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Green Chemistry Using Bismuth Salts Bismuth (III) Iodide Catalyzed Deprotection of Acetals and Ketals in H₂O

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**Green Chemistry Using Bismuth Salts.
Bismuth(III) Iodide Catalyzed
Deprotection of Acetals and Ketals
in H₂O.**

Aaron D. Bailey

Advisor: Dr. Ram Mohan
Research Honors Senior Thesis
Illinois Wesleyan University
Spring 2007

Approval Page

Green Chemistry Using Bismuth Salts.
Bismuth(III) Iodide Catalyzed
Deprotection of Acetals and Ketals in H₂O.

By

Aaron Bailey

A Paper Submitted in Partial Fulfillment of the Requirement for Research Honors in
Chemistry

Approved:



April 27, 2007

Ram S. Mohan, Ph.D. Research Advisor

Illinois Wesleyan University, April 23, 2007

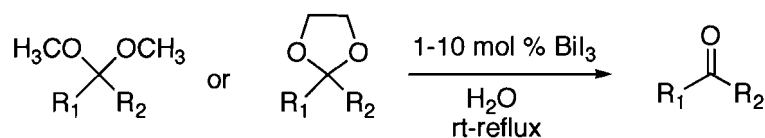
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Abstract

Since the Pollution Prevention Act was passed in 1990, synthetic organic chemists have focused on the use of environmentally friendly reagents. Often, many synthetic labs use metal catalysts (compounds containing Hg, Ni, Pb, & Sn) that are toxic to or have detrimental effects on the environment. Unlike many heavy metal compounds, bismuth and its compounds have been found to be relatively non-toxic and environmentally friendly. Due to poor shielding of the nucleus by the *f* electrons bismuth compounds have been shown to be efficient Lewis acid catalysts for many reactions.

The goal of this project to utilize bismuth compounds, specifically bismuth(III) iodide, as catalysts for the deprotection of acetals in water. Water is an attractive solvent because it is inexpensive, non-toxic, and non-flammable. The deprotections of cyclic and acyclic acetals and ketals were carried out in good yields using catalytic amounts of bismuth(III) iodide. Furthermore, it has been observed that these reactions exhibit chemoselectivity, for e.g. an acetal can be selectively cleaved in the presence of a TBDMS (*tert*-butyldimethyl silyl) group.



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1. Introduction

1.A. Green Chemistry:

Synthetic organic chemistry is an important branch of organic chemistry and finds applications in numerous chemical industries. The overall goal of organic synthesis has primarily been to discover the most efficient pathway to creating a desired compound. Unfortunately, in the search for the most efficient pathways little consideration has been given to the toxicity of the reagents themselves, or the by-products of the reactions. Due to increasing environmental awareness, green chemistry principles are being adopted by many research labs. At present many industrial processes use reaction catalysts derived from toxic metals, such as nickel, mercury, and lead. Many of these catalysts have toxic effects on the environment and biological systems. To help alleviate these environmental problems the United States Congress passed the Pollution Prevention Act in 1990 with the goal of minimizing pollution through waste management, source reduction, and more ideally, source prevention.¹ Since this legislation, efforts have been focused on replacing highly toxic reagents and catalysts by greener alternatives. Several research groups have attempted to replace toxic reagents, solvents, and catalysts, with environmentally benign alternatives in an effort to discover efficient and environmentally friendly synthetic routes.

The ideal environmentally friendly synthesis condition is one that involves the use of non-toxic compounds under solvent free conditions. As new synthetic routes using environmentally friendly compounds are being discovered, the cost of the chemicals as well as the relative success of the reaction (i.e. kinetic data, obtained yield, etc.) must be taken into consideration.

One of the major goals of green chemistry is to develop reactions in environmentally friendly solvents. Many reactions are currently carried out in dichloromethane and benzene, which are undesirable solvents due to their toxic nature. While many synthetic reactions can be carried out in less toxic solvents such as dimethylformamide or toluene, the most ideal solvent is water. It has been found that many organic reactions are able to be carried out in water. Water is the most environmentally friendly solvent because it is non-toxic, non-flammable and readily available. Hence many reactions are currently being conducted in water as a solvent. This observation contradicts the long held belief that because most organic compounds are insoluble in water, a chemical reaction will not occur if run in water. However, it has been recently shown that in superheated water alone, some organic reactions occur.² Breslow proposed that a hydrophobic attraction between the catalyst and non-soluble organic reagents is the reason why some organic reactions (for e.g. Diels-Alder cycloaddition) proceed more efficiently in water.³ The hydrophobic effect is the tendency of nonpolar species to aggregate in water. Breslow was able to support his theory experimentally through the salt effect on a Diels-Alder reaction in water. Breslow observed an increase in reaction rates when salts, such as LiCl or NaCl, were added to the solution. The author concluded that LiCl and NaCl cause a salting-out effect and a thus decrease of organic compounds in water. This decrease in solubility increases the hydrophobic effect of the reaction and can be attributed to the rate acceleration.

At present many research groups are conducting studies that examine the effects of replacing toxic reagents (for example mercury based catalysts) for more environmentally friendly reagents (for e.g. bismuth and lanthanide based catalysts).

1.B. Bismuth and Related Compounds:

Over the past decade research efforts in the area of synthetic organic chemistry have been focused on increasing the use of environmentally friendly compounds as catalysts and reagents. Bismuth compounds have been recently employed as effective green catalysts to replace toxic catalysts (e.g. compounds of mercury, lead, and indium) in organic reactions. Bismuth is the 83rd element in the periodic table, with an atomic mass of 209.980 amu, and is produced as a by-product of copper and tin refining.⁴ Although bismuth is radioactive, an extremely long half life ($t_{1/2} \sim 2 \times 10^{18}$ years) makes it practically a stable element. Notwithstanding its heavy metal status, bismuth and its compounds are relatively non-toxic and can be utilized for a variety of different medicinal purposes (Pepto-Bismol). Many of the heavy metals have a relatively high toxicity and if used in reactions can be present in by-products. One of the principal factors contributing to the low toxicity of bismuth is the poor solubility of the metal in aqueous solutions at moderate pH values such as those found in biological fluids.⁵ As can be seen from table 1, many bismuth compounds are less toxic than NaCl.

Table 1: LD₅₀ Values of Common Compounds³¹

Compound	LD ₅₀ (g/kg)	Species & Route
Sodium chloride, NaCl	3.8	Rat, oral
Mercury chloride, HgCl ₂	0.001	Rat, oral
Bismuth oxide, Bi ₂ O ₃	5.0	Rat, oral
Bismuth nitrate, Bi(NO ₃) ₃ ·5H ₂ O	4.4	Rat, oral
Bismuth oxychloride, BiOCl	22	Rat, oral
Bismuth chloride, BiCl ₃	3.3	Rat, oral
Indium chloride, InCl ₃	1.1	Rat, oral
Scandium chloride, ScCl ₃	3.9	Rat, oral
Cerium chloride, CeCl ₃	2.1	Rat, oral
Samarium chloride, SmCl ₃	2.9	Rat, oral
Ytterbium chloride, YbCl ₃	4.8	Rat, oral
Nickel(II) chloride, NiCl ₂	0.105	Rat, oral
Tin(II) dichloride dihydrate, SnCl ₂ ·2H ₂ O	0.7	Rat, oral

Since bismuth compounds are relatively non-toxic, bismuth compounds have been used as environmentally friendly catalysts in organic synthesis.⁶ Many bismuth compounds exhibit Lewis acid behavior. This Lewis acidity of bismuth(III) compounds is a consequence of poor shielding of the *f* electrons (Bi electron configuration: [Xe]

$4f^{14}5d^{10}6s^26p^3$) allowing bismuth to accept an electron pair readily.^{6b} Bismuth exists in two common oxidation states, + 3 [bismuth(III) halides, bismuth(III) subsalicylate] and +5 [bismuth(V) fluoride, $\text{Ph}_3\text{Bi}(\text{OAc})_2$, Ph_3BiCO_3].⁴ Bismuth compounds are suitable Lewis acid catalysts for organic reactions due to their ease of handling and non-corrosive nature. As a result numerous studies have been carried out to demonstrate the effectiveness of Lewis acidity of bismuth compounds and their effects on different organic reactions.⁷

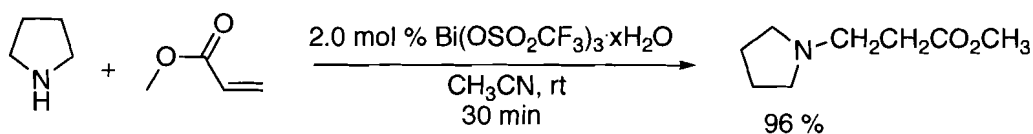
Several bismuth (III) catalysts, as well as a few lanthanide compounds are commercially available at low cost (table 2).⁸ As a result of increased attention to green chemistry, bismuth compounds become attractive as catalysts in place of other, more toxic, metal catalysts derived from indium, mercury, and lead compounds. Bismuth triflate, $\text{Bi}(\text{OTf})_3 \cdot x\text{H}_2\text{O}$ is one of the most commonly used bismuth-based catalysts. This compound exhibits enhanced Lewis acidic behavior due to the strongly electron withdrawing triflate group.^{6b} It has been shown to be an effective catalyst for the carbon-carbon bond forming Michael-type reactions (scheme 1).⁹ Bismuth triflate has also been proven to be an effective catalyst for the allylation of acetals (scheme 2).¹⁰ This reaction (Hosomi-Sakurai reaction) is typically carried out with highly corrosive titanium tetrachloride (TiCl_4) at -78°C .¹¹

Table 2: Common Metal Compounds⁸

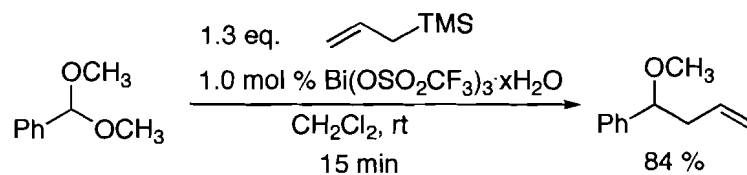
Compound	Cost/100g	Cost/mol
BiI ₃ (99 %)	\$ 143	\$ 840
BiBr ₃ (98 %)	\$ 96	\$ 431
BiCl ₃ (> 98 %)	\$ 138	\$ 435
Bi(OTf) ₃ ·xH ₂ O	\$ 628	\$ 4121
Bi(NO ₃) ₃ ·5H ₂ O (> 98 %)	\$ 25	\$ 123
CeCl ₃ (beads, 99.9%)	\$ 288	\$ 956
CeCl ₃ ·7H ₂ O (99.9 %)	\$ 42	\$ 156
Ce(OTf) ₃ ·xH ₂ O	\$ 187	\$ 5568
ScCl ₃ (99.9 %)	\$ 1876	\$ 2939
ScCl ₃ ·xH ₂ O (99.9 %)	\$ 5680	\$ 8594
Sc(OTf) ₃ (99 %)	\$ 3320	\$ 16241
Dy(OTf) ₃ (98 %)	\$ 920	\$ 5609

*Aldrich Chemical Company, 2007 catalog

Scheme 1



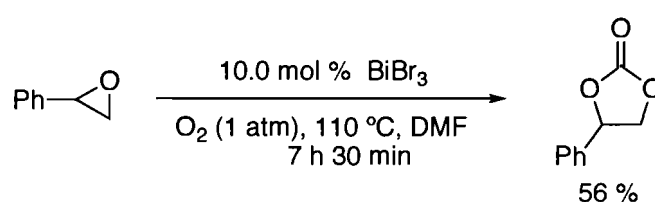
Scheme 2



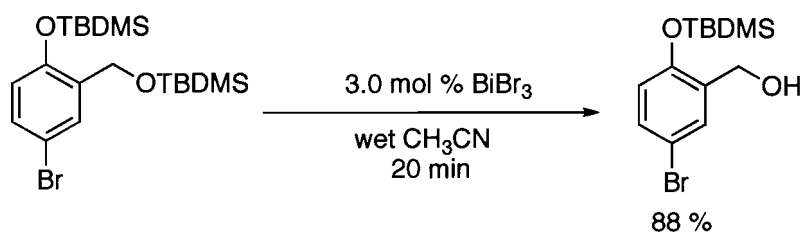
Bismuth triflate is not the only bismuth compound that exhibits catalytic behavior. There have been many studies that show that bismuth halides are useful catalysts in organic synthesis. Specifically, bismuth bromide has been shown to catalyze the formation of cyclic carbonates from terminal epoxides (scheme 3).¹² The authors propose that the reaction involves an epoxide ring opening with the incorporation and oxidation of the carbonyl group of DMF by O₂. The replacement of BiBr₃ by BiCl₃ did not lead to carbonate formation; instead a mixture of chlorohydrins was obtained. No bromohydrins were detected using BiBr₃ as the catalyst. The reaction of the epoxide with CO₂ catalyzed by BiBr₃ in THF did not give any carbonate.

The selective deprotection of a TBDMS protected 1° alcohol in the presence of a phenolic system has also been reported (scheme 4).¹³ This reaction is believed to be catalyzed by HBr that is generated *in situ* from the reaction of bismuth bromide and water. Bismuth bromide is a stable solid and is therefore much easier to handle than concentrated HBr, a highly corrosive acid, which makes this reaction condition more appealing.

Scheme 3

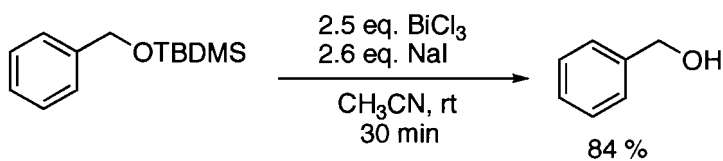


Scheme 4

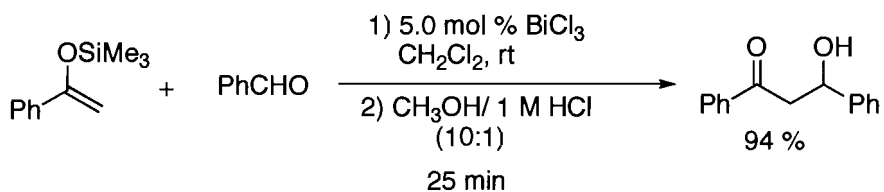


Bismuth chloride has also been shown to demonstrate catalytic behavior in many organic reactions including the cleavage of *tert*-butyldimethylsilyl ethers (scheme 5)¹⁴ and Mukaiyama aldol reaction (scheme 6).¹⁵

Scheme 5

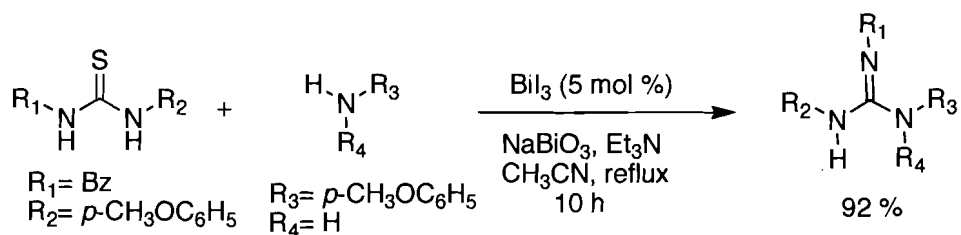


Scheme 6



Despite the numerous studies with these bismuth (III) halide compounds, there have been few studies that utilize bismuth (III) iodide. Recently, bismuth iodide has been used as a catalyst in guanylation reactions (scheme 7).¹⁶

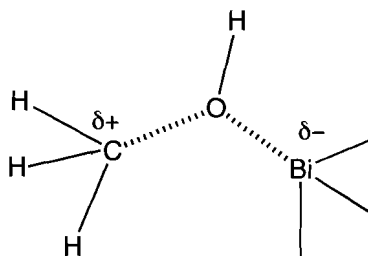
Scheme 7



Bismuth iodide exists as a black crystalline solid with a melting point of 408 °C. This bismuth salt is unique in that the intermolecular bond lengths between the bismuth metal and the iodide ion are the same as the intramolecular bond lengths. The salt is characterized by Bi^{3+} filling the octahedral holes in a close packed array of iodide (I^-) ions. The crystal structure can be described as largely ionic with a stereochemically inactive lone pair on bismuth.⁴ Mechanistic studies were conducted by Keramane to determine how a bismuth(III) halide behaves when used as a catalyst in halogenation of alcohols.¹⁷ The results showed that 1° alcohols did not react with BiCl_3 while 2° alcohols gave a mixture of alkenes (30 %) and alkyl chloride (70 %). Tertiary alcohols (3°) gave the corresponding chloride in good yields. No bromination was observed with BiBr_3 . Both BiCl_3 and BiBr_3 catalyzed the conversion of benzylic and allylic alcohols to give an ether product but no such reaction was observed with BiI_3 . Based on these results and previously reported data on complexes between Bi(III) compounds and alcohols, amines, and amides, the authors propose that bismuth(III) bromide and chloride form a complex with the alcohol while BiI_3 is inactive. This coordination is facilitated by the electronegative atom (halide) on the bismuth atom which makes the latter especially Lewis acidic. By coordinating to these functional groups the bond between the functional

group and a neighboring carbon atom weakens. This carbon atom becomes electrophilic and is highly susceptible to attack by nucleophiles (scheme 8).

Scheme 8



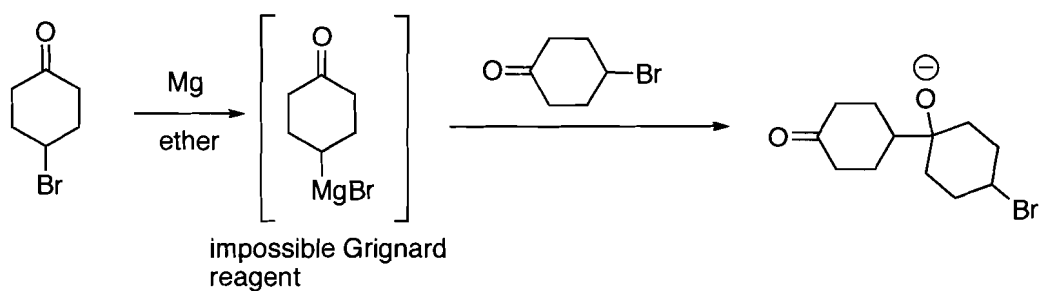
The authors hypothesized that this is a direct effect of the Hard-Soft acid base principle in which the soft Bi^{3+} ion binds more readily to soft Br^- or I^- anions than hard Cl^- or OH^- ions. Thus, halogenation occurs only in BiCl_3 because Cl^- and OH^- are two equivalent hard bases and bismuth is able to exchange a chloride ion for a hydroxyl group. Furthermore, the bulky iodide ion hinders the approach and the coordination of hydroxide to bismuth and prevents BiI_3 from catalyzing an elimination reaction.¹⁷

1.C. Acetals:

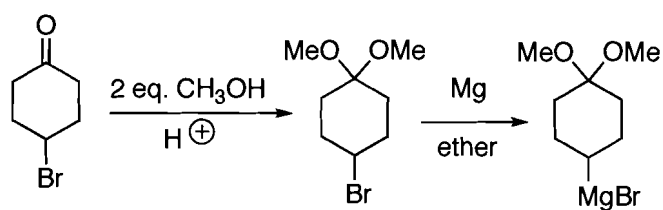
Protecting groups are commonly used during the course of a multi-step synthesis. Of the many different protecting groups for aldehydes and ketones, acetals are among the most common. Aldehydes and ketones are electrophilic and are therefore susceptible to nucleophilic attack by Grignard reagents and other strong nucleophiles (scheme 9A). To prevent such reactions from occurring, carbonyl compounds are frequently protected as acetals (Scheme 9B). The formation of an acetal can be accomplished by using two

equivalents of an alcohol in the presence of a Brønsted acid (scheme 10A).¹⁸ However, in practice, acetal synthesis is often achieved using trialkylorthoformate (Scheme 10B). Recently, bismuth triflate was shown to catalyze the conversion of aldehydes and ketones to acetals using trialkylorthoformate (scheme 11).¹⁹

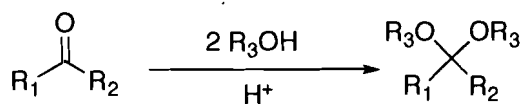
Scheme 9A



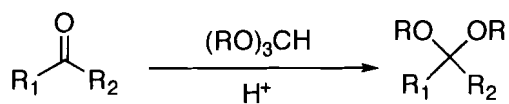
Scheme 9B



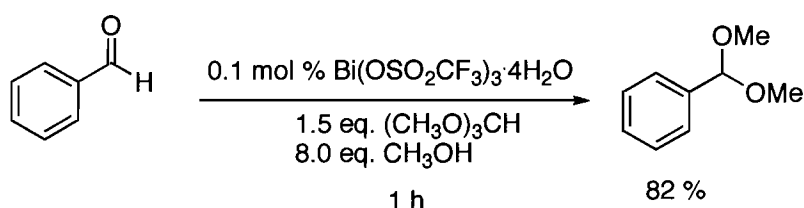
Scheme 10A



Scheme 10B

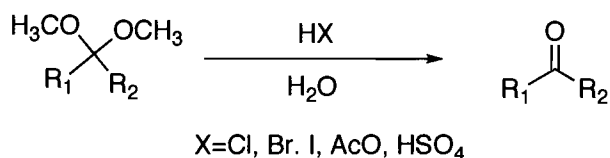


Scheme 11



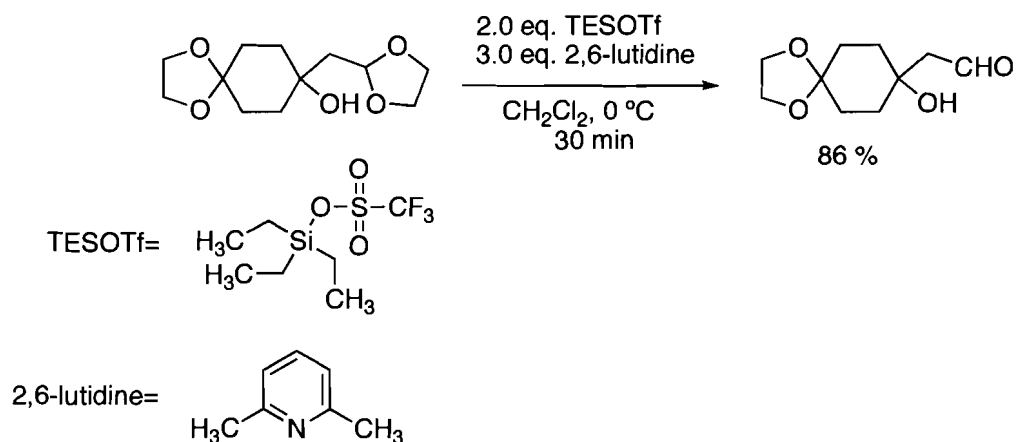
In the course of a total synthesis it is often necessary to protect carbonyl groups to ensure that there will be no nucleophilic attack at the carbonyl carbon. Usually, it is necessary to regenerate the desired carbonyl group. Hence mild methods for the deprotection of acetals have received considerable attention. The most common method to deprotect acetals is under dilute aqueous acid conditions (scheme 12).²⁰

Scheme 12

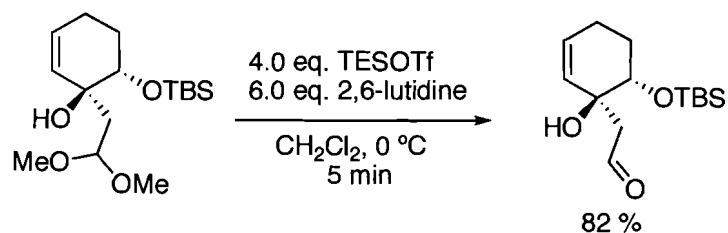


Many methods have been developed for the deprotection of acetals using a variety of Lewis acids as catalysts. Many of these reactions are chemoselective. Recently it has been reported that triethylsilyltriflate (TESOTf)-2,6-lutidine can be used as an effective catalyst for the chemoselective deprotection of acetals over ketals (scheme 13).²¹ This reaction was found to be stereoselective (scheme 14) and the corresponding aldehyde was obtained in good yields. However, the use of a high catalyst load does not make this reaction especially efficient or green.

Scheme 13

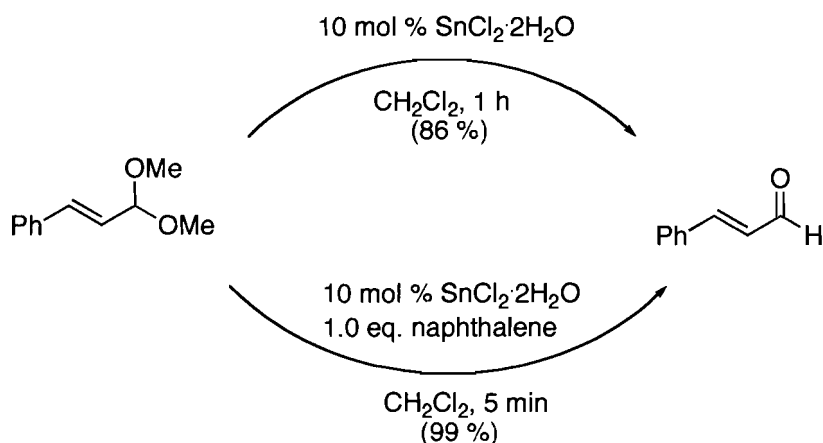


Scheme 14



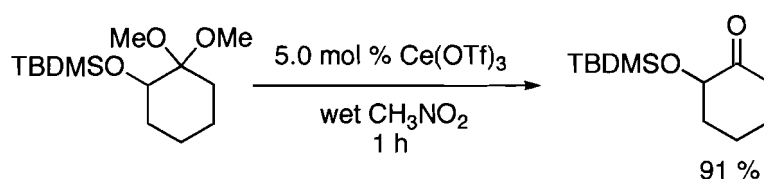
The use of tin dichloride dihydrate as a catalyst for the deprotection of acetals has been reported (scheme 15).²² The reaction conditions required a promoter (naphthalene or C_{60}) in order to drive the reaction to completion. The authors proposed that the promoters were acting as a phase-transfer catalyst by creating arene complexes with tin dichloride.²² The use of toxic tin and the use of 1.0 equiv. of a promoter does not make this reaction very green and detracts from its utility.

Scheme 15



A chemoselective method for the deprotection of acetals using cerium(III) triflate has been reported (scheme 16).²³ The authors report that a catalytic amount of cerium(III) triflate can be used in wet CH_3NO_2 to chemoselectively deprotect acetals in the presence of THP ethers, TBDMS ethers, esters, and benzyl ethers.

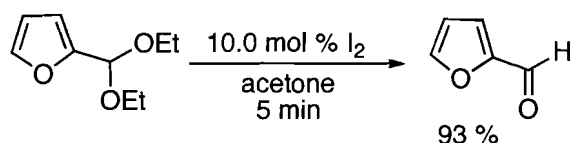
Scheme 16



In the course of a total synthesis of complex molecules, neutral deprotection methods are advantageous due to the likelihood of the presence of acid sensitive functional groups in the same compound. The deprotection of acetals under neutral conditions using I_2 in acetone has been reported.²⁴ The authors reported that acid sensitive groups were unaffected by the reaction conditions and deprotection of acetals to the corresponding carbonyl compound was achieved in good yields (scheme 17). The *in situ* generation of molecular iodine via sodium iodide oxidation using CuSO_4 in acetone

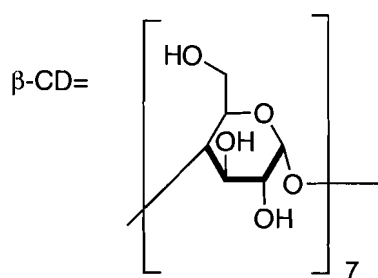
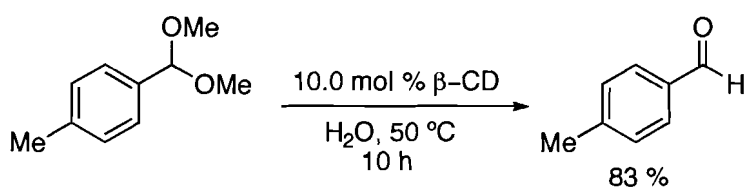
has also been reported.²⁵ This procedure has the advantage of avoiding the use and handling of corrosive iodine.

Scheme 17



The deprotection of acetals using environmentally friendly β -cyclodextrin has been reported.²⁶ β -Cyclodextrin (β -CD) is a cyclic oligosaccharide with hydrophobic cavities allowing the deprotection to be carried out in water. The reaction conditions reported were mild and the desired products were obtained in good yields (scheme 18).

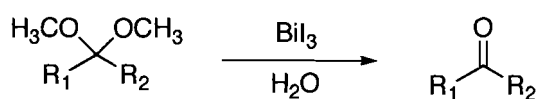
Scheme 18



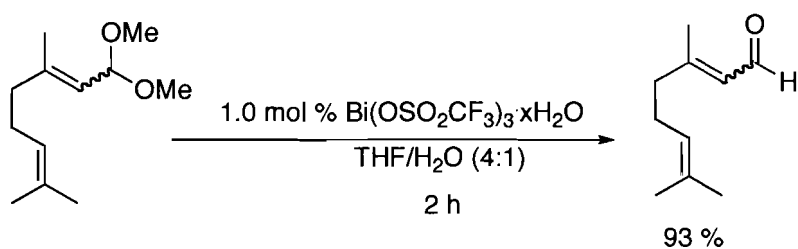
1.D. Goals

The goal of this research was to develop methods for deprotecting acetals using bismuth(III) iodide in water (scheme 19). This reaction method is advantageous because it avoids the use of organic solvents during the reaction. As stated previously, water is the most environmentally friendly solvent; it is non-toxic, non-flammable and inexpensive. Previously the deprotection of acetals has been catalyzed by bismuth(III) triflate (scheme 20)²⁷, bismuth(III) nitrate pentahydrate (scheme 21)²⁸, and bismuth(III) chloride (scheme 22).²⁹

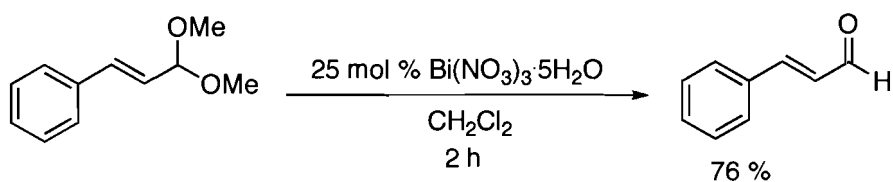
Scheme 19



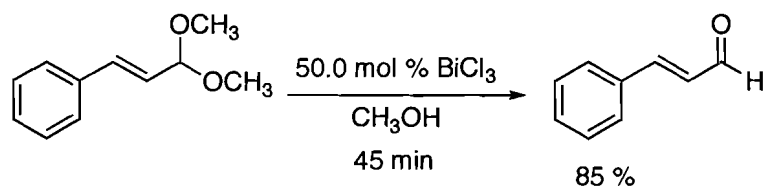
Scheme 20



Scheme 21



Scheme 22



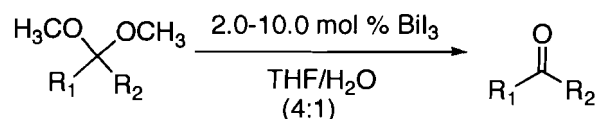
This project was designed to explore the utility of bismuth(III) iodide, a relatively underutilized Bi(III) catalyst, and to develop an efficient/chemoselective method that could be applied to the deprotection of acetals. The results and optimized reaction conditions are described below.

2. Results and Discussion:

2.A. Deprotection of Acetals Catalyzed by BiI₃ in THF/H₂O Solvent System

The deprotection of acetals catalyzed by Bi(OTf)₃ (0.1 mol %) in aqueous THF (4:1, THF:H₂O, v/v) has been reported.²⁷ This same methodology was applied using bismuth(III) iodide in place of Bi(OTf)₃. The reactions were first carried out using 2.0-10.0 mol % BiI₃ in the aforementioned solvent system (scheme 23). Many acetals underwent deprotection in relatively short reaction times to give the corresponding carbonyl compounds in moderate yields. This method was applied to different types of acetals and preliminary results indicated that bismuth(III) iodide would be an effective catalyst for a deprotection of *O,O*-acetals.

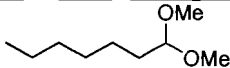
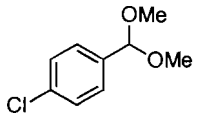
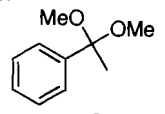
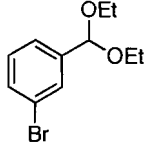

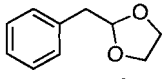
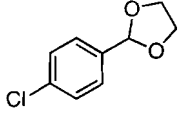
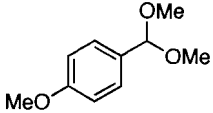
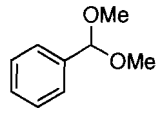
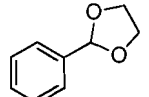
Scheme 23



The previous study, which used bismuth triflate, was performed in the THF/H₂O solvent system to avoid the use of chlorinated solvents (used previously in a deprotection reactions using bismuth(III) nitrate as a catalyst).^{27,28} It was reported that the bismuth triflate was probably hydrolyzed under the reaction conditions to triflic acid which in turn was the active catalyst in the reaction. [Also, THF/H₂O was used to ensure that the organic compounds would readily dissolve in the solvent system. THF was chosen as a co-solvent because it is relatively environmentally friendly compared to other common organic solvents (benzene, dichloromethane, etc.).] Similar reasoning led us to consider

the same solvent system for the deprotection reaction using bismuth(III) iodide. These reaction conditions were applied to a variety of different acetals and ketals (Table 3).

Table 3: BiI₃ Catalyzed Deprotection of Acetals in THF/H₂O (4:1)

Entry	Acetal	BiI ₃ (mol %)	Temp. (° C)	Time	Yield ^a (%)
1 ^b		5.0	reflux	1 h 45 min	42
2 ^b	CH ₃ (CH ₂) ₁₀ CH(OMe) ₂	2.0	reflux	3 h	98
3 ^b		5.0	rt	29 h	89
4		5.0	rt	2 h	70
5		2.0	rt	5 h 20 min	99
6		5.0	reflux	3 h 30 min	86
7 ^b		5.0	reflux	31 h	93
8 ^{b,c}		5.0	reflux	2 h 25 min	76
9		5.0	rt	2 h 45 min	>100 ^d
10a		5.0	rt	1 h	66
11a		5.0	rt	17 h 30 min	68

a=all products were >97 % pure unless otherwise stated. b= crude product was a mixture of the carbonyl compound and starting material; yield shown corresponds to crude product. c=product was purified on flash chromatography using EtOAc/hexanes (20:80) as the solvent. d= product and impurities present in crude product.

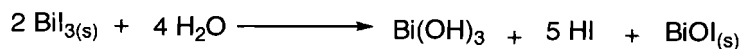
A variety of acetals and ketals underwent deprotection in the THF/H₂O solvent system (Table 3). It was observed that aromatic acetals facilitated the conversion from acetal to carbonyl and, with the exception to entry 3 no starting material was observed in the crude product. However, in entries 1, 2, and 7, the crude product contained a mixture of starting material, product, and other impurities. It is likely that the impurities arose from Aldol condensation of product under the acidic reaction conditions. Based on this assumption it is not unreasonable that these reactions did not give high yields of the desired product.

2.B Modification of Solvent System

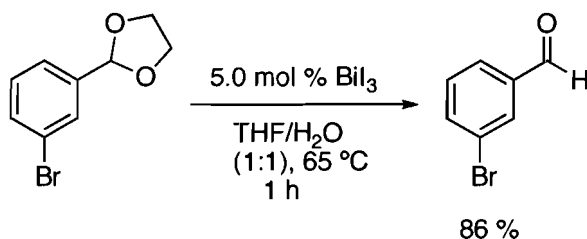
Bismuth(III) iodide is known to hydrolyze in aqueous media to hydroiodic acid (scheme 24). This was verified by a simple pH test of the reaction mixture solution using universal indicator paper. The pH of the reaction mixture was tested before work-up and was found to be consistently ~2-4. The hydrolysis of bismuth(III) iodide occurs more readily in warm water.⁴ This accounts for the lower pH observed in reactions carried out at 100 °C than reactions performed at room temperature. If HI was the active catalyst i, then one would expect the deprotection to occur in aqueous solutions as shown in scheme 12. It was decided to vary the solvent composition by increasing the relative proportion of water and to observe the effects of a more aqueous solvent. A reaction was performed in a 1:1 (v/v) mixture of THF and water. As expected, there was a decrease in solubility of the substrate as the ratio of water in the solvent system was increased. However, surprisingly the reaction time and yield improved for deprotection of 2-(3-bromophenyl)-1,3-dioxolane (scheme 25). Based on this observation, the deprotection reactions were

attempted in water alone. Gratifyingly, the deprotection of acetals catalyzed by BiI₃ in water worked quite well.

Scheme 24

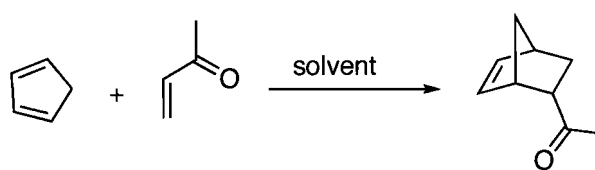


Scheme 25



Due to the poor solubility of organic compounds in water, it has been assumed that organic reactions will not work well in aqueous systems. In 1980, however, the Diels-Alder reaction was studied using water as a solvent and the observed rate of the reaction was increased significantly when water was substituted for an organic solvent (scheme 26).³⁰ It was later proven by using salting-in and salting-out agents in the Diels-Alder reaction that water could be used as a better solvent than many traditional organic solvents.³ Based on the study, the authors concluded that the hydrophobic effect was contributing to the good conversion of organic reactants to products in aqueous media. The authors proposed that the interaction of the catalyst and the organic reagent is maximized due to hydrophobic pockets formed by the organic reagents in water.

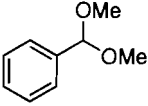
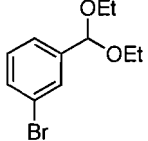
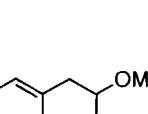
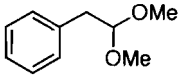
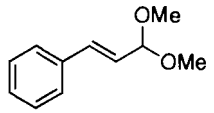
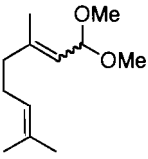
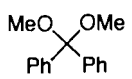
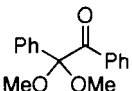
Scheme 26



<u>Solvent</u>	<u>Rate ($\times 10^5, \text{M}^{-1} \text{s}^{-1}$)</u>
isooctane	5.94
methanol	75.5
water	4400

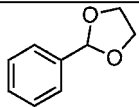
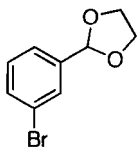
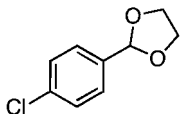
The benefits of a similar hydrophobic effect can be hypothesized for the deprotection of acetals catalyzed by BiI_3 in water. The hydrophobic organic compounds could obtain maximum interaction with the catalyst (BiI_3) due to formation of a hydrophobic pocket. This hypothesis is supported by the improved reaction times and high yields after changing the reaction solvent to H_2O (Table 4). This solvent system was also shown to be effective for deprotection of cyclic acetals in good yields and short reaction times (Table 5).

Table 4: BiI₃ Catalyzed Deprotection of Acyclic Acetals in H₂O

Entry	Acetal	BiI ₃ (mol %)	Temp.	Time	Yield (%) ^a
1		1.0	rt	22 h	57
2a		1.0	reflux	45 min	85
2b		1.0	rt	20 h	89
3 ^b		1.0	reflux	1 h	87
4		1.0	rt	1 h 40 min	91
5		1.0	rt	50 min	95
6	CH ₃ (CH ₂) ₁₀ CH(OMe) ₂	1.0	rt	27 h	68
7		1.0	reflux	1 h 30 min	94
8		15.0	reflux	28 h	93

a=Refers to yield of crude product. All products were >97 % pure unless otherwise stated . b= crude product was a mixture of product and other impurities

Table 5: BiI₃ Catalyzed Deprotection of Cyclic Acetals in H₂O

Entry	Acetal	BiI ₃ (mol %)	Temp.	Time	Yield (%) ^a
1 ^a		5.0	reflux	2 h	50
2a		5.0	reflux	45 min	92
2b		1.0	rt	22 h	82
3		1.0	reflux	1 h 25 min	85

^a= Ethylene glycol present in crude product.

Although the majority of the deprotections could be carried out at room temperature (Table 4), significant rate acceleration was noted at higher temperature (Table 4, entries 2a, 2b). Phenylacetaldehyde dimethyl acetal (Table 4, entry 3) was deprotected in the best yield/purity when the reaction was heated at reflux temperatures. As described earlier, the lower yield is most likely due to the enolizable aldehyde product. A lower isolated yield in the deprotection of dodecanal dimethyl acetal (Table 4, entry 6) was similarly attributed to aldol condensation of dodecanal product under the acidic reaction conditions.

Although the deprotection of benzaldehyde dimethyl acetals (table 4, entry 1) and 2-phenyl-1,3-dioxolane (table 5, entry 1) went to completion (progress followed by GC),

the product benzaldehyde was obtained in a low yield. This was attributed to loss of the somewhat volatile product on the rotary evaporator during the final stages of work-up.

Cyclic acetals (dioxolanes) were also readily deprotected using BiI_3 as a catalyst. However, it was observed that these acetals underwent deprotection at a significantly slower rate at room temperature (table 5, entry 2b) and reflux conditions were the optimal conditions for their deprotection. It was also observed that more impurities are present in the crude product mixture. It is likely that the deprotected diol side product is not completely removed in the aqueous work-up and is therefore still present in the crude product.

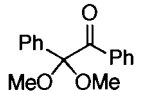
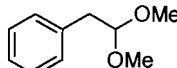
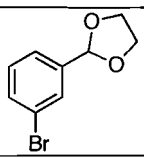
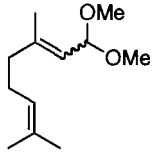
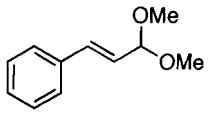
2.C. Comparison of Catalyst Systems

When compared to previously reported Lewis acid catalyzed deprotection reactions (e.g. those employing BiCl_3 , $\text{Bi}(\text{OTf})_3 \cdot x\text{H}_2\text{O}$, $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$, $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$), bismuth(III) iodide appears to be a synthetically useful catalyst for the deprotection of acetals. Previously reported for the deprotection of acetals are compared to BiI_3 in Table 6. By comparison, the bismuth(III) iodide catalyst system is more efficient for the deprotection of acetals (Table 6).

The deprotection of benzil monodimethyl acetal (Table 6, entry 1) to benzil catalyzed by BiI_3 proceeded in high yields; however, previous deprotection methods using $\text{Bi}(\text{OTf})_3 \cdot x\text{H}_2\text{O}$ gave poor conversion (67 % ketal; 33 % benzil) of the ketal to the product.²⁷ Phenylacetaldehyde dimethyl acetal (Table 6, entry 2) and 2-(3-bromophenyl)-1,3-dioxolane (Table 6, entry 3) were both converted to the corresponding carbonyl compound in higher yields and lower reaction times using BiI_3 than with

Bi(OTf)₃·xH₂O. Citral dimethyl acetal (Table 6, entry 4) was deprotected in higher yields and in half the reaction time in the BiI₃ catalyst system when compared to Bi(OTf)₃·xH₂O.

Table 6: Comparison of Catalyst Systems

Entry	Acetal	Catalyst (mol %)	Solvent	Time	Temp.	Yield (%)
1	a	Bi(OTf) ₃ ·xH ₂ O(0.1)	THF/H ₂ O ^a	12 h	reflux	33
	b	BiI ₃ (15.0)	H ₂ O	28 h	reflux	93
						
2	a	Bi(OTf) ₃ ·xH ₂ O(0.1)	THF/H ₂ O ^a	3 h	reflux	55
	b	Bi(NO ₃) ₃ ·5H ₂ O(25.0)	CH ₂ Cl ₂	2 h	rt	NR
	c	SnCl ₄ ·2H ₂ O(10.0)	CH ₂ Cl ₂	2 h	rt	62
	d	BiI ₃ (1.0)	H ₂ O	1 h	reflux	87
						
3	a	Bi(OTf) ₃ ·xH ₂ O(0.1)	THF/H ₂ O ^a	6 h	reflux	89
	b	BiI ₃ (5.0)	H ₂ O	45 min	reflux	92
						
4	a	Bi(OTf) ₃ ·xH ₂ O(0.1)	THF/H ₂ O ^a	2 h	rt	93
	b	BiI ₃ (1.0)	H ₂ O	50 min	rt	95
						
5	a	Bi(NO ₃) ₃ ·5H ₂ O(25.0)	CH ₂ Cl ₂	2 h	rt	76
	b	BiCl ₃ (50.0)	CH ₃ OH	45 min	rt	85
	c	SnCl ₄ ·2H ₂ O(10.0)	CH ₂ Cl ₂	1 h	rt	86
	d	BiI ₃ (1.0)	H ₂ O	1 h 40 min	rt	91
						

a= THF/H₂O mixture 4:1 (v/v)

Compared to the $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ catalyzed conditions, bismuth(III) iodide in water is a more efficient catalyst for the conversion of phenylacetaldehyde dimethyl acetal and cinnamaldehyde dimethyl acetal to the corresponding aldehydes. The deprotection of phenylacetaldehyde dimethyl acetal was not successful using up to 25 mol % $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ catalyst in CH_2Cl_2 .²⁸ The conversion of cinnamaldehyde dimethyl acetal to cinnamaldehyde was also more efficient with BiI_3 as the catalyst (Table 6, entry 5d) than with $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ (Table 6, entry 5a).

It has been previously reported that BiCl_3 was used to deprotect acetals in methanol.²⁹ Comparatively BiI_3 is a more efficient catalyst because the catalyst load (1-15 mol %) is significantly less than that for the BiCl_3 catalyst system (50.0 mol %). Also, cinnamaldehyde dimethyl acetal was obtained in better yields using BiI_3 as a catalyst than BiCl_3 .

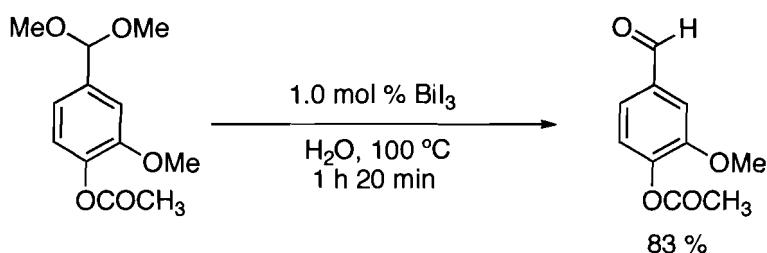
Tin dichloride dihydrate is a reported Lewis acid catalyst used for the deprotection of acetals.²² Bismuth(III) iodide has been observed to catalyze deprotection more efficiently than the original tin dichloride dihydrate system. The tin catalyst system was modified to use naphthalene or C_{60} as a promoter to drive the reaction to completion. With this system the tin catalyst was able to catalyze the deprotection of phenylacetaldehyde dimethyl acetal and cinnamaldehyde dimethyl acetal more easily; however, in the bismuth(III) iodide system we avoid the use of toxic tin dichloride (LD_{50} see Table 1) and stoichiometric promoter reagents.

2.D. Chemoselectivity

It has been shown (Tables 4 & 5) that bismuth(III) iodide can be used as an effective catalyst for the deprotection of acetals in water. None of the aforementioned acetals however contained any acid sensitive functional groups or other types of protecting groups. To demonstrate the chemoselectivity of the BiI_3 catalyzed deprotection of acetals different acid sensitive compounds and protecting groups were tested using H_2O as the solvent.

Vanillin acetate dimethyl acetal was subjected to the reaction conditions, it was found that the acetal was cleaved but the ester group remained unaffected (scheme 27). Under strong acidic conditions esters are hydrolyzed to their corresponding acids and alcohols. This chemoselectivity demonstrates that if any acid is being produced in the reaction of BiI_3 in water, then there is an insufficient amount available to cleave the ester in vanillin acetate.

Scheme 27

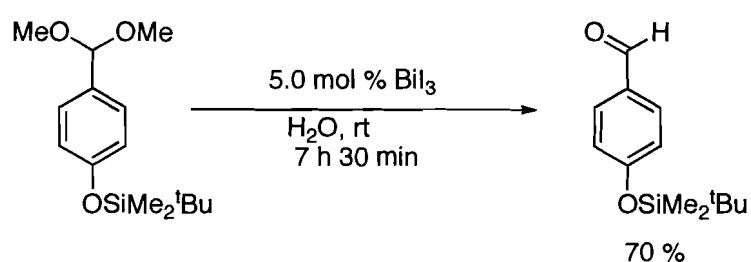


The chemoselective nature of this reaction was further extended to selectively cleave acetals while leaving *tert*-butyldimethylsilyl ethers (TBDMS ethers) unaffected. These ethers are common stable protecting groups for alcohols in organic synthesis and are readily cleaved by a variety of conditions (fluoride ions or aqueous acid).³² Often in

total synthesis there is a need to selectively cleave one protecting group in preference to another.

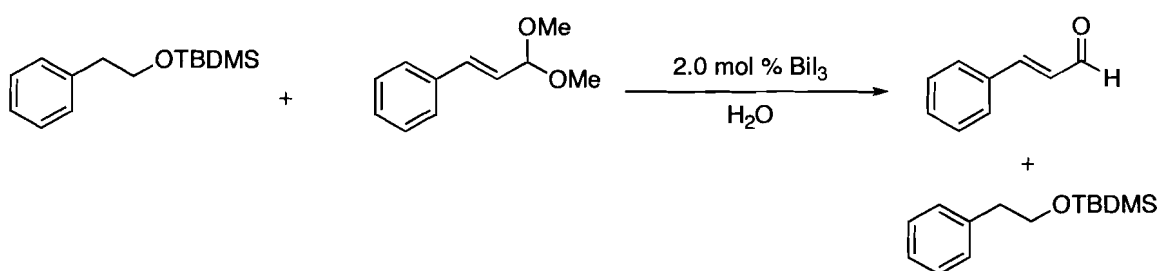
The reaction conditions were applied to an acetal containing a TBDMS protected phenol (scheme 28). Using 5.0 mol % BiI_3 at room temperature the desired aldehyde was obtained in good yields and no cleavage of the TBDMS ether was observed (^1H NMR) under these conditions.

Scheme 28



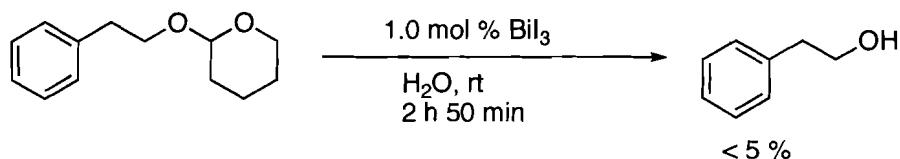
Similar chemoselectivity was observed when a mixture of cinnamaldehyde dimethyl acetal and the TBDMS protected alcohol of 2-phenylethanol was stirred in water in the presence of 2.0 mol % BiI_3 . It was observed that the acetal was selectively deprotected while the TBDMS ether was not affected (scheme 29).

Scheme 29



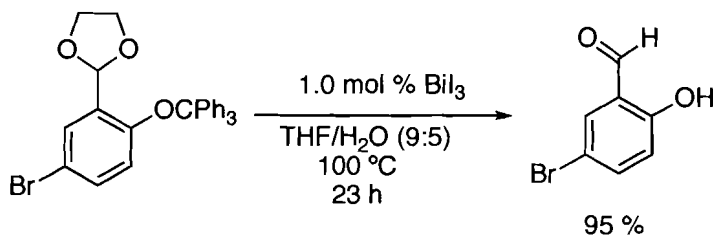
The deprotection of tetrahydropyranyl ethers was attempted using BiI_3 in H_2O as a catalyst. It was found that THP ethers derived from phenethyl alcohol (scheme 30) were stable at mild reaction conditions (< 5% alcohol formed).

Scheme 30



The reaction conditions were also applied to trityl ethers but both the acetal and the trityl group in the aromatic phenol shown in scheme 31 remained unaffected in H_2O . However, the both groups could be cleaved in aqueous THF at reflux conditions.

Scheme 31



The observed chemoselectivity with BiI_3 makes this an attractive deprotection method, especially in the area of total synthesis.

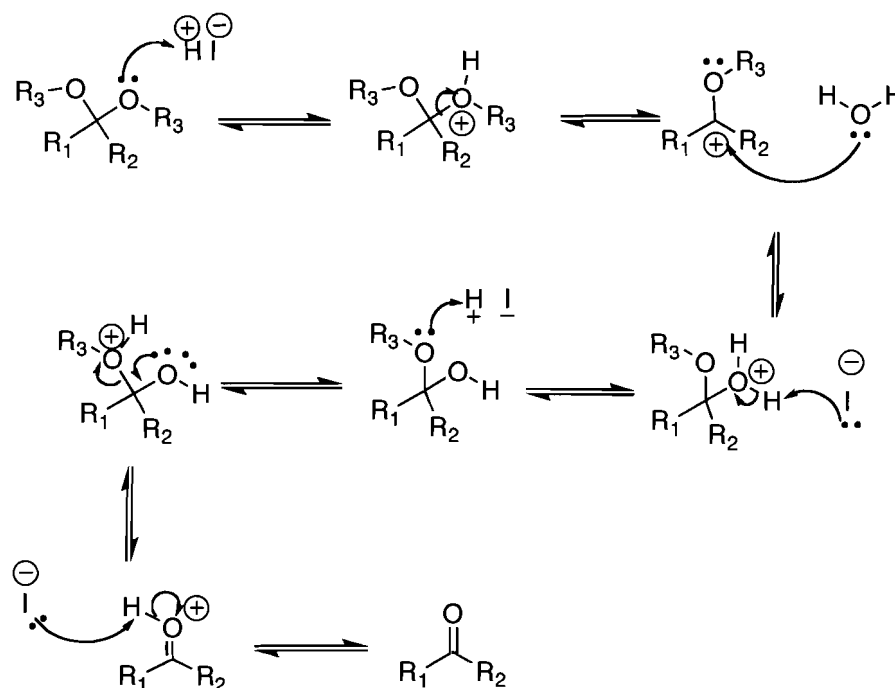
2.E. Mechanistic Study

The pH of the reaction mixture was checked prior to work-up and was found to be in the range 2-4. Lower pH was associated with reactions that were heated (pH~2) and the higher pH was observed in reactions run at room temperature (pH~4). However,

some acid-sensitive groups survived the reaction conditions. There are two possible mechanisms to account for the observed deprotection. One is the coordination of the metal to the acetal thus making the carbon more susceptible to attack by H_2O . A second possibility is that the deprotection is catalyzed by HI (scheme 32) generated from hydrolysis of BiI_3 (scheme 24). Most of the experimental data suggests the deprotection is most likely catalyzed by HI.

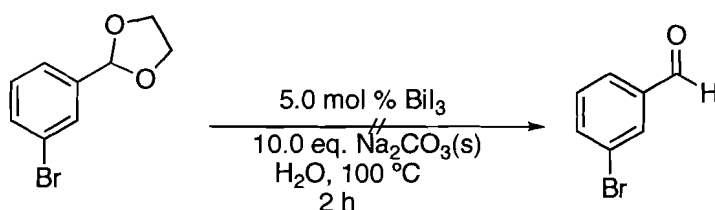
One convincing evidence for this is the observation that bismuth(III) halides are not stable in water.^{4b} Bismuth(III) iodide is expected to hydrolyze in water to the corresponding acid (HI) and bismuth(III) hydroxide ($\text{Bi}(\text{OH})_3$). This is consistent with the low pH of the reaction. Knowing this, it can be concluded that an acid is being produced *in situ*. During the reaction a red precipitate is formed. While no chemical analysis has been performed on the precipitate it can be hypothesized that this is bismuth oxyiodide (BiOI).^{4a}

Scheme 32



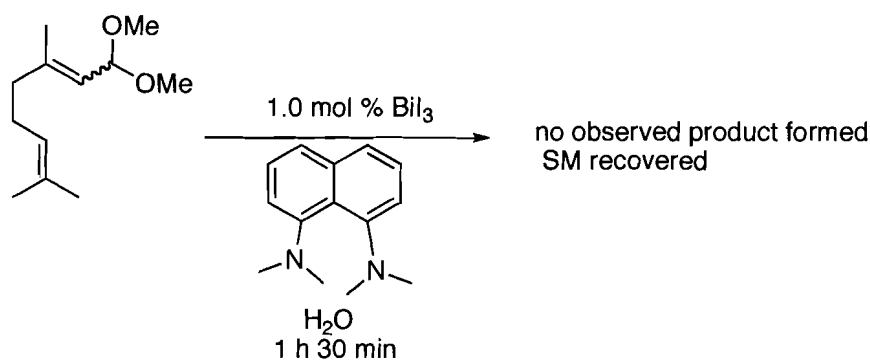
The experimental evidence indicates that HI is being formed, but it does not rule out coordination of bismuth to the acetal carbon. To determine if HI was the active catalyst in the reaction control experiments were run. The deprotection of 2-(3-bromophenyl)-1,3-dioxolane was unsuccessful when carried out in the presence of 10.0 equivalents of solid Na_2CO_3 (scheme 33).

Scheme 33



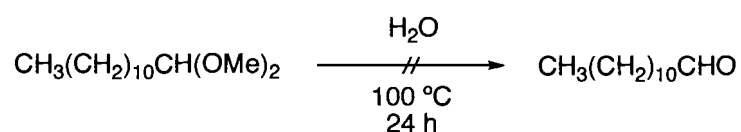
The deprotection of citral dimethyl acetal was attempted using 1.0 mol % BiI_3 in the presence of a proton sponge™ [1,8-Bis(dimethylamino)naphthalene] (scheme 34). When the reaction was allowed to run for 1 h 30 min (the amount of time for deprotection in the absence of the sponge was 50 minutes, Table 4, entry 5) and no product was formed and the starting material was recovered.

Scheme 34



A control experiment was also carried out to determine if the reaction was being catalyzed by BiI_3 and not just water. It has been previously reported that deprotection of some acetals and ketals can be performed in superheated water (205-250 °C).² The control reaction (scheme 35) showed that there is no conversion of acetal to aldehyde upon heating in water to 100 °C suggesting that the deprotection of the acetals is being catalyzed by the hydrolysis of BiI_3 .

Scheme 35



Based on the control experiments, the pH of the reaction consistently between 2 and 4, and the observation of the chemoselectivity of the reactions it can be concluded that HI is the active catalyst in the deprotection reactions. Under the current reaction conditions the acid concentration generated is insufficient to affect some of the tested acid sensitive groups (OTBDMS, THP, esters).

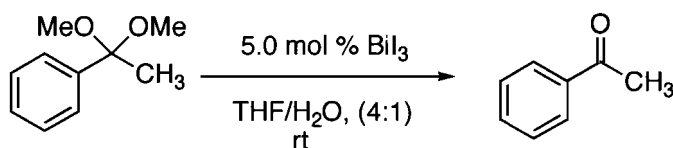
3. Conclusions

An environmentally-friendly method for the deprotection of a wide range of acetals and ketals in H₂O using BiI₃ as a catalyst has been developed. Under the reaction conditions, TBDMS ethers, THP ethers, and esters are not affected. The use of a relatively non-toxic catalyst, bismuth iodide and water as a solvent make this method an attractive option for the deprotection of acetals and ketals. Mechanistic studies suggest that HI generated by hydrolysis of BiI₃ is the active catalyst.

4. Experimental

General: All chemicals were purchased from the Aldrich Chemical Company, Acros Chemical Company, Lancaster, Bedoukian or Fisher. All reactions were performed in deionized water. NMR spectra were recorded on a JEOL Eclipse NMR Spectrometer at 270 MHz (^1H) or 67.5 MHz (^{13}C) in CDCl_3 (unless otherwise stated) as the solvent. Thin-layer chromatography was performed on alumina backed silica gel plates. Spots were visualized under UV light and by spraying the plate with phosphomolybdic acid followed by heating. All products have previously been reported in the literature and were characterized by ^1H and ^{13}C NMR spectroscopy. Product purity was also checked by GC analysis on a Varian 3800 capillary GC instrument equipped with a capillary column (CP-Sil 8) (column oven: 100 °C for 3 min, then heat to 220 °C at 30 °C/min, hold at 220 °C for 4 min). Acetals were purchased from commercial sources or synthesized from the corresponding carbonyl compound using a literature method.¹⁹

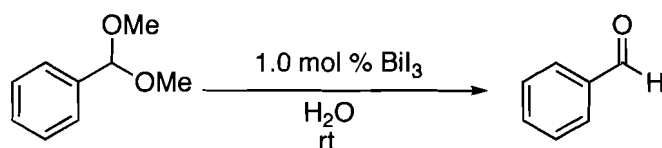
Deprotection of (1,1-dimethoxyethyl)benzene in THF/ H_2O (ADB2005)



A mixture (1,1-dimethoxyethyl)benzene (1.00 g, 6.022 mmol) in THF/ H_2O (10.0 mL, 4:1) was stirred as BiI_3 (0.1775 g, 0.301 mmol, 5.0 mol %) was added and reaction progress was followed by GC. After 2 h 55 min, EtOAc (40 mL) was added to the reaction mixture and the biphasic mixture was filtered through a bed of celite. The aqueous layer from the biphasic filtrate was extracted with EtOAc (20 mL) and the

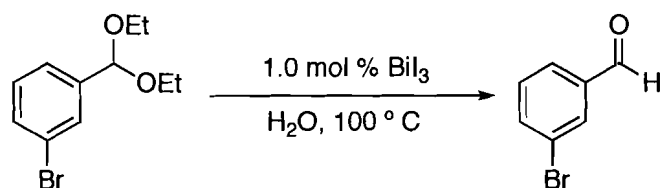
combined organic layers were washed with 5 % aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL), 10 % aqueous Na_2CO_3 (2x10 mL), saturated NaCl (10 mL), and dried (Na_2SO_4). The solvents were removed on a rotary evaporator to yield 0.5084 g (70 %) of a clear liquid. ^1H NMR : δ 2.59 (s, 3H), 7.52 (m, 3H), 7.96 (m, 2H). ^{13}C NMR (6 peaks): δ 26.2, 127.9, 128.2, 132.8, 136.8, 197.6 GC: > 98 % Product (ret. Time= 4.482 min)

Deprotection of Benzaldehyde dimethyl acetal (ADB2133)



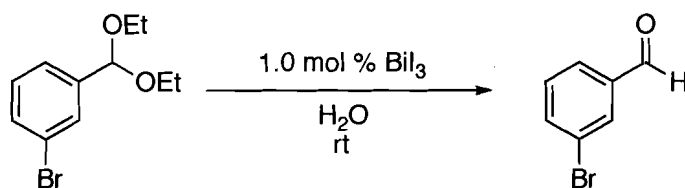
A mixture benzaldehyde dimethyl acetal (0.5142 g, 3.38 mmol) in H_2O (5.0 mL) was stirred as BiI_3 (0.020 g, 0.0338 mmol, 1.0 mol %) was added and reaction progress was followed by TLC (EtOAc/Hexanes, 20/80). After 1 h, EtOAc (40 mL) was added to the reaction mixture and the biphasic mixture was filtered through a bed of celite. The aqueous layer from the biphasic filtrate was extracted with EtOAc (20 mL) and the combined organic layers were washed with 5 % aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL), 10 % aqueous Na_2CO_3 (10 mL), saturated NaCl (10 mL), and dried (Na_2SO_4). The solvents were removed on a rotary evaporator to yield 0.2028 g (57 %) of a clear liquid. ^1H NMR: δ 7.45 (m, 3H), 7.80 (m, 2H), 9.90 (s, 1H). ^{13}C NMR (5 peaks): δ 129.0, 129.7, 134.5, 136.5, 192.4

Deprotection of 1-bromo-3-(diethoxymethyl)benzene (ADB2037)



A mixture 1-bromo-3-(diethoxymethyl)benzene (1.01 g, 3.90 mmol) in H₂O (10.0 mL) was stirred as BiI₃ (0.0230 g, 0.0390 mmol, 1.0 mol %) was added. The reaction was heated at reflux and reaction progress was followed by GC. After 45 min, EtOAc (40 mL) was added to the reaction mixture and the biphasic mixture was filtered through a bed of celite. The aqueous layer from the biphasic filtrate was extracted with EtOAc (20 mL) and the combined organic layers were washed with 5 % aqueous Na₂S₂O₃ (10 mL), 10 % aqueous Na₂CO₃ (10 mL), saturated NaCl (10 mL), and dried (Na₂SO₄). The solvents were removed on a rotary evaporator to yield 0.6164 g (85 %) of a clear liquid. ¹H NMR: δ 7.39 (t, 1H, *J*= 7.7 Hz), 7.76 (m, 2H), 7.95 (s, 1H), 9.97 (s, 1H). ¹³C NMR (7 peaks): δ 123.2, 128.3, 130.5, 132.1, 137.1, 137.8, 190.6 GC: >99 % Product (ret. Time= 5.352 min)

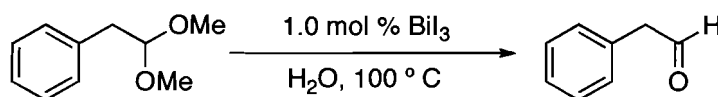
Deprotection of 1-bromo-3-(diethoxymethyl)benzene (KKT1013) (Reaction Performed by Kendall Tasche)



A mixture 1-bromo-3-(diethoxymethyl)benzene (0.5093 g, 1.97 mmol) in H₂O (5.0 mL) was stirred as BiI₃ (0.0124 g, 0.0197 mmol, 1.0 mol %) was added and reaction

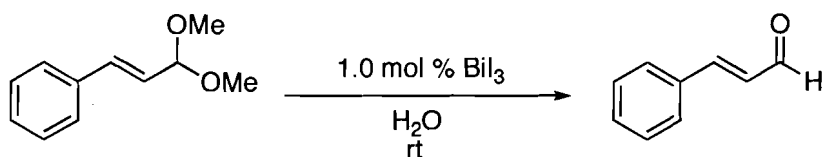
progress was followed by GC. After 20 h, EtOAc (40 mL) was added to the reaction mixture and the biphasic mixture was filtered through a bed of celite. The aqueous layer from the biphasic filtrate was extracted with EtOAc (20 mL) and the combined organic layers were washed with 5 % aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL), 10 % aqueous Na_2CO_3 (10 mL), saturated NaCl (10 mL), and dried (Na_2SO_4). The solvents were removed on a rotary evaporator to yield 0.3253 g (89 %) of a clear liquid. ^1H NMR: δ 7.44 (t, 1 H, J = 7.7 Hz), 7.78 (q, 2 H, J = 7.7 Hz), 7.99 (s, 1 H), 9.94 (s, 1 H); ^{13}C NMR (7 peaks): δ 123.1, 128.2, 130.5, 132.1, 137.1, 137.8, 190.6

Deprotection of (2,2-dimethoxyethyl)benzene (ADB2115)



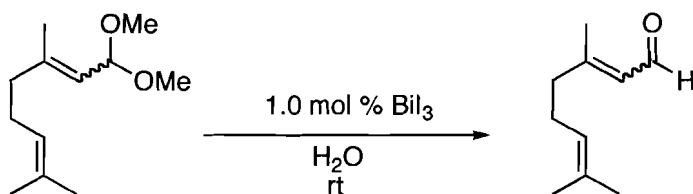
A mixture (2,2-dimethoxyethyl)benzene (1.01 g, 6.076 mmol) in H_2O (10.0 mL) was stirred as BiI_3 (0.0358 g, 0.06076 mmol, 1.0 mol %) was added. The reaction was heated at reflux and reaction progress was followed by GC. After 1 hour, EtOAc (40 mL) was added to the reaction mixture and the biphasic mixture was filtered through a bed of celite. The aqueous layer from the biphasic filtrate was extracted with EtOAc (20 mL) and the combined organic layers were washed with 5 % aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL), 10 % aqueous Na_2CO_3 (10 mL), saturated NaCl (10 mL), and dried (Na_2SO_4). The solvents were removed on a rotary evaporator to yield 0.6337 g (87 %) of clear liquid. ^1H NMR: δ 3.69 (d, 2 H, J = 2.5 Hz), 7.35 (m, 5 H), 9.75 (t, 1 H, J = 2.2 Hz)

Deprotection of Cinnamaldehyde dimethyl acetal (ADB2131)



A mixture of cinnamaldehyde dimethyl acetal (0.5064 g, 2.84 mmol) in H_2O (5.0 mL) was stirred as BiI_3 (0.0168 g, 0.0284 mmol, 1.0 mol %) was added and reaction progress was followed by TLC (EtOAc/Hexanes, 20/80). After 1 h 40, EtOAc (40 mL) was added to the reaction mixture and the biphasic mixture was filtered through a bed of celite. The aqueous layer from the biphasic filtrate was extracted with EtOAc (20 mL) and the combined organic layers were washed with 5 % aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL), 10 % aqueous Na_2CO_3 (10 mL), Saturated NaCl (10 mL), and dried (Na_2SO_4). The solvents were removed on a rotary evaporator to yield 0.3403 g (91 %) of a clear liquid. ^1H NMR: δ 6.75 (m, 2H), 7.55 (m, 5H), 9.71 (d, 1H, $J=7.7$ Hz). ^{13}C NMR (7 peaks): δ 128.1, 128.1, 128.7, 130.8, 133.6, 152.3, 193.2

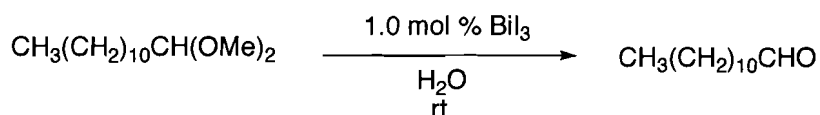
Deprotection of Citral Dimethyl Acetal (ADB2087)



A mixture of citral dimethyl acetal (1.03 g, 5.19 mmol) in H_2O (10 mL) was stirred as BiI_3 (0.0306 g, 0.0519 mmol, 1.0 mol %) was added. Reaction progress was followed by TLC (EtOAc/Hexane, 10/90). After 50 min, EtOAc (40 mL) was added to the reaction mixture and the biphasic mixture was filtered through a bed of celite. The

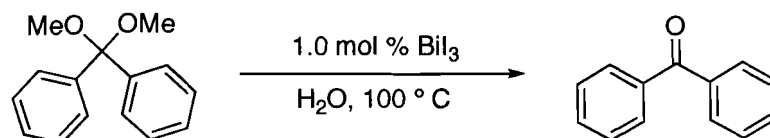
aqueous layer from the biphasic filtrate was extracted with EtOAc (15 mL) and the combined organic layers were washed with 5 % aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL), 10 % aqueous Na_2CO_3 (10 mL), saturated NaCl (10 mL), and dried (Na_2SO_4). The solvents were removed on a rotary evaporator to yield 0.7505 g (95 %) of a clear liquid. ^1H NMR: δ 1.58 (d, 3 H $J=4.5$), 1.66 (s, 3 H), 1.96 (s, 3 H), 2.20 (d, 4 H, $J = 13.9$ Hz), 5.05 (m, 1 H), 5.87 (m, 1 H), 9.89 (d, 1 H, $J = 8.4$ Hz), 9.98 (d, 1 H $J = 8.2$ Hz). ^{13}C NMR (15 peaks): δ 17.5, 24.8, 25.4, 26.9, 32.4, 40.4, 122.1, 122.4, 127.2, 128.5, 132.7, 133.5, 163.7, 190.6, 191.1: GC: > 99 % Product (ret. Time= (33 %) 5.260 min & (66 %) 5.418 min)

Deprotection of dodecanal dimethyl acetal (KKT1015)
(Reaction Performed by Kendall Tasche)



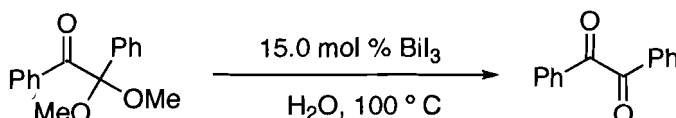
A mixture dodecanal dimethyl acetal (1.0126 g, 4.395 mmol) in H_2O (10.0 mL) was stirred as BiI_3 (0.02591 g, 0.04395 mmol, 1.0 mol %) was added and reaction progress was followed by GC. After 26 h 50 min, EtOAc (40 mL) was added to the reaction mixture and the biphasic mixture was filtered through a bed of celite. The aqueous layer from the biphasic filtrate was extracted with EtOAc (20 mL) and the combined organic layers were washed with 5 % aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL), 2.0 M NaOH (2x10 mL), saturated NaCl (10 mL), and dried (Na_2SO_4). The solvents were removed on a rotary evaporator to yield 0.5517 g (68 %) of a yellow liquid. ^1H NMR: δ 0.852 (t, 3H, $J= 6.5$ Hz), 1.26 (m, 16H), 1.60 (m, 2H), 2.39 (m, 2H), 9.74 (t, 1H, $J= 1.7$ Hz) GC: 97 % Product (ret. Time= 6.20 min)

Deprotection of benzophenone dimethyl ketal (ADB2073)



A mixture benzophenone dimethyl ketal (1.07 g, 4.69 mmol) in H₂O (10.0 mL) was stirred as BiI₃ (0.0276 g, 0.0469 mmol, 1.0 mol %) was added. The reaction was heated at reflux and reaction progress was followed by GC. After 1 hour 30 min, EtOAc (40 mL) was added to the reaction mixture and the biphasic mixture was filtered through a bed of celite. The aqueous layer from the biphasic filtrate was extracted with EtOAc (20 mL) and the combined organic layers were washed with 5 % aqueous Na₂S₂O₃ (10 mL), 10 % aqueous Na₂CO₃ (10 mL), saturated NaCl (10 mL), and dried (Na₂SO₄). The solvents were removed on a rotary evaporator to yield 0.7999 g (94 %) of a white solid. ¹H NMR: δ 7.49 (m). ¹³C NMR (5 peaks): δ 128.2, 130.0, 132.3, 137.5, 196.7

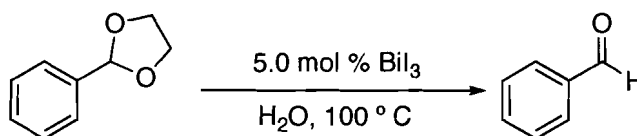
Deprotection of 2,2-dimethoxy-1,2-diphenylethanone (ADB2051)



A mixture of 2,2-dimethoxy-1,2-diphenylethanone (0.99 g, 3.86 mmol) in H₂O (10 mL) was stirred as BiI₃ (0.342 g, 0.579 mmol, 15.0 mol %) was added to the reaction. The reaction was heated at reflux and reaction progress was followed by TLC (CH₂Cl₂). After 28 h 25 min, EtOAc (40 mL) was added to the reaction mixture and the biphasic mixture was filtered through a bed of celite. The aqueous layer from the biphasic filtrate was extracted with EtOAc (20 mL) and the combined organic layers were washed with 5

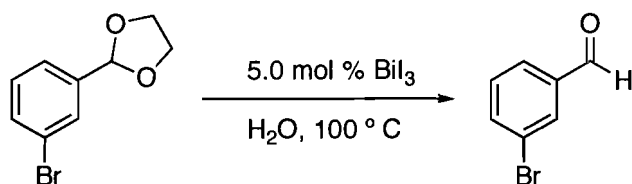
% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL), 10 % aqueous Na_2CO_3 (10 mL), saturated NaCl (10 mL), and dried (Na_2SO_4). The solvents were removed on a rotary evaporator to yield 0.7623 g (93 %) of a yellow solid. ^1H NMR: δ 7.42 (m, 4H) 7.48 (m, 2H), 7.95 (m, 4 H). ^{13}C NMR (5 peaks): δ 128.9, 129.6, 132.7, 134.8, 194.4

Deprotection of 2-phenyl-1,3-dioxolane (ADB2029)



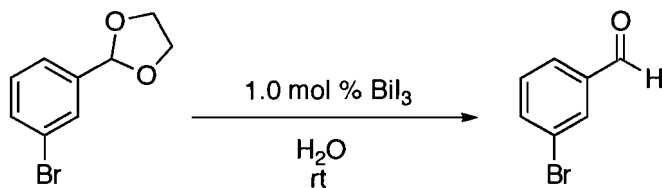
A mixture 2-phenyl-1,3-dioxolane (0.500 g, 3.33 mmol) in H_2O (5.0 mL) was stirred as BiI_3 (0.0982 g, 0.0333 mmol, 5.0 mol %) was added. The reaction was heated at reflux and reaction progress was followed by GC. After 2 h, EtOAc (40 mL) was added to the reaction mixture and the biphasic mixture was filtered through a bed of celite. The aqueous layer from the biphasic filtrate was extracted with EtOAc (20 mL) and the combined organic layers were washed with 5 % aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL), 10 % aqueous Na_2CO_3 (10 mL), saturated NaCl (10 mL), and dried (Na_2SO_4). The solvents were removed on a rotary evaporator to yield 0.1756 g (50 %) of a clear liquid. ^1H NMR: δ 7.45 (m, 3H), 7.81 (m, 2H), 9.91 (s, 1H). ^{13}C NMR (5 peaks): δ 128.9, 129.6, 134.4, 136.3, 192.4; GC: δ >97 % Product (ret. Time= 3.905 min)

Deprotection of 2-(3-bromophenyl)-1,3-dioxolane (ADB2057)



A mixture of 2-(3-bromophenyl)-1,3-dioxolane (0.5114 g, 2.232 mmol) in H₂O (5 mL) was stirred as BiI₃ (0.0658 g, 0.112 mmol, 5.0 mol %) was added to the reaction. The reaction was heated at reflux and reaction progress was followed by TLC (CH₂Cl₂). After 28 h 25 min, EtOAc (40 mL) was added to the reaction mixture and the biphasic mixture was filtered through a bed of celite. The aqueous layer from the biphasic filtrate was extracted with EtOAc (20 mL) and the combined organic layers were washed with 5 % aqueous Na₂S₂O₃ (10 mL), 10 % aqueous Na₂CO₃ (10 mL), saturated NaCl (10 mL), and dried (Na₂SO₄). The solvents were removed on a rotary evaporator to yield 0.7623 g (93 %) of a yellow solid. ¹H NMR: δ 7.42 (t, 1H, *J* = 7.7 Hz) 7.76 (m, 2H), 7.95 (s, 1 H) 9.97 (s, 1H). ¹³C NMR (7 peaks): δ 123.1, 128.2, 130.4, 132.0, 137.0, 137.7, 190.5; GC: ~97 % product (ret. Time= 5.356 min)

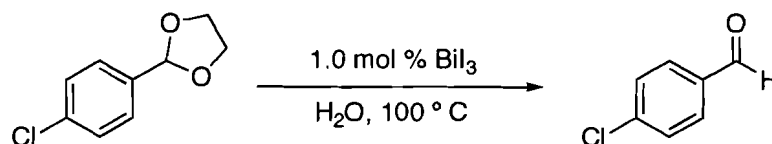
Deprotection of 2-(3-bromophenyl)-1,3-dioxolane (ADB2101)



A mixture of 2-(3-bromophenyl)-1,3-dioxolane (0.5036 g, 2.198 mmol) in H₂O (5.0 mL) was stirred as BiI₃ (0.01296 g, 0.02198 mmol, 1.0 mol %) was added to the

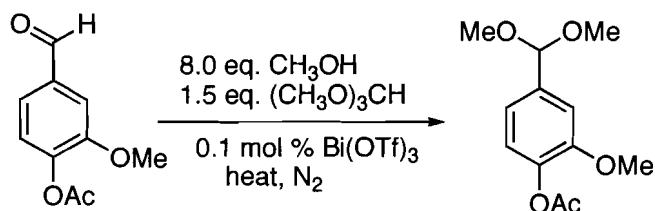
reaction and reaction progress was followed by GC. After 21 h 45 min, EtOAc (40 mL) was added to the reaction mixture and the biphasic mixture was filtered through a bed of celite. The aqueous layer from the biphasic filtrate was extracted with EtOAc (20 mL) and the combined organic layers were washed with 5 % aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL), 10 % aqueous Na_2CO_3 (10 mL), saturated NaCl (10 mL), and dried (Na_2SO_4). The solvents were removed on a rotary evaporator to yield 0.338 g (82 %) clear liquid. ^1H NMR: δ 7.43 (t, 1H, $J = 7.6$ Hz), 7.78 (m, 2H), 8.00 (m, 1H), 9.94 (s, 1H); ^{13}C NMR (7 peaks): δ 123.1, 128.2, 130.5, 131.9, 137.0, 137.7, 190.5; GC: >96 % Product (ret. Time 5.352 min)

Deprotection of 2-(4-chlorophenyl)-1,3-dioxolane (ADB2047)



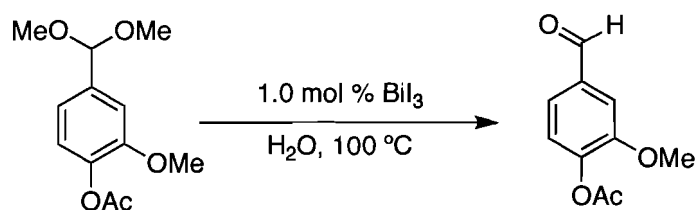
A mixture 2-(4-chlorophenyl)-1,3-dioxolane (1.00 g, 5.417 mmol) in H_2O (10.0 mL) was stirred as BiI_3 (0.0319 g, 0.05417 mmol, 1.0 mol %) was added. The reaction was heated at reflux and reaction progress was followed by GC. After 1 h 25 min, EtOAc (40 mL) was added to the reaction mixture and the biphasic mixture was filtered through a bed of celite. The aqueous layer from the biphasic filtrate was extracted with EtOAc (20 mL) and the combined organic layers were washed with 5 % aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL), 10 % aqueous Na_2CO_3 (10 mL), saturated NaCl (10 mL), and dried (Na_2SO_4). The solvents were removed on a rotary evaporator to yield 0.6502 g (85 %) of white solid. ^1H NMR: δ 7.52 (d, 2H, $J = 8.4$ Hz), 7.83 (d, 2H, $J = 4.7$ Hz), 9.97 (s, 1H). ^{13}C NMR (5 peaks): δ 129.1, 130.6, 134.3, 140.5, 190.6 GC: >98 % Product (ret. Time= 4.84 min)

Synthesis of Vanillin Acetate dimethyl acetal (ADB2063)



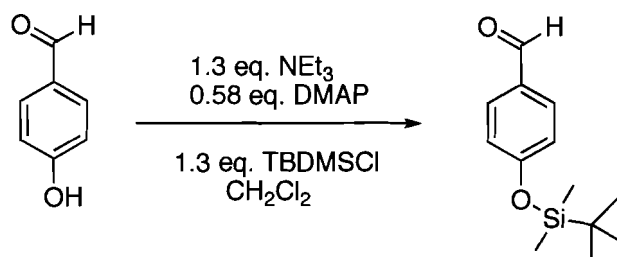
A mixture of vanillin acetate (3.02 g, 15.55 mmol) in CH_3OH (5.04 mL, 124.40 mmol, 8.0 equivalents) and trimethyl orthoformate (2.78 g, 2.55 mL, 23.33 mmol, 8.0 equivalents) was stirred as $\text{Bi}(\text{OTf})_3$ (0.0102 g, 0.01555 mmol, 0.1 mol %) was added to the reaction. The reaction was heated at reflux and progress was followed by TLC (EtOAc/Hexanes, 50/50). After 2 h 5 min the reaction was cooled to room temperature and saturated NaHCO_3 (15 mL) was added and the mixture was stirred for 15 min. The mixture was extracted with ether (40 mL) and the organic layer was washed with H_2O (4x15 mL), saturated NaCl (10 mL) and dried (Na_2SO_4). The solvent was removed on a rotary evaporator to yield 2.23 g (96 %) of a gold colored liquid. ^1H NMR (acetone- d_6): δ 2.23 (s, 3H), 3.32 (s, 6H), 3.85 (s, 3H), 5.37 (s, 1H), 7.01 (m, 3H)

Deprotection of Vanillin Acetate Acetal (ADB2067)



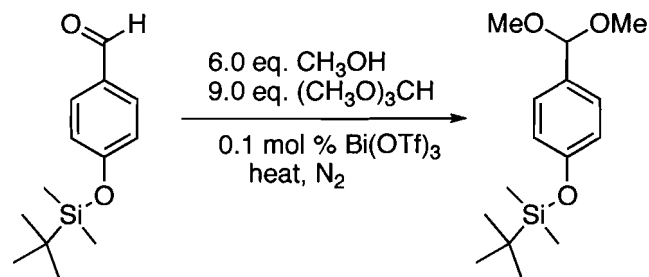
A mixture of vanillin acetate dimethyl acetal (0.2023 g, 0.842 mmol) in H₂O (2.5 mL) was stirred as BiI₃ (0.00497 g, 0.00842 mmol, 1.0 mol %) was added resulting in a light red mixture. The reaction was heated at reflux and progress was followed by GC. After 1 hour 15 min, EtOAc (40 mL) was added to the reaction mixture and the biphasic mixture was filtered through a bed of celite. The aqueous layer from the biphasic filtrate was extracted with EtOAc (20 mL) and the combined organic layers were washed with 5 % aqueous Na₂S₂O₃ (10 mL), 10 % aqueous Na₂CO₃ (10 mL), saturated NaCl (10 mL), and dried (Na₂SO₄). The solvents were removed on a rotary evaporator to yield 0.1362 g (83 %) of a white solid. ¹H NMR: δ 2.33 (s, 3 H), 3.89 (s, 3 H), 7.21 (d, 1 H, *J* = 7.9 Hz), 7.44 (d, 2 H, *J* = 8.2 Hz), 9.29 (s, 1 H). ¹³C NMR (10 peaks): δ 20.6, 51.1, 110.8, 123.4, 124.7, 135.2, 144.8, 151.9, 168.3, 191.1; GC: > 99 % Product (ret. Time= 7.135 min)

Synthesis of ADB2089



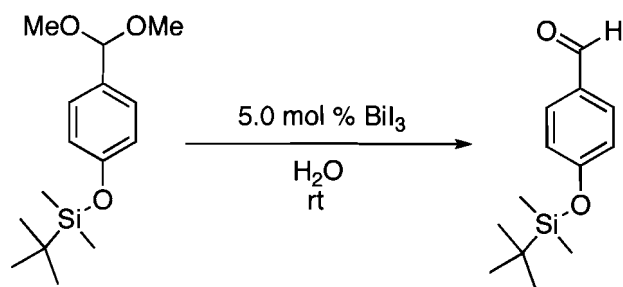
An ice cold solution of 4-hydroxybenzaldehyde (2.07 g, 16.951 mmol) in CH_2Cl_2 (30 mL) was stirred, as triethylamine (2.23 g, 3.07 mL, 22.04 mmol, 1.3 equivalents), DMAP (1.20 g, 9.832 mmol, 0.58 equivalents) and TBDMS-Cl (3.32 g, 22.04 mmol, 1.3 equivalents) were added sequentially. Reaction progress was followed by TLC (EtOAc/Hexane, 10/90). After 2 h the reaction was diluted with CH_2Cl_2 (40 mL) and washed with H_2O (6x15 mL), saturated NaCl (10 mL), and dried (Na_2SO_4). The solvent was removed on a rotary evaporator to yield 3.72 g of a yellow liquid. The crude product was purified using flash chromatography on 80 g of silica (EtOAc/Hexane, 5/95) to yield 2.92 g (73 %) of a gold colored liquid. ^1H NMR: δ 0.23 (s, 6 H), 0.98 (s, 9 H), 6.94 (d, 2H, $J=8.42$ Hz), 7.79 (d, 2 H, $J=8.64$ Hz), 9.87 (s, 1H).

Synthesis of ADB2099



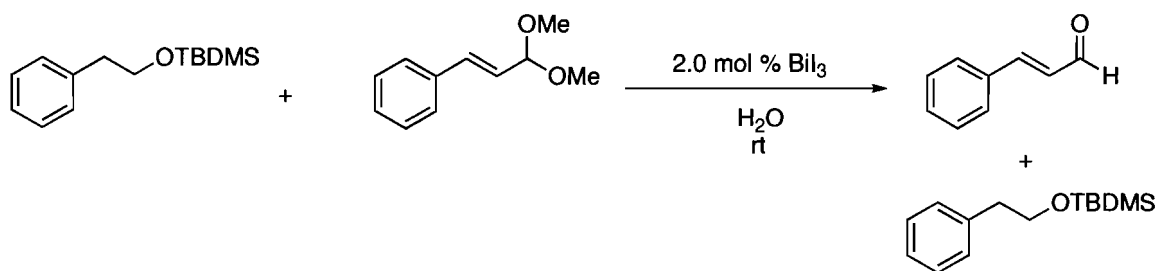
A solution of 4-(*tert*-butyldimethylsilyloxy)benzaldehyde (2.12 g, 8.97 mmol) in CH_3OH (2.18 mL, 53.8 mmol, 6.0 equivalents) and trimethyl orthoformate (7.61 g, 7.85 mL, 71.76 mmol, 8.0 equivalents) was stirred as $\text{Bi}(\text{OTf})_3$ (0.006 g, 8.97×10^{-3} mmol, 0.1 mol %) was added to the reaction. The reaction was heated at reflux and reaction progress was followed by NMR. After 16 h 20 min the reaction was cooled to room temperature and saturated NaHCO_3 (15 mL) was added and the mix was stirred for 15 min. The mixture was extracted with ether (40 mL) and the organic layer was washed with H_2O (4x15 mL), saturated NaCl (10 mL) and dried (Na_2SO_4). The solvent was removed on a rotary evaporator to yield 2.23 g (96 %) of a gold colored liquid. ^1H NMR (acetone- d_6): δ 0.23 (s, 6 H), 1.00 (s, 9 H), 3.24 (s, 6 H), 5.34 (s, 1 H), 6.88 (m, 2 H), 7.31 (m, 2 H). ^{13}C NMR (9 peaks) (acetone- d_6): δ -4.6, 18.0, 25.3, 51.8, 102.8, 119.9, 128.1, 131.7, 155.7.

Deprotection of *t*-butyl(4-(dimethoxymethyl)phenoxy)dimethylsilane (ADB2117)



A mixture *t*-butyl(4-(dimethoxymethyl)phenoxy)dimethylsilane (0.5056 g, 1.79 mmol) in H_2O (5.0 mL) was stirred as BiI_3 (0.0528 g, 0.0895 mmol, 5.0 mol %) was added and reaction progress was followed by ^1H NMR. After 7 h 35 min, EtOAc (40 mL) was added to the reaction mixture and the biphasic mixture was filtered through a bed of celite. The aqueous layer from the biphasic filtrate was extracted with EtOAc (20 mL) and the combined organic layers were washed with 5 % aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL), aqueous 2.0 M NaOH (2x10 mL), saturated NaCl (10 mL), and dried (Na_2SO_4). The solvents were removed on a rotary evaporator to yield 0.2920 g (70 %) of a clear liquid. ^1H NMR: δ 0.23 (s, 6 H), 0.95 (s, 9 H), 6.95 (d, 2 H, J = 8.7 Hz), 7.79 (d, 2 H, J = 8.4 Hz), 9.87 (s, 1H); ^{13}C NMR (9 peaks): δ -4.5, 18.1, 25.4, 25.6, 120.4, 130.2, 131.8, 161.4, 190.8.

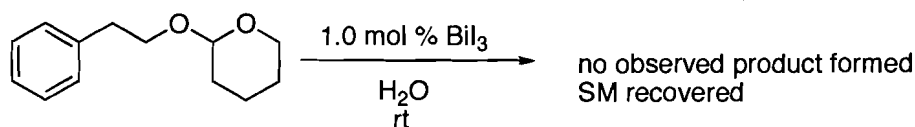
Control Experiment: (ADB2127)



A mixture of cinnamaldehyde dimethyl acetal (0.3087 g, 1.732 mmol), and *t*-butyldimethyl(phenethoxy)silane (0.3087 g, 1.306 mmol) in H₂O (5.0 mL) was stirred as BiI₃ (0.0179 g, 1.0 mol %) was added and reaction progress was followed by TLC (EtOAc/Hexanes, 30/70). After 1 h 45 min, EtOAc (40 mL) was added to the reaction mixture and the biphasic mixture was filtered through a bed of celite. The aqueous layer from the biphasic filtrate was extracted with EtOAc (20 mL) and the combined organic layers were washed with 5 % aqueous Na₂S₂O₃ (10 mL), aqueous 2.0 M NaOH (2x10 mL), saturated NaCl (10 mL), and dried (Na₂SO₄). The solvents were removed on a rotary evaporator to yield 0.4836 g (90 %) of a clear liquid. The product was determined to be a mixture of cinnamaldehyde and *t*-butyldimethyl(phenethoxy)silane. ¹H NMR (cinnamaldehyde): δ 6.79 (m, 2H), 7.48 (m, 5 H), 9.74 (d, 1 H, *J* = 7.6 Hz) ¹H NMR (*t*-butyldimethyl(phenethoxy)silane): δ 0.02 (s, 6H), 0.88 (s, 9 H), 2.05 (m, 2H), 2.78 (m, 2H), 7.48 (m, 5 H)

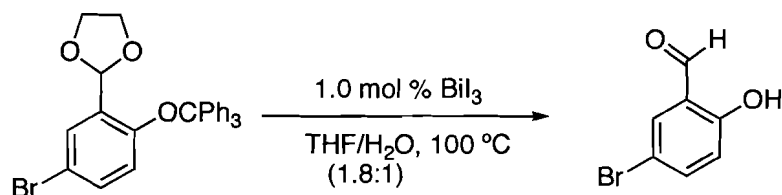
Control Experiment (KKT1043)

(Reaction Performed by Kendall Tasche)



A mixture 2-phenethoxytetrahydro-2H-pyran (0.3039 g, 1.473 mmol) in H₂O (3.0 mL) was stirred as BiI₃ (0.0098 g, 0.01473 mmol, 1.0 mol %) was added and reaction progress was followed by TLC. After 3 h EtOAc (40 mL) was added to the reaction mixture and the biphasic mixture was filtered through a bed of celite. The aqueous layer from the biphasic filtrate was extracted with EtOAc (20 mL) and the combined organic layers were washed with 5 % aqueous Na₂S₂O₃ (10 mL), 10 % aqueous Na₂CO₃ (10 mL), saturated NaCl (10 mL), and dried (Na₂SO₄). The solvents were removed on a rotary evaporator to yield 0.2889 g (95 %) of a yellow liquid that was determined to be the starting material. ¹H NMR: δ 1.54 (m, 6H), 2.91 (m, 2H), 3.86 (m, 4H), 4.59 (m, 1H), 7.25 (m, 5H).

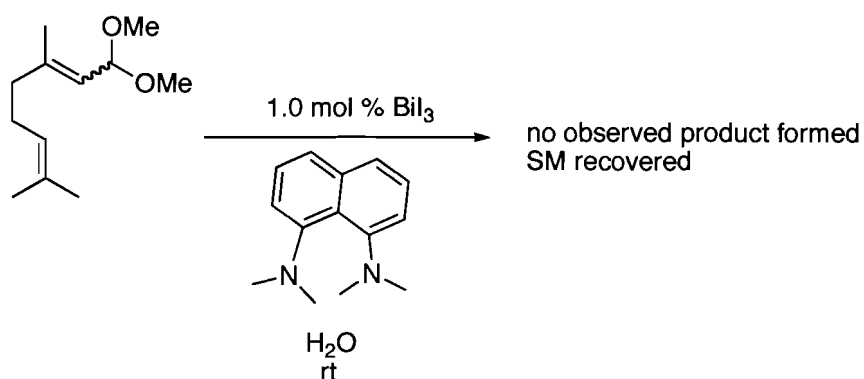
Deprotection of 2-(5-bromo-2-(trityloxy)phenyl)-1,3-dioxolane (ADB2129)



A solution of 2-(5-bromo-2-(trityloxy)phenyl)-1,3-dioxolane (2.01 g, 4.124 mmol) in THF/H₂O (20.0 mL, 9:5, v:v) was stirred as BiI₃ (0.024 g, 0.04121 mmol, 1.0

mol %) was added. The reaction was heated at reflux and reaction progress was followed by ^1H NMR. After 23 h, the THF was removed on a rotary evaporator and EtOAc (40 mL) was added to the concentrated product and the biphasic mixture was filtered through a bed of celite. The aqueous layer from the biphasic filtrate was extracted with EtOAc (20 mL) and the combined organic layers were washed with aqueous 2.0 M NaOH (40 mL). The aqueous layer was collected and cooled while aqueous 6.0 M HCl was added (pH \sim 1). The resulting precipitate was collected by suction filtration to yield 0.788 g (95 %) white solid. ^1H NMR: δ 7.66 (m, 3 H), 9.82 (s, 1 H), 10.92 (s, 1 H); ^{13}C NMR (7 peaks): δ 111.3, 119.7, 121.6, 127.8, 135.5, 139.6, 160.4

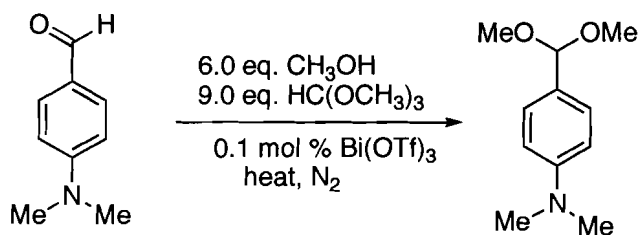
Control Experiment: (ADB2135)



A mixture of citral dimethy acetal (0.1027 g, 0.05179 mmol), proton sponge[™] (1,8-bis(dimethylamino)naphthalene) (0.0166 g, 0.0777 mmol) in H_2O (10 mL) was stirred as BiI_3 (0.0031 g, 5.179 μmol , 1.0 mol %) was added. Reaction progress was followed by TLC (EtOAc/Hexane, 10/90). After 1 h 30 min, EtOAc (40 mL) was added to the reaction mixture and the biphasic mixture was filtered through a bed of celite. The aqueous layer from the biphasic filtrate was extracted with EtOAc (15 mL) and the combined organic layers were washed with 5 % aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL), 10 % aqueous

Na₂CO₃ (10 mL), saturated NaCl (10 mL), and dried (Na₂SO₄). The solvents were removed on a rotary evaporator to yield 0.7505 g (95 %) of a clear liquid that was determined to be the starting material. ¹H NMR: δ 1.69 (m, 9 H), 2.05 (m, 4 H), 3.21 (s, 6 H), 5.01 (d, 1 H, *J*=6.2 Hz), 5.19 (m, 2 H),

Protection of 4-(dimethylamino)-benzaldehyde (ADB2123)



A solution of 4-(dimethylamino)-benzaldehyde (8.50 g, 0.570 mol) in CH₃OH (10.95 g, 13.84 mL, 0.3418 mol, 6.0 equivalents) and trimethylorthoformate (48.39 g, 50.0 mL, 0.456 mol, 8.0 equivalents) was stirred as Bi(OTf)₃ (0.0102 g, 0.01555 mmol, 0.1 mol %) was added to the reaction. The reaction was heated at reflux and progress was followed by ¹H NMR. After 24 h another portion of HC(OCH₃)₃ (9.13 g, 9.4 mL, 0.086 mol, 1.5 equivalents) was added to the reaction. After 26 h 30 min the reaction was cooled to room temperature and saturated NaHCO₃ (15 mL) was added and the mix was stirred for 15 min. The mixture was extracted with ether (40 mL) and the combined organic layers were washed with H₂O (4x15 mL), saturated NaCl (10 mL) and dried (Na₂SO₄). The solvent was removed on a rotary evaporator to yield 9.93 g (89 %) of a brown oil. ¹H NMR (acetone-d₆): δ 2.92 (s, 6H), 3.23 (s, 6H), 5.30 (s, 1H), 6.72 (m, 2H), 7.23 (m, 2H)

References

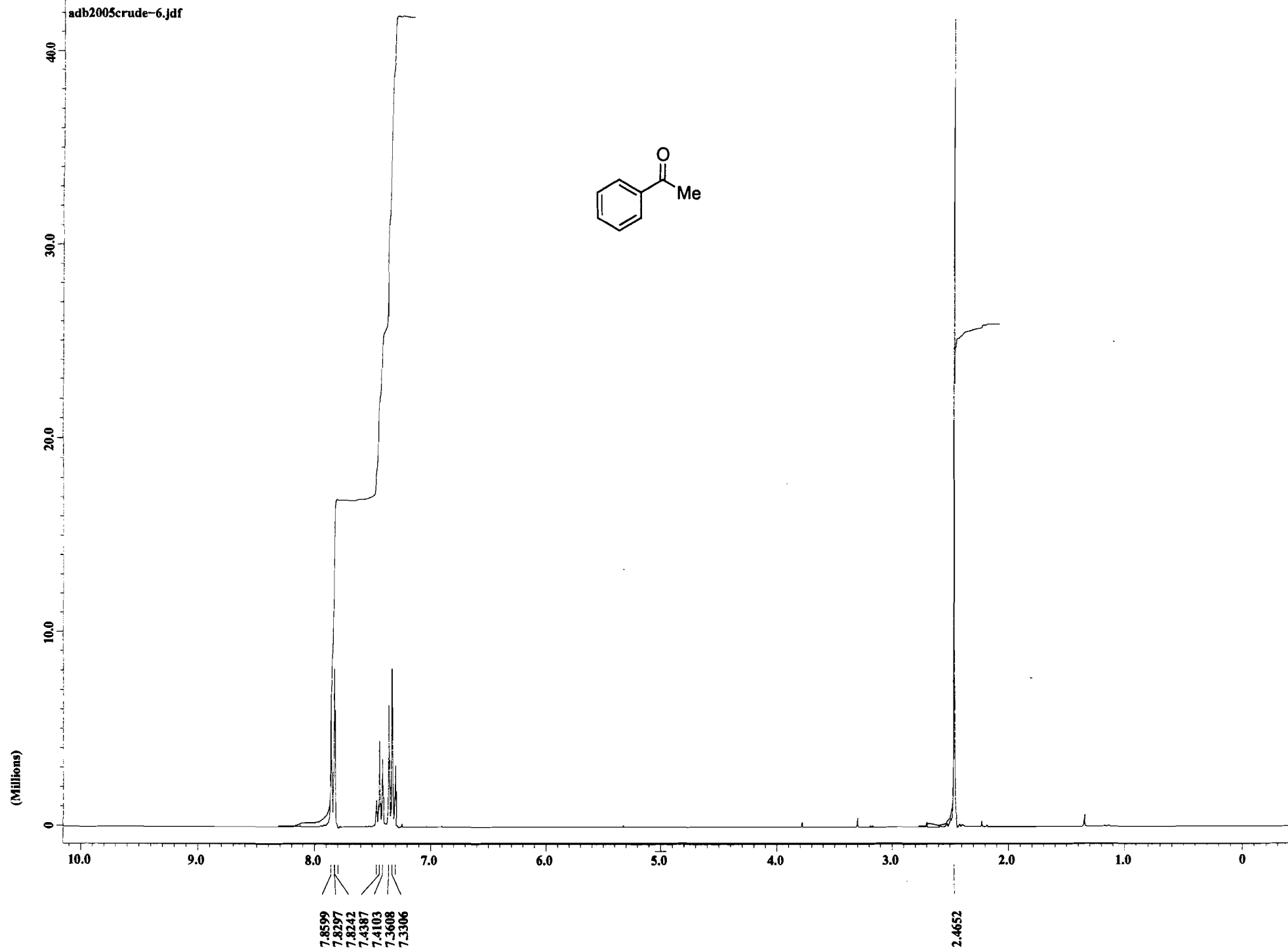
1. (a) EPA, Pollution Prevention Act of 1990, Web Page, <http://www.epa.gov/oppt/p2home/pubs/p2policy/act1990.htm> (b) The Pollution Prevention Act of 1990, codified as 42 U. S. C. 13101-13109 (c) Office of Pollution Prevention and Toxics (1996). 1994 Toxics Release Inventory, Public Data Release, Executive Summary, June, EPA-745-S-96-001, U. S. Environmental Agency, Washington, DC.
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Appendix:

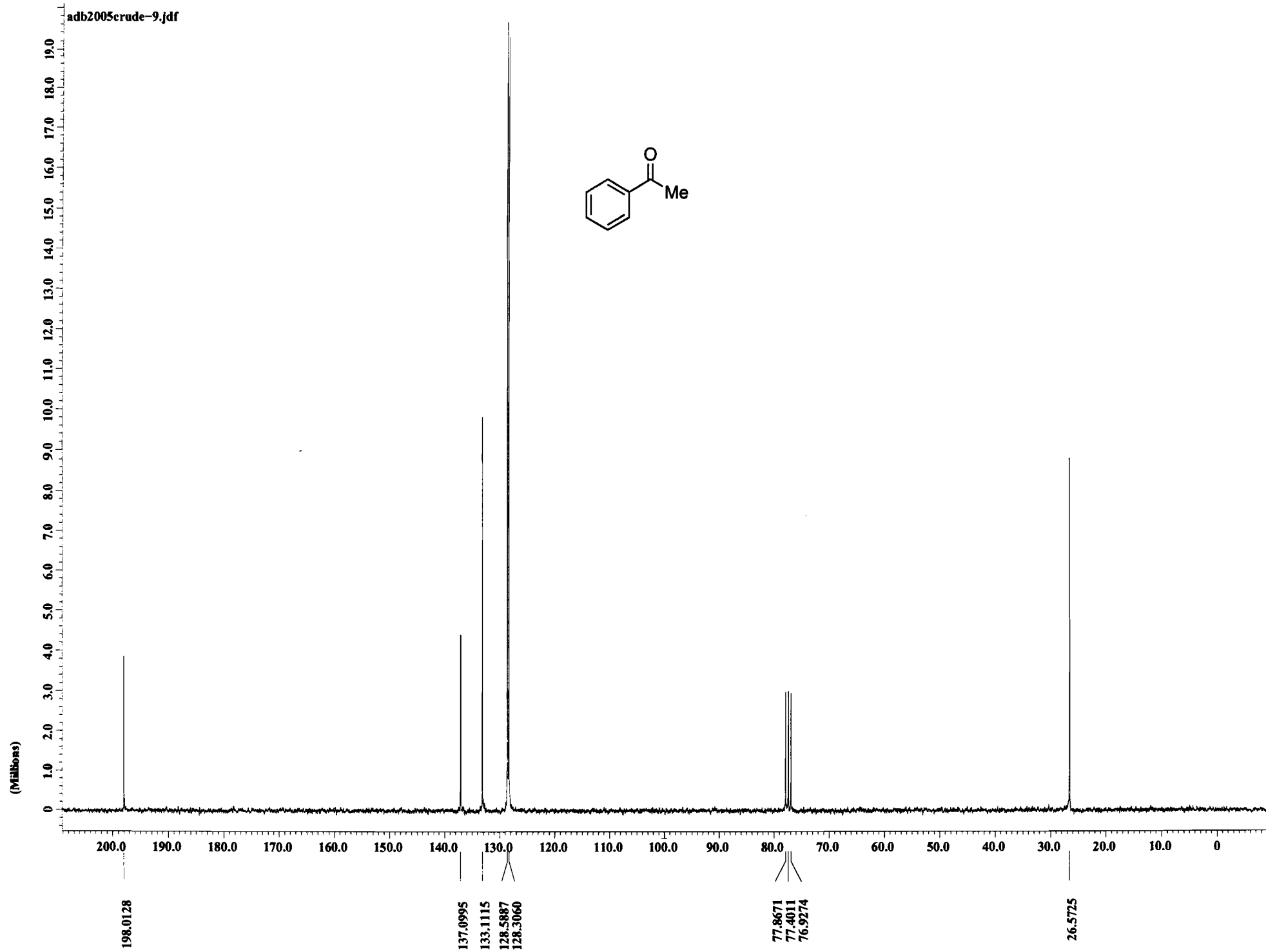
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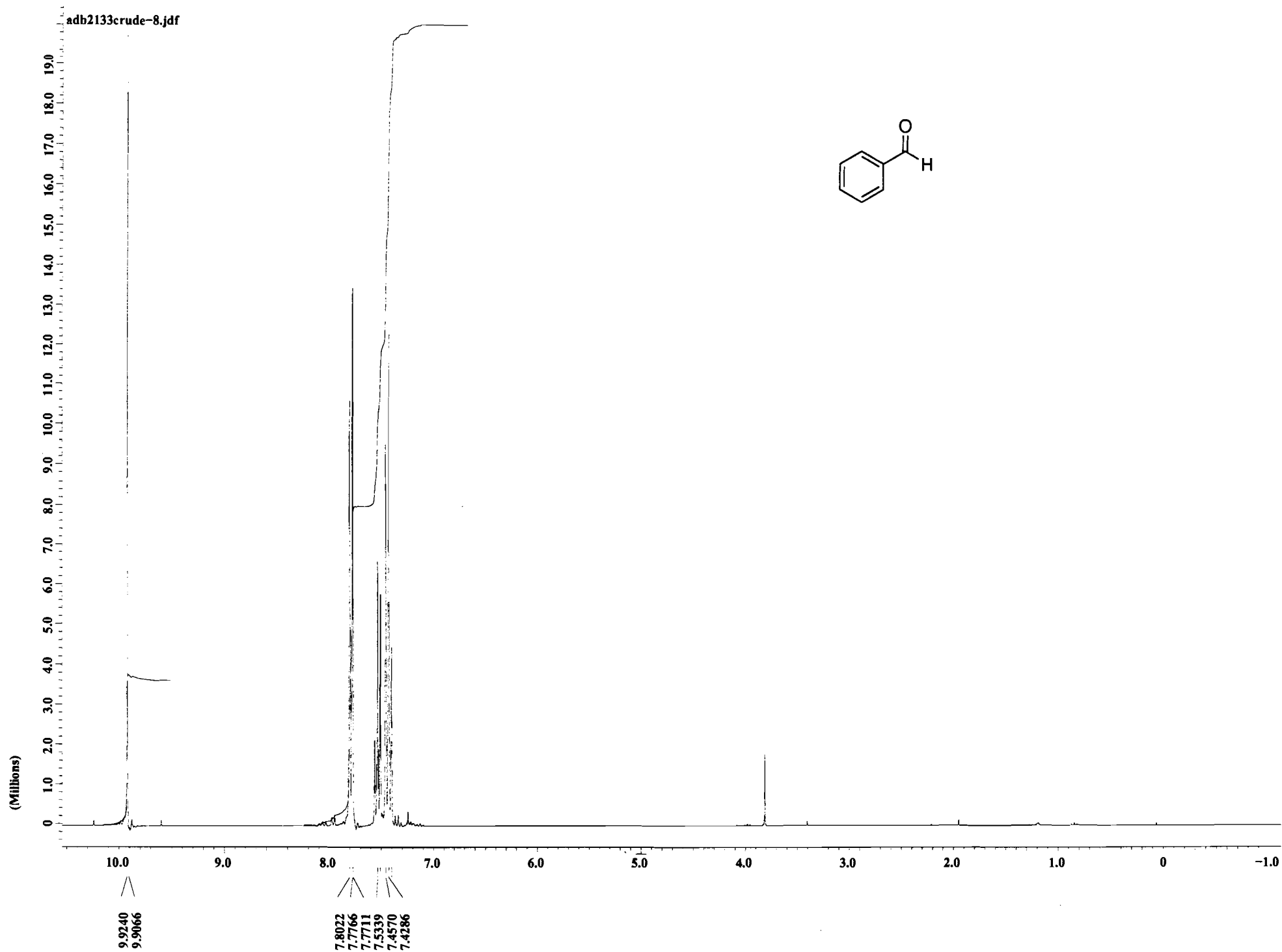


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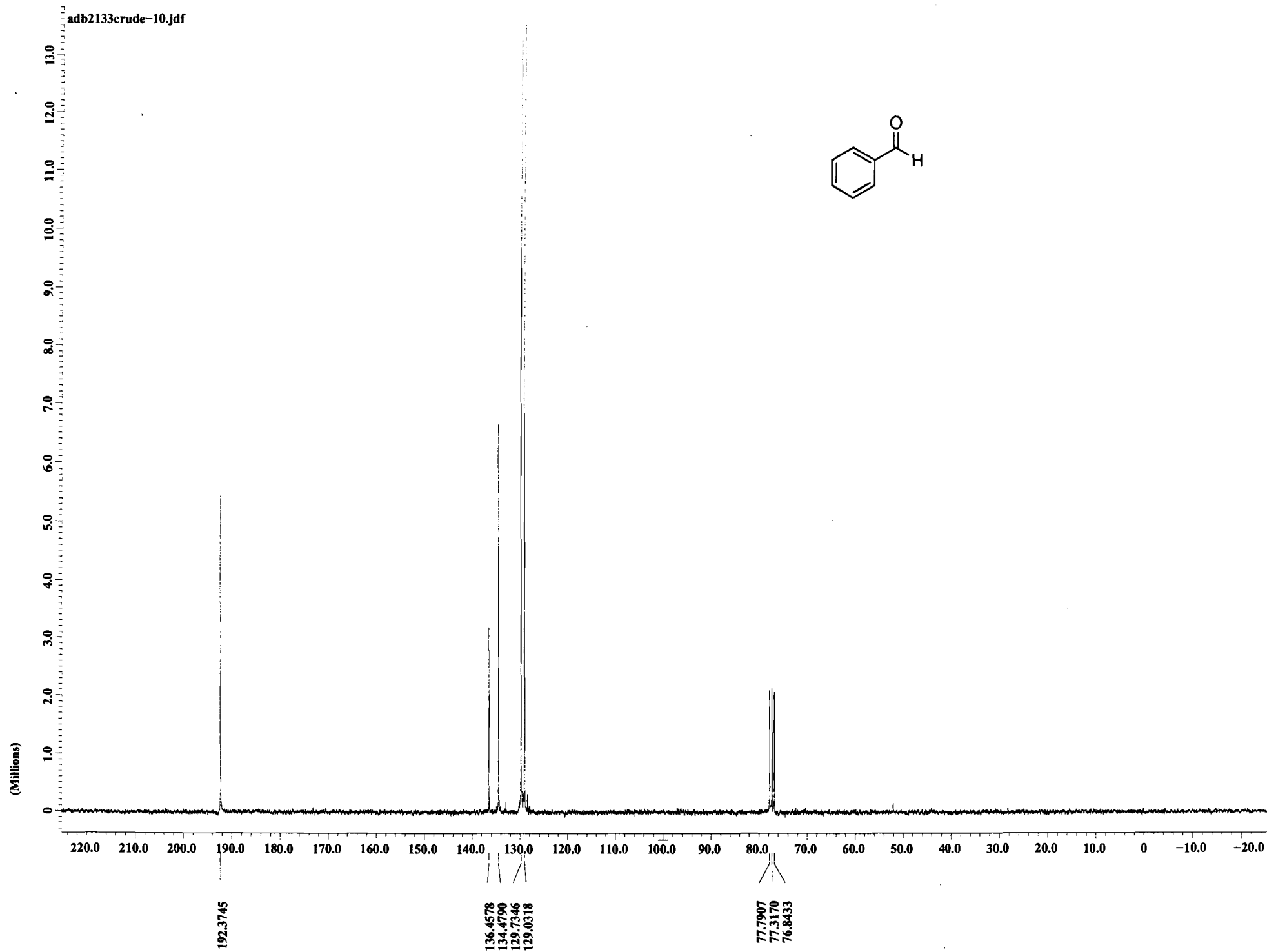


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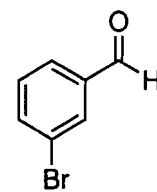
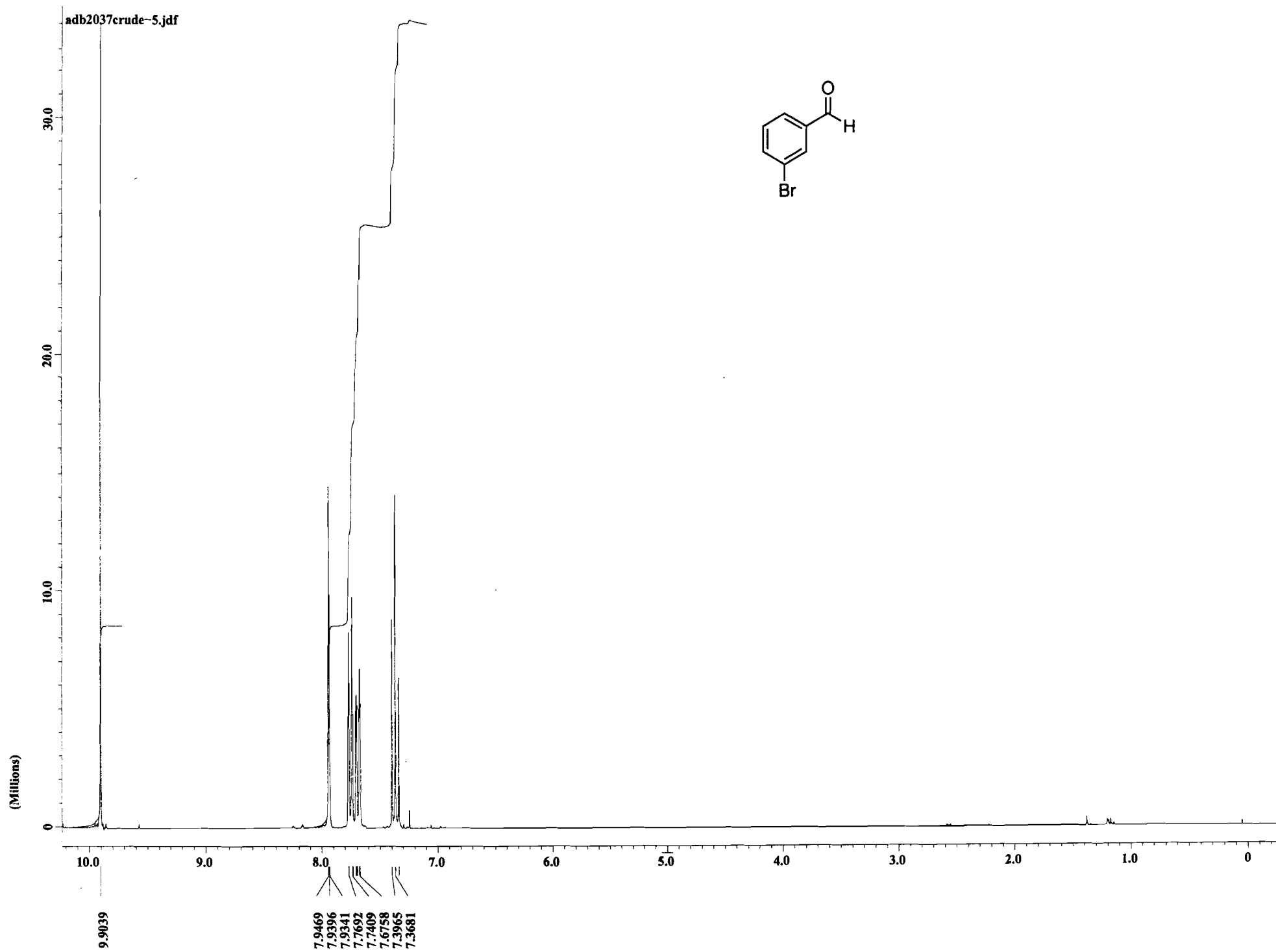


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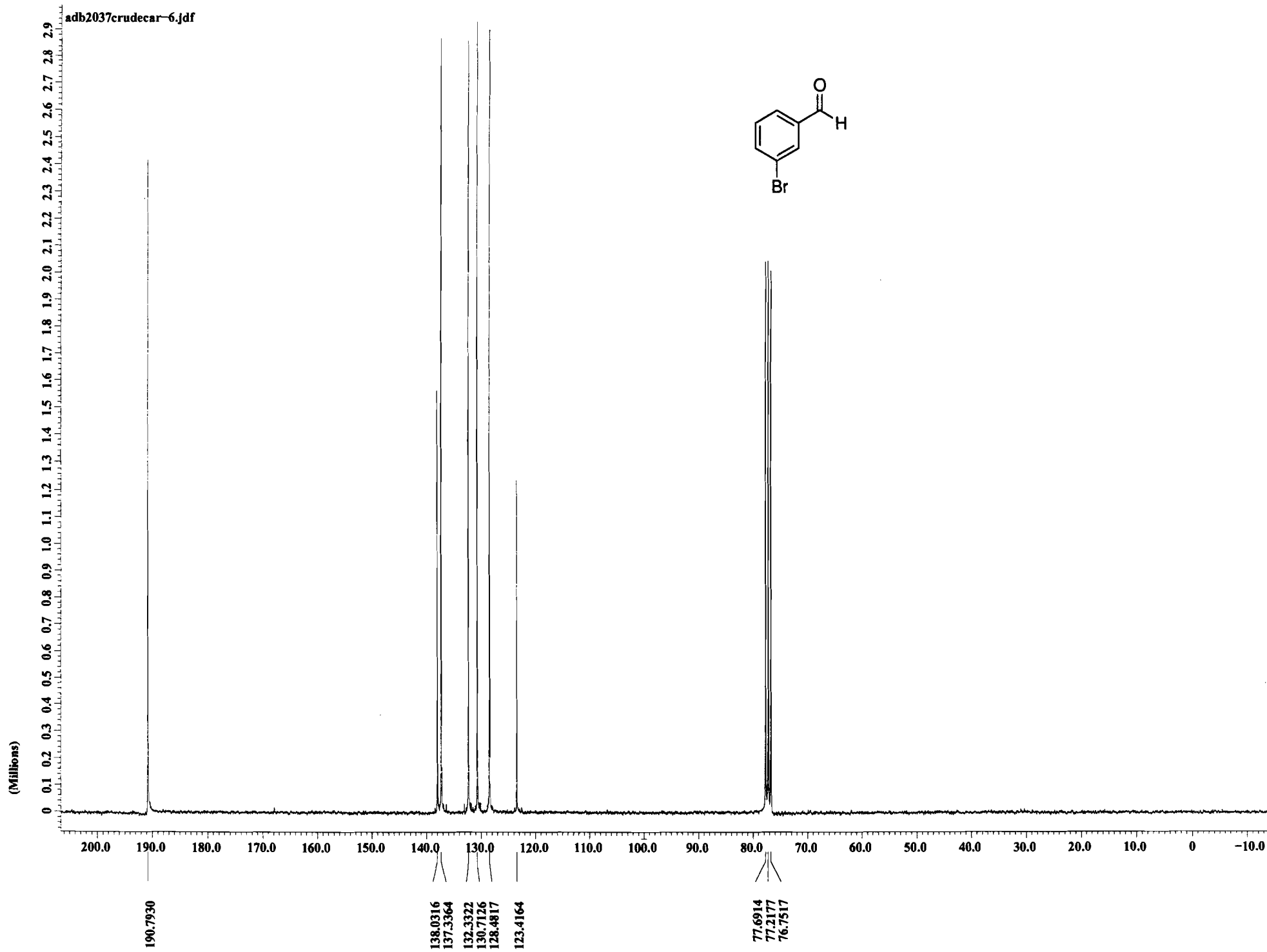


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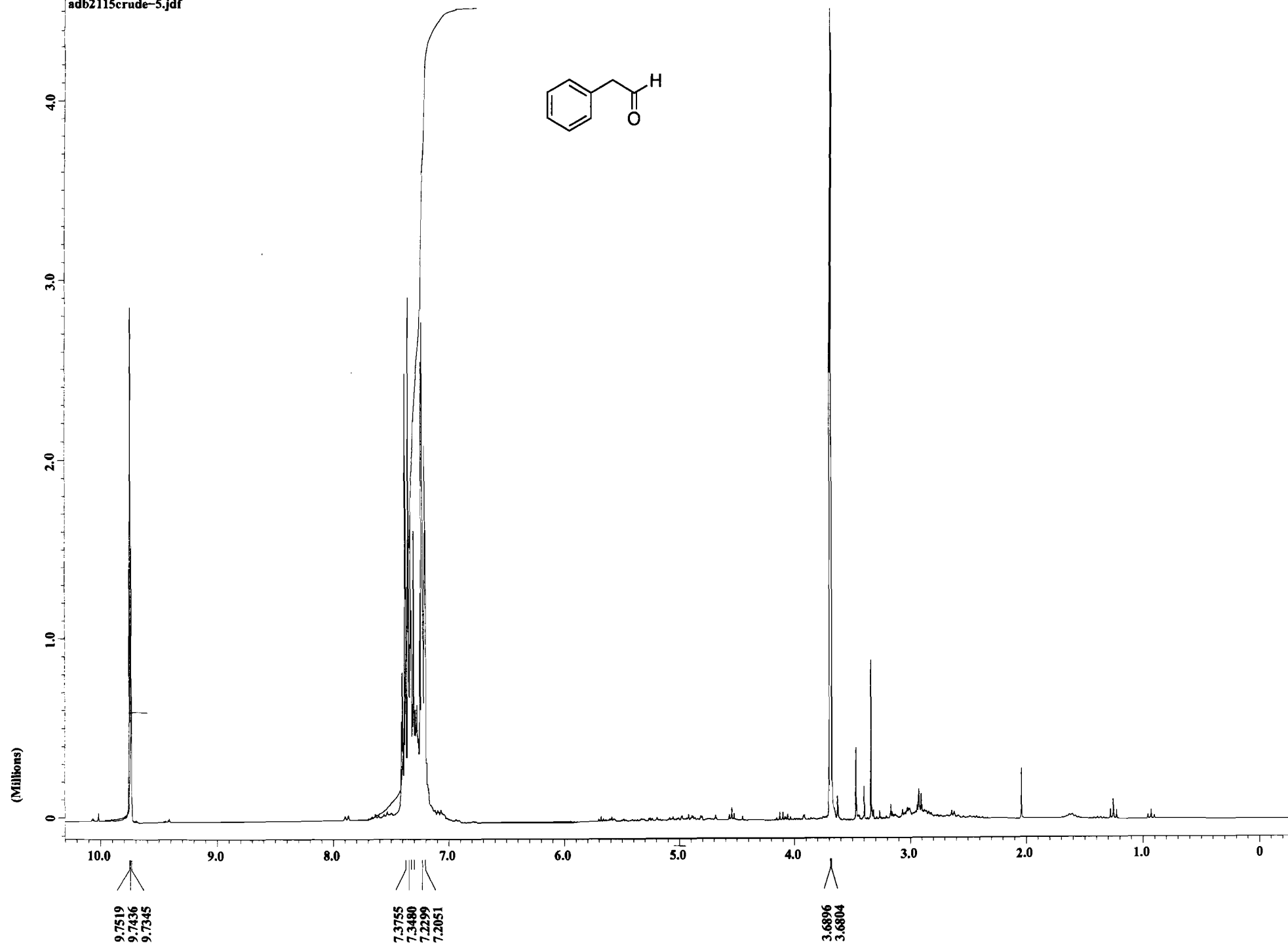
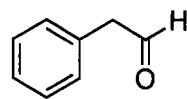
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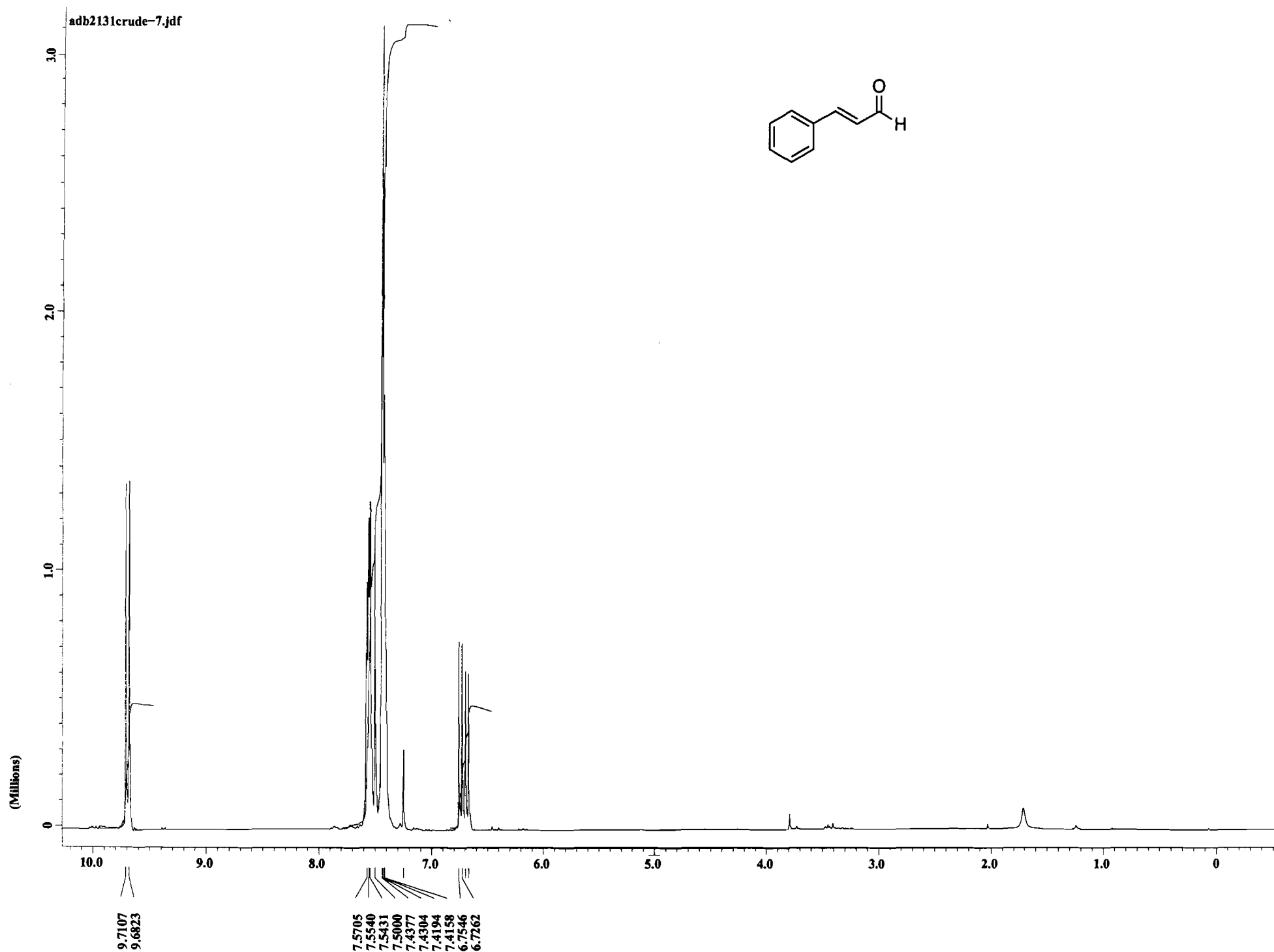
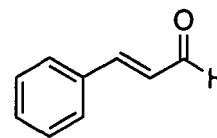
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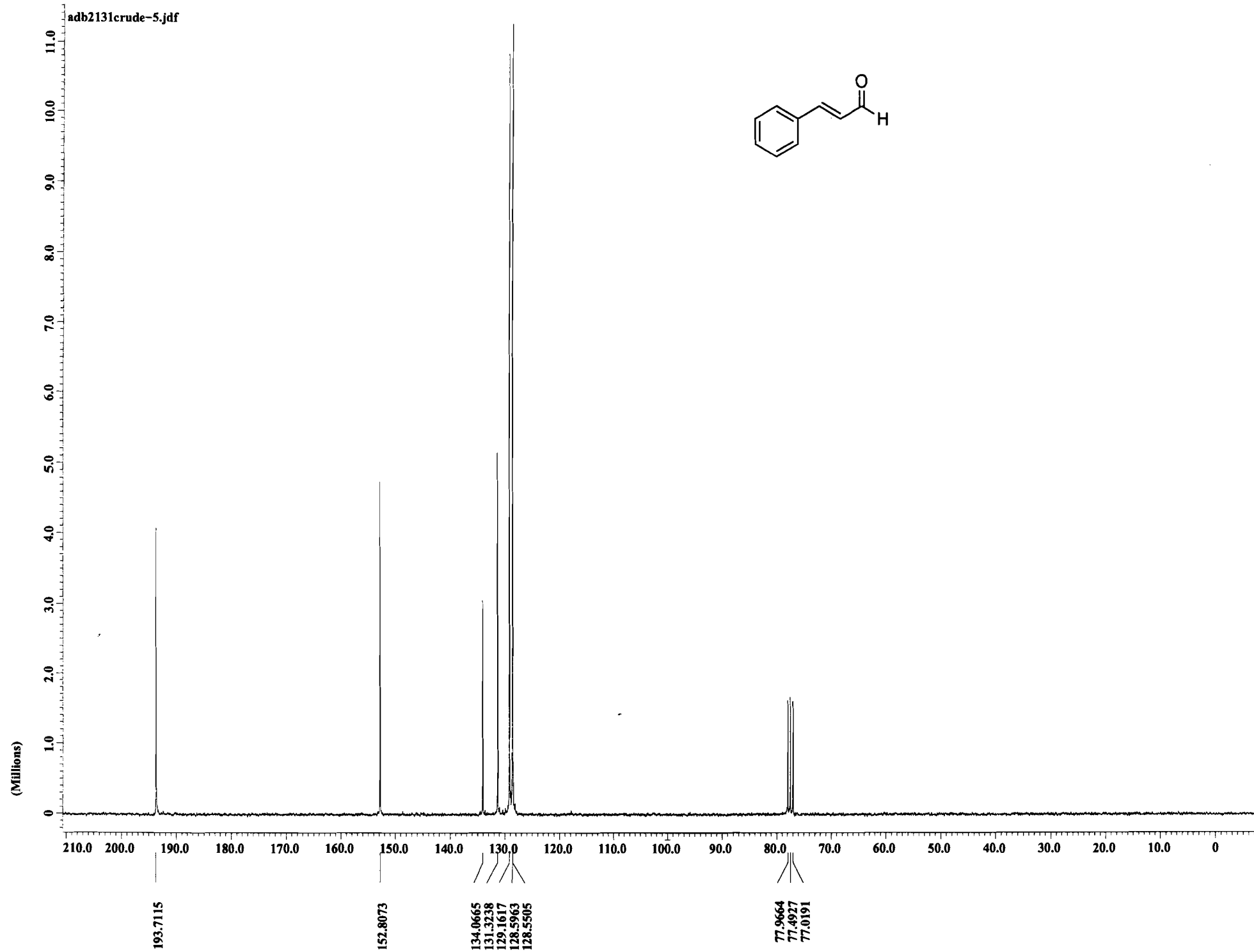


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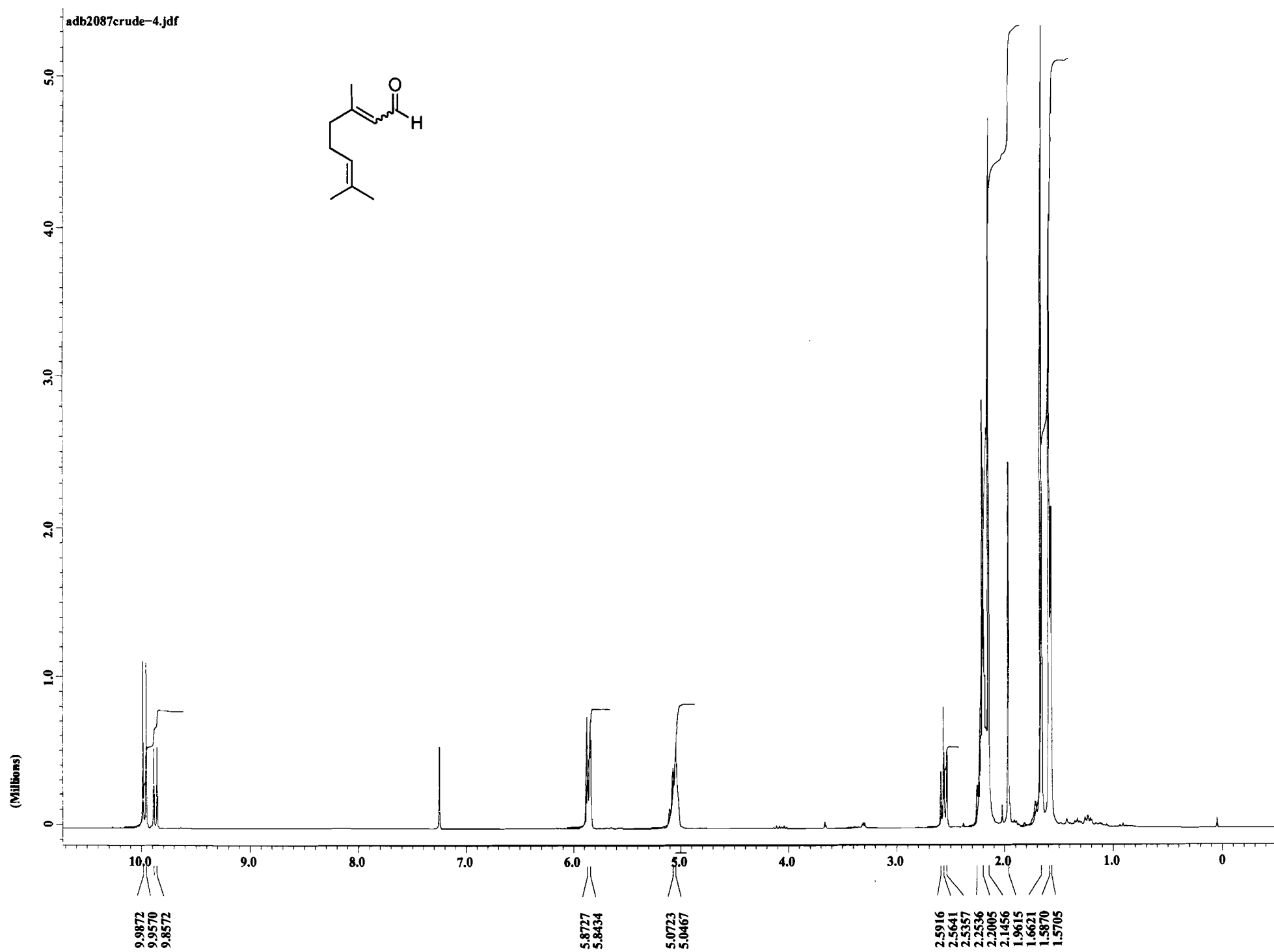


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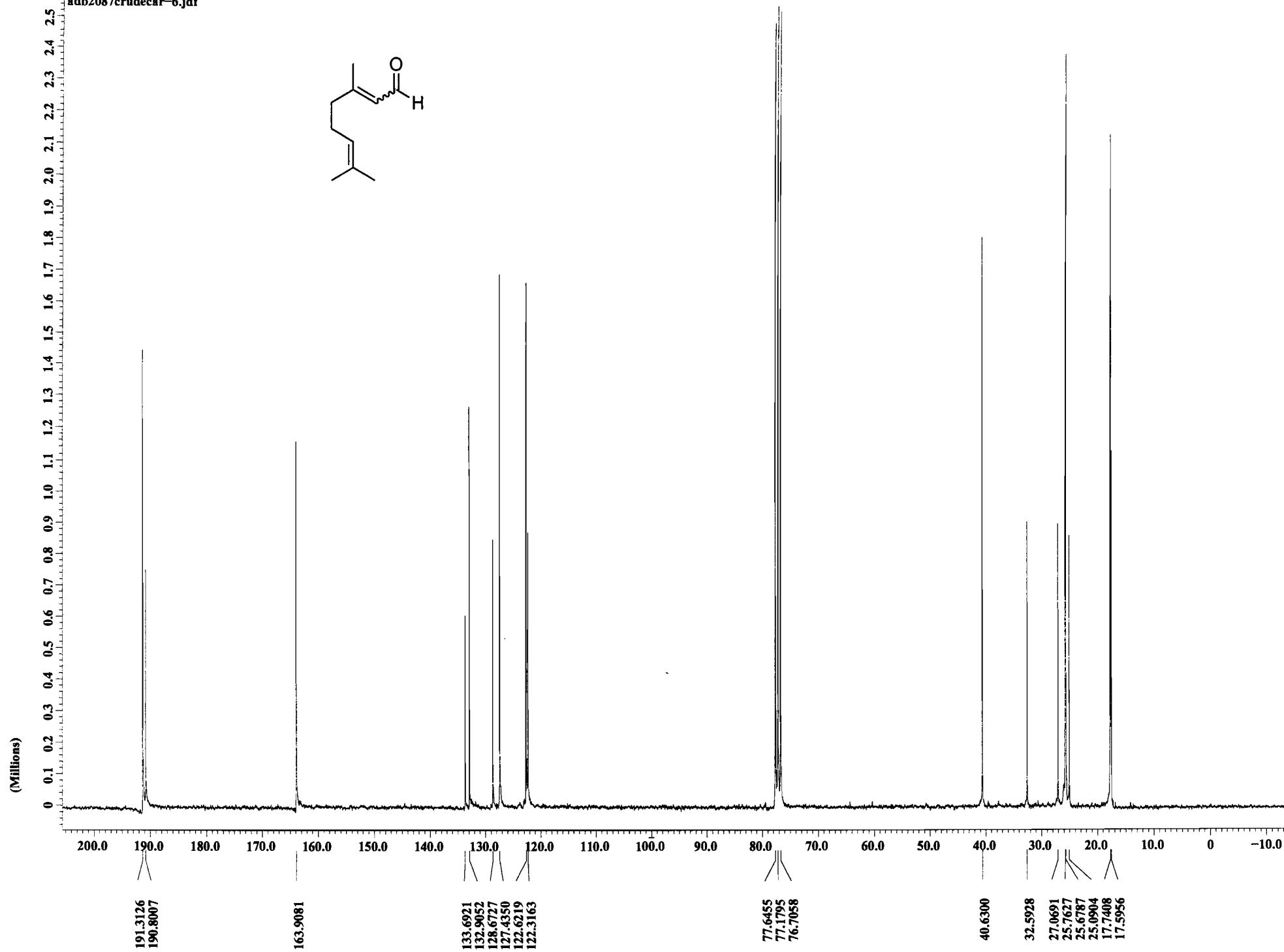


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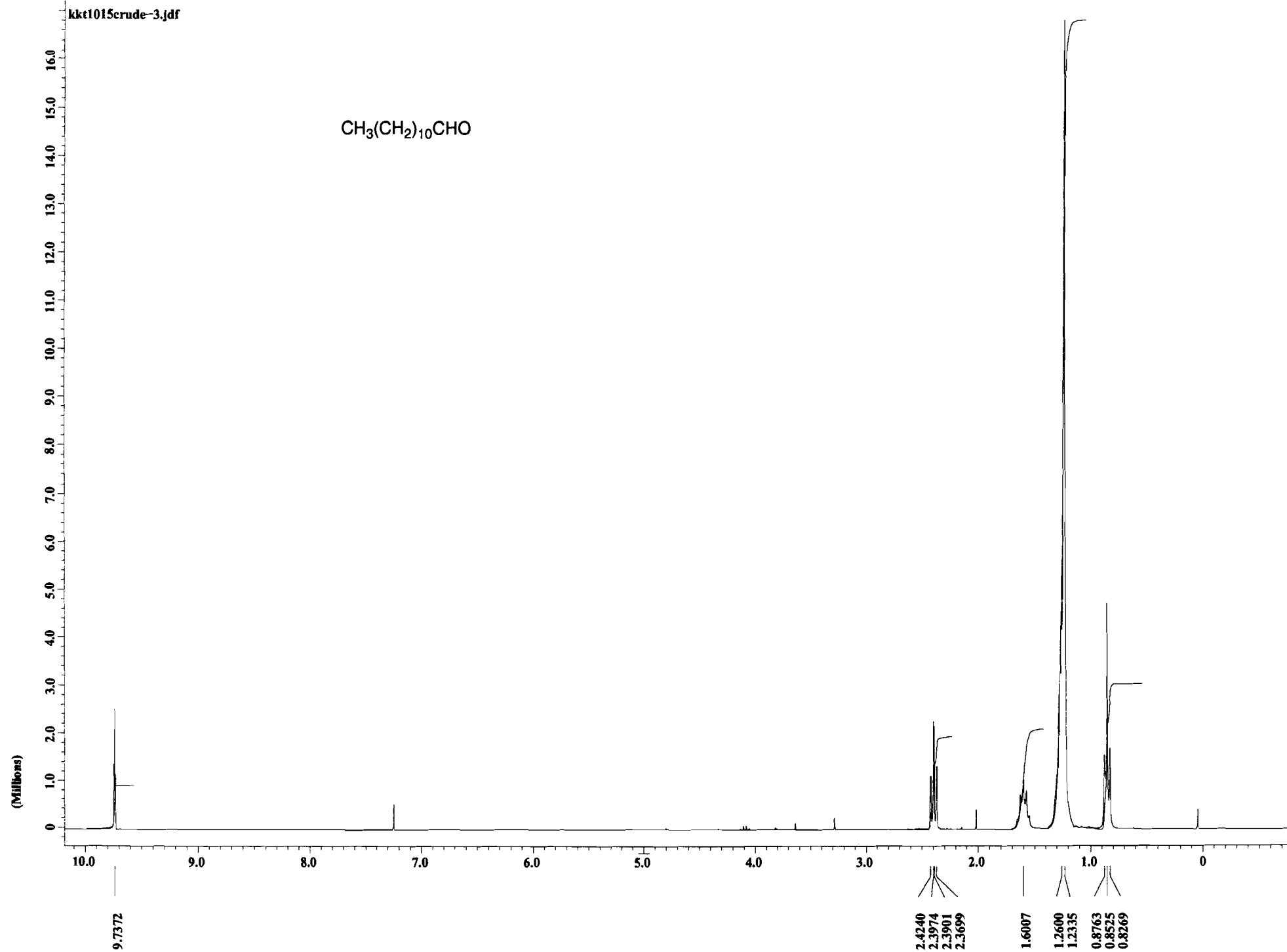
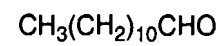
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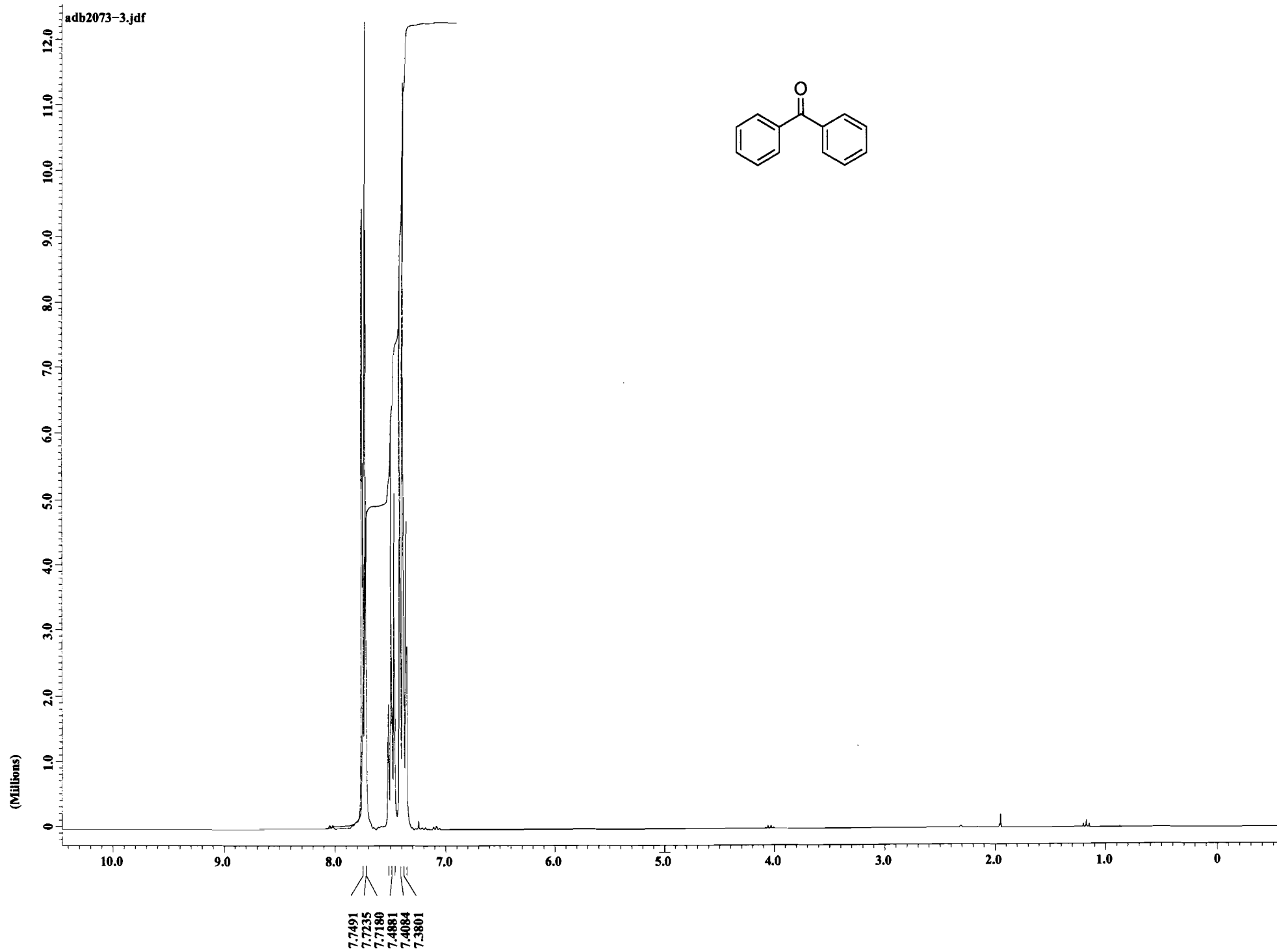


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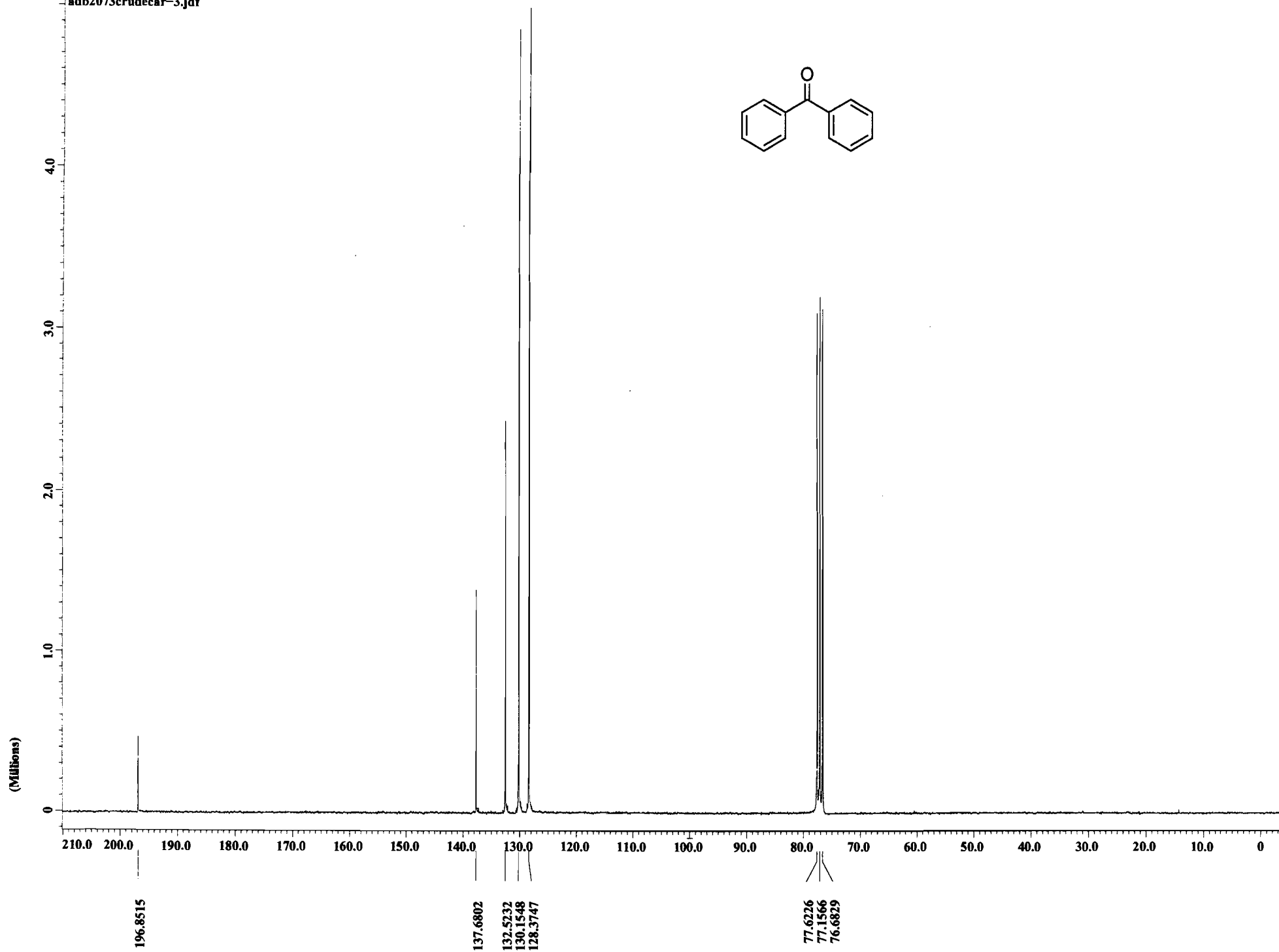
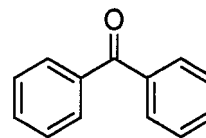
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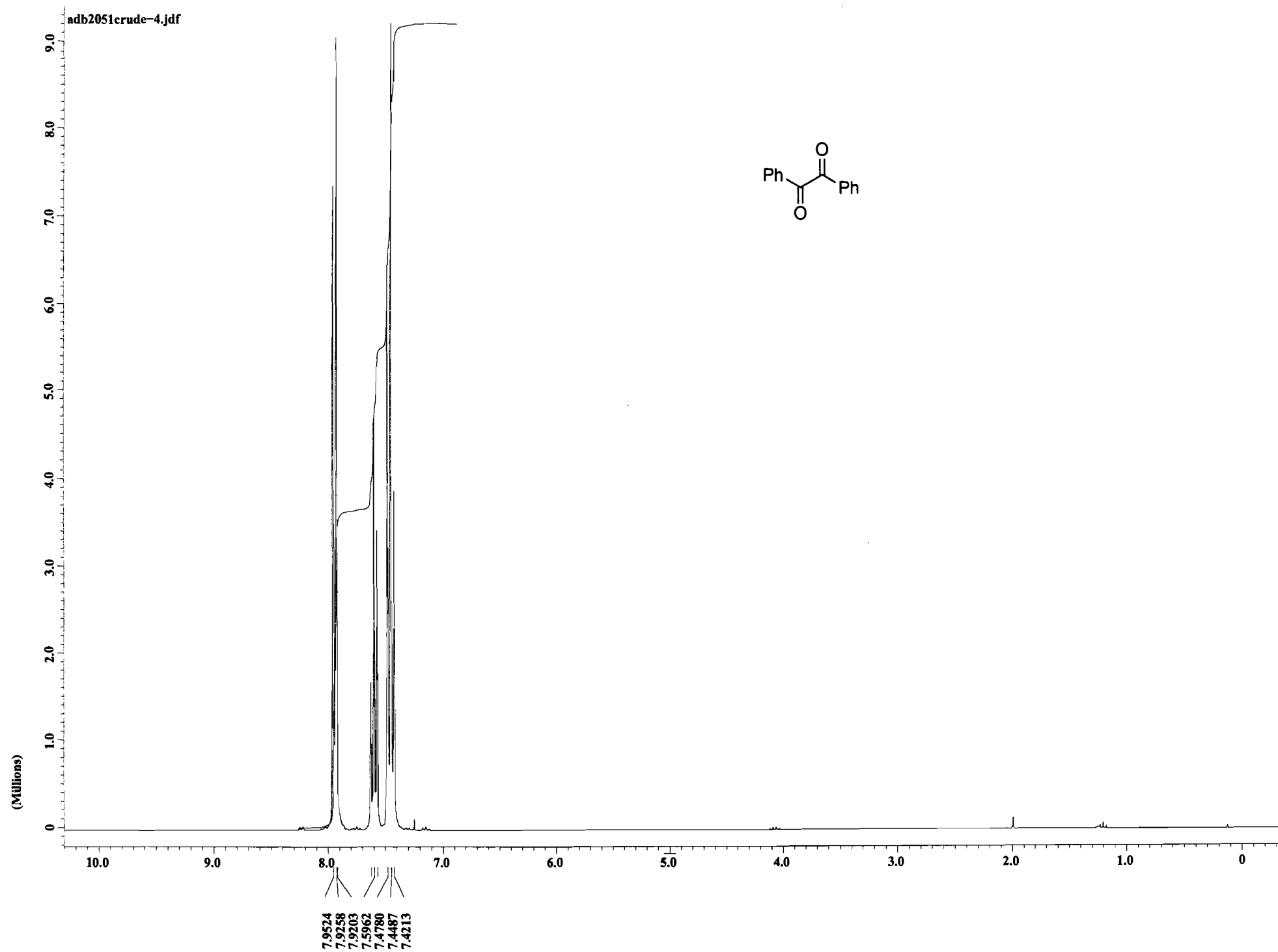


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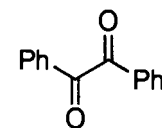
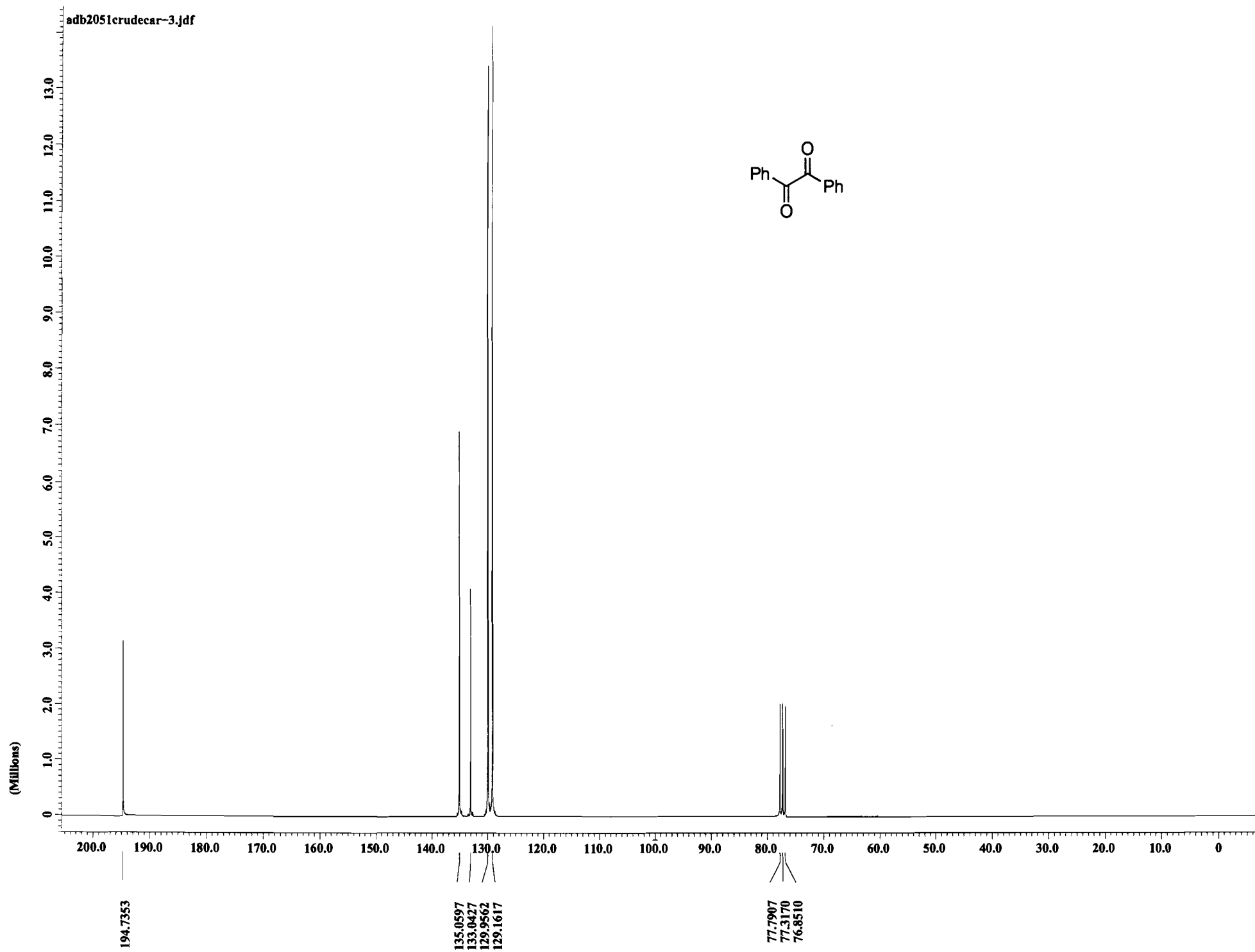


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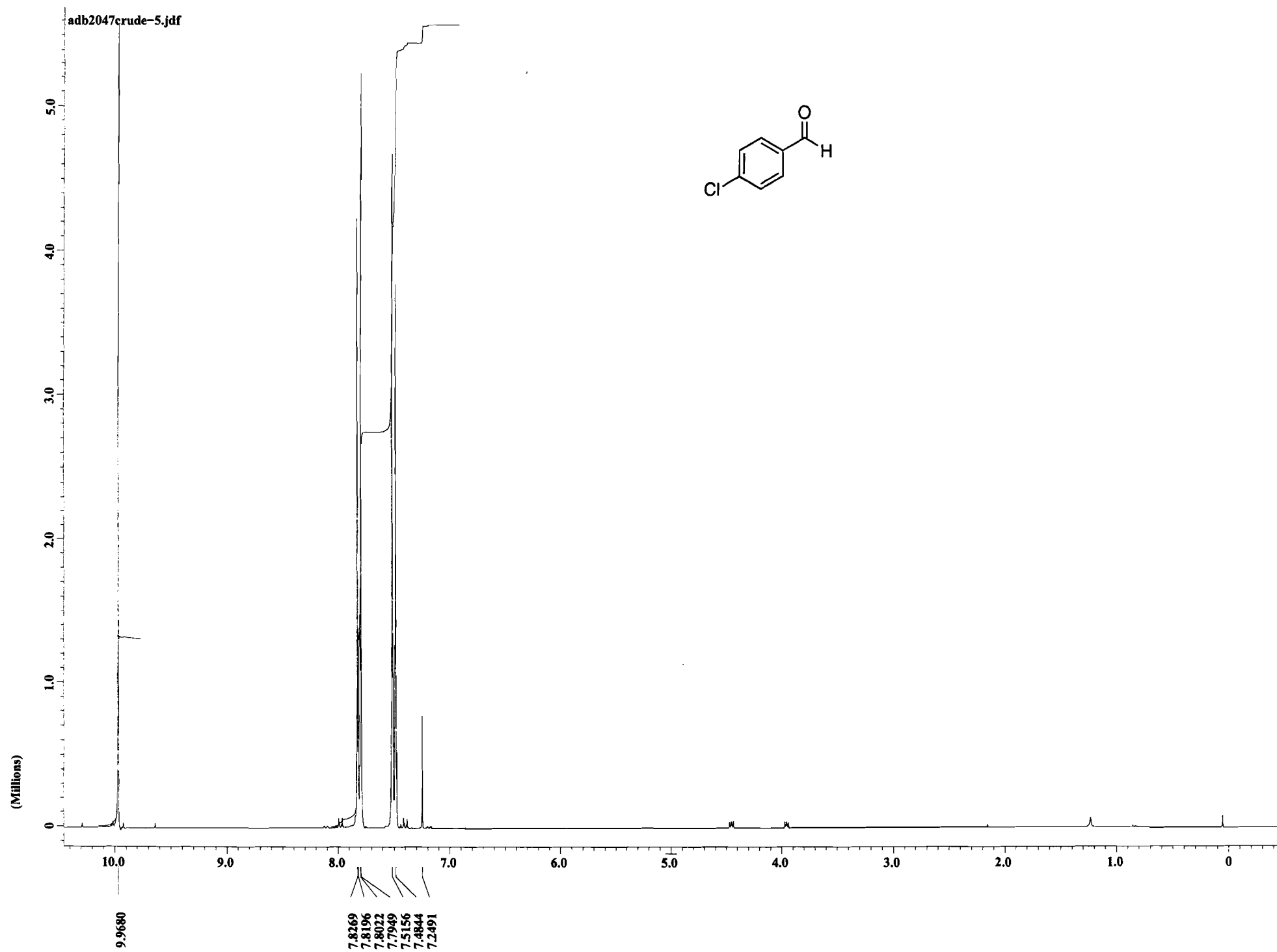
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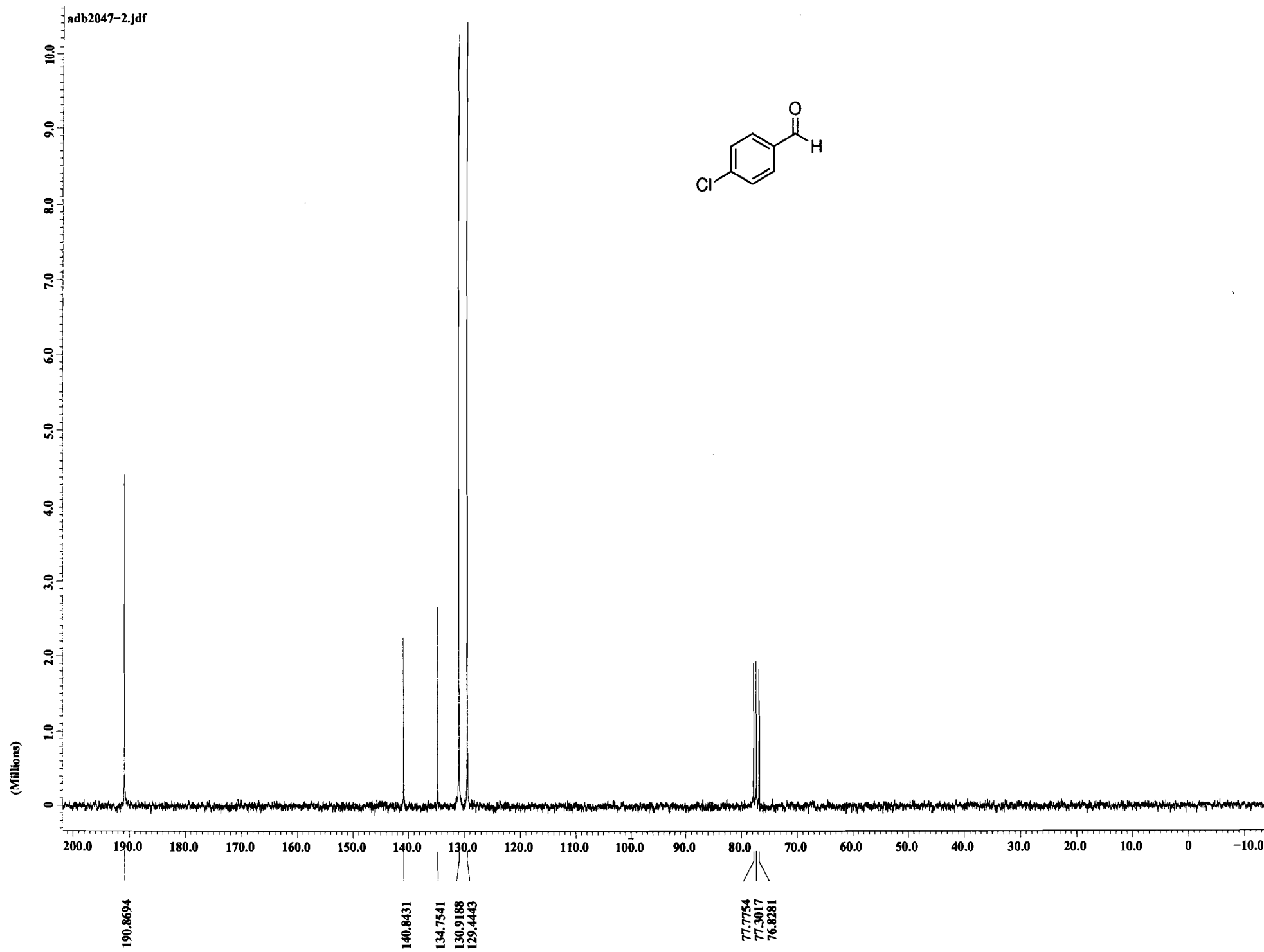
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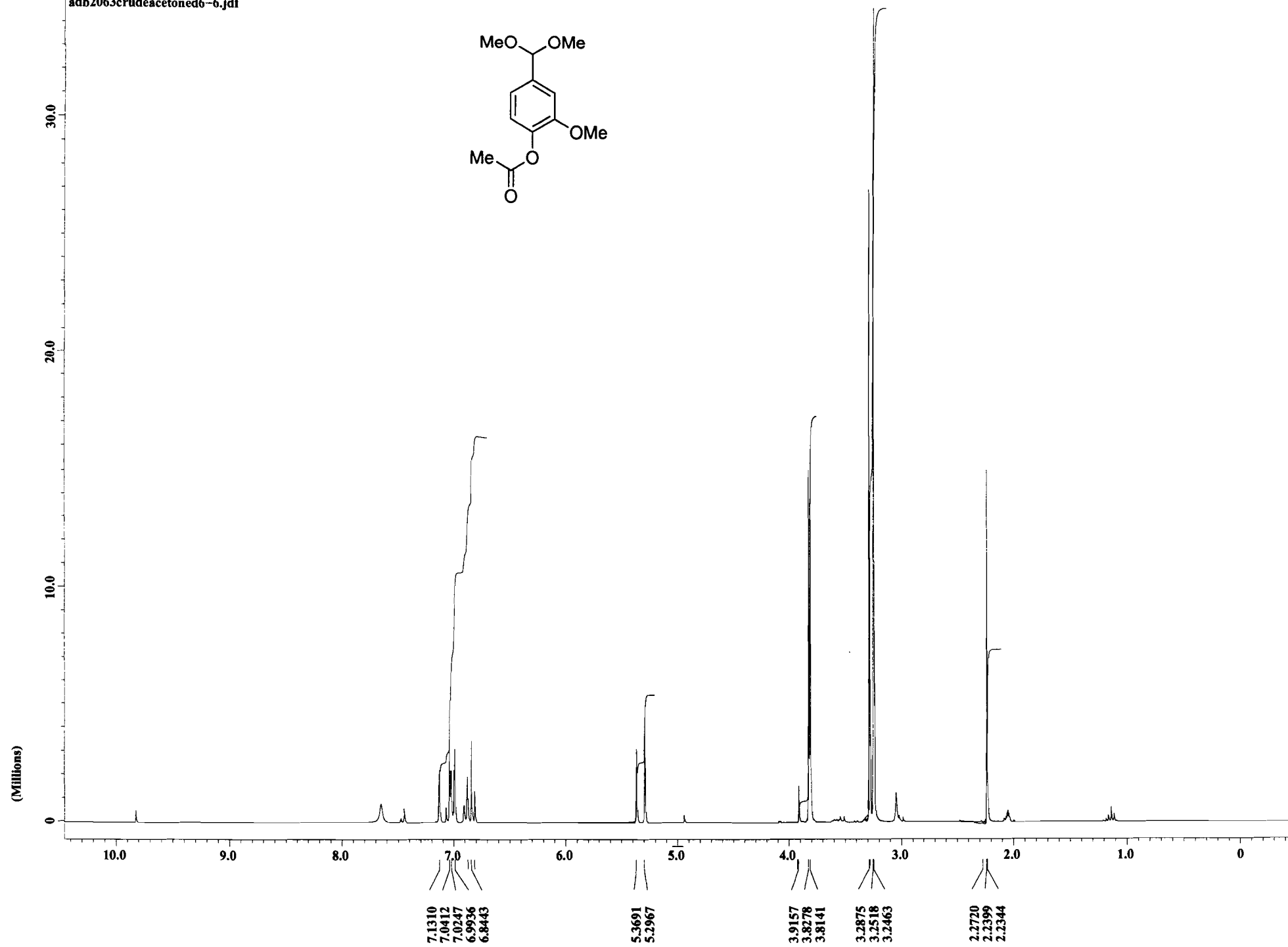


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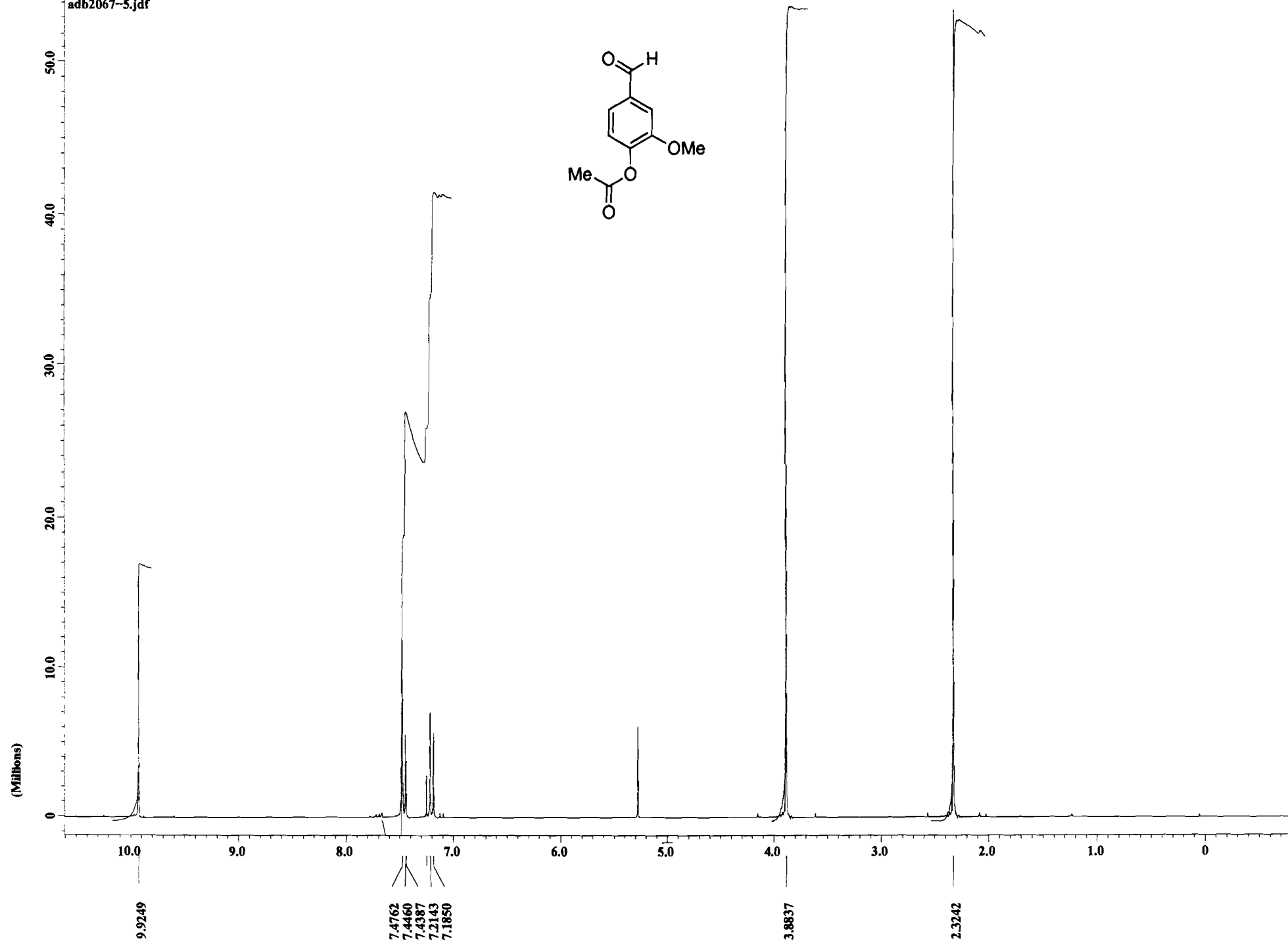
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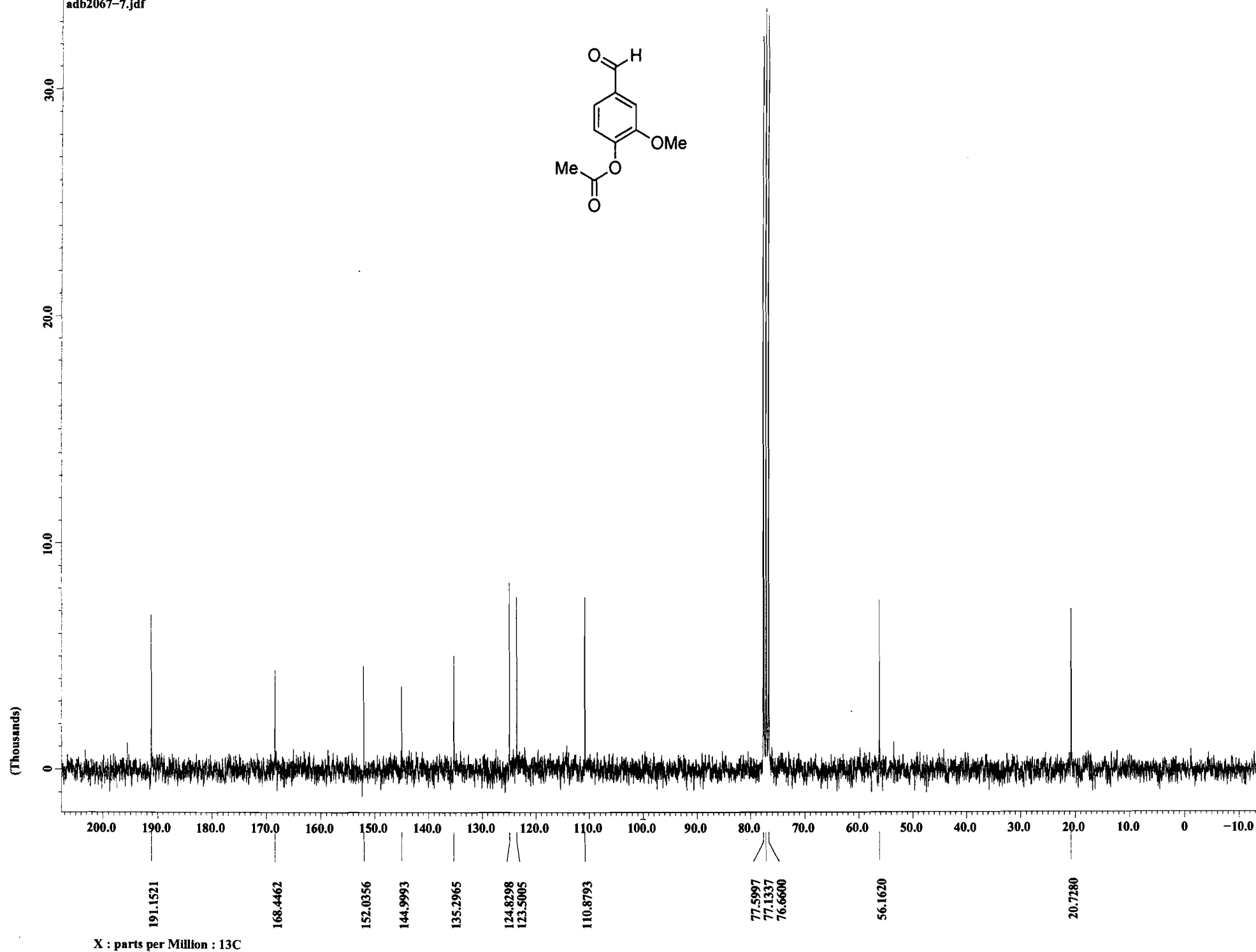
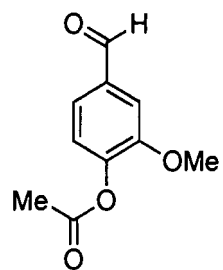


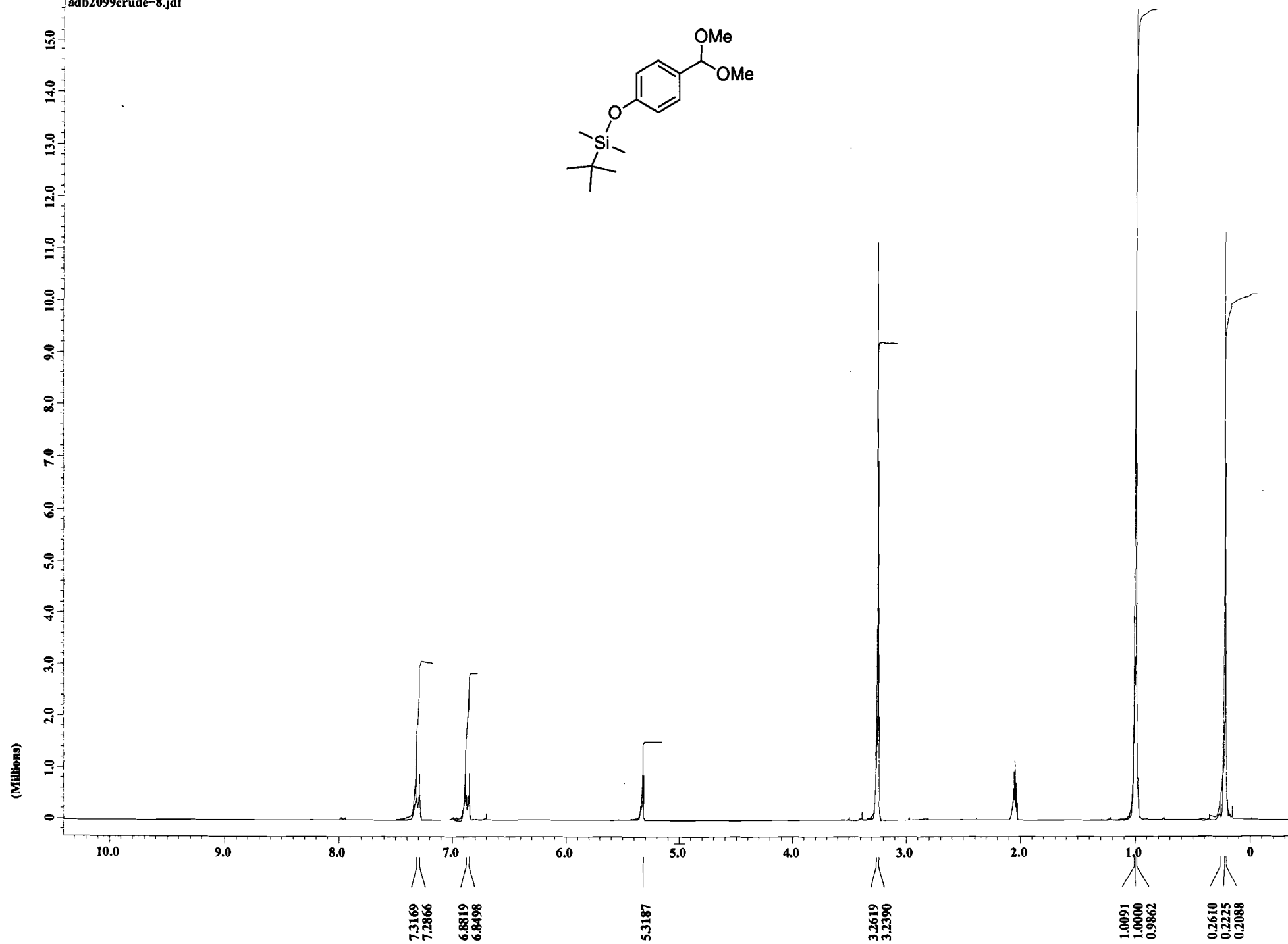
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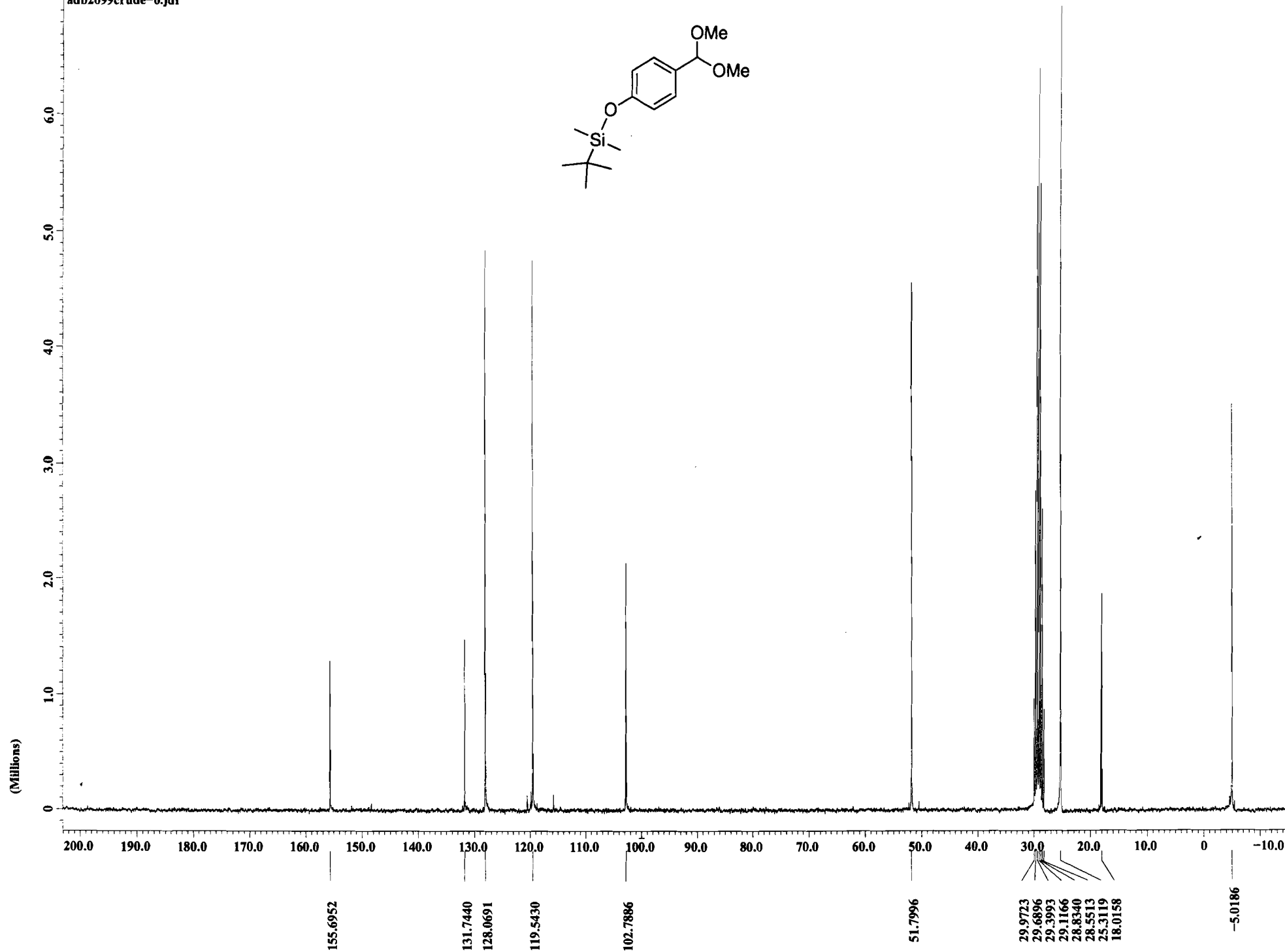
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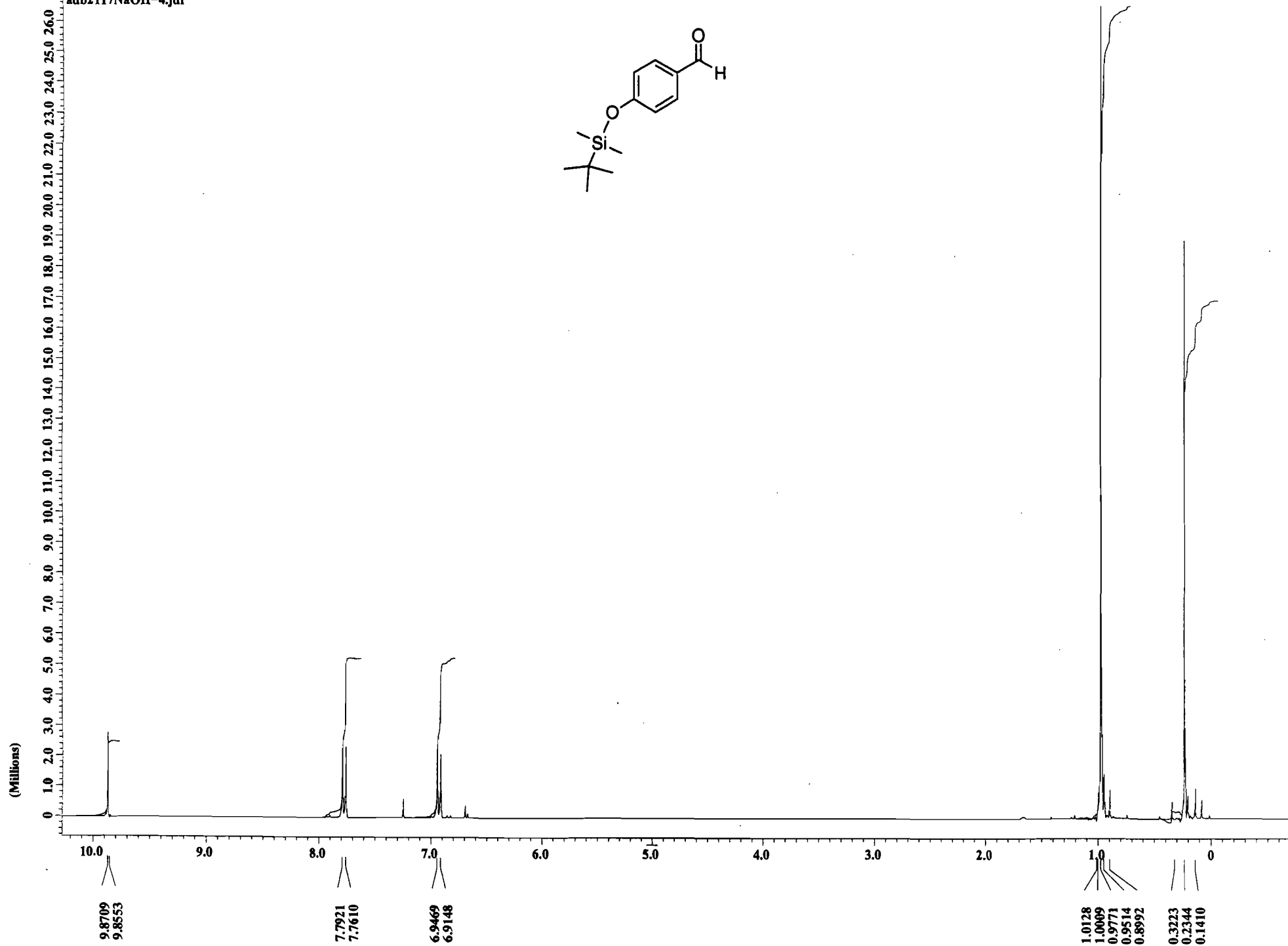
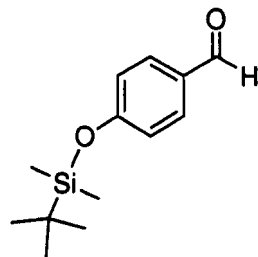


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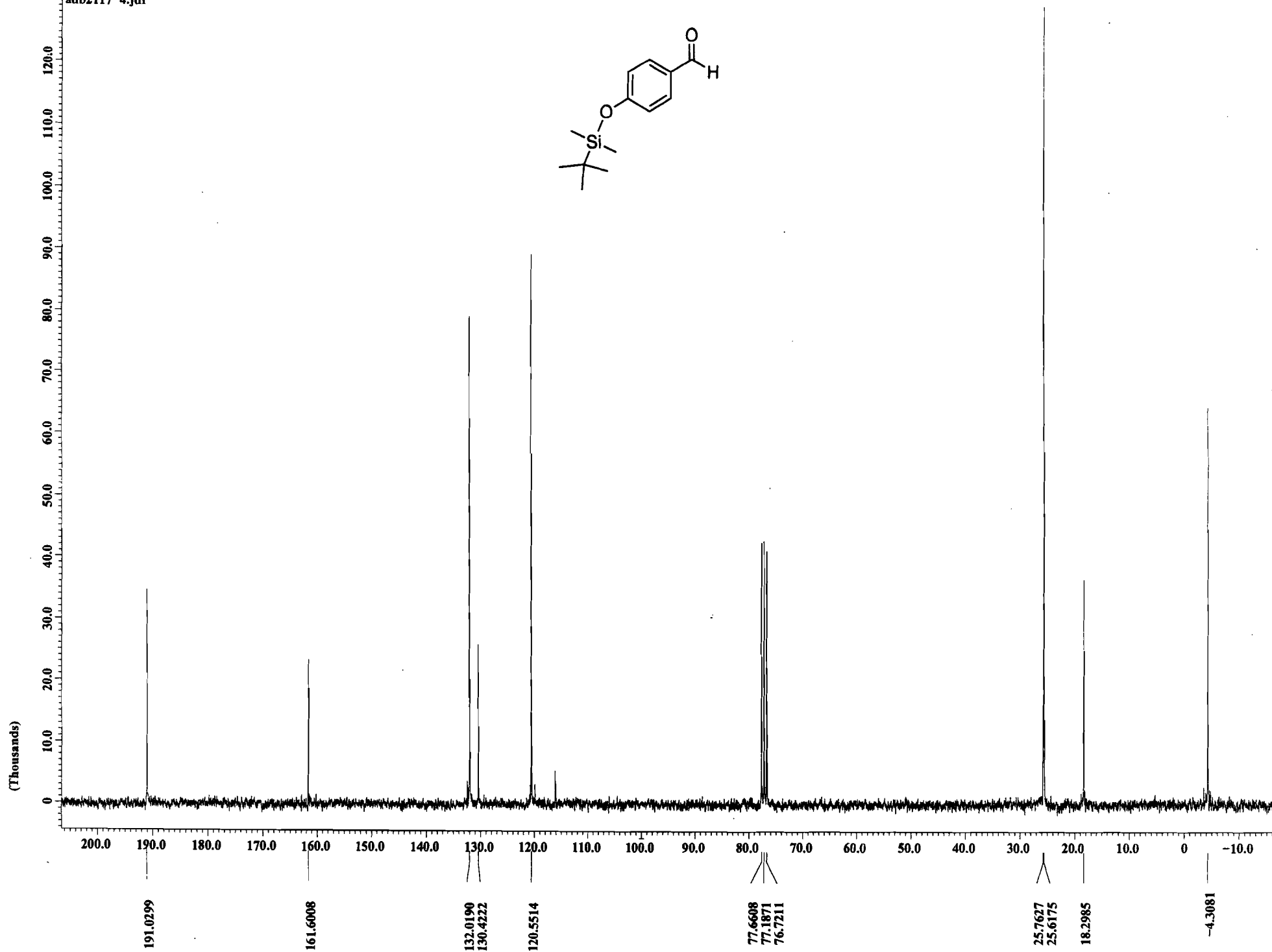
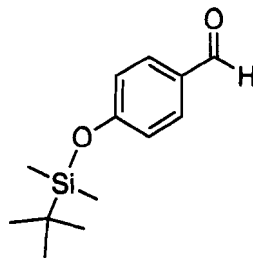
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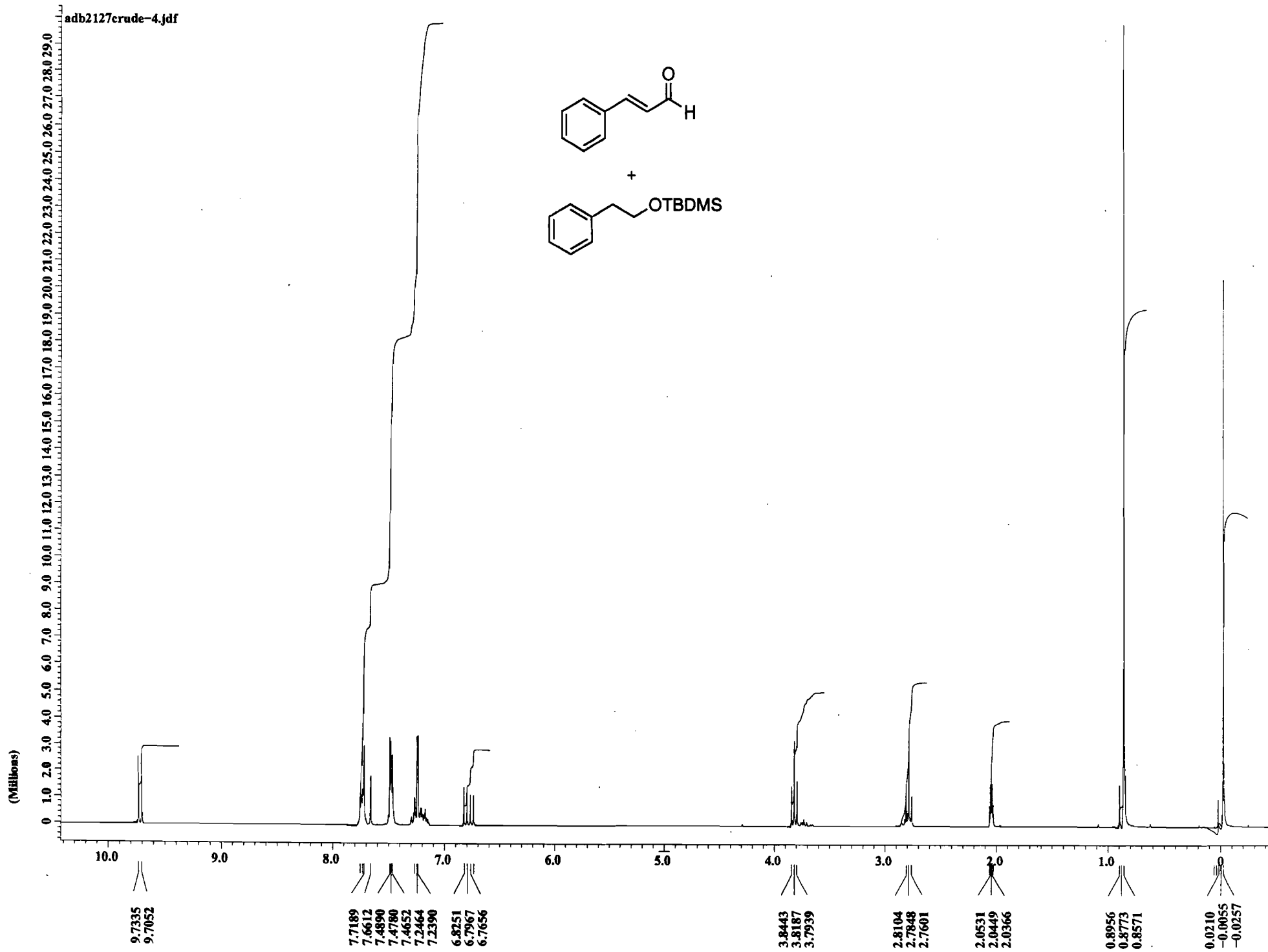
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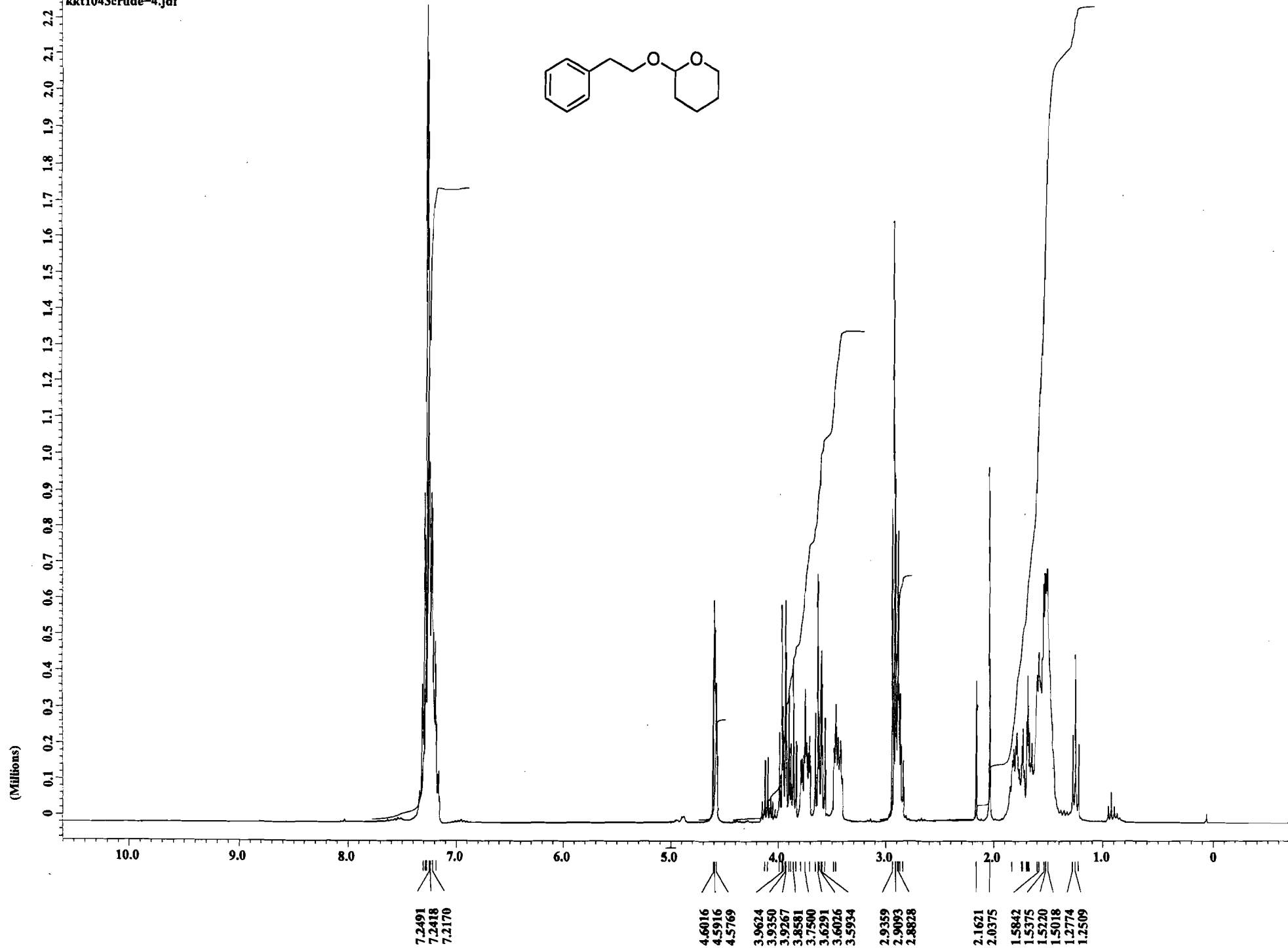
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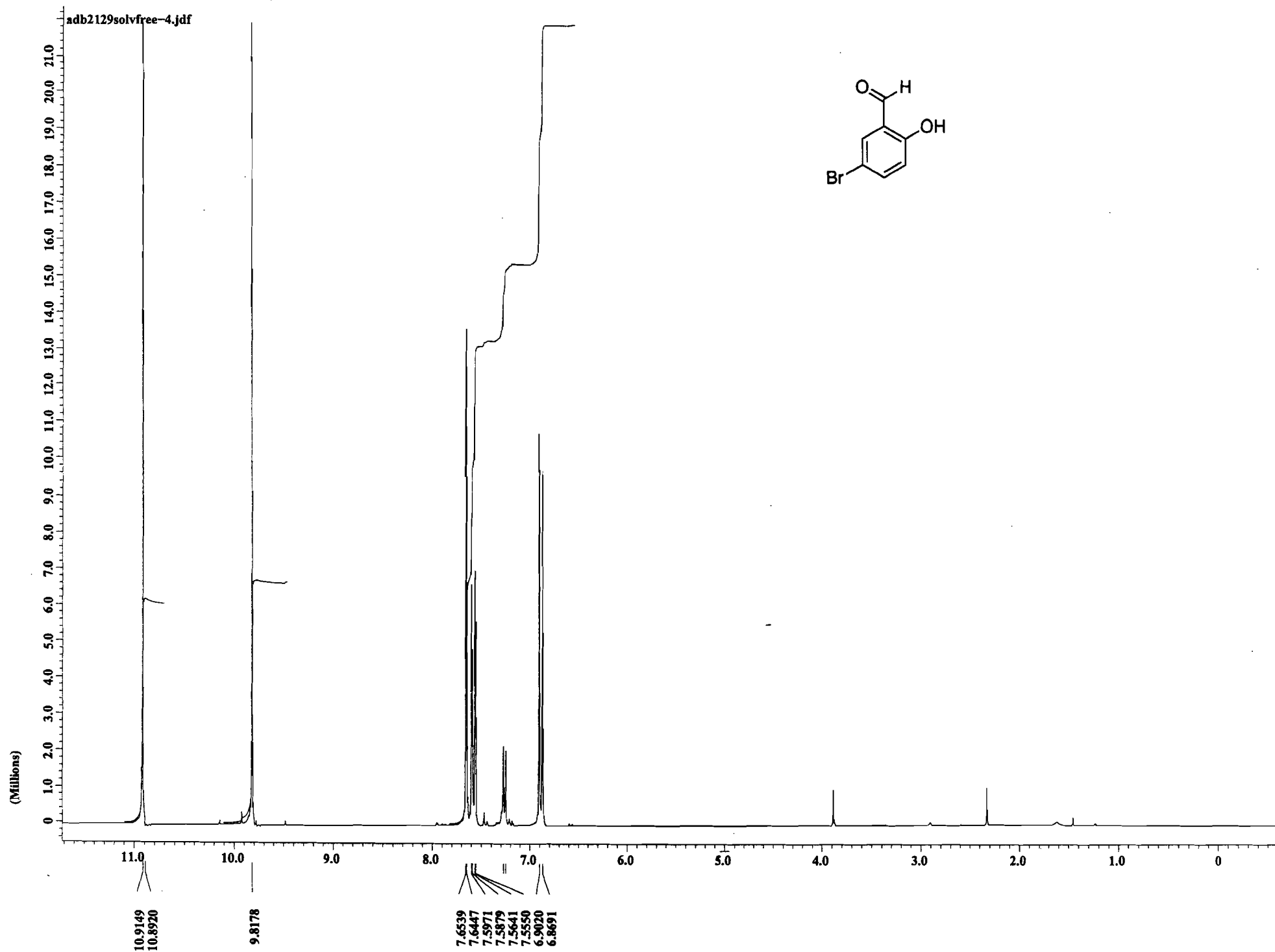


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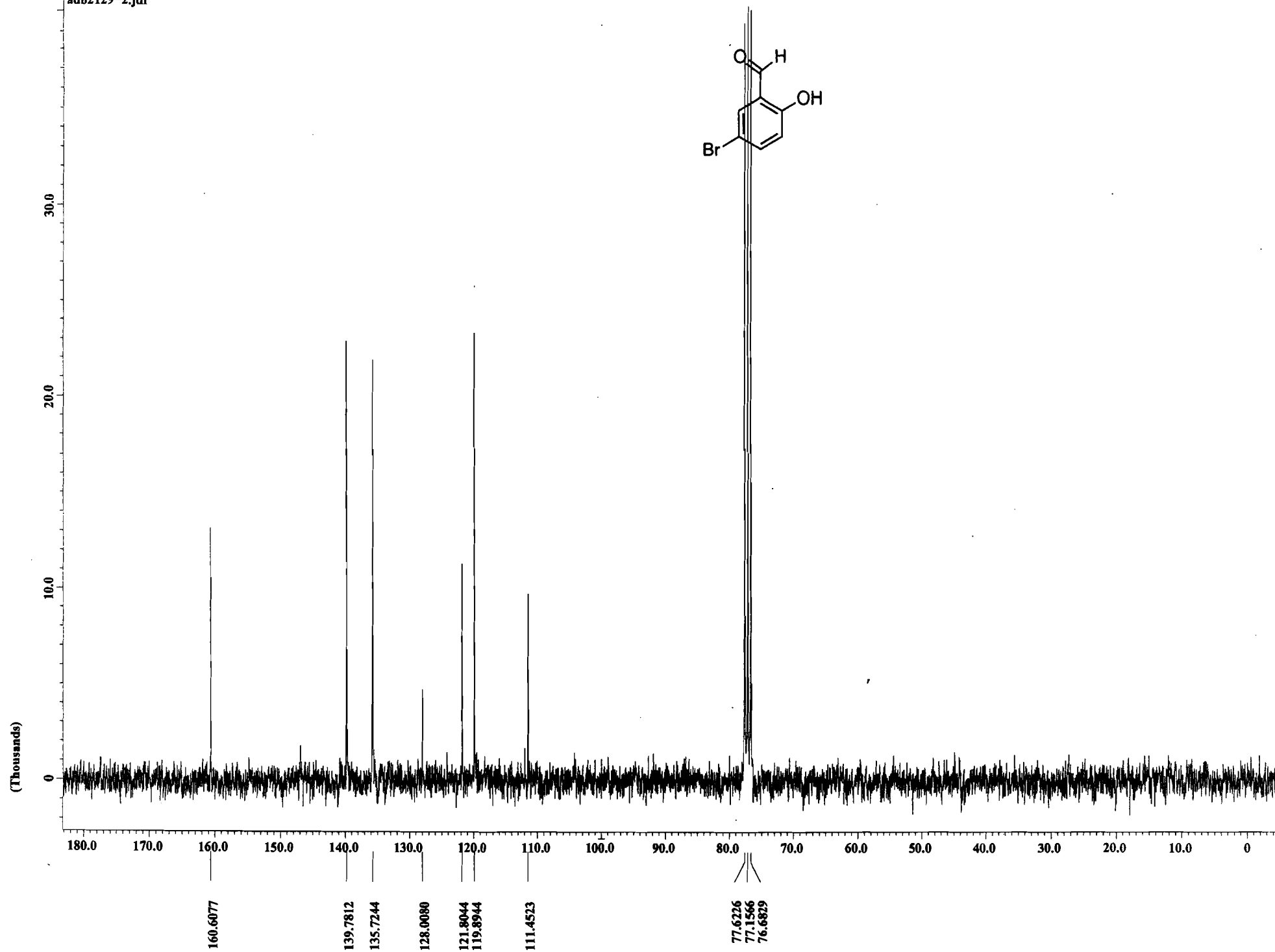


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adb2129-2.jdf



X : parts per Million : ^{13}C

