Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Electronic Supplementary Information for:

Copper-catalyzed tandem A^3-coupling – isomerization – hydrolysis reactions of aldehydes and terminal alkynes leading to chalcones

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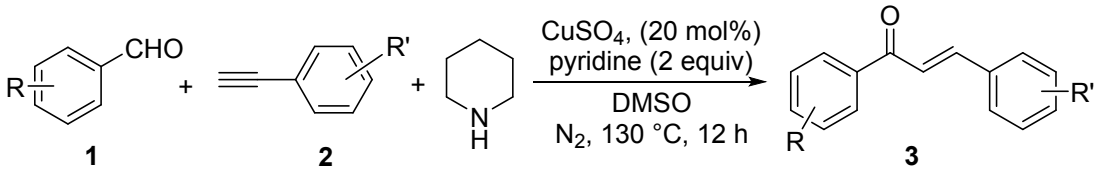
1. General Information

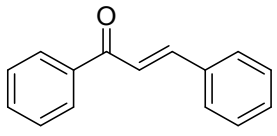
All chemicals were purchased from Adamas Reagent Ltd, energy chemical company, J&K Scientific Ltd, Alfa Aesa chemical company, etc. Unless otherwise noted, materials obtained from commercial suppliers were directly used without further purification. NMR spectra were recorded on BRUKER Avence III 500MHz spectrometers. Chemical shifts were reported in parts per million (ppm) down field from TMS with the solvent resonance as the internal standard. Coupling constants (*J*) were reported in Hz and referred to apparent peak multiplications. Qualitative analyses of the products were carried out on a SHIMADZU GCMS-QP2010 gas chromatograph mass spectrometer. The yield of the product **3aa** was based on GC analysis on an Agilent 7890B GC system by using dodecane as the internal standard.

2. General Procedure of the Tandem Reactions



To a 25 mL schlenk tube was added anhydrous $CuSO_4$ (16.0 mg, 0.1 mmol). Then, aldehyde **1** (52 μL, 0.5 mmol), terminal alkyne **2** (75 μL, 0.75 mmol), piperidine (74 μL, 0.75 mmol), pyridine (75 μL, 1 mmol) and dimethyl sulfoxide (1.5 mL) were added in sequence by syringe with nitrogen flowing at a double-rowed pipe. The reaction tube was then sealed and the resulting mixture was stirred at 130 °C for 12 h. After cooling to room temperature, water was added and the mixture was extracted with ethyl acetate for three times. The organic phases were combined, dried by anhydrous $NaSO_4$ and concentrated under vacuum. The residue was purified by chromatography on silica gel with ethyl acetate/petroleumether to give corresponding product **3**.

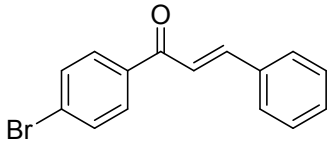
(*E*)-chalcone (CAS Registry Number 94-41-7)



This product (**3aa**) was synthesized from the reaction of benzaldehyde (**1a**) and phenylacetylene

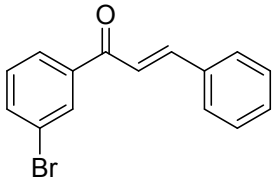
(**2a**) following the general procedure. Purification via silica gel column chromatography (petroleum ether/EtOAc = 50/1 v/v) afforded the desired product as a yellow crystal (73 mg, 70% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.44-7.47 (m, 3H), 7.52-7.58 (m, 3H), 7.60-7.63 (m, 1H), 7.67-7.69 (m, 2H), 7.84 (d, J = 15.5 Hz, 1H), 8.04-8.07 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 122.1, 128.5, 128.5, 128.6, 129.0, 132.8, 134.9, 138.2, 144.9, 190.6. GC-MS: *calcd* for $C_{15}H_{12}O$ (M^+): *m/z* = 208, found: 208; Melting Point: 52-57°C.

(*E*)-1-(4-bromophenyl)-3-phenylprop-2-en-1-one (CAS Registry Number 2403-27-2)



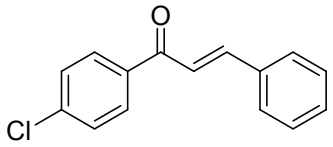
This product (**3ba**) was synthesized from the reaction of 4-bromobenzaldehyde (**1b**) and phenylacetylene (**2a**) following the general procedure. Purification via silica gel column chromatography (petroleum ether/EtOAc = 100/1 v/v) afforded the desired product as a yellow crystal (94 mg, 66% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.42-7.44 (m, 3H), 7.48 (d, J = 15.5 Hz, 1H), 7.64-7.66 (m, 4H), 7.82 (d, J = 15.5 Hz, 1H), 7.88-7.90 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 121.5, 127.9, 128.5, 129.0, 130.0, 130.8, 131.9, 134.7, 136.9, 145.4, 189.4. GC-MS: *calcd* for $C_{15}H_{11}OBr$ (M^+): *m/z* = 286; 288, found:; Melting Point: 96-98 °C.

(*E*)-1-(3-bromophenyl)-3-phenylprop-2-en-1-one (CAS Registry Number 22966-26-3)



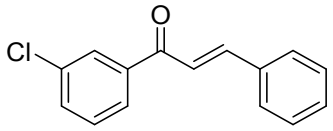
This product (**3ca**) was synthesized from the reaction of 3-bromobenzaldehyde (**1c**) and phenylacetylene (**2a**) following the general procedure. Purification via silica gel column chromatography (petroleum ether/EtOAc = 100/1 v/v) afforded the desired product as a yellow crystal (mg, % yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.38-7.48 (m, 5H), 7.65-7.67 (m, 2H), 7.70-7.72 (m, 1H), 7.83 (d, J = 15.5 Hz, 1H), 7.93-7.95 (m, 1H), 8.14-8.15 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 121.4, 123.0, 127.0, 128.6, 129.0, 130.2, 130.9, 131.5, 134.6, 135.6, 140.0, 145.7, 189.1. GC-MS: *calcd* for $C_{15}H_{11}OBr$ (M^+): *m/z* = 286; 288, found:; Melting Point: 92-95 °C (Lit.: °C).

(*E*)-1-(4-chlorophenyl)-3-phenylprop-2-en-1-one (CAS Registry Number 956-02-5)



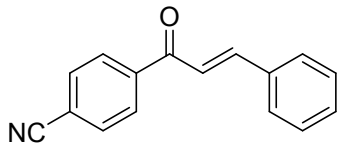
This product (**3da**) was synthesized from the reaction of 4-chlorobenzaldehyde (**1d**) and phenylacetylene (**2a**) following the general procedure. Purification via silica gel column chromatography (petroleum ether/EtOAc = 50/1 v/v) afforded the desired product as a white solid (80 mg, 66% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.42-4.35 (m, 3H), 7.47-7.50 (m, 3H), 7.64-7.66 (m, 2H), 7.82 (d, J = 15.5 Hz, 1H), 7.96-7.98 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 121.5, 128.5, 128.9, 129.0, 129.9, 130.7, 134.7, 136.5, 139.2, 145.3, 189.2. GC-MS: *calcd* for $C_{15}H_{11}OCl$ (M^+): *m/z* = 242, found: 242; Melting Point: 93-96 °C.

(*E*)-1-(3-chlorophenyl)-3-phenylprop-2-en-1-one (CAS Registry Number 20426-48-6)



This product (**3ea**) was synthesized from the reaction of 3-chlorobenzaldehyde (**1e**) and phenylacetylene (**2a**) following the general procedure. Purification via silica gel column chromatography (petroleum ether/EtOAc = 50/1 v/v) afforded the desired product as a white solid (75 mg, 62% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.46-7.51 (m, 5H), 7.58-7.60 (m, 1H), 7.67-7.69 (m, 2H), 7.86 (d, J = 15.5 Hz, 1H), 7.91-7.93 (m, 1H), 8.01 (t, J = 2.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 121.5, 126.6, 128.6, 128.6, 129.0, 130.0, 130.8, 132.7, 134.6, 134.9, 139.8, 145.7, 189.2. GC-MS: *calcd* for $C_{15}H_{11}OCl$ (M^+): *m/z* = 242, found:; Melting Point: 94-96°C.

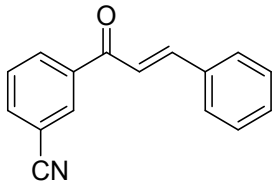
4-cinnamoylbenzonitrile (CAS Registry Number 31083-73-5)



This product (**3fa**) was synthesized from the reaction of 4-formylbenzonitrile (**1f**) and phenylacetylene (**2a**) following the general procedure. Purification via silica gel column chromatography (petroleum ether/EtOAc = 10/1 v/v) afforded the desired product as a white solid (95 mg, 82% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.42-7.48 (m, 4H), 7.65-7.67 (m, 2H), 7.80-

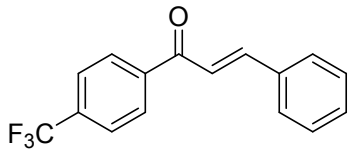
7.86 (m, 3H), 8.08-8.10 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 116.0, 118.0, 121.2, 128.7, 128.9, 129.1, 131.2, 132.5, 134.4, 141.5, 146.6, 189.2. GC-MS: *calcd* for $C_{16}H_{11}NO$ (M^+): *m/z* = 233, found: 233; Melting Point: 112-114°C.

3-cinnamoylbenzonitrile (CAS Registry Number 72344-12-8)



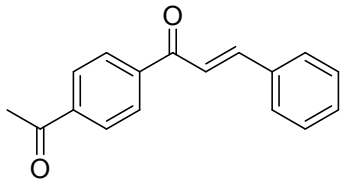
This product (**3ga**) was synthesized from the reaction of 3-formylbenzonitrile (**1g**) and phenylacetylene (**2a**) following the general procedure. Purification via silica gel column chromatography (petroleum ether/EtOAc = 10/1 v/v) afforded the desired product as a white solid (72 mg, 62% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.44-7.49 (m, 4H), 7.64-7.68 (m, 3H), 7.85-7.88 (m, 2H), 8.23-8.25 (m, 1H), 8.29-8.30 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 113.2, 118.0, 120.8, 128.7, 129.1, 129.7, 131.2, 132.1, 132.4, 134.4, 135.6, 139.1, 146.6, 188.3. GC-MS: *calcd* for $C_{16}H_{11}NO$ (M^+): *m/z* = 233, found: 233; Melting Point: 128-130 °C.

(*E*)-3-phenyl-1-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (CAS Registry Number 32120-33-5)



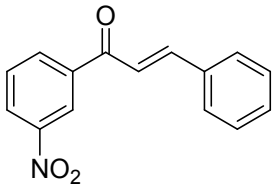
This product (**3ha**) was synthesized from the reaction of 4-(trifluoromethyl)benzaldehyde (**1h**) and phenylacetylene (**2a**) following the general procedure. Purification via silica gel column chromatography (petroleum ether/EtOAc = 50/1 v/v) afforded the desired product as a white solid (100 mg, 72% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.43-7.46 (m, 3H), 7.49 (d, *J* = 15.5 Hz, 1H), 7.65-7.67 (m, 2H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.83 (d, *J* = 15.5 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 121.6, 123.6 (q, J_{CF} = 267.5 Hz), 125.7, 125.6, 128.6, 128.8, 129.1, 131.0, 134.0 (d, *J* = 32.5 Hz), 134.5, 141.1, 146.1, 189.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ = -63.0. GC-MS: *calcd* for $C_{16}H_{11}F_3O$ (M^+): *m/z* = 276, found: 276; Melting Point: 113-116 °C.

(*E*)-1-(4-acetylphenyl)-3-phenylprop-2-en-1-one (CAS Registry Number 1420765-22-5)



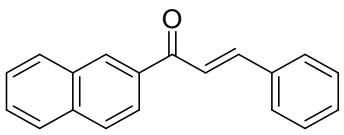
This product (**3ia**) was synthesized from the reaction of 4-acetylbenzaldehyde (**1i**) and phenylacetylene (**2a**) following the general procedure. Purification via silica gel column chromatography (petroleum ether/EtOAc = 20/1 v/v) afforded the desired product as a white solid (65 mg, 52% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.67 (s, 3H), 7.43-7.45 (m, 3H), 7.51 (d, J = 15.5 Hz, 1H), 7.65-7.67 (m, 2H), 7.83 (d, J = 15.5 Hz, 1H), 8.08 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 26.9, 121.8, 128.5, 128.6, 128.7, 129.1, 130.9, 134.6, 139.9, 141.6, 145.9, 190.0, 197.5. GC-MS: *calcd* for $C_{17}H_{14}O_2$ (M^+): *m/z* = 250, found: 250; Melting Point: 116-119 °C.

(*E*)-1-(3-nitrophenyl)-3-phenylprop-2-en-1-one (CAS Registry Number 16619-21-9)



This product (**3ja**) was synthesized from the reaction of 3-nitrobenzaldehyde (**1j**) and phenylacetylene (**2a**) following the general procedure. Purification via silica gel column chromatography (petroleum ether/EtOAc = 20/1 v/v) afforded the desired product as a white solid (42 mg, 33% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.45-7.48 (m, 3H), 7.53 (d, J = 15.5 Hz, 1H), 7.68-7.70 (m, 2H), 7.73 (t, J = 8.0 Hz, 1H), 7.90 (d, J = 15.5 Hz, 1H), 8.35-8.37 (m, 1H), 8.44-8.46 (m, 1H), 8.84 (t, J = 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 120.7, 123.3, 127.1, 128.8, 129.1, 129.9, 131.2, 134.1, 134.3, 139.5, 146.8, 148.4, 188.0. GC-MS: *calcd* for $C_{15}H_{11}NO_3$ (M^+): *m/z* = 253, found: 253; Melting Point: 124-126 °C.

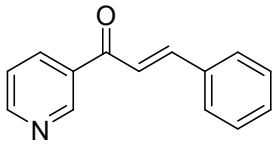
(*E*)-1-(naphthalen-2-yl)-3-phenylprop-2-en-1-one (CAS Registry Number 4782-69-8)



This product (**3ka**) was synthesized from the reaction of 2-naphthaldehyde (**1k**) and phenylacetylene (**2a**) following the general procedure. Purification via silica gel column

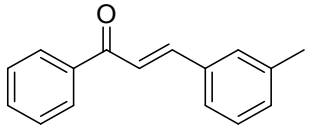
chromatography (petroleum ether/EtOAc = 50/1 v/v) afforded the desired product as a white solid (71 mg, 55% yield, *E/Z* = 8 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.43-7.46 (m, 3H), 7.54-7.61 (m, 3H), 7.68-7.72 (m, 3H), 7.88 (d, *J* = 15.5 Hz, 1H), 7.94-8.01 (m, 2H), 8.09-8.12 (m, 1H), 8.55 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 122.1, 124.5, 126.8, 127.9, 128.4, 128.5, 128.6, 128.6, 129.6, 130.0, 130.6, 132.6, 135.0, 135.5, 135.6, 144.8, 190.4. GC-MS: *calcd* for $C_{19}H_{14}O$ (M^+): *m/z* = 258, found: 258; Melting Point: 90-94 °C.

(*E*)-3-phenyl-1-(pyridin-3-yl)prop-2-en-1-one (CAS Registry Number 6314-59-6)



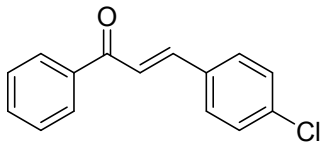
This product (**3la**) was synthesized from the reaction of nicotinaldehyde (**1l**) and phenylacetylene (**2a**) Purification via silica gel column chromatography (petroleum ether/EtOAc = 10/1 v/v) afforded the desired product as a white solid (71 mg, 68% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.44-7.45 (m, 5H), 7.65-7.67 (m, 5H), 7.85 (d, *J* = 15.5 Hz, 1H), 8.29-8.31 (m, 1H), 8.82 (s, 1H), 9.25 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 121.4, 128.6, 129.1, 131.0, 134.4, 135.9, 146.1, 149.8, 153.2, 189.2. GC-MS: *calcd* for $C_{14}H_{11}NO$ (M^+): *m/z* = 209, found: 209; Melting Point: 86-92 °C.

(*E*)-1-phenyl-3-(*m*-tolyl)prop-2-en-1-one (CAS Registry Number 16619-29-7)



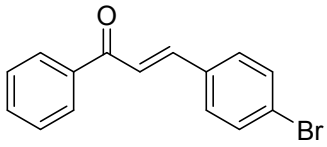
This product (**3ab**) was synthesized from the reaction of benzaldehyde (**1a**) and phenylacetylene (**2b**) Purification via silica gel column chromatography (petroleum ether/EtOAc = 50/1 v/v) afforded the desired product as a white solid (72mg, 65% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.40 (s, 3H), 7.22-7.25 (m, 1H), 7.32 (t, *J* = 7.0 Hz, 1H), 7.41-7.46 (m, 3H), 7.49-7.54 (m, 3H), 7.57-7.60 (m, 1H), 7.78 (d, *J* = 16.0 Hz, 1H), 8.01-8.03 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.4, 121.9, 125.3, 128.5, 128.6, 128.9, 129.1, 131.4, 132.7, 134.9, 138.3, 138.6, 145.1, 190.6. GC-MS: *calcd* for $C_{16}H_{14}O$ (M^+): *m/z* = 222, found: 222; Melting Point: 60-63 °C.

(*E*)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (CAS Registry Number 956-04-7)



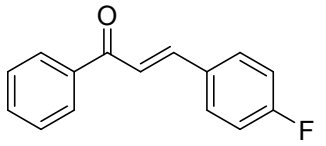
This product (**3ac**) was synthesized from the reaction of benzaldehyde (**1a**) and 1-chloro-4-ethynylbenzene (**2c**) Purification via silica gel column chromatography (petroleum ether/EtOAc = 50/1 v/v) afforded the desired product as a white solid (86 mg, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.39 (d, J = 8.5 Hz, 2H), 7.49-7.53 (m, 3H), 7.57-7.61 (m, 3H), 7.76 (d, J = 15.5 Hz, 1H), 8.01-8.02 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 122.5, 128.5, 128.7, 129.3, 129.6, 132.9, 133.4, 136.4, 138.0, 143.3, 190.2. GC-MS: *calcd* for $C_{15}H_{11}OCl$ (M^+): *m/z* = 242, found: 242; Melting Point: 105-107 °C.

(*E*)-3-(4-bromophenyl)-1-phenylprop-2-en-1-one (CAS Registry Number 1774-66-9)



This product (**3ad**) was synthesized from the reaction of benzaldehyde (**1a**) and 1-chloro-4-ethynylbenzene (**2d**) Purification via silica gel column chromatography (petroleum ether/EtOAc = 50/1 v/v) afforded the desired product as a white solid (64 mg, 45%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.50-7.57 (m, 7H), 7.58-7.62 (m, 1H), 7.74 (d, J = 16.0 Hz, 1H), 8.00-8.03 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 122.6, 124.8, 128.5, 128.7, 129.8, 132.2, 133.0, 133.8, 138.0, 143.4, 190.3. GC-MS: *calcd* for $C_{15}H_{11}OBr$ (M^+): *m/z* = 286; 288, found: 286; 288; Melting Point: 120-122 °C

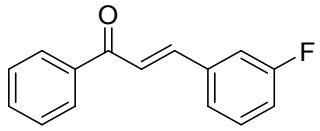
(*E*)-3-(4-fluorophenyl)-1-phenylprop-2-en-1-one (CAS Registry Number 1608-51-1)



This product (**3ae**) was synthesized from the reaction of benzaldehyde (**1a**) and 1-ethynyl-4-fluorobenzene (**2e**) Purification via silica gel column chromatography (petroleum ether/EtOAc = 50/1 v/v) afforded the desired product as a white solid (80 mg, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.11 (t, J = 8.5 Hz, 2H), 7.45-7.51 (m, 3H), 7.58-7.59 (m, 1H), 7.61-7.64 (m, 2H), 7.78 (d, J = 15.5 Hz, 1H), 8.01-8.02 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 116.1 (J_{CF} = 21.9 Hz), 121.8, 128.5 (d, J_{CF} = 21.9 Hz), 130.3, 130.3, 131.2, 132.8, 138.1, 143.5, 164.1 (d, J_{CF} = 250.4 Hz),

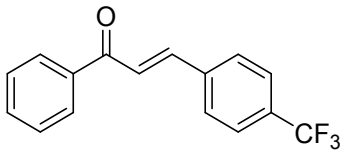
190.3. GC-MS: *calcd* for $C_{15}H_{11}OF$ (M^+): *m/z* = 226, found: 226; Melting Point: 78-82 °C.

(*E*)-3-(3-fluorophenyl)-1-phenylprop-2-en-1-one (CAS Registry Number 1608-52-2)



This product (**3af**) was synthesized from the reaction of benzaldehyde (**1a**) and 1-ethynyl-3-fluorobenzene (**2f**) Purification via silica gel column chromatography (petroleum ether/EtOAc = 50/1 v/v) afforded the desired product as a white solid (73 mg, 69%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.10-7.13 (m, 1H), 7.34-7.42 (m, 3H), 7.59-7.62 (m, 1H), 7.76 (d, *J* = 15.5 Hz, 1H), 8.01-8.03 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 114.4 (d, J_{CF} = 21.8 Hz), 117.3 (d, J_{CF} = 21.2 Hz), 123.2, 124.5, 128.6 (d, J_{CF} = 21.4 Hz), 130.5, 130.5, 133.0, 131.2 (d, J_{CF} = 6.4 Hz), 137.9, 143.3, 163.1 (d, J_{CF} = 245.5 Hz), 190.2. GC-MS: *calcd* for $C_{15}H_{11}OF$ (M^+): *m/z* = 226, found: 226; Melting Point: 87-92 °C.

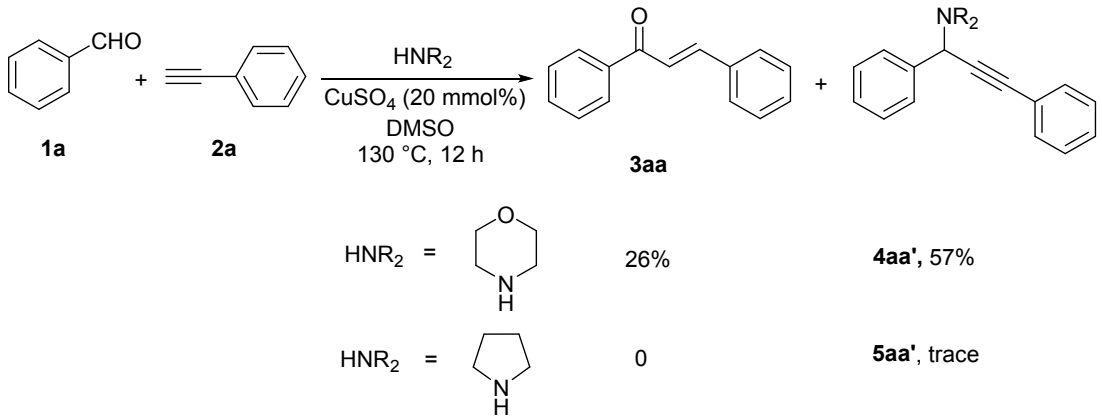
(*E*)-1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (CAS Registry Number 61637-11-4)



This product (**3ag**) was synthesized from the reaction of benzaldehyde (**1a**) and 1-ethynyl-3-fluorobenzene (**2g**) Purification via silica gel column chromatography (petroleum ether/EtOAc = 50/1 v/v) afforded the desired product as a white solid (93 mg, 68%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.51-7.55 (m, 2H), 7.58-7.63 (m, 2H), 7.67-7.76 (m, 4H), 7.81 (d, *J* = 16.0 Hz), 8.02-8.05 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 123.6, 123.8 (q, J_{CF} = 259.6 Hz), 125.9, 128.5, 128.6, 128.8, 125.9 (m), 131.8, 132.0, 133.1, 137.8, 138.3, 142.7, 190.6. GC-MS: *calcd* for $C_{16}H_{11}F_3O$ (M^+): *m/z* = 276, found: 276; Melting Point: 122-123 °C.

3. Control Experiments

3.1 Use of morpholine and pyrrolidine instead of piperidine

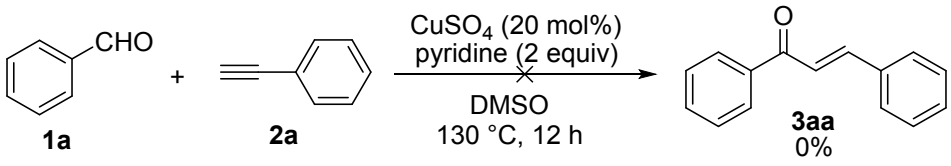


To a 25 mL schlenk tube was added anhydrous $CuSO_4$ (16.0 mg, 0.1 mmol). Then, benzaldehyde **1a** (52 μL, 0.5 mmol), phenylacetylene **2a** (75 μL, 0.75 mmol), morpholine (65 μL, 0.75 mmol) and dimethyl sulfoxide (1.5 mL) were added in sequence by syringe with nitrogen flowing at a double-rowed pipe. The reaction tube was then sealed and the resulting mixture was stirred at 130 °C for 12 h. After cooling to room temperature, water was added and the mixture was extracted with ethyl acetate. The organic phases were combined, dried by anhydrous $NaSO_4$ and concentrated under vacuum. Two products **3aa** and **4aa'** were detected by GC-MS and separated by chromatography on silica gel with ethyl acetate/petroleum ether (1/50 v/v) to afford yellow oils (27 mg and 81 mg, respectively).

4-(1,3-diphenylprop-2-yn-1-yl)morpholine (4aa') ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.60-2.66 (m, 4H), 3.69-3.76 (m, 4H), 4.81 (s, 1H), 7.28-7.32 (m, 6H), 7.49-7.52 (m, 2H), 7.62-7.64 (m, 2H). GC-MS: *calcd* for $C_{19}H_{19}NO$ (M^+): *m/z* = 277, found: 277.

The similar procedure was carried out with the use of pyrrolidine instead of piperidine. GC-MS analysis showed that no chalcone was obtained and the corresponding A^3 product **5aa'** was only trace.

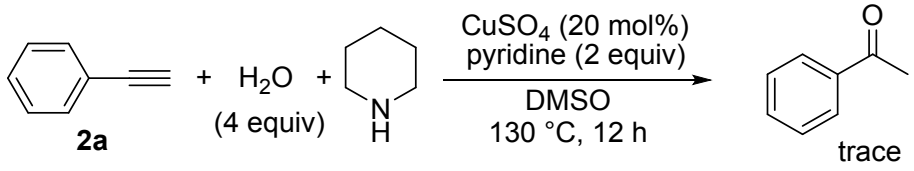
3.2 Reaction in the absence of piperidine



To a 25 mL schlenk tube was added anhydrous $CuSO_4$ (16.0 mg, 0.1 mmol). Then, benzaldehyde **1a** (52 μL, 0.5 mmol), phenylacetylene **2a** (75 μL, 0.75 mmol), pyridine (75 μL, 1 mmol) and dimethyl sulfoxide (1.5 mL) were added in sequence by syringe with nitrogen flowing at a double-rowed pipe. The reaction tube was then sealed and the resulting mixture was stirred at

130 °C for 12 h. After cooling to room temperature, water was added and the mixture was extracted with ethyl acetate. The organic phase was dried by anhydrous $NaSO_4$ and taken into analysis by GC-MS and no chalcone was detected.

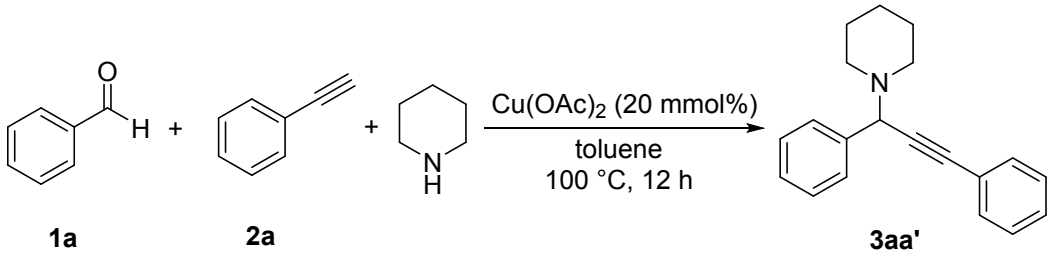
3.2 Reaction in the absence of aldehyde



To a 25 mL schlenk tube was added anhydrous $CuSO_4$ (16.0 mg, 0.1 mmol). Then phenylacetylene **2a** (75 μL, 0.75 mmol), piperidine (74 μL, 0.75 mmol), pyridine (75 μL, 1 mmol) and dimethyl sulfoxide (1.5 mL) were added in sequence by syringe with nitrogen flowing at a double-rowed pipe The reaction tube was then sealed and the resulting mixture was stirred at 130 °C for 12 h. After cooling to room temperature, water was added and the mixture was extracted with ethyl acetate. The organic phase was dried by anhydrous $NaSO_4$ and taken into analysis by GC-MS and only trace of acetophenone (<5%) was detected.

3.3 Transformation of the A^3 product

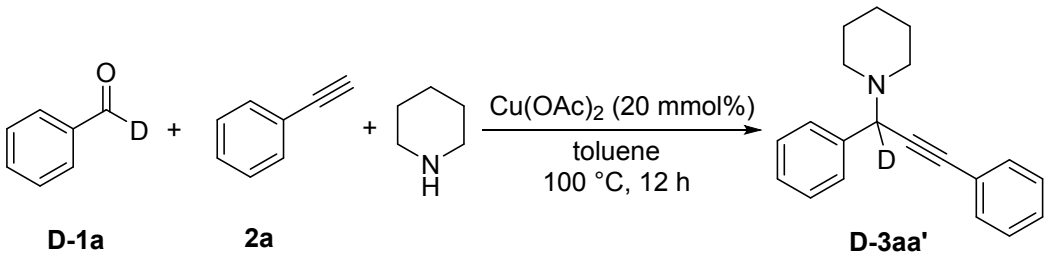
3.3.1 Synthesis of 3aa'



To a 100 mL schlenk tube was added anhydrous $Cu(OAc)_2$ (72.0 mg, 0.4 mmol). Then, benzaldehyde **1a** (208 μL, 2 mmol), phenylacetylene **2a** (300 μL, 3 mmol), piperidine (298 μL, 3 mmol), and toluene (10 mL) were added in sequence by syringe with nitrogen flowing at a double-rowed pipe. The reaction tube was then sealed and the resulting mixture was stirred at 100 °C for 12 h. After cooling to room temperature, the solvent was evaporated under vacuum. The residue was purified by chromatography on silica gel with ethyl acetate/petroleumether (1/50 v/v) to give the A^3 product **3aa' [1-(1,3-diphenylprop-2-yn-1-yl)piperidine]** (CAS Registry Number 1036-21-1) as a yellow solid (400 mg, 73% yield). ^1H NMR (500 MHz, $CDCl_3$) δ = 1.43-4.45 (m, 2H),

1.55-1.64 (m, 4H), 2.57 (br, 4H), 4.81 (s, 1H), 7.27-7.37 (m, 6H), 7.50-7.52 (m, 2H), 7.63 (d, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 24.4, 26.1, 50.7, 62.4, 86.0, 87.9, 123.3, 127.5, 128.1, 128.3, 128.6, 138.5.

3.3.2 Synthesis of D-3aa'

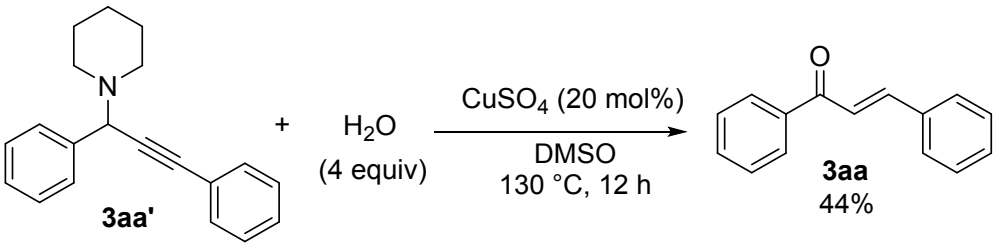


The D-labeled A^3 product **D-3aa'** was synthetic from the reaction of benzaldehyde-*d*, phenylacetylene and piperidine procedure under the conditions as described in **3.3.1**. **1-(1,3-diphenylprop-2-yn-1-yl-1-d)piperidine** (**D-3aa'**) (62% yield, yellow oil, 91% D-labeled at the propargyl position) ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.43-4.45 (m, 2H), 1.55-1.64 (m, 4H), 2.57 (br, 4H), 4.81 (s, 0.09H), 7.27-7.37 (m, 6H), 7.50-7.52 (m, 2H), 7.62-7.66 (m, 2H).

3.3.3 Reaction of 3aa' with water in the absence of a catalyst

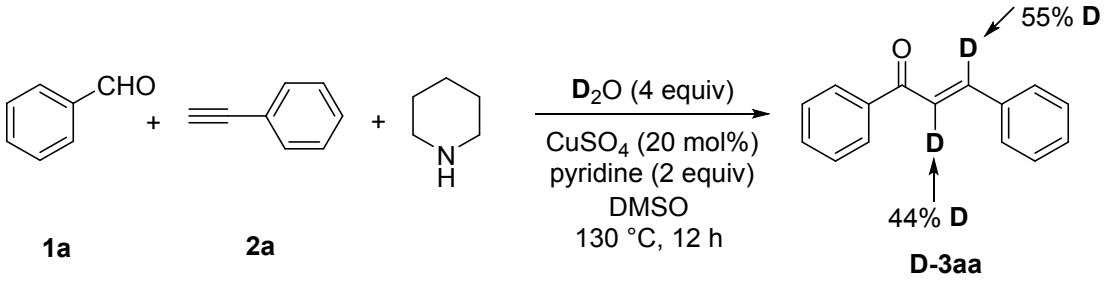
To a 25 mL schlenk tube was added A^3 product **3aa'** (137 mg, 0.5 mmol). Then, water (36 μL, 2 mmol) and dimethyl sulfoxide (1.5 mL) were added in sequence by syringe with nitrogen flowing at a double-rowed pipe. The reaction tube was then sealed and the resulting mixture was stirred at 130 °C for 12 h. After cooling to room temperature, water was added and the mixture was extracted with ethyl acetate. The organic phase was dried by anhydrous $NaSO_4$ and taken into analysis by GC-MS and no chalcone was detected. The starting material remained.

3.3.4 Reaction of 3aa' with water catalyzed by $CuSO_4$



To a 25 mL schlenk tube were added A[3] product **3aa'** (137 mg, 0.5 mmol) and anhydrous $CuSO_4$ (16.0 mg, 0.1 mmol). Then, water (36 μL, 2 mmol) and dimethyl sulfoxide (1.5 mL) were added in sequence by syringe with nitrogen flowing at a double-rowed pipe. The reaction tube was then sealed and the resulting mixture was stirred at 130 °C for 12 h. After cooling to room temperature, water was added and the mixture was extracted with ethyl acetate. The organic phase was dried by anhydrous $NaSO_4$ and taken into quantitative analysis by GC using dodecane as the internal standard.

3.3 Isotope labeled experiments



To a 25 mL schlenk tube was added anhydrous $CuSO_4$ (16.0 mg, 0.1 mmol). Then, benzaldehyde **1** (52 μL, 0.5 mmol), phenylacetylene **2** (75 μL, 0.75 mmol), piperidine (74 μL, 0.75 mmol), pyridine (75 μL, 1 mmol), $\mathbf{D}_2O$ (38 μL, 2 mmol) and dimethyl sulfoxide (1.5 mL) were added in sequence by syringe with nitrogen flowing at a double-rowed pipe. The reaction tube was then sealed and the resulting mixture was stirred at 130 °C for 12 h. After cooling to room temperature, water was added and the mixture was extracted with ethyl acetate for three times. The organic phases were combined, dried by anhydrous $NaSO_4$ and concentrated under vacuum. The residue was purified by chromatography on silica gel with ethyl acetate/petroleumether (1:50) to give corresponding product **D-3aa** in 66% yield. The product was then submitted to NMR analysis to identify the ratio of **D**-labeling on the two C=C carbons (Fig S1). It proved that partial of the hydrogen atoms on the C=C group were from water in the reaction system.

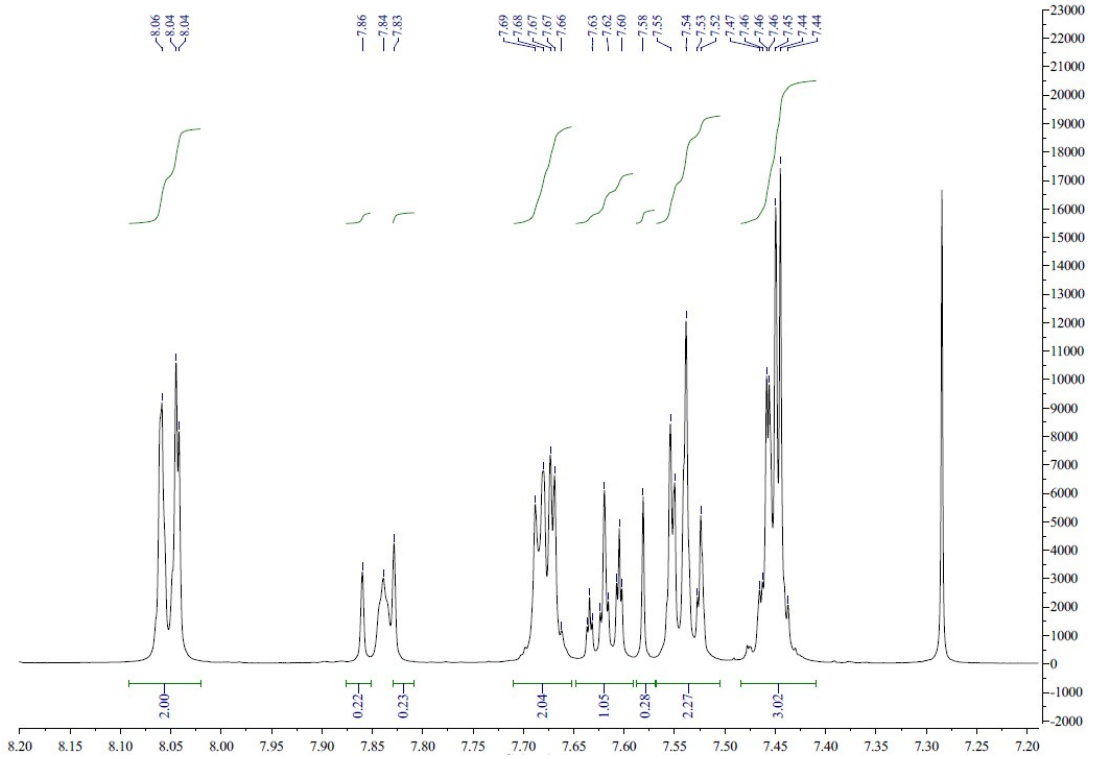
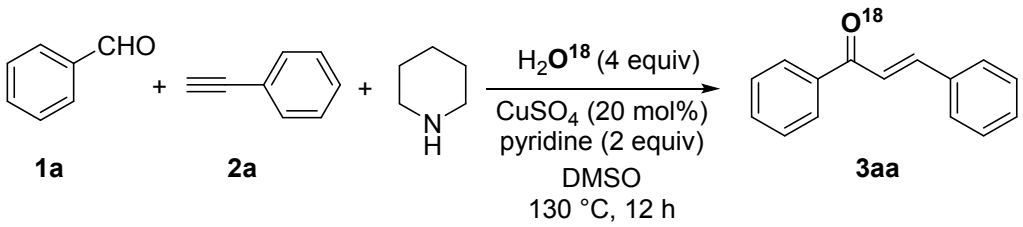
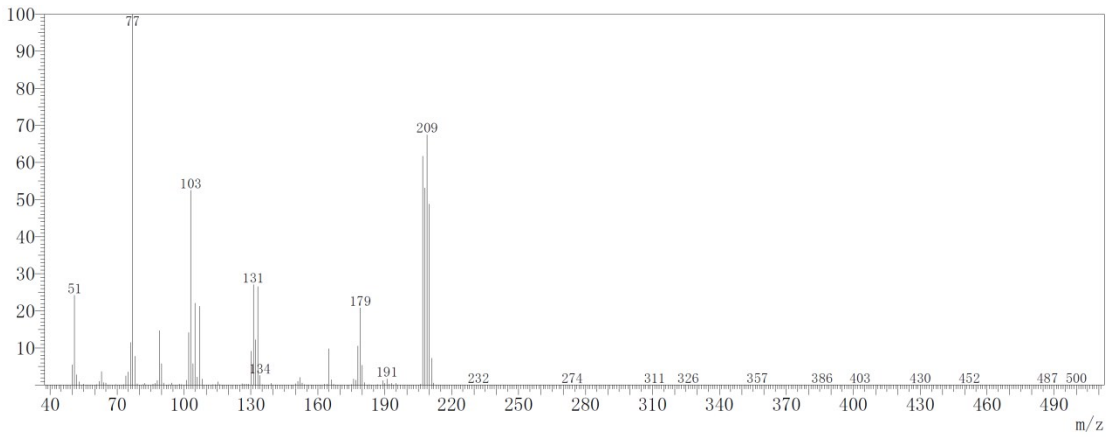


Fig S1 ^{1}HNMR spectrum of D-3aa (lower field area)



To a 25 mL schlenk tube was added anhydrous $CuSO_4$ (16.0 mg, 0.1 mmol). Then, benzaldehyde **1** (52 μL, 0.5 mmol), phenylacetylene **2** (75 μL, 0.75 mmol), piperidine (74 μL, 0.75 mmol), pyridine (75 μL, 1 mmol), H_2O^{18} (38 μL, 2 mmol) and dimethyl sulfoxide (1.5 mL) were added in sequence by syringe with nitrogen flowing at a double-rowed pipe. The reaction tube was then sealed and the resulting mixture was stirred at 130 °C for 12 h. After cooling to room temperature, water was added and the mixture was extracted with ethyl acetate. The organic phases were dried by anhydrous $NaSO_4$ and submitted to GC-MS analysis to identify the origination of oxygen atom of the carbonyl carbons (Fig S2). It is shown that the O-atom of the carbonyl group was generated from water.



m/z	*Intensity*	*Abundance*
206.95	814875	61.69
207.95	702585	53.18
209.00	890942	67.44
210.00	644174	48.76
211.00	96390	7.30

Fig S2 GC-MS spectra of 3aa with $H_2{}^{18}O$ as additive

To a 25 mL schlenk tube were added A[3] product **D-3aa'** (138 mg, 0.5 mmol) and anhydrous $CuSO_4$ (16.0 mg, 0.1 mmol). Then, water (36 μL, 2 mmol) and dimethyl sulfoxide (1.5 mL) were added in sequence by syringe with nitrogen flowing at a double-rowed pipe. The reaction tube was then sealed and the resulting mixture was stirred at 130 °C for 12 h. After cooling to room temperature, water was added and the mixture was extracted with ethyl acetate. The organic phase was dried by anhydrous $NaSO_4$ and concentrated under vacuum. The residue was purified by chromatography on silica gel with ethyl acetate/petroleumether (1:50) to give corresponding product **D-3aa** in 43% yield.

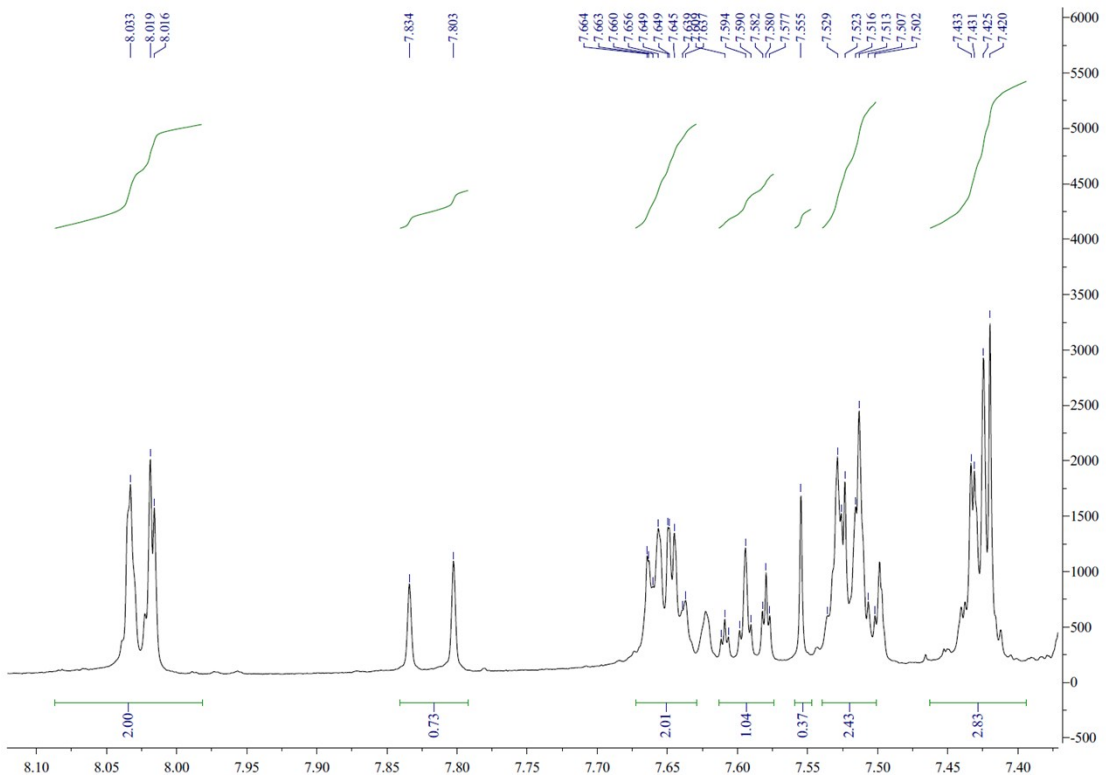
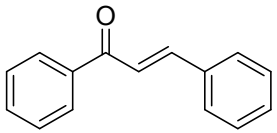


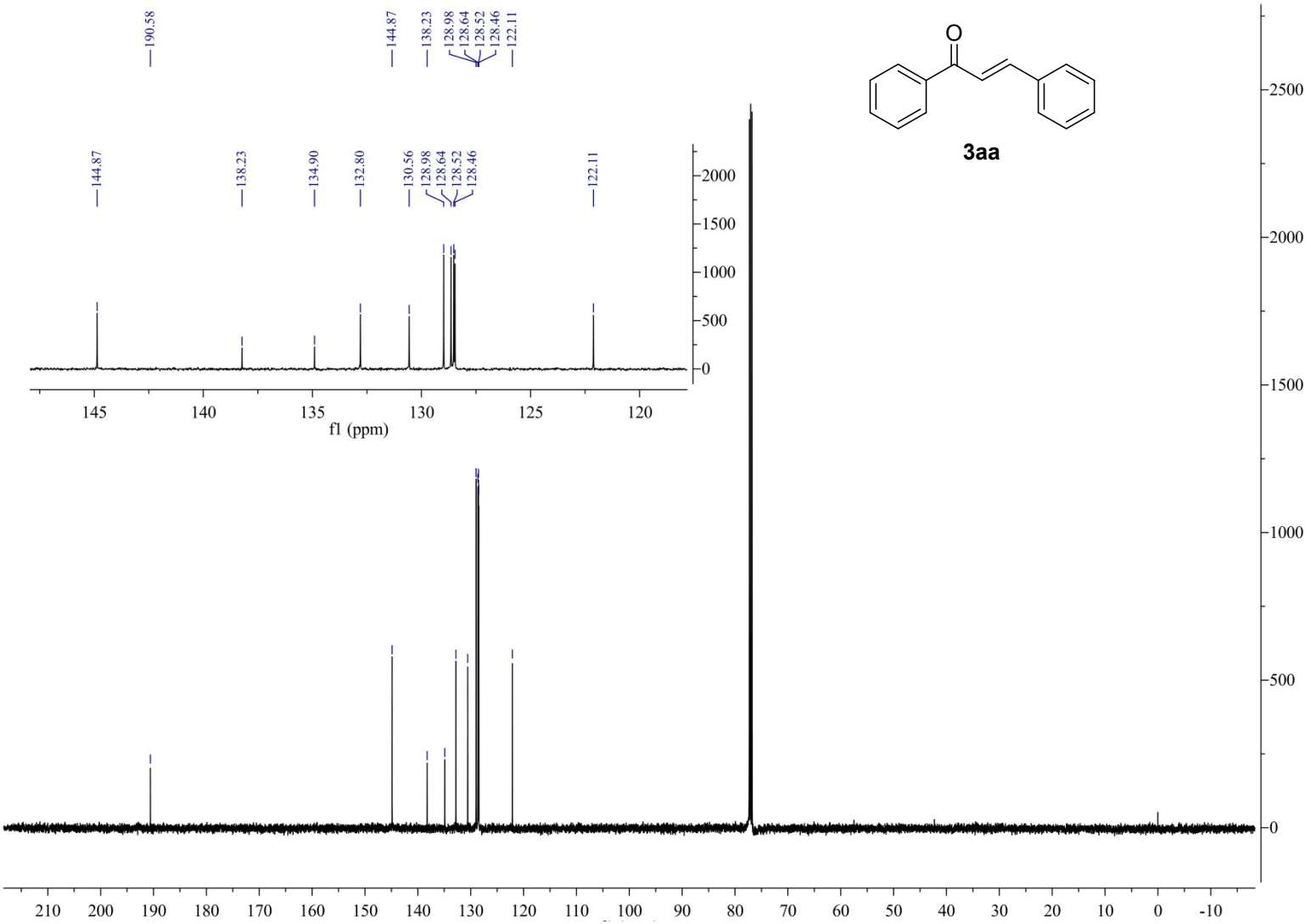
Fig S2 ^{1}HNMR spectrum of D-3aa (lower field area)

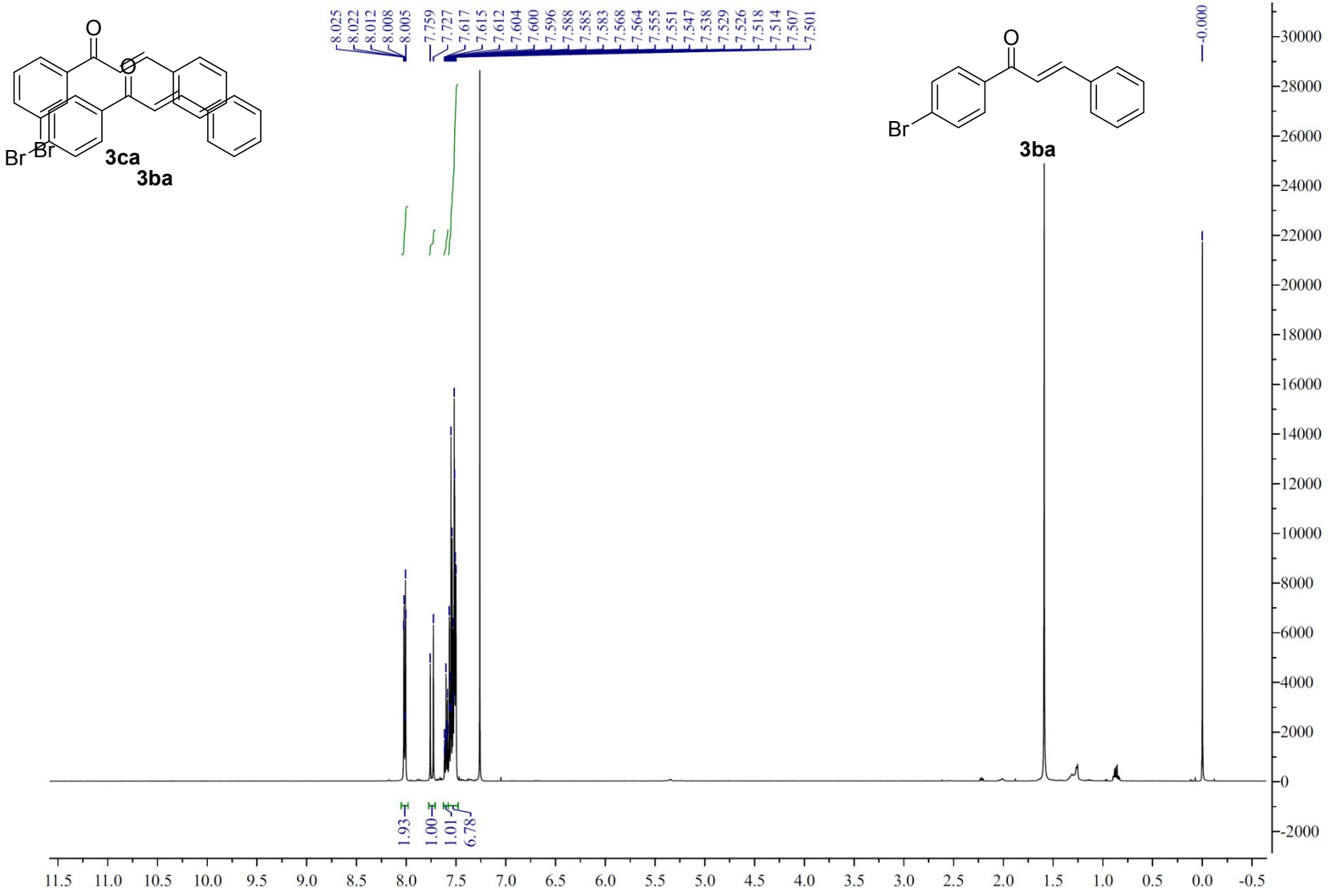
4. Copies for ^{1}H NMR and ^{13}C NMR spectra

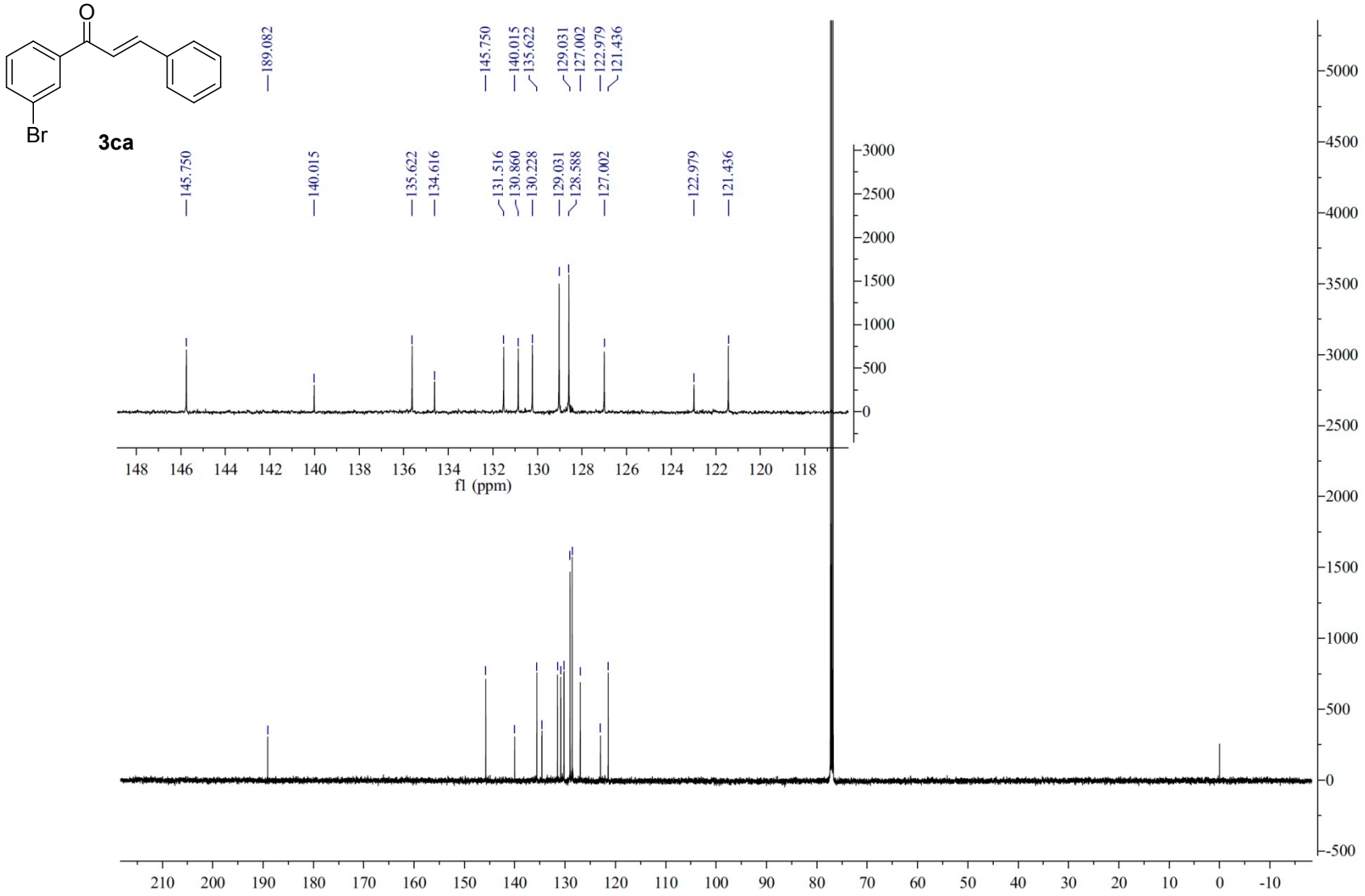


3aa

8.039
8.035
8.033
8.023
8.019
8.016
7.834
7.802
7.661
7.655
7.653
7.646
7.642
7.610
7.607
7.604
7.596
7.592
7.588
7.580
7.578
7.575
7.555
7.527
7.523
7.514
7.511
7.500
7.497
7.438
7.435
7.431
7.429
7.422
7.418
7.410
1.92
1.00
1.98
1.00
2.93
2.83
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
11.5 11.0 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0


190.58
144.87
138.23
128.98
128.64
128.52
128.46
122.11
O
3aa
144.87
138.23
134.90
132.80
130.56
128.98
128.64
128.52
128.46
122.11
2000
1500
1000
500
0
145
140
135
130
125
120
f1 (ppm)
2500
2000
1500
1000
500
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


3ca
3ba
3ba
8.025
8.022
8.012
8.008
8.005
7.759
7.727
7.617
7.615
7.612
7.604
7.600
7.596
7.588
7.585
7.583
7.568
7.564
7.555
7.551
7.547
7.538
7.529
7.526
7.518
7.514
7.507
7.501
-0.000
1.93
1.00
1.01
6.78


O
Br
3ca
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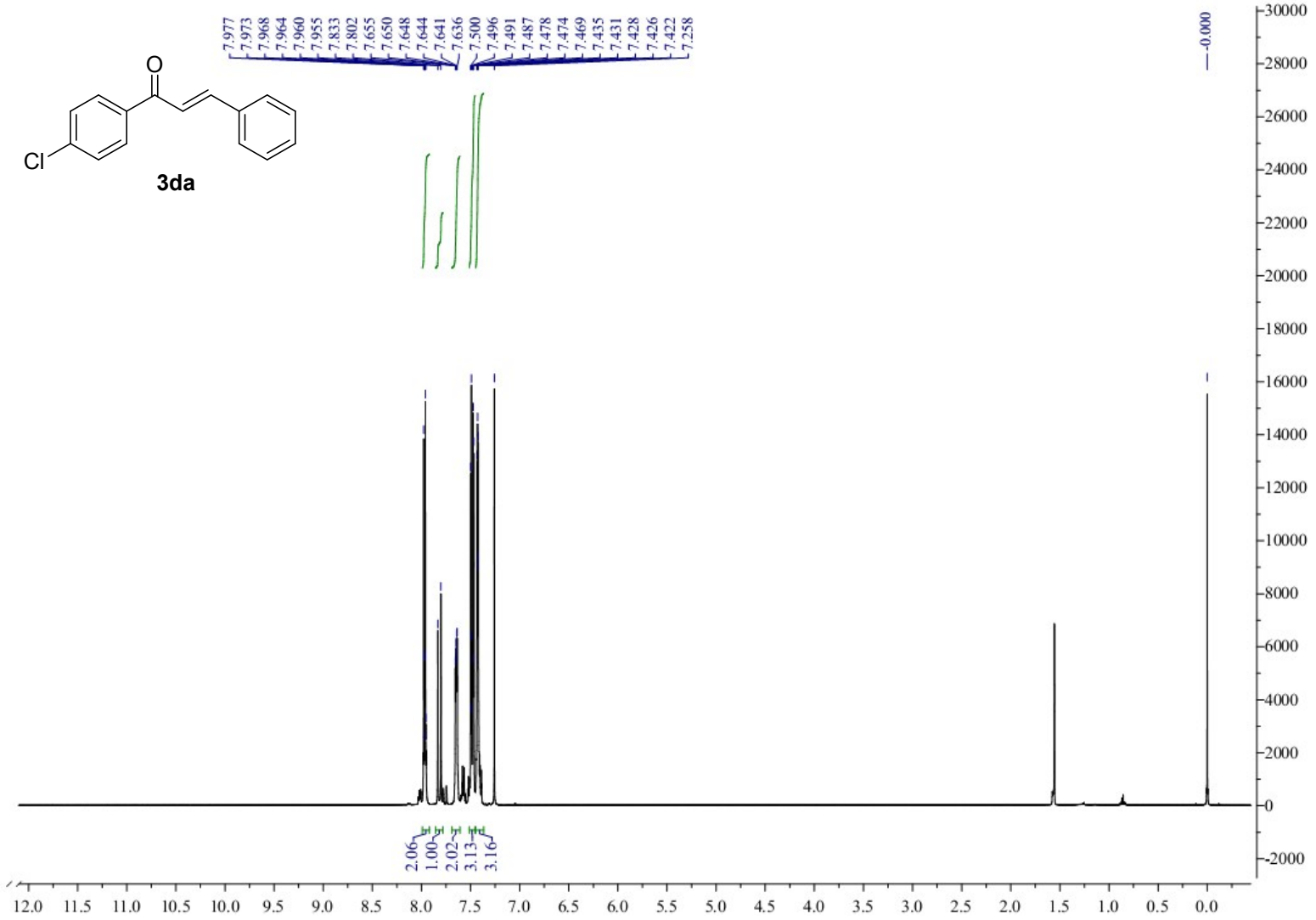
140.015
135.622
129.031
127.002
122.979
121.436
145.750
140.015
135.622
134.616
131.516
130.860
130.228
129.031
128.588
127.002
122.979
121.436
fl (ppm)


O
Cl
3da
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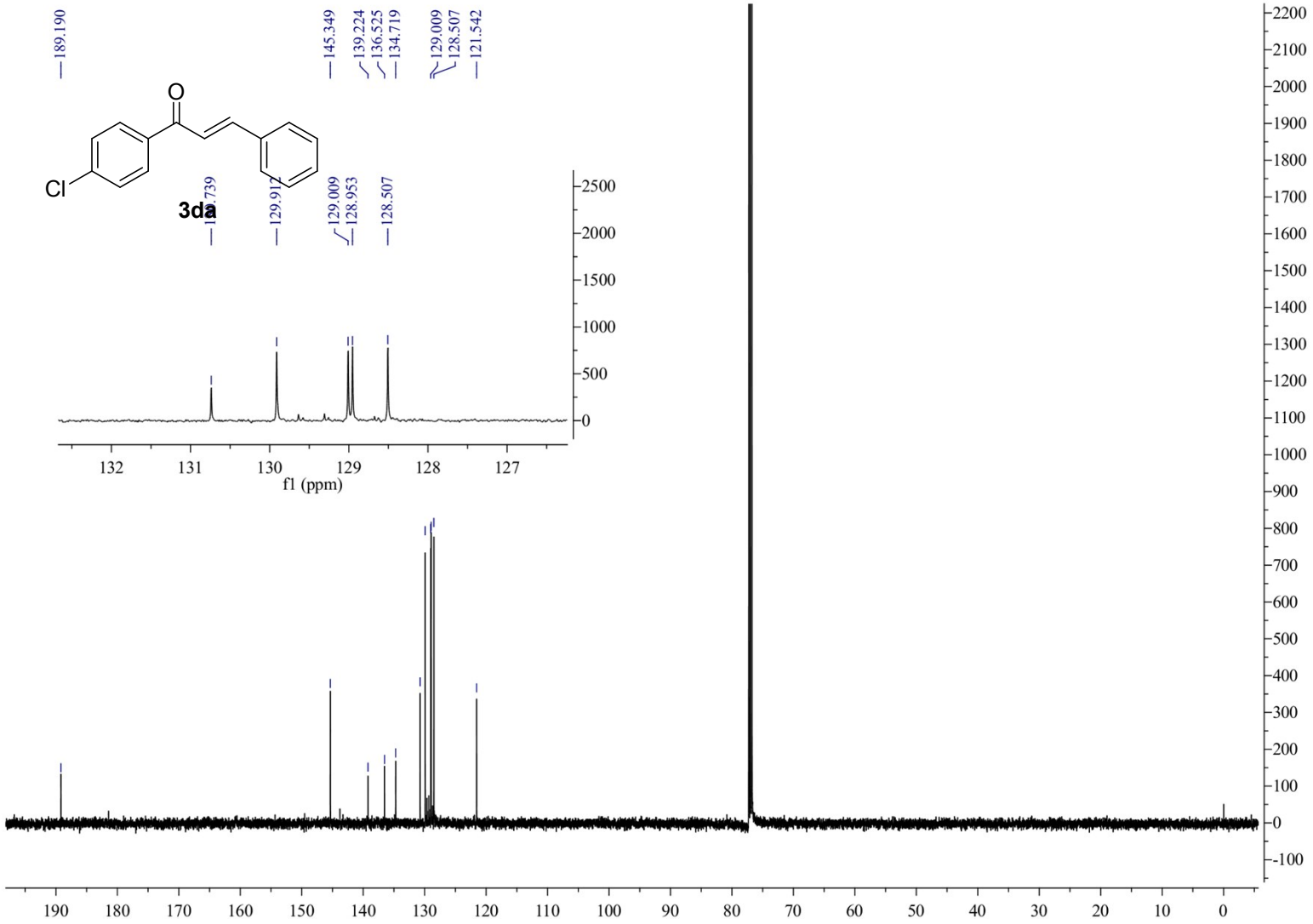
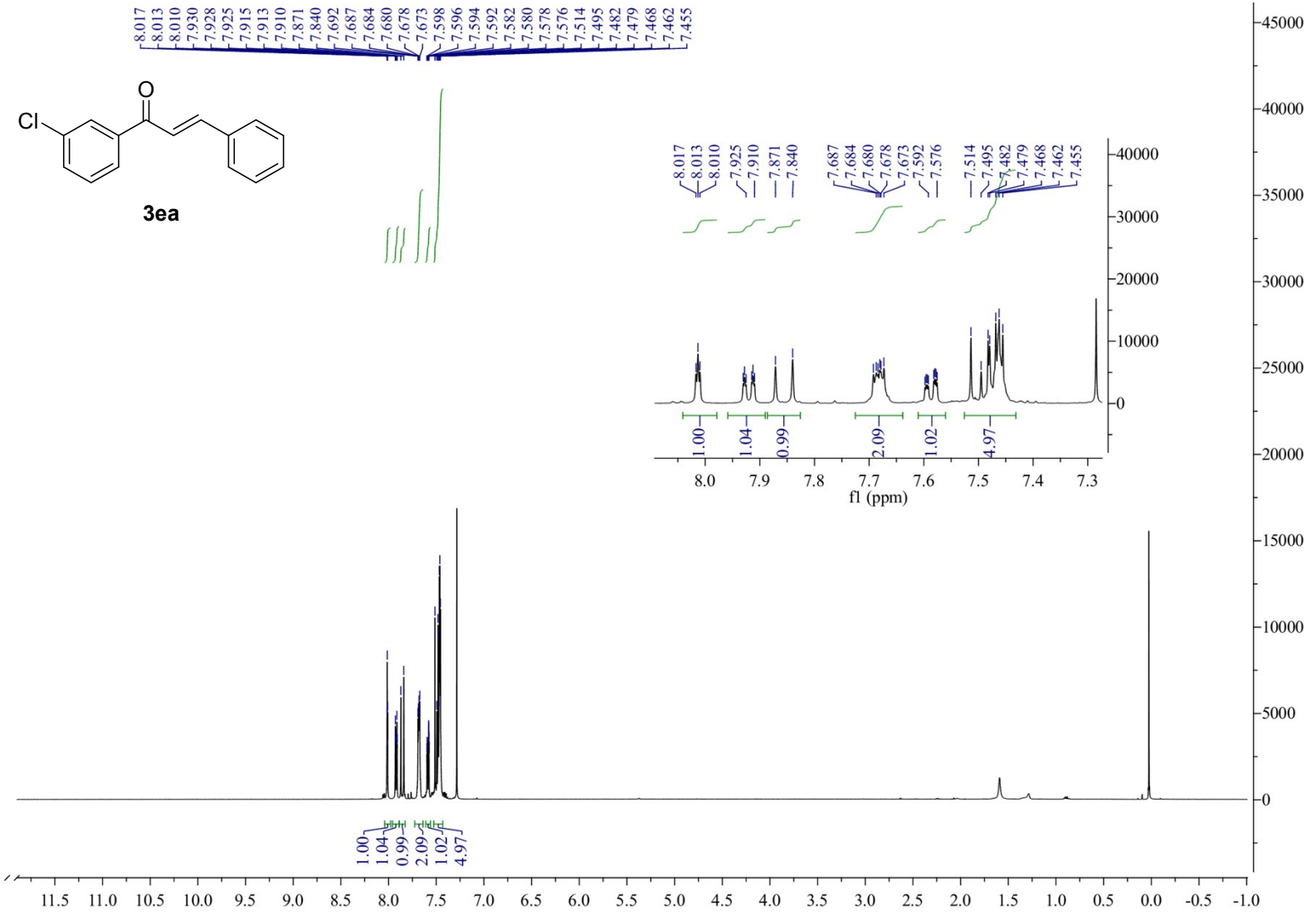
7.973
7.968
7.964
7.960
7.955
7.833
7.802
7.655
7.650
7.648
7.644
7.641
7.636
7.500
7.496
7.491
7.487
7.478
7.474
7.469
7.435
7.431
7.428
7.426
7.422
7.258
0.000
2.06
1.00
2.02
3.13
3.16


189.190
145.349
139.224
136.525
134.719
129.009
128.507
121.542
O
Cl
3da
129.917
129.009
128.953
128.507
f1 (ppm)


8.017
8.013
8.010
7.930
7.928
7.925
7.915
7.913
7.910
7.871
7.840
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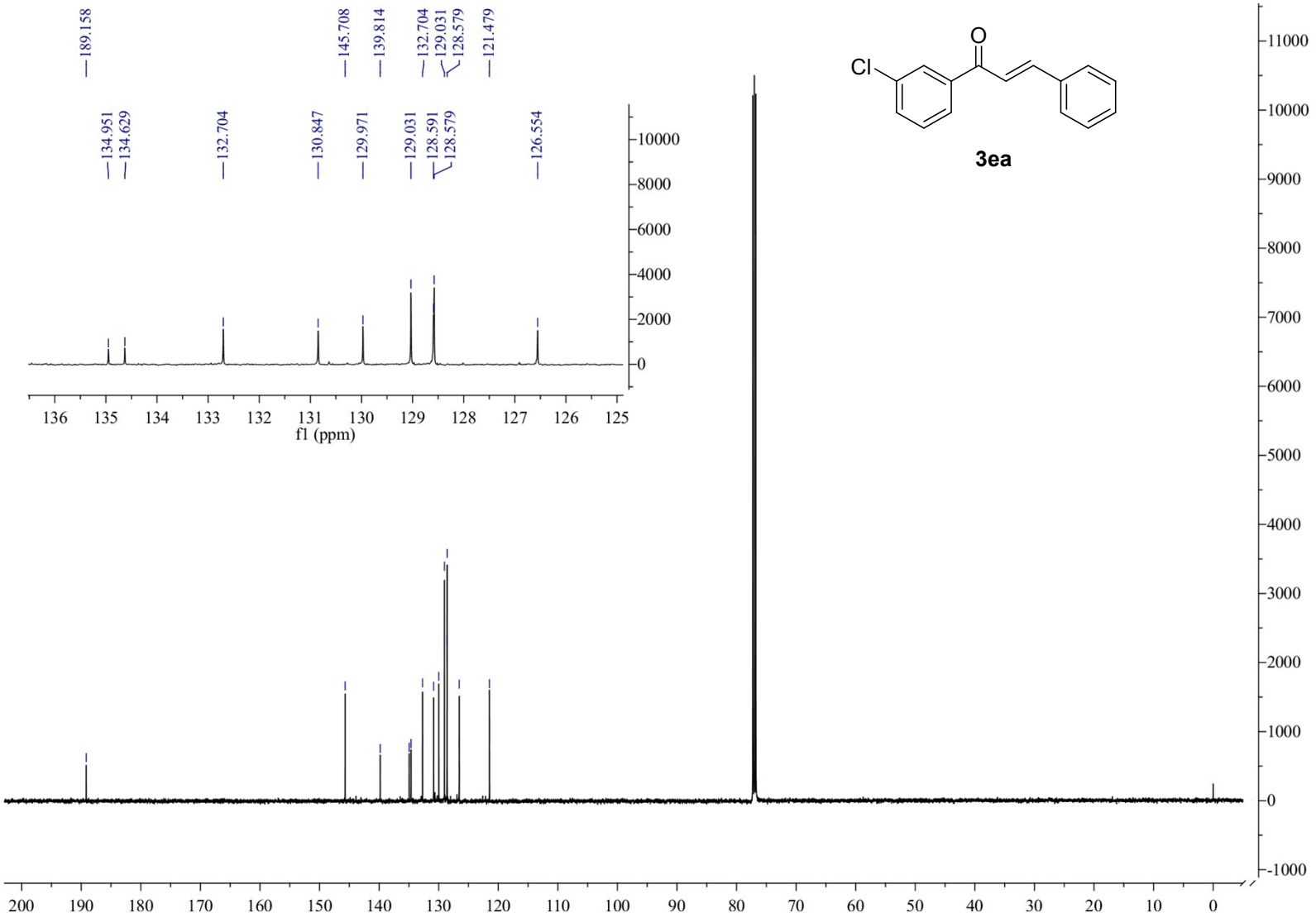
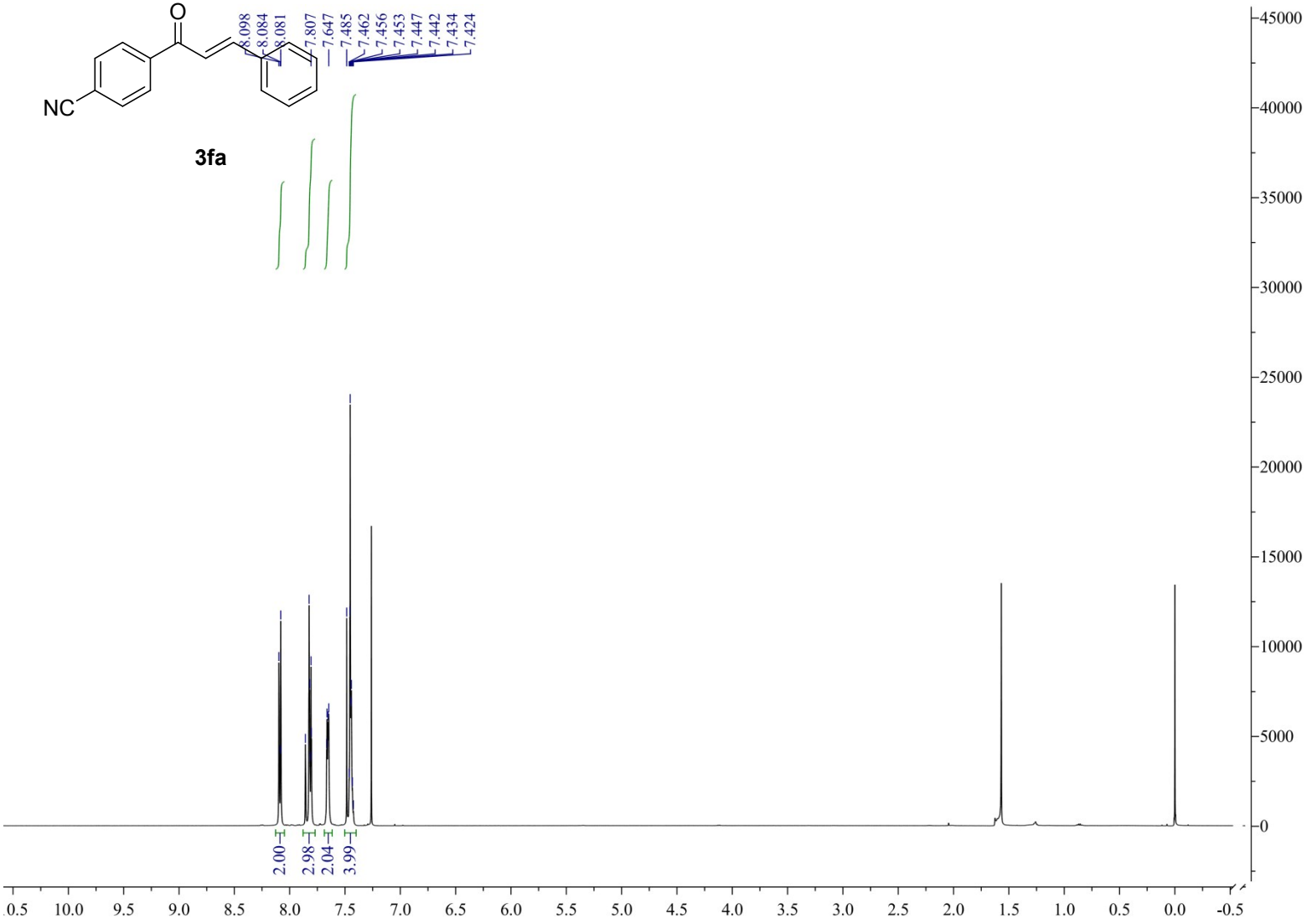
7.687
7.684
7.680
7.678
7.673
7.598
7.596
7.594
7.592
7.582
7.580
7.578
7.576
7.514
7.495
7.482
7.479
7.468
7.462
7.455
O
Cl
3ea
1.00
1.04
0.99
2.09
1.02
4.97
f1 (ppm)


189.158
145.708
139.814
132.704
129.031
128.579
121.479
134.951
134.629
132.704
130.847
129.971
129.031
128.591
128.579
126.554
f1 (ppm)
Cl
O
3ea


O
NC
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8.081
7.807
7.647
7.485
7.462
7.456
7.453
7.447
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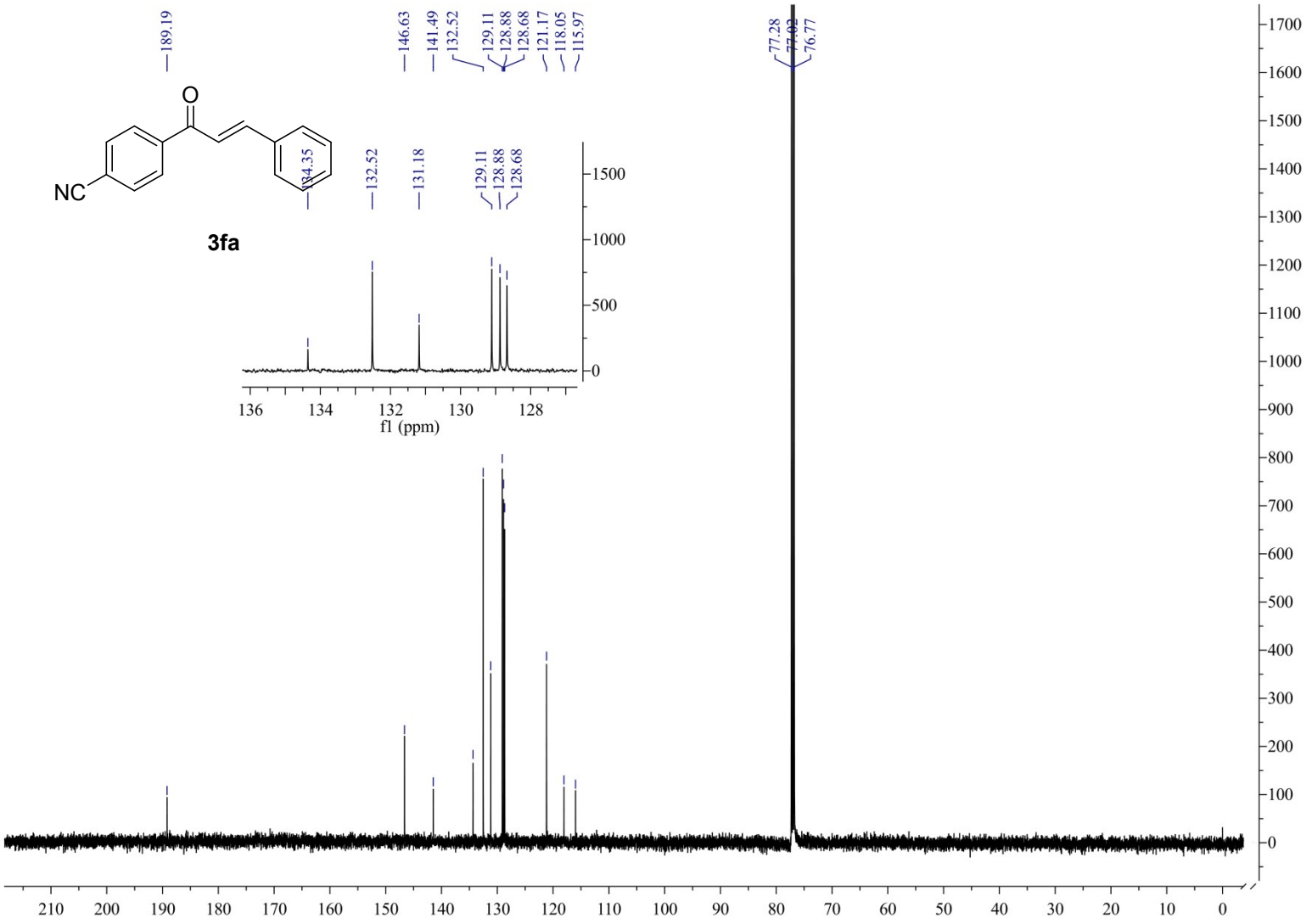
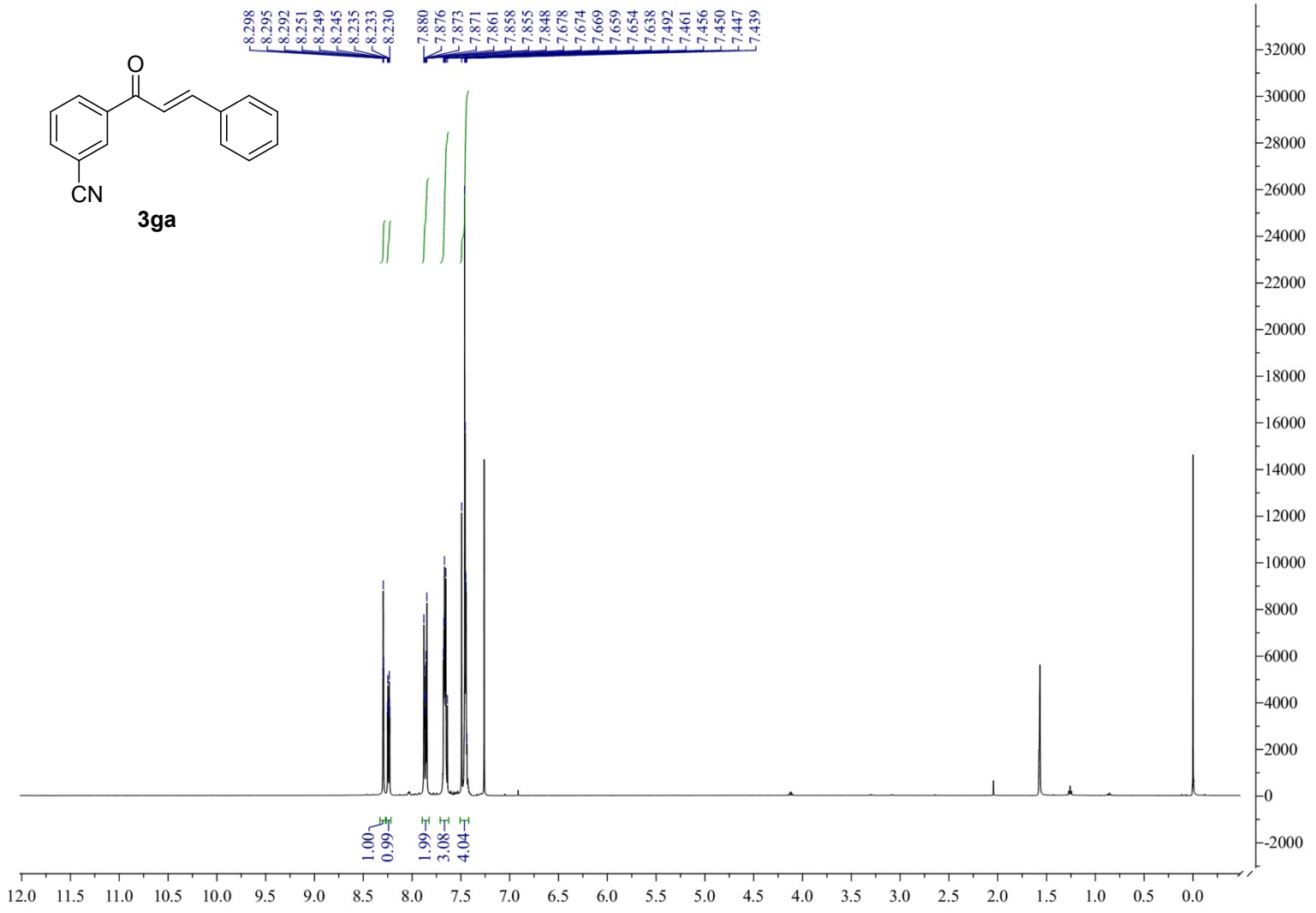
7.434
7.424
3fa
2.00
2.98
2.04
3.99
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


189.19
146.63
141.49
132.52
129.11
128.88
128.68
121.17
118.05
115.97
77.28
77.03
76.77
O
NC
3fa
134.35
132.52
131.18
129.11
128.88
128.68
fl (ppm)


O
CN
3ga
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8.251
8.249
8.245
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8.233
8.230
7.880
7.876
7.873
7.871
7.861
7.858
7.855
7.848
7.678
7.674
7.669
7.659
7.654
7.638
7.492
7.461
7.456
7.450
7.447
7.439
1.00
0.99
1.99
3.08
4.04
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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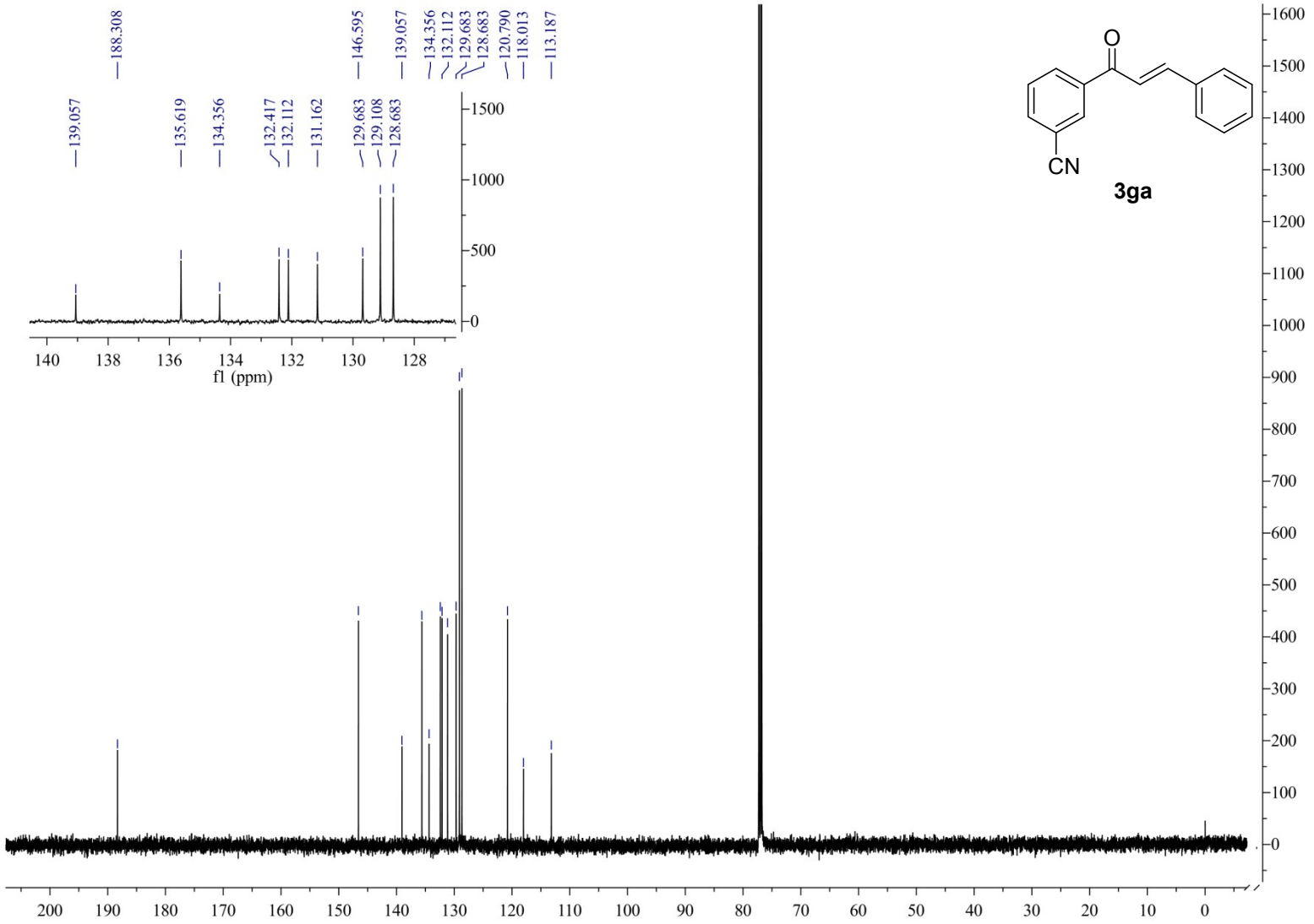
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129.683
128.683
120.790
118.013
113.187
139.057
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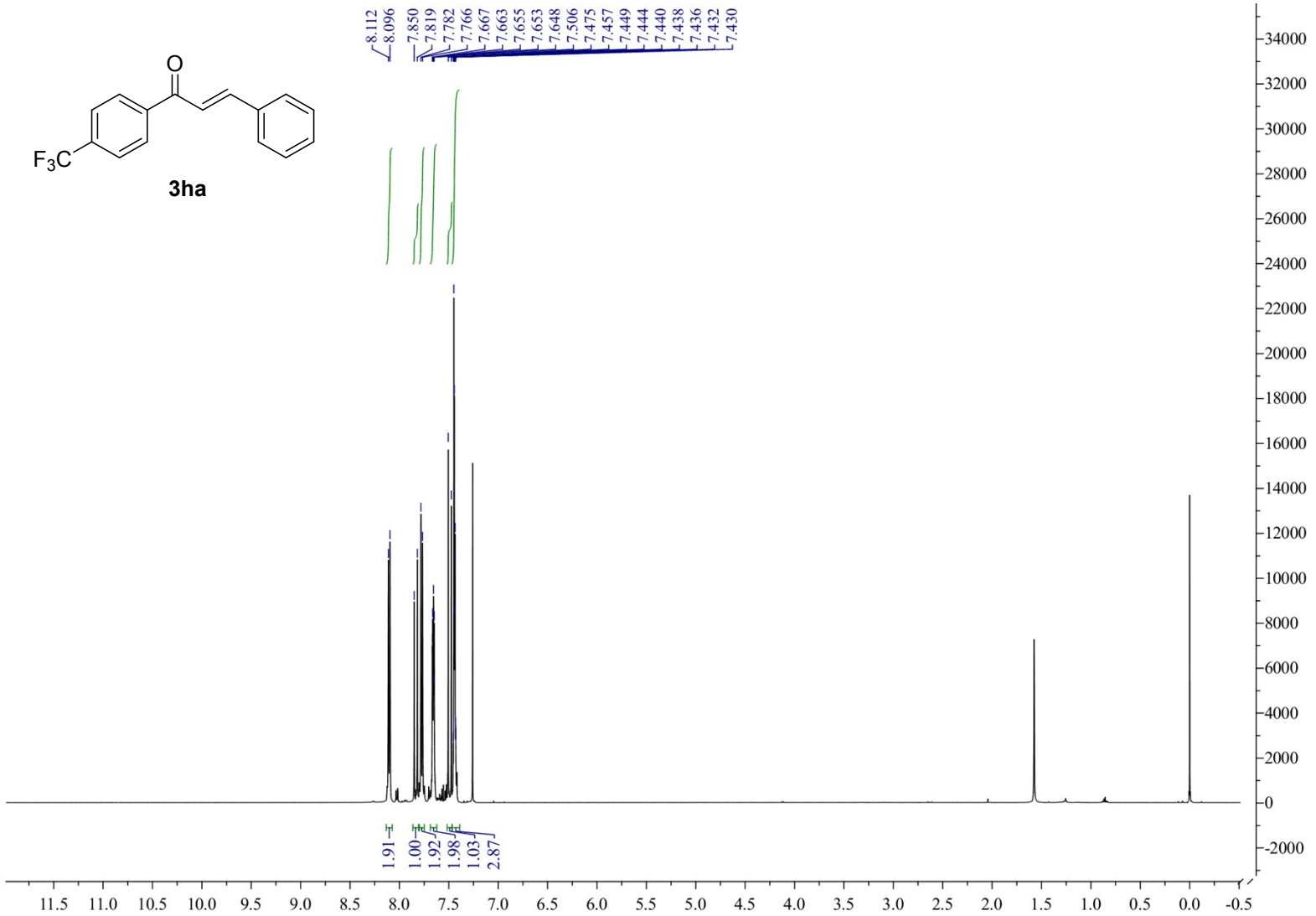
134.356
132.417
132.112
131.162
129.683
129.108
128.683
fl (ppm)
O
CN
3ga


O
F3C
3ha
8.112
8.096
7.850
7.819
7.782
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7.667
7.663
7.655
7.653
7.648
7.506
7.475
7.457
7.449
7.444
7.440
7.438
7.436
7.432
7.430
1.91
1.00
1.92
1.98
1.03
2.87
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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3.5
3.0
2.5
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1.5
1.0
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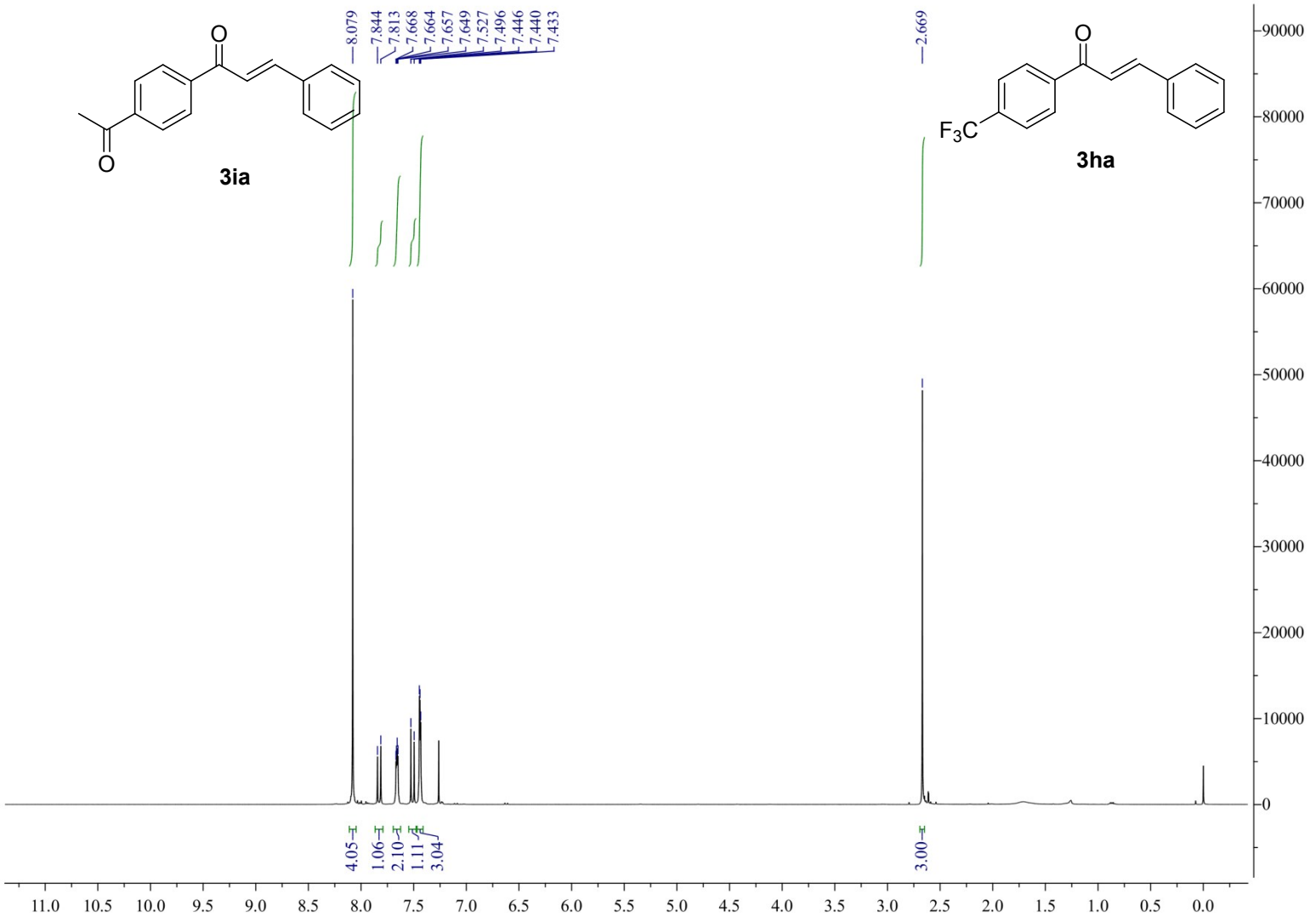
-0.5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7.813
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7.527
7.496
7.446
7.440
7.433
2.669
3ia
3ha
F3C
4.05
1.06
2.10
1.11
3.04
3.00
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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4.5
4.0
3.5
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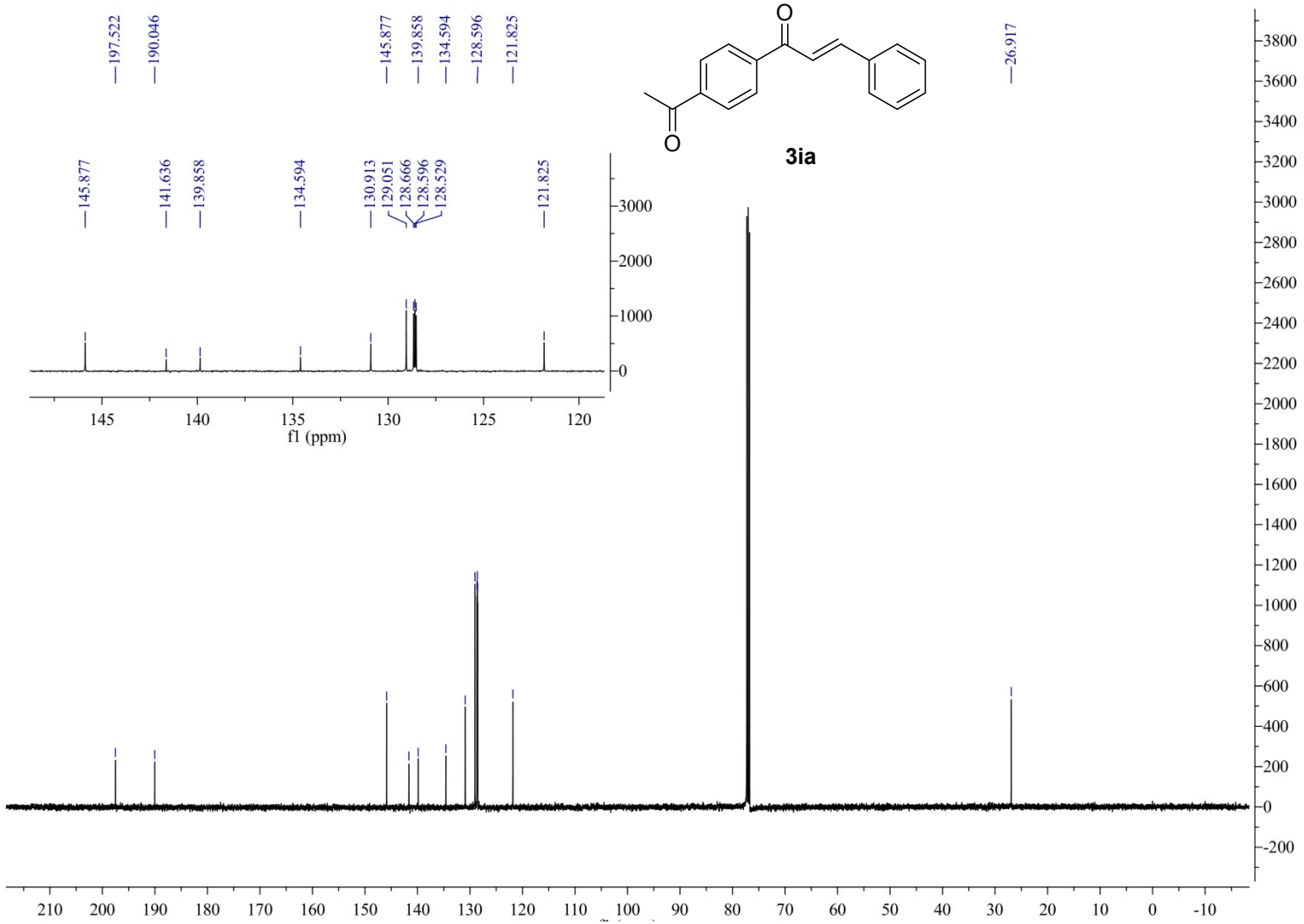
2.0
1.5
1.0
0.5
0.0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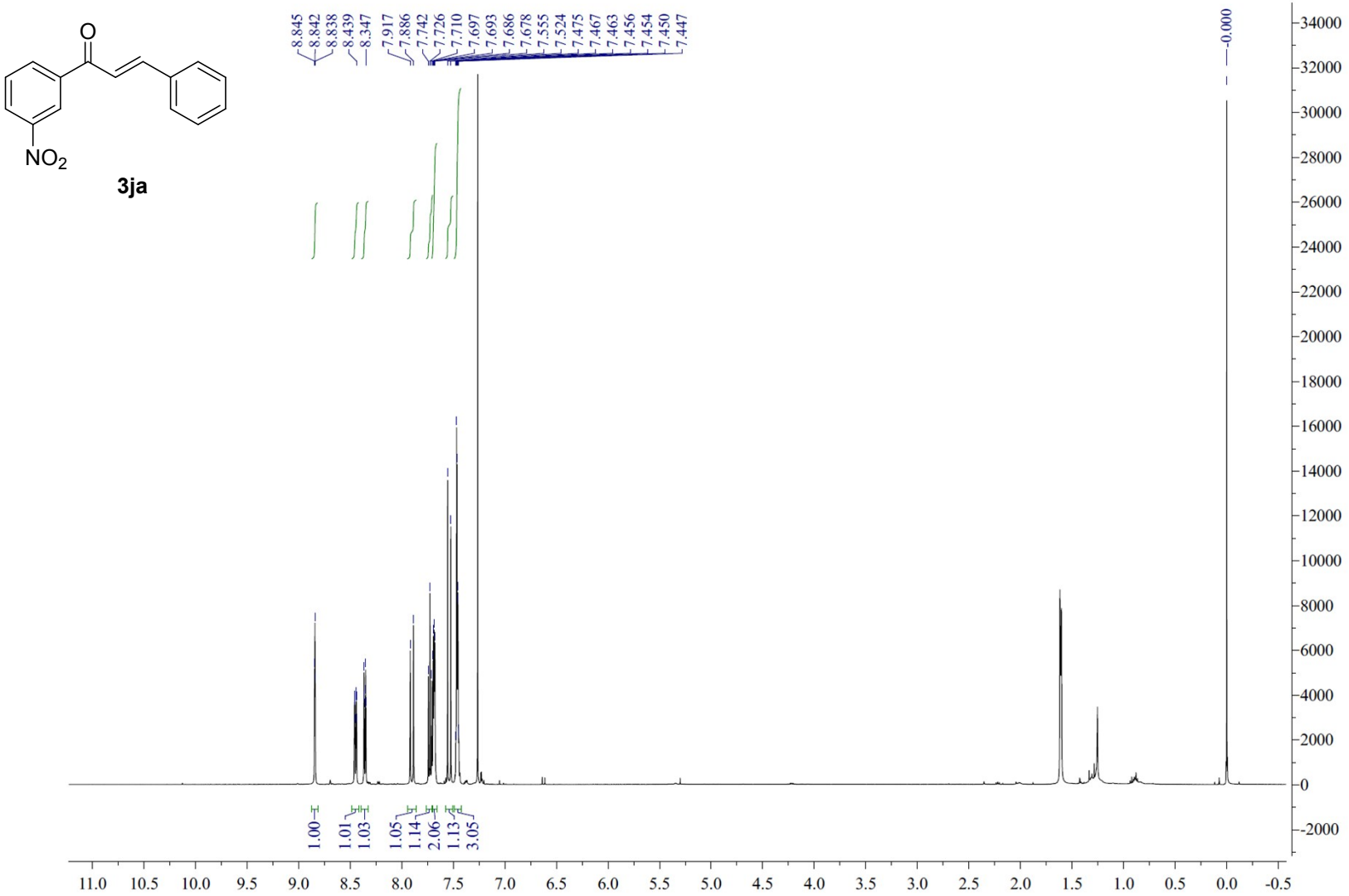
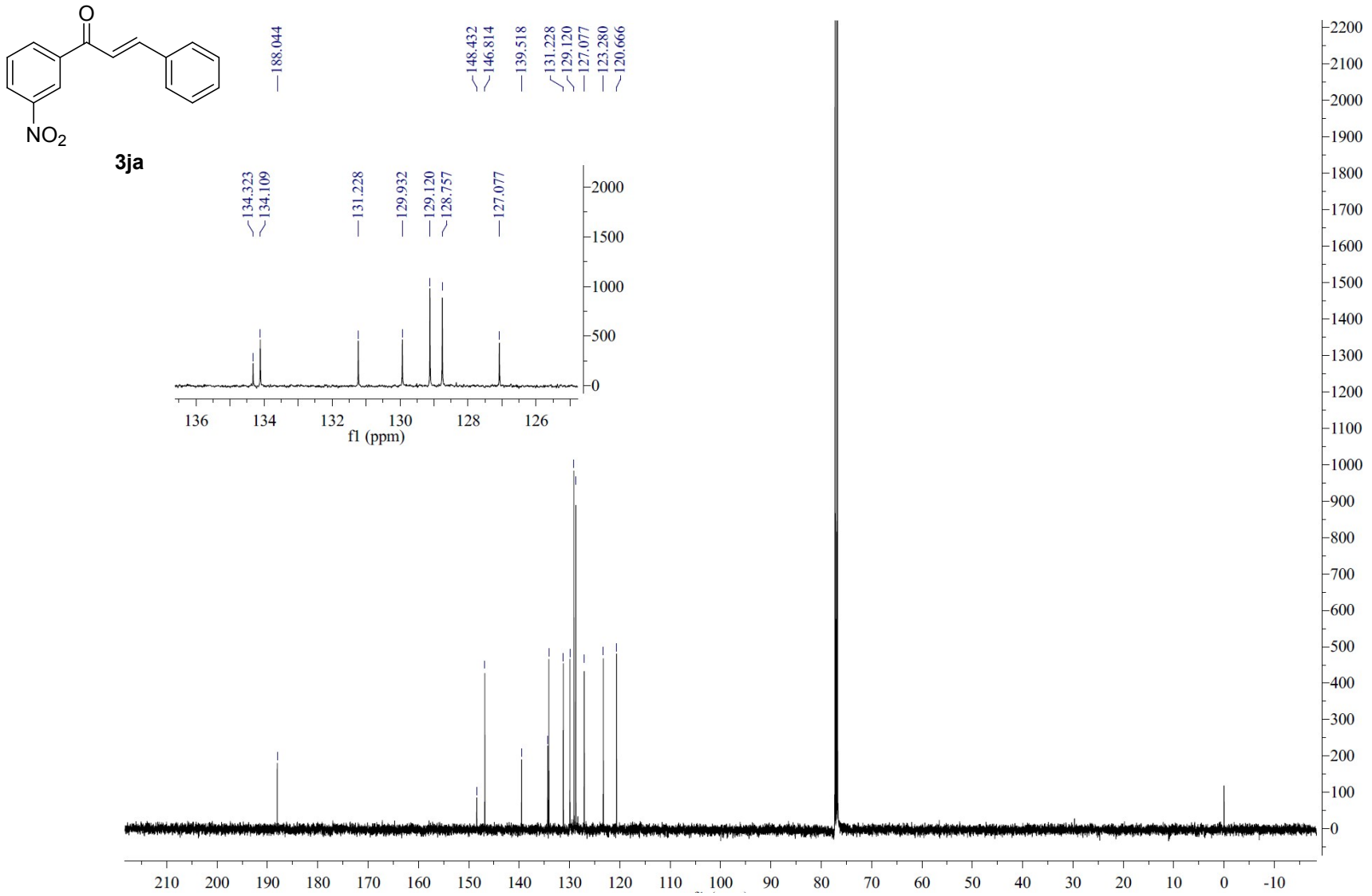
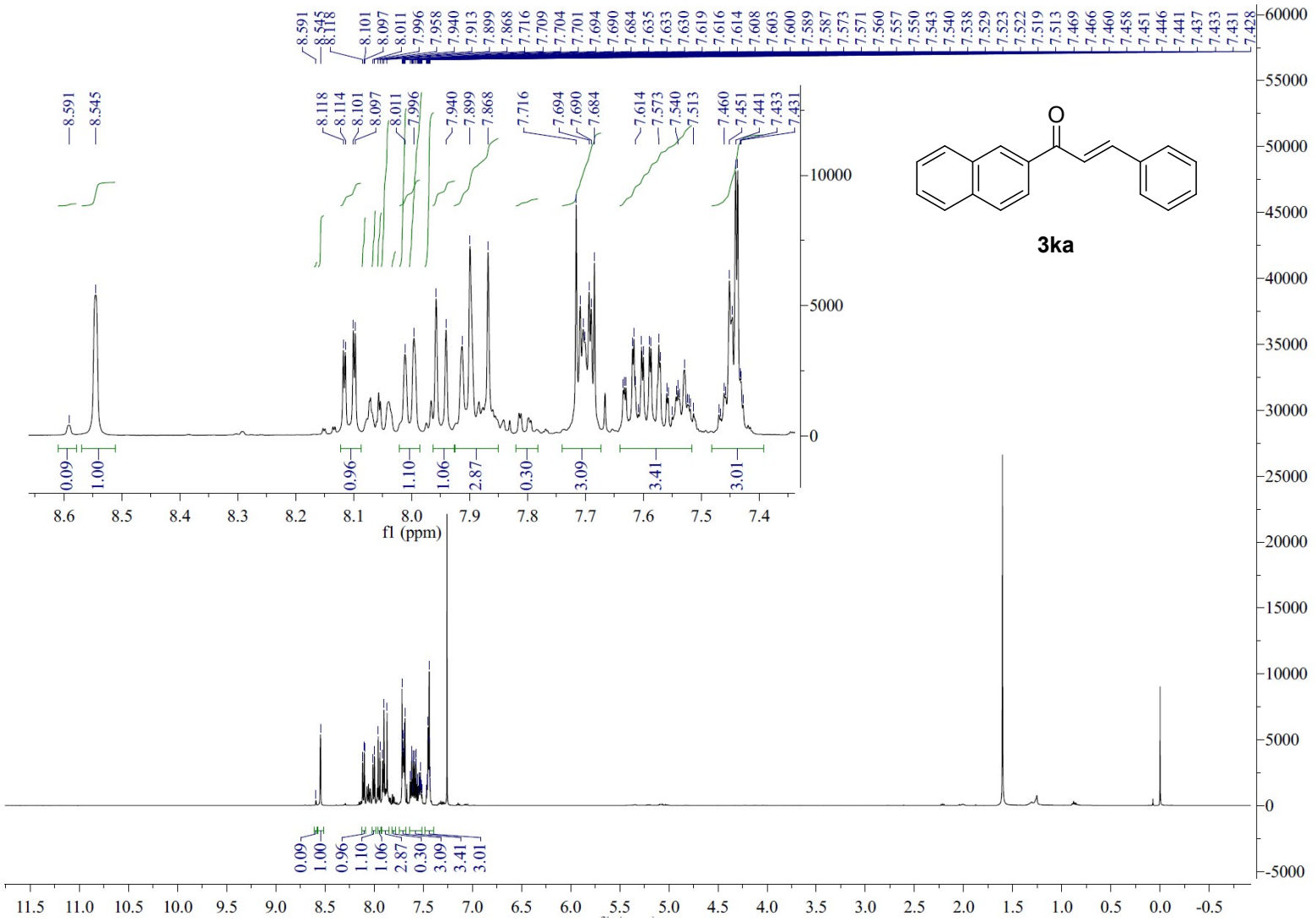
190.046
145.877
139.858
134.594
128.596
121.825
26.917
O
O
3ia
145.877
141.636
139.858
134.594
130.913
129.051
128.666
128.596
128.529
121.825
fl (ppm)


O
NO2
8.845
8.842
8.838
8.439
8.347
7.917
7.886
7.742
7.726
7.710
7.697
7.693
7.686
7.678
7.555
7.524
7.475
7.467
7.463
7.456
7.454
7.450
7.447
-0.000
1.00
1.01
1.03
1.05
1.14
2.06
1.13
3.05

3ja


O
NO2
3ja
188.044
148.432
146.814
139.518
131.228
129.120
127.077
123.280
120.666
134.323
134.109
131.228
129.932
129.120
128.757
127.077
f1 (ppm)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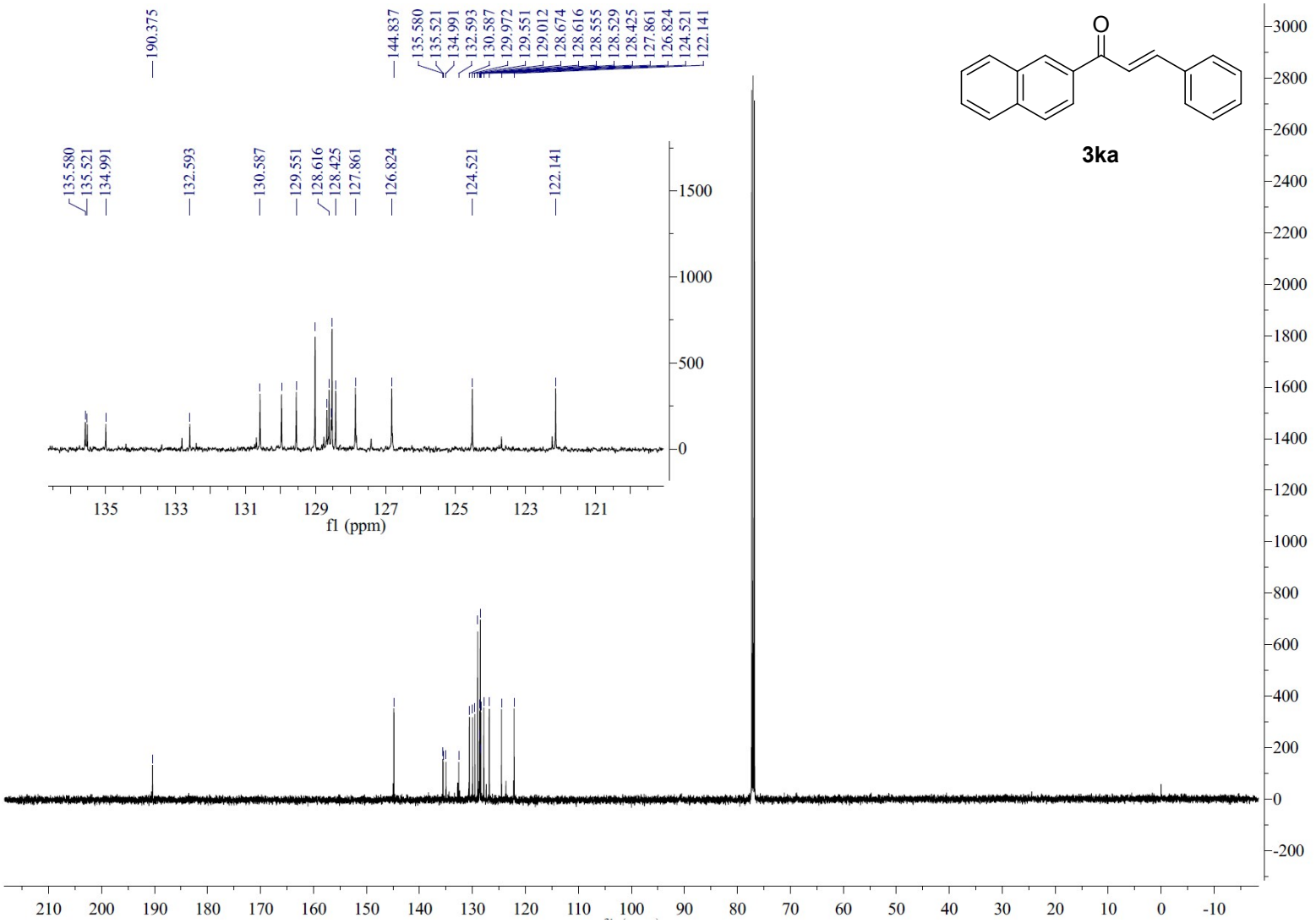
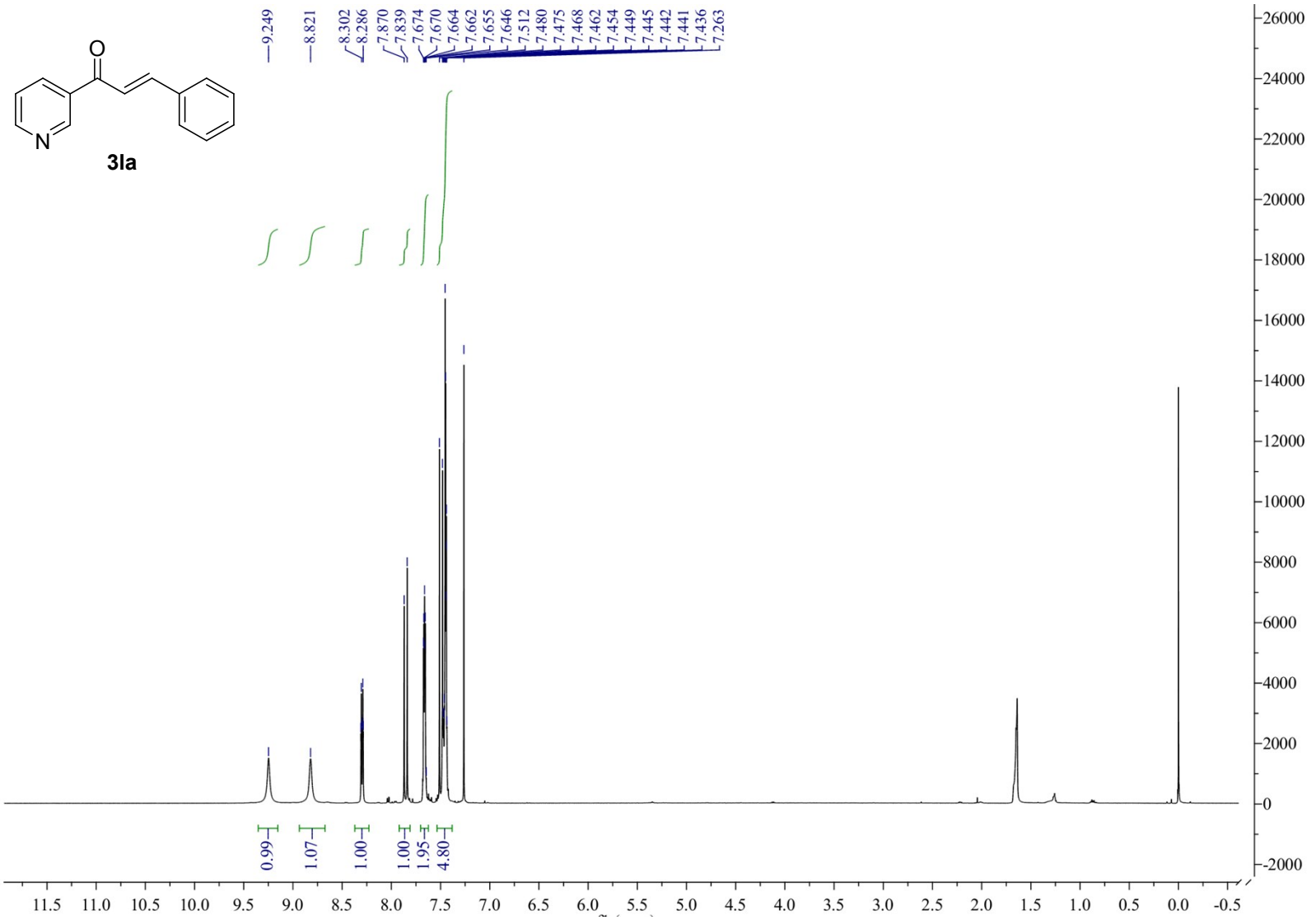
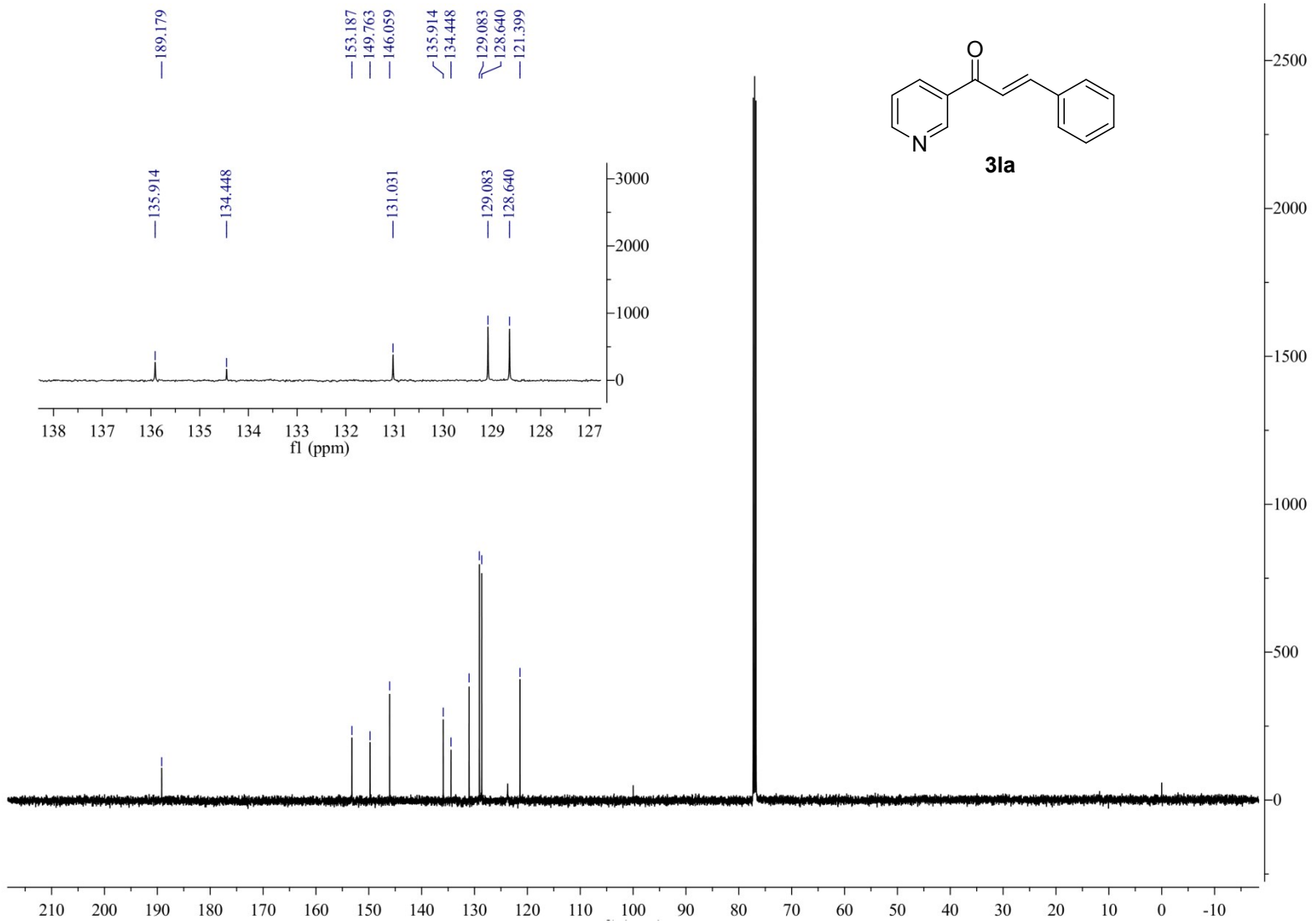
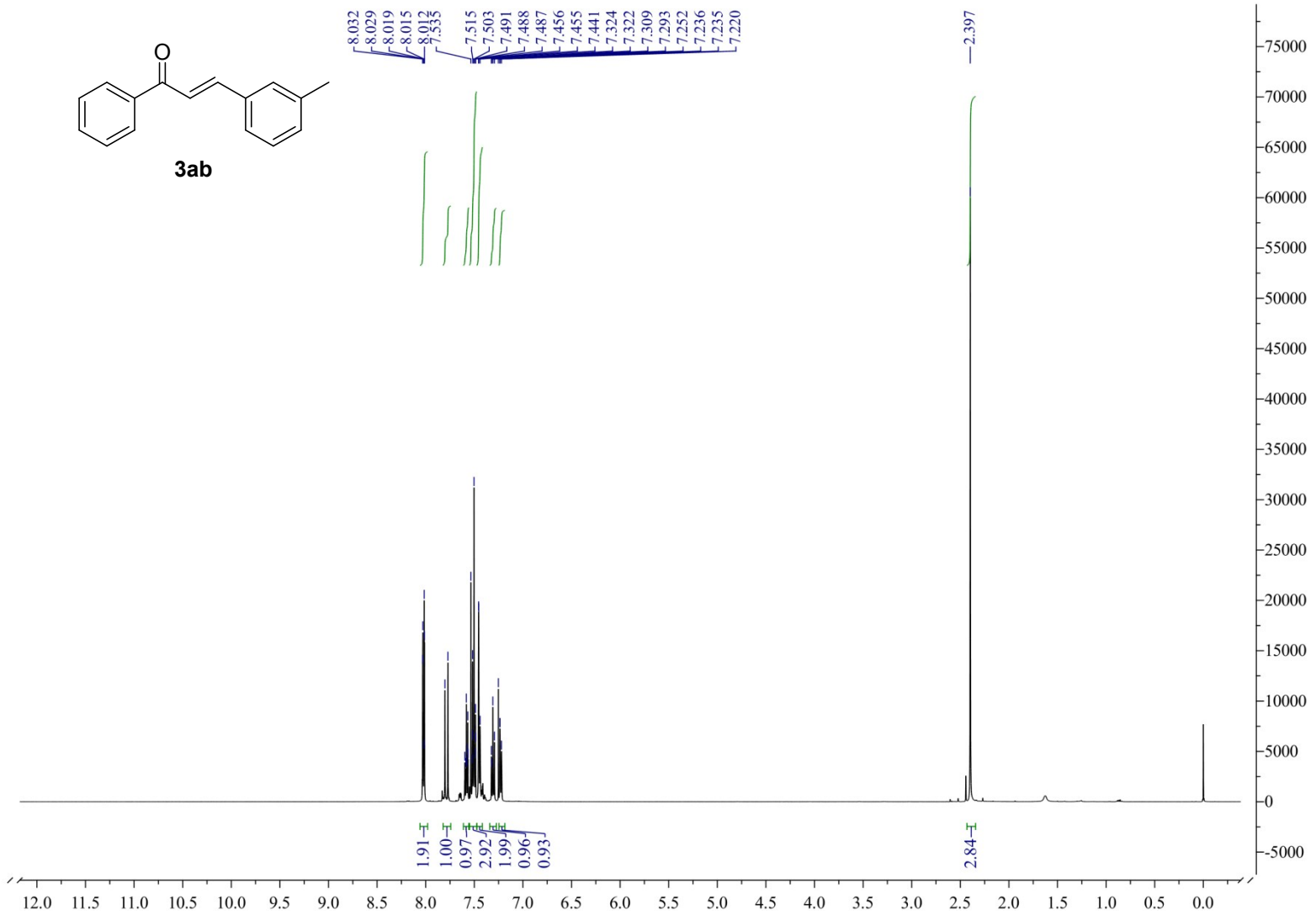
8.545
8.118
8.114
8.101
8.097
8.011
7.996
7.940
7.899
7.868
7.716
7.694
7.690
7.684
7.614
7.573
7.540
7.513
7.460
7.451
7.441
7.433
7.431
0.09
1.00
0.96
1.10
1.06
2.87
0.30
3.09
3.41
3.01
f1 (ppm)
O
3ka


190.375
144.837
135.580
135.521
134.991
132.593
130.587
129.972
129.551
129.012
128.674
128.616
128.555
128.529
128.425
127.861
126.824
124.521
122.141
O
3ka
f1 (ppm)


O
N
3la
9.249
8.821
8.302
8.286
7.870
7.839
7.674
7.670
7.664
7.662
7.655
7.646
7.512
7.480
7.475
7.468
7.462
7.454
7.449
7.445
7.442
7.441
7.436
7.263
0.99
1.07
1.00
1.00
1.95
4.80


189.179
153.187
149.763
146.059
135.914
134.448
129.083
128.640
121.399
O
N
3la
135.914
134.448
131.031
129.083
128.640
3000
2000
1000
0
138 137 136 135 134 133 132 131 130 129 128 127
f1 (ppm)
2500
2000
1500
1000
500
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


O
3ab
8.032
8.029
8.019
8.015
8.012
7.535
7.515
7.503
7.491
7.488
7.487
7.456
7.455
7.441
7.324
7.322
7.309
7.293
7.252
7.236
7.235
7.220
2.397
1.91
1.00
0.97
2.92
1.99
0.96
0.93
2.84
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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3.0
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2.0
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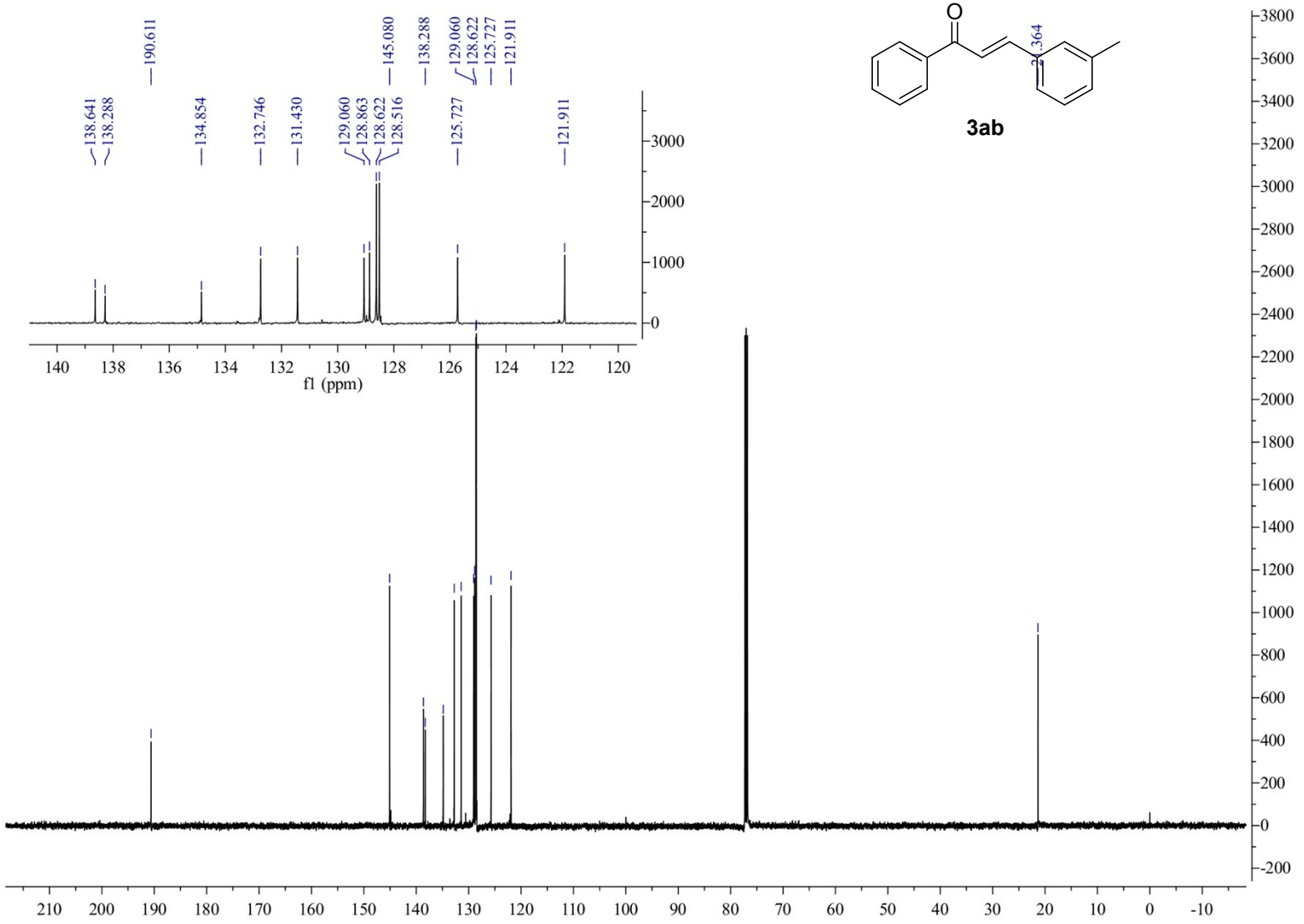
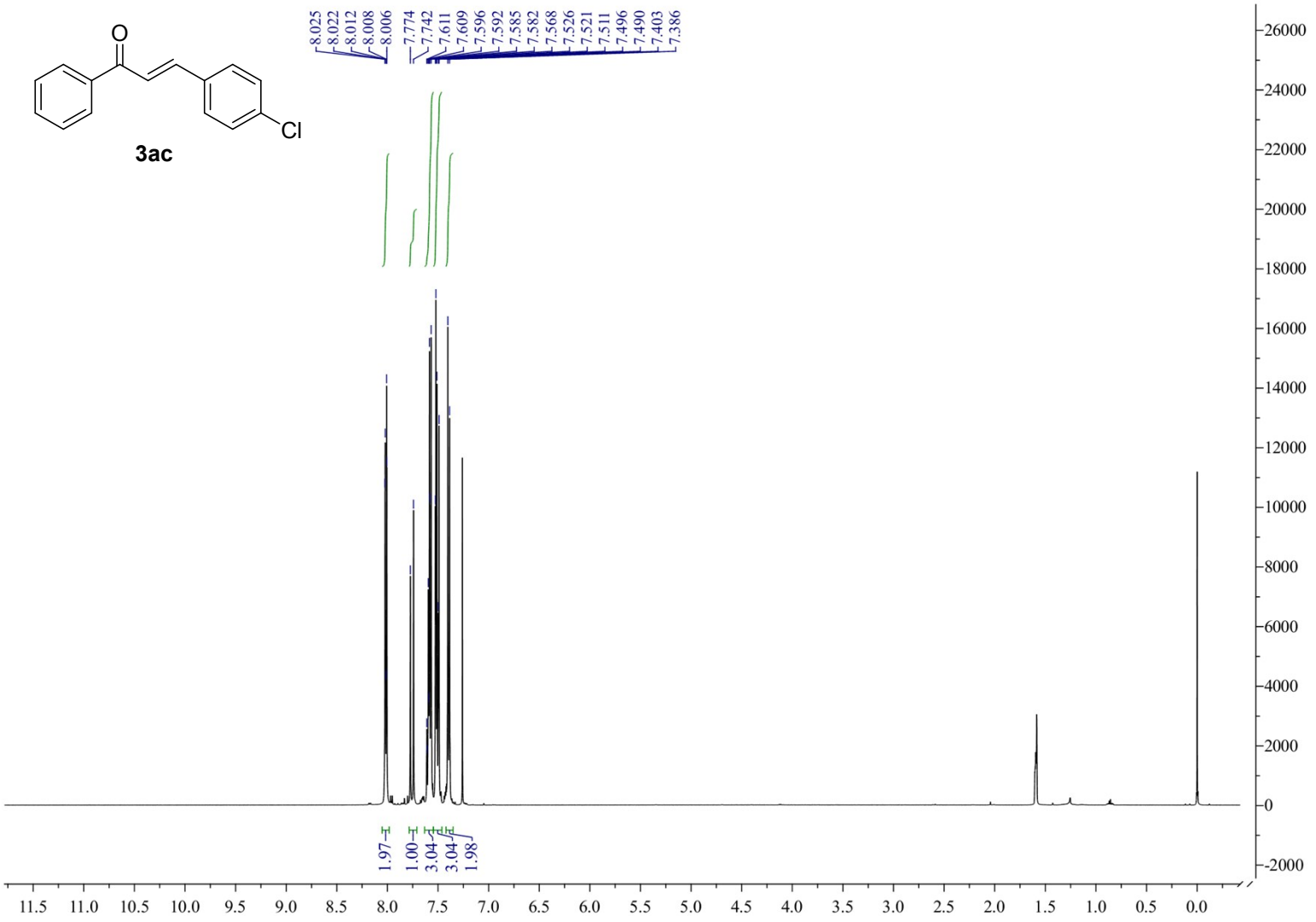

O
21.364
3ab
190.611
145.080
138.288
129.060
128.622
125.727
121.911
138.641
138.288
134.854
132.746
131.430
129.060
128.863
128.622
128.516
125.727
121.911
f1 (ppm)


O
Cl
3ac
8.025
8.022
8.012
8.008
8.006
7.774
7.742
7.611
7.609
7.596
7.592
7.585
7.582
7.568
7.526
7.521
7.511
7.496
7.490
7.403
7.386
1.97
1.00
3.04
3.04
1.98
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
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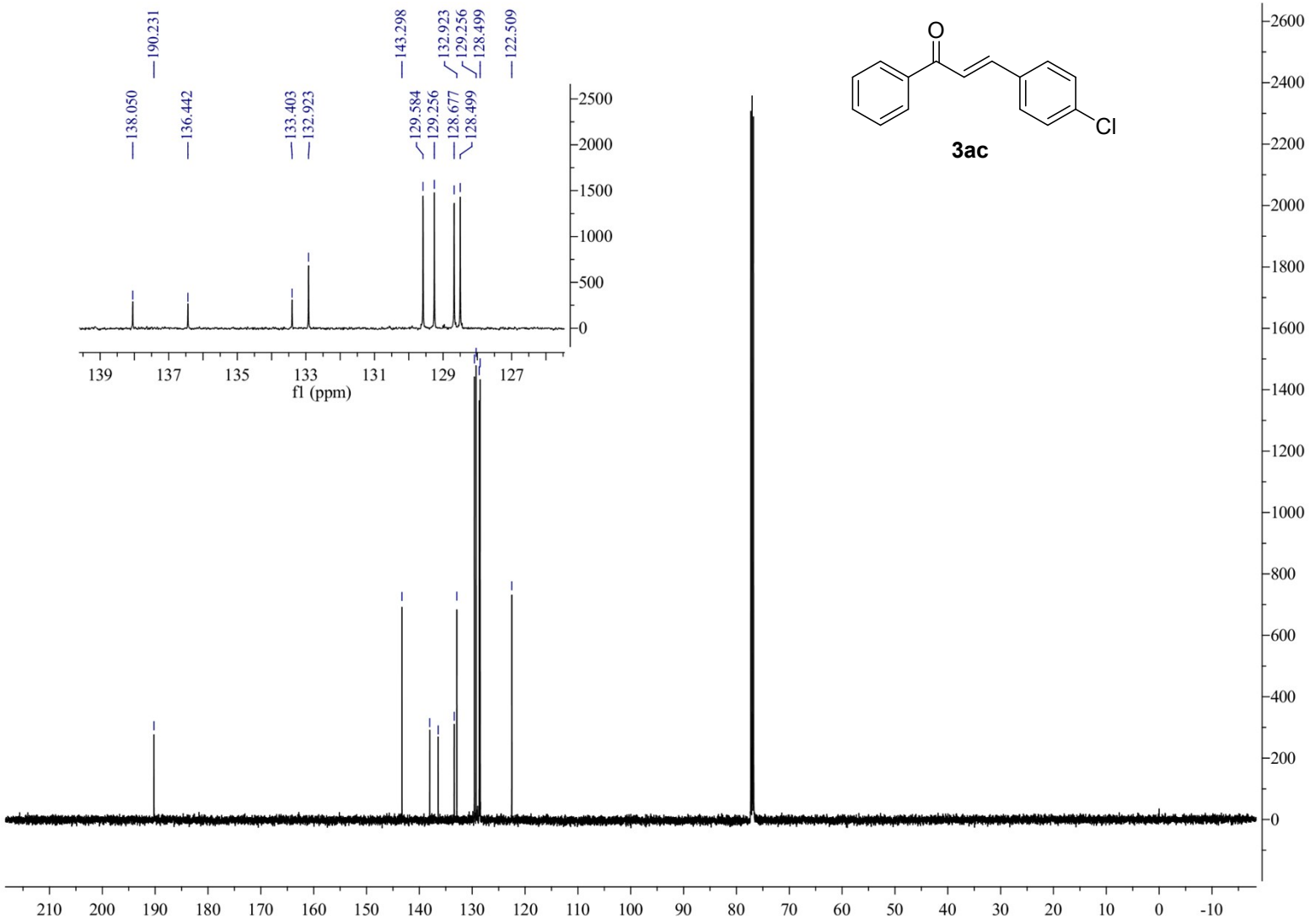
2.0
1.5
1.0
0.5
0.0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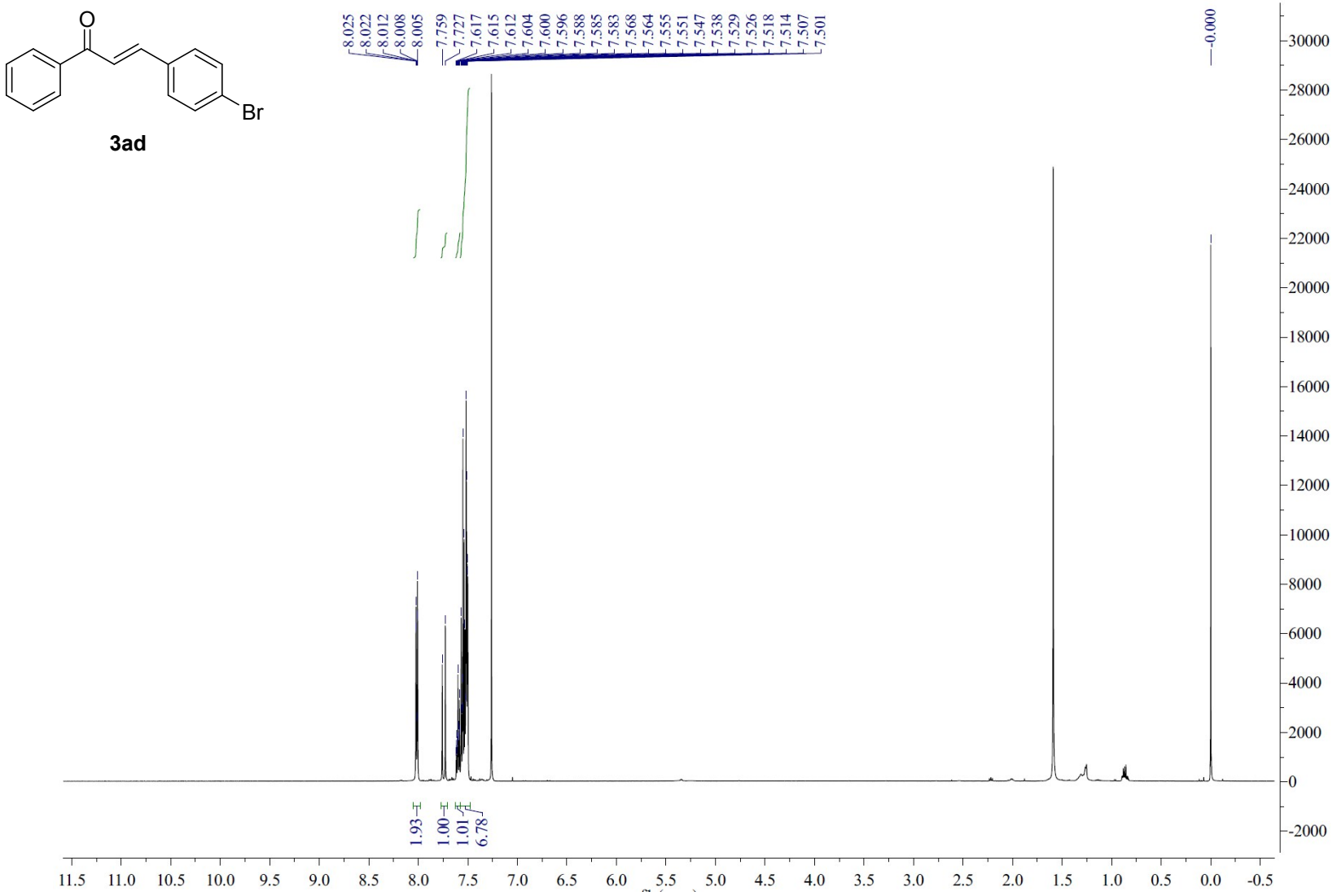
132.923
129.256
128.499
122.509
138.050
136.442
133.403
132.923
129.584
129.256
128.677
128.499
f1 (ppm)
O
Cl
3ac


O
Br
3ad
8.025
8.022
8.012
8.008
8.005
7.759
7.727
7.617
7.615
7.612
7.604
7.600
7.596
7.588
7.585
7.583
7.568
7.564
7.555
7.551
7.547
7.538
7.529
7.526
7.518
7.514
7.507
7.501
-0.000
1.93
1.00
1.01
6.78
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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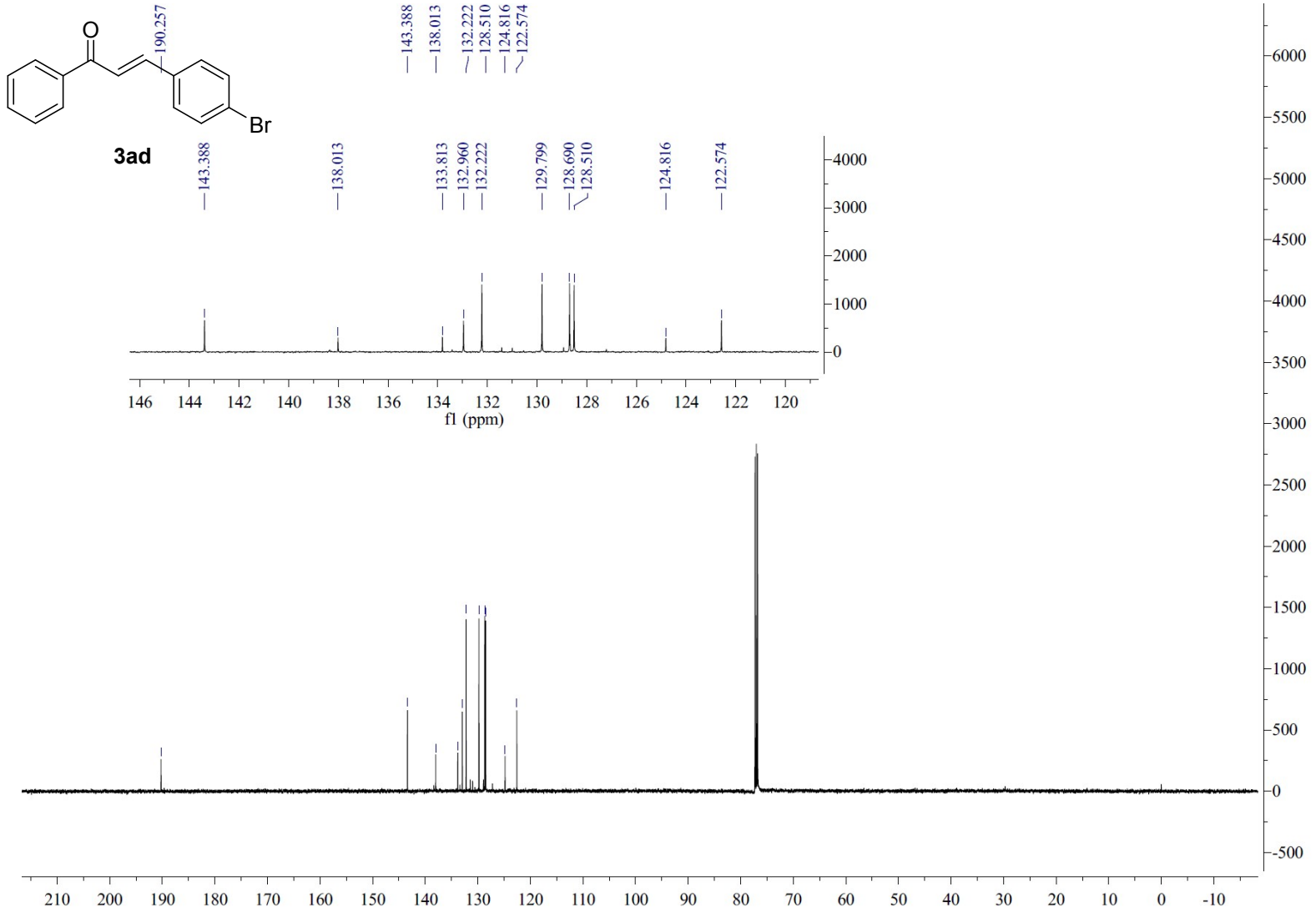
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


O
Br
190.257
143.388
138.013
132.222
128.510
124.816
122.574
3ad
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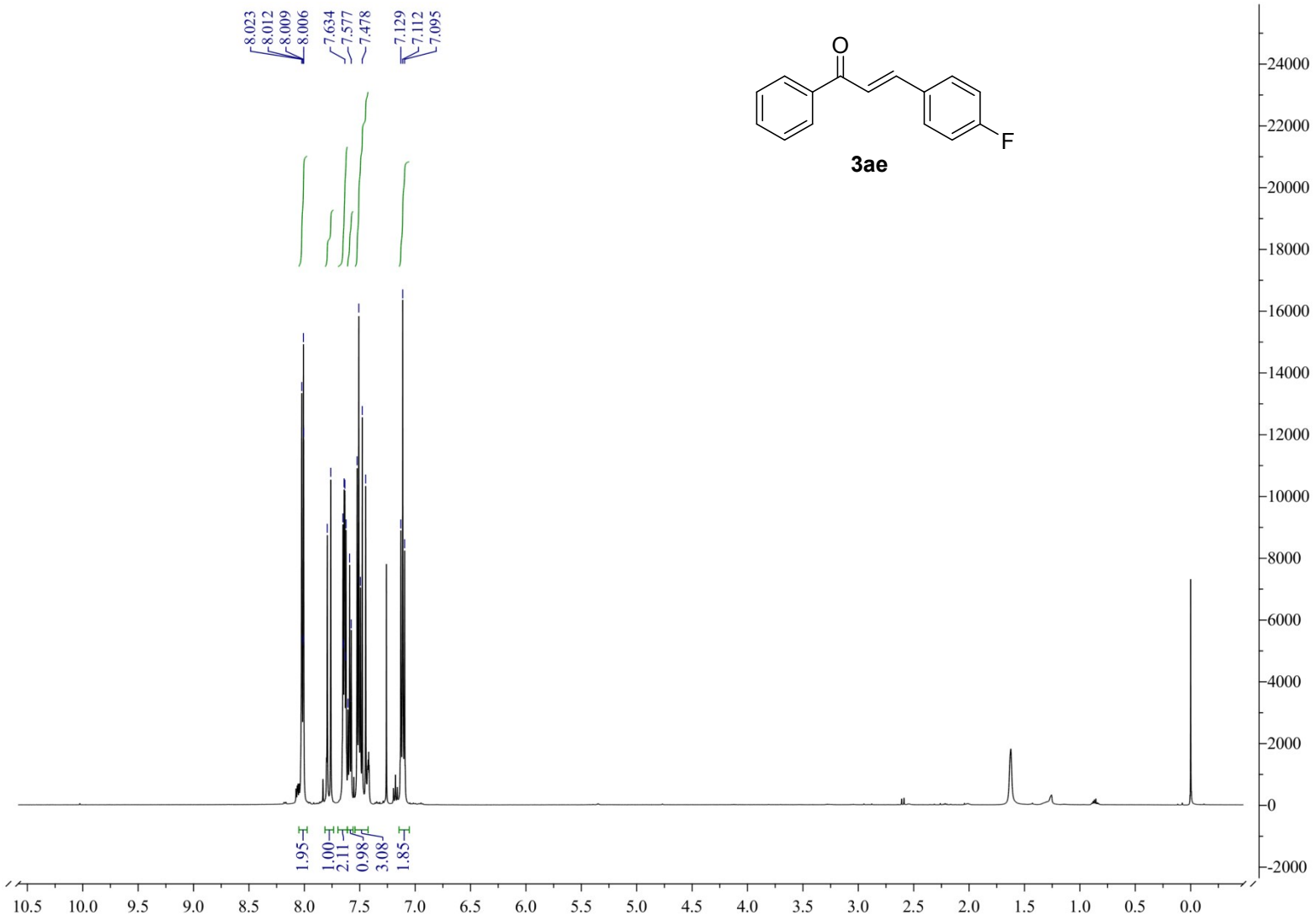
138.013
133.813
132.960
132.222
129.799
128.690
128.510
124.816
122.574
fl (ppm)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8.012
8.009
8.006
7.634
7.577
7.478
7.129
7.112
7.095
O
F
3ae
1.95
1.00
2.11
0.98
3.08
1.85
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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3.0
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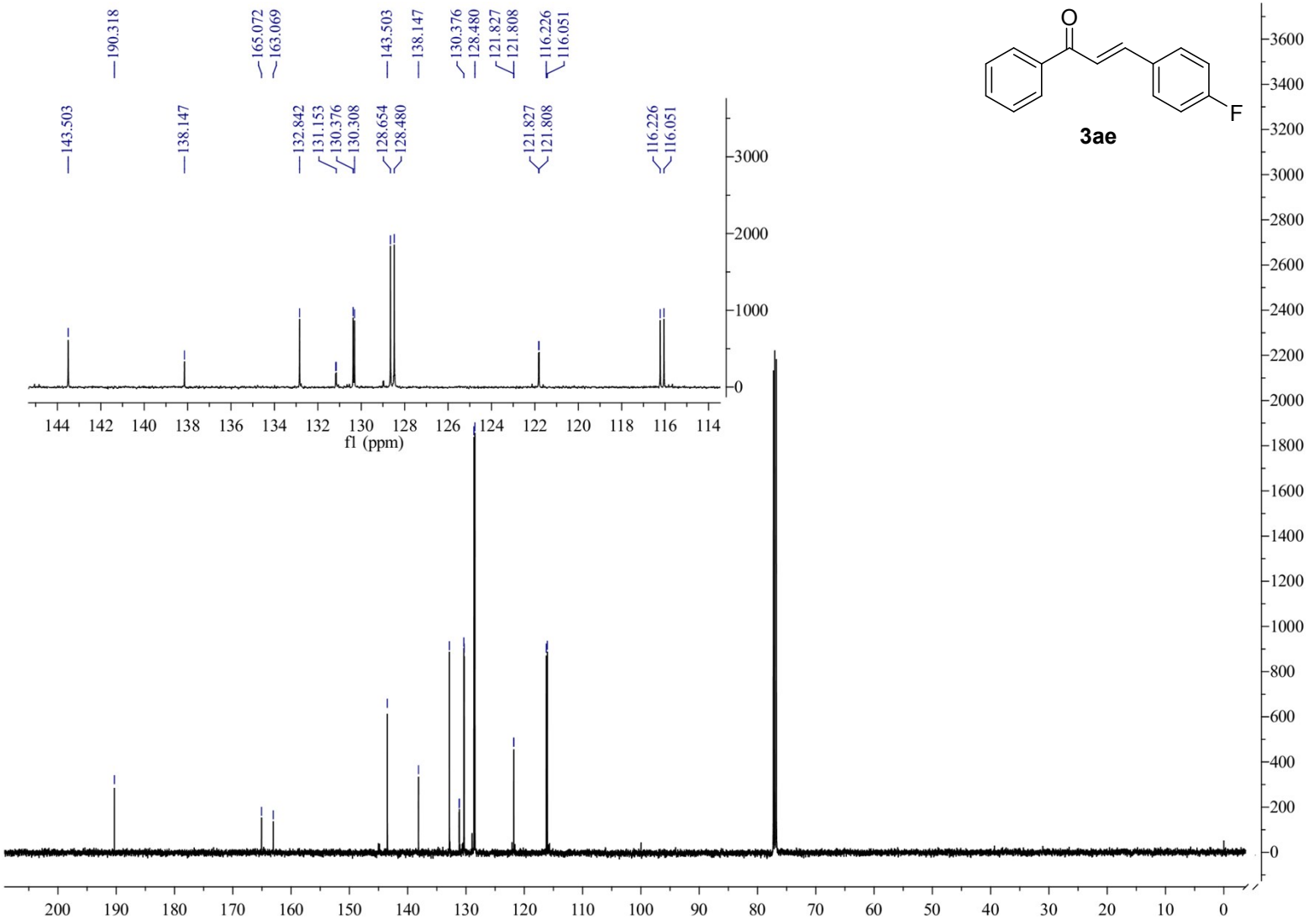
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163.069
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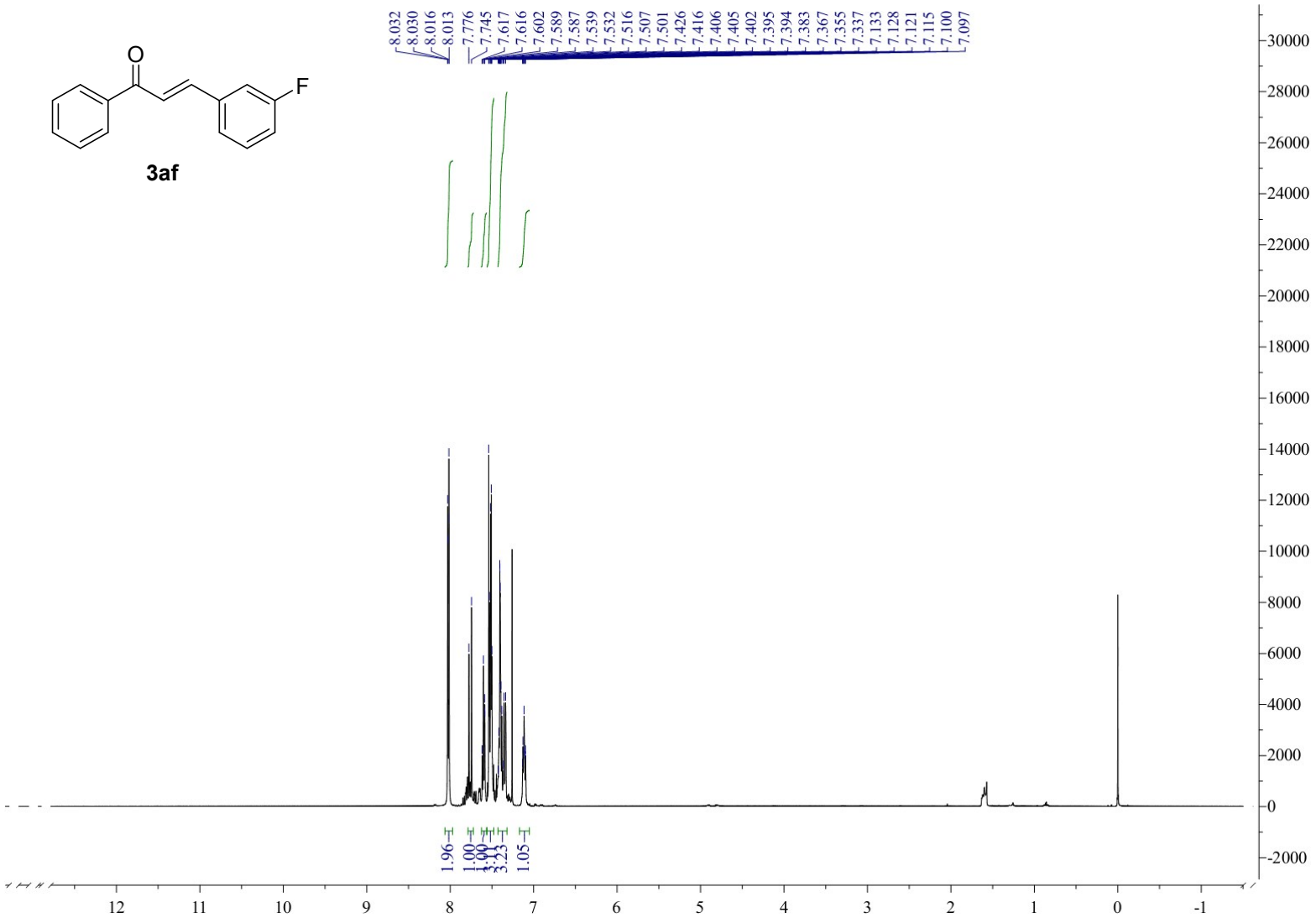
130.376
128.480
121.827
121.808
116.226
116.051
143.503
138.147
132.842
131.153
130.376
130.308
128.654
128.480
121.827
121.808
116.226
116.051
f1 (ppm)
O
F
3ae


O
F
3af
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8.030
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8.013
7.776
7.745
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7.616
7.602
7.589
7.587
7.539
7.532
7.516
7.507
7.501
7.426
7.416
7.406
7.405
7.402
7.395
7.394
7.383
7.367
7.355
7.337
7.133
7.128
7.121
7.115
7.100
7.097
1.96
1.00
1.00
3.23
1.05
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
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12
11
10
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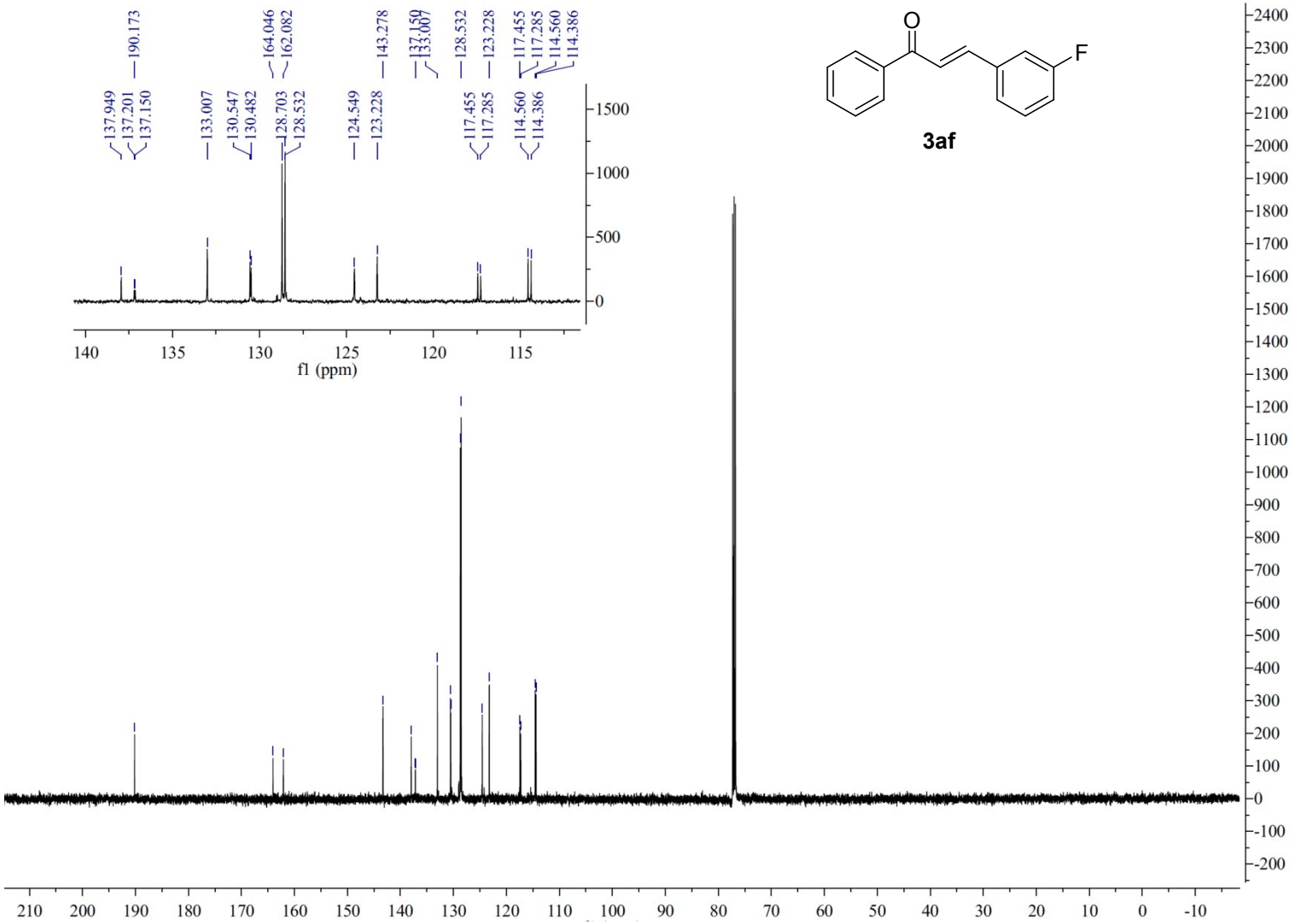
8
7
6
5
4
3
2
1
0
-1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162.082
143.278
137.150
133.007
128.532
123.228
117.455
117.285
114.560
114.386
137.949
137.201
137.150
133.007
130.547
130.482
128.703
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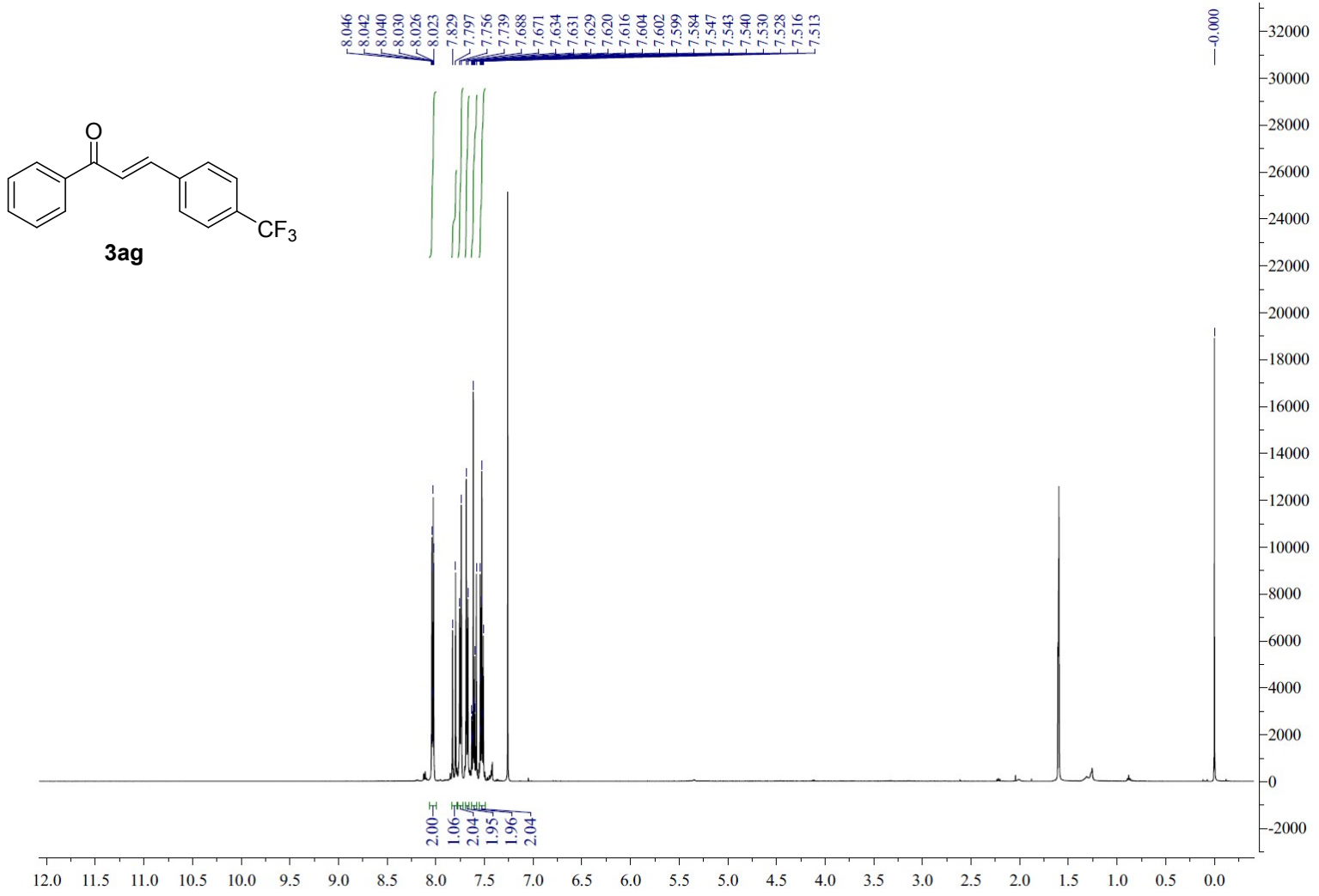
124.549
123.228
117.455
117.285
114.560
114.386
fl (ppm)
O
F
3af


O
CF3
3ag
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8.030
8.026
8.023
7.829
7.797
7.756
7.739
7.688
7.671
7.634
7.631
7.629
7.620
7.616
7.604
7.602
7.599
7.584
7.547
7.543
7.540
7.530
7.528
7.516
7.513
-0.000
2.00
1.06
2.04
1.95
1.96
2.04
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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4.0
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1.5
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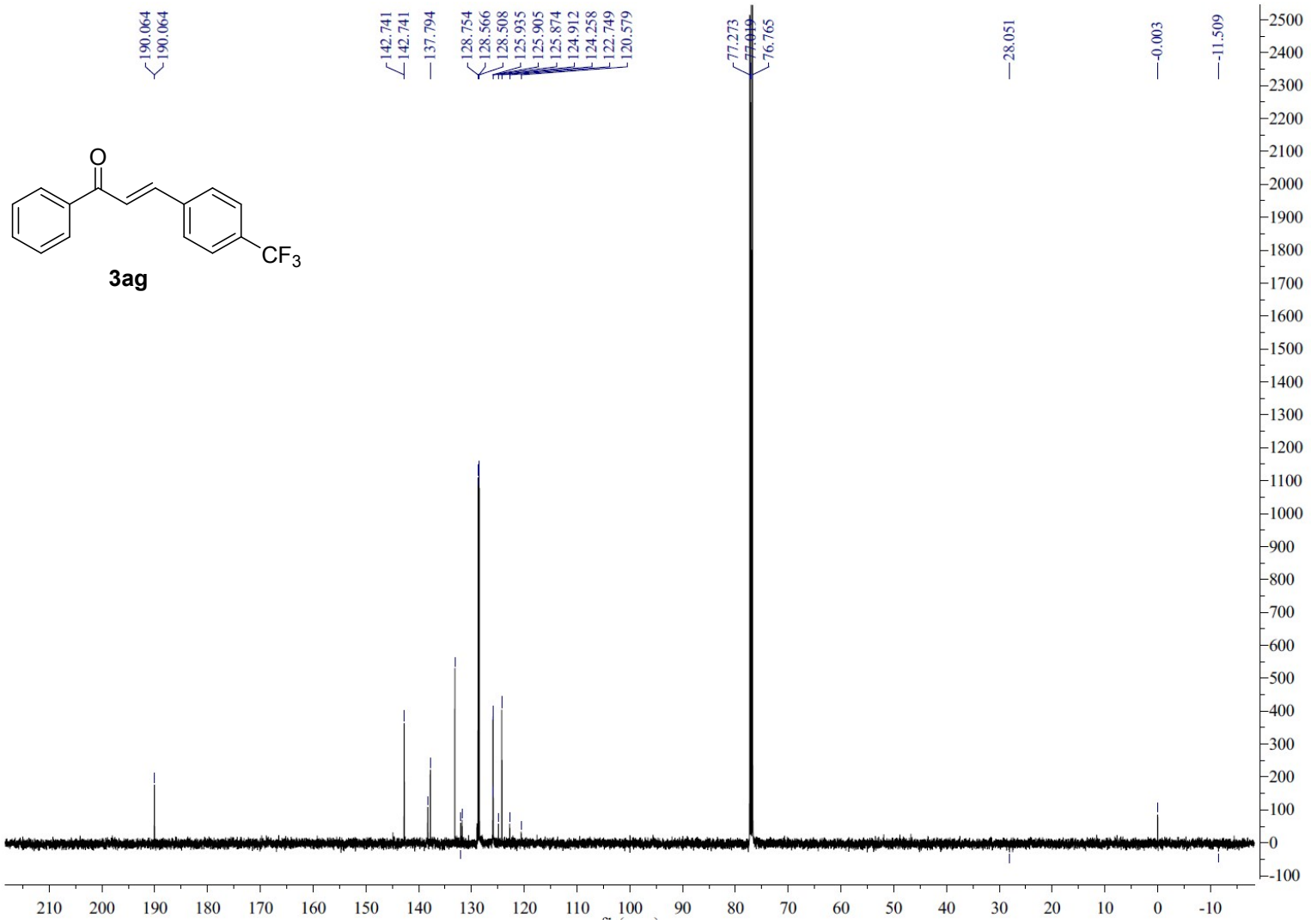
0.0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190.064
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142.741
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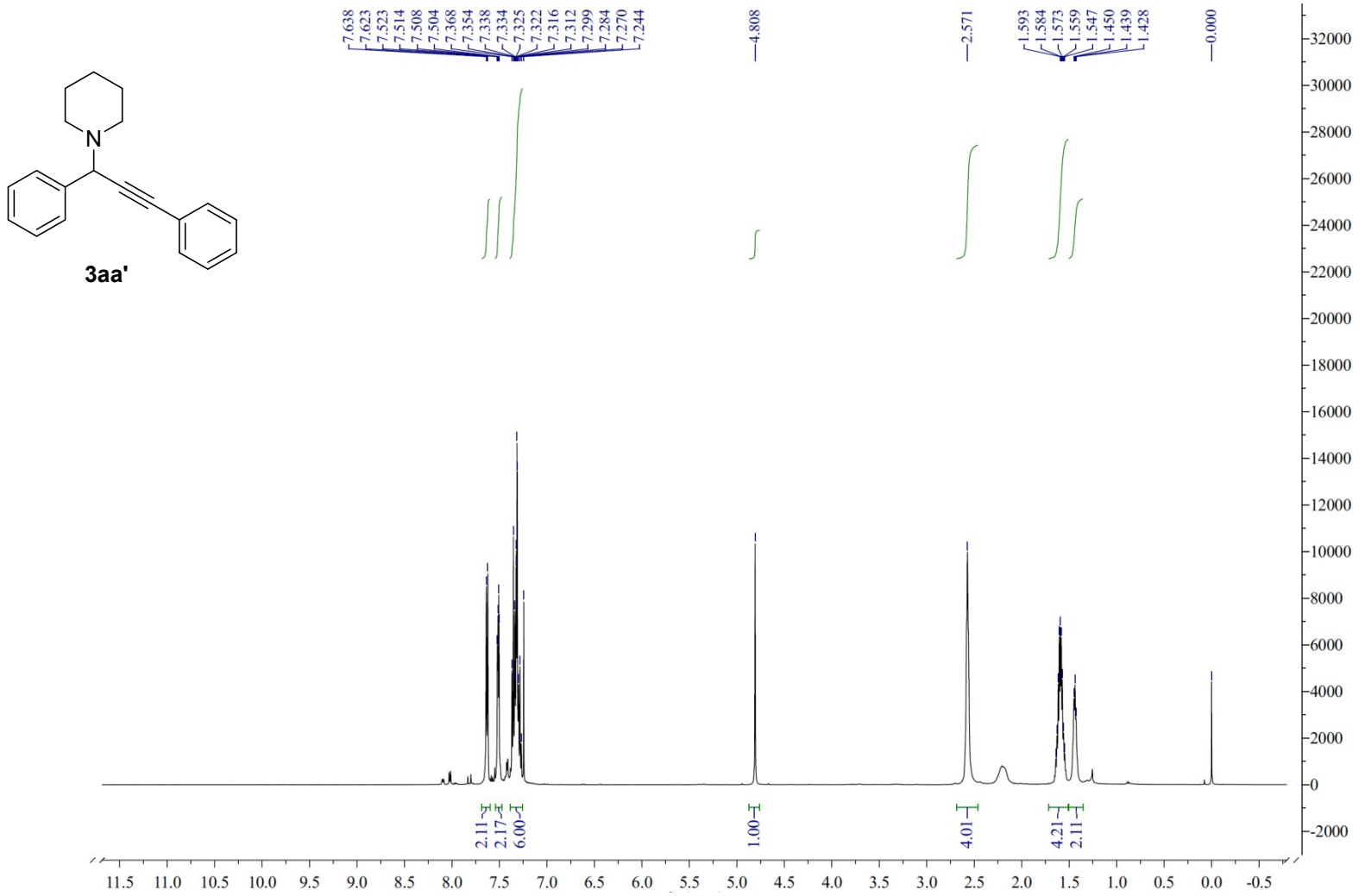
128.508
125.935
125.905
125.874
124.912
124.258
122.749
120.579
77.273
77.019
76.765
28.051
-0.003
-11.509
O
CF3
3ag


3aa'
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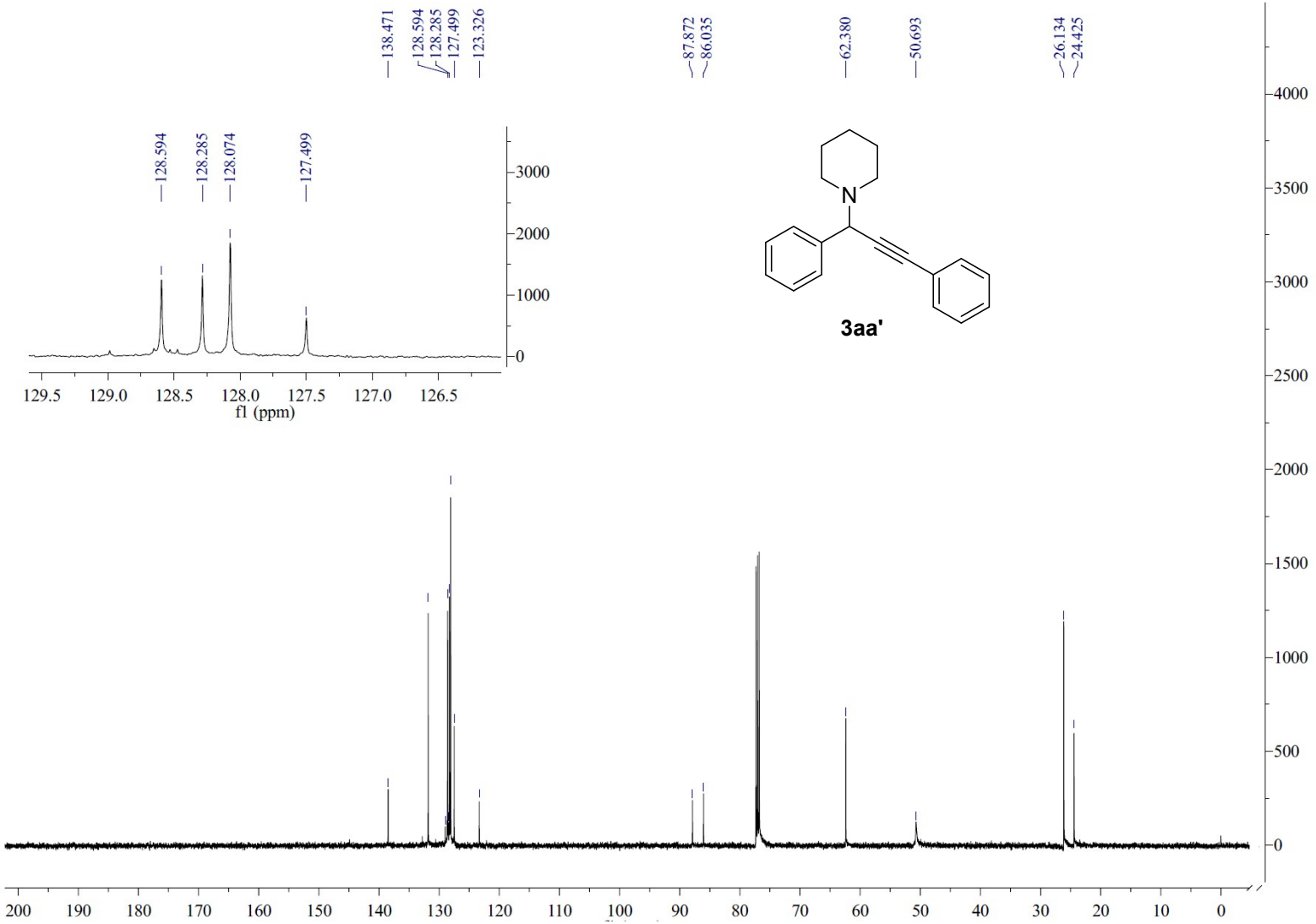
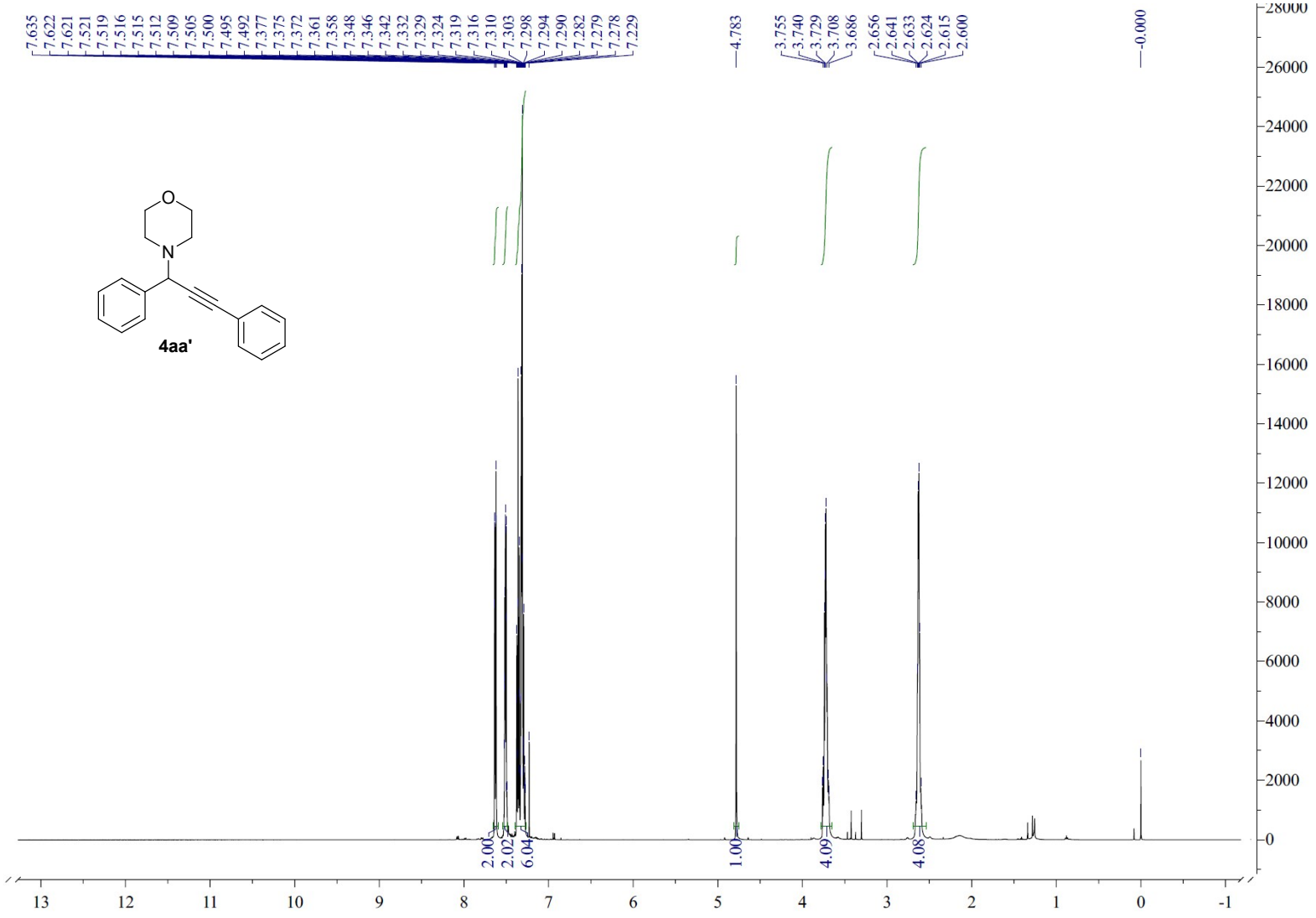
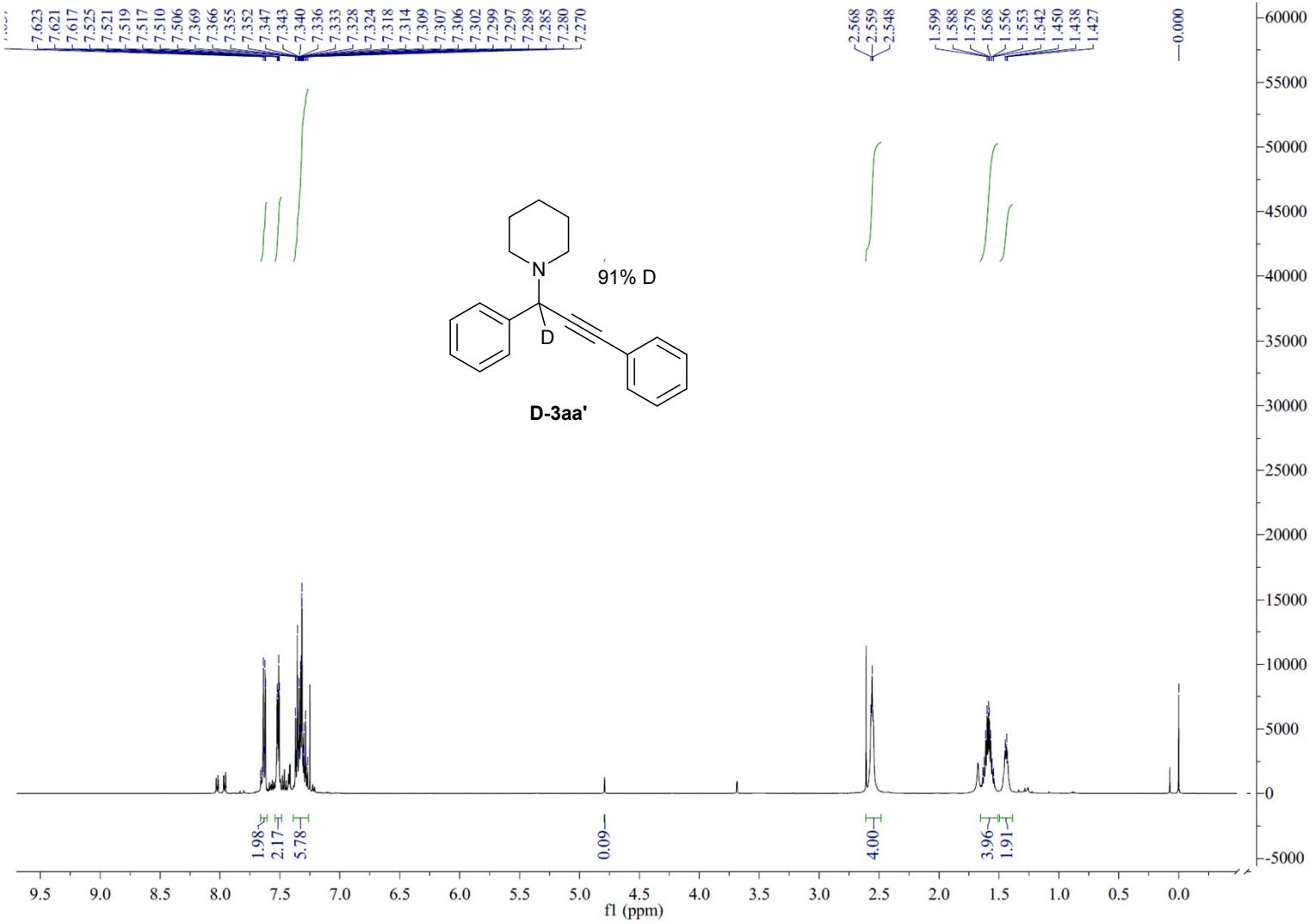
7.523
7.514
7.508
7.504
7.368
7.354
7.338
7.334
7.325
7.322
7.316
7.312
7.299
7.284
7.270
7.244
4.808
2.571
1.593
1.584
1.573
1.559
1.547
1.450
1.439
1.428
0.000
2.11
2.17
6.00
1.00
4.01
4.21
2.11


138.471
128.594
128.285
127.499
123.326
87.872
86.035
62.380
50.693
26.134
24.425
128.594
128.285
128.074
127.499
fl (ppm)
3aa'


7.635
7.622
7.621
7.521
7.519
7.516
7.515
7.512
7.509
7.505
7.500
7.495
7.492
7.377
7.375
7.372
7.361
7.358
7.348
7.346
7.342
7.332
7.329
7.324
7.319
7.316
7.310
7.303
7.298
7.294
7.290
7.282
7.279
7.278
7.229
4.783
3.755
3.740
3.729
3.708
3.686
2.656
2.641
2.633
2.624
2.615
2.600
-0.000
O
N
4aa'
2.00
2.02
6.04
1.00
4.09
4.08
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1


7.623
7.621
7.617
7.525
7.521
7.519
7.517
7.510
7.506
7.369
7.366
7.355
7.352
7.347
7.343
7.340
7.336
7.333
7.328
7.324
7.318
7.314
7.309
7.307
7.306
7.302
7.299
7.297
7.289
7.285
7.280
7.270
2.568
2.559
2.548
1.599
1.588
1.578
1.568
1.556
1.553
1.542
1.450
1.438
1.427
0.000
N
D
91% D
D-3aa'
1.98
2.17
5.78
0.09
4.00
3.96
1.91
f1 (ppm)