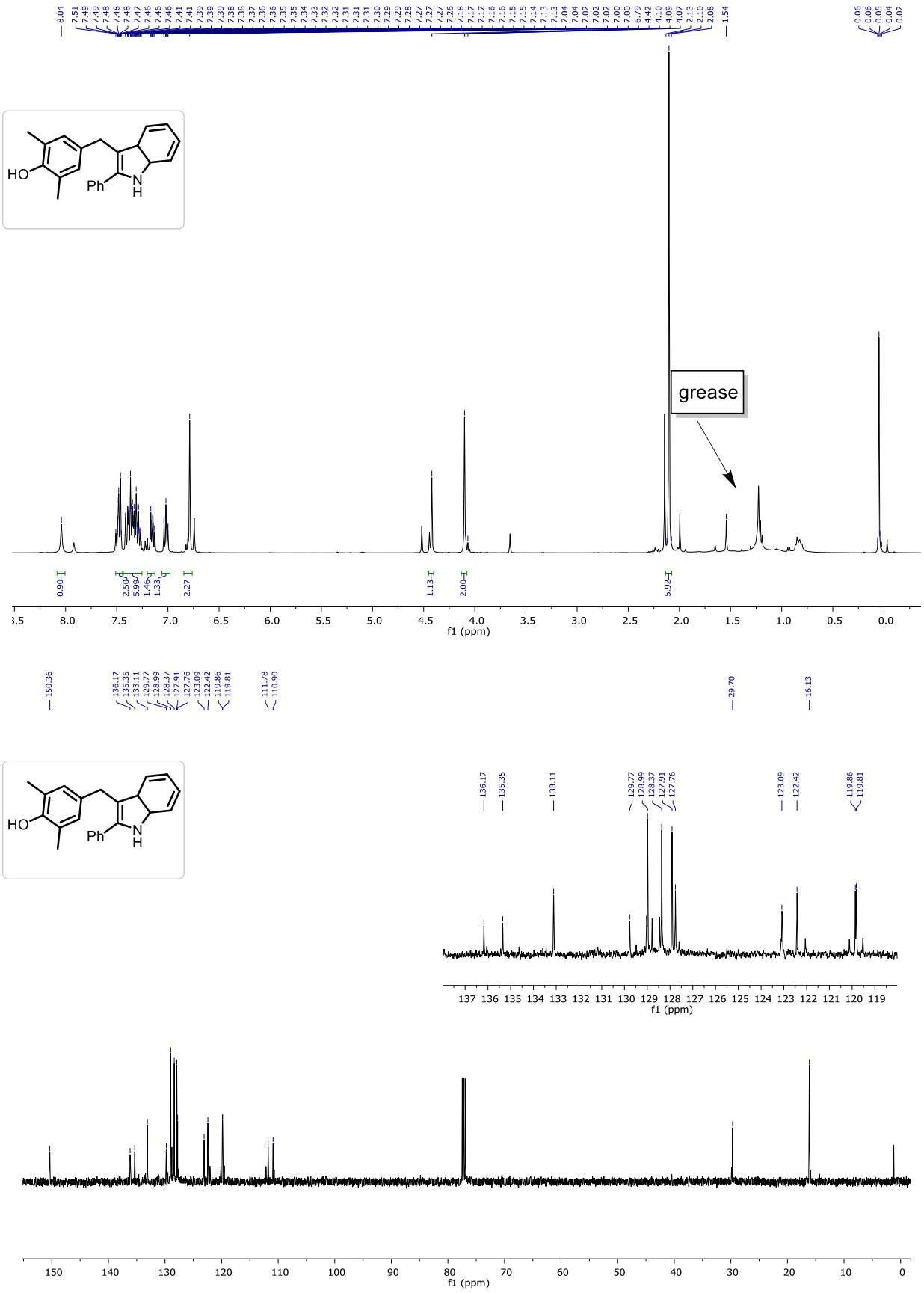
5-Methoxy-3-((1-methyl-1*H*-indol-3-yl)methyl)-1*H*-indole (12)

^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (126 MHz) NMR spectra of **12** in $CDCl_3$



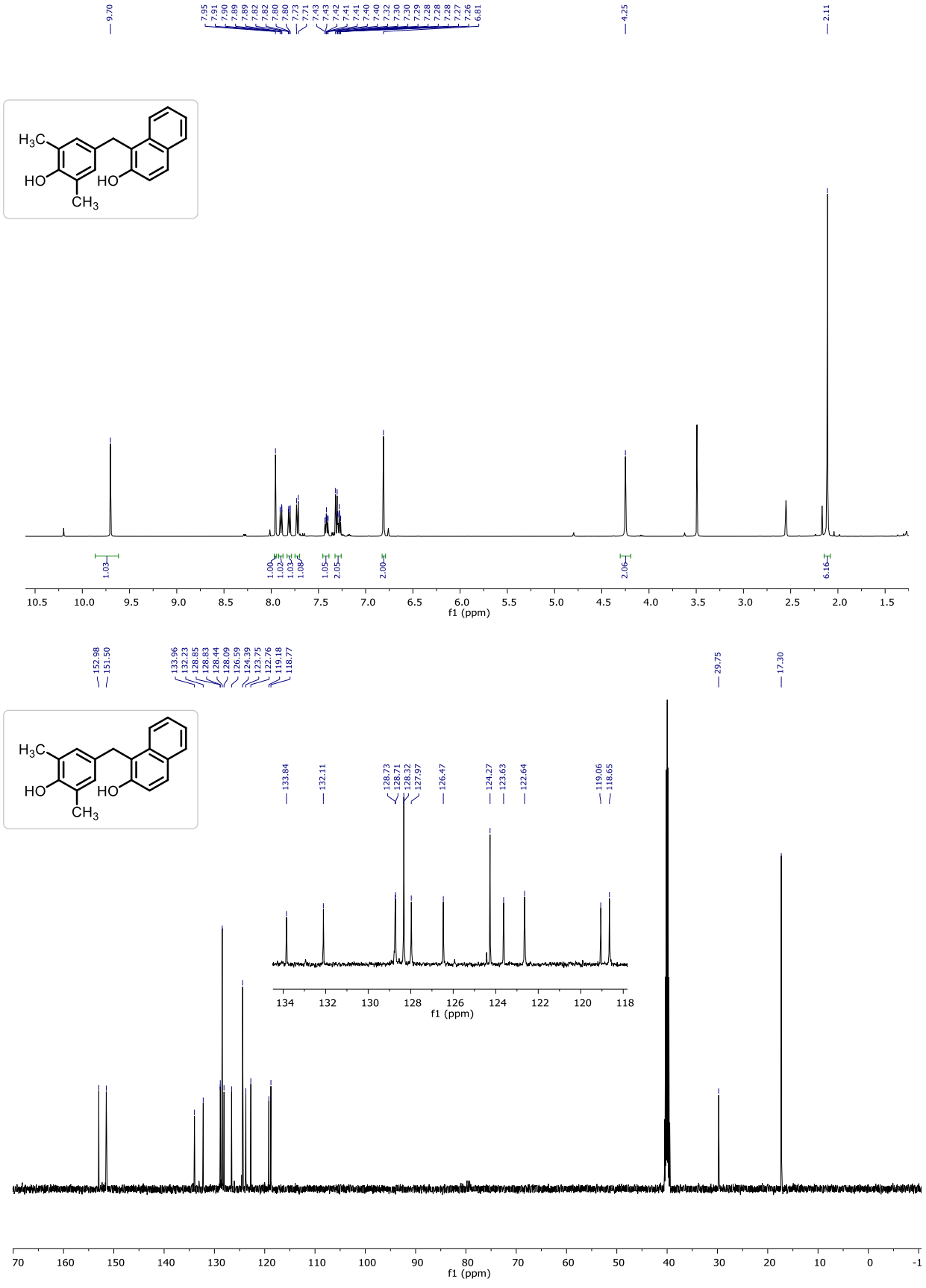
2,6-Dimethyl-4-((2-phenyl-3a,7a-dihydro-1*H*-indol-3-yl)methyl)phenol (13)

^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (126 MHz) NMR spectra of **13** in $CDCl_3$



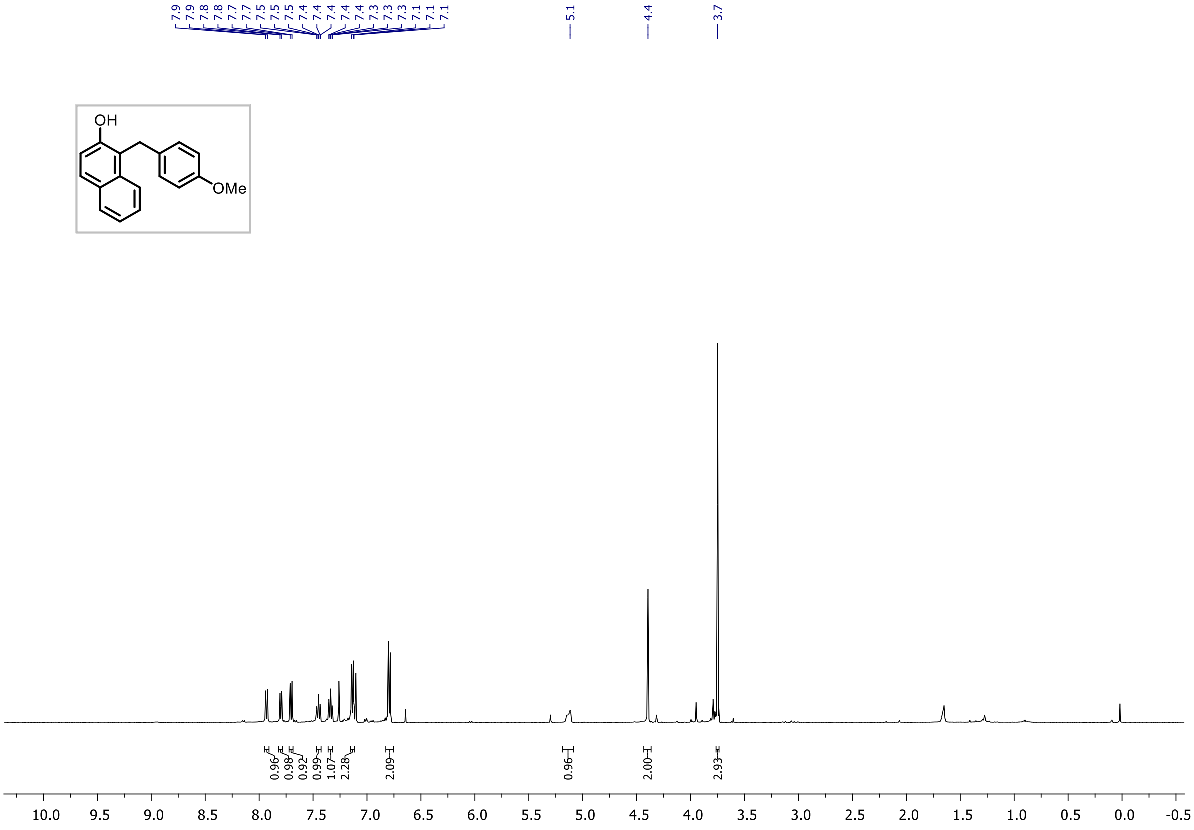
1-(4-Hydroxy-3,5-dimethylbenzyl)naphthalen-2-ol (14)

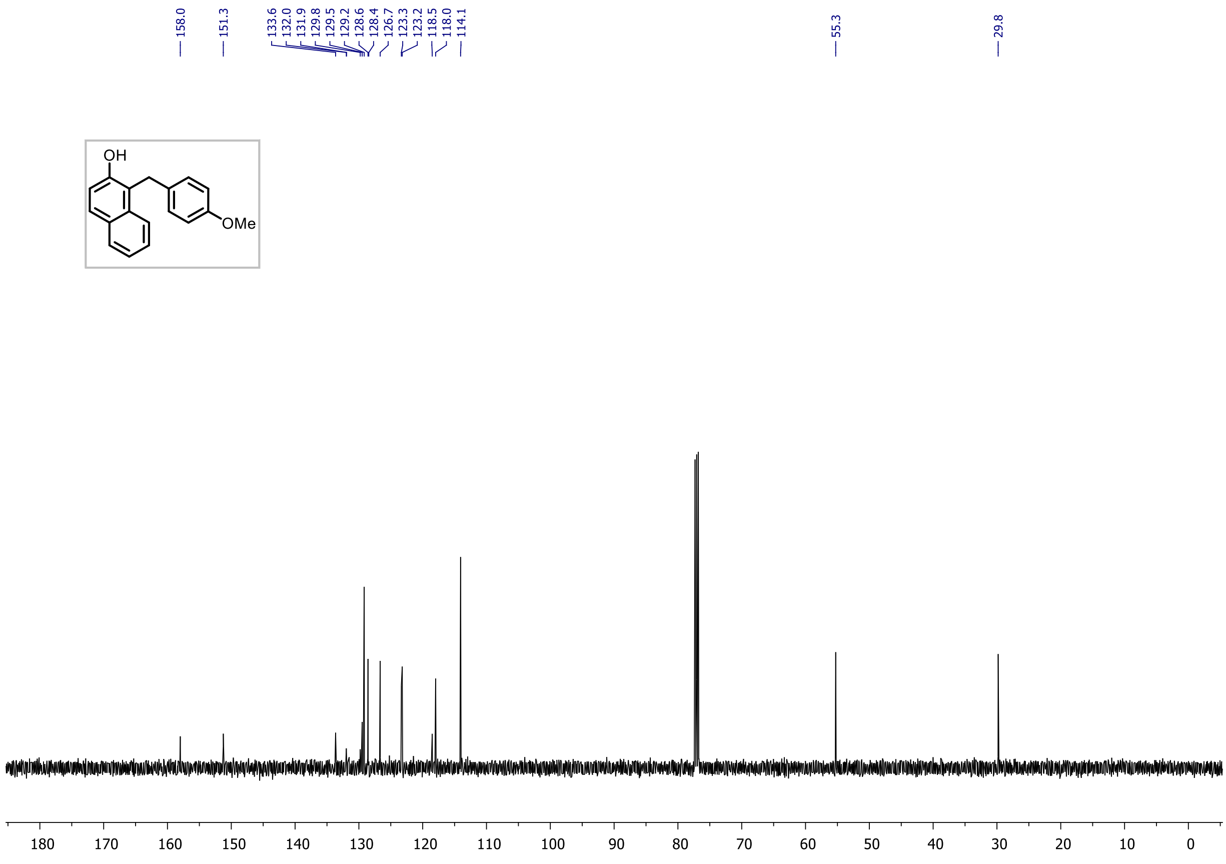
^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (126 MHz) NMR spectra of **14** in DMSO-d_6



1-(4-Methoxybenzyl)naphthalen-2-ol (15)

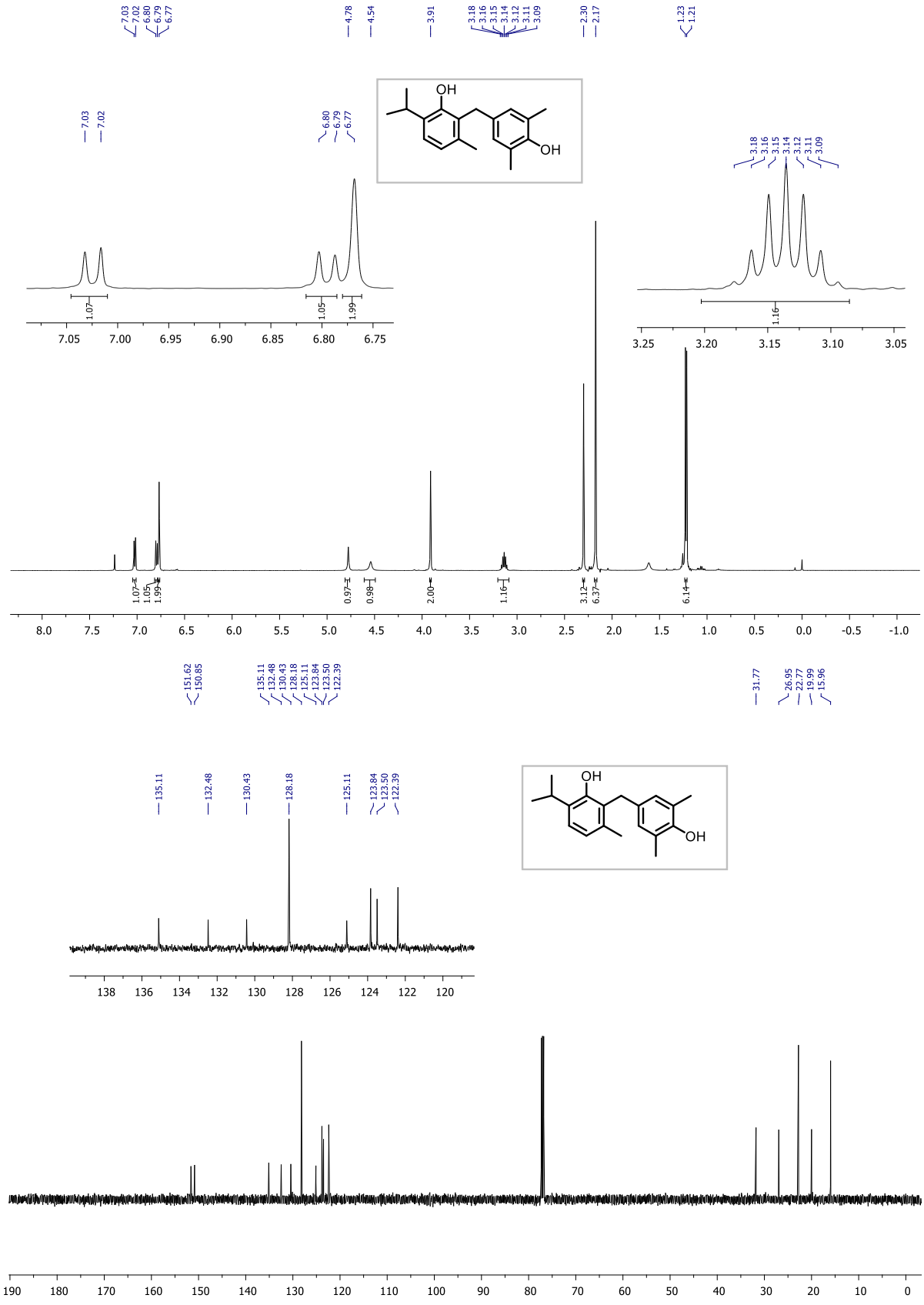
^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (126 MHz) NMR spectra of **15** in $CDCl_3$





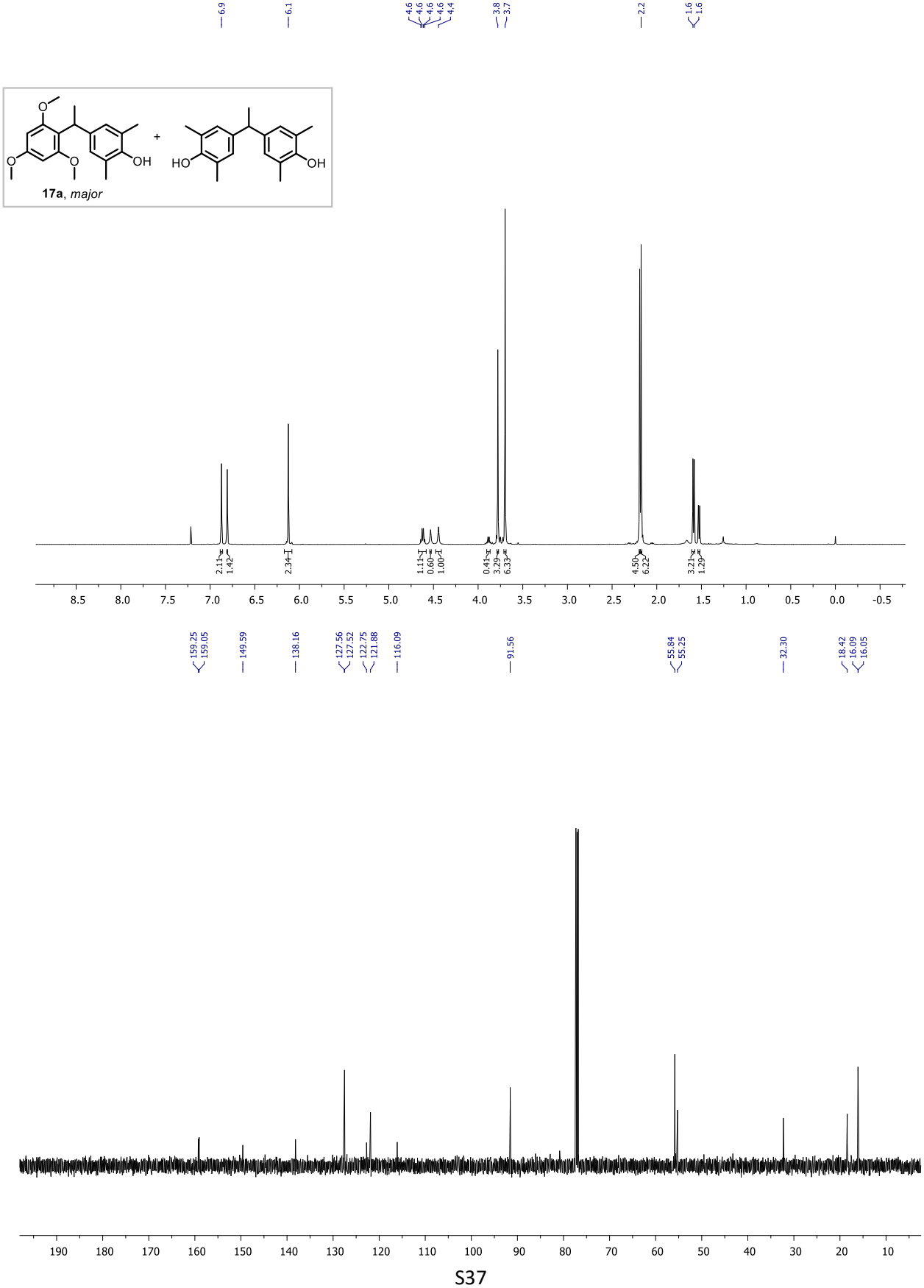
2-(4-Hydroxy-3,5-dimethylbenzyl)-6-isopropyl-3-methylphenol (16)

^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (126 MHz) NMR spectra of **16** in $CDCl_3$



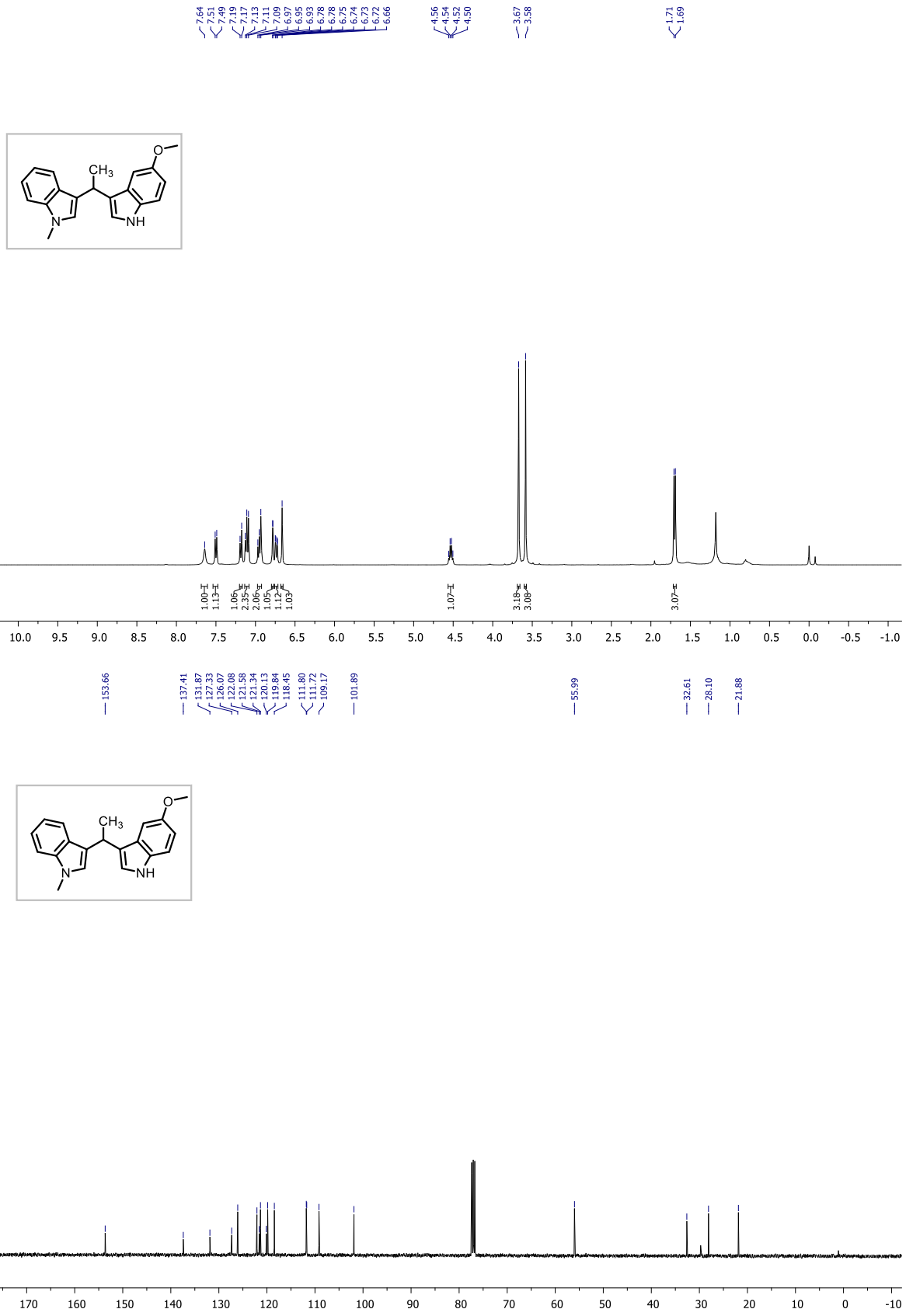
2,6-Dimethyl-4-(2,4,6-trimethoxybenzyl)phenol (17)

^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (126 MHz) NMR spectra of **17** in $CDCl_3$



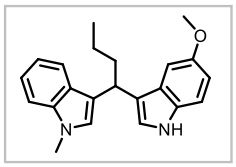
5-Methoxy-3-(1-(1-methyl-1*H*-indol-3-yl)ethyl)-1*H*-indole (18)

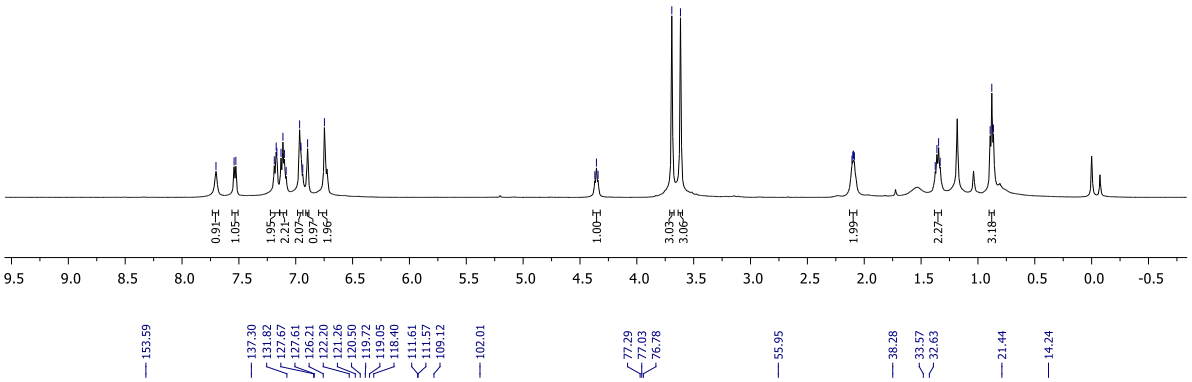
^{1}H (400 MHz) and $^{13}C\{^{1}H\}$ (101 MHz) NMR spectra of **18** in $CDCl_3$

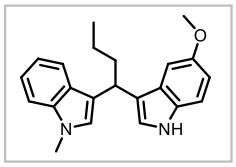


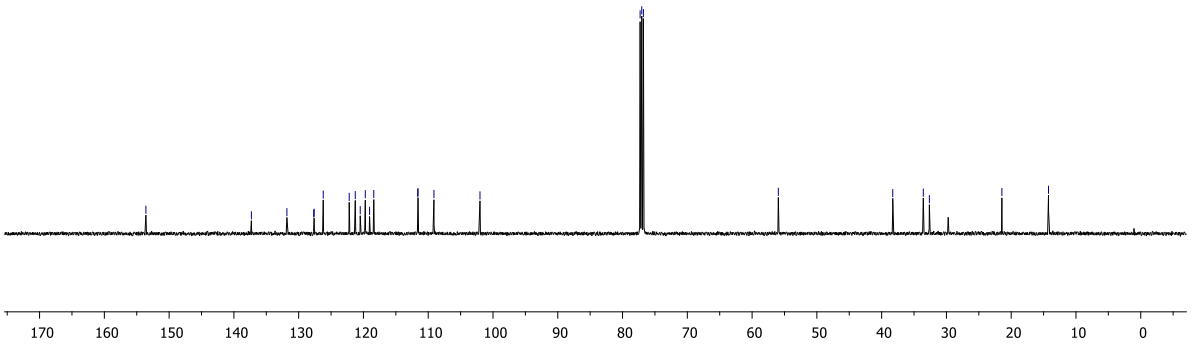
5-Methoxy-3-(1-(1-methyl-1*H*-indol-3-yl)butyl)-1*H*-indole (19)

^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (126 MHz) NMR spectra of **19** in $CDCl_3$



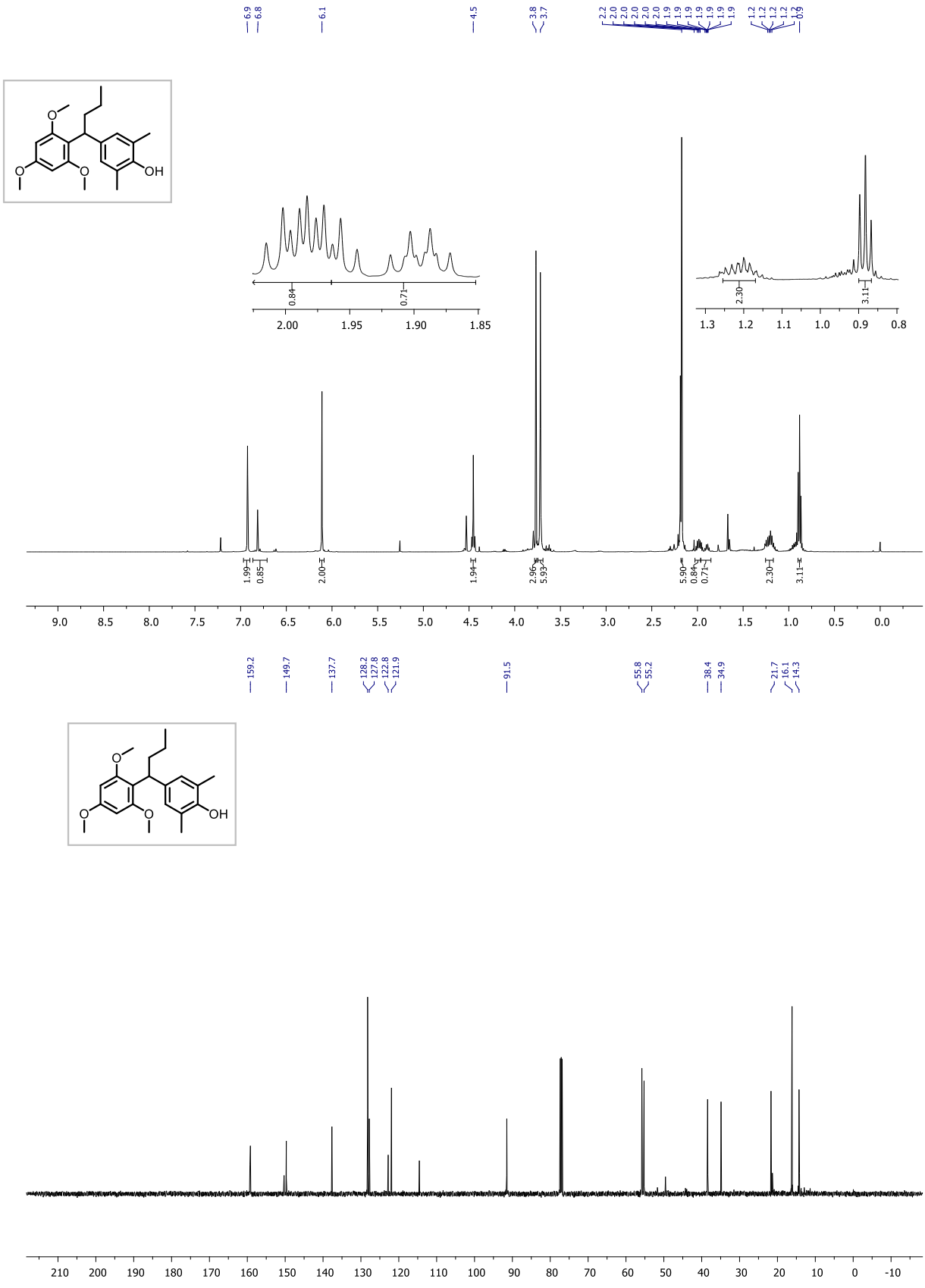






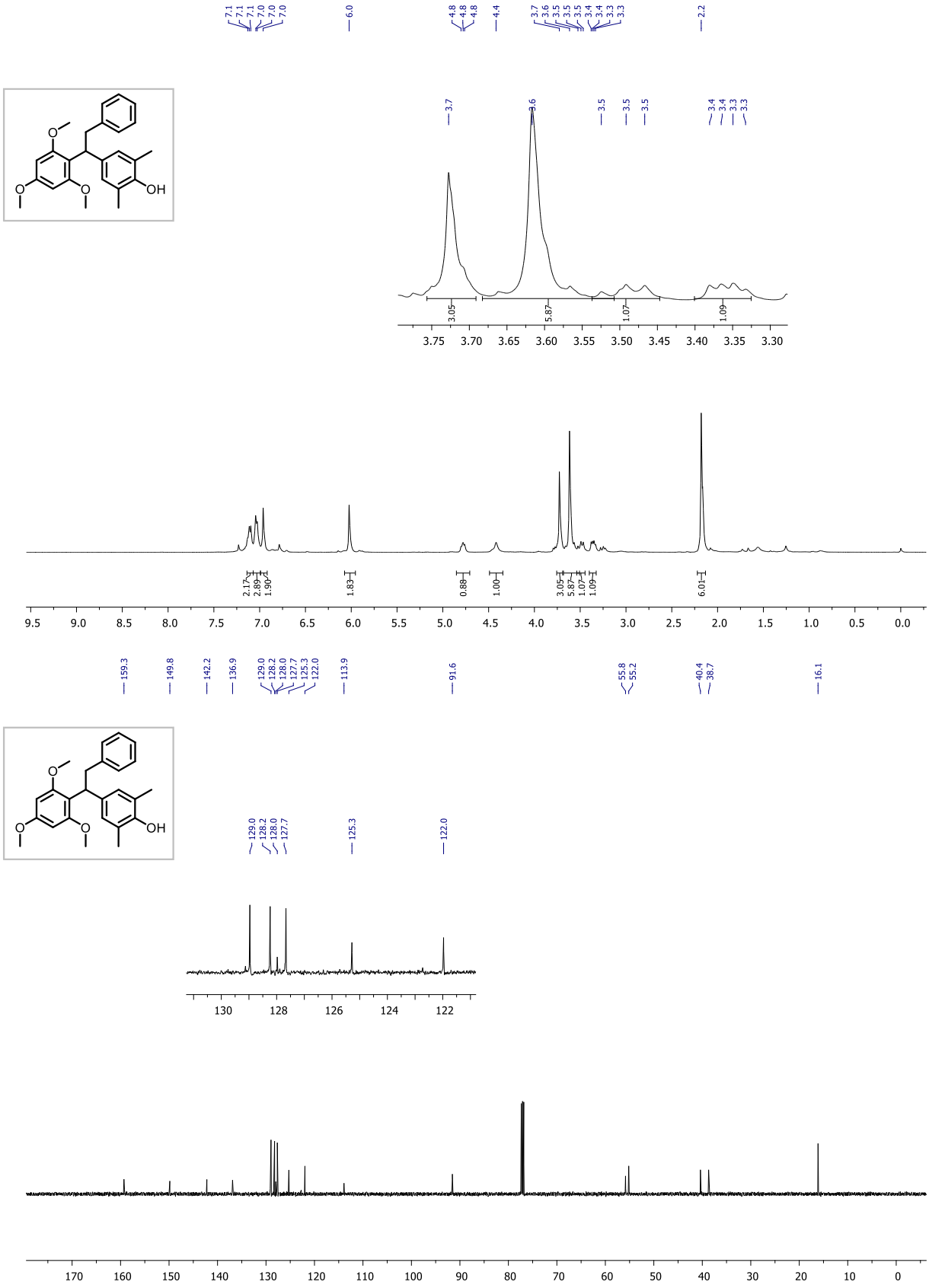
2,6-Dimethyl-4-(1-(2,4,6-trimethoxyphenyl)butyl)phenol (20)

^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (126 MHz) NMR spectra of **20** in $CDCl_3$



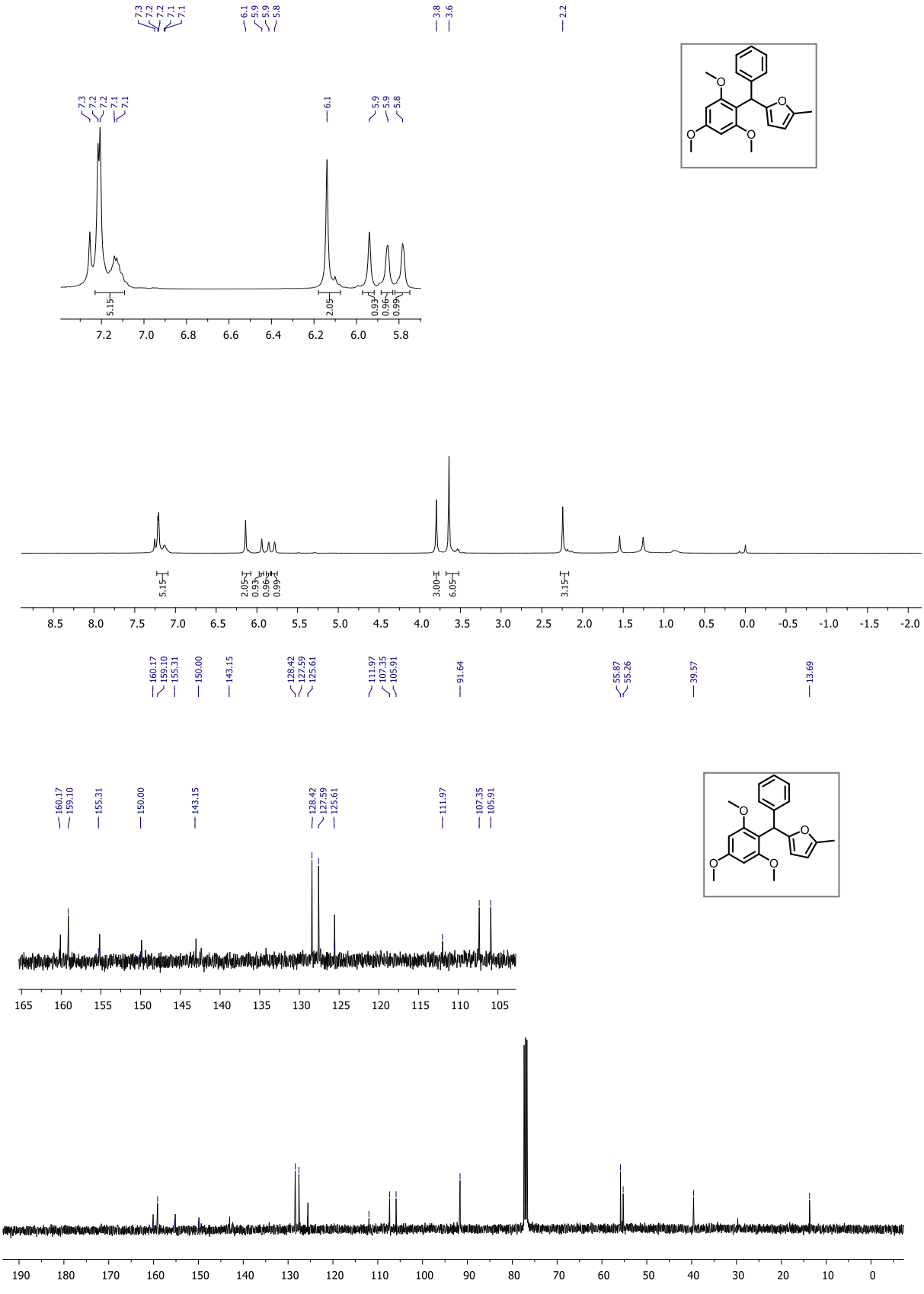
2,6-Dimethyl-4-(2-phenyl-1-(2,4,6-trimethoxyphenyl)ethyl)phenol (21)

^{1}H (400 MHz) and $^{13}C\{^{1}H\}$ (126 MHz) NMR spectra of **21** in $CDCl_3$



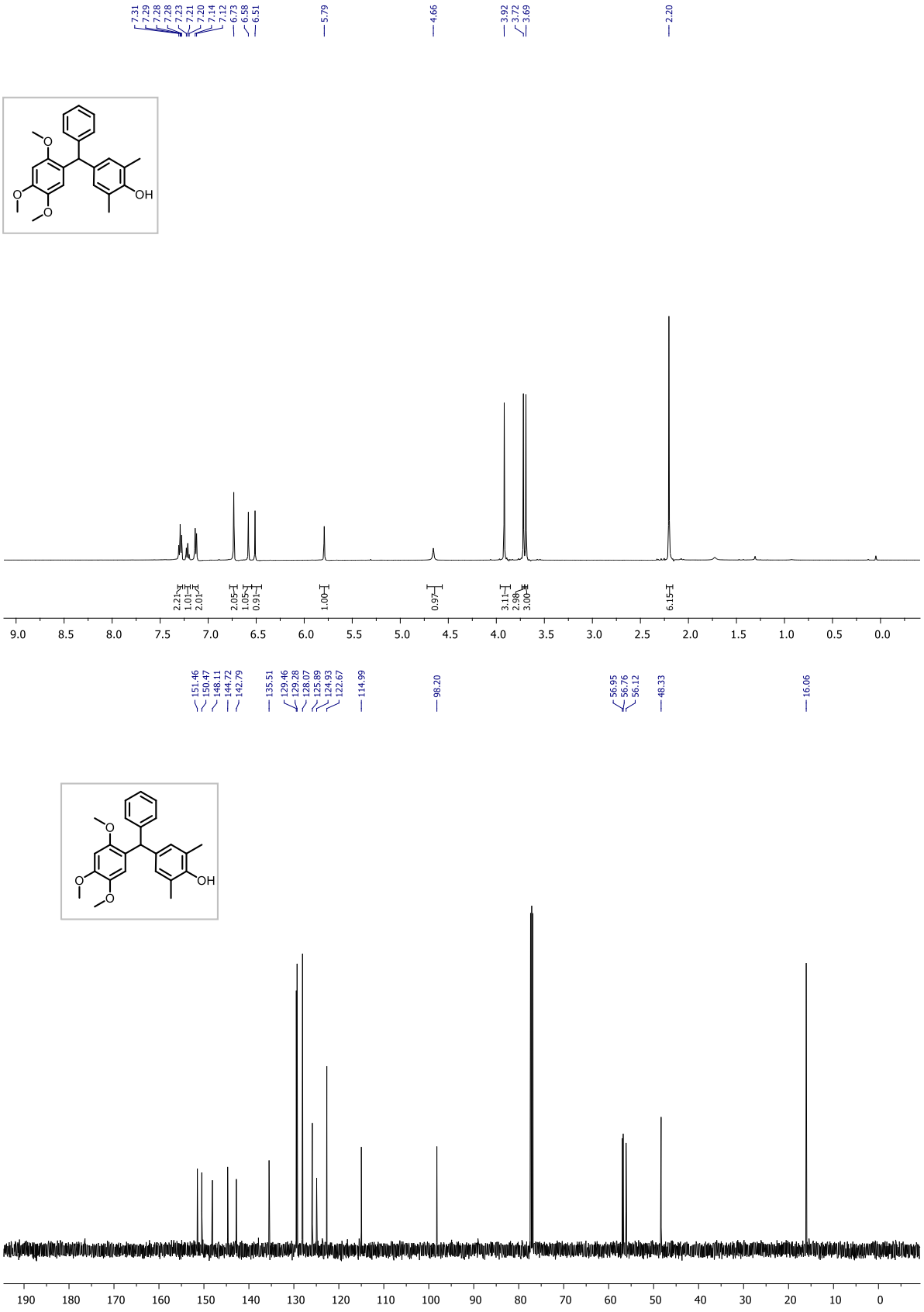
2-Methyl-5-(phenyl(2,4,6-trimethoxyphenyl)methyl)furan (22)

^{1}H (400 MHz) and $^{13}C\{^{1}H\}$ (101 MHz) NMR spectra of **22** in $CDCl_3$



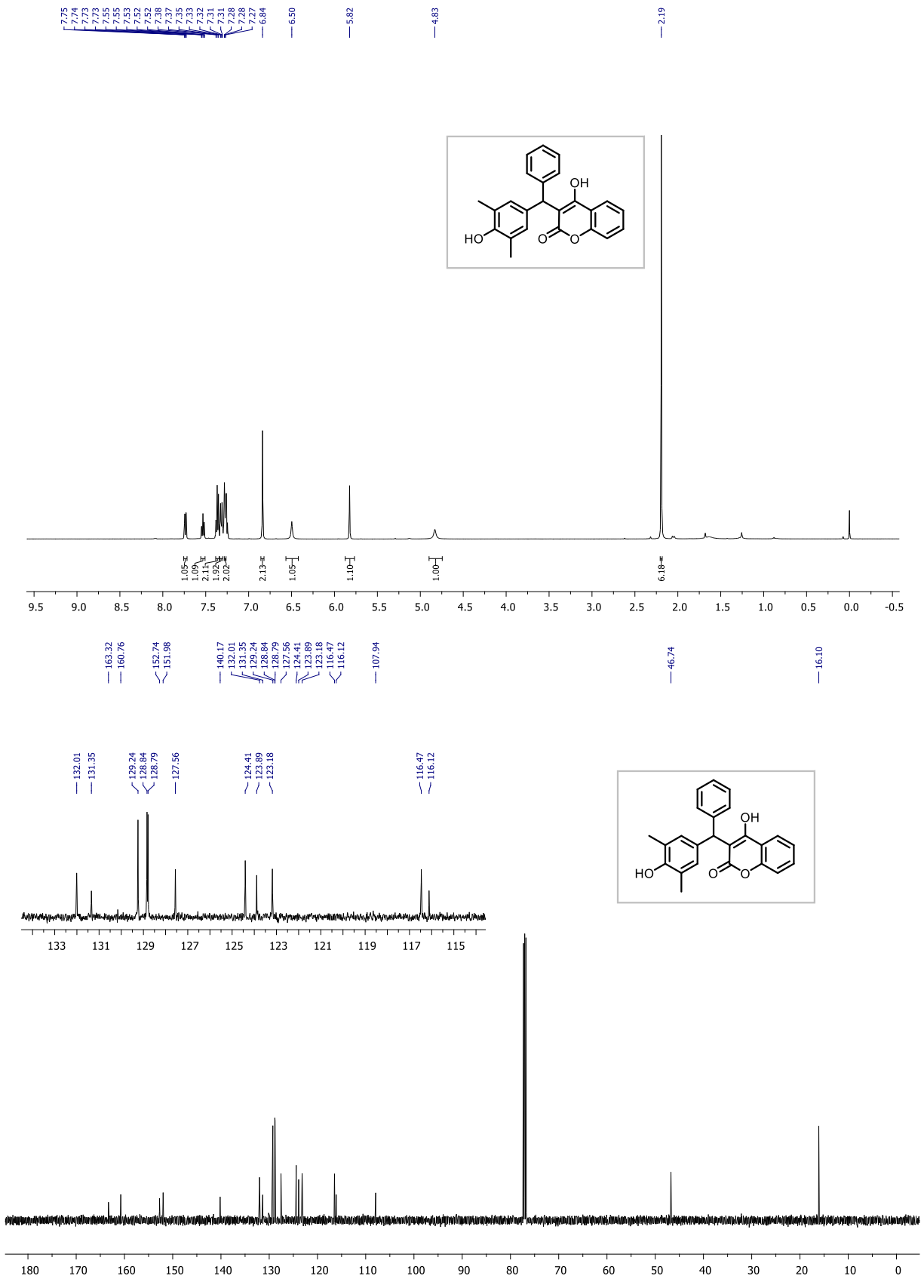
2,6-Dimethyl-4-(phenyl(2,4,5-trimethoxyphenyl)methyl)phenol (23)

^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (126 MHz) NMR spectra of **23** in $CDCl_3$



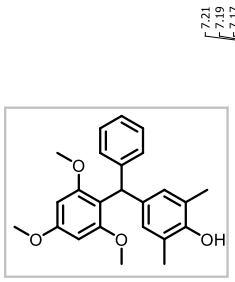
4-Hydroxy-3-((4-hydroxy-3,5-dimethylphenyl)(phenyl)methyl)-2*H*-chromen-2-one (24)

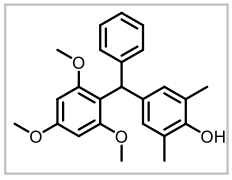
^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (126 MHz) NMR spectra of **24** in $CDCl_3$



4,4'-(Phenylmethylene)bis(2,6-dimethylphenol) (25)

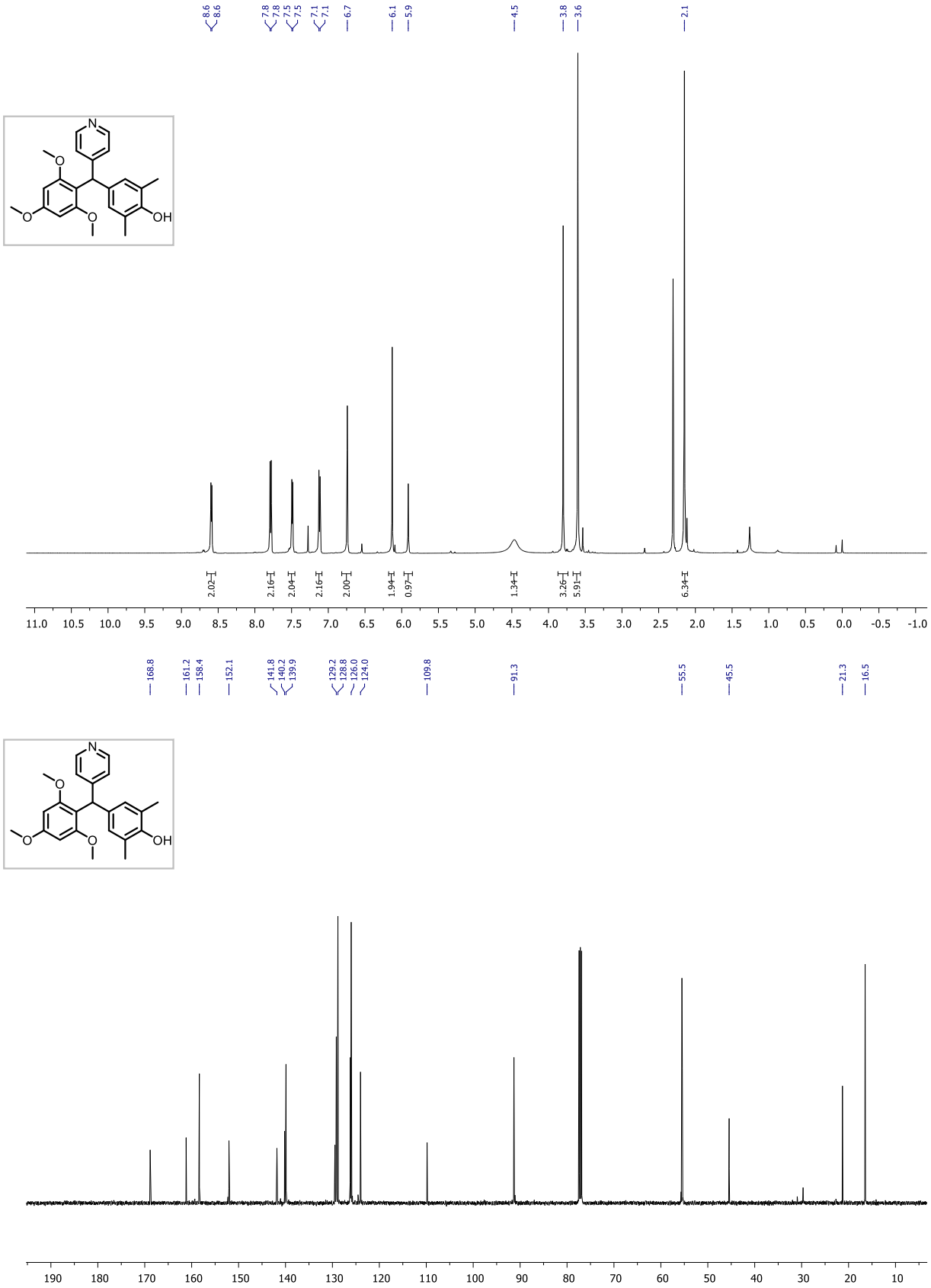
^{1}H (400 MHz) and $^{13}C\{^{1}H\}$ (126 MHz) NMR spectra of **25** in $CDCl_3$





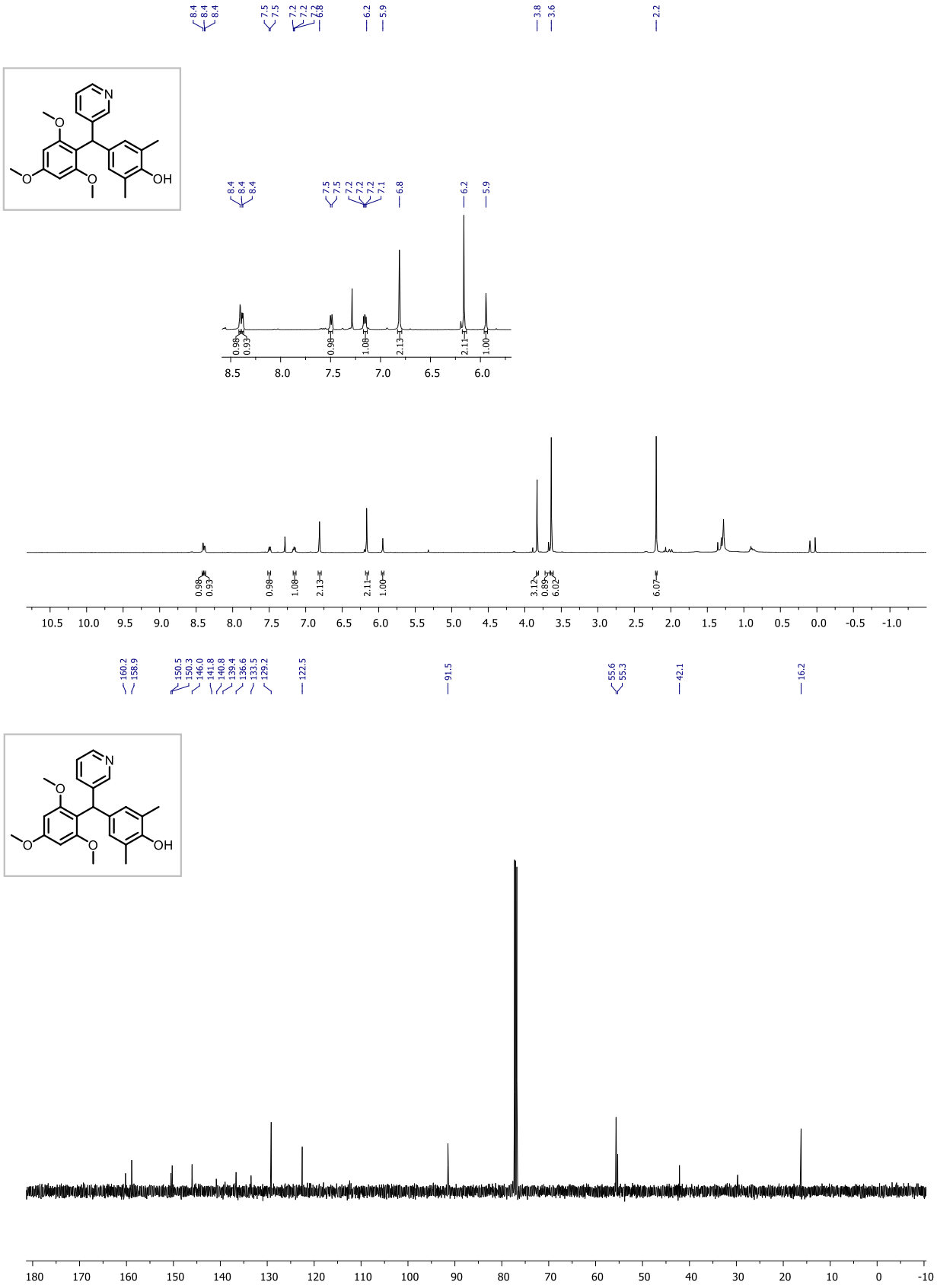
2,6-Dimethyl-4-(pyridin-4-yl(2,4,6-trimethoxyphenyl)methyl)phenol (26)

^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (126 MHz) NMR spectra of **26** in $CDCl_3$



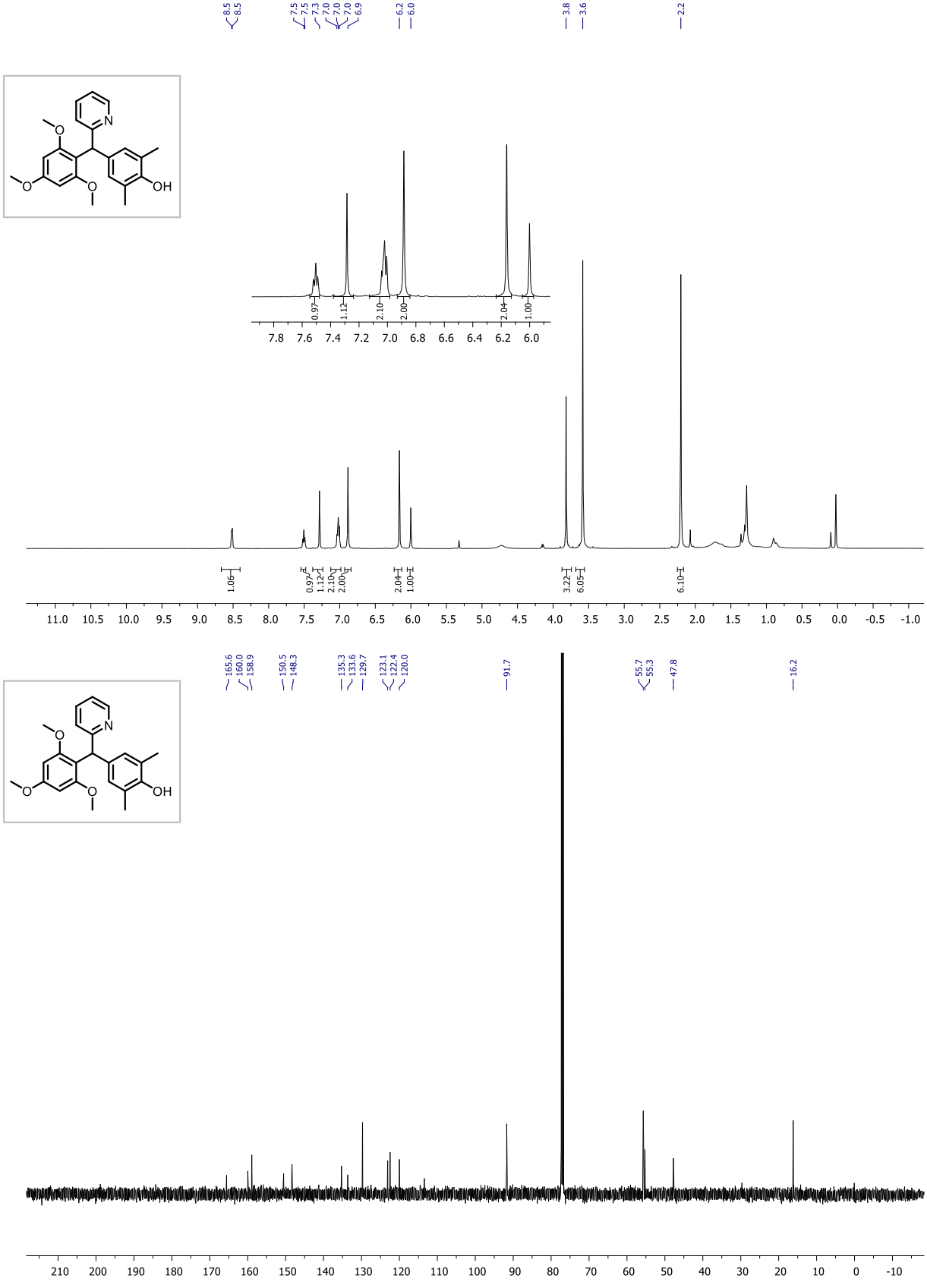
2,6-dimethyl-4-(pyridin-3-yl(2,4,6-trimethoxyphenyl)methyl)phenol (27)

^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (126 MHz) NMR spectra of **27** in $CDCl_3$



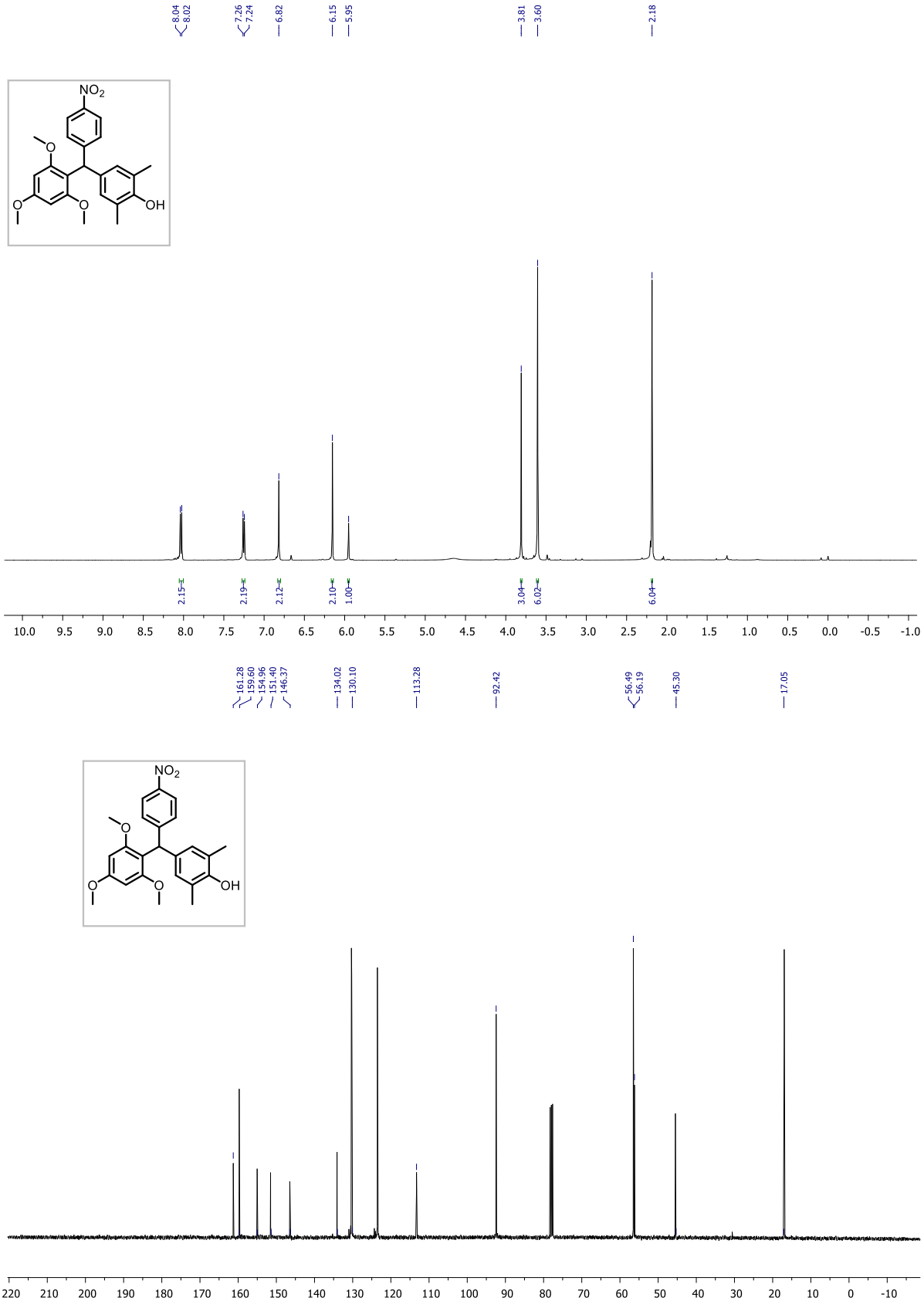
2,6-dimethyl-4-(pyridin-2-yl(2,4,6-trimethoxyphenyl)methyl)phenol (28)

^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (126 MHz) NMR spectra of **28** in $CDCl_3$



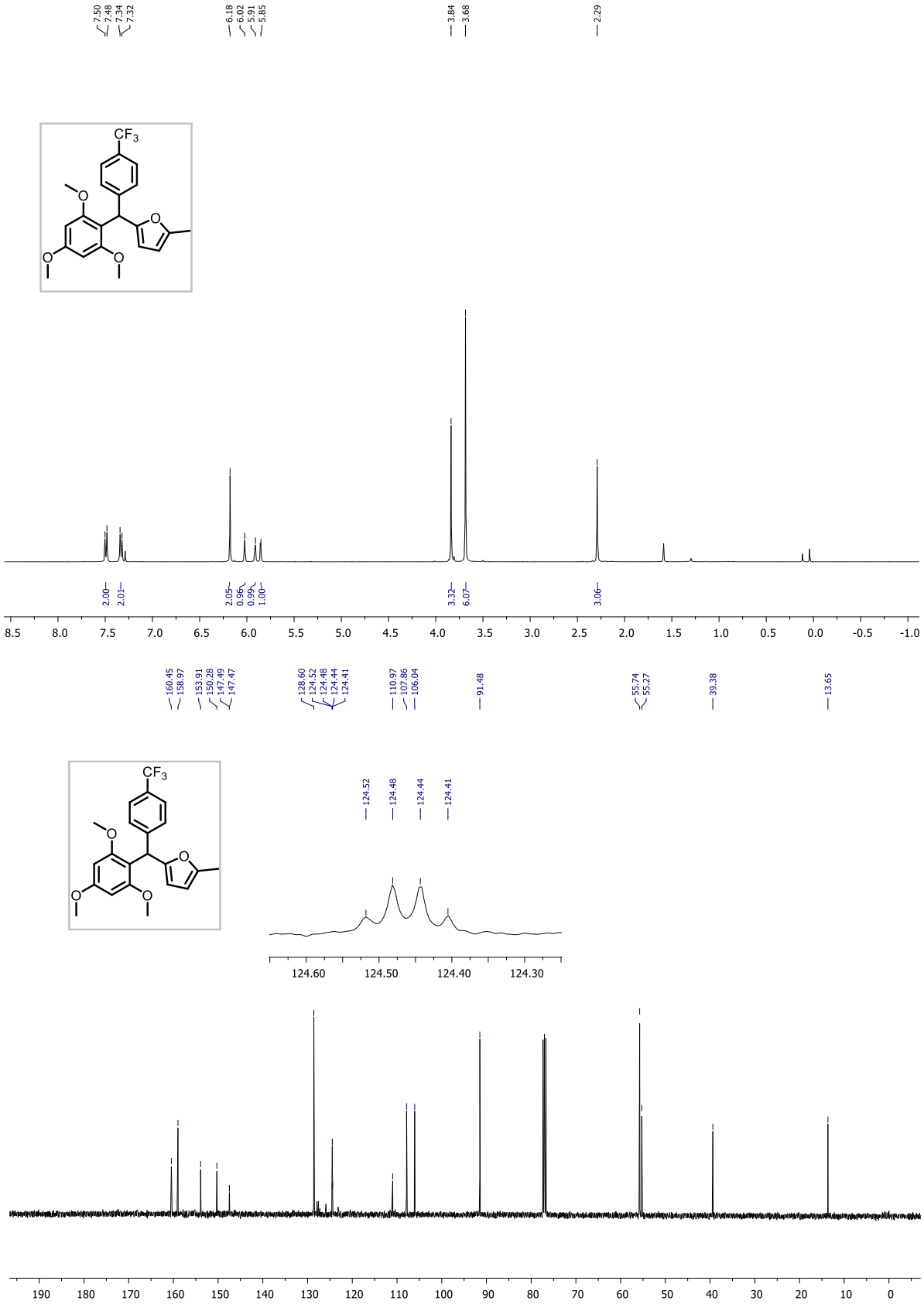
2,6-Dimethyl-4-((4-nitrophenyl)(2,4,6-trimethoxyphenyl)methyl)phenol (29)

^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (101 MHz) NMR spectra of **29** in $CDCl_3$



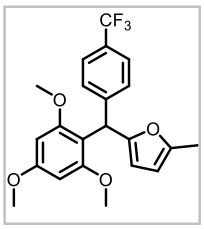
2-Methyl-5-((4-(trifluoromethyl)phenyl)(2,4,6-trimethoxyphenyl)methyl)furan (30)

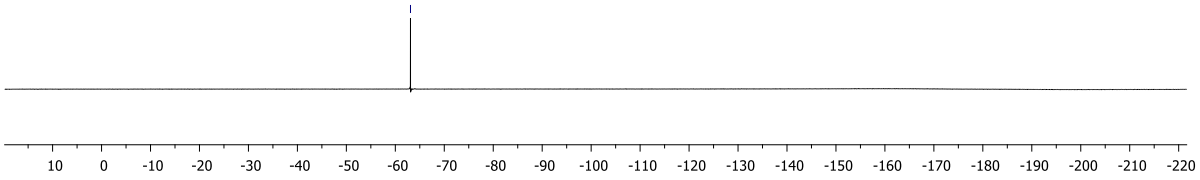
^{1}H (400 MHz), $^{13}C\{^{1}H\}$ (101 MHz) and ^{19}F NMR spectra of **30** in $CDCl_3$



^{19}F NMR (471 MHz, CDCl$_3$) δ -63.1

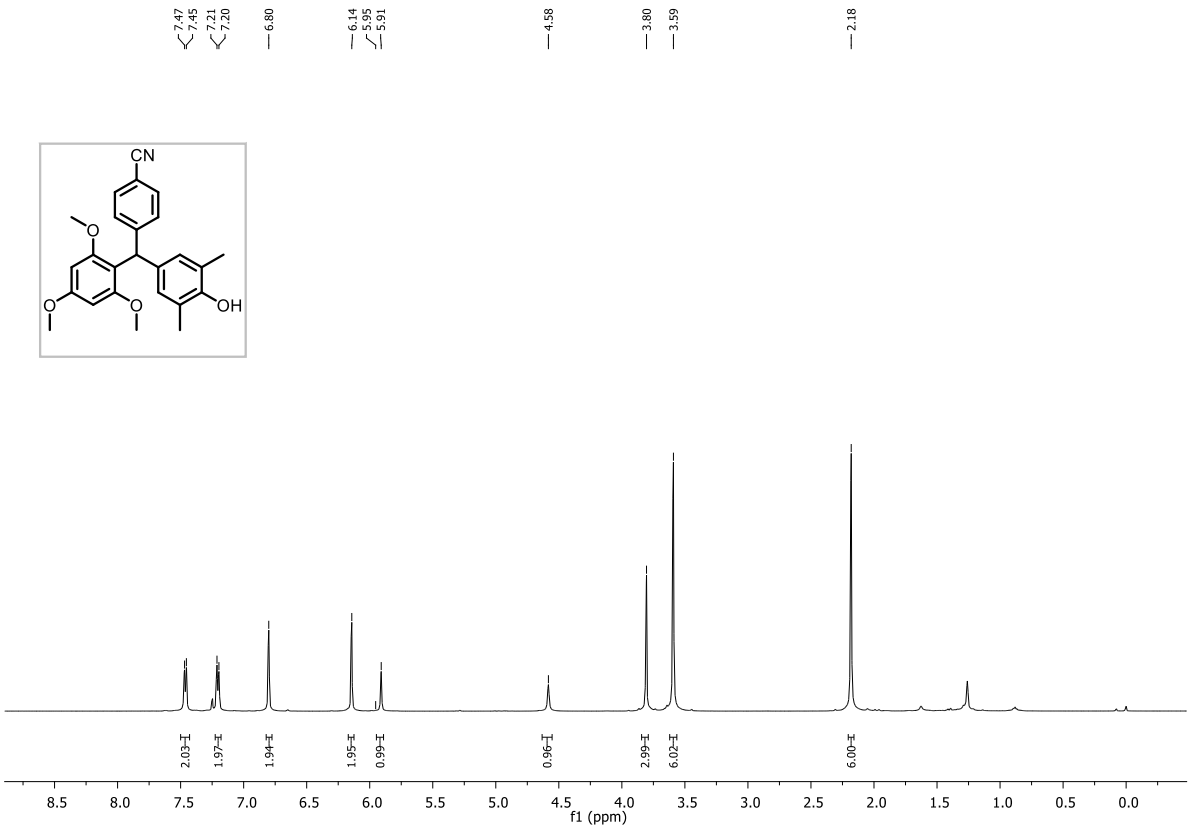
-63.10

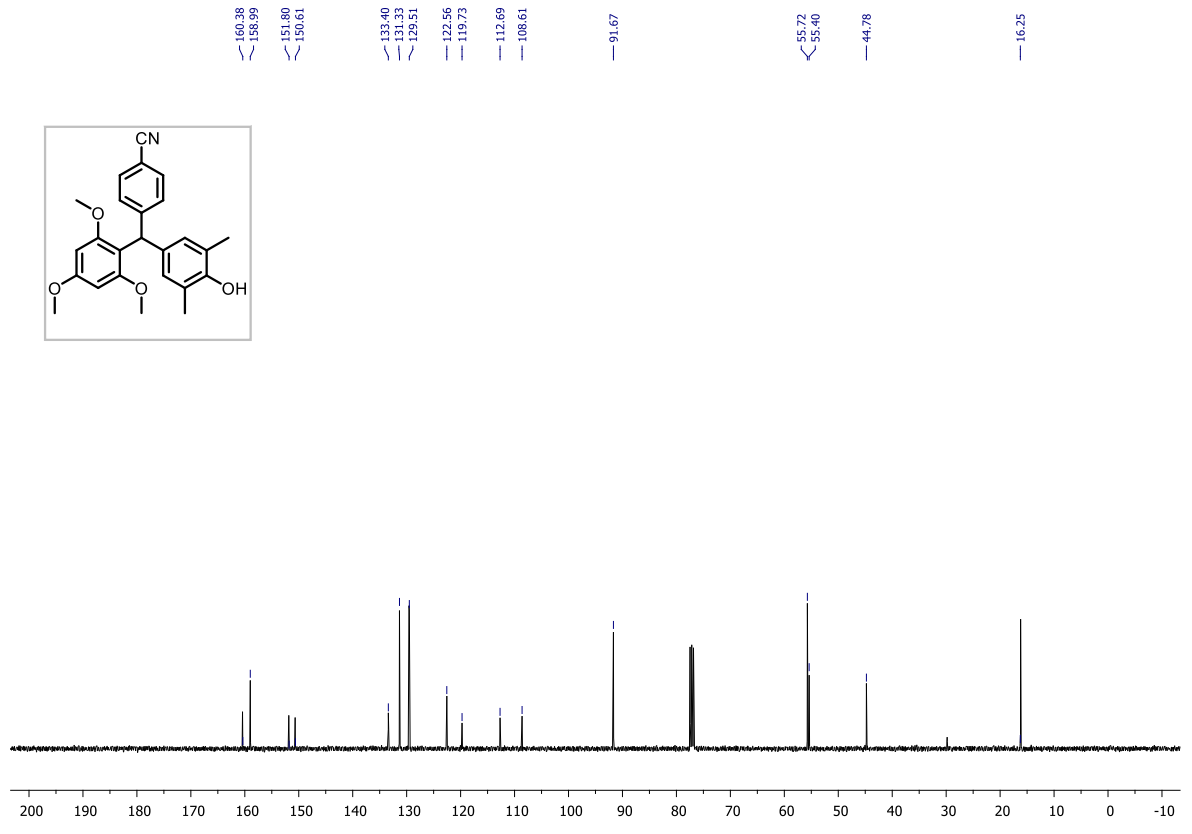




4-((4-Hydroxy-3,5-dimethylphenyl)(2,4,6-trimethoxyphenyl)methyl)benzonitrile (31)

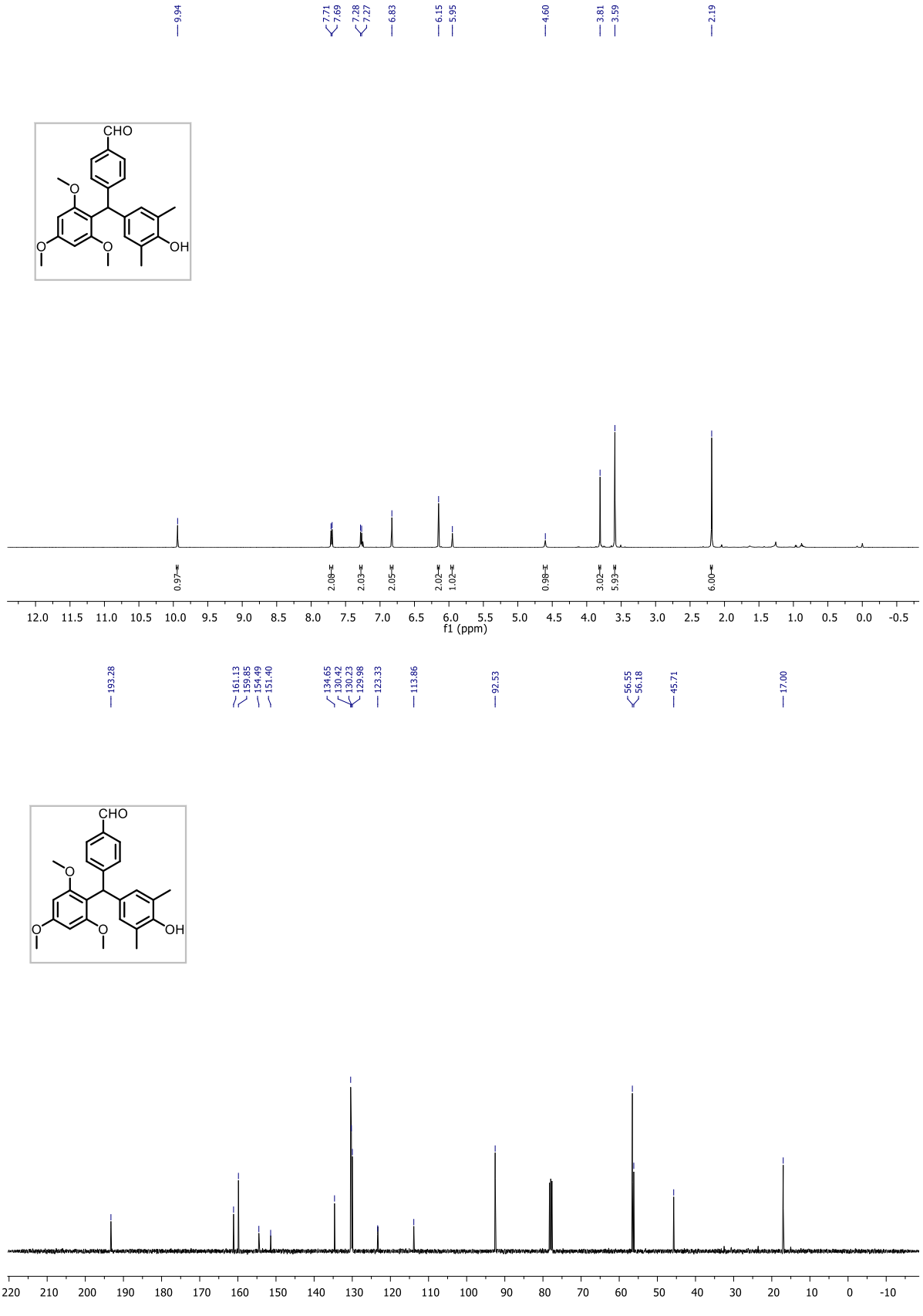
^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (101 MHz) spectra of **31** in $CDCl_3$





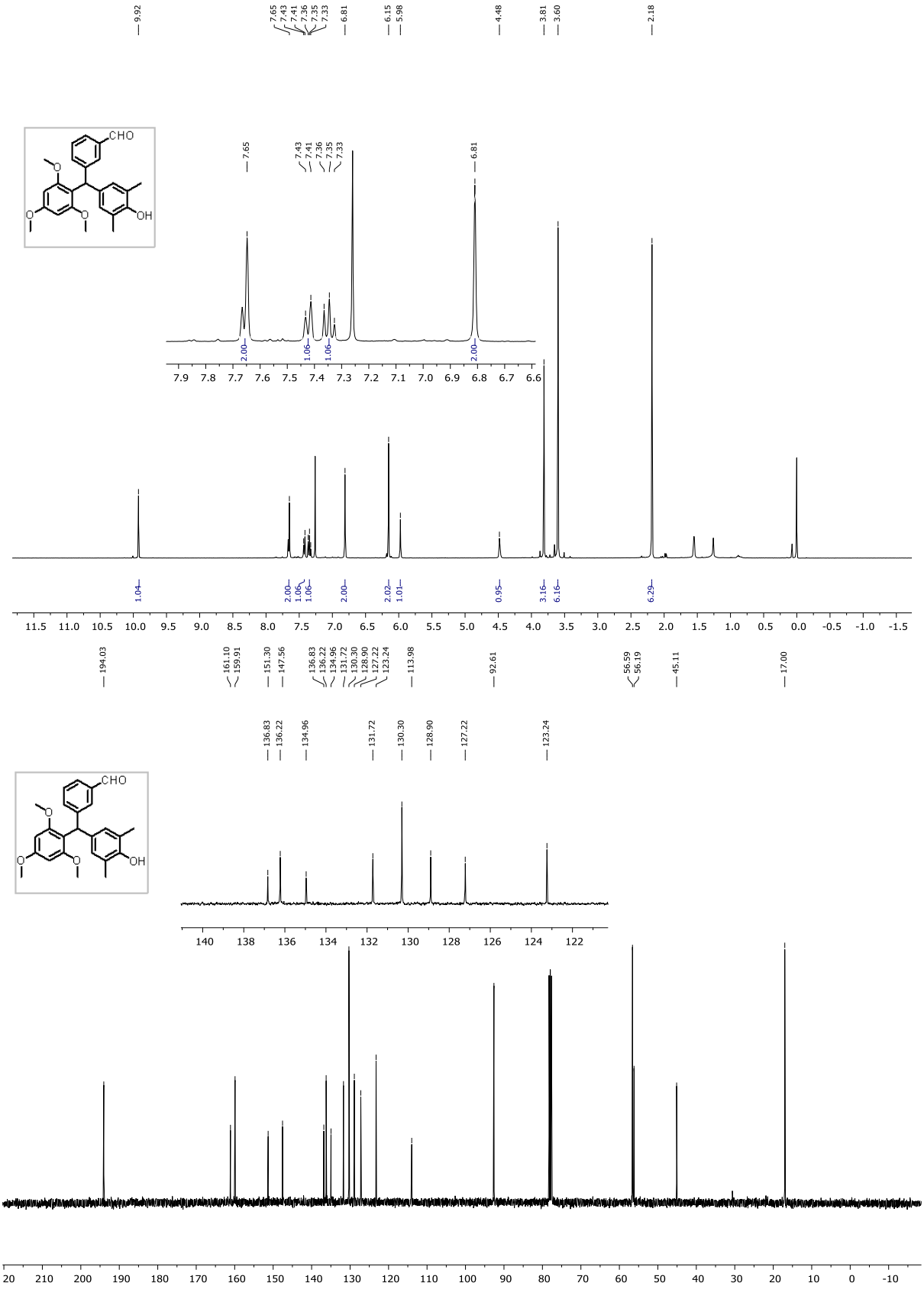
4-((4-Hydroxy-3,5-dimethylphenyl)(2,4,6-trimethoxyphenyl)methyl)benzaldehyde (32)

^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (101 MHz) spectra of **32** in $CDCl_3$



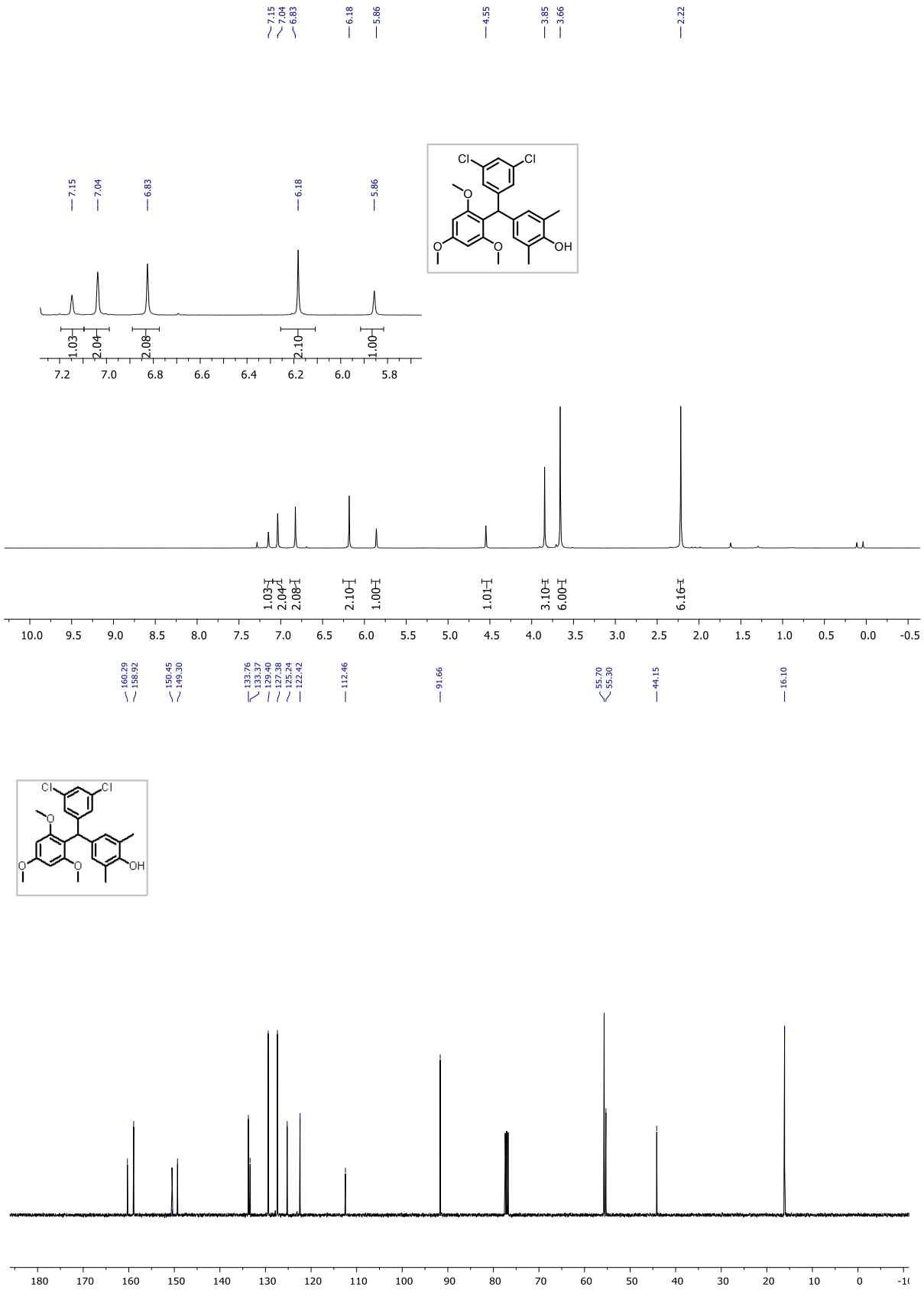
3-((4-Hydroxy-3,5-dimethylphenyl)(2,4,6-trimethoxyphenyl)methyl)benzaldehyde (33)

^{1}H (400 MHz) and $^{13}C\{^{1}H\}$ (101 MHz) spectra of **33** in $CDCl_3$



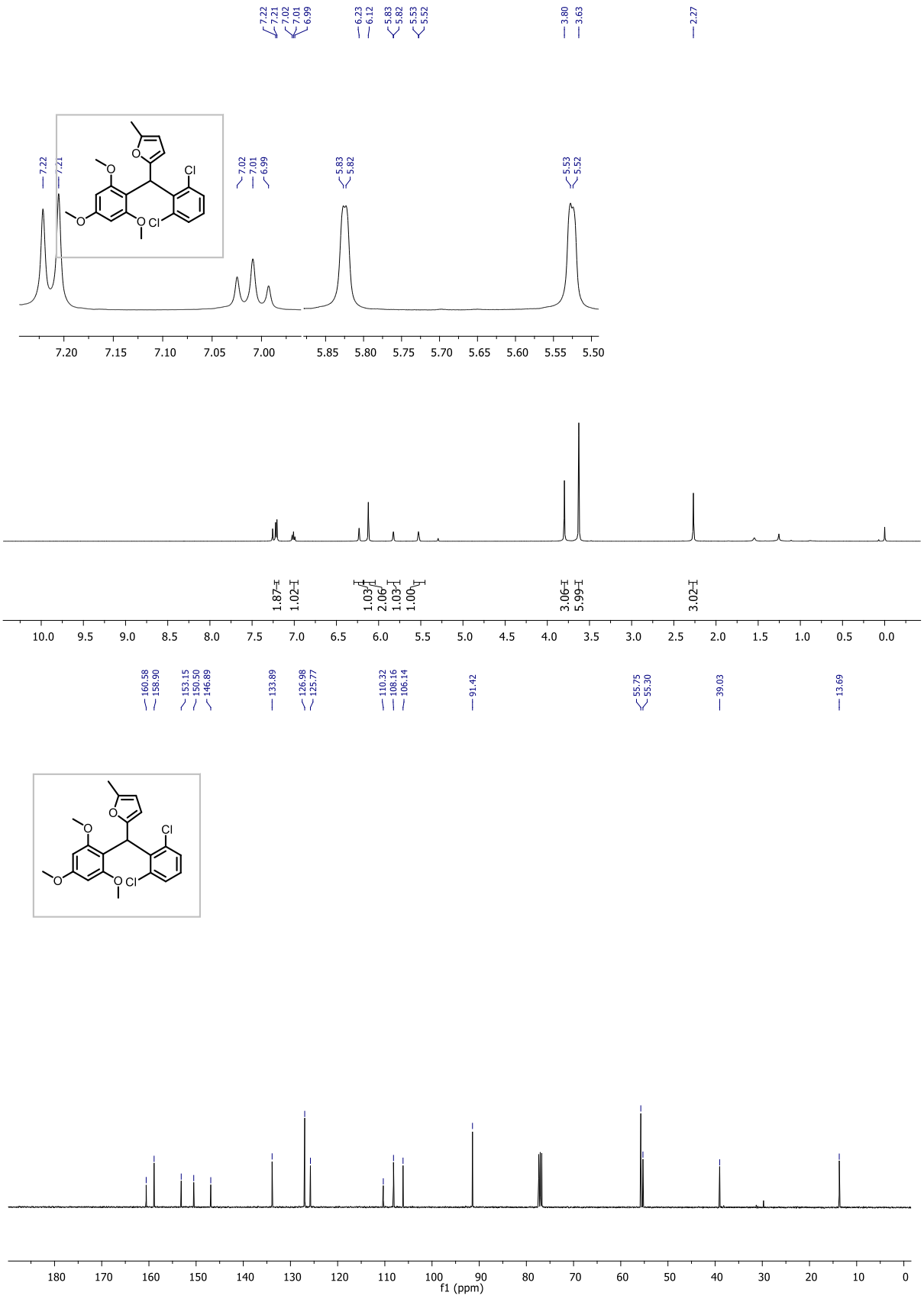
4-((3,5-Dichlorophenyl)(2,4,6-trimethoxyphenyl)methyl)-2,6-dimethylphenol (34)

^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (101 MHz) spectra of **34** in $CDCl_3$



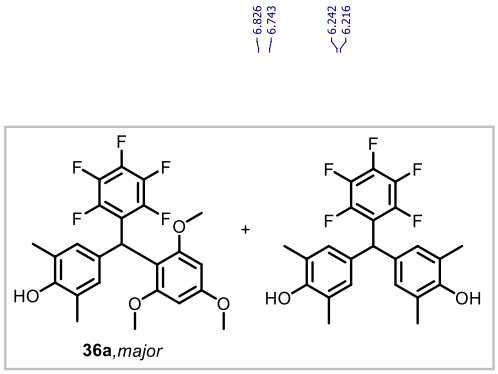
2-((2,6-Dichlorophenyl)(2,4,6-trimethoxyphenyl)methyl)-5-methylfuran (35)

^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (101 MHz) spectra of **35** in $CDCl_3$

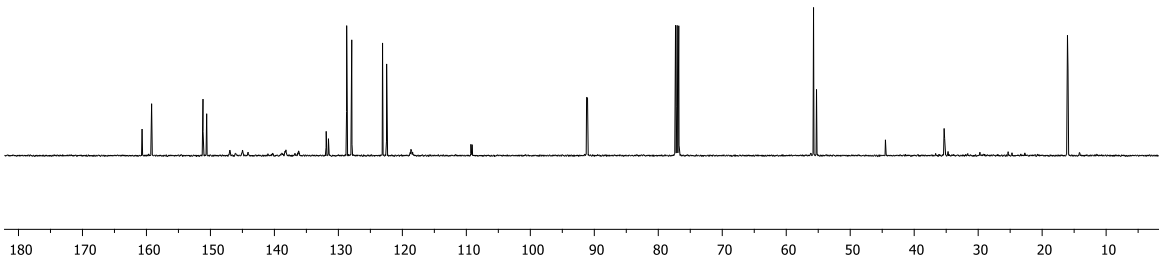


2,6-Dimethyl-4-((perfluorophenyl)(2,4,6-trimethoxyphenyl)methyl)phenol (36)

^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (126 MHz) spectra of **36** in $CDCl_3$

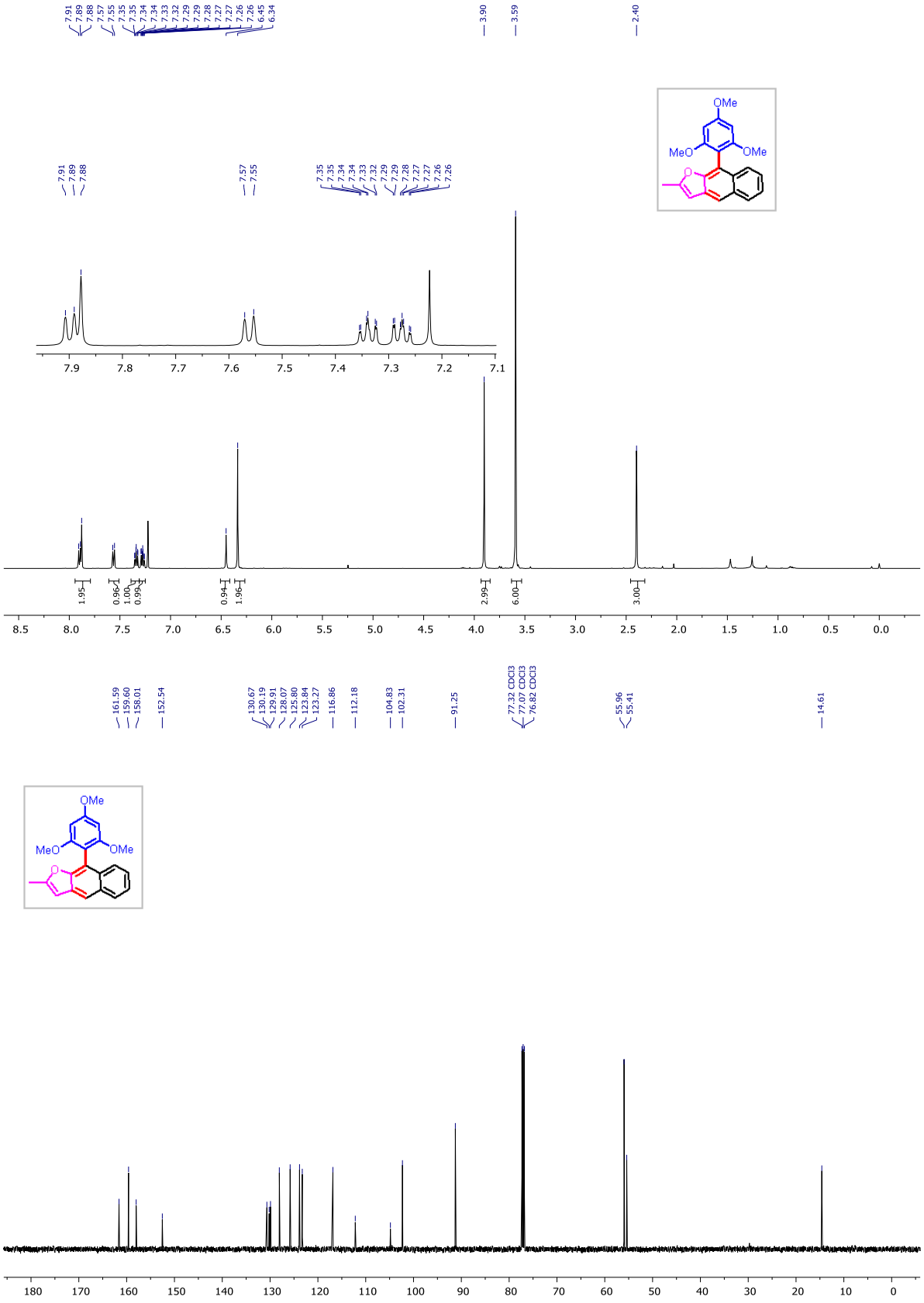


36a,*major*



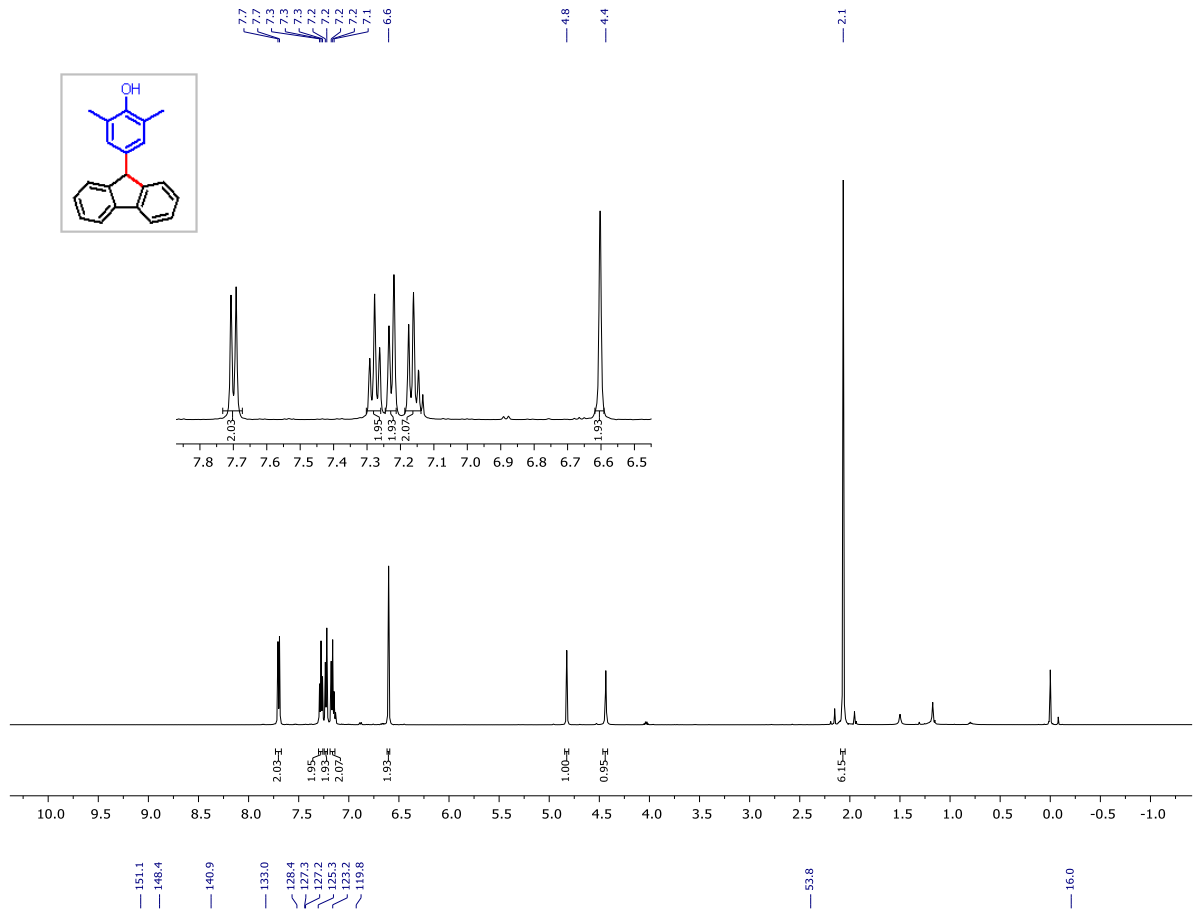
2-Methyl-9-(2,4,6-trimethoxyphenyl)naphtho[2,3-b]furan (37)

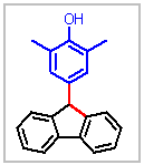
^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (126 MHz) spectra of **37** in $CDCl_3$



4-(9*H*-fluoren-9-yl)-2,6-dimethylphenol (38)

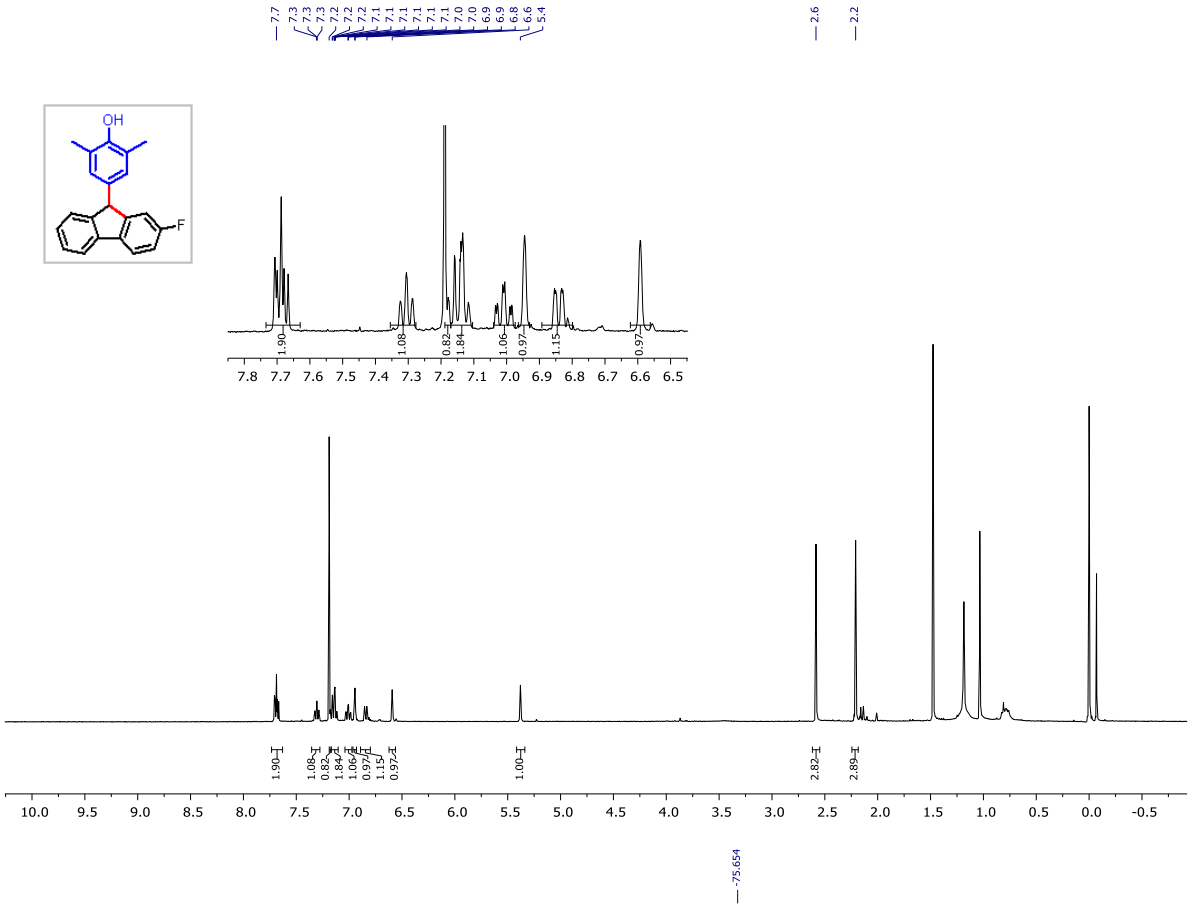
^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (126 MHz) spectra of **38** in $CDCl_3$

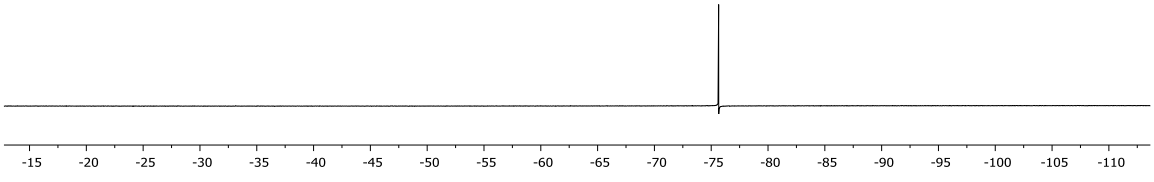




4-(2-Fluoro-9H-fluoren-9-yl)-2,6-dimethylphenol (39)

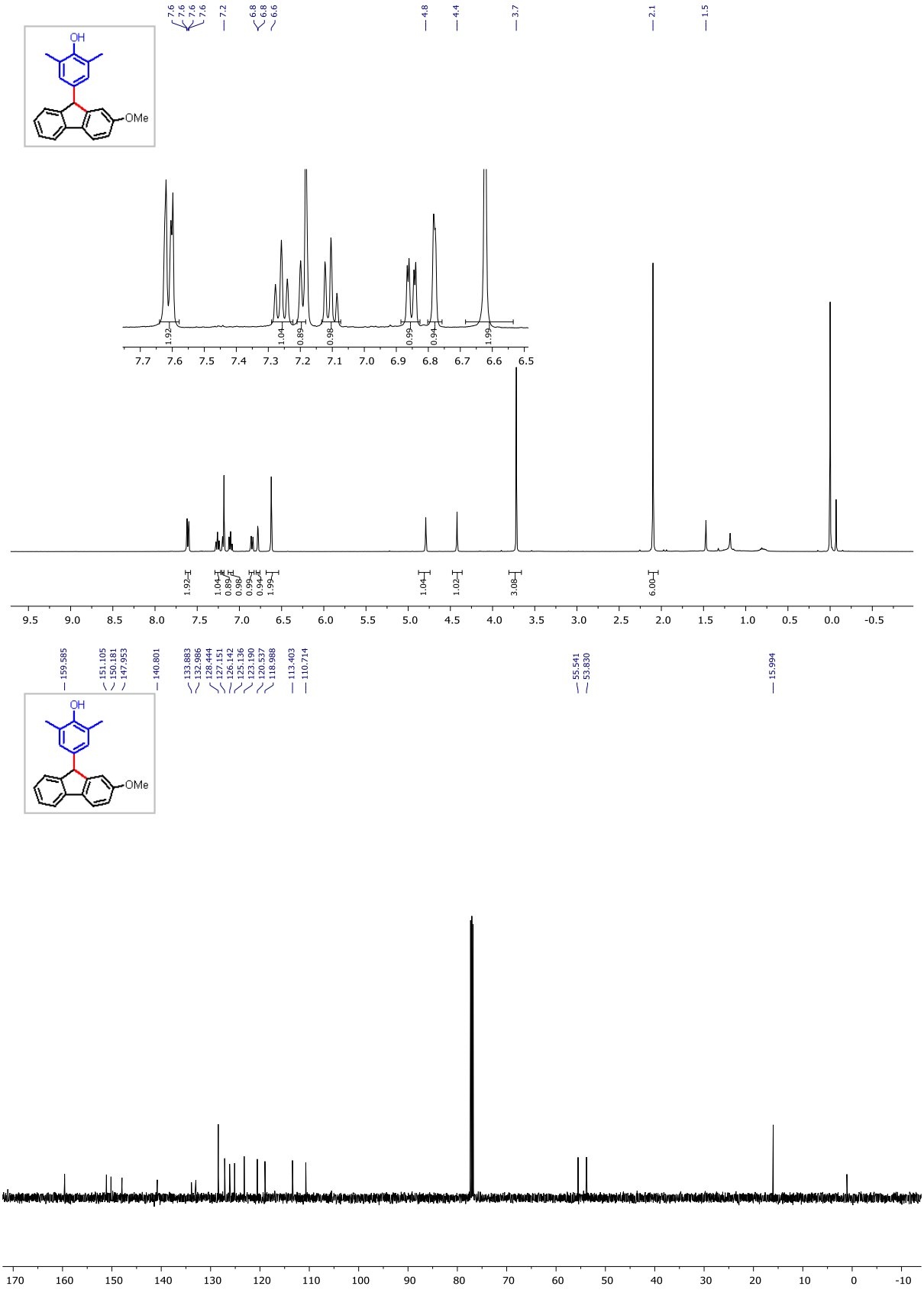
^{1}H (400 MHz) and ^{19}**F** (471 MHz) spectra of **39** in $CDCl_3$





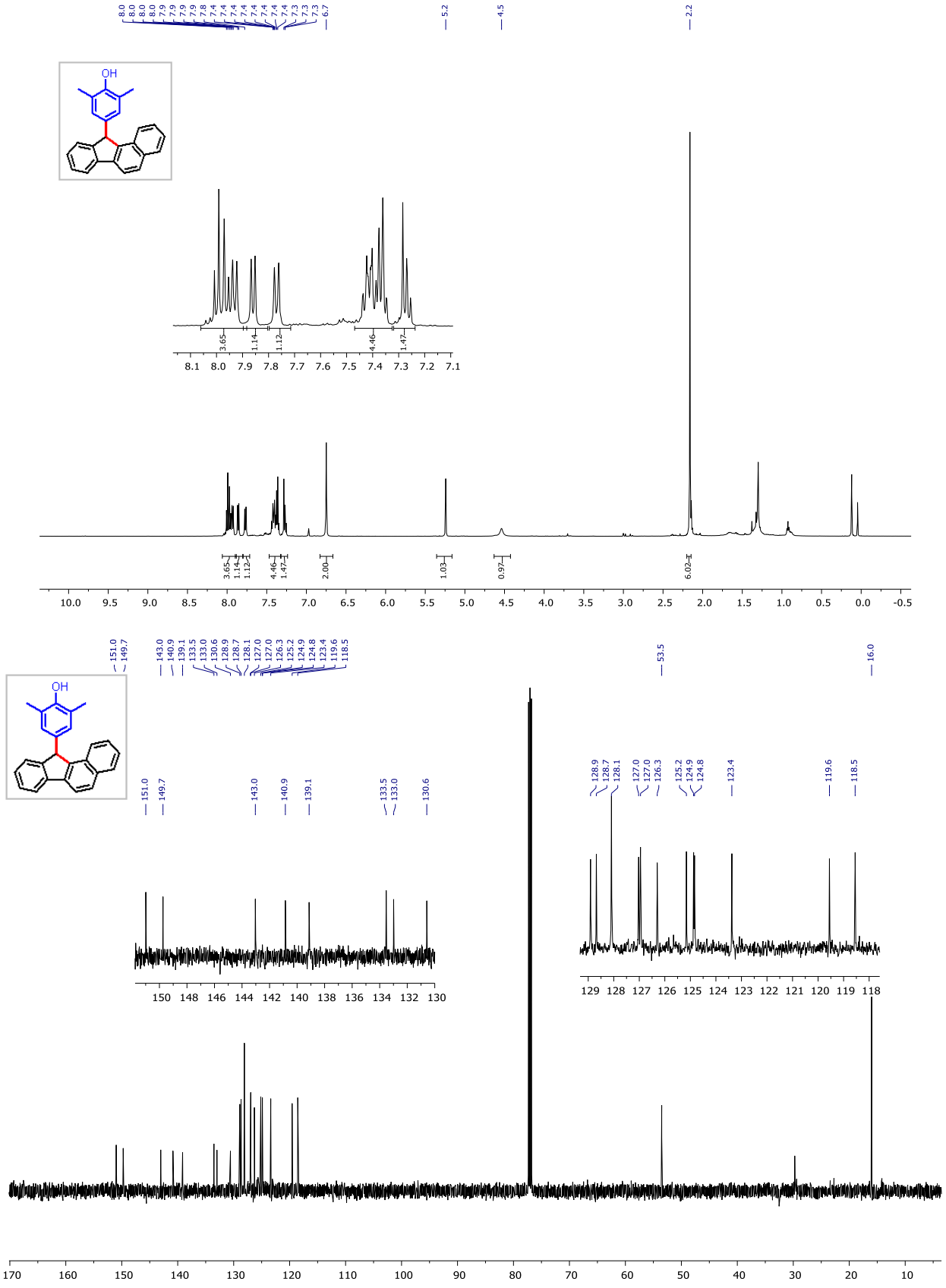
4-(2-Methoxy-9*H*-fluoren-9-yl)-2,6-dimethylphenol (40)

^{1}H (400 MHz) and $^{13}C\{^{1}H\}$ (126 MHz) spectra of **40** in $CDCl_3$



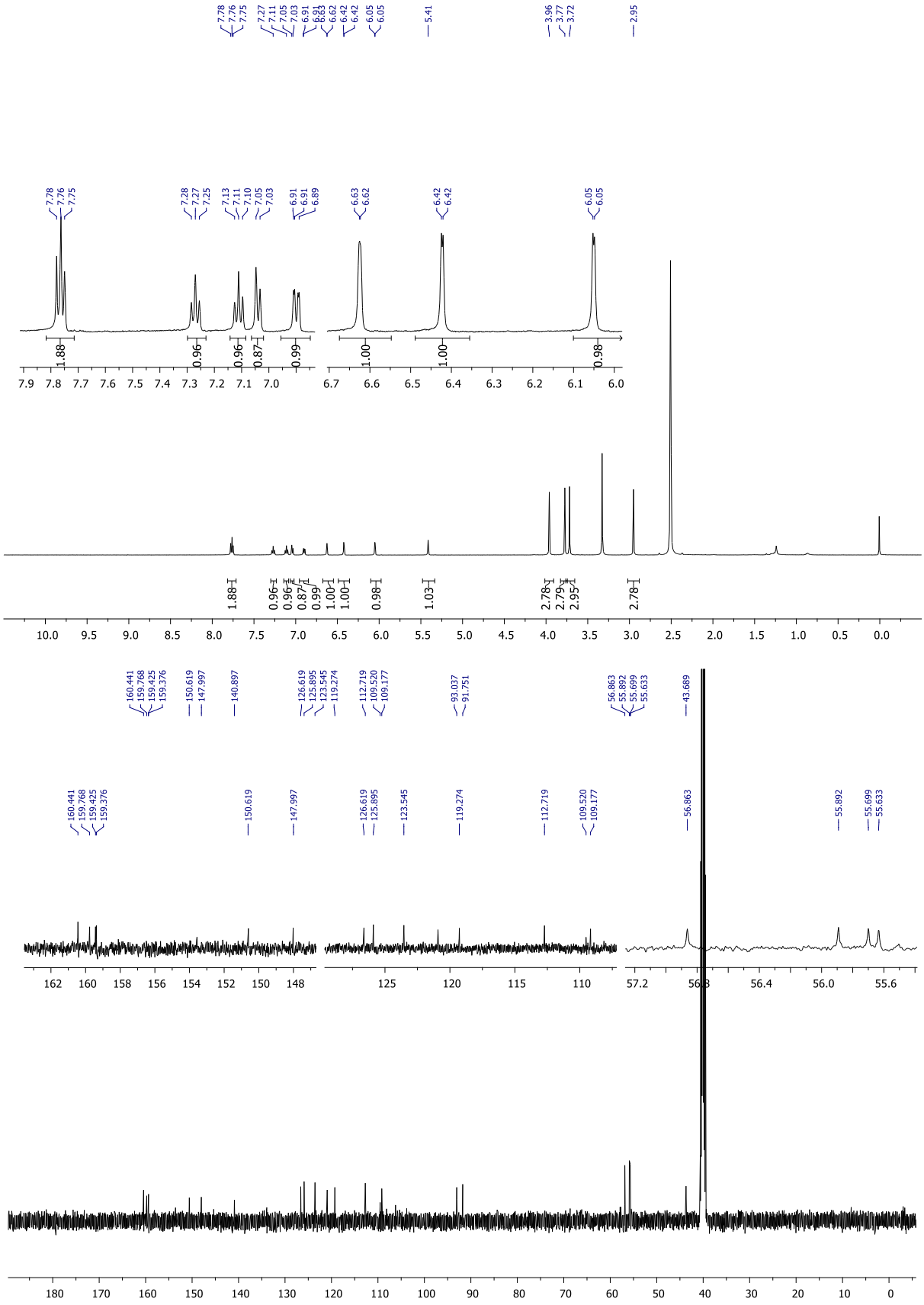
4-(11*H*-Benzo[a]fluoren-11-yl)-2,6-dimethylphenol (41)

^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (126 MHz) spectra of **41** in $CDCl_3$



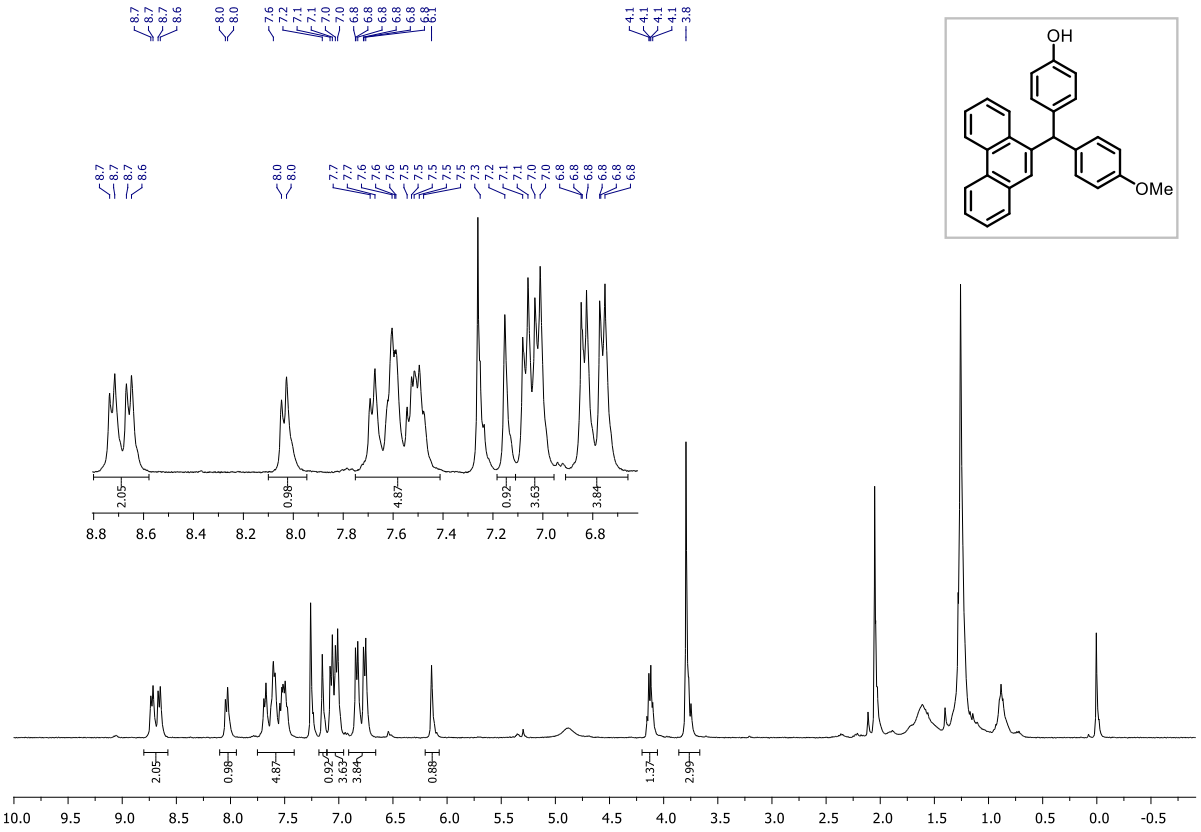
2-Methoxy-9-(2,4,6-trimethoxyphenyl)-9*H*-fluorene (42)

^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (126 MHz) spectra of **42** in DMSO-d_6



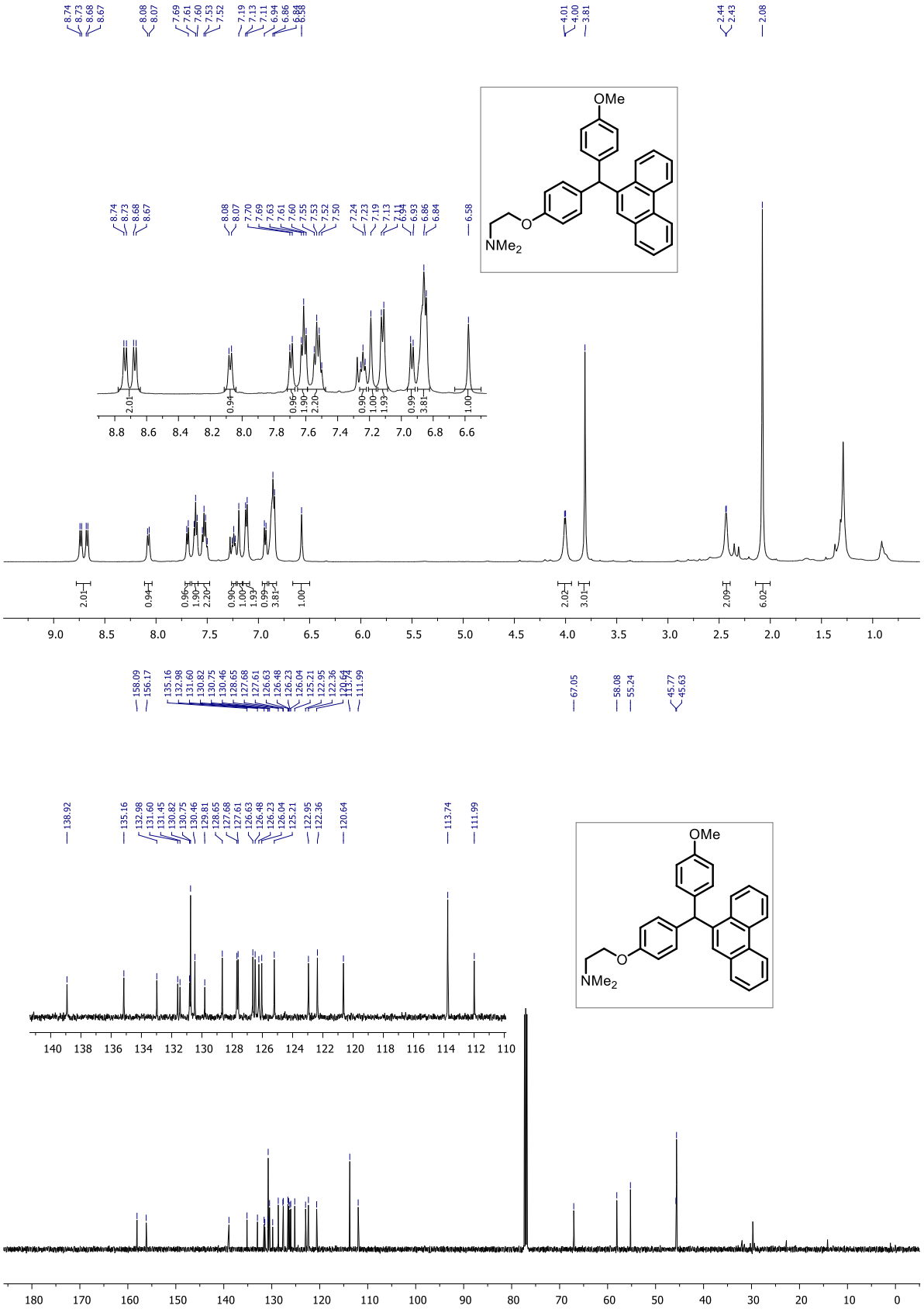
4-((4-Methoxyphenyl)(phenanthren-9-yl)methyl)phenol (43)

^{1}H (500 MHz) spectra of **43** in $CDCl_3$



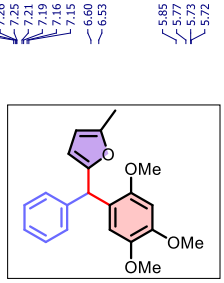
2-(4-((4-Methoxyphenyl)(phenanthren-9-yl)methyl)phenoxy)-N,N-dimethylethan-1-amine (44)

^{1}H (500 MHz) and ^{13}C (126 MHz) spectra of **44** in $CDCl_3$



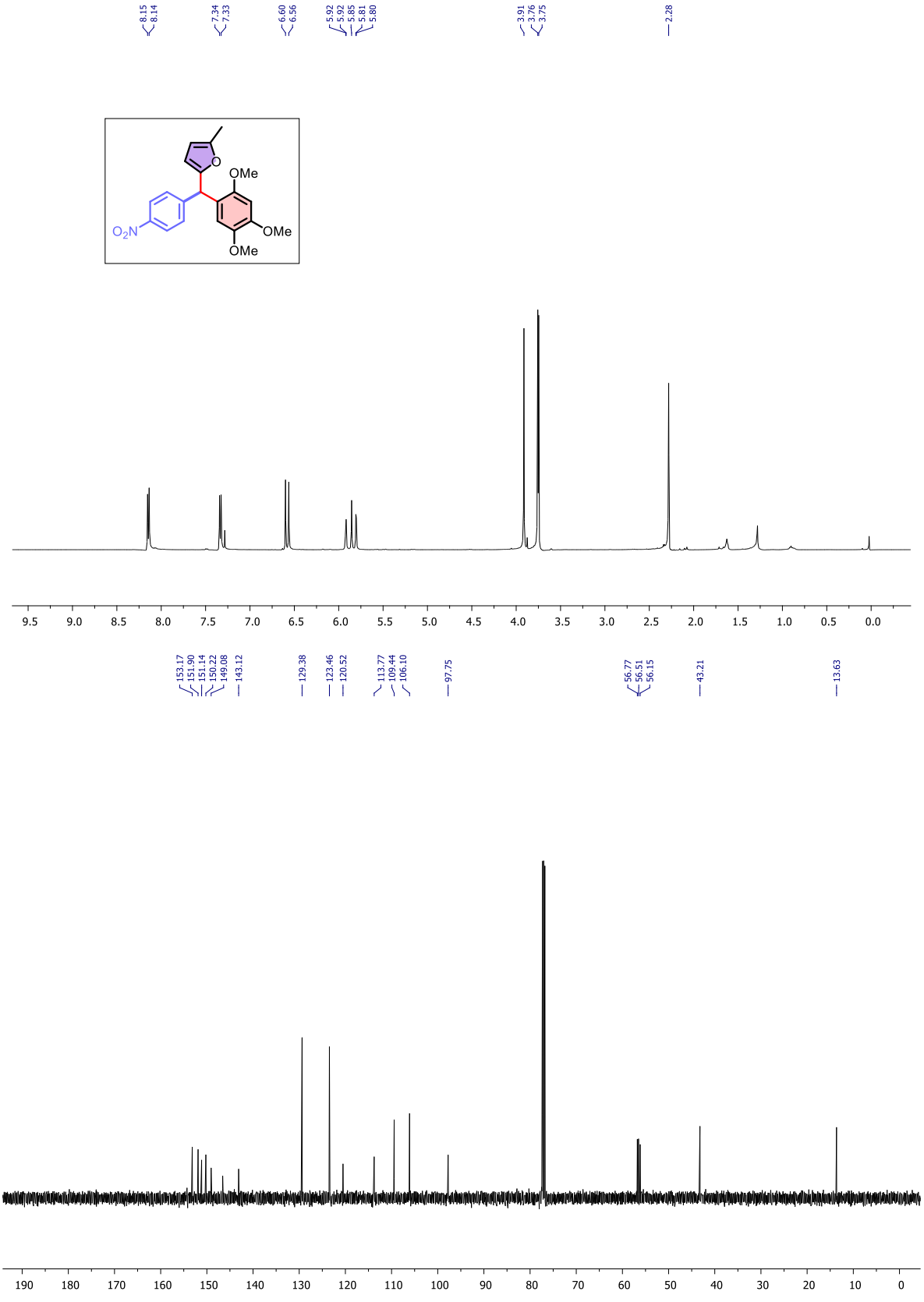
2-Methyl-5-(phenyl(2,4,5-trimethoxyphenyl)methyl)furan (45)

^{1}H (500 MHz) and ^{13}C (126 MHz) spectra of **45** in $CDCl_3$



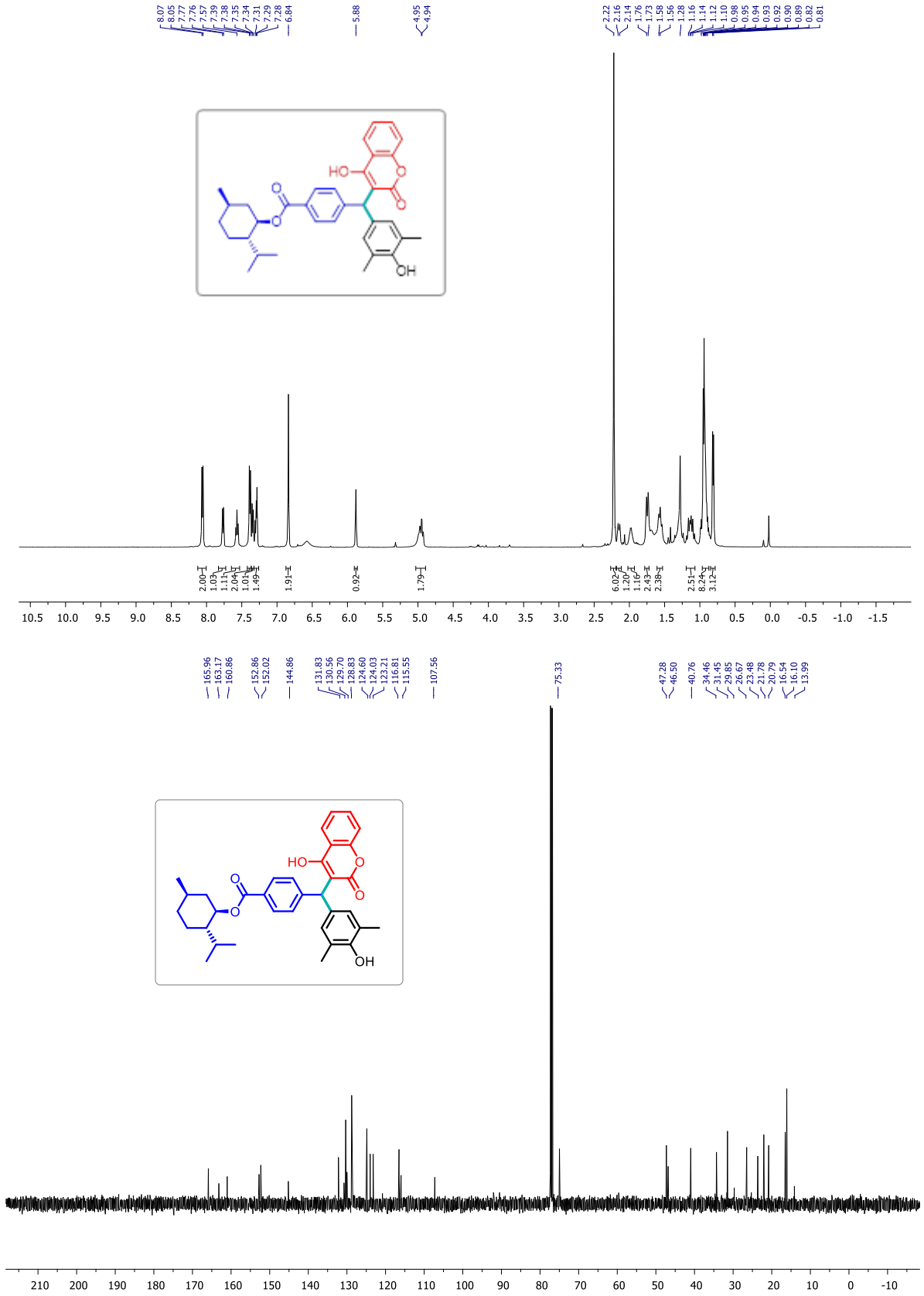
2-Methyl-5-((4-nitrophenyl)(2,4,5-trimethoxyphenyl)methyl)furan (46)

^{1}H (500 MHz) and ^{13}C (126 MHz) spectra of **46** in $CDCl_3$



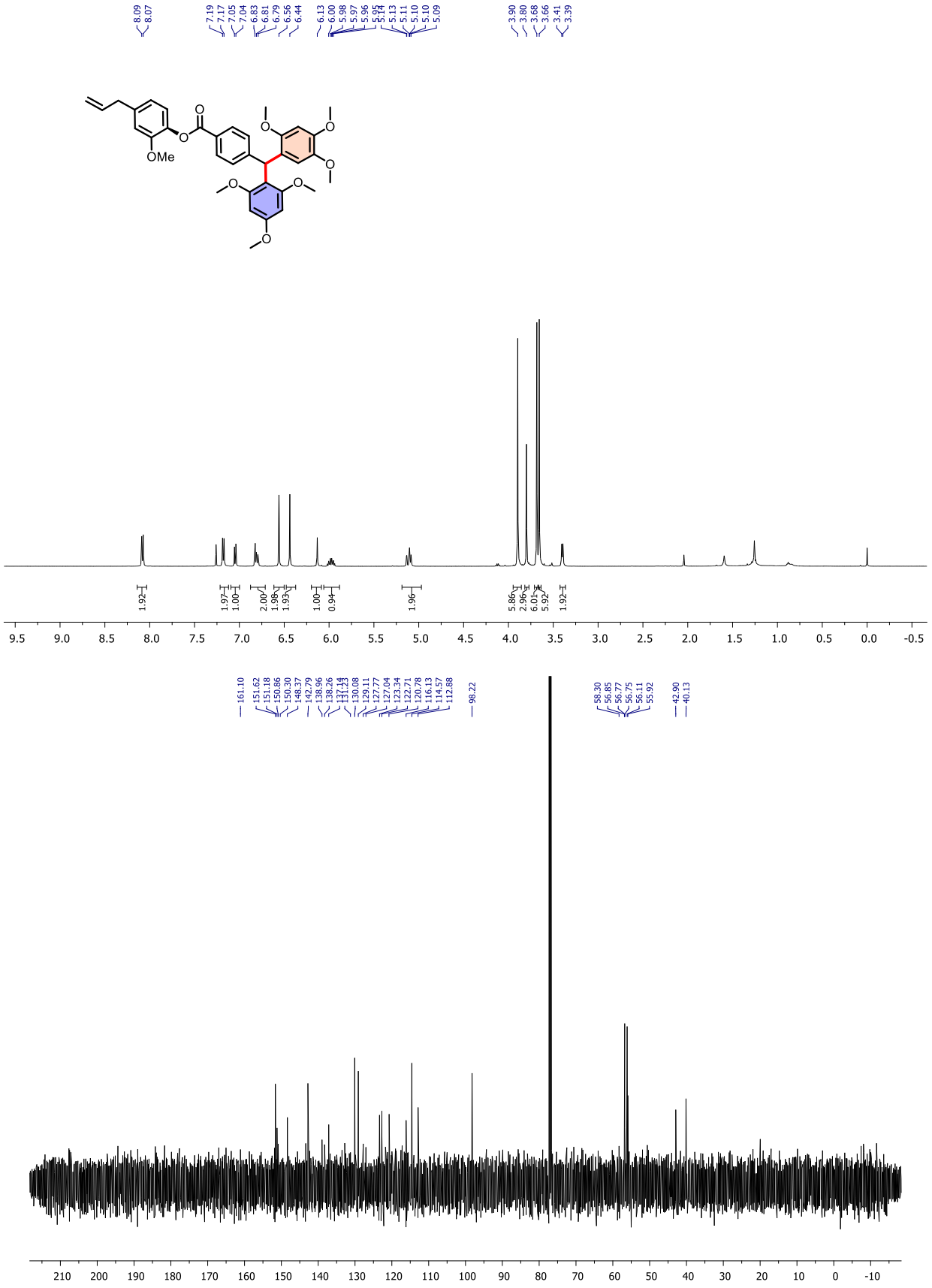
(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 4-(4-hydroxy-2-oxo-2H-chromen-3-yl)(4-hydroxy-3,5-dimethylphenyl)methyl)benzoate (47)

^{1}H (500 MHz) and ^{13}C (126 MHz) spectra of **47** in $CDCl_3$



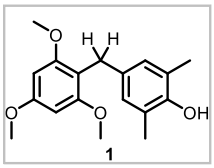
4-Allyl-2-methoxyphenyl 4-((2,4,5-trimethoxyphenyl)(2,4,6-trimethoxyphenyl)methyl)benzoate (48)

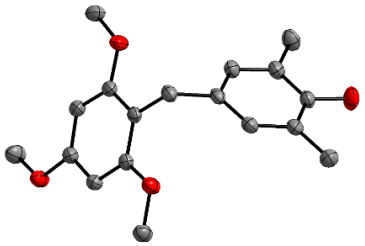
^{1}H (500 MHz) and ^{13}C (126 MHz) spectra of **48** in $CDCl_3$



11. Crystal data

2,6-Dimethyl-4-(2,4,6-trimethoxybenzyl)phenol (1, see Scheme 2, manuscript)

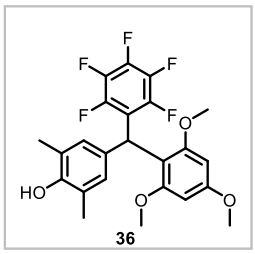


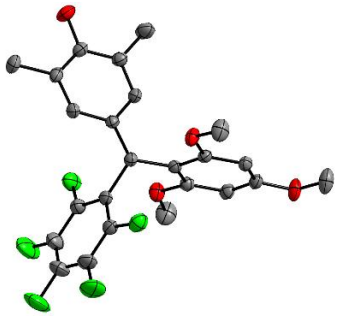


1

Compound number	**1**
CCDC number	CCDC 2190324
Empirical formula	$C_{18}H_{22}O_4$
Formula weight	302.373
Temperature, K	273.15
Crystal system	monoclinic
Space group	$P2_{1/n}$
a, b, c Å	7.0243(6), 20.5740(16), 11.0931(9)
α, β, γ (º)	90, 91.591(4), 90
V ($Å^3$)	1602.5(2)

2,6-Dimethyl-4-((perfluorophenyl)(2,4,6-trimethoxyphenyl)methyl)phenol (36, see Scheme 2, manuscript)





36

Compound number	**36**
CCDC number	CCDC 2190321
Empirical formula	$C_{24}H_{20}O_4F_5$
Formula weight	467.40
Temperature, K	293.15
Crystal system	triclinic
Space group	*P-1*
a, b, c Å	8.3761(5), 8.4007(5), 16.0336(9)
α, β, γ (º)	98.767(2), 99.704(2), 91.221(2)
V ($Å^3$)	1097.79(11)

12. Calculation of Green Metrics[6,7]

For compound 6 (when considering solvent)

Atom Economy = 100*{Molecular weight of the desired product}/ (Molecular weight of the starting materials)

Atom efficiency= {%yield of the desired product} *{%atom economy} / {100}

Reaction Mass efficiency= {Mass of the desired product}/ {Mass of all reactants} *100

E factor = {Total mass of waste}/ {mass of product} *100

Compound	F. wt. of Starting Material	F. wt of Product	Amount of Starting Used	Amount of product obtained	Amount of Catalyst used	% yield
6	{30+162.1+168.2} = 360.3	342.3	5*(30)+5.5*(162.1 +168.2)=1.97 g	1.52g	47.5 mg	89%

Amount of solvent taken = 5 ml= (1.6*5) g = **8 g**

Amount of solvent recovered = 4 ml= (1.6*4) g= **6.4 g**

Amount of solvent waste = (5-4) ml = 1 ml= (1.6*1) g = **1.6 g**

%Atom economy = 100*(342.3/360.3) = **95%**

%Atom efficiency = (89*95)/100 = **84.5%**

(Note: Since solvent and catalyst do not contribute to the mass of the product or the intermediate we have ignored the mass of the solvent and the catalyst in calculating the reaction mass efficiency)[6]

%Reaction mass efficiency = (Mass of the product/Total mass of the reagents) *100

= (1.52/1.97) *100 = **77.1%**

E factor calculation = {(Total mass of waste)/ (mass of product)} *100

= [{5*(30) +5.5*(162.1+168.2) +47.5+8000}- {1523.2+87.1+84.1+6400}/ (1523.2)] =**1.26 kg waste per** 1 kg of product.

When solvent not considered

Compound Number	Amount of Starting Material +5 mol% pTSA	Amount of the product	Waste = Amount of pdt - Amount of starting material	E factor=Amount of waste/Amount of product (solvent recovered hence not considered as waste)	Atom economy= {M.wt of the product/ M.wt of the Starting material} *100	Reaction Mass Efficiency = {Mass of the product/Total mass of the reagents} *100 {solvent & catalyst do not contribute to the mass of the product or

						the intermediate & hence not considered}
6	{0.5(30) + 0.55(162.1 + 168.2) + 4.7} mg = **201.4 mg**	**152.3 mg**	**49.1 mg**	49.1/152.3= **0.32**	{342.3/360.3} * 100 = **95%**	{152.3/196.7} *100 = 0.774 * 100 = **77.4%**

Process Mass Intensity Calculation for compound 6:

Amount of Formaldehyde used = 150 mg (5 mmol)

Amount of 1,3,5-Trimethoxy benzene used = 925.1 mg (5.5 mmol)

Amount of 4-Hydroxy coumarin used = 891.55 mg (5.5 mmol)

% yield of the product = 89%

Solvent used:

1,1,1,3,3,3-Hexafluoroisopropanol = 5 ml (density 1.6 g/ml) = (1.6*5) g = 8000 mg

Catalyst used:

Para-toluene sulphonic acid monohydrate = 5 mol% = 47.5 mg

Amount of Product obtained = 1523 mg

Process Mass Intensity = (Mass of all materials used)/Mass of product obtained

Process Mass Intensity = (925.1+891.55+150+47.5+8000) /1523 =10,014.15/1523 = 6.57 mg /mg of the product =6.57 kg/kg of the product.

However, we have efficiently recovered 4 ml (out of 5 ml) of the used solvent 1,1,1,3,3,3-hexafluoroisopropanol.

So, when considering solvent recovery

Process Mass Intensity = (925.1+891.55+150+47.5+1600)/1523 =

2.37 mg/mg of the product =2.37 kg/kg of the product.

(Note: For the calculation of E factor, the amount of solvent as well as the silica used in column chromatography was not considered.)[7]

Calculation of Green Metrics for anti-breast cancer agent compound 43 (with solvent)

Compound	F.wt. of Starting Material	F.wt. of Product	Amount of Starting Used	Amount of product obtained	Amount of Catalyst used	% yield
43	{206.2+108.1 +94.1} = 408.4	390.5	0.5(206.2) + 0.55(108.1+94.1) mg = 214.3 mg	148.3 mg	4.7 mg	76%

%Atom economy = 100*(390.5/408.4) = **95.6%**

%Atom efficiency = (76*95.6)/100 = **72.7%**

Note: Since solvent and catalyst do not contribute to the mass of the product or the intermediate we have ignored the mass of the solvent and the catalyst in calculating the reaction mass efficiency)[6]

% Reaction mass efficiency = (Mass of the product/Total mass of the reagents) *100

= (148.3/214.3) *100 = **69.2%**

E-factor calculation = {(Total mass of waste)/ (mass of product)} *100

= [{(0.5*206.2) + 0.55(108.1+94.1) + 4.7 + (0.5*1.6*1000)}- {(148.3+13.2+10.1 + (0.4*1.6*1000)}/148.3] = **1.4 kg waste per 1 kg of product.**

Process Mass Intensity Calculation for compound 43:

Amount of Anthraldehyde used = 103.1 mg (0.5 mmol)

Amount of Anisole used = 59.4 mg (0.55 mmol)

Amount of Phenol used = 51.7 mg (0.55 mmol)

yield of the product = 148.3 mg (76 %)

Solvent used:

1,1,1,3,3,3-Hexafluoroisopropanol = 0.5 ml (density 1.6 g/ml) = (1.6*0.5) g = 800 mg

Catalyst used:

Para-toluene sulphonic acid monohydrate = 5 mol% = 4.75 mg

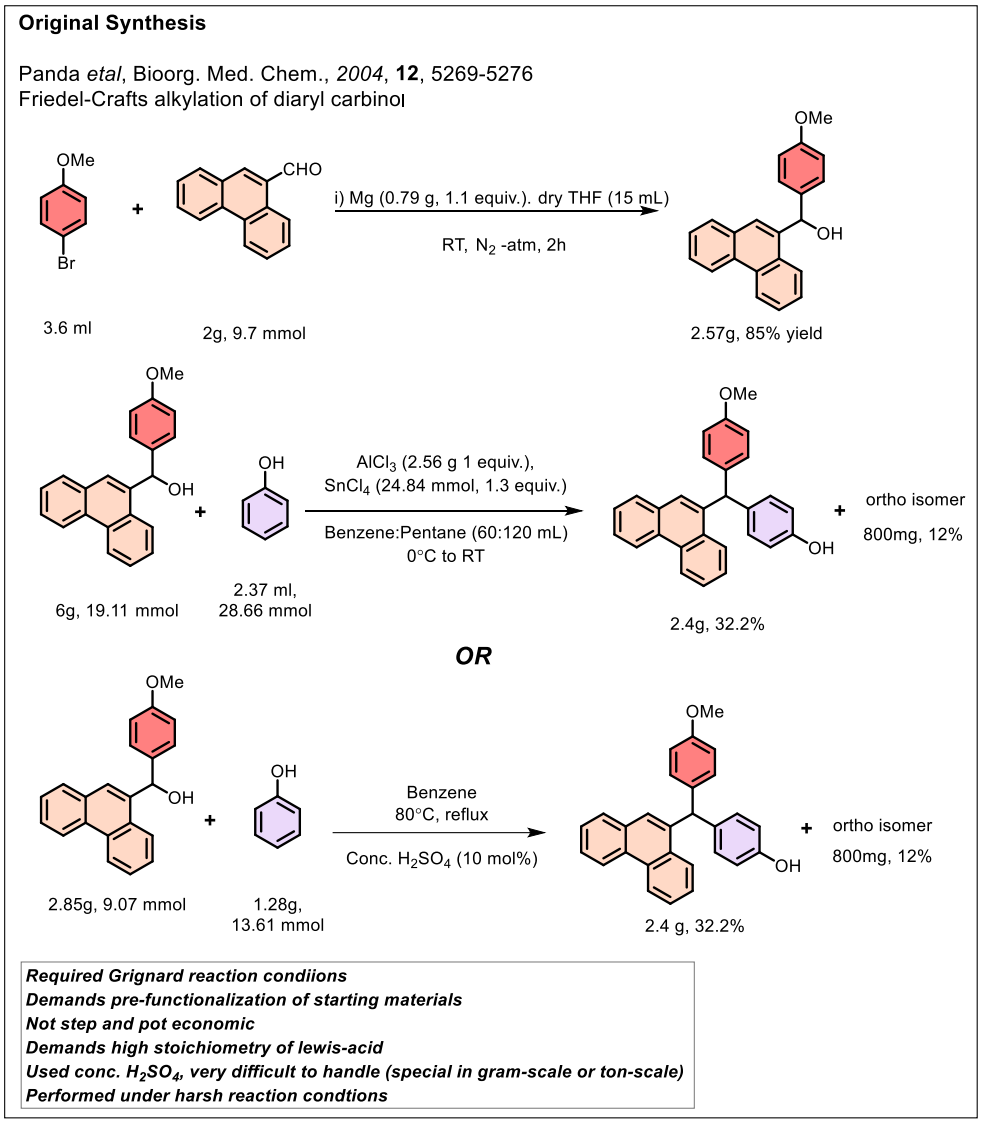
Amount of Product obtained = 148.3 mg

Process Mass Intensity = (Mass of all materials used)/Mass of product obtained

Process Mass Intensity (when solvent recovered not considered) = (103.1+59.4+51.7+4.75+800) /148.3 = (1018.95/148.3) = 6.87 mg /mg of the product = 6.87 kg/kg of the product.

Note: For the calculation of E factor, the amount of solvent as well as the silica used in column chromatography was not considered.[7]

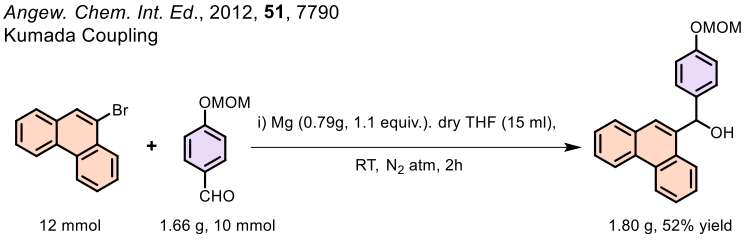
13. Previous synthetic routes comparison of anti-breast cancer agent (43)



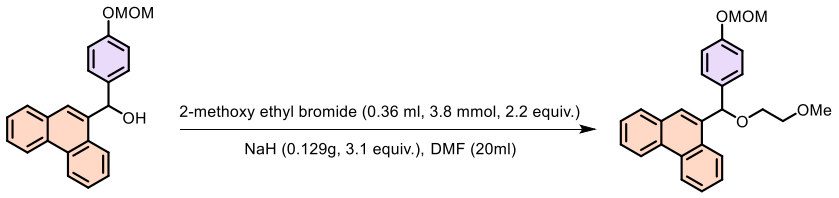
Jarvo's Method

Angew. Chem. Int. Ed., 2012, **51**, 7790

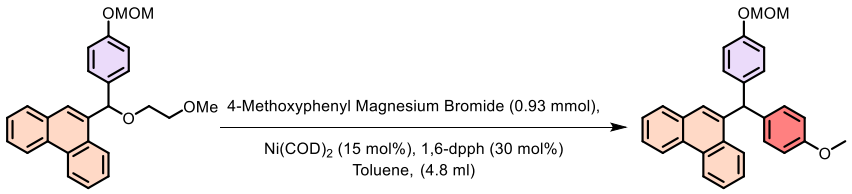
Kumada Coupling

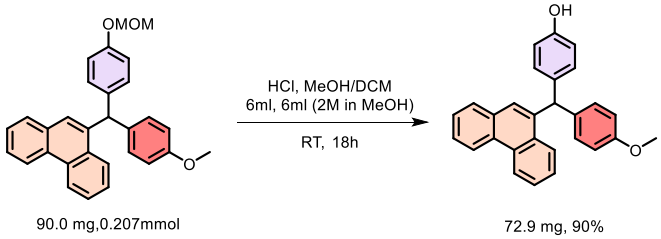


12 mmol 1.66 g, 10 mmol 1.80 g, 52% yield



600 mg 557 mg, 80%

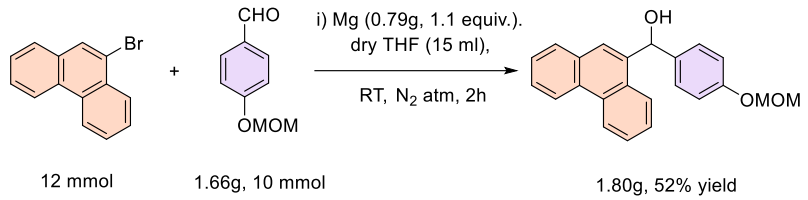




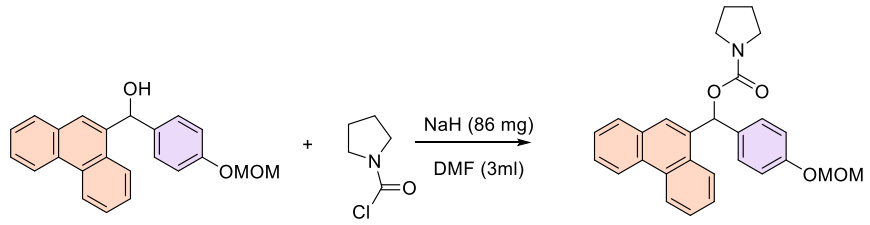
90.0 mg,0.207mmol 72.9 mg, 90%

Required Grignard reaction condiions
Demands pre-functionalization of starting materials
Not step and pot economic
Performed under harsh reaction condtions
Demands expensive metal-complexes

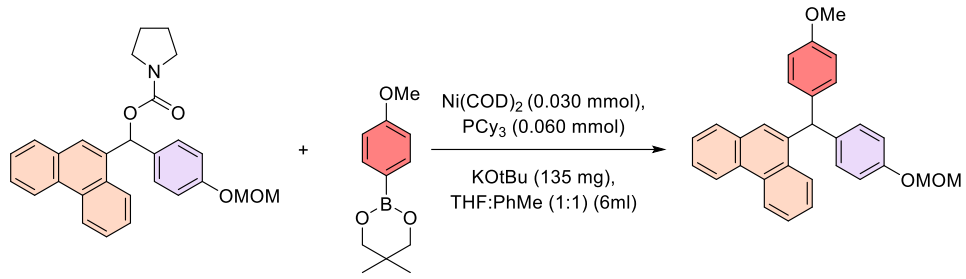
Jarvo's Method
J. Am. Chem. Soc., 2013, **135**, 3303-3306
Suzuki Miyaura Coupling



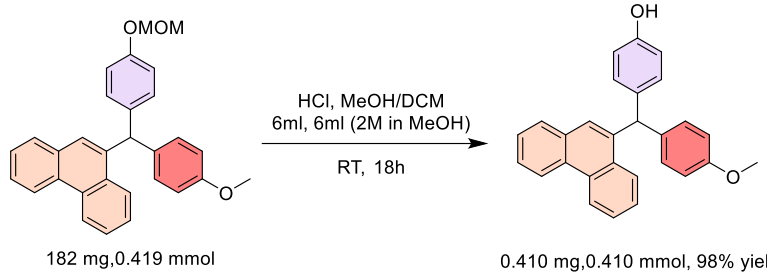
12 mmol 1.66g, 10 mmol 1.80g, 52% yield



689 mg 0.243 ml 604 mg, 68% yield



200 mg 266 mg 182 mg, 93% yield



182 mg,0.419 mmol 0.410 mg,0.410 mmol, 98% yield

Required Grignard reaction condiions
Demands pre-functionalization of starting materials
Not step and pot economic
Demands high stoichiometry of bases
Used expensive metal-complexes
Performed under harsh reaction condtions

14. References:

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