Supporting Information

Silane-mediated, facile C−H and N−H Methylation using Formaldehyde

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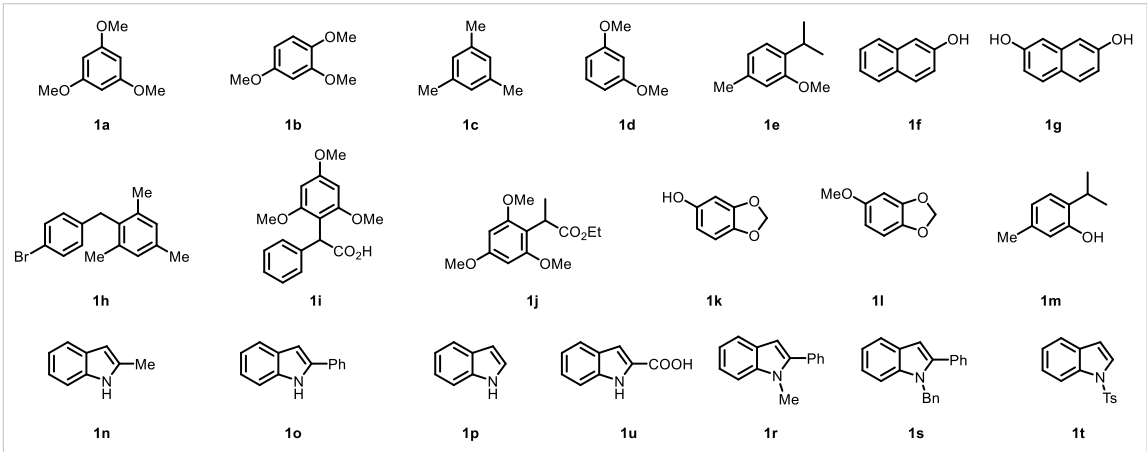
1. General Information:

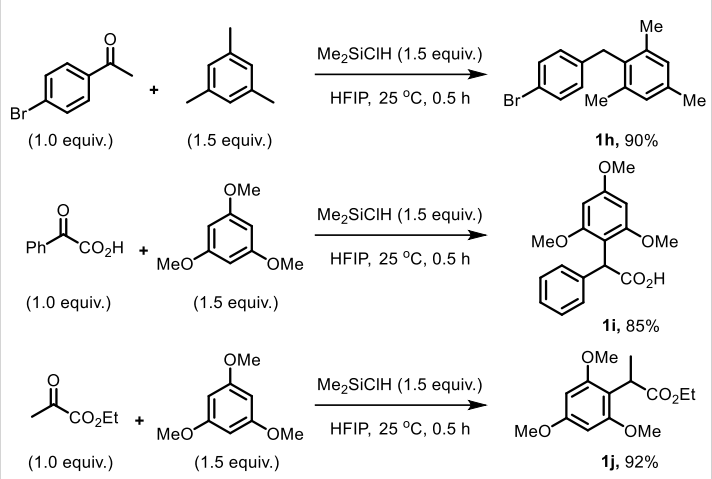
All reagents and solvents were of pure analytical grade. Analytical thin-layer chromatography (TLC) was carried out using 0.2 mm commercial silica gel plates (silica gel 60, F254, EMD Chemical). The vials (Wheaton® Standard Scintillation Vials, 1 dram, 15x45 mm with PTFE lined cap attached) were purchased 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. All reactions were run in flame- or oven-dried glassware. ^{1}H-NMR and ^{13}C-NMR were recorded on 400 MHz and 500 MHz spectrometers using $CDCl_3$ as a solvent; 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). Coupling constants were 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). All reagents, such as aldehydes, ketone, isatin, thiols, trityl salt, and silanes, were purchased from Sigma-Aldrich, TCI, or Alfa Aesar.

2. Synthesis of starting metrical

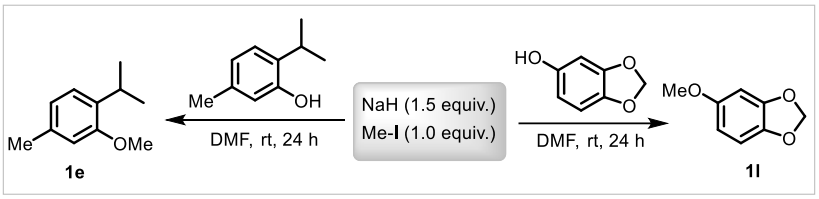
Synthesis of arenes and heteroarenes: Compound number **1a**, **1b**, **1c**, **1d**, **1f**, **1g**, **1k**, **1m**, **1n**, **1o** and **1u** are commercially available and **1e**, **1h**, **1i**, **1j**, **1l**, **1m**, **1r**, **1s** and **1t** are synthesized.



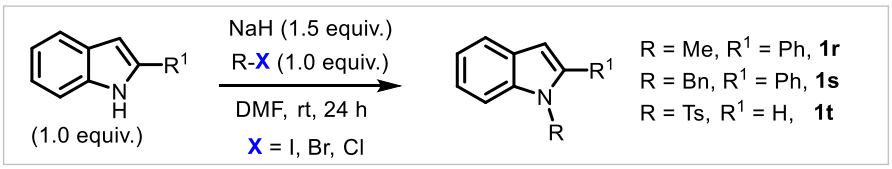
Synthesis of 1h, 1i, and 1j: A 5 mL reaction vial is charged with carbonyl compounds (0.5 mmol, 1.0 equiv.), chlorodimethylsilane (Me_2SiClH, 0.75 mmol, 1.5 equiv.), and arenes (0.75 mmol, 1.5 equiv.) in HFIP (0.5 mL) solvent. The reaction mixture was stirred at 25 °C for 0.5 h. After completion of the reaction (monitored by TLC analysis), HFIP was evaporated, and the residue was purified by column chromatography using a gradient of hexane−ethyl acetate to afford the corresponding products **1h**, **1i**, and **1j** in excellent yields.



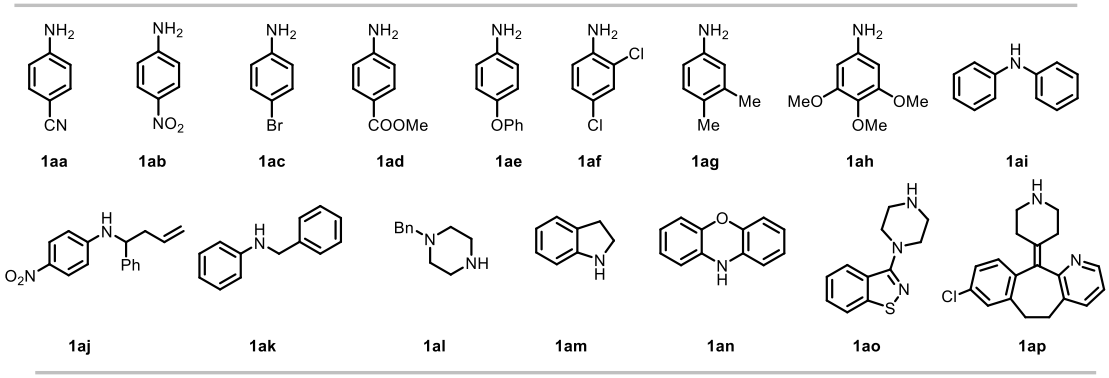
Synthesis of 1e and 1l: According to the reported method[1], phenol derivatives (3.0 mmol, 1.0 equiv.) were dissolved in DMF (15 mL), and the resultant solution was cooled to 0 °C, sodium hydride (60% dispersion in mineral oil, 4.5 mmol, 1.5 equiv.) was then added and stirred for 30 minutes. After adding MeI (3.0 mmol, 1.0 equiv.) the reaction was stirred and monitored by TLC until phenol derivatives were entirely consumed. Subsequently, the reaction mixture was poured into saturated aqueous NH_4Cl, and ethyl acetate was used to extract it. The organic layer was washed with brine, dried with Na_2SO_4, and filtered, and the residue was purified by column chromatography.



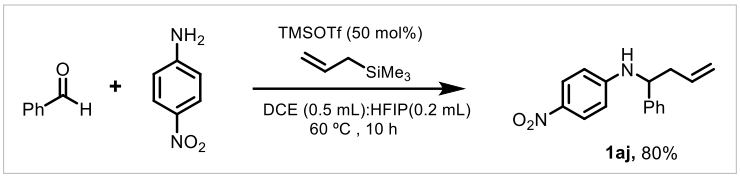
Synthesis of indole derivative 1r, 1s, and 1t: Similarly, according to the reported method[1], indole derivatives (3.0 mmol, 1.0 equiv.) were added in DMF (15 mL) at 0 °C, NaH (60% dispersion in mineral oil, 4.5 mmol, 1.5 equiv.) was slowly added into the reaction mixture. The reaction was stirred at 0 °C for 30 minutes after adding MeI (3.0 mmol, 1.0 equiv.). The reaction mixture was continuously stirred and monitored using thin-layer chromatography (TLC) until the complete consumption of indole derivatives was confirmed. After that, the reaction mixture was poured into saturated aqueous NH_4Cl, and ethyl acetate was used to extract it. The organic layer was washed with brine, dried with Na_2SO_4, and filtered, and the residue was purified by column chromatography.



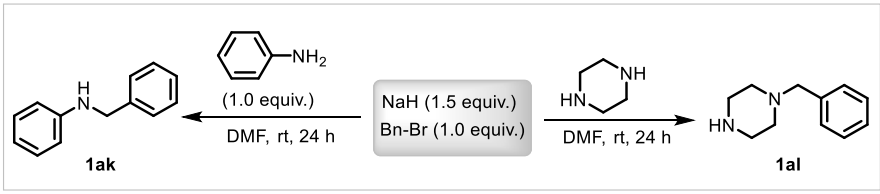
Synthesis of anilines and heterocyclic amines: Compound number **1aa**, **1ab**, **1ac**, **1ad**, **1ae**, **1af**, **1ag**, **1ah**, **1ai**, **1am**, **1an**, **1ao** and **1ap** are commercially available and **1aj**, **1ak**, and **1al** are synthesized.



Synthesis of 1aj: A 5 mL reaction vial is charged with benzaldehyde (0.5 mmol, 1.0 equiv.), 4-nitro-aniline (0.75 mmol, 1.5 equiv.), and allyltrimethylsilane (0.75 mmol, 1.5 equiv.) in DCE:HFIP (0.5 mL:0.2 mL) solvent. The reaction mixture was stirred at 60 ºC for 10. h. After completion of the reaction (monitored by TLC analysis), the solvent was evaporated, and the residue was purified by column chromatography using a gradient of hexane−ethyl acetate to afford the corresponding products **1aj** in 80% yields.

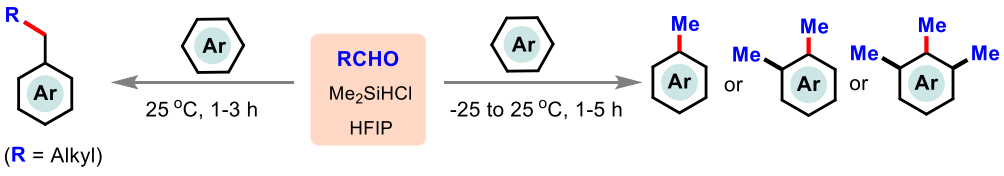


Synthesis of 1ak, and 1al: According to the reported mehod[1], amine derivatives (3.0 mmol, 1.0 equiv.) were added in DMF (15 mL) at 0 °C, NaH (60% dispersion in mineral oil, 4.5 mmol, 1.5 equiv.) was slowly added into the reaction mixture. The reaction was stirred at 0 °C for 30 minutes after adding BnBr (3.0 mmol, 1.0 equiv.). The reaction mixture was continuously stirred and monitored using thin-layer chromatography (TLC) until the complete consumption of amine derivatives was confirmed. After that, the reaction mixture was poured into saturated aqueous NH_4Cl, and ethyl acetate was used to extract it. The organic layer was washed with brine, dried with Na_2SO_4, and filtered, and the residue was purified by column chromatography.



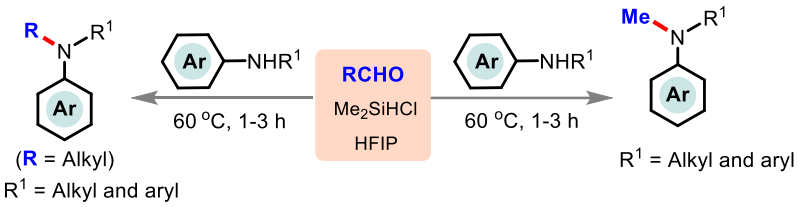
3. General procedure

3.1 General experimental procedure for the methylation and alkylation of arenes (GP1)



A 5 mL reaction vial is charged with paraformaldehyde (3.0 to 5.0 equiv.), chlorodimethylsilane (Me_2SiClH, 2.0 to 5.0 equiv.), and arenes (0.2 mmol, 1.0 equiv.) in HFIP (0.5 mL) solvent. The reaction mixture was stirred at -25 to 25 ºC for 1-5 h. After completion of the reaction (monitored by TLC analysis), HFIP was evaporated, and the residue was purified by column chromatography using a gradient of hexane−ethyl acetate to afford the corresponding methylated products in good to excellent yields.

3.2 General experimental procedure for the methylation and alkylation of amines (GP2)



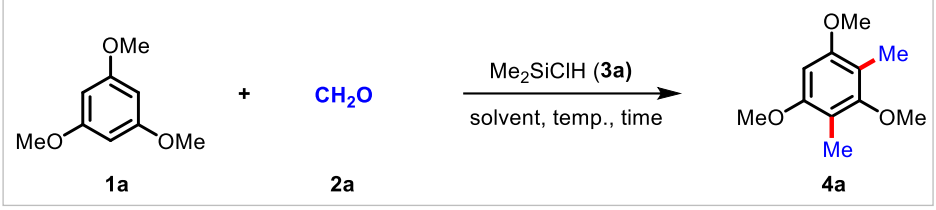
A 5 mL reaction vial is charged with paraformaldehyde (0.6 mmol, 3.0 equiv.), chlorodimethylsilane (Me_2SiClH, 0.4 mmol, 2.0 equiv.), and amines (0.2 mmol, 1.0 equiv.) in HFIP (0.5 mL) solvent. The reaction mixture was stirred at 60 ºC for 1 h–3 h. After completion of the reaction (monitored by TLC analysis), HFIP was evaporated, and the residue was purified by column chromatography using a gradient of hexane−ethyl acetate to afford the corresponding methylated products in good to excellent yields.

4. Reaction optimization for methylation:

4.1. Reaction optimization for C(sp^2)–H methylation:

C(sp^2)–H methylation is rather challenging over N–H methylation. To establish the optimal reaction conditions for C–methylation, we commenced our investigation using 1,3,5-trimethoxybenzene (**1a**) as a model substrate in the presence of (*para*)-formaldehyde (CH_2O, **2a**) and dimethylchlorosilane (Me_2SiClH, **3a**) as a reducing agent with HFIP as solvent (Table S1). First, we screened the reaction at room temperature and under heating conditions (60 ºC) and found no product formation with nonspecific decomposition in the reaction mixture (Table S1, entries 1 and 2). However, lowering the temperature from 0 ºC to -25 ºC could give promising results with a yield up to 40% (Table S1, entries 3 and 4). Screening of other solvents, such as $PhCF_3$, DCE, and TFE, revealed HFIP to be the most effective solvent for this transformation (Table S1, entries 5–7). To further improve the yield, we modulated the mole ratio of (*para*)-formaldehyde and witnessed a significant rise in the yield of **4a** with 5.0 equiv. (Table S1, entry 8). However, any subsequent elevation to 10.0 equiv. was found to have a detrimental effect on the reaction (Table S1, entry 9). Silanes such as Et_3SiH and Ph_3SiH were found to be inappropriate for the titled methylation (Table S1, entries 10 and 11). In the absence of Me_2SiClH, no product was observed under otherwise standard conditions (Table S1, entry 12). Reaction time is also an important parameter, and up to 84% yield of **4a** was achieved after 2 h (Table S1, entry 13).

Table S1: Reaction optimization for C(sp^2)–H methylation[a]



Entry	CH_2O **(2a)**	Silane	Solvent	Temp. (°C)	% Yield of **4a**
1	3.0 equiv.	Me_2SiClH	HFIP	rt	trace
2	3.0 equiv.	Me_2SiClH	HFIP	60	trace
3	3.0 equiv.	Me_2SiClH	HFIP	0	20
4	3.0 equiv.	Me_2SiClH	HFIP	-25	40
5	3.0 equiv.	Me_2SiClH	$PhCF_3$	60	trace
6	3.0 equiv.	Me_2SiClH	DCE	60	trace
7	3.0 equiv.	Me_2SiClH	TFE	60	trace
8	5.0 equiv.	Me_2SiClH	HFIP	-25	86
9	10.0 equiv.	Me_2SiClH	HFIP	-25	50
10[b]	5.0 equiv.	Et_3SiH	HFIP	-25	trace
11[c]	5.0 equiv.	Ph_3SiH	HFIP	-25	trace
12[d]	5.0 equiv.	-	HFIP	-25	trace
13[e]	5.0 equiv.	Me_2SiClH	HFIP	-25	84
14	5.0 equiv.	Me_2SiClH	$PhCF_3$	-25	trace
15	5.0 equiv.	Me_2SiClH	DCE	-25	trace
16	5.0 equiv..	Me_2SiClH	TFE	-25	35
17	5.0 equiv.	Me_2SiClH	$(CH_3)_2CHOH$	-25	trace

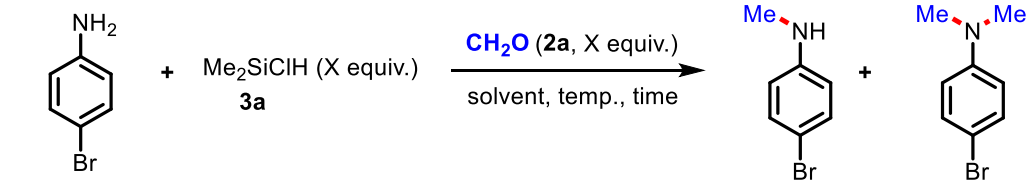
[a]Reaction conditions: **1a** (1.0 equiv., 0.2 mmol), **2a** (5.0 equiv., 1.0 mmol, M.W.: 30.02 as monomer), and Me_2SiClH (**3a**, 4.0 equiv., 0.8 mmol) in HFIP (0.5 mL) for 5 h. [b]Et_3SiH (4.0 equiv., 0.8 mmol). [c]Ph_3SiH (4.0 equiv., 0.8 mmol). [d]Without **3a**. [e]2 h. All are isolated yields. DCE = 1,2-dichloroethane, TFE = 2,2,2-trifluoroethanol, $PhCF_3$ = trifluorotoluene and HFIP = 1,1,1,3,3,3-Hexafluoro-2-propanol.

Subsequent screening of alternative solvents, including $PhCF_3$, DCE, TFE, and $(CH_3)_2CHOH$ under the optimal reaction conditions, indicated that HFIP was the most effective solvent for this transformation (see Table S1, entries 14–17). Nonetheless, TFE (2,2,2-trifluoroethanol) yielded the desired product (**4a**) in 35% yield at -25 °C.

4.2. Reaction optimization for *N*-methylation:

To establish the optimal reaction conditions, we commenced our investigation for the reductive *N*-methylation by attempting the reaction of easily accessible 4-bromoaniline and paraformaldehyde (**2a**) as model substrates and dimethylchlorosilane (Me_2SiClH, **3a**) as a reducing agent (Table S2). First, we screened the reaction at room temperature, we found the desired product **5c** with a low yield in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) solvent (entry 1). After that, when we conducted a reaction at 60 °C in HFIP for 12 h the target product **5c** formed in good yield of 70% (entry 2). We next screened several solvents such as trifluorotoluene ($PhCF_3$), and dichloroethane (DCE) trace amount of product is formed, and in trifluoroethanol (TFE) **6c** formed as a major product, (entries 3-5). Furthermore, variation of silane led to dimethyl product **6c** as a major product instead of **5c** (entries 6-7). Without silane (**3a**, reducing reagent) no product formed (entry 8). Later we start variation of paraformaldehyde low 1.0 equiv. to high 6.0 equiv. but in both conditions, a low yield of product formed (entries 8-9). Now we fix the solvent HFIP reducing reagent Me_2SiClH and start the optimization of time we observed that 3 h is sufficient for our reaction (entry 10).

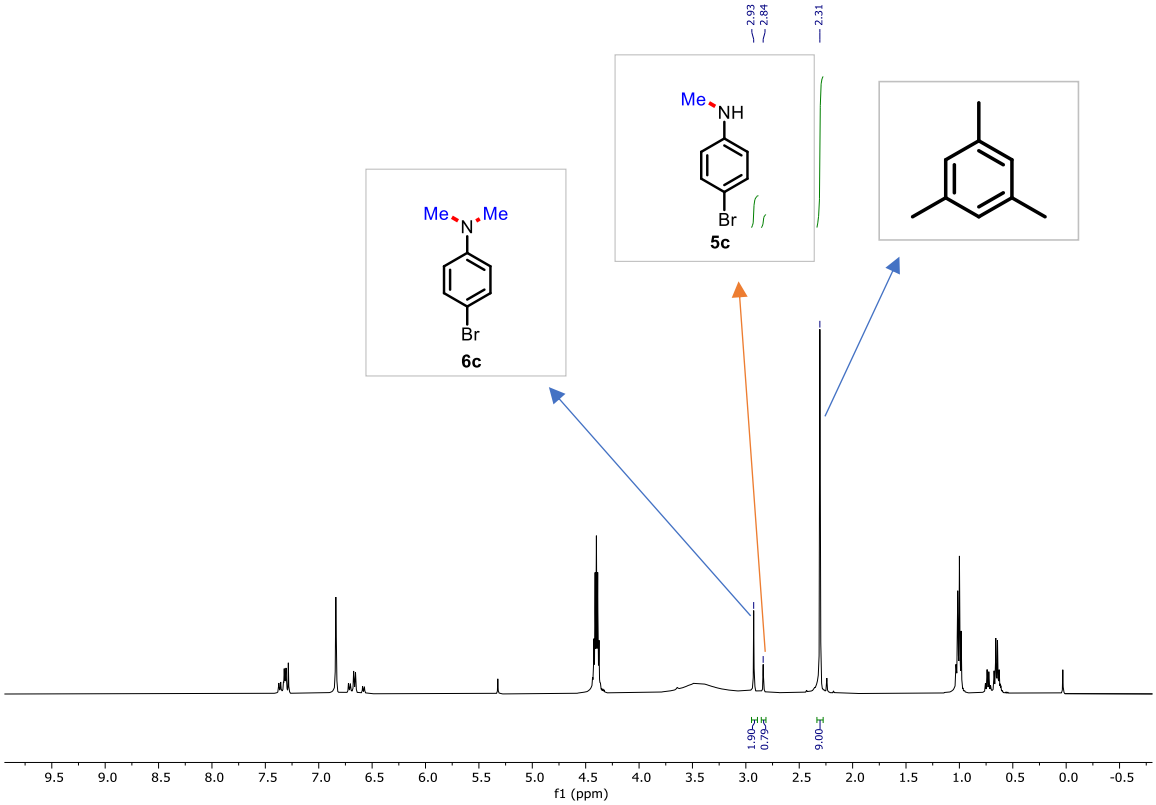
Table S2. Variations of the Reaction Conditions[a]



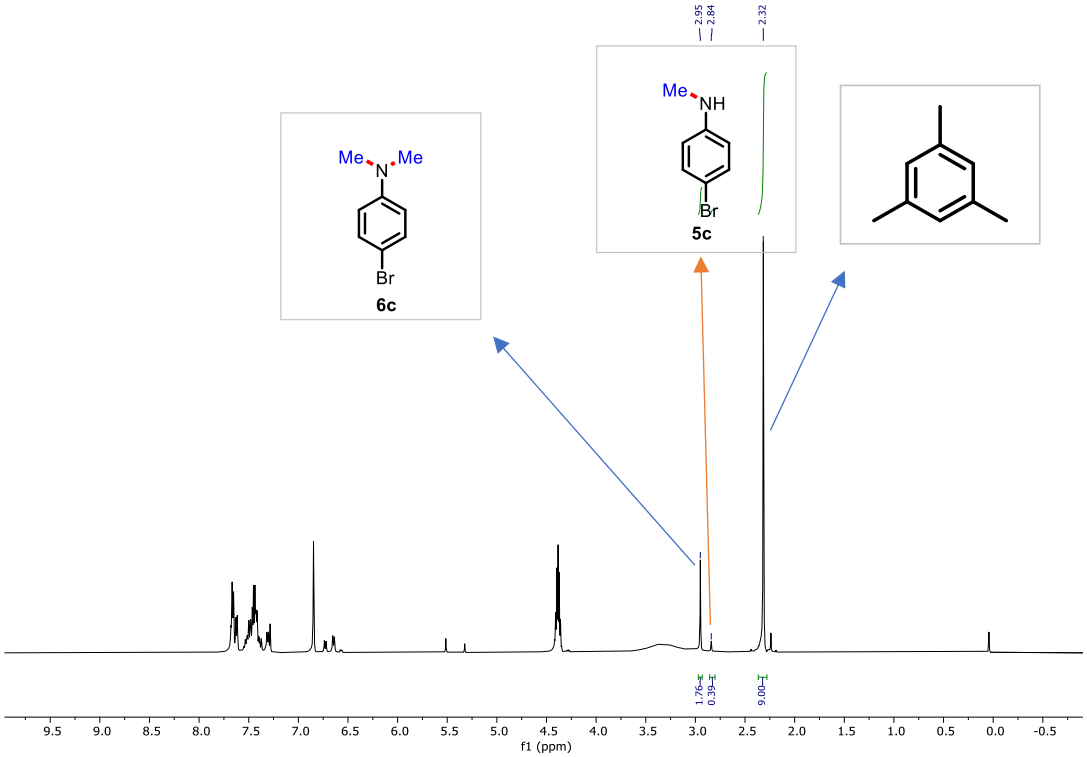
Entry	Silane	CH_2O	Solvent	Temperature	% Yield of 5c/6c	Time (h)
1	Me_2SiClH	3.0	HFIP	25	20	12
2	Me_2SiClH	3.0	HFIP	60	70/15	12
3	Me_2SiClH	3.0	$PhCF_3$	60	0/0	12
4	Me_2SiClH	3.0	DCE	60	0/0	12
5	Me_2SiClH	3.0	TFA	60	20/30	12
6[b]	Et_3SiH	3.0	HFIP	60	26/32	12
7[c]	Ph_3SiH	3.0	HFIP	60	13/29	12
8	-	3.0	HFIP	60	0/0	12
8	Me_2SiClH	1.0	HFIP	60	20/5-	12
9	Me_2SiClH	6.0	HFIP	60	Trace	12
10[d]	**Me_2SiClH**	**3.0**	**HFIP**	**60**	**70/15**	**3**

[a]Reaction condition: **9a** (0.2 mmol), Me_2SiClH (0.4 mmol), and CH_2O (0.6 mmol, M.W.: 30.02 as monomer) for 12 h at 60 °C in HFIP (0.5 mL). [b]Et_3SiH. [c]Ph_3SiH. [d]3 h at 60 °C.

^{1}H NMR (500 MHz, $CDCl_3$) of crude reaction mixture with Et_3SiH using mesitylene as an internal standard

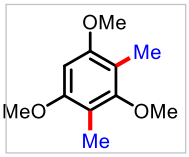


^{1}H NMR (500 MHz, $CDCl_3$) of crude reaction mixture with Ph_3SiH using mesitylene as an internal standard



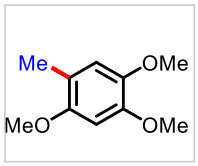
5. Characterization data of synthesized products

1,3,5-Trimethoxy-2,4-dimethylbenzene (4a)[2]



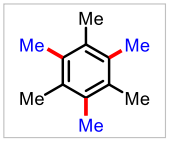
General procedure (**GP1**) was followed using 1,3,5-trimethoxybenzene (33 mg, 0.2 mmol), paraformaldehyde (30 mg, 1.0 mmol, 5.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.8 mmol, 4.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 05:95) to afford the title compound as a white solid (34 mg, 86%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.28 (s, 1H), 3.82 (s, 6H), 3.68 (s, 3H), 2.10 (s, 6H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 158.0, 156.8, 111.6, 91.8, 60.3, 55.9, 8.7.

1,2,4-Trimethoxy-5-methylbenzene (4b)[2]



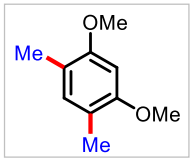
General procedure (**GP1**) was followed using 1,2,4-trimethoxybenzene (33 mg, 0.2 mmol), paraformaldehyde (30 mg, 1.0 mmol, 5.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.8 mmol, 4.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 05:95) to afford the title compound as a white solid (35 mg, 95%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.68 (s, 1H), 6.50 (s, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 2.16 (s, 3H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 151.8, 147.6, 142.9, 118.1, 115.1, 98.0, 56.7, 56.4, 56.4, 15.6.

1,2,3,4,5,6-Hexamethylbenzene (4c)[3]



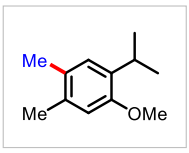
General procedure (**GP1**) was followed using mesitylene (24 mg, 0.2 mmol), paraformaldehyde (50 mg, 1.64 mmol, 8.0 equiv), chlorodimethylsilane (Me_2SiClH, 1.2 mmol, 6.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, Hexane) to afford the title compound as a white solid (29mg, 90%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.25 (s, 9H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 132.2, 16.9.

1,5-Dimethoxy-2,4-dimethylbenzene (4d)[2]



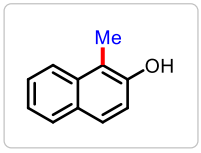
General procedure (**GP1**) was followed using 1,3-dimethoxybenzene (28 mg, 0.2 mmol), paraformaldehyde (30 mg, 1.0 mmol, 5.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.8 mmol, 4.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 05:95) to afford the title compound as a white solid (30 mg, 92%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.90 (s, 1H), 6.44 (s, 1H), 3.84 (s, 6H), 2.15 (s, 6H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 156.5, 132.5, 117.8, 95.5, 55.8, 15.3.

1-Isopropyl-2-methoxy-4,5-dimethylbenzene (4e)[4]



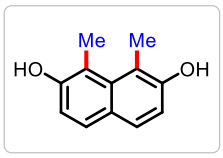
General procedure (**GP1**) was followed using 5-isopropyl-2-methylphenol (30 mg, 0.2 mmol), paraformaldehyde (18 mg, 0.6 mmol, 3.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 05:95) to afford the title compound as a brown solid (28.5 mg, 80%); **^{1}H NMR** (400 MHz, CHLOROFORM-*D*) δ 7.05 (s, 1H), 6.74 (s, 1H), 3.87 (s, 3H), 3.36 (p, *J* = 6.9 Hz, 1H), 2.33 (s, 3H), 2.29 (s, 3H), 1.29 (d, *J* = 6.9 Hz, 6H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 154.9, 134.4, 134.3, 128.2, 127.5, 112.5, 55.7, 26.5, 23.0, 19.9, 19.1.

1-Methylnaphthalen-2-ol (4f)[5]



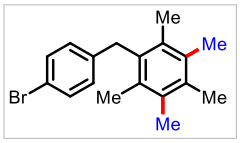
General procedure (**GP1**) was followed using naphthalen-2-ol (29 mg, 0.2 mmol), paraformaldehyde (30 mg, 1.0 mmol, 5.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.8 mmol, 4.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 05:95) to afford the title compound as a light green solid (23 mg, 73%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 5.8 Hz, 1H), 7.77 (d, *J* = 6.4 Hz, 1H), 7.62 (d, *J* = 8.6 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 1H), 7.34 (t, *J* = 6.2 Hz, 1H), 7.07 (d, *J* = 8.8 Hz, 1H), 4.95 (s, 1H), 2.54 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 150.6, 134.0, 129.3, 128.6, 127.5, 126.4, 123.3, 117.7, 115.3, 10.6.

1,8-Dimethylnaphthalene-2,7-diol (4g)[5]



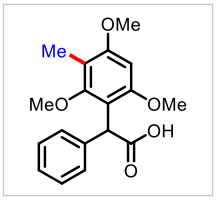
General procedure (**GP1**) was followed using naphthalen-2-ol (29 mg, 0.2 mmol), paraformaldehyde (30 mg, 1.0 mmol, 5.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.8 mmol, 4.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 05:95) to afford the title compound as a light green (22.5 mg, 60%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 4.93 (s, 2H), 2.70 (s, 6H); **^{13}C {^{1}H}** NMR (101 MHz, $CDCl_3$) δ 152.6, 136.4, 128.4, 126.2, 116.0, 114.9, 15.7.

1-(4-Bromobenzyl)-2,3,4,5,6-pentamethylbenzene (4h)



General procedure (**GP1**) was followed using 2-(4-bromobenzyl)-1,3,5-trimethylbenzene (57.8 mg, 0.2 mmol), paraformaldehyde (50 mg, 1.64 mmol, 8.0 equiv), chlorodimethylsilane (Me_2SiClH, 1.2 mmol, 6.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, Hexane) to afford the title compound as a white solid (54 mg, 85%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 4.06 (s, 2H), 2.28 (s, 3H), 2.25 (s, 6H), 2.15 (s, 6H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 139.8, 133.5, 133.3, 132.8, 132.8, 131.5, 129.8, 119.5, 35.7, 17.1, 17.0, 17.0. **HRMS** (ESI) m/z: $[M+Na]^+$ calculated for $C_{18}H_{21}BrNa$ 339.0724; found 339.0730.

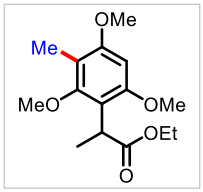
2-Phenyl-2-(2,4,6-trimethoxy-3,5-dimethylphenyl) acetic acid (4i)



General procedure (**GP1**) was followed using 2-phenyl-2-(2,4,6-trimethoxyphenyl)acetic acid (60 mg, 0.2 mmol), paraformaldehyde (30 mg, 1.0 mmol, 5.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.8 mmol, 4.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, MeOH:DCM: 02:98) to afford the title compound as a white solid (61 mg, 92%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.39 (s, 1H), 7.27 (d, *J* = 7.8 Hz, 2H), 7.24 – 7.18 (m, 2H), 7.15 (t, *J* = 7.2 Hz, 1H), 6.29 (s, 1H), 5.37 (s, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.52 (s, 3H), 2.05 (s, 3H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 179.0, 158.7, 157.6, 156.1, 138.5, 129.2, 128.1, 126.9, 113.9, 112.1, 92.2,

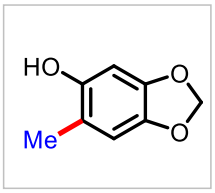
61.1, 55.9, 55.8, 47.0, 9.3. **HRMS** (ESI) m/z: $[M+Na]^+$ calculated for $C_{18}H_{20}O_5Na$ 339.1208; found 339.1209.

Ethyl 2-(2,4,6-trimethoxy-3-methylphenyl) propanoate (4j)



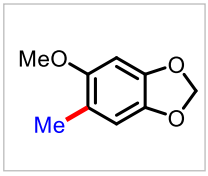
General procedure (**GP1**) was followed using ethyl 2-(2,4,6-trimethoxyphenyl)propanoate (60 mg, 0.2 mmol), paraformaldehyde (30 mg, 1.0 mmol, 5.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.8 mmol, 4.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 20:80) to afford the title compound as a colourless viscous (48 mg, 85%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.26 (s, 1H), 4.16 – 4.06 (m, 2H), 4.01 (q, *J* = 7.1 Hz, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.71 (s, 3H), 2.09 (s, 3H), 1.39 (d, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 175.5, 157.8, 157.2, 156.2, 116.4, 111.5, 91.8, 61.2, 60.4, 55.7, 55.6, 35.6, 16.6, 14.4, 9.0. **HRMS** (ESI) m/z: $[M+Na]^+$ calculated for $C_{15}H_{22}O_5Na$ 305.1365; found 305.1357.

6-Methylbenzo[*d*][1,3]dioxol-5-ol (4k)



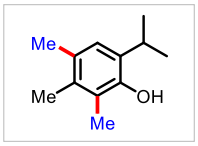
General procedure (**GP1**) was followed using benzo[*d*][1,3]dioxol-5-ol (28 mg, 0.2 mmol), paraformaldehyde (30 mg, 1.0 mmol, 5.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.8 mmol, 4.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 05:95) to afford the title compound as a brown solid (18 mg, 60%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.3, 6.6, 6.4, 5.9, 4.6, 2.2; **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 148.1, 146.2, 141.3, 115.2, 110.2, 101.0, 98.0, 15.8.

5-Methoxy-6-methylbenzo[*d*][1,3]dioxole (4l)



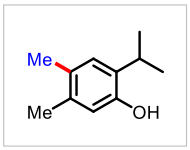
General procedure (**GP1**) was followed using benzo[*d*][1,3]dioxol-5-ol (28 mg, 0.2 mmol), paraformaldehyde (30 mg, 1.0 mmol, 5.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.8 mmol, 4.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 05:95) to afford the title compound as a brown solid (23 mg, 70%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.64 (s, 1H), 6.50 (s, 1H), 5.87 (s, 2H), 3.76 (s, 3H), 2.14 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 152.5, 146.0, 140.7, 118.7, 110.6, 101.0, 94.7, 56.5, 16.1.

3-Isopropyl-2,4,6-trimethylphenol (4m)[5]



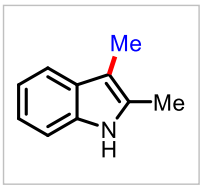
General procedure (**GP1**) was followed using 5-isopropyl-2-methylphenol (30 mg, 0.2 mmol), paraformaldehyde (30 mg, 1.0 mmol, 5.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.8 mmol, 4.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc/Hexane: 05:95) to afford the title compound as a brown solid (28.5 mg, 80%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.87 (s, 1H), 4.59 (s, 1H), 3.12 (h, *J* = 6.9 Hz, 1H), 2.26 (s, 3H), 2.21 (s, 3H), 2.18 (s, 3H), 1.27 (d, *J* = 6.9 Hz, 7H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 149.0, 133.4, 130.6, 128.4, 124.6, 122.1, 27.2, 22.9, 20.5, 15.9, 12.4.

5-Isopropyl-2,4-dimethylphenol (4n)[5]



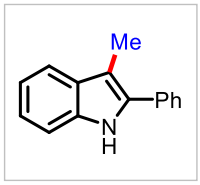
General procedure (**GP1**) was followed using 5-isopropyl-2-methylphenol (30 mg, 0.2 mmol), paraformaldehyde (18 mg, 0.6 mmol, 3.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 05:95) to afford the title compound as a brown solid (23 mg, 70%);**^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.93 (s, 1H), 5.48 (s, 1H), 4.12 (s, 1H), 3.12 (h, *J* = 6.9 Hz, 1H), 2.29 (s, 3H), 2.27 (s, 3H), 1.22 (d, *J* = 6.9 Hz, 6H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 150.1, 133.5, 132.3, 129.1, 126.1, 123.8, 26.8, 22.9, 20.8, 16.1.

2,3-Dimethyl-1*H*-indole (4o)[6]



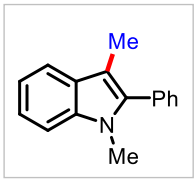
General procedure (**GP1**) was followed using 2-methyl-1*H*-indole (26 mg, 0.2 mmol), paraformaldehyde (30 mg, 1.0 mmol, 5.0 equiv), triethyl silane (Et_3SiH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 02:98) to afford the title compound as a white solid (20 mg, 68%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.46 (d, *J* = 9.1 Hz, 1H), 7.22 (d, *J* = 6.5 Hz, 1H), 7.12 – 7.05 (m, 2H), 2.33 (s, 3H), 2.22 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 135.3, 130.8, 129.5, 121.0, 119.1, 118.0, 110.1, 107.2, 11.6, 8.6.

3-Methyl-2-phenyl-1*H*-indole (4p)[6]



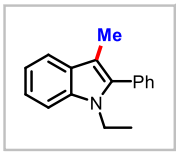
General procedure (**GP1**) was followed using 2-phenyl-1*H*-indole (39 mg, 0.2 mmol), paraformaldehyde (15 µL, 0.5 mmol, 2.5 equiv), triethyl silane (Et_3SiH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 02:98) to afford the title compound as a white solid (38 mg, 90%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.69 – 7.64 (m, 1H), 7.62 – 7.58 (m, 2H), 7.51 (t, *J* = 7.8 Hz, 2H), 7.42 – 7.36 (m, 2H), 7.28 – 7.17 (m, 2H), 2.51 (s, 3H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 135.9, 134.1, 133.4, 130.1, 128.9, 127.8, 127.4, 122.4, 119.6, 119.1, 110.8, 108.8, 9.8.

1,3-Dimethyl-2-phenyl-1*H*-indole (4r)[6]



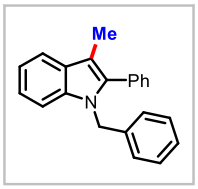
General procedure (**GP1**) was followed using 1-methyl-2-phenyl-1*H*-indole (41 mg, 0.2 mmol), paraformaldehyde (30 µL, 1.0 mmol, 5.0 equiv), triethyl silane (Et_3SiH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, Hexane) to afford the title compound as a white solid (35.5 mg, 80%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.8 Hz, 1H), 7.50 (t, *J* = 7.2 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 3H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.28 (d, *J* = 7.0 Hz, 1H), 7.17 (t, *J* = 6.9 Hz, 1H), 3.63 (s, 3H), 2.30 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 137.8, 137.3, 132.3, 130.8, 130.7, 128.5, 127.9, 121.8, 119.2, 118.9, 109.4, 108.7, 31.1, 9.5.

1-Ethyl-3-methyl-2-phenyl-1*H*-indole (4s)[6]



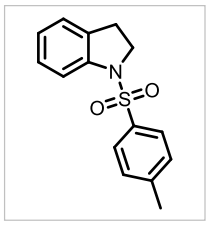
General procedure (**GP1**) was followed using 1-ethyl-2-phenyl-1*H*-indole (44.2 mg, 0.2 mmol), paraformaldehyde (30 µL, 1.0 mmol, 5.0 equiv), triethyl silane (Et_3SiH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, Hexane) to afford the title compound as a white solid (35.5 mg, 75%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.8 Hz, 1H), 7.52 – 7.46 (m, 2H), 7.45 – 7.35 (m, 4H), 7.27 – 7.22 (m, 1H), 7.17 – 7.12 (m, 1H), 4.08 (q, *J* = 7.2 Hz, 2H), 2.25 (s, 3H), 1.24 – 1.18 (m, 3H); **^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)** δ 137.2, 136.0, 132.5, 130.6, 128.7, 128.4, 127.8, 121.6, 119.0, 118.9, 109.5, 108.8, 38.6, 15.4, 9.3.

1-Benzyl-3-methyl-2-phenyl-1*H*-indole (4t)[6]



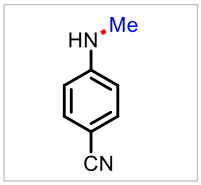
General procedure (**GP1**) was followed using 1-benzyl-2-phenyl-1*H*-indole (57 mg, 0.2 mmol), paraformaldehyde (30 µL, 1.0 mmol, 5.0 equiv), triethyl silane (Et_3SiH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, Hexane) to afford the title compound as a white solid (46 mg, 77%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 – 7.64 (m, 1H), 7.45 – 7.34 (m, 5H), 7.27 – 7.17 (m, 6H), 6.98 (d, *J* = 8.2 Hz, 2H), 5.26 (s, 2H), 2.35 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 138.6, 137.9, 136.9, 132.1, 130.7, 129.0, 128.7, 128.5, 128.0, 127.1, 126.2, 122.1, 119.5, 119.0, 110.3, 109.3, 47.7, 9.6.

1-Tosylindoline (4u)[7]



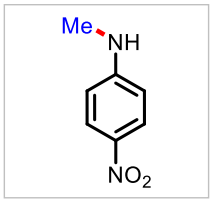
General procedure (**GP1**) was followed using 1-tosyl-1*H*-indole (60 mg, 0.2 mmol), paraformaldehyde (30 mg, 1.0 mmol, 5.0 equiv), chlorodimethylsilane (Me_2ClSiH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 20:80) to afford the title compound as a colorless viscous (41 mg, 75%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 16.1, 8.2 Hz, 3H), 7.27 – 7.16 (m, 3H), 7.07 (d, *J* = 7.5 Hz, 1H), 6.97 (t, *J* = 7.5 Hz, 1H), 3.91 (t, *J* = 8.3 Hz, 2H), 2.88 (t, *J* = 8.5 Hz, 2H), 2.36 (s, 3H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 144.1, 142.1, 134.1, 131.9, 129.8, 127.8, 127.4, 125.2, 123.8, 115.1, 50.1, 28.0, 21.6.

4-(Methylamino) benzonitrile (5a)[8]



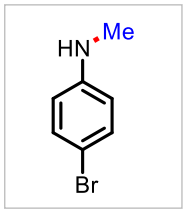
General procedure (**GP2**) was followed using 4-amino benzonitrile (24 mg, 0.2 mmol), paraformaldehyde (18 mg, 0.6 mmol, 3.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 15:85) to afford the title compound as a white solid (17.5 mg, 66%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.9 Hz, 2H), 6.55 (d, *J* = 8.9 Hz, 2H), 4.28 (s, 1H), 2.87 (d, *J* = 5.2 Hz, 3H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 152.3, 133.8, 120.7, 112.0, 98.7, 30.1

_N_-Methyl-4-nitroaniline (5b)[8]



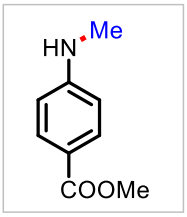
General procedure (**GP2**) was followed using 4-nitroaniline (28 mg, 0.2 mmol), paraformaldehyde (18 mg, 0.6 mmol, 3.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 20:80) to afford the title compound as a yellow solid (18.5 mg, 60%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 9.2 Hz, 2H), 6.52 (d, *J* = 9.3 Hz, 2H), 4.66 (s, 1H), 2.93 (d, *J* = 5.2 Hz, 3H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 154.4, 138.0, 126.5, 110.8, 30.3

4-Bromo-_N_-methylaniline (5c)[8]



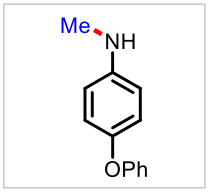
General procedure (**GP2**) was followed using 4-bromoaniline (34 mg, 0.2 mmol), paraformaldehyde (18 mg, 0.6 mmol, 3.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 05:95) to afford the title compound as a yellow viscous (32 mg, 70%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31 – 7.21 (m, 2H), 6.48 (d, *J* = 8.9 Hz, 2H), 3.73 (s, 1H), 2.81 (s, 3H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 148.4, 132.0, 114.1, 108.9, 30.8.

Methyl 4-(methylamino) benzoate (5d)[8]



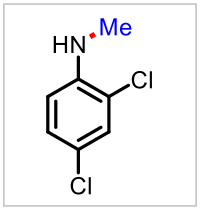
General procedure (**GP2**) was followed using methyl 4-aminobenzoate (30 mg, 0.2 mmol), paraformaldehyde (18 mg, 0.6 mmol, 3.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 10:90) to afford the title compound as a white solid (25 mg, 75%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.9 Hz, 2H), 6.55 (d, *J* = 8.7 Hz, 2H), 4.19 (s, 1H), 3.85 (s, 3H), 2.88 (s, 3H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 167.5, 153.0, 131.6, 118.3, 111.2, 51.7, 30.3.

_N_-Methyl-4-phenoxyaniline (5e)[8]



General procedure (**GP2**) was followed using 4-phenoxy aniline (37 mg, 0.2 mmol), paraformaldehyde (18 mg, 0.6 mmol, 3.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 20:80) to afford the title compound as a yellow solid (34 mg, 85%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.29 (t, *J* = 8.0 Hz, 2H), 7.02 (t, *J* = 7.3 Hz, 1H), 6.94 (d, *J* = 8.9 Hz, 4H), 6.63 (d, *J* = 8.9 Hz, 2H), 2.85 (s, 3H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 159.3, 147.7, 146.0, 129.6, 122.0, 121.4, 117.2, 113.5, 31.4.

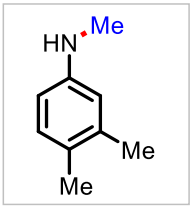
2,4-Dichloro-_N_-methylaniline (5f)[8]



General procedure (**GP2**) was followed using 2,4-dichloroaniline (32 mg, 0.2 mmol), paraformaldehyde (18 mg, 0.6 mmol, 3.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 05:95) to afford the title compound as a colorless liquid (29.5 mg, 85%);**^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.25

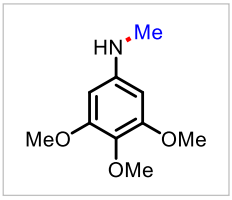
(d, *J* = 2.4 Hz, 1H), 7.12 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.55 (d, *J* = 8.7 Hz, 1H), 4.31 (s, 1H), 2.89 (s, 3H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 143.9, 128.7, 127.9, 121.1, 119.4, 111.3, 30.6.

N,3,4-Trimethylaniline (5g)[8]



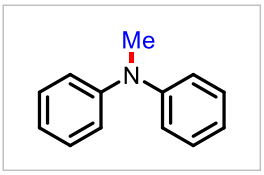
General procedure (**GP2**) was followed using 3,4-dimethylaniline (24 mg, 0.2 mmol), paraformaldehyde (18 mg, 0.6 mmol, 3.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 10:90) to afford the title compound as a colourless viscous (19.5 mg, 73%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.97 (d, *J* = 8.1 Hz, 1H), 6.47 (s, 1H), 6.42 (d, *J* = 7.9 Hz, 1H), 2.82 (s, 3H), 2.22 (s, 3H), 2.18 (s, 3H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 147.7, 137.4, 130.4, 125.4, 114.5, 110.1, 31.3, 20.2, 18.8.

3,4,5-Trimethoxy-*N*-methylaniline (5h)



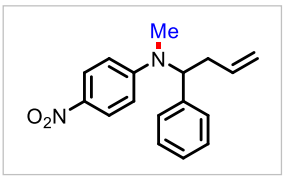
General procedure (**GP2**) was followed using 3,4,5-trimethoxyaniline (37 mg, 0.2 mmol), paraformaldehyde (18 mg, 0.6 mmol, 3.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 20:80) to afford the title compound as a black viscous (26.5 mg, 67%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.85 (s, 2H), 3.83 (s, 6H), 3.76 (s, 3H), 2.82 (s, 3H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 154.1, 146.3, 130.2, 90.1, 61.2, 56.1, 31.2. **HRMS** (ESI) m/z: $[M+Na]^+$ calculated for $C_{10}H_{15}NO_3Na$ 220.0950; found 220.0950.

N-Methyl-*N*-phenylaniline (5i)[8]



General procedure (**GP2**) was followed using diphenylamine (34 mg, 0.2 mmol), paraformaldehyde (18 mg, 0.6 mmol, 3.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 05:95) to afford the title compound as a colorless viscous (35.5 mg, 97%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30 (t, *J* = 8.0 Hz, 4H), 7.06 (d, *J* = 9.8 Hz, 4H), 6.98 (t, *J* = 7.3 Hz, 2H), 3.34 (s, 3H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 149.2, 129.3, 121.4, 120.6, 40.4.

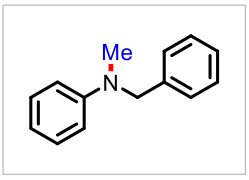
N-Methyl-4-nitro-*N*-(1-phenylbut-3-en-1-yl) aniline (5j)



General procedure (**GP2**) was followed using 4-nitro-*N*-(1-phenylbut-3-en-1-yl) aniline (54 mg, 0.2 mmol), paraformaldehyde (18 mg, 0.6 mmol, 3.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 05:95) to afford the title compound as a yellow solid (48 mg, 85%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 9.5 Hz, 2H), 7.38 (t, *J* = 7.3 Hz, 2H), 7.33 (d, *J* = 7.2 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 9.5 Hz, 2H), 5.85 – 5.74 (m, 1H), 5.26 (dd, *J* = 9.8, 5.6 Hz, 1H), 5.21 (d, *J* = 17.1 Hz, 1H), 5.10 (d, *J* = 10.2 Hz, 1H), 2.98 – 2.91 (m, 1H), 2.87 (s, 3H), 2.80 (dd, *J* = 15.4, 9.0 Hz, 1H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 154.9, 139.5, 137.3, 134.5, 128.9, 127.9, 126.9, 126.4, 118.1,

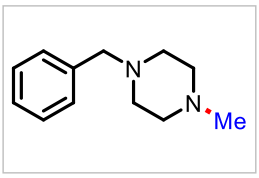
110.9, 61.0, 36.2, 32.6. **HRMS** (ESI) m/z: $[M+Na]^+$ calculated for $C_{17}H_{18}N_2O_2Na$ 305.1266; found 305.1254.

_N_-Benzyl-_N_-methylaniline (5k)[8]



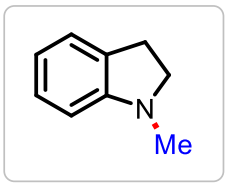
General procedure (**GP2**) was followed using *N*-benzyl aniline (37 mg, 0.2 mmol), paraformaldehyde (18 mg, 0.6 mmol, 3.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 10:90) to afford the title compound as a viscous liquid (38 mg, 96%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.21 (t, *J* = 7.5 Hz, 2H), 7.16 – 7.10 (m, 5H), 6.65 (d, *J* = 8.7 Hz, 2H), 6.61 (t, *J* = 7.2 Hz, 1H), 4.42 (s, 2H), 2.90 (s, 3H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 149.9, 139.2, 129.3, 128.7, 127.0, 126.9, 116.7, 112.5, 56.7, 38.6.

1-Benzyl-4-methylpiperazine (5l)[8]



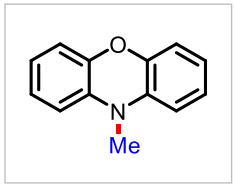
General procedure (**GP2**) was followed using 1-benzylpiperazine (35 mg, 0.2 mmol), paraformaldehyde (18 mg, 0.6 mmol, 3.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, MeOH:DCM: 05:95) to afford the title compound as a colorless viscous (30 mg, 78%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 4.4 Hz, 4H), 7.19 (dt, *J* = 8.9, 4.4 Hz, 1H), 3.47 (s, 2H), 2.48 (s, 8H), 2.29 (s, 3H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 137.9, 129.3, 128.4, 127.3, 63.0, 55.0, 52.7, 45.8.

1-Methylindoline (5m)[8]



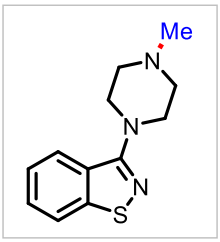
General procedure (**GP2**) was followed using indoline (24 mg, 0.2 mmol), paraformaldehyde (18 mg, 0.6 mmol, 3.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 20:80) to afford the title compound as a colorless liquid (22.5 mg, 85%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.11 – 7.06 (m, 2H), 6.70 – 6.64 (m, 1H), 6.50 (d, *J* = 7.9 Hz, 1H), 3.29 (t, *J* = 8.2 Hz, 2H), 2.95 (t, *J* = 8.2 Hz, 2H), 2.76 (s, 3H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 153.5, 130.4, 127.5, 124.4, 117.9, 107.4, 56.3, 36.4, 28.9.

10-Methyl-10*H*-phenoxazine (5n)[8]



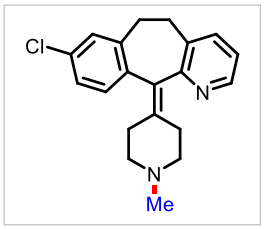
General procedure (**GP2**) was followed using indoline (37 mg, 0.2 mmol), paraformaldehyde (18 mg, 0.6 mmol, 3.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 20:80) to afford the title compound as a colorless viscous (32 mg, 80%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.93 – 6.85 (m, 2H), 6.77 – 6.70 (m, 4H), 6.56 (d, *J* = 8.1 Hz, 2H), 3.08 (s, 3H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 145.7, 135.2, 123.9, 121.0, 115.4, 111.5, 31.0.

3-(4-Methylpiperazin-1-yl) benzo[*d*]isothiazole (5o)



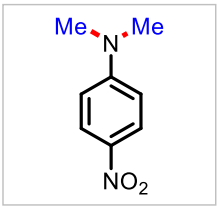
General procedure (**GP2**) was followed using 3-(piperazin-1-yl)benzo[*d*]isothiazole (44 mg, 0.2 mmol), paraformaldehyde (18 mg, 0.6 mmol, 3.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, MeOH:DCM: 05:95) to afford the title compound as a yellow solid (40 mg, 85%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.1 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 3.67 – 3.48 (m, 4H), 2.76 – 2.59 (m, 4H), 2.40 (s, 3H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 163.9, 152.9, 128.1, 127.7, 124.0, 124.0, 120.7, 54.9, 50.0, 46.2. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{12}H_{16}N_3S$ 234.1065; found 234.1057.

8-Chloro-11-(1-methylpiperidin-4-ylidene)-6,11-dihydro-5*H*-benzo [5,6] cyclohepta[1,2-b] pyridine (5p)



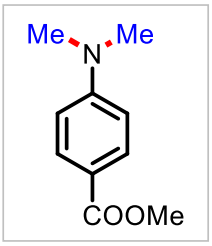
General procedure (**GP2**) was followed using 8-chloro-11-(piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-b]pyridine (62 mg, 0.2 mmol), paraformaldehyde (18 mg, 0.6 mmol, 3.0 equiv), triethyl silane (Et_3SiH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, MeOH:DCM: 05:95) to afford the title compound as a white solid (58 mg, 89%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.52 (d, *J* = 5.3 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.31 (s, 1H), 7.28 – 7.21 (m, 3H), 3.58 – 3.43 (m, 2H), 3.19 – 3.05 (m, 2H), 3.03 – 2.83 (m, 4H), 2.77 (t, *J* = 10.5 Hz, 4H), 2.69 (s, 3H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 156.7, 146.6, 139.7, 137.7, 137.5, 135.2, 134.4, 133.5, 133.0, 130.3, 129.0, 126.2, 122.4, 56.1, 44.8, 31.6, 31.4, 29.5, 29.2. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{20}H_{22}N_2Cl$ 325.1472; found 325.1459.

N, N-Dimethyl-4-nitroaniline (6b)[8]



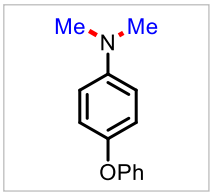
General procedure (**GP2**) was followed using 4-nitroaniline (28 mg, 0.2 mmol), paraformaldehyde (18 mg, 0.6 mmol, 3.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 05:95) to afford the title compound as a yellow solid (15 mg, 45%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 9.5 Hz, 2H), 6.59 (d, *J* = 9.5 Hz, 2H), 3.10 (s, 6H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 154.3, 137.0, 126.2, 110.3, 40.4.

Methyl 4-(dimethylamino) benzoate (6d)[8]



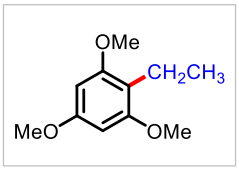
General procedure (**GP2**) was followed using 4-aminobenzoate (30 mg, 0.2 mmol), paraformaldehyde (18 mg, 0.6 mmol, 3.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 10:90) to afford the title compound as a white solid (6 mg, 15%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 9.2 Hz, 1H), 6.64 (d, *J* = 9.2 Hz, 1H), 3.85 (s, 2H), 3.03 (s, 6H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 167.6, 153.4, 131.4, 117.0, 110.8, 51.6, 40.2.

N, *N*-Dimethyl-4-phenoxyaniline (6e)[8]



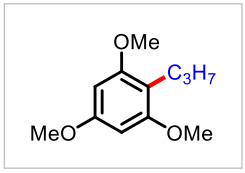
General procedure (**GP2**) was followed using 4-phenoxy aniline (37 mg, 0.2 mmol), paraformaldehyde (18 mg, 0.6 mmol, 3.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 20:80) to afford the title compound as a yellow solid (5 mg, 10%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28 (t, *J* = 6.8 Hz, 2H), 7.01 (t, *J* = 7.3 Hz, 1H), 7.00 – 6.92 (m, 4H), 6.75 (d, *J* = 9.0 Hz, 2H), 2.94 (s, 6H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 159.2, 147.8, 147.5, 129.6, 122.1, 121.1, 117.3, 114.1, 41.4.

2-Ethyl-1,3,5-trimethoxybenzene (7a)[9]



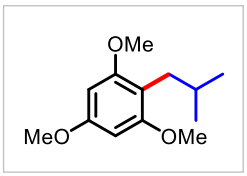
General procedure (**GP1**) was followed using 1,3,5-trimethoxybenzene (34 mg, 0.2 mmol), acetaldehyde (1.0 mmol, 5.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 05:95) to afford the title compound as a white solid (30 mg, 77%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.15 (s, 2H), 3.81 (s, 9H), 2.59 (q, *J* = 7.4 Hz, 2H), 1.06 (t, *J* = 7.4 Hz, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 159.1, 158.7, 113.5, 90.7, 55.8, 55.4, 16.0, 14.2.

1,3,5-Trimethoxy-2-propylbenzene (7b)[9]



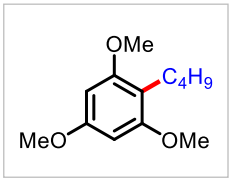
General procedure (**GP1**) was followed using 1,3,5-trimethoxybenzene (34 mg, 0.2 mmol), propionaldehyde (1.0 mmol, 5.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 05:95) to afford the title compound as a white solid (34 mg, 81%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.14 (s, 2H), 3.81 (s, 3H), 3.79 (s, 6H), 2.55 – 2.51 (m, 2H), 1.50 – 1.43 (m, 2H), 0.92 (d, *J* = 7.3 Hz, 3H); **^{13}C {^{1}H}** NMR (101 MHz, $CDCl_3$) δ 159.0, 112.0, 93.0, 90.6, 55.8, 55.4, 24.7, 22.9, 14.3.

2-Isobutyl-1,3,5-trimethoxybenzene (7c)[9]



General procedure (**GP1**) was followed using 1,3,5-trimethoxybenzene (34 mg, 0.2 mmol), isobutyraldehyde (1.0 mmol, 5.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 05:95) to afford the title compound as a white solid (33 mg, 73%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.14 (s, 2H), 3.81 (s, 3H), 3.78 (s, 6H), 2.44 (d, *J* = 7.3 Hz, 2H), 1.83 (hept, *J* = 6.9 Hz, 1H), 0.86 (d, *J* = 6.7 Hz, 6H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 159.3, 159.2, 111.3, 90.6, 55.7, 55.4, 31.5, 28.7, 22.7.

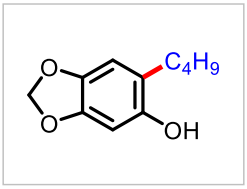
2-Butyl-1,3,5-trimethoxybenzene (7d)[9]



General procedure (**GP1**) was followed using 1,3,5-trimethoxybenzene (34 mg, 0.2 mmol), butyraldehyde (1.0 mmol, 5.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 05:95) to afford the title

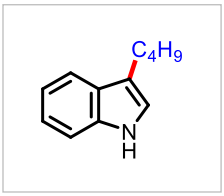
compound as a white solid (33.5 mg, 75%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.14 (s, 2H), 3.81 (s, 3H), 3.80 (s, 6H), 2.58 – 2.54 (m, 2H), 1.44 – 1.39 (m, 2H), 1.36 – 1.33 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 3H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 159.1, 158.9, 112.2, 90.7, 55.8, 55.4, 32.0, 22.9, 22.4, 14.2.

6-Butylbenzo[d][1,3]dioxol-5-ol (7e)



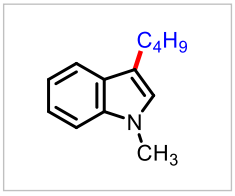
General procedure (**GP1**) was followed using benzo[d][1,3]dioxol-5-ol (28 mg, 0.2 mmol), butyraldehyde (1.0 mmol, 5.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 05:95) to afford the title compound as a yellow liquid (33 mg, 85%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.59 (s, 1H), 6.39 (s, 1H), 5.86 (s, 2H), 4.70 (s, 1H), 2.53 – 2.47 (m, 2H), 1.58 – 1.50 (m, 2H), 1.41 – 1.33 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 147.8, 146.0, 141.4, 120.5, 109.4, 101.0, 98.3, 32.4, 29.6, 22.6, 14.1. **HRMS** (ESI) m/z: $[M-H]^-$ calculated for $C_{11}H_{13}O_3$; 193.0865 found 193.0860.

3-Butyl-1*H*-indole (7f)[10]



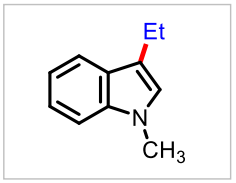
General procedure (**GP1**) was followed using 1*H*-indole (24 mg, 0.2 mmol), butyraldehyde (1.0 mmol, 5.0 equiv), triethyl silane (Et_3SiH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 05:95) to afford the title compound as a colourless viscous (19 mg, 55%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.19 (t, *J* = 6.9 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 6.97 (s, 1H), 2.76 (t, *J* = 7.7 Hz, 2H), 1.71 (p, *J* = 7.6 Hz, 2H), 1.45 – 1.40 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 136.4, 127.7, 121.9, 121.1, 119.1, 117.3, 111.1, 32.4, 24.9, 22.8, 14.1.

3-Butyl-1-methyl-1*H*-indole (7g)[10]



General procedure (**GP1**) was followed using 1-methyl-1*H*-indole (26 mg, 0.2 mmol), butyraldehyde (1.0 mmol, 5.0 equiv), triethyl silane (Et_3SiH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, Hexane) to afford the title compound as a colorless viscous (28 mg, 75%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 9.9 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.37 (t, *J* = 8.2 Hz, 1H), 7.26 (t, *J* = 7.4 Hz, 1H), 6.97 (s, 1H), 3.87 (s, 3H), 2.91 (t, *J* = 7.2 Hz, 2H), 1.90 – 1.79 (m, 2H), 1.58 (dt, *J* = 14.8, 7.4 Hz, 2H), 1.12 (t, *J* = 7.4 Hz, 3H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 137.2, 128.1, 126.1, 121.5, 119.2, 118.5, 115.7, 109.2, 32.8, 32.6, 24.9, 22.8, 14.2.

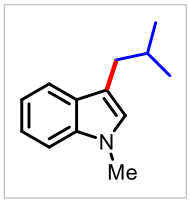
3-Ethyl-1-methyl-1*H*-indole (7h)[10]



General procedure (**GP1**) was followed using 1-methyl-1*H*-indole (26 mg, 0.2 mmol), acetaldehyde (1.0 mmol, 5.0 equiv), triethyl silane (Et_3SiH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, Hexane) to afford the title compound as a colourless viscous (19 mg, 60%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.3 Hz, 1H), 7.31 (d, *J* = 8.3 Hz,

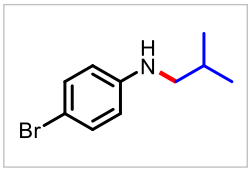
1H), 7.24 (t, *J* = 6.9 Hz, 2H), 7.12 (t, *J* = 6.8 Hz, 1H), 6.85 (s, 1H), 3.76 (s, 3H), 2.81 (q, *J* = 7.3 Hz, 2H), 1.35 (t, *J* = 7.5 Hz, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 137.2, 127.9, 125.5, 121.5, 119.2, 118.6, 117.4, 109.2, 32.7, 18.4, 14.9.

3-Isobutyl-1-methyl-1*H*-indole (7i)[10]



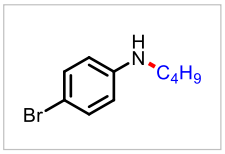
General procedure (**GP1**) was followed using 1-methyl-1*H*-indole (26 mg, 0.2 mmol), isobutyraldehyde (1.0 mmol, 5.0 equiv), triethyl silane (Et_3SiH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, Hexane) to afford the title compound as a colorless viscous (26 mg, 70%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 – 7.58 (m, 1H), 7.39 – 7.21 (m, 2H), 7.18 – 7.06 (m, 1H), 6.86 (s, 1H), 3.78 (s, 3H), 2.79 – 2.45 (m, 2H), 2.09 – 1.86 (m, 1H), 1.00 (d, *J* = 16.7 Hz, 6H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 137.2, 127.9, 125.5, 121.6, 119.2, 118.6, 117.4, 109.2, 32.7, 18.4, 14.9.

4-Bromo-*N*-isobutylaniline (7j)[8]



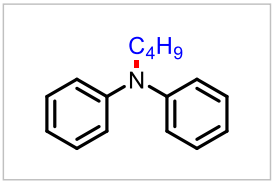
General procedure (**GP2**) was followed using 4-bromoaniline (34 mg, 0.2 mmol), isobutyraldehyde (1.0 mmol, 5.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 05:95) to afford the title compound as a colourless viscous (35 mg, 77%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 9.0 Hz, 2H), 6.47 (d, *J* = 8.9 Hz, 2H), 3.72 (s, 1H), 2.89 (d, *J* = 6.8 Hz, 2H), 1.87 (dp, *J* = 13.4, 6.7 Hz, 1H), 0.97 (d, *J* = 6.6 Hz, 6H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 147.7, 132.0, 114.3, 108.5, 51.9, 28.1, 20.6.

4-Bromo-*N*-butylaniline (7k)[8]



General procedure (**GP2**) was followed using 4-bromoaniline (34 mg, 0.2 mmol), butyraldehyde (1.0 mmol, 5.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 05:95) to afford the title compound as a colourless viscous (34 mg, 75%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.9 Hz, 2H), 6.47 (d, *J* = 8.9 Hz, 2H), 3.62 (s, 1H), 3.07 (t, *J* = 7.2 Hz, 2H), 1.59 (p, *J* = 7.4 Hz, 2H), 1.45 – 1.40 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 147.6, 132.0, 114.3, 108.7, 43.8, 31.6, 20.4, 14.0.

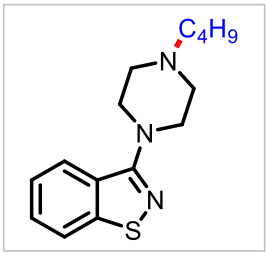
***N*-Butyl-*N*-phenylaniline (7l)[8]**



General procedure (**GP2**) was followed using diphenylamine (34 mg, 0.2 mmol), butyraldehyde (1.0 mmol, 5.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 05:95) to afford the title compound as a white solid (35 mg, 77%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 7.3 Hz, 4H), 6.97 (d, *J* = 7.5 Hz, 4H), 6.92 (t, *J* = 7.3 Hz, 2H), 3.71 – 3.64 (m, 2H), 1.64 (p, *J* = 7.6 Hz, 2H), 1.36 –

1.33 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H); **^{13}C {^{1}H} NMR (**126 MHz, $CDCl_3$) δ 148.3, 129.4, 121.1, 121.0, 52.2, 29.7, 20.4, 14.1.

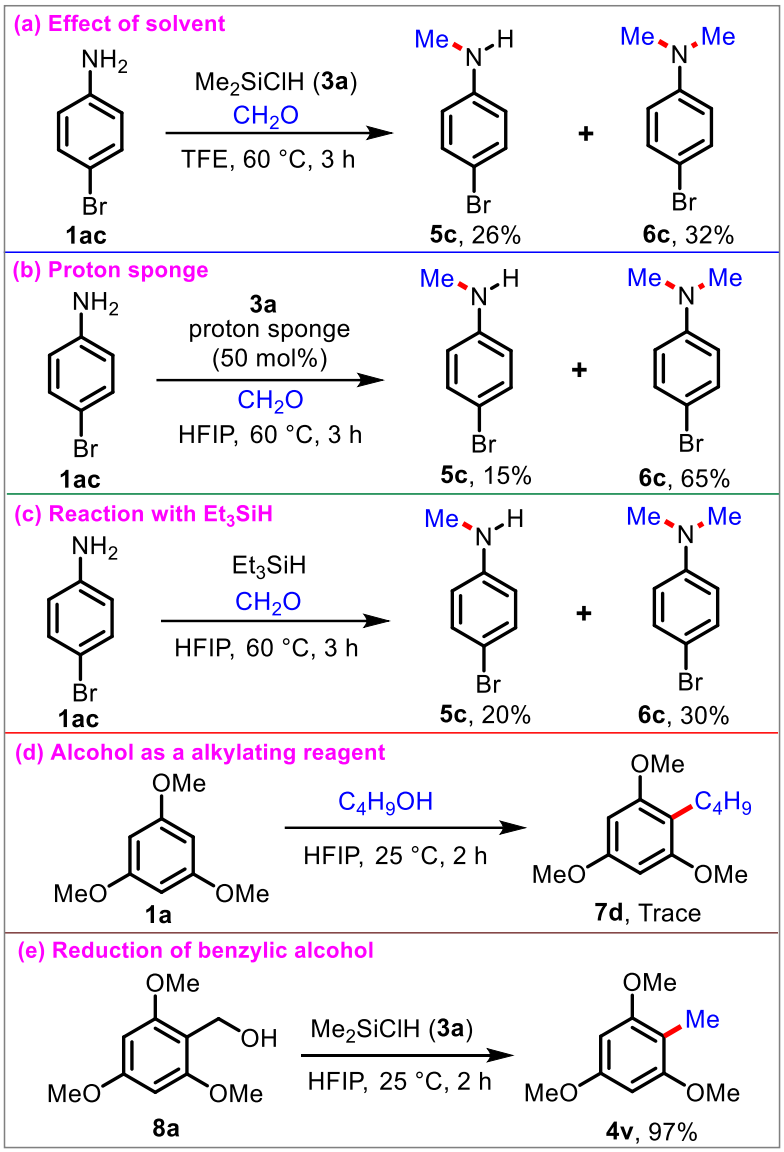
3-(4-Butylpiperazin-1-yl) benzo[*d*] isothiazole (7m)



General procedure (**GP2**) was followed using 3-(piperazin-1-yl)benzo[*d*]isothiazole (44 mg, 0.2 mmol), butyraldehyde (1.0 mmol, 5.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, MeOH:DCM: 03:97) to afford the title compound as a yellow liquid (39 mg, 70%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.2 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.52 – 7.41 (m, 1H), 7.34 (t, *J* = 8.1 Hz, 1H), 3.65 – 3.55 (m, 4H), 2.76 – 2.68 (m, 4H), 2.51 – 2.41 (m, 2H), 1.66 – 1.52 (m, 2H), 1.43 – 1.15 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 163.9, 152.8, 128.1, 127.7, 124.0, 124.0, 120.7, 58.6, 53.0, 49.8, 28.8, 20.8, 14.1. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{15}H_{22}N_3S$; 276.1534 found 276.1538.

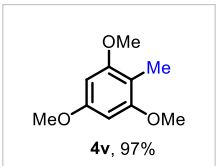
6. Control experiments

Control experiments were conducted, as shown in Scheme S1, to probe the possible reaction pathway for the methylation approach. From our prior studies[11] and based on previous reports[12] we anticipated the role of the H-bond donation ability (HBD) of HFIP for the selective mono *N*–methylation of primary amines. We have performed the reactions of *p*-bromo aniline (**1ac**) and (*para*)-formaldehyde with Me_2SiClH at 60 °C in TFE (2,2,2-trifluoroethanol) as a solvent (Scheme 1Sa). We have observed that in comparison to HFIP, the reaction conducted in TFE exhibited significantly lower selectivity and yield. Further, the methylation of *p*-bromo aniline was carried out in the presence of a proton scavenger (*N*, *N*, *N'*, *N'*-tetramethyl-1,8-naphthalene diamine), and the formation of *N*, *N*-di-methylated product **6c** over the **5c** suggested the presence of acidic environment are crucial for the selective mono-methylation (Scheme 1Sb). Substituting Et_3SiH for the more acidic Me_2SiClH in the methylation of *p*-bromoaniline under optimized conditions produced the *N*, *N*-di-methylated product as the major one. This further clarified the essential role of a suitable acidic environment for achieving selective mono-methylation (Scheme 1Sc). To unravel the mechanistic details of C–methylation, we utilized alcohol as a C1 source instead of butanal under the same conditions. This led to the traces of C–alkylated **7d**, helping to eliminate the possibility of a conventional Friedel–Crafts mechanism (Scheme 1Sd). We subsequently confirmed the viability of the alkylation followed by a reduction in the context of C–methylation. Hence, we examined compound **8a** (an intermediate in FC alkylation) as a reactant under the optimized reaction conditions, yielding the desired methylated product in high yields. (Scheme 1Se).



Scheme 1S. Control Experiments. (a) **1ac** (0.2 mmol), **3a** (0.4 mmol), and CH_2O (0.6 mmol) in TFE. (b) **1ac** (0.2 mmol), **3a** (0.4 mmol), CH_2O (0.6 mmol), and proton sponge (1,8-Bis (dimethyl amino) naphthalene, 0.1 mmol) in HFIP. (c) **1ac** (0.2 mmol), Et_3SiH (0.4 mmol), and CH_2O (0.6 mmol) in HFIP. (d) **1a** (0.2 mmol) and C_4H_9OH (0.6 mmol) in HFIP. (e) **8a** (0.2 mmol), **3a** (0.4 mmol) in HFIP.

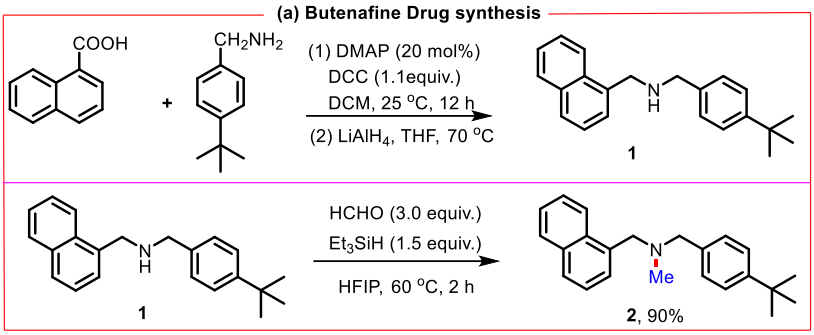
1,3,5-Trimethoxy-2-methylbenzene (4v)[2]



General procedure (**GP1**) was followed using (2,4,6-trimethoxyphenyl) methanol (**8a**, 40 mg, 0.2 mmol) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 05:95) to afford the title compound as a colorless viscous (35 mg, 97%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.15 (s, 2H), 3.82 (s, 9H), 2.04 (s, 3H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 159.0, 107.0, 93.1, 90.7, 55.9, 55.5, 7.8.

7. Late-stage modification

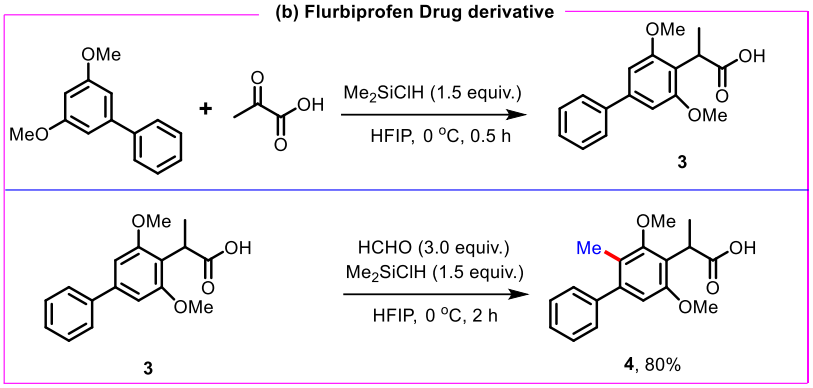
(a) Butenafine Drug synthesis (2)



Synthesis of 1: A reaction vial was charged with 1-naphthoic acid (5.0 mmol), DDC (5.5 mmol), DMAP (20 mol%), and (4-(*tert*-butyl) phenyl)-methanamine (7.5 mmol) in DCM (1.0 mL) at room temperature. The diethyl ether was added to quench the reaction in the reaction mixture. Then the reaction mixture was filtrated through a paid of celite and the filtrate was washed with a 1*N* solution of HCl, saturated $NaHCO_3$ solution, and brine. The collected organic layer was dried and concentrated. The coupling product amide compound was purified by using column chromatography (SiO_2, EtOAc/Hexane = 15/85). After the first step of the reaction, the solution of amide (0.2 mmol, 1.0 equiv.) in dry THF (2.0 mL) was added into $LiAlH_4$ (43 mg, 1.1 mmol, 5.0 equiv.) dropwise under N_2 atmosphere at 0 °C. After that, the reaction mixture was stirred for 12 h at 70 °C in an oil bath, and then add several drops of saturated brine solution until the evolution of H_2 stopped. Then the solution was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The reaction mixture was evaporated and purification was done by column chromatography (SiO_2, EtOAc/Hexane = 80/20) to afford the desired product **1** in good yield.

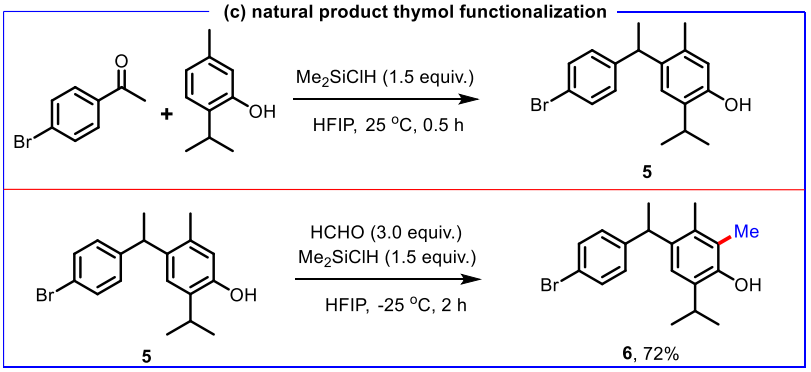
***N*-(4-(*tert*-butyl)benzyl)-*N*-methyl-1-(naphthalen-1-yl)-methanamine (2)[8]:** General procedure (**GP2**) was followed using *N*-(4-(*tert*-butyl)benzyl)-1-(naphthalen-1-yl)-methanamine (**1**, 60.6 mg, 0.2 mmol) paraformaldehyde (18 mg, 0.6 mmol, 3.0 equiv), Et_3SiH (0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 15:85) to afford the **2** as a light yellow viscous (58 mg, 90%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 – 7.68 (m, 4H), 7.49 (d, *J* = 8.3 Hz, 1H), 7.42 – 7.34 (m, 2H), 7.33 – 7.21 (m, 4H), 3.60 (s, 2H), 3.48 (s, 2H), 2.16 (s, 3H), 1.25 (s, 9H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 149.9, 137.2, 136.2, 133.5, 132.9, 128.8, 128.0, 127.82, 127.78, 127.5, 127.4, 126.0, 125.6, 125.3, 62.1, 61.7, 42.5, 34.6, 31.5.

(b) 2-(3,5-dimethoxy-2-methyl-[1,1'-biphenyl]-4-yl) propanoic acid (4)



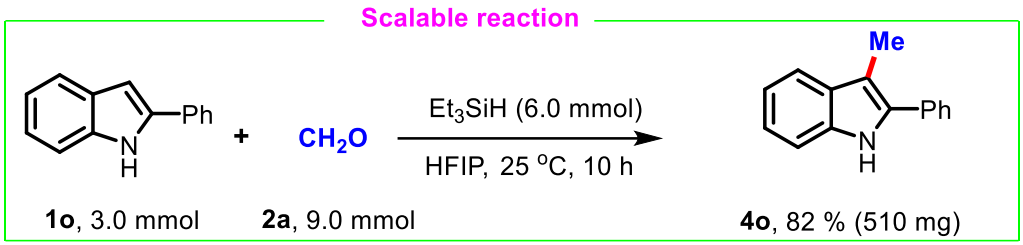
General procedure (**GP1**) was followed using 4-(1-(4-bromophenyl)ethyl)-2-isopropyl-5-methylphenol (**3**, 77.2 mg, 0.2 mmol) paraformaldehyde (18 mg, 0.6 mmol, 3.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, MeOH:DCM: 03:97) to afford the **4** as a colorless viscous (48 mg, 80%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.40 (m, 2H), 7.38 – 7.31 (m, 3H), 6.60 (s, 1H), 4.24 (q, *J* = 7.0 Hz, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 2.14 (s, 3H), 1.47 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 180.7, 157.0, 155.4, 142.7, 142.0, 129.3, 128.2, 127.0, 122.5, 121.1, 109.0, 61.0, 55.7, 35.8, 16.1, 13.8. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{18}H_{21}O_4$ 301.1440; found: 301.1438

(c) Synthesis of 4-(1-(4-Bromophenyl) ethyl)-6-isopropyl-2,3-dimethylphenol (6)



General procedure (**GP1**) was followed using 4-(1-(4-bromophenyl)ethyl)-2-isopropyl-5-methylphenol (**5**, 66.4 mg, 0.2 mmol) paraformaldehyde (18 mg, 0.6 mmol, 3.0 equiv), chlorodimethylsilane (Me_2SiClH, 0.4 mmol, 2.0 equiv) to give a crude mixture which was purified by using column chromatography (SiO_2, EtOAc:Hexane: 05:95) to afford the **6** as a colorless viscous (50 mg, 72%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.99 (s, 1H), 4.66 (s, 1H), 4.29 (q, *J* = 7.0 Hz, 1H), 3.21 – 3.12 (m, 1H), 2.19 (s, 3H), 2.09 (s, 3H), 1.59 (d, *J* = 3.1 Hz, 3H), 1.29 (t, *J* = 6.6 Hz, 6H); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 149.5, 146.4, 135.2, 133.3, 131.4, 130.7, 129.5, 122.5, 121.9, 119.5, 41.0, 27.7, 22.94, 22.89, 15.6, 12.6. **HRMS** (ESI) m/z: $[M+Na]^+$ calculated for $C_{19}H_{23}OBrNa$ 369.0830; found: 369.0819.

8 Scale-up reaction

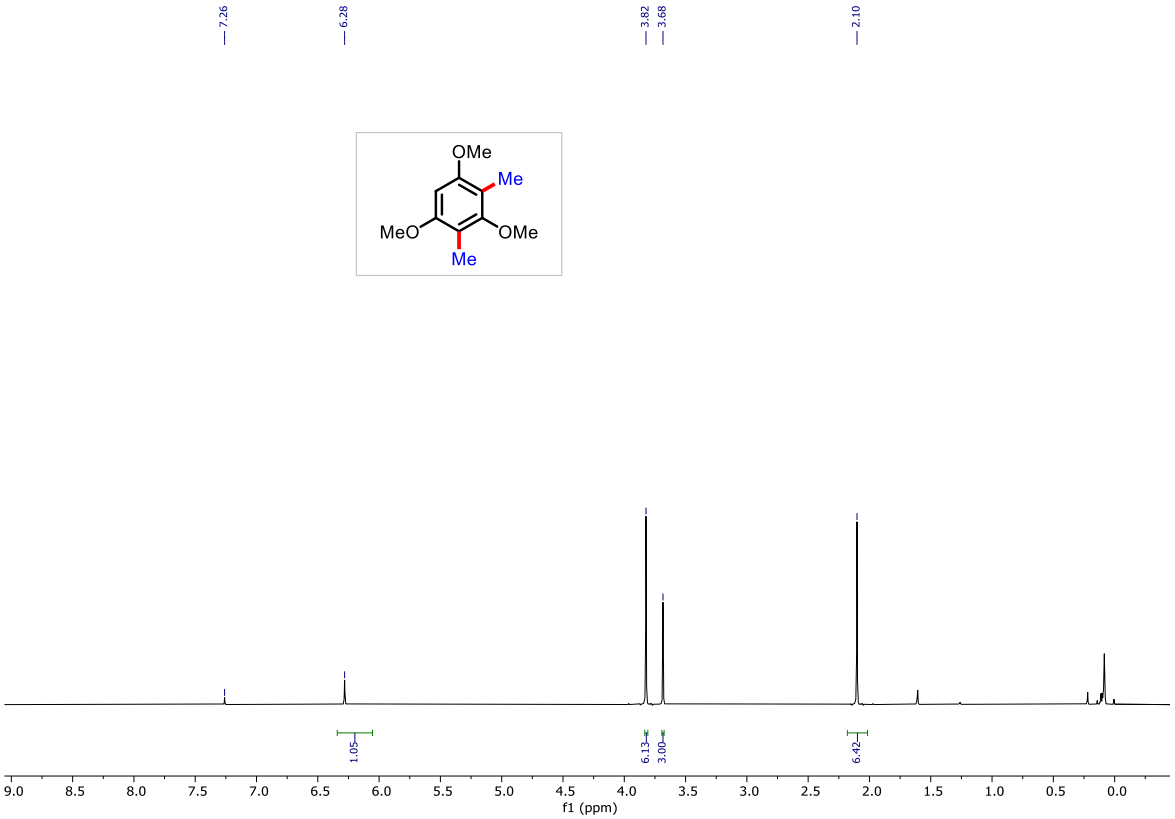


A scale-up reaction was performed according to the general procedure (**GP1**) to show the synthetic efficiency of our designed protocol. For this, a reaction was carried out using **1o** (3.0 mmol, 1.0 equiv.), **2a** (formalin, 37% solution in H_2O, 9.0 mmol, 3.0 equiv.), and Et_3SiH (6.0 mmol, 2.0 equiv.) under the optimal reaction condition. After completion of the reaction, the reaction mixture was evaporated in vacuo, and the residue was purified by column chromatography using a gradient of pure hexane to afford the product **4o** as a white solid (510 mg, 82%).

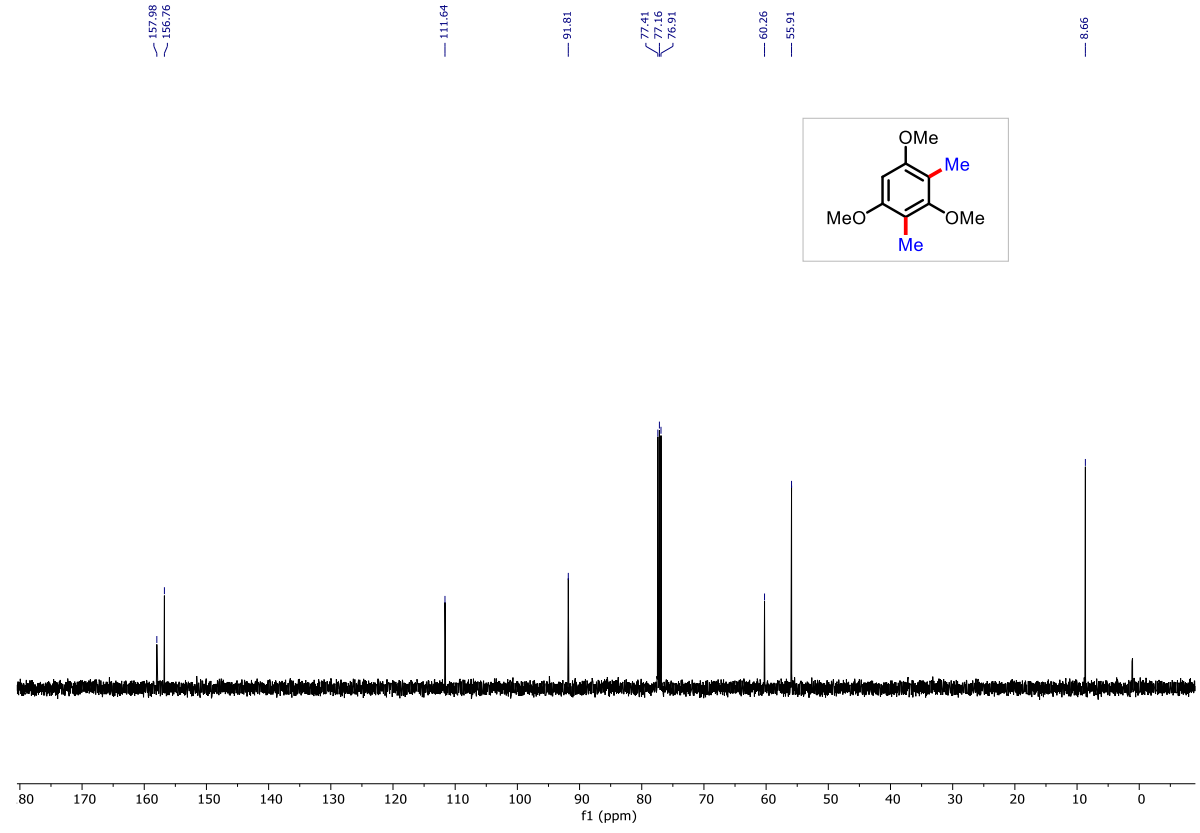
9. Copies of ^{1}H and ^{13}C {^{1}H} NMR spectra of starting materials and products

1,3,5-Trimethoxy-2,4-dimethylbenzene (4a)

^{1}H NMR (500 MHz, $CDCl_3$)

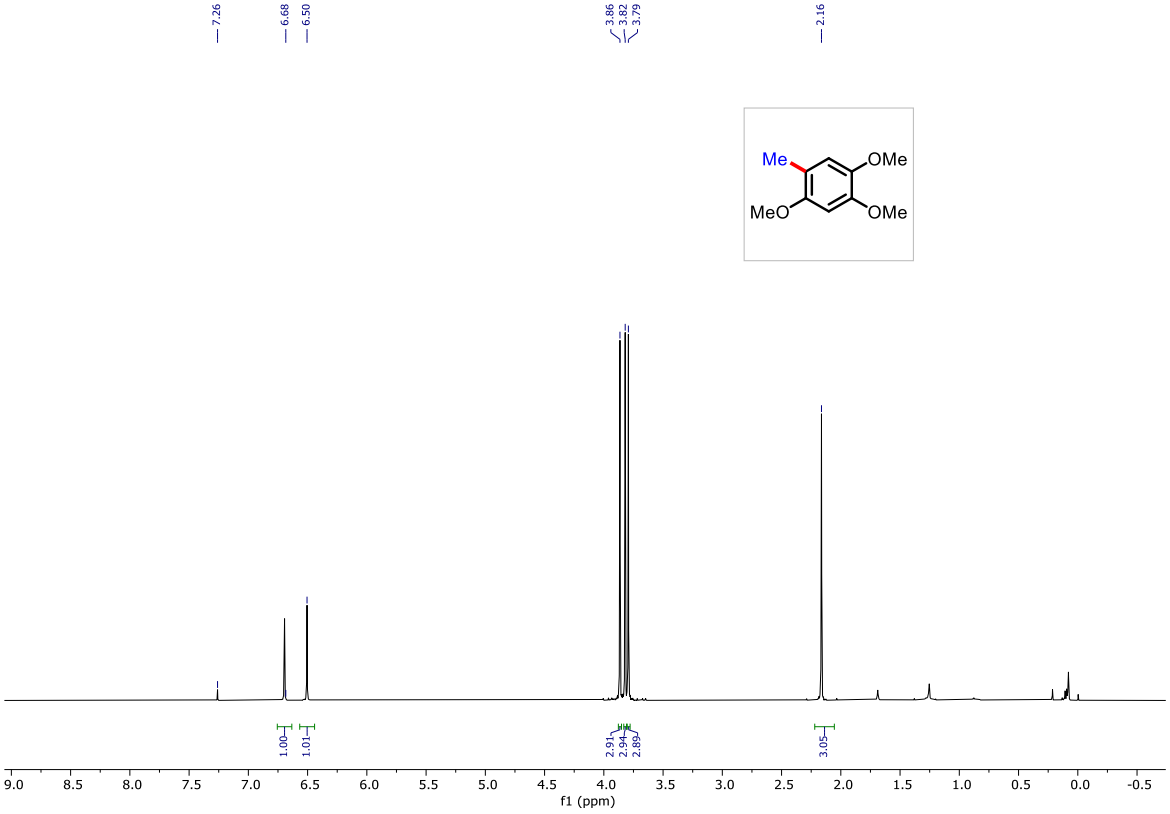


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

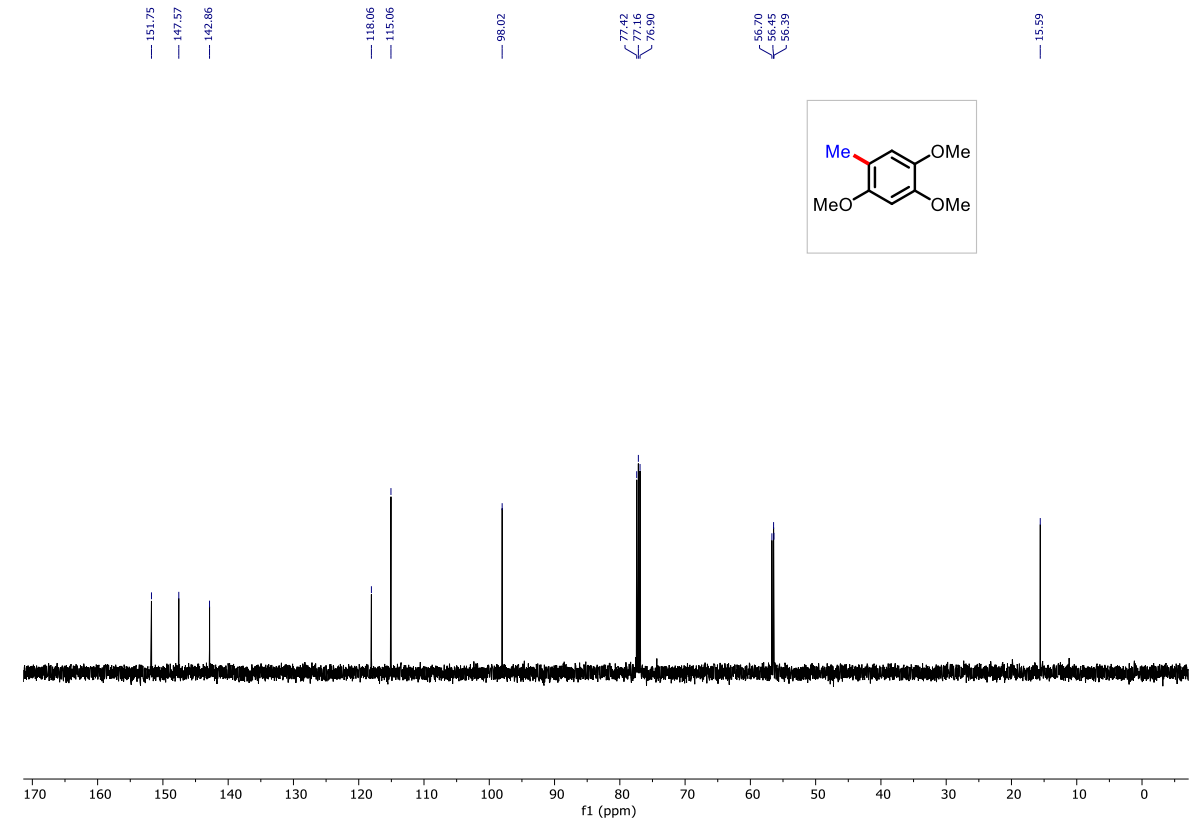


1,2,4-Trimethoxy-5-methylbenzene (4b)

^{1}H NMR (500 MHz, $CDCl_3$)

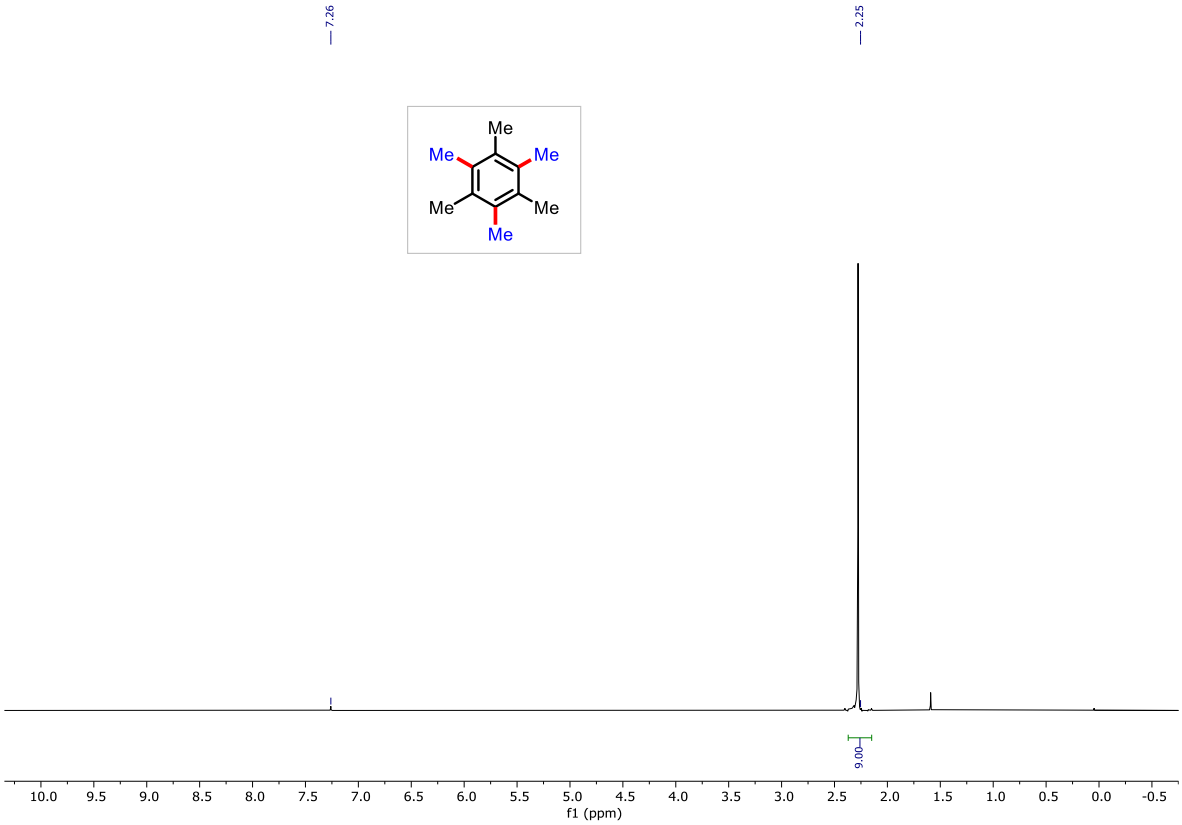


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

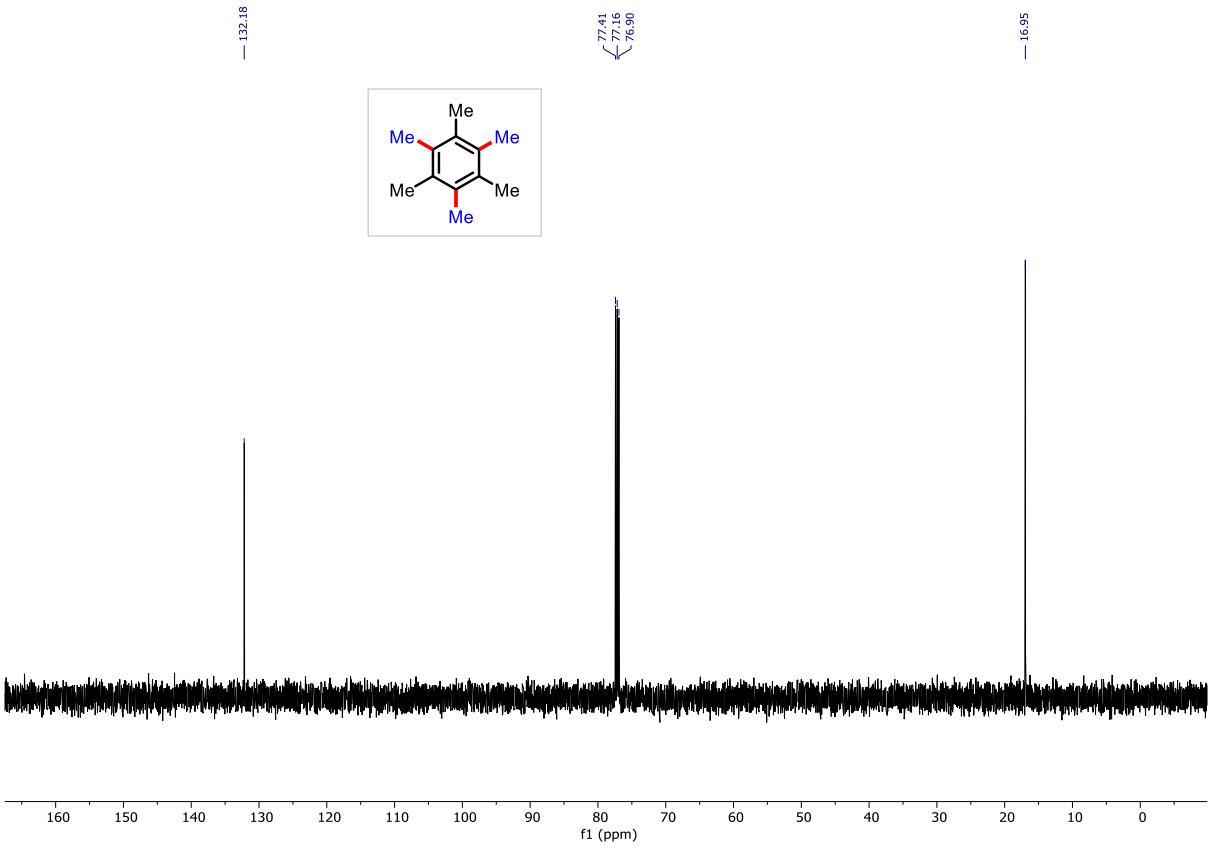


1,2,3,4,5,6-Hexamethylbenzene (4c)

^{1}H NMR (500 MHz, $CDCl_3$)

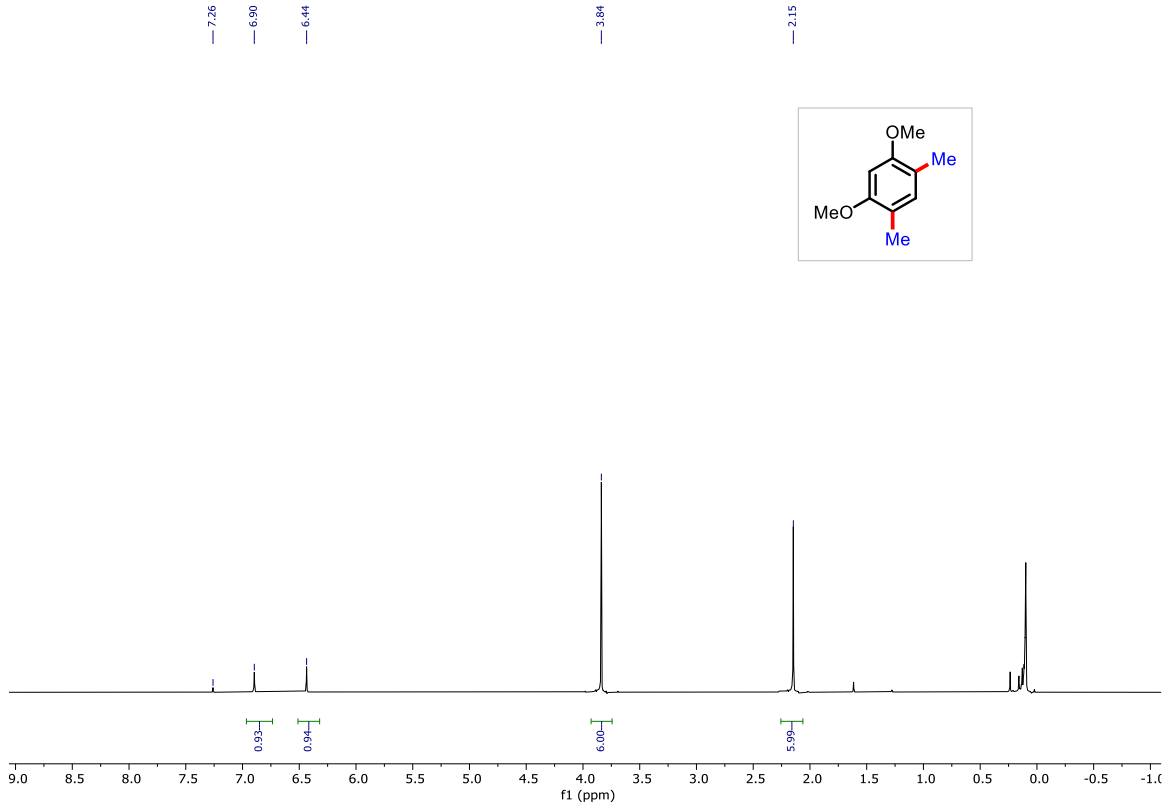


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

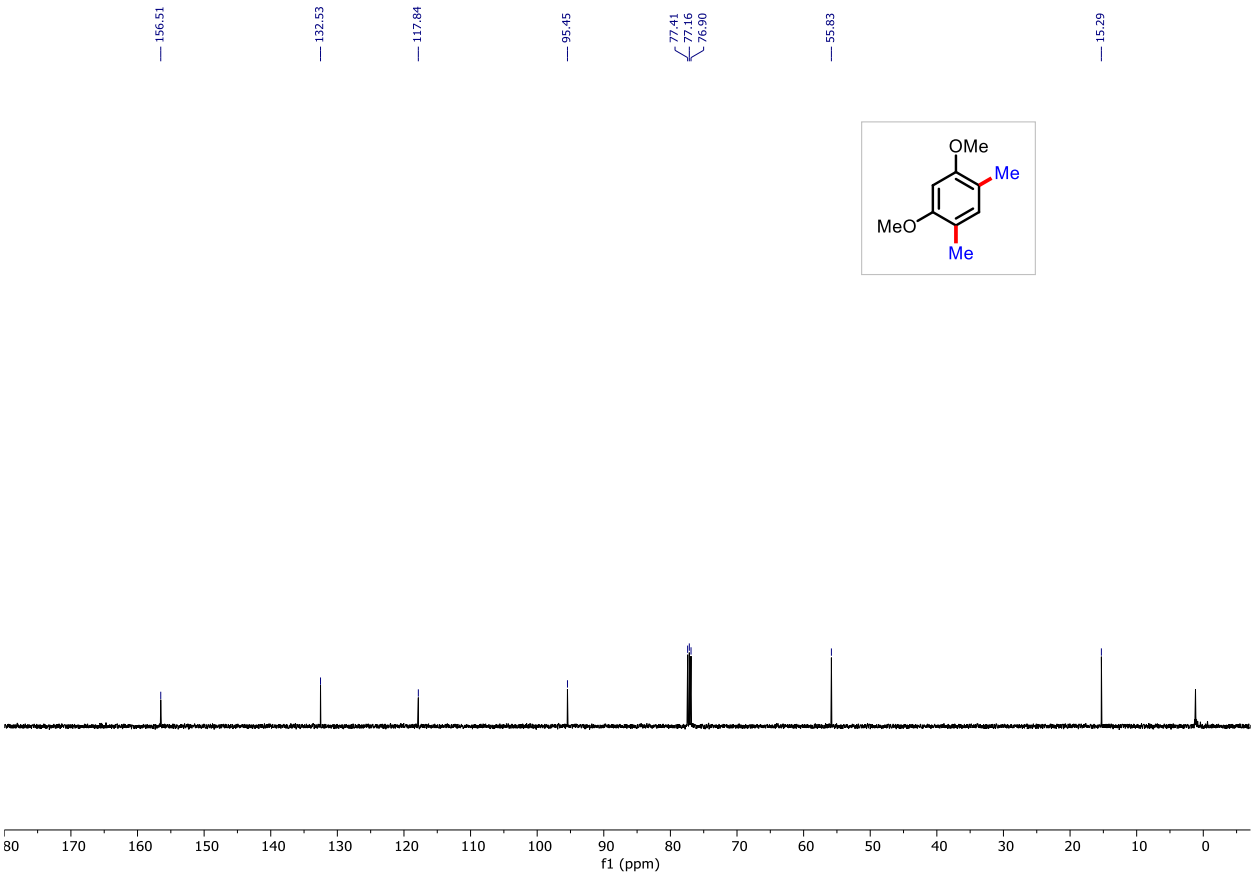


1,5-Dimethoxy-2,4-dimethylbenzene (4d)

^{1}H NMR (500 MHz, $CDCl_3$)

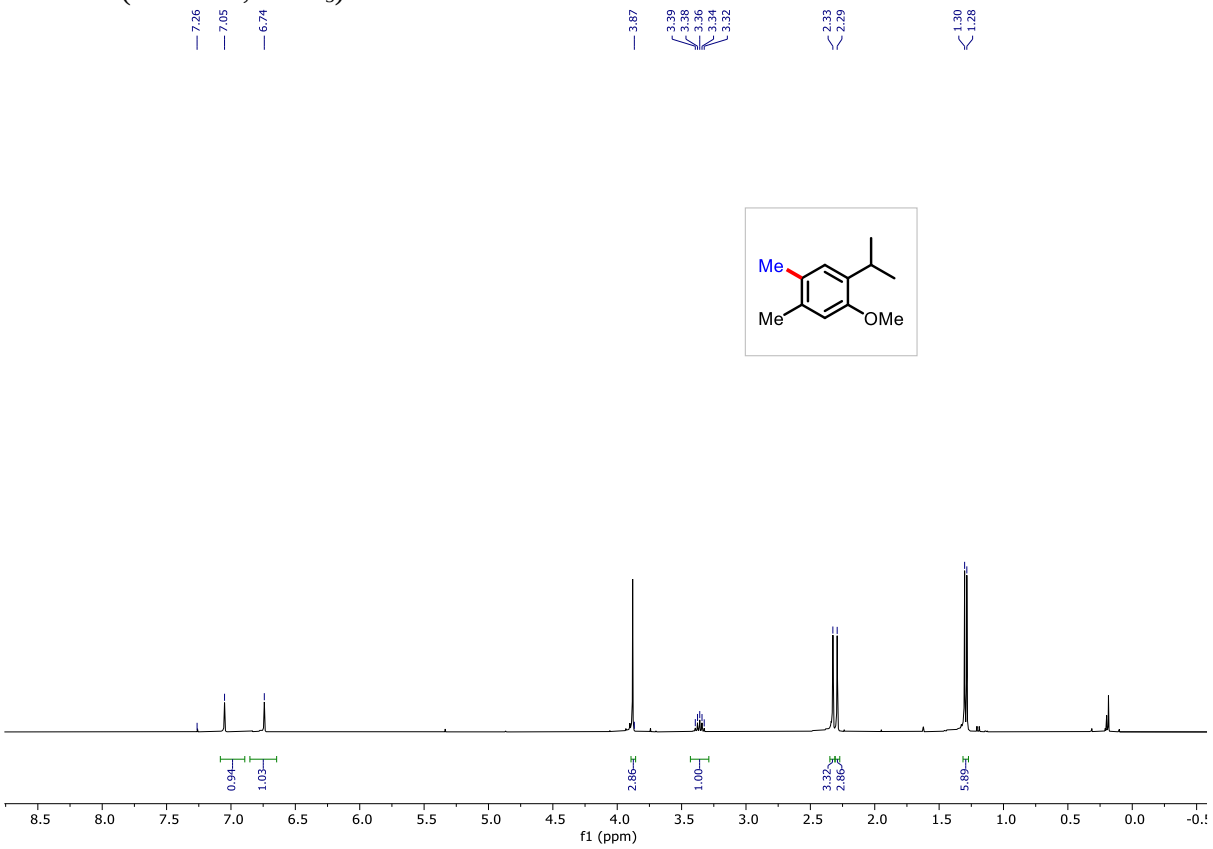


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

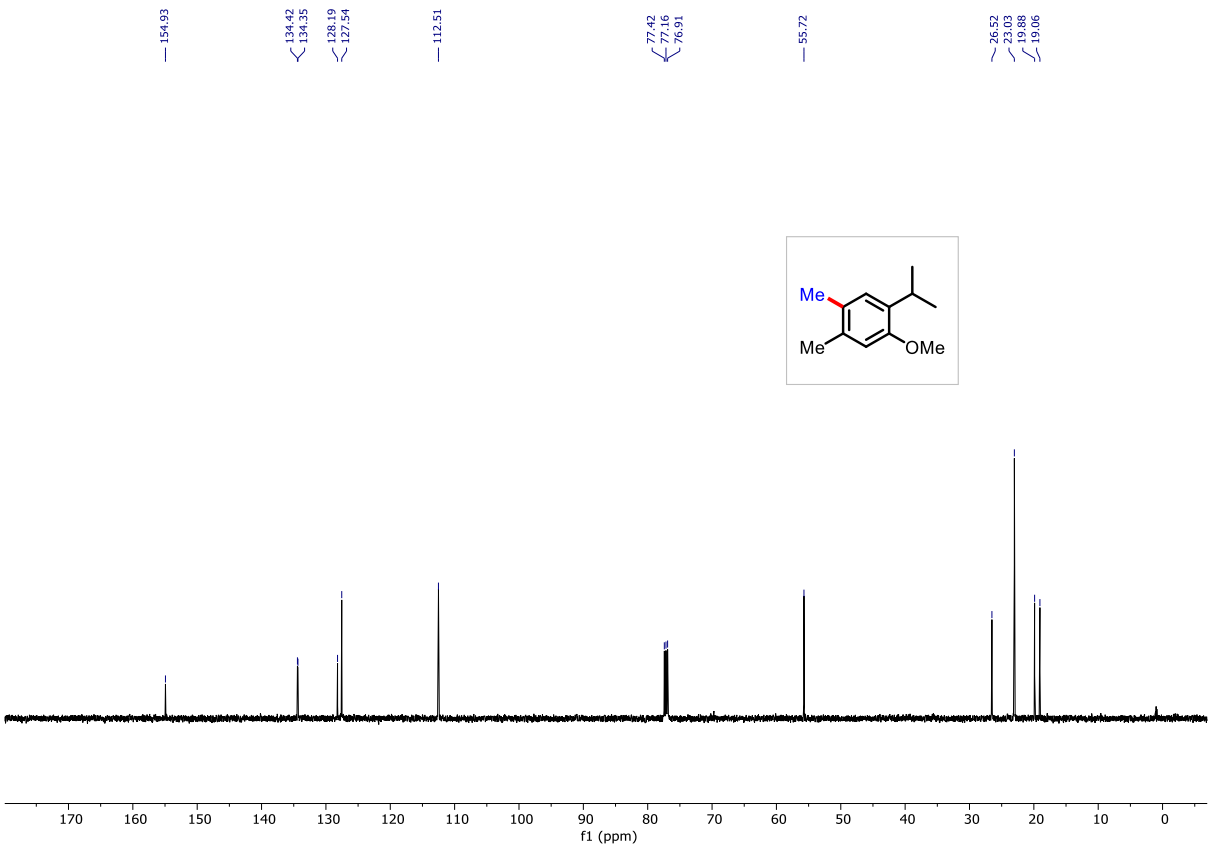


1-Isopropyl-2-methoxy-4,5-dimethylbenzene (4e)

^{1}H NMR (500 MHz, $CDCl_3$)

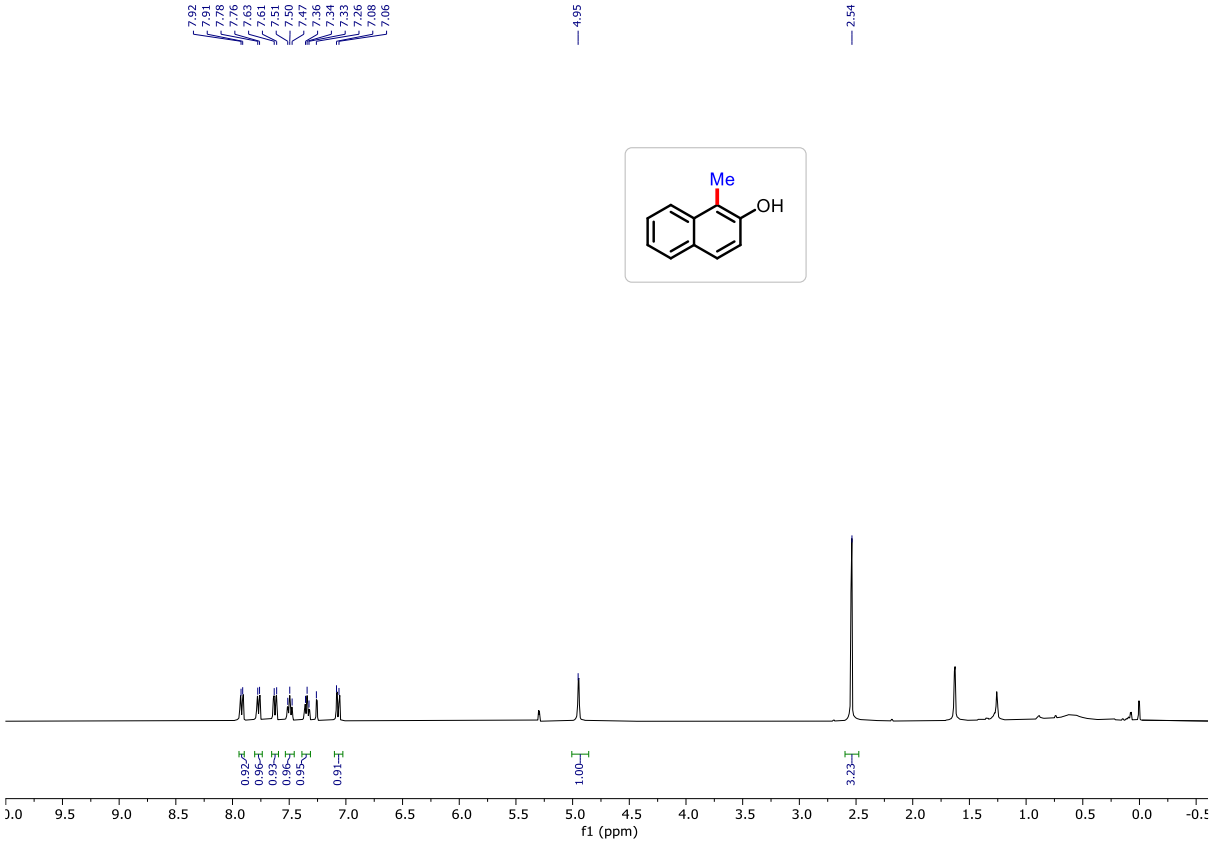


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

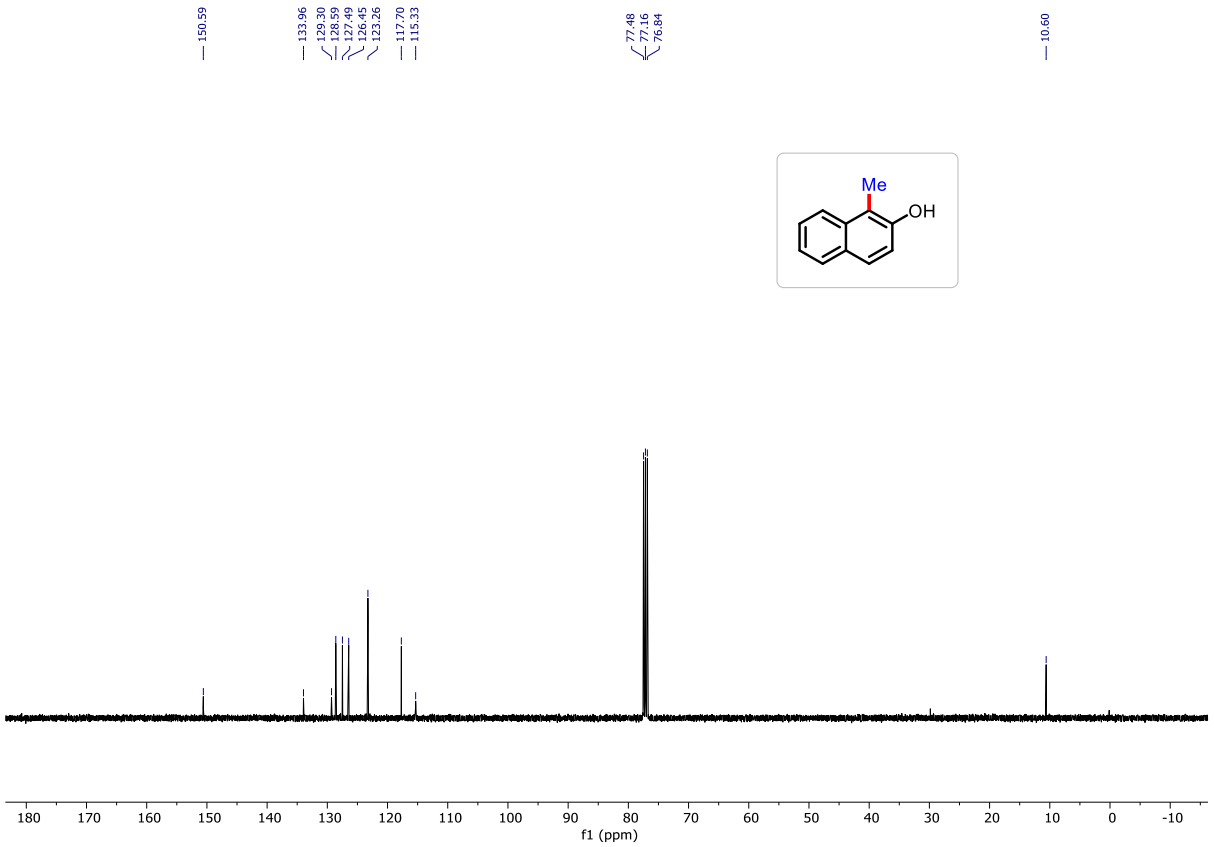


1-Methylnaphthalen-2-ol (4f)

^{1}H NMR (400 MHz, $CDCl_3$)

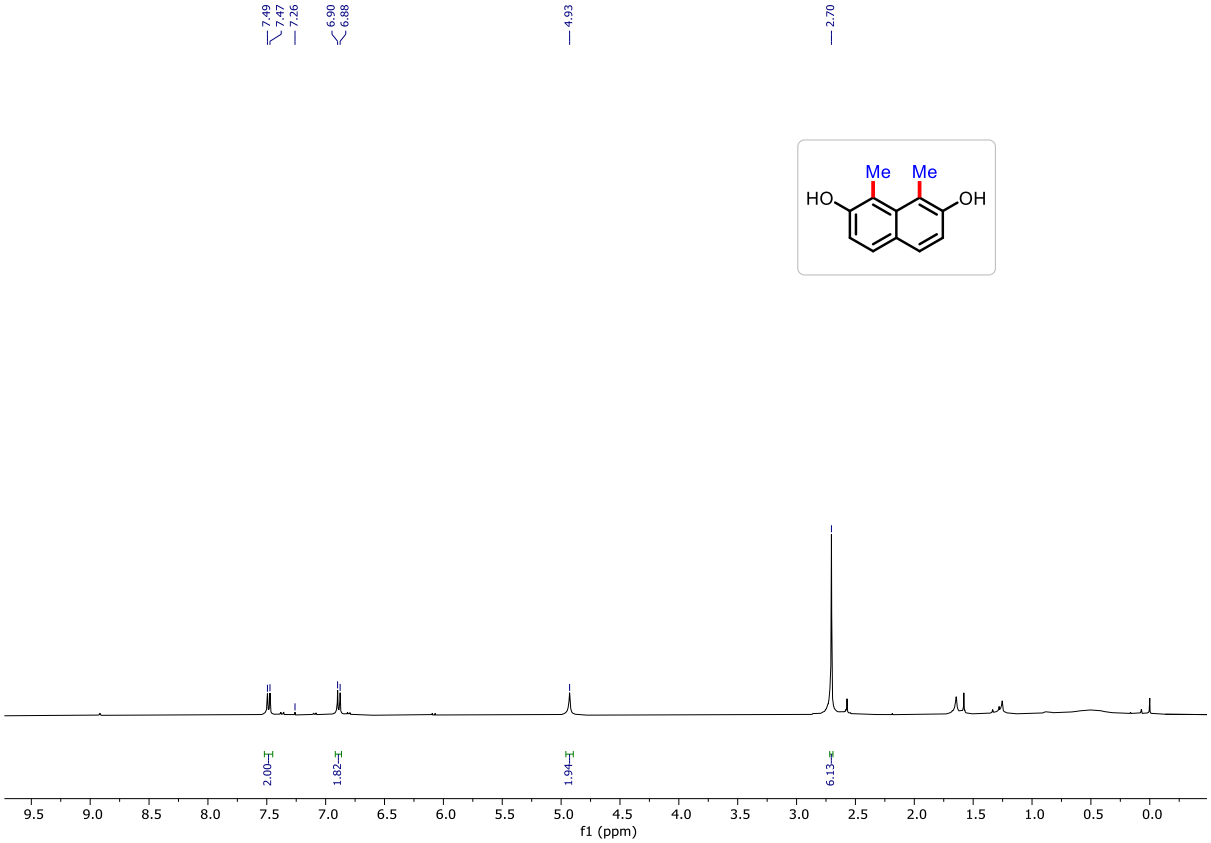


^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$)

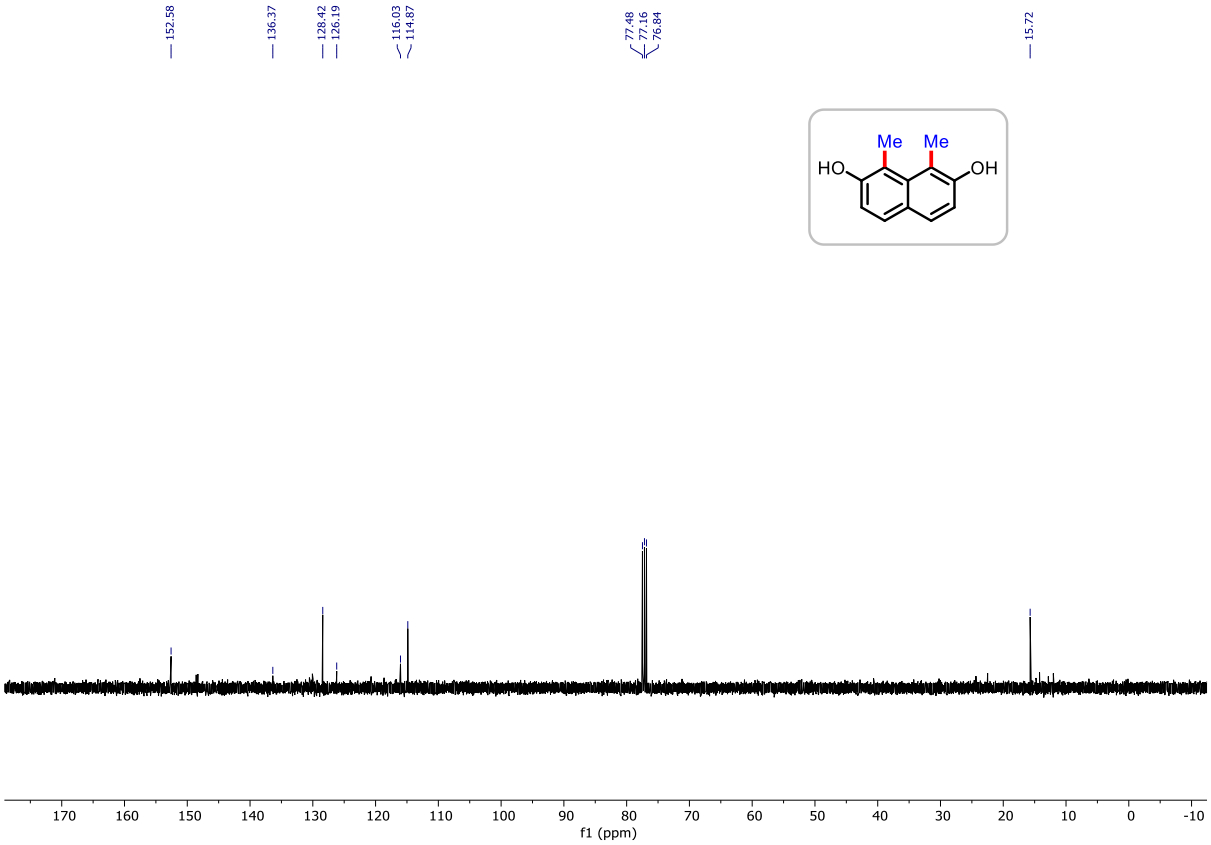


1,8-Dimethylnaphthalene-2,7-diol (4g)

^{1}H NMR (400 MHz, $CDCl_3$)

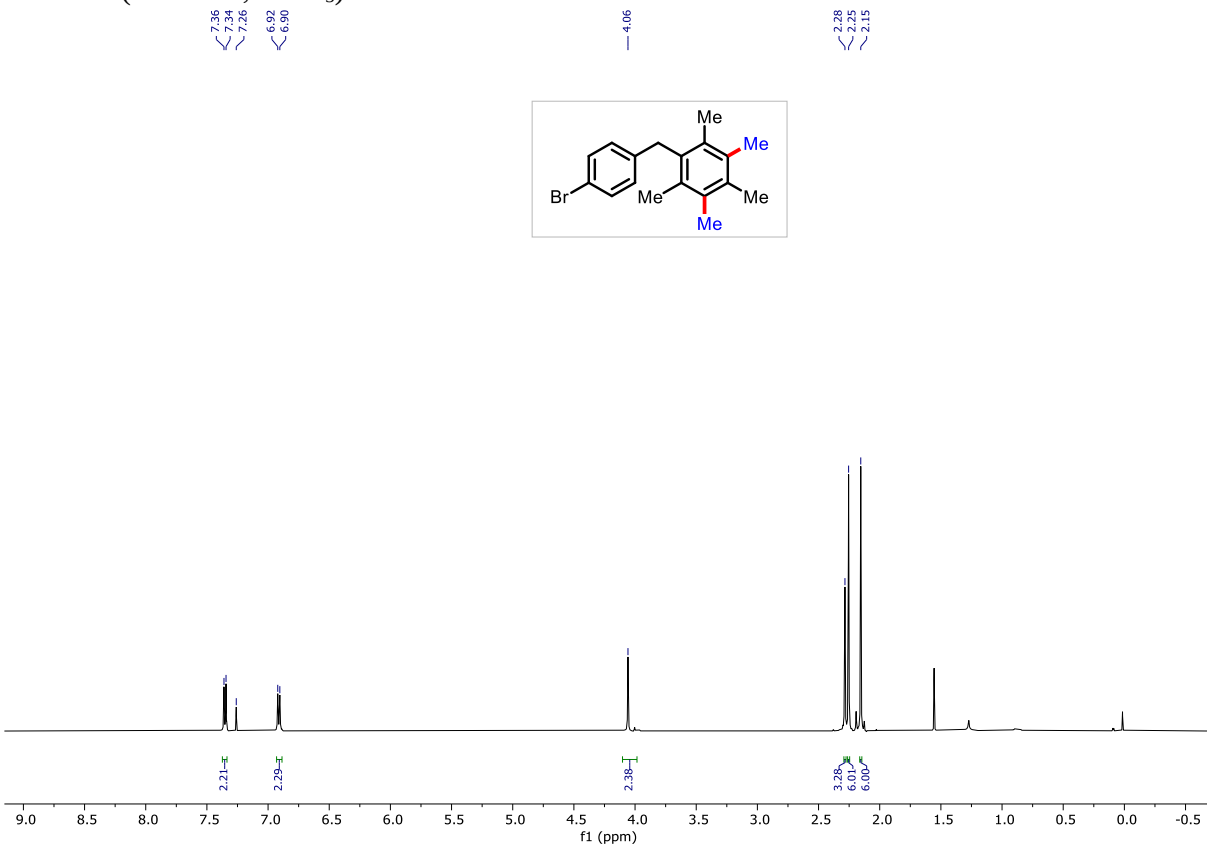


^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$)

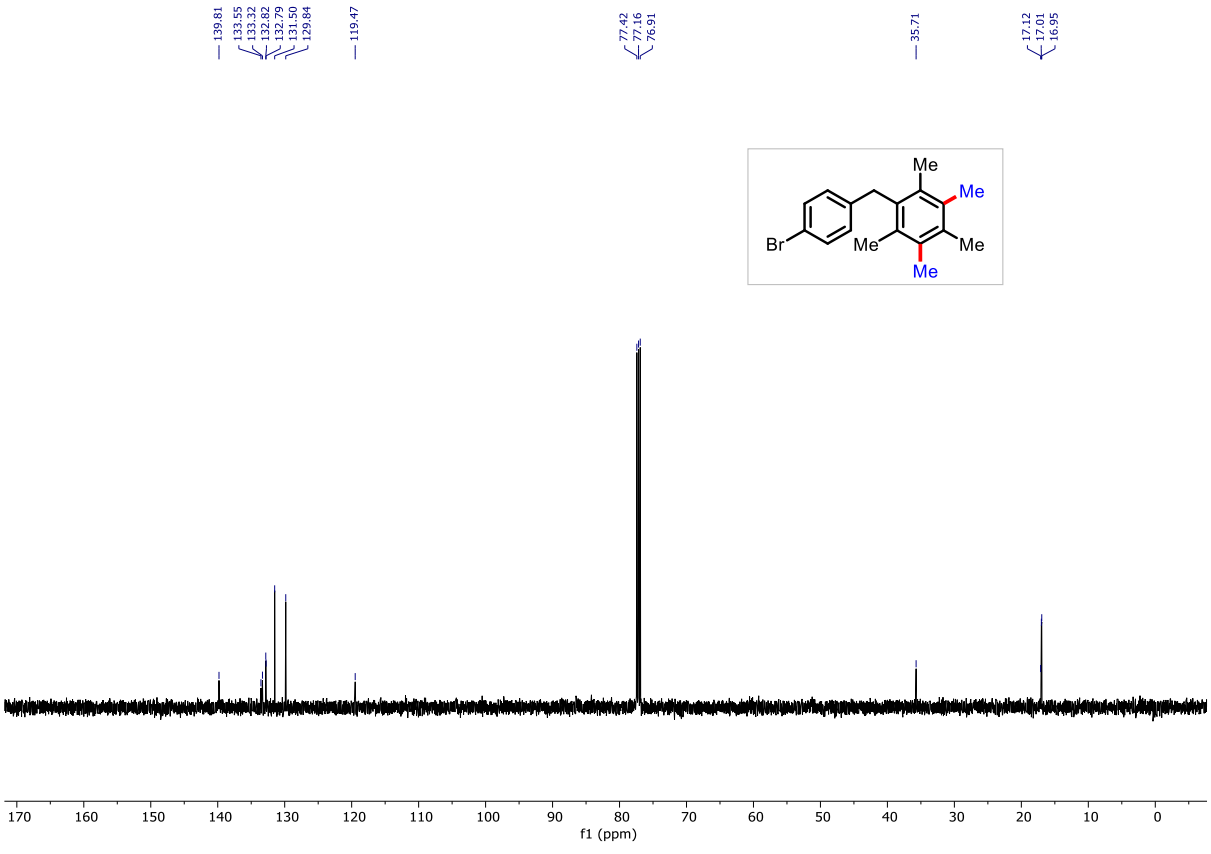


1-(4-Bromobenzyl)-2,3,4,5,6-pentamethylbenzene (4h)

^{1}H NMR (400 MHz, $CDCl_3$)

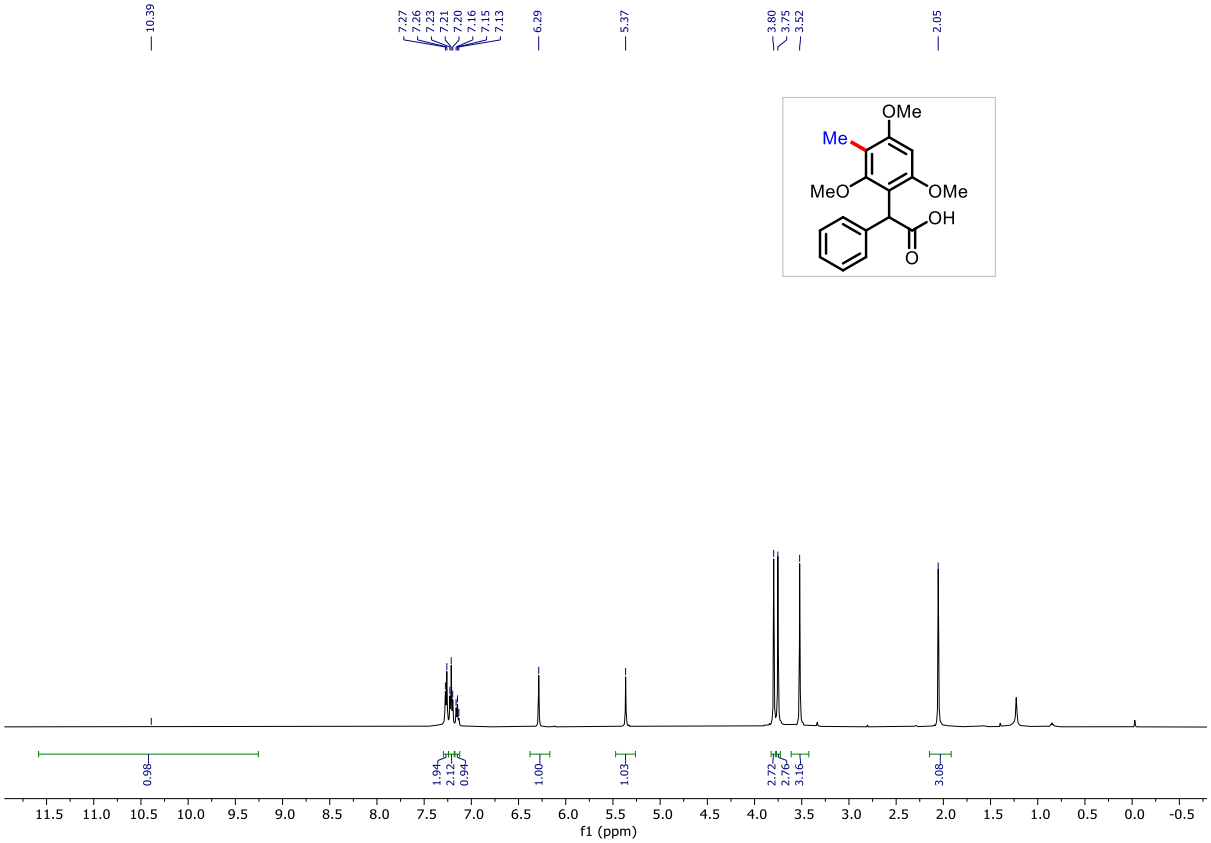


^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$)

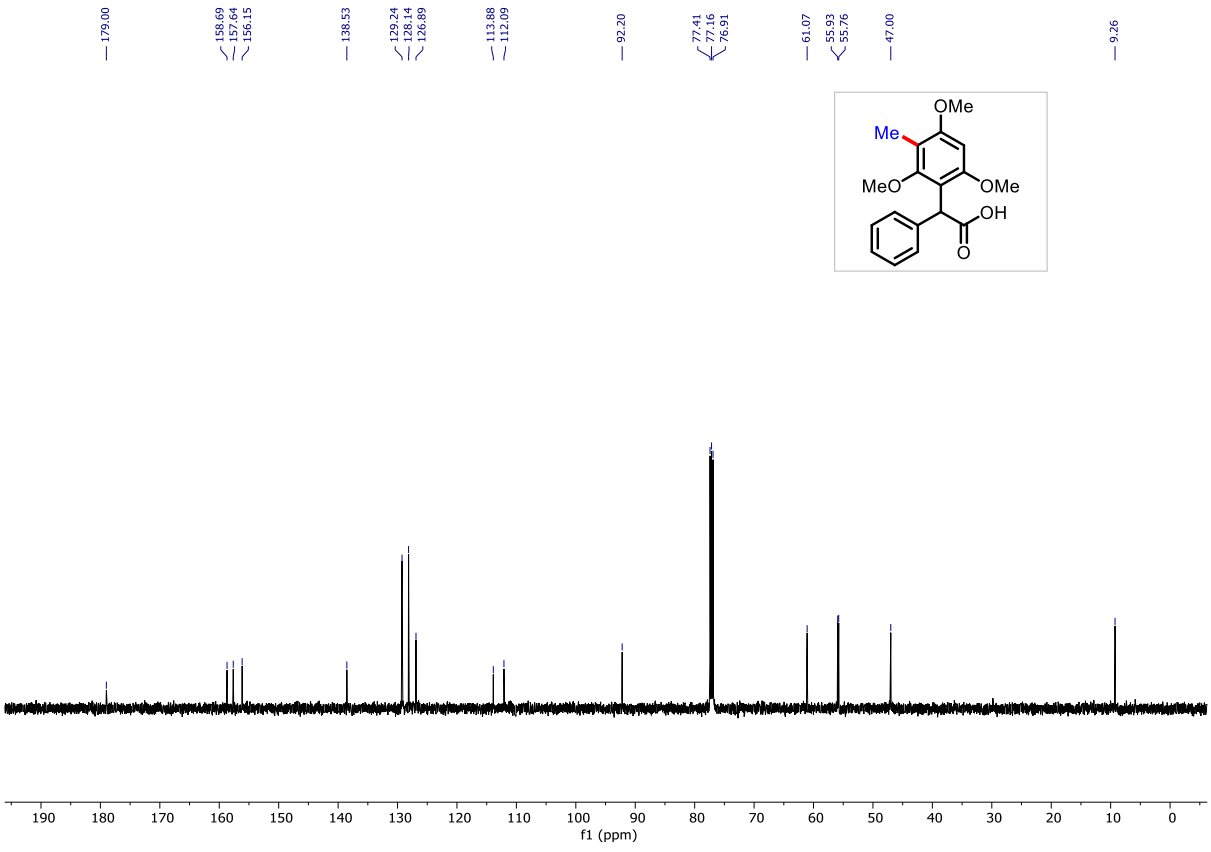


2-Phenyl-2-(2,4,6-trimethoxy-3,5-dimethylphenyl) acetic acid (4i)

^{1}H NMR (500 MHz, $CDCl_3$)

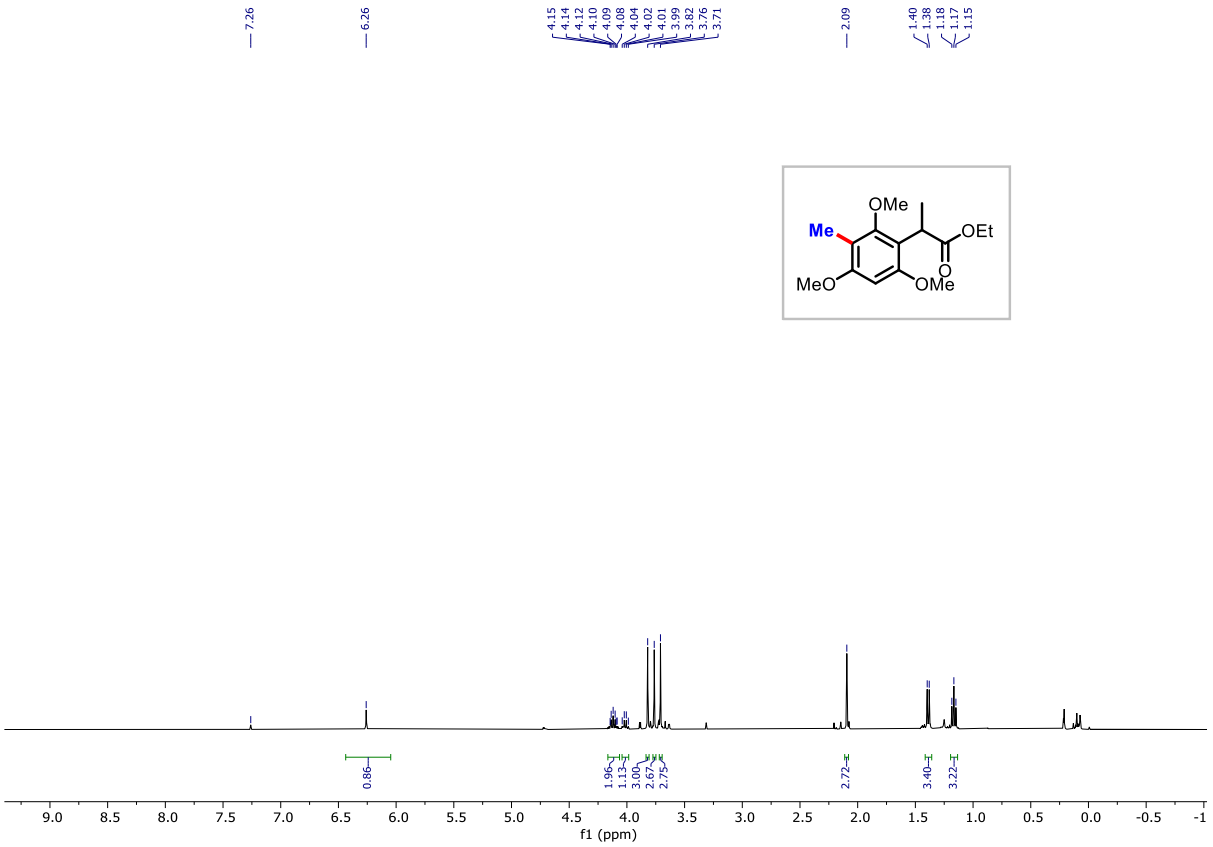


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

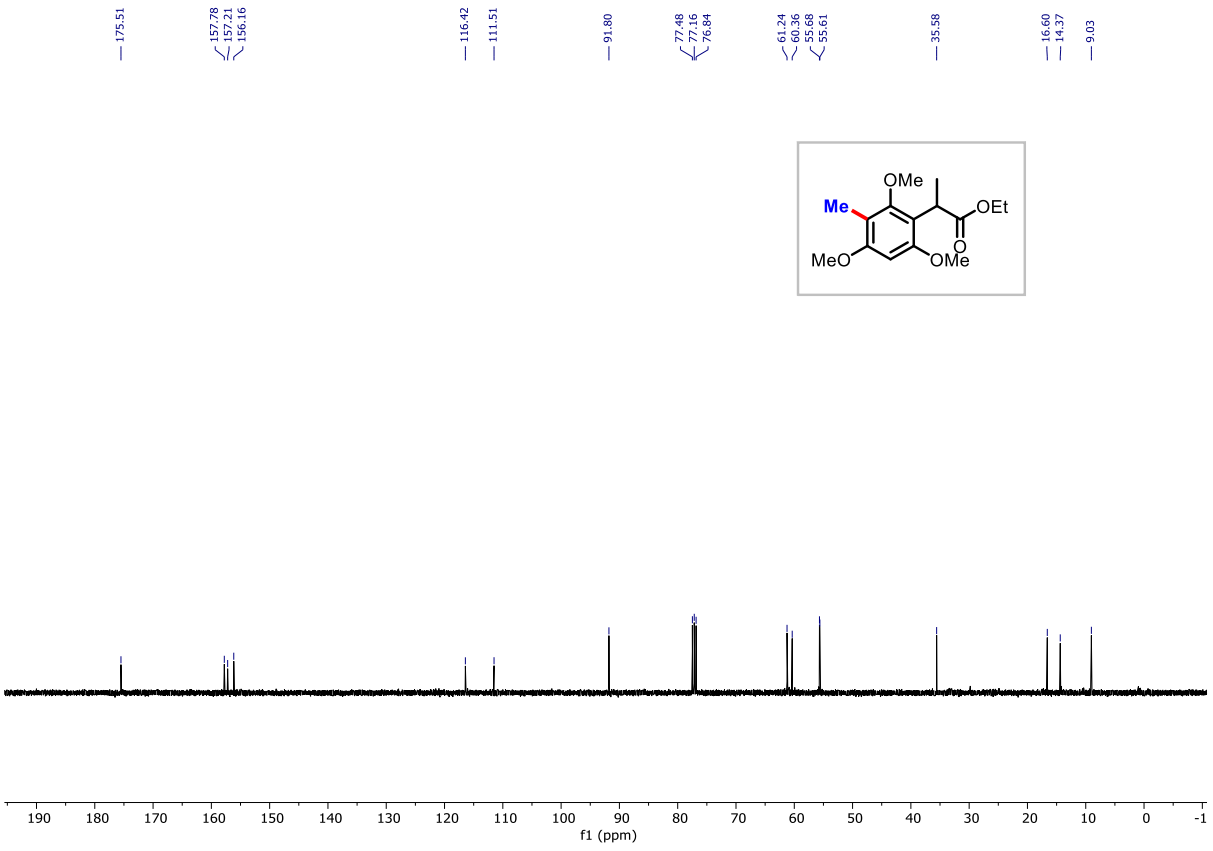


Ethyl 2-(2,4,6-trimethoxy-3-methylphenyl) propanoate (4j)

^{1}H NMR (101 MHz, $CDCl_3$)

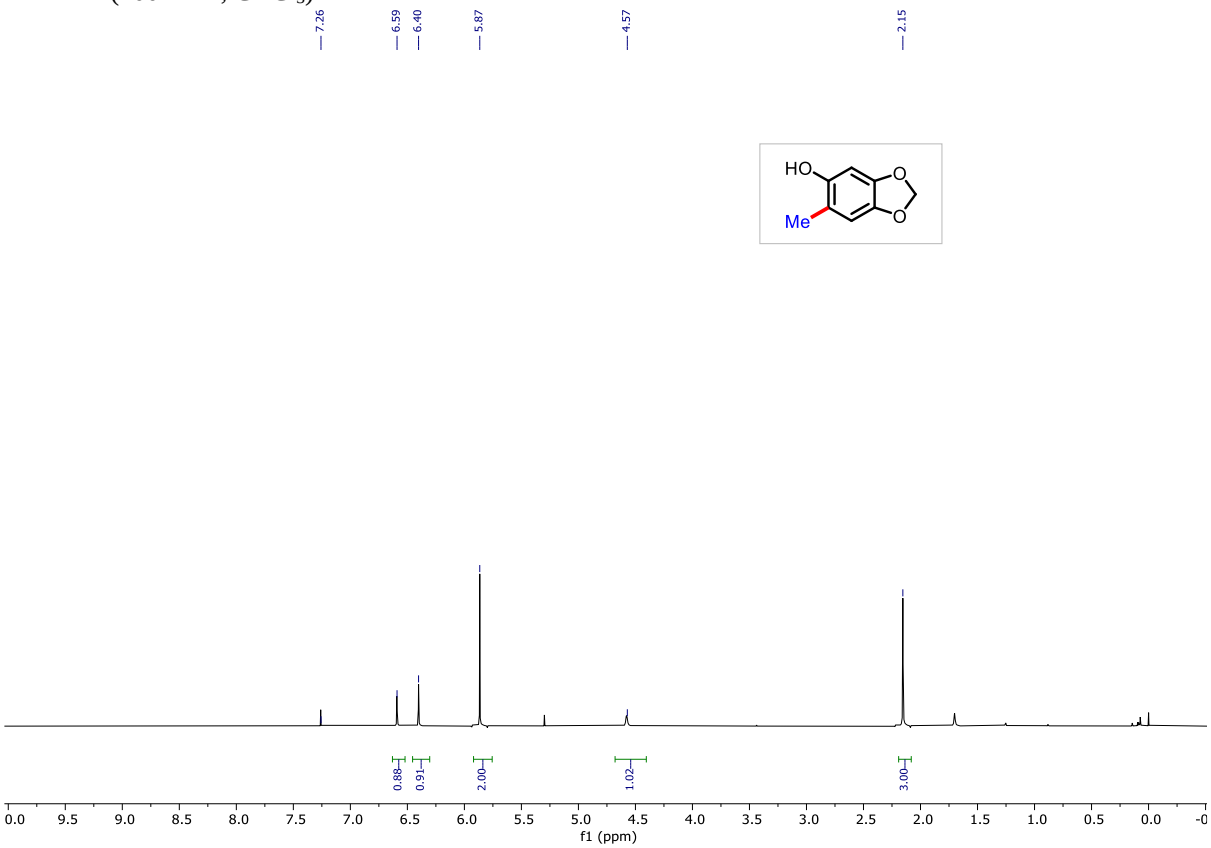


^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$)

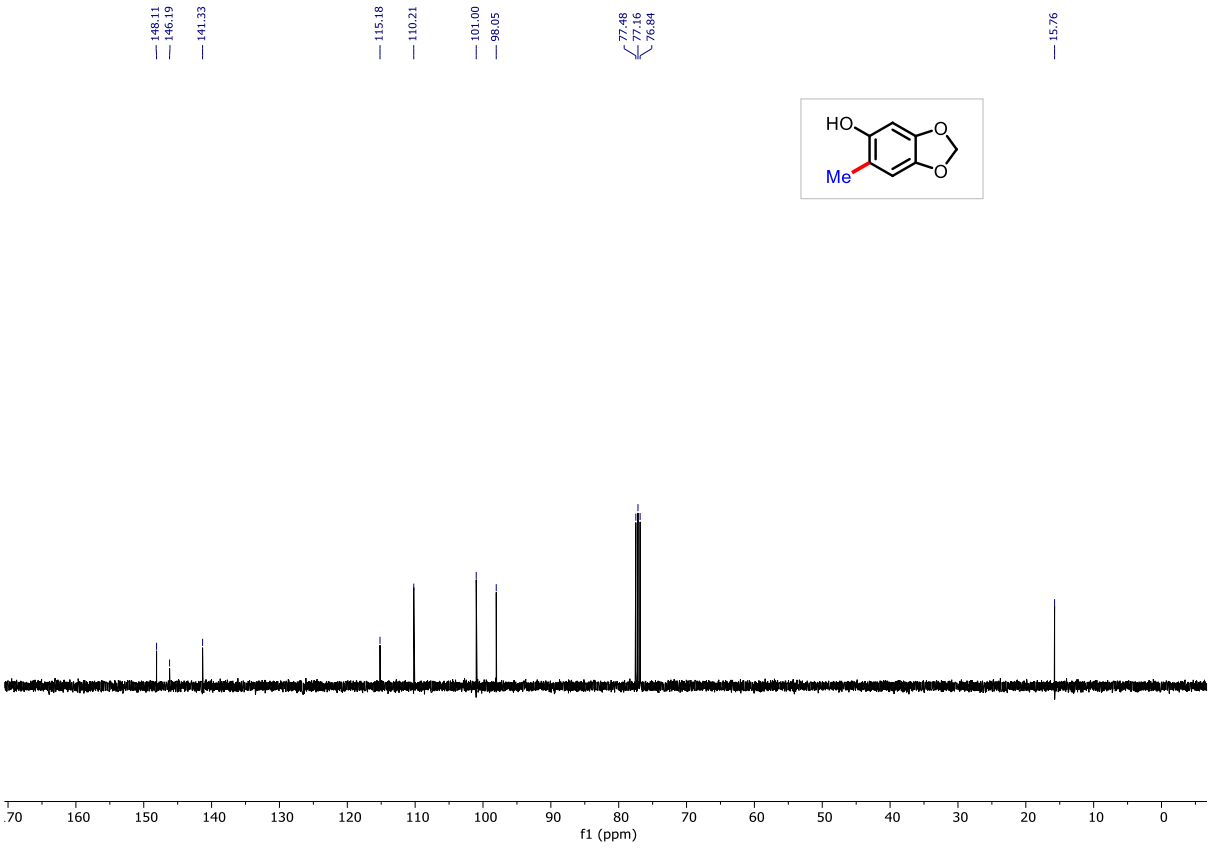


6-Methylbenzo[*d*][1,3]dioxol-5-ol (4k)

^{1}H NMR (400 MHz, $CDCl_3$)

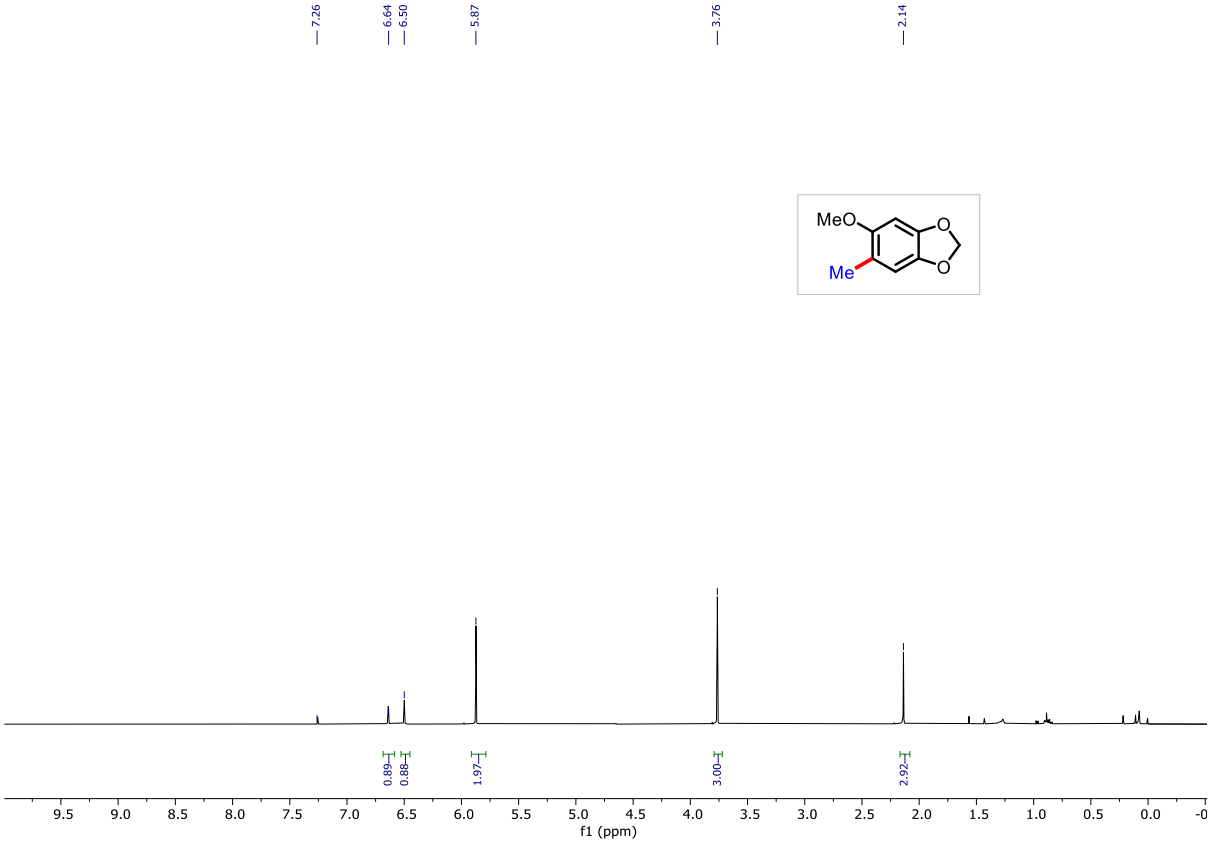


^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$)

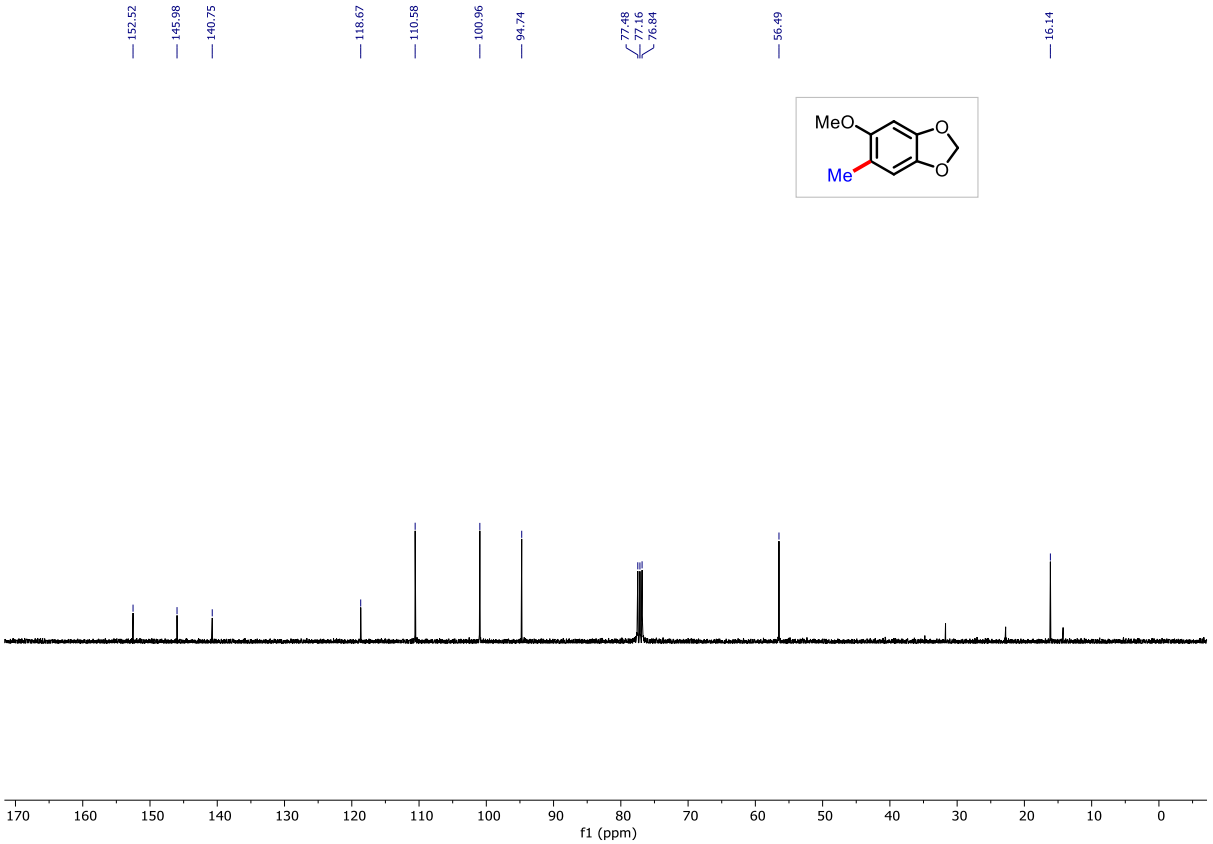


5-Methoxy-6-methylbenzo[*d*][1,3]dioxole (4l)

^{1}H NMR (500 MHz, $CDCl_3$)

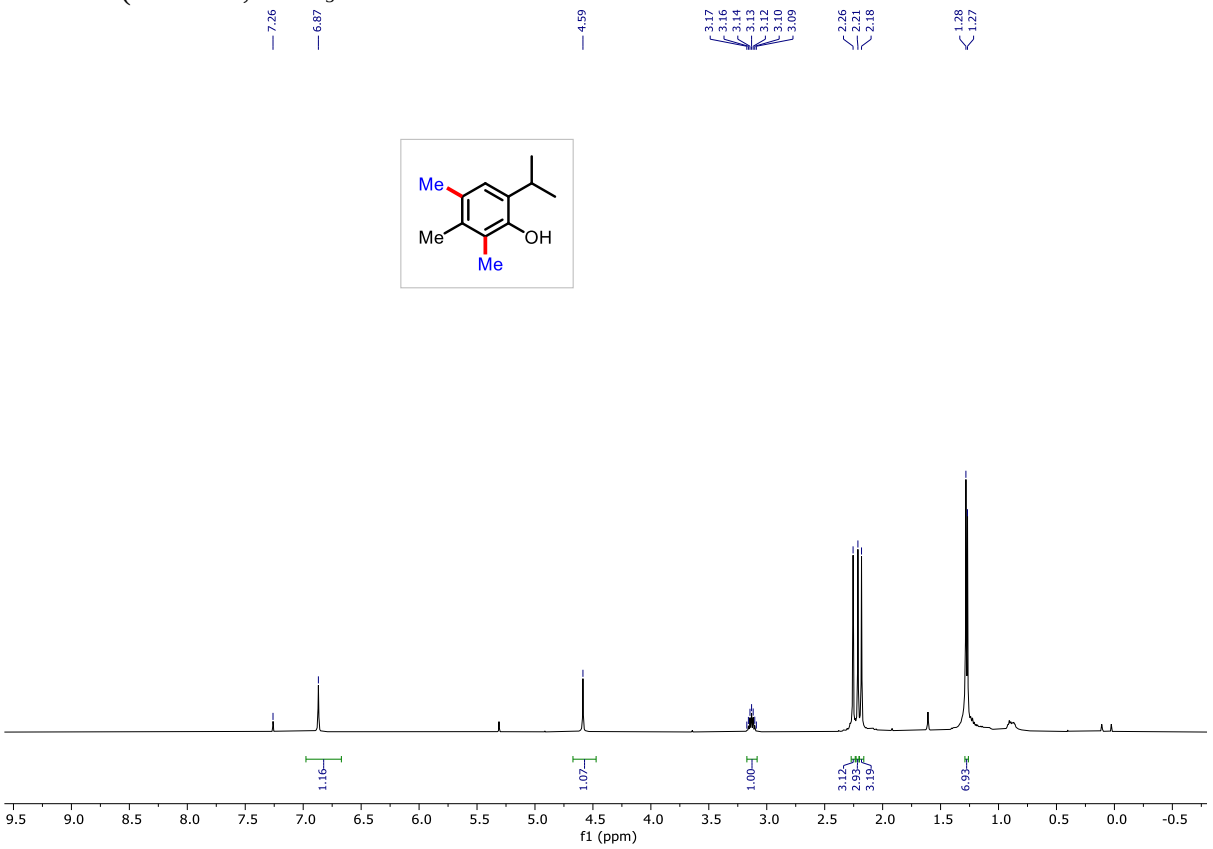


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$

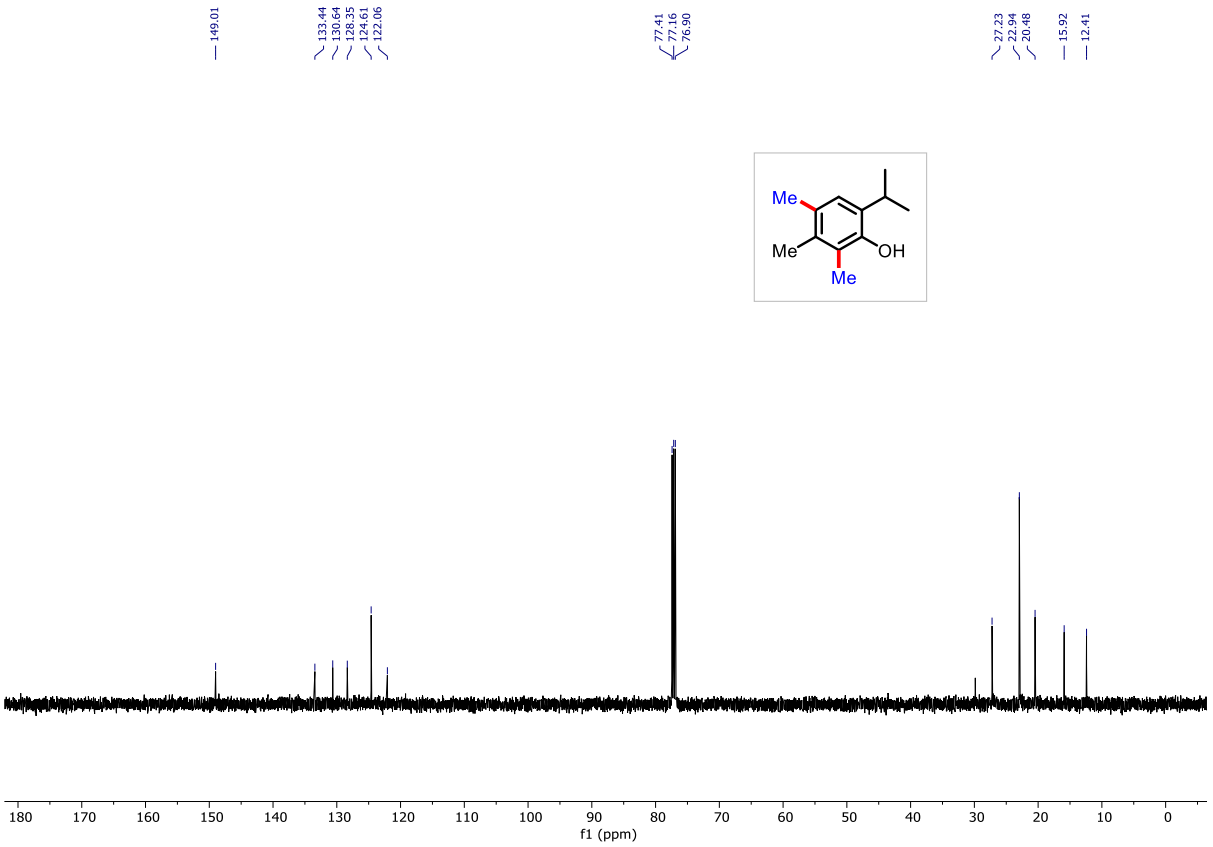


3-Isopropyl-2,4,6-trimethylphenol (4m)

^{1}H NMR (500 MHz, $CDCl_3$

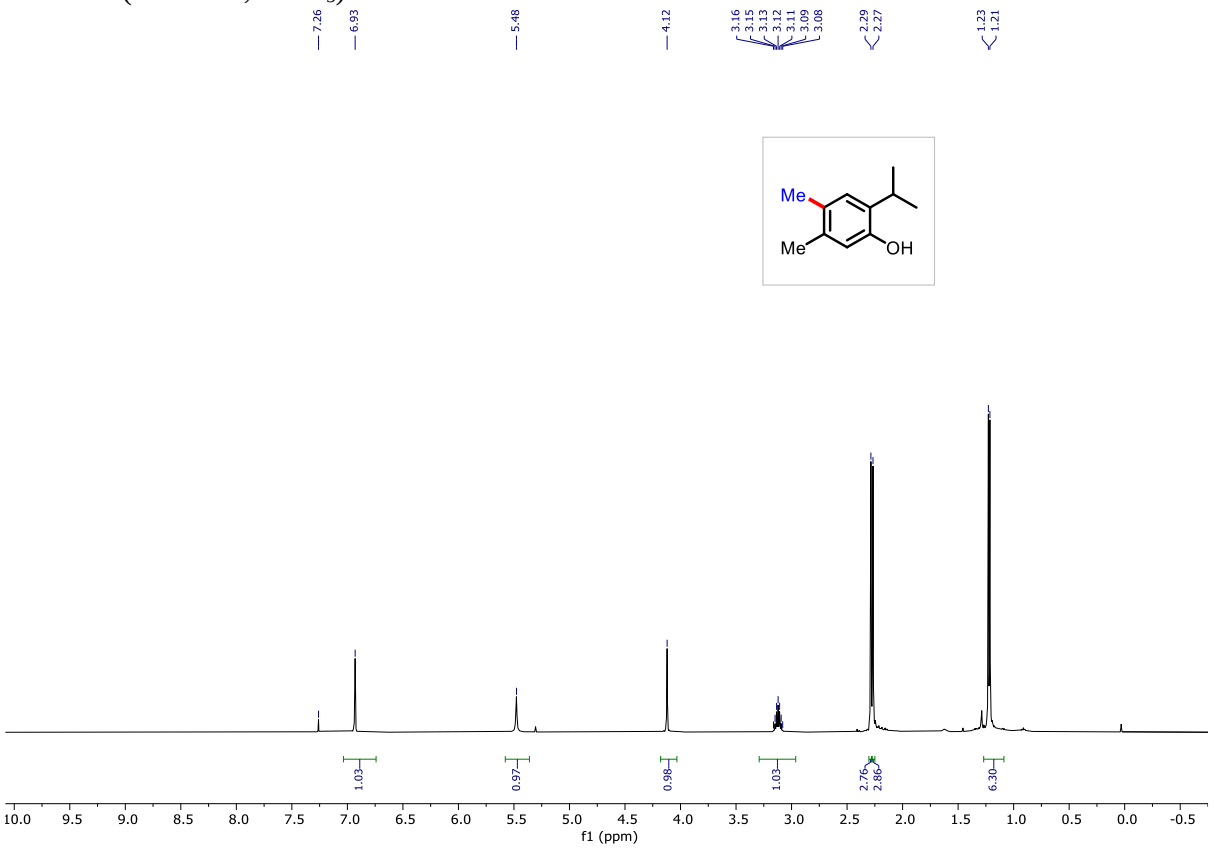


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

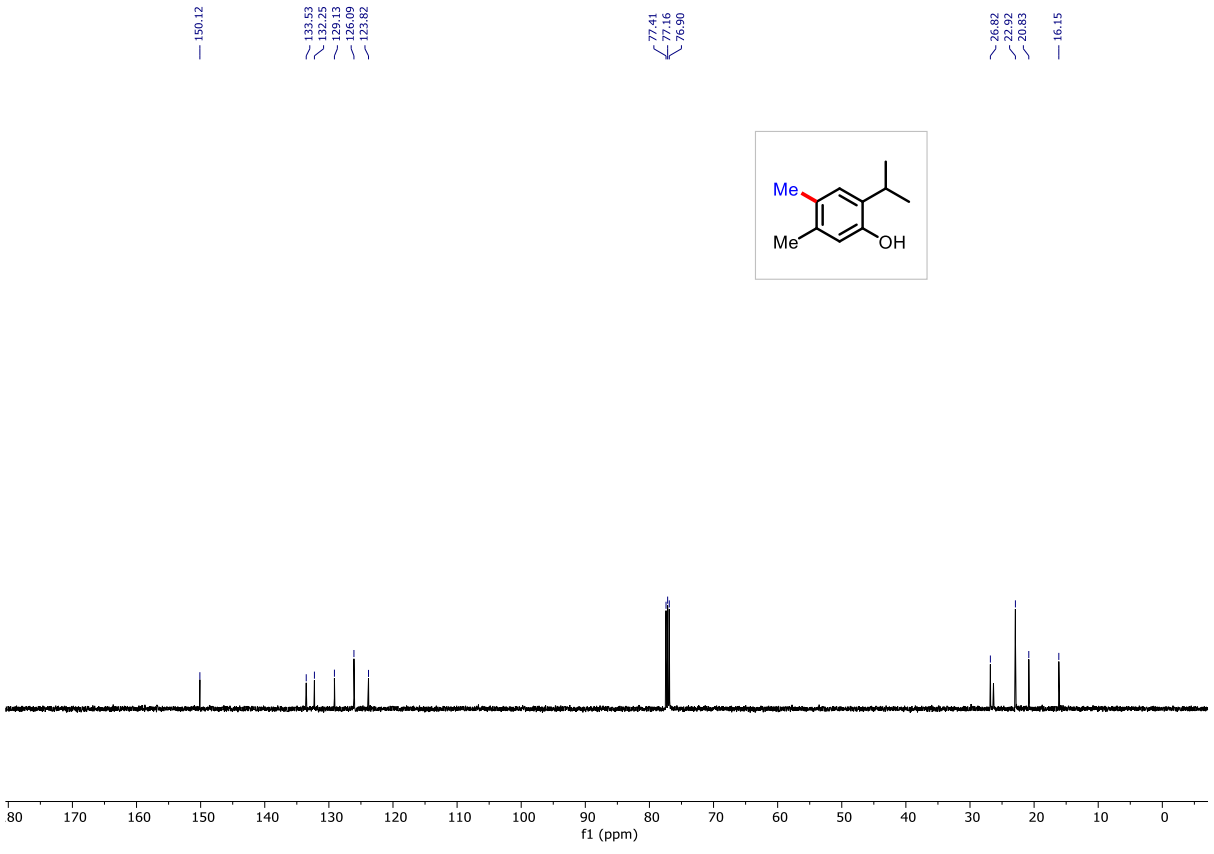


5-Isopropyl-2,4-dimethylphenol (4n)

^{1}H NMR (500 MHz, $CDCl_3$)

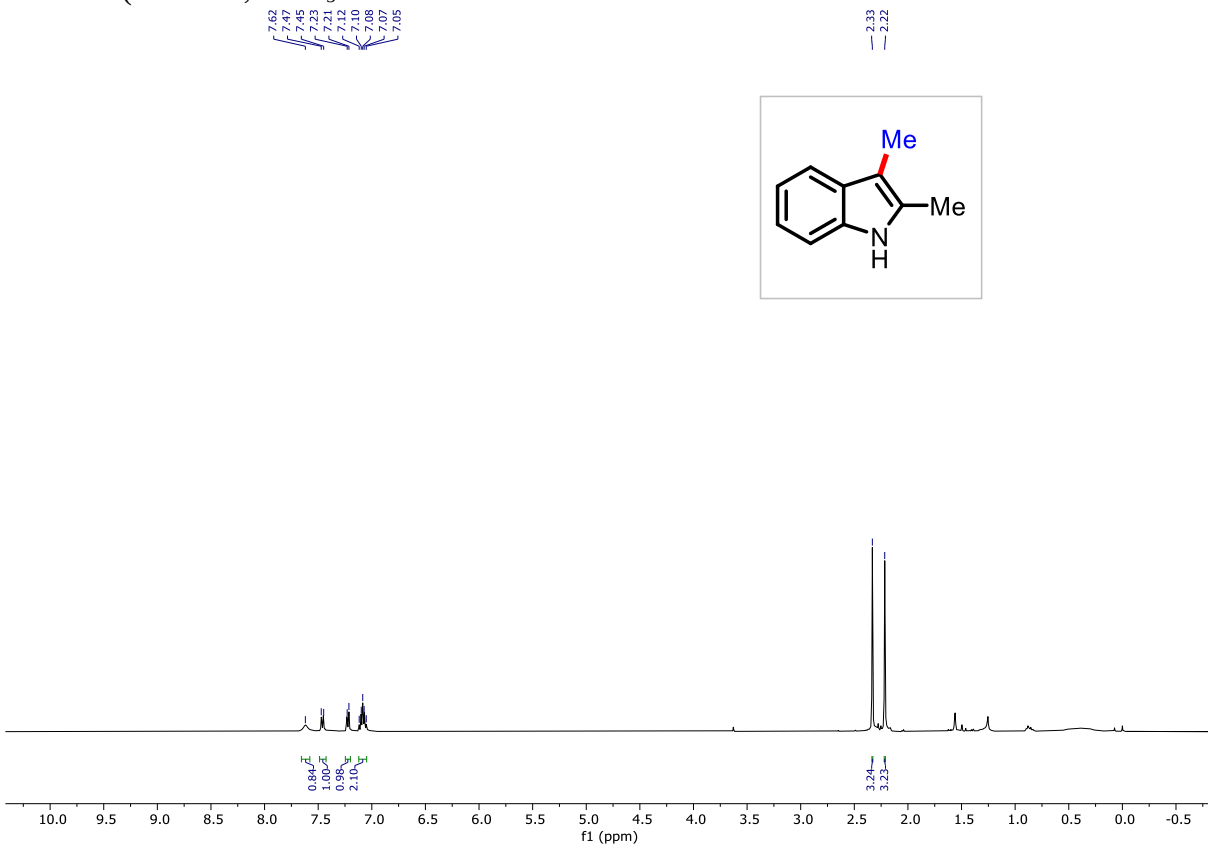


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

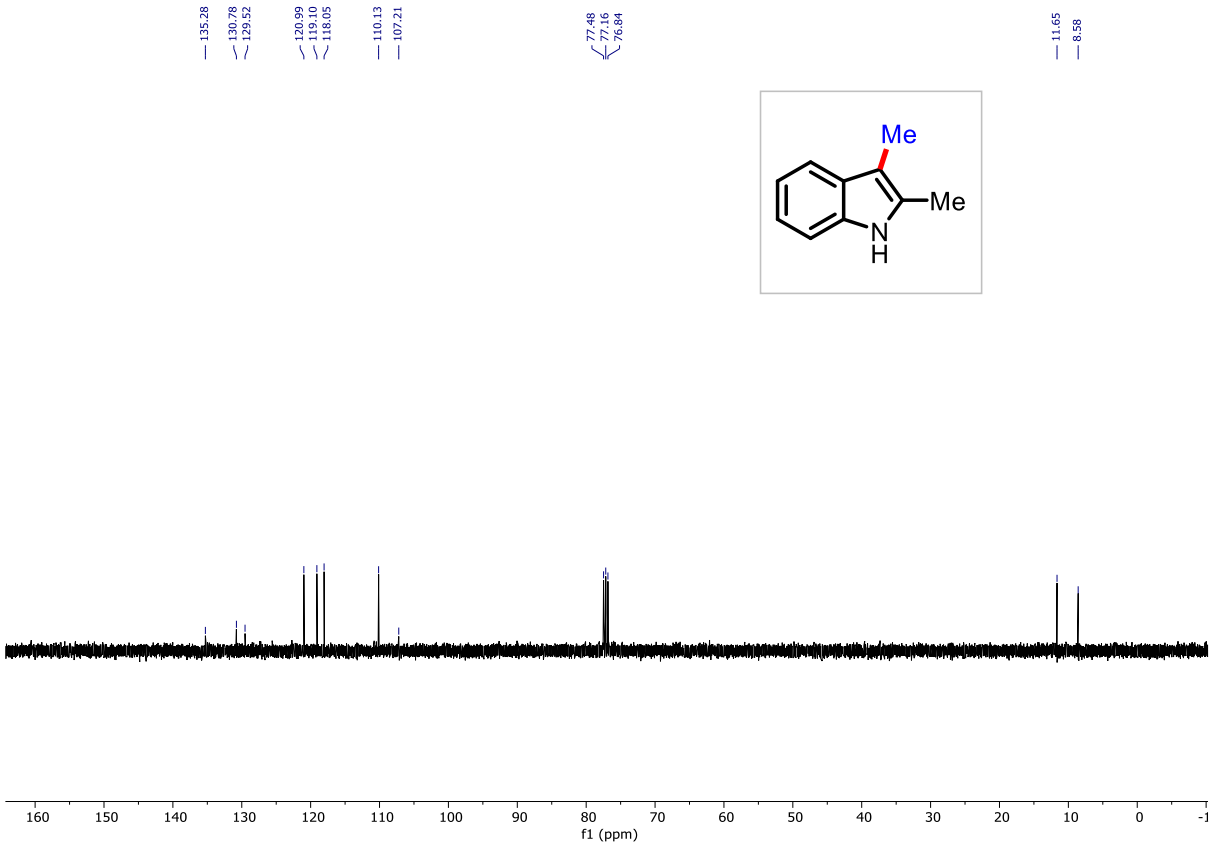


2,3-Dimethyl-1*H*-indole (4o)

^{1}H NMR (500 MHz, $CDCl_3$

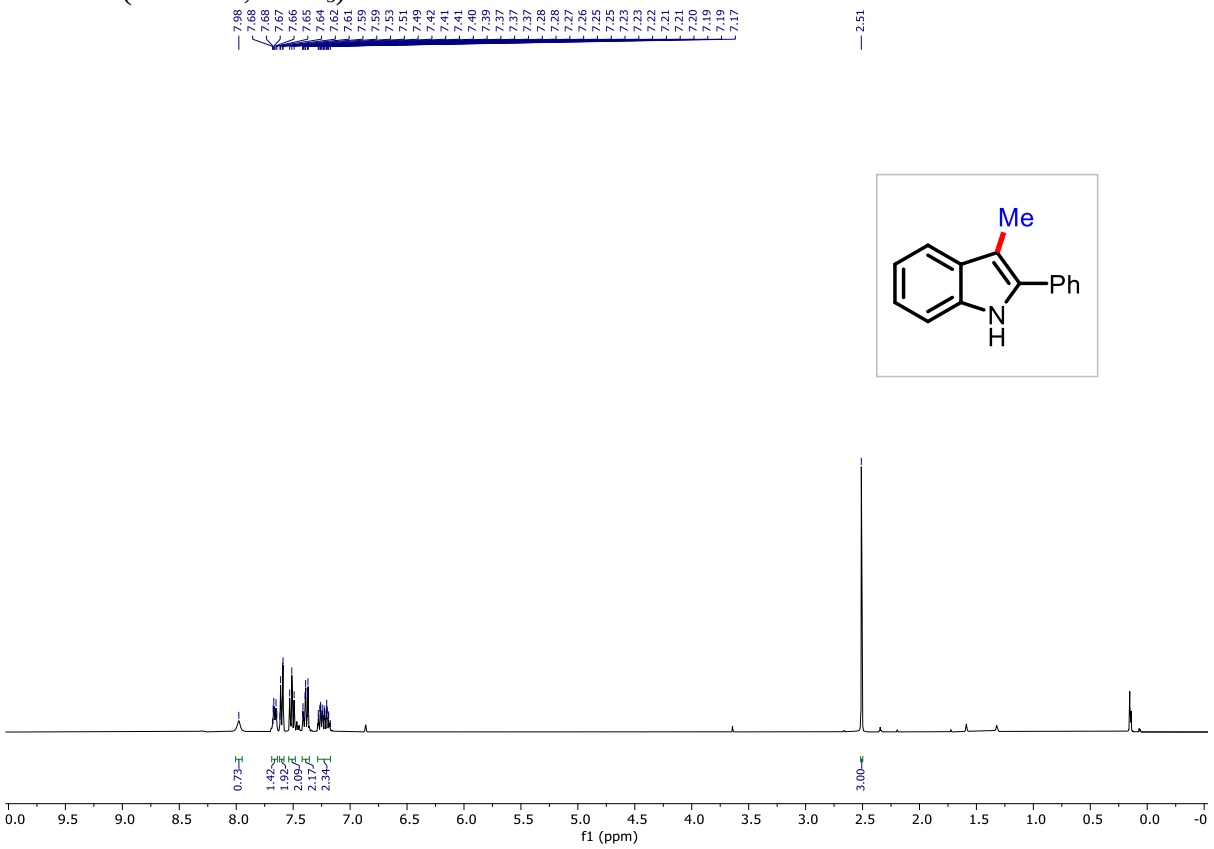


^{13}C **{^{1}H}** NMR (101 MHz, $CDCl_3$)

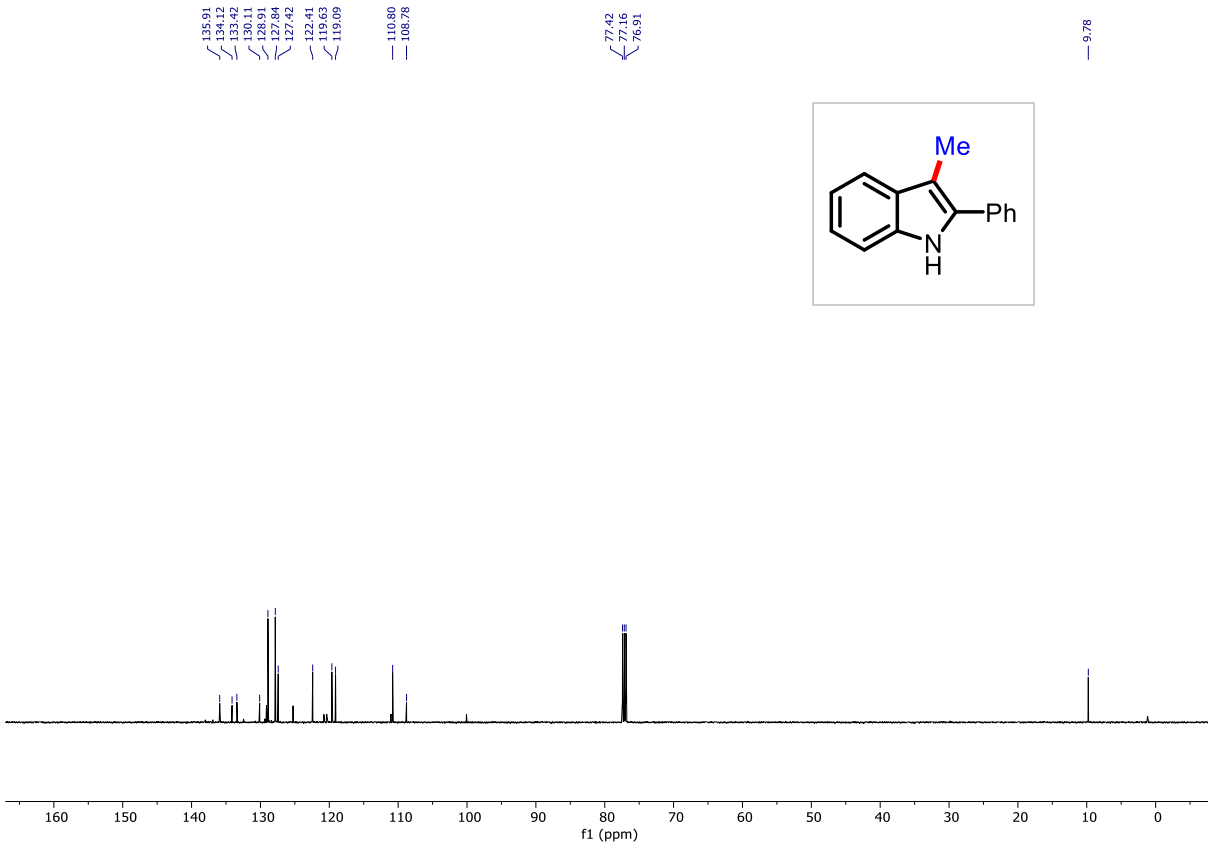


3-Methyl-2-phenyl-1*H*-indole (4p)

^{1}H NMR (400 MHz, $CDCl_3$)

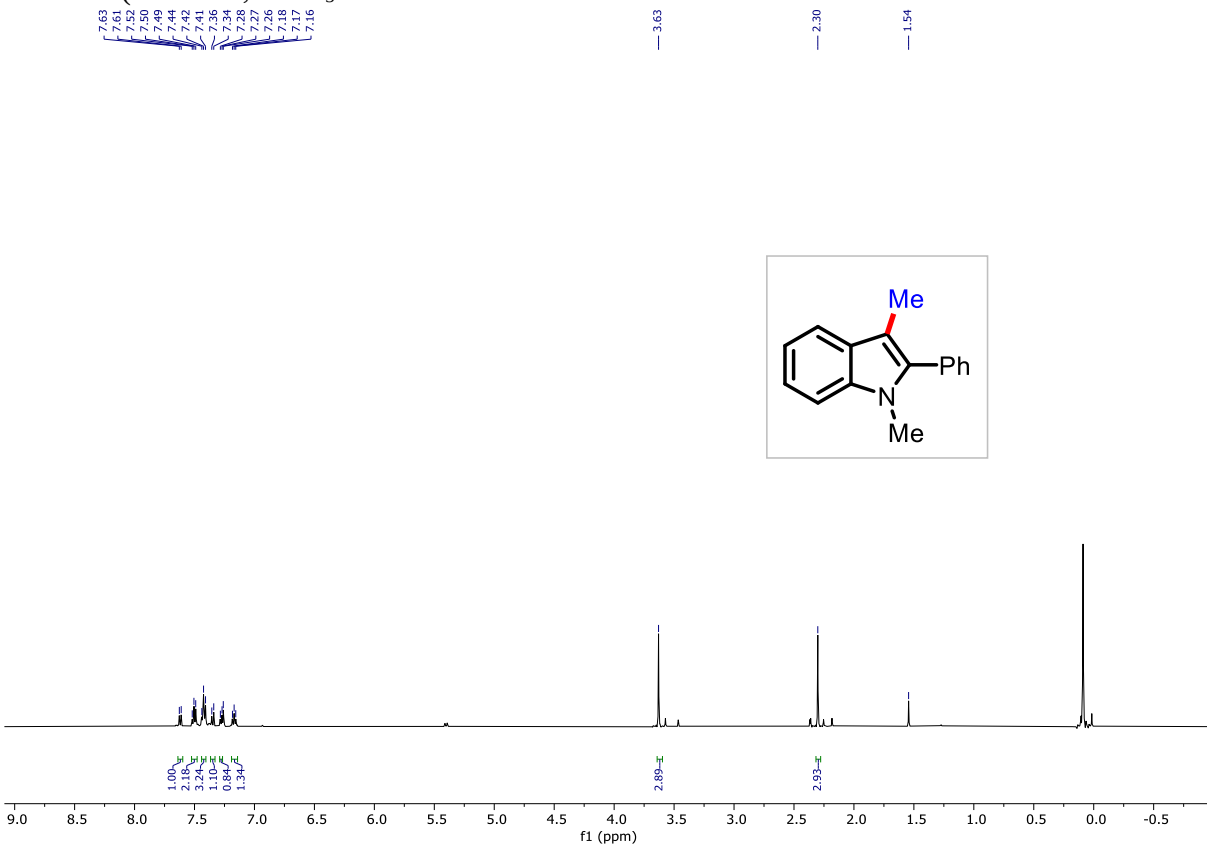


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

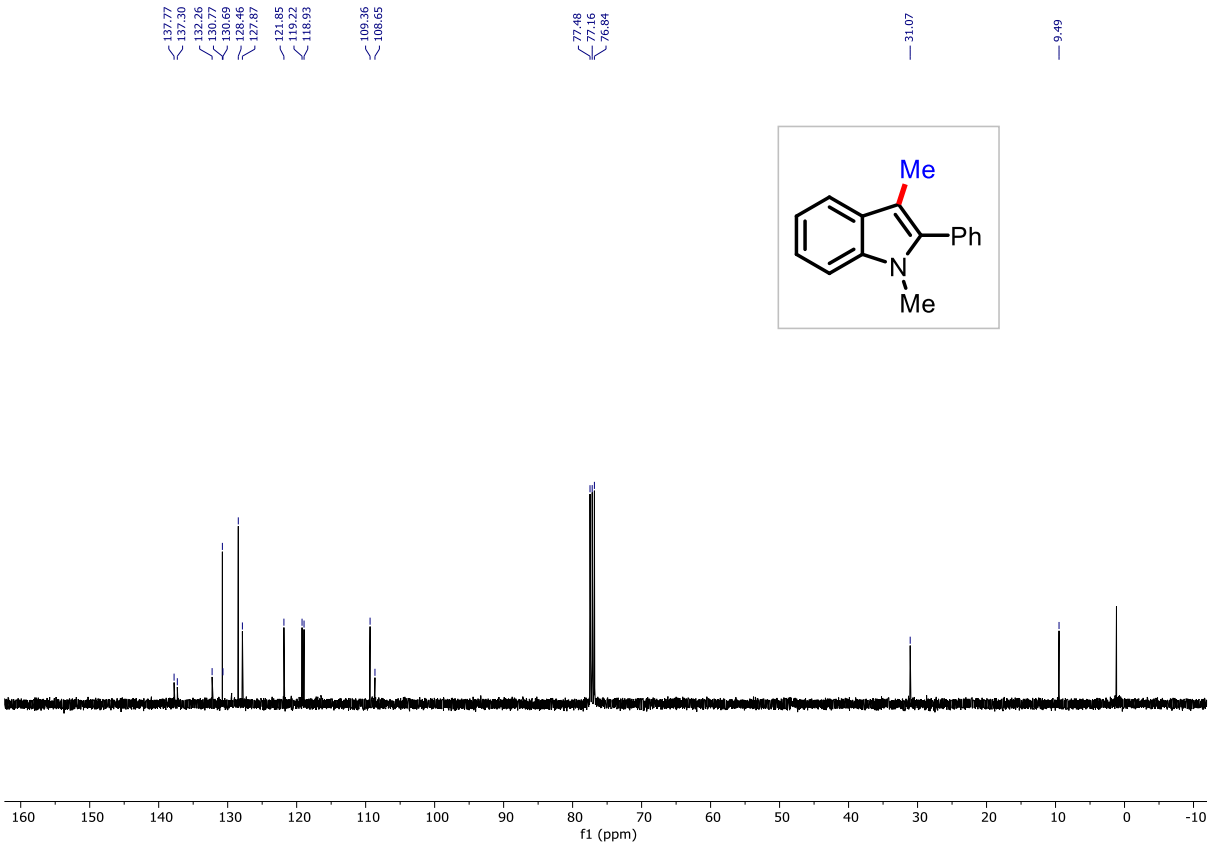


1,3-Dimethyl-2-phenyl-1*H*-indole (4s)

^{1}H NMR (500 MHz, $CDCl_3$

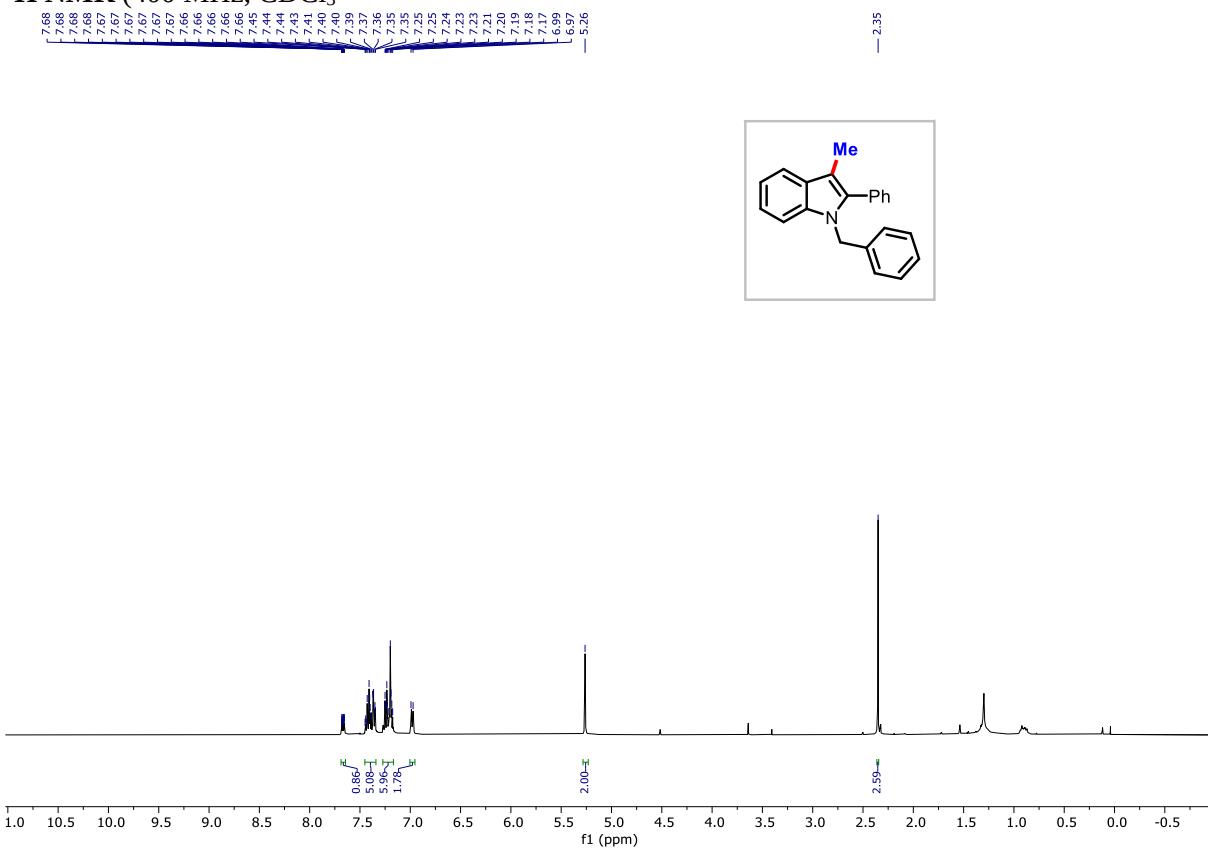


^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$)

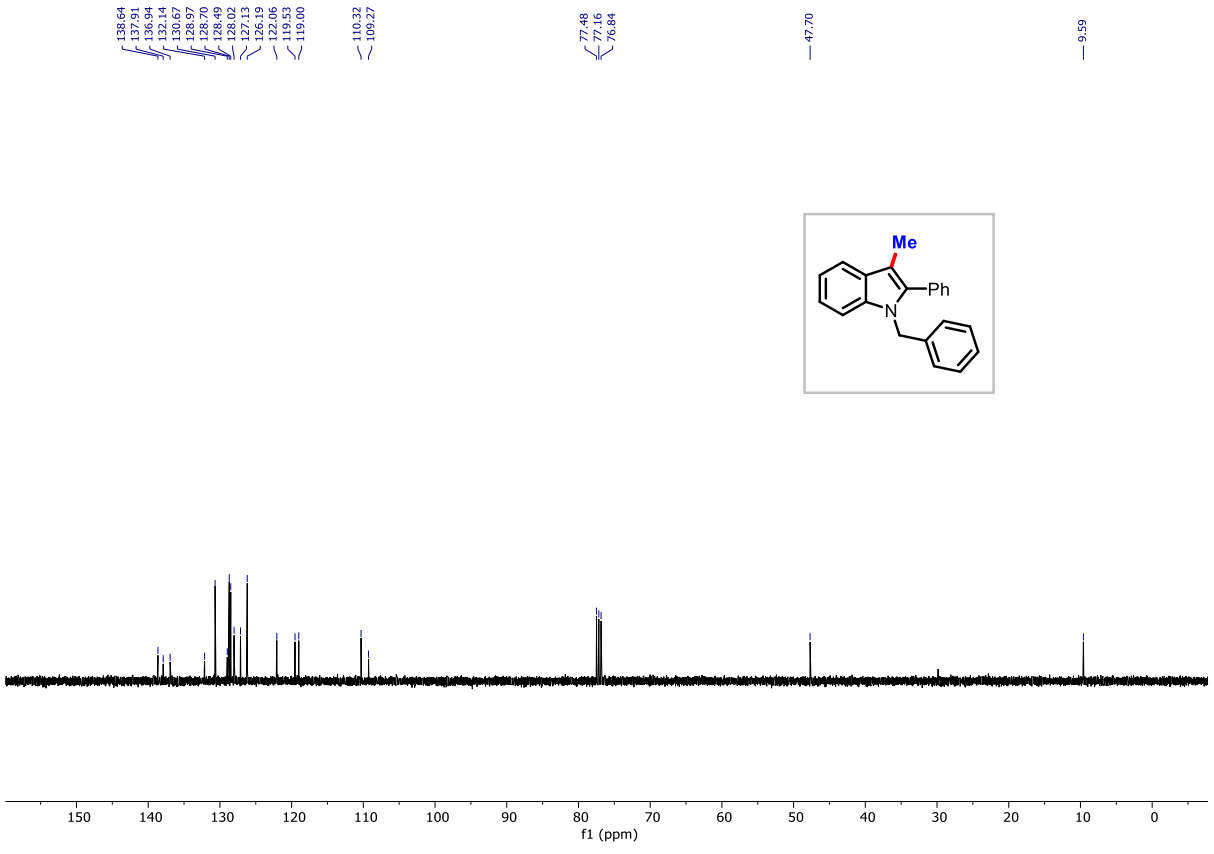


1-Benzyl-3-methyl-2-phenyl-1*H*-indole (4t)

^{1}H NMR (400 MHz, $CDCl_3$

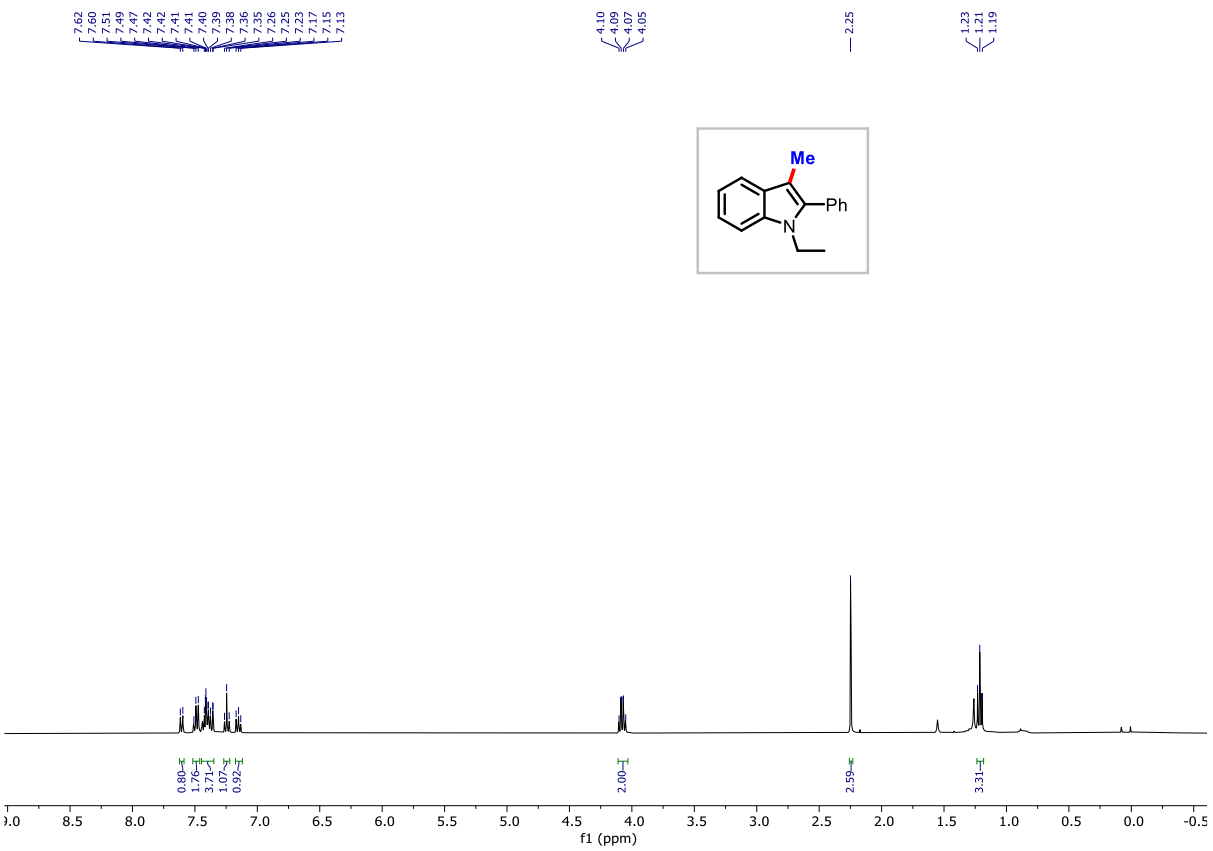


^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$)

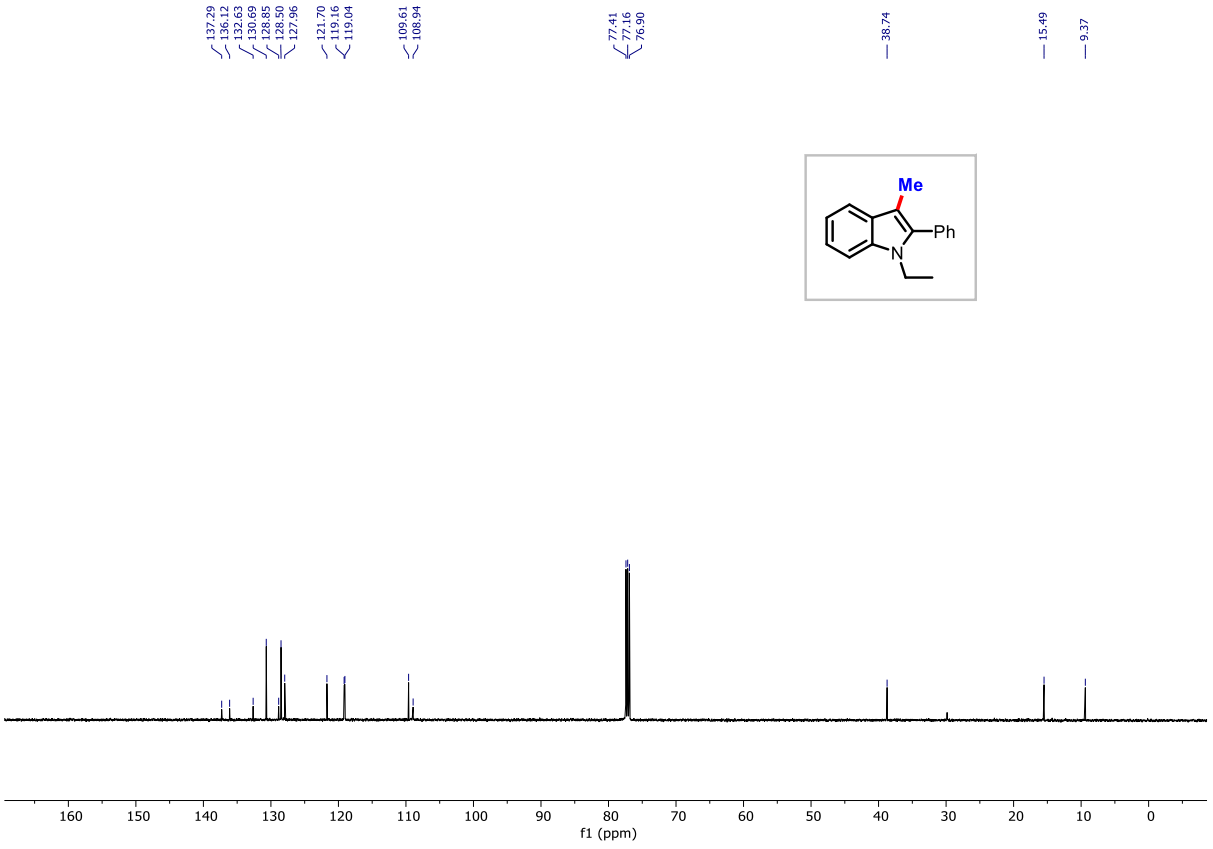


1-Ethyl-3-methyl-2-phenyl-1*H*-indole

^{1}H NMR (400 MHz, $CDCl_3$)

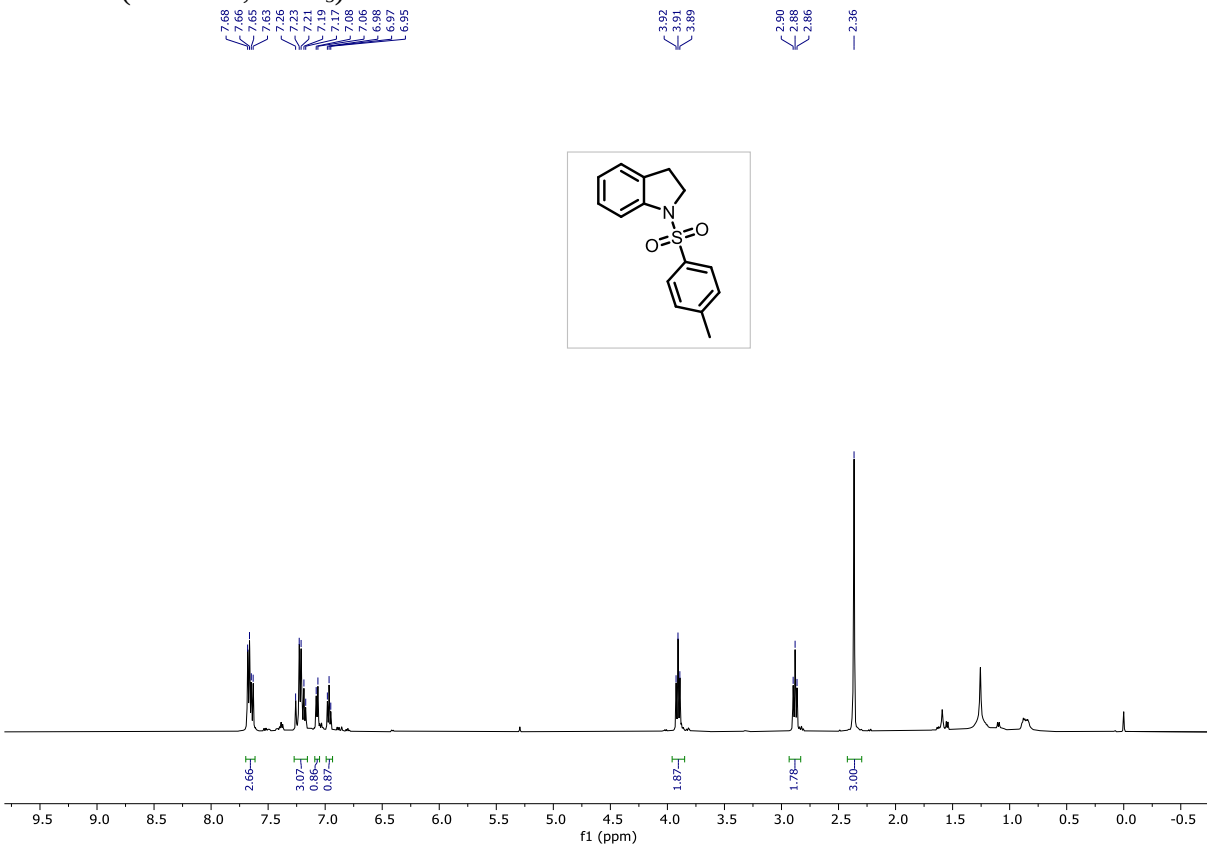


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

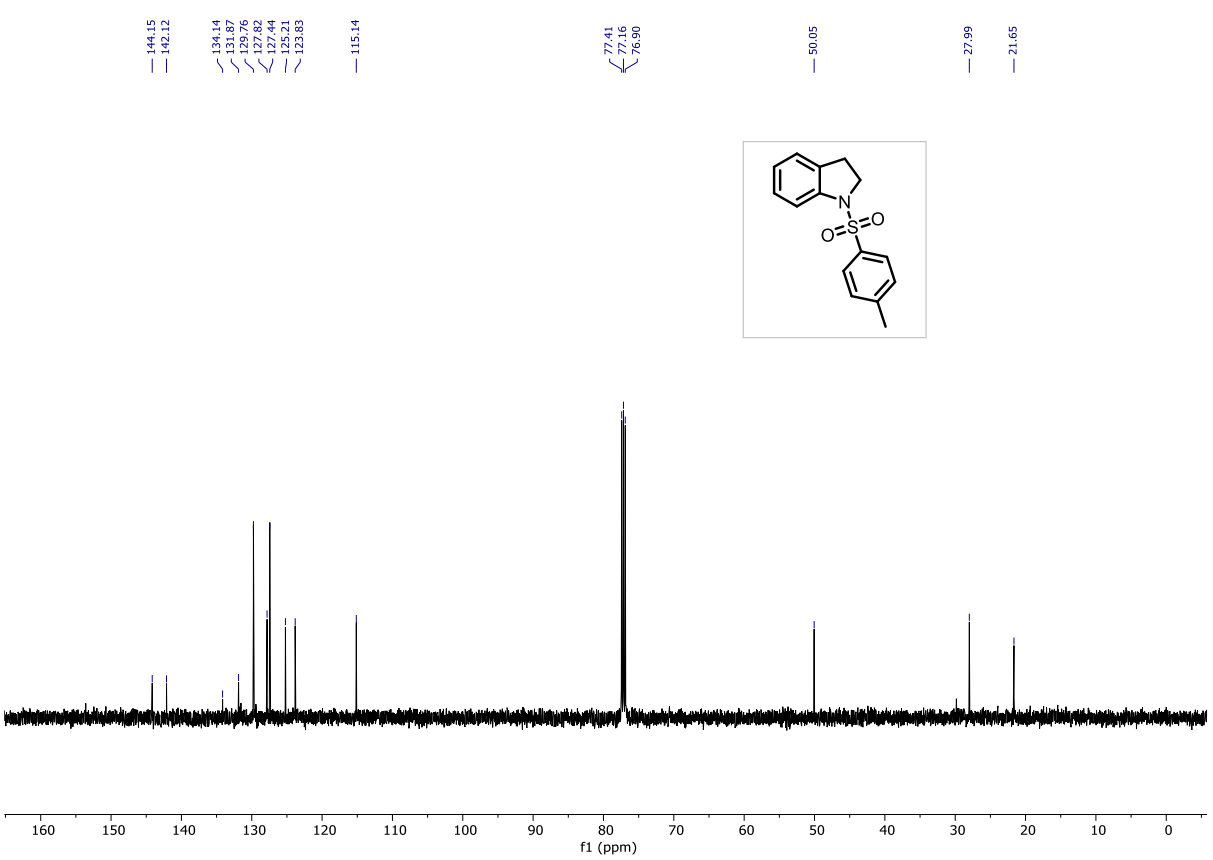


1-Tosylindoline (4u)

^{1}H NMR (500 MHz, $CDCl_3$)

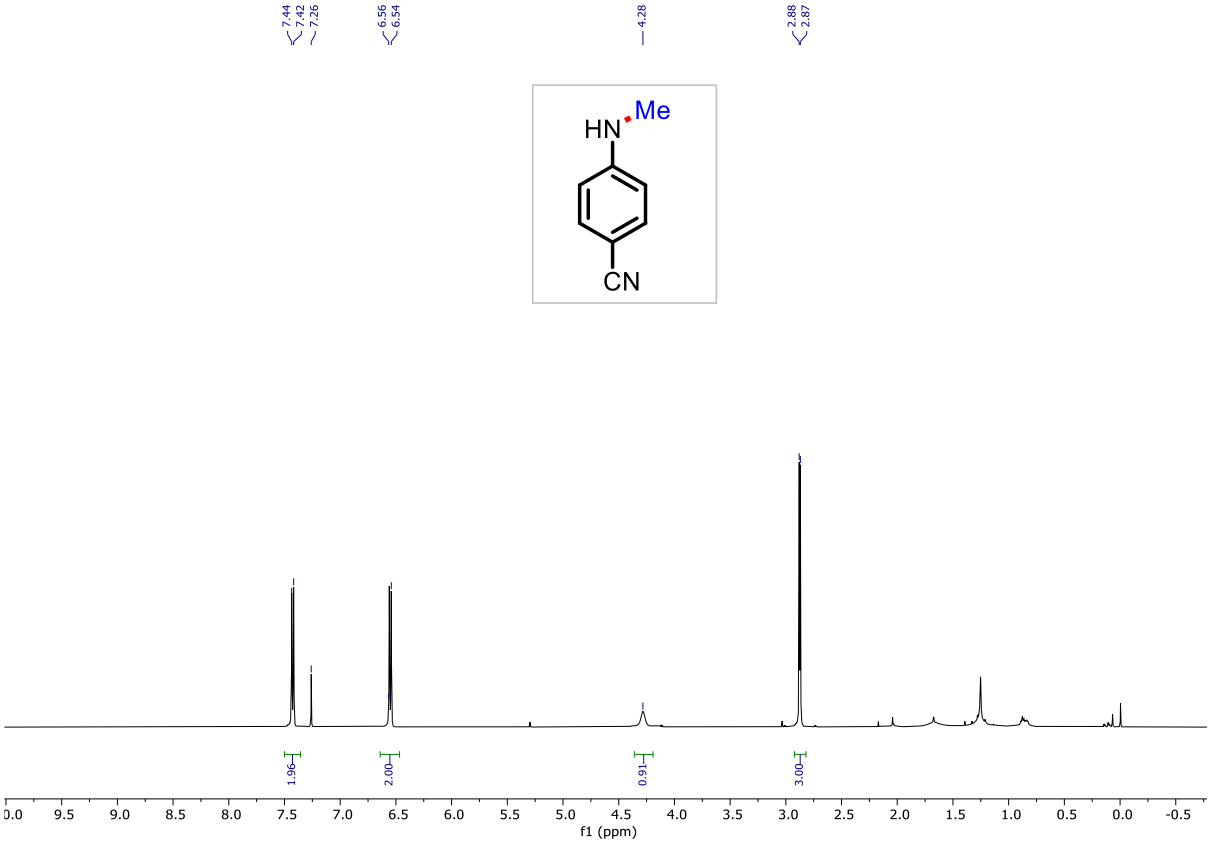


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

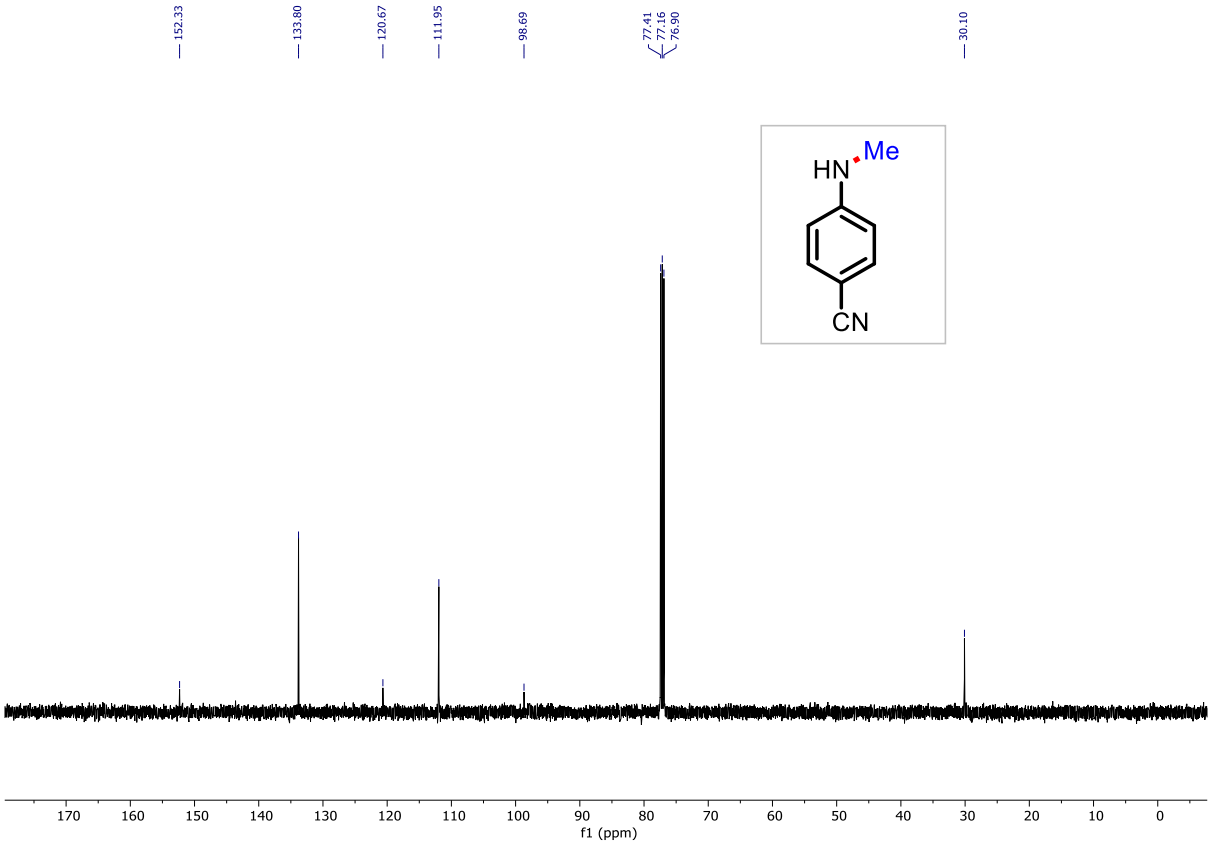


4-(Methyl amino) benzonitrile (5a)

^{1}H NMR (500 MHz, $CDCl_3$)

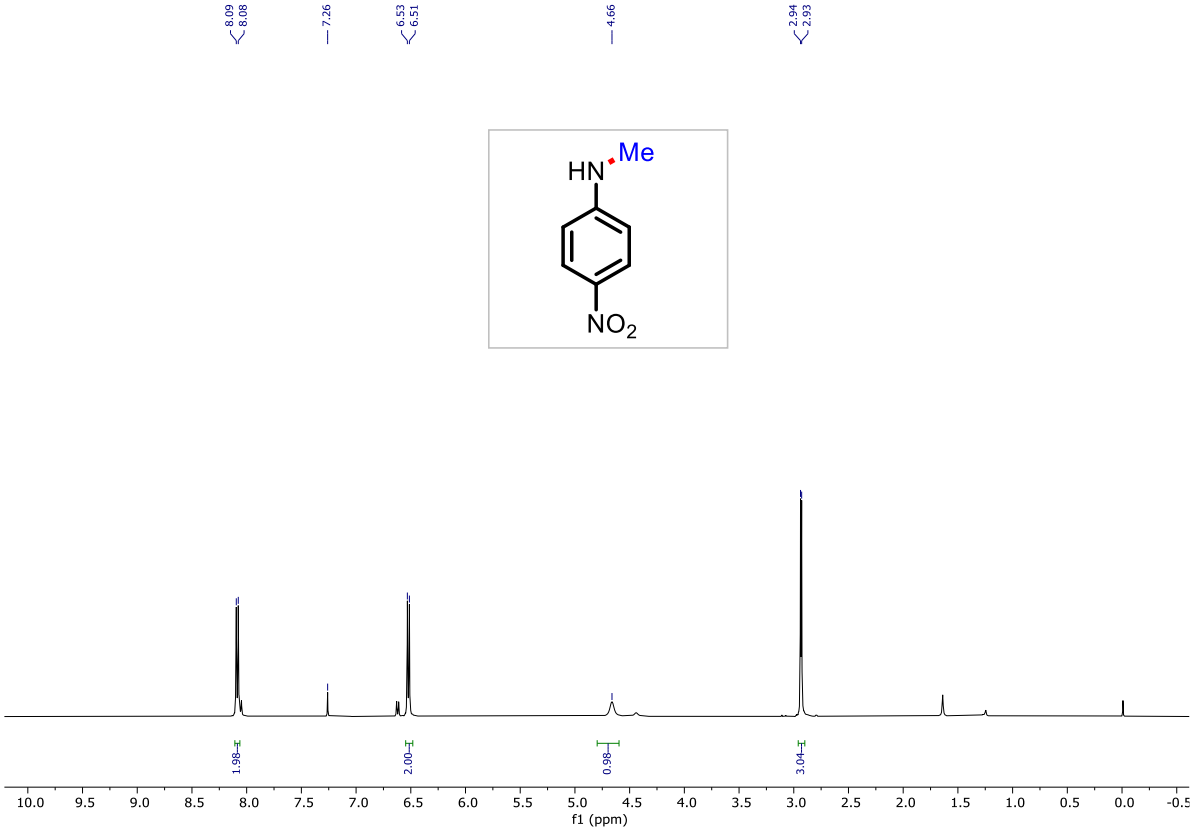


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

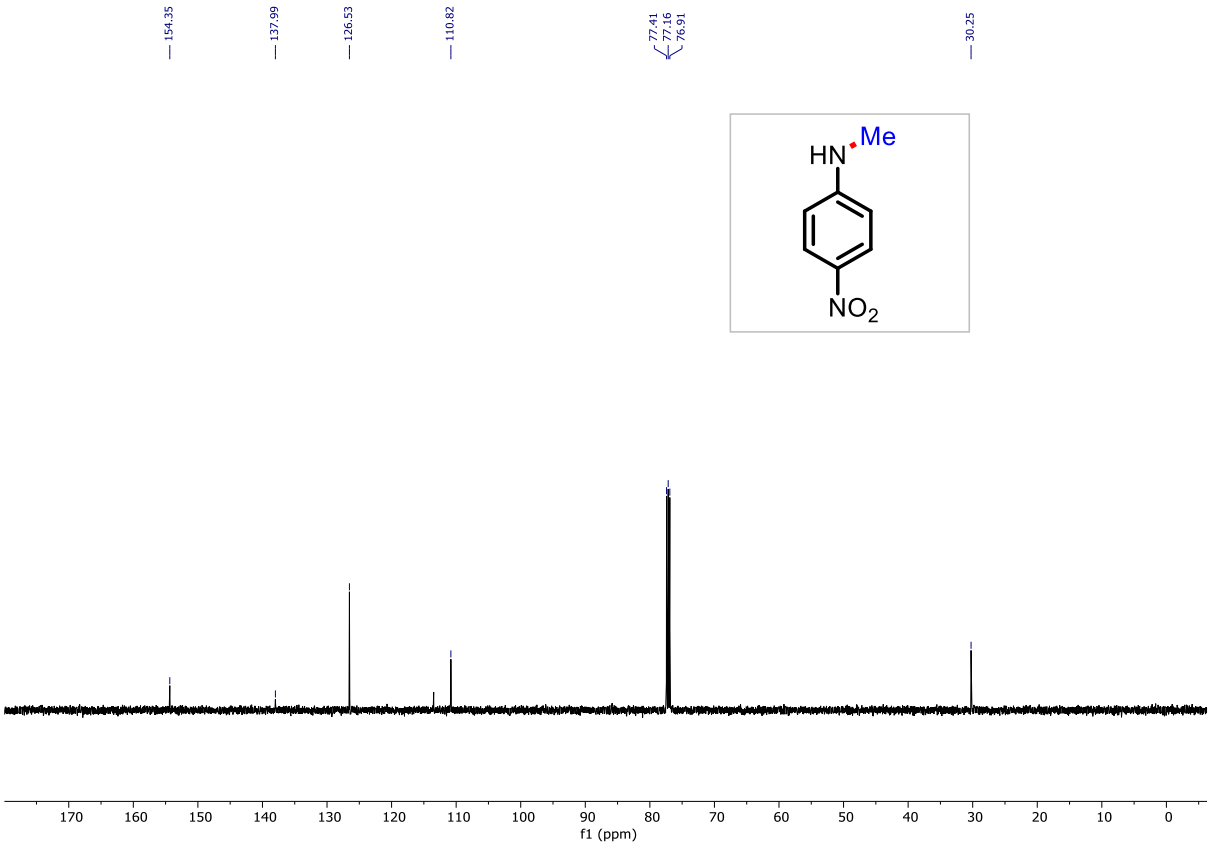


N-Methyl-4-nitroaniline (5b)

^{1}H NMR (500 MHz, $CDCl_3$)

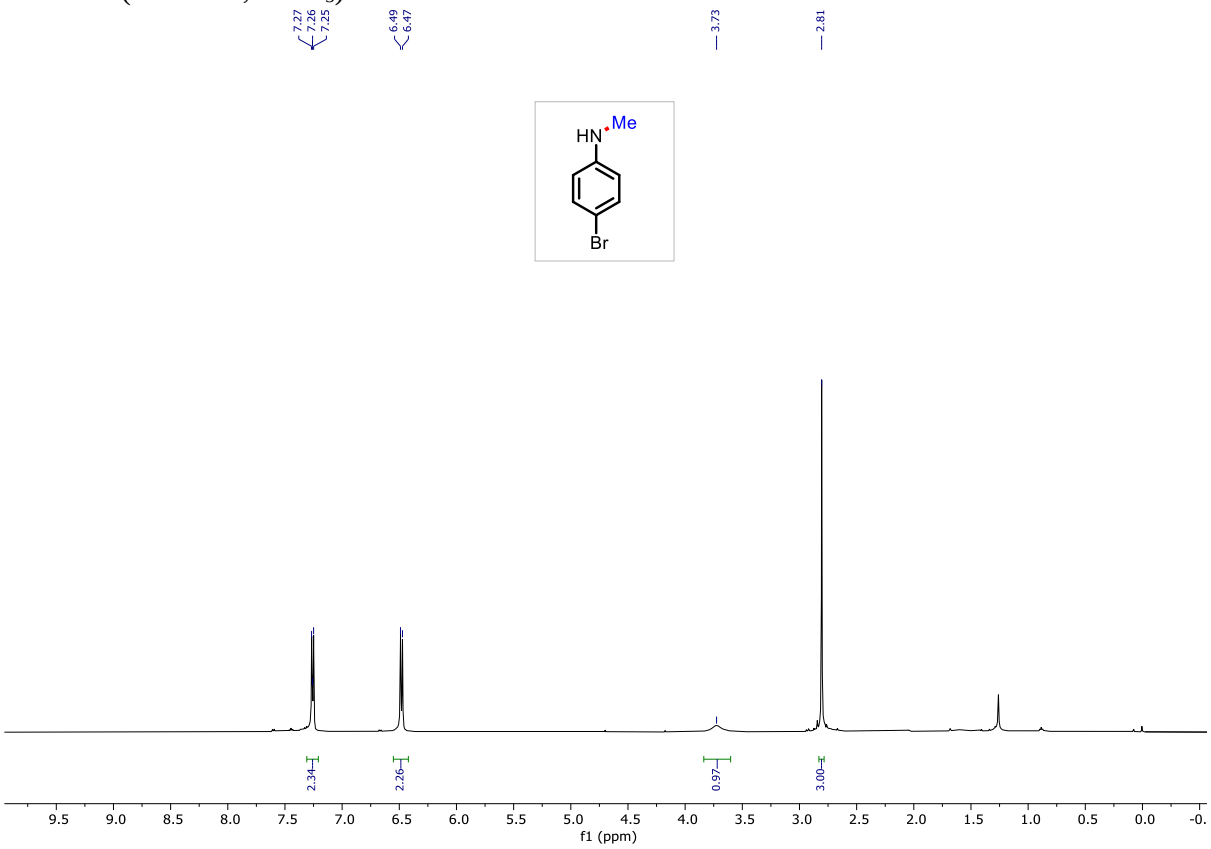


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

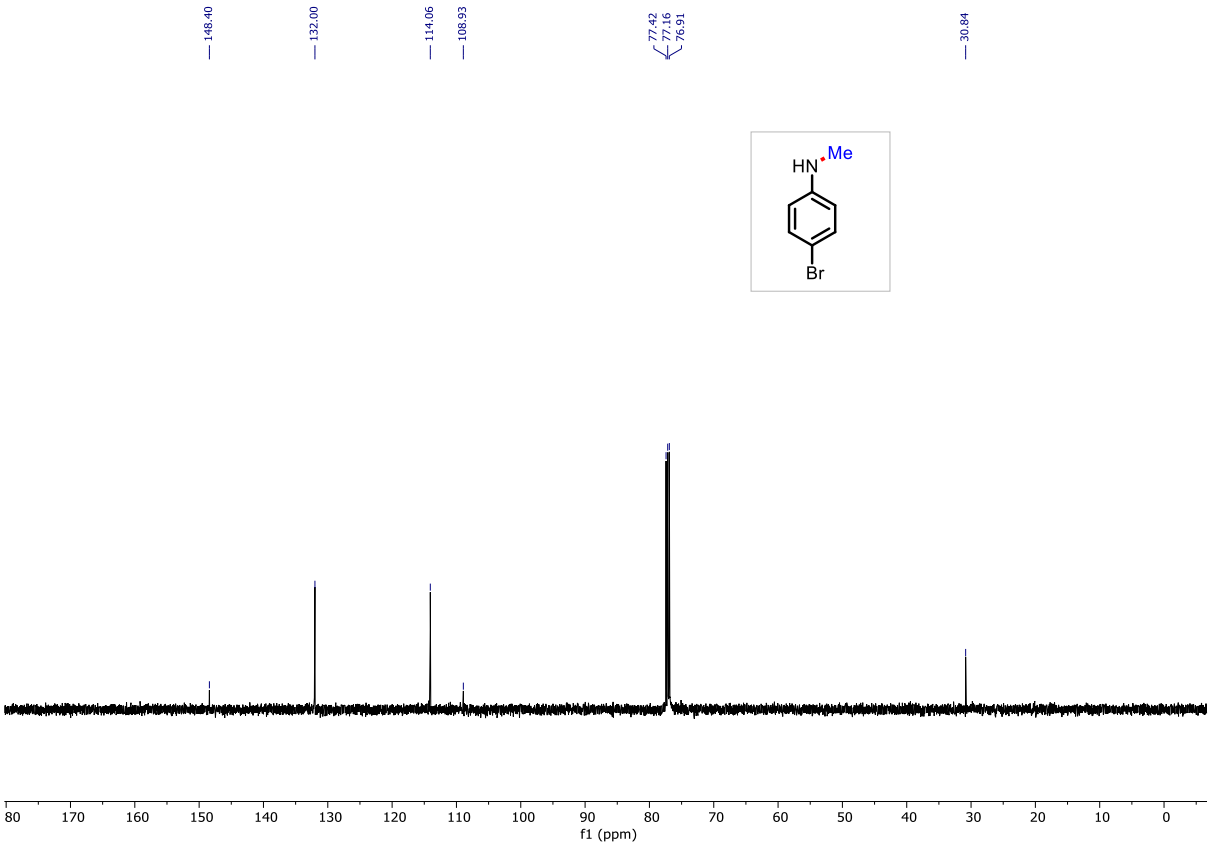


4-Bromo-*N*-methylaniline (5c)

^{1}H NMR (500 MHz, $CDCl_3$)

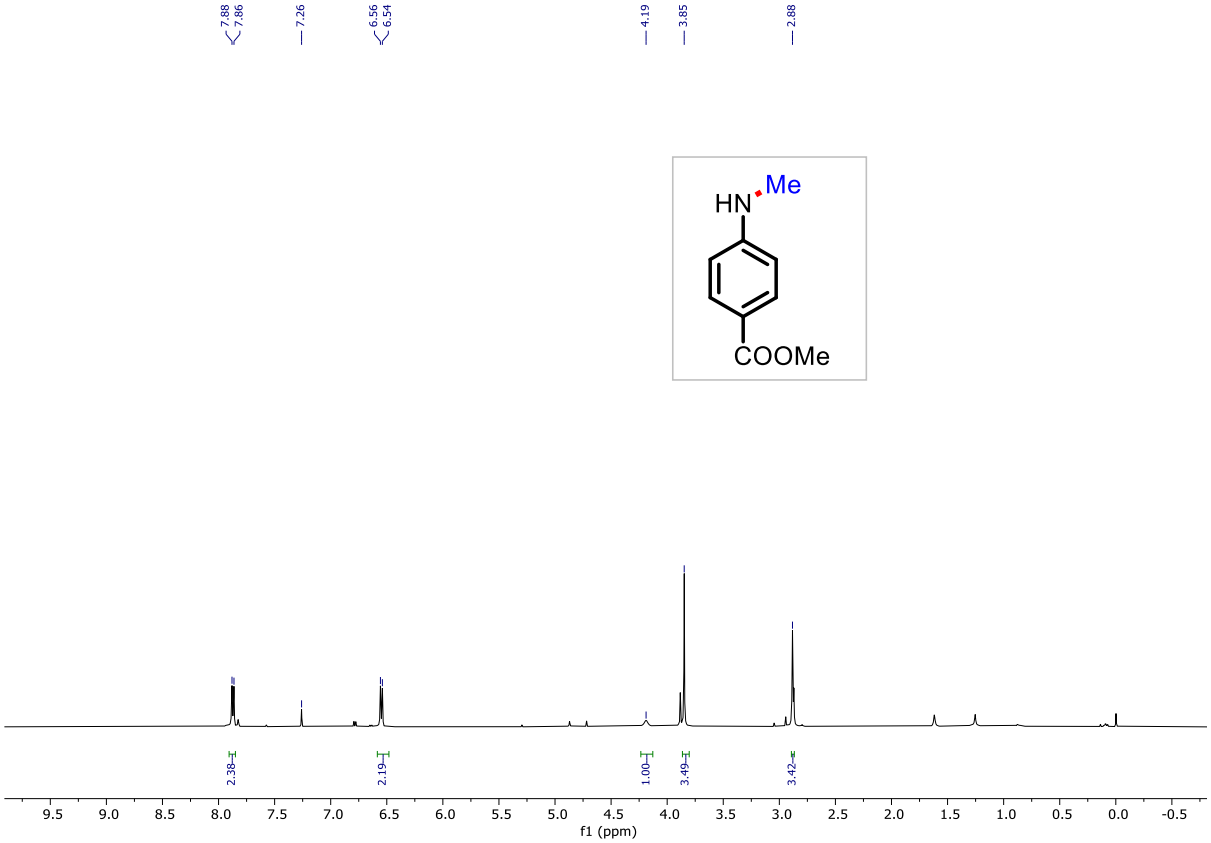


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

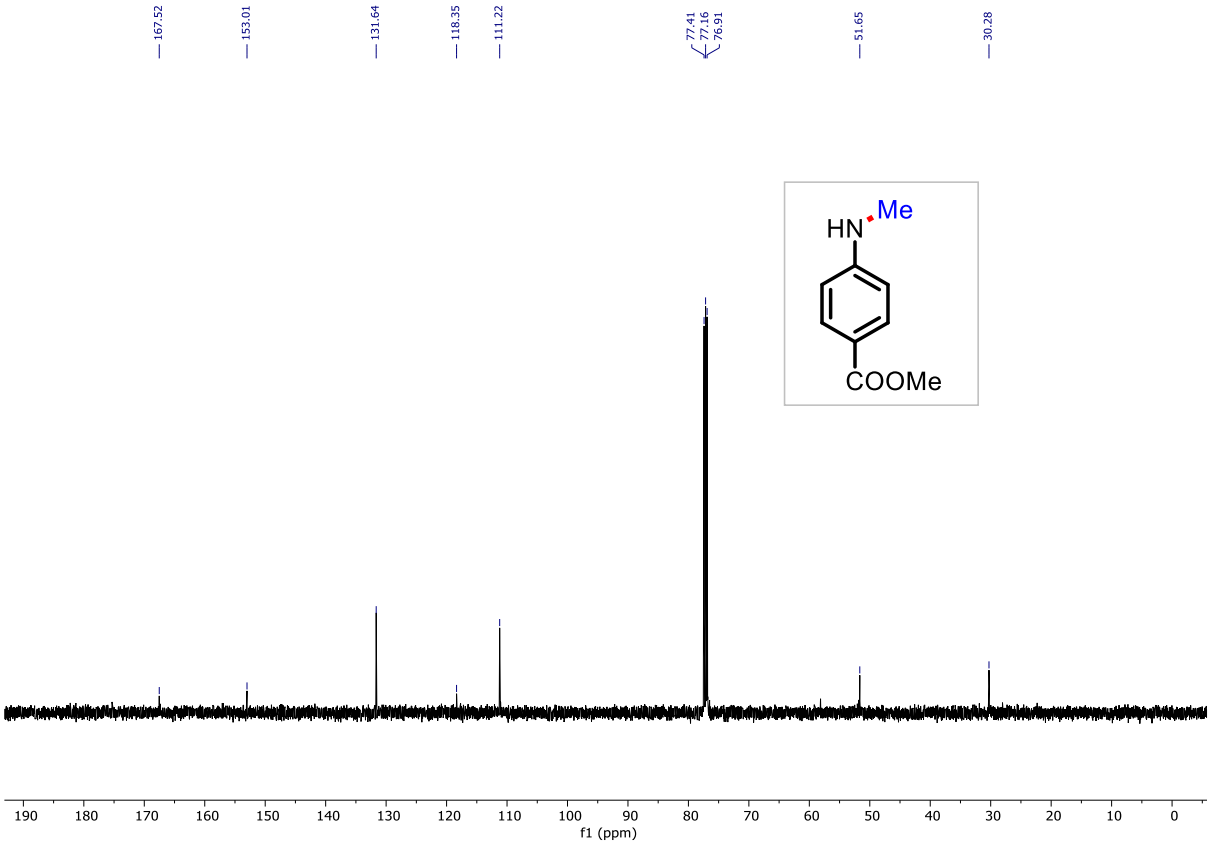


Methyl 4-(methylamino) benzoate (5d)

^{1}H NMR (500 MHz, $CDCl_3$)

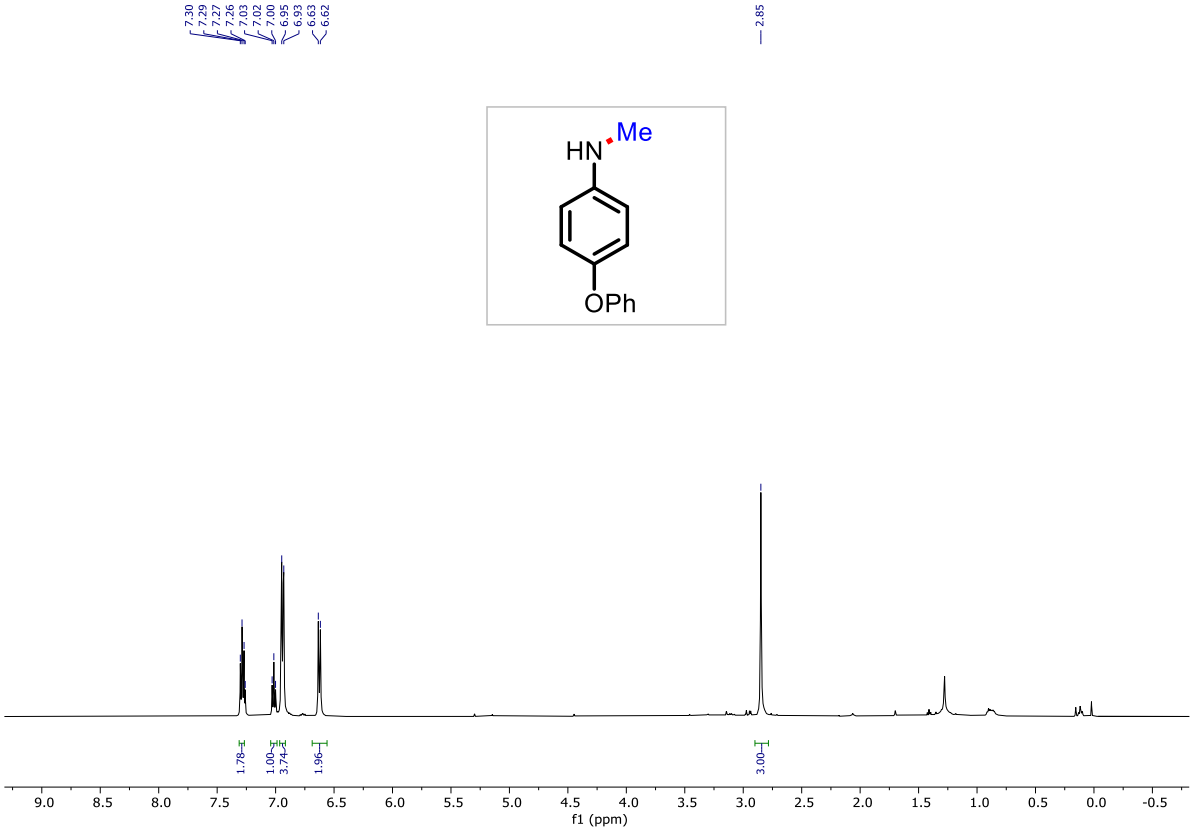


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

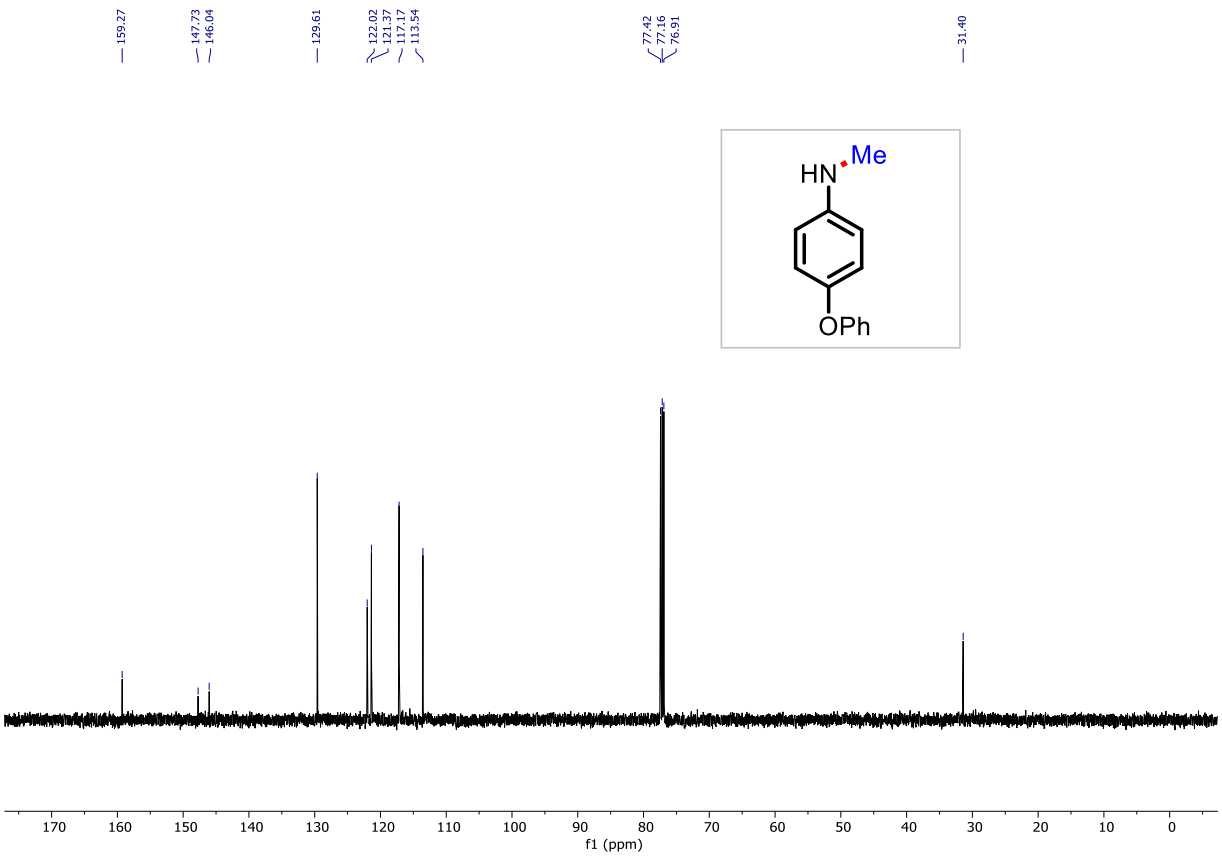


N-Methyl-4-phenoxyaniline (5e)

^{1}H NMR (500 MHz, $CDCl_3$)

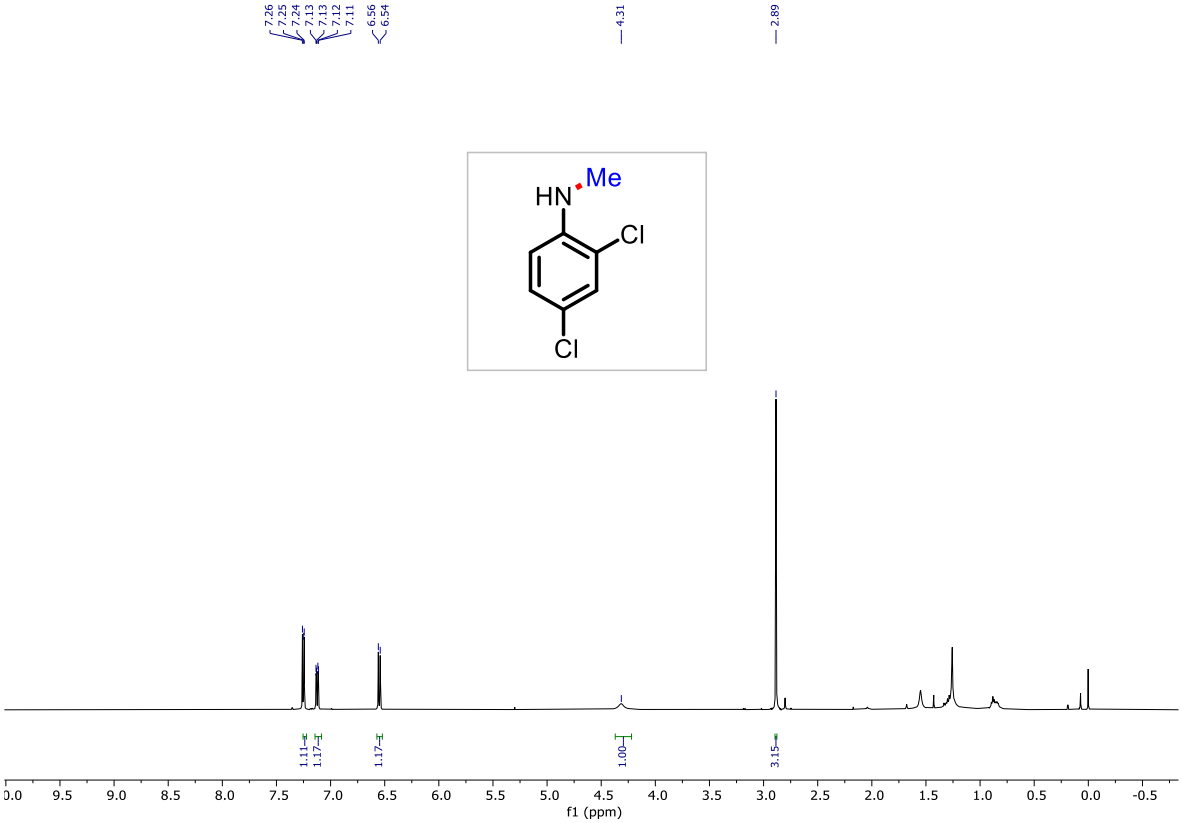


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

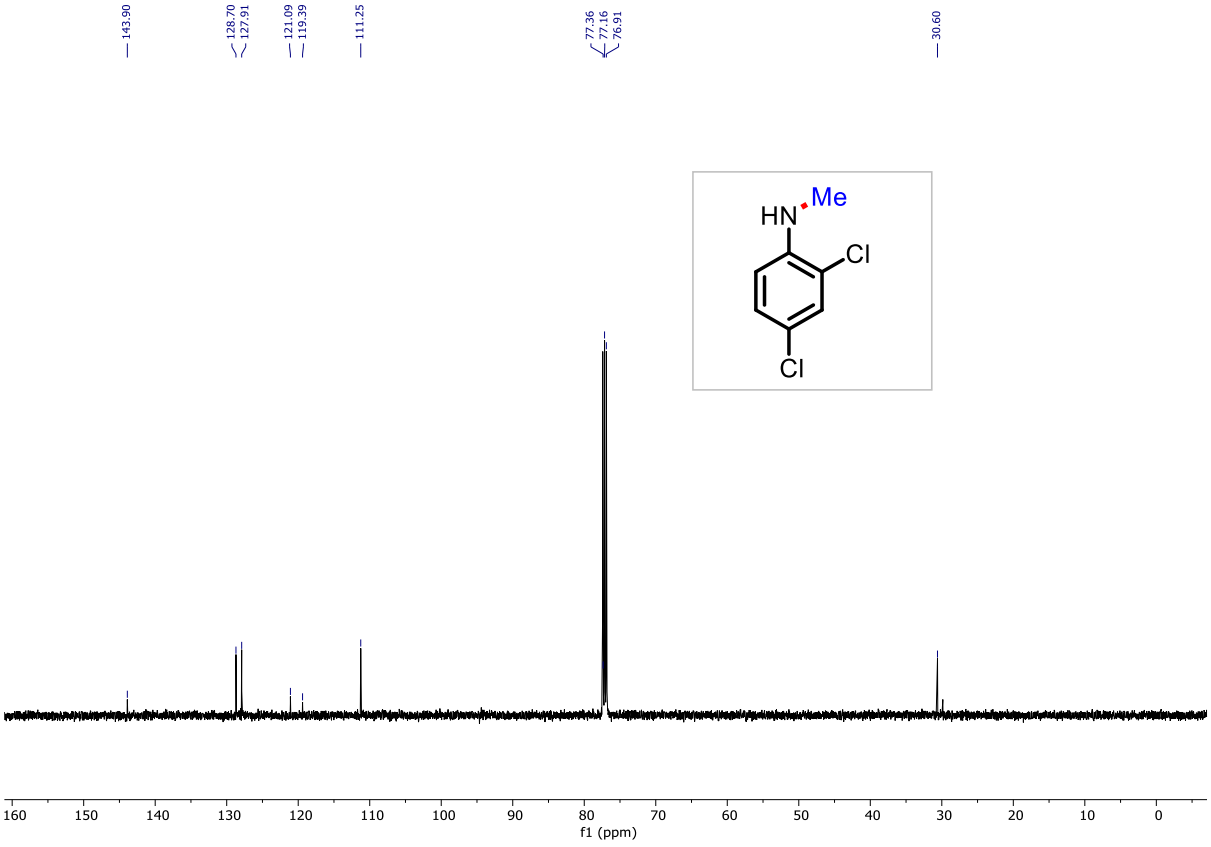


2,4-Dichloro-*N*-methylaniline (5f)

^{1}H NMR (500 MHz, $CDCl_3$)

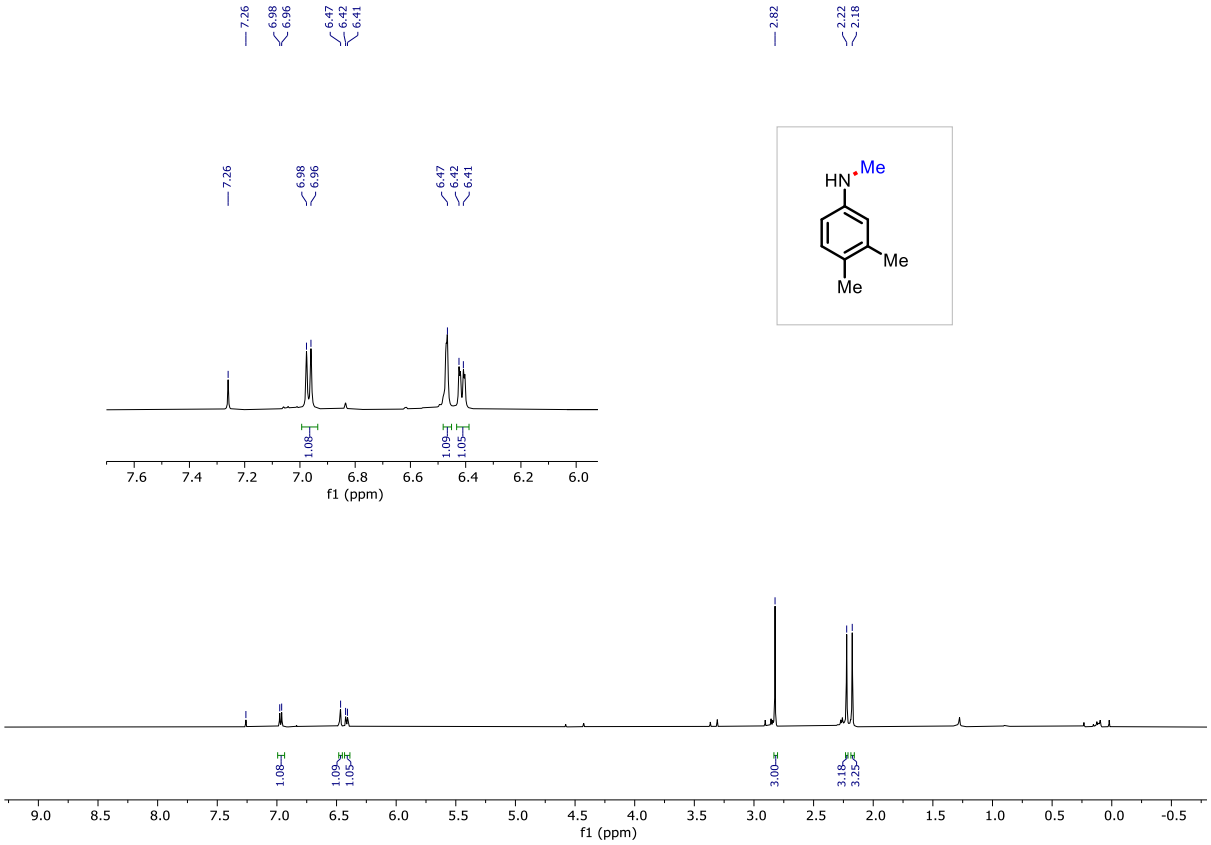


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

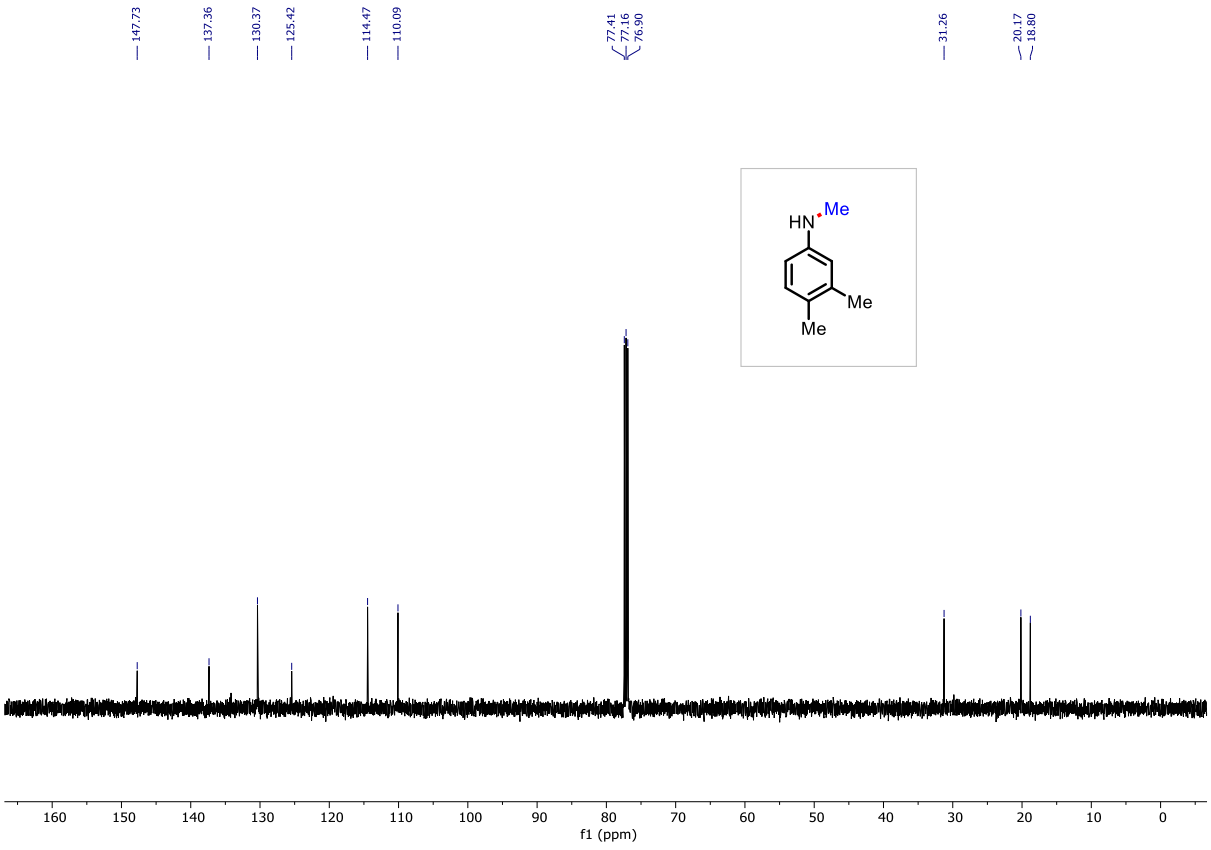


N,2,4-Trimethylaniline (5g)

^{1}H NMR (500 MHz, $CDCl_3$)

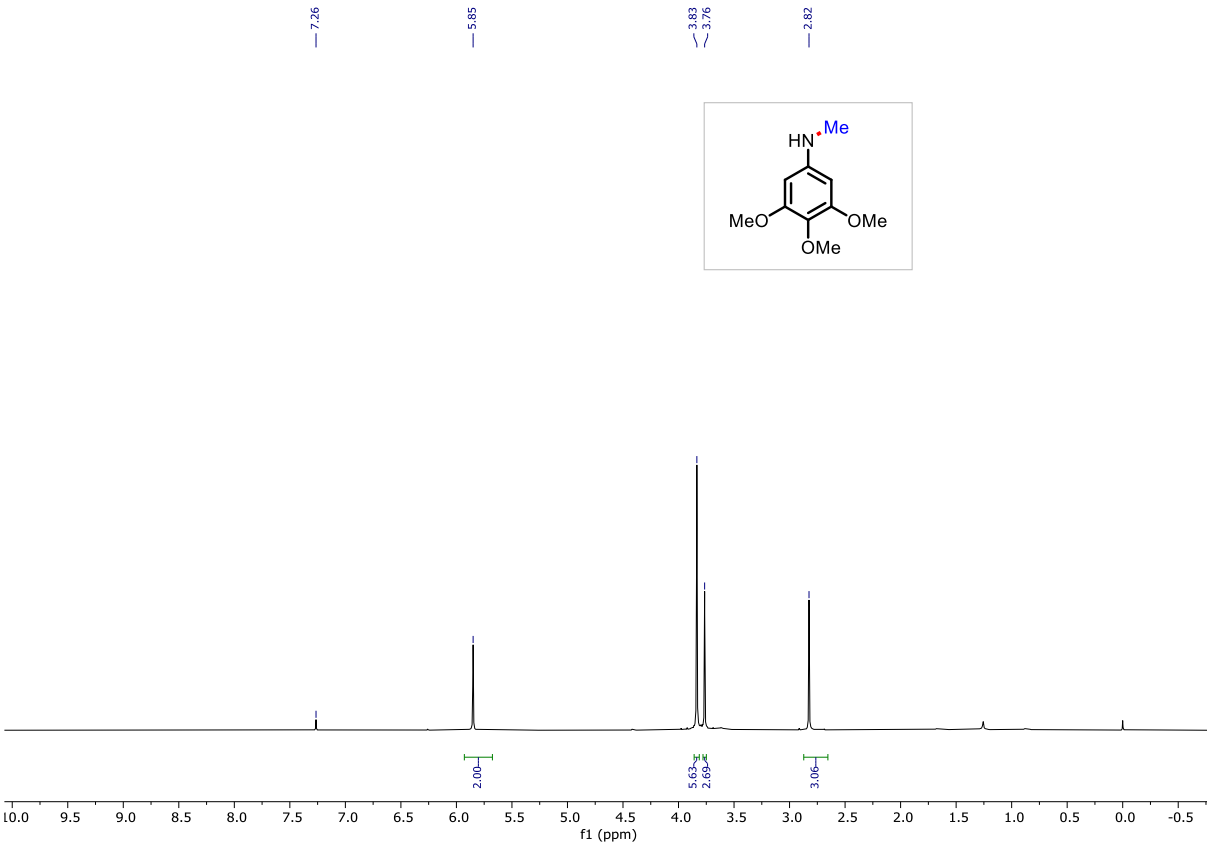


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

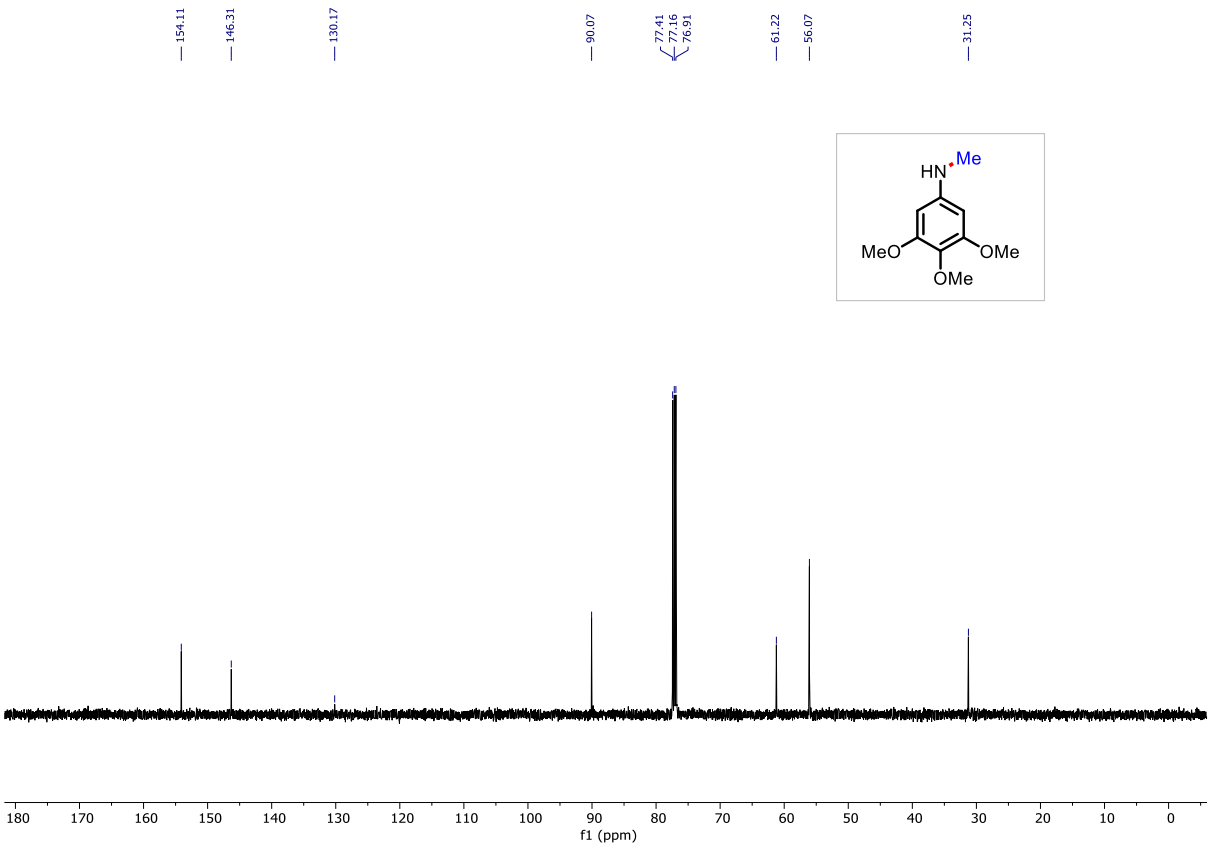


3,4,5-Trimethoxy-*N*-methylaniline (5h)

^{1}H NMR (500 MHz, $CDCl_3$)

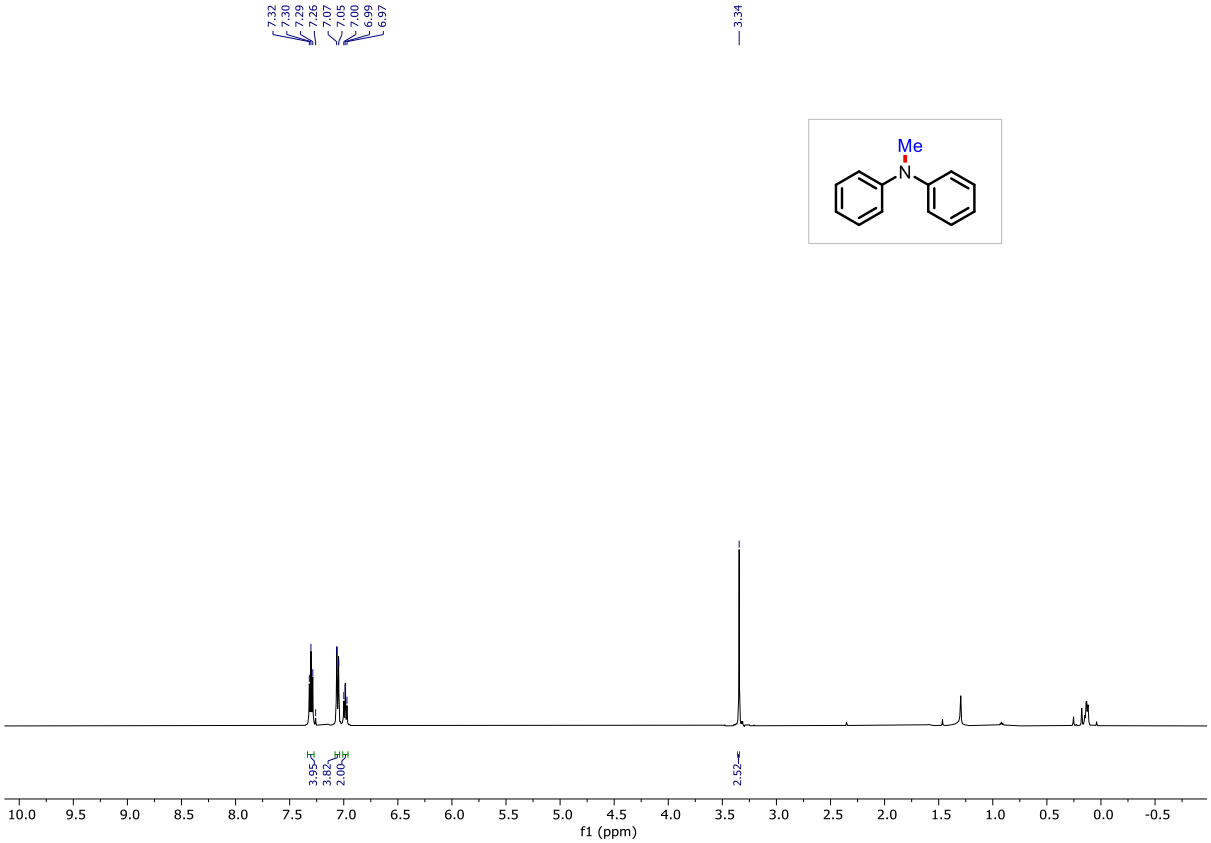


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

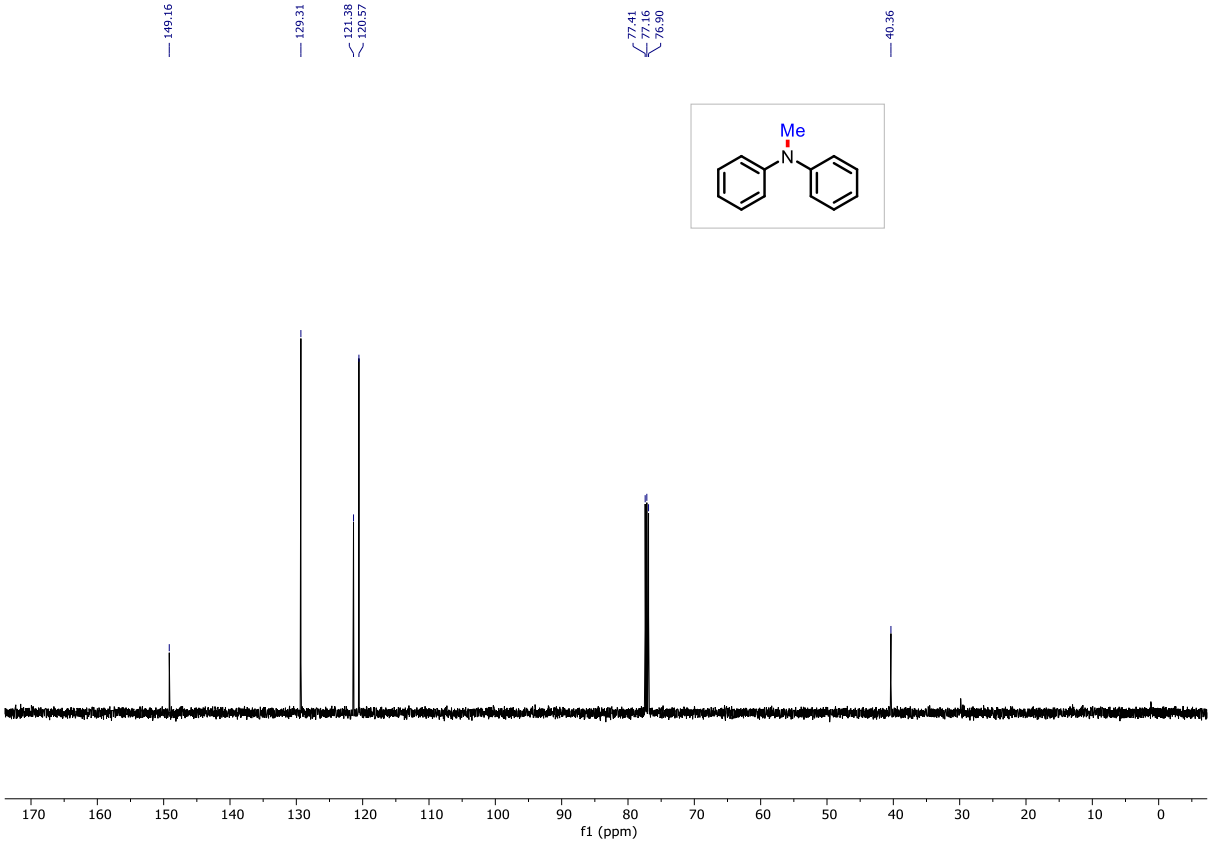


N-Methyl-*N*-phenylaniline (5i)

^{1}H NMR (500 MHz, $CDCl_3$)



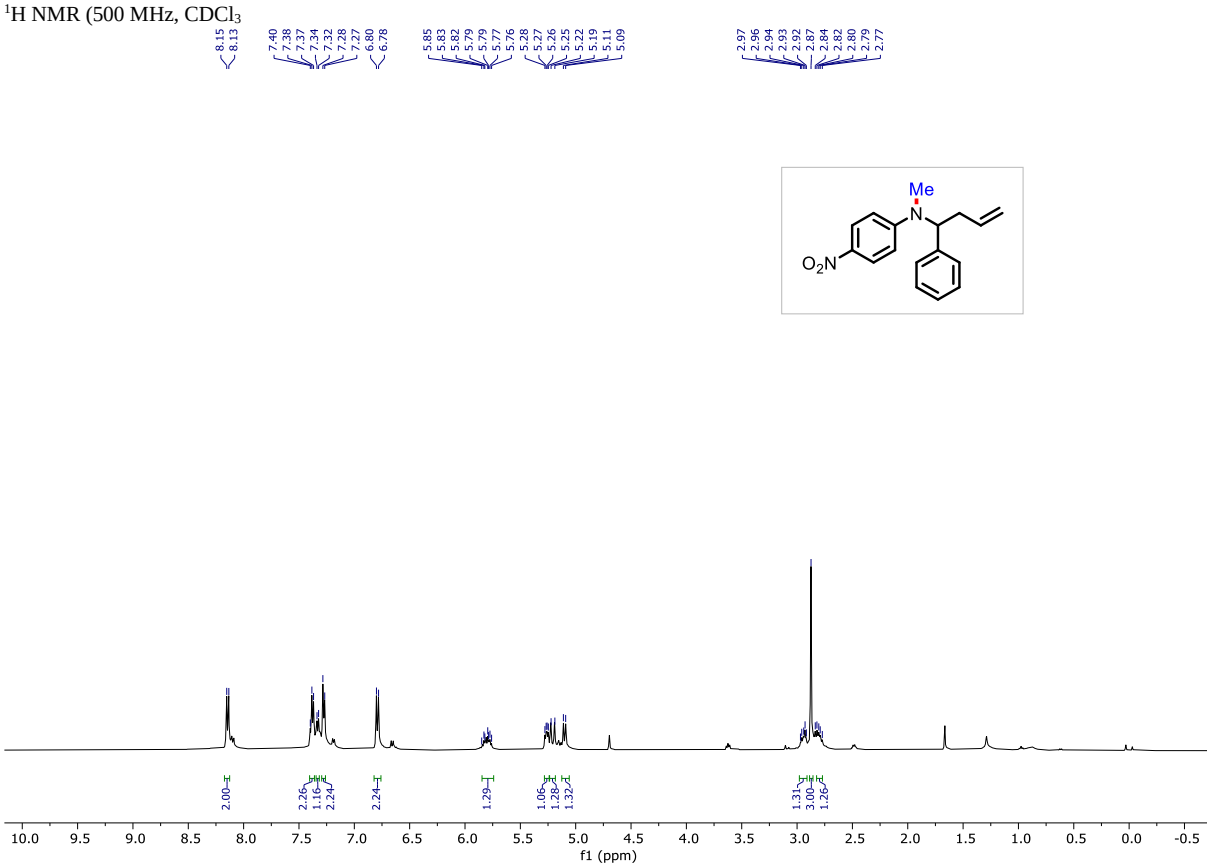
^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)



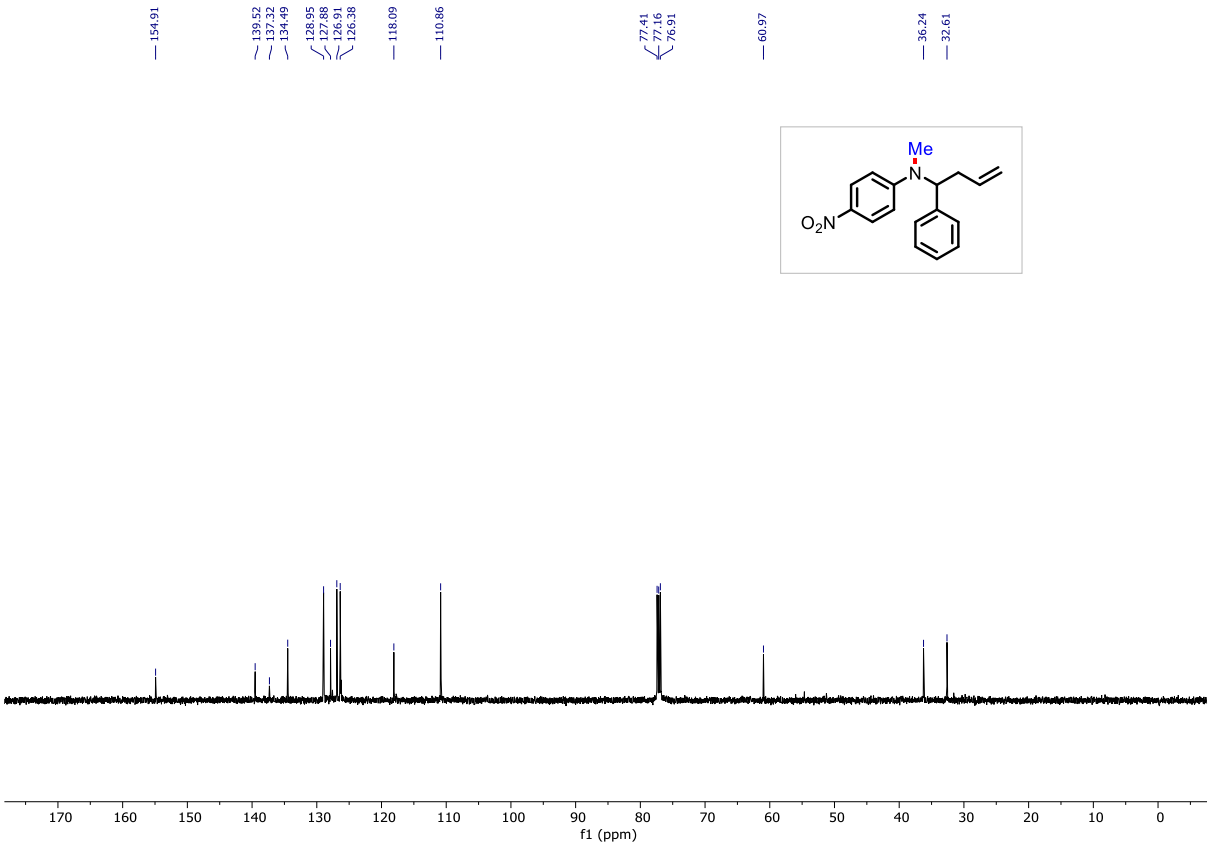
N-Methyl-4-nitro-*N*-(1-phenylbut-3-en-1-yl) aniline (5j)

^{1}H NMR (500 MHz, $CDCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$

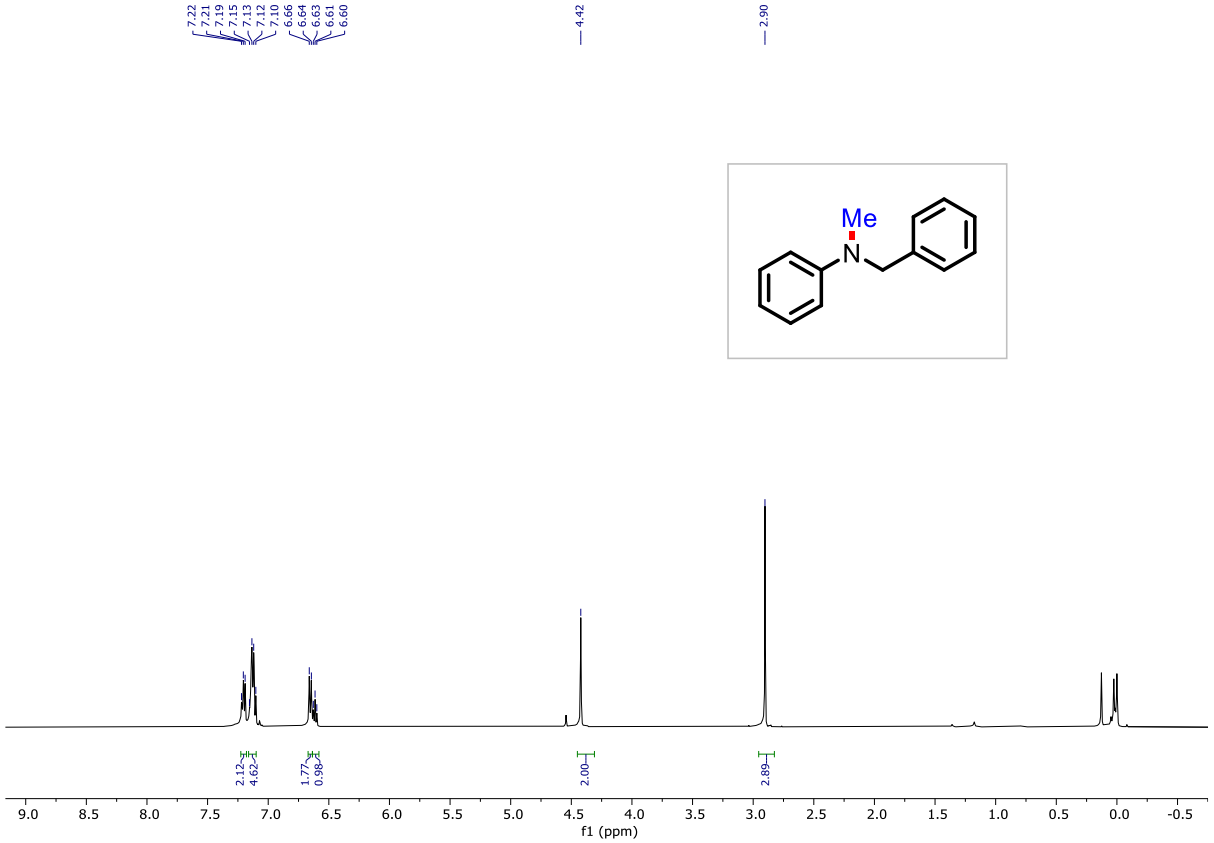


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

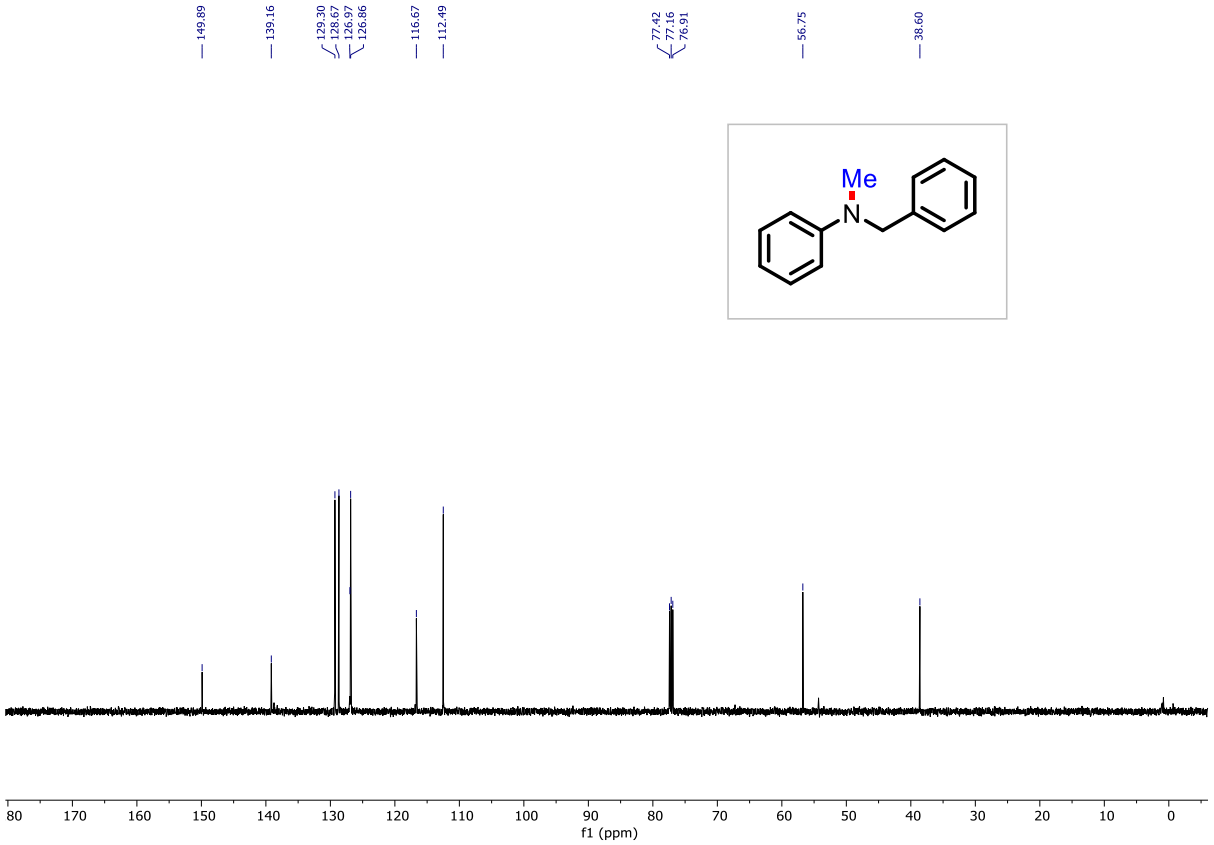


N-Benzyl-*N*-methylaniline (5k)

^{1}H NMR (500 MHz, $CDCl_3$)

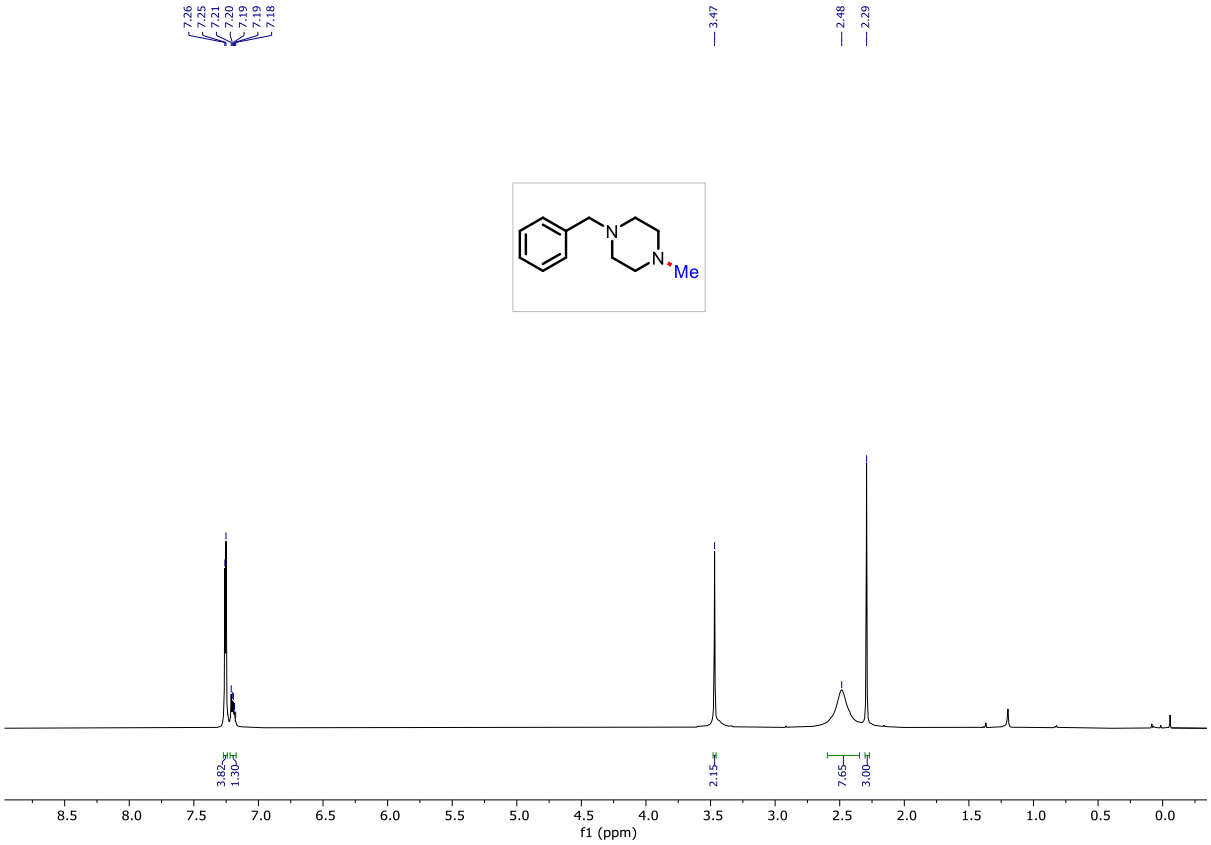


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

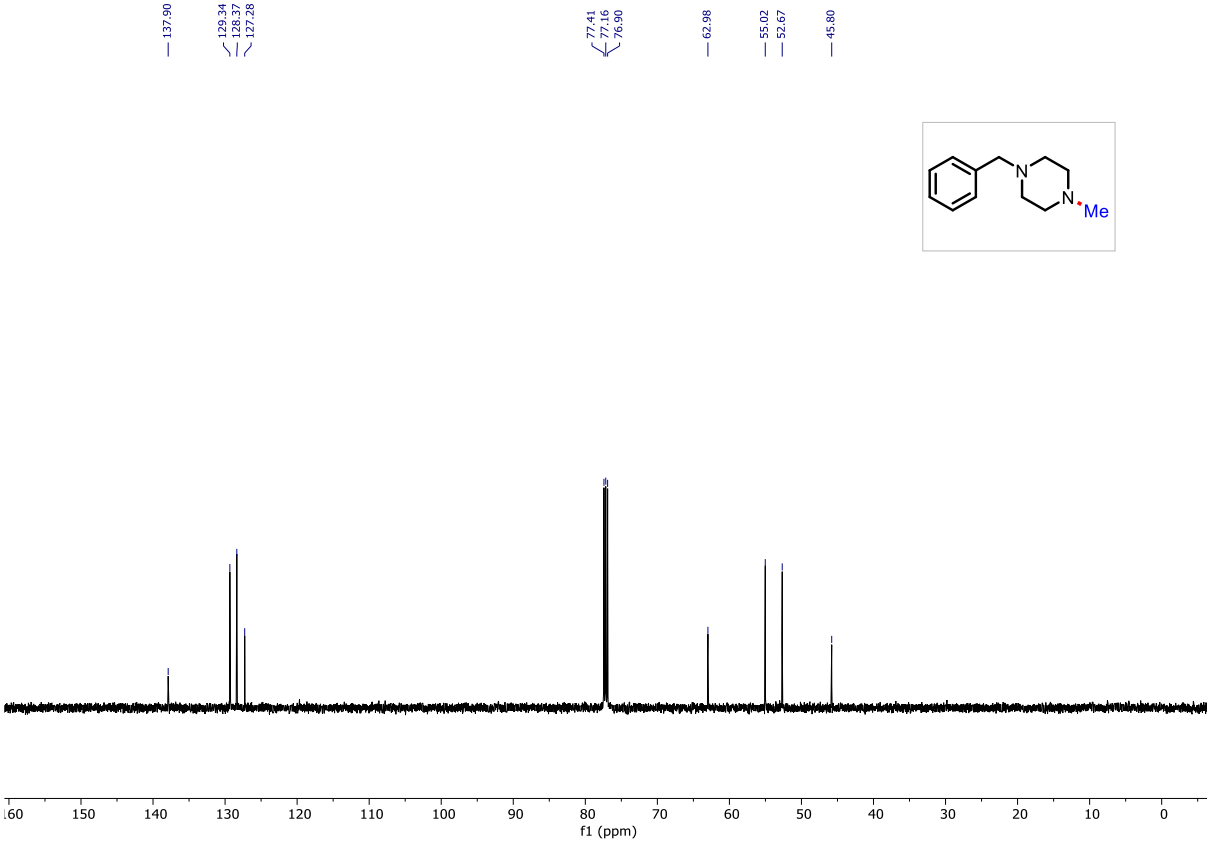


1-Benzyl-4-methylpiperazine (5l)

^{1}H NMR (500 MHz, $CDCl_3$)

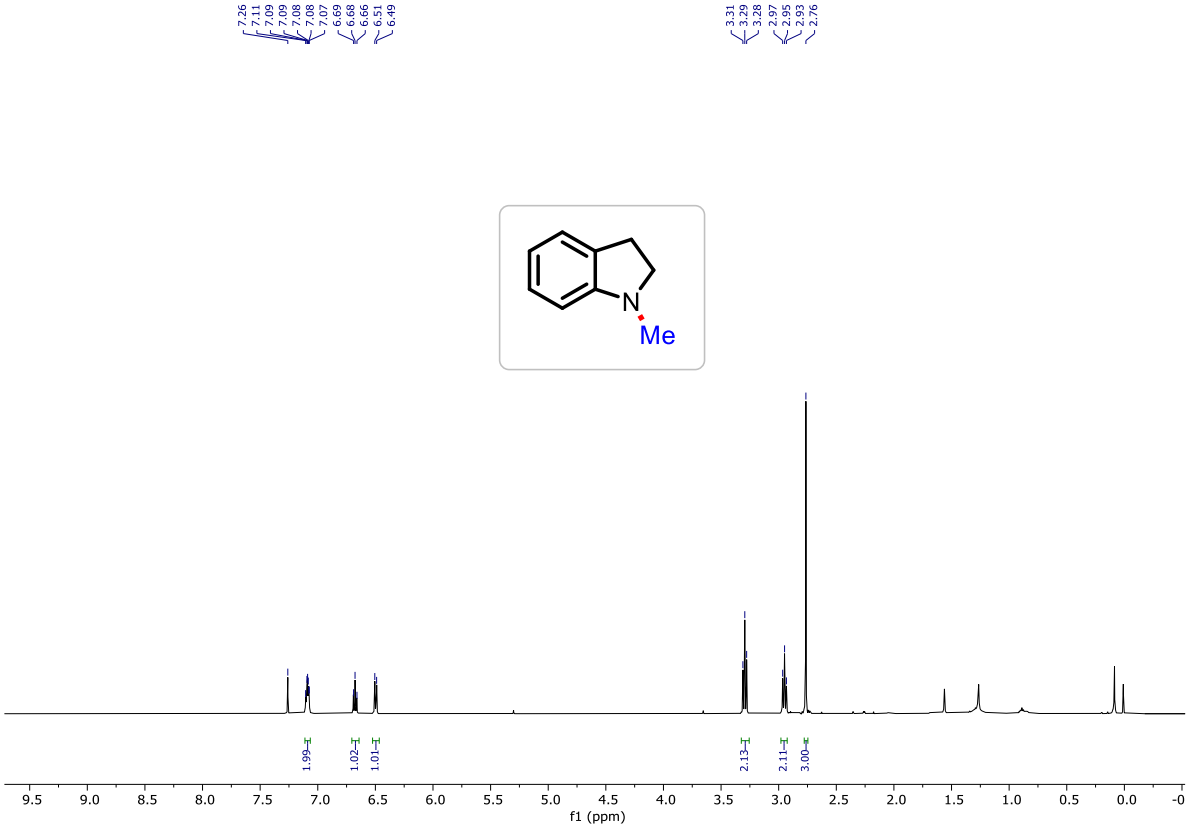


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

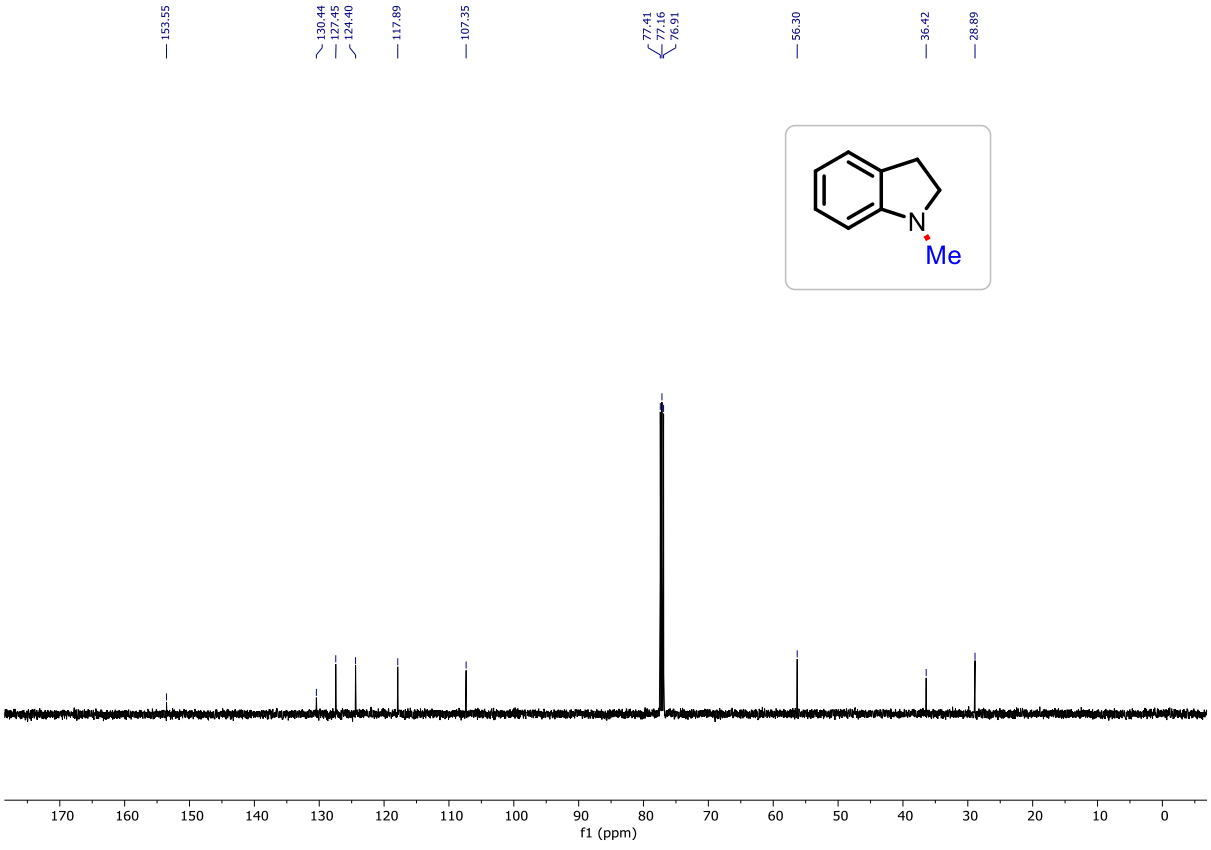


1-Methylindoline (5m)

^{1}H NMR (500 MHz, $CDCl_3$)

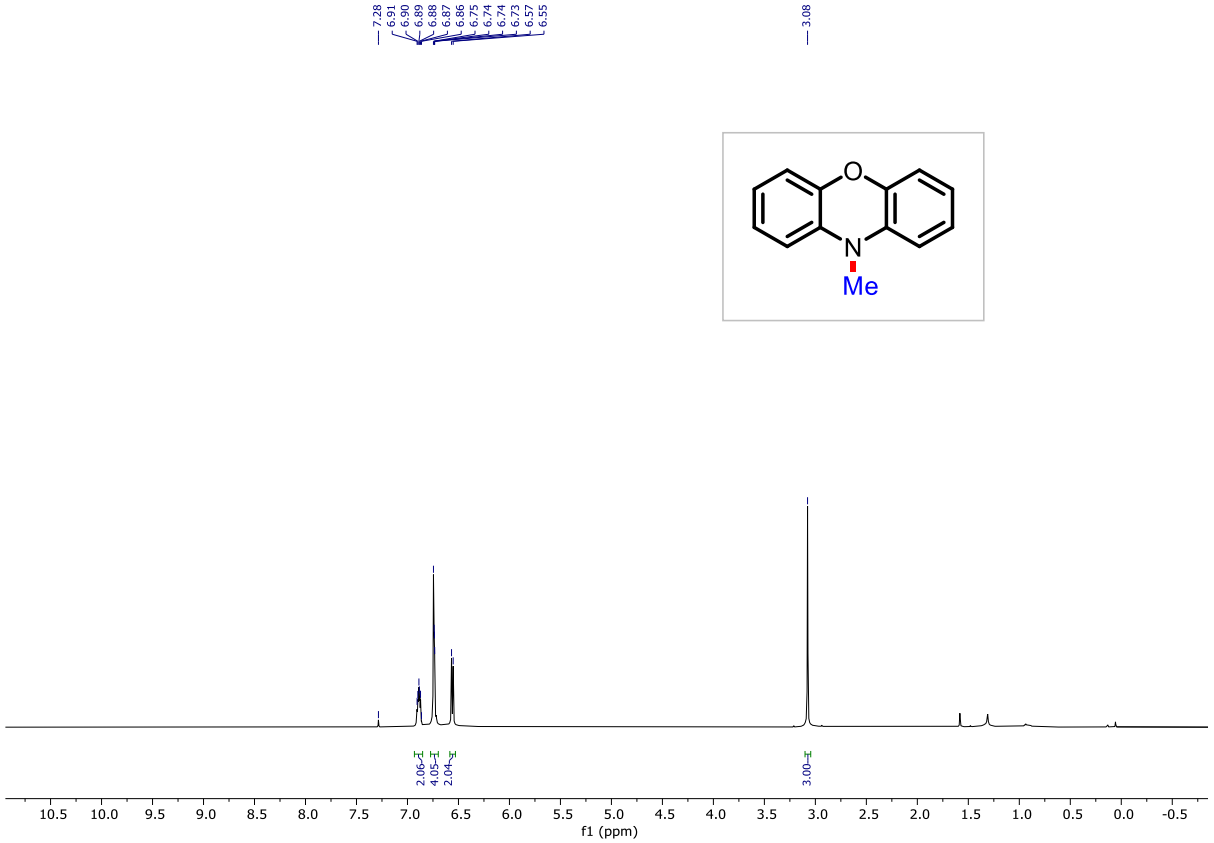


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

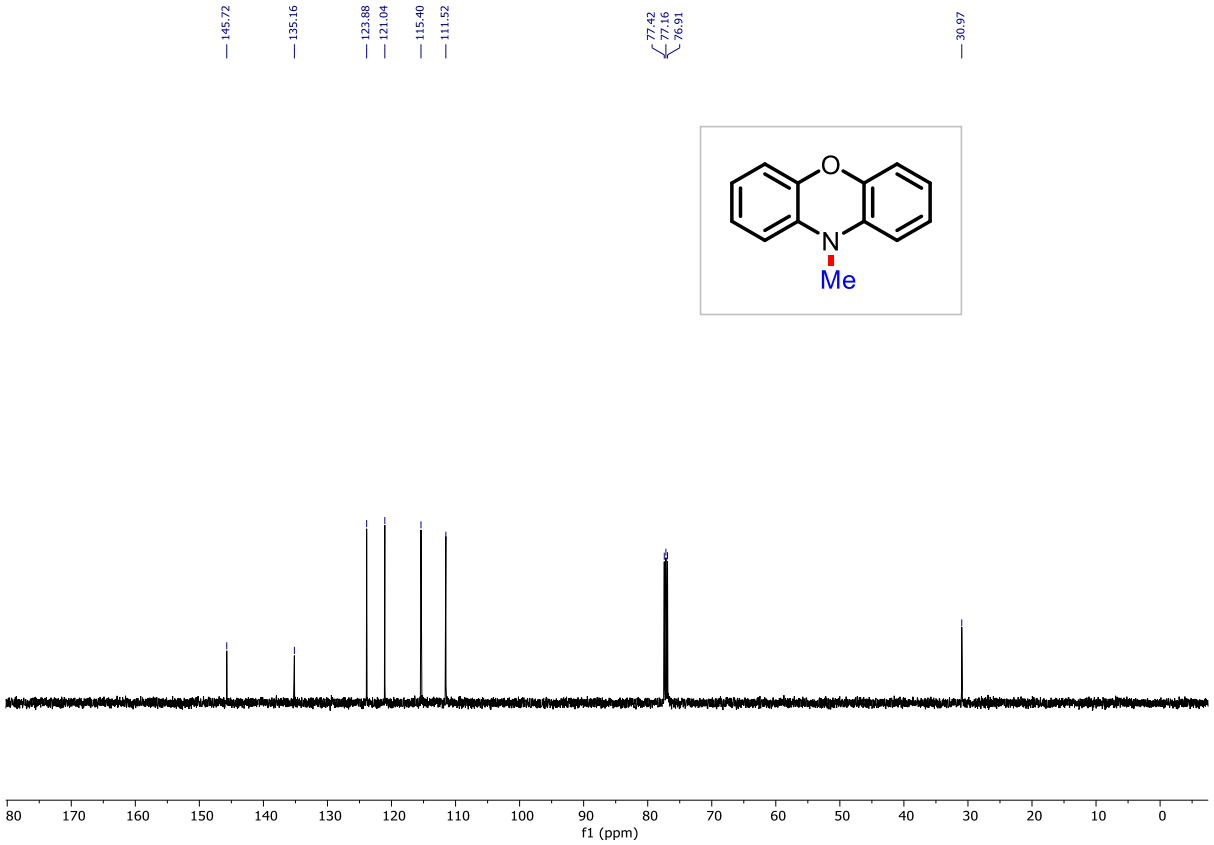


10-Methyl-10*H*-phenoxazine (5n)

^{1}H NMR (500 MHz, $CDCl_3$)

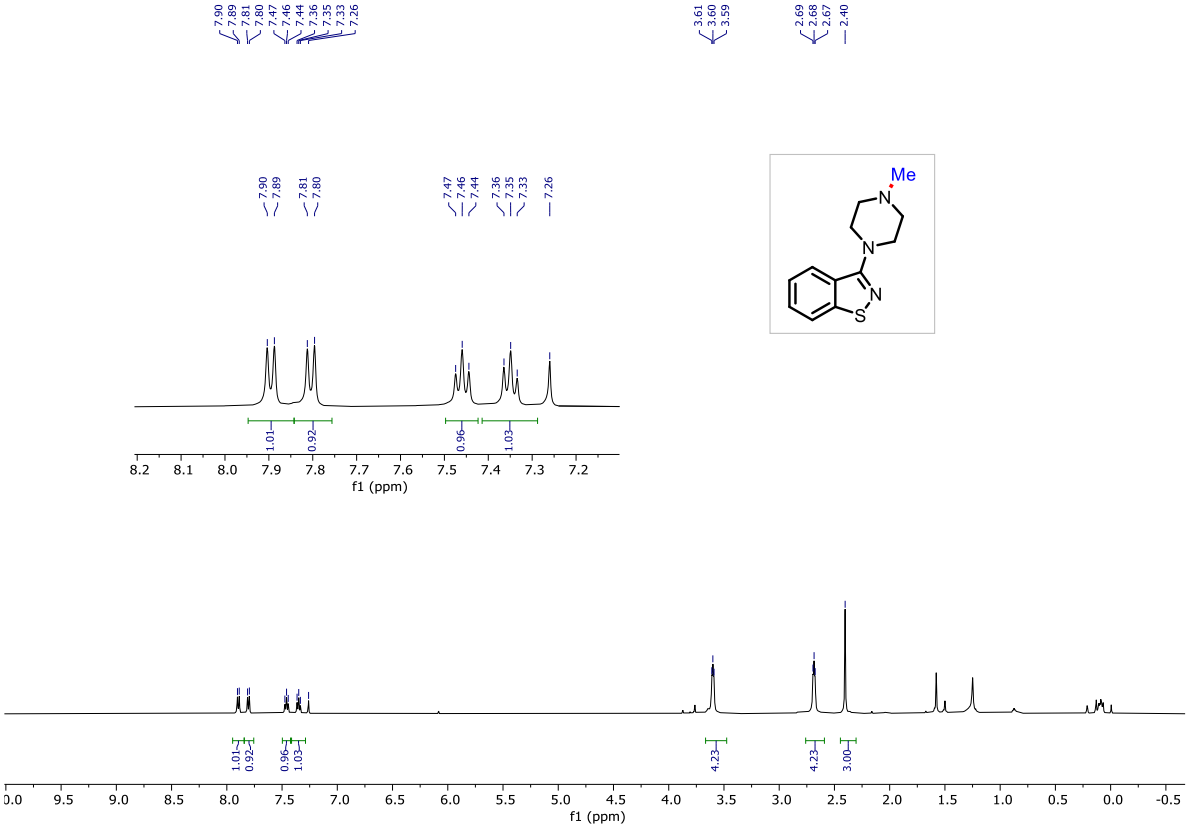


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

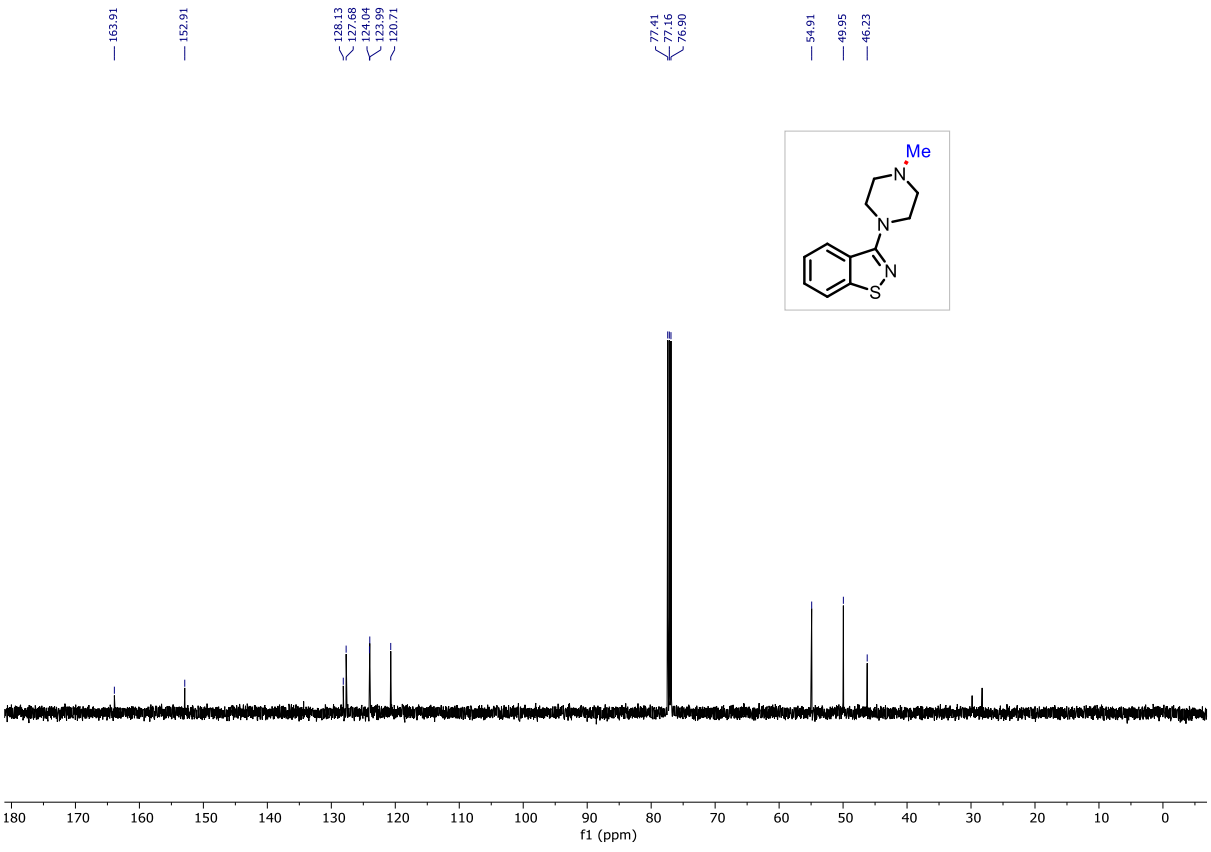


3-(4-Methylpiperazin-1-yl) benzo[*d*]isothiazole (5o)

^{1}H NMR (500 MHz, $CDCl_3$)

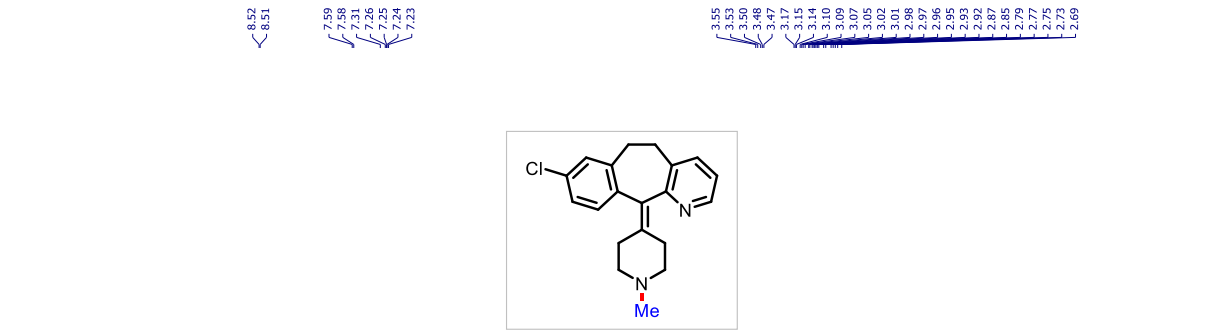


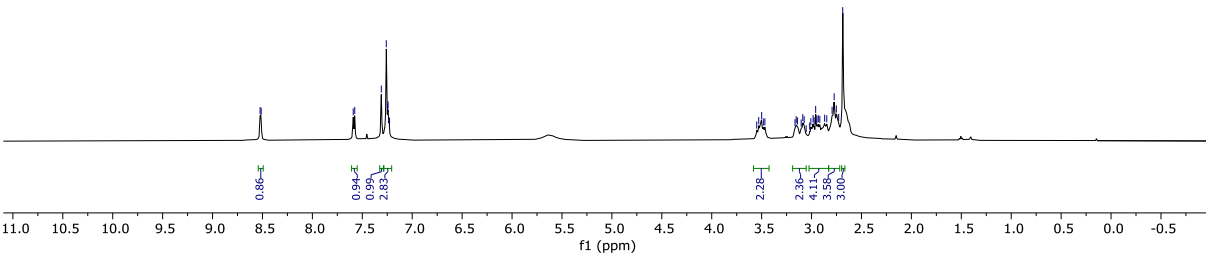
^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)



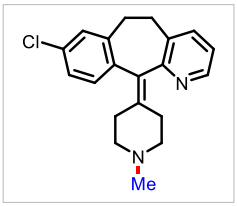
8-Chloro-11-(1-methylpiperidin-4-ylidene)-6,11-dihydro-5H-benzo [5,6] cyclohepta[1,2-b] pyridine (5p)

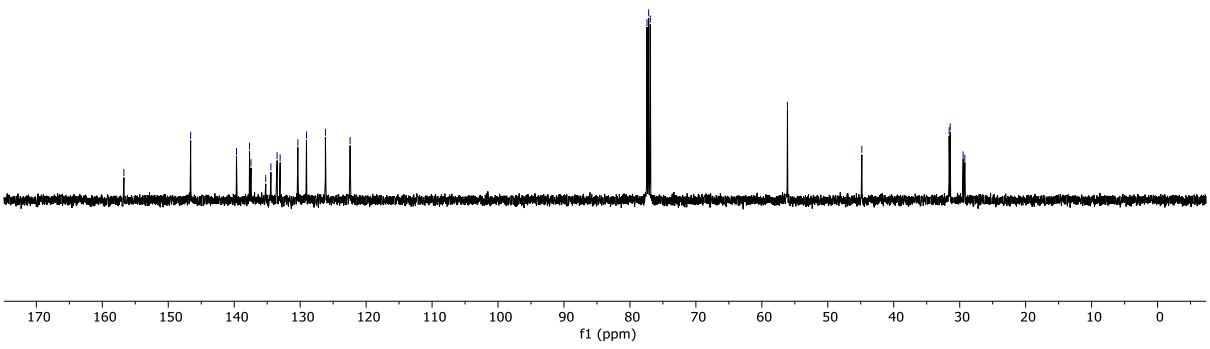
^{1}H NMR (500 MHz, $CDCl_3$)





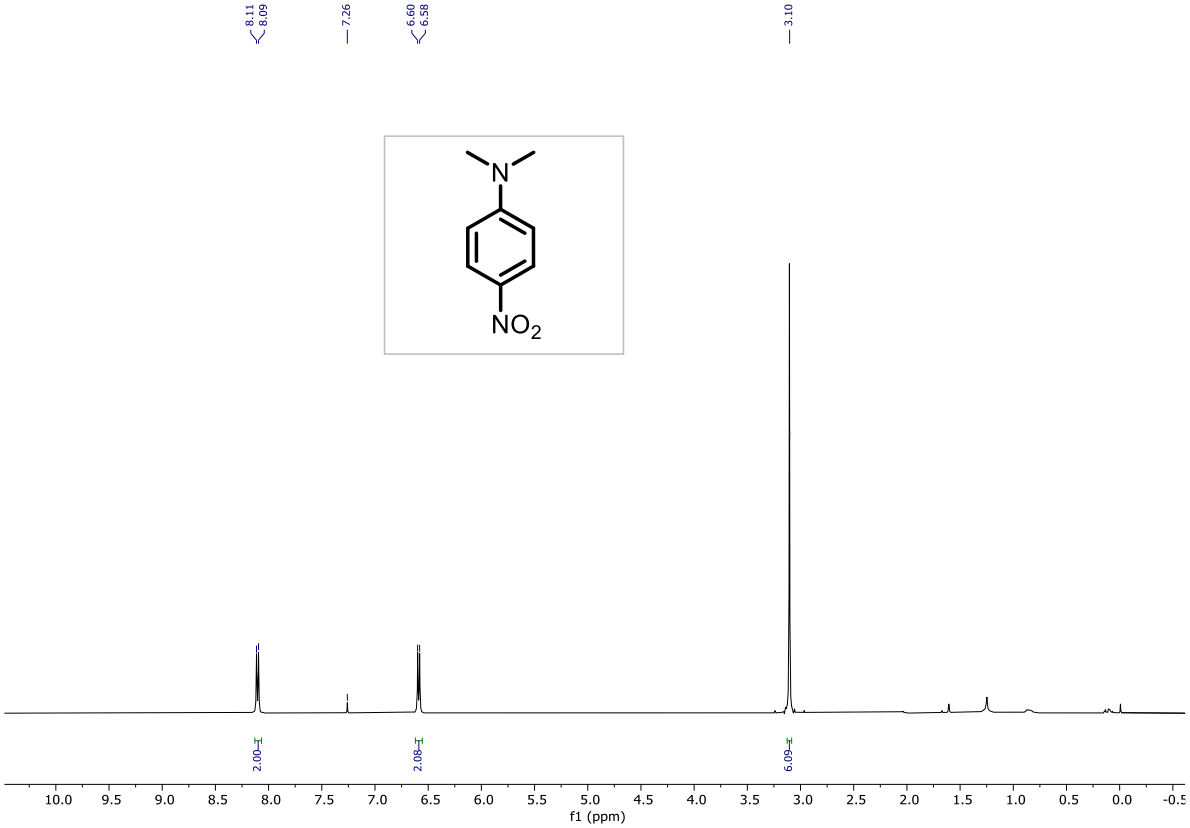
^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)



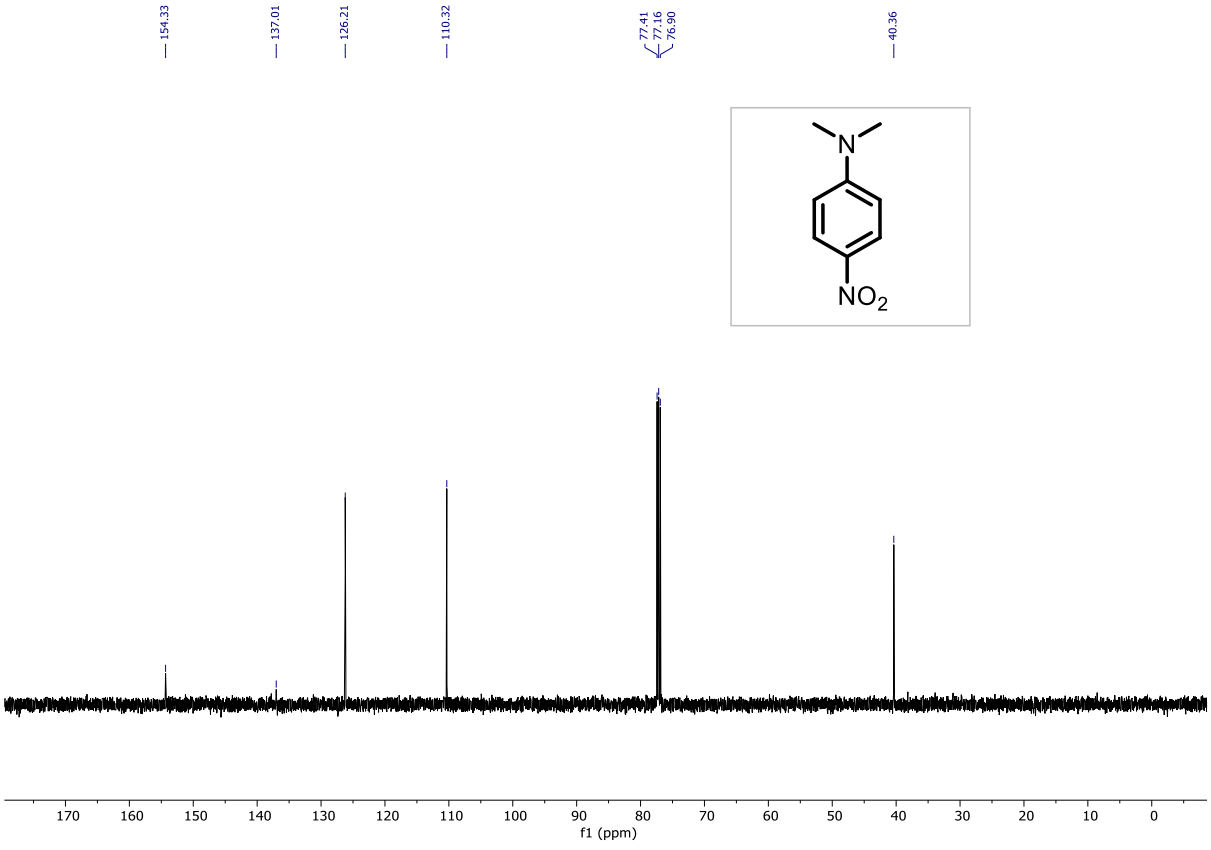


N, N-Dimethyl-4-nitroaniline (6b)

^{1}H NMR (500 MHz, $CDCl_3$)

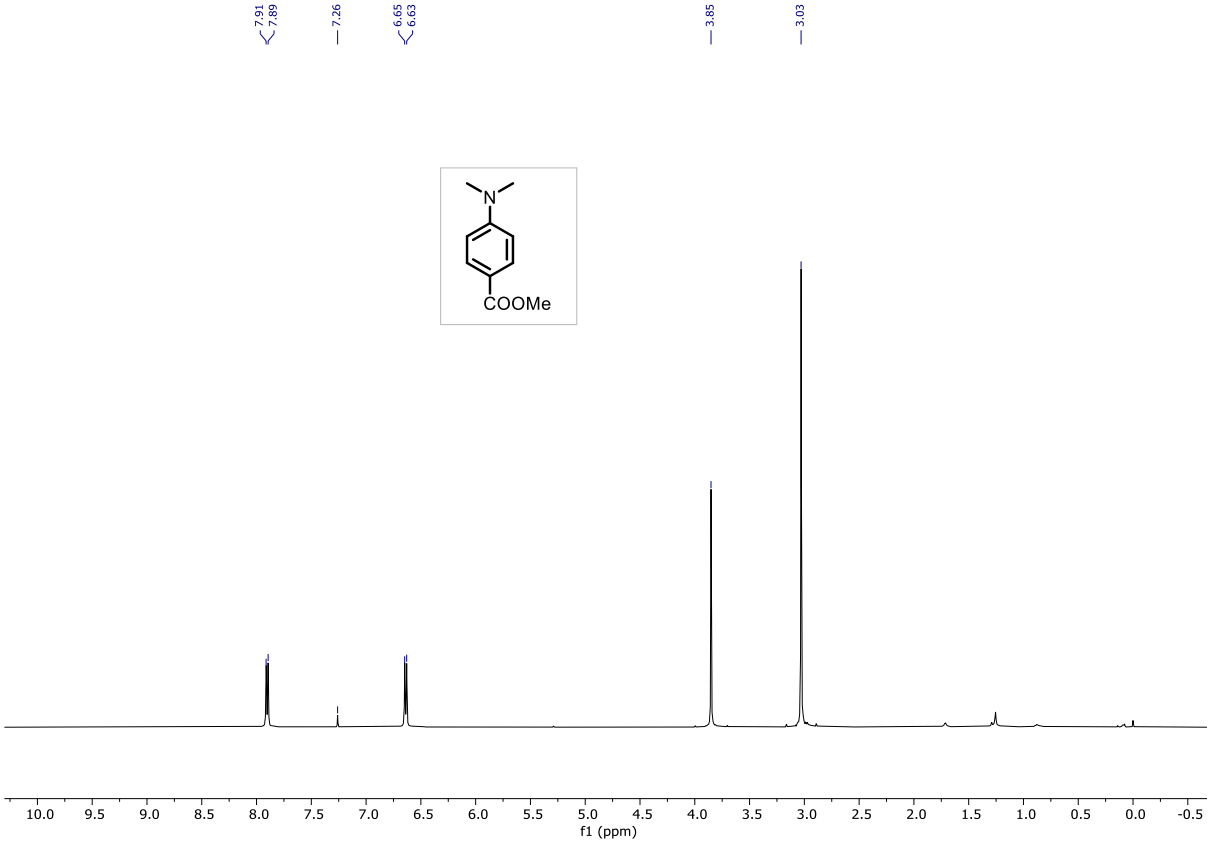


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

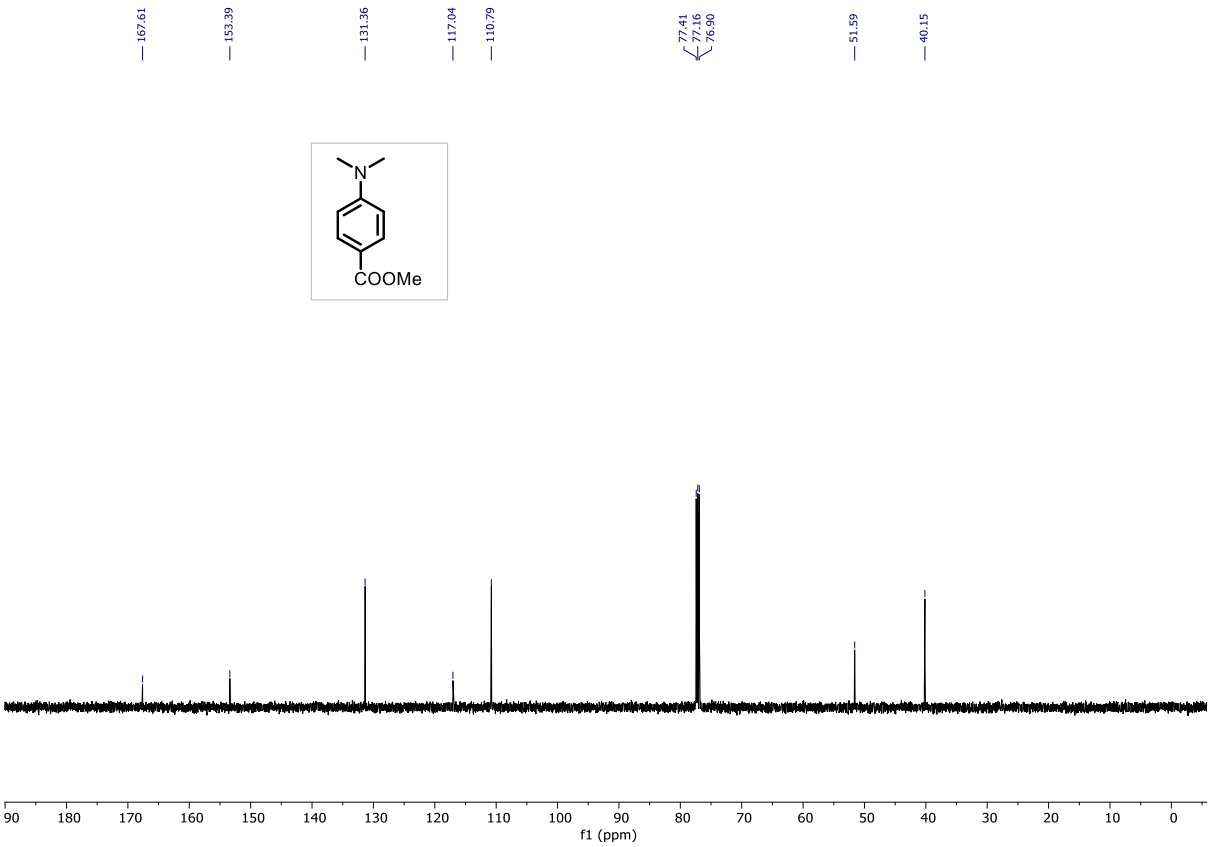


Methyl 4-(dimethylamino) benzoate (6d)

^{1}H NMR (500 MHz, $CDCl_3$)

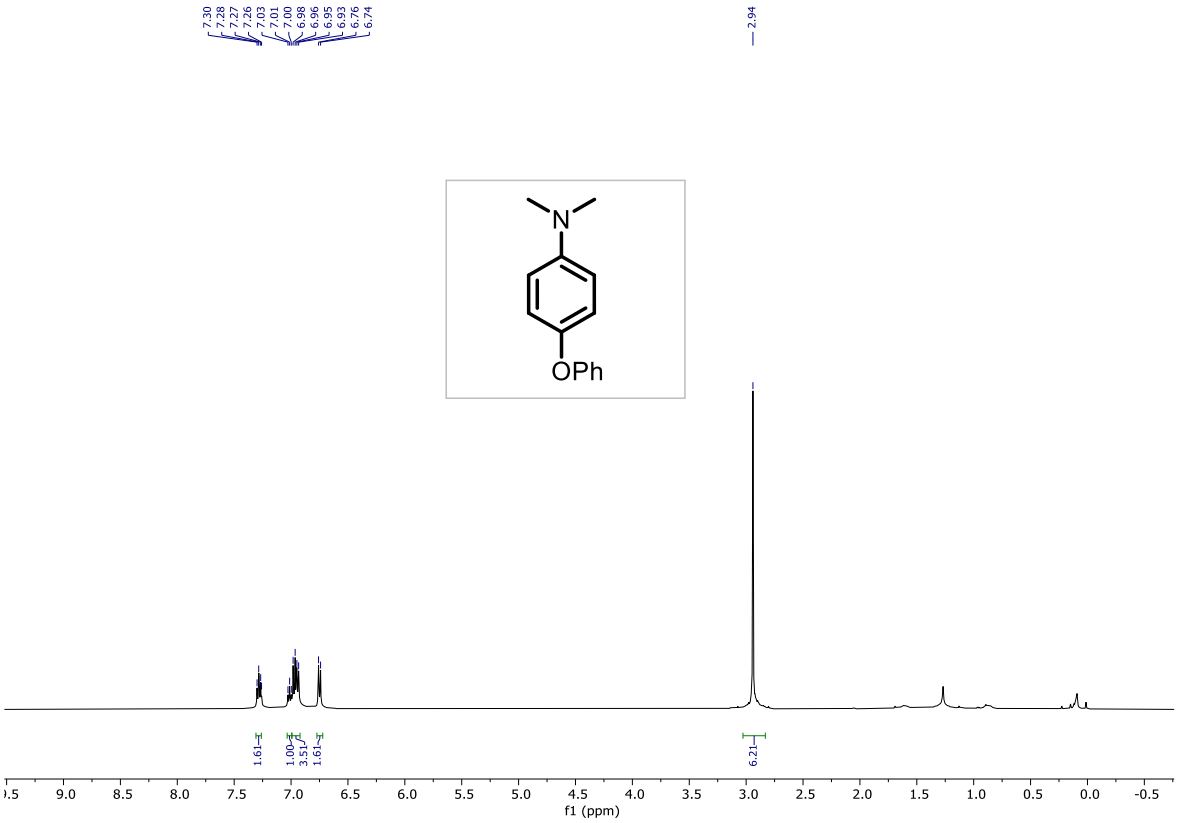


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

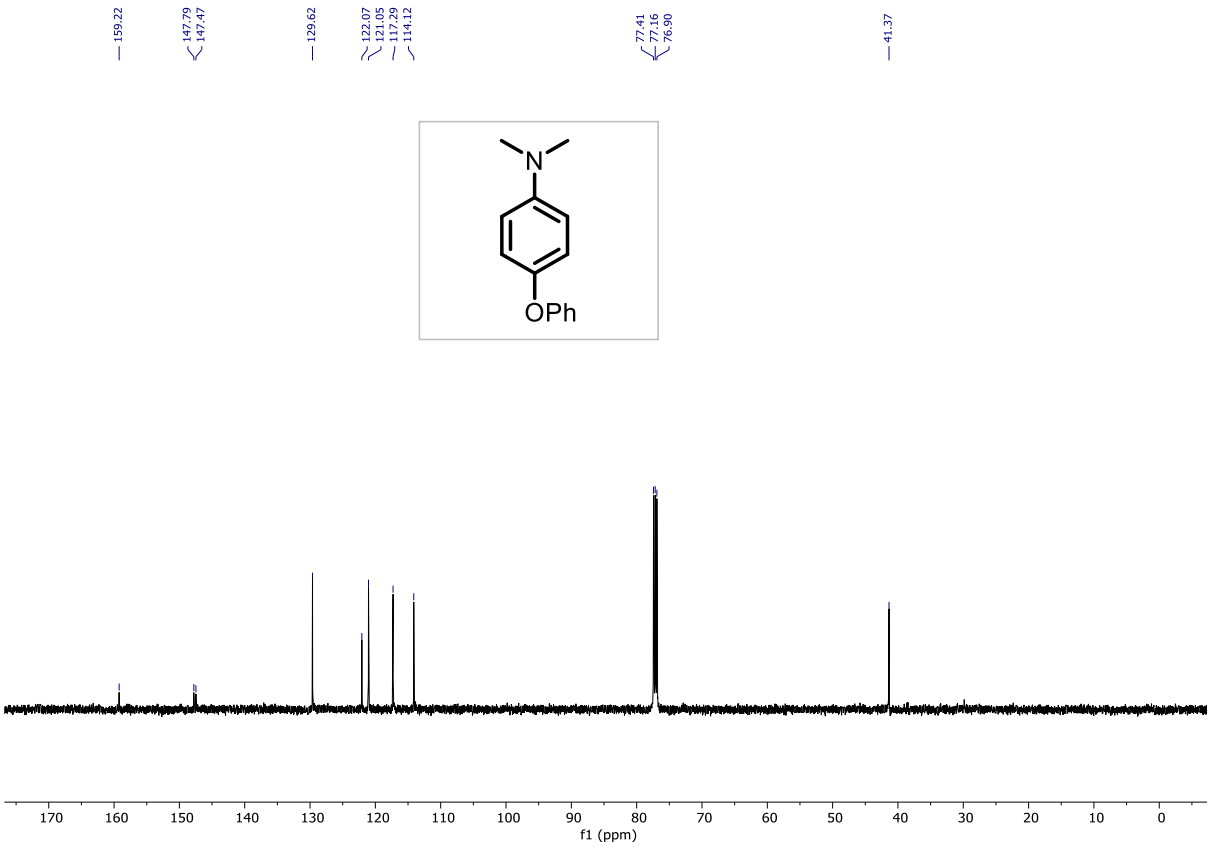


N, *N*-Dimethyl-4-phenoxyaniline (6e)

^{1}H NMR (500 MHz, $CDCl_3$)

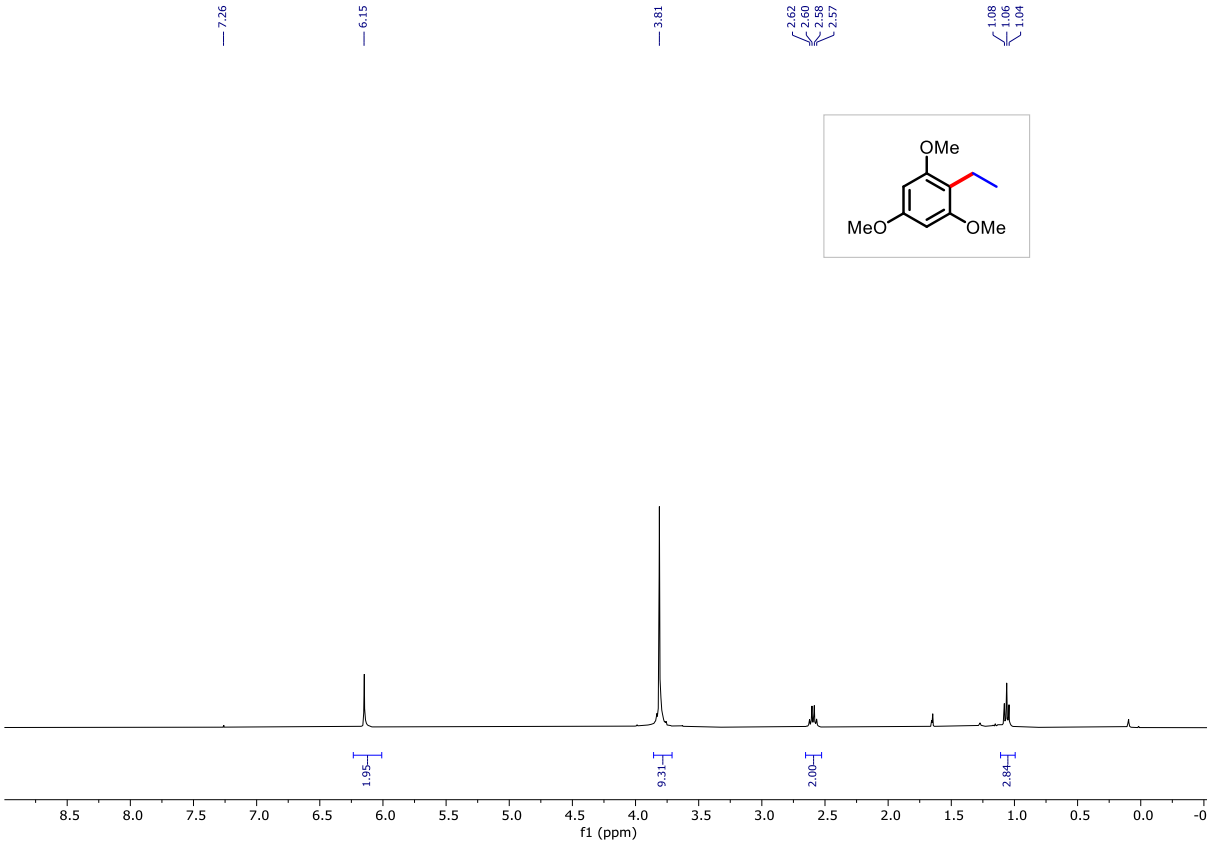


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

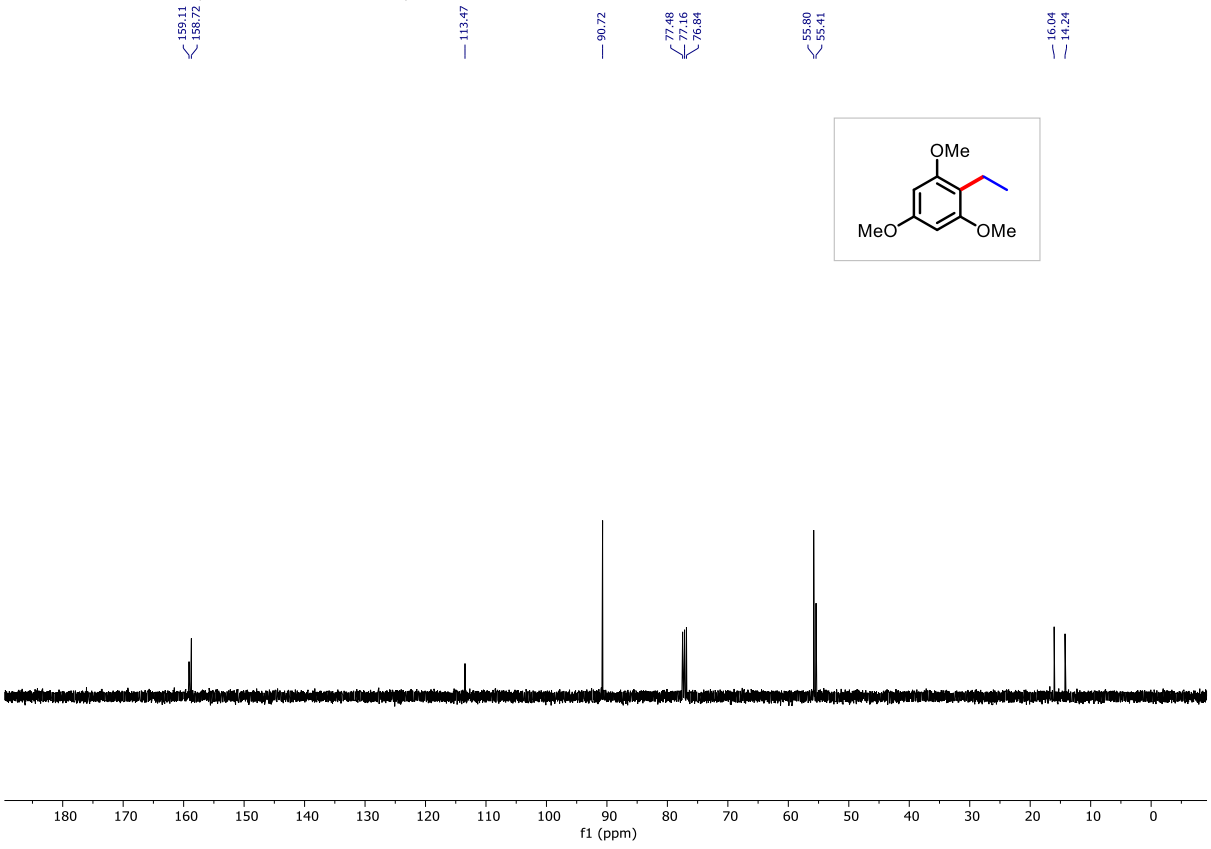


2-Ethyl-1,3,5-trimethoxybenzene (7a)

^{1}H NMR (400 MHz, $CDCl_3$)

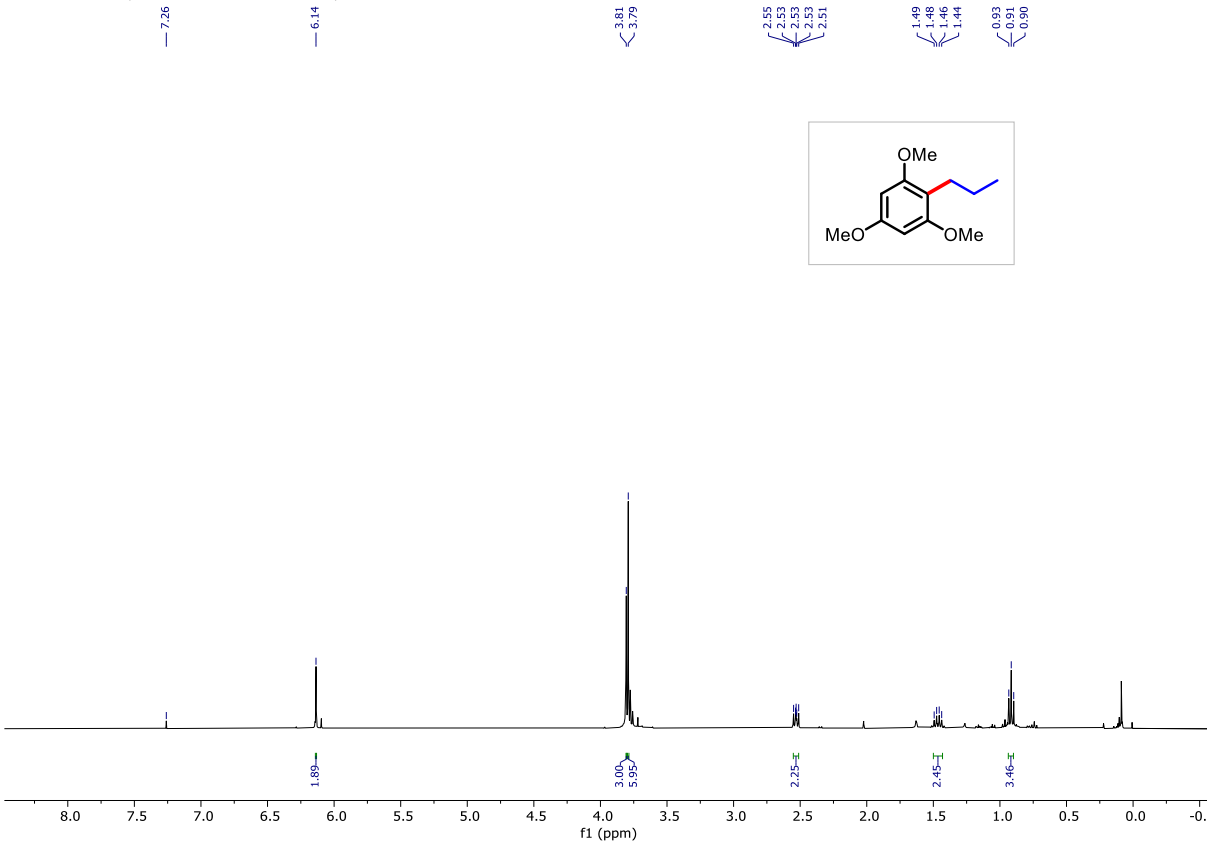


^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$)

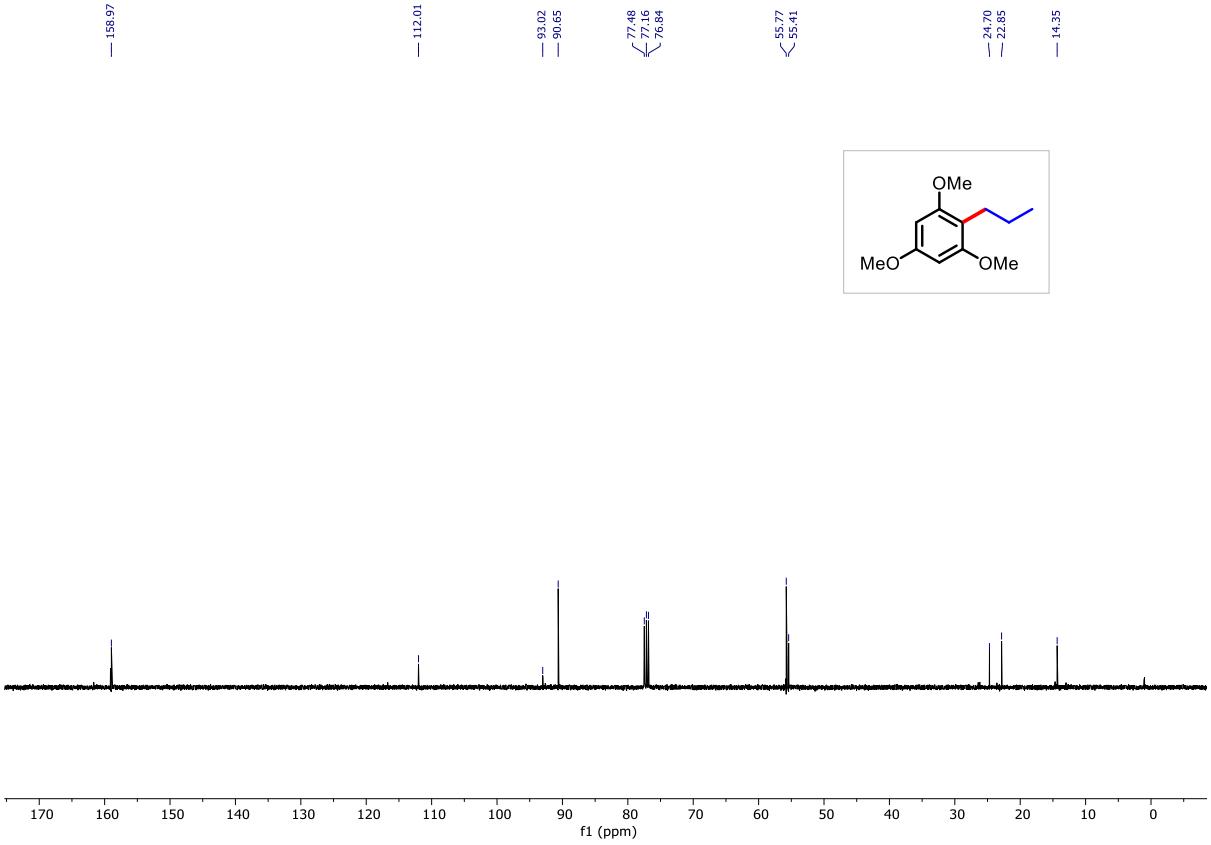


1,3,5-Trimethoxy-2-propylbenzene (7b)

^{1}H NMR (400 MHz, $CDCl_3$)

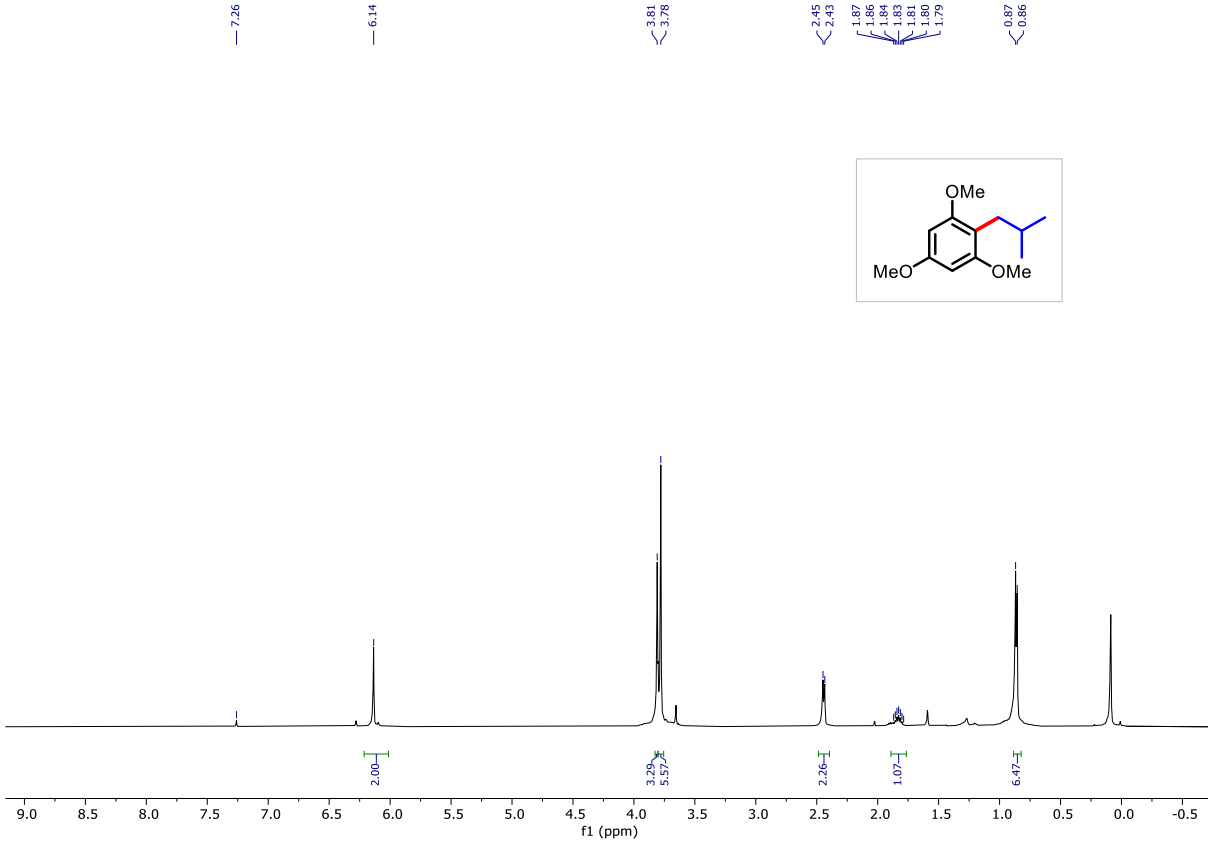


^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$)

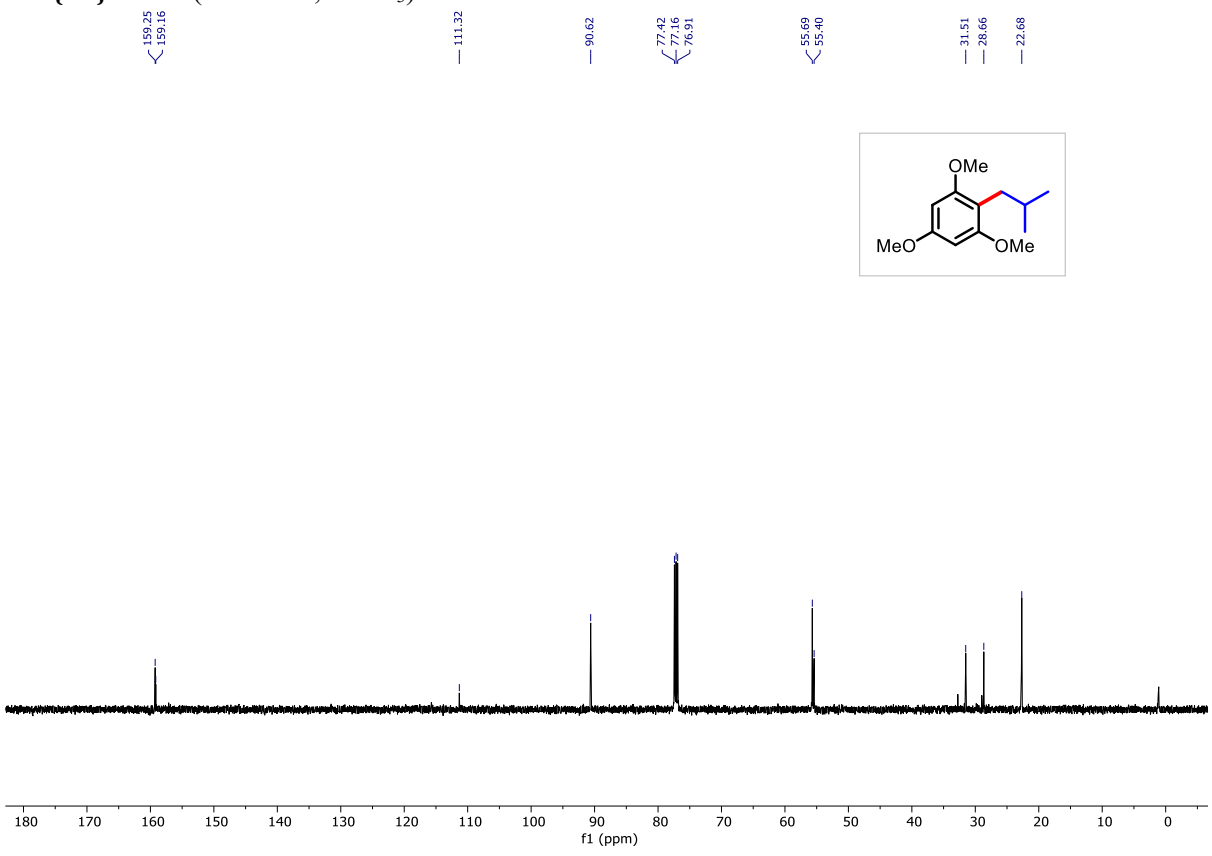


2-Isobutyl-1,3,5-trimethoxybenzene (7c)

^{1}H NMR (500 MHz, $CDCl_3$)

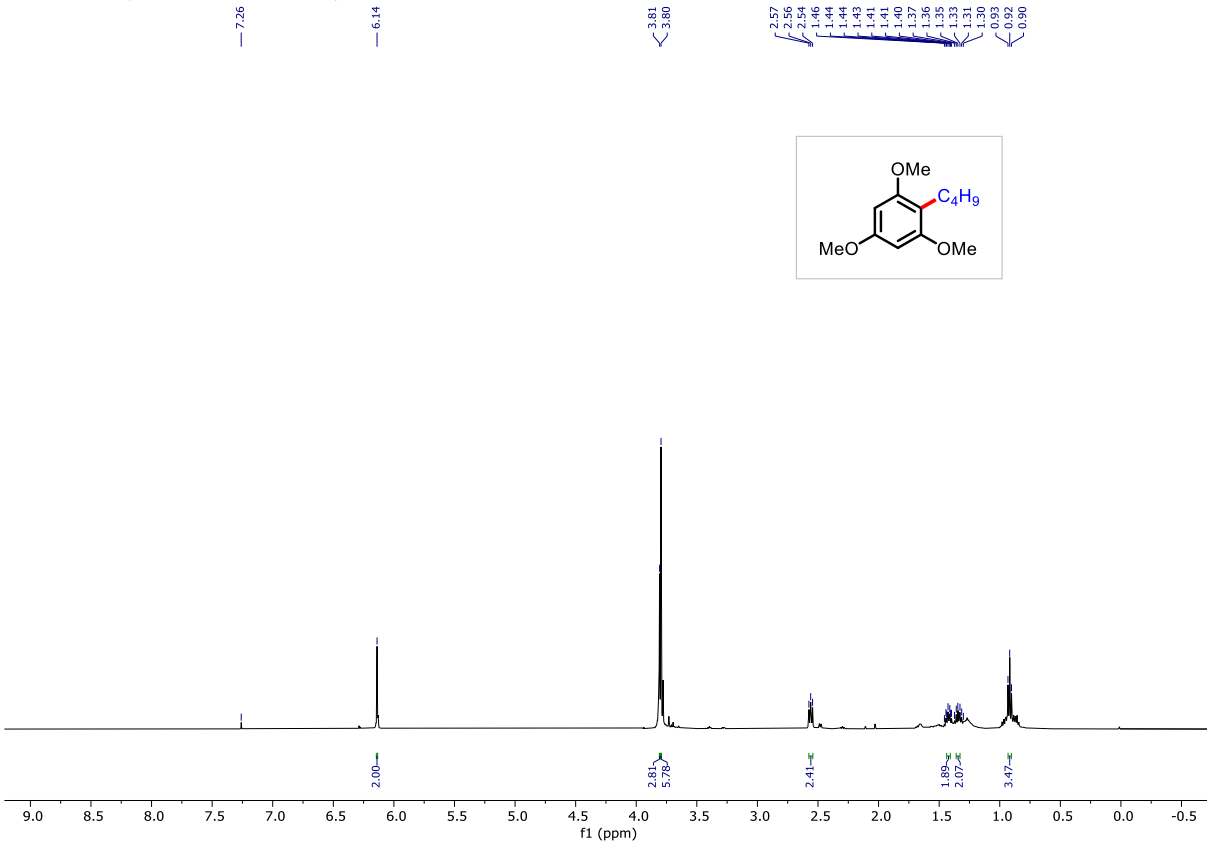


^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$)

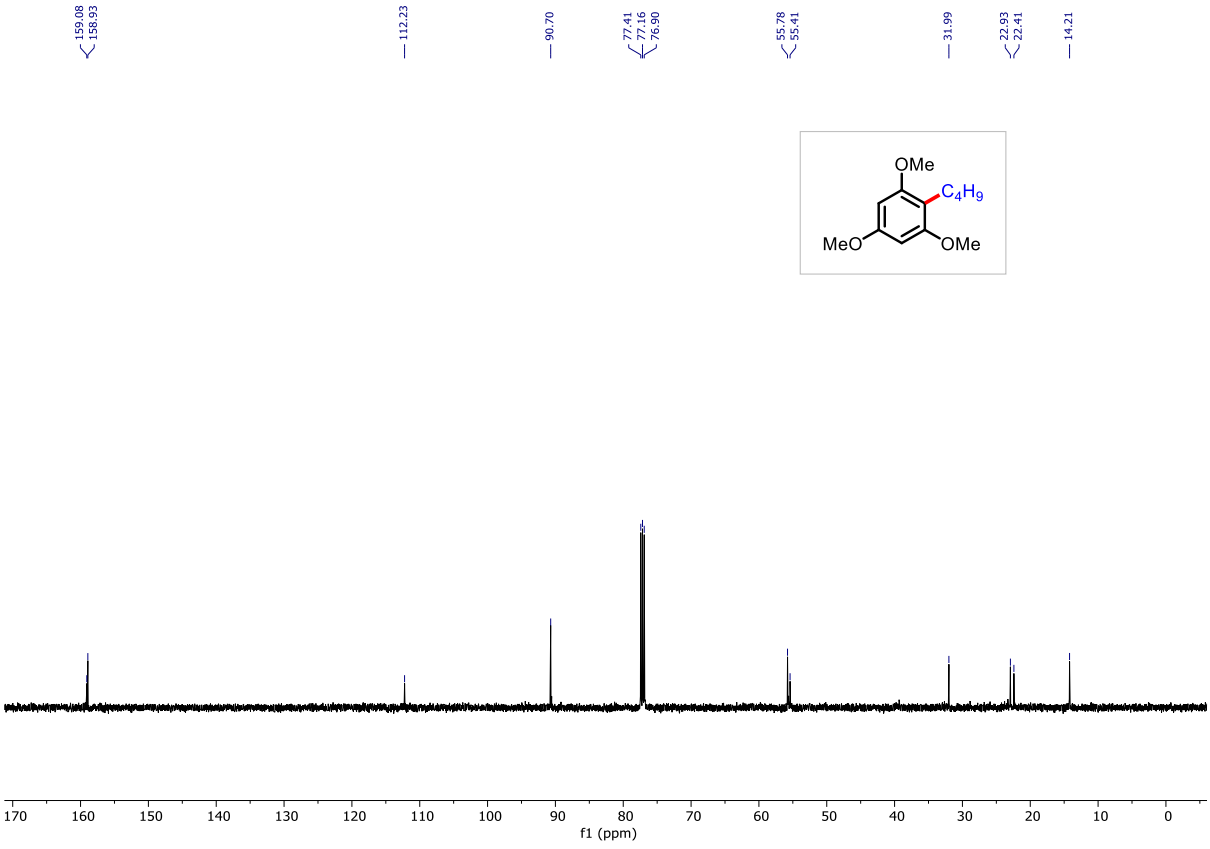


2-Butyl-1,3,5-trimethoxybenzene (7d)

^{1}H NMR (500 MHz, $CDCl_3$)

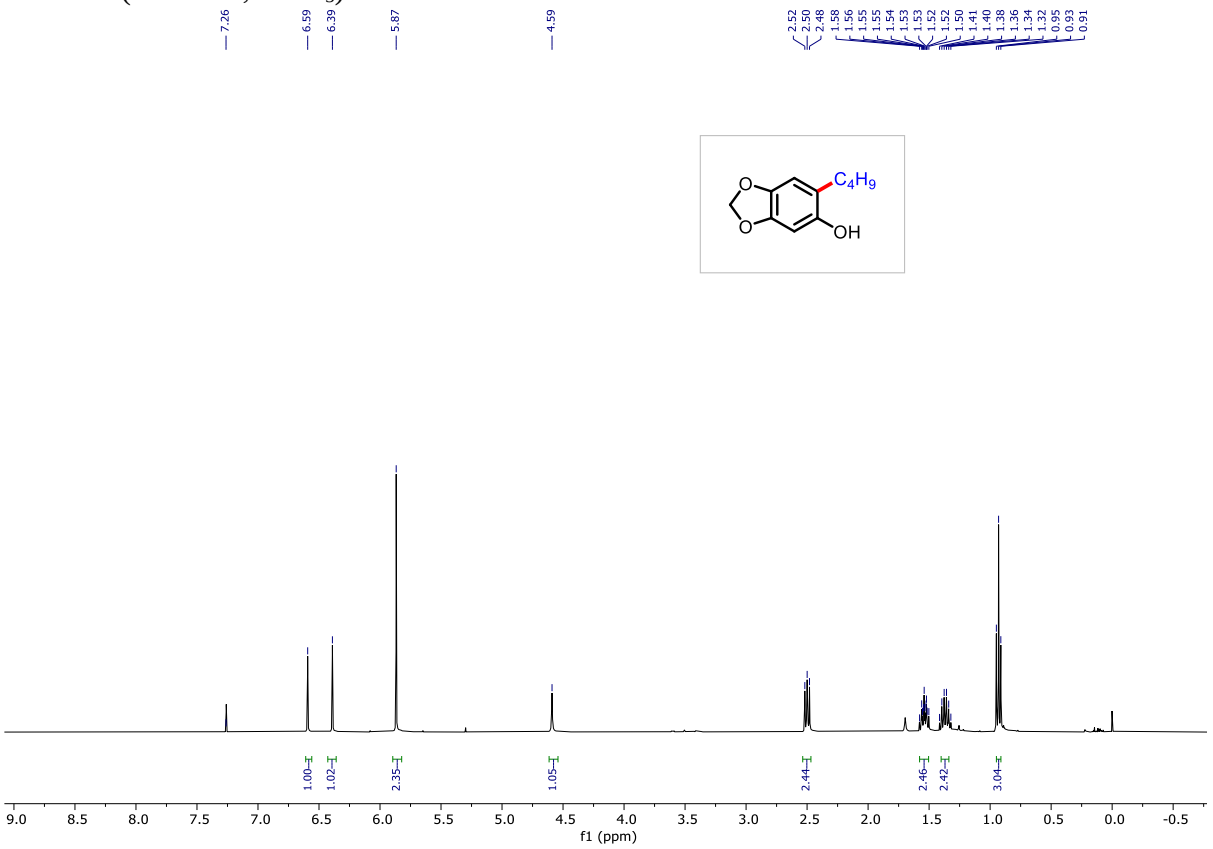


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

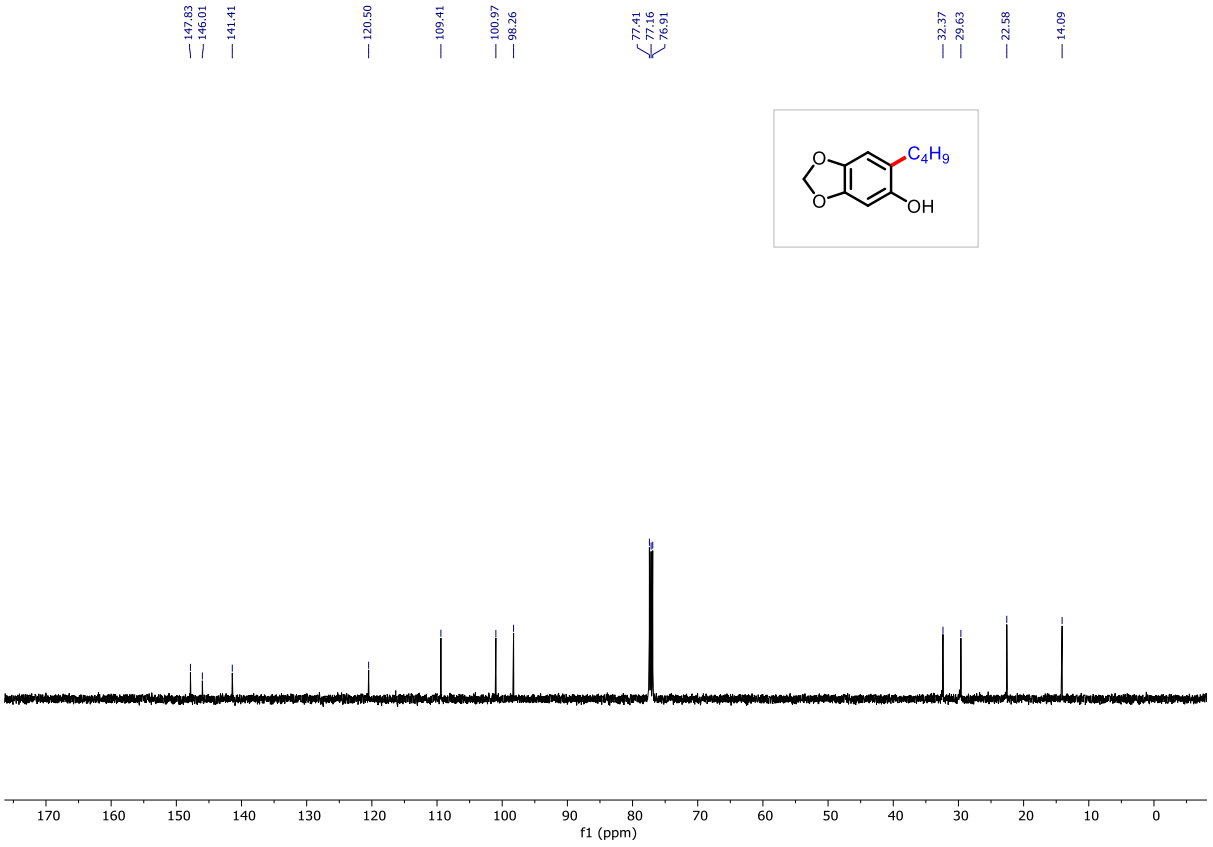


6-Butylbenzo[*d*][1,3]dioxol-5-ol (7e)

^{1}H NMR (400 MHz, $CDCl_3$)

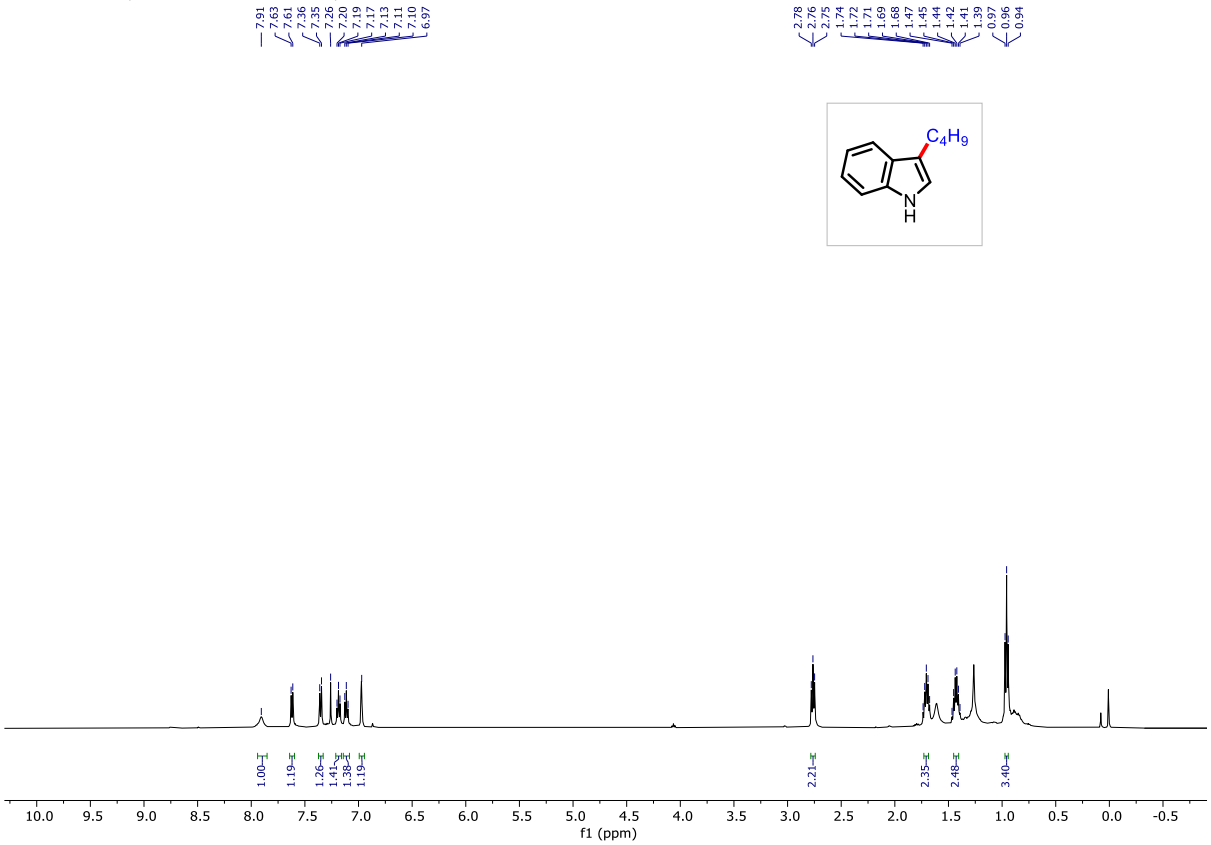


^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$)

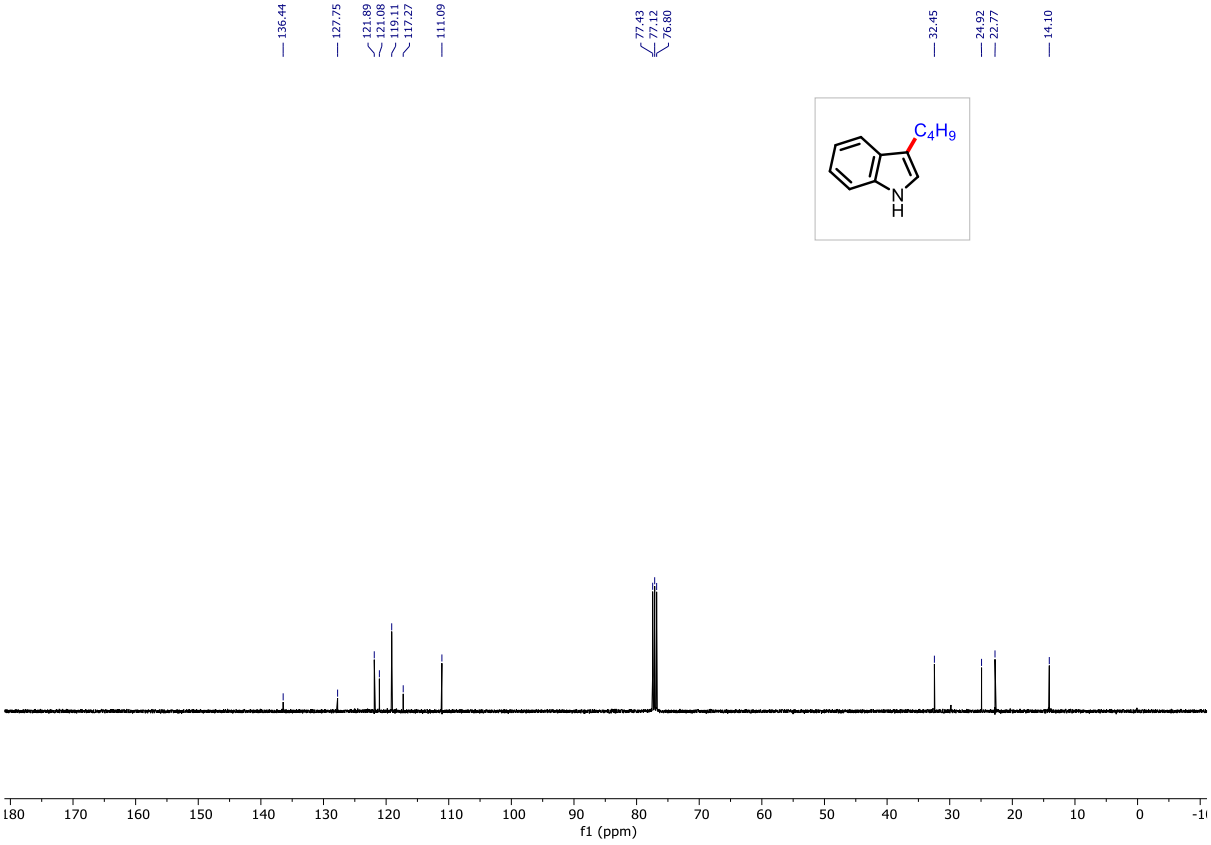


3-Butyl-1*H*-indole (7f)

^{1}H NMR (500 MHz, $CDCl_3$)

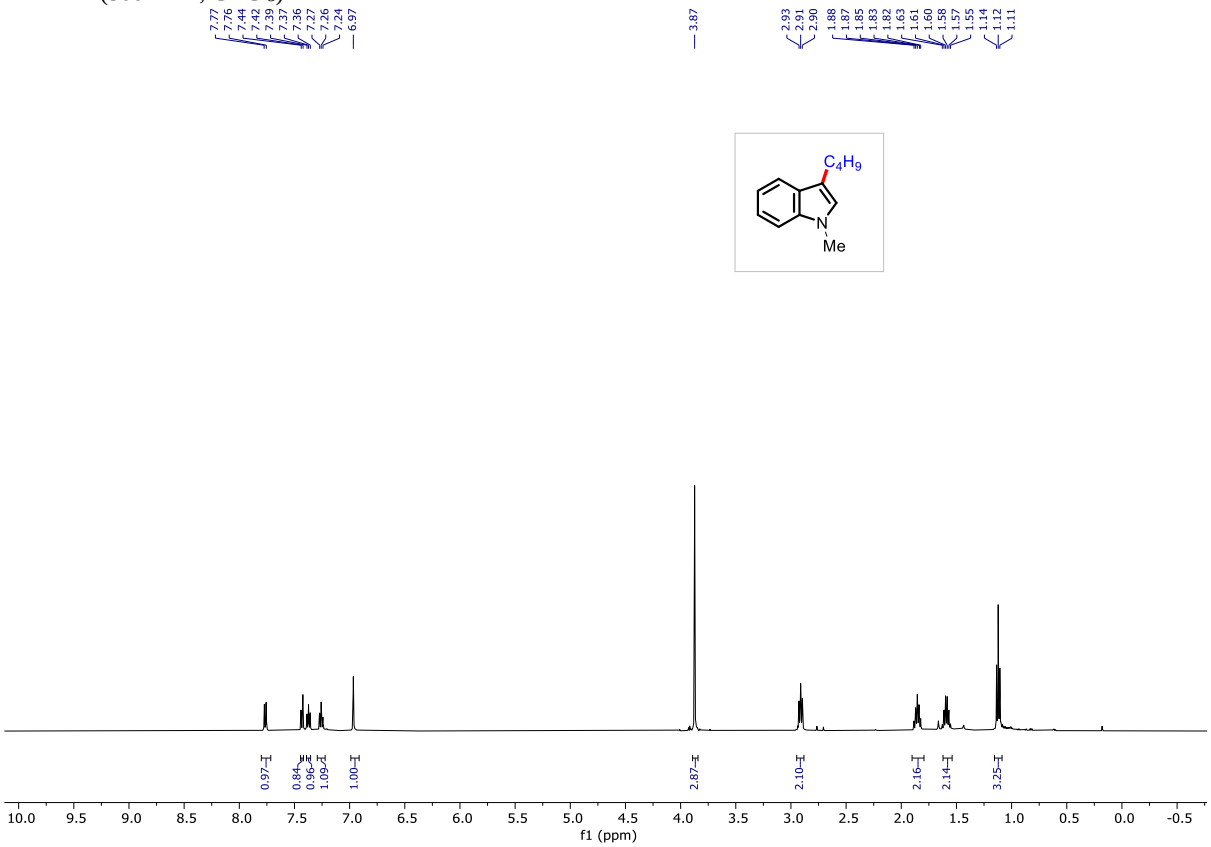


^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$)

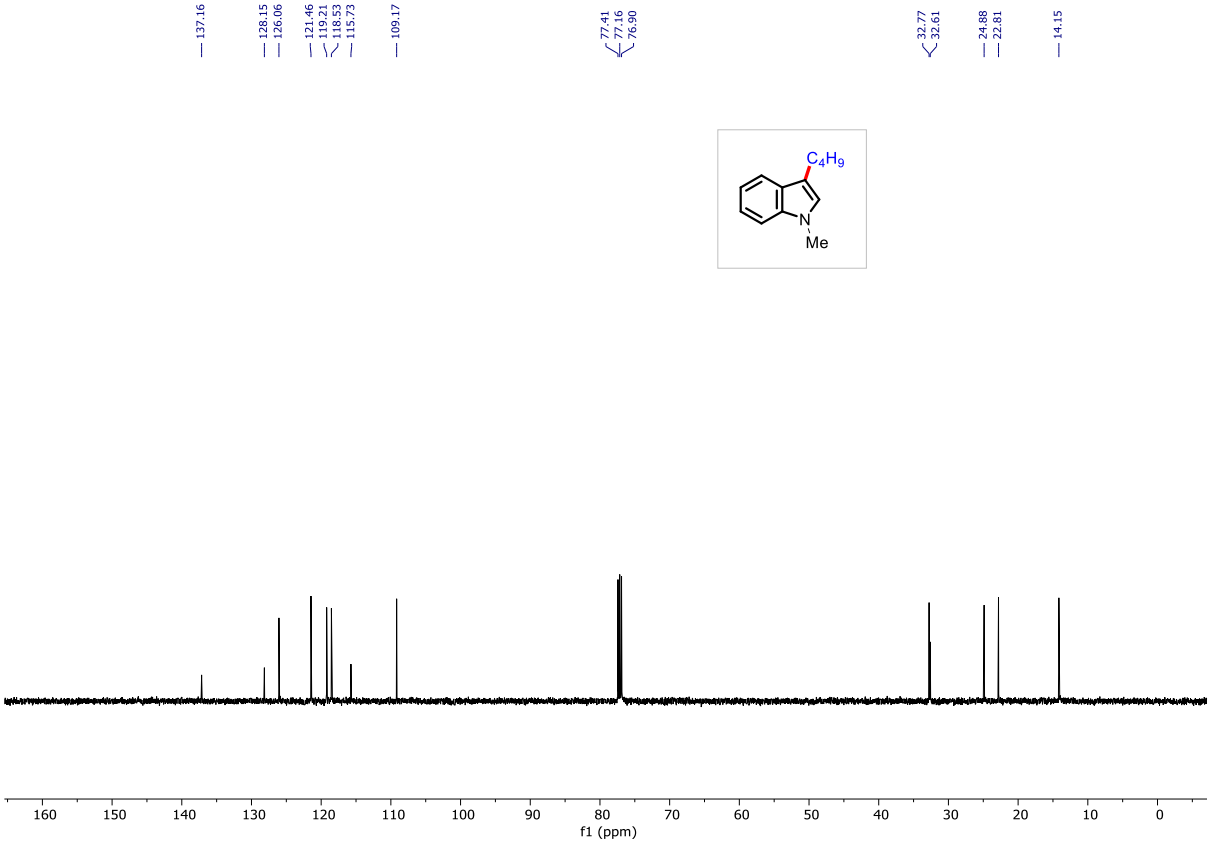


3-Butyl-1-methyl-1*H*-indole (7g)

^{1}H NMR (500 MHz, $CDCl_3$)

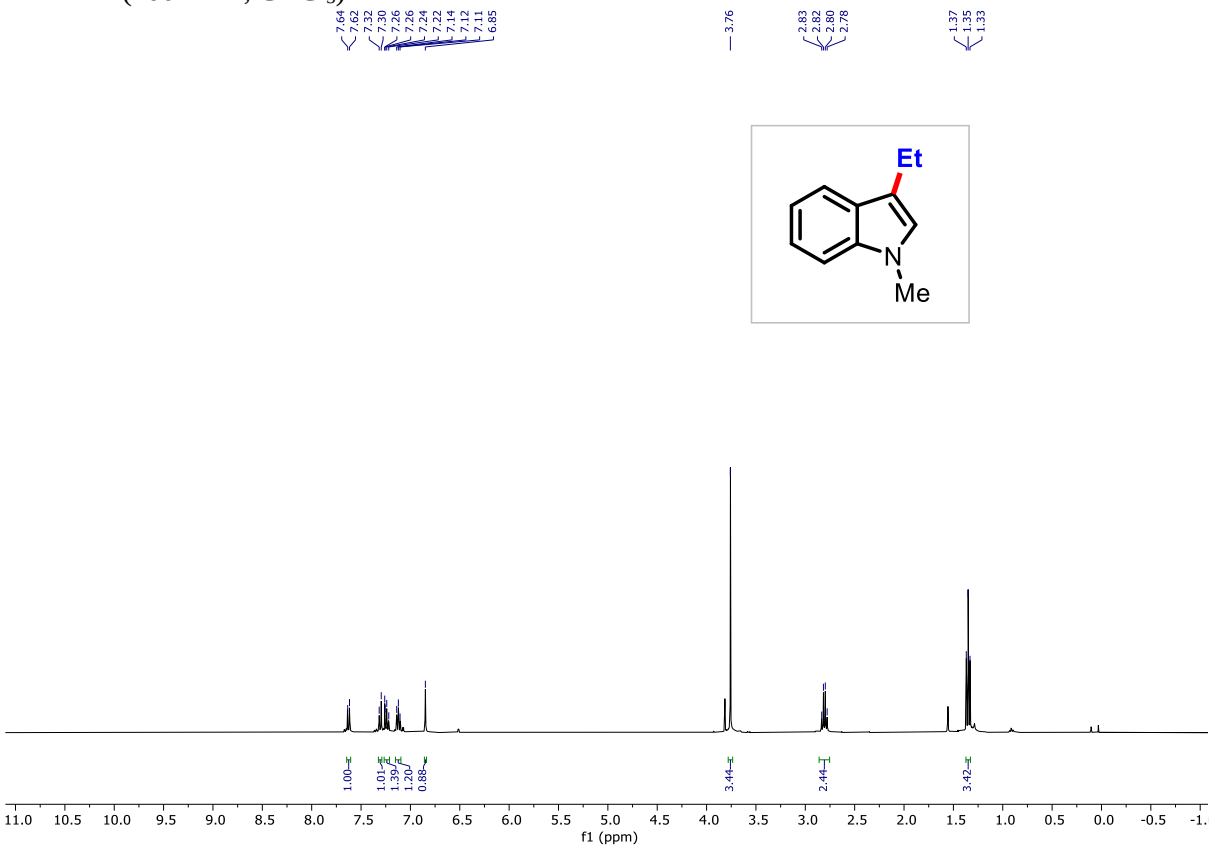


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

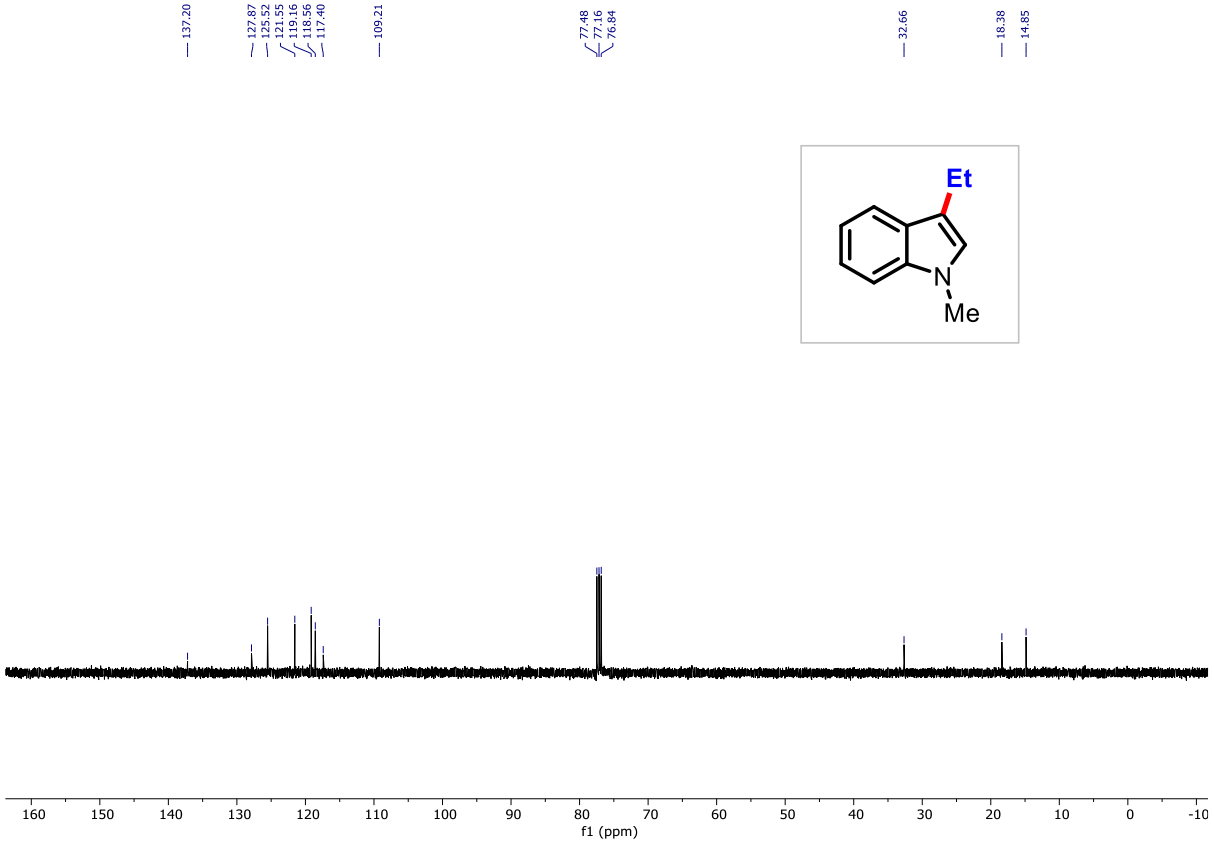


3-Ethyl-1-methyl-1H-indole (7h)

^{1}H NMR (400 MHz, $CDCl_3$)

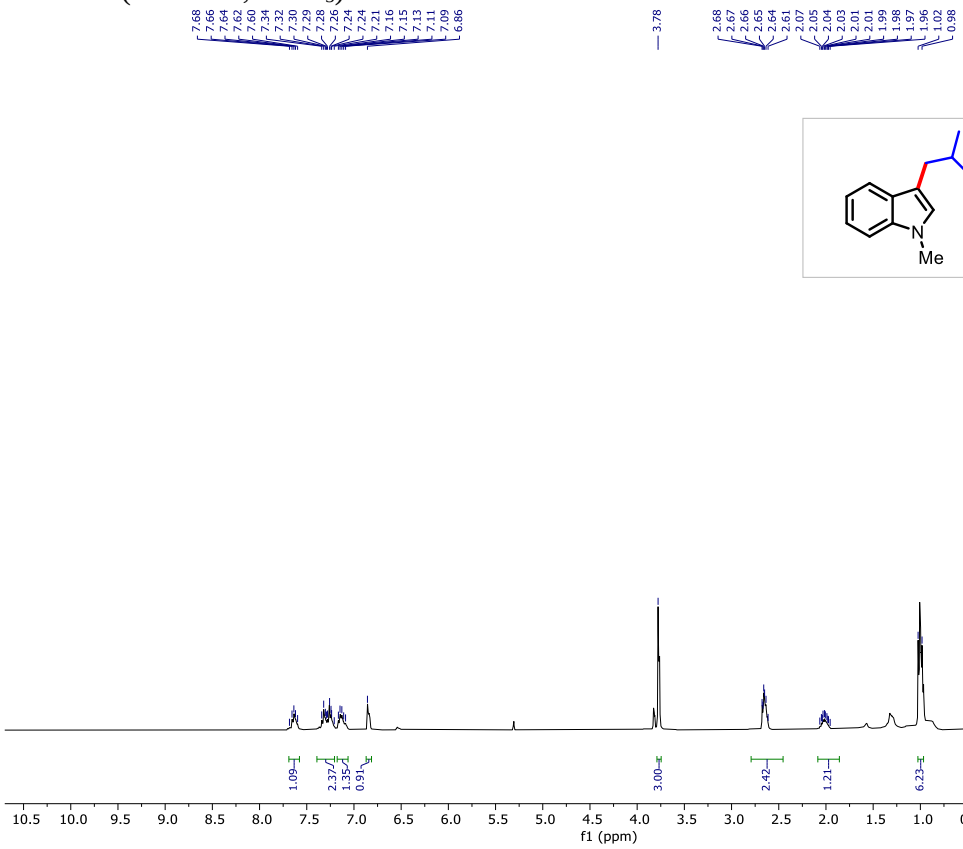


^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$)

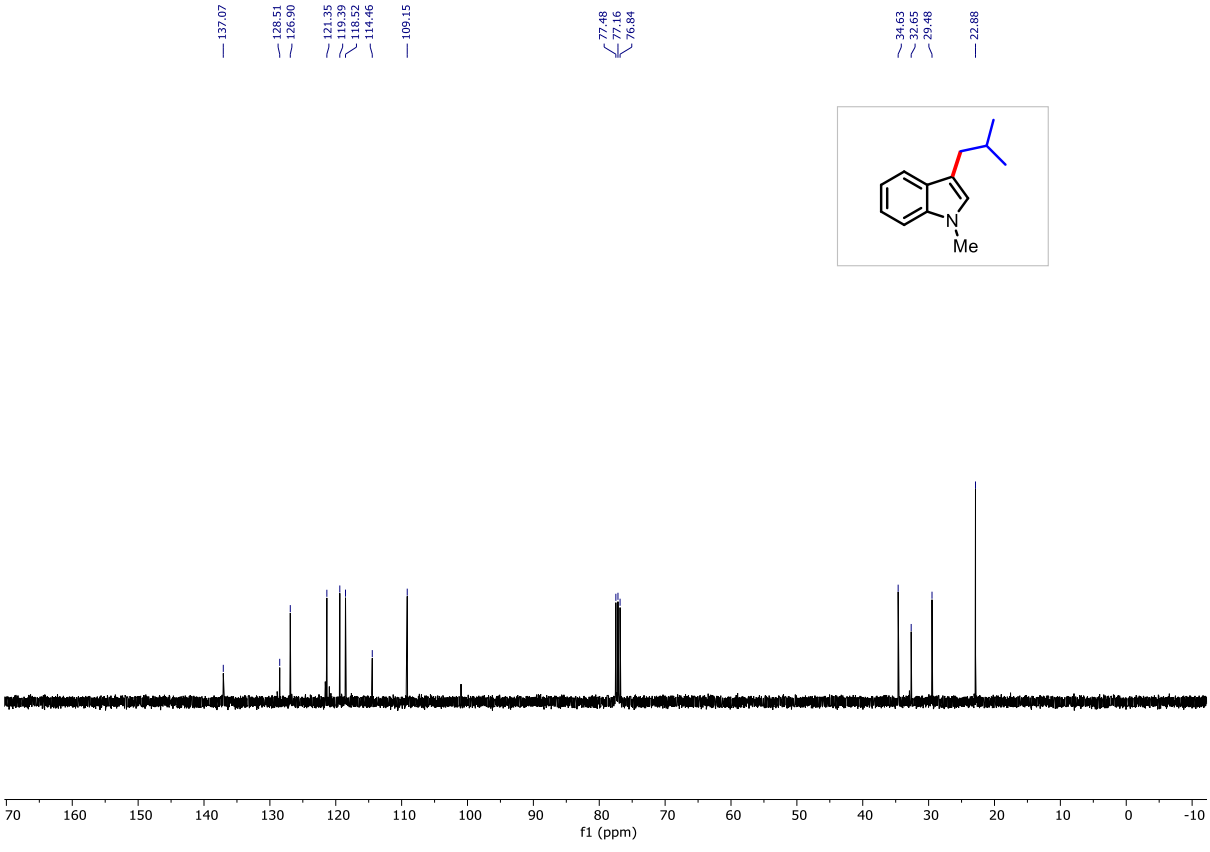


3-Isobutyl-1-methyl-1*H*-indole (7i)

^{1}H NMR (400 MHz, $CDCl_3$)

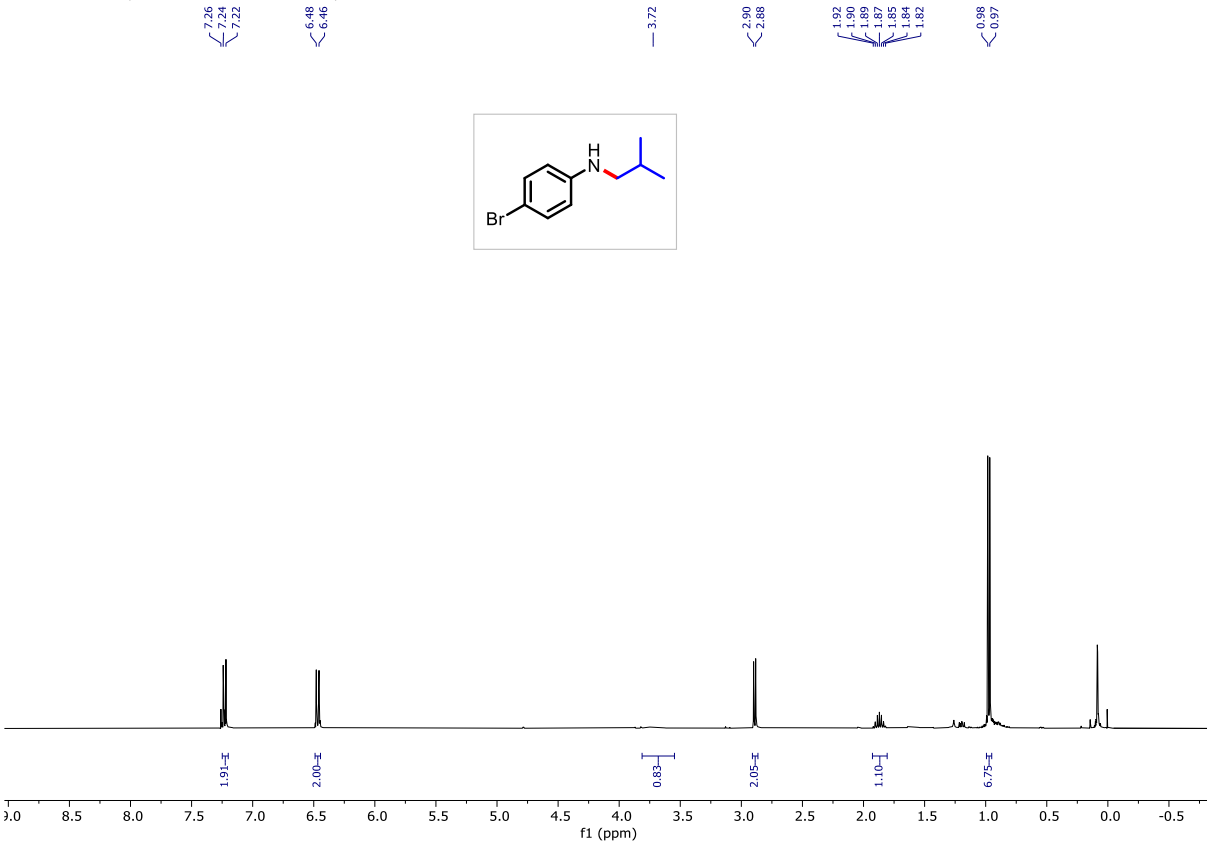


^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$)

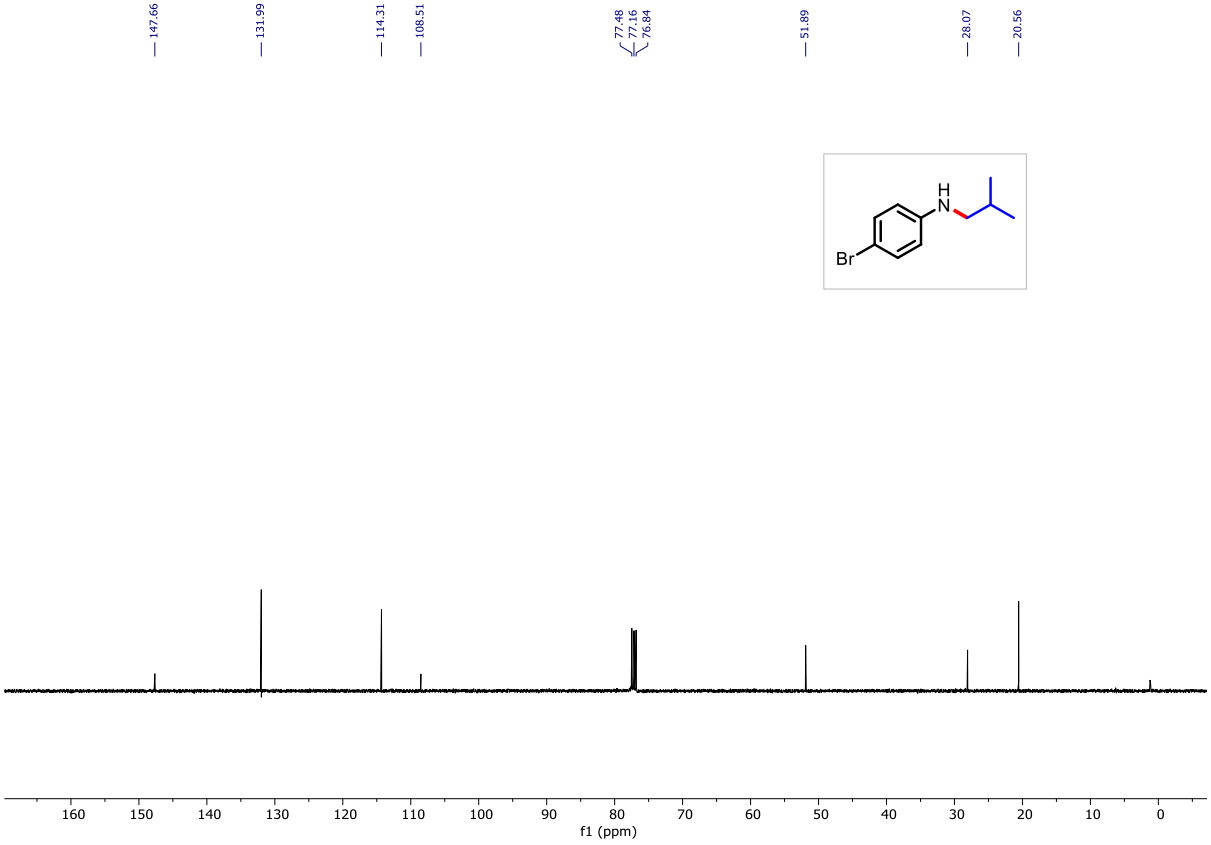


4-Bromo-*N*-isobutylaniline (7j)

^{1}H NMR (400 MHz, $CDCl_3$)

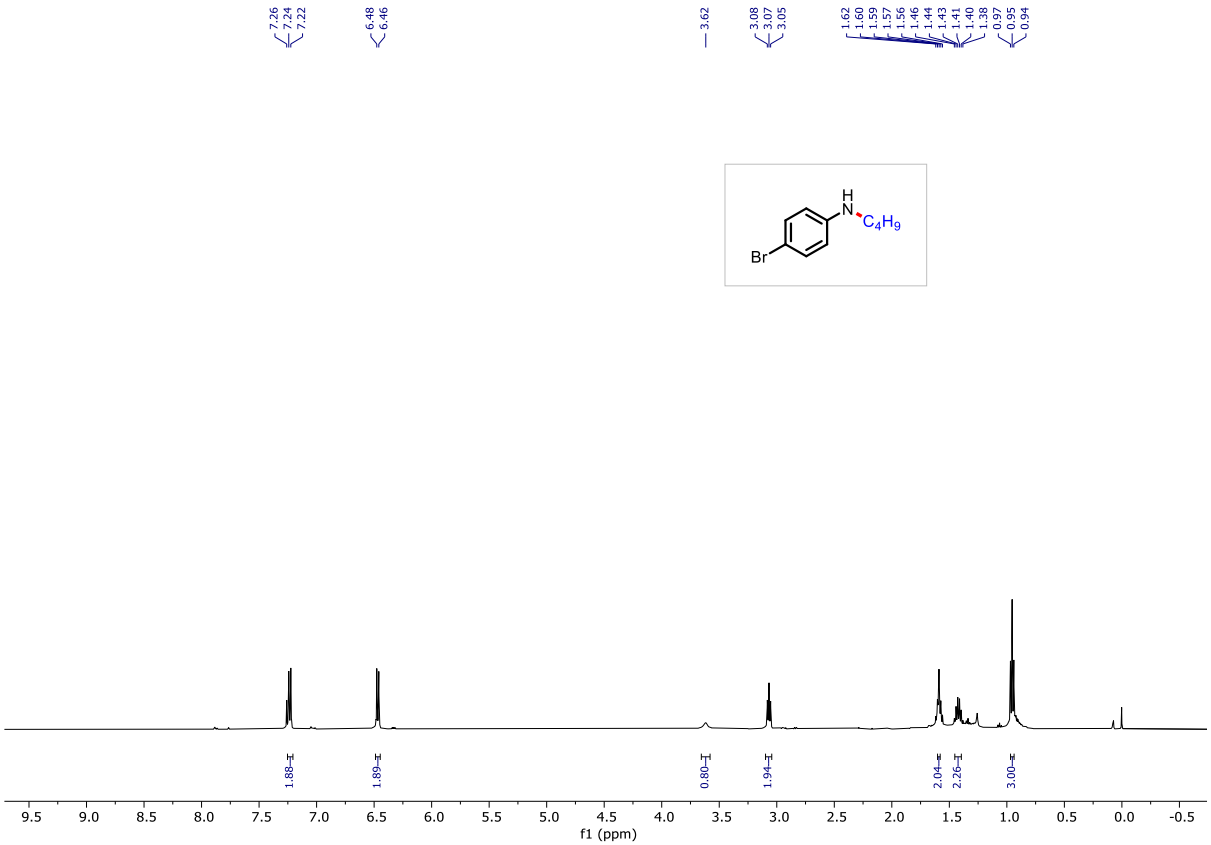


^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$)

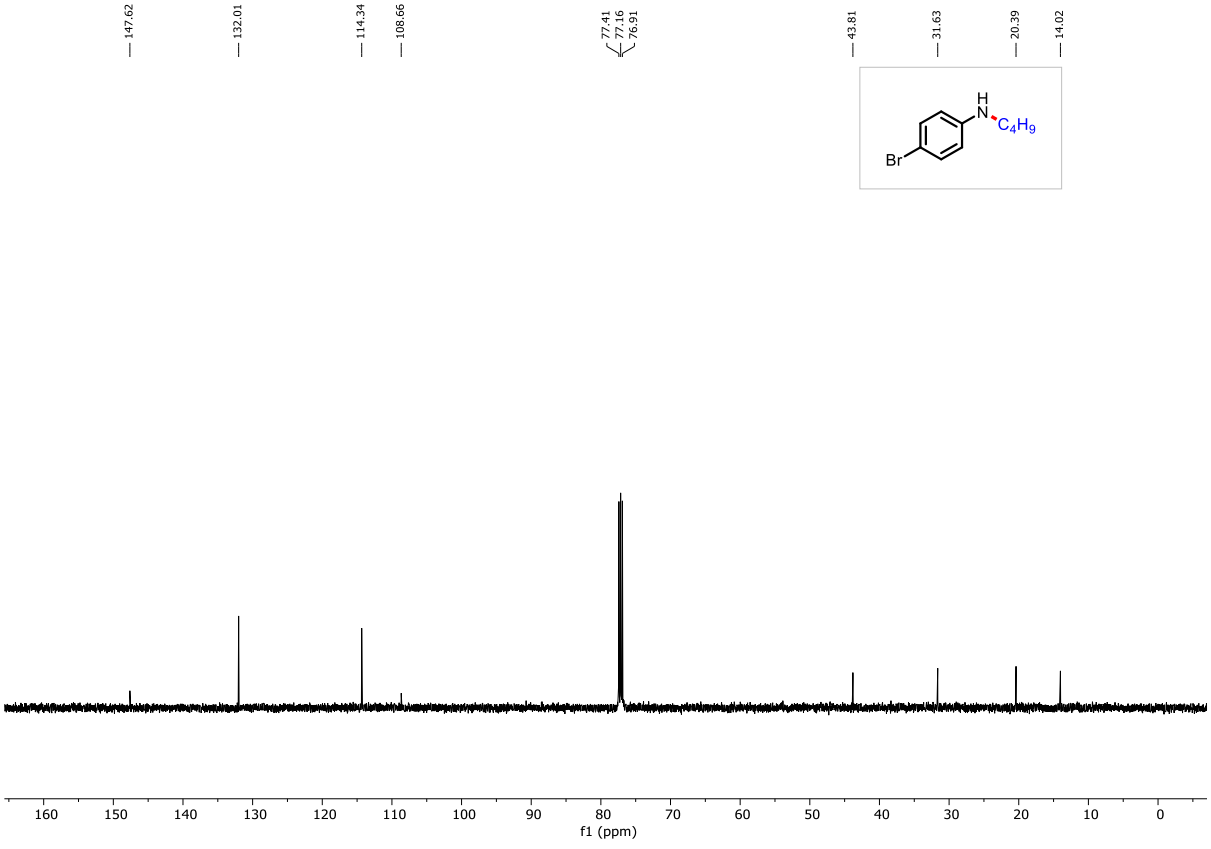


4-Bromo-*N*-butylaniline (7k)

^{1}H NMR (500 MHz, $CDCl_3$)

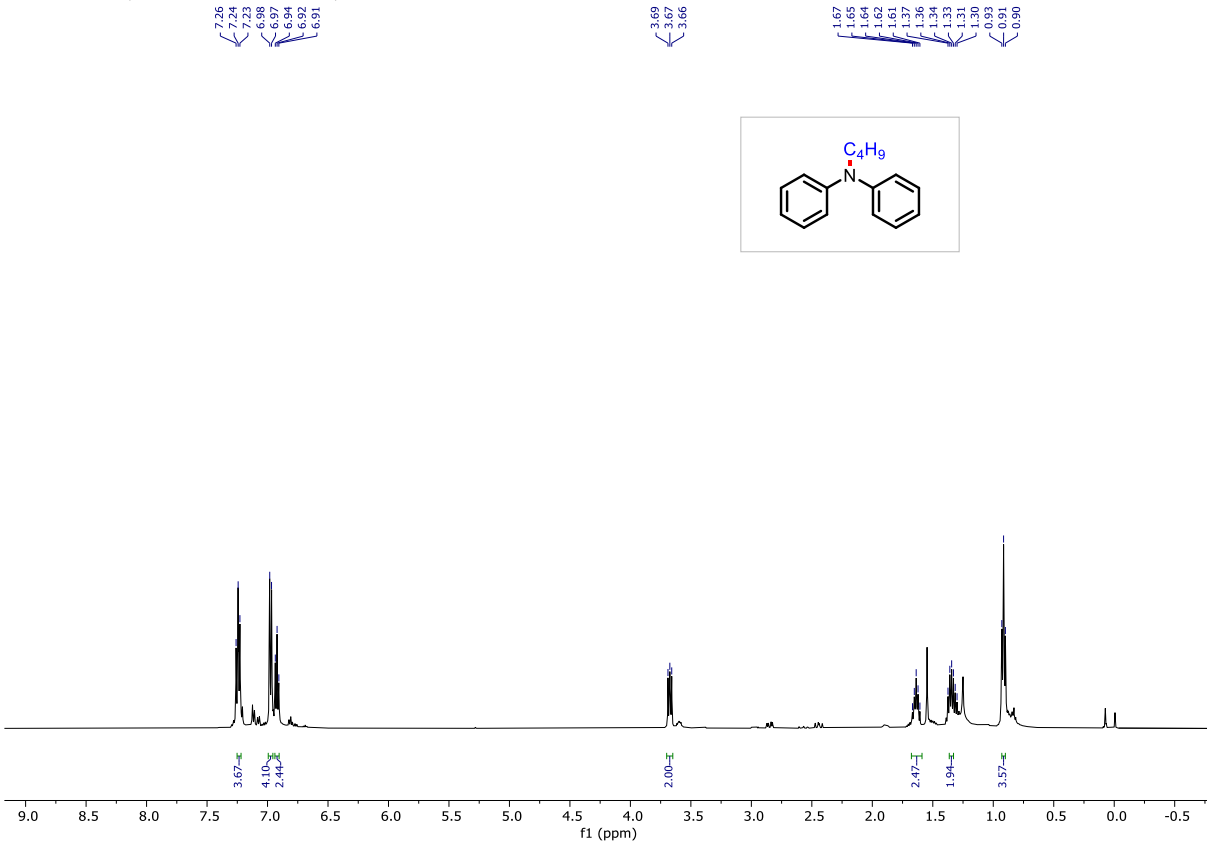


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

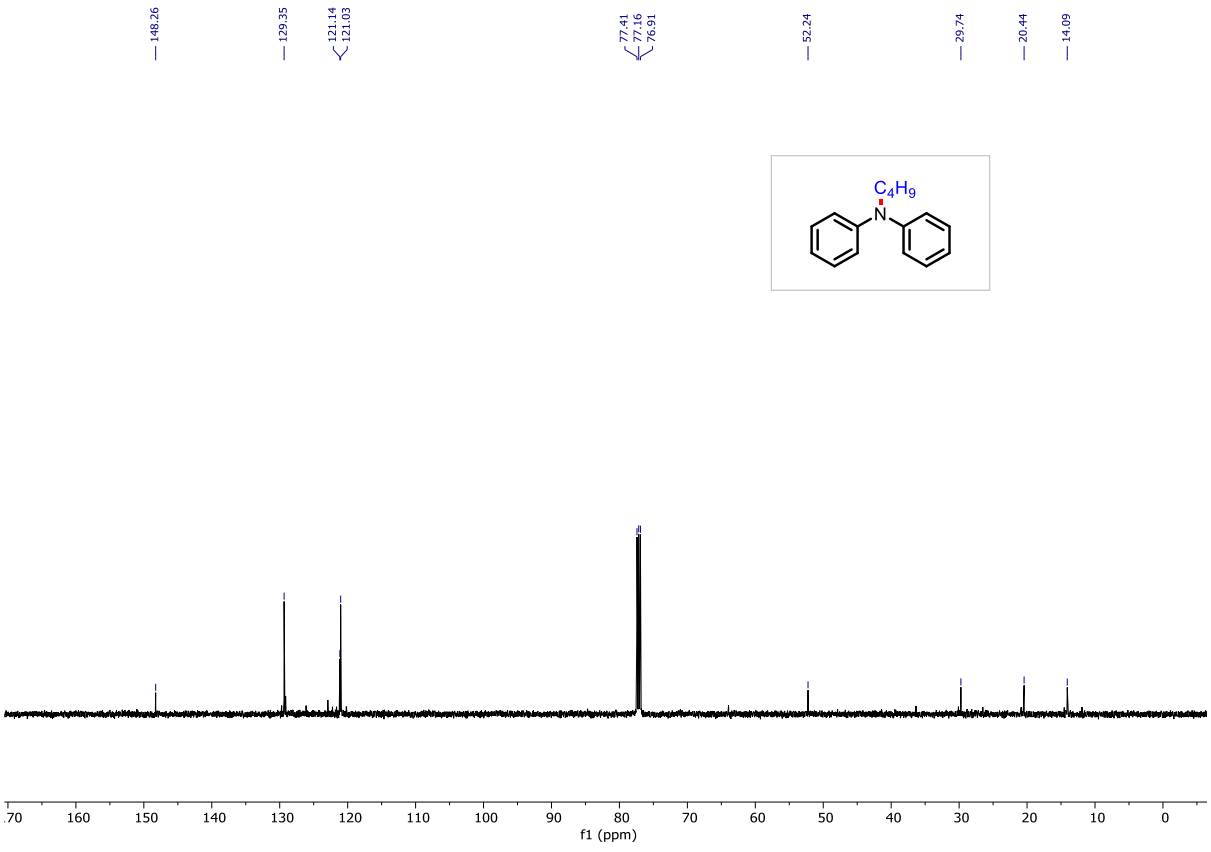


N-butyl-*N*-phenylaniline (7l)

^{1}H NMR (500 MHz, $CDCl_3$)

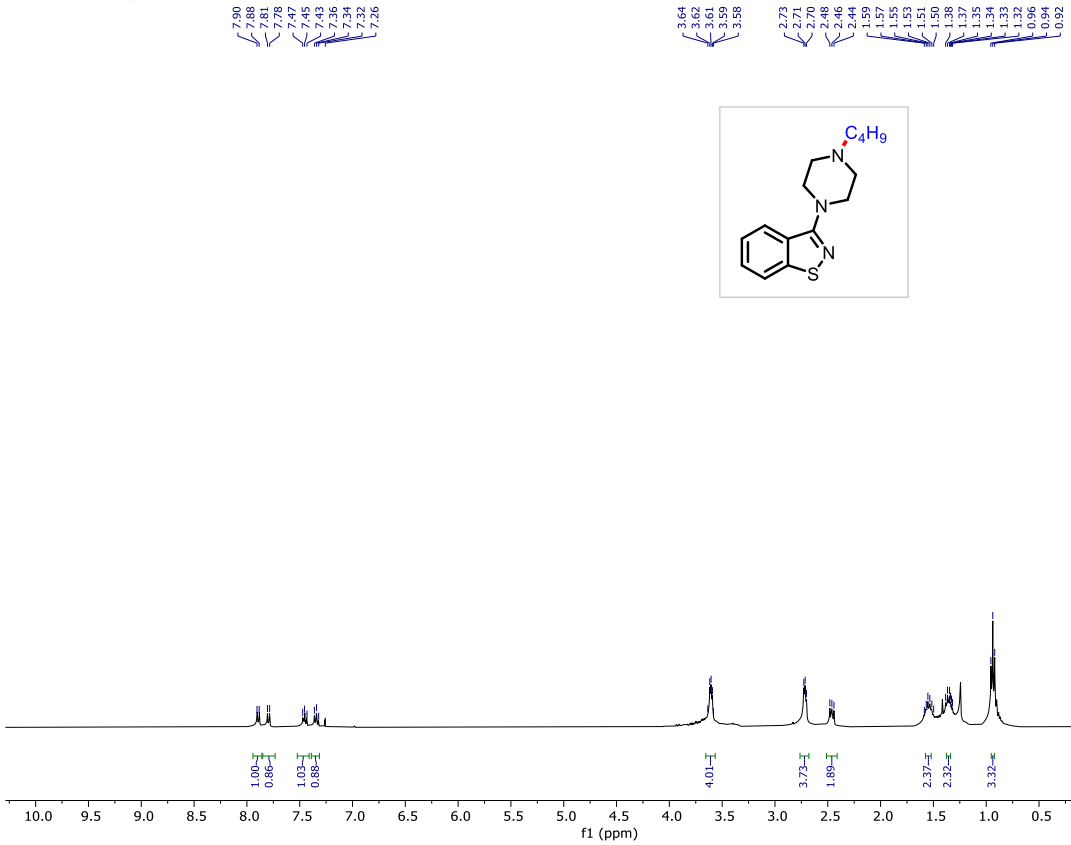


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

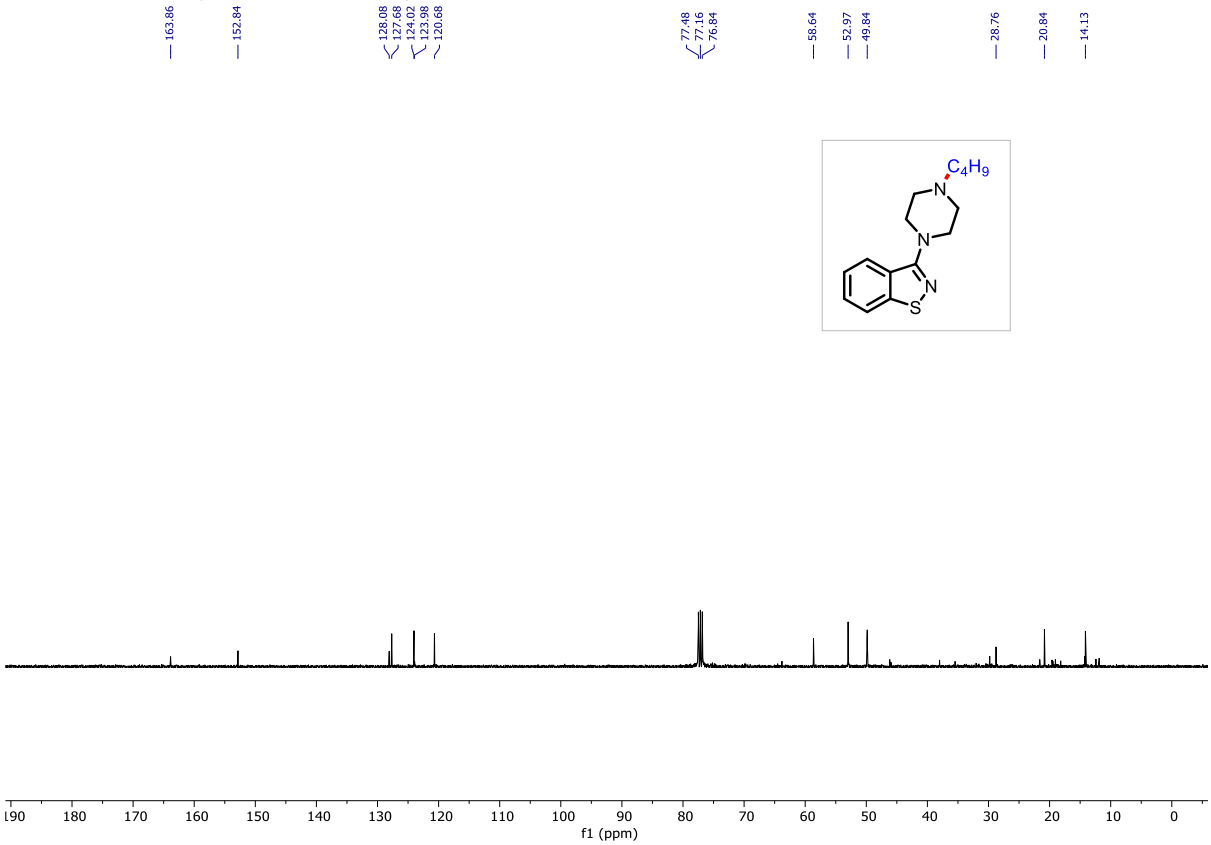


3-(4-Butylpiperazin-1-yl) benzo[*d*] isothiazole (7m)

^{1}H NMR (400 MHz, $CDCl_3$)

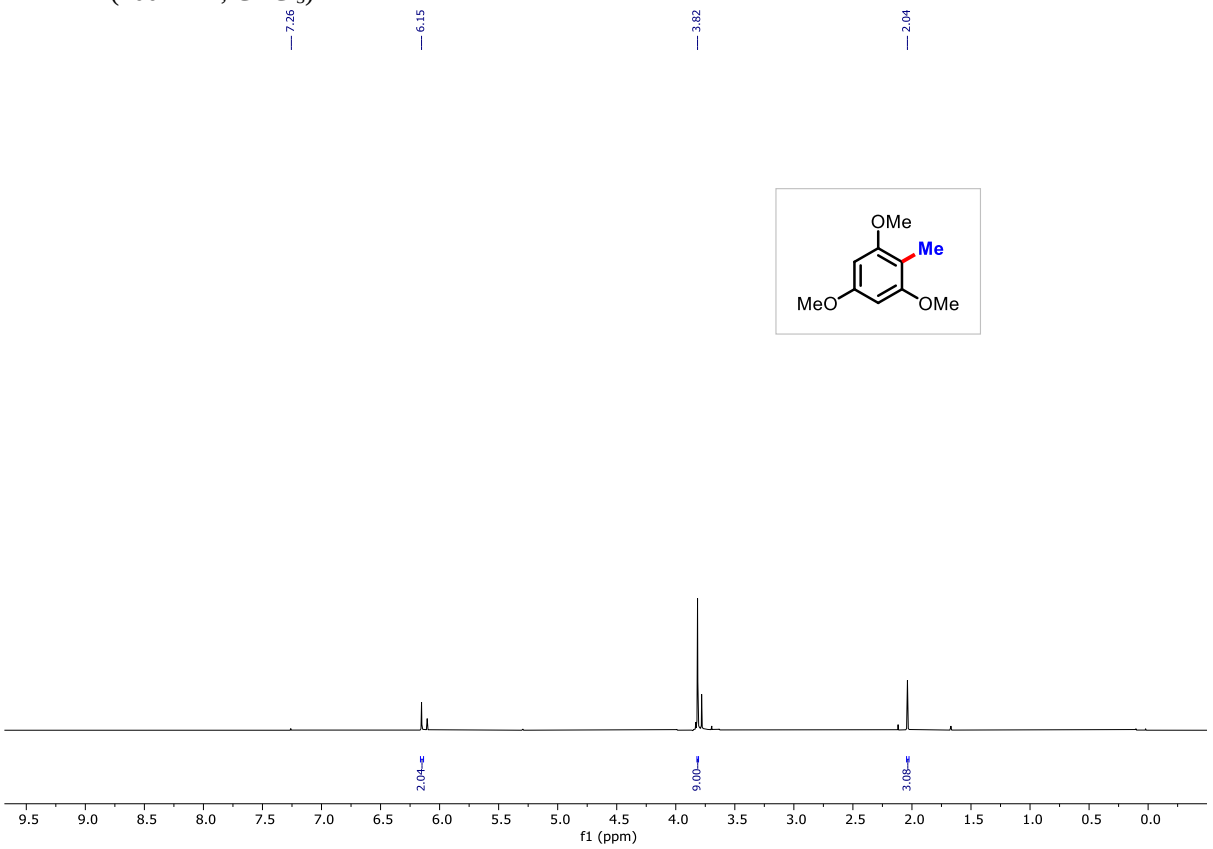


^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$)

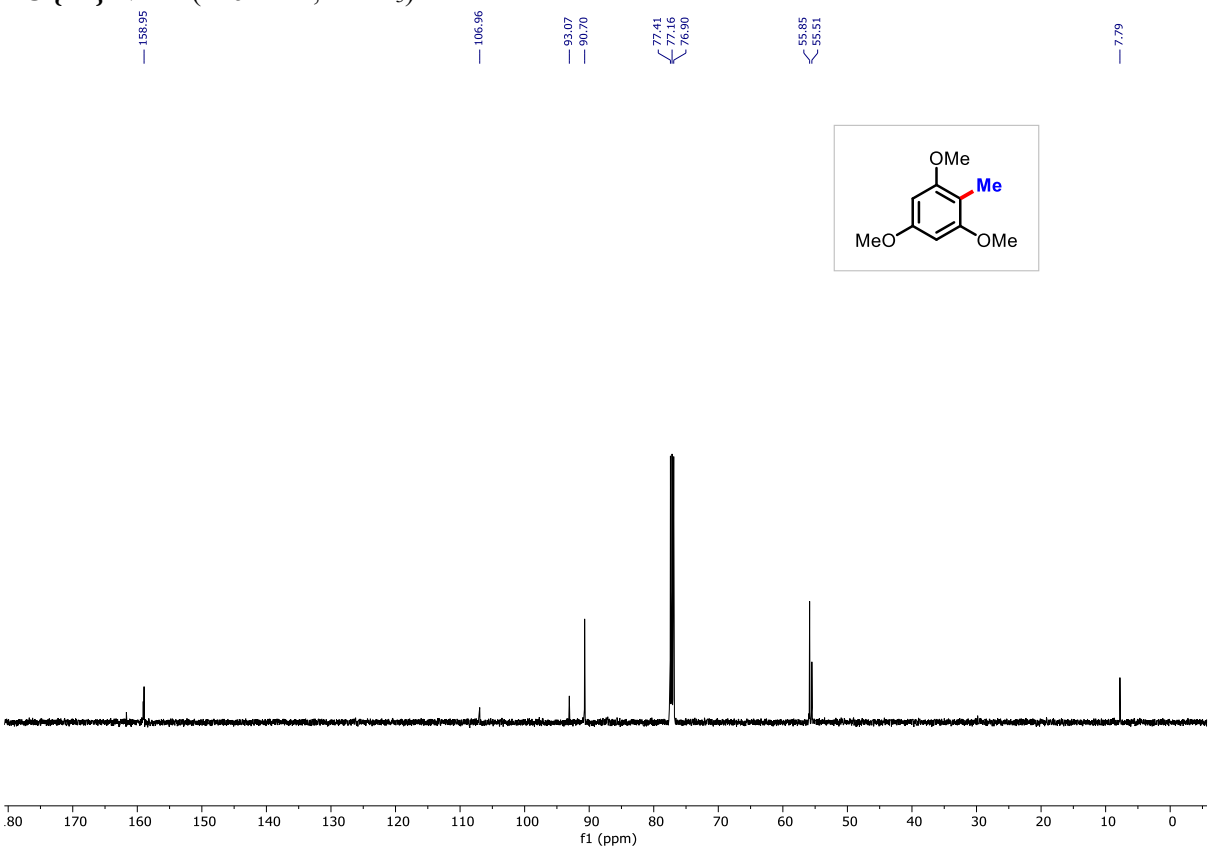


1,3,5-Trimethoxy-2-methylbenzene (4v)

^{1}H NMR (400 MHz, $CDCl_3$)

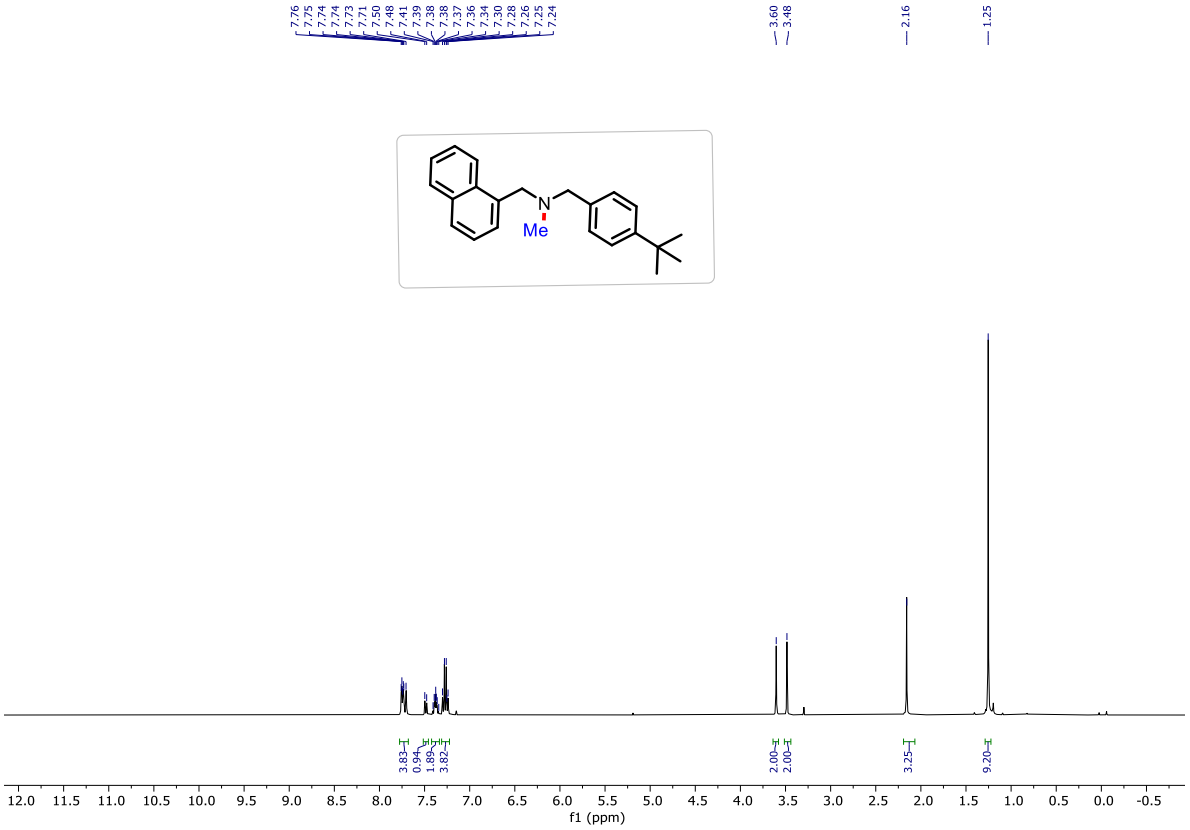


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

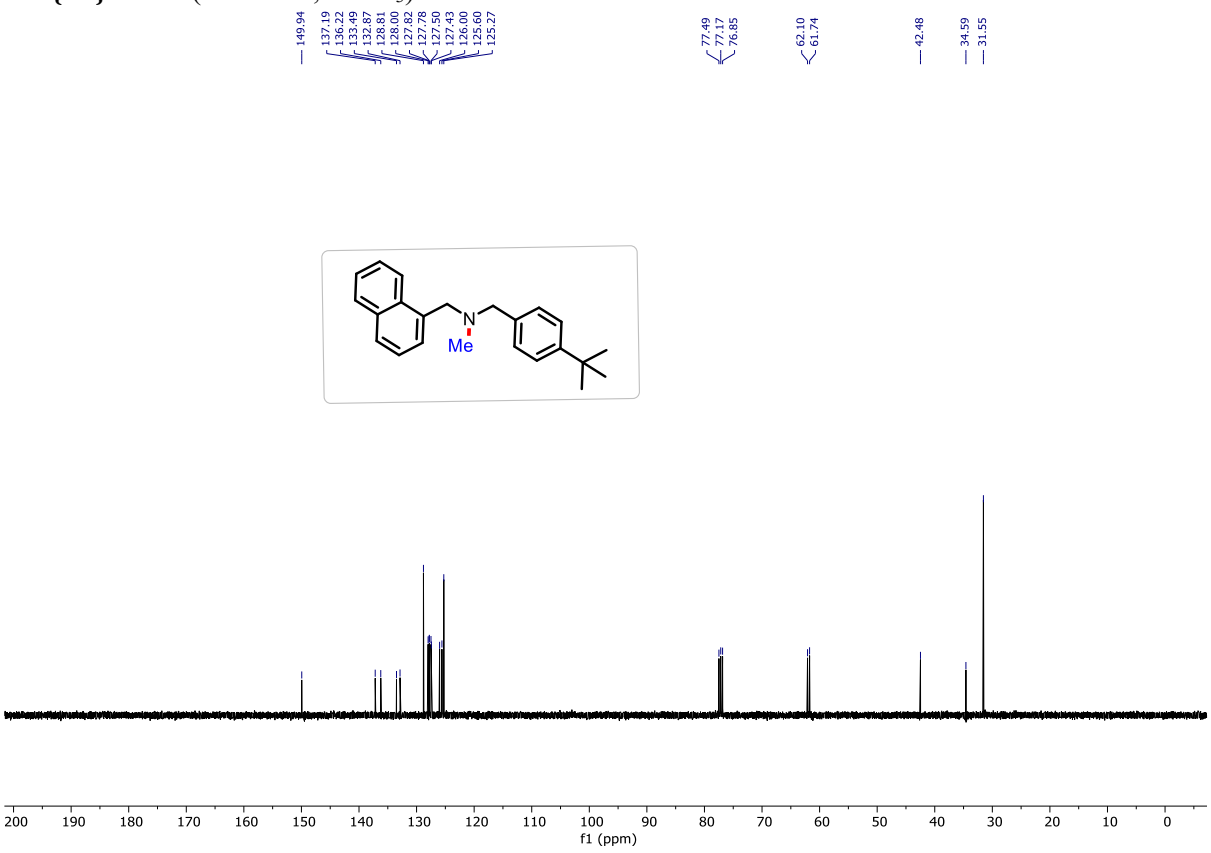


N-(4-(*tert*-butyl)benzyl)-*N*-methyl-1-(naphthalen-1-yl)-methanamine (2)

^{1}H NMR (400 MHz, $CDCl_3$)

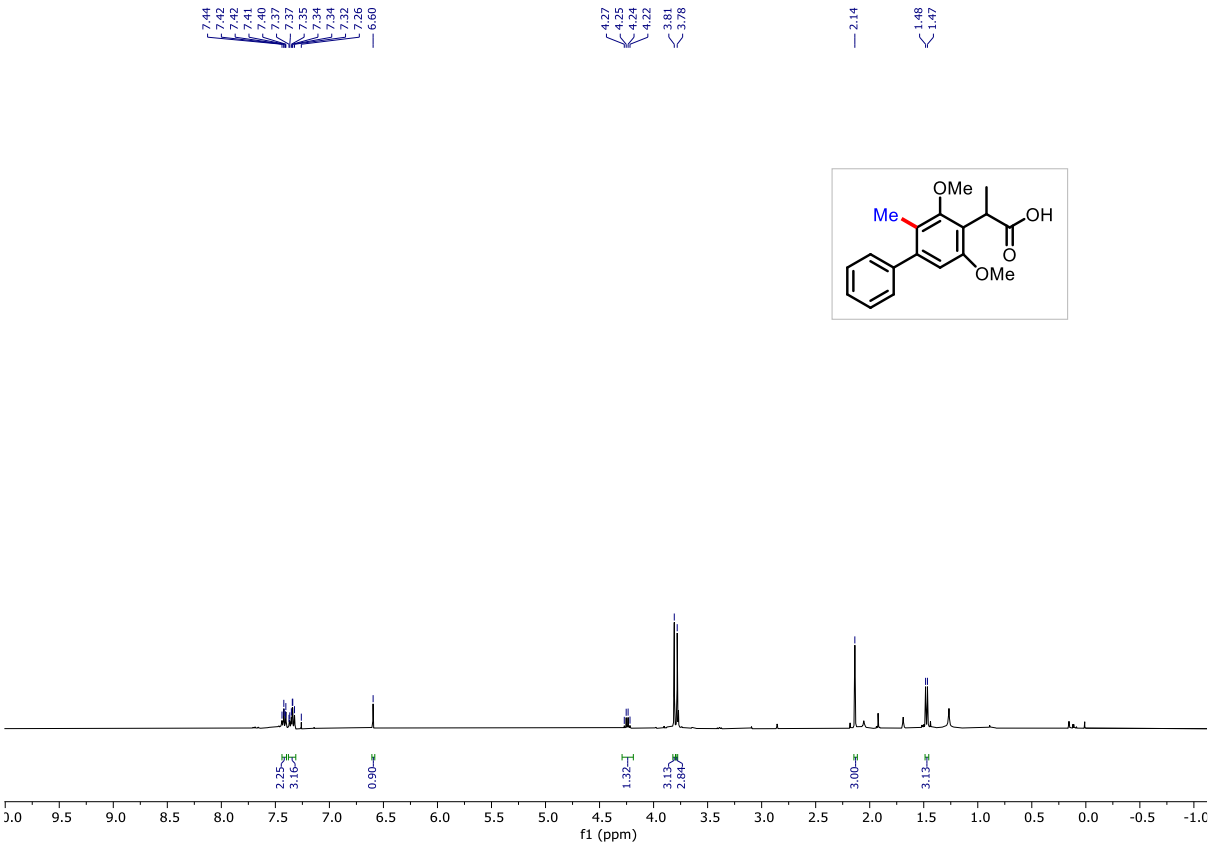


^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$)

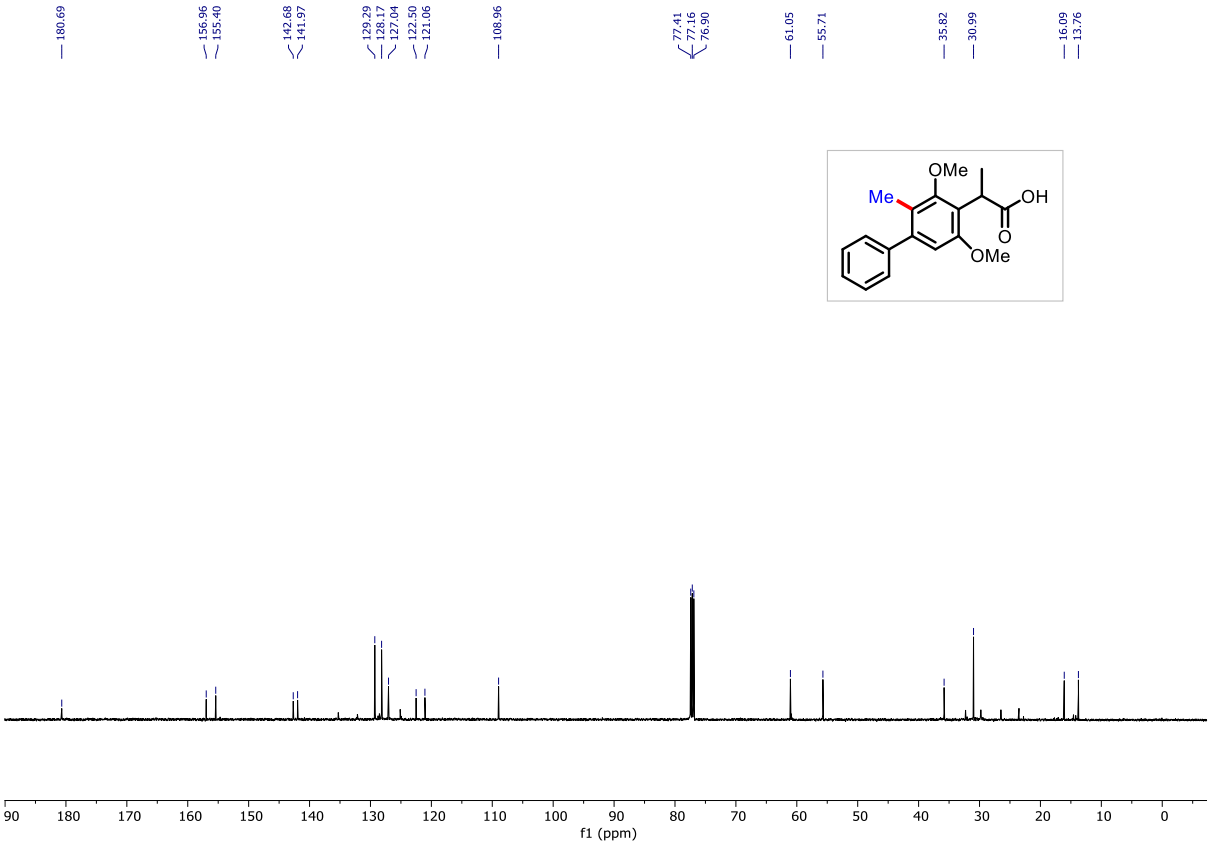


2-(3,5-Dimethoxy-2-methyl-[1,1'-biphenyl]-4-yl) propanoic acid (4)

^{11}H NMR (400 MHz, $CDCl_3$)

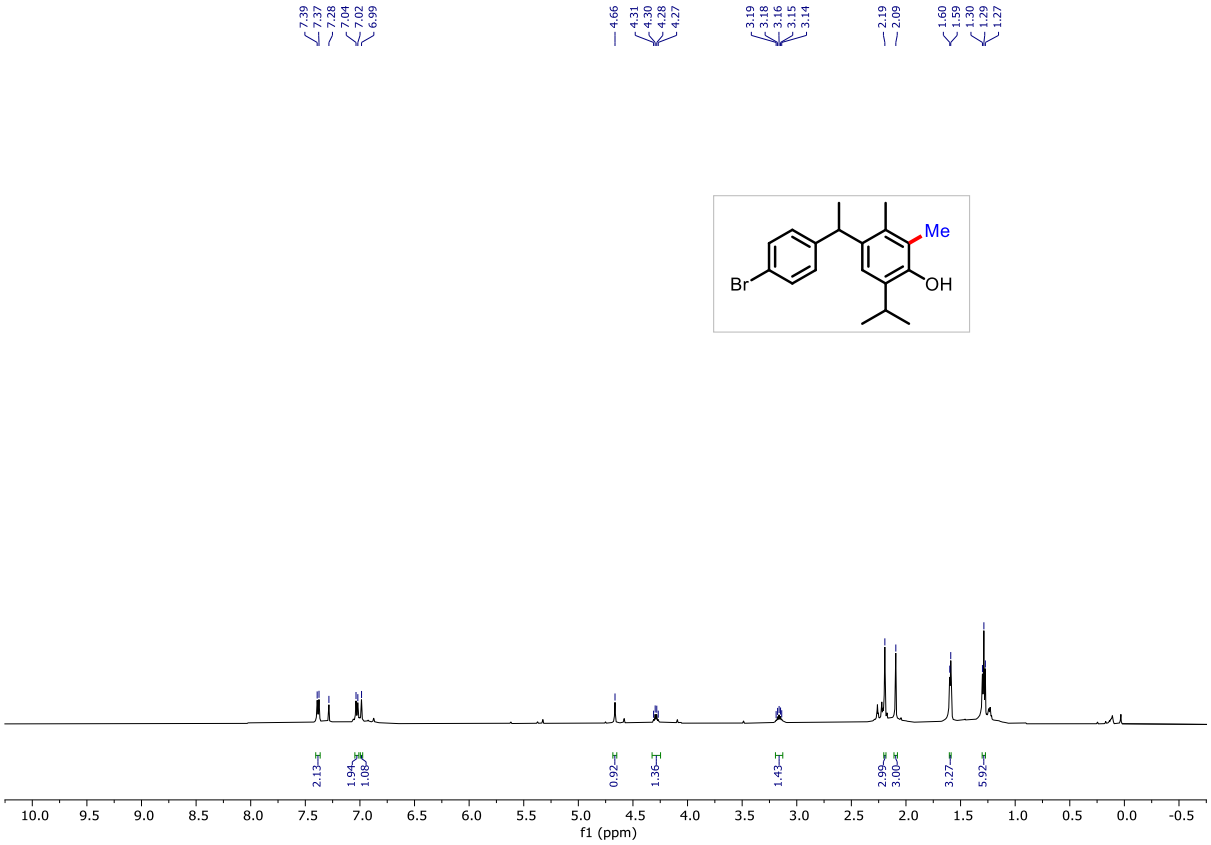


^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)

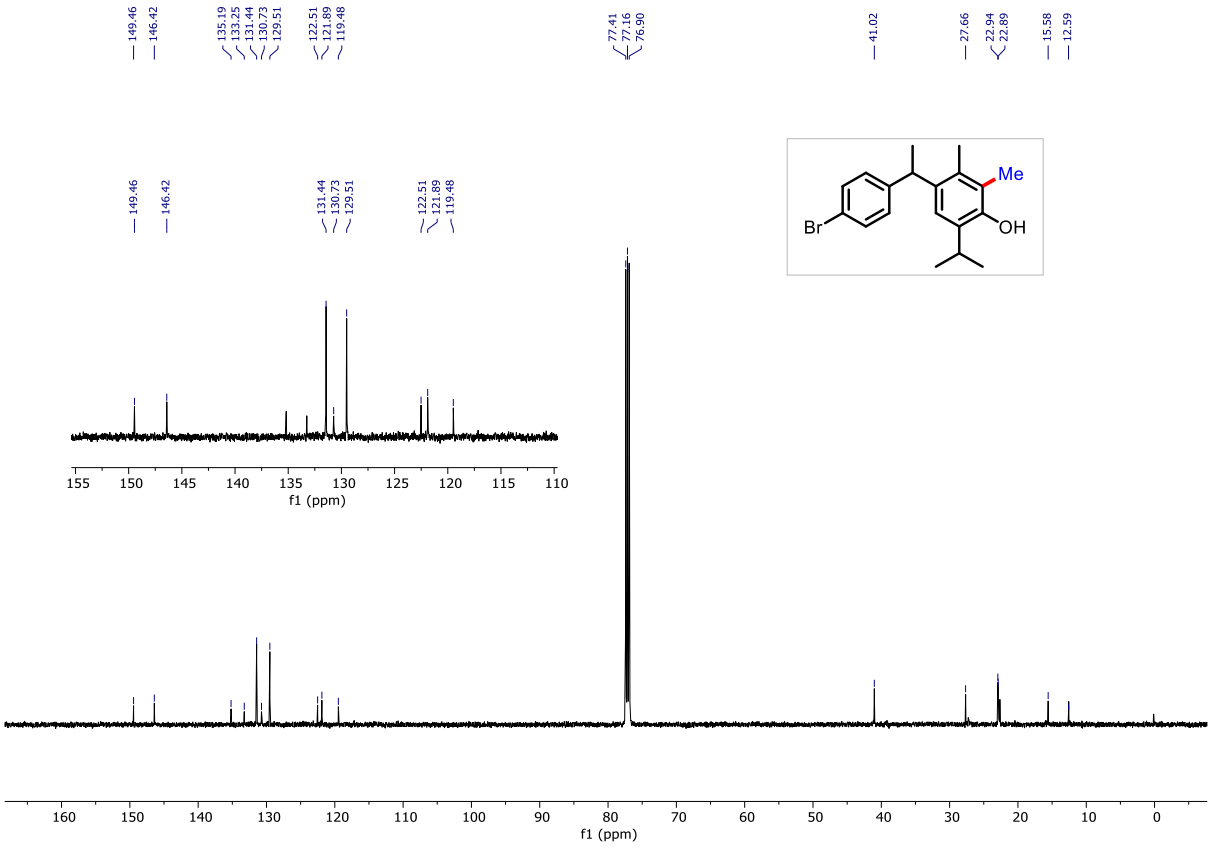


4-(1-(4-Bromophenyl) ethyl)-6-isopropyl-2,3-dimethylphenol (5)

^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)



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