Synthesis of Chiral Cyclopentanones through Reactions with Vinyl Sulfoxonium Salts

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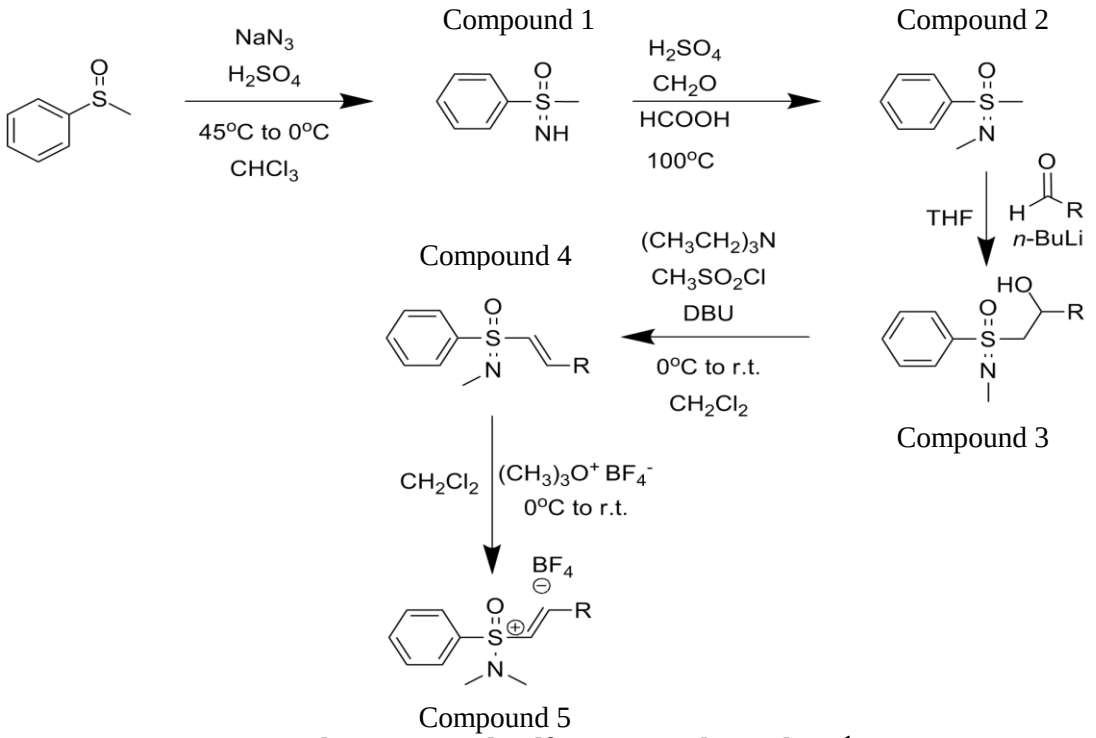
Synthetic derivations are often driven by the usefulness and application of certain molecules. Cyclopentanones are a class of molecules that serve an integral function in the structure of many biologically active compounds, including prostaglandins, estrone, and Bimatoprost.[6] To investigate synthetic routes to form cyclopentanones, we started by drawing from methods previously derived in the synthesis of γ-lactones.[2] Our group has previously shown that γ-lactones, which also play important roles in important biologically active molecules, can be synthesized using vinyl sulfoxonium salts and lithium enediolates. Keeping close to the methods used to synthesize the γ-lactones, we attempted to synthesize cyclopentanones using two different ketones and two different substituted vinyl sulfur salts. From here, the methodology shifted slightly to methods derived from Johnson and co-workers, and Huckin and Weiler, wherein the sulfoxonium salt was subjected to reaction with a β-ketoester, instead of a ketone.[1,4] In this case, only one β-ketoester and one vinyl sulfoxonium salt were used, while other variables were changed to see possible effects. Most recently, we moved on to investigate a different method derived from our past work, where we subject a sulfoxonium ylide to react with an acrylate, and then intercept the enolate intermediate with a ketene in a continued attempt to form cyclopentanone.[1,3] 4-Methoxy substituted vinyl sulfoxonium salts fall in the scope of investigation for their electron-donating electronic effect on possible product synthesis. Acetone, 3-methyl-2-butanone, dimethyl vinyl sulfonium salt, and phenyl vinyl sulfoxonium salt fall into the scope of investigation for their potential to affect cyclopentanone yields.

Experiment and Results:

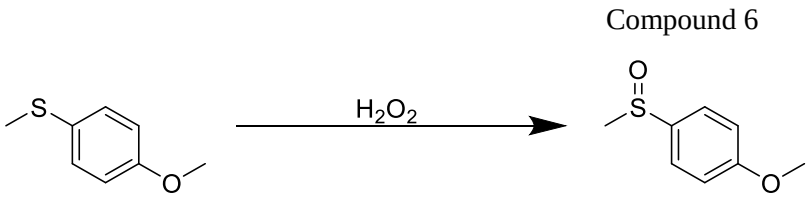
Sulfoxonium Salts:

Similar to our previous work with diastereoselective synthesis of γ-lactones[2], our route towards the synthesis of cyclopentanones utilized vinyl sulfoxonium salts. The synthesis of vinyl sulfoxonium salts typically follows five steps: sulfoximine generation (Compound 1), nitrogen methylation (Compound 2), aldol addition (Compound 3), dehydration (Compound 4), and salt formation (Compound 5). This process is outlined in scheme 1 and is partly derived from Johnson's studies.[1]



Scheme 1: Vinyl Sulfoxonium Salt Synthesis[1]

As part of our studies, we investigated the synthesis and possible effects of a 4-methoxyphenyl vinyl sulfoxonium salt. In this process, hydrogen peroxide and 4-methoxythioanisole were used to generate a sulfoxide compound[5] (Compound 6), which was then taken through the five steps in the vinyl sulfoxonium salt synthesis, resulting in a total of six steps and a methoxy group on the final product.



Scheme 2: Oxidation of 4-methoxythioanisole[5]

Table 1 shows the highest yield attained at each step of the vinyl sulfoxonium salt synthesis, along with the scale of the reaction at that yield. The substituent group R from scheme 1 is a phenyl ring for all salts generated during this investigation. The standard salt synthesis results and the 4-methoxy synthesis results are separated to show a comparison between the two. As shown, the standard salt synthesis had much larger yields for four of the five commons steps, due to various factors that impacted yield of the 4-methoxy salt.

Table 1: Vinyl Sulfoxonium Salt Synthesis Yields and Scales

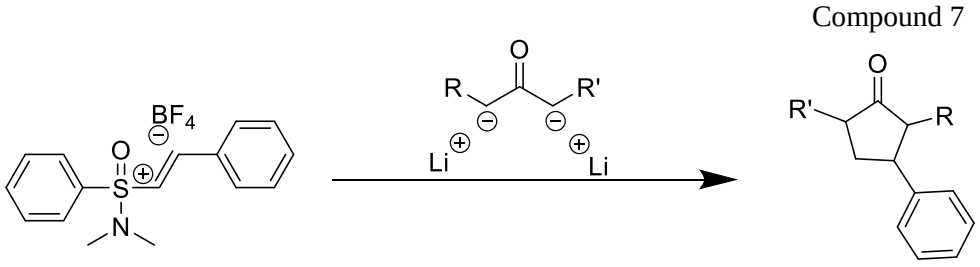
Synthesis Step	Standard Salt Yield	Scale Standard Salt (mmol)	4-methoxy Salt Yield	Scale 4-methoxy Salt (mmol)
Sulfoxide Formation[6]	N/A	N/A	80%	32.4
Sulfoximine Generation[1]	86%	36.1	16%	26.3
Nitrogen Methylation[2]	91%	28.2	76%	4.2
Aldol Addition[3]	81%	20.1	55%	3.2
Dehydration[4]	99%	19.4	69%	1.8
Salt Formation[5]	68%	4.3	91%	1.2

[1] represents Compound 1; [2] represents Compound 2; [3] represents Compound 3; [4] represents Compound 4; [5] represents Compound 5; [6] represents Compound 6

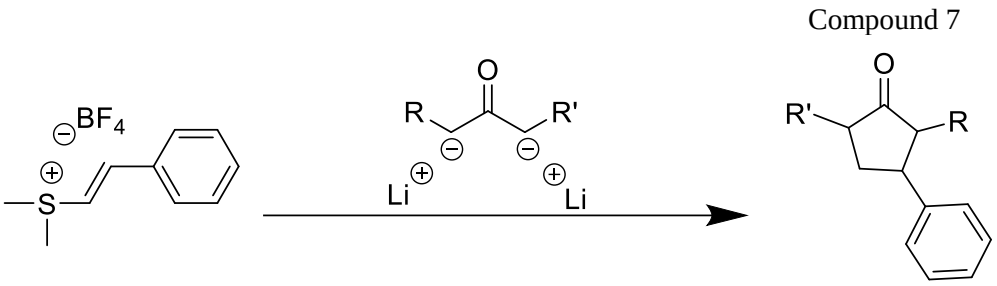
All yields for the standard salt synthesis are for purified products, while the first few yields of the 4-methoxy salt synthesis are for impure products, along with the last yield, due to a failure of the compound to crystallize. All impurities resulting from the sulfoxide formation (Compound 6) were removed after the sulfoximine was generated (Compound 1); however, a mostly insoluble black oil resulted during the generation of the sulfoximine. Attempts were made to remove all of it, but it was not completely removed until after the nitrogen was methylated (Compound 2). It is believed that the generation of this black oil is the reason behind such a low yield during the generation of the sulfoximine in the case of the 4-methoxy compound.

Cyclopentanone Synthesis:

Method 1:



Scheme 2: Proposed Synthesis of Cyclopentanones using Vinyl Phenyl Sulfoxonium Salt[1,2]



Scheme 3: Proposed Synthesis of Cyclopentanones using Dimethyl Sulfonium Salt[1,2]

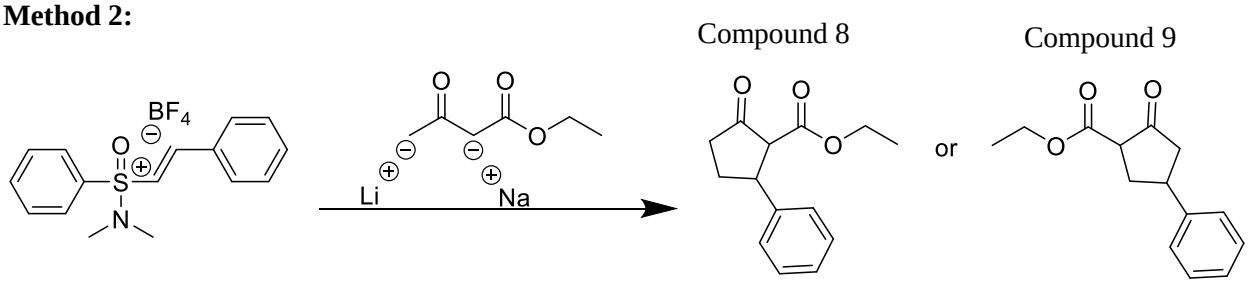
The proposed synthesis of cyclopentanones was derived from our group's procedure developed for γ-lactone synthesis.[2] Each ketone was deprotonated with two equivalents of *n*-butyl lithium at -78 °C to produce the resulting dianion shown above. The dianion and the sulfoxonium salt were mixed in tetrahydrofuran at -78 °C in hopes of forming the cyclopentanone compound 7 shown on the right. Two different sulfur salts (vinyl phenyl sulfoxonium and dimethyl vinyl sulfonium) were utilized to see if changing the substituents on the salt would help in total conversion to desired product. In a similar regard, two different ketones (acetone and 3-methyl-2-butanone) were utilized during the process to see if the substituents of the R groups would affect overall conversion. It was determined that the overall conversion stayed quite low for all experiments run.

Table 2: Method 1 Cyclopentanone Compound 7 Results

Experiment	Sulfur Salt	Ketone	GC-MS Conversion
1	Vinyl Phenyl	Acetone	0.0%
2	Vinyl Phenyl	Acetone	NMR
3	Vinyl Phenyl	3-methyl-2-butanone	1.21%
5	Vinyl Phenyl	Acetone	0.0%
6	Dimethyl	Acetone	NMR
7	Dimethyl	Acetone	0.4%

NMR - Some original samples were lost over time, but NMR scans still exist for this data.

Method 2:



Scheme 4: Proposed Cyclopentanone Synthesis using Ethyl Acetoacetate[1,4]

Although similar to the previous method, this method was drawn from the work done by Huckin and Weiler, who utilized β-ketoesters, dianions, and a two-step deprotonation process.[4] The ethyl acetoacetate was deprotonated first by sodium hydride at 0 °C and then by *n*-butyllithium at -78 °C. The

resulting dianion was mixed in tetrahydrofuran at -78 °C or -25 °C in hopes of forming either cyclopentanone compound 8 or cyclopentanone compound 9 shown above. In this process, only one β-ketoester and one sulfoxonium salt were investigated, with explorations in many areas in an attempt to increase conversion rates. Although conversion rates were much higher than in method one, it was found after much investigation that the product being generated was most likely not the desired product, leading us to move on to method three.

Table 3: Method 2 Cyclopentanone Compound 8 and Cyclopentanone Compound 9 Results

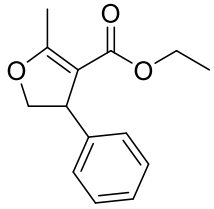
Experiment	1	2	3	4	5	6	7	8	9	10	11	12	13
Salt Equivalents	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Diisopropyl amine Equivalents	0.0	2.78	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
n-butyl lithium Equivalents	1.32	2.64	1.32	2.64	1.0	1.0	1.32	1.32	1.32	1.32	1.32	1.0	2.0
Sodium Hydride Equivalents	1.32	0.0	1.98	3.96	1.0	1.5	1.5	1.5	1.5	1.5	1.5	2.0	1.0
Dianion Equivalents	1.32	1.32	1.32	2.64	1.0	1.0	1.32	1.32	1.32	1.32	1.32	1.0	1.0
Time at -78 °C (min)	30	30	30	30	30	240	50	480	480	480	480	480	480
Time at -25 °C (min)	0.0	0.0	0.0	0.0	0.0	0.0	Over night	0.0	0.0	0.0	0.0	0.0	0.0
Salt Scale (mmol)	0.38	0.32	0.38	0.38	0.27	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Quenching Agent*	1	1	1	1	1	1	1	1	2	3	4	1	1
Pentane washes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kept at room temperature	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No
Conversion on GC-MS (%)	10.5	0.0	42.5	23.7	9.43	10.0	28.2	54.9	31.6	46.6	22.5	59.2	43.0

*Quenching agent 1 = NH_4Cl; quenching agent 2 = CH_3OH; quenching agent 3 = 0.1 M HCl; quenching agent 4 = CH_3COOH

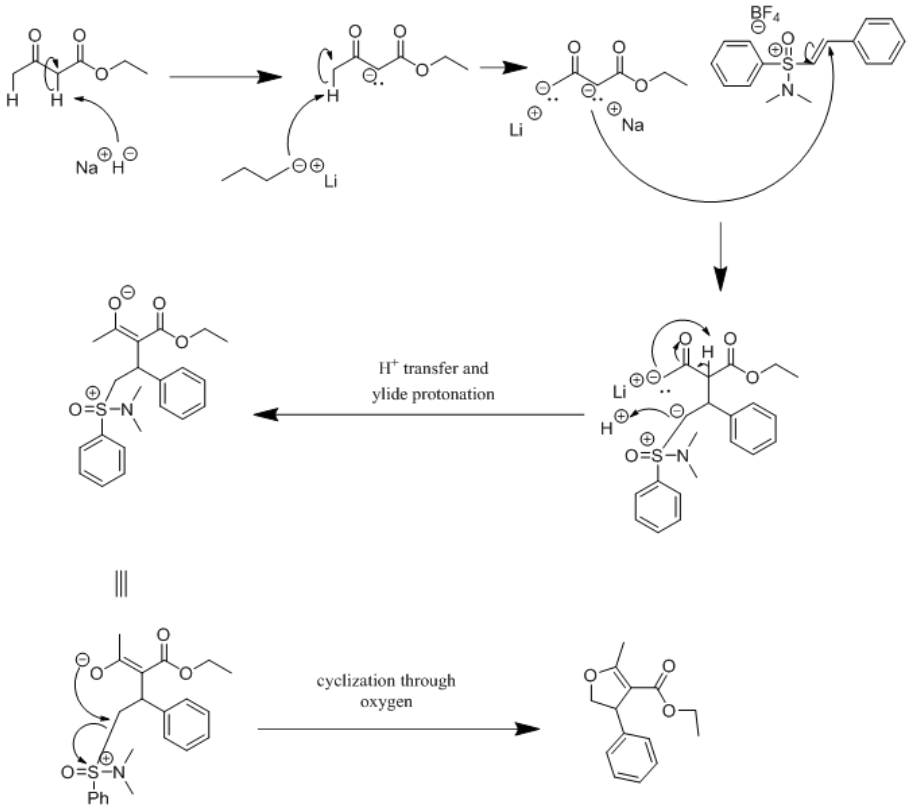
Attempts at increasing the conversion rate as determined by GC-MS were successful over time, but eventually, it was discovered that the product being generated could not be cyclopentanone. After much investigation, it was believed that the structure of the main compound being generated from this

reaction was the compound shown in scheme five (Compound 10). The proposed formation of this product is shown in scheme six. Once this was discovered, we decided to move on to method three for cyclopentanone generation.

Compound 10

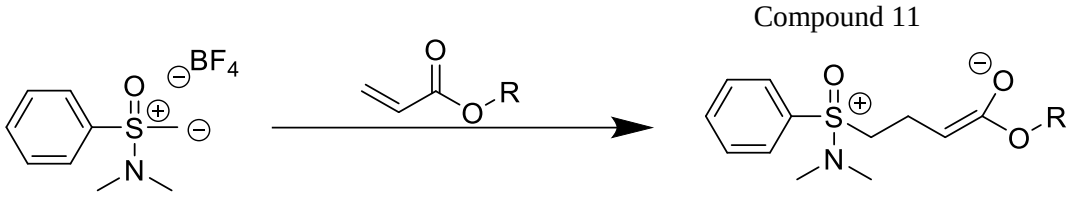


Scheme 5: Proposed Structure of Product from Ethyl Acetoacetate and Sulfoxonium Salt Reaction

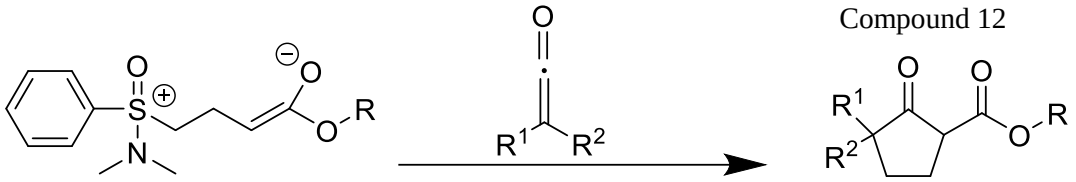


Scheme 6: Proposed Formation of Product from Ethyl Acetoacetate and Sulfoxonium Salt Reaction

Method 3:



Scheme 7: Proposed Synthesis of Intermediate used to form Cyclopentanone[1,3]



Scheme 8: Proposed Synthesis of Cyclopentanone by Intercepting the Intermediate[1,3]

The proposed synthesis of cyclopentanones was taken from previous work done by our group, except the acrylate in this reaction was replacing an aldehyde in the previous reaction.[3] The sulfoxonium salt in tetrahydrofuran was deprotonated by *n*-butyl lithium at -78 °C and then, ethyl acrylate was added to this mixture at -78 °C. Diphenylketene was added to the pot at -78 °C, in an attempt to intercept the intermediate (Compound 11) and form the cyclopentanone compound (Compound 12) shown in scheme eight. Not many reactions have been conducted to study this synthesis, but so far, there has been no conversion to desired products.

Conclusion and Discussion:

We proposed three different syntheses for the generation of cyclopentanone, based upon both previous work done in our lab[2,3] and the work done by Johnson and co-workers, as well as Huckin and Weiler.[1,4] The first method focused on the use of dianions that were generated by ketones and sulfoxonium salts.[1,2] The first method of synthesis showed very low conversion rates, even when changing the ketone or the sulfoxonium salt, which implied that a different mechanistic approach was most likely necessary. The second method was similar to first, in that it utilized both dianions and sulfoxonium salts, except these dianions were generated from β-ketoesters.[1,4] The second method of synthesis showed much greater conversion rates and showed much promise in optimizing the overall reaction conditions. However, with the lack of cyclopentanone generation, the method proved to be less novel than we had originally hoped. The third method moved away from dianions and focused more on the reaction between acrylates, ketenes, and sulfoxonium salts in a one-pot reaction mixture.[1,3] The third method of synthesis had a very limited number of investigative reactions run, so further exploration into this method may be pertinent for the development of the cyclopentanone synthesis. Although the original

reactions using Method 3 show little promise, it may be possible to find a novel route to cyclopentanone synthesis by tweaking the reaction conditions or reactants.

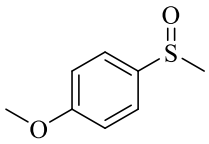
The sulfoxonium salts used were part of previously demonstrated syntheses conducted by our lab and they stem from, in part, the work previously done by Johnson.[1] Several sulfoxonium salts were used during the course of this project, pairing the sulfoxonium salts to the desired task at hand based upon sterics, electronic activity, ease of synthesis, and previous results. The 4-methoxy substituted sulfoxonium salt formed was a novel adaptation of previously demonstrated syntheses. The low yields and other related problems with the 4-methoxy substituted sulfoxonium salt demonstrate the challenges that present themselves when synthesizing sulfoxonium salts. Further studies focus on further analysis into the third method of cyclopentanone generation and possible ways to make the reaction successful. If unsuccessful, other methods may prove necessary to attempt, in order to generate the desired product.

Supporting Information:

General Procedure for the Preparation of Vinyl Sulfoxonium Salts:

Sulfoxide Formation:

1.

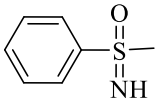


methyl(4-methoxyphenyl)sulfoxide[5]

Hydrogen peroxide (30.80 mmol, 0.95 equiv) was added slowly to a stirring solution of liquid 1-methoxy-4-(methylthio)benzene (5.0 g, 32.42 mmol, 1.0 equiv) at room temperature. The solution reacted violently, initially, before being warmed to 70 °C for 2 h. The solution was extracted with dichloromethane (60 mL x 3) and the combined organics were dried with Na_2SO_4. The solvent was removed to afford methyl(4-methoxyphenyl)sulfoxide as an impure oil (5.6 g), which was 80% desired product, as determined by GC-MS. GC-MS m/z found: 170.0, calcd: 170.0.

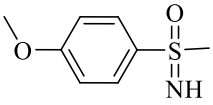
Sulfoximine Generation:

2a.



S-methyl S-phenylsulfoximine[1]

2b.



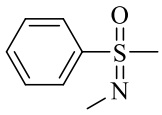
S-methyl-S-(4-methoxyphenyl)sulfoximine[1]

2a. Methylphenyl sulfoxide (5.06 g, 36.1 mmol) was added to sodium azide (2.54 g, 39.1 mmol) in chloroform (40 mL) at 0 °C. Sulfuric acid (16 g, 8.75 mL) was added dropwise via a dropping funnel over 30 min. When the slow addition was finished, the ice bath was removed, and the reaction was allowed to warm to room temperature. The solution was heated to 45 °C and stirred overnight. The reaction was then quenched by addition of deionized water at 0 °C. All white salts were dissolved after the water was added. The crude product was extracted with dichloromethane (60 mL x 3) to remove undesired products. The aqueous layer was basified with 20% NaOH solution to ca. pH 9. The aqueous layer was extracted with dichloromethane (60 mL x 3) and the combined organics were dried over Na_2SO_4. The solvent was removed to afford S-methyl S-phenylsulfoximine as a yellow oil (4.82 g, 86%). ^{1}H NMR (200MHz, $CDCl_3$, TMS) δ 8.04 - 7.98 (d, 2H), 7.64 - 7.50 (m, 3H), 3.10 (s, 3H), 2.70 (s, 1H).

2b. Methyl(4-methoxyphenyl)sulfoxide (5.6 g, 32.9 mmol) was added to sodium azide (2.35 g, 36.2 mmol) in chloroform (40 mL) at 0 °C. Sulfuric acid (16 g, 8.75 mL) was added dropwise via a dropping funnel over 30 min. When the slow addition was finished, the ice bath was removed, and the reaction was allowed to warm to room temperature. The solution was heated to 45 °C and stirred overnight. The reaction was then quenched by addition of deionized water at 0 °C. All white salts were dissolved after the water was added. The crude product was extracted with dichloromethane (60 mL x 3) to remove undesired products. The aqueous layer was basified with 20% NaOH solution to ca. pH 9. The aqueous layer was extracted with dichloromethane (60 mL x 3) and the combined organics were dried over Na_2SO_4. The solvent was removed to afford S-methyl-S-(4-methoxyphenyl)sulfoximine as an oil (0.783 g, 16%). ^{1}H NMR (200MHz, $CDCl_3$, TMS) δ 7.98 - 7.89 (d, 2H), 7.07 - 6.97 (d, 2H), 3.89 (s, 3H), 3.10 (s, 3H), 2.74 (s, 1H). GC-MS m/z found: 185.0, calcd: 185.0.

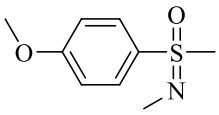
Nitrogen Methylation:

3a.



N-(methyl)-S-methyl-S-phenylsulfoximine[1]

3b.



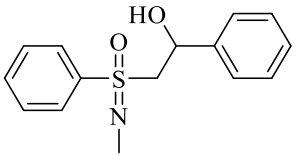
N-(methyl)-S-methyl-S-(4-methoxyphenyl)sulfoximine[1]

3a. A stirred mixture of S-methyl S-phenylsulfoximine (4.37 g, 28.2 mmol), formic acid (97%, 21.9 mL, 564 mmol), and formaldehyde (36.5% in H_2O, 43.7 mL, 578 mmol) was heated to 100 °C for 48-60 h. After cooling down to room temperature, formic acid was removed on a rota-evaporator connected to high vacuum to afford a yellow oil. The oil was dissolved in 2N H_2SO_4 (100 mL). The aqueous solution was extracted with dichloromethane (50 mL x 4) to remove formaldehyde polymer and then basified with NaOH (20%) solution to ca. pH 9. The aqueous solution was extracted with dichloromethane (60 mL x 3) and the combined organics were dried over Na_2SO_4. The solvent was removed to give N-(methyl)-S-methyl-S-phenylsulfoximine as a yellow salt (4.33 g, 91%). ^{1}H NMR (200MHz, $CDCl_3$, TMS) δ 7.94 - 7.87 (d, 2H), 7.66 - 7.54 (m, 3H), 3.09 (s, 3H), 2.66 (s, 3H).

3b. A stirred mixture of S-methyl-S-(4-methoxyphenyl)sulfoximine (0.783 g, 4.23 mmol), formic acid (97%, 3.29 mL, 84.6 mmol), and formaldehyde (36.5% in H_2O, 6.56 mL, 86.9 mmol) was heated to 100 °C for 48-60 h. After cooling down to room temperature, formic acid was removed on a rota-evaporator connected to high vacuum to afford a yellow oil. The oil was dissolved in 2N H_2SO_4 (100 mL). The aqueous solution was extracted with dichloromethane (50 mL x 4) to remove formaldehyde polymer and then basified with NaOH (20%) solution to ca. pH 9. The aqueous solution was extracted with dichloromethane (60 mL x 3) and the combined organics were dried over Na_2SO_4. The solvent was removed to give N-(methyl)-S-methyl-S-(4-methoxyphenyl)sulfoximine as an oil (0.644 g, 76%). ^{1}H NMR (200MHz, $CDCl_3$, TMS) δ 7.86 - 7.78 (d, 2H), 7.10 - 7.02 (d, 2H), 3.90 (s, 3H), 3.07 (s, 3H), 2.64 (s, 3H).

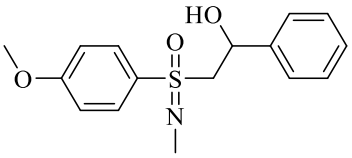
Aldol Addition:

4a.



(N-methylphenylsulfonimidoyl)ethanol[1]

4b.



4-methoxy substituted 4a.[1]

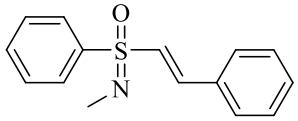
4a. To a solution of N-(methyl)-S-methyl-S-phenylsulfoximine (3.4 g, 20.1 mmol, 1 equiv) in THF (0.4 M) at 0 °C was added *n*-butyllithium in hexanes (1.92 M, 20.1 mmol, 1 equiv) dropwise and cooled to -78 °C. Benzaldehyde (3.29 mL, 32.2 mmol, 1.6 equiv) was added dropwise and the reaction was slowly warmed to room temperature overnight. The reaction was quenched with HCl:H_2O (2 mL: 6 mL) and neutralized with solid $NaHCO_3$. Extracted with dichloromethane (15 mL x 3) and the collected organics were dried with Na_2SO_4. Chromatographed through neutral silica with 5% ethyl acetate:hexane to remove unreacted benzaldehyde, followed by 20% ethyl acetate:hexane to yield the substituted (N-methylphenylsulfonimidoyl)ethanol as a clear or yellow liquid (4.49 g, 81%). ^{1}H NMR (200MHz, $CDCl_3$, TMS) δ 7.94 - 7.85 (d, 2H), 7.69 - 7.51 (m, 3H), 7.41 - 7.19 (m, 6H), 6.42 (s, 1H), 3.53 - 3.37 (t, 1H), 3.12 - 3.01 (d, 1H), 2.68 (s, 3H).

4b. To a solution of N-(methyl)-S-methyl-S-(4-methoxyphenyl)sulfoximine (0.644 g, 3.23 mmol, 1 equiv) in THF (0.4 M) at 0 °C was added *n*-butyllithium in hexanes (2.5 M, 3.23 mmol, 1 equiv) dropwise and lowered to -78 °C. Benzaldehyde (0.53 mL, 5.17 mmol, 1.6 equiv) was added dropwise and then the reaction mixture was transferred to a 0 °C bath for 2 h. The ice bath was removed and the reaction mixture was allowed to stir at room temperature for 1 h. The reaction was quenched with HCl:H_2O (0.65 mL: 1.9 mL) and neutralized with solid $NaHCO_3$. Extracted with dichloromethane (20 mL x 3) and the collected organics were dried with Na_2SO_4. Chromatographed through neutral silica with 5% ethyl acetate:hexane to remove unreacted benzaldehyde, followed by 20% ethyl acetate:hexane to yield the 4-methoxy substituted (N-methylphenylsulfonimidoyl)ethanol as a liquid (0.539 g, 55%). ^{1}H NMR (400MHz, $CDCl_3$, TMS) δ 7.83 - 7.79 (d, 2H), 7.41 - 7.28 (m, 4H), 7.26 - 7.23 (m, 1H), 7.05 - 7.01

(d, 2H), 6.54 (s, 1H), 5.57 - 5.53 (d, 1H), 3.88 (s, 3H), 3.39 - 3.35 (m, 1H), 3.07 - 3.03 (d, 1H), 2.67 (s, 3H). DR found: 3:1.

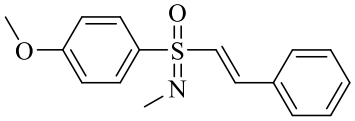
Dehydration:

5a.



***trans*-(N-methylphenylsulfonimidoyl)ethene**[1]

5b.



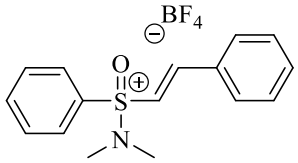
4-methoxy substituted 5a.[1]

5a. The substituted (N-methylphenylsulfonimidoyl)ethanol (5.35 g, 19.4 mmol, 1 equiv) was dissolved in a flame-dried flask in dichloromethane (0.157 M) and cooled to 0 °C. Triethylamine (13.5 mL, 97.2 mmol, 5 equiv) followed by methanesulfonyl chloride (4.51 mL, 58.3 mmol, 3 equiv) were added and stirred for 3 h at 0 °C. DBU (17.4 mL, 117 mmol, 6 equiv) was added and stirred for 15 min at 0 °C before warming to room temperature overnight. The next day, the reaction was diluted with ether (0.03 M) and washed with equivalent amounts of water, followed by aqueous saturated NH_4Cl, and then 10% $NaHCO_3$. The organic layer was dried with $MgSO_4$ to give the corresponding *trans*-(N-methylphenylsulfonimidoyl)ethene (4.95 g, 99%), which was deemed sufficiently pure by NMR. ^1H NMR (400MHz, $CDCl_3$, TMS) δ 7.97 - 7.93 (q, 2H), 7.60 - 7.51 (m, 4H), 7.49 - 7.45 (m, 2H), 7.39 - 7.34 (m, 3H), 6.88 - 6.83 (d, 1H), 2.81 (s, 3H).

5b. The 4-methoxy substituted (N-methylphenylsulfonimidoyl)ethanol (0.539 g, 1.76 mmol, 1 equiv) was dissolved in a flame-dried flask in dichloromethane (0.157 M) and cooled to 0 °C. Triethylamine (1.23 mL, 8.82 mmol, 5 equiv) followed by methanesulfonyl chloride (0.41 mL, 5.29 mmol, 3 equiv) were added and stirred for 3 h at 0 °C. DBU (1.58 mL, 10.6 mmol, 6 equiv) was added and stirred for 15 min at 0 °C before warming to room temperature overnight. The next day, the reaction was diluted with ether (0.03 M) and washed with equivalent amounts of water, followed by aqueous saturated NH_4Cl, and then 10% $NaHCO_3$. The organic layer was dried with $MgSO_4$ to give the corresponding 4-methoxy substituted *trans*-(N-methylphenylsulfonimidoyl)ethene (0.350 g, 69%), which was deemed sufficiently pure by NMR. ^1H NMR (200MHz, $CDCl_3$, TMS) δ 7.91 - 7.84 (d, 2H), 7.58 - 7.31 (m, 6H), 7.05 - 6.97 (d, 2H), 6.90 - 6.80 (d, 1H), 3.85 (s, 3H), 2.81 (s, 3H).

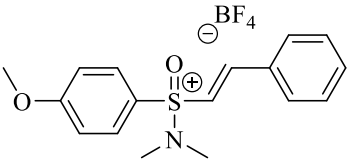
Vinyl Phenyl Sulfoxonium Salt Formation:

6a.



Vinyl Phenyl Sulfoxonium Salt[1]

6b.



4-methoxy Sulfoxonium Salt[1]

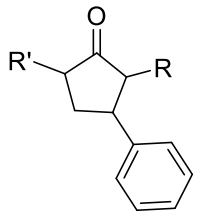
6a. The *trans*-(N-methylphenylsulfonimidoyl)ethene (1.01 g, 4.28 mmol, 1 equiv) was placed in a flame-dried flask, dissolved in dichloromethane (0.3 M), and cooled to 0 °C. Trimethyloxonium tetrafluoroborate (1.01 g, 6.85 mmol, 1.8 equiv) was added all at once to the flask and the solution was allowed to warm to room temperature overnight. The next day, the reaction was quenched with deionized water (50 mL), extracted with dichloromethane (3 x 50 mL), and the combined organics were dried with Na_2SO_4. The crude product solution was concentrated to about 0.167 M in dichloromethane and placed in a beaker in a jar filled with ether to allow for vapor/liquid diffusion-mediated crystallization of the product (0.967 g, 69%). ^{1}H NMR (200MHz, $CDCl_3$, TMS) δ 8.32 - 8.24 (d, 2H), 8.01 - 7.76 (m, 7H), 7.57 - 7.39 (m, 3H), 3.14 (s, 6H).

6b. The *trans*-(N-methylphenylsulfonimidoyl)ethene (0.350 g, 1.22 mmol, 1 equiv) was placed in a flame-dried flask, dissolved in dichloromethane (0.3 M), and cooled to 0 °C. Trimethyloxonium tetrafluoroborate (0.324 g, 2.19 mmol, 1.8 equiv) was added all at once to the flask and the reaction was allowed to warm to room temperature overnight. The next day, the reaction was quenched with deionized water (40 mL), extracted 3 times with dichloromethane (40 mL x 3), and the combined organics were dried with Na_2SO_4. The crude product solution was concentrated to about 0.167 M in dichloromethane and placed in a beaker in a jar filled with ether to allow for vapor/liquid diffusion-mediated crystallization of the product, but crystallization was unsuccessful. (0.433 g, 91%). ^{1}H NMR (200MHz, $CDCl_3$, TMS) δ 8.25 - 8.16 (d, 2H), 7.85 (s, 2H), 7.82 - 7.75 (d, 2H), 7.53 - 7.34 (m, 3H), 7.28 - 7.20 (d, 2H), 3.94 (s, 3H), 3.11 (s, 6H).

General Procedure for the Preparation of Cyclopentanones:

Method 1:

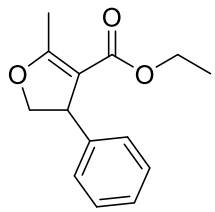
7.



n-Butyllithium in hexanes (1.92 M, 2.42 M, and 2.48 M, 1.0 mmol, 2.64 equiv for vinyl phenyl sulfoxonium and 3.05 equiv for dimethyl vinyl sulfonium) was added dropwise to a stirring solution of acetone/3-methyl-2-butanone (0.037 mL for acetone and 0.053 mL for 3-methyl-2-butanone, 0.5 mmol, 1.32 equiv for acetone and 1.53 equiv for 3-methyl-2-butanone) in tetrahydrofuran (2 mL) at 0 °C for and allowed to stir for 15 min. Cooling bath was removed and the reaction was stirred at room temperature for 30 min. The mixture was transferred dropwise to the sulfur salt (0.38 mmol for vinyl phenyl sulfoxonium and 0.33 mmol for dimethyl vinyl sulfonium, 1 equiv) suspended in tetrahydrofuran (3 mL) at -78 °C. The mixture was stirred for 30 min, warmed to room temperature over 1 h, and then gradually heated to 50 °C. The reaction was kept at 50 °C for 30 min, before being allowed to cool to room temperature. The reaction was then cooled to 0 °C and quenched with aqueous saturated NH_4Cl solution (2 mL). The solution was extracted with dichloromethane (20 mL x 3), washed with brine, and the combined organics were dried with Na_2SO_4. The crude product was chromatographed through silica, eluting with pure hexane, to provide product and unknown impurity as a clear or yellow oil. For Acetone: ^{1}H NMR (200MHz, $CDCl_3$, TMS) δ 7.34 - 7.28 (m, 5H), 6.85 - 6.73 (d, 2H), 6.36 - 6.25 (d, 2H), 2.24 - 2.14 (m, 2H). GC-MS m/z found: 160.1, calcd: 160.1. For 3-methyl-2-butanone: ^{1}H NMR not isolated product. GC-MS m/z found: 188.1, calcd: 188.1.

Method 2:

8.

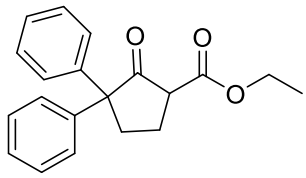


Pentane (2 ml per 100 mg sodium hydride and oil) was added to 60% sodium hydride (15 mg, 0.375 mmol, 1.5 equiv) in oil at room temperature. The mixture was stirred for a short period of time, before being allowed to settle. The liquid top layer was removed and these steps were repeated a second time. After this, tetrahydrofuran (2 mL) was added to the mixture and the mixture was cooled to 0 °C. Ethyl acetoacetate (0.0421 mL, 0.33 mmol, 1.32 equiv) was added dropwise and the reaction was allowed

to stir for 15 min at 0 °C. *n*-Butyllithium in hexanes (2.5 M, 0.33 mmol, 1.32 equiv) was then added dropwise and the reaction was stirred for a further 15 min at 0 °C. This solution was added to a stirring suspension of vinyl phenyl sulfoxonium salt **6a.** (89.8 mg, 0.25 mmol, 1 equiv) in tetrahydrofuran (3 mL) at -78 °C for 8 h, and then quenched at -78 °C with saturated aqueous NH_4Cl. The solution was extracted with dichloromethane (20 mL x 3), washed with brine, and the combined organics were dried with Na_2SO_4. The dried organics were concentrated and then run through a silica gel column. The major product eluted off the column after 400 mL of 1% ethyl acetate:hexane had been used as elutant and all products came off by 5% ethyl acetate:hexane. The final products were clear or yellow oils (31.9 mg, 54.9% conversion via crude GC-MS). ^{1}H NMR (400MHz, $CDCl_3$, TMS) δ 7.31 - 7.25 (m, 2H), 7.23 - 7.18 (m, 3H), 4.76 - 4.69 (t, 1H), 4.36 - 4.28 (m, 2H), 4.08 - 3.93 (m, 2H), 2.32 (s, 3H), 1.09 - 1.04 (t, 3H). ^{13}C NMR (400MHz, $CDCl_3$, TMS) δ 169.15, 165.68, 144.19, 128.42, 127.18, 126.68, 107.35, 78.58, 77.33, 77.01, 76.69, 59.29, 48.34, 14.16, 14.10. IR 3029, 2926, 2855, 1696, 1639, 1603, 1494, 1454, 1382, 1330, 1314, 1252, 1201, 1131, 1112, 1081, 1030, 1016, 988, 964, 921, 841, 781, 758723, 698, 665, 614, 540, 492. GC-MS m/z found: 232.1, calcd: 232.1.

Method 3:

9.



(Dimethylamino)methylphenyl oxosulfonium fluoroborate was placed under high vacuum for 30 min. After drying, the sulfoxonium salt (68 mg, 0.25 mmol) was suspended in anhydrous THF (1.5 mL) and stirred at −78 °C. *n*-Butyllithium (2.5 M in hexane, 0.1 mL, 0.25 mmol) was added dropwise at −78 °C, and the solution was stirred for 45 min. Ethyl acrylate (0.027 mL, 0.25 mmol) was added dropwise, and the reaction was stirred for another 1.5 h at −78 °C. Finally, diphenylketene solution (0.25 mmol ketene in 0.7 mL THF) was added to the reaction over 1 h. After being stirred for a further 4 h at −78 °C, the reaction was gradually allowed to warm to room temperature overnight in the cooling bath. The total reaction time was typically 20 h. The solvent was then removed to give the crude product, which contained no desired products. GC-MS m/z found: 182.1, 268.1, 239.1, 218, 185, 169 180.1, 186, 250, calcd:308.1

References:

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2. Nicholas J. Peraino, Kraig A. Wheeler, Nessan J. Kerrigan. Diastereoselective Synthesis of γ-Lactones through Reaction of Enediolates with α,β-Unsaturated Sulfoxonium Salts. *Organic Letters*. **2015**, *17*, 1735-1737.

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4. S. N. Huckin, L. Weiler. Aldol Type Condensations of Beta-Keto Ester Dianions. *Canadian Journal of Chemistry*. **1974**, *52*, 2157-2164.

5. F. Shi, M. K. Tse, H. M. Kaiser, M. Beller. Self-Catalyzed Oxidation of Sulfides with Hydrogen Peroxide: A Green and Practical Process for the Synthesis of Sulfoxides. *Advanced Synthesis & Catalysis*. **2007**, *349*, 2425-2430.

6. C. Oh, K. Y. Lee, Y. H. Kim, J. E. Joo, " Yonsung Fine Chemical Co., Ltd." U.S. Patent 20130253218 A1, filed May 23, 2013, and published September 26, 2013

Supporting Information Index

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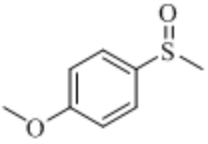

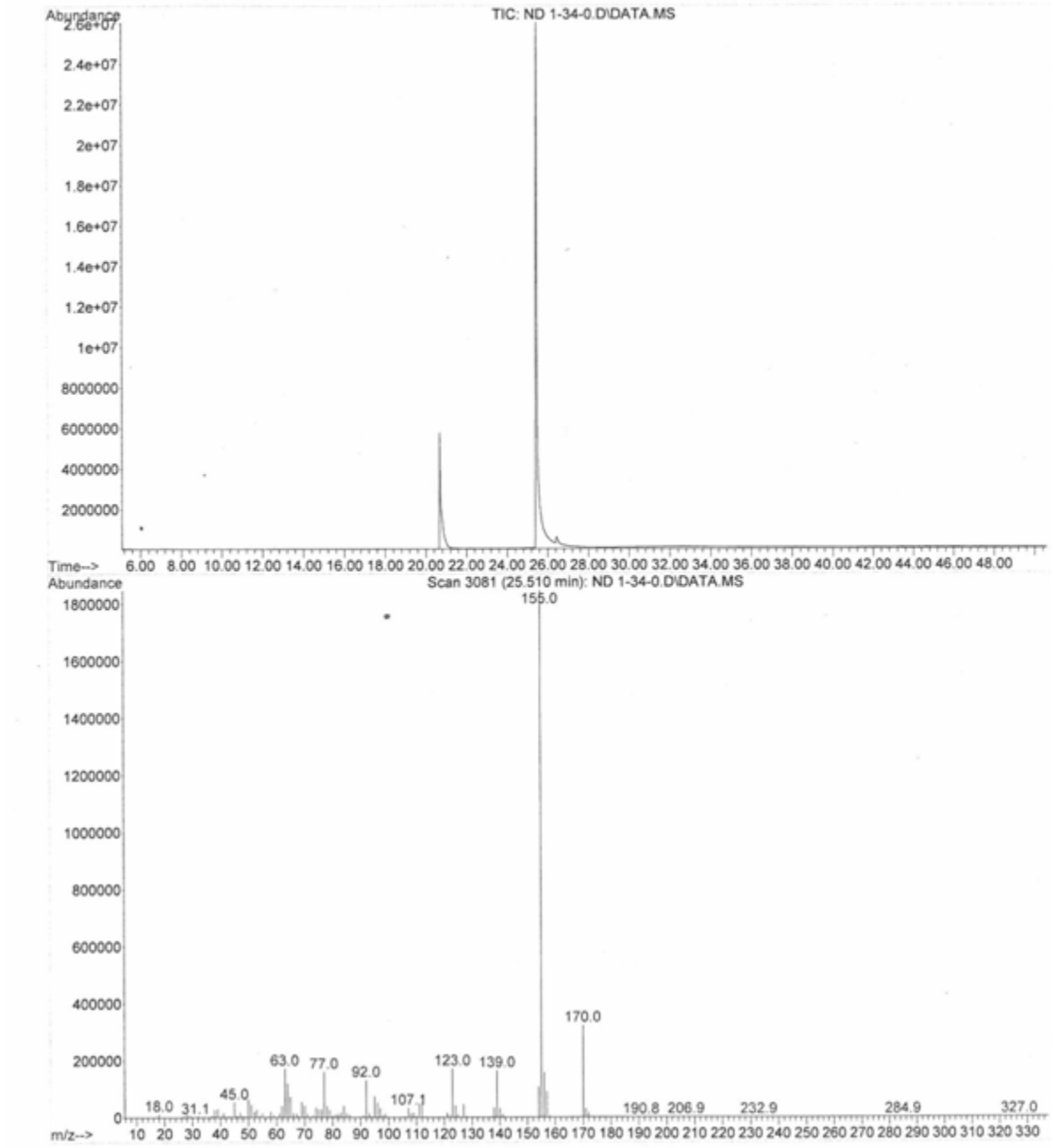

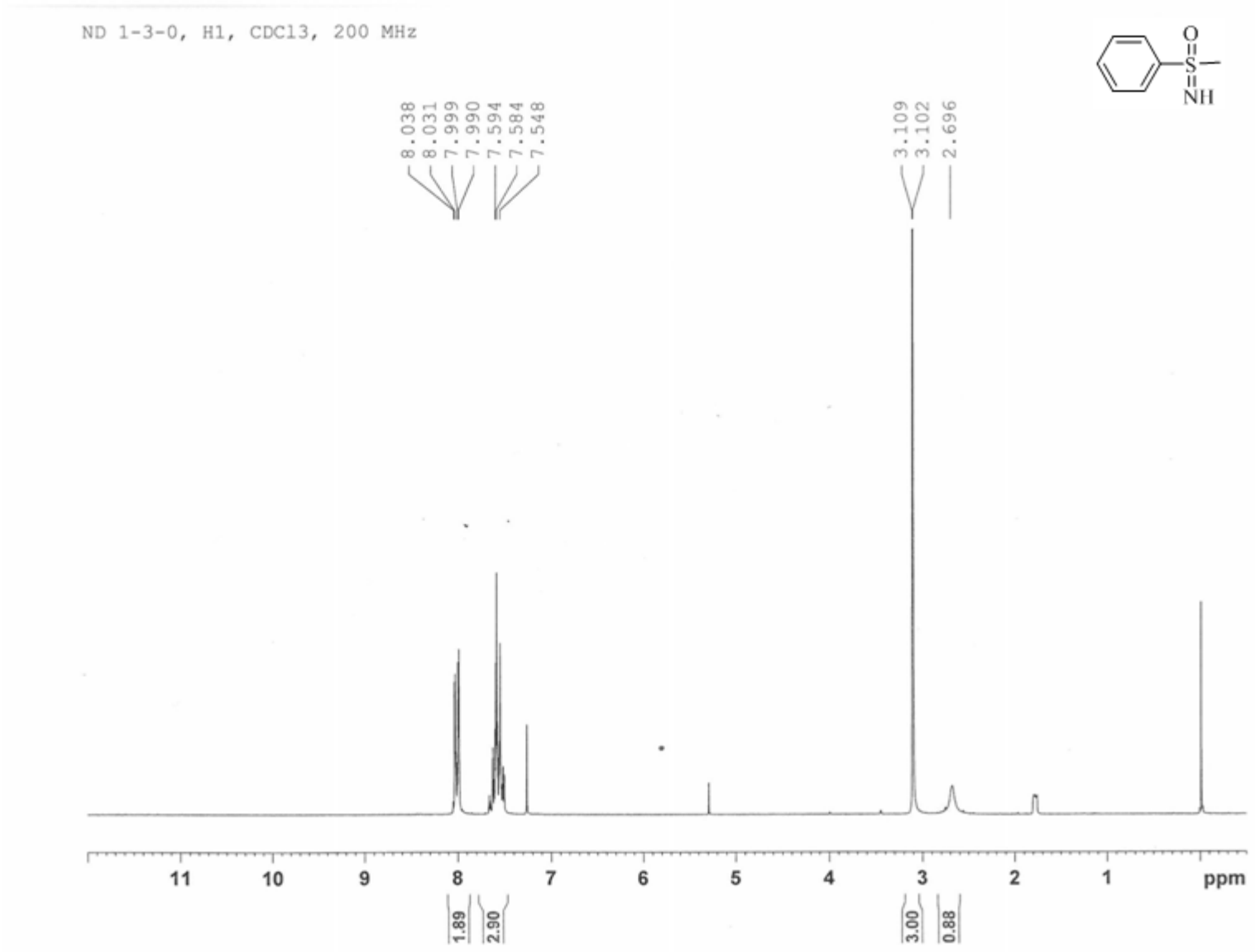
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3.00
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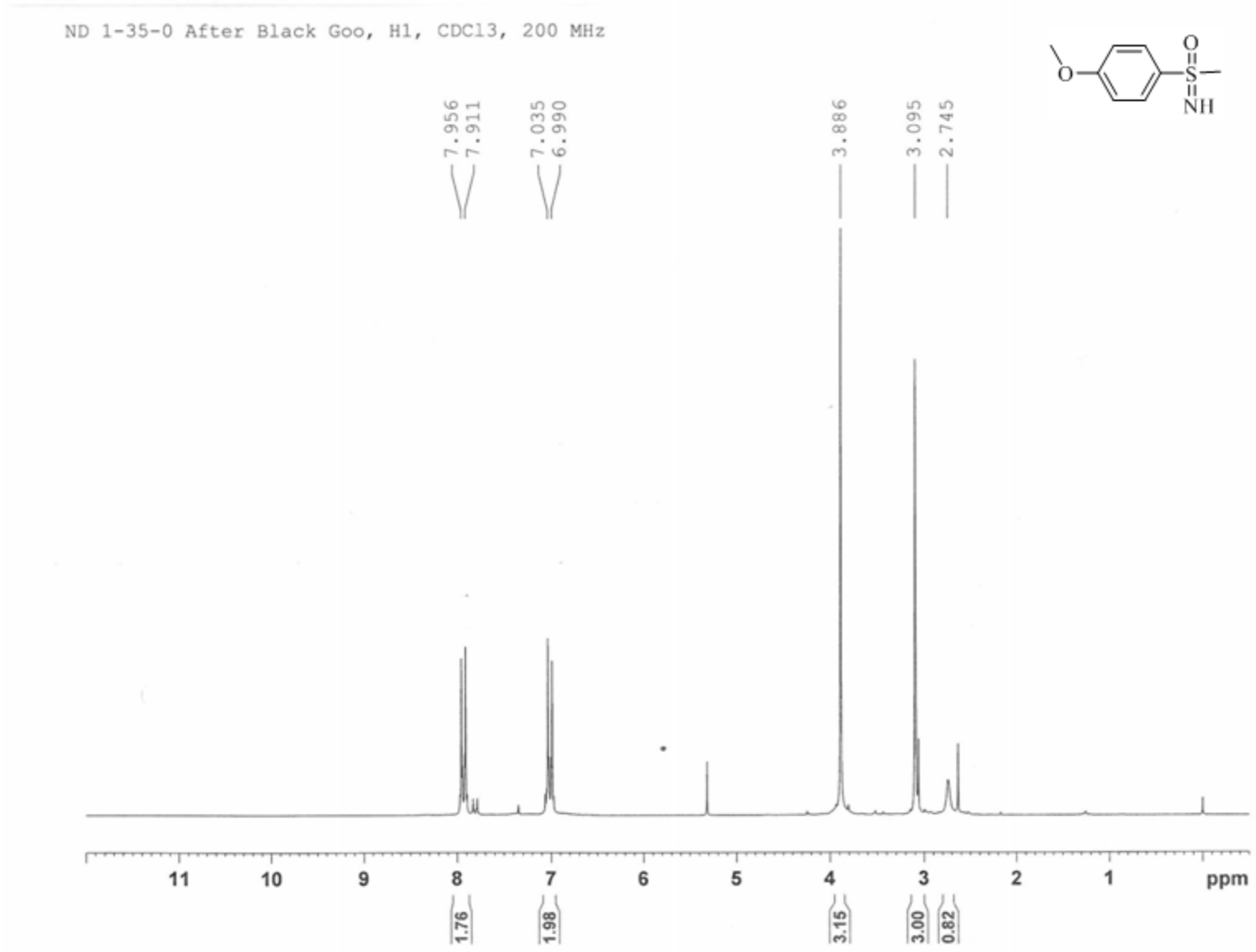
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8
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2
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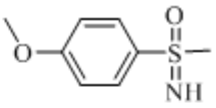

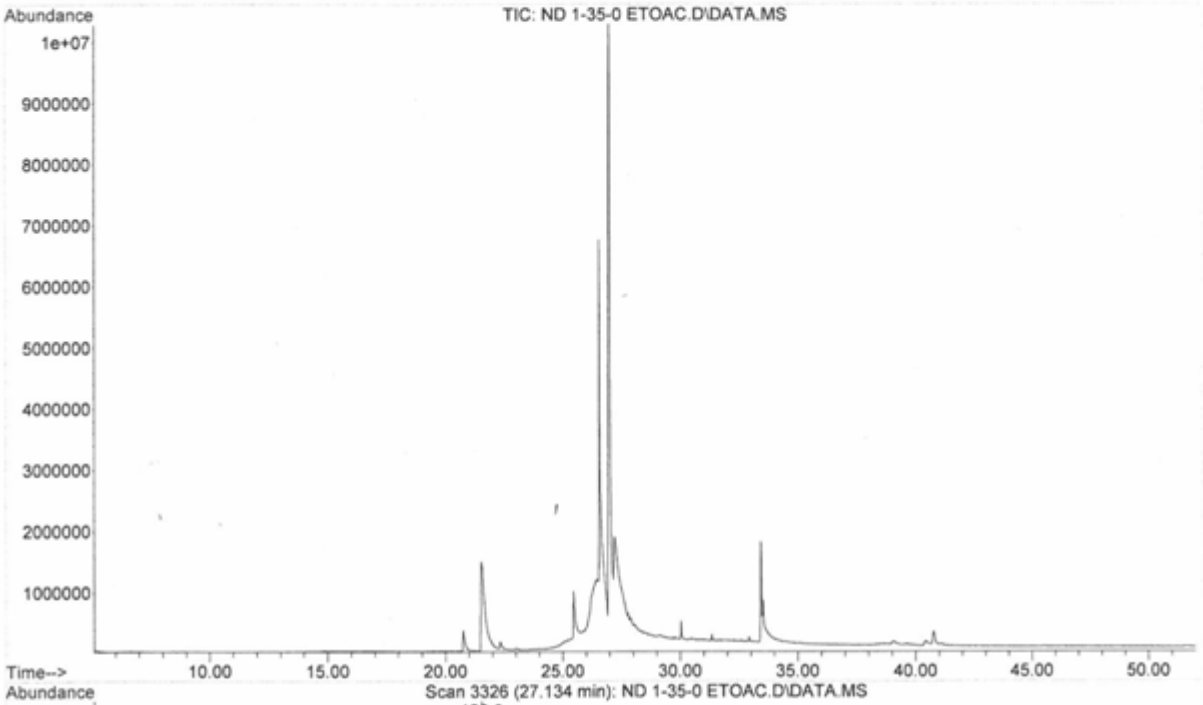

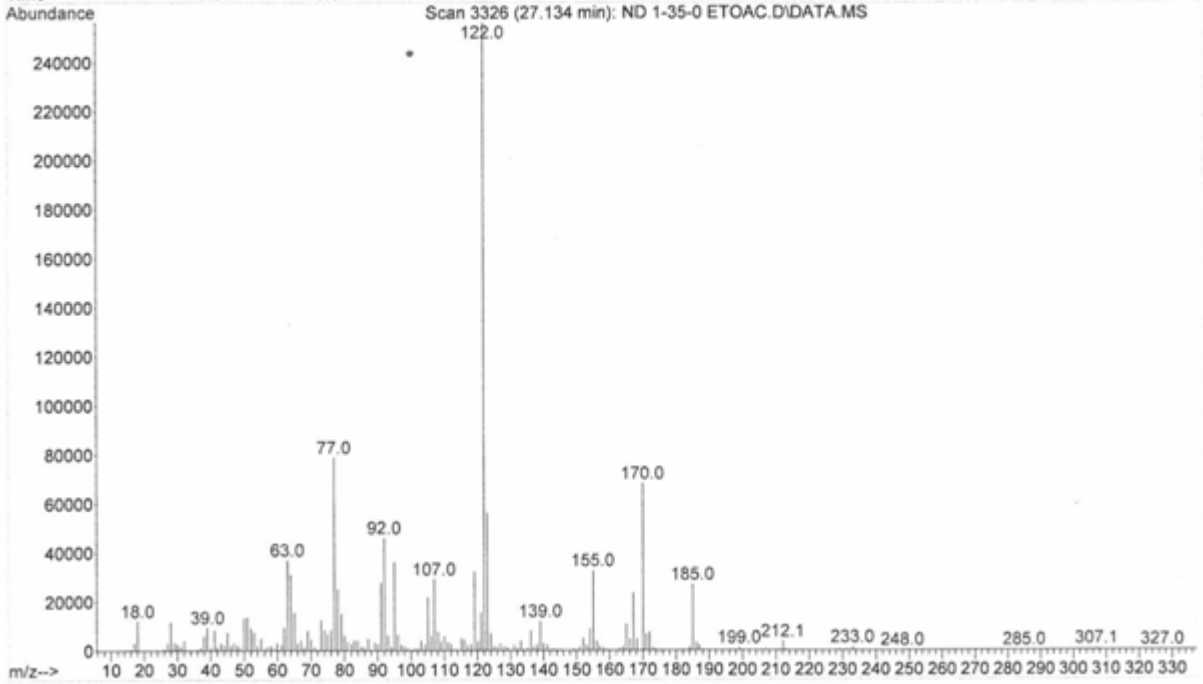

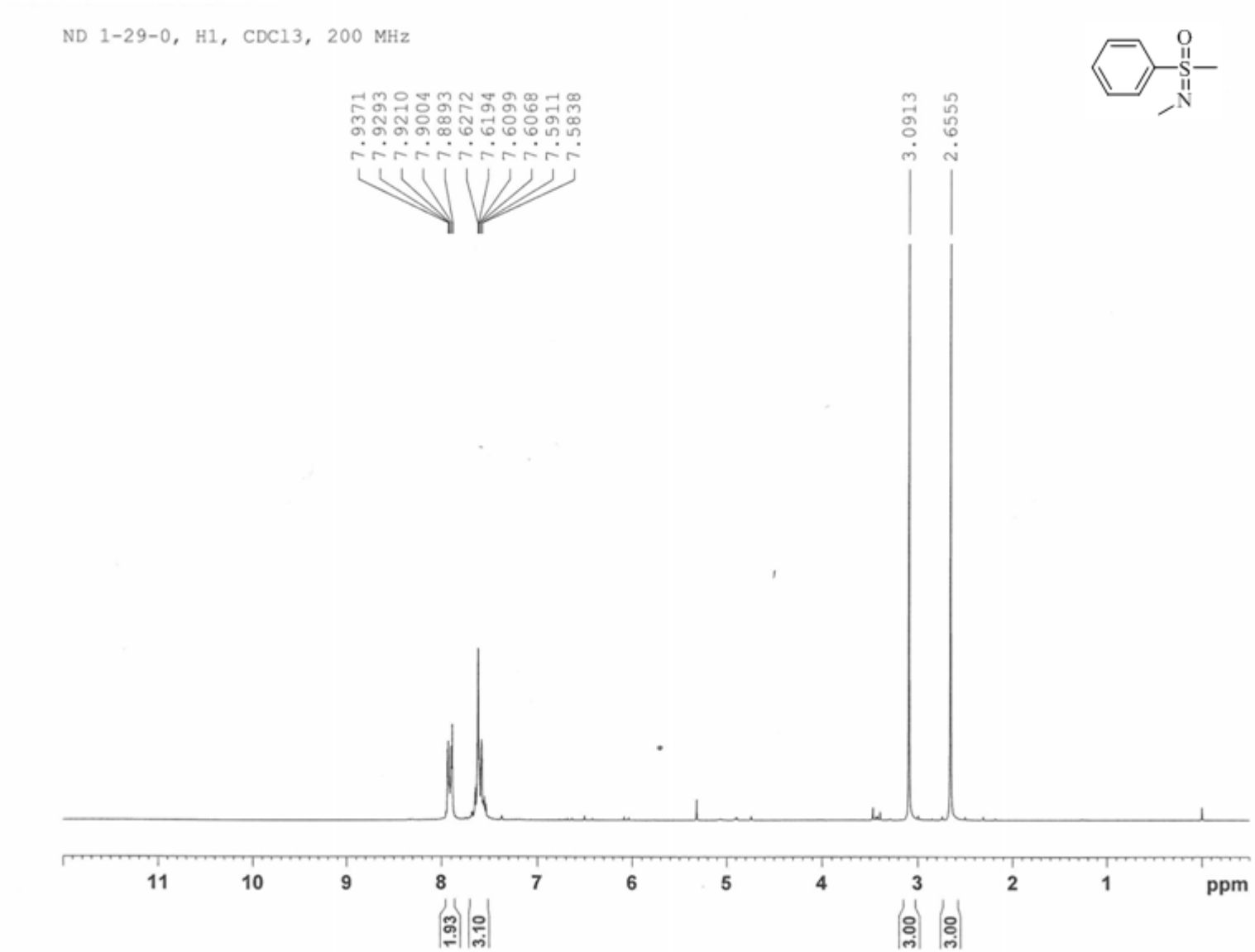
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7
6
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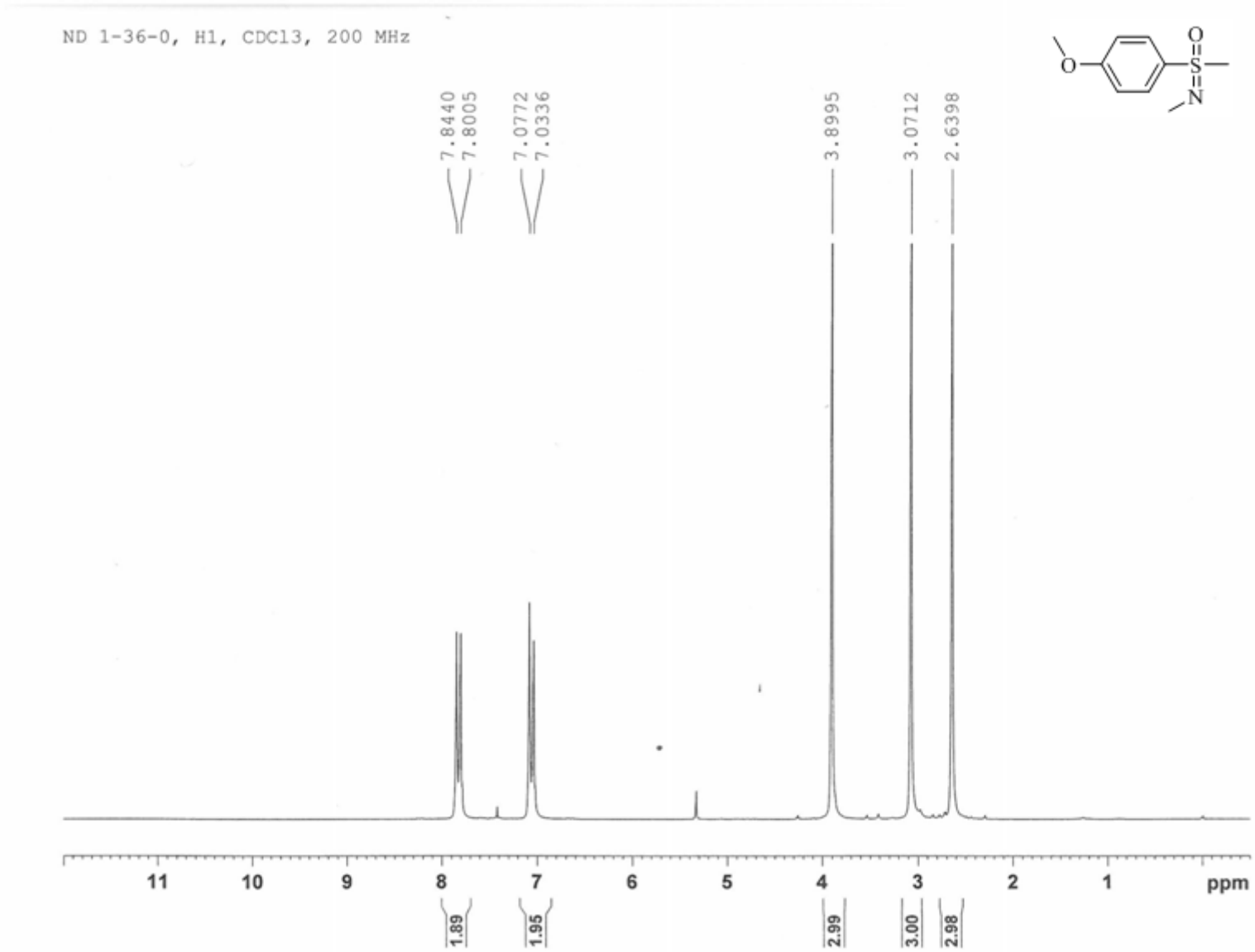
3.00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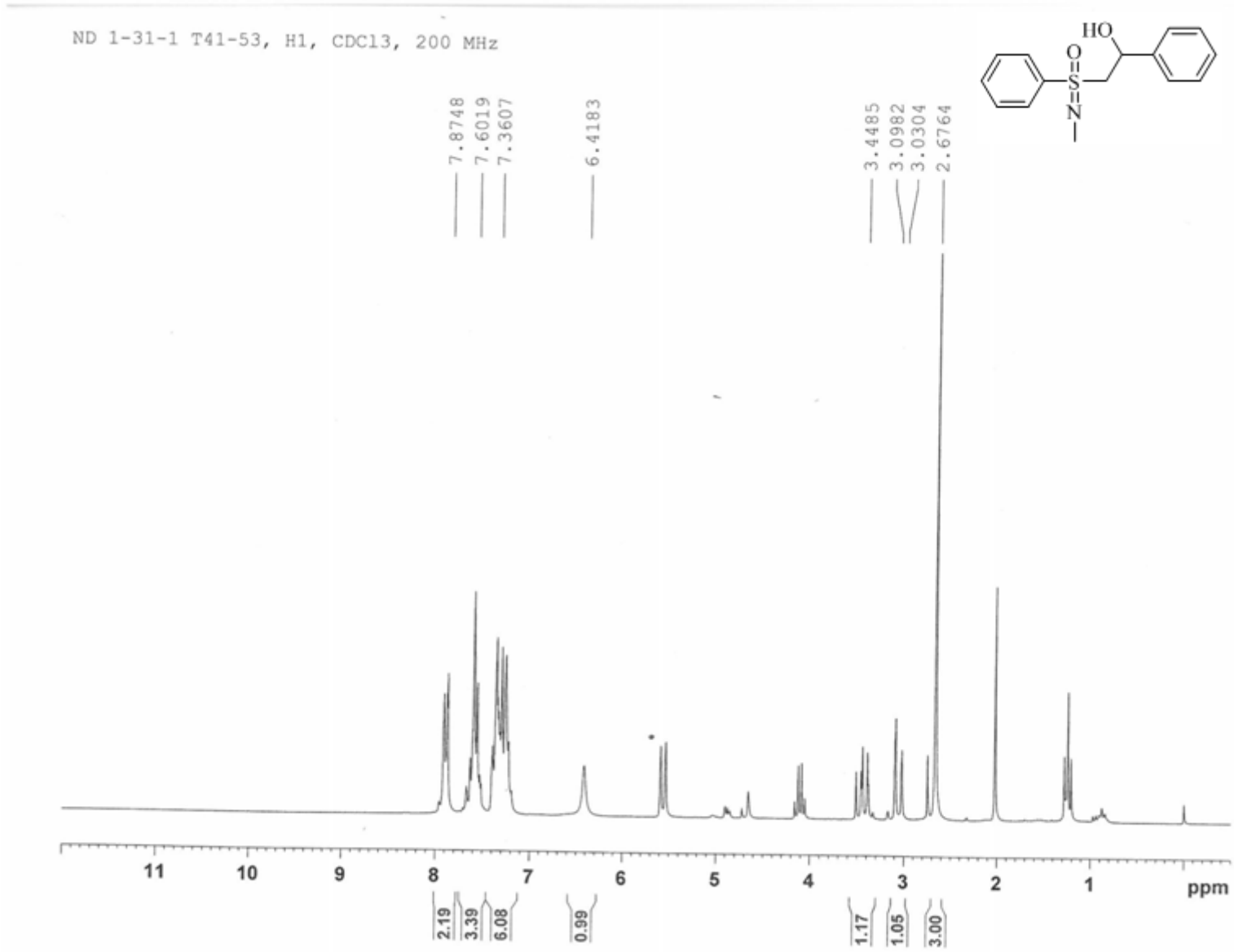
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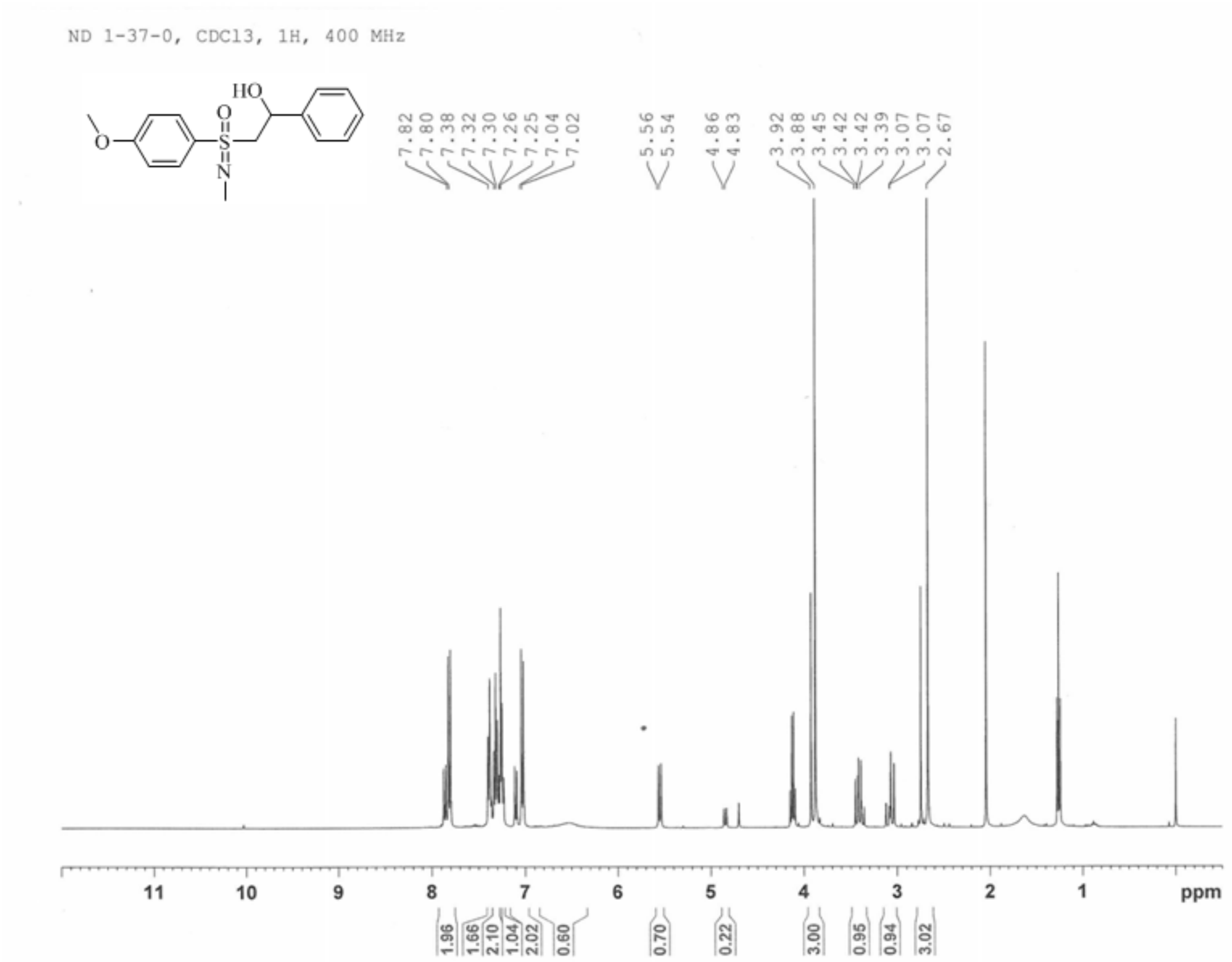
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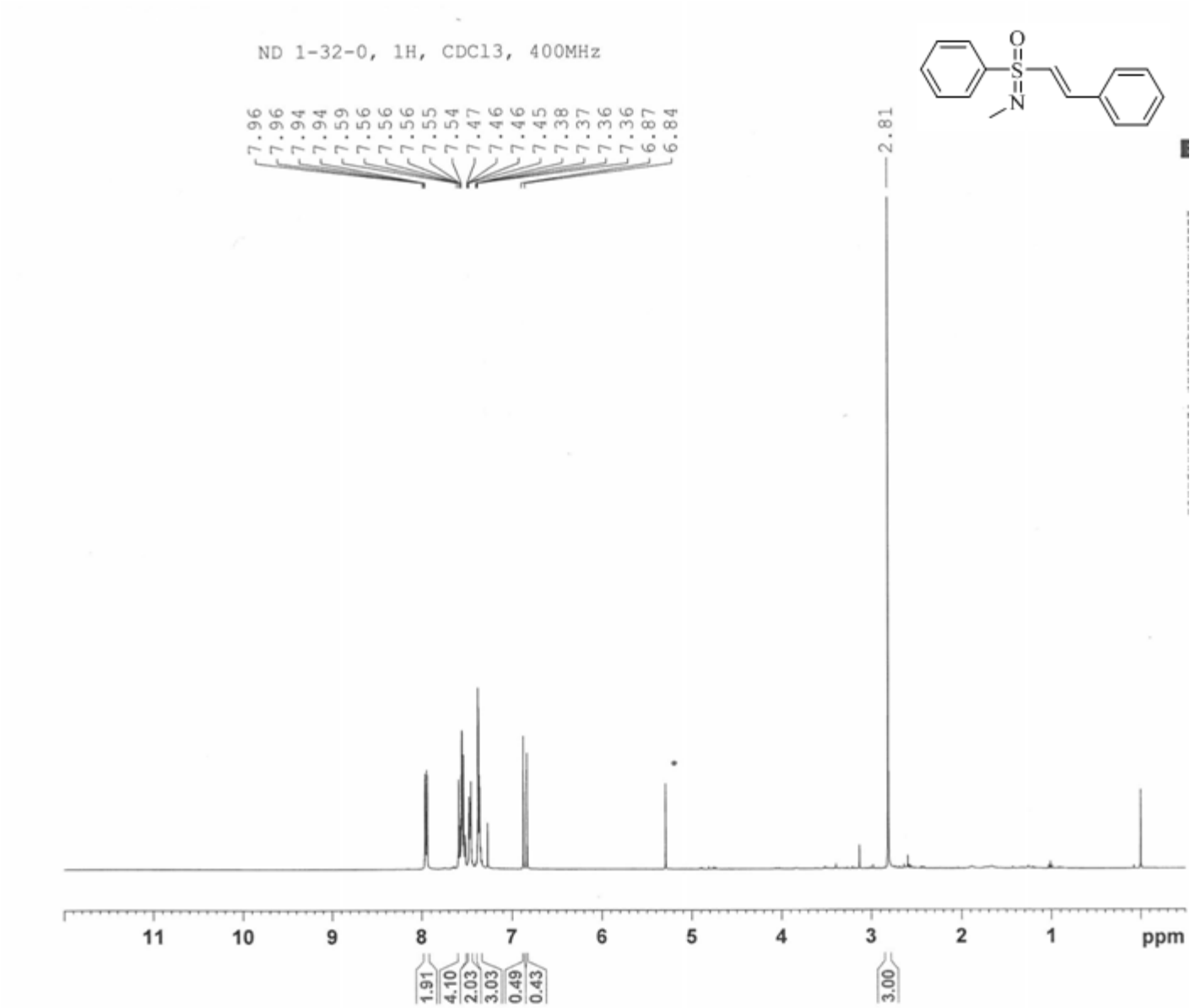
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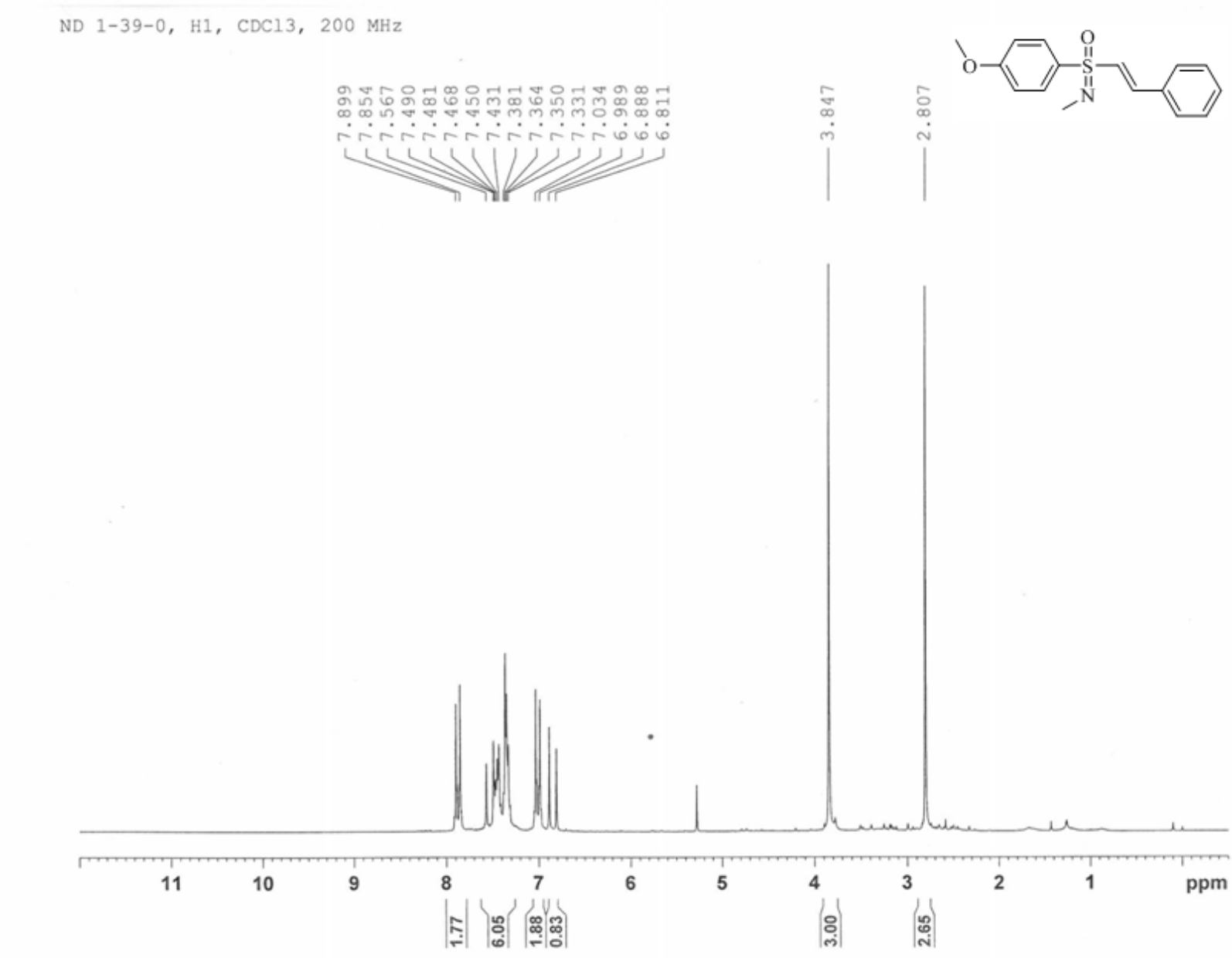
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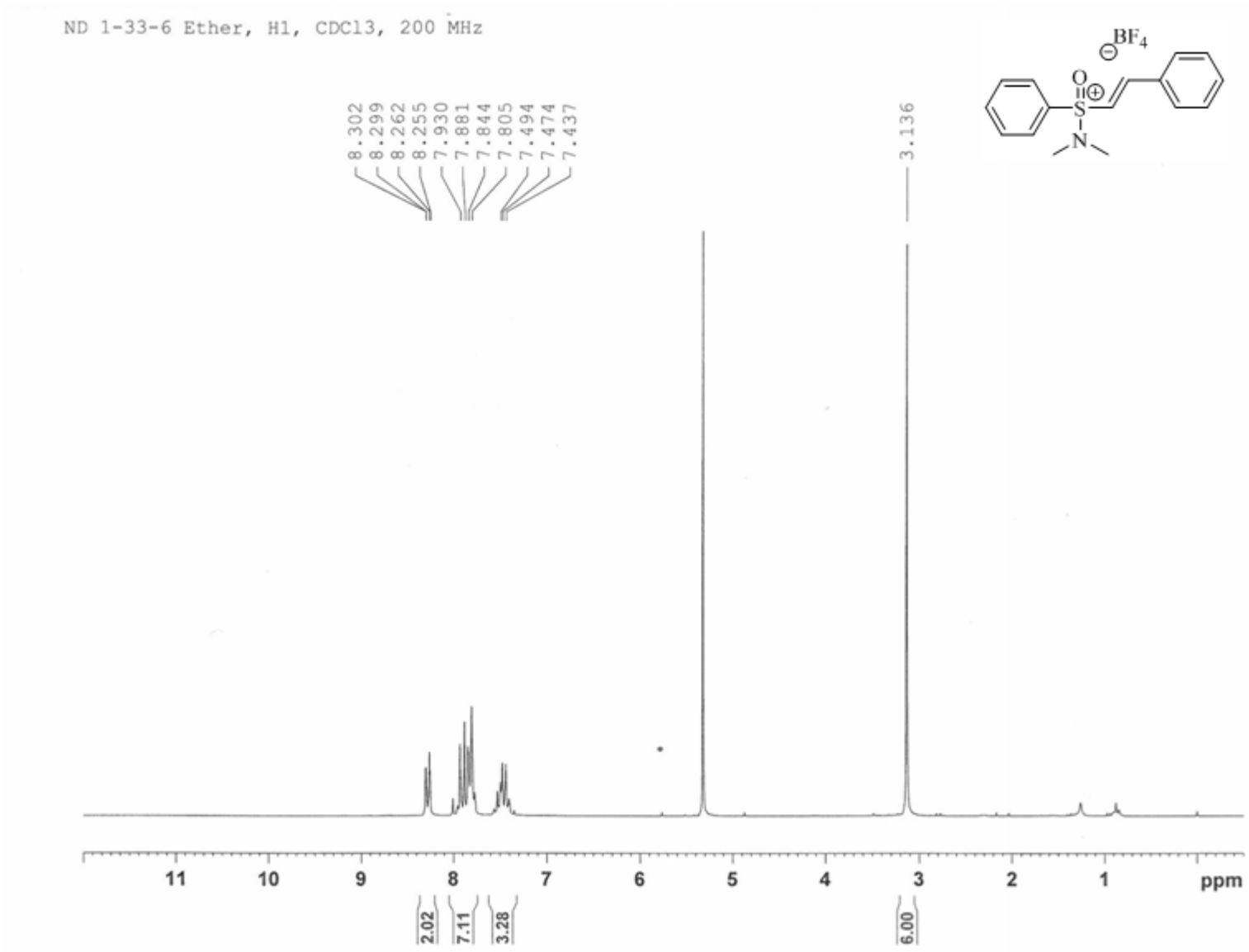
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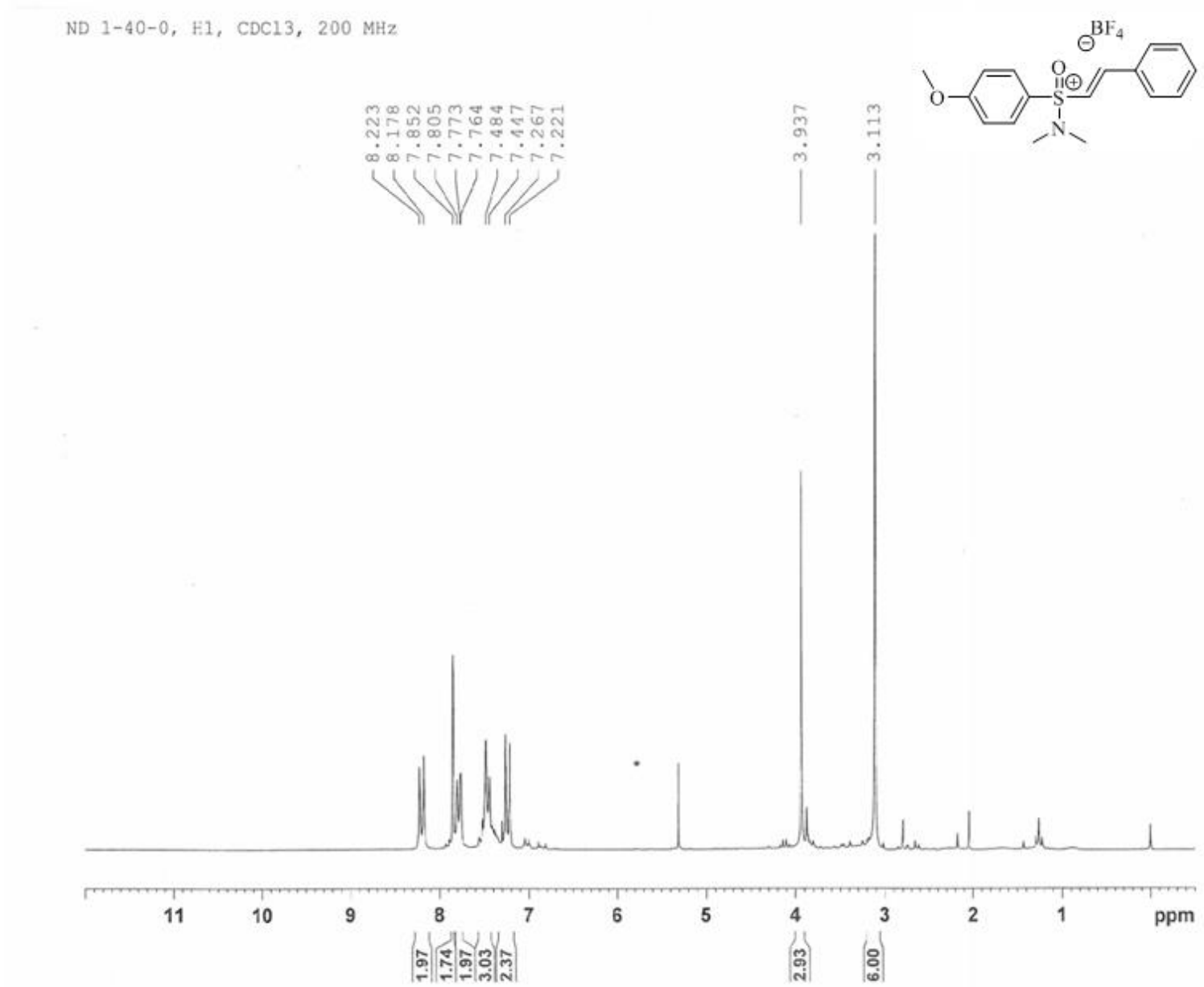
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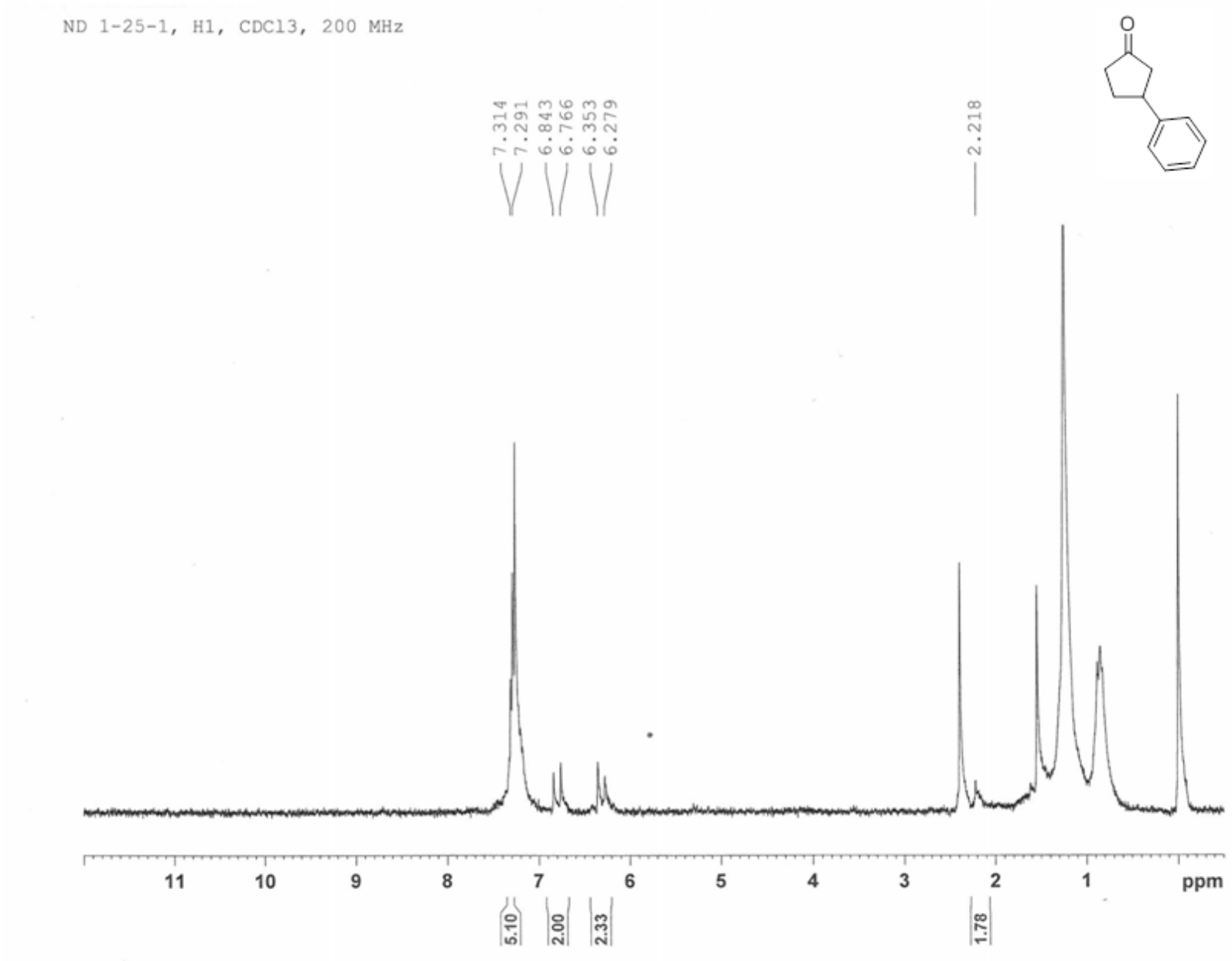
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Vial Number: 0
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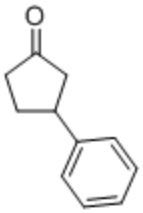
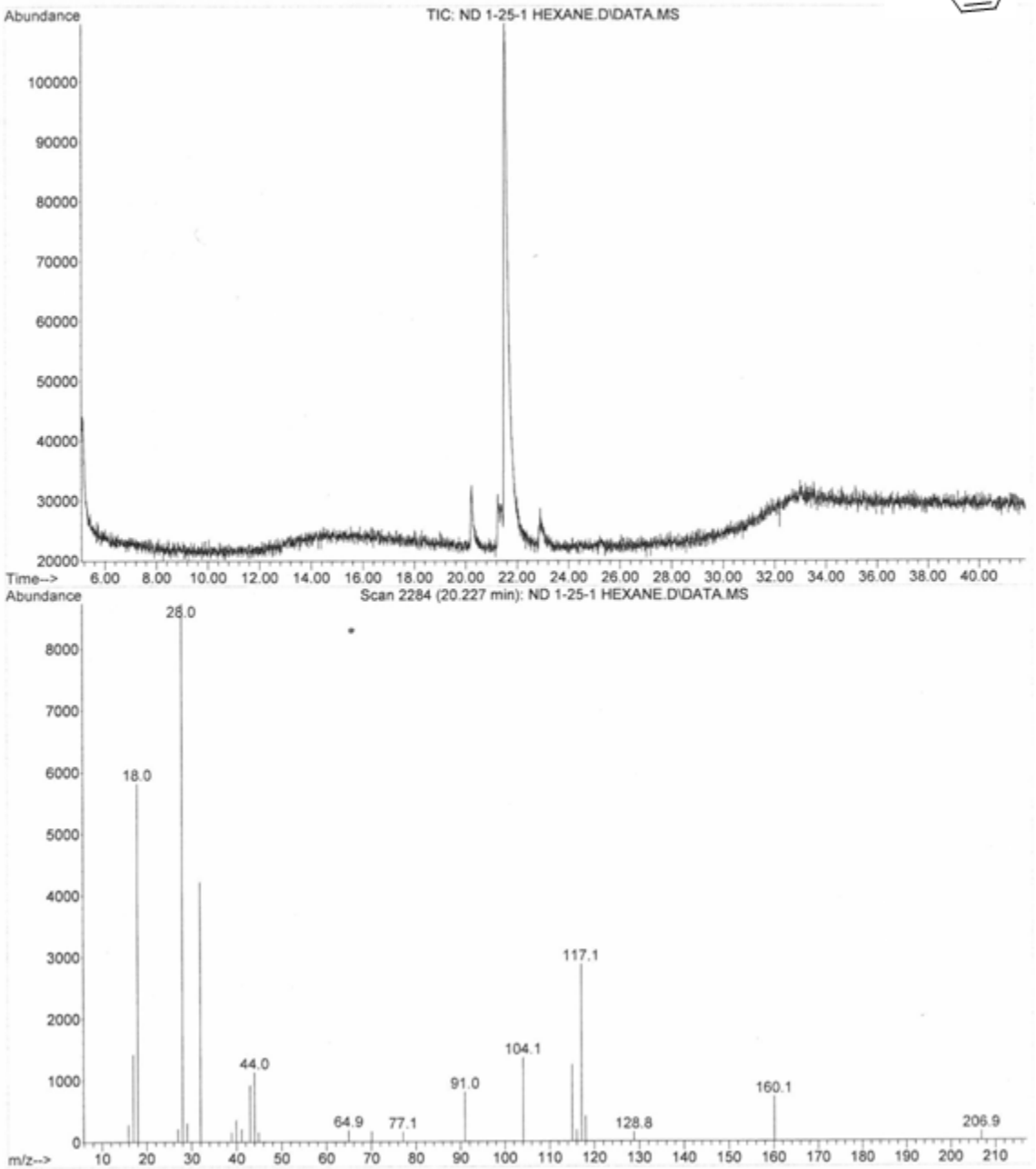
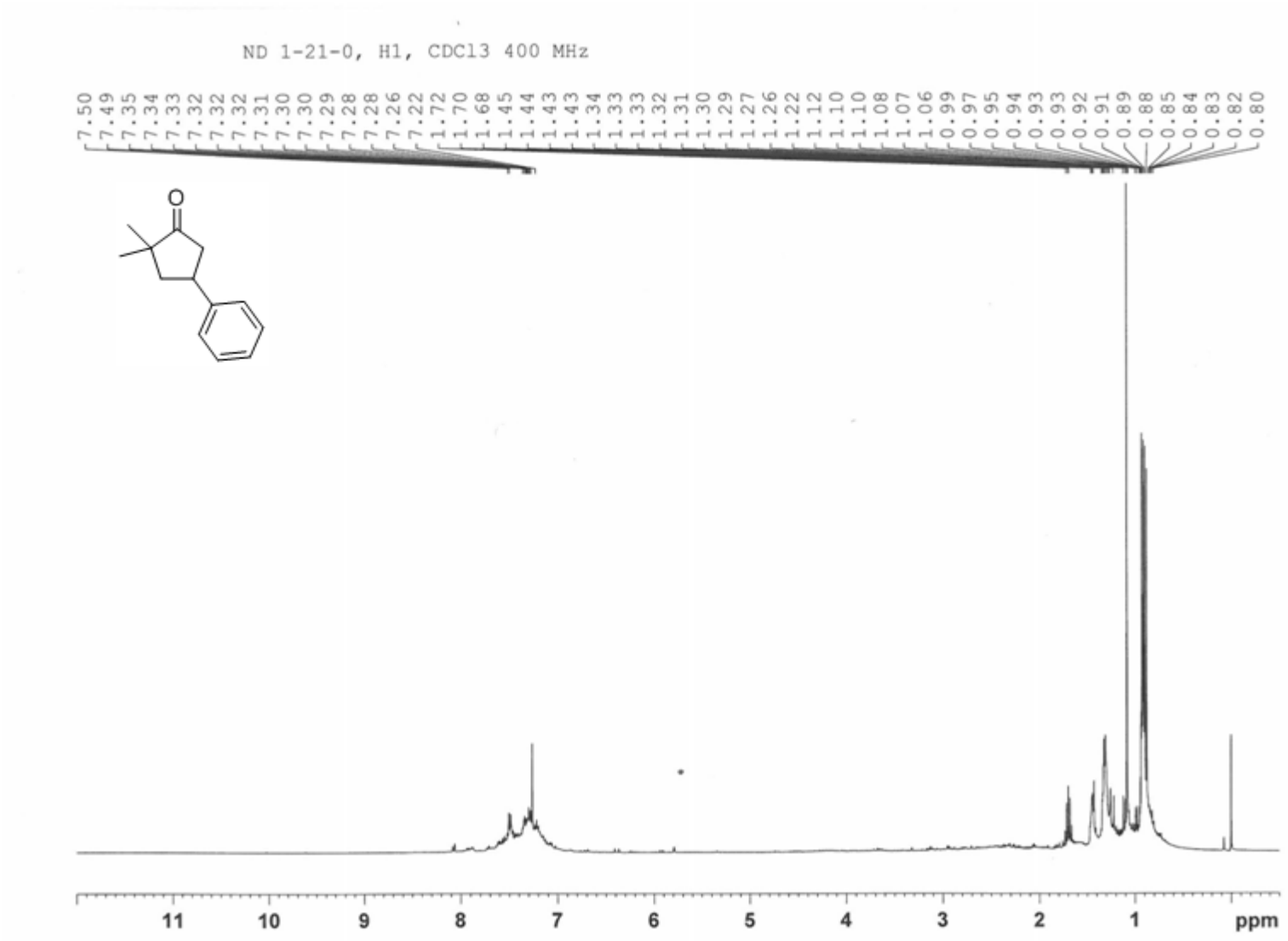
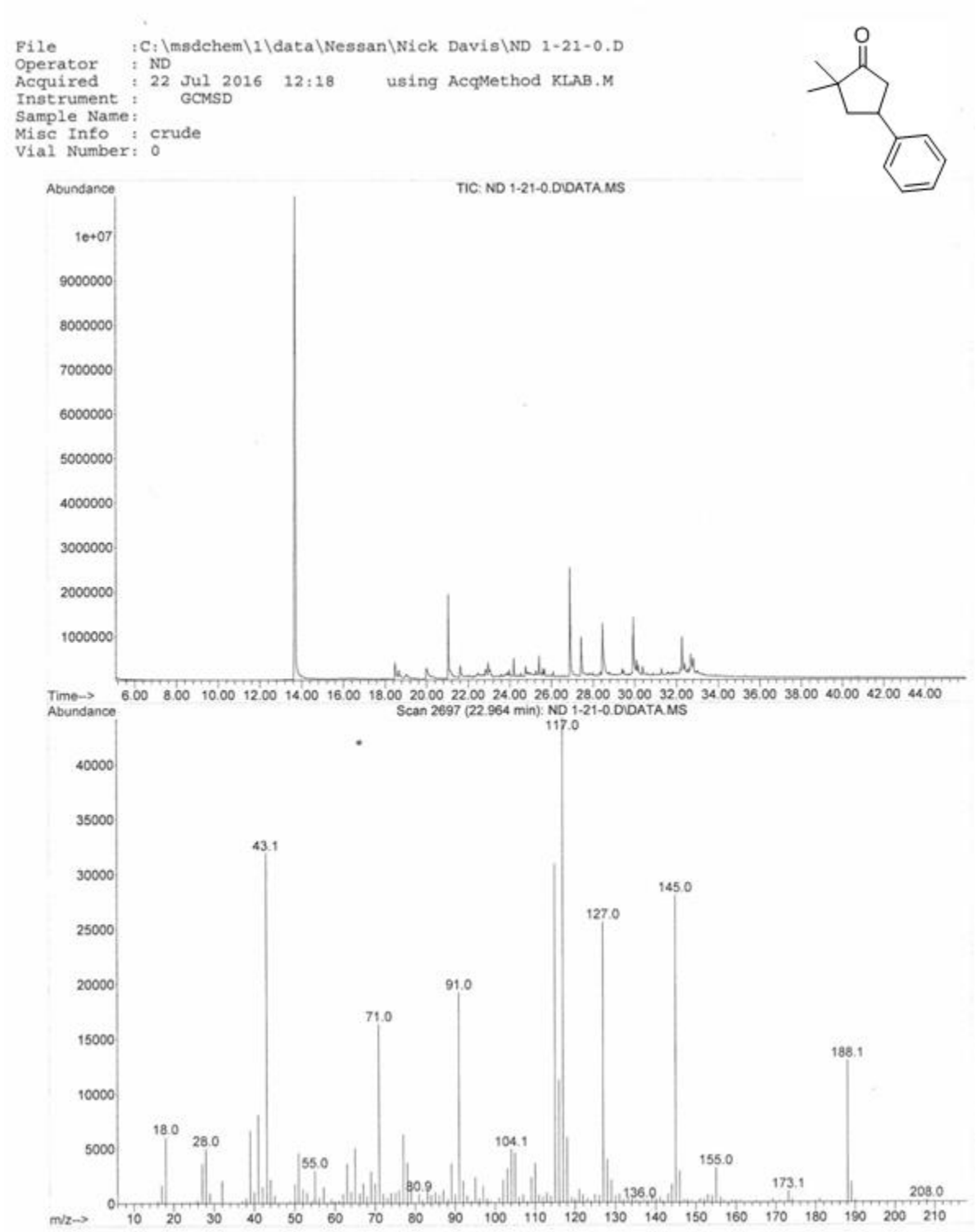
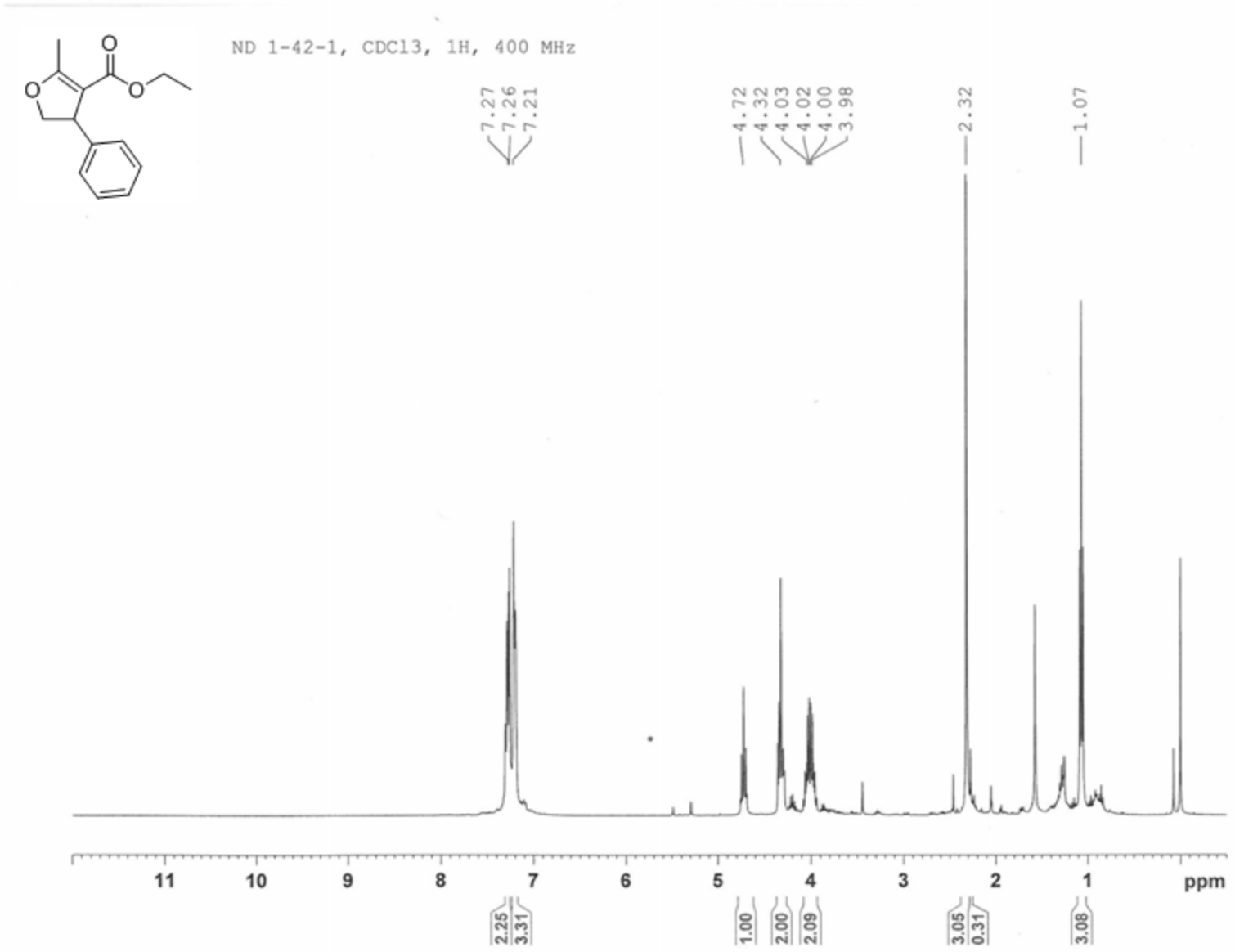
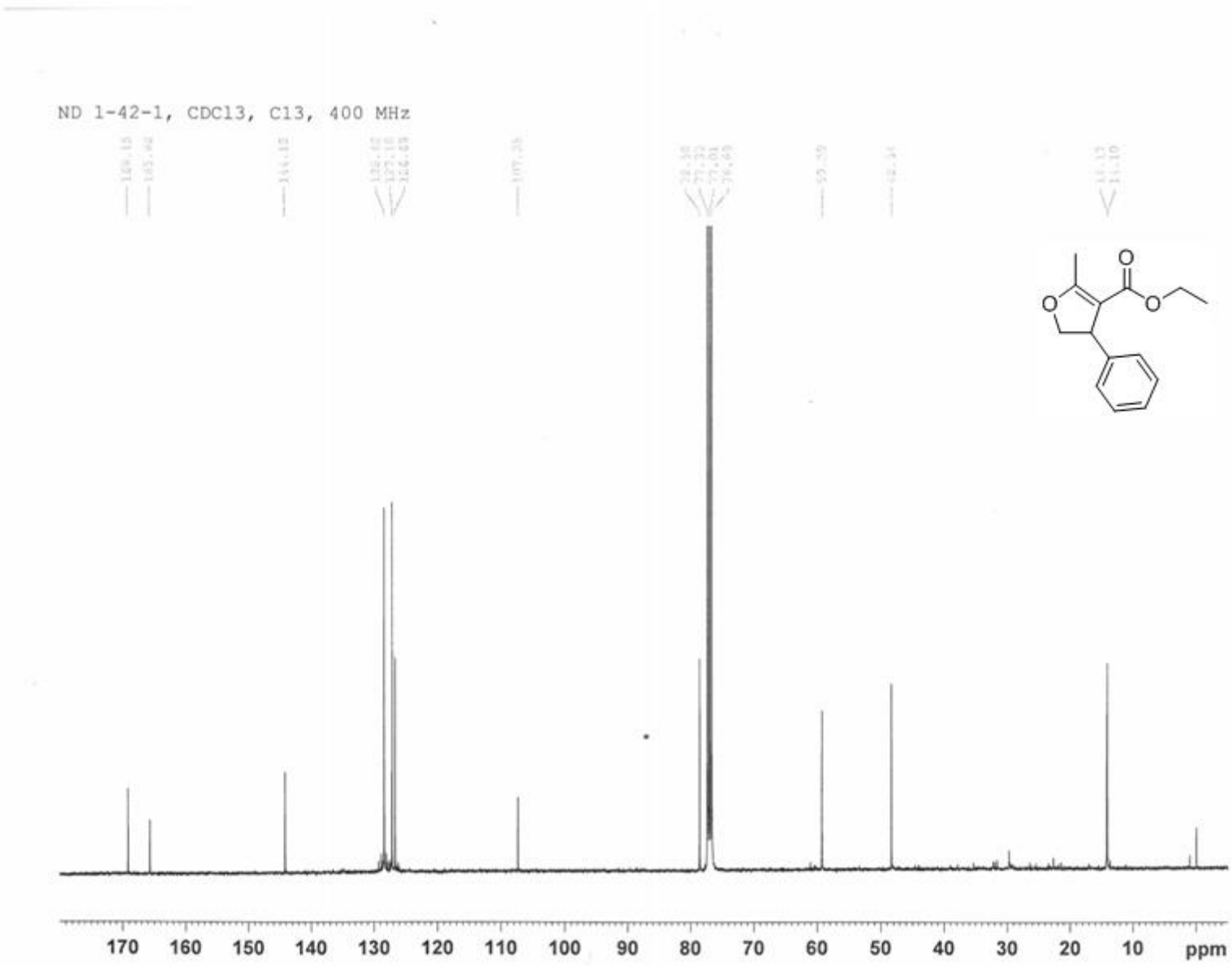


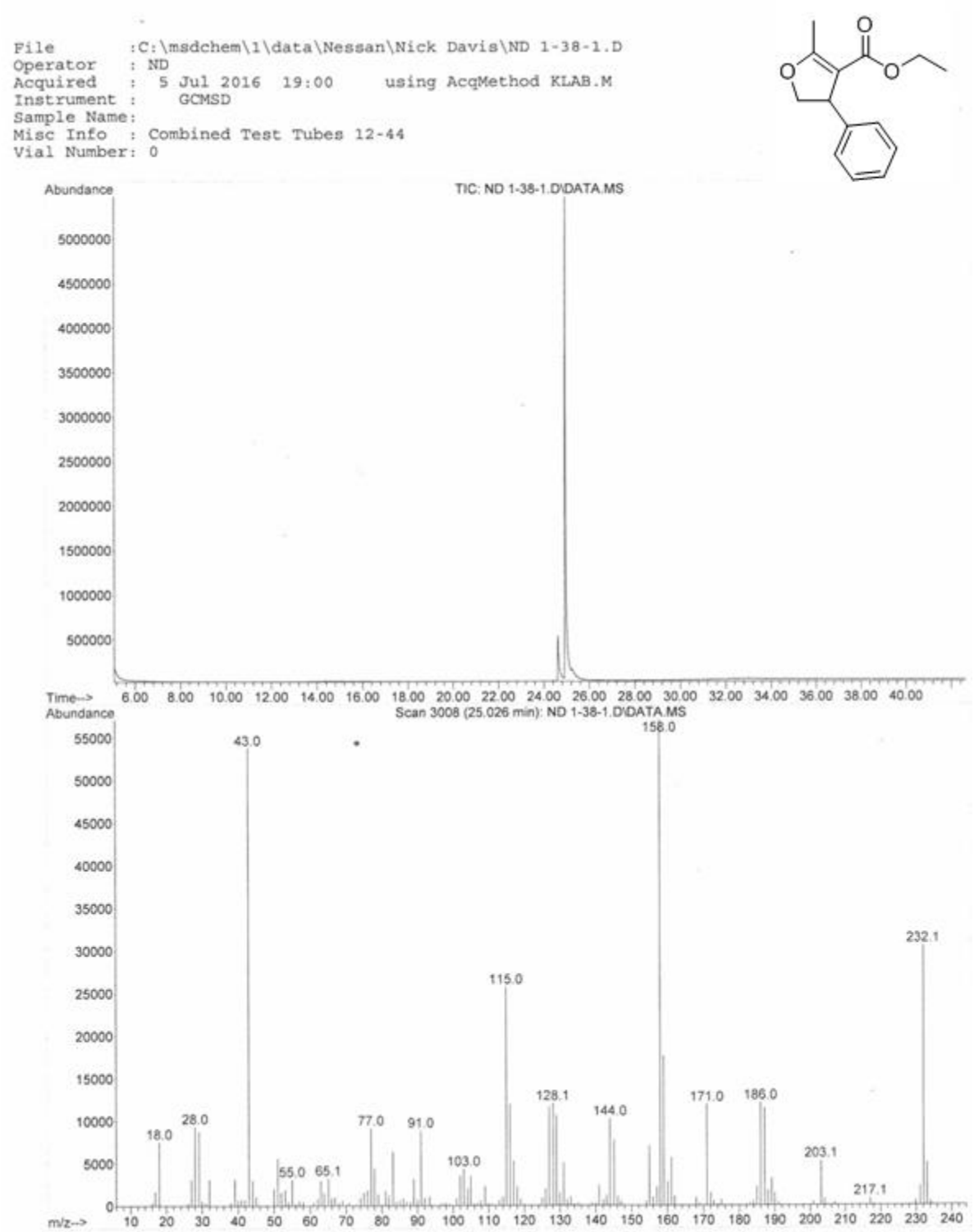


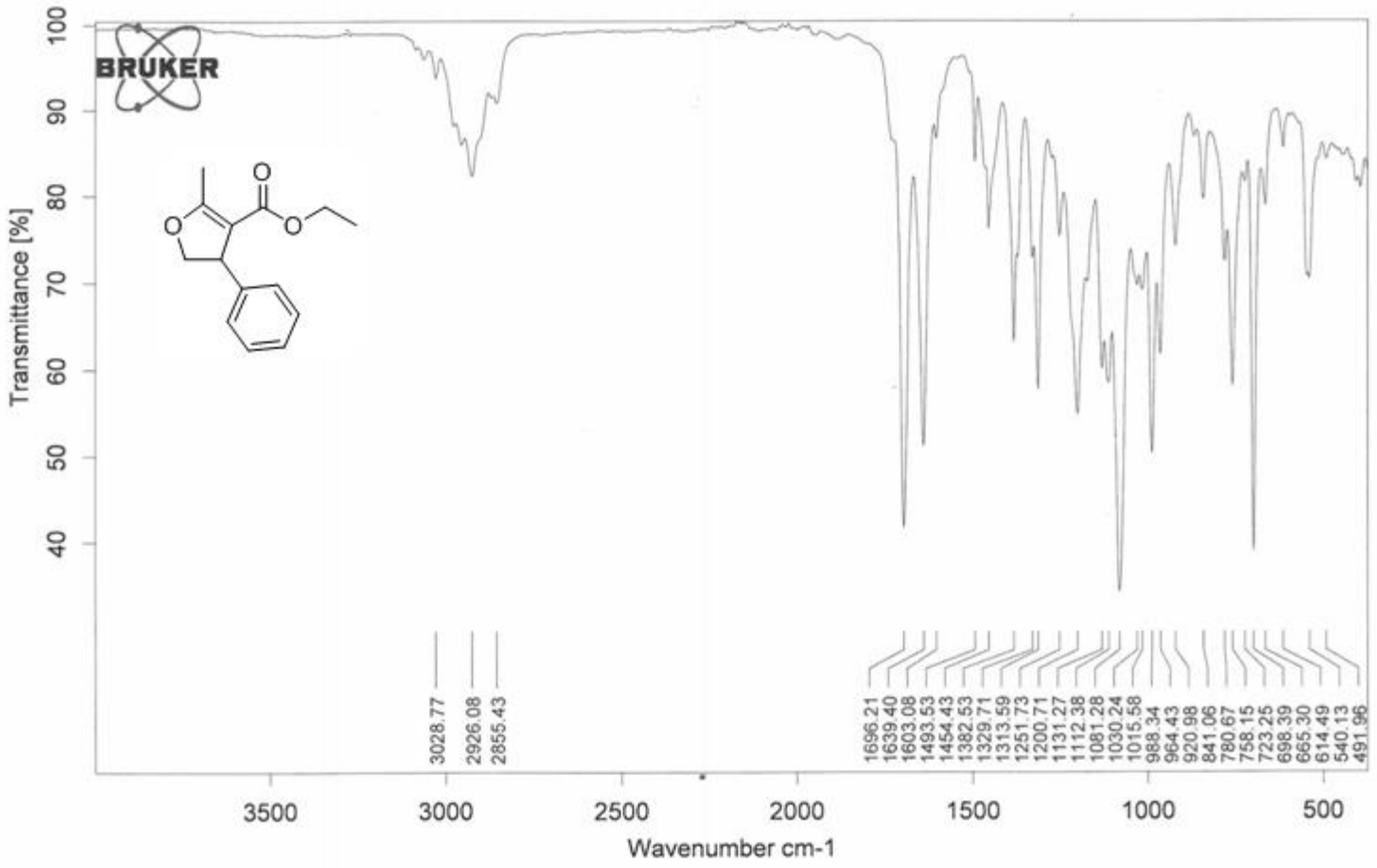

ND 1-21-0, H1, CDCl3 400 MHz
7.50
7.49
7.35
7.34
7.33
7.32
7.32
7.32
7.31
7.30
7.30
7.29
7.28
7.28
7.26
7.22
1.72
1.70
1.68
1.45
1.44
1.43
1.43
1.34
1.33
1.33
1.32
1.31
1.30
1.29
1.27
1.26
1.22
1.12
1.10
1.10
1.08
1.07
1.06
0.99
0.97
0.95
0.94
0.93
0.93
0.92
0.91
0.89
0.88
0.85
0.84
0.83
0.82
0.80
O
11
10
9
8
7
6
5
4
3
2
1
ppm


File :C:\msdchem\1\data\Nessan\Nick Davis\ND 1-21-0.D
Operator : ND
Acquired : 22 Jul 2016 12:18 using AcqMethod KLAB.M
Instrument : GCMSD
Sample Name:
Misc Info : crude
Vial Number: 0
O
Abundance
TIC: ND 1-21-0.D\DATA.MS
1e+07
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
Time-->
6.00 8.00 10.00 12.00 14.00 16.00 18.00 20.00 22.00 24.00 26.00 28.00 30.00 32.00 34.00 36.00 38.00 40.00 42.00 44.00
Abundance
Scan 2697 (22.964 min): ND 1-21-0.D\DATA.MS
117.0
40000
35000
43.1
30000
145.0
127.0
25000
20000
91.0
71.0
15000
188.1
10000
18.0
28.0
104.1
5000
55.0
155.0
80.9
173.1
136.0
208.0
0
m/z-->
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210


ND 1-42-1, CDCl3, 1H, 400 MHz
7.27
7.26
7.21
4.72
4.32
4.03
4.02
4.00
3.98
2.32
1.07
11
10
9
8
7
6
5
4
3
2
1
ppm
2.25
3.31
1.00
2.00
2.09
3.05
0.31
3.08


ND 1-42-1, CDCl3, C13, 400 MHz
O
O
O
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


File :C:\msdchem\1\data\Nessan\Nick Davis\ND 1-38-1.D
Operator : ND
Acquired : 5 Jul 2016 19:00 using AcqMethod KLAB.M
Instrument : GCMSD
Sample Name:
Misc Info : Combined Test Tubes 12-44
Vial Number: 0
Abundance
TIC: ND 1-38-1.D\DATA.MS
Time-->
Abundance
Scan 3008 (25.026 min): ND 1-38-1.D\DATA.MS
m/z-->



C:\Program Files\OPUS_65\MEAS\ND 1-42-1.0	ND 1-42-1	ATR platinum Diamond 1 Refl	27/07/2016

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File       :C:\msdchem\1\data\Nessan\Nick Davis\ND 1-53-0.D
Operator   : ND
Acquired   : 28 Oct 2016  11:05     using AcqMethod KLAB.M
Instrument :   GCMSD
Sample Name: ND 1-53-0
Misc Info  : Crude
Vial Number: 1
```