

Studies of bimetallic nanocatalysts and synthesis of tricyclic pyrone molecules for Alzheimer's Disease

by

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B.S., Northwest A&F University, 2012
M.S., Northwest A&F University, 2016

AN ABSTRACT OF A DISSERTATION

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DOCTOR OF PHILOSOPHY

Department of Chemistry
College of Arts and Sciences

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Abstract

In the industry, 80% of products were produced by catalysts, and most of the catalysts are tiny particles with sizes less than 25 nm. In the first project (discussed in Chapter 1 and Chapter 2), we selected two types of bimetallic nanocatalysts (Pd/Au and Cu/Au) for our studies. The goals are to use the nanocatalysts (Pd/Au and Cu/Au nanoclusters) to produce products with opposite stereochemistry. A pair of chiral substituted poly-vinyl-N-pyrrolidones (CSPVP) were designed and synthesized for the stabilization of nanocatalyst colloids (in water or dimethylformamide) to synthesize products with opposite stereochemistry using different oxidants such as tertiary-butyl hydrogen peroxide (TBHP) or hydrogen peroxide. We first studied the nanocatalyst colloid using achiral poly-vinyl-N-pyrrolidones (PVP) to explore new catalytic reactions. Phthalan, indene, norbornene and their derivatives were applied to these nanocatalysts using 30% hydrogen peroxide or TBHP as oxidant. Results suggest that Cu/Au tends to activate sp^3 carbons, and these carbons are connected to benzene ring or oxygen, while Pd/Au exhibits catalytic potential to oxidize sp^2 carbons. Chapter 1 focuses on the syntheses of chiral polymers and the corresponding colloidal nanocatalysts. In the following chapter, a series of substrates were treated with nanocatalyst colloids in different ingredients. Some of these substrates were treated with CSPVP supported colloid, and results remain to be carefully studied. In the second project (discussed in Chapter 3), two tricyclic pyrones were synthesized for the investigation of Alzheimer's disease in a rat model. We also attempted to synthesize a novel tricyclic pyrone to avoid the formation of two stereoisomers by the insertion of an alkene.

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Major Professor
Dr. Duy H. Hua

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Abstract

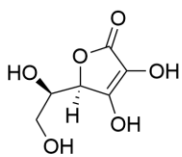
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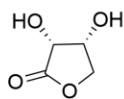
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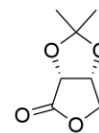
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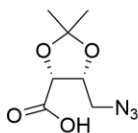
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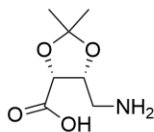
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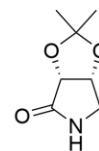
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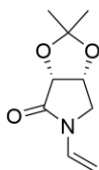
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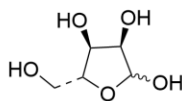
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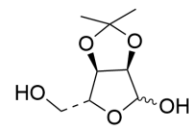
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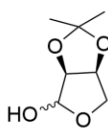
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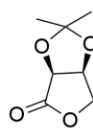
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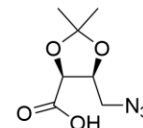
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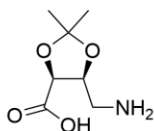
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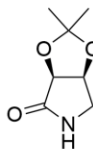
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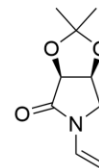
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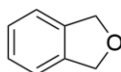
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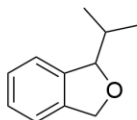
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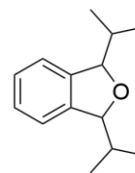
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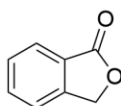
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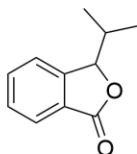
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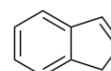
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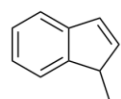
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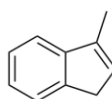
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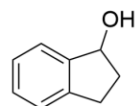
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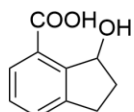
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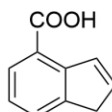
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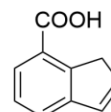
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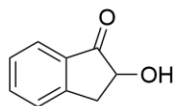
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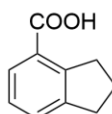
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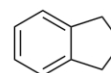
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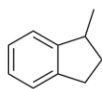
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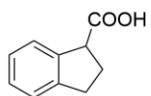
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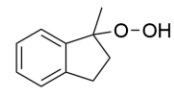
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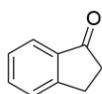
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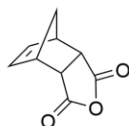
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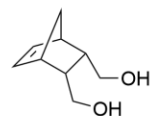
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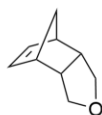
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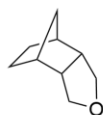
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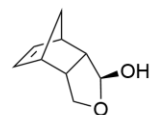
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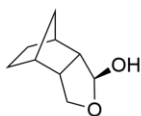
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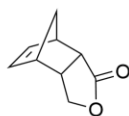
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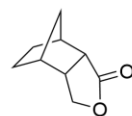
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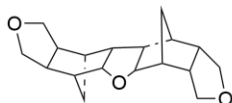
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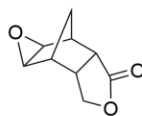
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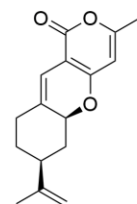
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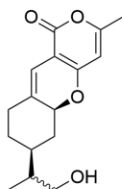
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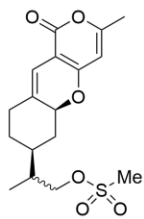
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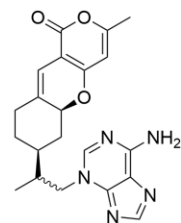
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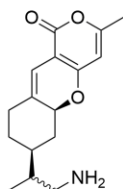
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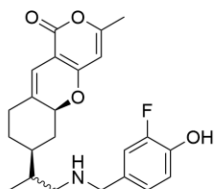
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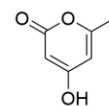
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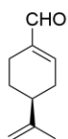
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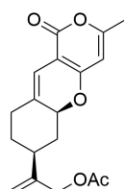
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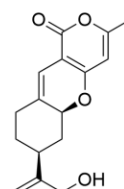
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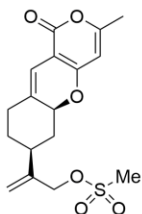
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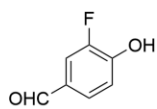
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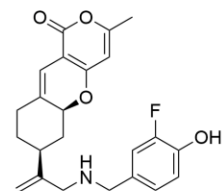
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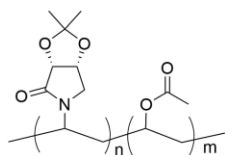
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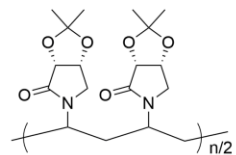
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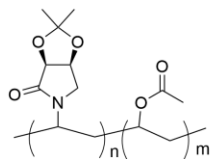
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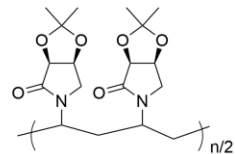
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P-1-R



COP-1-S



P-1-S

List of Abbreviations

PVP	Poly- <i>N</i> -vinyl-pyrrolidinone
NPs	nanoparticles
NCs	nanoclusters
CSPVP	Chiral substituted poly- <i>N</i> -vinyl-pyrrolidinone
AIBN	Azobis(isobutyronitrile)
NVP	<i>N</i> -vinylpyrrolidone
DMF	<i>N,N</i> -Dimethylfomaide
HRMS	High resolution mass spectra
M _w	Weight average molecular
M _n	Number average molecular weight
GPC	Gel permeation chromatography
NMR	Nuclear magnetic resonance
DMSO	Dimethyl sulfoxide
TBHP	<i>tert</i> -Butyl hydroperoxide
HOMO	Highest occupied molecular orbital
LUMO	Lowest unoccupied molecular orbital
DCM	Dichloromethane
EA	Ethyl Acetate
FDA	Food and drug administration
AD	Alzheimer's disease
APP	Amyloid precursor protein
NFTs	Neurofibrillary tangles
NMDA	<i>N</i> -Methyl- <i>D</i> -aspartic acid
NMDAR	<i>N</i> -Methyl- <i>D</i> -aspartic acid receptor
CCK	Cholecystokinin
A β	β -amyloid
LTP	Long-term potentiation
THF	Tetrahydrofuran
DMA	Dimethylacetamide

SLS or MALS

δ

Static (Multiangle) light scattering

delta, chemical shift

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Thanks to staff members in the chemistry department including Mr. Jim Hodgson, Dr. Simon Sham, Mr. Ron Jackson, Mr. Tobe Eggers, Dr. Tingting Liu, Ms. Mary Dooley, Ms. Kimberly Ross, and others during my study.

Dedication

Thanks so much to my parents, Mr. Fangqing Tong and Mrs. Hao Wu, who taught me ABC when I was a child and taught me right from wrong when I was a teenager. They always devote their endless love to me and do their most and best for me. I will never forget their crying for my leaving, their happiness for my happiness, their pride for my little success, their worry for my frustration. I am always their highest priority in any case. At now, their faces are wrinkled; their hairs are becoming white; their walking is slow. Their love and support for me will never change.

Thanks so much to my beloved girlfriend, Yuqiao Liu, who has been waiting for me for years and years. We share happiness and sorrows; we talk about past and future; we face opportunities and challenges. We will love and hold each other until the last breath.

Chapter 1 - Synthesis and Characterization of Chiral Substituted Polyvinylpyrrolidones and Bimetallic Nanoclusters

1.1. Introduction and Background

In the last decades, heterogeneous catalysts have been applied in many critical industrial procedures to accelerate reaction with low cost, high conversion and product selectivity.^{1, 2} In industry, more than 80% of chemical products were produced by catalysts.^{2, 3} In 2019, the global catalyst market size was valued at USD 33.9 billion and was expected to grow in an annual growth rate of 4.4% from 2020 to 2027.² Most industrial catalysts exist as small nanoparticles with their sizes less than 25 nm in high ratios of surface/volume^{4, 5}. The methods of preparing nanocatalysts can be divided into two classes, the Top-Down and Bottom-Up methods (see **Figure 1**). It has been widely accepted that nanoparticles (NPs) at the lower end of the nanoscale (composed of less than ~100 atoms) are often referred to as nanoclusters (NCs).⁶ An obvious different optical properties in NCs and NPs with larger size can be observed.⁷ For Au colloidal nanoparticles with sizes larger than 5 nm, an intensive red colors can be observed by a naked eye.^{8, 9}

Prior to our report,¹⁰ ligands or polymers are necessary to prevent the aggregation of NPs or NCs. In some cases, these stabilizers (ligands or polymers) are considered unfavorable for their application in catalytic reactions.¹¹ The catalytic activity of stabilized NCs or NPs can be jeopardized by: (1). The deactivation of the metal surface caused by functional groups of polymers; (2). The blocking of reagents access caused by steric hindrance.^{12, 13}

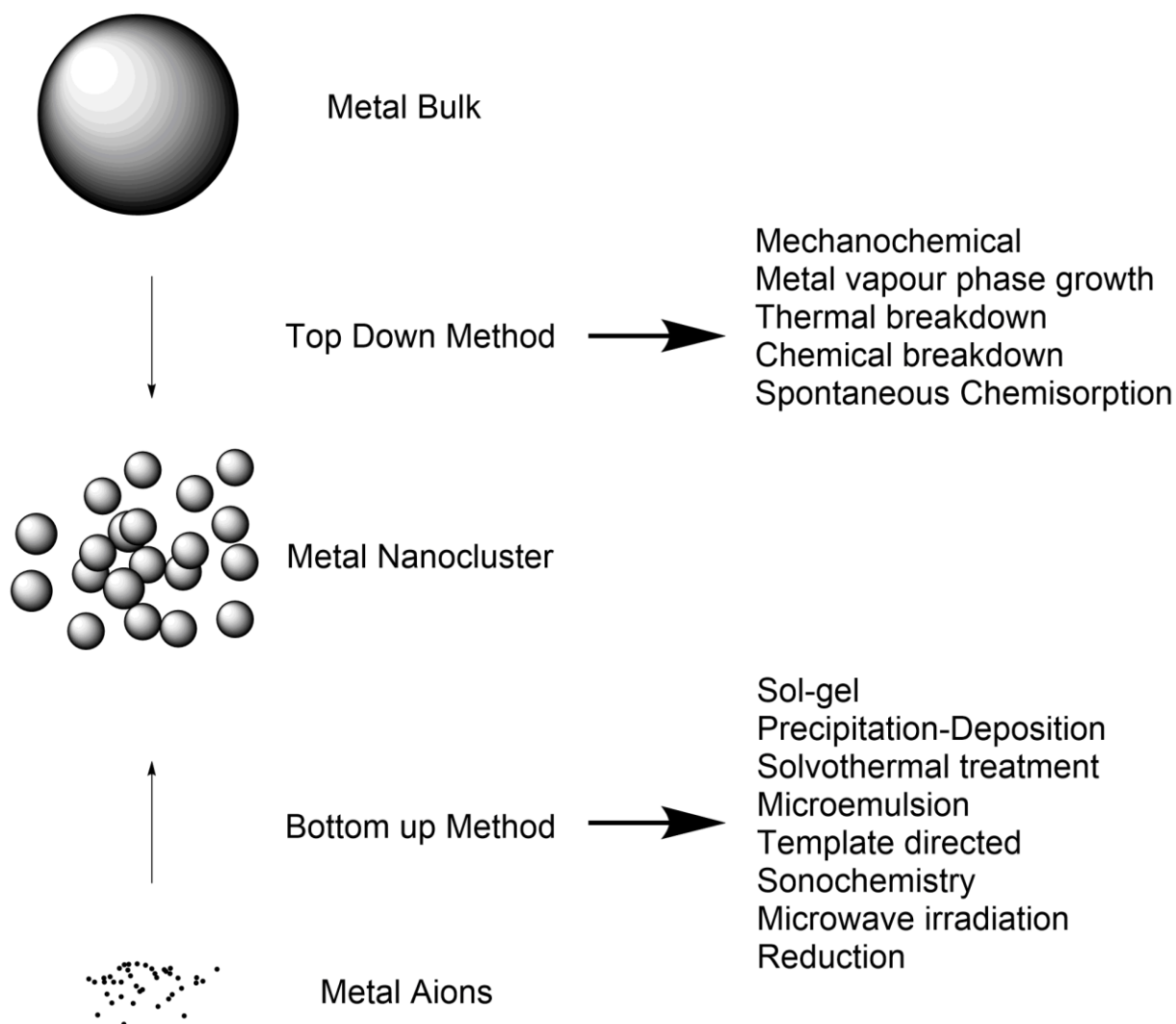


Figure 1. Methods to prepare nanocatalysts.

It is widely accepted that the formation process of nanocatalysts include two stages of nucleation and growth.¹⁴ For the nucleation, lots of initial cores of NCs are formed rapidly and the number of atomic particles increases.^{15, 16} In this stage, the structure of these initial cores (or nuclei) are influenced by the type of polymer, reducing ability of the reducing reagent and the temperature. The growth stage refers the growth process of nanoclusters from its initial cores. In this stage, the initial cores (or nuclei) begin to decrease with the diffusion of small nuclei to the surface of larger nuclei. This process is much slower than nucleation to give the final NCs and NPs.^{15, 17} Also, the

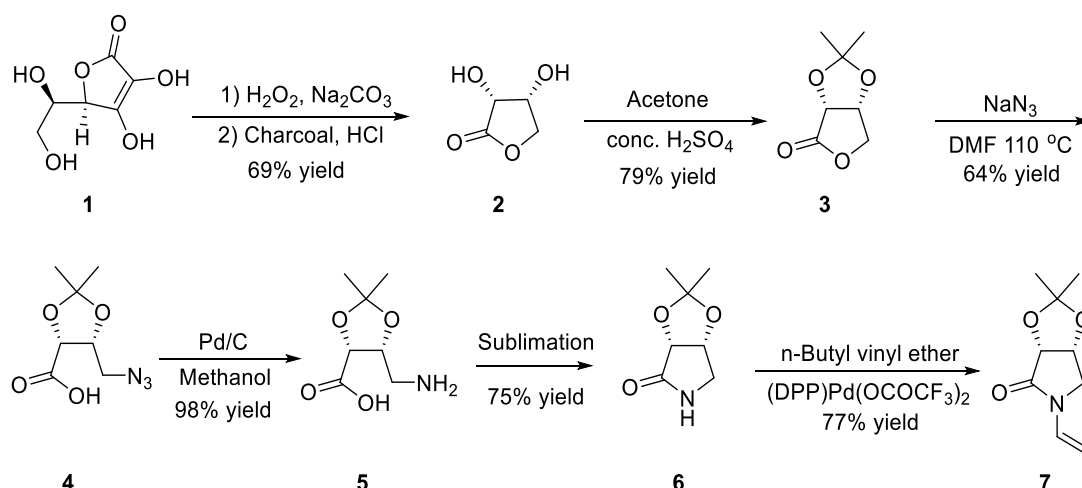
size and connections between metals and polymers can be affected by the length of polymers. In 2017, Alexander and his coworkers simulated the ratios of metal-polymer bonded monomers (to total monomers) using polymers in different lengths. The polymers with lengths ranging from 220 units to 1540 units exhibit percentages of metal-bonded monomer units/total monomer units from 52% to 16%, respectively.¹⁸ In 2013, Kamil and his coworkers reported their research on the influence of polymer length on the size of nanoparticles by preparing a series of Au colloidal nanoparticles with different PEGs ranging from the M_w of 2k to 48k to give the corresponding Au nanoparticles sizes ranging from 15 nm to 175 nm (by transmission electron microscopy).¹⁹

1.2. Preparation of Chiral Substituted Poly-*N*-vinylpyrrolidones (CSPVP) and Bimetallic Nanocatalysts

In 2016, Hua and his coworkers published their studies on chiral substituted poly-*N*-vinylpyrrolidone (CSPVP) stabilized bimetallic nanocatalysts with good enantioselectivity in various oxidation reactions¹⁰. The design and synthesis of CSPVP are two starting points to obtain nanocatalysts and to establish chiral pockets and reactive sites for catalytic reactions. In order to catalyze substrates with opposite enantioselectivities, a pair of CSPVP with opposite stereochemistry were designed by Hua, and I participated in the syntheses of these chiral polymers and the preparation of corresponding NCs.

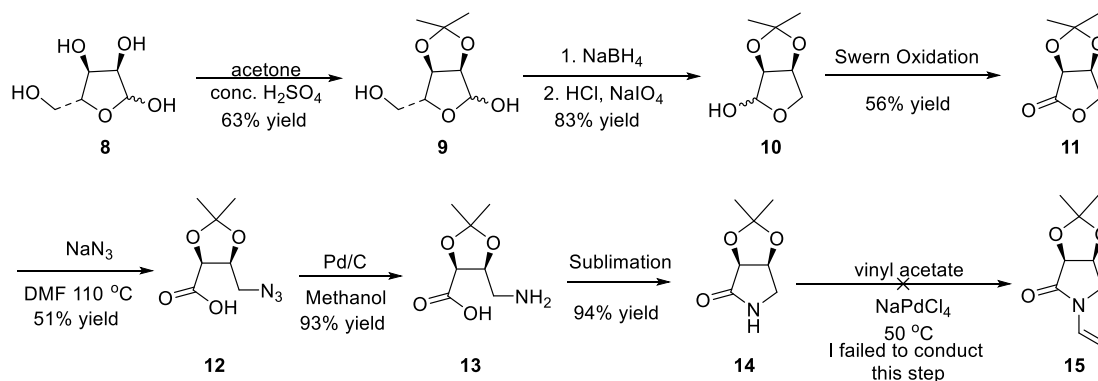
1.2.1. Synthesis of the Precursor for P-1-R

In order to synthesize **P-1-R** (see **Scheme 1**), the inexpensive and commercially available *D*-isoascorbic acid (**1**) was selected as the starting material for the multi-step synthesis of the **P-1-R**. *D*-isoascorbic acid (**1**) was treated with hydrogen peroxide to cleave the double bond and potassium carbonate to hydrolyze the ester at 42 °C for 12 h. Then, active charcoal was added into the solution with the temperature increased to 80 °C and stirred for 30 min to quench unreacted hydrogen peroxide. The reaction mixture was filtered through Celite, and the filtrate was acidified with HCl (6 N) to pH ~ 1. The filtrate was concentrated to dryness, diluted with ethyl acetate, heated to reflux. The organic layer containing desired product was sealed and crystalized at a fridge to obtain *D*-erythrone (**2**) in a yield of 69%.^{20, 21} After that, *D*-erythrone (**2**) was treated with distilled acetone under the catalysis of concentrated sulfuric acid, and stirred for 12 h at 25 °C to give the acetonide (**3**) in a yield of 79%.^{21, 22} The acetonide (**3**) was converted to azido-acid (**4**) in a yield of 64% by treating it with sodium azide in *N,N*-dimethylformamide (DMF) at 120 °C for 12 h.²¹ After that, the azido-acid (**4**) was reduced by Pd/C under hydrogen atmosphere (30 psi) in methanol at 25 °C for 12 h. The reaction mixture was filtered, concentrated to dryness, washed with ethyl ether to give amino acid (**5**) in a yield of 98% as dry powders.²¹ The collected dry powders were then sublimated slowly under vacuum (0.1 - 0.5 mm Hg) at 130 °C to furnish the cyclized amide product (**6**) in a yield of 75%.²¹ The collected lactam (**6**) was treated with *n*-butyl vinyl ether and a catalyst, 4,7-diphenyl-1,10-phenanthroline palladium bis (trifluoroacetate) $[(DPP)Pd(OCOCF_3)_2]$ ²³, at 75 °C for 3 h to furnish the *N*-vinylpyrrolidone (**7**) as the precursor for **P-1-R** in a yield of 77%.



Scheme 1. Synthesis of the precursor of P-1-R.

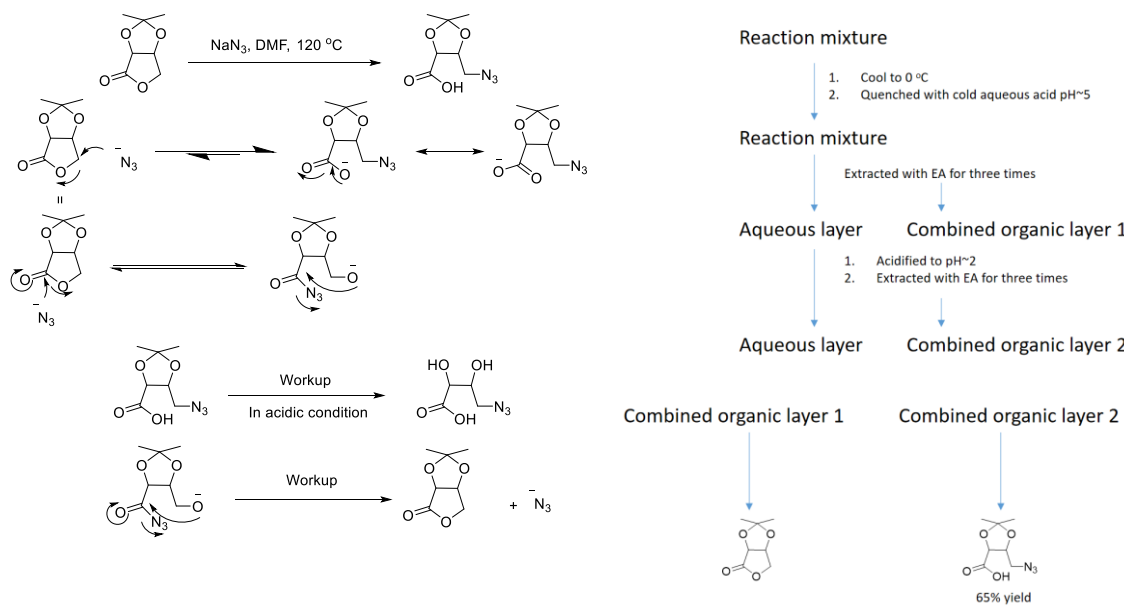
1.2.2. Synthesis of the Precursor for P-1-S



Scheme 2. Synthesis of the precursor of P-1-S.

The opposite-stereoisomeric polymer was also designed (see **Scheme 2**) to compare their difference in catalytic enantioselectivity. The synthesis of its precursor was started by treating *D*-ribose, an inexpensive and commercially available material, with acetone and a catalytic amount of concentrated sulfuric acid at 25 °C (stirred for 12 h) to afford acetone (9) in a yield of 63%.²² Acetone (9), a mixture of α and β anomers in the ratio of 3.8:1, was reduced by sodium

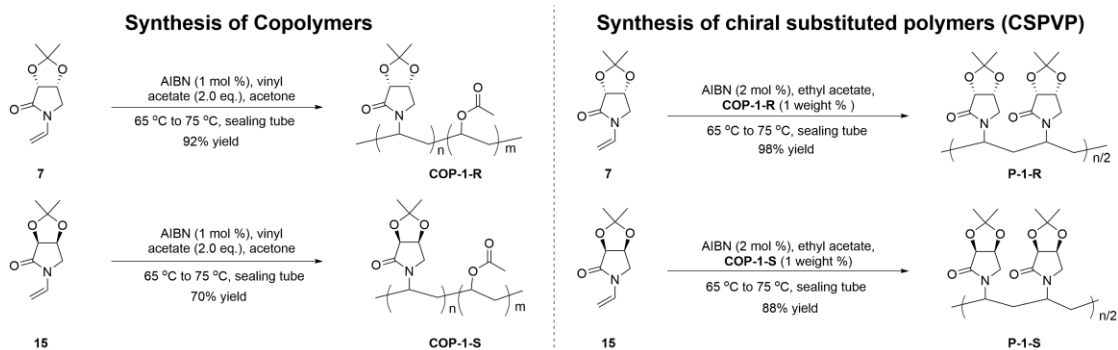
borohydride at 25 °C for 3 h. After that, the unreacted sodium borohydride (NaBH₄) was quenched by acidifying the reaction solution to pH~5 with 1N HCl. Then, the reduced intermediate was oxidatively cleaved by sodium periodate for 5 h at 25 °C to yield lactol (**10**) in a yield of 83%.²⁴ After that, Swern oxidation was used to convert lactol (**10**) to lactone (**11**) in a yield of 56%.²⁵ Lactone (**11**) was then treated with sodium azide and distilled DMF at 120 °C for 12 h to azido acid (**12**) in a yield of 51%.²¹ The dried azido acid (**12**) was reduced with Pd/C under hydrogen pressure (30 psi) in methanol at 25 °C for 12 h to afford amino acid (**13**) in a yield of 93%. Subsequent sublimation using a sublimator under vacuum (0.05 mm Hg) and heat (130 °C) was conducted to furnish the cyclized amide (**14**) as crystals in a yield of 94%. The sublimated crystals (**14**) were first mixed with vinyl acetate, a catalytic amount of sodium palladium chloride (Na₂PdCl₄), potassium carbonate in a glove box (sensitive to oxygen and water).²⁶ The reaction mixture was then heated to 50 °C for 12 h under argon and failed to produce vinyl amide (**15**) as the major product due to the presence of water, which may convert vinyl amide to imide under the catalysis of Na₂PdCl₄. Then, Dr. Fan (a postdoctoral fellow in Hua's laboratory) used a reported catalyst of (DPP)Pd(OCOCF₃)₂²³ for this vinylation by mixing crystals of **14**, *n*-butyl vinyl ether at 75 °C (open to air) to produce vinyl amide of **15** (75% to 80% yield). The reaction is tolerated to the presence of water and air.



Scheme 3. Discussion of azide displacement reaction.

In the synthesis of azido carboxylic acid (see **Scheme 3**), the workup process is the key point to improve the yield. There are two carbons (the carbonyl C2 and C5 adjacent to the oxygen) can be attacked by nucleophilic azide ions to give an acetyl azido or an azido carboxylic acid respectively. The azido carboxylic acid is more thermodynamically stable than acetyl azido due to the resonance stabilization of carboxylate ion is more stable than alkoxide ion. 12 h is required to convert most lactone to carboxylic acid. In order to extract the azido carboxylic acid from the aqueous layer, it is necessary to convert most carboxylic acid from COO^- to COOH ($\text{pK}_a = 5$) by acidifying the reaction mixture to $\text{pH} \sim 3$. However, the acetonide can be hydrolyzed to the corresponding diol in acidic conditions. Hence, a low temperature is needed to decrease the hydrolysis of acetonide to improve the isolated yield of azido carboxylic acid.

1.3. Synthesis of Substituted Chiral N-vinylpyrrolidones (CSPVPs) from the Corresponding Vinyl Lactams



Scheme 4. Syntheses of copolymers and polymers.

The synthetic routes for copolymers²⁷ and polymers from corresponding precursors are showed in **Scheme 4**. Copolymers are used as a type of surfactant during the polymerization to produce large polymers. A significant decrease of P-1-R's size (viscosity) was observed if the polymerization process was conducted in the absence of COP-1-R. The reaction solution for **COP-1-R** was prepared by dissolving the vinyl lactam (**7**), vinyl acetate (2.0 eq.), and 1 mol % of azobisisobutyronitrile (AIBN) in a distilled and argon-degassed solution of acetone in a sealable tube under a nitrogen atmosphere (glove box), which is then sealed by capping with a Teflon screw cap containing a Teflon O-ring. The tightly sealed tube was transferred to a hood and heated to 65 °C to 75 °C for 24 h to furnish **COP-1-R** in a yield of 92%. The preparation of the reaction solution of **COP-1-S** was prepared by mixing vinyl lactam (**15**), vinyl acetate (2.0 eq.), and 1 mol % of azobisisobutyronitrile (AIBN) and distilled and argon-degassed acetone in an aforementioned seal tube in a dry box under nitrogen atmosphere to get rid of the influence from water and air. The

reaction solution was transferred out to a hood. The reaction mixture was then heated to about 70 °C for 24 h to furnish **COP-1-S** in a yield of 70%.

The reaction solution to synthesize **P-1-R** was prepared by dissolving the vinyl lactam (**7**), 1 weight % of **COP-1-R** and 2 mol % of azobisisobutyronitrile (AIBN) in a distilled and argon-degassed solution of ethyl acetate (prepared in a dry box). The prepared solution was then transferred out to a hood and heated to about 70 °C for 16 h to afford **P-1-R** in a yield of 98%. The solution to synthesize **P-1-S** was obtained by mixing the vinyl lactam (**15**), 1 weight % of **COP-1-S** and 2 mol % of azobisisobutyronitrile (AIBN) and distilled and argon-degassed ethyl acetate in a seal tube (operated in a dry box). The sealed tube was then moved to a hood and heated to about 70 °C for 24 h to afford **P-1-S** in a yield of 88%. The polymerization procedure usually finished in 24 h with an obvious increase of viscosity of the reaction solution. These reacted mixtures were worked up identically by dissolving corresponding reaction mixture in chloroform. To a solution of pentane, the chloroform was added in dropwise with vigorous stirring. The white precipitates were then collected and dried under vacuum to give white powders as the desired copolymer. In this section, Dr. Fan completed the syntheses of **12** to **15** and the syntheses of **1S** polymers.

1.4. Preparation of Pd/Au and Cu/Au Nanocatalysts



Scheme 5. Synthesis of nanocatalyst colloid.

To prepare a 21.9 mL (10 mM) nanocatalyst colloid (see **Scheme 5**), a solution was prepared by mixing 83 mg (2.2 mmol, 0.11 eq.) of 40k PVP, 21.67 mg (0.055 mmol, 1.0 eq.) of $\text{H AuCl}_4 \cdot 3\text{H}_2\text{O}$, 16.2 mg (0.164 mmol, 3.0 eq.) of CuCl [or 48.1 mg (0.164 mmol, 3.0 eq.) of Na_2PdCl_4] in 30 mL deionized water (or DMF). To it, 10.3 mg (0.273 mmol, 5.0 eq.) of NaBH_4 was added at 0 °C and stirred for 2 hours at 25 °C, saved in fridge for catalytic reactions.²⁸ The concentration of the catalyst was calculated by following equations:

$$c = \frac{\text{mol}_{\text{Na}_2\text{PdCl}_4} + \text{mol}_{\text{CuCl}}}{V_{\text{solution}}}$$

$$c = \frac{\text{mol}_{\text{H AuCl}_4 \cdot 3\text{H}_2\text{O}} + \text{mol}_{\text{CuCl}}}{V_{\text{solution}}}$$

The total mol of the catalytic colloid is calculated by adding the mol of two types of metallic ions. The total mol is then divided by the volume of solution (deionized water or DMF). In this preparation, the total mol of two metallic ions is $\text{H AuCl}_4 \cdot 3\text{H}_2\text{O}$ (0.055 mmol) + CuCl (0.164

mmol) = 0.219 mmol. The concentration of the colloid is calculated by dividing the total mol of metallic ions with the volume of deionized water (21.9 mL) to give following concentration: 0.219 mmol/ 21.9 mL = 10 mM. The concentrations of catalytic colloid can be adjusted by the volume of the solution.

1.5. Characterization of Poly-N-vinylpyrrolidones

Undoubtedly, it is necessary to measure the molecular weights of the synthesized polymers to understand and optimize the design of polymer-supported nanocatalysts. First, Ubbelohde Viscometer was applied to measure the viscosities of various lengths of polymers synthesized by using different amounts of radical initiator AIBN in the polymerization process. After that, Zhaoyang Ren (a Ph.D. student in our lab) measured the molecular weights of our synthesized chiral polymers by using high resolution mass spectra (HRMS).

1.5.1. Studies of Intrinsic Viscosities of Different Lengths of P-1-R using Different Amounts of AIBN by Ubbelohde Viscometer

$$M_n = \frac{\sum NiMi}{\sum Ni} \qquad M_w = \frac{\sum NiM^2}{\sum NiMi}$$

Scheme 6. The equations of weight average molecular (M_w) weight and number average molecular weight (M_n).

Weight average molecular weight (M_w) and number average molecular weight (M_n) are important properties to describe weight distributions of polymers. The equations to describe M_w

and M_n are showed in **Scheme 6**. For newly synthesized polymers, their (absolute) weight average molecular weight (M_w) is usually measured by static (multiangle) light scattering (SLS or MALS) apparatus.²⁹ The instrument for the measurement of (absolute) weight average molecular (M_w) is not connected to an HPLC as a high concentration of sample solution is required to ensure the accuracy of weight average molecular (M_w). An HPLC with an SLS or DLS detector is mainly used to measure the distribution of weight average molecular (M_w). The polymer's absolute number average molecular weight (M_n) is usually measured by an osmometer (no standard sample needed).²⁹ Then, polymers with known molecular weights are used as standards to measure the relationship between their molecular weights and viscosities. However, the SLS apparatus is not available to us, and chiral substituted poly-vinyl-N-pyrrolidones, synthesized from our laboratory, have not been reported previously and their molecular weights are unknown, which is difficult to find a suitable and available gel permeation chromatography (GPC) column for our new polymers (give the same retention time for **P-1-R** prepared by different concentrations of AIBN). Hence, we used an Ubbelohde viscometer to study relative correlations between the trends of their molecular weights and the amounts of AIBN in their polymerization reactions, which would allow us to study the relative sizes of synthetic polymers and future optimization of the preparation of colloidal nanocatalysts.

In order to measure the intrinsic viscosity from a specific type of polymers, a series of polymer's colloids (in methanol) in different concentrations were prepared at 6 mg/mL, 5 mg/mL, 4 mg/mL, 3 mg/mL, 2 mg/mL and a control sample (0 mg/mL). The coordination between PVPs' reduced viscosities and AIBN concentrations is plotted in **Figure 2**, while the coordination of **P-1-R** is plotted in **Figure 3**. The specific viscosities of each colloid were measured by the formulation of $\eta_{sp} = (t_n - t_0)/t_0$, with t_n being the time span of the colloid surface passing the two

tick-mark rings of a Ubbelohde viscometer, and t_0 is the time span from the control sample (0 mg/mL). The intrinsic viscosity of the specific type of polymers was calculated by extrapolation ($[\eta] = \lim \eta_{sp}/c$, c is expressed in mg/mL).³⁰ The intrinsic viscosities from different types of polymers synthesized with 0.1 mol %, 0.2 mol %, and 0.4 mol % of AIBN were measured, and their correlation between AIBN concentrations and intrinsic viscosities was graphed (see **Figure 4**). Results indicated the higher concentration of AIBN applied in the polymerization, the shorter the polymer length.

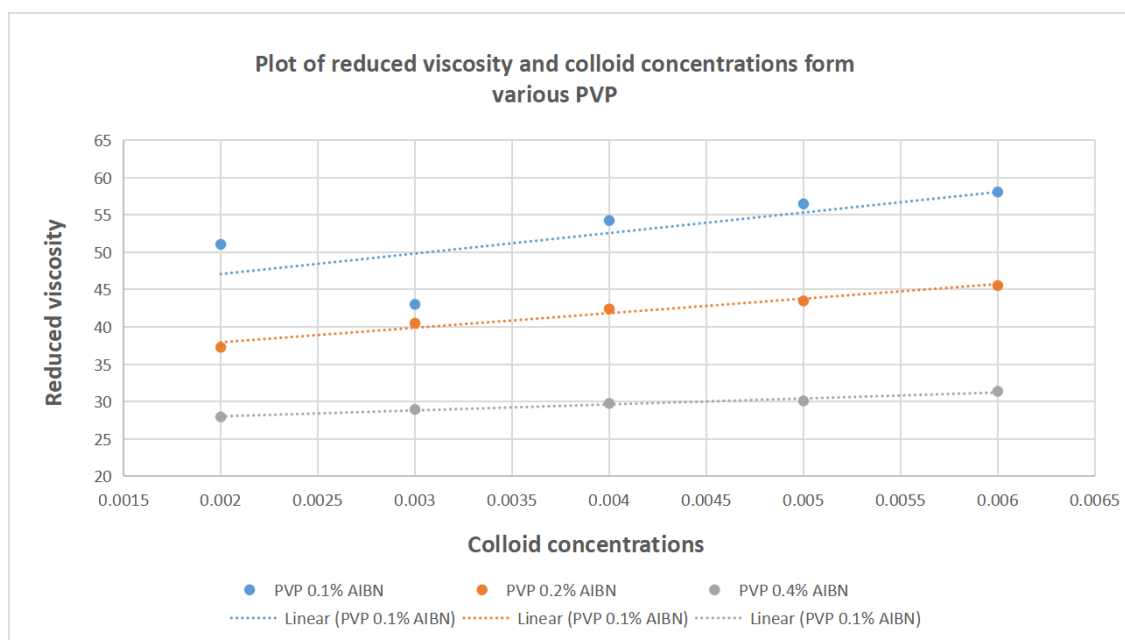


Figure 2. Correlation of reduced viscosities from different PVPs (synthesized with different amounts of AIBN) in different concentrations.

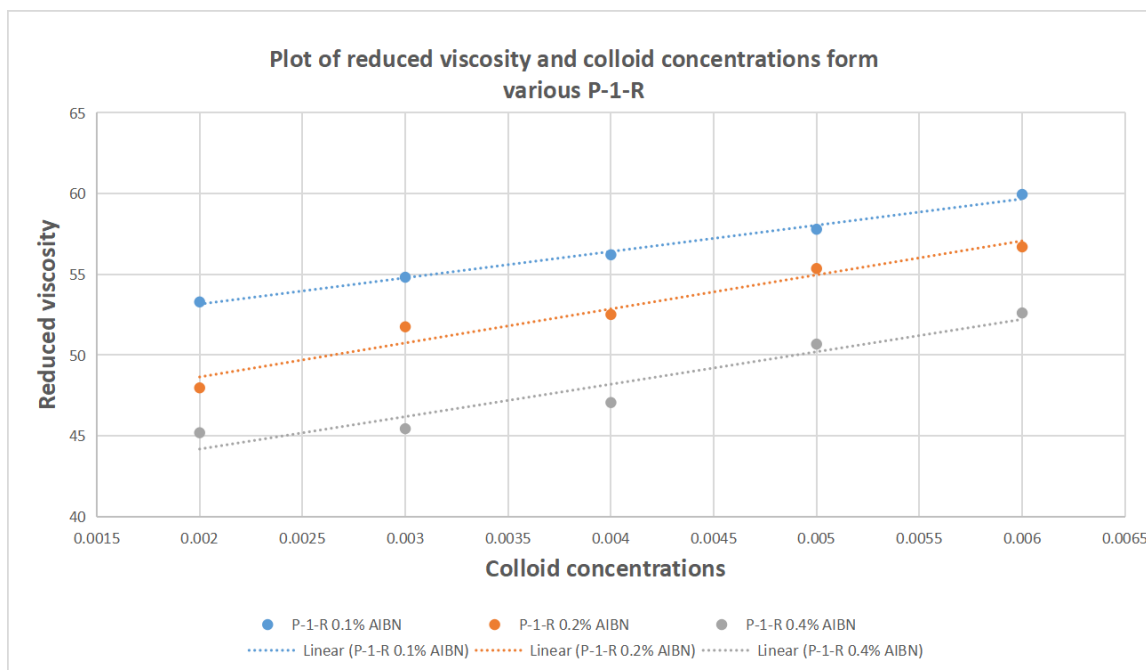


Figure 3. Correlation of reduced viscosities from different P-1-R (synthesized with different amounts of AIBN) in different concentrations.

To measure the intrinsic viscosities of three types of PVPs prepared in different concentrations of AIBN (1 mol %, 2 mol % and 4 mol %), three sets of solutions were prepared in the concentrations of 6 mg/mL, 5 mg/mL, 4 mg/mL, 3 mg/mL, 2 mg/mL, 0 mg/mL. Their correlations between colloidal concentrations and reduced viscosities are plotted in **Figure 2**. For PVPs prepared in different concentrations of AIBN, a higher concentration of AIBN tends to give a set of smaller value of reduced viscosities. For a set of PVP solutions prepared in a specific concentration of AIBN, higher colloidal concentrations tend to afford larger value of reduced viscosities. By extrapolating, the PVP prepared in different AIBN concentrations of 1 mol %, 2 mol % and 4 mol % afford intrinsic viscosities of 41.67 dL/g, 34.04 dL/g, 26.42 dL/g respectively. In **Figure 3**, a same trend can be found. The measured intrinsic viscosities of **P-1-R** prepared in AIBN concentrations of 1 mol %, 2 mol % and 4 mol % are 49.90 dL/g, 44.44 dL/g, 40.16 dL/g

respectively. Then, the correlations between intrinsic viscosities and AIBN concentrations are plotted in **Figure 4**. The value of intrinsic viscosity is proportional to the logarithm value of molecular weight, which means that a larger value of intrinsic viscosity gives a larger (or longer) linear polymer. Based on that relationship, the two lines in **Figure 4** exhibit that a shorter linear polymer will be obtained if a higher concentration of AIBN is involved in the polymerization procedure.

PVPs and **P-1-R** with different lengths were prepared by using 0.1 mol %, 0.2 mol %, and 0.4 mol % of AIBN. The three types of **P-1-R** were applied in the preparation of nanocatalyst colloids. The colloid prepared **P-1-R** in 0.4 mol % AIBN is less stable than its 0.2% counterpart when acetonitrile was used to solubilize the substrates and polymers in subsequent oxidation reactions. This is in agreement with the previous statement that the shorter polymers tend to contact more with nanocatalysts and contact less with water. With the addition of acetonitrile as a kind of hydrogen-bond breaker, the hydrogen bonds between polymers and water decreased dramatically leading to a substantial decrease of solubility of polymers. The longer polymer lengths with more connections to water by hydrogen bonds are still soluble in the mixed solvent system, and even their solubility was impaired by acetonitrile. For the short polymer colloids with less connections to water through hydrogen bonds, it tends to have a lower solubility than the long polymer colloids in acetonitrile-water solution. In addition, the solubility of **P-1-R** prepared with 0.1 mol % AIBN has a low solubility in water, which is difficult to prepare a concentrated colloidal solution as high as 10 mM nanoclusters in water. The results suggested that the **P-1-R** prepared with 0.2 mol % AIBN is the optimal selection for the preparation of colloidal nanocatalysts.

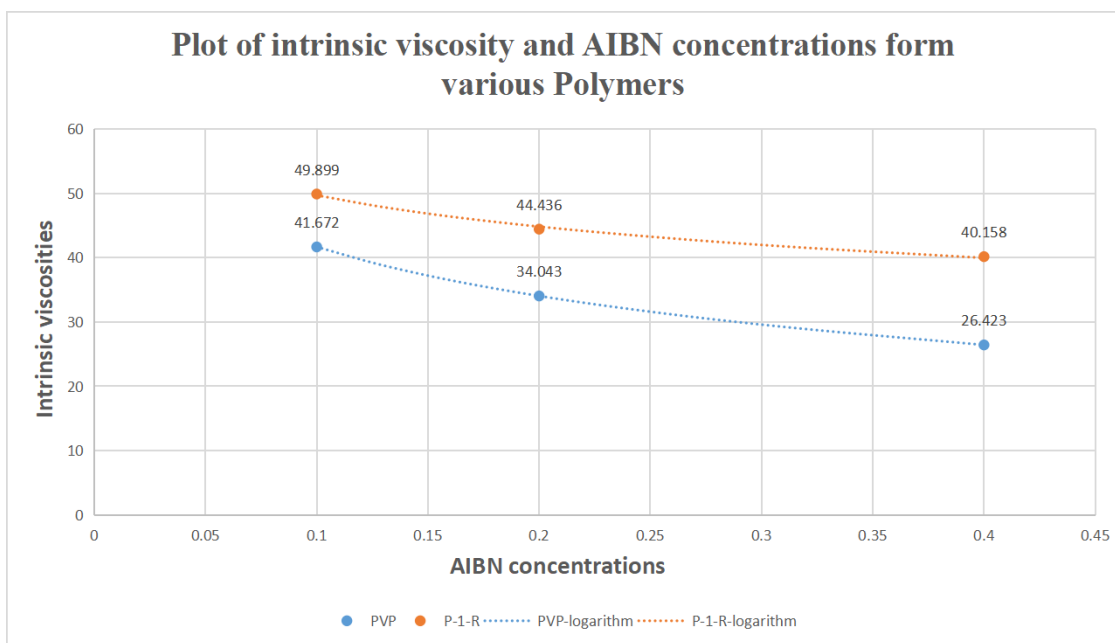


Figure 4. Correlation of intrinsic viscosity and different PVP (synthesized from different amounts of AIBN) in different concentrations.

1.7. Conclusion

In this section, characterization of polymers was conducted. According to the intrinsic viscosity results obtained by using an Ubbelohde viscometer, the higher the concentration of AIBN, the shorter the polymer length. In the water-acetonitrile system, CSPVP synthesized with 0.2 mol % of AIBN provides the optimal length of polymer for the preparation of concentrated nanocatalyst colloid in water/acetonitrile solution.

1.8. General Information

Characterizations:

NMR spectra: All NMR spectra were obtained from Varian (400 MHz for ^1H NMR and 100 MHz for ^{13}C), Bruker Avance Neo (400 MHz for ^1H NMR and 100 MHz for ^{13}C), and Bruker WB (600 MHz for ^1H NMR and 150 MHz for ^{13}C) located at the Chemistry and Biochemistry Building (CBC 128), Kansas State University. The solutions for NMR (CDCl_3 , DMSO- d_6 , and D_2O) were purchased from Fisher, Inc. or VWR, Inc.

Mass spectra: Mass spectra (non-high-resolution) data were obtained from a Waters LCMS located in the aforementioned CBC building. The high-resolution mass spectra were obtained from an LCT Premier time of flight mass spectrometer (Waters, Inc.).

Optical rotation: All optical rotation measurements were carried out from a Perkin-Elmer 241 polarimeter in our Laboratory (CBC 412).

Viscosity: All viscosity data were measured by a Ubbelohde viscometer ($d\varnothing = 0.7\text{-}0.8\text{ mm}$).

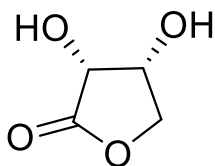
Reagents:

All reagents were purchased from Fisher, Inc. or VWR, Inc.

All distilled or dried solvents over appropriate reagents were referred to “Purification of Laboratory Chemicals”.³¹

1.9. Syntheses

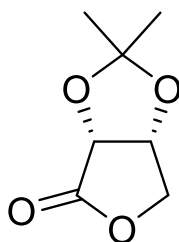
(3*R*,4*R*)-Dihydro-3,4-dihydroxy-2(3*H*)-furanone (2) (The preparation was followed by a reported method)²⁰(from tzb-1-84)



To a cold solution of 17.6 g (100 mmol) *D*-isoascorbic acid (**1**), 21.2 g (200 mmol) of sodium carbonate, 20.5 mL (200 mmol) of 30% hydrogen peroxide in 500 mL deionized water, the reaction mixture was stirred at 42 °C for 12 h. After the solution was cooled to room temperature, 8 g activated charcoal was added and stirred at 80 °C for 30 min to quench the unreacted hydrogen peroxide. The reaction mixture was filtered through Celite while hot. The filtrate was then acidified with HCl (6 N) to pH ~ 1, concentrated on a rotary evaporator, vacuumed using an oil pump to give a dry solid (18 g). The crude product (containing inorganic NaCl salt) was then diluted with 200 mL of ethyl acetate, heated to reflux for 30 minutes, and the mixture was filtered while hot. The hot filtrate with the desired product was saved. The solid was recovered and mixed with 200 mL of ethyl acetate, heated to reflux, and filtered. This process was repeated for 3 times in total. The combined organic solution was sealed with para-film, cooled in a fridge for 12 h. Crystallized white solids were collected by filtration to give 8.1 g (69% yield) of the titled compound **2**: M.p. 97-98 °C; $[\alpha]_D^{22} = -73.2$ (c 0.5, H₂O); ¹H NMR (400 MHz, D₂O): δ 5.75 (dd, *J* = 7.2, 3.2 Hz, 1 H, OH), 5.34 (s, 1 H, OH), 4.39 – 4.34 (m, 1 H), 4.26 (dt, *J* = 10, 3.2 Hz, 1 H),

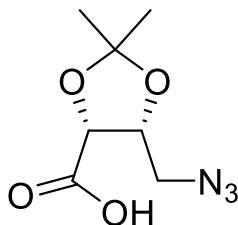
4.24 – 4.19 (m, 1 H), 4.03 (dd, $J = 10, 3.2$ Hz 1 H); ^{13}C NMR (400 MHz, D_2O): δ 177.1, 72.5, 70.1, 69.0; MS (ESI, MeOH): $m/z = 141.4$ ($[\text{M} + \text{Na}]^+$).

2,3-*O*-Isopropylidene-*D*-erythrone (3) (The preparation was followed by a reported method)²²(from tzb-4-27)



To a solution of 10 g (84 mmol) of (3*R*,4*R*)-dihydro-3,4-dihydroxy-2(3*H*)-furanone (**2**) in 250 mL distilled acetone, 0.45 mL (245 mg, 2.5 mmol, 2 mol % equivalence) of concentrated sulfuric acid was added dropwise. The reaction solution was stirred at room temperature for 12 h, added with 2 g (23.8 mmol) sodium bicarbonate and stirred at room temperature for 2 h, diluted with 50 mL water and extracted with 200 mL diethyl ether for three times. The collected organic layer was then dried over sodium sulfate, filtered through Celite, evaporated with a rotary evaporator followed by vacuum to yield 16 g of 2,3-*O*-isopropylidene-*D*-erythrone (**3**) as a white solid (79% yield): M.p. 67-68 °C; $[\alpha]_{\text{D}}^{22} = -114.6$ (c 1.5, acetone); ^1H NMR δ (400 MHz, CDCl_3): δ 4.85 (dd, $J = 6, 4$ Hz, 1 H), 4.72 (d, $J = 6$ Hz, 1 H), 4.48 (d, $J = 11$ Hz, 1 H), 4.41 (dd, $J = 11, 4$ Hz, 1 H), 1.42 (s, 3 H), 1.34 (s, 3 H); ^{13}C NMR δ (100 MHz, CDCl_3): δ 174.8, 113.9, 75.8, 74.8, 70.5, 26.9, 25.6; MS (ESI, MeOH): $m/z = 181.3$ ($[\text{M} + \text{Na}]^+$), 95.6. The spectral data is in agreement with the previously reported data²².

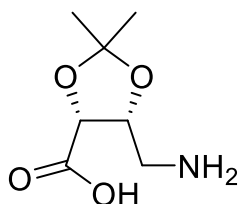
(2*R*,3*R*)-4-Azido-4-deoxy-2,3-*O*-isopropylidene-*D*-erythronic acid (4) (The preparation was followed by a reported method)²¹ (from tzb-3-59)



To a flame-dried and argon-purged flask, 1 g (6.3 mmol) of 2,3-*O*-isopropylidene-*D*-erythrone (3), 1.44 g (22.15 mmol) of sodium azide were added, and the flask was dried under vacuum and replaced with argon for three times. After that, 5 mL of distilled DMF was added, the reaction mixture was then heated to 125 °C and stirred for 12 hours. Then, the reaction mixture was allowed to cool to 25 °C, filtered through Celite. The filtrate was diluted with dichloromethane: methanol (10:1) and 100 mL diethyl ether to precipitate non-polar impurities. The mixture was then filtered through Celite and washed with 50 mL ethyl acetate. The filtrate was evaporated and concentrated to give 1.6 g of crude products. It was diluted with 20 mL water (pH~7) and 100 mL DCM, and the water layer was extracted with 50 mL DCM twice. The combined organic layer was saved separately. While the aqueous layer was acidified to pH ~ 2 and extracted with 100 mL DCM for three times to give the corresponding organic solution. The two extracts (extracted from the acidic and neutral conditions) were dried over anhydrous sodium sulfate, concentrated to dryness separately. Finally, the organic layer from the neutral aqueous layer gave 220 mg lactone (3). while the organic layer from the acidic aqueous layer furnished 810 mg (64% yield) desired product (4). ¹H NMR δ (400 MHz, CDCl₃): δ 9.52 – 9.0 (bs, 1 H, OH), 4.67 (d, *J* = 7.2 Hz, 1 H), 4.60 – 4.56 (m, 1 H), 3.60 (dd, *J* = 13.2, 3.2 Hz, 1 H), 3.40 (dd, *J* = 13.2,

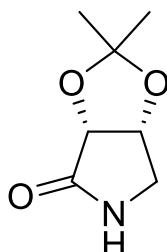
6 Hz, 1 H), 1.63 (s, 3 H), 1.42 (s, 3 H); ^{13}C NMR δ (400 MHz, CDCl_3): δ 172.2, 112.2, 73.8, 70.8, 52.0, 27.1, 26.2; **MS** (ESI, MeOH): m/z = 224.1 ($[\text{M} + \text{Na}]^+$), 143.6, 85.6. The spectral data is in agreement with the previously reported data²¹.

(2*R*,3*R*)-4-Amino-4-deoxy-2,3-*O*-isopropylidene-*D*-erythronic acid (5) (The preparation was followed by a reported method)²¹ (from tzb-3-61)



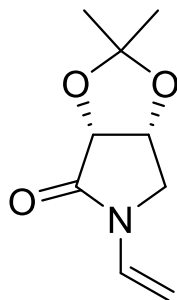
To a hydrogenation bottle, 530 mg of (2.6 mmol) (2*R*,3*R*)-4-azido-4-deoxy-2,3-*O*-isopropylidene-*D*-erythronic acid (**4**) and 25 mg (2 weight %) of 5% Pd/C were mixed in 10 mL methanol. The bottle was attached to a hydrogenation apparatus, purged with hydrogen at 30 psi pressure and shook for 12 h. The mixture was then filtered through Celite, washed with 20 mL methanol. The filtrate was collected and concentrated on a rotary evaporator to give 500 mg of light yellow powder. The light powder was then washed with 20 mL diethyl ether, and the washed solid was vacuumed to dryness to obtain 442 mg (98% yield) of desired product (**5**) as a white solid. ^1H NMR (400 MHz, DMSO-d_6): δ 4.39 (d, J = 7.2 Hz, 1 H), 4.31 – 4.24 (m, 1 H), 2.76 (t, J = 8 Hz, 2 H), 1.39 (s, 3 H), 1.23 (s, 3 H); ^{13}C NMR δ (400 MHz, D_2O): δ 174.09, 111.07, 76.76, 72.45, 40.58, 26.50, 24.21; **MS** (ESI, MeOH): m/z = 176.1 ($[\text{M} + \text{H}]^+$), 198.1 ($[\text{M} + \text{Na}]^+$). The spectral data is in agreement with the previously reported data²¹.

(-)-(3a*R*,6a*R*)-Tetrahydro-2,2-dimethyl-4*H*-1,3-dioxolo[4,5-*c*]pyrrol-4-one (6) (The preparation was followed by a reported method)²¹(from tzb-3-77)



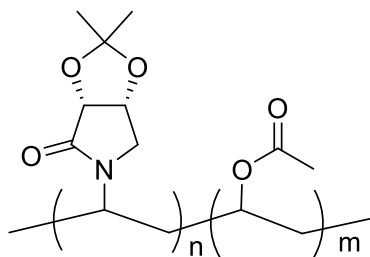
To a sublimator, 1.33 g (7.55 mmol) of (2*R*,3*R*)-4-amino-4-deoxy-2,3-*O*-isopropylidene-*D*-erythronic acid (**5**) was transferred into the bottom of the sublimator carefully. The sublimator was vacuumed slowly to a pressure of 0.1 - 0.5 mm Hg. After that, the sublimator was heated to 130 °C slowly until there was no more white-solid formed in the wall of the sublimator. Then, the apparatus was cooled to room temperature and the vacuum was released. The powder and crystals on the wall and cold finger were collected to give 900 mg (75% yield) of desired product (**6**): M.p. 148-149 °C; $[\alpha]_D^{22} = -60.3$ (c 0.78, MeOH); ¹H NMR δ (400 MHz, CDCl₃): δ 6.31 (bs, 1 H, NH), 4.79 (t, *J* = 5.9 Hz, 1 H), 4.58 (d, *J* = 5.9 Hz, 1 H), 3.59 (dd, *J* = 11.5, 4.8 Hz, 1 H), 3.49 (d, *J* = 11.5 Hz, 1H), 1.49 (s, 3H), 1.39 (s, 3H); ¹³C NMR δ (100 MHz, CDCl₃): δ 174.4, 114.3, 75.7, 74.9, 45.9, 27.0, 25.9; **MS** (ESI, MeOH): *m/z* = 158.4 ([*M* + *H*]⁺). The spectral data is in agreement with the previously reported data²¹.

(-)-(3a*R*,6a*R*)-5-Ethenyl-tetrahydro-2,2-dimethyl-4*H*-1,3-dioxolo[4,5-*c*]pyrrol-4-one (7) (The preparation was followed by a reported method)²³ (from tzb-3-77)



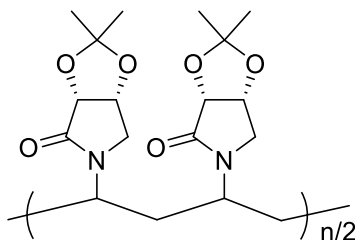
To a solution of 50 mL distilled *n*-butyl vinyl ether, 900 mg (5.7 mmol) amide (**6**) and 180 mg (0.28 mmol) of 4,7-diphenyl-1,10-phenanthroline palladium bis(trifluoroacetate) (DPP)Pd(OCOCF₃)₂²³ were added. After stirred at 70 to 80 °C for 3 hours, the reaction mixture was cooled to room temperature, washed with 10 mL water twice, and the combined organic layer was dried over anhydrous sodium sulfate, evaporated to dryness, purified on a silica gel column, eluted with hexane: acetone = 10:1 to yield 810 mg (77% yield) of desired product **7**: M.p. 81-82 °C; [α]_D²² = -20.1 (c 1.0, CHCl₃); ¹H NMR δ (400 MHz, CDCl₃): δ 7.05 (dd, *J* = 16.0, 9.2 Hz, 1 H, CH=), 4.82 – 4.79 (m, 1 H), 4.70 (d, *J* = 6.4 Hz, 1 H), 4.53 (d, *J* = 9.2 Hz, 1 H, =CH₂), 4.48 (d, *J* = 16 Hz, 1 H, =CH₂), 3.65 (dd, *J* = 10, 1.5 Hz, 1 H), 3.64 (dd, *J* = 10, 4 Hz, 1 H), 1.39 (s, 3 H), 1.35 (s, 3 H); ¹³C NMR δ (100 MHz, CDCl₃): δ 169.4, 129.2, 113.0, 96.7, 78.1, 72.1, 48.7, 27.2, 25.9; MS (ESI, MeOH): *m/z* = 184.0 ([M + H]⁺). HRMS-ESI: *m/z* [M + H]⁺ calculated for C₉H₁₄NO₃⁺: 184.0974 found: 184.0952.

Poly(3*R*,4*R*-3,4-dimethyl-*N*-vinylpyrrolidinone-co-vinyl acetate) [P(DVP-co-VAc)] (COP-1-R**) (The preparation was followed by a reported method)²⁷ (from tzb-4-44)**



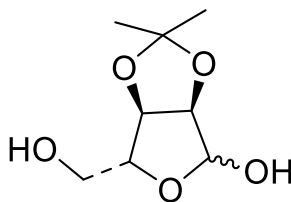
To a screw-sealing tube, a solution of 80 mg (0.437 mmol) of dried *N*-vinylpyrrolidinone (7), 0.718 mg (4.37 μ mol) of dried azobisisobutyronitrile (AIBN), and 80.5 μ L (0.873 mmol) of dried and degassed vinyl acetate in 0.2 mL of dried and degassed acetone were prepared in the nitrogen-maintained glove box. After the tube was capped with a Teflon cap with a Teflon O-ring, the tube was transferred to a hood and stirred at 70 $^{\circ}$ C for 24 h. The reaction mixture was then allowed to cool to 25 $^{\circ}$ C and diluted with chloroform. The prepared solution was added dropwise into a vigorously stirring solution of pentane. The white precipitate was collected by filtration, washed with pentane, and dried under vacuum to give 143 mg (92% yield) of copolymer **COP-1-R** as white solids. $^1\text{H NMR}$ δ (400 MHz, CDCl_3): δ 4.90 – 4.40 (m, 3 H), 3.60 – 3.00 (m, 3 H), 2.13 (s, 3H), 2.10 – 1.20 (m, 10H); $^{13}\text{C NMR}$ δ (100 MHz, CDCl_3): δ 172.5 – 169.0 (m), 112.0 (s), 77.23, 72.3, 47.0 – 42.0 (m), 37.0 – 32.0 (m), 27.3, 25.4, 21.2.

Poly[(3a*R*,6a*R*)-2,2-dimethyl-5-vinyl-dihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrol-4(5*H*)-one] (P-1-R) (from tzb-4-63)



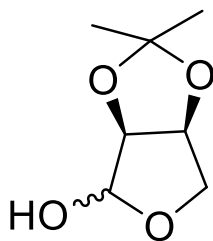
To a screw-sealing tube, a solution of 0.45 g (2.45 mmol) of vinyl lactam **7**, 4.5 mg of copolymer **COP-1-R**, 0.81 mg (4.9 μ mol) of AIBN in 1 mL of degassed ethyl acetate was prepared in a glove box maintained with nitrogen. After the tube was capped with a Teflon cap with a Teflon O-ring, the tube was then transferred to a hood and stirred at 75 °C for 16 h. After the reaction mixture was cooled to 25 °C, the reaction mixture was diluted with chloroform. The solution was then added dropwise to a solution of pentane with white solid precipitated. The white solid was then collected and dried under vacuum to give 0.44 g (98% yield) of chiral polymer (**P-1-R**) as white powders: $^1\text{H NMR}$ δ (400 MHz, CDCl_3): δ 4.80 – 4.45 (bs, 2 H, CHO), 3.8 – 3.0 (m, 3 H, CHN, CH_2N), 1.80 – 1.2 (m, 8 H, CH_2 , 2 CH_3); $^{13}\text{C NMR}$ δ (100 MHz, CDCl_3): δ 171.6 (m), 112.1 (bs, O-C-O), 78.0 (bs, C-O), 72.4 (bs, C-O), 47.0 – 43.0 (m, CHN and CH_2N), 36.5 – 31.0 (m, CH_2), 27.4 (bs), 25.4 (bs).

***D*-2,3-*O*-(1-Methylethylidene)-ribofuranose (**9**)** (The preparation was followed by a reported method)²² (from **tzB-1-31**)



To a round bottom flask, were added 15 g (0.1 mol) of *D*-ribose (**8**), 30 g (0.2 mol) of copper sulfate, 100 mL distilled acetone. The reaction mixture was stirred at 25 °C for 12 h with the color changed from light blue to darker blue. Then, the reaction mixture was filtered through Celite and washed with 200 mL acetone. The filtrate was dried over anhydrous sodium sulfate, evaporated to dryness to obtain 12 g (63% yield) desired product of **9** as light-yellow oil: **¹H NMR** (400 MHz, CDCl₃): δ 5.52 (d, *J* = 6.0 Hz, 1H), 5.41 (d, *J* = 5.4 Hz, 1H), 4.81 (d, *J* = 5.9 Hz, 1H), 4.58 (d, *J* = 5.9 Hz, 1H), 4.39 (br s, 1H), 4.20 (br s, 1H), 3.71 (br s, 2H), 1.49 (s, 3H), 1.33 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ 112.2, 102.7, 87.6, 86.7, 81.6, 63.5, 26.3, 24.7. The spectral data is in agreement with the previously reported data³².

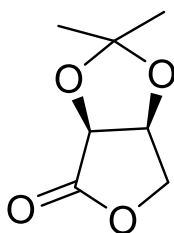
(3a*S*,4*S*,6a*S*)-2,2-Dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol (10**)** (The preparation was followed by a reported method)²⁴ (from tzb-1-28)



To a round bottom flask over an ice bath, were added 18 g (95 mmol) of alcohol (**9**), 300 mL deionized water and 100 mL ethanol. To the solution, 5.3 g (140 mmol) of sodium borohydride in 46 mL water was added dropwise and stirred for 3 h at 25 °C. After the reaction mixture was acidified to pH~5 with 1 N HCl, a slurry mixture of 24 g (113 mmol) of sodium metaperiodate and 80 mL water was added into the flask over 5 min. The reaction mixture was then left to stir for 5

h, filtered and rinsed with ethanol. The filtrate was concentrated to 75 mL, extracted with 100 mL ethyl acetate for three times. The combined organic layer was then dried over sodium sulfate, filtered through Celite, concentrated to dryness to furnish 15.2 g (83% yield) desired product of **10** as light-yellow oil: **¹H NMR** (400 MHz, CDCl₃): δ 5.43 (s, 1H, C1-H), 4.87 (dd, *J* = 6, 3.6 Hz, 1H, C3-H), 4.61 (d, *J* = 6 Hz, 1H, C2-H), 4.11 (dd, *J* = 10.4, 3.6 Hz, 1H, C4-H), 4.06 (d, *J* = 10.4 Hz, 1H, C4-H), 2.80 – 2.70 (bs, 1H, OH), 1.48 (s, 3H), 1.33 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ 112.3, 101.8, 85.1, 80.0, 72.0, 26.2, 24.7; α:β anomers (3.8:1): **¹H NMR** (400 MHz, CDCl₃): δ 5.00 – 4.90 (m, 1H, C1-H), 4.76 (dd, *J* = 6, 3.6 Hz, 1H, C3-H), 4.49 (d, *J* = 6 Hz, 1H, C2-H), 3.95 (d, *J* = 10.4 Hz, 1H, C4-H), 3.55 (dd, *J* = 10.4, 3 Hz, 1H, C4-H), 1.80 – 1.60 (bs, 1H, OH), 1.55 (s, 3H), 1.38 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ 113.4, 97.4, 79.6, 78.3, 67.6, 26.0, 24.9. The spectral data is in agreement with the previously reported data³³.

(3a*S*,6a*S*)-2,2-Dimethyl-dihydrofuro[3,4-*d*][1,3]dioxol-4(3a*H*)-one (11) (The preparation was followed by a reported method)²⁵ (from **tz**-3-41)



To a round bottom flask containing 2 g (3 Å) of molecular sieves, it was dried under vacuum and replaced with argon for three times. After the flask was cooled to 25 °C, 8.9 mL (9.75 g, 125 mmol) of dried dimethyl sulfoxide in 25 mL dichloromethane was added under argon. Then, the solution was cooled over a dry-ice acetone bath to -78 °C followed by the addition of 5.3 mL

(7.87g, 62.5 mmol) dried oxalyl chloride in 25 mL dichloromethane dropwise. After the solution was stirred for 15 min, 5 g (31.25 mmol) of dried lactol (**10**) in dichloromethane was added and stirred at -78 °C for 2 hours. Then, 27 mL (187.5 mmol) of triethylamine was added, and the temperature was allowed to increase to 25 °C and stirred for another 2 hours. The reaction mixture was diluted with 100 mL water, acidified with 1 N HCl to pH~3, extracted with 150 mL dichloromethane for three times. The combined organic layer was then dried over anhydrous sodium sulfate, filtered through a thin layer of silica gel, washed with dichloromethane, concentrated to dryness to yield 2.8 g (56% yield) desired product of **11** as a white waxy solid. **¹H NMR** (400 MHz, CDCl₃): δ 4.89 (dd, *J* = 6, 4 Hz, 1H), 4.76 (d, *J* = 6 Hz, 1H), 4.47 (d, *J* = 11 Hz, 1H), 4.42 (dd, *J* = 11, 4 Hz, 1H), 1.50 (s, 3H), 1.41 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ 174.1, 114.1, 75.5, 74.6, 70.2, 26.8, 25.7. The spectral data is in agreement with the previously reported data²⁵.

Chapter 2 - Oxidative Reactions Catalyzed by Bimetallic Nanoclusters

2.1. Introduction and Background

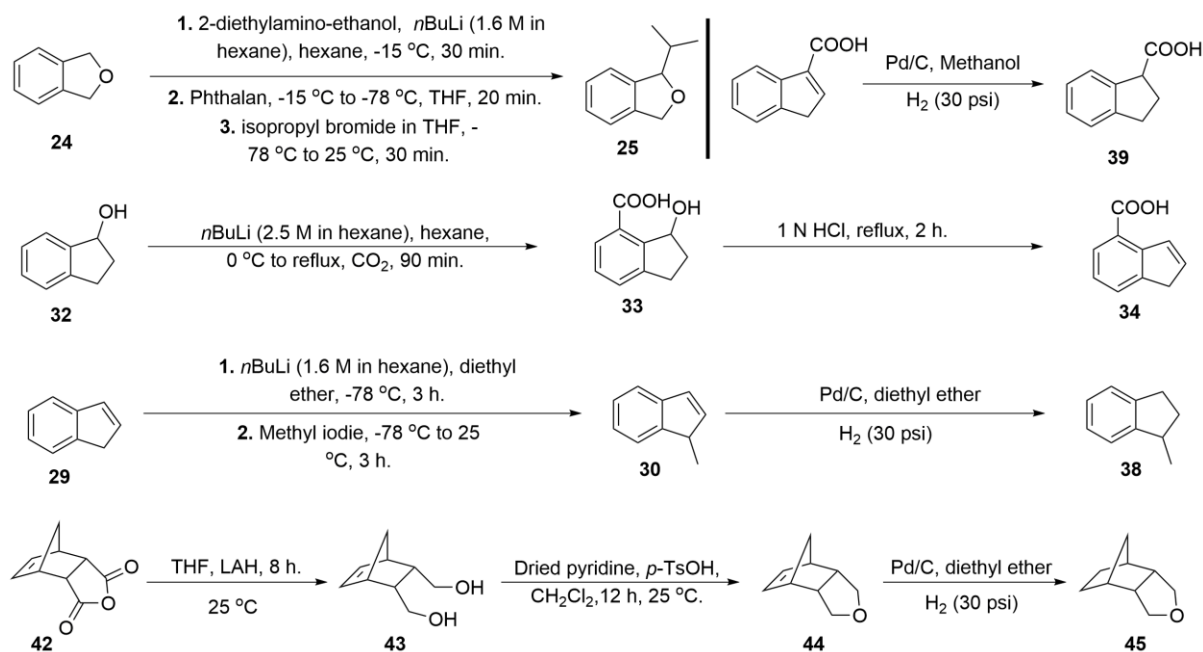
In our previous work, Hua designed a series of different CSPVP-supported nanocatalysts with different substituents at C5 onto the pyrrolidinone ring, which exhibited excellent enantioselectivities in catalytic reactions¹⁰. For the purpose of preparing two colloidal nanocatalysts with opposite enantioselectivities, Hua designed a pair of chiral polymers with opposite stereochemistry described in Chapter 1. The nanocatalysts prepared by this pair of CSPVPs are expected to display opposite enantioselectivities in catalytic reactions. Before exploring the enantioselectivities of CSPVP-supported colloidal nanocatalysts, we first studied a series of oxidative reactions using substrates such as phthalan, norbornene, indene, indane and their derivatives by using different PVP-supported bimetallic colloidal nanocatalysts (Pd/Au and Cu/Au) and different oxidants (TBHP, H₂O₂) in two types of solution system (DMF and H₂O/CH₃CN) to uncover the chemical reactivity.

Before discussing oxidative results, a brief introduction about the colloidal nanocatalysts, oxidants and substrates is discussed. In 1989, Haruta firstly reported his discovery that aerobic CO can be catalyzed by Au NCs at low temperatures, which influenced academia and industry significantly.³⁴ After that, lots of research were conducted to explore the applications of noble NCs in C-C bond coupling,³⁵ aerobic alcohol oxidation,³⁶ asymmetric oxidation of secondary alcohols.³⁷ For C-H functionalization, the C-H activation is the rate determining step in the NCs catalyzed procedure due to the high C-H bond energy (about 98 kcal/mol). Generally, the electrons

are involved in the catalytic process of C-H activation through a single electron transfer mechanism. Due to that property, metallic NCs are allowed to activate C-H bond as an active catalyst.³⁸ In 2011, Tsukuda proposed a mechanism to explain the activation aerobic oxygen in catalytic oxidation using PVP capped Au NCs as catalysts. The oxygen is absorbed and activated to form peroxo-like species to activate the C-H bond by taking the proton off.^{39, 40} Then, the substrate is converted to ketone.⁴¹

To facilitate the discussion of the catalytic oxidation of C-H bond, I would like to propose a mechanism to explain our experimental results based on following studies: 1. In the oxidation catalyzed by PVP-capped Au NCs and O₂, the electrons flew from anionic Au on NCs into the LUMO (π^*) of oxygen, generating superoxo or peroxo type species;¹⁶ 2. For bimetallic nanoclusters Au and Pd are miscible in any proportion,⁴² which means small amount of Au atoms still exist on the Pd-rich surface; 3. Cu/Au and Pd/Au colloidal nanocatalysts were prepared in the ratio of 3:1, and the electronegativities (EN) of Cu, Pd, Au, C and O are 1.90, 2.20, 2.54, 2.55, 3.44 respectively.⁴³ Based on previous statements, the catalytic reaction may be facilitated by increasing the electron-density of oxygen onto oxidants (TBHP or H₂O₂).

2.2. Syntheses of Substrates



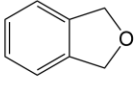
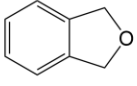
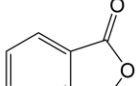
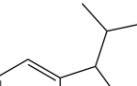
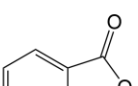
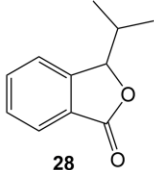
Scheme 7. Syntheses of substrates for catalytic reactions.

In **Scheme 7**, the syntheses for substrates are displayed. To obtain isopropyl phthalan (**25**), 2-diethylamino-ethanol was mixed with *n*-butyllithium (1.6 M in hexane) in hexane. The reaction mixture was stirred at -15 °C for 30 min. Then, phthalan (**24**) was added and stirred for 20 min. After the reaction mixture was cooled to -78°C, THF was added followed by the addition of isopropyl bromide. The reaction mixture was allowed to warm up to 25 °C and stirred for 15 min to yield isopropyl phthalan (**25**) in a yield of 72%.⁴⁴ The substrate of indene-4-carboxylic acid (**34**) was synthesized from 1-indanol (**32**) by treating it with *n*-BuLi (2.5 M in hexane) at 0 °C. Then, the reaction mixture was heated to reflux and bubbled with aerobic CO₂ for 2 h to yield compound **33** in a yield of 26%. The carboxylic acid of **33** was dissolved with 1 N HCl. The reaction mixture was then heated to reflux for 2h to eliminate the alcohol to olefin of **34** in a yield of 72%. To obtain

indane-4-carboxylic acid (**39**), a hydrogenation bottle containing 1*H*-indene-3-carboxylic acid, 5% Pd/C, methanol was shook for 12 h under hydrogen atmosphere to give indane-3-carboxylic acid in a yield of 91%. 1-methyl-indene (**30**) was prepared by treating indene (**29**) with *n*-BuLi (1.6 M in hexane) at -78 °C for 3 h. Then the reaction mixture was added with methyl iodide and stirred for 3 h, and the temperature was allowed to warm up to room temperature to afford the desired product **30** in a yield of 46%.⁴⁵ The compound was then transferred into hydrogenation bottle and mixed with 5% Pd/C and methanol. The hydrogenation bottle was then attached onto a hydrogenation apparatus, purged with hydrogen in a pressure of 30 psi, shook for 12 h at 25 °C to give 1-methylindane in a yield of 95%. The norbornene substrates of **44** and **45** were synthesized from carbic anhydride (**42**) by reduced it with lithium aluminium hydride (LAH) in THF at 25 °C for 8 h to furnish diol **43** in a yield of 43%. The diol **43** was then mixed with pyridine in CH₂Cl₂ to give alkoxide ions. To the reaction mixture, *p*-toluene sulfonic acid was added slowly over 12 h to yield the cyclized product **44** in a yield of 60%.⁴⁶ To a hydrogenation bottle, compound **44**, diethyl ether, Pd/C was added. A hydrogenation was conducted in this bottle by shaking it at 25 °C for 12 h to afford compound **45** in a yield of 95%.

2.3. Oxidation of Derivatives of Phthalan

Table 1. Results of catalytic oxidations of phthalan and its derivative.

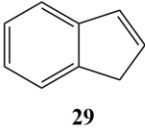
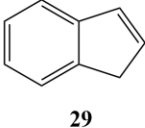
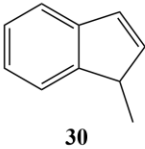
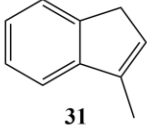
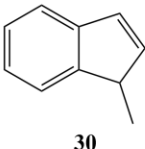
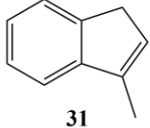
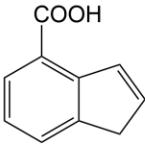
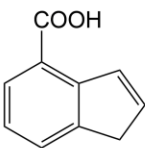
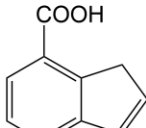
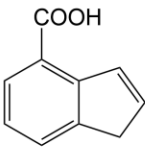
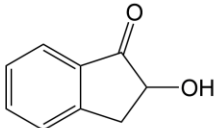
Entry	Substrates	Catalyst	Oxidant	°C/ h	Product	recovered
1	 24	None	H ₂ O ₂ , 10 eq.	25 °C / 24 h	-	-
2	 24	Cu/Au - 40k PVP, 5% mol (20 mM)	H ₂ O ₂ , 10 eq.	25 °C / 24 h	 27 58% yield	26 %
3	 25	Cu/Au - 40k PVP, 5% mol (20 mM)	H ₂ O ₂ , 10 eq.	25 °C / 45 h	 27 24% yield  28 20% yield	-

In this section, phthalan (**24**) and its derivative (**25**) were selected and treated with different colloidal nanocatalysts (Pd/Au-PVP or Cu/Au-PVP) and different oxidants (H₂O₂ or TBHP) (see **Table 1**). Firstly, an oxidative reaction was set up by dissolving phthalan (**24**) and 10 equivalents of 30% H₂O₂ (in H₂O) in a solution of H₂O/CH₃CN without nanocatalyst. The reaction exhibited no progress at 25 °C for 24 h. Once the catalyst (Cu/Au-PVP) was added, the conversion from phthalan to isobenzylfuranone (**27**) in the catalytic reaction increased to 58% within 24 h. The results suggested that the Cu/Au nanocatalyst is an indispensable reagent to activate the C-H bond of phthalan in this catalytic oxidation. During this oxidation, no intermediate, such as lactol or peroxide, was found or isolated, indicating the oxidation from intermediate (lactol or peroxide) to lactone of **27** is faster than the oxidation from starting material of **24** to the intermediate.

In order to study the regioselectivity of C-H bonds in tertiary and secondary carbons, isopropyl phthalan (**25**) was synthesized⁴⁴ and treated with H₂O₂ under the catalysis of Cu/Au nanocatalysts in H₂O/CH₃CN solution system. The oxidative reaction was finished in 45 h at 25 °C to furnish lactone of **27** and isopropyl phthalanone of **28** as oxidative products with yields of 24% and 20%, respectively. Results indicated that there is no significant difference in activating C-H bonds connecting to tertiary and secondary types of carbon adjacent to aromatic ring and oxygen in this oxidative reaction.

2.4. Oxidation of Indene and their Derivatives

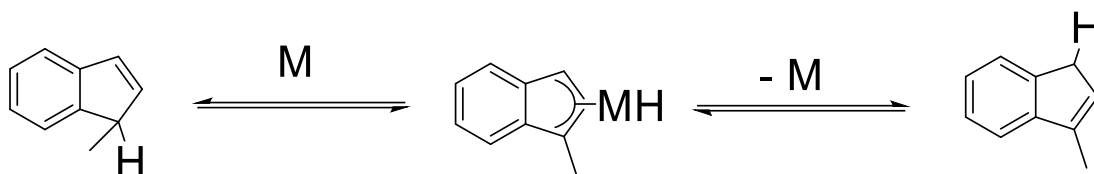
Table 2. Results of catalytic oxidations of indene and its derivatives.

Entry	Substrates	Catalyst	Oxidant	°C/ h	Product	recovered
1	 29	Pd/Au-40kPVP in H ₂ O (10 mM) 1% mol	TBHP, 1.5 eq.	80 °C / 48 h	Decomposed	–
2	 29	Cu/Au-40kPVP in H ₂ O (10mM) 0.5% mol	H ₂ O ₂ , 1.5 eq.	80 °C / 48 h	Decomposed	–
3	 30	Pd/Au-40kPVP in DMF (10mM) 1% mol	TBHP, 1.5 eq.	25 °C / 12 h	 31 100% conversion (Based on NMR)	–
4	 30	Pd/Au-40kPVP in H ₂ O (25 mM) 1% mol	TBHP, 1.5 eq.	25 °C / 12 h	 31 15% conversion (Based on NMR)	85%
5	 34	Pd/Au-40kPVP in DMF (25 mM) 1% mol	TBHP, 1.5 eq.	25 °C / 12 h	Decomposed	–
6	 34	Pd/Au-40kPVP in H ₂ O (25 mM) 1% mol	TBHP, 1.5 eq.	25 °C / 24 h	 34a 100% conversion (Based on NMR)	–
7	 34	Cu/Au-40kPVP in H ₂ O (10 mM) 1% mol	H ₂ O ₂ , 2.0 eq.	50 °C / 16 h	 35 45% yield	–

The previous oxidation results suggested that the C-H bond adjacent to a benzene ring and an oxygen atom can be easily activated and oxidized to a lactone. In order to investigate oxidative result(s) of a sp^2 carbon adjacent to a benzene ring, we selected indene (**29**) and its derivatives of **30** and **34** for the studies (see **Table 2**). To begin with, a pair of oxidative reactions were set up with indene as the substrate to compare the oxidative differences from Cu/Au and Pd/Au nanocatalysts. Indene, PVP-supported Cu/Au (in H_2O) and 1.5 equiv of 30% H_2O_2 were dissolved in H_2O/CH_3CN . For the second reaction, indene, PVP-supported Pd/Au (in H_2O) and 1.5 equiv of 70% TBHP were dissolved in H_2O/CH_3CN . There was no oxidative progress for the pair of reactions with temperature went up until they began to decompose at $80^\circ C$, which may be caused by the formation of π complex or allyl complex.

In the next stage, another pair of reactions were set up using 1-methylindene (**30**) as substrate. In this batch, the substrate was treated with Pd/Au colloidal nanocatalysts in different solutions to compare the oxidative differences in H_2O and DMF. The pair of reaction mixtures were prepared by dissolving substrate **30**, TBHP (70% in water) in different solutions of H_2O and DMF. The two reaction mixtures were left to stir at $25^\circ C$ for 12 h with conversion rates of 100% and 15% in DMF and H_2O , respectively. Results demonstrated that the olefin migration reaction proceeded faster in DMF than in water solution. In this reaction, no oxidative product was found. Therefore, the necessity of oxidants to this migrating reaction is uncertain. I proposed a plausible mechanism for the migration reaction in **Scheme 8**. The tertiary carbon-hydrogen bond is inserted by a metal atom, and the metal-H is migrated by the π -allyl mechanism to give 3-methylindene (**31**). The different conversion rates in DMF and H_2O may be caused by that the metal atom in the

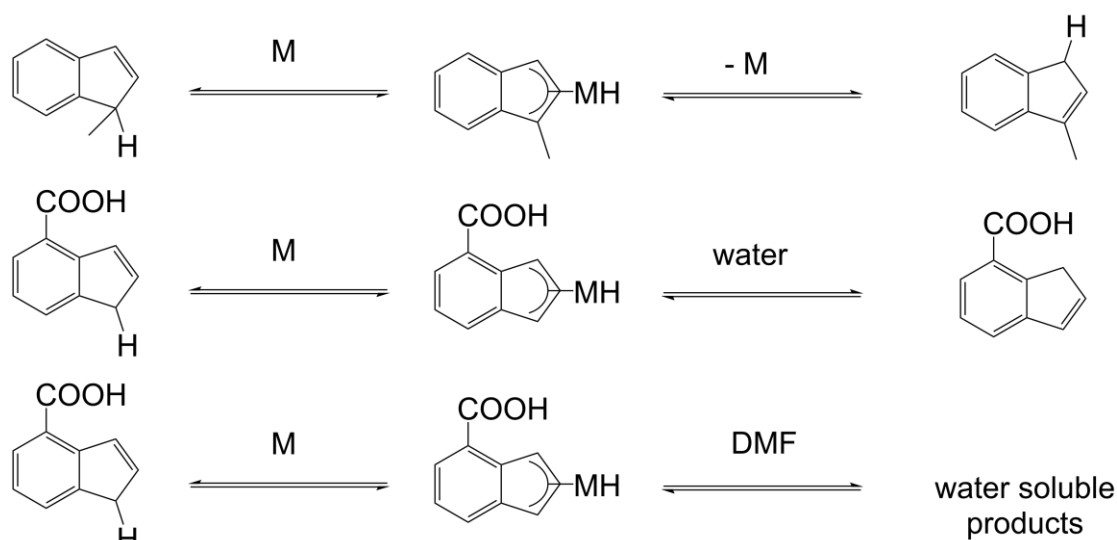
water solution has a higher possibility to chelate with a proton rather than participating in a migration reaction.



Scheme 8 Proposed mechanism for the migration of 1-methyl-indene.

In order to study the sp^2 carbon oxidation influenced by carboxylic acid in the benzene ring, three oxidative reactions were set up in different conditions using 1*H*-indene-4-carboxylic acid (**34**) as the substrate. A pair of oxidative reactions were set up by dissolving substrate **34**, 1.5 eq. TBHP (70% in water), and Pd/Au-PVP nanocatalysts in solutions of DMF or water. For the pair of reactions, the substrate decomposed in DMF solution, while the substrate in the water solution gave the migrated 1*H*-indene-7-carboxylic acid (**34a**) at a conversion rate of 100%. For these results, I proposed a plausible mechanism to explain the differences in different solutions and substrates (**Scheme 9**). Comparing with the complex of 1-methylindene (**30**) and metallic atom, its 1*H*-indene-4-carboxylic acid (**34**) counterparts is more electrophilic caused by the existence of carboxylic acid group as an electron-withdrawing group, which gives the 1*H*-indene-4-carboxylic acid (**34**) complex a lower LUMO energy level. For the 1*H*-indene-4-carboxylic acid (**34**) complex in water solution, the abundant protons tend to chelate with the metallic atoms, which gives less metal-oxidant complex than DMF solution. In the DMF solution, the number of metal-oxidant complex increases. The facilitated metal-oxidant complexes are more nucleophilic and tend to give a higher HOMO energy level. The decreased LUMO energy level caused by carboxylic acid and the increased HOMO energy level lead to a low energy barrier, which allows the oxidation of

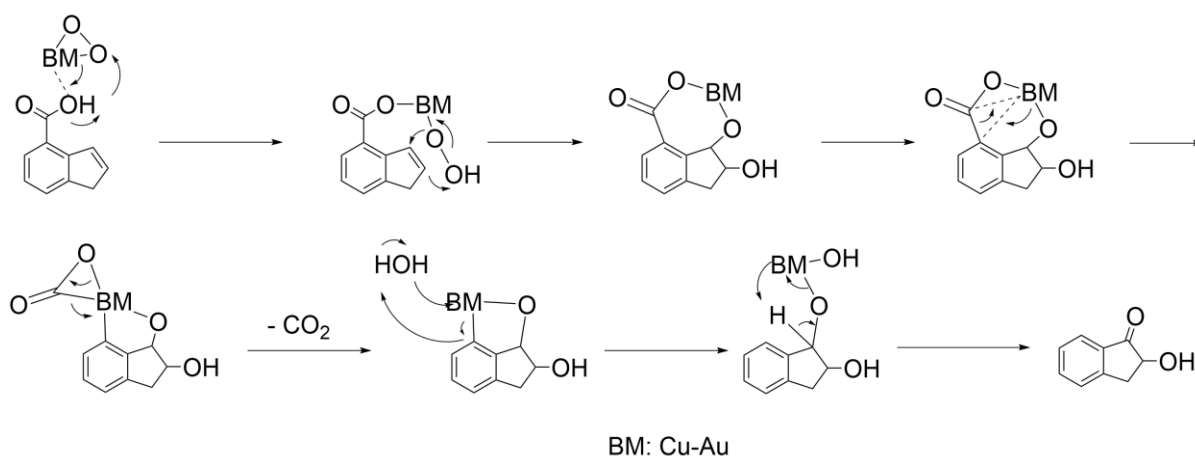
metal-substrate progress at 25 °C. The oxidized substrates tend to experience further oxidation due to the further decreased LUMO energy level caused by the removal of the electron-rich olefin and the introduction of oxygen as an electron-withdrawing group. Therefore, the 1*H*-indene-4-carboxylic acid (**34**) tends to be decomposed in DMF solution and migrated in water solution, while 1-methylindene (**34**) tends to be migrated in both DMF and water solution due to a higher LUMO energy level from the metal-substrate complex.



Scheme 9. Proposed mechanism for the migration of indene-4-carboxylic acid and explanations for different results.

The decomposition of carboxylic acid **34** suggests that the potential to oxidize the sp^2 carbon under certain reaction conditions. Therefore, an oxidative reaction was set up for carboxylic acid **34** using Cu/Au-PVP colloid and 30% hydrogen peroxide in water solution at 50 °C for 60 h. In this oxidative reaction, an oxidation of the olefin was observed by degrading the carboxylic acid in the benzene ring. I proposed a mechanism for the formation of (**35**). In **Scheme 10**, the Au-Cu-O-O complex is inserted into the O-H bond. Then, the olefin is oxidized by the peroxide complex

to produce the corresponding diol with one oxygen chelated with Au-Cu complex. A rearrangement takes place to insert Au-Cu complex between the carbonyl and the benzene ring followed by a release of carbon dioxide as gas. The metal-benzene bond is hydrolyzed by H₂O to finish the decarboxylation process. After that, carbon adjacent to the benzene ring and an oxygen atom is oxidized to a ketone as the desired product.

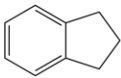
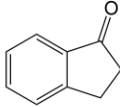
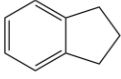
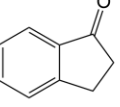
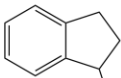
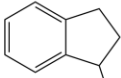
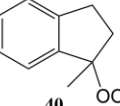
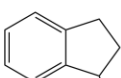
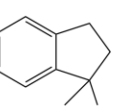
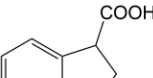
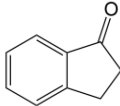
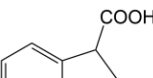
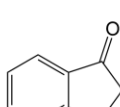
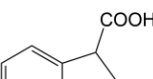
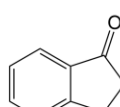


Scheme 10. Proposed mechanism for the oxidation of 2-indene-4-carboxylic acid.

In this section, a series of oxidative reactions of indene and its derivatives were investigated. The results suggested that the electron-rich sp² carbon cannot be easily oxidized due to the nucleophilicity of these alkenyl substrates. In order to introduce oxygen into this moiety in water, Cu/Au can be used to enhance the electron conductivity from the substrate to oxidant.

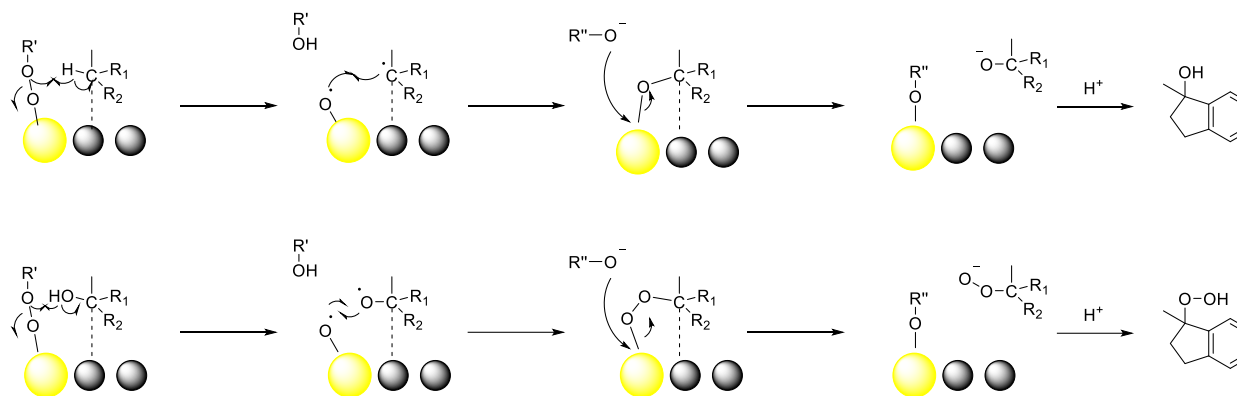
2.5. Oxidation of Indane and Indene and their Derivatives

Table 3. Results of catalytic oxidations of indane and its derivatives.

Entry	Substrates	Catalyst	Oxidant	°C/ h	Product	recovered
1	 37	Cu/Au-40kPVP in H ₂ O (10 mM) 0.5% mol	H ₂ O ₂ , 1.5 eq.	50 °C / 72 h	 41 8 % conversion	–
2 ^a	 37	Cu/Au-1R in H ₂ O (10 mM) 2% mol	H ₂ O ₂ , 1.5 eq.	50 °C / 72 h to 25 °C / 15 h	 41 6 % to 35% conversion	–
3	 38	Cu/Au-40kPVP in H ₂ O (10 mM) 1% mol	H ₂ O ₂ , 2.0 eq.	50 °C / 48 h	very low conversion (Based on NMR)	–
4	 38	Pd/Au-40kPVP in H ₂ O (10 mM) 1% mol	TBHP, 1.5 eq.	50 °C / 72 h	 40 10% conversion (Based on NMR)	–
5	 38	Pd/Au-40kPVP in DMF (25 mM) 1% mol	TBHP, 1.5 eq.	50 °C / 24 h	 40 14% yield	20 %
6	 39	Pd/Au-40kPVP in DMF (25 mM) 1% mol	TBHP, 1.5 eq.	50 °C / 20 h	 41 30% conversion from NMR	–
7	 39	Pd/Au-40kPVP in H ₂ O (25 mM) 1% mol	TBHP, 1.5 eq.	50 °C / 20 h	 41 40% yield	45 %
8	 39	Cu/Au- 40kPVP in H ₂ O (25 mM) 1% mol	H ₂ O ₂ , 1.5 eq.	50 °C / 20 h	 41 16% conversion (Based on NMR)	–

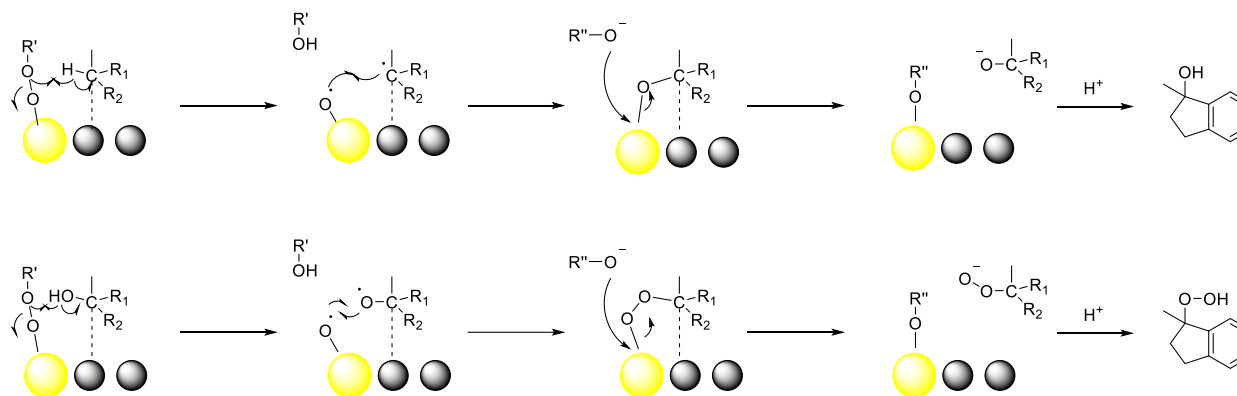
In this section, indane (**37**) and its derivatives **38** and **39** were selected as substrates to investigate the oxidative reaction of sp^3 carbon adjacent to a benzene ring using nanocatalysts (see **Table 3**). Initially, indane (**37**) was treated with an oxidative system prepared by dissolving 30% H_2O_2 and Cu/Au-PVP nanocatalysts in a water solution. The reaction progressed slowly (7% conversion) at 50 °C in 72 h. In order to study the effects from pH on this oxidative reaction, an oxidative reaction was set up in the same conditions as the previous one with extra potassium carbonate added. Significant progress was then detected at 25 °C in 15 h with a conversion rate of 35%. The results suggested the oxidative reaction prefers basic conditions.

For the purpose of investigating differences of tertiary and secondary carbons adjacent to a benzene ring in these oxidative reactions, a couple of different oxidative reactions were conducted using 1-methylindane (**38**) as the substrate in different oxidative conditions. For the aqueous batch, only a 10% conversion rate was observed, while the DMF batch converted approximate 50% of starting materials to an oxidative product **40** based on the NMR data. However, only 14% yield was obtained after column chromatography, which may be caused by the decomposition of the peroxide **40**. The mechanism of oxidizing 1-methyl-indane (**38**) to product **40** is described in **Scheme 11**. In **scheme 11**, the 1-methylindane (**38**) and TBHP are connected by bimetallic atoms to form an electron transfer chain, which decrease the electron density of the substrate but increase the electron density of the oxidant. After that, a radical reaction takes place to convert 1-methylindane (**38**) to 1-methyl-1-indanol as the intermediate. Then, the alcohol undergoes a radical reaction to cleave the O-H to give the peroxide **40** rapidly due to the C-CH₃ is not electron-deficient enough to get cleaved.



Scheme 11. Catalytic oxidation of 1-methylindane.

With an electron-withdrawing group connecting to a tertiary carbon, indanyl-1-carboxylic acid (**39**) was selected as the substrate to study the oxidation outcomes of the tertiary carbon in different reaction conditions. In these reactions, the Pd/Au nanocatalyst using TBHP exhibited better catalytic activity than Cu/Au nanocatalysts using H_2O_2 and the Pd/Au in water solution displayed a stronger oxidative activity than its DMF counterparts. In **Scheme 12**, the indanyl-1-carboxylic acid (**39**) and TBHP are chelated with the bimetallic atoms to form an electron transfer chain to decrease the electron density of the substrate and increase the electron density of the oxidant. Then, a radical reaction takes place to activate the C-H bond as the C-H bond is weakened by the decreased electron density. The cleaved C-H bond is then oxidized to a lactol. In the next stage, the carboxylic acid undergoes a radical reaction to cleave the C-COOH bond, which is weakened by its electron-deficiency, to release the carboxylic group as CO_2 gas. The substrate is then oxidized to a diol and converted to the indanone (**41**) immediately.

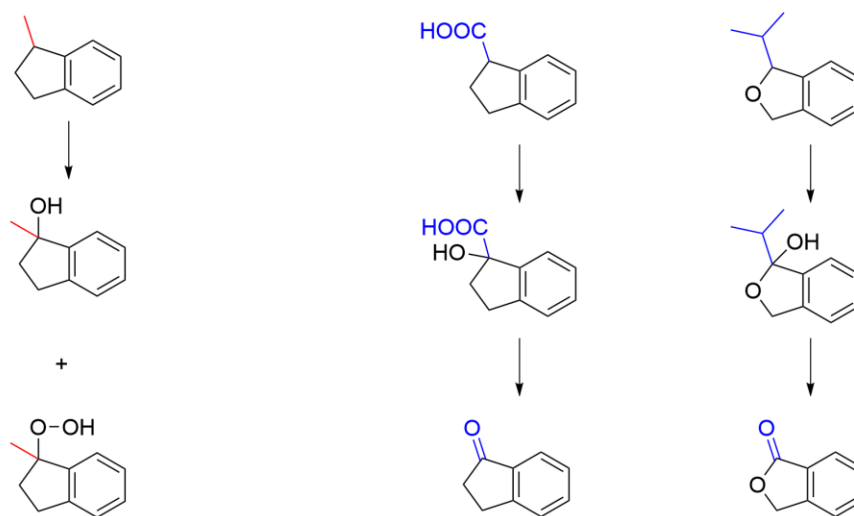


Scheme 12. Catalytic oxidation of indane-1-carboxylic acid.

Differ from previous substrates, the indanyl-1-carboxylic acid (**39**) is an acid. In the DMF solution, compound **39** may supply their protons to oxidants, which decreases the nucleophilicity of oxidants. In the water solution, a slightly higher conversion rate was observed, this difference can be explained by the dilution of protons from the substrates in the protic solution ($\text{H}_2\text{O}/\text{CH}_3\text{CN}$). In **Scheme 13**, I compared the oxidative results (second oxidation step) from 1-methylindane, 1-indane-carboxylic acid and *iso*-propylphthalan. Due to their electron-deficiency of the C-C bonds, different oxidative products were obtained. For the 1-methyl-1-indanol, the reactive carbon is only attached to an oxygen atom. It is not electron-deficient enough to cleave the C- CH_3 bond even under the facilitation of the bimetallic electron-transfer chain. In terms of the reactive carbon in 1-methyl-1-indane-carboxylic acid, the C-COOH bond is weakened by the carboxylic group as an electron-withdrawing group. Therefore, the reaction happens at 50 °C. For the phthalan one, the reactive carbon is attached to two oxygen, which makes it more electron-deficient than another two intermediates. Hence, the *iso*-propyl-phthalanol can be oxidized to lactone at 25 °C. In this section, we studied a series of catalytic oxidation of the C-C or C-H bond adjacent to a benzene

ring. The results suggested that the electron-deficiency decides the possibility to cleavage the C-C bond. Moreover, pH value plays an important role in facilitating the oxidants.

Not electron-deficient enough to cleavage the C-C bond Electron-deficient enough to cleavage the C-C bond

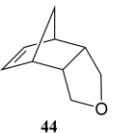
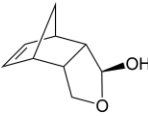
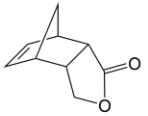
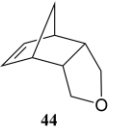
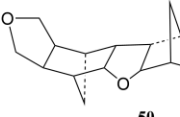
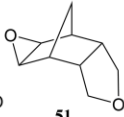
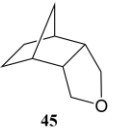
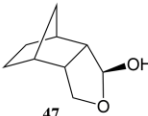
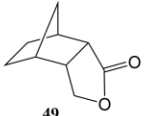
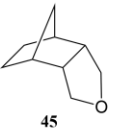
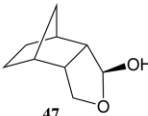
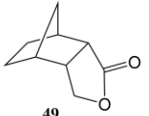
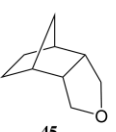
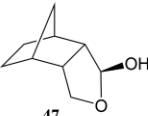
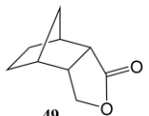


Scheme 13. Cleavage of C-C bond is decided by the electron-deficiency of these carbons.

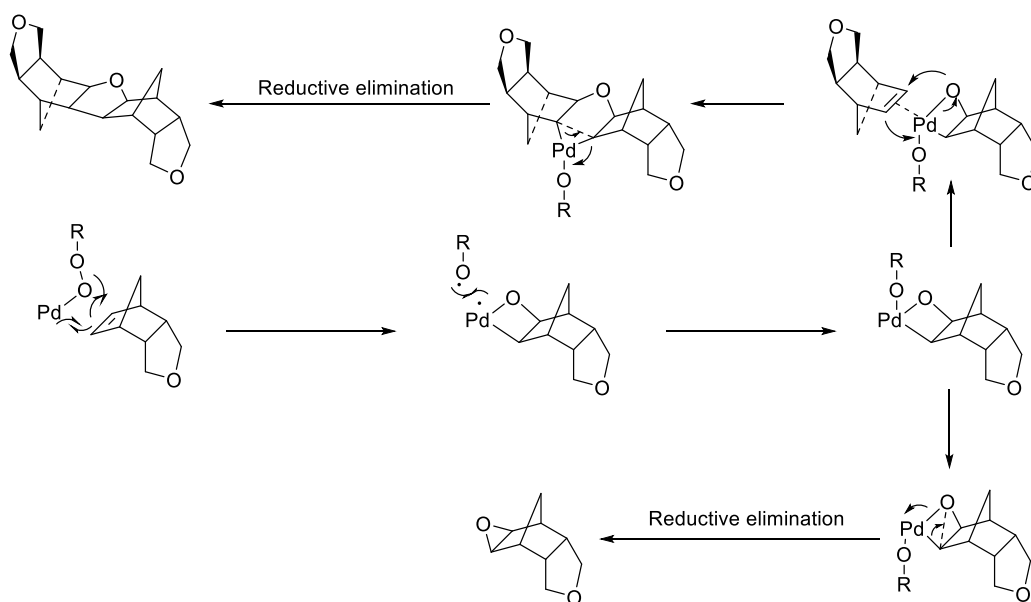
2.6. Oxidation of Derivatives of Norbornene **44** and Norbornane **45**

In our continuing study of other oxidative reactions using PVP-supported nanocatalysts, norbornene **44** and norbornane **45** with rigid rings were selected to explore more catalytic reactions (Table 4). For norbornene **44**, an oxidative reaction was set up using Cu/Au-PVP nanocatalysts and 30% H₂O₂ in water solution at 25°C to produce lactol **46** and lactone **48** in low yields of 6% and 8% respectively. Decomposition of products was also found in this reaction.

Table 4. Results of catalytic oxidations for Norbornene derivatives.

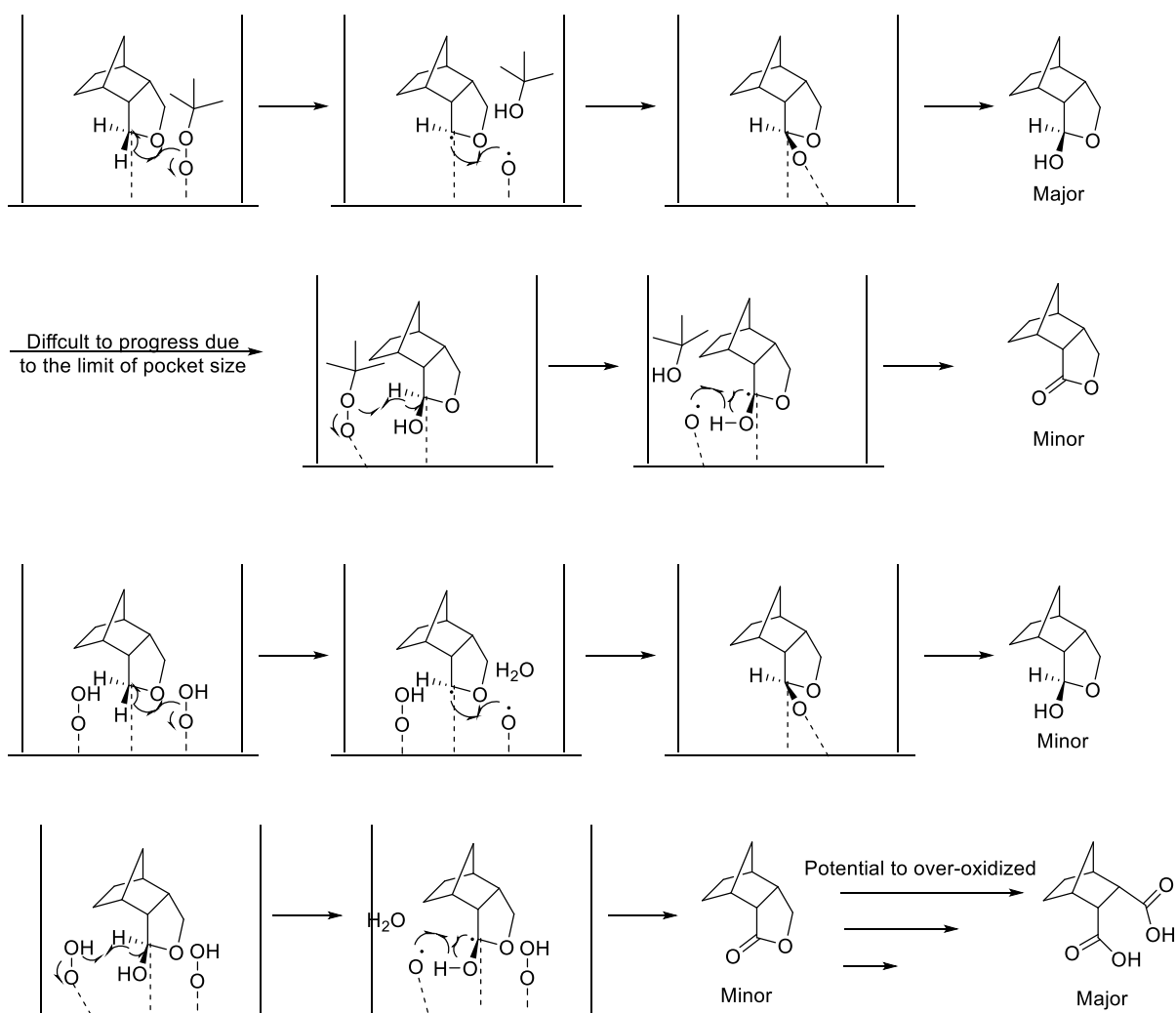
Entry	Substrates	Catalyst	Oxidant	°C/ h	Product	recovered
1	 44	Cu/Au - 40k PVP, 2.5% mol (4 mM)	H ₂ O ₂ , 15 eq.	25 °C / 72 h	 46 6% yield  48 8% yield	10 %
2	 44	Pd/Au - 40k PVP, 2% mol (1.6 mM)	TBHP, 1.2 eq.	25 °C / 144 h	 50 24% yield  51 9% yield	16 %
3	 45	Cu/Au - 40k PVP, 2.5% mol (25 mM)	TBHP, 1.5 eq.	50 °C / 12 h	 47 53% yield  49 16% yield	13 %
4	 45	Cu/Au - 40k PVP, 2.5% mol (9 mM)	H ₂ O ₂ , 15 eq.	25 °C/ 16 h	 47 7% yield  49 7% yield	-
5	 45	Pd/Au - 40k PVP, 2.5% mol (25 mM)	TBHP, 1.5 eq.	50 °C / 12 h	 47 31% conversion Based on NMR  49 3% conversion Based on NMR	-

Then, norbornene **44** was treated with another type of oxidative condition using Pd/Au-PVP nanocatalysts and TBHP in H₂O/CH₃CN solution at 25°C. It took about 6 days to convert a portion of starting material **44** to dimer **50** and epoxide **51** with isolated yields of 24% and 9%, respectively. I proposed a mechanism to explain the formations of dimer **50** and epoxide **51** in **Scheme 14**. Differ from previous oxidations, the oxidation of olefin is conducted by palladium, which is usually chelated with electron-rich double bond. The activated peroxide-metal complex undergoes a radical reaction to form a four-member ring. Then, the palladium can chelate with another olefin to introduce another olefin **44** into this four-member ring to produce a six-member ring. A reductive elimination happens to furnish dimer **50** as the desired product. At low temperature, the four-member ring intermediate is allowed to survive long enough to meet another olefin **44** to form the dimer **50**. As the temperature increases, the four-member ring has an increasing possibility to experience a reductive elimination to produce the epoxide **51** before the presence of another olefin **44**.



Scheme 14. Proposed mechanism for the formation of dimer and epoxide.

After that, norbornane **45** was treated with different nanocatalysts and different oxidants in $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ solution. In these oxidative reactions, H_2O_2 tends to give a lower yield of oxidative products in the catalysis of Cu/Au-PVP nanocatalysts. Under the oxidation of 1.5 equivalents of 70% TBHP in water, Cu/Au nanocatalysts exhibited relatively better oxidative results than their Pd/Au counterparts by producing lactol **47** and lactone **49** in yields of 53% and 16%.



Scheme 15. Different oxidative results using different oxidants.

In this section, low separating yields were obtained once H_2O_2 was involved as the oxidant, while its TBHP counterparts tend to give higher yields with cleaner reactions. The results can be explained by the size of reaction pockets covering reaction sites (**Scheme 15**). The co-insertion of oxidant and substrate is necessary for oxidative reactions. The endo hydrogen atom is less accessible for the radical produced by TBHP, but it is accessible for the radical produced by H_2O_2 . Due to the small size of H_2O_2 , a substrate may be surrounded by several H_2O_2 molecules which are ready to oxidize norbornene or norbornane to the dicarboxylic acid as the major product. I failed to separate the dicarboxylic acid by column, but the mass spectral data showed the existence of the dicarboxylic acid.

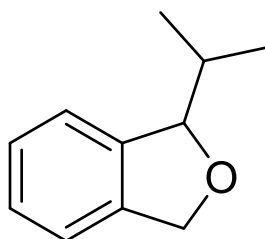
2.7. Conclusion

In this chapter, several substrates were selected to investigate the catalytic properties of PVP-supported bimetallic nanocatalysts (Pd/Au or Cu/Au) with different oxidants (TBHP and H_2O_2). The results suggest that we can optimize these oxidative reactions from the following aspects: 1. For the oxidants, TBHP is more nucleophilic than H_2O_2 as the tertiary carbon is an electron-donating group. Also, the deprotonation for oxidants is important as the complex of metal-oxidant prefers basic conditions in synergistic catalysis. In terms of the substrates, their nucleophilicity is usually affected by their electron-deficiency and rigidity; 2. Comparing the different results in TBHP and H_2O_2 , the TBHP tends to give a cleaner reaction than H_2O_2 , and even TBHP is a stronger oxidant than H_2O_2 ; 3. It seems that the size distribution of the pocket covering the reaction sites is mainly depends on the bulkiness of polymers. Therefore, the dimerization reaction needs 6 days to furnish the desired product with a yield of 24%. In order to

expand the application of our oxidation system, we also introduced DMF as a type of solution to conduct reactions favor aprotic solutions.

2.8. Synthetic Procedures

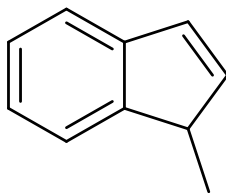
1,3-Dihydro-1-isopropyl-2-benzofuran (25) (The preparation was followed by a reported method)⁴⁴ (from tzb-3-147)



To a flame-dried and argon-purged flask, 1.59 mL (12 mmol) of 2-diethylamino-ethanol and 12 mL of distilled hexane were added, and the flask was cooled to -15 °C. To it, 15 mL (24 mmol) of *n*-butyllithium (1.6 M in hexane) was injected dropwise and the solution was stirred for 30 min at -15 °C. During that time, the color of the solution changed to orange. Then, a solution of 480 mg (4 mmol) of phthalan (**24**) in 2 mL of dried hexane was added via syringe. The reaction mixture was stirred for 20 min with the color of the reaction solution changed to dark red gradually. After the flask was cooled to -78°C, 16 mL of distilled THF was added dropwise followed by the addition of a solution of 1.878 mL (20 mmol) isopropyl bromide in 2 mL THF. The reaction mixture was warmed to 25 °C and stirred for 15 min. The reaction mixture was diluted with 20 mL water, extracted with 20 mL diethyl ether for three times. The combined organic layer was dried

over anhydrous sodium sulfate, filtered through Celite, concentrated on a rotary evaporator to give 900 mg of crude product. The crude product was purified on a silica gel column and eluted with a mixture of pentane: diethyl ether (40:1) to obtain 465 mg (72% yield) of desired product **25** as oil. **¹H NMR** (400 MHz, CDCl₃): δ 7.27-7.17 (m, 4 H, Ar-Hs), 5.14 – 5.09 (m, 3 H, CH₂O and CHO), 2.07 (d, J = 3.2, 6.8 Hz, 1 H, CH), 1.06 (d, J = 7.2 Hz, 3 H, CH₃), 0.81 (d, J = 6.8 Hz, 3 H, CH₃); **¹³C NMR** (100 MHz, CDCl₃): δ 140.9, 139.9, 127.3, 127.0, 121.6, 120.9, 88.8, 73.2, 33.9, 19.0, 16.2. MS (ESI, MeOH): m/z = 162.8 ([M + H]⁺). The spectral data is in agreement with the previously reported data.⁴⁷

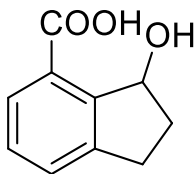
1-Methyl-(1*H*)-indene (30) (The preparation was followed by a reported method)⁴⁵ (from tzb-4-124)



To a solution containing 6 g (51.8 mmol) of indene (**29**) and 40 mL distilled diethyl ether, 32.4 mL (51.8 mmol) of *n*-butyllithium (1.6 M in hexane) was added dropwise at - 78 °C and stirred for 3 h. Then, 12.8 mL (207 mmol) methyl iodide was added carefully, and the reaction solution was left to stir for 3 h with the temperature was allowed to increase to 25 °C. After that, the reaction solution was quenched with 20 mL aqueous ammonium chloride and extracted with 40 mL diethyl ether for three times. The combined organic layer was then dried over anhydrous sodium sulfate and concentrated over a rotary evaporator to remove most solution. The

concentrated solution was distilled at 80 °C under a reduced pressure (0.05 mm Hg) by connecting to an oil pump, and the middle fraction was collected to obtain 3.2 g pure 3-methyl-1-indene (**30**) as colorless oil in a 46% yield. **¹H NMR** (400 MHz, CDCl₃): δ 7.45 (d, *J* = 5.4 Hz, 2 H), 7.38 (d, *J* = 7.2 Hz, 1 H), 7.28 (d, *J* = 7.2 Hz, 1 H), 7.23 (ddd, *J* = 7.2, 7.2, 1.2 Hz, 1 H), 6.81 (dd, *J* = 6.4, 1.2 Hz, 1 H), 6.51 (dd, *J* = 6.4, 2.0 Hz, 1 H), 3.52 (m, 1 H), 1.35 (d, *J* = 7.6 Hz, 3 H, CH₃); **¹³C NMR** (150 MHz, CDCl₃): δ 149.22, 143.95, 141.40, 130.17, 126.42, 124.78, 122.65, 121.04, 45.14, 16.04; **MS** (ESI, CH₃CN/H₂O): *m/z* = 131.16 ([*M* + *H*]⁺). The spectral data is in agreement with the previously reported data⁴⁵.

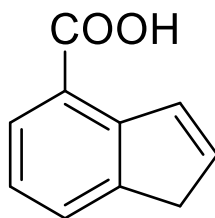
2,3-Dihydro-3-hydroxy-(1*H*)-indene-4-carboxylic acid (33**)** (The preparation was followed by a reported method)⁴⁸ (from tzb-4-149)



To a flame-dried and argon-purged three-neck round bottom flask equipped with a condenser and a glass tube connected to a gaseous source of carbon dioxide, 1.5 g (11.2 mmol) dried 1-indanol (**32**) in 10 mL freshly distilled hexane was added and cooled to 0 °C. To it, a solution of 9.84 mL (24.6 mmol) *n*-butyllithium (2.5 M in hexane) was added dropwise over 5 min with the color of the solution changed to dark red and white solids precipitated out. After the reaction mixture was heated to reflux, carbon dioxide gas was introduced into the reaction mixture through the glass tube and the mixture was stirred for 90 min while CO₂ gas was added. Then, the mixture

was cooled to 25 °C and filtered to collect the white solid containing the desired product. The collected solid was dissolved in 10 mL 1 N aqueous hydrochloride acid. The aqueous solution was extracted with diethyl ether three times. The combined organic layer was dried over sodium sulfate, concentrated to dryness, loaded onto a silica gel column, and eluted with a gradient mixture of pentane and diethyl ether to give 513 mg (26% yield) desired product **33** as a light-yellow solid. **¹H NMR** (400 MHz, CDCl₃): δ 7.45 (d, *J* = 5.4 Hz, 2 H), 7.38 (d, *J* = 7.2 Hz, 1 H), 7.28 (d, *J* = 7.2 Hz, 1 H), 7.23 (ddd, *J* = 7.2, 7.2, 1.2 Hz, 1 H), 6.81 (dd, *J* = 6.4, 1.2 Hz, 1 H), 6.51 (dd, *J* = 6.4, 2.0 Hz, 1 H), 3.52 (m, 1 H), 1.35 (d, *J* = 7.6 Hz, 3 H, CH₃); **¹³C NMR** (150 MHz, CDCl₃): δ 149.22, 143.95, 141.40, 130.17, 126.42, 124.78, 122.65, 121.04, 45.14, 16.04; **MS** (ESI, CH₃CN/H₂O): *m/z* = 179.158 ([M + H]⁺). The spectral data is in agreement with the previously reported data (page 212 in the cited paper).⁴⁸

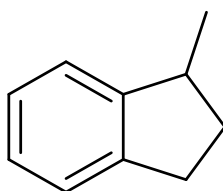
1*H*-Indene-4-carboxylic acid (34) (The preparation was followed by a reported method)⁴⁹
(from tzb-4-139)



To a round bottom flask equipped with a condenser, were added 2.5 mL of THF, 100 mg (0.56 mmol) of 2,3-dihydro-3-hydroxy-1*H*-indene-4-carboxylic acid (**33**) and a solution of 2.8 mL (2.8 mmol) of 1 N aqueous hydrochloride acid. Then, the solution was heated to reflux and stirred for 2 h. The reaction solution was cooled to 25 °C and extracted with 15 mL dichloromethane for

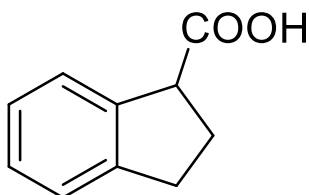
three times. The combined organic layer was dried over sodium sulfate and concentrated to dryness to obtain 65 mg (72 % yield) desired product **34**. **¹H NMR** (600 MHz, CDCl₃): δ 8.08 (d, *J* = 7.8 Hz, 1 H), 7.77 (d, *J* = 5.4 Hz, 1 H, =CH), 7.71 (d, *J* = 7.8 Hz, 1 H), 7.33 (dd, *J* = 7.8, 7.8 Hz, 1 H), 6.82 (td, *J* = 5.4, 1.8 Hz, 1 H, =CH), 3.48 (brd, *J* = 1.8 Hz, 2 H); **¹³C NMR** (150 MHz, CDCl₃): δ 172.88, 146.65, 145.01, 137.50, 132.77, 129.00, 128.51, 124.39, 121.79, 38.87. MS (ESI, MeOH): *m/z* = 161.2 ([M + H]⁺). (No reported data available)

1-Methylindane (**35**) (from tzb-4-126)



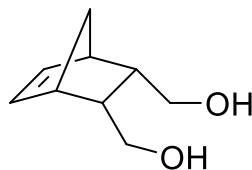
To a hydrogenation bottle, were added 680 mg (5.23 mmol) 1-methylindene (**30**), 50 mg 5% Pd/C and 10 mL of diethyl ether. The hydrogenation bottle was attached to a hydrogenation apparatus, and the bottle was purged with hydrogen gas. The reaction mixture was then shaken under 30 psi of hydrogen for 12 h, removed from the hydrogenator, filtered over Celite, washed with diethyl ether. The filtrate was concentrated to dryness on a rotary evaporator and then under vacuum at 0 °C to give 650 mg (95 % yield) of 1-methylindane (**35**) as colorless oil. **¹H NMR** (600 MHz, CDCl₃): δ 7.26 - 7.15 (m, 4 H), 3.22 (m, 1 H), 2.93 (m, 1 H), 2.88 (m, 1 H), 2.32 (m, 1 H), 1.63 (m, 1 H), 1.31 (d, *J* = 6.6 Hz, 3 H); **¹³C NMR** (150 MHz, CDCl₃): δ 148.79, 143.94, 126.14 (2 C), 124.38, 123.22, 39.46, 34.81, 31.50, 19.92; **MS** (ESI, CH₃CN/H₂O): *m/z* = 133.694 ([M + H]⁺). The spectral data is in agreement with the previously reported data.⁵⁰

Indane-1-carboxylic acid (39) (from tzb-4-119)



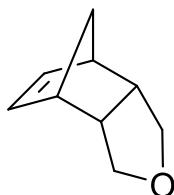
To a hydrogenation bottle, were added 670 mg (4.19 mmol) 1*H*-indene-3-carboxylic acid, 70 mg of 5% Pd/C and 30 mL diethyl ether. Then, the hydrogenation bottle was attached to a hydrogenation apparatus, and the bottle was purged with hydrogen gas under a pressure of 30 psi. The reaction mixture was then shaken under 30 psi of hydrogen for 12 h, filtered through Celite, washed with diethyl ether. The filtrate was concentrated to dryness on a rotary evaporator to obtain 610 mg (91 % yield) of desired product **39** as a colorless oil. **¹H NMR** (600 MHz, CDCl₃): δ 7.46 (d, *J* = 7.8 Hz, 1 H), 7.20 - 7.30 (m, 3 H), 4.11 (dd, *J* = 8.4, 6.0 Hz, 1 H), 3.15 (ddd, *J* = 14.4, 8.4, 6.0 Hz, 1 H), 2.96 (ddd, *J* = 14.4, 8.4, 6.0 Hz, 1 H), 2.48 (m, 1 H), 2.39 (m, 1 H); **¹³C NMR** (150 MHz, CDCl₃): δ 180.46, 144.19, 140.03, 127.81, 126.56, 124.99, 124.75, 49.99, 31.75, 28.67; **MS** (ESI, CH₃CN/H₂O): *m/z* = 163.125 ([*M* + *H*]⁺). The spectral data is in agreement with the previously reported data.⁵¹

Bicyclo[2.2.1]hept-5-ene-2,3-diol,(1*R*,2*R*,3*S*,4*S*) (43) (from tzb-3-116)



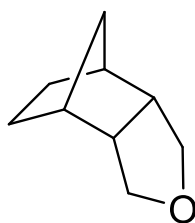
To a solution of 40 g (244 mmol) of carbic anhydride (**42**) in 100 mL dried THF cooled by an ice-bath, 18.5 g (30 mmol) of lithium aluminum hydride was added slowly and carefully. The reaction was allowed to warm up to 25 °C and stirred for 8 h. After that, the reaction was quenched with 40 mL 15% aqueous sodium hydroxide, diluted with 100 mL. The aqueous layer was extracted with ethyl acetate for three times, dried with sodium sulfate, filtered through Celite, concentrated to dryness on a rotary evaporator. The crude was loaded to a silica gel to yield 16 g (43% yield) desired product **43** as white wax. **¹H NMR** (600 MHz, CDCl₃): δ 6.04 (dd, *J* = 1.8 Hz, 2 H), 4.17 (brs, 2 H, OH), 3.63 (dd, *J* = 10.8, 4.2 Hz, 2 H), 3.36 (dd, *J* = 10.8, 10.8 Hz, 2 H), 2.80 (dd, *J* = 1.8 Hz, 2 H), 2.53 (m, 2 H), 1.40 (dd, *J* = 10.2, 7.8 Hz, 2 H); **¹³C NMR** (150 MHz, CDCl₃): δ 134.81 (2 C), 63.43 (2 C), 49.94 (2 C), 46.55 (2 C), 45.09 (2 C). The spectral data is in agreement with the previously reported data.⁵²

***Endo*-4-oxatricyclo[5.2.1.0^{2,6}]-8-decene (**44**)** (The preparation was followed by a reported method)⁴⁶ (from tzb-3-87)



To a flame-dried and argon-purged three-neck flask equipped with a separate funnel, were added 1.5 g (11.03 mmol) of diol (**43**), 3.5 mL of dried pyridine, and 7.5 mL of distilled dichloromethane. To it, a mixture of 1.89 g (9.93 mmol) *p*-toluene sulfonyl chloride in dried dichloromethane was added from a separatory funnel dropwise over 12 h. The reaction mixture was then washed with 10 mL water twice, dried over sodium sulfate, and concentrated to dryness on a rotary evaporator. The concentrated crude product was then loaded onto a silica gel column to yield 800 mg (60 % yield) of desired product **44** as a white solid. **¹H NMR** (400 MHz, CDCl₃): δ 6.23 (s, 2 H, =CH), 3.63 – 3.57 (m, 2 H, CH₂O), 3.46 (dd, *J* = 8.8, 2 Hz, 2 H, CH₂O), 2.94 – 2.85 (m, 4 H, CH-C= and C10-Hs), 1.55 (d, *J* = 8 Hz, 1 H, C10-H), 1.46 (d, *J* = 8 Hz, 1 H, C10-H); **¹³C NMR** (100 MHz, CDCl₃): δ 135.0 (2C), 70.0 (2C), 52.6 (1C), 47.9 (2C), 45.8 (2C); **MS** (ESI, MeOH): *m/z* (%) = 137.19 (*M* + H⁺, 100). The spectral data is in agreement with the previously reported data⁴⁶.

Endo-4-oxatricyclo[5.2.1.0^{2,6}]-decane (45) (from tzb-4-107)



To a hydrogenation bottle, were added 200 mg (1.47 mmol) of norbornene (**44**), 20 mg of 5% Pd/C and 10 mL of diethyl ether. The hydrogenation bottle was attached onto a hydrogenation apparatus, and the bottle was purged with hydrogen gas under a pressure of 30 psi. The reaction mixture was then shaken under 30 psi of hydrogen for 12 h, filtered through Celite, and the solids

were washed with diethyl ether. The filtrate was concentrated to dryness on a rotary evaporator. The crude was vacuum at 0° C to obtain 160 mg of desired product (**45**) (95 % yield) as a colorless oil. **¹H NMR** (400 MHz, CDCl₃): δ 3.88 (d, J = 9.6 Hz, 2 H, CH₂O), 3.40 – 3.35 (m, 2 H, CH₂O), 2.55 – 2.49 (m, 2 H), 2.21 – 2.18 (m, 2 H), 1.60 – 1.43 (m, 4 H), 1.32 – 1.26 (m, 2 H); **¹³C NMR** (100 MHz, CDCl₃): δ 68.9, 45.9, 42.5, 40.6, 23.1; **MS** (ESI, MeOH): m/z (%) = 139.22 (M + H⁺, 100). The spectral data is in agreement with the previously reported data⁵³.

2.7. Catalytic Oxidations

Preparation of 40k PVP capped Cu/Au or Pd/Au colloid (from tzb-3-131)

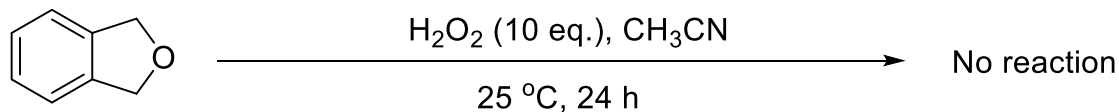
To a solution of 83.5 mg (2.2 mmol, 0.11 eq.) 40k PVP, 21.67 mg (0.055 mmol, 1.0 eq.) of $\text{HAuCl}_4 \cdot 3\text{H}_2\text{O}$, 16.2 mg (0.164 mmol, 3.0 eq.) of CuCl in 30 mL deionized water, 10.3 mg (0.273 mmol, 5.0 eq.) of NaBH_4 was added at 0 °C. Then, the reaction mixture was left to stir for 2 hours, saved in fridge for reactions. The concentration of the catalyst was calculated by following equations:

$$c = \frac{\text{mol}_{\text{Na}_2\text{PdCl}_4} + \text{mol}_{\text{CuCl}}}{V_{\text{solution}}}$$

$$c = \frac{\text{mol}_{\text{HAuCl}_4 \cdot 3\text{H}_2\text{O}} + \text{mol}_{\text{CuCl}}}{V_{\text{solution}}}$$

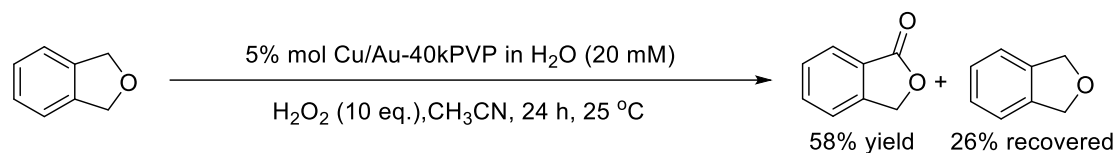
The total mole amount of catalysts is calculated by adding the mole amounts of two types of metallic ions. The total mole amount is then divided by the volume of solution (deionized water or DMF). In this batch, the total mole amount of two metallic ions is $\text{HAuCl}_4 \cdot 3\text{H}_2\text{O}$ (0.055 mmol) + CuCl (0.164 mmol) = 0.219 mmol. Then, the concentration is calculated by dividing the total mole amount of metallic ions with the volume of deionized water (30 mL): 0.219 mmol/ 30 mL = 7.3 mM. Different concentrations in rest catalytic reactions were adjusted by the volume of solution.

Oxidation of phthalan (24) without catalyst (from tzb-3-144)



A reaction mixture containing 50 mg (0.415 mmol) of phthalan (**24**), 0.47 mL (4.15 mmol) of 30% hydrogen peroxide in water, 1 mL water, and 0.5 mL acetonitrile, was stirred for 24 h at 25 °C. No product was found and only starting material was observed by NMR.

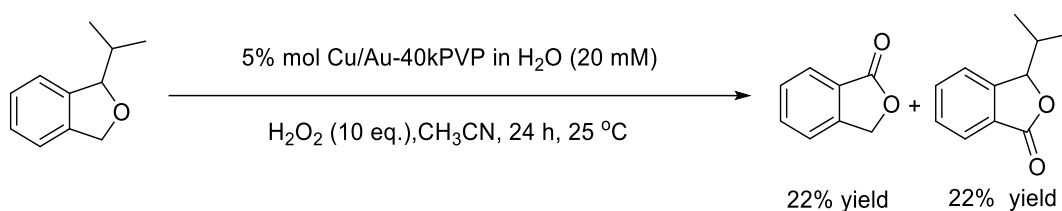
Oxidation of phthalan (24**) with Cu/Au- 40kPVP (in H₂O) and H₂O₂ to 1(3*H*)-Isobenzofuranone (**27**) (from tzb-3-141)**



To a reaction mixture containing 2.1 mL (20 mM, 0.042 mmol) of Cu/Au-40kPVP (in H₂O) colloid, 100 mg (0.83 mmol) of phthalan (**24**) was added, 1 mL acetonitrile was added to dissolve insoluble substrates followed by the addition of 0.94 mL (8.3 mmol) of 30% hydrogen peroxide as the oxidant. The reaction mixture was left to stir for 24 h, diluted with 5 mL water, extracted with 10 mL diethyl ether for three times. The collected organic layer was dried on sodium sulfate, concentrated to dryness over a rotary evaporator, loaded to a silica gel column to obtain 13.5 mg (14% recovery) phthalan (**24**) and 60 mg (58% yield) 1(3*H*)-isobenzofuranone **27** as the major product. ¹H NMR (600 MHz, CDCl₃): δ 7.95 (d, *J* = 7.8 Hz, 1 H), 7.71 (dd, *J* = 7.8, 7.8 Hz, 1 H), 7.56 (dd, *J* = 7.8, 7.8 Hz, 1 H), 7.52 (d, *J* = 7.8 Hz, 1 H), 5.35 (s, 2 H); ¹³C NMR (150 MHz,

CDCl₃): δ 171.14, 146.54, 134.04, 129.07, 125.82, 125.77, 122.11, 69.68. MS (ESI, MeOH): m/z = 135.8 ($[M + H]^+$). The spectral data is in agreement with the previously reported data⁵⁴.

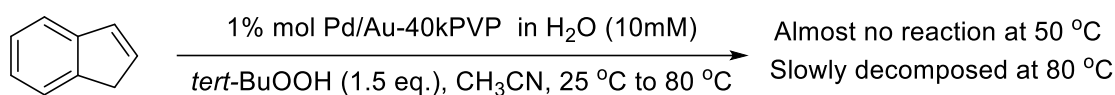
Oxidation of 1,3-dihydro-1-isopropyl-2-benzofuran (25) with Cu/Au- 40kPVP (in H₂O) and H₂O₂ to 1(3*H*)-isobenzofuranone (27) and 3-isopropyl-1(3*H*)-isobenzofuranone (28) (from tzb-3-149)



To a reaction mixture containing 1.5 mL (20 mM, 0.03 mmol) of Cu/Au-40kPVP (in H₂O) colloid, 100 mg (0.62 mmol) of 1,3-dihydro-1-isopropyl-2-benzofuran (**25**), 4 mL acetonitrile was added to dissolve insoluble substrate. Then, 0.7 mL (6.2 mmol) of 30% hydrogen peroxide in water was added. After the reaction was stirred for 24 h at 25 °C, the reaction mixture was diluted with 5 mL water, extracted with 10 mL diethyl ether for three times. The collected organic layer was dried on sodium sulfate, evaporated to dryness over a rotary evaporator, which was loaded to a silica gel column and eluted with hexane and diethyl ether to obtain 20 mg (22% yield) of 1(3*H*)-isobenzofuranone **27** and 22 mg (22% yield) 3-isopropyl-1(3*H*)-isobenzofuranone (**28**). Compound **28**: ¹H NMR (600 MHz, CDCl₃): δ 7.91 (d, J = 11.4 Hz, 1 H), 7.68 (dd, J = 11.4, 11.4 Hz, 1 H), 7.54 (dd, J = 11.4, 11.4 Hz, 1 H), 7.46 (d, J = 11.4 Hz, 1 H), 5.35 (d, J = 5.4 Hz, 1 H), 2.30 (qqd, J = 10.8, 10.8, 5.4 Hz, 1 H), 1.14 (d, J = 10.8 Hz, 1 H), 0.81 (d, J = 10.8 Hz, 1 H); ¹³C NMR (150 MHz, CDCl₃): δ 170.86, 148.88, 133.86, 129.06, 126.73, 125.66, 122.12, 85.66, 32.36,

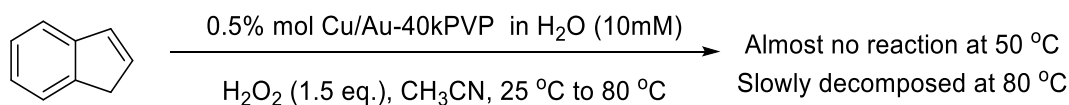
18.71, 15.64. MS (ESI, MeOH): $m/z = 177.9$ ($[M + H]^+$). The spectral data is in agreement with the previously reported data⁵⁵.

Oxidation of (1*H*)-indene (29) with Pd/Au- 40kPVP (in H₂O) and TBHP to decompose (from tzb-4-117)



To a reaction mixture containing 0.86 mL (10 mM, 0.0086 mmol) of Pd/Au-40kPVP (in H₂O) colloid, 100 mg (0.86 mmol) of 1*H*-indene (**29**), 2.0 mL acetonitrile was added to dissolve insoluble substrate followed by the addition of 0.163 mL (1.27 mmol) TBHP (70% in water). After the reaction was stirred for 2 d at 50 °C, no progress was detected from NMR spectra. Then, the temperature was increased to 80 °C and stirred for 2 d to give a material, which NMR indicated a mixture of unidentifiable products. No further study was carried out for this reaction.

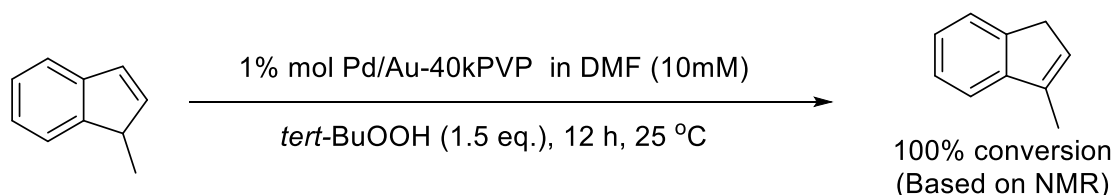
Oxidation of (1*H*)-indene (29) with Cu/Au- 40kPVP (in H₂O) and H₂O₂ to decompose (from tzb-4-121)



To a reaction mixture containing 0.86 mL (10 mM, 0.0086 mmol) of Cu/Au-40kPVP (in H₂O) colloid, 100 mg (0.86 mmol) (1*H*)-indene (**29**), 2.0 mL acetonitrile was added to dissolve

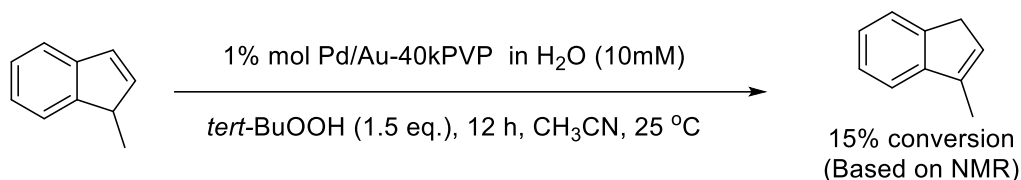
insoluble substrates followed by the addition of 0.142 mL (1.29 mmol) of 30% H₂O₂ in water. After the reaction was stirred for 2 d at 50 °C, no progress was observed from NMR spectra. Then, the temperature was increased to 80 °C and stirred for 2 d to give a material, which NMR indicated a mixture of unidentifiable products. No further study was carried out for this reaction.

Oxidation of 1-methyl-(1*H*)-indene (30**) with Pd/Au- 40kPVP (in DMF) and TBHP to 3-methyl-(1*H*)-indene (**31**) (from tzb-4-135)**



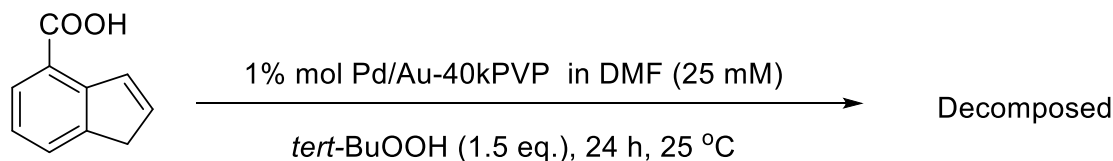
To a solution of 0.32 mL (25 mM 0.008 mmol) of Pd/Au-40kPVP (in DMF) colloid, 100 mg (0.8 mmol) 1-methyl-(1*H*)-indene (**30**), 0.154 mL (1.2 mmol) 70% TBHP in water was added. After the reaction was stirred for 12 h at 25 °C, all the 1-methyl-(1*H*)-indene (**30**) was converted to 3-methyl-(1*H*)-indene **31** (Based on ¹H NMR). **¹H NMR** (400 MHz, CDCl₃): δ 7.48 (d, *J* = 7.2 Hz, 1 H), 7.37 (d, *J* = 7.2 Hz, 1 H), 7.34 (dd, *J* = 7.2, 7.2 Hz, 1 H), 7.23 (ddd, *J* = 7.2, 7.2, 1.6 Hz, 1 H), 6.23 (d, *J* = 1.6 Hz, 1 H), 3.35 (dd, *J* = 2.0, 2.0 Hz, 2 H), 2.20 (dd, *J* = 4.0, 2.4 Hz, 3 H); **¹³C NMR** (100 MHz, CDCl₃); **MS** (ESI, CH₃CN/H₂O): *m/z* = 131.107 ([*M* + *H*]⁺): δ 146.12, 144.33, 139.94, 128.75, 126.04, 124.44, 123.95, 118.83, 37.67, 13.05. These data are in agreement with the data from the literature.⁵⁶

Oxidation of 1-methyl-(1*H*)-indene (30) with Pd/Au- 40kPVP (in H₂O) and TBHP to 3-methyl-(1*H*)-indene (31) (from tzb-4-136)



To a reaction mixture containing 0.32 mL (25 mM, 0.008 mmol) of Pd/Au-40kPVP (in H₂O) colloid, 100 mg (0.8 mmol) of 1-methyl-1*H*-indene (**30**), 1.28 mL acetonitrile was added to dissolve the insoluble starting material followed by the addition of 0.154 mL (1.2 mmol) of 70% TBHP in water. After the reaction was stirred for 12 h at 25 °C, about 15% of the 1-methyl-1*H*-indene (**30**) was converted to 3-methyl-(1*H*)-indene (**31**) based on NMR spectra. (Indicated by ¹H NMR)

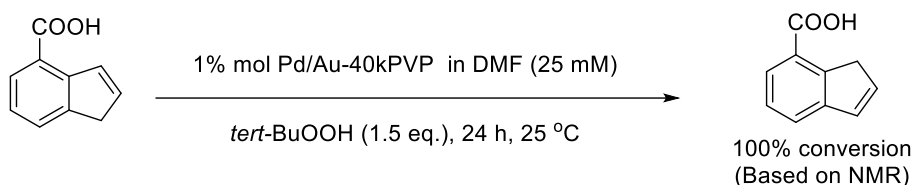
Oxidation of (1*H*)-indene-4-carboxylic acid (34) with Pd/Au- 40kPVP (in DMF) and TBHP to decompose (from tzb-4-131,134,140)



To a reaction mixture containing 0.125 mL (25 mM, 0.003 mmol) of Pd/Au-40kPVP (in DMF) colloid, 50 mg (0.3 mmol) 1*H*-indene-4-carboxylic acid (**34**), 0.06 mL (0.47 mmol) of 70%

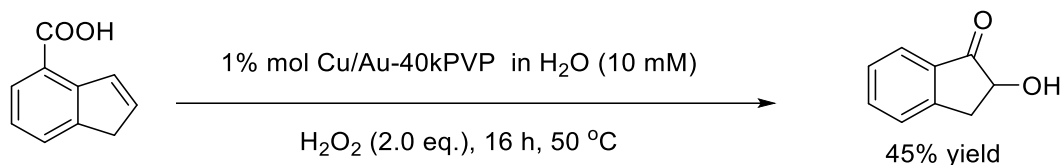
TBHP in water was added as the oxidant. After the reaction was stirred for 24 h at 25 °C, no identifiable material can be observed from ^1H NMR spectra.

Oxidation of (1*H*)-indene-4-carboxylic acid (34**) with Pd/Au- 40kPVP (in H₂O) and TBHP to (**34a**) (from tzb-4-141)**



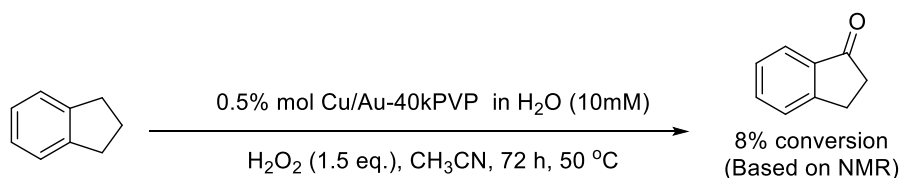
To a reaction mixture containing 0.125 mL (25 mM, 0.003 mmol) of Pd/Au-40kPVP (in DMF) colloid, 50 mg (0.3 mmol) of 1*H*-indene-4-carboxylic acid (**34**), 1.28 mL acetonitrile was added to dissolve the insoluble starting material followed by the addition of 0.06 mL (0.47 mmol) of 70% TBHP. After the reaction was stirred for 24 h at 25 °C, all the 1*H*-indene-4-carboxylic acid (**34**) was converted to 1*H*-indene-7-carboxylic acid (**34a**). ^1H NMR (400 MHz, CDCl₃): δ 8.07 (d, J = 8.0 Hz, 1 H), 7.59 (dd, J = 1.6, 1.6 Hz, 1 H), 7.50 (d, J = 8.0 Hz, 1 H), 7.37 (dd, J = 8.0, 8.0 Hz, 1 H), 7.28 (m, 1 H), 3.58 (d, J = 0.8 Hz, 2 H). (No reported data available in Scifinder in April 2022)

Oxidation of (1*H*)-indene-4-carboxylic acid (34**) with Cu/Au- 40kPVP (in H₂O) and H₂O₂ to 2-hydroxyl-1-indanone (**35**) (from tzb-4-146)**



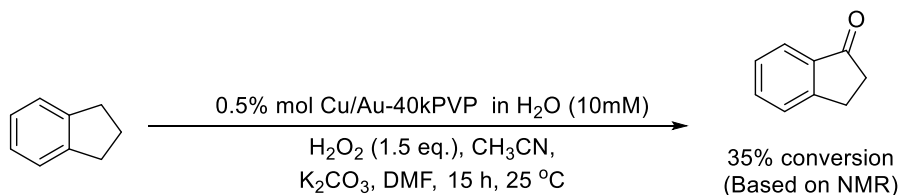
To a reaction mixture containing 0.625 mL (1 mM, 0.00625 mmol) of Cu/Au-40kPVP (in H₂O) colloid, 100 mg (0.625 mmol) of 1*H*-indene-4-carboxylic acid (**34**), 1.28 mL acetonitrile was added to dissolve the insoluble starting material followed by the addition of 0.142 mL (1.25 mmol) of 30% H₂O₂ in water. After the reaction was stirred for 12 h at 50 °C, the reaction mixture was diluted with 5 mL water and extracted with 10 mL diethyl ether for three times. The collected organic layer was dried on sodium sulfate, concentrated to dryness over a rotary evaporator, loaded to a silica gel column to furnish about 45 mg (45% yield) 2-hydroxyl-1-indanone (**35**). ¹H NMR (400 MHz, CDCl₃): δ 7.81 (d, *J* = 7.6 Hz, 1 H), 7.66 (ddd, *J*_{1,2} = 7.6, 7.6 Hz, *J*_{1,3} = 1.2, 1 H), 7.49 (d, *J* = 7.6 Hz, 1 H), 7.44 (dd, *J* = 7.6, 7.6 Hz, 1 H), 4.56 (dd, *J* = 8.0, 5.2 Hz, 1 H), 3.61 (dd, *J* = 16.4, 8.0 Hz, 1 H), 3.04 (dd, *J* = 16.4, 5.2 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 206.30, 150.87, 147.93, 135.90, 128.08, 126.84, 124.48, 74.33, 35.15; MS (ESI, MeOH): *m/z* = 148.9 ([*M* + *H*]⁺). These data are in agreement with the data from the literature.⁵⁷

Oxidation of indane (37) with Cu/Au- 40kPVP (in H₂O) and H₂O₂ to 1-indanone (41) (from tzb-4-120)



To a reaction mixture containing 0.4 mL (10 mM, 0.004 mmol) of Cu/Au-40kPVP (in H₂O) colloid, 100 mg (0.86 mmol) of indane (**37**), 2.0 mL acetonitrile was added to dissolve insoluble substrate followed by the addition of 0.146 mL (1.29 mmol) 30% H₂O₂ in water as the oxidant. After the reaction was stirred for 3 d at 50 °C, there was only a small portion of indane (**37**) was converted to 1-indanone (**41**) (6% conversion). ¹H NMR (400 MHz, CDCl₃): δ 7.79 (d, *J* = 8.0 Hz, 1 H), 7.61 (dd, *J* = 8.0, 8.0 Hz, 1 H), 7.50 (d, *J* = 7.2, 8.0 Hz, 1 H), 7.39 (dd, *J* = 8.0, 8.0 Hz, 1 H), 2.21 (dd, *J* = 6.0, 6.0 Hz, 2 H), 2.72 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃): δ 207.20, 155.21, 137.10, 134.64, 127.31, 126.72, 123.76, 36.24, 25.83. MS (ESI, MeOH): *m/z* = 133.1 ([M + H]⁺). The spectral data is in agreement with the previously reported data⁵⁸.

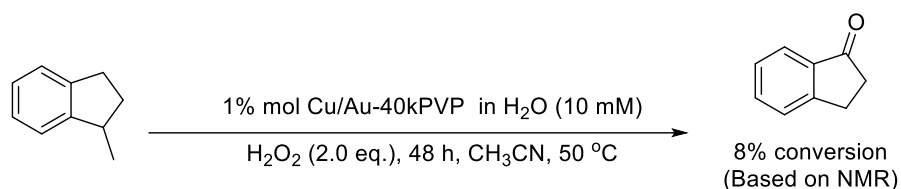
Oxidation of indane (37**) with Cu/Au- 1R (in H₂O) and H₂O₂ in basic condition to 1-indanone (**41**) (from tzb-4-122)**



To a reaction mixture containing 0.4 mL (10 mM, 0.004 mmol) of Cu/Au-1R (in H₂O) colloid, 100 mg (0.86 mmol) of indane (**37**), 2.0 mL acetonitrile was added to dissolve insoluble substrates, followed by the addition of 0.146 mL (1.29 mmol) of 30% H₂O₂ in water as the oxidant. After the reaction was stirred for 3 d at 50 °C, there was only a small portion of indane (**37**) was converted to 1-indanone (**41**) (6% conversion). Then, the reaction mixture was cooled to 25 °C,

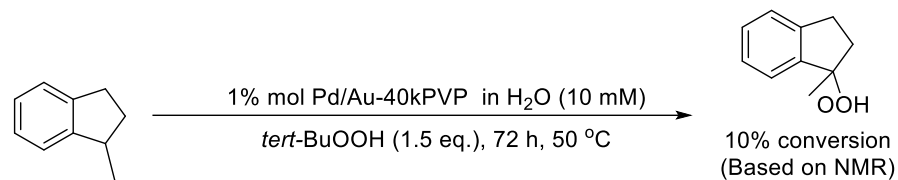
added with 20 mg (0.145 mmol) of potassium carbonate and stirred for 15 hours with its conversion rate increased from 6% to 35%. (Indicated by NMR)

Oxidation of 1-methyl-indane (38) with Cu/Au- 40kPVP (in H₂O) and H₂O₂ to (41) 1-indanone (from tzb-4-128)



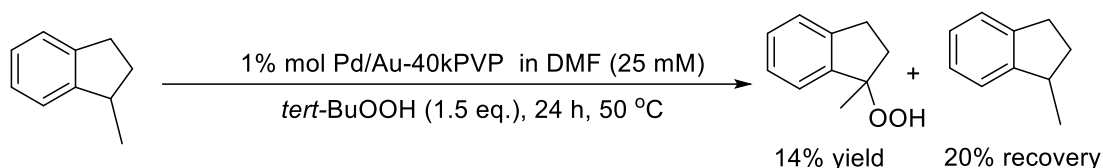
To a reaction mixture containing 0.8 mL (10 mM, 0.008 mmol) of Cu/Au-40kPVP (in H₂O) colloid, 100 mg (0.8 mmol) of 1-methylindane (**38**), 0.181 mL (1.6 mmol) 30% H₂O₂ in water was added. After the reaction was stirred for 48 h at 50 °C, approximate 8% of starting material (**38**) was converted to 1-indanone (**41**). (Indicated by ¹H NMR)

Oxidation of 1-methyl-indane (38) with Pd/Au- 40kPVP (in H₂O) and TBHP to 1-methyl-indanyl hydrogen peroxide (40) (from tzb-4-129)



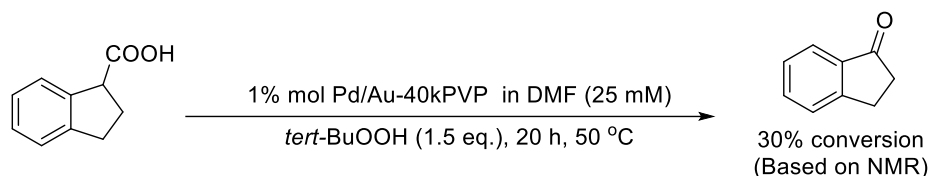
To a reaction mixture containing 0.8 mL (10 mM, 0.008 mmol) of Pd/Au-40kPVP (in H₂O) colloid, 100 mg (0.8 mmol) of 1-methylindane (**38**), 0.154 mL (1.2 mmol) 70% TBHP in water was added as the oxidant. After the reaction mixture was stirred for 72 h at 50 °C, around 10% of starting material was converted to 1-methyl-indanyl hydrogen peroxide (**40**). (Indicated by ¹H NMR)

Oxidation of 1-methyl-indane (38**) with Pd/Au- 40kPVP (in DMF) and TBHP to 1-methyl-indanyl hydrogen peroxide (**40**) (from tzb-4-133)**



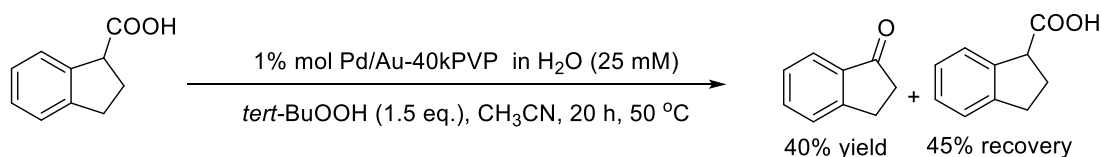
To a reaction mixture containing 0.2 mL (25 mM, 0.008 mmol) of Pd/Au-40kPVP (in DMF) colloid, 100 mg (0.8 mmol) of 1-methylindane (**38**), 0.154 mL (1.2 mmol) 70% TBHP in water was added. After the reaction was stirred for 24 h at 50 °C, the reaction mixture was diluted with 5 mL water and extracted with 10 mL diethyl ether for three times. The collected organic layer was dried on sodium sulfate, concentrated to dryness on a rotary evaporator, loaded to a silica gel column to obtain about 21 mg (14% yield) 1-methylindane-1-hydrogenperoxide (**40**). ¹H NMR (400 MHz, CDCl₃): δ 7.41 (d, *J* = 7.2 Hz, 1 H), 7.34 – 7.26 (m, 3 H), 3.05 (m, 1 H), 2.80 (m, 1 H), 2.51 (m, 1 H), 2.15 (m, 1 H), 1.68 (s, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ 145.17, 143.18, 129.01, 126.47, 125.10, 123.81, 92.99, 36.40, 29.95, 22.61. (No reported data available in Scifinder in April 2022) (The data was compared with 1-methyl-indan-1-ol)⁵⁹

Oxidation of indane-1-carboxylic acid (39) with Pd/Au- 40kPVP (in DMF) and TBHP to 1-indanone (41) (from tzb-4-142)



To a reaction mixture containing 0.13 mL (25 mM, 0.003 mmol) of Pd/Au-40kPVP (in DMF) colloid, 50 mg (0.3 mmol) indane-1-carboxylic acid (**39**), 0.06 mL (0.47 mmol) 70% TBHP in water was added. After the reaction was stirred for 20 h at 50 °C, around 30% of carboxylic acid (**39**) was converted to 1-indanone (**41**). (Indicated by ¹H NMR)

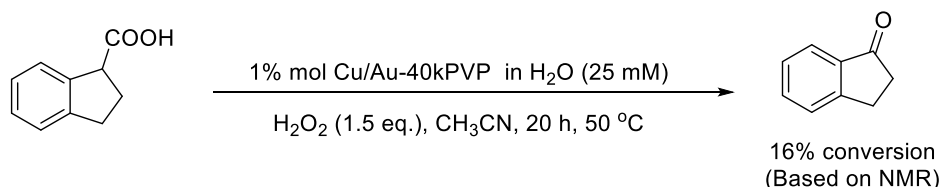
Oxidation of indane-1-carboxylic acid (39) with Pd/Au- 40kPVP (in H₂O) and TBHP to 1-indanone (41) (from tzb-4-143)



To a reaction mixture containing 0.13 mL (25 mM, 0.003 mmol) of Pd/Au-40kPVP (in H₂O) colloid, 50 mg (0.3 mmol) of indane-1-carboxylic acid (**39**), 0.26 mL acetonitrile was added to dissolve the substrate. Then, 0.06 mL (0.47 mmol) of 70% TBHP in water was added as the oxidant. After the reaction mixture was stirred for 20 h at 50 °C, the reaction mixture was diluted with 5 mL water and extracted with 10 mL diethyl ether for three times. The collected organic

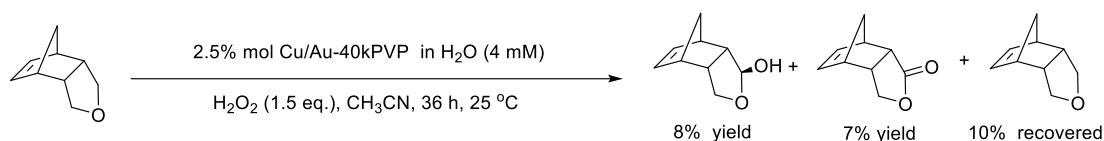
layer was dried over sodium sulfate, concentrated to dryness on a rotary evaporator, loaded to a silica gel column to obtain about 20 mg starting material (**39**) (45% recovery) and 15 mg (40% yield) 1-indanone (**41**). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.79 (d, J = 8.0 Hz, 1 H), 7.61 (dd, J = 8.0, 8.0 Hz, 1 H), 7.50 (d, J = 7.2, 8.0 Hz, 1 H), 7.39 (dd, J = 8.0, 8.0 Hz, 1 H), 2.21 (dd, J = 6.0, 6.0 Hz, 2 H), 2.72 (m, 2 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 207.20, 155.21, 137.10, 134.64, 127.31, 126.72, 123.76, 36.24, 25.83. MS (ESI, MeOH): m/z = 133.1 ($[\text{M} + \text{H}]^+$). The spectral data is in agreement with the previously reported data⁵⁸.

Oxidation of indane-1-carboxylic acid (39**) with Cu/Au- 40kPVP (in H_2O) and H_2O_2 to 1-indanone (**41**) (from tzb-4-145)**



To a reaction mixture containing 0.13 mL (25 mM, 0.003 mmol) of Pd/Au-40kPVP (in H_2O) colloid, 50 mg (0.3 mmol) of indane-1-carboxylic acid (**39**), 0.26 mL acetonitrile was added to dissolve the substrate. After that, 0.05 mL (0.47 mmol) of 30% H_2O_2 in water was added as the oxidant. After the reaction was stirred for 20 h at 50 $^\circ\text{C}$, 16% of carboxylic acid (**39**) was converted to 1-indanone (**41**).

Oxidation of *endo*-4-oxatricyclo[5.2.1.0^{2,6}]-8-decene (44**) with Cu/Au- 40kPVP (in H₂O) and H₂O₂ to 3-*exo*-hydroxy-*endo*-4-oxatricyclo[5.2.1.0^{2,6}]-8-decene (**46**) and 3-oxo-*endo*-4-oxatricyclo[5.2.1.0^{2,6}]-8-decene (**48**) (from tzb-3-137)**

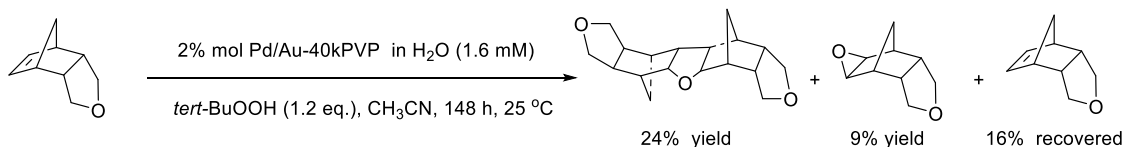


To a reaction mixture containing 7.5 mL (4 mM, 0.03 mmol) of Cu/Au-40kPVP (in H₂O) colloid, 150 mg (1.1 mmol) *endo*-4-oxatricyclo[5.2.1.0^{2,6}]-8-decene (**44**), 10.0 mL acetonitrile was added to dissolve all the insoluble substrate followed by the addition of 1.875 mL (16.5 mmol) of 30% H₂O₂ in water as the oxidant. After the reaction mixture was stirred for 3 d at 25 °C, the reaction mixture was diluted with 5 mL water and extracted with 10 mL diethyl ether for three times. The collected organic layer was dried on sodium sulfate, concentrated to dryness on a rotary evaporator, loaded to a silica gel column to obtain about 15 mg (10% recovery) starting material **44** and 10 mg (8% yield) 3-*exo*-hydroxy-*endo*-4-oxatricyclo[5.2.1.0^{2,6}]-8-decene **46** and 9 mg (7% yield) 3-oxo-*endo*-4-oxatricyclo[5.2.1.0^{2,6}]-8-decene (**48**).

Compound **46**: ¹H NMR (400 MHz, CDCl₃): δ 6.20 (dd, *J* = 5.6, 2.8 Hz, 1 H, =CH), 6.09 (dd, *J* = 5.6, 2.8 Hz, 1 H, =CH), 4.99 (d, *J* = 2.4 Hz, 1 H, OCHO), 3.97 (dd, *J* = 9, 7.6 Hz, 1 H, CHO), 3.46 (dd, *J* = 9, 2 Hz, 1 H, CHO), 3.05 – 2.82 (m, 4 H), 2.64 (s, 1 H, OH), 1.45 (d, *J* = 8 Hz, 1 H, C10-H), 1.36 (d, *J* = 8 Hz, 1 H, C10-H); ¹³C NMR (100 MHz, CDCl₃): δ 134.7 (=C), 134.4 (C=), 100.4 (O-C-O), 69.3 (C-O), 55.5, 51.9, 46.0, 45.8, 44.9; MS (ESI, MeOH): *m/z* (%) = 153.10 (M + H⁺, 100). The spectral data is in agreement with the previously reported data⁶⁰.

Compound **48**: ^1H NMR (400 MHz, CDCl_3): δ 6.35 – 6.26 (m, 2H, $\text{CH}=\text{CH}$), 4.31 (dd, J = 10, 8.8 Hz, 1 H, CHO), 3.82 (dd, J = 10, 3.2 Hz, 1 H, CHO), 3.38 – 3.34 (m, 1 H), 3.28 (dd, J = 9.2, 4.4 Hz, 1 H), 3.16 – 3.08 (m, 2H), 1.67 (d, J = 8.4 Hz, 1 H, C10-H), 1.49 (d, J = 8.4 Hz, 1 H, C10-H). ^{13}C NMR (100 MHz, CDCl_3): δ 178.1 (C=O), 137.0 (C=), 134.4 (C=), 70.3 (C-O), 51.9, 47.6, 46.2, 45.8, 40.3; MS (ESI, MeOH): m/z (%) = 151.18 ($\text{M} + \text{H}^+$, 80). The spectral data is in agreement with the previously reported data⁶¹.

Oxidation of *endo*-4-oxatricyclo[5.2.1.0^{2,6}]-8-decene (44**) with Pd/Au- 40kPVP (in H_2O) and TBHP to dodecahydro-1,4:6,9-dimethanodibenzofurano[2,3-*b*:7,8-*b'*]bisoxolane (**50**) and 4-oxa-tricyclo[5.2.1.0]-8,9-*exo*-epoxydecane (**51**) (from tzb-3-86)**

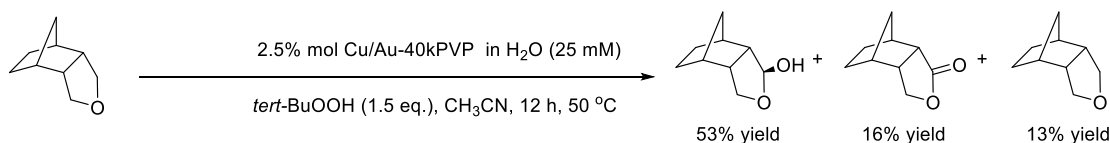


To a reaction mixture containing 6.4 mL (1.6 mM, 0.01 mmol) of Pd/Au-40kPVP (in H_2O) colloid, 70 mg (0.515 mmol) of *endo*-4-oxatricyclo[5.2.1.0^{2,6}]-8-decene (**44**), 12 mL acetonitrile was added to dissolve the rest insoluble substrate followed by the addition of 0.08 mL (0.618 mmol) of 70% TBHP in water as the oxidant. After the reaction was stirred for 6 d at 25 $^\circ\text{C}$, the reaction mixture was diluted with 5 mL water and extracted with 10 mL diethyl ether for three times. The collected organic layer was dried on sodium sulfate, concentrated to dryness, loaded to a silica gel column to obtain about 11 mg (16% recovery) starting material (**44**), 18 mg (24% yield) dodecahydro-1,4:6,9-dimethanodibenzofurano[2,3-*b*:7,8-*b'*]bisoxolane (**50**) and 6 mg (9% yield) 4-Oxa-tricyclo[5.2.1.0]-8,9-*exo*-epoxydecane (**51**).

Compound **50**: $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 4.25 (d, J = 6.4 Hz, 2 H, CHO), 3.90 (dd, J = 17.2, 9.6 Hz, 4 H, CH_2O), 3.32 (ddd, J = 17.2, 10, 6.8 Hz, 4 H, CH_2O), 2.55 – 2.41 (m, 4 H), 2.25 (d, J = 4.8 Hz, 2 H), 2.16 – 2.06 (m, 4 H), 1.60 (d, J = 12.4 Hz, 2 H), 1.26 (dt, J = 12.4, 2 Hz, 2 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 84.8 (2C, CHO), 68.8 (2C, CH_2O), 68.2 (2C, CH_2O), 49.0 (2C), 47.1 (2C), 46.2 (2C), 44.6 (2C), 43.7 (2C), 37.3 (2C); **MS** (ESI, MeOH): m/z (%) = 289.117 ($\text{M} + \text{H}^+$, 30), 311.177 ($\text{M} + \text{Na}^+$, 100). **HRMS**-ESI: m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{18}\text{H}_{25}\text{O}_3$: 289.1798, found: 289.1801.

Compound **51**: $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 3.95 (d, J = 10.4 Hz, 2 H, CH_2O), 3.44 (dd, J = 10.4, 6.8 Hz, 2 H, CH_2O), 3.27 (s, 2H, 2 x CH-O), 2.73 – 2.65 (m, 2 H), 2.58 – 2.51 (m, 2 H), 1.46 (d, J = 10 Hz, 1 H), 0.84 (d, J = 10 Hz, 1 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ = 68.2 (2C, C-O), 49.5 (2C, C-O epoxide), 46.2 (2C), 39.8 (2C), 29.6 (1C); **MS** (ESI, MeOH): m/z (%) = 152.899 ($\text{M} + \text{H}^+$; 50). The spectral data is in agreement with the previously reported data⁶².

Oxidation of *endo*-4-Oxatricyclo[5.2.1.0^{2,6}]-8-decane (45**) with Cu/Au- 40kPVP (in H_2O) and TBHP to 3-*exo*-hydroxy-*endo*-4-oxatricyclo[5.2.1.0^{2,6}]-8-decane (**47**) and 3-oxo-*endo*-4-oxatricyclo[5.2.1.0^{2,6}]-8-decane (**49**) (from tzb-5-20)**



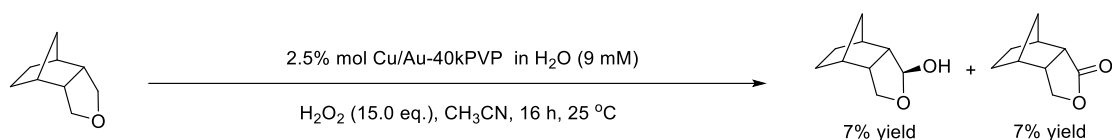
To a reaction mixture containing 0.8 mL (25 mM, 0.02 mmol) of Cu/Au-40kPVP (in H_2O) colloid, 100 mg (0.73 mmol) of *endo*-4-oxatricyclo[5.2.1.0^{2,6}]-8-decane (**45**), 0.4 mL acetonitrile was added to dissolve the rest insoluble substrate followed by the addition of 0.15 mL (1.18 mmol)

70% TBHP in water as the oxidant. After the reaction was stirred for 12 h at 50 °C, the reaction mixture was diluted with 5 mL water and extracted with 10 mL diethyl ether for three times. The collected organic layer was dried on sodium sulfate, concentrated to dryness, loaded to a silica gel column to obtain about 13 mg (13% recovery) starting material (**45**), 59 mg (53% yield) 3-*exo*-hydroxy-*endo*-4-oxatricyclo[5.2.1.0^{2,6}]-8-decane (**47**) and 19 mg (16% yield) 3-oxo-*endo*-4-oxatricyclo[5.2.1.0^{2,6}]-8-decane (**49**).

Compound **47**: ¹H NMR (400 MHz, CDCl₃): δ 5.37 (s, 1 H, OCHO), 3.96 (dd, *J* = 9.6, 2.0 Hz, 1 H, CH₂O), 3.87 (dd, *J* = 9.6, 7.2 Hz, 1 H, CH₂O), 3.65 – 3.40 (bs, 1 H, OH), 2.65 – 2.59 (m, 1 H), 2.48 – 2.44 (m, 1 H), 2.37 – 2.34 (m, 1 H), 2.20 – 2.17 (m, 1 H), 1.50 – 1.25 (m, 6 H); ¹³C NMR (100 MHz, CDCl₃): δ 99.2 (O-C-O), 66.8 (C-O), 53.1, 44.2, 42.0, 40.3, 39.1, 23.6, 22.5; MS (ESI, MeOH): *m/z* (%) = 155.20 (*M* + H⁺; 40). The spectral data is in agreement with the previously reported data⁶⁰.

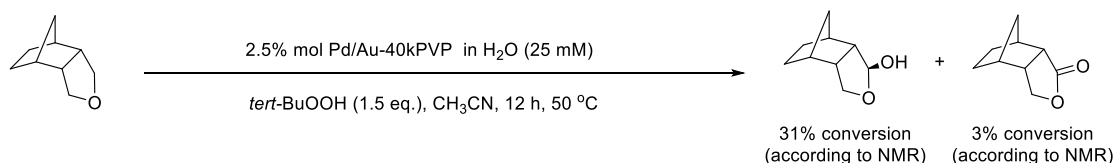
Compound **49**: ¹H NMR (400 MHz, CDCl₃): δ 4.30 (dd, *J* = 10, 8.4 Hz, 1 H, CH₂O), 4.25 (dd, *J* = 10, 3.2 Hz, 1 H, CH₂O), 2.99 (dd, *J* = 11.6, 5.6 Hz, 1 H, CHC=O), 2.92 – 2.84 (m, 1 H), 2.69 – 2.64 (m, 1 H), 2.38 – 2.34 (m, 1 H), 1.60 – 1.46 (m, 6 H); ¹³C NMR (100 MHz, CDCl₃): δ 178.8 (C=O), 68.4 (C-O), 46.8, 42.0, 41.9, 40.4, 39.9, 25.5, 21.6; MS (ESI, MeOH): *m/z* (%) = 153.17 (*M* + H⁺; 70). The spectral data is in agreement with the previously reported data⁶³.

Oxidation of *endo*-4-oxatricyclo[5.2.1.0^{2,6}]-8-decane (45**) with Cu/Au- 40kPVP (in H₂O) and H₂O₂ to 3-*exo*-hydroxy-*endo*-4-oxatricyclo[5.2.1.0^{2,6}]-8-decane (**47**) and 3-oxo-*endo*-4-oxatricyclo[5.2.1.0^{2,6}]-8-decane (**49**) (from tzb-5-41)**



To a reaction mixture containing 3 mL (9 mM, 0.054 mmol) of Cu/Au-40k PVP (in H₂O) colloid, 150 mg (1.08 mmol) of endo-4-oxatricyclo[5.2.1.0^{2,6}]-8-decane (**44**), 3 mL acetonitrile was added to dissolve the rest insoluble substrate, followed by the addition of 1.83 mL (16.2 mmol) of 30% H₂O₂ in water as the oxidant. After the reaction was stirred for 16 h at 25 °C, the reaction mixture was diluted with 5 mL water and extracted with 10 mL diethyl ether for three times. The combined organic layer was dried over sodium sulfate, evaporated to dryness, loaded to a silica gel column to furnish about 11 mg (7% yield) 3-exo-hydroxy-endo-4-oxatricyclo[5.2.1.0^{2,6}]-8-decane (**47**) and 12 mg (7% yield) 3-oxo-endo-4-oxatricyclo[5.2.1.0^{2,6}]-8-decane (**49**).

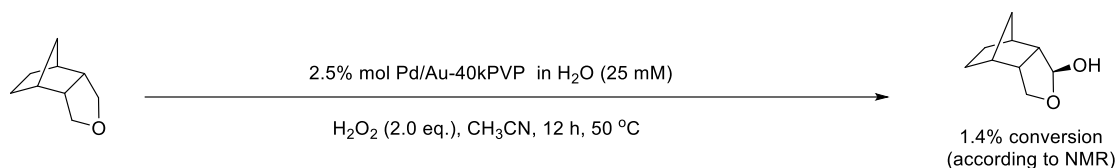
Oxidation of endo-4-oxatricyclo[5.2.1.0^{2,6}]-8-decane (45**) with Pd/Au- 40kPVP (in H₂O) and TBHP to 3-exo-hydroxy-endo-4-oxatricyclo[5.2.1.0^{2,6}]-8-decane (**47**) and 3-oxo-endo-4-oxatricyclo[5.2.1.0^{2,6}]-8-decane (**49**) (from tzb-5-15)**



To a reaction mixture containing 1.6 mL (25 mM, 0.04 mmol) of Pd/Au-40kPVP (in H₂O) colloid, 200 mg (1.58 mmol) OF endo-4-oxatricyclo[5.2.1.0^{2,6}]-8-decane (**45**), 0.8 mL acetonitrile was added to dissolve insoluble substrate followed by the addition of 0.3 mL (2.37 mmol) 70%

TBHP in water as the oxidant. After the reaction was stirred for 12 h at 50 °C, about 31% of the substrate was converted to 3-*exo*-hydroxy-*endo*-4-oxatricyclo[5.2.1.0^{2,6}]-8-decane (**47**).

Oxidation of *endo*-4-oxatricyclo[5.2.1.0^{2,6}]-8-decane (45**) with Pd/Au- 40kPVP (in H₂O) and H₂O₂ (from tzb-5-16)**



To a reaction mixture containing 0.8 mL (25 mM, 0.02 mmol) of Pd/Au-40kPVP (in H₂O) colloid, 100 mg (0.79 mmol) of *endo*-4-oxatricyclo[5.2.1.0^{2,6}]-8-decane (**45**), 0.4 mL acetonitrile was added to dissolve insoluble substrate, followed by the addition of 0.18 mL (1.58 mmol) 30% H₂O₂ in water as the oxidant. After the reaction was stirred for 12 h at 50 °C, no reaction progression was observed from NMR spectra. (Indicated by ¹H NMR)

Chapter 3 - Synthesis of Tricycle Pyrones as Potential Drugs for Alzheimer's Diseases

3.1. Introduction and Background

About 6.2 million Americans aged 65 and older are living with dementia caused by Alzheimer's disease (AD) in 2021. A 72% of them are age 75 or older. The number of patients with Alzheimer's disease grows rapidly. The estimated number of individuals with AD may grow to 12.7 million by 2050. AD and other dementias are heavy burdens for both families and the nation, which cost \$355 billion in 2021, and the cost may increase to \$ 1.1 trillion (in 2021 dollars) by 2050.⁶⁴ Currently, four types of drugs, including Donepezil⁶⁵, Galantamine⁶⁶, Rivastigmine⁶⁷ and Memantine⁶⁸, have been approved by FDA to treat cognitive symptoms. However, there is no drug approved by FDA exhibited the potential to cease the progression of AD, FDA has authorized the marketing of Aduhelm from Biogen last June.⁶⁹ Even Aduhelm showed its potential to reduce deposition of β -amyloid peptide, there was still no persuasive evidence demonstrating its treatment of AD.⁷⁰

At present, several hypotheses, including $A\beta$ ⁷¹, tau^{72, 73}, excitotoxic^{74, 75}, etc., were proposed to explain the mechanism of AD pathogenesis^{76, 77}. Among these hypotheses, the $A\beta$ -amyloid hypothesis is the most-developed one,⁷⁷ and even no persuasive evidence that there is a strong correlation between $A\beta$ deposition and neural atrophy and cognitive impairment was found⁷⁸. A brief introduction to the formation of Amyloid Precursor Protein (APP) has been involved in **Figure 5**. APP is a kind of transmembrane protein with its gene located at No. 21st

chromosome.⁷⁹ For APP, its ectodomain can be hydrolyzed by α -secretase and β -secretase. Its interdomain can be hydrolyzed by γ 40-secretase, γ 42-secretase.⁸⁰ The ectodomain cut by β -secretase is water-soluble and can be cleared and transferred from brain without deposition, while the ectodomain cut by α -secretase with the interdomain cut by γ 40-secretase or γ 42-secretase produce peptides with 40 and 42 units respectively, which are insoluble in water. The peptide with 42 units of amino acids is less soluble and toxic than the peptide with 40 units.^{81, 82}

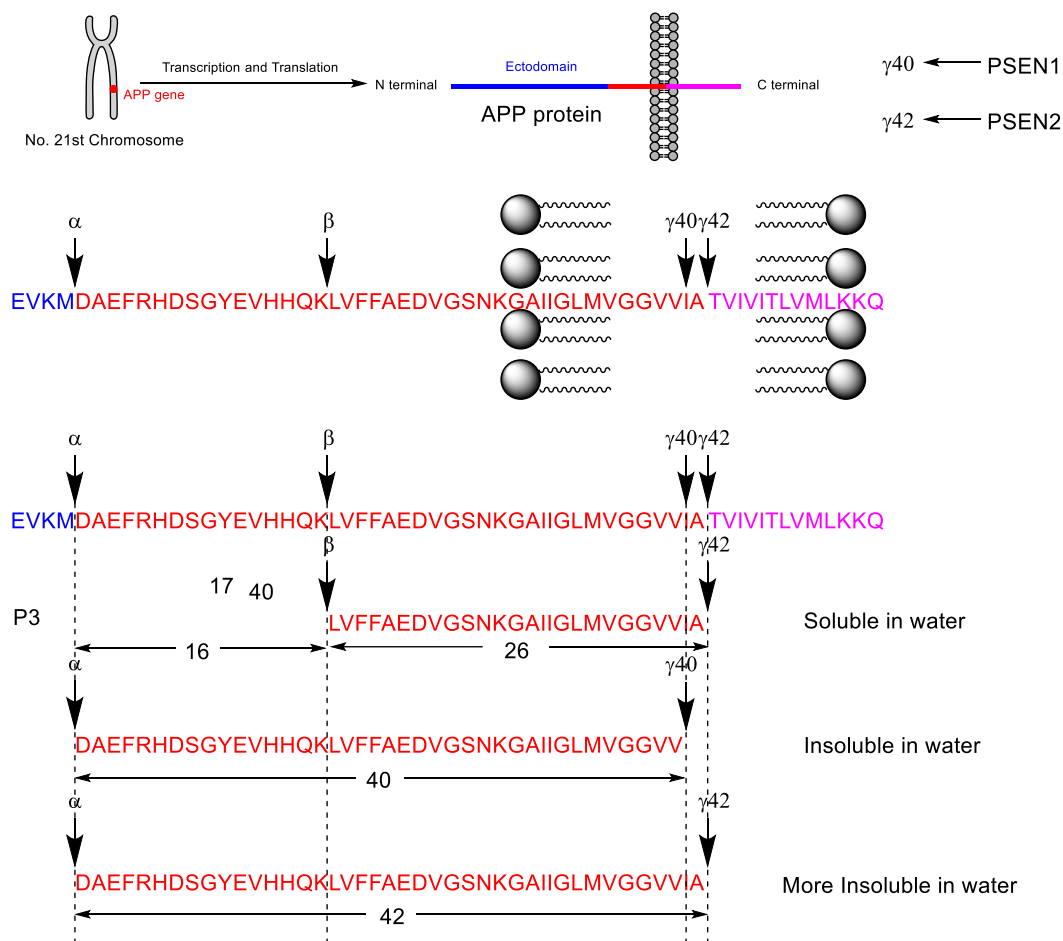


Figure 5. The formation of A β peptide.

The water-insoluble peptides with 40 and 42 units of amino acids can be deposited (mainly A β_{42}) and polymerized to dimer, oligomer and fibrils, which cannot be cleared from the brain directly.⁸² The full pathological mechanism of AD is unclear, but several studies suggested that the accumulation of the A β deposits blocks the communication between neurons and induces the apoptosis of neurons^{83, 84}. The second theory involves tau protein (see **Figure 6**). Tau protein stabilizes microtubules of the neuron. In AD, it is hyperphosphorylated and then detached from the microtubules, which causes the disassembly of microtubules and the aggregation of hyperphosphorylated tau protein. The accumulated tau proteins are then tangled and deposited to neurofibrillary tangles (NFTs) causing an apoptosis of neurons.^{72, 73}

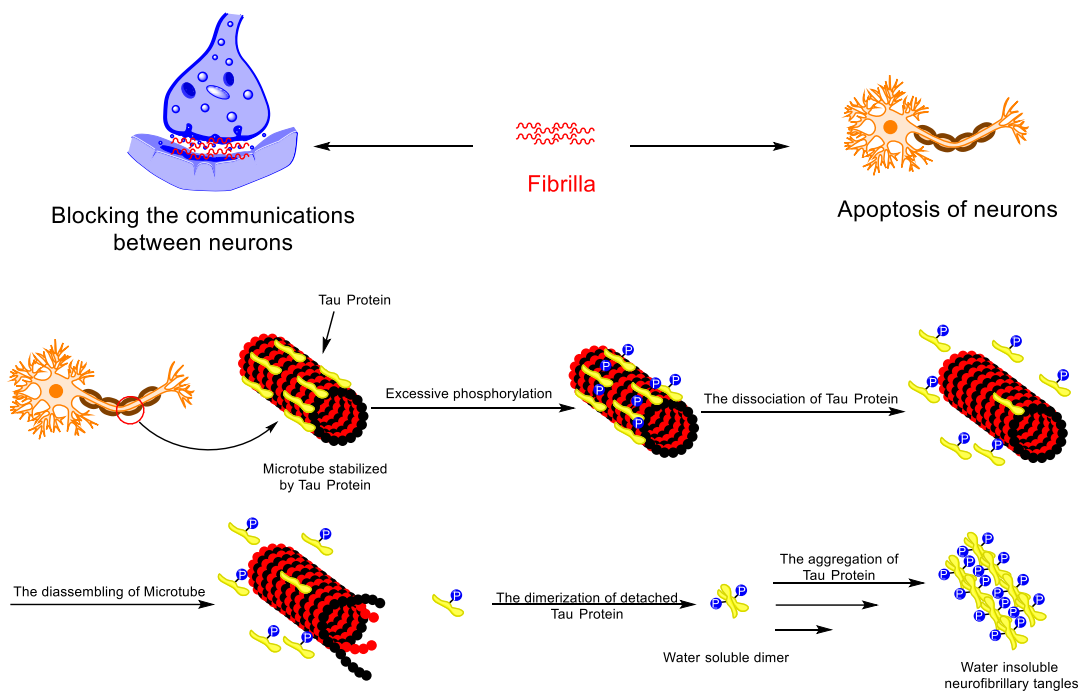


Figure 6. The formation of NFTs.

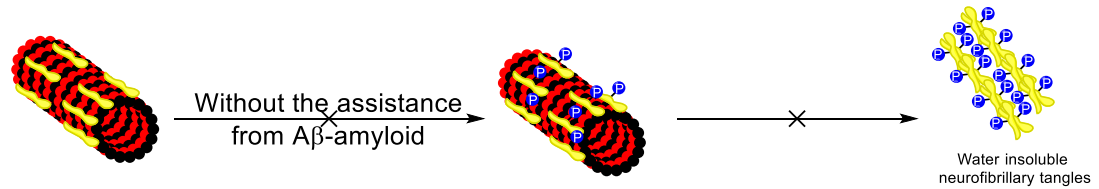
3.2. A Proposed Mechanism to for the amelioration of Alzheimer's Disease

Currently, there are lots of therapeutic strategies, containing N-Methyl-D-aspartic acid (NMDA) receptor (NMDAR) antagonism,⁸⁵ anti-amyloid agents,⁸⁶ inhibitors to tau hyperphosphorylation,⁸⁷ etc., were reported. In our previous work, **TP70** exhibited the excellent potential to protect MC65 cell line against its apoptosis induced by the deposition of A β oligomers,⁸⁸ which may also reduce the formation of neurofibrillary tangles (NFTs). Chen and his coworkers published their studies and found that the hippocampal long-term potentiation (LTP) can be activated by cholecystokinin (CCK) with the NMDAR blocked by NMDAR inhibitor⁸⁹. In Hua's previous work, **TP70** exhibited its potential to enhance the LTP of the hippocampus, but the exact mechanism is uncertain.⁹⁰ Chen's work⁸⁹ may supply an explanation to the mechanism of improvement the LTP from **TP70**, even no evidence can be provided. In **Figure 7**, three possible therapeutic mechanisms for **TP70** were proposed and described. As a type of moiety easy to penetrating blood brain barrier and available to oral intake, the TP70 may degrade amyloid plaques to monomers and clear the monomers with the assistance of **TP70** with an obvious decrease of A β level.⁹⁰ For the tau strategy, the level of β -amyloid-induced hyperphosphorylation of tau protein may be decreased,⁹¹ which prevents the apoptosis of neurons. In terms of the NMDAR therapeutic strategy, the NMDAR-dependent LTP can be activated by the release of CCK controlled by NMDAR.⁸⁹ Therefore, it is possible that the TP70-NMDAR complex may enhance the release of CCK and then enhance the NMDAR-dependent LTP.

The therapeutic strategy for the A β peptide by dissolving Amyloid plaques:



The therapeutic strategy for the Tau protein:



The therapeutic strategy for excitotoxicity as NMDAR antagonist:

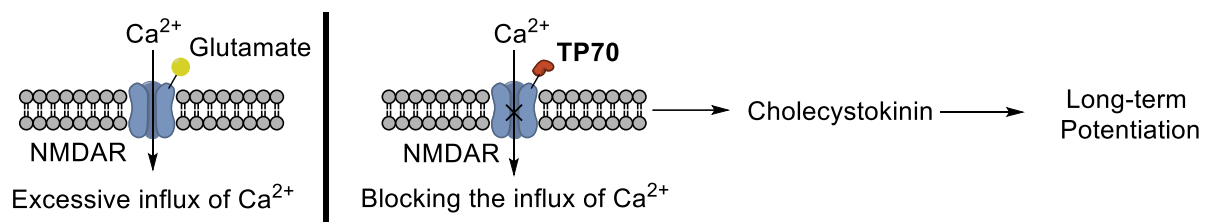
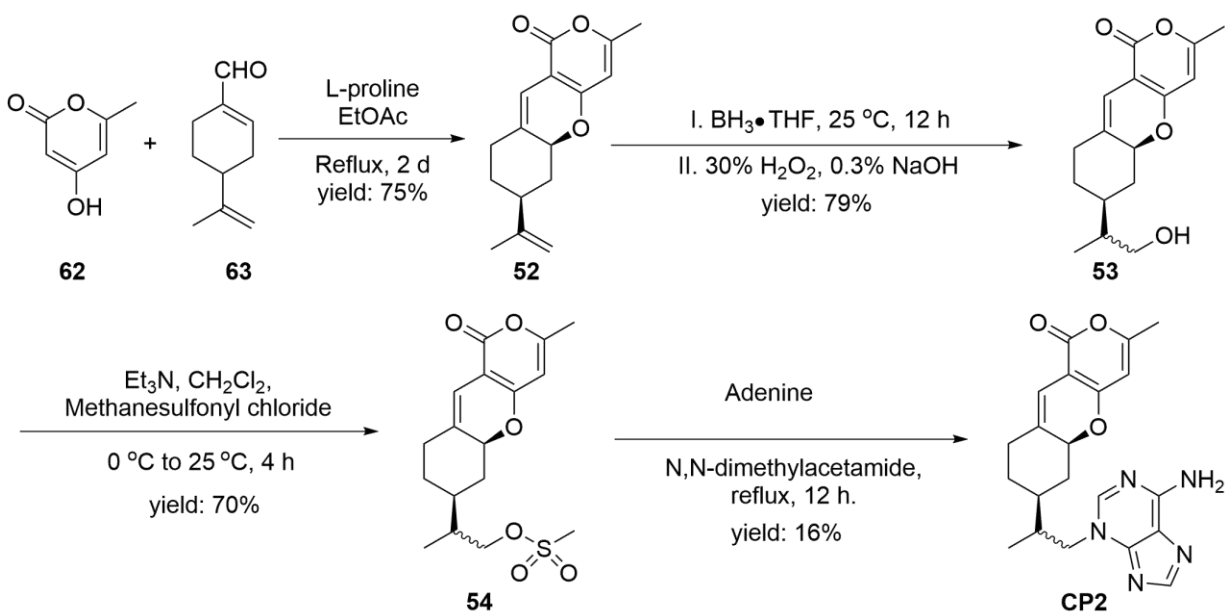


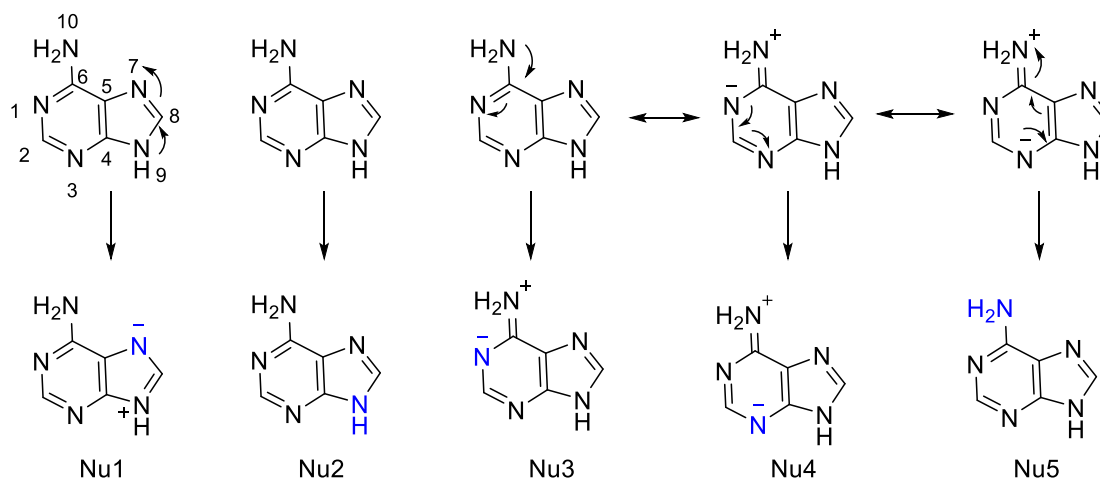
Figure 7. Proposed possible therapeutic mechanisms for TP70.

3.3. Syntheses of Tricyclic Pyrones



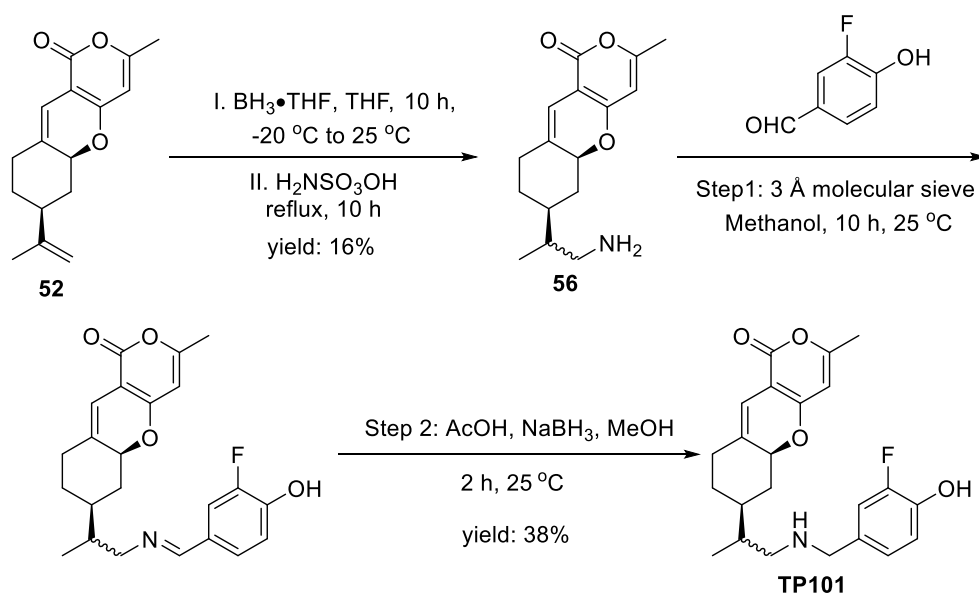
Scheme 16. Synthesis for CP2.

In **Scheme 16**, tricyclic pyrone **52** was derived from a one-pot reaction by heating a mixture of compound **62** and **63** and L-proline in ethyl acetate to reflux for 30 h, which couples perillaldehyde and 4-hydroxy-6-methyl-2*H*-Pyran-2-one to furnish tricyclic pyrone **52** with the L-proline as a ligand to afford tricyclic pyrone **52** in a yield of 75%.⁹² Then, the olefin **52** was treated with borane·tetrahydrofuran (BH₃·THF) complex in THF solution to give an alkylborane, as an intermediate, followed by the addition of hydrogen peroxide to convert alkylboranes to alkylborates. To the reaction solution, sodium hydroxide was added to furnish alcohol **53**.⁹³ The hydroxyl group in the alcohol **52** was then converted to mesylate **54** in 70% yield.⁹³ As a good leaving group, the mesylate **54** was substituted by adenine in an S_N2 reaction to furnish **CP2** in a yield of 16%.⁹³



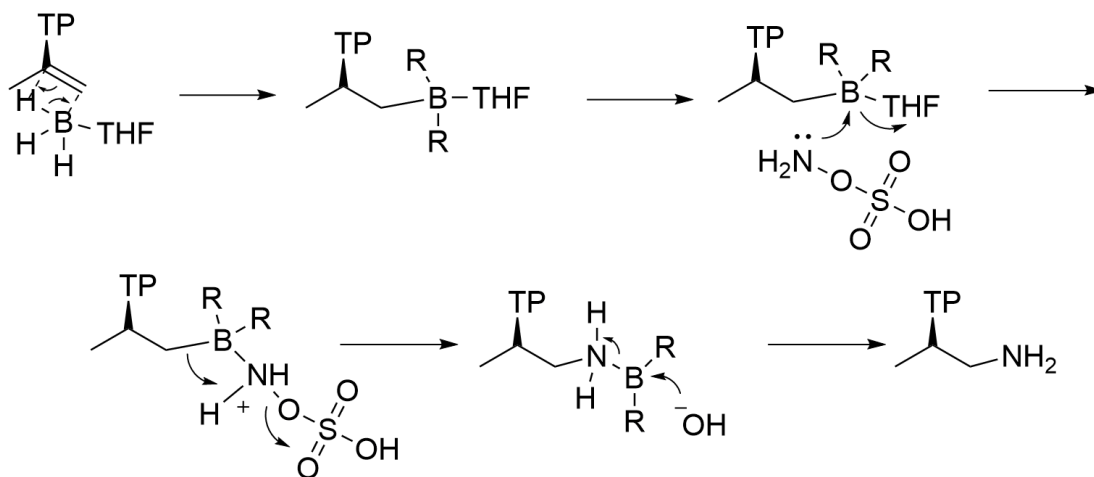
Scheme 17. Different nucleophilic status of the Adenine.

As a nucleophilic reagent, adenine exists in five different nucleophilic statuses (see **Scheme 17**). For the S_N2 reaction at high temperature and aprotic solution of dimethylacetamide (DMA), **Nu4** should be the most nucleophilic status. Due to the existence of these resonances, only a low yield of the desired product was obtained.



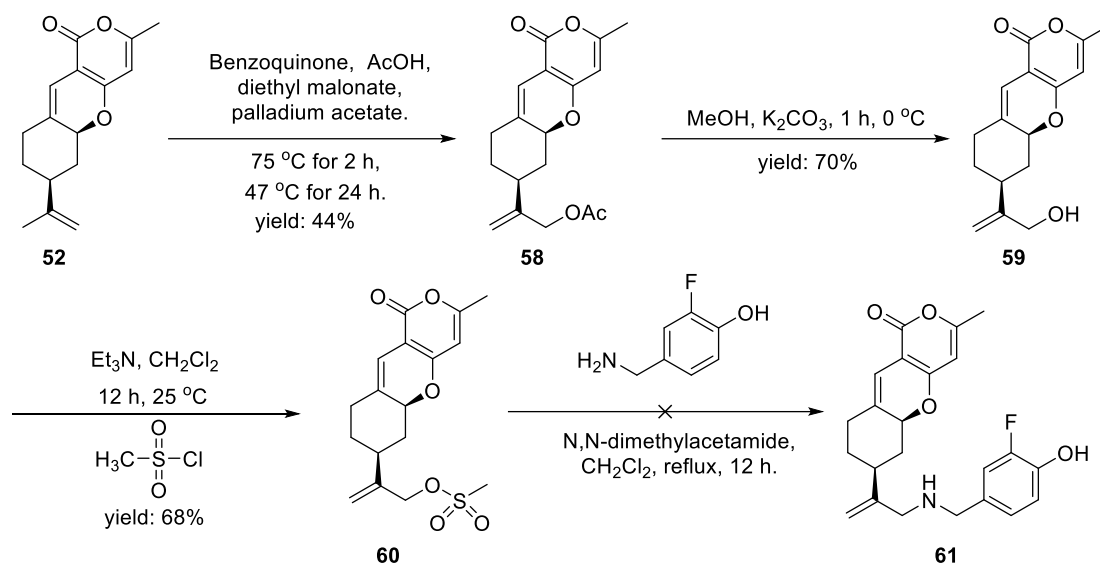
Scheme 18. Synthesis for TP101.

In **Scheme 18**, **TP101** was synthesized by treating tricycle pyrone **52** with $\text{BH}_3 \cdot \text{THF}$ complex followed by the addition of hydroxylamine sulfonic acid to give the amine **56** in a 40% yield.⁹⁴ After that, the amine **56** was condensed with a **56a** and carefully reduced by sodium cyanoborohydride to furnish **TP101** as the desired product in a yield of 38%.⁹⁴



Scheme 19. Proposed mechanism for amination.

In the amination step, the olefin **52** was treated with $\text{BH}_3 \cdot \text{THF}$ to give the borane complex. Then, the reaction mixture was transferred to a dried flask containing $\text{H}_2\text{NOSO}_3\text{H}$ and reflux for 10 h with only 16% yield obtained. The low yield may be caused by the existence of water. In order to enhance the reaction yield, molecular sieves could be a good choice to trap the water in this reaction. In **Scheme 19**, a mechanism was proposed to explain this reaction.⁹⁵ The $\text{BH}_3 \cdot \text{THF}$ first chelate with the olefin followed by a oxidative insertion. Then, an $\text{S}_\text{N}2$ reaction happens to give a borane-amine complex by displacing the THF ligand. After that, a rearrangement is conducted to for a C-N bond with C-B bond separated by the nitrogen. A base is then involved to attack the borane to start the amine away to produce the primary amine as the desired product.



Scheme 20. Synthesis for TP109.

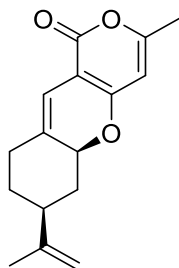
In order to eliminate the stereo-genic center, which produces two diastereomers, in **TP101** by avoiding the oxidation of the alkene function of **TP101**, Hua designed analog **TP109**. The synthetic strategy has been displayed in **Scheme 20**. To obtain it, the tricyclic pyrone (**52**) was mixed benzoquinone, diethyl malonate and palladium acetate to give acetate (**58**) with the olefin intact. Then, the acetate group in the acetate (**58**) was hydrolyzed with the existence of methanol and potassium carbonate to furnish alcohol (**59**) in a yield of 75%. Then, the alcohol (**59**) was treated with the methanesulfonyl chloride, Et₃N to furnish mesylate (**60**) in a yield of 68%. However, I failed to synthesize **TP109** at the last step. A postdoctoral fellow (Dr. Deepak Kumar Barange) in Hua's laboratory has successfully synthesized **TP109** in other synthetic strategies, and it has been submitted for biological evaluation in Dr. Simon Xie's laboratory at Redwood City, CA.

3.4. Conclusion

In this chapter, a series of small molecules with potential bioactivities to inhibit Alzheimer's diseases have been synthesized. In order to eliminate the stereo-genic center producing two diastereomers, a novel small molecule **TP109** was designed by Dr. Hua. However, I failed to synthesize the target molecule. Fortunately, the **TP109** was successfully synthesized by other postdoctoral fellows in Hua's laboratory.

3.5. Representative Syntheses

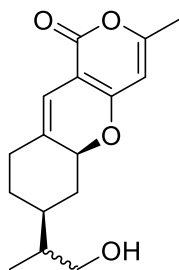
(5*aS*,7*S*)-7-Isoprenenyl-3-methyl-1*H*,7*H*-5*a*,6,8,9-tetrahydro-1-oxopyrano[4,3-*b*][1]benzopyran (**52**) (The preparation was followed by a reported method)⁹² (from **29**)



A reaction mixture was prepared by mixing 20 g (147 mmol) of 4-hydroxypyronone (**62**), 7.3 g (63.5 mmol) of L-proline, 25.9 g (147 mmol) of perillaldehyde (**63**) and 1000-mL ethyl acetate. The mixture was then heated to reflux for 30 h, filtered through Celite while hot to remove the L-proline, concentrated to 200 mL on a rotary evaporator. The concentrated solution was sealed and

transferred to the fridge for crystallization at 0 °C to obtain 28.4 g (75% yield) light yellow solid as desired product **52**. **¹H NMR** (400 MHz, CDCl₃): δ 6.12 (s, 1 H), 5.74 (s, 1 H), 5.10 (t, *J* = 5.2 Hz, 1 H), 4.75 (d, 2 H), 2.49 (d, 1 H), 2.21 (s, 3 H, CH₃), 2.21 - 2.00 (m, 3 H), 1.78 - 1.75 (m, 5 H), 1.32 (m, 1 H); **¹³C NMR** δ 163.4, 162.6, 161.7, 147.9, 132.3, 109.8, 109.6, 99.9, 97.5, 79.4, 43.6, 40.0, 32.5, 32.1, 20.9, 20.3; **MS** *m/z* = 259 ([*M* + *H*]⁺). The spectral data is in agreement with the previously reported data.⁹²

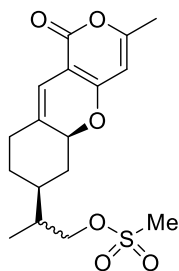
(5a*S*,7*S*)-7-[(1*R*) and (1*S*)-2-hydroxy-1-methylethyl]-3-methyl-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-*b*][1]benzopyran (53**) (The preparation was followed by a reported method)⁹³ (from **tzb-2-31**)**



To a cold solution of 20 g (77.52 mmol) of compound **52** in 400 mL of THF, 54.26 mL (54.26 mmol) of BH₃•THF complex (1.0 M in THF) was added dropwise under argon over an ice bath. After the solution was stirred at 0 °C for 2 h and 25 °C for 12 h, 80 mL of 0.5% NaOH aqueous solution and 60 mL of 30% H₂O₂ in water were added at 0 °C sequentially. The reaction mixture was then stirred for 2 h, diluted with 300 mL ethyl acetate, washed with aqueous solutions of NaHCO₃ and brine, dried on sodium sulfate, concentrated to dryness on a rotary evaporator, loaded to a silica gel column, eluted with a gradient mixture of hexane and ethyl acetate to obtain

17.0 g (79% yield) of alcohol **53** as the desired product. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 6.08 (s, 1 H, C4-H), 5.71 (s, 1 H, C10-H), 5.07 (t, $J = 5.2$ Hz, 1 H, C5a-H), 3.62 – 3.52 (m, 2 H, CH_2O), 2.46 (m, 1 H), 2.19 (s, 3 H, Me), 2.13 – 1.99 (m, 2 H), 1.73 – 1.51 (m, 3 H), 1.19 – 1.12 (m, 2 H), 0.92 (d, $J = 7$ Hz, 3 H, Me); $^{13}\text{C NMR}$ (CDCl_3) (two diastereomers) δ 163.5, 162.8, 161.6, 133.0, 109.0, 100.0, 97.4, 79.7, 79.6, 65.6, 39.9, 39.8, 39.4, 37.2, 37.1, 36.9, 32.4, 32.3, 31.1, 30.4, 28.5, 20.1, 13.2 (Me for a diastereomer), 13.1 (Me for another diastereomer). The spectral data is in agreement with the previously reported data⁹³.

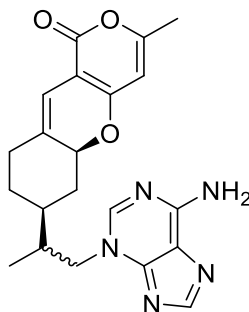
(5a*S*,7*S*)-7-[(1*R*) and (1*S*)-2-Hydroxy-1-methylethyl]- 3-methyl-1*H*,7*H*-5a,6,8,9- tetrahydro-1-oxopyrano[4,3-*b*][1]benzopyran (54**)** (The preparation was followed by a reported method)⁹³ (from tzb-2-33)



To a flame-dried and argon-purged round bottom flask, were adding 17 g (62.0 mmol) of alcohol **53**, 400 mL of freshly distilled dichloromethane, 32.4 mL (232.56 mmol) of distilled triethylamine. After the reaction mixture was cooled to 0 °C, 9.06 mL (116.28 mmol) of methane sulfonyl chloride was added dropwise. The solution was stirred for 4 h at 25 °C, quenched with an aqueous solution of sodium carbonate, extracted with dichloromethane for three times. The combined organic layer was washed with brine, dried on sodium sulfate, concentrated to dryness

over a rotary evaporator, loaded to a silica gel column, eluted with a gradient mixture of hexane and ethyl acetate to obtain 15.41 g (70% yield) of mesylate **54** as a mixture of two diastereomers. ¹H NMR (400 MHz, CDCl₃): δ 6.08 (s, 1 H, C4-H), 5.71 (s, 1 H, C10-H), 5.06 (m, 1 H, CHO), 4.18 – 4.08 (m, 2 H, CH₂O), 3.03 (s, 3 H, Me-S), 2.49 (d, *J* = 2.8 Hz, 1 H), 2.19 (s, 3 H, Me), 2.14 – 1.11 (m, 7 H), 0.98 (d, *J* = 6.8 Hz, 3 H, Me) ; ¹³C NMR (CDCl₃) δ 163.2, 162.4, 161.7, 132.1, 109.6, 105.2, 99.8, 79.2, 79.1, 72.3, 38.9, 37.5, 37.4, 37.3, 37.2, 36.9, 32.2, 32.1, 30.8, 28.6, 20.2, 13.3 (Me for a diastereomer), 13.2 (Me for another diastereomer). The spectral data is in agreement with the previously reported data⁹³.

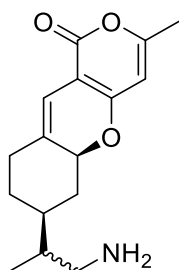
(5a*S*,7*S*)-7-[(1*R*) and (1*S*)- 2-(N3-adenyl)-1-methylethyl]-3-methyl-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-*b*][1]benzopyran (CP2) (The preparation was followed by a reported method)⁹³ (from tzb-2-34)



To a round bottom flask equipped with a condenser, were adding 15.41 g (43.5 mmol) of mesylate **54**, 5.9 g of adenine (43.5 mmol) under argon. After 240 mL freshly distilled N,N-dimethylacetamide (DMA) was added into the flask, the reaction mixture was left to stir at 170 - 180 °C for 8 h, cooled to 25 °C, concentrated to dryness on a rotary evaporator connecting to an oil pump. The concentrated crude was loaded to a silica gel column, eluted with a gradient mixture

of dichloromethane, ethyl acetate and methanol to afford 2.65 g **CP2** in a 16% yield. ^1H NMR (400 MHz, CDCl_3): δ 8.07 (s, C8 H of adenine), 7.98 and 7.97 (2 s, 1 H, C_2H of adenine; 2 diastereomers), 6.10 (s, 1 H, C10H), 5.72 and 5.71 (2s, 1 H, C4H), 5.02 (m, 1 H, C5a-H), 4.50 (dd, $J = 14, 7$ Hz, 1 H, CHN), 4.08 (2dd, $J = 14, 8$ Hz, 1 H, CHN; 2 diastereomers), 2.46 (m, 2 H), 2.20 and 2.19 (2s, 3 H, Me; 2 diastereomers), 2.10 – 1.22 (a series of m, 6H), 0.91 (d, $J = 47.0$ Hz, 3H, Me) ; ^{13}C NMR (CDCl_3) (2 diastereomers) δ 163.2 and 163.1, 162.4, 161.7, 154.4, 154.0, 150.7, 142.3, 131.7 and 131.6, 121.0, 199.8, 99.7, 97.3, 79.0, 78.8, 54.5 and 54.4, 38.9, 38.1 and 38.0, 37.1 and 36.9, 36.1, 32.0 and 31.9, 30.7, 27.6, 20.1, 13.3 and 13.2. The spectral data is in agreement with the previously reported data⁹³.

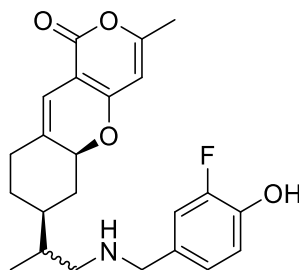
(5a*S*,7*S*)-7-[(1*R*) and (1*S*)-2-Amino-1-methylethyl]-3-methyl-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-*b*][1]benzopyran (56) (The preparation was followed by a reported method)⁹⁵ (from tzb-2-134)



To a flame-dried and argon-purged flask, 10 g (39 mmol) of dried tricyclic pyrone **52** and 300 mL of freshly distilled THF were added under argon. After the solution was cooled to $-20\text{ }^{\circ}\text{C}$, 24 mL (24 mmol, 0.6 eq.) 1 N $\text{BH}_3\cdot\text{THF}$ complex in THF was added dropwise over 5 min. Then, the reaction mixture was stirred for 10 h at $25\text{ }^{\circ}\text{C}$. The light-yellow reaction mixture was transferred

via a cannula to a 2-neck round bottom flask equipped with a condenser containing dried 6.8 g (60 mmol, 1.5 eq.) of hydroxylamine sulfonic acid under argon. Then, the reaction mixture was heated to reflux under argon and stirred for 10 h, diluted with 100 mL ethyl acetate, extracted with 100 mL 2 M aqueous solution of hydrochloride acid for three times. The combined aqueous layer was washed with 300 mL ethyl acetate, cooled to 0 °C, basified to pH~12 by using 15% aqueous solution of sodium hydroxide, extracted with 100 mL ethyl acetate twice. The combined organic layer was then washed with 100 mL brine, dried over sodium sulfate, filtered through Celite, concentrated on a rotary evaporator to afford 3.15 g (30% yield) desired product **56** as a light yellow powder without further purification: **¹H NMR** (400 MHz, CDCl₃): δ 6.07 (s, 1 H, C4H), 5.71 (s, 1 H, C10H), 5.07 (m, 1 H, C5aH), 2.73 (m, 1 H, 2 isomer, CHN), 2.58 (m, 1 H, 2 isomers, CHN), 2.46 (d, *J* = 13 Hz, 1H), 2.19 (s, 3 H, Me), 2.15–1.10 (m, 7 H), 0.91 (d, *J* = 7 Hz, 3 H, Me) ; **¹³C NMR** d 163.4, 162.7, 161.7, 132.9, 109.3, 100.0, 97.5, 79.8 and 79.7 (2 isomers), 66.0, 46.0 and 45.9 (2 isomers), 40.9, 39.1, 38.5 and 38.4 (2 isomers), 37.1, 32.6 and 32.4 (2 isomers), 31.3, 31.2, 28.6, 20.3, 15.5, 14.3. **HRMS** calcd for C₁₇H₂₂NO₃ (M+1) 276.1601, found 276.1610. The spectral data is in agreement with the previously reported data⁹⁴.

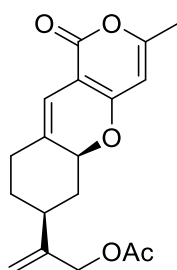
(5a*S*,7*S*)-3-Methyl-7-((1*R*) and (1*S*)-1-[(3-fluoro-4-hydroxy)benzylamino]propan-2-yl)-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-*b*][1]benzopyran (TP101) (The preparation was followed by a reported method)⁹⁴ (from tzb-2-135)



To flame-dried and argon-purged flask, 3.15 g (11.54 mmol) of dried amine **56**, 1.615 g (11.54 mmol, 0.9 eq.) of dried 4-hydroxy-3-fluorobenzaldehyde and 2.5 g of activated 3 Å molecular sieves were added under argon. To it, 60 mL dried methanol was added and stirred for 10 h at 25 °C under argon. After that, 0.7 mL of glacial acetic acid was added followed by the addition of 2.2 g (34.79 mmol, 2.5 eq.) of sodium cyanoborohydride in portions. The reaction mixture was left to stir for 2 h to reduce the imine to a secondary amine as the desired product. Then, the reaction mixture was filtered through Celite, diluted with 100 mL aqueous solution of ammonium hydroxide, extracted with 50 mL dichloromethane for four times. The combined organic layer was washed with 100 mL brine, dried over sodium sulfate, filtered through Celite, concentrated to dryness on a rotary evaporator. The dry crude was then loaded to a silica gel column (deactivated with ammonium hydroxide), eluted with a mixture solution of dichloromethane and methanol in a ratio of 15:1 to furnish 1.75 g (38% yield) **TP101**. **¹H NMR** (400 MHz, CDCl₃): δ 6.98 (dd, *J* = 11.6, 1.6 Hz, 1 H), 6.94 – 6.84 (m, 2 H), 6.07 (s, 1 H), 5.71 (s, 1 H), 5.10 – 4.99 (m, 1 H), 3.67 (s, 2 H), 2.66 – 2.59 (m, 1 H), 2.51 – 2.41 (m, 2 H), 2.19 (s, 3 H), 2.08 – 1.92 (m, 2 H), 1.73 – 1.44 (m, 4 H), 1.30 – 1.06 (m, 1 H), 0.92 and 0.91 (2 d, *J* = 6.8 Hz, 3 H, CH₃ of two diastereomers) ; **¹³C NMR** δ 163.52, 163.49, 162.8, 161.8, 152.9, 150.5, 143.9, 143.7, 132.9, 124.8, 118.4, 116.1, 115.9, 109.4, 100.0, 97.6, 79.8, 79.7, 53.5, 53.2, 53.1, 39.3, 38.9, 38.8, 37.5, 37.4, 36.9, 32.5, 32.4, 31.1, 28.5, 20.3, 14.8, 14.7; **MS** (electrospray ionization) *m/z*

400.1 (M+H⁺), 276.2, 147.4, 139.0; **HRMS** calcd for C₂₃H₂₇NO₄F⁺(M+H⁺) 400.1924, found 400.1924 (100%). The spectral data is in agreement with the previously reported data⁹⁴.

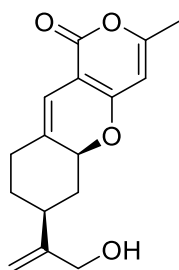
(5a*S*,7*S*)-7-[(3-acetoxy-1-propen-2-yl)]-3-methyl-1*H*,7*H*-5a,6,8,9-tetrahyro-1-oxopyranol[4,3-*b*][1]benzopyran (58) (The preparation was followed by a reported method)⁹⁶ (from tzb-2-30)



To a flame-dried and argon-purged flask, 200 mg (0.79) tricyclic pyrone **52**, 17 mg (78 mol) of palladium acetate, 0.25 g (2.3 mmol) of benzoquinone, and 25 mg (0.16 mmol) of diethyl malonate were added and purged with argon. To it, 5 mL of dried acetic acid was added and heated to 75 °C for 2 h and 47 °C for 24 h. The reaction mixture was cooled to 25 °C, filtered through Celite, washed with aqueous sodium bicarbonate, water, and brine, dried on sodium sulfate, filtered through Celite, concentrated to dryness on a rotary evaporator, loaded to silica gel column, eluted with a mixture of hexane: ethyl acetate (1: 15) to furnish 0.11 g (44% yield) desired product **58**. **¹H NMR** (400 MHz, CDCl₃): δ 6.12 (s, 1 H), 5.73 (s, 1 H), 5.12 (s, 1 H, =CH₂), 5.10 - 5.09 (m, 1 H, CHO), 5.02 (s, 1 H, =CH₂), 4.58 (s, 2 H, CH₂OAc), 2.51 (dt, *J* = 14, 4 Hz, 1 H), 2.28 - 2.24 (m, 2 H), 2.20 (s, 3 H, Me), 2.11 (s, 3 H, CH₃CO), 2.11 ~ 2.05 (m, 1 H), 1.93 – 1.89 (m, 1 H), 1.77 (dd, *J* = 12, 11 Hz, 1 H), 1.36 – 1.31 (m, 1 H); **¹³C NMR** d 170.9, 163.4, 162.7, 161.9, 146.4,

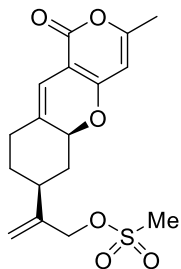
131.8, 112.9, 110.0, 99.9, 97.5, 79.2, 66.1, 40.0, 39.5, 32.4, 32.3, 21.2, 20.3. **HRMS** calcd for $C_{18}H_{21}O_5$ ($M+H^+$) 317.1389, found 317.1396.

(5a*S*,7*S*)-7-[(3-Hydroxy-1-propen-2-yl)]-3-methyl-1*H*,7*H*-5a,6,8,9-tetrahyro-1-oxopyrano[4,3-*b*][1]benzopyran (59) (from tzb-2-147)



To a cold solution of 0.62 g (1.9 mmol) acetoxy tricyclic pyrone **58** in 15 mL of methanol, 0.54 g (3.9 mmol) of potassium carbonate was added and stirred at 0 °C for 1 h. To it, a solution of 1 N hydrochloric acid was added to neutralize the pH ~ 5, extracted with dichloromethane for three times. The combined organic layer was washed with aqueous ammonium chloride, water, brine, dried on sodium sulfate, concentrated to dryness over a rotary evaporator, loaded to silica gel column, eluted with a gradient mixture of hexane: ether to furnish 0.37 g (70% yield) desired product **59**. **¹H NMR** (400 MHz, $CDCl_3$): δ 6.12 (s, 1 H), 5.73 (s, 1 H), 5.13 – 5.12 (m, 1 H, CHO), 5.11 (s, 1 H, =CH₂), 4.94 (s, 1 H, =CH₂), 4.15 (d, J = 7 Hz, 2 H, CH₂O), 2.51 (dt, J = 14, 4 Hz, 1 H), 2.34 - 2.23 (m, 2 H), 2.20 (s, 3 H, Me), 2.18 ~ 2.08 (m, 1 H), 1.93 – 1.83 (m, 1 H), 1.77 (q, J = 12 Hz, 1 H), 1.40 – 1.28 (m, 1 H) ; **¹³C NMR** δ 163.5, 162.7, 161.7, 151.4, 132.2, 109.5, 109.4, 99.9, 97.4, 79.3, 64.9, 40.2, 38.9, 32.4 (2 C), 20.2; **HRMS** calcd for $C_{16}H_{19}O_4$ ($M+H^+$) 275.1283, found 275.1305.

(5a*S*,7*S*)-7-[(3-methanesulfonyloxy-1-propen-2-yl)]-3-methyl-1*H*,7*H*-5a,6,8,9-tetrahyro-1-oxopyranol[4,3-*b*][1]benzopyran (60) (The preparation was followed by a reported method)⁹³ (from tzb-3-20)



To a flame-dried and argon-purged flask, were added 873 mg (3.19 mmol) of TP alcohol **59**, 548 mg (4.78 mmol) of methane sulfonyl chloride, 1.33 mL (9.56 mmol) of triethylamine in 20 mL dichloromethane. After the reaction mixture was stirred for 2 h at 25 °C under argon, a solution of 365 mg (3.2 mmol) of methane sulfonyl chloride and 0.89 mL (6.4 mmol) of triethylamine in 10 mL dichloromethane were added and stirred for 12 h at 25 °C under argon. The solution was then diluted with 30 mL of dichloromethane, washed with aqueous sodium bicarbonate, water, brine, dried on sodium sulfate, filtered through Celite, concentrated over a rotary evaporator to dryness. The concentrated dryness was loaded to a silica gel column, eluted with a gradient mixture of hexane, diethyl ether and ethyl acetate to obtain 768 mg (68% yield) desired product **60**. **¹H NMR** (400 MHz, CDCl₃): δ 6.10 (s, 1 H), 5.71 (s, 1 H), 5.26 (s, 1 H, =CH₂), 5.14 (s, 1 H, =CH₂), 5.11 (dd, *J* = 12, 5 Hz, 1 H, CHO), 4.70 (s, 2 H, CH₂O), 3.03 (s, 3 H, S-CH₃), 2.51 (dt, *J* = 14, 3 Hz, 1 H), 2.37 - 2.20 (m, 2 H), 2.19 (s, 3 H, Me), 2.15 ~ 2.03 (m, 1 H), 1.95 – 1.89 (m, 1 H), 1.77 (dd, *J* = 12, 11 Hz, 1 H), 1.32 (qd, *J* = 13, 4 Hz, 1 H) ; **¹³C NMR** d 163.4,

162.6, 161.9, 144.8, 131.5, 116.1, 110.1, 99.9, 97.5, 78.9, 71.5, 39.8, 38.7, 38.1, 32.2, 32.1, 20.3;

HRMS calcd for $\text{C}_{17}\text{H}_{21}\text{O}_6\text{S}$ ($\text{M}+\text{H}^+$) 353.1059, found 353.1044.

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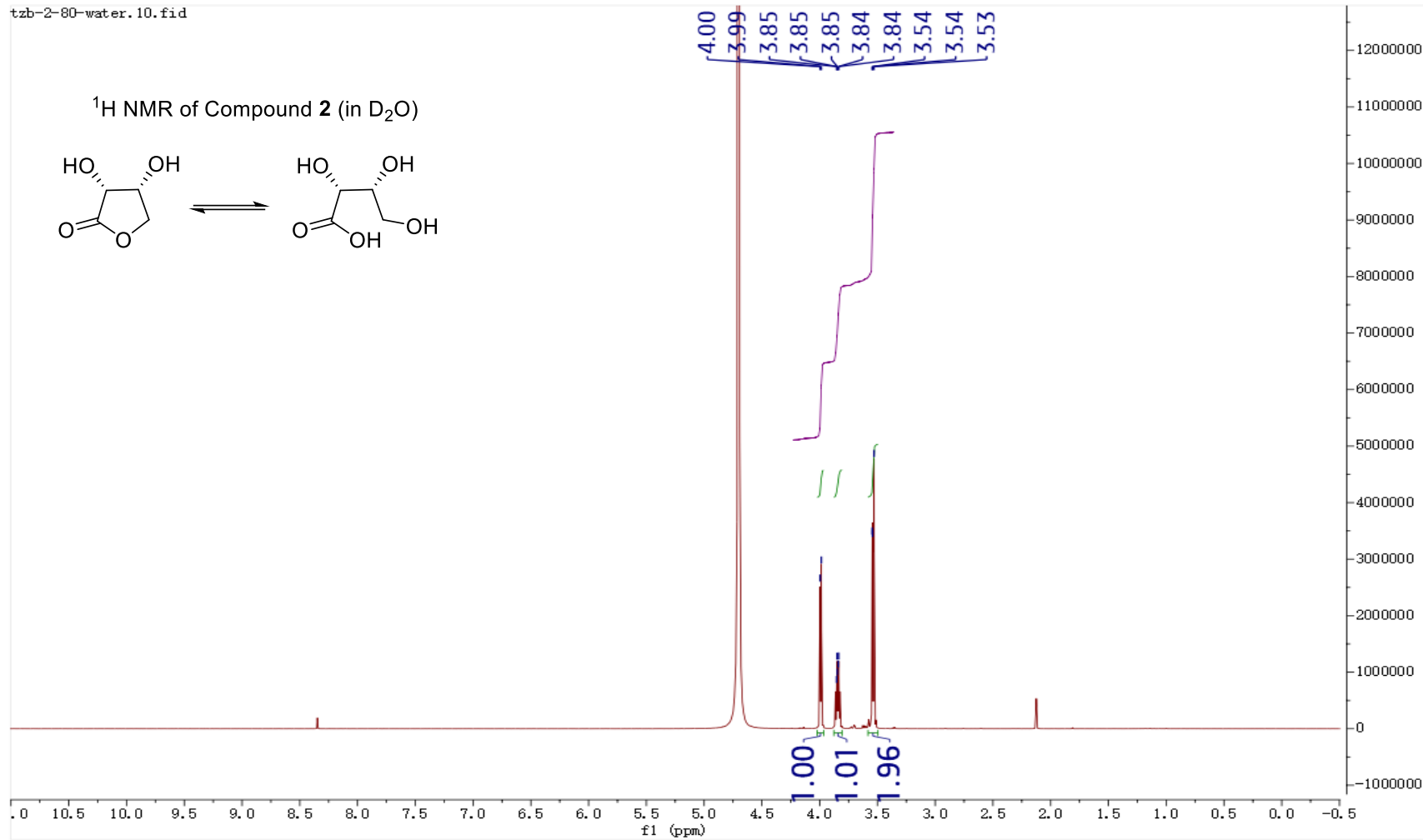
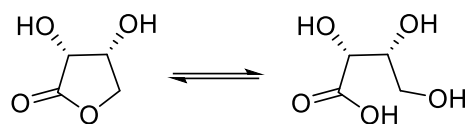
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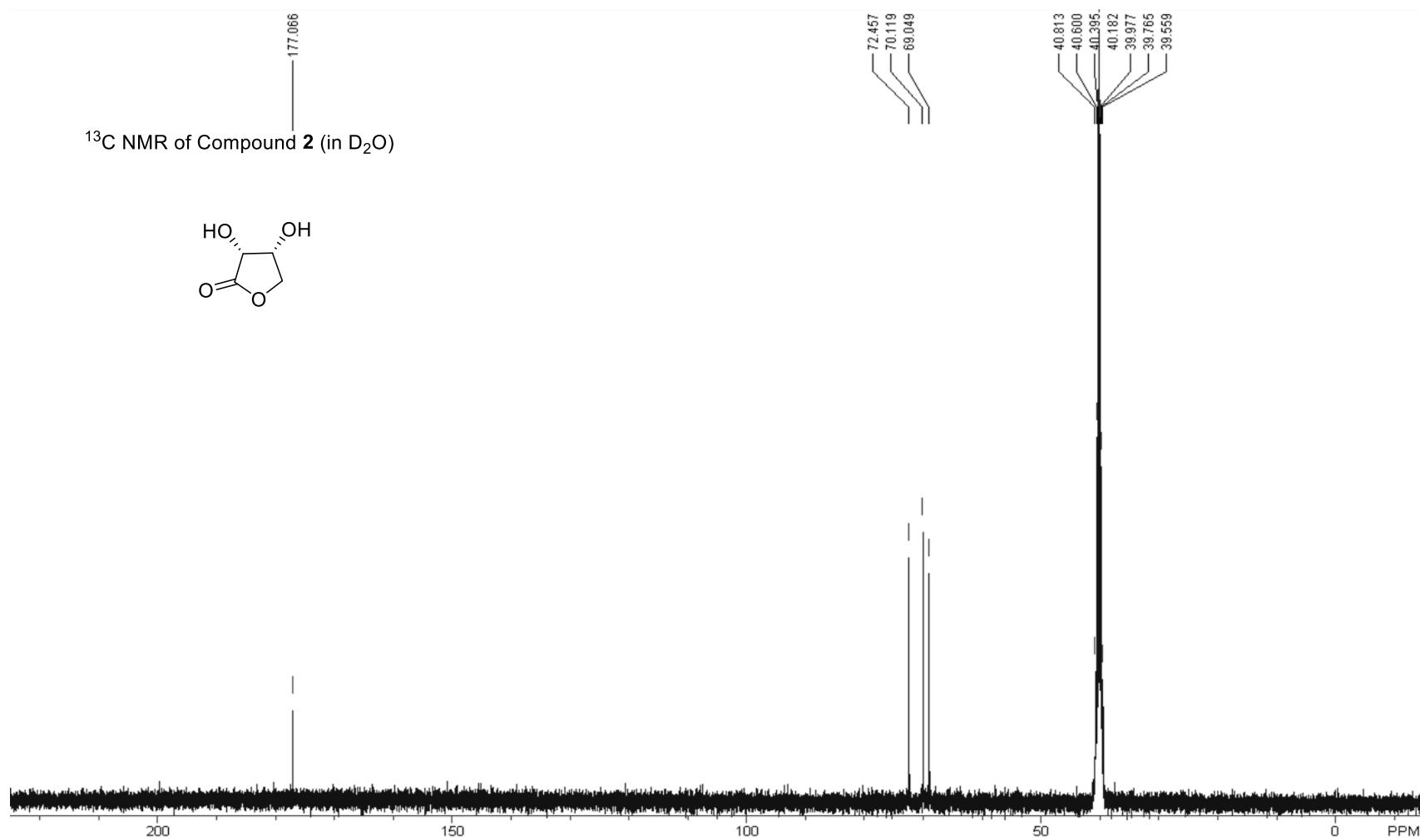
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Appendix A - ^1H -NMR, ^{13}C -NMR Spectrum

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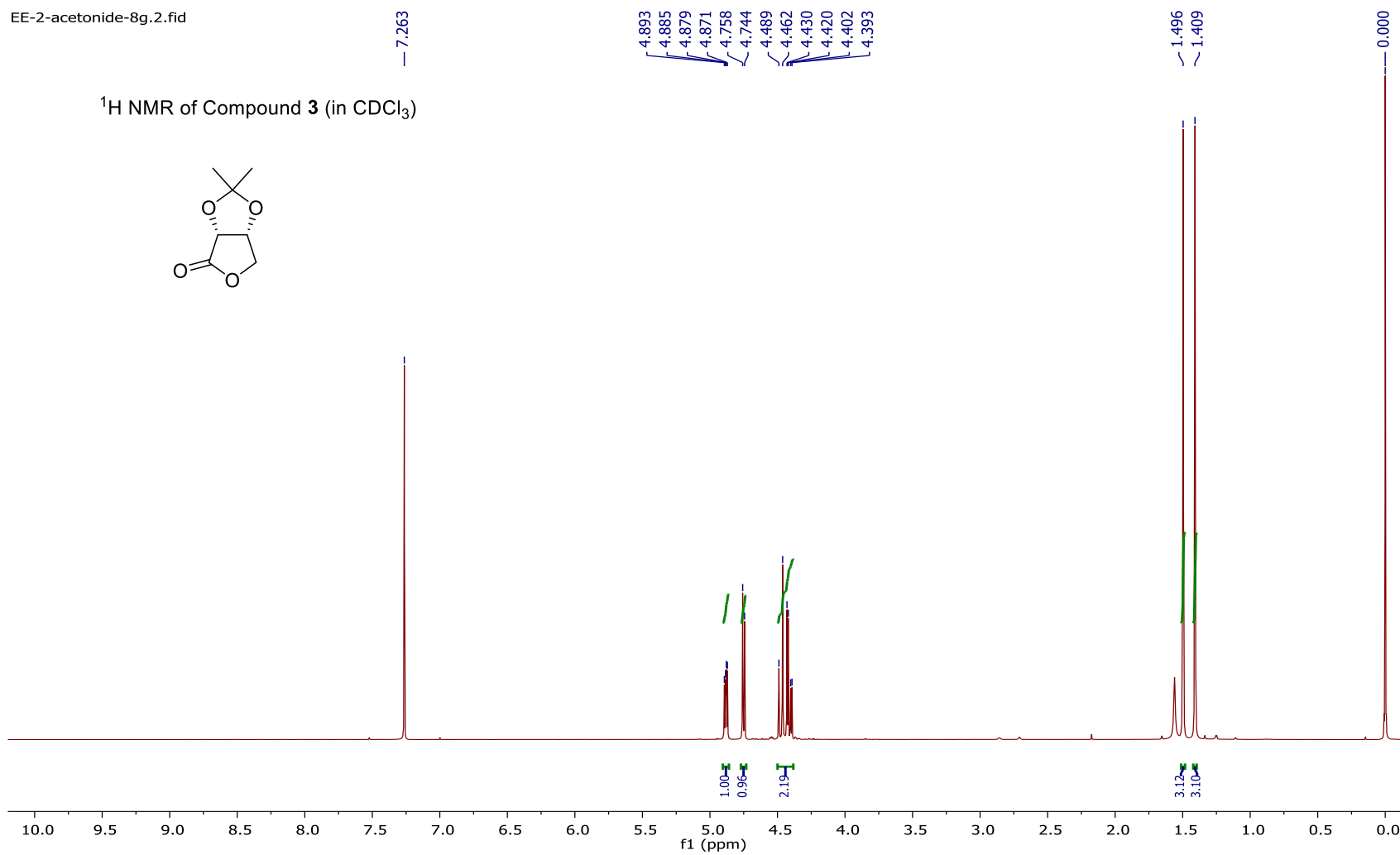
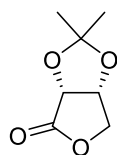
^1H NMR of Compound **2** (in D_2O)





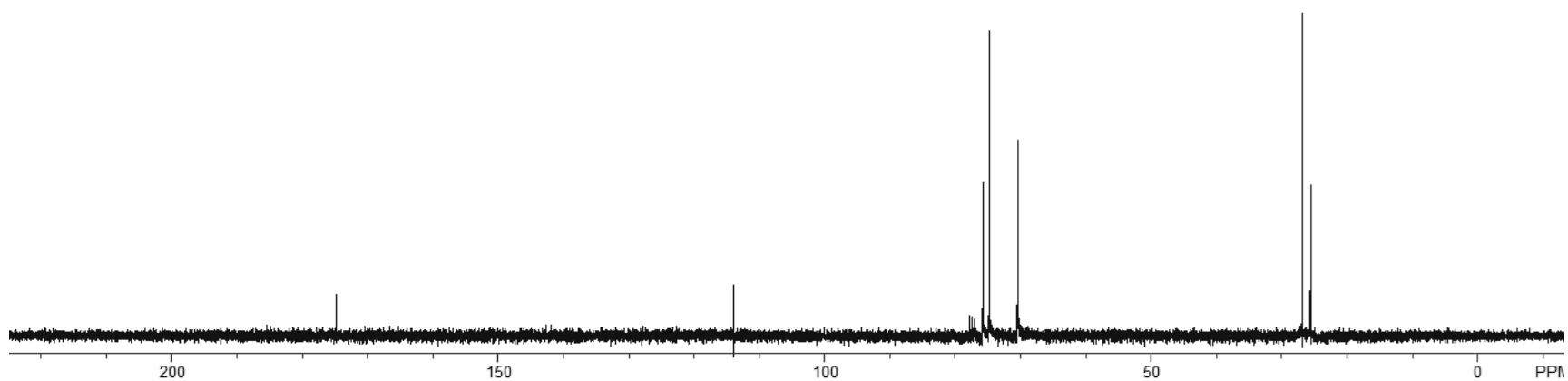
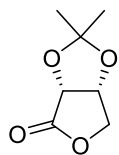
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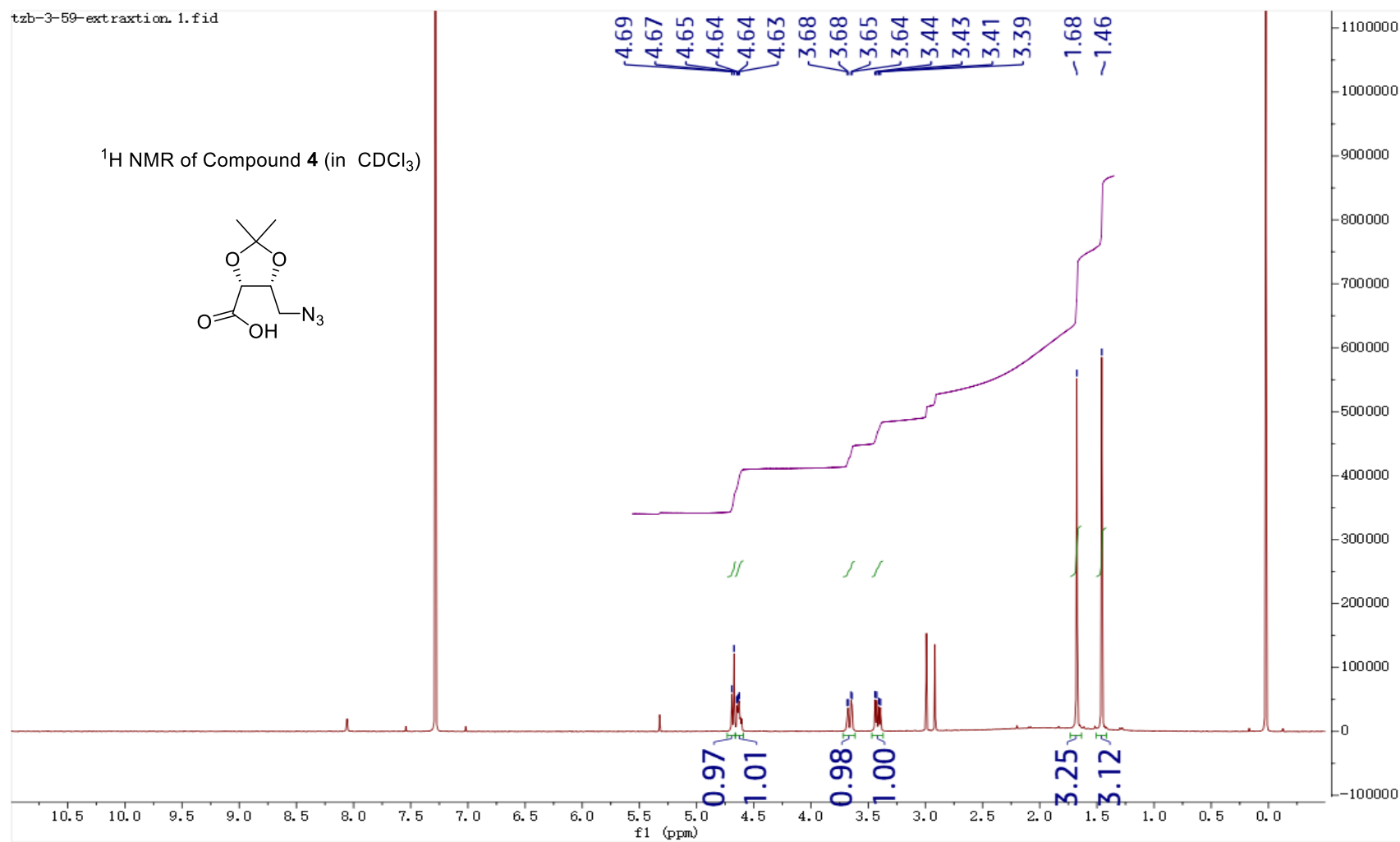
^1H NMR of Compound **3** (in CDCl_3)





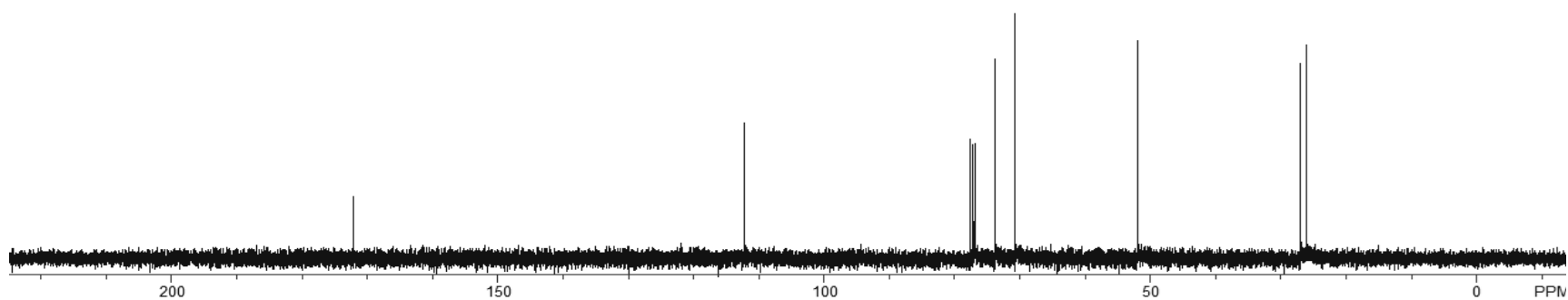
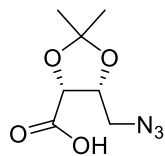
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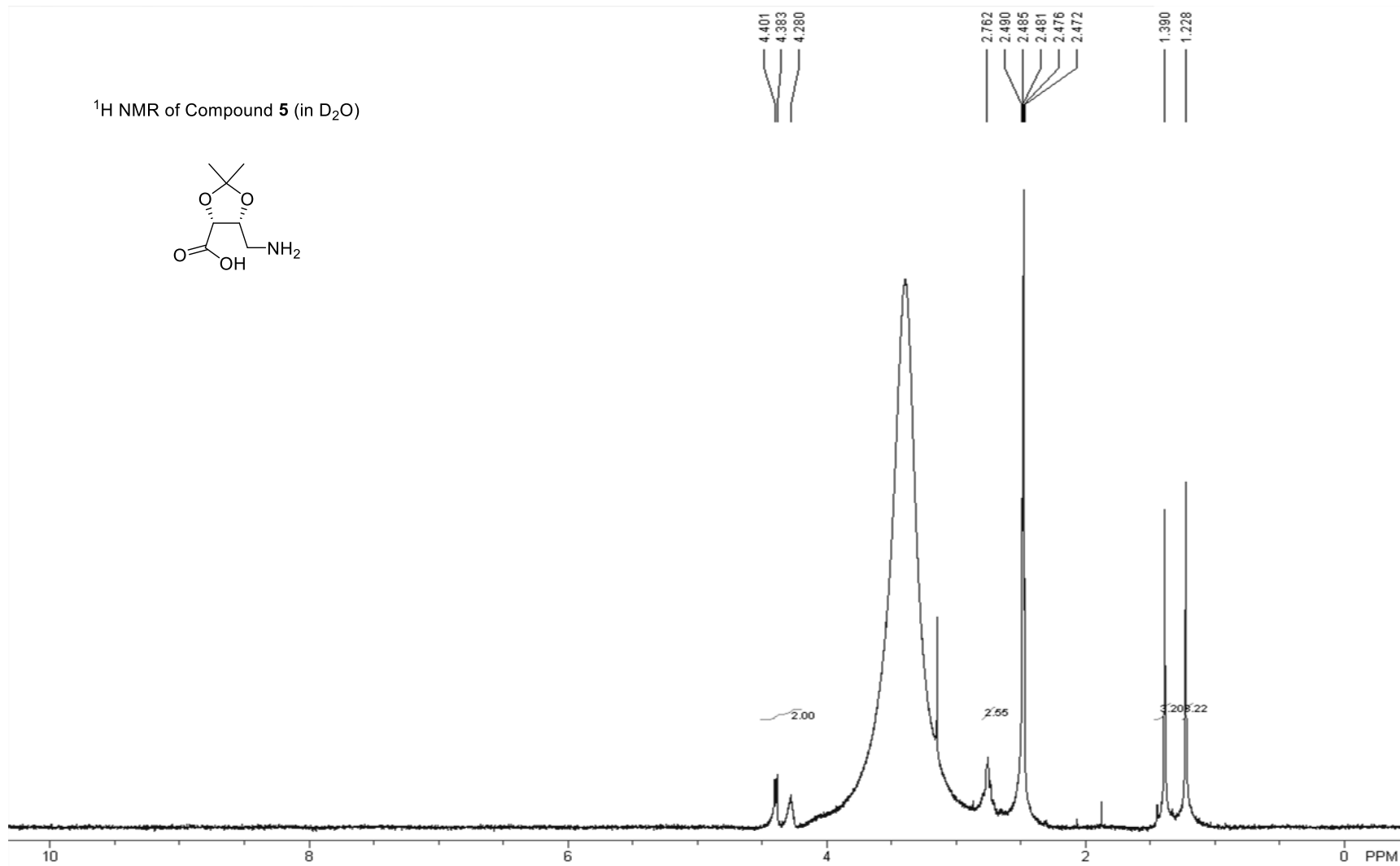
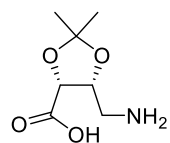




^{13}C NMR of Compound **4** (in CDCl_3)



^1H NMR of Compound **5** (in D_2O)



amino acid 13C.1.fid

— 174.086

— 111.065

— 76.762

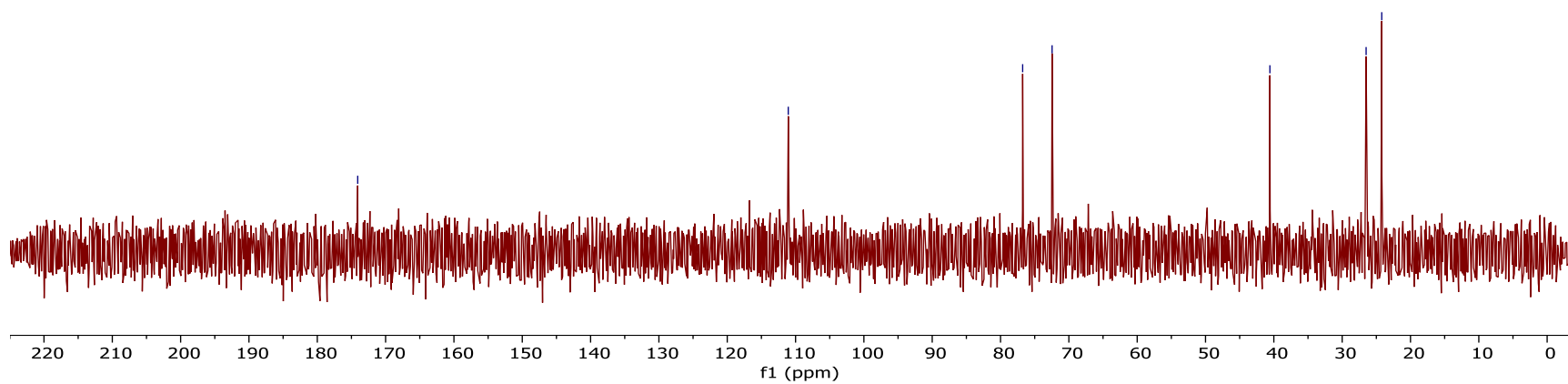
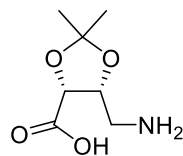
— 72.454

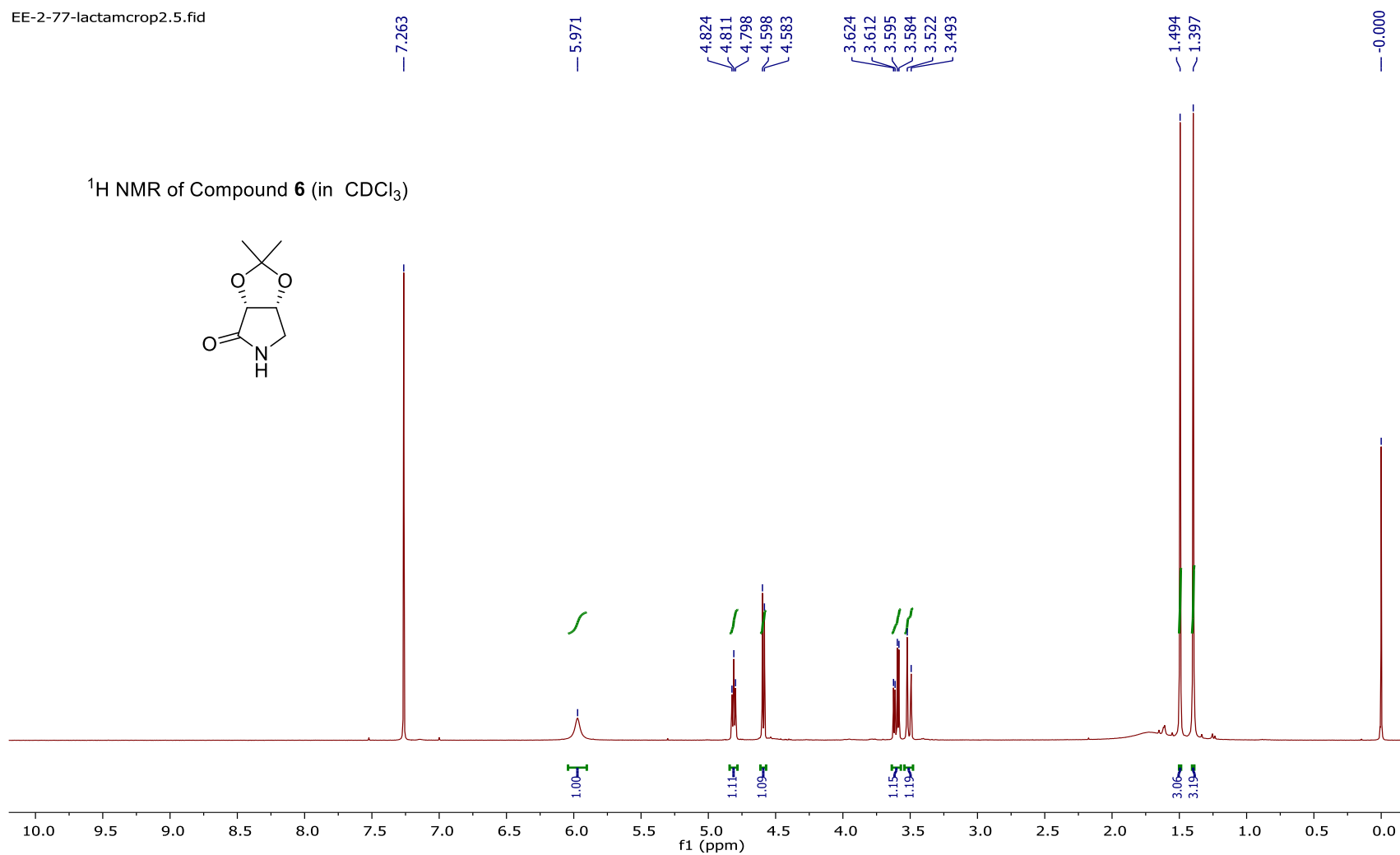
— 40.579

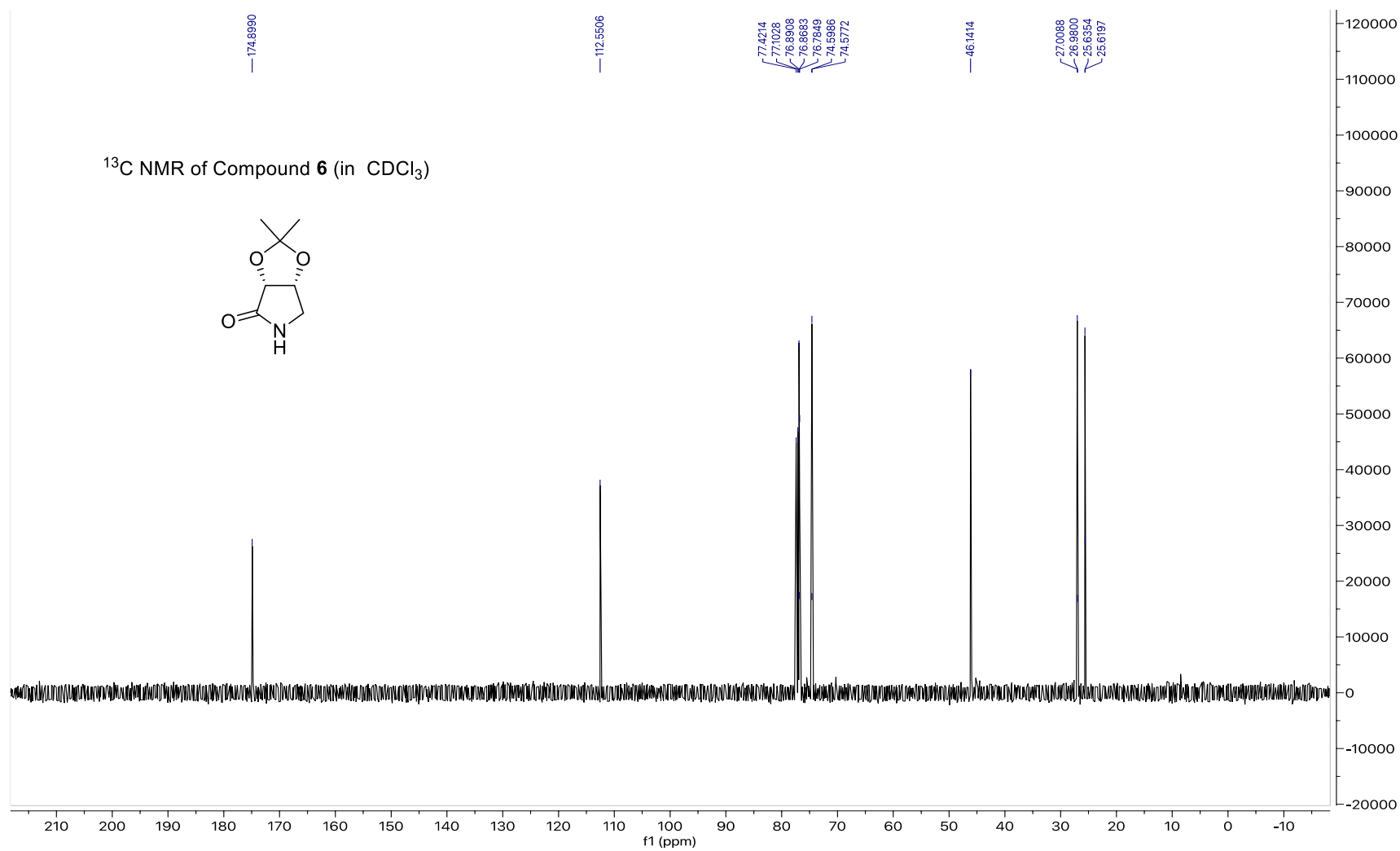
— 26.495

— 24.206

^{13}C NMR of Compound **5** (in D_2O)

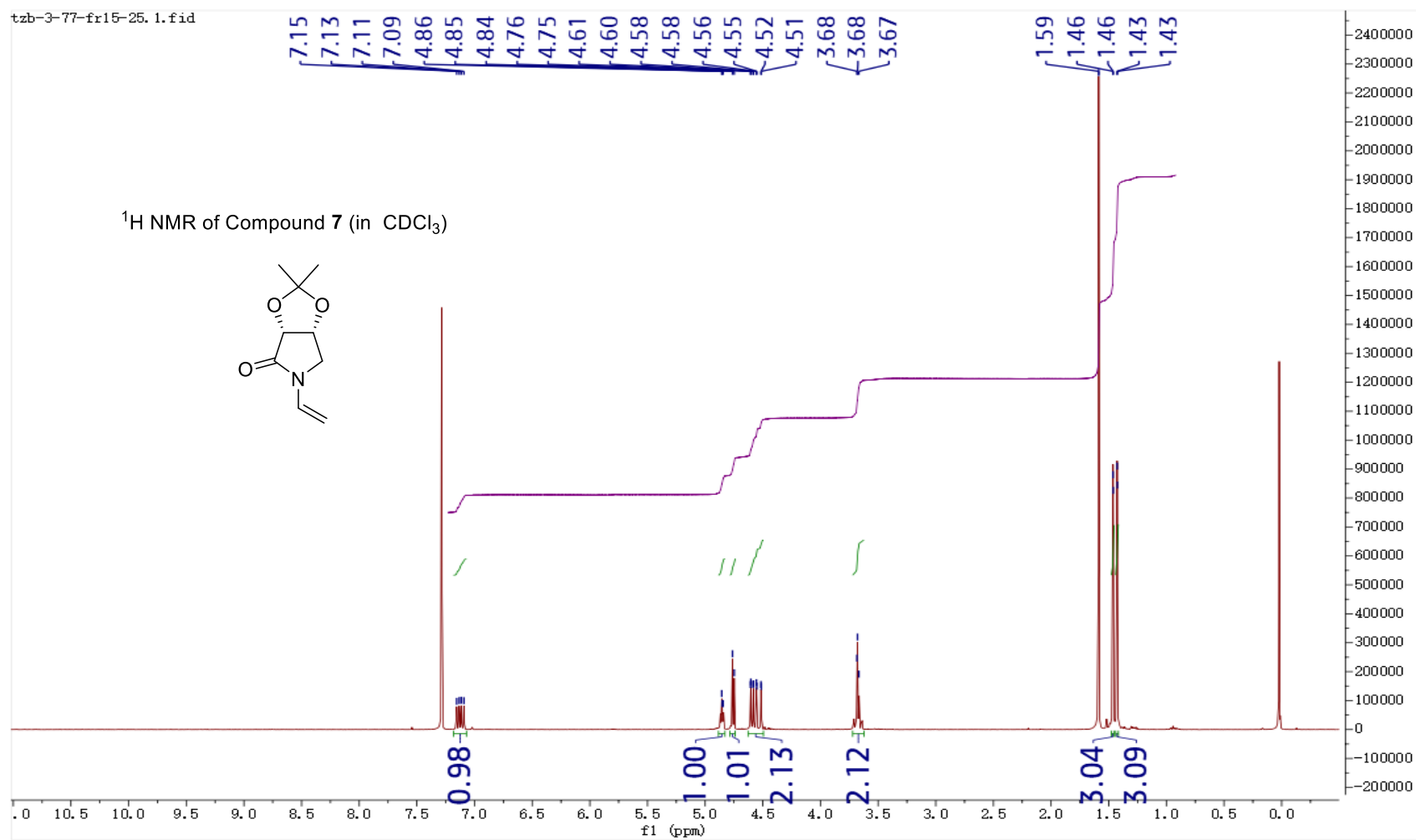
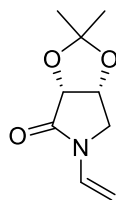


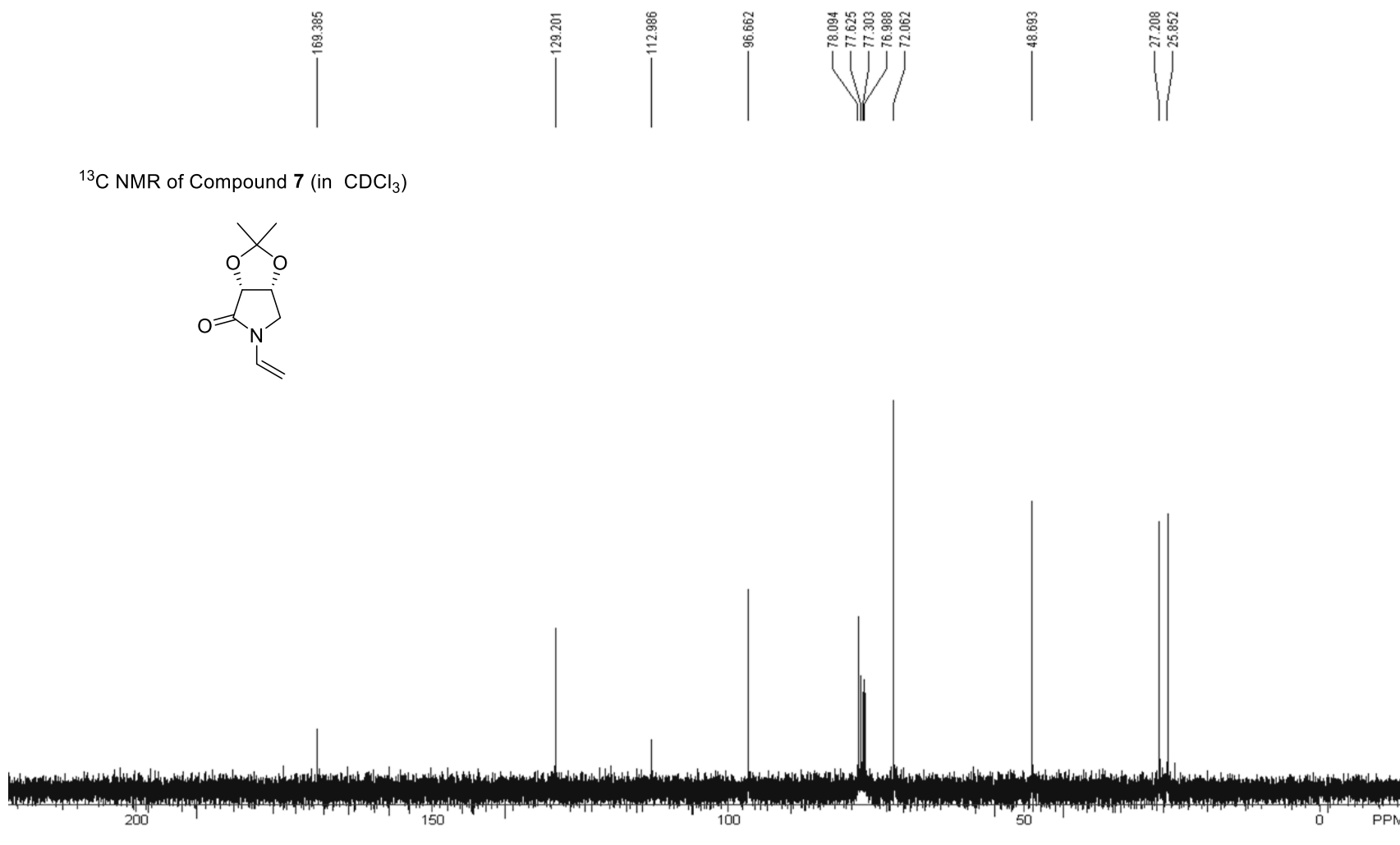


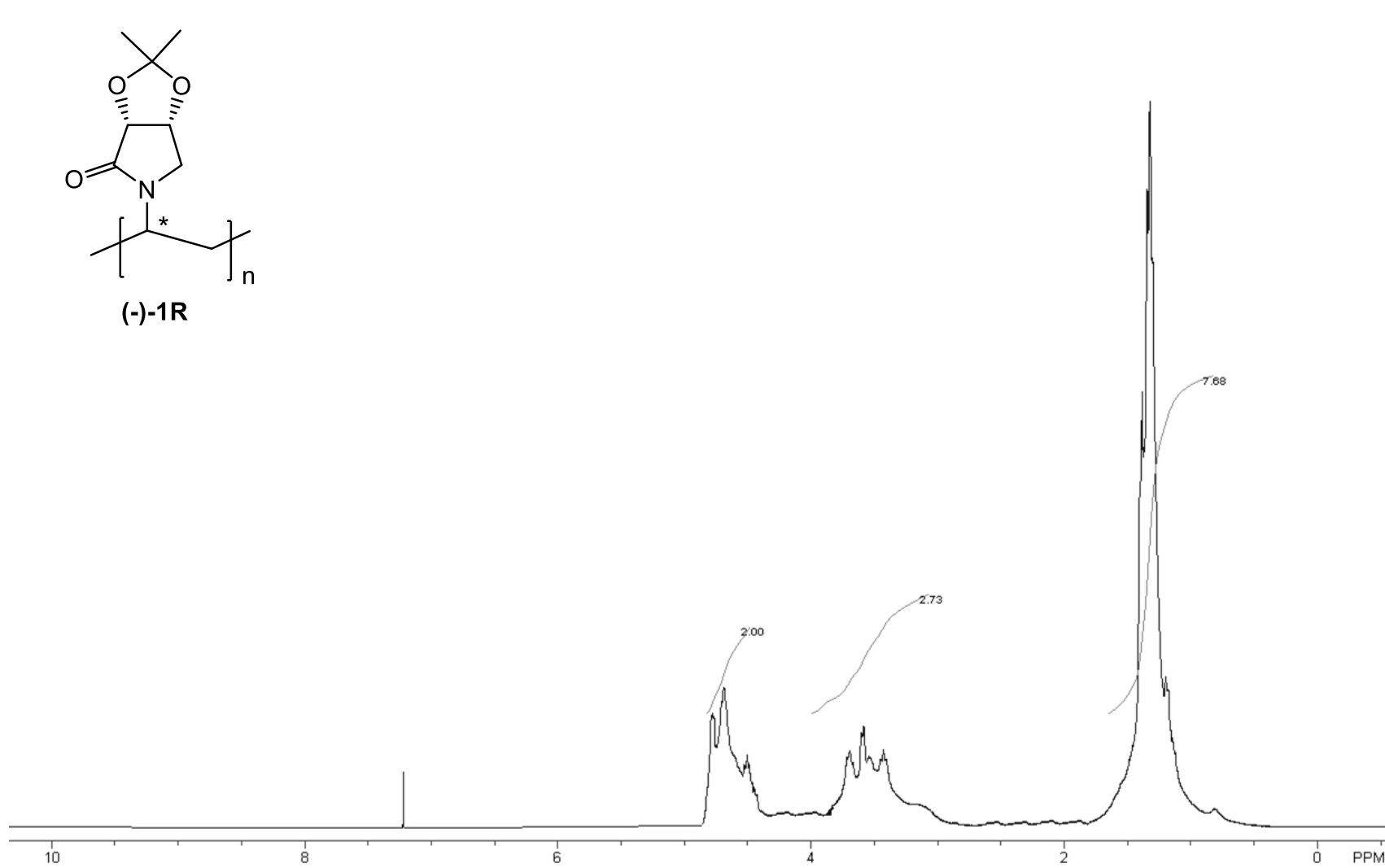
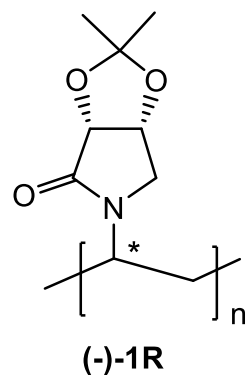


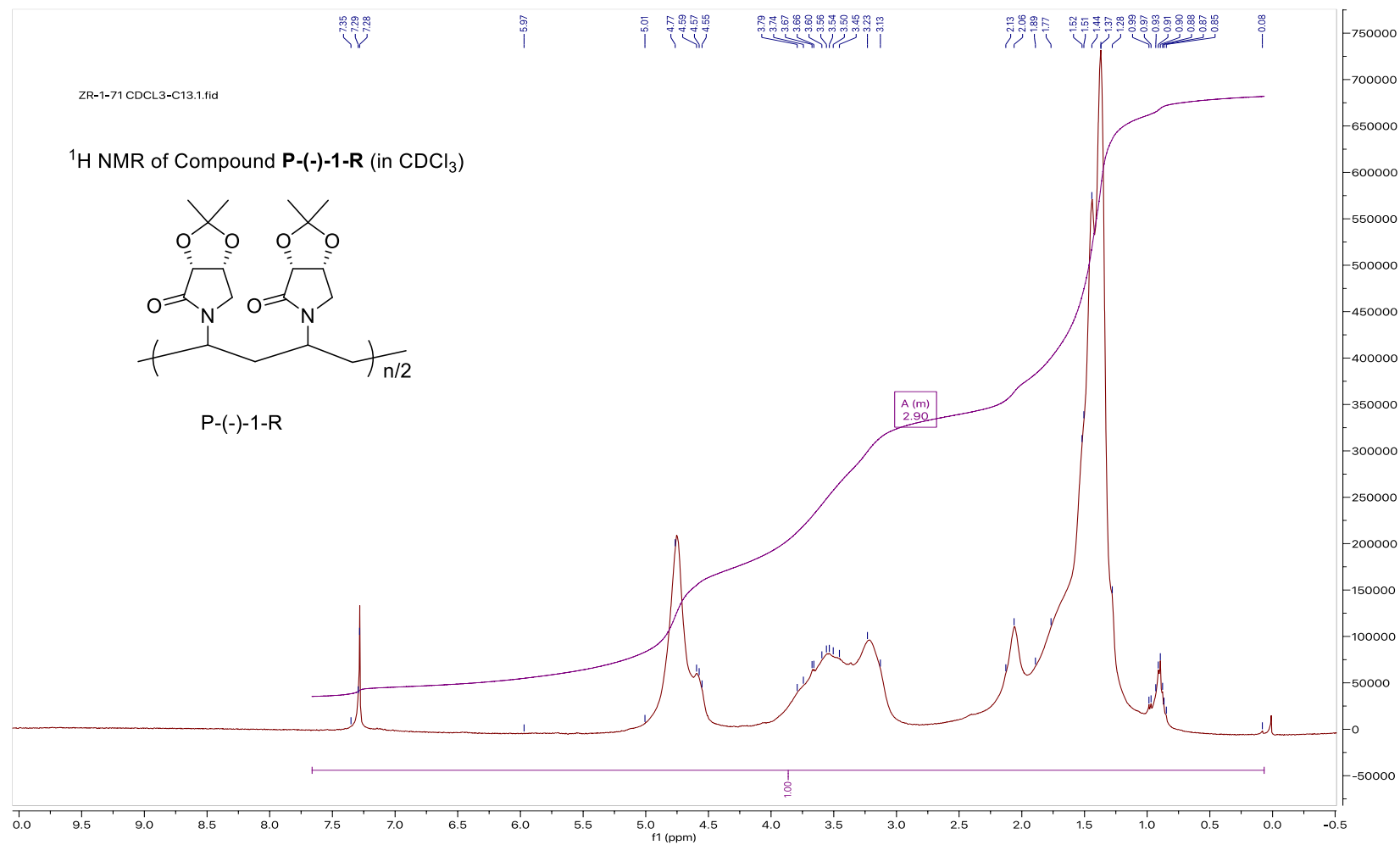
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^1H NMR of Compound **7** (in CDCl_3)



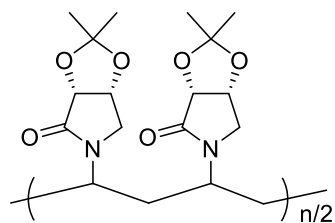




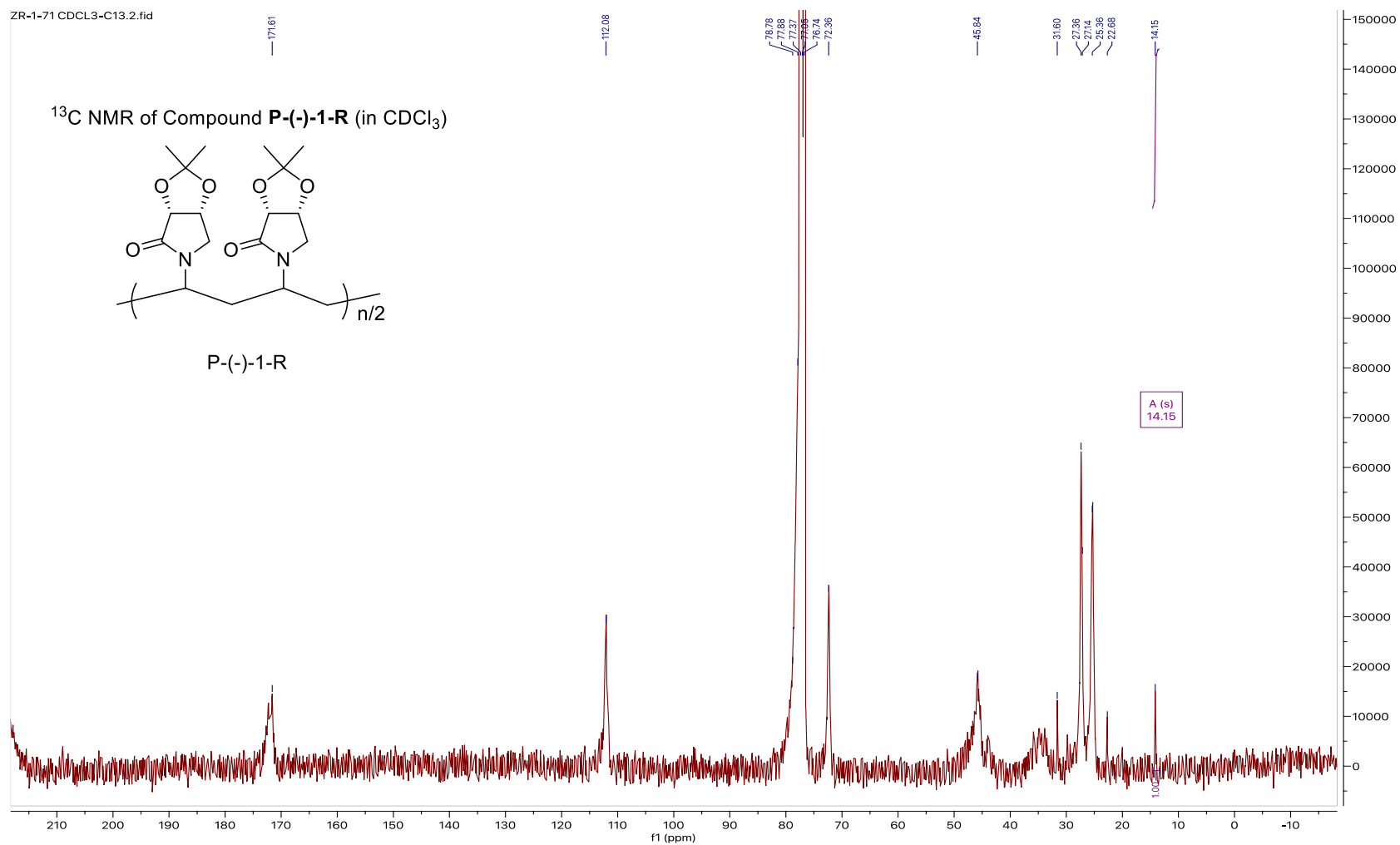


ZR-1-71 CDCL3-C13.2.fid

^{13}C NMR of Compound **P-(-)-1-R** (in CDCl_3)

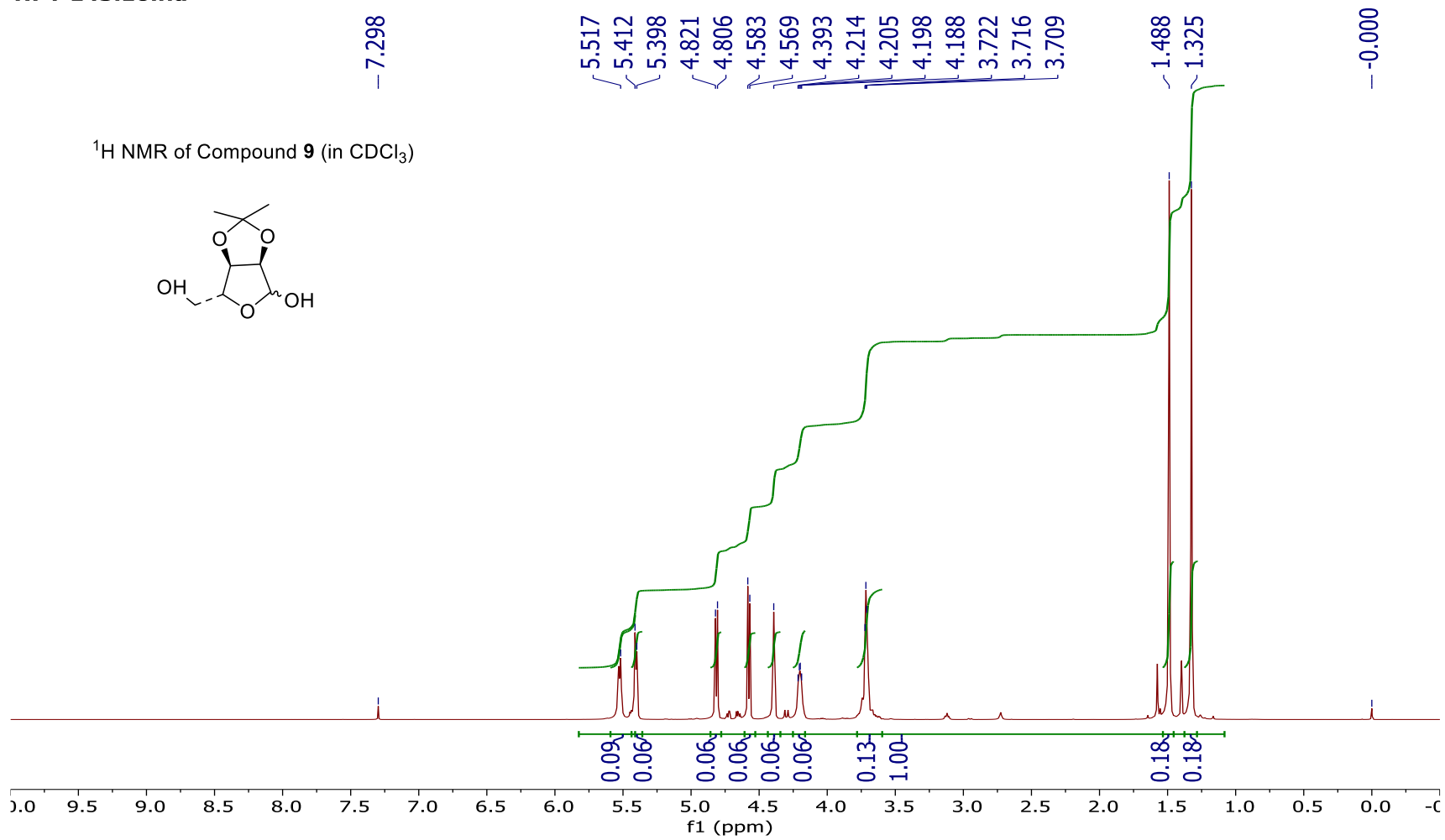
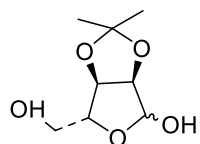


P-(-)-1-R



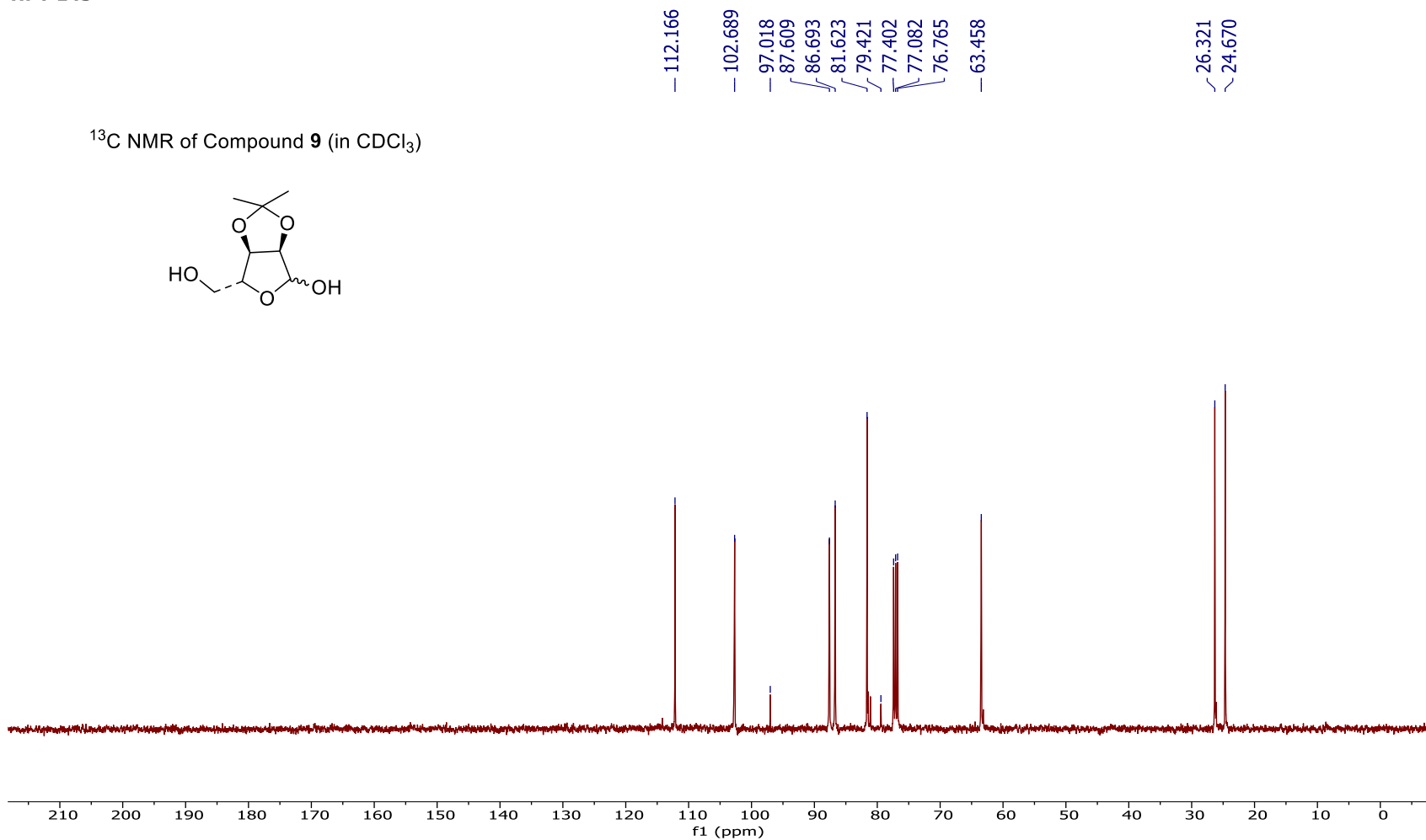
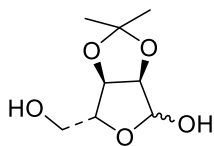
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¹H NMR of Compound **9** (in CDCl₃)



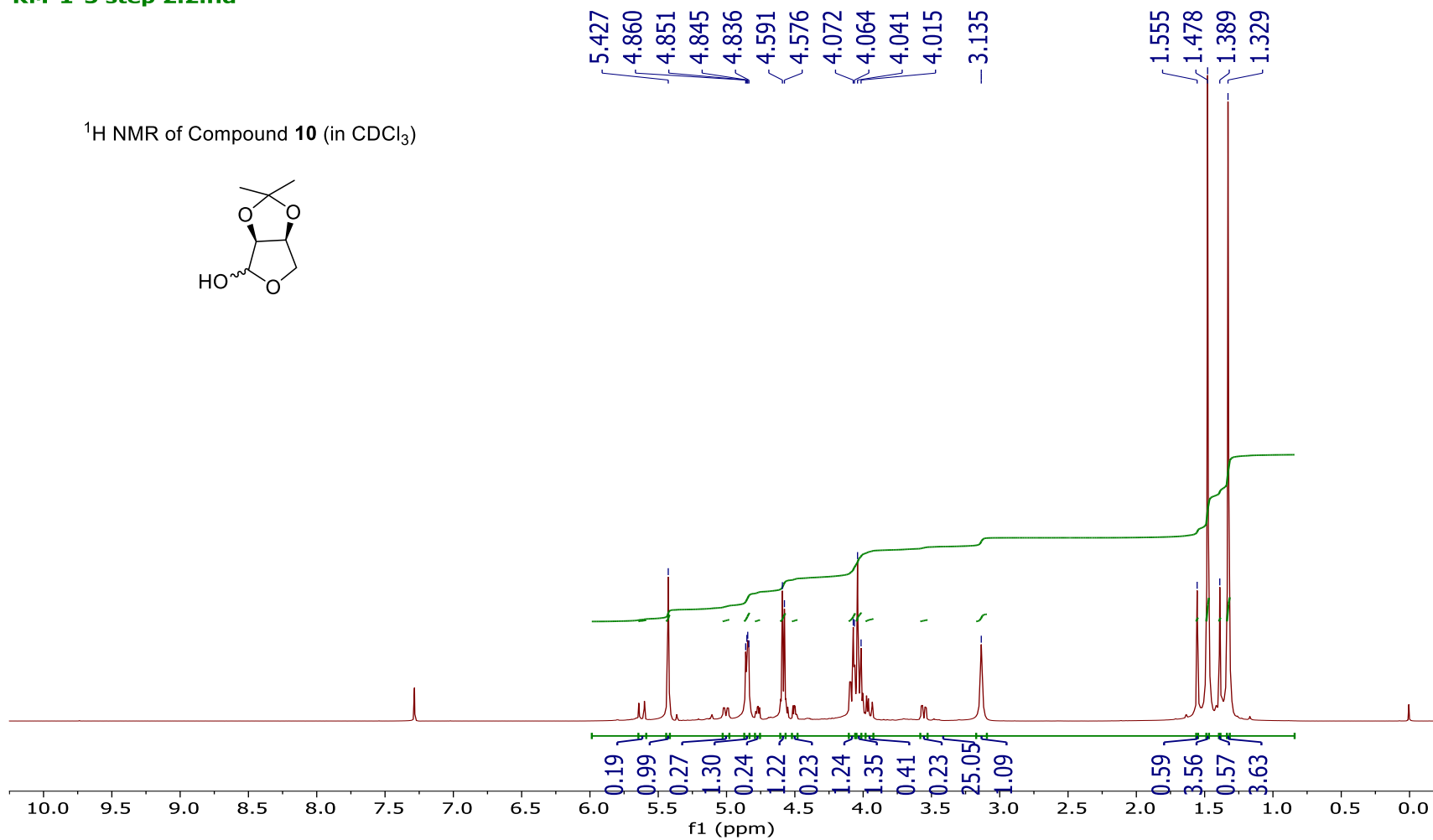
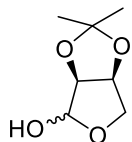
HF4-145

^{13}C NMR of Compound **9** (in CDCl_3)

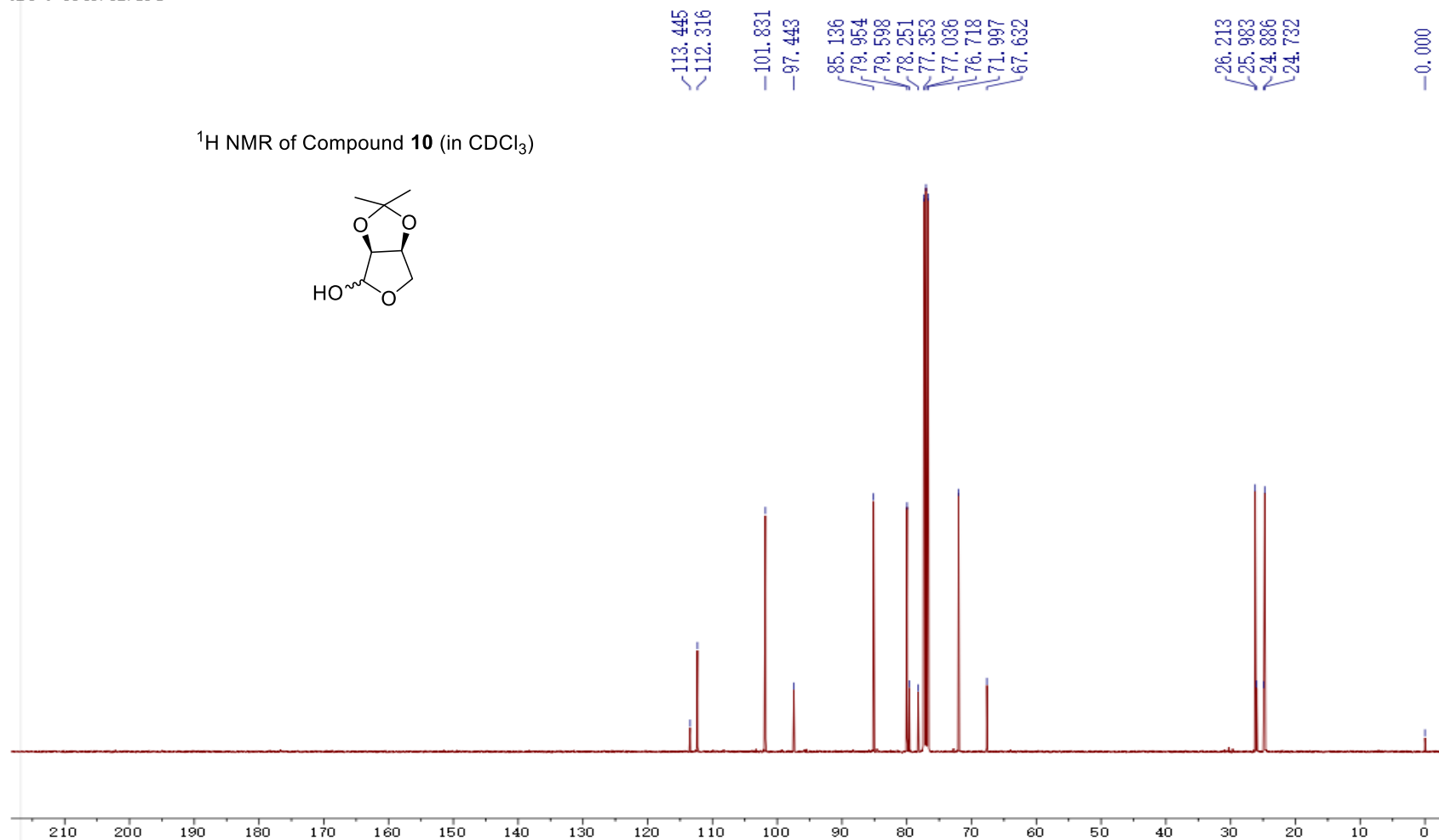
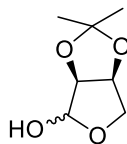


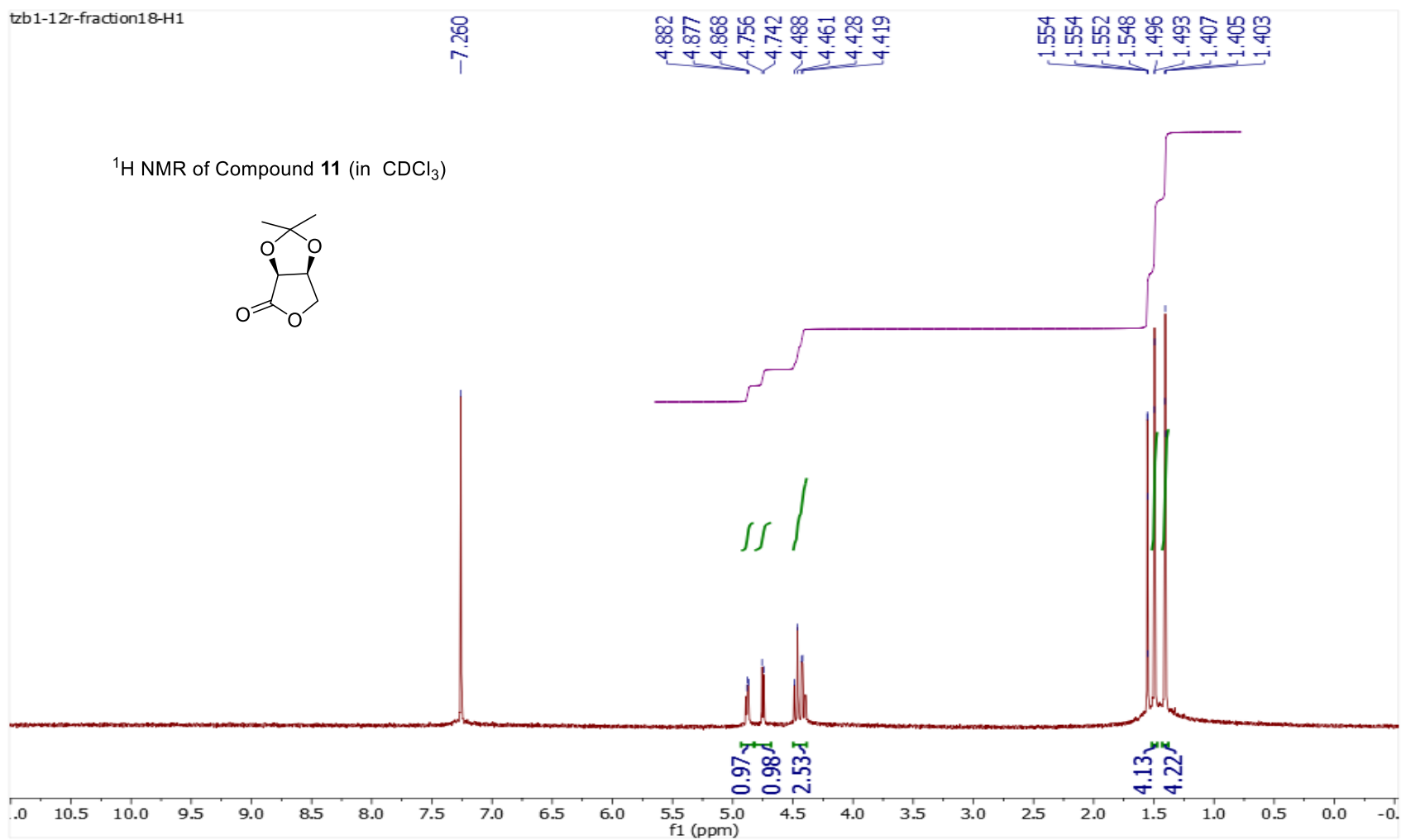
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^1H NMR of Compound **10** (in CDCl_3)



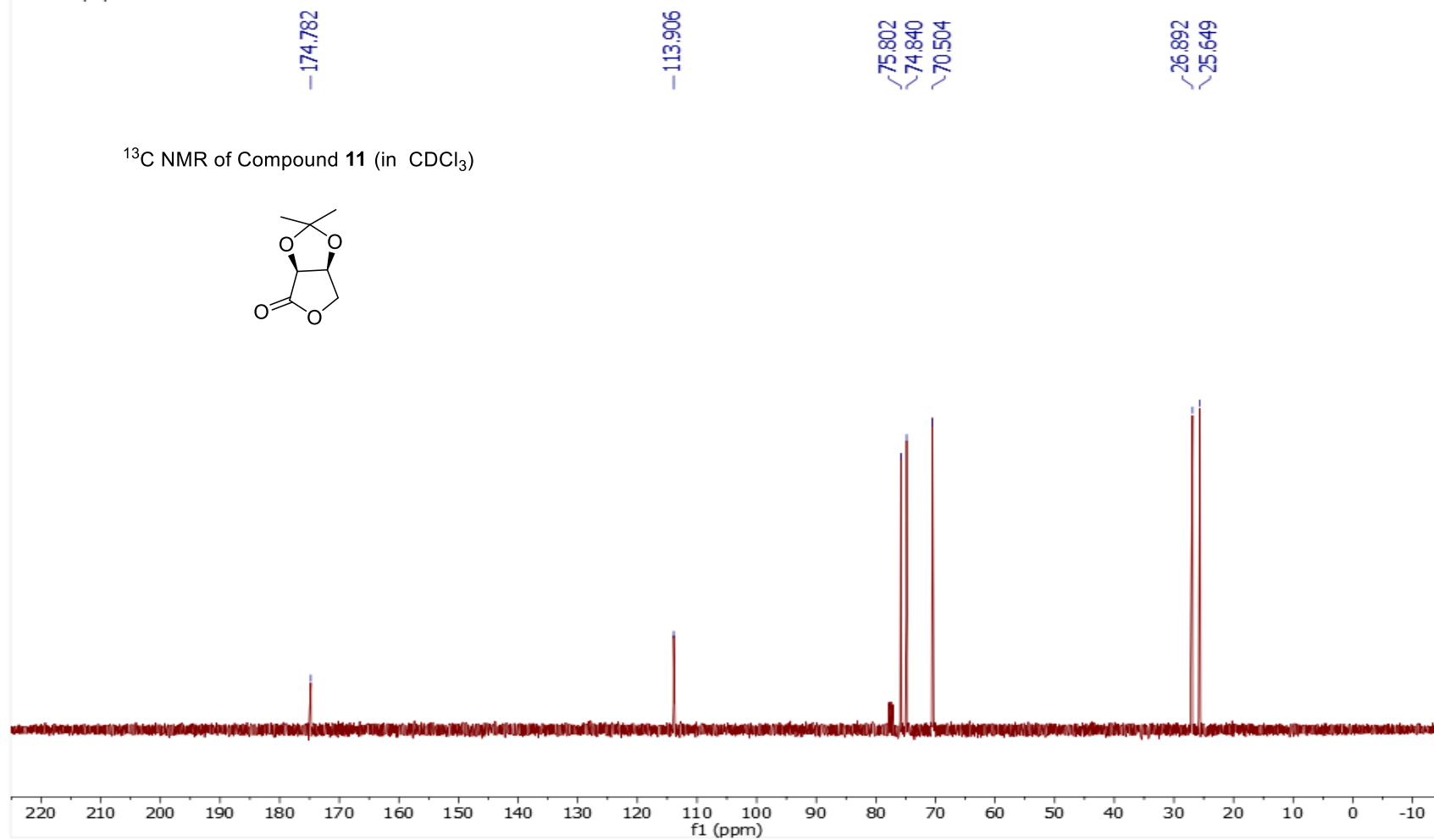
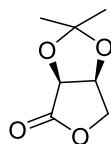
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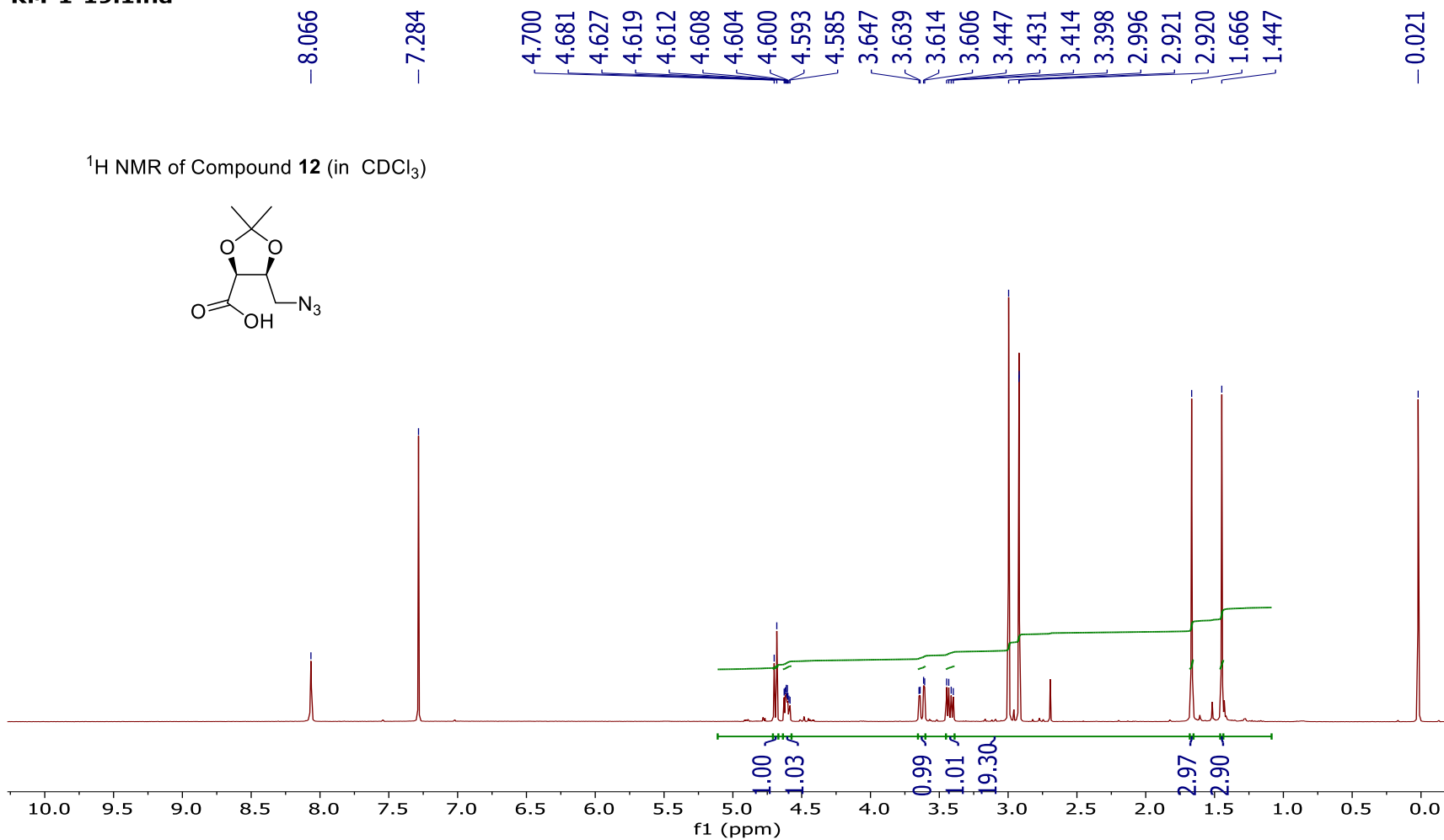
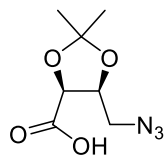
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^{13}C NMR of Compound **11** (in CDCl_3)



KM-1-19.1.fid

^1H NMR of Compound **12** (in CDCl_3)



TZB1-16A-C13-f7-9

—174.099

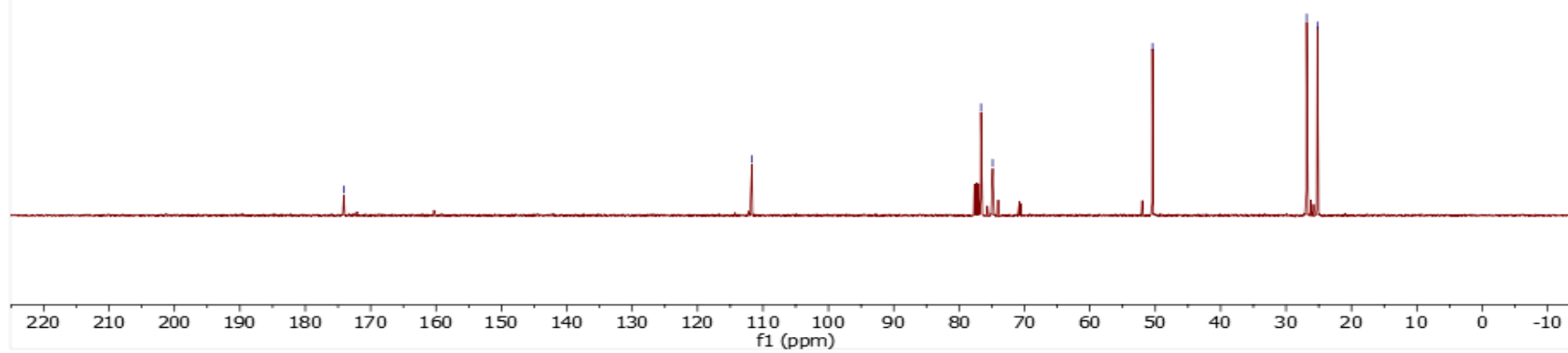
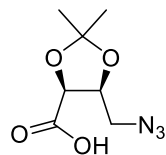
—111.676

76.651
74.857

—50.427

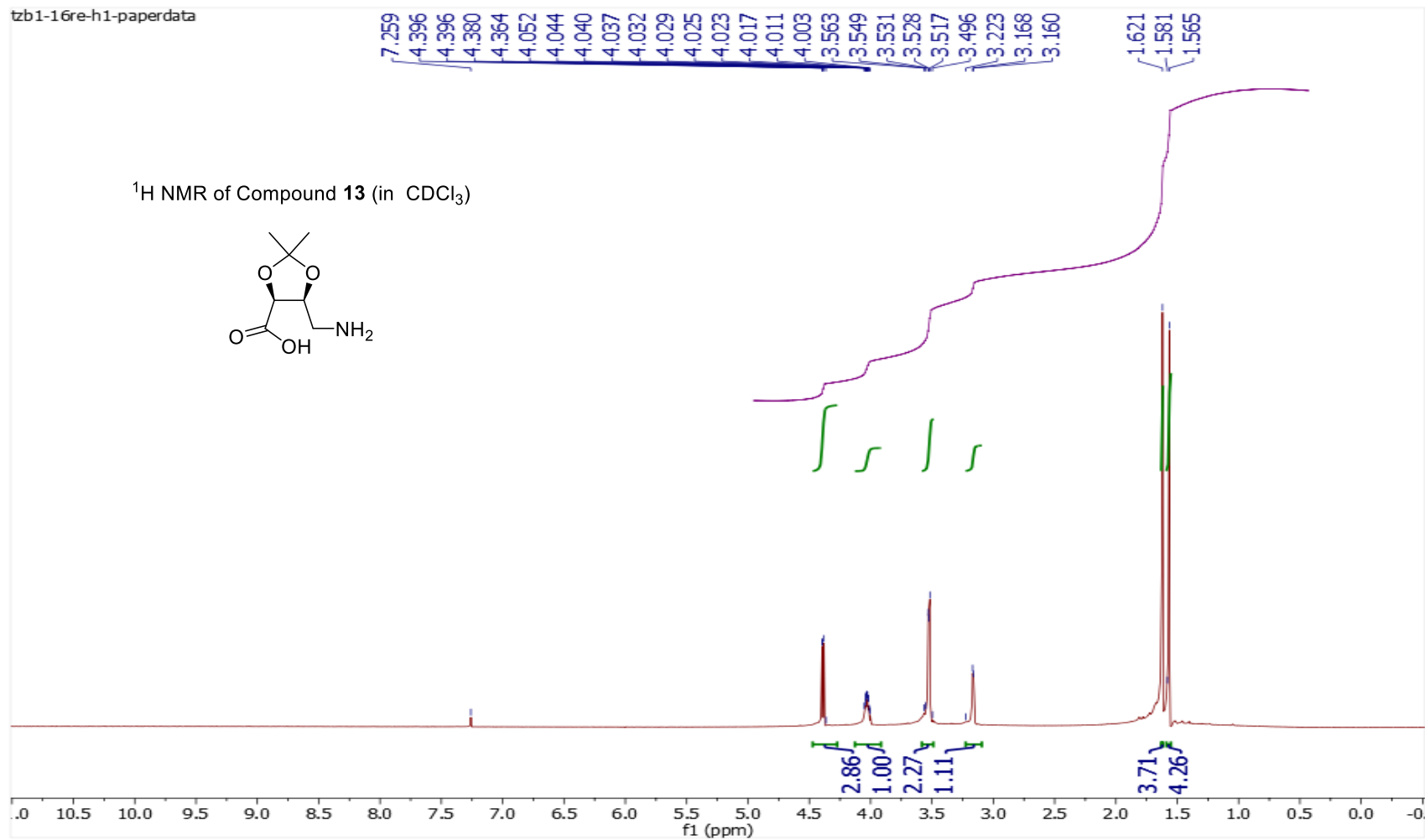
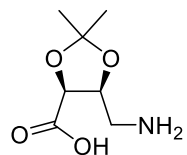
26.844
25.198

^{13}C NMR of Compound **12** (in CDCl_3)



tzbl-16re-h1-paperdata

^1H NMR of Compound **13** (in CDCl_3)



tzbl-16-re-C13-paperdata

172.118

5

112.167

73.851

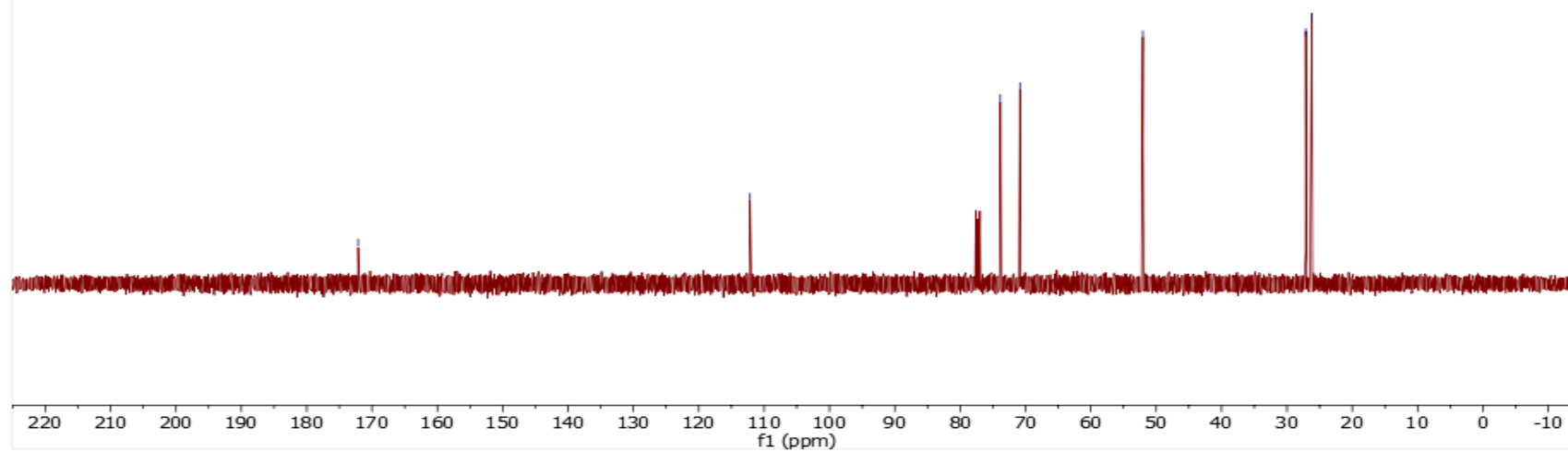
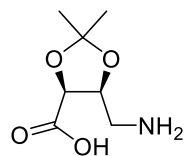
70.844

52.039

27.102

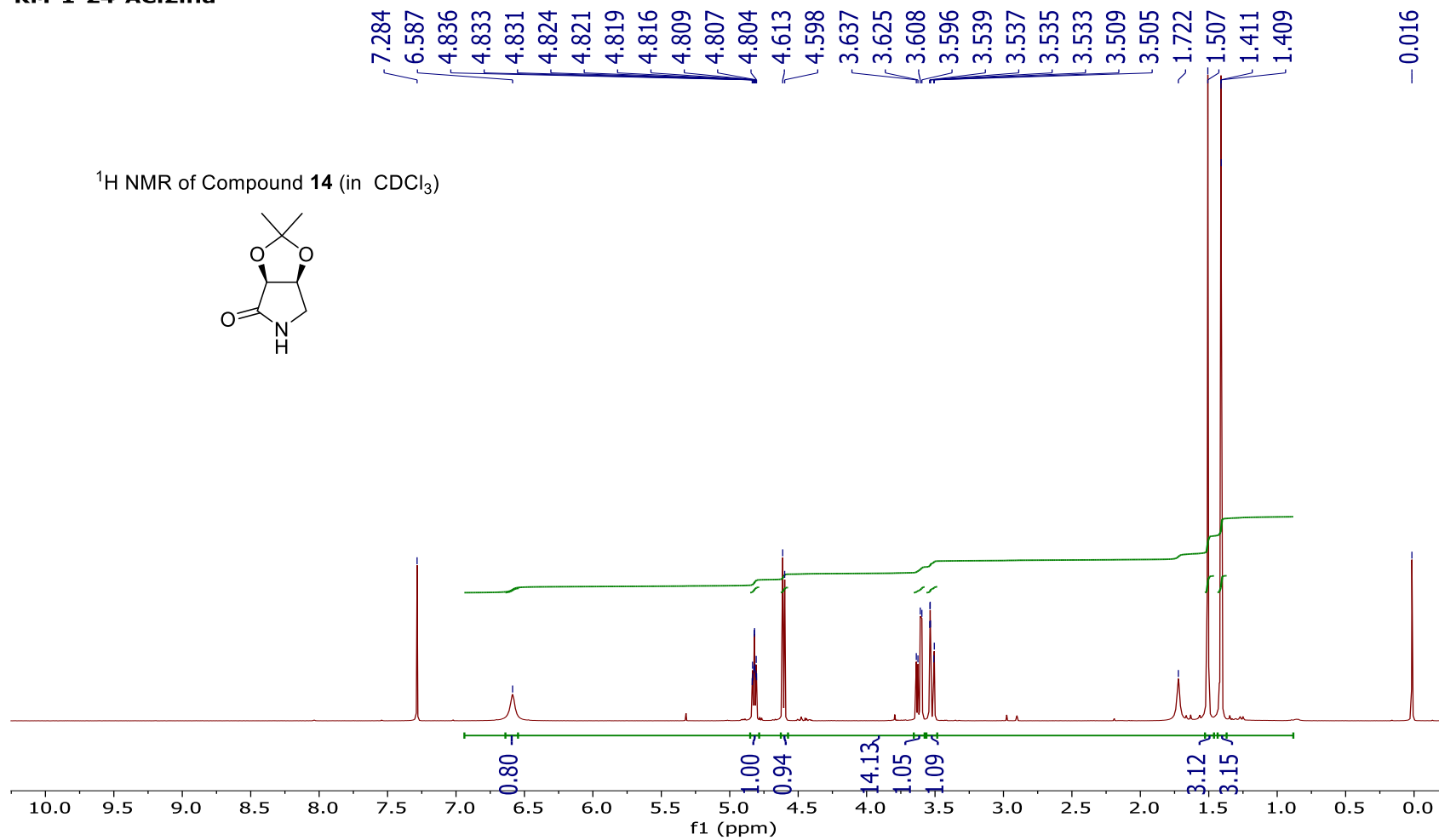
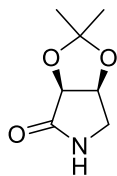
26.200

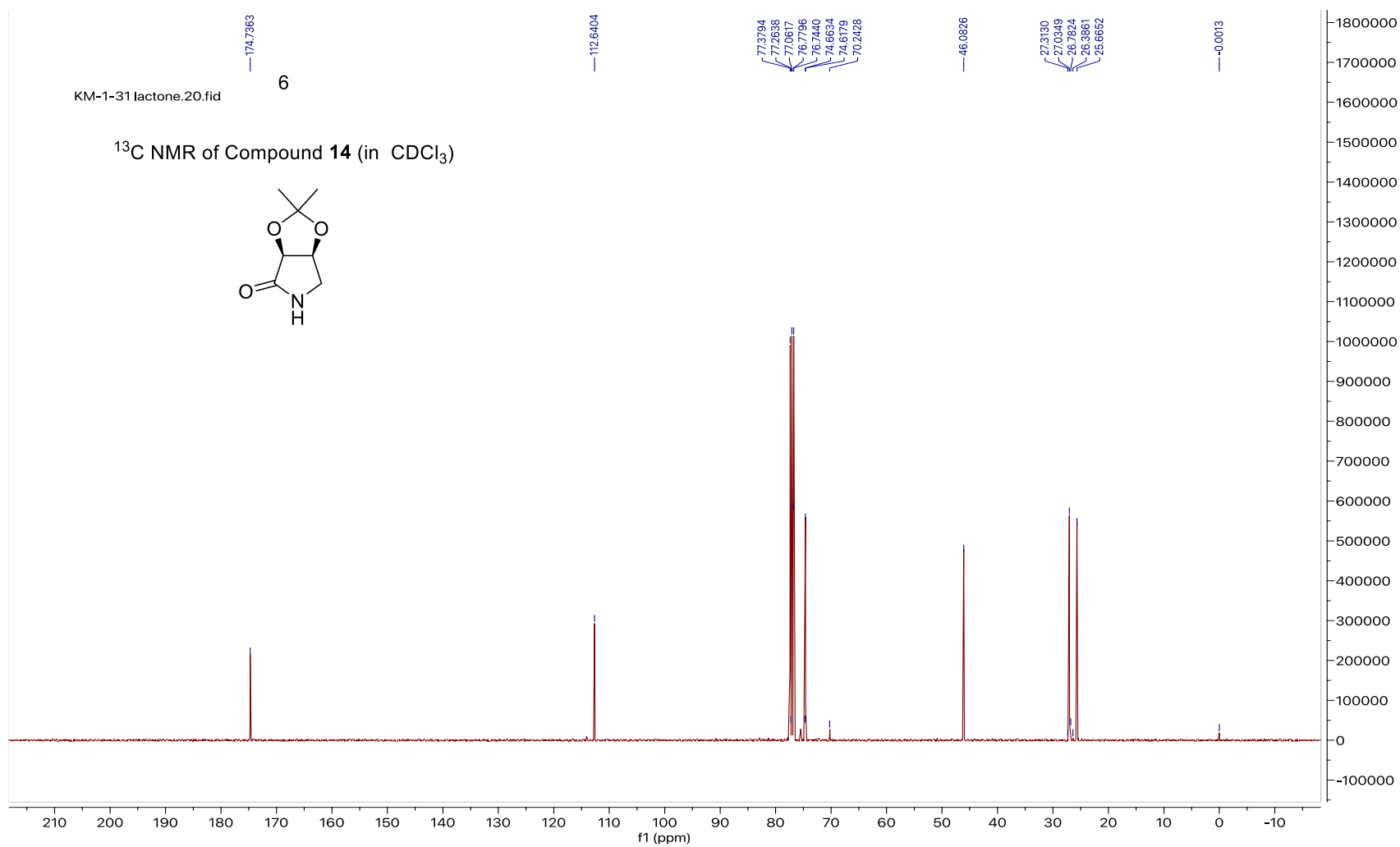
^{13}C NMR of Compound **13** (in CDCl_3)



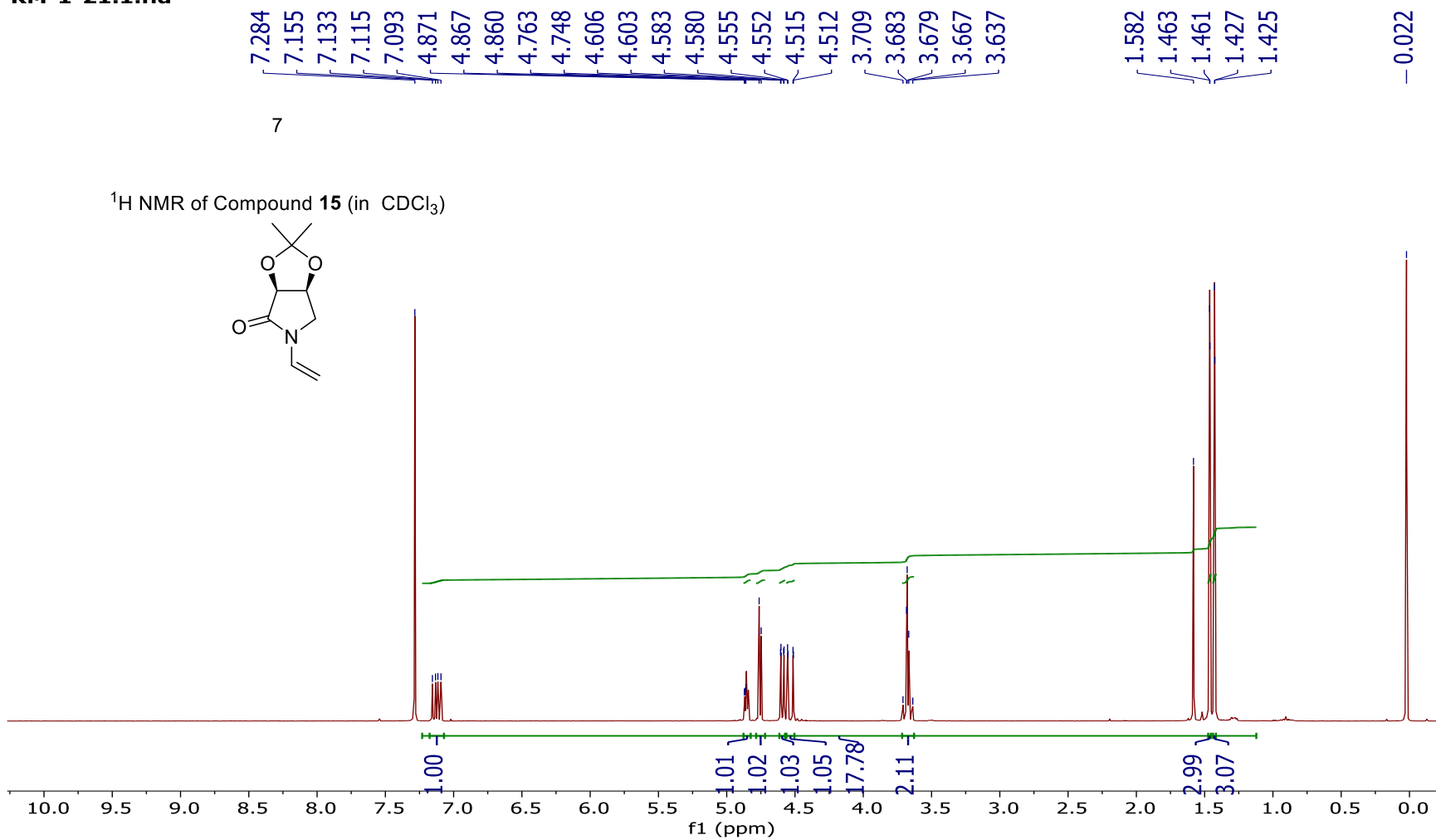
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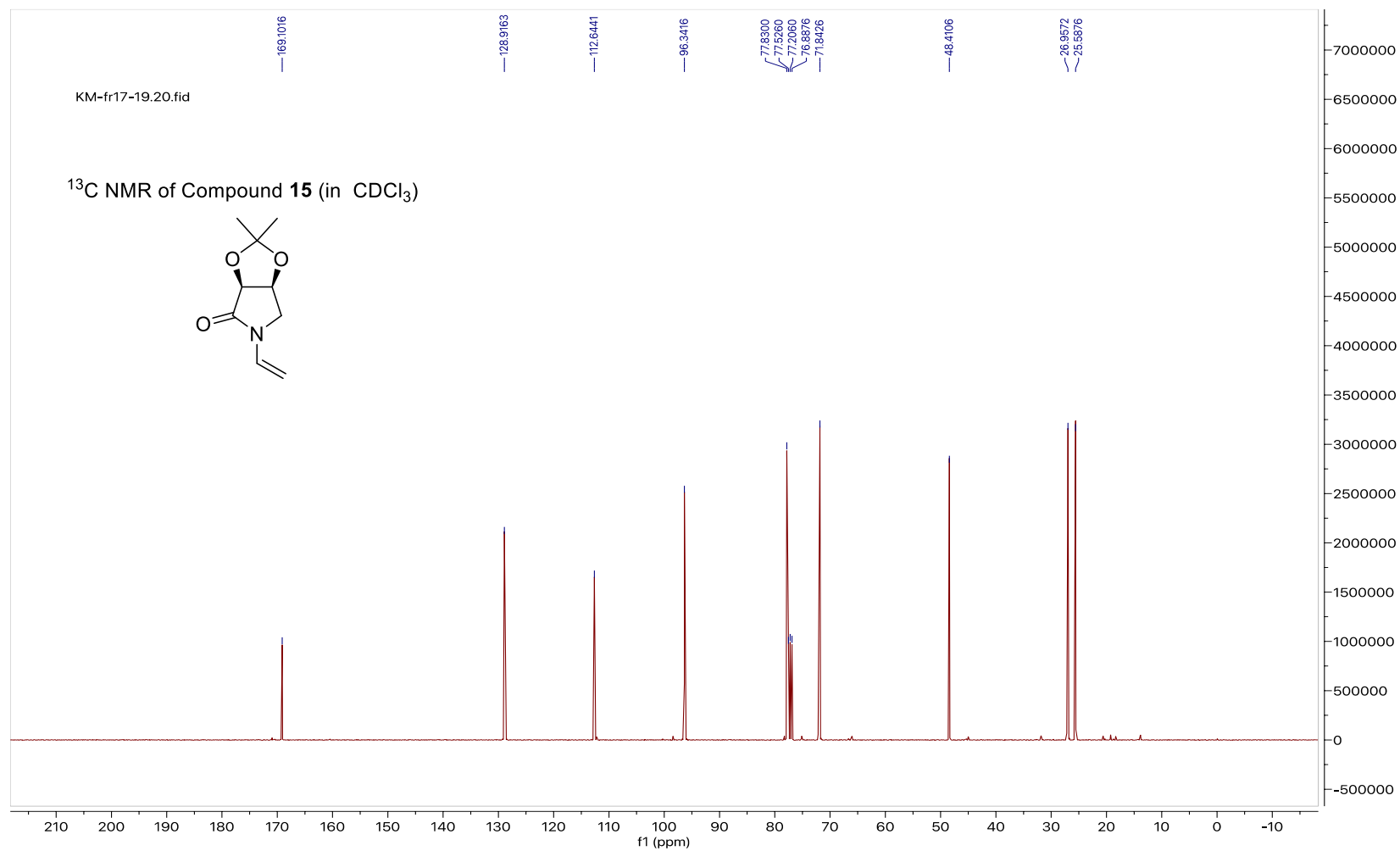
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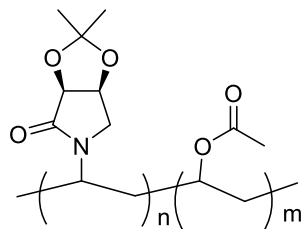
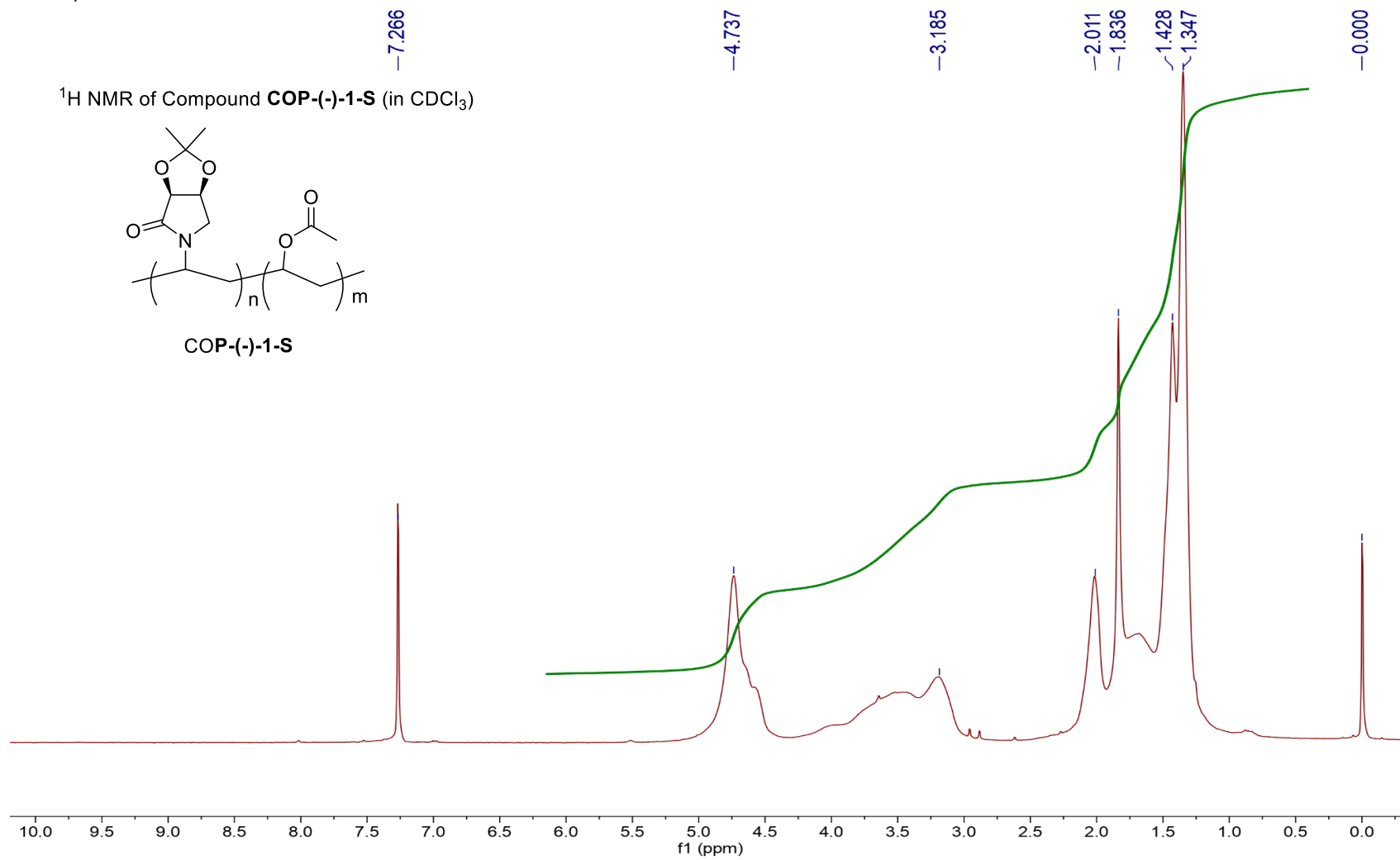




KM-1-21.1.fid





¹H NMR of Compound **COP-(-)-1-S** (in CDCl₃)**COP-(-)-1-S**

HF5-23-pure.20.fid

—171.515

—112.026

—77.970

—72.266

—45.806

—35.527

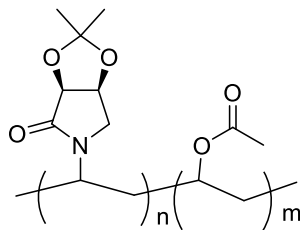
~27.303

~25.369

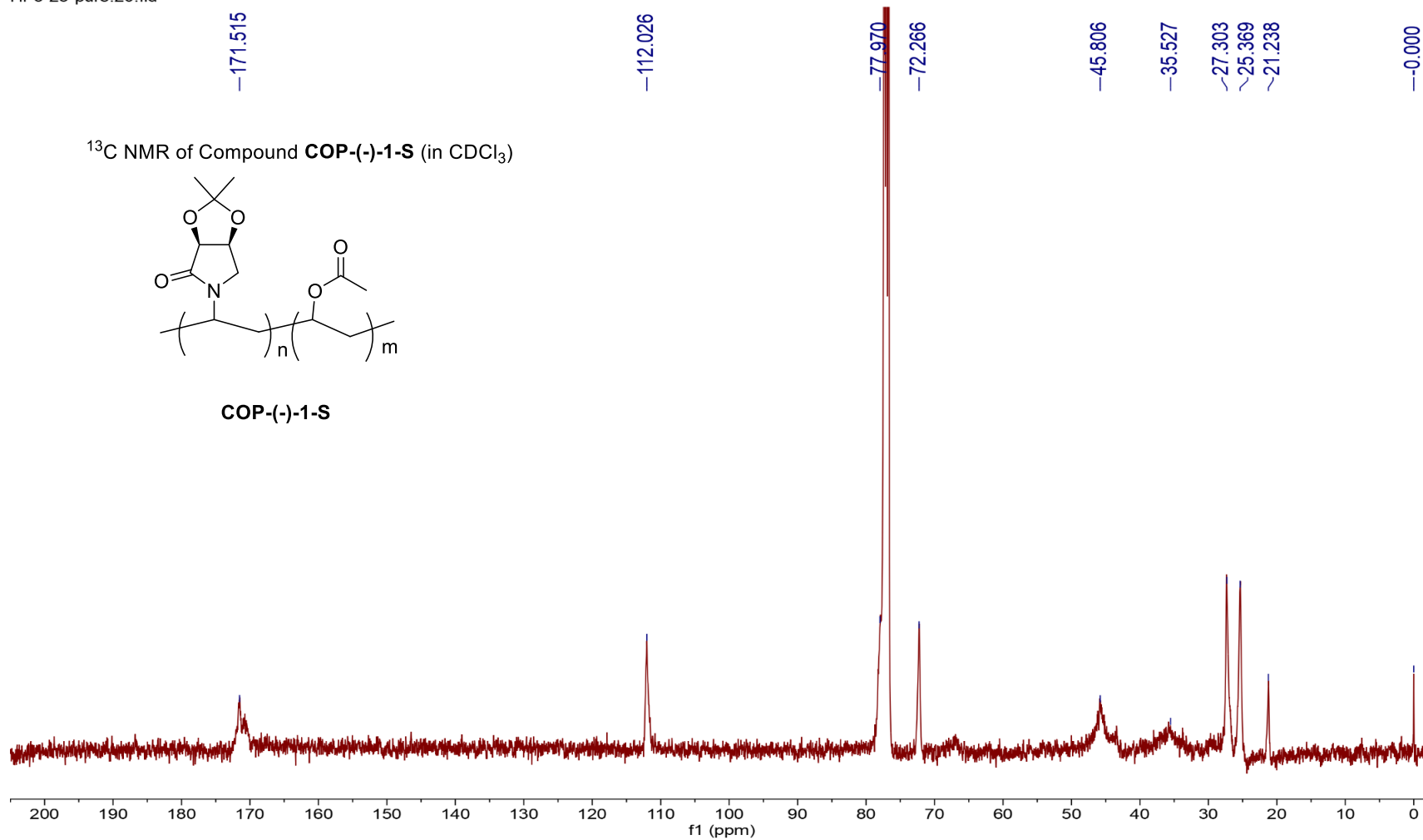
~21.238

—0.000

^{13}C NMR of Compound **COP-(-)-1-S** (in CDCl_3)

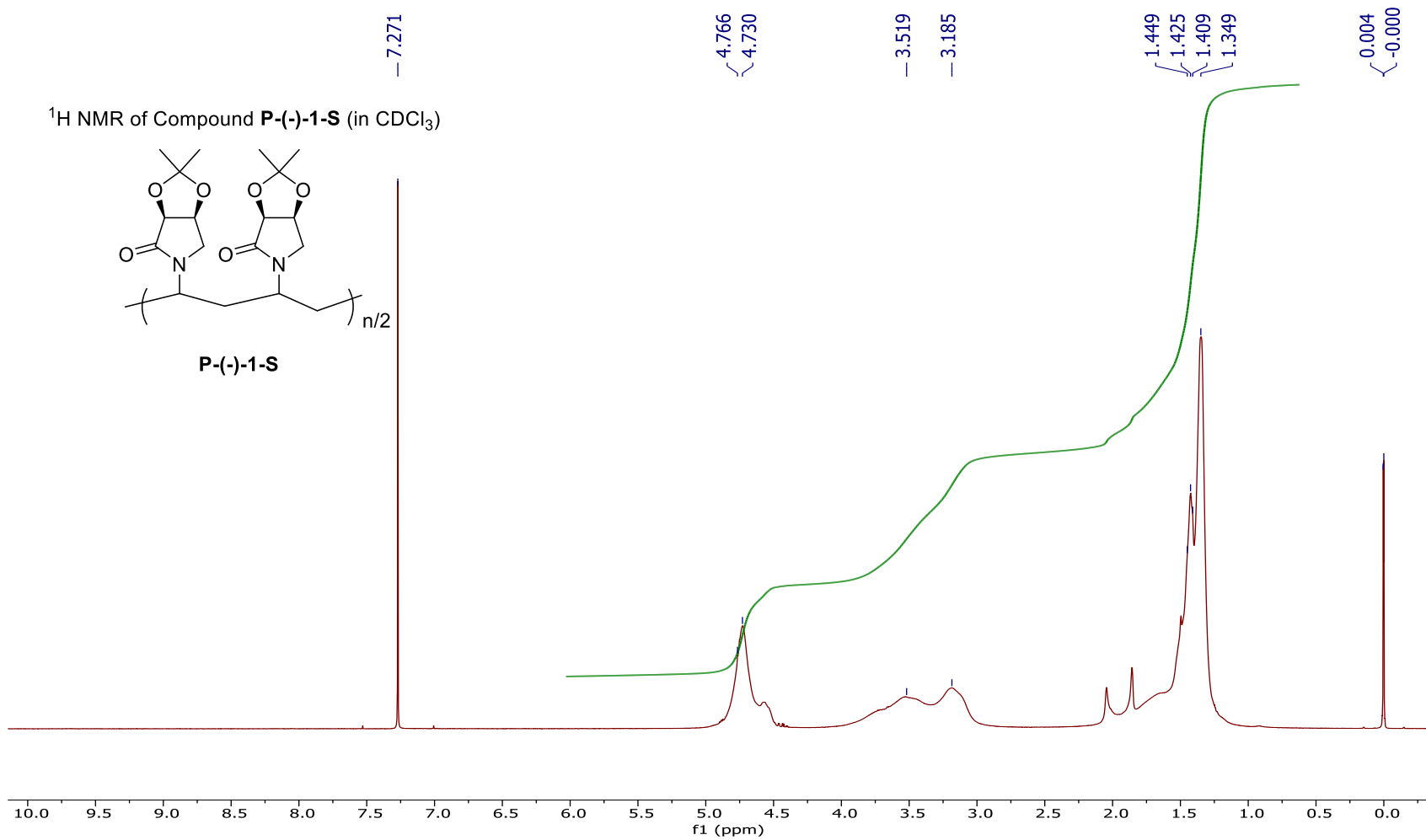
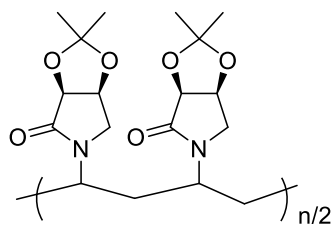


COP-(-)-1-S

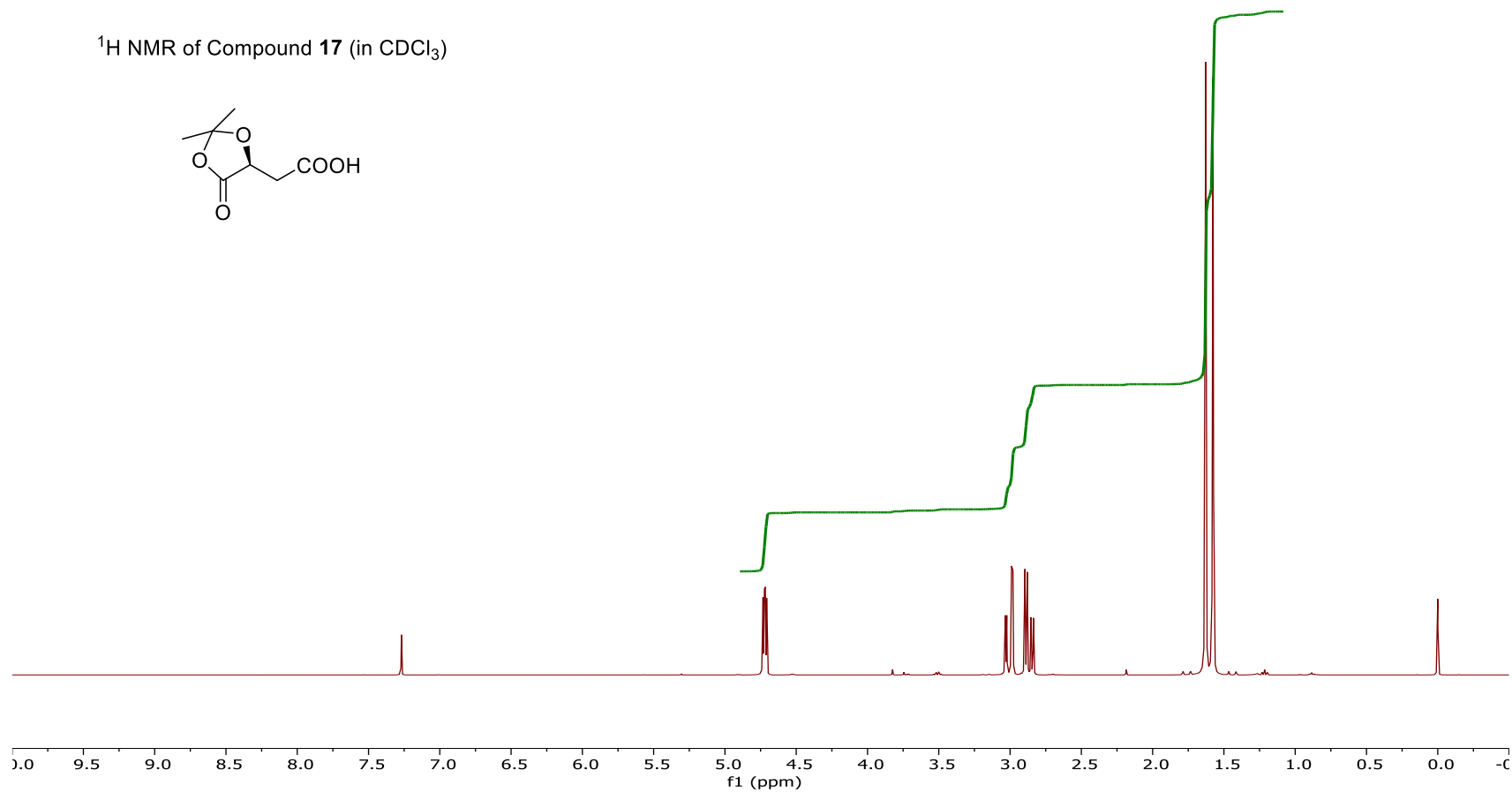
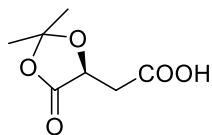


HF5-52.10.fid —

^1H NMR of Compound **P-(-)-1-S** (in CDCl_3)



^1H NMR of Compound **17** (in CDCl_3)



DJH-1-108.20.fid

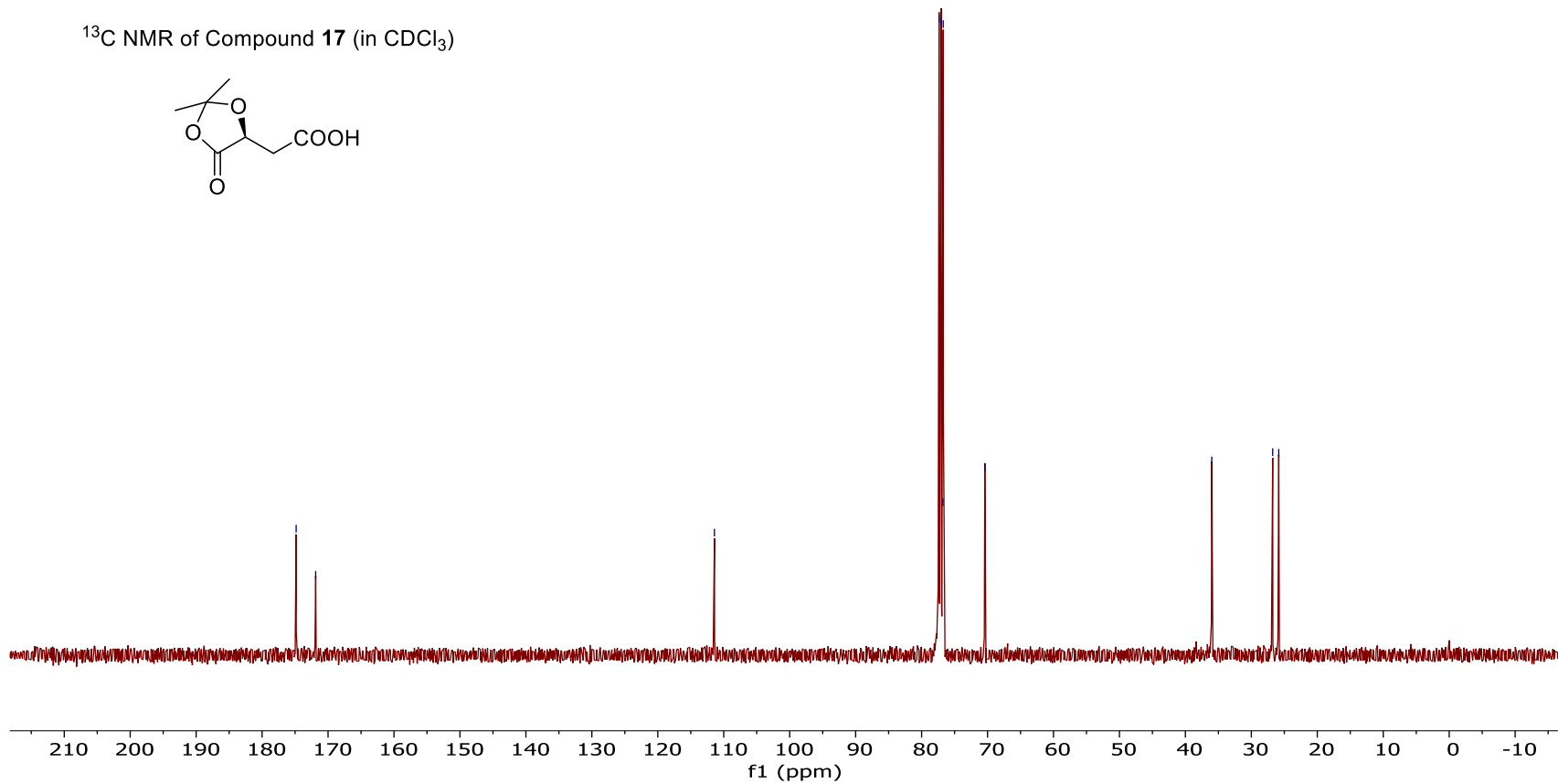
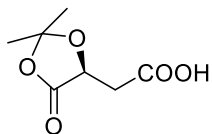
174.836
171.877

111.410

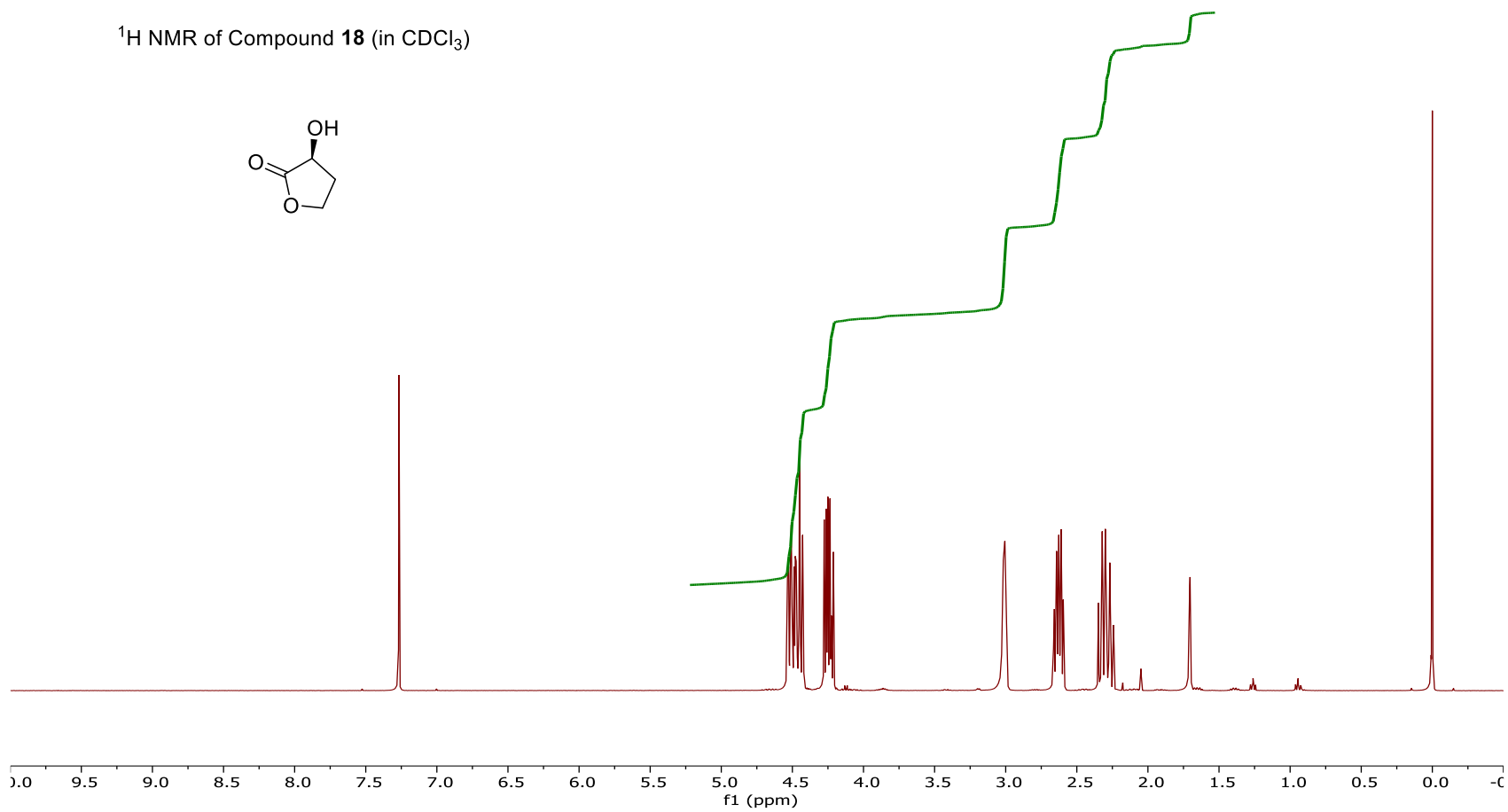
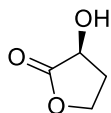
77.355
77.039
76.770
76.718
70.416

36.002
26.767
25.845

^{13}C NMR of Compound **17** (in CDCl_3)



^1H NMR of Compound **18** (in CDCl_3)



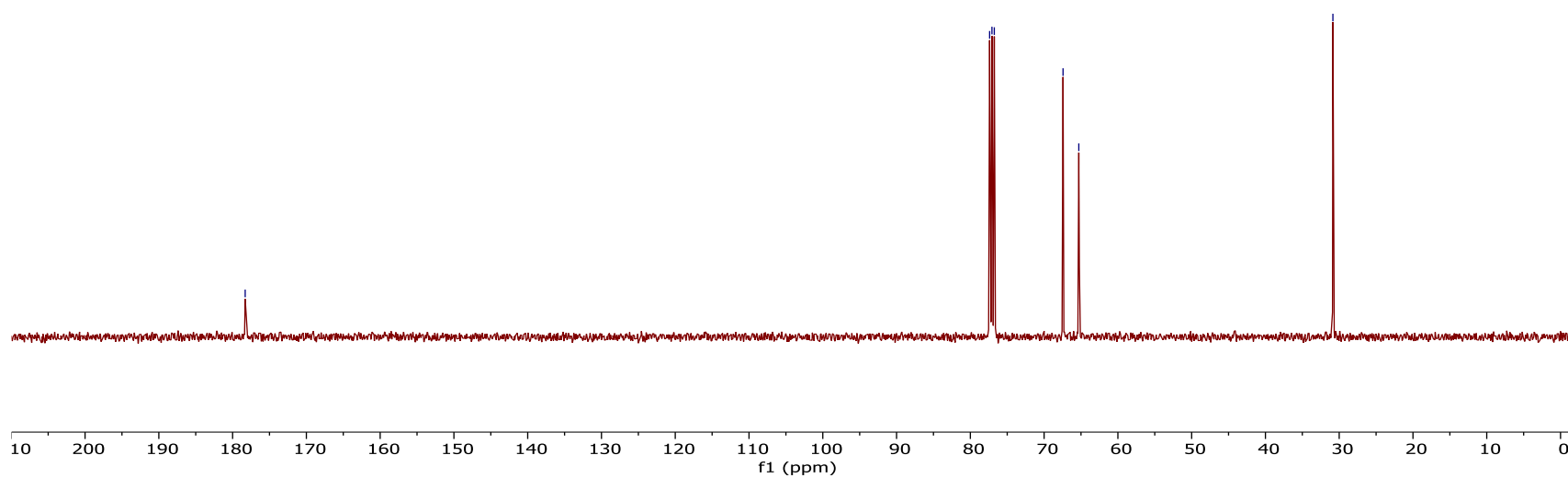
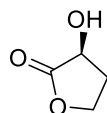
EE-hydroxylactonecheck-10-8-21.2.fid

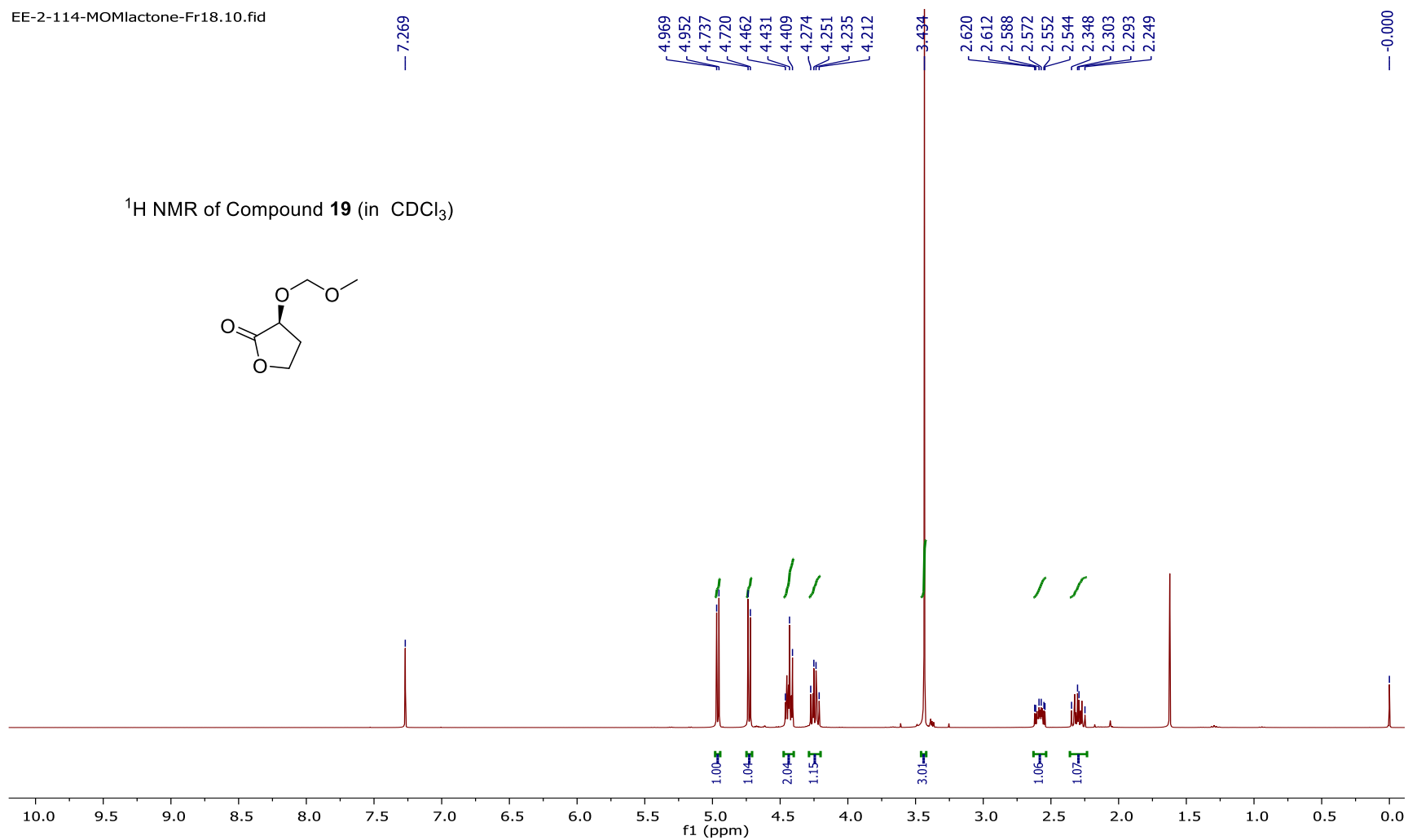
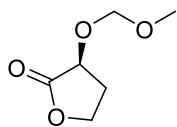
— 178.294

77.387
77.069
76.752
67.434
65.296

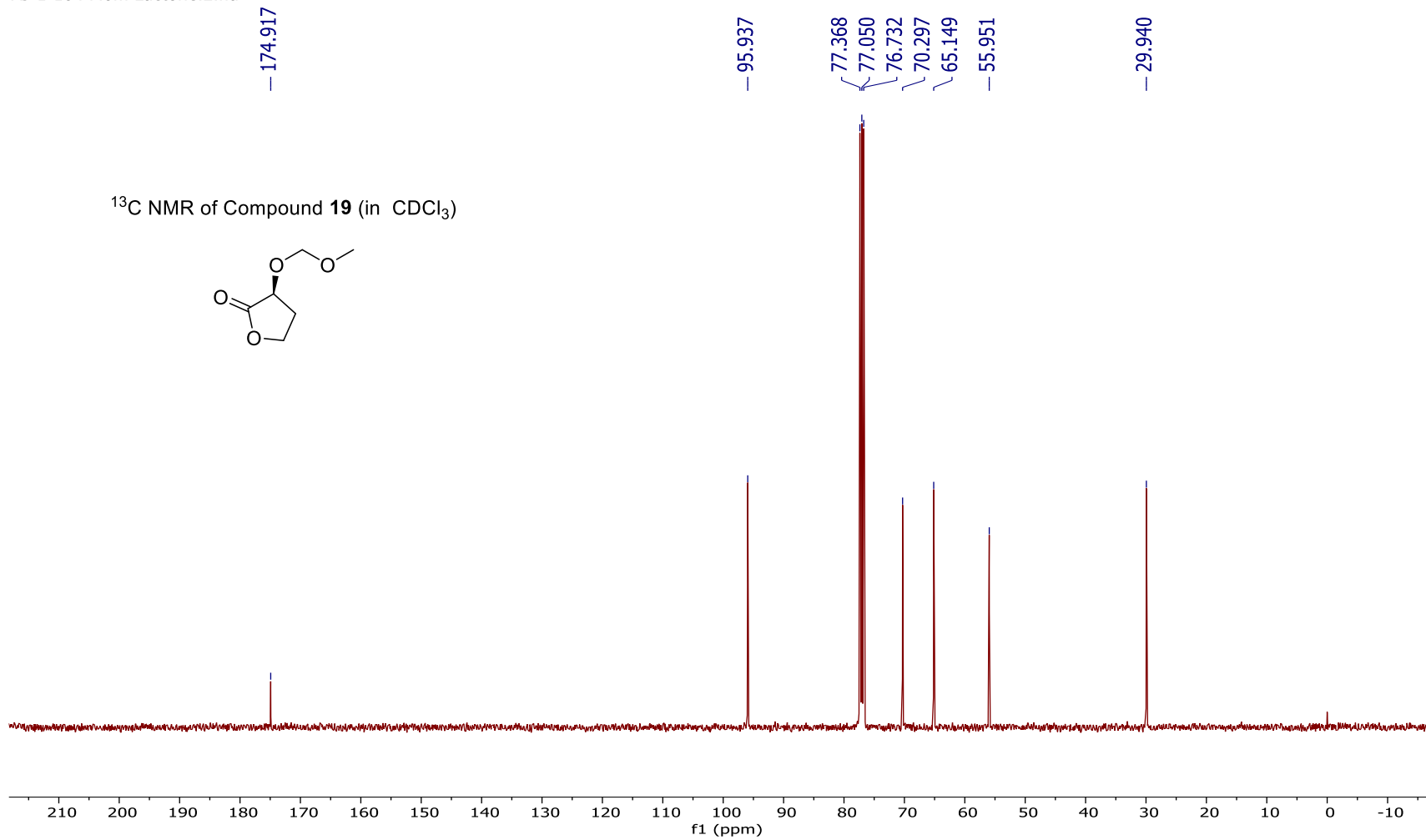
— 30.853

^{13}C NMR of Compound **18** (in CDCl_3)



¹H NMR of Compound **19** (in CDCl₃)

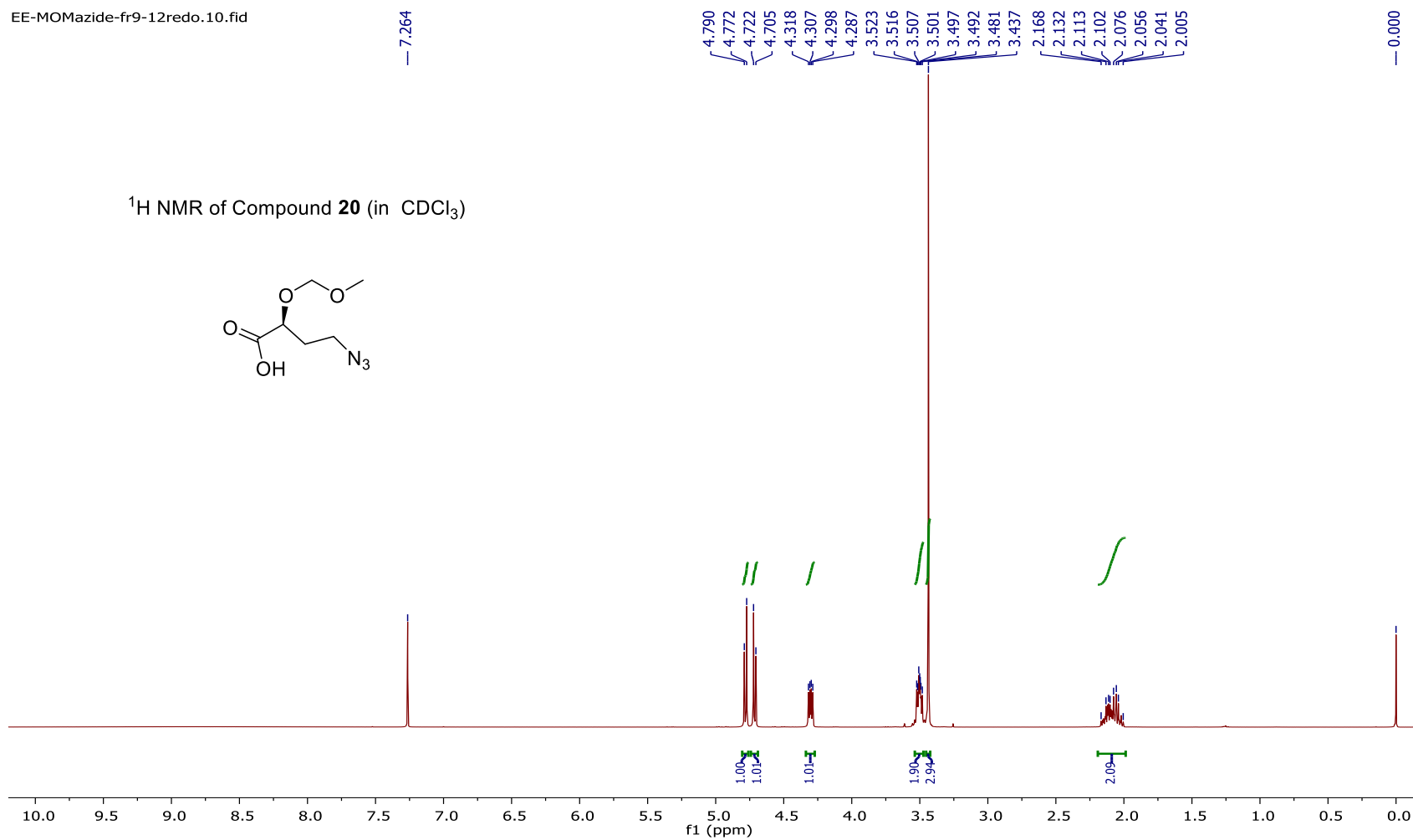
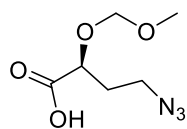
AJ-1-104 Mom Lactone.2.fid



EE-MOMazide-fr9-12redo.10.fid

— 7.264

^1H NMR of Compound **20** (in CDCl_3)



EE-2-88-MOMazide.3.fid

—176.292

—163.501

—96.500

77.367

77.050

76.732

—56.331

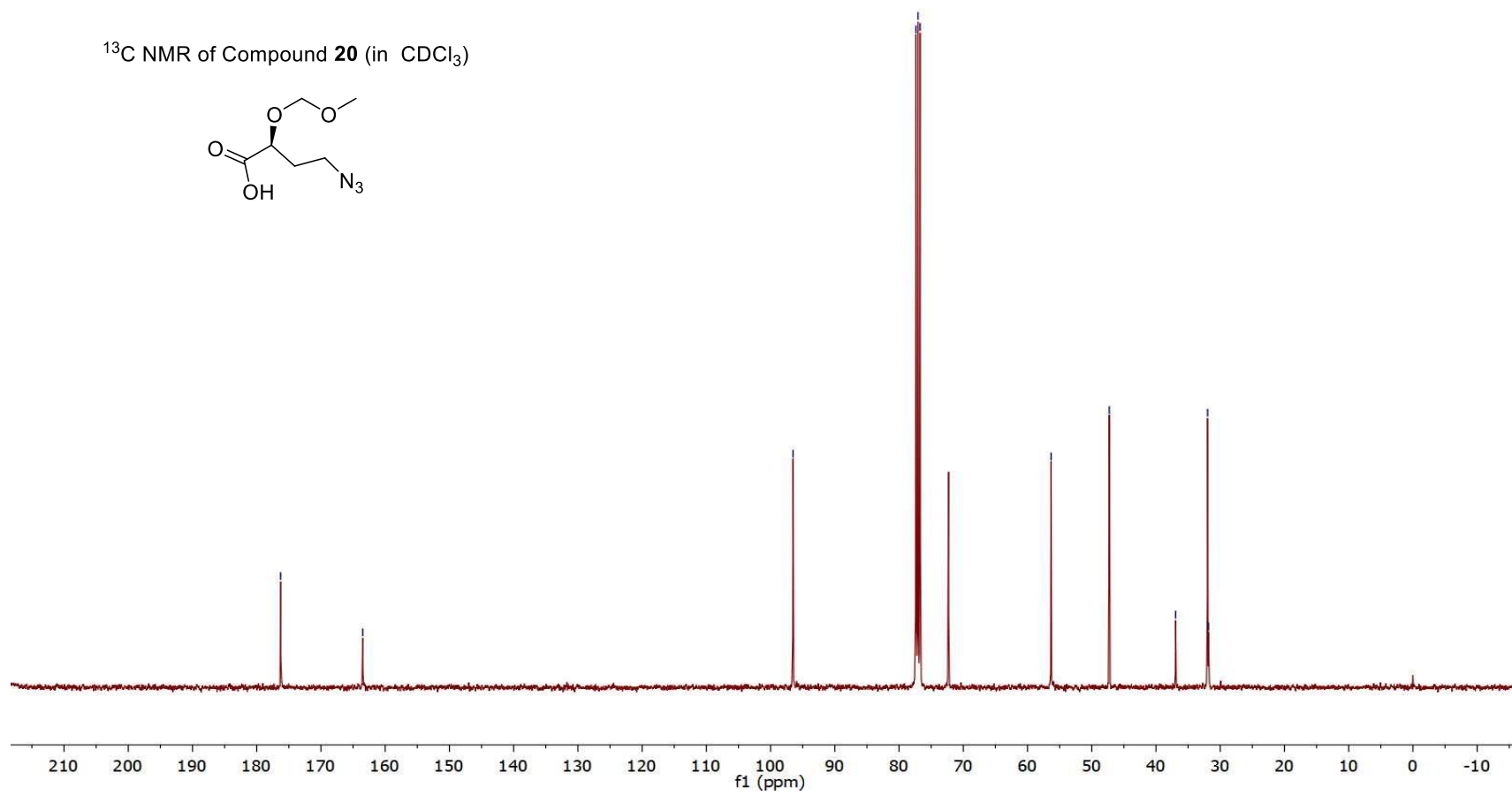
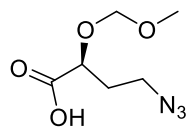
—47.268

36.945

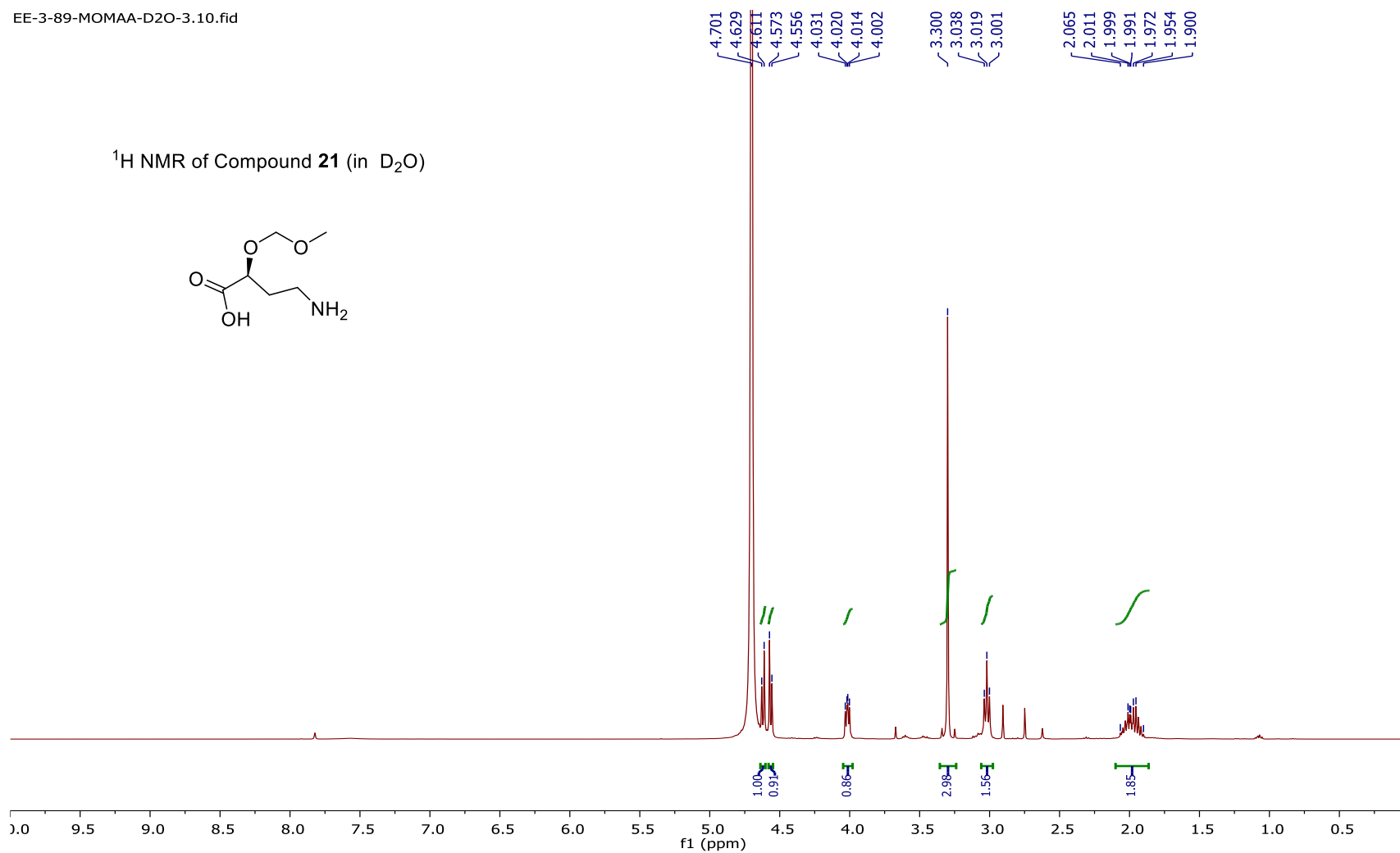
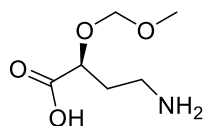
31.959

31.830

^{13}C NMR of Compound **20** (in CDCl_3)



^1H NMR of Compound **21** (in D_2O)



EE-3-89-MOMAA-D2O-3.11.fid

— 178.381

— 95.451

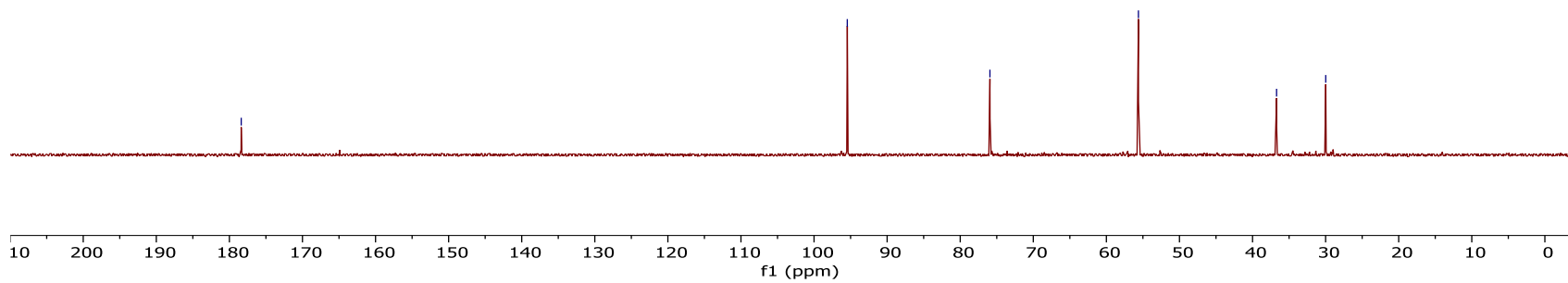
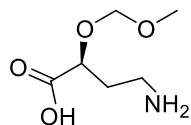
— 75.933

— 55.613

— 36.712

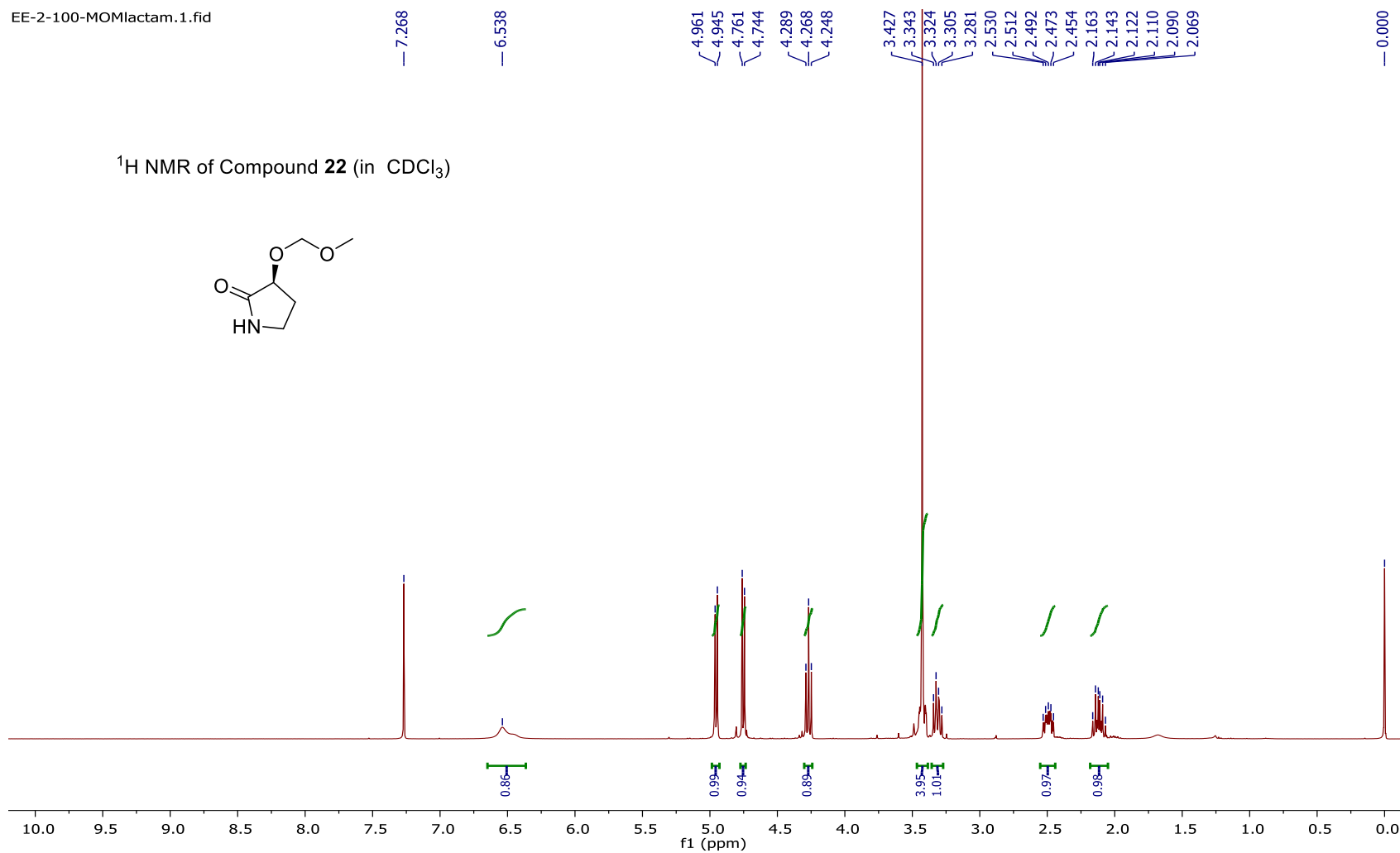
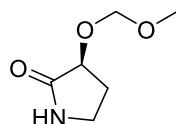
— 29.986

^{13}C NMR of Compound **21** (in D_2O)



EE-2-100-MOMlactam.1.fid

¹H NMR of Compound **22** (in CDCl₃)



EE-2-79-lactam.10.fid

—175.659

—96.245

77.352

77.036

76.718

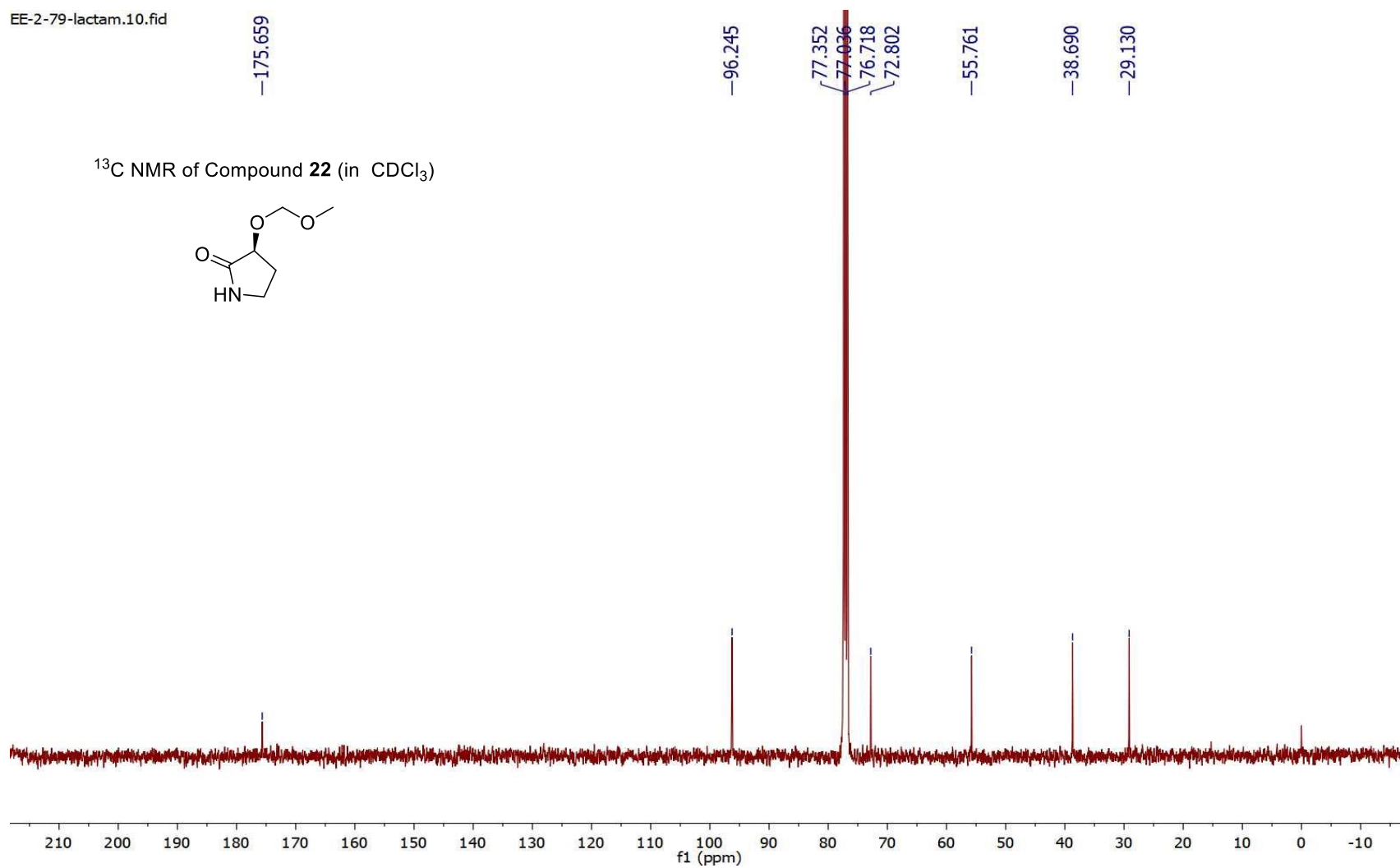
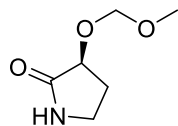
72.802

—55.761

—38.690

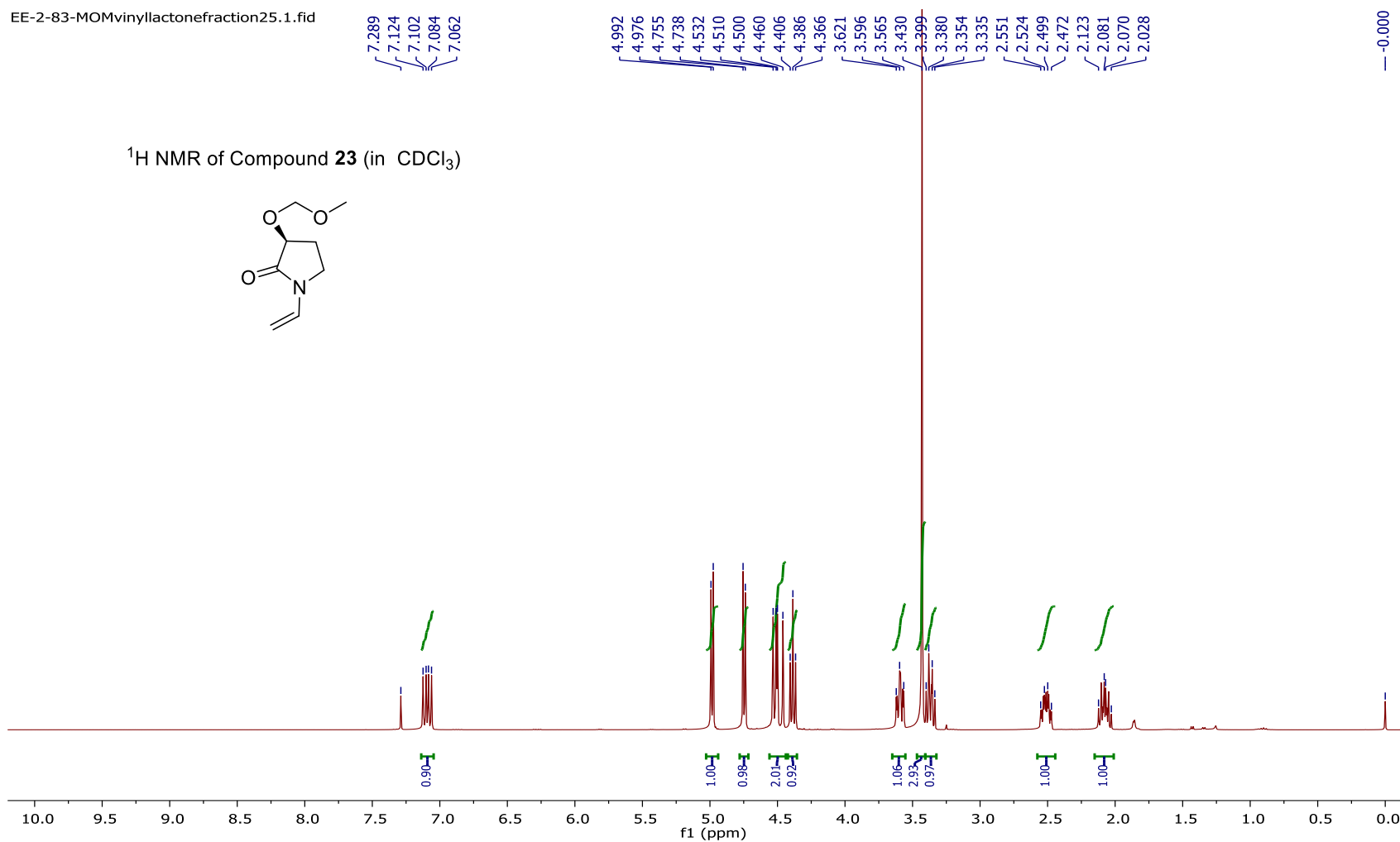
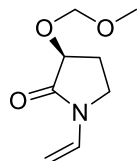
—29.130

^{13}C NMR of Compound **22** (in CDCl_3)



EE-2-83-MOMvinylactonefraction25.1.fid

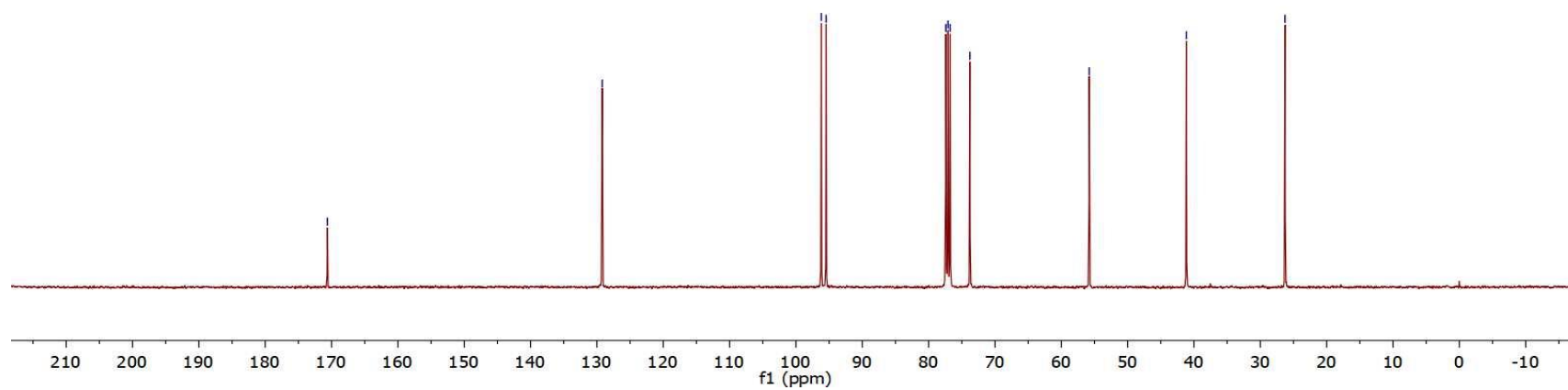
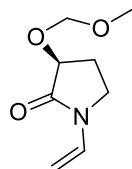
^1H NMR of Compound **23** (in CDCl_3)

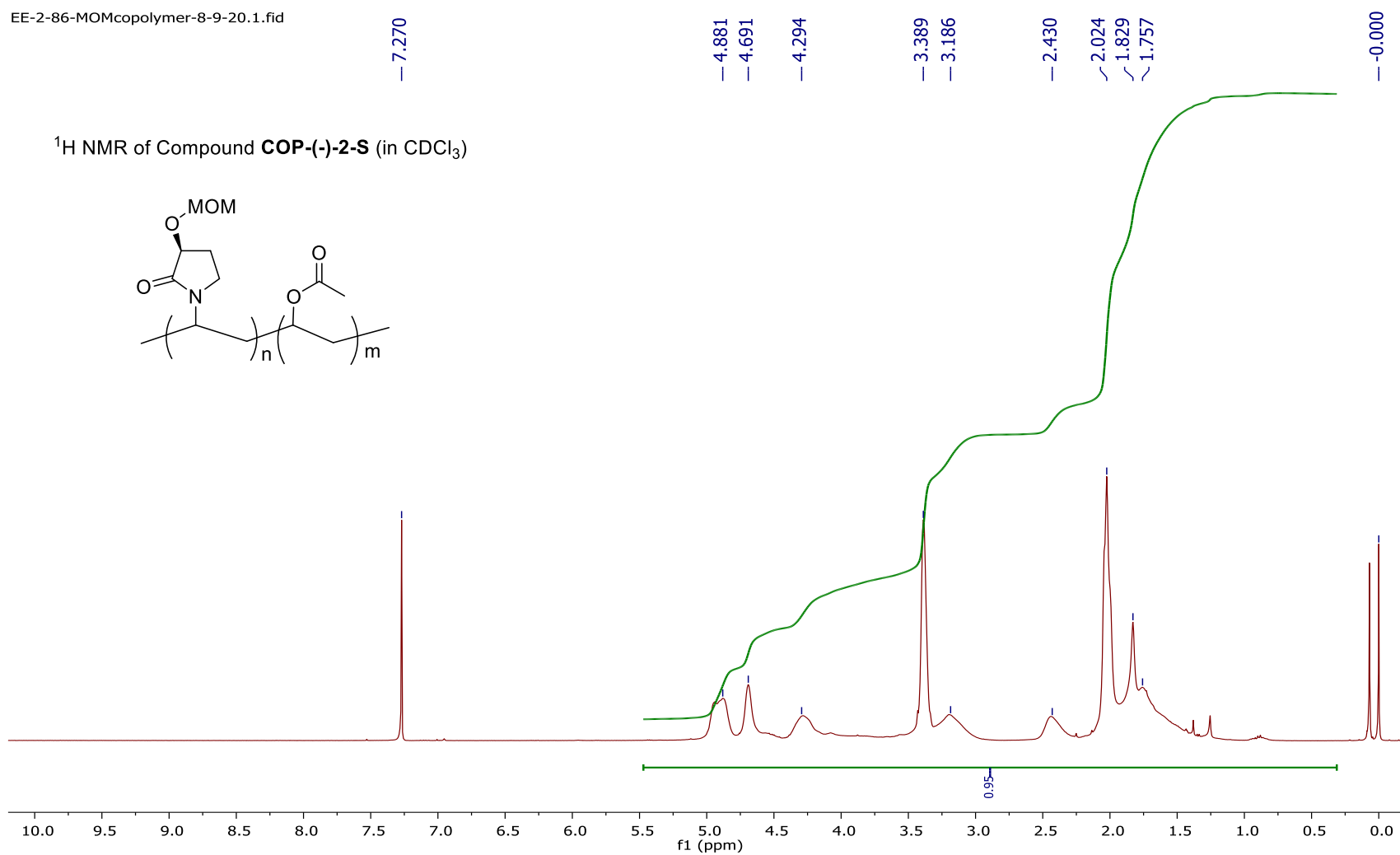
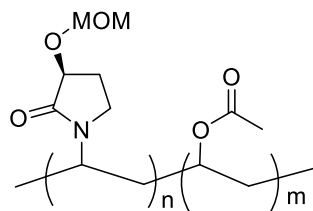


EE-2-83-MOMvinylactonefraction25.2x6



^{13}C NMR of Compound **23** (in CDCl_3)



¹H NMR of Compound **COP-(-)-2-S** (in CDCl₃)

EE-2-86-MOMcopolymer-8-10-2015

171.795
169.352

76.329
76.011
75.693

54.592

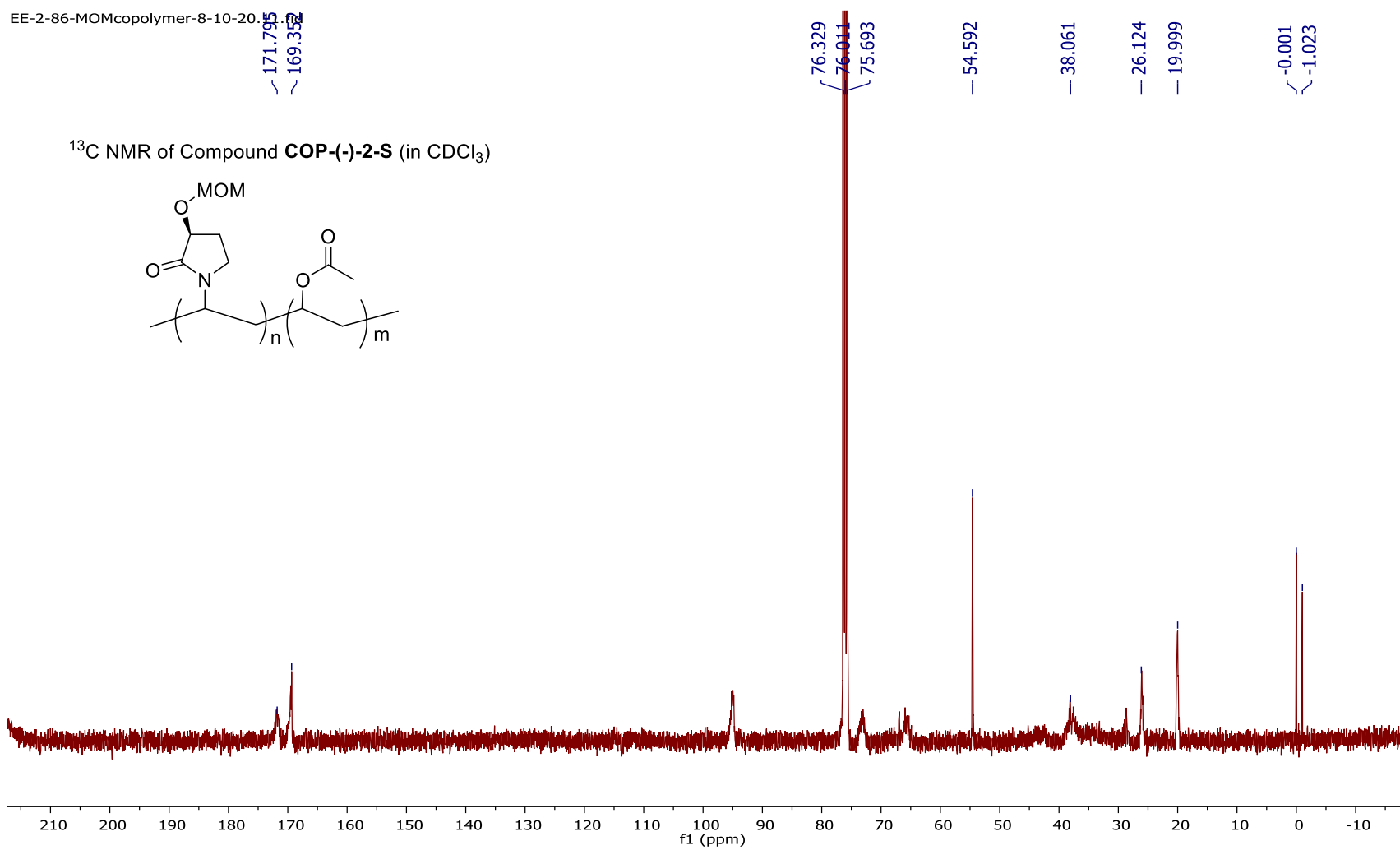
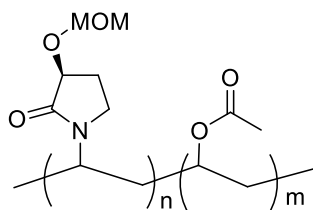
38.061

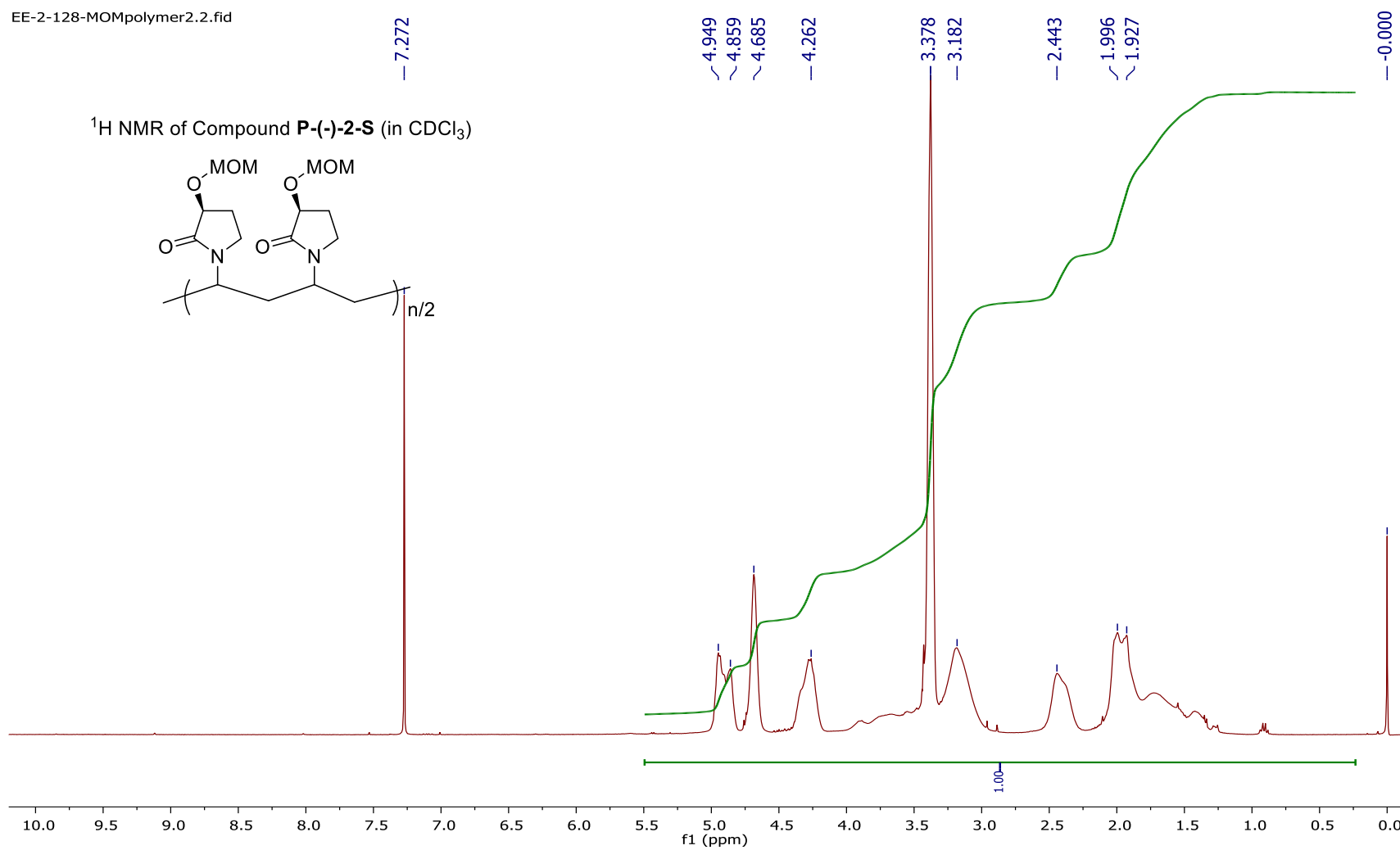
26.124

19.999

-0.001
-1.023

^{13}C NMR of Compound **COP-(-)-2-S** (in CDCl_3)





-128-MOMpolymer3.1.fid

— 172.919

— 96.111

77.361

77.043

76.725

74.642

74.077

— 55.607

45.234

43.739

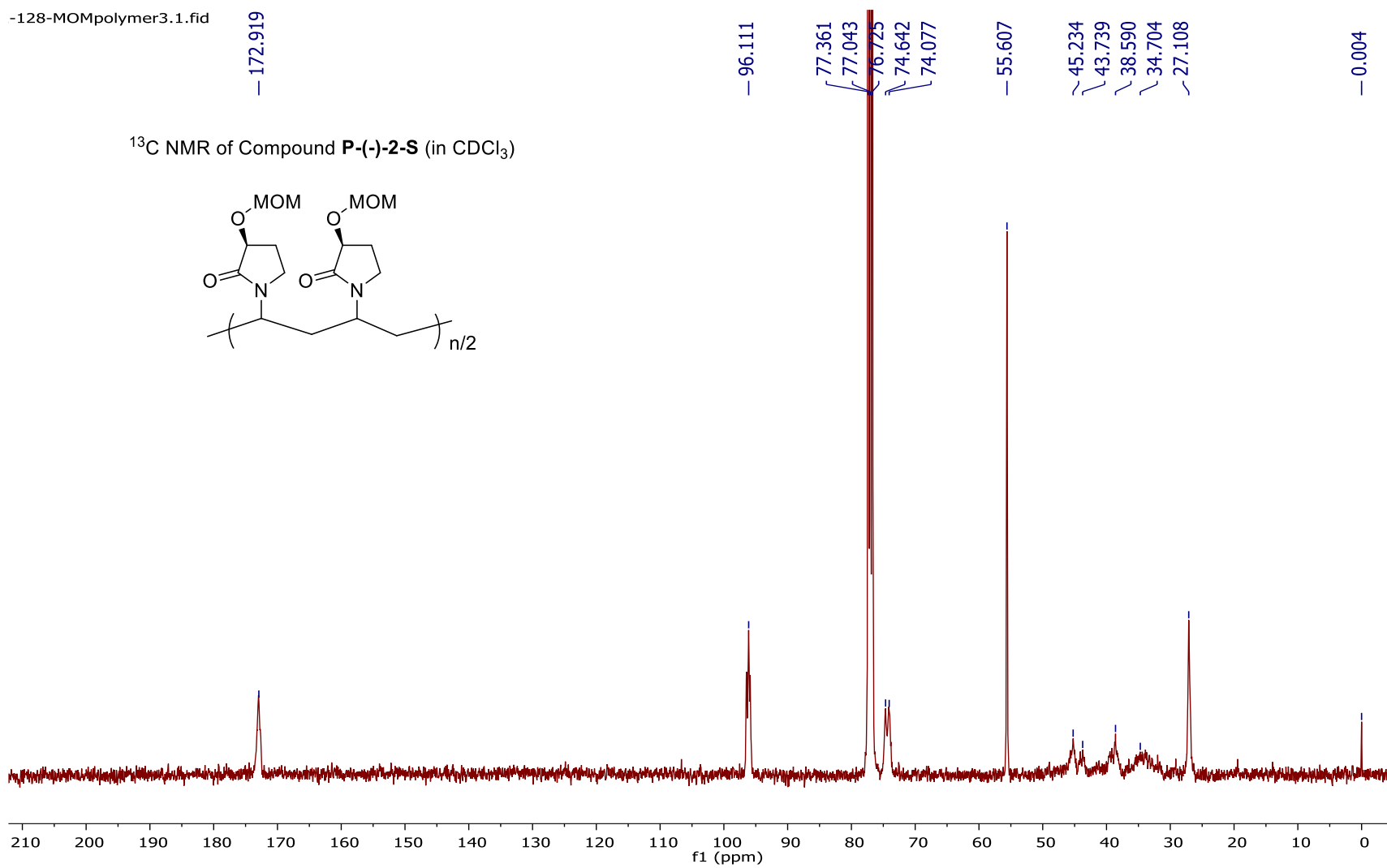
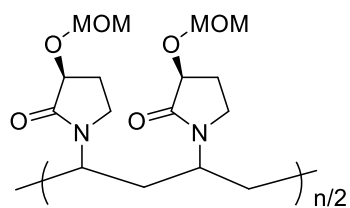
38.590

34.704

27.108

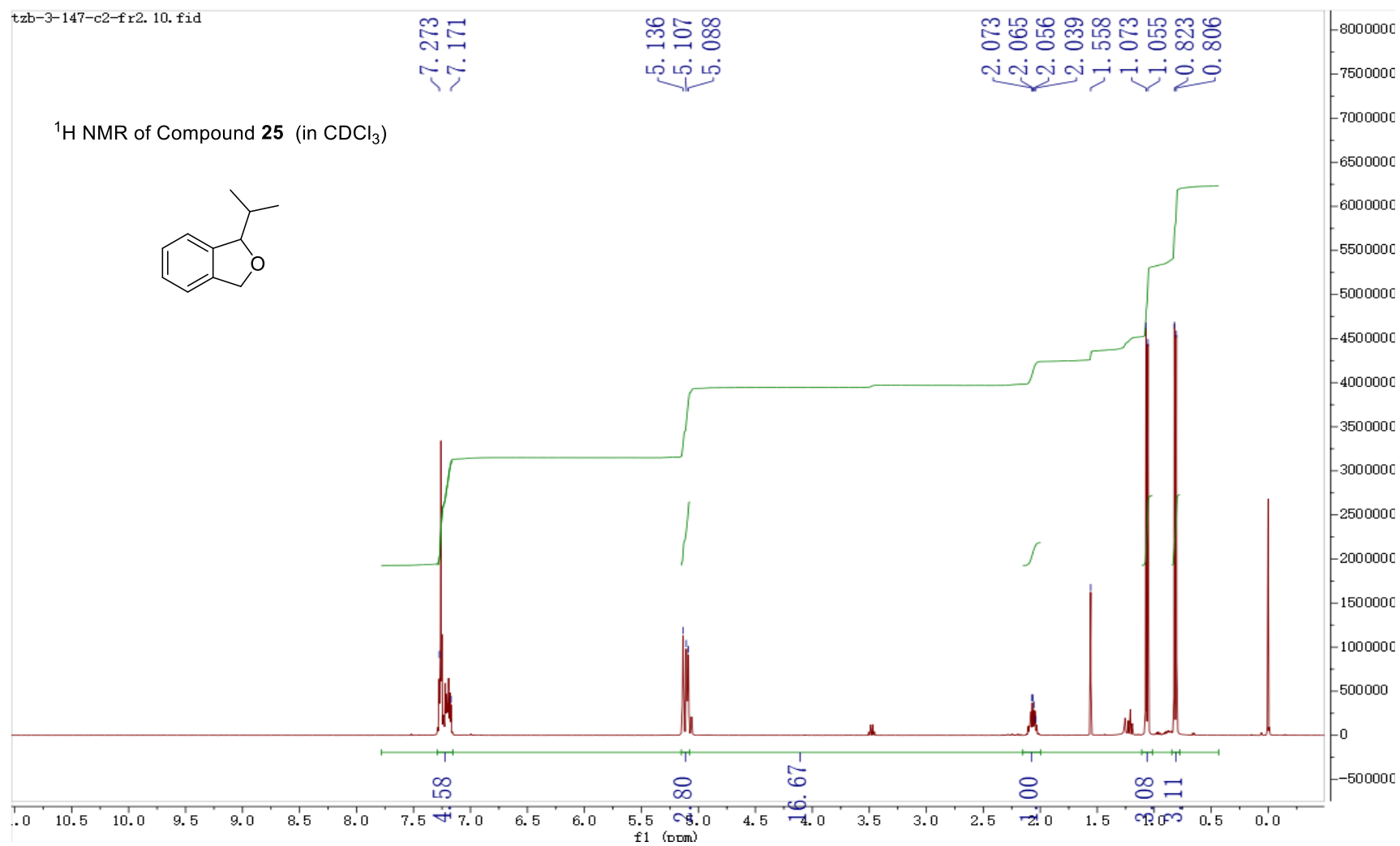
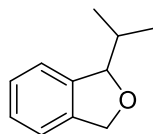
— 0.004

^{13}C NMR of Compound **P-(-)-2-S** (in CDCl_3)



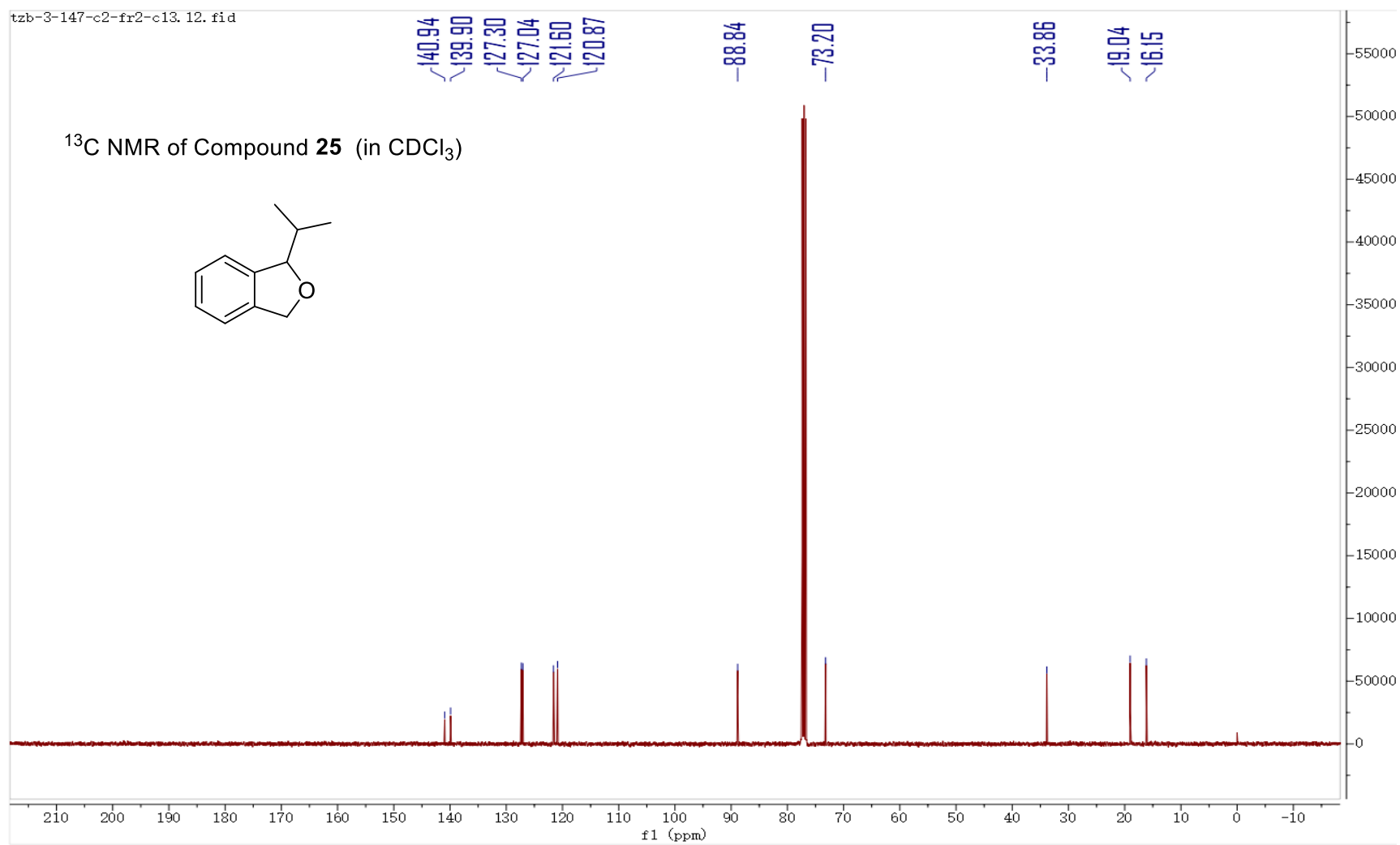
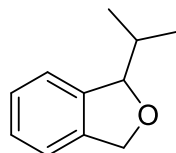
tzb-3-147-c2-fr2. 10. fid

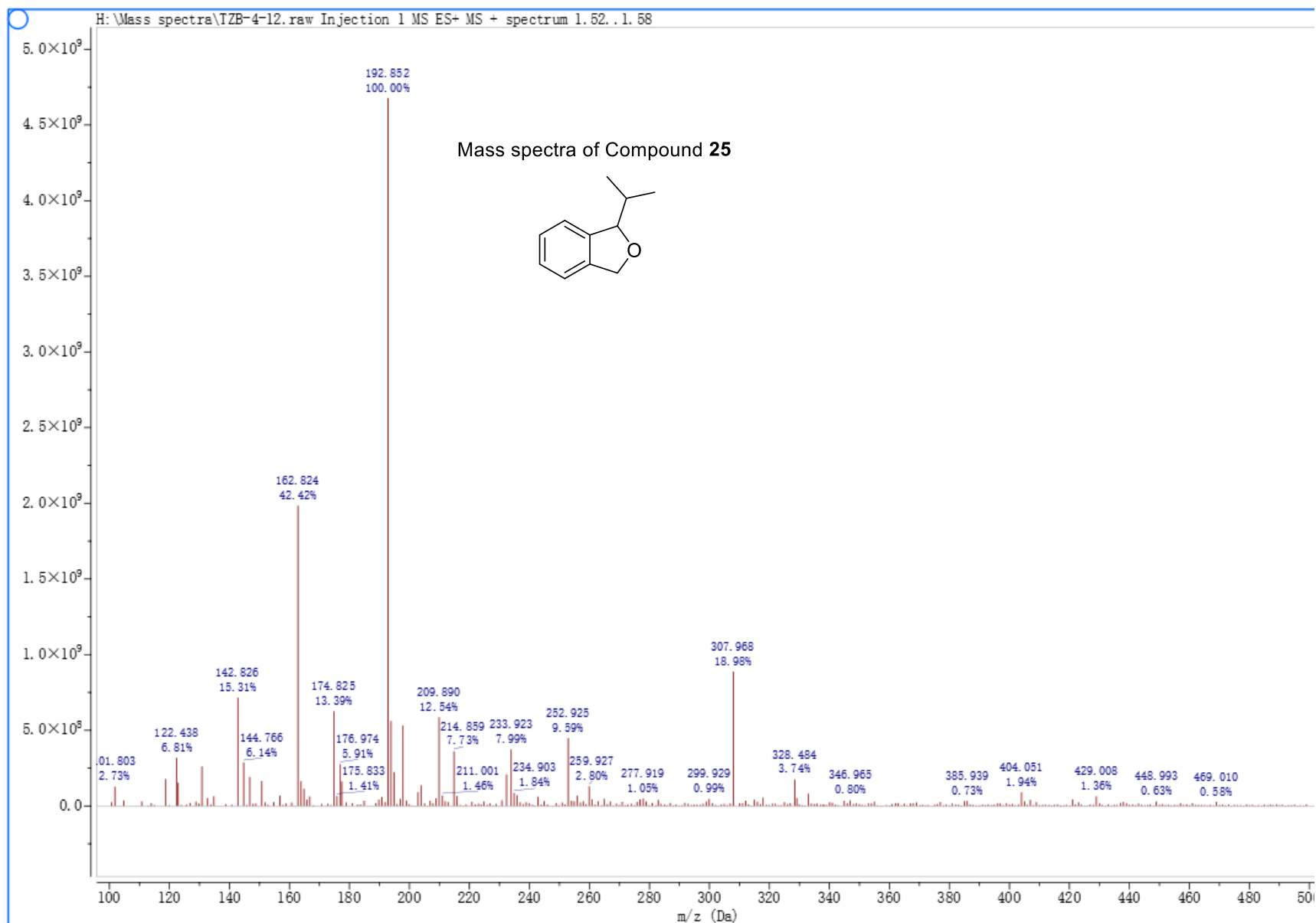
^1H NMR of Compound **25** (in CDCl_3)

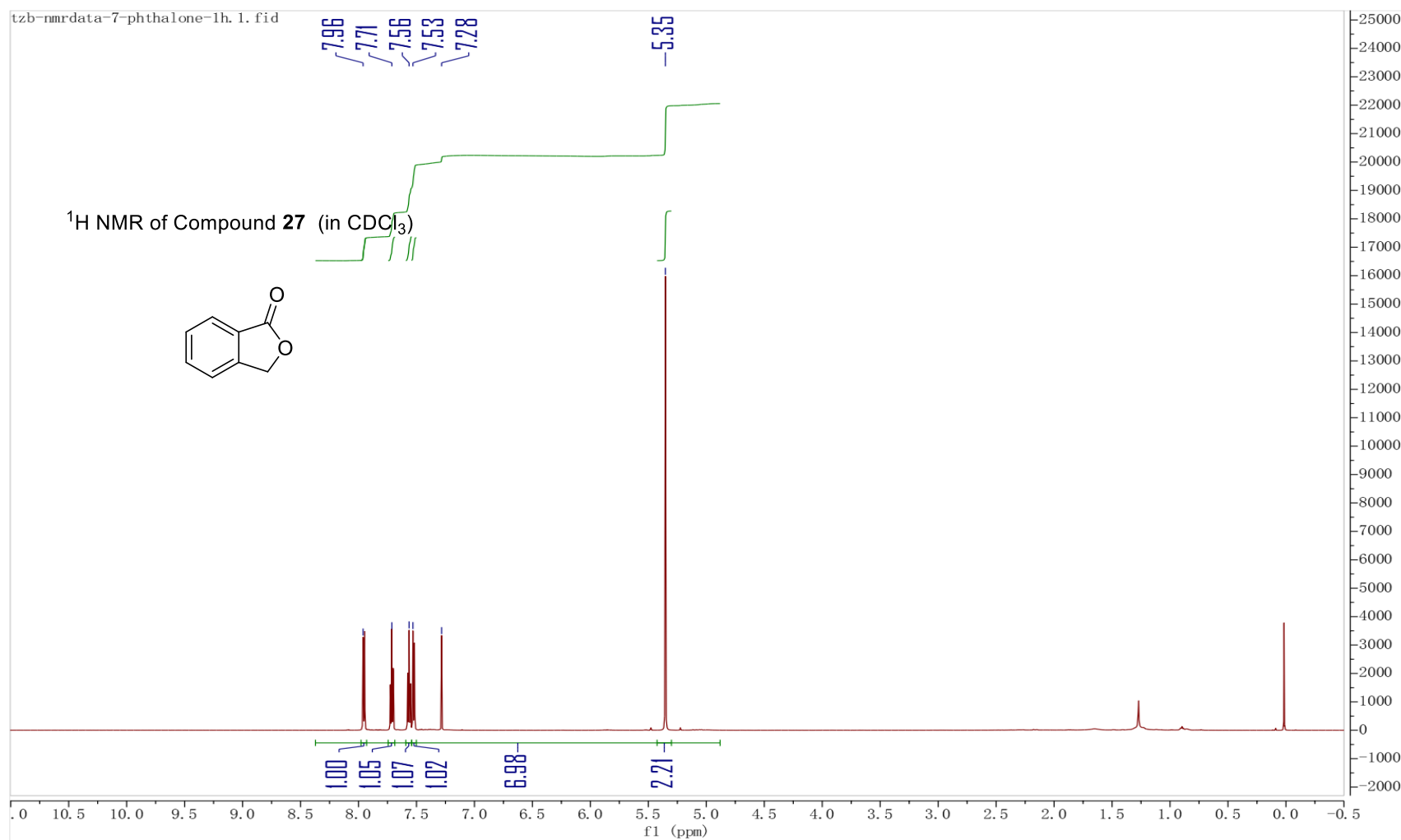


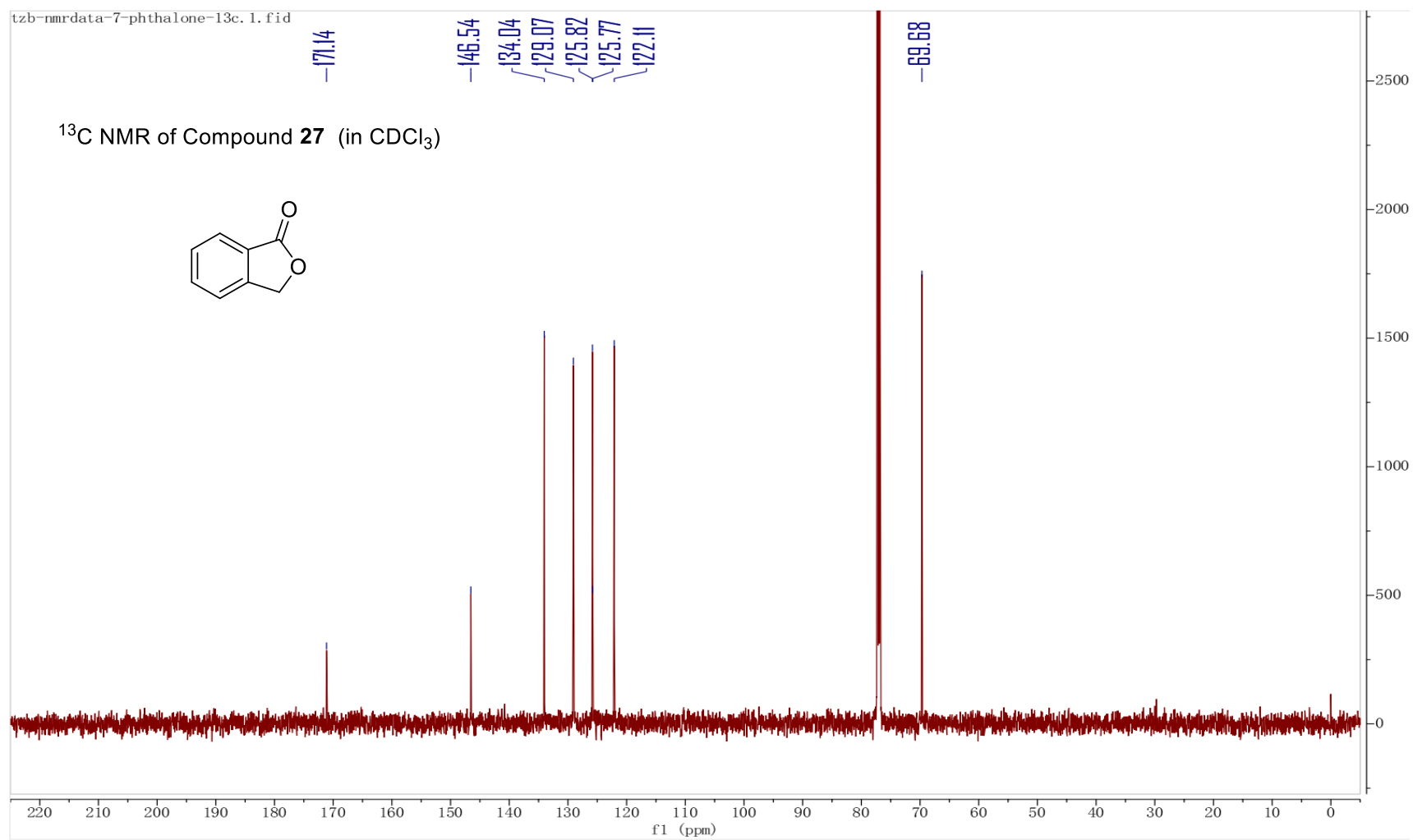
tzb-3-147-c2-fr2-c13.12.fid

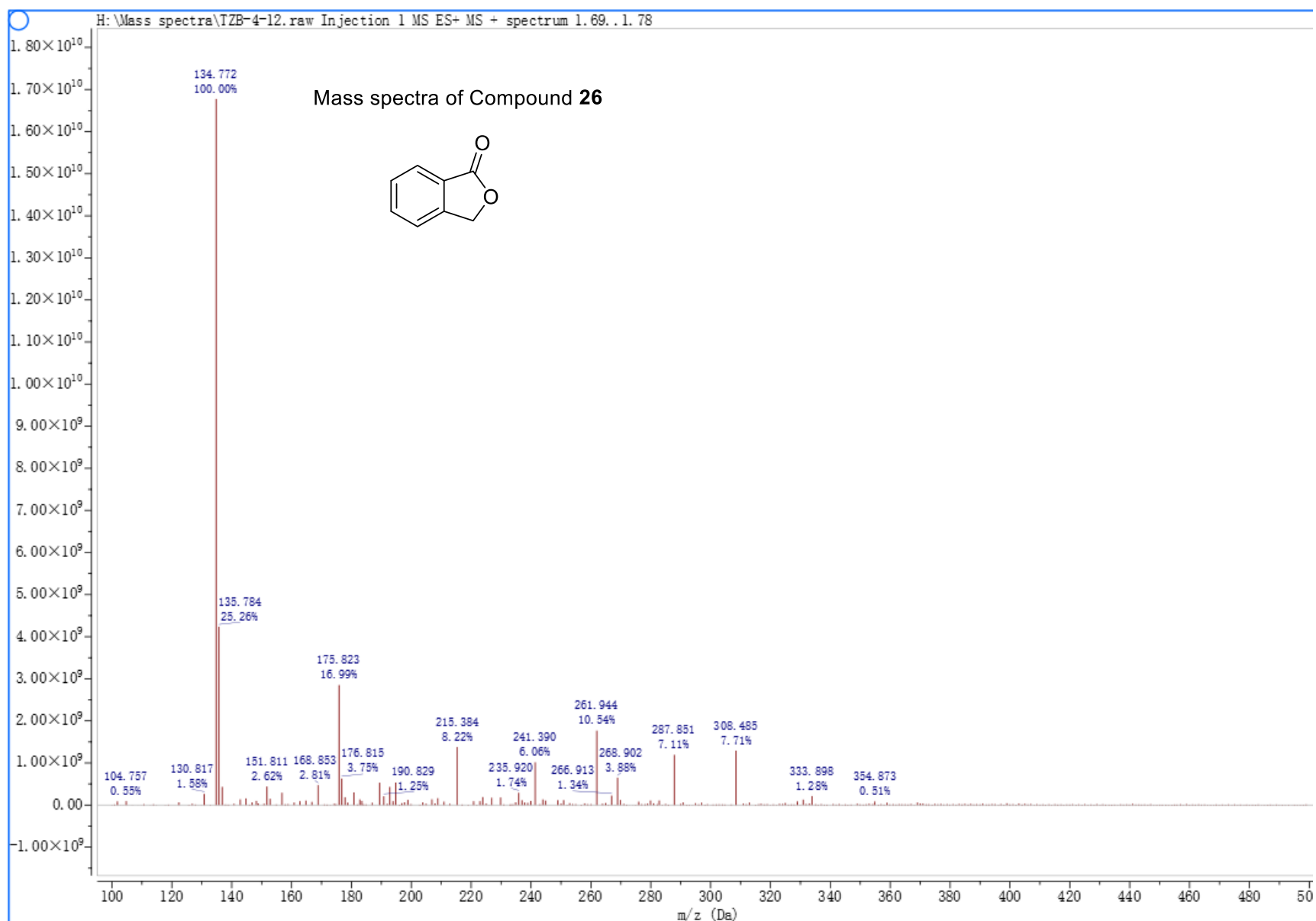
^{13}C NMR of Compound **25** (in CDCl_3)





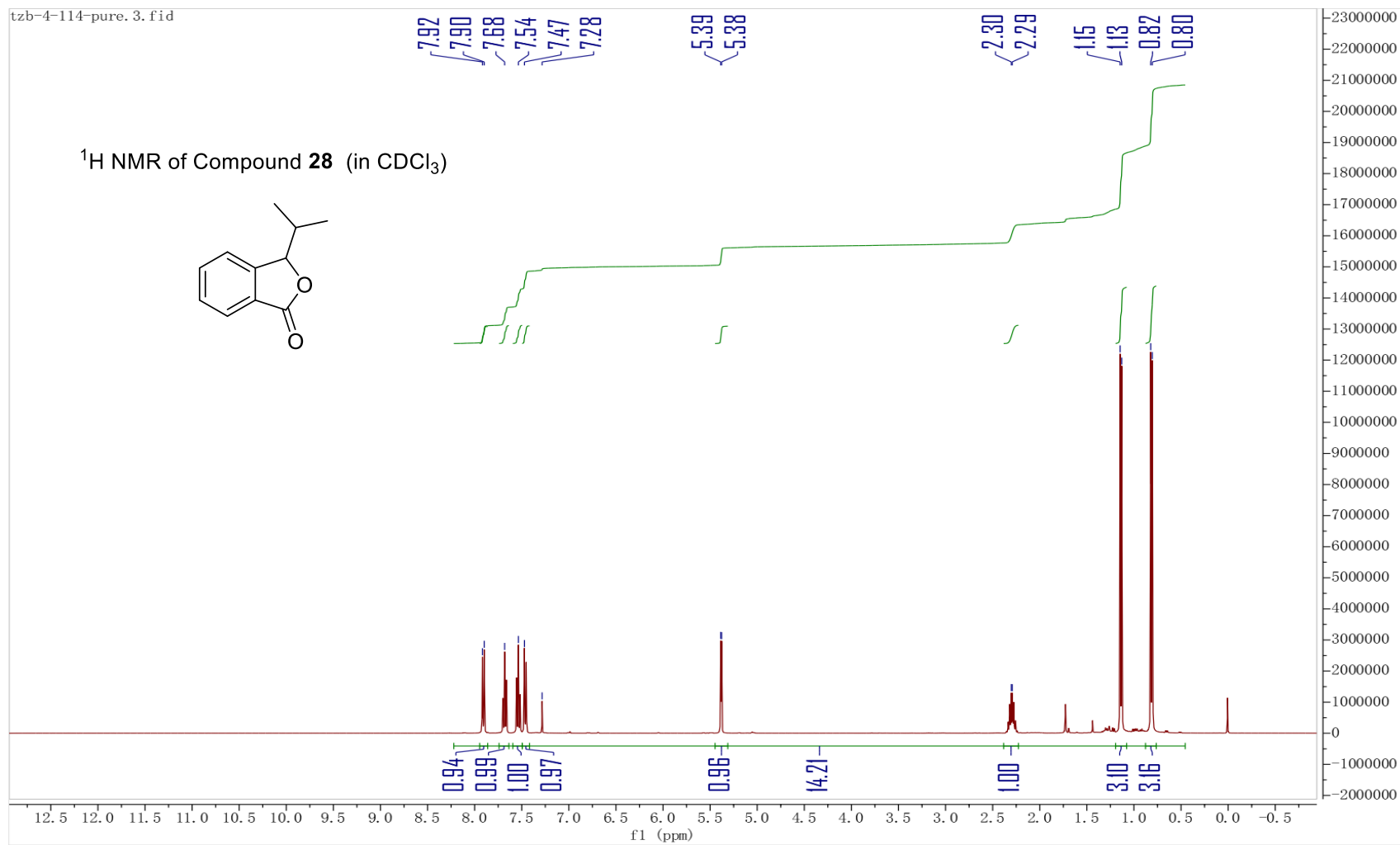
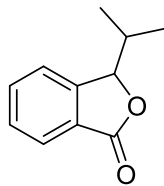


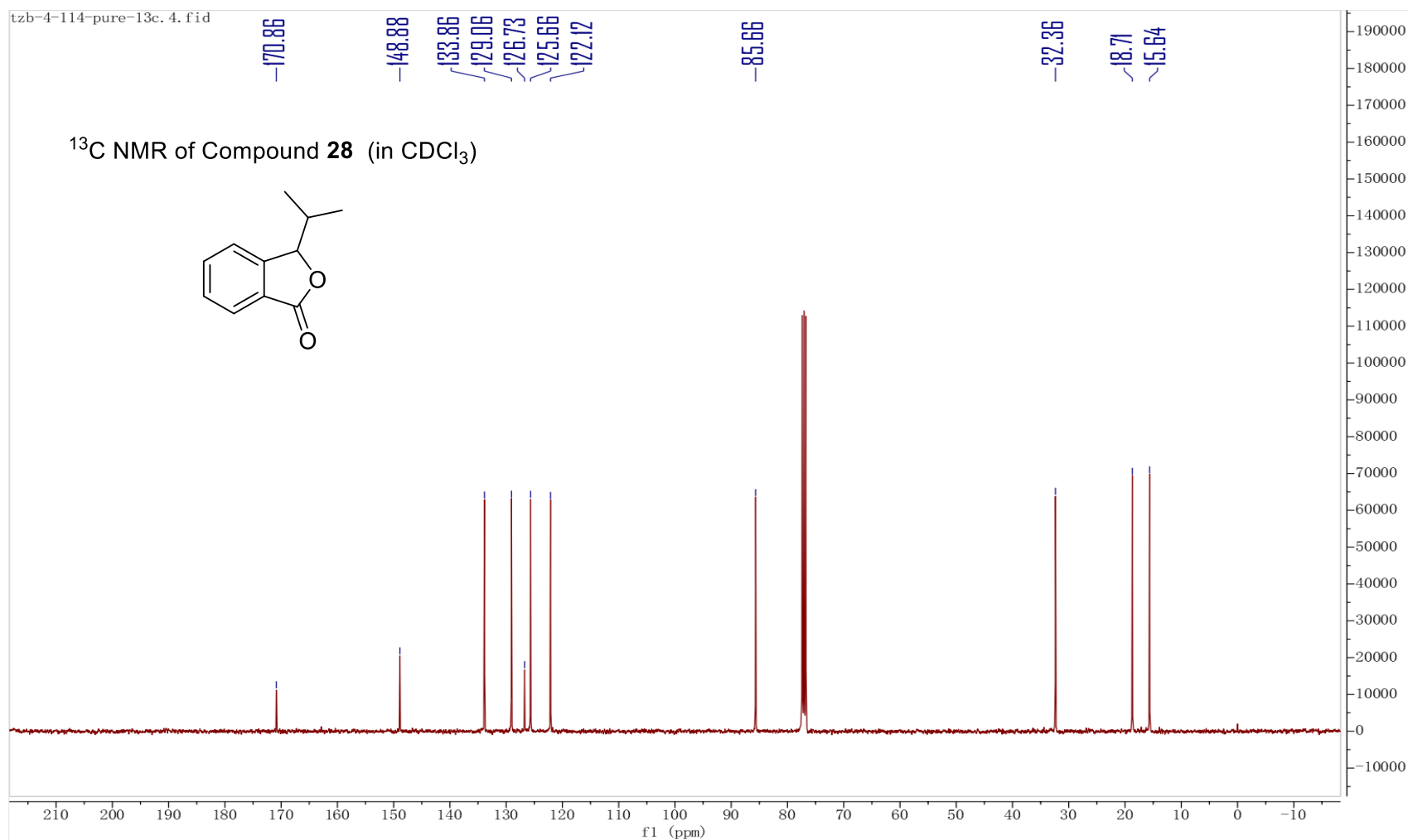


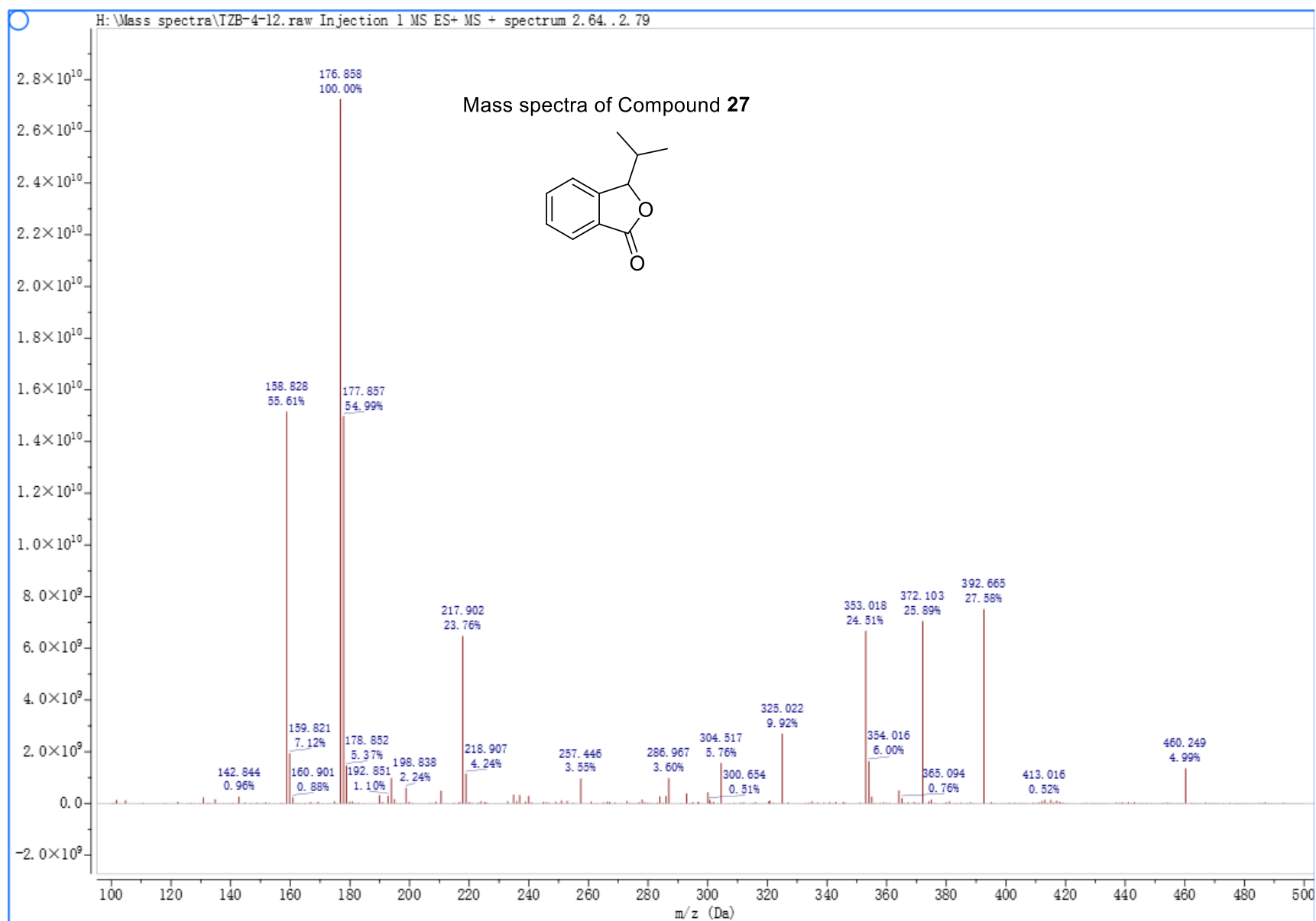


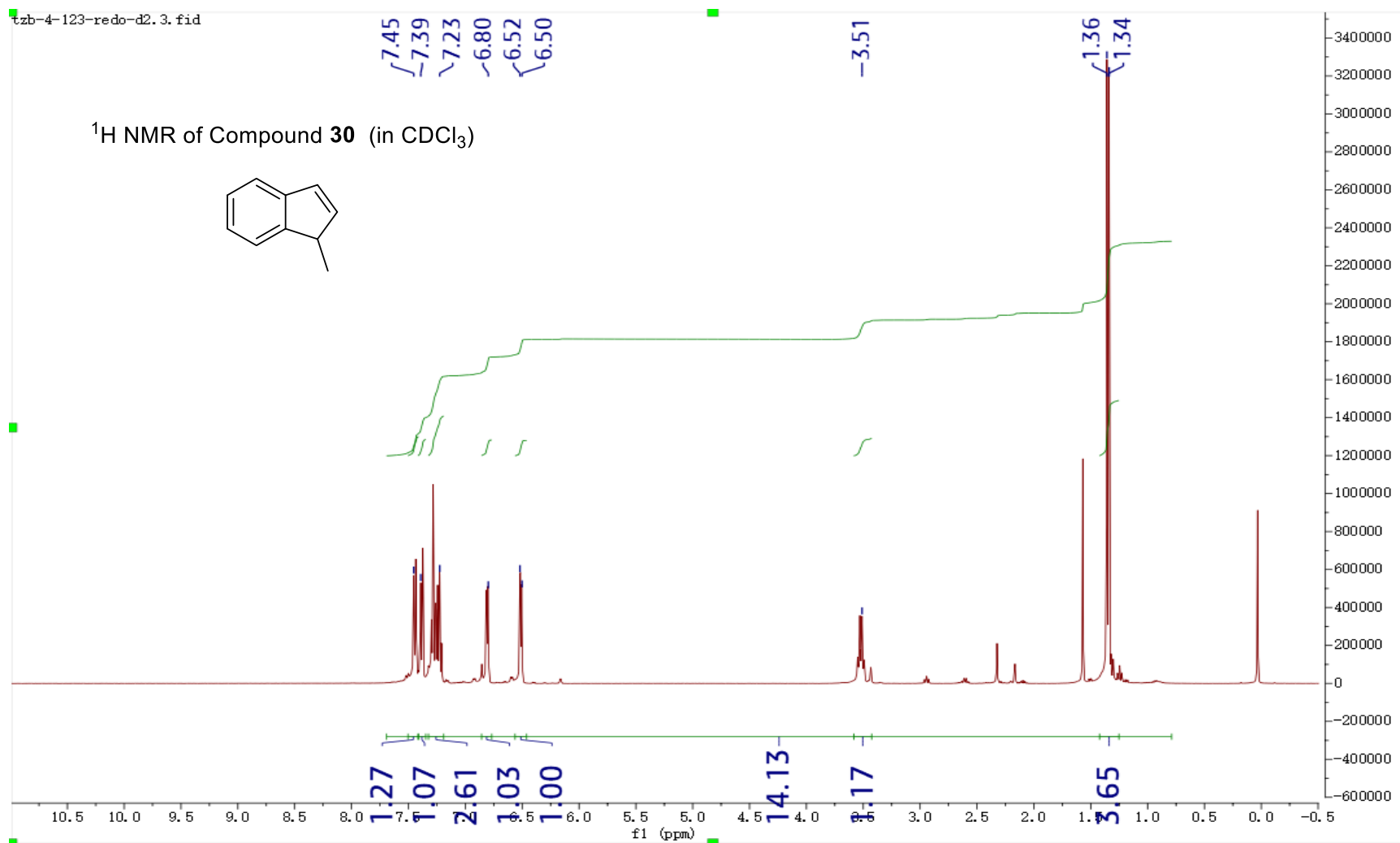
tzb-4-114-pure. 3. fid

^1H NMR of Compound **28** (in CDCl_3)



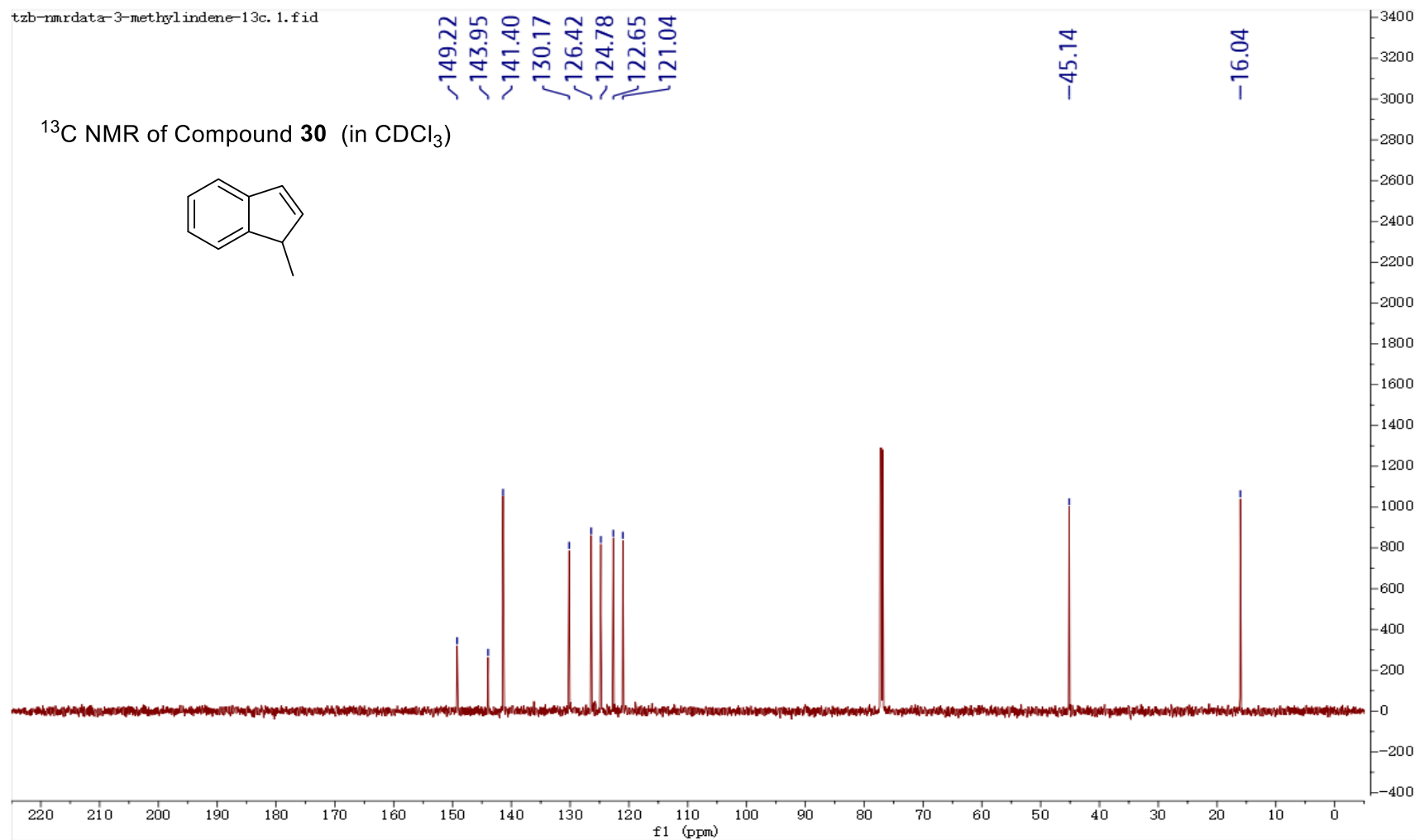
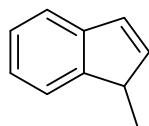


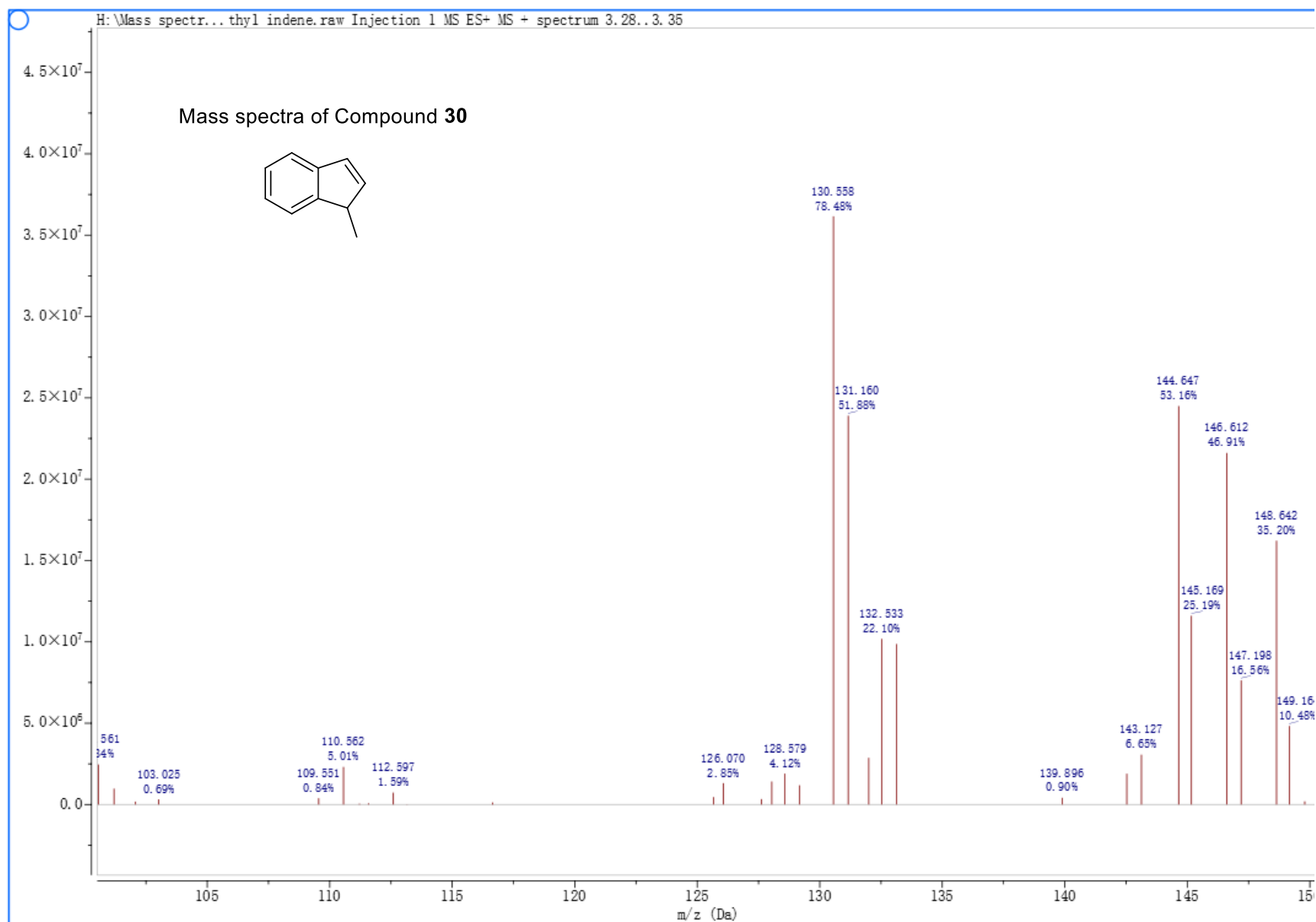


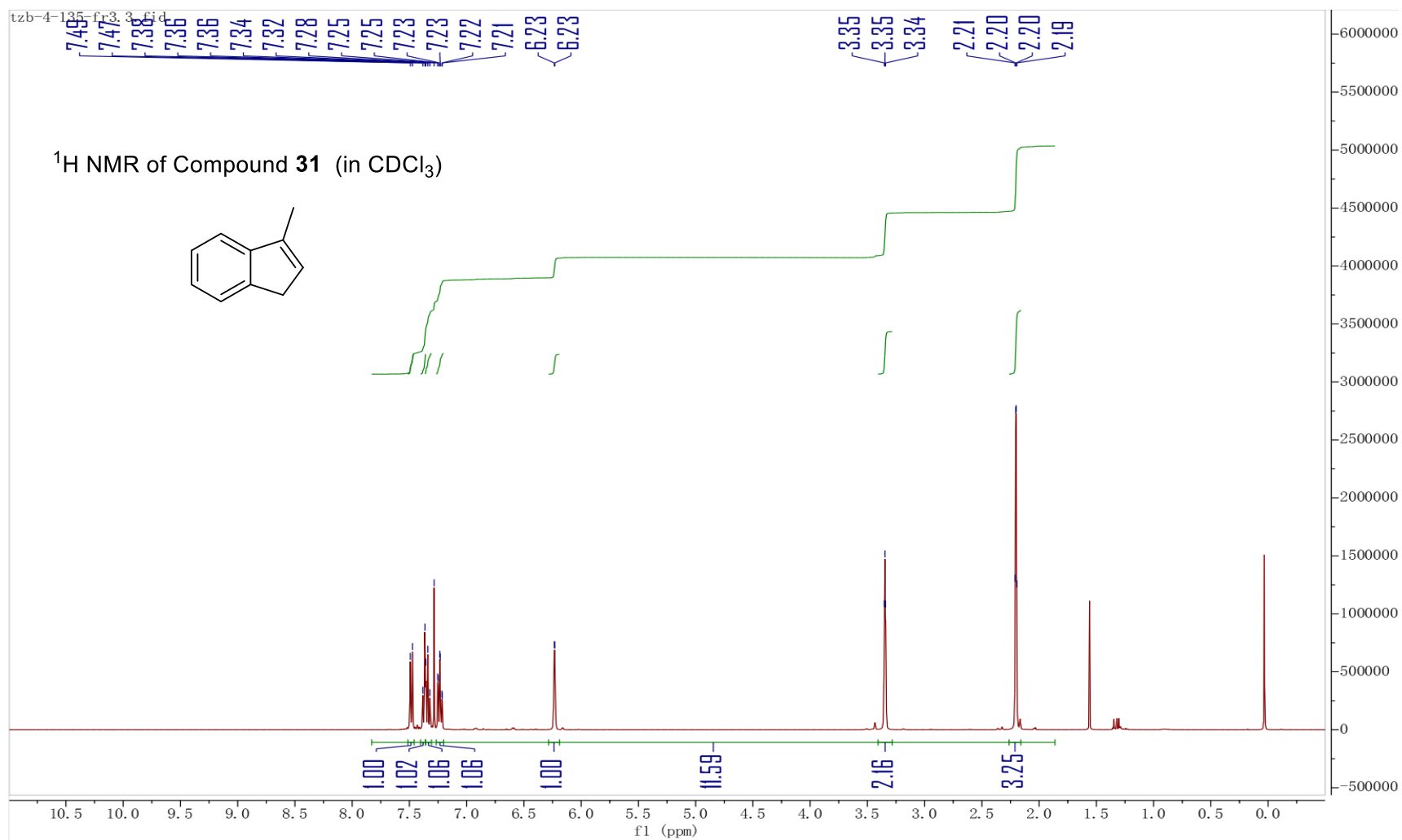


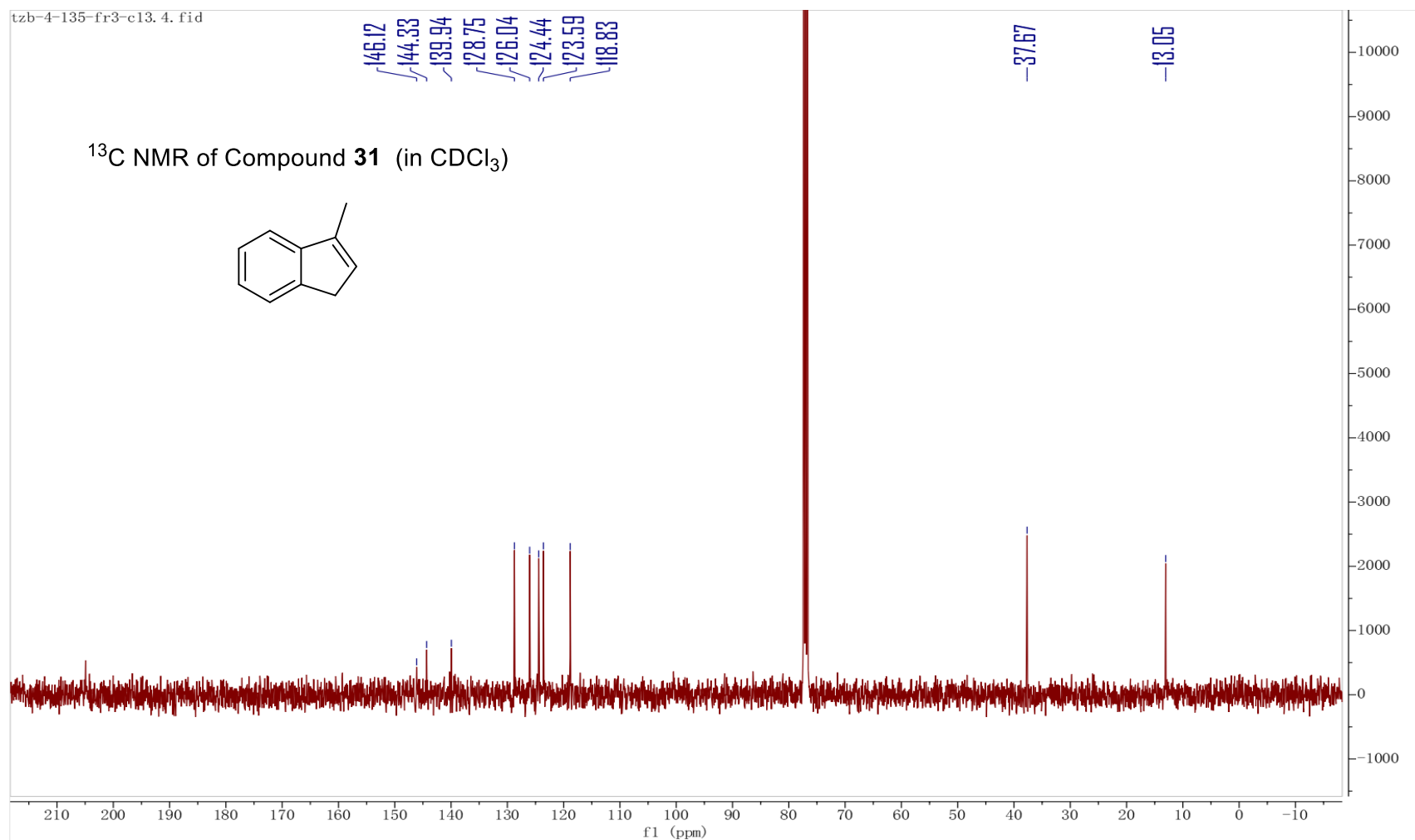
tzbr-nmrdata-3-methylindene-13c.1.fid

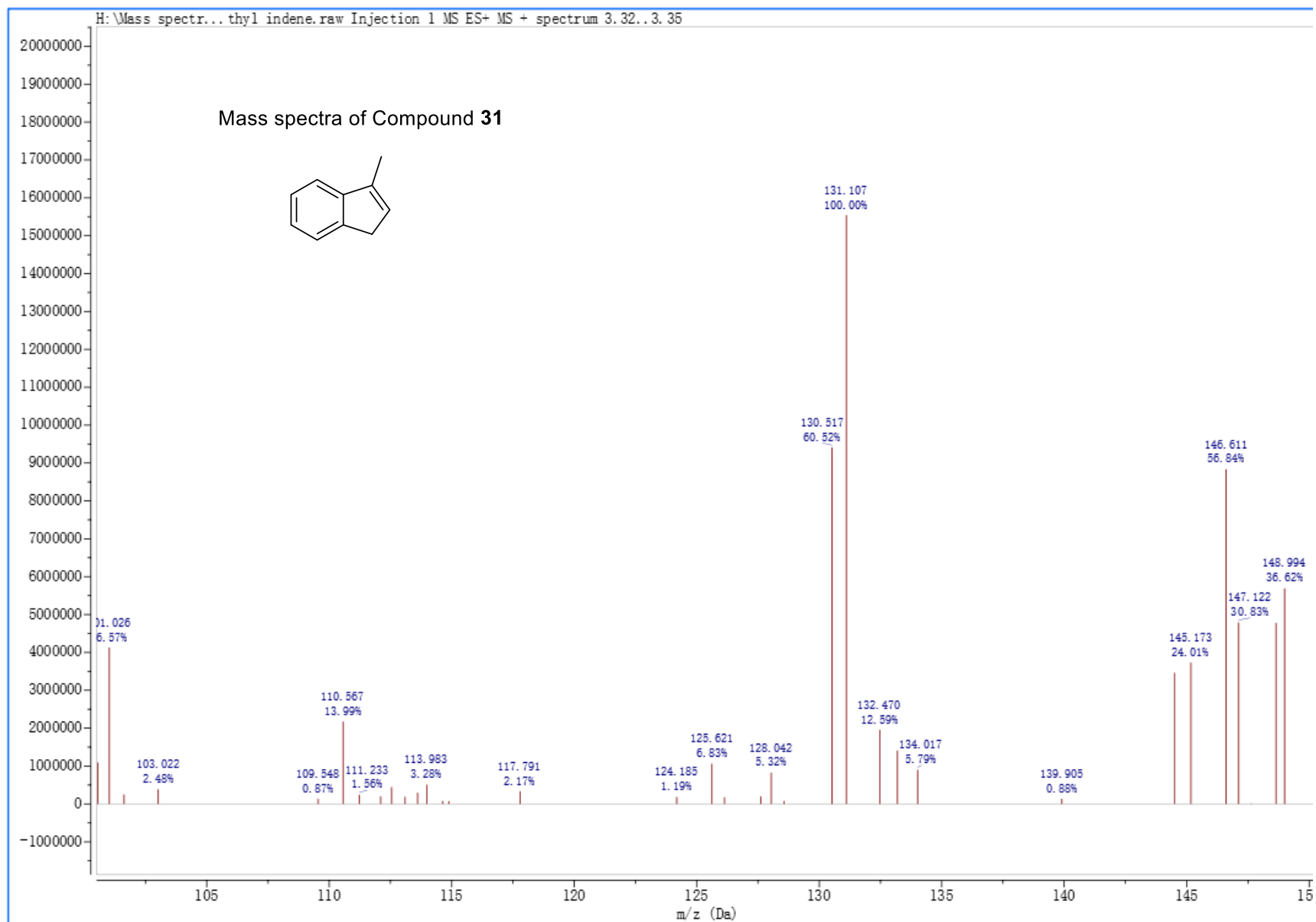
^{13}C NMR of Compound **30** (in CDCl_3)





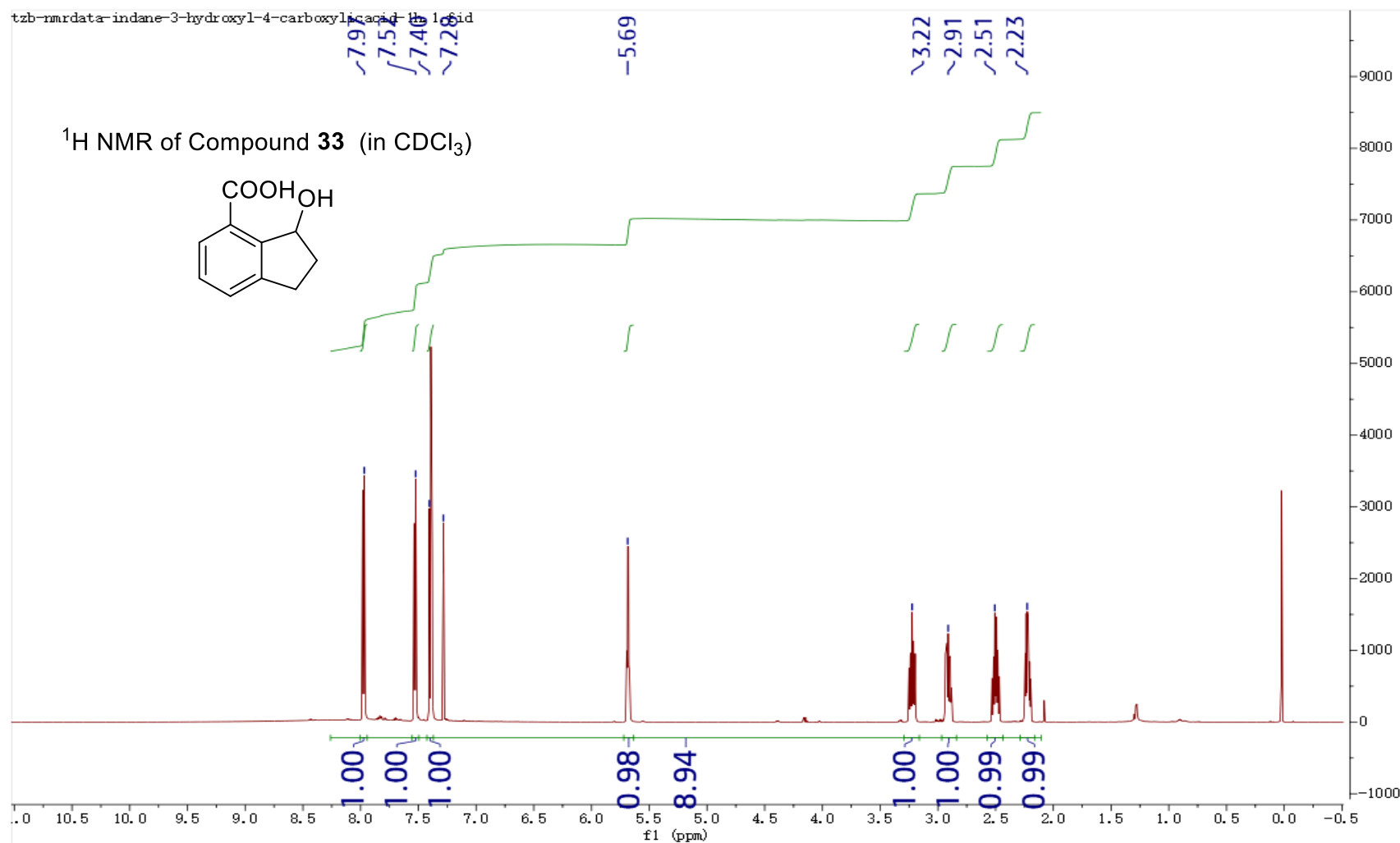
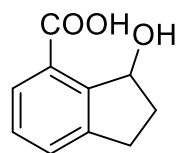






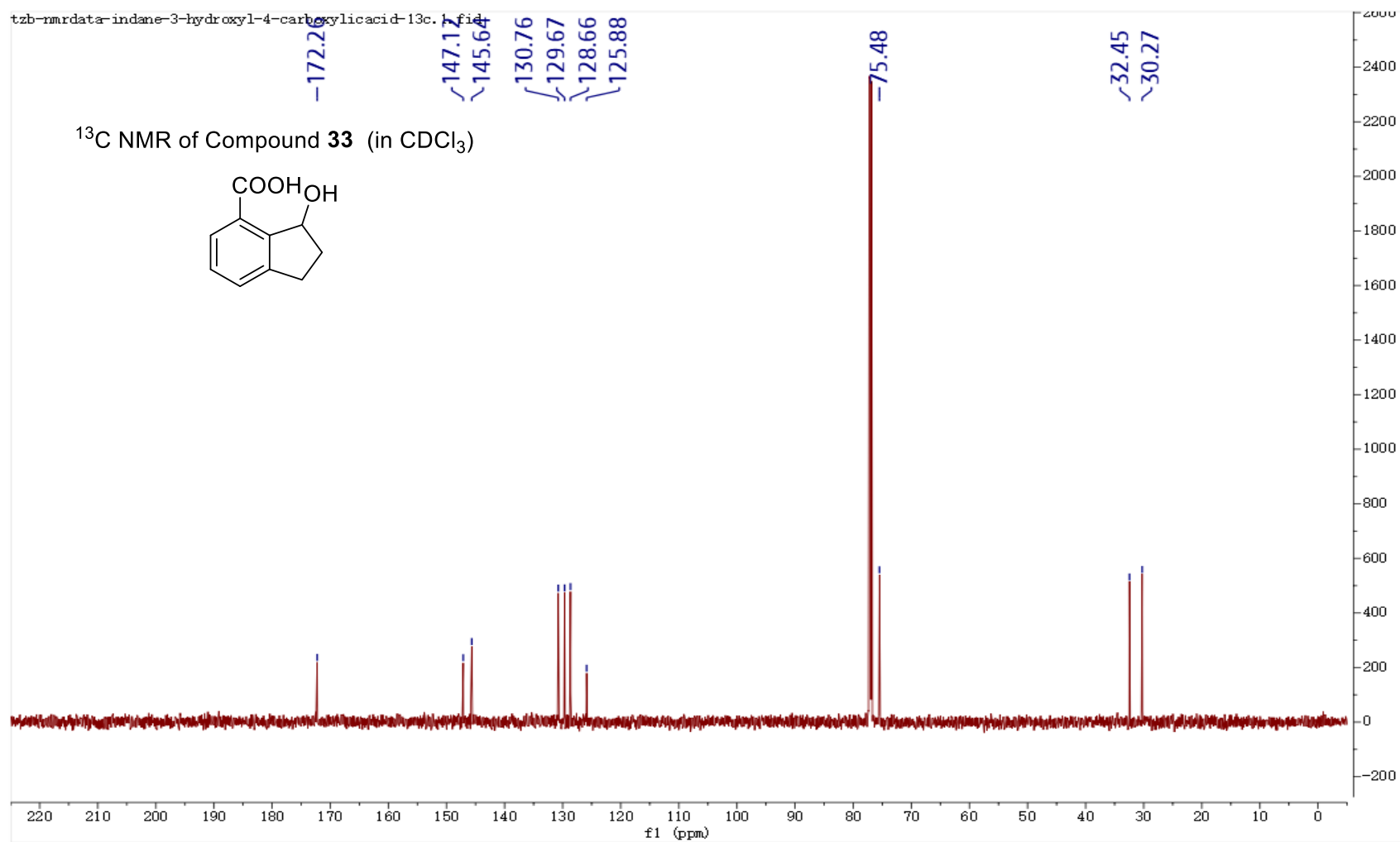
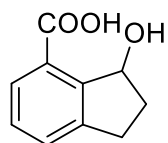
tzbr-nmrdata-indane-3-hydroxyl-4-carboxylic-acid-16-16id

^1H NMR of Compound **33** (in CDCl_3)

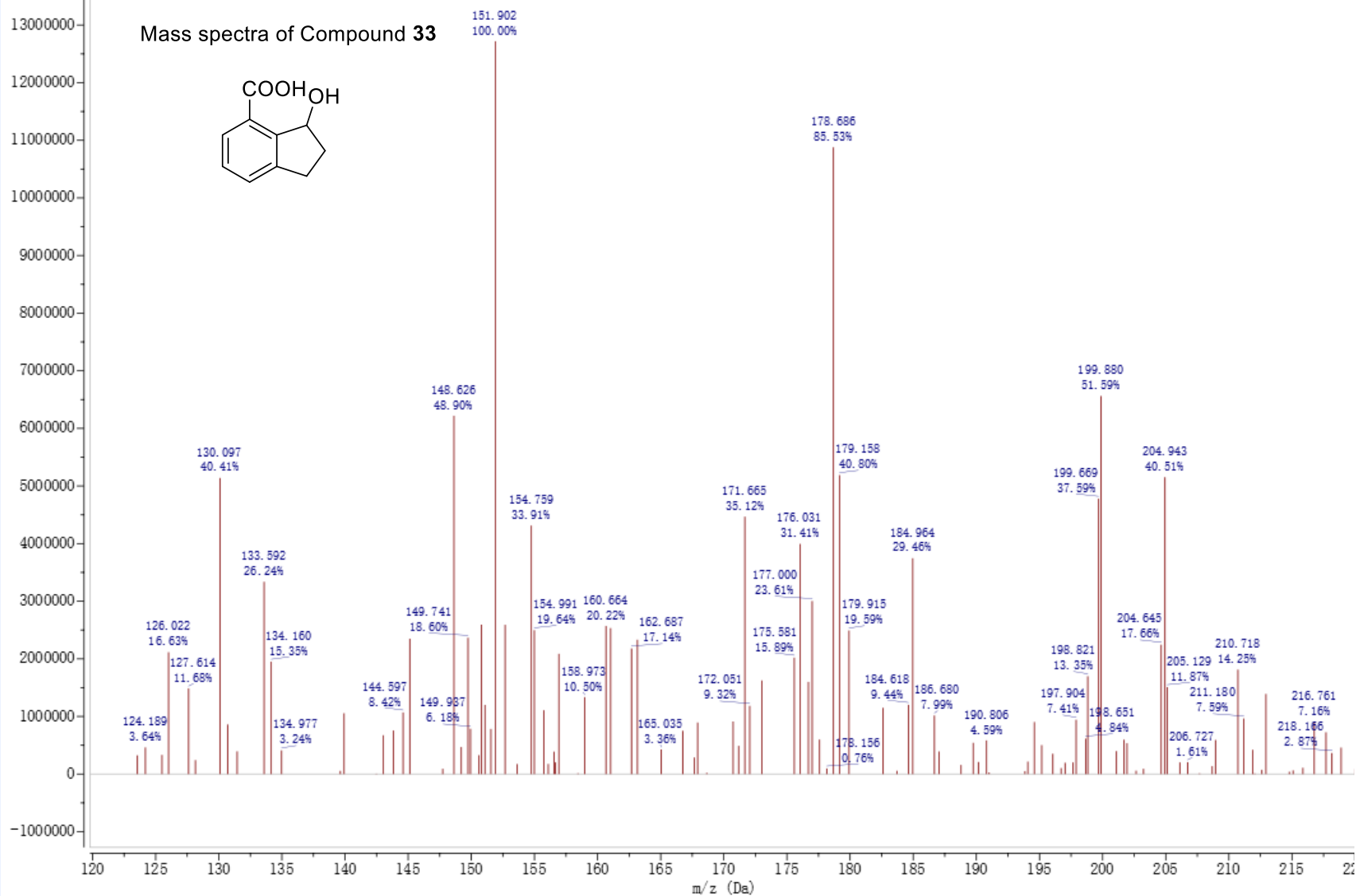
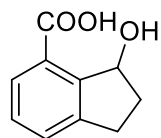


tzbnmrdata-indane-3-hydroxyl-4-carboxylicacid-13c.fid

^{13}C NMR of Compound **33** (in CDCl_3)

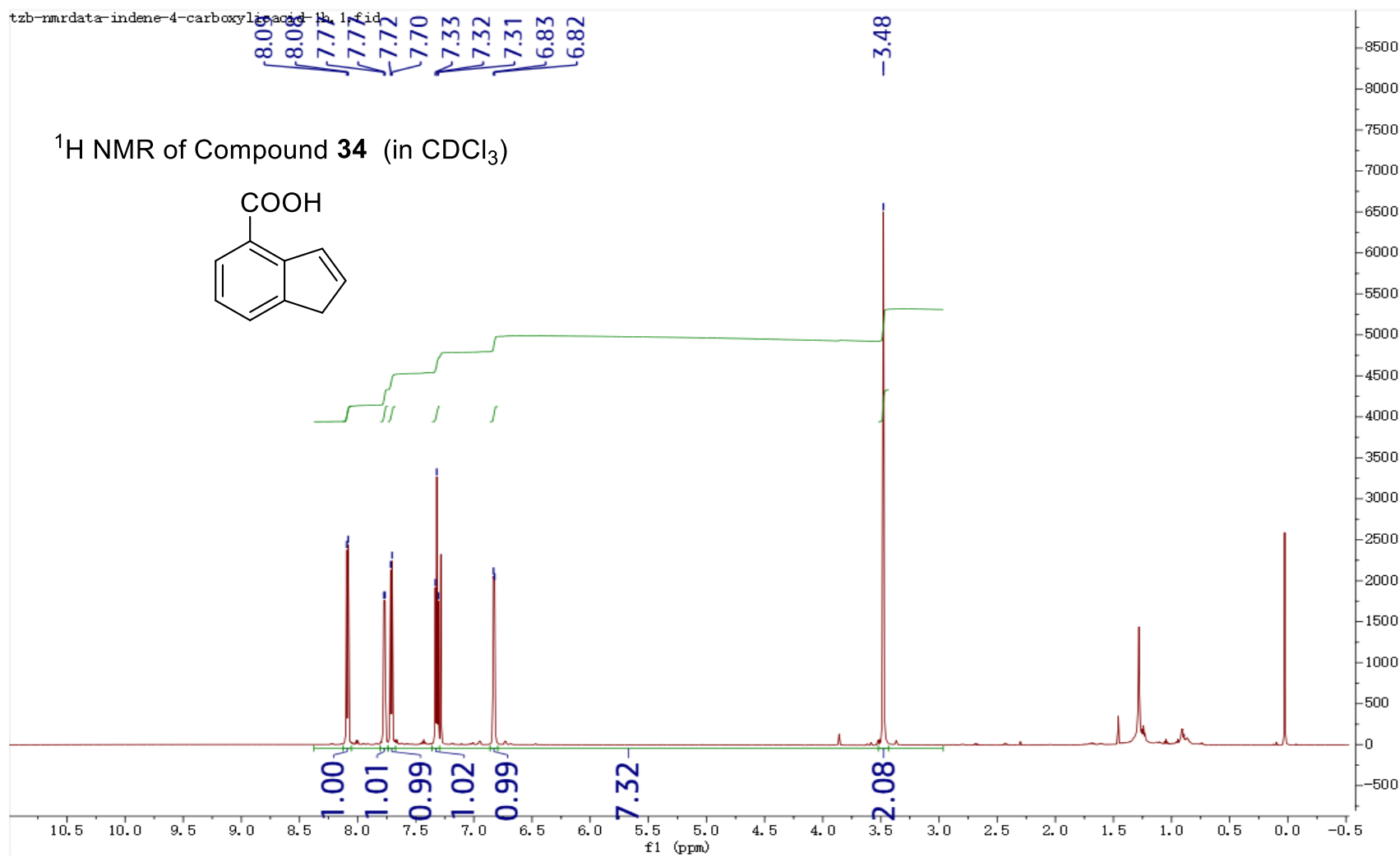
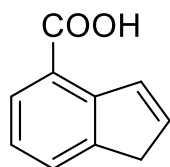


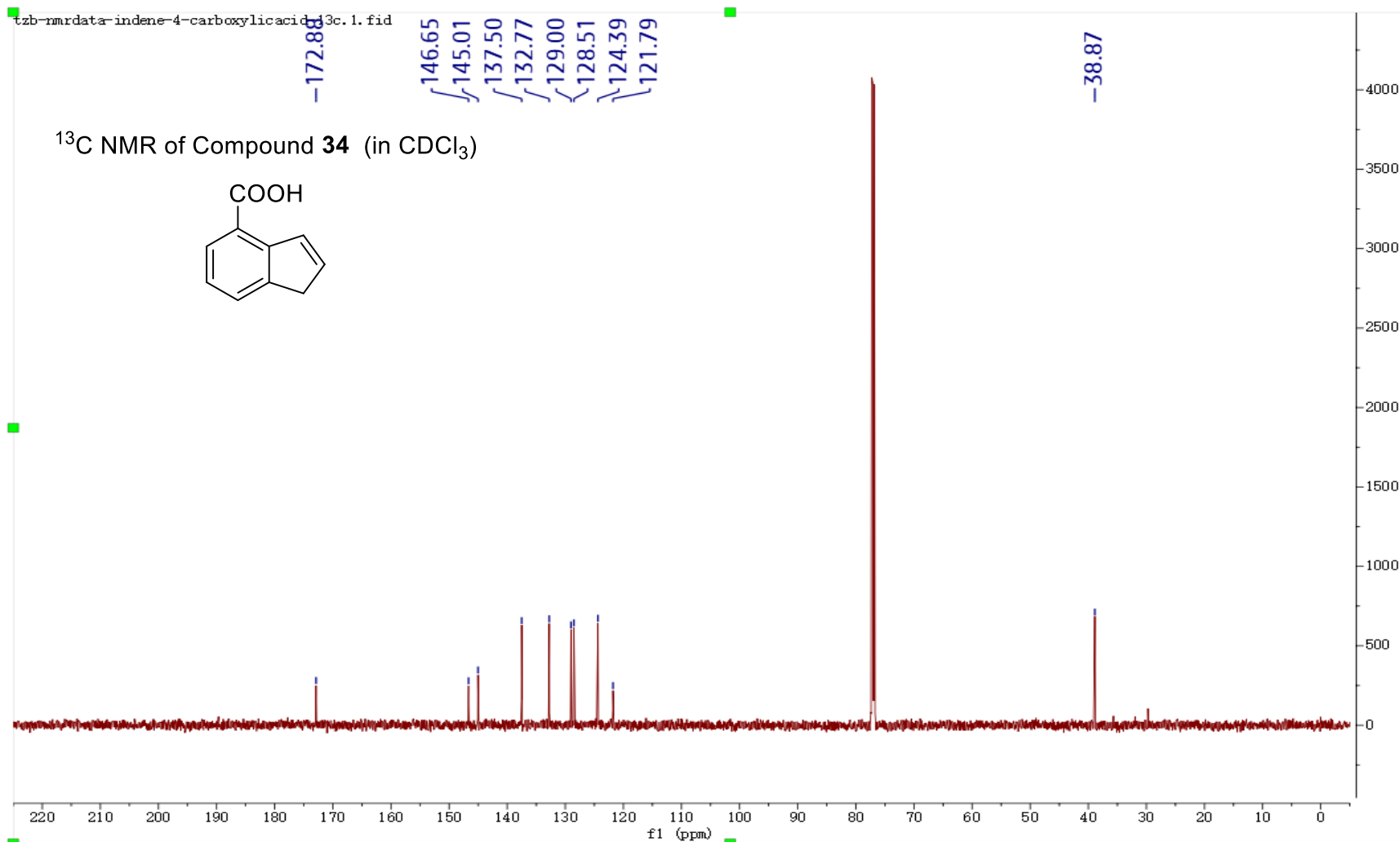
Mass spectra of Compound 33

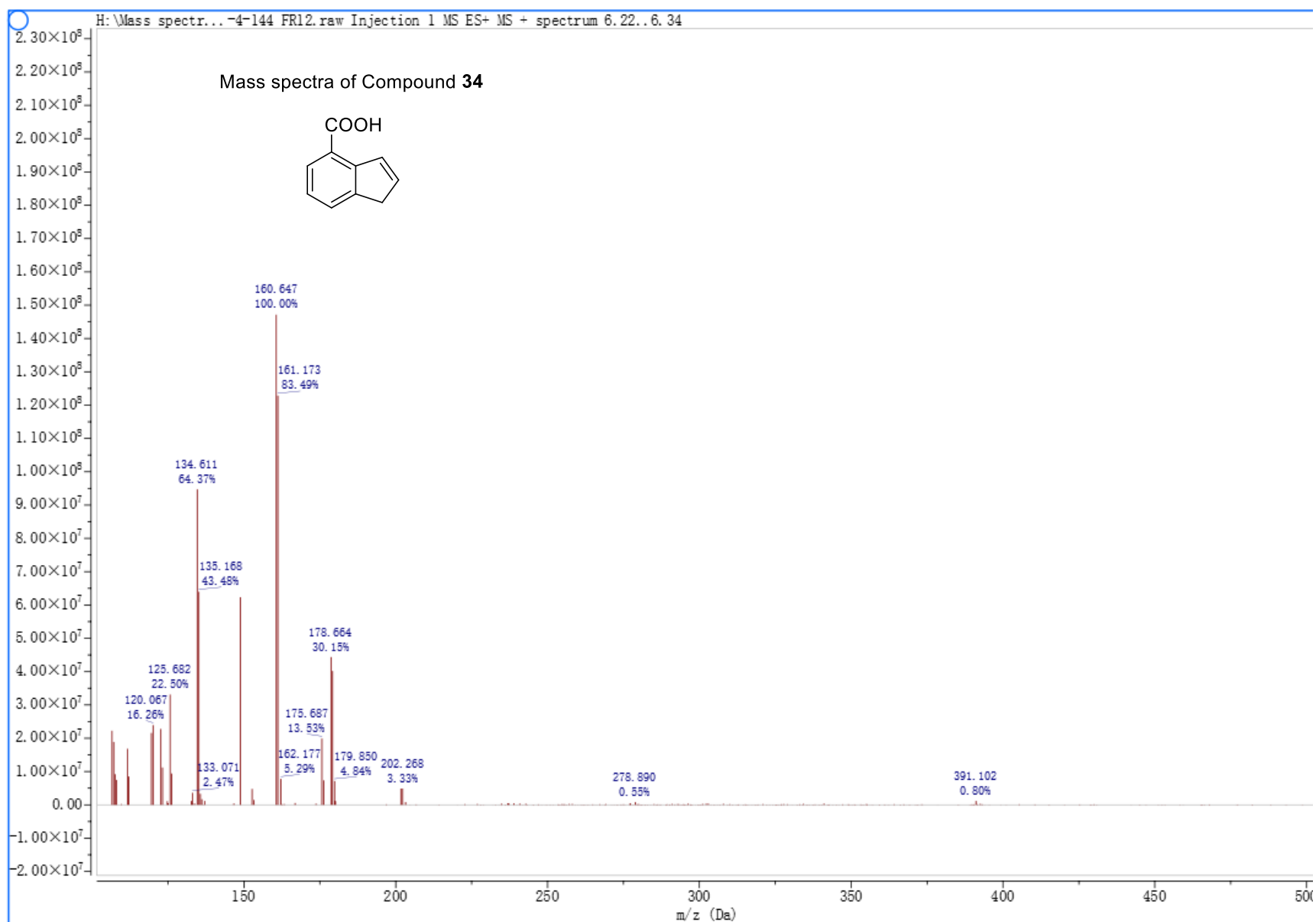


tzbr-nmrdata-indene-4-carboxylic-acid-H-1.fid

^1H NMR of Compound **34** (in CDCl_3)

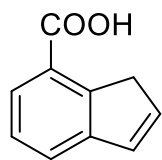






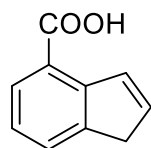
tzb-4-141-2d-rt. 10.fid

^1H NMR of Compound **35** with CH_3CN (in CDCl_3)

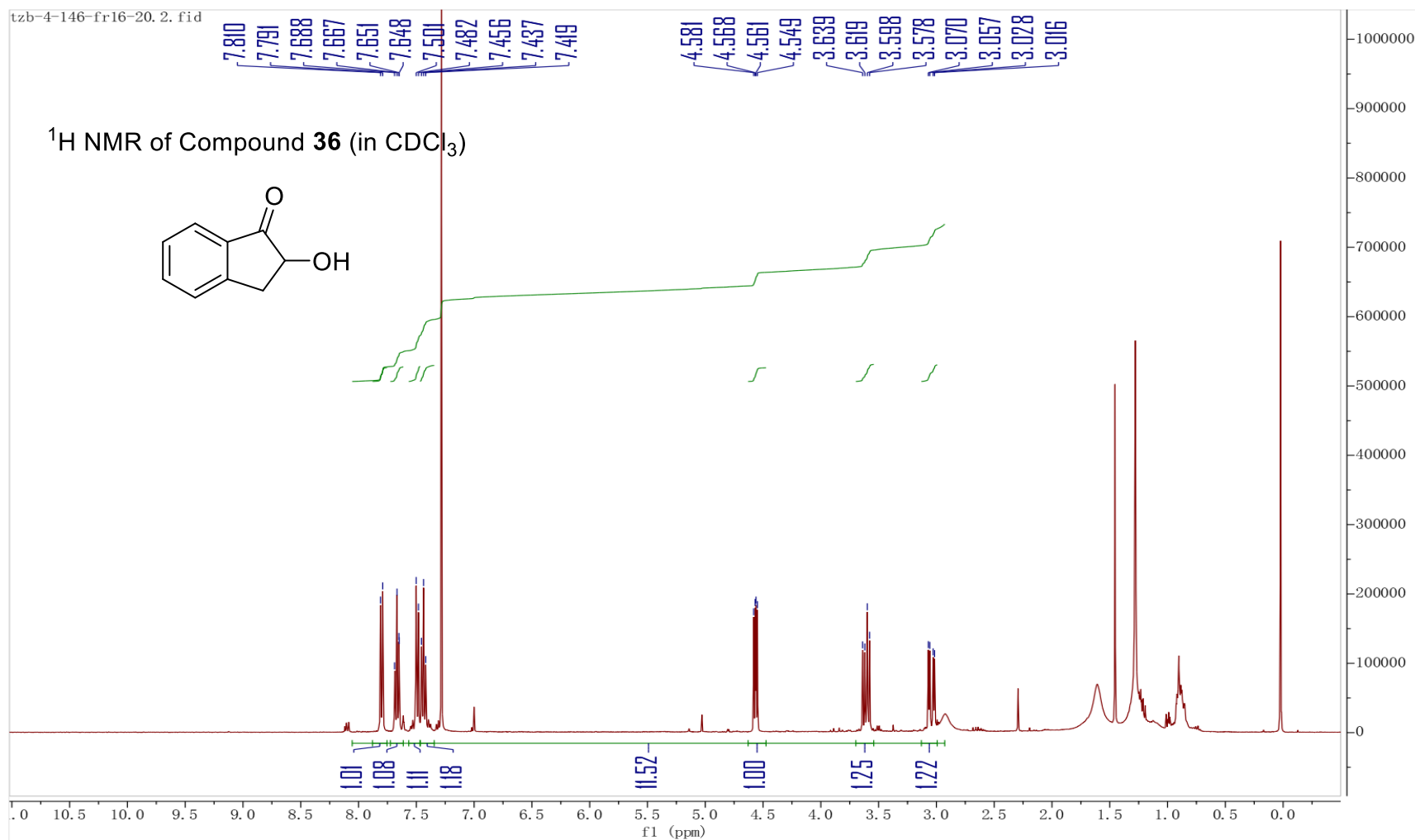


tzb-4-140-1h-rt. 1.fid

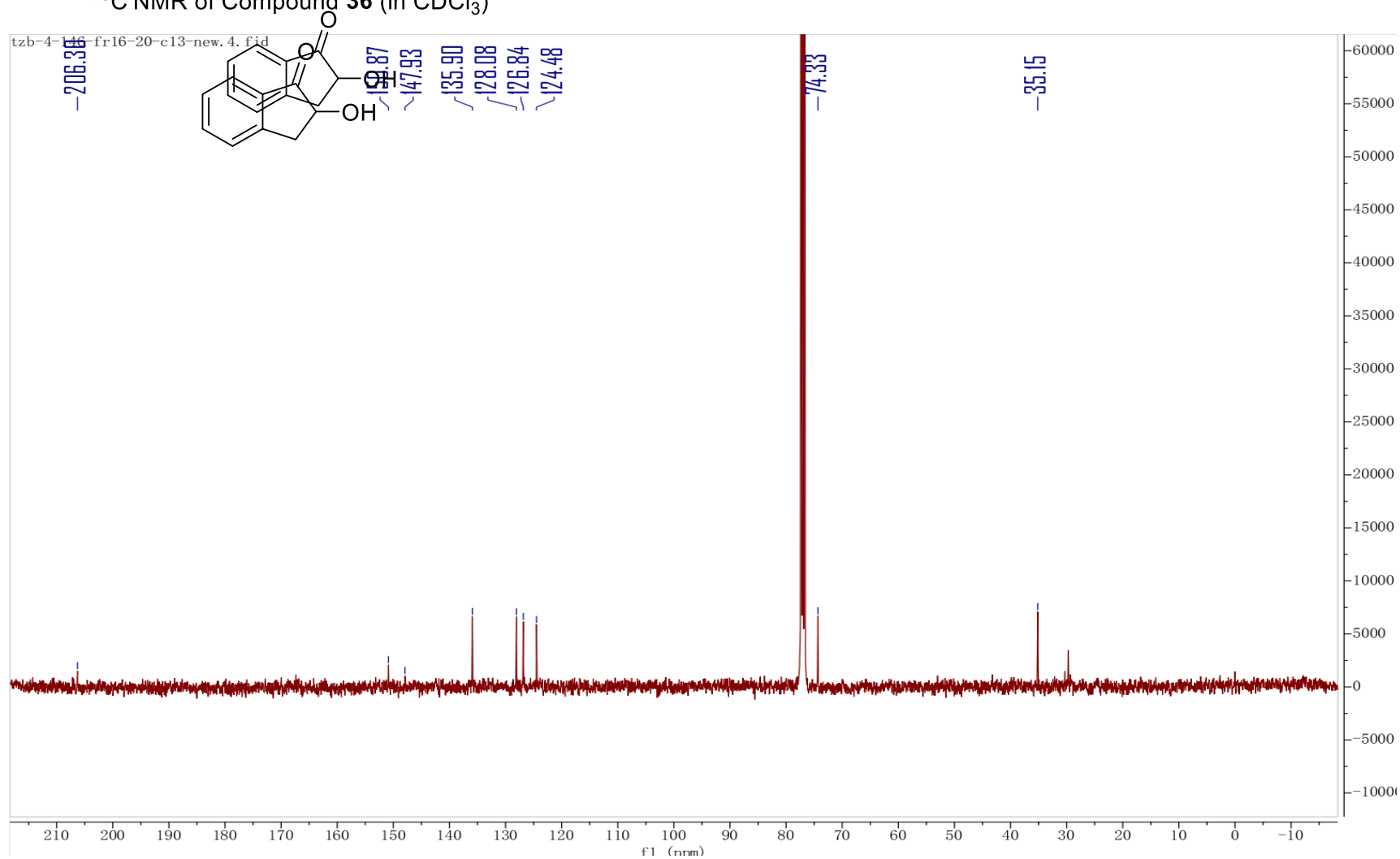
^1H NMR of Compound **34** with CH_3CN (in CDCl_3)



10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

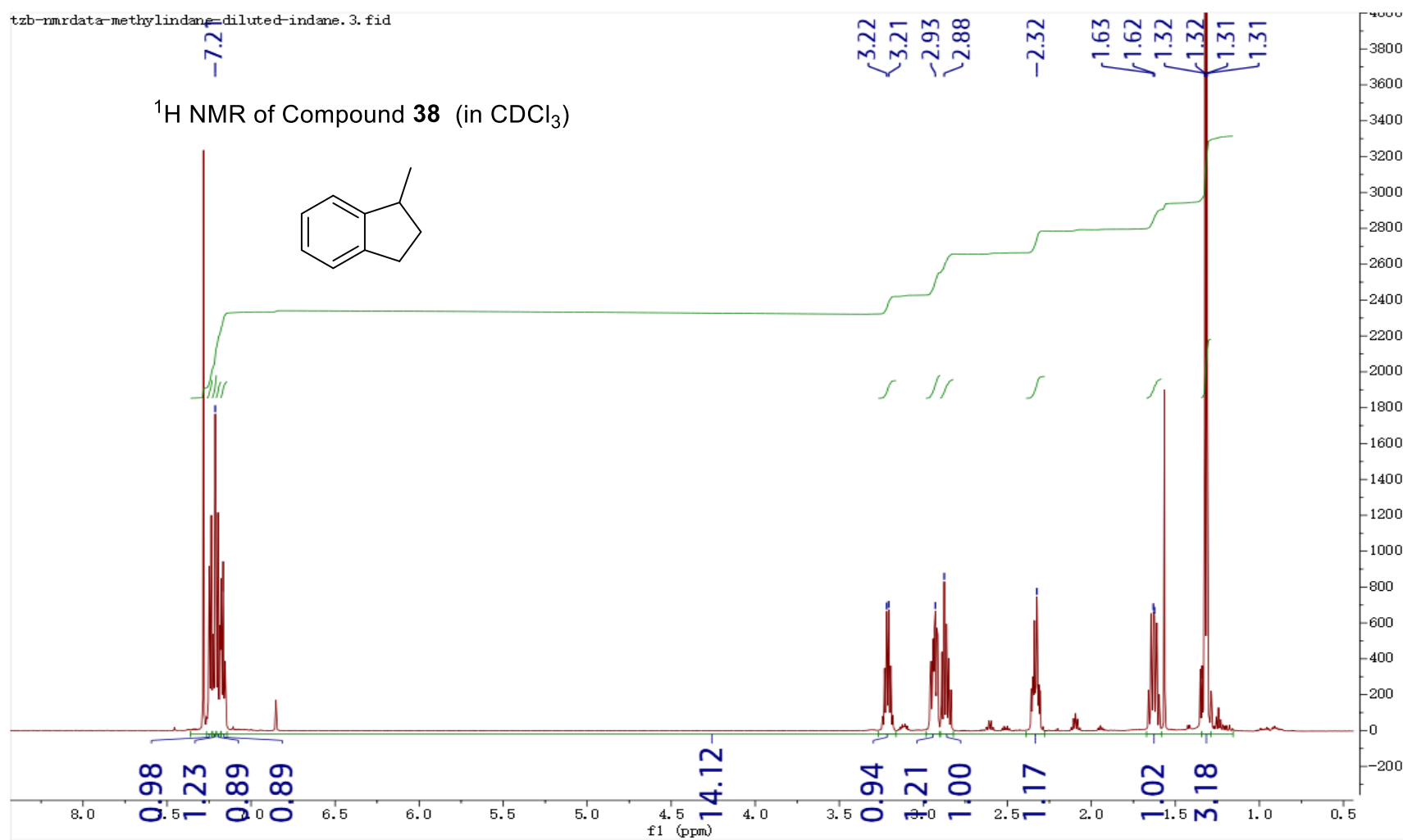
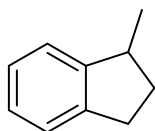


Mass spectra of Compound **36**
 ^{13}C NMR of Compound **36** (in CDCl_3)



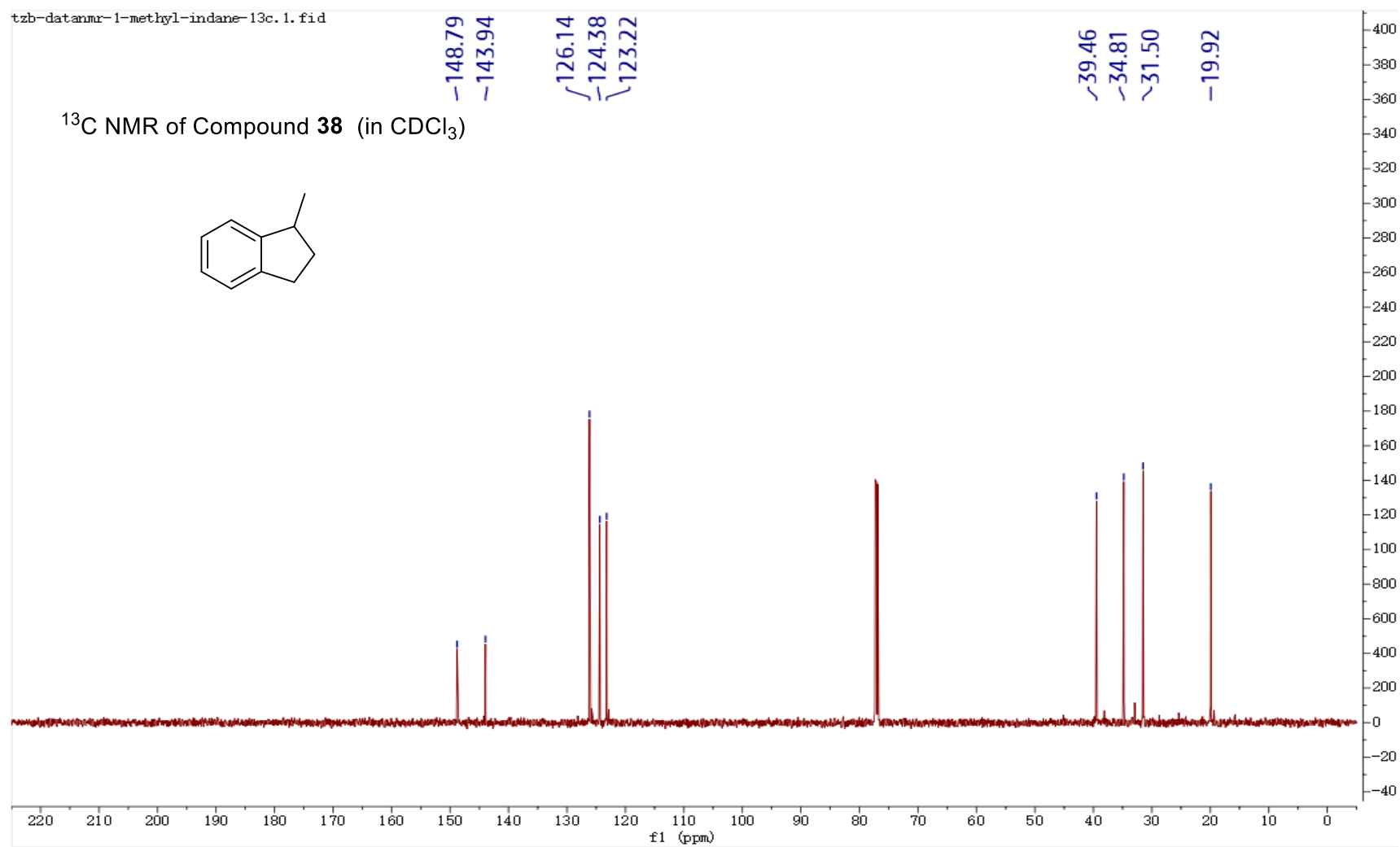
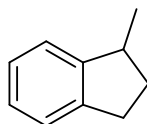
tzb-nmrdata-methylindane-diluted-indane.3.fid

¹H NMR of Compound **38** (in CDCl₃)

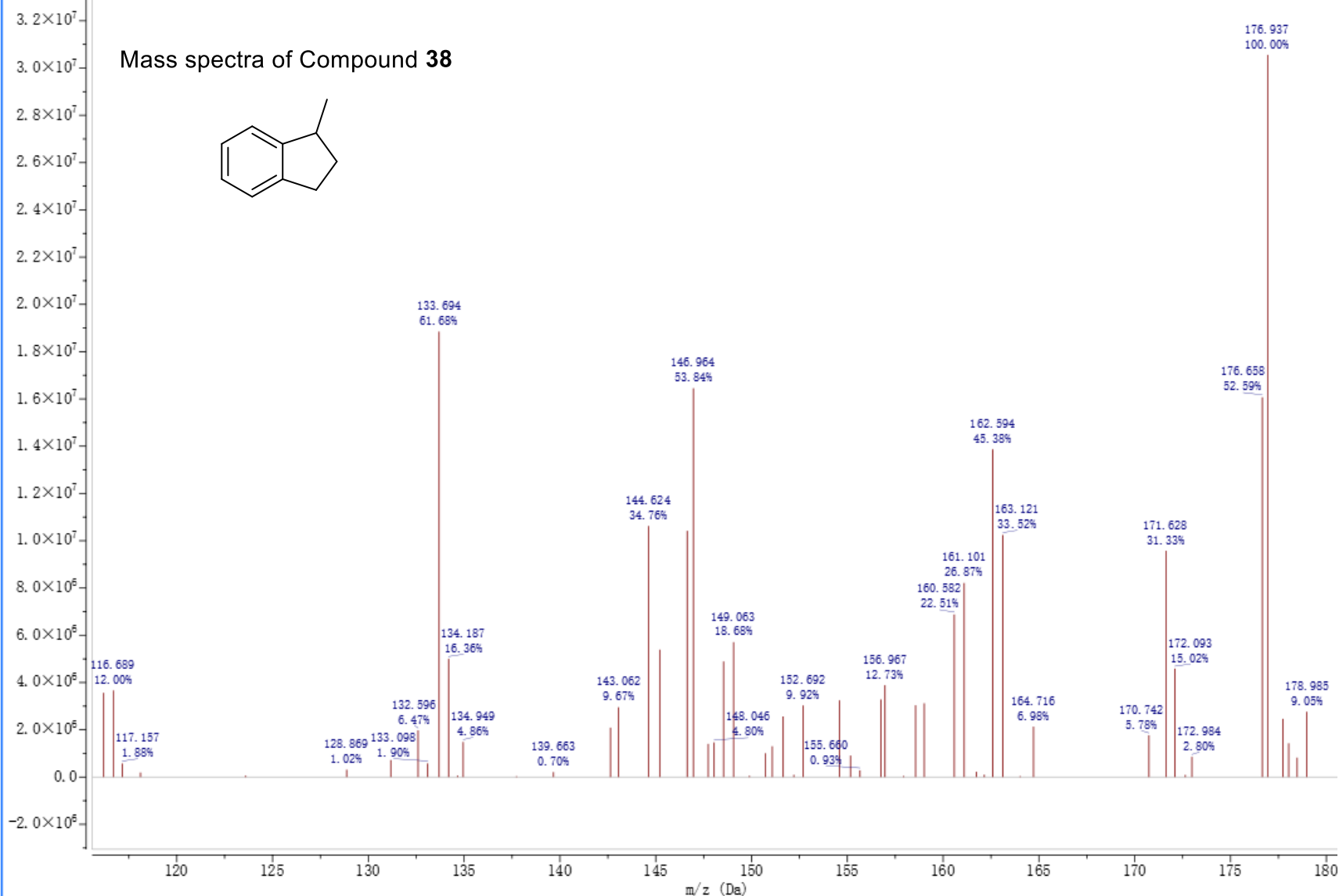
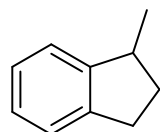


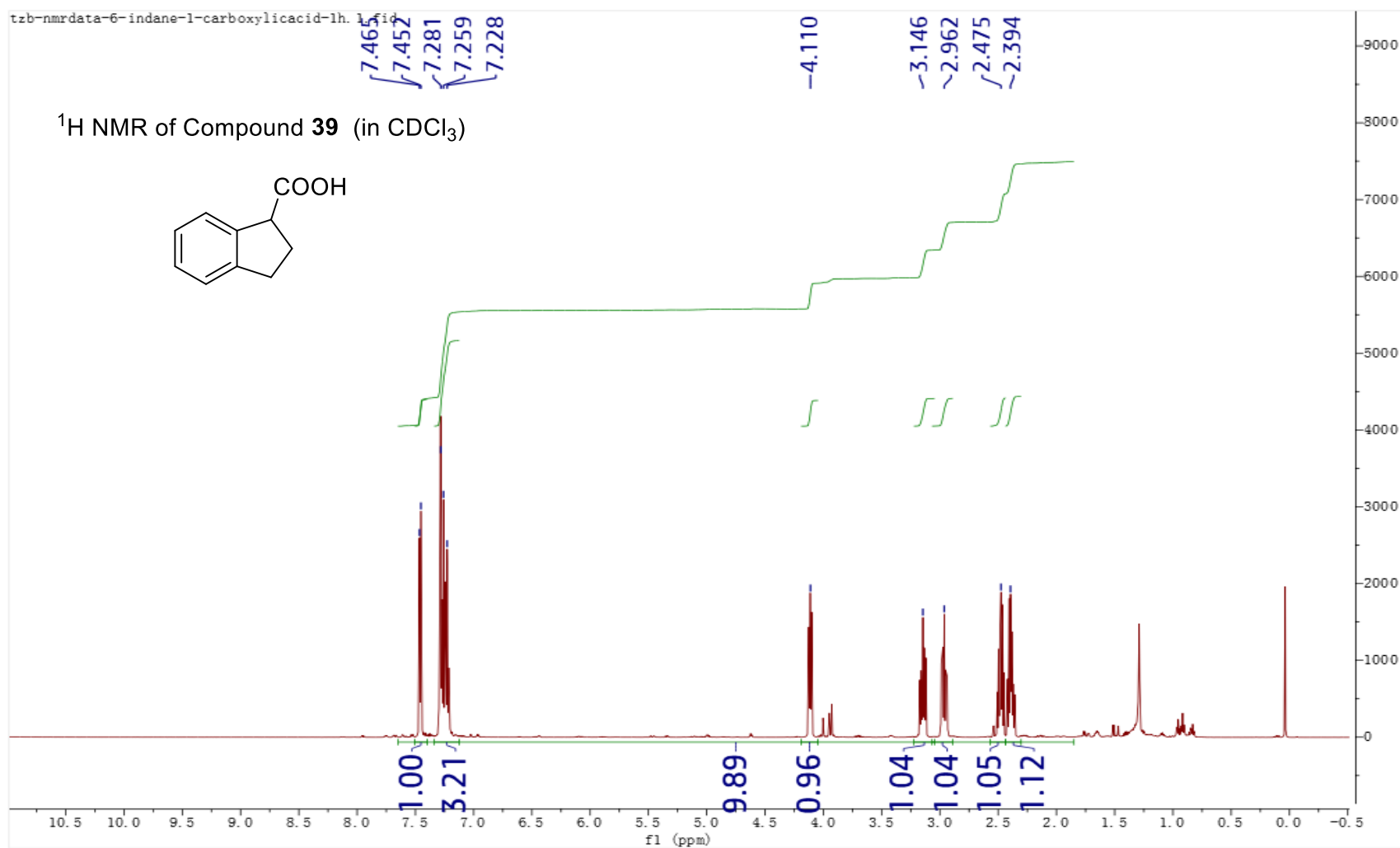
tzbdatanmr-1-methyl-indane-13c.1.fid

^{13}C NMR of Compound **38** (in CDCl_3)



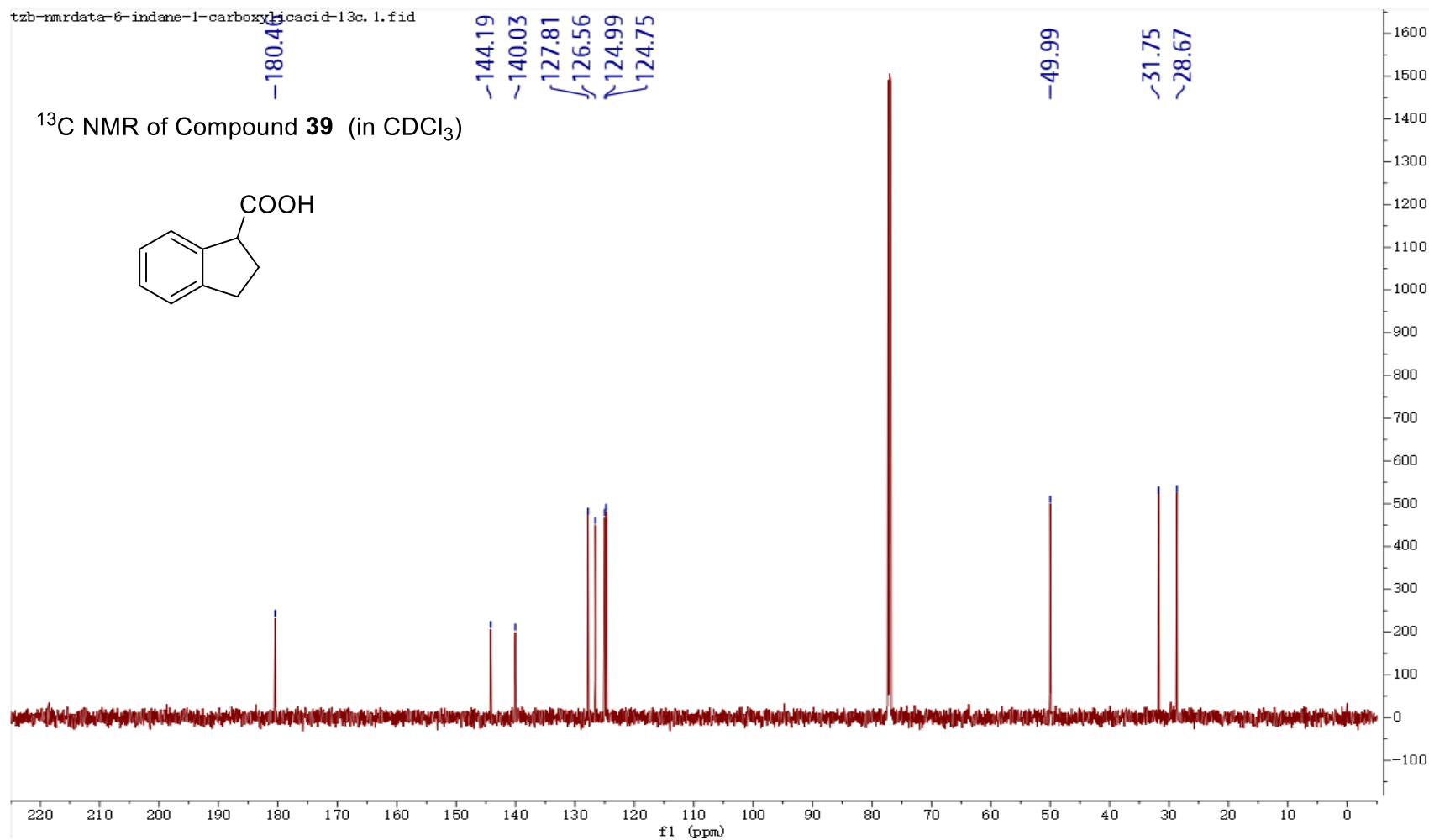
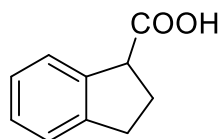
Mass spectra of Compound 38

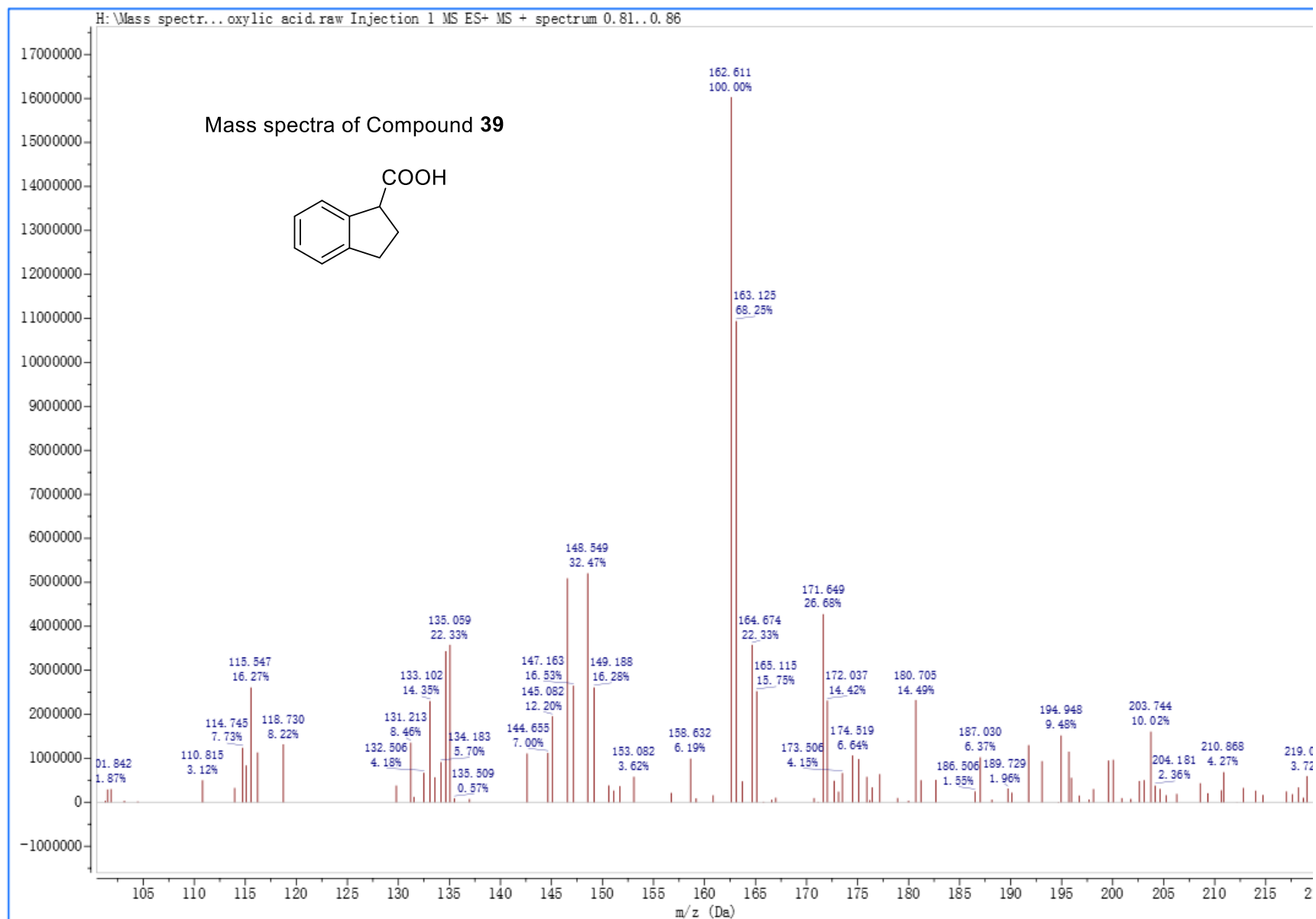




tzb-nmrdata-6-indane-1-carboxylic acid-13c.1.fid

^{13}C NMR of Compound **39** (in CDCl_3)

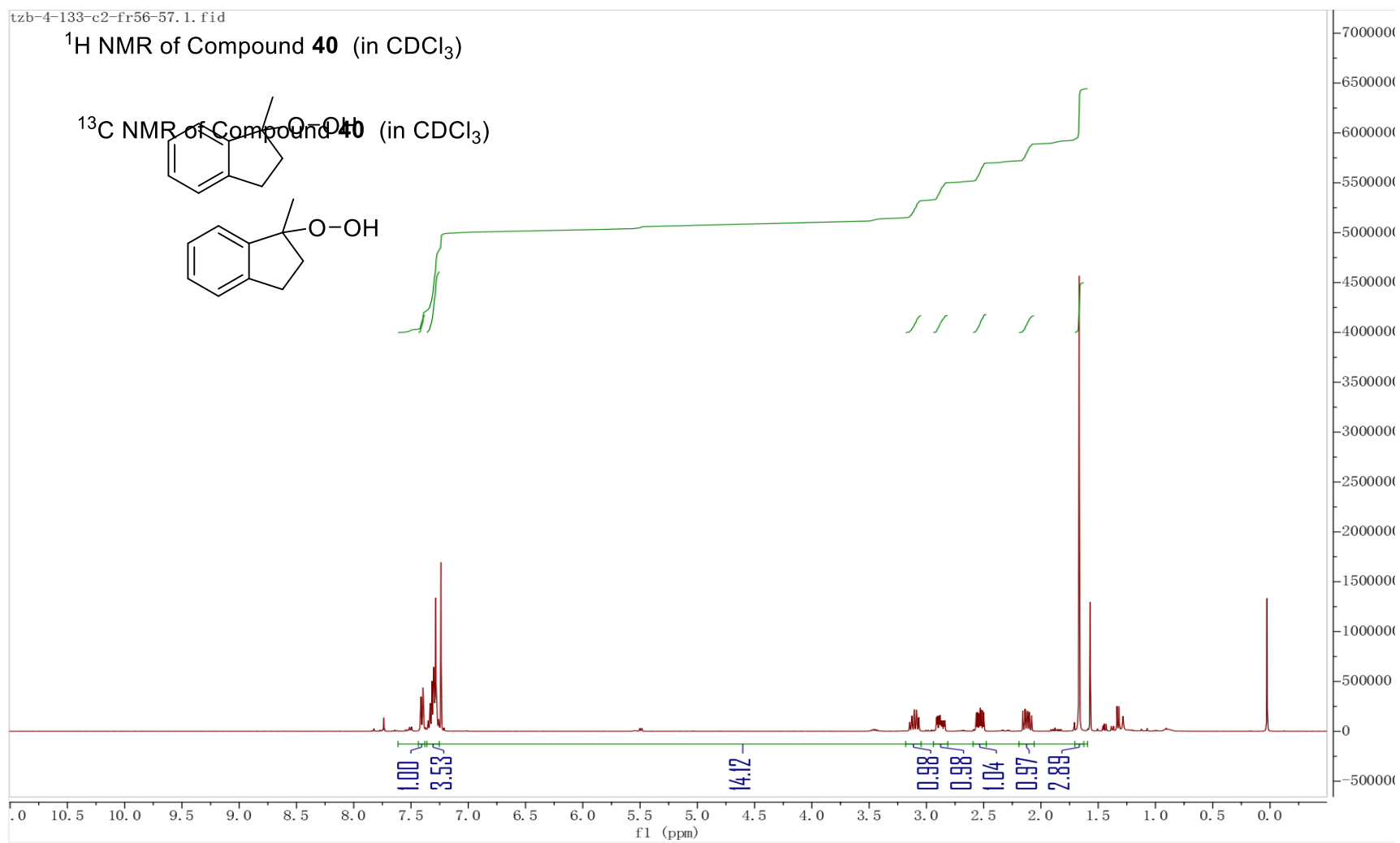
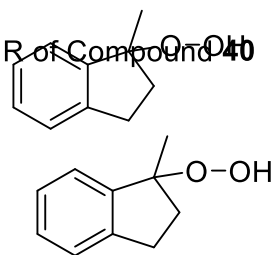


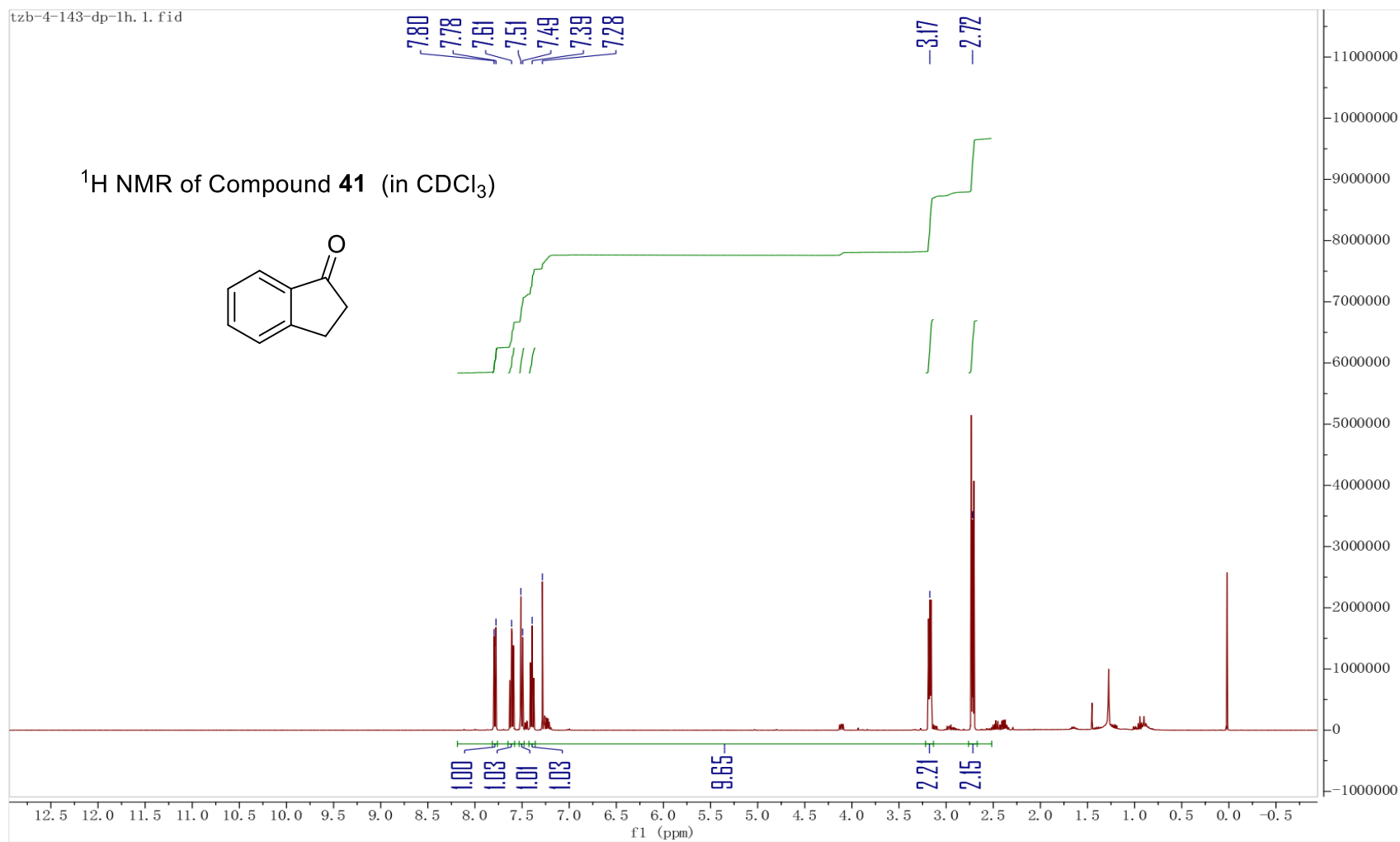


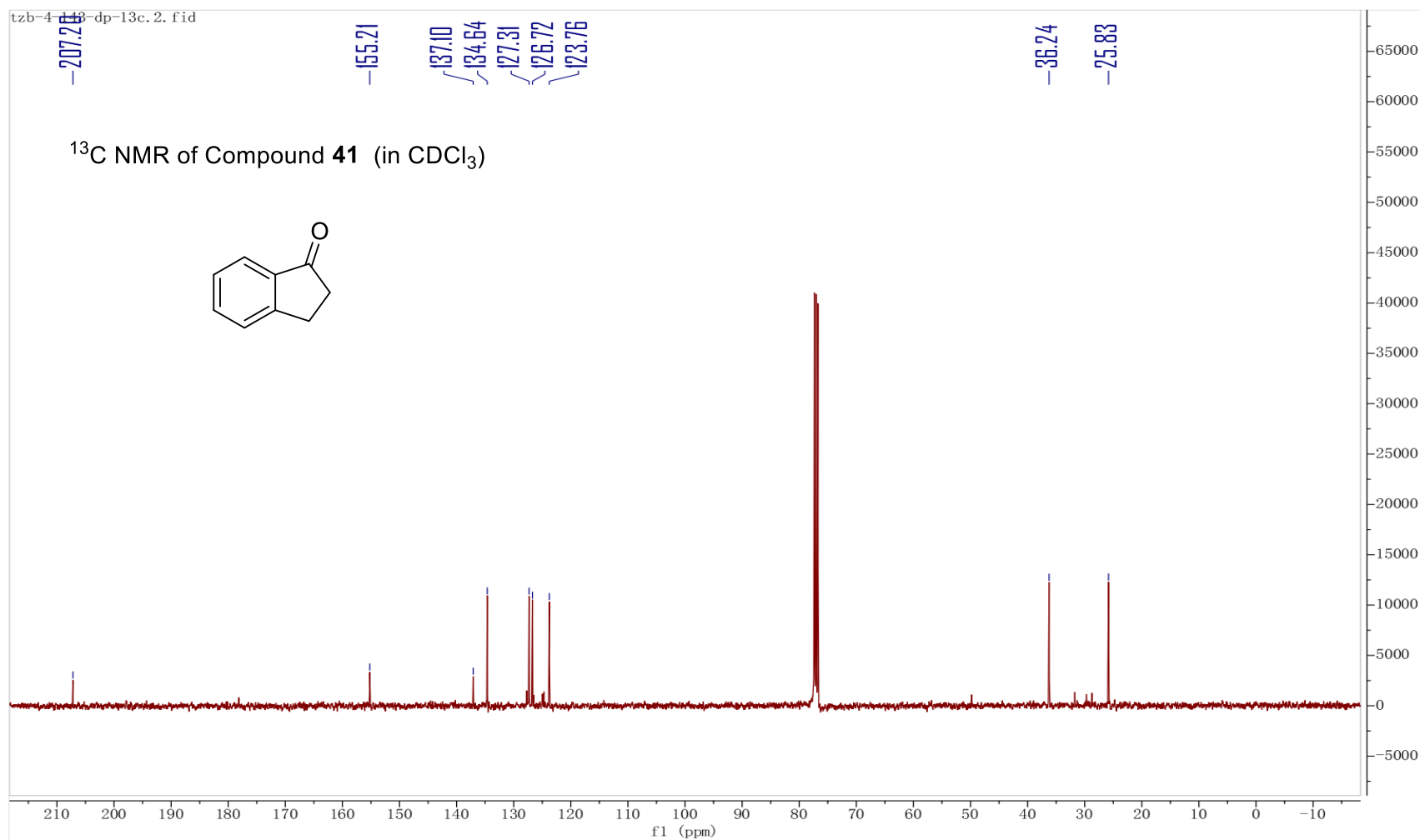
tzb-4-133-c2-fr56-57.1.fid

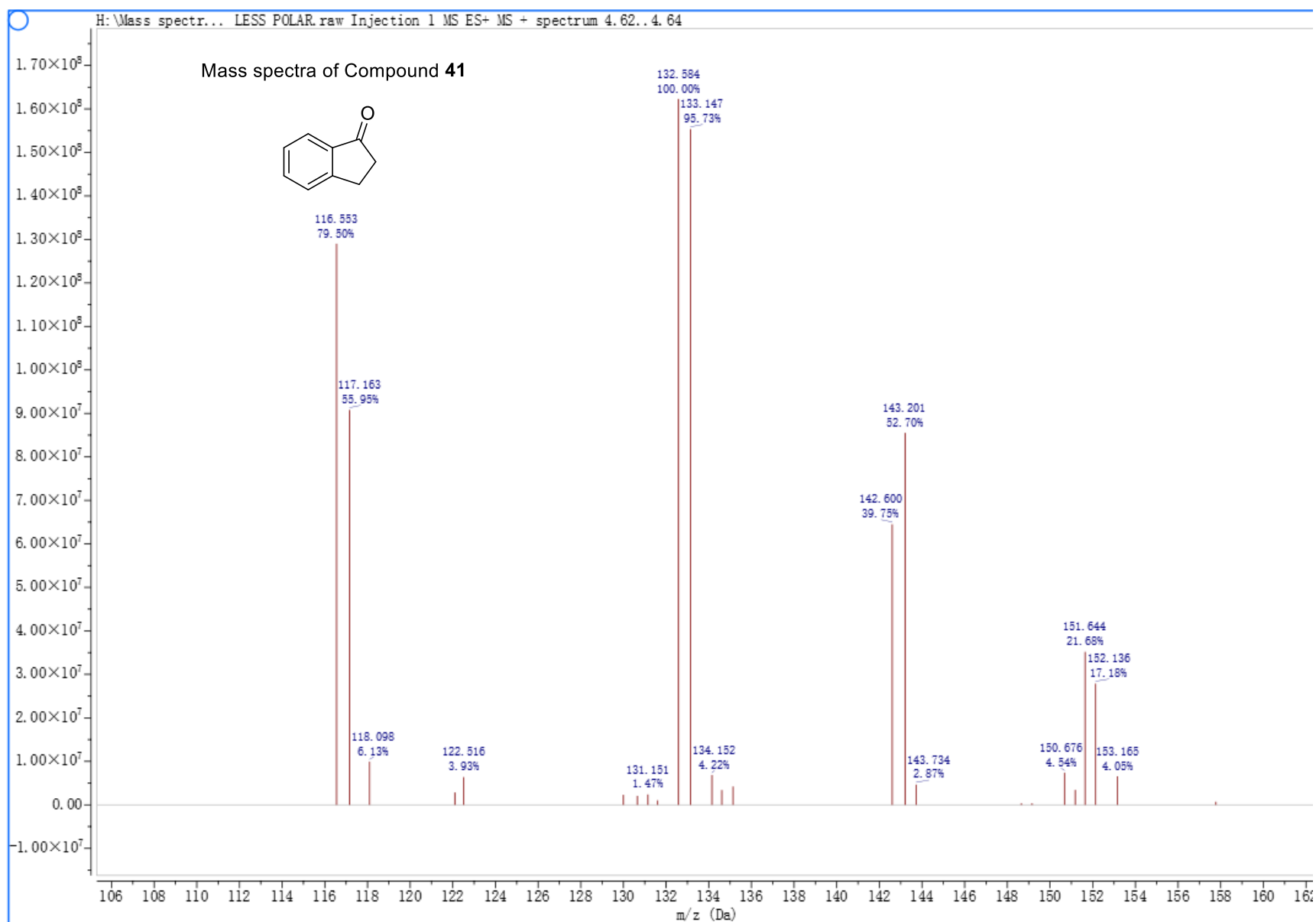
^1H NMR of Compound **40** (in CDCl_3)

^{13}C NMR of Compound **40** (in CDCl_3)

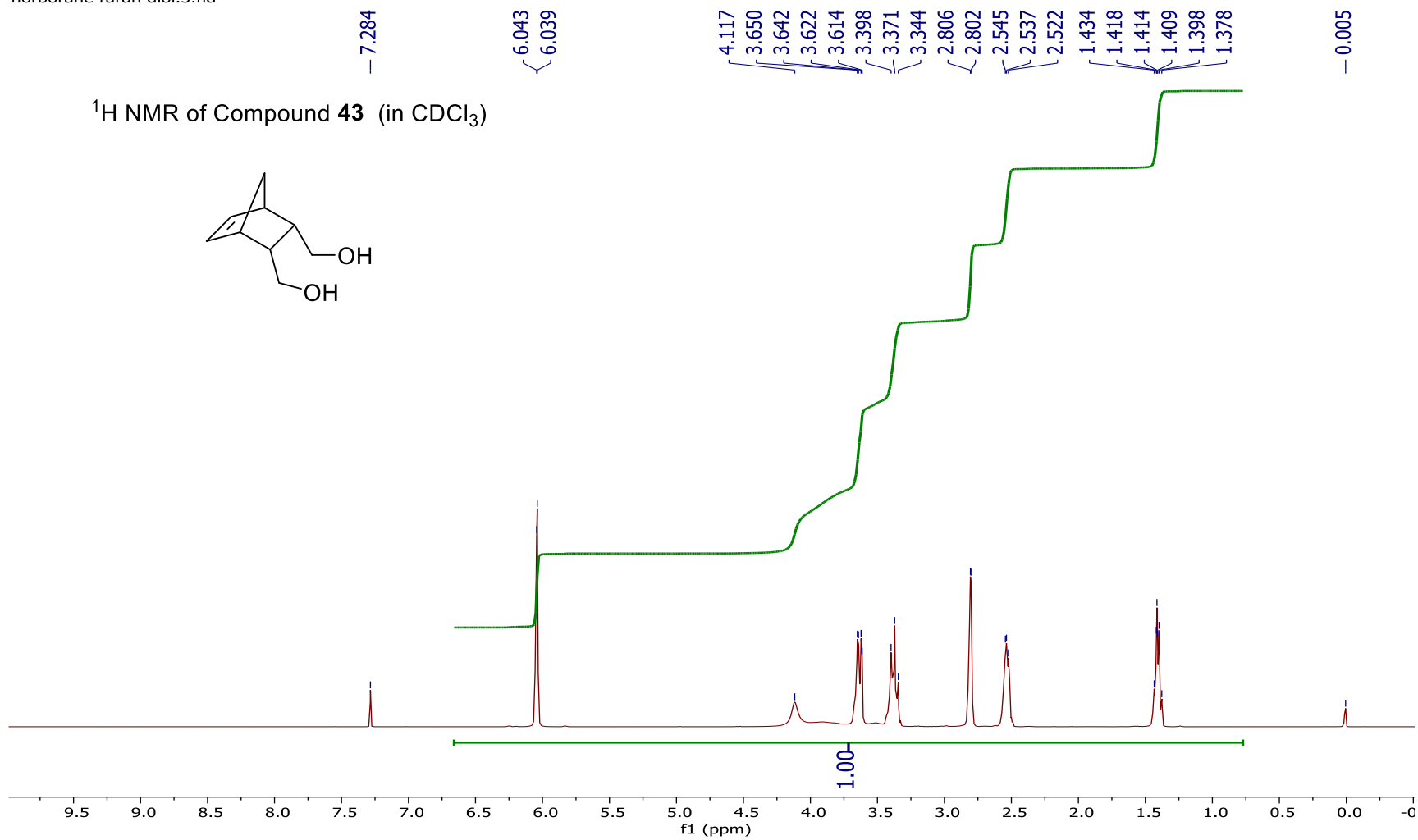






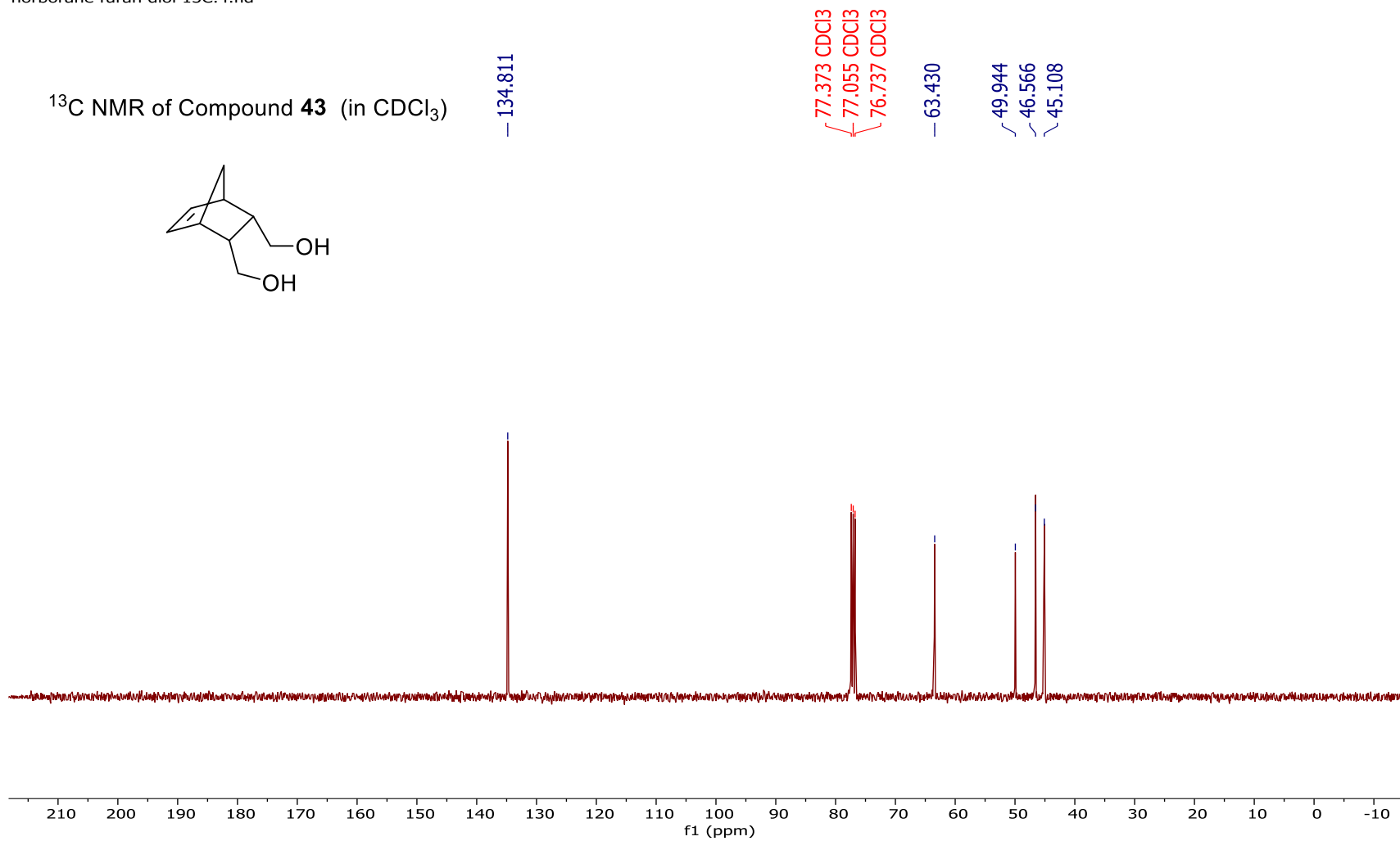
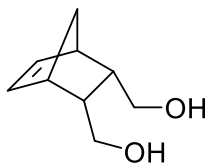


norborane furan diol.3.fid

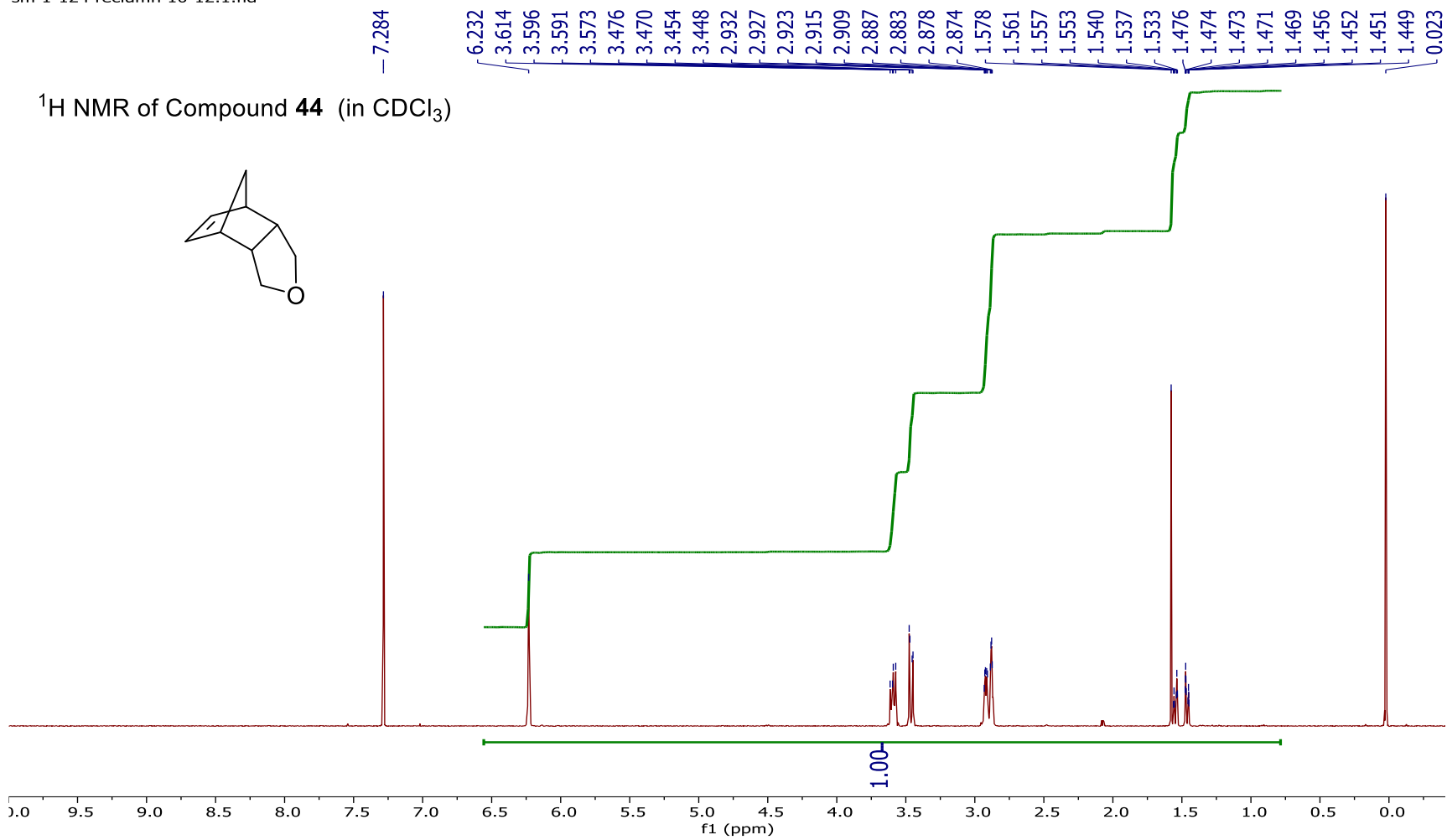


norborane furan diol 13C.4.fid

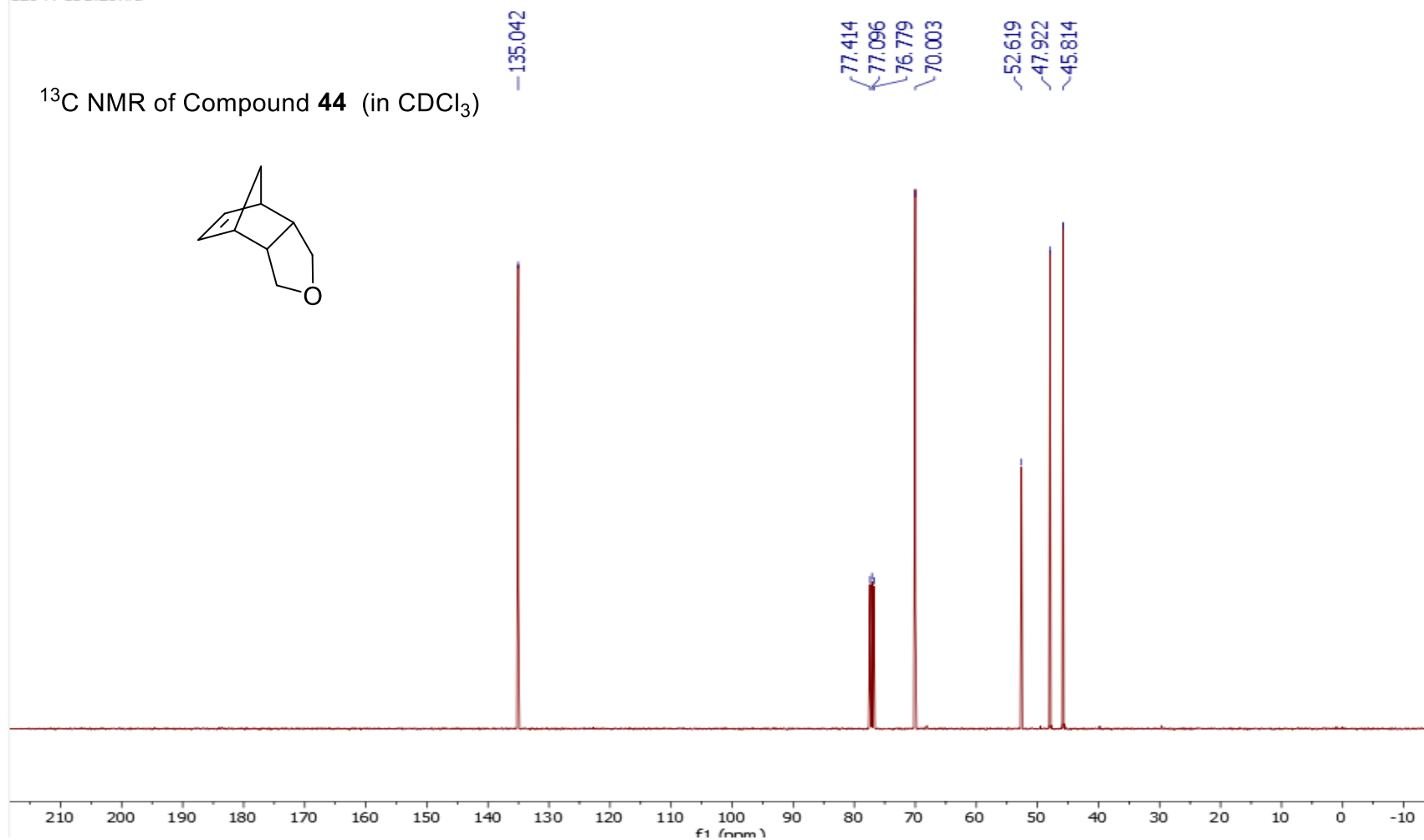
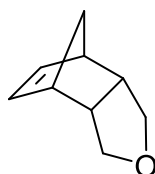
^{13}C NMR of Compound **43** (in CDCl_3)



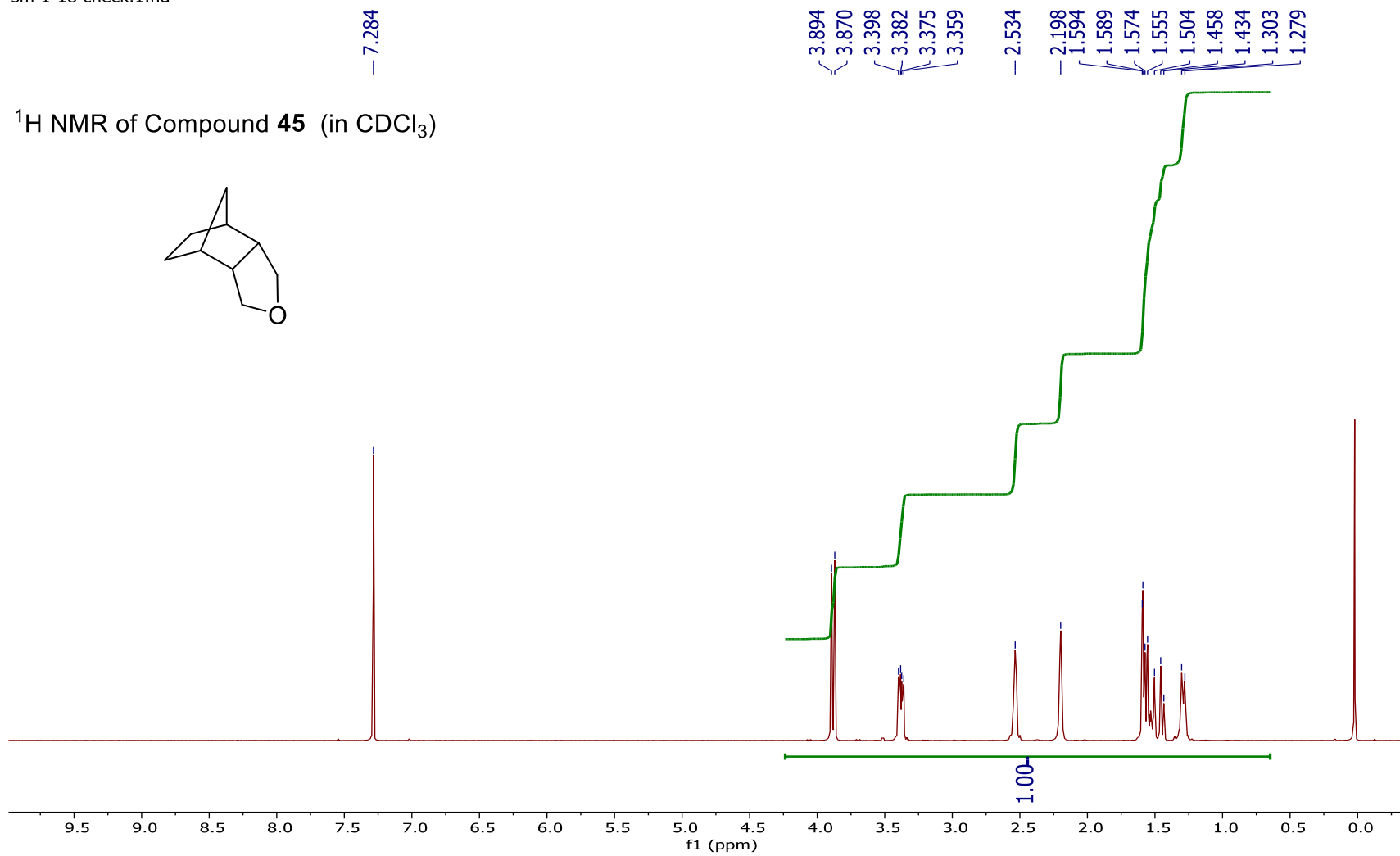
sm 1-124 reclusm 10-12.1.fid



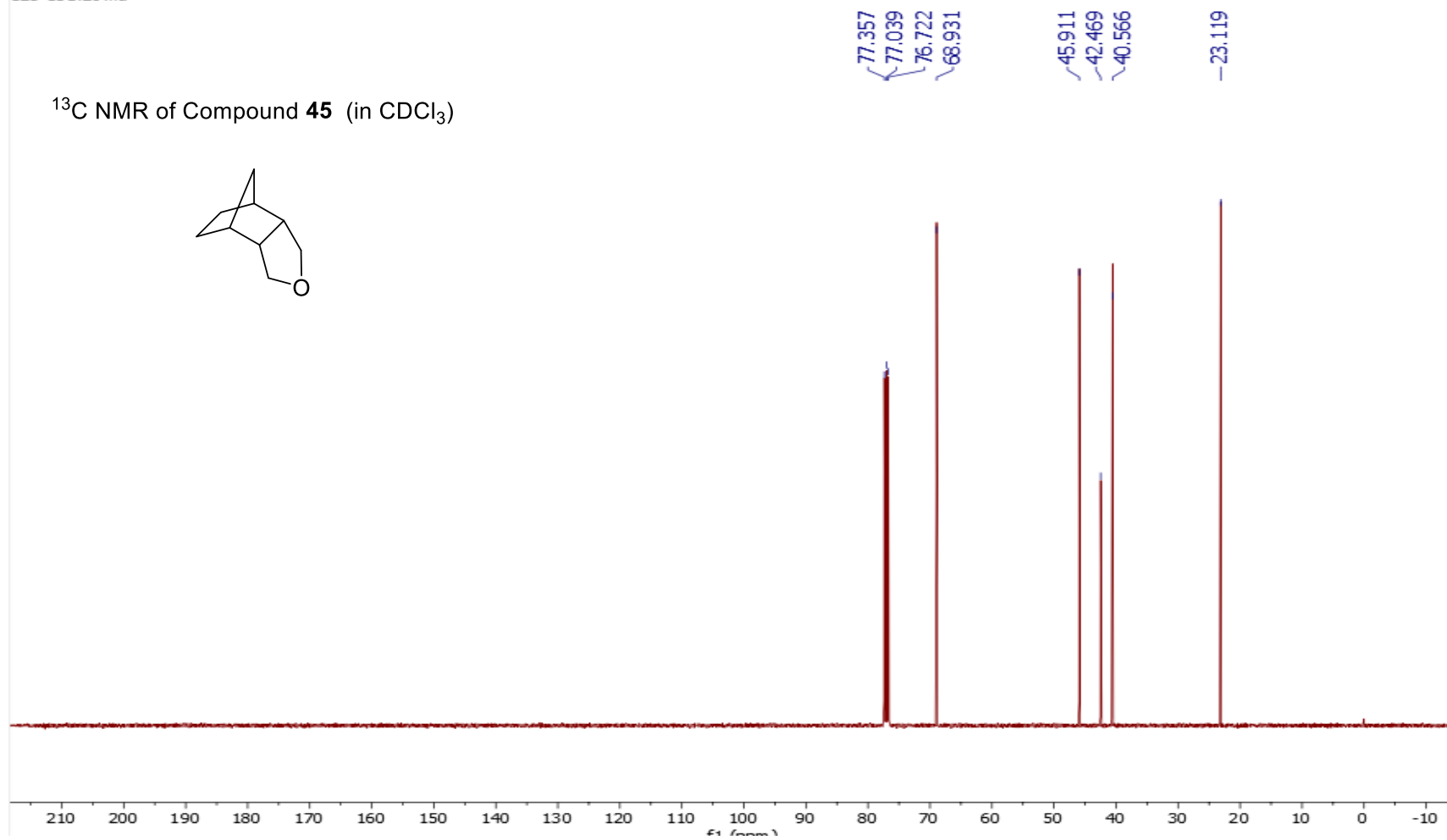
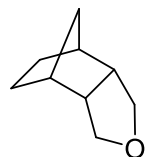
^{13}C NMR of Compound **44** (in CDCl_3)



sm 1-18 check.1.fid

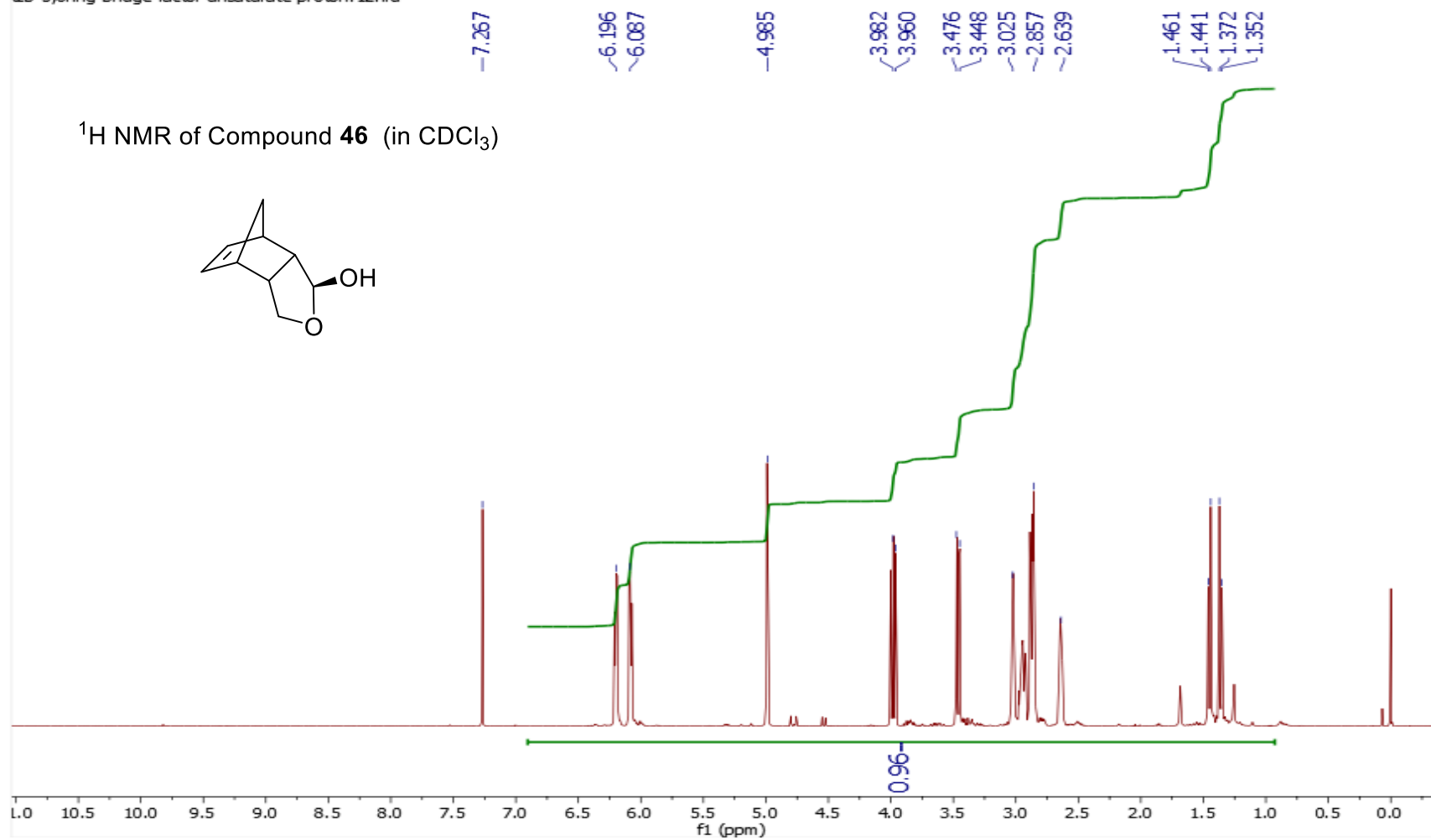
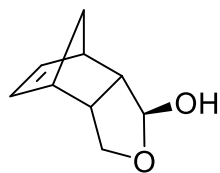


^{13}C NMR of Compound **45** (in CDCl_3)

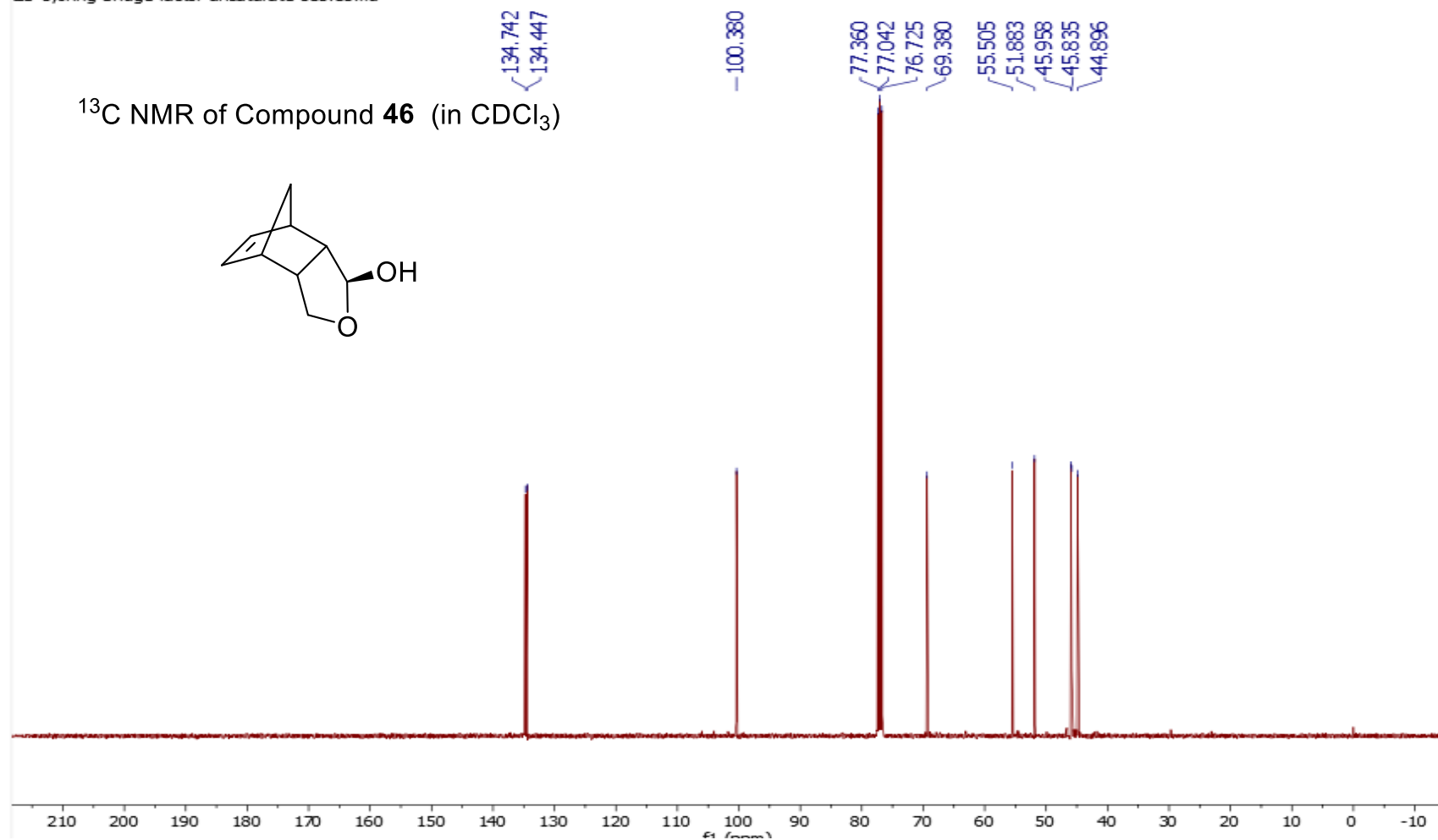
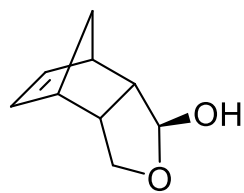


tzb-5,6ring-bridge-lactol-unsaturate-proton. 12.fid

^1H NMR of Compound **46** (in CDCl_3)

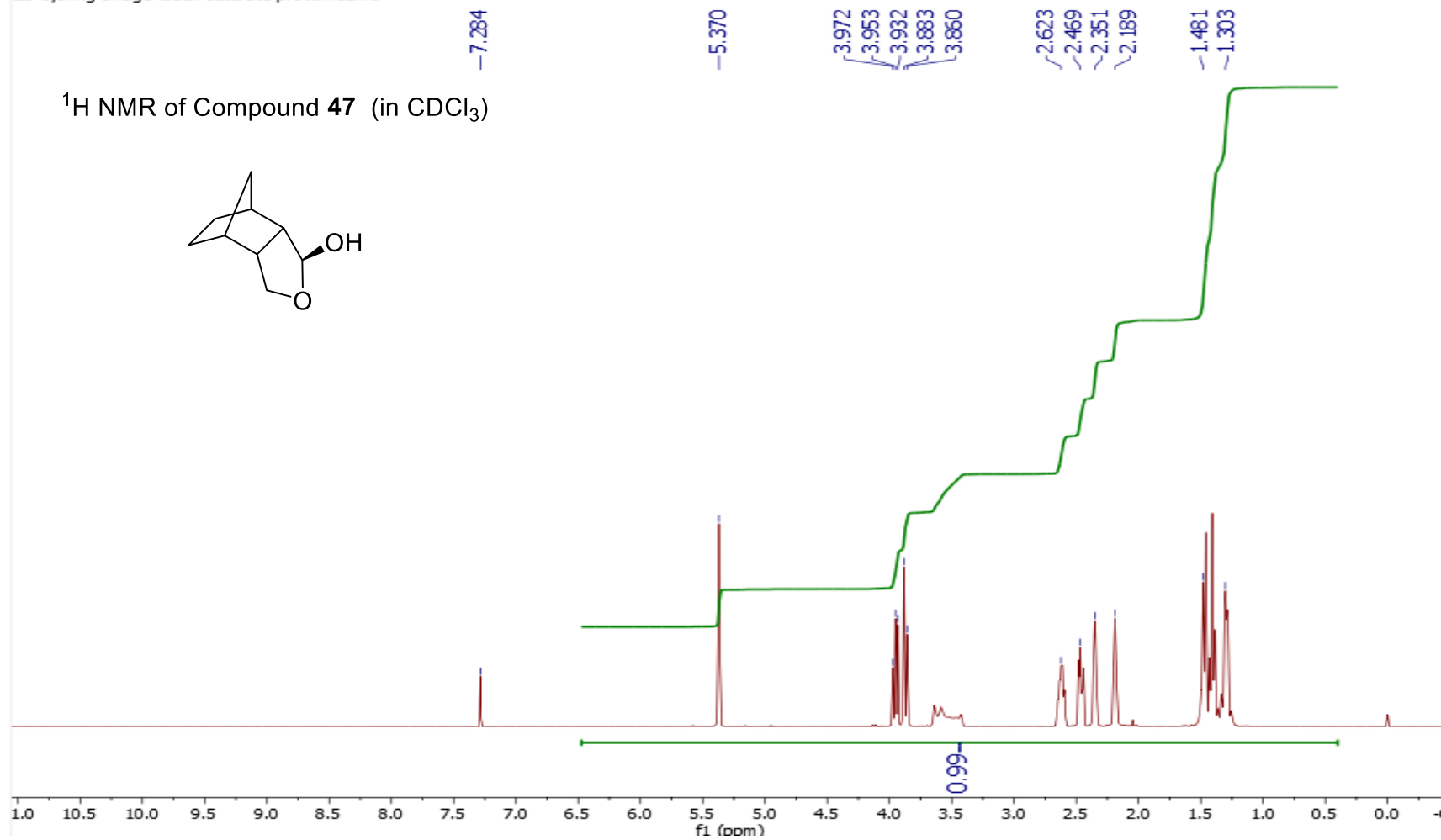
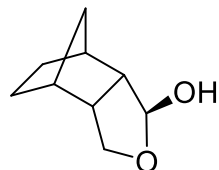


^{13}C NMR of Compound **46** (in CDCl_3)



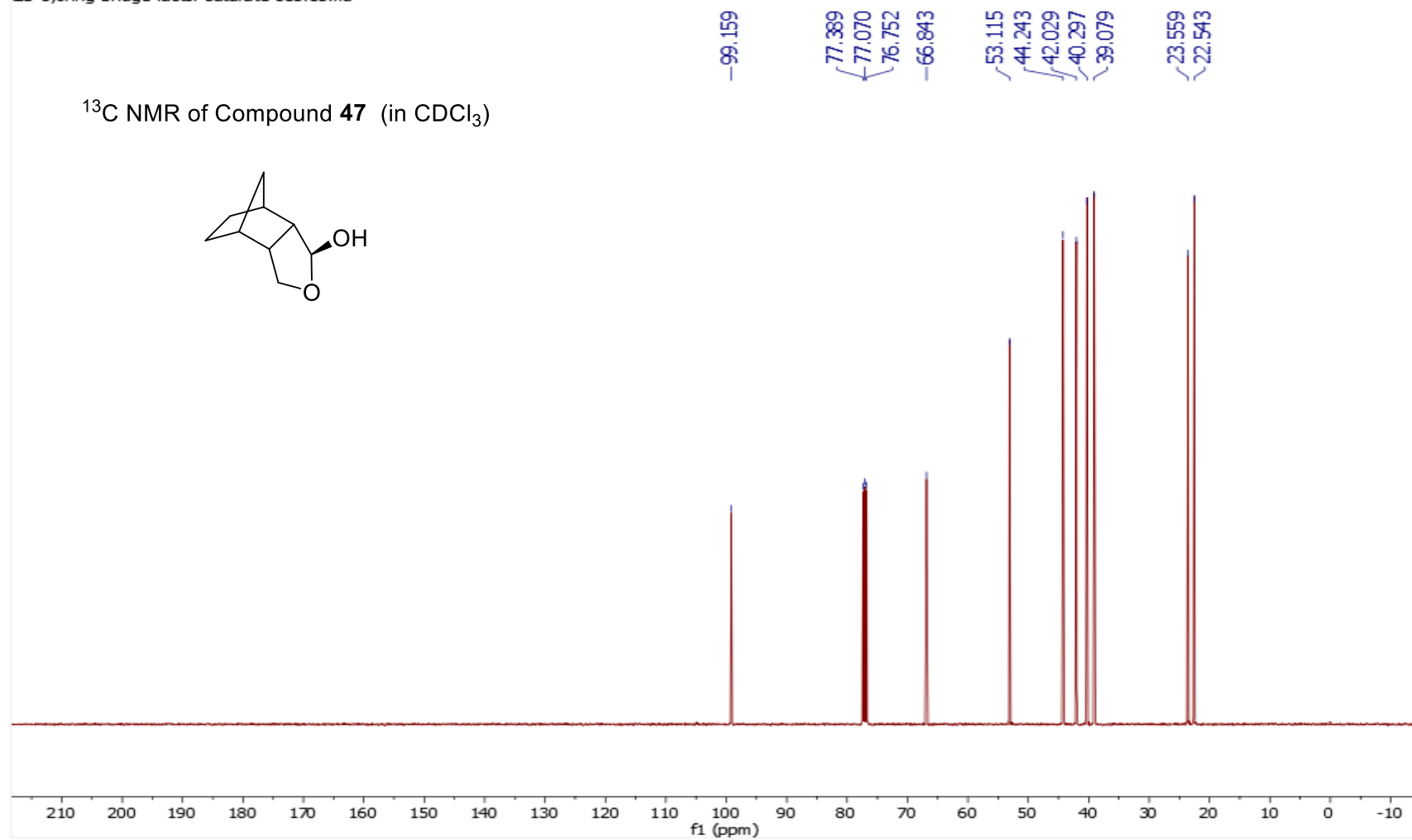
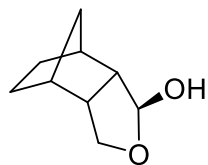
tzb-5,6ring-bridge-lactol-saturate-proton.12.fid

^1H NMR of Compound **47** (in CDCl_3)



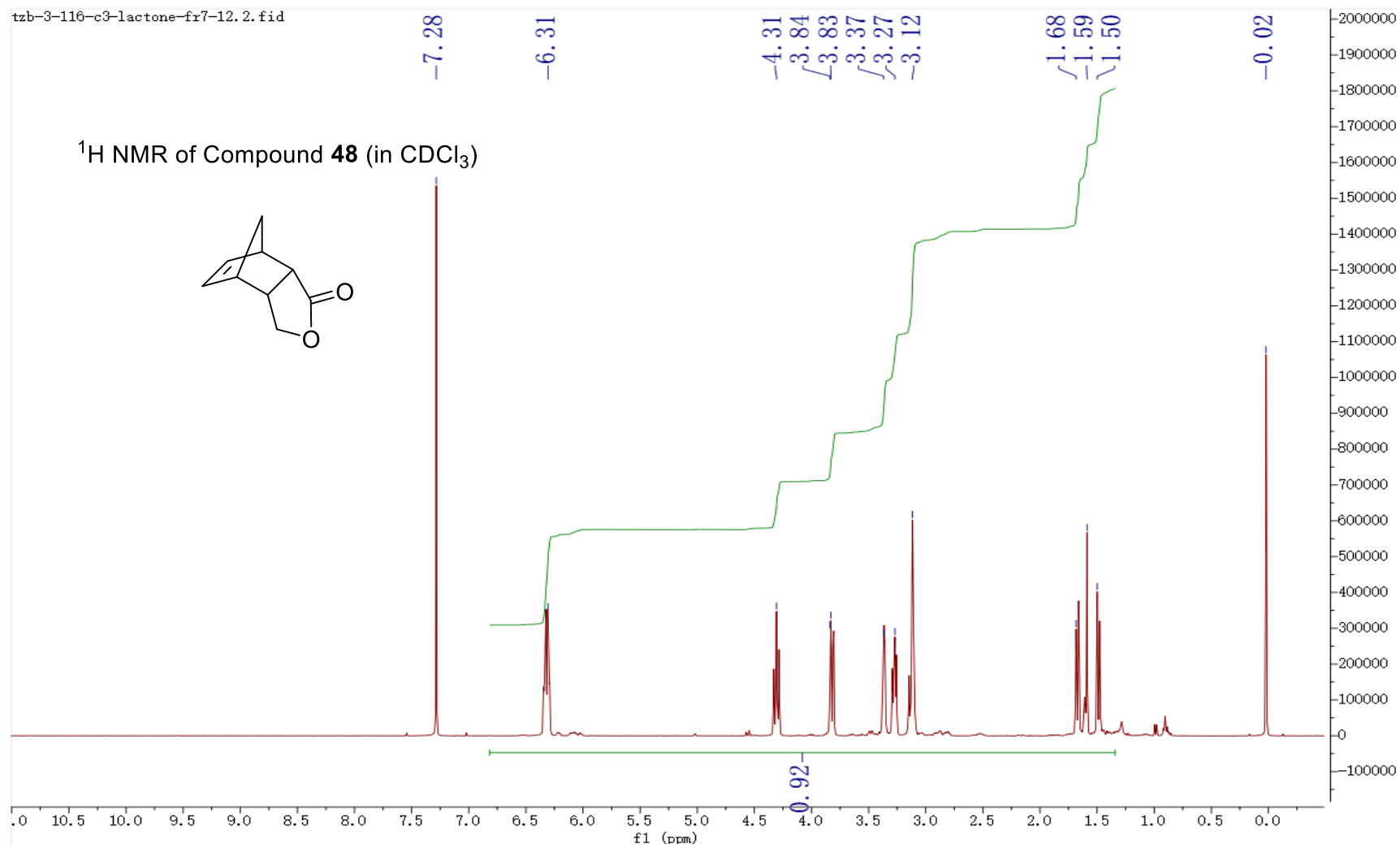
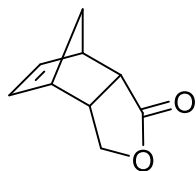
tzb-5,6ring-bridge-lactol-saturate-c13.13.fid

^{13}C NMR of Compound **47** (in CDCl_3)



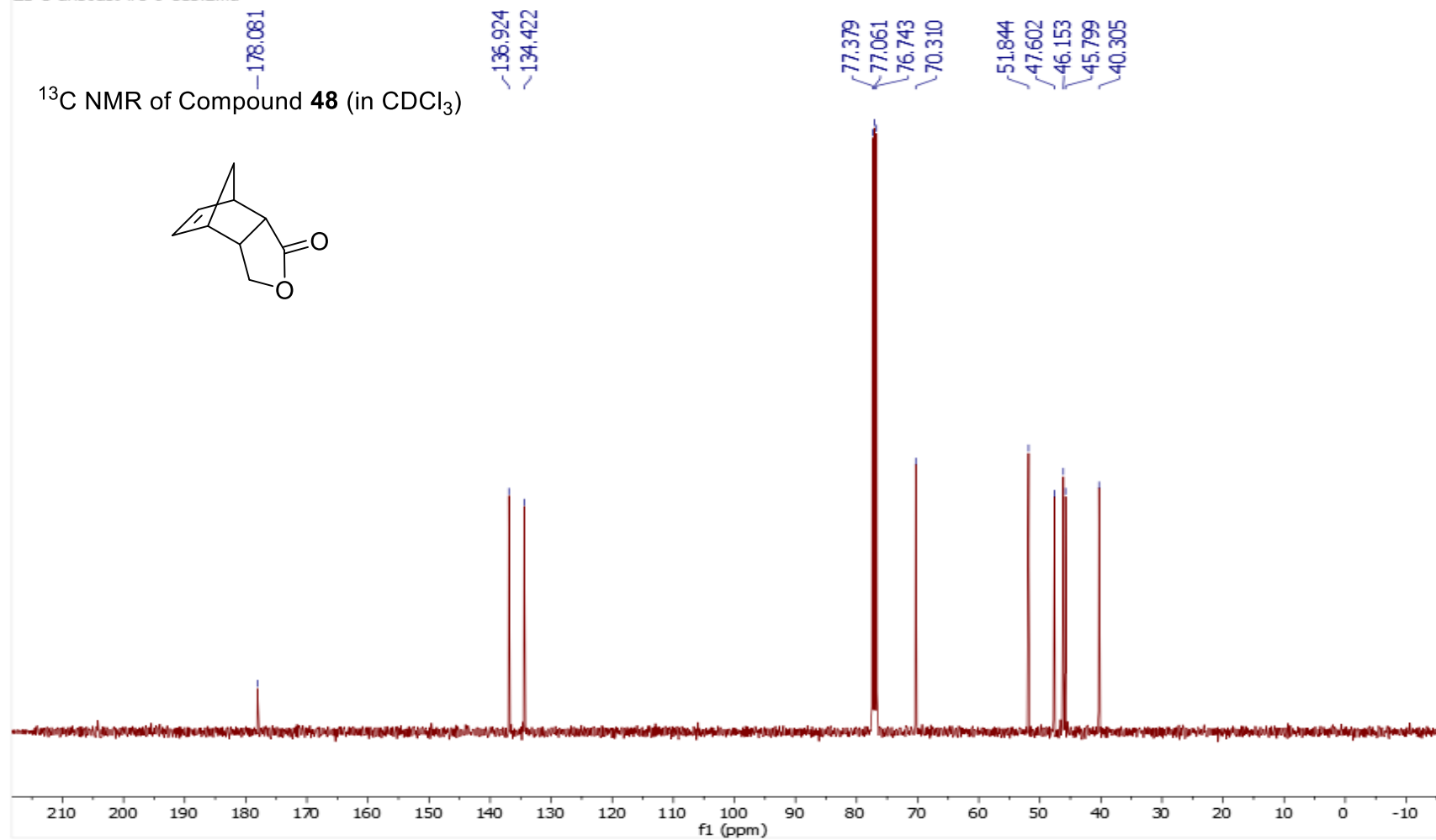
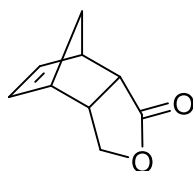
tzb-3-116-c3-lactone-fr7-12.2.fid

¹H NMR of Compound **48** (in CDCl₃)



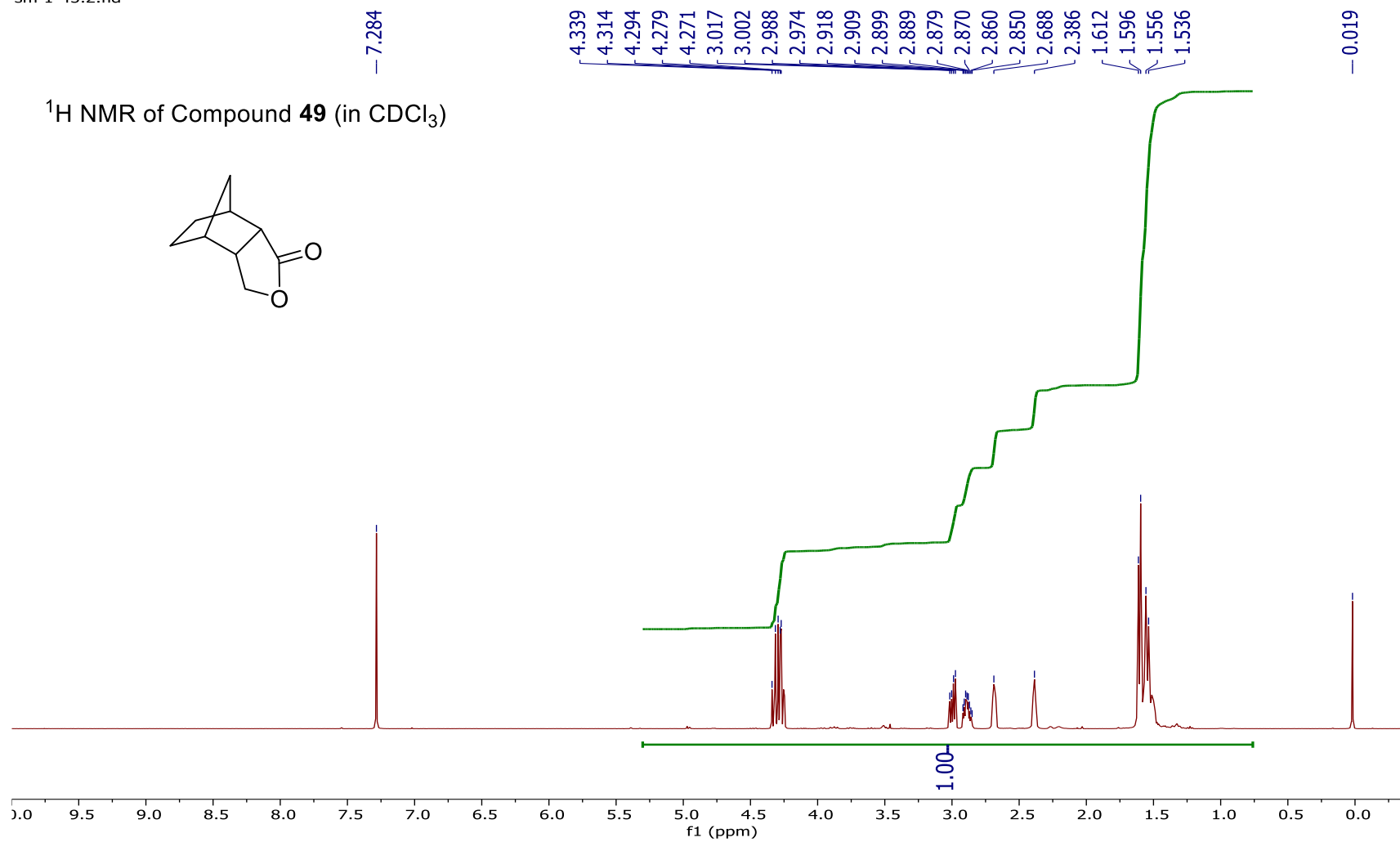
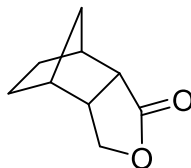
tzb-3-unstlact-fr8-9-c13.2.fid

^{13}C NMR of Compound **48** (in CDCl_3)



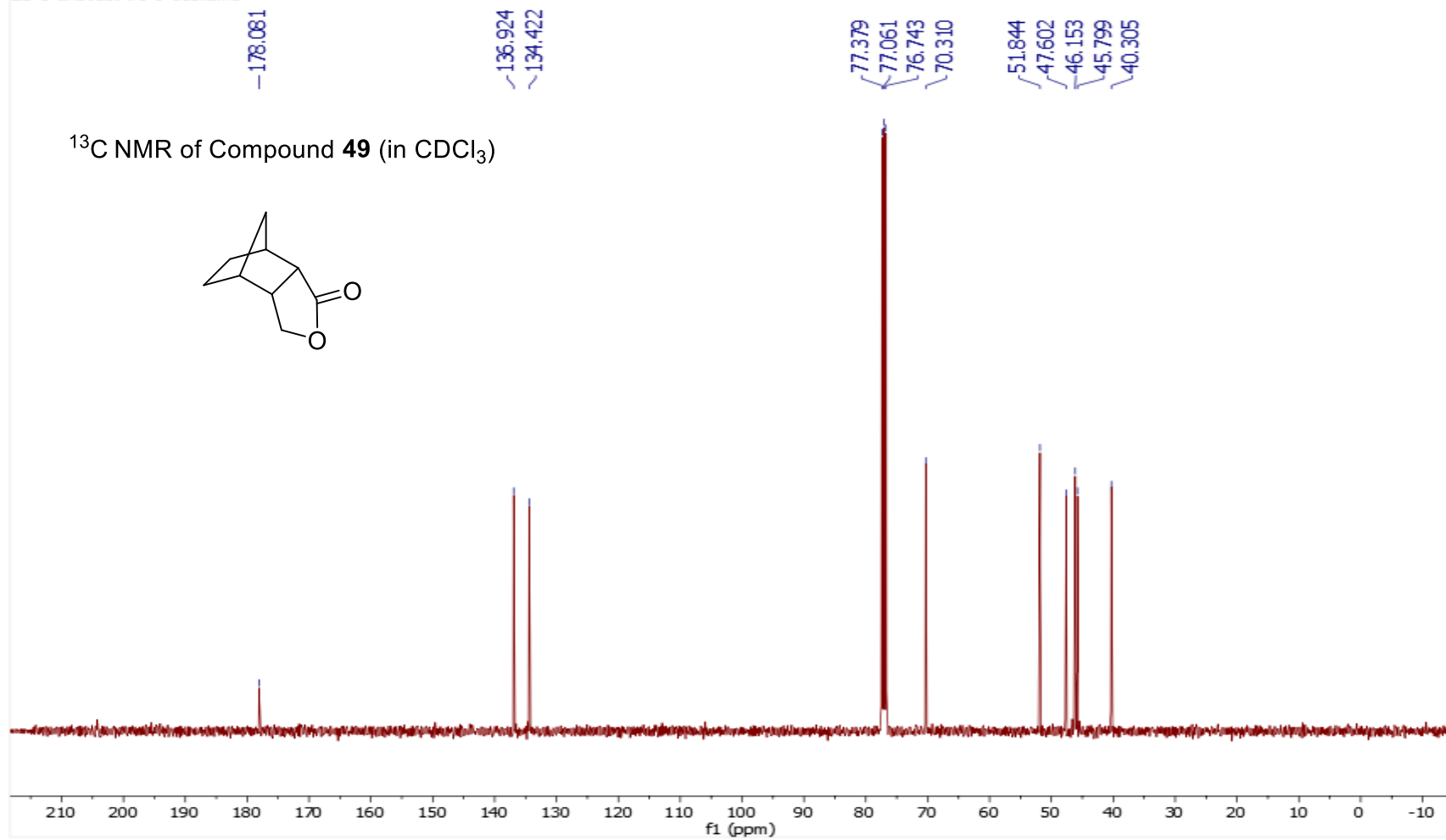
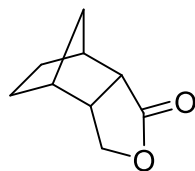
sm 1-45.2.fid

^1H NMR of Compound **49** (in CDCl_3)

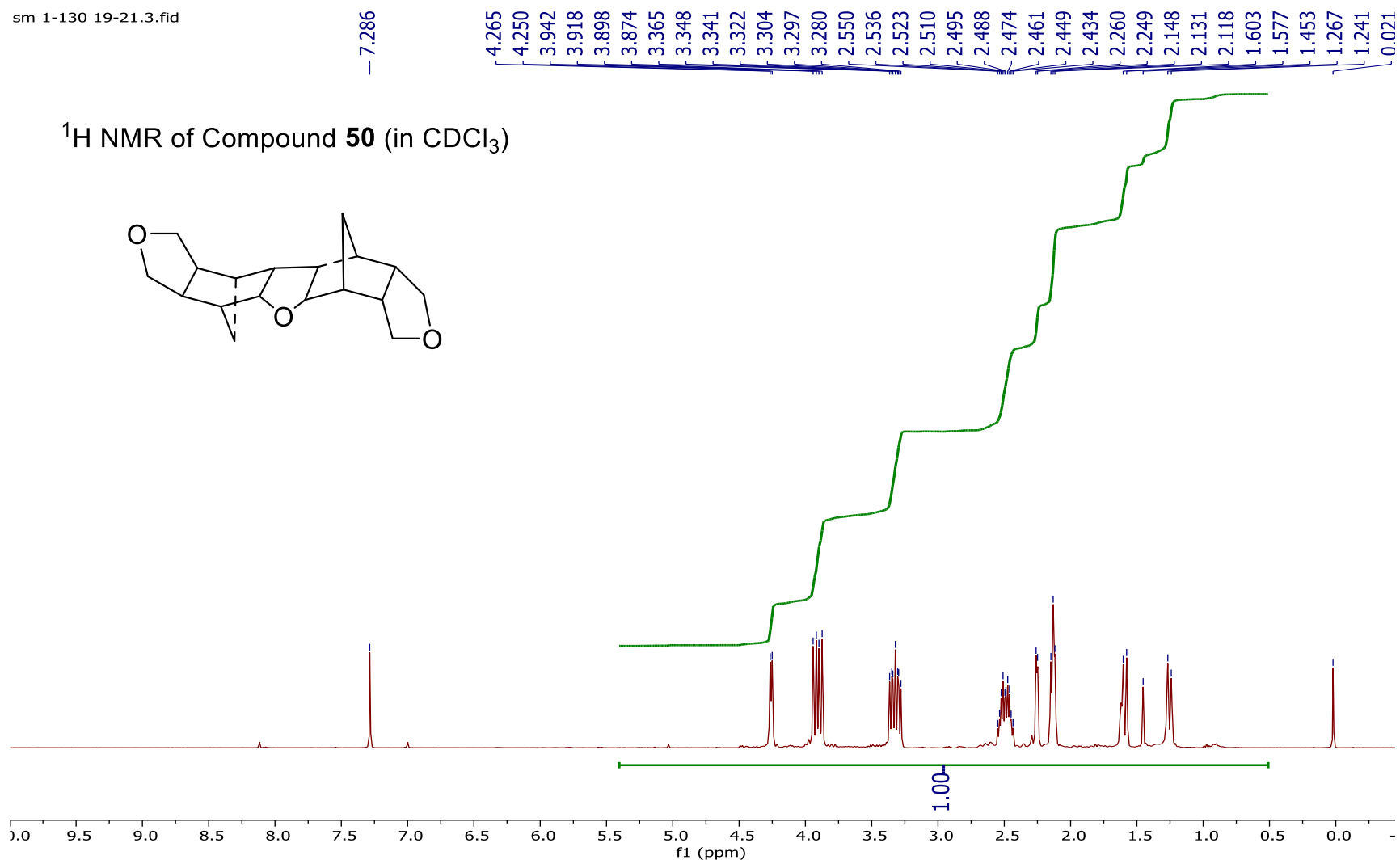


tzb-3-unstlact-fr8-9-c13.2.fid

^{13}C NMR of Compound **49** (in CDCl_3)

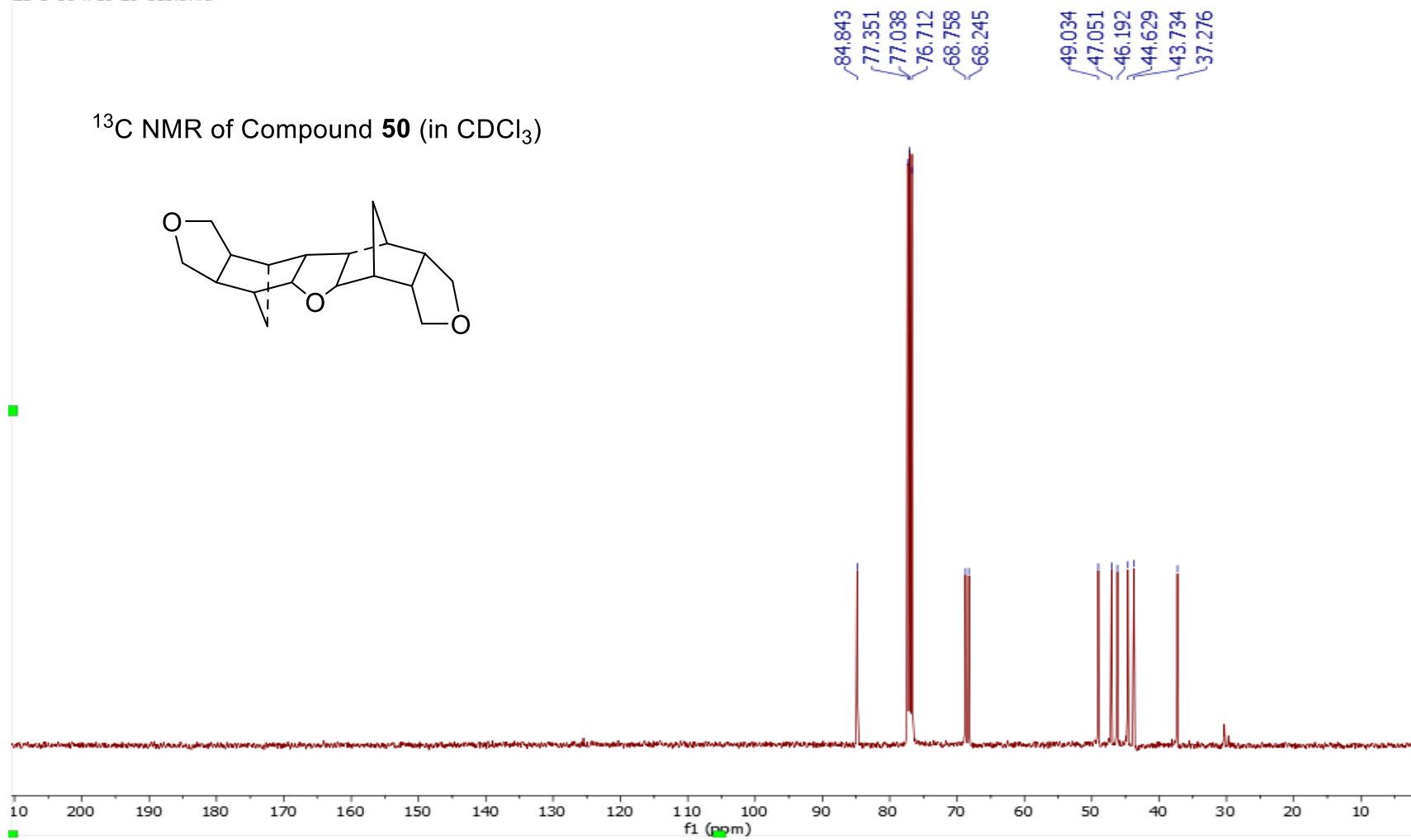
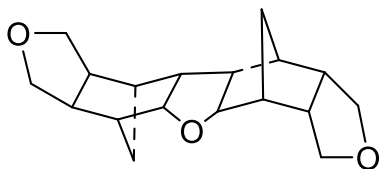


sm 1-130 19-21.3.fid



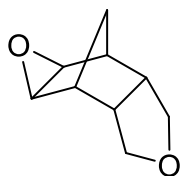
zb-3-86-fr 16-20 -c13.3.fid

^{13}C NMR of Compound **50** (in CDCl_3)

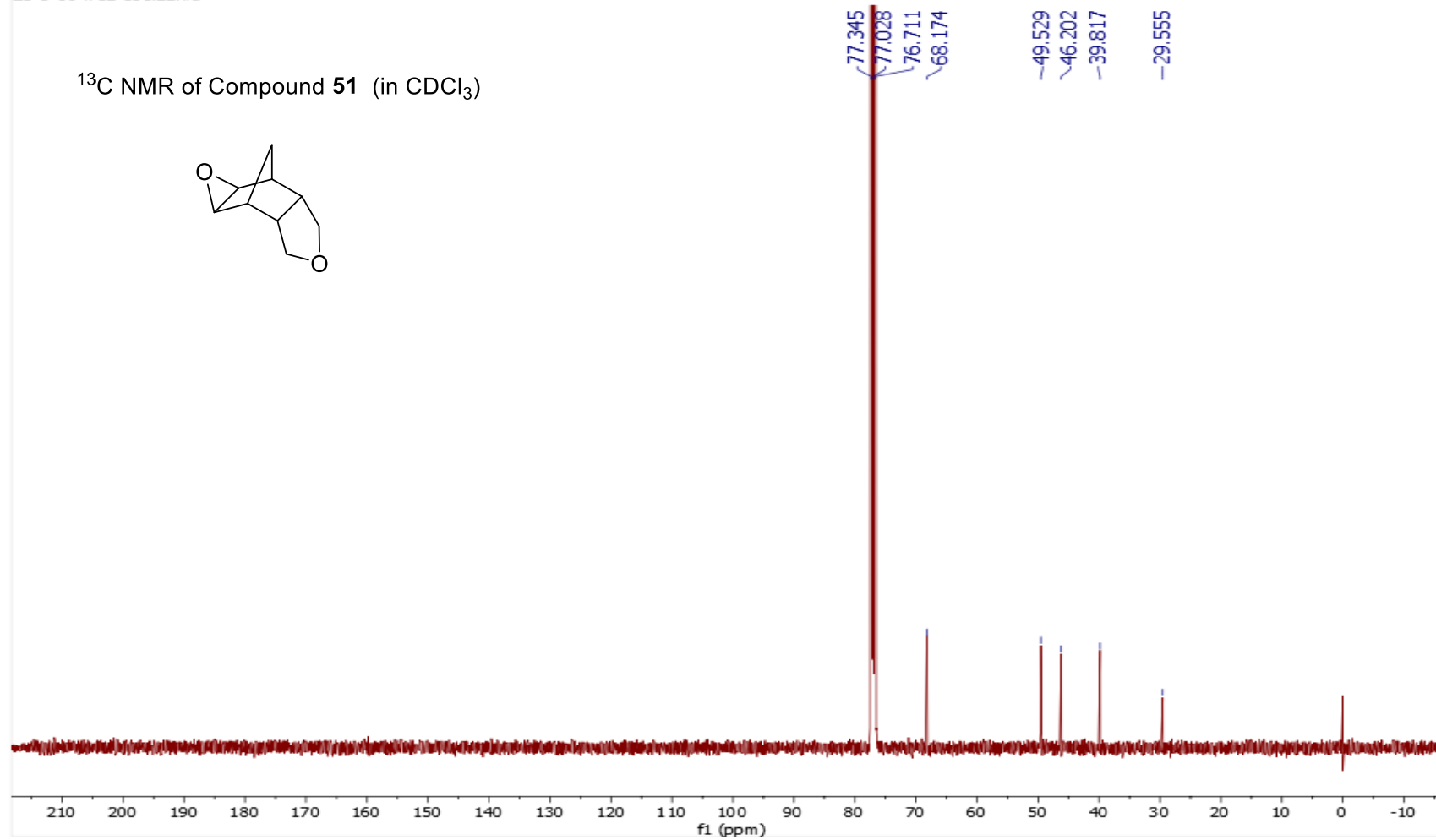
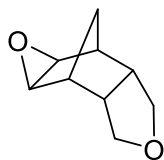


tzb-3-86-fr 12.10.fid

^1H NMR of Compound **51** (in CDCl_3)

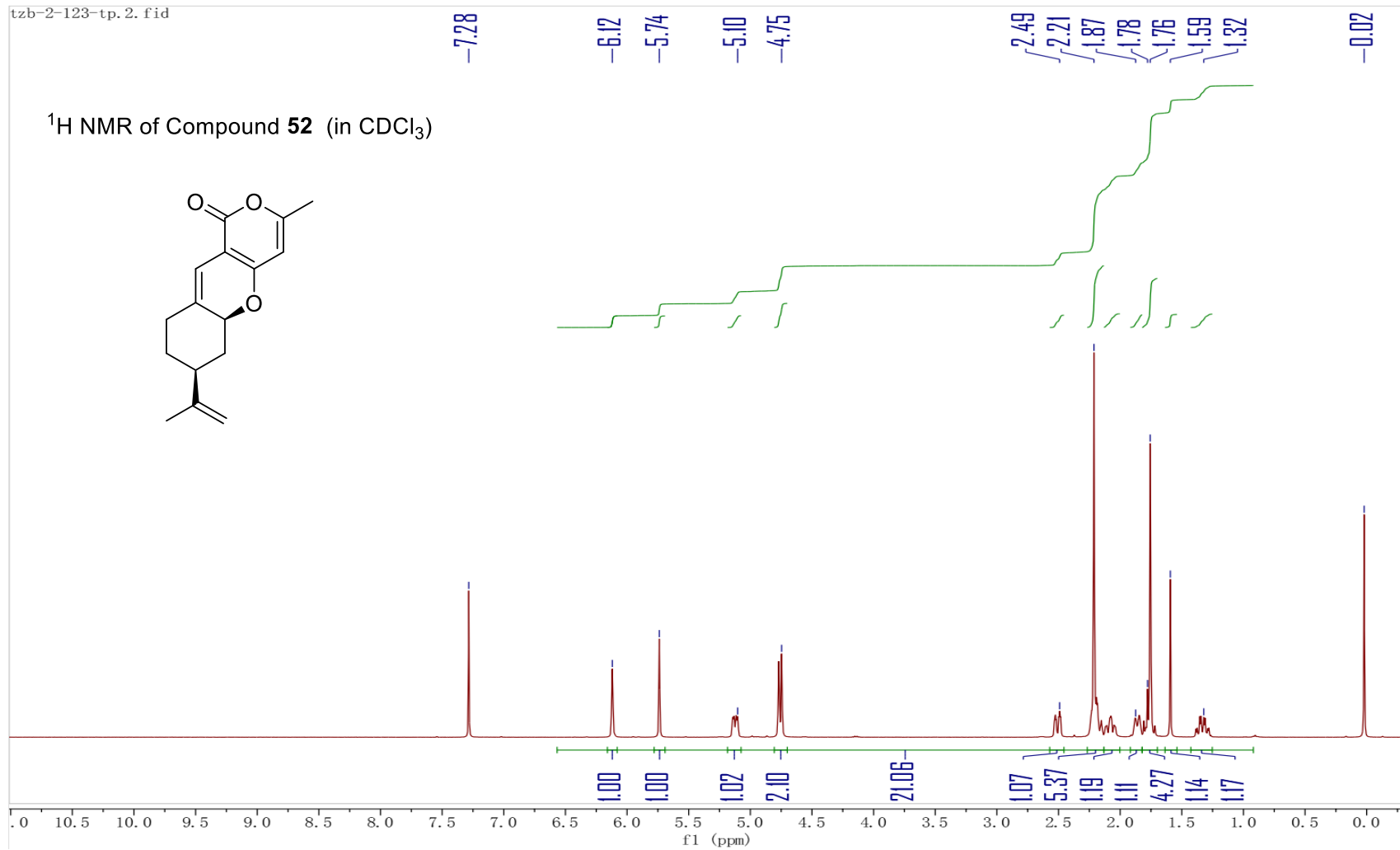
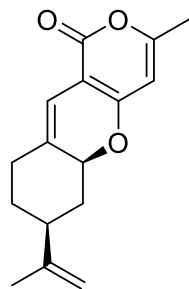


^{13}C NMR of Compound **51** (in CDCl_3)



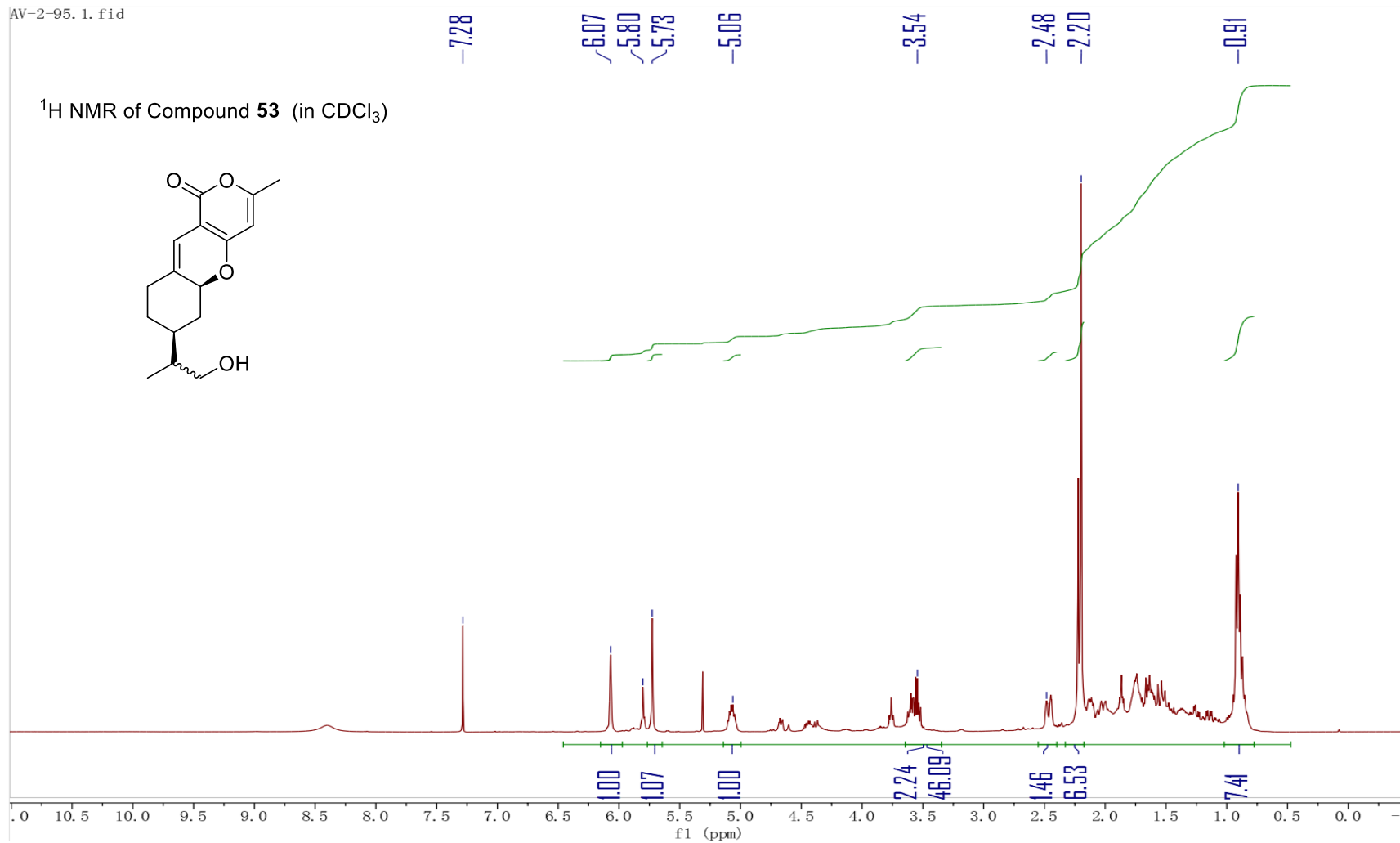
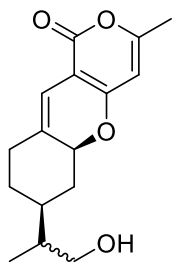
tzb-2-123-tp.2. fid

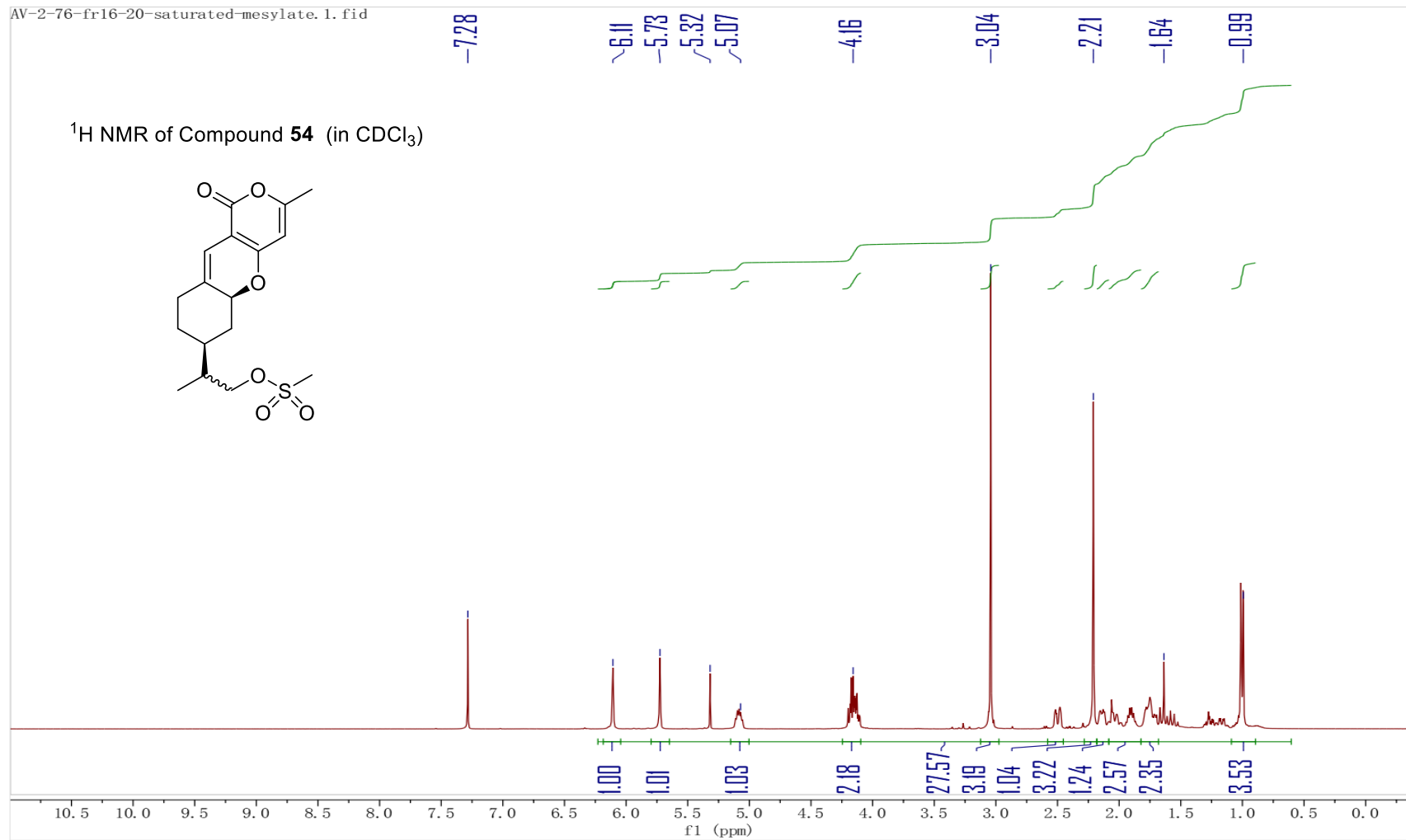
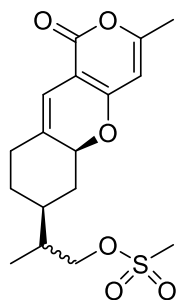
¹H NMR of Compound **52** (in CDCl₃)

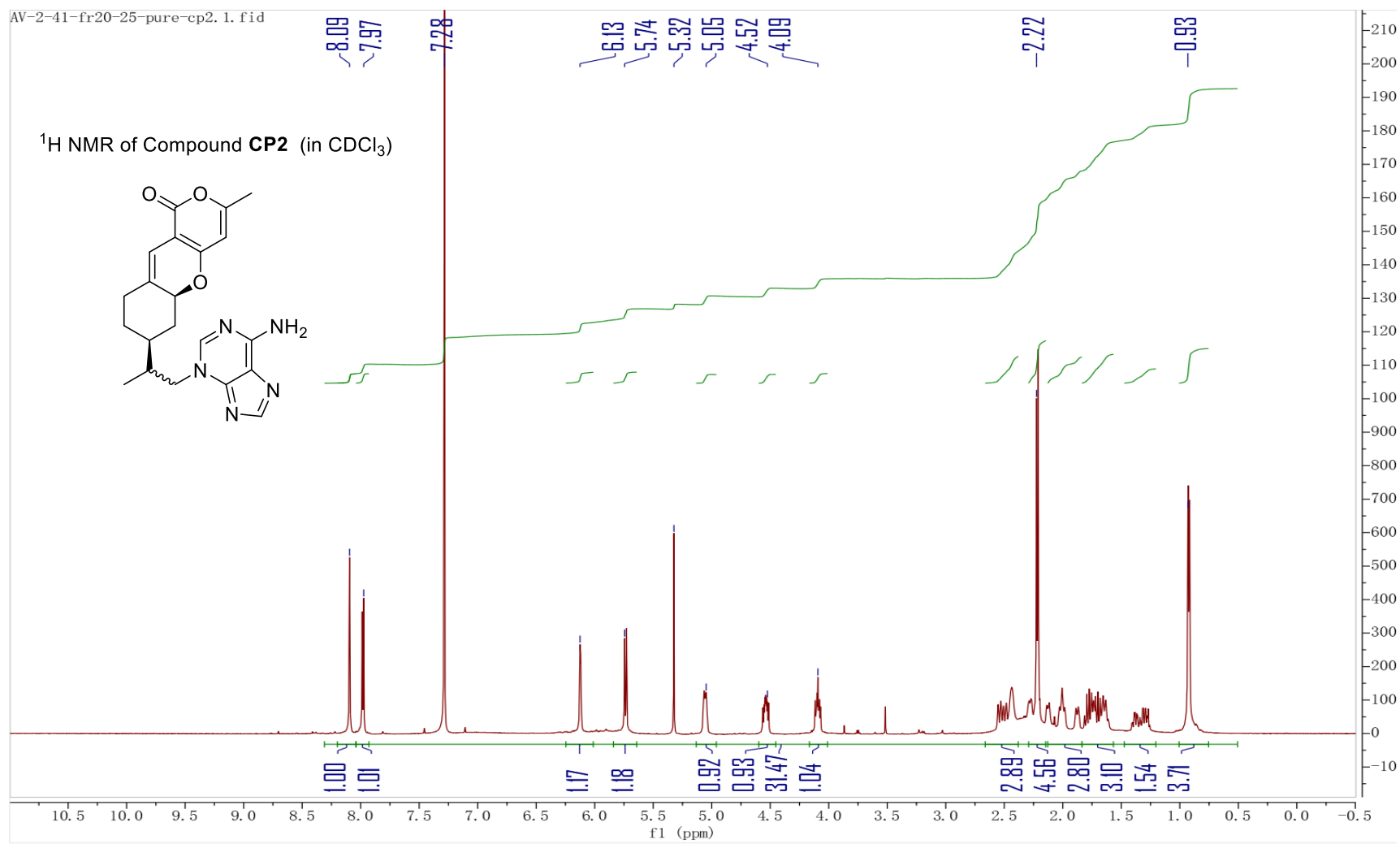


AV-2-95.1.fid

^1H NMR of Compound **53** (in CDCl_3)

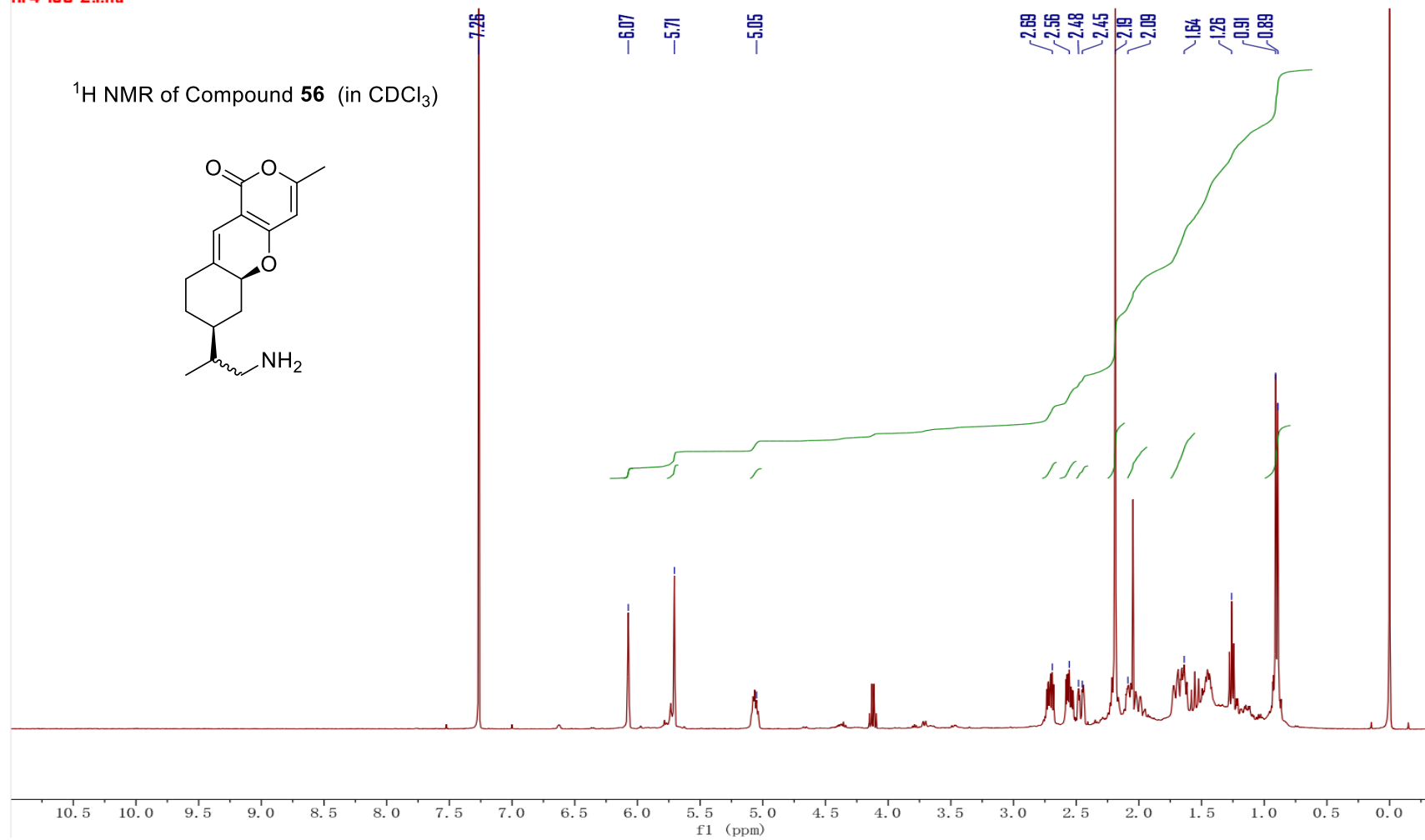
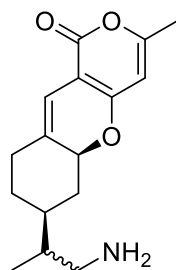


¹H NMR of Compound **54** (in CDCl₃)



HF4-130-2.1.fid

^1H NMR of Compound **56** (in CDCl_3)



HF4-135-crude.1.fid

^1H NMR of Compound **TP101** (in CDCl_3)

