NOVEL METHODOLOGIES VIA THE CATALYTIC CARBOCUPRATION OF ALKYNOATES AND THE TOTAL SYNTHESIS OF (+)-ASPERGILLIDE B

by

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ABSTRACT

This dissertation highlights three novel reactions that involve an initial trimethylsilyl trifluoromethanesulfonate (TMSOTf) mediated catalytic carbocupration of alkynoates. In addition to finding that a specific proton source (TFA) provides (Z)-substituted α,β- unsaturated esters, we established that the intermediate TMS allenolate could undergo highly diastereoselective carbon-carbon, deuterium, and silyl bond forming reactions in a single flask. Also, we have been successful in vicinally functionalizing ynoates via the initial carbocupration followed by a secondary electrophilic capture of the TMS allenolate intermediate. Not only did we provide disubstituted and trisubstituted alkenes, we report the synthesis of a tetrasubstituted alkene in high level of diastereoselectivity and yield as well. Seeing that organocuprate additions to activated multiple bonds are an important tool in synthetic organic chemistry, it should be apparent that these catalytic, diastereoselective carbocupration reactions should be useful when forming substituted alkenes in organic synthesis.

The second part of this dissertation focuses on the successful total synthesis of (+)-aspergillide B. It belongs to a family of biologically active natural products that contain C-glycoside subunits and a *trans*-olefin as part of the macrocyclic structure. The synthesis is best summarized by the highly diastereoselective oxocarbenium allylation to forge the α-C glycoside subunit, followed by a cross metathesis and Yamaguchi macrolactonization.

LIST OF ABBREVIATIONS AND SYMBOLS

$[\alpha]^{24}_{D}$	rotation @ 24 °C on Na^{+} D-line
9-BBN	9-borabicyclo[3.3.1.]nonane
Bn	benzyl
Bz	benzoyl
CM	cross metathesis
CSA	camphorsufonic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutyl aluminum hydride
DIPEA	diisopropyl ethyl amine
DMAP	4-dimethyl amino pyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
d.r.	diastereomeric ratio
E	entgegen (opposite, *trans*-)
eq. or equiv	equivalents

EWG	electron withdrawing group
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectroscopy
Hz	hertz
IBX	*o*-iodoxybenzoic acid
IC_{50}	50% median inhibition concentration
Im or Imid	imidazole
IR	infrared
J	coupling constant
KHMDS	potassium hexamethyl disilazide
LDA	lithium diisopropylamide
LiHMDS or LHMDS	lithium *bis*(trimethylsilyl)amide
M	molar
MEM	methoxy ethoxy methyl
MHz	megahertz
mmol	millimole
mol	mole
MTBE	*tert*-butyl methyl ether
N	normal
NA	not applicable
*n*BuLi	*n*-butyllithium
NMO	*N*-methylmorpholine oxide
NMR	nuclear magnetic resonance

NOE	nuclear Overhauser enhancement
NR	no reaction
o-	*ortho*-
-OTf	trifluoromethane sulfonate (triflate)
p-	*para*-
PPTS	pyridinium *p*-toluene sulfonate
PTSA (TsOH)	*p*-toluenesulfonic acid
Py (pyr)	pyridine
Red-Al	bis(2-methoxyethoxy)aluminum hydride
(*R*)-	rectus (clockwise)
RCM	ring closing metathesis
rt	room temperature
(*S*)-	sinister (counterclockwise)
SAR	structure-activity relationship
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyl diphenyl silyl
TBS	*t*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy free radical
TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TMS	trimethylsilyl

TMSOTf	trimethylsilyl trifluoromethanesulfonate
TPS	triphenylsilyl
Z-	zuzammen (together, *cis*-)

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CHAPTER 1: A HIGHLY STEREOSELECTIVE TMSOTF-MEDIATED CATALYTIC CARBOCUPRATION

1.1 Introduction

Over the past few decades, considerable attention has been given to the stoichiometric carbocupration of alkynoates with organocopper-lithium reagents for the synthesis of α,β-unsaturated esters.[1] It is of great importance because this reaction offers a stereoselective route to valuable substituted alkenes, which are useful in natural product synthesis. These reactions usually proceed with high yields and stereoselectivities, but this depends on a variety of conditions such as temperature, copper reagent, solvent effects, and external chelating ligands. This dissertation will discuss the efforts toward and development of a new catalytic carbocupration reaction and how we have transformed a stoichiometric carbocupration reaction into a diastereoselective, catalytic process.[2b]

The first chapter of this dissertation focuses on previous research done on the stoichiometric carbocupration of alkynoates including Corey and Katzenellenbogen's first report,[4] as well as, Jennings group's research leading up to and including the first catalytic carbocupration of alkynoates affording the *E*-olefin and the *Z*-α,β-unsaturated ester in good yield and high diastereoselectivity.[1a,b] Chapter two will highlight our success in vicinally functionalizing propiolate esters via the initial catalytic carbocupration followed by a secondary electrophilic capture of the TMS allenolate intermediate.[2c] Chapter three will discuss a third catalytic, diastereoselective carbocupration reaction; however, this is also a silyl bond forming process, not

just a carbon-carbon bond forming reaction in a single flask.[2d] Chapter four will focus on our total synthesis of (+)-aspergillide B, as well as, the work of several other groups towards this same target.[4,5] It will highlight our unique formation of the α-C glycoside intermediate, and discuss our synthetic strategy in detail.

1.2 Organocuprate conjugate addition and carbocupration chemistry

In 1941, Kharash and Tawney reported the first 1,4-addition, also known as conjugate addition, of a Grignard reagent to an α,β-unsaturated ketone in the presence of a small amount of Cu(I) salt. In 1952, Gilman et al. discovered that addition of two equivalents of MeLi to Cu(I) salts resulted in an organocuprate reagent and could also perform the 1,4-addition reaction to enones.[1a] Therefore, for over 60 years, organocuprates [$M(CuR_2)$] have been highly efficient nucleophiles for C-C bond forming reactions and are still among the most useful synthetic reagents in transition metal organometallics.[1b] As delineated in figure 1.1, this attractive conjugate addition reaction has two key attributes that make it so appealing: 1) the enolate **2** may be trapped with various electrophiles. 2) For correctly substituted enones, a new stereocenter may be generated.

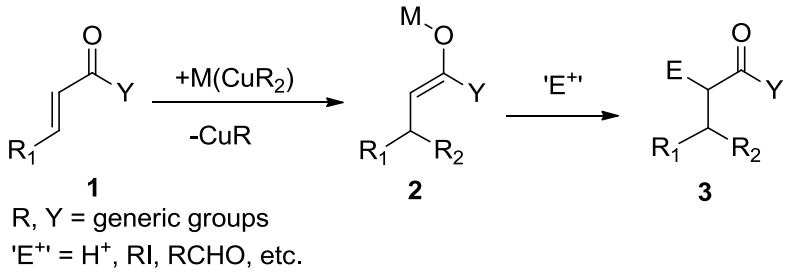


Figure 1.1. Cuprate Mediated 1,4-addition of 'MR' to α-β-unsaturated Systems[1b]

Two of the more accepted mechanistic possibilities for the conjugate addition reaction are shown below in figure 1.2 and are said to involve "black box" intermediates because no additional species has been detected in the C-C bond forming process from the π-complex **4** to the enolate **8** (figure 1.2).[1b] One mechanistic possibility goes through a Cu(III) intermediate **5** and the other through a Cu(I) species **6**. It is possible that the formation of a **5** occurs via an oxidative addition followed by reductive elimination to the π-adduct **7**. Alternatively, the π-complex **4** may undergo 1,2-migratory insertion, also known as carbocupration, and form **6**, which may be rearranged to the same adduct **7**. Then, release of the cuprate should afford **8**, which may be trapped with various electrophiles.

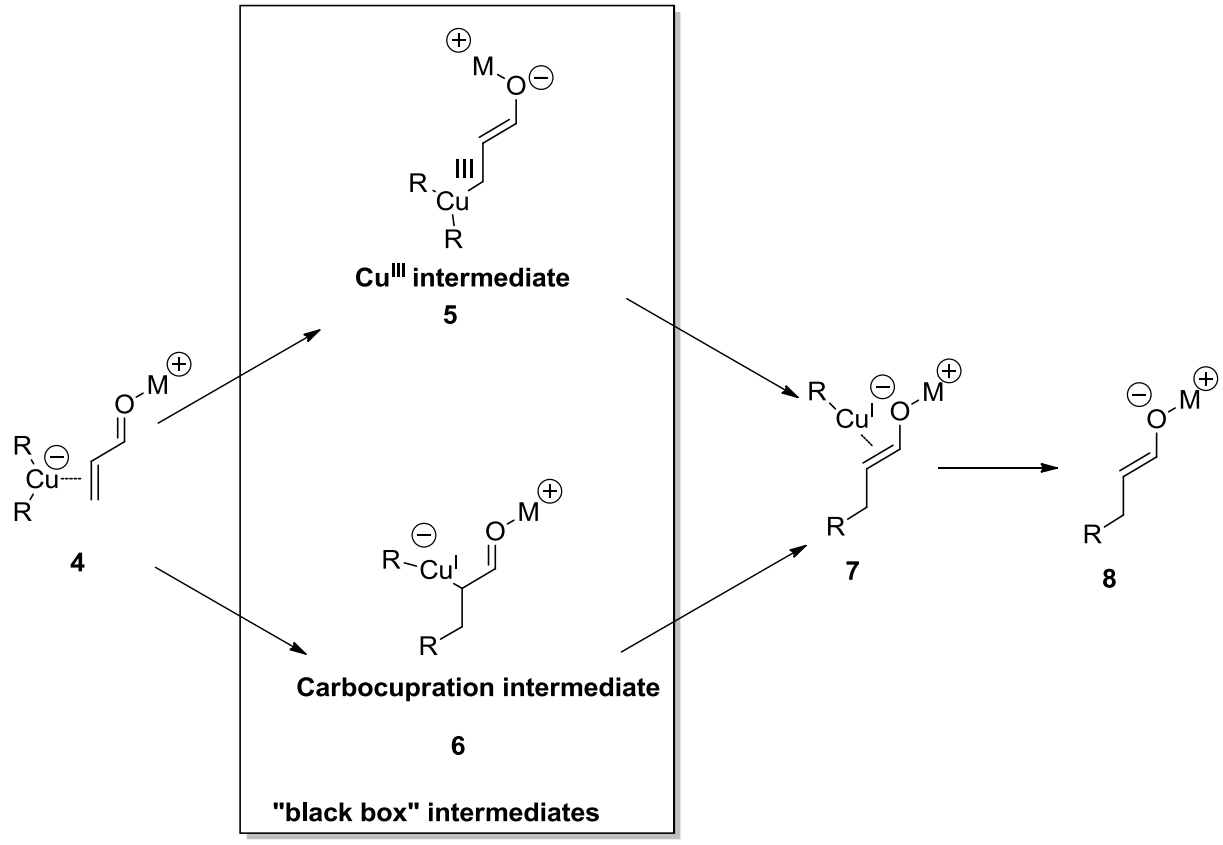


Figure 1.2 Oxidative Addition vs. Carbocupration for the 1,4-cuprate Addition to Acrolein[1b]

In addition, organocuprates are not limited to reactions with α,β-unsaturated ketones, but also readily react with acetylenic compounds. Since the first report on the carbocupration of acetylene in the early 1970's, organocuprates have been widely used for this C-C bond forming transformation as well. Once again, there are many mechanistic variations for the carbocupration of acetylene, but one has become more accepted due to its theoretical and experimental support.[1a] The reaction pathway may be viewed as a "trap-and-bite" mechanism shown below in figure 1.3.

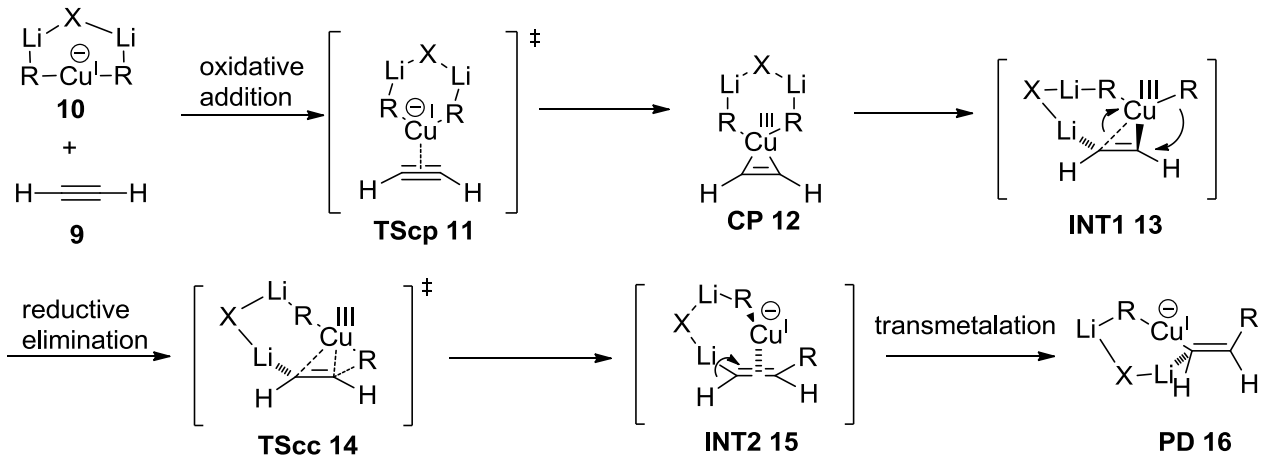


Figure 1.3. The "Trap and Bite" Pathway of the Carbocupration of Acetylene[1a]

According to Nakamura and Mori, the six-centered homocuprate inserts itself by way of oxidative addition (**CP 12**), and then opens up and "traps" the acetylene (**INT1 13**). Then, it transfers electrons and "bites" the substrate to form the C-C bond (**TScc 14**), which is thought to be the rate-determining step of the carbocupration reaction. Since the C-Cu(III) bond is very unstable, the activation energy for the reductive elimination C-C bond forming step becomes small (<20 kcal mol^{-1}) and presumably making the transformation more favorable. Finally, the

transmetalation from lithium to Cu(I) by way of the intermediate **15** should provide the product **16**.

In addition to Nakamura and Mori's report, they surmise that the conjugate addition reaction pathway only has one major difference from the "trap and bite" mechanism above (figure 1.3). In both reactions, it is thought that the stable C-Cu (I) bond is converted to an unstable C-Cu(III) bond (**5**), and the only variation being the product of conjugate addition remains as a lithium enolate complexed with Cu(I) (**7**), whereas the initial product (**INT2 15**) reacts further via transmetalation to generate **PD 16**.

1.3 Corey and Katzenellenbogen's first stoichiometric carbocupration of alkynoates

The first stoichiometric carbocupration of alkynoates was reported by Corey and Katzenellenbogen and furnished α,β-unsaturated esters in high yields and diastereoselectivity.[3] They found that the stereochemistry of the products was highly dependent upon the nature of the solvent and the temperature of the reaction. As depicted below in figure 1.4, when the reaction was carried out at –78 °C in THF, *cis* addition took place exclusively, and **18** was afforded in 95% yield and with stereochemical purity greater than 99%.

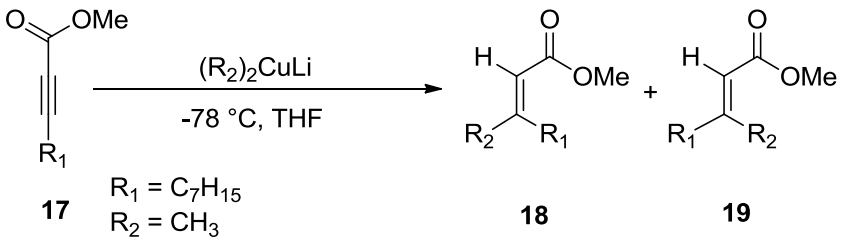


Figure 1.4. Stereospecific Synthesis of **18**[3]

Corey and Katzenellenbogen reported that the addition to ynoates proceeds *cis* selectively in THF at low temperature, whereas *cis/trans* mixtures are obtained at higher temperatures.[3] As delineated below in figure 1.5, the former result was explained by Krause later in terms of *cis*-**22** and the loss of stereoselectivity through isomerization of the vinyl cuprate *cis*-**22** to *trans*-**22** via an allenolate **23** by increasing the reaction temperature.[1c]

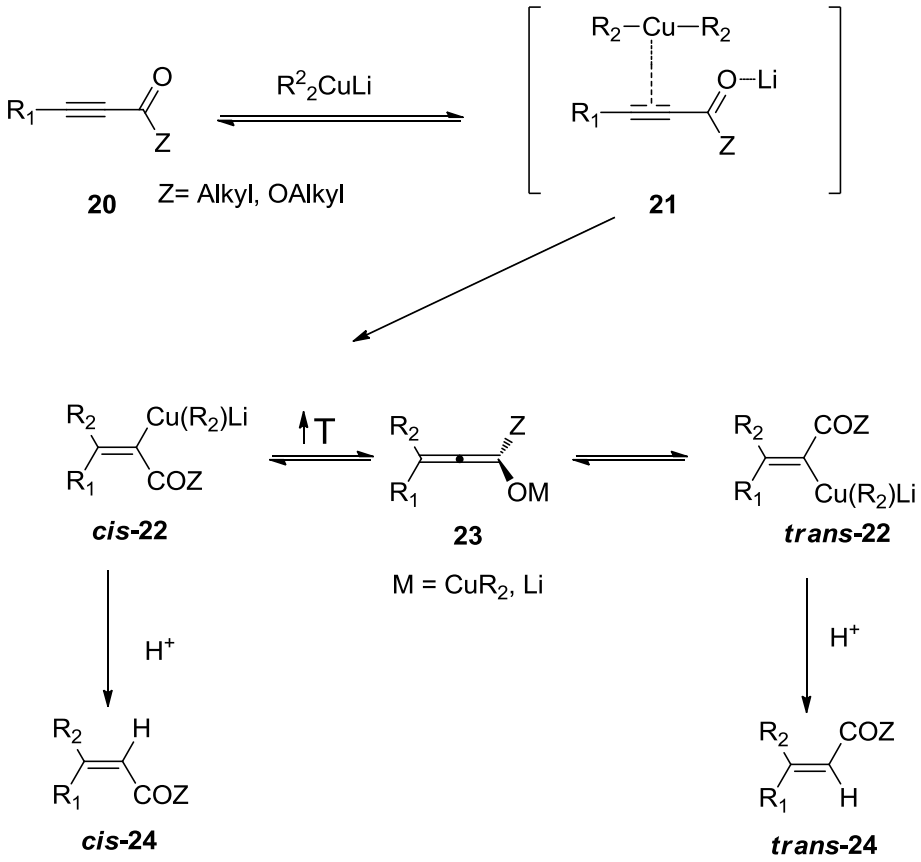


Figure 1.5. Reaction Scheme for the Formation of *cis*/*trans* Mixtures[1c]

Therefore, researchers reported that the diastereoselectivity was hard to control via protonation of allenoates at higher temperatures and may depend on acidity or steric properties of the proton source, and advised using conditions that favor the formation of the alkenylcuprates **22** rather than allenolates **23** to optimize steresoselectivity.[1c]

1.4 Lewis acid additives

Most notably, the significant effect of additives was shown by cuprate conjugate additions in the presence of chlorotrimethylsilane (TMSCl).[6] TMSCl frequently resulted in a dramatic increase in the rates of the reactions, affected the stereochemical outcome of the cuprate reactions, and allowed reactions to proceed which otherwise would have failed. One of many proposals for the origin of these effects was Corey and Boaz's theory.[6d] Depicted below in figure 1.6, they suggested that TMSCl accelerates the conjugate addition of cuprates to α,β-unsaturated ketones by silylation of complex **26** to give the silyl enol ether **27** of a β- "Cu^{III}" adduct, which would designate the silylation as the rate-limiting step rather than the C-C bond forming step and provide **28**. In 1985, results from a study of the ^{13}C and ^{17}O kinetic isotope effects were observed for the chloromethylsilane-mediated reaction of cyclohexenone **25** and were consistent with Corey's proposal that TMSCl traps an intermediate π complex **27** with the specification that silylation is the rate-determining step.[6d]

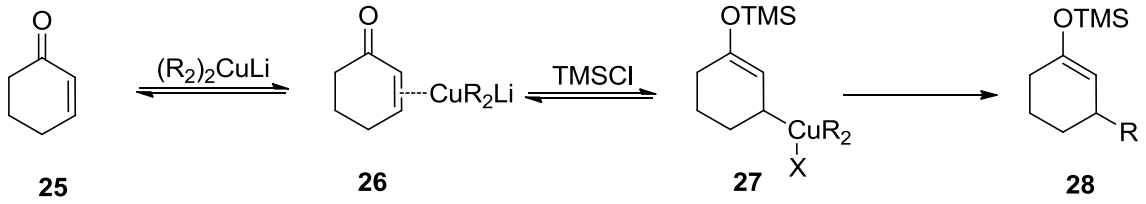


Figure 1.6. Corey and Boaz's Theory[6d]

Also, it has been shown that not only do Lewis acid additives such as TMSCl accelerate the carbocupration of alkynoates, but also isomerize the intermediate vinyl cuprate to the TMS

allenolate thus releasing the bound organocuprate, which will be discussed in greater detail in section 1.5.[1c,6]

1.5 TMSCl-mediated catalytic carbocupration of alkynoates

To this point, only the stoichiometric carbocupration of alkynoates has been reported, which brought about investigating the possibility of using catalytic amounts of copper(I)-lithium salt and converting this stoichiometric process into a catalytic one. Preliminary work based on the catalytic activities of Cu(I) salts towards ynoates reported by Munch-Petersen, Klein, and Jalander was very disappointing.[7] It seemed that the catalyst turnover was not occurring due to the stability of the intermediate vinyl cuprate **29**. There was no isomerization to the allenoate **30**; therefore, the cuprate was not being released back into the catalytic cycle (figure 1.7).

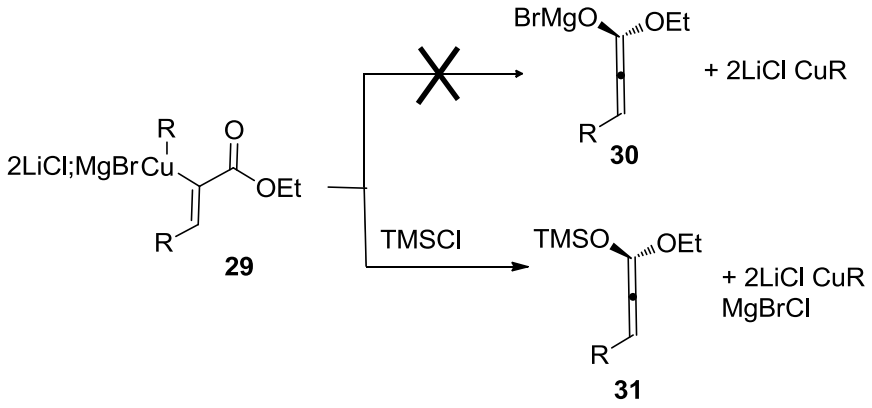


Figure 1.7. TMS-mediated Isomerization of **29**-**31**

Based on the previous observation that Lewis acid additives accelerate conjugate addition of cuprates to Michael acceptors, it was thought that TMSCl might induce an isomerization of the vinyl cuprate **29** to form the TMS-allenolate **31** and allow for only a catalytic amount of Cu^1 catalyst.[6] As shown in figure 1.8, it was also envisioned that *syn*-carbocupration of ethyl

propiolate with diphenylmagnesiocuprate should furnish the vinyl cuprate which should then be isomerized, by addition of TMSCl, to the TMS allenoate via release of the organocuprate.

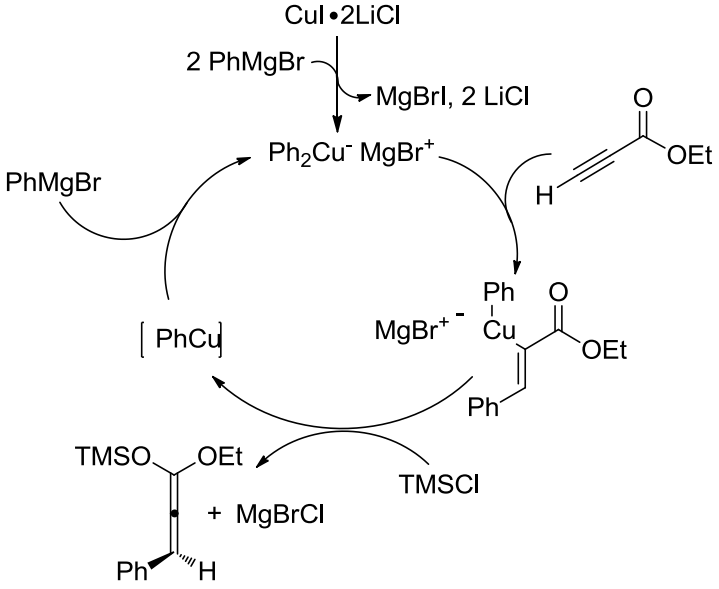


Figure 1.8. Catalytic Carbocupration via a TMS Allenolate

With this in mind, Dr. Jennings and former graduate student Kailas Sawant found that the addition of TMSCl to the reaction mixture presumably lead to **31** and allowed for the turnover of the copper(I) salt.[2a] They performed a number of reactions and summarized the effect of temperature and catalyst loading on the TMSCl-mediated carbocupration reaction shown in figure 1.9.

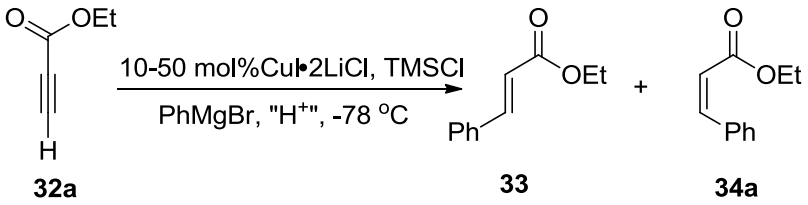


Figure 1.9. Catalytic Carbocupration of Alkynoates

The results are delineated in table 1.1 and led to two remarkable effects with respect to yield and diastereoselectivity. Firstly, it was observed that diastereoselectivity was influenced by reaction temperature with 30 mol % catalyst loading. Warming the reaction mixture from –50 °C to –35 °C produced a lower E/Z ratio with a slightly lower yield, and no catalysis was recorded at 0 °C. If the reaction was carried out at –78 °C with 30 mol% Cu(I), a significant increase in diastereoselectivity for the *E*-isomer **33** was observed (entry 7). It was also found that both the reaction and protic quench must be performed at –78 ° C or the isomeric ratio decreased to 3:1.

Second, the higher the catalyst loading, the better the yield and diastereoselectivity were reported for the *E*-isomer **33.** This trend is shown in entries 5-9, with 50 mol % catalyst loading being the best in both respects.

Table 1.1. TMSCl-CuI•2LiCl Catalyzed Carbocupration of **32a** with PhMgBr in THF

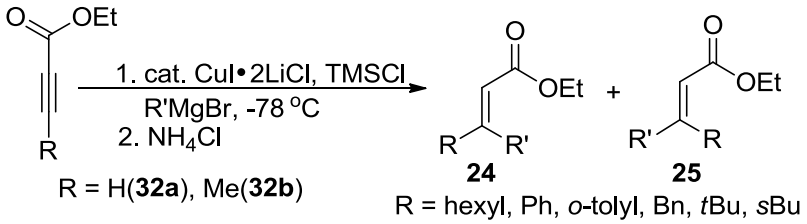
#	Temperature [°C]	Catalyst	mol%	Yield %	*E*[a]	*Z*
1	0	CuI•2LiCl	30	28	91	9
2	-35	CuI•2LiCl	30	72	64	36
3	-50	CuI•2LiCl	30	85	78	22
4[b]	-78	CuI•2LiCl	30	75	76	24
5	-78	CuI•2LiCl	10	44	43	57
6	-78	CuI•2LiCl	20	85	70	30
7	**-78**	**CuI•2LiCl**	**30**	**87**	**90**	**10**
8	**-78**	**CuI•2LiCl**	**40**	**90**	**92**	**8**
9	**-78**	**CuI•2LiCl**	**50**	**91**	**95**	**5**

(a) *E*/*Z* ratio determined by ^{1}H NMR spectroscopy (360 MHz) of the crude reaction mixture. (b) Reaction warmed to 0 °C, then quenched with NH_4Cl.

The scope of the reaction was expanded by performing the reaction with various aliphatic and aromatic Grignard reagents (table 1.2), all proceeding fairly well with mediocre to excellent yields and good diastereoselectivities, except for the very low yielding, sterically hindered 2-Mesityl organocuprate (entry 9). The reaction proceeded well in coordinating solvents such as

THF and DME, but Et_2O did not allow for the carbocupration under these conditions. Interestingly, they introduced a substituted alkynoate **32b** (entries 12-14) and were pleased to observe it to be catalytic and selective.

Table 1.2. TMSCl-CuI·2LiCl Catalyzed Carbocupration (50 mol%) of **32a** and **32b** with Various Grignard Reagents



#	Ester	Solvent	Grignard reagent	Yield [%]	E[a]	Z
1	32a	THF	PhMgBr[b]	91	95	5
2	32a	Et_2O	PhMgBr	< 5	NR	NR
3	32a	DME	PhMgBr	92	93	7
4	32a	THF	MeMgBr[b]	87	87	13
5	32a	THF	*hexyl*MgBr[b]	91	88	12
6	32a	THF	*tert*-butylMgCl[c]	77	88	12
7	32a	THF	*sec*-butylMgCl[d]	88	95	5
8	32a	THF	*o*-tolylMgCl[e]	71	97	3
9	32a	THF	MesitylMgBr[f]	23	98	2
10	32a	THF	$PhCH_2MgCl$[b]	92	97	3
11[g]	32a	THF	$PhCH_2MgCl$	89	93	7
12[g]	32b	THF	PhMgBr[b]	55	87	13
13	32b	THF	PhMgBr	72	89	11
14	32b	THF	$PhCH_2MgCl$[h]	74	91	9

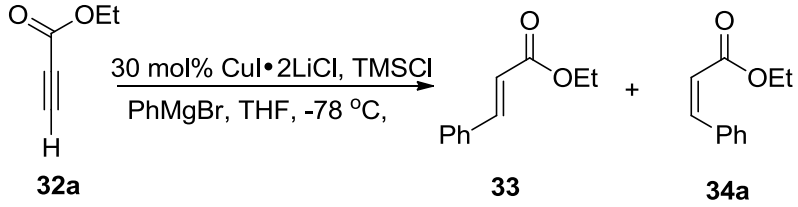
[a] *E*/*Z* ratio determined by ^{1}H NMR spectroscopy (30 MHz) of the crude reaction mixture. [b]Resulting products are commercially available. [c] Ref. 8a [d]Ref. 8b [e] Ref. 8c [f] Ref. 8d [g] Reactions ran with 30 mol% CuI·2LiCl. [h]Ref. 8e.

In conclusion, Jennings and Sawant observed the extraordinary effect of catalyst loading on stereochemical induction and accomplished the first highly diastereoselective TMSCl-promoted

catalytic carbocupration of α,β-acetylenic esters with the use of sub-stoichiometric amounts (as low as 30 mol%) of copper(I) salt in conjunction with a series of Grignard reagents. Also, they expanded the scope of the reaction to include substituted alkynoates.

1.6 Variations of the TMSCl-mediated catalytic carbocupration of alkynoates

With the work accomplished by Jennings and Sawant in mind, we decided to explore different reaction conditions starting with varying the protic quench in hope of finding catalytic, diastereoselective conditions for the *Z*-isomer (figure 1.10).



32a **33** **34a**

Figure 1.10. Catalytic Carbocupration of Alkynoates with 30 mol% Cu(I)

Prior to the results shown below in table 1.3, only ammonium chloride had been used to quench the reaction and was done so at –78 °C (entry 1).[1a] Therefore, we utilized other proton sources ranging from small ones (MeOH) to larger ones (PTSA) and found that the ammonium chloride quench was still the most optimal for the (*E)*-ethyl cinnamate **33**. The other quenches reduced selectivity, but still favored the (*E*)-isomer and gave no remarkable results toward affording the *Z*-isomer **34a** selectively.

Table 1.3 CuI•LiCl Promoted Carbocupration with a Variety of Proton Sources

#	mol %	TMS-X	Quench	Yield %	*E*[a]	*Z*
1	30	Cl	NH_4Cl	87	9	1
2	30	Cl	MeOH	86	6	1
3	30	Cl	H_2O	68	4	1
4	30	Cl	HCl	60	3	1
5	30	Cl	TFA	76	3	1
6	30	Cl	PPTS	62	4	1
7	30	Cl	CSA	63	3	1
8	30	Cl	PTSA	65	3	1

(a) *E*/*Z* ratio determined by ^{1}H NMR (360 or 500 MHz) from the crude reaction mixture

Next, we were interested in changing the catalyst and observing how it would affect the outcome of the reaction. In table 1.4, a variety of reactions are delineated using CuI, CuBr, and CuCl in conjunction with LiCl, LiBr, and LiI in different sequences and using ammonium chloride as the proton source. To our dismay, our results were still in favor on the *E*-isomer **33** and actually less selective.

Table 1.4. TMSCl-CuX•LiX Catalyzed Carbocupration of **32a** with PhMgBr in THF

#	mol%	Catalyst	Quench	Yield [%]	E^a	Z
1	30	CuI•LiCl	NH_4Cl	87	9	1
2	30	CuI•LiBr	NH_4Cl	65	2	1
3	30	CuI•LiI	NH_4Cl	60	5	1
4	30	CuBr•LiCl	NH_4Cl	95	2	1
5	30	CuBr•LiBr	NH_4Cl	92	1	1
6	30	CuBr•LiI	NH_4Cl	55	3	1
7	30	CuCl•LiCl	NH_4Cl	70	4	1
8	30	CuCl•LiBr	NH_4Cl	80	2	1
9	30	CuCl•LiI	NH_4Cl	55	8	1

(a) *E*/*Z* ratio determined by ^{1}H NMR (360 or 500 MHz) from the crude reaction mixture.

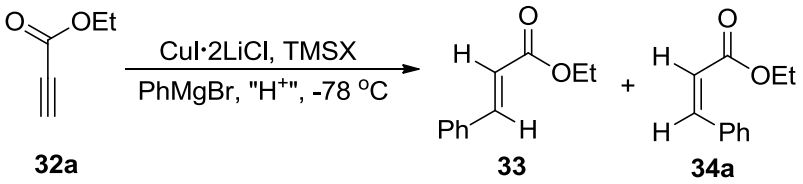
1.7 A highly stereoselective TMSOTf-mediated catalytic carbocupration of alkynoates

After some of our preliminary work shown in table 1.3 and 1.4, we decided to change the Lewis acid additive from TMSCl to TMSOTf. Our initial reasoning behind using TMSOTf was its increased Lewis acidity compared to TMSCl, and we surmised that TMSOTf would lead to amplified catalytic efficiency and allow for a much lower catalyst loading. We were pleased to observe (table 1.5) that the first reaction we tried with TMSOTf and 30 mol% copper (entry 5) worked well and led us to believe that we could lower the catalyst loading and incorporate a suitable proton source and hopefully provide the (*Z*)-substituted olefin **34a**.

As shown in table 1.5 and previously in table 1.1, we initially observed that TMSCl readily promoted the catalytic carbocupration of ethyl propiolate **32a** at high catalyst loadings with PhMgBr. The reaction afforded good yields and diastereoselectivities for (*E*)-ethyl cinnamate **33** after quenching with NH_4Cl. However, proton addition to the TMS allenolate intermediate with TFA as the quenching source led to a decrease in *E* selectivity (entry 4). Then,

by switching the Lewis acid from TMSCl to TMSOTf and maintaining TFA as the proton source showed degradation of the *E* selectivity and provided a comparable yield. Further lowering the catalyst loading to 20 mol% and maintaining the TFA quench dramatically changed the selectivity providing the (*Z*)-ethyl cinnamate in a 5:1 ratio. Much to our delight, dropping the catalyst loading down to 10 mol% (6:1), then 5 mol% led to a 91% yield and an exceptional 13:1 ratio for the *Z*-isomer **25a**[9a] (entry 8). Also, catalyst loadings even as low as 3 mol% gave high levels of diastereoselectivity, but the yield decreased. Other proton sources were examined (entries 10-14), but were inferior to TFA with respect to selectivity and yield. This reaction proceeded well in THF, but not in other ethereal solvents such as Et_2O and MTBE.[2b]

Table 1.5. CuI•2LiCl Promoted Carbocupration of **32a** with PhMgBr



32a **33** **34a**

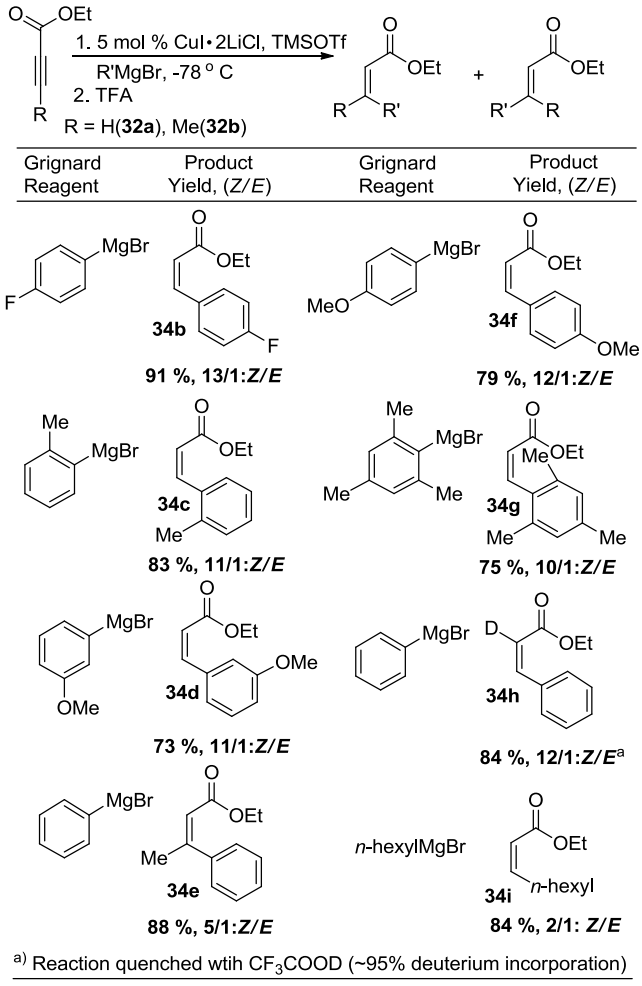
#	Mol%	TMS-X	Quench	Yield %	*E*[a]	*Z*
1	50	Cl	NH_4Cl	91	20	1
2	40	Cl	NH_4Cl	90	12	1
3	30	Cl	NH_4Cl	87	9	1
4	30	Cl	TFA	76	3	1
5	30	OTf	TFA	81	2	1
6	20	OTf	TFA	85	1	5
7	10	OTf	TFA	84	1	6
8	**5**	**OTf**	**TFA**	**91**	**1**	**13**
9	**3**	**OTf**	**TFA**	**81**	**1**	**12**
10	5	OTf	NH_4Cl	85	1	7
11	5	OTf	PPTS	55	1	4
12	5	OTf	TfOH	71	1	5
13	5	OTf	CSA	57	1	6
14	5	OTf	HCl	63	1	6
15[b]	5	OTf	TFA	<5	NR	NR
16[c]	5	OTf	TFA	<5	NR	NR

(a) *E*/*Z* ratio determined by ^{1}H NMR (350 or 500 MHz) from the crude reaction mixture. (b) reaction ran in Et_2O (c) reaction ran in *t*BuOMe

With this information in hand, we examined the scope of the TMSOTf promoted catalytic carbocupration of **32a** and **32b** (table 1.6). To our delight, the reactions proceeded with ortho, meta, and para-substituted aryl Grignard reagents to provide the *Z*-olefins **34a**-**34i**[9] in good yields and high levels of diastereoselectivities irrespective of steric or electronic differences resident in the arene. For instance, the sterically hindered mesityl Grignard reagents underwent catalytic carbocupration selective for the *Z*-olefin **34g** in 75% yield with TMSOTf, whereas no

reaction was observed when TMSCl was the Lewis acid promoter.[2a] Also, both the 4-fluoro and 4-methoxyphenyl Grignard reagents afforded **34b** and **34f** in good yields and high levels of *Z* diastereoselectivity (12-13:1). In addition, quenching the TMS allenolate with TFA-D readily allowed for the chemo- and diastereoselective introduction of a deuterium atom α to the carbonyl moiety as predicted and afforded **34h**. Also, we found that TMSOTf carbocupration of substituted ynoates **32b** was feasible and furnished **34e** in a comparable yield of 88%, but a slightly diminished 1/5:*E/Z* ratio. Lastly, we observed that aliphatic Grignard reagents underwent TMSOTf mediated catalytic carbocupration and provided **34i** in a comparable 84% yield to that of the aromatic ones. To our dismay, the selectivity was significantly lower (2:1) in favor of the *Z* product.

Table 1.6. TMSOTf-CuI•2LiCl Catalyzed Carbocupration (5 mol%) with Various Grignard Reagents



In addition, it is worth noting that we performed the catalytic carbocupration reaction under the same conditions (5 mol% copper, TFA quench) as delineated in table 1.6 except three different Lewis acid additives were chosen: TMS-Br, TMS-Cl, and TMS-I. All three Lewis acids provided comparable yields (88%), and TMS-Br and TMS-I provided **34a** in a 1:10 *E/Z* ratio. However, when TMSCl was used as the Lewis acid, the *Z*-selectivity for **34a** decreased to 1:3 *E/Z*.

1.8 Further investigation of catalyst loading and ammonium chloride on selectivity

Thus far, the catalyst loading had the most dramatic effect on the *E/Z* selectivity of the catalytic carbocupration reaction. The lower the catalyst loading, the more selective the reaction was for the *Z*-isomer, and the higher the loading, the more selective for the *E*-olefin. With this being said, we tried a couple of reactions in hope of being able to explain this remarkable effect. We envisioned that the *Z*-isomer was initially being formed at –78 °C, but when larger catalyst loadings were being used, a conjugate addition was taking place and isomerizing the Z-alkene **34a** to the *E*-ethyl cinnamate **33**. We surmised that the iodide from the CuI•2LiCl catalyst could act as a nucleophile and isomerize the *cis*-alkene to the *trans*-alkene; therefore, we submitted the *Z*-α-β-unsaturated ester **34a** back to 30 mol% CuI•2LiCl in THF and allowed it to stir for 24 hours at room temperature. After NMR analysis, the *Z*-selectivity had decreased from 13:1 to 5.8:1 Z:*E* . Next, **34a** was placed back into 30 mol% CuI•2LiCl in THF followed by the addition of ammonium chloride and allowed it to stir for 24 hours at room temperature. Our reasoning behind this was to see if the ammonia played a role in the isomerization. Unfortunately, no change was reported, and it is still not exactly clear how the selectivity is driven towards the *E* or the *Z* olefin when changing the two important factors of catalyst loading and proton source.

1.9 Conclusion

In conclusion, Jennings and Kailas' work has shown that TMSCl, temperature, and catalyst loading have remarkable effects on the yields and selectivities of the carbocupration of alkynoates.[2a] With this in mind, we were able to accomplish the first highly diastereoselective catalytic carbocupration of α,β-acetylenic esters.[2b] Not only does TMSOTf allow for catalytic carbocupration of ynoates with 5 mol% Cu(I), but also the incorporation of TFA as the proton source provides selectively the (*Z*)-substituted α,β-unsaturated esters. Thus far, the reaction has few limitations, but one does include its decreased selectivity with aliphatic Grignard reagents.

CHAPTER TWO: VICINAL FUNCTIONALIZATION OF PROPIOLATE ESTERS VIA A TANDEM CATALYTIC CARBOCUPRATION-MUKAIYAMA ALDOL REACTION SEQUENCE

2.1. Introduction

Chapter two highlights our new catalytic carbocupration reaction that constructs two carbon-carbon bonds in one flask and provides Baylis-Hillman type alkenes with high levels of diastereoselectivity.[2c] The construction of these synthetically important and useful compounds is of great interest to the organic field and may be accomplished from many different approaches. Therefore, this chapter discusses a few of these and includes insight on the vicinal functionalization of olefinic or acetylenic compounds to achieve multiple carbon-carbon bond forming reactions, in particular a Michael addition via a Kharash or Gilman reagent followed by an electrophilic quench, to afford β-branched Baylis Hillman adducts.[10] Although, this multiple carbon-carbon bond forming reaction is well known, very little has been reported on the vicinal functionalization of α,β-acetylenic esters via a silyl allenolate.[11] Previously in chapter one, we showed our interest in developing a diastereoselective, catalytic carbocupration of ynoates; therefore, along this same line, we investigated the vicinal functionalization of propiolate esters via a tandem catalytic carbocupration-Mukaiyama aldol reaction sequence and envisioned trapping a silyl allenolate in situ with an electrophilic partner.[2c] Herein, we report a two carbon-carbon bond forming process in a single pot that is not only good yielding, but highly diastereoselective.

2.2 Baylis-Hillman-type adducts

One well-documented approach for constructing two carbon-carbon bonds in one flask is vicinal functionalization of olefinic or acetylenic compounds to afford Baylis-Hillman-type adducts. A general Baylis-Hillman reaction (figure 2.1) involves the coupling of activated alkenes **36** with carbon electrophiles **35** under the influence of a tertiary amine, such as DABCO.[12] It results in the formation of a carbon-carbon bond between the α-position of an activated alkene and the electrophile containing an electron-deficient sp^2 carbon atom to provide **37**.

Figure 2.1. Baylis Hillman Reaction[12]

A variety of activated alkenes as well as aldehydes have been used over the years and the reaction has been shown to be chemo, regio, diastereo, and enantioselective and affords many useful synthetic intermediates. Aliphatic, aromatic, hetero-aromatic, α,β-unsaturated, and functionalized aldehydes in conjunction with acrylic esters, acrylonitrile, vinyl ketones, phenyl vinyl sulphone, phenyl vinylsulphonate, vinyl phosphonate, allenic acid esters, and acrolein have all been employed to afford aldol-type products, which are some of the most useful intermediates in organic chemistry (figure 2.2).[12]

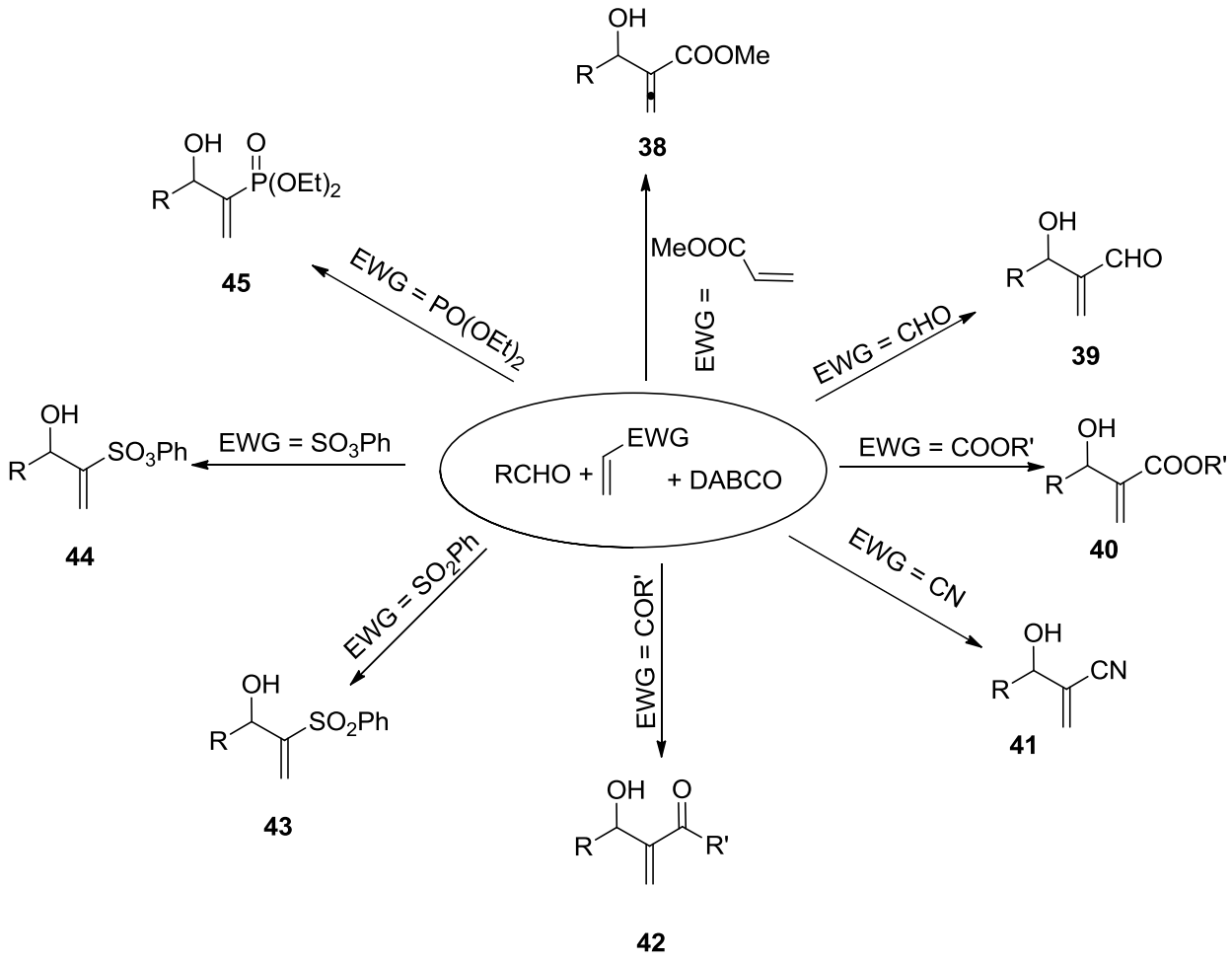


Figure 2.2. Baylis-Hillman Reaction with RCHO and Various Activated Alkenes[12]

Also, Baylis-Hillman adducts are synthetically important precursors for chemically and biologically important compounds having an array of multifunctional groups.[13] In fact, the acrylate unit features in a large number of naturally occurring, biologically active compounds. For example, conocandin **46** (a fungistatic antibiotic), eremophildienoic acid **47**, the fatty acid derivative of β-alanine **48**, the sesquiterpene gerin **49**, the monoterpene dialdehyde **50**, the tremetone derivative **51**, and probably the most studied antitumor agent vernolepin **52** (figure 2.3).

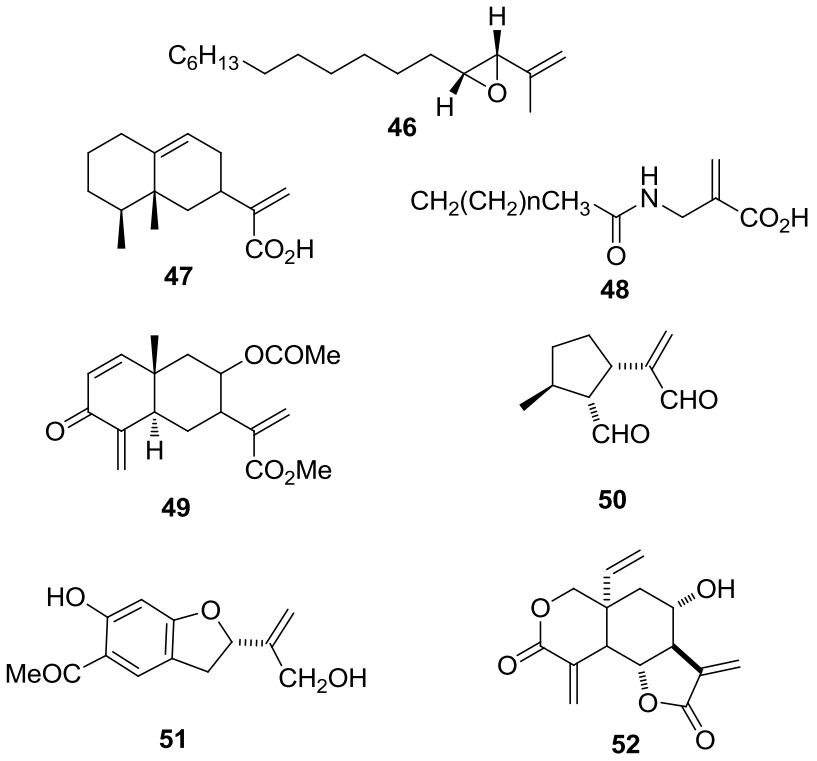


Figure 2.3. Natural Occurrence of Baylis-Hillman Type Adducts[13]

In addition, Baylis-Hillman type compounds may be used to synthesize strained heterocyclic systems, which are attractive targets due to their high reactivity and potential for acting as chiral templates. For example, Howell et al. prepared 3-alkylidene-2-methyleneoxetanes **55** via Baylis-Hillman-type adducts (figure 2.4).[14]

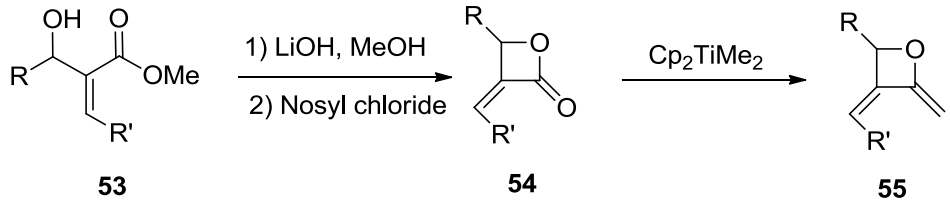


Figure 2.4. Synthesis of 3-alkylidene-2-methyleneoxetanes[14]

Aldol product **53** was hydrolyzed and cyclized to afford lactone **54** followed by methylenation with dimethyltitanocene to furnish **55**, which is a uniquely strained heterocycle and target for synthetic development.

2.3. Vicinal functionalization of α,β-unsaturated carbonyl compounds to afford β-branched Baylis Hillman adducts

Unfortunately, the original Baylis-Hillman system has serious limitations, for instance, β-substituted acrylate olefins do not normally undergo the Baylis-Hillman reaction, and reaction rates can be days to even weeks. Due to the versatility and usefulness of these β-branched Baylis-Hillman adducts, a lot of attention has been given to forming multiple bonds in one pot and affording these attractive compounds. For example, Wei and workers synthesized (*Z*)-*β*-bromo Baylis-Hillman ketones using a one-pot three component process to vicinally functionalize α,β-acetylenic ketones and formed a carbon-carbon and a carbon-bromine bond in one pot (figure 2.5).[10e] Their system used a stoichiometric amount of $MgBr_2$ as both the bromine source and Lewis acid promoter for the Michael-type addition of **56**. After the bromo addition, an active bromo-allenolate intermediate **57** was formed, which was quenched with an aldehyde to furnish a bromo-Baylis-Hillman adduct **58** in good *Z*-selectivity and yield at room temperature.

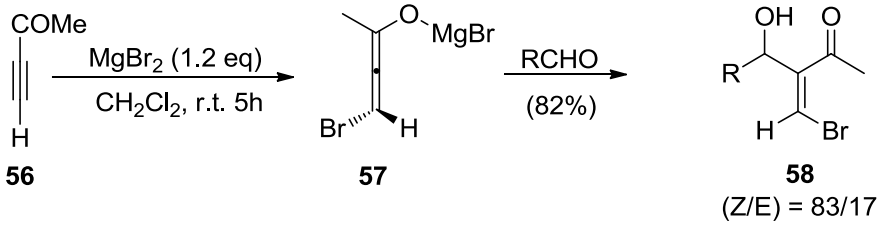


Figure 2.5. $MgBr_2$ Mediated Reaction for Synthesis of β-bromo Baylis-Hillman Ketones[10e]

Also, utilization of Kharash or Gilman reagents for Michael additions followed by electrophilic quench is a common approach to the vicinal functionalization of α,β-unsaturated carbonyl compounds. However, there are only a few reports regarding the vicinal functionalization of α-β-acetylenic esters to afford β-substituted Baylis-Hillman type products. One of the few examples involving reactions with esters was reported by Wei and co-workers, and they observed that a stoichiometric carbocupration of **59** under Corey's conditions with Gilman reagents followed by electrophilic quenching with an aldehyde led to β-hydroxy-α-olefinic esters **61** in good yields and dr (figure 2.6).[10j] Both aromatic and aliphatic esters were used as the substrates for the Michael addition, as well as aromatic and aliphatic Grignard reagents were used for the carbocupration. High diastereoselectivity was reported in most cases (95:1 *Z*/*E*), except when using substituted propiolate derivatives. It was thought that steric effects of the two terminal groups of the allenolate were responsible for the decreased *Z*/*E* selectivity of the β,β-disubstituted Baylis-Hillman type products. They expanded the scope of the reaction by investigating substituted propiolate derivatives; however, only aromatic aldehydes were used as the electrophiles in the reaction sequence.

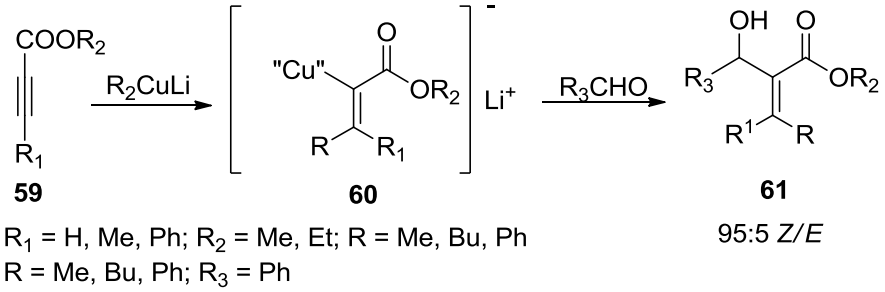
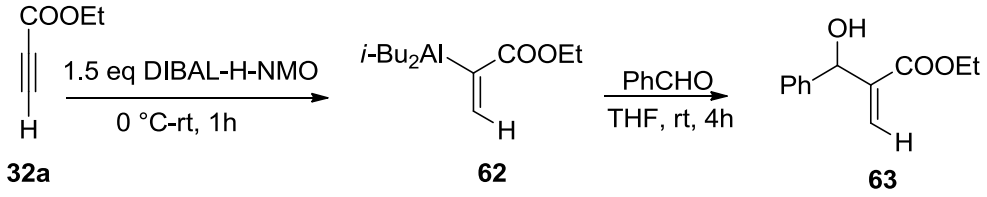


Figure 2.6. Synthesis of Unusual Baylis-Hillman Adducts[10j]

2.4 Vinylalumination for the synthesis of Baylis-Hillman adducts

Another approach to preparing β-substituted Baylis-Hillman type adducts was taken by Ramachandran and workers, and they investigated the vinylalumination of a variety of carbonyl compounds with DIBAL-H and *N*-oxide (NMO).[15] Most notably, they observed the vinylalumination of ethyl propiolate **32a** to provide **62**. Then, they examined the reaction with benzaldehyde and upon hydrolysis afforded **63** in 95% yield and excellent dr. They were also successful in doing this with activated ketones and other activated carbonyl compounds. Although this reaction was advantageous to prior vinylaluminations, it still had its drawbacks of being neither catalytic nor a multiple bond forming process. In order to provide β-branched Baylis-Hillman adducts, the appropriate substituted propiolate starting material must be utilized and often resulted in lower yields.



32a **62** **63**

Figure 2.7. Vinylalumination for Synthesis of **63**[15]

2.5 Vicinal functionalization of propiolate esters via a tandem catalytic carbocupration-Mukaiyama aldol reaction sequence

As stated above, the electrophilic capture of allenes derived from carbonyl compounds has been reported[10,11] (section 2.3), but a one pot, catalytic vicinal functionalization of α,β-acetylenic esters via a silyl allenolate had not yet been investigated until our research, which is

reported herein.[1c] Our approach involves a tandem catalytic carbocupration-Mukaiyama aldol reaction sequence. It is comparable to a Mukaiyama aldol reaction, which is a very powerful stoichiometric transformation of a Lewis acid mediated addition of an enol silane **64** to a carbonyl compound (PhCHO) to afford a crossed aldol product **65**.[16] This process was discovered by T. Mukaiyama in the early 1970's, and since then there have been many variations to the reaction, but the initial, general reaction is depicted below (figure 2.8).

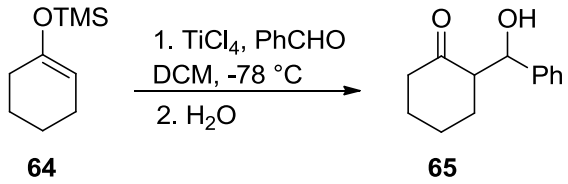


Figure 2.8. General Mukaiyama Aldol Reaction[16]

Based on our interest in developing a diastereoselective, catalytic carbocupration of α,β-acetylenic esters, we envisioned generating the silyl allenolate and trapping it with an electrophile in situ. In our previous work, we showed that TMSOTf not only accelerated the carbocupration of ynoates, but it also isomerized the intermediate vinyl cuprate to the TMS allenolate thus releasing the bound organocuprate.[2a,2b] Comparable to the catalytic cycle in figure 1.8, we surmised *syn*-carbocupration of ethyl propiolate with dialkyl or aryl magnesiocuprate should furnish the vinyl cuprate, which should then be isomerized by the addition of TMSOTf to the TMS allenolate via release of the organocuprate. Presumably, the cuprate should then react with the RMgBr and complete the catalytic cycle. Finally, the electrophilic capture of the TMS allenolate with an aldehyde should provide the desired aldol, Baylis-Hillman type product via a catalytic carbocupration/Mukaiyama aldol reaction sequence (figure 2.9).

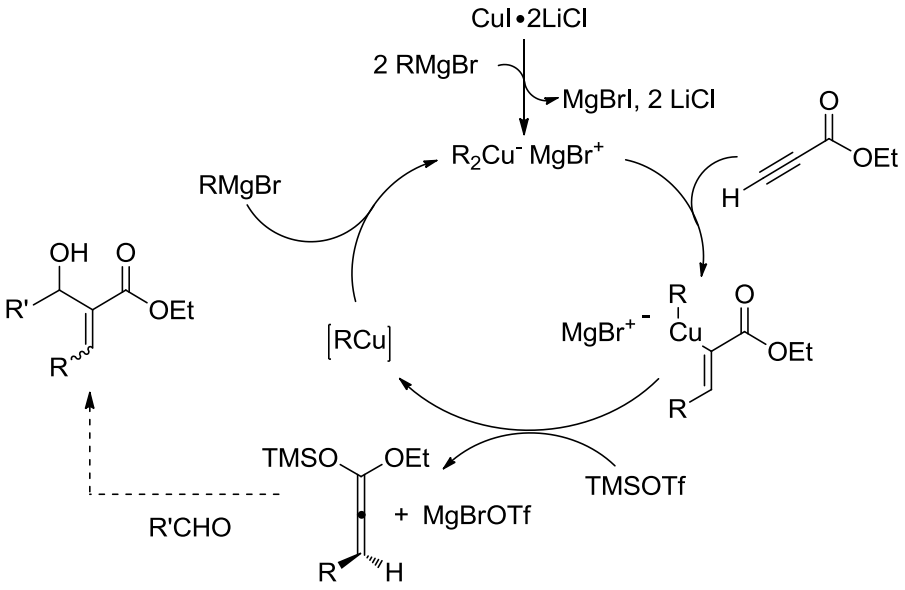


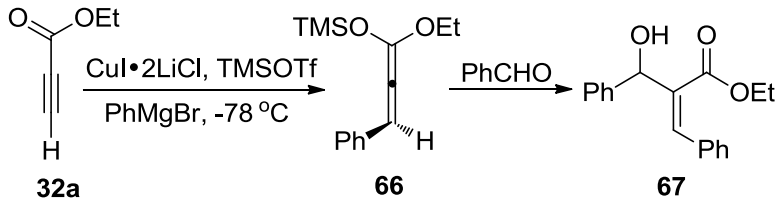
Figure 2.9. Catalytic Cycle for the Synthesis of Aldol, Baylis-Hillman Type Products

As shown in table 2.1, we investigated a number of factors that affected the carbocupration of **32a** to afford **67**. In our first attempt, we observed that 5 mol% CuI•2LiCl with PhMgBr followed by the addition of benzaldehyde and warming the reaction to room temperature did afford **67**[15] with an exceptional 20:1 d.r. for the (*Z*)-aldol product; however, with a reaction time of 1 or 3 hours, the reaction was low yielding (13-20%) over the two step process (entry 1 and 2). Our thinking was that the 30 mol% excess of TMSOTf was responsible for the activation of the aldehyde toward nucleophilic addition.

With **67** in hand and excellent dr, our efforts were directed towards improving the overall yield of the reaction. First, we allowed the reaction temperature to remain at -78 °C for 3 to 5 hours, which provided an improved yield of 30% (entry 3). Unfortunately, increasing the reaction time to 5 or even 21 hours did not improve the overall yield and entry 5 provided an inferior yield of 21%. Based on these results, we reasoned it was possible that the addition of a stoichiometric amount of Lewis acid would increase the electrophilicity of the aldehyde acceptor

and hopefully improve the overall yield by enhancing the capture of the nucleophilic TMS allenolate. Pleasingly, the addition of $TiCl_4$ and BF_3•OEt_2 did increase the overall yield of the one pot, two carbon-carbon bond forming process nearly 2-fold with yields of 40 (entry 6) and 59% (entry 7) and excellent dr of >20:1 *Z*/*E*. As shown in entry 8, increasing the catalyst loading to 30 mol% Cu(I) and using TMSCl instead of TMSOTf as the Lewis acid additive maintained a dr of 20:1 for the *Z*-product, but resulted in a lower yield. Also, we lowered the equivalence of TMSOTf from 1.3 to 1.05 equiv and found that the yield decreased to 32%. It is worth noting that in all cases the remaining material was a mixture of (*Z*)-α,β-unsaturated ester **34a** and starting material **32a**.

Table 2.1. Vicinal Functionalization of **32a** via a Catalytic Carbocupration/ Mukaiyama Aldol Reaction Sequence



32a **66** **67**

no.	mol%	T (˚C)	time (h)	additive	yield (%)	*Z*/*E*[a]
1	5	rt	1	none	13	>20:1
2	5	rt	3	none	20	>20:1
3	5	-78	3	none	30	>20:1
4	5	-78	5	none	30	>20:1
5	5	-78	21	none	22	>20:1
6	5	-78	3	$TiCl_4$	40	>20:1
7	**5**	**-78**	**3**	**BF_3•OEt_2**	**59**	**>20:1**
8[b]	30	-78	3	BF_3•OEt_2	40	>20:1
9[c]	5	-78	3	BF_3•OEt_2	32	>20:1

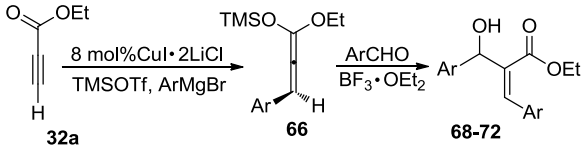
[a] *E/Z* ratio determined by ^{1}H NMR (360 or 500 MHz) from the crude reaction mixture. [b] Reaction ran with TMSCl in place of TMSOTf. [c] Reaction ran with 1.05 equiv TMSOTf instead of 1.3 equiv as reported in entries 1-7.

With our optimal conditions for the vicinal functionalization of **32a** in hand, we decided to investigate the scope of the reaction with a series of aromatic Grignard reagents and aldehydes. Initially, we observed that 4-fluorophenyl MgBr **68a** in conjunction with benzaldehyde **68b** provided **68** in a 55% yield and exceptional dr of >20:1 for the *Z*-aldol product. However pleased with this reaction, we decided to increase the catalyst loading from 5 to 8 mol%, and we observed an increase in yield from 55% to 61%. Increasing the catalyst loading above 8 mol% did not lead to amplified results, but we did have our new optimized conditions with 8 mol% of CuI•2LiCl and 1.3 equiv TMSOTf. As delineated in Table 2.1, we

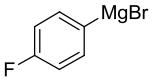
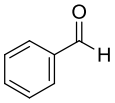
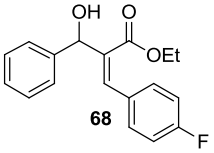
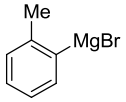
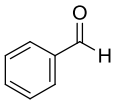
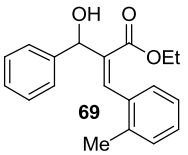
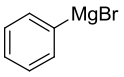
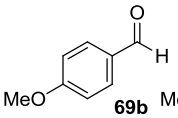
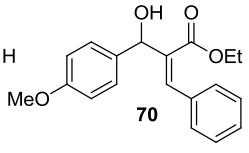
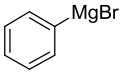
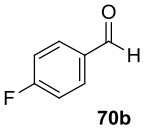
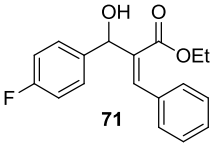
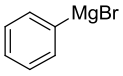
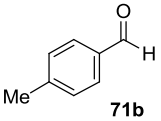
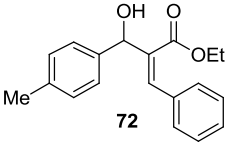
continued our investigation of the vicinal functionalization of **32a** with aromatic Grignards and aldehydes. When utilizing *o*-tolyl MgBr **69a** for the carbocupration and PhCHO **68b** as the electrophilic coupling partner, the reaction proceeded and **69** was isolated in 58% yield with a 15:1 dr for the *Z*-aldol isomer. We surmised that the slight degradation in selectivity from 20:1 for **68** was due to the more sterically hindered *o*-tolyl Grignard reagent. It is worth recalling that when the electrophilic quench of the silyl allenolate derived from **32a** with the *o*-tolyl Grignard reagent was a proton, the dr was slightly lower (11:1) than that of the Ph derived silyl allenolate (dr of 13:1 *Z*/*E*).[2b] The only other reaction sequence we observed with a lower level of diastereoselectivity was when anisaldehyde **69b** was utilized as the electrophilic partner with PhMgBr **70a**. The aldol product **70** was furnished in an overall 53% yield, but was a 7/1 *Z*/*E* mixture.

Much to our delight, the vicinal functionalization of **32a** with PhMgBr and the electron-poor 4-fluorobenzaldehyde **70b** provided the β-hydroxy-α-olefinic ester **71** in 63% yield and >20:1 dr. Also, the catalytic addition of the diphenylcuprate to **32a** followed by nucleophilic addition of the TMS allenolate to *p*-tolylaldehyde **71b** furnished **72** in 58% yield over the one pot, two-step process with a >20:1 dr.

Table 2.2. Vicinal Functionalization of **32a** via a Catalytic Carbocupration/Mukaiyama Aldol Reaction Sequence with Aromatic Grignard Reagents and Aldehydes



32a **66** **68-72**

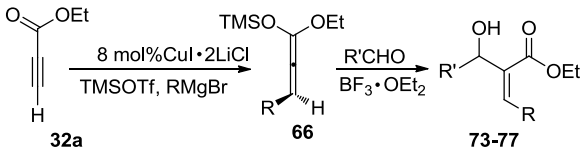
Grignard Reagent	Aldehyde	Product Yield, (*Z*/*E*)[a,b]
 **68a**	 **68b**	 **68** **61%, >20/1:*Z*/*E***
 **69a**	 **68b**	 **69** **56%, 15/1:*Z*/*E***
 **70a**	 **69b**	 **70** **53%, 7/1:*Z*/*E***
 **70a**	 **70b**	 **71** **63%, >20/1:*Z*/*E***
 **70a**	 **71b**	 **72** **58%, >20/1:*Z*/*E***

[a] *E*/*Z* ratio determined by ^{1}H NMR (360 or 500 MHz) from the crude reaction mixtures. [b] Yields are of the isolated pure compounds.

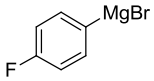
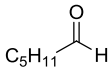
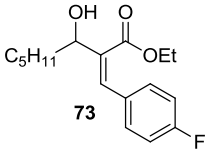
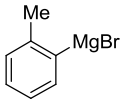
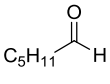
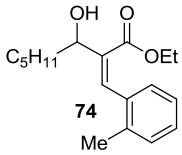
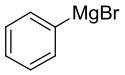
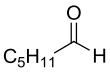
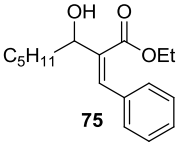
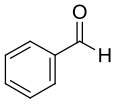
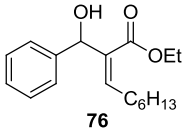
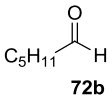
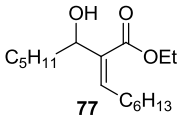
With the information from table 2.2 in hand, we further investigated the scope of the tandem catalytic carbocupration-Mukaiyama aldol reaction of **32a** with both aromatic and aliphatic Grignard reagents and aldehydes. In Table 2.3, the catalytic addition of the 4-

fluorophenyl Grignard reagent to **32a** followed by treatment with hexanal **72b** provided the *Z*-aldol product **73** in 62% yield an exceptional dr of >20:1. Comparably, initial carbocupration with **69a** and **70a** followed by the electrophilic quench with hexanal **72b** provided the β-hydroxy-α-olefinic esters **74** and **75** in virtually identical yields of 54 and 55%, while maintaining the excellent dr of >20:1. Pleasingly, we observed that using an aliphatic Grignard reagent **71a** had little effect on diastereoselectivity or yield. Thus, the catalytic carbocupration of **32a** with hexylMgBr **71a** followed by nucleophilic addition of the TMS allenolate to benzaldehyde **68b** afforded a 54% yield and virtually identical >20:1 dr for *Z*-aldol product **76**. Previously, when we had used hexylMgBr **71a** for the carbocupration of **32a** and quenched the intermediate TMS allenolate with a proton, a disappointing 2:1 dr was observed versus that of the aromatic derived silyl allenolates with diastereoselectivities from 10-13:1 for the Z product.[2b] Based on these observations, it appeared that the nucleophilic addition of an aliphatic TMS allenolate is dependent on the steric environment of the approaching proton or aldehyde electrophile. Similarly, utilizing an aliphatic Grignard reagent **71a** and aldehyde **72b** furnished **77** in 48% yield and an analogous dr of 20:1, as seen with compounds **73-76**.

Table 2.3. Vicinal Functionalization of **32a** via a Catalytic Carbocupration/Mukaiyama Aldol Reaction Sequence with Various Grignard Reagents and Aldehydes



32a **66** **73-77**

Grignard Reagent	Aldehyde	Product Yield, (*Z*/*E*)[a,b]
 **68a**	 **72b**	 **73** **62%, >20/1:*Z*/*E***
 **69a**	 **72b**	 **74** **54%, >20/1:*Z*/*E***
 **70a**	 **72b**	 **75** **55%, >20/1:*Z*/*E***
hexylMgBr **71a**	 **68b**	 **76** **54%, >20/1:*Z*/*E***
hexylMgBr **71a**	 **72b**	 **77** **48%, >20/1:*Z*/*E***

[a] *E*/*Z* ratio determined by ^{1}H NMR (360 or 500 MHz) from the crude reaction mixture. [b] Yields are of the isolated, pure compounds.

2.6. Vicinal functionalization of the β-substituted-α-β-acetylenic ester

After our observations delineated in table 2.2 and 2.3, we decided to attempt the vicinal functionalization of the β-substituted-α,β-acetylenic ester **32b** in hope of furnishing a highly stereodefined β-hydroxy-α-tetrasubstituted ester **79**. Thus, carbocupration of **32b** with *o*-tolylMgBr under the same conditions in table 2.2 and 2.3 did in fact afford the tetra-substituted TMS allenolate **78** and provided the aldol adduct **79** after quenching the nucleophilic allenolate with BF_3•OEt_2 and PhCHO in a 61% overall yield. To our dismay, the selectivity dramatically decreased from >20:1 to 1.6:1 *E*/*Z* in favor of the *E*-β-hydroxy-α-olefinic ester **79**.

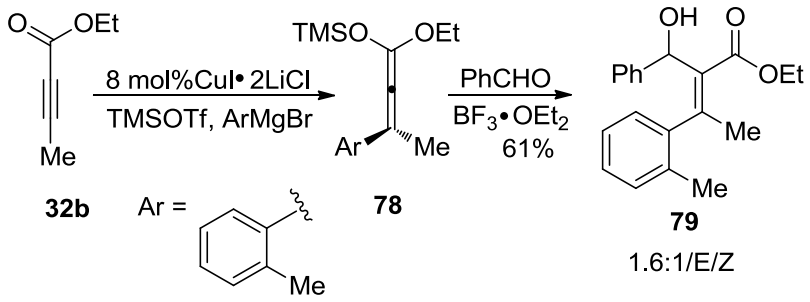
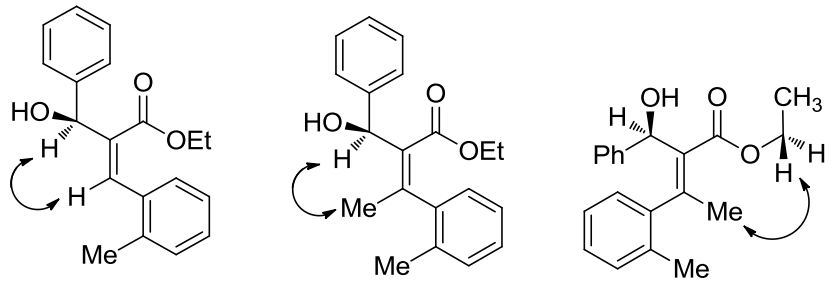


Figure 2.10. Synthesis of Tetra-substituted α-β-acetylenic Ester **79**

2.7. Key NOE enhancements for aldol products 69 and 79 and an intriguing splitting pattern observed for 76

As depicted in figure 2.11, the olefin geometry of **69** was determined by ^{1}H NMR. The strong 1D NOE for both the methine allylic and β-vinylic protons provided proof for the assigned *Z*-olefin geometry. The other aldol-type products **67-77** were assigned according to this observation.

The stereochemical determination of **79** was more challenging due to assigning the vinyl methyl group versus that of the aromatic moiety. Pleasingly, the $^{1}H -^{13}C$ NMR correlation spectroscopy (HMBC) provided a four-bond cross-correlation peak between the allylic methyl protons and the carbonyl of the ester functional group. With the peak assignments now designated accordingly, a strong NOE for both the methine aldol and β-methyl protons provided unquestionable proof for the *Z*-olefin geometry. Also, a strong NOE between the β-methyl and the methylene protons of the ethyl group that resides in the ester functional group provided substantial evidence for the *E*-olefin isomer.

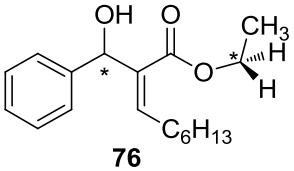


69 ***Z*-79** ***E*-79**

Figure 2.11. Key NOE Enhancements for **69**, **79**-***E***, and **79**-***Z***

It is worth noting that an unusual splitting pattern was observed for the methylene protons of the ethyl group resident in the ester moiety of the aldol product **76**. When analyzing the ^{1}H NMR of this compound, we observed two doublets of quartets overlapping one another (figure 2.12) at 4.0 ppm for the diastereotopic methylene protons in compound **76**. While a simple quartet was observed for all the other compounds, we surmised that the alcohol moiety and carbonyl of the ester group of this particular aldol product were hydrogen bonding and thus, making the compound more rigid and allowing for these protons to be influenced by the methine

allylic proton at the chiral center. Therefore, ^{2}J and ^{3}J coupling was observed for each of the diastereotopic protons and resulted in this intriguing J_{ab} splitting pattern.



76

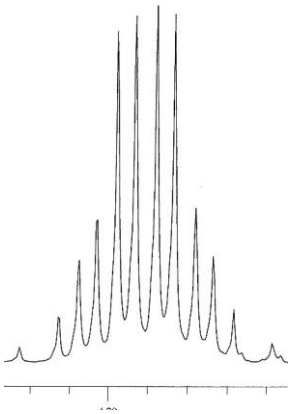


Figure 2.12. Signal for Methylene Protons of Ethyl Ester in Compound **76**

2.8. Conclusion

In conclusion, we have made great efforts toward providing synthetically important Baylis-Hillman adducts via a Mukaiyama aldol type reaction sequence. We have thoroughly investigated the initial carbocupration of ynoates with RMgBr to furnish the TMS allenolate intermediate followed by the addition of a Lewis acid and an electrophilic coupling partner (RCHO) to provide β-hydroxy-α-olefinic esters. Therefore, we have made aldol products in an attractive one pot, two step process. Thus, we have shown that the vicinal functionalization of propiolate esters via a tandem catalytic carbocupration-Mukaiyama aldol sequence with catalyst loadings as low as 8 mol% readily provides the β-hydroxy-α-olefinic esters in good yields and excellent diastereoselectivities for a series of aromatic and aliphatic Grignard reagents and

aldehydes. In addition, we have isolated a tetrasubstituted olefinic ester via a tetrasubstituted TMS allenolate in good yield.[2c] During our efforts, we also uncovered an unusual splitting pattern for methylene protons of an ethyl group resident in an ester moiety.

CHAPTER THREE: VICINAL FUNCTIONALIZATION OF PROPIOLATE ESTERS VIA CATALYTIC CARBOCUPRATION: STEREOSELECTIVE FORMATION OF SUBSTITUTED VINYL SILANES

3.1 Introduction

Chapter three will discuss some of the more successful diastereoselective olefination methods including the olefination of aldehydes with Horner-Wadsworth-Emmons (HWE) stabilized phosphonate esters, the Still-Gennari modification of the HWE reaction, and the classical stabilized Wittig ylide reagents.[17] As previously discussed, a less utilized process for the stereoselective synthesis of olefins involves the partial reduction of propiolate esters with cuprate complexes (i.e., Gilman or Kharash reagents). Corey and Katzenellenbogen initially reported the stoichiometric carbocupration of ethyl propiolate with Gilman reagents and subsequent electrophiles providing α,β-unsaturated esters with high levels of diastereoselectivity.[3] However, very little attention has been given to the catalytic carbocupration of ynoates with Kharash reagents. Thus, we have reported on the stereoselective synthesis of both *E* and *Z* α-β-unsaturated esters via catalytic carbocupration of propiolate esters, and then we further expanded this by demonstrating a vicinal functionalization via a tandem catalytic carbocupration-Mukaiyama aldol reaction sequence (see chapter 1 and 2).[2b,c] During this process, we stumbled upon the vicinal functionalization of propiolate esters via a catalytic carbocupration-silicon group migration sequence.[18] We have observed that catalyst loadings as low as 5 mol% allow for good yields and excellent diastereoselectivities with a series of Grignard reagents for the synthesis of substituted *E*-vinyl silanes.[2d] These α-TMS-α,β-

unsaturated esters are incredibly useful synthons in organic chemistry. Thus, it will be discussed how these compounds could be easily transformed into stabilized Peterson reagents[19] and serve as precursors for higher-order nucleophillic allyl silanes.[20]

3.2. The classical Wittig reaction and modifications involving phosphoryl-stabilized carbanions

The Wittig reaction has become widely used since the 1950's for the preparation of alkenes from aldehydes with phosphonium ylides and has changed the course of olefin synthesis.[17d] The conventional Wittig reaction entails the reaction of a phosphonium ylide **81** with an aldehyde or a ketone, and the stereoselectivity of the resulting alkene **82** is dependent on the phosphorus ylide (figure 3.1).

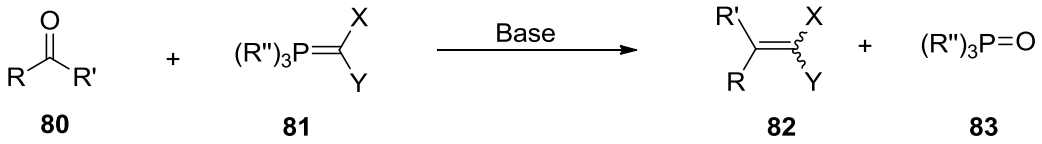


Figure 3.1. General Wittig olefination reaction[17d]

"Stabilized" ylides have at least one strong electronwithdrawing group that stabilizes the negative charge on the carbon and usually favors *E*-alkenes. "Semi-stabilized" ylides have at least one aryl or alkenyl substituent, which are less stabilizing and normally provide mixed results. Then, "nonstablilized" ylides have one alkyl substituent that does not stabilize the negative charge and usually favors *Z*-alkenes. However, there have been modifications to the classical Wittig reaction due to purification, reactivity, and stereocontrol issues.

One such modification was reported by Horner and co-workers who were the first to react phosphonates **85** with aldehydes and ketones to afford our compounds of interest, *E*-α,β-unsaturated esters **33** (figure 3.2).[17a,b]

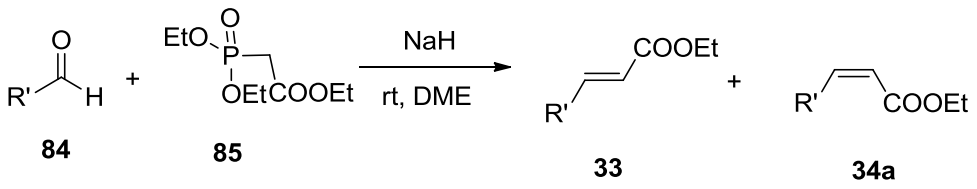


Figure 3.2. Synthesis of α,β-unsaturated Ester **34a** via HWE Olefination Reaction[17b]

Wadsworth and Emmons further defined this reaction, and it became known as the Horner-Wadsworth-Emmons reaction.[17b] There are a number of advantages associated with the utilization of phosphonate carbanions **85** instead of phosphonium ylides or "Wittig" reagents, including they are known to be more nucleophilic and react with a wider variety of aldehydes and ketones under milder conditions, produce water soluble phosphate byproducts that allow for much easier separation, and are cheaper to make. Thus, the HWE reaction is a classical method for the selective preparation of *E*-α,β-unsaturated esters. However, when α-branched phosphonates were utilized for the formation of trisubstituted esters, the *E*-*Z* selectivity was not always predictable. Aromatic substituted phosphonates proceeded efficiently providing predominately the *E*-olefin, but aliphatic substituted phosphonates were not so predictable and were dependent on the steric bulk of the phosphonate.

Another modification to the classical Wittig reaction and to the Horner-Wadsworth-Emmons reaction is the Still-Gennari olefination reaction.[17c] Still and Gennari found a solution to a longstanding problem and showed that unsaturated esters may be prepared from a variety of aldehydes with high *Z* selectivity. When using electrophilic bis(trifluoroethyl) phosphonoesters

86a and KN(TMS)$_2$/18-crown-6 (figure 3.3), aliphatic and aromatic aldehydes were transformed to *Z* disubstituted cinnamic esters **87** in good to excellent yield (75-95%).

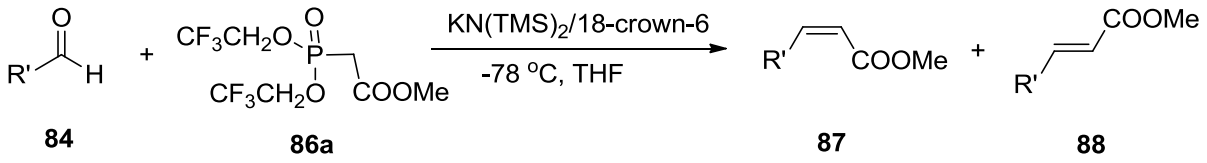


Figure 3.3. Still-Gennari Reaction to Afford **87**[17c]

In addition, the substituted triflouroethyl phosphonoester **86b** with KN(TMS)$_2$/18-crown-6 is an effective phosphonate for furnishing the *Z* trisubstituted unsaturated ester **89** (figure 3.4). Aromatic and aliphatic aldehydes provided good yields (80-95%) and excellent dr (30-50:1 *Z*/*E*).

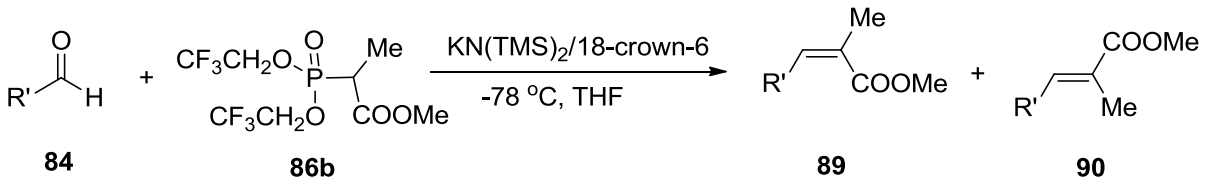


Figure 3.4. Still-Gennari Olefination to Afford Trisubstituted *Z*-α,β-unsaturated Esters[17c]

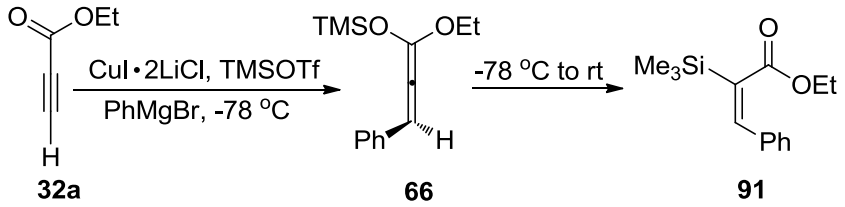
3.3. Vicinal functionalization of propiolate esters via catalytic carbocupration: stereoselective formation of substituted vinyl silanes

Previously, it was discussed that there have been a multitude of investigations into the stoichiometric carbocupration of propiolate esters for providing α,β-unsaturated esters with high levels of diastereoselectivity.[10] However, one area that has not been as popular is the catalytic carbocupration of ynoates. As highlighted in chapters 1 and 2, we have reported the stereoselective synthesis of both *E*- and *Z*- α,β-unsaturated esters, as well as aldol products by catalytic carbocupration via a TMS allenolate.[2a-c] During this process, we observed that excess TMSOTf did not promote the second carbon-carbon bond formation as desired by our catalytic

carbocupration-Mukaiyama aldol reaction conditions.[2d] Instead, a tautomerization of the TMS allenolate to a stereodefined α-TMS-α,β-unsaturated ester resulted upon warming the reaction to room temperature. Due to the synthetic potential of the formed product, we decided to further investigate this reaction.

As delineated in table 3.1, we analyzed what equivalency of TMSOTf was needed to perform the tautomerization from the TMS allenolate **66** to the *E*-vinyl silane **91**. Thus, our standard catalytic carbocupration reaction conditions previously described for **32a**, 1.3 equiv of TMSOTf, and PhMgBr afforded **91** in only a 43% yield with a dr of >20:1 *E*/*Z* upon warming the reaction to rt. A mixture of *E* and *Z* α-β-unsaturated esters (**33** and **34a**) were the remaining mass balance, as a result of the proton quench of the intermediate TMS allenolate **66**. Increasing the equiv of TMSOTf to 2.3 increased our yield to 86% and further increasing to 3.3 equiv of TMSOTf afforded the vinyl silane **91** in 92% yield and maintained the excellent >20:1 dr for the *E* isomer. Increasing the catalyst loading to 10 and 20 mol% slightly increased the yield when using 3.3 equivalence of TMSOTf, but switching from THF to MTBE or Et_2O decreased the yield to 15% and 0%, respectively. When the initial carbocupration was performed at a different temperature such as -10 ˚C or -40 ˚C followed by warming the reaction mixture to room temperature **91** was afforded in slightly lower yields of 80 and 85% (entries 8 and 9). Lastly, portionwise addition of TMSOTf did have a slight effect on the overall yield of **91**, but did not degrade the *E*-olefin selectivity.

Table 3.1. Vicinal Functionalization of **32a** via a Catalytic Carbocupration-silicon Group Migration Sequence



32a **66** **91**

entry	CuI•2LiCl mol%	TMSOTf equiv	solvent	yield %[a]	*E*/*Z*[b]
1	5	1.3	THF	43[c]	>20/1
2	5	2.3	THF	86	>20/1
3	**5**	**3.3**	**THF**	**92**	**>20/1**
4	**10**	**3.3**	**THF**	**95**	**>20/1**
5	**20**	**3.3**	**THF**	**98**	**>20/1**
6	5	3.3	Et_2O	NR	NR
7	5	3.3	MTBE	15[c]	>20/1
8[d]	5	3.3	THF	80	>20/1
9[e]	5	3.3	THF	85	>20/1
10[f]	5	1.3 then 1	THF	72[c]	>20/1
11[g]	5	1.3 then 2	THF	90	>20/1

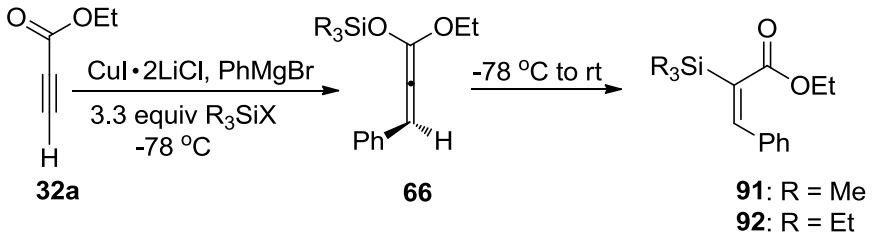
[a] Purified isolated yield of vinyl silane. [b] *E*/*Z* ratio determined by ^{1}H NMR (360 or 500 MHz) from the crude reaction mixture. [c] Remaining mass balance was the α-β-unsaturated ester from the proton quench of the TMS allenolate. [d] Reaction ran at -10 ˚C. [e] Reaction ran at -40 ˚C. [f] Reaction ran with 1.3 equiv of TMSOTf followed by addition of 1 equiv before warming to rt. [g] Reaction ran with 1.3 equiv of TMSOTf followed by addition of 2 equiv before warming to rt.

With the optimized conditions in hand from table 3.1 (entry 3), we decided to investigate a variety of vinyl silanes with respect to their migratory aptitude and catalytic activity. As shown in table 3.2, all of the TMS-X (X = Cl, Br, I) Lewis acids showed high levels of activity with yields between 67 to 89% using 3.3 equiv for the desired vinyl silane **91** or the α,β-unsaturated ester side product. Notably, there seemed to be a trend with respect to Lewis acidity.

For instance, TMSCl-mediated carbocupration provided a 67% yield for **91**, whereas TMSBr and TMSI furnished the desired vinyl silane in greater yields of 80 and 89% via the same TMS allenolate intermediate. Previously, we showed that TMSOTf afforded **91** in a slightly higher yield of 92%. Evidently, there is a direct correlation between Lewis acidity of the silane promoter and tautomerization of the TMS allenolate. Pleasingly, all three halides and TMSOTf provided the *E*-isomer with a >20:1 ratio.

In addition, utilization of TESCl and TESOTf for catalytic carbocupration proceeded fairly smoothly, but provided mixed results with respect to the TES group migration from the allenolate to the vinyl silane. The yield of **92** was only 32% with TESCl, but was 88% with TESOTf, and excellent diastereoselectivities were maintained (entries 4 and 5). Once again, it appeared that Lewis acidity played an important role in tautomerizing the TES allenolate to the vinyl silane. Then, we examined TBSCl and TBSOTf as the additive for the catalytic carbocupration of **32a** and received disappointing results. We observed no formation of either the desired vinyl silane or the α,β-unsaturated ester, although all of the starting material was consumed. It is our belief that both TBS additives do not promote the initial catalytic carbocupration, and the excess Grignard reagent simply helped to decompose the starting material **32a**.

Table 3.2. Vicinal Functionalization of **32a** via a Catalytic Carbocupration-silicon Migration Sequence with Various Silane Promoters



entry	CuI•2LiCl mol%	R_3SiX	yield %[a]	*E*/*Z*[b]
1	5	TMSCl	67[c]	>20/1
2	5	TMSBr	80	>20/1
3	5	TMSI	89	>20/1
4	5	TESOTf	88	>20/1
5	5	TESCl	32[c]	>20/1
6	5	TBSOTf	NR	NR
7	5	TBSCl	NR	NR

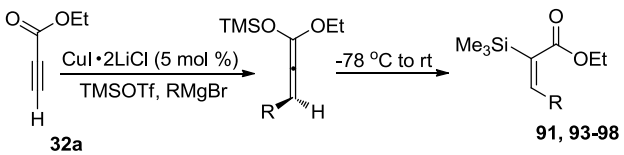
[a] Purified, isolated yield of vinyl silane. [b] *E*/*Z* ratio determined by ^{1}H NMR (360 or 500 MHz) from the crude reaction mixture. [c] Remaining mass balance was the α-β-unsaturated ester from the proton quench of the TMS allenolate or decomposed material.

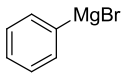
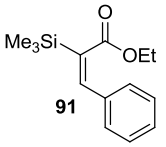
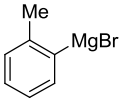
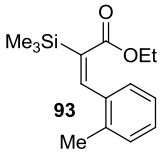
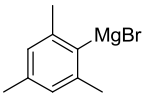
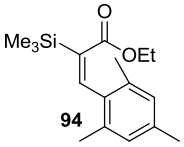
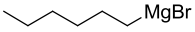
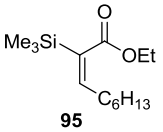
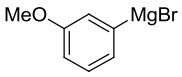
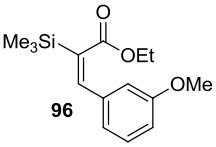
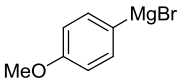
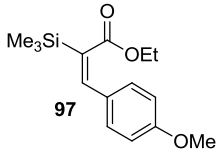
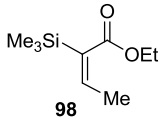
To expand the scope of the reaction even further, we decided to investigate the catalytic carbocupration-silicon group migration sequence with various Grignard reagents (table 3.3). Given the utility of the final product vinyl silanes, we hoped for an excellent stereoselective synthesis with a series of Grignard reagents, like we had seen thus far with PhMgBr. Much to our delight, the carbocupration-TMS tautomerization readily proceeded with 5 mol% Cu(I) catalyst and 3.3 equiv TMSOTf with a variety of aromatic Grignard reagents (1.2 equiv) to afford compounds **91** and **93-98** as practically one isomer, >20:1 for the α-TMS-α,β-unsaturated esters as determined by ^{1}H NMR. Likewise, two aliphatic Grignard reagents performed

marvelously well. The addition of hexylMgBr to **32a** led to **95** in a 93% yield and dr of greater than 20:1 for the *E*-isomer. Correspondingly, MeMgBr worked pleasingly well and provided vinyl silane **98** in 85% yield and as a single *E* isomer. Unfortunately, we did not have immediate success with alkenyl and alkynyl Grignard reagents and led to the decomposition of **32a**.

In addition, there are a couple of key points that value further discussion. Firstly, is that all the tandem reaction processes occurred in very high yield with the lowest yield being 85% for both aromatic and aliphatic Grignard reagents. Also, all the products **91** and **93-98** are formed via a two bond forming process in single flask and are isolated as a single diastereomer, which is quite remarkable.

Table 3.3. Vicinal Functionalization of **32a** with Various Grignard Reagents



Grignard reagent	product yield, (*E*/*Z*)[a,b]
	 **91** 92% (*E*/*Z* > 20/1)
	 **93** 88% (*E*/*Z* > 20/1)
	 **94** 92% (*E*/*Z* > 20/1)
	 **95** 93% (*E*/*Z* > 20/1)
	 **96** 88% (*E*/*Z* > 20/1)
	 **97** 90% (*E*/*Z* > 20/1)
CH_3MgBr	 **98** 85% (*E*/*Z* > 20/1)

[a] *E*/*Z* ratio determined by ^1H NMR (360 or 500 MHz) from the crude mixture. [b] Yields are of the isolated, pure compounds.

Following these observations, we decided to attempt the catalytic carbocupration-silicon group migration sequence with two other starting materials (figure 3.5). As anticipated and analogous to **32a**, the catalytic carbocupration-TMS tautomerization of methyl propiolate **99** readily proceeded under the same previous conditions and afforded the α-TMS-β-phenyl-α,β-unsaturated ester **101** in 90% yield as a single *E*-isomer. Thus far, all of the vinyl silanes have involved the carbocupration of propiolate esters that lack substitution at the β-carbon to afford tri-substituted vinyl silanes. Therefore, we thought it was important to examine ethyl-2-butynoate **102** under the standardized conditions. Much to our surprise, the catalytic carbocupration of **102** with 5 mol% Cu(I) catalyst, 3.3 equiv TMSOTf, and 1.2 equiv PhMgBr proceeded to the TMS allenolate intermediate **103**, and subsequent tautomerization furnished the tetrasubstituted alkene **104** in 85% yield as a single *E*-isomer. This remarkable result greatly expanded this catalytic carbocupration reaction to include diastereoselective tetrasubstituted α-TMS-β,β-disubstituted-α,β-unsaturated esters. In addition, this reaction was quite notable, given that Knochel and workers had reported a similar stoichiometric reaction that did not provide high levels of diastereoselectivity.[18]

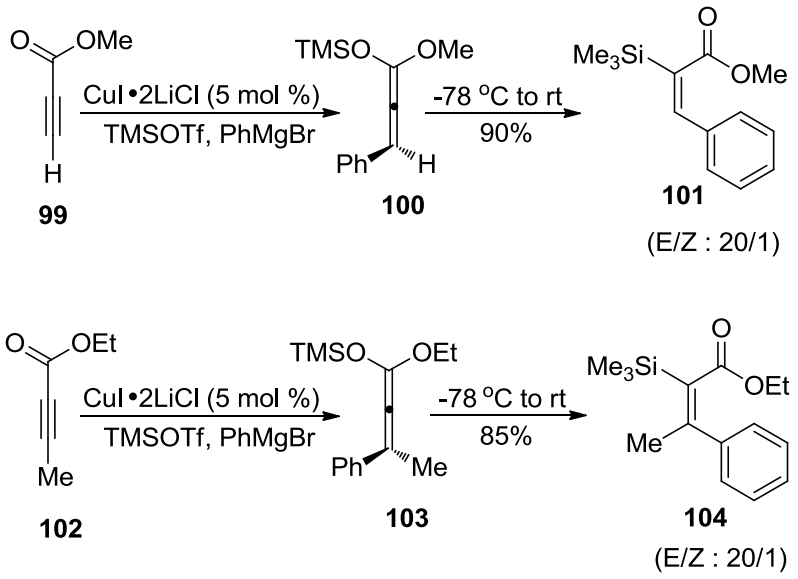


Figure 3.5. Catalytic Carbocupration-TMS Tautomerization of **99** and **104**

As depicted in figure 3.6, the olefin geometry of **91** was determined by ^{1}H NMR. The strong 1D NOE for both the silane methyl groups and β-vinylic proton provided proof for the assigned *E*-olefin geometry. In addition, the ^{1}H NMR chemical shifts for **91**-**98** mirror that of Zweifel's similar vinyl silanes.[20b] On the basis of the NOE experiment and by analogy to Zweifel's observations, the remaining vinyl silanes were assigned as the *E*-isomer. The stereochemical determination of the tetrasubstituted vinyl silane **104** was assigned in a similar fashion. A strong NOE for both the silane methyl groups and the β-methyl protons provided proof for the assigned *E*-olefin geometry.

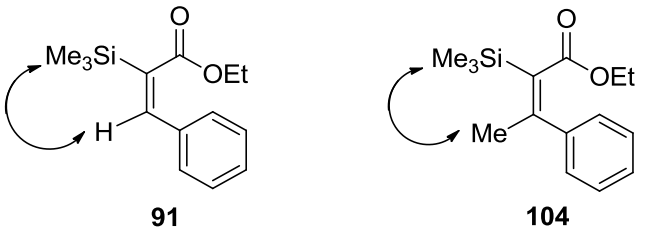


Figure 3.6. Key NOE Enhancements for **91** and **104**

3.4. Vinyl silanes as useful synthons in organic chemistry

The final products, α-TMS-α,β-unsaturated esters **91**-**98** are incredibly useful synthons in organic chemistry. For example, they are only an olefin reduction and deprotonation away from a series of stabilized Peterson reagents.[19] Similar to the Wittig reagents, silicon Peterson reagents **105** have become widely used for the synthesis of substituted olefins from ketones or aldehydes. In figure 3.7, the R'' group of the silicon reagent may be an electronwithdrawing group such as COOR, which is an analogue of the HWE phosphonate reagent and affords α,β – unsaturated esters.[19a]

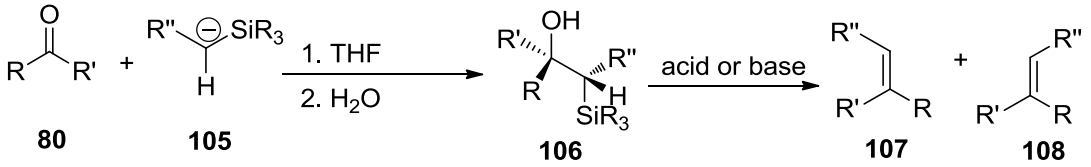


Figure 3.7. Peterson Olefination Reaction[19a]

The addition of the α-silyl carbanions **105** to carbonyl compounds give rise to β-hydroxysilanes **106**, and upon treatment with base (NaH, KH, KOt-Bu), it undergoes a stereospecific *syn*-elimination. Alternatively, if you treat the reaction with dilute acid or a Lewis acid (AcOH, H_2SO_4, BF_3•OEt_2), it results in *anti*-elimination. Therefore, either the *E* or *Z*-alkene **107** or **108** can be produced by choosing acidic or basic conditions. Thus, we surmise that if we were to take any of the provided vinyl silanes **91**-**98** and treat them with an organocuprate, the

resulting silyl enolate **109** should then react with an aldehyde in situ to afford **110**. Upon treatment with a base or acid, elimination should occur to afford either **111** or **112**.

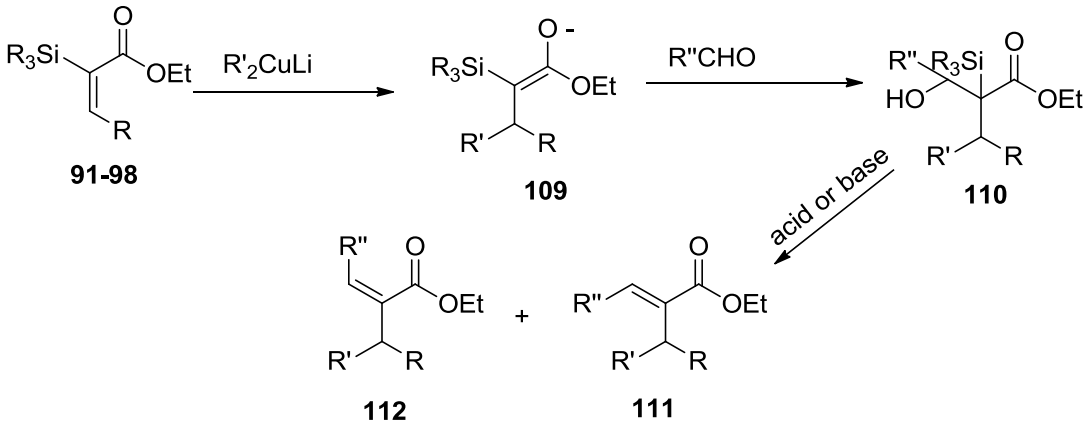


Figure 3.8. Vinyl Silanes for the Synthesis of **111** and **112**

In addition, vinyl silanes **95** and **98** could serve as precursors for higher-order nucleophilic allyl silanes.[20] Allyl silanes can react with various electrophiles in the presence of a Lewis acid and promote a useful carbon-carbon bond forming reaction. Therefore, we should be able to treat **98** with LDA, followed by the addition of chlorotrimethylsilane to deprotonate/deconjugate the vinyl silane and provide **113**. Thus, **113** should react with an electrophile such as PhCHO in the presence of a Lewis acid and afford **114** (figure 3.9). In addition, we should be able to utilize a chiral Lewis acid and make this an asymmetric allylation.

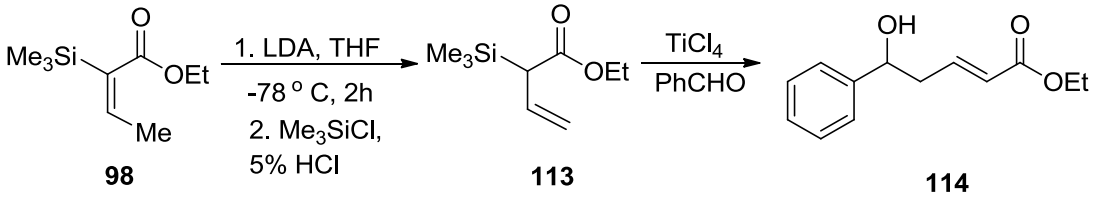
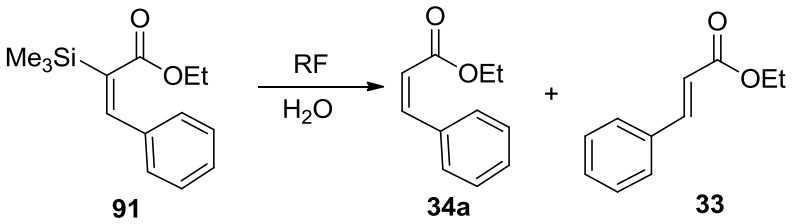


Figure 3.9. Reaction of **98** with PhCHO to Afford Alcohol **114**

3.5. Protodesilylation

After achieving the *E*-vinyl silanes, we decided to investigate the protodesilylation of **91** under various conditions. We envisioned that the removal of the TMS moiety under thermodynamic conditions followed by a protic work up would afford the *E*-α,β-unsaturated ester **33**. Delineated in table 3.4, we observed the removal of the trimethylsilyl group with varying solvents, temperatures, and fluorine reagents. Performing the reaction with TBAF in various solvents (Et_2O, DCM, hexane, toluene, or MTBE) at 0 ˚C for 3 hours did afford the α,β-unsaturated esters in good yield; however, the *E*-isomer was only slightly preferred over the *Z*-olefin with entry 1 being the most selective (3:1 *E*/*Z*). Unfortunately, refluxing the reaction mixture at 100 ˚C for 12 hours in toluene did not increase the selectivity for **33**, and using HF as the desilylating reagent gave similar results.

Table 3.4. Protodesilylation of **91**



91 **34a** **33**

entry	Reagent	solvent	Temperature [˚C]	*E*	*Z*	Yield [%]
1	TBAF	Et_2O/H_2O	0	3	1	80
2	TBAF	DCM	0	1.5	1	75
3	TBAF	hexane	0	1.6	1	80
4	TBAF	toluene	0	2	1	86
5	TBAF	MTBE	0	1.5	1	80
6	TBAF	toluene	100	2	1	70
7	HF	THF	0	3	1	80

3.6. Conclusion

In conclusion, some successful diastereoselective olefination reactions have been discussed, in particular the HWE and Still-Gennari olefinations that afford our compounds of interest, α,β-unsaturated esters.[17] Thus, we highlighted our successful carbocupration-silicon group migration sequence that is not only diastereoselective for *E*- olefins, but is also catalytic.[2d] We have shown that the vicinal functionalization of propiolate esters with catalyst loadings as low as 5 mol% allows for good yields and excellent diastereoselectivities (>20:1) with a series of Grignard reagents for the synthesis of *E*-vinyl silanes. Fortunately, we were able to expand the catalytic reaction process even further and provide a tetrasubstituted α-TMS-β,β-disubstituted-α,β-unsaturated ester in excellent yield and dr. In addition, these vinyl silanes have potential to be valuable Peterson reagents, another widely used reagent for olefination reactions.[19] Also, **95** and **98** could serve as precursors for allyl silanes, which could be employed in carbon-carbon

bond forming allylation reactions.[20] In our efforts to protodesilylate the vinyl silane **91**, we provided the *E*- α,β-unsaturated ester, but failed at making this process highly selective.

CHAPTER FOUR: CONVERGENT SYNTHESIS OF (+)-ASPERGILLIDE B VIA A HIGHLY DIASTEREOSELECTIVE OXOCARBENIUM ALLYLATION

4.1. Introduction

Marine derived organisms continue to be a rich source of natural products because of their chemical diversity and medicinal relevance.[21] One such family of biologically active compounds is the aspergillides, which consists of three 14-membered macrolides that contain either an α or β-C glycoside subunit and a *trans*-olefin as part of the macrocyclic structure.[5,22,23] In addition to their unique structural motif, aspergillides A, B, and C have shown cytotoxic properties against mouse lymphocytic leukemia cells.[4b] Based on the limited biological data and intriguing structures of these compounds, there has been great interest in these natural products. Therefore, this chapter will discuss the isolation and somewhat complicated structural elucidation of the aspergillides. In addition, it will discuss the previous syntheses of aspergillide B and the key transformations reported by Uenishi and researchers, Marco and workers, She and co-workers, and Fuwa's group.[5] In addition, it will highlight our convergent synthesis of (+)-aspergillide B via a highly diastereoselective oxocarbenium allylation followed by a cross-metathesis and final Yamaguchi macrolactonization.[4a]

4.2 Isolation and structural elucidation

Aspergillides A, B, and C were recently isolated in 2008 from the marine fungus *Aspergillus ostianus* strain 01F313 cultured within a bromine modified medium by Kusumi and

co-workers.[4b] A, B, and C showed toxicity against the mouse L1210 murine leukemia cell line with LD_{50} values of 2.1, 71, and 2.0 μg/ml, respectively. Their absolute configurations were elucidated by the modified Mosher's method and chemical conversions, as well as 1D and 2D NMR spectra, and the original structures are shown below in figure 4.1.

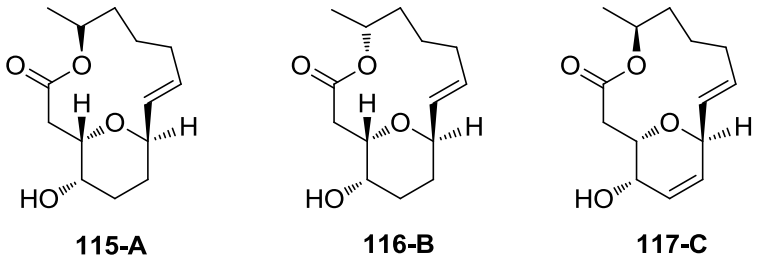


Figure 4.1. Original Structures of Aspergillides A (**115**), B (**116**), C (**117**)

However, the chemical synthesis of the presumed aspergillide A by Uenishi provided aspergillide B and shed light on a structural discrepancy between the two natural products.[5d] Following this report, Kusumi and Ooi provided structural revisions of both aspergillide A and B by means of X-ray crystallography, and the correct structures are depicted below in figure 4.2.[4c] We originally thought we were synthesizing the more biologically active aspergillide A, but following the report on structural revisions of aspergillide A and B, we were actually making aspergillide B **119**. The characteristic features of aspergillide A, B, and C are that they are fourteen membered macrolides that contain either an α or β-C glycoside subunit and a *trans*-olefin as part of the macrocyclic structure, as well as two other stereogenic centers (C-4 and C-13).

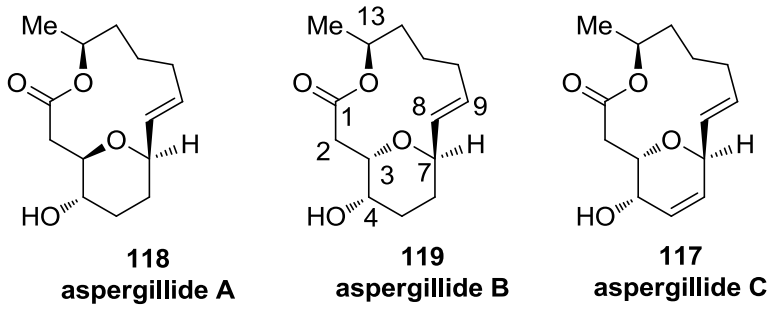


Figure 4.2. Revised Structures of Aspergillide A (**118**), B (**119**), C (**117**)

Based on HMBC and NMR analysis data of aspergillide B, Kusumi and co-workers proposed the structure of our target, aspergillide B **119** (figure 4.2 B).[4b] They found it to have a molecular formula of $C_{14}H_{22}O_4$ and IR absorption at 3440 and 1727 cm^{-1} that indicated the presence of a hydroxyl group and ester group. The *E*-configuration of the macrocyclic olefin was determined by the *J* value (15.8 Hz) of the H-8/H-9 coupling in the ^1H NMR spectra. ^{13}C NMR confirmed the presence of an ester carbon, two olefinic carbons, four oxymethine carbons, and six methylene carbons. HMBC revealed the ester linkage between C-1 and C-13, and other HMBC correlation peaks indicated an ether linkage forming the tetrahydropyran ring. Then, with the structural revisions by means of X-ray crystallography and Uenshi's synthesis of aspergillide B, it was affirmed that H-3 and H-7 are *trans* to one another, thereby making it contain an α-C glycoside subunit. Although the absolute stereochemistry of C-4 of aspergillide B had been determined by the modified Mosher's method, that at C-13 was assumed by Kusumi to be opposite to that at C-13 of aspergillide A **118**. This in fact was not the case and upon Uenishi's report, it was found to be the exact opposite of this assumption.[5d] In addition, aspergillide B was reported having a specific rotation of $[\alpha]^{31}_D$ -97.2 (*c* 0.27, MeOH). [2b] Our compound of interest, the enantiomer of aspergillide B, was also synthesized and was reported having a rotation of $[\alpha]^{20}_D$ of +84 (*c* 0.12, MeOH).[5c]

4.3. First total synthesis of aspergillide B

Uenishi and Hande were the first to describe the total synthesis of aspergillide B.[5d] Their 15 step stereoselective synthesis involved key transformations, such as the Yamaguchi macrolactonization to afford aspergillide B **119** and the cross metathesis of **121S** and **122** to prepare seco acid **120**. Tetrahydropyran **122** was constructed in three steps using the SN2'-type cyclization of **123** by a Pd(II) catalyst. This intermediate was derived by the cross-metathesis of compound **124** and allylic alcohol **125**. Figure 4.3 shows the retrosynthetic analysis as described by Uenishi *et al*.

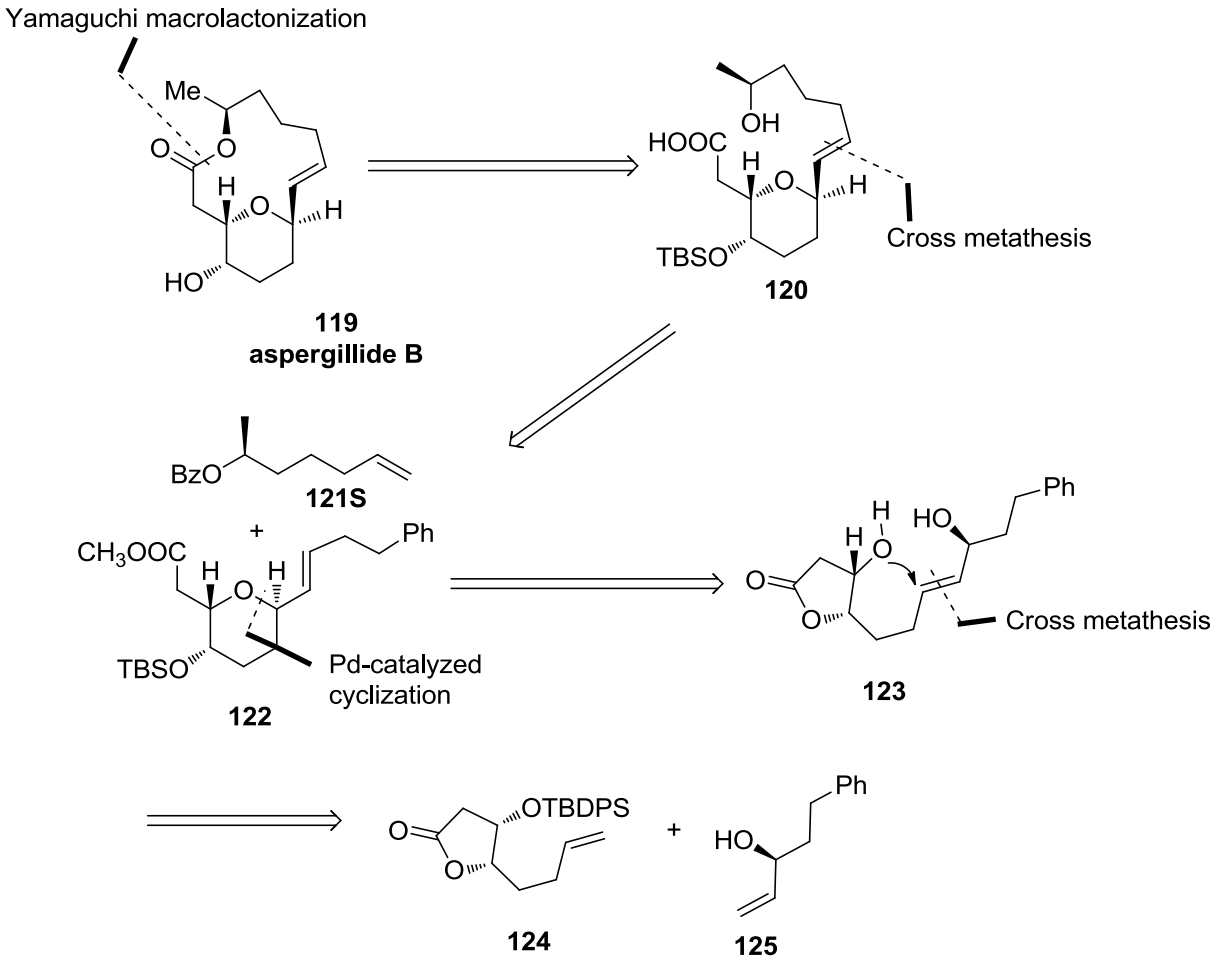


Figure 4.3. Uenishi's Retrosynthetic Analysis of Aspergillide B

Uenishi's first key reaction involved the synthesis of the *trans*-(E)-tetrahydropyran via Pd(II)-catalyzed cyclization as shown in figure 4.4. They synthesized the intermediate **124** from commercially available tetrahydrofurfuryl alcohol over a series of steps, including the Sharpless asymmetric dihydroxylation reaction using AD-mix-α-accompanied by lactonization. Next, olefin **124** was submitted to a cross-metathesis reaction with Grubbs II catalyst and coupling partner **126S** to furnish **127**. After desilylation with TBAF, the key cyclization of **123** was carried out with 15 mol% $PdCl_2(CH_3CN)_2$ in THF and afforded the desired *trans*-(E)-THP intermediate **128**.

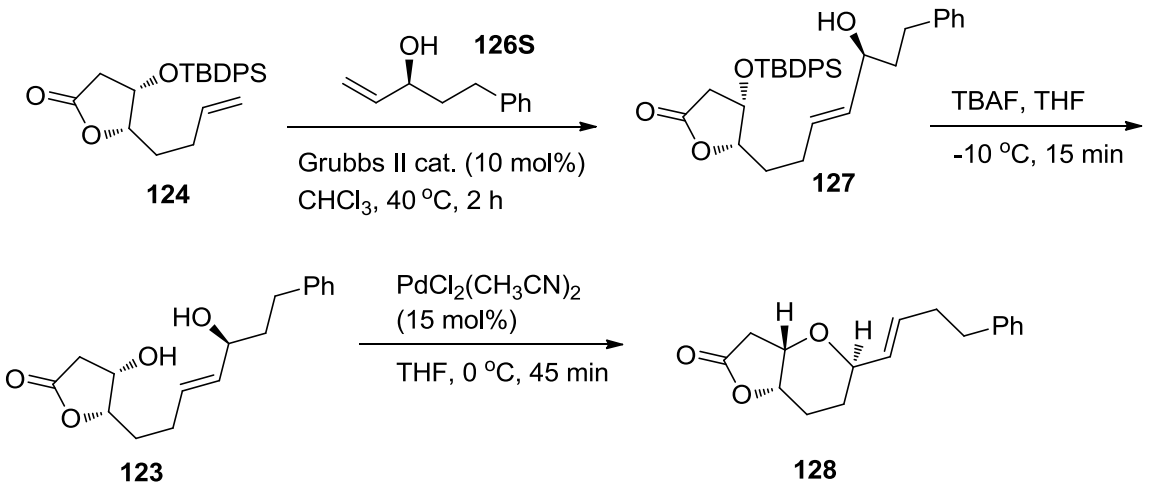


Figure 4.4. Uenishi's Synthesis of Key Intermediates

Having completed the synthesis of the key intermediate **128**, the next major transformation was a second cross-metathesis of **122** with **121S** in the presence of 10 mol% Grubbs-II catalyst to afford **129**. Hydrolysis of benzoate and methyl ester in **129** was carried out in one step followed by the standard Yamaguchi macrolactonization to afford macrolactone **130**. Deprotection of the silyl ether with TBAF provided aspergillide B **119**, and subsequent ^{1}H NMR, ^{13}C NMR, HRMS, rotation, and IR data matched that of the previously reported data for the target structure aspergillide B.[4b]

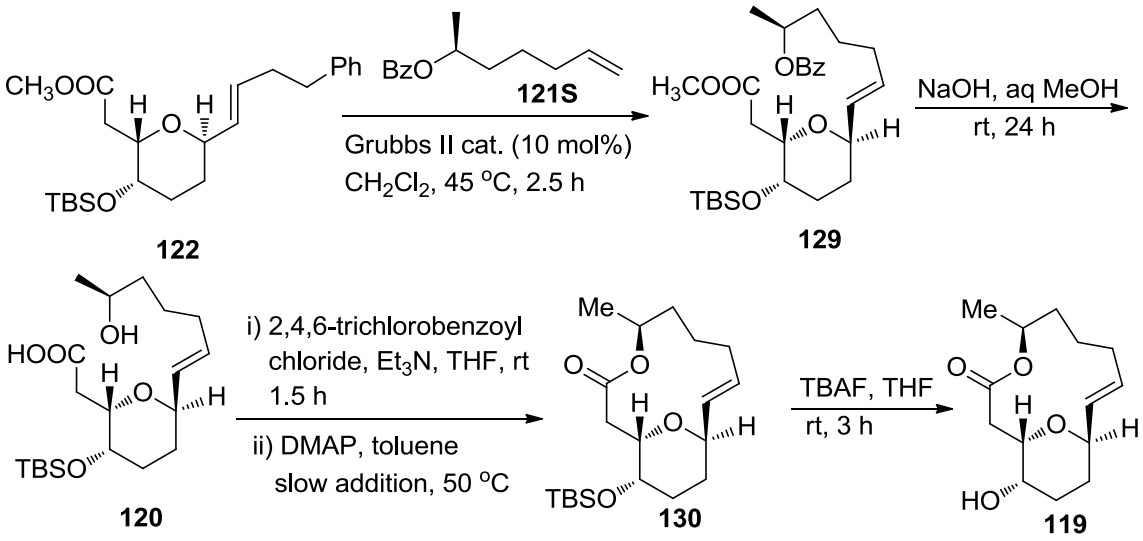


Figure 4.5. Uenishi's Synthesis of Aspergillide B

4.4. Marco and co-worker's synthesis of aspergillide B

The stereoselective synthesis of aspergillide B was reported by Marco *et al*. utilizing a cross metathesis and C-glycosidation via a Mukaiyama-type aldol reaction, followed by a Yamaguchi macrolactonization as the key features of the synthesis.[5a] The retroanalysis is delineated in figure 4.6. They envisioned aspergillide B **119** could be derived from the Yamaguchi macrolactonization of **131**, which in turn could be obtained by cross metathesis of tetrahydropyran **132** and alcohol **133**. They planned to obtain **132** by means of an anomeric Mukaiyama-type alkylation of a lactol derivative by reduction of lactone **134**. Compound **134** was thought to be obtained by functional modification of **135**, which in turn could be derived from **136** through Ru-catalyzed double bond isomerization. Intermediate **136** could be derived from the aldehyde **137** via Brown's asymmetric allylation, which in turn could be derived from the known alcohol **138**.

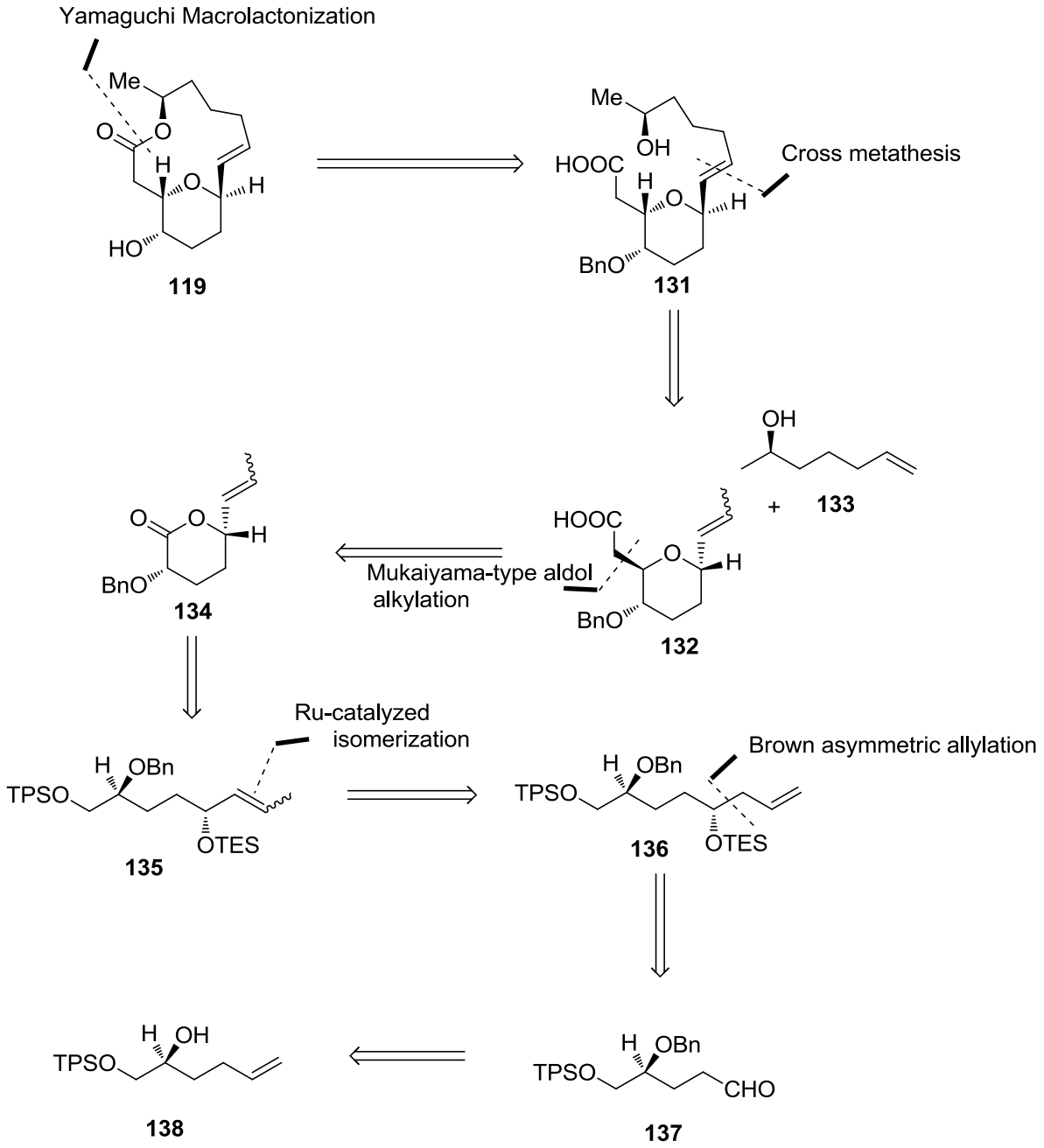


Figure 4.6. Marco and Co-worker's Retrosynthetic Analysis

Marco and co-workers synthesized the intermediate lactone **134** over a series of steps, including a Brown's asymmetric allylboration and an isomerization of a terminal olefinic bond. However, their first key step was the Mukaiyama-type aldol reaction to afford **132**. First, they

reduced the lactone **134** and quenched with Ac_2O to yield the acetylated lactol **130**. Then, trimethylsilyl enolate of *tert*-butyl thioacetate in the presence of BF_3•OEt_2 and TMSOTf was used to treat **139**, and upon hydrolysis furnished the desired *trans*-2,6-disubstituted tetrahydropyran **132** in 55% yield, along with the undesired epimer (21%).

Next, the key cross metathesis reaction was performed on the acid **132** with 20 mol% Grubbs II catalyst and coupling partner **133** to afford the hydroxy acid **131** as a 7:3 *E/Z* mixture. Subsequent macrolactonization was carried out by means of the Yamaguchi procedure and afforded **140**, and cleavage of the benzyl group with DDQ provided **119**, which showed physical and spectral properties identical to those published for aspergillide B.[5d, 4c]

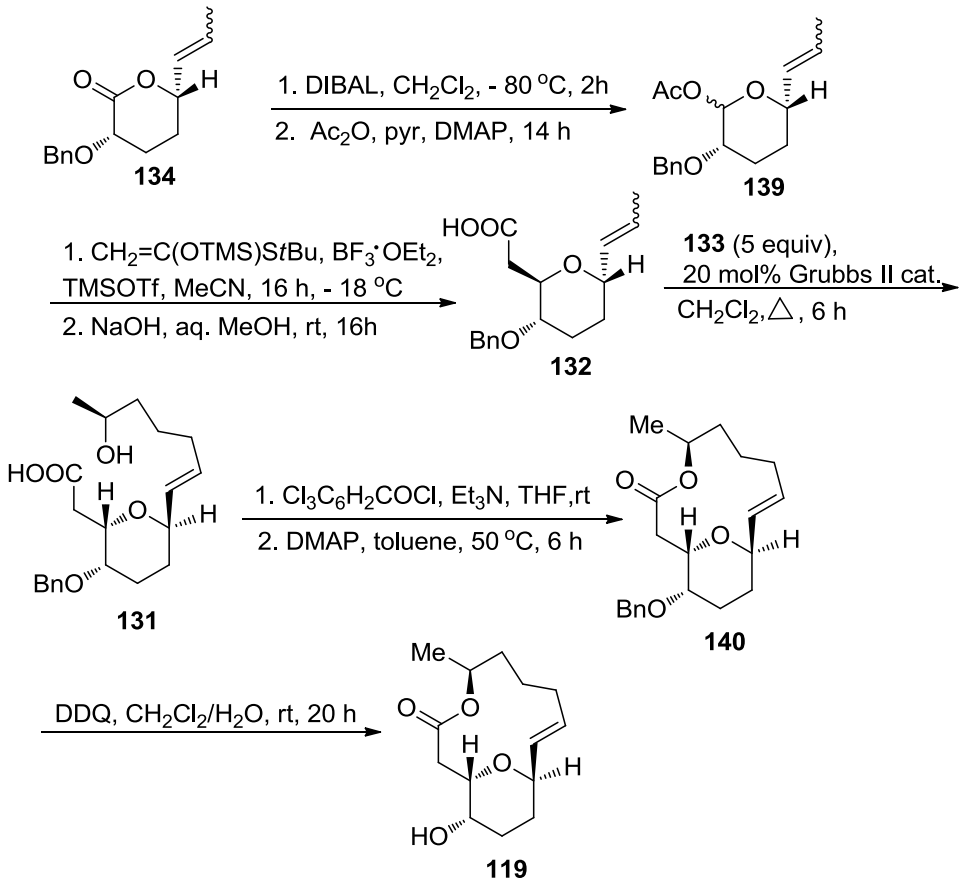


Figure 4.7. Marco and Co-worker's Synthesis of Aspergillide B

4.5. She's synthesis of (+)-aspergillide B

She's concise total synthesis of (+)-aspergillide B, the enantiomer of the natural sample, reported in 2009 featured the C-glycosylation reaction for constructing the 2,6-*trans*-substituted pyran core and an *E*-selective Julia-Kocienski olefination on an elaborate substrate.[5c] The retrosynthetic analysis is shown below in figure 4.8. She *et al*. dissected the natural product into two segments, a sulphone **142** and a 2,6-*trans*-trisubstituted pyran derivative **146**. Thus, (+)-aspergillide B **141** could be synthesized via two key transformations, including a Julia-Kocienski olefination with **142** and **146** followed by macrolactonization. Compound **142** could be easily prepared by the ring opening of (*S*)-2-methyloxirane **143** with allylMgBr **144**. The aldehyde **145** could be derived from **146** via IBX oxidation and Pd/C-catalyzed hydrogenation, which could be obtained from galactose **147** by C-glycosylation.

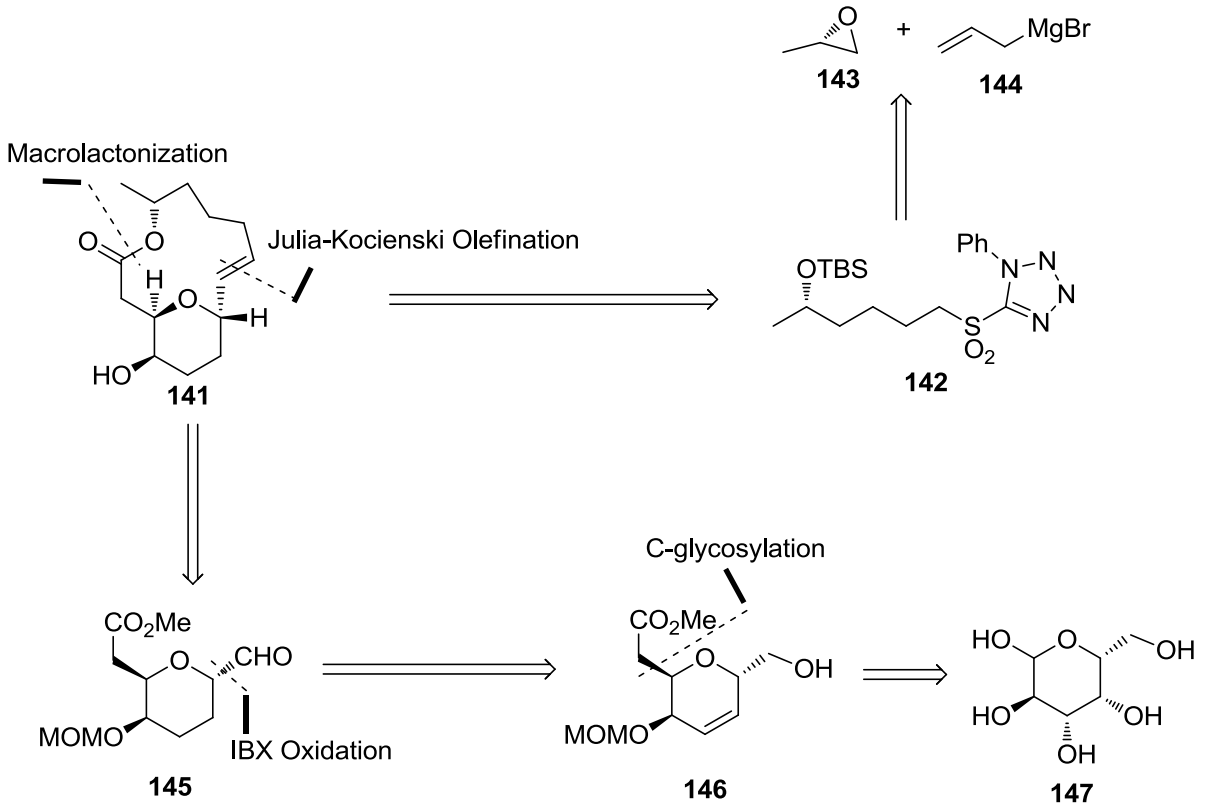


Figure 4.8. She's Retrosynthetic Analysis

She *et al*. synthesized the sulfone **142** over a series of steps beginning with the regioselective ring opening of epoxide **143** with allylmagnesium bromide. Also, the intermediate **146** was furnished over multiple steps from the starting material D-galactose pentaacetate, and then further oxidized and hydrogenated to the aldehyde **145**. With these essential segments **142** and **145** in hand, they performed the key Julia-Kocienski olefination in order to construct the *E*-olefin and install the desired side chain. After a series of trials, they found the best *E/Z* ratio (9:1) for the desired product **148** was obtained by treating **142** with LiHMDS in THF/HMPA at -78 ˚C to room temperature in the presence of **145**. Removal of the TBS group with $3HF{\bullet}NEt_3$ and hydrolysis of the methyl ester afforded the *seco* acid **149**. Then, they were successful in the inversion of the chiral center at C-13 and formation of the macrolactone **150** via a Mitsunobu

reaction by treatment of the hydroxy acid **149** with PPh_3 and DIAD. Deprotection of the MOM group with $LiBF_4$ provided (+)-aspergillide B **141** with identical spectral properties to the natural product (-)-aspergillide B, except for the optical rotation with the opposite sign and similar value ($[\alpha]^{20}_D$ +84, *c* 0.12, MeOH; lit.[5d,4c] $[\alpha]^{31}_D$ -97.2, *c* 0.27, MeOH).

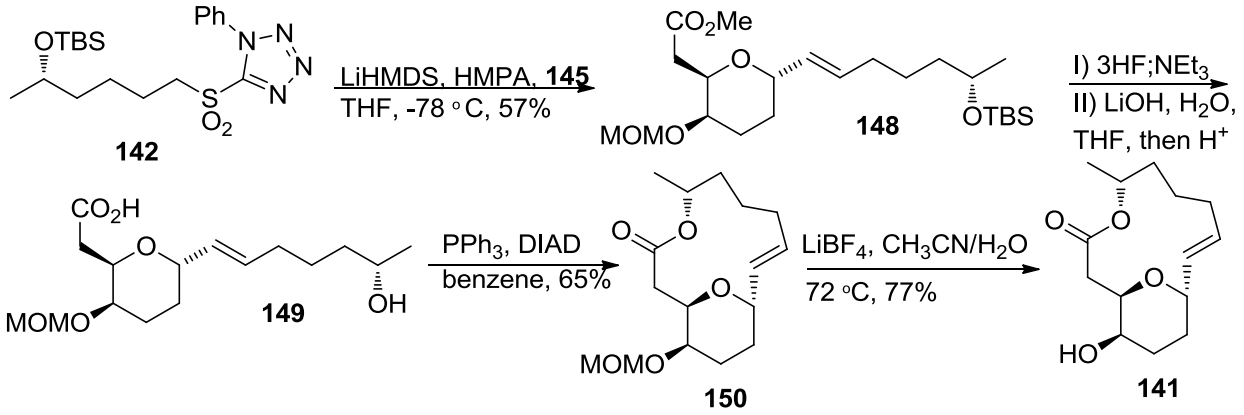


Figure 4.9. She's Synthesis of (+)-Aspergillide B **141**

4.6. Fuwa's synthesis of aspergillide B

Recently, Fuwa *et al*. completed the synthesis of aspergillide B in 2010.[5e] Their synthesis was unique from the other syntheses reported because it involved a hydroxy-directed, highly chemoselective cross-metathesis and a diastereoselective intramolecular oxa-conjugate cyclization as the key transformations to provide the 2,6-substituted tetrahydropyran intermediate. Their retroanalysis (figure 4.10) is depicted below and shows that natural product aspergillide B **119** could be derived from **151** by Yamaguchi macrolactonization. The latter was planned to be accessed via the Suzuki-Miyaura coupling of vinyl iodide **153** and **152**, which in turn could be derived from an intramolecular oxa-conjugate cyclization. They expected that **154** could be forged by a chemoselective olefin cross metathesis (CM).

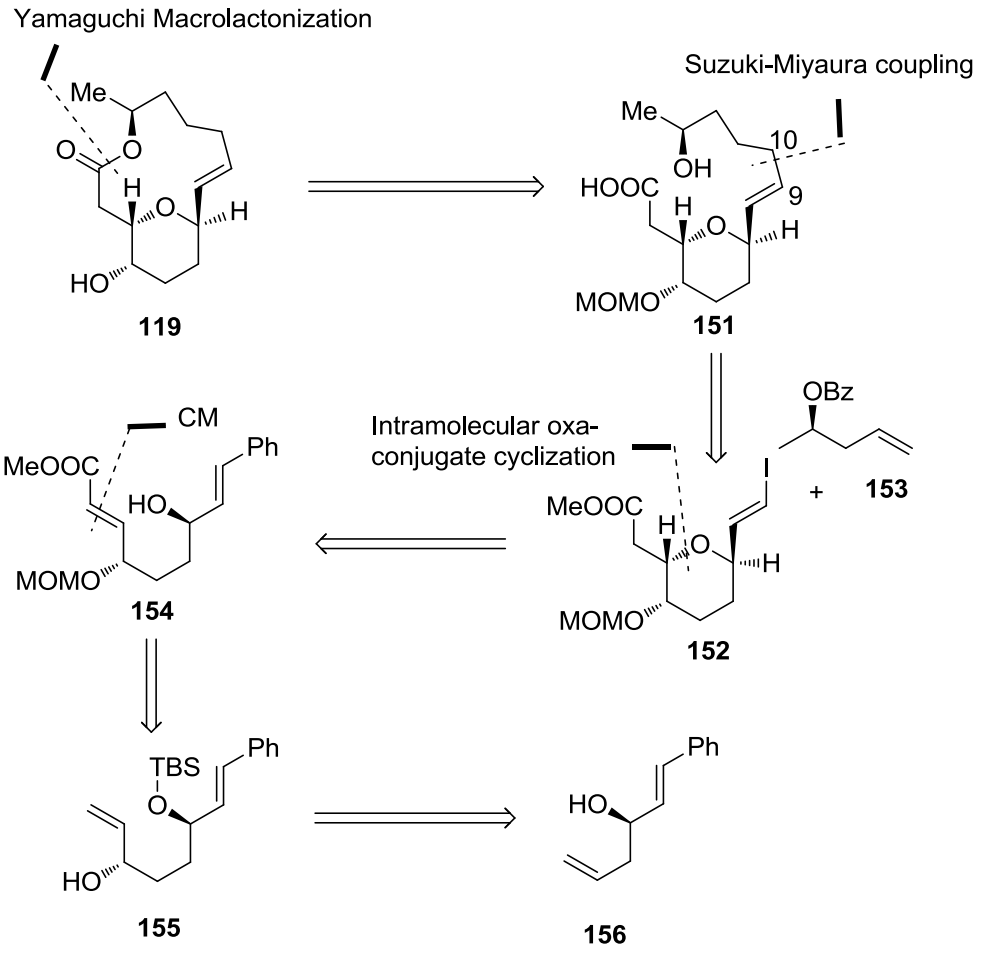


Figure 4.10. Fuwa's Retrosynthetic analysis

Kuwa and co-workers completed intermediate **155** over a series of steps starting with **156** and multiple reactions including a hydroboration and Sharpless asymmetric epoxidation. Their first key step was the chemoselective olefin CM of **155** with methyl acrylate and 5 mol% of Grubbs second-generation catalyst to provide **157** in excellent yield and dr (*E/Z* >20:1) without any undesirable interaction at the styrene moiety (figure 4.11). It is also worth noting that no ring closing metathesis (RCM) was observed, which was quite remarkable. They proposed that the reason for such chemoselectivity was due to H-bonding of the allylic alcohol with the chlorine atoms in Grubbs II catalyst, which leads to an unfavorable conformational constraint for

the RCM. Then, protection of the secondary alcohol in **154** followed by the deprotection of the TBS group with TBAF was effectively carried out to forge the key intermediate **154**.

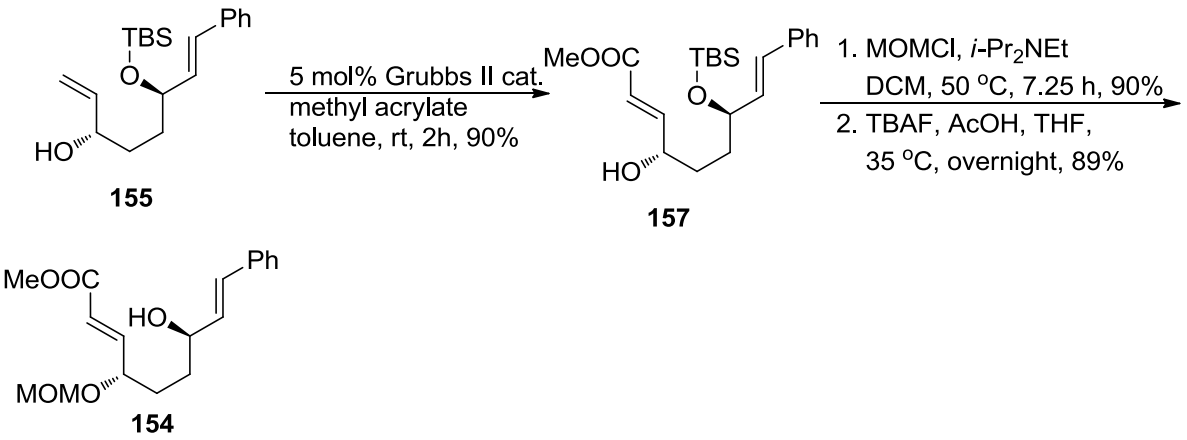


Figure 4.11. Fuwa's Synthesis of Intermediate **154**

As depicted in figure 4.12, Kuwa's next major transformation was the intramolecular-conjugate cyclization of **154** by submitting it to kinetic conditions (KO*t*-Bu in THF at -78 ˚C) to provide the 2,6-*trans*-tetrahydropyran intermediate **158** (dr = 17:1). Kuwa and co-workers also found that alternatively the treatment of **154** with DBU in toluene at 135 ˚C afforded the thermodynamically favored 2,6-*cis*-THP. Thus, either *syn* or *anti* could be synthesized from the same intermediate **154** by just changing the reaction conditions. With the desired *trans*-tetrahydropyran **158** in hand, they continued to the completion of aspergillide B by carrying out an ozonolysis followed by a Takai olefination to provide the (*E*)-vinyl iodide **152**. Then, Suzuki-Miyaura coupling of **152** with alkylborane derived from olefin **153** with $PdCl_2(dppf)•CH_2Cl_2/Ph_3As$ catalyst forged the *E*-olefin **159**. The last three steps were virtually identical to Uenishi's hydrolysis and Yamaguchi macrolactonization[5d] and She's $LiBF_4$ removal

of the MOM group[5c] to furnish aspergillide B **119**, whose spectroscopic properties and specific rotation were in full accordance with the natural sample.[5d,4c]

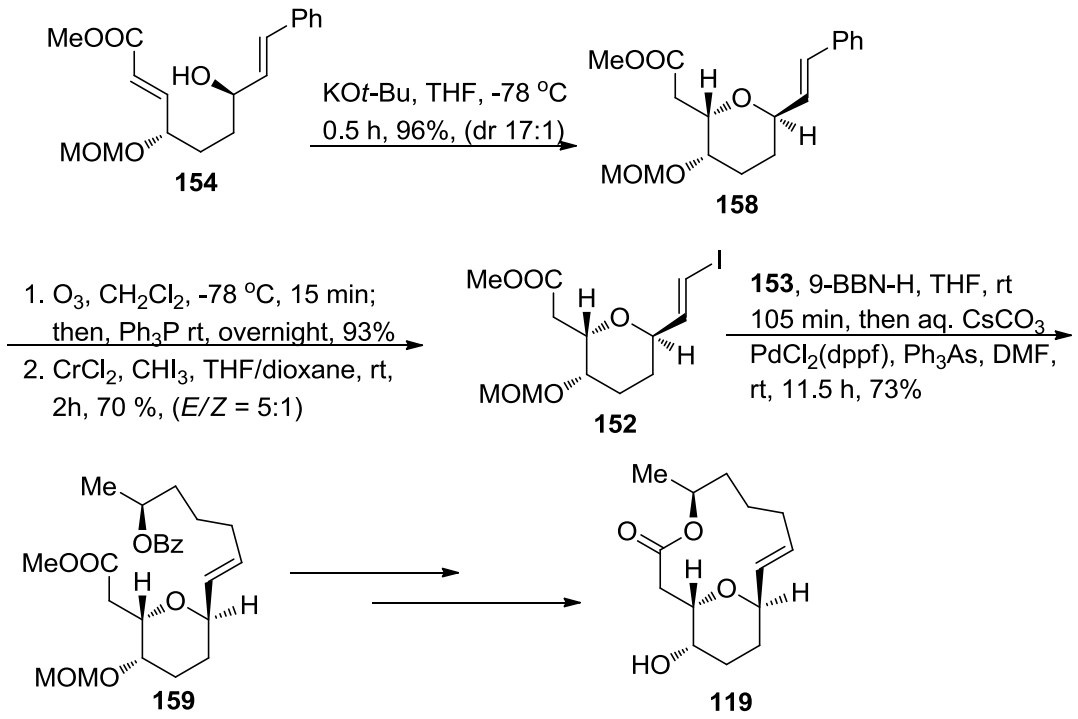


Figure 4.12. Fuwa's Synthesis of Aspergillide B

4.7. Our convergent total synthesis of (+)-aspergillide B

This portion of the dissertation highlights our convergent synthesis of (+)-aspergillide B via a highly diastereoselective oxocarbenium allylation.[4a] As shown in figure 4.13, the most obvious disconnection is the formation of the 14-membered ring via Yamaguchi macrolactonization of **160**.[24] Compound **161** should be formed by the cross metathesis with intermediate **162**. The latter should be derived from **163** by a Ru-catalyzed terminal olefin isomerization protocol. The key α-C-glycoside segment **163** should arise from a stereoselective oxocarbenium allylation process from the lactone **164**.

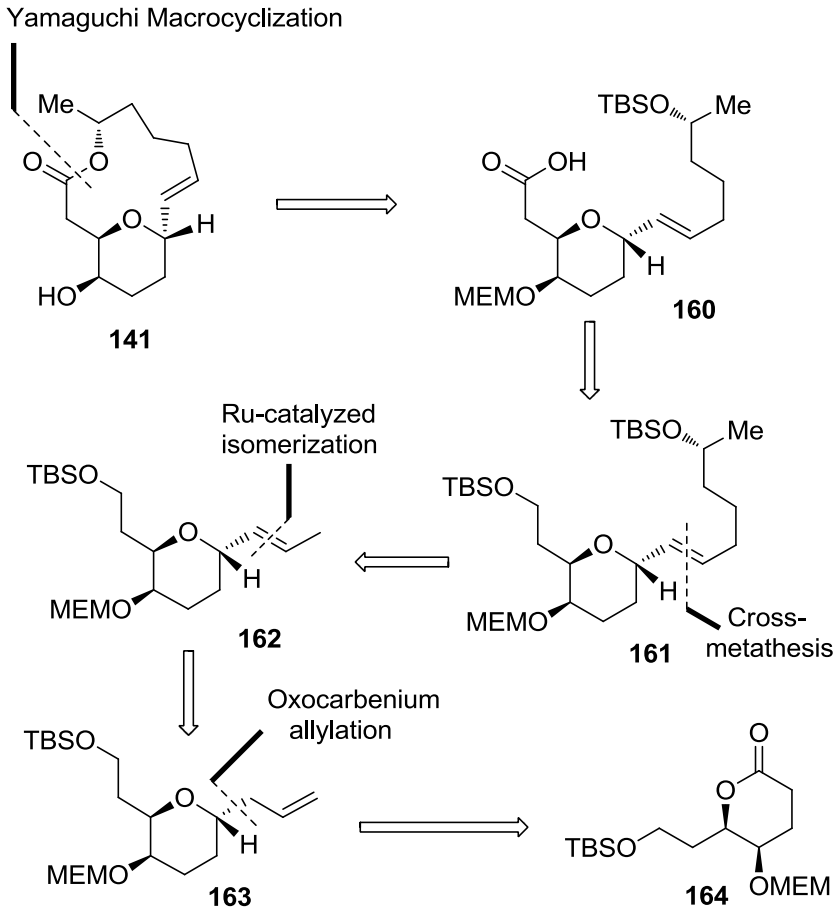


Figure 4.13. Retrosynthetic Analysis for (+)-Aspergillide B

Our synthetic route for (+)-aspergillide B required the synthesis of the chiral alkenol **166** as shown below in figure 4.14. A copper-catalyzed Grignard addition of 3-butenylmagnesium bromide to (*R*)-propylene oxide **165** was carried out at -78 ˚C upon addition and warmed to room temperature overnight to readily provide the secondary alkenol in 88% yield. Then, we protected the free secondary alcohol with the standard TBSCl and imidazole silylating reagents and afforded the TBS-protected chiral alkenol **166**.[25]

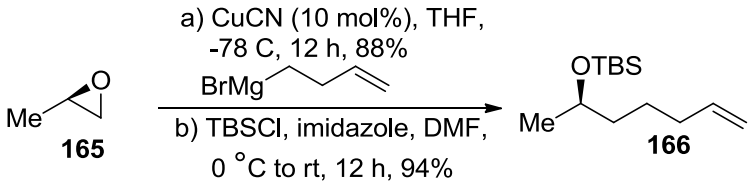


Figure 4.14. Synthesis of Intermediate **166**

With alkenol **166** in hand, we shifted our focus to the completion of the α-C-glycoside portion of our natural product, but first we had to set the table for the addition of alkoxyallyl diisopinocamphenyl borane to a TBS aldehyde. Thus, MEM-Cl and diisopropylamine were added sequentially to a solution of allyl alcohol **167** to forge allyl MEM **168**.

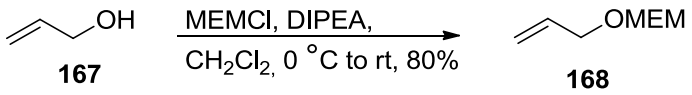


Figure 4.15. Synthesis of **168**

With **168** readily in hand, we were now able to use sec-butyl lithium, (-)-IPC_2BOMe, and allyl MEM **168** to generate a chiral pinane *Z*-MEM-acetal crotyl borane reagent, which could then react with TBS protected aldehyde[26] **169** in situ to forge the MEM protected diol **170** with a dr of >95:5 for the *syn* diastereomer and 94% ee and 75% yield (figure 4.16).[27] Ester formation with acryloyl chloride in the presence of Et_3N and DMAP provided the acrylate ester **171** in 85% yield. With **171** in hand, we proceeded to carry out olefin ring closing metathesis with Grubbs' second generation carbene catalyst **172** to afford the α,β-unsaturated lactone **173**.[28] We were also pleased to find that performing this reaction under high dilution (0.01M toluene) dramatically increased the yield to 96% versus only a 40% conversion of starting material to the desired product **173** when 0.1 M toluene was used for the ring closing reaction. Next, reduction

of the olefin in **173** was carried out with H_2 and Pd/C under atmospheric pressure to furnish lactone **174**. With **174** in hand, partial reduction of the lactone with DIBAL provided the intermediate lactol, which was immediately trapped with Ac_2O to provide **175** in 80% yield over two steps.

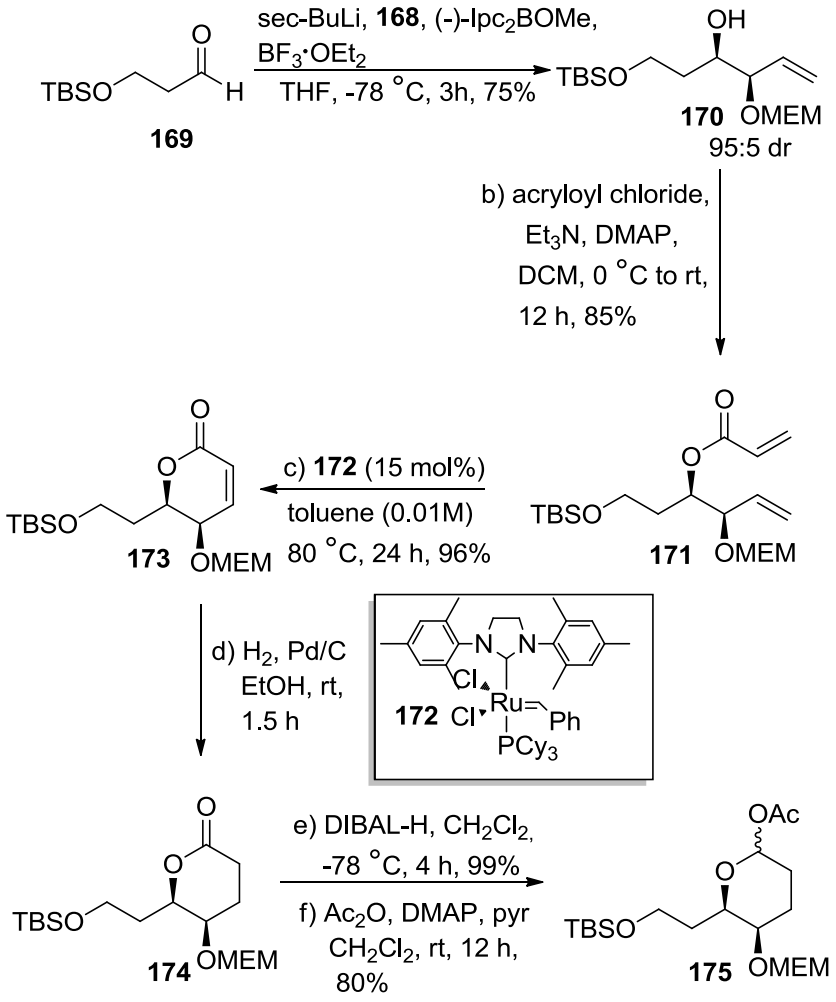


Figure 4.16. Synthesis of Intermediate **175**

With the completion of oxocarbenium precursor **175**, we proceeded to forming the α-C-glycoside subunit of (+)-aspergillide B **141** via a stereoselective oxocarbenium allylation. Based

on Jennings' previous syntheses, we hoped to stereoselectively deliver the targeted α-C-glycoside with high levels of dr and yield by the treatment of acetate **175** with BF_3•OEt_2 at -78 ˚C.[29] As delineated in figure 4.17, under these reaction conditions, two possible conformers **176** and **177** are possible. Conformer **176** should place the C5 substituent in the pseudo axial position while the MEM acetal at C4 would be in the pseudo equatorial position. Alternatively, conformer **177** would place the C5 side chain into the pseudo equatorial position and the C-4 MEM acetal in the axial position. Based on our previous observations and Woerpel's reports, we expected that **177** would be the reaction conformation and the allylTMS nucleophile would approach from the axial position and proceed through a chair like transition state similar to **177**.[29-31] As expected, the α-C-glycoside **163** was furnished with a very high dr (>20:1) as a single stereoisomer in 85% yield.

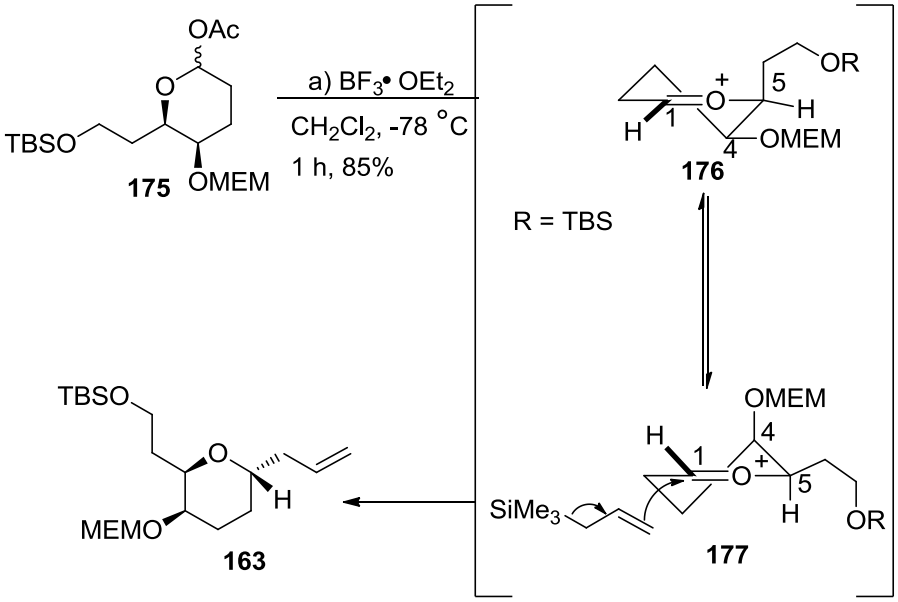


Figure 4.17. Synthesis of Intermediate **163**

With α-C-glycoside **163** in hand, an olefin isomerization was required before the convergent cross-metathesis. According to Hanessian's report on terminal olefin isomerization

with Grubbs second generation catalyst **172** in MeOH, we decided to carry out this procedure as shown in figure 4.18.[32] Fortunately, when we carried out the reaction with **163** with catalyst **172** in MeOH, the isomerized product **162** was obtained in a 65% yield and an 8/1 *E/Z* mixture. Subsequently, the *E* selective cross-metathesis of the olefin **162** and TBS protected chiral alkenol **166** was achieved and compound **161** was isolated in 67% yield and *E/Z* ratio of >20:1. Next, we were successful in selectively deprotecting the primary TBS group with TBAF in the presence of a secondary one to afford the free primary alcohol **178** in 65% yield. Then, the primary alcohol moiety in **178** was oxidized with TEMPO and $PhI(OAc)_2$ and forged aldehyde **179** in 70% yield.[33] The aldehyde in **179** was readily oxidized to the carboxylic acid **160** in an excellent yield via the Lingren-Kraus-Pinnick conditions and set the final stage for ring closure.[34]

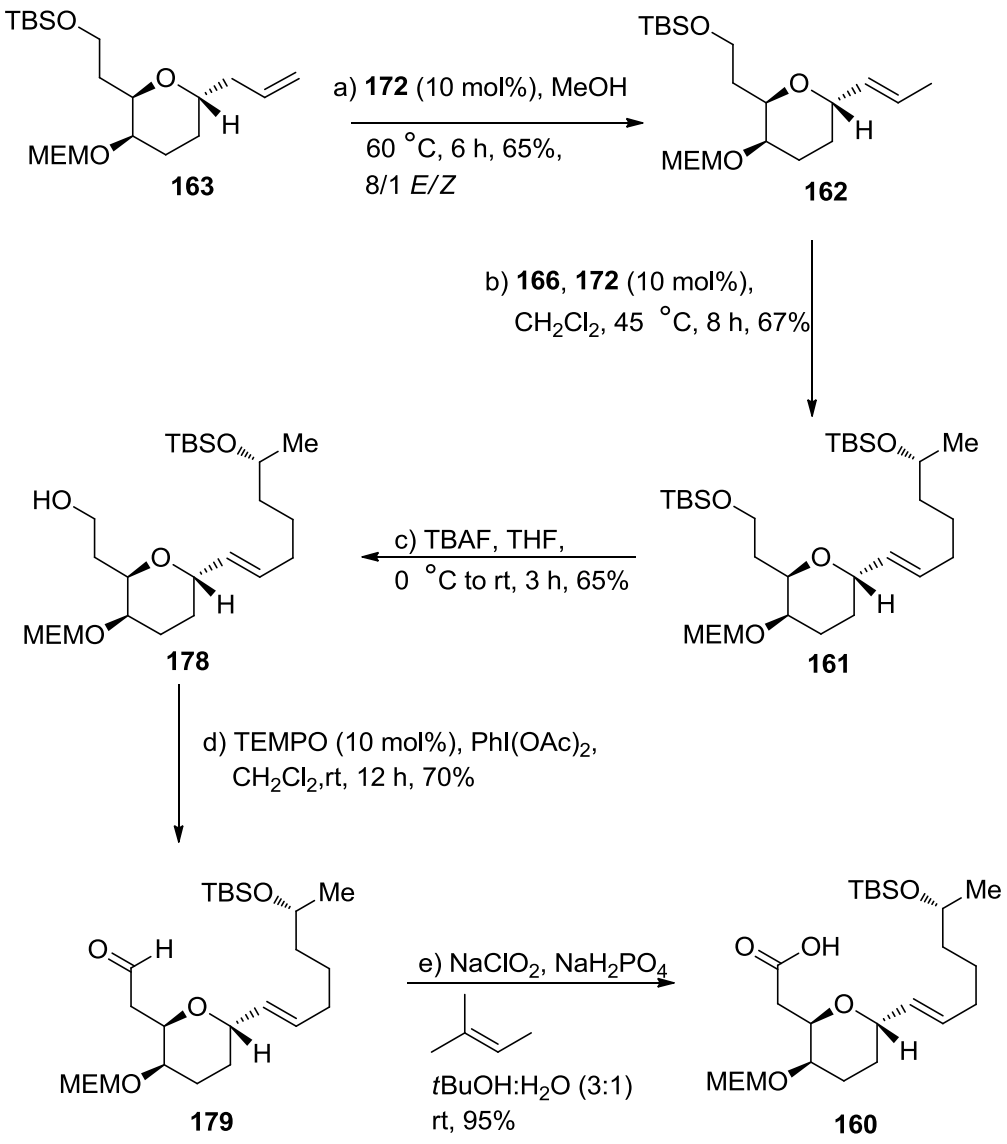


Figure 4.18. Synthesis of Intermediate **160**

In addition to the successful reactions delineated above, we attempted a cross metathesis reaction and oxidation that failed to provide us with the desired products. Our reasoning behind these failed reactions was to shorten the overall steps in our synthesis. For example, as shown below in figure 4.19, we attempted the cross metathesis of **162** and an unprotected alkenol **180** in

DCM at 45 ˚C to afford **181**. Unfortunately, dimerization of both starting materials was observed, but no product was obtained.

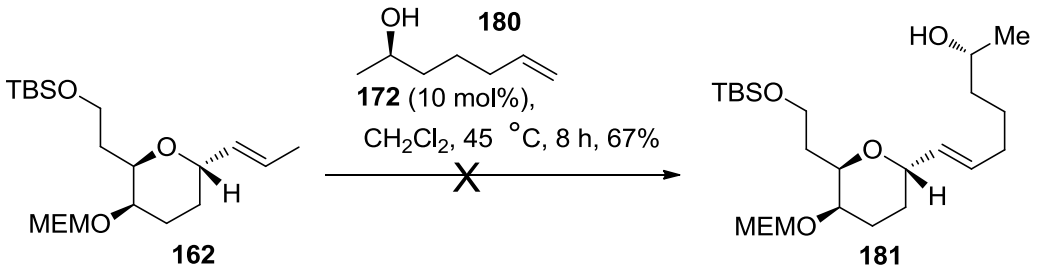


Figure 4.19. Failed Cross-metathesis

Also, we performed the deprotection of both the primary and secondary TBS groups with TBAF and afforded the diol **182** (figure 4.19). We were also successful in selectively oxidizing the free primary alcohol to the aldehyde **183** via TEMPO and $PhI(OAC)_2$ in the presence of the secondary free OH.[33] To our dismay, we attempted to further oxidize the aldehyde moiety to the carboxylic acid **184**, and the desired product was not isolated, and to the best of our knowledge, the starting material was decomposed.

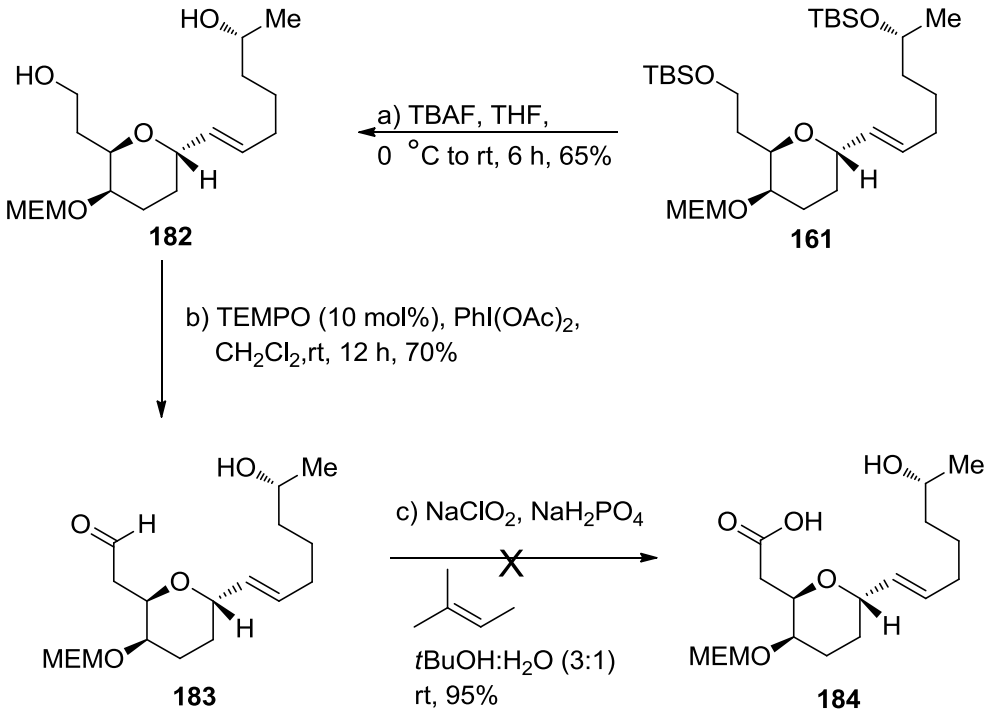


Figure 4.20. Failed Oxidation of **183**

With the TBS protected carboxylic acid **160** in hand, we proceeded forward to the deprotection and final macrocyclization to afford (+)-aspergillide B **141** as shown in figure 4.21. Therefore, we accomplished the deprotection of the secondary TBS group in **160** with Et_3N•3HF and afforded the hydroxy-carboxylic acid compound **185** in 63% yield. Under Yamaguchi macrolactonization standard conditions (**186**, Et_3N, and DMAP), the MEM protected macrolactone **187** was isolated in 75% yield.[24] Finally, the MEM deprotection of **187** readily furnished (+)-aspergillide B in 85% yield. The spectral data and HRMS were all in accordance to the natural sample.[4c,5d] The optical rotation ($[\alpha]^{rt}_D$ +84, *c* = 0.0054g/ml, MeOH) confirmed that **132** is the enantiomer of the natural aspergillide B.[5c]

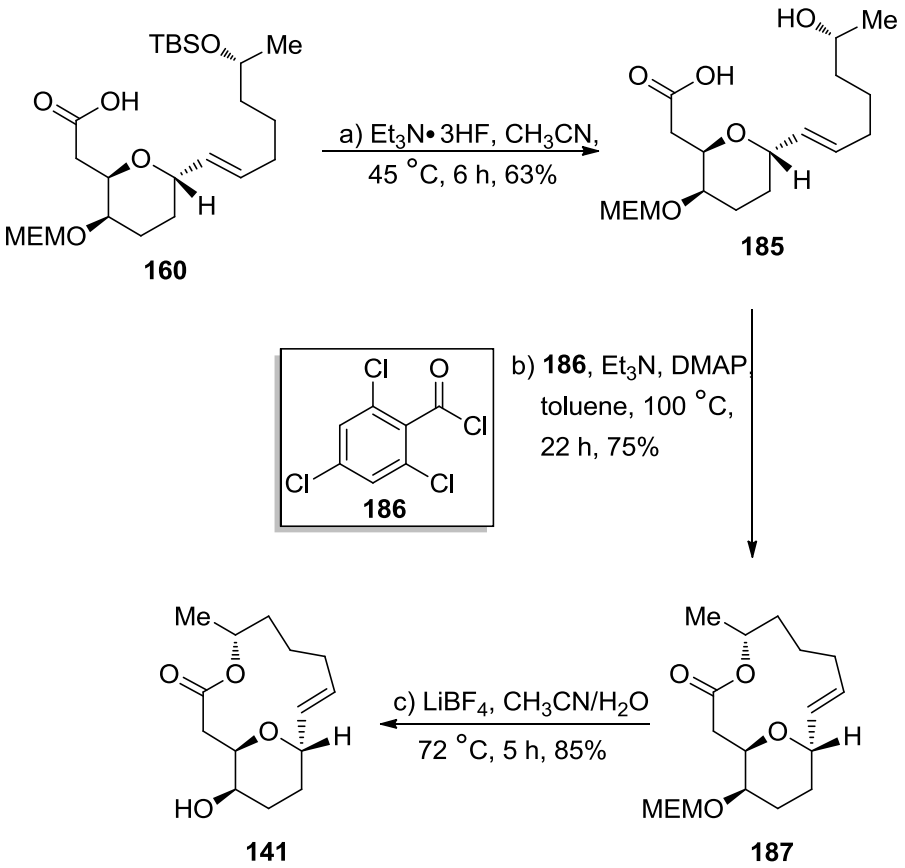


Figure 4.21. Synthesis of (+)-Aspergillide B **141**

4.8. Conclusion

In conclusion, this chapter has highlighted synthetic routes taken for synthesizing aspergillide B, one of the marine natural products belonging to the aspergillide family along with A and C.[5] These biologically active natural products also have unique structural features that have made them appealing to synthetic chemists. In this chapter, we discussed Uenishi's first total synthesis of aspergillide B, which also shed light on a structural discrepancy between aspergillide A and B.[5d] Their key transformations included cross metathesis and an SN2'-type cyclization with a Pd(II) catalyst to forge the 2,6-substituted tetrahydropyran intermediate. In addition, Marco and researchers completed aspergillide B with their main features being a cross

metathesis and C-glycosidation via a Mukaiyama-type aldol reaction, followed by a Yamaguchi macrolactonization.[5a] Following this in 2009, She reported the first synthesis of the enantiomer of aspergillide B, (+)-aspergillide B, which featured a C-glycosylation reaction for constructing the 2,6-*trans*-substituted pyran core and an *E*-selective Julia-Kocienski olefination.[5d] More recently, Fuwa reported the total synthesis of aspergillide B via a hydroxy-directed, highly chemoselective cross-metathesis and a diastereoselective intramolecular oxa-conjugate cyclization as the key transformations to provide the 2,6-substituted tetrahydropyran.[5e] In addition, this chapter highlights our synthesis of (+)-aspergillide B.[4a] Our convergent synthesis was unique from all other syntheses reported because we completed the α-C-glycoside segment from a highly diastereoselective oxocarbenium allylation process followed by a Ru-catalyzed terminal olefin isomerization protocol. The late stage convergence allows for the synthesis of a variety of analogues to examine bioactivity of "aspergillide like" compounds against tumor cell lines and further develop the SAR of the aspergillide family of natural products.

CONCLUSION

In conclusion, this dissertation highlights our efforts toward the carbocupration of alkynoates and shows how we have significantly expanded the scope and contributed to this branch of chemistry. Not only have we been the first to introduce the TMSOTf mediated catalytic carbocupration of alkynoates, we have greatly expanded the idea of vicinal functionalization as well. In general, we have performed these reactions with good selectivity and yield, which should make them very appealing to synthetic chemists. Our work has included multiple carbon-carbon bonds in one flask, as well as the construction of a carbon-silicon bond. Also, disubstituted, trisubstituted, and even tetrasubstituted α,β-unsaturated esters were produced selectively and efficiently.

Furthermore, we have shown the convergent total synthesis of (+)-aspergillide B. Due to the limited amount of biological data and its unique structural features, there has been great synthetic interest in these marine derived natural products. We described the synthesis of (+)-aspergillide B by means of a highly diastereoselective oxocarbenium allylation followed by a cross-metathesis and final Yamaguchi macrolactonization.

Therefore, we have described three novel methodologies utilizing the TMSOTf mediated catalytic carbocupration of alkynoates as well as the total synthesis of a natural product via an oxocarbenium allylation. These methodologies and total synthesis should be of importance to organic chemists and of use to this field in future research.

EXPERIMENTAL

General Procedure The NMR spectra were recorded with either a 360 or 500 MHz Bruker spectrometer. ^{1}H and ^{13}C NMR spectra were obtained using $CDCl_3$ as the solvent with either tetramethylsilane (TMS: $\delta = 0.00$ ppm) or chloroform ($CHCl_3$: $\delta = 7.26$ ppm) as the internal standard. Chemical shifts are given in δ (ppm) and coupling constants (*J*) in Hz. FTIR spectra were recorded on a BIO-RAD FTS-40 spectrometer. HRMS determination was performed in the laboratory of mass spectrometry at the University of Alabama. A JASCO P-1030 Polarimeter at the University of Alabama Birmingham was used for optical rotations ($[\alpha]^{24}_{D}$). Column chromatography was performed using 60-200 μm silica gel. Analytical thin layer chromatography was performed on silica coated glass plates with F-254 indicator. Visualization was accomplished by UV light (254 nm) and $KMnO_4$. All starting materials and solvents were commercially available (Aldrich or Alfa Aesar) and were used without further purification.

General Experimental Procedure for Preparation of **34a**-**34i**: CuI (0.029 g, 0.15 mmol) and LiCl (0.013 g, 0.30 mmol) were placed in a 100 mL round bottom flask (flame dried under vacuum) under Ar. Dry THF (20 mL) was added to the salts, and the mixture was stirred at room temperature for a period of 0.5 h until complete dissolution had occurred. The clear, light yellow homogeneous solution was cooled to –78 °C, and **32** (0.29 g, 3.0 mmol) was added, followed by TMSOTf (1.05 eq., 0.57 mL, 3.15 mmol). After 5 minutes at –78 °C, RMgBr (1.2

eq., 1.2 mL, 3.6 mmol) was added dropwise with a syringe, and the solution was stirred at –78 °C for 1 h. Trifluoroacetic acid (1.2 eq., 0.5 mL, 3.6 mmol) was added to quench the reaction at –78 °C, and the mixture was allowed to warm to room temperature and stir for 30 min. The product was washed with sat. $NaHCO_3$ (20 mL) and extracted with Et_2O (3 X 25 mL), and the combined organic layers were washed with deionized water followed by saturated NH_4Cl. The organic layer was separated, dried with $MgSO_4$, and concentrated in vacuo to give the crude product, which was then analyzed by ^1H NMR spectroscopy to determine diastereoselectivity. Column chromatography of the crude material (10% ethyl acetate in hexanes) afforded the pure cinnamate products **34a** – **34i** as yellow oils.

34a: 0.48 g (91%); ^1H NMR (360 MHz, $CDCl_3$) δ 7.4 (m, 5H), 6.9 (d, *J*=12.7 Hz, 1H), 5.9 (d, *J*=12.7 Hz, 1H), 4.2 (q, *J*=7.3 Hz, 2H), 1.2 (t, *J*=7.3 Hz, 3H)[9a]

34b: 0.53 g (91%); ^1H NMR (360 MHz, $CDCl_3$) δ 7.7 (dd, *J*=8.8, 2.9 Hz, 2H), 7.1 (dd, *J*=8.8, 8.4 Hz, 2H) 6.9 (d, *J*=12.5 Hz, 1H), 5.9 (d, *J*=12.5 Hz, 1H), 4.2 (q, *J*=7.0 Hz, 2H), 1.3 (t, *J*=7.0 Hz, 3H) ^{13}C NMR (125 MHz, $CDCl_3$) 164.9 (d, *J*=249.3 Hz), 161.9, 142.0, 132.0 (d, *J*=8.8 Hz), 130.8 (d, *J*=2.8 Hz), 119.5, 114.9 (d, *J*=21.0 Hz), 60.2, 14.0 IR: 2983, 2361, 1719, 1601, 1509, 1159, 1031, 853 cm^{-1} HRMS (EI) calculated for $C_{11}H_{11}FO_2$ $[M]^+$: 194.0743, found: 194.0745.[9b]

34c: 0.47 g (83%); ^1H NMR (360 MHz, $CDCl_3$) δ 7.3 (m, 4H), 7.2 (d, *J*=12.3 Hz, 1H), 6.1 (d, *J*=12.3 Hz, 1H), 4.2 (q, *J*=7.3 Hz, 2H), 2.3 (s, 3H) 1.2 (t, *J*=7.3 Hz, 3H)[9c]

34d: 0.45 g (73%); ^1H NMR (360 MHz, $CDCl_3$) δ 7.3 (m, 2H), 7.18 (m, 1H), 6.9 (d, *J*=12.5 Hz, 1H), 6.9 (m, 1H), 5.9 (d, *J*=12.5 Hz, 1H), 4.2 (q, *J*=7.0 Hz, 2H), 3.9 (s, 3H) 1.2 (t, *J*=7.0 Hz, 3H)[9d]

34e: 0.50 g (88%); ^1H NMR (360 MHz, $CDCl_3$) δ 7.4 (m, 4H), 7.2 (m, 1H), 5.9 (q, *J*=1.6 Hz, 1H), 4.2 (q, *J*=7.2Hz, 2H), 2.2 (d, *J*=1.6 Hz, 3H) 1.3 (t, *J*=7.2 Hz, 3H)[9e]

34f: 0.49 g (79%); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.7 (d, *J*=8.8 Hz, 2H), 6.9 (d, *J*=8.8 Hz, 2H), 6.8 (d, *J*=12.5 Hz, 1H), 5.8 (d, *J*=12.5 Hz, 1H), 4.2 (q, *J*=7.0 Hz, 2H), 3.8 (s, 3H) 1.2 (t, *J*=7.0 Hz, 3H)[9f]

34g: 0.49 g (75%); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.0 (d, *J*=11.8 Hz, 1H), 6.8 (s, 2H), 6.1 (d, *J*=11.8 Hz, 1H), 4.1 (q, *J*=7.3 Hz, 2H), 2.2 (s, 3H), 2.1 (s, 6H), 1.1 (t, *J*=7.3 Hz, 3H)[9g]

34h: 0.45 g (84%); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.4 (m, 5H), 6.9 (br s, 1H), 4.2 (q, *J*=7.3 Hz, 2H), 1.2 (t, J=7.3 Hz, 3H)[9h]

34i: 0.46 g (84%); ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.3 (dt, *J*=11.5, 1.7, 1H), 5.8 (dt, *J*=11.6, 1.6, 1H), 4.1 (q, *J*=7.3 Hz, 2H), 2.6 (m, 2H), 1.4-1.3 (m, 8H), 1.3 (t, *J*=7.3 Hz, 3H), 0.96 (t, *J*=7.9 Hz, 3H)[9i]

General Procedure for the preparation of **67-77, 79:** CuI (0.046 g, 0.24 mmol) and LiCl (0.020 g, 0.48 mmol) were placed in a 100 mL round bottom flask (flame dried under vacuum) under Ar. Dry THF (20 mL) was added to the salts, and the mixture was stirred at room temperature for a period of 0.5 h until complete dissolution had occurred. The clear, light yellow homogeneous solution was cooled to –78 °C, and **32a** (**32b** was used for preparation of compound **79**) (0.29 g, 3.0 mmol) was added, followed by TMSOTf (1.05 eq., 0.57 mL, 3.15 mmol). After 5 minutes at –78 °C, RMgBr (1.6 eq., 2.4 mL, 4.8 mmol) was added dropwise with a syringe, and the solution was stirred at –78 °C for 1 h. A solution of RCHO (1.3 eq., 0.40 mL, 3.9 mmol), BF_3•OEt_2 (1.3eq, 3.9 mmol, 0.49 mL), and dry THF (5 mL) was also stirred at –78 °C under Ar for 1 hr and then added via syringe to the reaction mixture and allowed to stir for 3 hr. Saturated NH_4Cl (2 mL) was added to quench the reaction at –78 °C. Immediately, the

product was extracted with Et_2O (3 X 25 mL), and the combined organic layers were washed with deionized water followed by saturated NH_4Cl. The organic layer was separated, dried with $MgSO_4$, and concentrated in vacuo to give the crude product, which was then analyzed by ^1H NMR spectroscopy to determine diastereoselectivity. Column chromatography of the crude material (5% ethyl acetate in hexanes) afforded the pure aldol products **67** – **77**, **79** as yellow oils.

67: 0.50 g (59%); ^1H NMR (360 MHz, $CDCl_3$) δ 7.3 (m, 10H), 7.0 (s, 1H), 5.6 (d, *J*=5.6 Hz, 1H), 4.1 (q, *J*=7.3 Hz, 2H), 3.2 (d, *J*=6.1 Hz, 1H), 1.0 (t, *J*=7.2 Hz, 3H)[15]

68: 0.57 g (61%); ^1H NMR (360 MHz, $CDCl_3$) δ7.3 (m, 6 H), 7.0 (m, 2H), 6.9 (s, 1H), 5.6 (br s, 1H), 4.0 (q, *J* = 7.3Hz), 2.9 (br s, 1H), 0.98 (t, *J* = 7.0Hz).^{13}C NMR (125 MHz, $CDCl_3$) δ168.3, 162.5 (d, *J* = 248.4Hz), 140.9, 135.8, 133.4, 131.4 (d, *J* = 3.5Hz), 130.3 (d, *J* = 8.2Hz), 128.3, 127.8, 126.6, 115.1 (d, *J* = 21.1Hz), 75.3, 60.8, 13.5. IR (CH_2Cl_2): 3442, 3059, 2987, 1714, 1608, 1507, 1379, 1236, 1033, 841, 735 cm^{-1}. R_f = 0.15, 20% EtOAc in hexanes. HRMS (EI) calculated for $C_{18}H_{17}O_3F$ $[M]^+$: 300.1162 found: 300.1168.

69: 0.50 g (56%); ^1H NMR (360 MHz, $CDCl_3$) δ 7.3 (m, 9H), 5.7 (s, 1H), 4.0 (q, *J* = 7.3Hz, 2H), 2.4 (s, 3H), 0.92 (t, *J* = 7.0Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ168.1, 141.3, 136.32, 136.30, 135.7, 135.6, 129.5, 128.4, 127.94, 127.91, 127.8, 126.5, 125.3, 75.3, 60.6, 19.8, 13.3. IR (CH_2Cl_2): 3432, 2980, 2938, 1703, 1375, 1217, 1033, 758, 701 cm^{-1}. R_f = 0.18, 20% EtOAc in hexanes. HRMS (EI) calculated for $C_{19}H_{20}O_4$ $[M]^+$: 296.1413 found: 296.1412.

70: 0.47 g (53%); ^1H NMR (360 MHz, $CDCl_3$) δ7.3 (m, 7H), 6.9 (s, 1H), 6.8 (m, 2H), 5.5 (d, J = 5.7Hz), 4.0 (q, *J* = 7.3Hz), 3.8 (s, 3H), 3.0 (d, J = 5.7Hz), .94 (t, J = 6.9Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ168.6, 159.3, 136.1, 135.5, 134.2, 133.2, 128.4, 128.1, 128.0, 127.9, 113.8, 75.1, 60.7, 55.2, 13.5. IR (CH_2Cl_2): 3471, 2980, 1714, 1612, 1503, 1250, 1027, 846, 698 cm^{-1}. R_f =

0.16, 20% EtOAc in hexanes. HRMS (EI) calculated for $C_{19}H_{20}O_4$ $[M]^+$: 312.1362 found: 312.1353.

71: 0.57 g (63%); ^{1}H NMR (360 MHz, $CDCl_3$) δ7.4 (m, 2H), 7.3 (m, 5H), 7.1 (m, 2H), 6.9 (s, 1H) 5.6 (d, *J* = 6.0Hz, 1H), 4.1 (q, *J* = 7.3Hz, 2H), 3.1 (d, *J* = 6.0Hz, 1H), 0.96 (t, *J* = 6.9Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ168.5, 163.4 (d, *J* = 246.5Hz), 136.9 (d, *J* = 2.7Hz), 135.6, 135.2, 135.0, 128.4, 128.35 (d, *J* = 8.2 Hz), 128.31, 128.1, 115.2 (d, *J* = 22.0Hz), 75.1, 60.9, 13.5. IR (CH_2Cl_2): 3441, 3056, 2984, 1707, 1594, 1518, 1371, 1228, 1042, 850, 751, 702 cm^{-1}. R_f = 0.18, 20% EtOAc in hexanes. HRMS (EI) calculated for $C_{18}H_{17}O_3F$ $[M]^+$: 300.1162 found: 300.1167.

72: 0.52 g (58%); ^{1}H NMR (360 MHz, $CDCl_3$) δ7.2 (m, 9H), 6.9 (s, 1H), 5.5 (s, 1H), 4.0 (q, *J* = 7.3Hz, 2H), 2.9 (br s, 1H), 2.3 (s, 3H), 0.94 (t, *J* = 7.0Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ168.6, 138.1, 137.6, 136.0, 135.5, 134.7, 129.1, 128.4, 128.1, 128.0, 126.5, 75.5, 60.8, 21.1, 13.5. IR (CH_2Cl_2): 3469, 3055, 2980, 1703, 1383, 1262, 1217, 905, 728 cm^{-1}. R_f = 0.19, 20% EtOAc in hexanes. HRMS (EI) calculated for $C_{19}H_{20}O_3$ $[M]^+$: 296.1412 found: 296.1416.

73: 0.55 g (62%); ^{1}H NMR (360 MHz, $CDCl_3$) δ7.2 (m, 2H), 7.0 (m, 2H), 6.8 (s, 1H), 4.4 (td, *J* = 6.8, 0.45 Hz, 1H), 4.1 (q, *J* = 7.3 Hz, 2H), 1.7 (m, 2H), 1.3 (m, 6H), 1.1 (t, *J* = 7.0Hz, 3H), 0.89 (t, *J* = 7.3Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ167.30, 143.5 (d, *J* = 268.5), 133.5, 128.2, 127.4, 126.3, 125.9, 75.6, 60.4, 31.6, 29.0, 29.2, 29.5, 22.6, 14.0 IR (CH_2Cl_2): 3446, 2930, 2859, 1718, 1602, 1507, 1217, 743 cm^{-1}. R_f = 0.22, 20% EtOAc in hexanes. HRMS (EI) calculated for $C_{17}H_{23}O_3F$ $[M]^+$: 294.1631 found: 294.1635.

74: 0.47 g (54%); ^{1}H NMR (360 MHz, $CDCl_3$) δ7.1 (m, 4H), 7.0 (s, 1H), 4.4 (m, 1H), 4.0 (q, *J* = 7.3Hz, 2H), 2.7 (br d, 1H), 2.3 (s, 3H), 1.7 (m, 2H), 1.3 (m, 6H), 0.90 (t, *J* = 7.0Hz, 3H), 0.89 (t, *J* = 7.0Hz, 3H). ^{13}C NMR (90 MHz, $CDCl_3$) δ168.6, 137.3, 135.8, 135.7, 134.4, 129.6, 128.0,

127.8, 125.4, 74.3, 60.5, 36.4, 31.6, 25.4, 22.6, 19.8, 14.0, 13.5. IR (CH_2Cl_2): 3428, 2930, 2867, 1711, 1371, 1228, 1021, 754 cm^{-1}. R_f = 0.27, 20% EtOAc in hexanes. HRMS (EI) calculated for $C_{18}H_{26}O_3[M]^+$: 290.1882 found: 290.1884.

75: 0.46 g (55%); ^{1}H NMR (360 MHz, $CDCl_3$) δ7.3 (m, 5H), 6.8 (s, 1H), 4.4 (td, *J* = 6.4, 0.7 Hz, 1H), 4.1 (q, *J* = 7.3Hz, 2H), 2.6 (br s, 1H), 1.7 (m, 2H), 1.3 (m, 6H), 1.1 (t, *J* = 7.0Hz, 3H) 0.9 (t, *J* = 7.0Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ168.9, 136.9, 135.5, 133.1, 128.3, 128.1, 128.0, 74.6, 60.8, 36.2, 31.6, 25.4, 22.5, 13.9, 13.7. IR (CH_2Cl_2): 3432, 2924, 2856, 1708, 1374, 1219, 1021, 748, 691 cm^{-1}. R_f = 0.30, 20% EtOAc in hexanes. HRMS (EI) calculated for $C_{17}H_{24}O_3$ $[M]^+$: 276.1725 found: 276.1732.

76: 0.45 g (54%); ^{1}H NMR (360 MHz, $CDCl_3$) δ7.3 (m, 5H), 6.2 (td, *J* = 6.8, 0.91Hz, 1H), 5.4 (d, *J* = 7.3Hz, 1H), 4.1 (m, 2H), 3.2 (d, *J* = 7.3Hz, 1H), 2.5 (m, 2H), 1.4 (m, 8H), 1.2 (t, *J* = 7.3Hz, 3H), 0.89 (t, *J* = 7.0Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ167.2, 144.3, 142.2, 133.4, 128.2, 127.3, 126.2, 75.5, 60.4, 31.6, 29.4, 29.1, 29.0, 22.5, 13.99, 13.98. IR (CH_2Cl_2): 3432, 2923, 2855, 1722, 1462, 1387, 1213, 1029, 705 cm^{-1}. R_f = 0.23, 20% EtOAc in hexanes. HRMS (EI) calculated for $C_{18}H_{26}O_3[M]^+$: 290.1882 found: 290.1879.

77: 0.41 g (48%); ^{1}H NMR (360 MHz, $CDCl_3$) δ6.1 (td, *J* = 7.3, 0.7Hz, 1H), 4.2 (q, *J* = 7.3Hz, 2H), 4.17 (m, 1H), 2.7 (d, *J* = 7.3Hz, 1H), 2.4 (m, 2H), 1.6 (m, 2H), 1.3 (t, *J* = 7.0Hz, 3H), 1.26 (m, 14H), 0.86 (t, *J* = 7.0Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ167.8, 142.1, 134.2, 74.5, 60.3, 36.5, 31.6, 31.5, 29.4, 29.1, 28.9, 25.6, 22.5, 14.2, 14.2, 14.0, 13.9. IR (CH_2Cl_2): 3439, 2934, 2863, 1711, 1466, 1375, 1206, 1040, 735 cm^{-1}. R_f = 0.27, 20% EtOAc in hexanes. HRMS (EI) calculated for $C_{17}H_{32}O_3$ $[M]^+$: 284.2351 found: 284.2354.

79 ***E/Z***: 0.57 g (61%); ^{1}H NMR (360 MHz, $CDCl_3$) δ(*E*) 7.2 (m, 9H), 5.07 (d, *J* = 10.7Hz, 1H), 4.05 (m, 2H), 3.90 (d, *J* = 10.7Hz, 1H), 2.4 (s, 3H), 2.3 (s, 3H), 1.1 (t, *J* = 7.0Hz, 3H). (*Z*) 7.2

(m, 9H), 5.14 (d, *J* = 9.8Hz, 1H), 4.1 (m, 2H), 3.7 (d, *J* = 9.8Hz, 1H), 2.27 (s, 3H), 2.2 (s, 3H), 1.0 (t, *J* = 7.3Hz, 3H). IR (CH_2Cl_2): 3488, 3062, 2980, 1714, 1444, 1311, 1244, 1195, 1134, 1044, 1011, 739, 690 cm^{-1}. R_f = 0.29, 20% EtOAc in hexanes. HRMS (EI) calculated for $C_{20}H_{22}O_3$ $[M]^+$: 310.1569 found: 310.1560.

General Experimental Procedure for the synthesis of **91**, **93-98***:* CuI (0.029 g, 0.15 mmol) and LiCl (0.013 g, 0.30 mmol) were placed in a 100 mL round bottom flask (flame dried under vacuum) under Ar. Dry THF (20 mL) was added to the salts, and the mixture was stirred at room temperature for a period of 0.5 h until complete dissolution had occurred. The clear, light yellow homogeneous solution was cooled to –78 °C, and **32a** (0.294 g, 3.0 mmol) was added, followed by TMSOTf (3.3 eq., 1.8 mL, 9.9 mmol). After 5 minutes at –78 °C, RMgBr (1.2 eq., 1.2 mL, 3.6 mmol) was added dropwise with a syringe, and the solution was stirred at –78 °C for 1 h. The mixture was allowed to warm to room temperature, and then the product was extracted with H_2O (10 mL) and Et_2O (3 X 25 mL). The combined organic layers were washed with deionized water followed by saturated NH_4Cl. The organic layer was separated, dried with $MgSO_4$, and concentrated in vacuo to give the crude product, which was then analyzed by ^1H NMR spectroscopy to determine diastereoselectivity. Column chromatography of the crude material (3% ethyl acetate in hexanes) afforded the vinyl silane products **91**, **93-98** as yellow oils.

91: 0.68 g (92%); ^1H NMR (500 MHz, $CDCl_3$) δ 7.3 (m, 5H), 6.8 (s, 1H), 4.2 (q, *J*=7.2Hz, 2H), 1.2 (t, *J*=7.2Hz, 3H), 0.22 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ171.9, 141.3, 138.7, 136.5, 128.4, 128.3, 128.2, 60.4, 14.1, -1.6. IR (CH_2Cl_2): 2954, 1711, 1601, 1490, 1213, 1038, 852,

753, 696 cm^{-1}. R_f = 0.66, 20% EtOAc in hexanes. HRMS (EI) calculated for $C_{14}H_{20}O_2Si$ $[M]^+$: 248.1233 found: 248.1239.

93: 0.69 g (88%); ^1H NMR (500 MHz, $CDCl_3$) δ7.2 (m, 4H), 7.1 (s, 1H), 4.1 (q, *J*= 7.2Hz, 2H), 2.3 (s, 3H), 1.1 (t, *J* = 7.2Hz, 3H), 0.29 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ171.3, 142.1, 139.4, 136.6, 135.6, 129.8, 128.1, 127.6, 125.5, 60.0, 19.6, 14.0, -1.4. IR (CH_2Cl_2): 2958, 1703, 1605, 1369, 1198, 1030, 760, 669 cm^{-1}. R_f = 0.81, 20% EtOAc in hexanes. HRMS (EI) calculated for $C_{15}H_{22}O_2Si$ $[M]^+$: 262.1389 found: 262.1392.

94: 0.80 g (92%); ^1H NMR (500 MHz, $CDCl_3$) δ7.1 (s, 1H), 6.9 (s, 2H), 4.0 (q, *J*= 7.2Hz, 2H), 2.3 (s, 3H), 2.2 (s, 6H), 1.0 (t, *J* = 7.2Hz, 3H), 0.35 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ169.9, 146.0, 140.6, 136.1, 134.7, 134.3, 127.5, 59.5, 20.8, 19.3, 13.7, -1.4. IR (CH_2Cl_2): 2957, 2912, 1712, 1605, 1442, 1327, 1242, 1190, 1043, 855 cm^{-1}. R_f = 0.77, 20% EtOAc in hexanes. HRMS (EI) calculated for $C_{17}H_{26}O_2Si$ $[M]^+$: 290.1702 found: 290.1707.

95: 0.68 g (93%); ^1H NMR (500 MHz, $CDCl_3$) δ6.2 (7, *J*=6.9Hz, 1H), 4.2 (q, *J* = 7.2Hz, 2H), 2.3 (m, 2H), 1.3 (t, *J*=7.2Hz, 3H), 1.3 (m, 8H), 0.88 (t, *J* = 6.9Hz, 3H), 0.13 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ170.5, 151.8, 135.9, 59.8, 31.6, 31.5, 29.0, 28.9, 22.5, 14.3, 14.0, -1.3. IR (CH_2Cl_2): 2962, 1711, 1373, 1183, 1042, 669 cm^{-1}. R_f = 0.88, 20% EtOAc in hexanes. HRMS (EI) calculated for $C_{14}H_{28}O_2Si$ $[M\text{-}CH_3]^+$: 241.1624 found: 241.1622.

96: 0.73 g (88%); ^1H NMR (500 MHz, $CDCl_3$) δ7.0 (m, 4H), 6.8 (s, 1H), 4.2 (q, *J*=7.2Hz, 2H), 3.8 (s, 3H), 1.3 (t, *J*= 7.2Hz, 3H), 0.27 (s, 9H).^{13}C NMR (125 MHz, $CDCl_3$) δ171.9, 159.5, 140.9, 138.9, 137.9, 129.2, 120.7, 114.5, 113.0, 60.4, 55.1, 14.1, -1.7. IR (CH_2Cl_2): 2961, 2898, 1704, 1597, 1579, 1468, 1250, 1194, 1035, 847, 777, 688 cm^{-1}. R_f = 0.68, 20% EtOAc in hexanes. HRMS (EI) calculated for $C_{15}H_{22}O_3Si$ $[M]^+$: 278.1338 found: 278.1338.

97: 0.75 g (90%); ^{1}H NMR (500 MHz, $CDCl_3$) δ7.3 (d, *J*= 8.5Hz, 2H), 6.8 (d, *J* = 8.5Hz, 2H), 6.7 (s, 1H), 4.2 (q, *J*= 7.2Hz, 2H), 3.8 (s, 3H), 1.3 (t, *J* = 7.2Hz, 3H), 0.26 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ171.9, 159.7, 140.7, 135.6, 129.6, 128.9, 113.5, 60.0, 54.9, 14.0, -1.8. IR (CH_2Cl_2): 2961, 2894, 1704, 1608, 1509, 1257, 1202, 1039, 995, 851 cm^{-1}. R_f = 0.68, 20% EtOAc in hexanes. HRMS (EI) calculated for $C_{15}H_{22}O_3Si$ $[M]^+$: 278.1338 found: 278.1346.

98: 0.47 g (85%); ^{1}H NMR (500 MHz, $CDCl_3$) δ6.3 (q, *J*= 6.9Hz, 1H), 4.2 (q, *J*= 7.2Hz, 2H), 1.9 (d, *J*= 6.9Hz, 3H), 1.3 (t, *J*= 7.2Hz, 3H), 0.13 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ170.3, 146.3, 137.1, 59.8, 17.6, 14.3, -1.4. IR (CH_2Cl_2): 2957, 1716, 1612, 1339, 1198, 1032, 847 cm^{-1}. R_f = 0.53, 20% EtOAc in hexanes. HRMS (EI) calculated for $C_9H_{18}O_2Si$ $[M\text{-}CH_3]^+$: 171.0841 found: 171.0839.

General Experimental Procedure for the synthesis of **92***:* CuI (0.029 g, 0.15 mmol) and LiCl (0.013 g, 0.30 mmol) were placed in a 100 mL round bottom flask (flame dried under vacuum) under Ar. Dry THF (20 mL) was added to the salts, and the mixture was stirred at room temperature for a period of 0.5 h until complete dissolution had occurred. The clear, light yellow homogeneous solution was cooled to –78 °C, and **32a** (0.29 g, 3.0 mmol) was added, followed by TES-X (X = Cl, OTf) (3.3 eq., 1.8 mL, 9.9 mmol). After 5 minutes at –78 °C, phenylmagnesium bromide (1.2 eq., 1.2 mL, 3.6 mmol) was added dropwise with a syringe, and the solution was stirred at –78 °C for 1 h. The mixture was allowed to warm to room temperature, and then the product was extracted with H_2O (10 mL), Et_2O (3 X 25 mL). The combined organic layers were washed with deionized water followed by saturated NH_4Cl. The organic layer was separated, dried with $MgSO_4$, and concentrated in vacuo to give the crude product, which was then analyzed by ^{1}H NMR spectroscopy to determine diastereoselectivity.

Column chromatography of the crude material (3% ethyl acetate in hexanes) afforded the pure vinyl silane **92** as a yellow oil.

92: 0.76 g (88%); ^{1}H NMR (500 MHz, $CDCl_3$) δ7.3 (m, 5H), 6.8 (s, 1H), 4.2 (q, *J*= 7.2Hz, 2H), 1.2 (t, *J*= 7.2Hz, 3H), 1.0 (t, *J*= 7.6Hz, 9H), 0.78 (q, *J* = 7.6Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ172.1, 142.1, 136.7, 136.1, 128.4, 128.3, 128.2, 60.4, 14.1, 7.2, 3.0. IR (CH_2Cl_2): 2957, 2872, 1708, 1601, 1456, 1190, 1006, 740, 696 cm^{-1}. R_f = 0.77, 20% EtOAc in hexanes. HRMS (EI) calculated for $C_{17}H_{26}O_2Si$ $[M-C_2H_5]^+$: 261.1311 found: 261.1312.

General Experimental Procedure for the synthesis of **101***:* CuI (0.029 g, 0.15 mmol) and LiCl (0.013 g, 0.30 mmol) were placed in a 100 mL round bottom flask (flame dried under vacuum) under Ar. Dry THF (20 mL) was added to the salts, and the mixture was stirred at room temperature for a period of 0.5 h until complete dissolution had occurred. The clear, light yellow homogeneous solution was cooled to –78 °C, and **99** (0.29 g, 3.0 mmol) was added, followed by TMSOTf (3.3 eq., 1.8 mL, 9.9 mmol). After 5 minutes at –78 °C, phenylmagnesium bromide (1.2 eq., 1.2 mL, 3.6 mmol) was added dropwise with a syringe, and the solution was stirred at –78 °C for 1 h. The mixture was allowed to warm to room temperature, and then the product was extracted with H_2O (10 mL) and Et_2O (3 X 25 mL), and the combined organic layers were washed with deionized water followed by saturated NH_4Cl. The organic layer was separated, dried with $MgSO_4$, and concentrated in vacuo to give the crude product, which was then analyzed by ^{1}H NMR spectroscopy to determine diastereoselectivity. Column chromatography of the crude material (3% ethyl acetate in hexanes) afforded the pure vinyl silane **101**as yellow oil.

101: 0.63 g (90%); ^{1}H NMR (500 MHz, $CDCl_3$) δ7.3 (m, 5H), 6.9 (s, 1H), 3.7 (s, 3H), 0.27 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ172.4, 141.5, 138.2, 136.4, 128.4, 128.3, 128.0, 51.4, -1.7. IR (CH_2Cl_2): 2957, 1716, 1605, 1428, 1209, 1021, 946, 843, 758, 696 cm^{-1}. R_f = 0.73, 20% EtOAc in hexanes. HRMS (EI) calculated for $C_{13}H_{18}O_2Si$ $[M]^+$: 234.1076 found: 234.1085.

General Experimental Procedure for the synthesis of **104***:* CuI (0.029 g, 0.15 mmol) and LiCl (0.013 g, 0.30 mmol) were placed in a 100 mL round bottom flask (flame dried under vacuum) under Ar. Dry THF (20 mL) was added to the salts, and the mixture was stirred at room temperature for a period of 0.5 h until complete dissolution had occurred. The clear, light yellow homogeneous solution was cooled to –78 °C, and **102** (0.29 g, 3.0 mmol) was added, followed by TMS-OTf (3.3 eq., 1.8 mL, 9.9 mmol). After 5 minutes at –78 °C, phenylmagnesium bromide (1.2 eq., 1.2 mL, 3.6 mmol) was added dropwise with a syringe, and the solution was stirred at –78 °C for 1 h. The mixture was allowed to warm to room temperature, and then the product was extracted with H_2O (10 mL) and Et_2O (3 X 25 mL), and the combined organic layers were washed with deionized water followed by saturated NH_4Cl. The organic layer was separated, dried with $MgSO_4$, and concentrated in vacuo to give the crude product, which was then analyzed by ^{1}H NMR spectroscopy to determine diastereoselectivity. Column chromatography of the crude material (3% ethyl acetate in hexanes) afforded the pure vinyl silane product **104** as a yellow oil.

104: 0.67 g (85%); ^{1}H NMR (500 MHz, $CDCl_3$) δ7.3 (m, 5H), 3.9 (q, J = 7.2Hz, 2H), 2.2 (s, 3H), 0.92 (t, J= 7.2Hz, 3H), 0.29 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ171.9, 151.9, 144.1, 128.6, 127.8, 127.2, 126.5, 59.7, 23.9, 13.8, 0.33. IR (CH_2Cl_2): 2961, 2902, 1704, 1597, 1442,

1261, 1209, 1091, 1035, 839, 754, 702 cm^{-1}. R_f = 0.73, 20% EtOAc in hexanes. HRMS (EI) calculated for $C_{15}H_{22}O_2Si$ $[M]^+$: 262.1389 found: 262.1387.

***tert*-Butyldimethyl (1-methylhex-5-enyloxy)silane (166):** 3-butenylmagnesium bromide (2.5 eq., 43 mL, 43 mmol) was added dropwise to (*R*)-propylene oxide **165** and CuCN (0.15g, 1.7 mmol) in THF (20 mL) over a period of 30 minutes at -78 ˚C. The yellow mixture was allowed to warm to ambient temperature overnight and was quenched with saturated NH_4Cl. The product was extracted with DCM (3 X 25 mL), and the combined organic layers were washed with brine. The organic layer was separated, dried with $MgSO_4$, and concentrated to give the crude product (1.7 g, 89%), which was then analyzed by ^1H NMR spectroscopy. To a solution of the crude product (1.7 g, 15 mmol) in DMF was added imidazole (3 eq., 3.0g, 45 mmol) and then TBS-Cl (1.5 eq., 3.4 g, 22.5 mmol) at 0 ˚C and was allowed to warm to room temperature for 24 h. The reaction was quenched with a large excess of water and extracted with DCM (3 X 25 mL), dried with $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography on silica gel (5% EtOAc-hexanes) yielded 3.2 g (94%) of TBS-protected alkenol **166** as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ5.8 (m, 1H), 4.9 (m, 2H), 3.8 (m, 1H), 2.0 (m, 2H), 1.1 (d, *J* = 5.9 Hz, 3H), 0.89 (s, 9H), 0.047 (s, 6H).

3-(2-Methoxyethoxymethoxy)propene (168): MEM-Cl (2.0 eq., 27 mL, .24 mol) and diisopropylethylamine (1.5 eq., 31 mL, 0.18 mol) were added sequentially to a solution of allylic alcohol **167** (7.0 g, .12 mol) in DCM (120 mL) at 0 ˚C and stirred to room temperature for 16 h. The reaction was quenched with 1M HCl (50 mL) and diluted with DCM, and the aqueous layer was extracted with DCM (3 X 25 mL). The combined organic layers were washed with

brine and dried over $MgSO_4$, filtered, and concentrated. Purification over silica (10% EtOAc-hexanes) afforded the desired clear oil **168** (14 g, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ5.9 (m, 1H), 5.3 (m, 1H), 5.2 (m, 1H), 4.7 (s, 2H), 4.1 (dt, *J* = 1.4, 5.7 Hz, 2H), 3.7 (m, 2H), 3.6 (m, 2H), 3.4 (s, 3H).

1-*tert*-Butyldimethylsilanyloxy)-4-(2-methoxyethoxymethoxy)hex-5-en-3-ol (170): Sec-BuLi (0.80 eq., 51 mL, 71 mmol) was added dropwise to a solution of **168** (13 g, 89 mmol) in THF (178 mL) at -78 ˚C. A resultant bright yellow mixture was stirred at -78 ˚C for 30 minutes. A solution of (-)-β-methoxydiisopinocampheylborane (1.1 eq., 31 g, 98 mmol) in THF (98 mL) was added dropwise via cannula. After stirring at -78 ˚C for 1 h, boron trifluoride etherate (1.3 eq., 15 mL, 118 mmol) was added, followed by a pre-cooled solution of TBS-aldehyde **169** (16g, 89 mmol) in THF (89 mL) via cannula. Stirring was continued at -78 ˚C for 4 h, then the reaction mixture was oxidized with 3M NaOH (48 mL) and 30% H_2O_2 (49 mL) at 0 ˚C and allowed to warm to ambient temperature and stirred overnight (at least 8 h). The layers were separated and the aqueous solution washed with Et_2O (3 X 25 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography using 30% EtOAc-hexanes afforded the desired product **170** (22 g, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ5.7 (m, 1H), 5.3 (m, 2H), 4.8 (d, *J* = 6.9 Hz, 1H), 4.7 (d, *J* = 6.9, 1H), 3.9 (m, 1H), 3.8 (m, 4H), 3.6 (m, 1H), 3.5 (m, 2H), 3.4 (s, 3H), 1.7 (m, 2H),), 0.88 (s, 9H), 0.055 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ134.7, 119.6, 93.0, 81.1, 72.0, 71.7, 67.3, 61.1, 58.9, 35.0, 25.9, 18.2, 5.46. IR (CH_2Cl_2): 2961, 3474, 2952, 2926, 2891, 2854, 2359, 1473, 1254, 1098, 1036, 832, 780 cm^{-1}. R_f = 0.27, 30% EtOAc in hexanes. $[\alpha]^{24}_D$ = -38.4˚ (c 0.015 g/ml, CH_2Cl_2). HRMS (EI) calculated for $C_{16}H_{34}O_5Si$ $[M]^+$: 335.2254 found: 335.2247.

1-[2-(*tert*-butyldimethylsilanyloxy)ethyl]-2-(2-methoxyethoxymethoxy)but-3-enyl ester (171): Acryloyl chloride (2.0 eq., 2.3 mL, 28 mmol) was added dropwise to a solution of **170** (5.5 g, 14 mmol) in DCM (47 mL), NEt_3 (2.2 eq., 4.3 mL, 31 mmol), and DMAP (.12 g, 0.98 mmol) at 0 ˚C and allowed to warm to room temperature and stir overnight. The orange reaction mixture was quenched with saturated $NaHCO_3$, and then filtered over celite rinsing with DCM. The layers were separated and the aqueous solution washed with DCM (3 X 25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography over silica gel with 10% EtOAc-hexanes afforded the desired product **171** (4.6 g, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ6.4 (dd, *J* = 16, 1.6 Hz, 1H), 6.1 (m, 1H), 5.8 (dd, *J* = 9.1, 1.3 Hz, 1H), 5.7 (m, 1H), 5.3 (m, 1H), 5.2 (m, 1H), 4.7 (d, *J* = 6.9 Hz, 1H), 4.6 (d, *J* = 7.0 Hz, 1H), 4.2 (m, 1H), 3.8 (m, 1H), 3.6 (m, 6H), 3.4 (s, 3H), 1.9 (m, 2H),), 0.87 (s, 9H), 0.013 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ165.5, 133.9, 130.8, 128.5, 119.7, 92.9, 77.6, 72.1, 71.7, 67.0, 59.3, 59.0, 33.4, 25.9, 18.2, -5.47. IR (CH_2Cl_2): 2922, 2879, 1734, 1630, 1468, 1406, 1254, 1186, 1093, 1041, 827, 775 cm^{-1}. R_f = 0.50, 30% EtOAc in hexanes. $[\alpha]^{24}_D$ = -15.6˚ (c 0.013 g/ml, CH_2Cl_2). HRMS (EI) calculated for $C_{19}H_{36}O_6Si$ $[M]^+$: 388.2281 found: 388.2292.

6-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]-5-(2-methoxyethoxymethoxy)-5,6-dihydropyran-2-one (173): To a solution of **171** (2.4 g, 6.3 mmol) refluxing in toluene (628 mL) at 80 ˚C was added Grubbs second generation catalyst (.15 eq., .80 g, .94 mmol) in toluene (94 mL) dropwise to the refluxing solution. It was added over 6 h and allowed to stir for an additional 24 h. Upon consumption of the starting material, the reaction mixture was concentrated and purified by flash chromatography using 30% EtOAc-hexanes and afforded the

desired product **173** (2.2 g, 96%). ^{1}H NMR (500 MHz, $CDCl_3$) δ7.1 (m, 1H), 6.2 (d, *J* = 9.8 Hz, 1H), 4.9 (d, *J* = 7.2 Hz, 1H), 4.8 (d, *J* = 7.2 Hz, 1H), 4.6 (m, 1H), 4.0 (m, 1H), 3.9 (m, 1H), 3.8 (m, 2H), 3.7 (m, 1H), 3.5 (m, 2H), 3.4 (s, 3H), 2.1 (m, 3H), 1.9 (m, 1H),), 0.90 (s, 9H), 0.080 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ163.4, 143.7, 123.3, 95.2, 71.5, 67.6, 67.3, 59.0, 58.4, 33.3, 25.9, 18.9, -5.41. IR (CH_2Cl_2): 2926, 2885, 2654, 2359, 1729, 1473, 1250, 1088, 1031, 827, 780 cm^{-1}. R_f = 0.14, 30% EtOAc in hexanes. $[\alpha]^{24}_D$ = -10.7˚ (c 0.015 g/ml, CH_2Cl_2). HRMS (EI) calculated for $C_{17}H_{32}O_6Si$ $[M]^+$: 361.2046 found: 361.2066.

6-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]-5-(2-methoxyethoxymethoxy) tetrahydropyran-2-one (174): To a solution of **173** (1.8g, 5.1 mmol) in EtOH (10 mL) at room temperature was added Pd/C (10 %) in one portion. The reaction vessel was evacuated under vacuum and placed under atmospheric H_2 balloon pressure. The reaction was allowed to stir at rt for 1.5 hr until complete consumption of the starting material was observed via TLC analysis. The reaction was filtered through a plug of celite and concentrated in vacuo to afford **174** (1.8g, 99%) without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ4.8 (d, *J* = 7.2 Hz, 1H), 4.7 (d, *J* = 7.2 Hz, 1H), 4.5 (m, 1H), 3.9 (m, 1H), 3.8 (m, 1H), 3.7 (m, 3H), 3.5 (t, *J* = 4.5 Hz, 2H), 3.4 (s, 3H), 2.6 (m, 1H), 2.5 (m, 1H), 2.2 (m, 1H),), 2.0 (m, 2H), 1.8 (m, 1H), 0.086 (s, 9H), 0.034 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ170.6, 94.0, 78.8, 71.6, 69.5, 67.6, 59.0, 58.5, 34.6, 25.9, 25.5, 24.3, 18.2, -5.43. IR (CH_2Cl_2): 2937, 2885, 1739, 1639, 1468, 1363, 1244, 1097, 1026, 837, 775 cm^{-1}. R_f = 0.14, 30% EtOAc in hexanes. $[\alpha]^{24}_D$ = +6.7˚ (c 0.013 g/ml, CH_2Cl_2). HRMS (EI) calculated for $C_{17}H_{34}O_6Si$ $[M]^+$: 287.1679 found: 287.1682.

6-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]-5-(2-methoxyethoxymethoxy) tetrahydropyran-2-yl acetate (175): To a solution of **174** (1.3g, 3.5 mmol) in anhydrous DCM (35 mL) was added DIBAL-H (2.5 eq., 8.8 mL, 8.8 mmol) at -78 ˚C. Once the reaction went to completion (4 h), the reaction mixture was quenched with saturated $NaHCO_3$, diluted with DCM, and warmed to room temperature under magnetic stirring. After washing with NH_4Cl, the organic layer was separated and the aqueous layer washed with DCM (3 X 25 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo to yield the crude lactol (1.3 g, 99%). The crude lactol (1.3 g, 3.5 mmol) was directly dissolved in dry DCM and pyridine (3.0 eq., .85 mL, 11 mmol), Ac_2O (2.5 eq., 0.90 mL, 8.8 mmol), and DMAP (1.0 eq., 0.43 g, 3.5 mmol) were added sequentially and the mixture was stirred for 12 h at room temperature until complete consumption of the starting material was observed via TLC analysis. The reaction mixture was quenched with saturated $NaHCO_3$ and the layers were separated. The aqueous layer was washed with DCM (3 X 30 mL) and the combined organic layer was washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography over silica gel with 20% EtOAc-hexanes afforded the desired product **175** (1.2 g, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) Minor diastereomer δ 6.2 (m, 1H), 4.9 (d, J = 7.3 Hz, 1H), 4.8 (d, J = 6.9 Hz, 1H), 4.1 (m, 1H), 3.8 (m, 5H), 3.6 (t, J = 4.4 Hz, 2H), 3.4 (s, 3H), 2.2 (m, 2H), 2.1 (s, 3H), 2.0 (m, 2H), 1.8 (m, 2H), 0.90 (s, 9H), 0.064 (s, 6H). Major diastereomer δ 5.7 (dd, *J* = 7.9, 2.0 Hz, 1H), 4.8 (d, *J* = 7.3 Hz, 1H), 4.7 (d, *J* = 6.9 Hz, 1H), 3.7 (m, 5 H), 3.6 (bs, 1H), 3.5 (t, *J* = 4.4 Hz, 2H), 3.4 (s, 3H), 2.1 (m, 2H), 2.0 (s, 3H), 1.9 (m, 2H), 1.7 (m, 2H), 0.89 (s, 9H), 0.052 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 94.3, 92.3, 75.2, 71.7, 70.6, 69.1, 67.3, 59.1, 34.9, 25.9, 23.2, 22.1, 21.2, 18.3, -5.41. IR (CH_2Cl_2): 2937, 2885, 2860, 1755, 1464, 1363, 1244, 1201, 1103, 1045,

843, 781 cm^{-1}. R_f = 0.35, 30% EtOAc in hexanes. $[\alpha]^{24}_D$ = -15.6˚ (c 0.013 g/ml, CH_2Cl_2). HRMS (EI) calculated for $C_{19}H_{38}O_7Si$ $[M]^+$: 406.2387 found: 406.2394.

2-[6-Allyl-3-(2-methoxyethoxymethoxy)tetrahydropyran-2-yl]ethoxy]-*tert*-butyl dimethylsilane (163): To a solution of **175** (0.40g, 0.98 mmol) in anhydrous DCM (5 mL) was added BF_3•OEt_2 (2.0 eq., 0.082 mL, 0.65 mmol) and allylTMS (2.5 eq., 0.10 mL, 0.81 mmol) at -78 ˚C. After 1 h, the reaction mixture was quenched with saturated NH_4Cl, the layers were separated, and the aqueous layer extracted with DCM (3 X 10 mL). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography over silica gel with 10-20% EtOAC-hexanes provided the α-C-glycoside subunit **163** (0.32 g, 85%). ^1H NMR (500 MHz, $CDCl_3$) δ 5.8 (m, 1H), 5.0 (m, 2H), 4.8 (d, *J* = 6.8 Hz, 1H), 4.7 (d, *J* = 6.8 Hz, 1H), 4.0 (m, 1H), 3.7 (m, 6H), 3.5 (m, 2H), 3.3 (s, 3H), 2.2 (m, 2H), 1.9 (m, 1H), 1.8 (m, 2H), 1.7 (m, 2H), 1.3 (m, 1H), 0.09 (s, 9H), 0.03 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.2, 116.5, 94.1, 72.9, 71.7, 70.3, 69.2, 67.0, 59.8, 58.9, 38.4, 29.7, 27.7, 25.9, 24.2, 18.3, -5.31. IR (CH_2Cl_2): 3100, 2932, 2874, 2359, 1640, 1463, 1250, 1092, 1046, 843, 780 cm^{-1}. R_f = 0.57, 30% EtOAc in hexanes. $[\alpha]^{24}_D$ = +21.4^o (c 0.013 g/mL, CH_2Cl_2). HRMS (EI) calculated for $C_{20}H_{40}O_5Si$ $[M]^+$: 389.2723 found: 334.2721.

***tert*-Butyl-{2-[3-(2-methoxyethoxymethoxy)-6-propenyltetrahydropyran-2-yl)] ethoxy}dimethylsilane (162):** Grubbs' catalyst (0.10 eq., 0.030g, 0.031 mmol) was added to a solution of olefin **163** (0.12g, 0.31 mmol) in MeOH (8.3 mL) at room temperature. The suspension was then heated to 60 ˚C for 4 h until complete consumption of the starting material was observed via TLC analysis. Reaction mixture was concentrated in vacuo and then further

purified by flash chromatography using 7% EtOAc-hexanes to afford **162** (0.078g, 65%). ^{1}H NMR (500 MHz, $CDCl_3$) δ5.6 (m, 2H), 4.8 (d, *J* = 7.0 Hz, 1H), 4.7 (d, *J* = 7.0 Hz, 1H), 4.2 (m, 1H), 3.9 (dt, *J* = 9.8, 3.4 Hz, 1H), 3.7 (m, 5H), 3.5 (t, *J* = 4.6 Hz, 2H), 3.4 (s, 3H), 1.9 (m, 2H), 1.8 (m, 2H), 1.7 (d, *J* = 6.4 Hz, 3H), 1.5 (m, 2H), 0.90 (s, 9H), 0.056 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ130.8, 127.3, 94.1, 72.8, 71.7, 70.9, 69.6, 67.1, 59.7, 59.0, 32.0, 26.2, 25.9, 23.9, 18.3, 17.9, -5.31. IR (CH_2Cl_2): 2954 2927, 2874, 2886, 2852, 2363, 2332, 1738, 1461, 1389, 1359, 1253, 1093, 1040, 844, 779 cm^{-1}. R_f = 0.57, 30% EtOAc in hexanes. $[\alpha]^{24}_D$ = +14.6^o (c 0.011 g/mL, CH_2Cl_2). HRMS (EI) calculated for $C_{20}H_{40}O_5Si$ $[M]^+$: 389.2618 found: 390.2618.

2-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]-6-[6-(*tert*-butyldimethylsilanyloxyhept-1-en 3-(2-methoxyethoxymethoxy)tetrahydropyran (161): To a solution of **162** (0.035 g, 0.090 mmol) in anhydrous DCM (5.3 mL) was added alkenol **166** (5.0 eq., 0.10 g, 0.45 mmol) and Grubbs catalyst (0.10 eq., 0.0076 g, 0.0090 mmol) and then refluxed at 45 ˚C for 8 h. Once all of the starting material was consumed, the reaction mixture was concentrated in vacuo and purified by flash chromatography with 6% EtOAc-hexanes to provide **161** (0.35 g, 67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.6 (m, 1H), 5.5 (m, 1H), 4.8 (d, *J* = 6.9 Hz, 1H), 4.7 (d, *J* = 6.9 Hz, 1H), 4.2 (m, 1H), 3.9 (m, 1H), 3.7 (m, 6H), 3.5 (t, *J* = 4.4 Hz, 2H), 3.4 (s, 3H), 1.9 (m, 4H), 1.7 (m, 4H), 1.4 (m, 4H), 1.1 (d, *J* = 6.1 Hz, 3H), 0.9 (s, 18H), 0.04 (s, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.5, 129.7, 94.1, 72.7, 71.7, 70.8, 69.7, 68.4, 67.0, 59.7, 59.0, 39.2, 32.4, 25.9, 25.8, 25.3, 23.9, 23.7, 18.3, 18.1, -4.71. IR (CH_2Cl_2): 2930, 2858, 2356, 1466, 1362, 1260, 1089, 1039, 830, 766 cm^{-1}. R_f = 0.80, 30% EtOAc in hexanes. $[\alpha]^{24}_D$ = +7.2^o (c 0.013 g/mL, CH_2Cl_2). HRMS (EI) calculated for $C_{30}H_{62}O_6Si_2$ $[M]^+$: 575.4163 found: 575.4149.

2-[6-[6-(*tert*-Butyldimethylsilanyloxy)hept-1-enyl]-3-(2-methoxyethoxymethoxy) tetrahydropyran-2-yl]ethanol (178): To a solution of **161** (0.13 g, 0.23 mmol) in THF (3 mL) was added TBAF (3 eq., 0.69 mL, 0.69 mmol) at 0 ˚C and the mixture was immediately warmed to room temperature for 3 h. Upon consumption of all of the starting material, the reaction was quenched with excess amounts of water and left stirring for 15 min. The layers were separated and the aqueous solution washed with EtOAc (3 X 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography over silica gel with 30% EtOAc-hexanes afforded the desired product **178** (0.68 g, 65%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.7 (m, 1H), 5.5 (dd, *J* = 15.4, 5.4 Hz, 1H), 4.8 (d, *J* = 6.9 Hz, 1H), 4.7 (d, *J* = 6.9 Hz, 1H), 4.3 (m, 1H), 4.0 (dt, *J* = 9.8, 3.2 Hz, 1H), 3.8 (m, 4H), 3.7 (m, 2H), 3.5 (t, *J* = 4.7 Hz, 2H), 3.4 (s, 3H), 2.6 (bs, 1H), 2.0 (m, 4H), 1.7 (m, 4H), 1.4 (m, 4H), 1.1 (d, *J* = 6.0 Hz, 3H), 0.87 (s, 9H), 0.032 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ133.4, 129.2, 94.2, 73.1, 72.8, 71.7, 71.2, 68.4, 67.2, 61.3, 59.0, 39.1, 32.4, 31.1, 25.8, 25.2, 23.8, 23.7, 23.7, 18.1, -4.41. IR (CH_2Cl_2): 3456, 2935, 2886, 2856, 2365, 1646, 1464, 1367, 1255, 1130, 1091, 1038, 836, 776, 658 cm^{-1}. R_f = 0.55, 80% EtOAc in hexanes. $[\alpha]^{24}_D$ = +2.4^o (c 0.010 g/mL, CH_2Cl_2). HRMS (EI) calculated for $C_{24}H_{48}O_6Si$ $[M-C_4H_9]^+$: 403.2516 found: 403.2528.

[6-[6-(*tert*-Butyl-dimethyl-silanyloxy)-hept-1-enyl]-3-(2-methoxy-ethoxymethoxy)-tetrahydro-pyran-2-yl]-acetaldehyde (179): To **178** (0.040 g, 0.085 mmol) in anydrous DCM (0.42 mL) was added $PhI(OAc)_2$ (1.1 eq., 0.030 g, 0.094 mmol) and TEMPO (0.10 eq., 0.0014 g, 0.0085 mmol) at room temperature and allowed to stir for 12 h until complete consumption of the starting material was observed via TLC analysis. The reaction mixture was quenched with saturated $NaHCO_3$ and the aqueous layer extracted with DCM (3 X 1 mL). The

combined organics were washed with brine, filtered, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography on silica gel (15% EtOAc-hexanes) yielded 27 mg (70%) of TBS-protected aldehyde **179**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.8 (s, 1H), 5.7 (m, 1H), 5.5 (dd, *J* = 15.4, 5.4 Hz, 1H), 4.8 (d, *J* = 6.9 Hz, 1H), 4.7 (d, *J* = 7.3 Hz, 1H), 4.4 (m, 1H), 4.2 (m, 1H), 3.8 (m, 2H), 3.7 (m, 2H), 3.5 (t, *J* = 4.4 Hz, 2H), 3.4 (s, 3H), 2.7 (m, 2H), 2.0 (m, 2H), 1.8 (m, 2H), 1.4 (m, 6H), 1.1 (d, *J* = 6.3 Hz, 3H), 0.87 (s, 9H), 0.035 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ201.2, 133.5, 128.9, 94.1, 72.1, 71.7, 71.3, 69.0, 68.4, 67.3, 59.0, 46.9, 43.5, 39.1, 32.4, 25.9, 25.2, 23.8, 23.7, 18.1, -4.41. IR (CH_2Cl_2): 2938, 2855, 2717, 2362, 1725, 1457, 1373, 1247, 1098, 1037, 972, 835, 778, 663 cm^{-1}. R_f = 0.48, 50% EtOAc in hexanes. $[\alpha]^{24}_D$ = $+5.0^o$ (c 0.016 g/mL, CH_2Cl_2). HRMS (EI) calculated for $C_{24}H_{48}O_6Si$ $[M]^+$: 458.3064 found: 458.3065.

[6-[6-(*tert*-Butyldimethylsilanyloxy)hept-1-enyl]-3-(2-methoxyethoxymethoxy) tetrahydropyran-2-yl]-acetic acid (160): Aldehyde **179** (0.047g, 0.10 mmol) was dissolved in a mixture of *t*BuOH:H_2O (3:1), (0.080 mL). The resulting clear solution was stirred vigorously at ambient temperature and 2-methyl-2-butene (8.0 eq., 0.090 mL 0.82 mmol) was added in one portion followed by sodium dihydrogen phosphate monobasic (6.0 eq., 0.073 g, 0.61 mmol) and $NaClO_2$ (6.0 eq., 0.055 g, 0.61 mmol). The combined mixture was stirred for 4.5 h at room temperature and subsequently quenched with 2 mL of a saturated solution of NH_4Cl and stirred until distinct separation of layers was observed. The mixture was partitioned between EtOAc (5 mL) and H_2O (3 mL) in a separatory funnel. The organic layer was separated and the aqueous layer was extracted wit 3 X 10 mL portions of EtOAc. The combined organics were washed with brine, dried over anhydrous $MgSO_4$, filtered, and then concentrated under

reduced pressure to afford the crude acid. The crude material was judged pure by ^{1}H-NMR and used without further purification to afford the compound **160** (0.047 g, 95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.7 (m, 1H), 5.5 (dd, *J* = 15.8, 5.0 Hz, 1H), 4.8 (d, *J* = 6.9 Hz, 1H), 4.7 (d, *J* = 7.3 Hz, 1H), 4.3 (m, 2H), 3.8 (m, 4H), 3.5 (t, *J* = 4.7 Hz, 2H), 3.4 (s, 3H), 2.7 (m, 2H), 2.0 (m, 2H), 1.8 (m, 2H), 1.4 (m, 6H), 1.1 (d, *J* = 6.0 Hz, 3H), 0.89 (s, 9H), 0.053 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ175.7, 133.7, 128.6, 94.1, 71.8, 71.7, 71.7, 70.0, 68.5, 67.3, 59.0, 39.1, 34.8, 32.4, 25.9, 25.7, 25.2, 23.8, 23.5, 18.1, -4.71. IR (CH_2Cl_2): 3423, 3261, 2957, 2924, 2857, 2344, 2251, 1723, 1645, 1571, 1460, 1375, 1261, 1098, 1032, 829, 791, 732 cm^{-1}. R_f = 0.50, 50% EtOAc in hexanes. $[\alpha]^{24}_{D}$ = +5.0^{o} (c 0.016 g/mL, CH_2Cl_2). HRMS (EI) calculated for $C_{24}H_{48}O_6Si$ $[M\text{-}C_4H_9]^{+}$: 417.2309 found: 417.2295.

[6-(6-Hydroxyhept-1-enyl)-3-(2-methoxyethoxymethoxy)tetrahydropyran-2-yl acetic acid (185): Acid **160** (0.030 g, 0.063 mmol) was dissolved in CH_3CN (2.6 mL) and $3NEt_3$•3HF (30 eq., 0.31 mL, 1.9 mmol) was added dropwise to the solution. The reaction mixture was refluxed at 45 ˚C for 6 h or until the starting material was consumed followed by addition of EtOAc and saturated $NaHCO_3$ and allowed to stir for 5 min. The organic layer was separated and the aqueous layer was extracted wit 3 X 5 mL portions of EtOAc. The combined organics were washed with brine, dried over anhydrous $MgSO_4$, filtered, and then concentrated under reduced pressure. Flash chromatography on silica gel (10% MeOH-DCM) afforded **185** (0.014 g, 63%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.8 (m, 1H), 5.6 (dd, *J* = 15.4, 5.2 Hz, 1H), 4.9 (d, *J* = 7.0 Hz, 1H), 4.8 (d, *J* = 7.3 Hz, 1H), 4.4 (m, 1H), 4.3 (m, 1H), 3.8 (m, 4H), 3.6 (t, *J* = 4.5 Hz, 2H), 3.4 (s, 3H), 2.7 (m, 2H), 2.1 (m, 2H), 1.9 (m, 2H), 1.5 (m, 6H), 1.2 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ174.9, 133.8, 128.8, 94.0, 71.9, 71.8, 71.7, 69.8,

68.1, 67.3, 59.0, 38.3, 35.3, 32.1, 29.7, 24.9, 23.4, 23.0. IR (CH_2Cl_2): 3438, 2931, 2857, 2637, 2251, 2086, 1715, 1653, 1455, 1366, 1289, 1256, 1095, 1039, 981, 922, 841, 734 cm^{-1}. R_f = 0.42, 10% MeOH in CH_2Cl_2. $[\alpha]^{24}_D$ = +22.2^o (c 0.015 g/mL, CH_2Cl_2). HRMS (EI) calculated for $C_{24}H_{48}O_6Si$ $[M-H_2O]^+$: 342.2042 found: 342.2043.

14-(2-Methoxyethoxymethoxy)-5-methyl-4,15-dioxabicyclo[9.3.1]pentadec-9-en-3-one (187): To a solution of hydroxy acid **185** (0.020 g, 0.056 mmol) in THF (2.4 mL) cooled to 0˚ C was added NEt_3 (6.1 eq., 0.047 mL, 0.34 mmol) and 2,4,6-$Cl_3C_6H_2COCl$ **186** (3.9 eq., 0.034 mL, 0.22 mmol). After being stirred at room temperature for 4 h, the reaction mixture was diluted with toluene (19 mL) and added dropwise to a solution of DMAP (30 eq., 0.21 g, 1.7 mmol) in toluene (40 mL) refluxing at 100 ˚C over a period of 6.5 h and then left stirring overnight. The reaction mixture was cooled to room temperature, washed successively with 0.5M aq. HCl solution, saturated aqueous $NaHCO_3$ solution, and then brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (20% EtOAc-DCM) provided the macrolactone **187** (0.014 g, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.2 (dddd, *J* = 15.5, 11.0, 4.7, 1.9 Hz, 1H), 5.6 (dd, *J* = 15.8, 4.1 Hz, 1H), 5.0 (m, 1H), 4.8 (d, *J* = 7.3 Hz, 1H), 4.7 (d, *J* = 7.3 Hz, 1H), 4.5 (m, 1H), 4.2 (d, *J* = 11.0 Hz, 1H), 3.7 (m, 2H), 3.5 (t, *J* = 4.7 Hz, 2H), 3.4 (s, 3H), 2.6 (dd, *J* = 13.6, 11.6, 1H), 2.3 (dd, *J* = 13.6, 2.0 Hz, 2H), 2.2 (m, 1H), 2.1 (m, 1H), 2.0 (m, 2H), 1.8 (m, 3H), 1.6 (m, 3H), 1.2 (d, *J* = 6.3 Hz, 3H), 0.86 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ170.4, 137.9, 128.6, 93.8, 72.1, 71.7, 71.3, 70.0, 68.8, 67.1, 59.0, 39.9, 31.8, 30.6, 24.8, 23.9, 23.0, 19.1. IR (CH_2Cl_2): 2932, 1652, 1453, 1357, 1275, 1246, 1190, 1091, 1028, 969, 917, 795, 732 cm^{-1}. R_f

= 0.22, 10% EtOAc-DCM. $[\alpha]^{24}_{D}$ = +32.1^{o} (c 0.010 g/mL, CH_2Cl_2). HRMS (EI) calculated for $C_{18}H_{30}O_6$ $[M]^+$: 342.2042 found: 342.2049.

(+)-Aspergillide B (141): To a solution of **187** (0.010 g, 0.029 mmol) in CH_3CN (3.6 mL) and H_2O (0.14 mL) was added $LiBF_4$ (10 eq., 0.29 mL, 0.29 mmol) and heated to 72 ˚C for 5 h. The reaction mixture was quenched with water and the organic layer was separated and the aqueous layer was extracted wit 3 X 5 mL portions of EtOAc. The combined organics were washed with brine, dried over anhydrous $MgSO_4$, filtered, and then concentrated under reduced pressure. Flash chromatography on silica gel (40% EtOAc-hexanes) afforded (+)-aspergillide B **141** (0.006 g, 85%) as a colorless oil. ^{1}H NMR (500 MHz, d_6-benzene) δ 6.1 (dddd, *J* = 15.6, 10.8, 4.8, 1.6 Hz, 1H), 5.3 (dd, *J* = 15.6, 4.4 Hz, 1H), 5.0 (m, 1H), 4.3 (m, 1H), 4.0 (d, *J* = 11.2 Hz, 1H), 3.2 (brs, 1H), 2.7 (dd, *J* = 13.6, 11.6 Hz, 1H), 2.1 (dd, *J* = 13.6, 2.0 Hz, 1H), 2.0 (dddd, *J* = 13.6, 10.8, 4.8, 2.4 Hz, 1H), 1.8 (brs, 1H), 1.7-1.8 (m, 2H), 1.5-1.6 (3H, m), 1.3-1.4 (m, 3H), 1.0 (d, *J* = 6.4Hz, 3H), 0.9 (m, 1H). ^{13}C NMR (125 MHz, d_6-benzene) δ 169.8, 138.2, 129.1, 71.6, 69.9, 69.6, 67.3, 39.9, 32.1, 30.8, 27.8, 25.3, 22.6, 19.2 . IR (CH_2Cl_2): 3381, 2926, 1717, 1267, 1187, 1086, 1017, 965 cm^{-1}. R_f = 0.33, 60% EtOAc in hexanes. $[\alpha]^{24}_{D}$ = +84^{o} (c 0.0054 g/mL, MeOH). HRMS (EI) calculated for $C_{14}H_{22}O_4$ $[M]^+$: 254.1518, found 254.1513.

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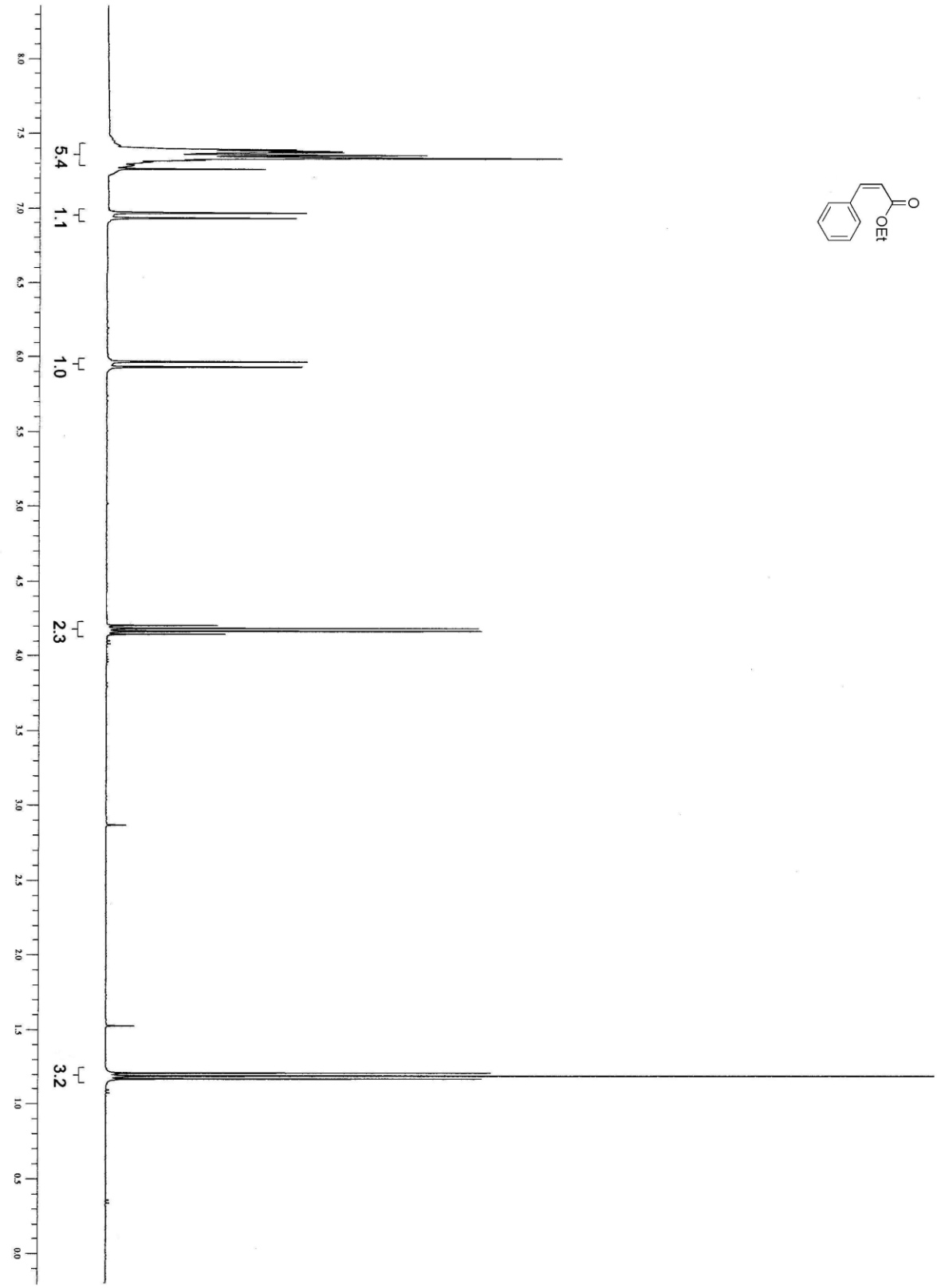
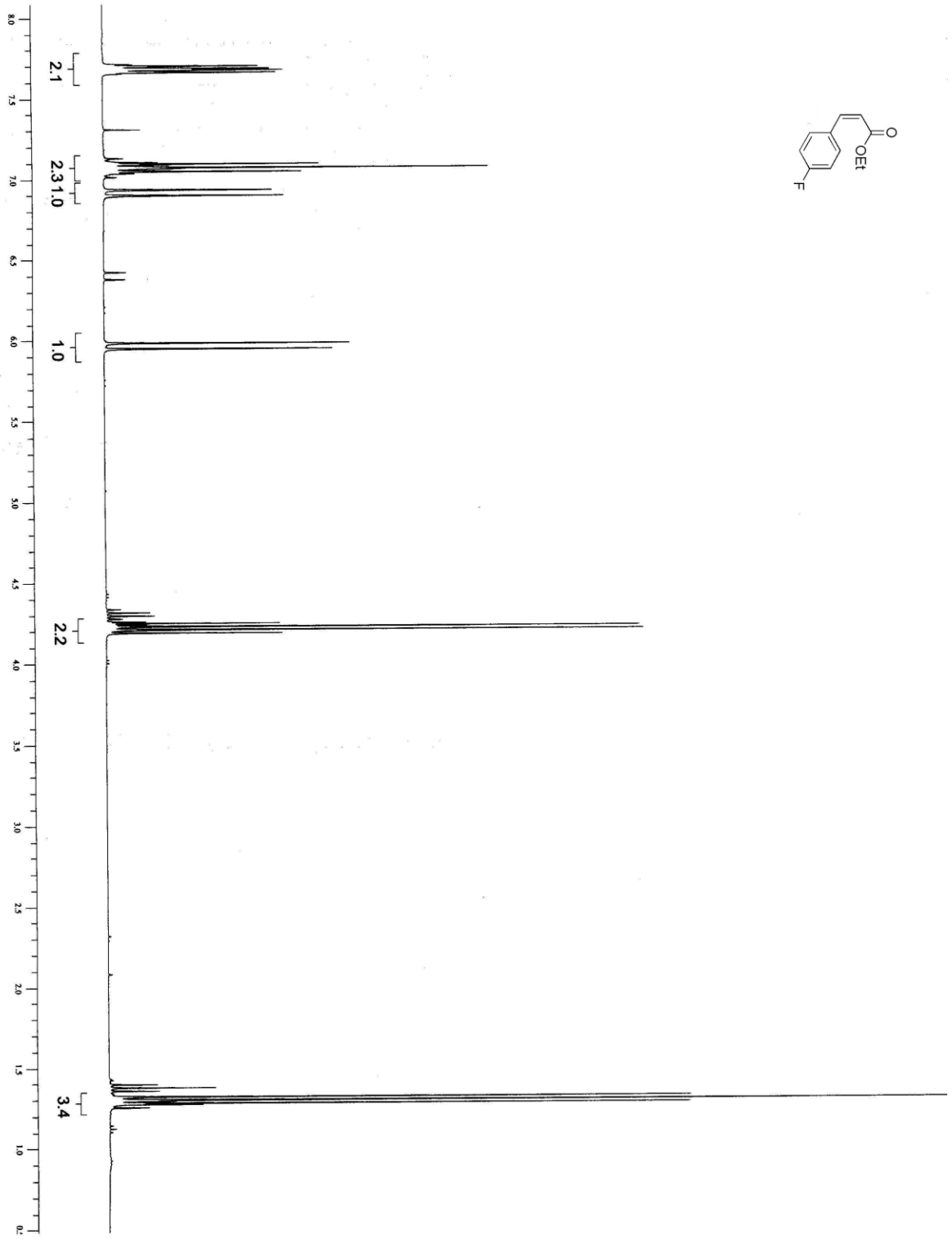
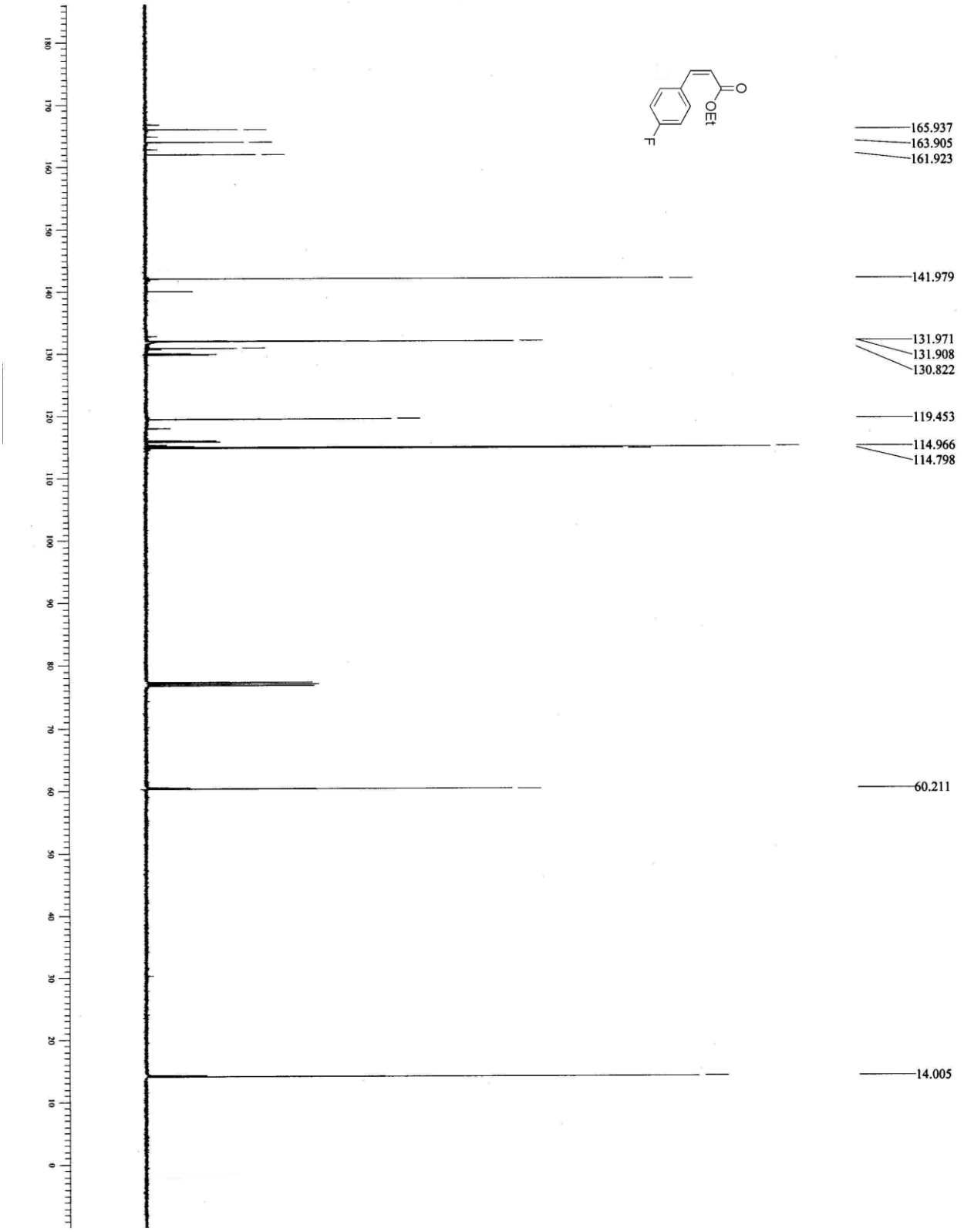
APPENDIX



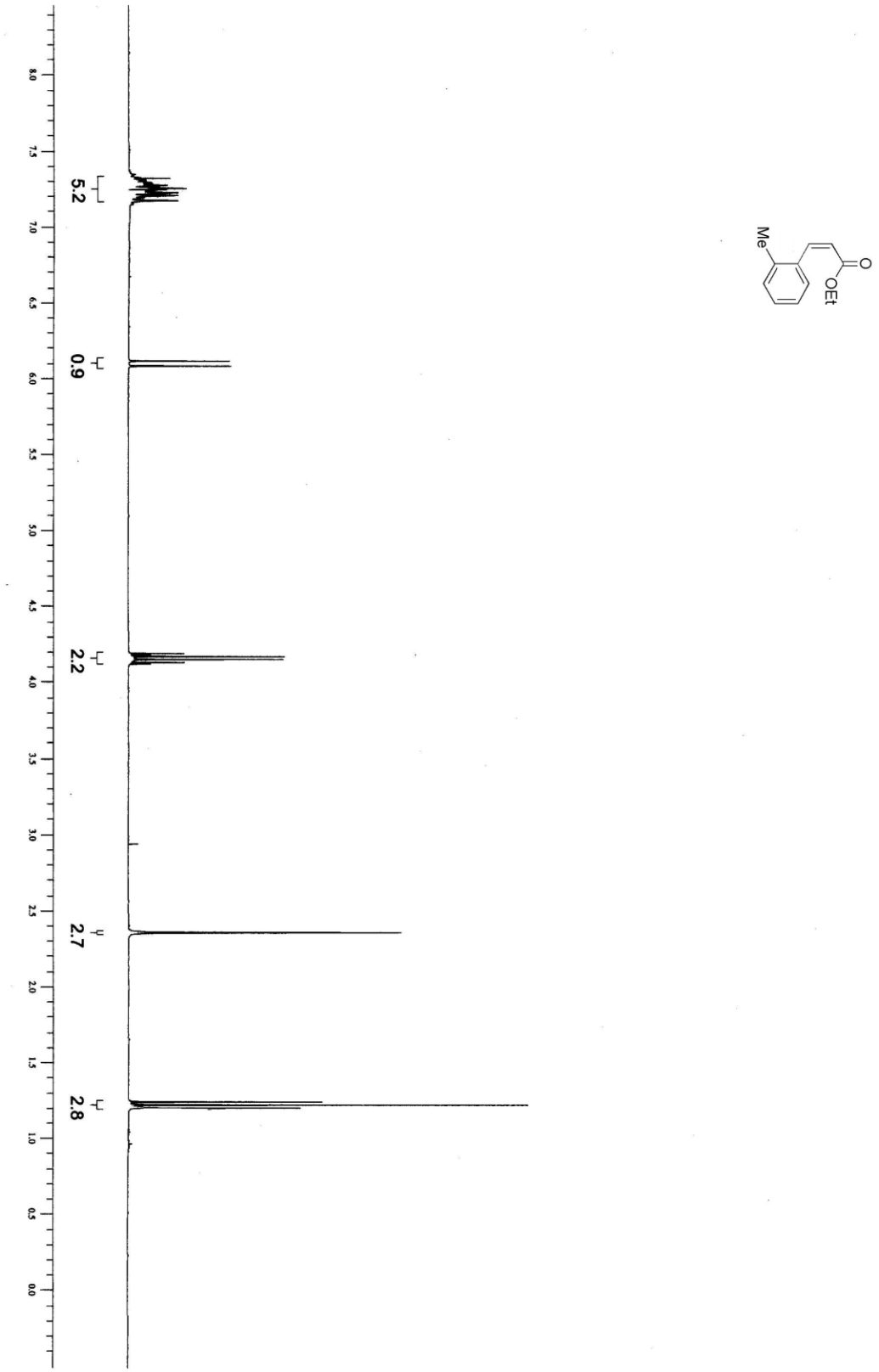
The ^{1}H NMR Spectrum (360 MHz, $CDCl_3$) of Compound **34a**



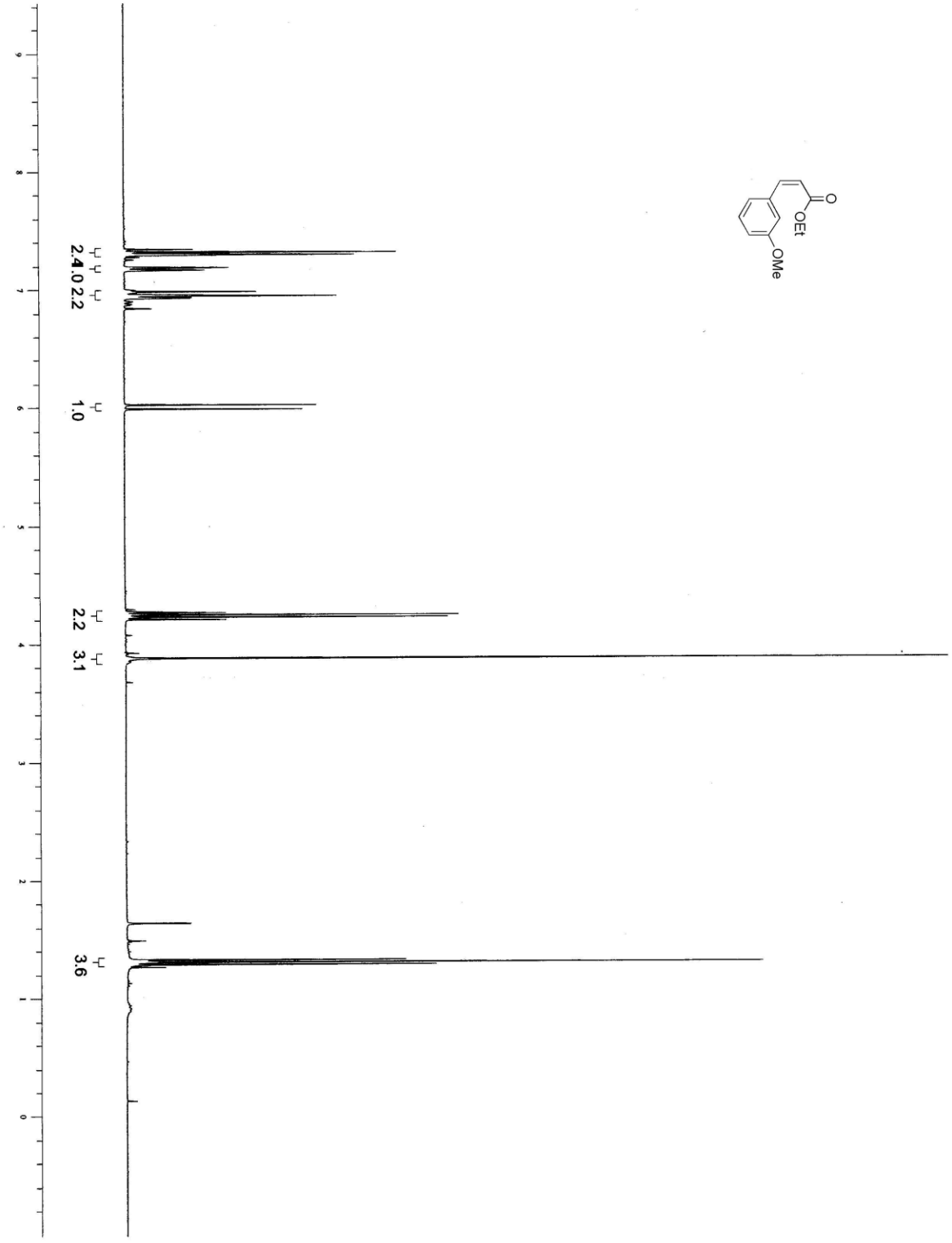
The ^{1}H NMR Spectrum (360 MHz, $CDCl_3$) of Compound **34b**



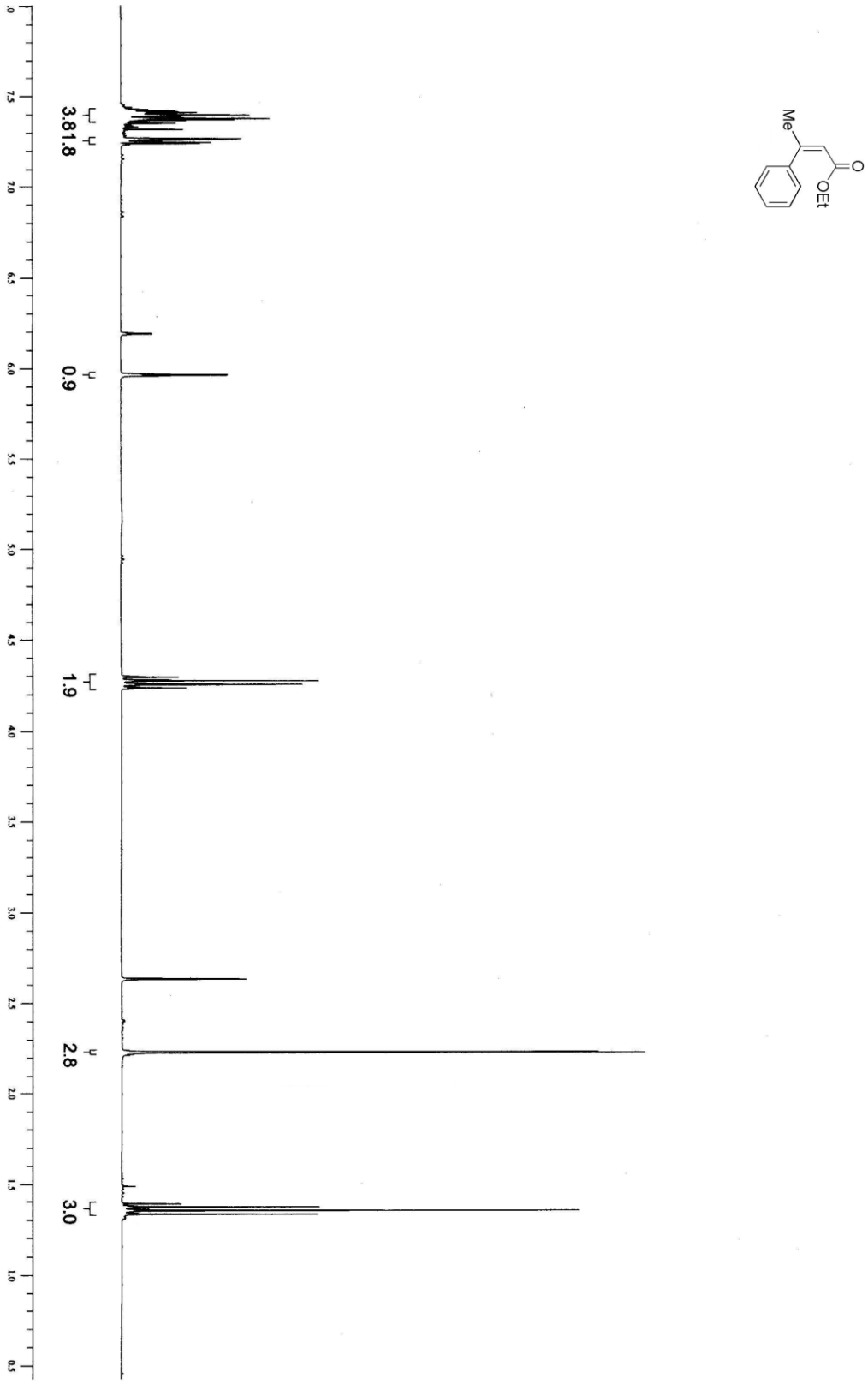
The ^{13}C NMR Spectrum (90 MHz, $CDCl_3$) of Compound **34b**



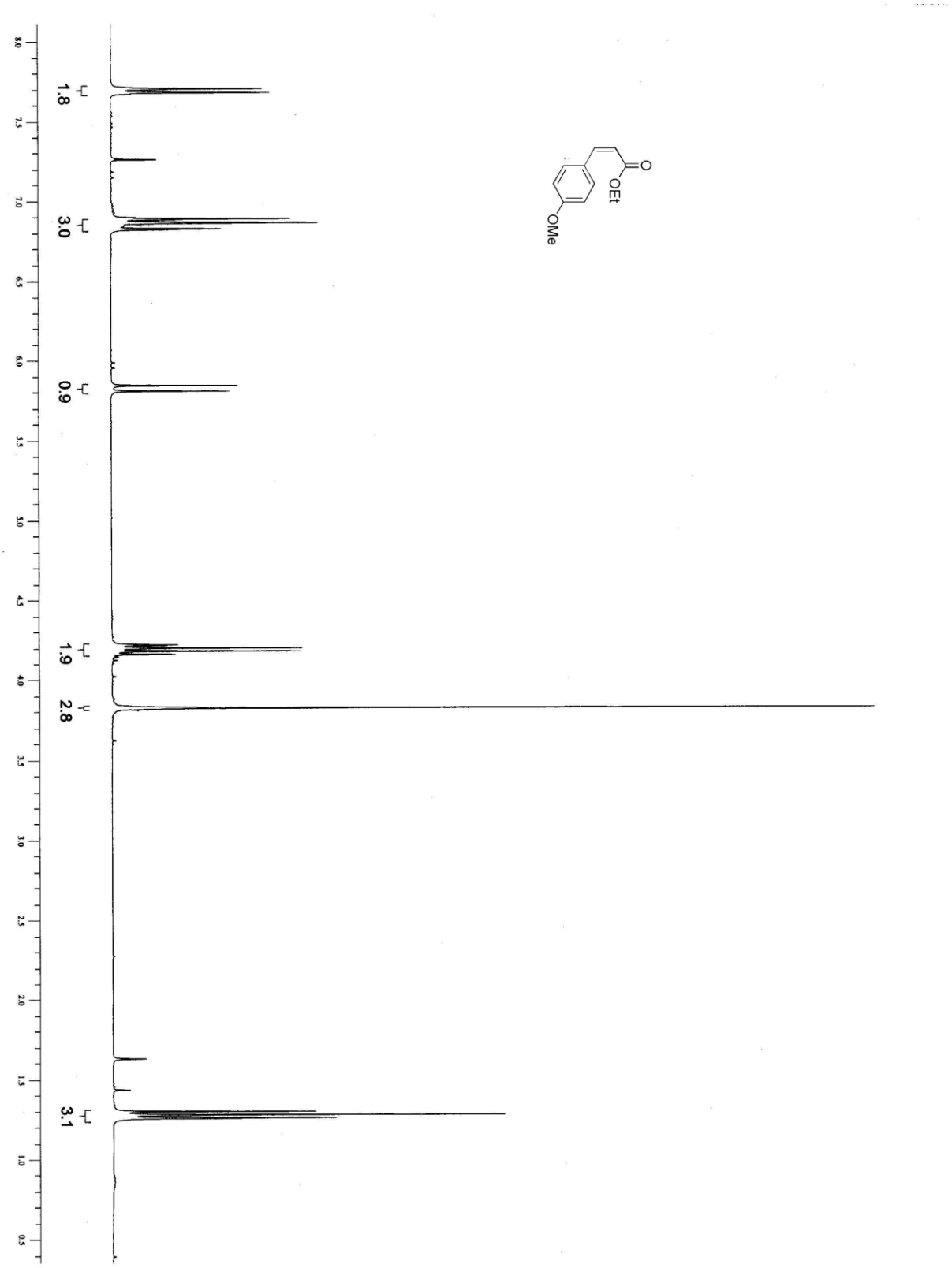
The ^{1}H NMR Spectrum (360 MHz, $CDCl_3$) of Compound **34c**



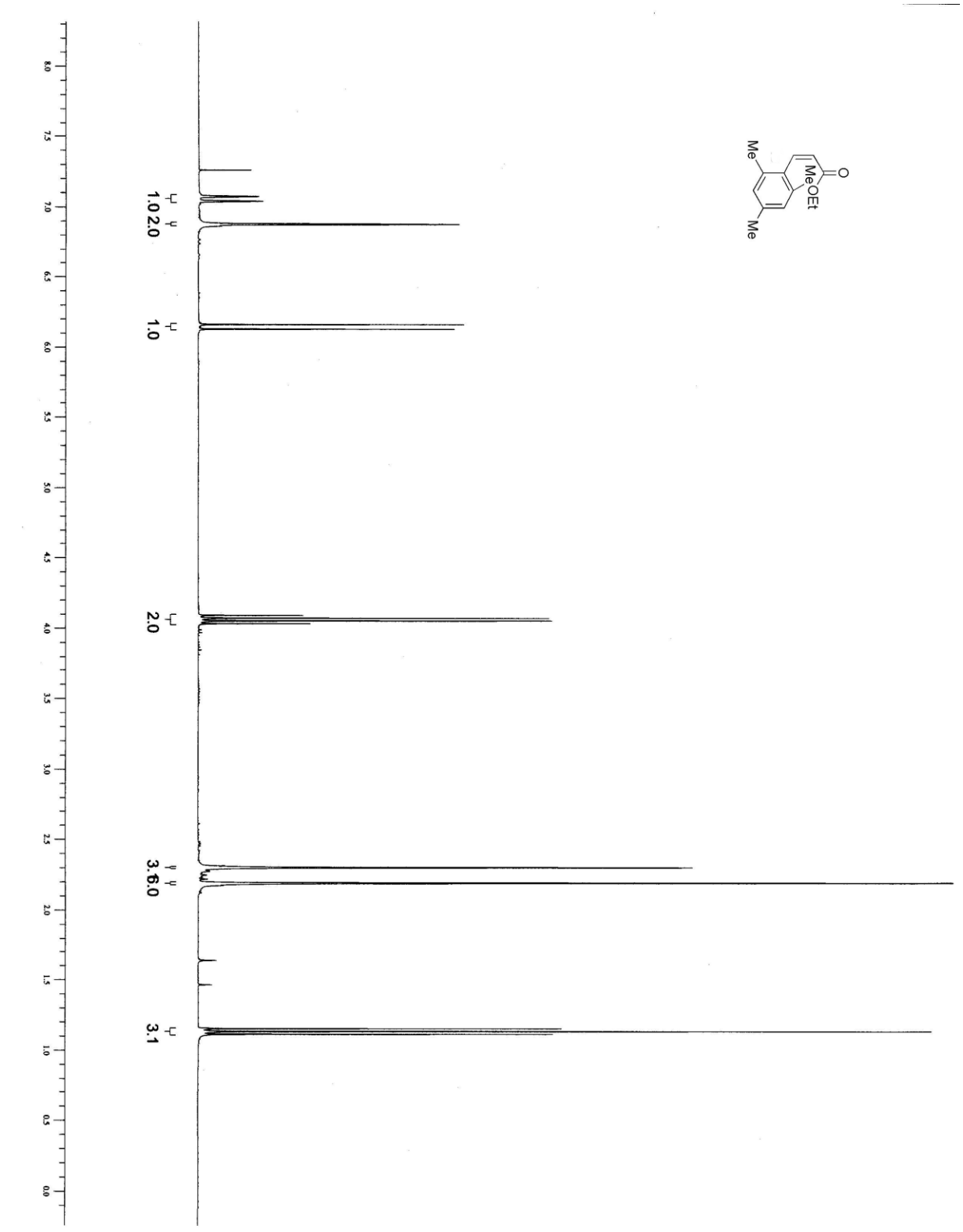
The ^{1}H NMR Spectrum (360 MHz, $CDCl_3$) of Compound **34d**



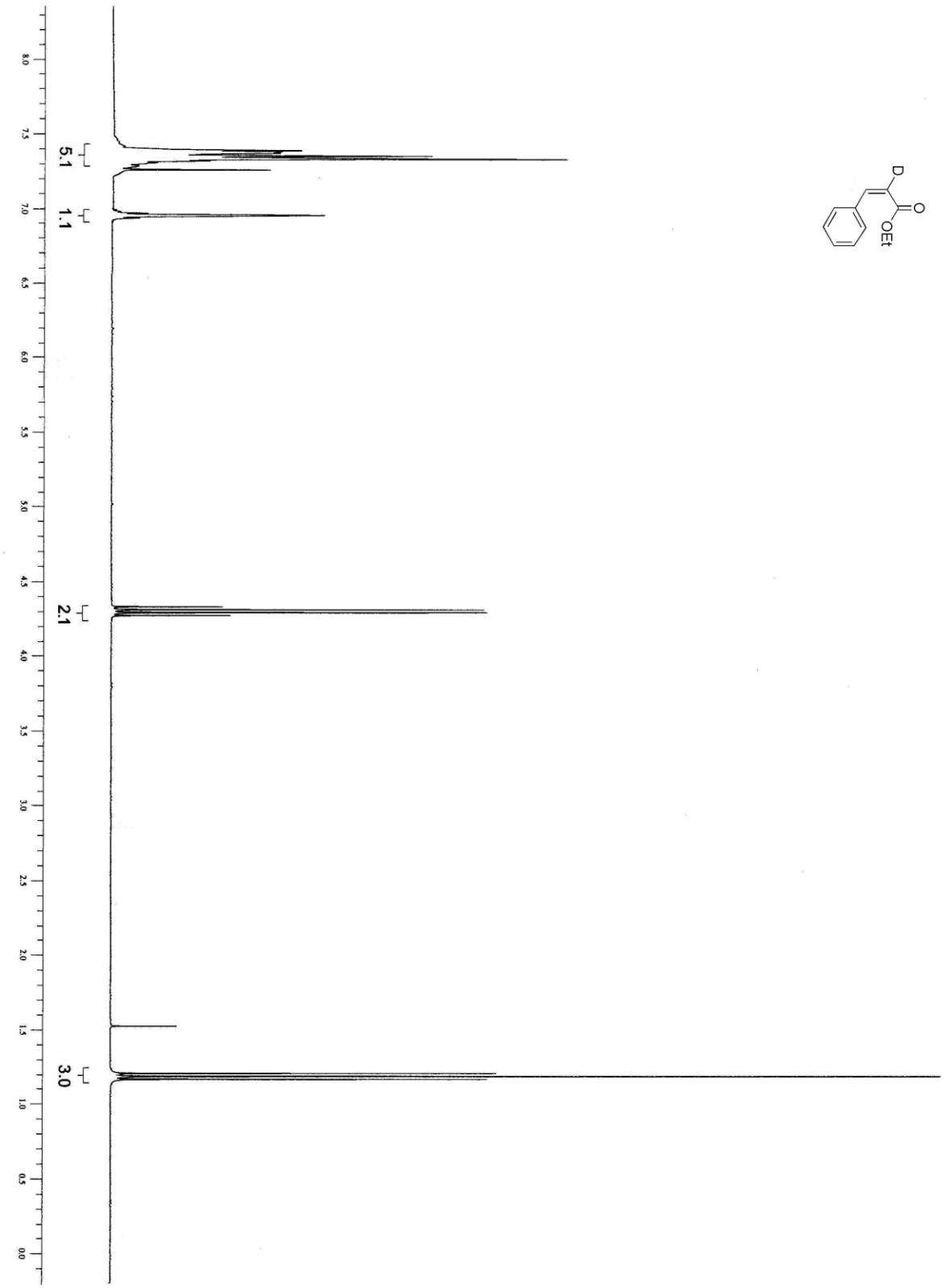
The ^{1}H NMR Spectrum (360 MHz, $CDCl_3$) of Compound **34e**



The ^{1}H NMR Spectrum (360 MHz, $CDCl_3$) of Compound **34f**



The ^{1}H NMR Spectrum (360 MHz, $CDCl_3$) of Compound **34g**



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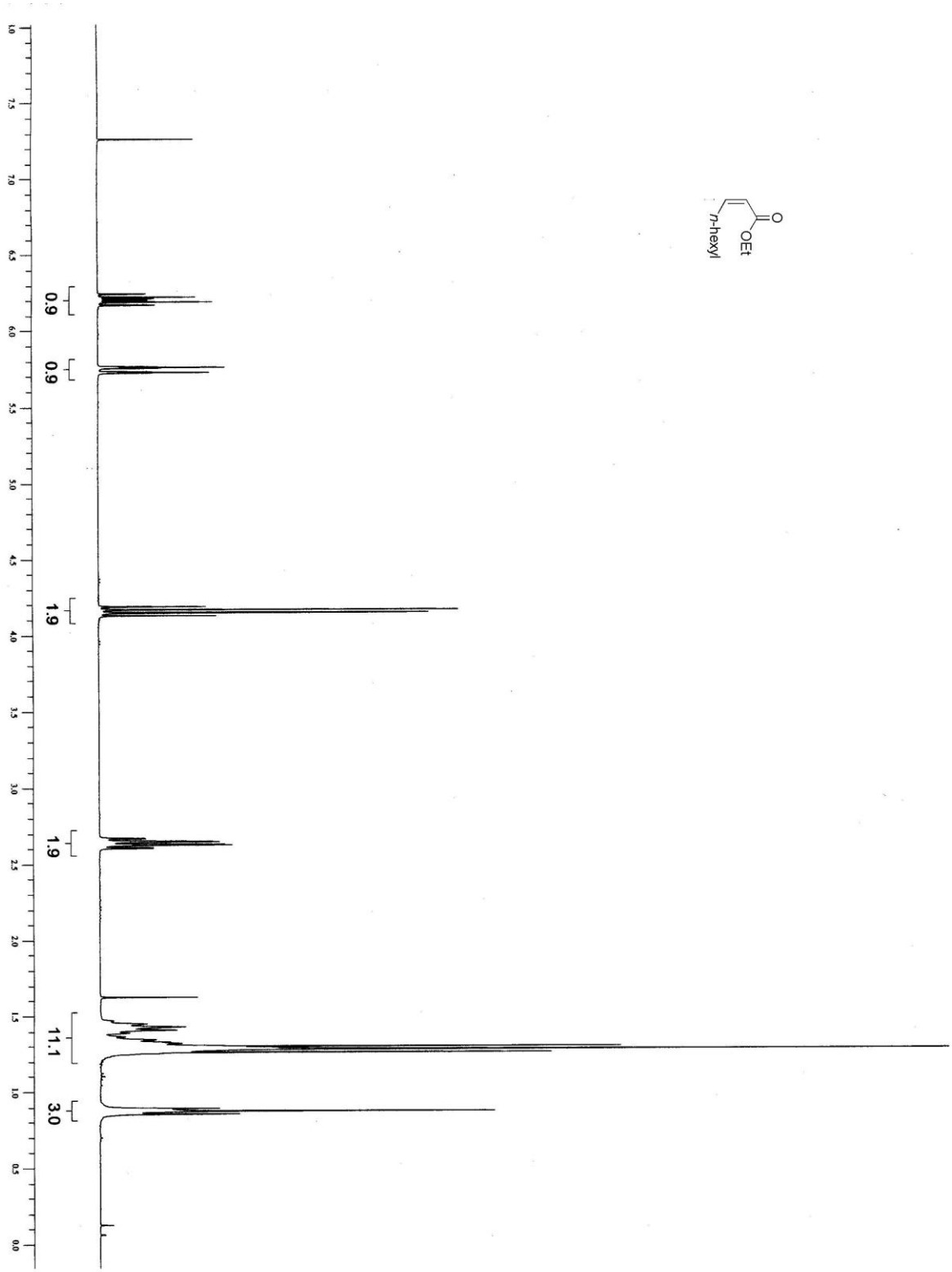
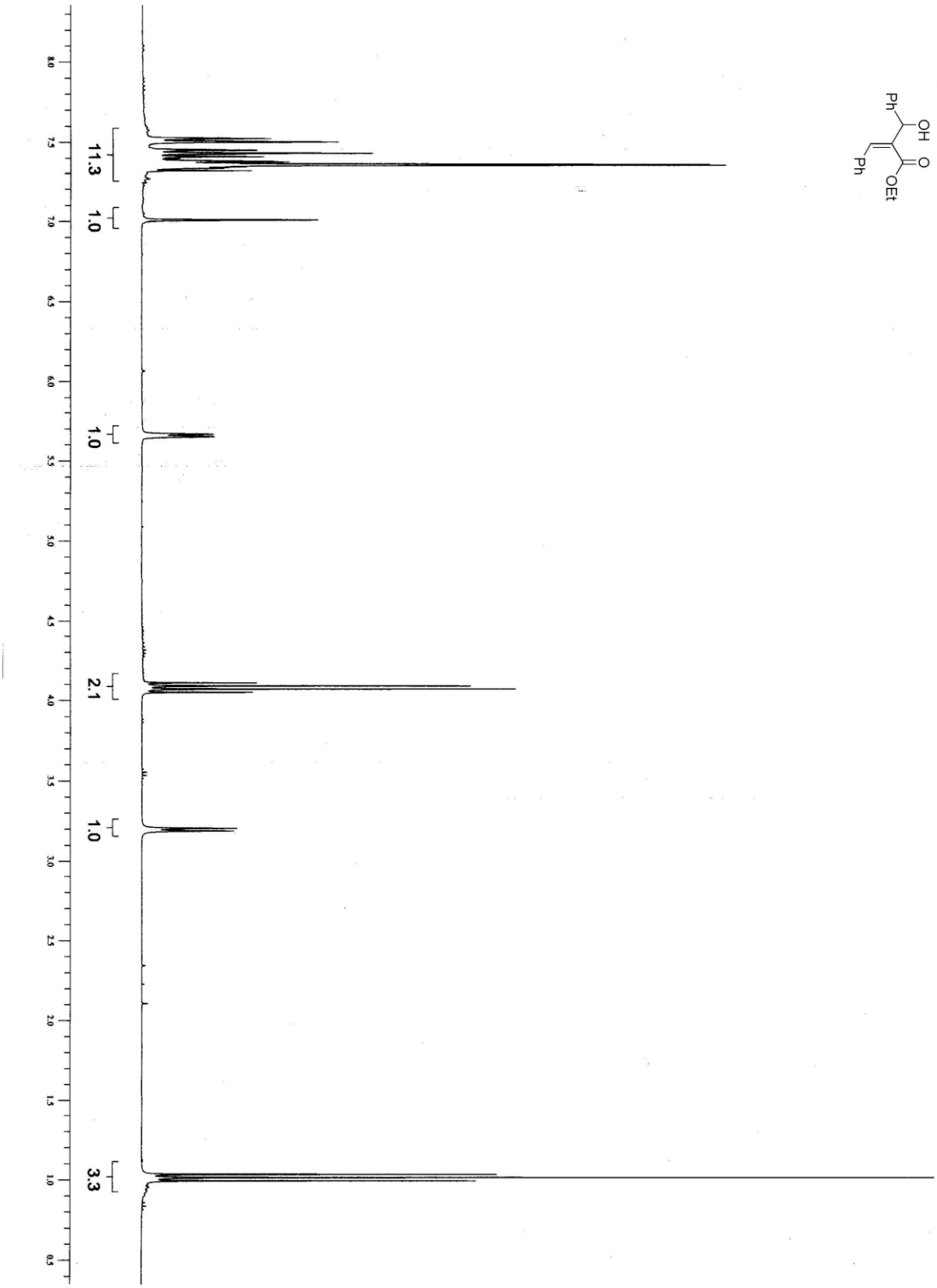
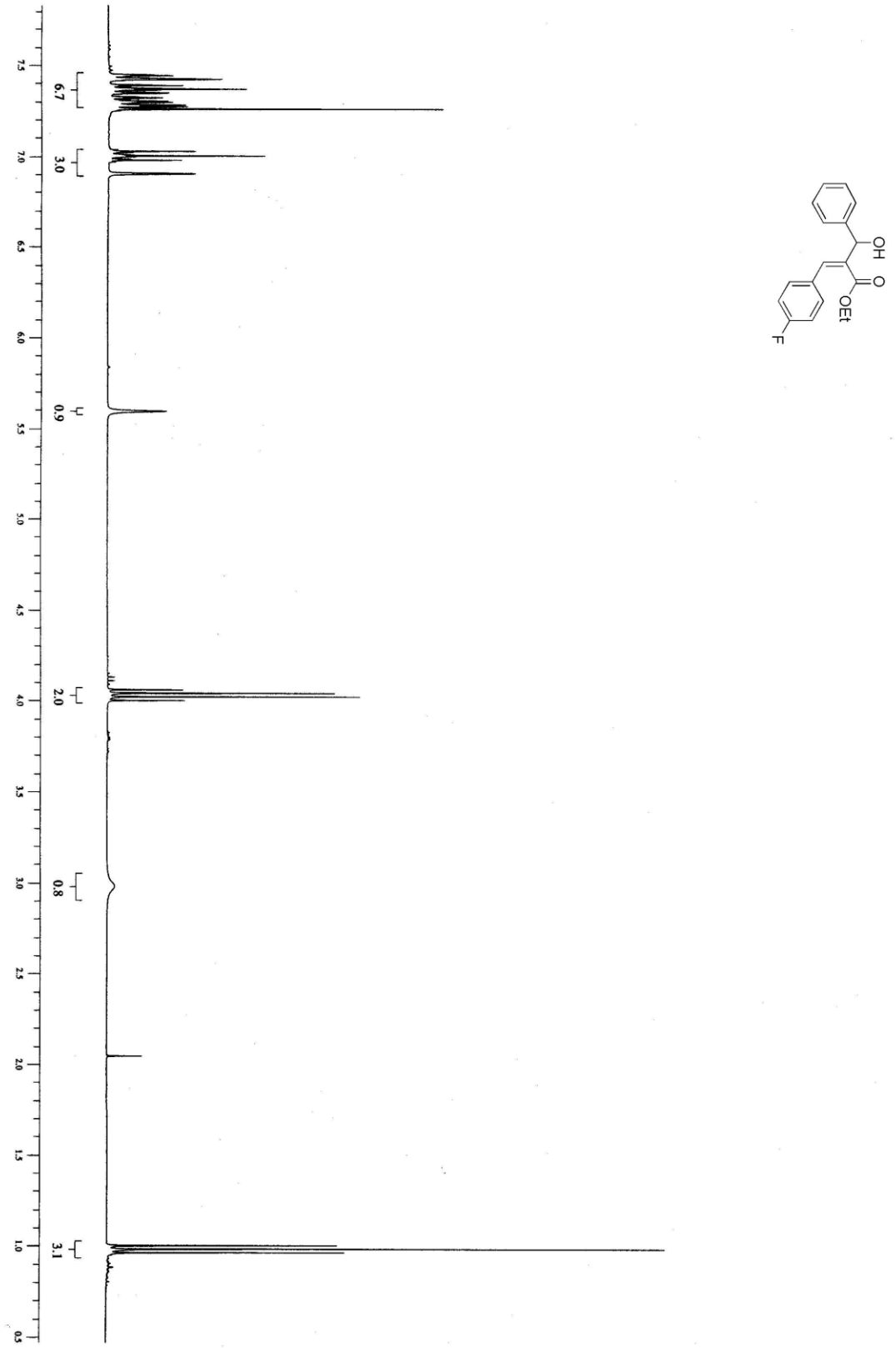


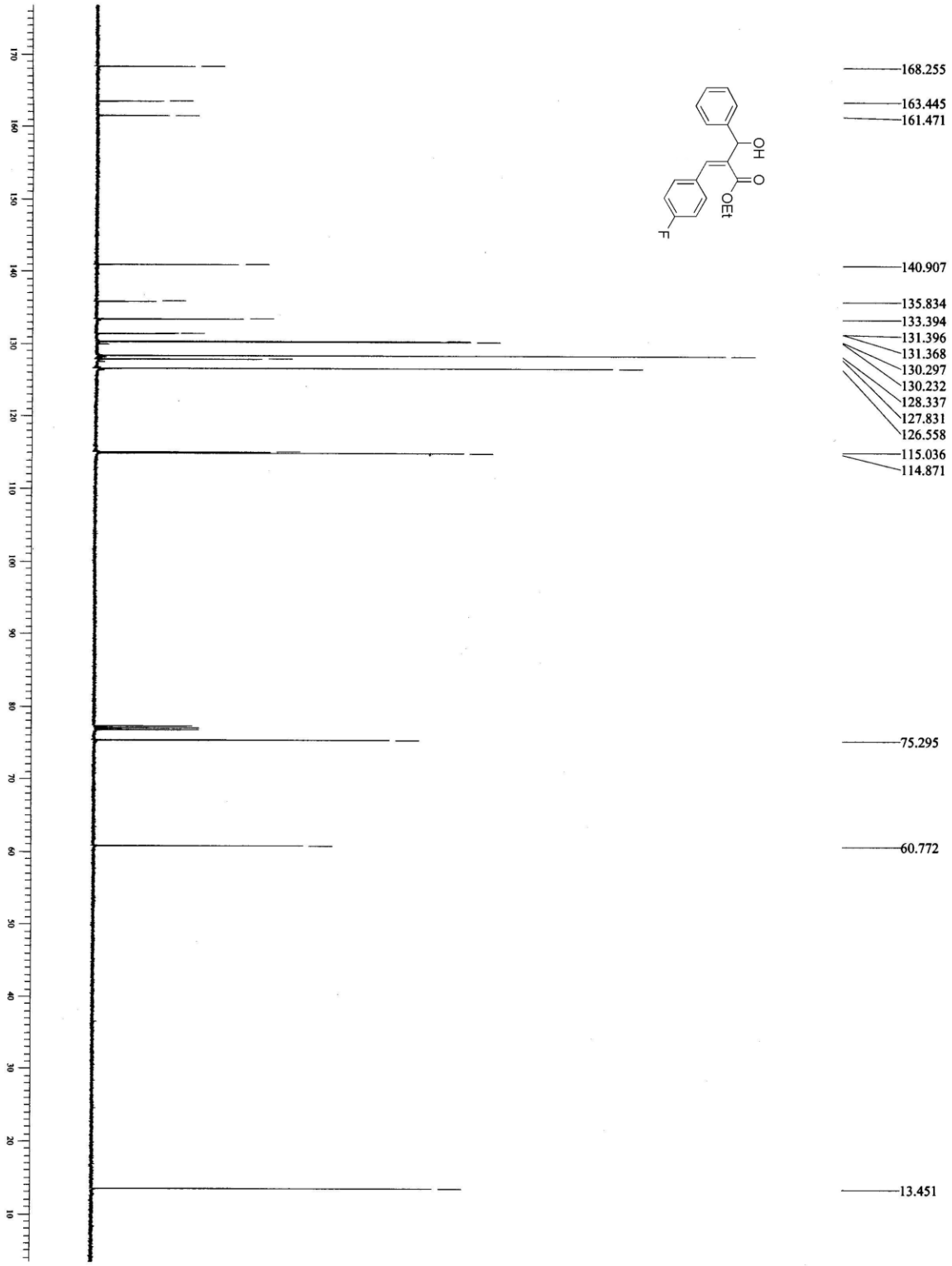
The ^{1}H NMR Spectrum (360 MHz, $CDCl_3$) of Compound **34i**



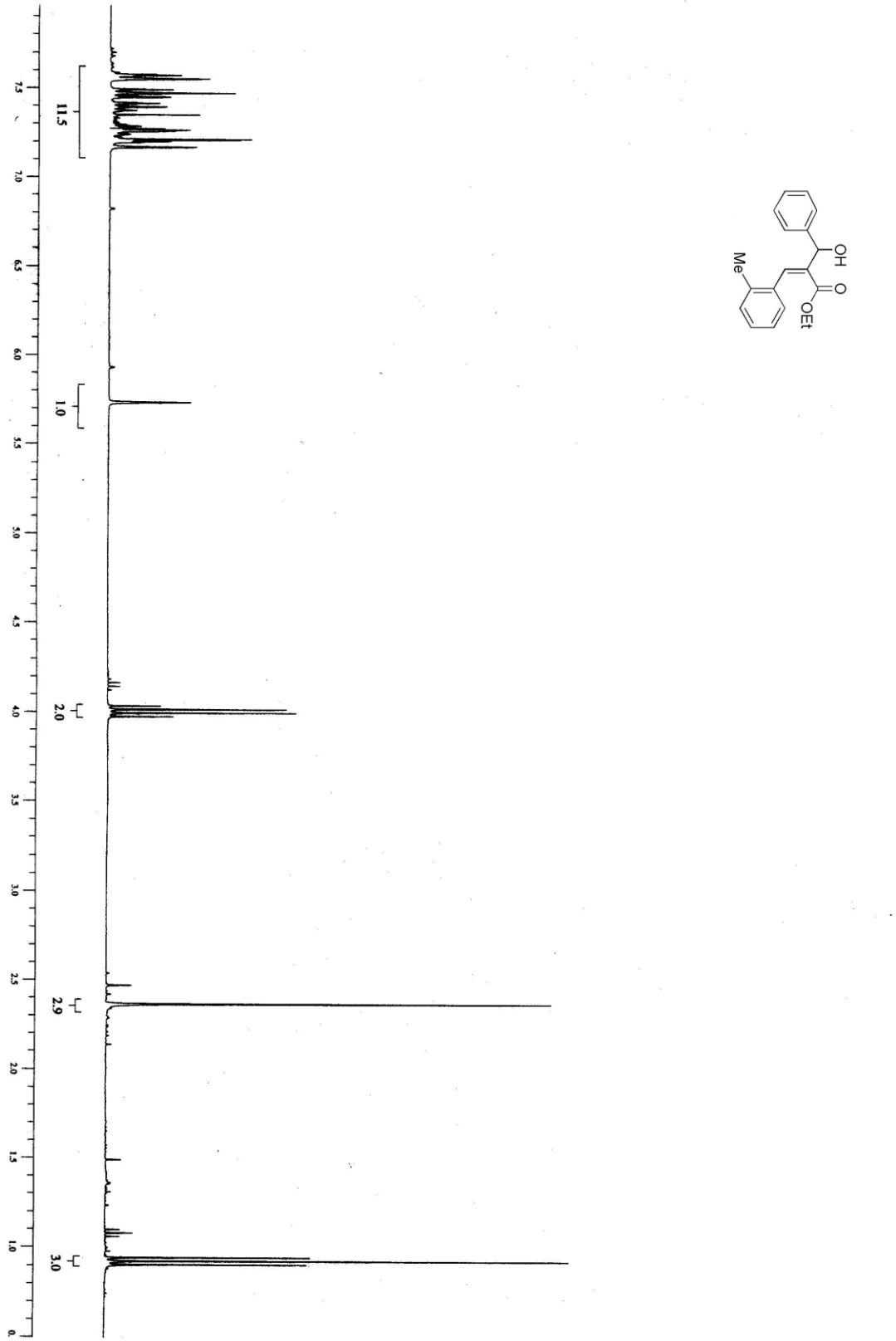
The ^{1}H NMR Spectrum (360 MHz, $CDCl_3$) of Compound **67**



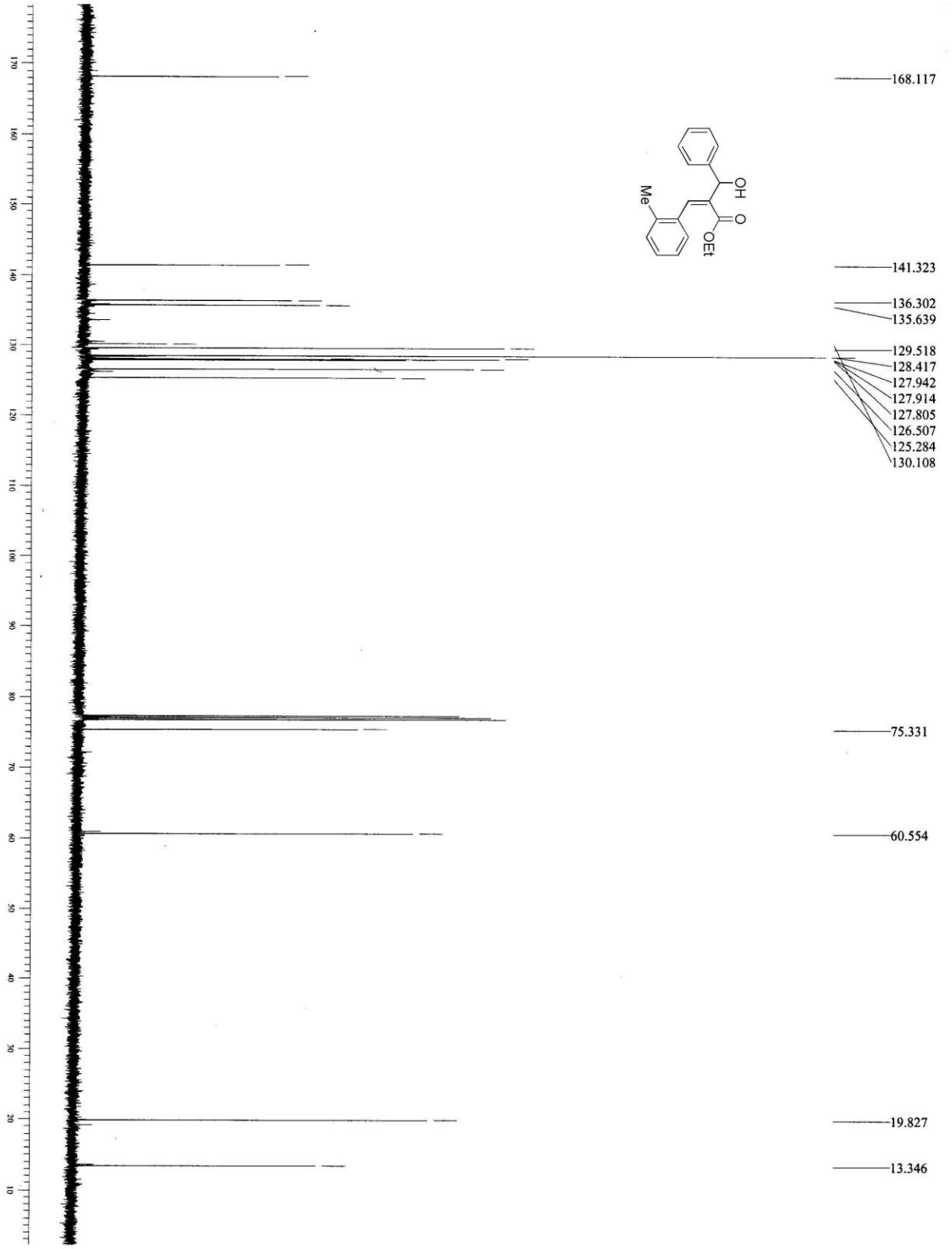
The ^{1}H NMR Spectrum (360 MHz, $CDCl_3$) of Compound **68**



The ^{13}C NMR Spectrum (90 MHz, $CDCl_3$) of Compound **68**



The ^{1}H NMR Spectrum (360 MHz, $CDCl_3$) of Compound **69**



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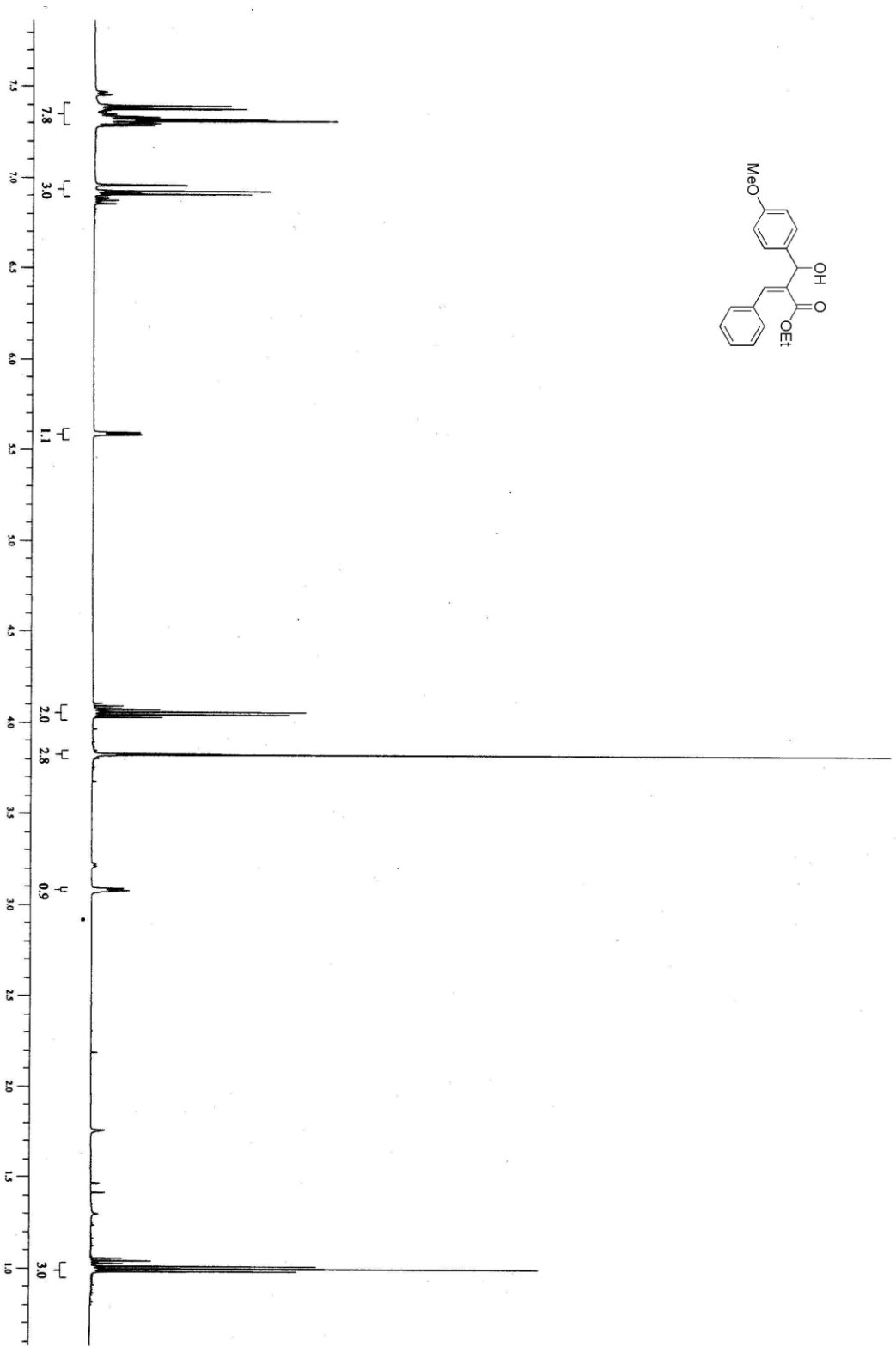

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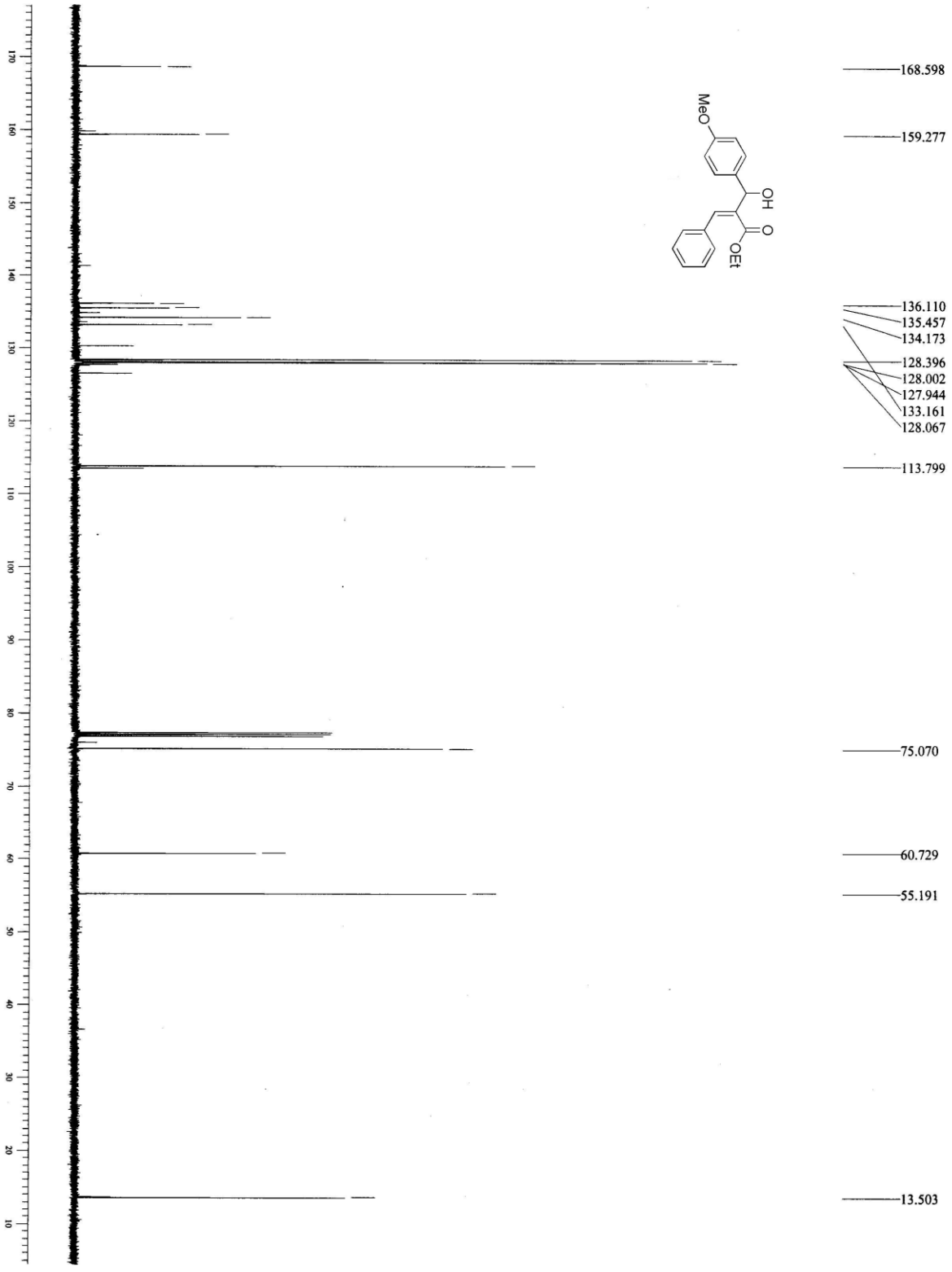

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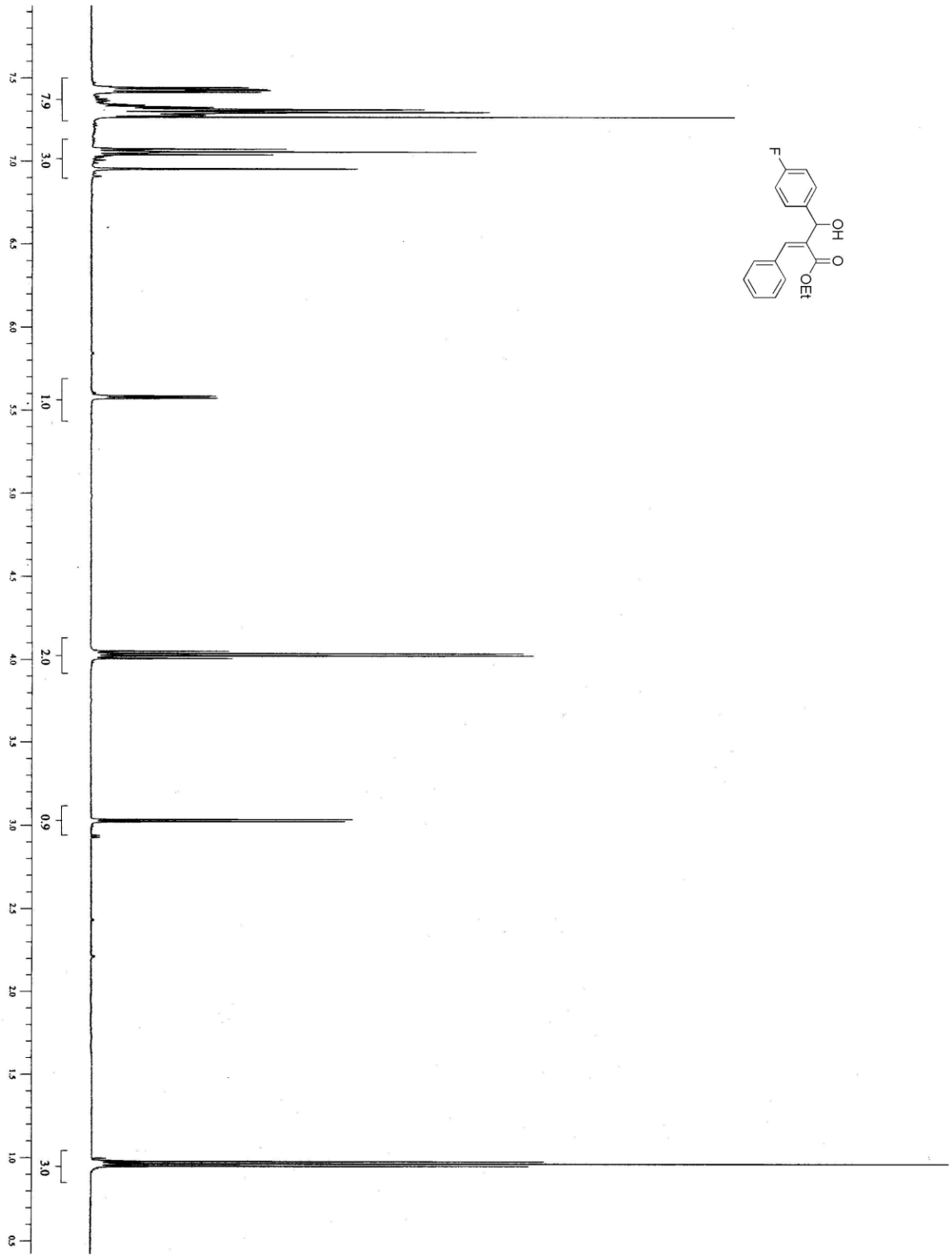
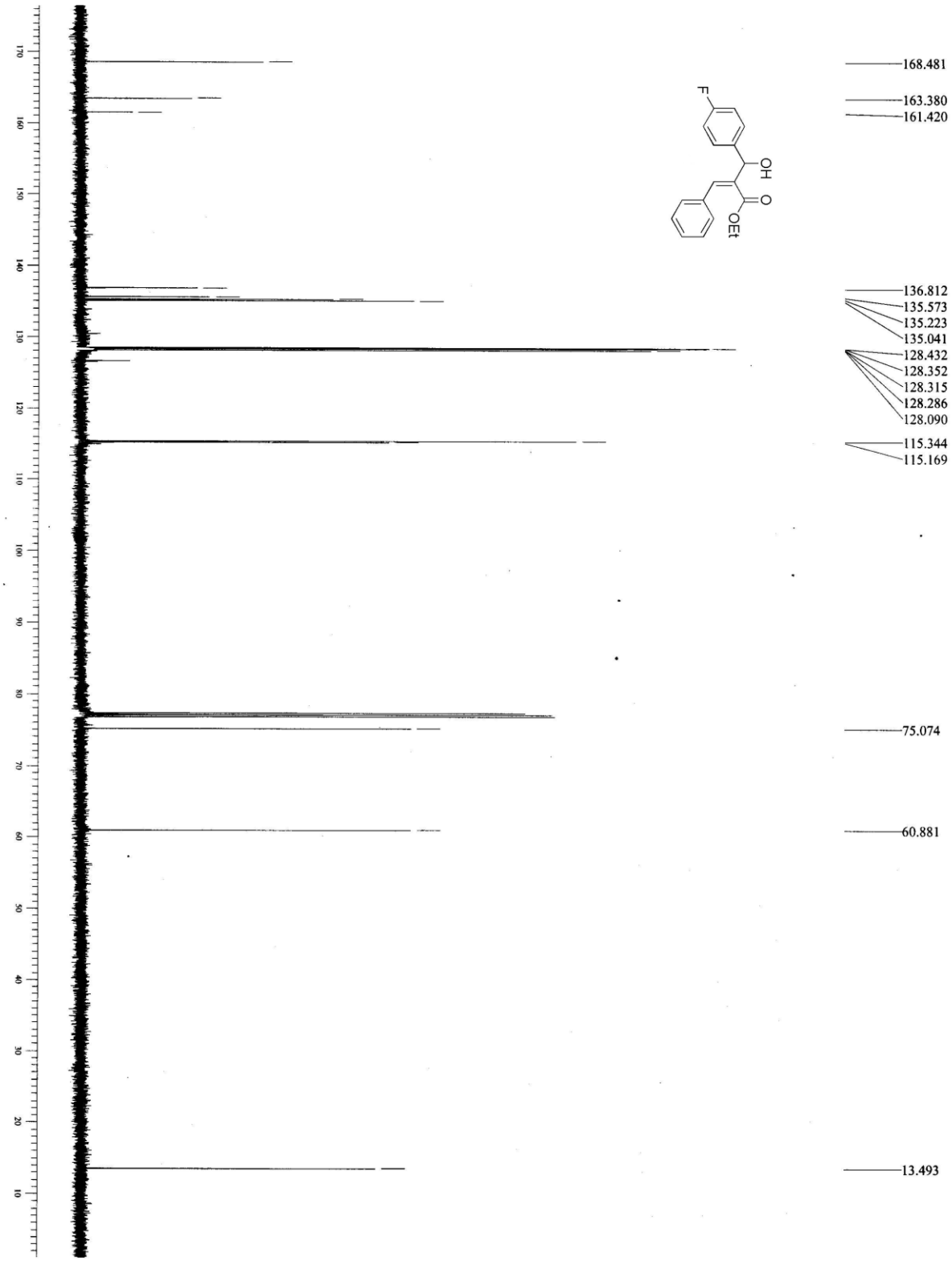


The ^{1}H NMR Spectrum (360 MHz, $CDCl_3$) of Compound **71**



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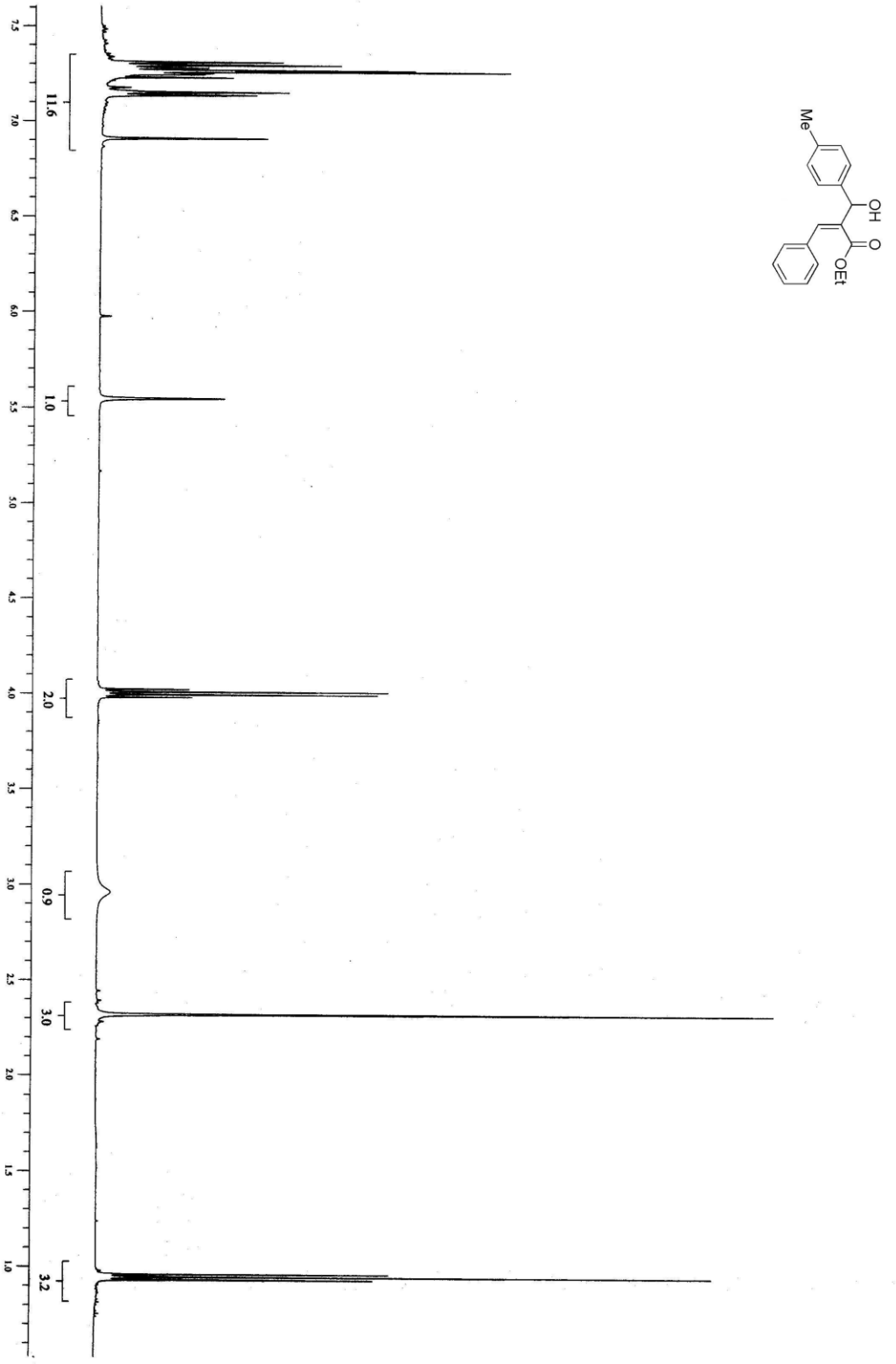

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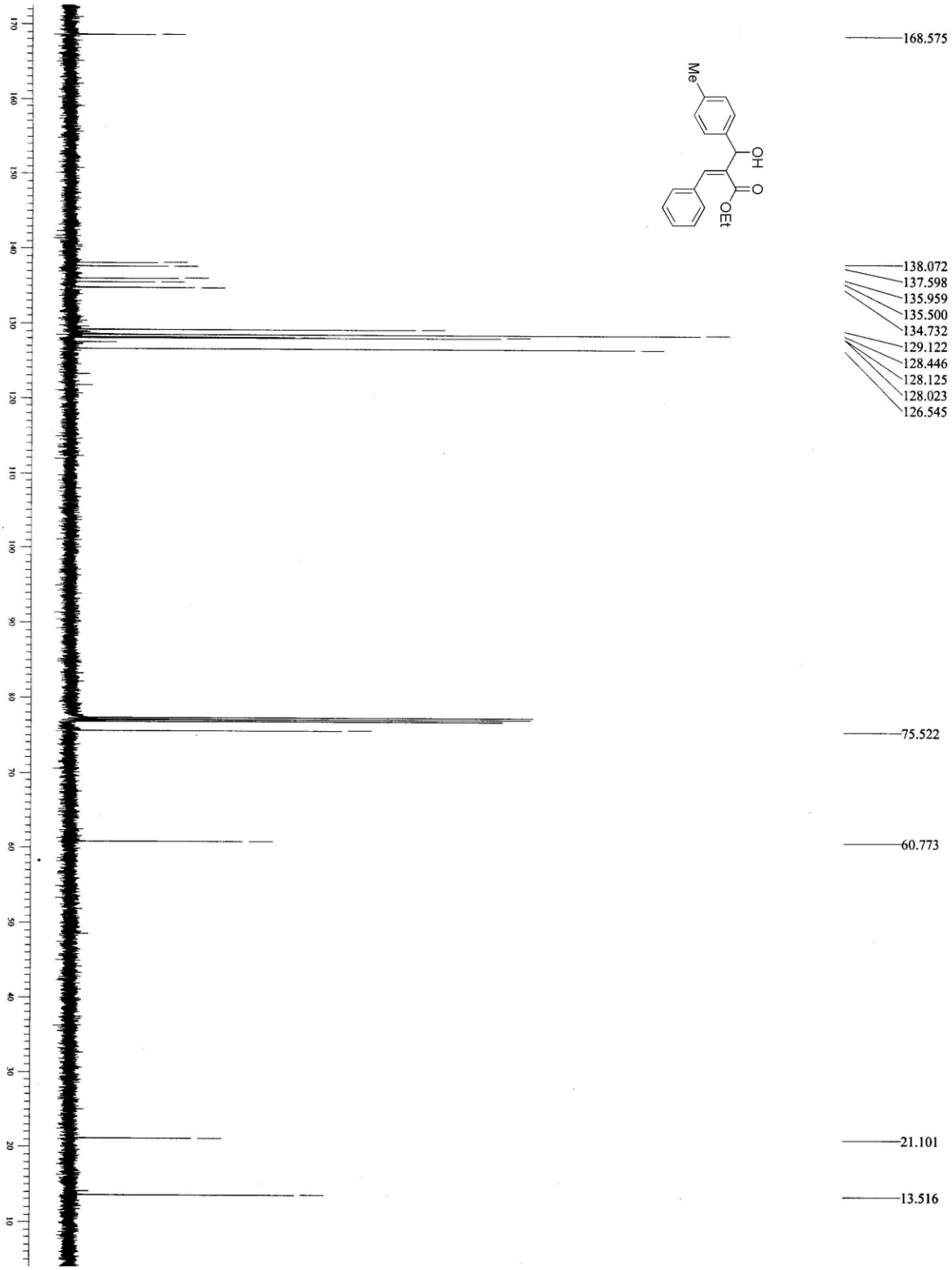

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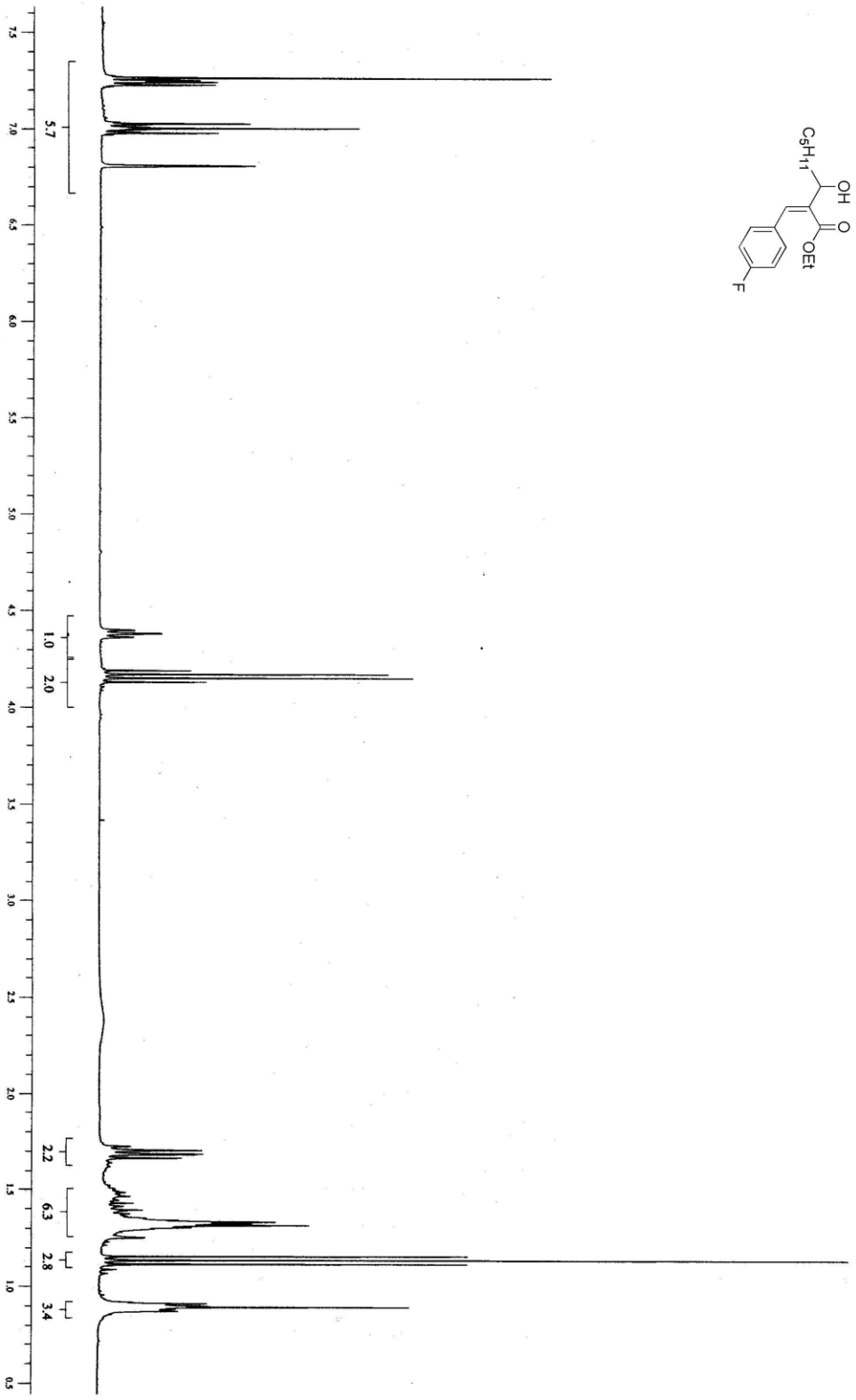

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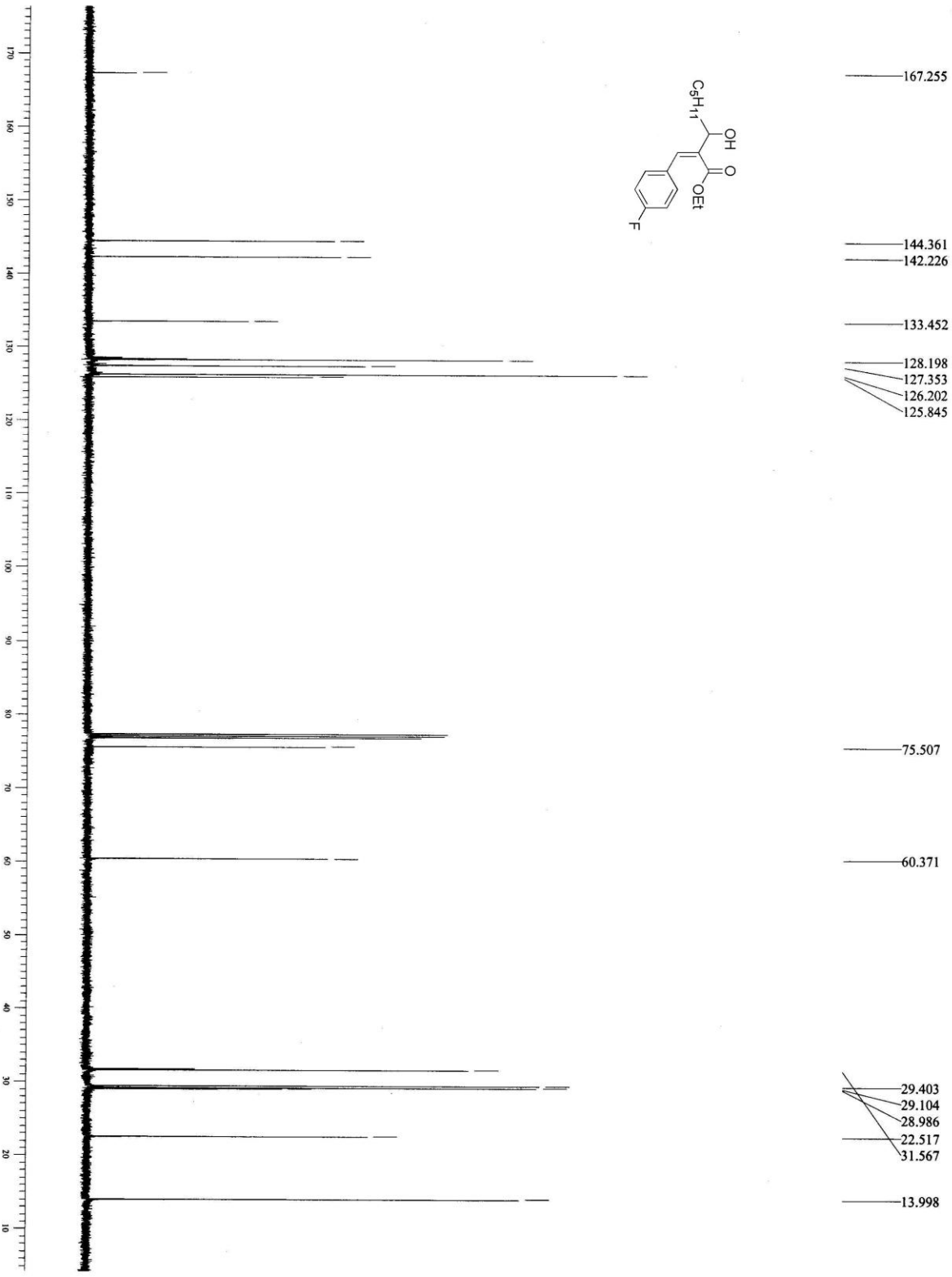

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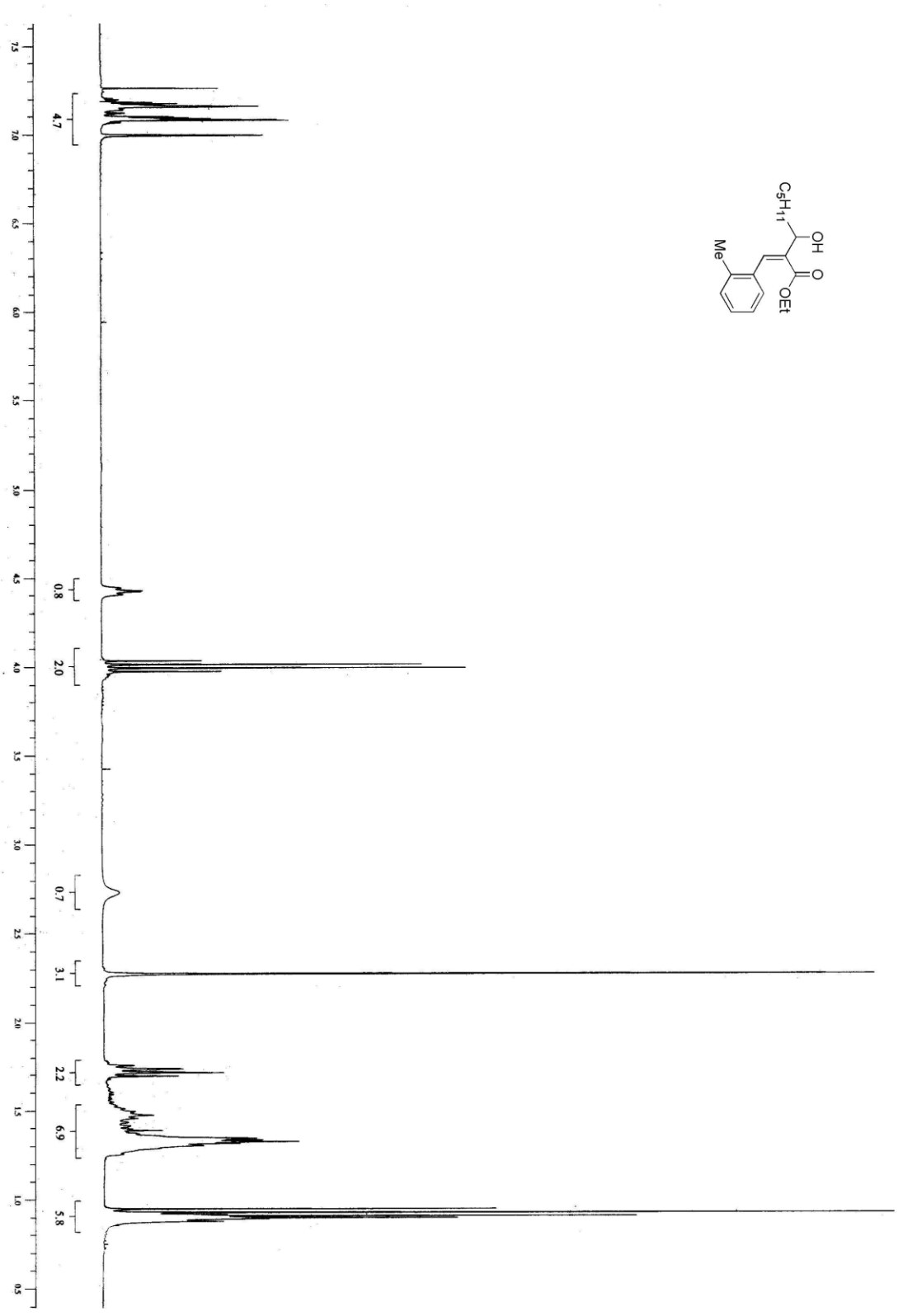

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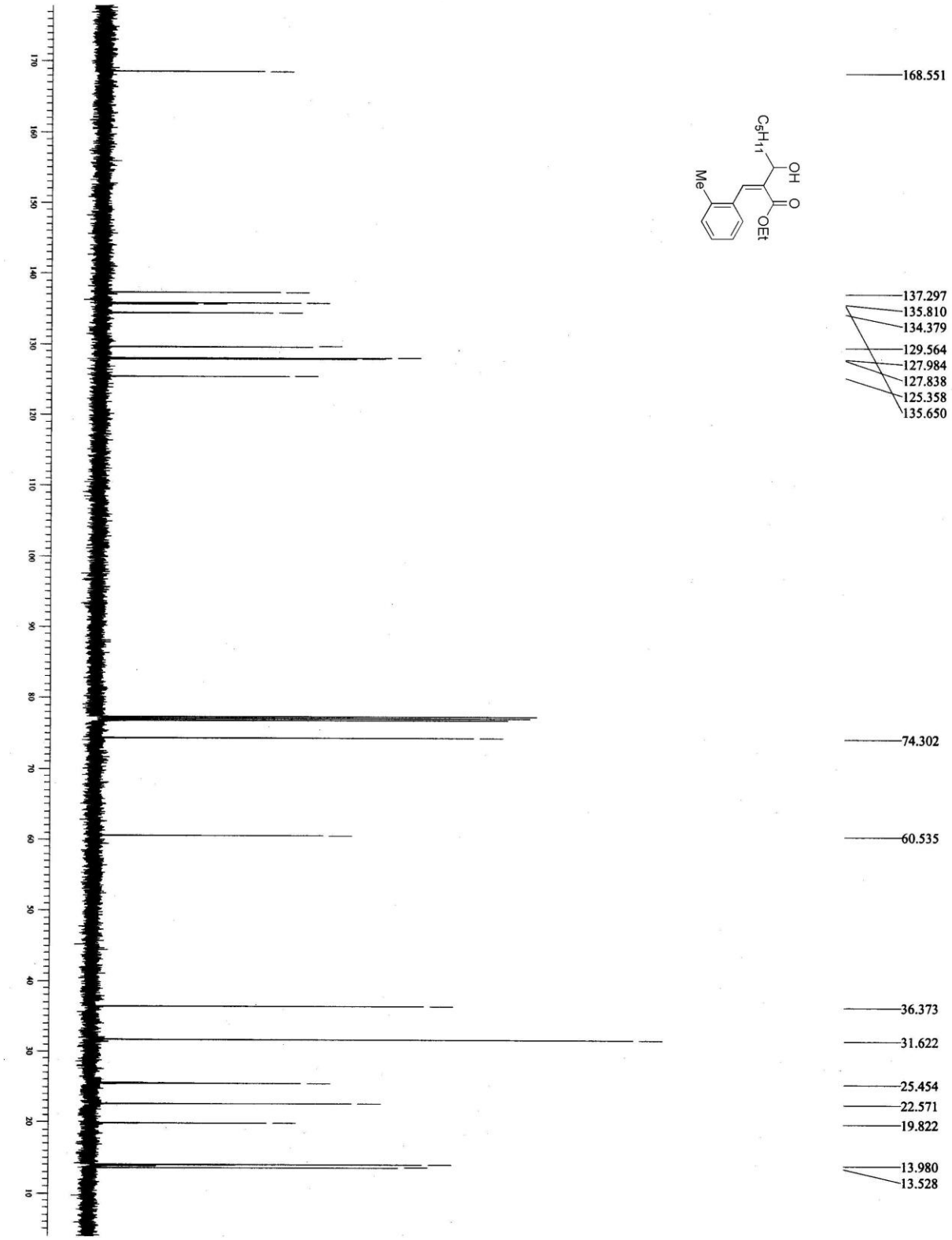

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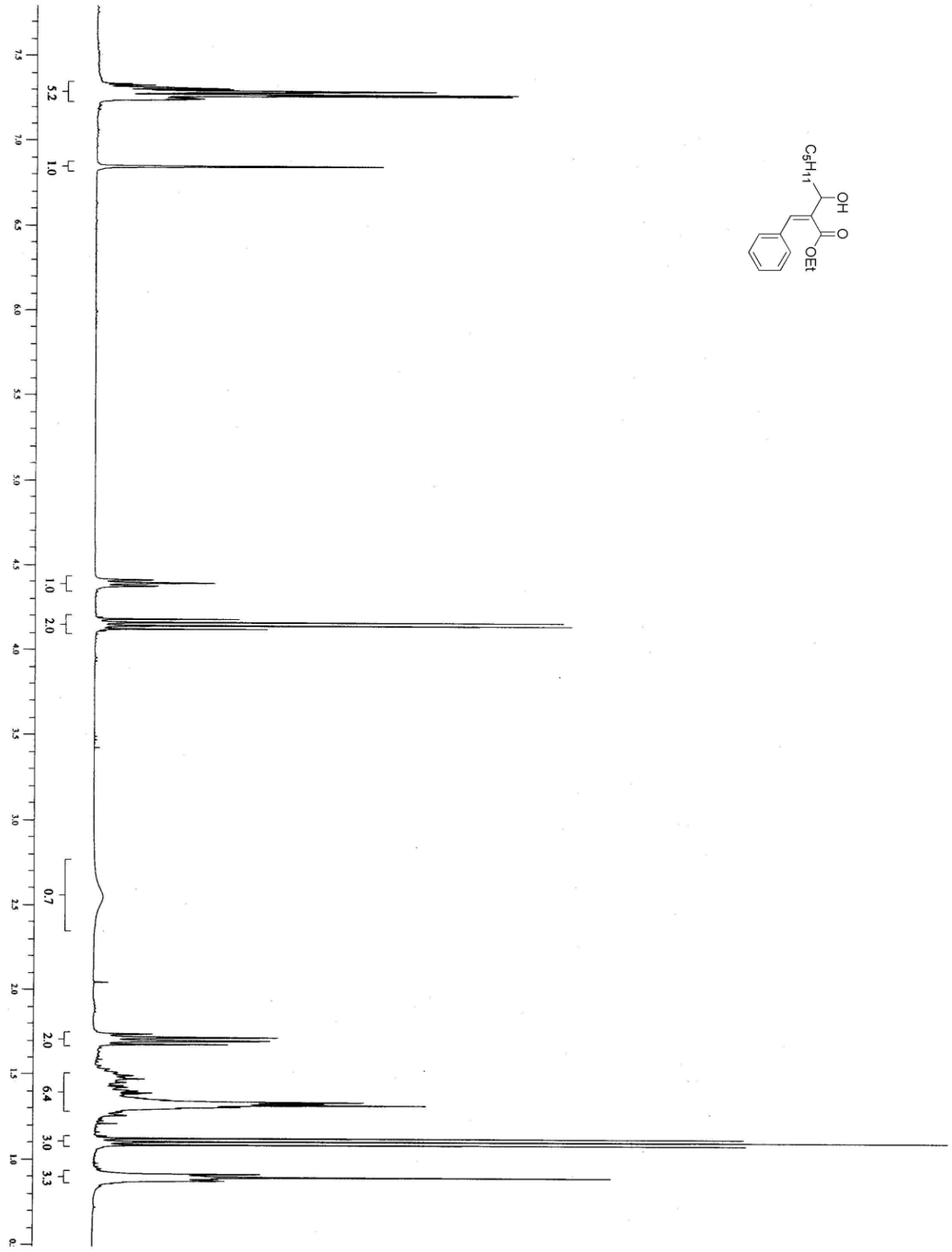

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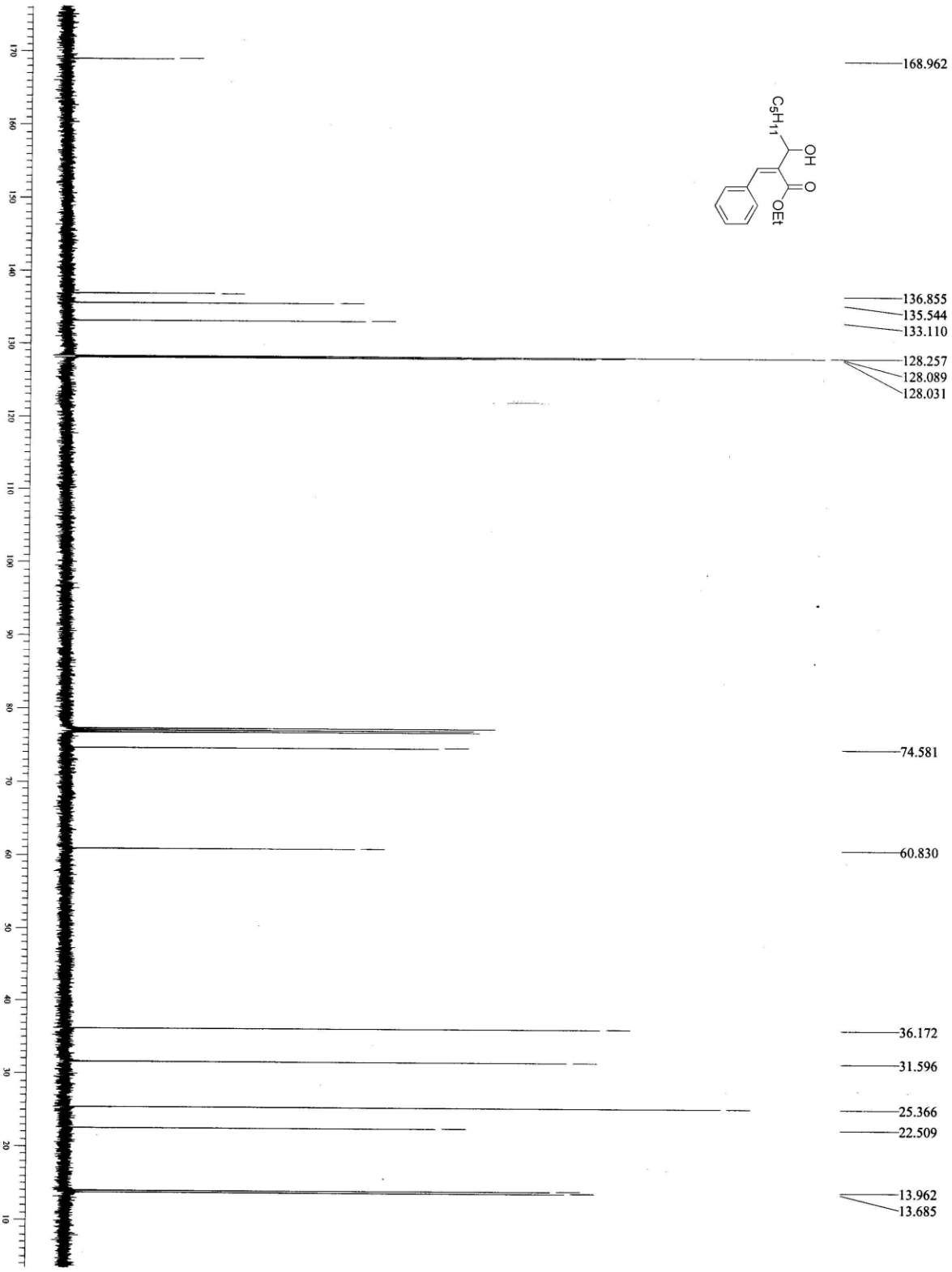

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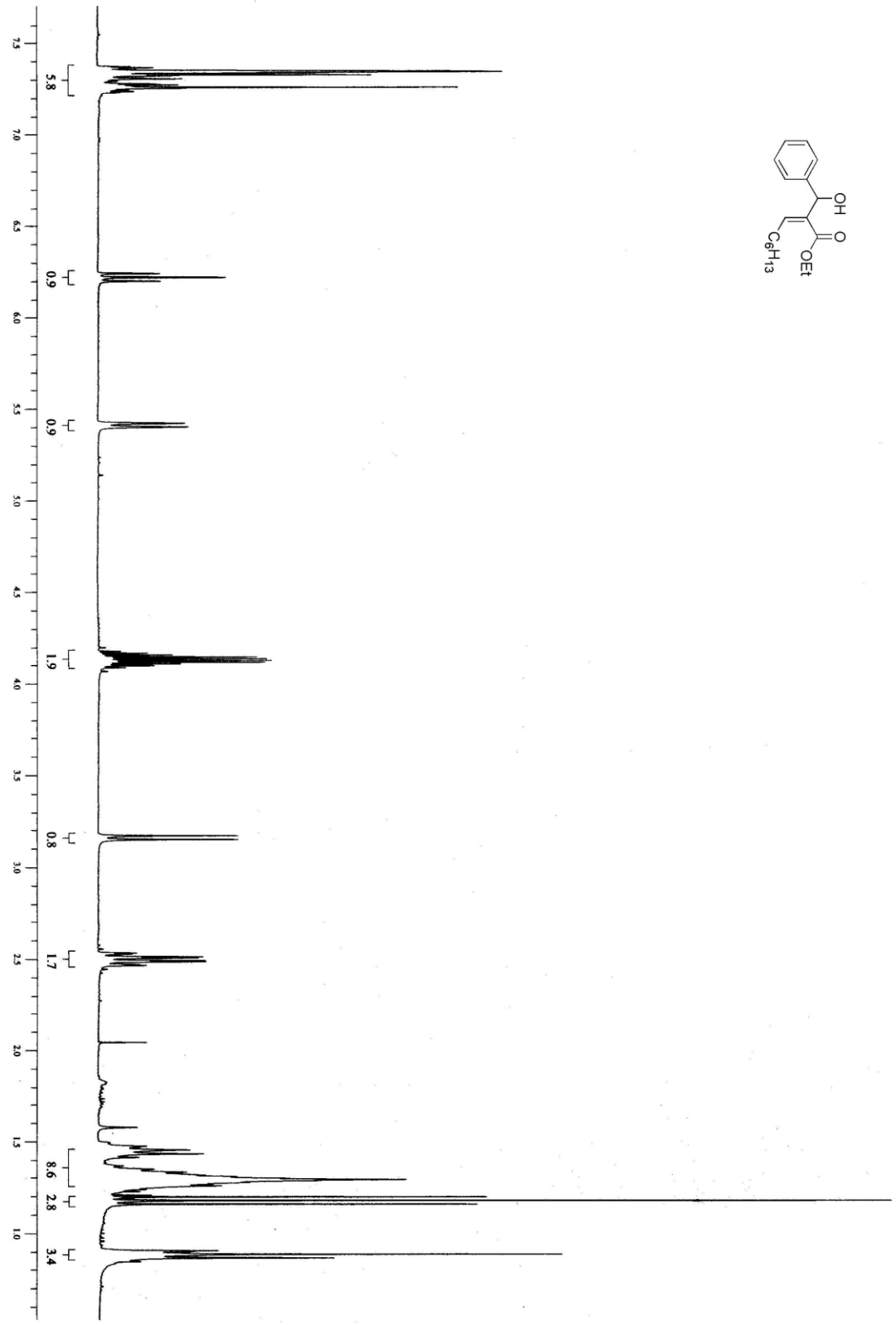

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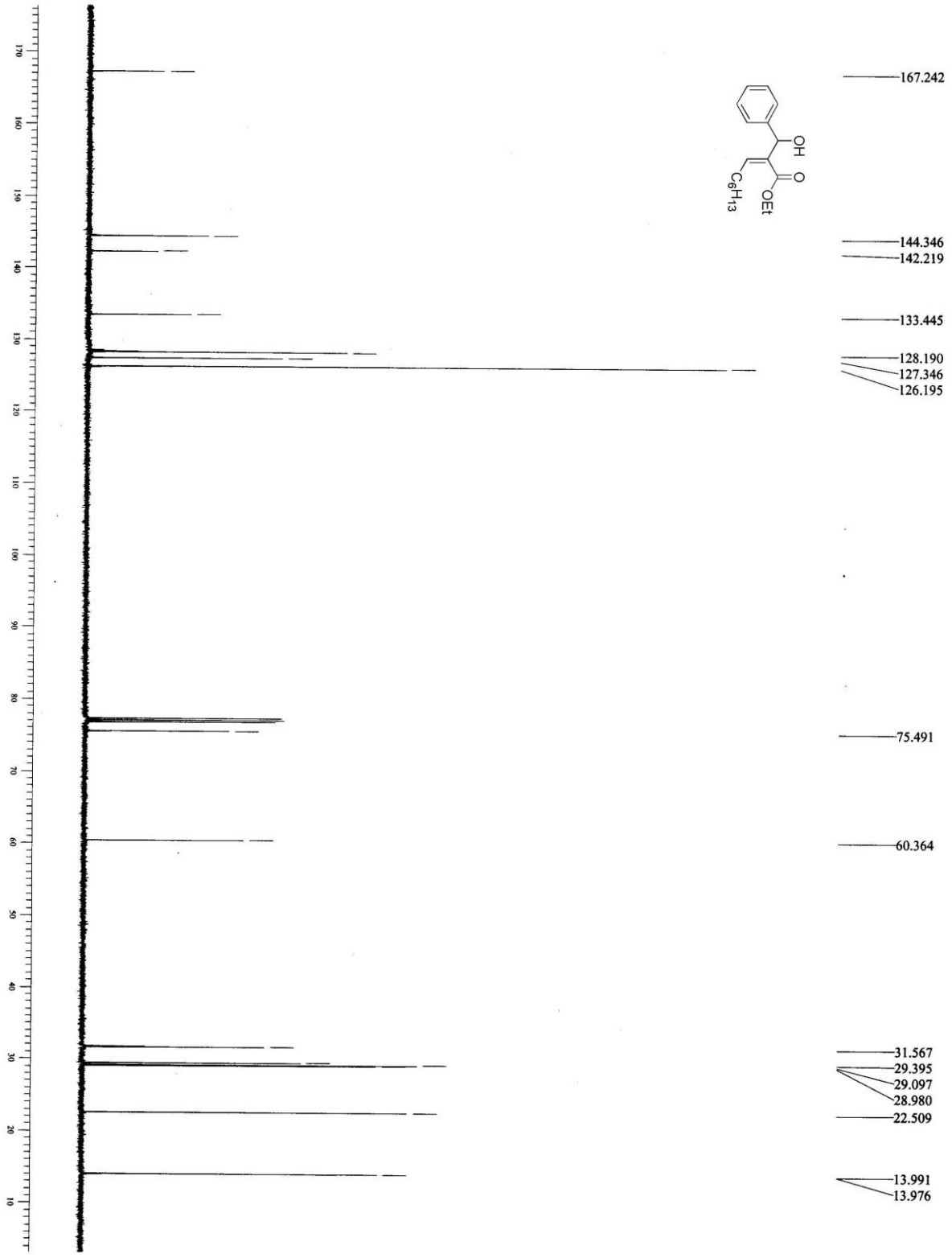

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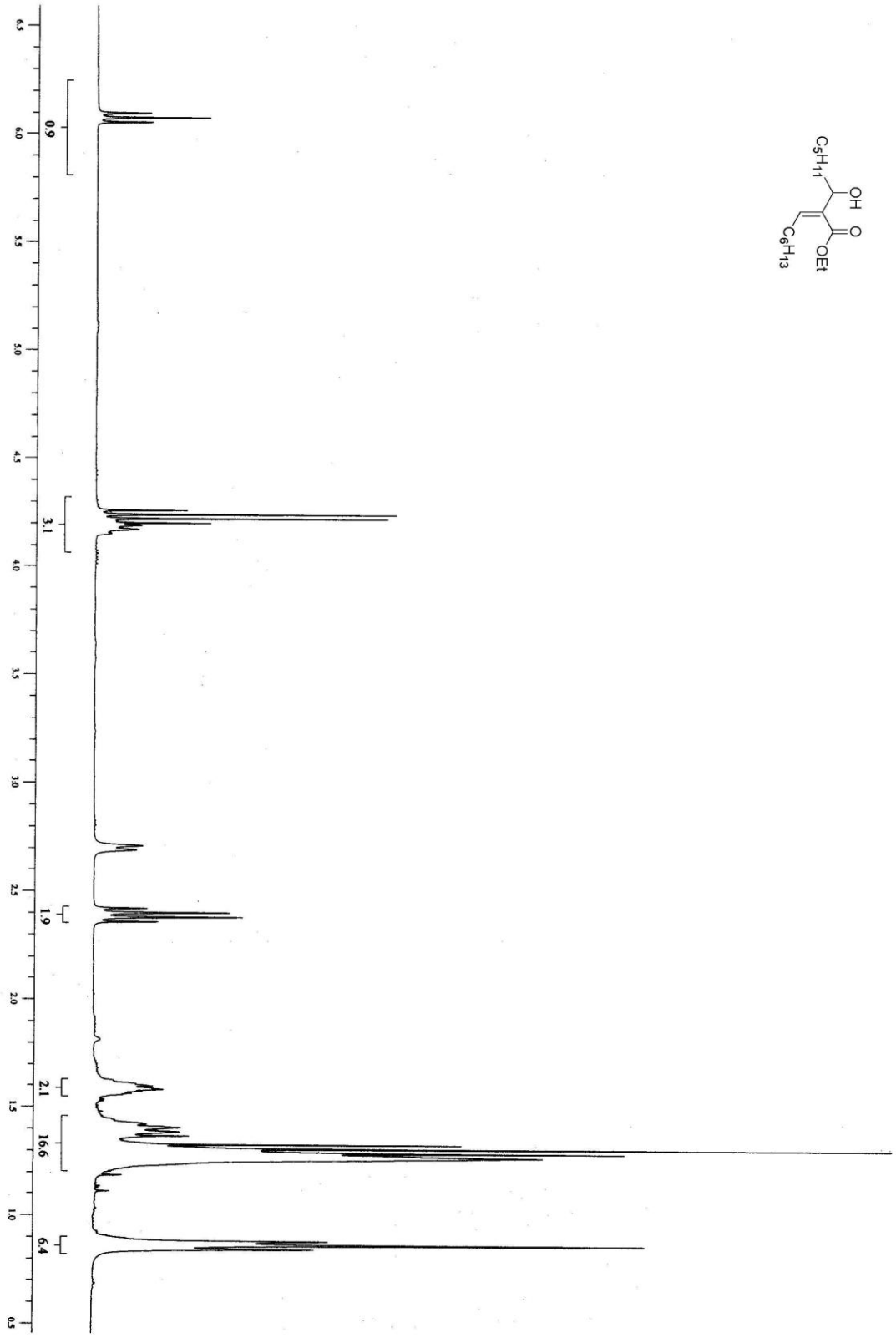

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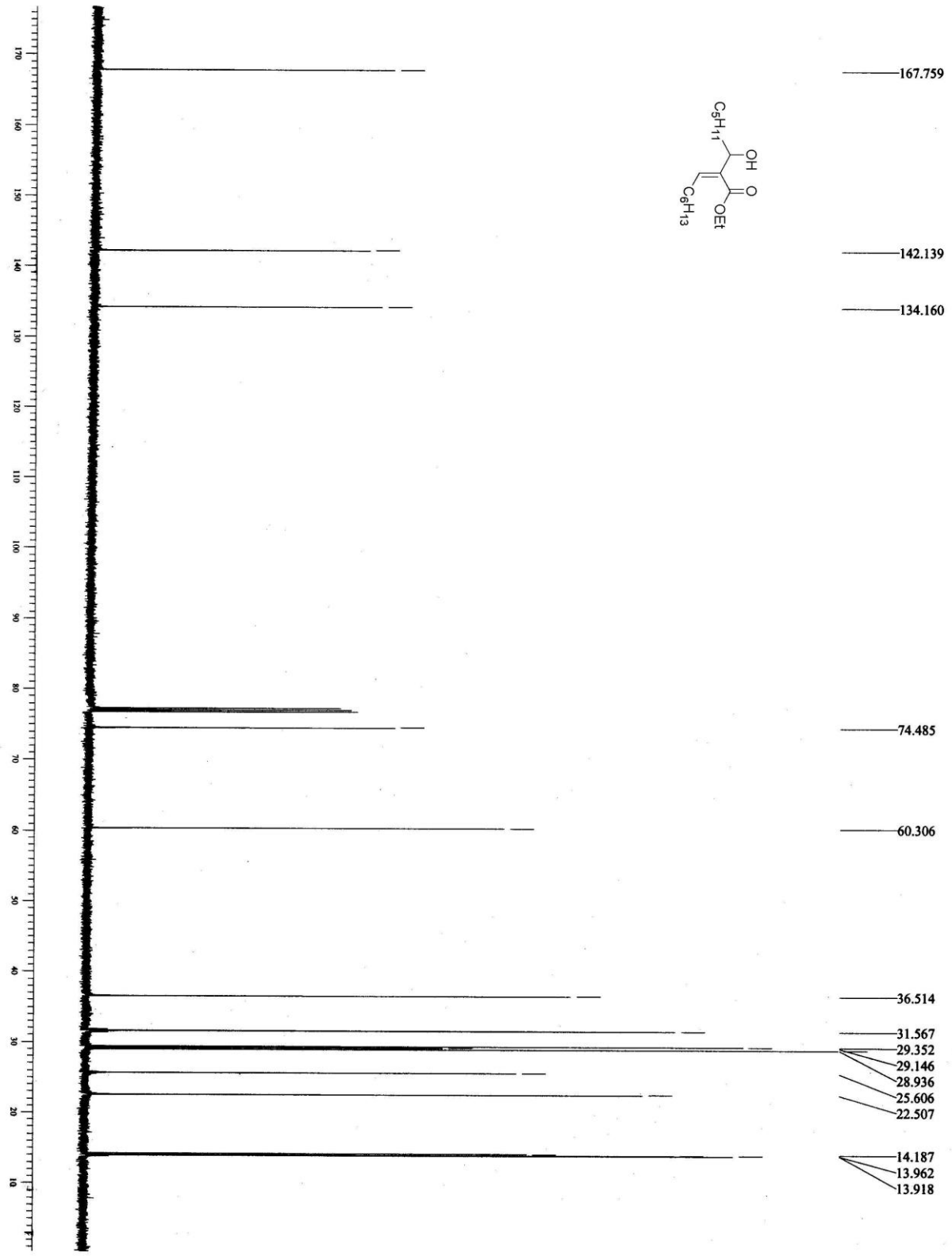

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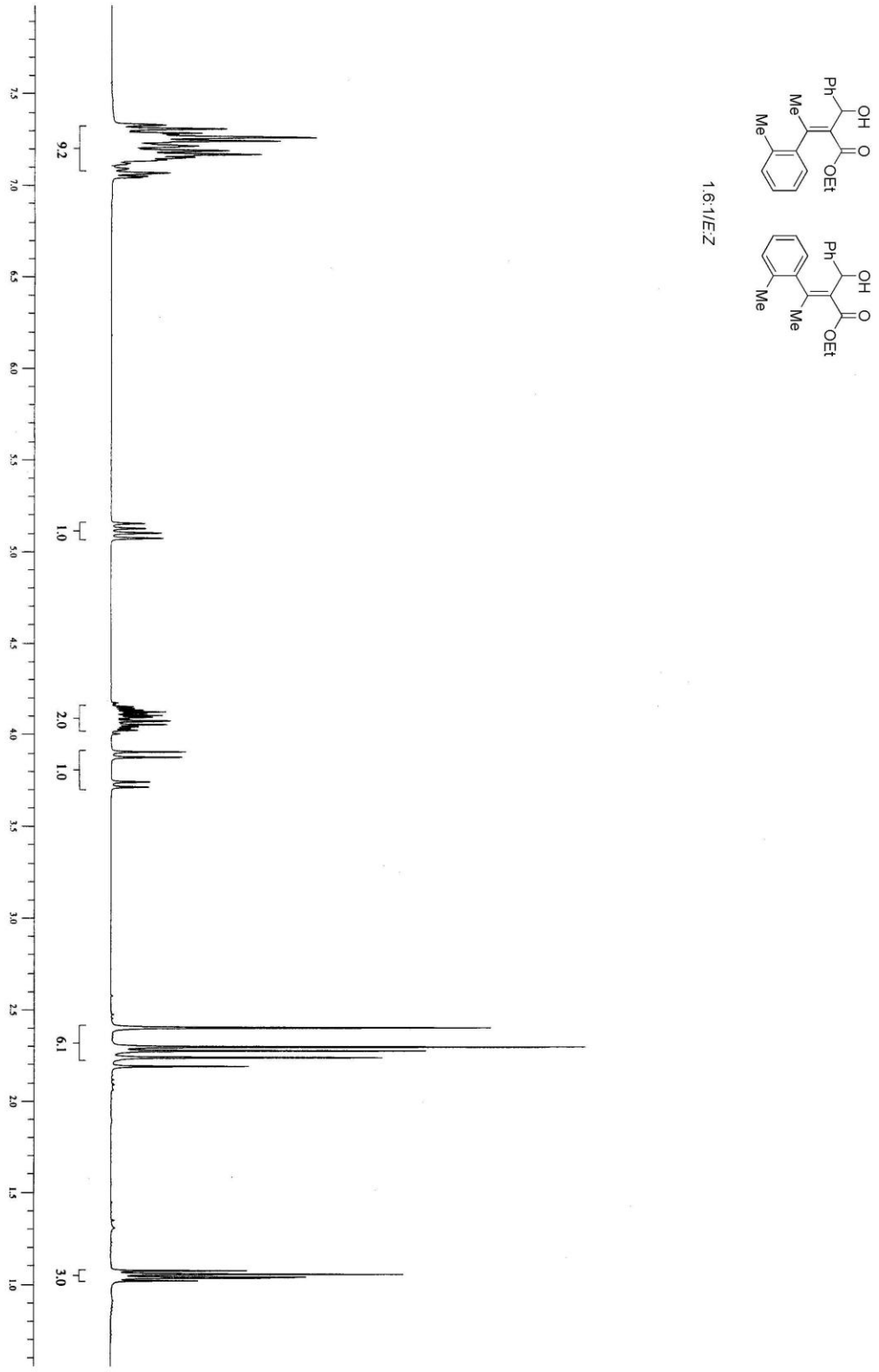
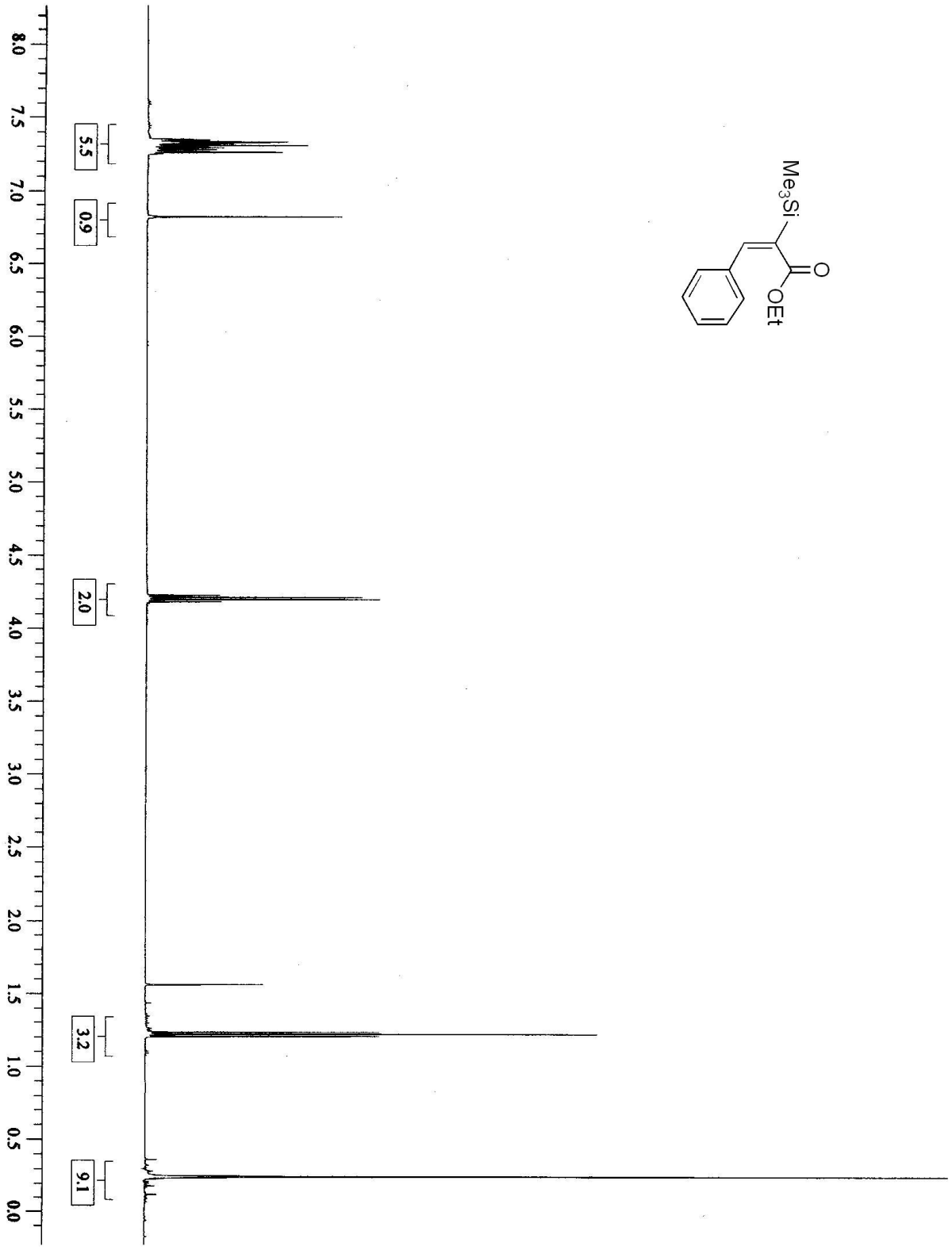
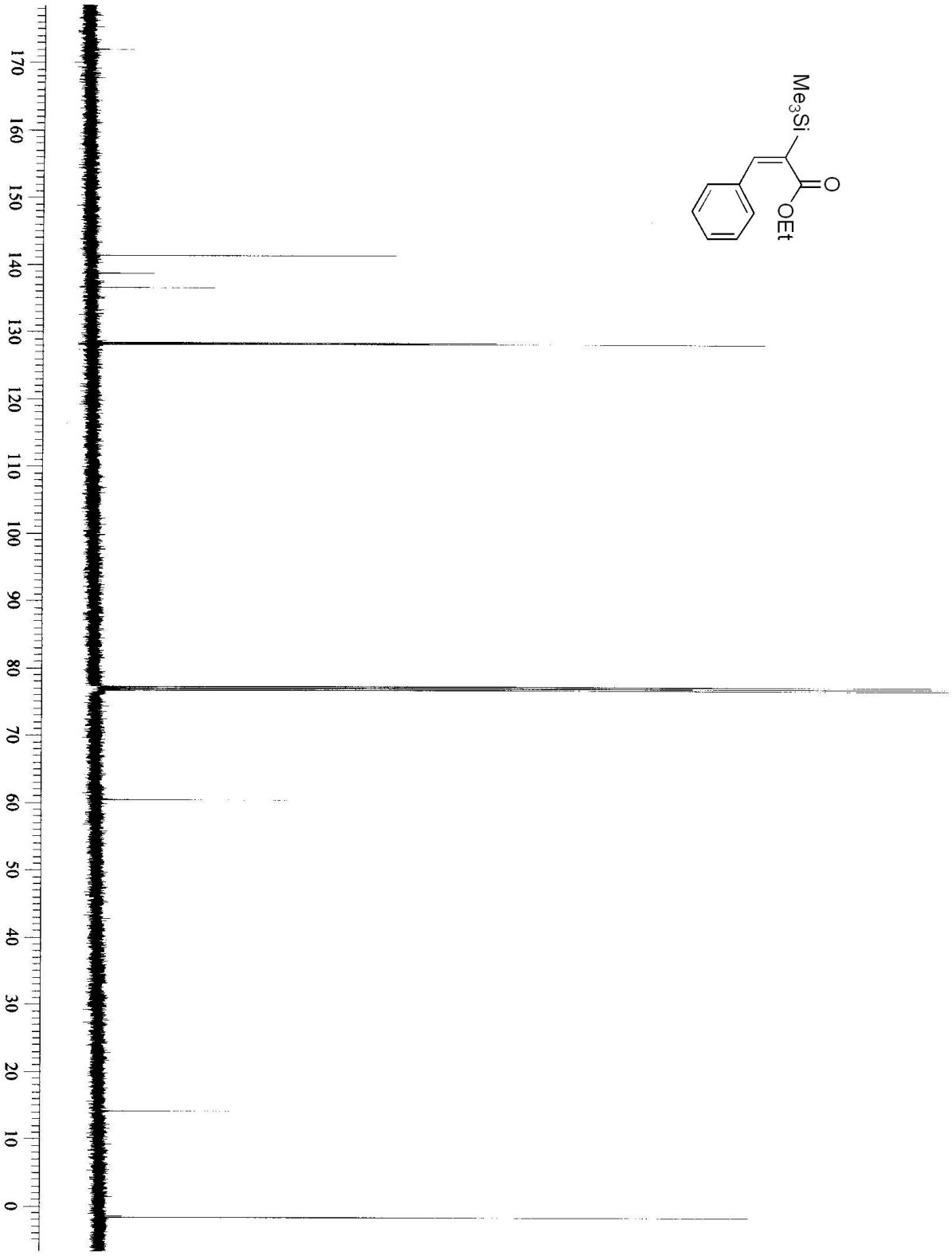


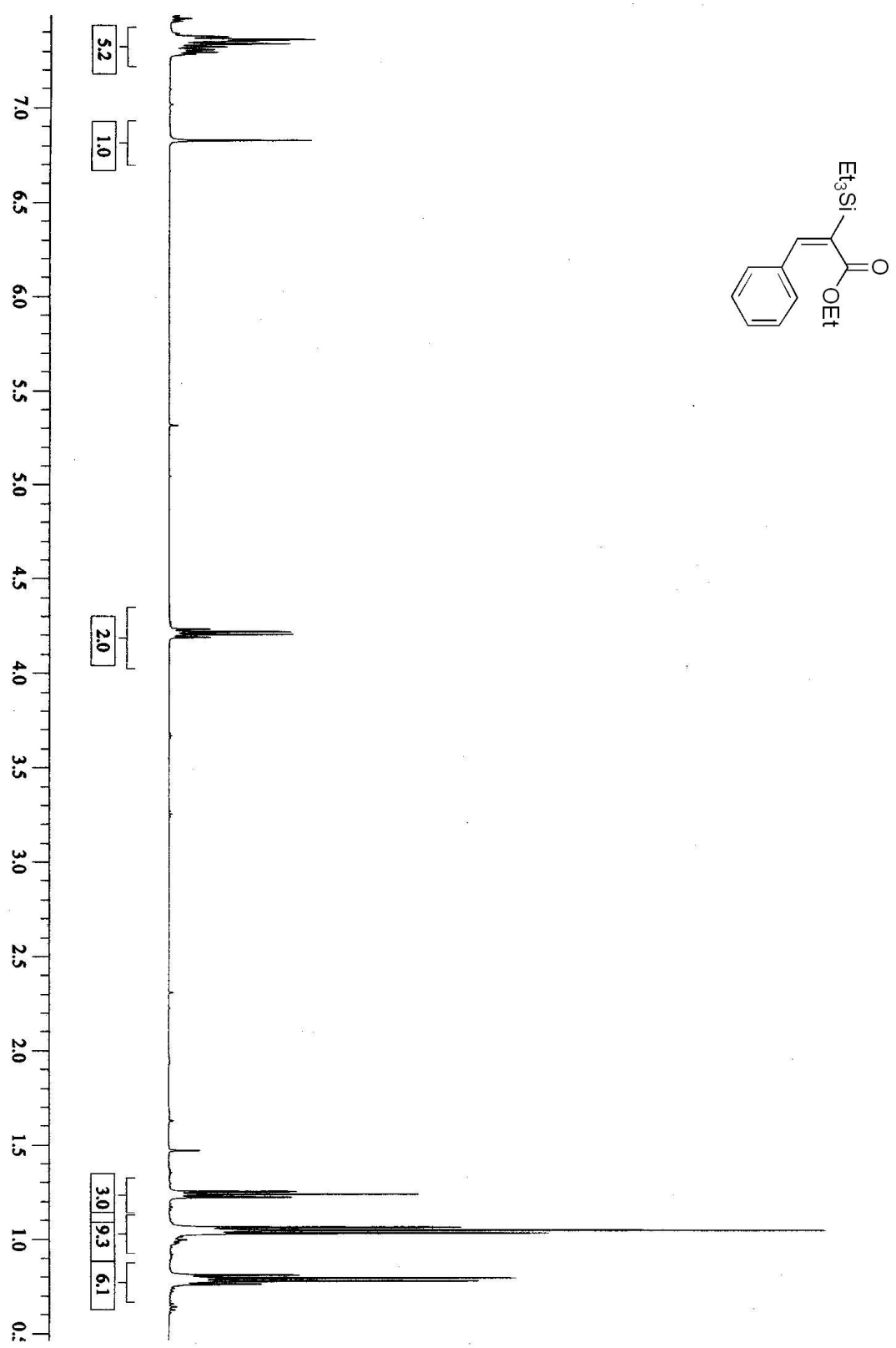
The ^{1}H NMR Spectrum (360 MHz, $CDCl_3$) of Compound **79**



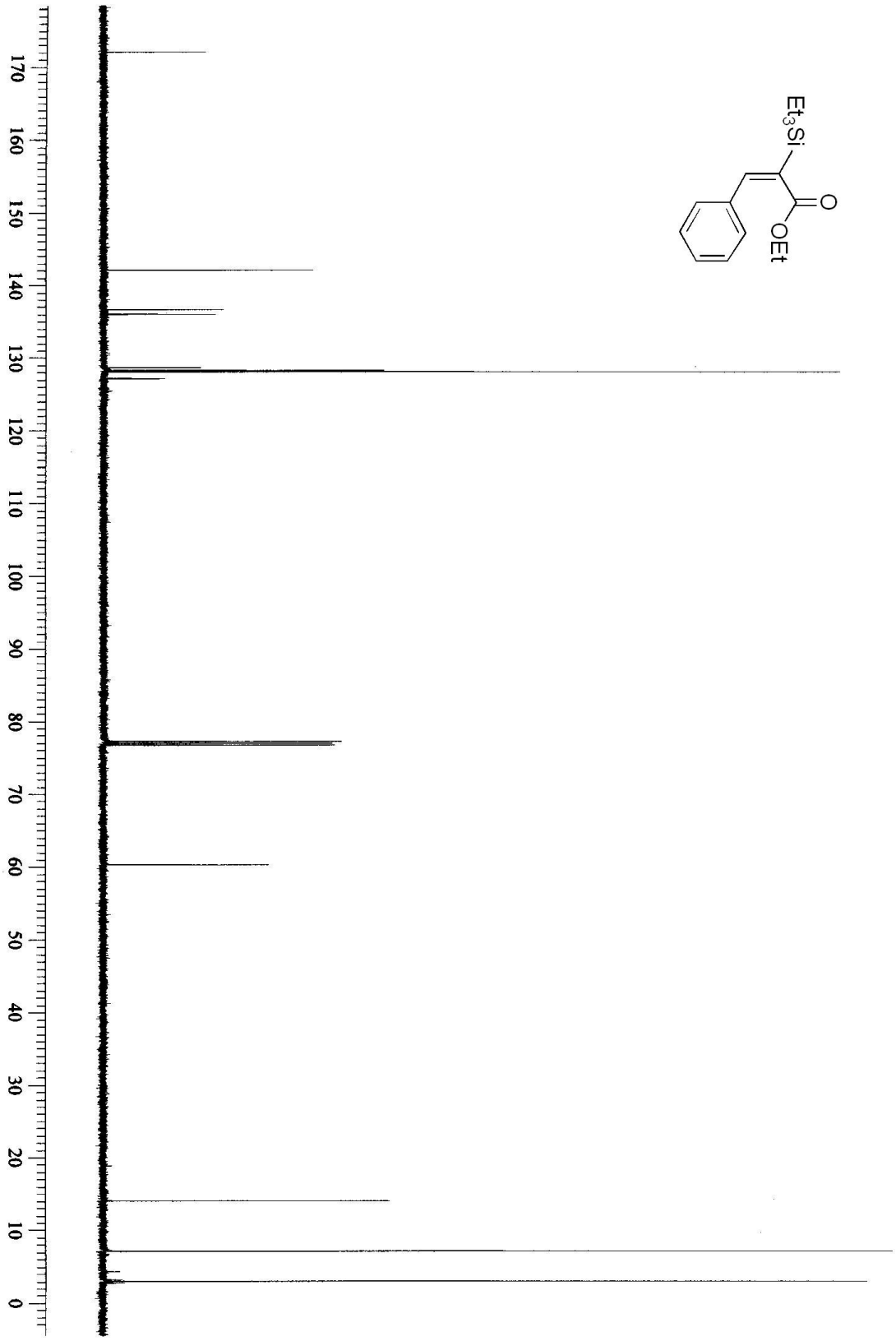
The ^{1}H NMR Spectrum (360 MHz, $CDCl_3$) of Compound **91**



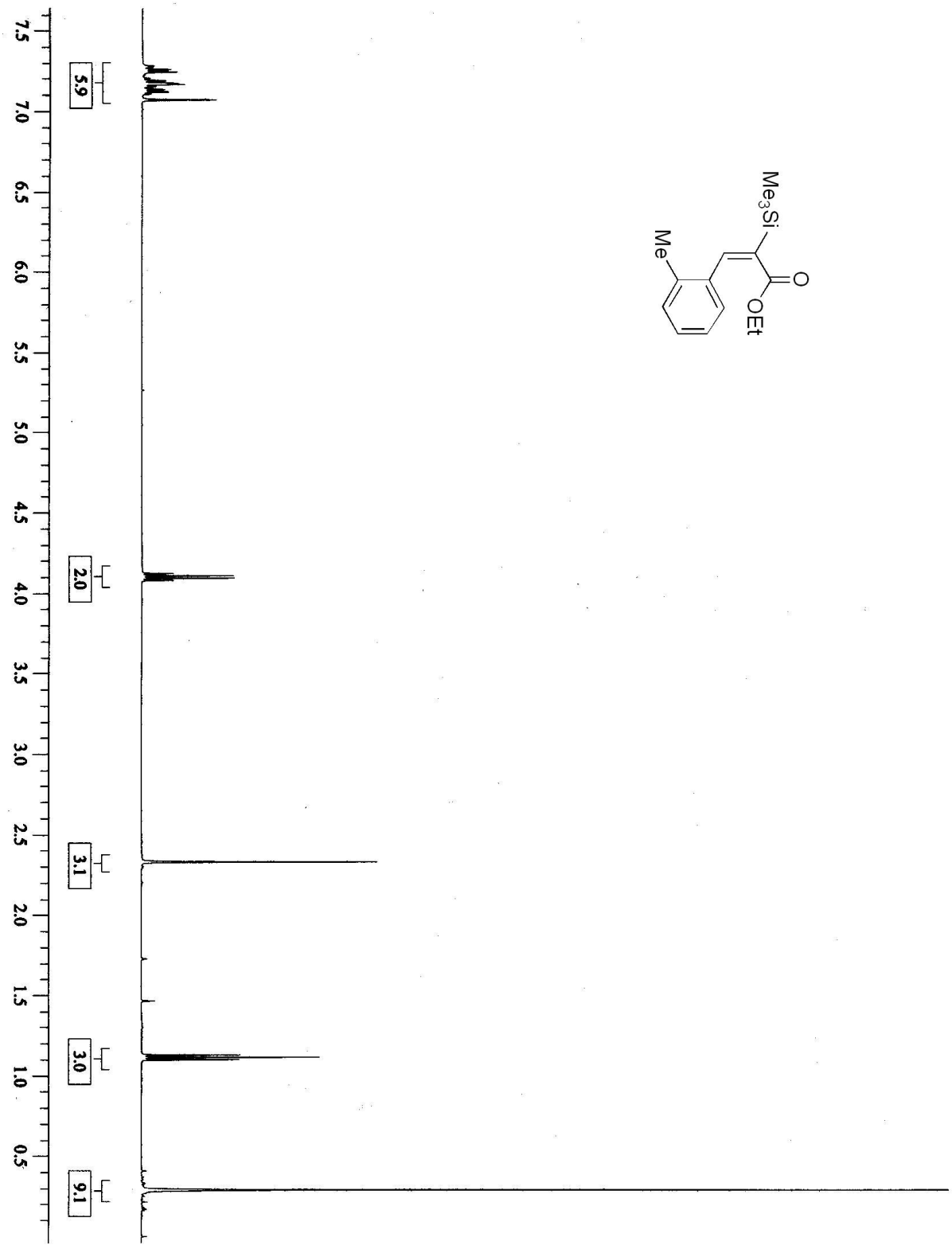
The ^{13}C NMR Spectrum (90 MHz, $CDCl_3$) of Compound **91**



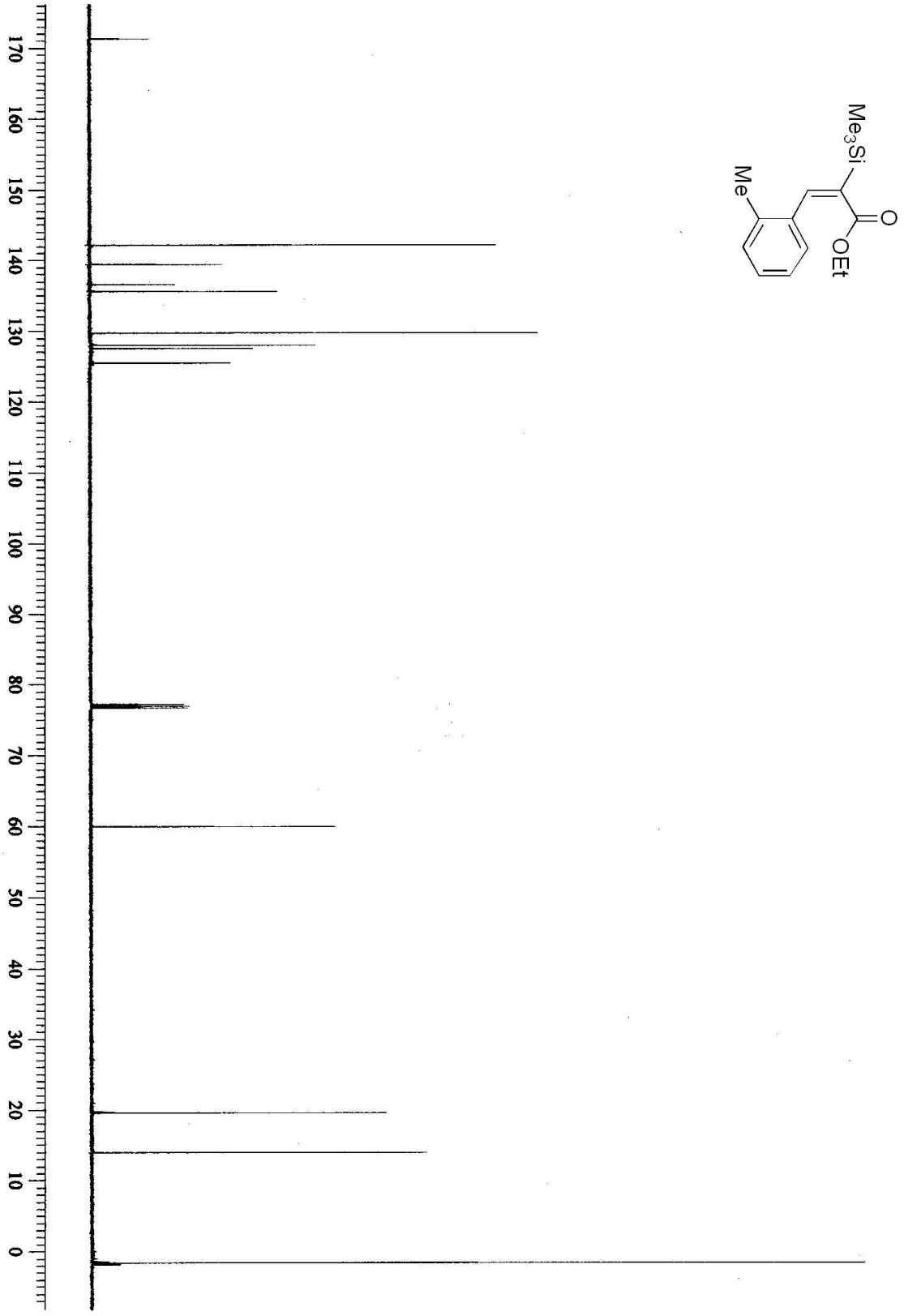
The ^{1}H NMR Spectrum (360 MHz, $CDCl_3$) of Compound **92**



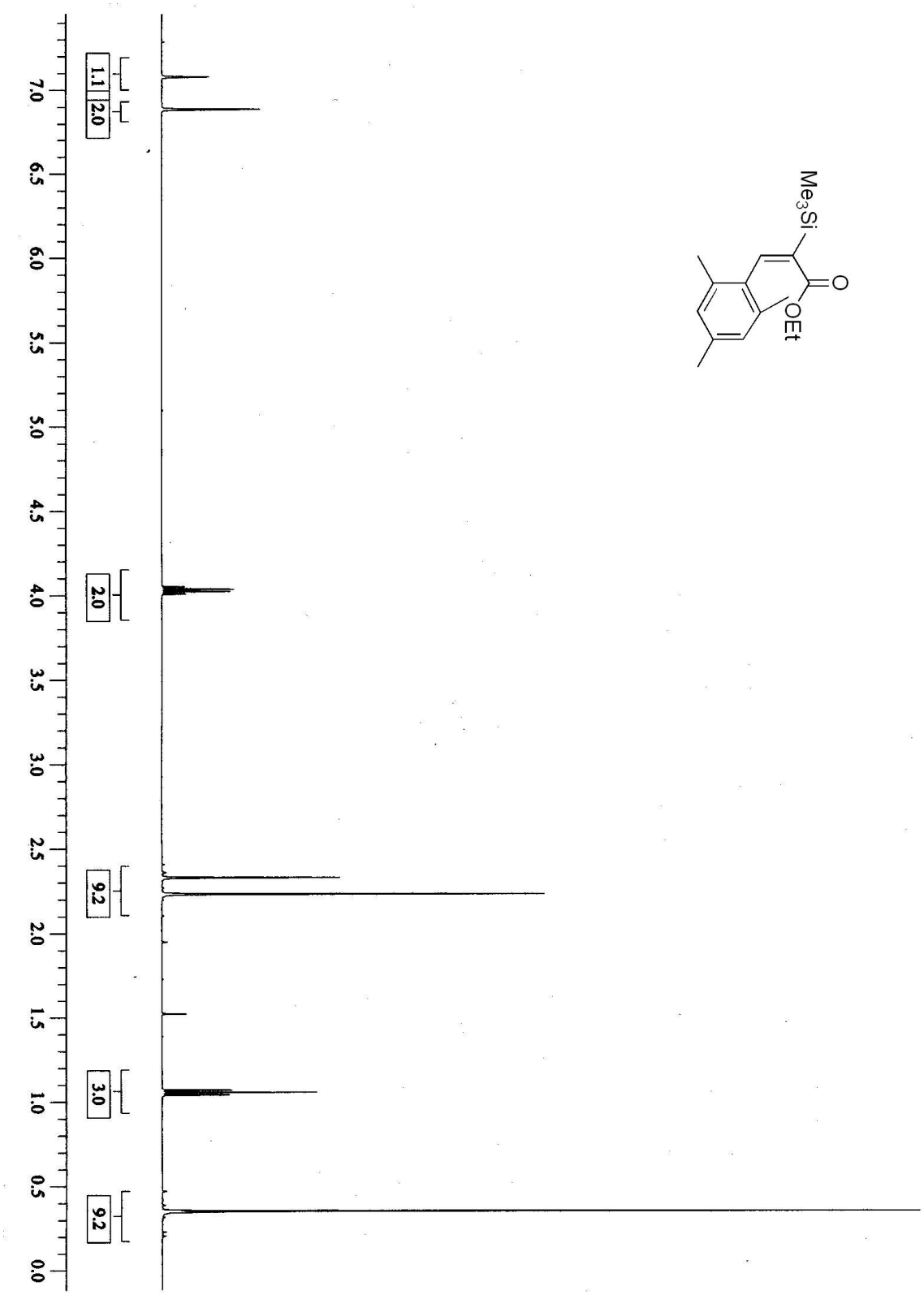
The ^{13}C NMR Spectrum (90 MHz, $CDCl_3$) of Compound **92**



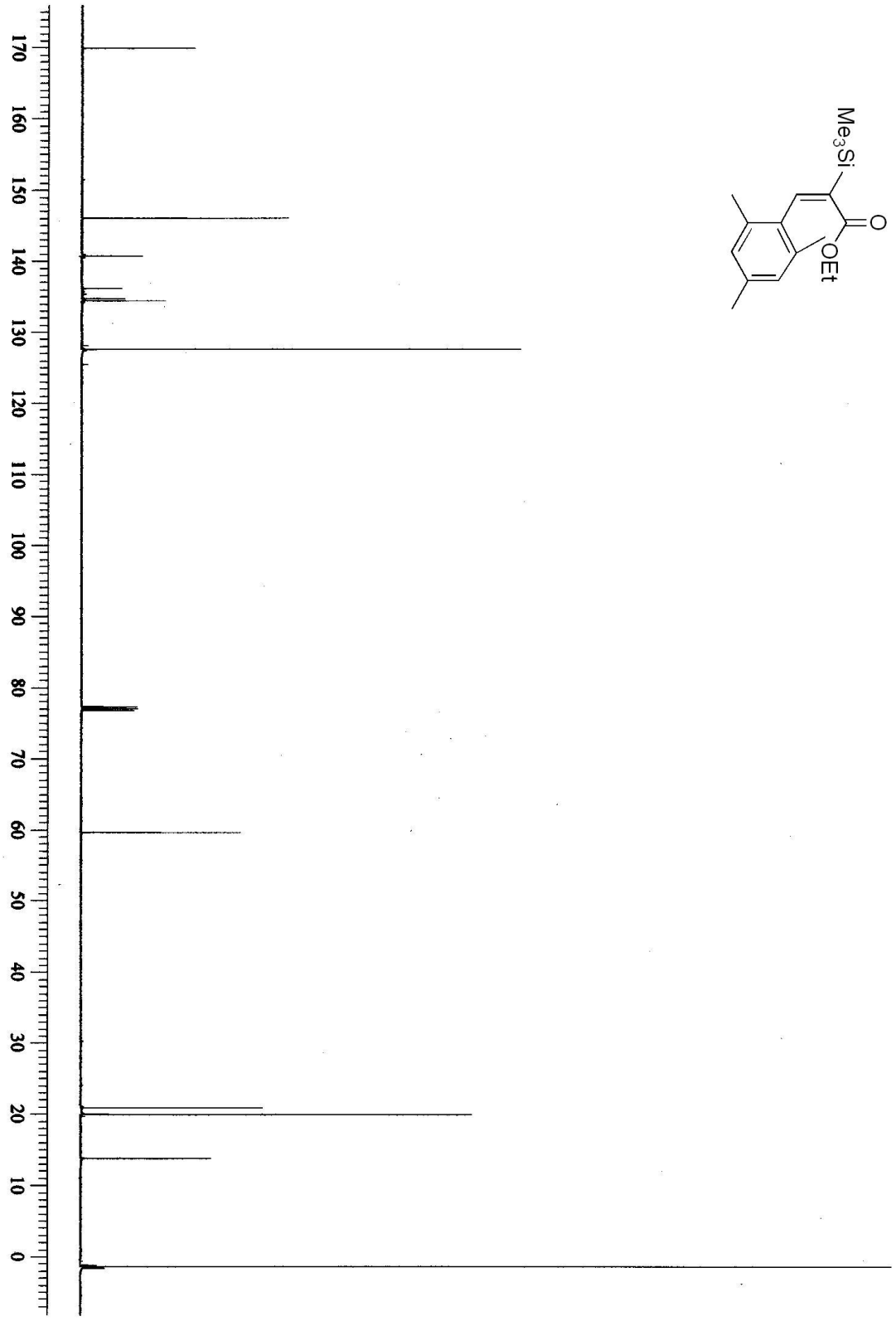
The ^{1}H NMR Spectrum (360 MHz, $CDCl_3$) of Compound **93**



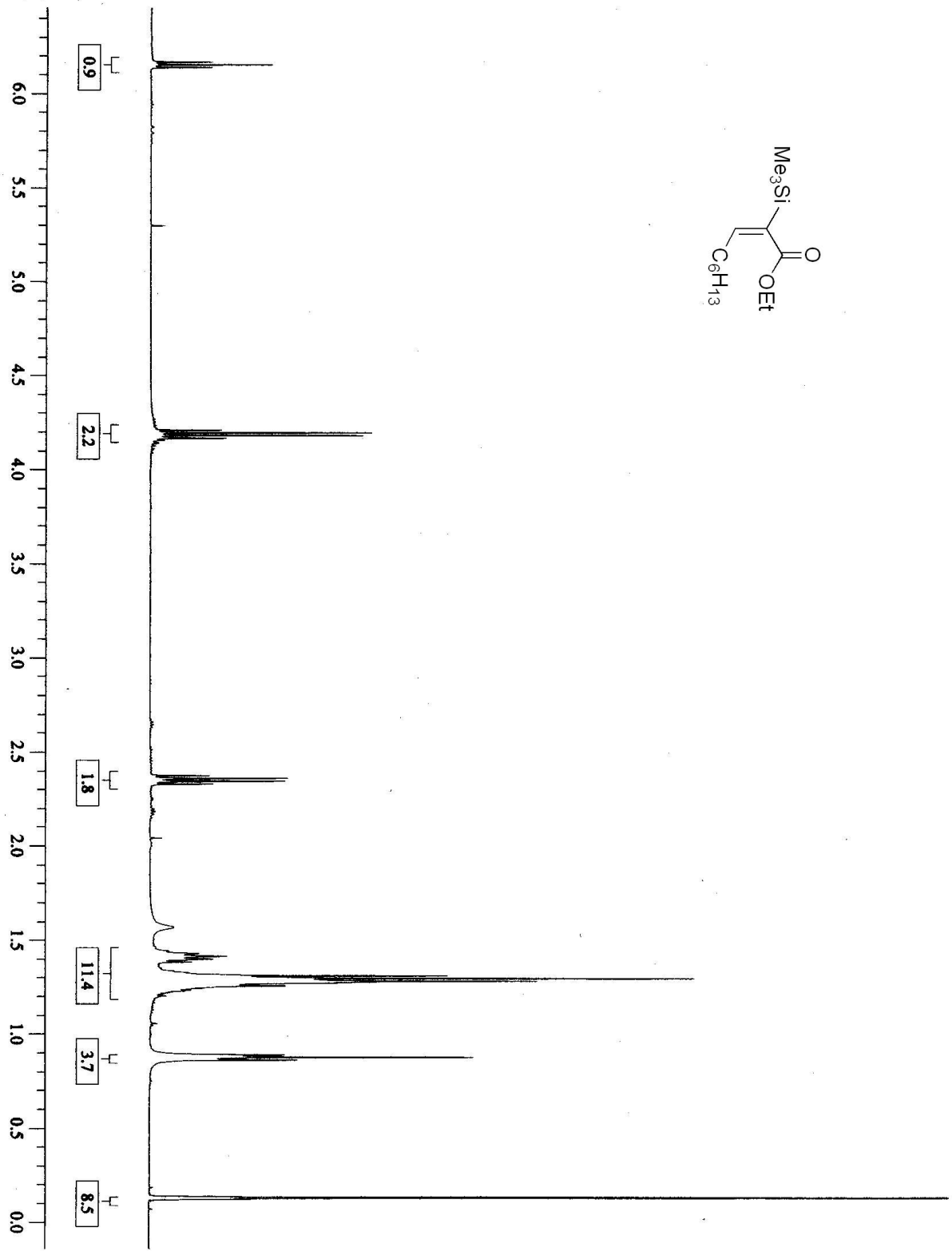
The ^{13}C NMR Spectrum (90 MHz, $CDCl_3$) of Compound **93**



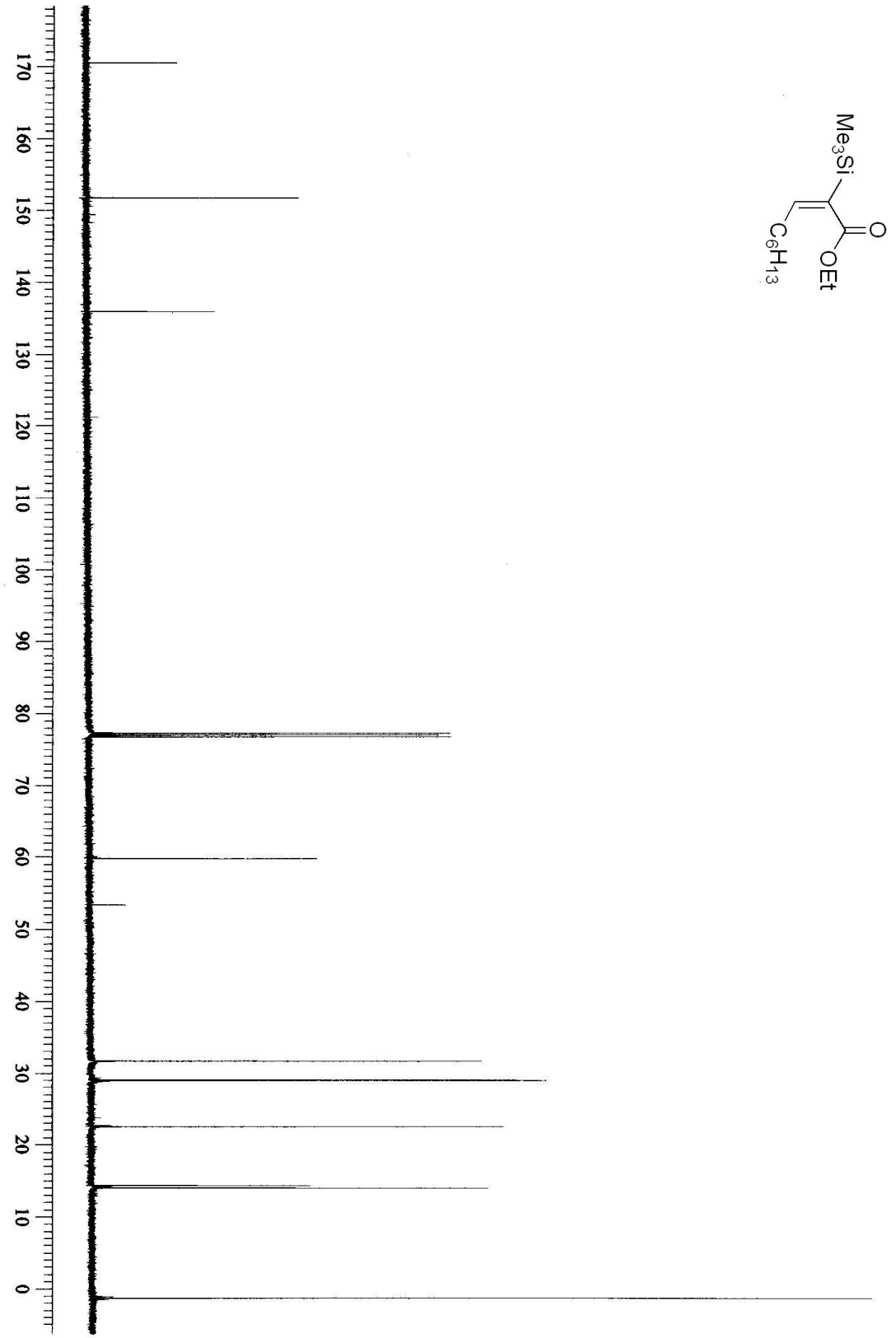
The ^{1}H NMR Spectrum (360 MHz, $CDCl_3$) of Compound **94**



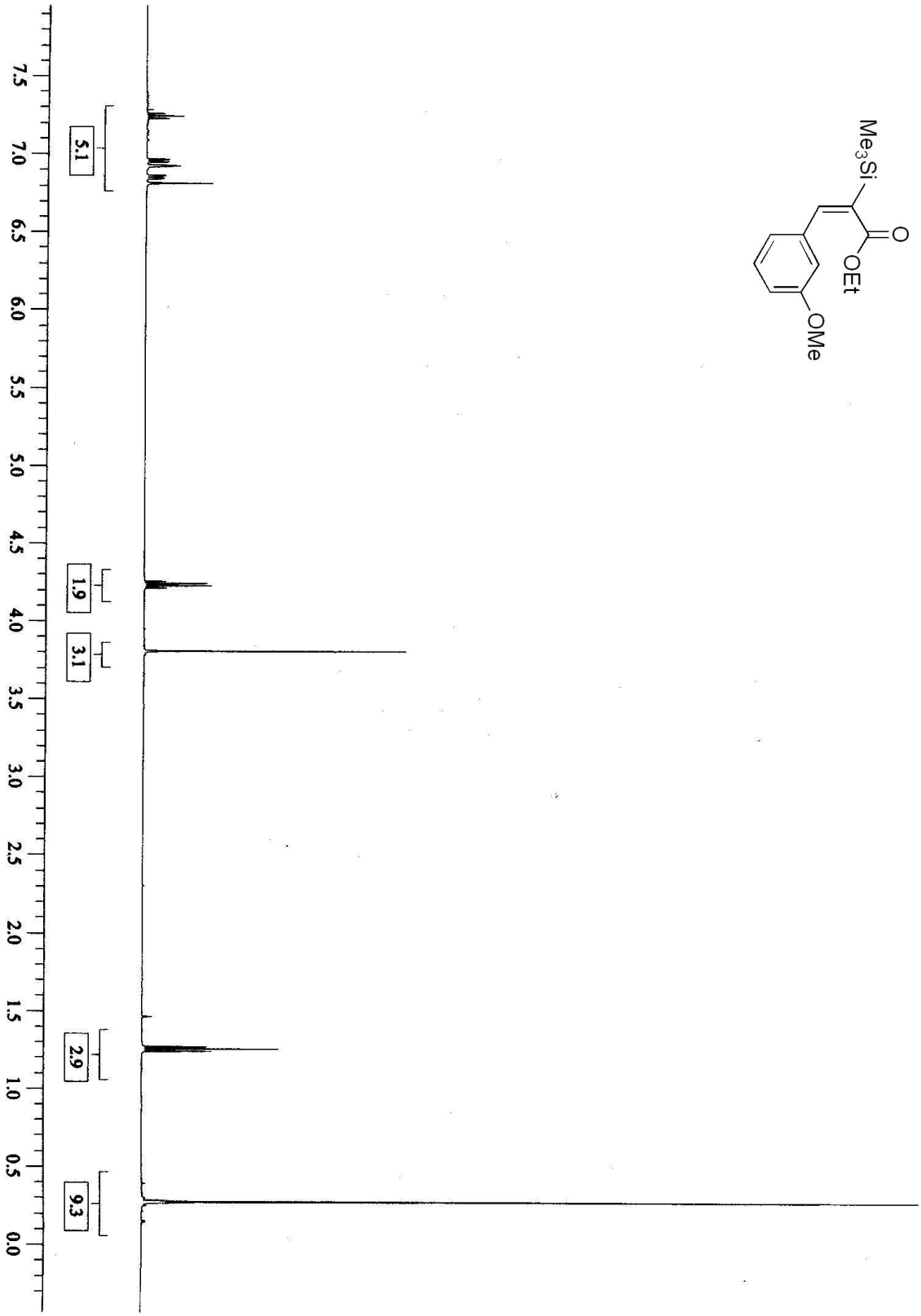
The ^{13}C NMR Spectrum (90 MHz, $CDCl_3$) of Compound **94**



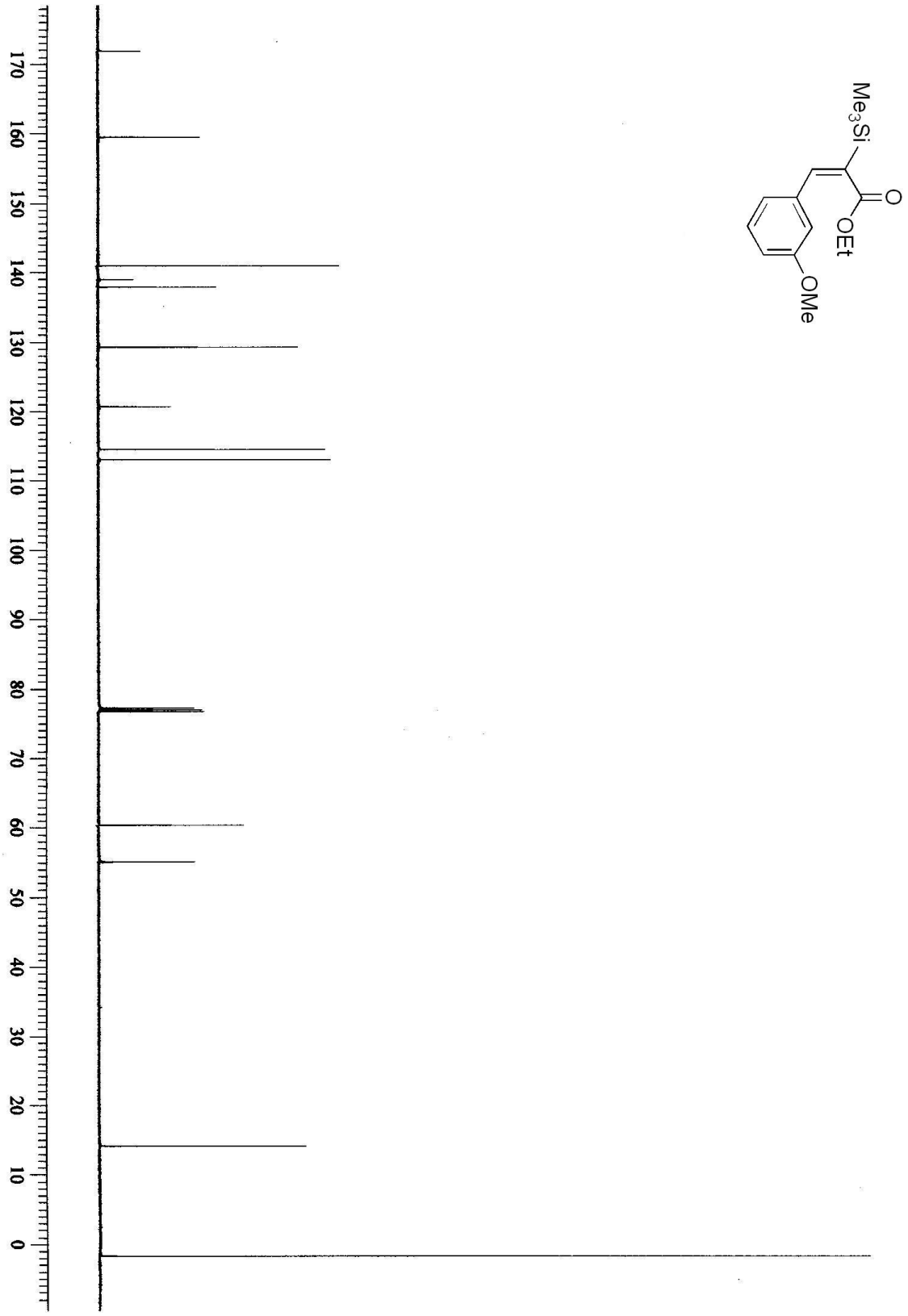
The ^{1}H NMR Spectrum (360 MHz, $CDCl_3$) of Compound **95**



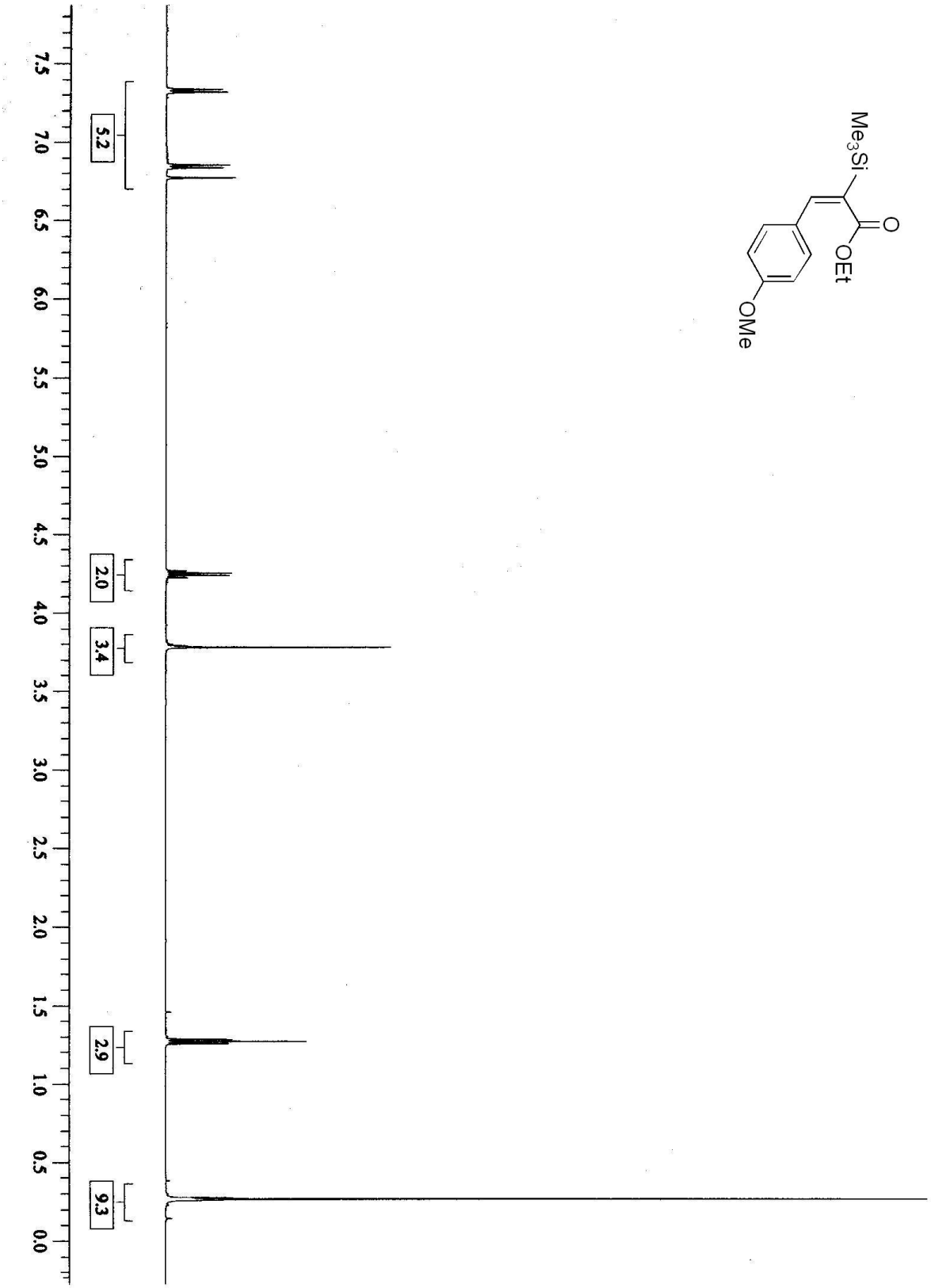
The ^{13}C NMR Spectrum (90MHz, $CDCl_3$) of Compound **95**



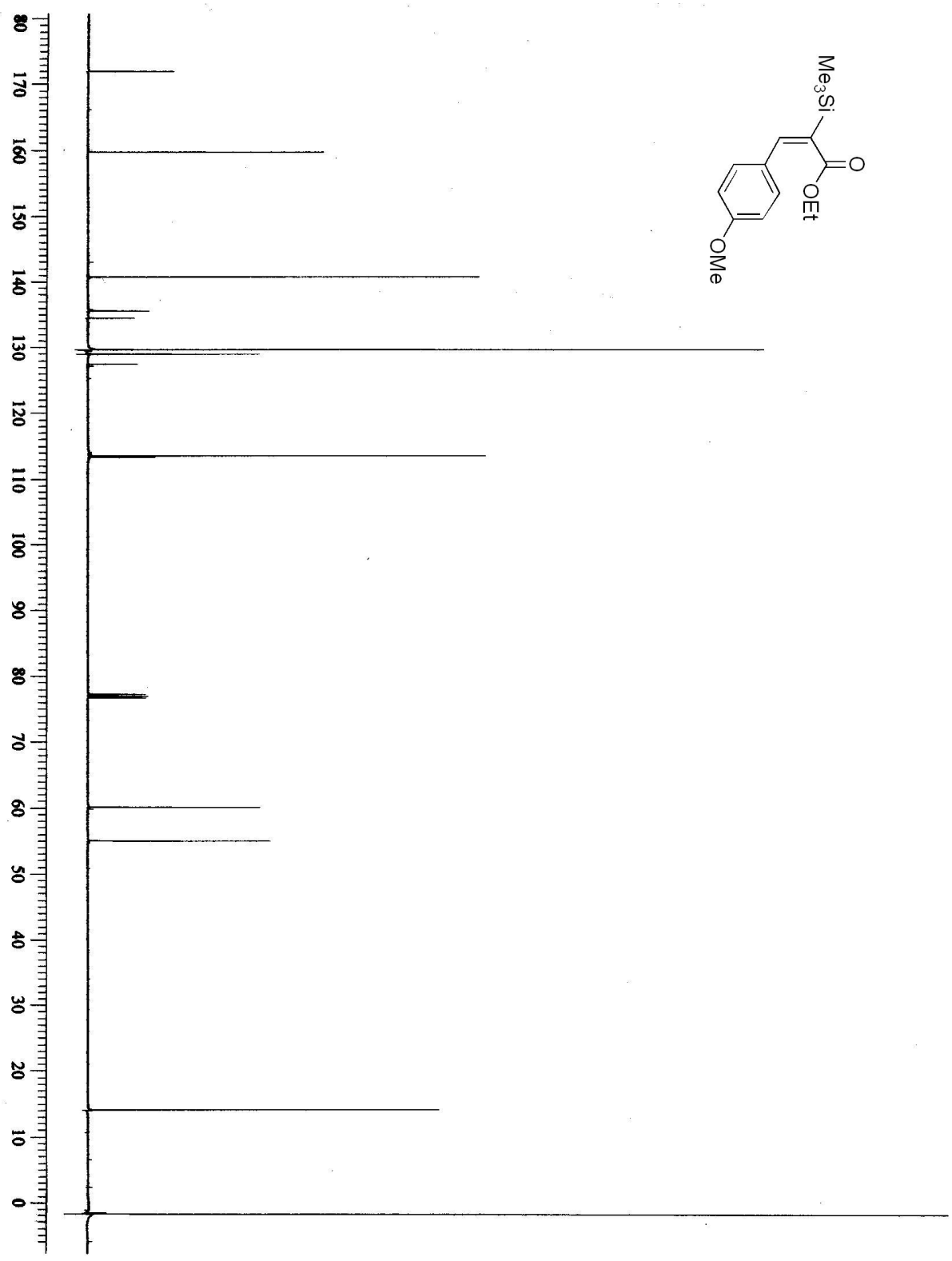
The ^{1}H NMR Spectrum (360 MHz, $CDCl_3$) of Compound **96**



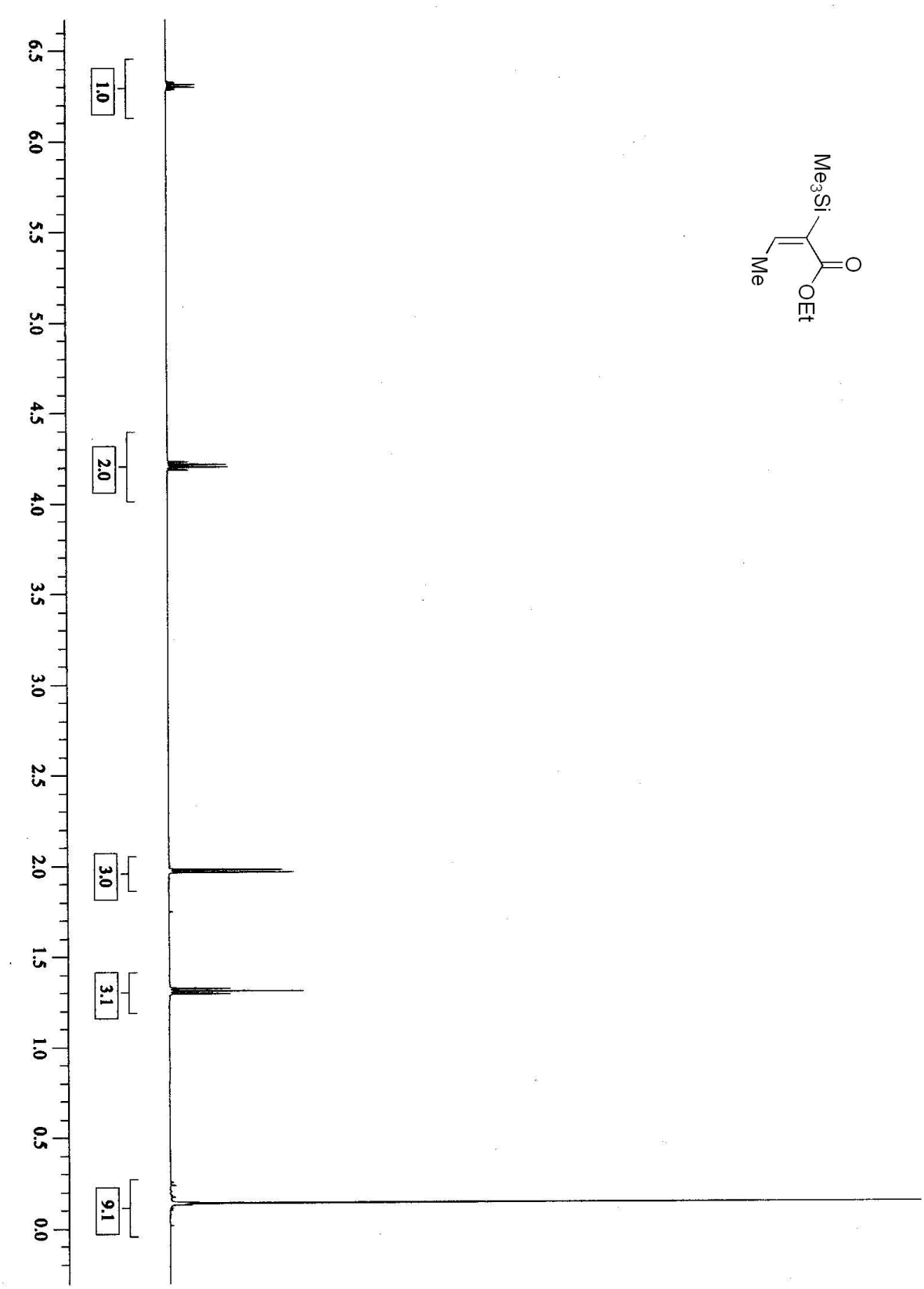
The ^{13}C NMR Spectrum (90 MHz, $CDCl_3$) of Compound **96**



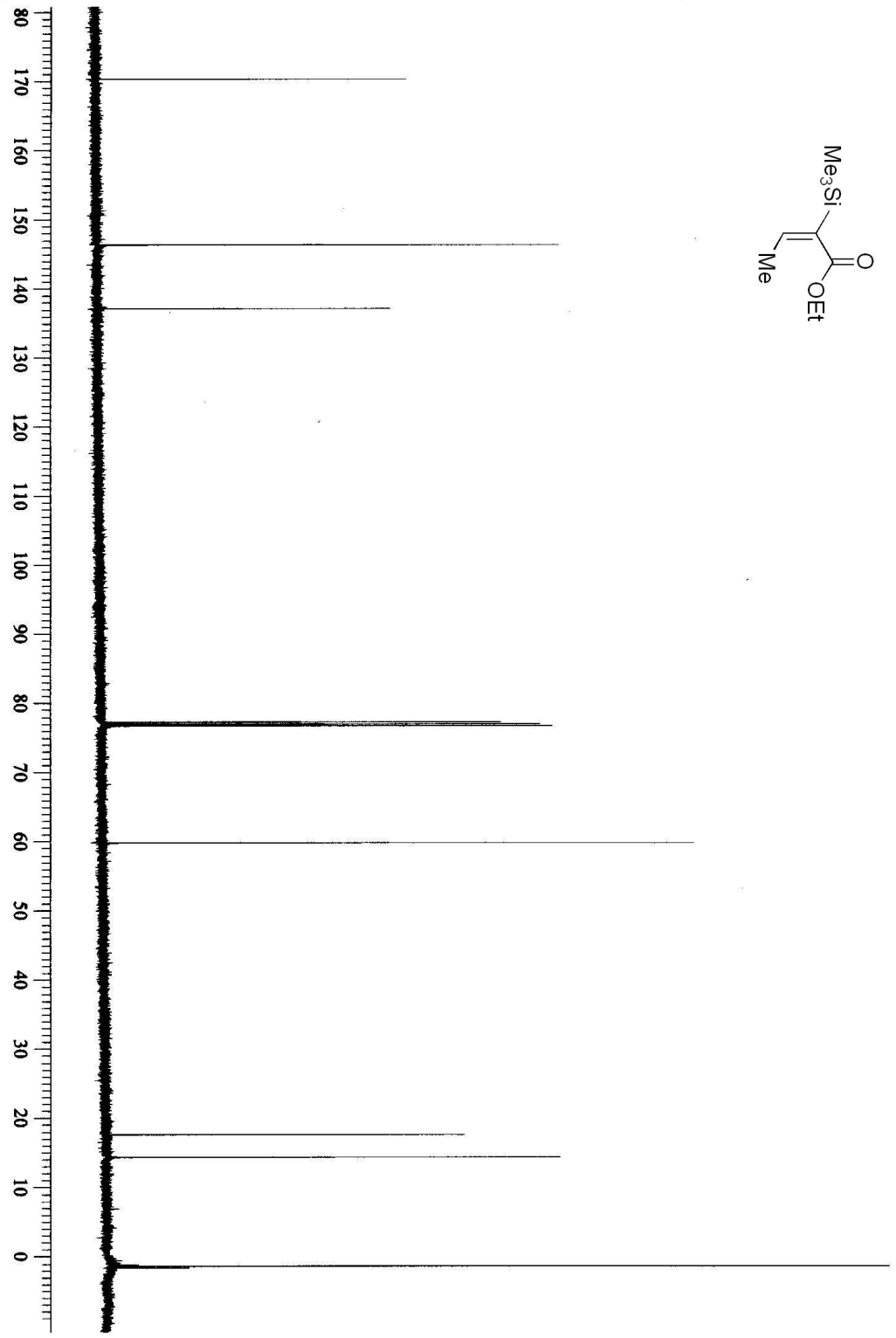
The ^{1}H NMR Spectrum (360 MHz, $CDCl_3$) of Compound **97**



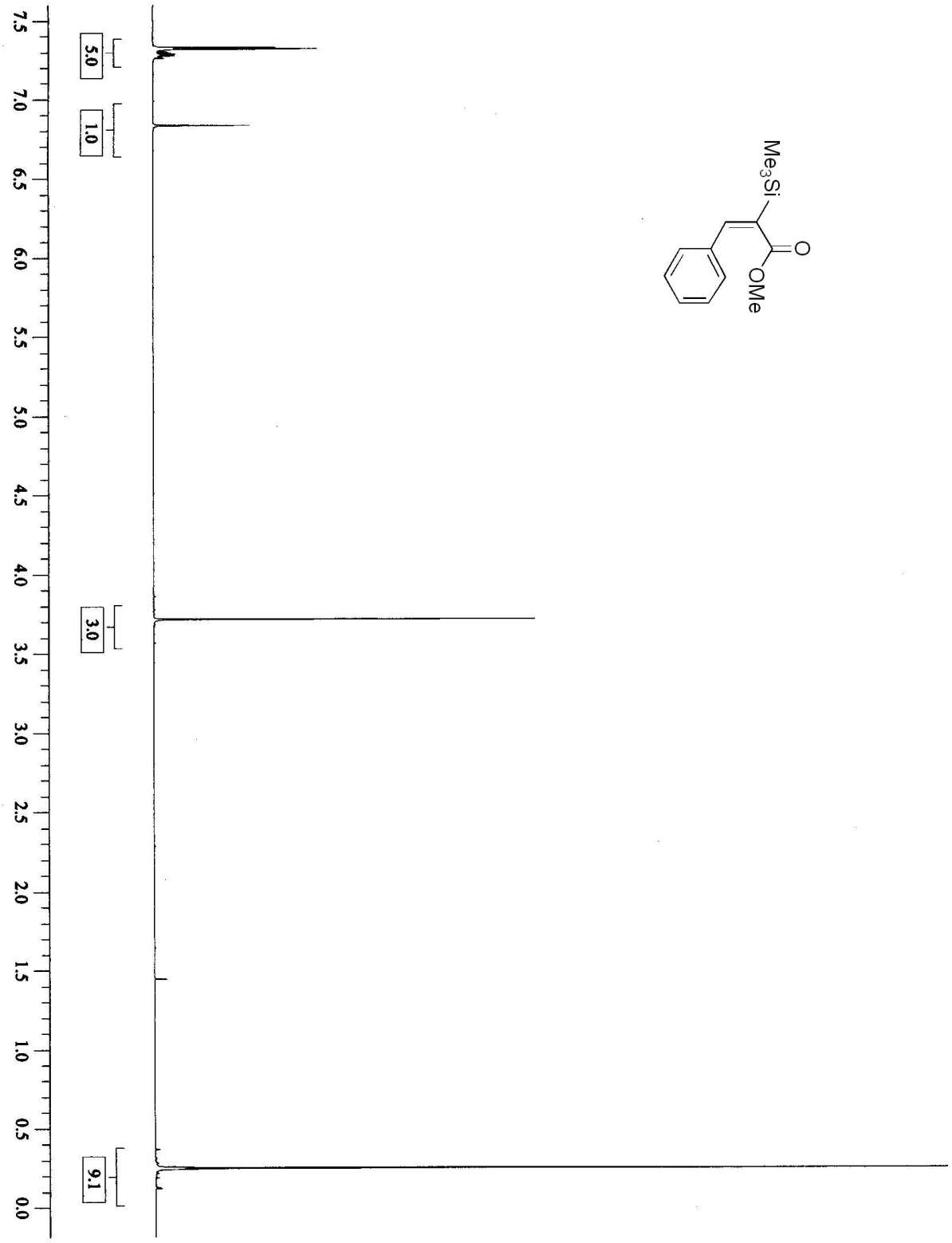
The ^{13}C NMR Spectrum (90 MHz, $CDCl_3$) of Compound **97**



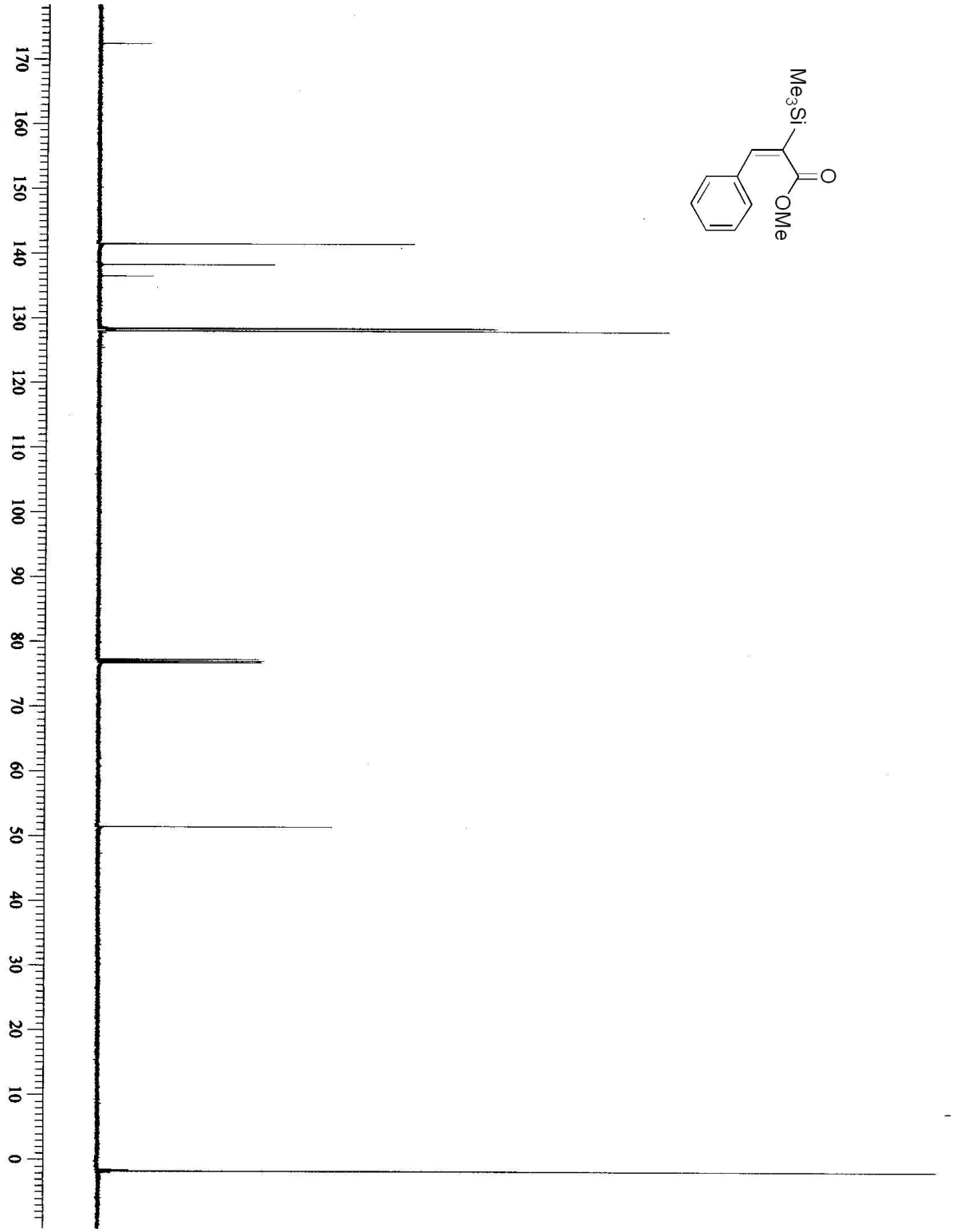
The ^{1}H NMR Spectrum (360 MHz, $CDCl_3$) of Compound **98**



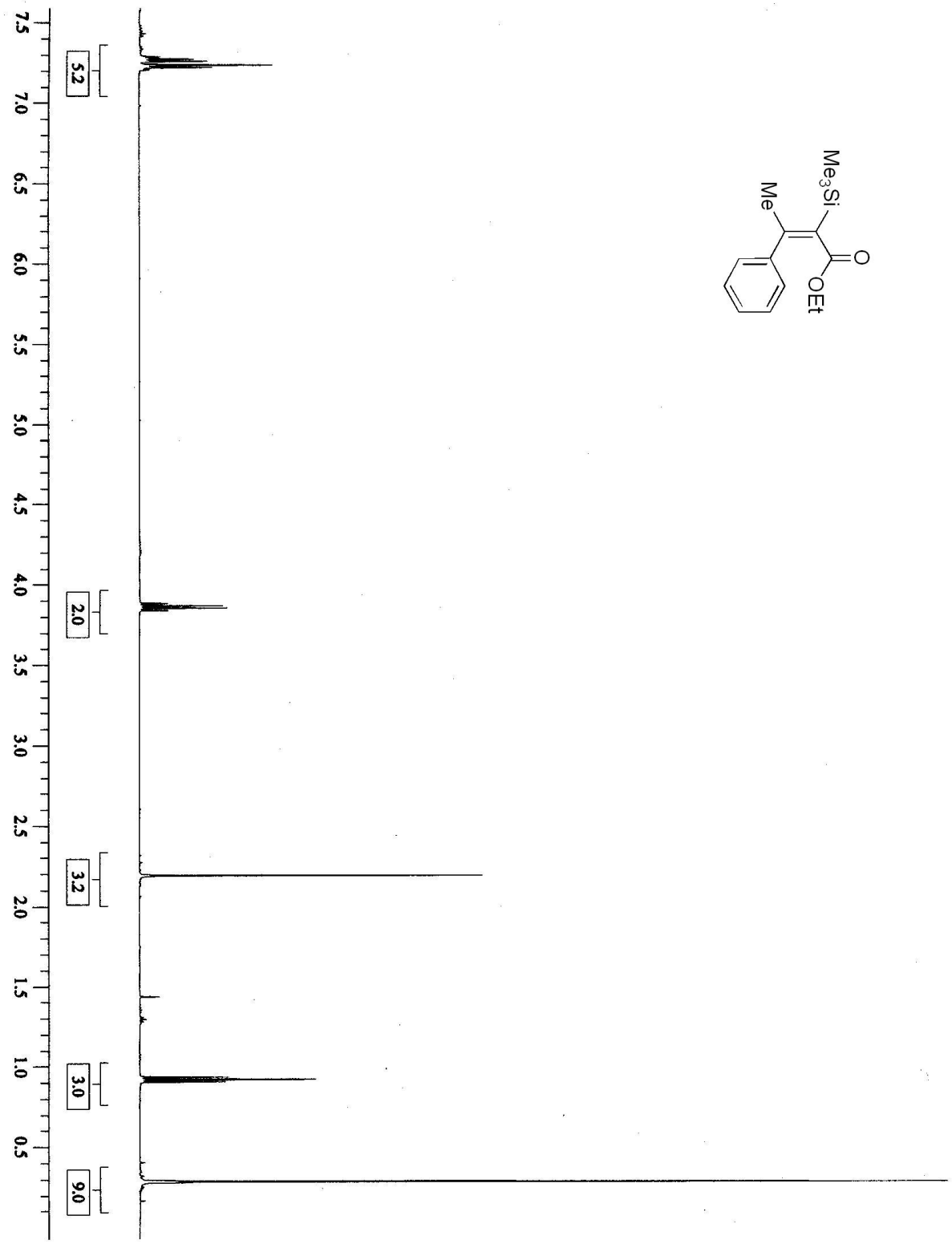
The ^{13}C NMR Spectrum (90 MHz, $CDCl_3$) of Compound **98**



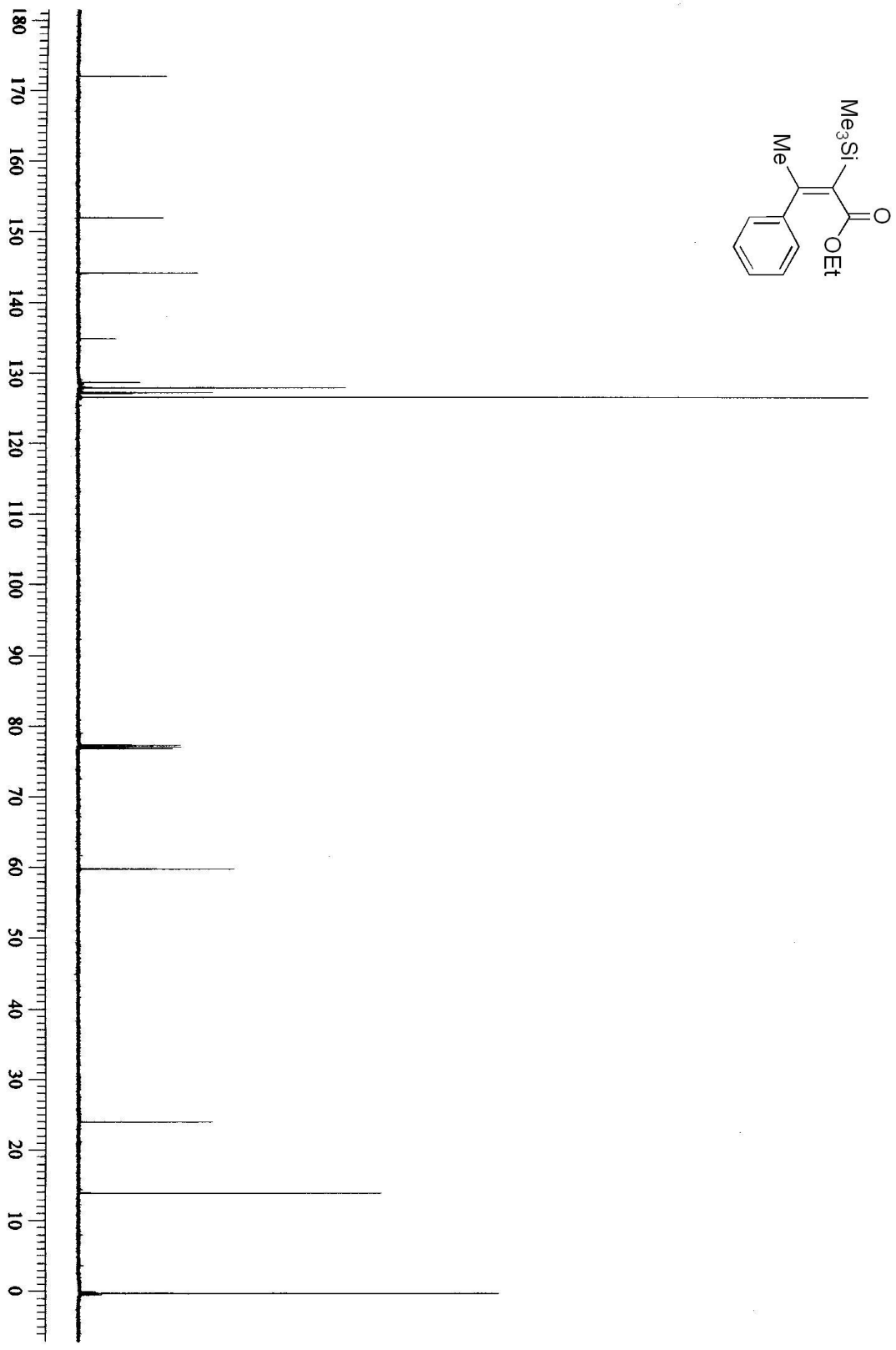
The ^{1}H NMR Spectrum (360 MHz, $CDCl_3$) of Compound **101**



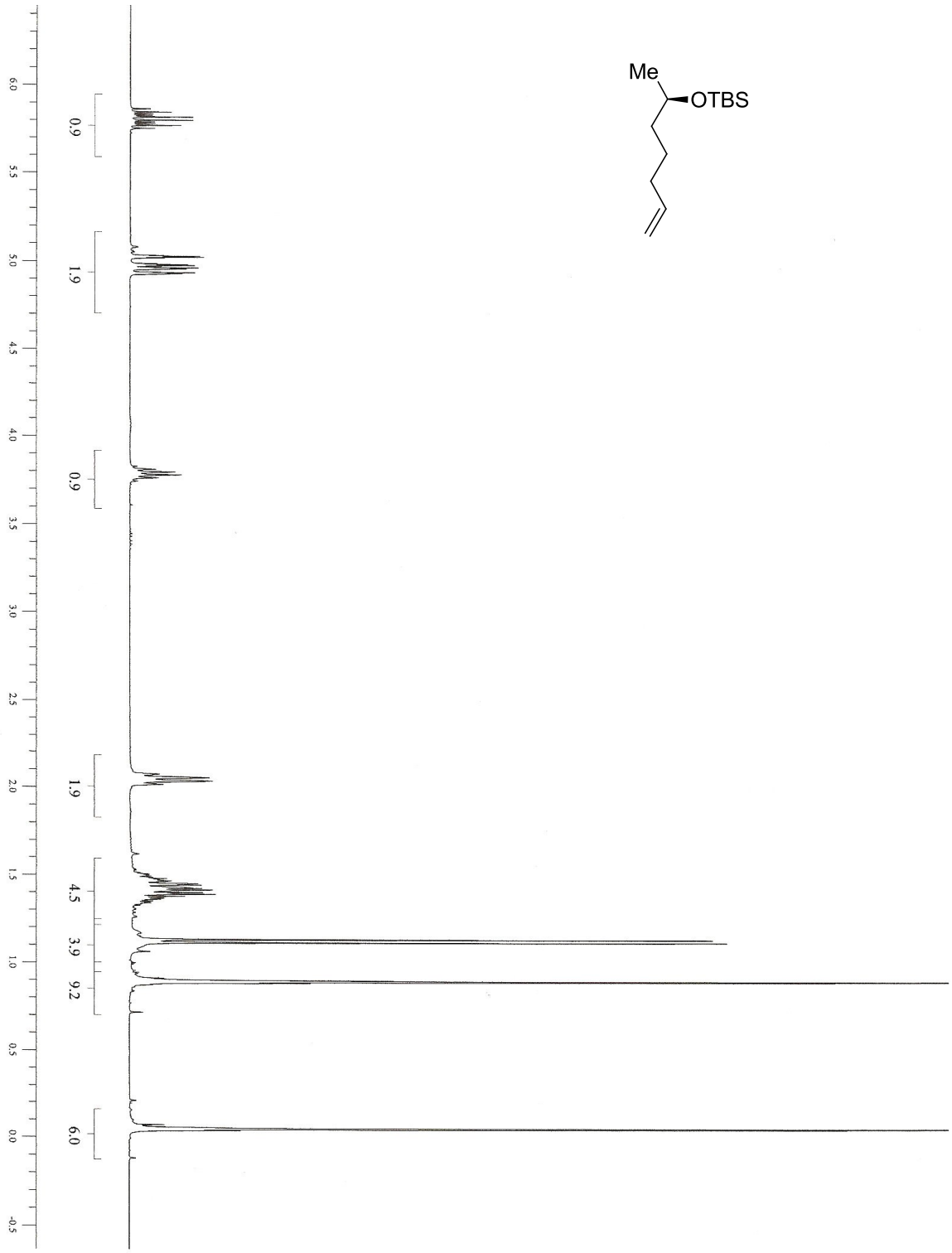
The ^{13}C NMR Spectrum (90 MHz, $CDCl_3$) of Compound **101**



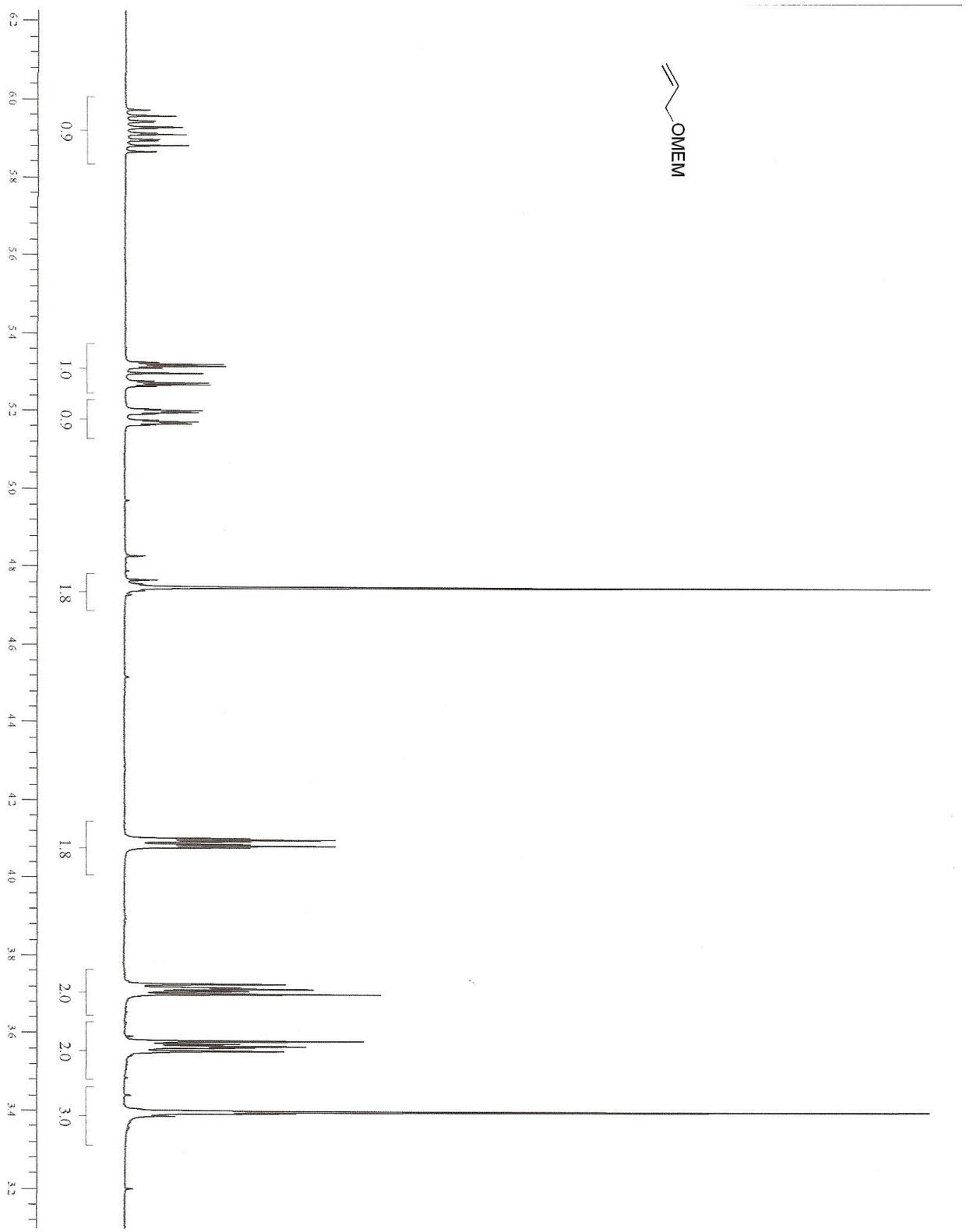
The ^{1}H NMR Spectrum (360 MHz, $CDCl_3$) of Compound **104**



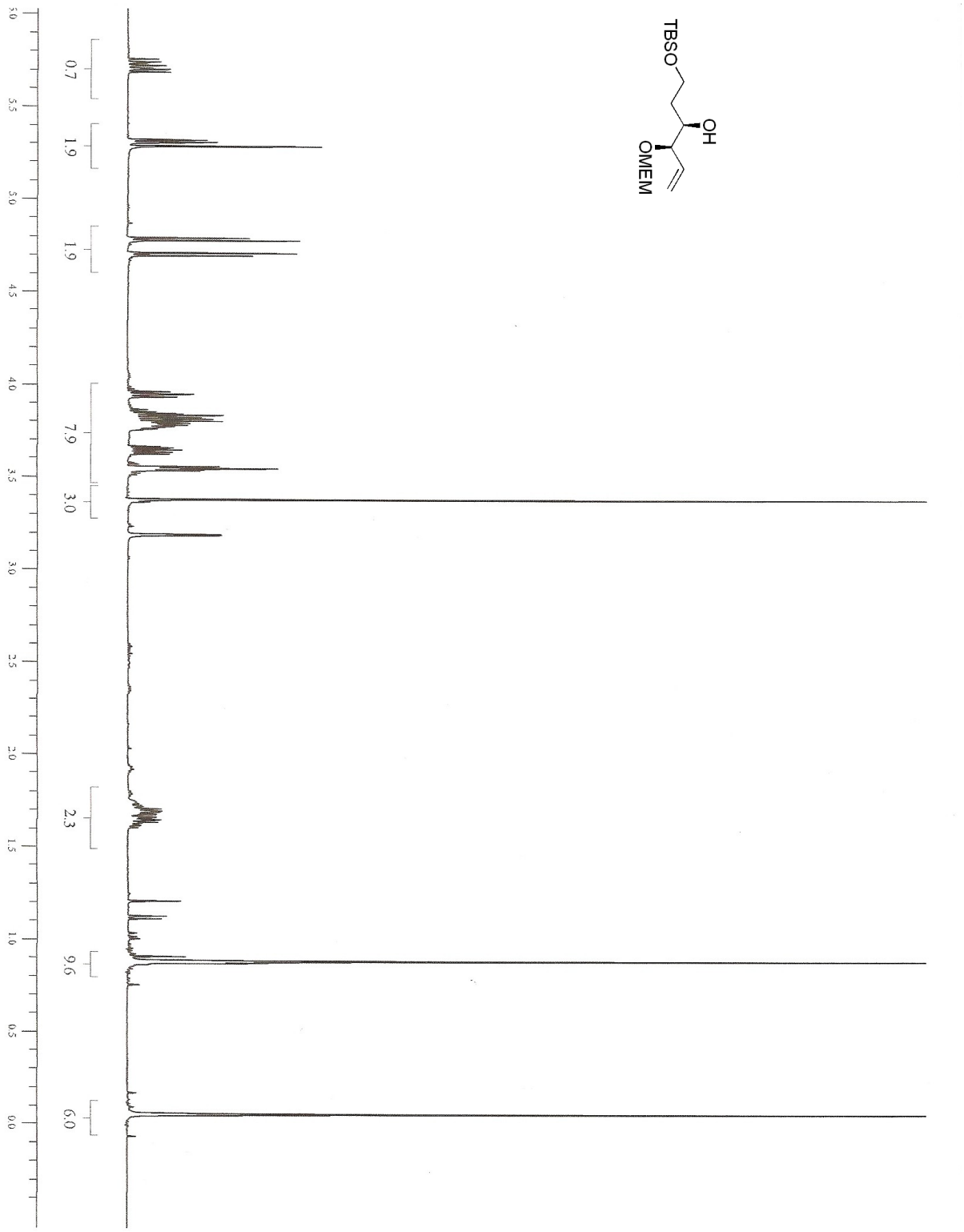
The ^{13}C NMR Spectrum (90 MHz, $CDCl_3$) of Compound **104**



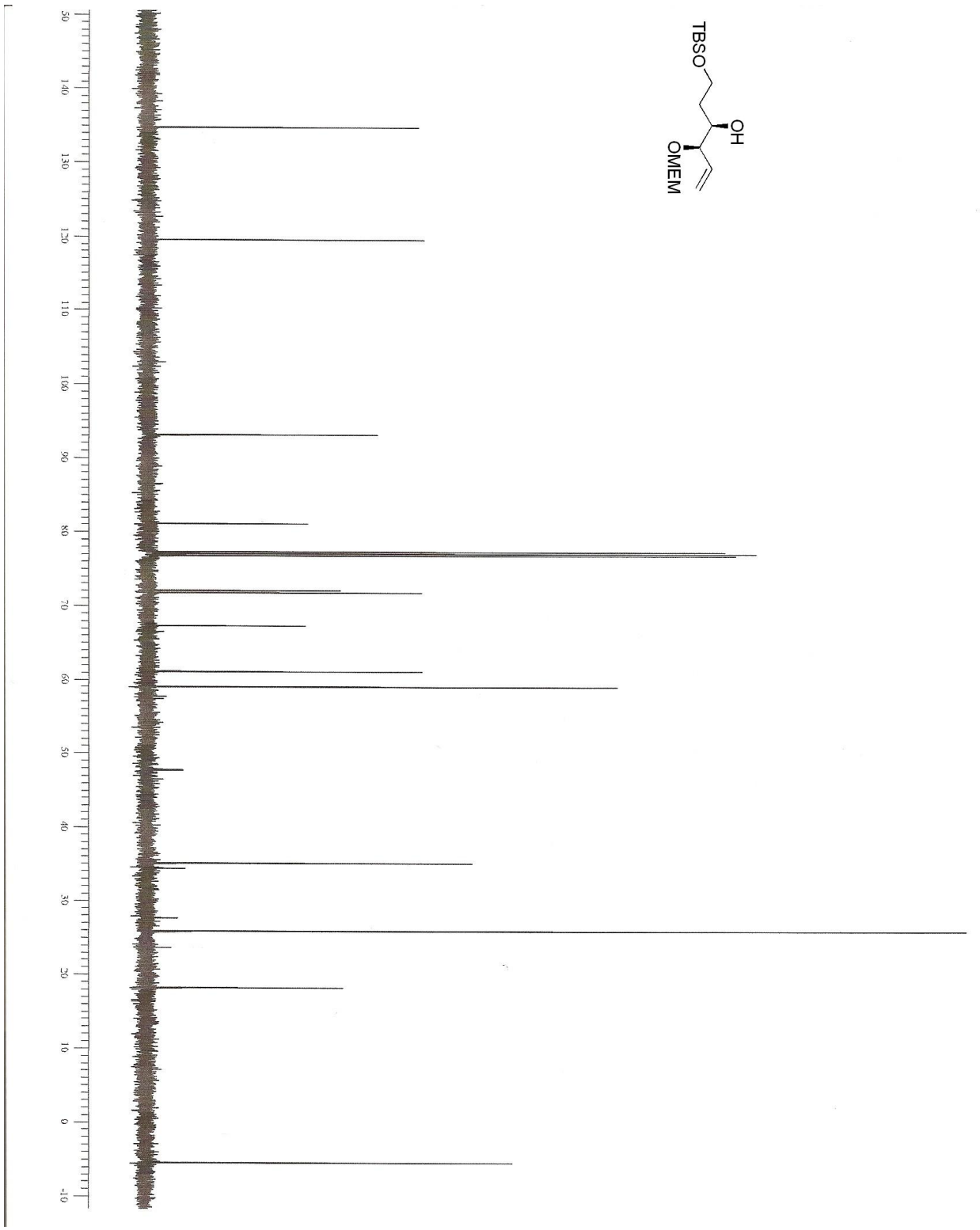
The ^{1}H NMR Spectrum (500 MHz, $CDCl_3$) of Compound **166**



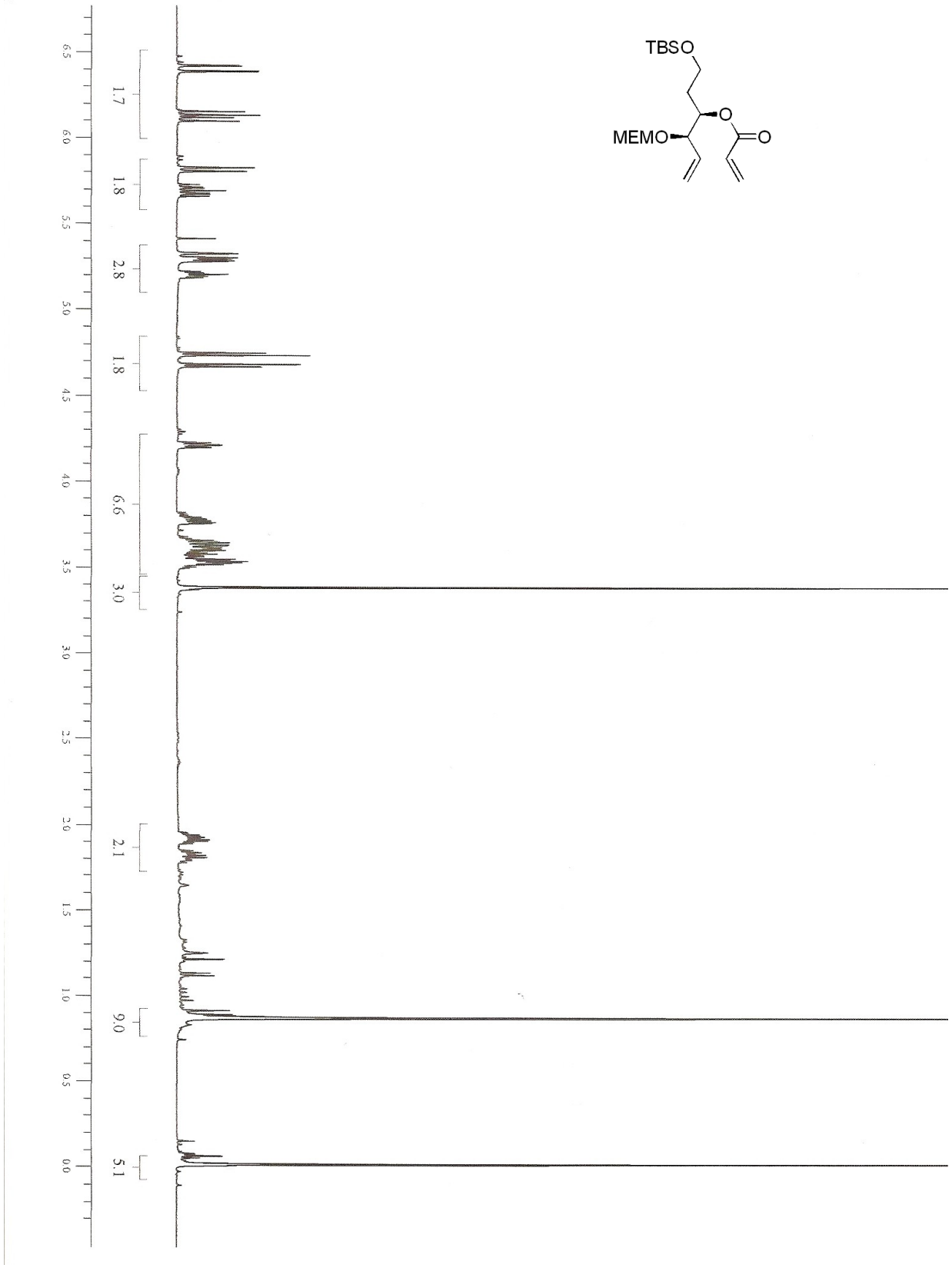
The ^{1}H NMR Spectrum (500 MHz, $CDCl_3$) of Compound **168**



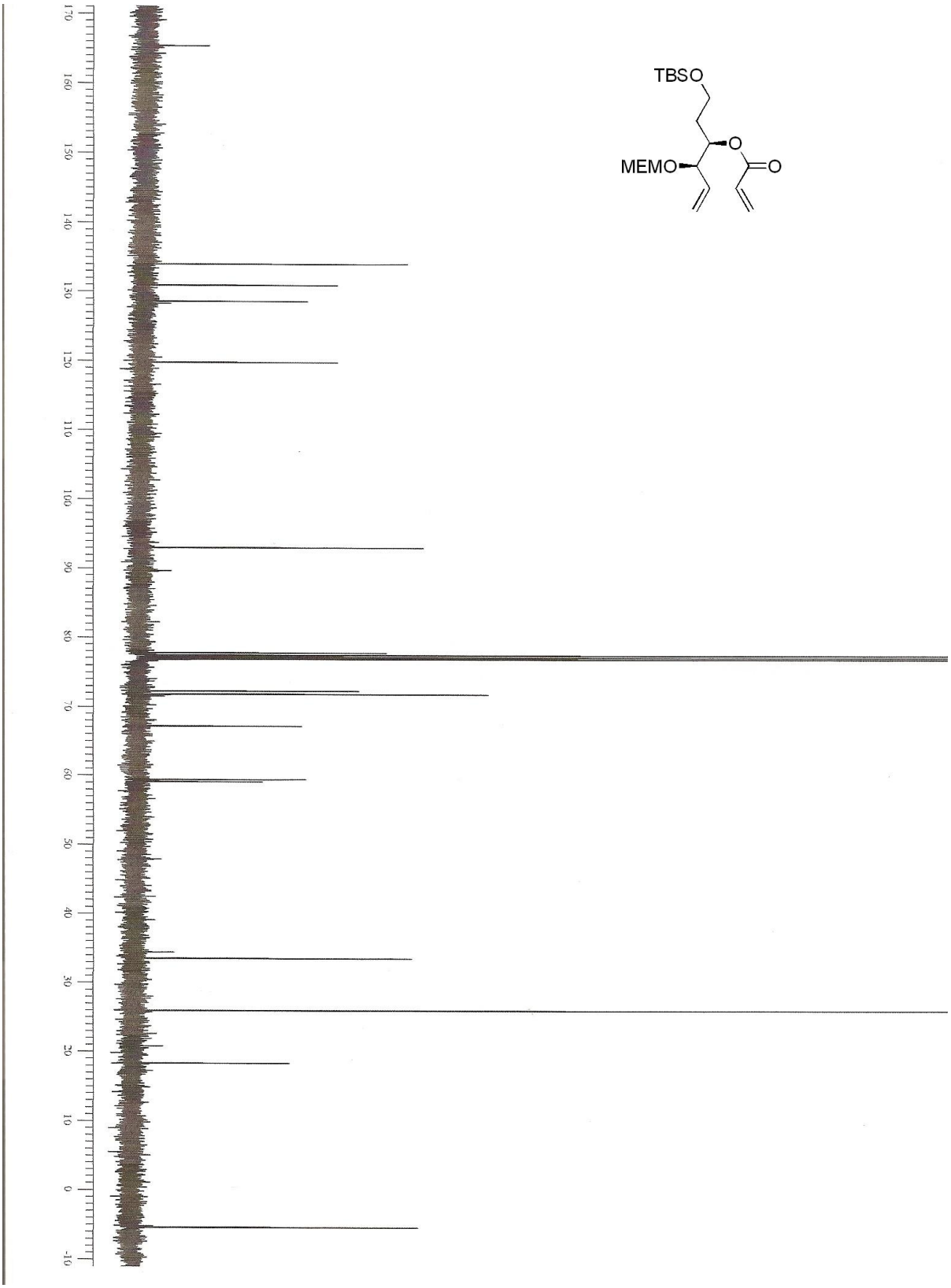
The ^{1}H NMR Spectrum (500 MHz, $CDCl_3$) of Compound **170**



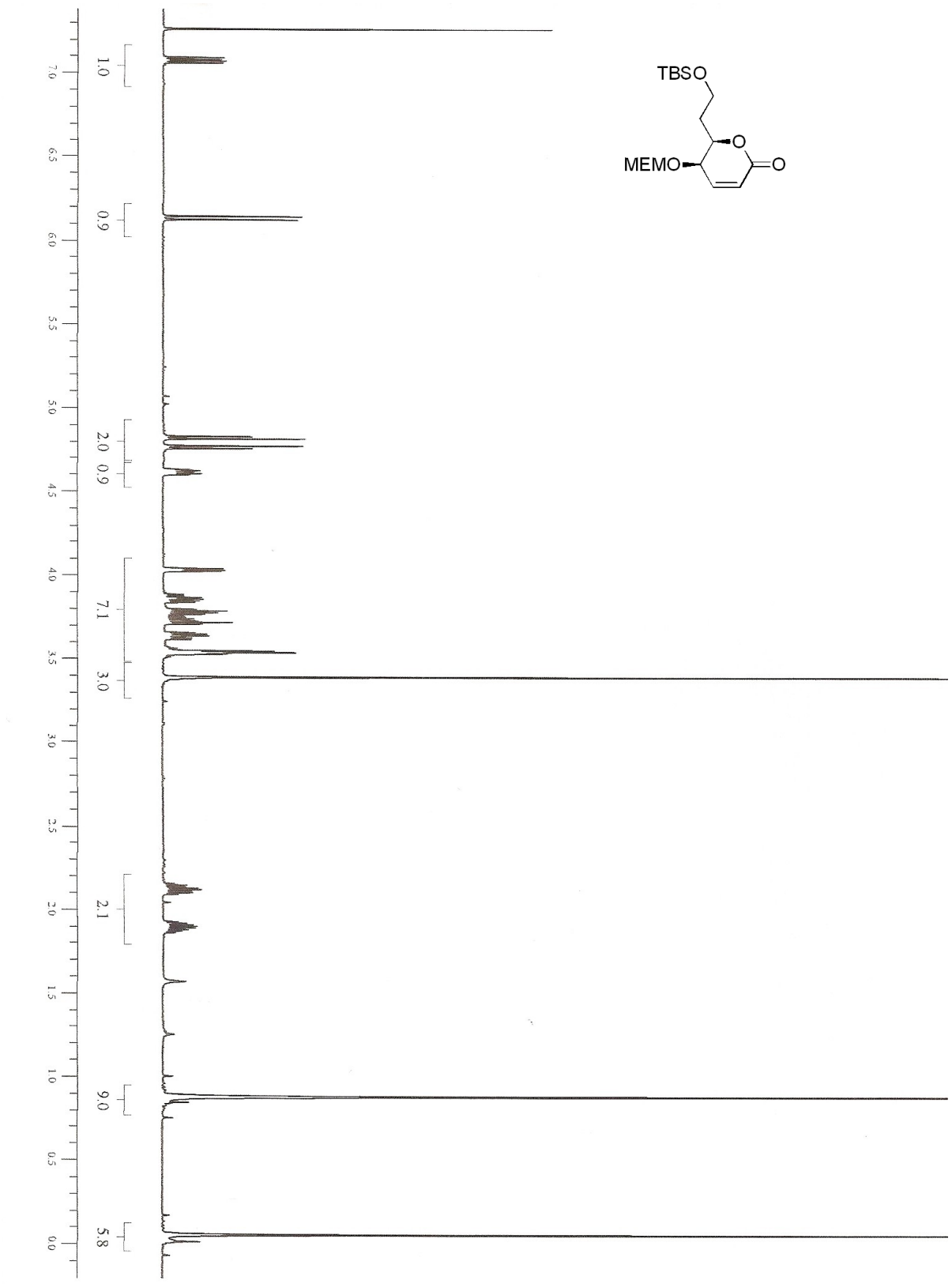
The ^{13}C NMR Spectrum (125 MHz, $CDCl_3$) of Compound **170**



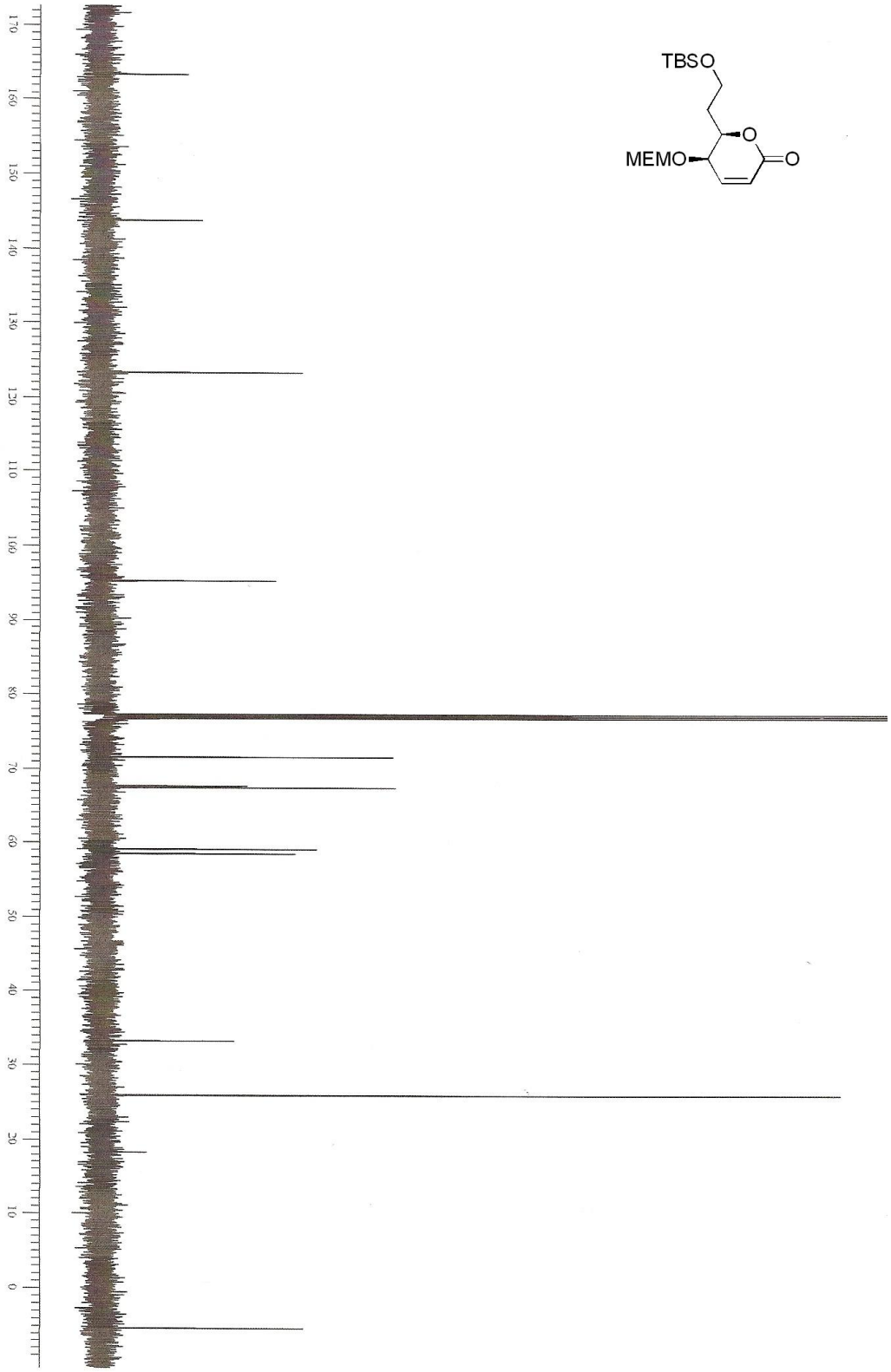
The ^{1}H NMR Spectrum (500 MHz, $CDCl_3$) of Compound **171**



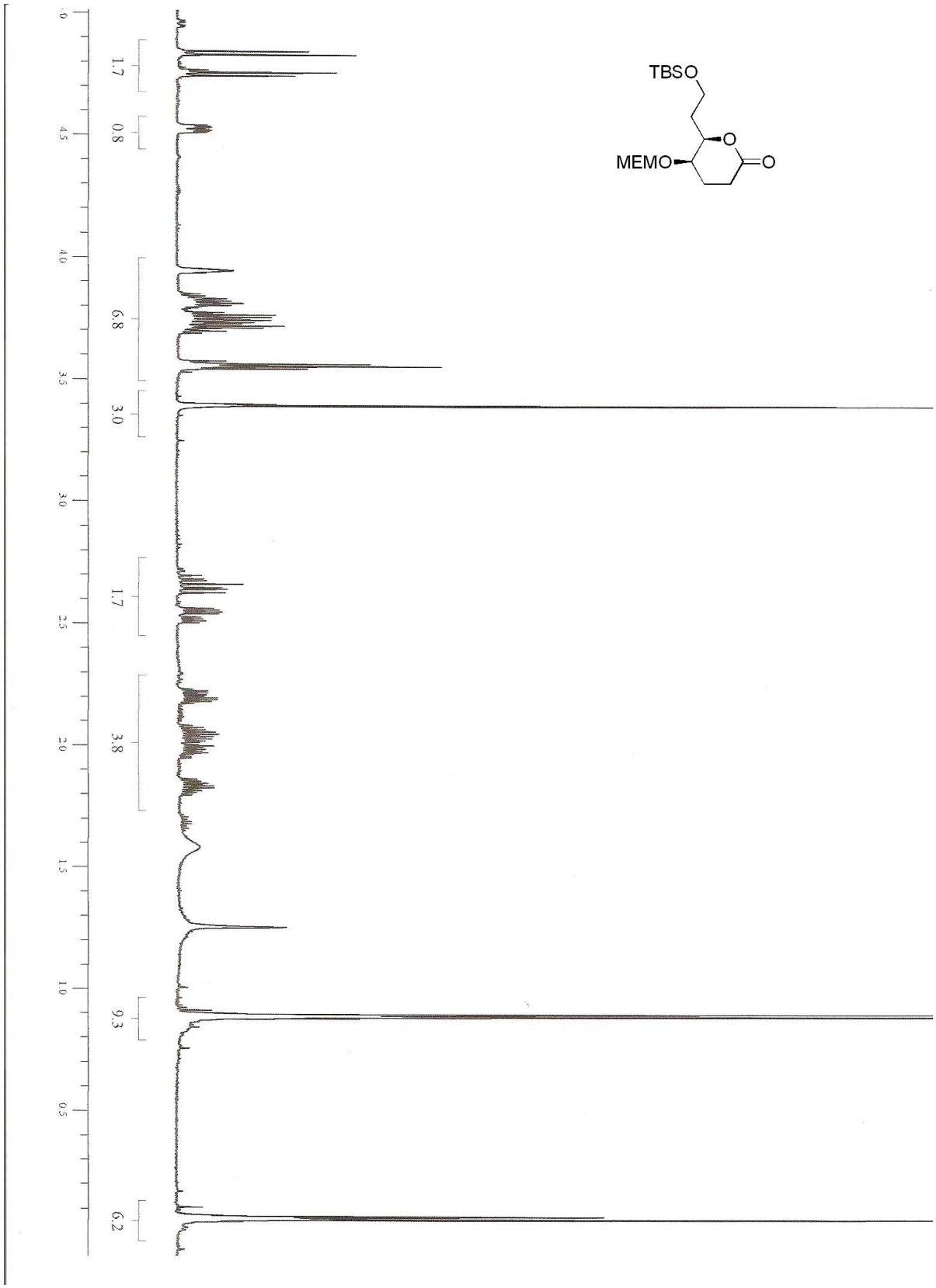
The ^{13}C NMR Spectrum (125 MHz, $CDCl_3$) of Compound **171**



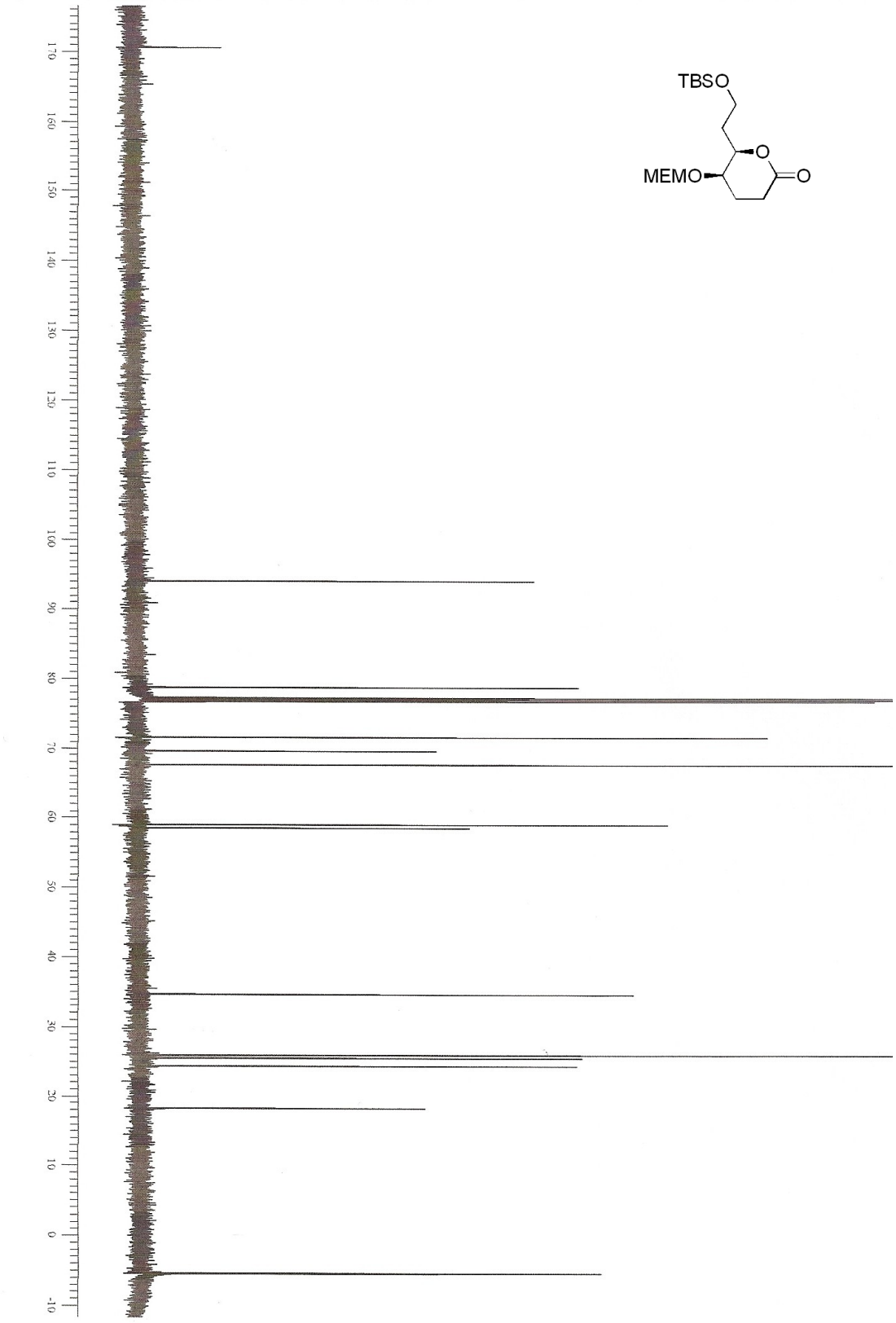
The ^{1}H NMR Spectrum (500 MHz, $CDCl_3$) of Compound **173**



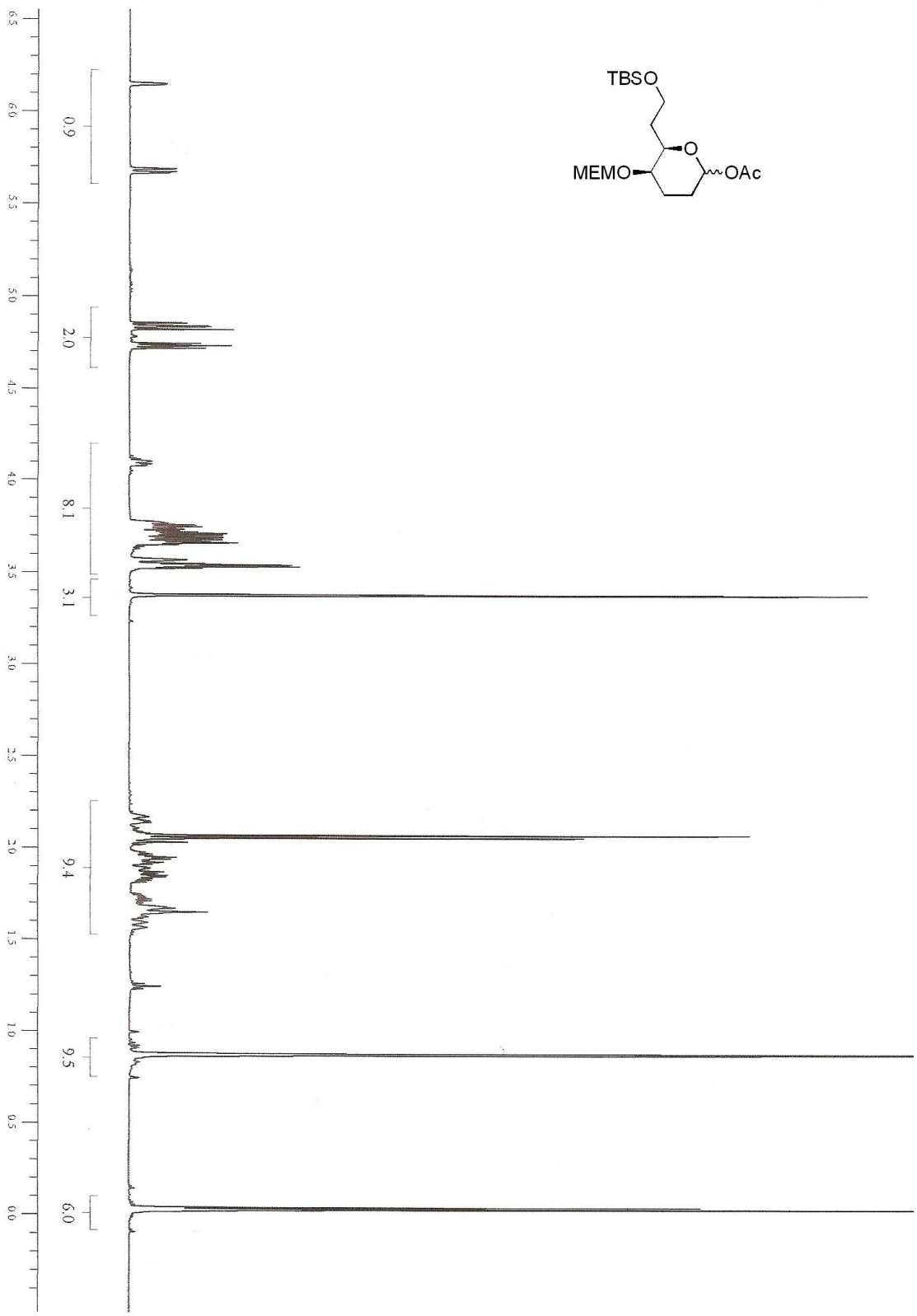
The ^{13}C NMR Spectrum (125 MHz, $CDCl_3$) of Compound **173**



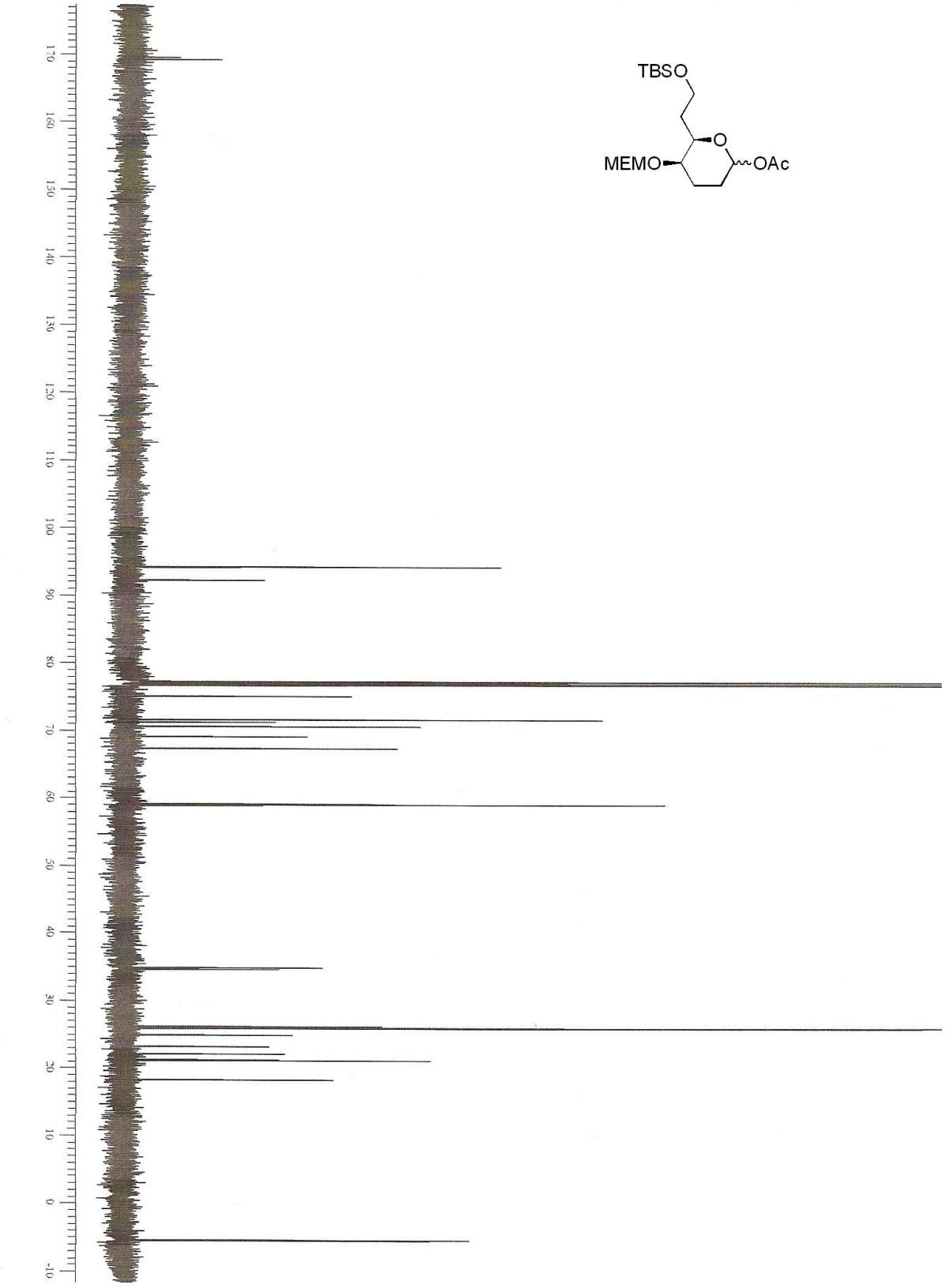
The ^{1}H NMR Spectrum (500 MHz, $CDCl_3$) of Compound **174**



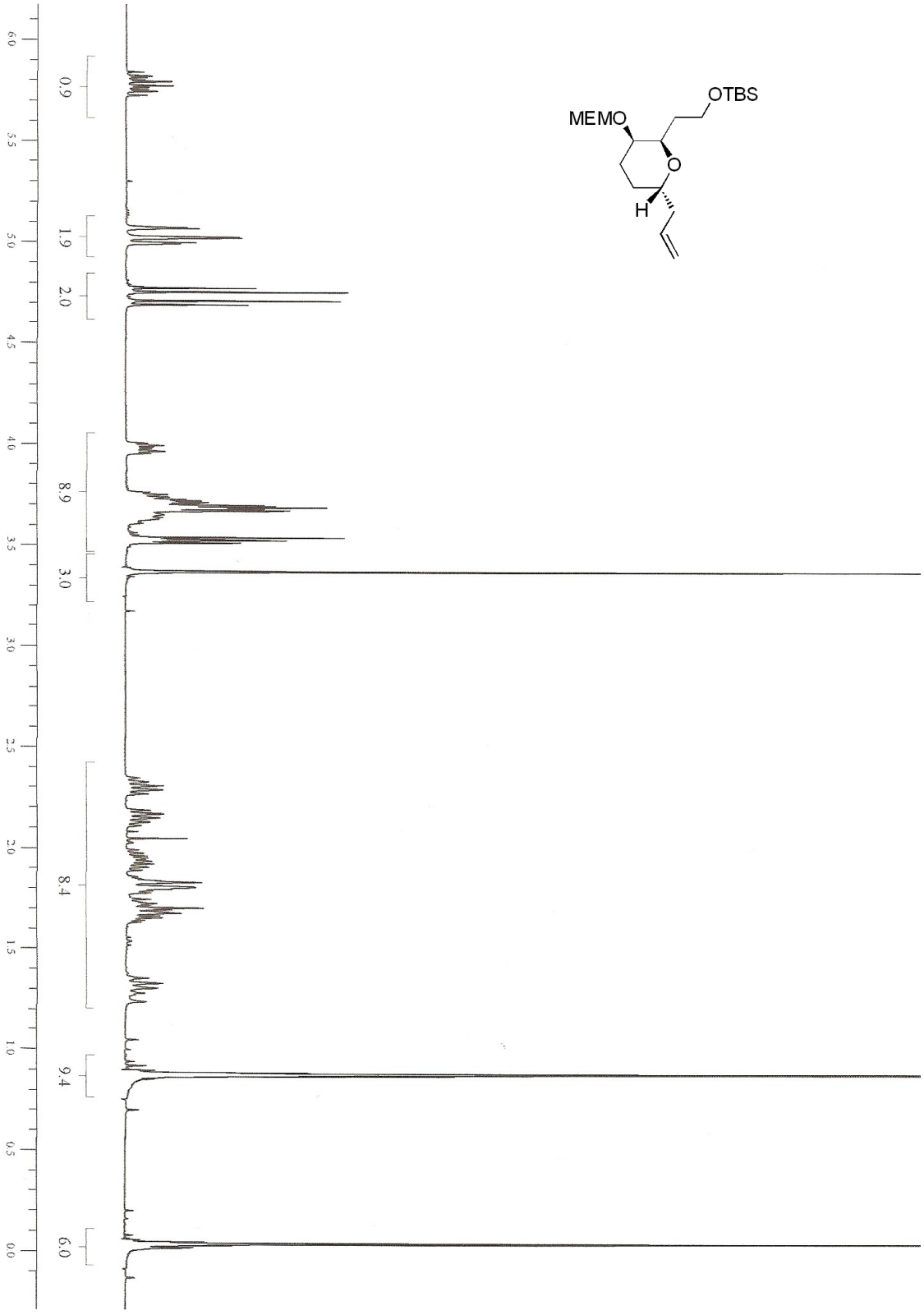
The ^{13}C NMR Spectrum (125 MHz, $CDCl_3$) of Compound **174**



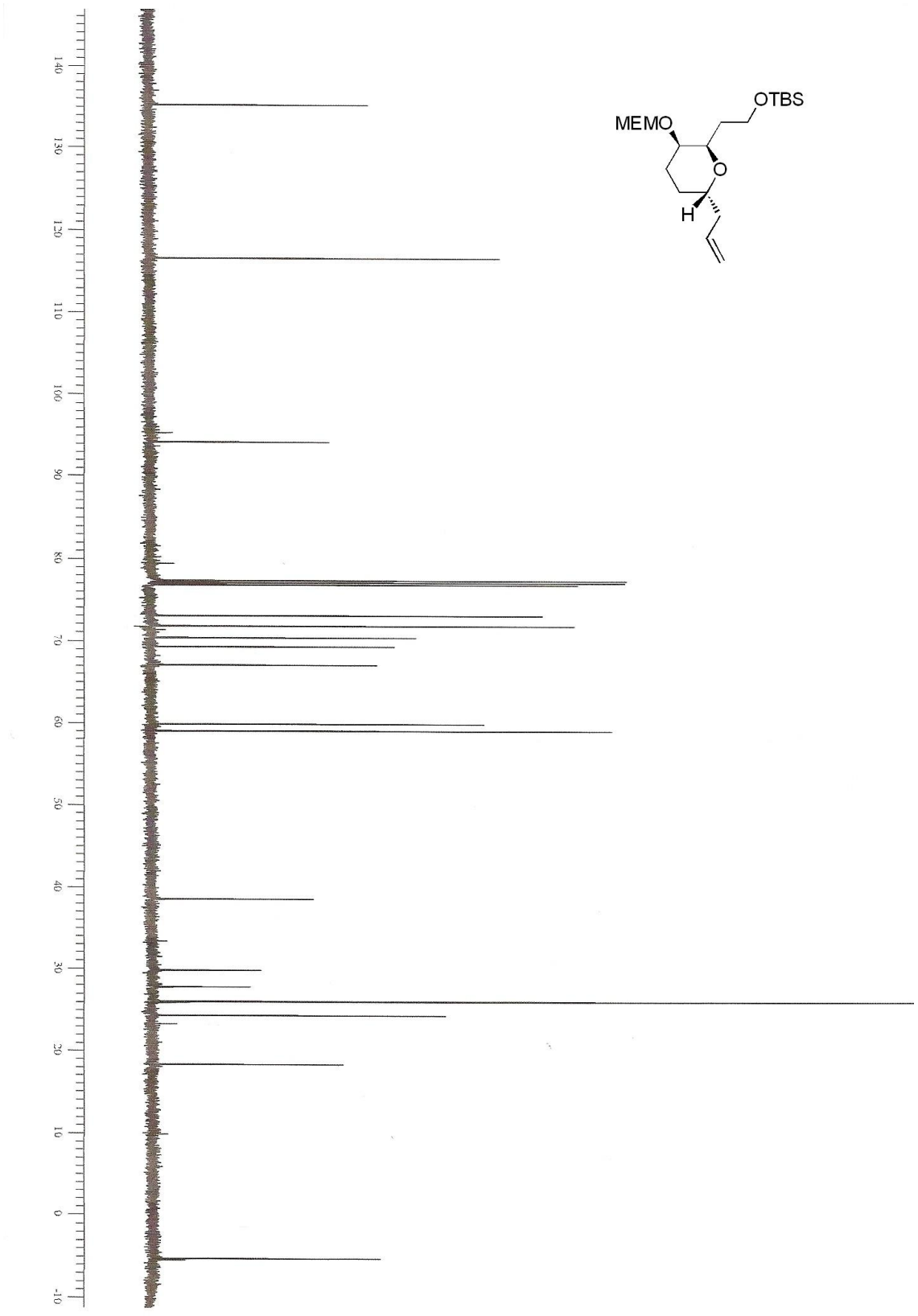
The ^{1}H NMR Spectrum (500 MHz, $CDCl_3$) of Compound **175**



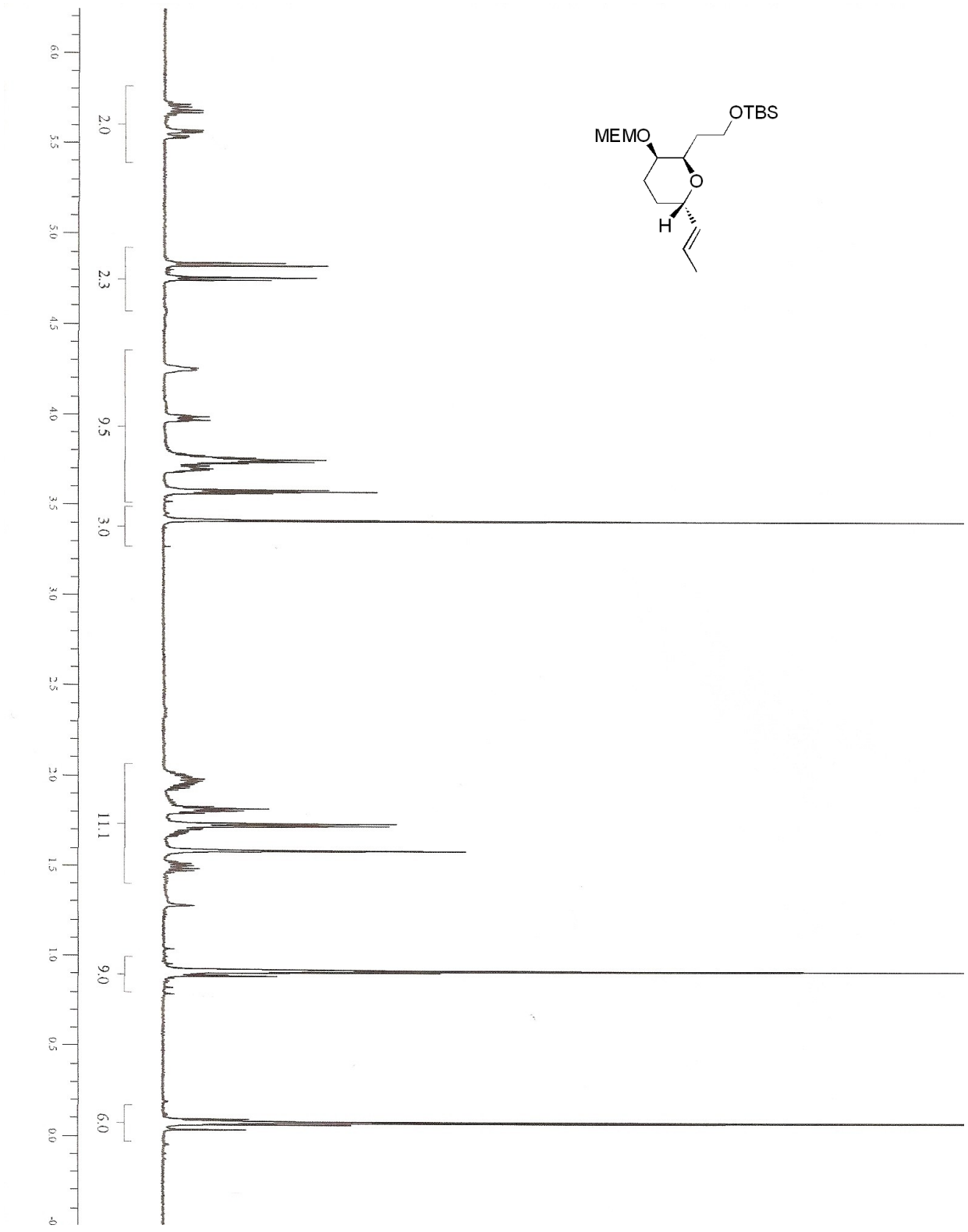
The ^{13}C NMR Spectrum (125 MHz, $CDCl_3$) of Compound **175**



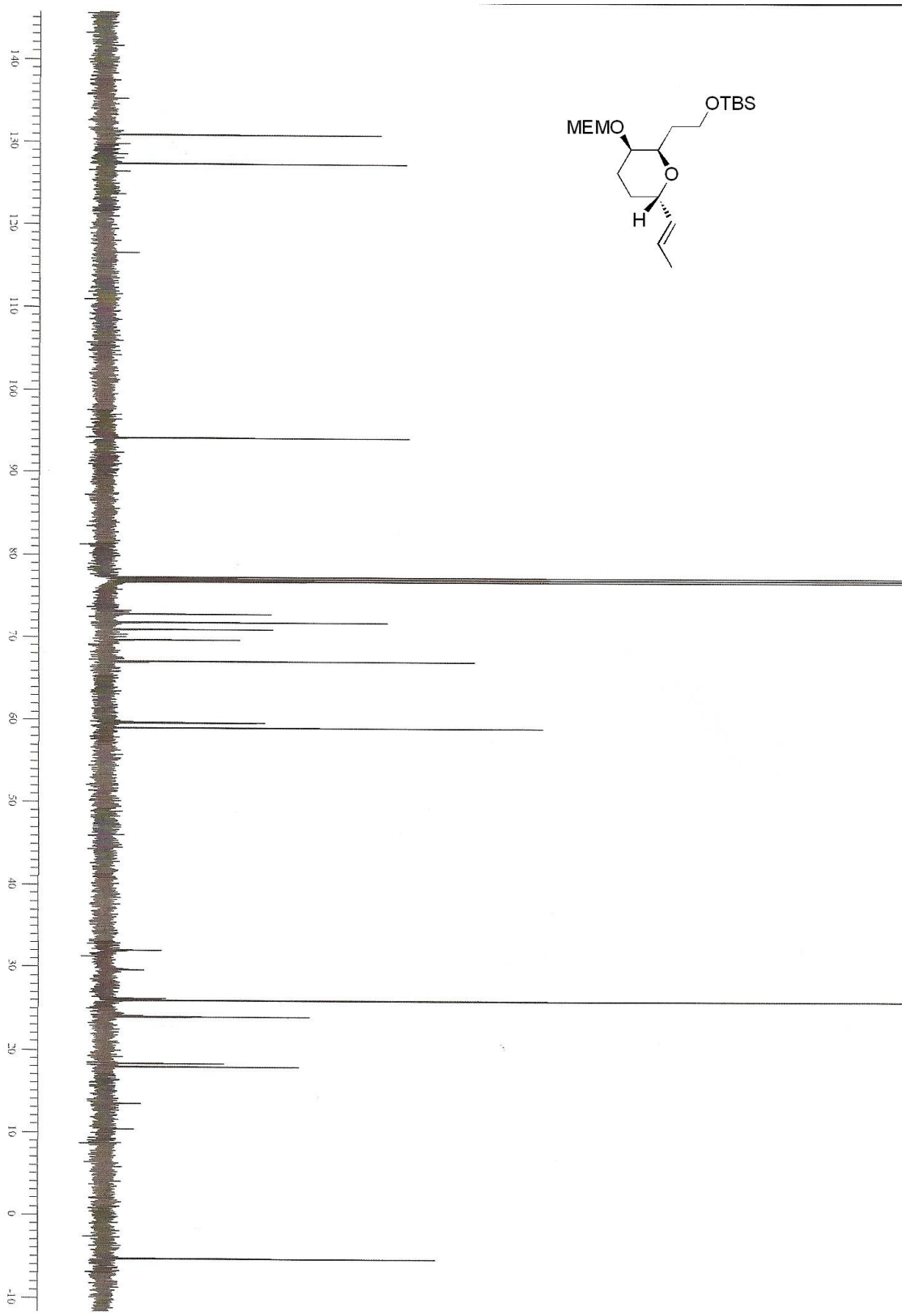
The ^{1}H NMR Spectrum (500 MHz, $CDCl_3$) of Compound **163**



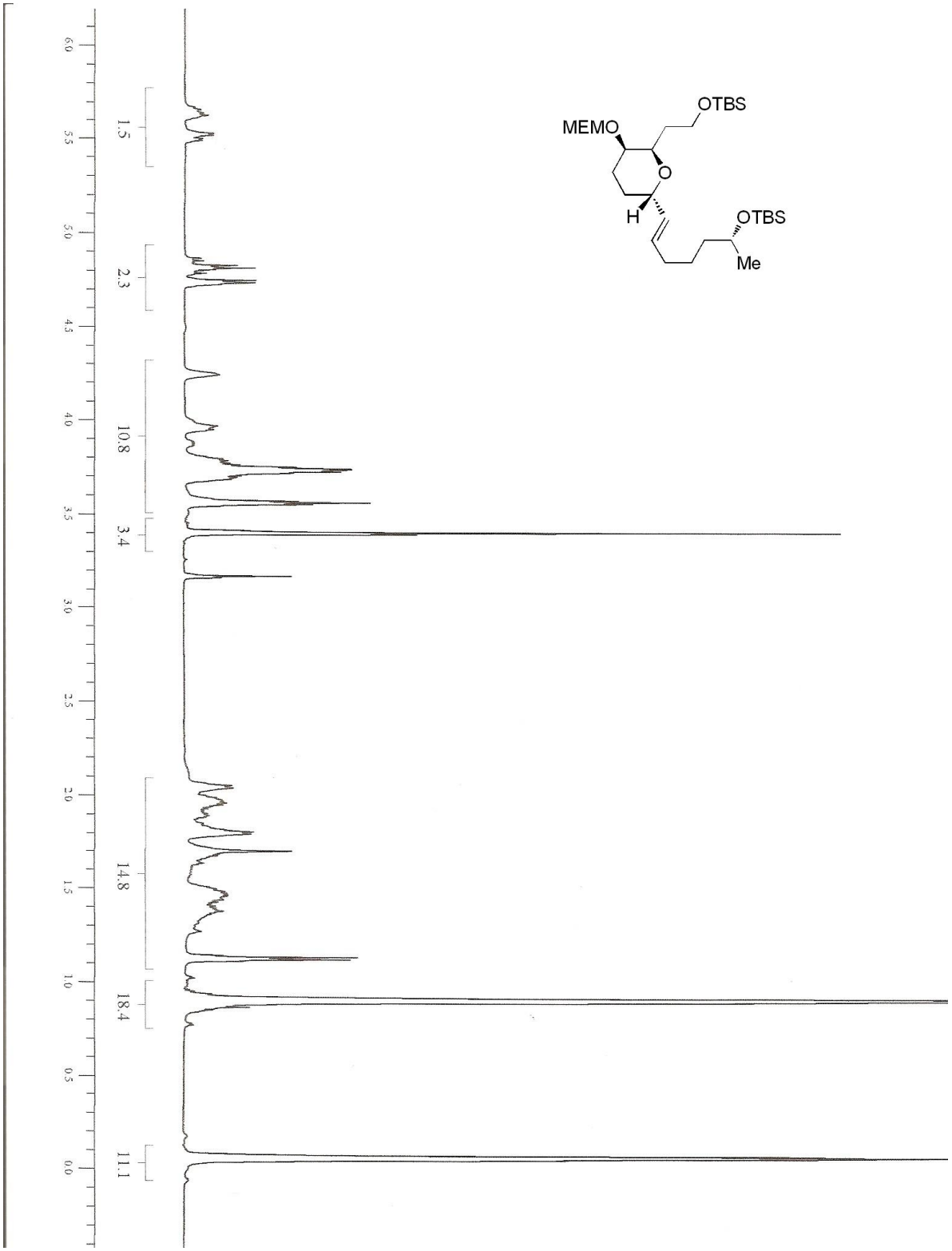
The ^{13}C NMR Spectrum (125 MHz, $CDCl_3$) of Compound **163**



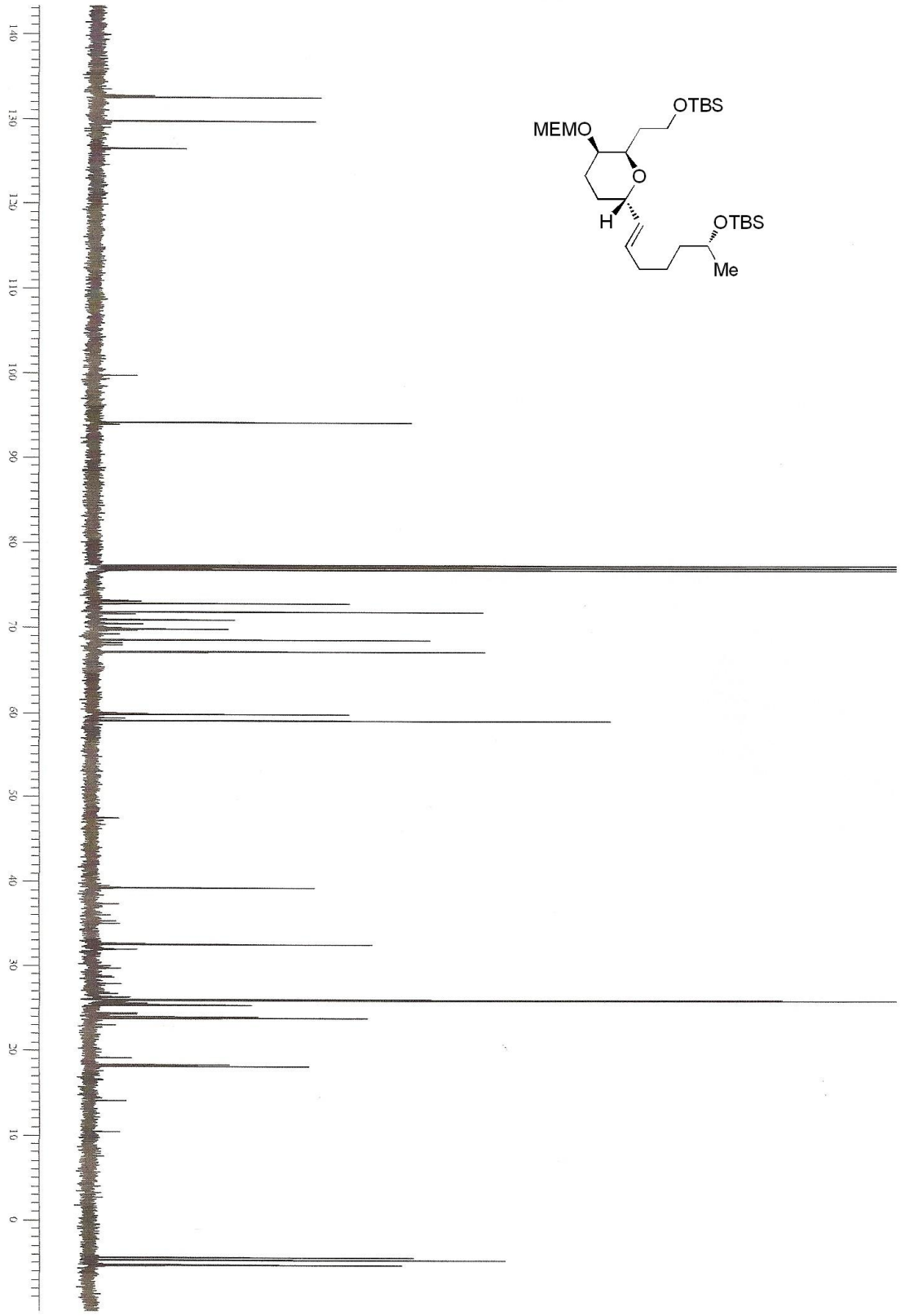
The ^{1}H NMR Spectrum (500 MHz, $CDCl_3$) of Compound **162**



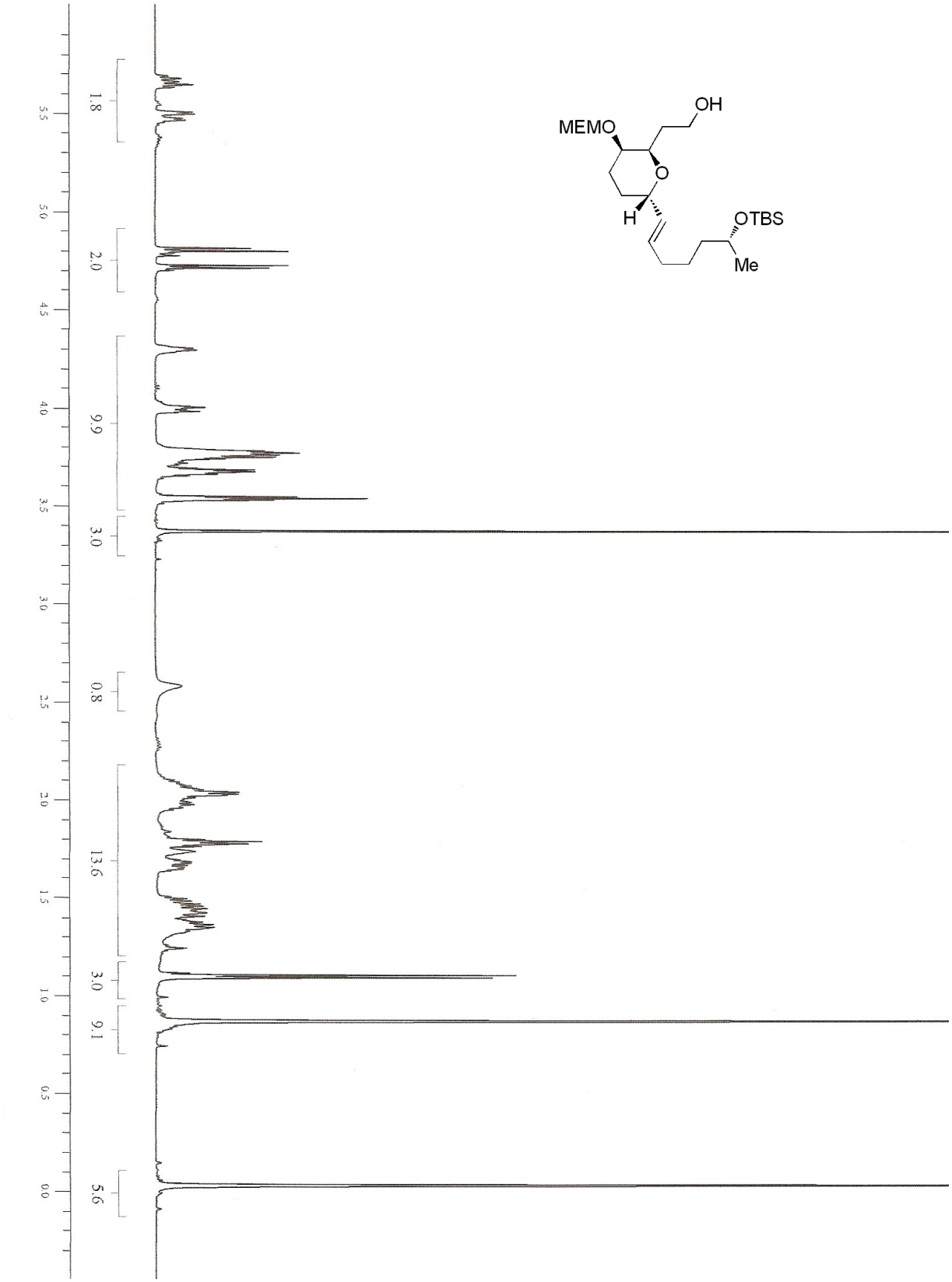
The ^{13}C NMR Spectrum (125 MHz, $CDCl_3$) of Compound **162**



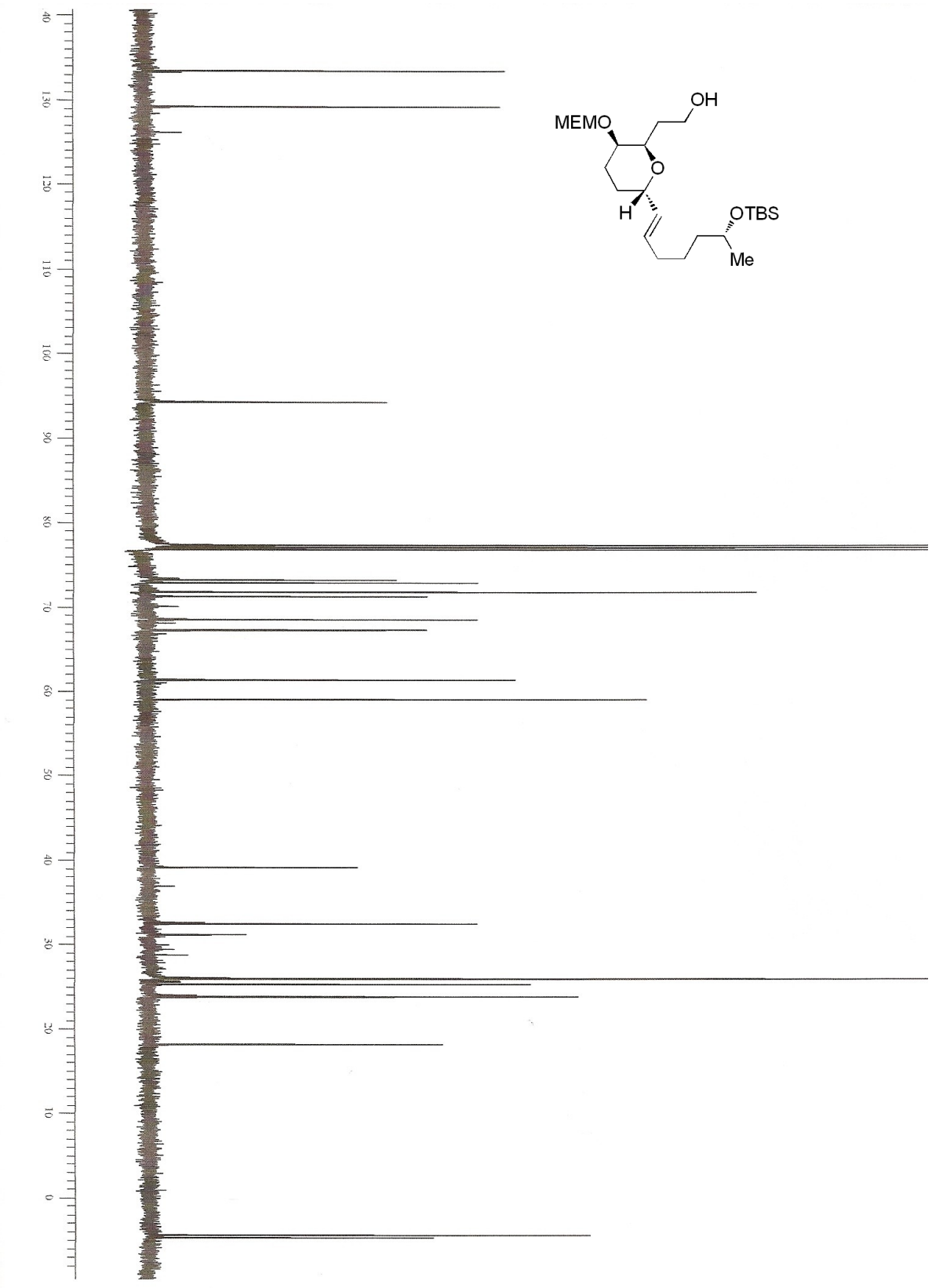
The ^{1}H NMR Spectrum (500 MHz, $CDCl_3$) of Compound **161**



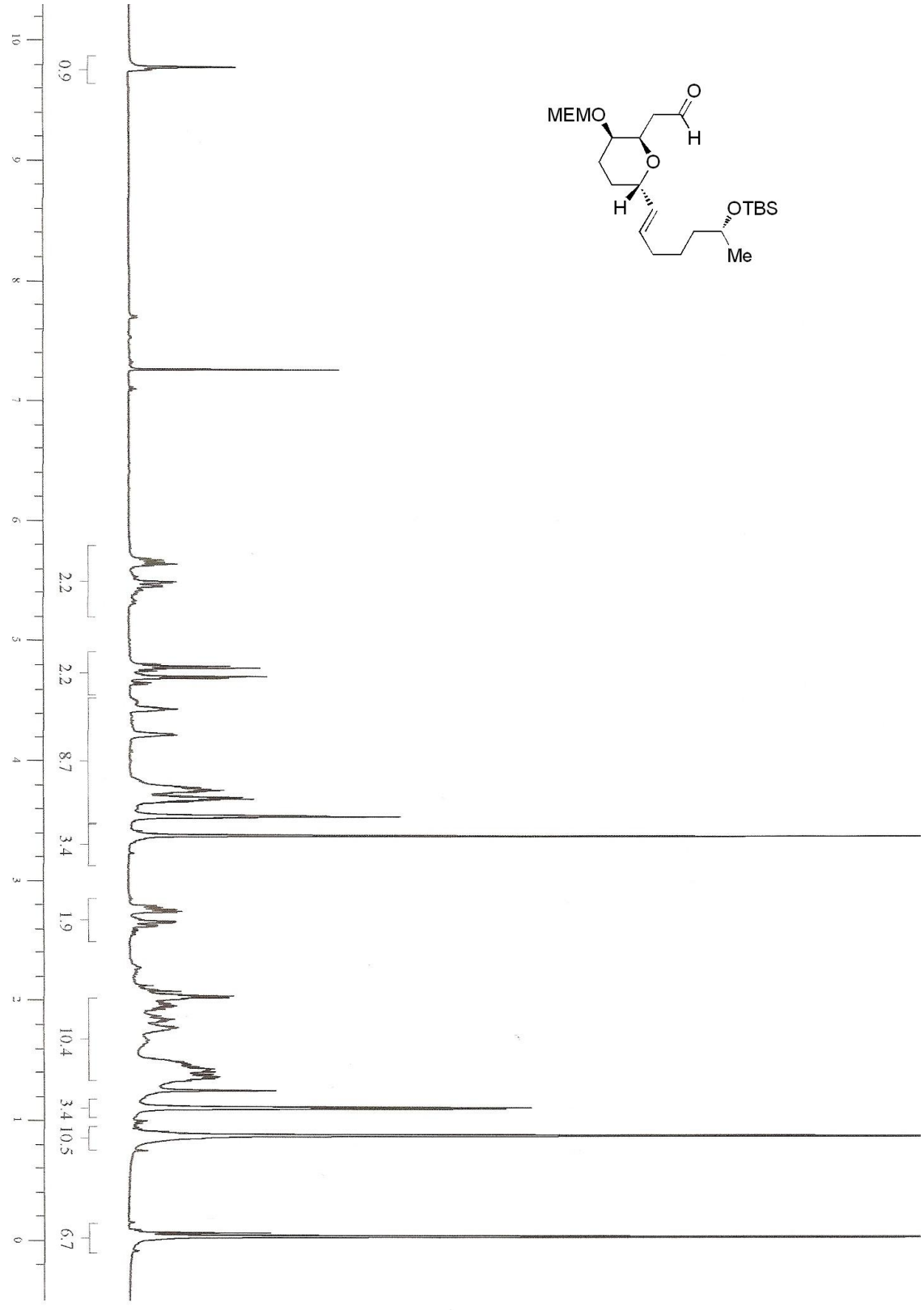
The ^{13}C NMR Spectrum (125 MHz, $CDCl_3$) of Compound **161**



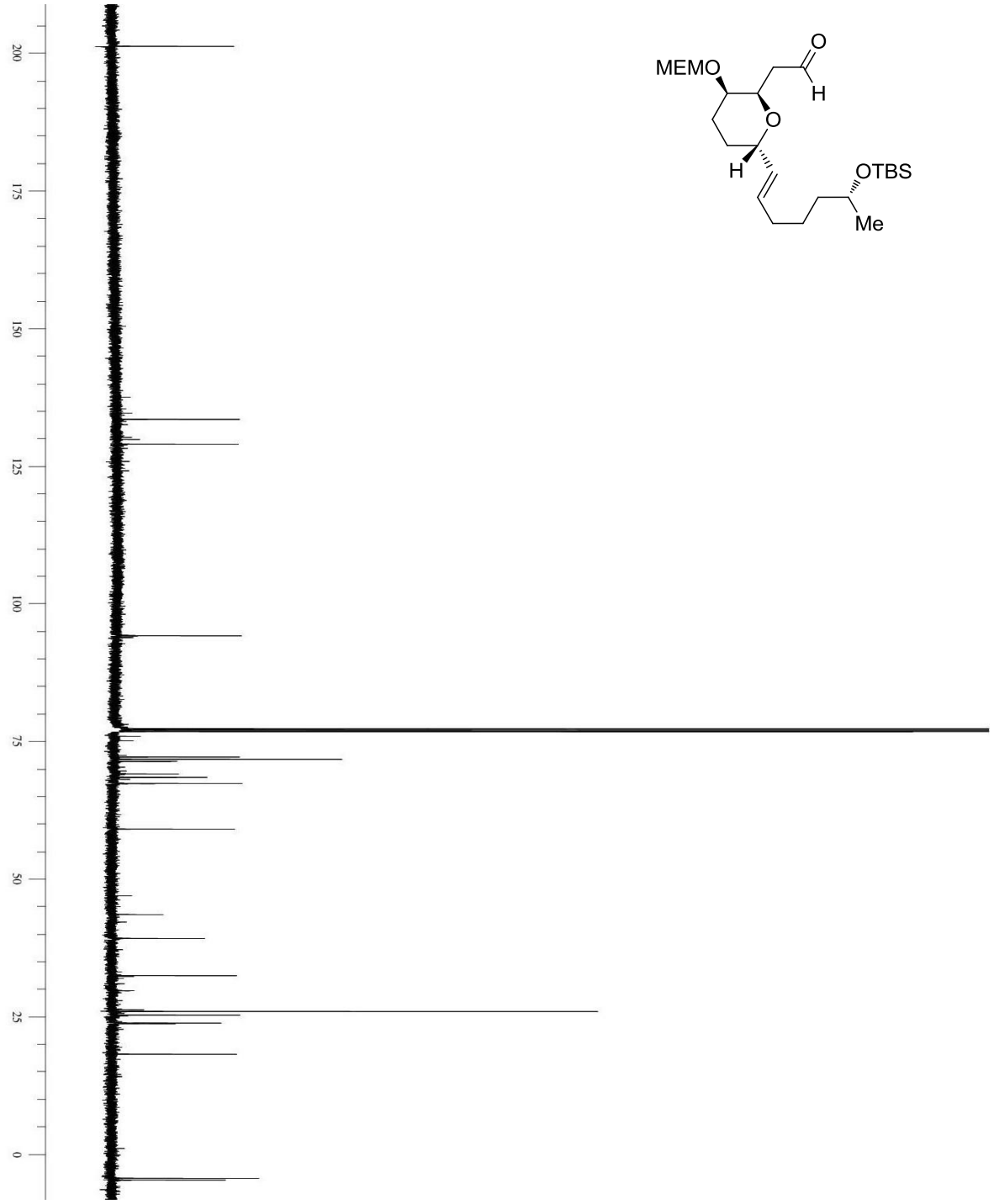
The ^{1}H NMR Spectrum (500 MHz, $CDCl_3$) of Compound **178**



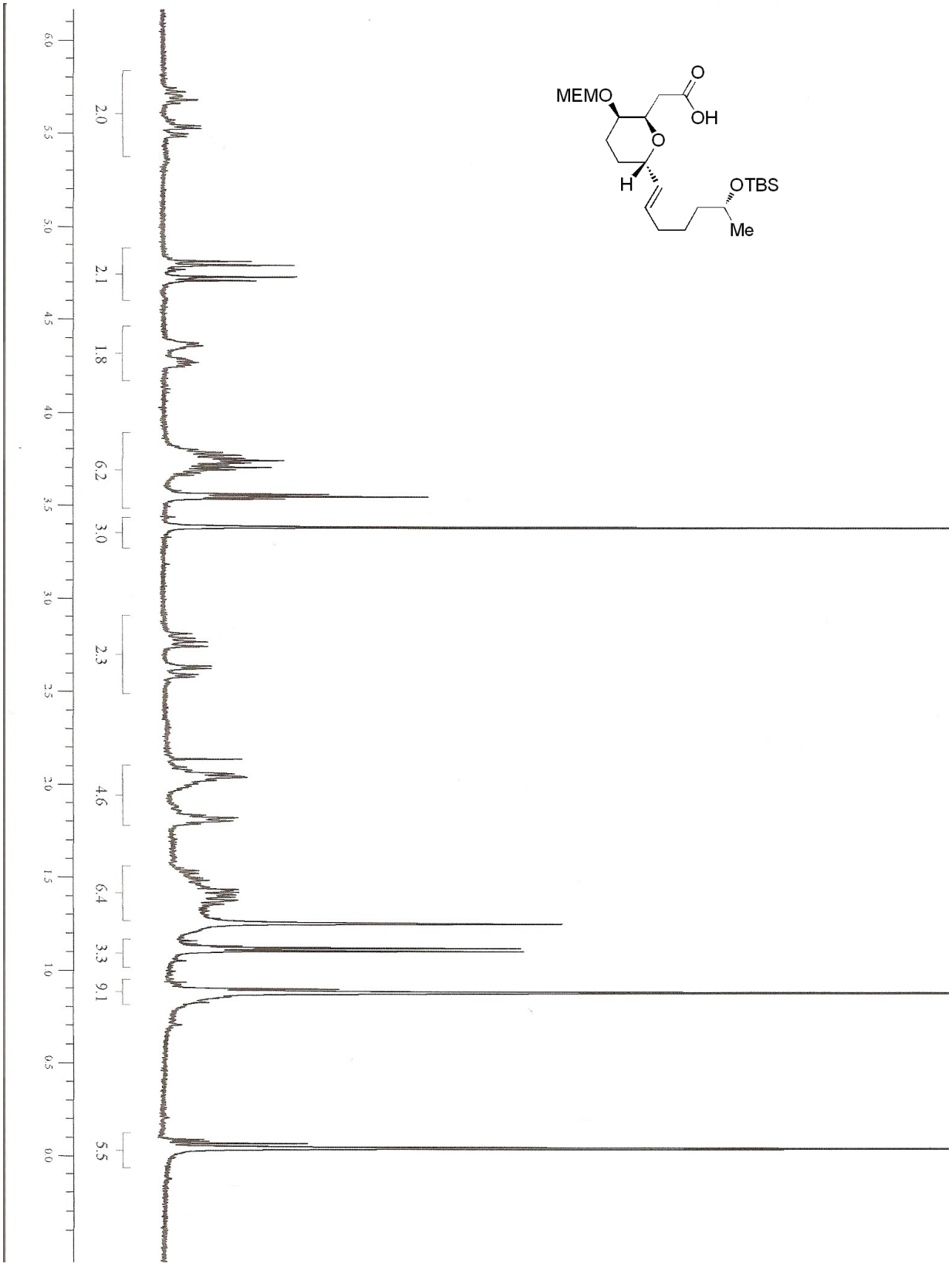
The ^{13}C NMR Spectrum (125 MHz, $CDCl_3$) of Compound **178**



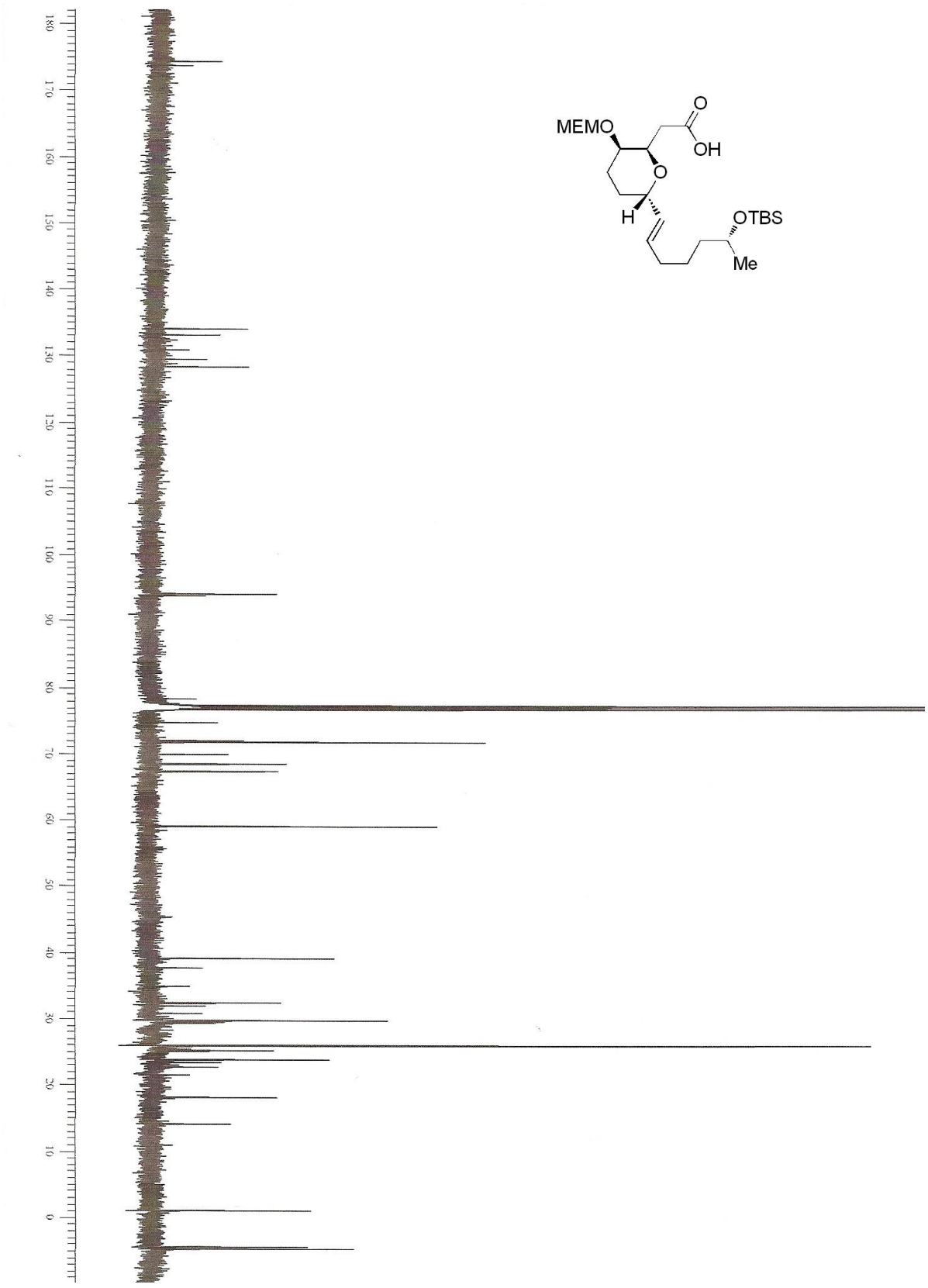
The ^{1}H NMR Spectrum (500 MHz, $CDCl_3$) of Compound **179**



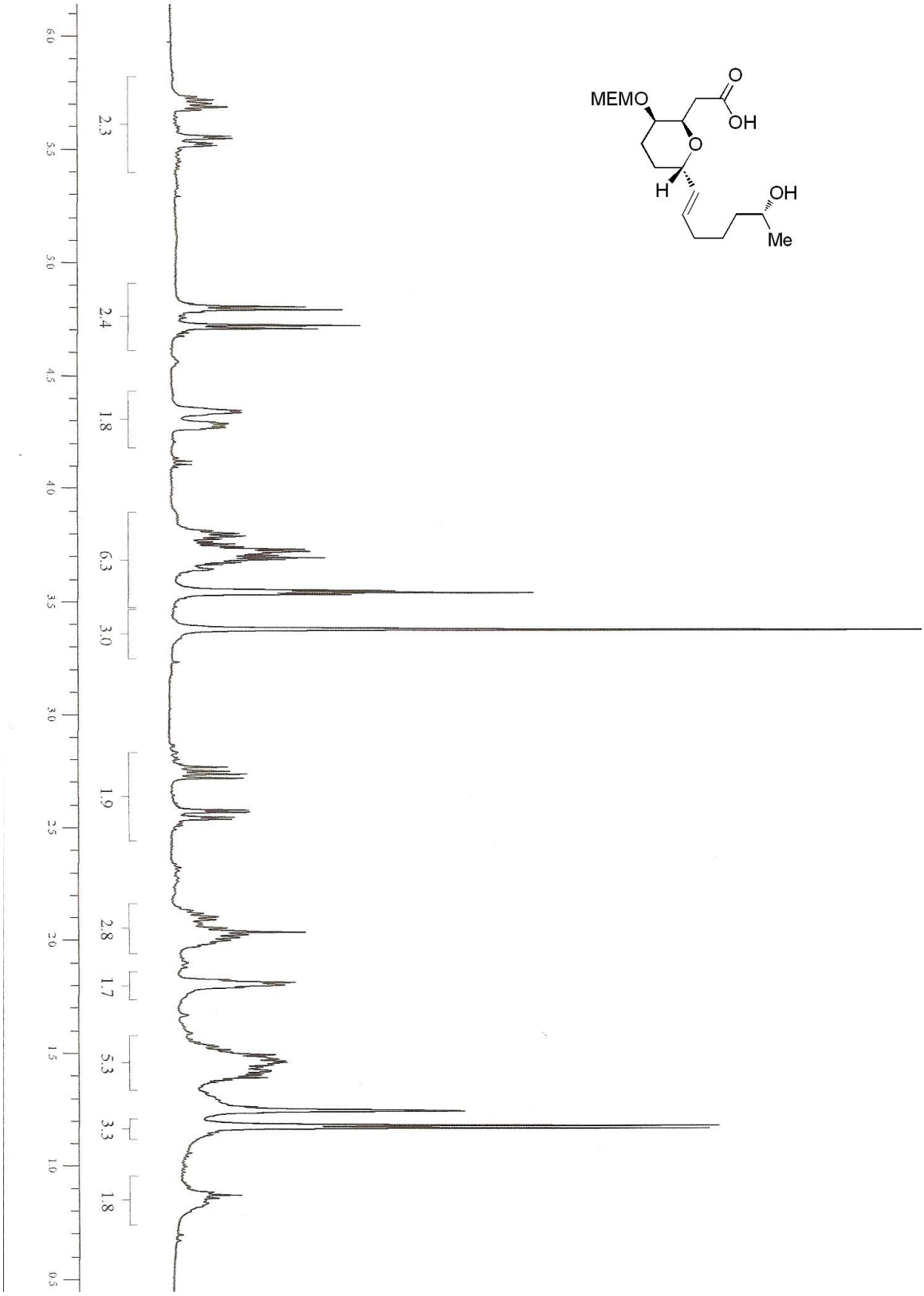
The ^{13}C NMR Spectrum (125 MHz, $CDCl_3$) of Compound **179**



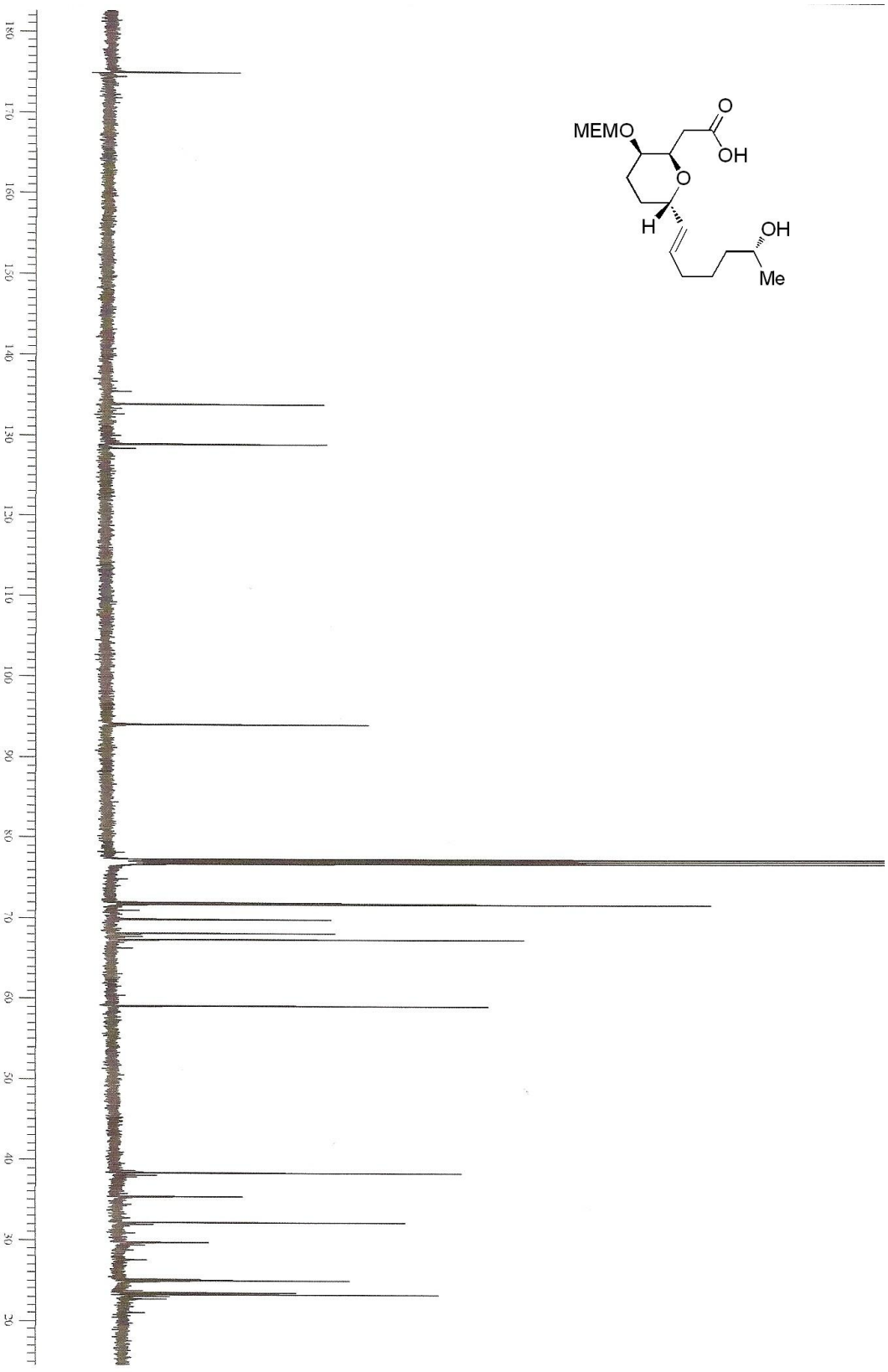
The ^{1}H NMR Spectrum (500 MHz, $CDCl_3$) of Compound **160**



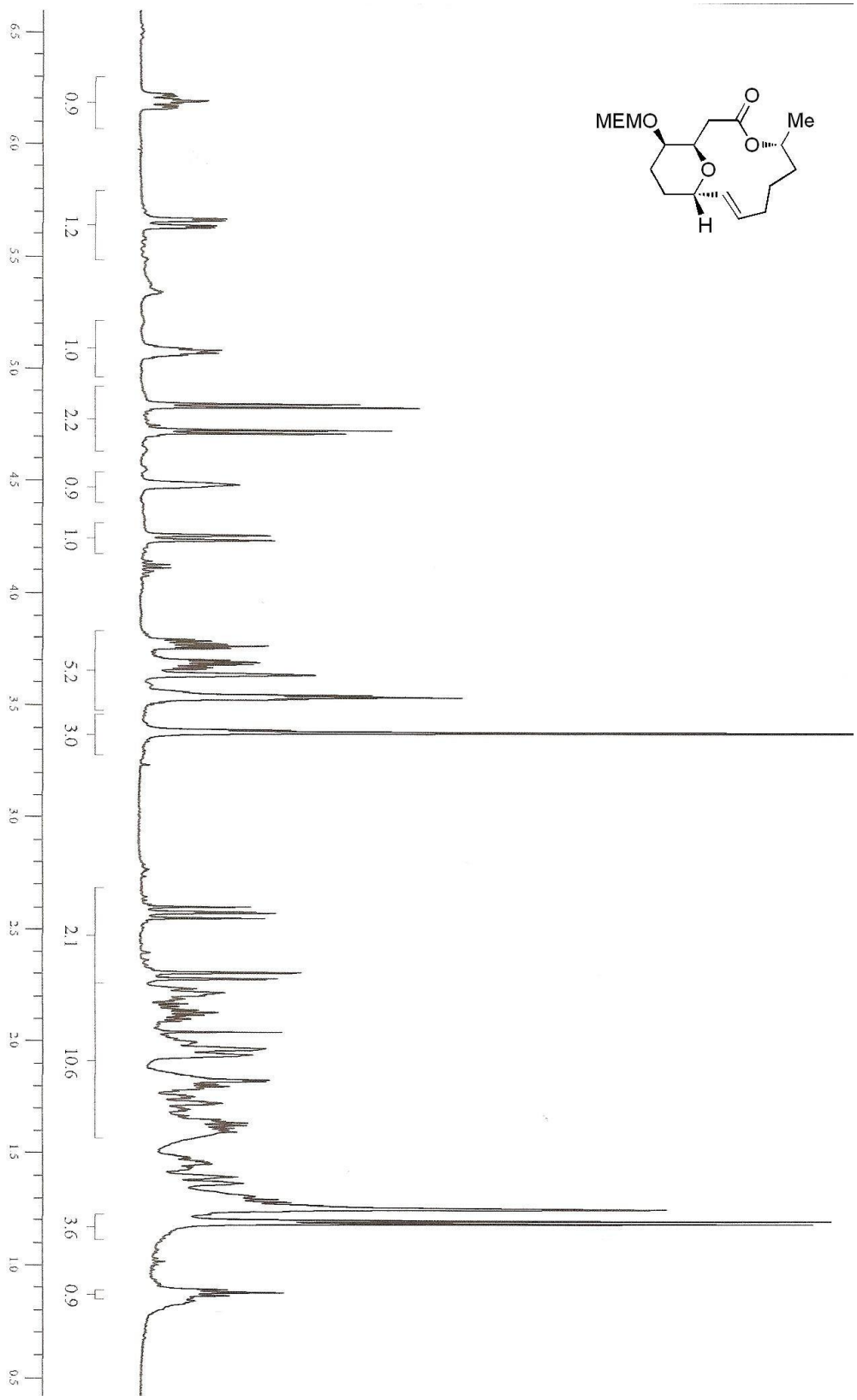
The ^{13}C NMR Spectrum (125 MHz, $CDCl_3$) of Compound **160**



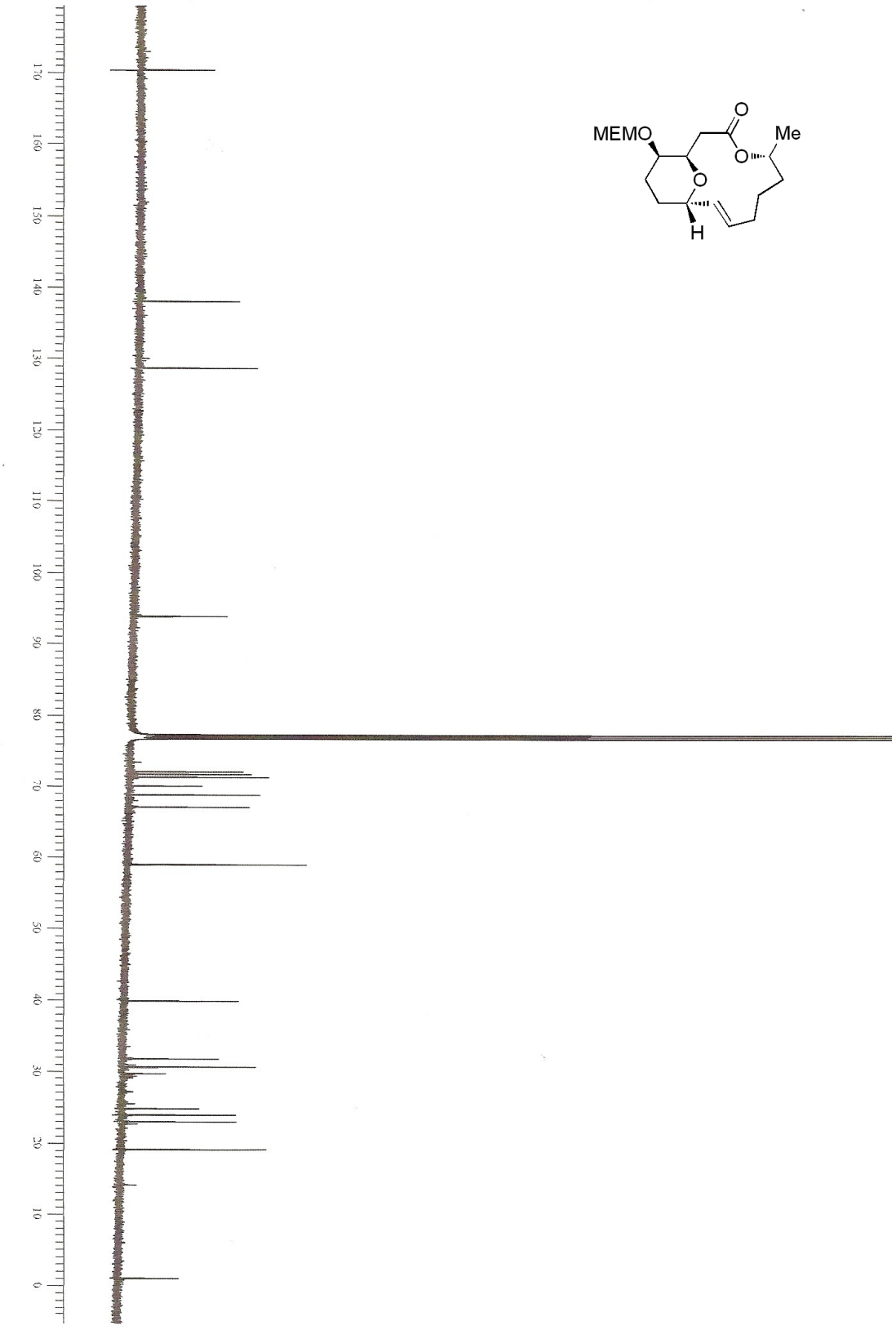
The ^{1}H NMR Spectrum (500 MHz, $CDCl_3$) of Compound **185**



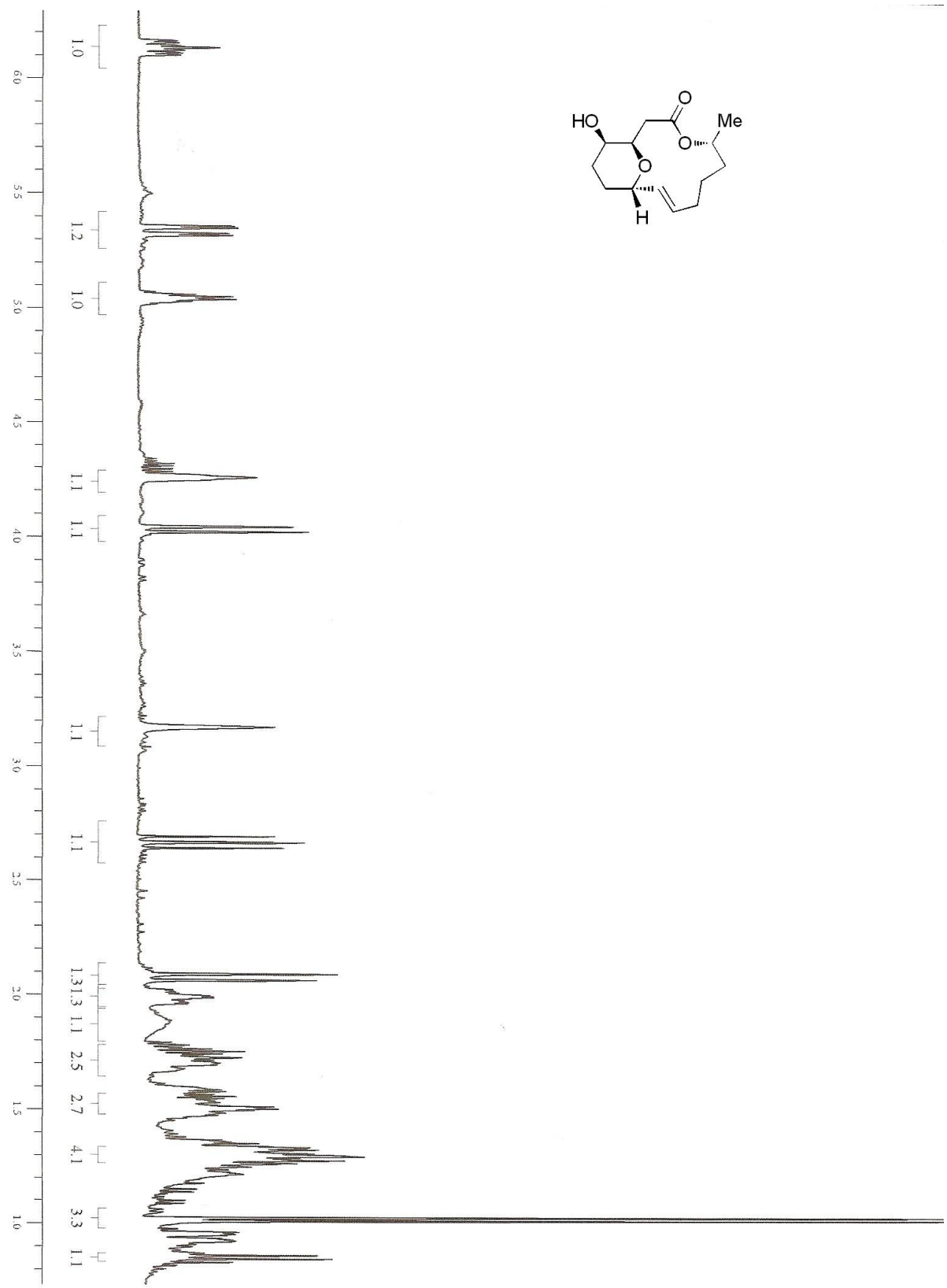
The ^{13}C NMR Spectrum (125 MHz, $CDCl_3$) of Compound **185**



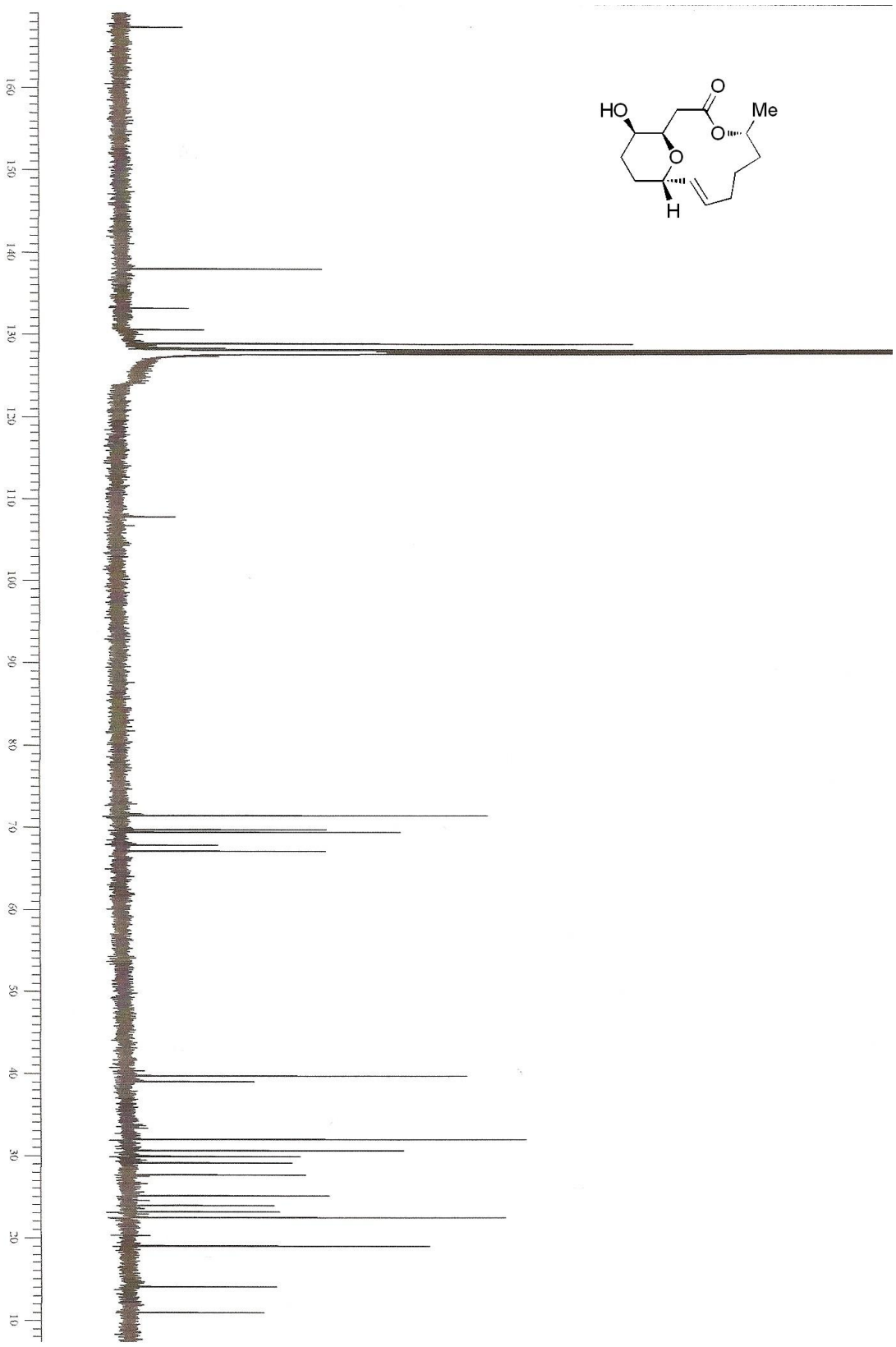
The ^{1}H NMR Spectrum (500 MHz, $CDCl_3$) of Compound **187**



The ^{13}C NMR Spectrum (125 MHz, $CDCl_3$) of Compound **187**



The ^{1}H NMR Spectrum (500 MHz, C_6D_6) of Compound **141**



The ^{13}C NMR Spectrum (125 MHz, C_6D_6) of Compound **141**