CHAPTER 2

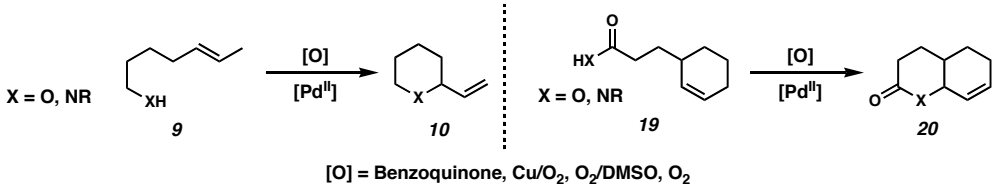
The Development of Palladium(II)-Catalyzed Oxidative Cyclizations in a Nonpolar Solvent Using Molecular Oxygen

2.1 INTRODUCTION AND BACKGROUND

2.1.1 Introduction

The oxidative kinetic resolution of secondary alcohols was the first stage of our program to develop asymmetric dioxygen-coupled palladium-catalyzed oxidation reactions. As a next step, we pursued oxidative heteroatom/olefin cyclization reactions of the types shown in Figure 2.1.1. Described herein is the development of cyclization reactions for several heteroatom nucleophiles and the extension to an asymmetric version for one type of substrate. This work demonstrates the need for highly specific conditions to carry out enantioselective aerobic palladium-catalyzed oxidative cyclization reactions.

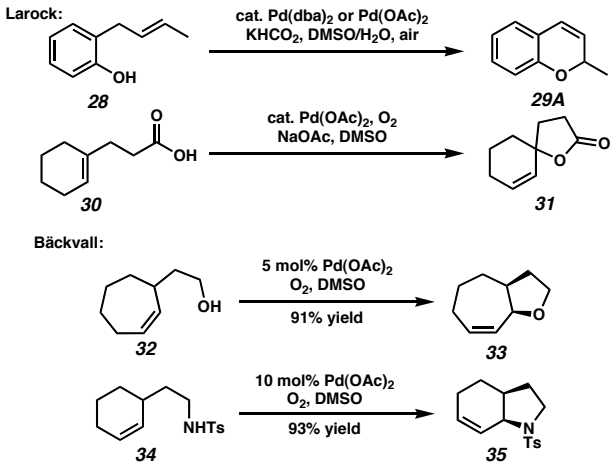
Figure 2.1.1 Oxidative cyclization reactions.



2.1.2 Background

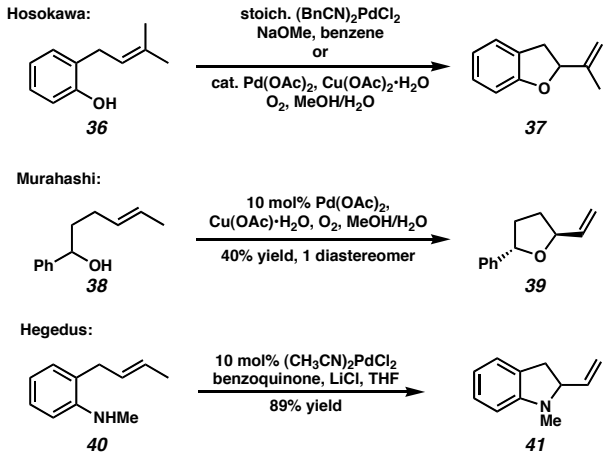
As described in Chapter 1, palladium(II) was selected for its versatility with the hope that it would be able to catalyze a number of different oxidative transformations. Indeed, the use of palladium(II) along with a variety of oxidants to catalyze heteroatom/olefin cyclizations has been known for several decades. Larock, Bäckvall and others have demonstrated that in DMSO solvent, it is possible to carry out racemic O_2-coupled palladium(II)-catalyzed oxidative cyclizations of olefin-appended nucleophiles such as phenols, alcohols, acids and tosylamides, as well as alcohol oxidations to ketones and aldehydes (Scheme 2.1.1).[1]

Scheme 2.1.1



Racemic cyclization reactions have also been developed that use copper/O_2 and benzoquinone reoxidation systems. In an early example, Hosokawa showed that palladium(II) could be used to cyclize olefin-appended phenols stoichiometrically (Scheme 2.1.2), and that the reaction could be made catalytic in the presence of copper and O_2.[2] Other substrates such as alcohols and amides have been reacted under similar conditions or with benzoquinone reoxidation by Murahashi, Hegedus, and others.[3]

Scheme 2.1.2

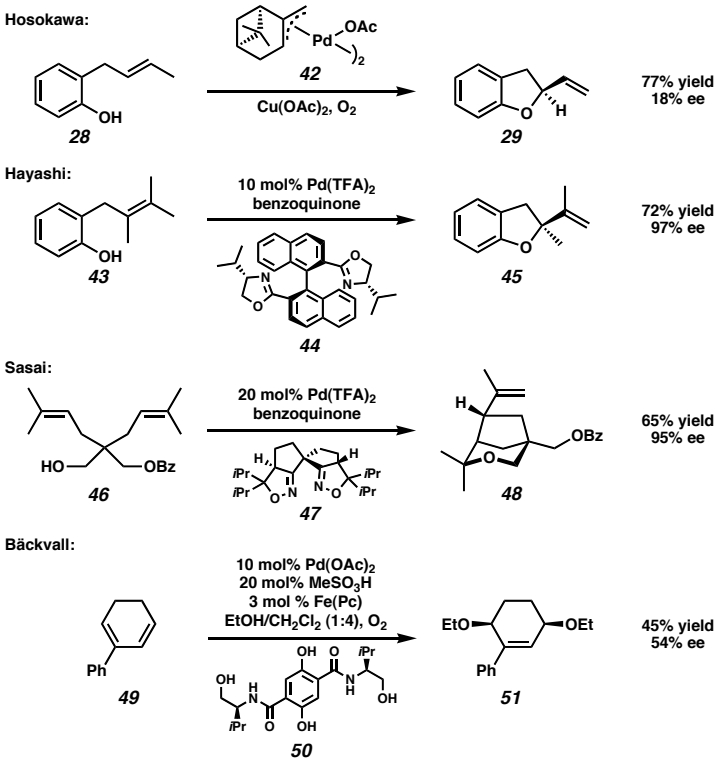


Although these examples constitute significant advances in racemic palladium(II)-catalyzed oxidation reactions, the conditions vary for different substrate types and many do not meet the ideal conditions for asymmetric reactions, i.e., that O_2 be used as the only stoichiometric oxidant in a noncoordinating solvent. Instead, the necessary use of cocatalysts, organic oxidants or DMSO has complicated the development of enantioselective oxidase-type cyclizations. For example, the use of the traditional copper/O_2 reoxidation system introduces a secondary catalytic cycle and another metal that could compete with palladium for the coordination of a chiral ligand. The use of benzoquinone requires the removal of stoichiometric amounts of organic compounds at

the end of a reaction,[4] and benzoquinone can itself act as a ligand.[5,6] DMSO is a highly donating solvent that could also interfere with the coordination of a chiral ligand to palladium.

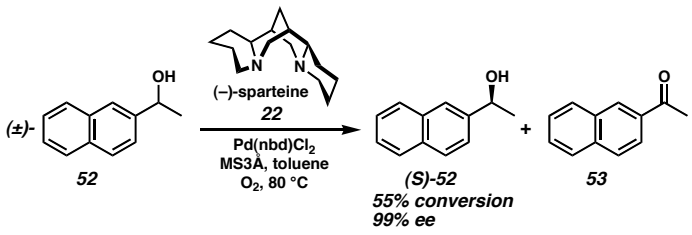
Despite the obstacles presented by the traditional oxidation systems, some important enantioselective examples have been reported and are illustrated in Scheme 2.1.3.[7] As early as 1981, Hosokawa and Murahashi described an asymmetric oxidative cyclization with a pinene-derived palladium complex (**42**).[8] More recently, Hayashi and Sasai have employed novel ligand frameworks (such as **44** and **47**) and benzoquinone as a reoxidant to obtain cyclized products with high enantioselectivity.[9,10] In an example from Bäckvall, a chiral benzoquinone generated in situ from **50** acts as ligand in an asymmetric dialkoxylation of **49**.[5] Although few in number, these examples established the potential for enantioselective palladium(II)-catalyzed oxidative cyclizations and dialkoxylations with copper and benzoquinone reoxidation systems. Nevertheless, the difficulties associated with the use of traditional reoxidants are borne out by the limited number of enantioselective reactions of this type.

Scheme 2.1.3



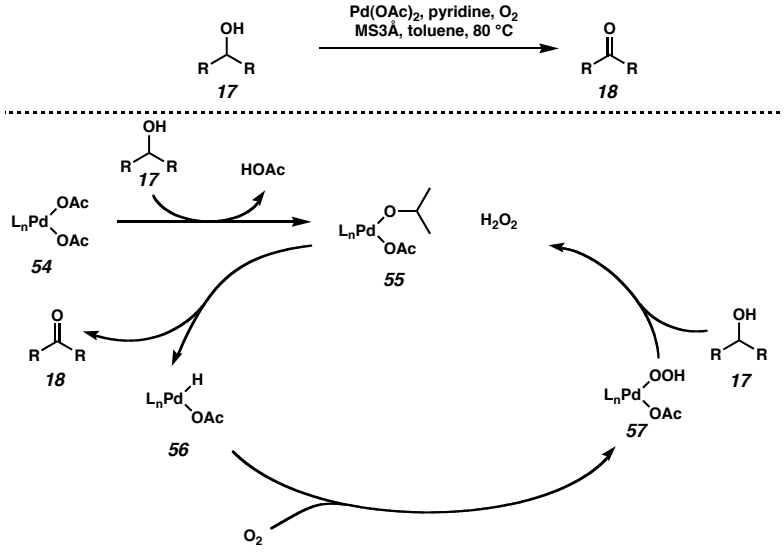
With the requirement that O_2 be the only stoichiometric oxidant, our palladium(II)-catalyzed asymmetric dehydrogenation of secondary alcohols (Scheme 2.1.4) provided a strong foundation for other asymmetric oxidation reactions.[11,12] This oxidation effects a kinetic resolution to yield enantioenriched alcohol, and was the first example of an asymmetric oxidase-type reaction in that it employs O_2 as the terminal oxidant.

Scheme 2.1.4



The basis for this chemistry was a racemic palladium(II)-catalyzed alcohol oxidation system reported in 1999 by Uemura and co-workers.[13] In Uemura's proposed mechanism, intermediate palladium alkoxide **55** is generated from **54**, which then undergoes β-hydrogen elimination to form a palladium hydroacetate (**56**) and the ketone product of oxidation (**18**, Figure 2.1.2). According to Uemura, dioxygen insertion directly into the palladium-hydride bond provides a palladium hydroperoxide intermediate (**57**). Protonation by alcohol generates a new palladium alkoxide (**55**) and completes the catalytic cycle.

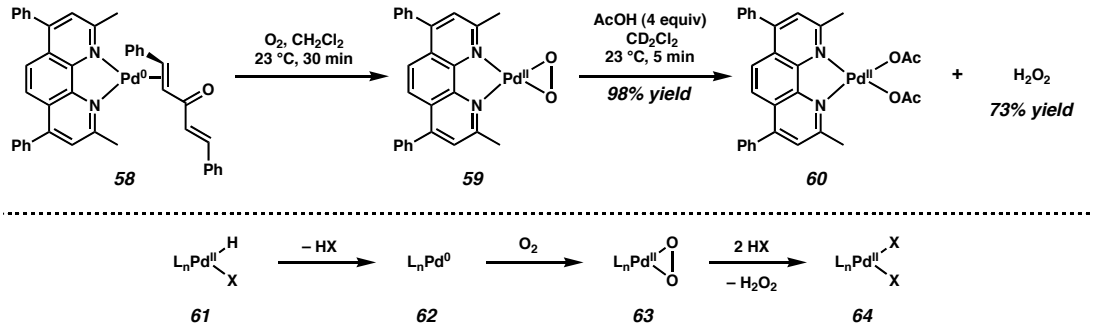
Figure 2.1.2 Uemura's proposed mechanism for the oxidation of secondary alcohols.



Stahl and co-workers have carried out extensive studies on the oxidation of alcohols by Uemura's system as well as by conditions that employ DMSO and O_2.[14] To model the catalyst reprocessing steps after β-hydrogen elimination in systems that use amine ligands, this group oxidized a bathrocuproine-ligated palladium(0) (**58**) with O_2 to obtain a palladium(II) peroxo species (**59**) that was characterized crystallographically (Scheme 2.1.5, top). Reaction of this complex with acetic acid rapidly produces the

bathrocuproine palladium(II) acetate (**60**) and hydrogen peroxide, which demonstrates that an amine-ligated palladium(0) species can be regenerated to an active palladium(II) complex via a peroxo intermediate. Whereas Uemura's proposed mechanism avoids palladium(0) altogether, Stahl's work provides evidence that a palladium(0) pathway is viable (Scheme 2.1.5, bottom).

Scheme 2.1.5

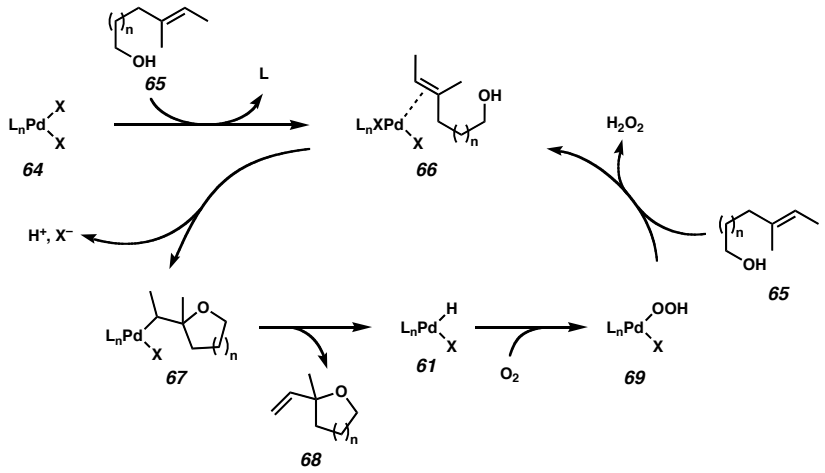


Significantly, Uemura's work provided an ideal platform for the development of an O_2-coupled enantioselective oxidation because it uses O_2 as the only reoxidant in a noncoordinating solvent (toluene), and requires the presence of a ligand (pyridine). We subsequently initiated an effort to apply our enantioselective alcohol oxidation to the development of asymmetric versions of reactions such as those shown in Figure 2.1.1. We envisioned that it would be possible to apply Uemura's conditions to the cyclization of heteroatoms onto pendant olefins.

A modified version of Uemura's mechanism provided a reasonable starting point for reaction development. In this scenario, a substrate such as **65** could displace a neutral (or anionic, not shown) ligand on palladium catalyst **64** to form an activated olefin complex (**66**). Nucleophilic attack to give **67** followed by β-hydrogen elimination leads to cyclized product (**68**) and a palladium hydride intermediate (**61**) analogous to that in the

alcohol oxidation mechanism (Figure 2.1.3). A wide range of substrates potentially could react in this manner to form a variety of heterocycles.[15]

Figure 2.1.3 A potential mechanism for the cyclization of heteroatoms with pendant olefins.



This chapter describes the application of Uemura's conditions to the cyclizations of heteroatoms onto pendant olefins and the development of an asymmetric version of the reaction.[16] This work establishes a proof-of-concept that heteroatom-olefin cyclizations that use O_2 as the sole stoichiometric oxidant are amenable to aerobic asymmetric catalysis. In the context of our program to develop enantioselective oxidase-type reactions, this work represented a crucial second phase of research beyond the groundbreaking initial developments.

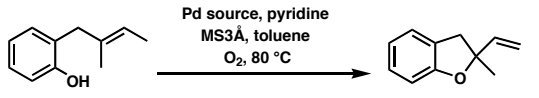
2.2 THE DEVELOPMENT OF NONENANTIOSELECTIVE PALLADIUM(II)-CATALYZED OXIDATIVE HETEROATOM/OLEFIN CYCLIZATIONS

2.2.1 The effect of palladium X^- ligand.

Our initial aim was to establish conditions for palladium(II)-catalyzed racemic aerobic cyclizations to which a chiral ligand eventually could be introduced. Thus, we began our investigation of aerobic oxidative cyclizations with 2-(*E*-2-methyl-2-

butenyl)phenol (**26**) using a variety of palladium(II) salts, pyridine, O_2, and MS3Å in toluene at 80 °C (Table 2.2.1). These conditions are modeled after Uemura's alcohol oxidation conditions,[13a] which, as stated above, were also employed as a starting point for our oxidative kinetic resolution chemistry.[11a] Surprisingly, Pd(nbd)Cl_2, which is the most effective catalyst for the kinetic resolution chemistry, was ineffective for the cyclization of **26** to dihydrofuran **27** (entry 1). Treatment of **26** with a range of palladium(II) salts (entries 1-4) led to the discovery that the electron-deficient palladium(II) trifluoroacetate ($Pd(TFA)_2$) was most effective for producing **27** in good yield after reasonable reaction time (entry 4). Sources of palladium(0) were found to be poor catalysts for the reaction: $Pd_2(dba)_3$ resulted in the formation of palladium black and a small amount of product, (entry 5), and palladium black itself gave no reaction (entry 6). A control experiment (entry 7) indicated that palladium was necessary for cyclization.

Table 2.2.1 Optimization of palladium(II) source.[a]



26 ***27***

entry	Pd source	time	yield[c]
1.	Pd(nbd)Cl_2[b]	24 h	7%
2.	$PdCl_2$	24 h	27%
3.	$Pd(OAc)_2$	24 h	76%
4.	$Pd(TFA)_2$	60 min	87%
5.	$Pd_2(dba)_3$	24 h	25%
6.	Pd Black	24 h	NR
7.	None	24 h	NR

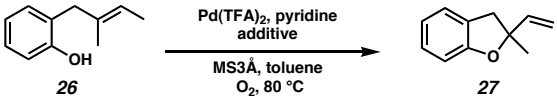
[a] 5 mol% Pd source, 20 mol% pyridine, 500 mg MS3Å/mmol substrate, 1 atm O_2, toluene (0.1 M), 80 °C. [b] nbd = norbornadiene. [c] Isolated yield.

2.2.2 The effect of exogenous base.

The effect of a range of exogenous bases was examined with the hope that proton consumption would accelerate the reaction (Table 2.2.2). Cesium carbonate, which

accelerated our oxidative kinetic resolution of secondary alcohols, in this case provided no benefit (entry 3). Sodium acetate presumably displaces CF_3COO^- from the palladium atom to give a less active catalyst (entry 2). Sodium carbonate exerts the most positive effect to give 95% yield in under 30 minutes (entry 4). The absence of pyridine causes a pronounced rate deceleration, along with the precipitation of palladium black. Although the ligand pyridine is itself basic, a molecule that can act as both a base and a ligand without inhibiting reactivity has not yet been identified. O_2 is also necessary for reaction to occur in high yield, although there appears to be a background reaction that leads to cyclization since the product is formed in greater than 5% yield in the absence of O_2 (entry 6). The presence of 30 equivalents of elemental mercury slowed the cyclization, but did not prevent reaction altogether, which contraindicates colloidal palladium or palladium nanoparticles as the relevant catalytic species (entry 7).[17]

Table 2.2.2 Optimization of basic additive.[a]



26 **27**

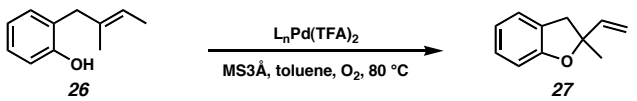
entry	ligand	additve	time	yield[b]
1.	pyridine	NaOAc	5 h	46%
2.	pyridine	KOAc	6 h	42%
3.	pyridine	Cs_2CO_3	5 h	42%[c]
4.	pyridine	Na_2CO_3	20 min	95%
5.	none	Na_2CO_3	24 h	39%
6.	pyridine	none, no O_2	24 h	24%[d]
7.[e]	pyridine	Na_2CO_3, Hg^0	5 h	84%[f]

[a] 5 mol% Pd, 20 mol% ligand, 2 equiv additive, 1 atm O_2. [b] Isolated yield. [c] Isolated along with a complex mixture of unidentified products. [d] Recovered starting material was isolated in 57% yield. [e] 5 mol% $(pyridine)_2Pd(TFA)_2$, 10 mol% pyridine. [f] Conversion determined by GC.

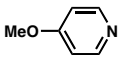
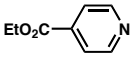
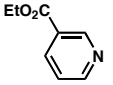
2.2.3 The effect of the nitrogen-containing ligand.

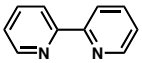
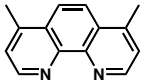
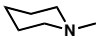
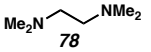
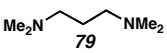
Although our optimization studies revealed pyridine to be a competent ligand, we carried out a small ligand screen of other nitrogen-containing ligands.[18] Each $L_nPd(TFA)_2$ complex was synthesized separately and characterized, rather than generated in situ, in order to limit uncertainty regarding the catalyst or catalyst precursor. Reactions were performed with either no additive, 40 mol% excess ligand, or both excess ligand and Na_2CO_3. As shown in Table 2.2.3, the use of substituted pyridyls less coordinating than pyridine, whether due to electronic (**70**, **72**, and **73**) or steric (**71**) reasons, result in the precipitation of palladium black in the absence of excess ligand. Bidentate nitrogen-containing ligands such as dipyridyl (**74**), 4,7-dimethyl-1,10-phenanthroline (**75**), TMEDA (**78**), or TMPDA (**79**) significantly slow the rate of reaction (entries 6-7, 10-11). The use of weak alkyl amine donors (**76**, **77**, and **79**) results in the precipitation of palladium black, even in the presence of excess ligand (entries 8-9, 11). Although some rate enhancement was observed for the nicotinate derivatives (**72** and **73**), pyridine offered the best combination of reactivity, catalyst stability, and availability.

Table 2.2.3 Oxidative cyclizations with substituted pyridyl and alkyl amine ligands.[a]



26 *27*

entry[b]	ligand	no additive	40% ligand	40% ligand + 40% Na_2CO_3
1.		98% 1 h	99% 1 h	99% 15 min
2.	 *70*	85% 2.5 h	96% 9 h	99% 2h
3.	 *71*	50% 24 h[c]	68% 24 h	91% 5h
4.	 *72*	84% 8 h[c]	99% 40 min	96% 15 min
5.	 *73*	70% 30 min[c]	99% 30 min	99% 5 min

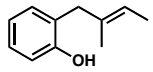
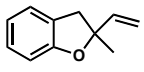
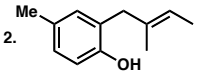
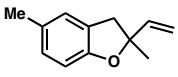
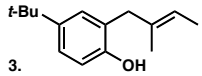
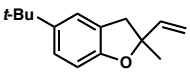
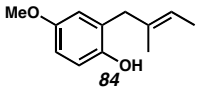
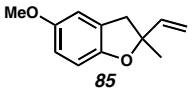
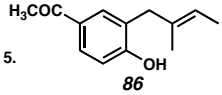
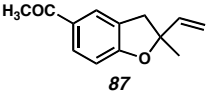
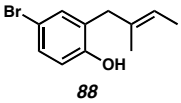
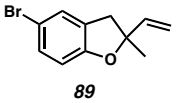
entry	ligand	no additive	40% ligand	40% ligand + 40% Na_2CO_3
6.[d]	 *74*	92% 18 h	97% 5 h	93% 5 h
7.[d]	 *75*	94% 8 h	96% 24 h	99% 24 h
8.	 *76*	82% 20 h[c]	90% 5 h[c]	92% 5 h[c]
9.	 *77*	15% 24 h[c]	15% 24 h[c]	10% 24 h[c]
10.[d]	 *78*	73% 12 h	97% 8 h	99% 8 h
11.[d]	 *79*	34% 20 h[c]	54% 20 h[c]	76% 11 h[c]

[a] 5 mol% $L_nPd(TFA)_2$, 500 mg/mmol MS3Å, 1 atm O_2, toluene (0.1 M), 80 °C. [b] Conversion determined by GC. [c] Palladium black precipitate was observed in the reaction mixture. [d] For entries 6, 7, 10 and 11, 20 mol% excess ligand was added.

2.2.4 Cyclizations of para*-substituted allyl-appended phenols.*

Under our optimized conditions, oxidative cyclization of a variety of *para*-substituted phenols occurs readily with 5 mol% $Pd(TFA)_2$, 20 mol% pyridine, 2 equiv Na_2CO_3 and 500 mg 3Å molecular sieves/mmol substrate at 0.1 M concentration in toluene under a balloon of oxygen (Table 2.2.4). Workup involves simple filtration through a pad of silica gel. Cyclizations of electron-rich phenols are especially facile and provide excellent yields in under 30 min (entries 1-4). An electron deficient phenol (**86**) serves as an excellent substrate as well, albeit with slower reaction time (entry 5). In contrast, a *p*-bromo-substituted substrate (**88**, entry 6) appears to react via alternate pathways that lead to decomposition, possibly via oxidative addition of palladium(0).[19] Finally, high yields and reasonable rates persist with reduced catalyst loading (2 mol%, entry 7).

Table 2.2.4 Oxidative cyclizations of phenols with para substitution.[a]

entry	substrate	product	time	yield
1.	 **26**	 **27**	20 min	95%
2.	 **80**	 **81**	20 min	99%
3.	 **82**	 **83**	25 min	90%
4.	 **84**	 **85**	15 min	89%
5.	 **86**	 **87**	25 h	93%
6.	 **88**	 **89**	24 h	33%
7.[b]	**26**	**27**	14 h	86%

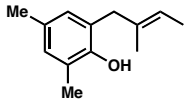
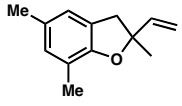
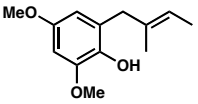
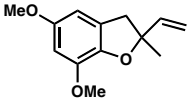
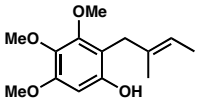
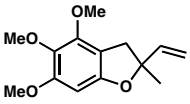
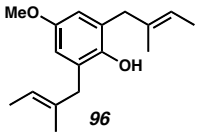
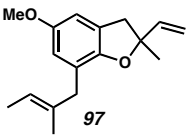
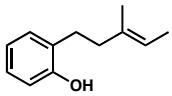
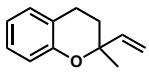
[a] 5 mol% $Pd(TFA)_2$, 20 mol% pyridine, 2 equiv Na_2CO_3, 500 mg MS3Å/mmol substrate, 1 atm O_2, toluene (0.1 M), 80 °C. [b] 2 mol% $Pd(TFA)_2$, 8 mol% pyridine.

2.2.5 Cyclizations of multiply substituted allyl-appended phenols.

Electron-rich phenols with additional substitution are also good substrates (entries 1-3, Table 2.2.5). Substitution ortho to the phenolic moiety is tolerated, with a slight

decrease in reaction rate (entry 4). Six-membered ring closure can also occur to give a dihydropyran product (**99**) under identical conditions (entry 5).

Table 2.2.5. Oxidative cyclizations of multiply substituted phenols.[a]

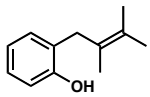
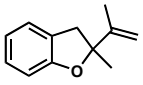
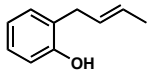
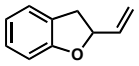
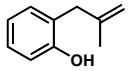
entry	substrate	product	time	yield
1.	 **90**	 **91**	20 min	85%
2.	 **92**	 **93**	40 min	80%
3.	 **94**	 **95**	10 min	86%
4.	 **96**	 **97**	2 h	93%
5.[b]	 **98**	 **99**	75 min	85%

[a] 5 mol% $Pd(TFA)_2$, 20 mol% pyridine, 2 equiv Na_2CO_3, 500 mg MS3Å/mmol substrate, 1 atm O_2, toluene (0.1 M), 80 °C. [b] The starting material was used as a 3.6:1 mixutre of olefin isomers.

2.2.6 Cyclizations of phenols with different olefin substitution patterns.

Cyclization onto a tetrasubstituted olefin (**45**) proceeds in good yield (Table 2.2.6, entry 1), as does cyclization of a disubstituted olefin (**28**, entry 2). For terminal olefin substrate **100**, reaction does not take place, presumably because exo cyclization occurs that leaves no β-hydrogens to be eliminated from the presumed palladium alkyl intermediate (similar to **67**, Figure 2.1.3).

Table 2.2.6. Oxidative cyclizations of phenols with different olefin substitution patterns.[a]

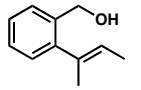
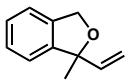
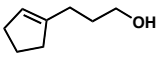
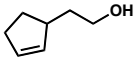
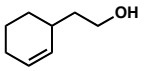
entry	substrate	product	time	yield
1.	 ***45***	 ***47***	25 min	80%
2.	 ***28***	 ***29***	3 h	74%
3.	 ***100***	NR	24 h	N/A

[a] 5 mol% $Pd(TFA)_2$, 20 mol% pyridine, 2 equiv Na_2CO_3, 500 mg MS3Å/mmol substrate, 1 atm O_2, toluene (0.1 M), 80 °C.

2.2.7 Oxidative cyclizations of primary alcohols with olefins.

In addition to phenols, we have investigated primary alcohol/olefin oxidative cyclizations. Remarkably, these reactions proceed to the heterocyclic ethers with, in most cases, little or no oxidation to the aldehyde under our optimized conditions (Table 2.2.7). In addition to benzyl alcohol **101**, cyclopentene (**103** and **105**) and cyclohexene (**107**) derivatives provide moderate to excellent yields of a spirocycle (**104**) and fused ring systems (**106**, **108**). The mode of oxidative reactivity – cyclization versus alcohol oxidation – appears dependent not only on the substrate (i.e., primary vs secondary alcohols) but also on the specific palladium source (cf. Uemura's work[13]).

Table 2.2.7 Oxidative cyclization of primary alcohols with pendant olefins.[a]

entry	substrate	product	time	yield
1.[b]	 ***101***	 ***102***	3 h	87%
2.	 ***103***	 ***104***	10 h	93%[c]
3.	 ***105***	 ***106***	7.5 h	69%[d]
4.	 ***107***	 ***108***	20 h	60%[e]

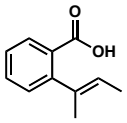
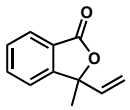
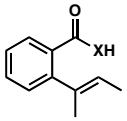
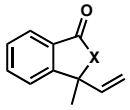
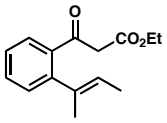
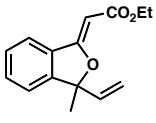
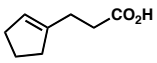
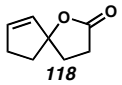
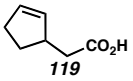
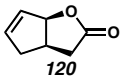
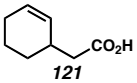
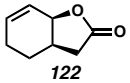
[a] 5 mol% $Pd(TFA)_2$, 20 mol% pyridine, 2 equiv Na_2CO_3, 500 mg MS3Å/mmol substrate, 1 atm O_2, toluene (0.1 M), 80 °C. [b] The starting material was used as a mixture of *E* and *Z* olefins. [c] Isolated with 7% of the aldehyde. [d] Isolated with 7% of an olefin isomer. [e] Isolated as a 5:2.3:1 mixture of **108**/olefin isomer/aldehyde.

2.2.8 Oxidative cyclizations of carboxylic acids and acid derivatives onto olefins.

To determine their viability as substrates, a range of carboxylic acids and carboxylic acid derivatives were synthesized and subjected to our optimized conditions. The synthesis and study of substrates **109**, **111**, **112**, **115**, and **117** were carried out by postdoctoral scholar Dr. Yeeman Ramtohul. For some carboxylic acid derivatives (**109**, **111**, **112**, **117**), the addition of an external stoichiometric base was found to be unnecessary, and exposure to 5 mol% $Pd(TFA)_2$, 20 mol% pyridine, 500 mg MS3Å/mmol substrate and 1 atm O_2 in toluene at 80 °C led to a variety of oxidatively cyclized products (Table 2.2.8, entries 1-3, 5). Benzoic acids (**109**) and amides (**111**, **112**) are cyclized in good to excellent yields (entries 1-3). A β-keto ester (**115**) undergoes cyclization as a vinylogous acid to form a heterocycle (**116**) rather than a carbocycle (entry 4). Primary acid derivatives react to form spirocycles (**118**) or fused

bicyclic systems (**120** and **122**), depending on the position of the olefin (entries 5-7). The cyclization of derivatives **119** and **121** is more facile with 10 mol% catalyst loading and is accelerated by the presence of 2 equiv Na_2CO_3.

Table 2.2.8 Oxidative cyclization of carboxylic acids and carboxylic acid derivatives.[a]

entry	substrate	product		time	yield
1.[b]	 **109**	 **110**		8 h	90%
2.[b]	 **111,112**	 **113,114**	X = NTs	8 h	88%
3.[b]			X = NOBn	4 h	82%
4.[b]	 **115**	 **116**		48 h	63% [c,d]
5.	 **117**	 **118**		48 h	62% [e]
6.	 **119**	 **120**		2 h	77% [f]
7.	 **121**	 **122**		12 h	86% [f,g]

[a] 5 mol% $Pd(TFA)_2$, 20 mol% pyridine, MS3Å, 1 atm O_2, toluene, 80 °C. [b] The starting material was used as a mixture of *E*:*Z* olefins. [c] 10 mol% pyridine, 2 equiv LiOAc. [d] 3:1 *Z*:*E*. [e] 10 mol% $Pd(TFA)_2$, 40 mol% pyridine. [f] 10 mol% $Pd(TFA)_2$, 40 mol% pyridine, 2 equiv Na_2CO_3. [g] Isolated with 6% of an olefin isomer.

2.2.9 Reaction scope and limitations.

The high yields, usually brief reaction times, and range of substrates that are characteristic of this aerobic palladium(II)-catalyzed oxidative cyclization demonstrate the utility of the nonenantioselective conditions – palladium, ligand, base, O_2, and solvent. Nearly identical conditions are applicable to five different types of nucleophiles: phenols, primary alcohols, carboxylic acids, a vinylogous acid, and amides. Electron-rich

phenols are excellent substrates, and multiple olefin substitution patterns are tolerated. Primary alcohols undergo oxidative cyclization without significant oxidation to the aldehyde, a fact that illustrates the range of reactivity available from various palladium(II) salts under differing conditions. In addition to the cyclization of a benzylic alcohol, non-benzylic alcohols can form both fused and spirocyclic ring systems; the same is true of acid derivatives. Undoubtedly the range of alcohol substrates could be increased.[20] While phenol/olefin, alcohol/olefin,[1a,2,21] and carboxylic acid/olefin[1c,22,23] cyclizations have been achieved before under palladium(II)/oxidant catalysis, our conditions differentiated themselves by meeting the criteria for extension to an asymmetric version: simplicity (i.e., one transition metal), capacity to accommodate a chiral ligand, acceleration by a ligand, and active catalysis in a noncoordinating solvent. Without a system of this type the development of a direct aerobic asymmetric cyclization has been shown to be limited.

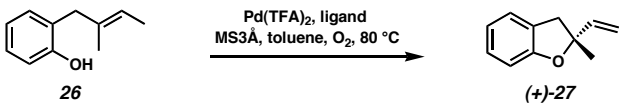
2.3 THE ELABORATION OF THE NONENANTIOSELECTIVE CONDITIONS TO AN ASYMMETRIC VERSION

2.3.1 Chiral ligand screen.

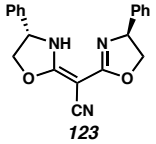
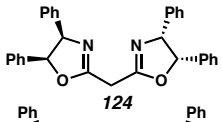
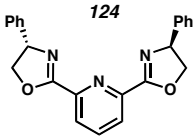
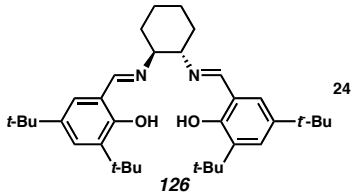
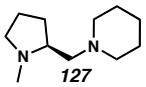
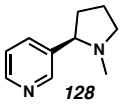
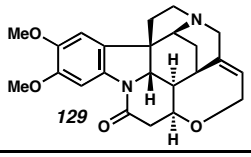
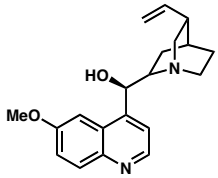
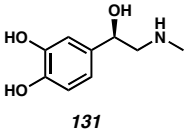
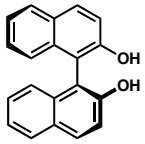
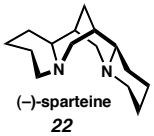
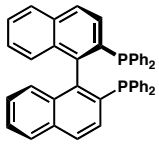
A number of chiral ligands were screened with the conditions established for the racemic cyclizations, including typical chiral ligands such as bisoxazolines (**123**, **124** and **125**, Table 2.3.1), as well as ligands less commonly used in catalysis such as brucine (**129**). The substitution of several different ligands in place of pyridine in the racemic conditions resulted in a nearly complete lack of reactivity (entries 1-4, 9); most of these ligands are bidentate. Other ligands, in particular, those expected to coordinate in a monodentate fashion (**128**, **129** and **130**), led to high conversion but with no selectivity

(entries 6-8). These general trends were in accordance with our observations of the performance of achiral mono- and bidentate nitrogen-containing ligands (Table 2.2.3). As we observed during the development of our oxidative kinetic resolution chemistry,[11a] the natural product (–)-sparteine (**22**) was by far the most successful at inducing asymmetry in the cyclization reaction (entry 11). Treatment of **26** with $Pd(TFA)_2$ in the presence of (–)-sparteine (**22**), MS3Å and O_2 in toluene provided 72% conversion to dihydrobenzofuran **(+)-27** in 76% ee after 24 h. The chiral bidentate ligand (*R*)-(+)-BINAP (**133**) produced the next highest level of enantioselectivity, but the reaction was marked by catalyst decomposition and low reactivity (entry 12). (*S*)-(–)-BINOL (**132**), like (–)-sparteine (**22**), remained an interesting exception to the generally unreactive bidentate ligands (entry 10).

Table 2.3.1[a] *Chiral ligand screen for the oxidative cyclization of* ***26***.



26 ***(+)-27***

entry	ligand	time	conversion[b]	ee[c]
1.	 ***123***	24 h	0%	–
2.	 ***124***	24 h	0%	–
3.	 ***125***	24 h	3%	0%
4.	 ***126***	24 h	0%	–
5.	 ***127***	6.5 h	71%	0%
6.	 ***128***	6.5 h	99%	0%
7.	 ***129***	24 h	72%	0%
8.	 ***130***	24 h	54%	0%
9.	 ***131***	24 h	7%	0%
10.	 ***132***	24 h	98%	0%
11.	 (–)-sparteine ***22***	36 h	72%	76%
12.	 ***133***	24 h	15%	32%

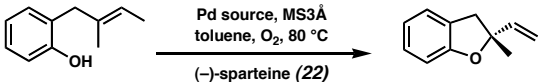
[a] 10 mol $Pd(TFA)_2$, 40 mol% ligand, 500 mg MS3Å/mmol substrate, 0.41 equiv tridecane internal GC standard, 1 atm O_2, toluene (0.1 M), 80 °C. [b] Conversion determined by GC. [c] Enantiomeric excess determined by chiral GC.

2.3.2. Optimization of the asymmetric reaction – screen of palladium sources.

With (–)-sparteine (**22**) as the best ligand for the induction of enantioselectivity in the cyclization, we set out to increase selectivity through an optimization of reaction conditions, namely palladium(II) source and basic additive. This seemed essential in light of what we had observed during the development of the nonenantioselective

reaction (cf. Tables 2.2.1 and 2.2.2), as well as with the kinetic resolution chemistry.[11a24] Palladium(II) halide sources provided product in some cases, but with degradation of enantiomeric excess (Table 2.3.2, entries 1-2, 4-5). $Pd(OAc)_2$ is more effective at inducing asymmetry than palladium halides, but at the expense of conversion (entry 6). The extent of asymmetric induction varied surprisingly in the presence of different palladium(II) sources. For example, $Pd(COD)Cl_2$ results in only 10% ee (entry 2), whereas $Pd(TFA)_2$ provides 76% ee (entry 7). It is remarkable that a seemingly minor change has such a large effect on enantioselectivity.[25] $Pd(TFA)_2$ remained the optimal palladium source, and it was found that the preformed complex of $Pd(TFA)_2$ and **22** ((sp)$Pd(TFA)_2$, **134**) gave slightly improved and more reliable results than the in situ-generated complex (entry 8). Generally, more electron-deficient palladium sources were more selective in the cyclization. However, switching the anion from trifluoroacetate to triflate resulted in degradation of the catalyst (formation of palladium black).

Table 2.3.2 Optimization of palladium source for the asymmetric oxidative cyclization of ***26****.*[a]



26 *(+)-27*

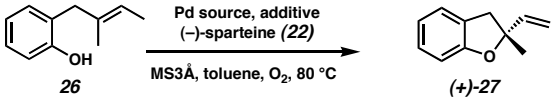
entry	Pd source	time	conv[b]	ee
1.	$Pd(nbd)Cl_2$	36 h	68%	12%
2.	$Pd(COD)Cl_2$	36 h	30%	10%
3.	$PdCl_2$	36 h	2%	12%
4.	$Pd(CH_3CN)_2Cl_2$	36 h	53%	12%
5.	$PdBr_2$	36 h	32%	8%
6.	$Pd(OAc)_2$	36 h	18%	51%
7.	$Pd(TFA)_2$	36 h	72%	76%
8.[c]	(sp)$Pd(TFA)_2$ (*134*)[d]	36 h	83%	77%
9.	$Pd(OTf)_2(CH_3CN)_4$	160 h	20%	16%

[a] 10 mol% palladium source, 40 mol% (–)-sparteine, 500 mg MS3Å/mmol substrate, 1 atm O_2, toluene (0.1 M), 80 °C. [b] Conversion measured by GC or by ^1H NMR. [c] 30 mol% (–)-sparteine. [d] sp = (–)-sparteine.

2.3.3 Optimization of the asymmetric reaction – effect of basic additives on the asymmetric oxidative cyclization.

Like the identity of the palladium source, a basic additive can affect reaction rate and selectivity. As in the nonenantioselective reaction, we have found that the addition of some exogenous inorganic bases can promote the catalytic activity (Table 2.3.3). There appears to be no obvious trend for rate enhancement or the effects on selectivity. The addition of NaOAc (entry 4) diminishes activity and selectivity to levels similar to those observed with $Pd(OAc)_2$ (Table 2.3.2, entry 6), presumably because acetate displaces trifluoroacetate to give the less selective acetate catalyst. The best results are obtained with $Ca(OH)_2$, the presynthesized complex, (sp)$Pd(TFA)_2$ (**134**), and 1 equiv of (–)-sparteine (**22**, entry 7) to provide 83% conversion and 77% ee.

*Table 2.3.3 Basic additives in the asymmetric oxidative cyclization of **26**.*[a]



26 *(+)-27*

entry	Pd source	additive	time	conv[b]	ee[b]
1.	$Pd(TFA)_2$	Na_2CO_3	3 d	56%	63%
2.	$Pd(TFA)_2$	Cs_2CO_3	3 d	58%	21%
3.	$Pd(TFA)_2$	K_2CO_3	3 d	26%	64%
4.	$Pd(TFA)_2$	NaOAc	3 d	18%	46%
5.[c]	(sp)$Pd(TFA)_2$ *(134)*	Na_2CO_3	36 h	53%	76%
6.[c]	(sp)$Pd(TFA)_2$ *(134)*	$CaCO_3$	3 d	75%	61%
7.[c]	(sp)$Pd(TFA)_2$ *(134)*	$Ca(OH)_2$	36 h	87%	81%

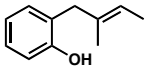
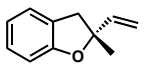
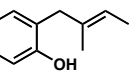
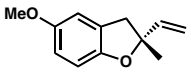
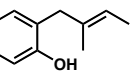
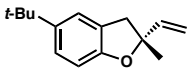
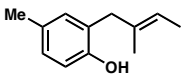
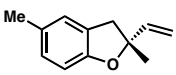
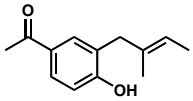
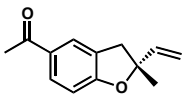
[a] 5 mol% Pd source, 20 mol% (–)-sparteine (**22**), 2 equiv additive, 500 mg MS3Å/mmol substrate, 1 atm O_2, toluene (0.1 M), 80 °C. [b] Measured by GC. [c] 10 mol% (sp)$Pd(TFA)_2$ (**134**), 100 mol% (–)-sparteine.

2.3.4 Enantioselective oxidative cyclization of phenol substrates.

Under the optimized conditions, phenol **26** was cyclized to provide dihydrobenzofuran **(+)-27** in 81% ee and 87% isolated yield (Table 2.3.4, entry 1).[26] Application of these conditions to other substrates that reacted well under the

nonenantioselective conditions proved less successful.[27] *p*-Methoxyphenol **84** is transformed with high selectivity to give **(+)-85** in 90% ee and 57% yield (entry 2). *t*-Butylphenol **82** and *p*-methylphenol **80** do not react quickly but the corresponding products are obtained with good enantiomeric excess (entries 3 and 4). *p*-Acylphenol **86** cyclizes, but with low %ee, perhaps indicative of a change in mechanism for this electron-poor substrate.

Table 2.3.4 Enantioselective cyclization of olefin-appended phenols.[a]

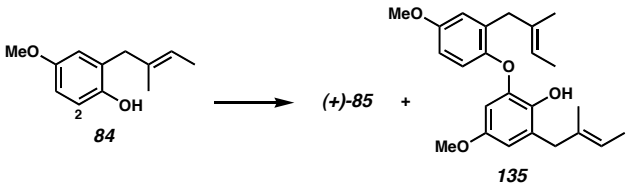
entry	substrate	product	time	yield[b]	ee[c]
1.	 **26**	 **(+)-27**	36 h	87%	81%
2.	 **84**	 **(+)-85**	24 h 60 h @ 55 °C	64% 57%	88% 90%
3.	 **82**	 **(–)-83**	36 h	47%	83%
4.	 **80**	 **(+)-81**	36 h	47%	86%
5.	 **86**	 **(–)-87**	24 h	60%	20%

[a] 10 mol% (sp)Pd(TFA)$_2$ (**134**), 100 mol% (–)-sparteine (**22**), 2 equiv Ca(OH)$_2$, 500 mg MS3Å/mmol substrate, 1 atm O_2, toluene (0.1 M), 80 °C. [b] Isolated yield. [c] Measured by GC.

Unfortunately, in the cyclization of substrate **84**, enantioenriched *p*-methoxy dihydrobenzofuran **(+)-85** is produced along with a dimeric aryl ether byproduct (**135**, Table 2.3.5). Although we have no direct evidence, this interesting byproduct could form via palladation ortho to the phenol, followed by coupling to another molecule of substrate.[28] The addition of various acids suppressed the formation of the byproduct, perhaps by protonolysis of the postulated palladium aryl species, but also depressed the

enantioselectivity of the cyclization (entry 3). Many of the substrates for the racemic reaction such as **90**, **92**, and **96** (Table 2.2.5) were designed to prevent dimerization by blocking the C2 position of the starting material, but most did not react under the slower enantioselective conditions.

*Table 2.3.5 Attempted suppression of dimerization of **84**.*[a]



entry	additve	time	(+)-84:135[b]	ee of (+)-85[c]
1.	amberlyst 15 resin (10 mol%)	24 h	5:3	87%
2.	TsOH·H_2O (10 mol%)	24 h	3:1	81%
3.	TsOH·H_2O (100 mol%)	80 h	6:1	50%
4.	none	16 h	2:1	86%

[a] 10 mol% (sp)Pd(TFA)$_2$ (**134**), 100 mol% (–)-sparteine (**22**), 500 mg MS3Å/mmol substrate 1 atm O_2, toluene (0.1 M), 80 °C. [b] Measured by ^{1}H NMR. [c] Measured by GC.

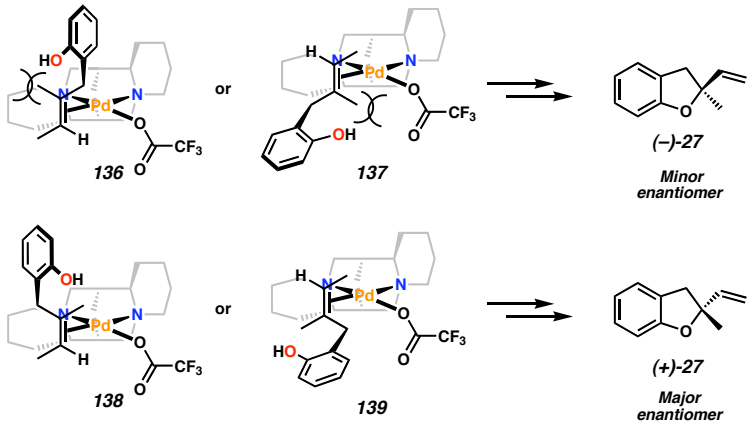
2.4 PROPOSED RATIONALE FOR THE OBSERVED STEREOCHEMISTRY

2.4.1 Rationale based on external nucleophilic attack.

In one possible mechanism for the asymmetric cyclization, ligand substitution of a trifluoroacetate anion by the olefin could occur to afford an activated olefin complex. Shown in Figure 2.4.1 are four possible diasteromeric configurations of the proposed (sp)Pd-bound olefin. For reasons to be discussed in Chapter 4, we have chosen to describe coordination of the olefin as limited to one coordination site at the metal center. Nucleophilic attack by phenol or phenoxide would occur anti to the palladium atom, from the external face of the coordinated olefin. Given this mode of attack, diastereomers **136** and **137** do not lead to the observed absolute stereochemistry of the major enantiomer of product. **136** and **137** may be disfavored due to steric clashing of the methyl groups on

the olefin with the (–)-sparteine (**22**) backbone, as in **136**, or with the trifluoroacetate ligand, as in **137**. For the diastereomers that do lead to the major observed enantiomer, it is difficult to predict which steric factors would cause **138** or **139** to be favored.

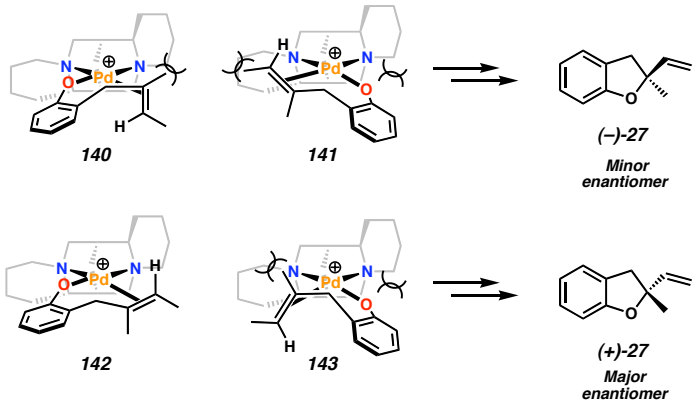
Figure 2.4.1 Stereochemical rationale for external nucleophilic attack.



2.4.2. Rationale based on internal C–O bond formation.

In another possible mechanism, both trifluoroacetate anions are displaced by the substrate to give a palladium-phenoxide-olefin chelate complex. Shown in Figure 2.4.2 are four possible diasteromeric configurations of the proposed (sp)Pd-bound substrate. Diastereomers **140** and **141** may be disfavored due to steric interactions between the methyl groups and the (–)-sparteine (**22**) backbone, and possibly between the phenoxide moiety and **22**. Of the two diasteromers that give the major enantiomer, we propose that **142** is most likely the favored disatereomer, with the fewest number of destabilizing steric interactions.

Figure 2.4.2 Stereochemical rationale for internal C–O bond formation.



2.5 CONCLUSION

Oxidase-type cyclizations of several different nucleophiles onto pendant olefins occur in excellent yield under simple conditions: palladium(II), pyridine, oxygen, inorganic base, and toluene. Reactivity is highly dependent on palladium source, basic additive, and ligand. The reaction can produce several different types of cyclic systems, including aryl and alkyl bicycles, and fused and spirocyclic motifs. These cyclizations are part of an ongoing effort in the Stoltz group to develop oxidase-type reactions that employ palladium(II) catalysis with molecular oxygen. To this end, the pyridine-based conditions we developed were suitable for extension to an enantioselective cyclization in the presence of the chiral ligand (–)-sparteine (**22**). While the asymmetric oxidative cyclization conditions are not yet general, we have established that it is possible to adapt a direct dioxygen-coupled reaction to aerobic asymmetric catalysis, which had not before been achieved for this class of reaction. The versatility and sensitivity to reaction conditions of this and other palladium(II)-catalyzed oxidations prompted us to investigate the mechanism of this reaction. These investigations are the subject of Chapter 3.

2.6 EXPERIMENTAL SECTION

2.6.1 Materials and Methods

Unless stated otherwise, reactions were conducted in flame-dried glassware under a nitrogen atmosphere with freshly distilled solvents. All commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized via UV and anisaldehyde or potassium permanganate staining. ICN silica gel (particle size 0.032-0.063 mm) was used for flash column chromatography. Analytical chiral GC was carried out on a Chiraldex G-TA column (30.0 m x 0.25 mm) from Bodman Industries. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 spectrometer (at 300 MHz and 75 MHz respectively) and are reported relative to Me_4Si (δ 0.0). Some ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 500 spectrometer (at 500 MHz and 125 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrometer or a Perkin Elmer BXII FT-IR spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the UC Irvine Mass Spectral Facility and from the California Institute of Technology Mass Spectral Facility. Optical rotations were recorded with a Jasco P-1010 polarimeter (Na lamp, 589 nm). X-Ray crystallographic data were obtained from the California Institute of Technology Beckman

Institute X-Ray Crystallography Laboratory. Elemental analyses were carried out by Desert Analytics Laboratory, Tuscon, AZ. $Pd(TFA)_2$ and other palladium salts were purchased from Strem Chemicals, Inc., Newburyport, MA. All other chemicals were purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI.

*2.6.2 General procedure for the oxidative cyclization of **26**. Palladium(II) source and additive optimization reactions shown in Tables 2.2.1 and 2.2.2.*

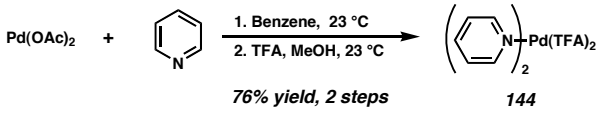
A thick-walled oven-dried 25 mL 15 cm long tube equipped with magnetic stir bar was charged with powdered molecular sieves (MS3Å, 125 mg, 500 mg MS3Å/mmol substrate), palladium source (0.0125 mmol, 0.05 equiv), and additive (0.50 mmol, 2.0 equiv), followed by toluene (2.5 mL), pyridine (4.0 μL, 0.050 mmol, 0.20 equiv), and phenol **26** (40.6 mg, 0.25 mmol, 1.0 equiv). The tube was evacuated and back-filled with O_2 (3x, balloon), heated to 80 °C, and allowed to stir under O_2 (1 atm, balloon). The reaction was monitored by TLC. Upon complete conversion, the crude reaction mixture was chromatographed on silica gel (1.5 x 10 cm, hexanes → 19:1 hexanes/EtOAc eluent). The filtrate was concentrated in vacuo to provide dihydrobenzofuran **27**.

*2.6.3 General procedure for the oxidative cyclization of **26**. Ligand optimization reactions shown in Table 2.2.3.*

A thick-walled oven-dried 10 mL 15 cm-long tube equipped with magnetic stir bar was charged with powdered molecular sieves (MS3Å, 50 mg, 500 mg MS3Å/mmol substrate), palladium complex (0.005 mmol, 0.05 equiv), and Na_2CO_3 (when indicated in Table 2.2.3, 4.2 mg, 0.040 mmol, 0.40 equiv), followed by toluene (1.0 mL), monodentate ligand (when indicated in Table 2, 0.040 mmol, 0.40 equiv) or bidentate ligand (when indicated in Table 2.2.3, 0.020 mmol, 0.20 equiv), pentadecane (GC

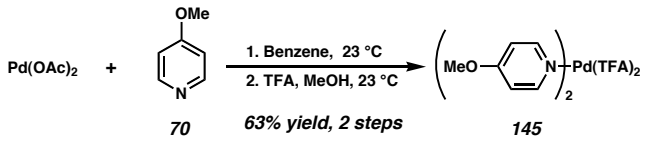
internal standard, 5.0 μL, 0.18 mmol) and phenol **26** (16.2 mg, 0.10 mmol, 1.0 equiv). The tube was evacuated and back-filled with O_2 (3x, balloon), heated to 80 °C, and allowed to stir under O_2 (1 atm, balloon). The reaction was monitored by GC for conversion to dihydrobenzofuran **27**.

2.6.4 Preparation of $L_nPd(TFA)_2$ complexes.

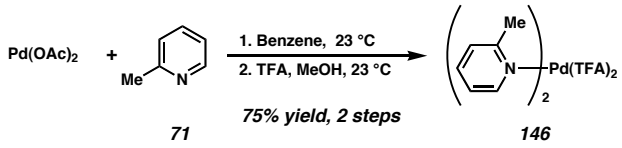


Bis(pyridine)bis(trifluoroacetate)palladium(II) 144. $Pd(OAc)_2$ (250 mg, 1.11 mmol, 1.0 equiv) was dissolved in benzene (15 mL, 0.07 M) and treated with pyridine (180 μL, 2.22 mmol, 2.0 equiv) under argon at 23 °C. The orange solution gradually became lighter with the formation of a nearly white precipitate. After 6 h, the volatiles were removed in vacuo to give $(pyridine)_2Pd(OAc)_2$ as a light colored powder (385 mg, 1.01 mmol, 91%). $(Pyridine)_2Pd(OAc)_2$ (380 mg, 0.993 mmol, 1.0 equiv) was combined with trifluoroacetic acid (2.06 mL, 26.8 mmol, 27 equiv) in methanol (15 mL, 0.66 M) open to the atmosphere at 23 °C. The solution gradually became yellow with the formation of a precipitate after stirring for 1.5 h, which was subsequently isolated via filtration (filtrate was reserved). The yellowish-gray solid was taken up in methanol and CH_2Cl_2 (5 mL each) and filtered to remove Pd black. The two yellow filtrates were combined and concentrated *in vacuo* to give **144** as a light yellow powder (402 mg, 0.819 mmol, 83% yield): mp 168 °C (dec); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55-8.53 (m, 4H), 7.87 (dddd, *J* = 7.8, 7.7, 1.6, 1.5 Hz, 2H), 7.44-7.41 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.1 ($^2J_{CF}$

= 37.5 Hz), 151.1, 139.8, 125.7, 114.1 (q, $^1J_{CF}$ = 289 Hz); HRMS (FAB$^+$) *m/z* calc'd for $[C_{14}H_{10}N_2O_4F_6Pd]^+$: 489.9680, found: 489.9573.

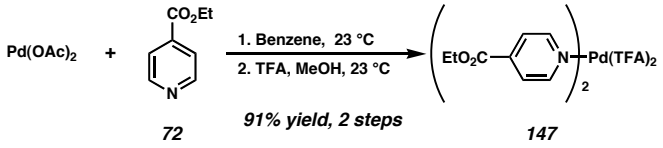


Bis(4-methoxypyridine)palladium(II)bis(trifluoroacetate) 145. $Pd(OAc)_2$ (100 mg, 0.445 mmol, 1.0 equiv) was dissolved in benzene (9 mL, 0.49 M) under argon at 23 °C and 4-methoxypyridine (90.3 μL, 0.890 mmol, 2.0 equiv) was added, upon which a pale yellow solid precipitated. After standing for 30 min, the solids were isolated via filtration and washed with additional benzene (5 mL) affording $(4\text{-methoxypyridine})_2Pd(OAc)_2$ (160 mg, 0.361 mmol, 81% yield). $(4\text{-Methoxypyridine})_2Pd(OAc)_2$ (82 mg, 0.184 mmol, 1.0 equiv) was taken up in trifluoroacetic acid (355 μL, 4.6 mmol, 25 equiv) and methanol (5 mL, 0.037 M). After stirring for 1.5 h, the light yellow solution was concentrated to dryness to give an oily residue. Benzene and CH_2Cl_2 were added (5 mL each), and the solvents removed *in vacuo* to afford **145** as a yellow powder (78 mg, 0.124 mmol, 78% yield): mp 179-180 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (dd, *J* = 6.1, 1.1 Hz, 4H), 6.87 (dd, *J* = 6.1, 1.1 Hz, 4H), 3.91 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 151.7, 111.7, 56.2; Anal. calc'd for $C_{16}H_{14}F_6N_2O_6Pd$: C, 34.90; H, 2.56; N, 5.09. Found: C, 34.87; H, 2.64; N, 4.83.

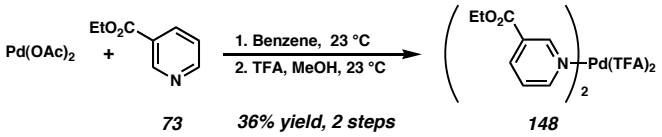


71 *146*

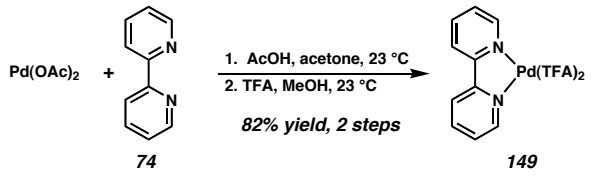
Bis(2-picoline)palladium(II)bis(trifluoroacetate) 146. $Pd(OAc)_2$ (100 mg, 0.445 mmol, 1.0 equiv) was dissolved in benzene (9.0 mL, 0.49 M) under argon at 23 °C and 2-picoline (**71**, 88 μL, 0.890 mmol, 2.0 equiv) was added. The dark orange solution gradually became light orange-yellow, along with the formation of a light precipitate. After 1 h the solids were isolated via filtration to afford $(2\text{-picoline})_2Pd(OAc)_2$ as yellow powder (148 mg, 0.36 mmol, 81% yield). $(2\text{-Picoline})_2Pd(OAc)_2$ (70 mg, 0.170 mmol, 1.0 equiv) was dissolved in methanol (5 mL, 0.034 M) at 23 °C in air and trifluoroacetic acid (328 μL, 4.3 mmol, 25 equiv) was added. The mixture was allowed to stand for 12 h during which time a light colored precipitate formed. The solids were isolated via filtration to provide **146** as a light yellow powder (77 mg, 0.158 mmol, 93% yield). The complex was further purified by recrystallization from a saturated acetone solution that was layered with pentane and allowed to stand: mp 189 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.99 (d, J = 5.5 Hz, 2H), 7.72 (ddd, J = 7.7, 7.7, 1.4 Hz, 2H), 7.30-7.23 (comp. m, 4H), 3.51 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1 (q, $^2J_{CF}$ = 37 Hz), 161.4, 152.3, 139.3, 126.3, 122.5, 113.9 (q, $^1J_{CF}$ = 290 Hz), 25.1; Anal. calc'd. for $C_{16}H_{14}F_6N_2O_4Pd$: C, 37.05; H, 2.72; N, 5.40. Found: C, 37.27; H, 2.84; N, 5.29.



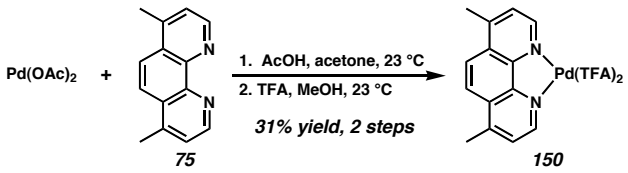
Bis(*iso*-ethylnicotinate)palladium(II)bis(trifluoroacetate) 147. $Pd(OAc)_2$ (100 mg, 0.445 mmol, 1.0 equiv) was dissolved in benzene (10.0 mL, 0.40 M) under argon at 23 °C and *iso*-ethylnicotinate (**72**, 122 μL, 0.891 mmol, 2.0 equiv) was added. The orange solution became yellow upon addition of the ligand. After stirring for 2 h, the solution was concentrated *in vacuo* to give (*iso*-ethylnicotinate)$_2$Pd(OAc)$_2$ as a light yellow powder (216 mg, 0.410 mmol, 92% yield). (*iso*-Ethylnicotinate)$_2$Pd(OAc)$_2$ (100 mg, 0.190 mmol, 1.0 equiv) was dissolved in methanol (8 mL) in air at 23 °C and trifluoroacetic acid (366 μL, 4.74 mmol, 25 equiv) was added. No color change was observed. After 1 h the solution was concentrated under reduced pressure to give **147** as a yellow powder (114 mg, 0.189 mmol, 99% yield). The complex was further purified by recrystallization from a saturated solution in acetone that was layered with pentane: mp 163-164 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (dd, J = 5.2, 1.7 Hz, 4H), 8.00 (dd, J = 5.2, 1.7 Hz, 4H), 4.46 (q, J = 7.2 Hz, 4H), 1.42 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 163.1, 151.8, 141.1, 125.1, 114.0 (d, $^2J_{CF}$ = 29 Hz), 63.0, 14.3; Anal. calc'd. for $C_{20}H_{18}F_6N_2O_8Pd$: C, 37.84; H, 2.86; N, 4.41. Found: C, 37.86; H, 3.04; N, 4.33.



Bis(ethylnicotinate)palladium(II)bis(trifluoroacetate) 148. $Pd(OAc)_2$ (100 mg, 0.445 mmol, 1.0 equiv) was dissolved in benzene (10.0 mL, 0.40 M) under argon at 23 °C and ethylnicotinate (**73**, 122 μL, 0.891 mmol, 2.0 equiv) was added. After 30 min, the yellow solution was concentrated to ca. 5 mL, upon which needles formed. The solids were isolated by filtration to give $(ethylnicotinate)_2Pd(OAc)_2$ as a pale yellow crystalline material (118 mg, 0.223 mmol, 50% yield). $(Ethylnicotinate)_2Pd(OAc)_2$ (60 mg, 0.114 mmol, 1.0 equiv) was taken up in methanol (5 mL) in air at 23 °C and trifluoroacetic acid (220 μL, 2.85 mmol, 25 equiv) was added. The solvents were removed in vacuo after 45 min to give an orange oily residue. Benzene (1 mL) was added, and the solvent was removed under reduced pressure to provide **148** as a pale yellow powder (53 mg, 0.083 mmol, 73% yield): mp 133-135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.13 (d, J = 1.7 Hz, 2H), 8.68 (dd, J = 5.5, 1.1 Hz, 2H), 8.52 (ddd, J = 8.0, 1.7, 1.7 Hz, 2H), 7.57 (ddd, 8.0, 5.8, 0.55 Hz, 2H), 4.47 (q, J = 7.2 Hz, 4H), 1.44 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0 (q, $^2J_{CF}$ = 37.6 Hz), 162.7, 153.7, 152.0, 140.8, 129.0, 125.4, 114.0 (q, $^1J_{CF}$ = 289 Hz), 62.8, 14.3; Anal. calc'd. for $C_{20}H_{18}F_6N_2O_8Pd$: C, 37.84; H, 2.86; N, 4.41. Found: C, 37.88; H, 2.91; N, 4.29.

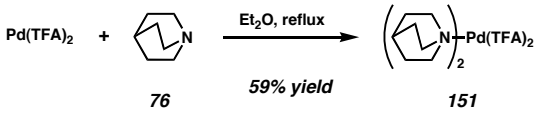


(Dipyridyl)palladium(II)bis(trifluoroacetate) 149. $Pd(OAc)_2$ (200 mg, 0.891 mmol, 1.0 equiv) was dissolved in acetone (20 mL) at 25 °C in air. Acetic acid (10 μL) was added to the solution, followed by dipyridyl (**74**, 167 mg, 1.07 mmol, 1.2 equiv). The mixture was allowed to stand at 25 °C for 1 h, during which time a yellow precipitate formed. The solid was isolated via filtration and washed with acetone to provide (dipyridyl)$Pd(OAc)_2$ as a pale yellow powder (330 mg, 0.867 mmol, 97% yield). (Dipyridyl)$Pd(OAc)_2$ (330 mg, 0.867 mmol, 1.0 equiv) was dissolved in MeOH at 25 °C. An excess of trifluoroacetic acid (1.67 mL, 21.7 mmol, 25 equiv) was added to the yellow solution, upon which a pale yellow precipitate formed immediately. This precipitate was isolated by filtration to afford **149** (359 mg, 0.735 mmol, 85% yield). Spectroscopic data were in accordance with that reported by Randaccio.[29]

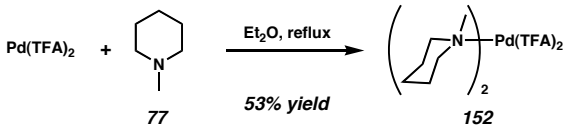


(4,7-Dimethyl-1,10-phenanthroline)palladium(II)bis(trifluoroacetate) 150. $Pd(OAc)_2$ (100 mg, 0.445 mmol, 1.0 equiv) was dissolved in acetone at 25 °C in a flask open to air. 4,7-Dimethyl-1,10-phenanthroline (**75**, 94 mg, 0.449 mmol, 1.01 equiv) was added as a solid, and the solution was allowed to stir for 10 min. The mixture was then allowed to

stand for 30 min during which time a crystalline solid appeared. This solid, (4,7-dimethyl-1,10-phenanthroline)$Pd(OAc)_2$, was isolated via filtration (75 mg, 0.173 mmol, 39% yield). (4,7-Dimethyl-1,10-phenanthroline)$Pd(OAc)_2$ (50 mg, 0.139 mmol, 1.0 equiv) was dissolved in methanol (5 mL) in air at 25 °C. Trifluoroacetic acid (267 μL, 3.47 mL, 25 equiv) was added to the orange solution which led immediately to the formation of a yellow precipitate. The mixture was allowed to stand for 15 min after which **150** was isolated by filtration as a yellow powder (59 mg, 0.110 mmol, 79% yield). Spectroscopic data were in agreement with that reported by Randaccio.[29]

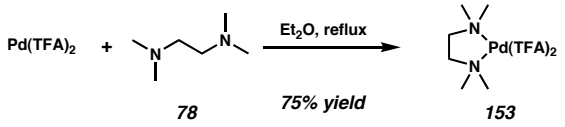


Bis(quinuclidine)palladium(II)bis(trifluoroacetate) 151. A solution of quinuclidine (**76**, 67 mg, 0.602 mmol, 2.0 equiv) in Et_2O (2 mL) was added dropwise to a stirring suspension of $Pd(TFA)_2$ (100 mg, 0.301 mmol, 1.0 equiv) in Et_2O (13 mL). The brown mixture was heated to reflux under argon for 6 h, then cooled to 25 °C, filtered, and concentrated *in vacuo* to provide a light brown powder. The powder was washed with pentane and dried under vacuum to provide **151** as a tan solid (98 mg, 0.177 mmol, 59% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.01-2.95 (m, 12H), 1.77 (sept, J = 3.2 Hz, 2H) 1.63-1.57 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 114.4 (d, $^1J_{CF}$ = 290 Hz), 51.8, 26.2, 19.7. Anal. calc'd for $C_{18}H_{26}F_6N_2O_4Pd$: C, 38.97; H, 4.72; N, 5.05. Found: C, 38.41; H, 4.67; N, 4.86.



77 152

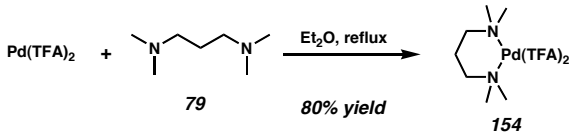
Bis(*N*-methylpiperidine)palladium(II)bis(trifluoroacetate) 152. A solution of *N*-methylpiperidine (**77**, 73 μL, 0.602 mmol, 2.0 equiv) in Et_2O (2 mL) was added dropwise to a stirring suspension of $Pd(TFA)_2$ (100 mg, 0.301 mmol, 1.0 equiv) in Et_2O (13 mL). The brown mixture was heated to reflux under argon for 6 h, then cooled to 25 °C, filtered, and concentrated in vacuo to provide a brown residue. Benzene (2 mL) was added, and the volatiles were removed under reduced pressure to provide **152** as a light brown powder (84 mg, 0.158 mmol, 53% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.77-2.72 (comp. m, 10H), 2.63-2.47 (m, 4H), 2.01-1.73 (comp. m, 6H), 1.40-1.27 (comp. m 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1 (q, $^2J_{CF}$ = 37 Hz), 114.4 (d, $^1J_{CF}$ = 290 Hz), 61.2, 52.7, 25.1, 23.2; Anal. calc'd for $C_{16}H_{26}F_6N_2O_4Pd$: C, 36.20; H, 4.94; N, 5.28. Found: C, 36.17; H, 4.69; N, 5.13.



78 153

(TMEDA)palladium(II)bis(trifluoroacetate) 153. A solution of TMEDA (**78**, 45 μL, 0.301 mmol, 1.0 equiv) in Et_2O (2 mL) was added dropwise to a stirring suspension of $Pd(TFA)_2$ (100 mg, 0.301 mmol, 1.0 equiv) in Et_2O (13 mL). The brown mixture was heated to reflux under nitrogen for 4 h during which time a precipitate formed. The mixture was cooled to 25 °C and the solids isolated via filtration to provide **153** (102 mg,

0.227 mmol, 75% yield): mp 175-178 °C (dec); ^{1}H NMR (300 MHz, CD_3OD) δ 2.85 (s, 4H), 2.66 (s, 12H); ^{13}C NMR (75 MHz, CD_3OD) δ 164.1 ($^2J_{CF}$ = 37.5 Hz), 116.1 ($^1J_{CF}$ = 289 Hz), 63.8, 51.1; HRMS (FAB$^+$) *m/z* calc'd for $[C_{10}H_{16}F_6N_2O_4PdNa]^+$: 470.9947, found: 470.9972.

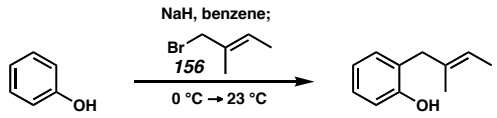


(*N*,*N*-tetramethylpropylenediamine)palladium(II)bis(trifluoroacetate) 154. A solution of *N*,*N*-tetramethylpropylenediamine (**79**, 50 μL, 0.301 mmol, 1.0 equiv) in Et_2O (2 mL) was added dropwise to a stirring suspension of $Pd(TFA)_2$ (100 mg, 0.301 mmol, 1.0 equiv) in Et_2O (13 mL), Upon heating to reflux under nitrogen, the brown mixture became a brown-orange solution with a brown precipitate. After 2 h, the mixture was cooled to 25 °C and the solids were isolated by filtration to afford **154** as a light brown powder (111 mg, 0.241 mmol, 80% yield). The compound could be further purified from a saturated solution in acetone that was layered with pentane: mp 135 °C (dec); ^{1}H NMR (300 MHz, CD_2Cl_2) δ 2.60 (s, 12H), 2.34 (m, 4H), 1.84 (m, 2H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 63.7, 52.2, 23.5; HRMS (FAB$^+$) *m/z* calc'd for $[C_{11}H_{18}N_2O_4F_6PdNa]^+$: 485.0103, found: 485.0107.

2.6.5 Synthesis of substituted phenols.

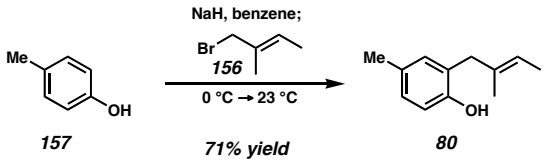
General procedure for the preparation of substituted phenols. Phenols **26**, **80**, **82**, **84**, **88**, **90**, **92**, **94**, **96** and **28** were synthesized by the modified procedure of Hurd and Hoffman.[30] To a stirring suspension of NaH (17.5 mmol, 1.1 equiv) in benzene (25 mL)

at 0 °C was added a benzene (15 mL) solution of the phenol (15.9 mmol, 1 equiv). The mixture was charged with (*E*)-1-bromo-2-methyl-but-2-ene (**156**, 17.5 mmol, 1.1 equiv, prepared according to literature procedure[31]) and allowed to warm to 23 °C. After 24 h stirring, benzene was removed under reduced pressure and H_2O (50 mL) and petroleum ether (50 mL) were added. The mixture was extracted with 20% aqueous NaOH (3 x 20 mL) and "Claisen's alkali" (20 mL; 6 g KOH in 5 mL H_2O diluted with 25 mL MeOH). The combined alkali extracts were acidified with 6 N H_2SO_4 and extracted with Et_2O (3 x 50 mL). Combination of the organics, drying over $MgSO_4$, concentration in vacuo and purification by flash column chromatography on silica gel (19:1 hexanes/EtOAc eluent) provided the *o*-substituted phenol.

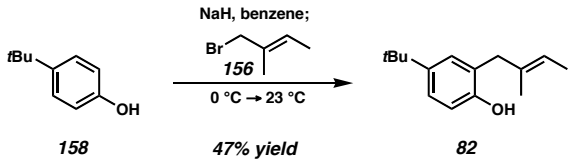


155 *87% yield* *26*

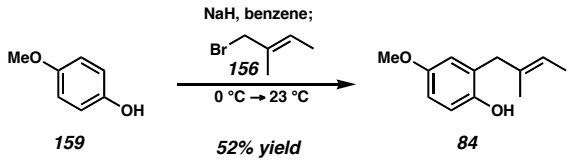
Phenol 26. 87% yield colorless oil: R_F 0.46 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19-7.07 (comp. m, 2H), 6.91-6.83 (comp. m, 2H), 5.51 (qq, *J* = 6.6, 1.7 Hz, 1H), 5.42 (br s, 1H,), 3.34 (s, 2H), 1.66 (d, *J* = 6.6 Hz, 3H), 1.61 (d, *J* = 1.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 135.1, 131.1, 128.0, 125.2, 121.4, 120.8, 116.1, 41.7, 15.7, 13.6; IR (film) 3459, 2916, 1454, 1219 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{11}H_{14}O]^+$: 162.1045, found 162.1044.



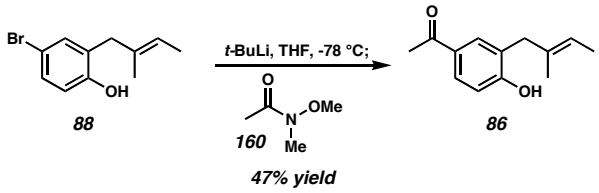
***p*-Methylphenol 80**. 71% yield colorless oil: R_F 0.40 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (d, *J* = 8.2 Hz, 1H,), 6.89 (s, 1H), 6.73 (d, *J* = 8.2 Hz, 1H), 5.49 (app. qd, *J* = 6.7, 0.9 Hz, 1H), 5.23 (s, 1H), 3.33 (s, 2H), 2.27 (s, 3H), 1.66 (d, *J* = 6.5 Hz, 3H), 1.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 135.3, 131.7, 129.9, 128.6, 124.8, 121.4, 116.0, 42.1, 20.7, 15.8, 13.7; IR (film) 3457, 2918, 1501, 1260, 1196, 1108 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{12}H_{16}O]^+$: 176.1201, found 176.1199.



***p*-*t*-Butylphenol 82**. 47% yield colorless oil: R_F 0.51 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.07 (d, *J* = 2.2 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 5.49 (q, *J* = 6.6 Hz, 1H), 5.24 (s, 1H), 1.66 (dd, *J* = 6.6, 1.1 Hz, 3H), 1.62 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 143.8, 135.7, 128.4, 125.2, 124.6, 121.7, 116.0, 43.0, 34.7, 32.3, 16.4, 14.2; IR (film) 3463, 2964, 2909, 2865, 1504, 1364, 1271 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{15}H_{22}O]^+$: 218.1671, found 218.1677.

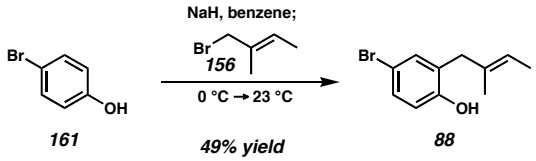


***p*-Methoxyphenol 84**. 52% yield colorless oil: R_F 0.46 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78-6.65 (comp. m, 3H), 5.48 (q, *J* = 6.6 Hz, 1H), 5.03 (br s, 1H), 3.77 (s, 3H), 3.33 (s, 2H), 1.65 (dq, *J* = 6.6, 1.1 Hz, 3H), 1.61 (d, *J* = 1.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 149.2, 134.9, 126.3, 121.6, 116.7, 112.7, 55.9, 42.2, 15.8, 13.7; IR (film) 3426, 2915, 1504, 1434, 1230, 1206 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{12}H_{16}O]^+$: 192.1150, found 192.1153.

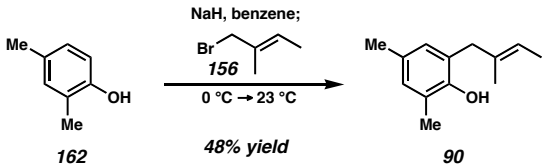


***p*-Acylphenol 86**. Bromophenol **88** (100 mg, 0.42 mmol, 1.0 equiv) was dissolved in THF and cooled to –78 °C. Upon dropwise addition of *t*-BuLi (1.7 M in pentane, 782 μL, 1.33 mmol, 3.2 equiv), the stirring solution became yellow. After 1.5 h, exchange was complete by TLC and as *N*-methoxy-*N*-methyl acetamide (**160**, 88 μL, 0.83 mmol, 2.0 equiv) was introduced, the yellow color dissipated. The mixture was allowed to stir at –78 °C for 1 h, then was quenched with 1:1 H_2O/saturated aqueous NH_4Cl (10 mL), warmed to 23 °C, and extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica gel (4:1 hexanes/EtOAc eluent) gave the *p*-acyl phenol

86 (40 mg, 0.20 mmol, 47% yield) as a white crystalline solid: R_F 0.23 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81-7.76 (comp. m, 2H), 6.87 (d, *J* = 8.3 Hz, 1H), 6.10 (s, 1H), 5.55 (qq, *J* = 6.4, 1.4 Hz, 1H), 3.42 (s, 2H), 2.56 (s, 3H), 1.67 (dd, *J* = 6.4, 1.4 Hz, 3H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 160.1, 134.8, 131.9, 130.5, 129.6, 125.0, 122.5, 116.1, 42.1, 26.6, 15.7, 13.7; IR (film) 3264, 2917, 1655, 1589, 1280 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{13}H_{16}O_2]^+$: 204.1150, found 204.1152.

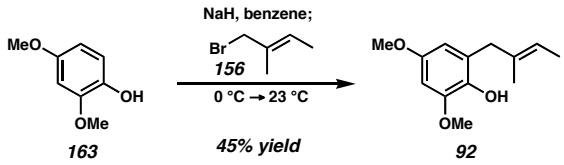


***p*-Bromophenol 88**. 49% yield pale green oil: R_F 0.51 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12-7.09 (comp. m, 2H), 6.61 (d, *J* = 8.8 Hz, 1H), 5.41 (q, *J* = 6.6 Hz, 1H), 5.33 (br s, 1H), 3.22 (s, 2H), 1.56 (d, *J* = 6.6 Hz, 3H), 1.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5, 134.5, 133.5, 130.9, 127.3, 122.3, 118.0, 112.8, 41.8, 15.7, 13.7; IR (film) 3453, 2916, 1403, 1411, 1263, 1216, 1108 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{11}H_{13}BrO]^+$: 240.0150, found 240.0151.

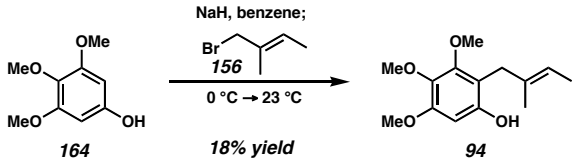


4,6-Dimethylphenol 90. 48% yield colorless oil: R_F 0.72 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (s, 1H), 6.75 (s, 1H), 5.54 (qq, *J* = 6.6, 1.7 Hz, 1H),

5.33 (s, 1H), 3.34 (s, 2H), 2.25 (s, 3H), 2.21 (s, 3H), 1.67 (dd, *J* = 6.6, 1.1 Hz, 3H), 1.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.4, 135.6, 130.2, 129.3, 124.6, 124.1, 121.5, 76.5, 42.6, 20.6, 16.0, 15.7, 13.7; IR (film) 3493, 2917, 1485, 1213, 1204 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{13}H_{18}O]^+$: 190.1358, found 190.1355.

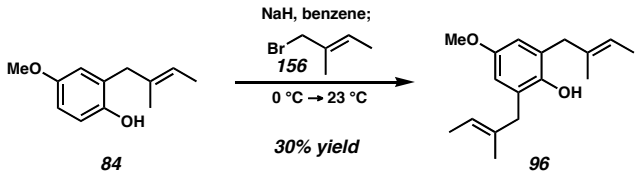


4,6-Dimethoxyphenol 92. Phenolic starting material (**163**) was synthesized by the procedure of Helquist and Bäckvall.[32] 45% yield colorless oil: R_F 0.52 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.38 (d, *J* = 2.8 Hz, 1H), 6.26 (d, *J* = 2.8 Hz, 1H), 5.28-5.27 (comp. m, 2H), 3.87 (s, 3H), 3.76 (s, 3H), 3.31 (s, 2H), 1.62-1.60 (comp. m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 147.0, 138.0, 134.6, 126.1, 120.2, 106.1, 97.1, 56.2, 55.9, 39.5, 16.1, 13.8; IR (film) 3521, 2916, 1613, 1497, 1227, 1199 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{13}H_{18}O_3]^+$: 222.1256, found 222.1255.

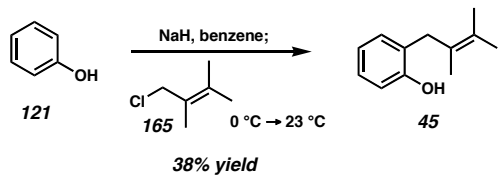


4,5,6-Trimethoxyphenol 94. 18% yield white crystalline solid: R_F 0.25 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.26 (s, 1H), 5.50-5.40 (m, 1H), 5.41 (s, 1H), 3.85 (s, 3H), 3.82 (s, 6H), 3.37 (s, 2H), 1.65 (s, 3H), 1.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 152.3, 151.9, 136.4, 135.5, 120.8, 110.5, 96.6, 61.4, 61.2,

56.0, 33.9, 15.9, 13.6; IR (film) 3417, 2937, 1607, 1462, 1414, 1126 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{14}H_{20}O_4]^+$: 252.1361, found 252.1352.

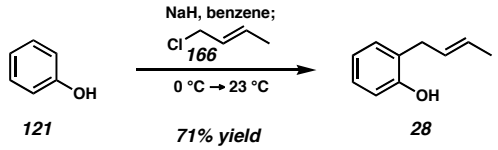


***p*-Methoxy-bis(alkyl)phenol 96**. 30% yield yellow oil: R_F 0.82 (4:1 hexanes/EtOAc eluent); ^1H NMR (300 MHz, $CDCl_3$) δ 6.54 (s, 2H), 5.38 (qq, *J* = 6.6, 1.1 Hz, 2H), 5.19 (s, 1H), 3.75 (s, 3H), 3.31 (s, 4H), 1.64 (dd, *J* = 5.5, 1.1 Hz, 6H), 1.31 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 147.7, 135.1, 126.9, 121.0, 114.3, 55.8, 41.4, 15.9, 13.7; IR (film) 3490, 2915, 1604, 1478, 1440, 1234, 1193 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{17}H_{24}O_2]^+$: 242.1307, found 242.1310.

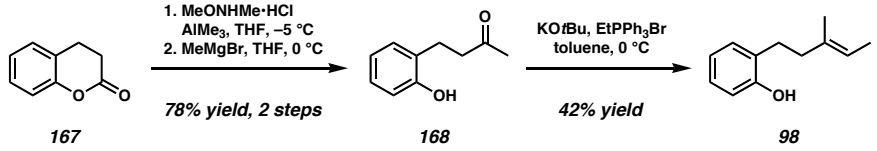


Tetrasubstituted olefin 45. Conversion of known 2,3-dimethyl-but-2-en-1-ol[33] to 1-chloro-2,3-dimethyl-but-2-ene (**165**) followed Corey's procedure.[34] Dimethyl sulfide (0.63 mL, 8.55 mmol, 1.6 equiv) was added to a solution of *N*-chlorosuccinimide (1.14 g, 8.55 mmol, 1.6 equiv) in CH_2Cl_2 (45 mL) at 0 °C. The mixture was stirred for 30 min and cooled to –20 °C. A solution of 2,3-dimethyl-but-2-en-1-ol (537 mg, 5.34 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was introduced dropwise over 5 min. The resulting clear, colorless solution was warmed to 0 °C and allowed to stir for 1 h, then poured into ice-

cold brine (20 mL). The layers were separated, and the aqueous portion extracted with Et_2O (3 x 20 mL). The organics were combined, washed with ice-cold brine (2 x 30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude, unstable 1-chloro-2,3-dimethyl-but-2-ene (**165**) was used immediately without further purification. NaH (60% in mineral oil, 214 mg, 5.34 mmol, 1.0 equiv) was suspended in benzene (5 mL), cooled to 0 °C, and subjected to a benzene (5 mL) solution of phenol (401 mg, 4.27 mmol, 0.8 equiv). The prepared allylic chloride was transferred to the phenoxide with additional benzene (10 mL). The mixture was allowed to warm to 23 °C and stirred for 12 h. Benzene was removed by rotary evaporation from the opaque, pink mixture, and H_2O (50 mL) and petroleum ether (50 mL) were added. The mixture was extracted with 20% aqueous NaOH (3 x 20 mL) and "Claisen's alkali" (10 mL; 6 g KOH in 5 mL H_2O diluted with 25 mL MeOH). The combined alkali extracts were acidified with 6 N H_2SO_4 and extracted with Et_2O (3 x 50 mL). The organics were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash column chromatography on silica gel (19:1 hexanes/EtOAc eluent) afforded **45** (286 mg, 1.62 mmol, 38% yield from phenol) as a slightly unstable, clear, colorless oil: R_F 0.52 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16-6.98 (comp. m, 2H), 6.83 (ddd, *J* = 7.7, 7.4, 1.1 Hz, 1H), 6.62 (d, *J* = 7.7 Hz, 1H), 4.79 (s, 1H), 3.35 (s, 2H), 1.63 (s, 3H), 1.53 (s, 3H), 1.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 130.7, 128.0, 127.4, 126.6, 126.5, 121.2, 116.1, 35.7, 21.2, 20.9, 18.6; IR (film) 3440, 2917, 2860, 1488, 1454, 1218 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{12}H_{16}O]^+$: 176.1201, found 176.1206.



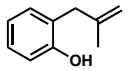
Phenol 28. Synthesized using the above procedure[30] for **26** from phenol (500 mg, 5.3 mmol) and crotyl chloride (**166**, predominantly trans, 4% 3-choloro-1-butene, 621 μL, 6.37 mmol). 71% yield of a colorless oil: R_F 0.41 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16-7.08 (comp. m, 2H), 6.90-6.80 (comp. m, 2H), 5.66-5.62 (comp. m 2H), 5.06 (s, 1H), 3.35 (d, J = 1.9 Hz, 2H), 1.72-1.70 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 130.5, 129.1, 128.1, 127.8, 126.1, 121.1, 116.1, 34.5, 18.1; IR (film) 3451, 2916, 1454, 752 cm^{-1}; HRMS (EI$^+$) m/z calc'd for $[C_{10}H_{12}O]^+$: 148.0888, found: 148.0883.



Homoallylic phenol 98. A solution of MeONHMe•HCl (4.88 g, 50.0 mmol, 2.5 equiv) in CH_2Cl_2 (40 mL) was cooled to –5 °C in an acetone/ice bath. $AlMe_3$ (2.0 M in toluene, 25.0 mL 50.0 mmol, 2.5 equiv) was introduced dropwise over 15 min, and the mixture allowed to stir for 1 h. Bubbling commenced upon addition of dihydrocoumarin (**167**, 2.53 mL, 20.0 mmol, 1.0 equiv) to the clear, colorless solution and the mixture was quenched after 10 min with saturated aqueous $NaHCO_3$ (15 mL). After extraction with CH_2Cl_2 (3 x 25 mL), the organics were combined, dried over Na_2SO_4, and concentrated to toluene. Following redissolution in THF (40 mL), MeMgBr (3 M in Et_2O, 16.7 mL, 50.0 mmol, 2.5 equiv) was added dropwise at 0 °C and the mixture allowed to stir for 15 min.

After quenching with saturated aqueous NH_4Cl (20 mL) and extraction with Et_2O, the combined organics were dried over $MgSO_4$ and concentrated under reduced pressure to yield a pale yellow oil which was purified by flash column chromatography on silica gel (9:1 hexanes/EtOAc eluent) to give methyl ketone **168** (2.56 g, 15.6 mmol, 78% yield) as a colorless oil. Dry potassium *t*-butoxide (4.72 g, 42.1 mmol, 2.7 equiv) was added slowly to a suspension of $EtPPh_3Br$ (15.6 g, 42.1 mmol, 2.7 equiv) in toluene (15 mL) at 0 °C. The mixture became viscous and turned from colorless to yellow to orange. The flask was supplied with additional toluene (15 mL), warmed to 23 °C, and allowed to stir for 2 h. The now red reaction mixture was re-cooled to 0 °C and subjected to a toluene (10 mL) solution of the methyl ketone (2.56 g, 15.6 mmol, 1 equiv). After warming to 23 °C and stirring for 3 h, consumption of the starting material was observed by TLC. The mixture was re-cooled to 0 °C, quenched with 1:1 H_2O/saturated aqueous NH_4Cl, and extracted with EtOAc (3 x 75 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the yellow residue on silica gel (19:1 hexanes/EtOAc eluent) and removal of the solvents by rotary evaporation provided **98** (1.15 g, 6.52 mmol, 42% yield) as a colorless oil, and as a mixture of olefin isomers: R_F 0.40 (4:1 hexane/EtOAc eluent); ^{1}H NMR (data for 3.6:1 mixture of olefin isomers based on the relative integration of peaks at δ 1.64 and 1.54; 300 MHz, $CDCl_3$) δ 7.18-7.09 (comp. m, 2H), 7.18-7.09 (comp. m, 2H), 6.94-6.89 (comp. m, 1H), 6.94-6.89 (comp. m, 1H), 6.79 (d, *J* = 7.7 Hz, 1H), 6.79 (d, *J* = 7.7 Hz, 1H), 5.35-5.27 (comp. m, 1H), 5.35-5.27 (comp. m, 1H), 5.09-5.05 (comp. m, 1H), 5.09-5.05 (comp. m, 1H), 2.78-2.71 (comp. m, 2H), 2.78-2.71 (comp. m, 2H), 2.41-2.29 (comp. m, 2H), 2.41-2.29 (comp. m, 2H), 1.79 (s, 3H), 1.71 (s, 3H), 1.63 (d, *J* = 6.6 Hz,

3H), 1.54 (d, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 153.6, 135.9, 130.5, 130.3, 128.7, 127.4, 127.3, 121.0, 120.2, 119.2, 115.5, 39.9, 31.9, 29.2, 28.7, 23.8, 16.1, 13.6, 13.3; IR (film) 3441, 2964, 2928, 2860, 1591, 1502, 1456, 1235 cm^{-1}; MS m/z calc'd for $[C_{12}H_{16}O]^+$ HRMS (NH_3CI): 176.1201, found 176.1199.



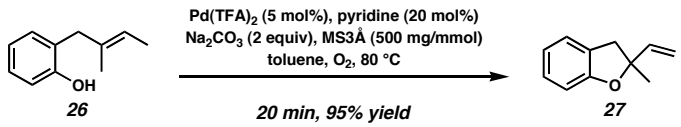
100

Phenol 100. Synthesized according to the method of Goering.[35] R_F 0.48 (4:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19-7.09 (comp. m, 2H), 6.92-6.83 (comp. m, 2H), 5.20 (s, 1H), 4.90 (app.d, J = 20.1 Hz, 2H), 3.20 (s, 2H), 1.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 144.9, 131.2, 128.2, 125.0, 121.0, 116.3, 112.6, 40.1, 22.3; IR (film) 3468, 2971, 2914, 1489, 1454, 1214, 753 cm^{-1}; HRMS (EI$^+$) m/z calc'd for $[C_{10}H_{12}O]^+$: 148.0888, found: 148.0894.

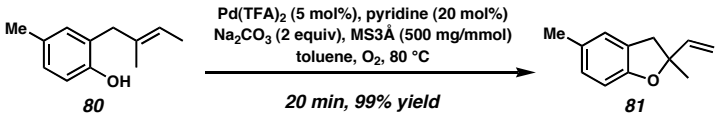
2.6.6 General procedure for the racemic oxidative cyclization of phenols shown in Tables 2.2.4, 2.2.5, and 2.2.6.

A thick-walled oven-dried 25 mL 15 cm long tube equipped with magnetic stir bar was charged with powdered molecular sieves (MS3Å, 125 mg, 500mg/mmol), $Pd(TFA)_2$ (4.2 mg, 0.0125 mmol, 0.05 equiv), and Na_2CO_3 (53 mg, 0.50 mmol, 2.0 equiv), followed by toluene (2.5 mL), pyridine (4.0 μL, 0.050 mmol, 0.20 equiv), and phenolic substrate (0.25 mmol, 1.0 equiv). The tube was evacuated and back-filled with O_2 (3 x, balloon), heated to 80 °C, and allowed to stir under O_2 (1 atm, balloon). The reaction was monitored by TLC. Upon complete conversion, which varied by substrate, the crude

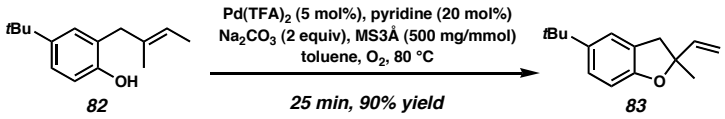
reaction mixture was filtered over silica gel (1.5 x 10 cm, hexane → 19:1 hexanes/EtOAc eluent). Concentration of the filtrate in vacuo provided the cyclized product.



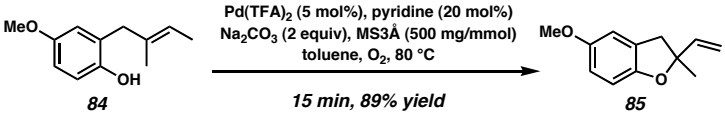
Dihydrobenzofuran 27. 20 min, 95% yield clear, colorless oil: R_F 0.67 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16-7.11 (comp. m, 2H), 6.87-6.79 (comp. m, 2H), 6.06 (dd, *J* = 17.0, 11.0 Hz, 1H), 5.33 (dd, *J* = 17.6, 1.1 Hz, 1H), 5.11 (dd, *J* = 11.0, 1.1 Hz, 1H), 3.19 (d, *J* = 15.4 Hz, 1H), 3.07 (d, *J* = 15.4 Hz, 1H), 15.7 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 141.7, 128.1, 126.5, 125.2, 120.4, 112.9, 109.6, 87.7, 42.3, 26.4; IR (film) 1481, 1245 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{11}H_{12}O]^+$: 160.0888, found 160.0888.



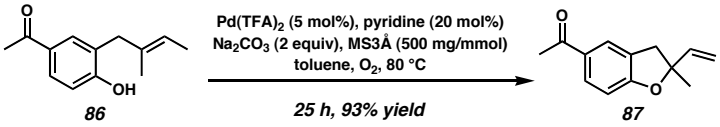
***p*-Methyldihydrobenzofuran 81**. 20 min, 99% yield clear, colorless oil: R_F 0.66 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.93 (d, *J* = 8.9 Hz, 1H), 6.70 (d, *J* = 7.9 Hz, 1H), 6.05 (dd, *J* = 17.3, 10.9 Hz, 1H), 5.32 (dd, *J* = 17.3, 1.2 Hz, 1H), 5.10 (dd, *J* = 10.6, 1.2 Hz, 1H), 3.16 (d, *J* = 15.5 Hz, 1H), 3.03 (d, *J* = 15.5 Hz, 1H), 2.29 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 142.0, 129.7, 128.6, 126.6, 125.9, 112.9, 109.2, 87.7, 42.3, 26.3, 21.0; IR (film) 2975, 2925, 1492, 1249 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{12}H_{14}O]^+$: 174.1045, found: 174.1047.



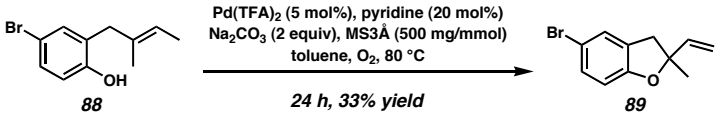
***p-t*-Butyldihydrobenzofuran 83**. 25 min, 90% yield clear, colorless oil: R_F 0.74 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17-7.14 (comp. m, 2H), 6.72 (d, *J* = 8.2 Hz, 1H), 6.06 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.32 (d, *J* = 17.0 Hz, 1H), 5.09 (d, 11.0 Hz, 1H), 3.18 (d, *J* = 15.4 Hz, 1H), 3.06 (d, *J* = 15.4 Hz, 1H), 1.56 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 143.4, 142.1, 126.2, 125.0, 122.3, 112.9, 108.8, 87.7, 42.5, 34.4, 32.0, 26.4; IR (film) 2964, 1494, 1250 cm^{-1}; HRMS (NH_3CI) m/z calc'd for $[C_{15}H_{20}O]^+$: 216.1514, found: 216.1515.



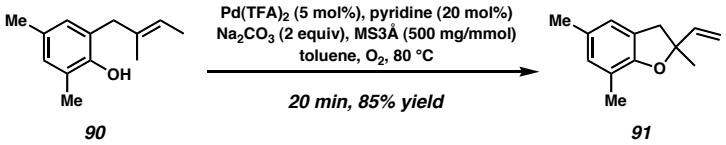
***p*-Methoxydihydrobenzofuran 85**. 15 min, 89% yield clear, colorless oil: R_F 0.57 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.74-6.65 (comp. m, 3H), 6.04 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.31 (dd, *J* = 17.6, 1.1 Hz, 1H), 5.10 (dd, *J* = 10.4, 1.1 Hz, 1H), 3.76 (s, 3H), 3.04 (d, *J* = 15.4 Hz, 1H), 3.16 (d, *J* = 15.4 Hz, 1H), 1.55 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 153.0, 141.8, 127.5, 113.0, 112.9, 111.5, 109.5, 87.8, 56.2, 42.7, 26.3; IR (film) 1488, 1226, 1140 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{12}H_{14}O_2]^+$: 190.0994, found: 190.0999.



***p*-Acyldihydrobenzofuran 87**. 25 h, 93% yield clear, colorless oil: R_F 0.30 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83-7.81 (comp. m, 2H), 6.81 (d, *J* = 9.2 Hz, 1H), 6.04 (dd, *J* = 17.4, 11.0 Hz, 1H), 5.32 (d, *J* = 17.0 Hz, 1H), 5.13 (d, *J* = 11.0 Hz, 1H), 3.22 (d, *J* = 15.6 Hz, 1H), 3.09 (d, *J* = 15.6 Hz, 1H), 2.54 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.9, 163.3, 141.1, 130.8, 130.7, 127.5, 126.0, 113.5, 109.3, 89.7, 41.5, 26.6, 26.4; IR (film) 2976, 1675, 1608, 1488, 1271 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{13}H_{14}O_2]^+$: 202.0994, found 202.0995.

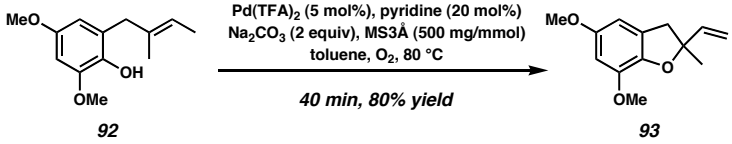


***p*-Bromodihydrobenzofuran 89**. 24 h, 33% yield: R_F 0.65 (4:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.20 (comp. m, 2H), 6.67 (d, *J* = 8.2 Hz, 1H), 6.02 (dd, *J* = 17.3, 11.0 Hz, 1H), 5.30 (d, *J* = 17.6 Hz, 1H), 5.11 (d, *J* = 11.0 Hz, 1H), 3.17 (d, *J* = 15.9 Hz, 1H), 3.05 (d, *J* = 15.9 Hz, 1H), 1.55 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 141.3, 131.0, 129.2, 128.2, 113.4, 112.2, 111.3, 88.66, 42.0, 26.2; IR (film) 1474, 1244; ; HRMS (NH_3CI) *m/z* calc'd for $[C_{11}H_{11}BrO]^+$: 237.9993, found: 237.9991.



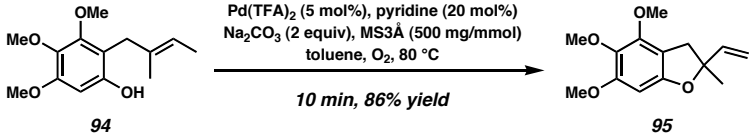
90 ***91***

4,6-Dimethyldihydrobenzofuran 91. 20 min, 85% yield clear, colorless oil: R_F 0.75 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (s, 1H), 6.76 (s, 1H), 6.03 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.29 (dd, *J* = 17.0, 1.1 Hz, 1H), 5.07 (dd, *J* = 10.4, 1.1 Hz, 1H), 3.13 (d, *J* = 15.4 Hz, 1H), 3.03 (d, *J* = 15.4 Hz, 1H), 2.25 (s, 3H), 2.20 (s, 3H), 1.55 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 142.2, 130.0, 129.5, 125.9, 123.0, 119.3, 112.6, 87.2, 42.6, 26.4, 20.9, 15.5; IR (film) 2973, 2922, 1482, 1233 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{13}H_{16}O]^+$: 188.1201, found 188.1198.

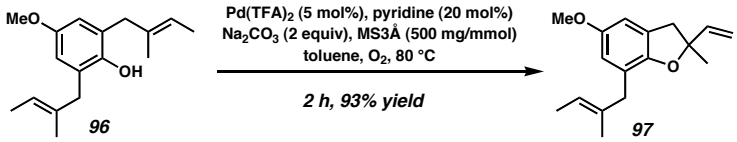


92 ***93***

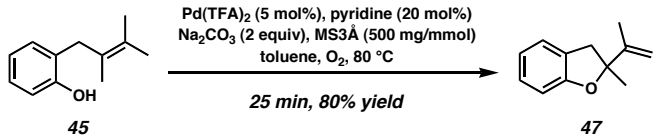
4,6-Dimethoxydihydrobenzofuran 93. 40 min, 80% yield clear, colorless oil: R_F 0.57 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.36 (d, *J* = 10.6 Hz, 1H), 6.35 (d, *J* = 10.6 Hz, 1H), 6.07 (dd, *J* = 17.2, 10.6 Hz, 1H), 5.31 (dd, *J* = 17.2, 1.20 Hz, 1H), 5.09 (dd, *J* = 10.3, 1.20 Hz, 1H), 3.86 (s, 3H), 3.76 (s, 3H), 3.18 (d, *J* = 15.5 Hz, 1H), 3.05 (d, *J* = 15.5 Hz, 1H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 154.7, 144.7, 141.6, 141.4, 127.3, 112.9, 101.3, 99.2, 56.2, 56.1, 43.0, 26.4; IR (film) 2972, 2938, 2837, 1617, 1498, 1217, 1150 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{13}H_{16}O_3]^+$: 220.1099, found 220.1101.



3,4,5-Trimethoxydihydrobenxofuran 95. 10 min, 86% yield clear, colorless oil: R_F 0.30 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (s, 1H), 6.04 (dd, *J* = 17.4, 10.5 Hz, 1H), 5.32 (dd, *J* = 17.4, 1.4 Hz, 1H), 5.11 (dd, *J* = 10.5, 0.9 Hz, 1H), 3.92 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 3.20 (d, *J* = 14.7 Hz, 1H), 3.07 (d, *J* = 14.7 Hz, 1H), 1.55 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 154.0, 150.3, 141.8, 135.1, 113.0, 108.5, 90.2, 88.5, 61.5, 60.2, 56.3, 40.6, 26.4; IR (film) 2935, 1616, 1472, 1196, 1120 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{14}H_{18}O_4]^+$: 250.1216, found 250.1205.

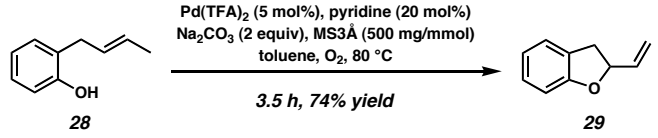


***p*-Methoxy-6-allyldihydrobenzofuran 97**. 2 h, 93% yield, clear, yellow oil: R_F 0.45 (19:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (d, *J* = 2.7 Hz, 1H), 6.49 (d, *J* = 2.7 Hz, 1H), 6.02 (dd, *J* = 17.0, 10.4 Hz, 1H), 5.34-5.26 (comp. m, 2H), 5.06 (dd, *J* = 10.7, 1.7 Hz, 1H), 3.74 (s, 3H), 3.23 (d, *J* = 2.7 Hz, 2H), 3.14 (d, *J* = 15.4 Hz, 1H), 3.03 (d, *J* = 15.4 Hz, 1H), 1.62-1.60 (comp. m, 6H), 1.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1, 151.8, 142.3, 134.4, 126.8, 122.7, 120.4, 114.0, 112.6, 108.7, 87.2, 56.1, 43.0, 39.5, 26.5, 16.0, 13.7; IR (film) 2931, 1479, 1440, 1233 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{17}H_{22}O_2]^+$: 258.1620, found 258.1613.



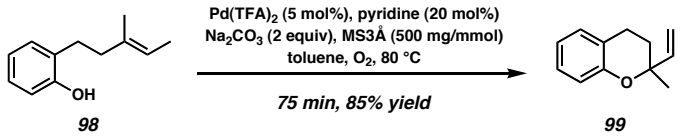
45 *47*

2'-Methyldihyrdobenzofuran 47. 25 min, 80% yield clear, colorless oil: R_F 0.63 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16-7.11 (comp. m, 2H), 6.79-6.87 (comp. m, 2H), 5.10 (s, 1H), 4.86 (s, 1H), 3.27 (d, *J* = 15.4 Hz, 1H), 3.03 (d, *J* = 15.9 Hz, 1H), 1.84 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 147.9, 128.2, 126.8, 125.2, 120.3, 110.2, 109.7, 90.0, 41.6, 26.3, 19.0; IR (film) 1402, 1462, 1249 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{12}H_{14}O]^+$: 173.0967, found 173.0968.



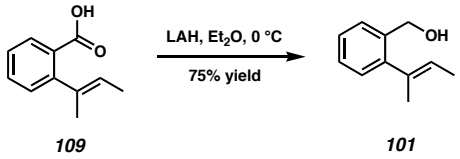
28 *29*

3'-*H*-dihydrobenzofuran 29. 3.5 h, 74% yield clear, colorless oil: R_F 0.70 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18-7.09 (comp. m, 2H), 6.87-6.79 (comp. m, 2H), 6.03 (ddd, *J* = 17.1, 10.2, 6.61 Hz, 1H), 5.39 (ddd, *J* = 17.1, 1.4, 1.1 Hz, 1H), 5.25-5.15 (comp. m, 2H), 3.38 (dd, *J* = 15.4, 9.1 Hz, 1H), 3.00 (dd, *J* = 15.4, 7.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 137.6, 128.3, 126.7, 125.1, 120.7, 117.1, 109.6, 83.7, 36.1; IR (film) 2961, 1597, 1480, 1230 cm^{-1}; HRMS *m/z* calc'd for $[C_{10}H_{10}O]^+$: 146.0732, found: 146.0721.



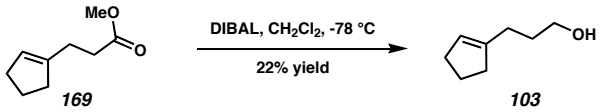
Dihydrobenzopyran 99. 75 min, 85% yield clear, colorless oil: R_F 0.62 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13-7.01 (comp. m, 2H), 6.87-6.78 (comp. m, 2H), 5.86 (dd, *J* = 17.6, 11.0 Hz, 1H), 5.12 (d, *J* = 17.3 Hz, 1H), 5.07 (dd, *J* = 11.0, 1.1 Hz, 1H), 2.73-2.68 (comp. m, 2H), 1.97-1.78 (comp. m, 2H), 1.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 141.4, 129.5, 127.5, 121.5, 119.9, 117.0, 114.1, 76.8, 31.9, 27.3, 22.7; IR (film) 1582, 1487, 1456, 1238 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{12}H_{14}O]^+$: 174.1045, found 174.1041.

2.6.7 Synthesis of primary alcohol substrates.

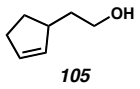


Benzyl alcohol 101. Lithium aluminum hydride (140 mg, 3.69 mmol, 2.6 equiv) was suspended in Et_2O (4 mL) in a two-necked flask equipped with reflux condenser and cooled to 0 °C. A solution of benzoic acid **109** (250 mg, 1.42 mmol, 1.0 equiv) in Et_2O (6 mL) was added dropwise to the stirring suspension over 5 min. Bubbling was observed, and the mixture was allowed to warm to 23 °C. After 5 h the reaction was recooled to 0 °C, quenched with 5:1 Et_2O/MeOH (20 mL) followed by 3 M HCl (20 mL), and allowed to stir for 12 h. Extraction with Et_2O (3 x 25 mL) was followed by combination of the organics, drying over $MgSO_4$ and removal of the solvents under

reduced pressure to provide yellow oil **101** (173 mg, 1.07 mmol, 75% yield) as a mixture of olefin isomers: R_F 0.29 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (data for 2.7:1 mixture of olefin isomers based on the relative integration of peaks at δ 5.60 and 5.41; 300 MHz, $CDCl_3$) δ 7.48-7.41 (comp. m, 1H), 7.48-7.41 (comp. m, 1H), 7.31-7.23 (comp. m, 2H), 7.31-7.23 (comp. m, 2H), 7.12-7.09 (m, 1H), 7.12-7.09 (m, 1H), 5.60 (app. qdd, *J* = 6.9, 3.2, 1.4 Hz, 1H), 5.41 (app. qdd, *J* = 6.9, 3.2, 1.4 Hz, 1H), 4.65 (d, *J* = 4.1 Hz, 2H), 4.60 (d, *J* = 3.7 Hz, 2H), 1.98-1.95 (m, 3H), 1.98-1.95 (m, 3H), 1.77 (d, *J* = 6.9 Hz, 3H), 1.36 (dq, *J* = 6.9, 1.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 145.1, 141.1, 138.0, 137.8, 136.5, 135.9, 128.8, 128.2, 127.9, 127.8, 127.7, 127.2, 127.0, 124.6, 122.9, 63.6, 63.4, 26.1, 18.5, 15.0, 14.1; IR (film) 3317, 2967, 2914, 1434, 1029 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{11}H_{14}O]^+$: 162.1045, found 162.1051.

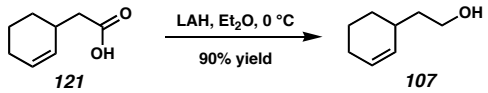


Primary alcohol 103. The methyl ester **169** (500 mg, 3.24 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (6 mL) and cooled to –78 °C. As neat DIBAL (1.27 mL, 7.13 mmol, 2.2 equiv) was slowly added to the mixture, the solution became yellow in color. After 1 h, the reaction was quenched with saturated aqueous Na^+/K^+ tartrate, allowed to warm to 23 °C and stirred for 12 h. The phases were separated and the aqueous layer extracted with CH_2Cl_2 (5 x 15 mL CH_2Cl_2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (19:1 hexanes/EtOAc eluent) to afford the known **103** (90 mg, 0.71 mmol, 22% yield) as a volatile, clear, colorless oil.



105

Primary alcohol 105. Known **105** was received as a generous gift from the group of Robert H. Grubbs.

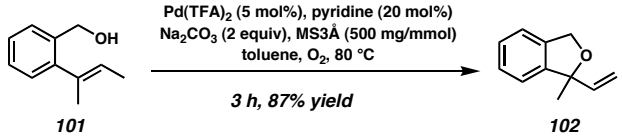


121 *107*

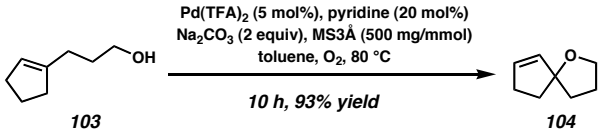
Primary alcohol 107. A suspension of LAH (70 mg, 1.85 mmol, 2.6 equiv) in Et_2O (7 mL) was cooled to 0 °C in an ice bath under argon. Carboxylic acid **121** (100 mg, 0.71 mmol, 1 equiv) was added to the cold suspension, dropwise, over 5 min, after which the mixture was allowed to warm to 23 °C. Upon consumption of the starting material after 10 h, the reaction was cooled to 0 °C and quenched by the addition of a solution of 5:1 Et_2O:MeOH (0.93 mL) then 3 M aq. HCl (2.8 mL). After warming to 23 °C, the layers were separated, and the aqueous layer was extracted with Et_2O (3 x 10 mL). The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated in vacuo to give **107** as a colorless oil (81 mg, 0.64 mmol, 90% yield) which was used without further purification: R_F 0.47 (2:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69 (ddd, *J* = 9.8, 6.1, 3.4 Hz, 1H), 5.57 (ddd, *J* = 10.0, 3.9, 1.9 Hz, 1H), 3.73 (ddd, *J* = 6.9, 6.6, 1.7 Hz, 2H), 2.29-2.17 (m, 1H), 2.01-1.94 (m, 1H), 1.85-1.46 (comp. m, 7H), 1.31-1.20 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.7, 127.6, 61.2, 39.3, 32.0, 29.2, 25.5, 21.6; IR (film) 3326, 2927, 1049 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_8H_{14}O]^+$: 126.1045, found: 126.1039.

2.6.8 General procedure for the oxidative cyclizations of primary alcohols shown in Table 2.2.7.

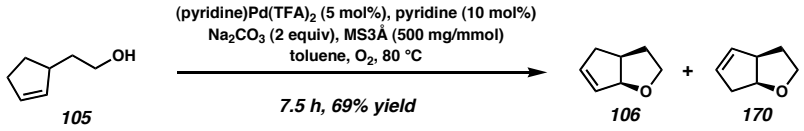
A thick-walled oven-dried 25 mL 15 cm long tube equipped with magnetic stir bar was charged with powdered molecular sieves (MS3Å, 125 mg, 500 mg/mmol), $Pd(TFA)_2$ (4.2 mg, 0.0125 mmol, 0.05 equiv), and Na_2CO_3 (53 mg, 0.50 mmol, 2.0 equiv), followed by toluene (2.5 mL), pyridine (4.0 μL, 0.050 mmol, 0.20 equiv), and primary alcohol substrate (0.25 mmol, 1.0 equiv). The tube was evacuated and back-filled with O_2 (3 x, balloon), heated to 80 °C, and allowed to stir under O_2 (1 atm, balloon). The reaction was monitored for conversion by TLC. Upon complete conversion, the crude reaction mixture was filtered over silica gel. Concentration in vacuo provided the cyclized product.



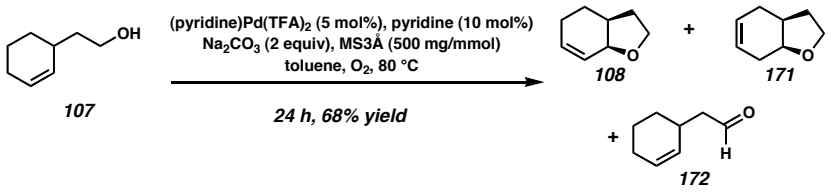
Dihydro-*iso*-benzofuran 102. 3 h, 87% yield clear, colorless oil: R_F 0.54 (4:1 hexanes/EtOAc eluent); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.13 (comp. m, 3H), 6.06 (dd, *J* = 17.0, 10.4 Hz, 1H), 5.22 (dd, *J* = 17.0, 1.4 Hz, 1H), 5.13 (d, *J* = 12.1 Hz, 1H), 5.08 (d, *J* = 12.6 Hz, 1H), 5.06 (dd, *J* = 10.4, 1.4 Hz, 1H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 142.1, 139.0, 127.7, 127.5, 121.6, 121.3, 112.6, 87.8, 71.4, 26.4; IR (film) 2976, 2848, 1029 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{11}H_{12}O]^+$: 160.0884, found 160.0888.



Spirocyclopentene 104. 10 h, 93% yield volatile, clear, colorless oil: R_F 0.46 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92-5.89 (m, 1H), 5.71-5.68 (m, 1H), 3.85 (t, *J* = 7.2 Hz, 2H), 2.54-2.44 (m, 1H), 2.35-2.32 (m, 1H), 2.05-1.84 (comp. m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.1, 133.8, 94.3, 67.4, 37.0, 36.8, 31.2, 26.6; HRMS (EI^+) *m/z* calc'd for $[C_8H_{12}O]^+$: 124.0888, found 124.0889.

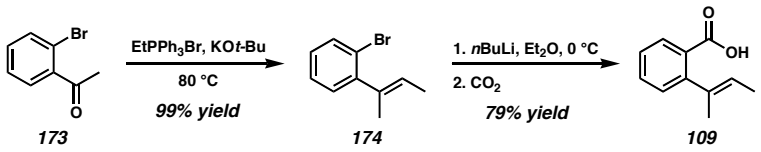


Fused cyclopentene 170. Cyclization was carried out with $(pyridine)_2Pd(TFA)_2$ (**144**, 6.1 mg, 0.0125 mmol, 0.05 equiv), pyridine (2.0 μL, 0.025 mmol, 0.10 equiv). The MS3Å were flame dried immediately prior to use. After 7.5 h, flash column chromatography of the crude reaction mixture on silica gel topped with Celite (pentane → 4:1 pentane/Et_2O eluent) provided **106** as a volatile clear colorless oil (19 mg, 0.17 mmol, 69% yield) that contained 7% of the olefin isomerized one position (**170**). Spectroscopic data for 33 was equivalent to that reported by Nicolaou.[36]



Fused cyclohexene 108. Cyclization was carried out with (pyridine)$_2$Pd(TFA)$_2$ (**144**, 6.1 mg, 0.0125 mmol, 0.05 equiv), pyridine (2.0 μL, 0.025 mmol, 0.10 equiv). The MS3Å were flame dried immediately prior to use. After 24 h, flash column chromatography of the crude reaction mixture on silica gel topped with Celite (pentane → 4:1 pentane/Et2O eluent) gave a volatile clear, colorless oil (21 mg. 0.169 mmol. 68% yield) that was a mixture of **108**, olefin isomer **171** and aldehyde **172** (5:2.3:1). **108** was spectroscopically identical to data reported by Andersson.[37] **171** was spectroscopically identical to data reported by Cossy.[38]

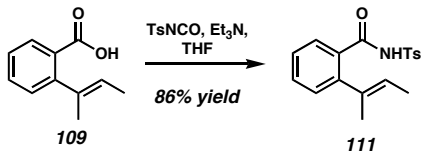
2.6.9 Synthesis of carboxylic acid and carboxylic acid derivative substrates.



Benzoic acid 109. To a suspension of potassium *t*-butoxide (1.12 g, 10.0 mmol, 2.7 equiv) in toluene (37 mL) was added EtPPh$_3$Br (3.71 g, 10.0 mmol, 2.7 equiv) and the mixture stirred at 0 °C for 10 min. The resulting orange suspension was warmed to 23 °C and stirred for an additional 1 h. The reaction mixture was cooled to 0 °C and subjected to dropwise addition of 2-bromoacetophenone (**173**, 0.5 mL, 3.71 mmol, 1.0 equiv). The mixture was heated at reflux for 8 h, then cooled to 23 °C and quenched with saturated

aqueous NH_4Cl (50 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting white solid was triturated with Et_2O and hexane (1:1, 50 mL) to separate $Ph_3P{=}O$ which was removed by filtration. The filtrate was concentrated under reduced pressure. Purification by flash column chromatography on silica gel (hexanes as eluent) afforded the bromostyrene (**174**) as a colorless oil (99% yield). A solution of the bromostyrene (**174**, 223 mg, 1.06 mmol, 1.0 equiv) in anhydrous Et_2O (2 mL) was treated dropwise with *n*-BuLi (2.5 M in hexane, 0.51 mL, 1.28 mmol, 1.2 equiv) at 0 °C. After 10 min, anhydrous CO_2 gas was bubbled through the reaction mixture for 5 min. The mixture was allowed to warm to 23 °C and stirred for an additional 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and washed with Et_2O (2 x 10 mL). The aqueous layer was then acidified with 2 N HCl to pH 1 and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to furnish benzoic acid **109** as a white solid (131 mg, 0.74 mmol, 79% yield): R_F 0.23 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (data for a 1.1:1 mixture of olefin isomers based on the relative integration of peaks at δ 1.79 and 1.40; 300 MHz, $CDCl_3$) δ 12.08 (br s, 1H), 12.08 (br s, 1H), 8.08 (d, *J* = 7.7 Hz, 1H), 7.96 (d, *J* = 7.7 Hz, 1H), 7.58-7.31 (comp. m, 2H), 7.58-7.31 (comp. m, 2H), 7.25 (d, *J* = 7.7 Hz, 1H), 7.18 (d, *J* = 7.7 Hz, 1H), 5.56-5.46 (comp. m, 1H), 5.56-5.46 (comp. m, 1H), 2.08-2.02 (comp. m, 3H), 2.08-2.02 (comp. m, 3H), 1.79 (d, *J* = 6.6 Hz, 3H), 1.40 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 173.1, 148.1, 144.8, 137.6, 133.0, 132.6, 131.2, 130.8, 130.4, 130.2,

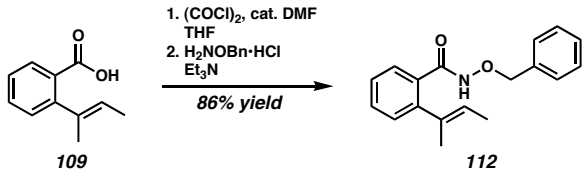
128.7, 126.9, 126.7, 123.3, 121.3, 25.6, 18.3, 14.7, 14.3; IR (film) 2979, 1693, 1408 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{11}H_{12}O_2]^+$: 176.0837, found 176.0835.



109 111

Tosyl amide 111. To a solution of acid **109** (2.0 g, 11.3 mmol, 1.0 equiv) in THF (28 mL) was added *p*-toluenesulfonyl isocyanate (2.6 mL, 17.0 mmol, 1.5 equiv) followed by dropwise introduction of Et_3N (2.4 mL, 17.0 mmol, 1.5 equiv). The mixture was then stirred at 60 °C for 1 h. After cooling to 23 °C, The solvent was removed in vacuo and the residue diluted with EtOAc (50 mL) and washed with 2 N HCl (20 mL). The organic layer was dried over Na_2SO_4 and the solvents were removed by rotary evaporation. Purification by flash column chromatography on silica gel (1:2 hexanes/Et_2O eluent) afforded tosyl amide **111** as a white foam (3.4 g, 10.3 mmol, 91% yield): R_F 0.15 (1:1 hexanes/Et_2O eluent); ^1H NMR (data for a 1:1 mixture of olefin isomers based on the relative integration of peaks at δ 5.72 and 5.50; 300 MHz, $CDCl_3$) δ 9.48 (br s, 1H), 9.18 (br s, 1H), 7.94 (d, *J* = 7.7 Hz, 4H), 7.76 (d, *J* = 7.7 Hz, 1H), 7.51 (d, *J* = 7.7 Hz, 1H), 7.44-7.13 (comp. m, 4H), 7.44-7.13 (comp. m, 4H), 7.08 (d, *J* = 7.2 Hz, 1H), 7.01 (d, *J* = 7.7 Hz, 1H), 5.72 (app. qd, *J* = 5.5, 1.1 Hz, 1H), 5.50 (app. qd, *J* = 5.5. 1.1 Hz, 1H), 2.36 (s, 3H), 2.35 (s, 3H), 1.86 (s, 3H), 1.75 (s, 3H), 1.66 (d, *J* = 6.6 Hz, 3H), 1.34 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 164.6, 144.9, 144.8, 144.1, 140.5, 136.9, 136.8, 136.0, 135.3, 135.2, 132.5, 131.7, 130.5, 129.7, 129.6, 129.4, 129.3, 129.1, 128.8, 128.3, 128.3, 127.3, 126.9, 126.8, 125.6, 25.9, 21.6, 18.1, 14.8, 14.1; IR (film) 3241,

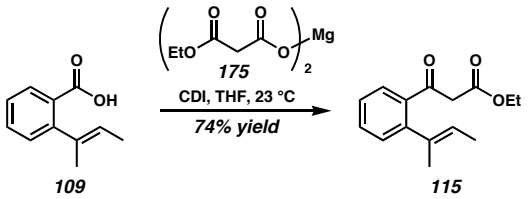
1699, 1426, 1168 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{18}H_{19}NO_3S + H]^+$: 330.1164, found 330.1157.



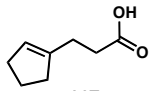
109 *112*

Benzyl hydroxamate 112. To a solution of acid **109** (200 mg, 1.13 mmol, 1.0 equiv) in THF (6 mL) was added oxalyl chloride (0.50 mL, 5.67 mmol, 5 equiv) followed by catalytic DMF (1 drop). After 2 h, the volatiles were removed in vacuo. The residue was diluted with THF (6 mL) and then treated with *o*-benzylhydroxylamine•HCl (362 mg, 2.27 mmol, 2.0 equiv) followed by Et_3N (0.8 mL, 5.67 mmol, 5 equiv). The mixture was stirred for 2 h, quenched by the addition of 2 N NaOH (10 mL), and extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with 2 N HCl (10 mL), dried over Na_2SO_4 and filtered. Evaporation of the solvents under reduced pressure followed by purification by flash column chromatography on silica gel (4:1 hexanes/EtOAc eluent) afforded **112** (273 mg, 0.95 mmol, 86% yield) as an oil: R_F 0.63 (2:1 hexanes/EtOAc eluent); ^1H NMR (data for 3:1 mixture of olefin isomers based on the relative integration of peaks at δ 1.61 and 1.25; 300 MHz, $CDCl_3$) δ 9.23 (s, 1H), 9.08 (s, 1H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.37-7.10 (comp. m, 7H), 7.37-7.10 (comp. m, 7H), 7.06 (d, *J* = 7.7 Hz, 1H), 6.97 (d, *J* = 7.7 Hz, 1H), 5.50-5.37 (comp. m, 1H), 5.50-5.37 (comp. m, 1H), 4.93 (s, 2H), 4.93 (s, 2H), 1.82 (comp. m, 3H), 1.82 (comp. m, 3H), 1.61 (d, *J* = 7.1 Hz, 3H), 1.25 (app. dd, *J* = 7.1, 1.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 166.1, 143.9, 140.0, 137.3, 136.3, 135.4, 131.0, 130.8, 130.4,

129.2, 129.1, 128.7, 128.6, 128.4, 127.0, 126.7, 125.4, 124.1, 77.8, 77.7, 25.8, 17.9, 14.7, 14.2; IR (film) 3189, 1652, 1496, 1023 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{18}H_{19}NO_2 + H]^+$: 282.1494, found 282.1497.

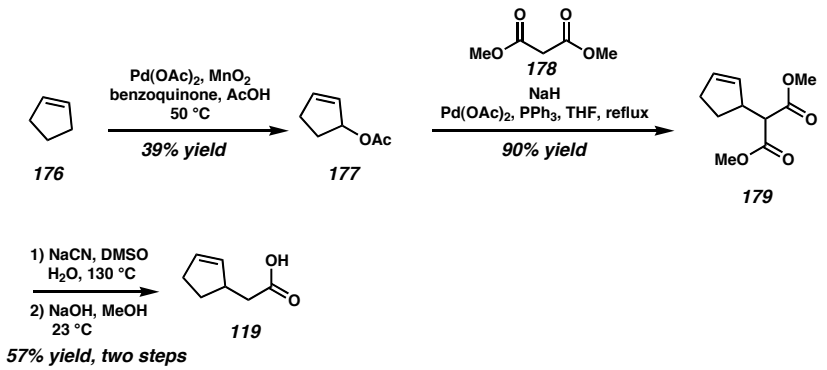


Ketoester 115. Prepared according to the modified procedure of Barco et al.[39] To a solution of acid **109** (1.4 g, 7.90 mmol, 1.0 equiv) in THF (79 mL) was added *N,N'*-carbonyldiimidazole (1.45 g, 8.74 mmol, 1.1 equiv) and the resulting solution was stirred for 1 h. Magnesium monoethyl malonate (**175**, 2.87 g, 11.9 mmol, 1.5 equiv, prepared according to literature procedure[6]) was introduced and the mixure heated at 80 °C for 24 h. After cooling to 23 °C, the solvent was removed under reduced pressure. The residue was diluted with 5% aqueous citric acid (75 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica gel (4:1 hexanes/EtOAc eluent) gave ketoester **115** (1.44 g, 5.8 mmol, 74% yield) as an oil: R_F 0.50 (2:1 hexanes/Et_2O eluent); ^1H NMR (isolated as 2.1:1 mixture of olefin isomers and keto-enols, data for the major keto-ester only; 300 MHz, $CDCl_3$) δ 7.62-7.09 (comp. m, 4H), 5.45-5.38 (comp. m, 1H), 4.14 (q, *J* = 7.3 Hz, 2H), 3.73 (s, 2H), 2.04 (s, 3H), 1.76 (d, *J* = 6.7 Hz, 3H), 1.22 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (data for carbonyl carbons of major keto-ester only; 75 MHz, $CDCl_3$) δ 198.6, 167.5; IR (film) 2980, 1743, 1692 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{15}H_{18}O_3]^+$: 246.1256, found 246.1256.



117

Carboxylic acid 117. See Lokensgard and references therein.[40] R_F 0.35 (2:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.36-5.32 (m, 1H), 2.54-2.20 (comp. m, 8H), 1.84-1.79 (comp. m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.2, 142.7, 124.3, 35.5, 33.0, 32.8, 26.4, 23.7; IR (film) 2957, 2895, 2843, 1705, 1446 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_8H_{12}O_2 + H]^+$: 140.0837, found 140.0836.



176 ***177*** ***179*** ***119***

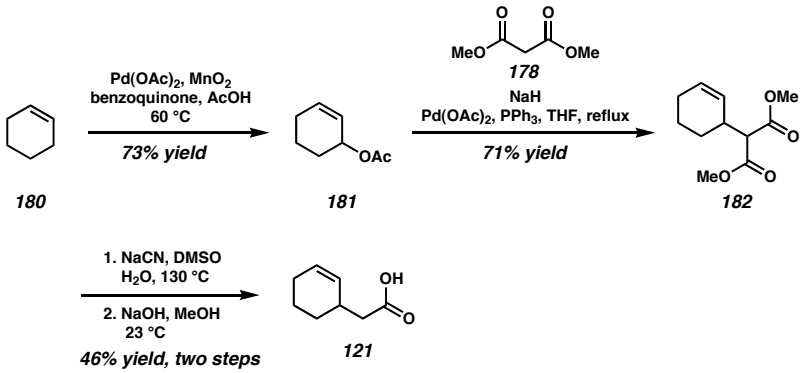
Cyclopentene acid 119. Known **119** was synthesized according to a route described by Andersson.[37] A mixture of $Pd(OAc)_2$ (247 mg, 1.1 mmol, 5 mol%), benzoquinone (2.85 g, 26.4 mmol, 120 mol%) and MnO_2 (383 mg, 4.4 mmol, 20 mol%) in acetic acid (50 mL) was stirred for 30 min at 50 °C. Cyclopentene (**176**, 1.95 mL, 22.0 mmol, 1.0 equiv) was added, the flask was equipped with a reflux condenser, and the mixture was allowed to stir at 50 °C under argon. After 20 h, the flask was cooled to 23 °C, 1:1 Et_2O:pentane was added (25 mL), and the mixture was allowed to stir for 30 min, during which time the brownish orange reaction mixture became black. The suspension was filtered over Celite with 1:1 pentane:Et_2O and water. The aqueous layer was separated from the

filtrate and extracted with Et_2O (3 x 25 mL). The organic layers were combined and washed with H_2O (25 mL), 1 M NaOH (25 mL), H_2O again (25 mL) and finally 1 M NaOH (25 mL). The organic extracts were then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a yellow residue, which was distilled under reduced pressure to give cyclopent-2-enyl-acetate (**177**) as a yellow oil (1.09 g, 8.63 mmol, 39% yield).[41]

To a suspension of NaH (342 mg, 8.56 mmol, 1.2 equiv) in THF (35 mL) under argon at 23 °C was added dimethylmalonate (**178**, 978 μL, 8.56 mmol, 1.2 equiv). The mixture was stirred for 10 min. To this was added $Pd(OAc)_2$ (48 mg, 0.214 mmol, 3 mol%) and PPh_3 (187 mg, 0.713 mmol, 10 mol%), followed by cyclopent-2-enyl acetate (**177**, 900 mg, 7.13 mmol, 1.0 equiv). The resulting bright yellow-green solution was heated under reflux for 10 h. The mixture was then partitioned between Et_2O and H_2O. The organic layer was separated, and the aqueous extracted with Et_2O (3 x 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the resulting brown residue on silica gel (9:1 hexanes/EtOAc eluent) gave dimethyl-2-(cyclopent-2-enyl)malonate (**179**, 1.27 g, 6.39 mmol, 90% yield).[42]

Dimethyl-2-(cyclopent-2-enyl)malonate (**179**, 755 mg, 3.81 mmol, 1.0 equiv), NaCN (373 mg, 7.62 mmol, 2.0 equiv) and H_2O (137 μL, 7.62 mmol, 2.0 equiv) were combined in DMSO (9 mL, 0.4 M). The flask was sealed and heated to 130 °C in an oil bath for 8 h, during which time the colorless solution became yellow and opaque. The mixture was cooled to 23 °C, quenched by the addition of H_2O (10 mL), and then extracted with E_2O (4 x 30 mL). The organics were combined, washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford methyl ester **169** as a yellow oil

(511 mg, 3.64 mmol, 96% yield), which was used without further purification. The methyl ester (198 mg, 1.41 mmol, 1.0 equiv) was hydrolyzed by dissolution in 10% aq. NaOH (7 mL, 0.2 M) and MeOH (7 mL, 0.2 M). After one hour of stirring at 23 °C, 1 M aq. HCl was added. The mixture was extracted with EtOAc (4 x 25 mL). The organics were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo to provide cyclopentene carboxylic acid **119** as a light yellow oil (105 mg, 0.83 mmol, 59% yield). Spectroscopic data was in accordance with that reported by Helmchen.[43]



Cyclohexene carboxylic acid 121. Known **121** was synthesized in a manner identical to that described above for **119**. A mixture of $Pd(OAc)_2$ (34 mg, 0.152 mmol, 5 mol%), benzoquinone (329 mg, 3.04 mmol, 10 mol%) and MnO_2 (2.90 mg, 33.4 mmol, 110 mol%) in acetic acid (75 mL) was stirred for 30 min at 60 °C. Cyclohexene (**180**, 3.09 mL, 30.4 mmol, 1.0 equiv) was added, the flask was equipped with a reflux condenser, and the mixture was allowed to stir at 60 °C under argon. After 52 h, the flask was cooled to 23 °C, 1:1 Et_2O:pentane was added (50 mL), and the mixture was allowed to stir for 30 min, during which time the brownish orange reaction mixture became black. The suspension was filtered over Celite with 1:1 pentane/Et_2O and water. The aqueous

layer was separated from the filtrate and extracted with 1:1 Et_2O/pentane (4 x 50 mL). The organic layers were combined and washed with H_2O (45 mL), 1 M NaOH (45 mL), H_2O again (45 mL) and finally 1 M NaOH (45 mL). The organic extracts were then dried over $MgSO_4$, filtered, and concentrated in vacuo to give a brown oil, which was distilled under reduced pressure to give cyclohex-2-enyl-acetate (**181**) as a yellow oil (3.13 g, 22.3 mmol, 73% yield).[41]

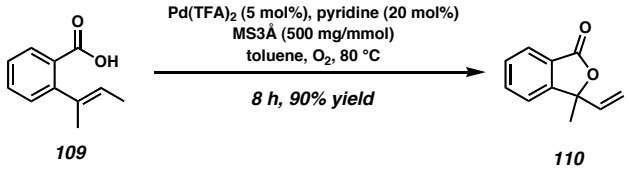
To a suspension of NaH (924 mg, 23.1 mmol, 1.2 equiv) in THF (80 mL) under argon at 23 °C was added dimethylmalonate (**178**, 2.66 mL, 23.1 mmol, 1.2 equiv). The mixture was stirred for 10 min. To this was added $Pd(OAc)_2$ (130 mg, 0.58 mmol, 3 mol%) and PPh_3 (506 mg, 1.93 mmol, 10 mol%), followed by cyclohex-2-enyl acetate (**181**, 2,7 g, 19.3 mmol, 1.0 equiv). The resulting bright yellow-green solution was heated at 60 °C for 3 h. The mixture was then partitioned between Et_2O and H_2O. The organic layer was separated, and the aqueous extracted with Et_2O (3 x 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the resulting brown residue on silica gel (9:1 hexanes/EtOAc eluent) gave dimethyl-2-(cyclohex-2-enyl)malonate (**182**, 2.93 g, 13.8 mmol, 71% yield).

Dimethyl-2-(cyclohex-2-enyl)malonate (**182**, 200 mg, 0.94 mmol, 1.0 equiv), NaCN (92 mg, 1.88 mmol, 2.0 equiv) and H_2O (34 μL, 1.88 mmol, 2.0 equiv) were combined in DMSO (2.5 mL, 0.4 M). The flask was sealed and heated to 130 °C in an oil bath for 2 h, during which time the colorless solution became yellow and opaque. The mixture was cooled to 23 °C, quenched by the addition of H_2O (10 mL), and then extracted with E_2O (4 x 10 mL). The organics were combined, washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the methyl ester of **121** as a yellow

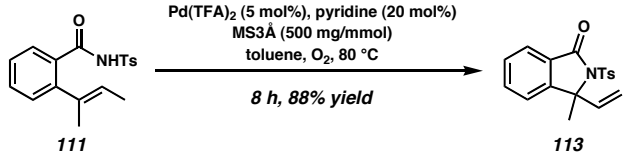
oil (71 mg, 0.46 mmol, 49% yield), which was used without further purification. The methyl ester (70 mg, 0.46 mmol, 1.0 equiv) was hydrolyzed by dissolution in 10% aq. NaOH (2 mL, 0.2 M) and MeOH (2 mL, 0.2 M). After one hour of stirring at 23 °C, 1 M aq. HCl was added. The mixture was extracted with EtOAc (4 x 10 mL). The organics were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo to provide cyclohexene carboxylic acid **121** as a light yellow oil (60 mg, 0.43 mmol, 93% yield). Spectroscopic data was in accordance with that reported by Helmchen.[44]

2.6.10 General procedure for the carboxylic acid and acid derivative oxidative cyclizations shown in Table 2.2.8.

In a thick-walled oven-dried 25 mL 15 cm-long tube equipped with magnetic stir bar, to a mixture of $Pd(TFA)_2$ (4.2 mg, 0.0125 mmol, 0.05 equiv) and powdered molecular sieves (MS3Å, 125 mg, 500 mg MS3Å/mmol substrate) in toluene (1.0 mL) was added pyridine (4.0 μL, 0.050 mmol, 0.20 equiv). The flask was evacuated and back-filled with O_2 (3 x, balloon) and the mixture heated at 80 °C for 10 min. The substrate (0.25 mmol, 1.0 equiv) was introduced and the reaction mixture heated at 80 °C under O_2 (1 atm, balloon) until completion of the reaction as indicated by TLC. The solvent was removed in vacuo and the residue purified directly by flash column chromatography on silica gel (hexane/EtOAc or hexane/Et_2O eluent) to give the cyclized product.

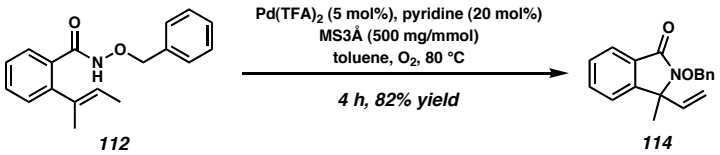


Lactone 110. 8 h. Purification by flash column chromatography on silica gel (2:1 hexanes/Et_2O eluent) afforded the desired product as an amorphous solid (90% yield): R_F 0.27 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.2, Hz, 1H), 7.66 (dd, *J* = 7.1, 7.0 Hz, 1H), 7.50 (dd, *J* = 7.1, 6.6, Hz, 1H), 7.38 (d, *J* = 6.6 Hz, 1H), 6.03 (dd, *J* = 17.6, 10.4 Hz, 1H), 5.38 (d, *J* = 17.6 Hz, 1H), 5.19 (d, *J* = 10.4 Hz, 1H), 1.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 152.7, 137.9, 134.3, 129.2, 125.9, 125.3, 121.7, 115.6, 86.8, 25.6; IR (film) 1762, 1267 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{11}H_{10}O_2]^+$: 174.0681, found: 174.0680.

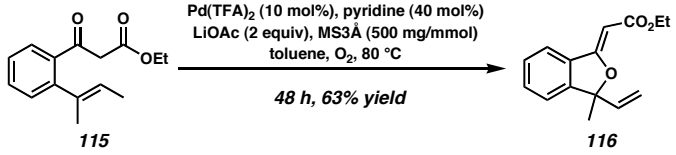


Tosylamide 113. 8 h. Purification by flash column chromatography on silica gel (2:1 hexanes/EtOAc eluent) gave a colorless foam (88% yield): R_F 0.24 (1:1 hexanes/Et_2O eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.1 Hz, 2H), 7.75 (d, *J* = 7.2 Hz, 1H), 7.62 (dd, *J* = 7.2, 6.6 Hz, 1H), 7.43 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.32-7.27 (comp. m, 3H), 6.07 (dd, *J* = 17.7, 10.2 Hz, 1H), 5.42 (d, *J* = 17.7 Hz, 1H), 5.38 (d, *J* = 10.5 Hz, 1H), 2.40 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 150.3, 145.0, 138.8, 136.8, 134.4, 129.5, 129.1, 128.9, 128.0, 124.9, 122.7, 117.0, 71.3, 24.9, 22.1; IR (film)

1730, 1466, 1360, 1169 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{18}H_{17}NO_3 + H]^+$: 328.1007, found: 328.1008.

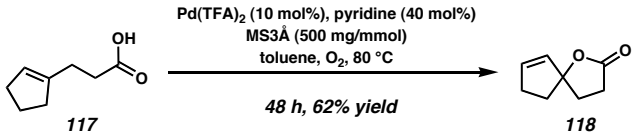


Benxyloxyamide 114. 4 h. Purification by flash column chromatography on silica gel (4:1 hexanes/EtOAc eluent) furnished the cyclized product as a colorless oil (82% yield): R_F 0.48 (2:1 hexanes/EtOAc eluent); ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.7 Hz, 1H), 7.58-7.35 (comp. m, 7H), 7.25 (d, *J* = 7.7 Hz, 1H), 5.76 (dd, *J* = 17.6, 10.4 Hz, 1H), 5.41 (d, *J* = 17.0 Hz, 1H), 5.29 (d, *J* = 10.4 Hz, 1H), 5.25 (d, *J* = 10.4 Hz, 1H), 5.15 (d, *J* = 9.9 Hz, 1H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 146.9, 138.3, 135.3, 132.5, 129.7, 128.9, 128.7, 128.6, 128.5, 123.9, 122.0, 117.1, 79.3, 66.9, 21.3; IR (film) 3070, 2979, 1711, 1460 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{18}H_{17}NO_2 + H]^+$: 280.1337, found: 280.1330.

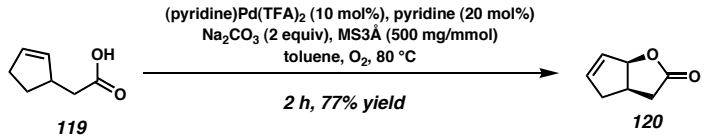


***iso*-Benzofuran 116**. A thick-walled oven-dried 25 mL 15 cm-long tube equipped with magnetic stir bar was charged with $Pd(TFA)_2$ (8.4 mg, 0.025 mmol, 0.10 equiv) and powdered molecular sieves (MS3Å, 125 mg, 500 mg/mmol), to which toluene (1.0 mL) and pyridine (8.0 μL, 0.100 mmol, 0.40 equiv) were added. The flask was evacuated and back-filled with O_2 (3 x, balloon) and the mixture heated at 80 °C for 10 min.

β-Ketoester **115** (61.5 mg, 0.25 mmol, 1.0 equiv) and anhydrous LiOAc (33 mg, 0.50 mmol, 2 equiv) were introduced, and the reaction mixture heated at 80 °C under O_2 (1 atm, balloon) until completion of the reaction as indicated by TLC. After 48 h, the solvent was removed in vacuo and the residue purified directly by flash column chromatography on silica gel (4:1 hexanes/Et_2O eluent) to afforded the *E*-isomer (**116a**, 16% yield) and *Z*-isomer (**116b**, 47% yield) as oils. **116a**: R_F 0.53 (2:1 hexanes/Et_2O eluent); ^{1}H NMR (300 MHz, acetone-d_6) δ 9.19 (d, J = 7.9 Hz, 1H), 7.63-7.58 (m, 1H), 7.54-7.46 (m, 2H), 6.13 (dd, J = 17.4, 10.7 Hz, 1H), 5.58 (s, 1H), 5.34 (dd, J = 17.4, 0.9 Hz, 1H), 5.13 (dd, J = 10.7, 0.9 Hz, 1H), 4.16 (q, J = 7.3 Hz, 2H), 1.68 (s, 3H), 1.26 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 169.5, 167.6, 150.6, 140.2, 132.7, 130.5, 129.2, 128.9, 122.1, 114.2, 92.0, 90.3, 59.8, 25.8, 14.9; IR (film) 2978, 1703, 1633 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{15}H_{16}O_3]^+$: 244.1099, found 244.1090. **116b**: R_F 0.19 (2:1 hexanes/Et_2O eluent); ^{1}H NMR (300 MHz, acetone-d_6) δ 7.82 (dd, J =7.7, 1.6 Hz, 1H), 7.61-7.46 (comp. m, 3H), 6.17 (dd, J = 17.0, 11.0 Hz, 1H), 5.54 (s, 1H), 5.40 (dd, J = 17.0, 1.1 Hz, 1H), 5.13 (dd J = 11.0, 1.1 Hz, 1H), 4.12 (app.qd, J = 7.1, 1.7 Hz, 2H), 1.71 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 166.2, 165.5, 148.1, 140.0, 132.9, 132.3, 129.6, 122.5, 122.4, 114.2, 93.4, 86.5, 59.3, 26.0, 14.9; IR (film) 2980, 1706, 1645 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{15}H_{16}O_3]^+$: 244.1099, found 244.1106.

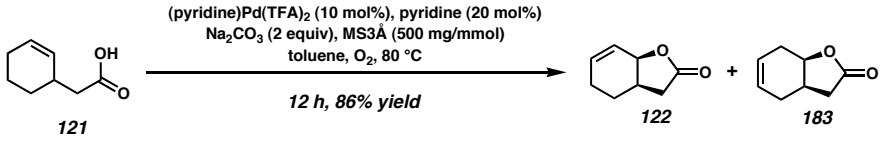


Spirolactone 118. A thick-walled oven-dried 25 mL 15 cm-long tube equipped with magnetic stir bar was charged with $Pd(TFA)_2$ (8.4 mg, 0.025 mmol, 0.10 equiv) and powdered molecular sieves (MS3Å, 125 mg, 500 mg/mmol). Toluene (1.0 mL) and pyridine (8.0 μL, 0.100 mmol, 0.40 equiv) were added. The flask was evacuated and back-filled with O_2 (3 x, balloon) and the mixture heated at 80 °C for 10 min. Acid **117** (35 mg, 0.25 mmol, 1.0 equiv) was introduced and the reaction mixture heated at 80 °C under O_2 (1 atm, balloon) until completion of the reaction as indicated by TLC. After 48 h, the solvent was removed in vacuo and the residue purified directly by flash column chromatography on silica gel (2:1 hexanes/EtOAc eluent) provided the spiro lactone (**118**, 22 mg, 0.16 mmol, 62% yield) as a colorless oil: R_F 0.29 (2:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.10-6.04 (m, 1H), 5.74-5.66 (m, 1H), 2.64-1.98 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 137.7, 131.9, 98.0, 36.4, 33.6, 31.3, 29.9; IR (film) 2938, 1769 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_8H_{10}O_2]^+$: 138.0681, found 138.0685.



Fused cyclopentenelactone 120. A thick-walled oven-dried 25 mL 15 cm-long tube equipped with magnetic stir bar was charged with powdered molecular sieves (MS3Å,

125 mg, 500 mg/mmol), which were flame dried immediately prior to use. $(Pyridine)_2Pd(TFA)_2$ (**144**, 12.3 mg, 0.025 mmol, 0.10 equiv) was added, followed by Na_2CO_3 (53 mg, 0.50 mmol, 2.0 equiv), pyridine (4.0 μL, 0.050 mmol, 0.20 equiv) toluene (1.0 mL), acid **119** (31.5 mg, 0.25 mmol) and more toluene (1.5 mL). The tube was purged with O_2 (3 x, balloon), and heated to 80 °C in an oil bath under a balloon of O_2. After 2 h, the crude reaction mixture was loaded onto a short column of silica gel and chromatographed (pentane → 2:1 pentane/Et_2O → Et_2O eluent) to provide the fused lactone (**120**, 24 mg, 0.19 mmol, 77% yield) as a colorless oil: R_F 0.45 (1:1 hexanes/EtOAc eluent). Spectroscopic data was in agreement with that reported by Griengl.[45]



Fused cyclohexenelactone 183. A thick-walled oven-dried 25 mL 15 cm-long tube equipped with magnetic stir bar was charged with powdered molecular sieves (MS3Å, 100 mg, 500 mg/mmol), which were flame dried immediately prior to use. $(Pyridine)_2Pd(TFA)_2$ (**144**, 9.8 mg, 0.020 mmol, 0.10 equiv) was added, followed by Na_2CO_3 (42 mg, 0.40 mmol, 2.0 equiv), pyridine (3.2 μL, 0.040 mmol, 0.20 equiv) toluene (1.0 mL), acid **121** (28.0 mg, 0.20 mmol) and more toluene (1.0 mL). The tube was purged with O_2 (3 x, balloon), and heated to 80 °C in an oil bath under a balloon of O_2. After 12 h, the crude reaction mixture was loaded onto a short column of silica gel and chromatographed (pentane → 4:1 pentane/Et_2O → 2:1 pentane/Et_2O eluent) to afford

the fused lactone (**122**, 24 mg, 0.17 mmol, 86% yield) as a colorless oil: R_F 0.52 (1:1 hexanes/EtOAc eluent). The product contained 6% of the olefin isomer in which the olefin is shifted one position further from the ring fusion (**183**). Spectroscopic data was in agreement with that reported by Pearson et al.[46]

*2.6.11 General procedure for asymmetric oxidative cyclization of **26**. Ligand screening trials shown in Table 2.3.1.*

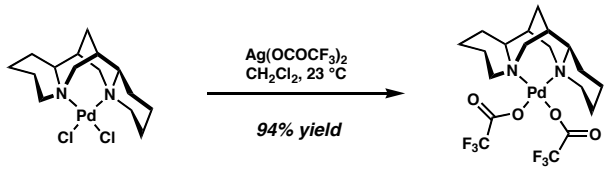
A thick-walled oven-dried 10 mL 15 cm long tube equipped with magnetic stir bar was charged with powdered molecular sieves (MS3Å, 50 mg, 500 mg/mmol), and $Pd(TFA)_2$ (3.3 mg, 0.010 mmol, 0.10 equiv), followed by toluene (1.0 mL), chiral ligand (0.040 mmol, 0.40 equiv), and tridecane as a GC internal standard (10.0 μL, 0.041 mmol, 0.41 equiv). The tube was evacuated, back-filled with O_2 (3 x, balloon), and heated to 80 °C for 10 min. Phenol **26** (16.2 mg, 0.10 mmol, 1.0 equiv) was added, and the mixture was allowed to stir under O_2 (1 atm, balloon) at 80 °C. The reaction was monitored for conversion and enantiomeric excess by achiral and chiral GC. Aliquots (0.10 mL) of the reaction mixture were collected, filtered through a pad of silica gel (EtOAc eluent), and analyzed (see below for details).

*2.6.12 General procedure for asymmetric oxidative cyclization of **26**. Palladium source and basic additive screening trials shown in Tables 2.3.2 and 2.3.3.*

A thick-walled oven-dried 10 mL 15 cm-long tube equipped with magnetic stir bar was charged with powdered molecular sieves (MS3Å, 50 mg, 500 mg/mmol), and palladium source (0.010 mmol, 0.10 equiv), followed by basic additive (for reactions shown in Table 2.3.3 only, 0.20 mmol, 2.0 equiv), toluene (1.0 mL), (–)-sparteine (**22**, 9.2 μL, 0.040 mmol, 0.40 equiv), and pentadecane as a GC internal standard (3.0 μL,

0.011 mmol, 0.11 equiv). The tube was evacuated, back-filled with O_2 (3 x, balloon), and heated to 80 °C for 20 min. Phenol **26** (16.2 mg, 0.10 mmol, 1.0 equiv) was added, and the mixture allowed to stir under O_2 (1 atm, balloon) at 80 °C. The reaction was monitored for conversion and enantiomeric excess by chiral GC or ^{1}H NMR. Aliquots (0.10 mL) of the reaction mixture were collected, filtered through a plug of silica gel (EtOAc eluent), and analyzed.

*2.6.13 The synthesis of (sp)Pd(TFA)$_2$ (**134**).*



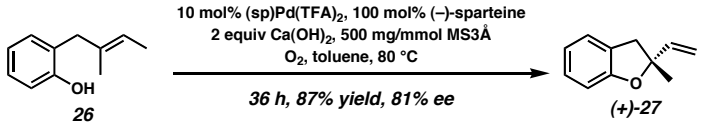
184 *134*

((–)-Sparteine)palladium(II)bis(trifluoracetate) (134) (sp)Pd(TFA)$_2$):[47] ((–)-Sparteine)$PdCl_2$[48] (**184**, 200 mg, 0.49 mmol, 1.0 equiv) and $Ag(OCOCF_3)_2$ (215 mg, 0.97 mmol, 2.0 equiv) were taken up in CH_2Cl_2 (10 mL, 0.05 M) under argon. The mixture was allowed to stir for 50 min, during which time a light colored precipitate formed in the orange solution. The solids (AgCl) were removed by filtration in air, and the filtrate was diluted with hexane (2 mL). The solvents were removed under reduced pressure to provide **134** as a bright yellow-orange powder (260 mg, 0.46 mmol, 94% yield). X-ray quality crystals were grown by slow diffusion of hexanes into a concentrated CH_2Cl_2 solution of the complex (see Appendix 2.2): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.55 (d, *J* = 11.5 Hz, 1H), 4.33 (d, *J* = 12.6 Hz, 1H), 3.69 (dd, *J* = 12.6, 3.3 Hz, 1H), 3.23 (t, *J* = 13.3 Hz, 1H), 3.04 (d, *J* = 13.8 Hz, 1H), 2.89 (d, *J* = 12.4 Hz, 1H), 2.76 (d, *J* = 13.3 Hz, 2H), 2.36-1.26 (comp. m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.2, 65.7,

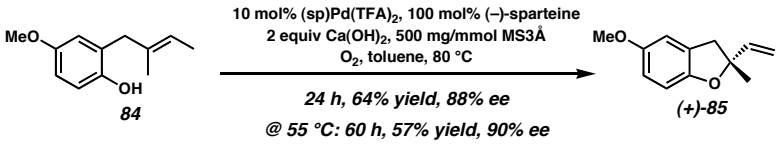
65.6, 63.7, 59.7, 49.0, 34.9, 34.7, 30.2, 27.5, 26.5, 24.2, 24.0, 23.4, 20.6; IR (film) 2942, 1683, 1409, 1194, 1138 cm^{-1}; HRMS (ES^+) *m/z* calc'd for $[C_{17}H_{26}N_2O_2F_3Pd - C_2O_2F_3]^+$: 453.0988, found 453.0974.

2.6.14 General procedure for the asymmetric oxidative cyclization of phenols shown in Table 2.3.4.

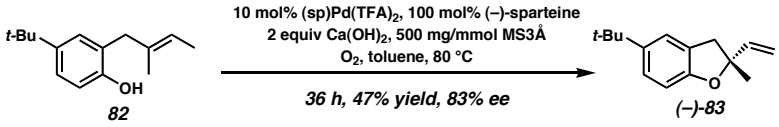
A thick-walled oven-dried 25 mL 15 cm long tube equipped with magnetic stir bar was charged with powdered molecular sieves (MS3Å, 125 mg, 500 mg/mmol), (sp)$Pd(TFA)_2$ (**134**, 14.2 mg, 0.025 mmol, 0.10 equiv), and oven-dried $Ca(OH)_2$ (37 mg, 0.50 mmol, 2.0 equiv), followed by toluene (2.5 mL), (–)-sparteine (60 μL, 0.25 mmol, 1.0 equiv), and phenolic substrate (0.25 mmol, 1.0 equiv). The tube was evacuated and back-filled with O_2 (3 x, balloon), heated to 80 °C, and allowed to stir under O_2 (1 atm, balloon). The reaction was monitored for conversion by TLC. Upon complete conversion, which varied by substrate, the crude reaction mixture was filtered over silica gel (1.5 x 10 cm, hexane → 19:1 hexanes/EtOAc eluent). Removal of the solvents in vacuo afforded the cyclized product. Enantiomeric excess was determined by chiral GC (see below for details).



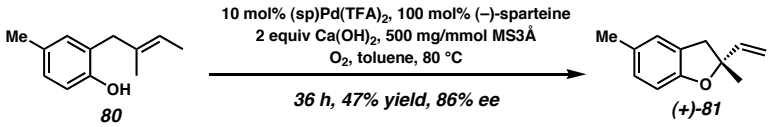
Dihydrobenzofuran (+)-27. 36 h, 87% yield: 81% ee; $[\alpha]_D^{23}$ +9.4 (*c* 1.0, $CHCl_3$). Remainder of spectroscopic data is identical to that reported above for **(±)-27**.



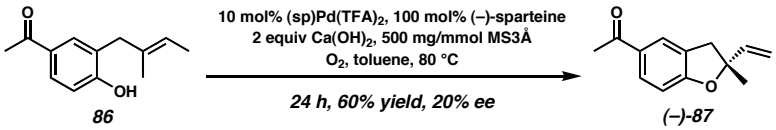
***p*-Methoxydihydrobenzofuran (+)-85.** For reaction at 80 °C: 24 h, 64% yield, 1.3:1 dihydrofuran **(+)-85**/**135**: 88% ee. For reaction at 55 °C: 60 h, 57% yield, 1:1 **(+)-85**/**135**: 90% ee; $[\alpha]_D^{22}$ +0.13 (*c* 0.86, $CHCl_3$). The remainder of spectroscopic data is identical to that reported above for **(±)-85**.



***p*-*t*-Butyldihydrobenzofuran (–)-83**. 36 h, 47% yield, 50% recovered starting material: 85% ee; $[\alpha]_D^{25.4}$ –3.55 (*c* 0.85, $CHCl_3$). Remainder of spectroscopic data is identical to that reported above for **(±)-83**.



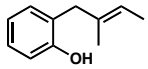
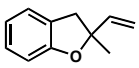
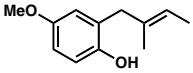
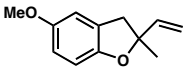
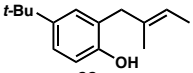
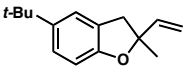
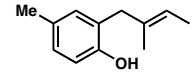
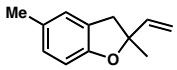
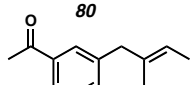
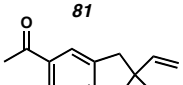
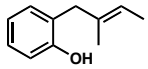
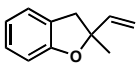
***p*-Methyldihydrobenzofuran (+)-81**. 36 h, 47% yield, 43% recovered starting material: 86% ee; $[\alpha]_D^{24.1}$ +1.05 (*c* 0.39, $CHCl_3$). Remainder of spectroscopic data is identical to that reported above for **(±)-81**.



***p*-Acyldihydrobenzofuran (–)-87**. 24 h, 60% yield: 20% ee; $[\alpha]_D^{26.0}$ –5.20 (*c* 0.42, $CHCl_3$). Remainder of spectroscopic data is identical to that reported above for **(±)-87**.

2.6.15 Methods for the determination of % conversion and % enantiomeric excess in the asymmetric oxidative cyclization of phenols.

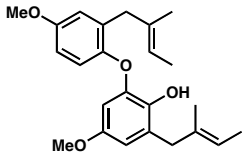
Table 2.6.1 Methods employed for the determination of % conversion and % enantiomeric excess.

entry	substrate	product	GC conditions	retention time of phenol (min)	retention time of S enationmer (min)	retention time of R enationmer (min)	retention time of pentadecane internal standard (min)
1.[a]	 26	 27	50 °C, 0 min; 2.0 °C/min to 150 °C 1.0 mL/min carrier gas flow	63.50	26.93	27.25	36.86
2.[a]	 84	 85	80 °C 5 min; 1.0 °C/min to 140 °C 15.0 °C/min to 180 °C 1.0 mL/min carrier gas flow	-------	48.37	48.79	-------
3.[b]	 82	 83	70 °C, 0 min; 1.0 °C/min to 160 °C 20.0 °C/min to 200 °C 1.0 mL/min carrier gas flow	-------	61.05	61.60	-------
4.[b]	 80	 81	70 °C, 0 min; 1.0 °C/min to 160 °C 20.0 °C/min to 200 °C 1.0 mL/min carrier gas flow	-------	38.02	38.40	-------
5.[b]	 86	 87	70 °C, 0 min; 1.0 °C/min to 200 °C 1.0 mL/min carrier gas flow	-------	78.86	79.29	-------
				retention time of phenol (min)	retention time of product (min)		retention time of tridecane internal standard (min)
6.[c]	 26	 27	160 °C 5 min; 20.0 °C/min to 250 °C 250 °C 6 min 1.0 mL/min carrier gas flow	3.46	6.36		2.20

[a] Assays conducted on Bodman Chiraldex GT-A column. [b] Assay conducted on CP Chirasil Dex CB column. [c] Assays conducted on Agilent DB-WAX column.

*2.6.16 General procedure for cyclization of **84** and attempted suppression of **135** as shown in Table 2.3.5.*

A thick-walled oven-dried 10 mL 15 cm-long tube equipped with magnetic stir bar was charged with powdered molecular sieves (MS3Å, 50 mg, 500 mg/mmol), and (sp)Pd(TFA)$_2$ (**134**, 5.6 mg, 0.010 mmol, 0.10 equiv), followed by acidic additive (0.01 mmol or 0.10 mmol, as indicated in Table 11, 0.10 or 1.0 equiv), toluene (1.0 mL), (–)-sparteine (**22**, 23.9 μL, 0.10 mmol, 1.0 equiv) and phenol **84** (19.2 mg, 0.10 mmol, 1.0 equiv). The tube was evacuated and backfilled with O_2 (3 x, balloon), and the mixture allowed to stir under O_2 (1 atm, balloon) at 80 °C. The reaction was monitored for conversion and enantiomeric excess by chiral GC or ^{1}H NMR. The crude reaction mixture was loaded onto silica gel and filtered (19:1 hexanes/EtOAc eluent). Enantiomeric excess was determined by analysis by chiral GC; product ratios were determined by analysis of the ^{1}H NMR spectrum of the product mixture.



135

Aryl ether dimer 135. R_F 0.48 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (d, *J* = 8.7 Hz, 1H), 6.79-6.70 (comp. m, 3H), 6.37 (d, *J* = 3.2 Hz, 1H), 6.11 (d, *J* = 3.2 Hz, 1H), 5.39 (s, 1H), 5.32 (m, 1H), 5.24 (m, 1H), 3.80 (s, 3H), 3.64 (s, 3H), 3.35 (s, 2H), 3.25 (s, 2H), 1.65-1.56 (comp. m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 152.8, 147.7, 145.3, 139.0, 134.6, 134.2, 133.1, 127.7, 121.0, 120.5, 120.4, 116.8, 112.4, 109.2, 101.2, 55.9, 55.8, 40.2, 39.5, 16.1, 16.0, 13.7, 13.6; IR (film) 3458, 2913,

1607, 1492, 1439, 1202 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{24}H_{30}O_4]^+$: 382.2141, found: 382.2144.

2.7 NOTES AND REFERENCES

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[24] Attempted cyclization under the chloroform-based rate-enhanced conditions for oxidative kinetic resolution ((sp)$PdCl_2$ (5 mol%), (–)-sparteine (**22**) (7 mol%), Cs_2CO_3 (0.4 equiv), $CHCl_3$ (0.1 M), O_2 (1 atm, balloon), 25 °C) resulted in no reaction.

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[27] For example, tetrasubstituted olefin-containing phenol **45**, which is Hayashi's most selectively cyclized substrate (see Ref. 9a), fails to cyclize under our optimized conditions.

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APPENDIX 2.1

Spectra Relevant to Chapter 2

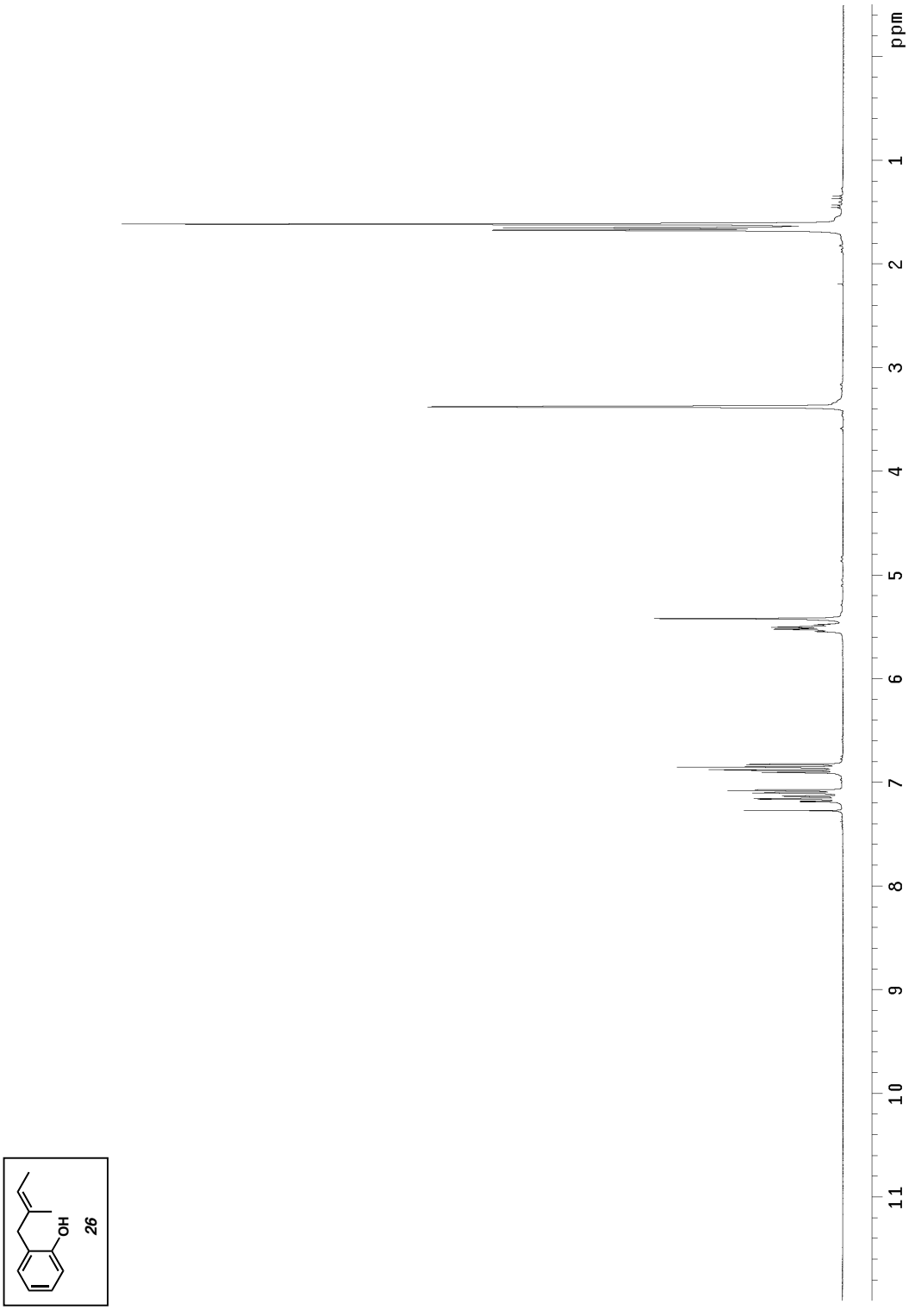


Figure A2.1.1 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of ***26***.

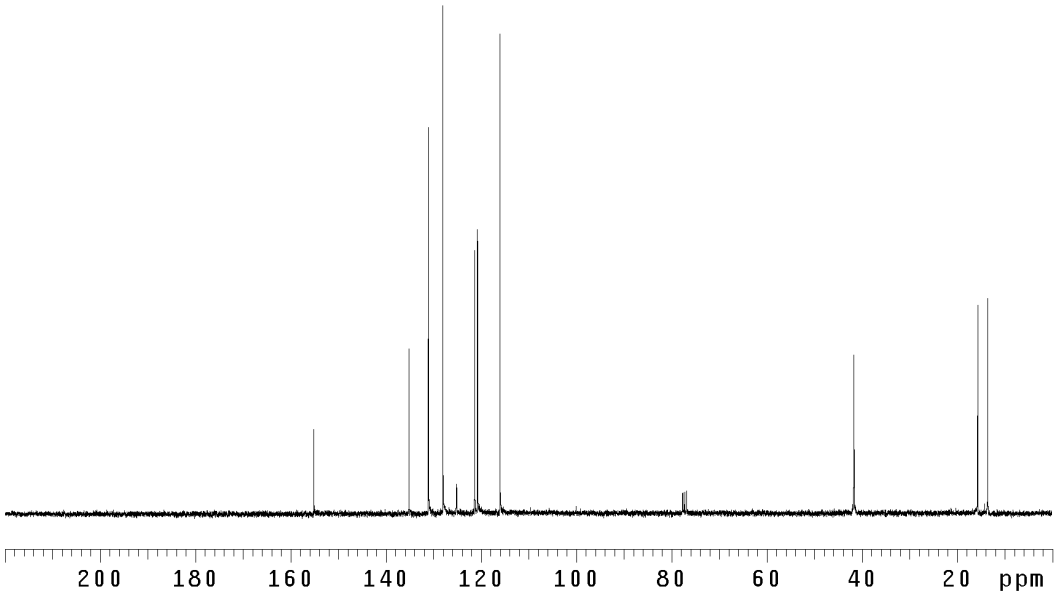


*Figure A2.1.2 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **26**.*

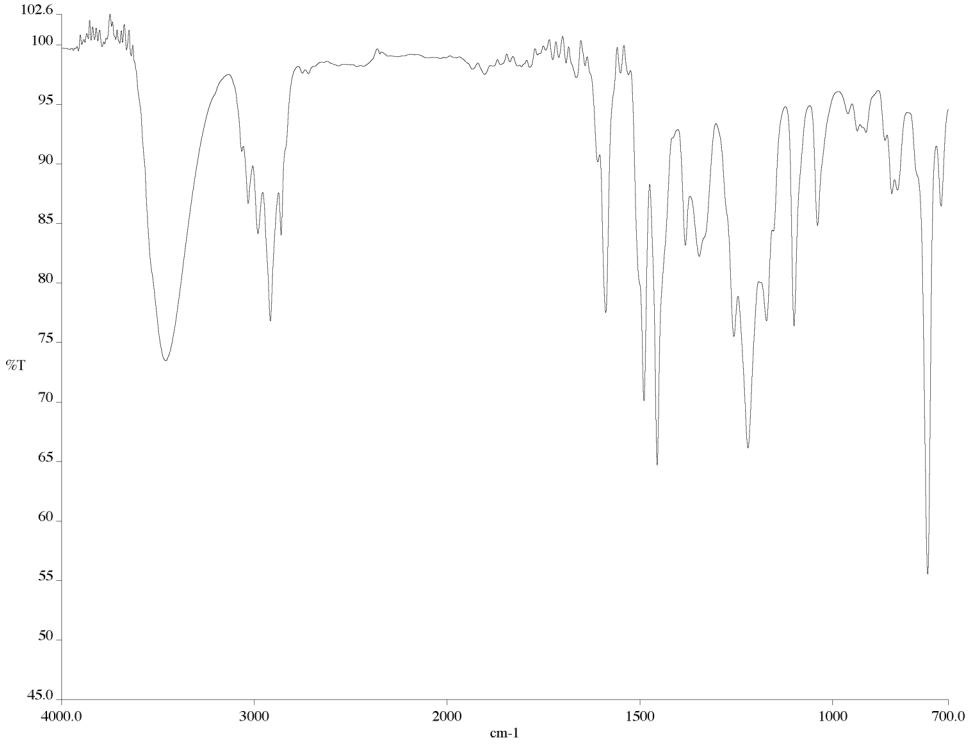


*Figure A2.1.3 IR spectrum (thin film/NaCl) of **26.***

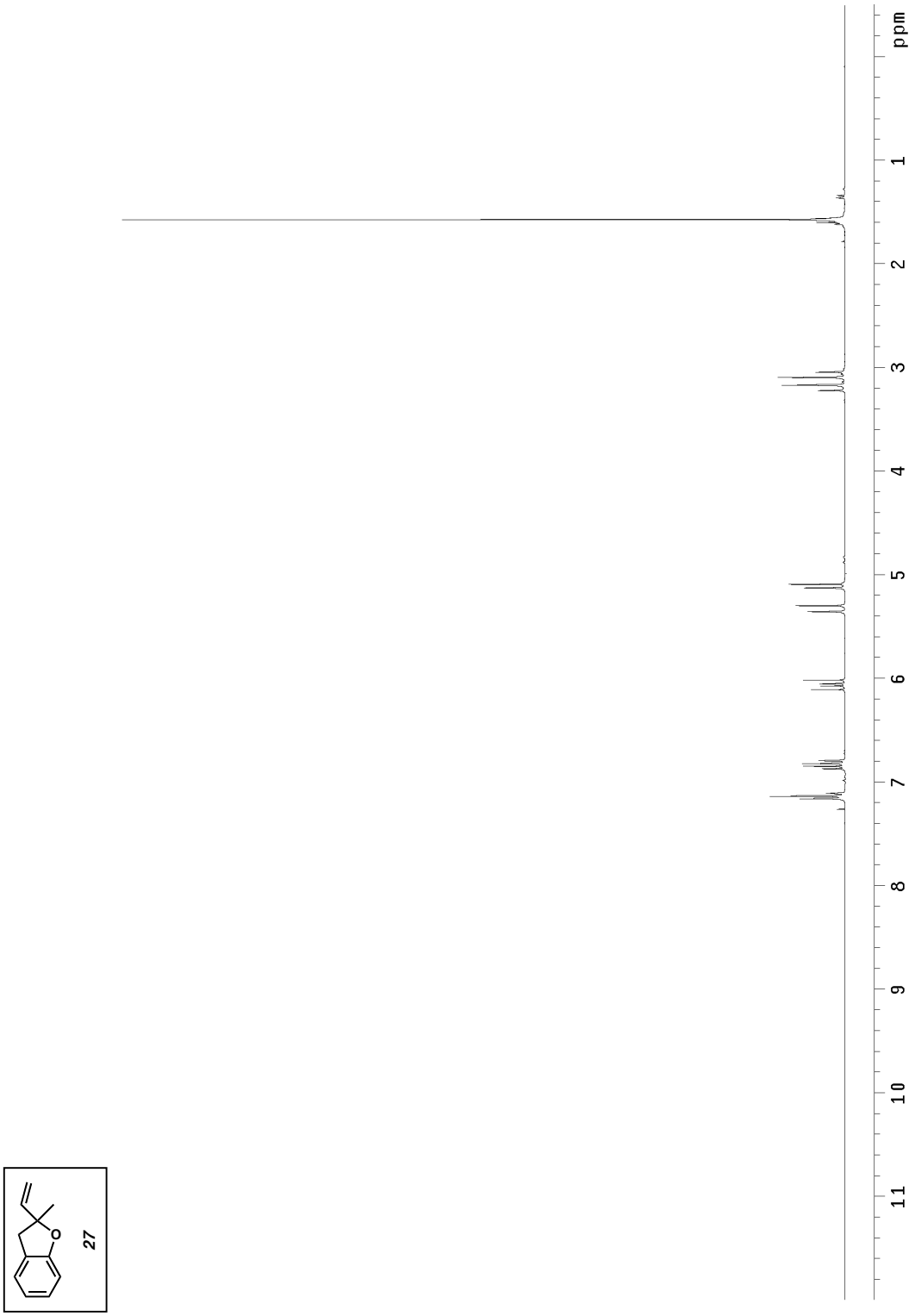


*Figure A2.1.4 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **27**.*

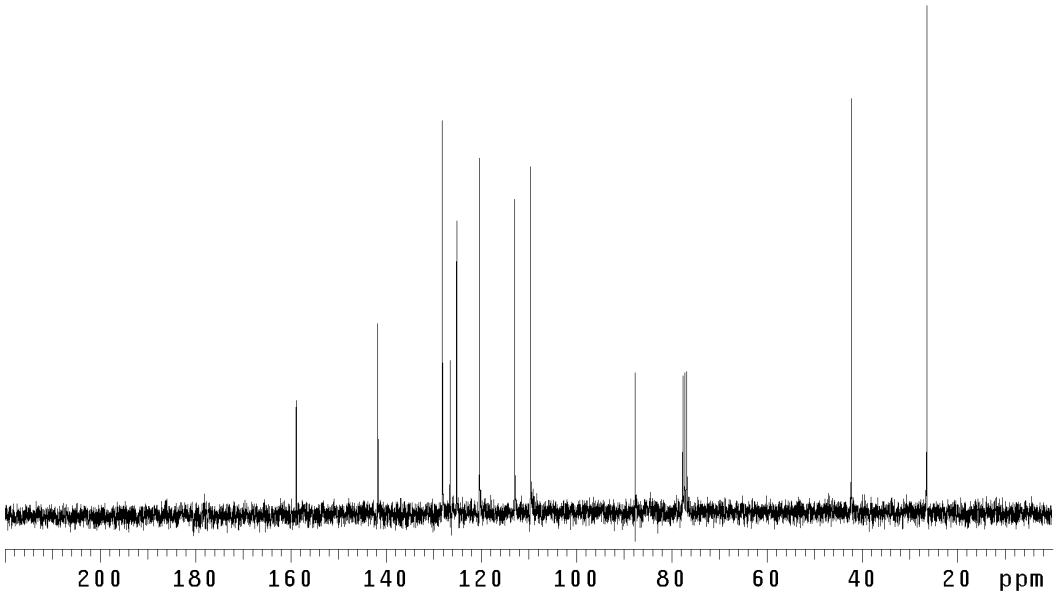


*Figure A2.1.5 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **27**.*

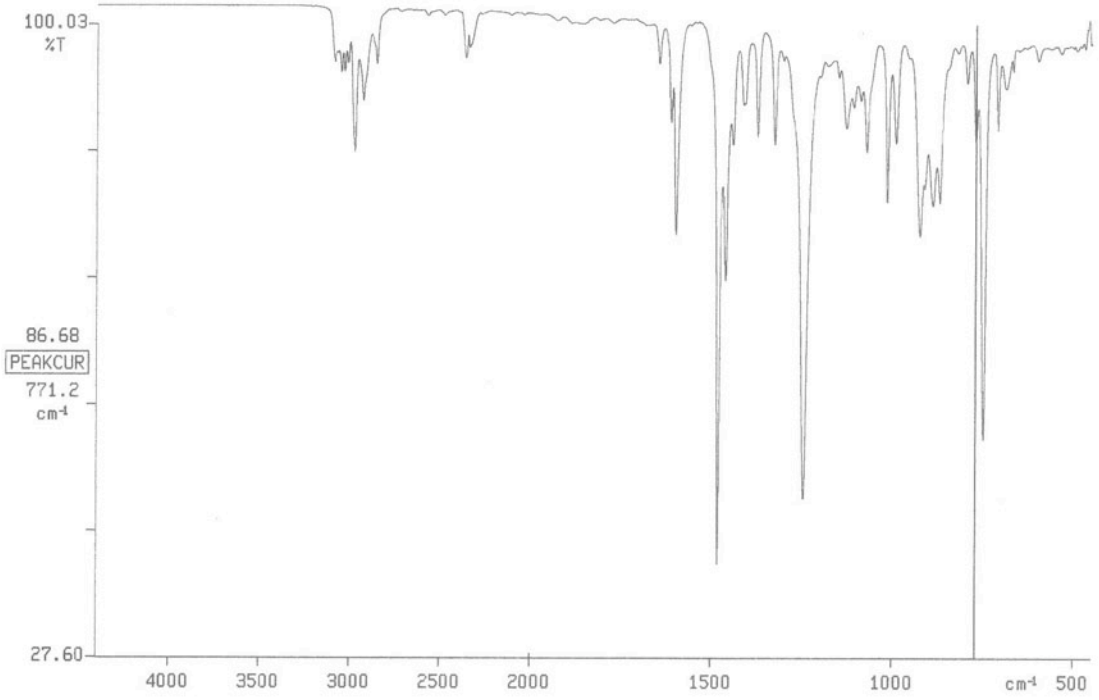


*Figure A2.1.6 IR spectrum (thin film/NaCl) of **27.***

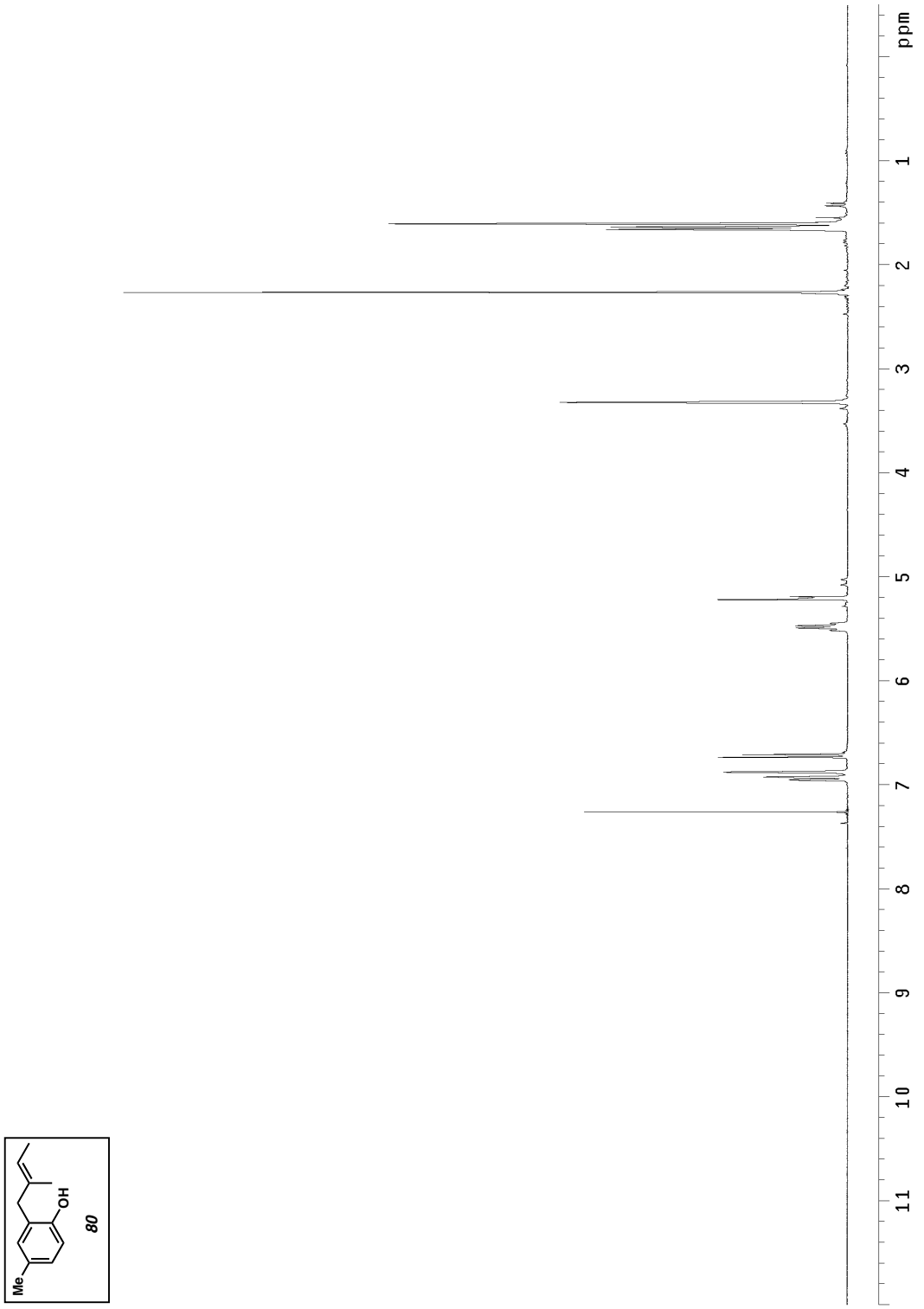


*Figure A2.1.7 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **80**.*

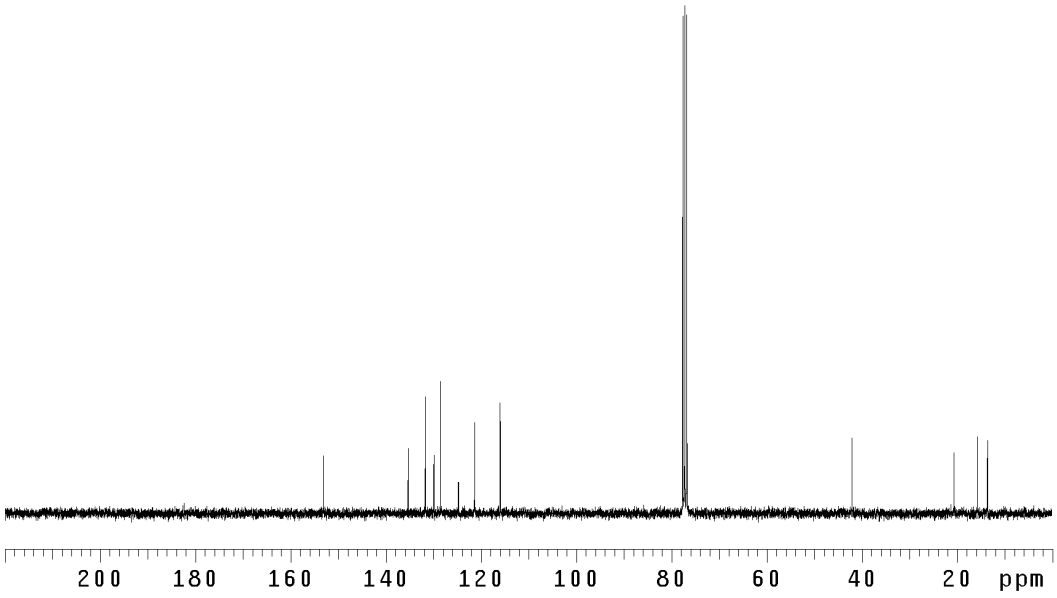


*Figure A2.1.8 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **80**.*

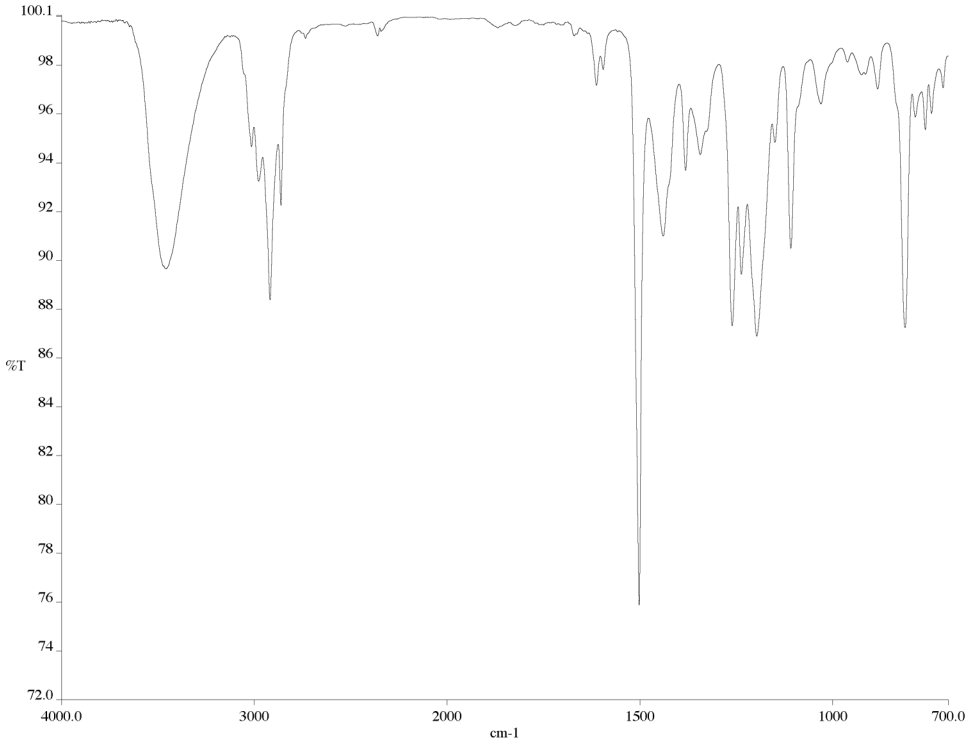


*Figure A2.1.9 IR spectrum (thin film/NaCl) of **80.***

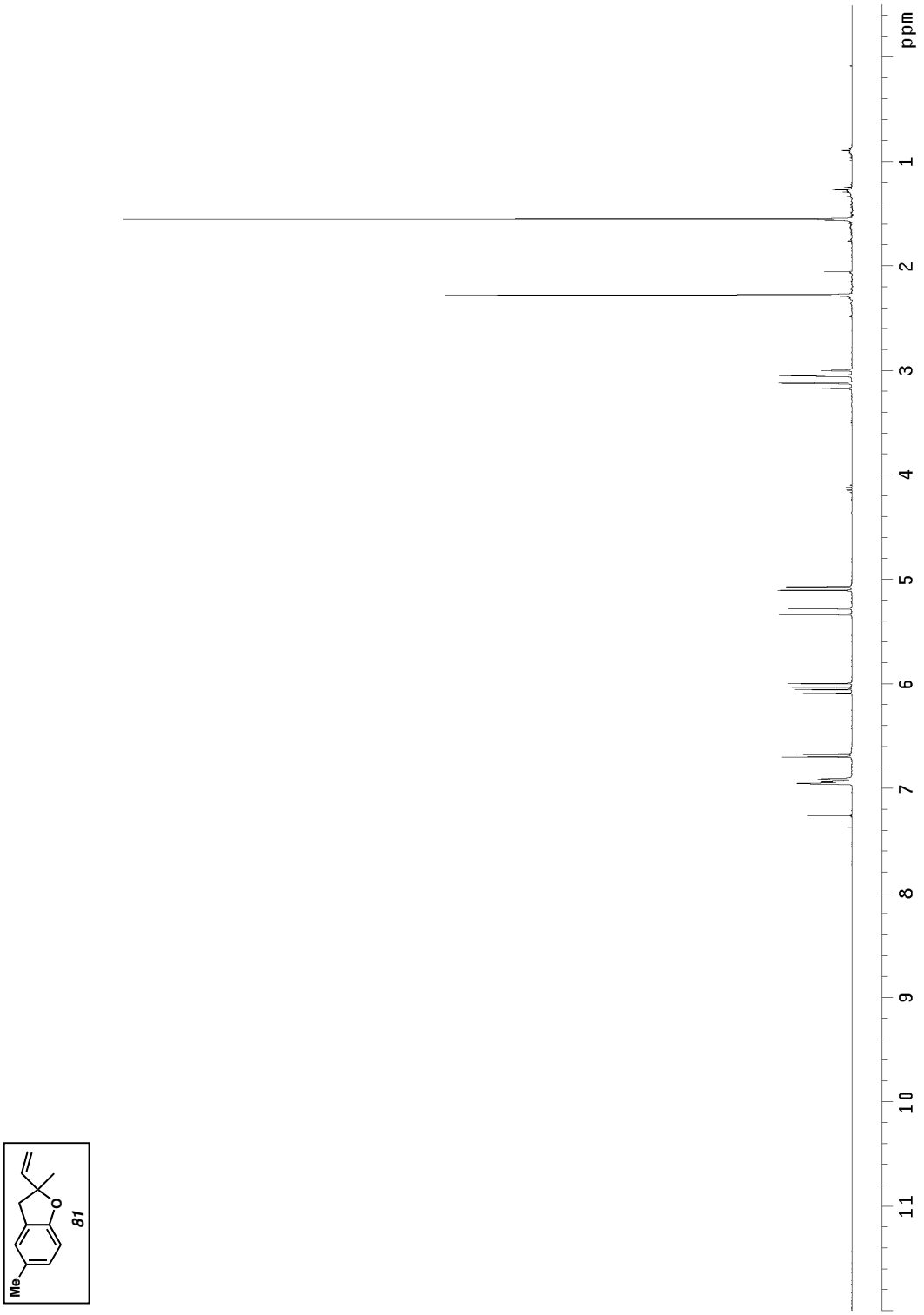


*Figure A2.1.10 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **81**.*

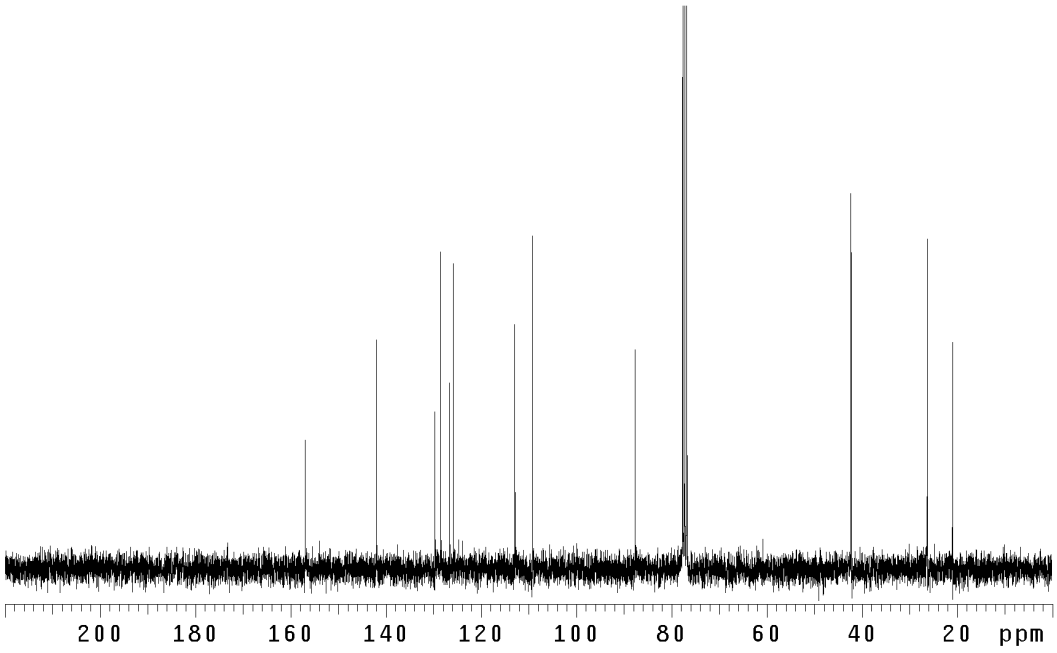


*Figure A2.1.11 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **81**.*

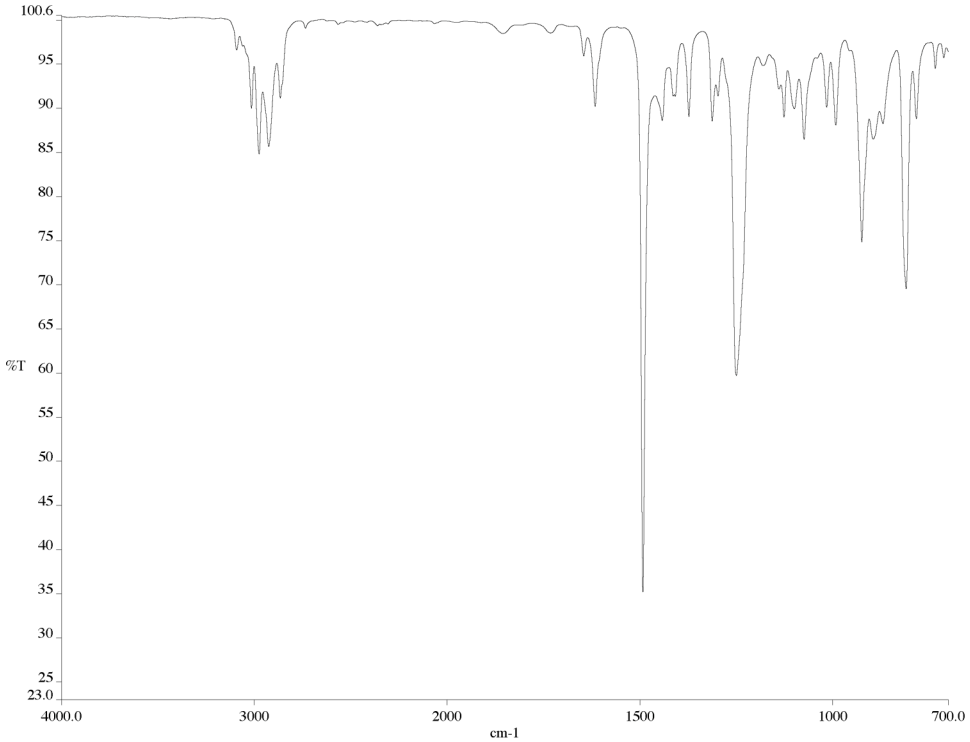


*Figure A2.1.12 IR spectrum (thin film/NaCl) of **81.***

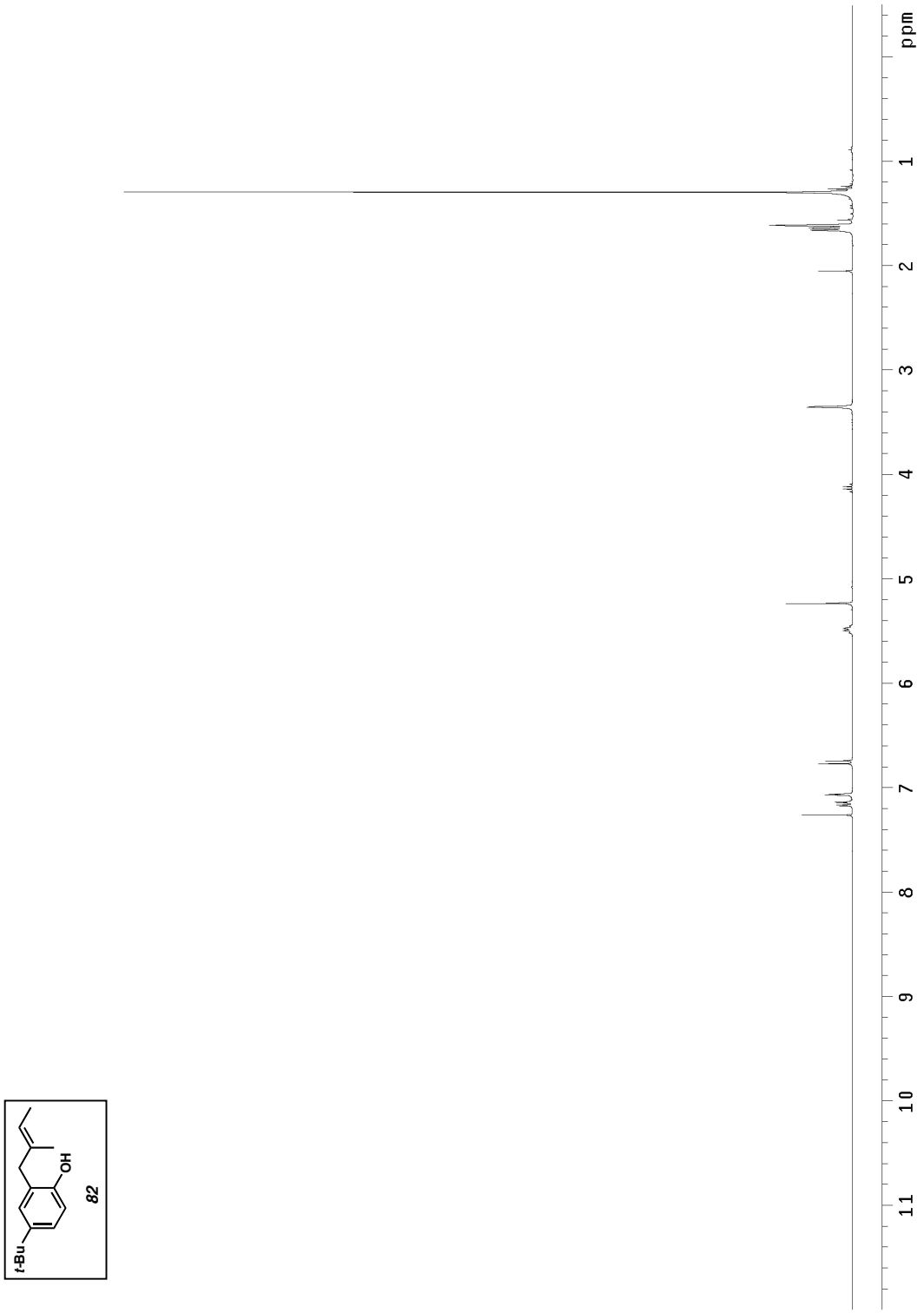


*Figure A2.1.13 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **82**.*

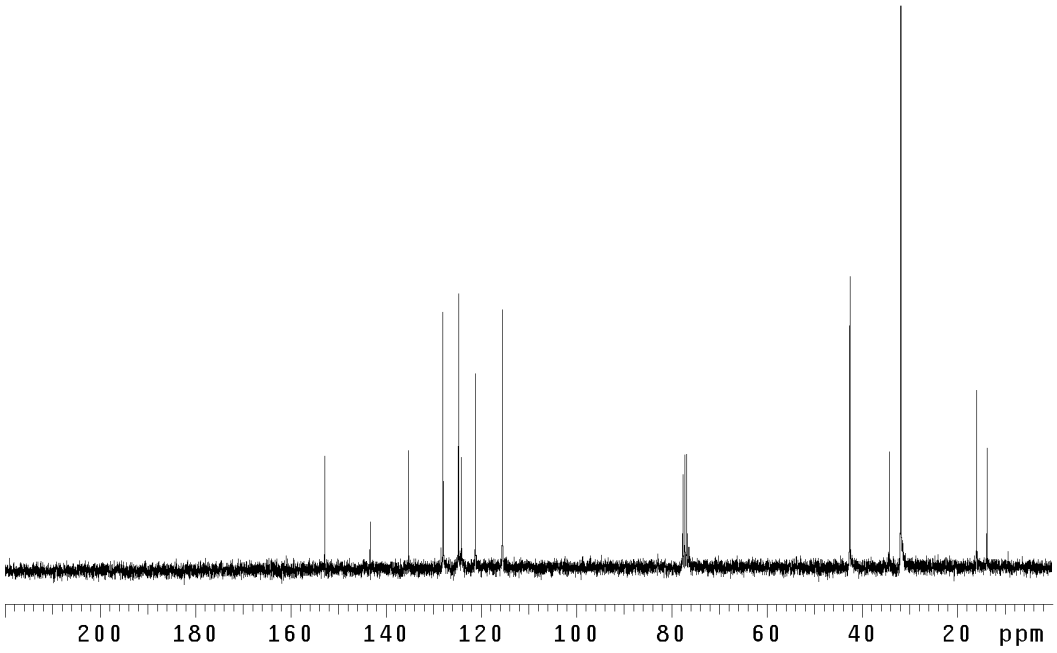


Figure A2.1.14 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of ***82***.

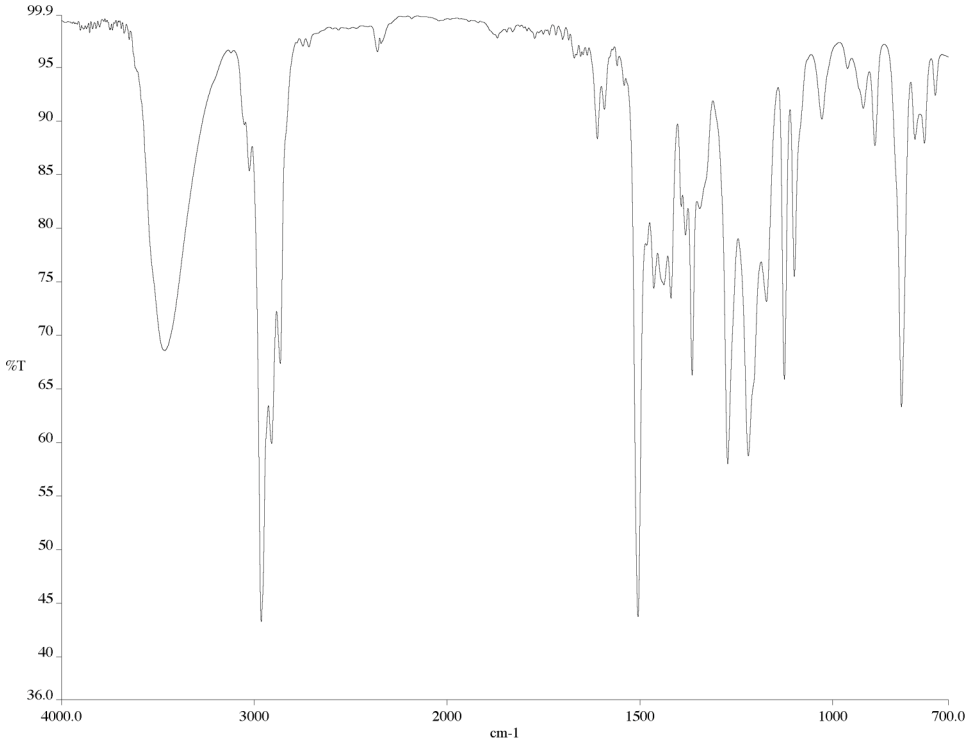


Figure A2.1.15 IR spectrum (thin film/NaCl) of ***82.***

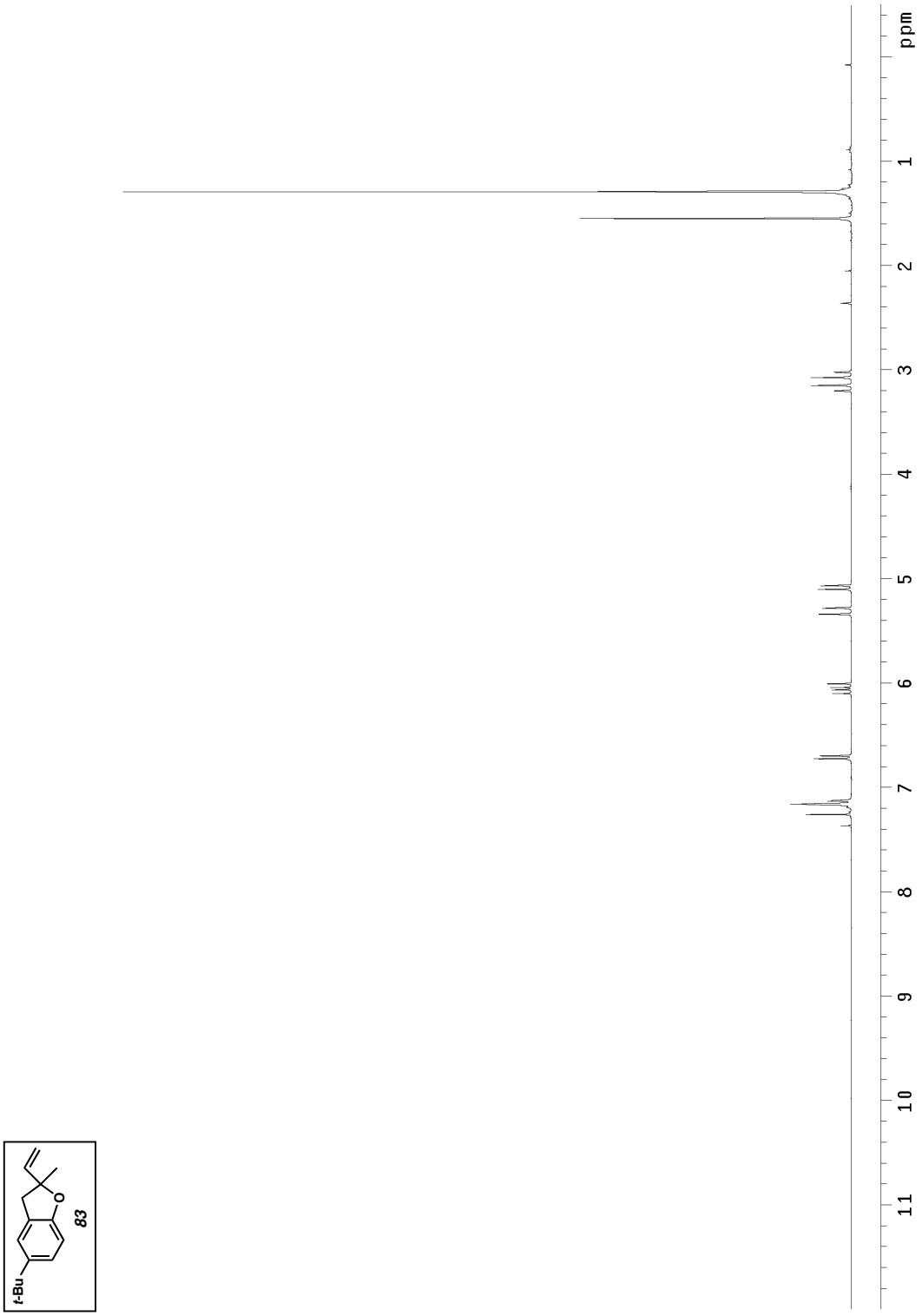


*Figure A2.1.16 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **83**.*

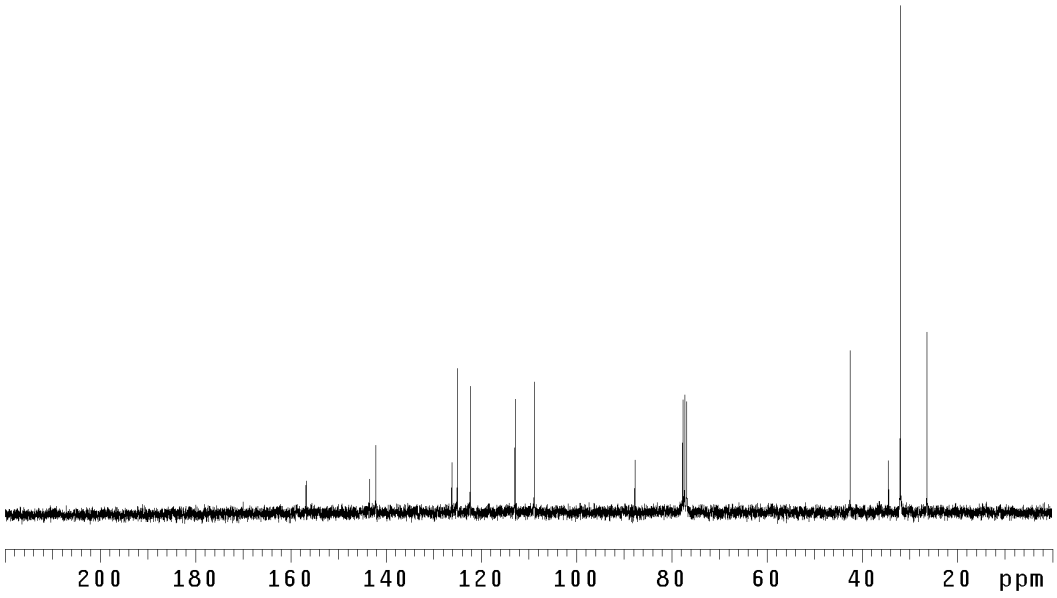


Figure A2.1.17 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of ***83***.

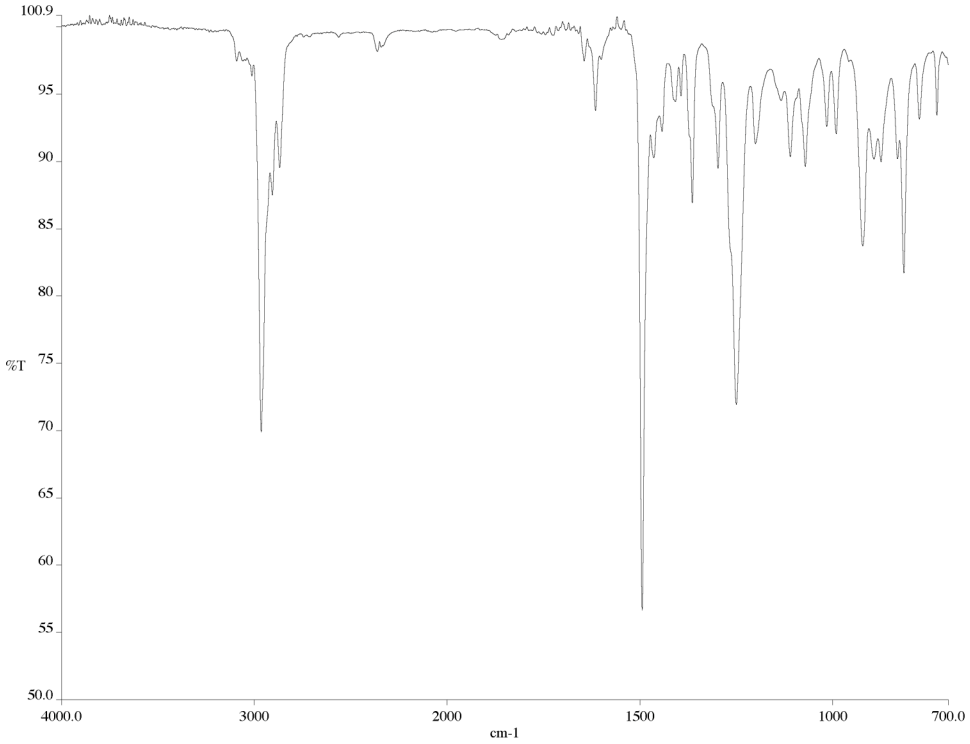


Figure A2.1.18 IR spectrum (thin film/NaCl) of ***83.***

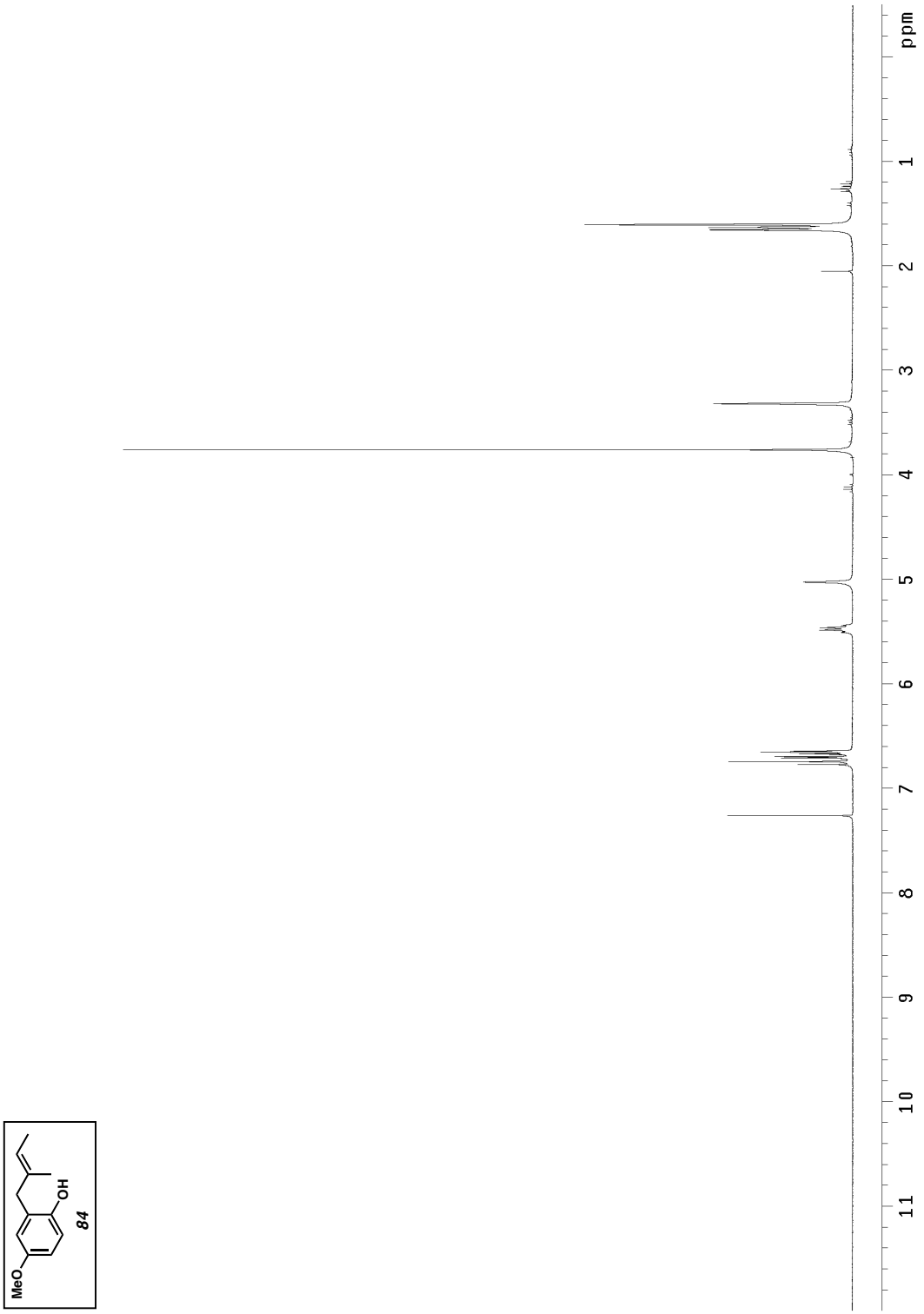


*Figure A2.1.19 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **84**.*

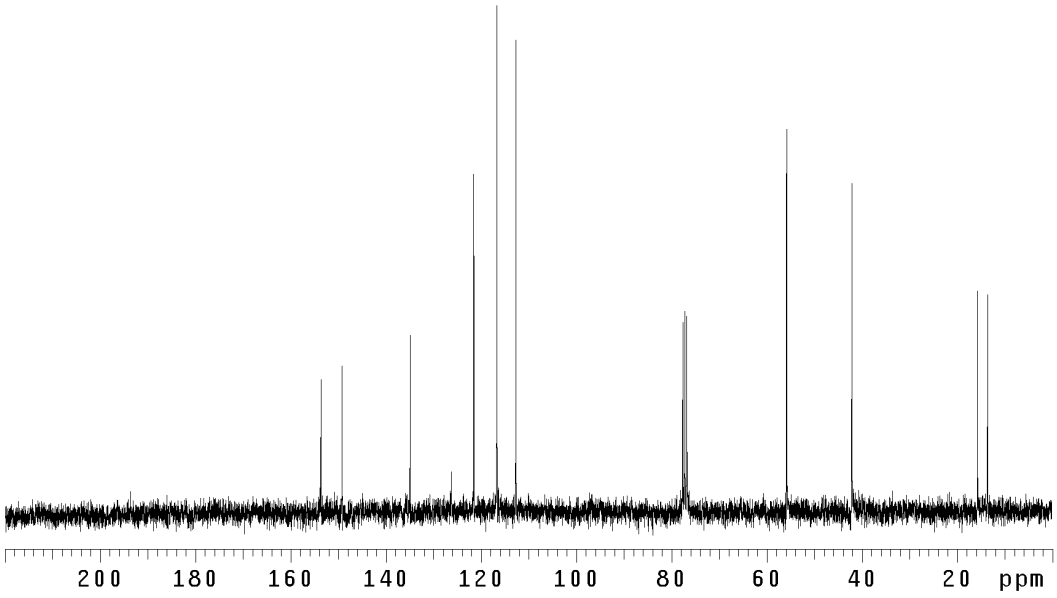


*Figure A2.1.20 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **84**.*

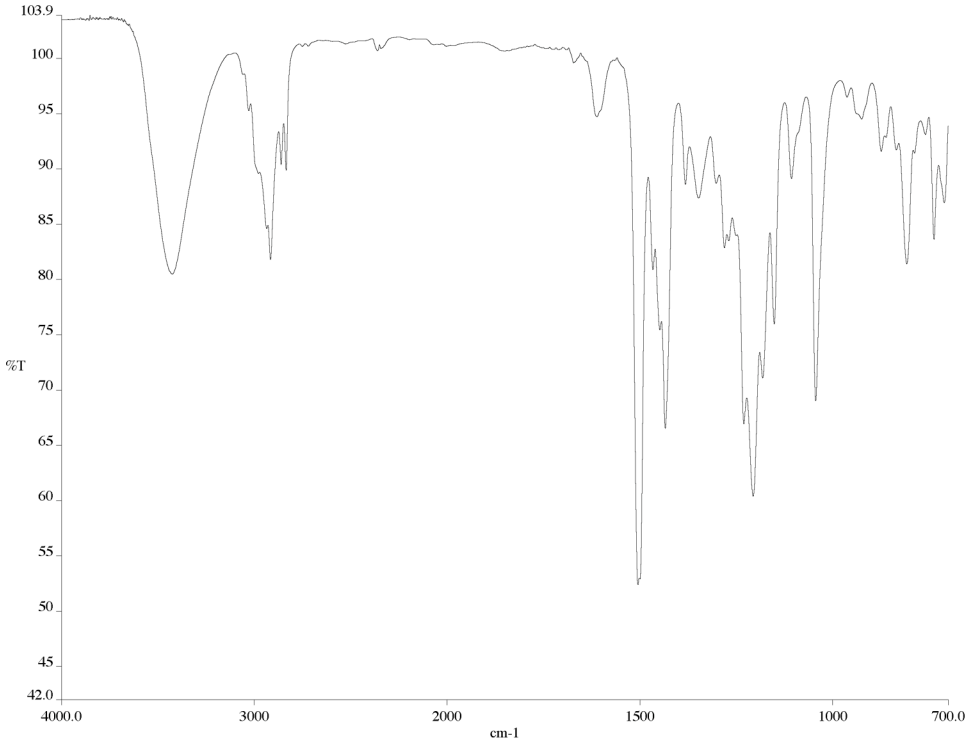


*Figure A2.1.21 IR spectrum (thin film/NaCl) of **84**.*

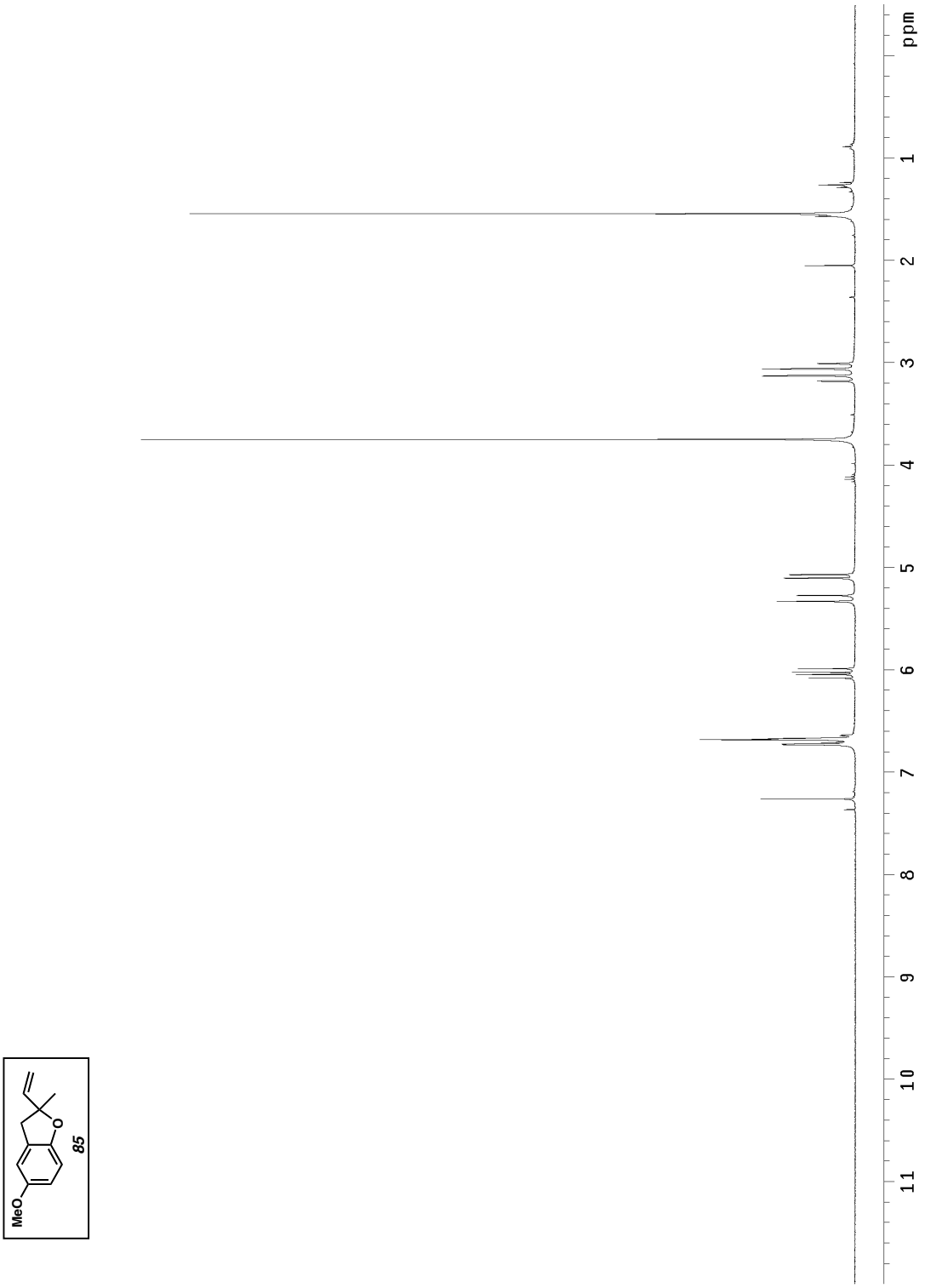


*Figure A2.1.22 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **85**.*

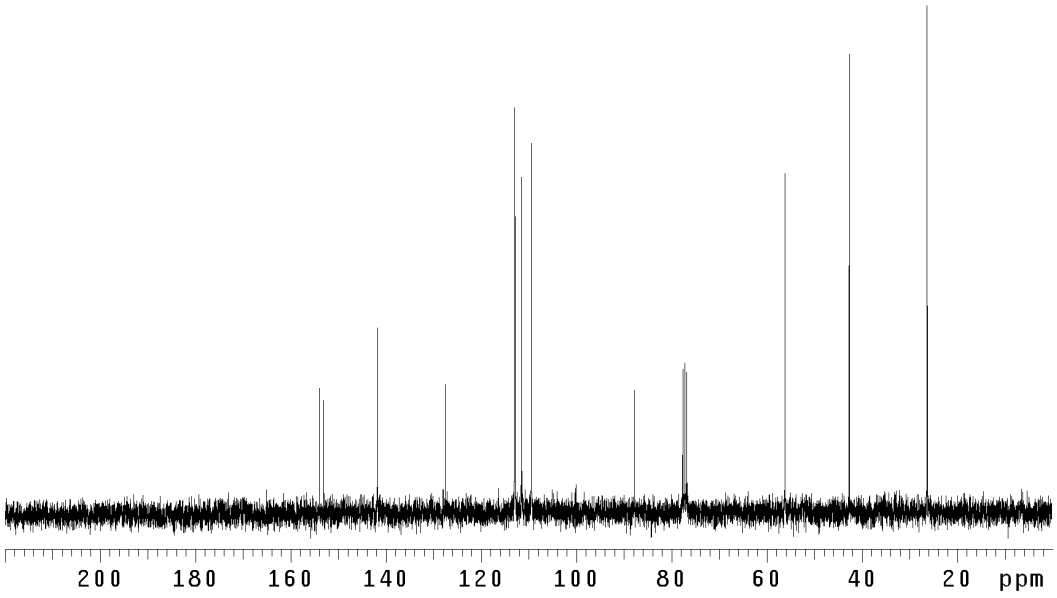


Figure A2.1.23 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of ***85****.*

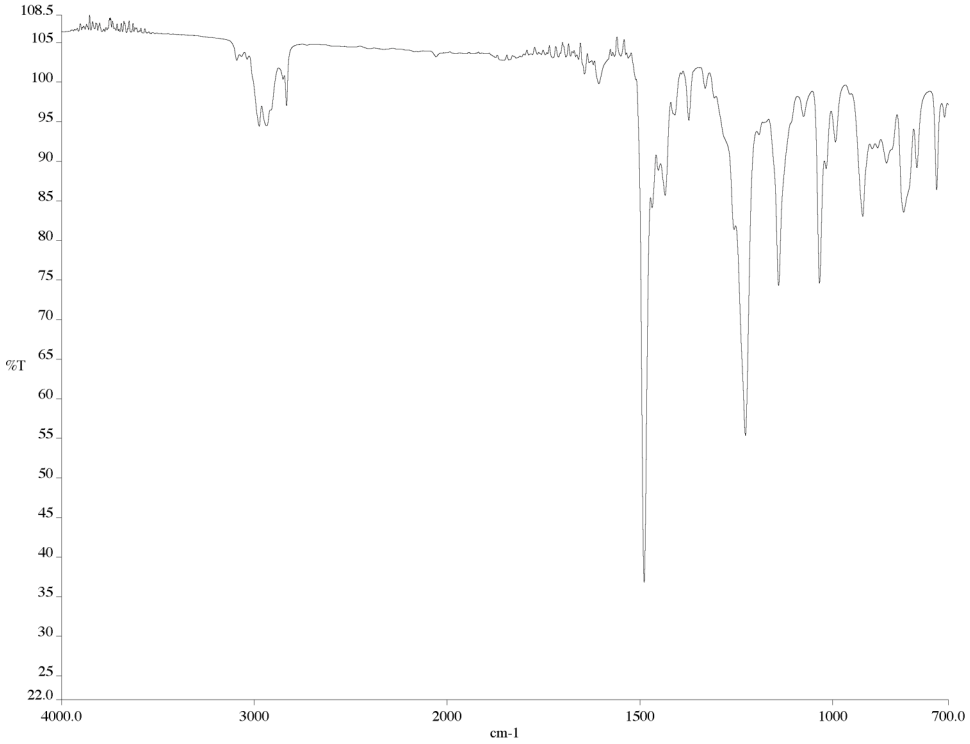


Figure A2.1.24 IR spectrum (thin film/NaCl) of ***85.***

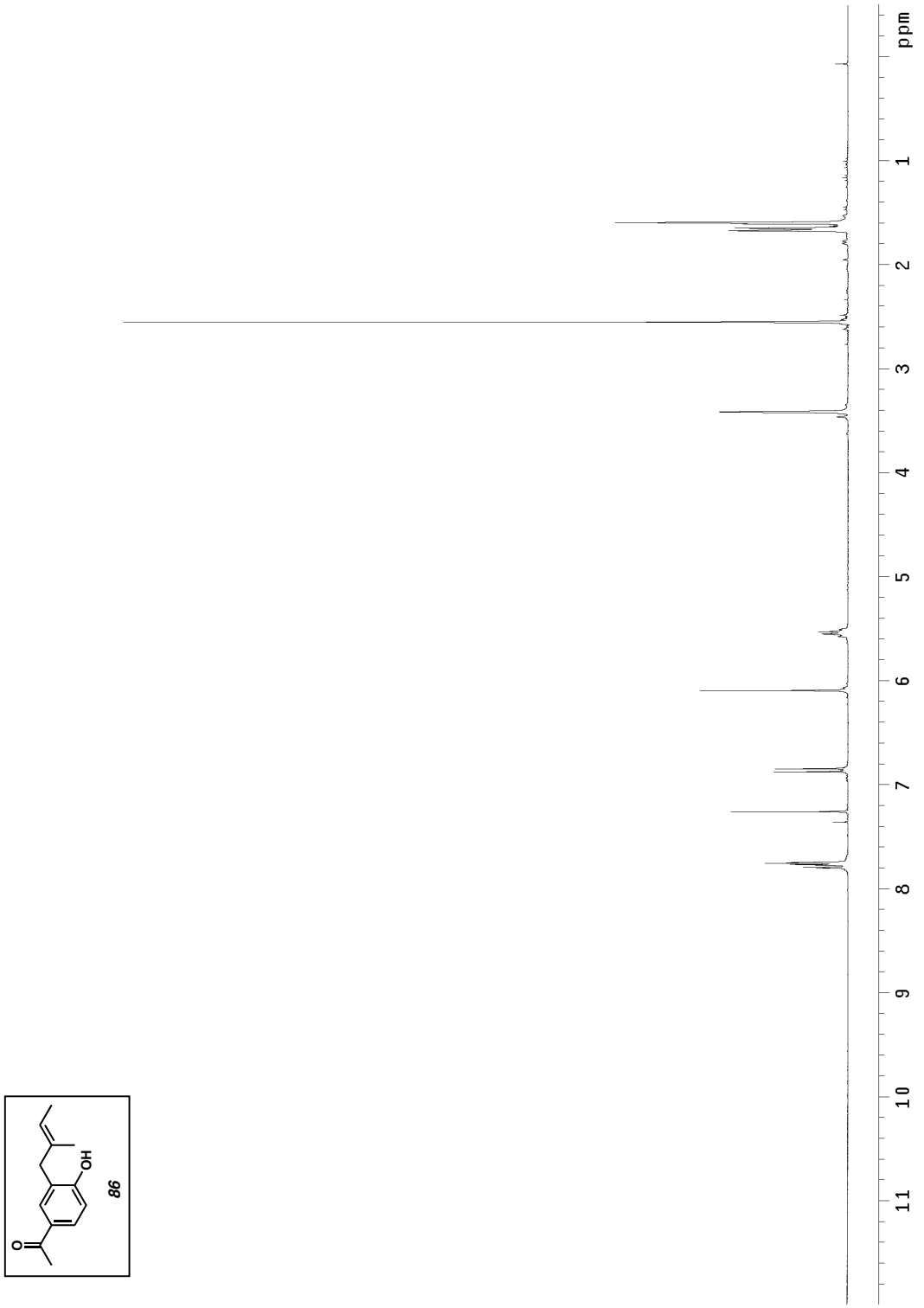


*Figure A2.1.25 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **86**.*

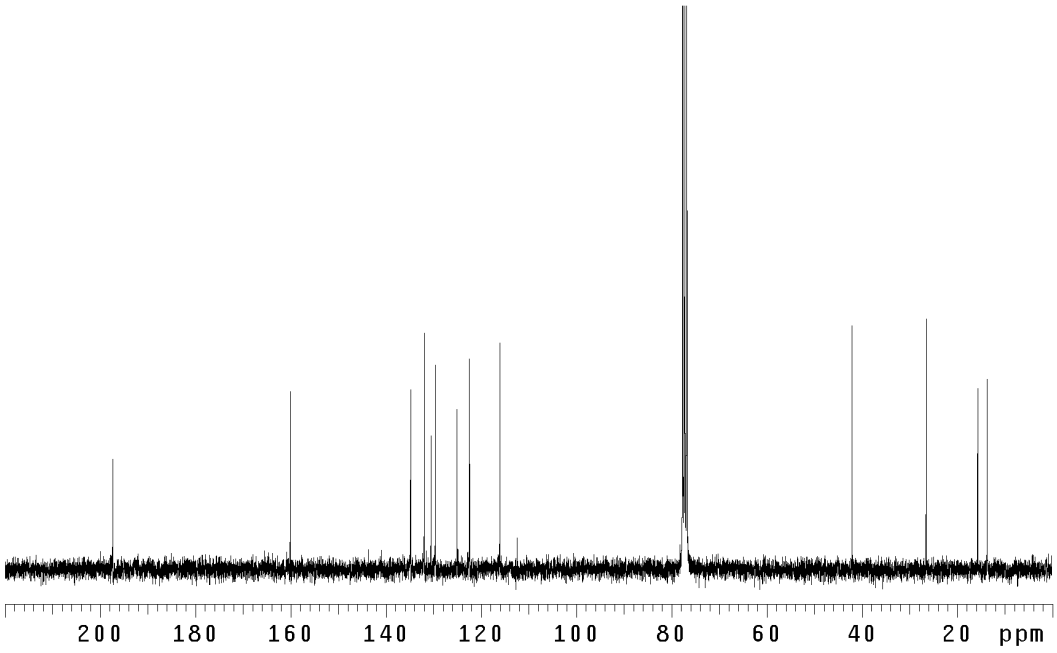


*Figure A2.1.26 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **86**.*

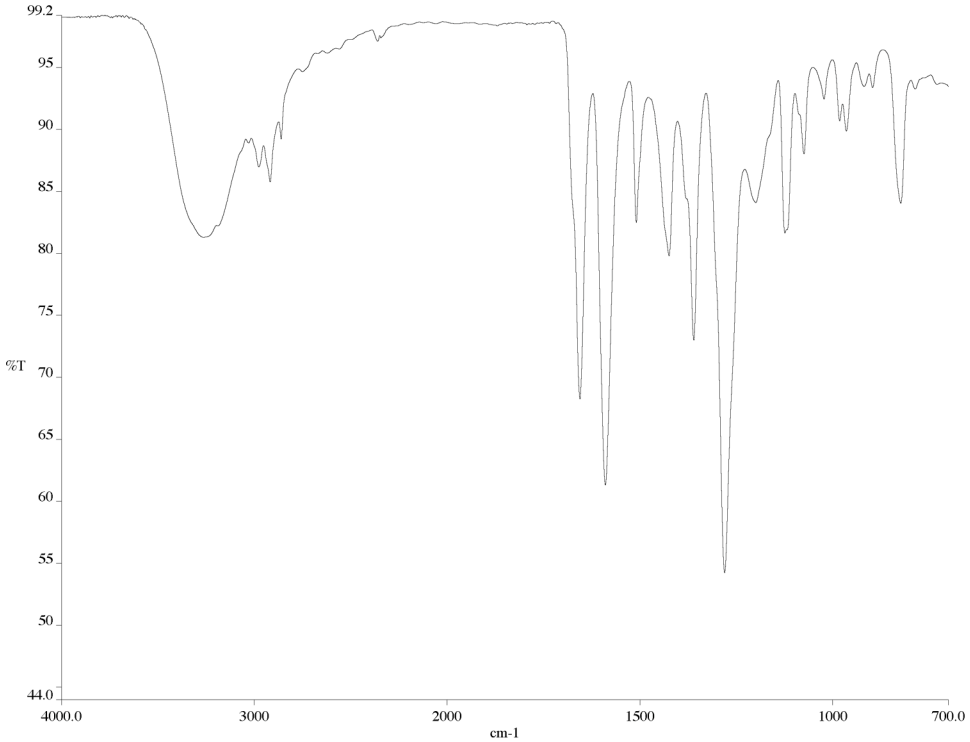


*Figure A2.1.27 IR spectrum (thin film/NaCl) of **86**.*

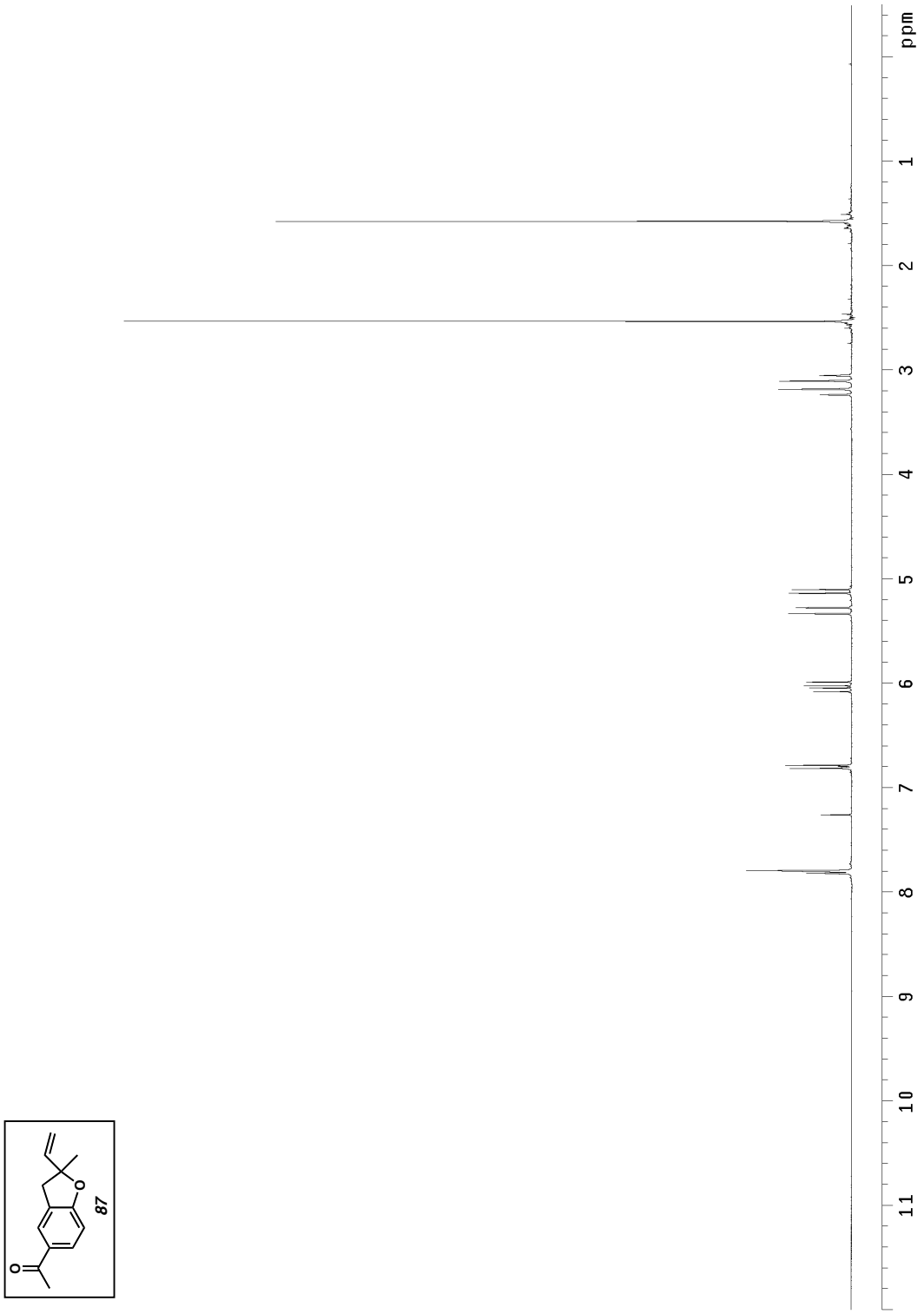


*Figure A2.1.28 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **87**.*

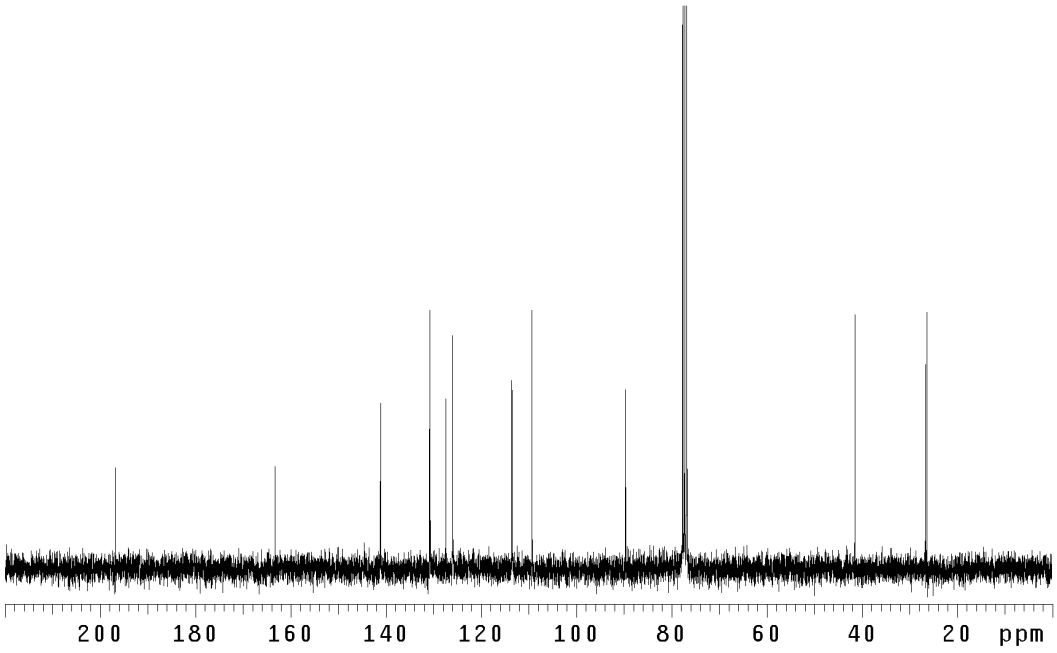


*Figure A2.1.29 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **87**.*

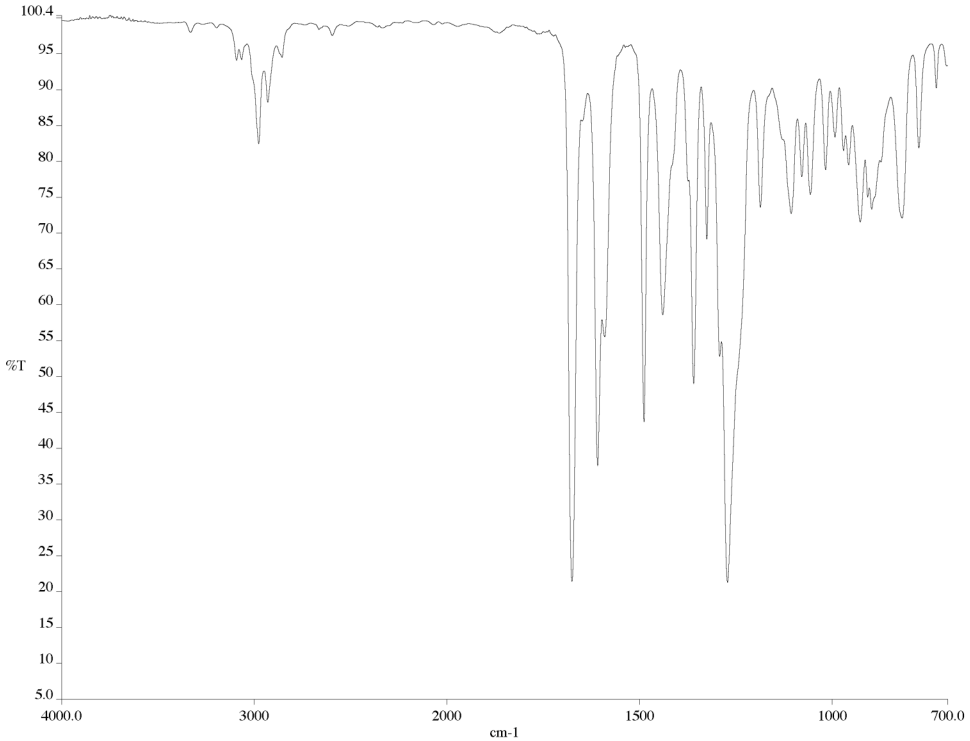


*Figure A2.1.30 IR spectrum (thin film/NaCl) of **87.***

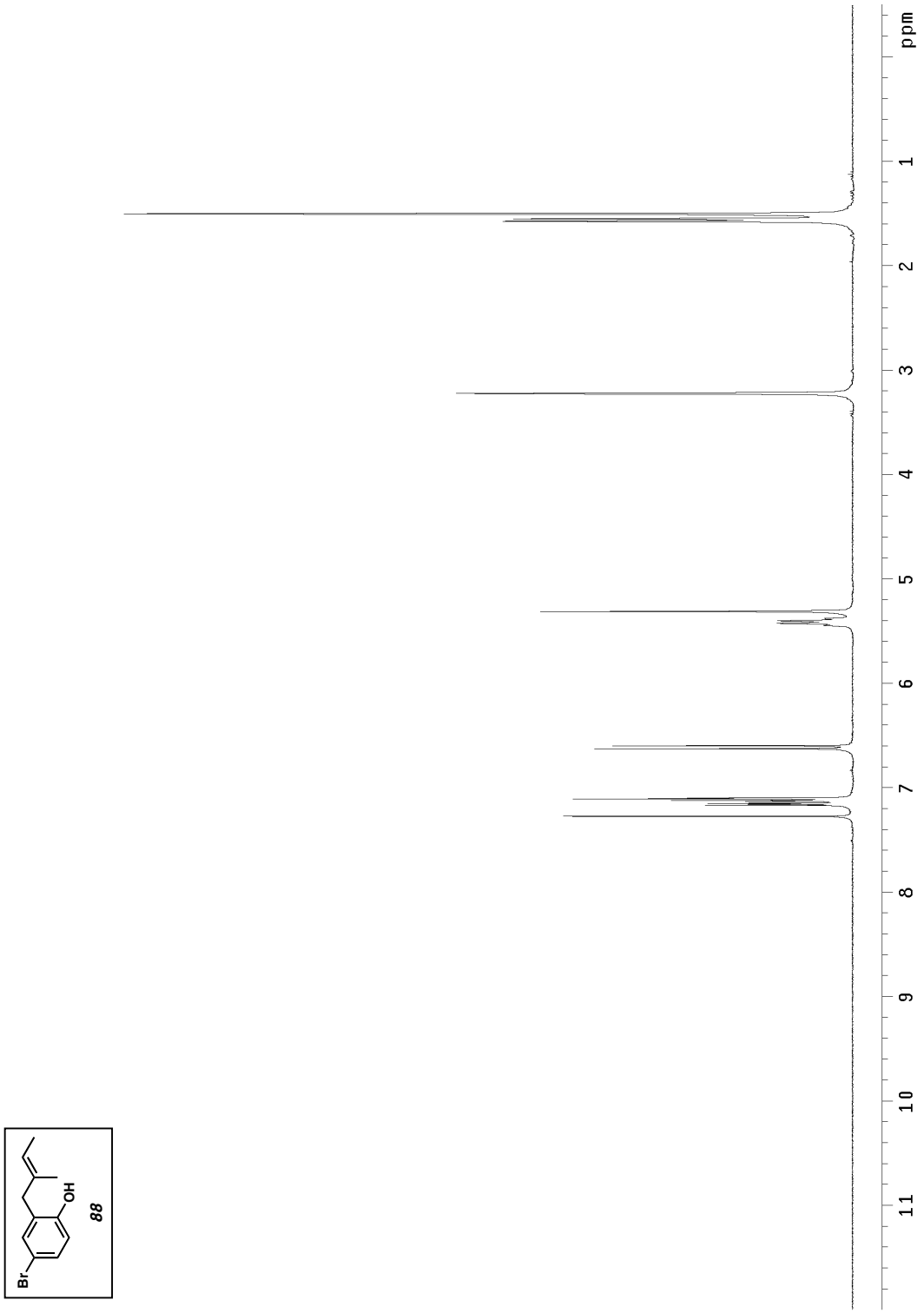


*Figure A2.1.31 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **88**.*

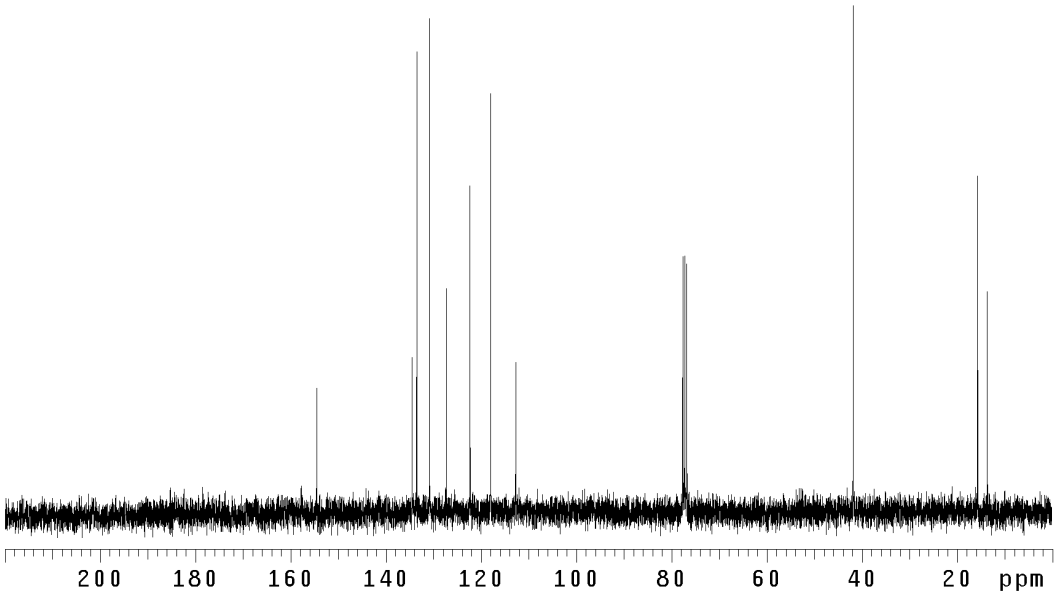


*Figure A2.1.32 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **88**.*

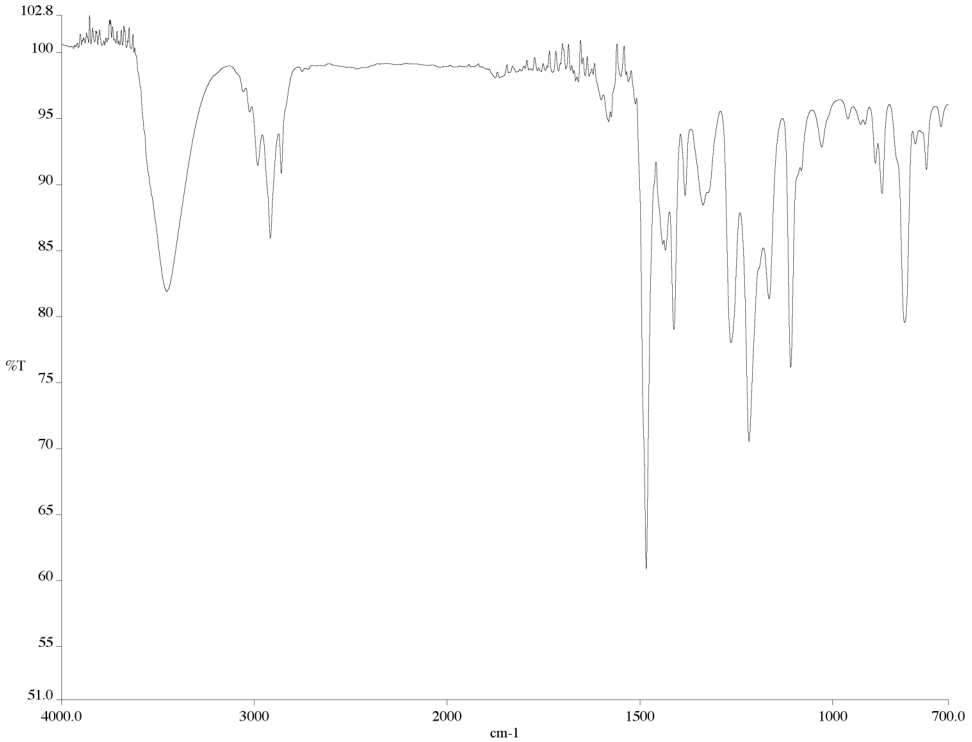


*Figure A2.1.33 IR spectrum (thin film/NaCl) of **88**.*

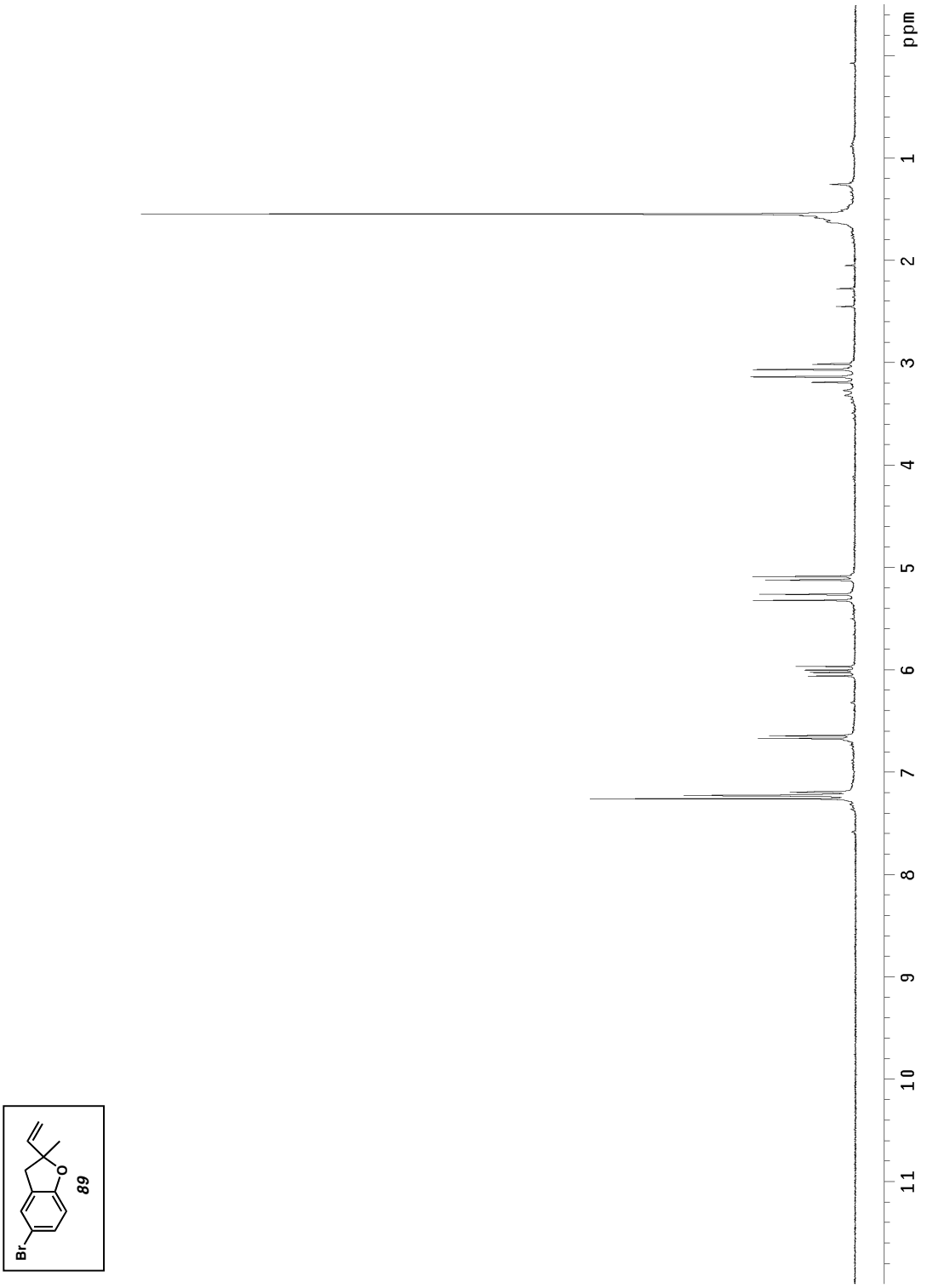


*Figure A2.1.34 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **89**.*

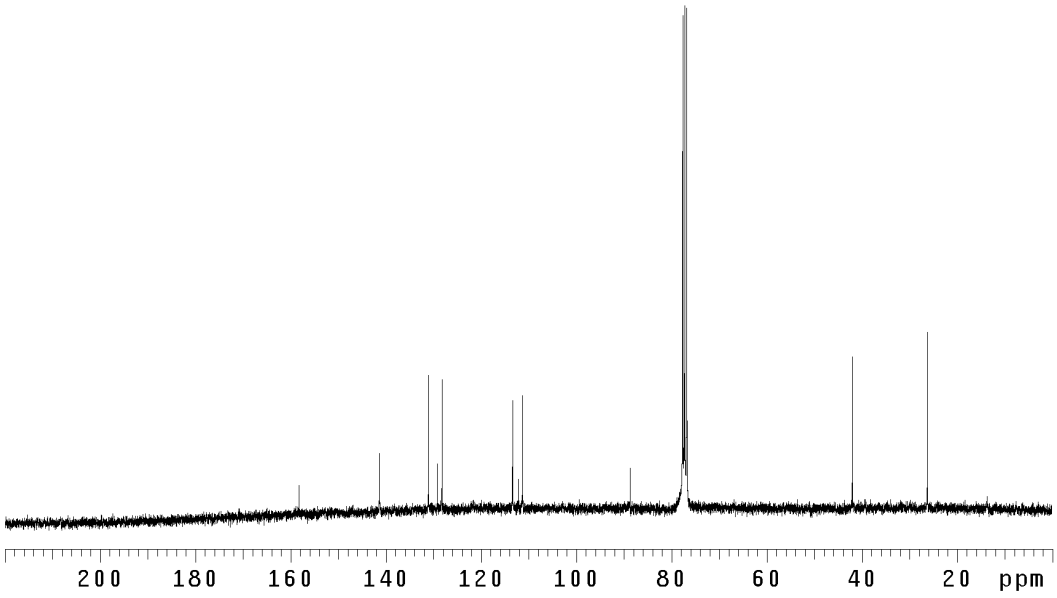


*Figure A2.1.35 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **89**.*

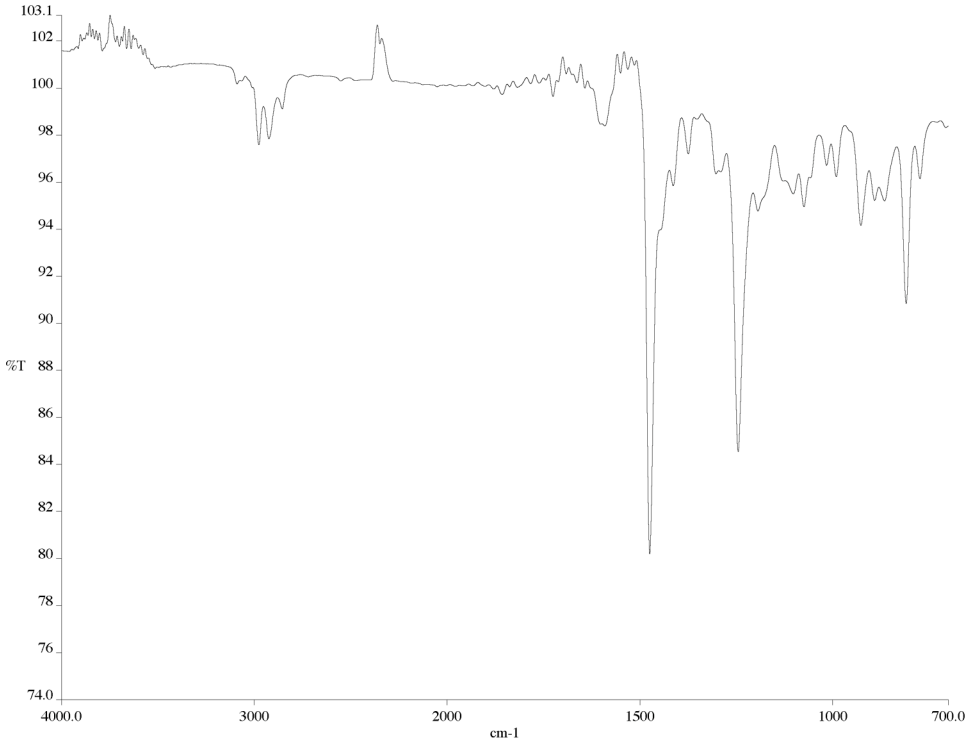


*Figure A2.1.36 IR spectrum (thin film/NaCl) of **89**.*

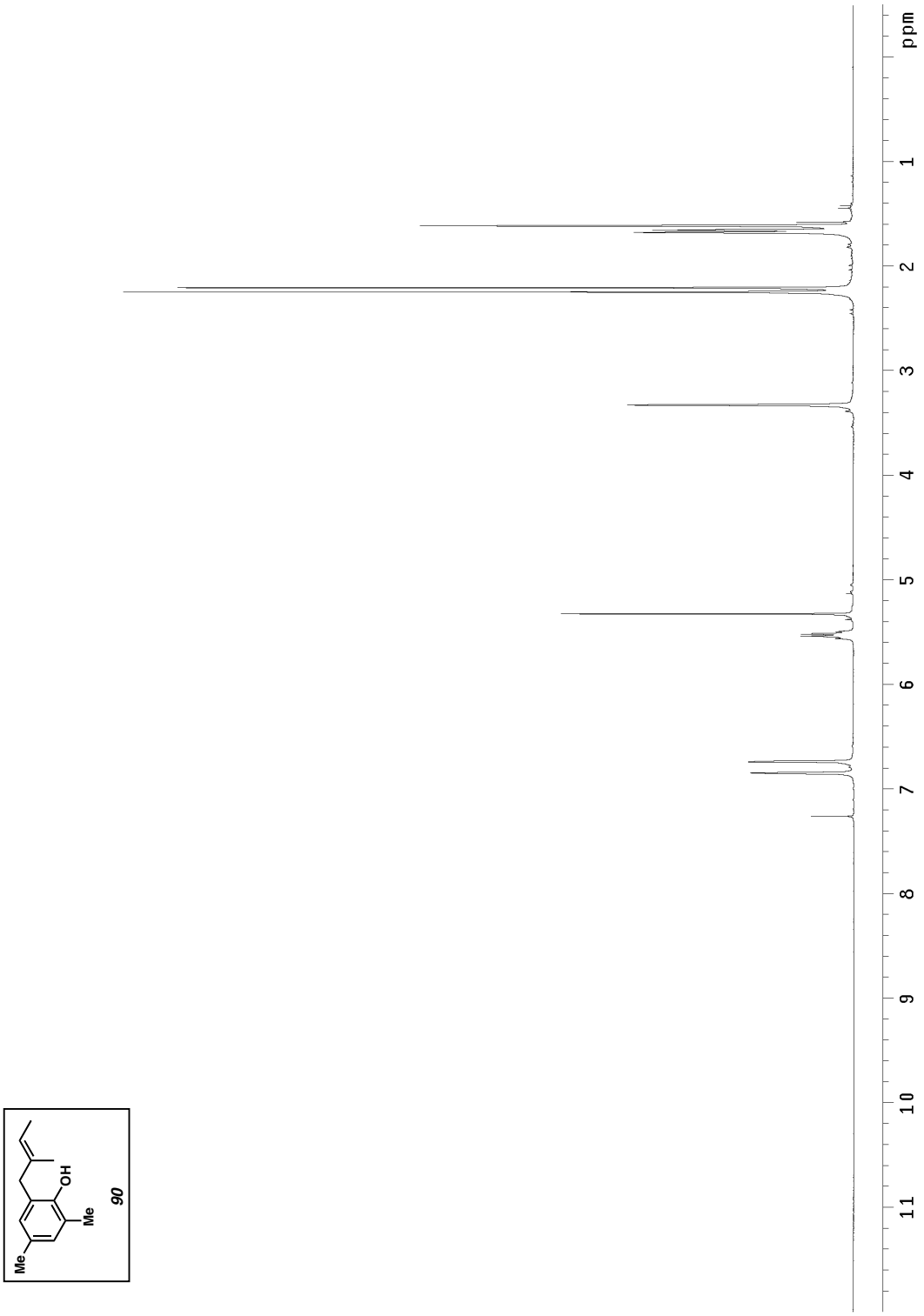


Figure A2.1.37 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of ***90***.

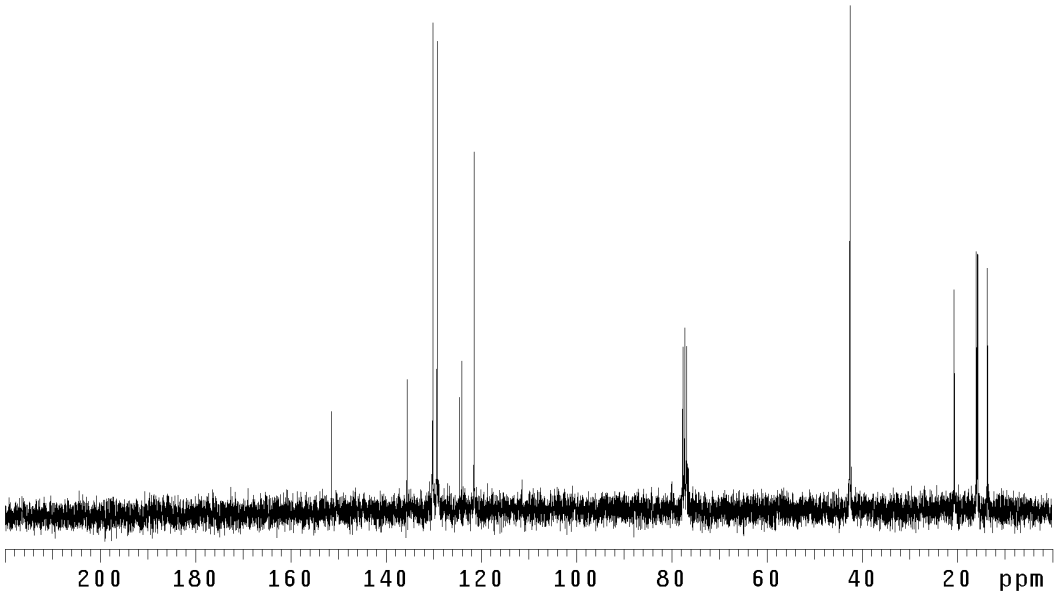


Figure A2.1.38 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of ***90***.

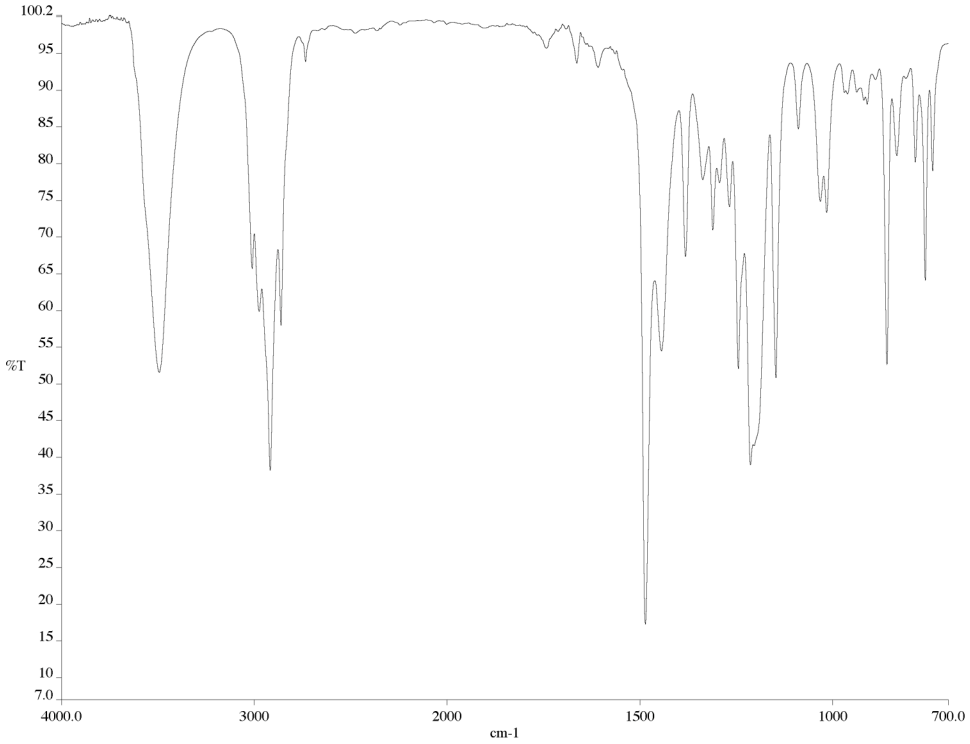


Figure A2.1.39 IR spectrum (thin film/NaCl) of ***90***.

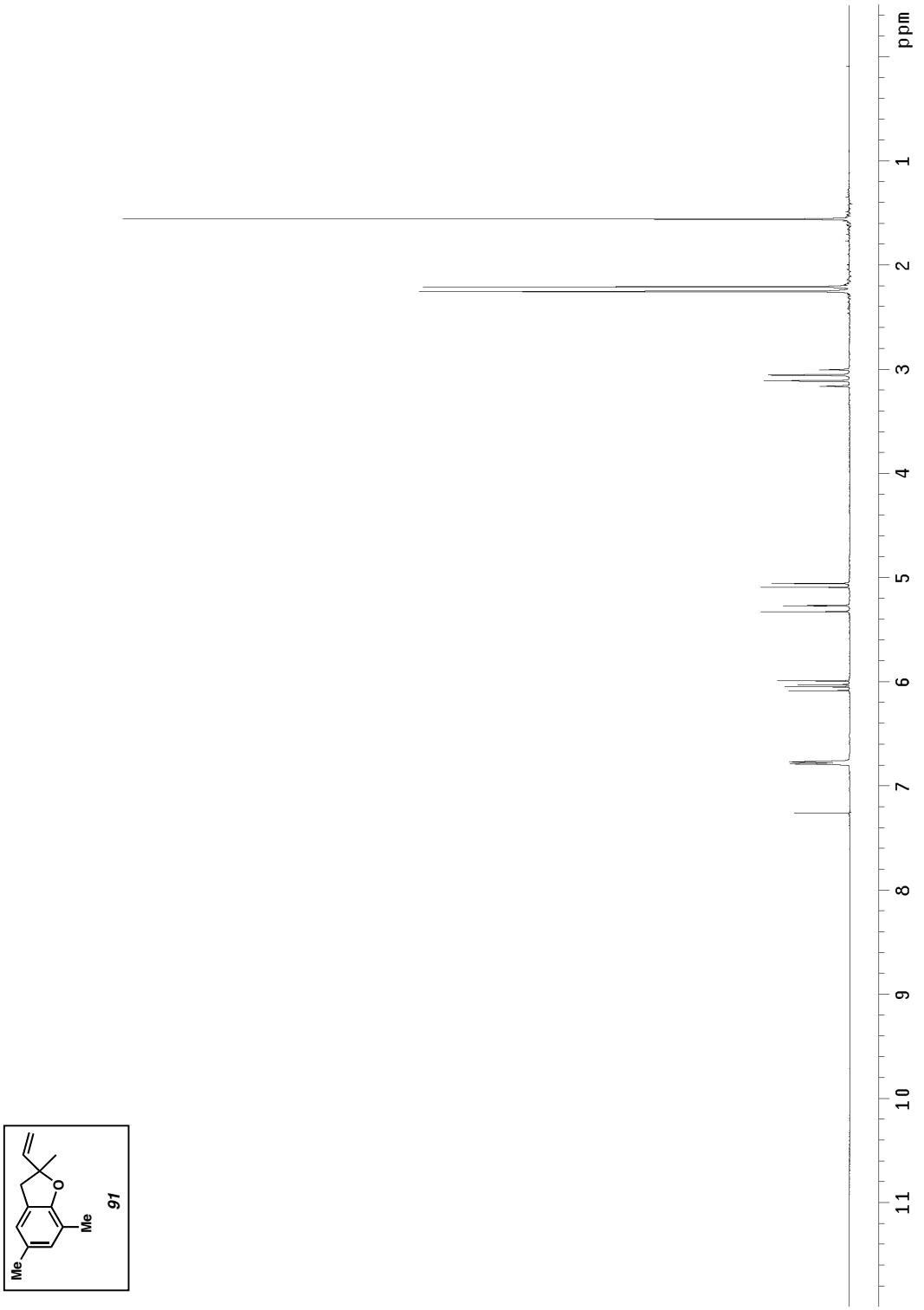


*Figure A2.1.40 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **91**.*

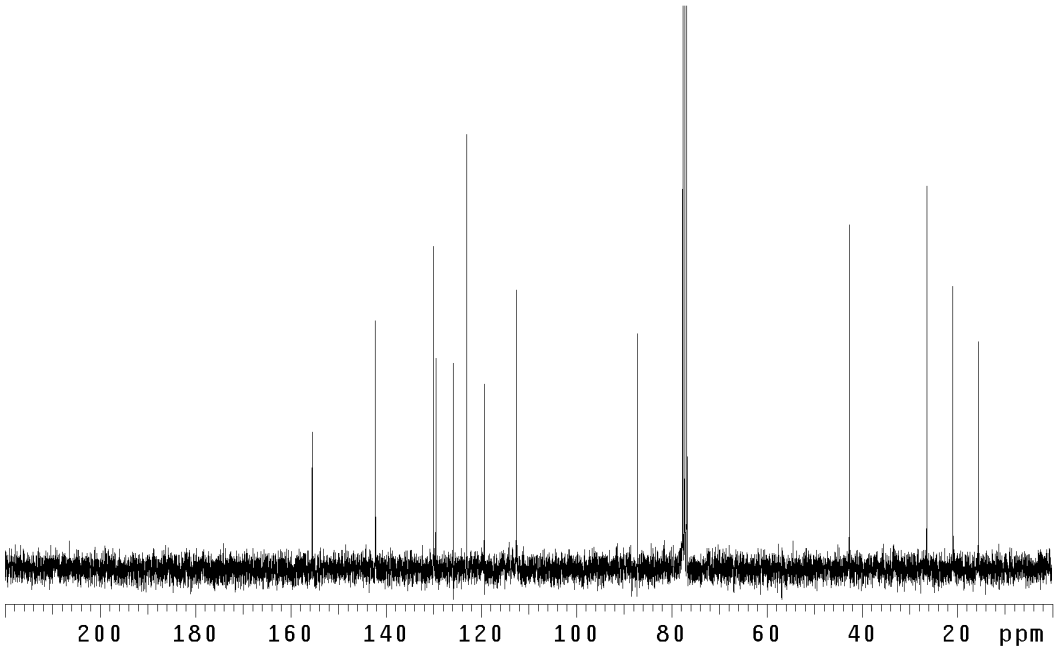


*Figure A2.1.41 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **91**.*

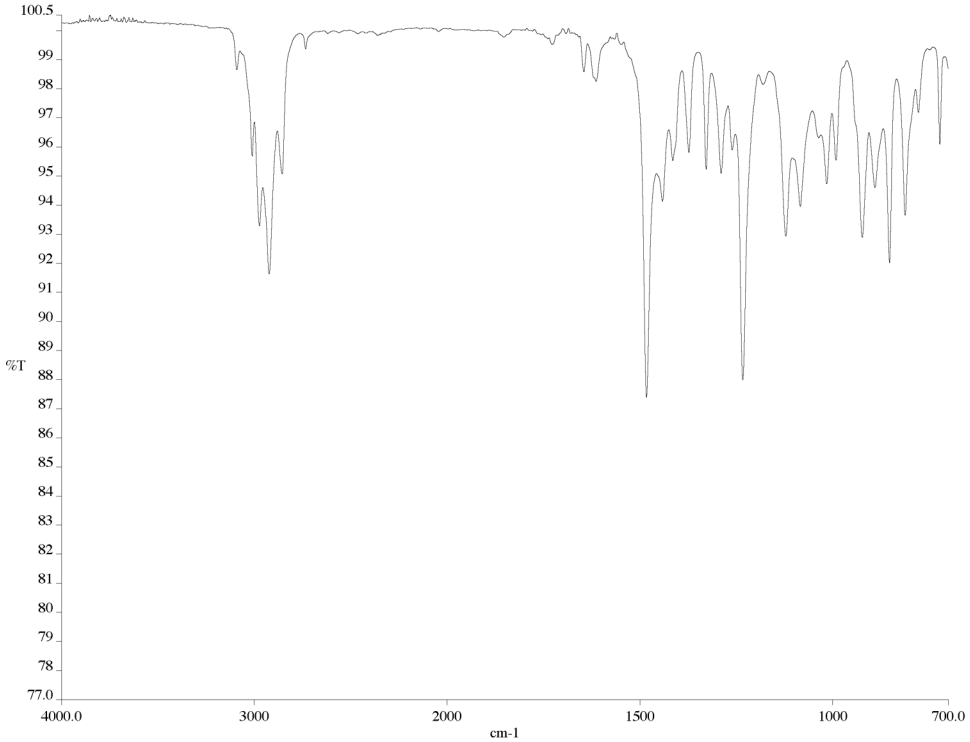


*Figure A2.1.42 IR spectrum (thin film/NaCl) of **91**.*

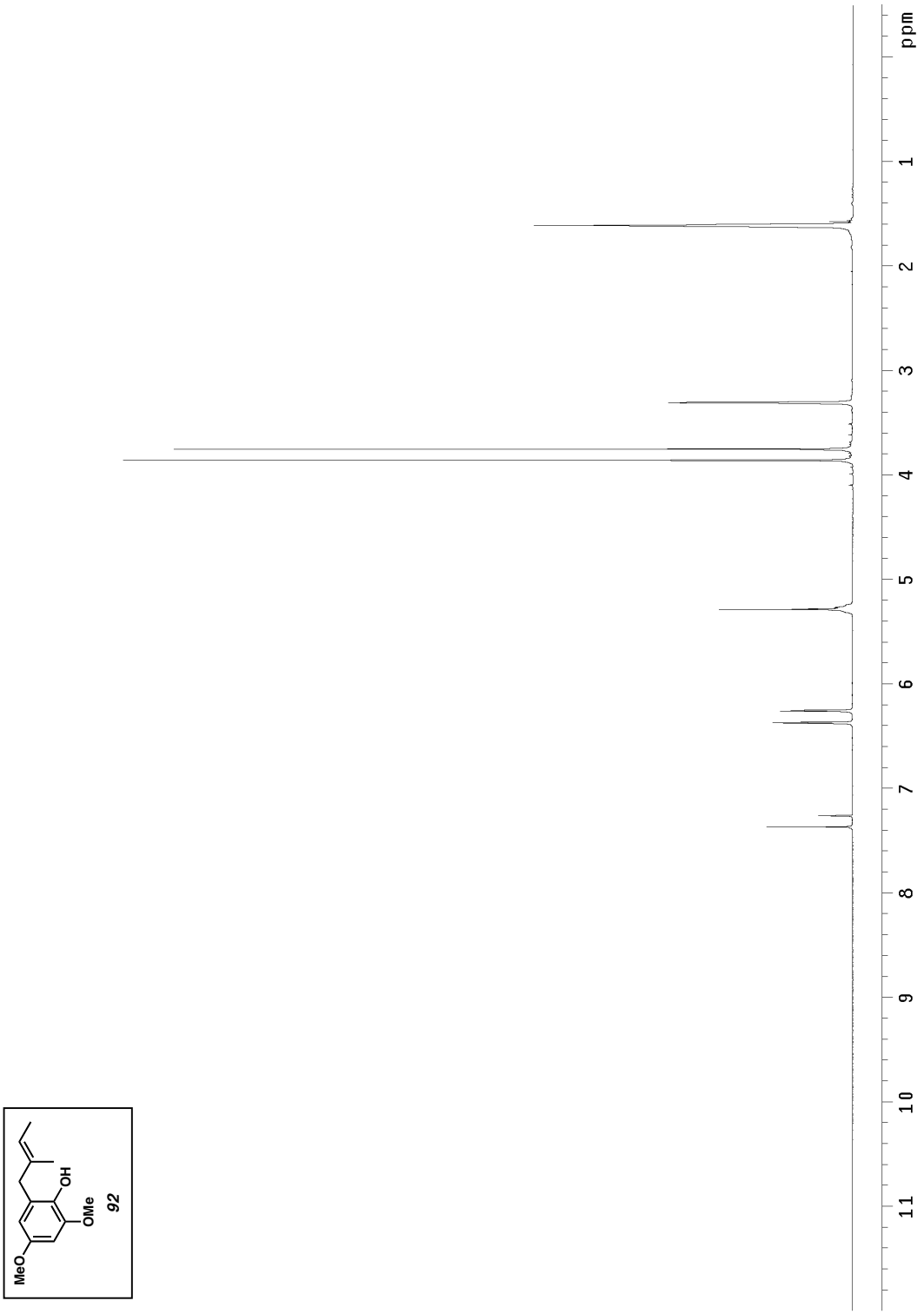


*Figure A2.1.43 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **92**.*

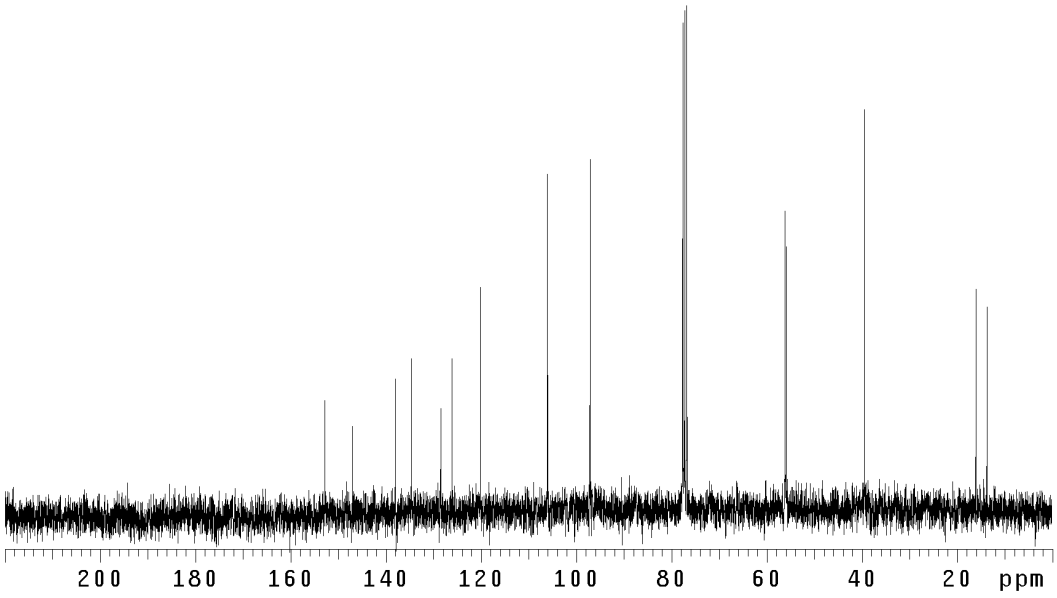


Figure A2.1.44 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of ***92***.

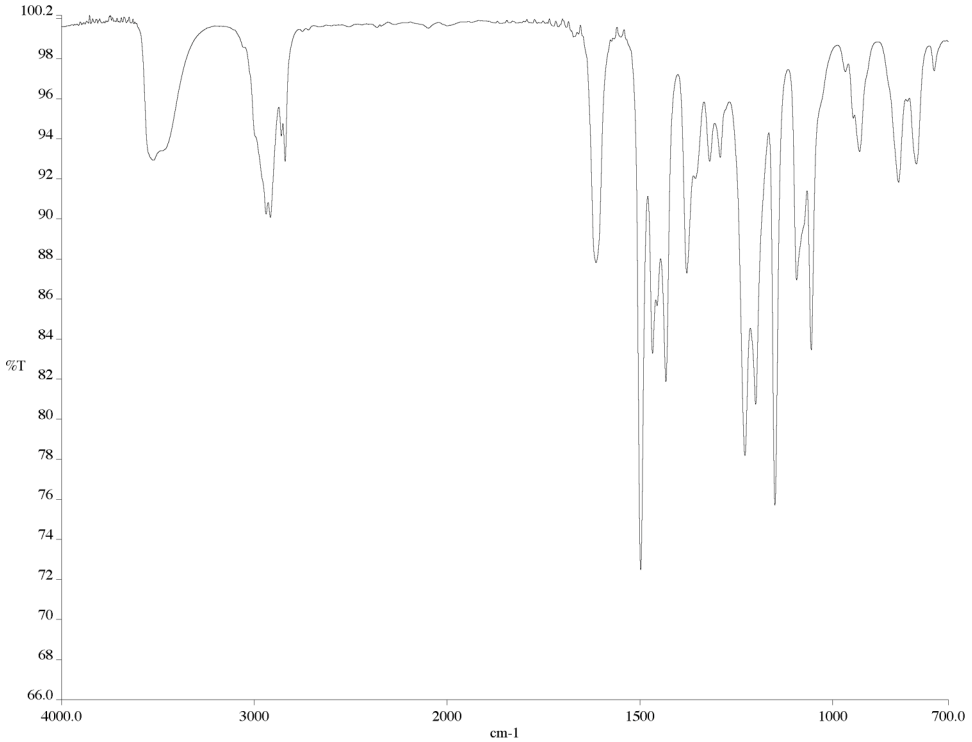


Figure A2.1.45 IR spectrum (thin film/NaCl) of ***92***.

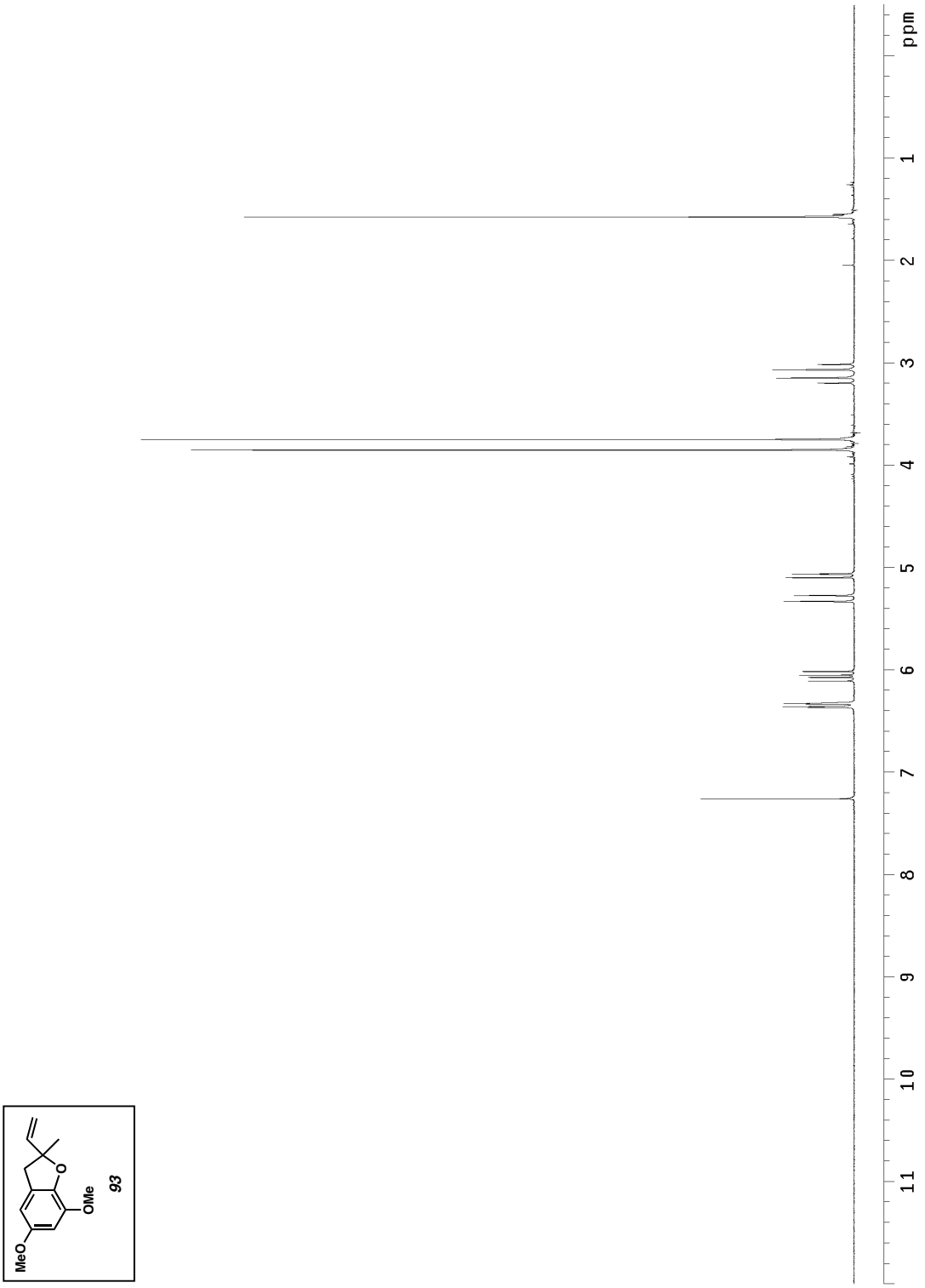


*Figure A2.1.46 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **93**.*

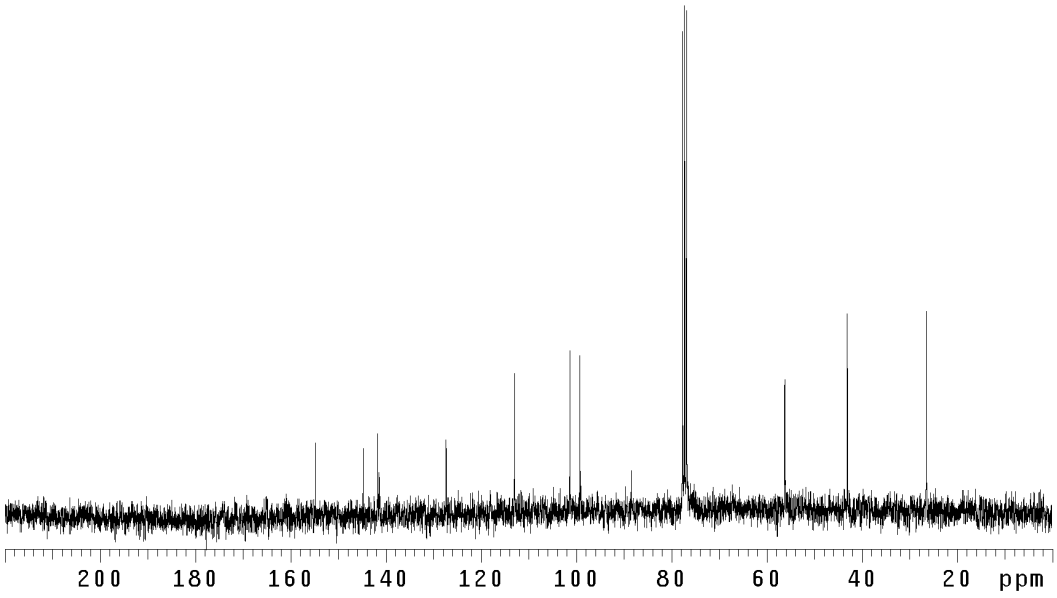


*Figure A2.1.47 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **93**.*

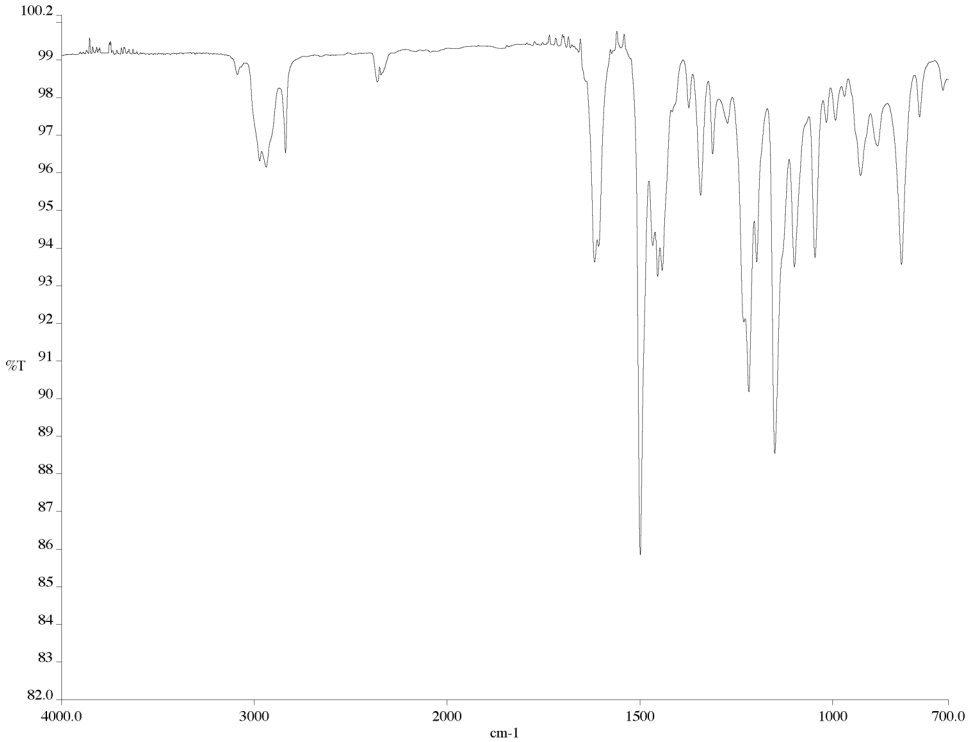


*Figure A2.1.48 IR spectrum (thin film/NaCl) of **93**.*

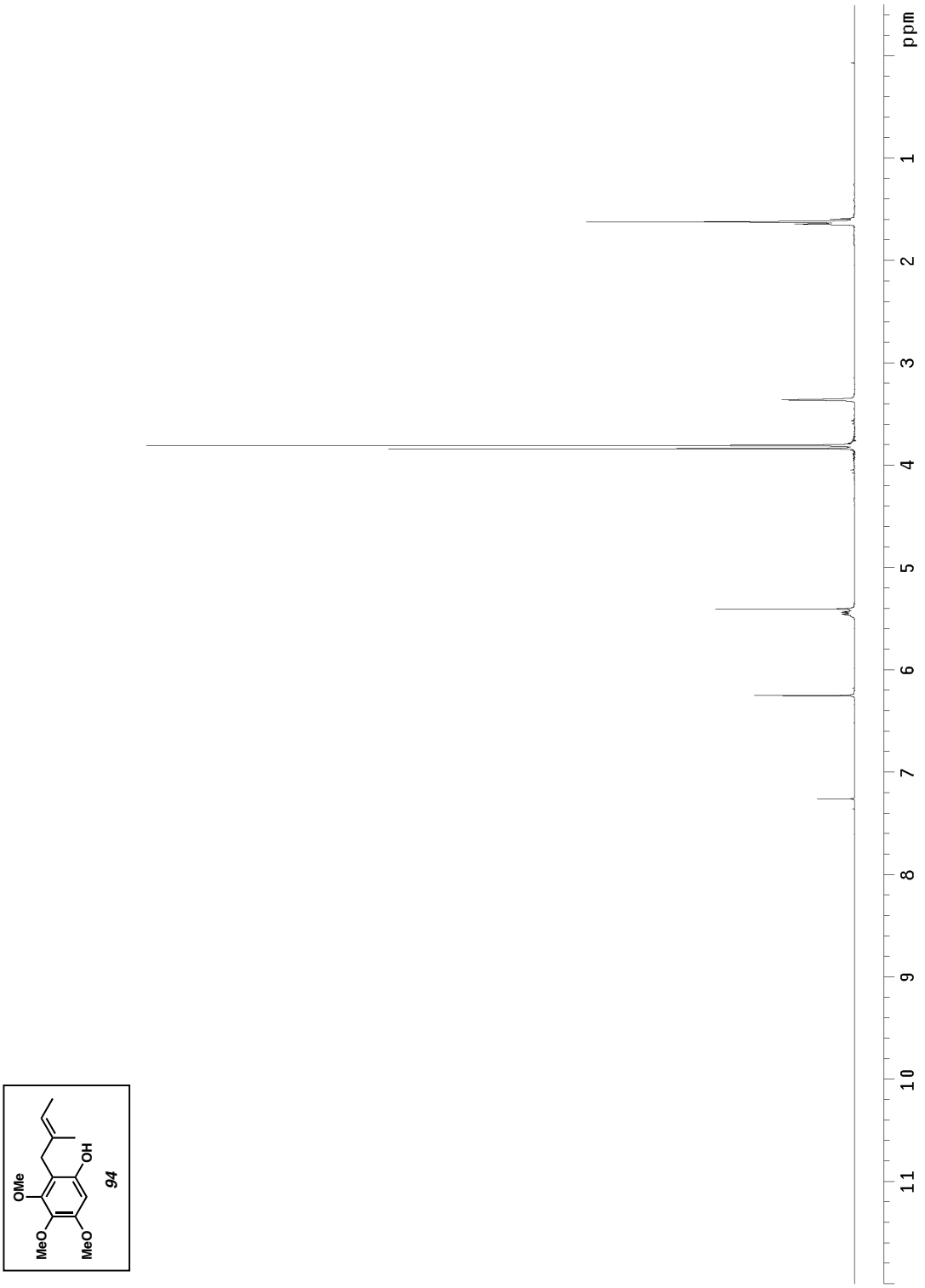


Figure A2.1.49 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of ***94****.*

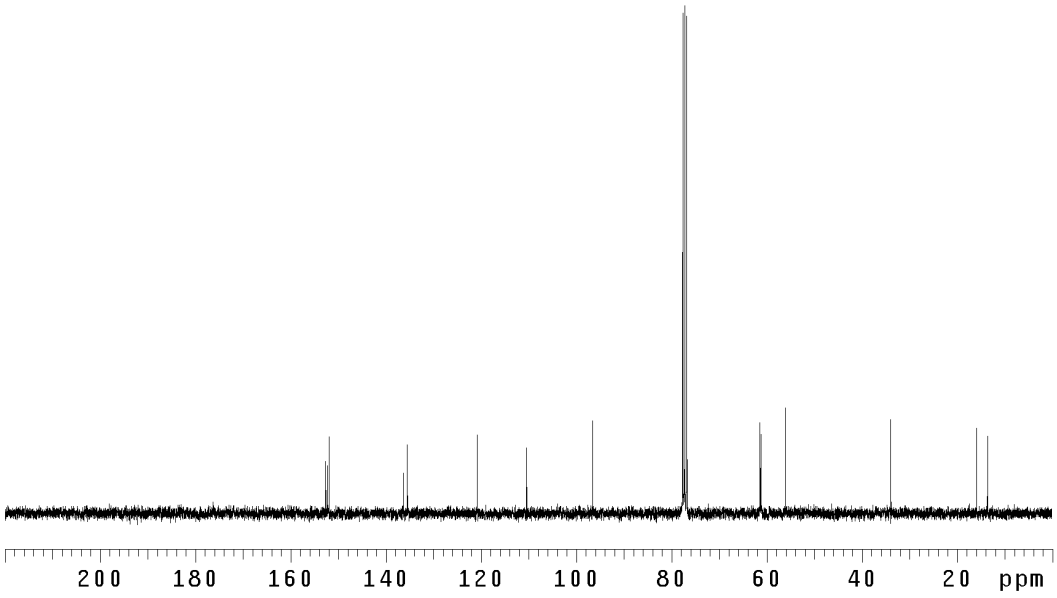


*Figure A2.1.50 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **94**.*

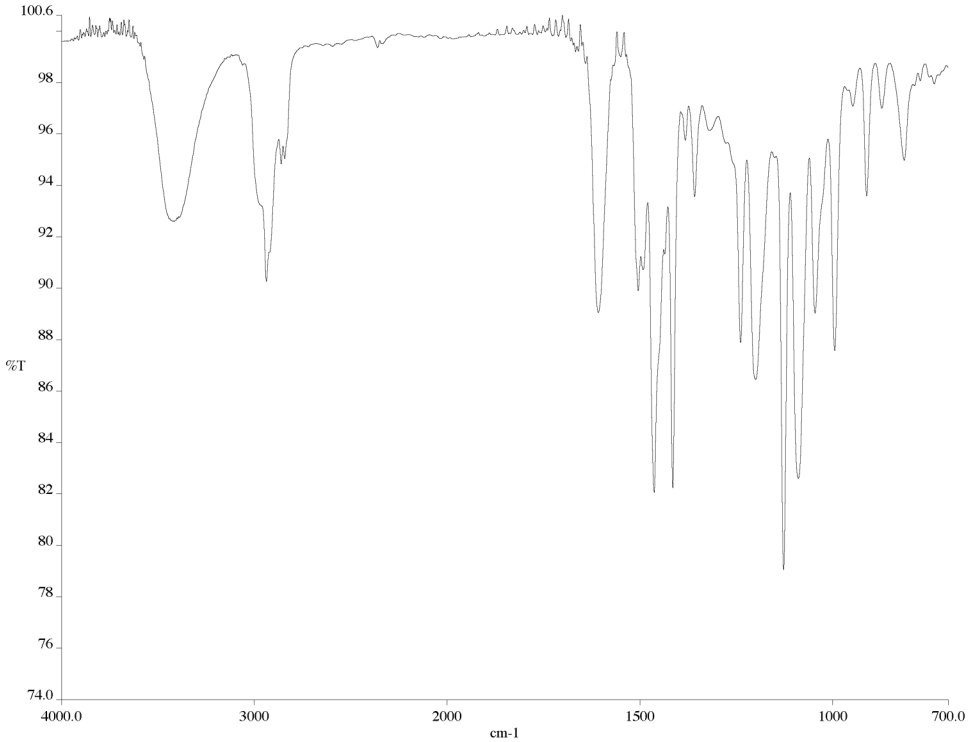


*Figure A2.1.51 IR spectrum (thin film/NaCl) of **94**.*

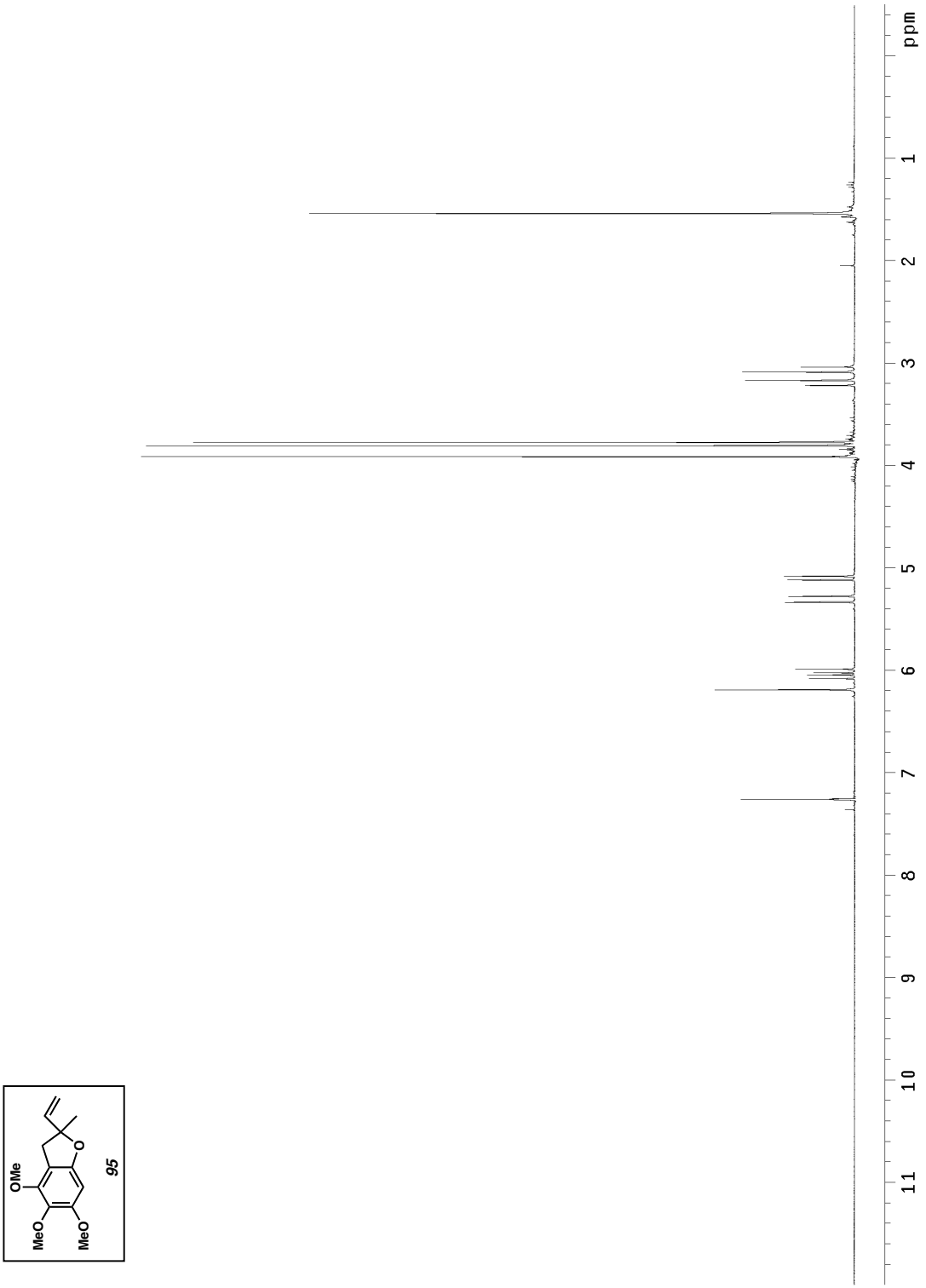


*Figure A2.1.52 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **95**.*

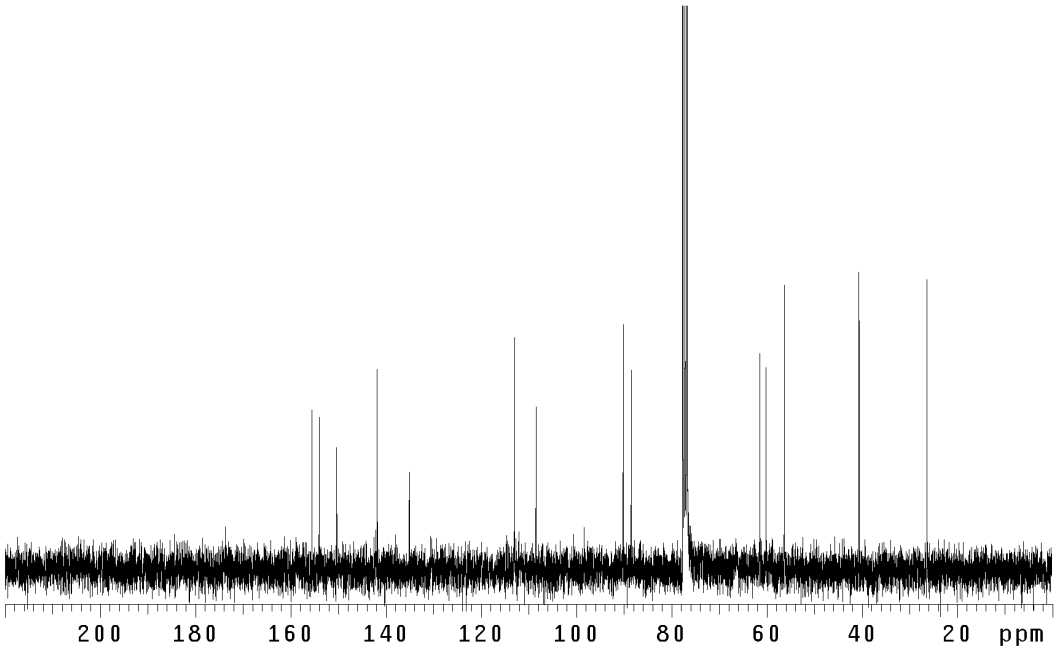


*Figure A2.1.53 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **95**.*

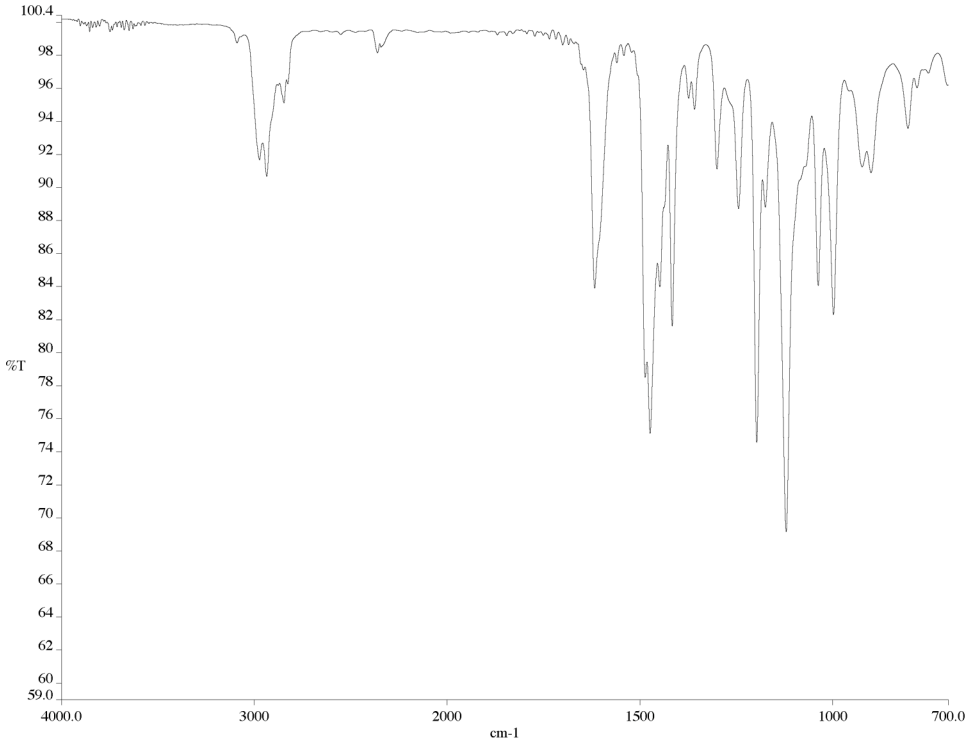


*Figure A2.1.54 IR spectrum (thin film/NaCl) of **95**.*

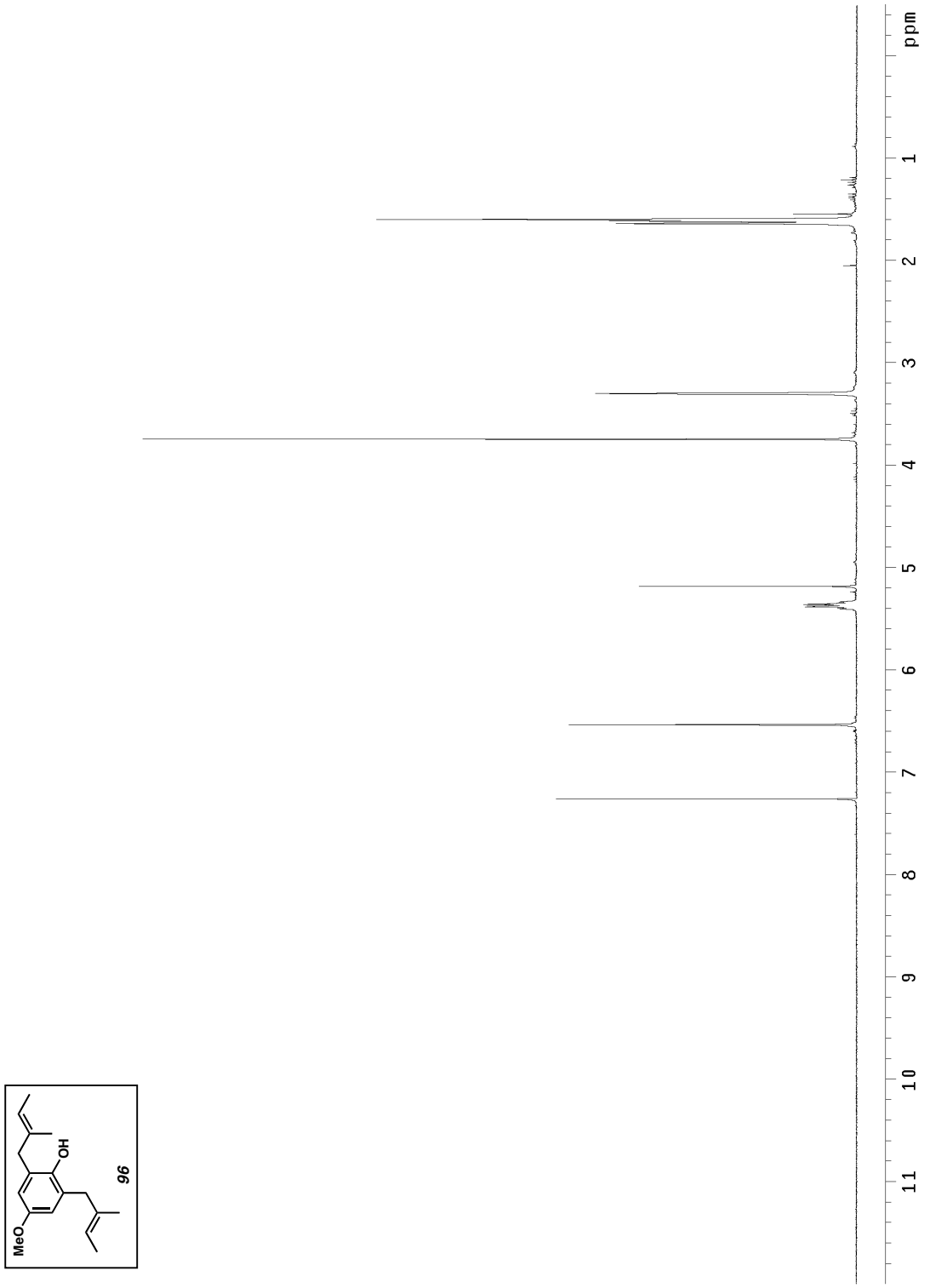


Figure A2.1.55 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of ***96***.

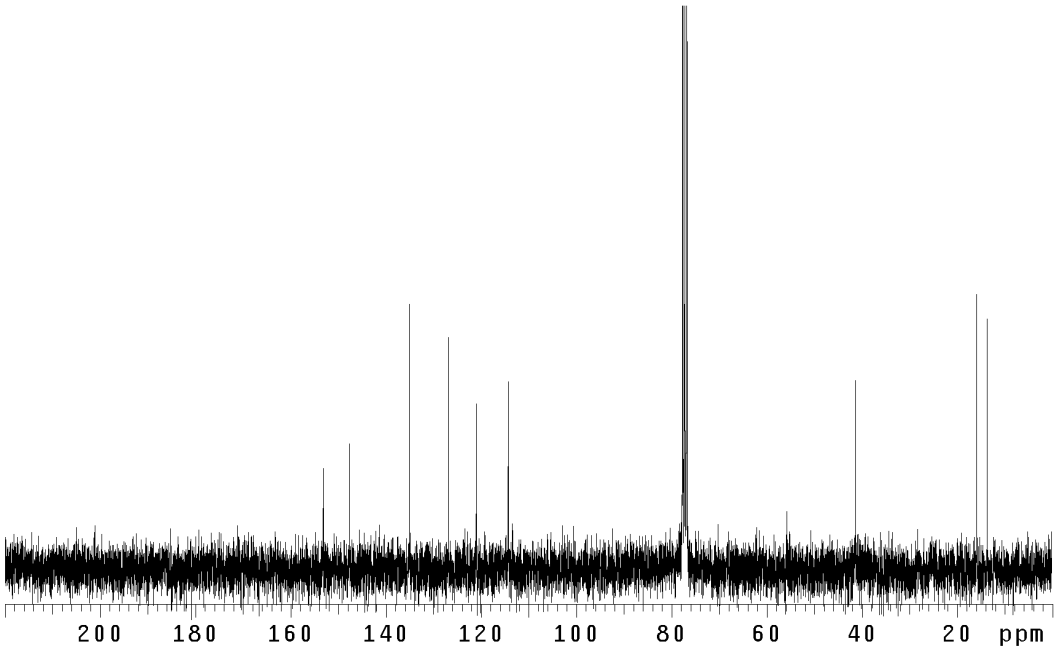


Figure A2.1.56 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of ***96***.

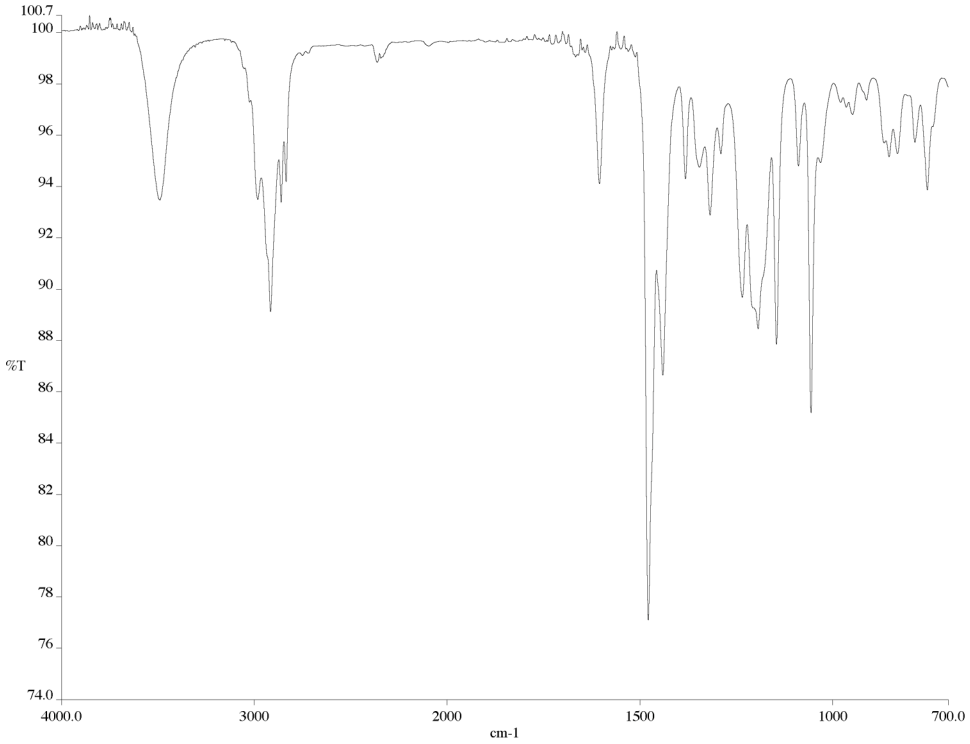


Figure A2.1.57 IR spectrum (thin film/NaCl) of ***96***.

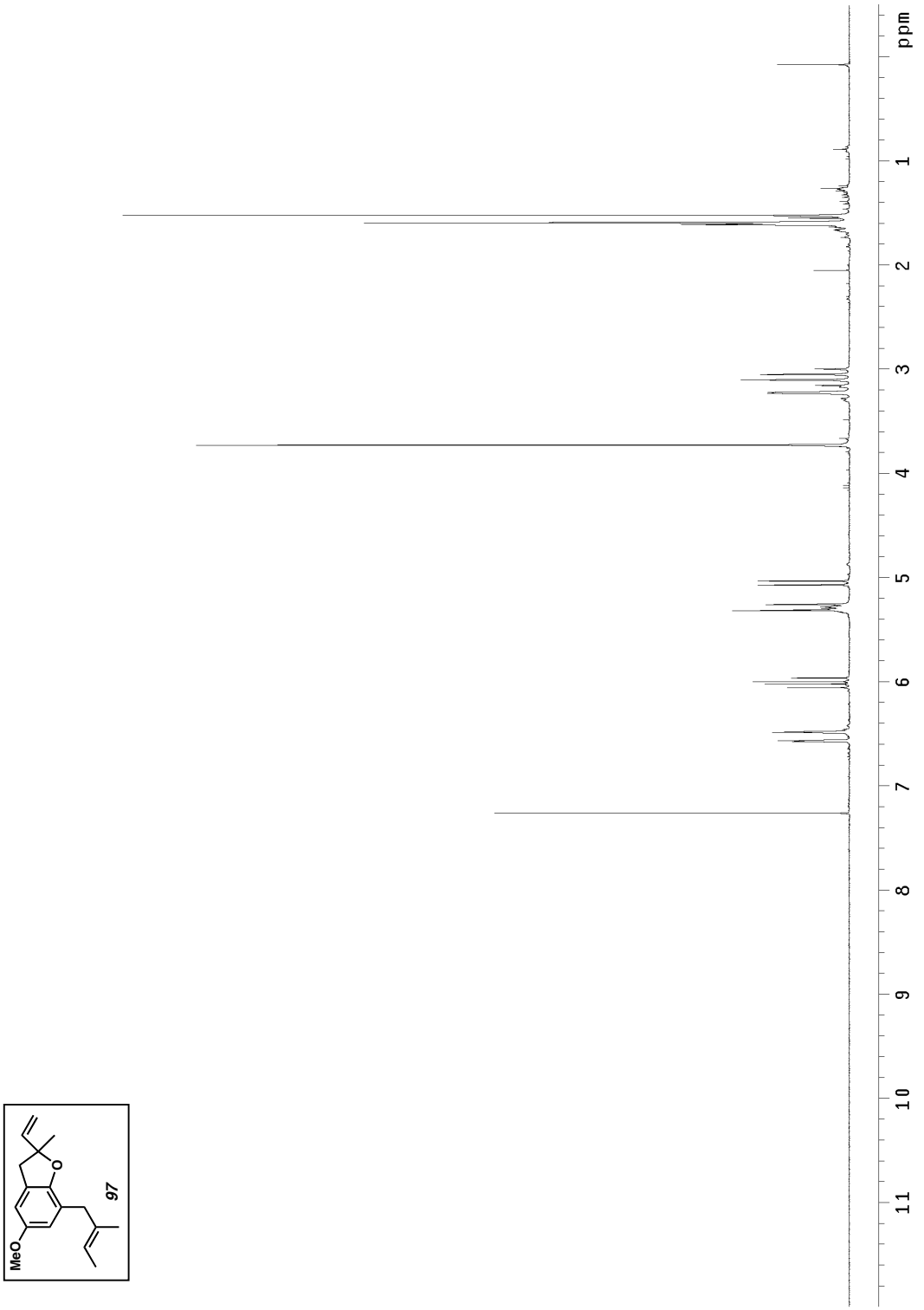


*Figure A2.1.58 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **97**.*

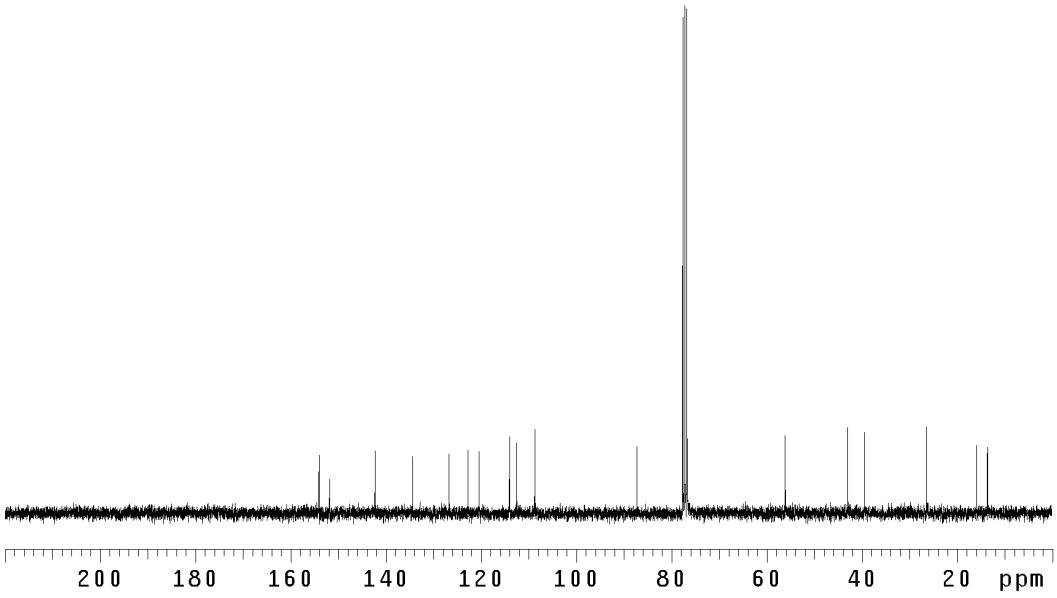


*Figure A2.1.59 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **97**.*

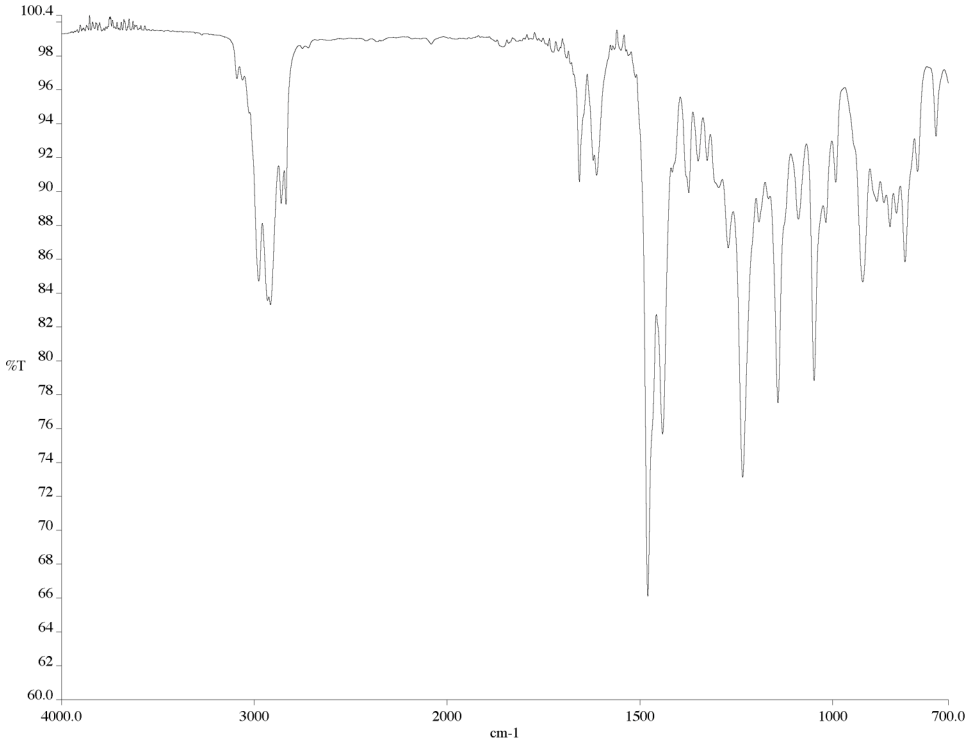


*Figure A2.1.60 IR spectrum (thin film/NaCl) of **97**.*

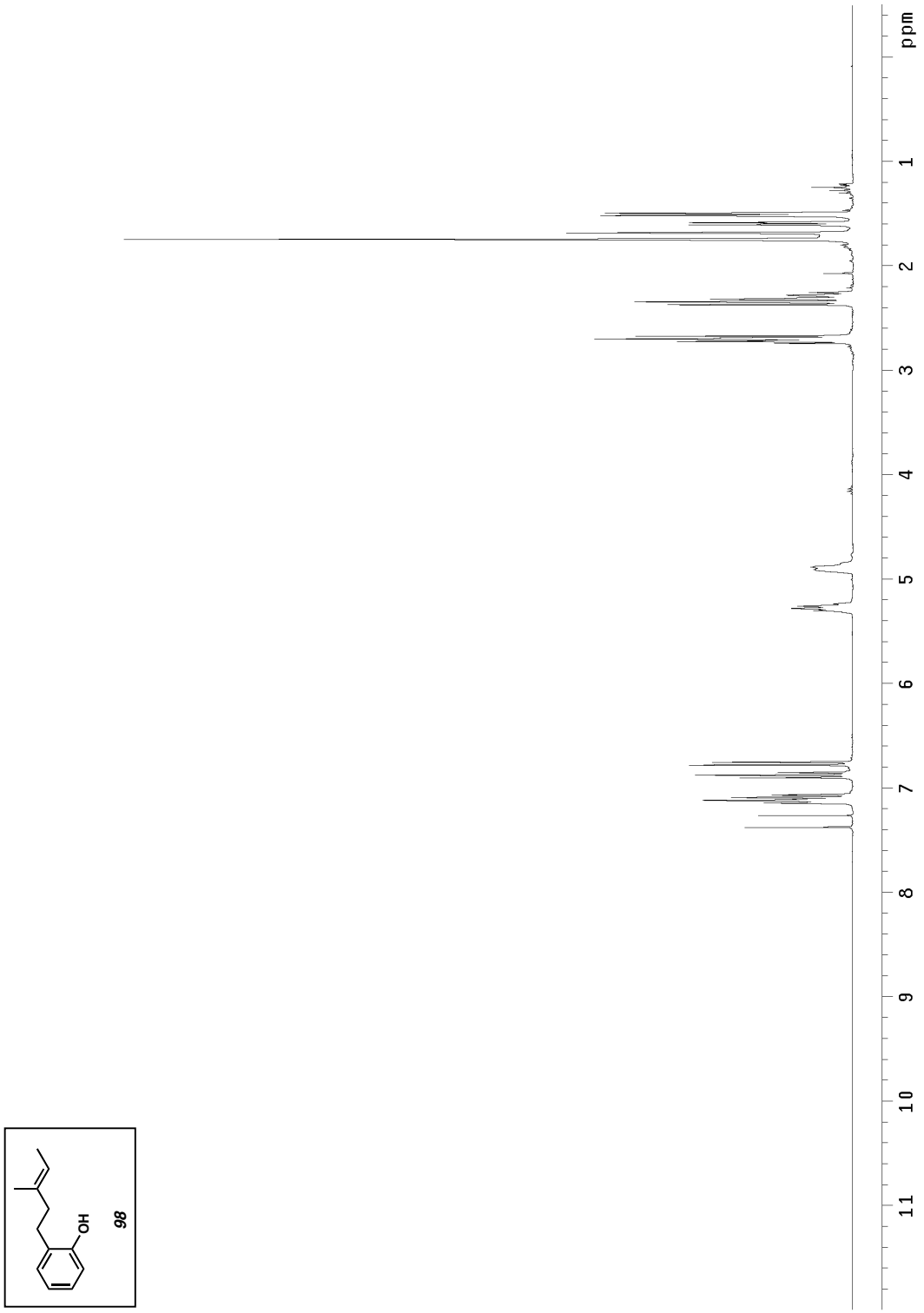


Figure A2.1.61 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of ***98***.

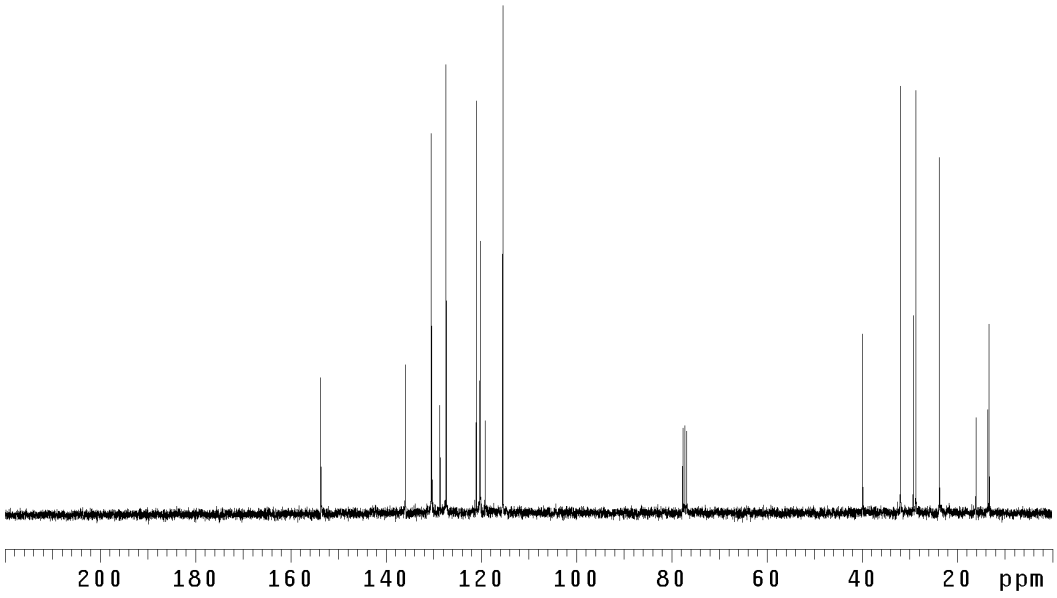


Figure A2.1.62 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of ***98***.

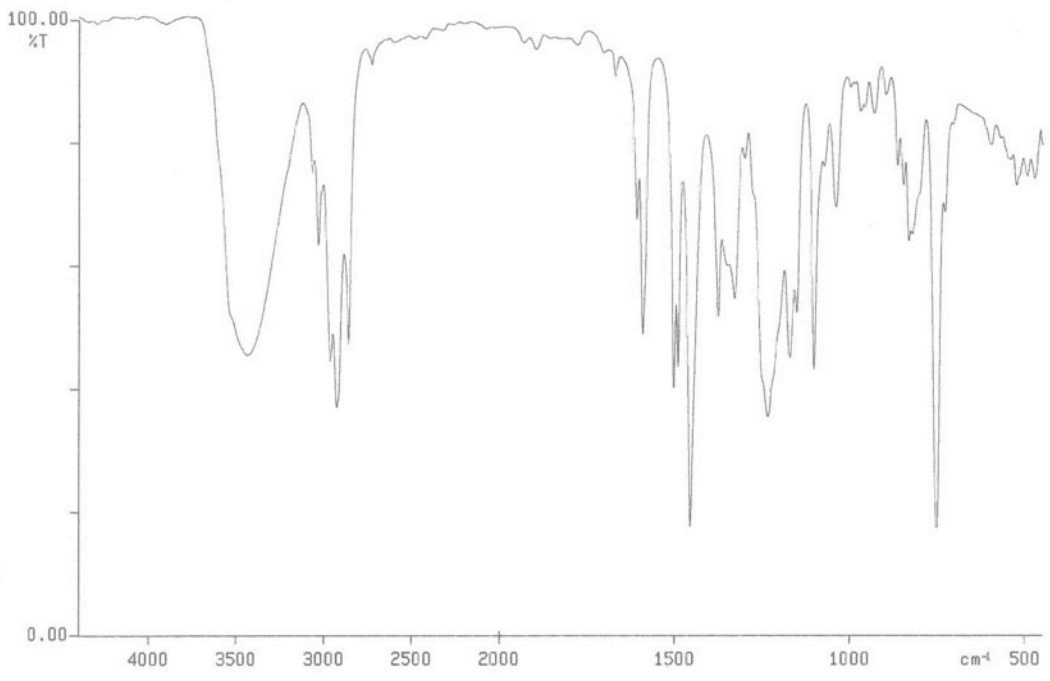


Figure A2.1.63 IR spectrum (thin film/NaCl) of ***98***.

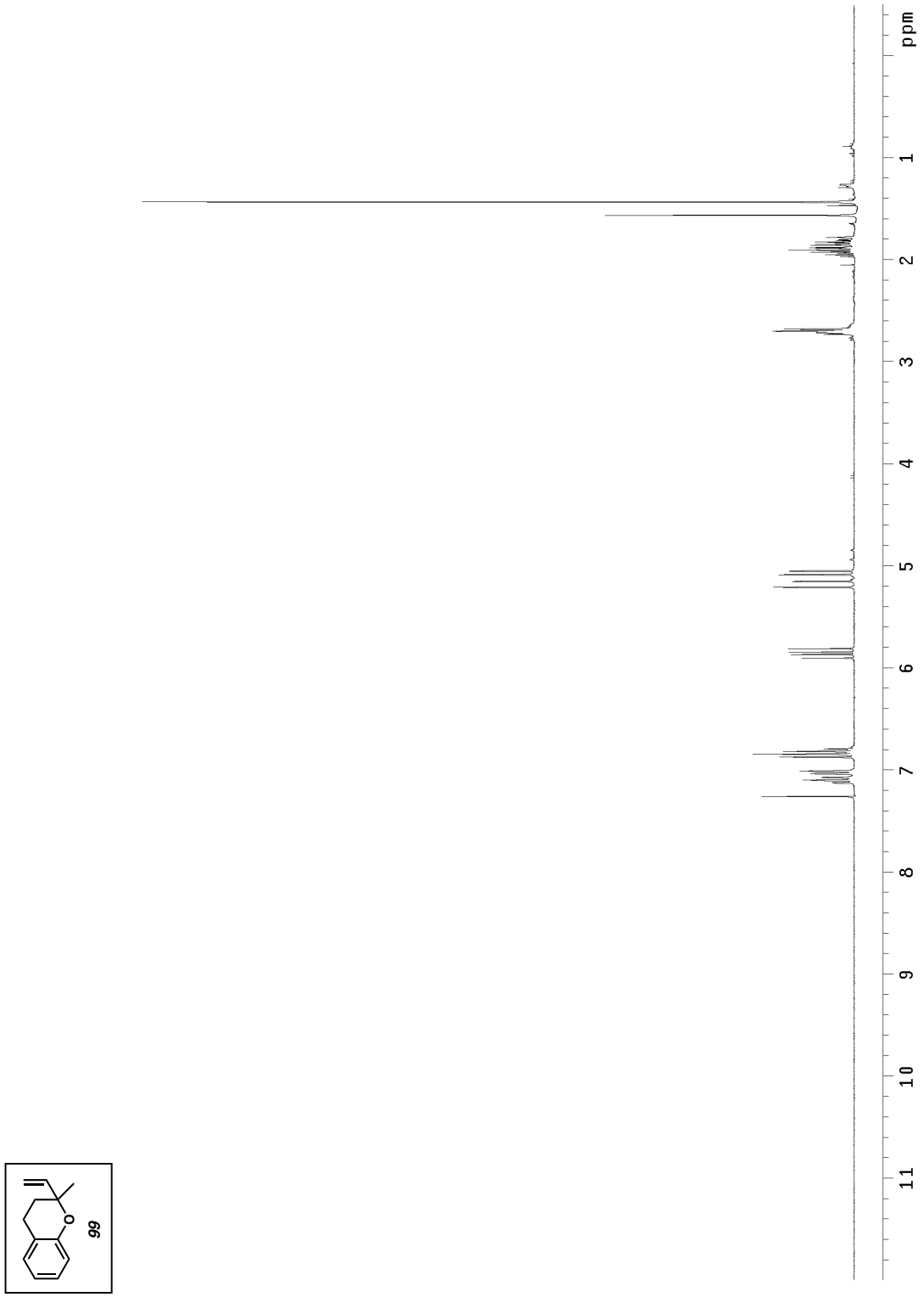


Figure A2.1.64 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of ***99***.

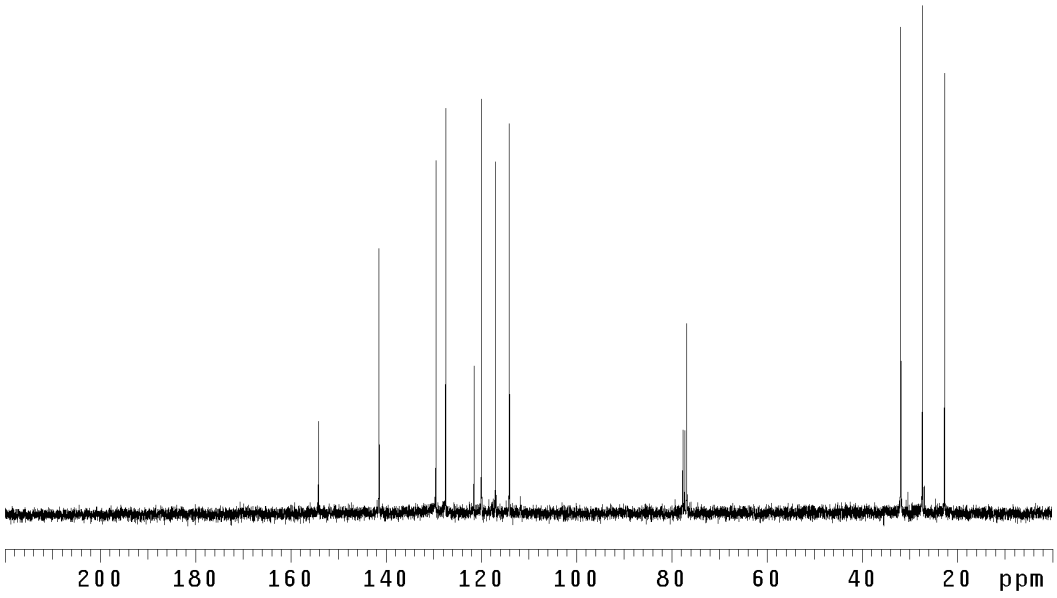


Figure A2.1.65 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of ***99***.

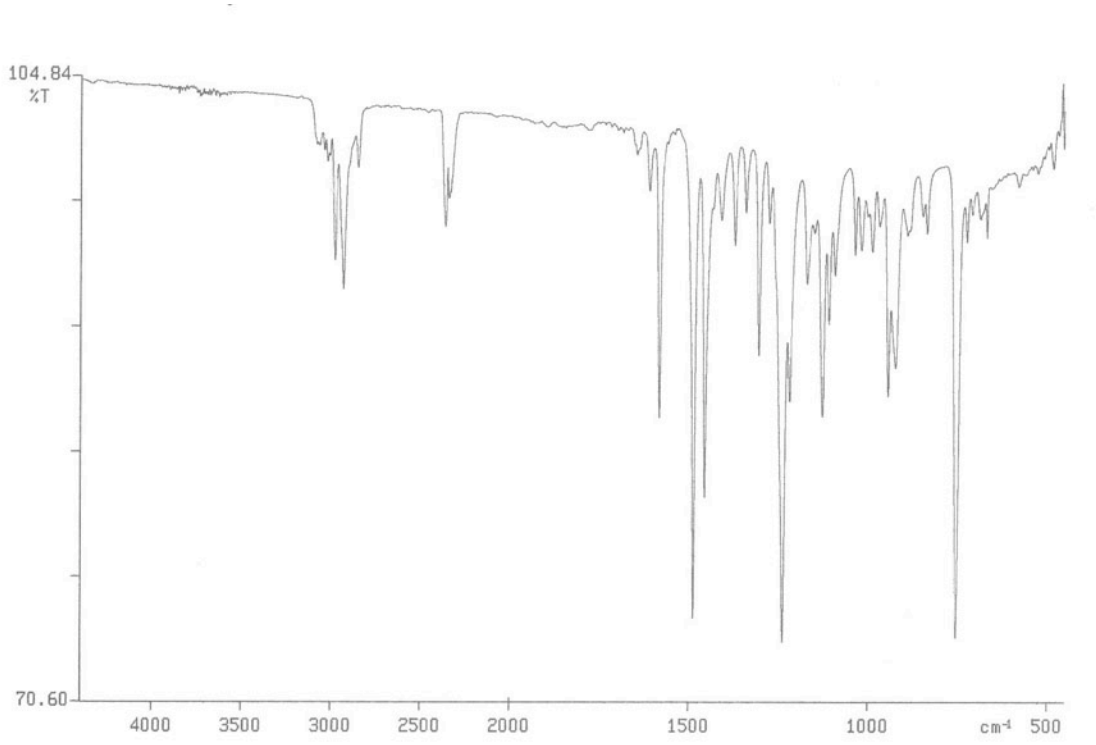


Figure A2.1.66 IR spectrum (thin film/NaCl) of ***99***.

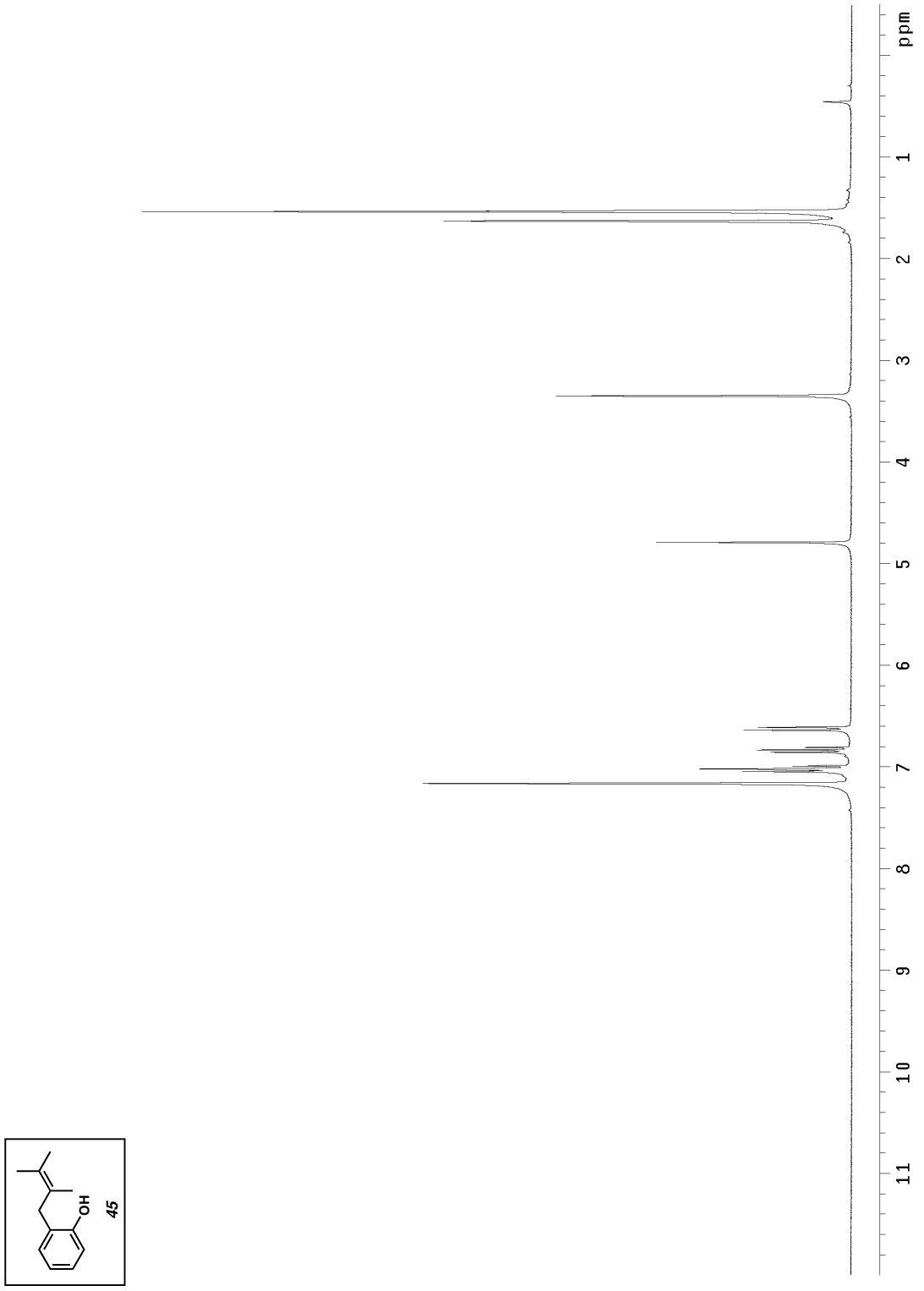


*Figure A2.1.67 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **45**.*

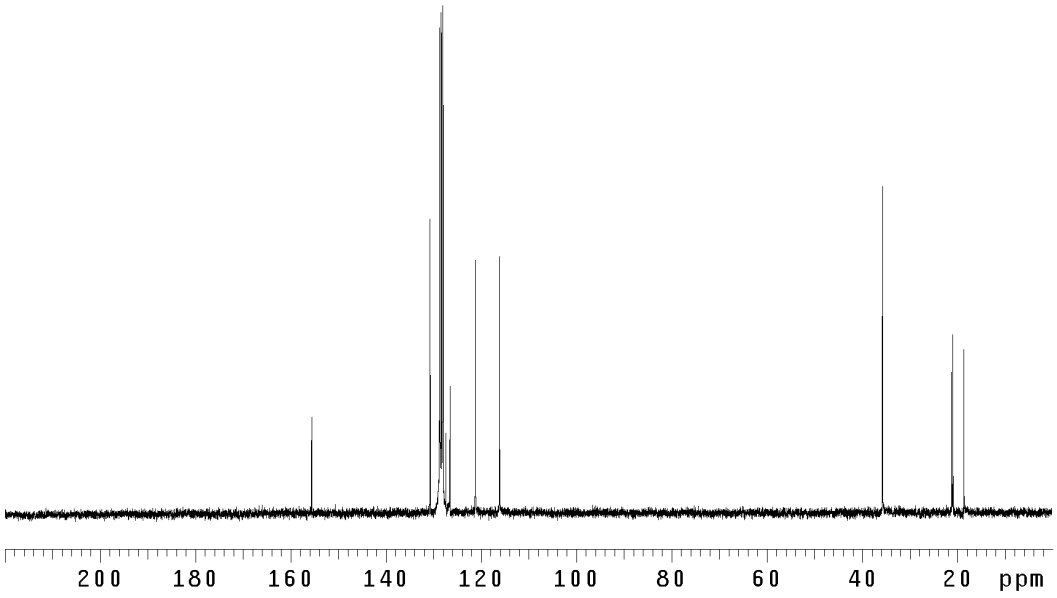


*Figure A2.1.68 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **45**.*

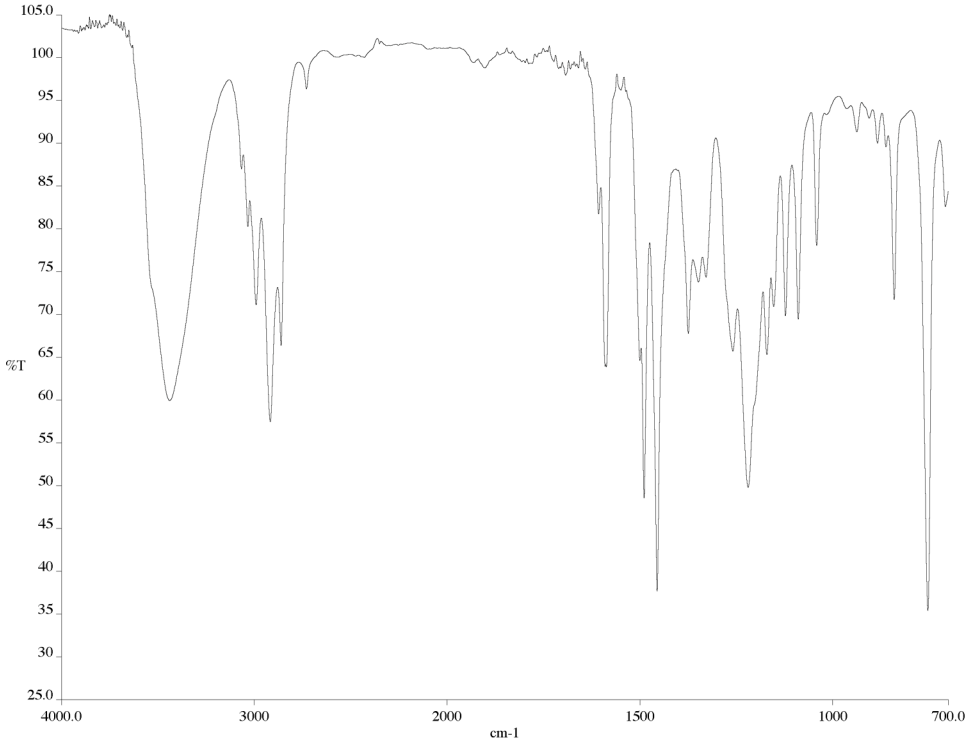


*Figure A2.1.69 IR spectrum (thin film/NaCl) of **45**.*

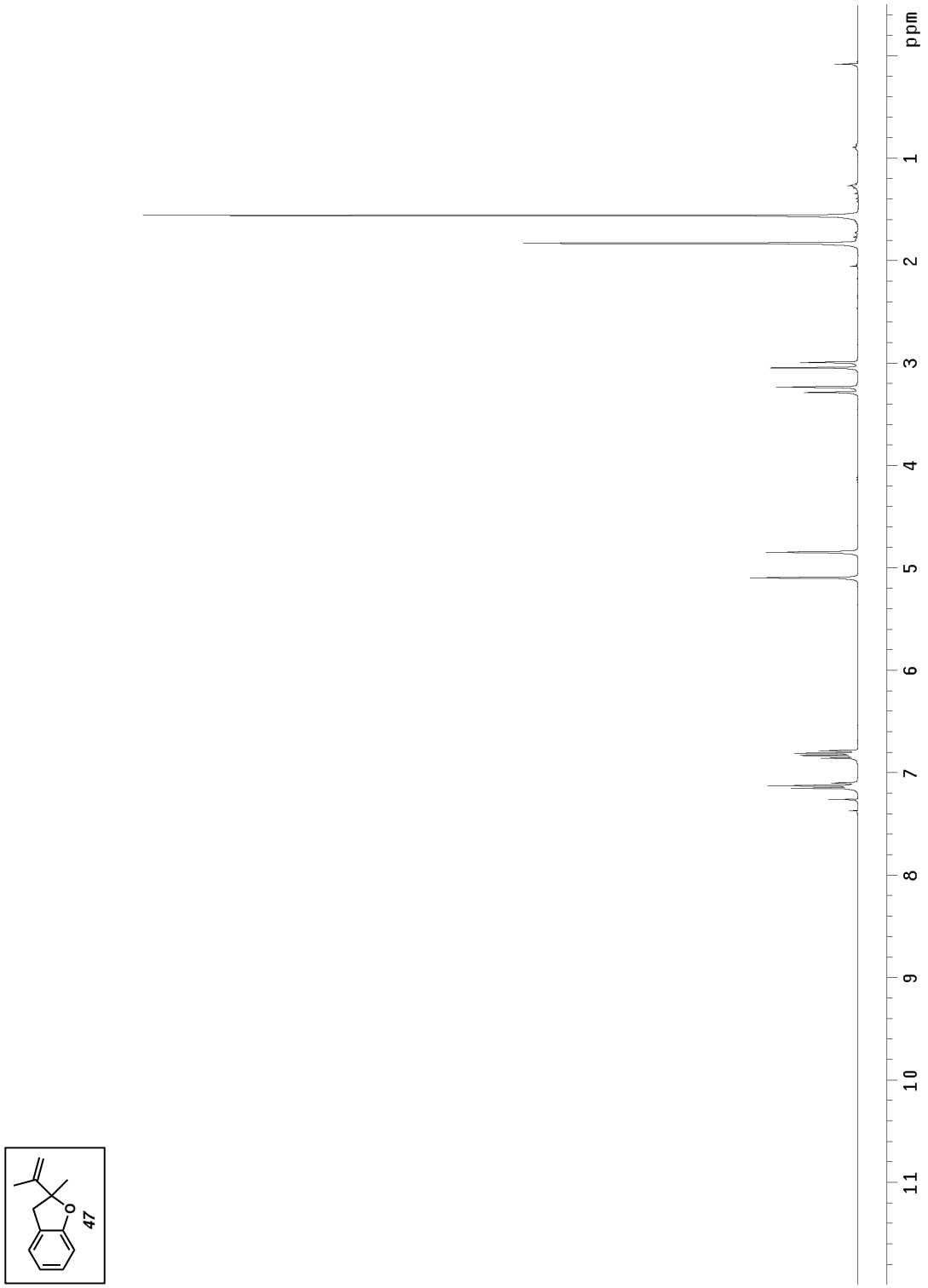


*Figure A2.1.70 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **47**.*

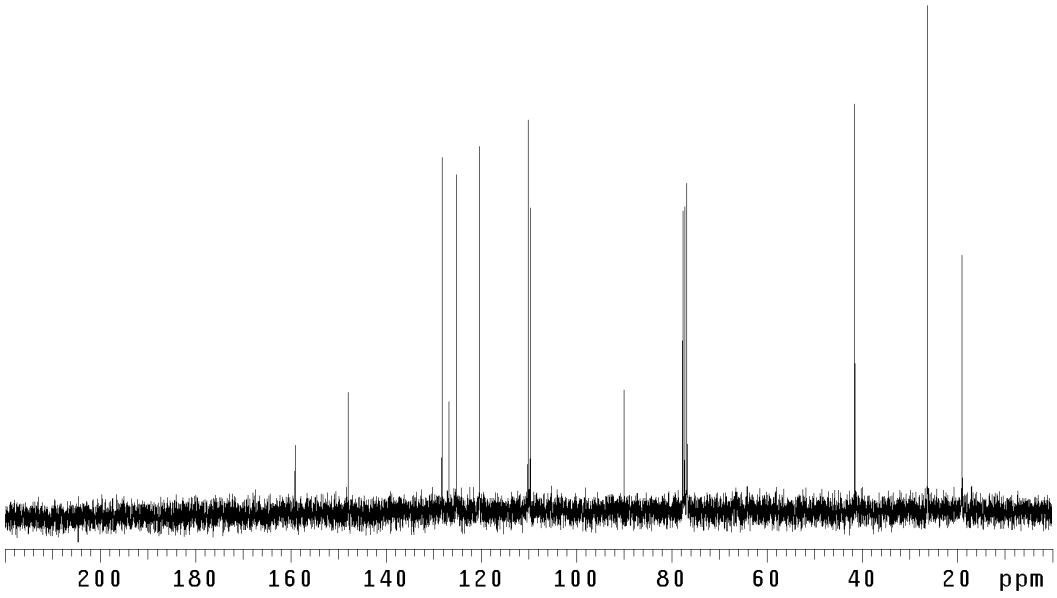


*Figure A2.71 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **47**.*

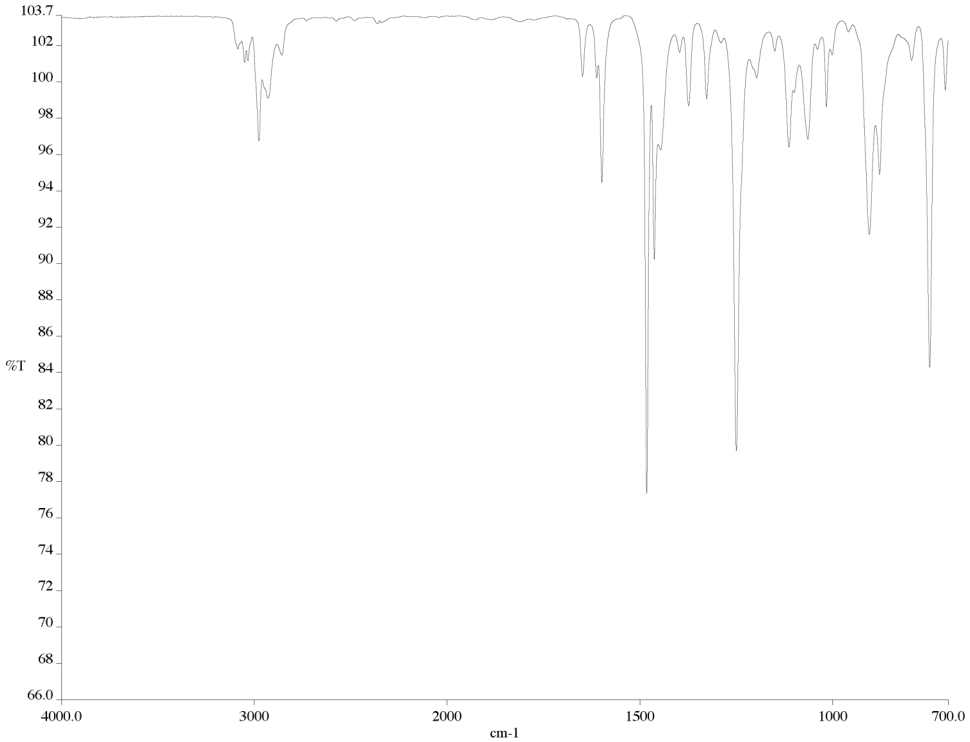


*Figure A2.1.72 IR spectrum (thin film/NaCl) of **47**.*

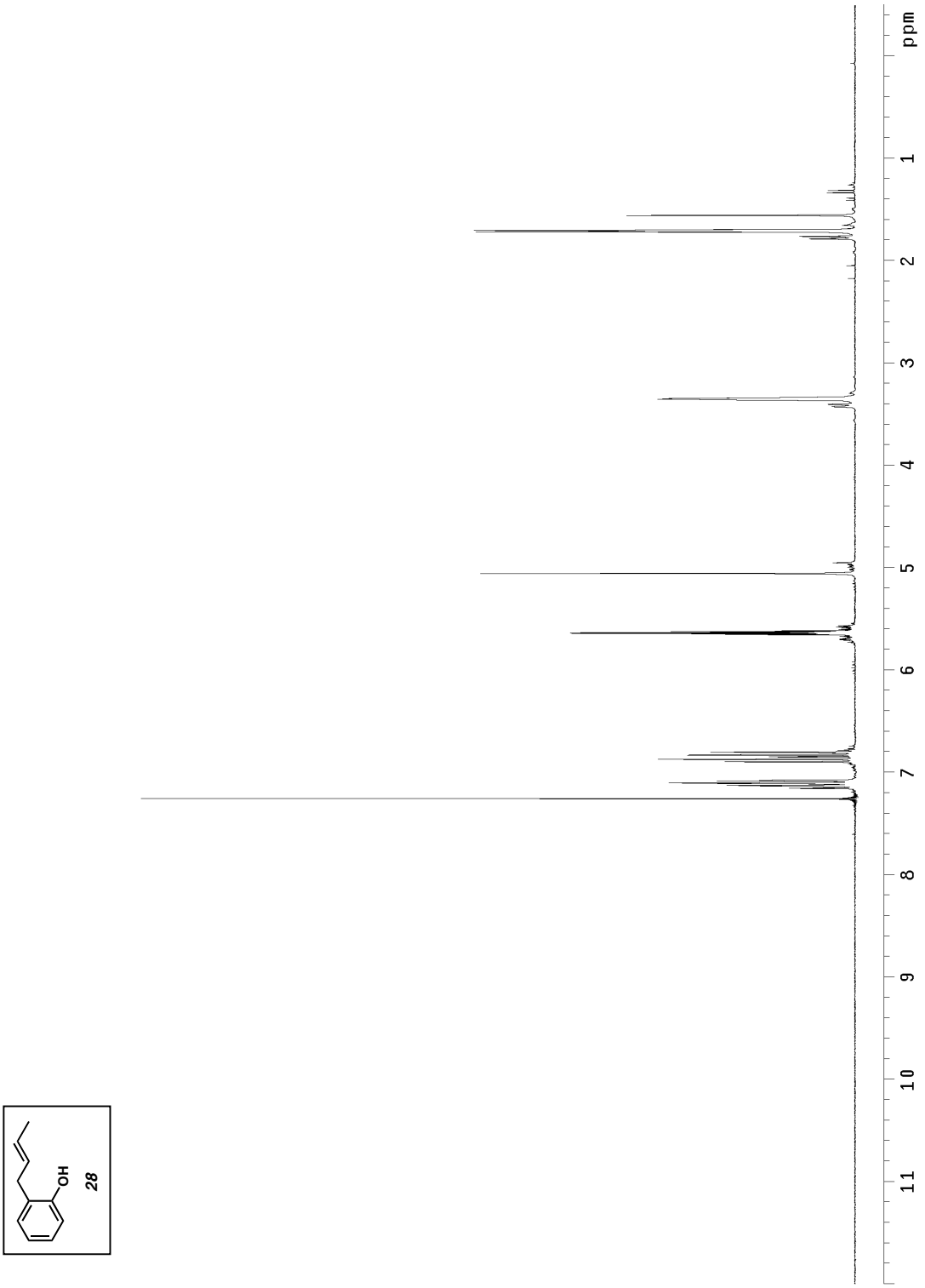


*Figure A2.1.73 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **28**.*

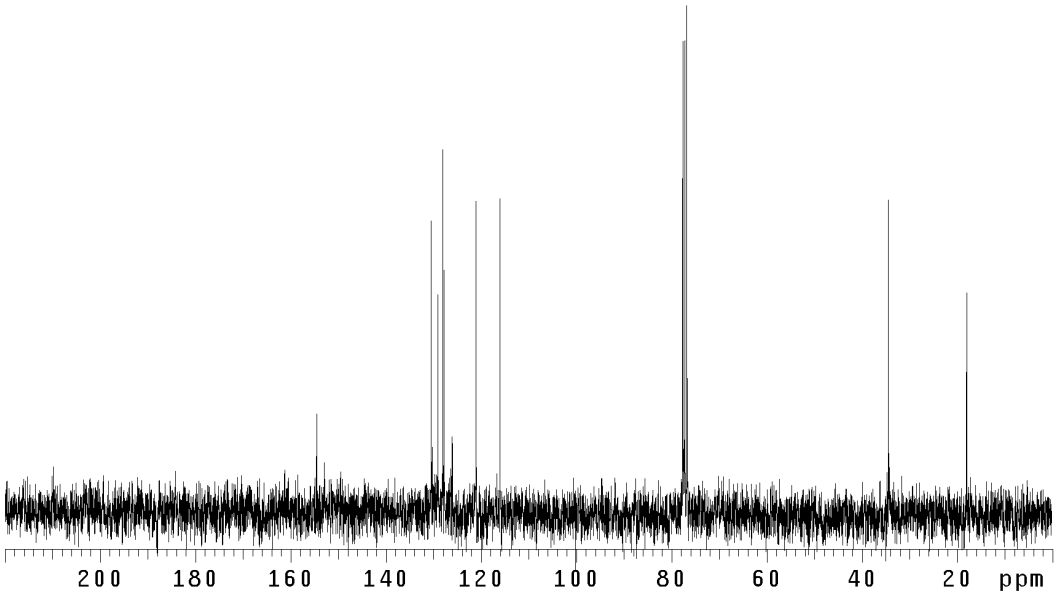


*Figure A2.1.74 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **28**.*

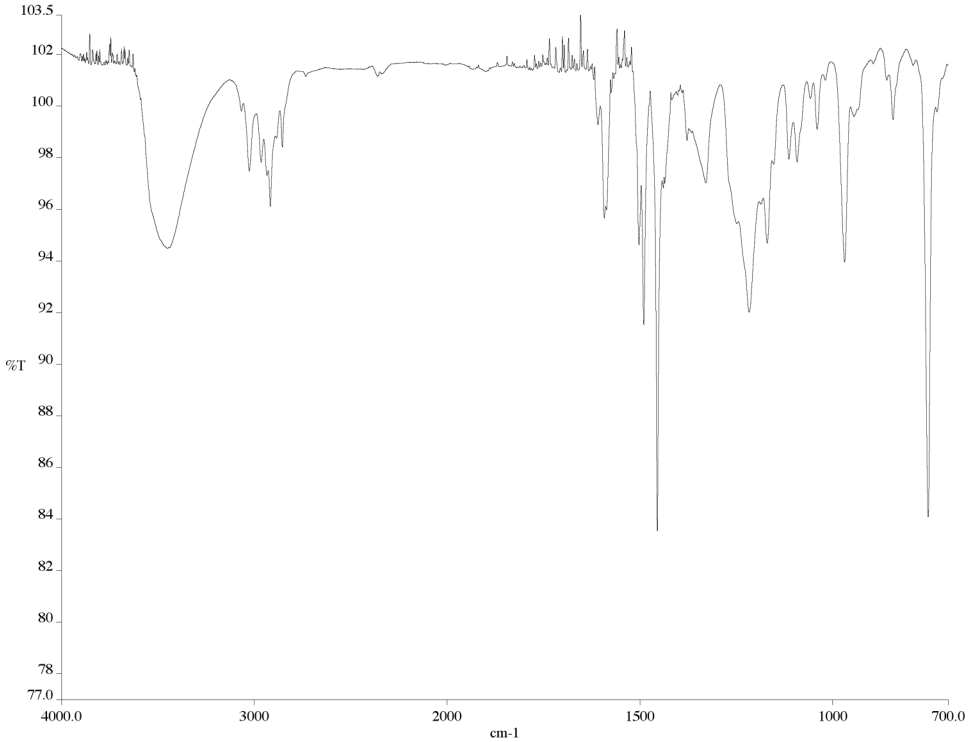


*Figure A2.1.75 IR spectrum (thin film/NaCl) of **28**.*

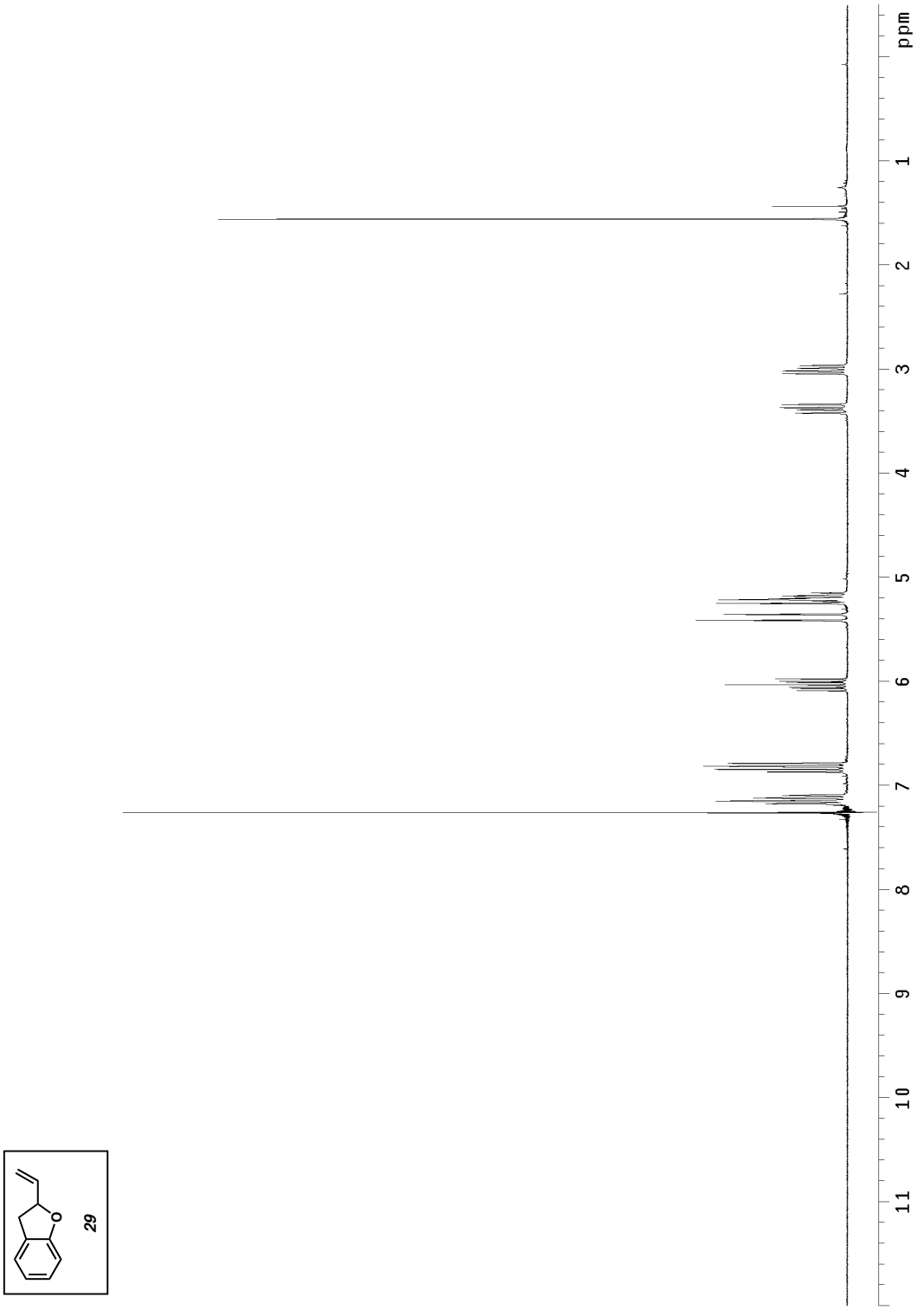


*Figure A2.1.76 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **29**.*

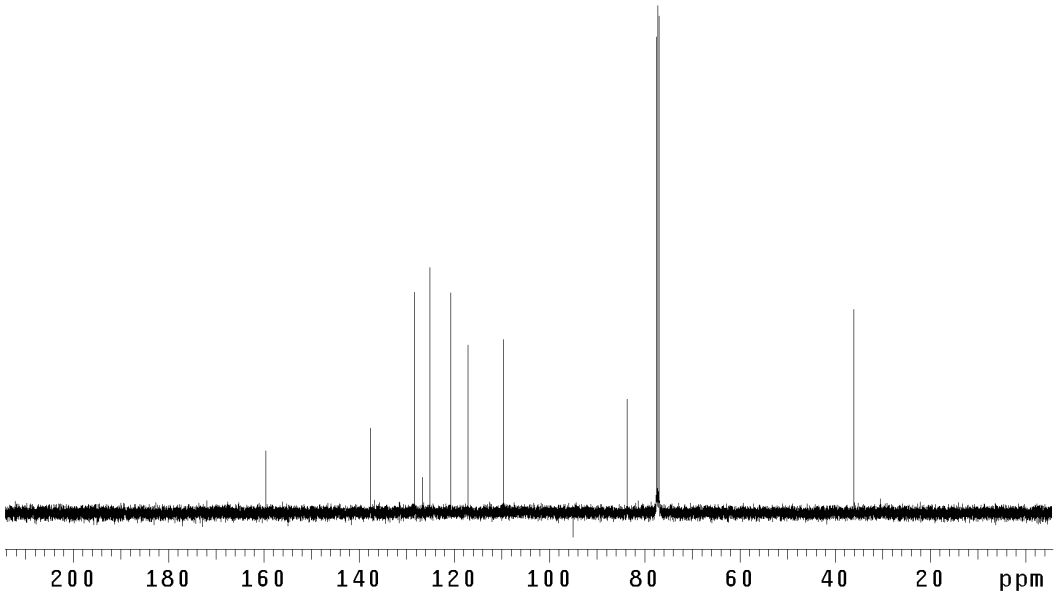


*Figure A2.1.77 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **29**.*

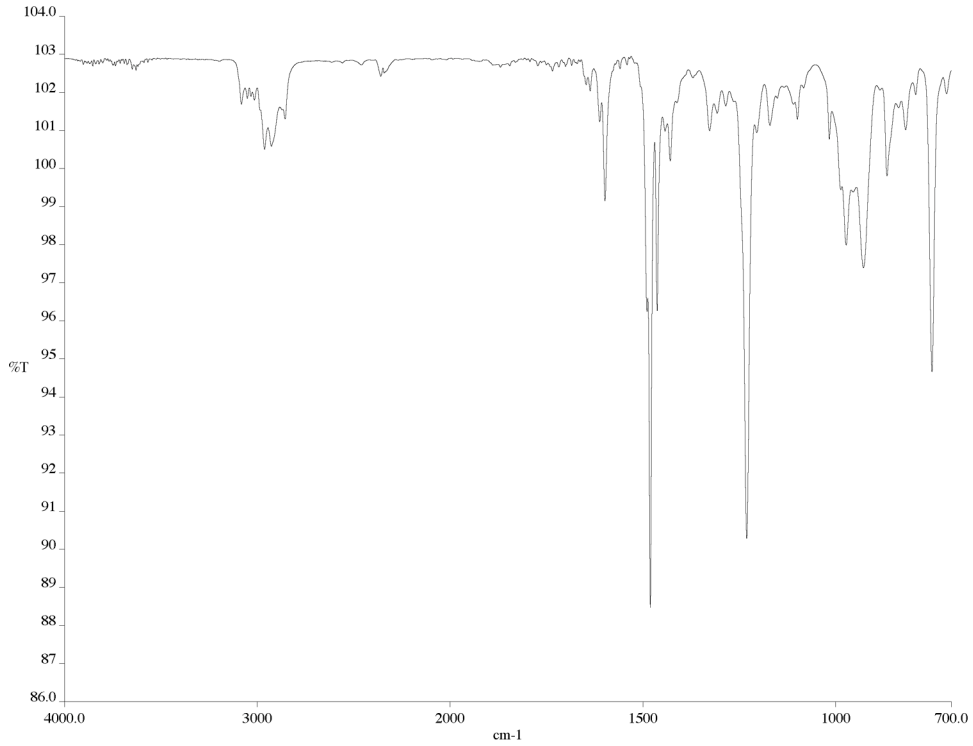


*Figure A2.1.78 IR spectrum (thin film/NaCl) of **29**.*

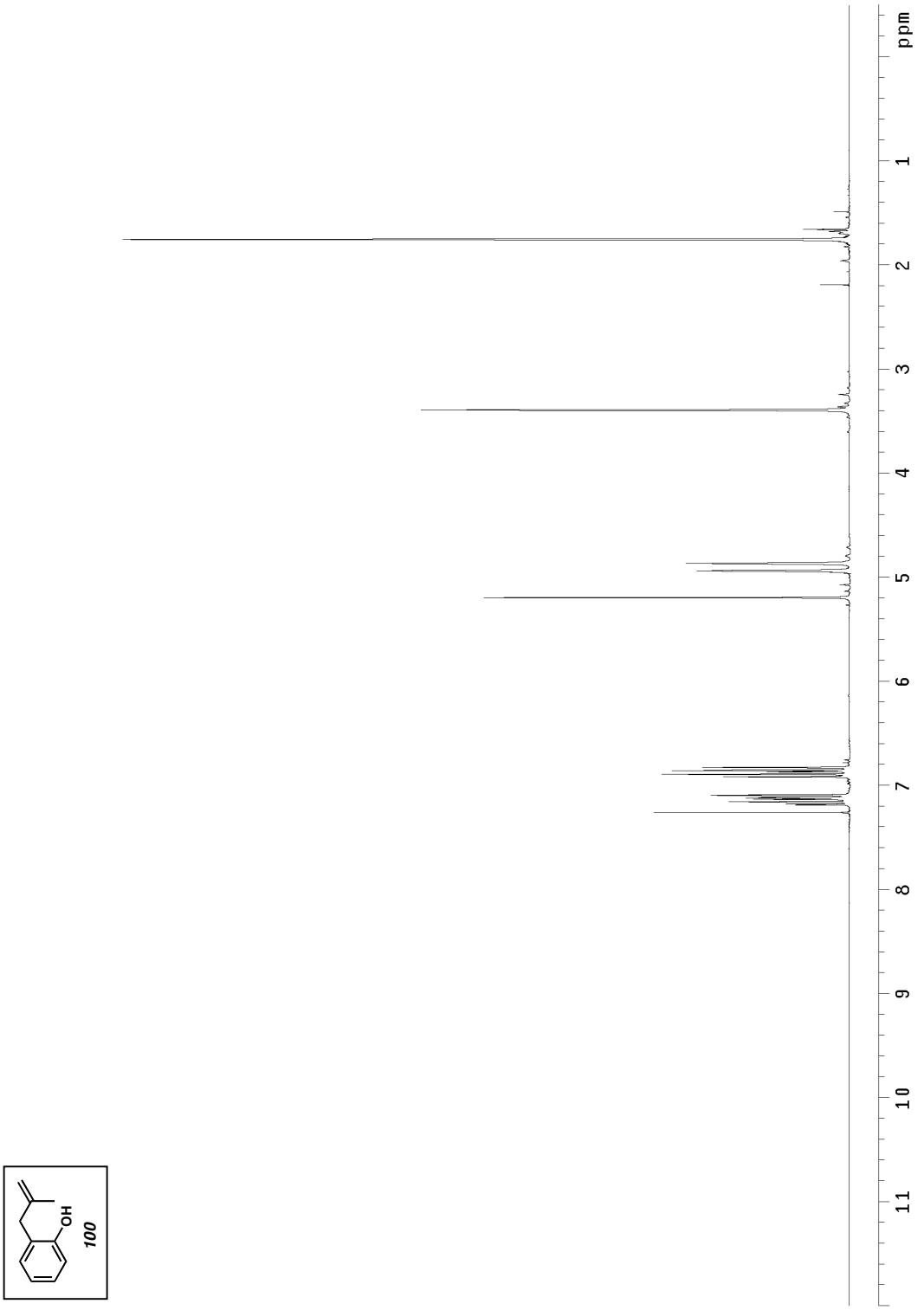


*Figure A2.1.79 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **100**.*

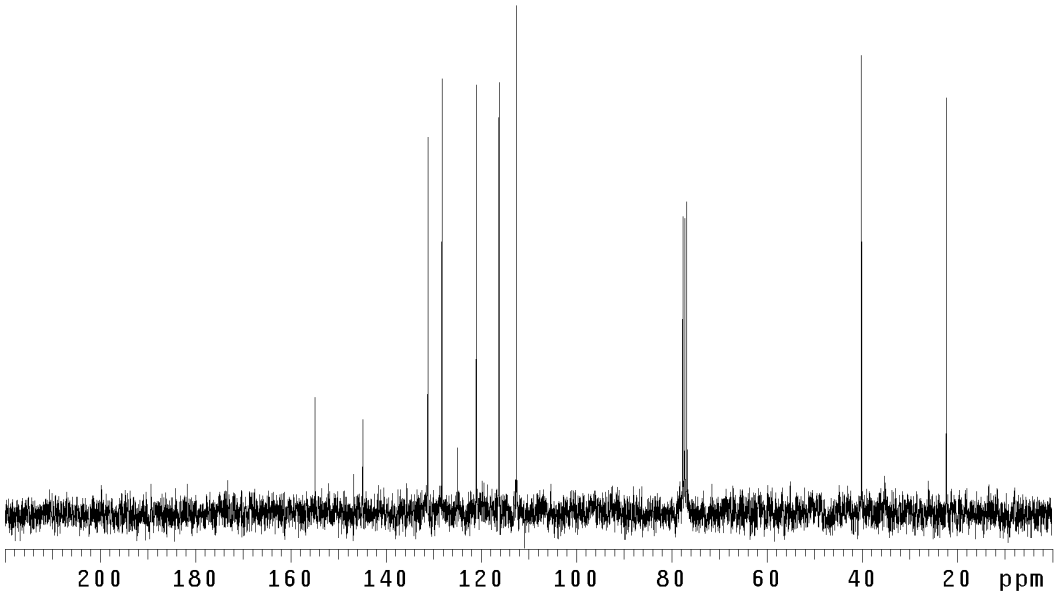


*Figure A2.1.80 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **100**.*

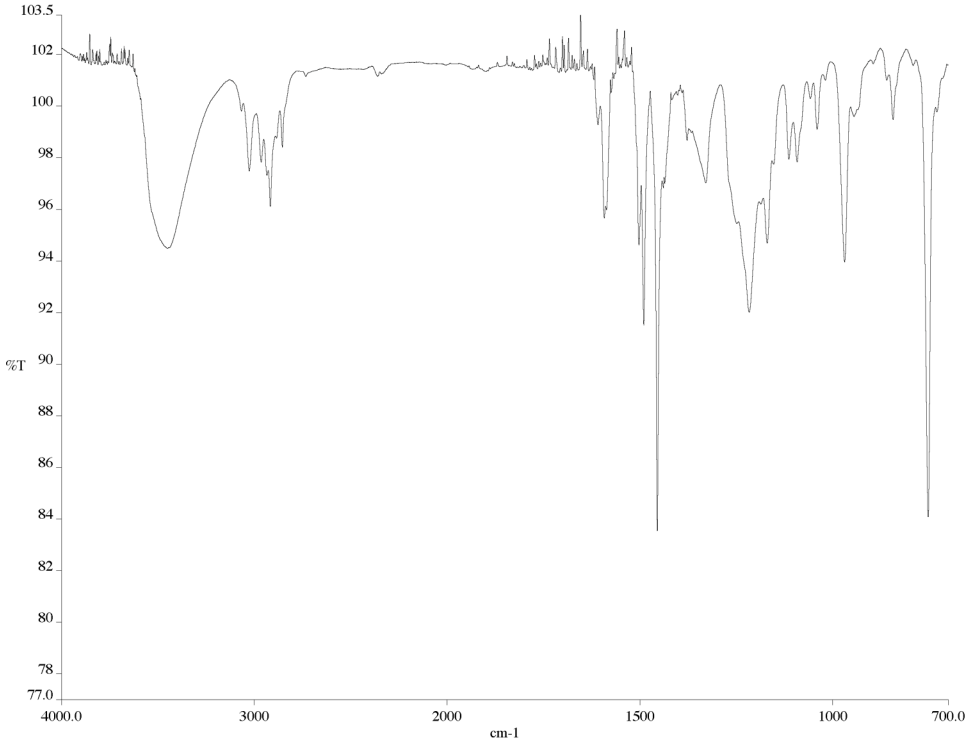


*Figure A2.1.81 IR spectrum (thin film/NaCl) of **100.***

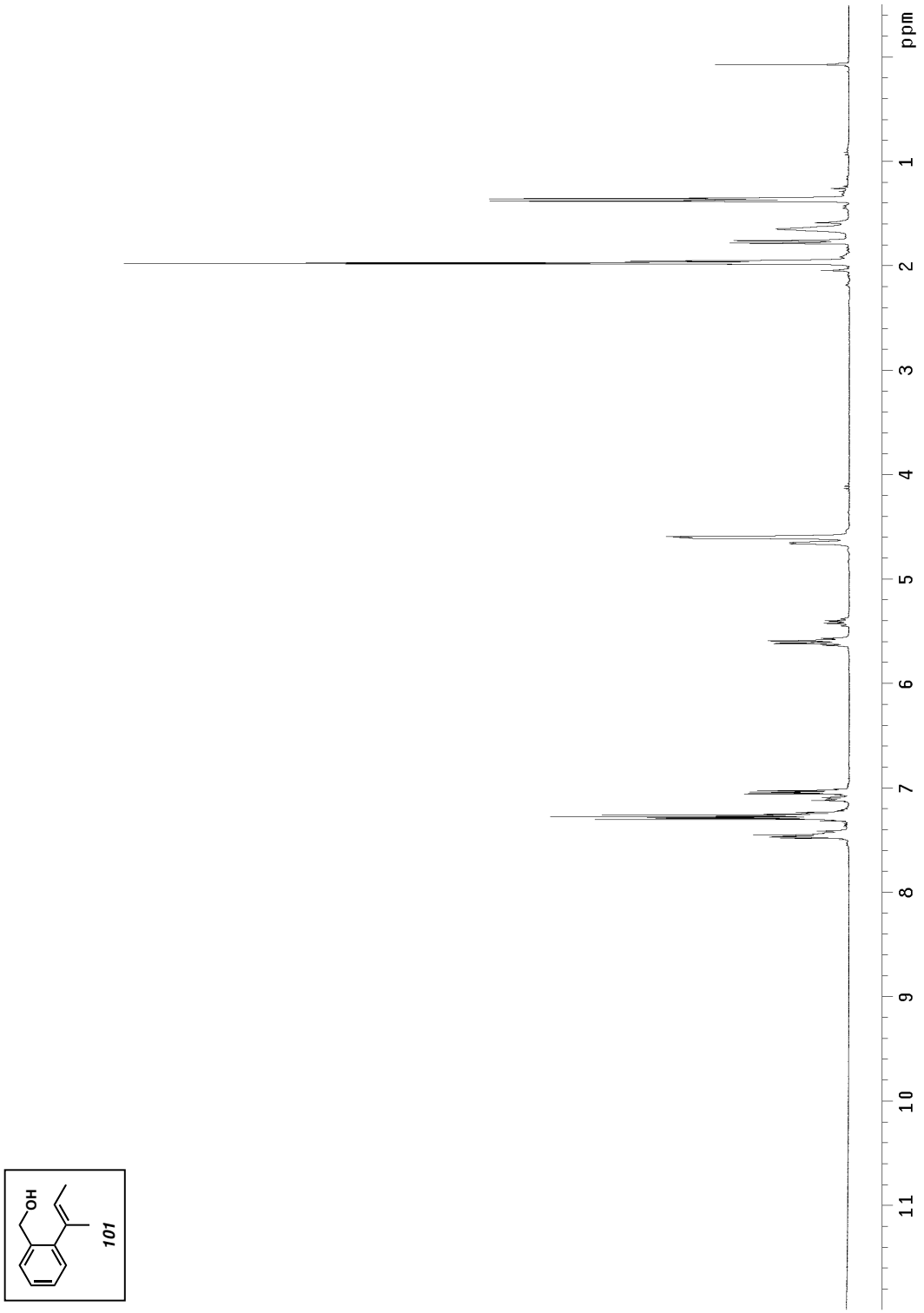


*Figure A2.1.82 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **101**.*

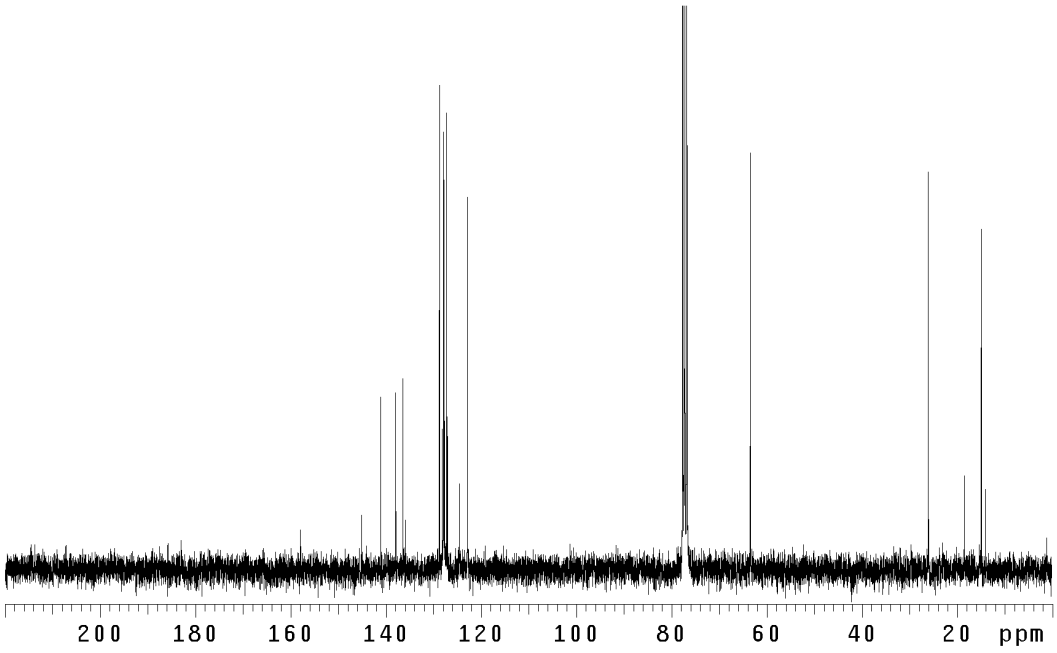


*Figure A2.1.83 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **101**.*

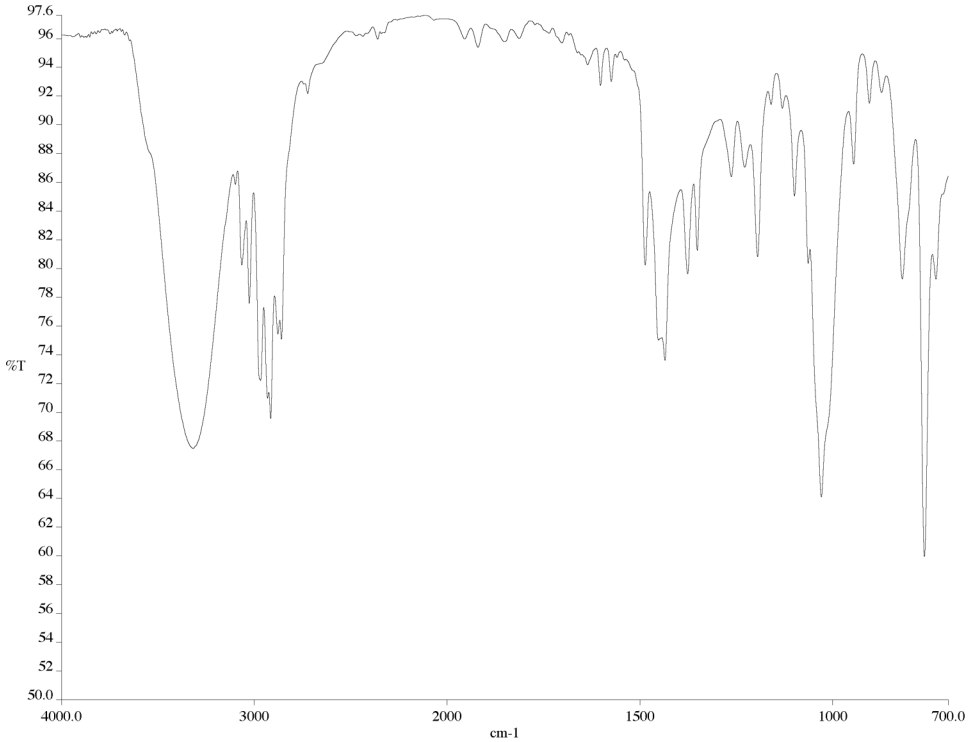


*Figure A2.1.84 IR spectrum (thin film/NaCl) of **101**.*

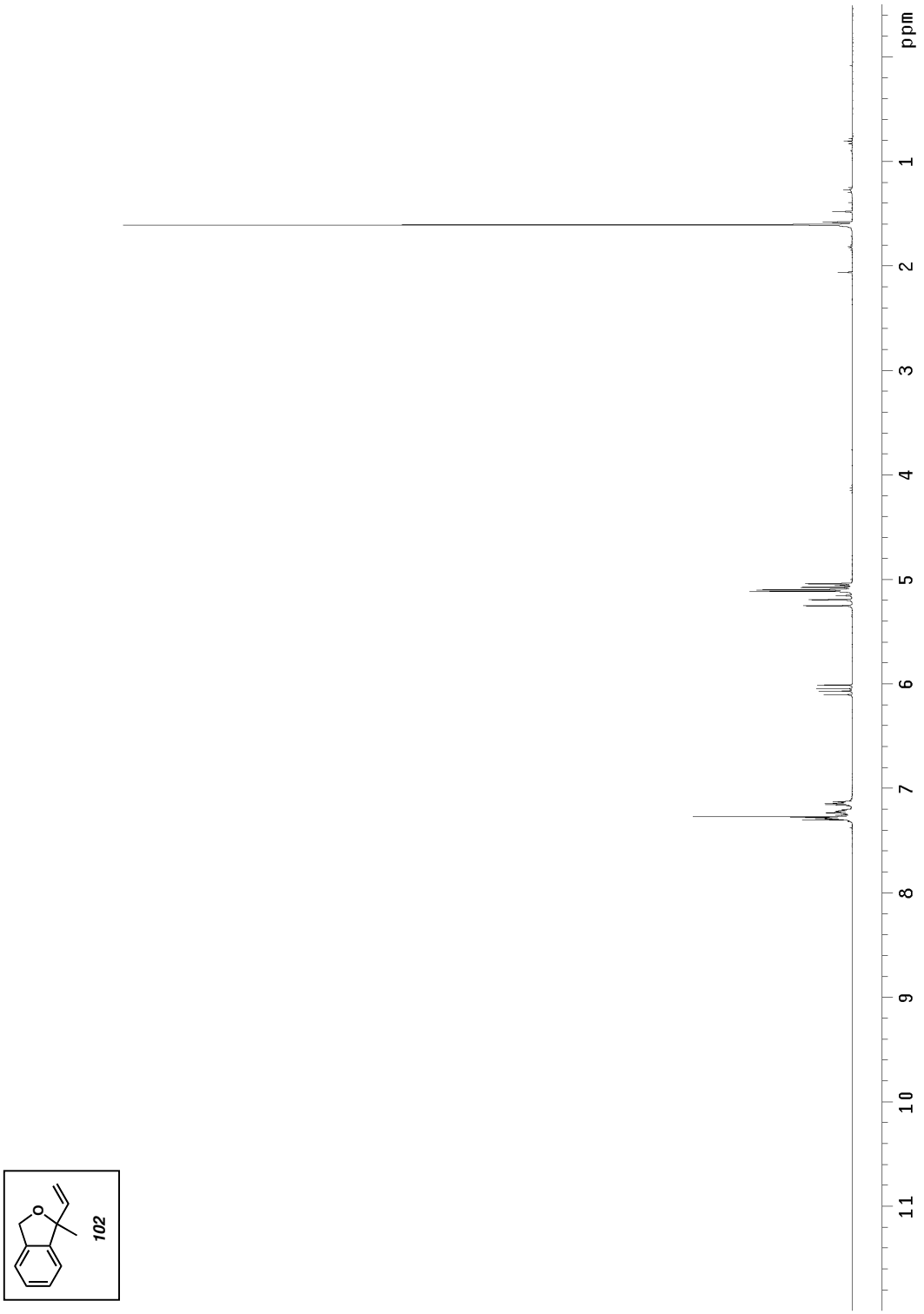


*Figure A2.1.85 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **102**.*

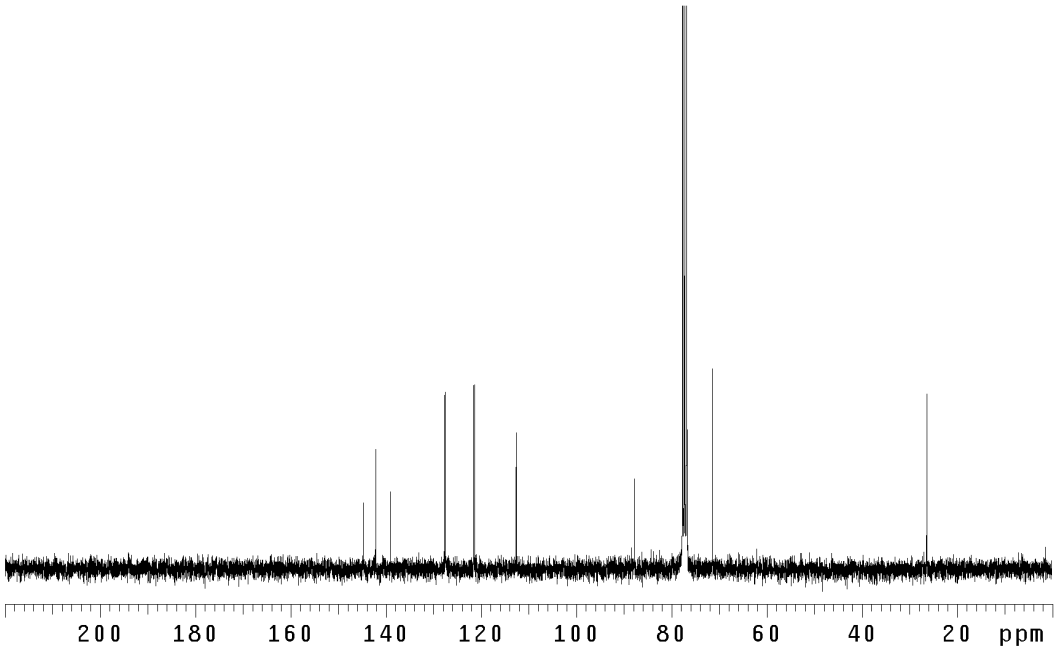


*Figure A2.1.86 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **102**.*

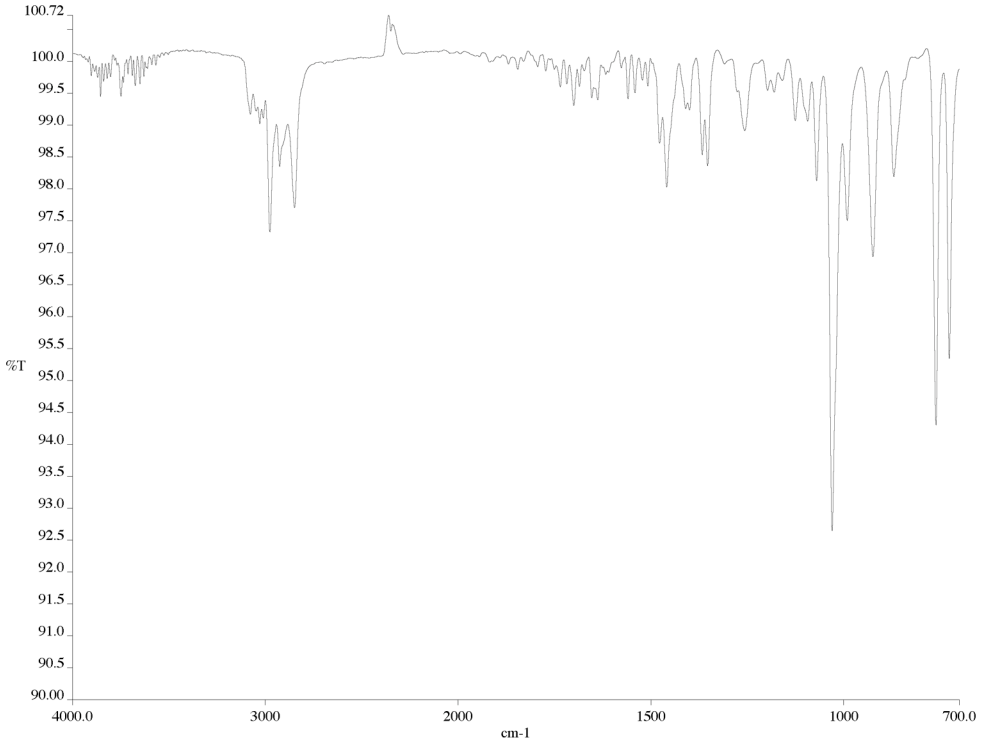


*Figure A2.1.87 IR spectrum (thin film/NaCl) of **102**.*

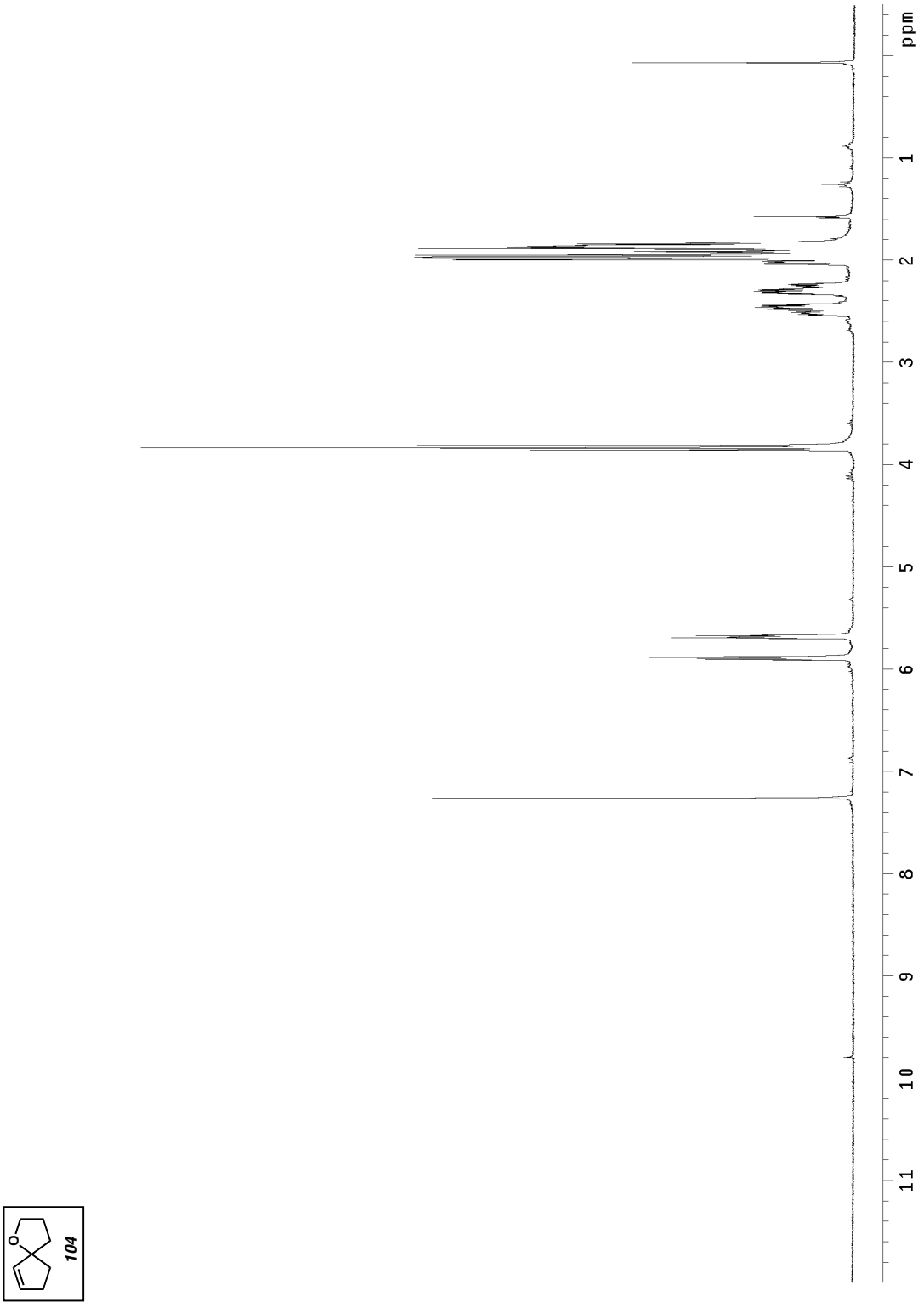


*Figure A2.1.88 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **104**.*

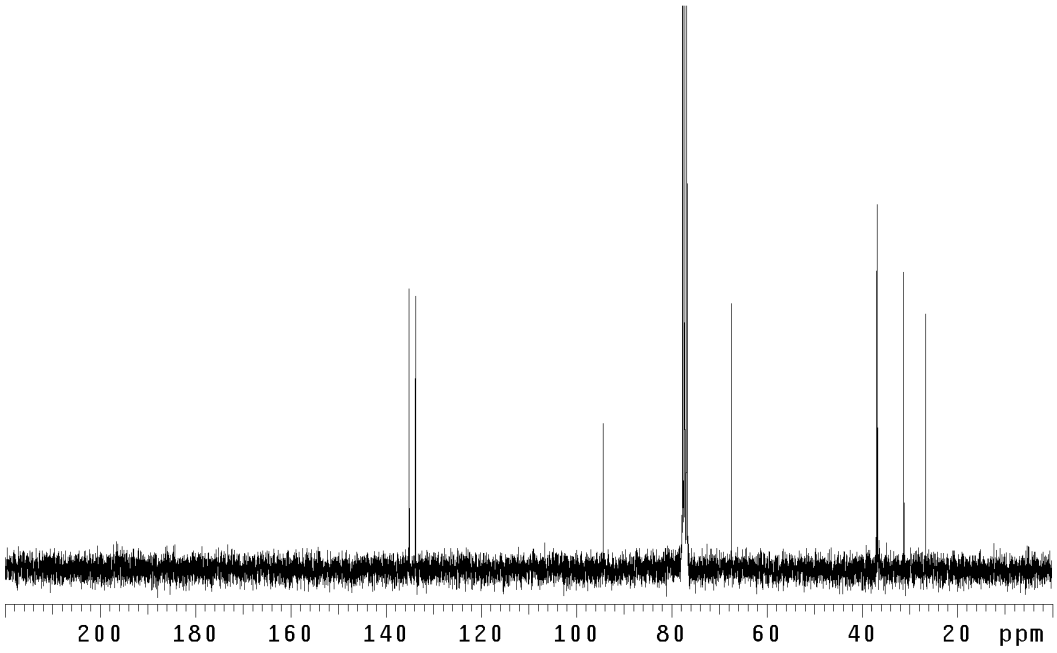


*Figure A2.1.89 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **104**.*

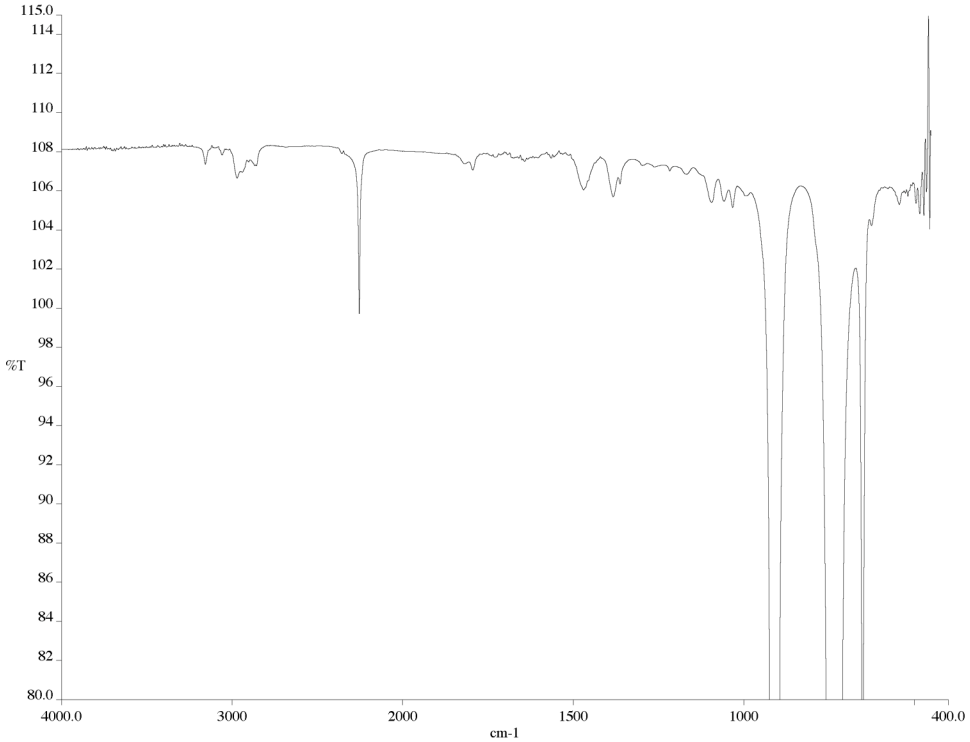


*Figure A2.1.90 IR spectrum (thin film/NaCl) of **104**.*

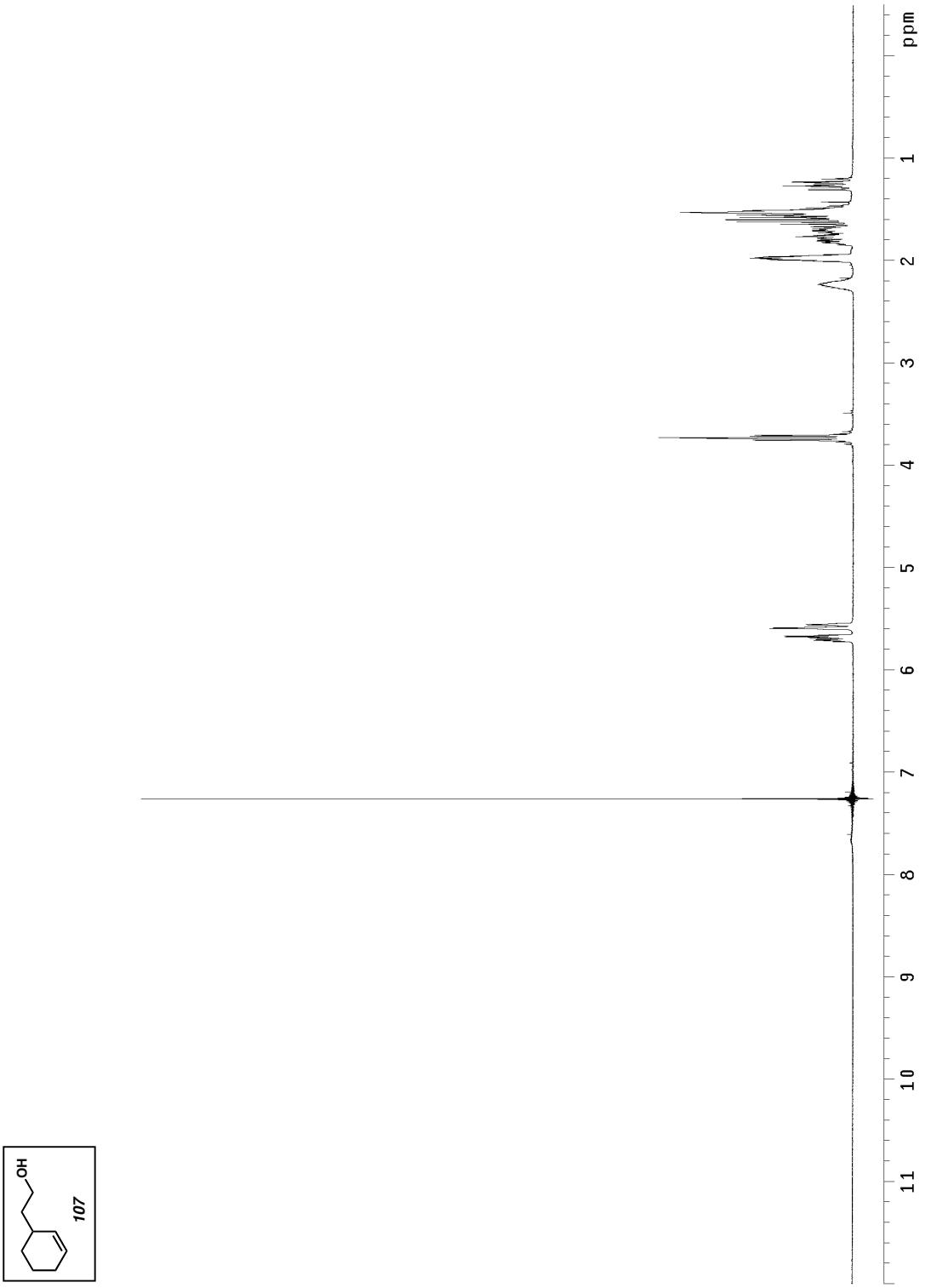


*Figure A2.1.91 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **107**.*

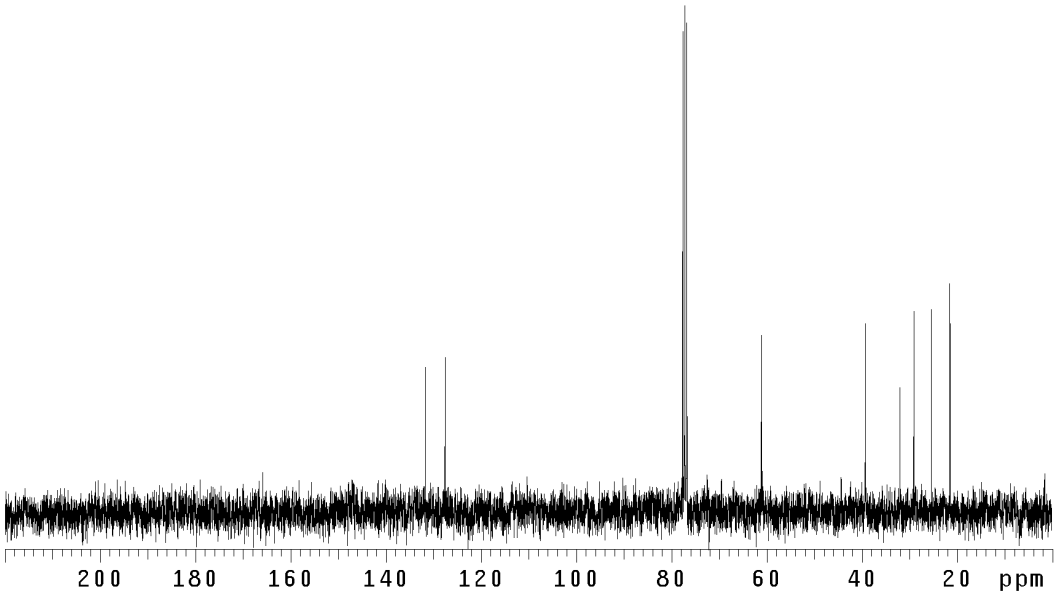


*Figure A2.1.92 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **107**.*

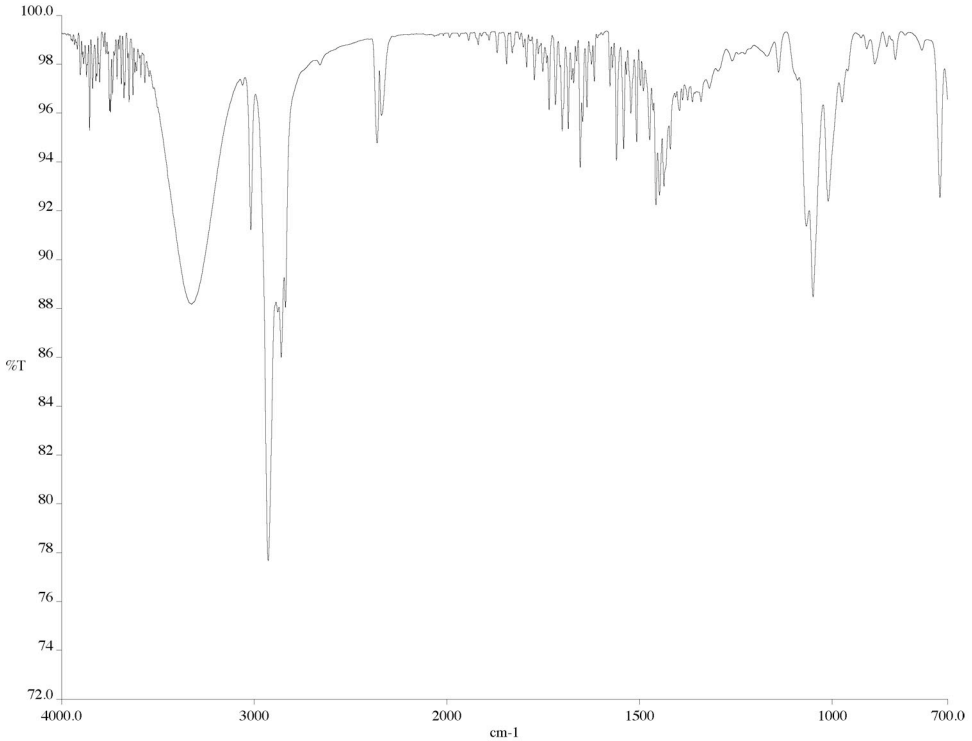


*Figure A2.1.93 IR spectrum (thin film/NaCl) of **107**.*

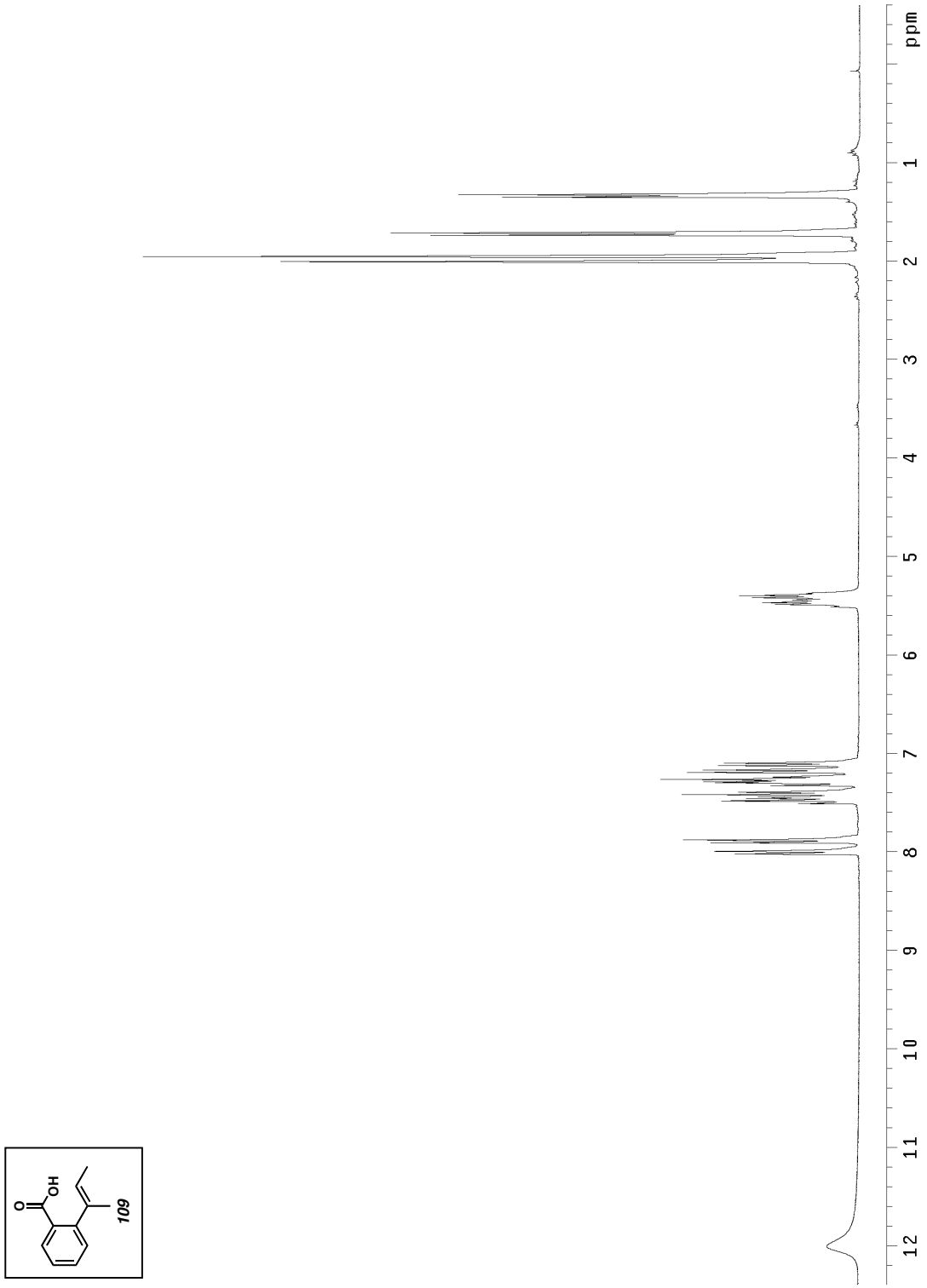


Figure A2.1.94 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of ***109***.

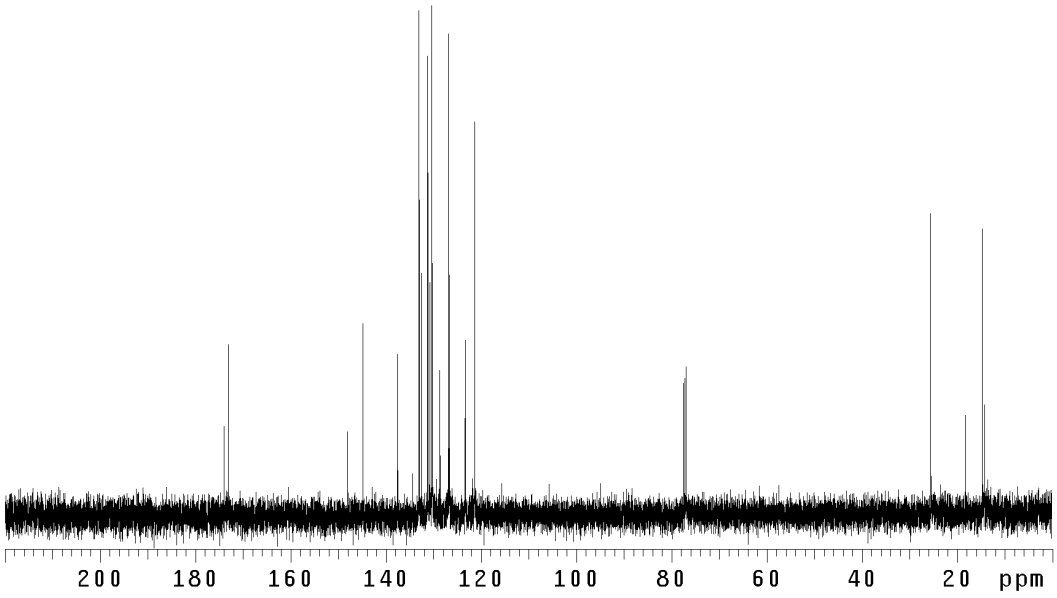


*Figure A2.1.95 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **109**.*

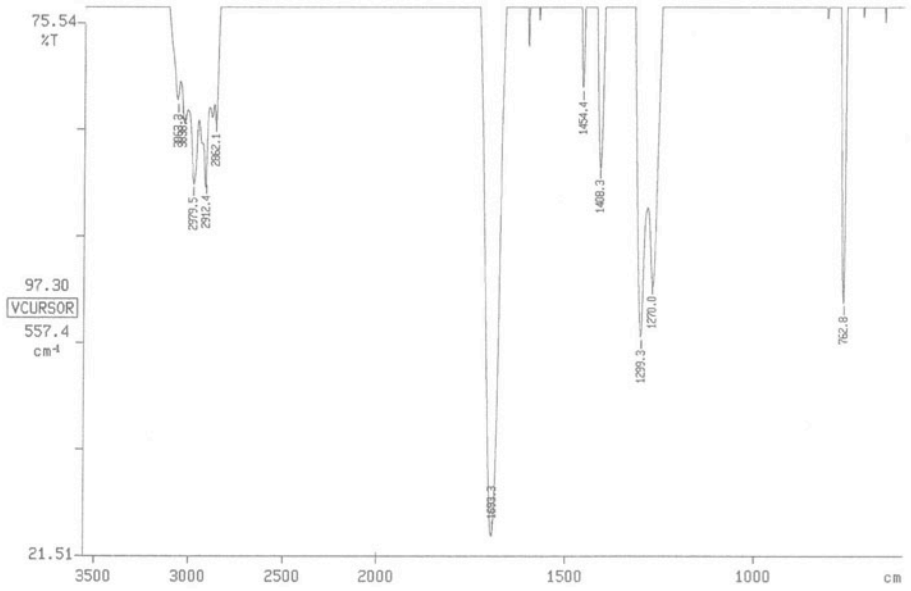


*Figure A2.1.96 IR spectrum (thin film/NaCl) of **109**.*

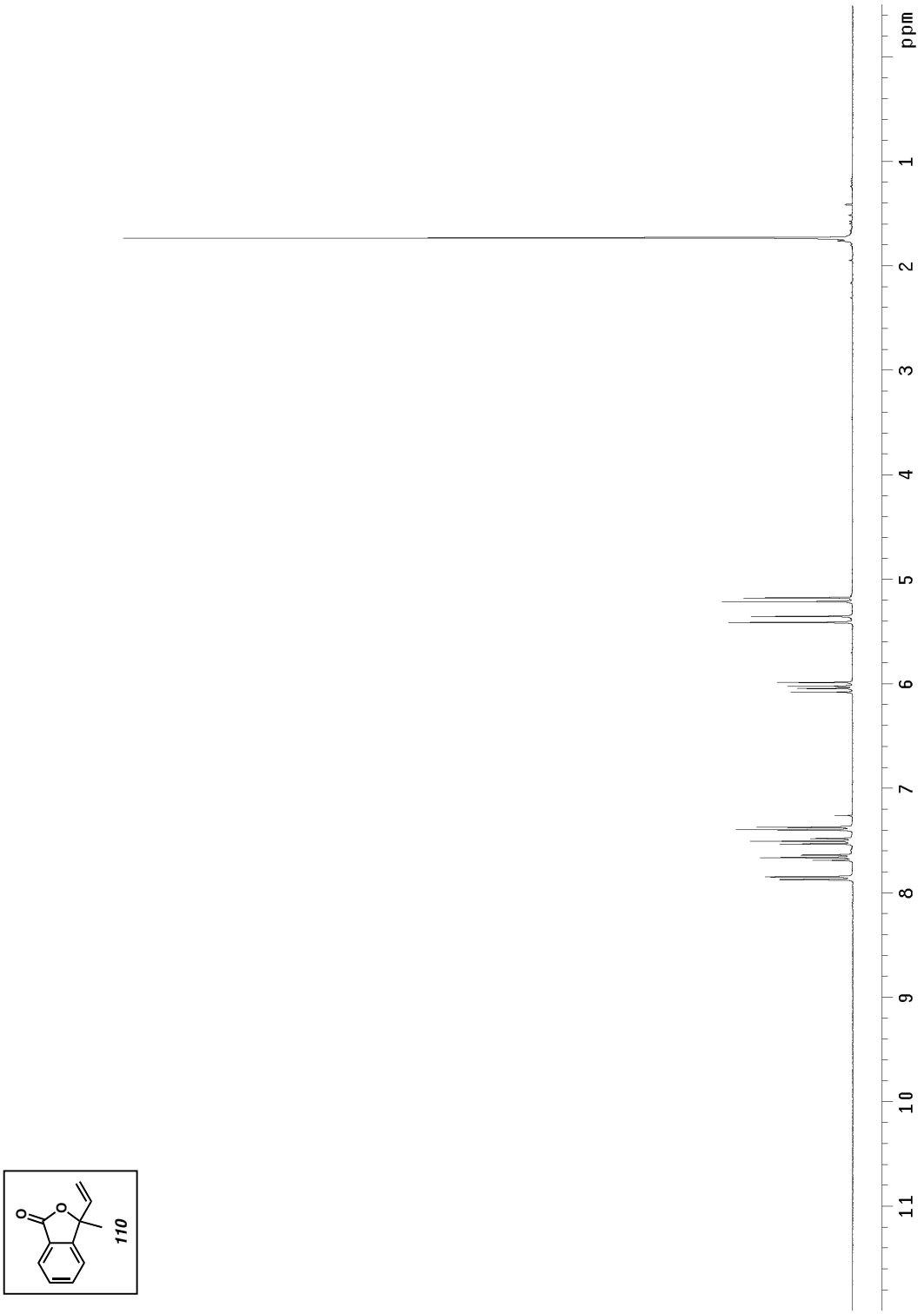


*Figure A2.1.97 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **110**.*

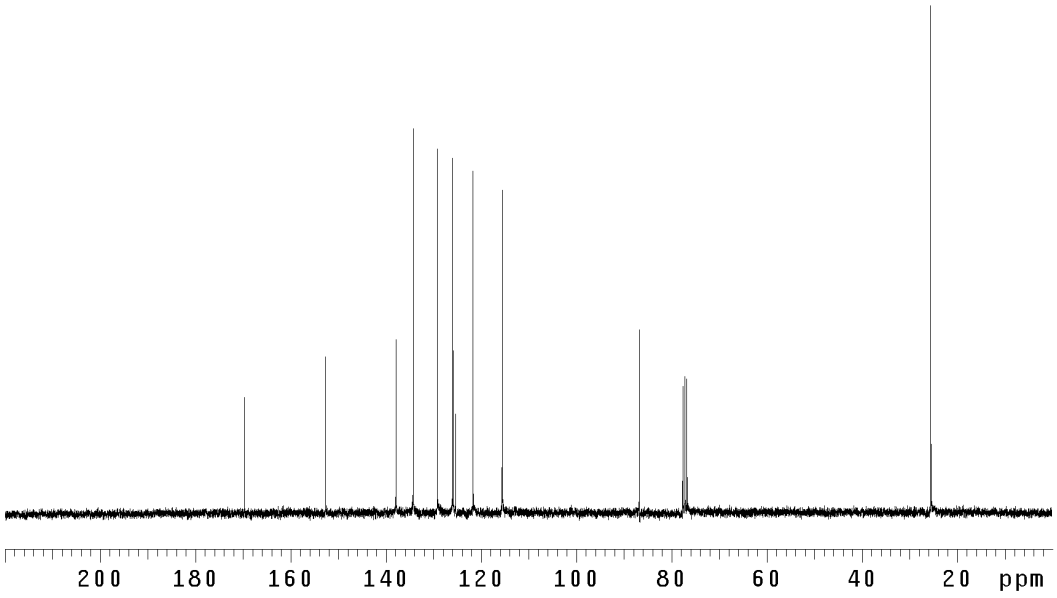


*Figure A2.1.98 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **110**.*

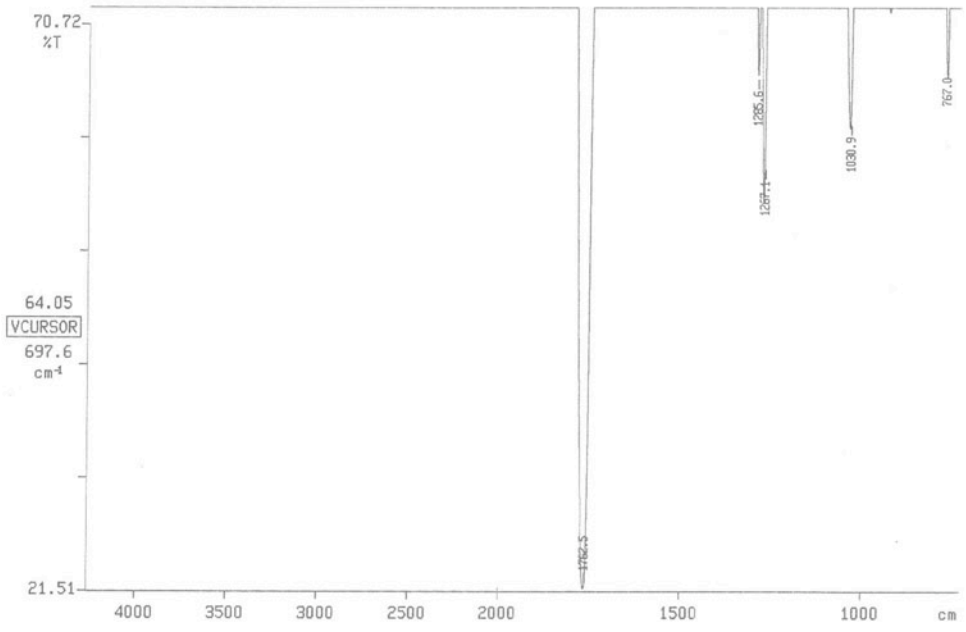


*Figure A2.1.99 IR spectrum (thin film/NaCl) of **110**.*

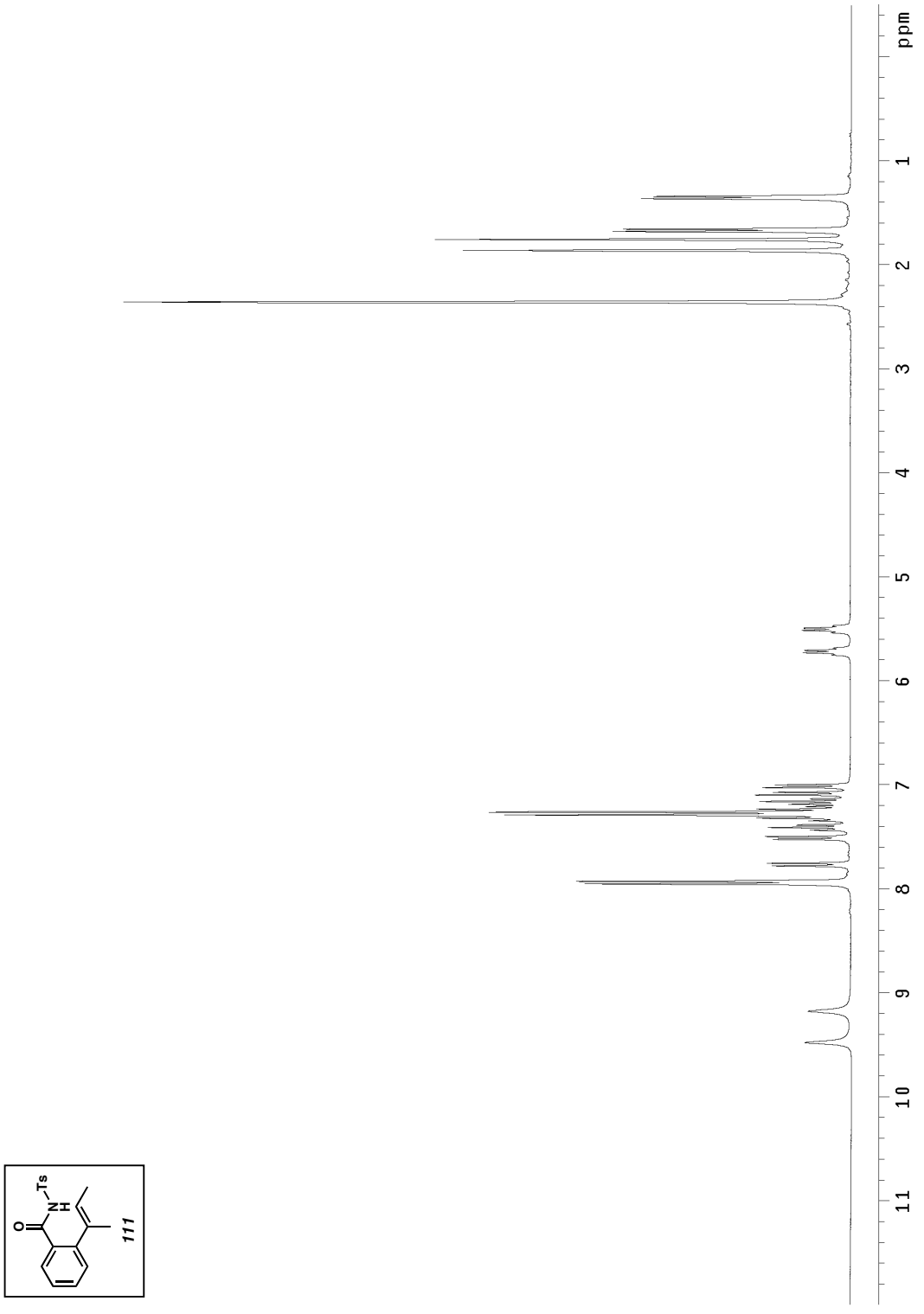


*Figure A2.1.100 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **111**.*

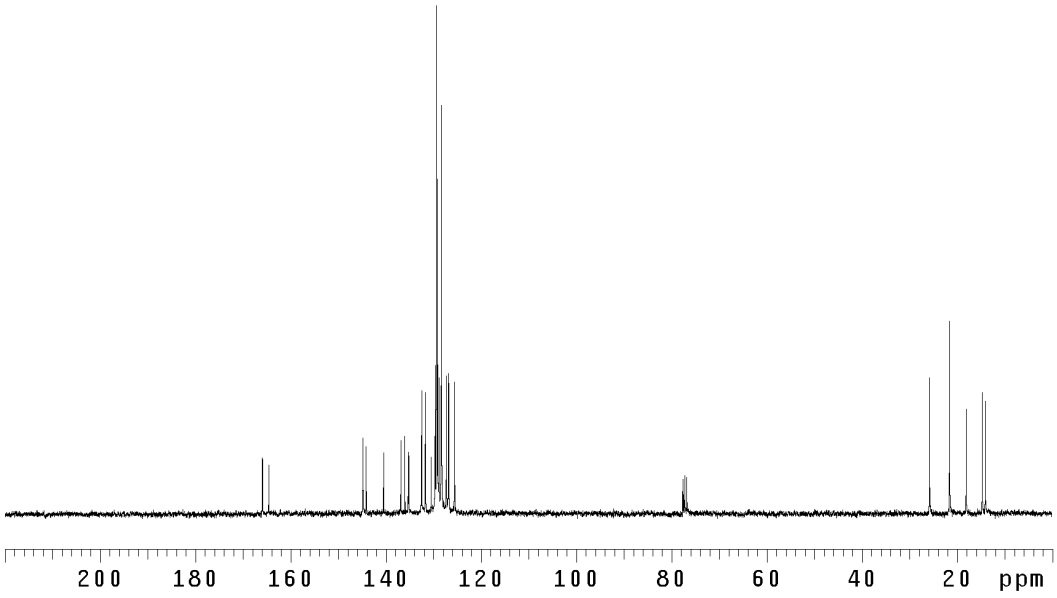


*Figure A2.1.101 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **111**.*

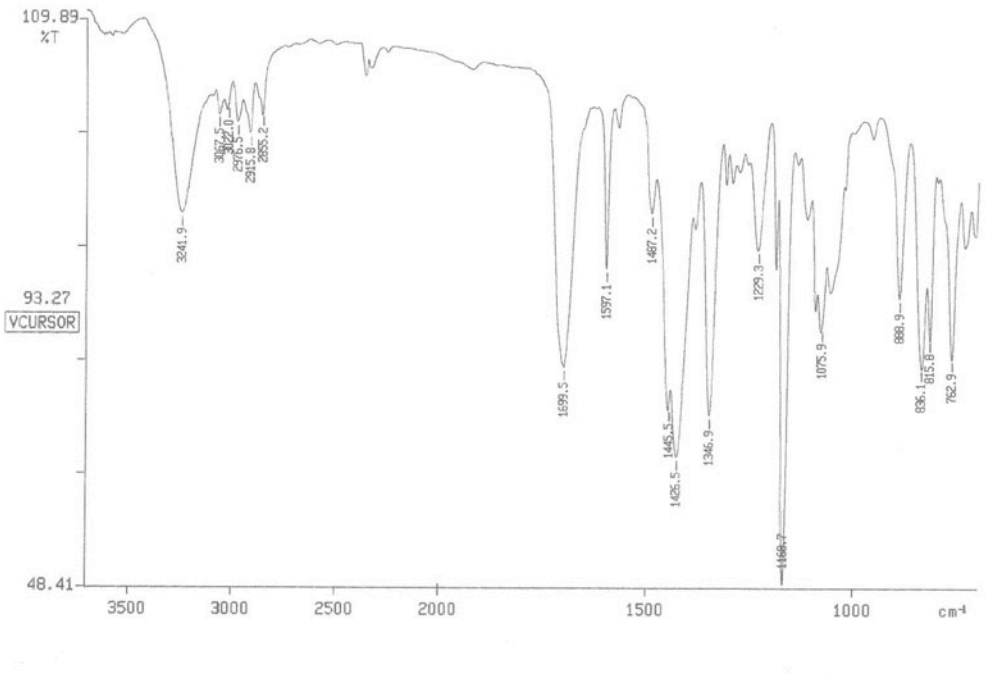


*Figure A2.1.102 IR spectrum (thin film/NaCl) of **111**.*

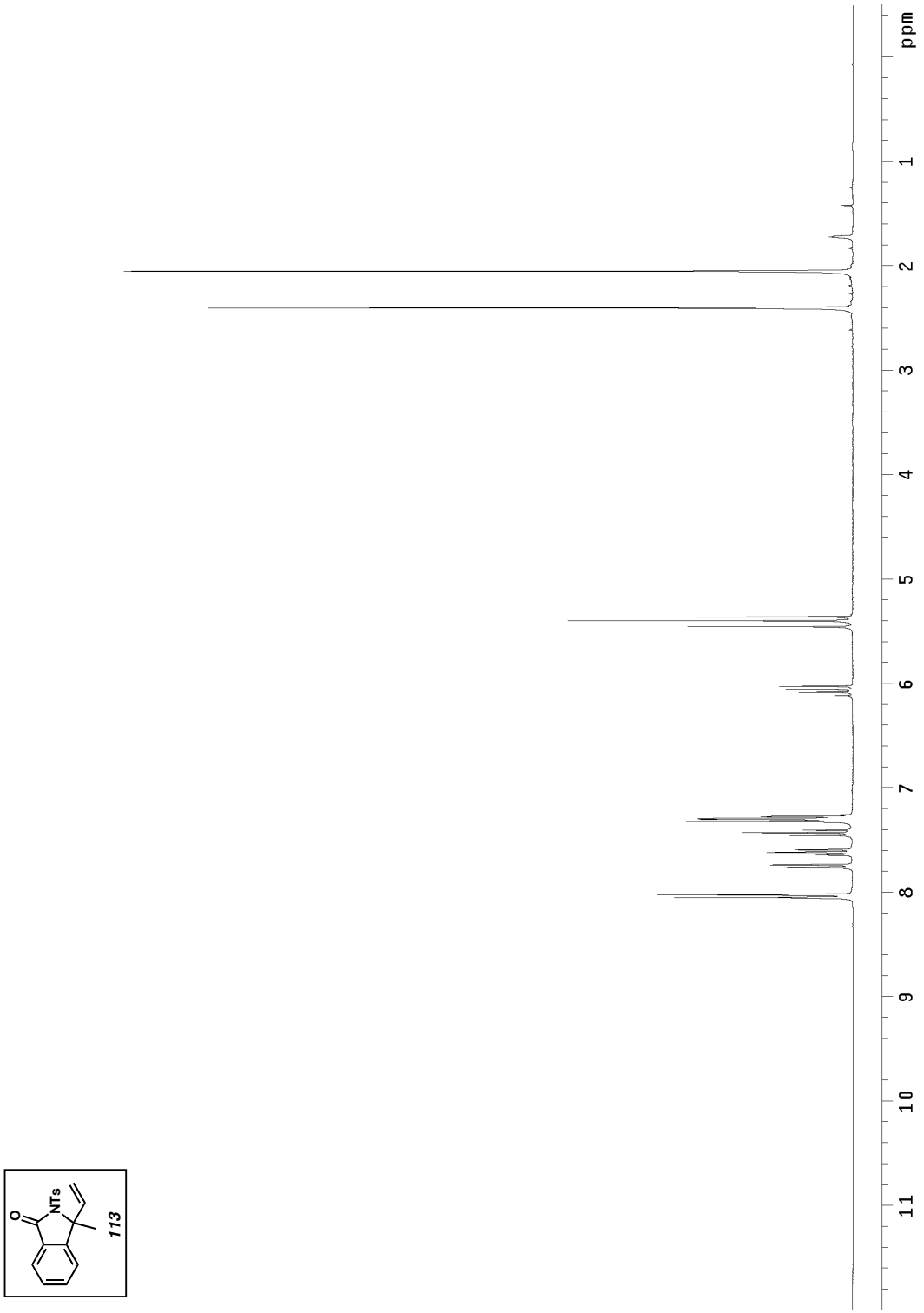


*Figure A2.1.103 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **113**.*

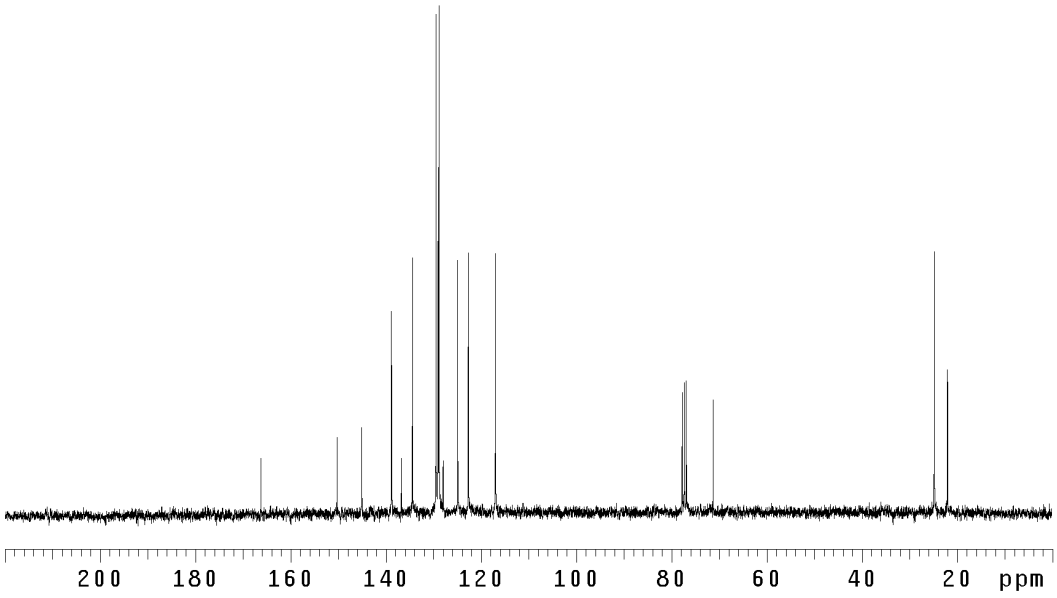


*Figure A2.1.104 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **113**.*

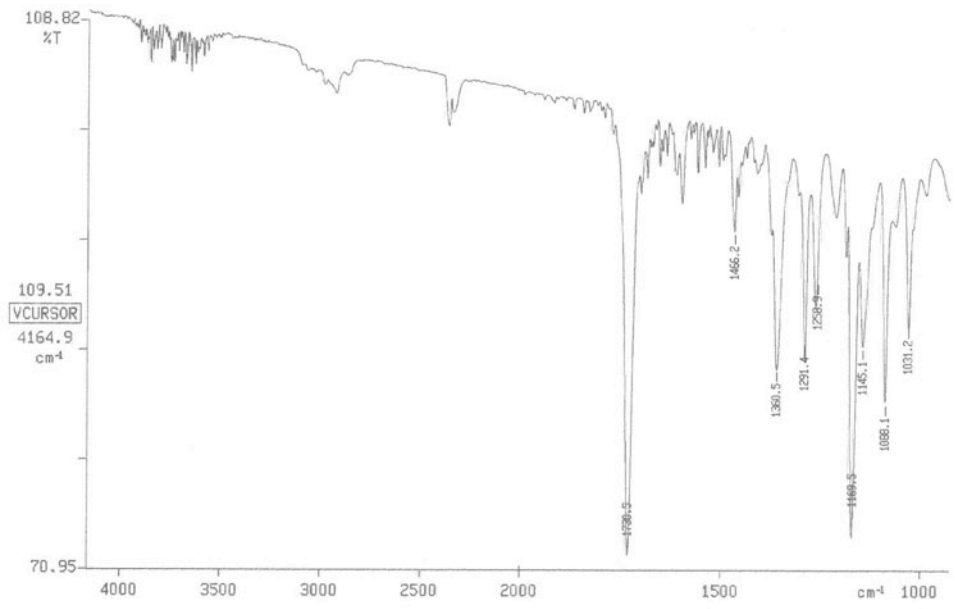


*Figure A2.1.105 IR spectrum (thin film/NaCl) of **113**.*

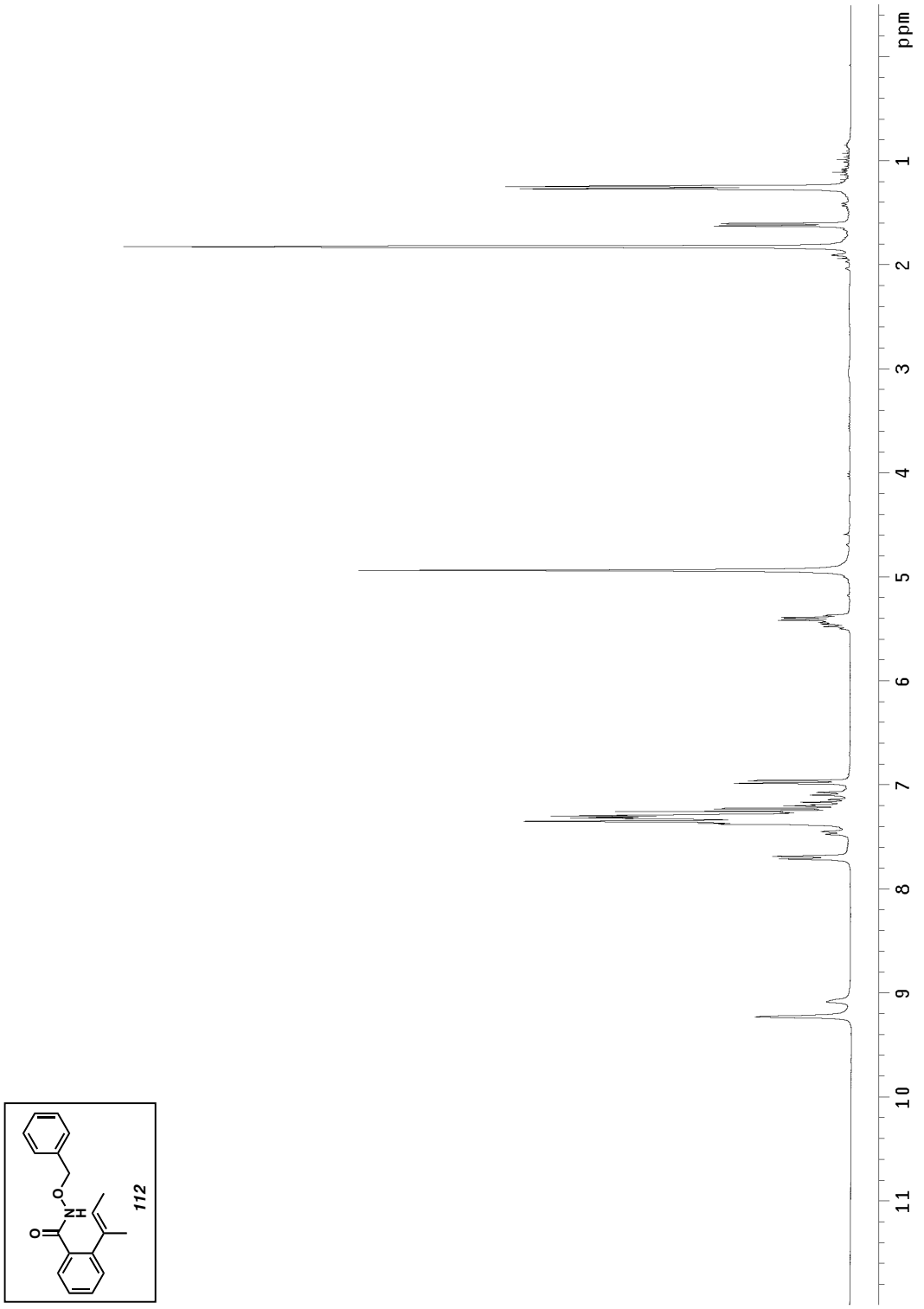


*Figure A2.1.106 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **112**.*

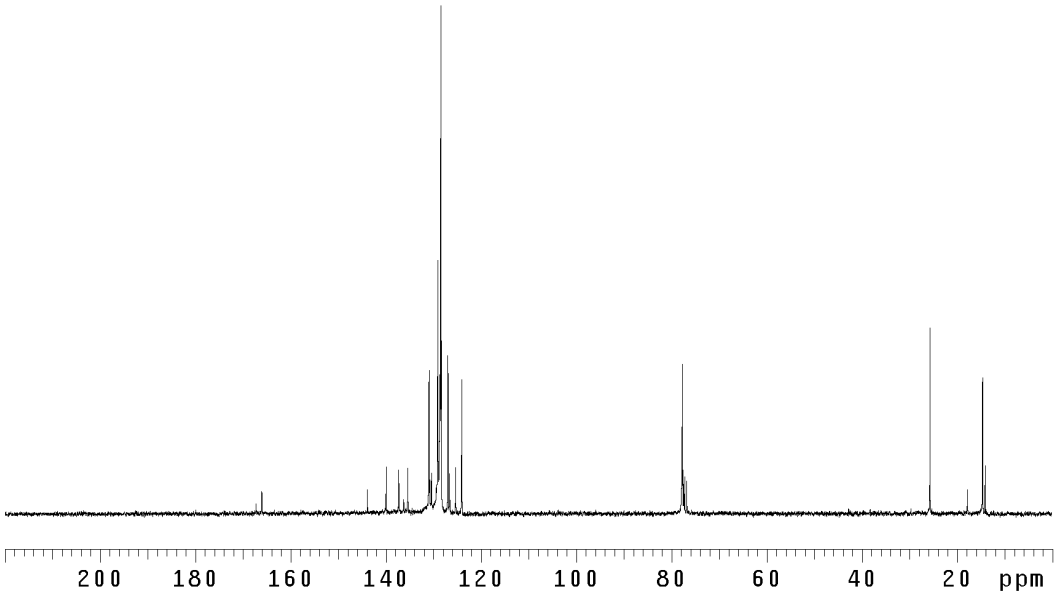


*Figure A2.1.107 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **112**.*

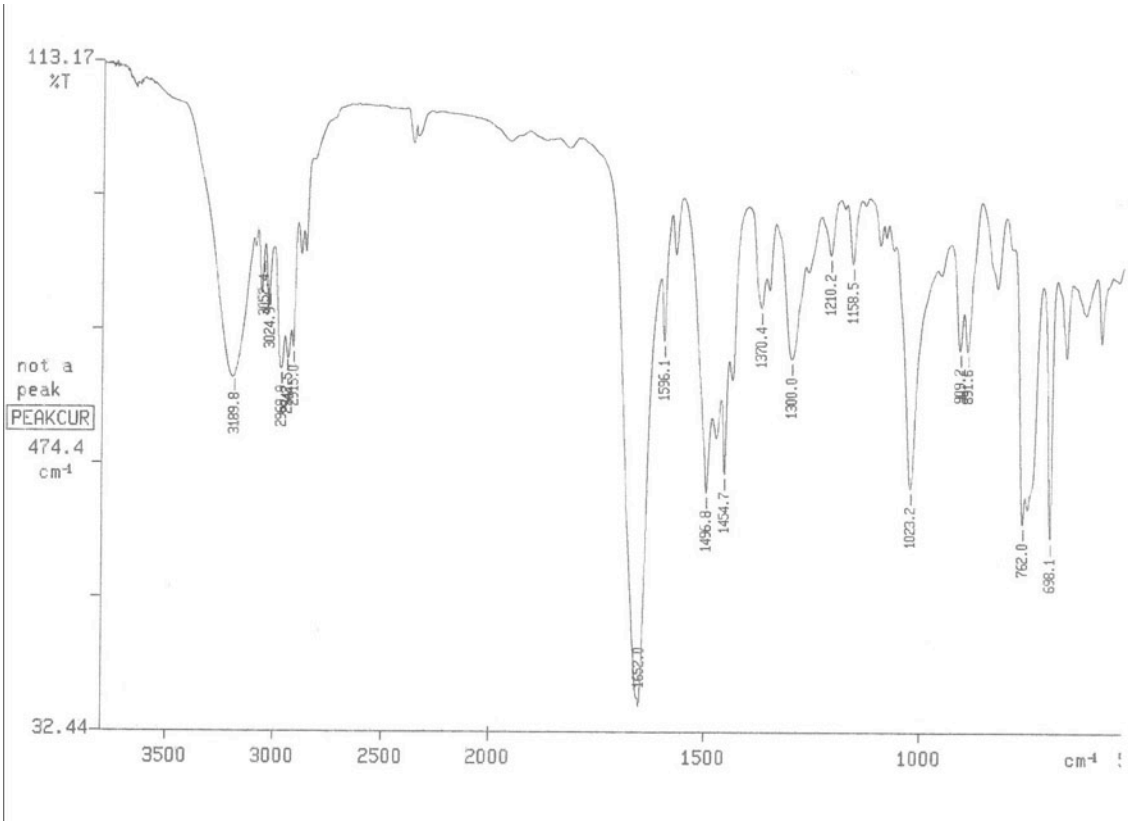


*Figure A2.1.108 IR spectrum (thin film/NaCl) of **112**.*

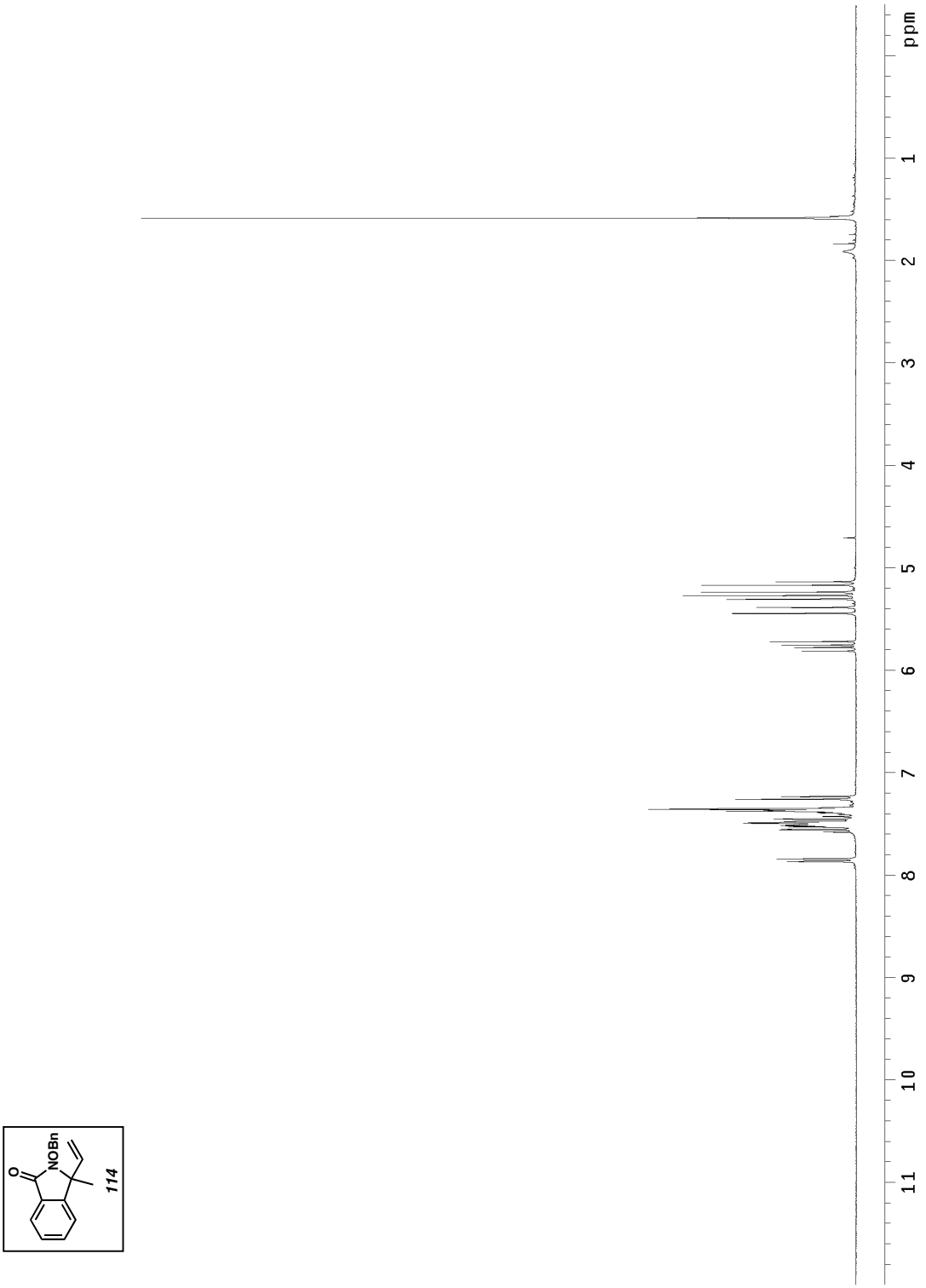


*Figure A2.1.109 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **114**.*

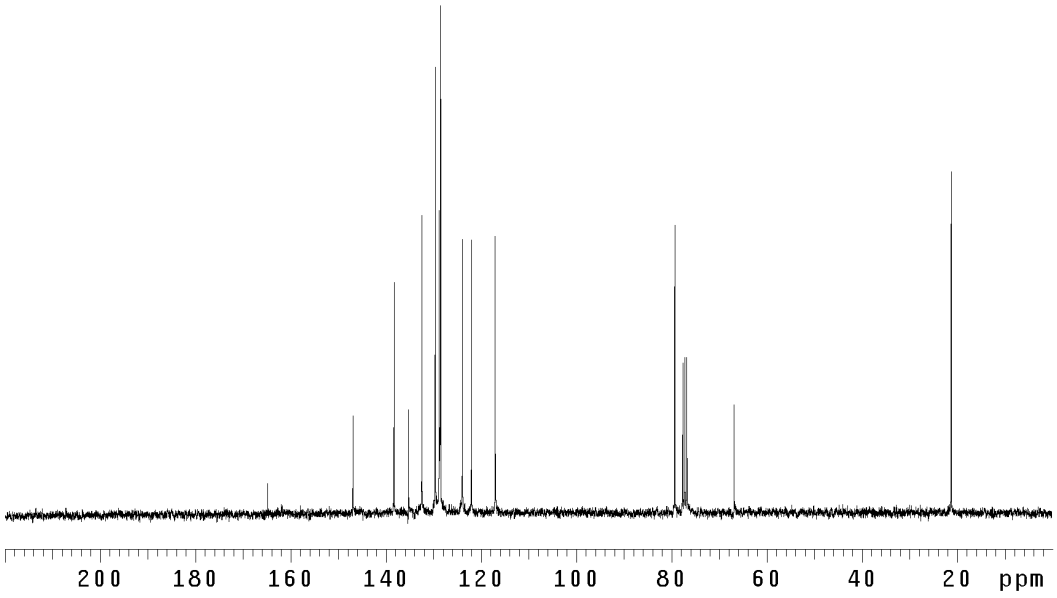


*Figure A2.1.110 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **114**.*

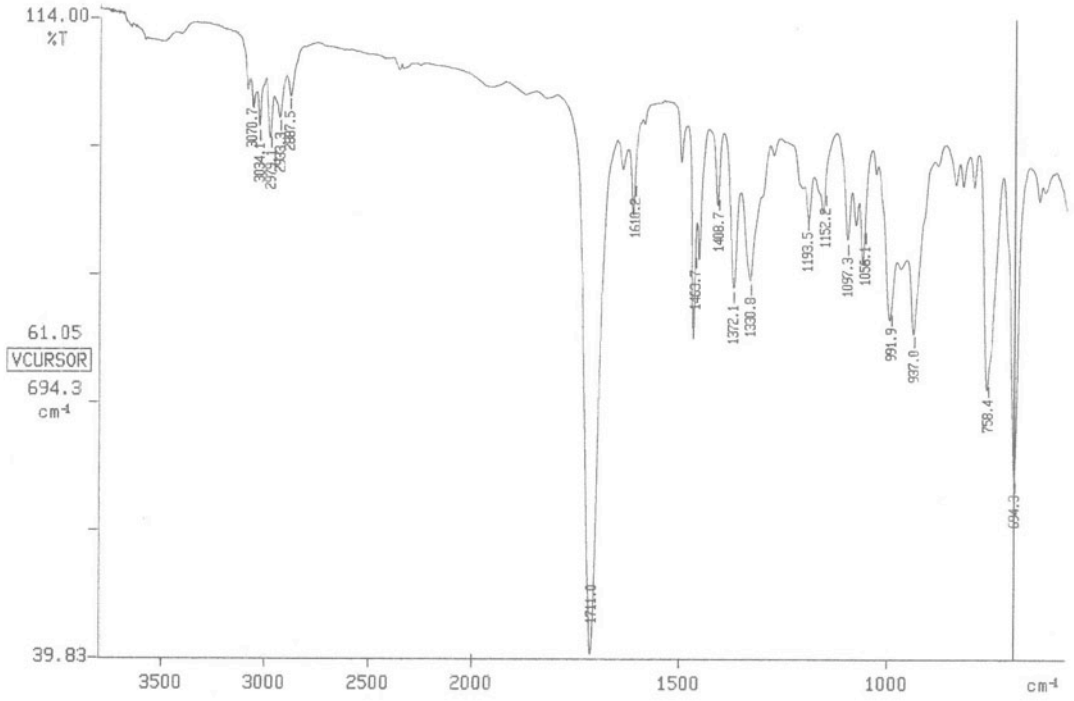


*Figure A2.1.111 IR spectrum (thin film/NaCl) of **114.***

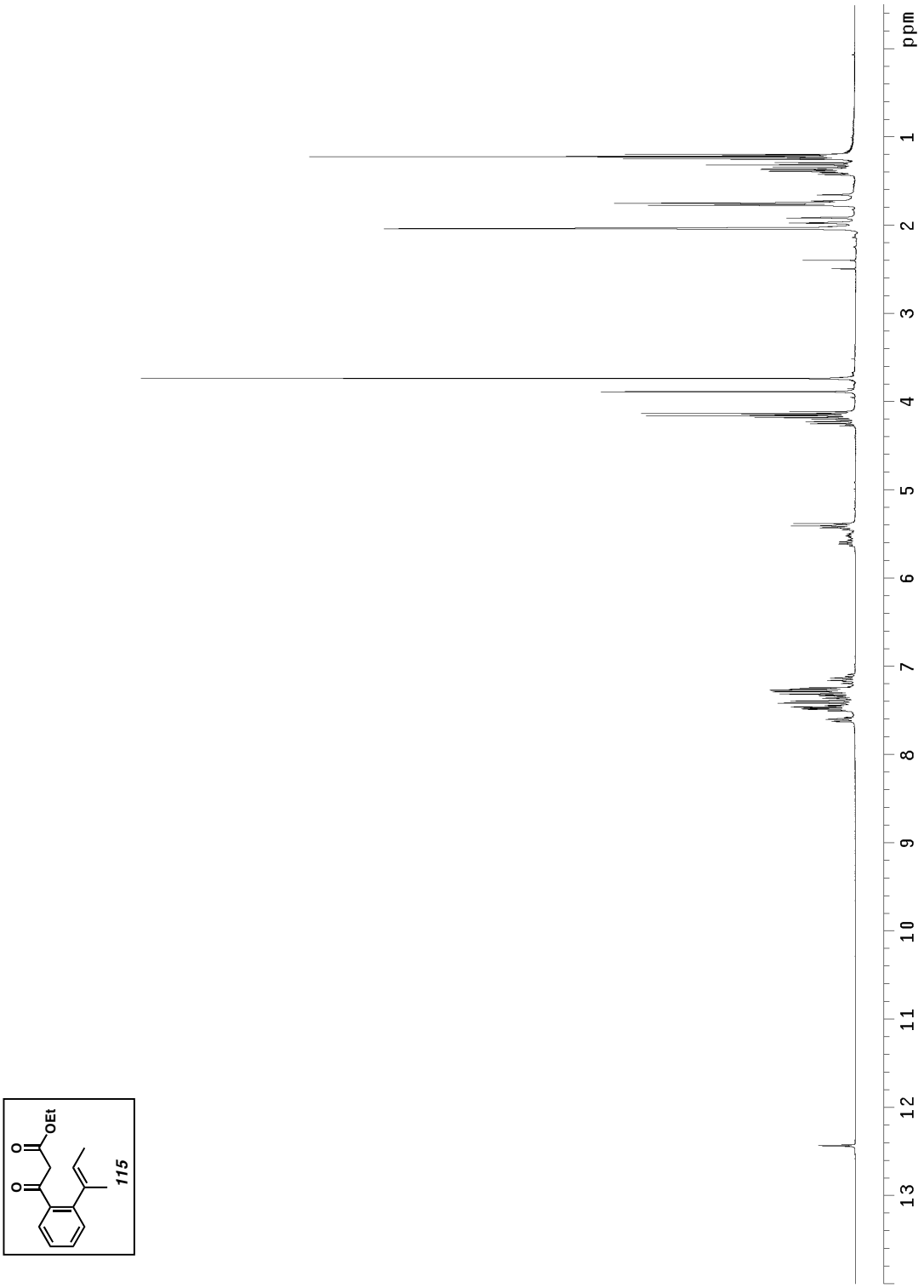


*Figure A2.1.112 ^{1}H NMR spectrum (300 MHz, acetone-d_6) of **115**.*

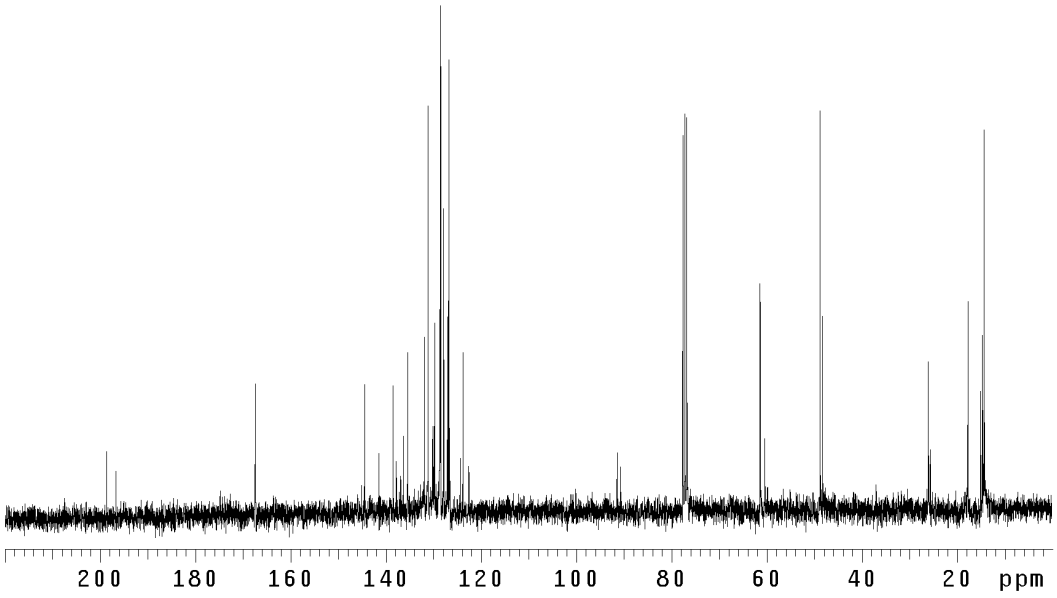


*Figure A2.1.113 ^{13}C NMR spectrum (75 MHz, acetone-d_6) of **115**.*

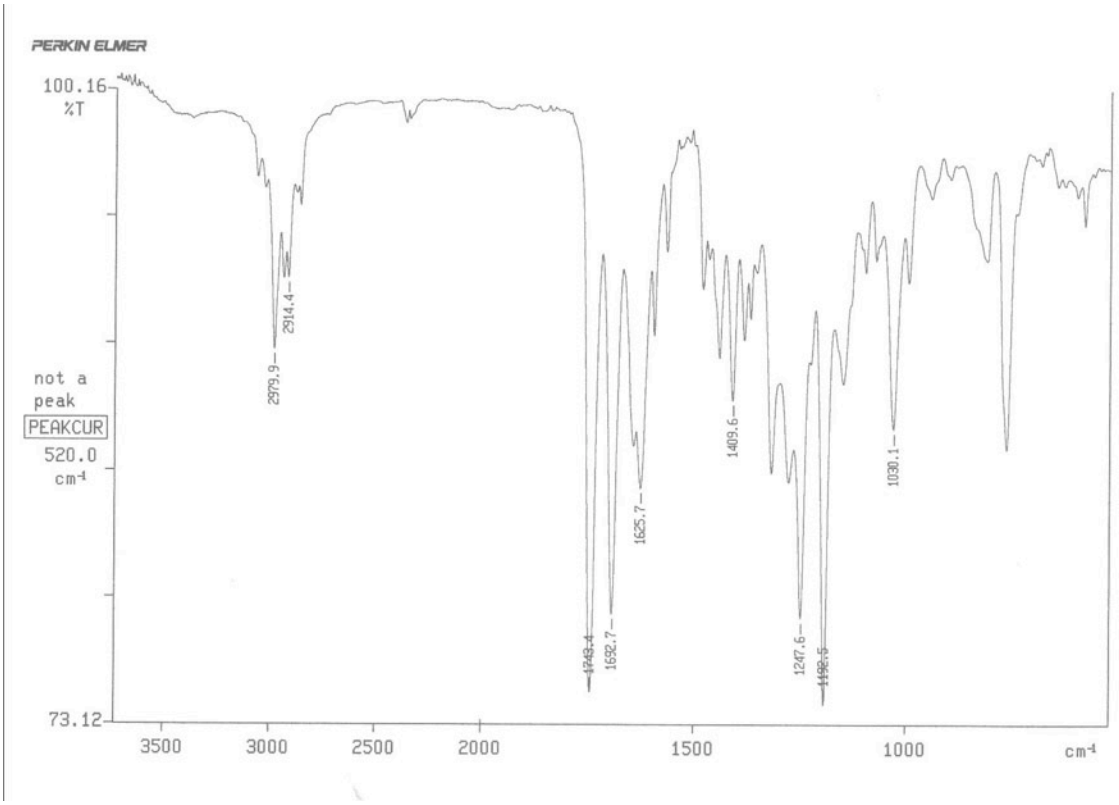


*Figure A2.1.114 IR spectrum (thin film/NaCl) of **115.***

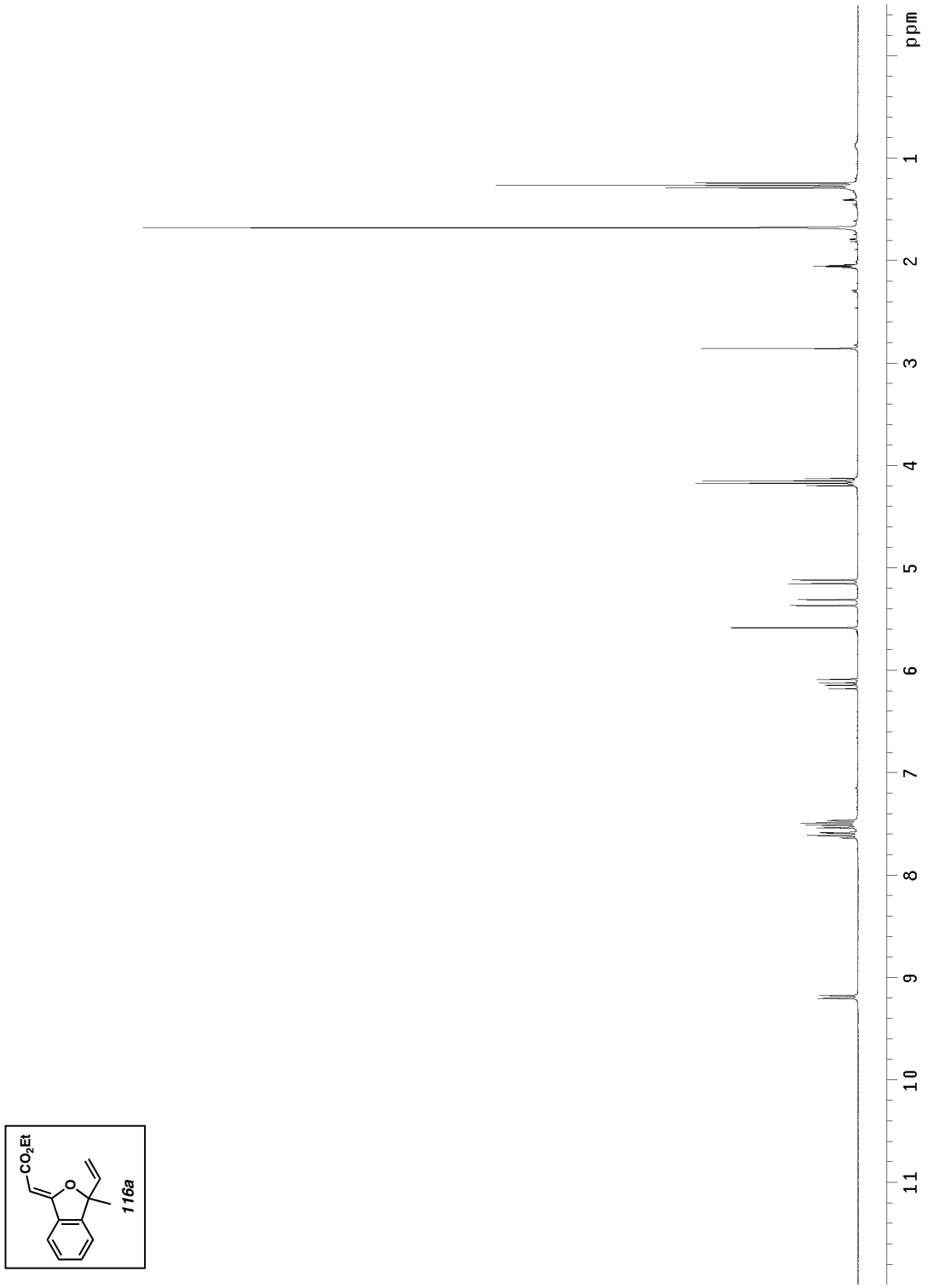


*Figure A2.1.115 ^{1}H NMR spectrum (300 MHz, acetone-d_6) of **116a**.*

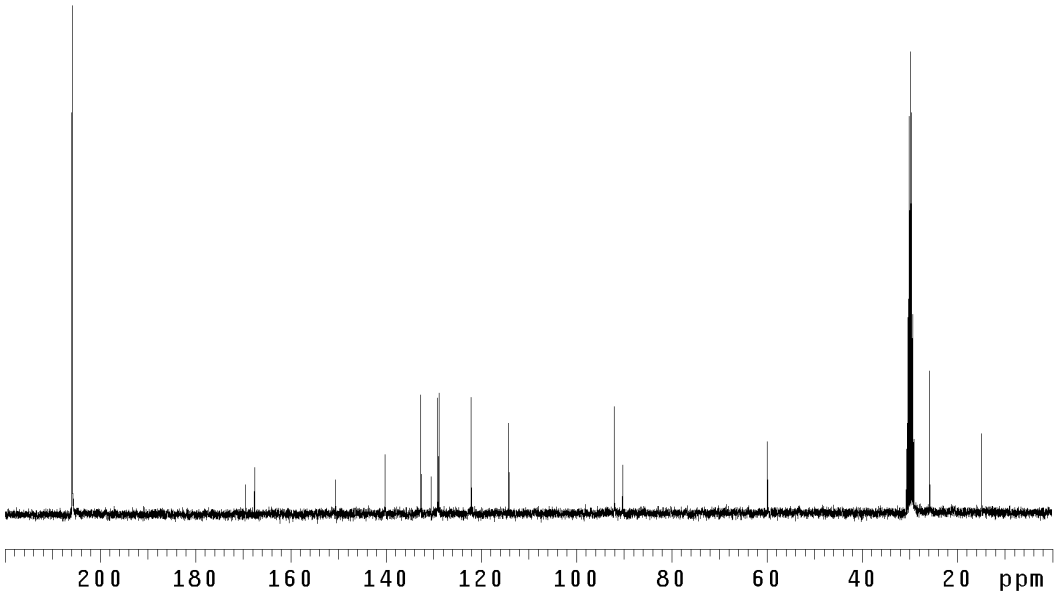


*Figure A2.1.116 ^{13}C NMR spectrum (75 MHz, acetone-d_6) of **116a**.*

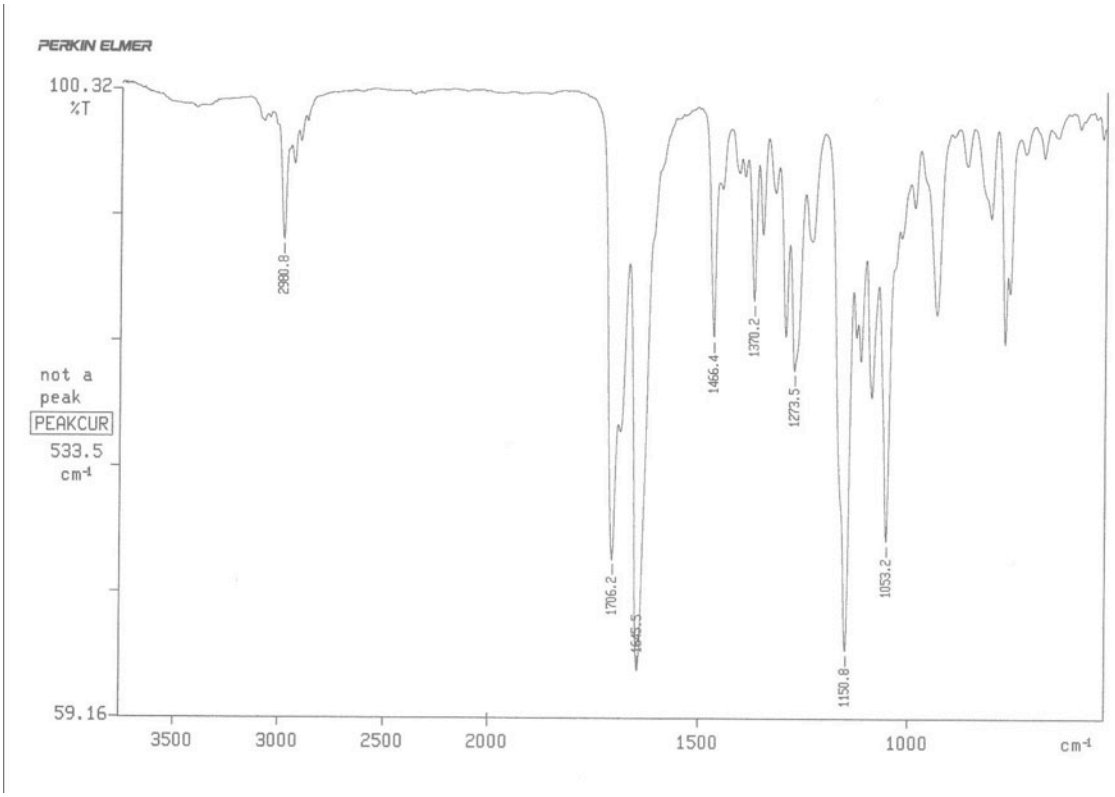


*Figure A2.1.117 IR spectrum (thin film/NaCl) of **116a**.*

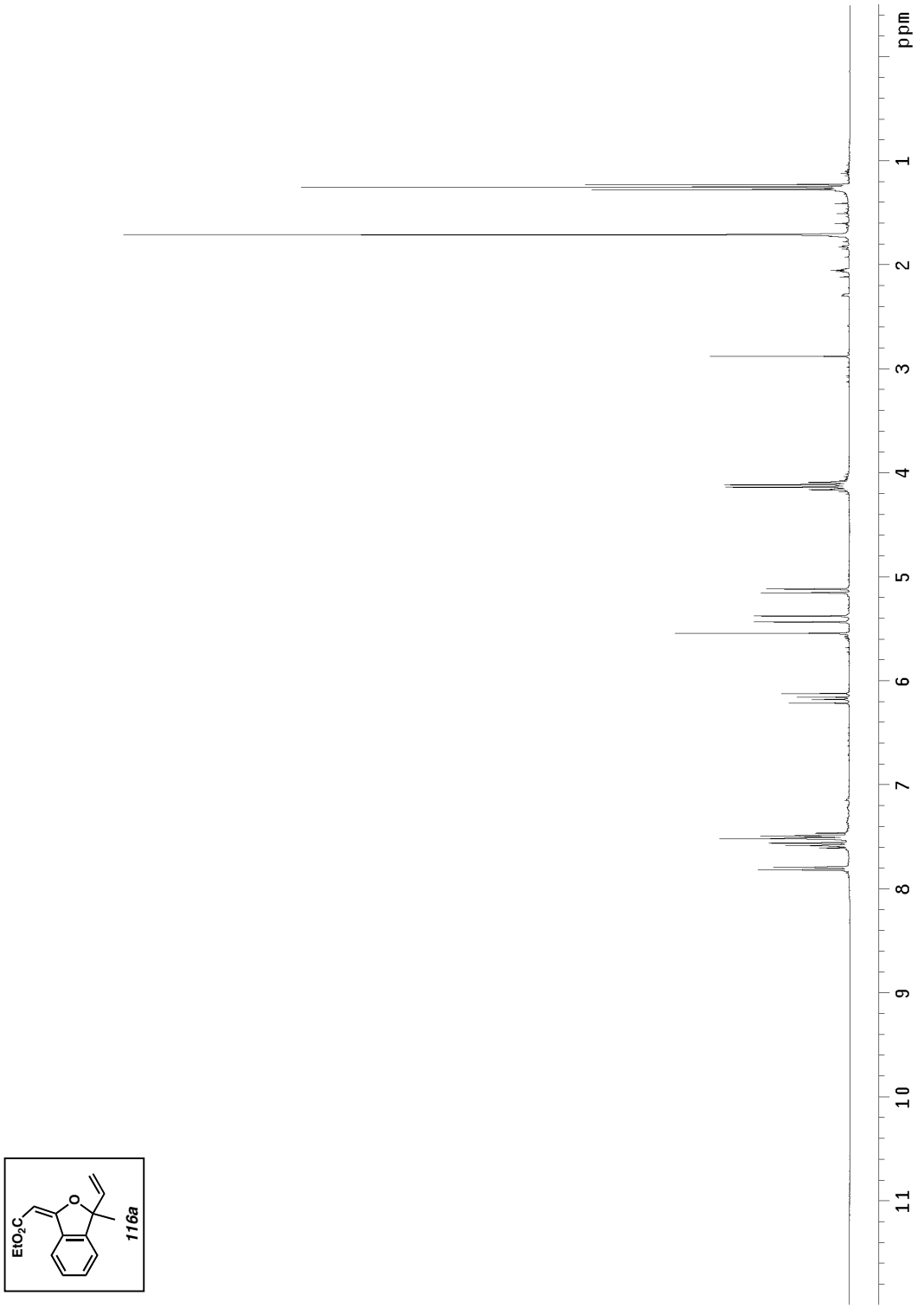


*Figure A2.1.118 ^{1}H NMR spectrum (300 MHz, acetone-d_6) of **116b**.*

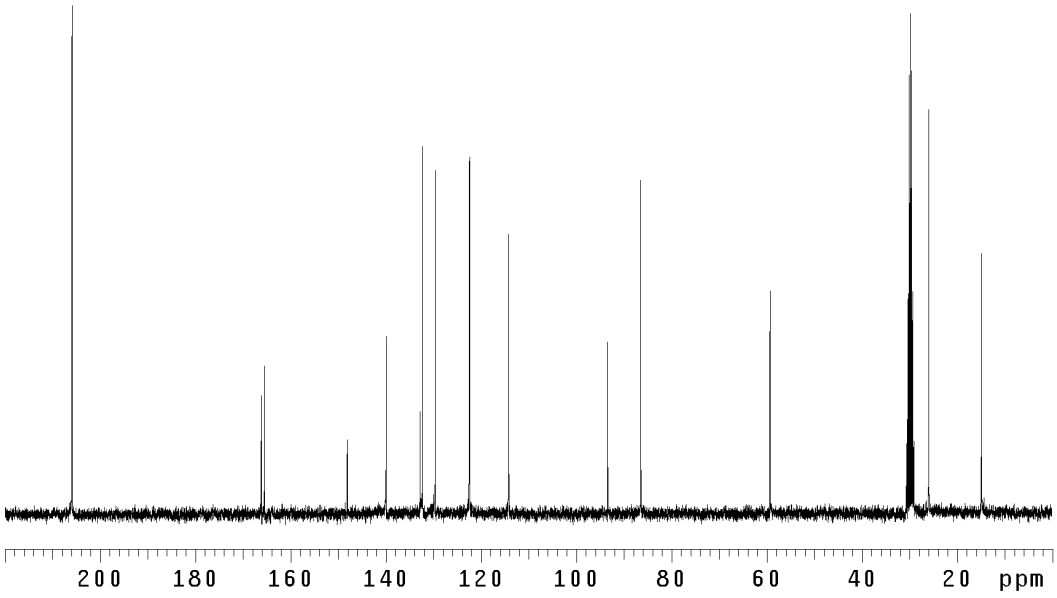


*Figure A2.1.119 ^{13}C NMR spectrum (75 MHz, acetone-d_6) of **116b**.*

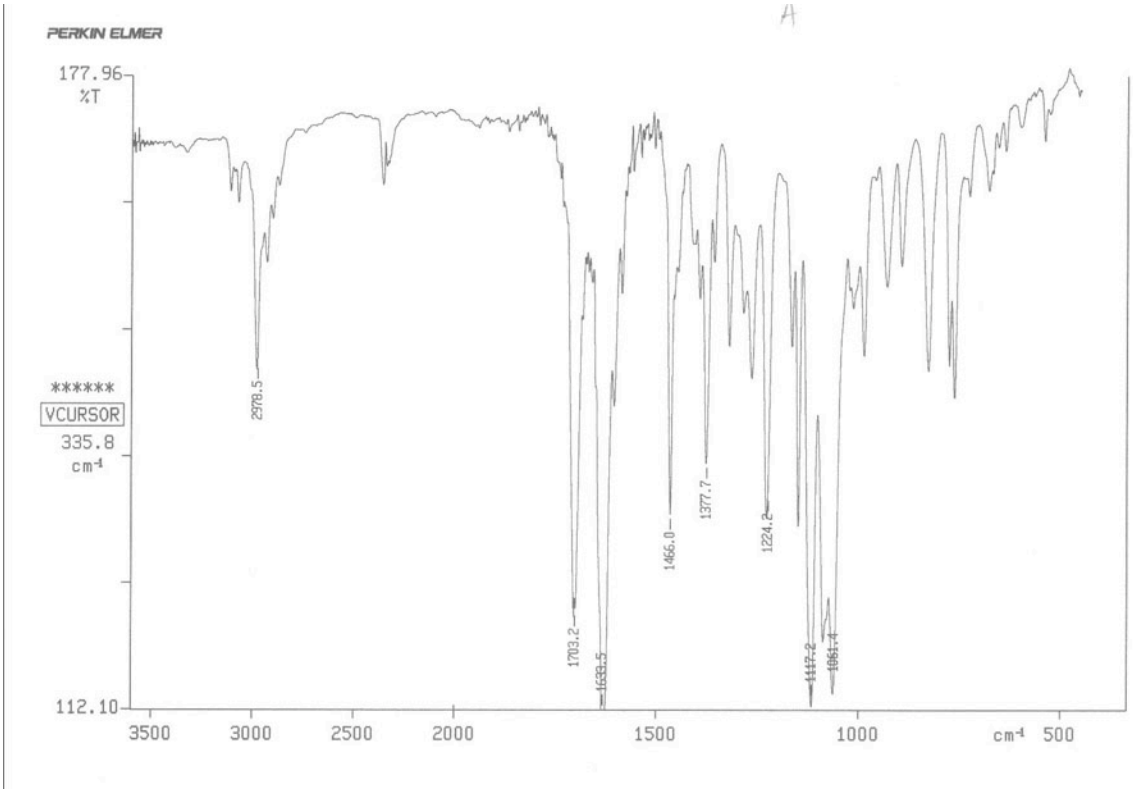


*Figure A2.1.120 IR spectrum (thin film/NaCl) of **116b**.*

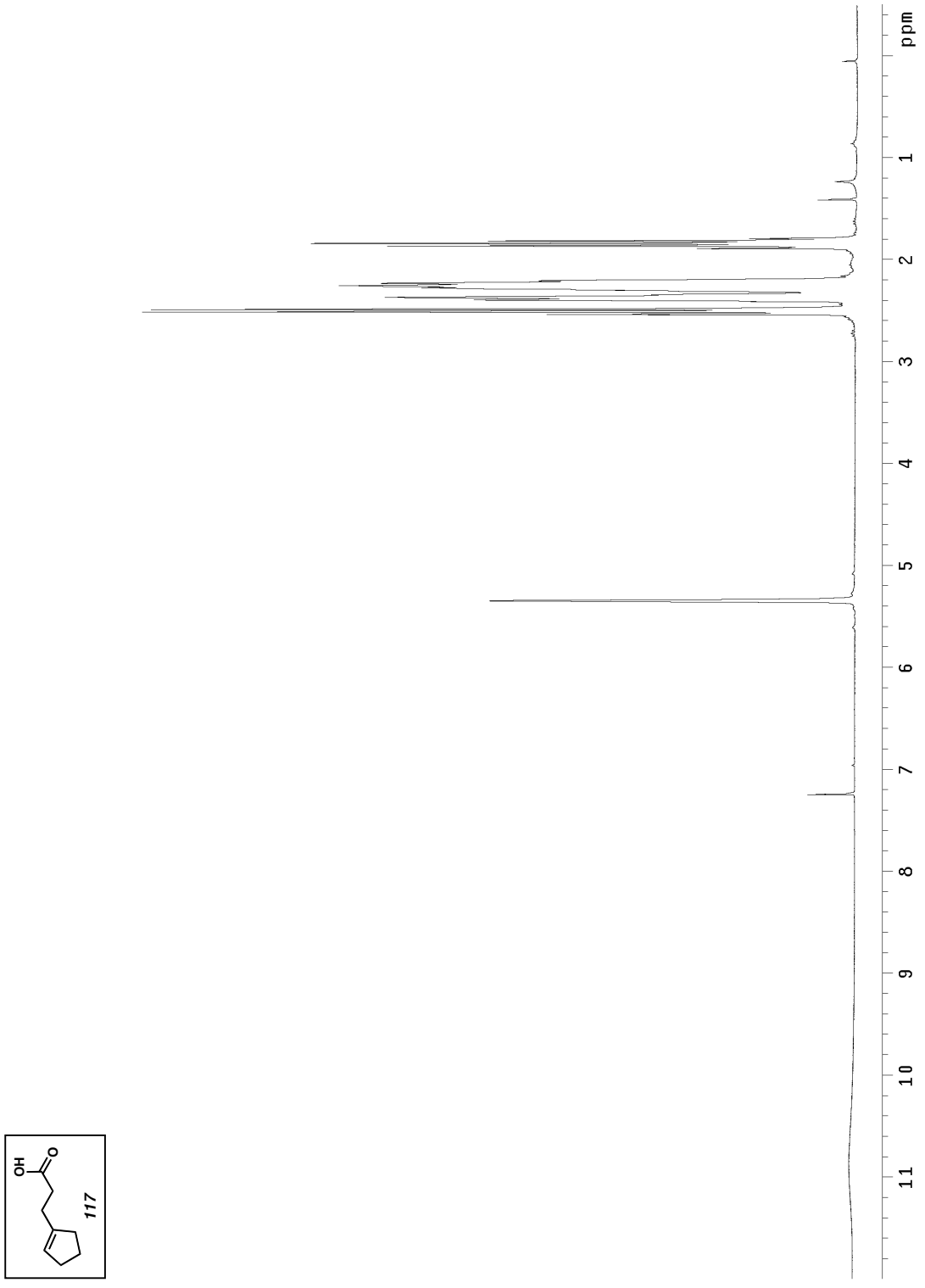


*Figure A2.1.121 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **117**.*

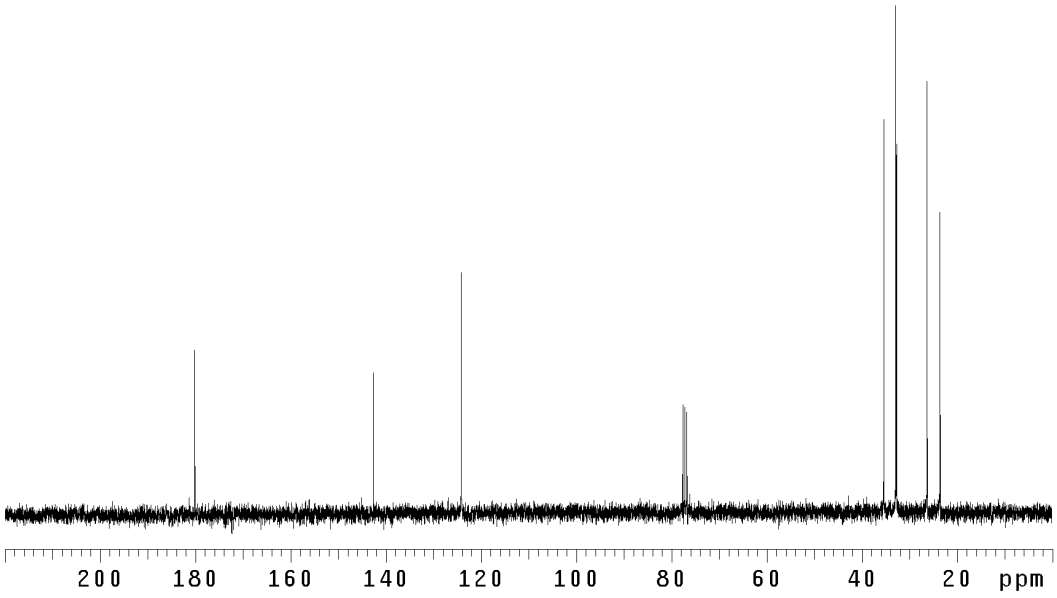


*Figure A2.1.122 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **117**.*

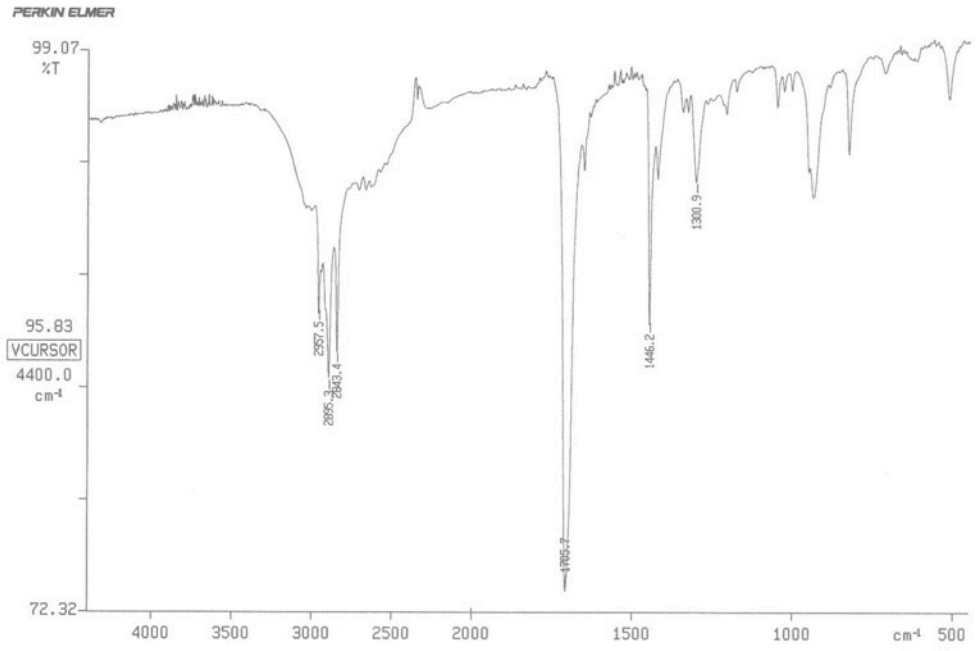


*Figure A2.1.123 IR spectrum (thin film/NaCl) of **117.***

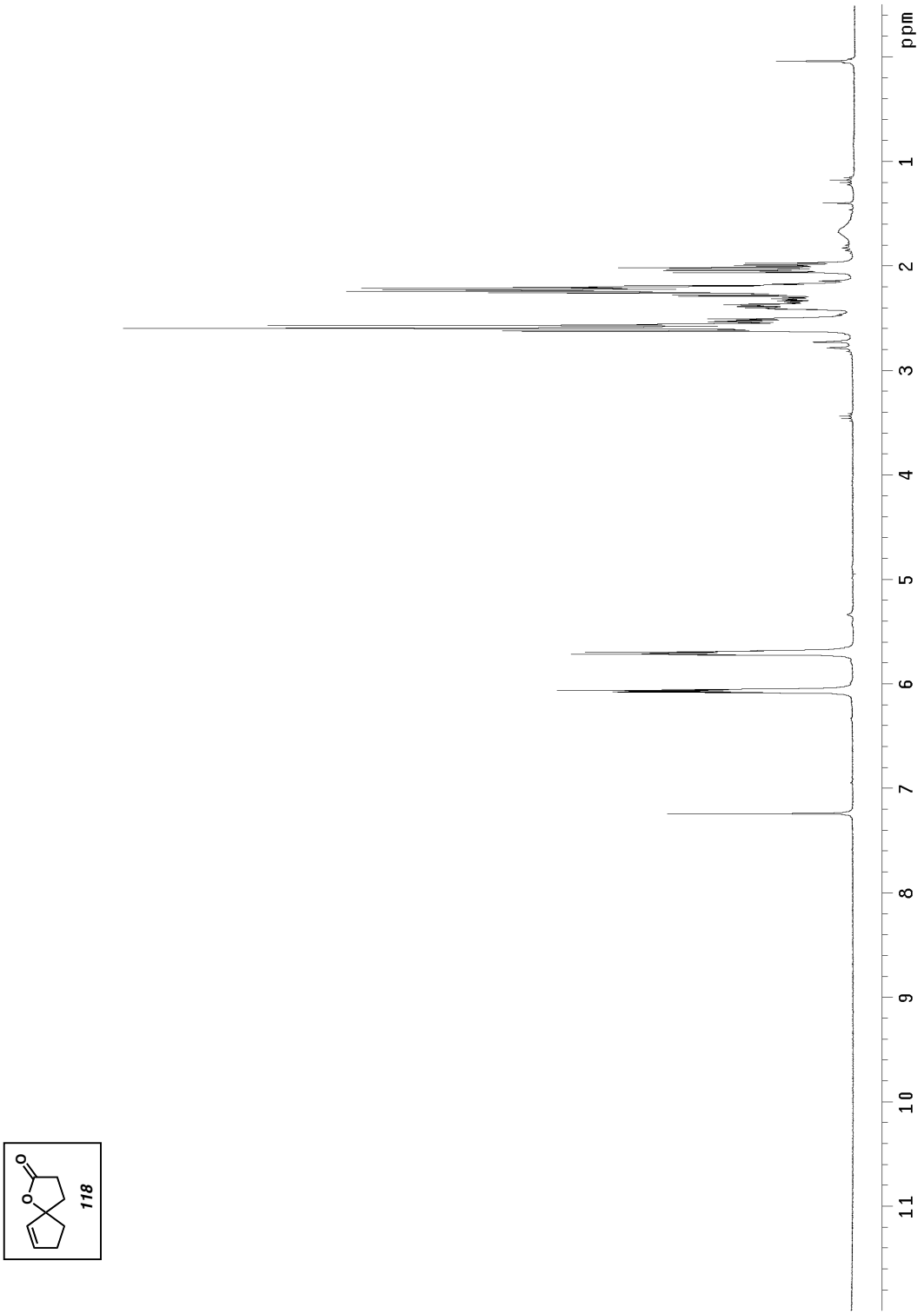


*Figure A2.1.124 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **118**.*

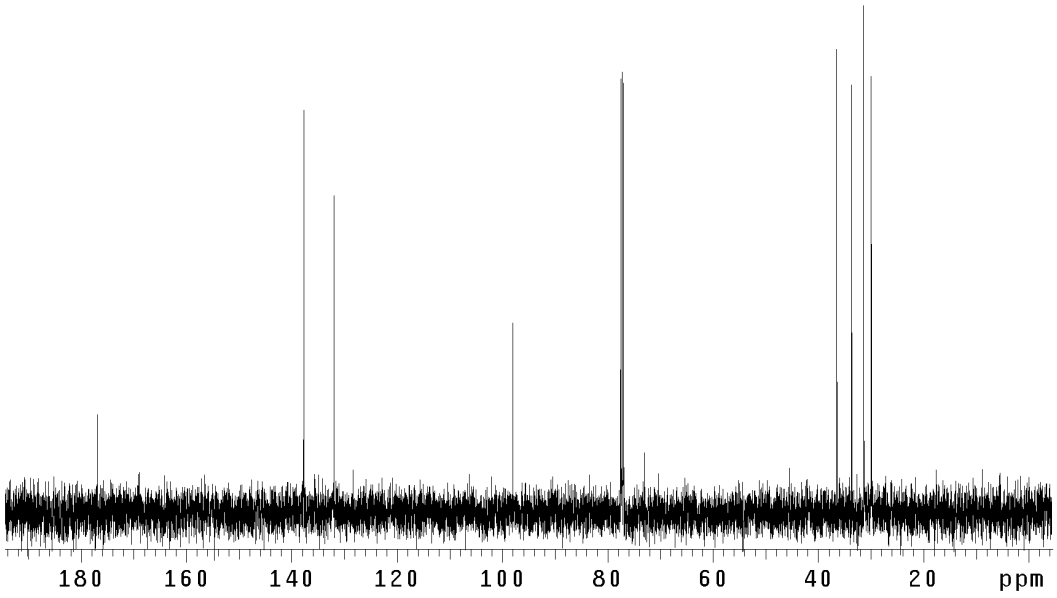


*Figure A2.1.125 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **118**.*

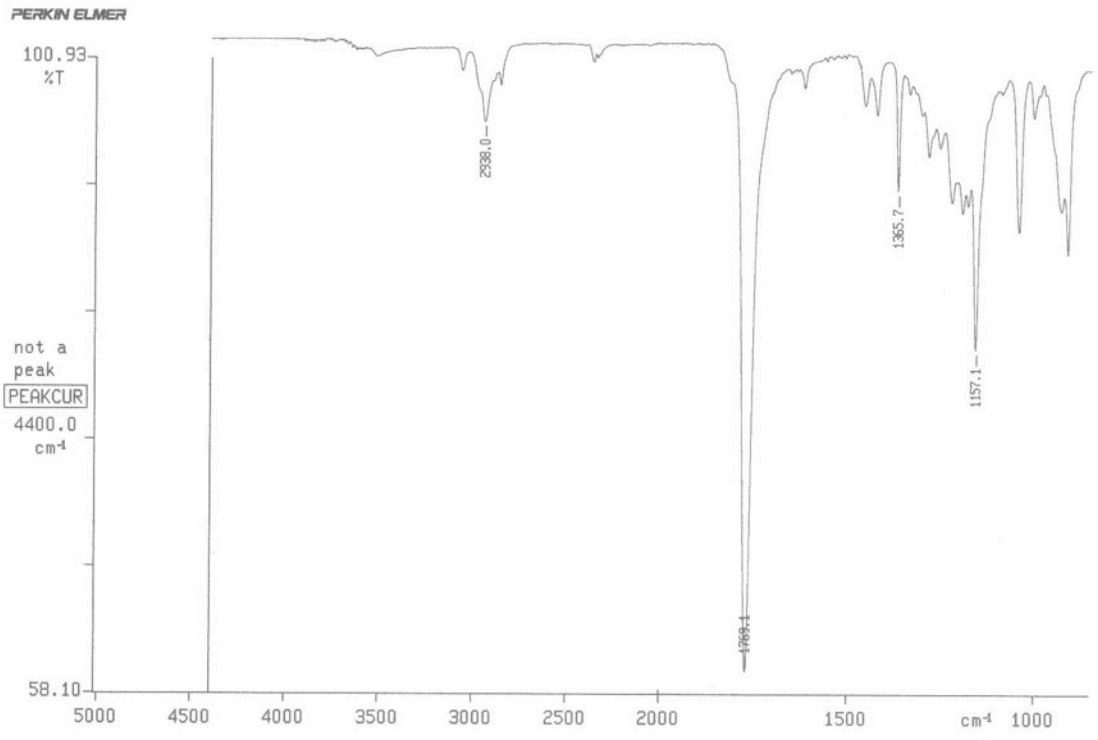


*Figure A2.1.126 IR spectrum (thin film/NaCl) of **118.***

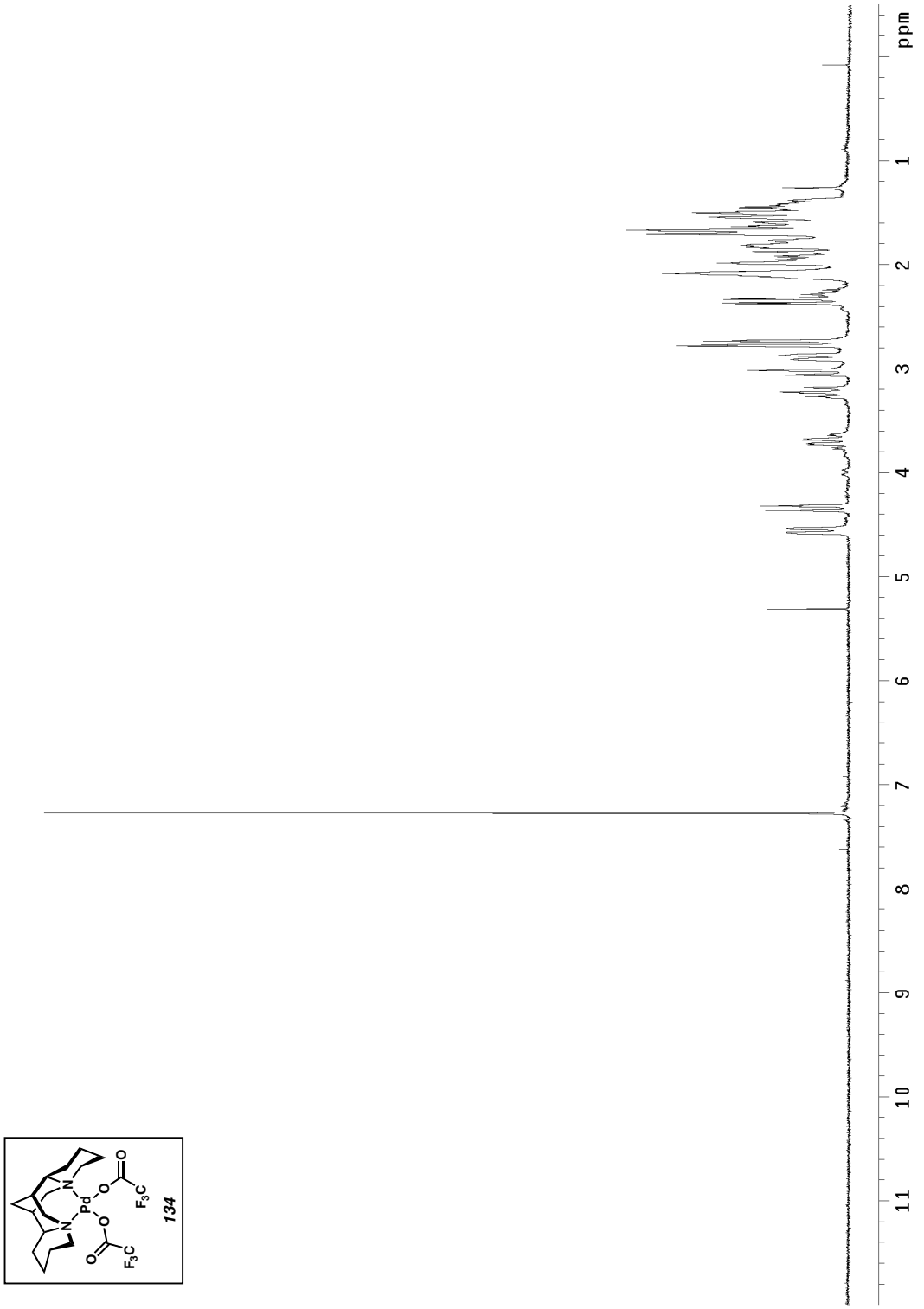


*Figure A2.1.127 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **134**.*

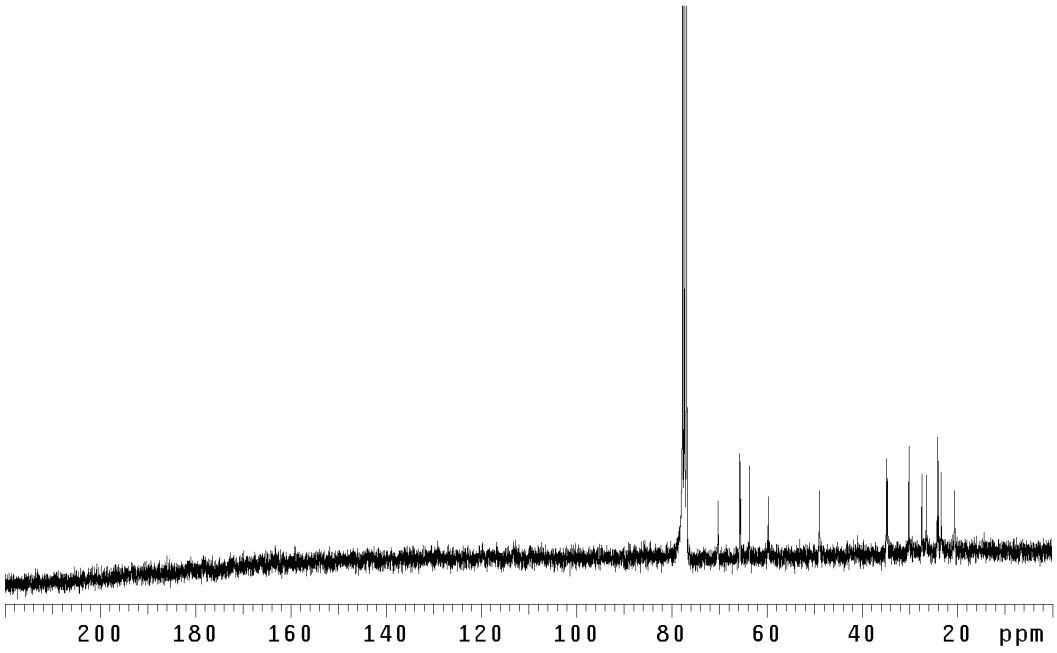


*Figure A2.1.128 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **134**.*

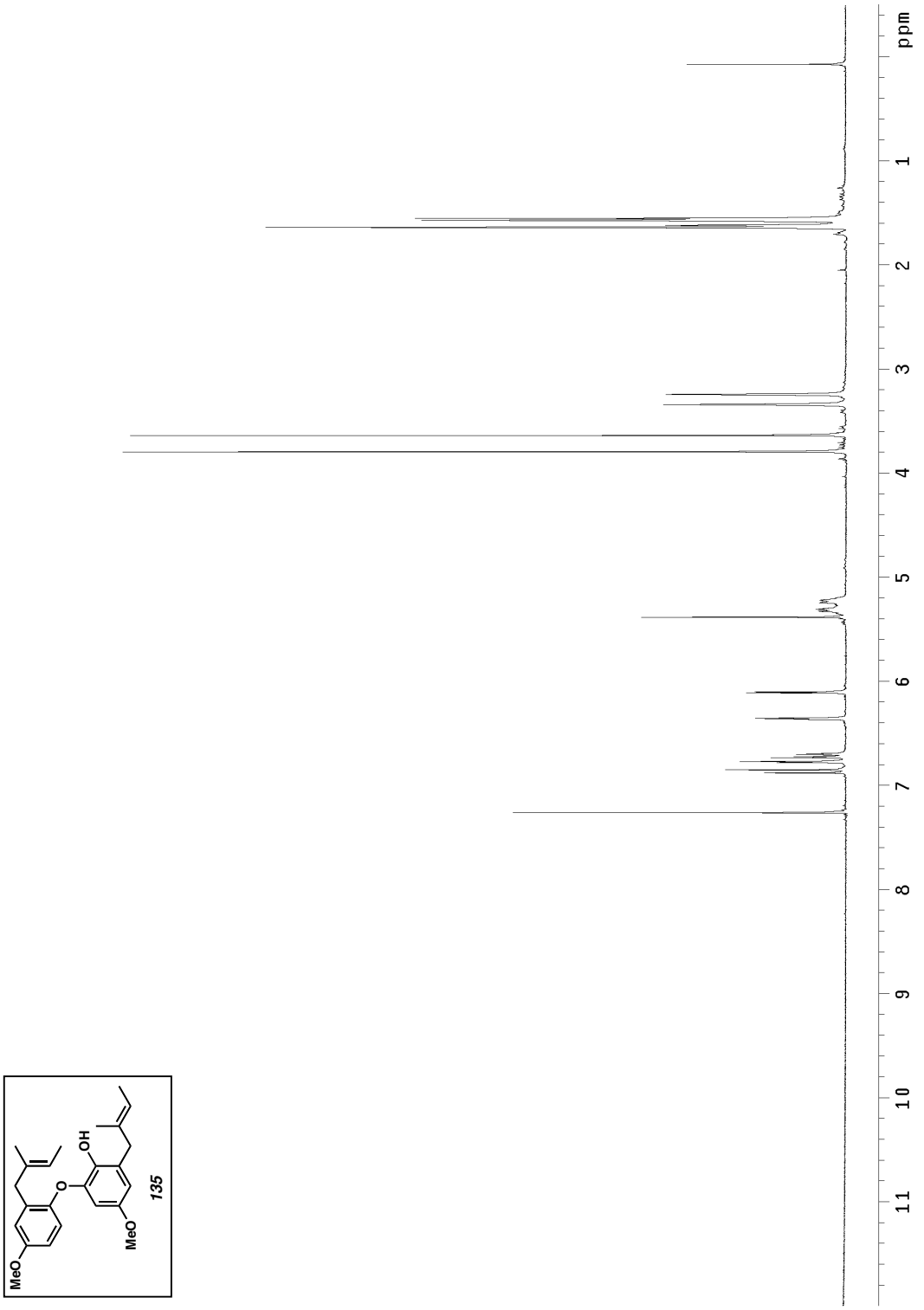


*Figure A2.1.129 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **135**.*

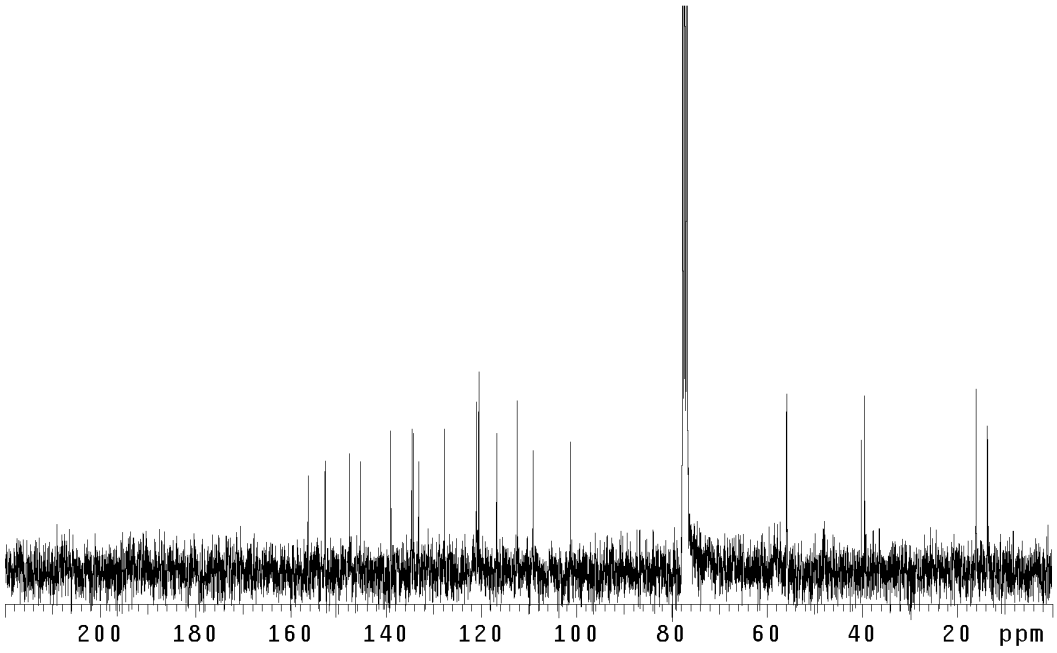


*Figure A2.1.130 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **135**.*

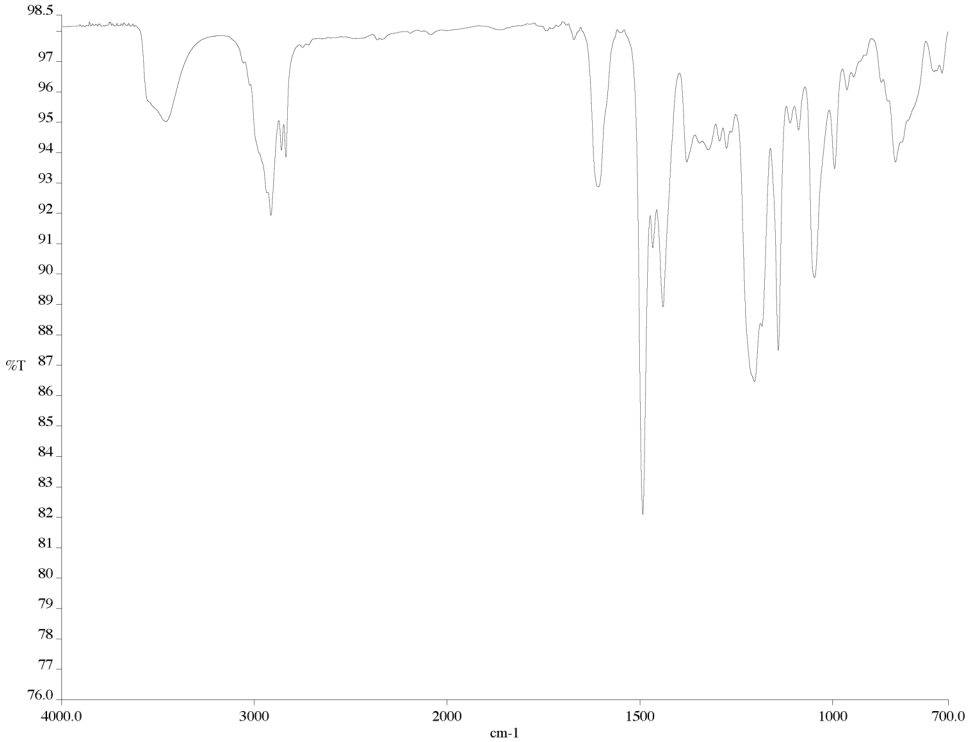


*Figure A2.1.131 IR spectrum (thin film/NaCl) of **135**.*

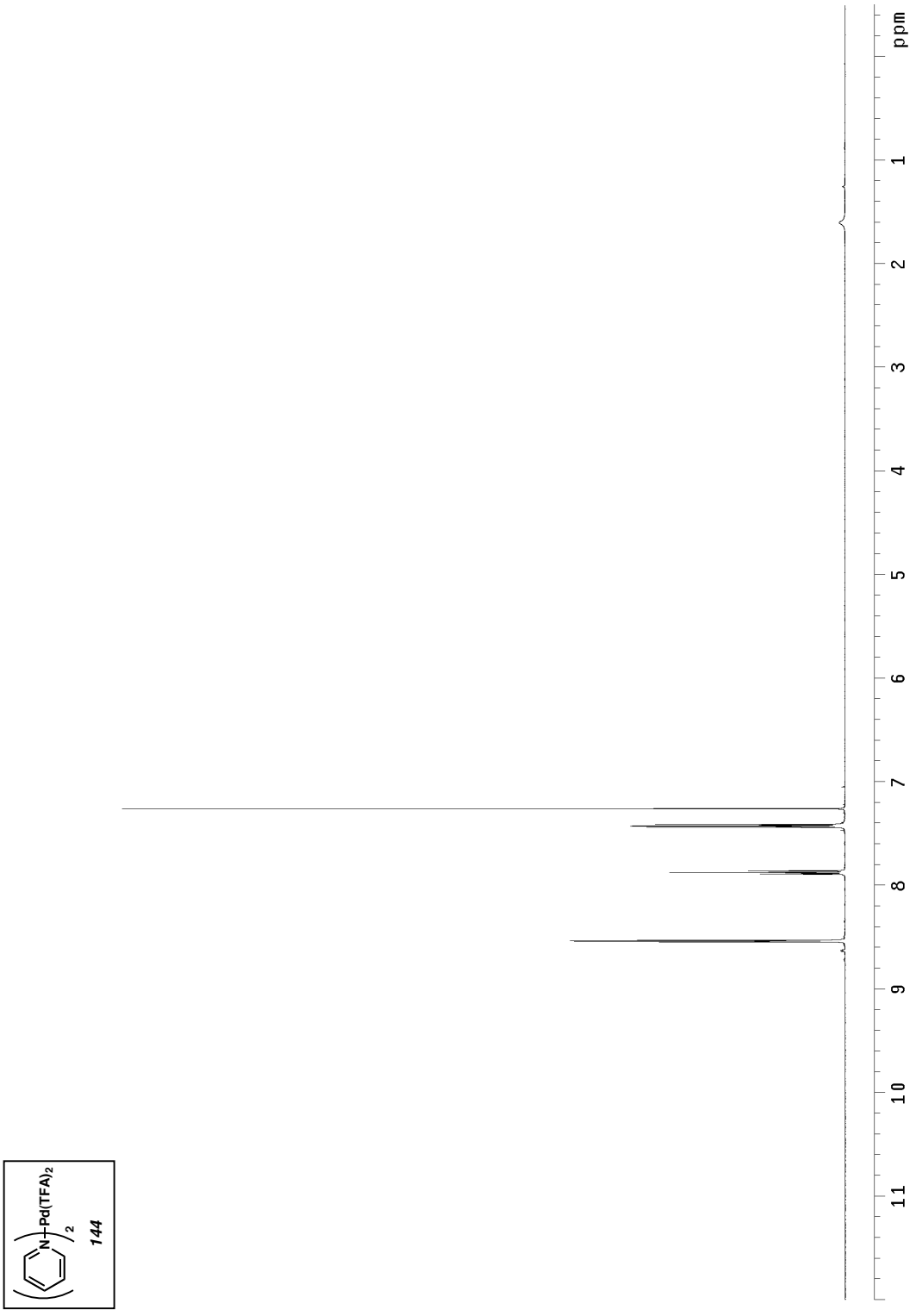


*Figure A2.1.132 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **144**.*

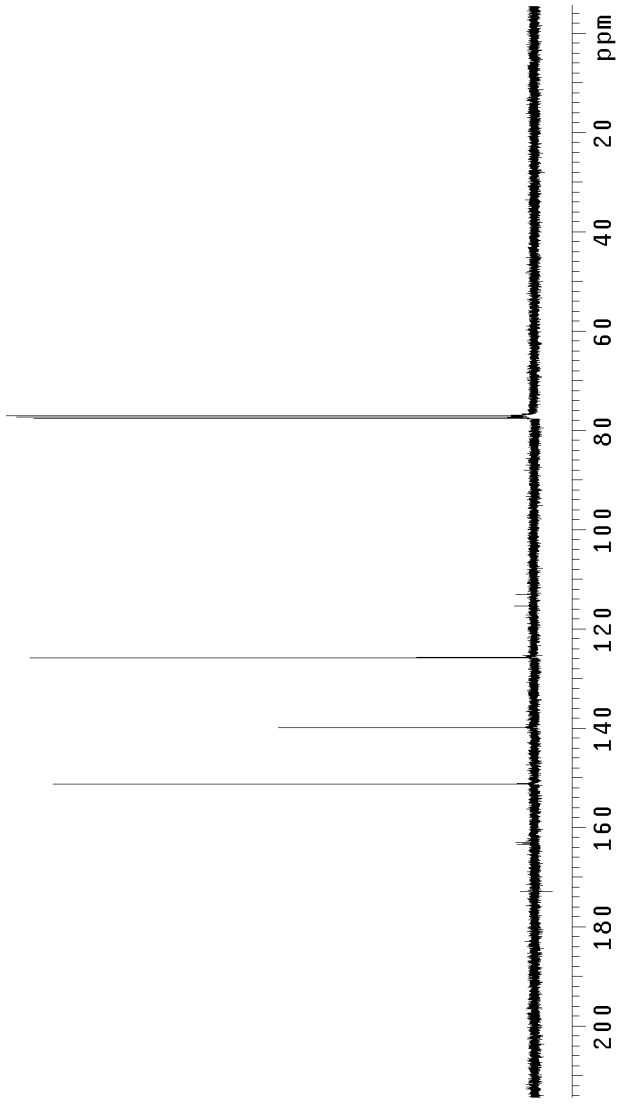


*Figure A2.1.133 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **144**.*

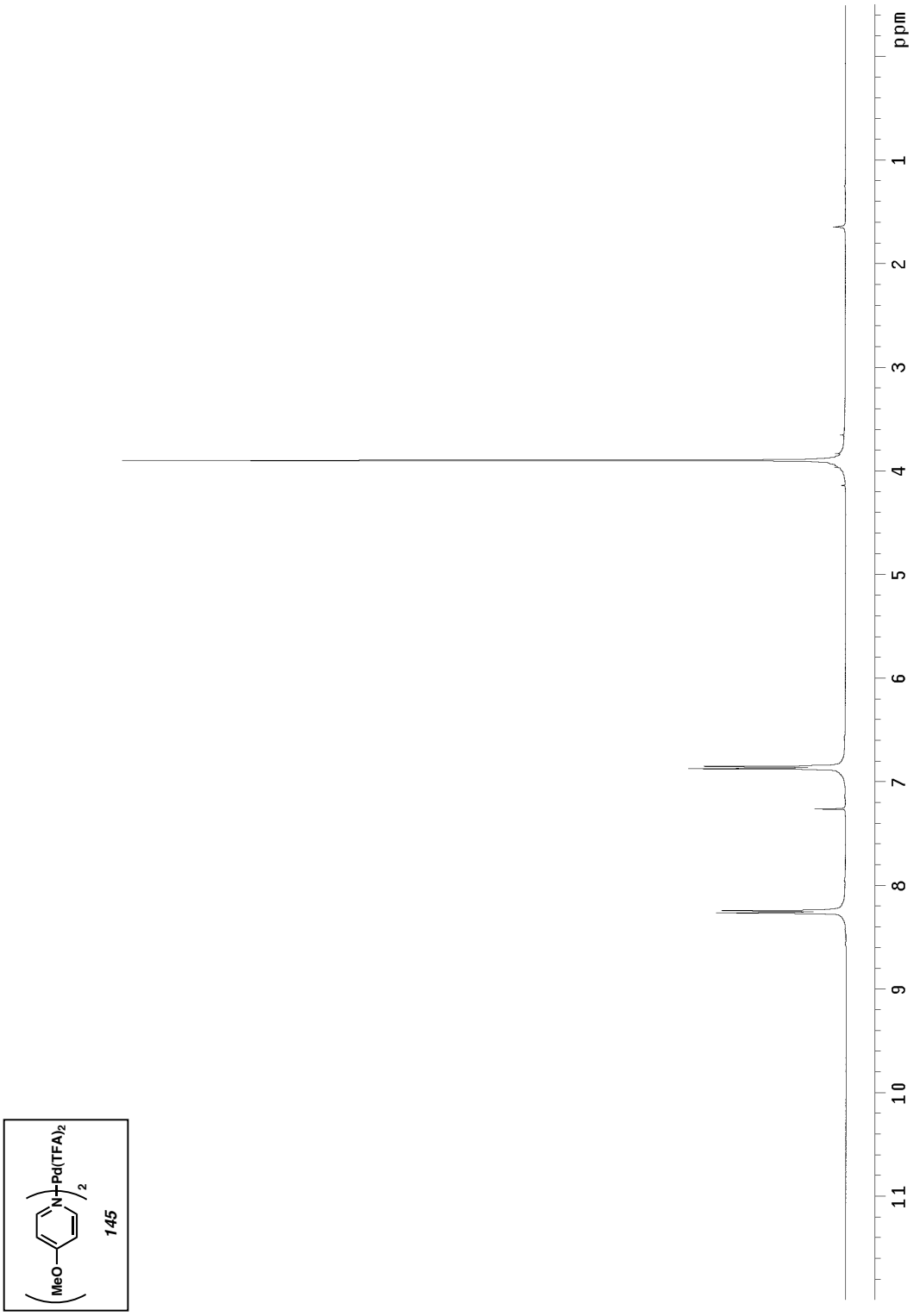


*Figure A2.1.134 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **145**.*

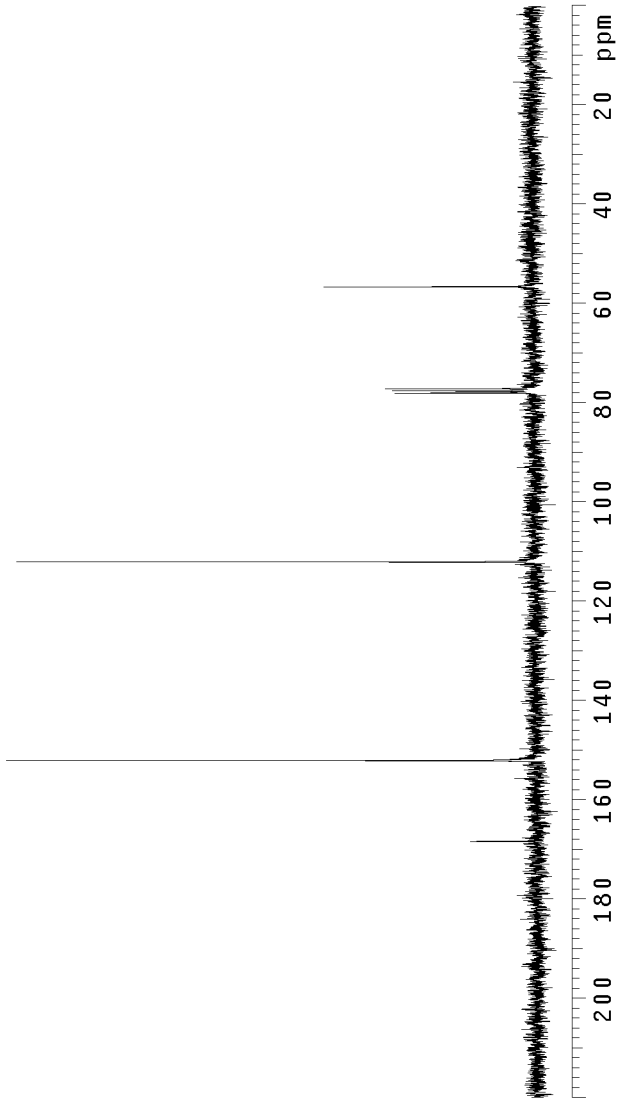


*Figure A2.1.135 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **145**.*

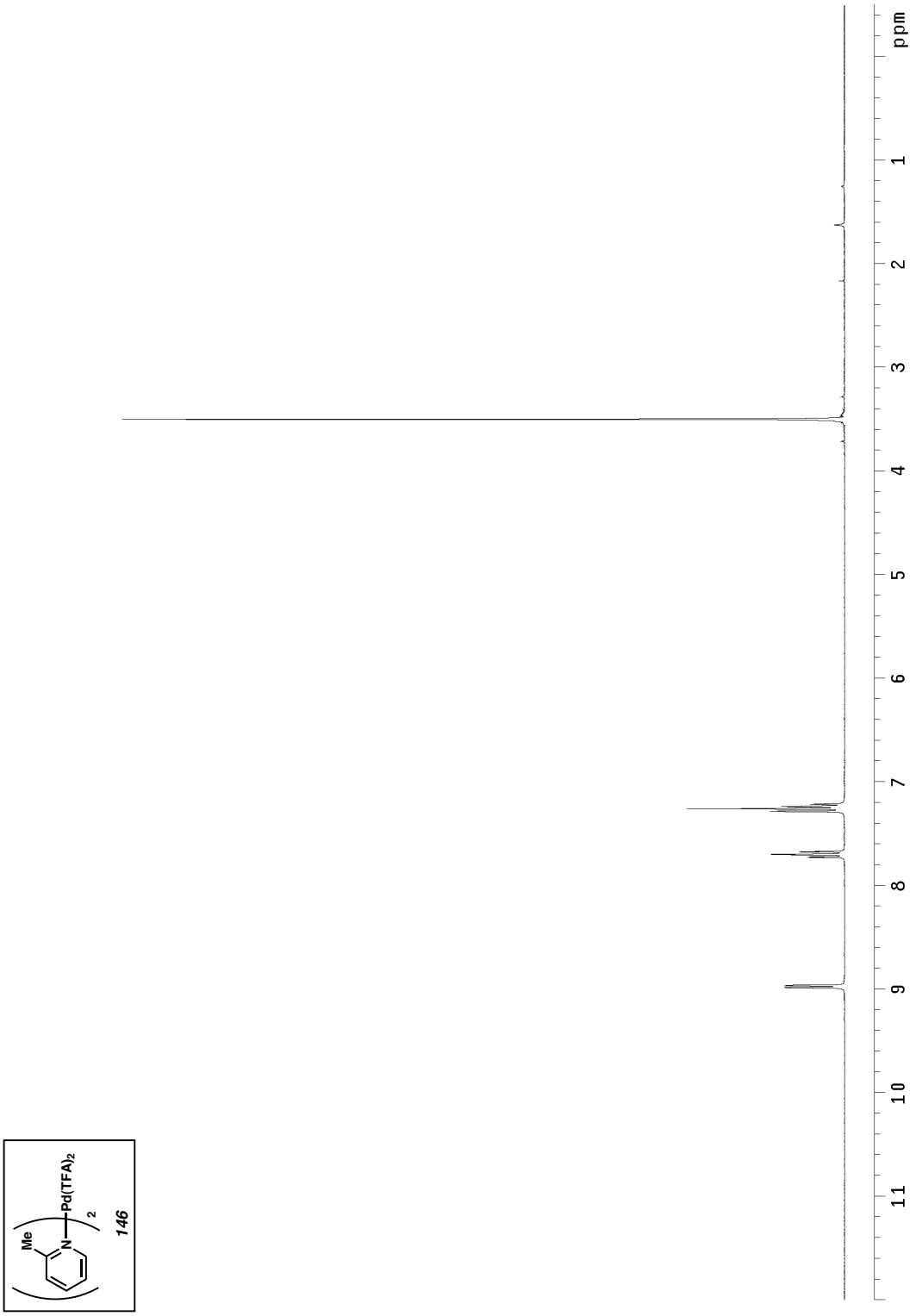


*Figure A2.1.136 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **146**.*

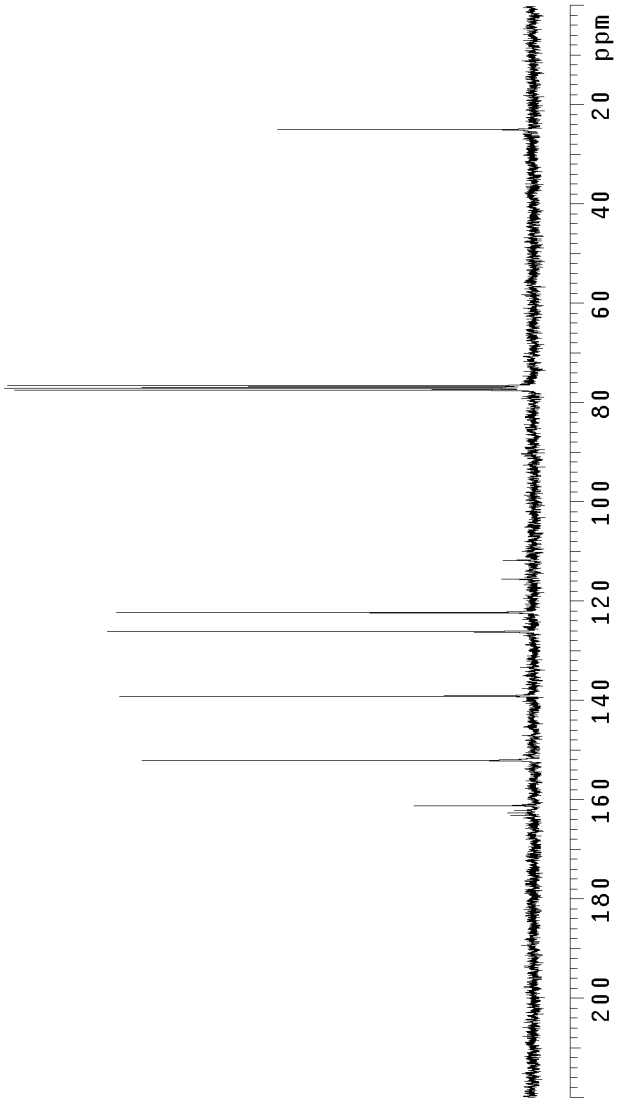


*Figure A2.1.137 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **146**.*

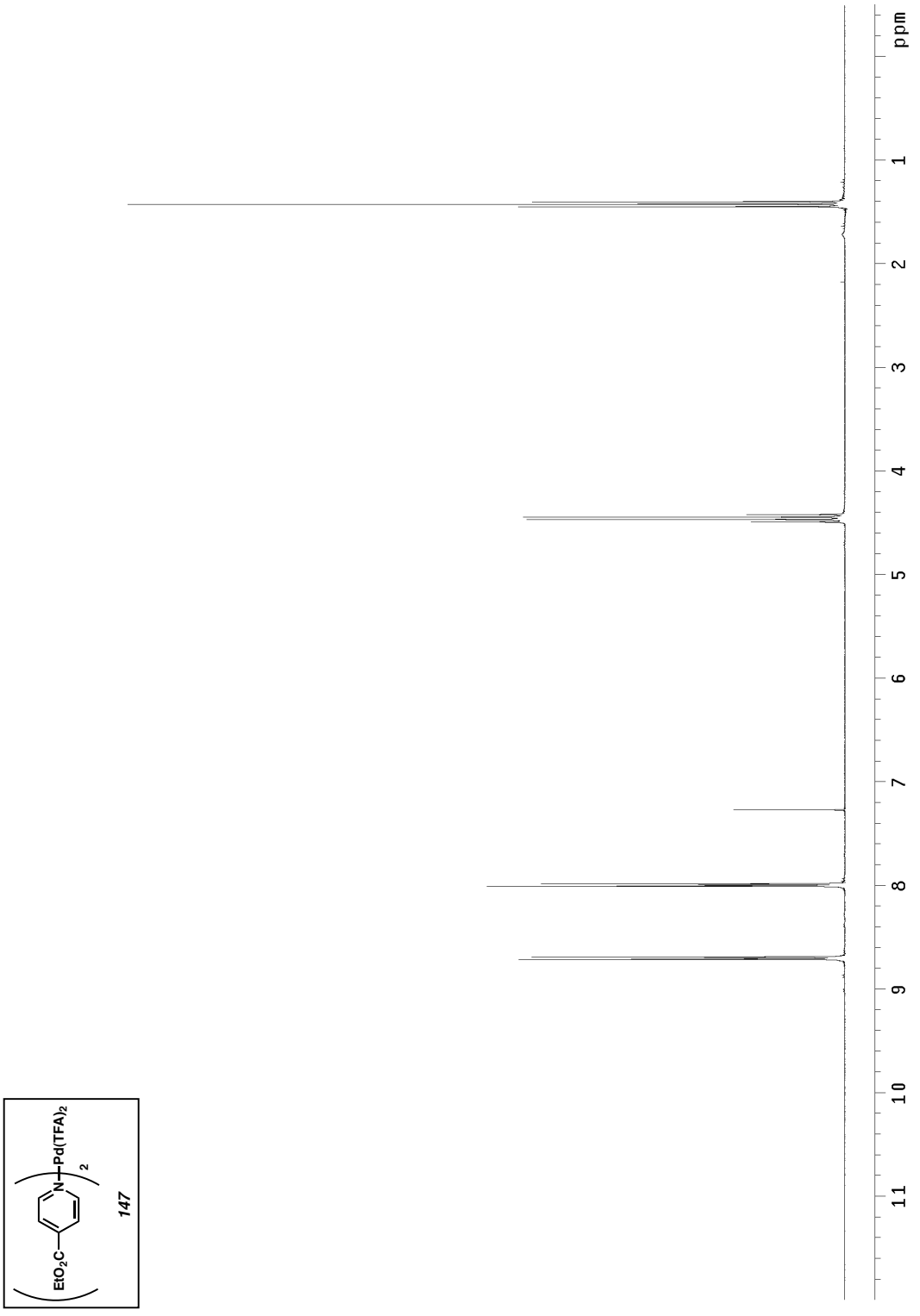


*Figure A2.1.138 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **147**.*

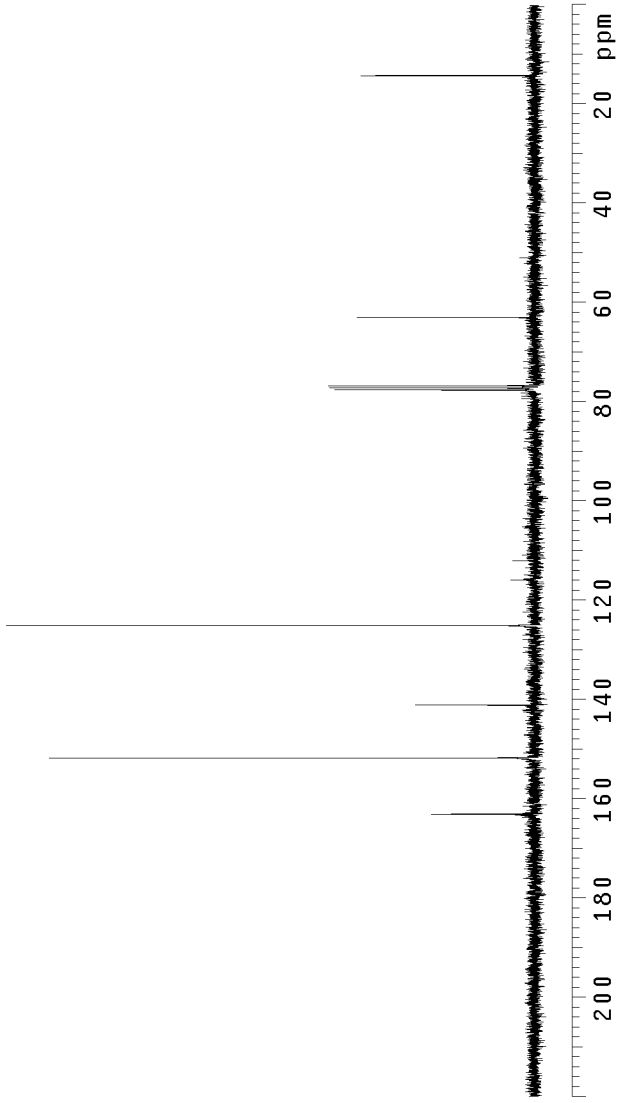


*Figure A2.1.139 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **147**.*

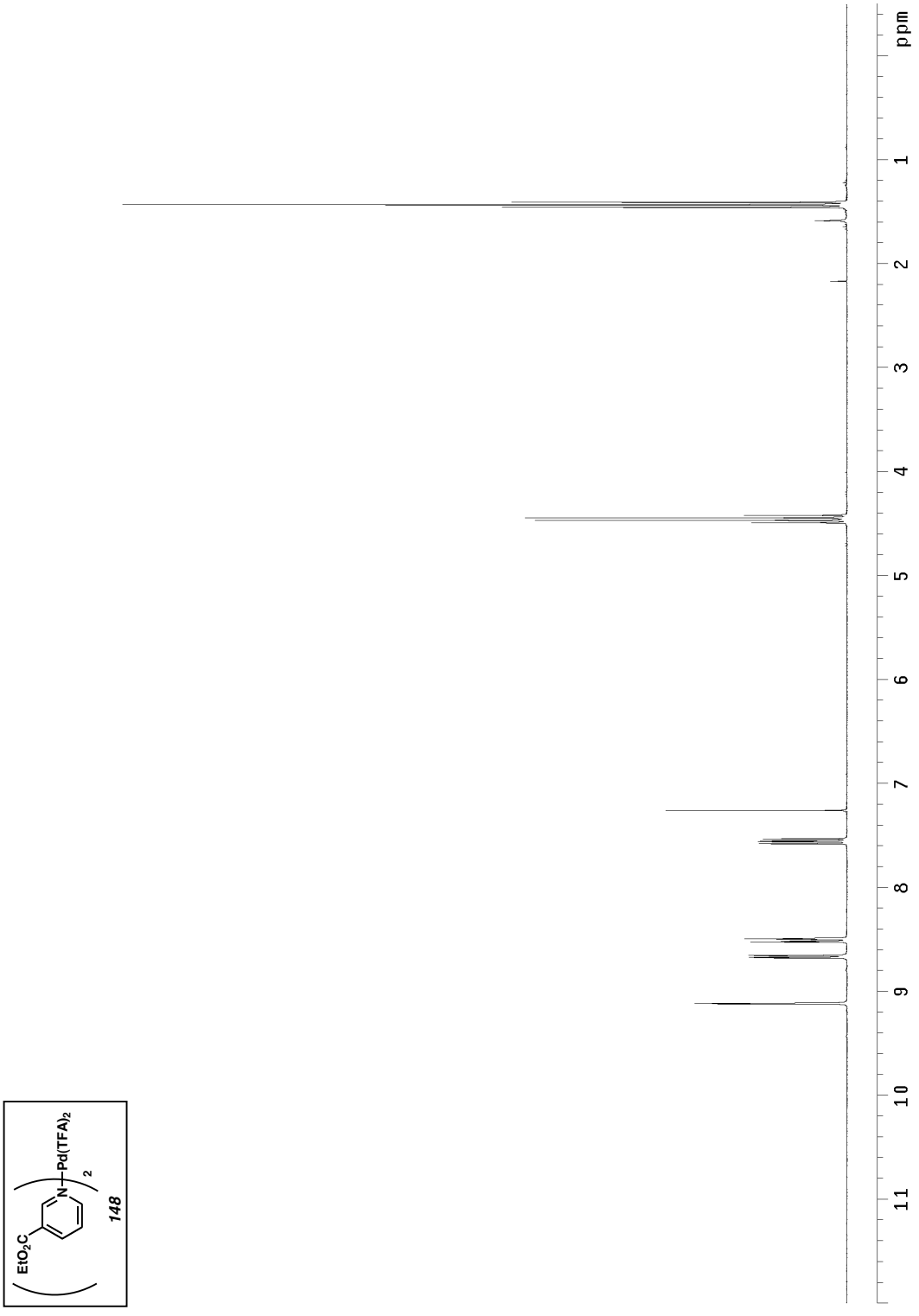


*Figure A2.1.140 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **148**.*

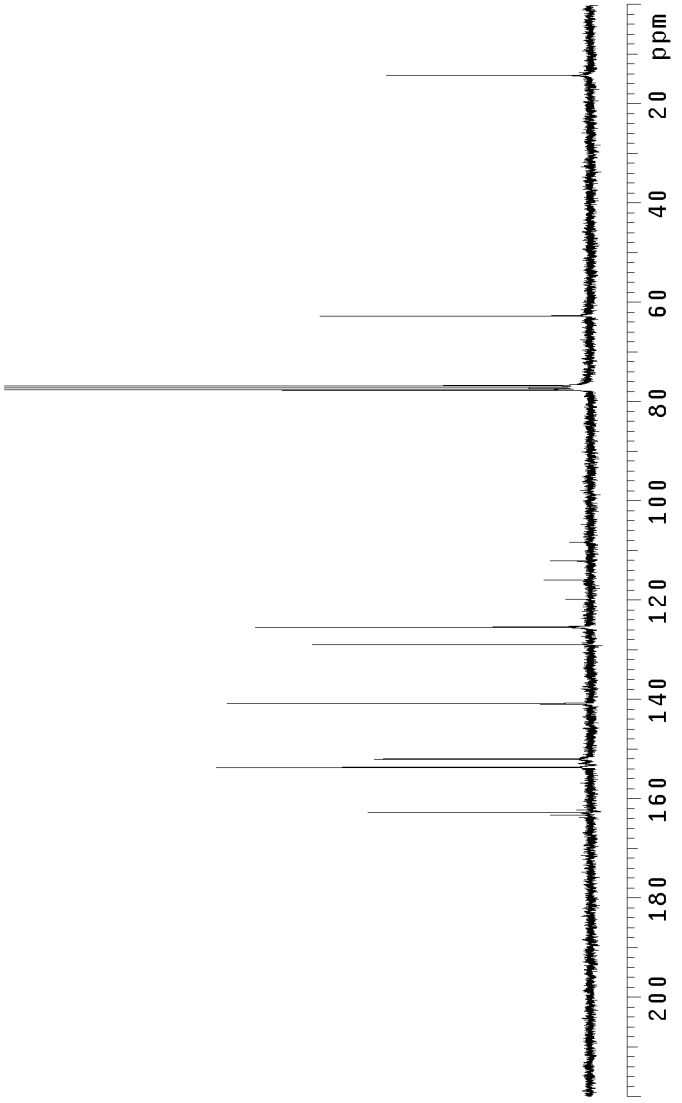


*Figure A2.1.141 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **148**.*

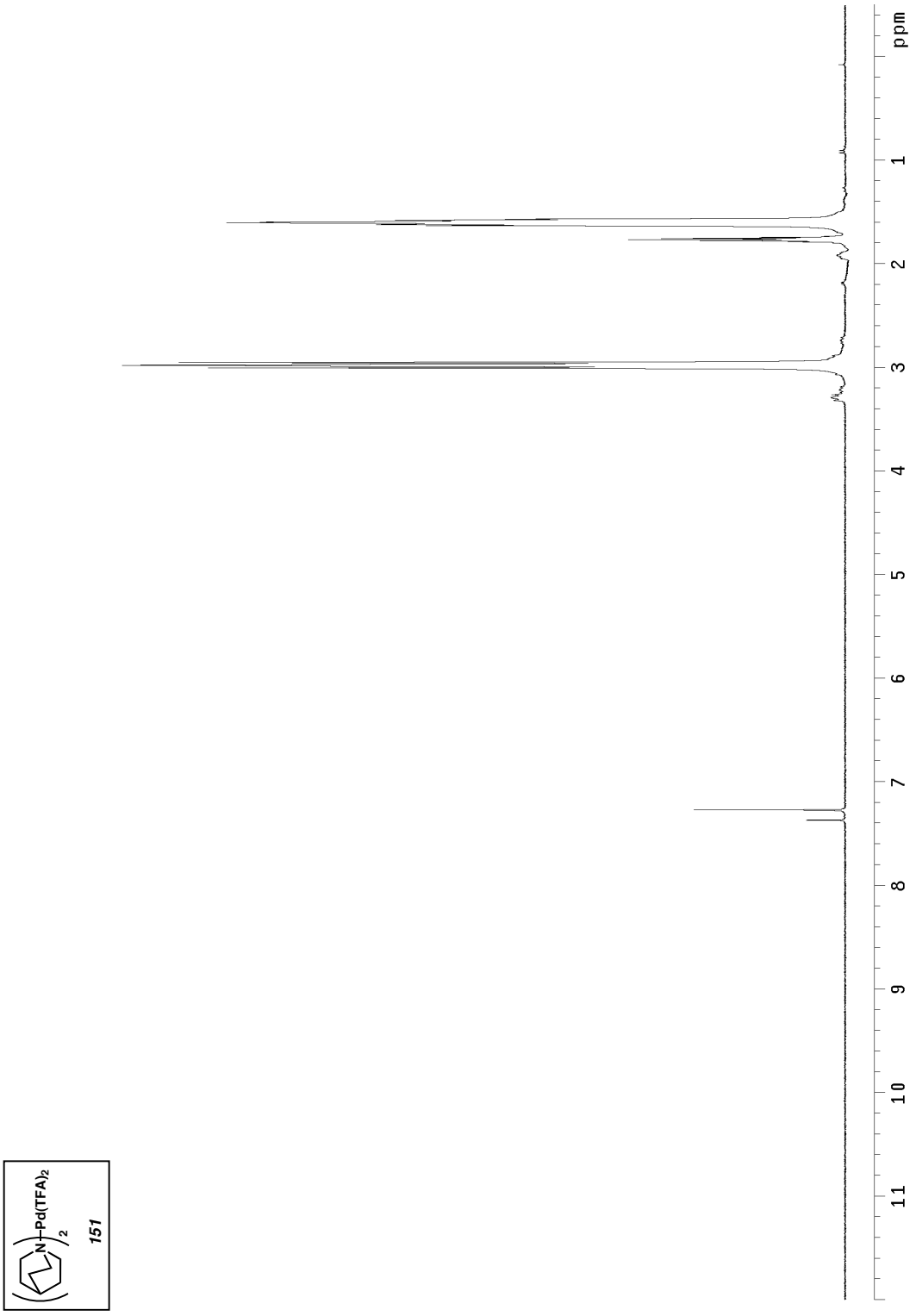


*Figure A2.1.142 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **151**.*

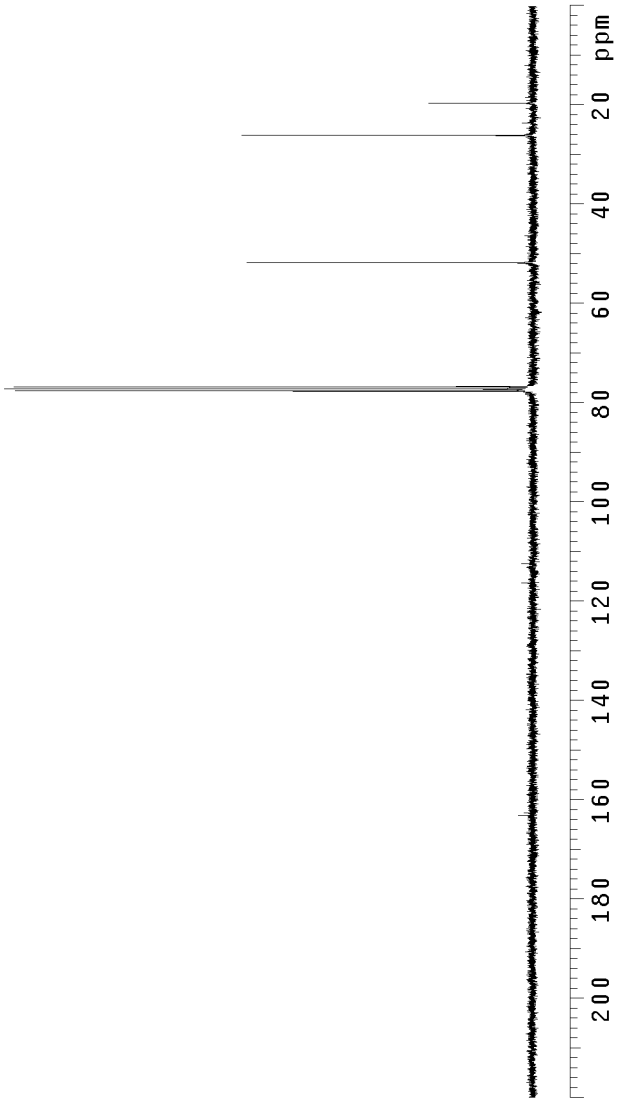


*Figure A2.1.143 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **151**.*

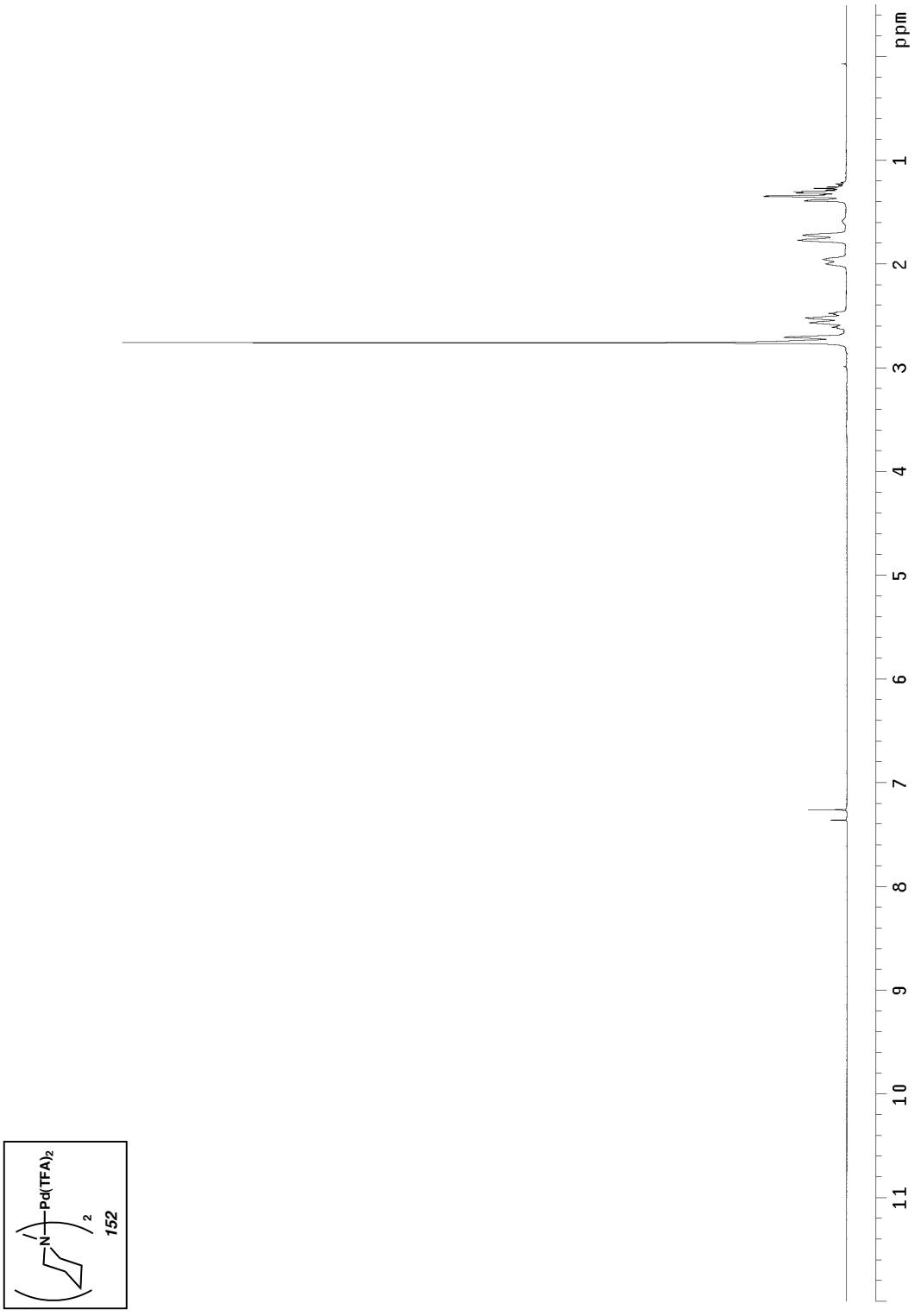


*Figure A2.1.144 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **152**.*

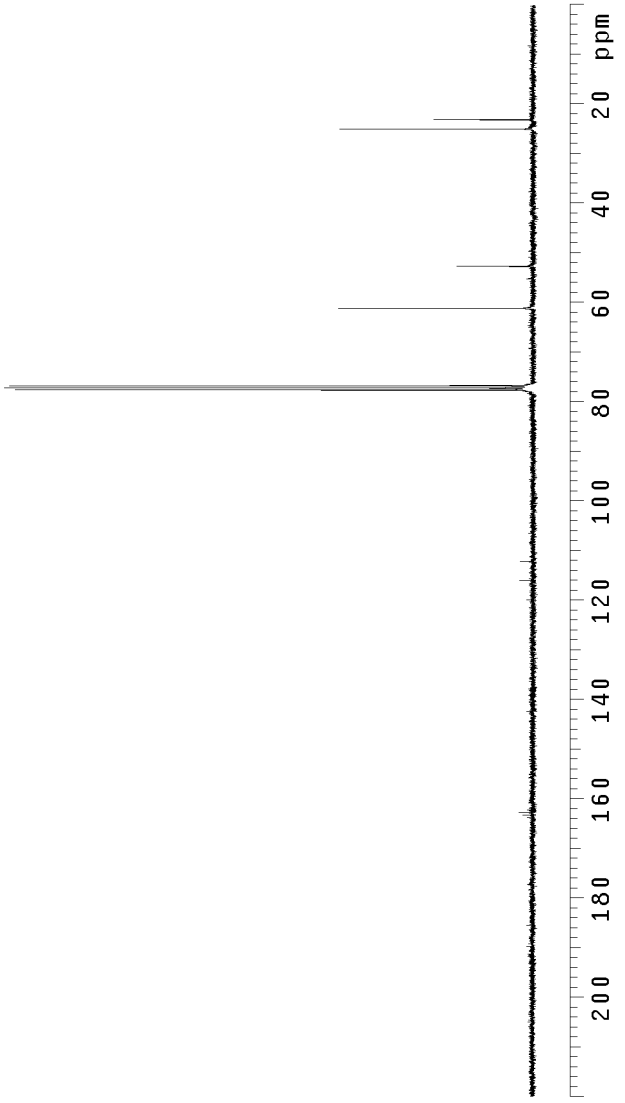


*Figure A2.1.145 ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **152**.*

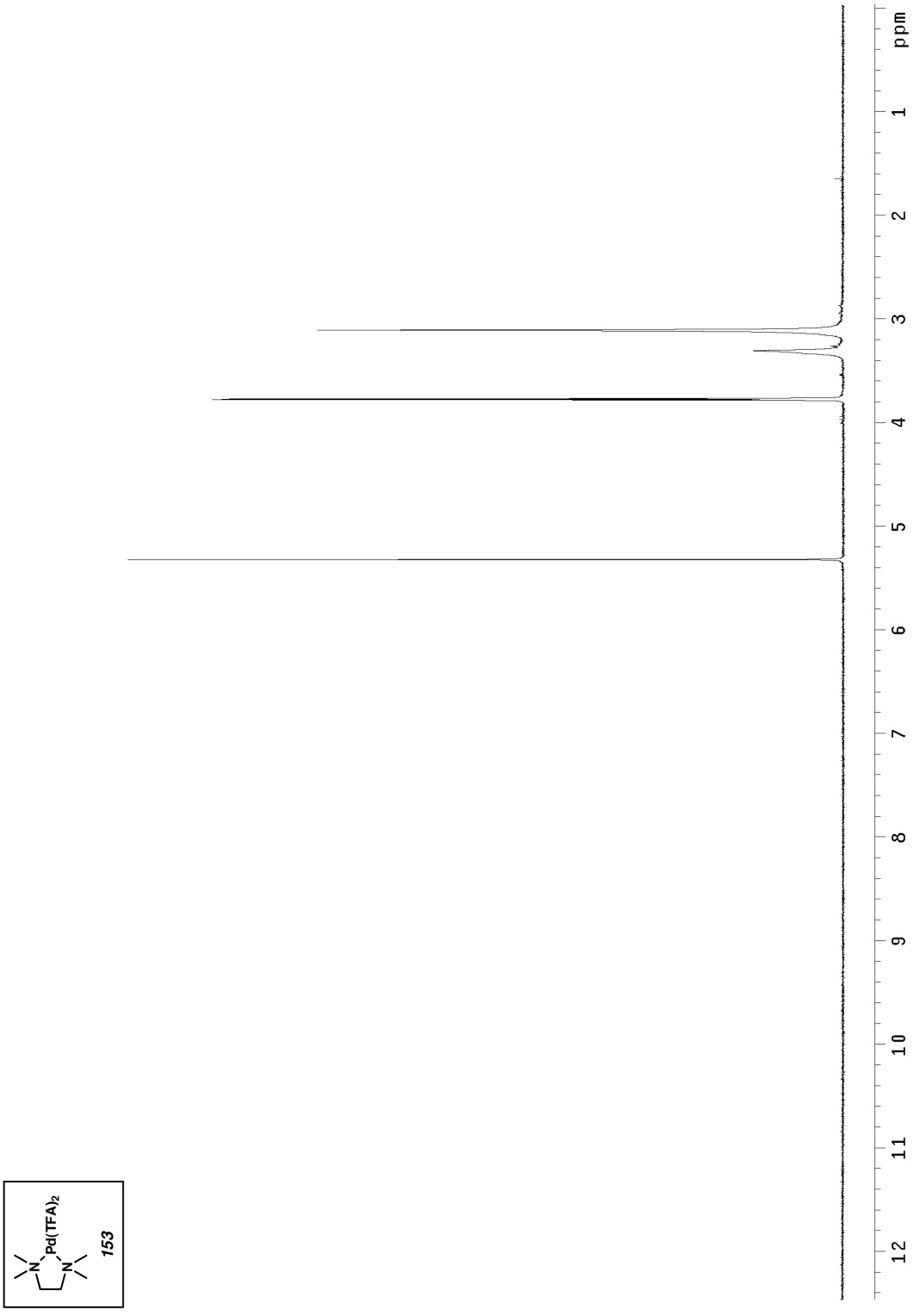


*Figure A2.1.146 ^{1}H NMR spectrum (300 MHz, CD_3OD) of **153**.*

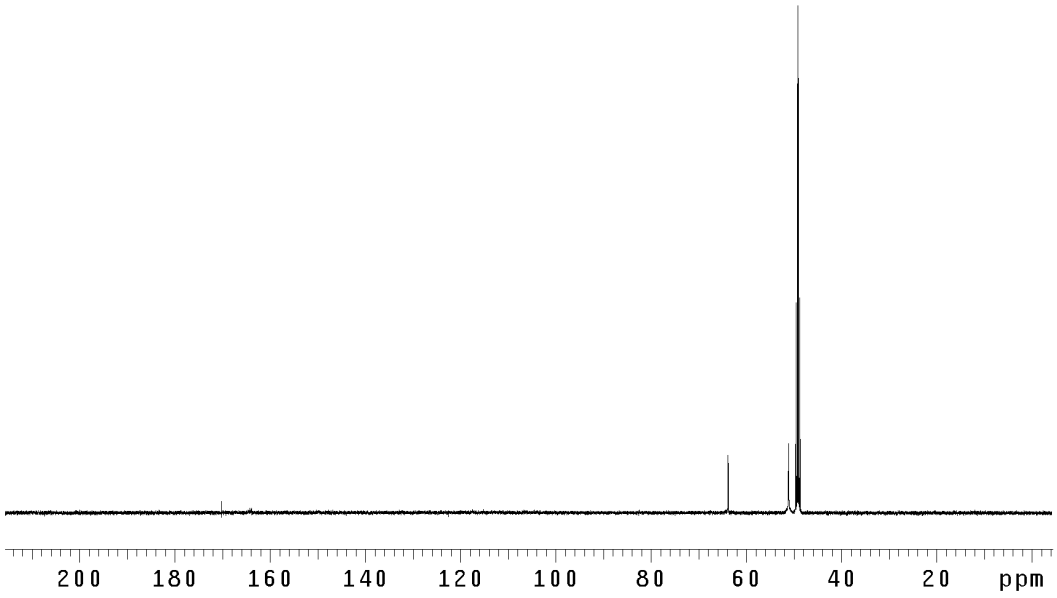


*Figure A2.1.147 ^{13}C NMR spectrum (75 MHz, CD_3OD) of **153**.*

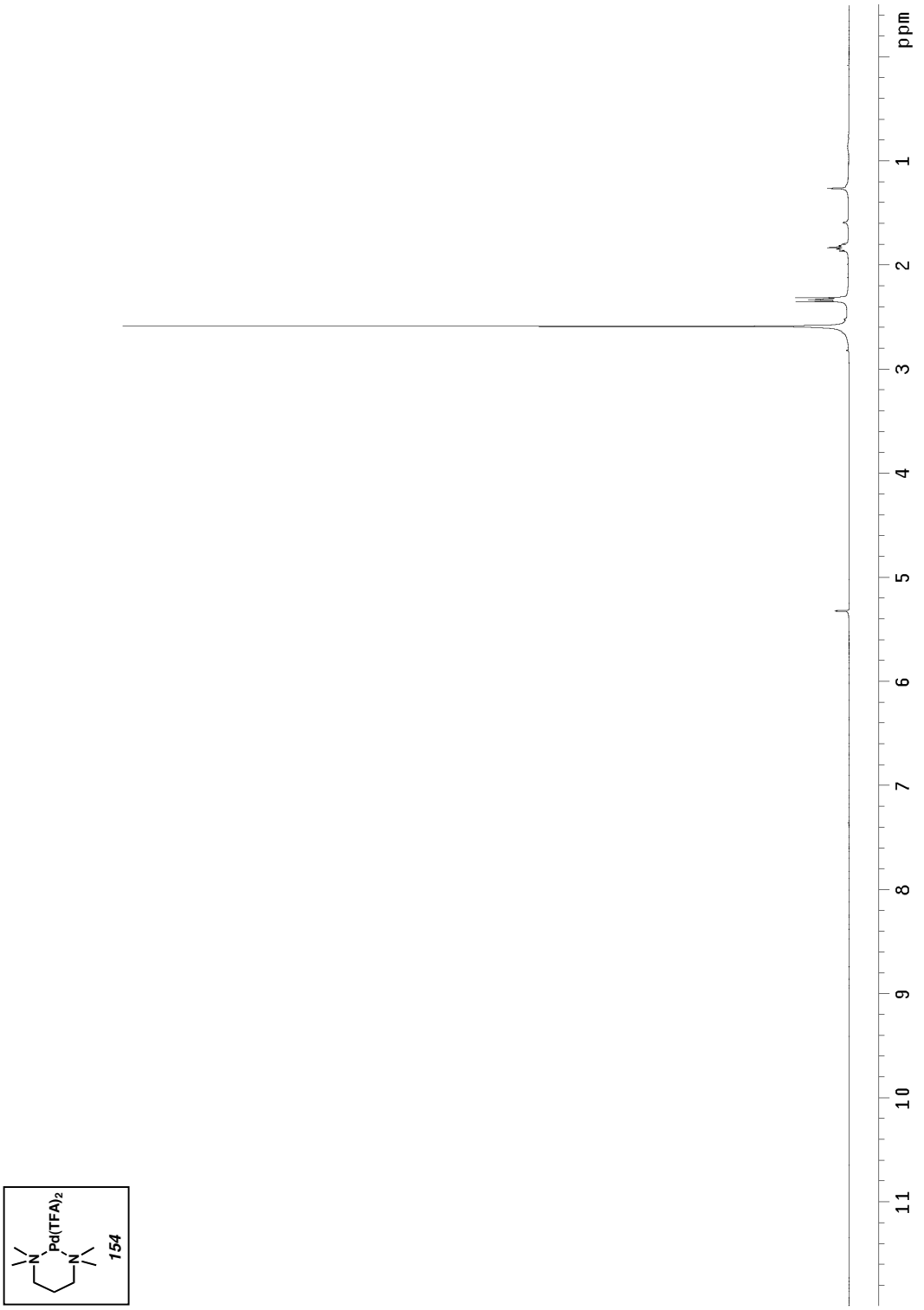


*Figure A2.1.148 ^{1}H NMR spectrum (300 MHz, CD_2Cl_2) of **154**.*

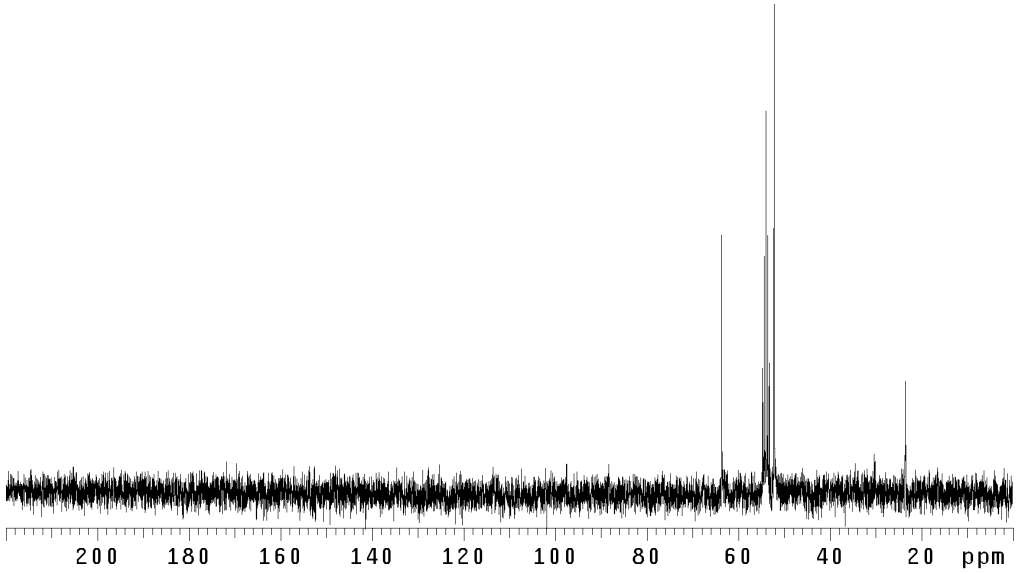
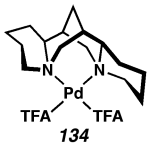


*Figure A2.1.149 ^{13}C NMR spectrum (75 MHz, CD_2Cl_2) of **154**.*

APPENDIX 2.2

X-ray Crystallographic Data for
*(sp)Pd(TFA)$_2$ (**134**)*

*Figure A2.2.1 (sp)Pd(TFA)$_2$ (**134**).*[1,2]



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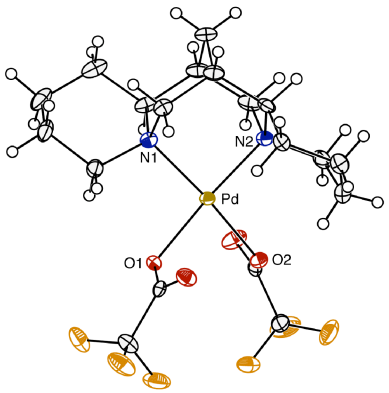
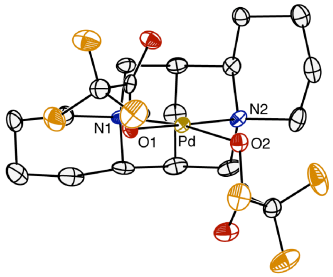
Selected bond lengths (Å) and angles (°)			
Pd–N1	2.038(2)	N1–Pd–N2	88.67(9)°
Pd–N2	2.066(2)	Cl1–Pd–Cl2	80.73(8)°
Pd–O1	2.0491(18)	N2–Pd–O1	175.95(9)°
Pd–O2	2.0615(17)	N1–Pd–O2	172.03(8)°
		N1–Pd–O1	95.01(8)°
		N2–Pd–O2	95.81(8)°
		Σ∠	708.20°

Top view:



Side view:



[1] The numbering in Figure A2.2.1 differs from that in the X-ray crystallographic report.

[2] The crystallographic data have been deposited at the Cambridge Database (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 192101.

*Crystal data and structure refinement for **134** (CCDC 192101).*

Empirical formula	$C_{19}H_{26}F_6N_2O_4Pd$
Formula weight	566.82
Crystallization solvent	Not stated
Crystal habit	Blade
Crystal size	0.21 x 0.21 x 0.05 mm^3
Crystal color	Golden yellow

Data collection

Preliminary photos	Rotation
Type of diffractometer	Bruker SMART 1000
Wavelength	0.71073 Å MoKα
Data collection temperature	98(2) K
θ range for 27174 reflections used in lattice determination	2.20 to 28.16°
Unit cell dimensions	a = 11.5600(6) Å b = 10.8671(5) Å β = 93.2600(10)° c = 16.7099(8) Å
Volume	2095.76(18) $Å^3$
Z	4
Crystal system	Monoclinic
Space group	$P2_1$
Density (calculated)	1.796 Mg/m^3
F(000)	1144
Data collection program	Bruker SMART v5.054
θ range for data collection	1.76 to 28.28°
Completeness to θ = 28.28°	95.4 %
Index ranges	$-15 \le h \le 15$, $-14 \le k \le 14$, $-21 \le l \le 21$
Data collection scan type	ω scans at 7 ϕ settings
Data reduction program	Bruker SAINT v6.022
Reflections collected	42557
Independent reflections	9696 [R_{int}= 0.0525]
Absorption coefficient	0.968 mm^{-1}
Absorption correction	None
Max. and min. transmission	0.9532 and 0.8225

Structure solution and refinement

Structure solution program	SHELXS-97 (Sheldrick, 1990)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Geometric positions
Structure refinement program	SHELXL-97 (Sheldrick, 1997)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	9696 / 1 / 607
Treatment of hydrogen atoms	Riding
Goodness-of-fit on F^2	1.329
Final R indices [I>2σ(I), 9061 reflections]	R1 = 0.0254, *w*R2 = 0.0473
R indices (all data)	R1 = 0.0290, *w*R2 = 0.0480
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$

Max shift/error	0.002
Average shift/error	0.000
Absolute structure parameter	-0.015(12)
Largest diff. peak and hole	0.788 and -0.420 e.Å^{-3}

Special refinement details

The unit cell contains two molecules per asymmetric unit. The two molecules are different from each other in the orientation of the carboxyl oxygen of the tri-fluoro acetate ligands. In one molecule the oxygens are cis to each other and in the second they are trans to each other (see Figures A2.2.2 and A2.2.3).

Refinement of F^2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

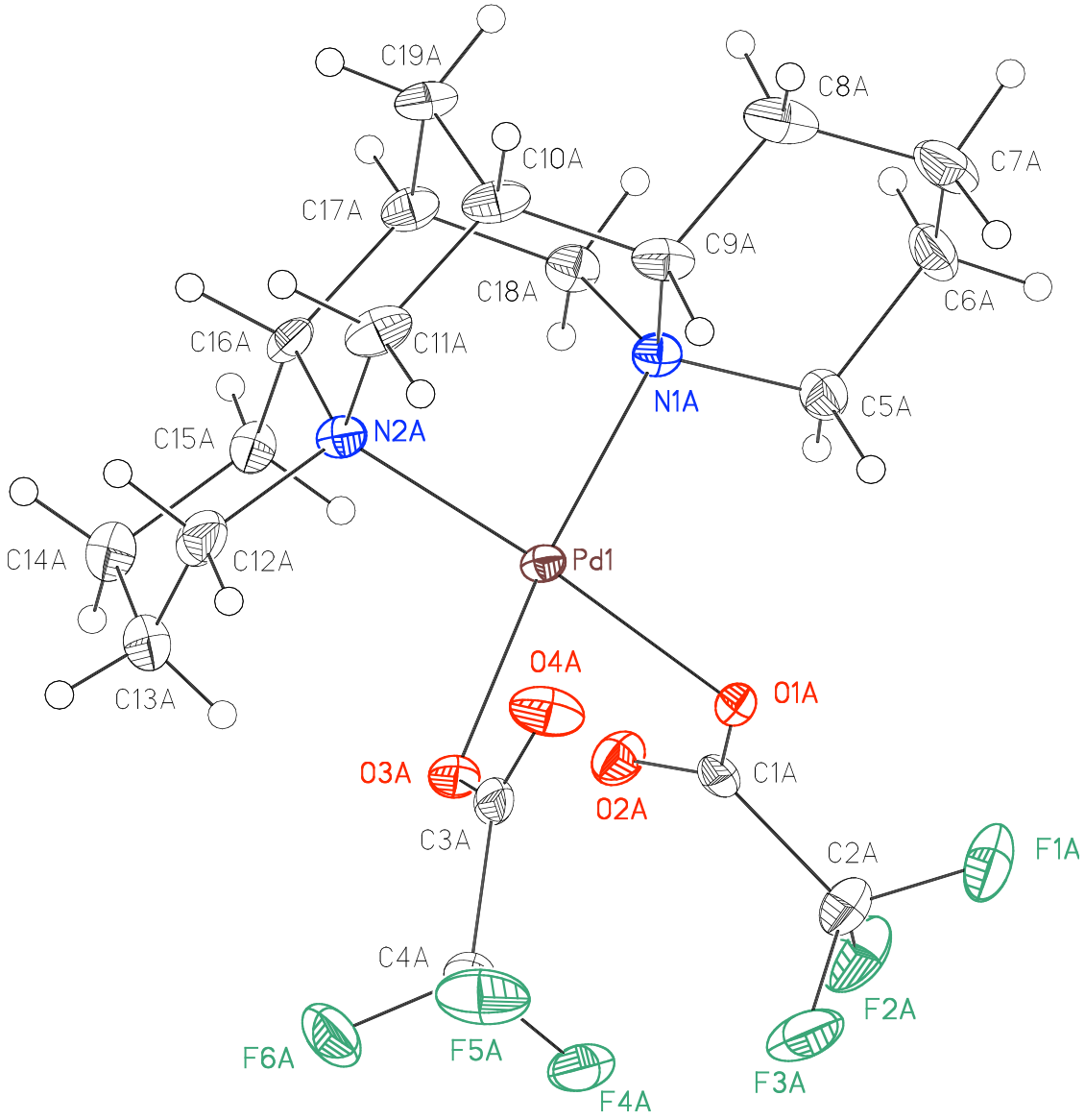


*Figure A2.2.2 Molecule A of(sp)palladium(II)(TFA)$_2$ (**134**) showing* trans *orientation of the carboxyl oxygen atoms.*

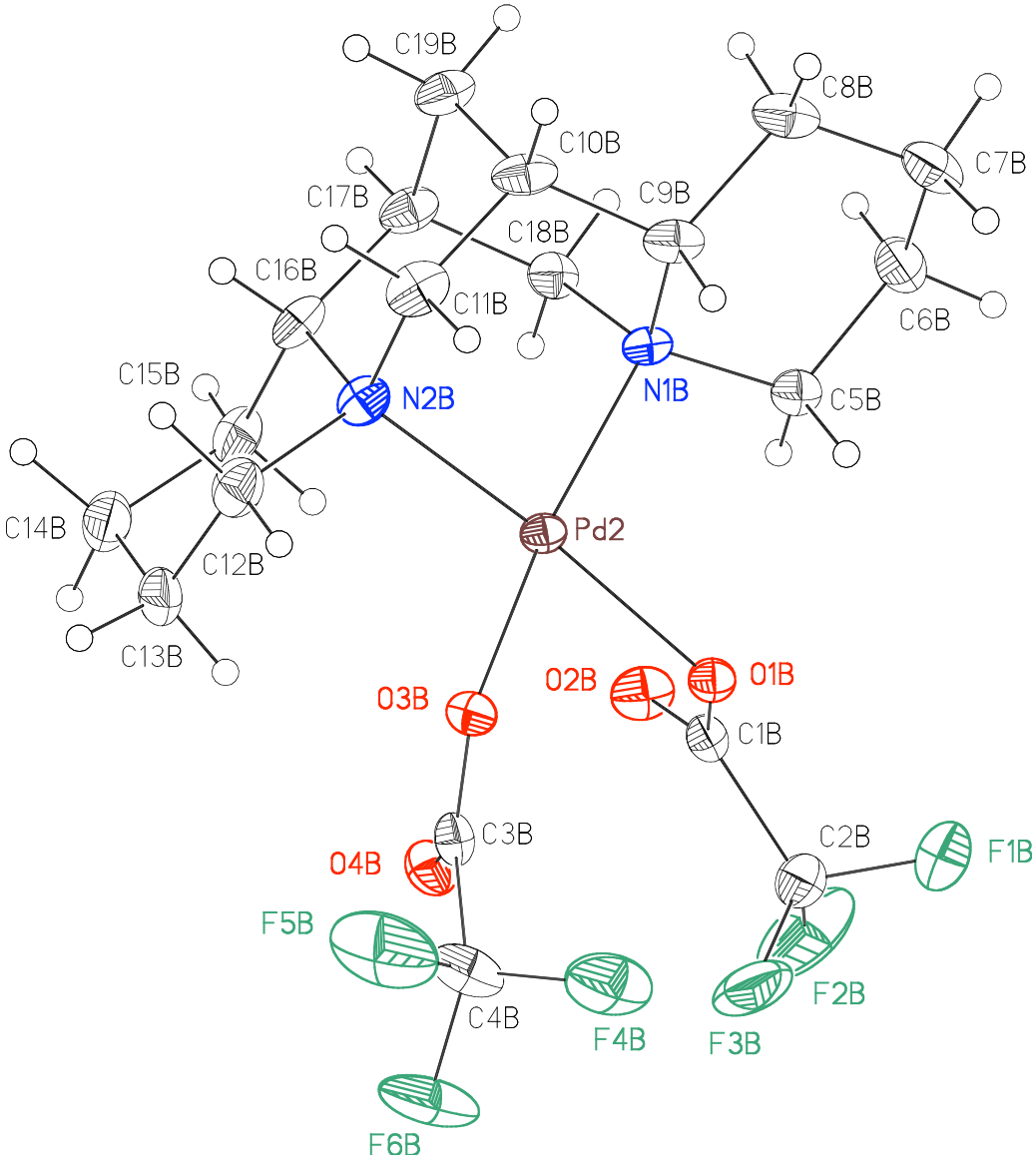


*Figure A2.2.3 Molecule B of(sp)palladium(II)(TFA)$_2$ (**134**) showing* cis *orientation of the carboxyl oxygen atoms.*

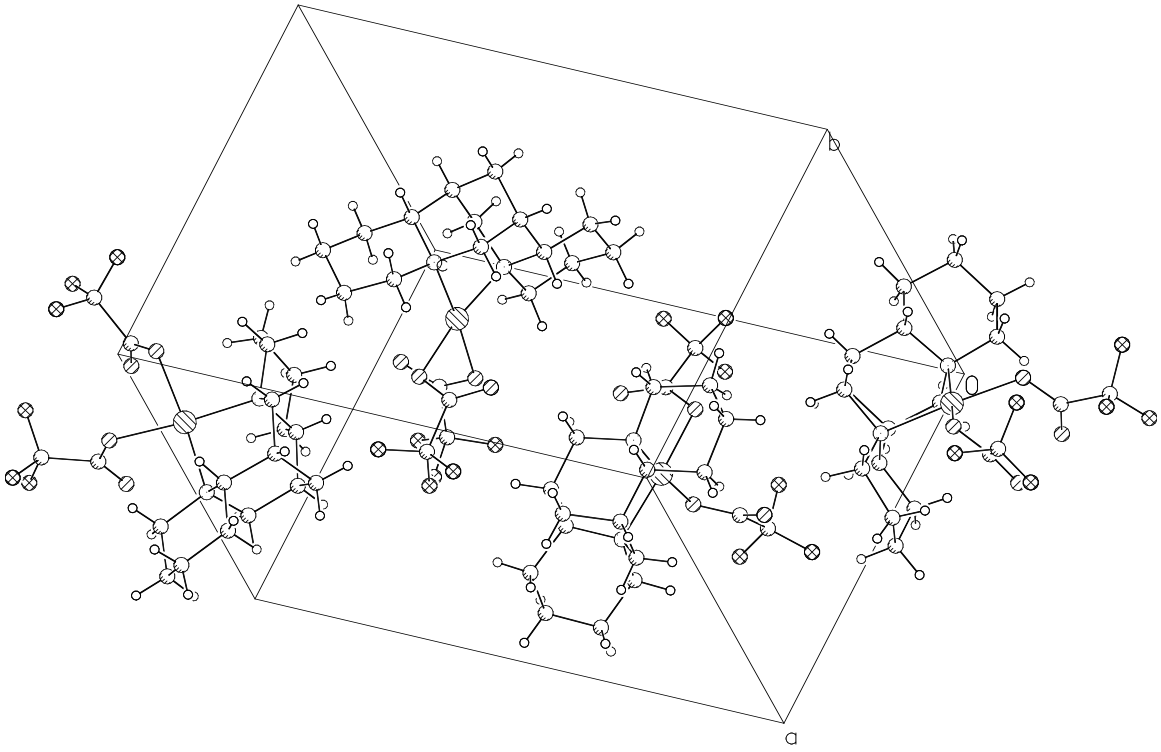


*Figure A2.2.4 Unit cell contents of (sp)Pd(TFA)$_2$ (**134**).*

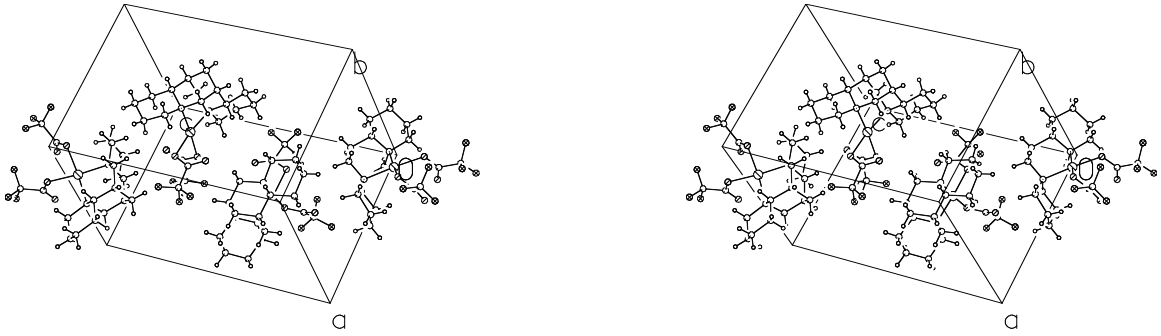


*Figure A2.2.5. Stereo view of unit cell contents of (sp)Pd(TFA)$_2$ (**134**).*

*Table A.2.2.1. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **134** (CCDC 192101). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.*

	x	y	z	U_{eq}
Pd(1)	4989(1)	6179(1)	6286(1)	13(1)
F(1A)	5664(2)	1918(2)	6438(1)	33(1)
F(2A)	6117(2)	2099(2)	7696(1)	35(1)
F(3A)	7292(2)	2730(2)	6830(1)	36(1)
F(4A)	8701(1)	4859(2)	5885(1)	30(1)
F(5A)	8941(1)	6233(2)	4999(1)	38(1)
F(6A)	9078(1)	6698(2)	6248(1)	43(1)
O(1A)	5403(2)	4345(2)	6276(1)	15(1)
O(2A)	5496(2)	4462(2)	7620(1)	22(1)
O(3A)	6771(1)	6317(2)	6359(1)	18(1)
O(4A)	6675(2)	6424(2)	5009(1)	27(1)
N(1A)	3230(2)	5908(2)	6068(1)	14(1)
N(2A)	4683(2)	8023(2)	6346(1)	15(1)
C(1A)	5620(2)	3954(2)	6983(2)	16(1)
C(2A)	6158(3)	2650(3)	6991(2)	23(1)
C(3A)	7169(2)	6295(3)	5660(2)	18(1)
C(4A)	8488(2)	6037(3)	5700(2)	20(1)
C(5A)	3010(2)	4536(2)	6032(2)	20(1)
C(6A)	1790(3)	4182(3)	5718(2)	25(1)
C(7A)	1546(3)	4701(3)	4890(2)	30(1)
C(8A)	1728(2)	6090(4)	4900(2)	27(1)
C(9A)	2924(2)	6489(2)	5263(2)	19(1)
C(10A)	3005(3)	7899(3)	5324(2)	22(1)
C(11A)	4210(3)	8397(3)	5528(2)	22(1)
C(12A)	5758(3)	8764(3)	6547(2)	25(1)
C(13A)	6274(3)	8523(3)	7379(2)	27(1)
C(14A)	5412(3)	8706(3)	8022(2)	26(1)
C(15A)	4324(3)	7967(3)	7797(2)	19(1)
C(16A)	3838(2)	8345(3)	6974(2)	17(1)
C(17A)	2625(2)	7843(3)	6750(2)	19(1)
C(18A)	2553(2)	6452(2)	6718(2)	18(1)
C(19A)	2190(3)	8379(3)	5948(2)	23(1)
Pd(2)	8900(1)	5505(1)	274(1)	15(1)
F(1B)	11387(2)	5575(2)	2662(1)	41(1)
F(2B)	10546(2)	3972(2)	3049(1)	66(1)
F(3B)	9646(2)	5683(3)	2985(1)	64(1)
F(4B)	8047(2)	7835(2)	2390(1)	48(1)
F(5B)	6367(2)	7864(2)	1801(2)	64(1)
F(6B)	6695(2)	6726(2)	2830(1)	50(1)
O(1B)	9902(2)	5660(2)	1319(1)	17(1)
O(2B)	9803(2)	3625(2)	1557(1)	25(1)
O(3B)	7790(2)	6487(2)	935(1)	19(1)
O(4B)	7526(2)	5036(2)	1873(1)	24(1)
N(1B)	10200(2)	4852(2)	-414(1)	16(1)
N(2B)	7778(2)	5383(2)	-722(1)	20(1)

C(1B)	9980(2)	4691(2)	1752(2)	17(1)
C(2B)	10376(3)	4982(3)	2619(2)	24(1)
C(3B)	7520(2)	6077(3)	1615(2)	19(1)
C(4B)	7139(3)	7128(3)	2166(2)	32(1)
C(5B)	11292(2)	4741(3)	113(2)	19(1)
C(6B)	12390(3)	4495(3)	-323(2)	26(1)
C(7B)	12578(2)	5527(3)	-920(2)	27(1)
C(8B)	11506(2)	5684(3)	-1477(2)	25(1)
C(9B)	10375(3)	5817(2)	-1048(2)	21(1)
C(10B)	9337(3)	5836(2)	-1668(2)	22(1)
C(11B)	8205(2)	6255(3)	-1330(2)	25(1)
C(12B)	6558(2)	5770(3)	-557(2)	26(1)
C(13B)	5957(3)	4896(3)	-5(2)	27(1)
C(14B)	5983(3)	3570(3)	-298(2)	29(1)
C(15B)	7232(3)	3223(3)	-456(2)	24(1)
C(16B)	7715(3)	4093(3)	-1059(2)	22(1)
C(17B)	8863(3)	3700(3)	-1383(2)	22(1)
C(18B)	9876(3)	3626(3)	-772(2)	19(1)
C(19B)	9156(3)	4579(3)	-2055(2)	24(1)

*Table A2.2.2 Selected bond lengths [Å] and angles [°] for **134** (CCDC 192101).*

Pd(1)-N(2A)	2.038(2)	N(2A)-Pd(1)-O(1A)	175.95(9)
Pd(1)-O(1A)	2.0491(18)	N(2A)-Pd(1)-O(3A)	95.81(8)
Pd(1)-O(3A)	2.0615(17)	O(1A)-Pd(1)-O(3A)	80.73(8)
Pd(1)-N(1A)	2.066(2)	N(2A)-Pd(1)-N(1A)	88.67(9)
		O(1A)-Pd(1)-N(1A)	95.01(8)
		O(3A)-Pd(1)-N(1A)	172.03(8)
Pd(2)-O(3B)	2.0411(18)	O(3B)-Pd(2)-O(1B)	80.69(7)
Pd(2)-O(1B)	2.0461(17)	O(3B)-Pd(2)-N(2B)	94.88(8)
Pd(2)-N(2B)	2.055(2)	O(1B)-Pd(2)-N(2B)	175.32(8)
Pd(2)-N(1B)	2.069(2)	O(3B)-Pd(2)-N(1B)	168.20(8)
		O(1B)-Pd(2)-N(1B)	96.24(8)
		N(2B)-Pd(2)-N(1B)	88.41(9)

*Table A2.2.3 Bond lengths [Å] and angles [°] for **134** (CCDC 192101).*

Pd(1)-N(2A)	2.038(2)	F(4A)-C(4A)	1.337(3)
Pd(1)-O(1A)	2.0491(18)	F(5A)-C(4A)	1.326(3)
Pd(1)-O(3A)	2.0615(17)	F(6A)-C(4A)	1.322(3)
Pd(1)-N(1A)	2.066(2)	O(1A)-C(1A)	1.267(3)
F(1A)-C(2A)	1.324(3)	O(2A)-C(1A)	1.215(3)
F(2A)-C(2A)	1.324(3)	O(3A)-C(3A)	1.279(3)
F(3A)-C(2A)	1.356(4)	O(4A)-C(3A)	1.208(3)

N(1A)-C(18A)	1.497(3)	F(2B)-C(2B)	1.320(4)
N(1A)-C(9A)	1.510(3)	F(3B)-C(2B)	1.313(3)
N(1A)-C(5A)	1.513(3)	F(4B)-C(4B)	1.337(4)
N(2A)-C(11A)	1.499(4)	F(5B)-C(4B)	1.321(4)
N(2A)-C(12A)	1.504(4)	F(6B)-C(4B)	1.323(4)
N(2A)-C(16A)	1.515(3)	O(1B)-C(1B)	1.278(3)
C(1A)-C(2A)	1.547(4)	O(2B)-C(1B)	1.218(3)
C(3A)-C(4A)	1.549(4)	O(3B)-C(3B)	1.276(3)
C(5A)-C(6A)	1.525(4)	O(4B)-C(3B)	1.210(3)
C(5A)-H(5A1)	0.9833	N(1B)-C(18B)	1.500(3)
C(5A)-H(5A2)	0.9833	N(1B)-C(5B)	1.503(4)
C(6A)-C(7A)	1.506(5)	N(1B)-C(9B)	1.512(3)
C(6A)-H(6A1)	0.9647	N(2B)-C(11B)	1.494(4)
C(6A)-H(6A2)	0.9647	N(2B)-C(16B)	1.511(4)
C(7A)-C(8A)	1.524(4)	N(2B)-C(12B)	1.512(4)
C(7A)-H(7A1)	0.9631	C(1B)-C(2B)	1.528(4)
C(7A)-H(7A2)	0.9631	C(3B)-C(4B)	1.547(4)
C(8A)-C(9A)	1.540(4)	C(5B)-C(6B)	1.523(4)
C(8A)-H(8A1)	0.9189	C(5B)-H(5B1)	0.9599
C(8A)-H(8A2)	0.9189	C(5B)-H(5B2)	0.9599
C(9A)-C(10A)	1.537(4)	C(6B)-C(7B)	1.525(4)
C(9A)-H(9A)	0.9915	C(6B)-H(6B1)	0.9586
C(10A)-C(11A)	1.516(4)	C(6B)-H(6B2)	0.9586
C(10A)-C(19A)	1.536(4)	C(7B)-C(8B)	1.516(4)
C(10A)-H(10A)	0.9403	C(7B)-H(7B1)	0.9092
C(11A)-H(11A)	0.9527	C(7B)-H(7B2)	0.9092
C(11A)-H(11B)	0.9527	C(8B)-C(9B)	1.533(4)
C(12A)-C(13A)	1.504(4)	C(8B)-H(8B1)	0.9403
C(12A)-H(12A)	0.9306	C(8B)-H(8B2)	0.9403
C(12A)-H(12B)	0.9306	C(9B)-C(10B)	1.540(4)
C(13A)-C(14A)	1.520(4)	C(9B)-H(9B)	0.9304
C(13A)-H(13A)	0.8949	C(10B)-C(19B)	1.521(4)
C(13A)-H(13B)	0.8949	C(10B)-C(11B)	1.524(4)
C(14A)-C(15A)	1.522(4)	C(10B)-H(10B)	0.8391
C(14A)-H(14A)	0.8992	C(11B)-H(11C)	0.9431
C(14A)-H(14B)	0.8992	C(11B)-H(11D)	0.9431
C(15A)-C(16A)	1.512(4)	C(12B)-C(13B)	1.519(4)
C(15A)-H(15A)	0.9319	C(12B)-H(12C)	0.9966
C(15A)-H(15B)	0.9319	C(12B)-H(12D)	0.9966
C(16A)-C(17A)	1.531(4)	C(13B)-C(14B)	1.522(4)
C(16A)-H(16A)	0.9875	C(13B)-H(13C)	0.9184
C(17A)-C(18A)	1.515(4)	C(13B)-H(13D)	0.9184
C(17A)-C(19A)	1.520(4)	C(14B)-C(15B)	1.530(4)
C(17A)-H(17A)	0.9316	C(14B)-H(14C)	0.9940
C(18A)-H(18A)	0.9431	C(14B)-H(14D)	0.9940
C(18A)-H(18B)	0.9431	C(15B)-C(16B)	1.511(4)
C(19A)-H(19A)	0.9047	C(15B)-H(15C)	0.9242
C(19A)-H(19B)	0.9047	C(15B)-H(15D)	0.9242
Pd(2)-O(3B)	2.0411(18)	C(16B)-C(17B)	1.523(4)
Pd(2)-O(1B)	2.0461(17)	C(16B)-H(16B)	0.8711
Pd(2)-N(2B)	2.055(2)	C(17B)-C(18B)	1.511(4)
Pd(2)-N(1B)	2.069(2)	C(17B)-C(19B)	1.526(4)
F(1B)-C(2B)	1.333(3)	C(17B)-H(17B)	0.9574

C(18B)-H(18C)	0.9088	C(5A)-C(6A)-H(6A2)	109.7
C(18B)-H(18D)	0.9088	H(6A1)-C(6A)-H(6A2)	108.2
C(19B)-H(19C)	0.9394	C(6A)-C(7A)-C(8A)	110.0(3)
C(19B)-H(19D)	0.9394	C(6A)-C(7A)-H(7A1)	109.7
		C(8A)-C(7A)-H(7A1)	109.7
N(2A)-Pd(1)-O(1A)	175.95(9)	C(6A)-C(7A)-H(7A2)	109.7
N(2A)-Pd(1)-O(3A)	95.81(8)	C(8A)-C(7A)-H(7A2)	109.7
O(1A)-Pd(1)-O(3A)	80.73(8)	H(7A1)-C(7A)-H(7A2)	108.2
N(2A)-Pd(1)-N(1A)	88.67(9)	C(7A)-C(8A)-C(9A)	113.8(3)
O(1A)-Pd(1)-N(1A)	95.01(8)	C(7A)-C(8A)-H(8A1)	108.8
O(3A)-Pd(1)-N(1A)	172.03(8)	C(9A)-C(8A)-H(8A1)	108.8
C(1A)-O(1A)-Pd(1)	110.64(17)	C(7A)-C(8A)-H(8A2)	108.8
C(3A)-O(3A)-Pd(1)	110.81(16)	C(9A)-C(8A)-H(8A2)	108.8
C(18A)-N(1A)-C(9A)	112.1(2)	H(8A1)-C(8A)-H(8A2)	107.7
C(18A)-N(1A)-C(5A)	108.9(2)	N(1A)-C(9A)-C(10A)	110.4(2)
C(9A)-N(1A)-C(5A)	110.3(2)	N(1A)-C(9A)-C(8A)	113.1(2)
C(18A)-N(1A)-Pd(1)	111.42(16)	C(10A)-C(9A)-C(8A)	110.9(2)
C(9A)-N(1A)-Pd(1)	106.03(15)	N(1A)-C(9A)-H(9A)	107.4
C(5A)-N(1A)-Pd(1)	108.01(15)	C(10A)-C(9A)-H(9A)	107.4
C(11A)-N(2A)-C(12A)	108.2(2)	C(8A)-C(9A)-H(9A)	107.4
C(11A)-N(2A)-C(16A)	110.7(2)	C(11A)-C(10A)-C(19A)	108.5(3)
C(12A)-N(2A)-C(16A)	106.2(2)	C(11A)-C(10A)-C(9A)	115.0(2)
C(11A)-N(2A)-Pd(1)	106.09(17)	C(19A)-C(10A)-C(9A)	110.2(2)
C(12A)-N(2A)-Pd(1)	113.19(17)	C(11A)-C(10A)-H(10A)	107.6
C(16A)-N(2A)-Pd(1)	112.48(16)	C(19A)-C(10A)-H(10A)	107.6
O(2A)-C(1A)-O(1A)	129.6(3)	C(9A)-C(10A)-H(10A)	107.6
O(2A)-C(1A)-C(2A)	118.4(3)	N(2A)-C(11A)-C(10A)	113.0(2)
O(1A)-C(1A)-C(2A)	112.0(2)	N(2A)-C(11A)-H(11A)	109.0
F(2A)-C(2A)-F(1A)	108.3(2)	C(10A)-C(11A)-H(11A)	109.0
F(2A)-C(2A)-F(3A)	106.8(2)	N(2A)-C(11A)-H(11B)	109.0
F(1A)-C(2A)-F(3A)	106.5(2)	C(10A)-C(11A)-H(11B)	109.0
F(2A)-C(2A)-C(1A)	112.8(2)	H(11A)-C(11A)-H(11B)	107.8
F(1A)-C(2A)-C(1A)	112.7(2)	N(2A)-C(12A)-C(13A)	113.1(2)
F(3A)-C(2A)-C(1A)	109.4(2)	N(2A)-C(12A)-H(12A)	109.0
O(4A)-C(3A)-O(3A)	130.1(2)	C(13A)-C(12A)-H(12A)	109.0
O(4A)-C(3A)-C(4A)	118.3(2)	N(2A)-C(12A)-H(12B)	109.0
O(3A)-C(3A)-C(4A)	111.6(2)	C(13A)-C(12A)-H(12B)	109.0
F(6A)-C(4A)-F(5A)	108.1(2)	H(12A)-C(12A)-H(12B)	107.8
F(6A)-C(4A)-F(4A)	106.2(2)	C(12A)-C(13A)-C(14A)	112.9(3)
F(5A)-C(4A)-F(4A)	106.3(2)	C(12A)-C(13A)-H(13A)	109.0
F(6A)-C(4A)-C(3A)	113.6(2)	C(14A)-C(13A)-H(13A)	109.0
F(5A)-C(4A)-C(3A)	111.7(2)	C(12A)-C(13A)-H(13B)	109.0
F(4A)-C(4A)-C(3A)	110.6(2)	C(14A)-C(13A)-H(13B)	109.0
N(1A)-C(5A)-C(6A)	114.3(2)	H(13A)-C(13A)-H(13B)	107.8
N(1A)-C(5A)-H(5A1)	108.7	C(13A)-C(14A)-C(15A)	108.8(3)
C(6A)-C(5A)-H(5A1)	108.7	C(13A)-C(14A)-H(14A)	109.9
N(1A)-C(5A)-H(5A2)	108.7	C(15A)-C(14A)-H(14A)	109.9
C(6A)-C(5A)-H(5A2)	108.7	C(13A)-C(14A)-H(14B)	109.9
H(5A1)-C(5A)-H(5A2)	107.6	C(15A)-C(14A)-H(14B)	109.9
C(7A)-C(6A)-C(5A)	110.0(3)	H(14A)-C(14A)-H(14B)	108.3
C(7A)-C(6A)-H(6A1)	109.7	C(16A)-C(15A)-C(14A)	109.9(2)
C(5A)-C(6A)-H(6A1)	109.7	C(16A)-C(15A)-H(15A)	109.7
C(7A)-C(6A)-H(6A2)	109.7	C(14A)-C(15A)-H(15A)	109.7

C(16A)-C(15A)-H(15B)	109.7	F(3B)-C(2B)-C(1B)	113.3(2)
C(14A)-C(15A)-H(15B)	109.7	F(2B)-C(2B)-C(1B)	111.8(3)
H(15A)-C(15A)-H(15B)	108.2	F(1B)-C(2B)-C(1B)	111.5(2)
C(15A)-C(16A)-N(2A)	110.2(2)	O(4B)-C(3B)-O(3B)	130.3(3)
C(15A)-C(16A)-C(17A)	114.4(2)	O(4B)-C(3B)-C(4B)	118.3(3)
N(2A)-C(16A)-C(17A)	111.4(2)	O(3B)-C(3B)-C(4B)	111.4(3)
C(15A)-C(16A)-H(16A)	106.8	F(5B)-C(4B)-F(6B)	107.7(3)
N(2A)-C(16A)-H(16A)	106.8	F(5B)-C(4B)-F(4B)	106.3(3)
C(17A)-C(16A)-H(16A)	106.8	F(6B)-C(4B)-F(4B)	106.9(3)
C(18A)-C(17A)-C(19A)	109.7(2)	F(5B)-C(4B)-C(3B)	112.3(3)
C(18A)-C(17A)-C(16A)	114.3(2)	F(6B)-C(4B)-C(3B)	113.1(3)
C(19A)-C(17A)-C(16A)	109.3(2)	F(4B)-C(4B)-C(3B)	110.2(2)
C(18A)-C(17A)-H(17A)	107.8	N(1B)-C(5B)-C(6B)	115.4(2)
C(19A)-C(17A)-H(17A)	107.8	N(1B)-C(5B)-H(5B1)	108.4
C(16A)-C(17A)-H(17A)	107.8	C(6B)-C(5B)-H(5B1)	108.4
N(1A)-C(18A)-C(17A)	113.0(2)	N(1B)-C(5B)-H(5B2)	108.4
N(1A)-C(18A)-H(18A)	109.0	C(6B)-C(5B)-H(5B2)	108.4
C(17A)-C(18A)-H(18A)	109.0	H(5B1)-C(5B)-H(5B2)	107.5
N(1A)-C(18A)-H(18B)	109.0	C(5B)-C(6B)-C(7B)	109.7(2)
C(17A)-C(18A)-H(18B)	109.0	C(5B)-C(6B)-H(6B1)	109.7
H(18A)-C(18A)-H(18B)	107.8	C(7B)-C(6B)-H(6B1)	109.7
C(17A)-C(19A)-C(10A)	106.5(2)	C(5B)-C(6B)-H(6B2)	109.7
C(17A)-C(19A)-H(19A)	110.4	C(7B)-C(6B)-H(6B2)	109.7
C(10A)-C(19A)-H(19A)	110.4	H(6B1)-C(6B)-H(6B2)	108.2
C(17A)-C(19A)-H(19B)	110.4	C(8B)-C(7B)-C(6B)	110.0(2)
C(10A)-C(19A)-H(19B)	110.4	C(8B)-C(7B)-H(7B1)	109.7
H(19A)-C(19A)-H(19B)	108.6	C(6B)-C(7B)-H(7B1)	109.7
O(3B)-Pd(2)-O(1B)	80.69(7)	C(8B)-C(7B)-H(7B2)	109.7
O(3B)-Pd(2)-N(2B)	94.88(8)	C(6B)-C(7B)-H(7B2)	109.7
O(1B)-Pd(2)-N(2B)	175.32(8)	H(7B1)-C(7B)-H(7B2)	108.2
O(3B)-Pd(2)-N(1B)	168.20(8)	C(7B)-C(8B)-C(9B)	114.4(2)
O(1B)-Pd(2)-N(1B)	96.24(8)	C(7B)-C(8B)-H(8B1)	108.7
N(2B)-Pd(2)-N(1B)	88.41(9)	C(9B)-C(8B)-H(8B1)	108.7
C(1B)-O(1B)-Pd(2)	115.68(17)	C(7B)-C(8B)-H(8B2)	108.7
C(3B)-O(3B)-Pd(2)	119.50(18)	C(9B)-C(8B)-H(8B2)	108.7
C(18B)-N(1B)-C(5B)	110.1(2)	H(8B1)-C(8B)-H(8B2)	107.6
C(18B)-N(1B)-C(9B)	112.2(2)	N(1B)-C(9B)-C(8B)	114.4(2)
C(5B)-N(1B)-C(9B)	109.0(2)	N(1B)-C(9B)-C(10B)	110.5(2)
C(18B)-N(1B)-Pd(2)	110.70(17)	C(8B)-C(9B)-C(10B)	109.9(2)
C(5B)-N(1B)-Pd(2)	108.31(16)	N(1B)-C(9B)-H(9B)	107.2
C(9B)-N(1B)-Pd(2)	106.40(16)	C(8B)-C(9B)-H(9B)	107.2
C(11B)-N(2B)-C(16B)	110.3(2)	C(10B)-C(9B)-H(9B)	107.2
C(11B)-N(2B)-C(12B)	107.2(2)	C(19B)-C(10B)-C(11B)	109.0(3)
C(16B)-N(2B)-C(12B)	107.5(2)	C(19B)-C(10B)-C(9B)	110.9(2)
C(11B)-N(2B)-Pd(2)	107.00(17)	C(11B)-C(10B)-C(9B)	114.0(2)
C(16B)-N(2B)-Pd(2)	112.13(17)	C(19B)-C(10B)-H(10B)	107.6
C(12B)-N(2B)-Pd(2)	112.68(17)	C(11B)-C(10B)-H(10B)	107.6
O(2B)-C(1B)-O(1B)	128.9(3)	C(9B)-C(10B)-H(10B)	107.6
O(2B)-C(1B)-C(2B)	119.2(3)	N(2B)-C(11B)-C(10B)	112.7(2)
O(1B)-C(1B)-C(2B)	111.9(2)	N(2B)-C(11B)-H(11C)	109.0
F(3B)-C(2B)-F(2B)	108.0(3)	C(10B)-C(11B)-H(11C)	109.0
F(3B)-C(2B)-F(1B)	106.2(3)	N(2B)-C(11B)-H(11D)	109.0
F(2B)-C(2B)-F(1B)	105.6(3)	C(10B)-C(11B)-H(11D)	109.0

H(11C)-C(11B)-H(11D)	107.8	N(2B)-C(16B)-C(17B)	111.6(2)
N(2B)-C(12B)-C(13B)	113.6(2)	C(15B)-C(16B)-C(17B)	115.1(2)
N(2B)-C(12B)-H(12C)	108.8	N(2B)-C(16B)-H(16B)	106.5
C(13B)-C(12B)-H(12C)	108.8	C(15B)-C(16B)-H(16B)	106.5
N(2B)-C(12B)-H(12D)	108.8	C(17B)-C(16B)-H(16B)	106.5
C(13B)-C(12B)-H(12D)	108.8	C(18B)-C(17B)-C(16B)	115.6(2)
H(12C)-C(12B)-H(12D)	107.7	C(18B)-C(17B)-C(19B)	109.6(2)
C(12B)-C(13B)-C(14B)	112.3(3)	C(16B)-C(17B)-C(19B)	108.7(2)
C(12B)-C(13B)-H(13C)	109.1	C(18B)-C(17B)-H(17B)	107.6
C(14B)-C(13B)-H(13C)	109.1	C(16B)-C(17B)-H(17B)	107.6
C(12B)-C(13B)-H(13D)	109.1	C(19B)-C(17B)-H(17B)	107.6
C(14B)-C(13B)-H(13D)	109.1	N(1B)-C(18B)-C(17B)	112.8(2)
H(13C)-C(13B)-H(13D)	107.9	N(1B)-C(18B)-H(18C)	109.0
C(13B)-C(14B)-C(15B)	109.0(3)	C(17B)-C(18B)-H(18C)	109.0
C(13B)-C(14B)-H(14C)	109.9	N(1B)-C(18B)-H(18D)	109.0
C(15B)-C(14B)-H(14C)	109.9	C(17B)-C(18B)-H(18D)	109.0
C(13B)-C(14B)-H(14D)	109.9	H(18C)-C(18B)-H(18D)	107.8
C(15B)-C(14B)-H(14D)	109.9	C(10B)-C(19B)-C(17B)	106.3(2)
H(14C)-C(14B)-H(14D)	108.3	C(10B)-C(19B)-H(19C)	110.5
C(16B)-C(15B)-C(14B)	110.4(3)	C(17B)-C(19B)-H(19C)	110.5
C(16B)-C(15B)-H(15C)	109.6	C(10B)-C(19B)-H(19D)	110.5
C(14B)-C(15B)-H(15C)	109.6	C(17B)-C(19B)-H(19D)	110.5
C(16B)-C(15B)-H(15D)	109.6	H(19C)-C(19B)-H(19D)	108.7
C(14B)-C(15B)-H(15D)	109.6		
H(15C)-C(15B)-H(15D)	108.1		
N(2B)-C(16B)-C(15B)	110.1(2)		