

Supporting Information

Hexafluoro-2-Propanol-Promoted Intermolecular Friedel-Crafts Acylation Reaction

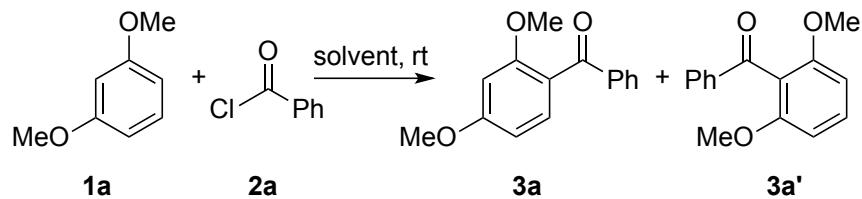
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Table S1. Examination of Concentration and Stoichiometry^a



entry	1a (equiv)	HFIP (mL)	yield, % ^b (3a/3a')
1	1	1	66 (91:9)
2	2	1	80 (92:8)
3	3	1	84 (91:9)
4	4	1	80 (92:8)
5	3	0.5	68 (92:8)
6	3	0.25	43 (92:8)
7 ^c	1	1	66 (92:8)

^aTo 1,3-dimethoxybenzene in HFIP, was added benzoyl chloride (0.75 mmol, 1 equiv).

The reaction mixture was stirred at rt for 5 h. ^bIsolated yields based on acyl chloride.

^cBenzoyl chloride was added portionwise over a period of 2 h.

General Information

Reactions were performed in oven-dried glassware or glass sample vial with a rubber-lined cap. Thin-layer chromatography (TLC) was performed using commercial glass-backed silica plates (250 microns) with an organic binder. Visualization was accomplished with UV light. Infrared (IR) spectra were acquired as thin films or solids. All nuclear magnetic resonance (NMR) spectra (¹H, ¹³C) were recorded on a 400/101 MHz instrument. NMRs were recorded in deuterated chloroform dimethyl sulfoxide. Chemical shifts are reported in parts per million (ppm) and are referenced to the center line of the solvent (δ 7.26 and 2.50 ppm with respect to CDCl₃ and DMSO-*d*₆ for ¹H NMR and δ 77.16 and 39.52 ppm with respect to CDCl₃ and DMSO-*d*₆ for ¹³C NMR, respectively). Coupling constants are given in Hertz (Hz). HRMS data were collected with an electrospray ion source (ESI). Melting points were determined on an automated melting point apparatus and are uncorrected.

List of known compounds

(2,4-Dimethoxyphenyl)(phenyl)methanone (3a),¹ (2,6-dimethoxyphenyl)(phenyl)methanone (3a'),² 1-(2,4-dimethoxyphenyl)ethan-1-one (3b),³ 1-(2,6-dimethoxyphenyl)ethan-1-one (3b'),⁴ phenyl(2,4,5-trimethoxyphenyl)methanone (3c),¹ 1-(2,4,5-trimethoxyphenyl)ethan-1-one (3d),⁴ 1-(2,4-dimethoxyphenyl)-2-methylpropan-1-one (3e),⁵ phenyl(2,4,6-trimethoxyphenyl)methanone (3f),⁶ 1-(2,4,6-trimethoxyphenyl)ethan-1-one (3g),⁷ (3,4-dimethoxyphenyl)(phenyl)methanone (3i),¹ (4-methoxyphenyl)(phenyl)methanone (3j),¹ phenyl(1H-pyrrol-2-yl)methanone (3l₂),⁸ phenyl(1H-pyrrol-3-yl)methanone (3l₃),⁹ (1H-indol-3-yl)(phenyl)methanone (3m),¹⁰ (2-methyl-1H-indol-3-yl)(phenyl)methanone (3n),¹¹ (1-methyl-1H-indol-3-yl)(phenyl)methanone (3o),¹² (1H-indol-3-yl)(4-methoxyphenyl)methanone (3p),¹³ 1-(1H-indol-3-yl)-2,2-dimethylpropan-1-one (3q),¹³ (2-methylbenzo[b]thiophen-3-yl)(phenyl)methanone (3r),¹⁴ benzoylferrocene (3t),¹⁵ (4-methoxyphenyl)(2,4,6-trimethoxyphenyl)methanone (3v),¹⁶ (4-chlorophenyl)(2,4,6-trimethoxyphenyl)methanone (3x),¹⁷ 4-chlorobutyl benzoate.¹⁸

General Procedure for Solvent Screening (main text, Table 1)

To a solution of 1,3-dimethoxybenzene (104 mg, 0.75 mmol, 1.0 equiv) in HFIP and/or specified solvent (1.0 mL) in an oven-dried N₂-flushed 2 dram vial, benzoyl chloride (87 μ L, 0.750 mmol, 1.0 equiv) was added. The resultant mixture was stirred at room temperature for 5 h. Reaction mixture was concentrated and crude was purified on a CombiFlash purification system using a silica flash column (90:10 hexanes/EtOAc) to afford **3a/3a'** as a mixture.

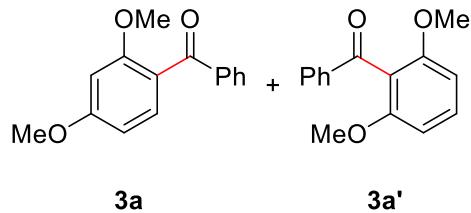
General Procedure for Concentration and Stoichiometry Screening (Table S1)

To a solution of 1,3-dimethoxybenzene (1.0–4.0 equiv as indicated in Table S1) in HFIP (1.0 mL, 0.5 mL or 0.25 mL as indicated in Table 2) in an oven-dried N₂-flushed 2 dram vial, benzoyl chloride (87 μ L, 0.750 mmol, 1.0 equiv) was added (for entry 7, total amount of benzoyl chloride was divided into five portions, and each portion was added at 30 min interval over a period of 2 h). The resultant mixture was stirred at room temperature for 5 h. Reaction mixture was concentrated and crude was purified on a CombiFlash purification system using a silica flash column (90:10 hexanes/EtOAc) to afford **3a/3a'** as a mixture.

General Procedure for the Friedel-Crafts reaction in HFIP

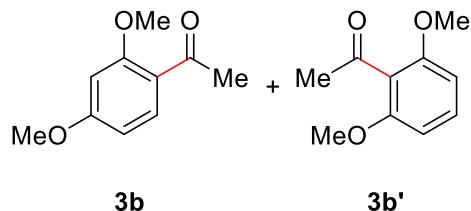
To a solution of arenes or heterocyclic arenes (2.25 mmol, 3.0 equiv) in HFIP (1.0 mL) in an oven-dried N₂-flushed 2-dram vial, acid chloride (0.750 mmol, 1.0 equiv) was added. The resultant mixture was stirred at room temperature for 5 h, unless otherwise noted. Reaction mixture was concentrated and crude was purified on a CombiFlash purification system using a normal phase silica flash column to afford ketone products.

Compound Preparation and Characterization



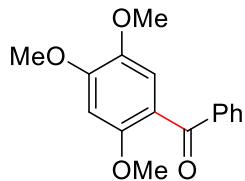
(2,4-Dimethoxyphenyl)(phenyl)methanone (3a)¹ and (2,6-dimethoxyphenyl)(phenyl)methanone (3a')²

Following the general procedure, 1,3-dimethoxybenzene (311 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87 μ L, 0.750 mmol, 1.0 equiv) to give the known ketones **3a/3a'** (152 mg, 84%, **3a/3a'** = 91/9) as a mixture.



1-(2,4-Dimethoxyphenyl)ethan-1-one (3b)³ and 1-(2,6-dimethoxyphenyl)ethan-1-one (3b')⁴

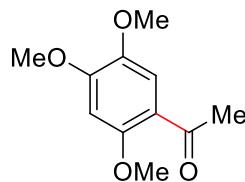
Following the general procedure, 1,3-dimethoxybenzene (311 mg, 2.25 mmol, 3.0 equiv) was reacted with acetyl chloride (53 μ L, 0.750 mmol, 1.0 equiv) to give the known ketones **3b/3b'** (109 mg, 81%, = 87/13) as a mixture.



3c

Phenyl(2,4,5-trimethoxyphenyl)methanone (3c)¹

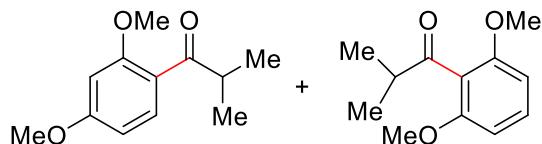
Following the general procedure, 1,2,4-trimethoxybenzene (378 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87 μ L, 0.750 mmol, 1.0 equiv) to give the known ketone **3c** (111 mg, 54%) as a yellow solid.



3d

1-(2,4,5-Trimethoxyphenyl)ethan-1-one (3d)⁴

Following the general procedure, 1,2,4-trimethoxybenzene (378 mg, 2.25 mmol, 3.0 equiv) was reacted with acetyl chloride (53 μ L, 0.750 mmol, 1.0 equiv) to give the known ketone **3d** (95 mg, 60%) as a white solid.

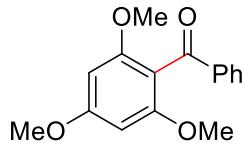


3e

3e'

1-(2,4-Dimethoxyphenyl)-2-methylpropan-1-one (3e)⁵ and 1-(2,6-dimethoxyphenyl)-2-methylpropan-1-one (3e')

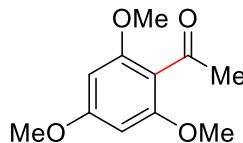
Following the general procedure, 1,3-dimethoxybenzene (311 mg, 2.25 mmol, 3.0 equiv) was reacted with isobutyryl chloride (79 μ L, 0.750 mmol, 1.0 equiv) to give the known ketones **3e/3e'** (95 mg, 61%, **3e/3e'** = 99/1, ratio was determined by GCMS) as a colorless oil.



3f

Phenyl(2,4,6-trimethoxyphenyl)methanone (3f)⁶

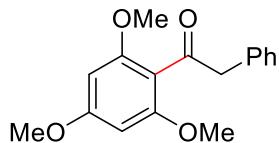
Following the general procedure, 1,3,5-trimethoxybenzene (378 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87 μ L, 0.750 mmol, 1.0 equiv) to give the known ketone **3f** (176 mg, 86%) as a white solid.



3g

1-(2,4,6-Trimethoxyphenyl)ethan-1-one (3g)⁷

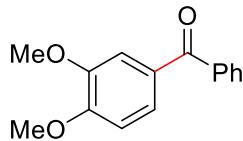
Following the general procedure, 1,3,5-trimethoxybenzene (378 mg, 2.25 mmol, 3.0 equiv) was reacted with acetyl chloride (53 μ L, 0.750 mmol, 1.0 equiv) to give the known ketone **3g** (145 mg, 92%) as a white solid.



3h

2-Phenyl-1-(2,4,6-trimethoxyphenyl)ethan-1-one (3h)

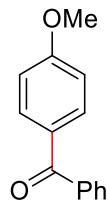
Following the general procedure, 1,3,5-trimethoxybenzene (378 mg, 2.25 mmol, 3.0 equiv) was reacted with phenylacetyl chloride (99 μ L, 0.750 mmol, 1.0 equiv) to give the title ketone (171 mg, 84%) as a yellow solid. Mp: 66–68 °C; TLC (20% EtOAc/hexanes): R_f = 0.50; ^1H NMR (400 MHz, CDCl_3) δ 7.37, 7.24 (m, 2H), 7.20 (dt, J = 5.8, 1.5 Hz, 3H), 6.06 (s, 2H), 4.03 (s, 2H), 3.80 (s, 3H), 3.73 (s, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ 201.6, 162.5, 158.3, 135.0, 130.0, 128.3, 126.6, 113.3, 90.7, 55.9, 55.5, 51.7. IR (neat) 1698 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{17}\text{H}_{19}\text{O}_4$ [$\text{M} + \text{H}$] $^+$: 287.1283, found: 287.1280.



3i

(3,4-Dimethoxyphenyl)(phenyl)methanone (3i)¹

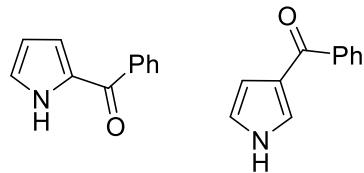
Following the general procedure, 1,2-dimethoxybenzene (311 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87 μ L, 0.750 mmol, 1.0 equiv) to give the known ketone **3i** (73 mg, 36%) as a white solid.



3j

(4-Methoxyphenyl)(phenyl)methanone (3j)¹

Following the general procedure, anisole (243 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87 μ L, 0.750 mmol, 1.0 equiv) to give the known ketone **3j** (69 mg, 34%) as a colorless oil.

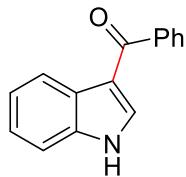


3l₂ + 3l₃

58% (72:28)

Phenyl(1H-pyrrol-2-yl)methanone (3l₂)⁸ and phenyl(1H-pyrrol-3-yl)methanone (3l₃)⁹

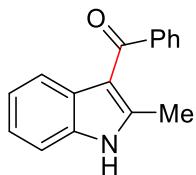
Following the general procedure, pyrrole (151 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87 μ L, 0.750 mmol, 1.0 equiv) to give the known ketones **3l₂** (86 mg, 42%) and **3l₃** (21 mg, 16%) as a brown solid.



3m

(1H-Indol-3-yl)(phenyl)methanone (3m)¹⁰

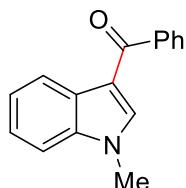
Following the general procedure, indole (264 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87 μ L, 0.750 mmol, 1.0 equiv) to give the known ketone **3m** (119 mg, 72%) as a pale yellow solid.



3n

(2-Methyl-1H-indol-3-yl)(phenyl)methanone (3n)¹¹

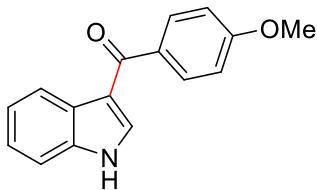
Following the general procedure, 2-methyl-1H-indole (295 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87 μ L, 0.750 mmol, 1.0 equiv) to give the known ketone **3n** (144 mg, 82%) as a yellow solid.



3o

(1-Methyl-1H-indol-3-yl)(phenyl)methanone (3o)¹²

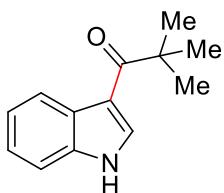
Following the general procedure, 1-methyl-1H-indole (295 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87 μ L, 0.750 mmol, 1.0 equiv) to give the known ketone **3o** (152 mg, 86%) as a white solid.



3p

(1H-Indol-3-yl)(4-methoxyphenyl)methanone (3p)¹³

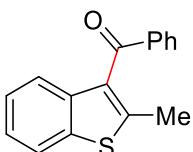
Following the general procedure, indole (264 mg, 2.25 mmol, 3.0 equiv) was reacted with 4-methoxybenzoyl chloride (103 μ L, 0.750 mmol, 1.0 equiv) to give the known ketone **3p** (99 mg, 53%) as a brown solid.



3q

1-(1H-Indol-3-yl)-2,2-dimethylpropan-1-one (3q)¹³

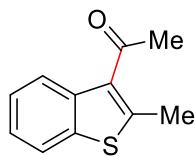
Following the general procedure, indole (264 mg, 2.25 mmol, 3.0 equiv) was reacted with pivaloyl chloride (92 μ L, 0.750 mmol, 1.0 equiv) to give the known ketone **3q** (137 mg, 91%) as a brown solid.



3r

(2-Methylbenzo[b]thiophen-3-yl)(phenyl)methanone (3r)¹⁴

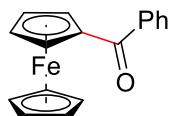
Following the general procedure, 2-methylbenzo[b]thiophene (334 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87 μ L, 0.750 mmol, 1.0 equiv) to give the known ketone **3r** (121 mg, 64%) as a white solid.



3s

1-(2-Methylbenzo[b]thiophen-3-yl)ethan-1-one (3s)

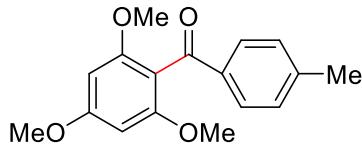
Following the general procedure, 2-methylbenzo[b]thiophene (334 mg, 2.25 mmol, 3.0 equiv) was reacted with acetyl chloride (53 μ L, 0.750 mmol, 1.0 equiv) to give title ketone (67 mg, 47%) as a white solid. Mp: 66–68 °C; TLC (20% EtOAc/hexanes): R_f = 0.40; 1 H NMR (400 MHz, CDCl₃) δ 8.18 (dt, J = 8.3, 0.9 Hz, 1H), 7.75 (ddd, J = 8.0, 1.3, 0.7 Hz, 1H), 7.41 (ddd, J = 8.3, 7.1, 1.3 Hz, 1H), 7.33 (ddd, J = 8.2, 7.1, 1.2 Hz, 1H), 2.79 (s, 3H), 2.66 (s, 3H); 13 C NMR (101 MHz, CDCl₃) 196.0, 149.1, 138.5, 137.4, 133.1, 125.3, 124.5, 123.9, 121.8, 32.0, 17.2; IR (neat) 1637 cm⁻¹; HRMS (ESI) *m/z* calcd for C₁₁H₁₁OS [M + H]⁺: 191.0531, found: 191.0529.



3t

Benzoylferrocene (3t)¹⁵

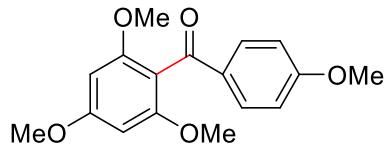
Following the general procedure, ferrocene (419 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87 μ L, 0.750 mmol, 1.0 equiv) to give the known ketone **3t** (135 mg, 62%) as a red solid.



3u

***p*-Tolyl(2,4,6-trimethoxyphenyl)methanone (3u)**

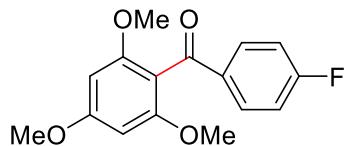
Following the general procedure, 1,3,5-trimethoxybenzene (378 mg, 2.25 mmol, 3.0 equiv) was reacted with 4-methylbenzoyl chloride (99 μ L, 0.750 mmol, 1.0 equiv) to give title ketone (190 mg, 93%) as a white solid. Mp: 142–144 °C; TLC (20% EtOAc/hexanes): R_f = 0.50; 1 H NMR (400 MHz, CDCl₃) δ 7.74 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 6.17 (s, 2H), 3.86 (s, 3H), 3.68 (s, 6H), 2.39 (s, 3H); 13 C NMR (101 MHz, CDCl₃) δ 194.8, 162.4, 158.7, 143.9, 135.9, 129.7, 129.2, 111.3, 90.8, 55.9, 55.6, 21.8; IR (neat) 1655 cm⁻¹; HRMS (ESI) *m/z* calcd for C₁₇H₁₉O₄ [M + H]⁺: 287.1283, found: 287.1279.



3v

(4-Methoxyphenyl)(2,4,6-trimethoxyphenyl)methanone (3v)¹⁶

Following the general procedure, 1,3,5-trimethoxybenzene (378 mg, 2.25 mmol, 3.0 equiv) was reacted with 4-methoxybenzoyl chloride (103 μ L, 0.750 mmol, 1.0 equiv) to give the known ketone 3v (189 mg, 83%) as a white solid.

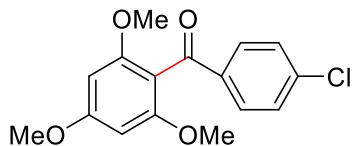


3w

(4-Fluorophenyl)(2,4,6-trimethoxyphenyl)methanone (3w)

Following the general procedure, 1,3,5-trimethoxybenzene (378 mg, 2.25 mmol, 3.0 equiv) was reacted with 4-fluorobenzoyl chloride (90 μ L, 0.750 mmol, 1.0 equiv) to give

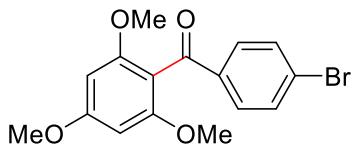
title ketone (161 mg, 79%) as a white solid. Mp: 152–154 °C; TLC (20% EtOAc/hexanes): R_f = 0.40; ^1H NMR (400 MHz, CDCl_3) δ 7.90–7.81 (m, 2H), 7.11–7.02 (m, 2H), 6.17 (s, 2H), 3.86 (s, 3H), 3.69 (s, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ 193.5, 165.9 (d, $J_{\text{C}-\text{F}} = 255$ Hz, 1C), 162.7, 158.8, 134.9 (d, $J_{\text{C}-\text{C}-\text{C}-\text{F}} = 3$ Hz, 1C), 132.2 (d, $J_{\text{C}-\text{C}-\text{C}-\text{F}} = 9$ Hz, 2C), 115.5 (d, $J_{\text{C}-\text{C}-\text{F}} = 22$ Hz, 2C), 110.7, 90.8, 55.9, 55.6; IR (neat) 1657 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{16}\text{H}_{16}\text{FO}_4$ [$\text{M} + \text{H}]^+$: 291.1033, found: 291.1032.



3x

(4-Chlorophenyl)(2,4,6-trimethoxyphenyl)methanone (3x)¹⁷

Following the general procedure, 1,3,5-trimethoxybenzene (378 mg, 2.25 mmol, 3.0 equiv) was reacted with 4-chlorobenzoyl chloride (96 μL , 0.750 mmol, 1.0 equiv) to give the known ketone **3x** (140 mg, 69%) as a white solid.

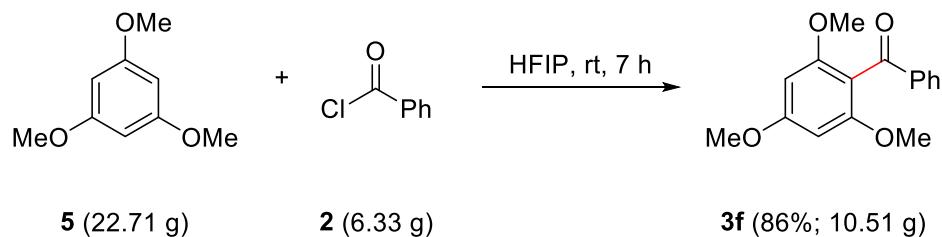


3y

(4-Bromophenyl)(2,4,6-trimethoxyphenyl)methanone (3y)

Following the general procedure, 1,3,5-trimethoxybenzene (378 mg, 2.25 mmol, 3.0 equiv) was reacted with 4-bromobenzoyl chloride (165 mg, 0.750 mmol, 1.0 equiv) to give the title ketone (151 mg, 74%) as a white solid. Mp: 188–190 °C; TLC (20% EtOAc/hexanes): R_f = 0.60; ^1H NMR (400 MHz, CDCl_3) δ 7.69 (d, $J = 8.6$ Hz, 2H), 7.54 (d, $J = 8.5$ Hz, 2H), 6.16 (s, 2H), 3.86 (s, 3H), 3.68 (s, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ 194.0, 162.8, 158.9, 137.2, 131.7, 131.1, 128.1, 110.4, 90.8, 55.9, 55.6; IR (neat) 1657 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{16}\text{H}_{16}\text{BrO}_4$ [$\text{M} + \text{H}]^+$: 351.0232, found: 351.0229.

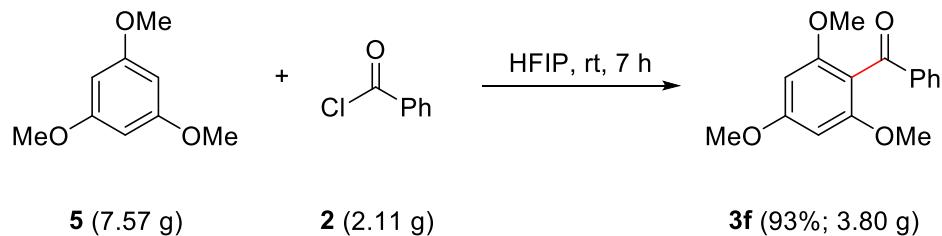
Scale-Up Reactions and HFIP Recycling



Initial reaction:

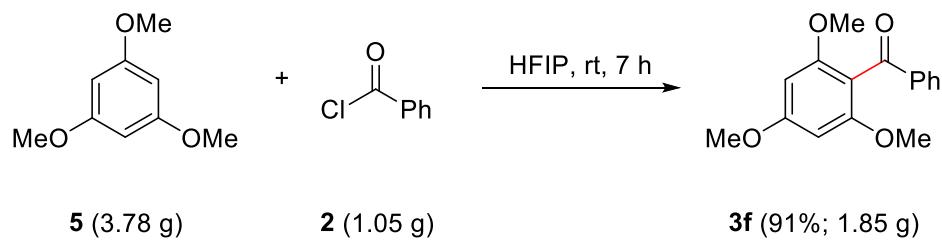
To a solution of 1,3,5-trimethoxybenzene (22.7 g, 135 mmol, 3.0 equiv) in HFIP (57 mL, 12 equiv) in an oven-dried flask benzoyl chloride (6.33 g, 5.22 mL, 45 mmol, 1.0 equiv) was added. The resultant mixture was stirred at room temperature for 7 h. HFIP solvent was recovered by distillation directly from the reaction pot (40–50 °C, under vacuum (5 millibar)) (46 mL, 81%). The remaining product was purified on a CombiFlash purification system using solid loading on a silica flash column (80:20 hexanes/EtOAc) to afford 3f (10.51 g, 86%) as a white solid.

Second reaction, using recovered HFIP



To a solution of 1,3,5-trimethoxybenzene (7.57 g, 45 mmol, 3.0 equiv) in HFIP (19 mL, 12 equiv), obtained by distillation from previous reaction, in an oven-dried flask, benzoyl chloride (2.11 g, 1.74 mL, 15 mmol, 1.0 equiv) was added. The resultant mixture was stirred at room temperature for 7 h. HFIP solvent was recovered by distillation as described above (18 mL, 95%). The crude was purified on a CombiFlash purification system using a silica flash column (80:20 hexanes/EtOAc) to afford 3f (3.80 g, 93%) as a white solid.

Third reaction, using doubly recovered HFIP



To a solution of 1,3,5-trimethoxybenzene (3.78 g, 22.5 mmol, 3.0 equiv) in HFIP (9.5 mL, 12 equiv), obtained by distillation from previous reaction, in an oven-dried flask, benzoyl chloride (1.05 g, 0.87 mL, 7.5 mmol, 1.0 equiv) was added. The resultant mixture was stirred at room temperature for 7 h. HFIP solvent was recovered by distillation (9 mL, 95%). The crude was purified on a CombiFlash purification system using a silica flash column (80:20 hexanes/EtOAc) to afford **3f** (1.85 g, 91%) as a white solid.

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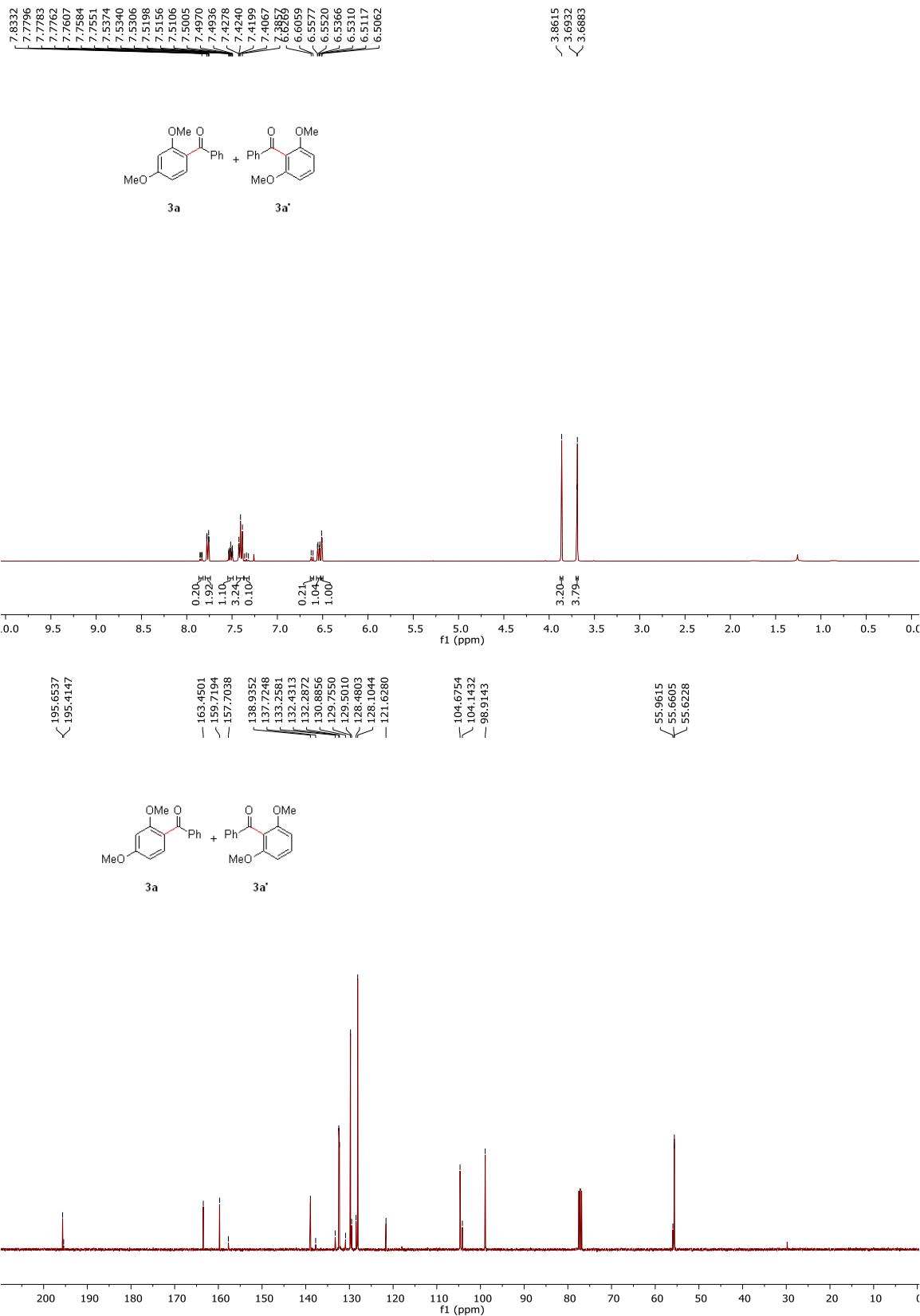
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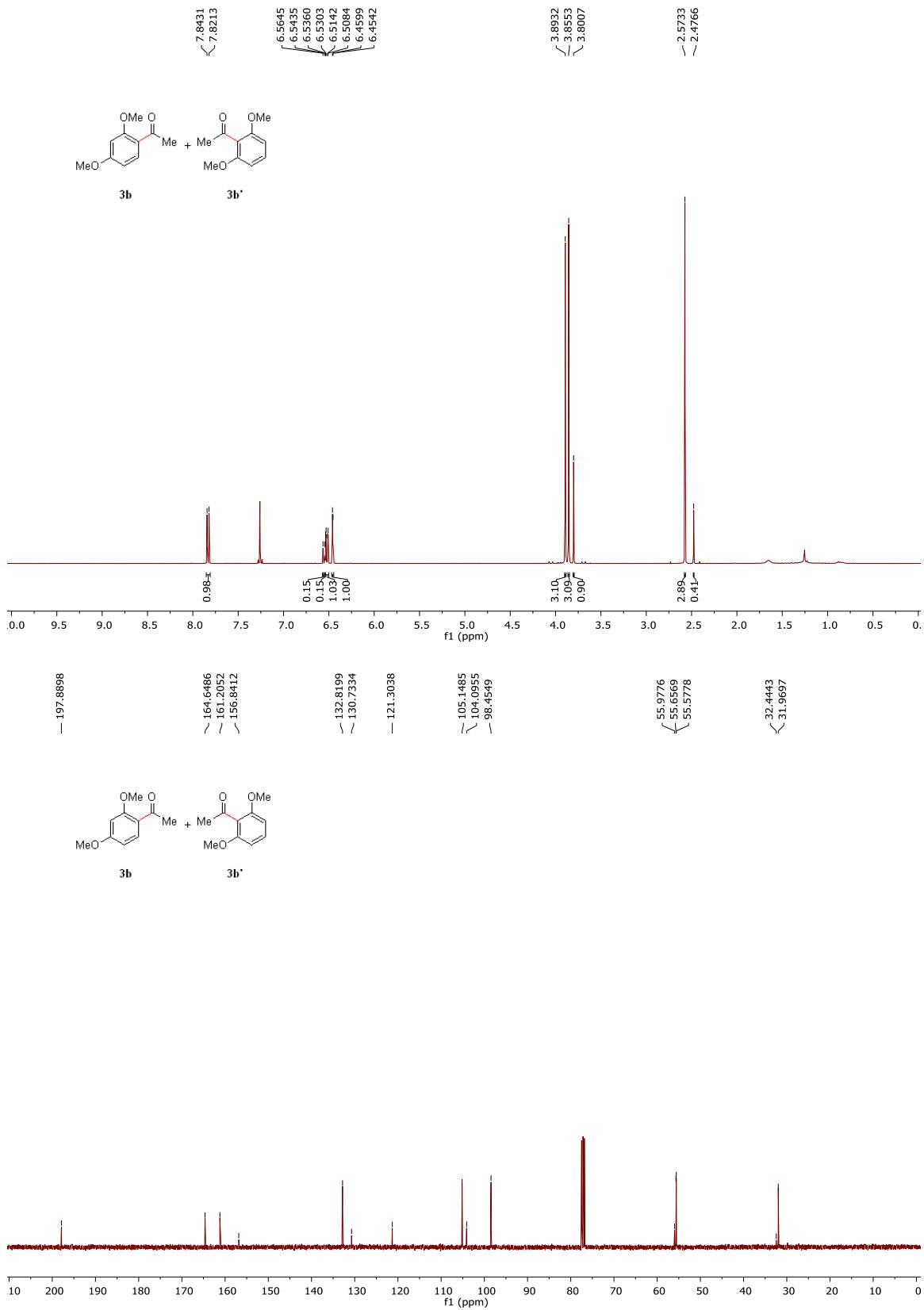
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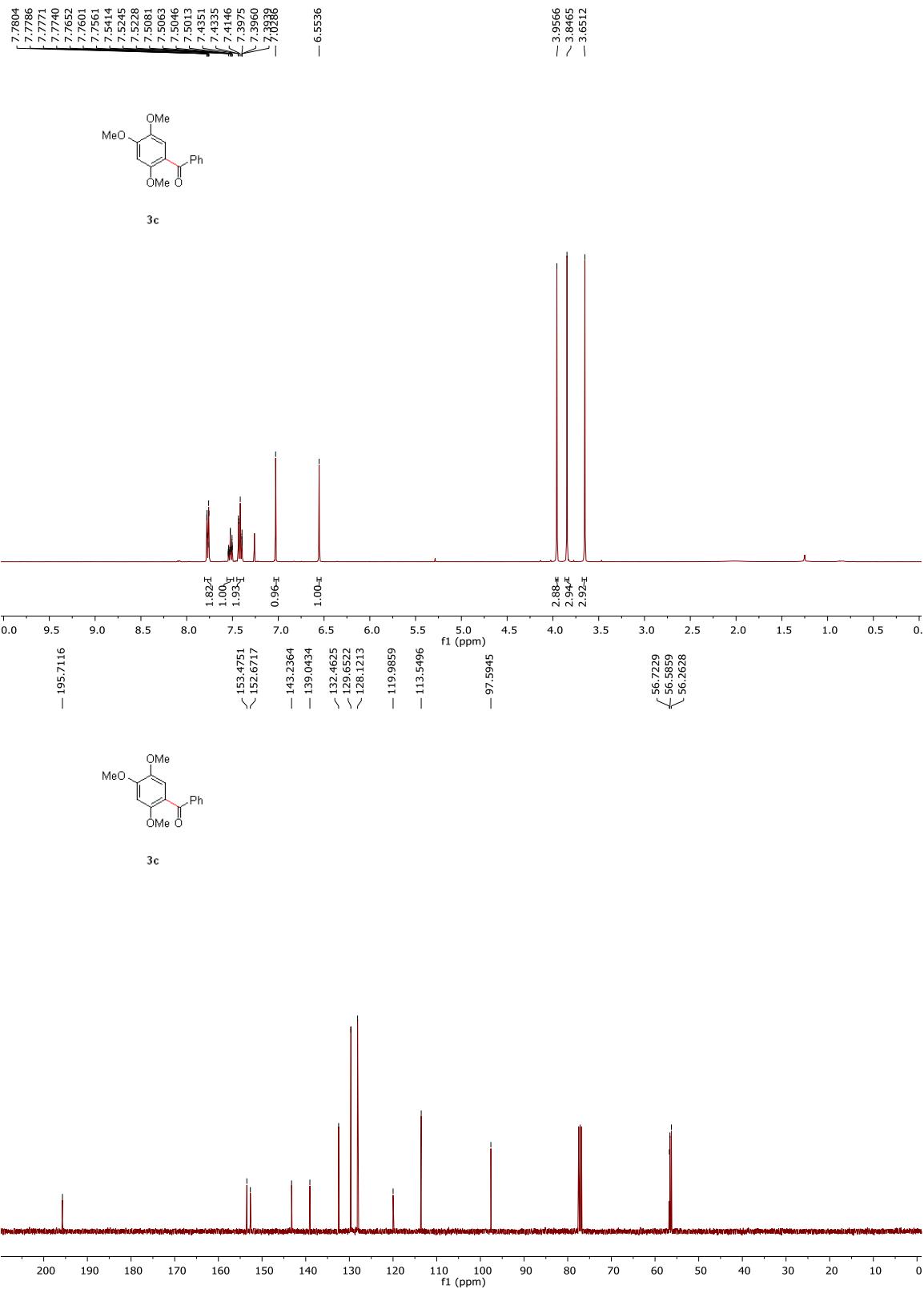
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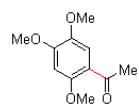
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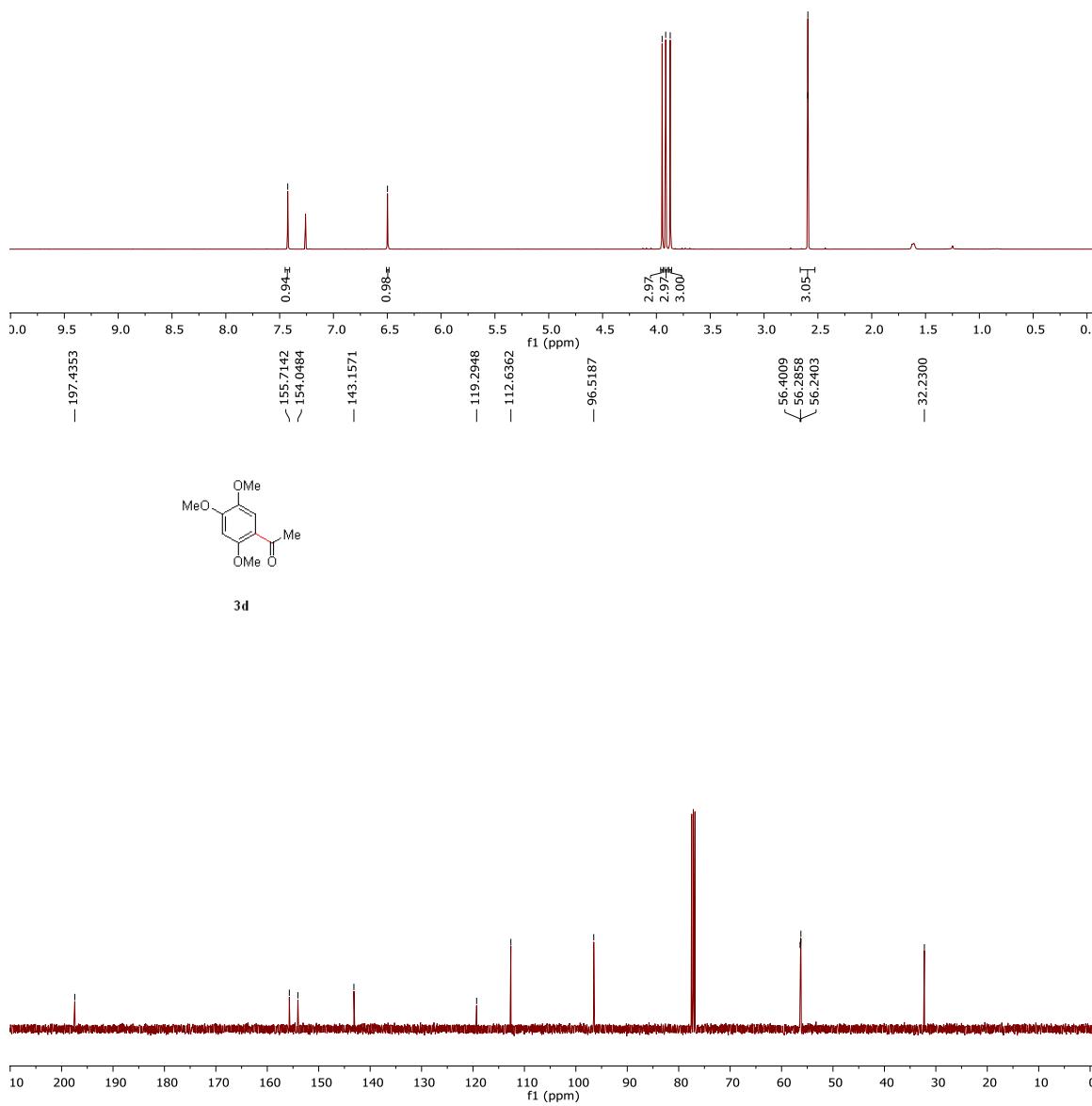


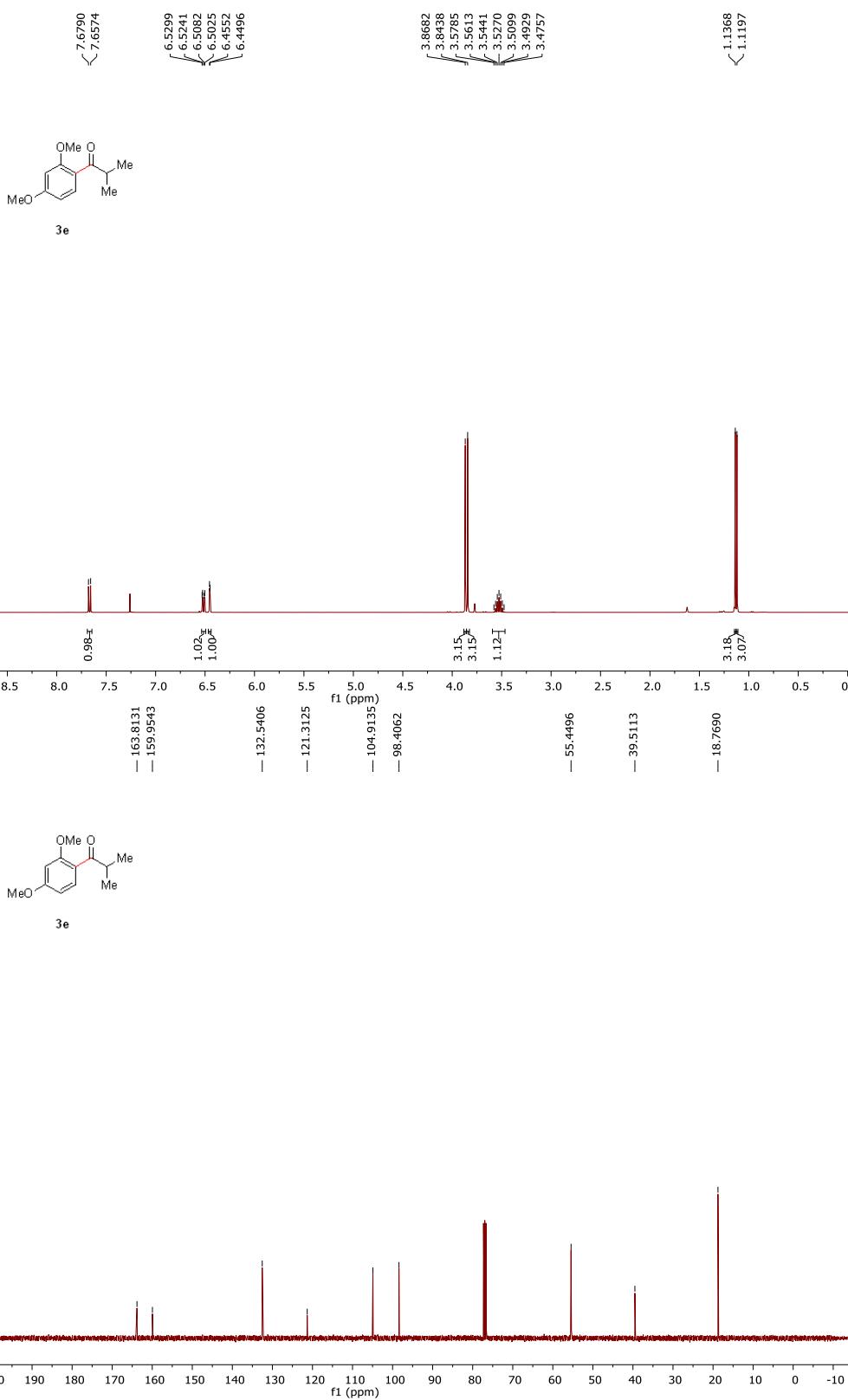


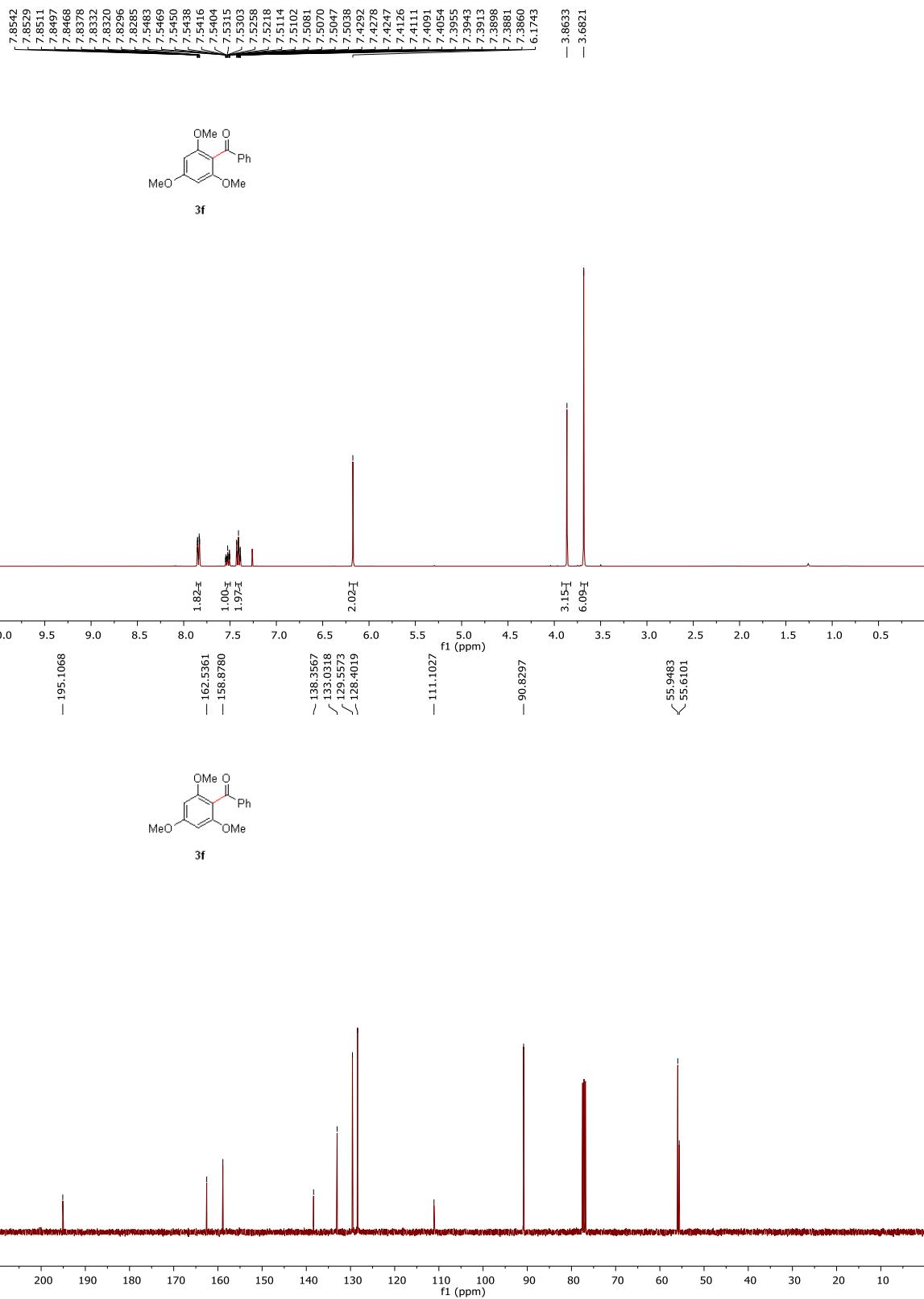
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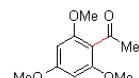


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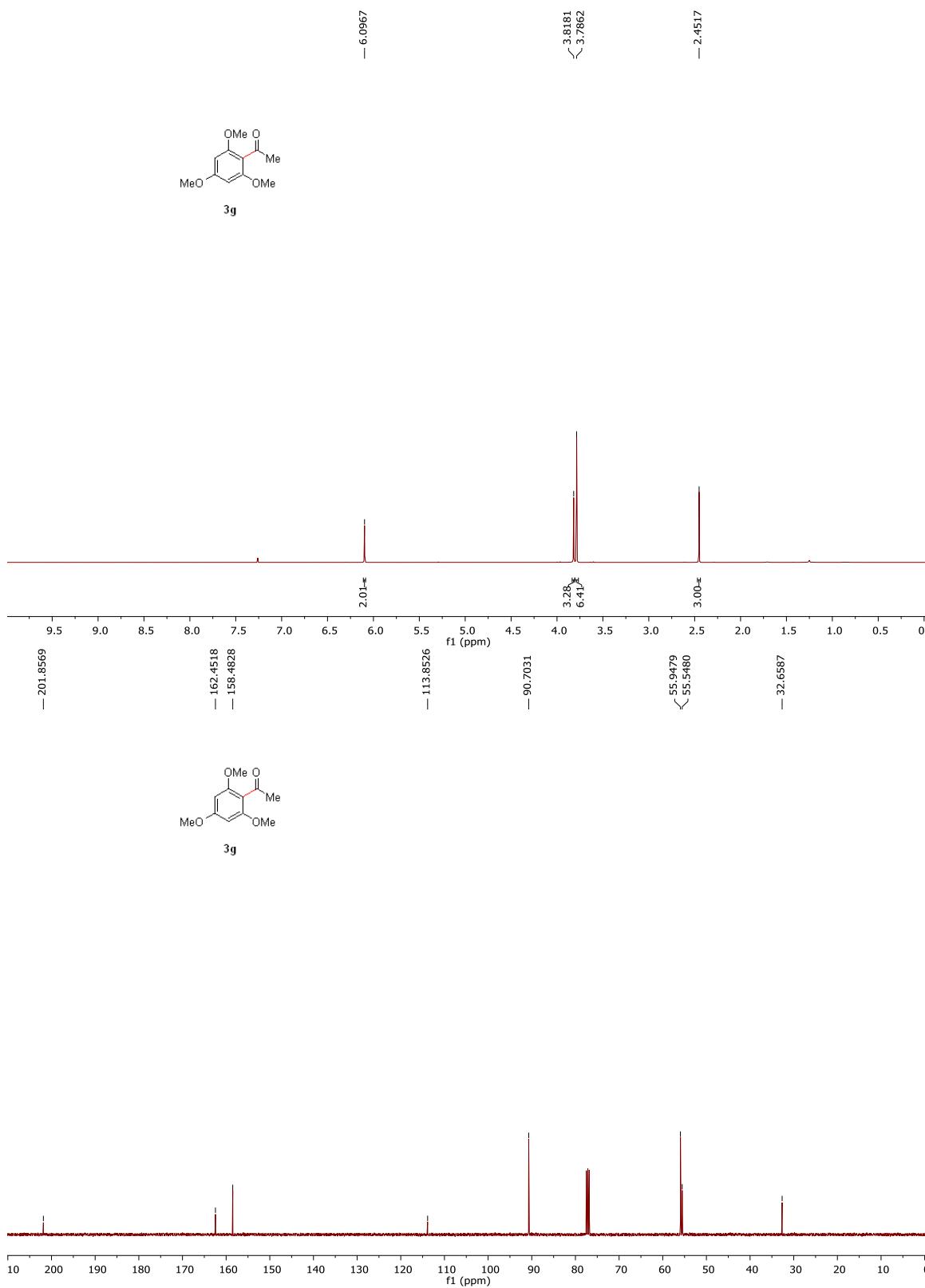


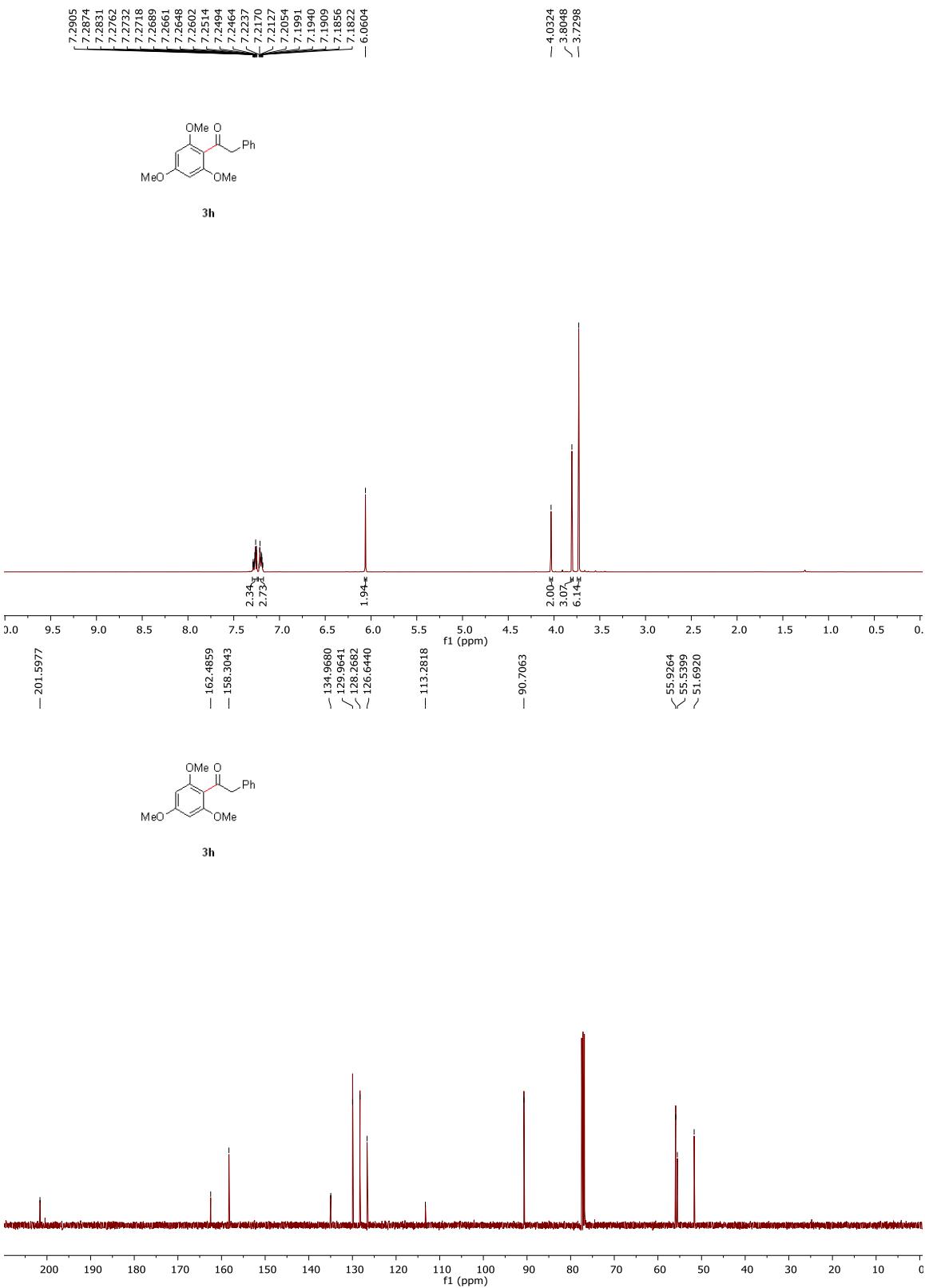




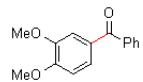


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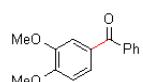
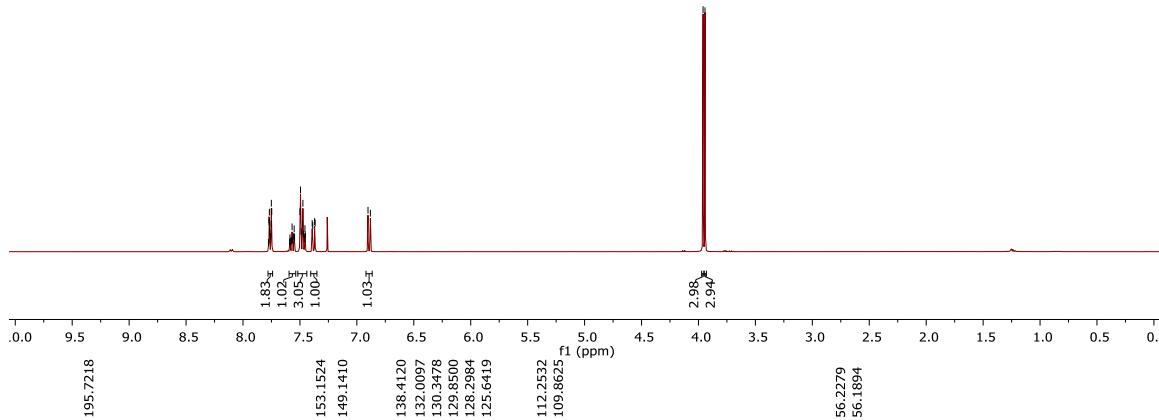




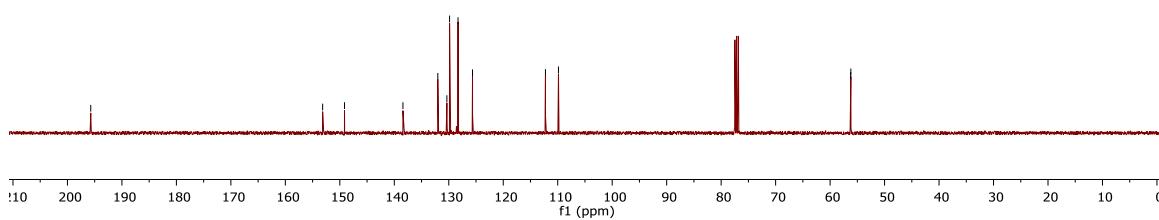
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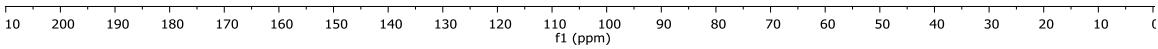
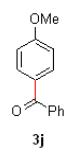
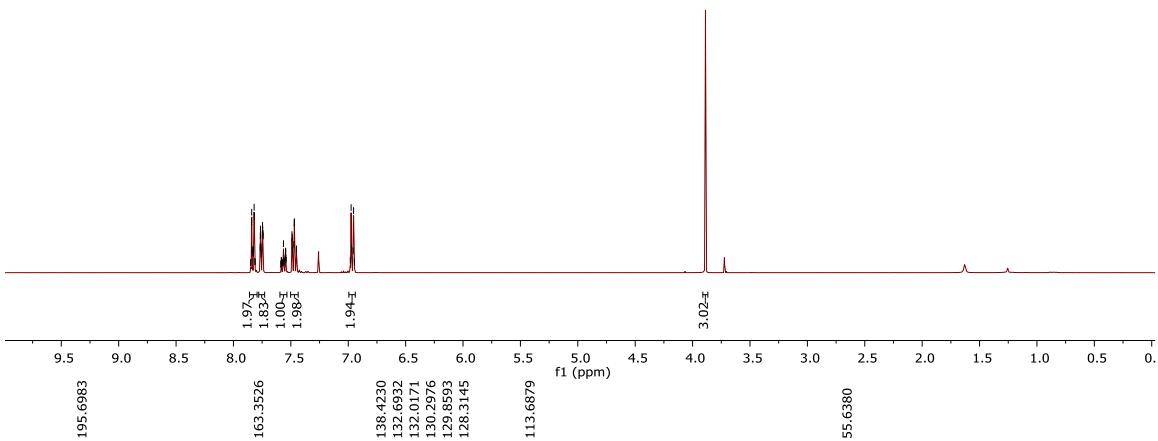
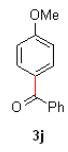
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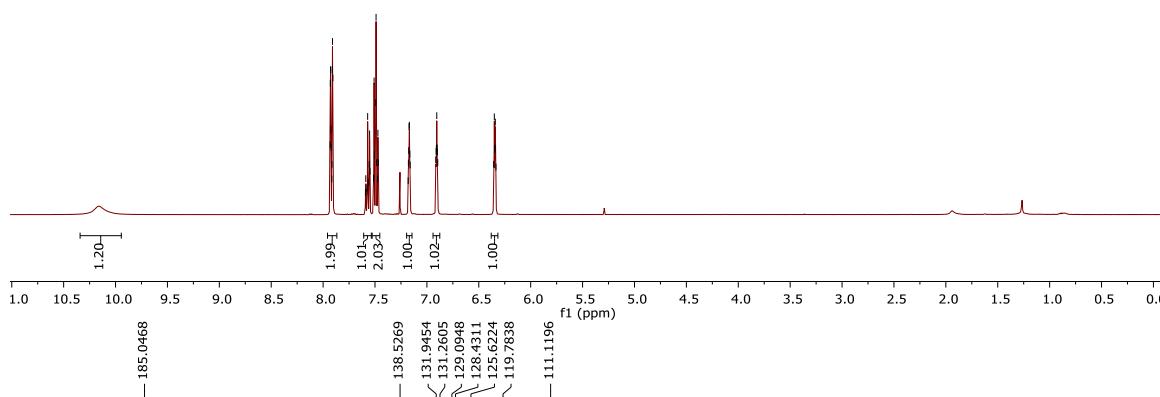
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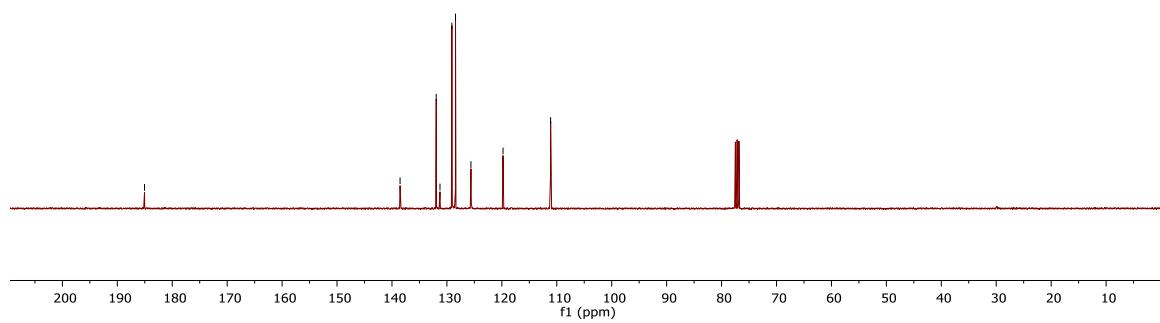
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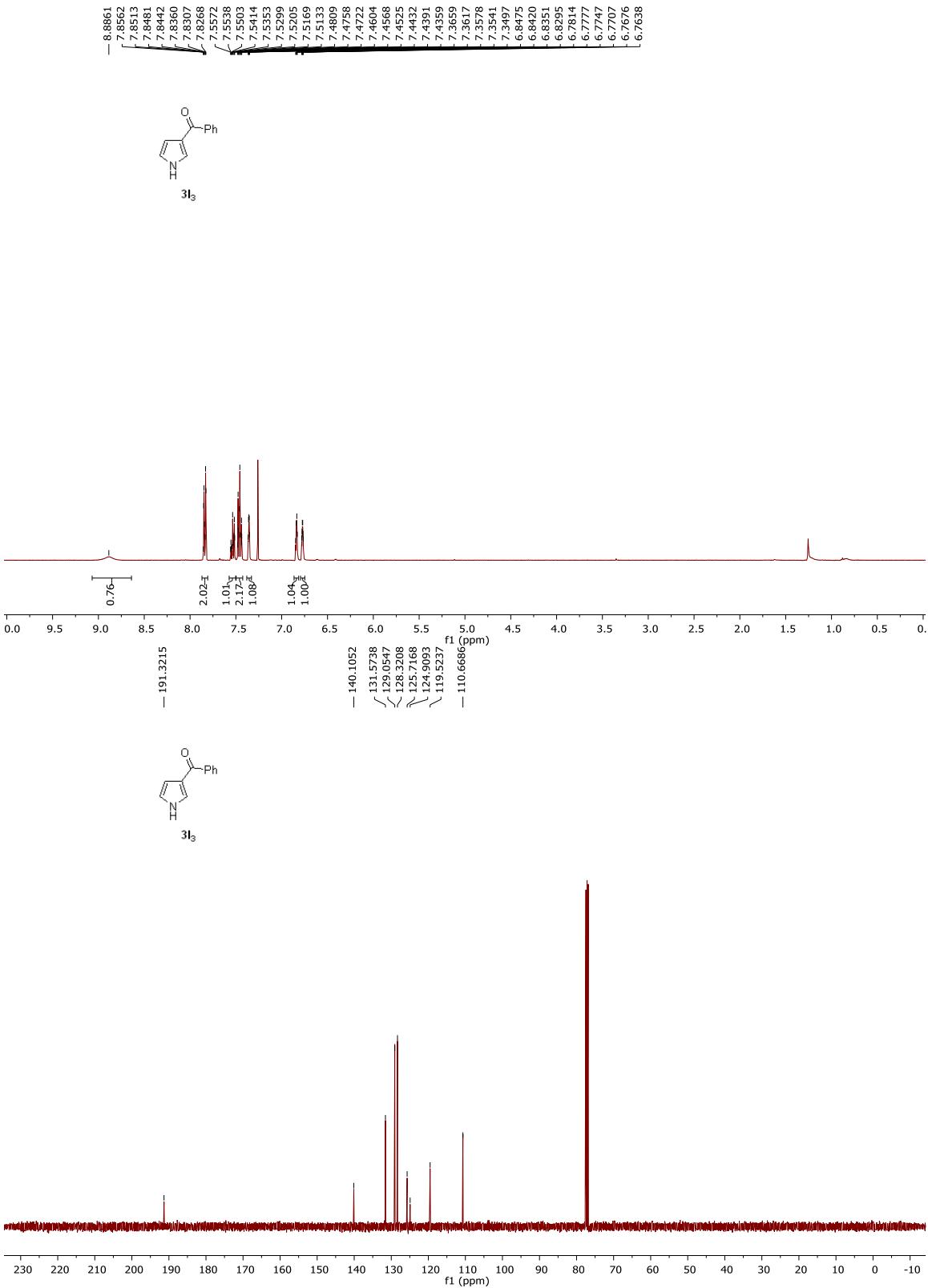


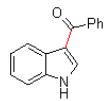
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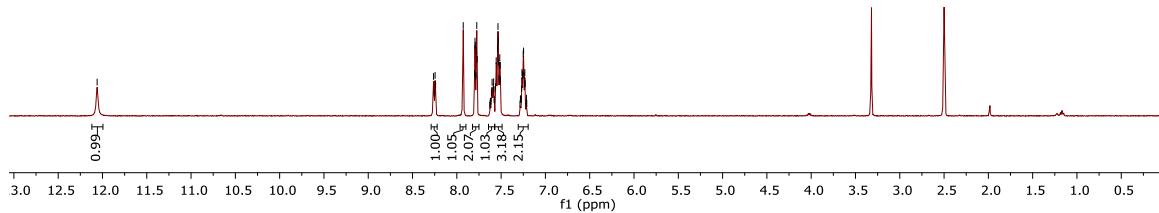
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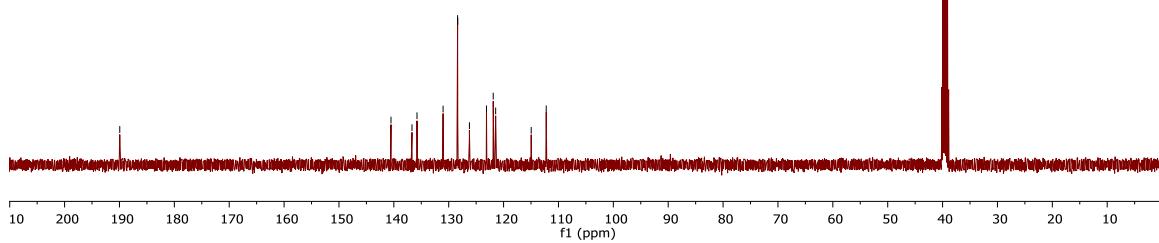


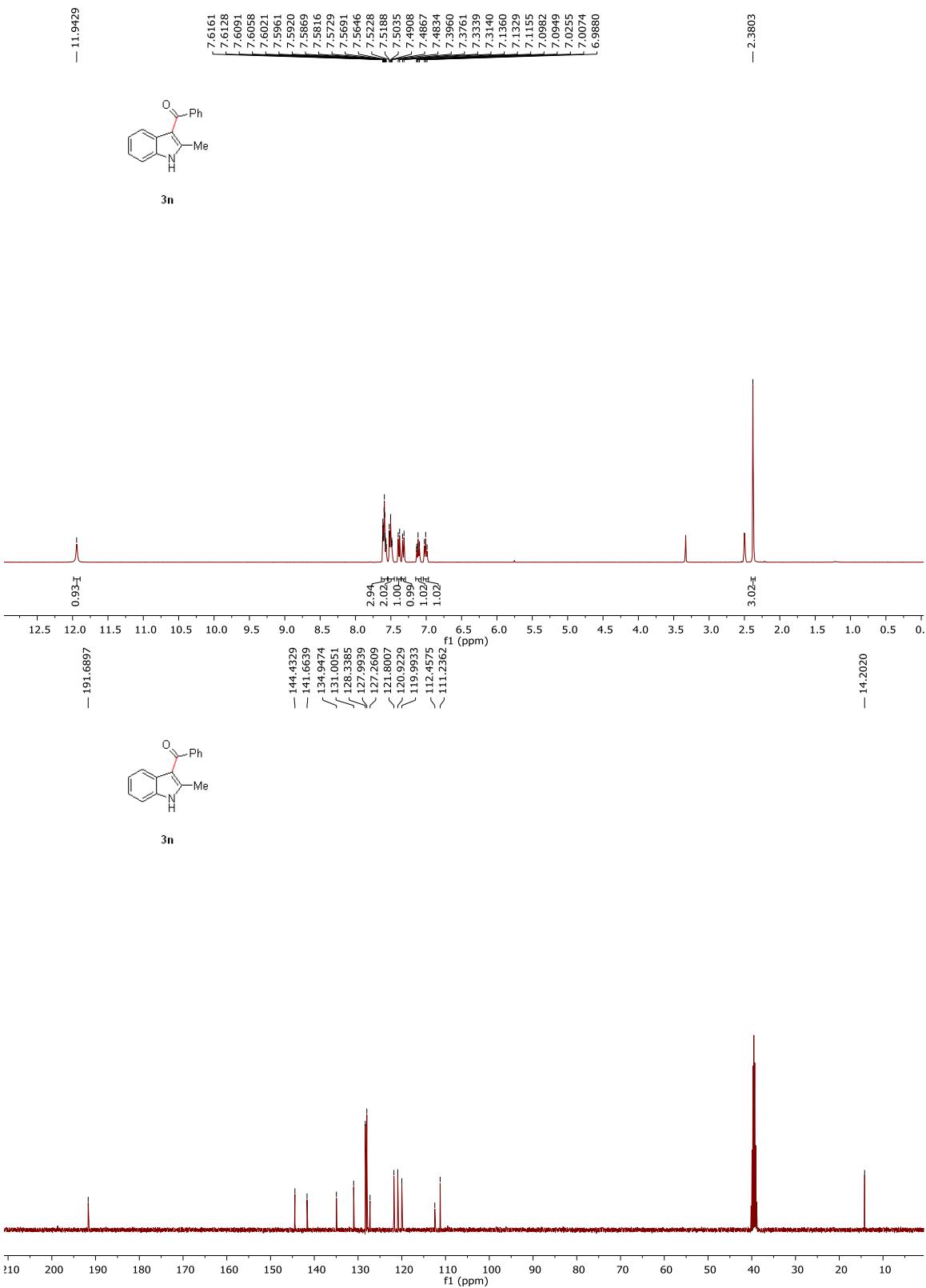


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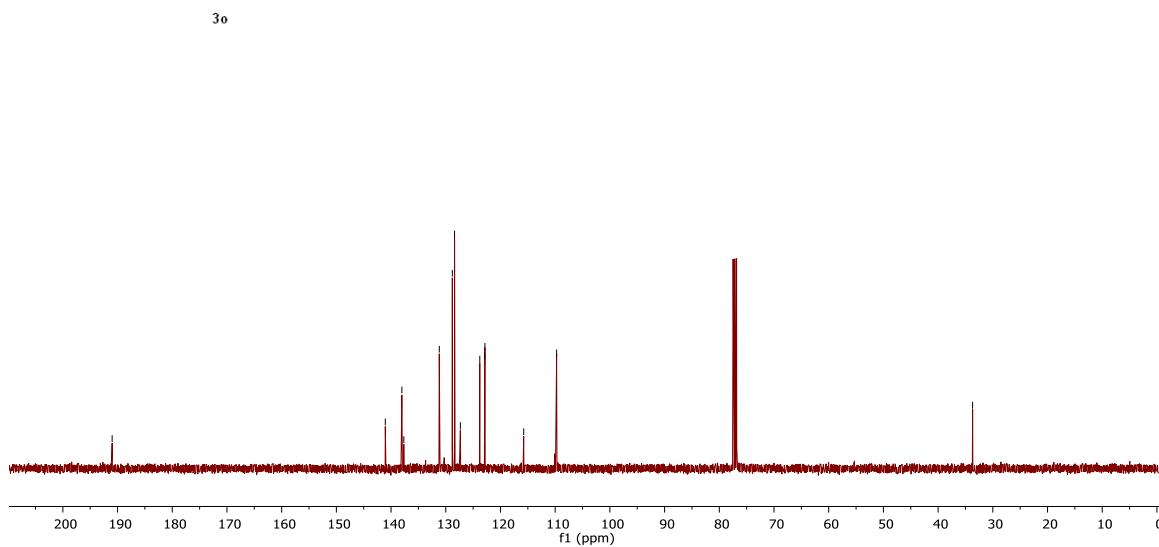
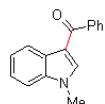
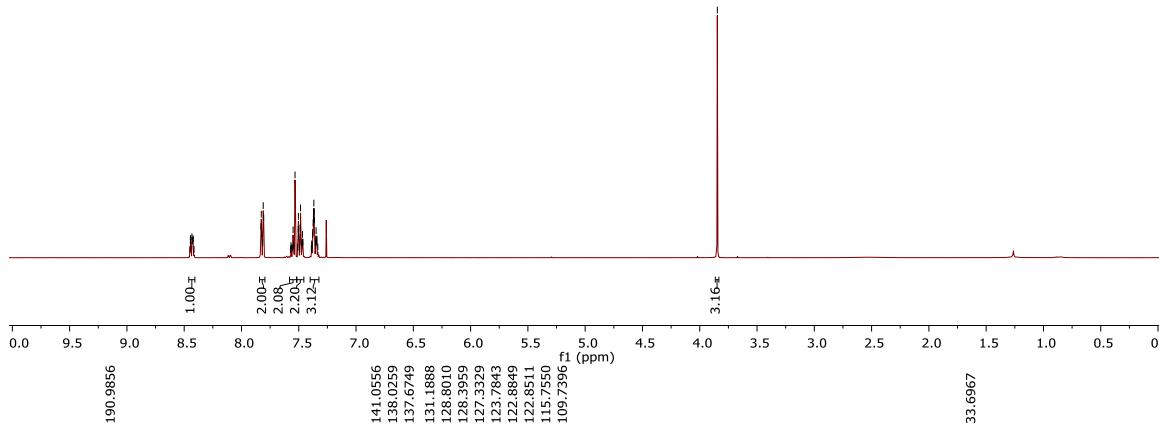


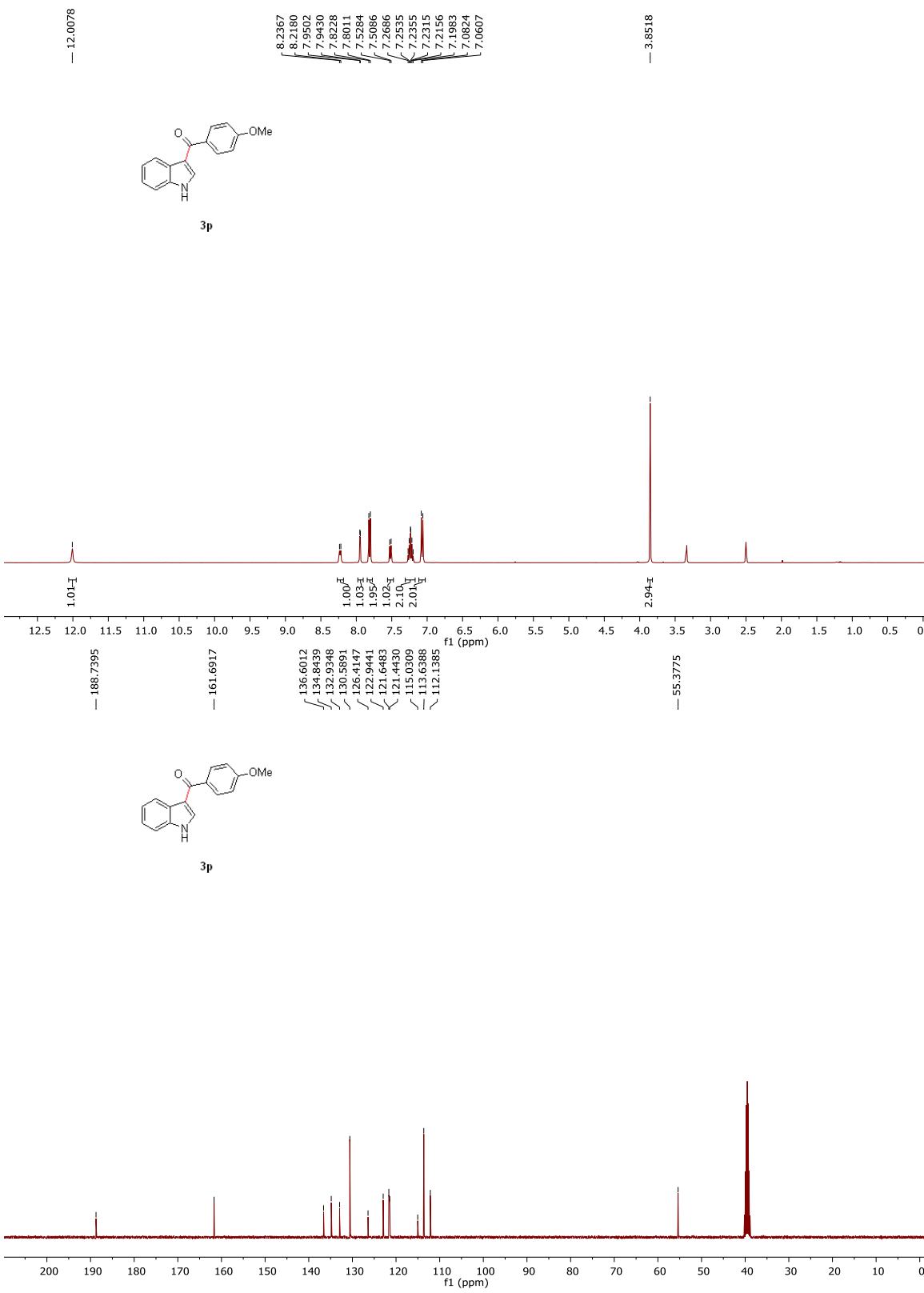
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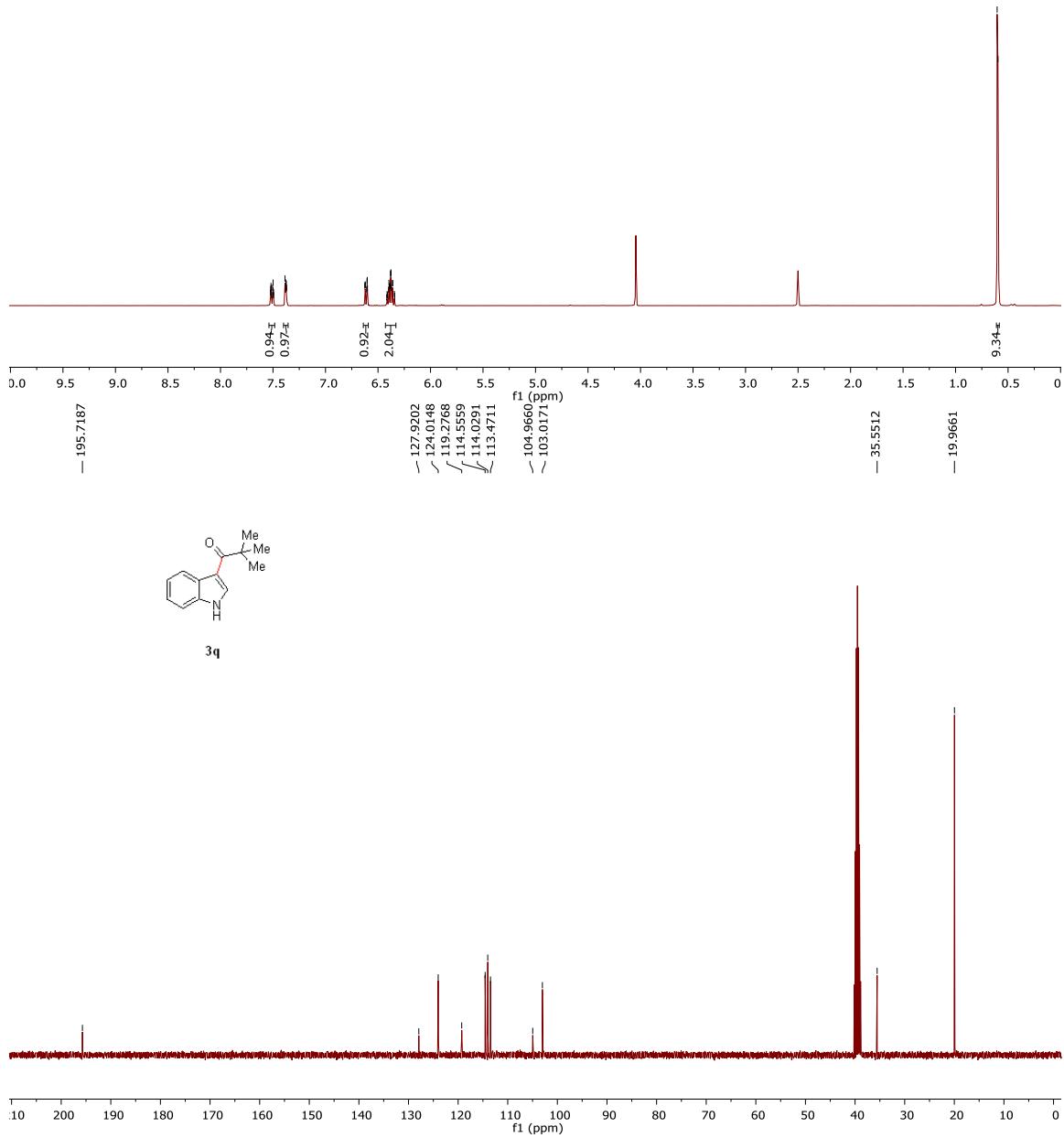
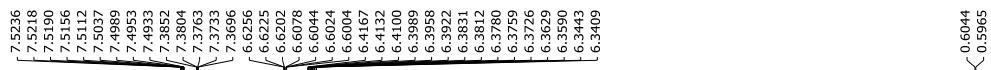


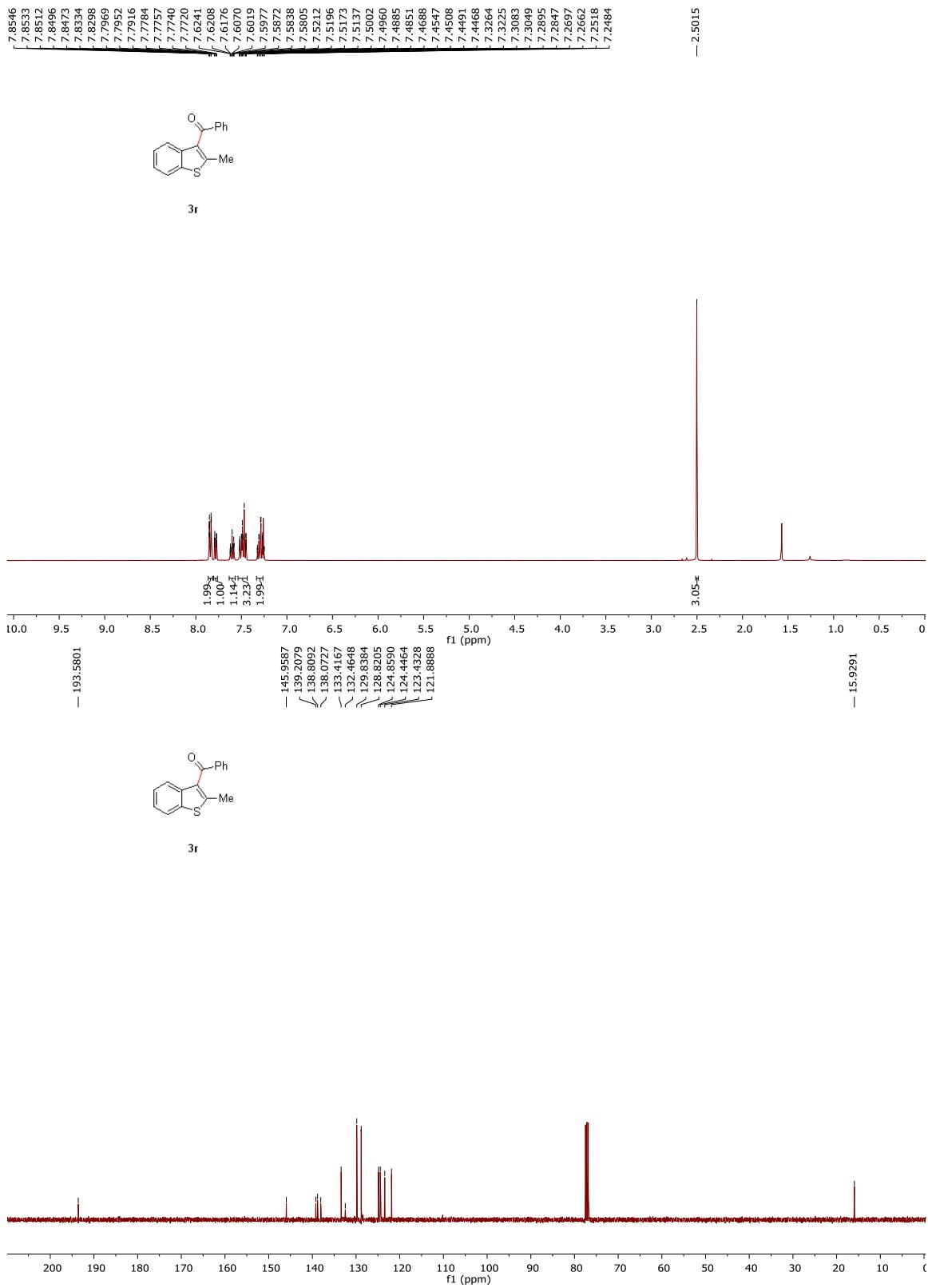


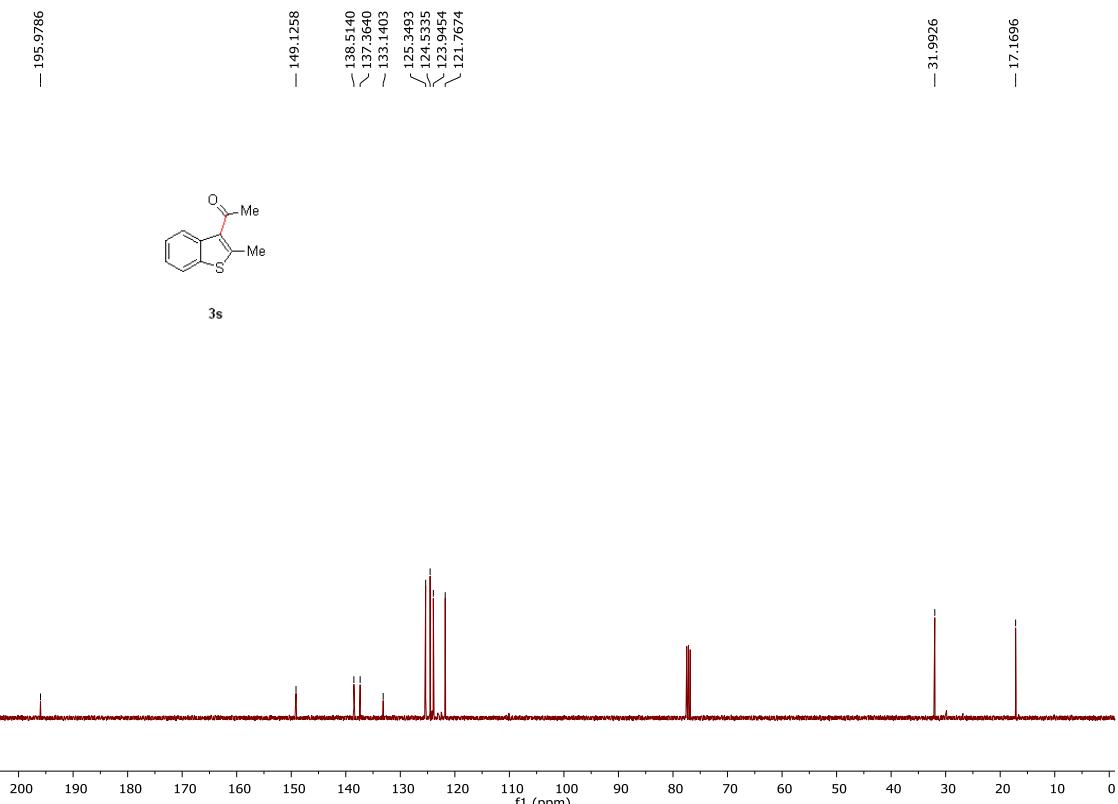
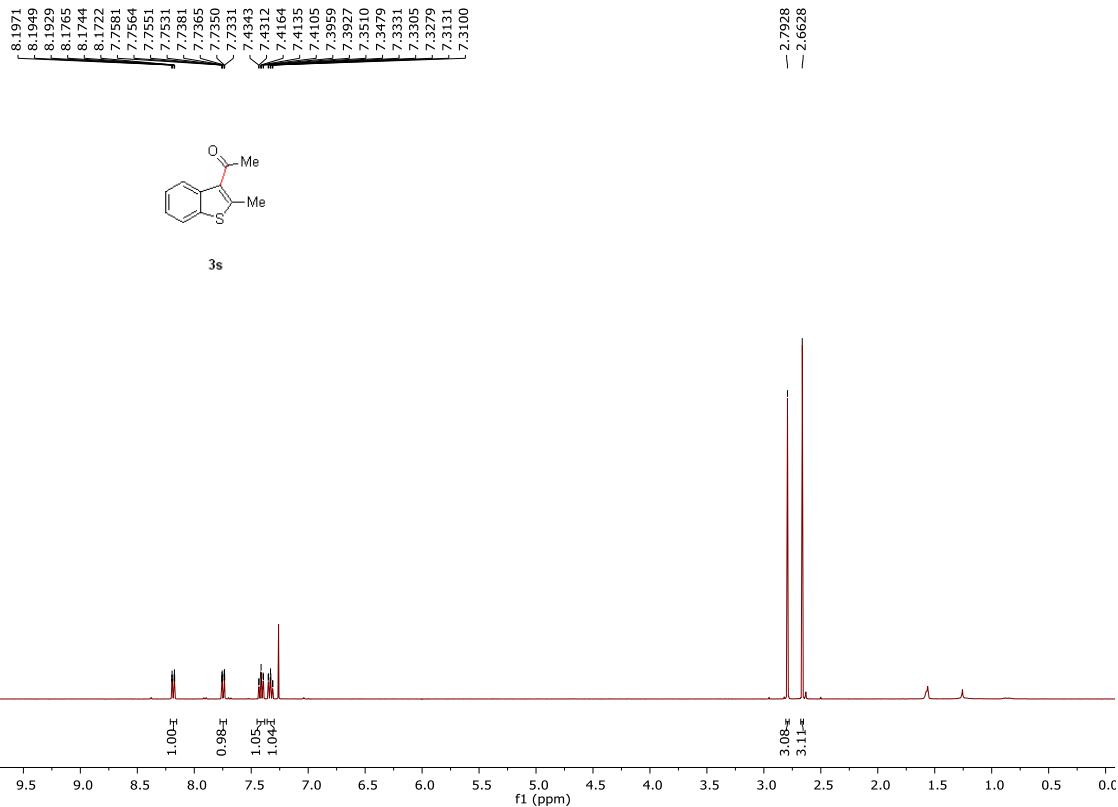
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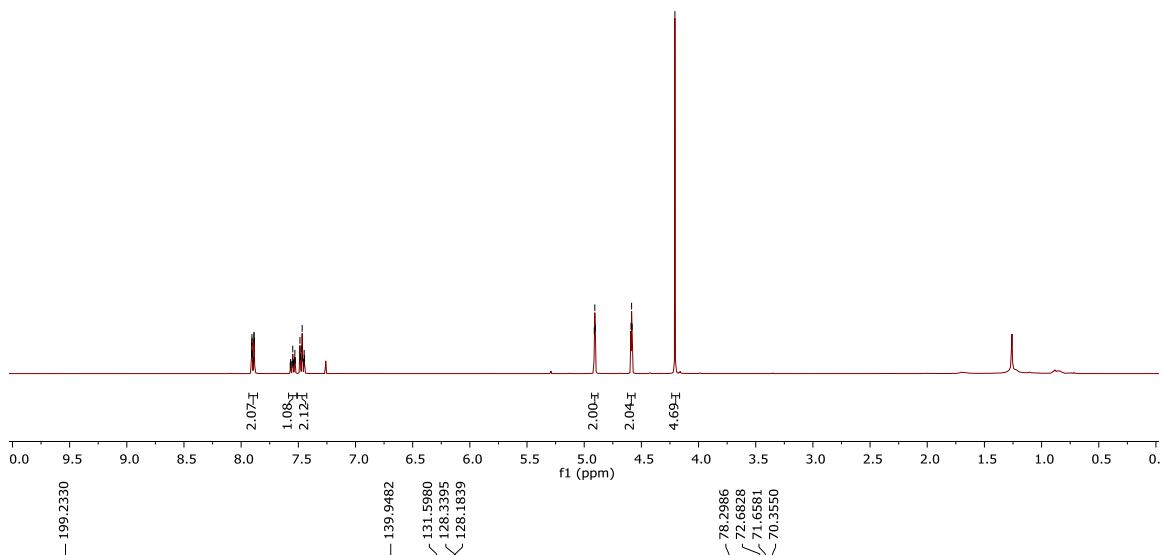




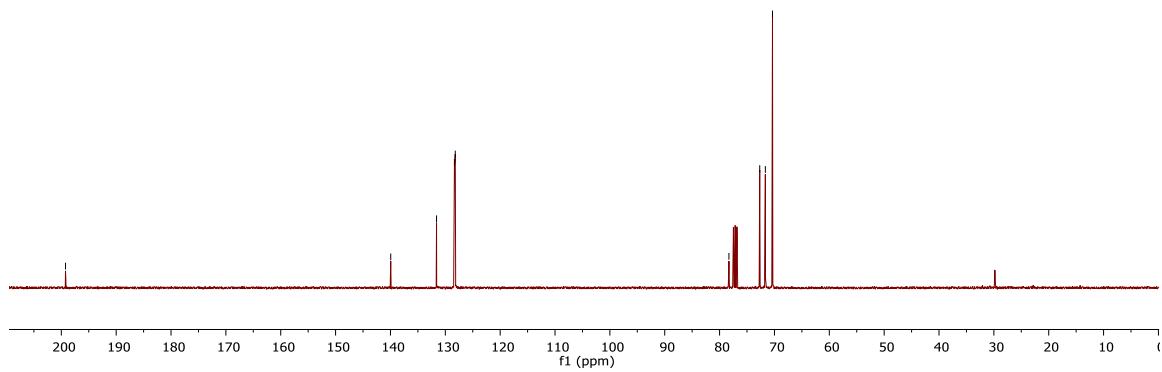
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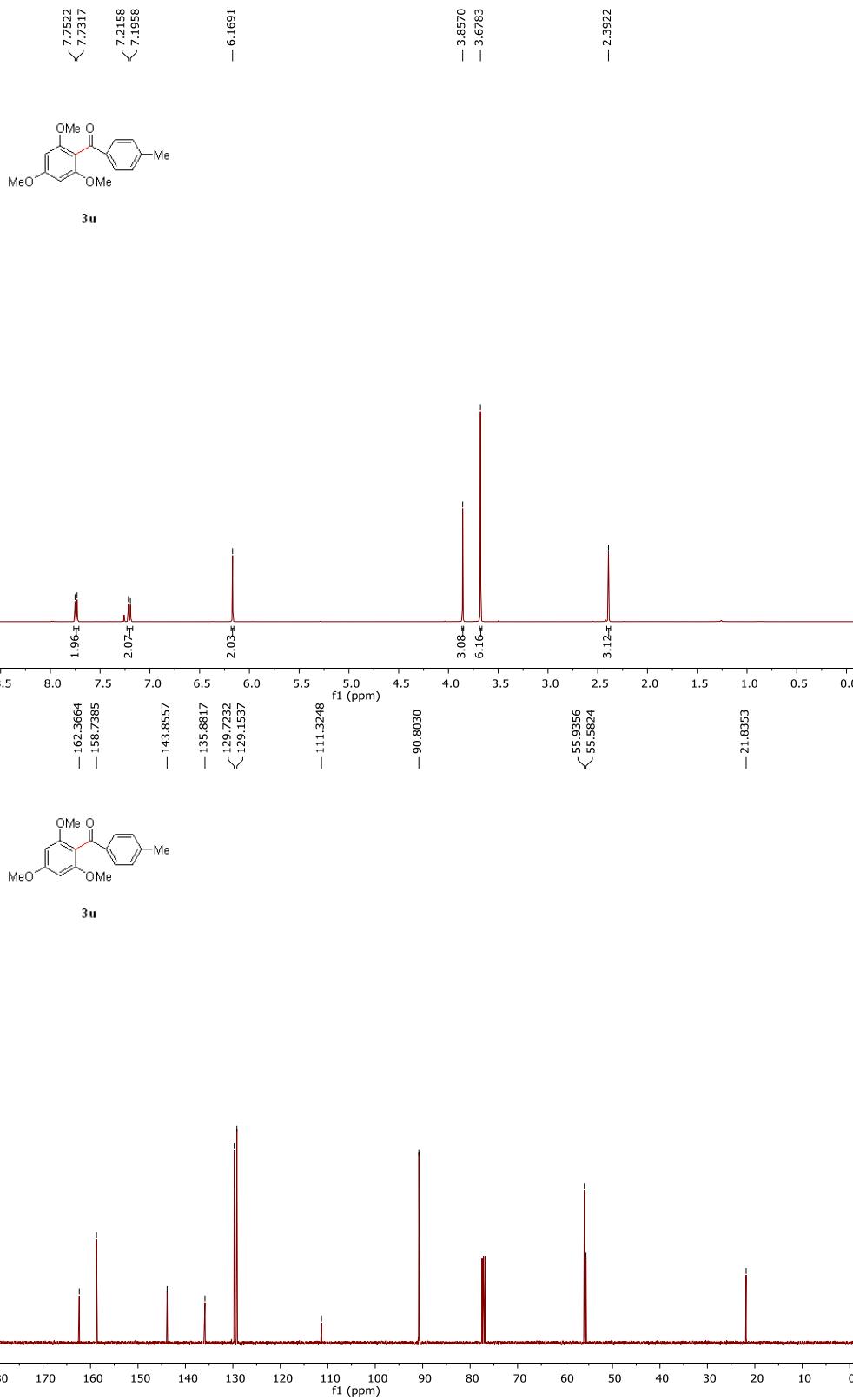


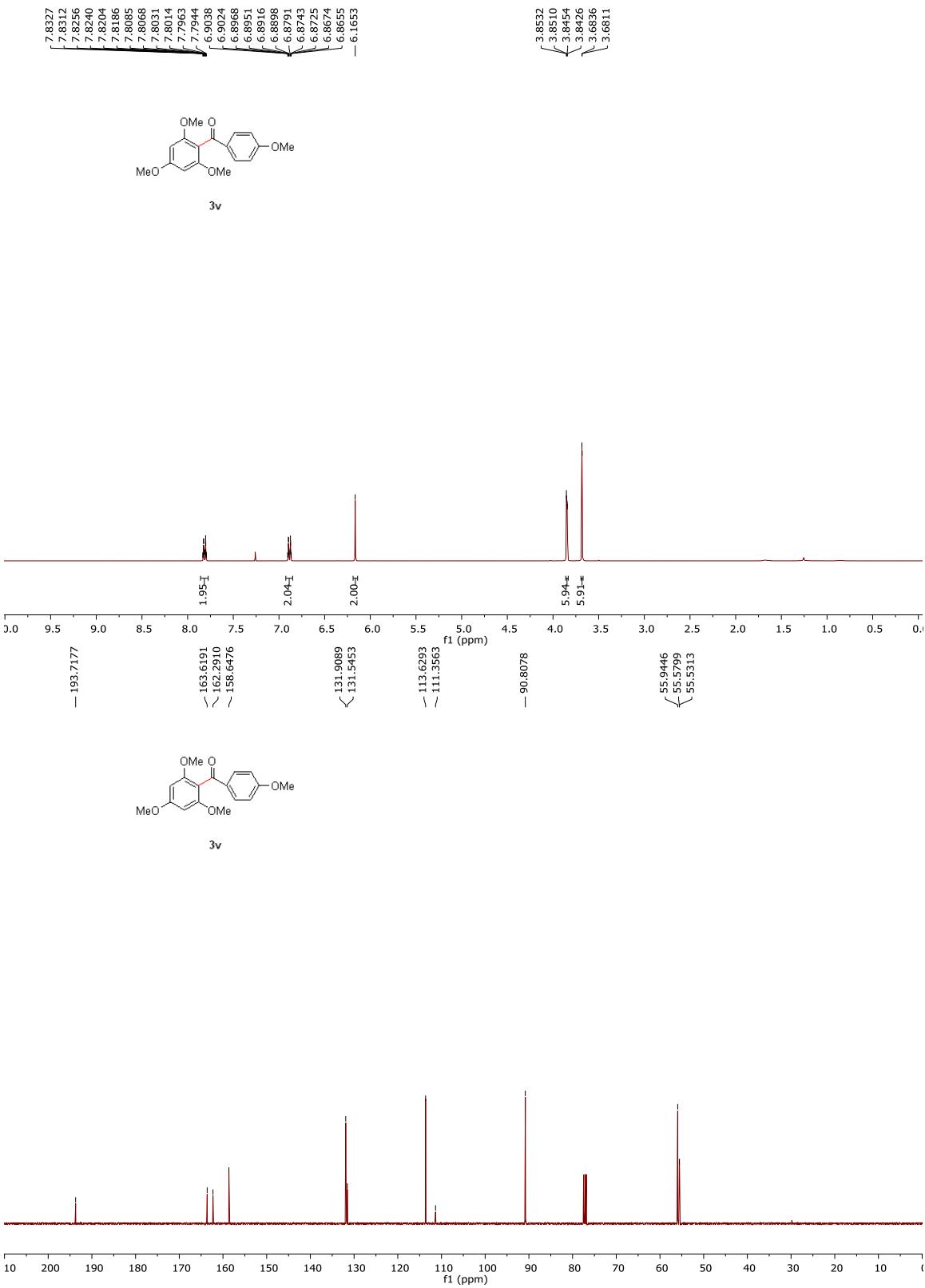
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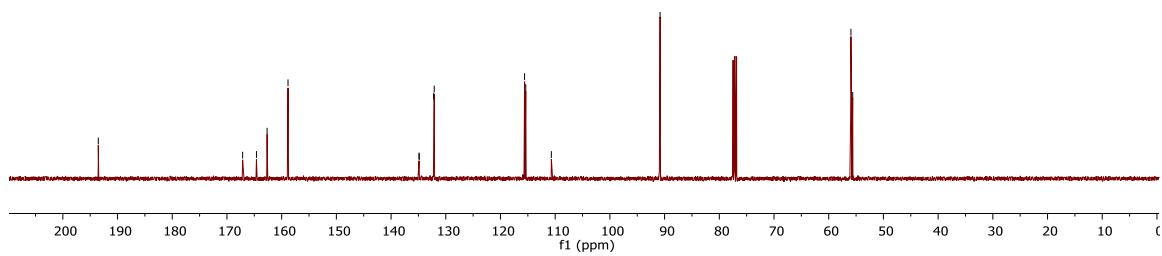
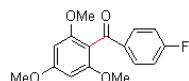
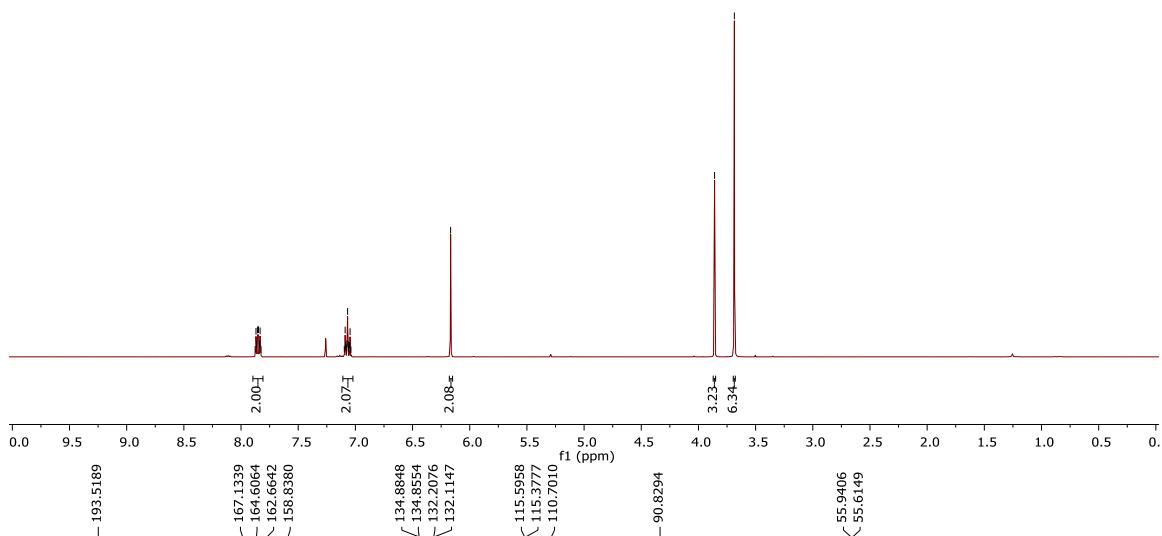
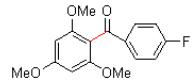


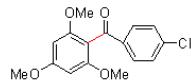
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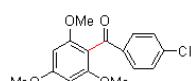
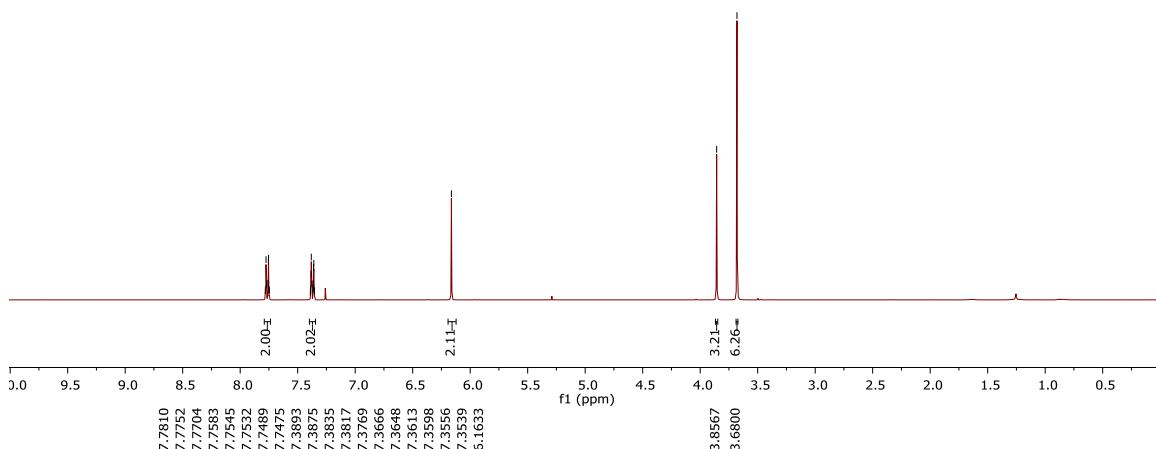








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