DEVELOPMENT OF A TANDEM, THREE-COMPONENT SYNTHESIS OF TETRAHYDROFURANS VIA SILYLATED β-LACTONE INTERMEDIATES IN THE TANDEM MUKAIYAMA ALDOL-LACTONIZATION

A Dissertation

by

T. ANDREW MITCHELL

Submitted to the Office of Graduate Studies of
Texas A&M University
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

May 2008

Major Subject: Chemistry

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Approved by:

Chair of Committee,	Daniel Romo
Committee Members,	David E. Bergbreiter
	Daniel A. Singleton
	Charles M. Kenerley
Head of Department,	David H. Russell

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ABSTRACT

Development of a Tandem, Three-Component Synthesis of Tetrahydrofurans *via* Silylated β-Lactone Intermediates in the Tandem Mukaiyama Aldol-Lactonization.

(May 2008)

T. Andrew Mitchell, B. S., Grove City College

Chair of Advisory Committee: Dr. Daniel Romo

Although initial attempts to convert *(R)*-4-trichloromethyl-β-lactone to ketoaldehydes or keto-β-lactones for stereoselective tetrahydrofuran (THF) synthesis were unsuccessful, several novel transformations of this malic acid surrogate were discovered. Radical alkylations and α-silylations of optically active (*R*)-trichloromethyl-2-oxetanone are described that maintain the integrity of the β-lactone. Alternate methods for selective dechlorinations of both the β-lactone and the derived Weinreb amide are presented.

The development of a diastereoselective, three-step strategy for the construction of substituted tetrahydrofurans from alkenyl-aldehydes based on the tandem Mukaiyama aldol-lactonization (TMAL) process and Mead reductive cyclization of keto-β-lactones is reported. Stereochemical outcomes of the TMAL process are consistent with models established for Lewis acid-mediated additions to α-benzyloxy and β-silyloxy aldehydes while reductions of the five-membered oxocarbenium ions are consistent with Woerpel's

models. Further rationalization for observed high diastereoselectivity in reductions of α-silyloxy five-membered oxocarbenium ions based on stereoelectronic effects is posited. A diagnostic trend for coupling constants of γ-benzyloxy-β-lactones was observed that should enable assignment of the relative configuration of these systems.

A single stereocenter generates as many as two C-C bonds, one C-O bond, and three stereocenters in a single reaction leading to substituted tetrahydrofurans (THFs) in a three-component process. This process utilizes the tandem Mukaiyama aldol-lactonization (TMAL) and proceeds through a silylated β-lactone intermediate. The results build on Mead's reductive cyclization (MRC) of keto-β-lactones and are in accordance with Woerpel's model for "inside attack" of oxocarbenium ions. Application to a THF fragment of colopsinol B is described.

A universal model was set forth that rationalizes the stereochemical outcome of the reaction between α- and β-substituted aldehydes and (*E*)- and (*Z*)-substituted ketene acetals in the $ZnCl_2$-mediated tandem Mukaiyama aldol-lactonization (TMAL).

DEDICATION

To my son, Simon

ACKNOWLEDGEMENTS

I would like to sincerely thank Prof. Daniel Romo for inspiring me in chemistry and in life; not only do I consider him a great advisor, but a true friend. I appreciate him being available when I needed help, but also allowing me to fall down and learn how to get back up. His guidance and patience are much appreciated and have allowed me to become an independent researcher. I would also like to thank his family for allowing me to be a part of their lives during my time at Texas A&M.

I would like to thank several professors, all of who either served on my committee or were prepared to do so if necessary; thanks to all of you for supporting me throughout my graduate career. I would like to thank both Prof. David Bergbreiter and Prof. Gary Sulikowski for excellent classes and support in this research. Unfortunately, I did not have the privilege of taking their classes, but I am very thankful for Prof. Daniel Singleton and Prof. Brian Connell for their insight, encouragement, and guidance throughout the course of my research. My sincere gratitude goes to both Prof. Carlos Gonzalez and Prof. Charles Kenerley for their time and support.

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the Romo group. Thanks to all others who taught me chemistry and shared their lives with me for a few years including Yingcai Wang, Guillermo Cortez, Anja Dilley, Gil Ma, Mahesh Peddibhotla, Ziad Moussa, Huda Henry-Riyad, and Siva. Next, I would like to thank my peers who went through the fire with me. Thanks to Ke Kong and Richard Duffy for making me laugh, teaching me chemistry, and being great friends for several years. Thanks to Vikram Purohit, Francisco Franco-Torres, Shaohui Wang, Seongho Oh, and Min Zhou for more of the same. I would like to thank those students whom I had the privilege of mentoring including Manuel Zancanella, Kay Morris, and Ashley Leonard. It was a joy to be able to play a small part in your chemistry adventure and to see you becoming independent scientists. Thank you for your friendship and effort; you are the type of students that are fun to teach. A special thanks to Manuel, Kay, Richard, Andrea and others who took a break on Fridays to enjoy Jin's (we had to get out of the building once in awhile). Sincere thanks to all other Romo group members who helped make chemistry fun including Changsuk Lee, Sung Wook Cho, Yatsandra Oyola, Henry Nguyen (special thanks for telling me that I made a good decision about post-docs), Gang Liu, Andrea Matla, Dorianne Castillo, Ta Chamni, Ravi Vallakati, and JC Reyes. Finally, I must thank my fellow β-lactoners Hong Woon Yang, Cunxiang Zhao, Yingcai Wang, Bill Schmitz, and others without whom I would not be writing this dissertation. "*If* I have seen further it is by standing on the shoulders of giants."

There are several other people that have made my time in graduate school memorable. First, I need to thank Brian Fisher, Walter Bradley, Bob Hildreth, Daniel Romo, Nick Repak, David Perry, and Blake Jennings for there mentorship in my

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I am greatly indebted to my entire family for years of support and encouragement. I would especially like to thank my parents for raising me the right way, for your example of how to live, and for teaching me what is the most important

thing in life. I hope that my life honors the sacrifices that you made for me. Thank you to Matt and Kevin for their encouragement, support, and fun memories over the years. Thanks to Renée and Kim for encouragement and for being sisters that I never had growing up. Kevin, thank you for sharing the journey through education with me; I am happy that we can now talk about it in the past tense. I would like to offer my sincere gratitude to the entire Vest family, both for accepting a yankee into the family and for being so much fun. A special thanks to Donald and Julie for their support and most importantly for the daughter they raised. Words cannot express how much I appreciate my wife. I am not ashamed to say that I need you; being with you has changed my life only for the better. Not only do you make me want to be a better man, you are helping me to become that man. You will always be my girl and my better half. Thank you to my son, Simon, who has already given me so much joy.

Finally, my greatest appreciation must go to the Lord of all creation, Jesus Christ. Without Him, we are but dust in the wind, but through Him all of life takes on purpose. "All Truth is God's Truth….Thou awakest us to delight in Thy praise; for Thou madest us for Thyself, and our heart is restless until it repose in Thee." (St. Augustine)

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CHAPTER I

INTRODUCTION: ADVENTURES WITH β-LACTONES: SYNTHESES, TRANSFORMATIONS, AND APPLICATIONS OF 2-OXETANONES

Overview

"Let me tell you the secret that has led me to my goal: my strength lies solely in my tenacity…Chance favors the prepared mind." --Louis Pasteur

This account describes syntheses, transformations, and applications of 2-oxetanones in the Romo group. After early inspiration from rapamycin and omuralide, we attempted to develop a repertoire of β-lactone transformations that could be utilized toward total synthesis and biological investigations. We have developed syntheses of these underutilized strained heterocycles that fall into three broad categories: Lewis acid-mediated processes, organonucleophile promoted cyclizations, and transformations of ketene dimers. We have developed several transformations toward other useful functionality including γ-lactones, β-lactams, substituted carbocycles, tetrahydrofurans, and novel spiroepoxy-β-lactones. Several natural products have been successfully synthesized including grandinolide, tetrahydrolipstatin and derivatives, okinonellin B, brefeldin A, belactosin C, dihydroplakevulin A, and salinosporamide A. Utilizing these natural products and derivatives, we have elucidated important information regarding structure activity relationships, enzyme inhibition, and other biological properties. In this account, we discuss several short stories in approximately chronological order concerning our investigations of these strained and versatile heterocycles.

This dissertation follows the style of the *Journal of the American Chemical Society*.

A Brief History of β-Lactones

Although the first β-lactone (2-oxetanone) was synthesized by Einhorn in 1883,[1] it was not until almost 100 years later that β-lactones began to emerge as valuable intermediates for organic synthesis.[2] In 1982, Wynberg and Staring,[3] building on earlier work by Borrmann and Wegler,[4] reported an efficient, asymmetric, and organocatalytic route to (*R*)- and (*S*)-4-trichloromethyl-2-oxetanones employing quinine and quinidine to facilitate the union of chloral and ketene (Figure 1.1). The utility of these β-lactones was demonstrated in concise and efficient syntheses of both L- and D-malic acids. Since that time, β-lactones have continued to gain prominence as versatile intermediates in synthesis,[5] integral components in bioactive natural products,[2] enzyme inhibitors with therapeutic potential,[6] and building blocks for polymer synthesis.[7]

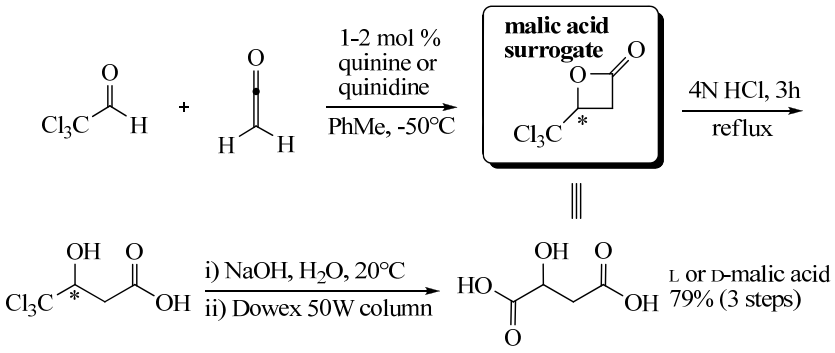


Figure 1.1. Wynberg's synthesis of 4-trichloromethyl-β-lactone

In 1992, as a NSF postdoctoral fellow in the Schreiber lab, Prof. Romo fortuitously stumbled upon his first β-lactone as an unexpected byproduct in model studies of the rapamycin tricarbonyl region (Figure 1.2). This auspicious discovery would be the spark of a significant portion of research in his independent career utilizing

these strained and versatile electrophiles. Since these early inspirations, his β-lactone research program has taken his research group on an adventure worth sharing.

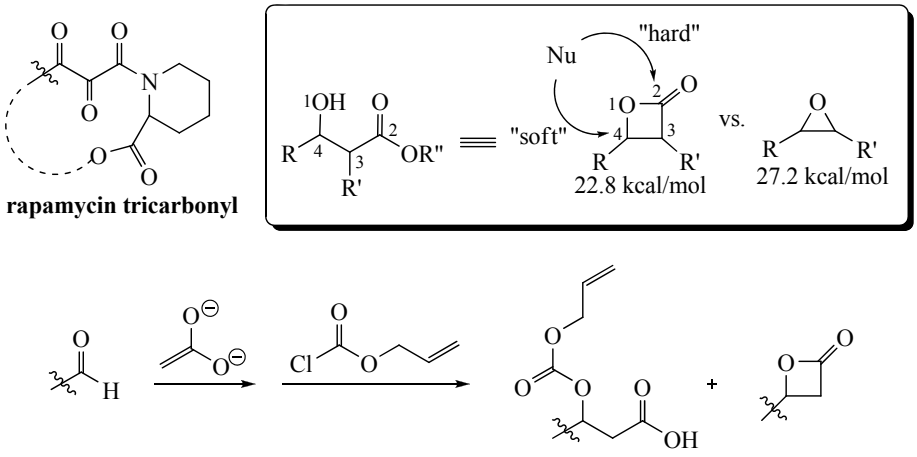


Figure 1.2. Initial inspiration for a β-lactone research program

The bicyclic β-lactone containing natural product, omuralide,[8] has also served as inspiration to our research program. Upon inspection of this biosynthetic precursor to the well-known natural product, (+)-lactacystin,[8] we reasoned that perhaps significant molecular simplification could be achieved by retrosynthetically cleaving the molecule through the middle to reveal an aldehyde-acid precursor. In the forward sense, this aldehyde-acid could conceivably undergo a productive, organonucleophile catalyzed aldol-lactonization that would simultaneously form two bonds (1 C-C and 1 C-O) and two stereocenters (Figure 1.3). Interestingly, this was one of the first targets in the Romo group and it was not until the requisite aldehyde-acid could be accessed *via* ozonolysis that this program was rejuvenated years later. Even then, heterocyclic systems were difficult to access for several reasons and carbocycles revealed themselves as the logical starting point for bis-cyclization studies.

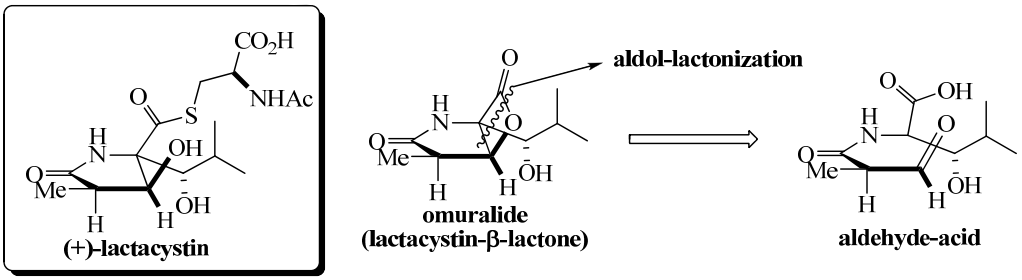


Figure 1.3. Inspiration from natural products omuralide and lactacystin

Building on success of the bis-cyclization of carbocycles, we have demonstrated the synthesis and application of a variety of bicyclic β-lactones (Figure 1.4).

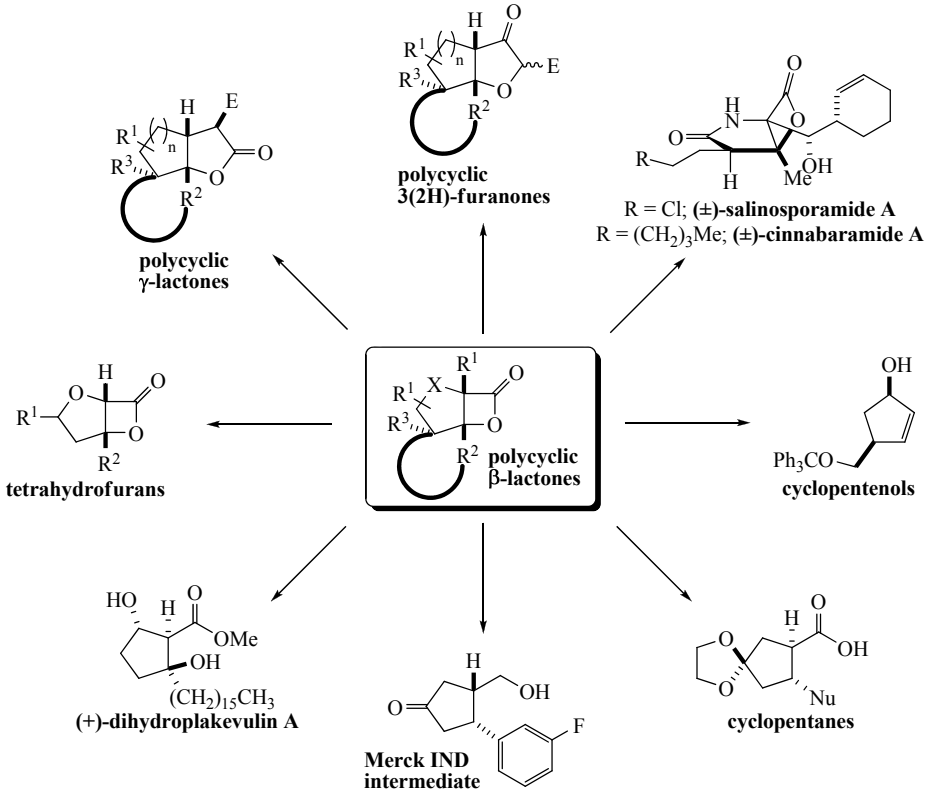


Figure 1.4. Transformations of bicyclic β-lactones

Utilizing other β-lactone methodology, we have demonstrated the synthesis, utility, and application of monocyclic β-lactones toward several structural motifs and natural products (Figure 1.5).

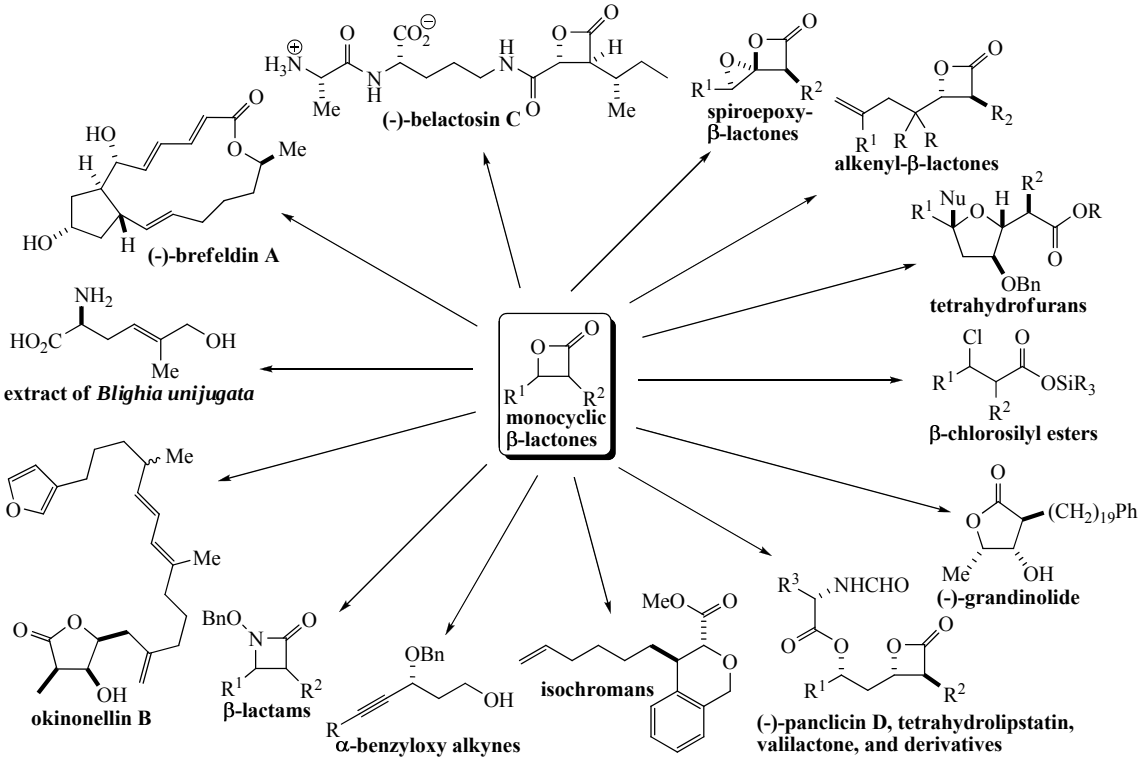


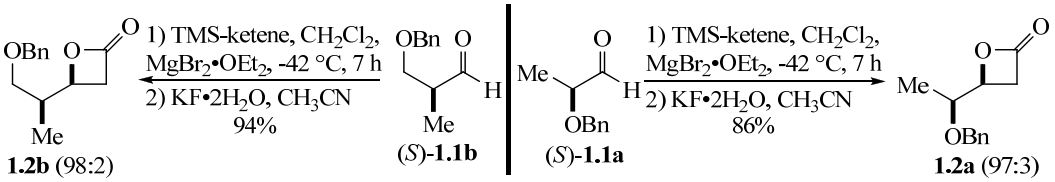
Figure 1.5. Transformations of monocyclic β-lactones

Both the moieties that can be accessed from β-lactones and β-lactones themselves are prominent features in many natural products. The natural products synthesized in our laboratory have been subjected to biological studies such as elucidation of structure activity relationships or enzyme interactions with the natural product. Herein, we discuss several short stories in approximate chronological order concerning our adventures with these strained and versatile heterocycles.

Synthetic and Mechanistic Studies of Lewis Acid Catalyzed [2+2] Cycloadditions of Aldehydes and Ketenes and Application toward Optically Active β-Lactones

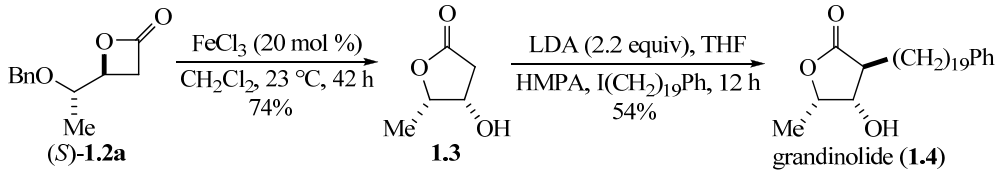
Metals have played a significant role in organic synthesis and Lewis acids have allowed innumerable transformations to occur that otherwise may never have been discovered. Our early reports investigated Lewis acid variants of the classic [2+2] cycloaddition between ketenes and aldehydes.[9] These studies proved fruitful as several interesting results sprung from our initial investigation of chelation controlled [2+2] cycloadditions (Scheme 1.1). Both α-benzyloxy aldehyde (*S*)-**1.1a** and β-benzyloxy aldehyde (*S*)-**1.1b** reacted smoothly with TMS-ketene in the presence of a stoichiometric amount of $MgBr_2$•OEt_2 to deliver the optically active β-lactones **1.2a** and **1.2b**, respectively, with excellent diastereoselectivity.[10]

Scheme 1.1



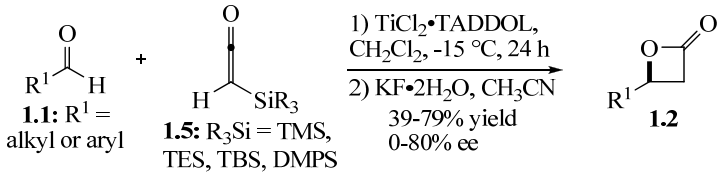
β-Lactone (*S*)-**1.2a**, derived from (*S*)-ethyl lactate, was subjected to $FeCl_3$-catalyzed transacylation-debenzylation to deliver γ-lactone **1.3** toward a concise total synthesis of (-)-grandinolide **1.4** (Scheme 1.2).[11] Alkylation of the dianion derived from LDA with 1-iodo-19-phenylnonadecane gave (-)-grandinolide **1.4** in 28% overall yield.

Scheme 1.2



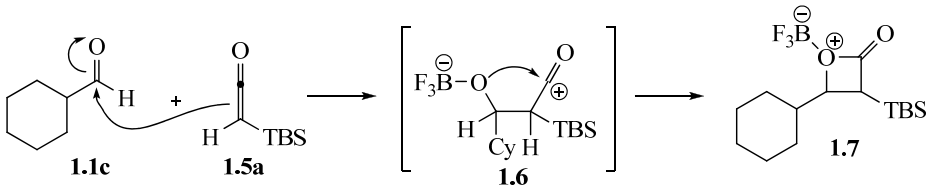
Studies toward a catalytic, asymmetric [2+2] cycloaddition utilizing readily available dichlorotitanium-TADDOL catalysts were also examined (Scheme 1.3).[12] After diastereoselectivity of the α-silyl-β-lactones was determined, the mixture was desilylated and the enantioselectivity was determined by chiral GC or HPLC. Although the optical purities of these β-lactones **1.2** were not synthetically useful, it was interesting to find that the *cis*-β-lactones gave slightly higher enantioselectivity than the *trans*-β-lactones.

Scheme 1.3



These observations led us to explore a deeper mechanistic understanding of this well-known transformation. Although it is generally accepted that these [2+2] cycloadditions are concerted, we concluded that this particular process was stepwise wherein the C-C bond is formed first followed by lactonization (Scheme 1.4). More intriguing was that the rate-limiting step of *trans*-β-lactone formation was found to be construction of the C-C bond, while for *cis*-β-lactone it was union of the C-O bond.[13]

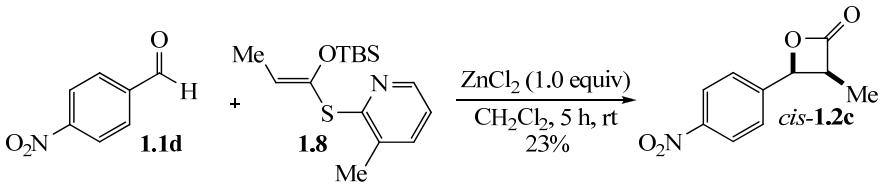
Scheme 1.4



$ZnCl_2$-Mediated *trans*-Selective Synthesis of β-Lactones *via* Tandem Mukaiyama Aldol-Lactonization (TMAL) Processes and Discovery of a Stereocomplimentary $SnCl_4$-Mediated *cis*-Selective Synthesis of β-Lactones

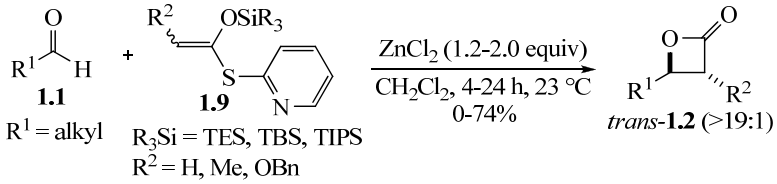
In 1994, Hirai and co-workers reported a single example of a *cis*-β-lactone **1.2c** produced in low yield from *p*-nitrobenzaldehyde **1.1d** and thiopyridyl ketene acetal **1.8** (Scheme 1.5).[14] This was the first example of β-lactone formation through a Mukaiyama aldol reaction.[15]

Scheme 1.5



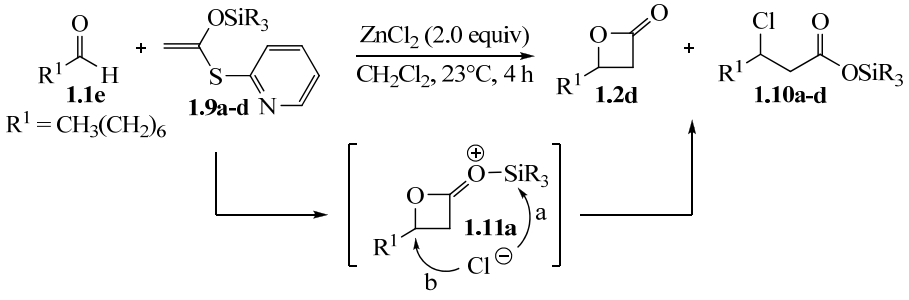
Building on the work of Hirai, we reported a similar synthesis *via* the tandem Mukaiyama aldol-lactonization (TMAL) that delivered *trans*-β-lactones **1.2** from *aliphatic* aldehydes **1.1** in good to moderate yields with high diastereoselectivity (Scheme 1.6).[16] In the course of optimization of various parameters, several important findings were reported.[17] First, the pyridine moiety of the thiopyridyl ketene acetal **1.9** was determined to be crucial to the success of this reaction, but also prevented the development of a catalytic version of the TMAL. Intimately connected to the thiopyridyl moiety is $ZnCl_2$ as this is the only Lewis acid to deliver *trans*-β-lactones **1.2** in the TMAL thus far. Experimental evidence also suggests that the Mukaiyama aldol is the rate-limiting step due to the fact that no typical aldol products are observed in the TMAL. Finally, the steric bulk of the silyl group of ketene acetal **1.9** was found to play a vital role in the outcome of this reaction.

Scheme 1.6



One important finding regarding the silyl protecting group of ketene acetals **1.9** was that isolated yields of β-lactones **1.2** were increased as much as 30% when TES was used instead of TBS (Table 1.1).[16] We also found that β-chlorosilyl esters **1.10a-d** were formed in greater yields as the size of the silyl group increased and when a very bulky silyl group (*i.e.* TBDPS) was utilized, this led to complete termination of the β-lactone pathway. We proposed the presence of a silylated β-lactone intermediate **1.11a** to account for these findings.[17]

Table 1.1. Effect of steric bulk of the silyl protecting group of ketene acetals **1.9a-d**

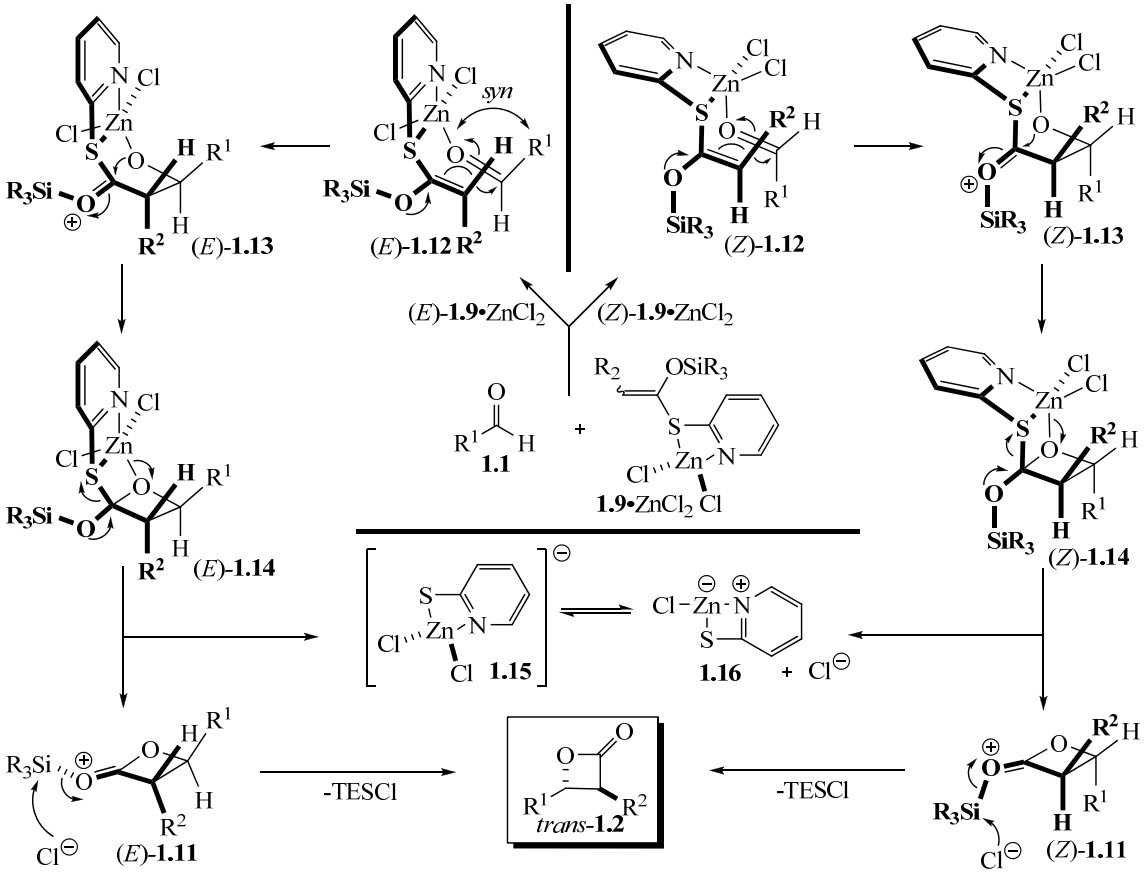


entry	SiR_3	**1.2d** (% yield)	**1.10** (% yield)
1	TES **(1.9a)**	66	<5 **(1.10a)**
2	TBS **(1.9b)**	53	8 **(1.10b)**
3	TIPS **(1.9c)**	20	40 **(1.10c)**
4	TBDPS **(1.9d)**	<5	56 **(1.10d)**

Our observations led us to propose highly-ordered, boat-like transition state arrangements **1.12** *en route* to silylated β-lactones **1.11** in the TMAL reaction (Scheme

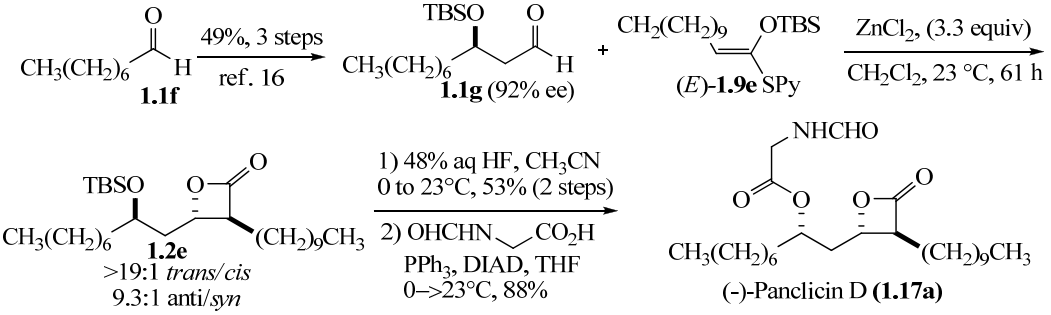
1.7).[17] The nature of the thiopyridyl ketene acetal **1.9** seems to enable a cyclic transition state due to poor overlap between the sulfur atom and the adjacent C(*2p*) π system leading to a high degree of sp^3 character and thus availability for coordination to zinc (II). In addition, zinc (II) Lewis acids are softer than titanium (IV), boron (III) and magnesium (II) Lewis acids, and thus are expected to have a higher affinity toward the soft sulfur atom. Therefore, upon initial formation of the 4-membered, tetrahedral zinc (II) thiopyridyl chelate **1.9**•$ZnCl_2$, it can adopt pin-wheel conformations depending on ketene acetal geometry. We propose that (*E*)- and (*Z*)-**1.9** adopt two different pin-wheel conformations that correspond to boat-like, trigonal bipyramidal zinc (II) complexes (*E*)- and (*Z*)-**1.12**.[18] Aldehyde **1.1** can then associate with zinc to form these diastereomeric trigonal bipyramidal zinc (II) complexes (*E*)- and (*Z*)-**1.12**. Initial C-C bond formation leads to boat-like, zwitterionic intermediates (*E*)- and (*Z*)-**1.13** resulting from initial *syn* or *anti* coordination with aldehyde **1.1**, respectively. Presumably, these boat-like intermediates (*E*)- and (*Z*)-**1.13** undergo more facile transannular lactonization compared to corresponding zwitterionic intermediates derived from either "open" or "chair-like" transition state arrangements (not shown) leading to fused ring systems (*E*)- and (*Z*)-**1.14**. Cleavage of the sulfur-carbon bond in this tetrahedral intermediate with prior or concomitant dissociation of the Zn-O bond releases ring strain and thus provides a driving force leading to diastereomeric silylated β-lactone intermediates (*E*)- and (*Z*)-**1.11**. Finally, the crucial silylated β-lactone intermediates (*E*)- and (*Z*)-**1.11** can either undergo invertive alkyl C-O ring scission (*c.f.* Table 1.1) or desilylation by the liberated chloride ion from complex **1.15** to deliver *trans*-β-lactones **1.2**.

Scheme 1.7



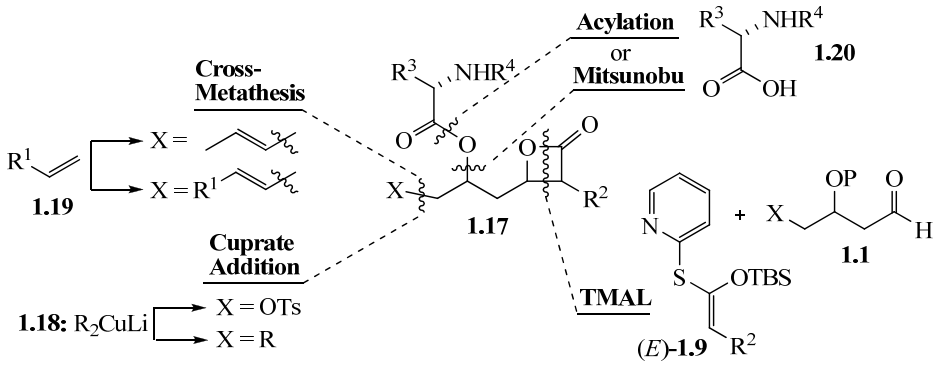
This methodology was applied to a fatty acid synthase (FAS) inhibitor, (-)-panclicin D **1.17a** and was one of our first reported examples of a substrate controlled diastereoselective TMAL (Scheme 1.8).[16] β-Silyloxy aldehyde **1.1g** was subjected to standard TMAL conditions with ketene acetal (*E*)-**1.9e** to deliver the required β-lactone **1.2e** in moderate yield with good diastereoselectivity. Although no *cis*-β-lactone was observed, a minor quantity of the undesired *syn*-β-lactone was formed. The synthesis was complete following silyl deprotection (the minor *syn*-β-lactone was separated at this point) and Mitsunobu inversion of the corresponding alcohol to deliver (-)-panclicin D **1.17a** in 20% overall yield from *n*-octanal **1.1f**.

Scheme 1.8



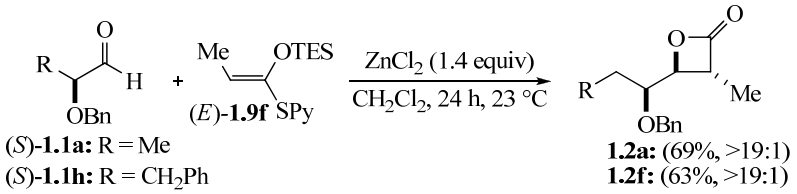
We demonstrated a convergent, "second generation" strategy ((-)-panclicin D was not resynthesized) toward (-)-panclicin D derivatives **1.17** that provided rapid access to tetrahydrolipstatin (orlistat), valilactone, and several other congeners (Scheme 1.9).[19] These natural products and derivatives were subjected to biological testing including inhibition studies of the thioesterase domain of fatty acid synthase (FAS).

Scheme 1.9



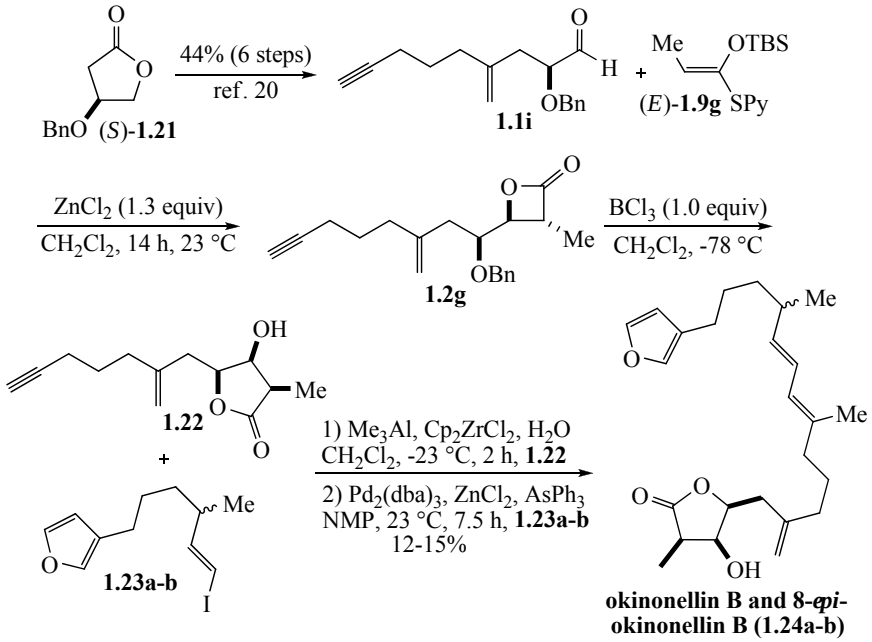
The scope of this diastereoselective TMAL was explored and some of the most successful TMAL substrates were found to be α-benzyloxy aldehydes **1.1a,h** (Scheme 1.10).[20] These reactions proceeded with good yield and excellent diastereoselectivity corresponding to chelation control models with less than 2% racemization in most cases (when R = Ph, significant racemization occurs due to increased acidity of the α-protons).

Scheme 1.10



This version of the TMAL was used toward the total synthesis of okinonellin B **1.24a-b** (Scheme 1.11).[21] L-Malic acid derived γ-lactone (*S*)-**1.21** provided the alkenyl-

Scheme 1.11

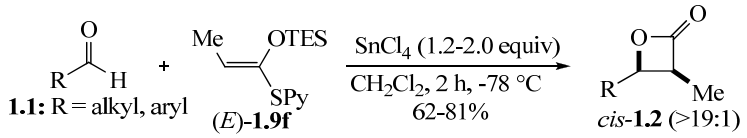


aldehyde **1.1i** which was subjected to standard TMAL conditions to give the desired β-lactone **1.2g** as a single diastereomer in good yield. Unfortunately, our previous conditions ($FeCl_3$, CH_2Cl_2, 23 ˚C) for the tandem transacylation-debenzylation[11] delivered the γ-lactone **1.22** in only 29% yield. Alternative conditions (BCl_3, CH_2Cl_2, -78 ˚C) proved to be sufficient as the γ-lactone **1.22** was obtained in good yield. The alkyne **1.22** underwent a one-pot coupling with both vinyl iodides **1.23a-b** separately to

deliver (8*S*, 21*S*, 22*S*, 23 *R*)- and (8*R*, 21*S*, 22*S*, 23 *R*)-okinonellin B **1.24a-b**, albeit in low yields. Based on optical rotation data, we speculated that the natural product configuration is (8*R*, 21*R*, 22*R*, 23*S*), but could not be sure as none was available for direct comparison.

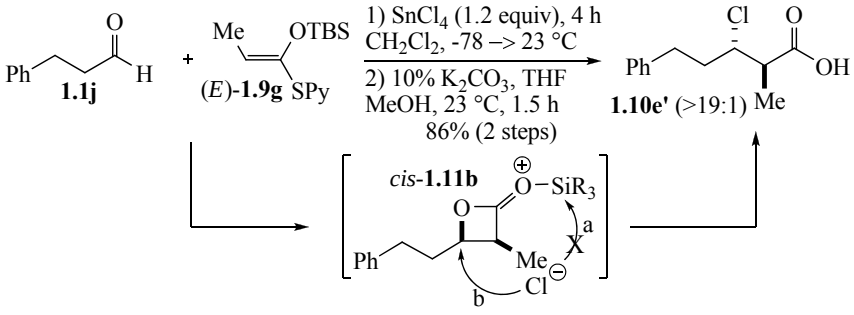
In the course of our studies with the $ZnCl_2$-mediated TMAL, we discovered a stereocomplimentary $SnCl_4$-mediated process that provides *cis*-β-lactones **1.2** in good to moderate yields and excellent diastereoselectivity (Scheme 1.12).[22] This reaction proceeds at cooler temperatures (-78 ˚C) and shorter reaction times (2 h).

Scheme 1.12



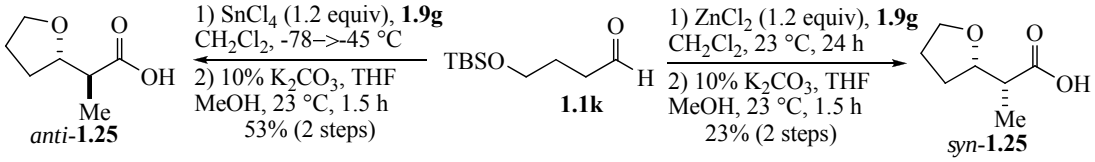
Similar to the $ZnCl_2$-mediated TMAL, β-chlorosilyl esters **1.10** were observed in the $SnCl_4$-mediated process (Scheme 1.13). The β-chlorosilyl ester **1.10e** was isolated as carboxylic acid **1.10e'** in excellent yield over two steps and presumably proceeds through silylated β-lactone *cis*-**1.11b**. X-ray analysis of carboxylic acid **1.10e'** supported the proposed invertive alkyl C-O scission of silylated β-lactone *cis*-**1.11b**.

Scheme 1.13



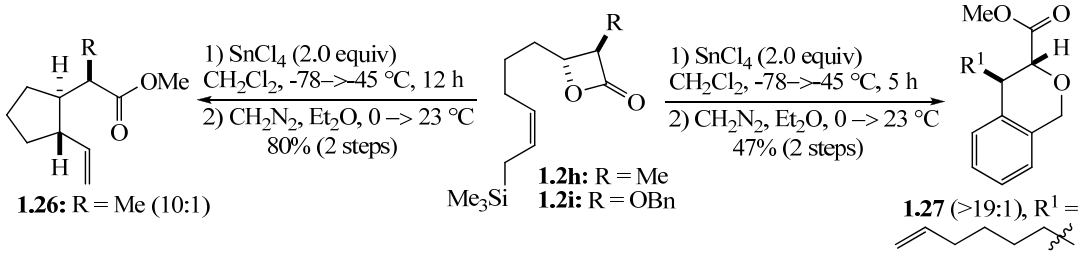
In both processes, several other interesting byproducts were observed that supported our hypothesis regarding a silylated β-lactone intermediate (Scheme 1.14). Epimeric THFs carboxylic acids **1.25** were obtained after hydrolysis of the corresponding silyl esters (not shown).

Scheme 1.14



We then attempted to intercept this silylated β-lactone with pendant nucleophiles to expand the scope of this methodology. Unfortunately, attempts with a pendant allylsilane did not give promising results. However, a stepwise version was previously explored and delivered cyclopentane **1.26** when R = Me in addition to an interesting Friedel Crafts byproduct **1.27** when R = OBn (Scheme 1.15).[23] Low yields (9%) of the desired cyclopentane (not shown) were observed when R = OBn.

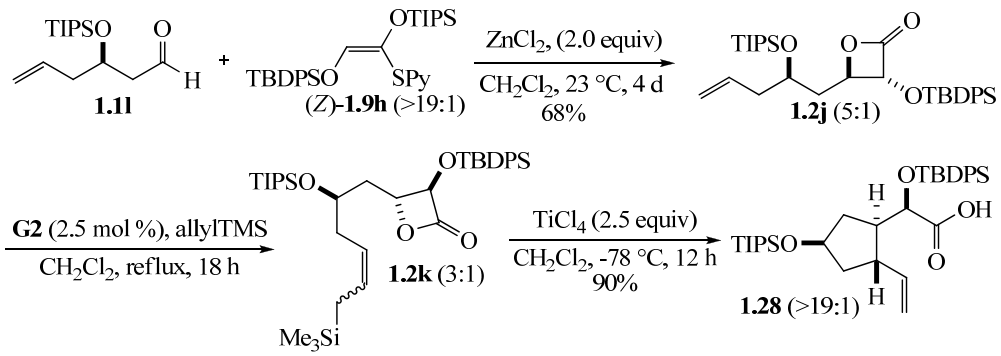
Scheme 1.15



This interesting but undesired isochroman **1.27** was avoided during the total synthesis of brefeldin A (not shown) in which a TBDPS protecting group on the ketene acetal (*Z*)-**1.9h** was utilized instead of the benzyl protecting group (Scheme 1.16).[24] The length of this reaction (4 days) was a new observation, but more importantly a *syn*-β-

lactone **1.2j** was produced as the major product for the first time in the diastereoselective TMAL instead of the usual *anti*-β-lactone (*c.f.* **1.2e**, Scheme 1.8). This was unexpected and led us to question whether this reversal resulted from the bulky oxygen substituent or if this was a more general trend based on ketene acetal geometry. Upon purification of the major diastereomer **1.2j** by MPLC and cross metathesis with allyltrimethylsilane, cyclization of an inconsequential mixture of alkenes **1.2k** promoted by $TiCl_4$ proceeded smoothly to deliver the crucial cyclopentane acid **1.28** as a single diastereomer.

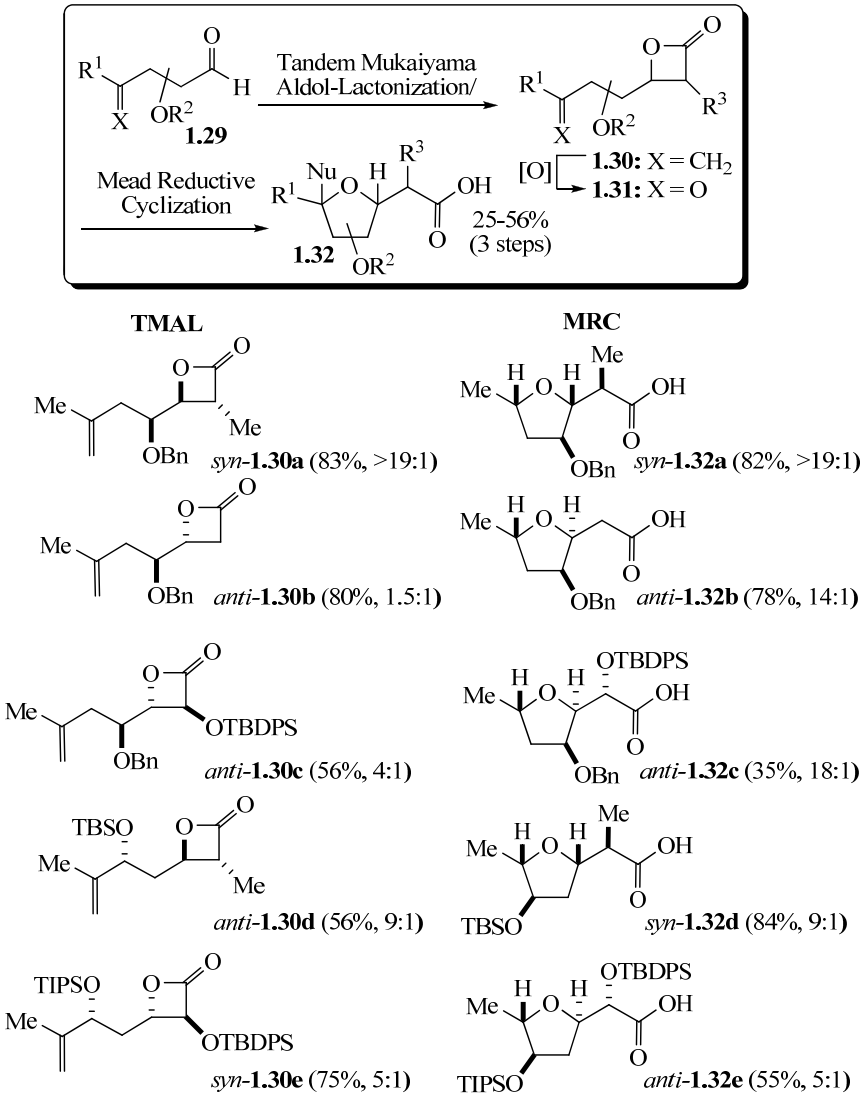
Scheme 1.16



Our next attempt to trap the proposed silylated β-lactone was with a ketone *via* stepwise tandem Mukaiyama aldol-lactonization[16] – Mead reductive cyclization[25] (TMAL-MRC). We attempted a stepwise MRC (Scheme 1.17) of keto-β-lactones **1.31** derived from the TMAL to access trisubstituted THFs **1.32** in order to understand each reaction before proceeding to a more complex one-pot, three-component variant.[26] The diastereoselective synthesis of β-lactones **1.30a-e** was consistent with previous reports except for γ-benzyloxy-β-lactone *anti*-**1.30c**, which explored a previously unexamined combination of α-benzyloxy aldehyde **1.29a** (not shown) and ketene acetal (*Z*)-**1.9h**. A similar question as posed previously (*c.f. syn*-**1.2j**, Scheme 1.15) regarding ketene acetal

geometry now loomed as γ-benzyloxy-β-lactone *anti*-**1.30c** departed from the chelation control trend and instead seemed to follow Felkin-Anh selectivity. The keto-β-lactones **1.31a-e** underwent invertive alkyl C-O scission to deliver oxocarbeniums that were stereoselectively reduced according to Woerpel's model to deliver THFs **1.32a-e**.[27] This stepwise TMAL-MRC assisted the development of a three-component TMAL-MRC with γ-ketoaldehydes, thiopyridyl ketene acetals, and silyl nucleophiles (*vide infra*).

Scheme 1.17



Another interesting observation from these studies was a coupling constant trend that should allow assignment of relative stereochemistry of these systems solely based on this property (Figure 1.6).[26] In the case of these γ-benzyloxy-β-lactones, the coupling constants for *syn* ($J_{4,5}$ = 4.5-6.0 Hz) and *anti* ($J_{4,5}$ = 2.7-3.6 Hz) diastereomers followed a clear trend that is also consistent with our previous studies.[20,21]

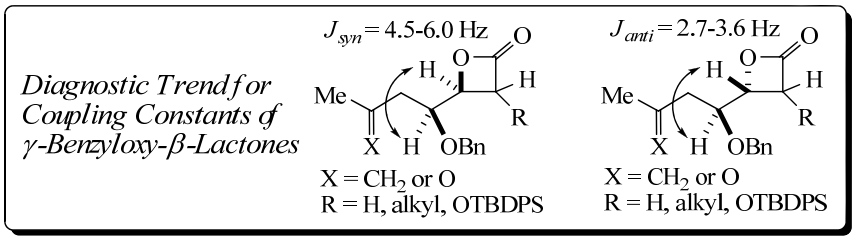


Figure 1.6. Diagnostic coupling constants of γ-benzyloxy-β-lactones

We envisioned a three-component TMAL-MRC synthesis of THFs **1.34** from ketoaldehydes (±)-**1.33**, thiopyridyl ketene acetals **1.9**, and silyl nucleophiles in which as many as two C-C and one C-O bond are formed in conjunction with three new stereocenters (Scheme 1.18).[28] After extensive optimization studies, we were pleased to observe moderate yields of several THFs **1.35** (Table 1.2).

Scheme 1.18

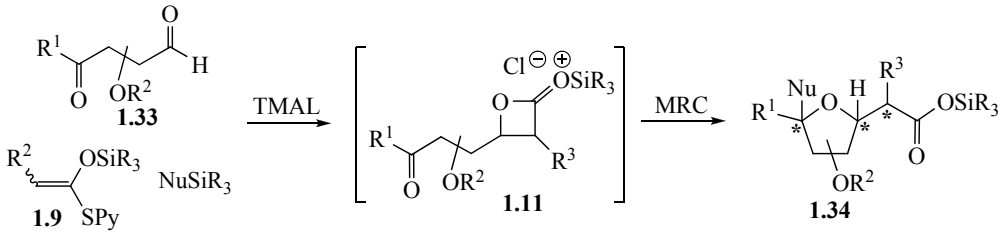
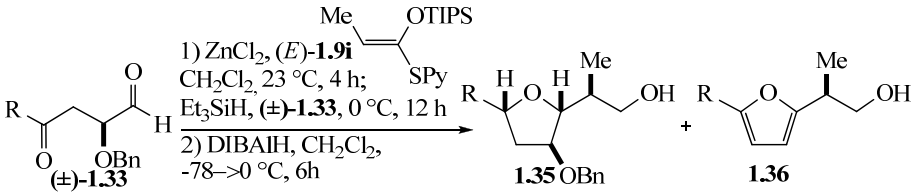
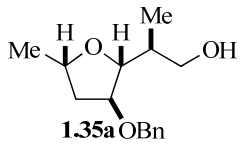
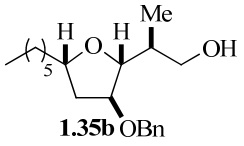
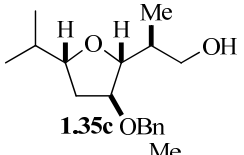
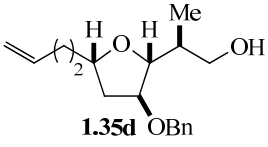
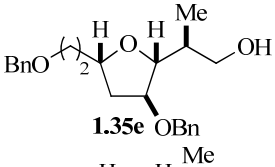
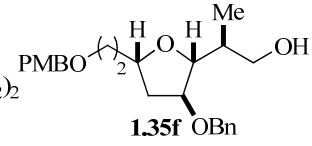


Table 1.2. Tandem, three-component synthesis of tetrahydrofurans **1.35**

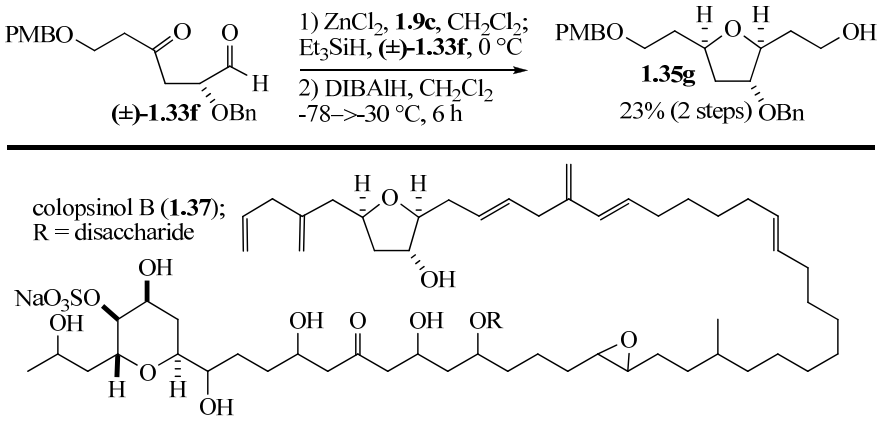


entry	ketoaldehyde **(1.33)**	major adduct **(1.35)**	**1.35/1.36**	% yield **(1.35)**	dr
1	(±)-**1.33a:** R = Me	 **1.35a**	6.2:1	54	>19:1
2	(±)-**1.33b:** R = *n*-hexyl	 **1.35b**	1.3:1	42	>19:1
3	(±)-**1.33c:** R = *i*-propyl	 **1.35c**	2.3:1	52	>19:1
4	(±)-**1.33d:** R = $CH_2CH(CH_2)_2$	 **1.35d**	3.0:1	49	>19:1
5	(±)-**1.33e:** R = $BnO(CH_2)_2$	 **1.35e**	3.5:1	54	>19:1
6	(±)-**1.33f:** R = $PMBO(CH_2)_2$	 **1.35f**	2.2:1	49	>19:1

Our prediction that the stereochemical outcome would follow the precedent set forth by the TMAL,[16] invertive alkyl C-O scission *via* the MRC,[25] and Woerpel's model for reduction of oxocarbenium ions[27] was supported by nOe enhancements and coupling constant analysis. Ultimately, the relative stereochemistry was confirmed with single crystal X-ray analysis of the benzoate ester of THF **1.35a**.

To highlight the utility of this methodology, we targeted the THF fragment of colopsinol B **1.37** (Scheme 1.19).[29] Treatment of α-benzyloxy-γ-ketoaldehyde (±)-**1.33f** with ketene acetal **1.9c** followed by reduction of the silyl ester with DIBAlH delivered THF **1.35g** in moderate yield considering the complexity generated in the TMAL-MRC.

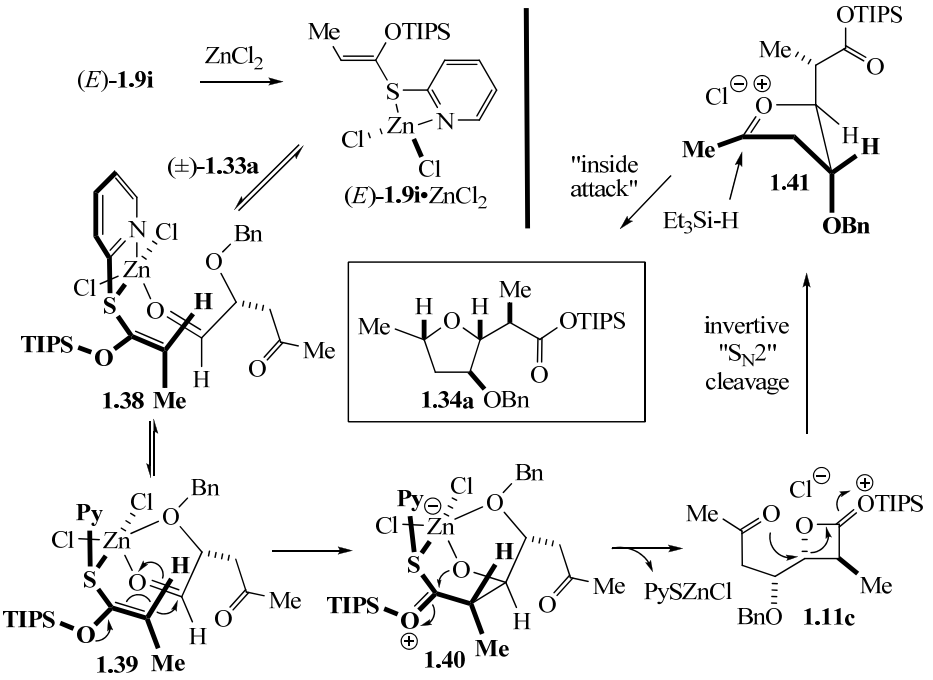
Scheme 1.19



A mechanistic pathway that rationalizes the stereochemical outcome of this tandem process is proposed based on a chelation-controlled TMAL process[28] and Woerpel's model[27] for oxocarbenium reductions (Scheme 1.20). Precoordination of $ZnCl_2$ and ketene acetal (*E*)-**1.9i** leads to tetrahedral complex (*E*)-**1.9**•$ZnCl_2$. Initial monodentate coordination with α-benzyloxy aldehyde (±)-**1.33a** leads to trigonal bipyramidal complex **1.38** involving bidentate chelation of Zn (II) with the thiopyridyl group. A highly ordered, boat-like transition state arrangement **1.39** is generated by ligand rearrangement leading to bidentate coordination with α-benzyloxy aldehyde (±)-**1.33a**. Chelation-controlled addition leads to high diastereoselectivity in the aldol step eventually providing silylated β-lactone **1.11c**. Subsequent invertive alkyl C-O cleavage delivers oxocarbenium **1.41**. The pseudoaxially disposed benzyloxy substituent enforces

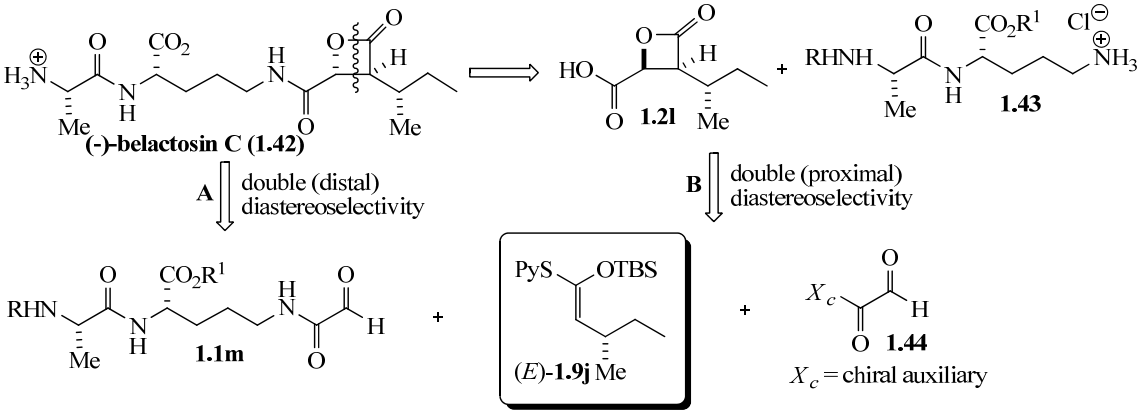
the stereoelectronically favorable envelope conformation and reduction occurs from the "inside" of the envelope as predicted by the Woerpel model[27] to give silyl ester **1.34a**.

Scheme 1.20



A unique application of the TMAL with chiral ketene acetals toward the total synthesis of biologically active (-)-belactosin C **1.42** was demonstrated (Scheme 1.21).[30]

Scheme 1.21

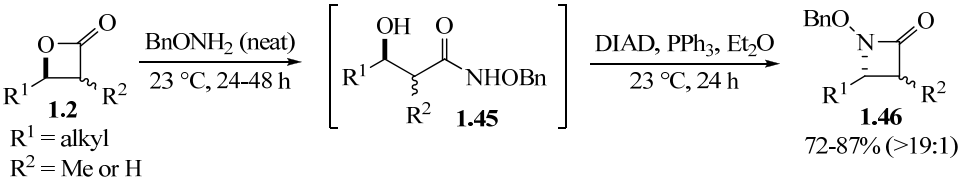


Strategy **B** utilizing a chiral auxiliary toward a proximal double diastereoselective TMAL proved to give better results and enable the synthesis and separation of an advanced intermediate *en route* to (-)-belactosin C **1.42**.

A Single-Pot, Mild Conversion of β-Lactones to β-Lactams and Application toward β-Lactam FAS Inhibitors

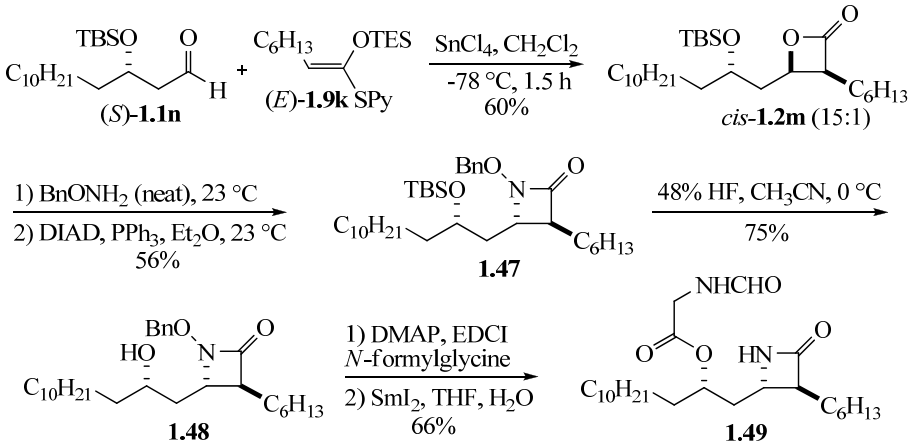
Ubiquitous moieties of natural products, β-lactams bear a striking resemblance to β-lactones and we investigated a single-pot conversion of β-lactones to β-lactams that would further our transformational repertoire of these versatile heterocycles (Scheme 1.22).[31] Acyl C-O ring-opening of β-lactones **1.2** with neat *O*-benzyloxyamine followed by Mitsunobu conditions at ambient temperature delivered the corresponding β-lactams **1.46** with inversion of configuration at the β-carbon. In all cases with α-alkyl-β-lactones, high stereochemical fidelity was observed. However, when the α-carbon was substituted with a heteroatom (*i.e.* OBn or $SiMe_3$), mixed results were obtained.

Scheme 1.22



This single-pot conversion of β-lactones to β-lactams was applied to the synthesis of the first β-lactam orlistat derivative **1.49** and others which were studied for the inhibition of FAS synthase (Scheme 1.23).[32]

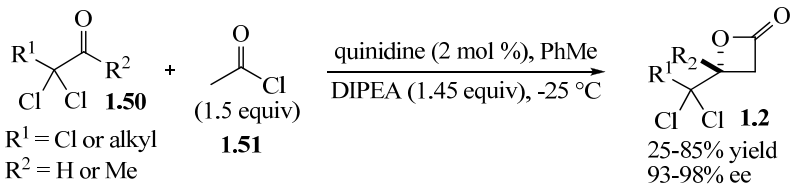
Scheme 1.23



Use of *In Situ* Generated Ketene in the Wynberg Process and New Transformations of the Resulting β-Lactones

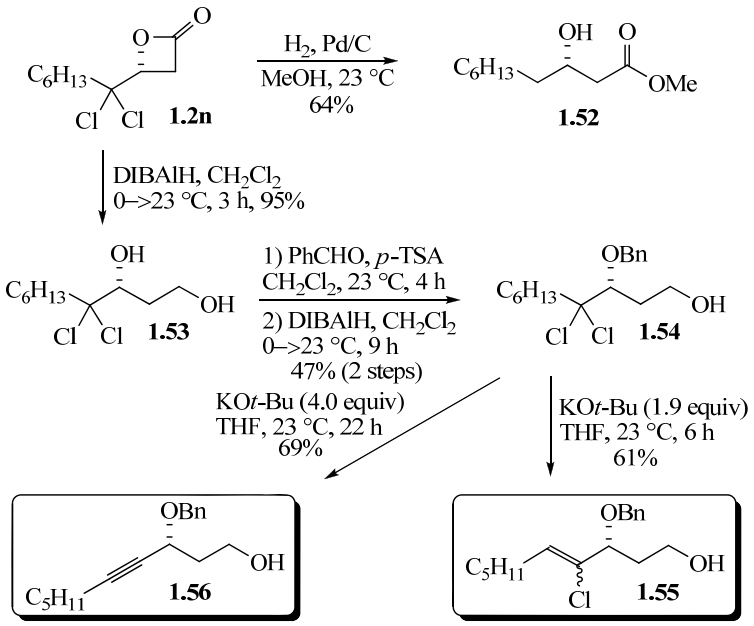
The utility of the commercially available 4-trichloromethyl-2-oxetanone has been well documented and its synthesis *via* the Wynberg process was truly groundbreaking.[3] As is the case with all landmark advances, however, there were disadvantages to this route including the need for both ketene generation and highly active aldehydes. It was our hope that a modified Wynberg process using *in situ* generated ketene could achieve similar results as the original. Indeed, β-lactones **1.2** were obtained in good to moderate yields with excellent enantioselectivities using *in situ* generated ketene (Scheme 1.24).[33]

Scheme 1.24



The dichloro-β-lactones were then utilized in further transformations (Scheme 1.25).[33] First, the dichloro-β-lactone **1.2n** was dechlorinated and ring-opened under hydrogenation conditions with methanol as both solvent and nucleophile. Upon formation of the mono-protected diol **1.53**, unsaturation in the form of either a vinyl chloride **1.55** or an alkyne **1.56** could be introduced with selective mono- or bis-elimination, respectively, simply by varying the amount of KO*t*-Bu present in the reaction.

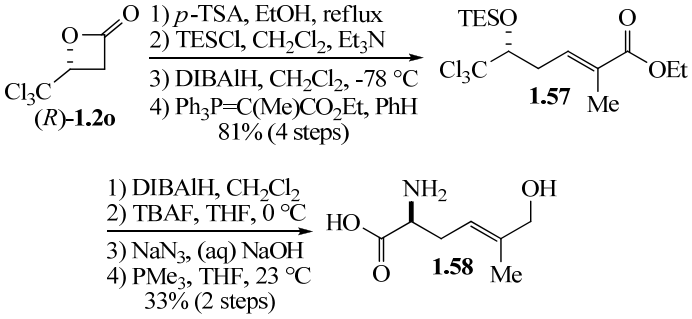
Scheme 1.25



The optically active 4-trichloromethyl-β-lactone was utilized in the total synthesis of a naturally occurring α-amino acid **1.58** from the seeds of *Blighia unijugata* (Scheme 1.26).[34] β-Lactone (*R*)-**1.2o** was treated with *p*-TSA followed by protection to deliver the β-silyloxy ester (not shown). The ester underwent half-reduction with DIBAlH and was subsequently treated with the Wittig reagent to provide α,β-unsaturated

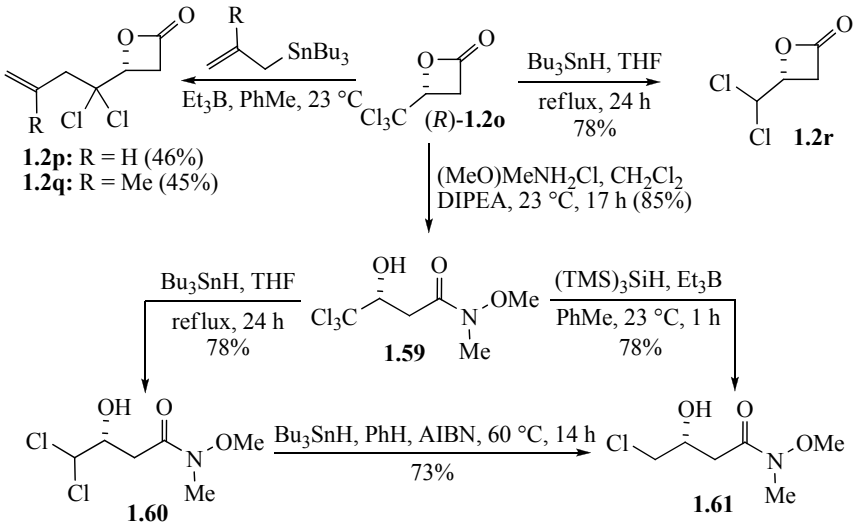
ester **1.57** in excellent yield. A second reduction followed by TBAF deprotection gave the corresponding diol (not shown). Treatment of the diol with NaN_3 and aqueous NaOH in THF selectively transformed the trichloromethyl carbinol moiety into the α-azido carboxylic acid which was then reduced under standard conditions to provide the α-amino acid **1.58**.

Scheme 1.26



The optically active 4-trichloromethyl-β-lactone (*R*)-**1.2o** and the ring-opened Weinreb amide **1.59** were utilized in radical transformations that further demonstrated its utility as a malic acid surrogate (Scheme 1.27).[35] A unique aspect of several of these

Scheme 1.27

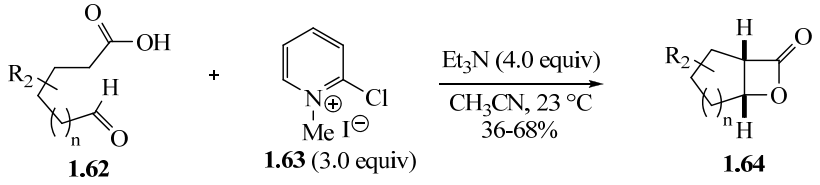


reactions is the ability to perform them while maintaining the integrity of the β-lactone. Treatment with allylstannanes provided the alkenyl-β-lactones **1.2p-q** while Bu_3SnH in refluxing THF smoothly provided the dichloro-β-lactone **1.2r**. The ring-opened trichloro Weinreb amide **1.59** easily provided both dichloro Weinreb amide **1.60** and monochloro Weinreb amide **1.61** *via* mono- and bis-dechlorination, respectively.

Development of an Intramolecular Wynberg Process toward Natural Products Inspired Synthesis of Polycyclic β-Lactones *via* Organonucleophile-Promoted Bis-Cyclization Processes

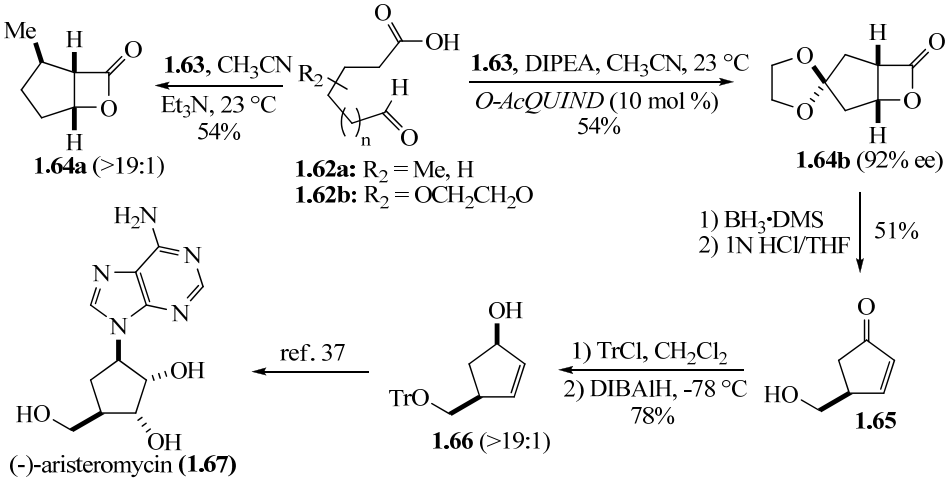
As mentioned previously, another shortcoming of the Wynberg process is the need for highly activated aldehydes. It was thought that perhaps an intramolecular version would eliminate the need for such aldehydes.[36] Although our initial studies toward the total synthesis of omuralide were met with frustration, our investigations toward carbocycles found greater initial success (Scheme 1.28).[37] When aldehyde-acid **1.62** was added to a solution of Mukaiyama's reagent **1.63** and Et_3N in CH_3CN at ambient temperature over 10 h *via* syringe pump, good to moderate yields of bicyclic-β-lactones **1.64** were isolated.

Scheme 1.28



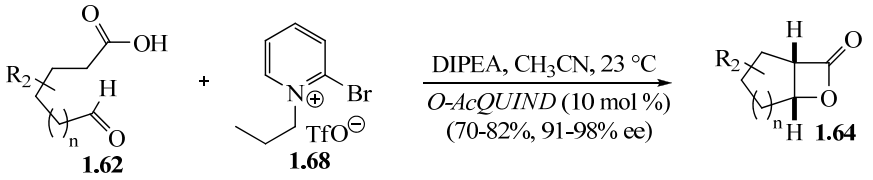
Both enantioselective and diastereoselective versions of this reaction showed great promise (Scheme 1.29). When aldehyde-acid **1.62a** was utilized, cyclopentane-fused β-lactone **1.64a** was observed in moderate yield and excellent diastereoselectivity. We were excited to find that bicyclic-β-lactones such as **1.64b** could be obtained with high optical purity with the use of *Cinchona alkaloids*. Bicyclic-β-lactone **1.64b** was transformed to cyclopentenone **1.65** followed by protection and reduction to deliver the alcohol **1.66** as a single diastereomer. Comparison of the optical rotations of cyclopentenol **1.66** to the known precursor of aristeromycin **1.67** indicated that optical purity was maintained.[38]

Scheme 1.29



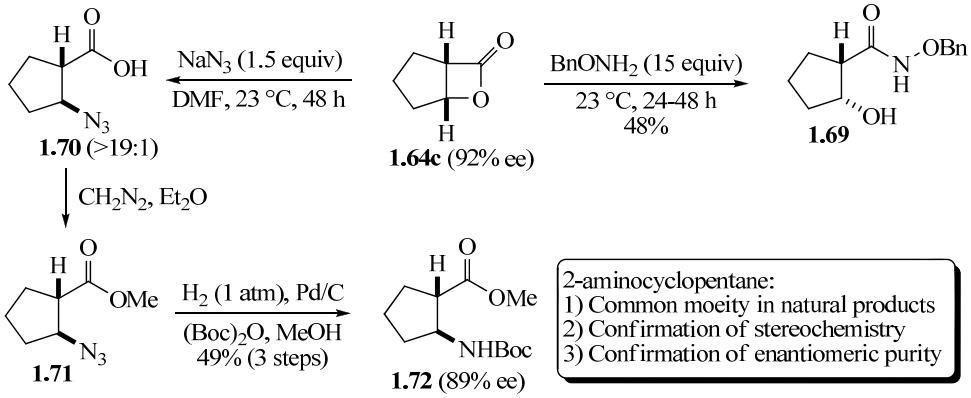
This method was then optimized further using a modified Mukaiyama's reagent **1.68** (Scheme 1.30).[39] This reagent allowed the use of dichloromethane as solvent due to increased solubility and increased yields by as much as 37% while maintaining excellent enantioselectivities.

Scheme 1.30



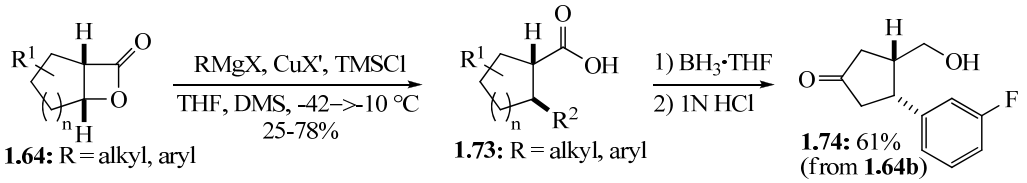
Several transformations of these bicyclic systems were then explored. Both acyl C-O and alkyl C-O nucleophilic ring-opening was executed with nitrogen nucleophiles demonstrating the hard-soft dichotomy imbedded within β-lactones (Scheme 1.31).[40] For example, β-lactone **1.64c** was treated with neat $BnONH_2$ to deliver hydroxamic acid derivative **1.69**. Also, invertive alkyl β-lactone cleavage with NaN_3 was demonstrated and the resulting azide **1.70** was converted to the common 2-aminocyclopentane **1.72**.

Scheme 1.31



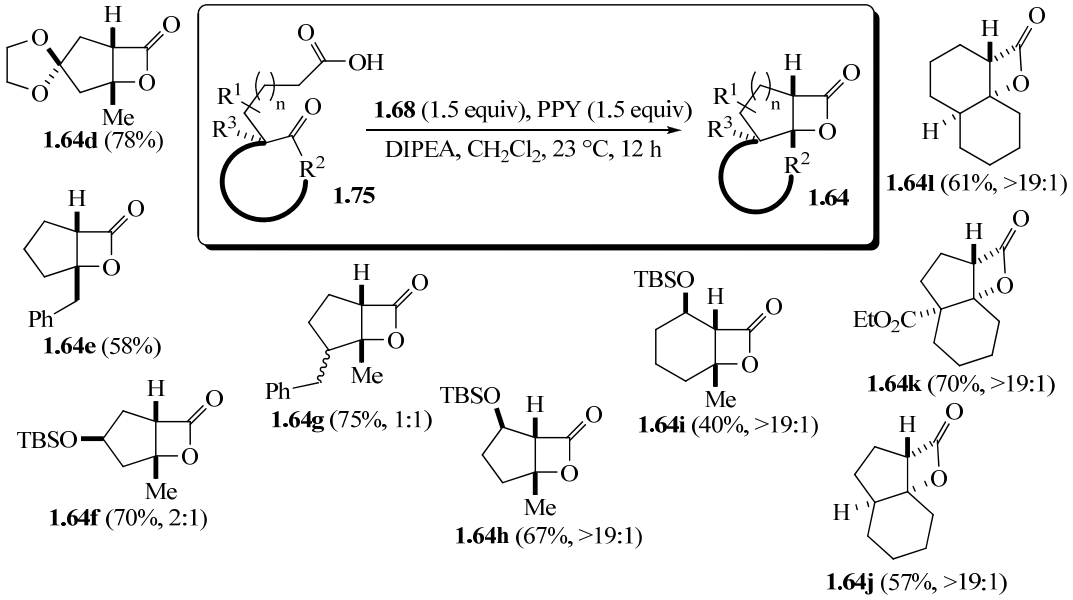
Carbon-based nucleophiles were attempted and applied to Merck IND intermediate **1.74** (Scheme 1.32).[41] Various Grignard reagents and copper sources delivered cyclopentanes **1.73** in good yields with excellent diastereoselectivity *via* S_N2-like inversion of the bicyclic-β-lactones **1.64**. This was applied to a concise synthesis of ketone **1.74**, a Merck IND intermediate utilized toward anti-HIV CCR5 antagonists.

Scheme 1.32



A significant expansion of the scope of this methodology was achieved with the use of more tractable keto-acid substrates **1.75** (Scheme 1.33).[42] A variety of bicyclic- and tricyclic-β-lactones **1.64** were synthesized in good yields and, in some cases, excellent diastereoselectivities. Due to the fact that ketones are substantially less reactive than aldehydes, a stronger nucleophilic promoter was necessary. We found that stoichiometric quantities of PPY effected this transformation quite well.

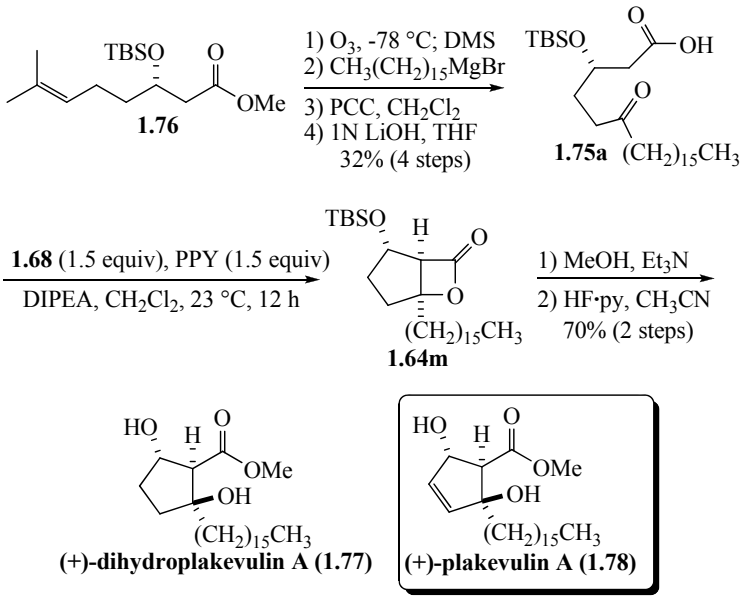
Scheme 1.33



We then applied this methodology toward the total synthesis of (+)-dihydroplakevulin A **1.77** (Scheme 1.34).[42] Keto-acid **1.75a** obtained from known β-silyloxy ester **1.76** was subjected to the optimized conditions to deliver bicyclic-β-

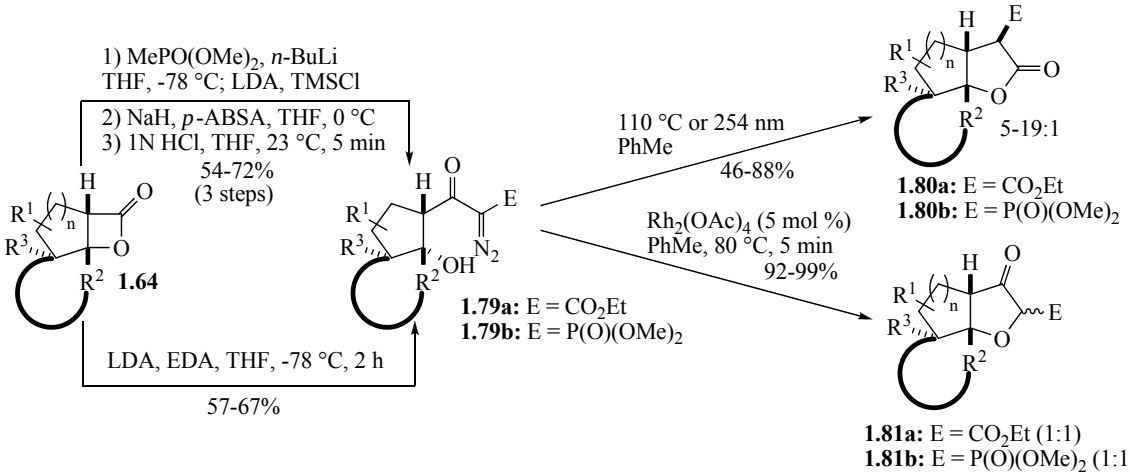
lactone **1.64m** in good yield as a single diastereomer (>19:1). Acyl C-O nucleophilic ring-opening followed by deprotection delivered (+)-dihydroplakevulin A **1.77** in 11% overall yield from ester **1.76**.

Scheme 1.34



These polycyclic-β-lactones were transformed to fused γ-lactones and 3(*2H*)-furanones *via* ring expansions and O-H insertions (Scheme 1.35).[43] First, δ-hydroxy-α-

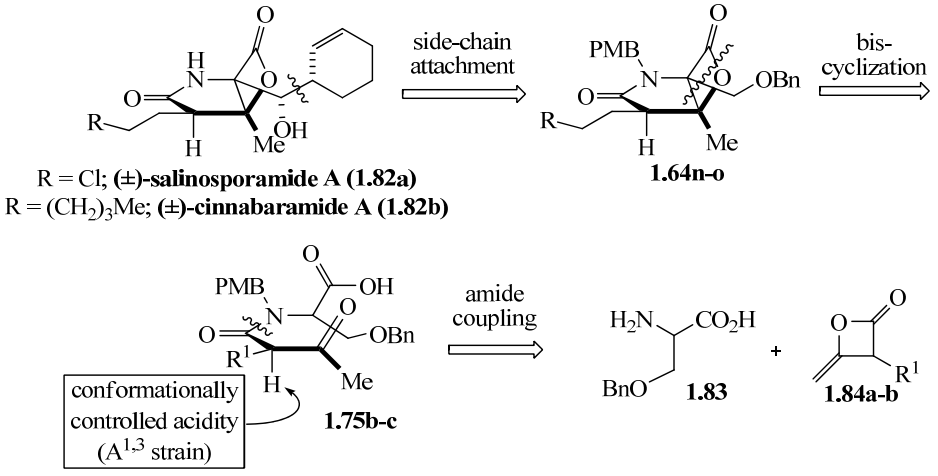
Scheme 1.35



diazo-β-ketoesters **1.79a** were synthesized directly with lithiated ethyl diazoacetate (EDA) and δ-hydroxy-α-diazo-β-phosphonates **1.79b** were produced by a simple three-step protocol. These intermediate diazo compounds then underwent either tandem Wolff rearrangement/lactonization to form γ-lactones **1.80a-b** or rhodium (II) catalyzed O-H insertion to deliver 3(2H)-furanones **1.81a-b**.

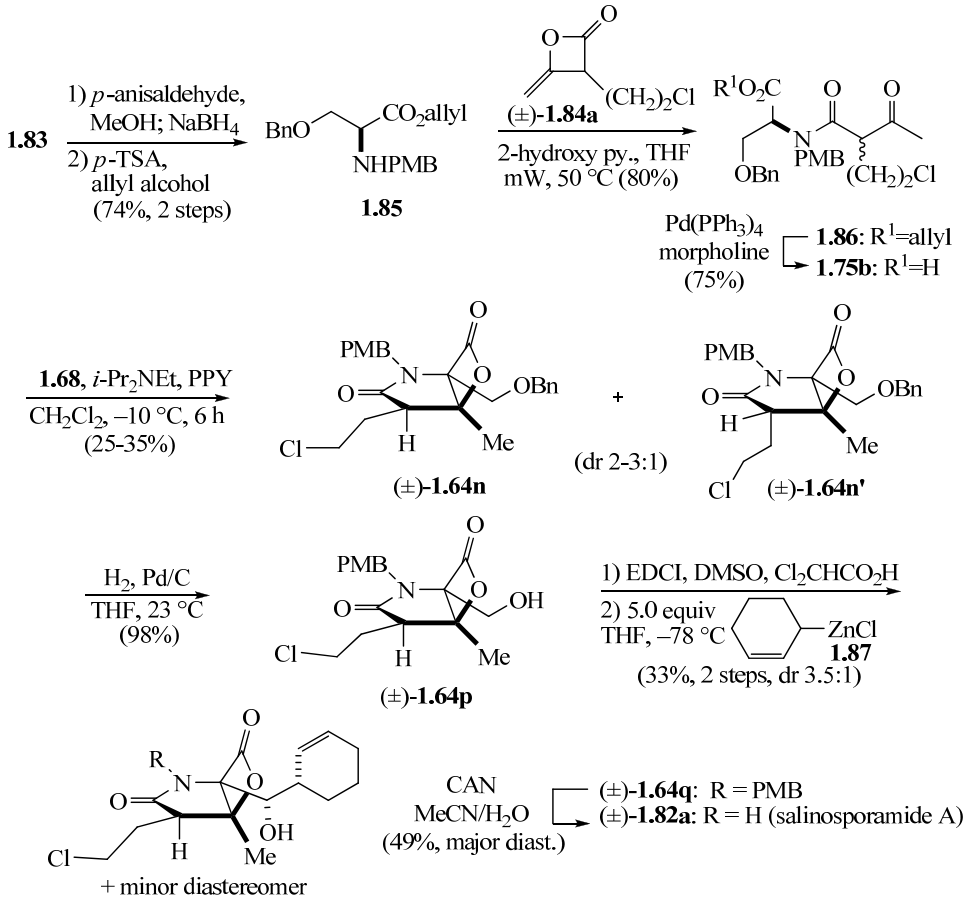
Bicyclic-β-lactones were also utilized toward the total synthesis of (±)-salinosporamide A **1.82a** and (±)-cinnabaramide A **1.82b** (Scheme 1.36).[44] Although omuralide (*c.f.* Figure 1.3) was our original target, the recently isolated and extremely potent (±)-salinosporamide A **1.82a** led us to reconsider. Although (±)-salinosporamide A **1.82a** and (±)-cinnabaramide A **1.82b** differ structurally only in the side chain (R), (±)-salinosporamide A **1.82a** has revealed fascinating information regarding inhibition of the 20S proteasome. Our original strategy toward omuralide was applied to a unified synthetic approach to (±)-salinosporamide A **1.82a** and (±)-cinnabaramide A **1.82b** invoking the organonucleophile-promoted bis-cyclization process.

Scheme 1.36



The total synthesis of (±)-salinosporamide A **1.82a** was achieved in only 9 steps from *O*-benzyl-L-serine **1.83** (Scheme 1.37).[44] Following protection of amine **1.83** and

Scheme 1.37

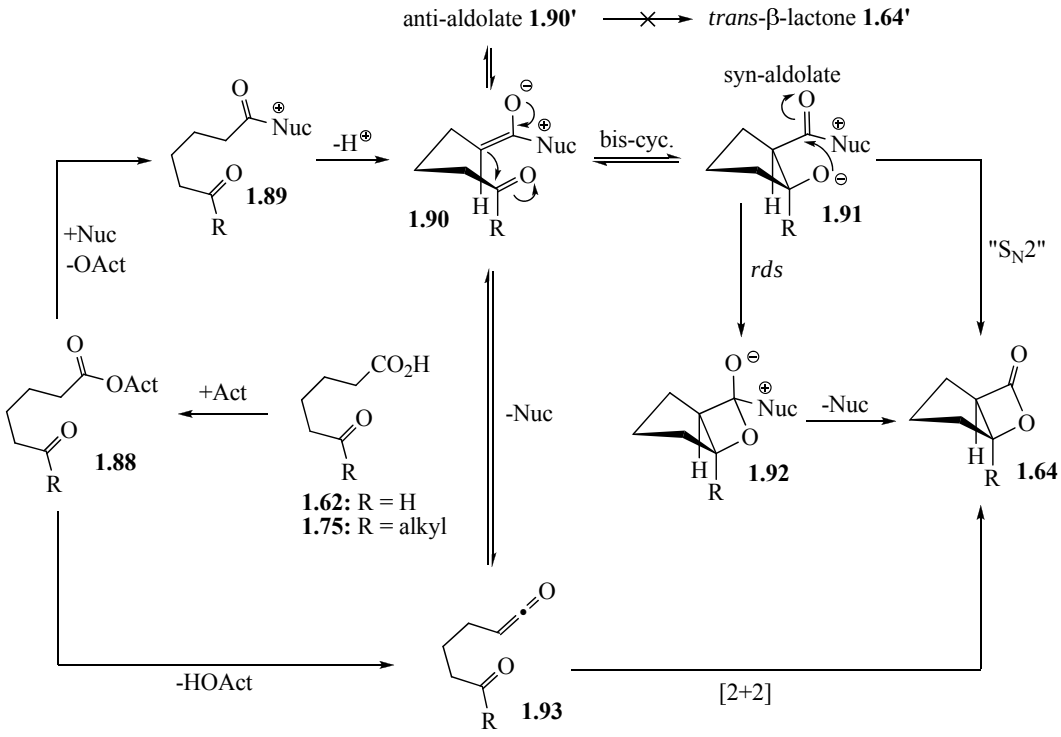


subsequent esterification, coupling with heteroketene dimer **1.84a** provided allyl esters **1.86**. After mild Pd-mediated ester deprotection, bis-cyclization proceeded in satisfactory yield and favored the diastereomer **1.64n** correlating to the relative configuration of (±)-salinosporamide A **1.82a**. It is important to note that if optically active heteroketene dimer **1.84a** were utilized, epimerization should be minimized during the bis-cyclization process due to conformationally controlled (by $A^{1,3}$ strain)

acidity thus constituting an asymmetric route to bicyclic-β-lactone **1.64n**. Hydrogenation and Moffatt oxidation delivered the aldehyde (not shown) which was subjected to the method developed by Corey to introduce the side chain *en route* to alcohol **1.64q**. Finally, PMB deprotection of lactam **1.64q** with CAN provided (±)-salinosporamide A **1.82a**.

An overall mechanism for the bis-cyclization process was set forth (Scheme 1.38).[42] Upon activation of the carboxylic acid and formation of an optically active acyl-

Scheme 1.38



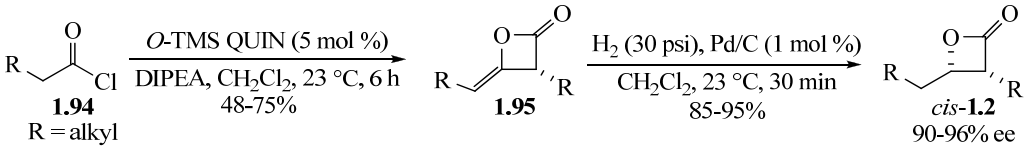
ammonium **1.89**, deprotonation delivers the crucial ammonium enolate **1.90** which presumably undergoes aldol-lactonization to bicyclic-β-lactone **1.64**. In the case of aldehyde-acids **1.62**, the mechanism most assuredly involves an aldol-lactonization process due to the observed high levels of asymmetric induction. Although the evidence

is less conclusive when evaluating keto-acids **1.75**, at this time we are inclined toward a similar aldol-lactonization mechanism instead of a concerted [2+2] cycloaddition.

Conversion of 4-Alkylidene-2-Oxetanones to β-Lactones and Unexpectedly Stable Spiroepoxy-β-Lactones

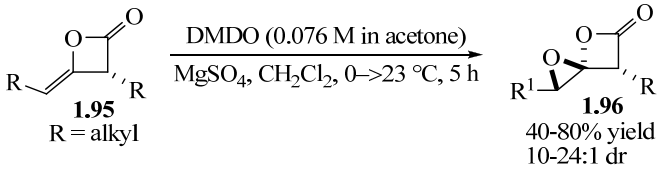
4-Alkylidene-2-oxetanones, or ketene dimers, are valuable intermediates in synthesis and we have shown that they are readily converted to β-lactones and spiroepoxy-β-lactones. Ketene dimerization based on the method of Calter, followed by hydrogenation delivered optically active, pseudosymmetric *cis*-β-lactones **1.2** in good yields and excellent enantioselectivities (Scheme 1.39).[45] Further manipulations of these systems produced mixed results. While epimerizations were dissatisfying and only partial conversions to the corresponding *trans*-β-lactones were obtained, alkylations provided α,α-disubstituted-β-lactones with good diastereoselectivity (not shown).

Scheme 1.39



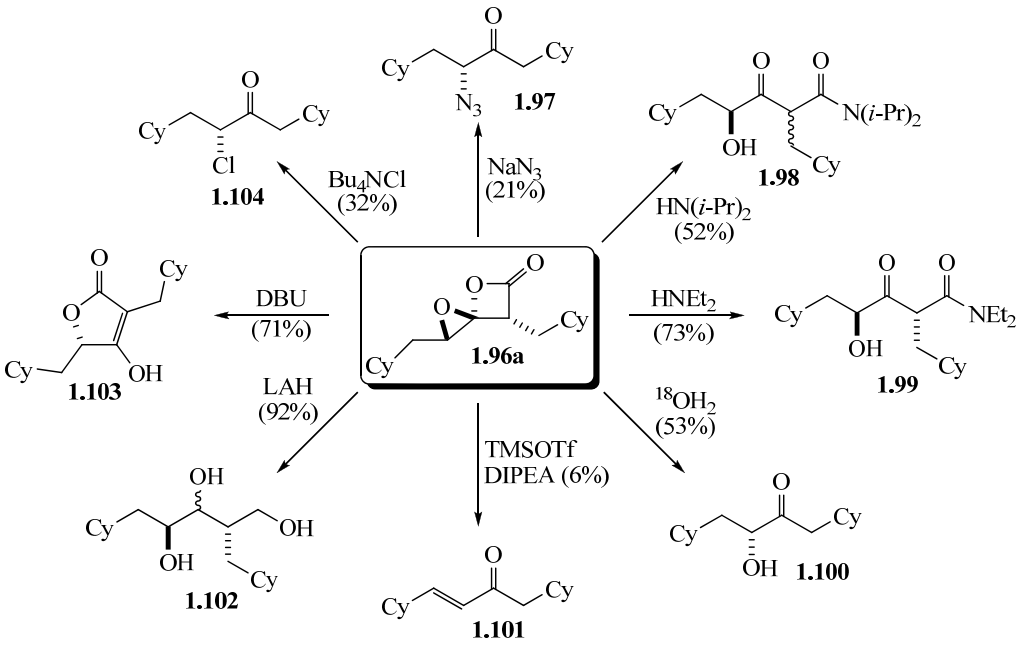
A novel ring system was discovered during attempts to oxidize ketene dimers *in situ* and further manipulate the products *en route* to highly functionalized systems (Scheme 1.40).[46] The spiroepoxy-β-lactones **1.96** were obtained in good to moderate yields and excellent diastereoselectivities when the corresponding ketene dimers **1.95** were treated with freshly prepared DMDO. The relative stereochemistry was confirmed by X-ray crystallography in one case (**1.96a:** R = CH_2Cy).

Scheme 1.40



Attempts to manipulate spiroepoxy-β-lactone **1.96a** led to interesting results (Scheme 1.41).[46] When treated with diisopropylamine, β-ketoamide **1.98** was obtained as a mixture of epimers. Interestingly, when treated with diethylamine, a single diastereomer of the β-ketoamide **1.99** was observed. A third amine base, DBU, delivered butenolide **1.103**. Another interesting experiment with isotopically labeled water showed that nucleophilic attack occurs at the epoxide moiety to deliver α-hydroxy ketone **1.100** in moderate yield.

Scheme 1.41



Conclusions and Future Directions

β-Lactones have emerged as valuable tools for the organic chemist and over the years Prof. Romo's research program has contributed to this arena. We developed syntheses of β-lactones *via* Lewis acid-mediated processes, organonucleophile-promoted bis-cyclizations, and conversion of ketene dimers. We have transformed these strained heterocycles into other useful functionality such as γ-lactones, β-lactams, carbocycles, THFs, and novel spiroepoxy-β-lactones. Several natural products have been synthesized including grandinolide, tetrahydrolipstatin and derivatives, okinonellin B, brefeldin A, belactosin C, dihydroplakevulin A, and salinosporamide A. Utilizing these natural products and derivatives, we have been able to elucidate important information regarding structure activity relationships, enzyme inhibition, and other biological properties. We hope to find continued success in the exploration of β-lactones.

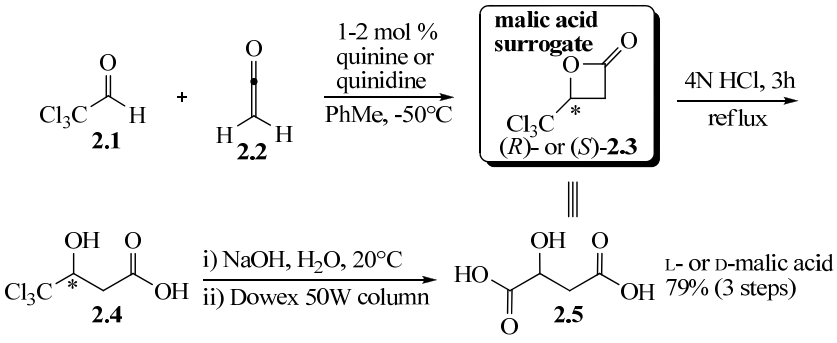
CHAPTER II

RADICAL REACTIONS OF OPTICALLY ACTIVE 4-TRICHLOROMETHYL-β-LACTONE: A POTENTIAL ROUTE TO β-LACTONE SUBSTRATES FOR TETRAHYDROFURAN SYNTHESIS*

Introduction

Although the first β-lactone (2-oxetanone) was synthesized by Einhorn in 1883,[1] it was not until almost 100 years later that these strained heterocycles began to emerge as valuable intermediates for organic synthesis.[2] In 1982, Wynberg and Staring,[3] building on earlier work of Borrmann and Wegler,[4] reported an efficient, asymmetric, and organocatalytic route to (*R*)- and (*S*)-4-trichloromethyl-2-oxetanones **2.3** employing quinine and quinidine to facilitate the union of chloral **2.1** and ketene **2.2** (Scheme 2.1). The utility of these β-lactones **2.3** was demonstrated in concise syntheses of both L- and D-malic acids **2.5**.

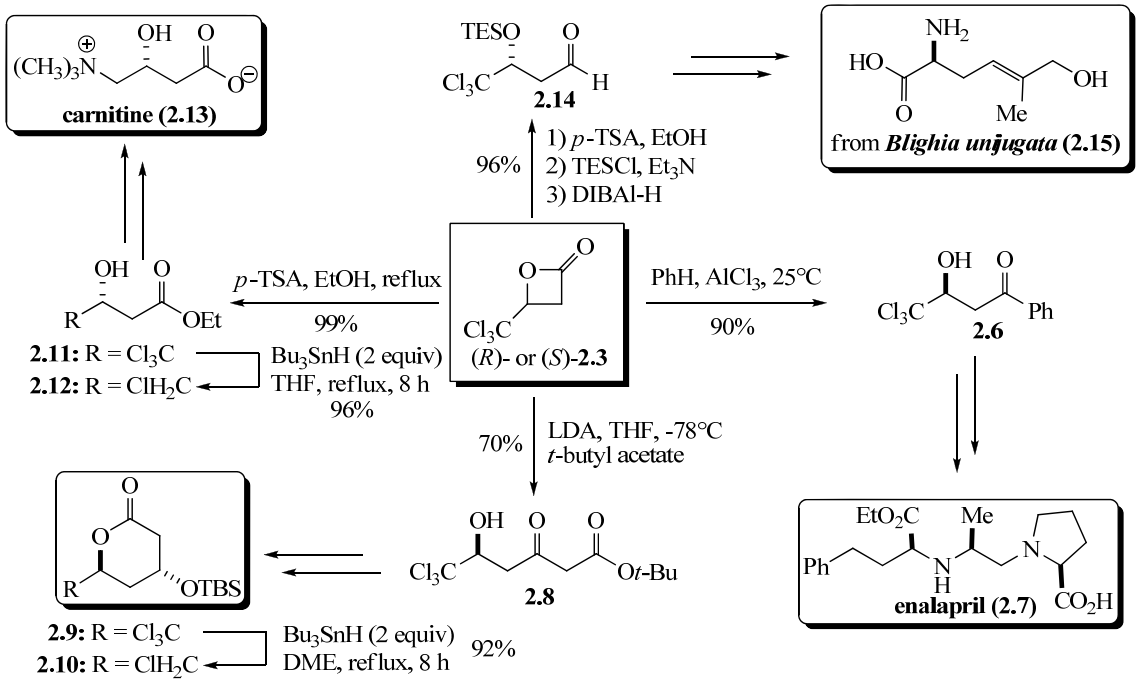
Scheme 2.1



*Reprinted with permission from "Radical Reactions and α-Silylations of Optically Active 4-Trichloromethyl-β-Lactone" by Mitchell, T. A.; Romo, D. *Heterocycles* **2005**, *66*, 627-637. Copyright 2005 *Heterocycles*. See Appendix B.

Fujisawa and coworkers, in collaboration with Wynberg's group, described several transformations of the (*S*)-4-trichloromethyl-β-lactone **2.3**, including a novel Friedel-Crafts acylation in a formal synthesis of enalapril **2.7**, an angiotensin converting enzyme (ACE) inhibitor (Scheme 2.2).[47] Fujisawa also reported a Claisen condensation with this β-lactone to give ketoester **2.8**, an intermediate en route to the synthetically useful δ-lactone **2.9**,[48] and selective dechlorination to deliver alkyl chloride **2.10**.[49] In similar fashion, Song and coworkers dechlorinated β-hydroxy ester **2.11** derived from β-lactone **2.3** to deliver chlorohydrin **2.12**, a useful intermediate toward the total synthesis of carnitine **2.13**.[50]

Scheme 2.2



Our group has also developed transformations of this commercially available chiral synthon (chiron) **2.3** and described its conversion into other useful intermediates.

For example, we prepared aldehyde **2.14** containing a masked α-amino acid functionality in the form of a protected trichloromethyl carbinol, a functionality readily converted to an α-azido ester.[51] This β-silyloxy aldehyde **2.14** was utilized toward the synthesis of a naturally occurring amino acid **2.15** isolated from the seeds of the tropical plant, *Blighia unijugata*.[34] Our recent interest in this useful chiron was toward substrates for further methodology development which will be discussed in subsequent chapters. We envisioned transformations of *(R)*-4-trichloromethyl-β-lactone to either ketoaldehydes or keto-β-lactones (Figure 2.1) which could in turn be stereoselectively manipulated into substituted tetrahydrofurans (THFs).[26,28] Although this initial goal was not realized, several novel transformations of this malic acid surrogate with orthogonal functionality of a trichloromethyl carbinol imbedded within an activated ester were discovered.

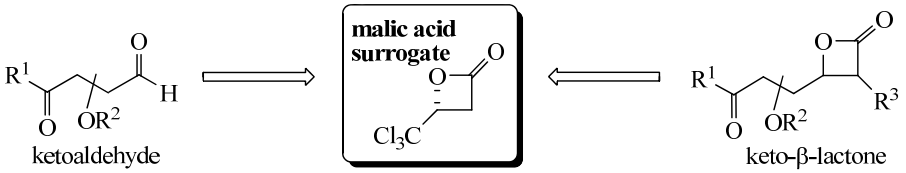
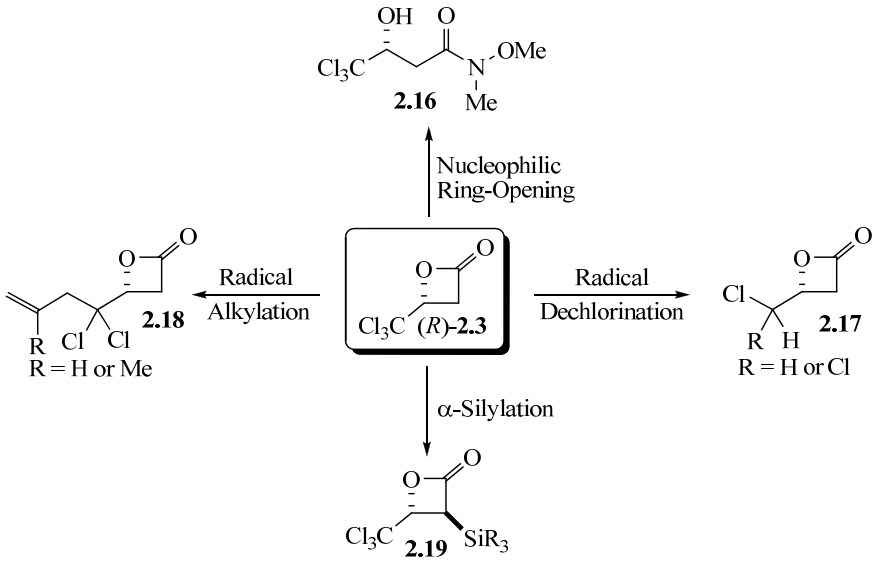


Figure 2.1. Original strategy toward substrates for tetrahydrofuran synthesis

A unique aspect of several of the described reactions is the ability to perform them while maintaining the integrity of the β-lactone (Scheme 2.3). Several of these transformations were designed to provide access to orthogonally protected malic acid surrogates to circumvent numerous protection/deprotection steps often required to employ this useful chiral synthon.[52] Although selective dechlorination of the trichloromethyl moiety is known for systems derived from these β-lactones, we now

report direct dechlorination in the presence of the β-lactone (*i.e.* **2.3** → **2.17**). Building on these results, we have developed a radical alkylation enabling C-C bond formation at the trichloromethyl center while maintaining the integrity of the β-lactone (*i.e.* **2.3** → **2.18**). Finally, we have found that α-silylation of β-lactone **2.3** is possible (*i.e.* **2.3** → **2.19**). Based on prior work,[53] this will enable α-alkylation while circumventing the problematic alkylation of α-unsubstituted β-lactones due to competing Claisen condensations.[54]

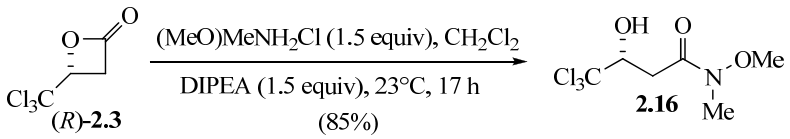
Scheme 2.3



Results and Discussion

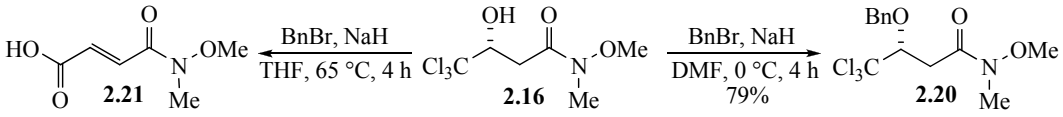
β-Lactone **2.3** was opened to Weinreb amide **2.16** in 85% yield, an orthogonal malic acid surrogate with a trichloromethyl carbinol and Weinreb amide. (Scheme 11).[55]

Scheme 2.4



Although β-hydroxy carbonyls are typically protected under acidic conditions, minimal attempts were undertaken to protect the alcohol with commercially available benzyl bromide under basic conditions (Scheme 2.5). Although our initial attempt using warm THF did not deliver the desired product **2.20**, neither was the expected α,β-unsaturated amide (not shown) produced. Interestingly, the acid-amide **2.21**, which most likely arises by the initial formation of the corresponding dichloro epoxide and then expected β-elimination, was isolated after aqueous work-up. When DMF was the solvent, however, the desired protection occurred in good yield to deliver amide **2.20**. Whether this divergent pathway is solely a result of temperature, a more complicated solvent effect, or a combination of both factors was not examined further.

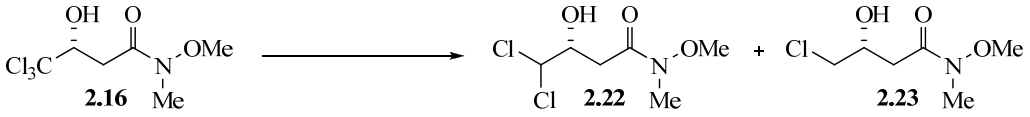
Scheme 2.5



Weinreb amide **2.16** was converted to the dichloride **2.22** by reductive dechlorination, without the need for additional radical initiator, by the method of Song and Fujisawa (Table 2.1, entry 1).[50] However, attempts to prepare the monochloride **2.23** directly from the trichloride **2.16** in this manner with 2.2 equivalents of Bu_3SnH were unsuccessful delivering primarily the dichloride **2.22** in 78% yield (entry 2). Standard radical dehalogenation conditions were then employed with 2,2'-azobisisobutyronitrile (AIBN) as initiator and the monochloride **2.23** was obtained in 77% yield (entry 3).[56] This constitutes a complimentary route to chiron **2.23** prepared previously by other methods including Noyori hydrogenation.[57] We investigated a tin-

free method for dechlorination involving tris(trimethylsilyl)silane[58] and this also delivered the monochloride **2.23** in similar yield (entry 4). It is worth noting that the dichloride can be obtained under all conditions studied by the use of 1.1 equivalent of hydrogen atom donor. Thus, selective radical dehalogenation of Weinreb amide **2.16** provides malic acid surrogates **2.22** and **2.23** without recourse to tin-mediated processes.

Table 2.1. Selective dechlorination of Weinreb amide **2.16**



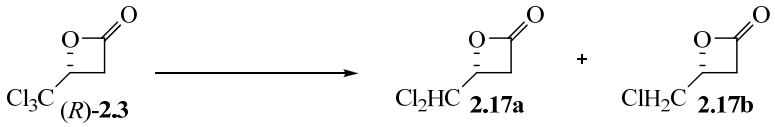
entry	Conditions	**2.22** (% yield)[a]	**2.23** (% yield)[a]
1	Bu_3SnH (1.1 equiv.), THF, reflux, 24 h	78	<5[b]
2	Bu_3SnH (2.2 equiv.), THF, reflux, 24 h	78	<5[b]
3	Bu_3SnH (2.1 equiv.), PhH, AIBN, 60 ˚C, 16 h	<5[b]	77
4	TMS_3SiH (2.1 equiv.), PhMe, Et_3B, 23 ˚C, 1 h	<5[b]	78

[a] Refers to isolated yields. [b] Trace amounts of the minor products were detected in crude ^{1}H NMR analysis but were removed by chromatography.

We next studied direct radical dechlorination of the trichloromethyl-β-lactone **2.3**. There are a few examples of radical cleavage at the γ-carbon of β-lactones, which proceed without cleavage of the ring.[59] For example, Crich has previously described radical dehalogenations of γ-bromo-β-lactones, and described the use of a full equivalent of Ph_2Se_2 (*i.e.* 2.0 equiv. of PhSeH) to suppress ring cleavage processes in favor of debromination.[59e] Similar to dechlorination of amide **2.16**, initiator-free conditions applied to β-lactone **2.3** delivered the dichloride **2.17a** in 70% yield with only a trace amount of monochloride **2.17b** present in the crude ^{1}H NMR spectrum (Table 2.2, entry

1). We also obtained the volatile monochloride **2.17b** when AIBN was added to the reaction, albeit in only 32% yield (entry 2). Attempted silicon-mediated dechlorination gave the dichloride **2.17a** in 57% yield with only 1.1 equivalent of silane (entry 3), but the monochloride **2.17b** proved difficult to separate from boron byproducts when 2.2 equivalents of silane were employed. Ultimately, the use of tributyltin hydride and triethylborane cleanly provided the monochloride **2.17b** with no dichloride detected, albeit in 25% yield (entry 4). The volatility of the monochloride **2.17b** undoubtedly contributes to lower yields in this case but may also be a result of alternative reaction pathways leading to highly volatile byproducts (*e.g.* **2.34b**, *vide infra*). To the best of our knowledge, these are the first direct reductive dechlorinations of γ-chloro-β-lactones that maintain the integrity of the strained heterocycle. In contrast to examples by Crich, these transformations may be possible due to the stabilizing effect of the resident chlorine atoms on the radical center.

Table 2.2. Dechlorination of 4-trichloromethyl-β-lactone *(R)*-**2.3**

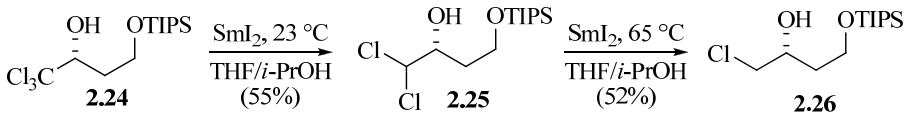


entry	conditions	**2.17a** (% yield)[a]	**2.17b** (% yield)[a]
1	Bu_3SnH (1.1-2.2 equiv), THF, reflux, 24 h	78	<5[b]
2	Bu_3SnH (2.1 equiv), PhH, AIBN, 60 ˚C, 16 h	<5[b]	32
3	TMS_3SiH (1.1 equiv), PhMe, Et_3B, 23 ˚C, 1 h	57[c]	<5[b]
4	Bu_3SnH (2.1 equiv), PhMe, Et_3B, 23 ˚C, 3 h	<5[b]	25

[a] Refers to isolated yields. [b] Trace amounts of the minor products were detected in crude ^1H NMR analysis but were removed by chromatography. [c] The product was difficult to isolate from byproducts.

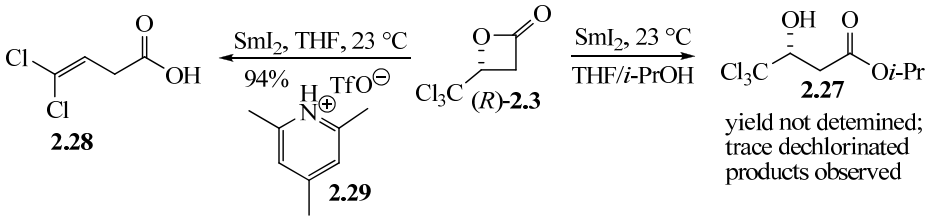
We thought that dechlorination would be possible using samarium diiodide (SmI_2) based on our success with the fully reduced, monoprotected diol **2.24** (Scheme 2.6). Monodechlorination was achieved at ambient temperature to provide dichloride **2.25**, while bis-dechlorination proceeded under more forcing conditions to provide monochloride **2.26**. Presumably, SmI_2 promotes consecutive single electron transfer (SET) processes (*vide infra*) and the resulting dichloromethyl anion abstracts a proton from *i*-PrOH.

Scheme 2.6



When these and related conditions were applied directly to β-lactone **2.3**, mixed results were obtained (Scheme 2.7). The exact conditions produced the ring-opened ester **2.27** with only minor quantities of the dichloride (not shown) and no β-lactones detected. We attempted to trap the dichloromethyl anion with a non-nucleophilic proton source, collidinium triflate **2.29**.[60] The dichloride **2.17a** was not formed, but known acid **2.28**[61] derived from ring scission was obtained in 94% yield.[62] Hydrogen atom sources, such as 1,4-cyclohexadiene, met with little success in attempts to capture the dichloromethyl radical presumably formed after single electron transfer (*vide infra*).

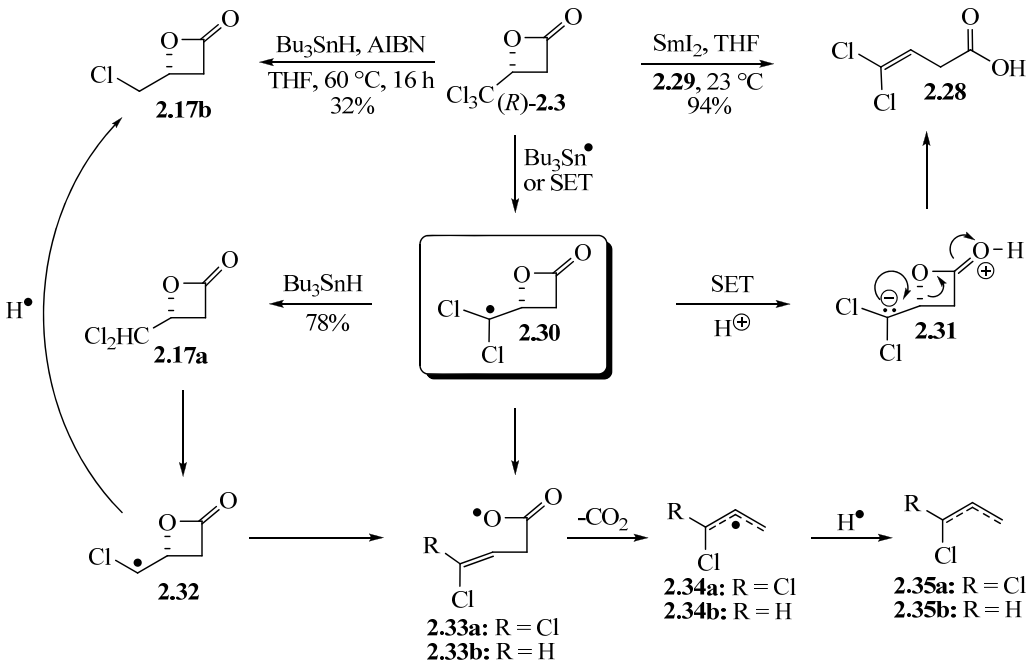
Scheme 2.7



As mentioned previously, we propose that SmI_2 promotes two consecutive single electron transfer (SET) processes to ultimately form the dichloromethyl anion **2.31** as opposed to the dichloromethyl radical **2.30** which is presumably formed under more conventional radical conditions (Scheme 2.8). Taken together, these reactions demonstrate an interesting dichotomy between radical and anionic dechlorination of γ-halo-β-lactones and may reflect the relative stability of an oxy radical versus an oxy anion. Based on the work of Crich,[59e] it is possible that dichloromethyl radical **2.30** could undergo fragmentation to the oxy radical **2.33a**. A more plausible explanation that accounts for the observed mono-dechlorination of β-lactone **2.3** is that radical **2.30** is inductively stabilized by *two* resident chlorine atoms, and therefore has sufficient lifetime to abstract a hydrogen atom from Bu_3SnH leading to dichloride **2.17a**. However, after formation of the monochloromethyl radical **2.32**, the aforementioned fragmentation to form oxy radical **2.33b** seems more likely due to the fact that this radical is inductively stabilized by only *one* resident chlorine atom. In the event that either radical **2.30** or **2.32** undergoes ring scission leading to oxy radical **2.33a** or **2.33b**, respectively, it would then undergo rapid decarboxylation as observed by Crich and finally reduction if another equivalent of hydrogen atom donor is present.[59e] This pathway would ultimately deliver the volatile dichloroalkenes **2.35a-b** (as mixtures of regioisomers). Although we have not detected these byproducts, the expected decrease in stability of monochloromethyl radical **2.32** versus dichloromethyl radical **2.30** may be reflected in decreased yields in the bis-dechlorination leading to monochloro-β-lactone **2.17b** (*c.f.* Table 2.2). In contrast, SET with SmI_2 to generate the dichloromethyl anion

2.31 from dichloromethyl radical **2.30** should be a favorable process due to similar inductive arguments (*vide supra*) in which *two* resident chlorine atoms favor the formation of dichloromethyl anion **2.31**. These inductive effects, in combination with a good leaving group (*i.e.* β-lactone moiety) alpha to the dichloromethyl anion and an effective activating agent (*i.e.* collidinium triflate), promote the formation of carboxylic acid **2.28** in excellent yield.

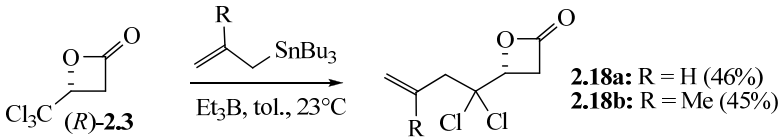
Scheme 2.8



Encouraged by successful dechlorinations in the presence of the β-lactone moiety and with some understanding of the reactivity of the dichloromethyl radical **2.30**, we focused our attention on tin-mediated C-C formation.[63] Several attempts with allylstannes, including allyltributylstannane, allyltriphenylstannane, and tetrallyltin, gave promising results, but could not be driven to completion with 1.1 equivalent and this was complicated further by the inability to separate product from starting material. However,

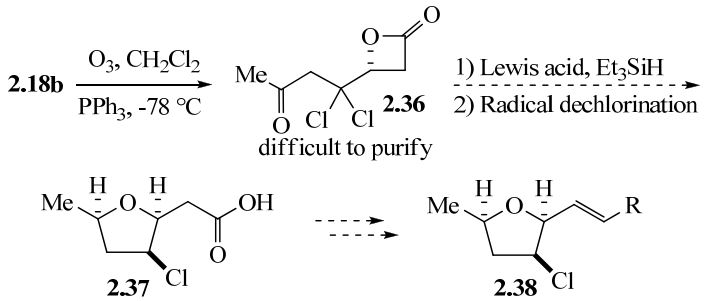
we ultimately found that treatment of β-lactone **2.3** with 2.5 equivalents of allyltributylstannane provided the monoalkylated product **2.18a** in 46% yield (Scheme 2.9). Employing methallyltributylstannane under similar conditions delivered β-lactone **2.18b** in 45% yield. Although the yields are moderate, this represents a novel functionalization of β-lactone **2.3** and this method should be amenable to radical alkylations of other trichloromethyl moieties.[64]

Scheme 2.9



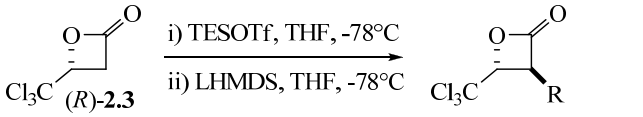
Application toward the rubrosides,[65] a family of natural products with a related chloro-THF substructure, failed to proceed as expected (Scheme 2.10). Ozonolysis of alkenyl-β-lactone **2.18b** seemed to deliver keto-β-lactone **2.36**, but purification was troublesome and this could be attributed to byproducts formed from β-elimination of a chloride or some other undesirable pathway. Lewis acid-mediated reductive cyclization[25] followed by radical dechlorination[58] from the less hindered face of THF **2.37** would presumably deliver chloride **2.38** as an intermediate to the rubrosides.

Scheme 2.10



In efforts to functionalize the α-carbon of β-lactone **2.3**, we studied enolization and subsequent trapping with various electrophiles. Prior attempts to alkylate α-unsubstituted β-lactones have proven to be difficult and inefficient due to both self-condensation (Claisen) and dialkylation with only a few examples being successful with highly reactive electrophiles.[54] Attempts to apply several of these reported methods to β-lactone **2.3** were unsuccessful. However, we discovered a novel α-silylation of β-lactone **2.3** when it was treated with lithium hexamethyl disilazide (LiHMDS) and silyl triflates at -78 ˚C (Scheme 2.11). The use of TESOTF provided a moderate yield of α-triethylsilyl-β-lactone **2.19a** with recovered starting material, while TIPSOTf was sluggish and lower yielding, possibly due to steric bulk of the TIPS group. We have not determined if this reaction proceeds through a direct α-silylation or by *O*-silylation followed by Brook rearrangement. This enables further functionalization at the α-carbon as previously demonstrated by Pons[66] and Mead.53

Scheme 2.11



2.19a: R = $SiEt_3$ (31%)
2.19b: R = Si*i*-Pr_3 (20%)

Conclusions

We have demonstrated several new transformations of the commercially available (*R*)-4-trichloromethyl-β-lactone including radical alkylations, α-silylations, and alternative, tin-free methods for mono- and bis-dechlorinations. Importantly, several of

these reactions can be conducted while maintaining the integrity of the β-lactone, thus enabling subsequent acylations or alkylations with the β-lactone moiety. A Weinreb amide derivative was readily prepared and then selectively dechlorinated providing access to malic acid surrogates with orthogonal functional groups. Chain extensions at the γ-carbon were possible *via* radical alkylations providing access to further functionalized γ-chloro-β-lactones. α-silylations of β-lactone were shown to be feasible albeit in low yield.

CHAPTER III

DEVELOPMENT OF A DIASTEREOSELECTIVE STEPWISE SYNTHESIS OF TETRAHYDROFURANS VIA MEAD REDUCTIVE CYCLIZATION (MRC) OF KETO-β-LACTONES DERIVED FROM THE TANDEM MUKAIYAMA ALDOL-LACTONIZATION (TMAL)*

Introduction

Tetrahydrofurans (THFs) are common heterocyclic motifs in natural products and thus many routes have been developed to access these moieties. These approaches can be divided into three major synthetic strategies (Figure 3.1).[67] In one strategy, an oxygen nucleophile displaces, adds to, or opens an activated group (G) such as a leaving group (*e.g.* mesylate),[68] an olefin (*e.g.* iodoetherification),[69] or a strained ring (*e.g.* epoxide)[70] to form a new C-O bond (Type I). In another strategy, a nucleophile adds to an oxocarbenium intermediate and a new C-C or C-H bond is formed (Type II).[71] Finally, several miscellaneous strategies have been developed including ring contractions of six-membered rings such as tetrahydropyrans[72]and δ-lactones.[73]

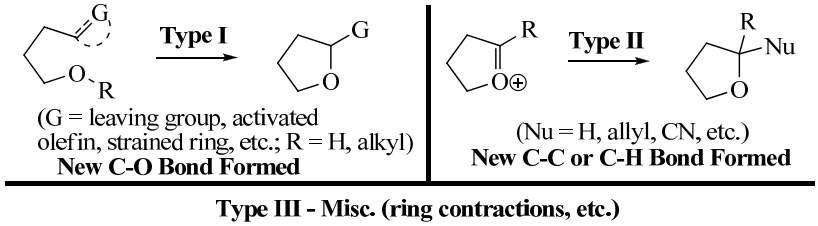


Figure 3.1. General strategies toward tetrahydrofurans

*Reprinted with permission from "Diastereoselective Synthesis of Tetrahydrofurans *via* Mead Reductive Cyclization of Keto-β-Lactones Derived from the Tandem Mukaiyama Aldol-Lactonization (TMAL) Process" by Mitchell, T. A.; Romo, D. *J. Org. Chem.* **2007**, *72*, 9053-9059. Copyright 2007 American Chemical Society. See Appendix B.

Some of the most elegant and efficient approaches to THFs are Type III strategies. For example, Overman developed the Prins-pinacol route to THFs[74] that has been applied to *trans*-kumausyne (Figure 3.2) and other members of the *Laurencia* family of marine natural products,[75] as well as (-)-citreoviral[76] and briarellin E.[77]

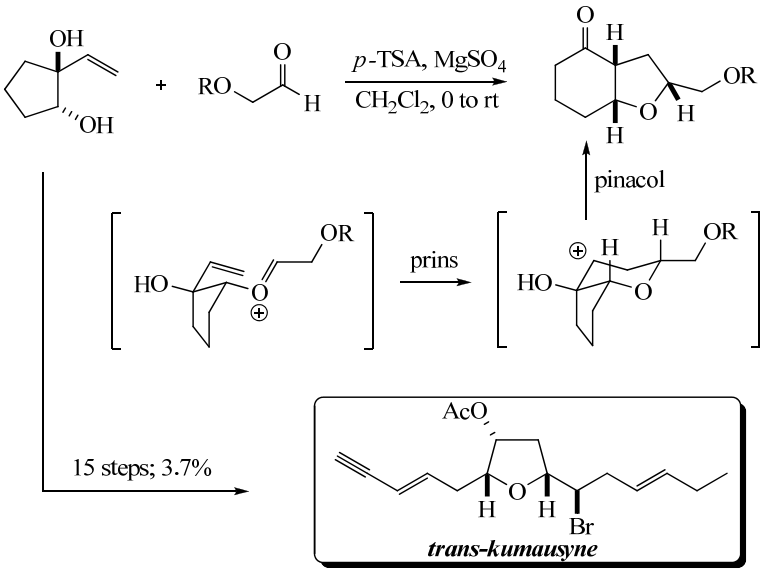


Figure 3.2. Overman's Prins-pinacol strategy toward *trans*-kumausyne

Roush and Micalizio[78] refined and expanded the [3+2] annulation of aldehydes and allylsilanes toward THFs first reported by Panek (Figure 3.3).[79] This elegant strategy has been applied to pectenotoxin II,[80] amphidinolide F,[81] asimicin (Figure 3.3),[82] (+)-bullatacin,[83] angelmicin B,[84] and haterumalide ND.[85]

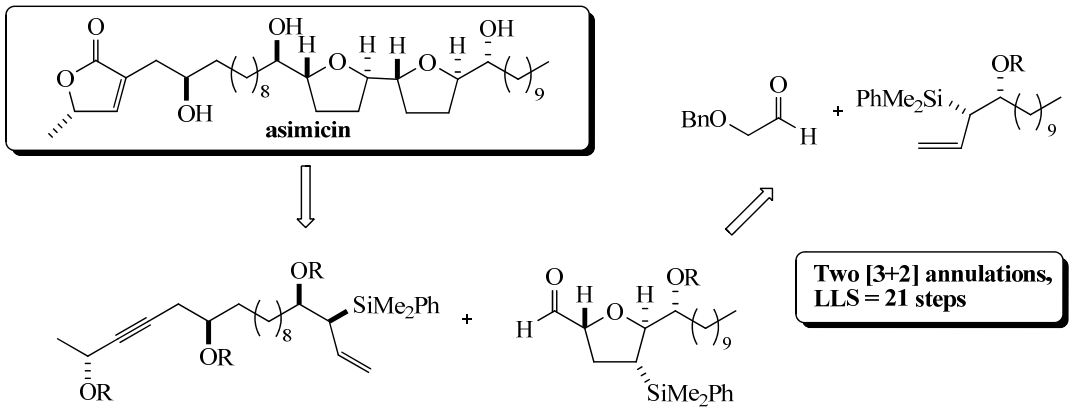


Figure 3.3. Roush's [3+2] annulation strategy toward asimicin

Lee developed a radical cyclization[86] approach to THFs and utilized this method in the total synthesis of pamamycin 607 (Figure 3.4),[87] (+)-methyl nonactate,[88] kumausallene,[89] and kumausyne.[90]

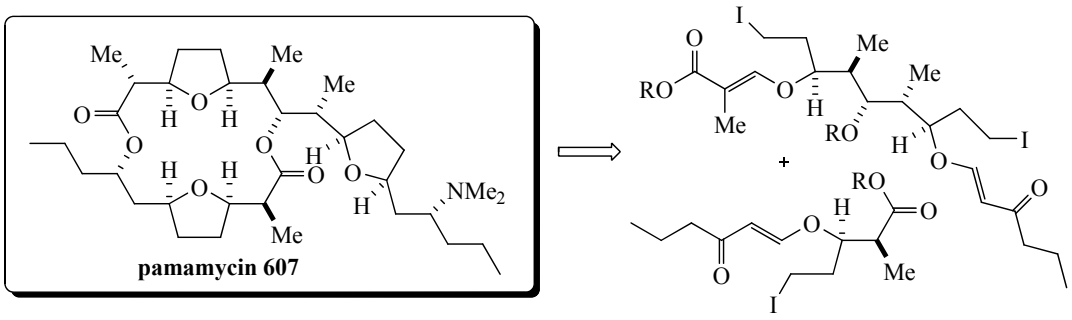
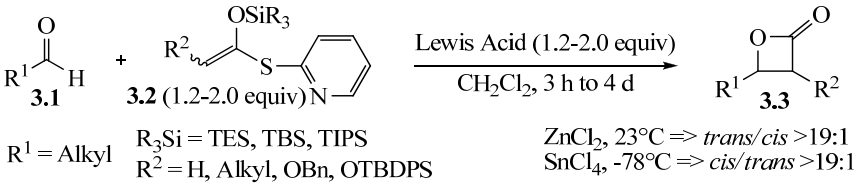


Figure 3.4. Lee's radical cyclization strategy toward pamamycin 607

β-Lactones continue to gain prominence as versatile intermediates in synthesis,[5] to be found as integral components in bioactive natural products,[2] and to demonstrate utility as enzyme inhibitors with therapeutic potential.[6] We have reported diastereoselective routes to both *cis*[22] and *trans*[16] β-lactones **3.3** *via* tandem

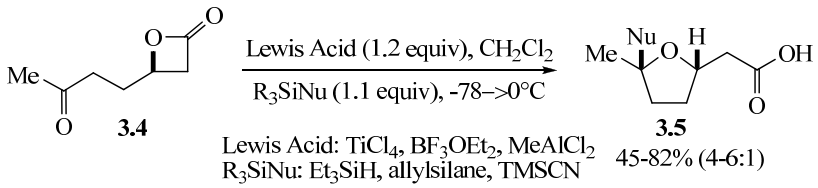
Mukaiyama[15] aldol-lactonization (TMAL) processes with aldehydes **3.1** and thiopyridyl ketene acetals **3.2** (Scheme 3.1). The TMAL was applied in total syntheses of panclicin D,[16] tetrahydrolipstatin/orlistat,[19] okinonellin B,[21] brefeldin A,[24] and belactosin C.[30]

Scheme 3.1



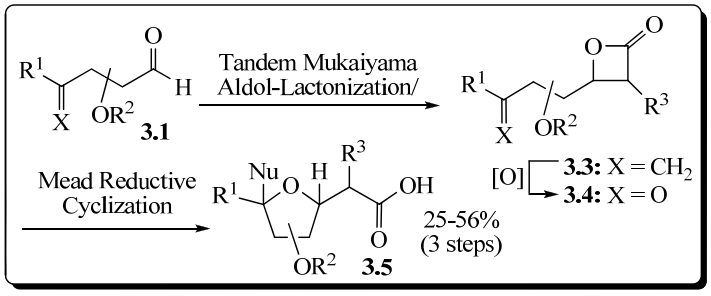
In addition, Mead demonstrated the utility of simple keto-β-lactones **3.4** for the synthesis of THFs **3.5** by a Lewis acid mediated, reductive cyclization (Scheme 3.2).[25]

Scheme 3.2



Building on these precedents, we envisioned a highly diastereoselective synthesis of substituted tetrahydrofurans **3.5** by combining the TMAL process and Mead reductive cyclization of substituted keto-β-lactones **3.4** (Scheme 3.3).[26]

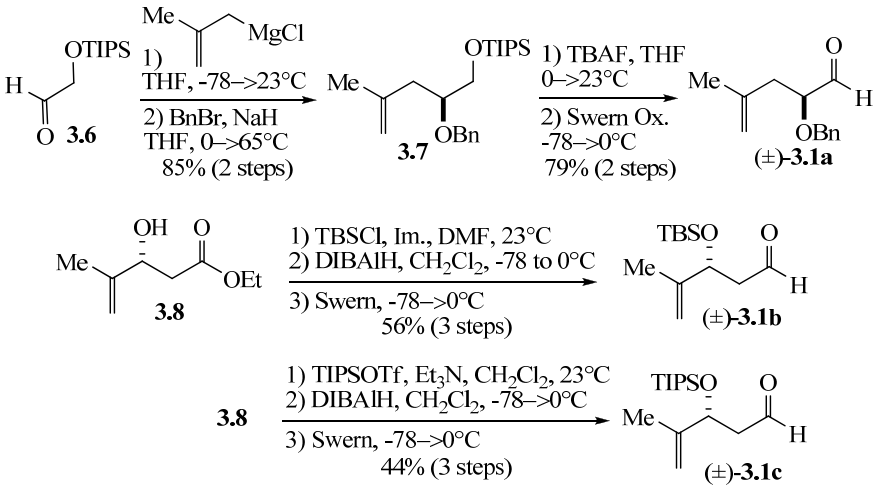
Scheme 3.3



Results and Discussion

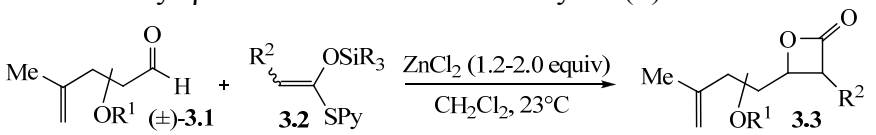
Herein, we report a hybrid of Type I and Type II strategies toward THFs that involves a Mead reductive cyclization (MRC)[25] of keto-β-lactones prepared by the tandem Mukaiyama aldol-lactonization (TMAL) process.[16] The required aldehydes (±)-**3.1a-c**, possessing either α- or β-oxygenation, were prepared in racemic fashion by standard procedures (Scheme 3.4). Aldehyde **3.6** was treated with methallylmagnesium magnesium chloride and the resulting alcohol was protected as the benzyl ether **3.7**. TBAF deprotection and Swern oxidation provided the α-benzyloxy aldehyde (±)-**3.1a**. Two similar β-silyloxy aldehydes (±)-**3.1b-c** that correspond to TMAL substrates previously utilized in our group were synthesized by similar sequences. After silyl protection of the β-hydroxy ester **3.8** with either TBSCl or TIPSOTf, we found that reduction with DIBAlH followed by Swern oxidation[91] was the most straightforward route to large scale production of aldehydes (±)-**3.1b-c**.

Scheme 3.4



Application of the TMAL process with α-benzyloxy aldehyde (±)-**3.1a** employing propionate-derived ketene acetal **3.2a** proceeded with high diastereoselectivity to give β-lactone *syn*-**3.3a** based on chelation control (Table 3.1, entry 1). Acetate-derived ketene acetal **3.2b** gave low diastereoselectivity as expected based on previous results with a slight preference for the Felkin-Anh derived β-lactone *anti*-**3.3b** (entry 2). Both of these TMAL reactions proceeded in comparable yield and diastereoselectivity at 0 °C with slightly increased reaction times. Previous examples of the $ZnCl_2$-mediated TMAL have proceeded at ambient temperature and this apparent increase in reactivity is presumably a result of increased electrophilicity of the aldehyde due to inductive effects of the α-benzyloxy substituent. The sterically demanding, oxygenated ketene acetal **3.2c** required prolonged reaction times with aldehyde (±)-**3.1a** to deliver moderate yields and divergent diastereoselectivity of either *anti*- or *syn*-β-lactone **3.3c** depending on the equivalents of $ZnCl_2$ that were employed (entries 4-5). When equimolar quantities of Lewis acid and ketene acetal **3.2c** were employed, β-lactone *anti*-**3.3c** was the major product, whereas when 6-10 equivalents of $ZnCl_2$ were utilized, the selectivity was reversed. The latter example (*i.e. syn*-**3.3c**, entry 5) represents the first instance of a *cis*-β-lactone produced in the $ZnCl_2$-mediated TMAL from an *aliphatic* aldehyde. Both of these results provided new insight regarding relative diastereoselectivity in the TMAL and will be discussed further in Chapter V. In the case of β-silyloxy aldehydes (±)-**3.1b-c**, β-lactones **3.3d-f** were obtained in acceptable yields and moderate diastereoselectivities and these results (entries 6-8) are consistent with Evans' model[92] and our previous studies.[16,19]

Table 3.1. Alkenyl-β-lactones **3.3a-f** from aldehydes (±)-**3.1a-c** *via* the TMAL



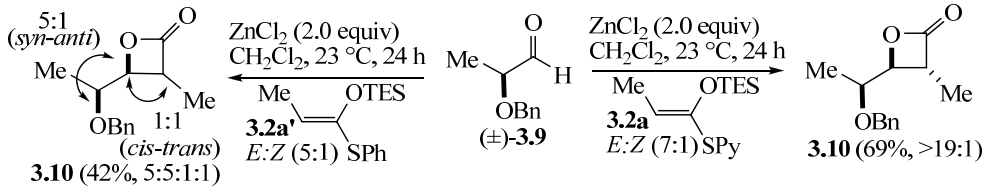
entry	aldehyde	ketene acetal	alkenyl-β-lactone[a]	time[b]	% yield[c]	dr[d]
1	(±)-**3.1a**	Me, OTES; **3.2a** SPy; *E:Z* (4:1)	Me, OBn, Me; *syn*-**3.3a**	14 h	83	>19:1[e]
2	(±)-**3.1a**	OTES; **3.2b** SPy	Me, OBn; *anti*-**3.3b**	9 h	80	1.5:1[e]
3	(±)-**3.1a**	OTES; **3.2b'** SPh	Me, OBn; *syn*-**3.3b**	24 h	68	2.7:1[e]
4	(±)-**3.1a**	OTIPS, TBDPSO, SPy; **3.2c:** *Z:E* (>19:1)	Me, OBn, OTBDPS; *anti*-**3.3c**	12 d	56[f]	4:1[e]
5	(±)-**3.1a**	OTIPS, TBDPSO, SPy; **3.2c:** *Z:E* (>19:1)	Me, OBn, OTBDPS; *syn*-**3.3c**	7 d	47[f]	1.7:1[e]
6	(±)-**3.1b**	Me, OTBS; **3.2d** SPy; *E:Z* (>19:1)	TBSO, Me, Me; *anti*-**3.3d**	28 h	59	9:1
7	(±)-**3.1b**	OTES; **3.2b** SPy	TBSO, Me; *anti*-**3.3e**	20 h	69[f]	2:1
8	(±)-**3.1c**	OTIPS, TBDPSO, SPy; **3.2c:** *Z:E* (>19:1)	TIPSO, Me, OTBDPS; *syn*-**3.3f**	10 d	75	5:1

[a] With the exception of *syn*-**3.3c**, only *trans* β-lactones (when applicable) were produced and the major diastereomer is displayed. [b] Entries 1-2 proceeded efficiently at 0 °C with increased reaction times. [c] Refers to purified yield (SiO_2) of both diastereomers. [d] Refers to relative stereochemistry and was determined by analysis of crude reaction mixture by ^{1}H NMR (300 MHz). [e] Diastereomers were separable by flash column chromatography. [f] Yield includes subsequent ozonolysis step.

Previous studies by Zhao utilizing propionate-derived *thiophenyl* ketene acetal **3.2a'** with α-benzyloxy aldehyde (±)-**3.9** demonstrated a significant decrease in

diastereoselectivity when compared to propionate-derived thiopyridyl ketene acetal **3.2a** (Scheme 3.5).[17] In contrast to thiopyridyl ketene acetal **3.2a**, thiophenyl ketene acetal **3.2a'** provides decreased relative diastereoselectivity (*i.e. syn* vs. *anti*) and shows no discrimination of internal diastereoselectivity (*i.e. cis* vs. *trans*) at the α-position of the β-lactone **3.10**. Based on these results, we proposed that acetate-derived thiophenyl ketene acetal **3.2b'** could effectively reverse the low relative diastereoselectivity observed with acetate-derived thiopyridyl ketene acetal **3.2b** (*i.e.* Table 3.1, entry 2 vs. entry 3). This reversal was indeed observed with thiophenyl ketene acetal **3.2b'** to provide α-unsubstituted-β-lactone *syn*-**3.3b** (entry 3), albeit with diminished diastereoselectivity (*i.e.* 5:1 → 2.7:1) from that observed by Zhao with propionate-derived thiophenyl ketene acetal **3.2a'** and α-benzyloxy aldehyde (±)-**3.9** (*vide supra*). This difference in reactivity between thiophenyl and thiopyridyl ketene acetals could be attributed to greater chelation between the monodentate thiophenyl ligand and $ZnCl_2$.

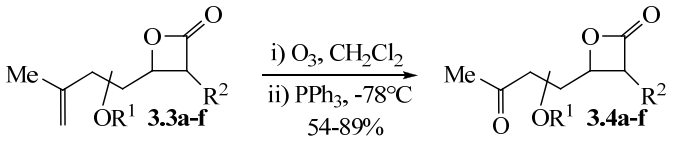
Scheme 3.5



Ozonolysis of alkenyl-β-lactones **3.3a-f** proceeded smoothly to deliver the required keto-β-lactones **3.4a-f** for MRC (Scheme 3.6).[93] The use of PPh_3 to reduce the ozonides proved to be more efficient leading to fewer byproducts compared to dimethyl sulfide and therefore simplified purification. Due to minor instability noted for keto-β-

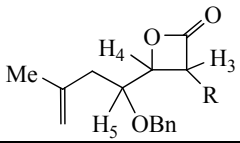
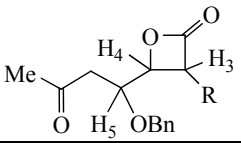
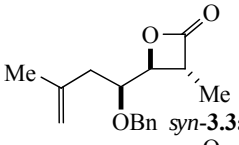
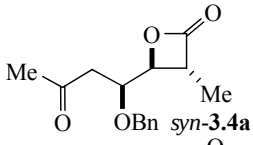
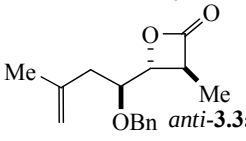
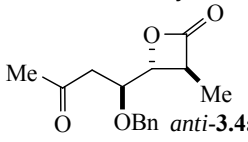
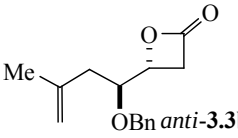
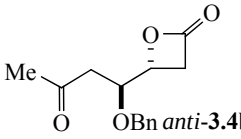
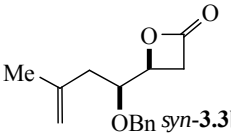
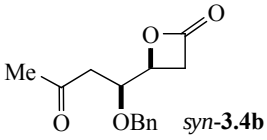
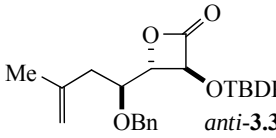
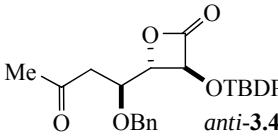
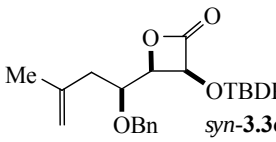
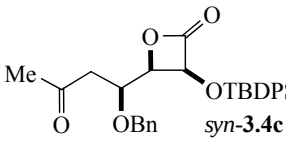
lactones **3.4a-f**, they were typically rapidly purified and used immediately in subsequent Mead reductive cyclizations.

Scheme 3.6



With the exception of β-lactones **3.3c,** stereochemical assignment of β-lactones **3.3a-f** obtained *via* the TMAL corresponded to previous reports and were subsequently confirmed by nOe analysis of the corresponding THFs **3.5a-f** (*vide infra*). The γ-benzyloxy-β-lactones **3.3a-c** and **3.4a-c** displayed a significant trend in coupling constants that may be a predictive tool for the assignment of relative (*i.e. syn* vs. *anti*) stereochemistry of these systems (Table 3.2). It is well established that the internal stereochemistry (*i.e. cis* vs. *trans*) of β-lactones is assigned based on coupling constant analysis and this is observed for γ-benzyloxy-β-lactones **3.3a-c** and **3.4a-c** (*cis*: $J_{3,4}$ = 5.7-6.0 Hz; *trans*: $J_{3,4}$ = 3.3-4.5 Hz).[94] To the best of our knowledge, the determination of relative stereochemistry of these systems has not previously been based solely on coupling constant analysis. In the case of γ-benzyloxy-β-lactones **3.3a-c** and **3.4a-c**, the coupling constants for *syn* ($J_{4,5}$ = 4.5-6.0 Hz) and *anti* ($J_{4,5}$ = 2.7-3.6 Hz) diastereomers followed a clear trend that is consistent with our previous studies.[20,21] This is likely due to subtle differences of dihedral angles of the lowest energy conformations based on torsional strain and cancellation of dipoles. Although subsequent nOe data for direct stereochemical assignment of THF *syn*- and *anti*-**3.5c** was inconclusive, tentative assignment of β-lactones **3.3c** and **3.4c** based on this coupling constant trend is plausible.

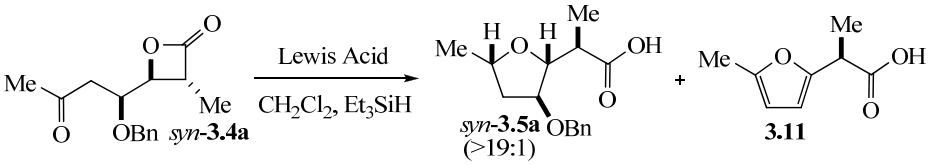
Table 3.2. Coupling constant analysis of γ-benzyloxy-β-lactones **3.3a-c** and **3.4a-c**

entry		$J_{4,5}$ (Hz)[a]	entry		$J_{4,5}$ (Hz)[a]
1	 *syn*-**3.3a**	6.0	7	 *syn*-**3.4a**	5.1
2	 *anti*-**3.3a**[b]	3.0	8	 *anti*-**3.4a**	NA[c]
3	 *anti*-**3.3b**	2.7	9	 *anti*-**3.4b**	3.3
4	 *syn*-**3.3b**	5.1	10	 *syn*-**3.4b**	4.5
5	 *anti*-**3.3c**[b]	3.0	11	 *anti*-**3.4c**	3.6
6	 *syn*-**3.3c**[b]	5.7	12	 *syn*-**3.4c**	6.0

[a] Determined by analysis of chromatographically pure β-lactones by ^{1}H NMR (300 MHz). [b] Minor diastereomers were carried directly to ozonolysis step and thus not fully characterized. [c] Not available. This keto-β-lactone was not prepared.

Initial studies of MRC of keto-β-lactone *syn*-**3.4a** employing conditions reported by Mead with $TiCl_4$ or BF_3•OEt_2 led to the desired THF *syn*-**3.5a** with significant quantities of furan **3.11** (Table 3.3, entries 1-2). Mead found that silyl triflates promoted cyclization of keto-β-lactones to THFs[95] and when triethylsilyl triflate (TESOTf) was added dropwise at -78 ˚C and warmed quickly to 0 ˚C, the ratio of THF to furan did not

Table 3.3. Optimization of Mead reductive cyclization of keto-β-lactone *syn*-**3.4a**



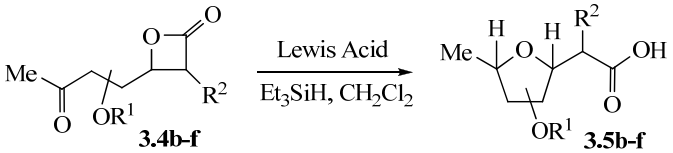
entry	Lewis Acid	conc. (M)[a]	method[b]	Et_3SiH (equiv.)	THF *syn*-**3.5a**/ furan **3.11**[c]	*syn*-**3.5a** (% yield)[d]
1	$TiCl_4$	0.05	A	1.2	1/5	ND
2	BF_3•OEt_2	0.05	B	1.2	1/1	ND
3	TESOTf	0.05	B	1.2	2/1	60
4	TESOTf	0.01	C	1.2	10/1	68
5	TESOTf	0.01	C	20.0	68/1	67
6	TESOTf	0.01	C	0.0	0/1	28 (98)[e]

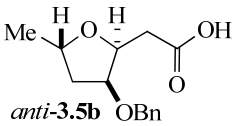
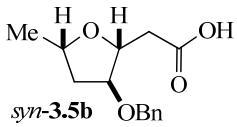
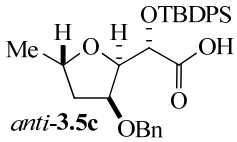
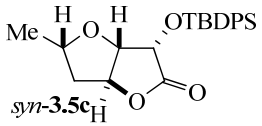
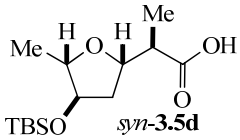
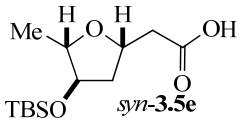
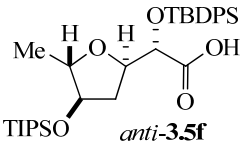
[a] Refers to the final concentration of keto-β-lactones in CH_2Cl_2. [b] Lewis acid (1.2 equiv) was added to a solution of keto-β-lactone and Et_3SiH in CH_2Cl_2 at -78 ˚C. Method A: $TiCl_4$ in CH_2Cl_2 (1.0 M) was added down the side of the flask and stirred for 4 h at -78 ˚C. Method B: Neat Lewis acid was added dropwise at -78 ˚C, quickly warmed to 0 ˚C, and stirred for 4 h. Method C: Lewis acid in CH_2Cl_2 (0.03 M) was added down the side of the flask and allowed to warm to 0 ˚C over 6 h. c Ratio determined by crude ^1H NMR (300 MHz) analysis. d Refers to isolated yield of inseparable mixture of THF and furan. e Significant loss of the furan occurred during purification leading to diminished yields. However, estimated yield based on crude weight and ^1H NMR analysis indicated a nearly quantitative reaction.

improve significantly, but did provide the desired THF **13a** as the major product (entry 3). After extensive experimentation, we found that when TESOTf was added down the side of the flask at -78 ˚C ("pre-cooled") as a dilute solution in CH_2Cl_2 and allowed to warm to 0 ˚C over 6 h, THF *syn*-**3.5a** was obtained in 62% yield with only 6% of furan **3.11** (entry 4). Further improvements resulted when a large excess of Et_3SiH (20.0 equiv) was employed and THF *syn*-**3.5a** was isolated in 67% yield as a single diastereomer (entry 5). A control experiment revealed that furan **3.11** was the only product formed in the absence of Et_3SiH (entry 6) and recently furan byproducts have been observed during reductions of 5-membered oxocarbenium ions.[96]

Using optimized conditions, γ-benzyloxy-keto-β-lactones **3.4b** were converted to THFs **3.5b** with efficient transfer of stereochemistry and only trace quantities of the corresponding furan (Table 3.4, entries 1-2). A stereoreinforcing effect may be operative with *anti*- and *syn*-β-lactones **3.4b** (dr, 14:1 vs 19:1, respectively) which may be due to a developing 1,3-diaxial interaction of the oxocarbenium intermediate (*cf.* **3.16**, *vide infra*) leading to greater selectivity for "inside attack."[27] In the case of keto-β-lactone *anti*-**3.4c**, TESOTf delivered a complex mixture of products, while BF_3•OEt_2 provided a cleaner, albeit slower reaction to provide THF *anti*-**3.5c** (entry 3). Although keto-β-lactone *syn*-**3.4c** proceeds in moderate yield with TESOTf, it delivers γ-lactone *syn*-**3.5c** (entry 4) instead of the desired carboxylic acid (not shown). In the case of δ-silyloxy-keto-β-lactones **3.5d-f**, there was less concern of furan formation based on our proposed mechanism (*vide infra*). Thus, the strong Lewis acid $TiCl_4$ previously utilized by Mead[25] promoted reductive cyclization in moderate to good yields with excellent levels of stereochemical transfer using 1.2 equivalents of Et_3SiH (entries 5-7). The relative stereochemistry of ring stereocenters of THFs **3.5a-b** and **3.5d-f** was confirmed by nOe enhancements observed for multiple protons, which also confirmed invertive ring cleavage during cyclization. The relative stereochemistry between the α-stereocenter and the THF rings is premised on invertive alkyl C-O scission of the *trans*-β-lactones by the pendant ketone, which are in turn based on coupling constant analysis (*vide supra*). Attempts to confirm relative stereochemistry of THFs *anti*-**3.5c** and *syn*-**3.5c** by nOe were inconclusive, but coupling constants of β-lactones **3.3c** and **3.4c** lend support to the tentatively assigned relative stereochemistry of THFs **3.5c** (*cf.* Table 3.2).

Table 3.4. Mead reductive cyclization (MRC) of keto-β-lactones **3.4b-f**

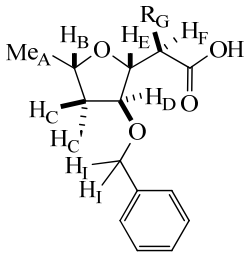


entry	keto-β-lactone	Lewis Acid	tetrahydrofuran	% yield[a]	dr[b]
1	*anti*-**3.4b** (>19:1)	TESOTf[c]	 *anti*-**3.5b**	82	14:1
2	*syn*-**3.4b** (>19:1)	TESOTf[c]	 *syn*-**3.5b**	78	>19:1
3	*anti*-**3.4c** (18:1)	BF_3•OEt_2[d]	 *anti*-**3.5c**	51(35)[f]	18:1
4	*syn*-**3.4c** (18:1)	TESOTf[c]	 *syn*-**3.5c**	40[f]	18:1
5	*anti*-**3.4d** (9:1)	$TiCl_4$[e]	 *syn*-**3.5d**	84	9:1
6	*anti*-**3.4e** (2:1)	$TiCl_4$[e]	 *syn*-**3.5e**	68	2:1
7	*syn*-**3.4f** (5:1)	$TiCl_4$[e]	 *anti*-**3.5f**	55	5:1

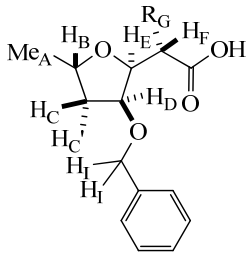
[a] Refers to isolated yields of mixture of diastereomers. [b] Ratio determined by crude ^{1}H NMR (300 MHz) analysis. [c] TESOTf in CH_2Cl_2 (0.03 M) was added to a solution of keto-β-lactone and Et_3SiH (20 equiv) in CH_2Cl_2 at -78 ˚C and allowed to warm to 0 ˚C over 5 h. [d] BF_3•OEt_2 in CH_2Cl_2 (0.03 M) was added to a solution of keto-β-lactone and Et_3SiH (20 equiv) in CH_2Cl_2 at -78 ˚C and allowed to warm to 0 ˚C over 5 h. This reaction was then stirred for 3 d at 0-10 ˚C. [e] $TiCl_4$ in CH_2Cl_2 (1.0 M) was added to a solution of keto-β-lactone and Et_3SiH (1.2 equiv) in CH_2Cl_2 at -78 ˚C and stirred for 4 h. [f] Yield in parentheses refers to recovered keto-β-lactone *anti*-**3.4c**.

Coupling constant analysis of THFs **3.5a-c** (Table 3.5) and THFs **3.5d-f** (Table 3.6) lends support to the proposed relative stereochemistry. The stereochemical outcome is consistent with invertive alkyl C-O ring cleavage by the pendant ketone followed by reduction of the oxocarbenium as predicted by the Woerpel model (*vide infra*).[27]

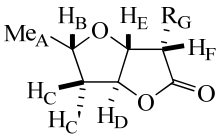
Table 3.5. Coupling constant analysis of tetrahydrofurans **3.5a-c**



syn-**3.5a:** R_G = Me
syn-**3.5b:** R_G = H



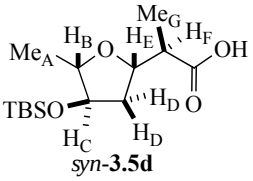
anti-**3.5b:** R_G = H
anti-**3.5c:** R_G = OTBDPS



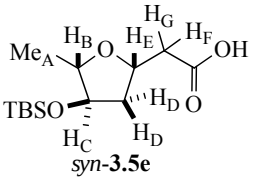
syn-**3.5c:** R_G = OTBDPS

H	*syn*-**3.5a** mult *J* (Hz)	*anti*-**3.5b** mult *J* (Hz)	*syn*-**3.5b** mult *J* (Hz)	*anti*-**3.5c** mult *J* (Hz)	*syn*-**3.5c** mult *J* (Hz)
A	d	d	d	d	d
	6.0	6.0	6.0	6.0	6.0
B	ddq	ddq	ddq	ddq	ddq
	5.0,6.0,10.5	5.5,6.0,9.5	5.5,6.0,10.0	5.0,6.0,10.0	5.0,6.0,10.0
C	ddd	ddd	ddd	dd	dd
	1.0,5.0,13.5	1.5,5.5,13.0	1.5,5.5,13.0	5.0,13.5	5.0,14.0
C’	ddd	ddd	ddd	ddd	ddd
	6.5,10.5,13.5	5.0,9.5,13.0	6.5,10.0,13.0	6.5,11.0,13.5	4.5,10.0,14.0
D	ddd	ddd	ddd	dd	dd
	1.0,3.0,6.5	1.5,5.0,5.0	1.5,3.0,6.5	2.5,6.5	4.5,4.5
E	dd	dt	ddd	dd	d
	3.0,6.0	5.0,7.0	3.0,6.0,7.5	2.5,4.5	4.5
F	dq	d	dd	d	s
	6.0,7.0	7.0	6.0,15.5	4.5	--
G	d	d	dd	--	--
	7.0	7.0	7.5,15.5	--	--
I	d	d	d	s	--
	11.5	12.0	12.5	--	--
I’	d	d	d	s	--
	11.5	12.0	12.5	--	--

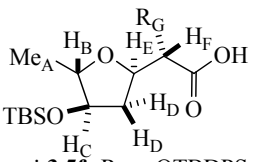
Table 3.6. Coupling constant analysis for tetrahydrofurans **3.5d-f**



syn-**3.5d**



syn-**3.5e**



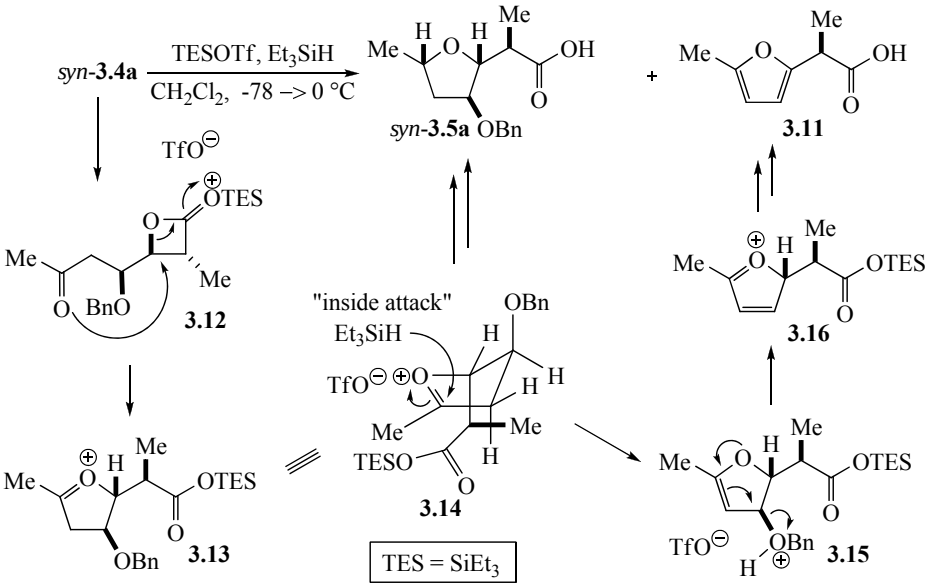
anti-**3.5f:** R_G = OTBDPS

H	*syn*-**3.5d** mult *J* (Hz)	*syn*-**3.5e** mult *J* (Hz)	*anti*-**3.5f** mult *J* (Hz)
A	d	d	d
	6.5	6.5	6.5
B	dq	dq	dq
	4.0,6.5	4.0,6.5	6.0,6.5
C	ddd	ddd	ddd
	3.5,4.0,6.5	3.0,4.0,6.5	6.0,7.0,7.0
D	ddd	ddd	ddd
	3.5,6.5,13.0	3.0,6.5,13.0	7.0,7.0,12.5
D’	ddd	ddd	ddd
	6.5,8.5,13.0	6.5,9.0,13.0	7.0,7.0,12.5
E	ddd	dddd	ddd
	3.5,7.0,8.5	5.5, 6.5, 7.0,9.0	5.5,7.0,7.0
F	dq	dd	d
	7.0,7.0	5.5, 15.5	5.5
G	d	dd	--
	7.0	7.0, 15.5	--

Regarding the mechanism of this process for benzyloxy-substituted systems, the reductive cyclization leading to THF *syn*-**3.5a** and furan **3.11** is presented as an example (Scheme 3.7). Pendant ketone cleavage attack on the silylated β-lactone **3.12** *via* invertive alkyl C-O scission delivers the oxocarbenium **3.13** in line with previous proposals by Mead.[25] The stereoelectronically favored envelope conformation **3.14** places the benzyloxy substituent in the pseudoaxial orientation as proposed by Woerpel and reduction occurs *via* “inside attack” of Et_3SiH.[27] Alternatively, the competing pathway leading to furan **3.11** could involve α-deprotonation of oxocarbenium **3.14**

leading to dihydrofuran **3.15** which is essentially an activated alkyl enol ether. Acid-mediated β-elimination of benzyl alcohol would provide conjugated oxocarbenium **3.16**. Aromatization and hydrolysis of the labile triethylsilyl ester would then deliver furan **3.11** and may occur upon reaction work-up.

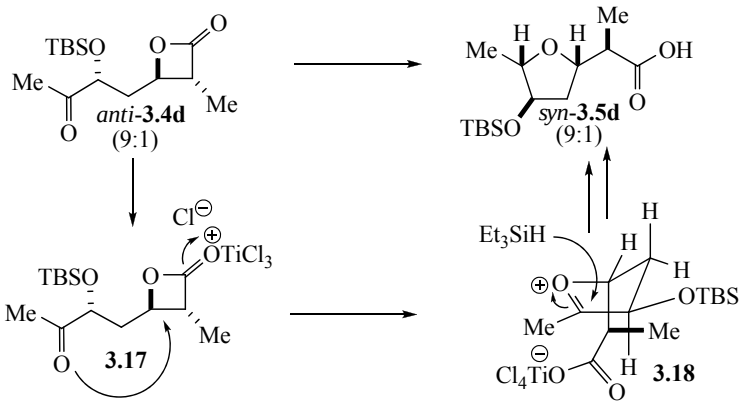
Scheme 3.7



In the case of δ-silyloxy-keto-β-lactones **3.5d-f,** based on Woerpel's findings with related α-benzyloxy oxocarbenium intermediates which provided diastereomeric ratios of 5-6:1, we expected only moderate selectivity for the reduction of the corresponding α-silyloxy oxocarbenium intermediates.[27,97] We were pleased to find, however, that the diastereoselectivity of this reduction was >19:1 since the diastereomeric ratio of the THFs **3.5d-f** matched the diastereomeric ratio of the precursor keto-β-lactones **3.5d-f** (Scheme 3.8). There appear to be several factors governing this increase in selectivity. Woerpel has shown that hydrogen atoms prefer to reside in the pseudoaxial position adjacent to an oxocarbenium in both five and six-membered rings

for favorable hyperconjugation between the C-H bond and the *2p* orbital of the oxocarbenium.[27b] Less studied by Woerpel were the effects of α-silyloxy oxocarbeniums and both steric and electronic differences between silyloxy and benzyloxy moieties could influence the stereochemical outcome. The decreased electron density at the oxygen of a silyloxy moiety[98] compared to the oxygen of a benzyloxy moiety dictates the increased preference for the α-silyloxy pseudoequatorial orientation. Simple steric considerations also dictate that the more bulky silyloxy group should reside in the pseudoequatorial position to a greater degree than a benzyloxy substituent. Additionally, developing gauche interactions between the methyl and the pseudoequatorial silyloxy substituent in the presumed transition state also enforces "inside attack" of Et_3SiH. These effects combine with the preferred "inside attack" leading to high diastereoselectivity for α-silyloxy oxocarbenium ions.[27]

Scheme 3.8



Conclusions

In summary, we developed a three-step strategy for the diastereoselective synthesis of THFs from alkenyl-aldehydes proceeding through β-lactone intermediates.

The strategy involves the TMAL process and Mead's reductive cyclization of keto-β-lactones. The stereoselectivity of the latter process is rationalized by Woerpel's model for "inside attack" of oxocarbeniums. An increase in selectivity for certain α-silyloxy oxocarbenium ions was observed and is rationalized based on stereoelectronic effects building on Woerpel's findings. The stereoselectivity of the TMAL process for γ-benzyloxy and δ-silyloxy aldehydes with several thiopyridyl ketene acetals was defined including a reversal in selectivity when a thiophenyl ketene acetal was employed. A correlation between relative stereochemistry and coupling constants was observed that provides a predictive method for the stereochemical assignment of γ-benzyloxy-β-lactones. This TMAL-MRC strategy should prove useful for the synthesis of tetrahydrofurans found in natural products.

CHAPTER IV

DEVELOPMENT OF A TANDEM, THREE-COMPONENT SYNTHESIS OF TETRAHYDROFURANS FROM KETOALDEHYDES, THIOPYRIDYL KETENE ACETALS, AND SILYL NUCLEOPHILES*

Introduction

Synthetic processes that form multiple bonds and stereocenters in a single reaction mixture without isolating the intermediates have become commonplace in recent years and are known as tandem, domino, multi-component, or cascade reactions.[99] Previously, we reported stereoselective routes to both *cis*[22] and *trans*[16] β-lactones *via* tandem Mukaiyama[15] aldol-lactonization (TMAL) processes. This methodology has been utilized in total syntheses of (-)-panclicin D,[16] tetrahydrolipstatin/orlistat,[19] okinonellin B,[21] brefeldin A,[24] and belactosin C.[30] In the course of these studies, we observed several interesting byproducts under certain conditions that led us to propose silylated β-lactone intermediates in the TMAL. Prior to that, Mead utilized simple keto-β-lactones toward the synthesis of tetrahydrofurans (THFs),[25] and recently we combined these two methods in a stepwise tandem Mukaiyama aldol-lactonization – Mead reductive cyclization (TMAL-MRC) to obtain substituted THFs with high diastereoselectivity.[26] Although there are several approaches toward THFs, many routes rely on either C-O bond formation of relatively complex precursors or proceed through

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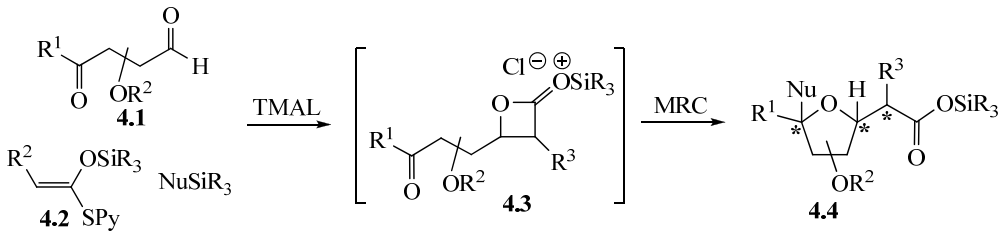
*Reprinted with permission from "Highly, Diastereoselective Tandem, Three-Component Synthesis of Tetrahydrofurans from Ketoaldehydes *via* Silylated-β-Lactone Intermediates" by Mitchell, T. A.; Zhao, C.; Romo, D. *Angew. Chem., Int. Ed.* **2008**, *in press*. Copyright 2008 Wiley-VCH. See Appendix B.

oxocarbenium ions derived from *O*-glycosides. We set out to study the possibility of intercepting the proposed silylated β-lactone **4.3** in the TMAL process in order to provide a three-component (TMAL-MRC) synthesis of THFs **4.4** from α-benzyloxy-γ-ketoaldehydes **4.1**, thiopyridyl ketene acetals **4.2**, and silyl nucleophiles in which as many as two C-C and one C-O bond are formed in conjunction with three new stereocenters (Scheme 4.1).

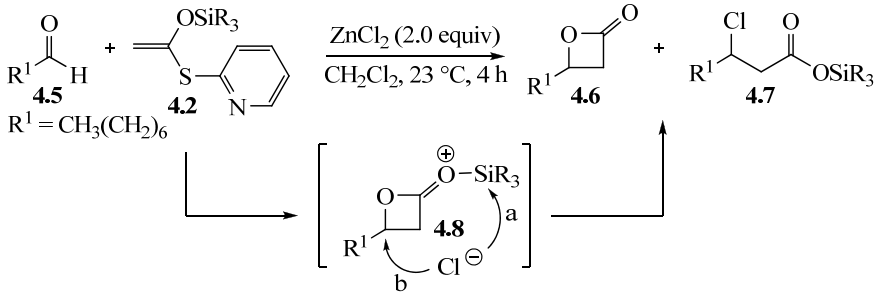
Scheme 4.1



Results and Discussion

Herein, we describe experimental evidence for silylated β-lactone intermediates toward diastereoselective THF synthesis based on the TMAL,[16,20] MRC of keto-β-lactones,[25,26] and Woerpel's model for the reduction of oxocarbenium ions.[27] Initial studies of the TMAL with octanal **4.5** showed a drastic dependence on the size of the protecting group of the ketene acetal **4.2a-d** (Table 4.1).[16] The presumed silylated β-lactone **4.8** delivered either β-lactone **4.6** (entry 1, pathway a) with TES protected ketene acetal **4.2a** or β-chloro silyl ester **4.7d** with bulky TBDPS protected ketene acetal **4.2d** (entry 4, pathway b).[28] Silyl ester **4.7d** was purified by flash column chromatography and none of the corresponding carboxylic acid was detected by crude ^{1}H NMR analysis, thus providing strong evidence for the proposed silylated β-lactone intermediate **4.8**.

Table 4.1. Effect of the silyl protecting group of ketene acetals **4.2a-d** in the TMAL

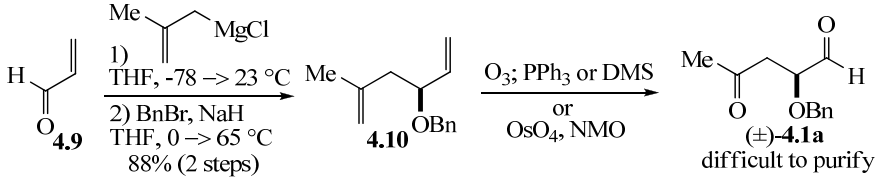


entry	SiR_3	**4.6** (% yield)	**4.7** (% yield)
1	TES **(4.2a)**	66[a]	<5[b] **(4.7a)**
2	TBS **(4.2b)**	53[a]	8[b] **(4.7b)**
3	TIPS **(4.2c)**	20[a]	40[b] **(4.7c)**
4	TBDPS **(4.2d)**	<5[c]	56[a] **(4.7d)**

[a] Refers to isolated yields. [b] Estimated based on crude ^{1}H NMR analysis. [c] Not detected based on crude ^{1}H NMR (300 MHz) analysis.

In order to prepare the desired α-benzyloxy-γ-ketoaldehyde (±)-**4.1a** to rapidly test the three-component TMAL-MRC and thereby further our understanding of the TMAL, a known procedure was chosen (Scheme 4.2).[100] Although the synthesis of bis-olefin **4.10** was straightforward *via* Grignard addition to acrolein **4.9** and subsequent benzyl protection, accessing the desired ketoaldehyde (±)-**4.1a** proved to be troublesome under a variety of oxidation conditions.

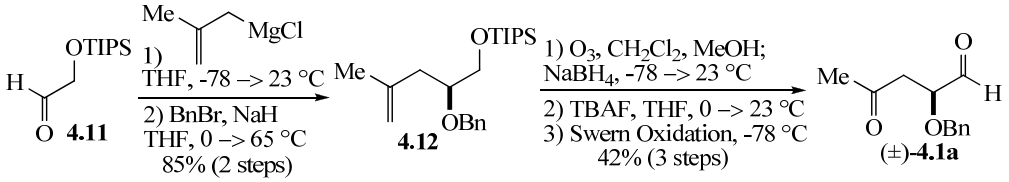
Scheme 4.2



Our second approach to α-benzyloxy-γ-ketoaldehyde (±)-**4.1a** was more dependable, albeit significantly longer (Scheme 4.3). Known aldehyde **4.11** was treated

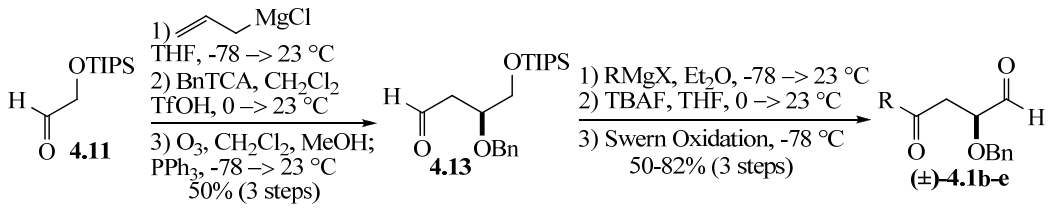
with methallylmagnesium chloride and the resulting alcohol was protected as the benzyl ether **4.12** (which was also utilized in the stepwise TMAL-MRC). Reductive ozonolysis followed by TBAF deprotection gave a ~1:1 mixture of diols that underwent Swern oxidation to provide pure ketoaldehyde (±)-**4.1a**.[101] Although ketoaldehyde (±)-**4.1a** could be stored neat for several weeks at 0 ˚C, we opted to store large quantities of the stable diol mixture and access the required substrate in smaller portions immediately before each set of reactions.

Scheme 4.3



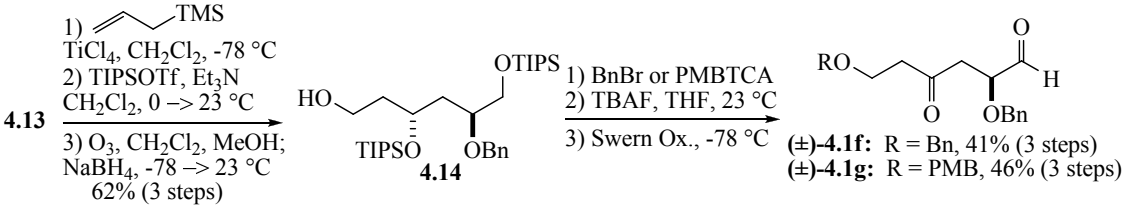
More complex α-benzyloxy-γ-ketoaldehydes (±)-**4.1b-g** were synthesized by related pathways (Scheme 4.4). Treatment of aldehyde **4.11** with allylmagnesium chloride, protection with benzyl trichloroacetimidate (BTCA) and subsequent ozonolysis delivered aldehyde **4.13**. The necessary Grignard reagents were then utilized, followed by TBAF deprotection and Swern oxidation of the inconsequential mixture (~1:1) of diols to access the required ketoaldehydes (±)-**4.1b-e** (*vide infra*).

Scheme 4.4



In order to introduce functionalized ketone side chains, a lengthy but straightforward sequence was undertaken (Scheme 4.5). Aldehyde **4.13** was treated with allyltrimethylsilane and $TiCl_4$ to provide a single diastereomer of the resulting secondary alcohol (not shown). Although the relative stereochemistry was not confirmed, ample precedent suggests the formation of the chelation controlled product as shown.[102] Even though the newly created stereocenter would eventually be destroyed, this procedure (as opposed to the Grignard) avoided a troublesome mixture of diastereomers and therefore allowed each subsequent step to be carried out with confidence. Silyl protection of the secondary alcohol followed by reductive ozonolysis gave primary alcohol **4.14**. Protection with benzyl bromide or *p*-methoxybenzyl trichloroacetimidate (PMBTCA), TBAF deprotection of both silyl ethers, and Swern oxidation gave the corresponding α-benzyloxy-γ-ketoaldehydes (±)-**4.1f-g**.

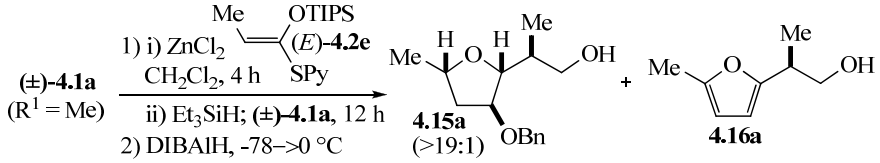
Scheme 4.5



In order to provide additional evidence for the silylated β-lactone intermediate (*c.f.* **4.3**, Scheme 4.1) while providing access to trisubstituted THFs, we first optimized the three-component TMAL-MRC with α-benzyloxy-γ-ketoaldehyde (±)-**4.1a** and ketene acetal (*E*)-**4.2e**. We found that pre-coordination of the more readily prepared ketene acetal (*E*)-**4.2e** with $ZnCl_2$ and reduction of the resulting silyl ester (*c.f.* **4.4**, Scheme 4.1) to the primary alcohol **4.15a** with DIBAlH provided optimal results (Table

4.2). Regardless of the relative amount of Et_3SiH, initial attempts delivered furan **4.16a** as the major product (entries 1-4). Although the yield of THF **4.15a** was unsatisfactory, we were pleased to observe only the expected diastereomer (>19:1). Decreasing reaction temperature showed a significant increase in the relative amount of THF **4.15a**, although furan **4.16a** remained the major product (entry 5). An increase in the amount of Lewis acid delivered THF **4.15a** as the major product in moderate yield (entry 6), but when $ZnCl_2$ and Et_3SiH were increased further, we obtained THF **4.15a** in slightly decreased yield (entry 7). Although crude ^{1}H NMR analysis indicated an improved ratio of THF **4.15a** to furan **4.16a**, several minor and unidentified byproducts arise when these slightly harsher conditions are utilized. Finally, complete optimization was achieved after 12 h at 0 ˚C to deliver THF **4.15a** in satisfactory yield (entry 8).

Table 4.2. Optimization of the TMAL-MRC to tetrahydrofuran **4.15a**



entry	$ZnCl_2$ (equiv)	(*E*)-**4.2e** (equiv)	Et_3SiH (equiv)	temp (˚C)	**4.15a**/**4.16a**[a] (% yield **4.15a**)[b]
1	2.0	2.0	0.0	23	**4.16a** only (0)
2	2.0	2.0	2.0	23	1.0/3.5 (11)
3	2.0	2.0	10.0	23	1.0/3.5 (9)
4	2.0	2.0	50.0	23	1.0/3.5 (10)
5	2.0	2.0	10.0	0→23	1.0/2.0 (24)
6	4.0	1.2	10.0	0→23	2.0/1.0 (42)
7	8.0	1.2	100.0	0→23	9.0/1.0 (38)
8	4.0	1.2	10.0	0	6.2/1.0 (54)

[a] Determined by crude ^{1}H NMR (300 MHz) analysis. [b] Isolated yield over two steps.

In addition to nOe enhancements, single crystal X-ray analysis of the *para*-bromobenzoate **4.15a'** (Figure 4.1) confirmed relative stereochemistry and this provides substantial evidence for the proposed mechanistic pathway (*vide infra*).

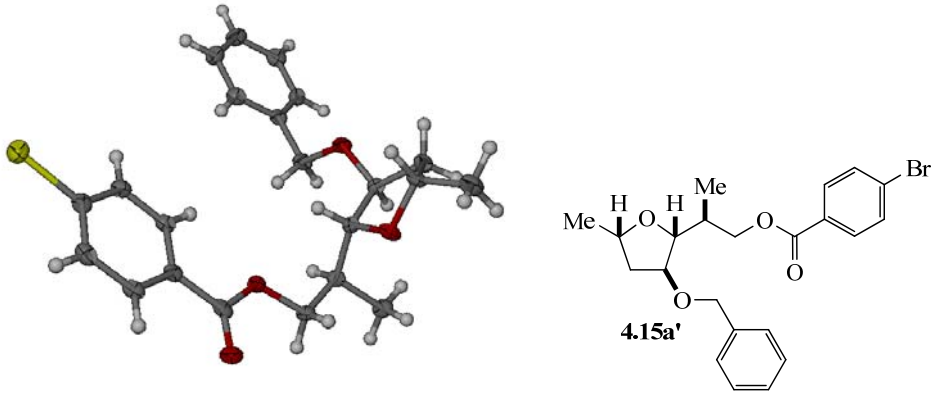
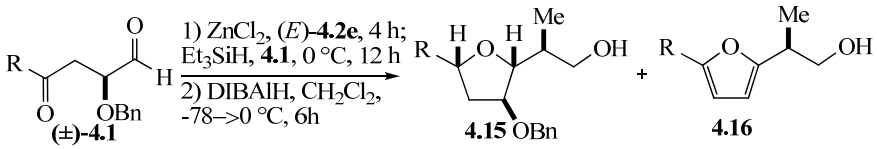
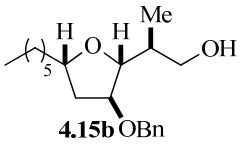
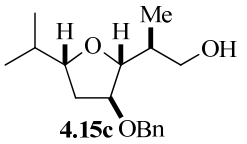
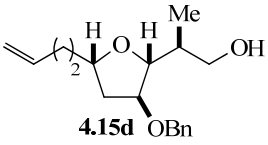
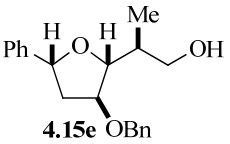
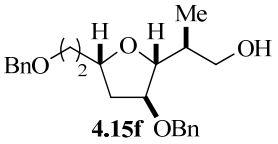
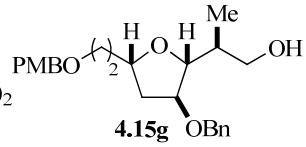


Figure 4.1. ORTEP rendering of a single crystal X-ray structure of **4.15a'**

Functionalized α-benzyloxy-γ-ketoaldehydes (±)-**4.1b-g** with ketene acetal (*E*)-**4.2e** delivered THFs **4.15b-g** in moderate yields with furans **4.16b-g** isolated as significant byproducts (Table 4.3). The general trend of these reactions seems to indicate that greater steric bulk of the ketone moiety inhibits the production of the desired THF and increases formation of the furan. In the case of the phenyl substituted ketoaldehyde (±)-**4.1e**, the desired THF **4.15e** is isolated in only 13% yield, while furan **4.16e** is produced in 48% yield (entry 4). Although this could also be a result of steric interactions, it is possible that increased stability of the oxocarbenium favors elimination to the intermediate dihydrofuran (*vide infra*) over reduction with Et_3SiH. Additionally, THF **4.15g** was isolated in diminished yields due to PMB deprotection, but was minimized when DIBAlH reduction was maintained at cooler temperatures (entry 6).

Table 4.3. TMAL-MRC of functionalized α-benzyloxy-γ-ketoaldehydes (±)-**4.1b-g**

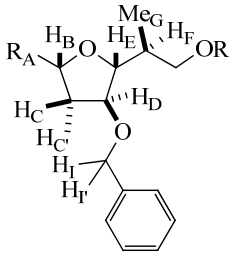


entry	ketoaldehyde **(4.1)**	major adduct **(4.15)**	**4.15/4.16**	% yield **4.15**[a]	dr[b]
1	(±)-**4.1b:** R = *n*-hexyl	 **4.15b**	1.3:1	42	>19:1
2	(±)-**4.1c:** R = *i*-propyl	 **4.15c**	2.3:1	52	>19:1
3	(±)-**4.1d:** R = $CH_2CH(CH_2)_2$	 **4.15d**	3.0:1	49	>19:1
4	(±)-**4.1e:** R = phenyl	 **4.15e**	1:5	13	>19:1
5	(±)-**4.1f:** R = $BnO(CH_2)_2$	 **4.15f**	3.5:1	54	>19:1
6	(±)-**4.1g:** R = $PMBO(CH_2)_2$	 **4.15g**	2.2:1	49[c]	>19:1

[a] Isolated yield over two steps. [b] Determined by crude ^{1}H NMR (300 MHz) analysis. [c] DIBAlH reduction was slowly warmed from -78 to -30 ˚C over 6 h in order to prevent PMB deprotection.

In addition to nOe enhancements for selected examples and the X-ray crystal structure for THF **4.15a'**, coupling constant analysis of THFs **4.15a-g** lend additional confirmation of the relative stereochemistry (Tables 4.4-4.5).

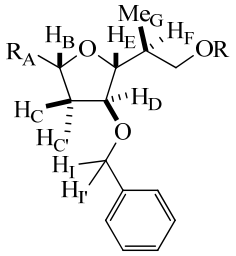
Table 4.4. Coupling constant analysis of tetrahydrofurans **4.15a-c**



4.15a: R_A = Me, R = H
4.15a': R_A = Me, R = Ar
4.15b: R_A = *n*-hexyl, R = H
4.15c: R_A = *i*-Pr, R = H

H	**4.15a** mult *J* (Hz)	**4.15a'** mult *J* (Hz)	**4.15b** mult *J* (Hz)	**4.15c** mult *J* (Hz)
A	d	d	m	m
	6.0	6.5	--	--
B	ddq	ddq	m	ddq
	5.5,6.0,10.0	5.0,6.5,10.0	--	5.5,7.0,10.0
C	ddd	ddd	ddd	ddd
	2.0,5.5,13.0	1.5,5.0,13.0	2.5,5.0,13.0	2.0,5.5,13.0
C'	ddd	ddd	ddd	ddd
	7.0,10.0,13.0	6.0,10.0,13.0	7.0,10.0,13.0	7.0,10.0,13.0
D	ddd	ddd	ddd	ddd
	2.0,4.0,7.0	1.5,3.5,6.0	2.0,4.0,7.0	2.0,4.0,7.0
E	dd	dt	dd	dd
	4.0,5.0	3.5,5.0	4.0,5.0	4.0,5.0
F	m	m	m	m
	--	--	--	--
G	d	d	d	d
	7.0	7.0	7.0	7.0
I	d	d	d	d
	12.0	12.0	12.0	12.0
I'	d	d	d	d
	12.0	12.0	12.0	12.0

Table 4.5. Coupling constant analysis of tetrahydrofurans **4.15d-g**



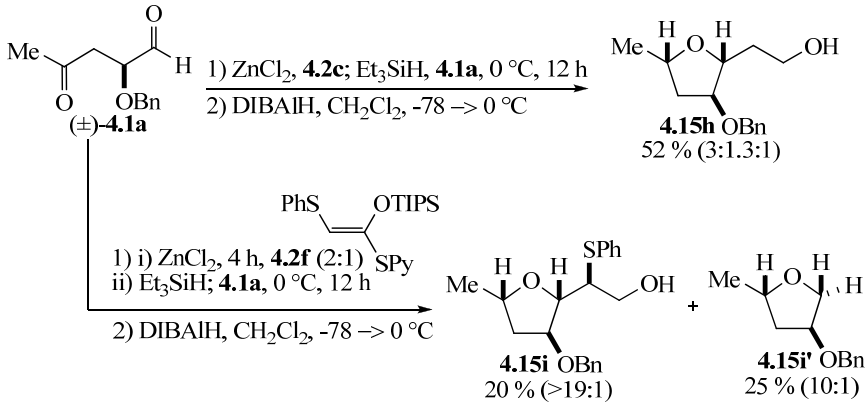
4.15d: $R_A = CH_2CH(CH_2)_2$
4.15e: $R_A = C_6H_5$
4.15f: $R_A = PMBO(CH_2)_2$
4.15g: $R_A = BnO(CH_2)_2$

H	**4.15d** mult *J* (Hz)	**4.15e** mult *J* (Hz)	**4.15f** mult *J* (Hz)	**4.15g** mult *J* (Hz)
A	m	m	m	m
	--	--	--	--
B	m	dd	m	m
	--	5.5,10.5	--	--
C	ddd	ddd	ddd	ddd
	2.0,5.5,13.0	2.0,5.5,13.0	2.0,5.5,13.0	2.0,5.5,13.0
C'	ddd	ddd	ddd	ddd
	7.0,10.0,13.0	7.0,10.5,13.0	7.0,10.0,13.0	7.0,10.5,13.0
D	ddd	ddd	ddd	ddd
	2.0,4.5,6.5	2.0,4.0,7.0	2.0,4.0,6.5	2.0,4.5,7.0
E	dd	dt	dd	dd
	4.5,4.5	4.0,5.0	4.0,5.0	4.0,4.5
F	m	m	m	m
	--	--	--	--
G	d	d	d	d
	7.5	7.0	7.0	7.0
I	d	d	d	d
	11.5	12.0	11.5	11.2
I'	d	d	d	d
	11.5	12.0	11.5	11.2

When ketoaldehyde (±)-**4.1a** was treated with various ketene acetals or silyl nucleophiles, mixed results were obtained. Ketene acetal **4.2c** provided THF **4.15h** in good yield but with poor diastereoselectivity while ketene acetal **4.2g** delivered THF **4.15i** in excellent diastereoselectivity but with diminished yield (Scheme 4.6). Although ketene acetal **4.2c** was expected to deliver low diastereoselectivity, we were somewhat

surprised by the result with ketene acetal **4.2f** given the success of previous examples. Much of the mass balance in the case of heteroatom substituted ketene acetals is accounted for by the production of undesired THF **4.15i'** (25% isolated yield in this case with ketene acetal **4.2f**) in which the ketoaldehyde (±)-**4.1a** presumably undergoes self-condensation and reduction with no incorporation of ketene acetal. There is an inverse relationship between size of the substituent on the ketene acetal and reactivity which corresponds to previous TMAL studies. Similar results were obtained in the TMAL-MRC when several other heteroatom containing ketene acetals (*i.e.* SMe, OMe, OTBS, OTBDPS) were tested with less favorable results.

Scheme 4.6



When allyltrimethylsilane was utilized as nucleophile, THF **4.15j** was isolated as a single diastereomer, albeit in lower yield (Scheme 4.7). In this case, several minor and unidentified byproducts arise in addition to increased quantities of furan **4.16a**, but it is important to note that an additional C-C bond is constructed with high stereocontrol of the resulting quaternary center. The relative stereochemistry of THFs **4.15h-j** was confirmed with nOe enhancements and coupling constant analysis (Table 4.6).

Scheme 4.7

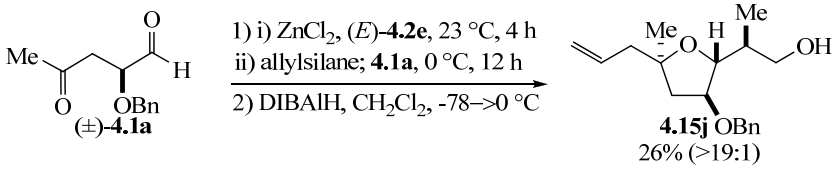
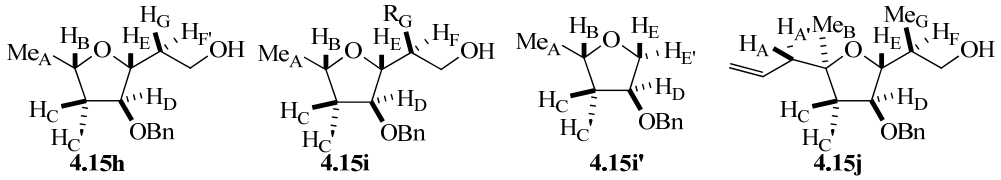


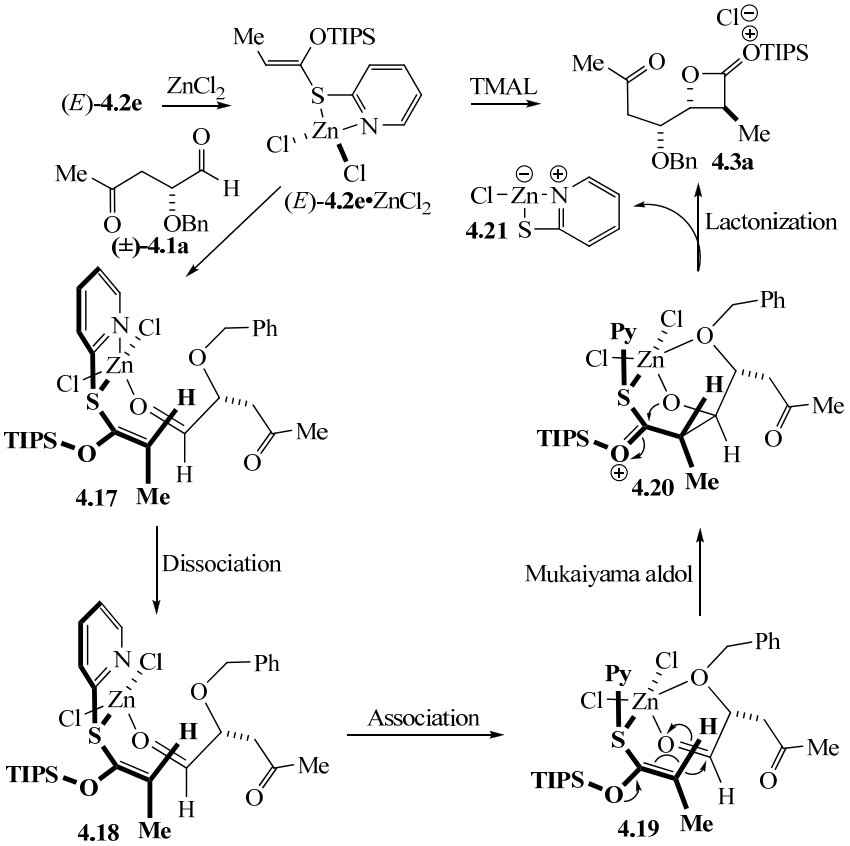
Table 4.6. Coupling constant analysis of tetrahydrofurans **4.15h-j**



H	**4.15h** mult *J* (Hz)	**4.15i** mult *J* (Hz)	**4.15i'** mult *J* (Hz)	**4.15j** mult *J* (Hz)
A	d	d	d	s
	6.0	6.0	6.0	--
B	ddq	ddq	m	dd/dd
	5.5,6.0,10.0	5.0,6.0,10.0	--	7.5,13.5/6.5,13.5
C	ddd	ddd	ddd	dd
	2.0,5.5,13.0	1.5,5.0,13.0	0.9,5.1,12.9	4.5,13.0
C'	ddd	ddd	ddd	dd
	7.0,10.0,13.0	6.5,10.0,13.0	6.6,9.9,12.9	7.0,13.0
D	ddd	ddd	m	ddd
	2.0,4.0,7.0	1.5,3.0,6.5	--	4.5,5.5,7.0
E	ddd	dd	dd/dd	dd
	4.0,4.5,8.5	3.0,3.0	2.7,9.6/5.1,9.6	5.0,5.5
F	dddd	ddd	--	m
	4.0,4.5,7.5,14.0	3.0,5.5, 8.0	--	--
G	dddd	--	--	d
	4.0,6.0,8.5,14.0	--	--	7.5
I	D	d	d	d
	11.5	12.0	12.0	12.0
I'	D	d	d	d
	11.5	12.0	12.0	12.0

A plausible mechanism for this tandem process can be set forth based on the experimental evidence gathered to date.[28] Upon stirring ketene acetal (*E*)-**4.2e** with $ZnCl_2$ in CH_2Cl_2 for 4 h, the tetrahedral complex (*E*)-**4.2e**•$ZnCl_2$ is formed (Scheme 4.8).

Scheme 4.8

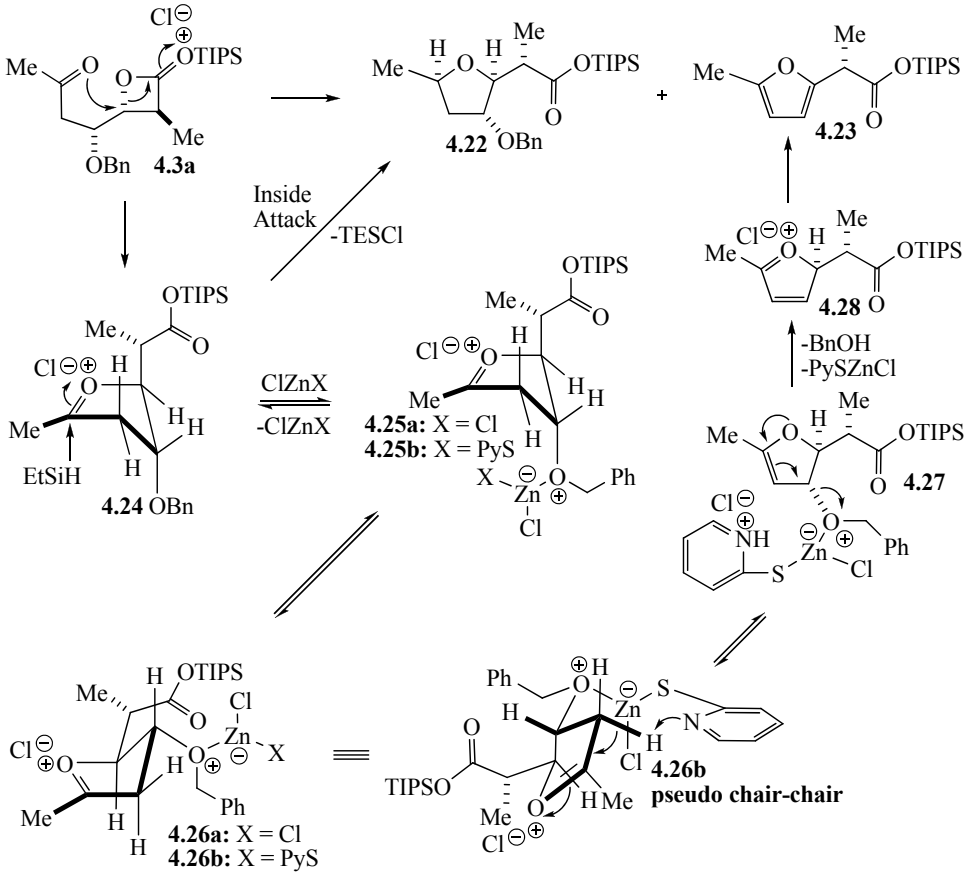


The results suggest that α-benzyloxy-γ-ketoaldehyde (±)-**4.1a** then complexes in monodentate fashion to pre-coordinated ketene acetal (*E*)-**4.2e**•$ZnCl_2$ to deliver a highly ordered, trigonal-bipyramidal boat-like transition state arrangement **4.17**. After dissociation of the pyridyl nitrogen (*i.e.* **4.18**) and ligand rearrangement, the benzyloxy moiety then coordinates with zinc to give rise to another highly ordered, boat-like transition state arrangement **4.19**. Due to the fact that no aldol products have been

isolated in the TMAL, the Mukaiyama aldol is presumably the rate-limiting step and provides a boat-like intermediate zinc alkoxide **4.20**. A facile transannular lactonization then delivers the crucial silylated β-lactone **4.3a** with concomitant production of a weaker (compared to $ZnCl_2$) Lewis acid, thiopyridyl zinc chloride (PySZnCl) **4.21**.

Upon invertive alkyl C-O cleavage[25] of the silylated β-lactone **4.3a**, the resulting oxocarbenium **4.24** can proceed to three different pathways (Scheme 4.9). First, desired

Scheme 4.9



"inside attack" on the favored envelope conformation **4.24** can be achieved to deliver THF silyl ester **4.22** when the benzyloxy substituent resides in the favored pseudoaxial orientation.[27] However, the benzyloxy substituent can also coordinate to either Lewis

acid (*i.e.* $ZnCl_2$ or PySZnCl) in an equilibrium process which would presumably drive the conformational equilibrium to the pseudoequatorially inclined conformers **4.26a-b**. Under the optimized conditions (*cf.* Table 4.2, entry 8), excess $ZnCl_2$ should deliver conformers **4.25-4.26a**, but would presumably revert to the desired envelope conformation **4.24** to give THF silyl ester **4.22** *via* "inside attack." The third pathway arises when PySZnCl **4.21** predominates and conformer **4.26b** becomes the major contributor which seems primed to achieve an eight-membered pseudo chair-chair arrangement leading to deprotonation of the properly aligned α-proton by the pyridine nitrogen. Upon formation of dihydrofuran **4.27**, elimination of activated benzyl alcohol followed by aromatization of the conjugated oxocarbenium **4.28** ultimately delivers furan **4.23**.

To highlight the utility of this methodology, we targeted the THF fragment of colopsinol B (Figure 4.2).[29] Colopsinol B was isolated from the dinoflagellate *Amphidinium* and is structurally related to the amphidinolides.[67d] It possesses DNA

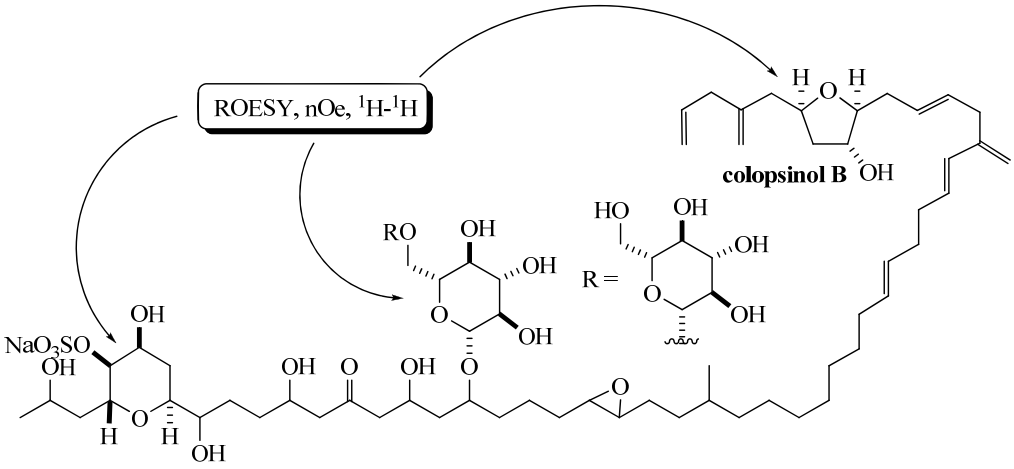
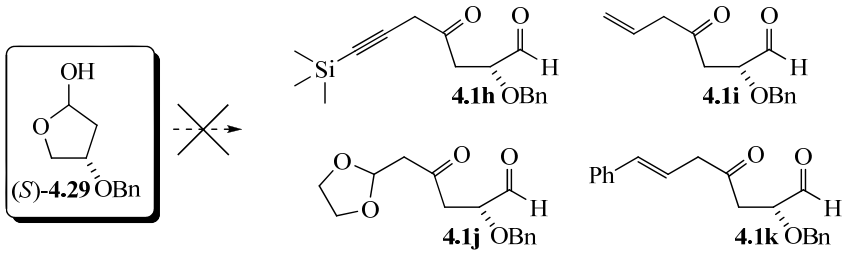


Figure 4.2. Colopsinol B with relative stereochemistry of rings

polymerase inhibitory activity and the structure was determined by extensive NMR and MS techniques. The relative stereochemistry of the ring systems were determined by nOe and ROESY correlations and ^{1}H-^{1}H coupling constants. To date, no synthetic studies toward colopsinol B have been published.

The need for functionalized ketones and the desire to minimize the length of the synthetic sequence led us to pursue the construction of ketoaldehydes **4.1h-k** (Scheme 4.10). Our early attempts to synthesize an optically active substrate from the L-malic acid derived lactol (*S*)-**4.29** with the necessary functionality to obtain an advanced colopsinol B THF fragment were met with disappointment. For a variety of reasons, none of these more complex α-benzyloxy-ketoaldehydes **4.1h-k** could be accessed.

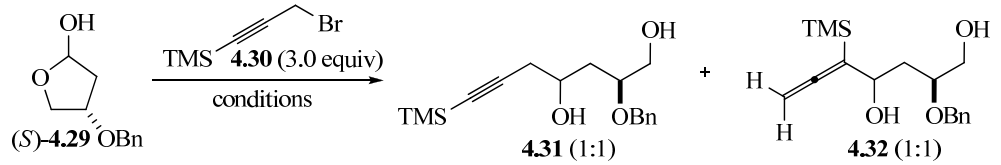
Scheme 4.10



One interesting result sprang from these investigations (Table 4.7). Attempted opening of lactol (*S*)-**4.29** to the alkynes **4.31** with the Grignard derived from TMS-propargyl bromide **4.30** provided allenes **4.32** as the only detectable product.[103] We were pleased to find that another reaction that is known for aldehydes translated to this lactol (*S*)-**4.29** very well. When latent aldehyde (*S*)-**4.29** was treated with In/$InCl_3$ and propargyl bromide **4.30** in refluxing THF, alkynes **4.31** were isolated in excellent yield

after minimal optimization (entry 3).[104] Unfortunately, several attempts to oxidize diols **4.31** to the α-benzyloxy-γ-ketoaldehyde (*c.f.* **4.1h**, Scheme 4.10) were unsuccessful.

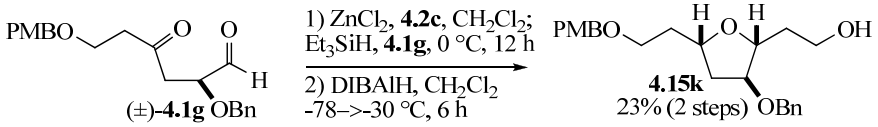
Table 4.7. Nucleophilic additions to lactol (*S*)-**4.29** with TMS-propargyl bromide



entry	conditions	**4.31** (% yield)	**4.32** (% yield)
1	Mg°, Et_2O or THF, -78 → 23 °C, 16 h	<5	67
2	In° (4.0 equiv), $InCl_3$ (20 mol %), THF, reflux, 24 h	53	<5
3	In° (3.0 equiv), $InCl_3$ (10 mol %), THF, reflux, 24 h	86	<5

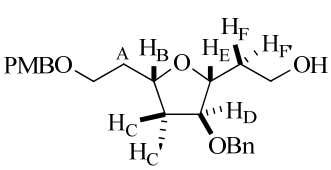
After these dissatisfying results, we chose to utilize α-benzyloxy-γ-ketoaldehyde (±)-**4.1g** toward a racemic colopsinol B THF fragment **4.15k** (Scheme 4.11). Under typical conditions with ketene acetal **4.2c**, the alcohols were formed as a mixture of diastereomers similar to that observed previously. The major diastereomer **4.15k** could be separated and isolated in 23% yield over two steps. Although the yield is slightly lower than the previous example with ketene acetal **4.2c** (*c.f.* Scheme 4.6), this follows the trend of increased quantities of furan when the steric bulk of the ketone substituent increases (*c.f.* Table 4.3). It is important to emphasize that two new stereocenters are formed in addition to one C-C and one C-O bond toward a natural product fragment.

Scheme 4.11

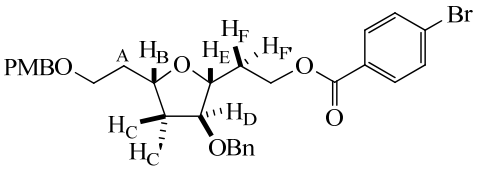


Unfortunately, attempts to grow suitable crystals of the corresponding benzoate ester **4.15k'** for X-ray analysis in order to confirm the relative stereochemistry of **4.15k** were unsuccessful. However, coupling constant and nOe analysis of THFs **4.15k**, **4.15k'**, and **4.15h** (*c.f.* Table 4.6) all support a correlation of relative stereochemistry to the proposed structure of colopsinol B **4.33** (Table 4.8).

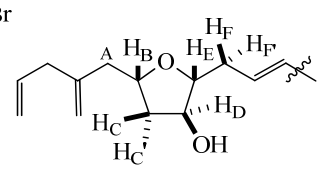
Table 4.8. Coupling constant analysis of tetrahydrofurans **4.15k**, **4.15k'**, and **4.33**



4.15k



4.15k'

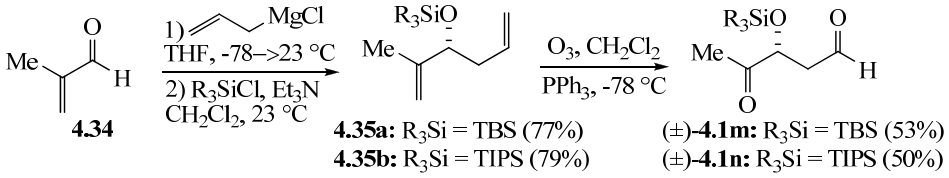


colopsinol B **(4.33)**

H	**4.19k** mult *J* (Hz)	**4.19k'** mult *J* (Hz)	**4.31** mult *J* (Hz)
A	m	m	m
	--	--	--
B	m	m	m
	--	--	--
C	ddd	ddd	ddd
	2.0,5.5,13.0	2.0,5.5,13.0	2.5,5.5,13.1
C'	ddd	ddd	ddd
	7.0,9.5,13.0	7.0,10.0,13.0	6.4,9.8,13.1
D	ddd	ddd	ddd
	2.0,4.0,7.0	2.0,3.5,7.0	2.5,2.9,6.4
E	ddd	ddd	dt
	4.0,4.5,8.5	3.5,4.5,8.0	2.9,6.1
F	m	m	m
	--	--	--
G	m	m	m
	--	--	--
I	d	d	--
	12.0	11.5	--
I'	d	d	--
	12.0	11.5	--

In preliminary studies with β-silyloxy-γ-ketoaldehydes (±)-**4.15m-n**, some promising results were obtained. We were pleased to find that these substrates could be accessed quickly (Scheme 4.12) in a similar manner as previously attempted with α-benzyloxy-γ-ketoaldehyde (±)-**4.1a** (*c.f.* Scheme 4.2). Methacrolein **4.34** was treated with allylmagnesium chloride and the resulting alcohols were protected as the appropriate silyl ethers **4.35a-b**. Ozonolysis delivered the corresponding β-silyloxy-γ-ketoaldehydes (±)-**4.1m-n** in moderate yields. The success of this oxidation compared to the aforementioned unsuccessful result is most likely due to the fact that these systems are generally less reactive than α-benzyloxy-γ-ketoaldehyde (±)-**4.1a** and therefore less susceptible to the formation of byproducts.

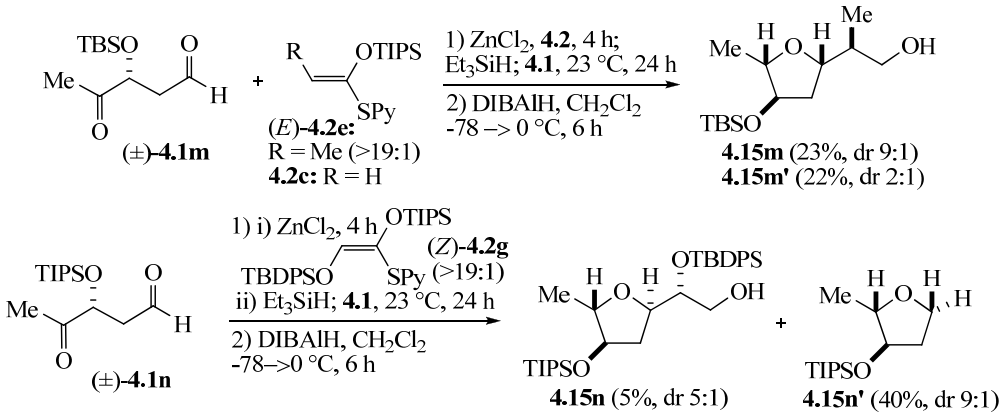
Scheme 4.12



With ketoaldehyde (±)-**4.1m** in hand, it was treated with (*E*)-**4.2e** (>19:1) under slightly modified tandem conditions to deliver the desired THF **4.15m** in low yield but good diastereoselectivity (Scheme 4.13). The TMAL seems to follow precedent observed in total syntheses of (-)-panclicin D[16] and derivatives[19] and the subsequent MRC[25] is in accordance with that previously observed in our stepwise approach toward THFs.[26] Treatment of ketoaldehyde (±)-**4.1m** with **4.2c** provided THF **4.15m'** in comparable yield but poor diastereoselectivity as expected. When bulky ketene acetal

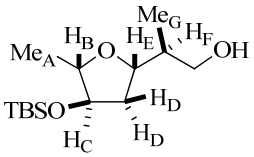
(*Z*)-**4.2g** was utilized, only trace quantities of the desired THF **4.15n** were obtained with 40% of undesired THF **4.15n'** observed with good diastereoselectivity. This product presumably arises in similar fashion as observed previously with bulky ketene acetals (*c.f.* Scheme 4.6) in which ketoaldehyde (±)-**4.1n** undergoes self-condensation and reduction with no incorporation of ketene acetal (*Z*)-**4.2g**. We were disappointed to observe this type of undesired THF **4.15n'** again, but the byproduct does lend support to our earlier findings in the stepwise TMAL-MRC (*c.f.* Scheme 3.8) which demonstrated high diastereoselectivity for α-silyloxy oxocarbenium reductions.[26] This example seems to be a more precise measurement of the diastereoselectivity (~9:1) of nucleophilic attack on α-silyloxy oxocarbenium intermediates compared to previous trisubstituted examples (*c.f.* **3.5d-f** and **4.15m-n**) in which matched or mismatched cases are operative.

Scheme 4.13

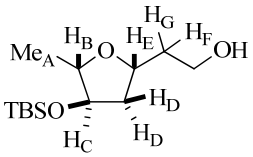


Both coupling constant analysis and nOe enhancements supported the relative stereochemical assignment of THFs **4.15m** and **4.15m'** while THFs **4.15n** and **4.15n'** were assigned tentatively based on precedent from our previous studies concerning both the TMAL[16] and MRC[25,26] (Table 4.9).

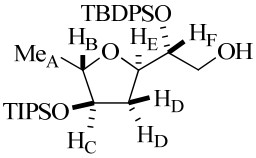
Table 4.9. Coupling constant analysis of tetrahydrofurans **4.15m-n**



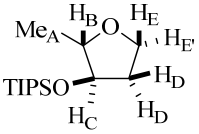
4.15m



4.15m'



4.15n



4.15n'

H	**4.15m** mult *J* (Hz)	**4.15m'** mult *J* (Hz)	**4.15n** mult *J* (Hz)	**4.15n'** mult *J* (Hz)
A	d	d	d	d
	6.5	6.5	6.5	6.5
B	dq	m	m	m
	6.5,6.5	--	--	--
C	ddd	m	m	m
	3.5,6.5,7.0	--	--	--
D	ddd	ddd	ddd	m
	3.5,6.5,13.0	3.0,6.0,12.5	6.0,9.5,13.0	--
D'	ddd	ddd	ddd	m
	7.0,9.5,13.0	6.5,9.0,12.5	3.0,6.5,13.0	--
E	ddd	m	m	m,m
	5.0,6.5,9.5	--	--	--
F	m	m	m	--
	--	--	--	--
G	d	m	--	--
	7.0	--	--	--

Conclusions

We have demonstrated a diastereoselective, three-component TMAL-MRC toward trisubstituted THFs employing α-benzyloxy-γ-ketoaldehydes, ketene acetals, and silyl nucleophiles that provides evidence for silylated β-lactone intermediates in the tandem Mukaiyama aldol-lactonization. These results build on Mead's reductive cyclization of keto-β-lactones and are in accordance with Woerpel's model for "inside attack" of oxocarbenium ions. Application toward a THF fragment of colopsinol B and preliminary studies with β-silyloxy-γ-ketoaldehydes wer demonstrated.

CHAPTER V

DEVELOPMENT OF A COMPREHENSIVE MODEL TO RATIONALIZE DIASTEREOSELECTIVITY IN THE TANDEM MUKAIYAMA ALDOL-LACTONIZATION (TMAL)

Introduction

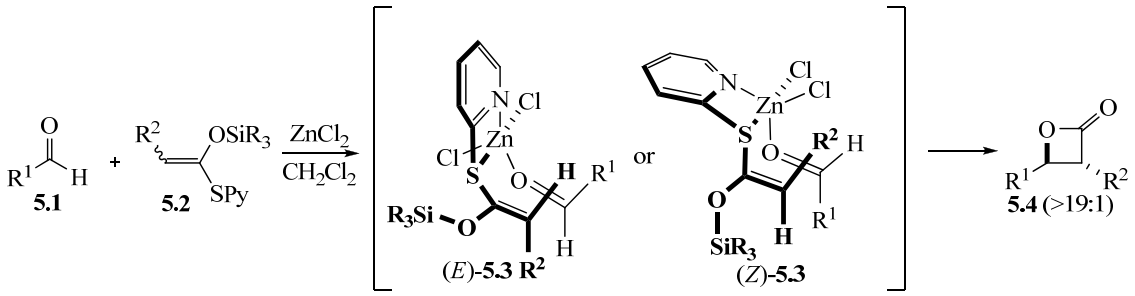
The tandem Mukaiyama aldol-lactonization (TMAL) reaction of aldehydes and thiopyridyl ketene acetals provides a highly diastereoselective approach to a variety of *trans*-1,2-disubstituted β-lactones.[16] Regarding the diastereoselectivity in the TMAL, there are two different categories which must be defined. We refer to *cis-trans* selectivity of the β-lactone as internal diastereoselectivity and *syn-anti* selectivity with respect to the stereochemistry of the alkyl C-O bond of the β-lactone as relative diastereoselectivity. Zhao proposed a comprehensive model to explain the internal diastereoselectivity and a rationalization for chelation-controlled products observed with α-benzyloxy aldehydes.[17] Yang and Wang both proposed models to rationalize the divergent selectivity of the TMAL toward the syntheses of (-)-panclicin D[105] and brefeldin A,[106] respectively. Both combined Zhao's model for internal selectivity with the 1,3-stereochemical induction model proposed by Evans.[92] These disparate results led us to consider various transition state arrrangements accessible in the TMAL.

Results and Discussion

Herein, we propose a universal model for the $ZnCl_2$-mediated TMAL process in an effort to rationalize previous results and to predict future stereochemical outcomes. Early studies of the TMAL between aldehydes **5.1** and thiopyridyl ketene acetals **5.2**

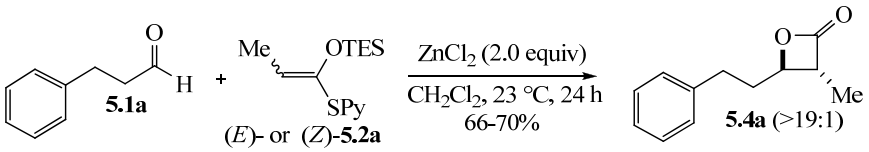
suggested stereoconvergent, trigonal bipyramidal boat-like transition state arrangements **5.3** toward *trans*-β-lactones **5.4**. Both (*E*)- and (*Z*)-ketene acetals **5.2** delivered *trans*-β-lactones **5.4** with excellent diastereoselectivity (Scheme 5.1).[17]

Scheme 5.1



For example, β-lactone **5.4a** was obtained from hydrocinnamaldehyde **5.1a** as a single diastereomer regardless of ketene acetal geometry indicating a stereoconvergent transition state arrangement. This trend has proven true for all TMAL reactions with aliphatic and achiral aldehydes (Scheme 5.2).

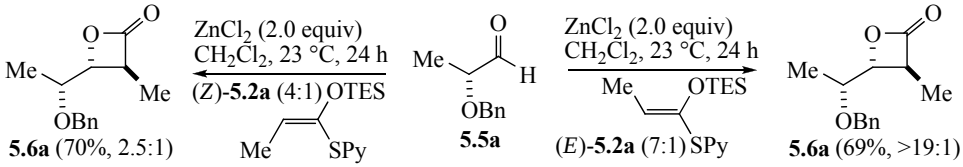
Scheme 5.2



In the case of aliphatic, chiral aldehydes, ketene acetal geometry is crucial to stereochemical outcome and seems to indicate a stereodivergent transition state arrangement. When α-benzyloxy aldehyde **5.5a** was treated with ketene acetal (*E*)-**5.2a**, a single diastereomer (*syn*-*trans*) of β-lactone **5.6a** was formed. In contrast, identical conditions with (*Z*)-**5.2a** delivered a greatly diminished ratio (2.5:1) of *trans*-β-lactones (Scheme 3).[17] Due to limitations of ketene acetal synthesis, we were not able to obtain

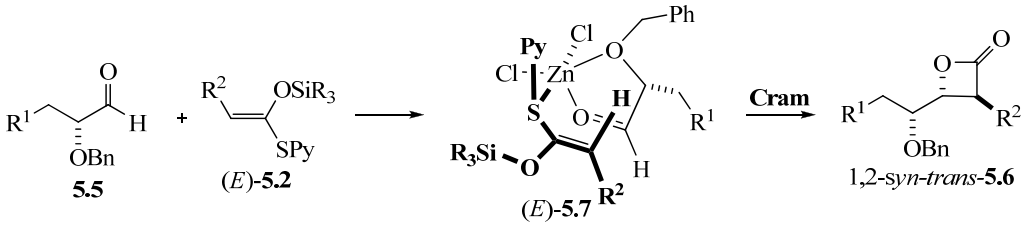
alkyl substituted ketene acetals (*i.e.* **5.2a**) with higher (*Z*)-selectivity than ~4:1 as shown.[107] It seems likely that *anti*-**5.6a** (not shown) could be accessed with at least moderate diastereoselectivity if enriched (*Z*)-**5.2a** (>19:1) could be obtained.

Scheme 5.3



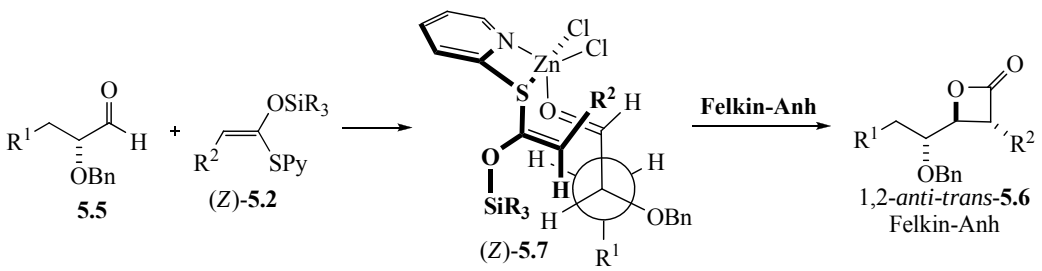
The stereochemical outcome of the TMAL between α-benzyloxy aldehydes **5.5** and ketene acetals (*E*)-**5.2** correlates to a boat-like transition state arrangement in which Cram chelation addition in *trans* fashion is operative (Scheme 5.4).[17]

Scheme 5.4



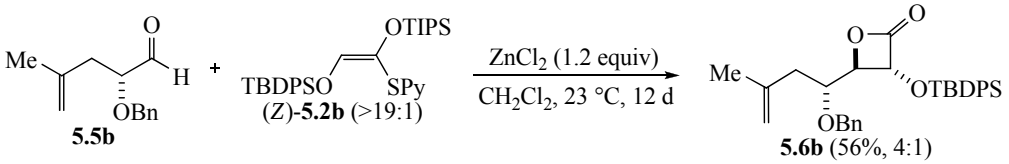
Although the stereochemical outcome with ketene acetal (*Z*)-**5.2** still correlates to Cram-chelation addition in *trans* fashion, the significant drop in diastereoselectivity suggests that Felkin-Anh addition in *trans* fashion is operative (Scheme 5.5).

Scheme 5.5



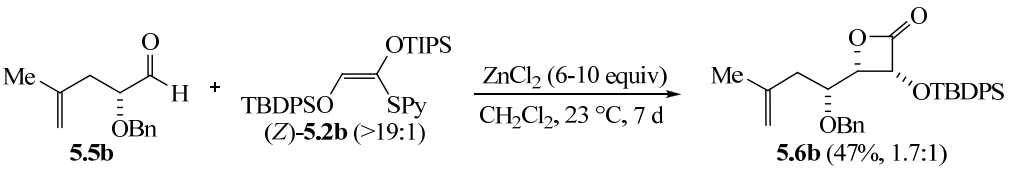
This transition state arrangement in which Felkin-Anh addition in *trans* fashion operates seemed to be confirmed when α-benzyloxy aldehyde **5.5b** was treated with (*Z*)-**5.2b** to deliver *anti*-β-lactone **5.6b** (Scheme 5.6). Unfortunately, the relative stereochemistry (*i.e. syn vs. anti*) has not been rigorously confirmed, but is supported by coupling constant evidence.[26]

Scheme 5.6



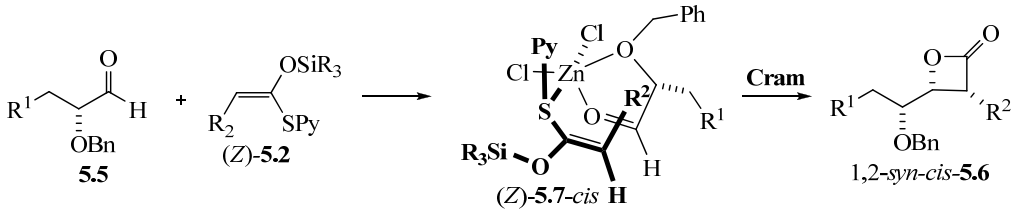
An interesting result was obtained when a large excess of $ZnCl_2$ was utilized. When α-benzyloxy aldehyde **5.5b** was treated with ketene acetal (*Z*)-**5.2b** under these conditions, *cis*-**5.6b** was obtained, albeit with low diastereoselectivity (Scheme 5.7).[26] The relative stereochemistry (*i.e. syn vs. anti*) has not been rigorously determined, but is supported by coupling constant evidence. Coupling constants to establish the internal stereochemistry is well-precedented,[94] and this constitutes the first example of the formation of a *cis*-β-lactone with an aliphatic aldehyde in the $ZnCl_2$-mediated TMAL.

Scheme 5.7



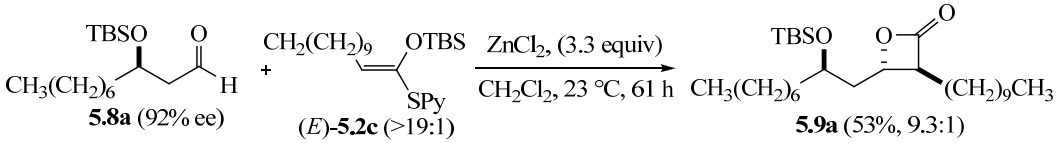
A plausible explanation for this reversal of diastereoselectivity could be that a large excess of $ZnCl_2$ slightly promotes Cram chelation in *cis* fashion (Scheme 5.8) instead of Felkin-Anh in *trans* fashion (*i.e.* Scheme 5.5).

Scheme 5.8



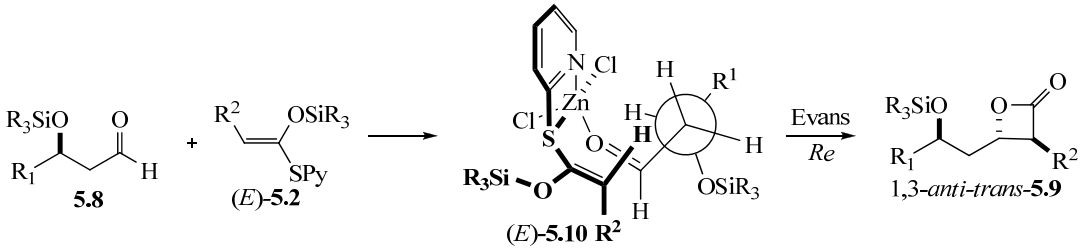
Treatment of β-silyloxy aldehyde **5.8a** with ketene acetal (*E*)-**5.2c** toward the total synthesis of (-)-panclicin D gave β-lactone **5.9a** in moderate yield and good diastereoselectivity (Scheme 5.9).[16]

Scheme 5.9



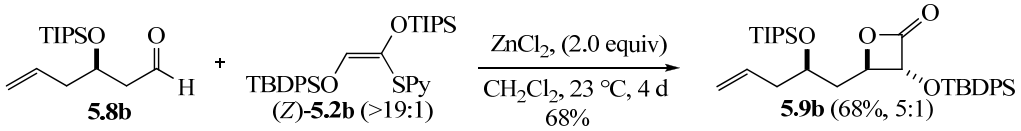
In this case, the stereochemical outcome correlates to a transition state arrangement in which the ketene acetal (*E*)-**5.2** attacks the β-silyloxy aldehyde **5.8** rom the *Re* face according to the Evans 1,3-asymmetric induction model[92] in *trans* fashion (Scheme 5.10).[105]

Scheme 5.10



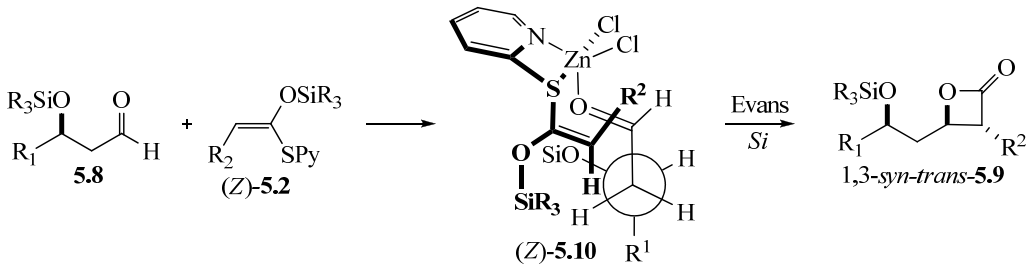
In contrast to the previous example, treatment of β-silyloxy aldehyde **5.8b** with ketene acetal (*Z*)-**5.2b** toward the total synthesis of brefeldin A delivered β-lactone **5.9b** in good yield and moderate diastereoselectivity (Scheme 5.11).[24]

Scheme 5.11



The stereochemical outcome of this TMAL reaction can also be rationalized using Evans 1,3-asymmetric induction[92] in *trans* fashion, but with ketene acetal (*Z*)-**5.2** attacking the β-silyloxy aldehyde **5.8** from the *Si* face. This stereodivergence was attributed to the avoidance of unfavorable non-bonded steric interactions between R^2 (*i.e.* OTBDPS) of ketene acetal (*Z*)-**5.2** and the β-silyloxy moiety (abbreviated OSi in transition state arrangement (*Z*)-**5.10** for clarity) of aldehyde **5.8**.[106]

Scheme 5.12



A summary of this universal model of the TMAL reaction portrays the stereochemical outcomes that can be rationalized by Cram chelation, Felkin-Anh, or Evans models in *trans* fashion (Figure 5.1).

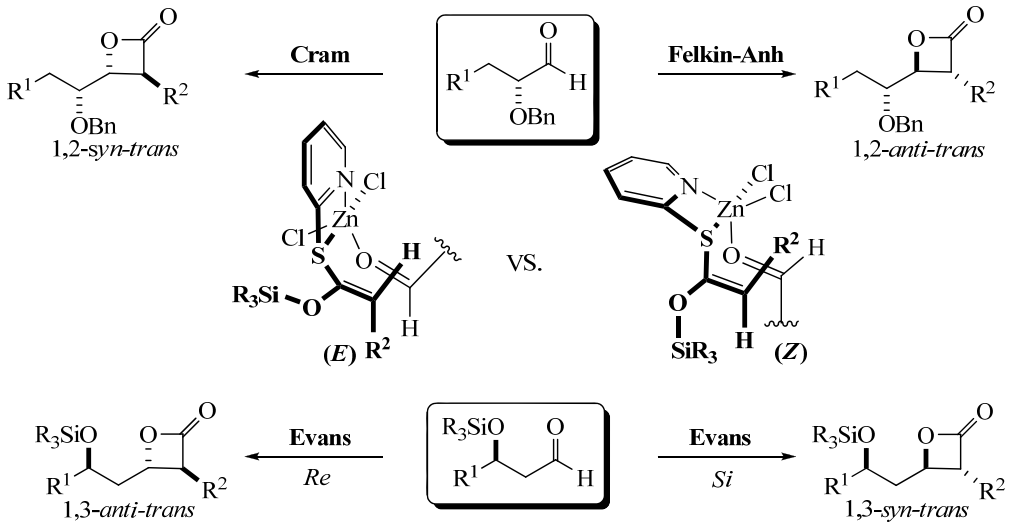


Figure 5.1. Universal model for diastereoselectivity in the TMAL

Conclusions

Although not complete, a comprehensive model is set forth that rationalizes the stereochemical outcome of the reaction between α- and β-substituted aldehydes and (*E*)- and (*Z*)-substituted ketene acetals in the $ZnCl_2$-mediated TMAL. Several experiments will be designed to further test this hypothesis including attempted chromatographic separation of (*E*)- and (*Z*)-substituted ketene acetals for use in the TMAL, other synthetic experiments, and molecular modeling of the proposed transition state arrangements.

CHAPTER VI

CONCLUSIONS

β-Lactones have emerged as valuable tools for the organic chemist toward other valuable structural motifs *en route* to natural products. We have demonstrated several new transformations of the commercially available (*R*)-4-trichloromethyl-β-lactone including radical alkylations, α-silylations, and alternative, tin-free methods for mono- and bis-dechlorinations. Importantly, several of these reactions can be conducted while maintaining the integrity of the β-lactone, thus enabling subsequent acylations or alkylations with the β-lactone moiety. A Weinreb amide was readily prepared and then selectively dechlorinated providing access to malic acid surrogates with orthogonal functional groups. Chain extensions at the γ-carbon were possible *via* radical alkylations providing access to further functionalized γ-chloro-β-lactones. α-silylations were shown to be feasible albeit in low yield.

We also developed a three-step strategy for the diastereoselective synthesis of THFs from alkenyl-aldehydes proceeding through β-lactone intermediates. The strategy involves the TMAL process and Mead's reductive cyclization of keto-β-lactones. The stereoselectivity of the latter process is rationalized by Woerpel's model for "inside attack" of oxocarbeniums. An increase in selectivity for certain α-silyloxy oxocarbenium ions was observed and is rationalized based on stereoelectronic effects building on Woerpel's findings. The stereoselectivity of the TMAL process for γ-benzyloxy and δ-silyloxy aldehydes with several thiopyridyl ketene acetals was defined including a reversal in selectivity when a thiophenyl ketene acetal was employed. A correlation

between relative stereochemistry and coupling constants was observed that provides a predictive method for the stereochemical assignment of γ-benzyloxy-β-lactones. This TMAL-MRC strategy should prove useful for the synthesis of tetrahydrofurans found in natural products.

In addition to the stepwise version, we developed a diastereoselective, three-component TMAL-MRC toward trisubstituted THFs employing α-benzyloxy-γ-ketoaldehydes, ketene acetals, and silyl nucleophiles that provides evidence for silylated β-lactone intermediates in the tandem Mukaiyama aldol-lactonization. These results build on our extension of Mead's reductive cyclization of keto-β-lactones and are in accordance with Woerpel's model for "inside attack" of oxocarbenium ions. Application toward a THF fragment of colopsinol B was demonstrated. We also presented preliminary studies with β-silyloxy-γ-ketoaldehydes in the tandem process.

A universal model is set forth that rationalizes the stereochemical outcome of the reaction between α- and β-substituted aldehydes and (*E*)- and (*Z*)-substituted ketene acetals in the $ZnCl_2$-mediated TMAL. Transition state arrangements based our previous results and stereochemical induction models (Cram chelation, Felkin-Anh, or Evans) provide a predictive tool for the diastereoselective TMAL. Several experiments will be designed to further test this hypothesis including attempted chromatographic separation of (*E*)- and (*Z*)-substituted ketene acetals for use in the TMAL, other synthetic experiments, and molecular modeling of the proposed transition state arrangements.

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APPENDIX A

EXPERIMENTAL AND SELECTED SPECTRAL DATA

General Procedures

All reactions were carried out under N_2 in oven-dried glassware (120 ˚C). All solvents were either distilled prior to use or obtained from a solvent purification system. Triethyl amine (Et_3N), diisopropylethyl amine (Hunig's base), and 2,6-lutidine were distilled from calcium hydride immediately prior to use. $ZnCl_2$ was fused under high vacuum (~0.5 mm Hg) and cooled to ambient temperature immediately prior to use. All other commercially available reagents were used as received. Brine refers to a saturated aqueous solution of sodium chloride and Rochelle's salt refers to a saturated aqueous solution of sodium potassium tartrate. Ether refers to diethyl ether unless otherwise noted. Flash column chromatography was carried out with Silica Gel 60Å (230-400 Mesh) as stationary phase as described by Still.[1] Thin layer chromatography was carried out with Silica Gel 60Å F254 glass plates (0.25 mm). Mass spectra were obtained with a High Resolution Electrospray Ionization (ESI) Mass Spectrometer. IR Spectra were recorded on a FTIR spectrometer. ^{1}H NMR spectra were recorded on a 500 or 300 MHz spectrometer and ^{13}C NMR spectra were recorded on a 125 or 75 MHz spectrometer. ^{1}H NMR chemical shifts are reported as δ in ppm relative to residual $CHCl_3$ (7.27 ppm) or residual C_6D_5H (7.16ppm) and deuterochloroform ($CDCl_3$ - 77.23 ppm) or deuterobenzene (C_6D_6 - 128.0 ppm) served as internal standards for all ^{13}C spectra. ^{1}H NMR coupling constants (*J*) are reported in Hertz (Hz), and multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), ddd (doublet of doublet of doublets), dddd (doublet of doublet of doublet of doublets), dt

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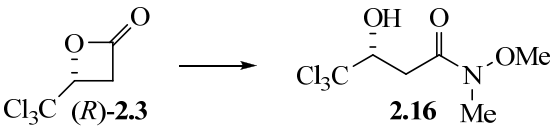
1 Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

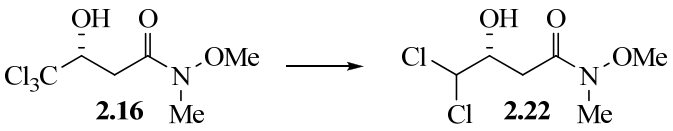
(doublet of triplets), dq (doublet of quartets), qq (quartet of quartets), m (multiplet), bs (broad singlet). Based on intensity in the ^{13}C spectra, both magnetic and chemical shift equivalent peaks are noted in parentheses. Only crucial nOe enhancements of THFs **3.5** and **4.15** are included. Yields of furans **4.16** are only tentatively reported if at all due to either volatility or difficulty in purification. For the same reasons, some of the furans **4.16** are either incompletely characterized or not included.

Chapter II – Radical Reactions of Optically Active 4-Trichloromethyl-β-Lactone: A Route to Potential β-Lactone Substrates for Tetrahydrofuran Synthesis

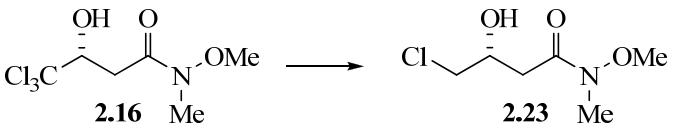


Trichloro Weinreb amide 2.16: To a solution of β-lactone **(2.3)** (500 mg, 2.68 mmol) in CH_2Cl_2 (25 mL) was added solid *N,O*-Dimethylhydroxylamine hydrochloride (392 mg, 4.02 mmol) followed by diisopropylethylamine (700 μL, 4.02 mmol) at 23 °C. This solution was stirred for 17 h and then quenched with sat. aq. NH_4Cl (20 mL) and diluted with ether (200 mL). The combined organic extracts were separated and washed with additional sat. aq. NH_4Cl (2 x 20 mL), water (2 x 20), and brine (2 x 20), and then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:ethyl acetate 60:40) delivered amide **2.16** (571 mg, 85%) as a white solid: R_f = 0.35 (hexanes:ethyl acetate 50:50); $[\alpha]^{23}$ +44.6 (1.00, $CHCl_3$); IR (thin film) 3384, 1684 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.95 (dd, J = 9.3, 16.5 Hz, 1H), 3.16 (dd, J = 2.4, 16.5 Hz, 1H), 3.24 (s, 3H), 3.75 (s, 3H), 4.48 (d, J = 4.2 Hz, 1H), 4.65 (ddd, J = 2.4, 4.2, 9.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.3, 34.5,

61.5, 79.2, 102.9, 171.2; ESI-HRMS calcd for $C_6H_{11}NO_3Cl_3$ [M + H] 249.9805, found 249.9803.

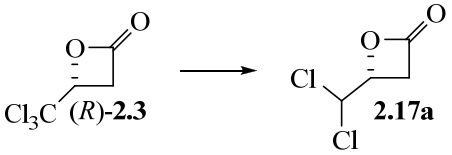


Dichloro Weinreb amide 2.22: To a solution of Weinreb amide **2.16** (2.50 g, 9.98 mmol) in THF (20 mL) was added tributyltin hydride (3.0 mL, 11.00 mmol) at 23 °C. This solution was refluxed for 24 h and then cooled and concentrated under reduced pressure. The residue was dissolved in acetonitrile, washed with hexanes to remove *n*-Bu_3SnCl, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:ethyl acetate 50:50) gave amide **2.22** (1.69 g, 78%) as a white solid: R_f 0.56 (hexanes:ethyl acetate 30:70); $[\alpha]^{23}$ +42.4 (1.00, $CHCl_3$); IR (thin film) 3355, 1649 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.89 (dd, *J* = 7.8, 17.1 Hz, 1H), 2.99 (dd, *J* = 3.9, 17.1 Hz, 1H), 3.23 (s, 3H), 3.74 (s, 3H), 4.09 (d, *J* = 4.8 Hz, 1H), 4.36-4.43 (m, 1H), 5.90 (d, *J* = 3.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.1, 33.5, 61.5, 72.8, 75.2, 171.9; ESI-HRMS calcd for $C_6H_{11}NO_3Cl_2Li$ [M + Li] 222.0276, found 222.0296.

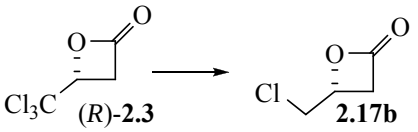


Chloro Weinreb amide 2.23: To a solution of Weinreb amide **2.16** (500 mg, 2.00 mmol) in toluene (5 mL) was added tris(trimethylsilyl)silane (1.3 mL, 4.20 mmol) and triethylborane (4.4 mL, 4.40 mmol) sequentially at 23 °C and open to the air. This solution was stirred for 2 h and then dissolved in acetonitrile, washed with hexanes to remove silyl byproducts, and concentrated under reduced pressure. Purification by flash

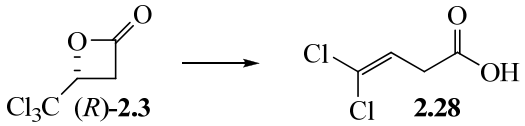
column chromatography (hexanes:ethyl acetate 30:70) afforded amide **2.23** (280 mg, 77%) as a pale red oil: R_f = 0.37 (hexanes:ethyl acetate 30:70); $[\alpha]^{23}$ +46.5 (1.00, $CHCl_3$); IR (thin film) 3423, 1643 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.73 (dd, *J* = 7.8, 17.1 Hz, 1H), 2.83 (dd, *J* = 3.9, 17.1 Hz, 1H), 3.22 (s, 3H), 3.63-3.65 (m, 2H), 3.73 (s, 3H), 3.98 (d, *J* = 4.2 Hz, 1H), 4.22-4.31 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.9, 35.3, 48.1, 61.4, 68.1, 172.6; ESI-HRMS calcd for $C_6H_{13}ClNO_3$ [M + H] 182.0584, found 182.0589.



Dichloromethyl-β-lactone 2.17a: To a solution of β-lactone **(2.3)** (3.00 g, 16.11 mmol) in THF (30 mL) was added tributyltin hydride (4.8 mL, 17.70 mmol) at 23 °C. This solution was refluxed for 24 h at which time it was cooled and concentrated under reduced pressure. Two sequential flash column purifications (pentane:ether 80:20) were required to remove all tin impurities and gave β-lactone **2.17a** (1.90 g, 78%) as a clear oil: R_f = 0.72 (hexanes:ethyl acetate 70:30); $[\alpha]^{23}$ +31.2 (1.00, $CHCl_3$); IR (thin film) 1846 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.58 (dd, *J* = 3.9, 16.8 Hz, 1H), 3.67 (dd, *J* = 6.0, 16.8 Hz, 1H), 4.81 (ddd, *J* = 3.9, 4.8, 6.0 Hz, 1H), 5.98 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.1, 70.6, 71.0, 165.7; ESI-HRMS calcd for $C_4H_4Cl_2O_2Li$ [M + Li] 160.9748, found 160.9741.

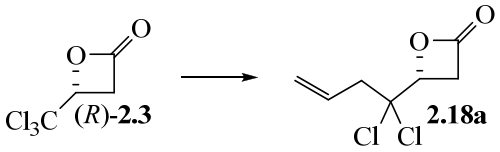


Chloromethyl-β-lactone 2.17b: To a solution of β-lactone **(2.3)** (1.00 g, 5.37 mmol) in toluene (6 mL) was added tributyltin hydride (3.0 mL, 11.00 mmol) followed by 11.0 mL of triethyl borane (1.0 M in hexanes, 11.00 mmol) at 23 °C and open to the air. After stirring for 5 h, the reaction was poured over a pad of silica gel and eluted with hexanes to remove tin byproducts and then eluted with ether to remove the product. Following removal of ether, the residue was purified by two sequential flash columns (pentane:ether 80:20) to obtain β-lactone **2.17b** (160 mg, 25%) as a clear oil: R_f = 0.35 (hexanes:ethyl acetate 70:30); $[\alpha]^{23}$ +10.2 (1.00, $CHCl_3$); IR (thin film) 1836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.42 (dd, *J* = 4.2, 16.5 Hz, 1H), 3.62 (dd, *J* = 5.7, 16.5 Hz, 1H), 3.81 (dd, *J* = 5.7, 12.3 Hz, 1H), 3.87 (dd, *J* = 4.8, 12.3 Hz, 1H), 4.71-4.78 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.7, 44.5, 68.6, 166.7; ESI-HRMS calcd for $C_4H_5ClO_2Li$ [M + Li] 127.0138, found 127.0141.

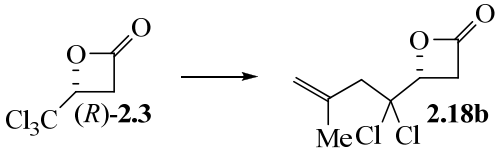


Carboxylic acid 2.28: To a mixture of β-lactone **(2.3)** (100 mg, 0.54 mmol) and collidinium triflate (473 mg, 1.61 mmol) at 23 °C was added 16.0 mL of SmI_2 solution (0.1 M in THF, 1.61 mmol). The solution was stirred for 2 h and then the reaction was quenched with sat. aq. $Na_2S_2O_3$, diluted with ether (100 mL), and the organics were washed with aq. 10% K_2CO_3 (3 x 20 mL). The combined aqueous extracts were acidified to pH 2 with 1 N HCl, washed with ethyl acetate (3 x 20 mL), and the

combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to deliver acid **2.28** (80 mg, 94% yield) as a pale yellow solid. Spectral data for this compound matched that previously reported.[61]

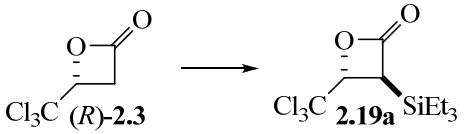


Allyl-β-lactone 2.18a: To a solution of β-lactone **(2.3)** (500 mg, 2.67 mmol) in toluene (3 mL) was added neat allyltributylstannane (2.1 mL, 6.68 mmol) followed by 6.7 mL of triethylborane (1.0 M in hexanes, 6.68 mmol) at 23 °C and open to the air. After stirring for 5 h, the crude reaction mixture was directly loaded on a silica column and purified by two successive gradient flash column purifications (pentane:ether 99:1 to 97:3) to deliver β-lactone **2.18a** (240 mg, 46%) as a clear oil: R_f = 0.60 (hexanes:ethyl acetate 70:30); $[\alpha]^{23}$ +12.5 (1.00, $CHCl_3$); IR (thin film) 3090, 3015, 1851, 1643 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.00 (ddt, *J* = 0.9, 7.5, 14.7 Hz, 1H), 3.13 (ddt, *J* = 1.2, 6.6, 14.7 Hz, 1H), 3.62 (dd, *J* = 5.7, 16.8 Hz, 1H), 3.72 (dd, *J* = 3.9, 16.8 Hz, 1H), 4.73 (dd, *J* = 3.9, 5.7 Hz, 1H), 5.28-5.39 (m, 2H), 5.89-6.03 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.8, 48.5, 72.7, 89.8, 122.2, 129.9, 165.7; ESI-HRMS calcd for $C_7H_8Cl_2O_2Li$ [M + Li] 201.0061, found 201.0070.



Methallyl-β-lactone 2.18b: To a solution of methallyltributylstannane (4.56 g, 2.95 mmol) in toluene (3 mL) was added β-lactone **(2.3)** (1.00 g, 5.28 mmol) at 23 °C

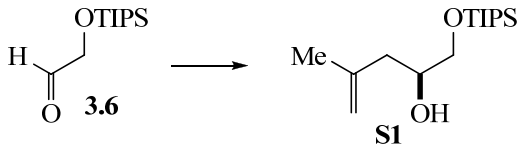
followed by 13.2 mL of triethylborane (1.0 M in hexanes, 13.2 mmol) at 23 °C and open to the air. After stirring for 6 h, the crude reaction mixture was directly loaded on a silica column and purified by two successive gradient flash column purifications (pentane:ether 99:1 to 97:3) to deliver β-lactone **2.18b** (495 mg, 45%) as a clear oil: R_f = 0.81 (hexanes:ethyl acetate 70:30); $[\alpha]^{23}$ +9.7 (1.00, $CHCl_3$); IR (thin film) 3082, 1855, 1647 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.97 (m, 3H), 3.07 (s, 2H), 3.62 (dd, *J* = 5.4, 16.8 Hz, 1H), 3.73 (dd, *J* = 3.9, 16.8 Hz, 1H), 4.79 (dd, *J* = 3.9, 5.4 Hz, 1H), 5.01-5.02 (m, 1H), 5.15-5.17 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.2, 41.7, 51.5, 72.5, 89.8, 119.5, 138.1, 165.8; ESI-HRMS calcd for $C_8H_{10}Cl_2O_2Li$ [M + Li] 215.0218, found 215.0223.



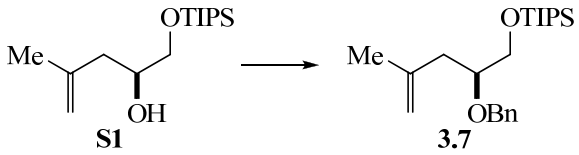
α-Silyl-β-lactone 2.19a: To a solution of β-lactone **(2.3)** (200 mg, 1.07 mmol) in THF (10 mL) was added TESOTf (250 μL, 1.07 mmol) dropwise at -78 °C followed by LiHMDS (1.0 mL, 1.07 mmol) down the side of the flask to ensure cooling. An additional 10 mL of THF was used to wash the side of the flask. The reaction was stirred for 1.5 h at -78 °C, quenched with sat. aq. NH_4Cl, and warmed to 23 °C. The mixture was diluted with ether (100 mL), separated, and washed with additional sat. aq. NH_4Cl (2 x 20 mL), water (2 x 20 mL), and brine (2 x 20 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (pentane:ether 95:5) delivered the β-lactone **2.19a** (100 mg, 31% yield, 50% based on recovered starting material) as a clear oil: R_f = 0.75

(hexanes:ethyl acetate 80:20); $[\alpha]^{23}$ +10.0 (1.00, $CHCl_3$); IR (thin film) 1841 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.79-0.84 (m, 6H), 1.03-1.08 (m, 9H), 3.46 (d, *J* = 3.9 Hz, 1H), 4.78 (d, *J* = 3.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 2.7, 7.1, 45.3, 78.5, 98.4, 167.9; ESI-HRMS calcd for $C_{10}H_{17}Cl_3O_2SiLi$ [M + Li] 309.0223, found 309.0229.

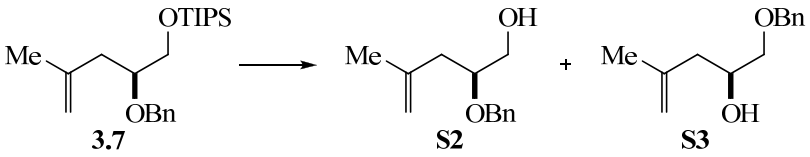
Chapter III – Development of a Diastereoselective Stepwise Synthesis of Tetrahydrofurans *via* Mead Reductive Cyclization (MRC) of Keto-β-Lactones Derived from the Tandem Mukaiyama Aldol-Lactonization (TMAL)



Primary Alcohol S1: To a solution of aldehyde **3.6** (8.50 g, 36.92 mmol) in ether (180 mL) was added a 0.5 M solution of 2-methylallylmagnesium chloride in THF (94.0 mL, 47.00 mmol) slowly at -78 °C. The reaction was allowed to warm quickly to 23 °C and was quenched with sat. aq. NH_4Cl (100 mL) after 2 h. After stirring vigorously for 30 min, the organic layer was separated and washed with additional sat. aq. NH_4Cl (2 x 50 mL), water (2 x 50 mL), and brine (2 x 50 mL). The residue was then dried over $MgSO_4$, filtered over a pad of SiO_2, and concentrated under reduced pressure to deliver alcohol **S1** (9.05 g, 90%) as a colorless oil: R_f = 0.47 (90:10 hexanes: ethyl acetate); IR (thin film) 3459, 3075 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.06-1.10 (m, 21H), 1.79 (br s, 3H), 2.20 (d, *J* = 6.3 Hz, 2H), 2.48 (d, *J* = 3.3 Hz, 1H), 3.56 (dd, *J* = 6.9, 9.9 Hz, 1H), 3.71 (dd, *J* = 3.9, 9.9 Hz, 1H), 3.80-3.90 (m, 1H), 4.80 (br s, 1H), 4.85 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.0(3), 18.1(6), 22.7, 41.7, 67.3, 70.0, 112.9, 142.5; ESI-HRMS calcd for $C_{15}H_{32}O_2SiLi$ [M + Li] 279.2332, found 279.2346.



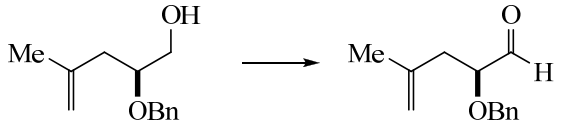
Benzyl ether 3.7: To a solution of alcohol **S1** (6.00 g, 22.01 mmol) in THF (220 mL) was added benzyl bromide (3.9 mL, 33.02 mmol) and NaH 1.32 g, 33.02 mmol, 60% dispersion in mineral oil) at 0 °C as a solid. The reaction was heated to 65 °C and was stirred for 8 h after which time it was cooled to 23 °C and quenched slowly with sat. aq. NH_4Cl (50 mL). The resulting mixture was stirred vigorously for 30 min, concentrated under reduced pressure, and diluted with ether (250 mL). The organic layer was separated and washed with additional sat. aq. NH_4Cl (2 x 50 mL), water (2 x 50 mL), and brine (2 x 50 mL). The residue was then dried over $MgSO_4$, filtered over a pad of SiO_2, and concentrated under reduced pressure to deliver benzyl ether **3.7** (7.50 g, 94%) with varying amounts of a product (not shown) derived from silyl migration which is removed following the subsequent deprotection as a pale yellow oil: R_f = 0.62 (95:5 hexanes:ethyl acetate); IR (thin film) 3068, 3030, 1117 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.07-1.09 (m, 21H), 1.75 (br s, 3H), 2.25 (dd, *J* = 6.6, 14.1 Hz, 1H), 2.34 (dd, *J* = 4.5, 14.1 Hz, 1H), 3.62-3.82 (m, 3H), 4.63 (d, *J* = 11.7 Hz, 1H), 4.74 (d, *J* = 11.7 Hz, 1H), 4.80 (br s, 1H), 4.81 (br s, 1H), 7.27-7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.1(3), 18.2(6), 23.1, 40.6, 66.2, 72.5, 78.9, 112.8, 127.6, 127.9(2), 128.4(2), 139.2, 143.0; ESI-HRMS calcd for $C_{22}H_{38}O_2SiLi$ [M + Li] 369.2801, found 369.2793.



Alcohols S2 and S3: To a solution of benzyl ether **3.7** (9.00 g, 24.81 mmol) in THF (250 mL) was added a 1.0 M solution of TBAF in THF (50.0 mL, 49.62 mmol) at 0 °C, stirred for 1.5 h, and allowed to warm to 23 °C. The solution was quenched with sat. aq. NH_4Cl (50 mL), stirred vigorously for 30 min, concentrated under reduced pressure, and diluted with ether (250 mL). The organic layer was separated and washed with additional sat. aq. NH_4Cl (2 x 50 mL), water (2 x 50 mL), and brine (2 x 50 mL). The solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Crude ^{1}H NMR analysis revealed a 9:1 mixture of primary alcohol **S2** to rearranged secondary alcohol **S3**. Purification by flash column chromatography (hexanes:ethyl acetate 85:15) delivered primary alcohol **S2** (2.17 g, 42%), secondary alcohol **S3** (282 mg, 5%) derived from silyl migration during the previous step, and a mixture of the two products (2.55 g, 50%) as colorless oils. Characterization data for primary alcohol **S3** matched that previously reported:[2] R_f = 0.18 (80:20 hexanes: ethyl acetate); IR (thin film) 3465, 3070, 3031, 1098 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78 (br t, *J* = 1.2 Hz, 3H), 1.96 (dd, *J* = 5.3, 7.0 Hz, 1H), 2.19-2.26 (m, 1H), 2.39-2.45 (m, 1H), 3.50-3.76 (m, 3H), 4.56 (d, *J* = 11.4 Hz, 1H), 4.69 (d, *J* = 11.4 Hz, 1H), 4.79-4.82 (m, 1H), 4.82-4.86 (m, 1H), 7.30-7.38 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9, 39.4, 64.1, 71.5, 78.1, 113.2, 127.7, 127.8(2), 128.4(2), 138.4, 142.1; ESI-HRMS calcd for $C_{13}H_{18}O_2Li$ [M + Li] 213.1467, found 213.1471. Characterization data for secondary alcohol **S3** matched

2 Hubbs, J. L.; Heathcock, C. H. *J. Am. Chem. Soc.* **2003**, *125*, 12836.

that previously reported:[3] R_f = 0.20 (80:20 hexanes: ethyl acetate); IR (thin film) 3454, 3071, 3032, 1099 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.78 (br s, 3H), 2.20-2.24 (m, 2H), 2.29 (d, *J* = 3.3, 1H), 3.40 (dd, *J* = 7.2, 9.6 Hz, 1H), 3.53 (dd, *J* = 3.6, 9.6 Hz, 1H), 3.95-4.05 (m, 1H), 4.58 (s, 2H), 4.78-4.82 (m, 1H), 4.84-4.88 (m, 1H), 7.36 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5, 41.9, 68.2, 73.4, 74.2, 113.2, 127.8(3), 128.4(2), 138.0, 142.1; ESI-HRMS calcd for $C_{13}H_{19}O_2$ [M + H] 207.1385, found 207.1358.

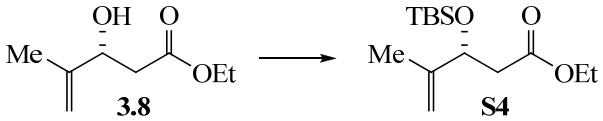


S2 (±)-**3.1a**

Representative procedure for the Swern Oxidation as described for α-benzyloxy aldehyde (±)-3.1a. To a solution of oxalyl chloride (1.3 mL, 14.54 mmol) in CH_2Cl_2 (50 mL) was added DMSO (2.1 mL, 29.08 mmol) dropwise at -78 °C and was stirred for 5 min. To this solution was added the primary alcohol **S2** (1.50 g, 7.27 mmol) in CH_2Cl_2 (25 mL) and stirred for 15 min at which time Et_3N (8.1 mL, 58.16 mmol) was added and stirred for an additional 2 h. The reaction was quenched with pH 7 buffer, stirred vigorously for 30 min, and allowed to warm to 23 °C. The crude aldehyde **(±)-3.1a** was diluted with ether (200 mL) and after separation from the aqueous layer was washed with water (3 x 50 mL) and brine (3 x 50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (95:5 hexanes:ethyl acetate) delivered pure aldehyde **(±)-3.1a** (1.35 g, 91%) as a pale yellow oil: R_f = 0.51 (80:20 hexanes: ethyl acetate); IR (thin film) 3076, 3031, 2721, 1732, 1103 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.75 (br s, 3H), 2.44 (d, *J* = 6.6 Hz, 2H),

3 Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 10160.

3.93 (dt, *J* = 2.1, 6.6 Hz, 1H), 4.59 (d, *J* = 11.7 Hz, 1H), 4.69 (d, *J* = 11.7 Hz, 1H), 4.83 (br s, 1H), 4.88 (br s, 1H), 7.30-7.38 (m, 5H), 9.67 (d, *J* = 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8, 38.4, 72.6, 81.9, 114.1, 128.07(2), 128.13, 128.6(2), 137.3, 140.4, 203.1; ESI-HRMS calcd for $C_{13}H_{16}O_2Li$ [M + Li] 211.1310, found 211.1297.



β-Silyloxy Ester S4: To a solution of β-hydroxy ester **3.8**[4] in DMF (150 mL) was added TBSCl (4.45 g, 29.52 mmol) and imidazole (3.01 g, 44.27 mmol) at 23 °C. This solution was stirred for 12 h and was quenched with sat. aq. NH_4Cl (50 mL) and stirred vigorously for 30 min. Upon dilution with ether (200 mL) and removal of the aqueous layer, the organic layer was washed with sat. aq. NH_4Cl (2 x 50 mL), water (2 x 50 mL), and brine (2 x 50 mL). The ethereal solution was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (95:5 hexanes:ethyl acetate) delivered β-silyloxy ester **S4** (6.59 g, 82%) as a pale yellow oil: R_f = 0.56 (90:10 hexanes:ethyl acetate); IR (thin film) 1740, 1087 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.05 (s, 3H), 0.87 (s, 9H), 1.27 (t, *J* = 7.2, 3H), 1.71-1.72 (m, 3H), 2.42 (dd, *J* = 4.5, 14.4 Hz, 1H), 2.55 (dd, *J* = 9.0, 14.4 Hz, 1H), 4.09-4.17 (m, 2H), 4.56 (dd, *J* = 4.5, 9.0 Hz, 1H), 4.80-4.81 (m, 1H), 4.96-4.97 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.2, -4.7, 14.4, 17.1, 18.2, 25.8(3), 42.7, 60.5, 74.0, 111.7, 146.8, 171.5; ESI-HRMS calcd for $C_{14}H_{28}O_3SiLi$ [M + Li] 279.1968, found 279.1969.

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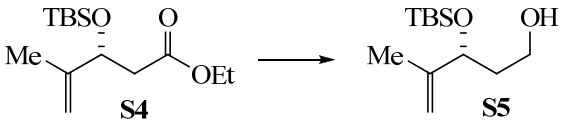
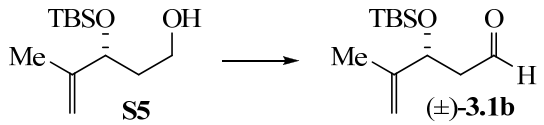
4 (a) Zibuck, R.; Streiber, J. M. *J. Org. Chem.* **1989**, *54*, 4717. (b) Wang, Y. G.; Kobayashi, Y. *Org. Lett.* **2002**, *4*, 4615.

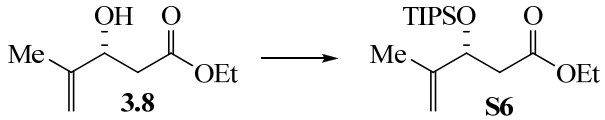


Primary Alcohol S5: To a solution of silyl ether **S4** (6.00 g, 19.20 mmol) in CH_2Cl_2 (240 mL) was added DIBAl-H (7.2 mL, 40.32 mmol) dropwise at -78 °C. This solution was immediately warmed to 0 °C and stirred for 4 h at which time it was quenched slowly with MeOH (20 mL). Upon addition of Rochelle's salt (100 mL), the mixture was stirred vigorously for 12 h at which time it was poured over Celite, washed with CH_2Cl_2 and concentrated under reduced pressure. The residue was dissolved in ether (250 mL) and washed with sat. aq. NH_4Cl (2 x 50 mL), water (2 x 50mL), and brine (2 x 50 mL). The ethereal solution was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:ethyl acetate 90:10) delivered pure alcohol **S5** (3.72 g, 84%) as a pale yellow oil: R_f = 0.33 (hexanes:ethyl acetate 80:20); IR (thin film) 3344, 3073, 1087, 1064 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.10 (s, 3H), 0.92 (s, 9H), 1.70-1.72 (m, 3H), 1.77-1.83 (m, 2H), 2.32 (t, *J* = 5.4 Hz, 1H), 3.66-3.82 (m, 2H), 4.31 (dd, *J* = 5.7, 6.0 Hz, 1H), 4.84-4.87 (m, 1H), 4.99-5.01 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.2, -4.7, 17.8, 18.2, 25.9(3), 37.9, 60.0, 75.4, 111.0, 147.1; ESI-HRMS calcd for $C_{12}H_{26}O_2SiLi$ [M + Li] 237.1862, found 237.1808.



β-silyloxy aldehyde (±)-3.1b was prepared according to the representative procedure for the Swern oxidation using oxalyl chloride (750 μL, 8.68 mmol) in CH_2Cl_2 (30 mL),

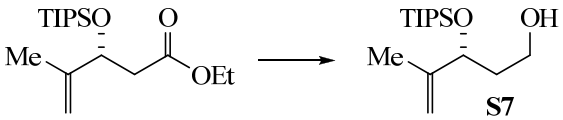
DMSO (1.2 mL, 17.36 mmol), alcohol **S5** (1.00 g, 4.34 mmol) in CH_2Cl_2 (10 mL), and Et_3N (4.9 mL, 34.71 mmol). Representative work-up with water (3 x 50 mL) and brine (3 x 50 mL) delivered crude aldehyde **(±)-3.1b**. Purification by flash column chromatography (hexanes:ethyl acetate 95:5) delivered aldehyde **(±)-3.1b** (803 mg, 81%) as a pale yellow oil: R_f = 0.46 (hexanes:ethyl acetate 90:10); IR (thin film) 2701, 1728, 1089 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.07 (s, 3H), 0.89 (s, 9H), 1.72-1.73 (m, 3H), 2.47 (ddd, *J* = 2.1, 4.5, 15.3 Hz, 1H), 2.66 (ddd, *J* = 3.0, 7.5, 15.3 Hz, 1H), 4.59 (dd, *J* = 4.5, 7.5 Hz, 1H), 4.85-4.87 (m, 1H), 5.01-5.02 (m, 1H), 9.77 (dd, *J* = 2.1, 3.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.2, -4.7, 17.5, 18.1, 25.8(3), 49.9, 72.2, 111.7, 146.3, 201.4; ESI-HRMS calcd for $C_{12}H_{24}O_2SiLi$ [M + Li] 235.1706, found 235.1683.



3.8 **S6**

β-Silyloxy Ester S6: To a solution of β-hydroxy ester **3.8**[5] (2.50 g, 15.80 mmol) in CH_2Cl_2 (150 mL) was added TIPSOTf (4.4 mL, 15.80 mmol) followed by Et_3N (2.2 mL, 15.80 mmol) and a crystal of DMAP at 23 °C. This solution was stirred for 2.5 h at which time it was quenched with sat. aq. NH_4Cl (50 mL), stirred vigorously for 30 min, and concentrated under reduced pressure. Upon dilution with ether (200 mL) and removal of the aqueous layer, the organic layer was washed with sat. aq. NH_4Cl (2 x 50 mL), water (2 x 50 mL), and brine (2 x 50 mL). The ethereal solution was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:ethyl acetate 95:5) delivered β-silyloxy ester **S6** (3.73

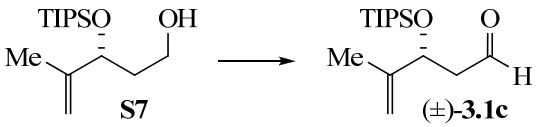
g, 75%) as a pale yellow oil: R_f = 0.79 (hexanes:ethyl acetate 80:20); IR (thin film) 1740, 1086 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05-1.07 (m, 21H), 1.25 (t, *J* = 7.2, 3H), 1.74-1.75 (m, 3H), 2.50 (dd, *J* = 6.9, 14.1 Hz, 1H), 2.61 (dd, *J* = 6.6, 14.1 Hz, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 4.69 (dd, *J* = 6.6, 6.9 Hz, 1H), 4.79-4.81 (m, 1H), 4.93-4.94 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.5(3), 14.3, 16.7, 18.1(6), 42.9, 60.4, 74.2, 112.0, 146.6, 171.2; ESI-HRMS calcd for $C_{17}H_{34}O_3SiLi$ [M + Li] 321.2437, found 321.2325.



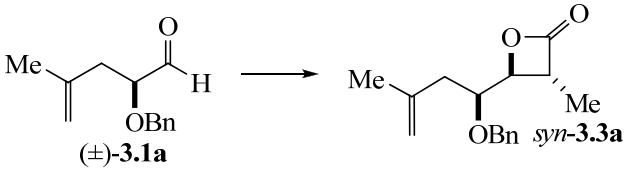
S7

Primary Alcohol S7: To a solution of β-silyloxy ester **S6** (2.70 g, 8.58 mmol) in CH_2Cl_2 (90 mL) was added DIBAl-H (3.8 mL, 21.46 mmol) dropwise at -78 °C. This solution was immediately warmed to 0 °C and stirred for 4 h at which time it was quenched slowly with MeOH (20 mL). Upon addition of Rochelle's salt (75 mL), the mixture was stirred vigorously for 21 h at which time it was poured over Celite, washed with CH_2Cl_2 and concentrated under reduced pressure. The residue was dissolved in ether (200 mL) and washed with sat. aq. NH_4Cl (2 x 50 mL), water (2 x 50mL), and brine (2 x 50 mL). The ethereal solution was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:ethyl acetate 80:20) delivered alcohol **S7** (1.70 g, 73%) as a pale yellow oil: R_f = 0.24 (hexanes:ethyl acetate 80:20); IR (thin film) 3341, 3073, 1091, 1061 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.06-1.09 (m, 21H), 1.71-1.72 (m, 3H), 1.76-2.00 (m, 2H), 2.32 (dd, *J* = 3.9, 6.6 Hz, 1H), 3.62-3.83 (m, 2H), 4.43-4.46 (m, 1H), 4.91-4.93 (m, 1H),

5.07-5.09 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.4(3), 17.9, 18.2(6), 37.3, 59.7, 75.5, 111.5, 146.6; ESI-HRMS calcd for $C_{15}H_{32}O_2SiLi$ [M + Li] 279.2332, found 279.2241.

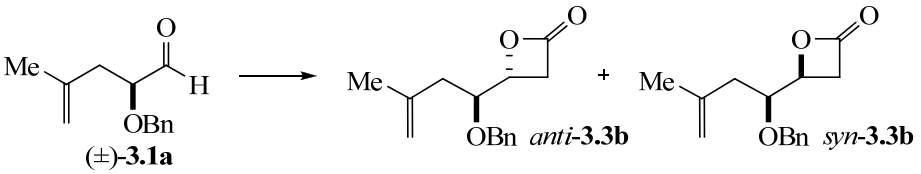


β-Silyloxy Aldehyde (±)-3.1c was prepared according to the representative procedure for the Swern oxidation using oxalyl chloride (925 μL, 10.78 mmol) in CH_2Cl_2 (30 mL), DMSO (1.5 mL, 21.56 mmol), alcohol **S7** (1.47 g, 5.39 mmol) in CH_2Cl_2 (20 mL), and Et_3N (6.0 mL, 43.12 mmol). Representative work-up with water (3 x 50 mL) and brine (3 x 50 mL) delivered crude aldehyde **(±)-3.1c**. Purification by flash column chromatography (hexanes:ethyl acetate 95:5) delivered aldehyde **(±)-3.1c** (1.18 g, 81%) as a pale yellow oil: R_f = 0.79 (hexanes:ethyl acetate 80:20); IR (thin film) 3077, 2722, 1726, 1101 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05-1.07 (m, 21H), 1.74-1.75 (m, 3H), 2.61-2.64 (m, 2H), 4.68 (dd, *J* = 5.7, 5.7 Hz, 1H), 4.88-4.90 (m, 1H), 5.06-5.08 (m, 1H), 9.78 (dd, *J* = 2.7, 2.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.4(3), 17.7, 18.09(3), 18.12(3), 49.8, 72.4, 111.9, 146.2, 201.6; ESI-HRMS calcd for $C_{15}H_{30}O_2SiLi$ [M + Li] 277.2175, found 277.2164.



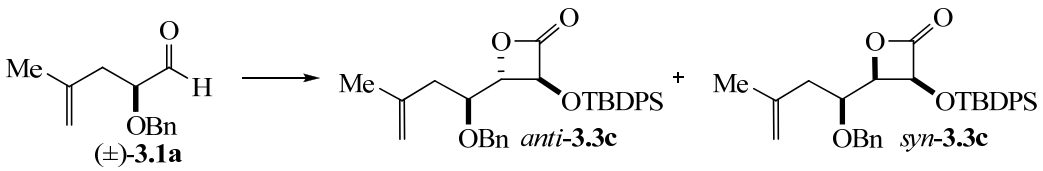
Representative procedure for the TMAL Reaction as described for γ-benzyloxy-alkenyl-β-lactone *syn*-3.3a. $ZnCl_2$ (273 mg, 2.00 mmol) was freshly fused at ~0.5 mm Hg and subsequently cooled to ambient temperature. The aldehyde **(±)-3.1a** (204 mg,

1.00 mmol) and ketene acetal **3.2a** (384 mg, 1.20 mmol) were each added as a solution in 5 mL of CH_2Cl_2 (final concentration of aldehyde in CH_2Cl_2 ~0.1 M). This suspension was stirred for 14 h at 23 °C and then quenched with pH 7 buffer, stirred vigorously for 30 min, and poured over Celite with additional CH_2Cl_2. After concentration under reduced pressure, the residue was dissolved in CH_2Cl_2 (final concentration of β-lactone in CH_2Cl_2 ~0.15 M) and treated with $CuBr_2$ (357 mg, 1.60 mmol). After stirring for 2.5 h, the crude β-lactone *syn*-**3.3a** was again poured over Celite and washed with ether (200 mL). The combined organic layer was washed with 10% aq. K_2CO_3 (3 x 50 mL), H_2O (2 x 50 mL), and brine (2 x 50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to deliver crude β-lactone *syn*-**3.3a** as a single diastereomer (>19:1) as judged by analysis of crude ^{1}H NMR (300 MHz). Purification by flash column chromatography (hexanes:ethyl acetate 95:5) delivered *syn*-**3.3a** (216 mg, 83%) as a colorless oil: R_f = 0.42 (80:20 hexanes:ethyl acetate); IR (thin film) 3071, 3031, 1827, 1119 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (d, *J* = 7.5 Hz, 3H), 1.78 (dd, *J* = 0.9, 1.2 Hz, 3H), 2.25 (ddd, *J* = 0.9, 6.3, 14.1 Hz, 1H), 2.40 (ddd, *J* = 1.2, 6.9, 14.1 Hz, 1H), 3.43 (dq, *J* = 4.2, 7.5 Hz, 1H), 3.74 (ddd, *J* = 6.0, 6.3, 6.9 Hz, 1H), 4.22 (dd, *J* = 4.2, 6.0 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.70 (d, *J* = 12.0 Hz, 1H), 4.83-4.86 (m, 1H), 4.88-4.91 (m, 1H), 7.29-7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.2, 22.7, 38.7, 47.5, 72.5, 76.8, 80.5, 114.2, 127.78, 127.82(2), 128.4(2), 137.9, 140.9, 171.5; ESI-HRMS calcd for $C_{16}H_{20}O_3Li$ [M + Li] 267.1572, found 267.1591.

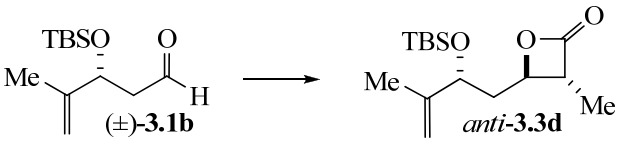


γ-benzyloxy-alkenyl-β-lactones 3.3b were prepared according to the representative procedure for the TMAL using $ZnCl_2$ (273 mg, 2.00 mmol), aldehyde **(±)-3.1a** (204 mg, 1.00 mmol), and ketene acetal **3.2b** (417 mg, 1.20 mmol) in CH_2Cl_2 (10 mL). The suspension was stirred for 9 h and subjected to the representative work-up and treated with $CuBr_2$ (357 mg, 1.60 mmol) for 2.5 h to deliver crude β-lactones **3.3b** as a mixture of diastereomers (1.5:1). Purification by flash column chromatography (pentane:ether 90:10) delivered *anti*-**3.3b** (116 mg, 47%), *syn*-**3.3b** (71 mg, 29%), and a mixture of **3.3b** (10 mg, 4%) as colorless oils. Characterization data for *anti*-**3.3b**: R_f = 0.26 (80:20 hexanes:ethyl acetate); IR (thin film) 3070, 3033, 1833, 1107 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.77 (dd, *J* = 0.9, 1.2 Hz, 3H), 2.13 (ddd, *J* = 0.9, 6.9, 14.1 Hz, 1H), 2.32 (ddd, *J* = 1.2, 6.6, 14.1 Hz, 1H), 3.34 (dd, *J* = 6.0, 15.9 Hz, 1H), 3.53 (dd, *J* = 4.2, 15.9 Hz, 1H), 4.02 (ddd, *J* = 2.7, 6.6, 6.9 Hz, 1H), 4.54 (ddd, *J* = 2.7, 4.2, 6.0 Hz, 1H), 4.64 (d, *J* = 11.4 Hz, 1H), 4.69 (d, *J* = 11.4 Hz, 1H), 4.77-4.80 (m, 1H), 4.86-4.89 (m, 1H), 7.30-7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 37.9, 39.5, 71.9, 73.6, 75.1, 114.0, 127.8, 127.9(2), 128.3(2), 137.8, 140.8, 167.9; ESI-HRMS calcd for $C_{15}H_{18}O_3Li$ [M + Li] 253.1416, found 253.1510. Characterization data for *syn*-**3.3b**: R_f = 0.17 (80:20 hexanes:ethyl acetate); IR (thin film) 3073, 3030, 1826, 1107 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.78 (dd, *J* = 1.2, 1.5 Hz, 3H), 2.30 (ddd, *J* = 0.9, 6.6, 13.8 Hz, 1H), 2.43 (ddd, *J* = 0.9, 6.3, 13.8 Hz, 1H), 3.27 (dd, *J* = 4.2, 16.2 Hz, 1H), 3.41 (dd, *J* = 6.0, 16.2 Hz,

1H), 3.72 (ddd, *J* = 5.1, 6.3, 6.6 Hz, 1H), 4.56 (ddd, *J* = 4.2, 5.1, 6.0 Hz, 1H), 4.64 (d, *J* = 11.7 Hz, 1H), 4.72 (d, *J* = 11.7 Hz, 1H), 4.81-4.85 (m, 1H), 4.87-4.91 (m, 1H), 7.28-7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 38.5, 39.7, 72.0, 72.3, 76.5, 114.2, 127.7, 127.8(2), 128.3(2), 137.8, 140.8, 167.7; ESI-HRMS calcd for $C_{15}H_{18}O_3Li$ [M + Li] 253.1416, found 253.1337.

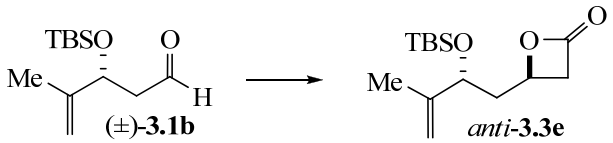


γ-benzyloxy-β-lactones 3.3c were prepared according to the representative procedure for the TMAL using $ZnCl_2$ (204 mg, 1.50 mmol), aldehyde **(±)-3.1a** (204 mg, 1.00 mmol), and ketene acetal **3.2c** (712 mg, 1.20 mmol) in CH_2Cl_2 (6 mL). The suspension was stirred for 12 d and subjected to the representative work-up and treated with $CuBr_2$ (357 mg, 1.60 mmol) for 5 h to deliver crude β-lactones **3.3c** as a mixture of diastereomers (4:1). Purification by flash column chromatography (hexanes: ethyl acetate 100:1) gave almost complete separation of the diastereomers, but due to minor impurities, both were characterized as the corresponding keto-β-lactones **3.4c**.

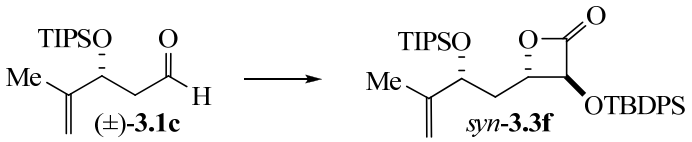


δ-silyloxy-alkenyl-β-lactones 3.3d were prepared according to the representative procedure for the TMAL using $ZnCl_2$ (537 mg, 3.94 mmol), aldehyde **(±)-3.1b** (690 mg, 3.02 mmol) and ketene acetal **3.2d** (1.02 g, 3.62 mmol) in CH_2Cl_2 (35 mL). The suspension was stirred for 28 h and subjected to the representative work-up and treated

with $CuBr_2$ (1.08 g, 4.83 mmol) for 1 h to deliver crude β-lactones **3.3d** as a mixture of diastereomers (9:1). Purification by flash column chromatography (pentane:ether 95:5) delivered an inseparable mixture of β-lactones **3.3d** (510 mg, 59%, dr 9:1) as a pale yellow oil. Characterization data for the major (*anti-trans*) diastereomer **3.3d**: R_f = 0.31 (hexanes:ethyl acetate 90:10); IR (thin film) 3074, 1827, 1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.08 (s, 3H), 0.91 (s, 9H), 1.39 (d, *J* = 7.5 Hz, 3H), 1.71-1.72 (m, 3H), 1.88 (ddd, *J* = 3.6, 9.0, 14.1 Hz, 1H), 2.03 (ddd, *J* = 4.2, 8.7, 14.1 Hz, 1H), 3.24 (dq, *J* = 4.2, 7.5 Hz, 1H), 4.23 (dd, *J* = 3.6, 8.7 Hz, 1H), 4.35 (ddd, *J* = 4.2, 4.2, 9.0 Hz, 1H), 4.83-4.84 (m, 1H), 4.96-4.97 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.1, -4.6, 12.7, 17.4, 18.4, 26.0(3), 41.5, 50.9, 72.9, 76.8, 111.7, 147.0, 172.3; ESI-HRMS calcd for $C_{15}H_{28}O_3SiLi$ [M + Li] 291.1968, found 291.1971.



δ-silyloxy-alkenyl-β-lactones 3.3e were prepared according to the representative procedure for the TMAL using $ZnCl_2$ (136 mg, 1.00 mmol), aldehyde **(±)-3.1b** (114 mg, 0.50 mmol), and ketene acetal **3.2b** (268 mg, 2.00 mmol) in CH_2Cl_2 (10 mL). The suspension was stirred for 20 h and subjected to the representative work-up and treated with $CuBr_2$ (670 mg, 1.50 mmol) for 3 h to deliver crude β-lactones **3.3e** as mixture of diastereomers (2:1). Purification by flash column chromatography (pentane:ether 90:10) delivered an inseparable mixture of β-lactones **3.3e** (91 mg, ~68% yield, dr 2:1) as a pale yellow oil contaminated with TBSOH. These β-lactones were characterized as the corresponding keto-β-lactones **3.4e**.



δ-silyloxy-alkenyl-β-lactones 3.3f were prepared according to the representative procedure for the TMAL using $ZnCl_2$ (545 mg, 4.00 mmol), aldehyde **(±)-3.1c** (541 mg, 2.00 mmol) and ketene acetal **3.2c** (2.15 g, 3.81 mmol) in CH_2Cl_2 (10 mL). This solution was stirred for 10 d at which time it was subjected to the representative work-up and treated with $CuBr_2$ (1.11 g, 4.97 mmol) for 5 h to deliver crude β-lactones **3.3f** as a mixture of diastereomers (5:1). Purification by flash column chromatography (pentane:ether 98:2) delivered an inseparable mixture of β-lactones **3.3f** (850 mg, 75%, dr 5:1) as a pale yellow oil. Characterization data for the major (*syn-trans)* diastereomer **3.3f**: R_f = 0.75 (hexanes:ethyl acetate 80:20); IR (thin film) 3077, 1850, 1114 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98-0.99 (m, 21H), 1.08 (s, 9H), 1.43-1.63 (m, 2H), 1.60-1.61 (m, 3H), 4.22 (dd, *J* = 4.2, 9.3 Hz, 1H), 4.32 (ddd, *J* = 2.7, 3.6, 10.8 Hz, 1H), 4.67 (d, *J* = 3.6, 1H), 4.89-4.90 (m, 2H), 7.39-7.75 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.3(3), 16.2, 18.1(3), 18.2(3), 19.3, 26.7(3), 38.9, 73.7, 79.4, 81.0, 113.3, 128.3(4), 130.6, 130.7, 131.6, 132.6, 135.7(2), 135.9(2), 145.2, 169.5; ESI-HRMS calcd for $C_{33}H_{50}O_4Si_2Li$ [M + Li] 573.3408, found 573.3301.

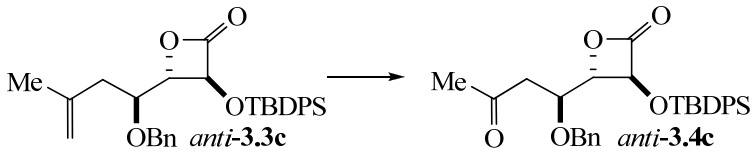
Representative procedure for ozonolysis of γ-benzyloxy-alkenyl-β-lactones as described for γ-benzyloxy-keto-β-lactone *syn*-3.4a (Procedure A). To a solution of γ-

benzyloxy-alkenyl-β-lactone *syn*-**3.3a** (518 mg, 1.99 mmol) in CH_2Cl_2 (40 mL) was added MeOH (162 μL, 4.00 mmol) at 23 °C. O_3 was bubbled with a gas dispersion tube at -78 °C until the solution turned blue (3 min) at which time O_2 was bubbled for twice the amount of time as O_3 (6 min) and then the reaction was quenched with PPh_3 (1.05 g, 4.00 mmol) at -78 °C. This solution was stirred for 6 h and allowed to warm to 23 °C at which time the solvent was removed under reduced pressure. Purification by flash column chromatography (hexanes:ethyl acetate 75:25) delivered *syn*-**3.4a** (466 mg, 89%) as a colorless oil: R_f = 0.53 (60:40 hexanes:ethyl acetate); IR (thin film) 1827, 1714, 1118 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (d, *J* = 7.5 Hz, 3H), 2.20 (s, 3H), 2.66 (dd, *J* = 5.4, 17.4 Hz, 1H), 2.85 (dd, *J* = 6.6, 17.4 Hz, 1H), 3.50 (dq, *J* = 4.2, 7.8 Hz, 1H), 4.19 (ddd, *J* = 5.1, 5.4, 6.6 Hz, 1H), 4.26 (dd, *J* = 4.2, 5.1 Hz, 1H), 4.62 (d, *J* = 11.4 Hz, 1H), 4.67 (d, *J* = 11.4 Hz, 1H), 7.27-7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.2, 31.0, 44.0, 47.2, 73.2, 74.1, 80.0, 127.9(2), 128.0, 128.5(2), 137.6, 171.2, 205.8; ESI-HRMS calcd for $C_{15}H_{19}O_4$ [M + H] 263.1283, found 263.1262.

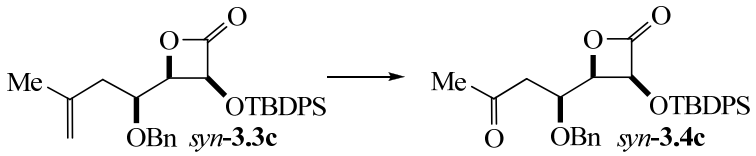
γ-benzyloxy-keto-β-lactone *anti*-3.4b was prepared according to the representative procedure for ozonolysis (Procedure A) using γ-benzyloxy-alkenyl-β-lactone *anti*-**3.3b** (246 mg, 1.00 mmol) in CH_2Cl_2 (20 mL), MeOH (81 μL, 2.00 mmol), and PPh_3 (525 mg, 2.00 mmol). Purification by flash column chromatography (hexanes:ethyl acetate 75:25) delivered *anti*-**3.4b** (217 mg, 88%) as a colorless oil: R_f = 0.40 (60:40 hexanes:ethyl acetate); IR (thin film) 1831, 1714, 1115 cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$) δ 2.18 (s, 3H), 2.52 (dd, *J* = 4.8, 17.1 Hz, 1H), 2.73 (dd, *J* = 7.5, 17.1 Hz, 1H), 3.36 (dd, *J* = 5.7, 16.2 Hz, 1H), 3.43 (dd, *J* = 4.5, 16.2 Hz, 1H), 4.38 (ddd, *J* = 3.3, 4.8, 7.5 Hz, 1H), 4.55 (ddd, *J* = 3.3, 4.5, 5.7 Hz, 1H), 4.65 (d, *J* = 11.1 Hz, 1H), 4.71 (d, *J* = 11.1 Hz, 1H), 7.27-7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.8, 38.4, 44.6, 71.7, 73.3, 74.4, 127.9, 128.0(2), 128.4(2), 137.6, 167.6, 205.2; ESI-HRMS calcd for $C_{14}H_{17}O_4$ [M + H] 249.1127, found 249.1102.

γ-benzyloxy-keto-β-lactone *syn*-3.4b was prepared according to the representative procedure for ozonolysis (Procedure A) using γ-benzyloxy-alkenyl-β-lactone *syn*-**3.3b** (246 mg, 1.00 mmol) in CH_2Cl_2 (20 mL), MeOH (81 μL, 2.00 mmol), and PPh_3 (525 mg, 2.00 mmol). Purification by flash column chromatography (hexanes:ethyl acetate 75:25) delivered *syn*-**3.4b** (215 mg, 87%) as a colorless oil: R_f = 0.37 (60:40 hexanes:ethyl acetate); IR (thin film) 1827, 1711, 1108 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 3H), 2.71 (dd, *J* = 6.0, 17.4 Hz, 1H), 2.89 (dd, *J* = 6.3, 17.4 Hz, 1H), 3.31 (dd, *J* = 4.2, 16.2 Hz, 1H), 3.41 (dd, *J* = 6.0, 16.2 Hz, 1H), 4.17 (ddd, *J* = 4.5, 6.0, 6.3 Hz, 1H), 4.59 (ddd, *J* = 4.2, 4.5, 6.0 Hz, 1H), 4.61 (d, *J* = 11.4 Hz, 1H), 4.68 (d, *J* = 11.4 Hz, 1H), 7.28-7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.8, 39.4, 43.9, 71.9, 73.0, 73.8, 127.8(2), 127.9, 128.4(2), 137.5, 167.5, 205.9; ESI-HRMS calcd for $C_{14}H_{17}O_4$ [M + H] 249.1127, found 249.1166.

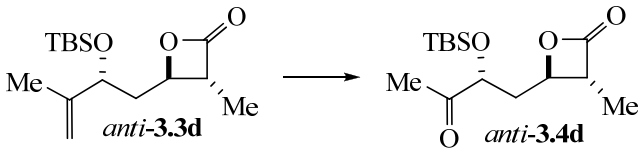


γ-benzyloxy-keto-β-lactones 3.3c were prepared according to the representative procedure for ozonolysis (Procedure A) using γ-benzyloxy-alkenyl-β-lactone *anti*-**3.3c** (*ca*. 225 mg, 0.44 mmol, dr 18:1) in CH_2Cl_2 (15 mL), MeOH (44 μL, 1.08 mmol), and PPh_3 (283 mg, 1.08 mmol). Purification by flash column chromatography (hexanes:ethyl acetate 90:10) delivered an inseparable mixture of keto-β-lactones **3.4c** (201 mg, 89%, 40% over two steps from **(±)-3.1a**, dr 18:1) as a pale yellow oil. Characterization data for the major diastereomer *anti*-**3.4c**: R_f = 0.28 (80:20 hexanes:ethyl acetate); IR (thin film) 3069, 1848, 1714, 1115, 1111 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 9H), 2.06 (s, 3H), 2.36 (dd, *J* = 5.7, 17.4 Hz, 1H), 2.63 (dd, *J* = 6.6, 17.4 Hz, 1H), 3.72 (ddd, *J* = 3.6, 5.7, 6.6 Hz, 1H), 3.98 (d, *J* = 11.1 Hz, 1H), 4.20 (d, *J* = 11.1 Hz, 1H), 4.53 (dd, *J* = 3.3, 3.6 Hz, 1H), 5.04 (d, *J* = 3.3 Hz, 1H), 6.95-7.98 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 26.6(3), 30.8, 44.0, 72.6, 73.1, 77.4, 82.7, 127.7(2), 127.9, 128.28(2), 128.30(2), 128.4(2), 130.5, 130.7, 131.4, 132.5, 135.7(2), 135.8(2), 137.3, 168.5, 205.7; ESI-HRMS calcd for $C_{30}H_{35}O_5Si$ [M + H] 503.2254, found 503.2160.



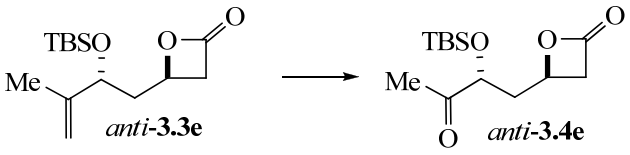
γ-benzyloxy-keto-β-lactone *syn*-**3.4c** was prepared according to the representative procedure for ozonolysis (Procedure A) using γ-benzyloxy-alkenyl-β-lactone *syn*-**3.3c**

(*ca*. 55 mg, 0.11 mmol) in CH_2Cl_2 (5 mL), MeOH (4 μL, 0.22 mmol), and PPh_3 (58 mg, 022 mmol). Purification by flash column chromatography (hexanes:ethyl acetate 90:10) delivered *syn*-**3.4c** (50 mg, 90%, 10% over two steps from **(±)-3.1a**) as a colorless oil: R_f = 0.26 (80:20 hexanes:ethyl acetate); IR (thin film) 3069, 1834, 1719, 1108 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 1.11 (s, 9H), 1.55 (s, 3H), 2.25 (dd, *J* = 4.8, 17.1 Hz, 1H), 2.33 (dd, *J* = 6.9, 17.1 Hz, 1H), 3.96 (dd, *J* = 5.7, 6.0 Hz, 1H), 4.44 (ddd, *J* = 4.8, 6.0, 6.9 Hz, 1H), 4.52 (d, *J* = 11.1 Hz, 1H), 4.69 (d, *J* = 5.7 Hz, 1H), 4.74 (d, *J* = 11.1 Hz, 1H), 7.10-7.85 (m, 15H); ^{13}C NMR (75 MHz, C_6D_6) δ 19.3, 26.7(3), 30.3, 44.2, 73.4, 73.6, 76.8, 78.7, 127.7, 127.8(2), 128.3(2), 128.4(2), 128.5(2), 130.6, 130.7, 131.8, 132.8, 135.8(2), 136.2(2), 138.8, 169.9, 204.3; ESI-HRMS calcd for $C_{30}H_{34}O_5SiLi$ [M + Li] 509.2336, found 509.2347.



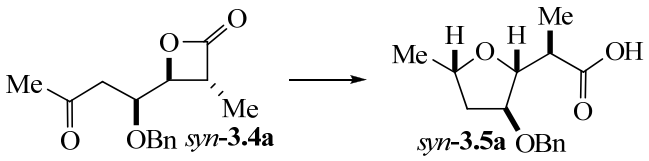
Representative procedure for ozonolysis (Procedure B) of δ-silyloxy-alkenyl-β-lactones as described for δ-silyloxy-keto-β-lactones 3.4d. To a solution of δ-silyloxy-alkenyl-β-lactones **3.3d** (285 mg, 1.02 mmol, dr 9:1) in CH_2Cl_2 (20 mL) was bubbled O_3 with a gas dispersion tube at -78 °C until the solution turned blue (2 min) at which time O_2 was bubbled for twice the amount of time as O_3 (4 min) and then the reaction was quenched with PPh_3 (535 mg, 2.04 mmol) at -78 °C. This solution was stirred for 12 h and allowed to warm to 23 °C at which time the solvent was removed under reduced pressure. Purification by flash column chromatography (hexanes:ethyl acetate 85:15) delivered an inseparable mixture of keto-β-lactones **3.4d** (207 mg, 72%, dr 9:1) as a pale

yellow oil. Characterization data for the major (*anti-trans*) diastereomer **3.4d**: R_f = 0.53 (hexanes:ethyl acetate 70:30); IR (thin film) 1830, 1721, 1123 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.10 (s, 3H), 0.11 (s, 3H), 0.95 (s, 9H), 1.41 (d, *J* = 7.5 Hz, 3H), 2.06-2.10 (m, 2H), 2.21 (s, 3H), 3.30 (dq, *J* = 4.2, 7.5 Hz, 1H), 4.18-4.22 (m, 1H), 4.31-4.37 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.2, -4.9, 12.4, 18.1, 25.4, 25.7(3), 38.7, 51.1, 75.3(2), 171.4, 210.4; ESI-HRMS calcd for $C_{14}H_{26}O_4SiLi$ [M + Li] 293.1760, found 293.1758.



δ-silyloxy-keto-β-lactones 3.4e were prepared according to the representative procedure for ozonolysis (Procedure B) using δ-silyloxy-alkenyl-β-lactones **3.3e** (91mg, 0.34 mmol, dr 2:1) in CH_2Cl_2 (7 mL) and PPh_3 (176 mg, 0.68 mmol). Purification by flash column chromatography (hexanes:ethyl acetate 80:20) delivered an inseparable mixture of keto-β-lactones **3.4e** (50 mg, 54%, dr 2:1) as a pale yellow oil. Characterization data for the major (*anti)* diastereomer **3.4e**: R_f = 0.46 (hexanes:ethyl acetate 70:30); IR (thin film) 1830, 1716, 1114 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.10 (s, 6H), 0.95 (s, 9H), 2.04-2.12 (m, 2H), 2.21 (s, 3H), 3.17 (dd, *J* = 4.2, 16.5 Hz, 1H), 3.60 (dd, *J* = 5.7, 16.5 Hz, 1H), 4.21 (dd, *J* = 4.2, 8.7 Hz, 1H), 4.64-4.72 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.0, -4.8, 18.2, 25.4, 25.8(3), 39.4, 43.6, 67.6, 75.5, 167.7, 210.5; ESI-HRMS calcd for $C_{13}H_{24}O_4SiLi$ [M + Li] 279.1604, found 279.1497.

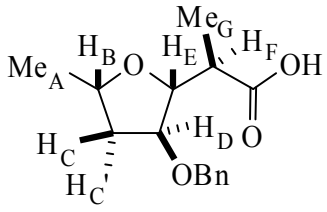
δ-silyloxy-keto-β-lactones 3.4f were prepared according to the representative procedure for ozonolysis (Procedure B) using δ-silyloxy-alkenyl-β-lactones **3.3f** (400mg, 0.71 mmol, dr 5:1)) in CH_2Cl_2 (15 mL) and PPh_3 (370 mg, 1.41 mmol). Purification by flash column chromatography (hexanes:ethyl acetate 90:10) delivered an inseparable mixture of keto-β-lactones **3.4f** (250 mg, 62%, dr 5:1) as a pale yellow oil. Characterization data for the major (*syn-trans*) diastereomer **3.4f**: R_f = 0.52 (hexanes:ethyl acetate 80:20); IR (thin film) 3073, 3053, 1846, 1713, 1158, 1114 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 0.92-0.94 (m, 21H), 1.09 (s, 9H), 1.37 (ddd, *J* = 2.4, 7.5, 14.7 Hz, 1H), 1.52 (ddd, *J* = 3.0, 10.8, 14.7 Hz, 1H), 2.00 (m, 3H), 4.04 (dd, *J* = 3.0, 7.5 Hz, 1H), 4.48 (d, *J* = 3.6 Hz, 1H), 4.74 (ddd, *J* = 2.4, 3.6, 10.8 Hz, 1H), 7.17-7.86 (m, 10H); ^{13}C NMR (75 MHz, C_6D_6) δ 12.3(3), 18.06(3), 18.07(3), 19.1, 25.5, 26.6(3), 38.0, 75.8, 77.4, 81.5, 128.3(2), 128.4(2), 130.6, 130.7, 131.9, 132.8, 135.9(2), 136.0(2), 168.1, 209.4; ESI-HRMS calcd for $C_{32}H_{48}O_5Si_2Li$ [M + Li] 575.3200, found 575.3287.



Representative procedure for Mead reductive cyclization of γ-benzyloxy-keto-β-lactones as described for THF *syn*-3.5a (Procedure A). To a solution of γ-benzyloxy-keto-β-lactone *syn*-**3.4a** (262 mg, 1.00 mmol) in CH_2Cl_2 (50 mL) was added Et_3SiH (3.2 mL, 20.0 mmol) slowly at -78 °C followed by TESOTf (274 μL, 1.20 mmol in 40 mL

CH_2Cl_2) down the side of the flask at -78 °C over 10 min to ensure cooling. Upon addition of 10 mL of CH_2Cl_2 to rinse down any remaining TESOTf, the solution was allowed to warm to 0 °C slowly over 5 h, quenched with pH 4 buffer (50 mL), and warmed to 23 °C with vigorous stirring. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to deliver crude THF **3.5a** as a single diastereomer (>19:1) with only trace quantities of furan **3.11** (68:1) as judged by analysis of crude ^{1}H NMR (500). Purification by gradient flash column chromatography (hexanes:ethyl acetate 80:20 to 60:40) delivered THF *syn*-**3.5a** (178 mg, 67%) as a colorless oil. A center fraction from the column was used for characterization: R_f = 0.46 (60:40 hexanes:ethyl acetate); IR (thin film) 3500-2300, 1708, 1091 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (d, *J* = 7.0 Hz, 3H), 1.29 (d, *J* = 6.0 Hz, 3H), 1.54 (ddd, *J* = 6.5, 10.5, 13.5 Hz, 1H), 2.11 (ddd, *J* = 1.0, 5.0, 13.5 Hz, 1H), 2.68 (dq, *J* = 6.0, 7.0 Hz, 1H), 4.01 (ddd, *J* = 1.0, 3.0, 6.5 Hz, 1H), 4.12 (dd, *J* = 3.0, 6.0 Hz, 1H), 4.21-4.28 (m, 1H), 4.49 (d, *J* = 11.5 Hz, 1H), 4.52 (d, *J* = 11.5 Hz, 1H), 7.27-7.37 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.8, 20.5, 40.1, 42.8, 71.4, 75.3, 81.9, 85.4, 127.88(2), 127.95, 128.6(2), 138.1, 178.7; ESI-HRMS calcd for $C_{15}H_{19}O_4$ [M - H] 263.1283, found 263.1271.

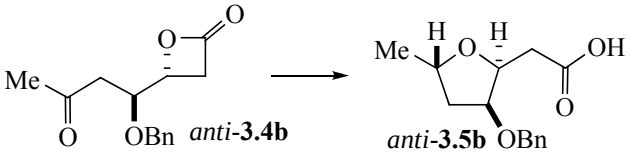
Crucial nOe Enhancements for *syn*-**3.5a**:



Irradiate H	Observed H	% nOe
A	C'	1.9
B	E	0.6
B	C	1.3
C	E	0.2
C'	F	0.8
D	F	0.9
D	C'	1.6
E	B	0.6
F	C'	0.3
G	D	0.6

syn-**3.4a** **11**

Furan 3.11 was prepared according to the representative procedure for Mead reductive cyclization (Procedure A) with the exception that Et_3SiH was not added, using γ-benzyloxy-keto-β-lactone *syn*-**3.4a** (180 mg, 0.69 mmol) in CH_2Cl_2 (30 mL) and TESOTf (190 μL, 0.83 mmol in 30 mL CH_2Cl_2). The representative work-up delivered furan **19** in seemingly excellent crude yield based on ^1H NMR analysis. Purification by gradient flash column chromatography (hexanes:ethyl acetate 80:20 to 60:40) delivered impure furan **3.11** (<30 mg, <28% yield) as a pale yellow oil: R_f = 0.42 (60:40 hexanes:ethyl acetate); IR (thin film) 3582-2359, 1714, 1219 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.53 (d, *J* = 7.5 Hz, 3H), 2.28 (s, 3H), 3.75-3.85 (m, 1H), 5.89-5.94 (m, 1H), 6.09 (d, *J* = 3.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 15.7, 39.4, 106.4, 107.3, 150.9, 151.9, 178.6; ESI-HRMS calcd for $C_8H_9O_3$ [M - H] 153.0552, found 153.0541.

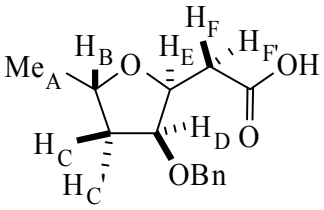


anti-**3.4b** *anti*-**3.5b** OBn

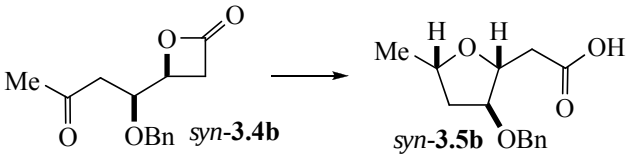
THF *anti*-3.5b was prepared according to the representative procedure for Mead reductive cyclization (Procedure A) using γ-benzyloxy-keto-β-lactone *anti*-**3.4b** (210 mg, 0.85 mmol) in CH_2Cl_2 (45 mL), Et_3SiH (2.75 mL, 17.00 mmol), and TESOTf (233 μL, 1.02 mmol in 35 mL CH_2Cl_2). The representative work-up delivered crude THFs **3.5b** as mixture of diastereomers (14:1) with only trace quantities of the corresponding furan (43:1). Purification by gradient flash column chromatography (hexanes:ethyl

acetate 80:20 to 50:50) delivered an inseparable mixture of THFs **3.5b** (175 mg, 82%, dr 14:1) as a white solid. A center fraction from the column was used for characterization. Characterization data for the major diastereomer *anti*-**3.5b**: R_f = 0.37 (50:50 hexanes:ethyl acetate); IR (thin film) 3500-2500, 1695, 1080 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 1.04 (d, *J* = 6.0 Hz, 3H), 1.05 (ddd, *J* = 5.0, 9.5, 13.0 Hz, 1H), 1.74 (ddd, *J* = 1.5, 5.5, 13.0 Hz, 1H), 2.77 (d, *J* = 7.0 Hz, 2H), 3.75 (ddd, *J* = 1.5, 5.0, 5.0 Hz, 1H), 4.04 (d, *J* = 12.0 Hz, 1H), 4.10-4.17 (m, 1H), 4.20 (d, *J* = 12.0 Hz, 1H), 4.40 (dt, *J* = 5.0, 7.0 Hz, 1H), 7.08-7.23 (m, 5H); ^{13}C NMR (125 MHz, C_6D_6) δ 21.2, 35.1, 39.3, 71.4, 73.4, 77.8, 80.2, 127.7(2), 127.8, 128.6(2), 138.7, 177.5; ESI-HRMS calcd for $C_{14}H_{17}O_4$ [M - H] 249.1127, found 249.1109.

Crucial nOe enhancements for *anti*-**3.5b**:



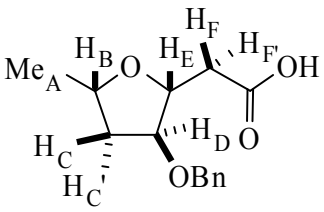
Irradiate H	Observed H	% nOe
A	E	0.3
B	F,F'	0.6
C	F,F'	0.5
C'	D	0.7
D	E	1.6
E	A	0.7
E	C'	0.2
F,F'	B	0.3



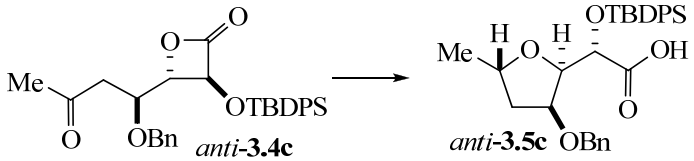
THF *syn*-3.5b was prepared according to the representative procedure for Mead reductive cyclization (Procedure A) using γ-benzyloxy-keto-β-lactone *syn*-**3.4b** (215 mg, 0.87 mmol) in CH_2Cl_2 (45 mL), Et_3SiH (2.81 mL, 17.40 mmol), and TESOTf (238 μL, 1.04 mmol in 35 mL CH_2Cl_2). The representative work-up delivered crude THF *syn*-

3.5b as a single diastereomer (>19:1) with only trace quantities of the corresponding furan (54:1). Purification by gradient flash column chromatography (hexanes:ethyl acetate 80:20 to 50:50) delivered *syn*-**3.5b** (170 mg, 78% yield) as a pale yellow oil. A center fraction from the column was used for characterization: R_f = 0.37 (50:50 hexanes:ethyl acetate); IR (thin film) 3567-2383, 1715, 1099 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 1.06 (d, *J* = 6.0 Hz, 3H), 1.15 (ddd, *J* = 6.5, 10.0, 13.0 Hz, 1H), 1.72 (ddd, *J* = 1.5, 5.5, 13.0 Hz, 1H), 2.26 (dd, *J* = 6.0, 15.5 Hz, 1H), 2.34 (dd, *J* = 7.5, 15.5 Hz, 1H), 3.55 (ddd, *J* = 1.5, 3.0, 6.5 Hz, 1H), 4.07-4.14 (m, 1H), 4.21 (d, *J* = 12.5 Hz, 1H), 4.23 (d, *J* = 12.5 Hz, 1H), 4.37 (ddd, *J* = 3.0, 6.0, 7.5 Hz, 1H), 7.09-7.26 (m, 5H); ^{13}C NMR (125 MHz, C_6D_6) δ 20.8, 39.6(2), 71.0, 75.0, 80.6, 83.6, 127.7, 127.8(2), 128.5(2), 138.8, 176.8; ESI-HRMS calcd for $C_{14}H_{17}O_4$ [M - H] 249.1127, found 249.1111.

Crucial nOe enhancements for *syn*-**3.5b**:



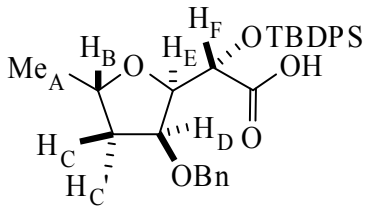
Irradiate H	Observed H	% nOe
A	C'	1.1
B	E	0.1
B	C	1.2
C	E	0.3
C'	F,F'	1.2
D	F,F'	1.8
E	B	1.2
F,F'	A	0.4



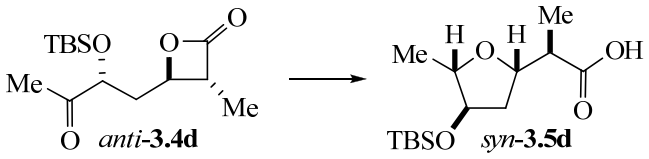
Representative procedure for Mead reductive cyclization of γ-benzyloxy-keto-β-lactones as described for THF 3.5c (Procedure B). To a solution of γ-benzyloxy-keto-β-lactones **3.4c** (199 mg, 0.40 mmol, dr 18:1) in CH_2Cl_2 (20 mL) was added Et_3SiH

(1.29 mL, 8.00 mmol) slowly at -78 °C followed by $BF_3{\cdot}OEt_2$ (61 μL, 0.48 mmol in 16 mL CH_2Cl_2) down the side of the flask at -78 °C over 10 min to ensure cooling. Upon addition of 10 mL of CH_2Cl_2 to rinse down any remaining $BF_3{\cdot}OEt_2$, the solution was allowed to warm to 0 °C slowly over 5 h, and then stirred at 0-10 °C for 3 d. The reaction was quenched with pH 4 buffer (50 mL), and warmed to 23 °C with vigorous stirring. The layers were separated and the aqueous layer was washed with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, concentrated under reduced pressure to deliver crude THF **3.5c** as a mixture of diastereomers (18:1, ~50% conversion) as determined by crude ^{1}H NMR (500 MHz). Purification by gradient flash column chromatography (hexanes:ethyl acetate 90:10 to 60:40) delivered recovered keto-β-lactone **3.4c** (70 mg, 35%, dr 18:1) as a pale yellow oil and an inseparable mixture of THFs **3.5c** (102 mg, 51%, dr 18:1) as a pale yellow oil. A center fraction of THF **3.5c** from the column was used for characterization. Characterization data for the major diastereomer *anti*-**3.5c**: R_f = 0.30 (70:30 hexanes:ethyl acetate); IR (thin film) 3437-2404, 1731, 1108 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (s, 9H), 1.27 (d, *J* = 6.0 Hz, 3H), 1.48 (ddd, *J* = 6.5, 11.0, 13.5 Hz, 1H), 2.03 (dd, *J* = 5.0, 13.5 Hz, 1H), 4.07 (dd, *J* = 2.5, 6.5 Hz, 1H), 4.16 (dd, *J* = 2.5, 4.5 Hz, 1H), 4.18-4.24 (m, 1H), 4.32 (s, 2H), 4.43 (d, *J* = 4.5 Hz, 1H), 7.23-7.70 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.7, 20.0, 27.2(3), 40.3, 71.5, 72.8, 75.8, 81.0, 86.1, 127.8(2), 127.9, 128.00(2), 128.04(2), 128.6(2), 130.36, 130.40, 132.3, 132.8, 136.0(2), 136.2(2), 138.1, 173.0; ESI-HRMS calcd for $C_{30}H_{35}O_5Si$ [M - H] 503.2254, found 503.2241.

Crucial nOe enhancements for *anti*-**3.5c**:



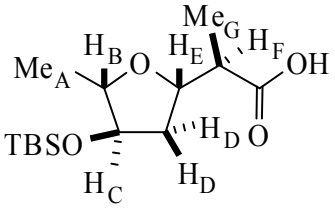
Irradiate H	Observed H	% nOe
A	C'	2.3
B	C	3.8
C	B	6.8
C'	A	4.1
C'	E	0.4
D	E	0.9
E	D	1.8



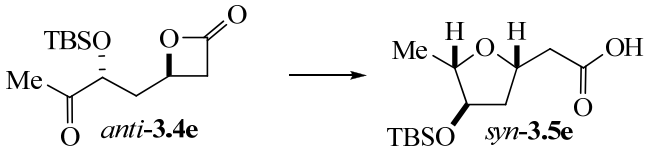
Representative procedure for Mead reductive cyclization of δ-silyloxy-keto-β-lactones as described for THFs 3.5d (Procedure C). To a solution of δ-silyloxy-keto-β-lactones **3.4d** (202 mg, 0.71 mmol, dr 9:1) in CH_2Cl_2 (15 mL) was added Et_3SiH (137 μL, 0.85 mmol) dropwise at -78 °C followed by $TiCl_4$ (846 μL, 1.0 M in CH_2Cl_2) down the side of the flask at -78 °C over 5 min to ensure cooling. Upon addition of 5 mL of CH_2Cl_2 to rinse down any remaining $TiCl_4$, the solution was stirred at -78 °C for 3 h, quenched with pH 7 buffer (50 mL), and warmed to 23 °C with vigorous stirring. The layers were separated and the aqueous layer was washed with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, concentrated under reduced pressure to deliver crude THFs **3.5d** a mixture of diastereomers (9:1) as judged by analysis of crude ^1H NMR (500 MHz). Purification by gradient flash column chromatography (hexanes:ethyl acetate 90:10 to 60:40) delivered an inseparable mixture of THFs **3.5d** (170 mg, 84%, dr 9:1) as a pale yellow oil. Characterization data for the major (*syn*) diastereomer **3.5d**: R_f = 0.49 (hexanes:ethyl acetate 60:40); IR (thin film)

3475-2460, 1707, 1250 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ -0.04 (s, 6H), 0.90 (s, 9H), 1.07 (d, *J* = 6.5 Hz, 3H), 1.14 (d, *J* = 7.0 Hz, 3H), 1.74 (ddd, *J* = 6.5, 8.5, 13.0 Hz, 1H), 1.78 (ddd, *J* = 3.5, 6.5, 13.0 Hz, 1H), 2.47 (dq, *J* = 7.0, 7.0 Hz, 1H), 3.67 (ddd, *J* = 3.5, 4.0, 6.5 Hz, 1H), 3.79 (dq, *J* = 4.0, 6.5 1H), 4.24 (ddd, *J* = 3.5, 7.0, 8.5 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ -4.8, -4.6, 13.3, 18.1, 19.1, 25.9(3), 39.0, 45.0, 78.3, 78.7, 82.5, 180.6; ESI-HRMS calcd for $C_{14}H_{27}O_4Si$ [M - H] 287.1679, found 287.1611.

Crucial nOe enhancements for **3.5d**:



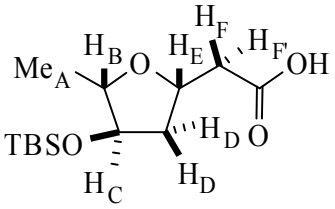
Irradiate H	Observed H	% nOe
A	F	0.3
B	E	1.3
C	F	0.2
E	B	0.6
F	C	0.7
F	A	0.3
G	C	0.4



THFs 3.5e were prepared according to the representative procedure for Mead reductive cyclization (Procedure C) using δ-silyloxy-keto-β-lactones **3.4e** (43 mg, 0.16 mmol, dr 2:1) in CH_2Cl_2 (4 mL), Et_3SiH (31 μL, 0.19 mmol) and $TiCl_4$ (31 μL, 1.0 M in CH_2Cl_2). The representative work-up delivered a mixture of diastereomers (2:1). Purification by gradient flash column chromatography (hexanes:ethyl acetate 90:10 to 60:40) delivered an inseparable mixture of **3.5e** (30 mg, 68%, dr 3:1) as a pale yellow oil. Characterization data for the major (*syn*) diastereomer **3.5e**: R_f = 0.33 (hexanes:ethyl acetate 60:40); IR (thin film) 3450-2450, 1711, 1257 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$)

δ 0.06 (s, 6H), 0.89 (s, 9H), 1.21 (d, *J* = 6.5 Hz, 3H), 1.80 (ddd, *J* = 6.5, 9.0, 13.0 Hz, 1H), 1.97 (ddd, *J* = 3.0, 6.5, 13.0 Hz, 1H), 2.59 (dd, *J* = 5.5, 15.5 Hz, 1H), 2.64 (dd, *J* = 7.0, 15.5 Hz, 1H), 3.82 (dq, *J* = 4.0, 6.5 Hz, 1H), 3.91 (ddd, *J* = 3.0, 4.0, 9.0 Hz, 1H), 4.46 (dddd, *J* = 5.5, 6.5, 6.5, 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.6, -4.5, 18.2, 19.5, 26.0(3), 40.8, 41.0, 73.9, 78.0, 83.2, 176.2; ESI-HRMS calcd for $C_{13}H_{25}O_4Si$ [M - H] 273.1522, found 273.1506.

Crucial nOe enhancements for **3.5e**:

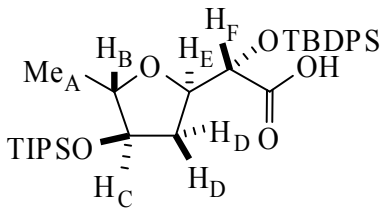


Irradiate H	Observed H	% nOe
A	F,F'	1.2
B	E	1.2
C	F,F'	0.3
E	B	0.7

THFs 3.5f were prepared according to the representative procedure for Mead reductive cyclization (Procedure C) using δ-silyloxy-keto-β-lactones **3.4f** (149 mg, 0.26 mmol, dr 5:1) in CH_2Cl_2 (8 mL), Et_3SiH (51 μL, 0.31 mmol), and $TiCl_4$ (314 μL, 1.0 M in CH_2Cl_2). The representative work-up delivered a mixture of diastereomers (5:1). Purification by gradient flash column chromatography (hexanes:ethyl acetate 90:10 to 60:40) delivered an inseparable mixture of THFs **3.5f** (83 mg, 55% yield, dr 5:1) as a pale yellow oil. Characterization data for the major (*anti*) diastereomer **3.5f**: R_f = 0.28 (hexanes:ethyl acetate 70:30); IR (thin film) 3528-2398, 1729, 1118 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 0.99-1.01 (m, 21H), 1.11 (d, *J* = 6.5 Hz, 3H), 1.22 (s, 9H), 1.83 (ddd, *J* =

7.0, 7.0, 12.5 Hz, 1H), 2.06 (ddd, *J* = 7.0, 7.0, 12.5 Hz, 1H), 3.73 (ddd, *J* = 6.0, 7.0, 7.0 Hz, 1H), 3.80 (dq, *J* = 6.0, 6.5 Hz, 1H), 4.26 (ddd, *J* = 5.5, 7.0, 7.0 Hz, 1H), 4.45 (d, *J* = 5.5 Hz, 1H), 7.20-7.83 (m, 10H); ^{13}C NMR (125 MHz, C_6D_6) δ 12.3(3), 18.1(6), 18.9, 19.6, 27.3(3), 36.7, 75.8, 78.2, 78.7, 81.2, 127.88(2), 127.91(2), 130.0, 130.1, 133.6, 133.7, 136.47(2), 136.53(2), 175.9; ESI-HRMS calcd for $C_{32}H_{49}O_5Si_2$ [M - H] 569.3119, found 569.3110.

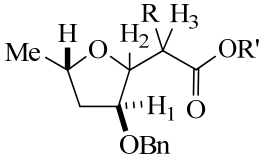
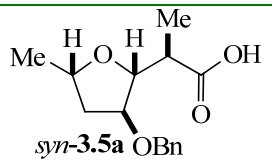
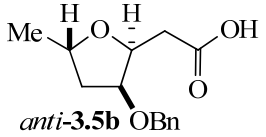
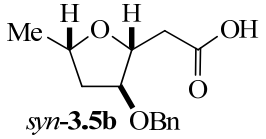
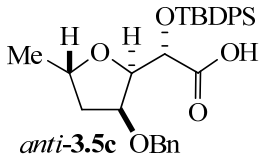
Crucial nOe enhancements for **3.5f**:



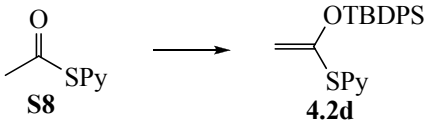
Irradiate H	Observed H	% nOe
A	E	0.3
B	F	0.9
C	E	0.8
E	C	0.1
F	B	0.1

Table A.3.1. Comparison of Crucial Coupling Constants for THFs 3.5a-c

Coupling constants (*J*) for THFs **3.5a-c** were not found to have a significant trend. Although similarity between the $J_{2,3}$ of THFs *syn*-**3.5a**, *syn*-**3.5b**, and *anti*-**3.5c** could indicate that the relative stereochemistry of THF *anti*-**3.5c** should be *syn* instead of *anti*, it is difficult to make this assumption due to the small data set and the large TBDPS group contained in THF *anti*-**3.5c** which likely alters the conformational preferences significantly.

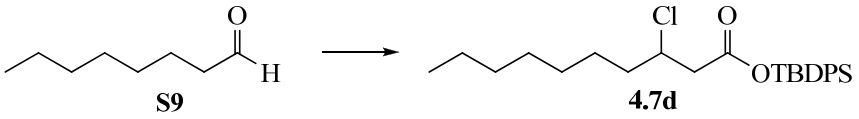
entry		*J* H_1-H_2 (Hz)	*J* H_2-H_3 (Hz)
1	 *syn*-**3.5a**	3.0	6.0
2	 *anti*-**3.5b**	5.0	7.0
3	 *syn*-**3.5b**	3.0	6.0, 7.5
4	 *anti*-**3.5c**	2.5	4.5

Chapter IV – Development of a Tandem, Three-Component Synthesis of Tetrahydrofurans from Ketoaldehydes, Thiopyridyl Ketene Acetals, and Silyl Nucleophiles

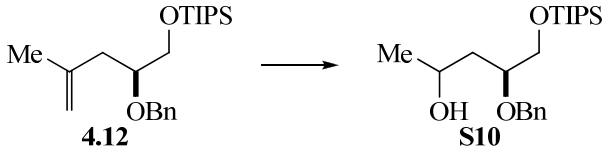


S8 **4.2d**

Ketene acetal 4.2d: To a solution of thioester **S8** (1.00 g, 6.53 mmol) in CH_2Cl_2 (65 mL) was added TBDPSOTf (2.06 mL, 6.53 mmol) dropwise at 0 °C followed by Hunig's base (1.14 mL, 6.53 mmol) dropwise at 0 °C. This solution was stirred for 24 h and was allowed to warm to 23 °C at which time it was quenched with pH 7 buffer and stirred vigorously for 30 min. The solution was diluted with pentane (200 mL) and separated. The combined organic solution was then washed with water (2 x 50 mL) and brine (2 x 50 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by deactivated flash column chromatography (pentane:ether:Et_3N 90:10:2) delivered ketene acetal **4.2d** (1.92 g, 75% yield) as a yellow oil: R_f = 0.74 (hexanes:ethyl acetate 70:30); IR (thin film) 3072, 3048, 1184 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (s, 9H), 4.50 (d, *J* = 1.8 Hz, 1H), 4.79 (d, *J* = 1.8 Hz, 1H), 7.08 (ddd, *J* = 1.0, 4.8, 7.3 Hz, 1H), 7.36-7.48 (m, 1H), 7.38-7.43 (m, 6H), 7.56 (ddd, *J* = 1.8, 7.3, 9.0 Hz, 1H), 7.71-7.74 (m, 4H), 8.48 (ddd, *J* = 1.0, 1.8, 4.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 26.5(3), 103.6, 120.7, 124.0, 127.8(4), 130.2(2), 132.0, 135.8(4), 136.7(2), 149.5, 149.8, 158.1; ESI-HRMS calcd for $C_{23}H_{26}NOSSi$ [M + H] 392.1504, found 392.1484.

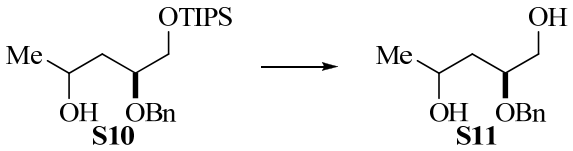


β-Chlorosilyl ester 4.7d was prepared according to the representative procedure for the TMAL using $ZnCl_2$ (800 mg, 5.85 mmol), octanal **(S9)** (600 μL, 3.90 mmol), and ketene acetal **4.2d** (2.74 g, 4.68 mmol, 67% pure) in CH_2Cl_2 (40 mL) but without $CuBr_2$ work-up. This solution was stirred for 21 h at which time it was quenched with pH 7 buffer and stirred vigorously for 30 min. The solution was poured over Celite, concentrated under reduced pressure, and dissolved in ether (200 mL). The ethereal solution was washed with brine (3 x 50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by gradient flash column chromatography (pentane:ether 98:2 to 96:4) delivered silyl ester **4.7d** (958 mg, 56% yield) as a yellow oil: R_f = 0.44 (hexanes:ethyl acetate 90:10); IR (thin film) 3072, 3050, 1731, 1192 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 0.88 (t, *J* = 7.0, 3H), 1.21 (s, 9H), 1.05-1.31 (m, 10H), 1.41-1.50 (m, 2H), 2.46 (dd, *J* = 5.1, 16.3 Hz, 1H), 2.69 (dd, *J* = 8.4, 16.3 Hz, 1H), 4.21-4.30 (m, 1H), 7.17-7.25 (m, 6H), 7.80-7.90 (m, 4H); ^{13}C NMR (75 MHz, C_6D_6) δ 14.4, 19.5, 23.1, 26.7, 27.3(3), 29.3, 29.5, 32.1, 38.2, 45.4, 58.7, 128.1(4), 130.5(2), 132.3(2), 135.9(4), 169.0; ESI-HRMS calcd for $C_{26}H_{37}ClO_2SiLi$ [M + Li] 451.2411, found 451.2408.



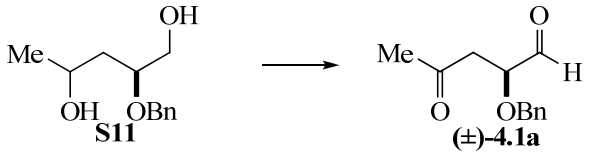
Alcohols S10: To a solution of alkene **4.12** (6.50 g, 17.92 mmol) in CH_2Cl_2 (60 mL) and MeOH (60 mL) was bubbled O_3 with a gas dispersion tube at -78 °C until the solution turned blue (10 min) at which time O_2 was bubbled for twice the amount of time

as O_3 (20 min) and then the reaction was quenched with $NaBH_4$ (2.71 g, 71.69 mmol) at -78 °C. This solution was stirred for 14 h and allowed to warm to 23 °C at which time the solvent was removed under reduced pressure. The residue was dissolved in ether (200 mL), quenched with sat. aq. NH_4Cl (50 mL), stirred vigorously for 15 min. The organic layer was separated and washed with additional sat. aq. NH_4Cl (2 x 50 mL), water (2 x 50 mL), and brine (2 x 50 mL). The solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:ethyl acetate 80:20) delivered silyl ethers **S10** (4.87 g, 74%, dr 1:1) as a pale yellow oil. This compound was not fully characterized.



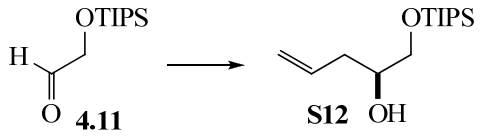
S10 **S11**

Representative procedure for TBAF deprotection as described for diols S11: To a solution of silyl ethers **S10** (4.87 g, 13.29 mmol) in THF (120 mL) was added a 1.0 M solution of TBAF in THF (27.0 mL, 26.58 mmol) at 0 °C, stirred for 1.5 h, and allowed to warm to 23 °C. The solution was quenched with sat. aq. NH_4Cl (50 mL), stirred vigorously for 15 min, concentrated under reduced pressure, and diluted with ethyl acetate (200 mL). The organic layer was separated and washed with additional sat. aq. NH_4Cl (2 x 50 mL), water (2 x 50 mL), and brine (2 x 50 mL). The solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by gradient flash column chromatography (hexanes:ethyl acetate 50:50 to 30:70 to 10:90) delivered diols **S2** (1.90 g, 68% over two steps from **4.12**) as a colorless oils. This compound was not fully characterized.

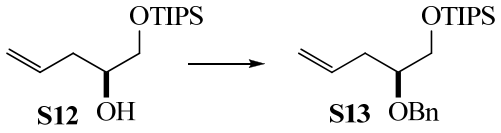


S11 **(±)-4.1a**

Representative procedure for the Swern oxidation as described for α-benzyloxy-γ-ketoaldehyde (±)-4.1a. To a solution of oxalyl chloride (2.6 mL, 29.88 mmol) in CH_2Cl_2 (50 mL) was added DMSO (4.2 mL, 59.76 mmol) dropwise at -78 °C and was stirred for 5 min. To this solution was added diols **S11** (1.57 g, 7.47 mmol) in CH_2Cl_2 (50 mL) and stirred for 15 min at which time Et_3N (16.7 mL, 119.52 mmol) was added and stirred for 2 h at -78 °C. The reaction was quenched with pH 7 buffer, stirred vigorously for 30 min, and allowed to warm to 23 °C. The mixture was diluted with ether (250 mL), separated from the aqueous layer, and washed with water (3 x 50 mL) and brine (3 x 50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:ethyl acetate 75:25) delivered ketoaldehyde **(±)-4.1a** (1.28 g, 83%) as a pale yellow oil: R_f = 0.46 (hexanes:ethyl acetate 30:70); IR (thin film) 3029, 2719, 1715, 1111 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.19 (s, 3H), 2.84 (dd, *J* = 6.6, 17.4 Hz, 1H), 2.91 (dd, *J* = 4.8, 17.4 Hz, 1H), 4.26 (ddd, *J* = 0.9, 4.8, 6.6 Hz, 1H), 4.66 (d, *J* = 11.7 Hz, 1H), 4.73 (d, *J* = 11.7 Hz, 1H), 7.30-7.39 (m, 5H), 9.78 (d, *J* = 0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.1, 44.3, 73.0, 79.3, 127.9(2), 128.0, 128.4(2), 137.1, 202.4, 204.5; ESI-HRMS calcd for $C_{12}H_{14}O_3Na$ [M + Na] 229.0841, found 229.0860.

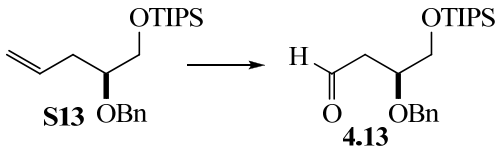


Representative procedure for Grignard addition as described for secondary alcohol S12. To a solution of aldehyde **4.11** (7.00 g, 32.34 mmol) in ether (240 mL) was added a 1.0 M solution of allylmagnesium chloride in ether (38.8 mL, 38.81 mmol) slowly at -78 °C. The reaction was allowed to warm quickly to 23 °C and quenched with sat. aq. NH_4Cl (100 mL) after 2 h. After stirring vigorously for 30 min, the organic layer was separated from the aqueous layer and washed with additional sat. aq. NH_4Cl (2 x 50 mL), water (2 x 50 mL), and brine (2 x 50 mL). The resulting solution was dried over $MgSO_4$, filtered over a pad of SiO_2, and concentrated under reduced pressure to deliver alcohol **S12** (7.94 g, 95%) as a colorless oil: R_f = 0.47 (80:20 hexanes: ethyl acetate); IR (thin film) 3448, 3080, 1113 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.06-1.08 (m, 21H), 2.24-2.29 (m, 2H), 3.52-3.58 (m, 1H), 3.70-3.79 (m, 1H), 5.07-5.17 (m, 2H), 5.79-5.93 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.0(3), 18.0(6), 37.7, 67.0, 71.4, 117.3, 134.6; ESI-HRMS calcd for $C_{14}H_{30}O_2SiLi$ [M + Li] 265.2175, found 265.2207.

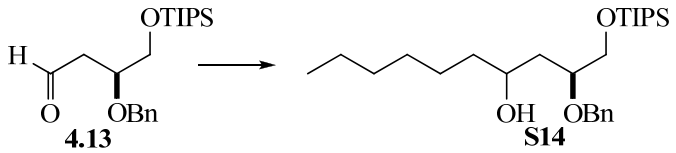


Benzyl ether S13: To a solution of alcohol **S12** (10.34 g, 40.00 mmol) and benzyltrichloroacetimidate (15.15 g, 60.00 mmol) in CH_2Cl_2 (125 mL) was added triflic acid (354 μL, 4.00 mmol) dropwise at 0 °C. The reaction was allowed to warm quickly to 23 °C and stirred for 24 h. The mixture was filtered over a pad of Celite, washed with CH_2Cl_2, quenched with sat. aq. $NaHCO_3$ (50 mL), and concentrated under reduced

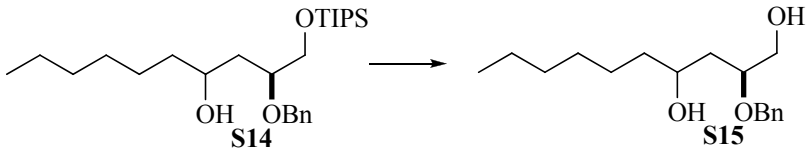
pressure. The residue was dissolved in ether (300 mL), washed with sat. aq. $NaHCO_3$ (2 x 50 mL), sat. aq. NH_4Cl (2 x 50 mL), and brine (2 x 50 mL). The resulting solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:ethyl acetate 98:2) delivered benzyl ether **S13** (10.30 g, 74%) as a pale yellow oil. This compound was not fully characterized.



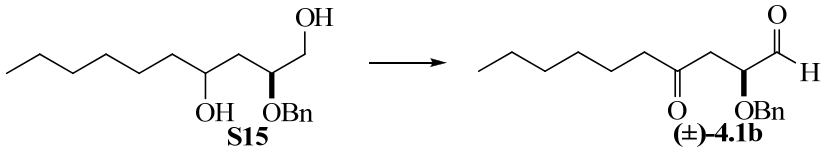
β-benzyloxy aldehyde 4.13: To a solution of benzyl ether **S13** (10.30 g, 29.54 mmol) in CH_2Cl_2 (100 mL) and MeOH (100 mL) was bubbled O_3 with a gas dispersion tube at -78 °C until the solution turned blue (10 min) at which time O_2 was bubbled for twice the amount of time as O_3 (20 min) and then the reaction was quenched with PPh_3 (9.30 g, 35.45 mmol) at -78 °C. This solution was stirred for 14 h and allowed to warm to 23 °C at which time the solvent was removed under reduced pressure. Purification by flash column chromatography (hexanes:ethyl acetate 96:4) delivered **4.13** (7.50 g, 53% over two steps from **S12**) as a colorless oil: R_f = 0.53 (80:20 hexanes:ethyl acetate); IR (thin film) 3032, 2722, 1728, 1094 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05-1.08 (m, 21H), 2.67 (ddd, *J* = 2.4, 6.9, 16.5 Hz, 1H), 2.74 (ddd, *J* = 2.1, 5.4, 16.5 Hz, 1H), 3.71 (dd, *J* = 6.3, 10.2 Hz, 1H), 3.87 (dd, *J* = 5.1, 10.2 Hz, 1H), 4.00-4.09 (m, 1H), 4.61 (d, *J* = 11.4 Hz, 1H), 4.70 (d, *J* = 11.4 Hz, 1H), 7.25-7.39 (m, 5H), 9.81 (dd, *J* = 2.1, 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.9(3), 17.9(6), 46.3, 65.1, 72.2, 75.2, 127.7, 127.8(2), 128.3(2), 138.3, 200.8; ESI-HRMS calcd for $C_{20}H_{34}O_3SiLi$ [M + Li] 357.2437, found 357.2441.



Secondary alcohols S14 were prepared according to the general procedure for Grignard addition using aldehyde **4.13** (830 mg, 2.37 mmol) in ether (20 mL) and a 2.0 M solution of hexylmagnesium chloride in ether (1.8 mL, 3.56 mmol) for 1.5 h. Representative work-up with sat. aq. NH_4Cl (2 x 20 mL), water (2 x 20 mL) and brine (2 x 20 mL) delivered crude alcohols **S14** as a pale yellow oil. This compound was not fully characterized.

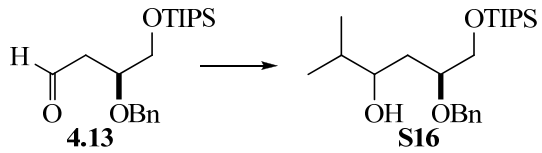


Diols S15 were prepared according to the general procedure for TBAF deprotection using silyl ethers **S14** (980 mg, 2.24 mmol) in THF (22 mL) and a 1.0 M solution of TBAF in THF (4.5 mL, 4.48 mmol) for 2.5 h. Representative work-up with sat. aq. NH_4Cl (2 x 20 mL), water (2 x 20 mL) and brine (2 x 20 mL) then purification by flash column chromatography (hexanes:ethyl acetate 60:40) delivered diols **S15** (480 mg, 72% over two steps from **4.13**, dr 1:1) as a colorless oil. This compound was not fully characterized.



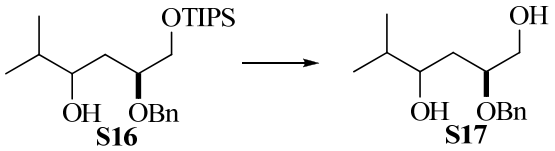
α-benzyloxy-γ-ketoaldehyde (±)-4.1b was prepared according to the general procedure for Swern oxidation using oxalyl chloride (343 μL, 4.00 mmol) in CH_2Cl_2 (10 mL),

DMSO (568 μL, 8.00 mmol), diols **S15** (280 mg, 1.00 mmol) in CH_2Cl_2 (10 mL), and Et_3N (2.2 mL, 16.00 mmol). Representative work-up with water (3 x 20 mL) and brine (3 x 20 mL) then purification by flash column chromatography (hexanes:ethyl acetate 90:10) delivered ketoaldehyde **(±)-4.1b** (209 mg, 76%) as a pale yellow oil: R_f = 0.53 (hexanes:ethyl acetate 70:30); IR (thin film) 3032, 2722, 1733, 1714, 1108 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.22-1.34 (m, 6H), 1.50-1.64 (m, 2H), 2.43 (t, *J* = 7.5 Hz, 1H), 2.81 (dd, *J* = 6.3, 17.4 Hz, 1H), 2.87 (dd, *J* = 5.1, 17.4 Hz, 1H), 4.28 (ddd, *J* = 0.9, 5.1, 6.3 Hz, 1H), 4.65 (d, *J* = 11.7 Hz, 1H), 4.72 (d, *J* = 11.7 Hz, 1H), 7.30-7.40 (m, 5H), 9.79 (d, *J* = 0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.5, 23.5, 28.8, 31.6, 43.3, 43.8, 73.3, 79.6, 128.1(2), 128.2, 128.6(2), 137.3, 202.7, 207.1; ESI-HRMS calcd for $C_{17}H_{24}O_3Li$ [M + Li] 283.1885, found 283.1923.



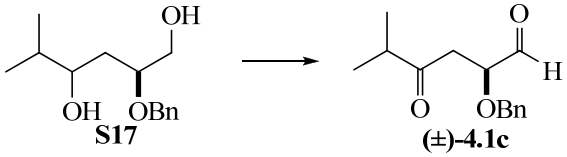
4.13 **S16**

Secondary alcohols S16 were prepared according to the general procedure for Grignard addition using aldehyde **4.13** (1.05 g, 3.00 mmol) in ether (30 mL) and a 2.0 M solution of isopropylmagnesium chloride in ether (2.3 mL, 4.50 mmol) for 1.5 h. Representative work-up with sat. aq. NH_4Cl (2 x 20 mL), water (2 x 20 mL) and brine (2 x 20 mL) delivered crude alcohols **S16** as a pale yellow oil. This compound was not fully characterized.



S16 **S17**

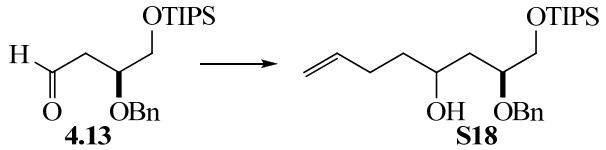
Diols S17 were prepared according to the general procedure for TBAF deprotection using silyl ethers **S16** (990 mg, 2.51 mmol) in THF (30 mL) and a 1.0 M solution of TBAF in THF (6.0 mL, 6.00 mmol) for 2 h. Representative work-up with sat. aq. NH_4Cl (2 x 20 mL), water (2 x 20 mL) and brine (2 x 20 mL) then purification by flash column chromatography (hexanes:ethyl acetate 60:40) delivered diols **S17** (504 mg, 70% over two steps from **4.13**, dr 1:1) as a colorless oil. This compound was not fully characterized.



S17 **(±)-4.1c**

α-benzyloxy-γ-ketoaldehyde (±)-4.1c was prepared according to the general procedure for Swern oxidation using oxalyl chloride (343 μL, 4.00 mmol) in CH_2Cl_2 (10 mL), DMSO (568 μL, 8.00 mmol), diols **S17** (238 mg, 1.00 mmol) in CH_2Cl_2 (10 mL), and Et_3N (2.2 mL, 16.00 mmol). Representative work-up with water (3 x 20 mL) and brine (3 x 20 mL) then purification by flash column chromatography (hexanes:ethyl acetate 85:15) delivered ketoaldehyde **(±)-4.1c** (198 mg, 85%) as a pale yellow oil: R_f = 0.81 (hexanes:ethyl acetate 60:40); IR (thin film) 3032, 2722, 1733, 1711, 1102 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (t, *J* = 6.6 Hz, 3H), 1.13 (t, *J* = 6.9 Hz, 3H), 2.61 (qq, *J* = 6.6, 6.9 Hz, 1H), 2.87 (dd, *J* = 6.0, 17.4 Hz, 1H), 2.93 (dd, *J* = 5.1, 17.4 Hz, 1H), 4.29 (ddd, *J* = 0.9, 5.1, 6.0 Hz, 1H), 4.65 (d, *J* = 11.7 Hz, 1H), 4.72 (d, *J* = 11.7 Hz, 1H),

7.26-7.40 (m, 5H), 9.80 (d, J = 0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9(2), 41.2, 41.7, 73.3, 79.6, 128.07(2), 128.14, 128.5(2), 137.3, 202.8, 210.6; ESI-HRMS calcd for $C_{14}H_{18}O_3Li$ [M + Li] 242.1416, found 242.1418.

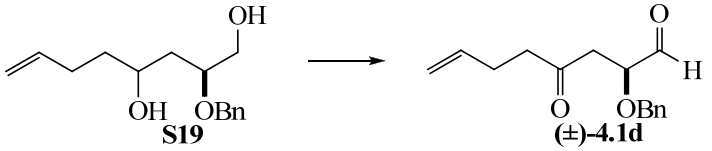


4.13 **S18**

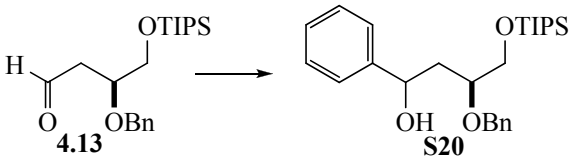
Secondary alcohols S18 were prepared according to the general procedure for Grignard addition using aldehyde **4.13** (800 mg, 2.28 mmol) in ether (40 mL) and a 1.0 M solution of 3-butenylmagensium bromide in THF (3.4 mL, 3.42 mmol) for 2 h. Representative work-up with sat. aq. NH_4Cl (2 x 20 mL), water (2 x 20 mL) and brine (2 x 20 mL) delivered crude alcohols **S18** as a pale yellow oil. This compound was not fully characterized.

S18 **S19**

Diols S19 were prepared according to the general procedure for TBAF deprotection using silyl ethers **S18** (780 mg, 1.92 mmol) in THF (40 mL) and a 1.0 M solution of TBAF in THF (3.8 mL, 3.84 mmol) for 1 h. Representative work-up with sat. aq. NH_4Cl (2 x 20 mL), water (2 x 20 mL) and brine (2 x 20 mL) then purification by flash column chromatography (hexanes:ethyl acetate 60:40) delivered diols **S19** (410 mg, 72% over two steps from **4.13**, dr 1:1) as a colorless oil. This compound was not fully characterized.

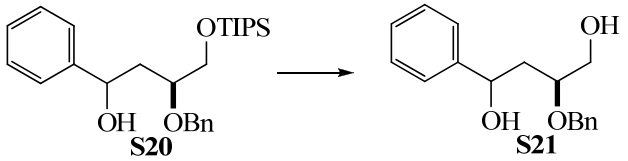


α-benzyloxy-γ-ketoaldehyde (±)-4.1d was prepared according to the general procedure for Swern oxidation using oxalyl chloride (275 μL, 3.20 mmol) in CH_2Cl_2 (10 mL), DMSO (454 μL, 6.40 mmol), diols **S19** (200 mg, 0.80 mmol) in CH_2Cl_2 (10 mL), and Et_3N (1.80 mL, 12.80 mmol). Representative work-up with water (3 x 20 mL) and brine (3 x 20 mL) then purification by flash column chromatography (hexanes:ethyl acetate 90:10) delivered ketoaldehyde **(±)-4.1d** (138 mg, 70%) as a pale yellow oil: R_f = 0.56 (hexanes:ethyl acetate 60:40); IR (thin film) 3066, 3032, 2719, 1733, 1717, 1113 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.30-2.40 (m, 2H), 2.53-2.58 (m, 2H), 2.82 (dd, *J* = 6.3, 17.1 Hz, 1H), 2.88 (dd, *J* = 4.8, 17.1 Hz, 1H), 4.28 (ddd, *J* = 0.9, 4.8, 6.3 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.72 (d, *J* = 12.0 Hz, 1H), 4.97-5.08 (m, 2 H), 5.73-5.87 (m, 1H), 7.28-7.40 (m, 5H), 9.78 (d, *J* = 0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.5, 42.3, 43.9, 73.4, 79.5, 115.5, 128.2(2), 128.3, 128.6(2), 136.8, 137.2, 202.7, 206.1; ESI-HRMS calcd for $C_{15}H_{19}O_3$ [M + H] 247.1334, found 247.1354.

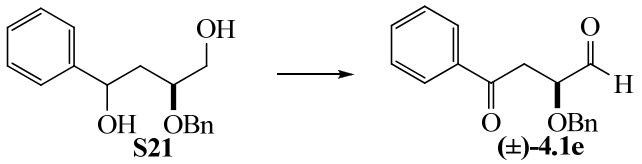


Secondary alcohols S20 were prepared according to the general procedure for Grignard addition using aldehyde **4.13** (1.05 g, 3.00 mmol) in ether (30 mL) and a 2.0 M solution of phenylmagnesium chloride in ether (2.3 mL, 4.50 mmol) for 1 h. Representative work-up with sat. aq. NH_4Cl (2 x 20 mL), water (2 x 20 mL) and brine (2 x 20 mL)

delivered crude alcohols **S20** as a pale yellow oil. This compound was not fully characterized.

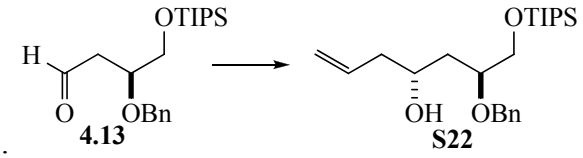


Diols S21 were prepared according to the general procedure for TBAF deprotection using silyl ethers **S20** (1.09 g, 2.54 mmol) in THF (30 mL) and a 1.0 M solution of TBAF in THF (6.0 mL, 6.00 mmol) for 2 h. Representative work-up with sat. aq. NH_4Cl (2 x 20 mL), water (2 x 20 mL) and brine (2 x 20 mL) then purification by flash column chromatography (hexanes:ethyl acetate 65:35) delivered diols **S21** (600 mg, 73% over two steps from **4.13**, dr 1:1) as a colorless oil. This compound was not fully characterized.



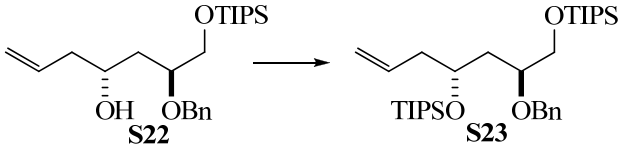
α-benzyloxy-γ-ketoaldehyde (±)-4.1e was prepared according to the general procedure for Swern oxidation using oxalyl chloride (343 μL, 4.00 mmol) in CH_2Cl_2 (10 mL), DMSO (568 μL, 8.00 mmol), diols **S21** (272 mg, 1.00 mmol) in CH_2Cl_2 (10 mL), and Et_3N (2.2 mL, 16.00 mmol). Representative work-up with water (3 x 20 mL) and brine (3 x 20 mL) then purification by flash column chromatography (hexanes:ethyl acetate 85:15) delivered ketoaldehyde **(±)-4.1e** (189 mg, 71%) as a pale yellow oil: R_f = 0.77 (hexanes:ethyl acetate 60:40); IR (thin film) 3066, 3032, 2717, 1736, 1683, 1108 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.42 (dd, *J* = 6.0, 17.7 Hz, 1H), 3.48 (dd, *J* = 5.1, 17.7

Hz, 1H), 4.48 (ddd, *J* = 0.6, 5.1, 6.0 Hz, 1H), 4.72 (d, *J* = 11.7 Hz, 1H), 4.78 (d, *J* = 11.7 Hz, 1H), 7.26-7.39 (m, 5H), 7.45-7.52 (m, 2H), 7.57-7.63 (m, 1H), 7.93-7.98 (m, 2H), 9.90 (d, *J* = 0.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.4, 73.4, 79.5, 128.2(2), 128.3(2), 128.6(2), 128.7(2) 133.6(2), 136.3, 137.3, 196.2, 202.8; ESI-HRMS calcd for $C_{17}H_{16}O_3Li$ [M + Li] 275.1259, found 275.1251.



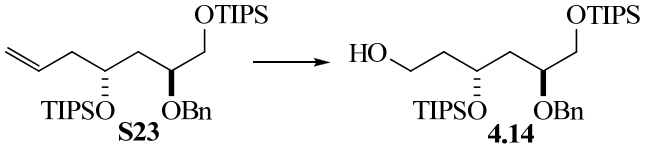
Secondary alcohol S22: To a solution of aldehyde **4.13** (1.00 g, 2.85 mmol) in CH_2Cl_2 (40 mL) was added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (3.42 mL, 3.42 mmol) down the side of the flask slowly at -78 °C followed by 5 mL of CH_2Cl_2 to rinse down any remaining $TiCl_4$. The solution quickly turned orange-red and after 10 minutes, allyltrimethylsilane (536 μL, 3.42 mmol) was added down the side of the flask in 10 mL of CH_2Cl_2 and then rinsed down with an additional 5 mL of CH_2Cl_2. The reaction was stirred at -78 °C for 2 h and quenched slowly with MeOH (5 mL). Upon addition of sat. aq. $NaHCO_3$ (20 mL), the reaction was stirred vigorously for 30 min and warmed to 23 °C. The mixture was diluted with ether (300 mL) and the organic layer was separated and washed with additional sat. aq. $NaHCO_3$ (2 x 20 mL), water (2 x 20 mL), and brine (2 x 20 mL). The resulting solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to deliver crude alcohol **S22** as a single diastereomer (>19:1) as judged by analysis of crude ^{1}H NMR (300 MHz). Purification by flash column chromatography (hexanes:ethyl acetate 97:3) delivered alcohol **S22** (860 mg, 77%) as a colorless oil: R_f = 0.51 (80:20 hexanes: ethyl acetate); IR (thin film) 3457, 3069, 3032,

1091 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.06-1.08 (m, 21H), 1.63-1.81 (m, 2H), 2.21-2.26 (m, 2H), 2.74 (br s, 1 H), 3.70-3.96 (m, 4H), 4.63 (d, *J* = 11.7 Hz, 1H), 4.75 (d, *J* = 11.7 Hz, 1H), 5.08-5.14 (m, 2H), 5.76-5.90 (m, 1H), 7.29-7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.1(3), 18.2(6), 38.3, 42.4, 66.1, 68.0, 72.7, 78.0, 117.7, 127.9, 128.1(2), 128.6(2), 135.2, 138.7; ESI-HRMS calcd for $C_{23}H_{40}O_3SiLi$ [M + Li] 399.2907, found 399.3074.



S22 **S23**

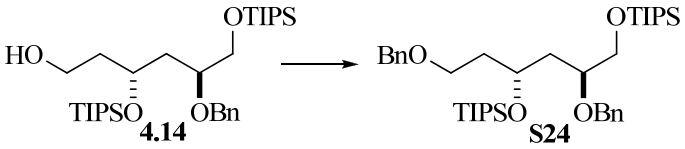
Bis-silyl ether S23: To a solution of alcohol **S22** (1.18 g, 3.02 mmol) in CH_2Cl_2 (60 mL) was added TIPSOTf (920 μL, 3.32 mmol) followed by Et_3N (505 μL, 3.62 mmol) at 0 °C. This solution was stirred for 1 h, warmed to 23 °C, and quenched with sat. aq. NH_4Cl (20 mL). The reaction was stirred vigorously for 15 min, diluted with ether (200 mL), and separated. The combined organic solution was washed with additional sat. aq. NH_4Cl (2 x 20 mL), water (2 x 20 mL), and brine (2 x 20 mL) and then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to deliver crude bis-silyl ether **S23** as a yellow oil. This compound was not characterized.



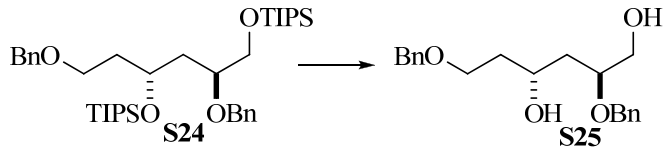
S23 **4.14**

Primary alcohol 4.14: To a solution of bis-silyl ether **S23** (1.66 g, 3.02 mmol) in CH_2Cl_2 (30 mL) and MeOH (30 mL) was bubbled O_3 with a gas dispersion tube at -78 °C until the solution turned blue (5 min) at which time O_2 was bubbled for twice the

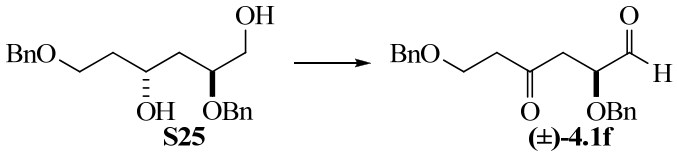
amount of time as O_3 (10 min) and then the reaction was quenched with $NaBH_4$ (686 mg, 18.12 mmol) at -78 °C. This solution was stirred for 20 h and allowed to warm to 23 °C at which time the solvent was removed under reduced pressure. The residue was dissolved in ether (200 mL), quenched with sat. aq. NH_4Cl (20 mL), stirred vigorously for 15 min. The organic layer was separated and washed with additional sat. aq. NH_4Cl (2 x 20 mL), water (2 x 20 mL), and brine (2 x 20 mL). The solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:ethyl acetate 95:5) delivered alcohol **4.14** (1.42 g, 81% over two steps from **S22**) as a pale yellow oil. This compound was not fully characterized.



Benzyl ether S24: To a solution of alcohol **4.14** (354 mg, 0.55 mmol) in THF (10 mL) was added benzyl bromide (99 μL, 0.83 mmol) and NaH (33 mg, 0.83 mmol, 60% dispersion in mineral oil) at 0 °C as a solid. The reaction was heated to 65 °C and was stirred for 14 h after which time it was cooled to 23 °C and quenched slowly with sat. aq. NH_4Cl (20 mL). The resulting mixture was stirred vigorously for 15 min, and diluted with ether (100 mL). The organic layer was separated and washed with additional sat. aq. NH_4Cl (2 x 10 mL), water (2 x 10 mL), and brine (2 x 10 mL). The residue was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to deliver crude benzyl ether **S24** as yellow oil. This compound was not fully characterized.

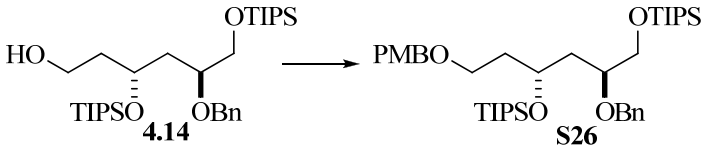


Diol S25 was prepared according to the general procedure for TBAF deprotection using bis-silyl ether **S24** (301 mg, 0.47 mmol) in THF (10 mL) and a 1.0 M solution of TBAF in THF (2.8 mL, 2.82 mmol) for 24 h. Representative work-up with sat. aq. NH_4Cl (2 x 10 mL), water (2 x 10 mL) and brine (2 x 10 mL) then purification by gradient flash column chromatography (hexanes:ethyl acetate 50:50 to 40:60) delivered diol **S24** (98 mg, 54% over two steps from alcohol **4.14**) as a colorless oil. This compound was not fully characterized.

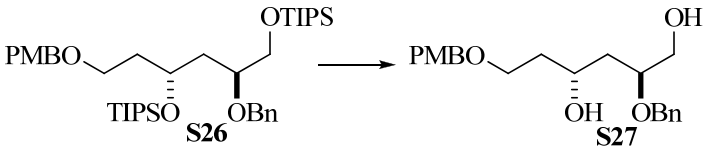


α-benzyloxy-γ-ketoaldehyde (±)-4.1f was prepared according to the general procedure for Swern oxidation using oxalyl chloride (103 μL, 1.20 mmol) in CH_2Cl_2 (5 mL), DMSO (170 μL, 2.40 mmol), diol **S25** (98 mg, 0.30 mmol) in CH_2Cl_2 (5 mL), and Et_3N (669 μL, 4.80 mmol). Representative work-up with water (3 x 10 mL) and brine (3 x 10 mL) then purification by flash column chromatography (hexanes:ethyl acetate 80:20) delivered ketoaldehyde **(±)-4.1f** (74 mg, 76%) as a pale yellow oil: R_f = 0.46 (hexanes:ethyl acetate 50:50); IR (thin film) 3029, 2719, 1714, 1099 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.73 (t, *J* = 6.0 Hz, 2H), 2.87 (dd, *J* = 6.6, 17.4 Hz, 1H), 2.95 (dd, *J* = 4.5, 17.4 Hz, 1H), 3.75 (t, *J* = 6.0 Hz, 2H), 4.29 (br dd, *J* = 4.5, 6.6 Hz, 1H), 4.51 (s, 2H), 4.65 (d, *J* = 11.4 Hz, 1H), 4.70 (d, *J* = 11.4 Hz, 1H), 7.28-7.37 (m, 10H), 9.77 (br s,

1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.5, 44.4, 65.1, 73.4(2), 79.4, 127.8(3), 128.25(2), 128.30, 128.5(2), 128.7(2), 137.3, 138.1, 202.6, 205.4; ESI-HRMS calcd for $C_{20}H_{22}O_4$ [M + H] 333.1678, found 333.1796.

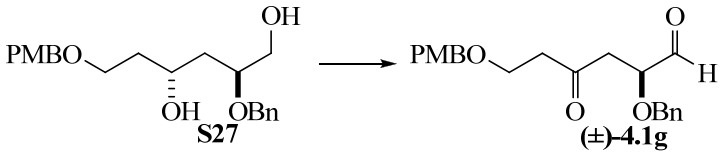


***p*-Methoxybenzyl ether S26:** To a solution of alcohol **4.14** (552 mg, 1.00 mmol) and PMBTCA (565 mL, 2.00 mmol) in CH_2Cl_2 (4 mL) was added CSA (24 mg, 0.10 mmol) as a solid at 23 °C. After stirring for 24 h, the reaction was filtered over a pad of Celite, washed with CH_2Cl_2, quenched with $NaHCO_3$ (10 mL), and stirred vigorously for 15 min. The resulting mixture was diluted with ether (100 mL), washed with $NaHCO_3$ (2 x 20 mL), sat. aq. NH_4Cl (2 x 20 mL), and brine (2 x 20 mL). The resulting solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:ethyl acetate 97:3) delivered *p*-methoxybenzyl ether **S26** (565 mg, 84%) as a pale yellow oil. This compound was not fully characterized.



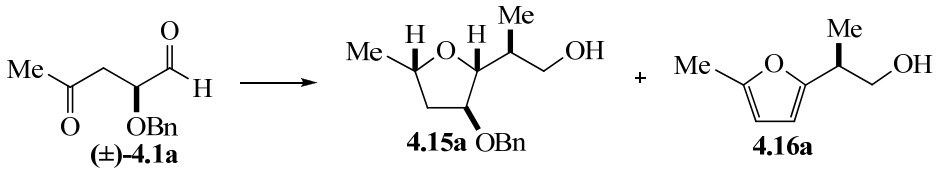
Diol S27 was prepared according to the general procedure for TBAF deprotection using bis-silyl ether **S26** (565 mg, 0.84 mmol) in THF (20 mL) and a 1.0 M solution of TBAF in THF (5.0 mL, 5.04 mmol) for 24 h. Representative work-up with sat. aq. NH_4Cl (2 x 20 mL), water (2 x 20 mL) and brine (2 x 20 mL) then purification by gradient flash

column chromatography (hexanes:ethyl acetate 50:50 to 40:60) delivered diol **S27** (202 mg, 56% over two steps from alcohol **4.14**) as a colorless oil. This compound was not fully characterized.



S27 **(±)-4.1g**

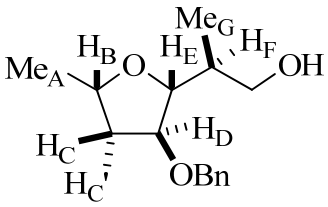
α-benzyloxy-γ-ketoaldehyde (±)-4.1g was prepared according to the general procedure for Swern oxidation using oxalyl chloride (343 μL, 4.00 mmol) in CH_2Cl_2 (10 mL), DMSO (568 μL, 8.00 mmol), diol **S27** (361 mg, 1.00 mmol) in CH_2Cl_2 (10 mL), and Et_3N (2.2 mL, 16.00 mmol). Representative work-up with water (3 x 20 mL) and brine (3 x 20 mL) and purification by flash column chromatography (hexanes:ethyl acetate 70:30) delivered ketoaldehyde **(±)-4.1g** (288 mg, 81%) as a pale yellow oil: R_f = 0.67 (hexanes:ethyl acetate 30:70); IR (thin film) 3031, 2719, 1717, 1105 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.71 (t, *J* = 6.0 Hz, 2H), 2.86 (dd, *J* = 6.6, 17.4 Hz, 1H), 2.94 (dd, *J* = 4.8, 17.4 Hz, 1H), 3.72 (t, *J* = 6.0 Hz, 2H), 3.81 (s, 3H), 4.28 (ddd, *J* = 0.6, 4.8, 6.6 Hz, 1H), 4.44 (s, 2H), 4.64 (d, *J* = 11.7 Hz, 1H), 4.70 (d, *J* = 11.7 Hz, 1H), 6.84-6.90 (m, 2H), 7.20-7.26 (m, 2H), 7.31-7.37 (m, 5H), 9.77 (d, *J* = 0.6, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.6, 44.5, 55.5, 64.9, 73.2, 73.5, 79.5, 114.0(2), 128.3(2), 128.4, 128.8(2), 129.6(2), 130.2, 137.3, 159.4, 202.7, 205.6; ESI-HRMS calcd for $C_{21}H_{24}O_5Li$ [M + Li] 363.1784, found 363.1772.



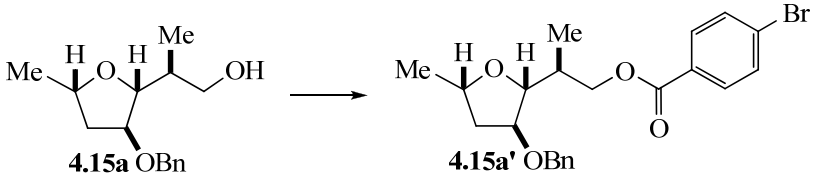
Representative procedure for the tandem process as described for THF 4.15a. $ZnCl_2$ (423 mg, 3.10 mmol) was freshly fused at ~0.5 mm Hg and subsequently cooled to ambient temperature. The ketene acetal **4.2e** (301 mg, 0.93 mmol) was added as a solution in CH_2Cl_2 (5 mL) and stirred for 4 h at 23 °C. The heterogeneous mixture was cooled to 0 °C, then Et_3SiH (6.3 mL, 38.80 mmol) and aldehyde **(±)-4.1a** (160 mg, 0.78 mmol) in CH_2Cl_2 (5 mL) were added sequentially and the reaction stirred for 12 h at 0 °C. The reaction was quenched with pH 7 buffer and stirred vigorously for 30 min, then poured over Celite with additional CH_2Cl_2 and dried with Na_2SO_4. Crude ^1H NMR (300 MHz) analysis revealed a 6.2:1 ratio of a single diastereomer (>19:1) of THF to furan silyl esters. Upon concentration under reduced pressure, the residue was dissolved in CH_2Cl_2 (20 mL). The resulting solution was treated with DIBAlH (830 μL, 4.66 mmol) at -78 °C, warmed to 0 °C quickly and stirred for 6 h. The reaction quenched with MeOH (5 mL) at 0 °C *dropwise*, treated with Rochelle's salt (10 mL), and stirred vigorously for 12 h. The resulting suspension was poured over Celite and washed with ether (200 mL). The combined organic solution was washed with sat. aq. NH_4Cl (2 x 20 mL), water (2 x 20 mL) and brine (2 x 20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by gradient flash column chromatography (hexanes:ethyl acetate 85:15 to 80:20) delivered THF **4.15a** (104 mg, 54%) as a colorless oil and furan **4.16a** as a pale yellow oil. Characterization data for THF **4.15a**: R_f = 0.56 (hexanes:ethyl acetate 60:40); IR (thin film) 3443, 1096, 1058

cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.94 (d, *J* = 7.0 Hz, 3H), 1.27 (d, *J* = 6.0 Hz, 3H), 1.54 (ddd, *J* = 7.0, 10.0, 13.0 Hz, 1H), 1.95-2.03 (m, 1H), 2.11 (ddd, *J* = 2.0, 5.5, 13.0 Hz, 1H), 3.58 (dd, *J* = 6.5, 11.0 Hz, 1H), 3.64 (dd, *J* = 4.5, 11.0 Hz, 1H), 3.93 (dd, *J* = 4.0, 4.5 Hz, 1H), 3.98 (ddd, *J* = 2.0, 4.0, 7.0 Hz, 1H), 4.16 (ddq, *J* = 5.5, 6.0, 10.0 Hz, 1H), 4.45 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 7.29-7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.4, 20.4, 37.8, 40.4, 66.6, 71.6, 74.5, 81.6, 87.9, 127.96(3), 128.00(2), 138.0; ESI-HRMS calcd for $C_{15}H_{22}O_3Li$ [M + Li] 251.1647, found 251.1686. Partial characterization data for furan **4.16a**: R_f = 0.75 (hexanes:ethyl acetate 60:40); ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, *J* = 6.9 Hz, 3H), 1.57-1.61 (m, 1H), 2.27 (d, *J* = 0.9 Hz, 3H), 2.99 (app sext, *J* = 6.6, 1H), 3.71 (dd, *J* = 5.7, 6.3 Hz, 1H), 5.88-5.89 (m, 1H), 5.97-5.98 (m, 1H).

Crucial nOe enhancements for **4.15a**:

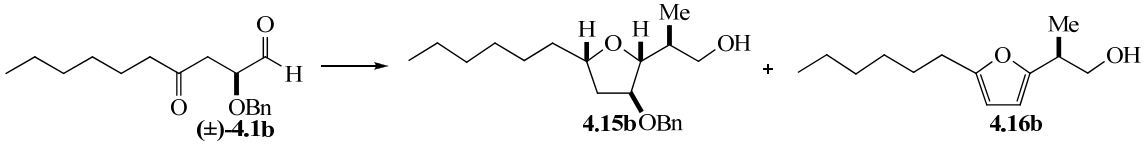


Irradiate H	Observed H	% nOe
A	C'	1.8
B	E	0.6
B	C	0.8
C	E	0.3
C'	I	0.3
D	F	0.5
D	C'	1.0
E	B	1.0
F	D	0.5
G	D	0.5



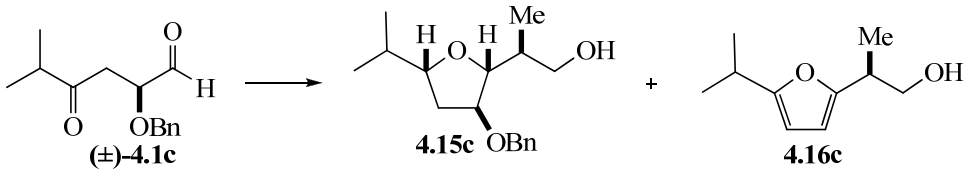
THF 4.15a': To a solution of THF **4.15a** in CH_2Cl_2 (2 mL) was added Et_3N (76 μL, 0.54 mmol), DMAP (2 mg, 0.02 mmol), and 4-bromobenzoyl chloride (59 mg, 0.27

mmol) at 23 °C and stirred for 2.5 h. The reaction was quenched with sat. aq. NH_4Cl (5 mL), stirred vigorously for 15 min, and diluted with ether (50 mL). The organic layer was separated from the aqueous layer and washed with additional sat. aq. NH_4Cl (2 x 10 mL), water (2 x 10 mL), and brine (2 x 10 mL). The resulting solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:ethyl acetate 95:5) delivered THF **4.15a'** (60 mg, 79%) as a white solid. Slow evaporation with hexanes:ether (1:1) over 24 h delivered THF **4.15a'** as a white crystalline compound: R_f = 0.84 (hexanes:ethyl acetate 70:30); IR (thin film) 3029, 1714, 1102 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.04 (d, *J* = 7.0 Hz, 3H), 1.27 (d, *J* = 6.5 Hz, 3H), 1.48 (ddd, *J* = 6.0, 10.0, 13.0 Hz, 1H), 2.10 (ddd, *J* = 1.5, 5.0, 13.0 Hz, 1H), 2.13-2.19 (m, 1H), 3.96 (dd, *J* = 3.5, 5.0 Hz, 1H), 3.98 (ddd, *J* = 1.5, 3.5, 6.0 Hz, 1H), 4.19 (dd, *J* = 5.0, 6.5, 10.0 Hz, 1H), 4.23 (dd, *J* = 7.0, 11.0 Hz, 1H), 4.33 (dd, *J* = 6.0, 11.0 Hz, 1H), 4.45 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 7.27-7.35 (m, 5H), 7.86-7.90 (m, 2H), 7.56-7.90 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.7, 20.4, 39.3, 40.3, 67.5, 71.4, 74.5, 82.2, 85.7, 127.8(2), 127.9, 128.2, 128.6(2), 129.5, 131.3(2), 131.9(2), 138.2, 166.0; ESI-HRMS calcd for $C_{22}H_{26}BrO_4$ [M + H] 433.1014/435.0994, found 433.1012/435.1005. Cambridge number for THF **4.15a'** is CCDC #681175.



THF 4.15b was prepared according to the representative procedure for the tandem process using $ZnCl_2$ (376 mg, 2.76 mmol), ketene acetal **4.2e** (269 mg, 0.83 mmol), Et_3SiH (5.6 mL, 34.50 mmol), and aldehyde **(±)-4.1b** (190 mg, 0.69 mmol) for 12 h.

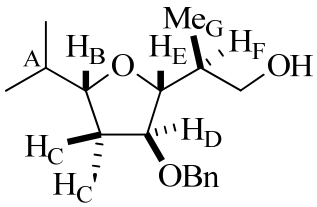
Representative work-up and crude ^{1}H NMR (300 MHz) analysis revealed a 1.3:1 ratio of a single diastereomer (>19:1) of THF to furan silyl esters. Representative reduction with DIBAlH (738 μL, 4.14 mmol) and purification by gradient flash column chromatography (hexanes:ether 85:15 to 80:20) delivered THF **4.15b** (92 mg, 42%) as a pale yellow oil and furan **4.16b** (29 mg, 20%) as a pale yellow oil. Characterization data for THF **4.15b**: R_f = 0.18 (hexanes:ethyl acetate 80:20); IR (thin film) 3437, 3029, 1069 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 0.88 (t, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 7.0 Hz, 3H), 1.18-1.61 (m, 10H), 1.29 (ddd, *J* = 7.0, 10.0, 13.0 Hz, 1H), 1.80-1.85 (m, 1H), 1.85 (ddd, *J* = 2.0, 5.5, 13.0 Hz, 1H), 2.10 (dd, *J* = 5.5, 6.0 Hz, 1H), 3.50-3.59 (m, 2H), 3.75 (ddd, *J* = 2.0, 4.0, 7.0 Hz, 1H), 3.99 (m, 1H), 4.02 (dd, *J* = 4.0, 5.0 Hz, 1H), 4.19 (d, *J* = 12.0 Hz, 1H), 4.27 (d, *J* = 12.0 Hz, 1H), 7.05-7.35 (m, 5H); ^{13}C NMR (125 MHz, C_6D_6) δ 12.4, 14.3, 23.0, 26.5, 29.7, 32.1, 35.6, 38.7, 38.9, 66.3, 71.2, 78.4, 81.8, 87.3, 127.79(2), 127.81(2), 128.0, 138.8; ESI-HRMS calcd for $C_{20}H_{32}O_3Li$ [M + Li] 327.2511, found 327.2515. Characterization data for furan **4.16b**: R_f = 0.33 (hexanes:ethyl acetate 80:20); IR (thin film) 3356, 3102, 1013 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, *J* = 6.9 Hz, 3H), 1.23-1.38 (m, 6H), 1.26 (d, *J* = 7.2 Hz, 3H), 1.56-1.67 (m, 2H), 2.58 (t, *J* = 7.5 Hz, 3H), 3.00 (app sext, *J* = 6.9, 1H), 3.68-3.73 (m, 1H), 5.87-5.91 (m, 1H), 5.96-5.99 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 15.3, 22.8, 28.16, 28.24, 29.1, 31.8, 36.3, 66.9, 105.1, 105.8, 155.6, 155.8; ESI-HRMS calcd for $C_{13}H_{22}O_2Li$ [M + Li] 217.1780, found 217.1777. Unambiguous nOe enhancements could not be obtained for THF **4.15b**.



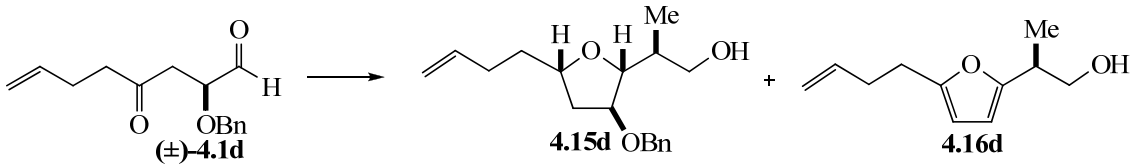
THF 4.15c was prepared according to the representative procedure for the tandem process using $ZnCl_2$ (398 mg, 2.92 mmol), ketene acetal **4.2e** (285 mg, 0.88 mmol), Et_3SiH (5.9 mL, 36.50 mmol), and aldehyde **(±)-4.1c** (170 mg, 0.73 mmol) for 12 h. Representative work-up and crude ^1H NMR (300 MHz) analysis revealed a 2.3:1 ratio of a single diastereomer (>19:1) of THF to furan silyl esters. Representative reduction with DIBAlH (781 μL, 4.38 mmol) and purification by gradient flash column chromatography (hexanes:ether 85:15 to 80:20) delivered THF **4.15c** (105 mg, 52%) as a colorless oil and furan **4.16c** (24 mg, 20%) as a colorless oil. Characterization data for THF **4.15c**: R_f = 0.42 (hexanes:ethyl acetate 70:30); IR (thin film) 3437, 3029, 1069 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 0.76 (d, *J* = 6.5 Hz, 3H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.96 (d, *J* = 6.5 Hz, 3H), 1.31 (ddd, *J* = 7.0, 10.0, 13.0 Hz, 1H), 1.53-1.61 (m, 1H), 1.76-1.82 (m, 1H), 1.77 (ddd, *J* = 2.0, 5.5, 13.0 Hz, 1H), 2.00 (dd, *J* = 5.5, 6.0 Hz, 1H), 3.49-3.57 (m, 2H), 3.68 (ddd, *J* = 5.5, 7.0, 10.0 Hz, 1H), 3.71 (ddd, *J* = 2.0, 4.0, 7.0 Hz, 1H), 3.99 (dd, *J* = 4.0, 5.0 Hz, 1H), 4.17 (d, *J* = 11.5 Hz, 1H), 4.26 (d, *J* = 11.5 Hz, 1H), 6.99-7.31 (m, 5H); ^{13}C NMR (125 MHz, C_6D_6) δ 12.3, 18.5, 19.4, 33.0, 36.2, 38.7, 66.1, 71.1, 81.6, 83.5, 86.9, 127.70(2), 127.72(2), 128.5, 138.7; ESI-HRMS calcd for $C_{17}H_{26}O_3Li$ [M + Li] 285.2042, found 285.2038. Characterization data for furan **4.16c**: R_f = 0.53 (hexanes:ethyl acetate 70:30); IR (thin film) 3353, 3108, 1018 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20-1.29 (m, 9H), 2.84-2.96 (m, 1H), 2.97-3.07 (m, 1H), 3.45-3.53 (m, 1H),

3.68-3.76 (m, 2H), 5.88 (app d, J = 3.0 Hz, 1H), 5.98 (app d, J = 3.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.3, 21.26, 21.29, 28.0, 36.3, 66.9, 103.1, 105.6, 155.5, 160.9; ESI-HRMS calcd for $C_{10}H_{16}O_2Li$ [M + Li] 175.1310, found 175.1306.

Crucial nOe enhancements for **4.15c**:

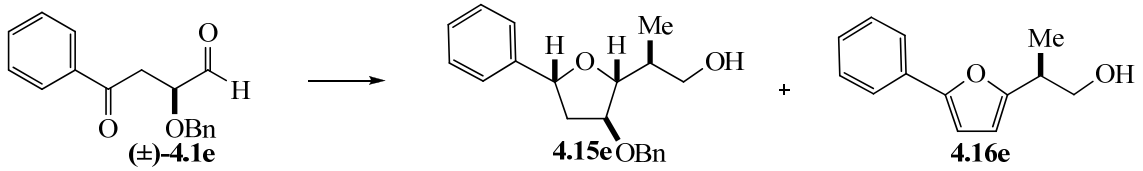


Irradiate H	Observed H	% nOe
A	B	1.5
B	E	NA
C	E	NA
C'	G	0.3
C'	A	0.5
D	A	NA
E	B	0.4
E	F	0.9
G	D	1.1
G	E	0.9



THF 4.15d was prepared according to the representative procedure for the tandem process using $ZnCl_2$ (221 mg, 1.62 mmol), ketene acetal **4.2e** (158 mg, 0.49 mmol), Et_3SiH (3.3 mL, 20.30 mmol), and aldehyde **(±)-4.1d** (100 mg, 0.41 mmol) for 12 h. Representative work-up and crude ^{1}H NMR (300 MHz) analysis revealed a 3:1 ratio of a single diastereomer (>19:1) of THF to furan silyl esters. Representative reduction with DIBAlH (434 μL, 2.44 mmol) and purification by gradient flash column chromatography (hexanes:ethyl acetate 85:15 to 80:20) delivered THF **4.15d** (58 mg, 49%) as a colorless oil and furan **4.16d** (10 mg, 14%) as a colorless oil. Characterization data for THF **4.15d**: R_f = 0.26 (hexanes:ethyl acetate 80:20); IR (thin film) 3426, 3063, 3032, 1063 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (d, J = 7.5 Hz, 3H), 1.57-1.64 (m,

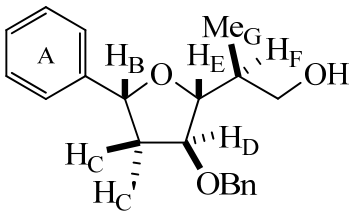
1H), 1.59 (ddd, *J* = 7.0, 10.0, 13.0 Hz, 1H), 1.69-1.76 (m, 1H), 1.95-2.02 (m, 1H), 2.10 (ddd, *J* = 2.0, 5.5, 13.0 Hz, 1H), 2.11-2.21 (m, 2H), 2.58 (dd, *J* = 6.0, 6.0 Hz, 1H), 3.55-3.67 (m, 2H), 3.92 (dd, *J* = 4.5, 4.5 Hz, 1H), 3.96 (ddd, *J* = 2.0, 4.5, 6.5 Hz, 1H), 4.01-4.07 (m, 1H), 4.46 (d, *J* = 11.5 Hz, 1H), 4.56 (d, *J* = 11.5 Hz, 1H), 4.96-5.06 (m, 2H), 5.79-5.87 (m, 1H), 7.29-7.39 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.3, 30.5, 34.5, 37.8, 38.6, 66.9, 71.6, 78.1, 81.2, 87.5, 115.0, 128.0(2), 128.1, 128.7(2), 138.0, 138.4; ESI-HRMS calcd for $C_{18}H_{26}O_3Li$ [M + Li] 297.2042, found 291.2045. Characterization data for furan **4.16d**: R_f = 0.42 (hexanes:ethyl acetate 80:20); IR (thin film) 3384, 3080, 1021 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, *J* = 7.0 Hz, 3H), 1.62 (br s, 1H), 2.37-2.42 (m, 2H), 2.67-2.73 (m, 2H), 3.00 (app sext, *J* = 6.5, 1H), 3.69-3.73 (m, 2H), 4.98-5.09 (m, 2H), 5.82-5.90 (m, 1H), 5.92 (app d, *J* = 3.0 Hz, 1H), 5.98 (app d, *J* = 3.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.3, 27.7, 32.3, 36.4, 66.9, 105.6, 105.8, 115.4, 137.8, 154.7, 155.8; CI-LRMS calcd for $C_{11}H_{17}O_2Li$ [M + H] 181.0, found 181.0. Unambiguous nOe enhancements could not be obtained for THF **4.15d**.



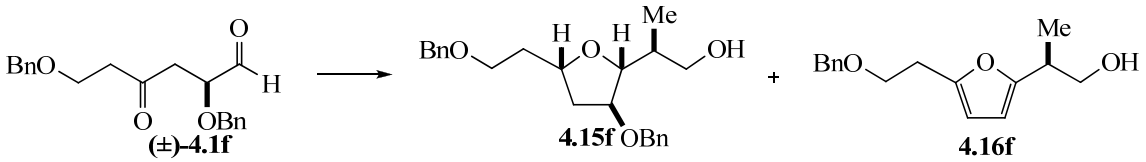
THF 4.15e was prepared according to the representative procedure for the tandem process using $ZnCl_2$ (346 mg, 2.54mmol), ketene acetal **4.2e** (246 mg, 0.76 mmol), Et_3SiH (5.1 mL, 31.50 mmol), and aldehyde **(±)-4.1e** (170 mg, 0.63 mmol) for 12 h. Representative work-up and crude ^{1}H NMR (300 MHz) analysis revealed a 1:5 ratio of a single diastereomer (>19:1) of THF to furan silyl esters. Representative reduction with

DIBAlH (674 μL, 3.78 mmol) and purification by gradient flash column chromatography (hexanes:ether 85:15 to 80:20 to 75:25) delivered THF **4.15e** (25 mg, 13%) as a colorless oil and furan **4.16e** (61 mg, 48%) as a colorless oil. Characterization data for THF **4.15e**: R_f = 0.14 (hexanes:ether 60:40); IR (thin film) 3423, 3029, 1043 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 0.98 (d, *J* = 7.0 Hz, 3H), 1.60 (ddd, *J* = 7.0, 10.5, 13.0 Hz, 1H), 1.65 (br s, 1H), 1.78-1.87 (m, 1H), 2.13 (ddd, *J* = 2.0, 5.5, 13.0 Hz, 1H), 3.48-3.56 (m, 2H), 3.81 (ddd, *J* = 2.0, 4.0, 7.0 Hz, 1H), 4.13 (dd, *J* = 4.0, 5.0 Hz, 1H), 4.18 (d, *J* = 12.0 Hz, 1H), 4.26 (d, *J* = 12.0 Hz, 1H), 5.02 (dd, *J* = 5.5, 10.5 Hz, 1H), 7.05-7.35 (m, 10H); ^{13}C NMR (125 MHz, C_6D_6) δ 12.5, 39.0, 41.6, 66.1, 71.3, 79.9, 82.0, 87.3, 126.2(2), 127.7, 127.8(2), 127.9, 128.59(2), 128.60(2), 138.7, 142.3; ESI-HRMS calcd for $C_{20}H_{24}O_3Li$ [M + Li] 319.1885, found 319.1889. Characterization data for furan **4.16e**: R_f = 0.25 (hexanes:ether 60:40); IR (thin film) 3353, 3060, 1018 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (d, *J* = 6.9 Hz, 3H), 1.58 (dd, *J* = 6.0, 6.6 Hz, 1H), 3.13 (app sext, *J* = 6.6, 1H), 3.74-3.88 (m, 2H), 6.20 (dd, *J* = 0.9, 3.3 Hz, 1H), 6.59 (d, *J* = 3.3 Hz, 1H), 7.20-7.70 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.4, 36.5, 66.7, 105.8, 107.6, 123.6(2), 127.2, 128.8(2), 131.1, 153.0, 157.2; ESI-HRMS calcd for $C_{13}H_{14}O_2Li$ [M + Li] 209.1154, found 209.1037.

Crucial nOe enhancements for **4.15e**:

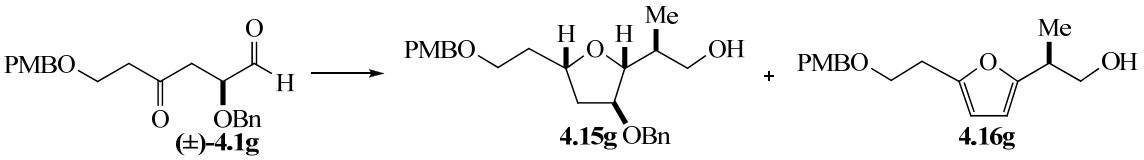


Irradiate H	Observed H	% nOe
A	D	NA
B	E	1.7
B	C	1.8
C	E	0.3
C’	G	0.8
D	C’	2.7
D	F	1.4
E	B	2.0
F	D	1.2
G	D	0.8



THF 4.15f was prepared according to the representative procedure for the tandem process using $ZnCl_2$ (114 mg, 0.83mmol), ketene acetal **4.2e** (81 mg, 0.25 mmol), Et_3SiH (1.7 mL, 10.40 mmol), and aldehyde **(±)-4.1f** (66 mg, 0.20 mmol) for 12 h. Representative work-up and crude ^1H NMR (300 MHz) analysis revealed a 3.5:1 ratio of a single diastereomer (>19:1) of THF to furan silyl esters. Representative reduction with DIBAlH (222 μL, 1.25 mmol) and purification by gradient flash column chromatography (hexanes:ethyl acetate 80:20 to 75:25) delivered THF **4.15f** (41 mg, 54%) as a colorless oil and furan **4.16f** as a pale yellow oil. Characterization data for THF **4.15f**: R_f = 0.30 (hexanes:ethyl acetate 80:20); IR (thin film) 3448, 3032, 1097 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 0.88 (d, *J* = 7.0 Hz, 3H), 1.32 (ddd, *J* = 7.0, 10.0, 13.0 Hz, 1H), 1.72-1.85 (m, 3H), 1.86 (ddd, *J* = 2.0, 5.5, 13.0 Hz, 1H), 1.95 (br s, 1H), 3.41-3.44 (m, 2H), 3.49-3.53 (m, 2H), 3.71 (ddd, *J* = 2.0, 4.0, 6.5 Hz, 1H), 3.97 (dd, *J* = 4.0, 5.0 Hz, 1H), 4.15 (d, *J* = 11.5 Hz, 1H), 4.16-4.21 (m, 1H), 4.24 (d, *J* = 11.5 Hz, 1H), 4.28 (s, 2H), 7.07-7.28 (m, 10H); ^{13}C NMR (125 MHz, C_6D_6) δ 12.4, 35.8, 38.7, 38.9, 66.2, 67.6, 71.2, 73.0, 75.9, 81.8, 87.2, 127.6, 127.7(2), 127.77, 127.80(2), 128.5(2), 128.6(2), 138.8, 139.2; ESI-HRMS calcd for $C_{23}H_{30}O_4Li$ [M + Li] 377.2304, found 377.2415. Partial characterization data for furan **4.16f**: R_f = 0.40 (hexanes:ethyl acetate 80:20); ^1H NMR (500 MHz, C_6D_6) δ 1.11 (d, *J* = 7.0 Hz, 3H), 2.75-2.85 (m, 1H), 2.80 (t, *J* = 6.5 Hz, 1H), 3.45 (dd, *J* = 6.0, 10.5 Hz, 1H), 3.50 (t, *J* = 6.5 Hz, 1H), 3.57 (dd, *J* =

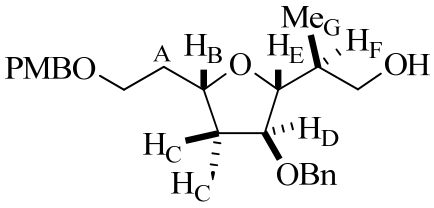
6.5, 10.5 Hz, 1H), 4.26 (s, 2H), 5.85 (app d, *J* = 3.0 Hz, 1H), 5.90 (app d, *J* = 3.0 Hz, 1H), 7.05-7.25 (m, 5H). Unambiguous nOe enhancements could not be obtained for THF **4.15f**.



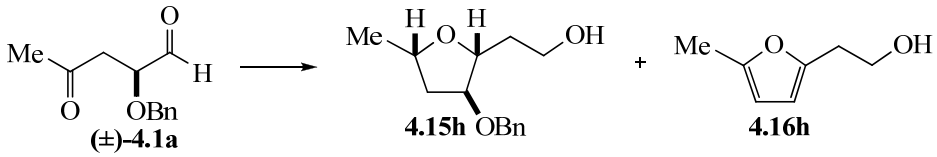
THF 4.15g was prepared according to the representative procedure for the tandem process using $ZnCl_2$ (262 mg, 1.92mmol), ketene acetal **4.2e** (188 mg, 0.58 mmol), Et_3SiH (3.9 mL, 24.00 mmol), and aldehyde **(±)-4.1g** (170 mg, 0.48 mmol) for 12 h. Representative work-up and crude ^1H NMR (300 MHz) analysis revealed a 2.3:1 ratio of a single diastereomer (>19:1) of THF to furan silyl esters. Representative reduction with DIBAlH (513 μL, 2.88 mmol) with slow warming from -78 °C to -30 °C to prevent PMB deprotection and purification by flash column chromatography (hexanes:ethyl acetate 80:20) delivered THF **4.15g** (93 mg, 49%) as a colorless oil and furan **4.16g** (37 mg, 27%) as a colorless oil. Characterization data for THF **4.15g**: R_f = 0.18 (hexanes:ethyl acetate 70:30); IR (thin film) 3454, 3029, 1094 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.92 (d, *J* = 7.0 Hz, 3H), 1.61 (ddd, *J* = 7.0, 10.5, 13.0 Hz, 1H), 1.80-1.92 (m, 2H), 1.93-2.01 (m, 1H), 2.11 (ddd, *J* = 2.0, 5.5, 13.0 Hz, 1H), 2.56 (dd, *J* = 5.5, 6.5 Hz, 1H), 3.52-3.67 (m, 4H), 3.81 (s, 3H), 3.91 (dd, *J* = 4.0, 4.5 Hz, 1H), 3.91 (ddd, *J* = 2.0, 4.0, 7.0 Hz, 1H), 4.12-4.19 (m, 1H), 4.42 (d, *J* = 11.5 Hz, 1H), 4.44 (d, *J* = 11.2 Hz, 1H), 4.45 (d, *J* = 11.5 Hz, 1H), 4.55 (d, *J* = 11.2 Hz, 1H), 6.86-6.90 (m, 2H), 7.24-7.28 (m, 2H), 7.28-7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.3, 35.5, 37.8, 38.7, 55.5, 66.8, 67.2, 71.6, 72.9, 76.1, 81.2, 87.7, 113.9(2), 127.97(2), 128.03, 128.7(2), 129.5(2),

130.7, 138.0, 159.3; ESI-HRMS calcd for $C_{24}H_{32}O_5Li$ [M + Li] 407.2410, found 407.2420. Characterization data for furan **4.16g**: R_f = 0.25 (hexanes:ethyl acetate 70:30); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (d, *J* = 6.9 Hz, 3H), 2.91 (t, *J* = 6.9 Hz, 2H), 2.95-3.06 (m, 1H), 3.67-3.73 (m, 2H), 3.69 (t, *J* = 6.9 Hz, 2H), 3.81 (s, 3H), 4.47 (s, 2H), 5.96-6.01 (m, 2H), 6.86-6.91 (m, 2H), 7.24-7.28 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.3, 29.1, 36.3, 55.4, 66.8, 72.8, 105.9, 106.5, 113.9(2), 129.5(2), 130.5, 152.1, 156.0, 159.4; ESI-HRMS calcd for $C_{17}H_{22}O_4Li$ [M + Li] 297.1678, found 297.1672.

Crucial nOe enhancements for **4.15g**:



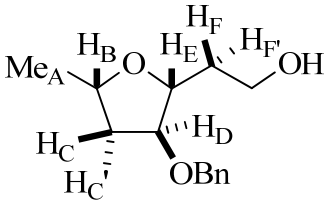
Irradiate H	Observed H	% nOe
A	F	NA
B	E	0.6
C	B	2.0
C	E	0.4
C’	D	2.5
C’	G	0.6
D	F	NA
E	B	NA
G	D	0.7
G	E	0.5



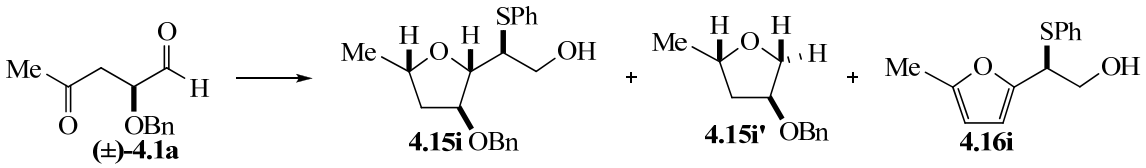
THF 4.15h was prepared according to the representative procedure for the tandem process using $ZnCl_2$ (390 mg, 2.82 mmol), ketene acetal **4.2c** (271 mg, 0.88 mmol), Et_3SiH (5.9 mL, 36.50 mmol), and aldehyde **(±)-4.1a** (150 mg, 0.73 mmol) for 12 h. Representative work-up and crude ^{1}H NMR (300 MHz) analysis revealed an indeterminate ratio of multiple THF diastereomers to furan silyl esters. Representative reduction with DIBAlH (780 μL, 4.38 mmol) and purification by gradient flash column

chromatography (hexanes:ethyl acetate 80:20 to 75:25 to 50:50) delivered the major THF **4.15h** (50 mg, 29%) as a pale yellow oil, inseparable minor THFs (39 mg, 23%) as a pale yellow oil, and furan **4.16h** as a pale yellow oil. Characterization data for THF **4.15h**: R_f = 0.55 (hexanes:ethyl acetate 60:40); IR (thin film) 3426, 3032, 1060 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.28 (d, *J* = 6.0 Hz, 3H), 1.63 (ddd, *J* = 7.0, 10.0, 13.0 Hz, 1H), 1.77 (dddd, *J* = 4.0, 4.5, 7.5, 14.0 Hz, 1H), 1.88 (dddd, *J* = 4.0, 6.0, 8.5, 14.0 Hz, 1H), 2.10 (ddd, *J* = 2.0, 5.5, 13.0 Hz, 1H), 2.70 (br s, 1H), 3.77 (ddd, *J* = 4.5, 6.0, 15.0 Hz, 1H), 3.77 (ddd, *J* = 4.0, 7.5, 15.0 Hz, 1H), 3.85 (ddd, *J* = 2.0, 4.0, 7.0 Hz, 1H), 4.02 (ddd, *J* = 4.0, 4.5, 8.5 Hz, 1H), 4.20 (ddq, *J* = 5.5, 6.0, 10.0 Hz, 1H), 4.47 (d, *J* = 11.5 Hz, 1H), 4.55 (d, *J* = 11.5 Hz, 1H), 7.28-7.39 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.0, 36.5, 39.5, 61.5, 71.7, 75.0, 84.2, 84.5, 127.9(2), 128.1, 128.7(2), 138.1; ESI-HRMS calcd for $C_{14}H_{20}O_3Li$ [M + Li] 243.1572, found 243.1568. Partial characterization data for furan **4.16h**: R_f = 0.65 (hexanes:ethyl acetate 60:40); ^1H NMR (300 MHz, $CDCl_3$) δ 2.77 (br s, 3H), 2.85 (app t, *J* = 6.0 Hz, 2H), 3.85 (app t, *J* = 6.0, 2H), 5.86-5.91 (m, 1H), 5.99 (app d, *J* = 2.7 Hz, 1H).

Crucial nOe enhancements for **4.15h**:



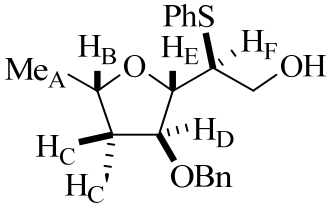
Irradiate H	Observed H	% nOe
A	C’	1.3
B	E	1.1
B	C	0.9
C	B	0.7
C’	D	1.0
C’	A	1.0
D	A	0.3
D	F	0.8
E	B	0.6
F	A	NA



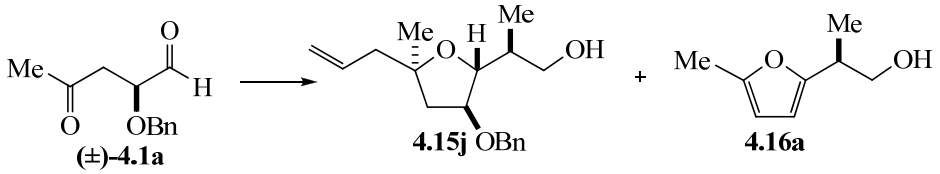
THF 4.15i was prepared according to the representative procedure for the tandem process using $ZnCl_2$ (344 mg, 2.52 mmol), ketene acetal **4.2f** (574 mg, 0.76 mmol, 55% purity), Et_3SiH (5.1 mL, 31.50 mmol), and aldehyde **(±)-4.1a** (127 mg, 0.62 mmol) for 12 h. Representative work-up and crude ^1H NMR (300 MHz) revealed a mixture of a single diastereomer (>19:1) of THF silyl ester, furan silyl ester, and undesired THF **4.15i'**. Representative reduction with DIBAlH (674 μL, 3.78 mmol) and purification by gradient flash column chromatography (hexanes:ether 85:15 to 80:20 to 75:25 to 70:30) delivered the major THF **4.15i** (42 mg, 20%) as a pale yellow oil, undesired THF **4.15i'** (29 mg, 25%) as a colorless oil, and furan **4.16i** as a pale yellow oil. Characterization data for THF **4.15i**: R_f = 0.44 (hexanes:ethyl acetate 70:30); IR (thin film) 3434, 3063, 3029, 1085 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 1.16 (d, *J* = 6.0 Hz, 3H), 1.54 (ddd, *J* = 6.5, 10.0, 13.0 Hz, 1H), 1.85 (ddd, *J* = 1.5, 5.0, 13.0 Hz, 1H), 1.85 (br s, 1H), 3.33 (ddd, *J* = 3.0, 5.5, 8.0 Hz, 1H), 3.75-3.89 (m, 2H), 4.12 (ddq, *J* = 5.0, 6.0, 10.0 Hz, 1H), 4.19 (ddd, *J* = 1.5, 3.0, 6.5 Hz, 1H), 4.21 (d, *J* = 12.0 Hz, 1H), 4.29 (d, *J* = 12.0 Hz, 1H), 4.29 (dd, *J* = 3.0, 3.0 Hz, 1H), 6.89-7.30 (m, 10H); ^{13}C NMR (125 MHz, C_6D_6) δ 20.1, 40.7, 54.8, 63.9, 71.2, 75.2, 82.8, 85.2, 126.7, 127.7, 127.9(2), 128.6(2), 129.2(2), 131.2(2), 136.6, 138.9; ESI-HRMS calcd for $C_{20}H_{24}O_3SLi$ [M + Li] 351.1606, found 351.1618. Characterization data for THF **4.15i'**: R_f = 0.67 (hexanes:ethyl acetate 70:30); IR (thin film) 3029, 1099 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (d, *J* = 6.0 Hz, 3H), 1.53

(ddd, J = 6.6, 9.9, 12.9 Hz, 1H), 2.16 (ddd, J = 0.9, 5.1, 12.9 Hz, 1H), 3.81 (dd, J = 2.7, 9.6 Hz, 1H), 4.08 (dd, J = 5.1, 9.6 Hz, 1H), 4.14-4.26 (m, 2H), 4.48 (d, J = 12.0 Hz, 1H), 4.53 (d, J = 12.0 Hz, 1H), 7.34 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 40.5, 71.3, 73.2, 74.5, 80.0, 127.8(2), 127.9, 128.7(2), 138.4; ESI-HRMS calcd for $C_{12}H_{16}O_2Li$ [M + Li] 199.1310, found 199.1276. Partial characterization data for furan **4.16i**: R_f = 0.54 (hexanes:ethyl acetate 70:30); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (br s, 3H), 3.83 (dd, J = 6.6, 11.4 Hz, 1H), 3.95 (dd, J = 6.6, 11.4, 1H), 4.33 (t, J = 6.6, 1H), 5.86-5.92 (m, 1H), 6.01 (app d, J = 3.0 Hz, 1H), 7.26-7.40 (m, 5H). Unambiguous nOe enhancements could not be obtained for THF **4.15i'**.

Crucial nOe enhancements for **4.15i**:



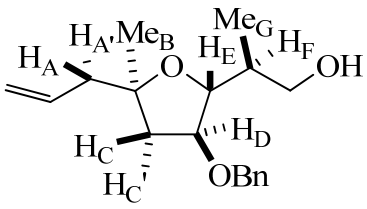
Irradiate H	Observed H	% nOe
A	C'	1.0
B	E	1.6
B	C	0.9
C	B	1.3
C	E	0.2
C'	D	1.5
C'	A	1.2
E	B	0.5
E	F	1.5
F	D	1.4
F	A	0.3



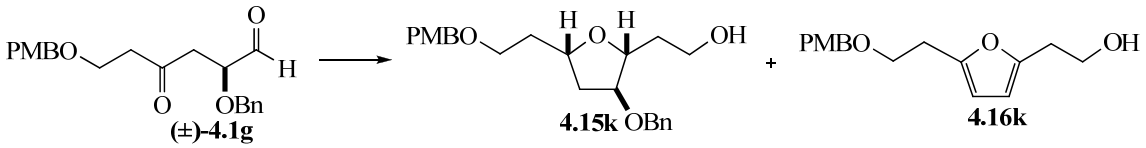
THF 4.15j was prepared according to the representative procedure for the tandem process using $ZnCl_2$ (264 mg, 1.94 mmol), ketene acetal **4.2e** (188 mg, 0.58 mmol), allyltrimethylsilane (3.8 mL, 24.25 mmol), and aldehyde **(±)-4.1a** (100 mg, 0.48 mmol)

for 12 h. Representative work-up and crude ^{1}H NMR (300 MHz) analysis revealed a 1.0:1.7 ratio of a single diastereomer (>19:1) of THF to furan silyl esters. Representative reduction with DIBAlH (519 μL, 2.91 mmol) and purification by gradient flash column chromatography (hexanes:ethyl acetate 90:10 to 85:15) delivered the major THF **4.15j** (37 mg, 26%) as a colorless oil and furan **4.16a** as a pale yellow oil. Characterization data for THF **4.15j**: R_f = 0.67 (hexanes:ethyl acetate 60:40); IR (thin film) 3443, 3069, 3029, 1066 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 0.93 (d, *J* = 7.5 Hz, 3H), 1.10 (s, 3H), 1.52 (dd, *J* = 7.0, 13.0 Hz, 1H), 1.81 (dd, *J* = 4.5, 13.0 Hz, 1H), 1.78-1.85 (m, 1H), 2.32 (dd, *J* = 7.5, 13.5 Hz, 1H), 2.43 (dd, *J* = 6.5, 13.5 Hz, 1H), 3.51-3.59 (m, 2H), 3.79 (ddd, *J* = 4.5, 5.5, 7.0 Hz, 1H), 4.06 (dd, *J* = 5.0, 5.5 Hz, 1H), 4.14 (d, *J* = 12.0 Hz, 1H), 4.25 (d, *J* = 12.0 Hz, 1H), 5.01-5.01 (m, 2H), 5.77-5.86 (m, 1H), 7.07-7.25 (m, 5H); ^{13}C NMR (125 MHz, C_6D_6) δ 12.3, 26.9, 38.8, 42.5, 45.1, 66.4, 71.7, 81.8, 82.0, 85.8, 117.7, 127.86(2), 127.91, 128.6(2), 135.1, 138.6; ESI-HRMS calcd for $C_{18}H_{26}O_3Li$ [M + Li] 297.2042, found 297.2085.

Crucial nOe enhancements for **4.15j**:

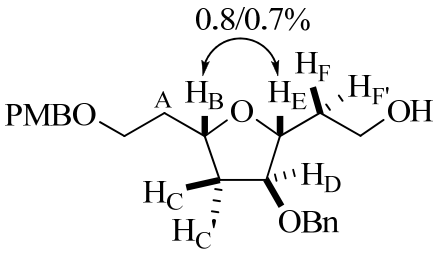


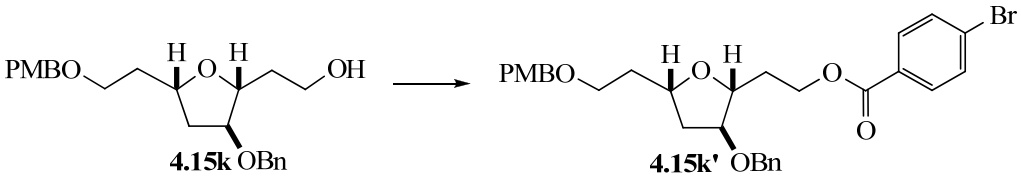
Irradiate H	Observed H	% nOe
A	B	1.0
A	E	0.7
A’	B	1.1
A’	E	0.9
B	D	0.5
B	C’	1.4
D	B	0.5
D	G	1.0
E	A	0.6
G	B	0.4



THF 4.15k was prepared according to the representative procedure for the tandem process using $ZnCl_2$ (466 mg, 3.42mmol), ketene acetal **4.2c** (353 mg, 1.14 mmol), Et_3SiH (6.1 mL, 38.00 mmol), and aldehyde **(±)-4.1g** (270 mg, 0.76 mmol) for 12 h. Representative work-up and crude ^1H NMR (300 MHz) analysis revealed an indeterminate ratio of multiple THF diastereomers to furan silyl esters. Representative reduction with DIBAlH (813 μL, 4.56 mmol) with slow warming from -78 °C to -30 °C to prevent PMB deprotection and purification by gradient flash column chromatography (hexanes:ethyl acetate 80:20 to 70:30 to 60:40 to 30:70) delivered the major THF **4.15k** (67 mg, 23%) as a pale yellow oil, inseparable minor THFs (56 mg, 19%) as a pale yellow oil, and furan **4.16k** as a pale yellow oil. Characterization data for THF **4.15k**: R_f = 0.42 (hexanes:ethyl acetate 50:50); IR (thin film) 3443, 3029, 1094 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.70 (ddd, *J* = 7.0, 9.5, 13.0 Hz, 1H), 1.71-1.93 (m, 4H), 2.10 (ddd, *J* = 2.0, 5.5, 13.0 Hz, 1H), 2.72 (br s, 1H), 3.51-3.58 (m, 2H), 3.76-3.86 (m, 2H), 3.81 (s, 3H), 3.83 (ddd, *J* = 2.0, 4.0, 7.0 Hz, 1H), 4.01 (ddd, *J* = 4.0, 4.5, 8.5 Hz, 1H), 4.17-4.25 (m, 1H), 4.42 (d, *J* = 11.5 Hz, 1H), 4.45 (d, *J* = 11.5 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 6.86-6.92 (m, 2H), 7.24-7.28 (m, 2H), 7.27-7.39 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.9, 36.3, 38.1, 55.5, 61.5, 67.2, 71.6, 72.9, 76.6, 83.7, 84.3, 113.9(2), 127.9(2), 128.0, 128.7(2), 129.5(2), 130.6, 138.1, 159.3; ESI-HRMS calcd for $C_{23}H_{30}O_5Li$ [M + Li] 387.2171, found 387.2165. Partial characterization data for furan **4.15k**: R_f = 0.62 (hexanes:ethyl acetate 50:50); ^1H NMR (300 MHz, $CDCl_3$) δ 2.86 (t, *J*

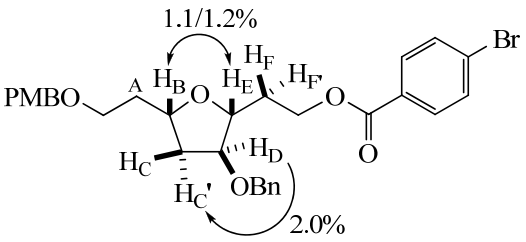
= 6.3 Hz, 2H), 2.91 (t, *J* = 6.9 Hz, 2H), 3.69 (t, *J* = 6.9 Hz, 2H), 3.75-3.90 (m, 2H), 3.82 (s, 3H), 4.48 (s, 2H), 5.98 (app d, *J* = 3.0 Hz, 1H), 6.01 (app d, *J* = 3.0 Hz, 1H), 6.84-6.93 (m, 2H), 7.22-7.30 (m, 2H). Crucial nOe enhancements for **4.15k**:

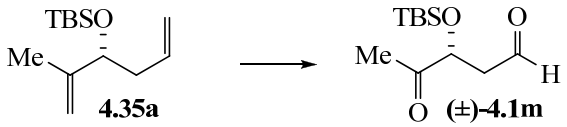




THF 4.15k': To a solution of THF **4.15k** in CH_2Cl_2 (500 μL) was added Et_3N (11 μL, 0.08 mmol), DMAP (3 mg, 0.03 mmol), and 4-bromobenzoyl chloride (6 mg, 0.03 mmol) at 23 °C and stirred for 3 h. The reaction was quenched with sat. aq. NH_4Cl (1 mL), stirred vigorously for 15 min, and diluted with ether (20 mL). The organic layer was separated from the aqueous layer and washed with additional sat. aq. NH_4Cl (2 x 5 mL), water (2 x 5 mL), and brine (2 x 5 mL). The resulting solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:ethyl acetate 90:10) delivered THF **4.15k'** (9 mg, 60%) as a colorless oil. Slow evaporation with hexanes:ether (1:1) over 24 h delivered THF **4.15k'** as colorless oil: R_f = 0.21 (hexanes:ethyl acetate 80:20); IR (thin film) 3032, 1719, 1099 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.66 (ddd, *J* = 7.0, 10.0, 13.0 Hz, 1H), 1.80-2.08 (m, 4H), 2.11 (ddd, *J* = 2.0, 5.5, 13.0 Hz, 1H), 3.50-3.60 (m, 2H), 3.80 (s, 3H), 3.85

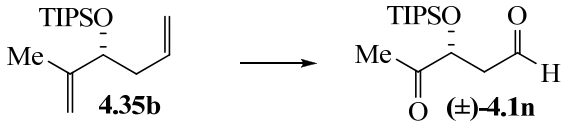
(ddd, *J* = 2.0, 3.5, 7.0, 1H), 4.02 (ddd, *J* = 3.5, 4.5, 8.0, 1H), 4.16-4.24 (m, 1H), 4.37-4.47 (m, 2H), 4.41 (d, *J* = 11.5 Hz, 1H), 4.44 (d, *J* = 11.5 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 6.86-6.90 (m, 2H), 7.24-7.26 (m, 2H), 7.26-7.38 (m, 5H), 7.54-7.60 (m, 2H), 7.86-7.92 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.8, 36.0, 38.2, 55.5, 62.6, 67.4, 71.5, 72.9, 76.2, 81.2, 83.8, 113.9(2), 127.8(2), 128.0, 128.2, 128.7(2), 129.4, 129.5(2), 130.7, 131.3(2), 131.9(2), 138.2, 159.3, 166.0; ESI-HRMS calcd for $C_{30}H_{33}BrO_6Li$ [M + Li] 575.1621/577.1600, found 575.1795/577.1785. Crucial nOe enhancements for **4.15k'**:



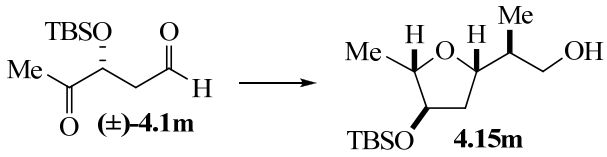


β-silyloxy-γ-ketoaldehyde (±)-4.1m was prepared according to the representative procedure for ozonolysis (Procedure B) using bis-olefin **4.35a** (1.00 g, 3.74 mmol) in CH_2Cl_2 (70 mL) and PPh_3 (1.91 g, 8.23 mmol). Purification by flash column chromatography (hexanes:ethyl acetate 85:15) delivered ketoaldehyde **(±)-4.1m** (560 mg, 55%) as a pale yellow oil: R_f = 0.63 (hexanes:ethyl acetate 60:40); IR (thin film) 2732, 1723, 1114 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.10 (s, 3H), 0.13 (s, 3H), 0.92 (s, 9H), 2.28 (s, 3H), 2.78 (m, 2H), 4.48 (dd, *J* = 5.4, 5.7 Hz, 1H), 9.74 (dd, *J* = 1.5, 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.0, -4.9, 17.9, 25.6(3), 26.0, 48.0, 73.9, 198.8,

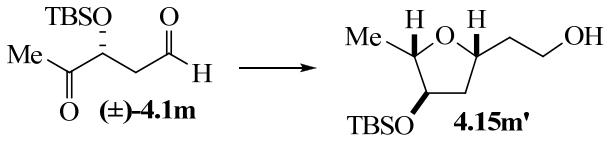
210.4; ESI-HRMS calcd for $C_{11}H_{23}O_3Si$ [M + H] 231.1416, found 231.1439. An alternative procedure could be utilized according to the general procedure for Swern oxidation using oxalyl chloride (1.5 mL, 16.84 mmol) in CH_2Cl_2 (20 mL), DMSO (2.4 mL, 33.68 mmol), the corresponding diols (987 mg, 4.21 mmol) in CH_2Cl_2 (20 mL), and Et_3N (9.4 mL, 67.36 mmol). Representative work-up with water (3 x 20 mL) and brine (3 x 20 mL) then purification by flash column chromatography (hexanes:ethyl acetate 90:10) delivered ketoaldehyde **(±)-4.1m** (485 mg, 50%) as a pale yellow oil.



β-silyloxy-γ-ketoaldehyde (±)-4.1n was prepared according to the representative procedure for ozonolysis (Procedure B) using bis-olefin **4.35b** (315 mg, 1.12 mmol) in CH_2Cl_2 (20 mL) and PPh_3 (646 mg, 2.46 mmol). Purification by flash column chromatography (hexanes:ethyl acetate 85:15) delivered ketoaldehyde **(±)-4.1n** (160 mg, 50%) as a pale yellow oil: R_f = 0.50 (hexanes:ethyl acetate 70:30); IR (thin film) 2727, 1719, 1122 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 0.93-0.96 (s, 21H), 1.99 (s, 3H), 2.27 (ddd, *J* = 1.8, 6.0, 16.5 Hz, 1H), 2.36 (ddd, *J* = 1.5, 5.4, 16.5 Hz, 1H), 4.37 (dd, *J* = 5.4, 6.0 Hz, 1H), 9.33 (dd, *J* = 1.5, 1.8 Hz, 1H); ^{13}C NMR (75 MHz, C_6D_6) δ 12.5(3), 18.0(3), 18.1(3), 25.6, 48.6, 74.9, 197.7, 208.7; ESI-HRMS calcd for $C_{14}H_{29}O_3Si$ [M + H] 273.1886, found 273.1953.

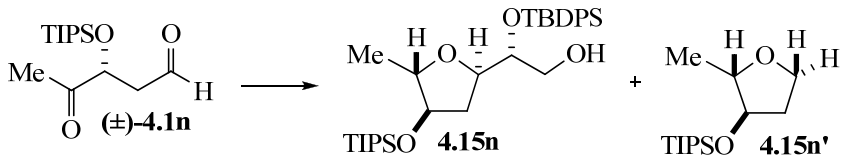


THF 4.15m was prepared according to the representative procedure for the tandem process using $ZnCl_2$ (279 mg, 2.05 mmol), ketene acetal **4.2e** (190 mg, 0.59 mmol, dr >19:1), Et_3SiH (4.1 mL, 25.60 mmol), and ketoaldehyde **(±)-4.1m** (120 mg, 0.52 mmol) for 24 h. Representative work-up and crude ^1H NMR (300 MHz) analysis revealed a 9:1 ratio of THF silyl esters. Representative reduction with DIBAlH (548 μL, 3.07 mmol) and purification by gradient flash column chromatography (hexanes:ethyl acetate 90:10 to 85:15) delivered THF **4.15m** (33 mg, 23%, dr 9:1) as a pale yellow oil: R_f = 0.30 (hexanes:ethyl acetate 70:30); IR (thin film) 3420, 1129 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ -0.01 (s, 3H), 0.00 (s, 3H), 0.82 (d, *J* = 7.0 Hz, 3H), 0.93 (s, 9H), 1.09 (d, *J* = 6.5, 3H), 1.59 (ddd, *J* = 3.5, 6.5, 13.0 Hz, 1H), 1.69 (ddd, *J* = 7.0, 9.5, 13.0 Hz, 1H), 1.77 (m, 1H), 1.99 (br s, 1H), 3.44-3.56 (m, 2H), 3.69 (dq, *J* = 6.5, 6.5 Hz, 1H), 3.79 (ddd, *J* = 3.5, 6.5, 7.0 Hz, 1H), 4.15 (ddd, *J* = 5.0, 6.5, 9.5 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ -4.7, -4.6, 12.1, 18.2, 19.1, 25.9(3), 37.7, 38.8, 66.0, 78.4, 81.1, 82.4; ESI-HRMS calcd for $C_{14}H_{30}O_3SiLi$ [M + Li] 281.2124, found 281.2095.



THF 4.1m' was prepared according to the representative procedure for the tandem process using $ZnCl_2$ (260 mg, 1.91 mmol), ketene acetal **2c** (174 mg, 0.57 mmol), Et_3SiH (3.9 mL, 23.85 mmol), and ketoaldehyde **(±)-4.1m** (110 mg, 0.48 mmol) for 24

h. Representative work-up and crude ^{1}H NMR (300 MHz) analysis revealed a 2:1 ratio of THF silyl esters. Representative reduction with DIBAlH (510 μL, 2.86 mmol) and purification by gradient flash column chromatography (hexanes:ethyl acetate 90:10 to 85:15) delivered THF **4.15m** (19 mg, 15%) and THF **4.15m''** (10 mg, 8%) as pale yellow oils. Characterization for the major diastereomer THF **4.15m'**: R_f = 0.35 (hexanes:ethyl acetate 70:30); IR (thin film) 3420, 1116 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ -0.024 (s, 3H), -0.019 (s, 3H), 0.92 (s, 9H), 1.07 (d, *J* = 6.5, 3H), 1.48 (ddd, *J* = 6.5, 9.0, 12.5 Hz, 1H), 1.52-1.61 (m, 2H), 1.64 (ddd, *J* = 3.0, 6.0, 12.5 Hz, 1H), 2.24 (br s, 1H), 3.65-3.68 (m, 3H), 3.75-3.80 (m, 1H), 4.11-4.16 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ -4.8, -4.6, 18.1, 19.4, 25.9(3), 38.3, 41.6, 61.2, 77.9, 78.3, 82.9; ESI-HRMS calcd for $C_{13}H_{28}O_3SiLi$ [M + Li] 267.1968, found 267.1960.



THF 4.15n was prepared according to the representative procedure for the tandem process using $ZnCl_2$ (522 mg, 3.83 mmol), ketene acetal **4.2g** (648 mg, 1.15 mmol), Et_3SiH (7.7 mL, 47.90 mmol), and ketoaldehyde **(±)-4.1n** (260 mg, 0.96 mmol) for 24 h. Representative work-up and crude ^{1}H NMR (300 MHz) analysis revealed a 5:1 ratio of THF silyl esters and undesired THF **4.15n'**. Representative reduction with DIBAlH (1.0 mL, 5.75 mmol) and purification by gradient flash column chromatography (hexanes:ether 99:1 to 90:10) delivered THF **4.15n** (29 mg, 5%, dr 5:1) as a pale yellow oil. Characterization data for THF **4.15n**: R_f = 0.30 (hexanes:ethyl acetate 80:20); IR (thin film) 3457, 1108 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04-1.07 (m, 21H), 1.09 (s,

9H), 1.17 (d, *J* = 6.5, 3H), 1.76 (ddd, *J* = 3.0, 6.5, 13.0 Hz, 1H), 2.12 (ddd, *J* = 6.0, 9.5, 13.0 Hz, 1H), 2.45 (dd, *J* = 5.5, 7.0 Hz, 1H), 3.54-3.67 (m, 2H), 3.80-3.86 (m, 1H), 3.85-3.90 (m, 1H), 3.98-4.02 (m, 1H), 4.24-4.30 (m, 1H), 7.35-7.74 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.3, 18.2(6), 19.7, 19.8(3), 27.3(3), 36.5, 64.3, 73.2, 77.9, 80.3, 83.3, 127.8(2), 127.9(2), 130.0(2), 133.6, 134.2, 136.0(2), 136.1(2); ESI-HRMS calcd for $C_{32}H_{52}O_4Si_2Li$ [M + Li] 563.3564, found 563.3464. Characterization data for THF **4.15n'**: R_f = 0.37 (hexanes:ethyl acetate 90:10); IR (thin film) 1127 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07-1.08 (m, 21H), 1.20 (d, *J* = 6.3, 3H), 1.80-1.88 (m, 1H), 2.03-2.15 (m, 1H), 3.78-3.86 (m, 1H), 3.87-3.98 (m, 2H), 4.01-4.06 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.3, 18.2(6), 19.5(3), 35.8, 66.8, 78.3, 82.7; CI-LRMS calcd for $C_{14}H_{31}O_2Si$ [M + H] 259, found 259.

Crystal and Molecular Structure Determination

X-ray Diffraction Laboratory
Department of Chemistry
Texas A&M University

Report:	November 28, 2007
Structure:	DRB_112707_Sii (Orig.: am-VI-309); CCDC #681175
Nattamai Bhuvanesh	(Sample from Andy Mitchell)

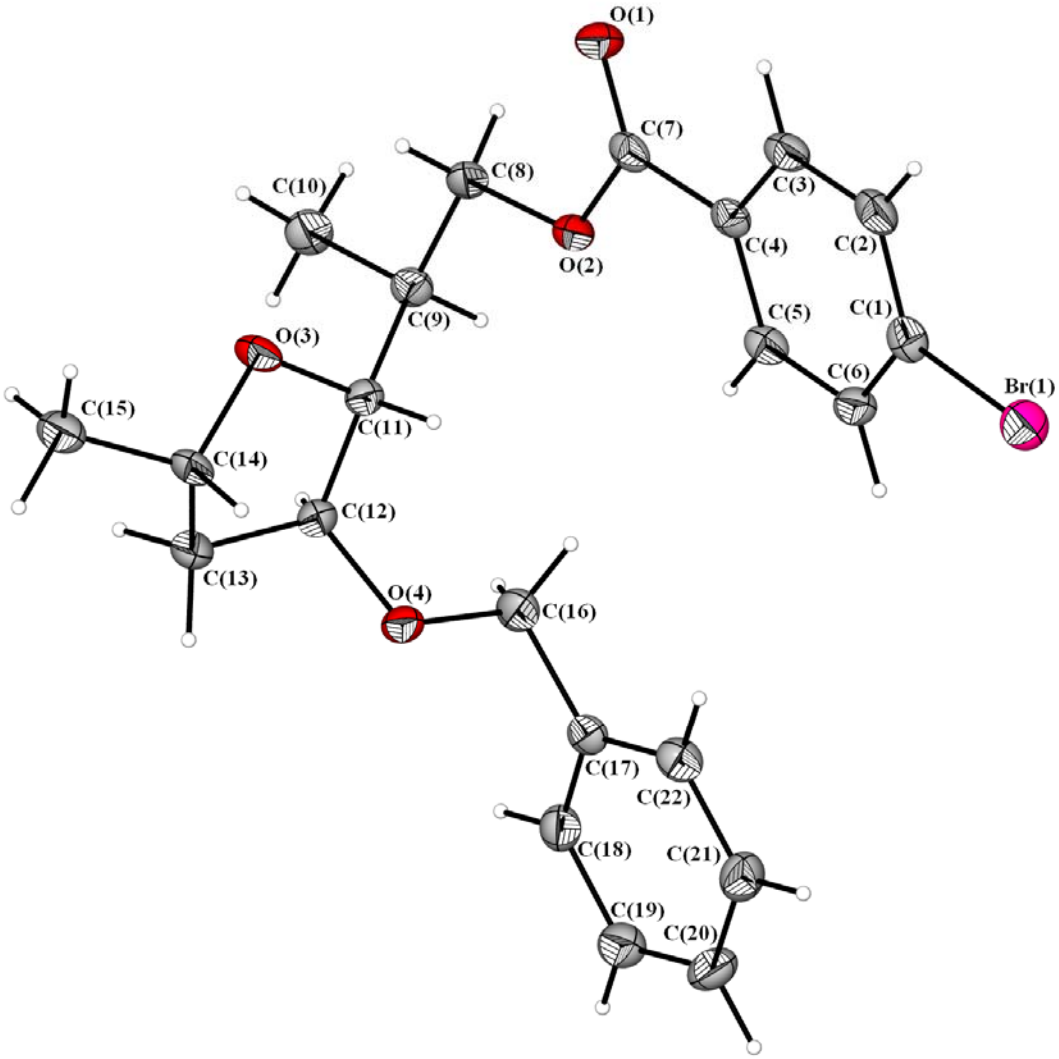

O(1)
C(7)
C(8)
C(10)
C(3)
C(4)
C(2)
O(2)
C(9)
C(5)
C(1)
O(3)
C(6)
Br(1)
C(15)
C(11)
C(14)
C(12)
C(13)
O(4)
C(16)
C(17)
C(22)
C(18)
C(21)
C(19)
C(20)

Table A.4.1. Crystal data and structure refinement for DRB1127b.

Identification code	drb1127b	
Empirical formula	C22 H25 Br O4	
Formula weight	433.33	
Temperature	110(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 18.996(16) Å	α= 90°.
	b = 5.709(5) Å	β= 115.272(9)°.
	c = 20.557(17) Å	γ = 90°.
Volume	2016(3) $Å^3$	
Z	4	
Density (calculated)	1.428 Mg/m^3	
Absorption coefficient	2.063 mm^{-1}	
F(000)	896	
Crystal size	0.50 x 0.15 x 0.10 mm^3	
Theta range for data collection	1.22 to 27.64°.	
Index ranges	-24<=h<=24, -7<=k<=7, -26<=l<=26	
Reflections collected	20029	
Independent reflections	4500 [R(int) = 0.0709]	
Completeness to theta = 27.64°	95.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8203 and 0.4252	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4500 / 0 / 246	
Goodness-of-fit on F^2	1.017	
Final R indices [I>2sigma(I)]	R1 = 0.0352, wR2 = 0.0788	
R indices (all data)	R1 = 0.0662, wR2 = 0.0934	
Largest diff. peak and hole	0.485 and -0.746 $e.Å^{-3}$	

Table A.4.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for DRB1127b. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	-2373(1)	10146(1)	1658(1)	32(1)
O(4)	1462(1)	-382(3)	2798(1)	25(1)
O(2)	620(1)	4169(3)	4217(1)	24(1)
O(3)	2449(1)	3648(3)	4170(1)	24(1)
O(1)	544(1)	7019(3)	4947(1)	28(1)
C(1)	-1577(1)	8801(4)	2501(1)	24(1)
C(4)	-383(1)	6950(4)	3709(1)	21(1)
C(5)	-665(1)	5724(4)	3057(1)	22(1)
C(11)	1812(1)	2019(4)	3902(1)	20(1)
C(18)	444(1)	-4535(5)	1786(1)	28(1)
C(6)	-1266(1)	6644(4)	2450(1)	24(1)
C(7)	297(1)	6088(4)	4362(1)	22(1)
C(17)	302(1)	-2385(4)	2039(1)	24(1)
C(9)	1623(1)	1231(4)	4521(1)	22(1)
C(16)	801(1)	-1595(5)	2795(1)	29(1)
C(13)	2763(1)	1100(5)	3452(1)	28(1)
C(20)	-602(2)	-3797(5)	628(1)	32(1)
C(14)	2765(1)	3677(4)	3643(1)	25(1)
C(22)	-304(1)	-973(5)	1578(1)	27(1)
C(3)	-718(1)	9107(4)	3748(1)	24(1)
C(8)	1322(1)	3280(4)	4809(1)	25(1)
C(19)	-3(1)	-5217(4)	1082(1)	30(1)
C(21)	-758(1)	-1671(5)	873(1)	32(1)
C(12)	2050(1)	61(4)	3510(1)	23(1)
C(2)	-1320(1)	10037(4)	3143(1)	26(1)
C(10)	2315(1)	95(4)	5145(1)	29(1)
C(15)	3557(2)	4830(4)	3962(1)	31(1)

Table A.4.3. Bond lengths [Å] and angles [°] for DRB1127b.

Br(1)-C(1)	1.908(3)
O(4)-C(16)	1.432(3)
O(4)-C(12)	1.436(3)
O(2)-C(7)	1.350(3)
O(2)-C(8)	1.461(3)
O(3)-C(11)	1.438(3)
O(3)-C(14)	1.444(2)
O(1)-C(7)	1.212(3)
C(1)-C(6)	1.389(3)
C(1)-C(2)	1.390(3)
C(4)-C(5)	1.400(3)
C(4)-C(3)	1.404(3)
C(4)-C(7)	1.494(3)
C(5)-C(6)	1.385(3)
C(5)-H(5)	0.9500
C(11)-C(9)	1.530(3)
C(11)-C(12)	1.553(3)
C(11)-H(11)	1.0000
C(18)-C(19)	1.386(3)
C(18)-C(17)	1.403(3)
C(18)-H(18)	0.9500
C(6)-H(6)	0.9500
C(17)-C(22)	1.394(3)
C(17)-C(16)	1.503(3)
C(9)-C(8)	1.528(3)
C(9)-C(10)	1.534(3)
C(9)-H(9)	1.0000
C(16)-H(16A)	0.9900
C(16)-H(16B)	0.9900
C(13)-C(14)	1.523(4)
C(13)-C(12)	1.529(3)
C(13)-H(13A)	0.9900

Table A.4.3 (continued).

C(13)-H(13B)	0.9900
C(20)-C(19)	1.383(4)
C(20)-C(21)	1.393(4)
C(20)-H(20)	0.9500
C(14)-C(15)	1.512(3)
C(14)-H(14)	1.0000
C(22)-C(21)	1.391(3)
C(22)-H(22)	0.9500
C(3)-C(2)	1.386(3)
C(3)-H(3)	0.9500
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(19)-H(19)	0.9500
C(21)-H(21)	0.9500
C(12)-H(12)	1.0000
C(2)-H(2)	0.9500
C(10)-H(10A)	0.9800
C(10)-H(10B)	0.9800
C(10)-H(10C)	0.9800
C(15)-H(15A)	0.9800
C(15)-H(15B)	0.9800
C(15)-H(15C)	0.9800
C(16)-O(4)-C(12)	112.88(17)
C(7)-O(2)-C(8)	115.93(17)
C(11)-O(3)-C(14)	105.78(16)
C(6)-C(1)-C(2)	122.2(2)
C(6)-C(1)-Br(1)	119.12(18)
C(2)-C(1)-Br(1)	118.64(19)
C(5)-C(4)-C(3)	119.7(2)
C(5)-C(4)-C(7)	121.8(2)
C(3)-C(4)-C(7)	118.4(2)
C(6)-C(5)-C(4)	120.2(2)
C(6)-C(5)-H(5)	119.9

Table A.4.3 (continued).

C(4)-C(5)-H(5)	119.9
O(3)-C(11)-C(9)	109.26(17)
O(3)-C(11)-C(12)	106.22(17)
C(9)-C(11)-C(12)	116.3(2)
O(3)-C(11)-H(11)	108.3
C(9)-C(11)-H(11)	108.3
C(12)-C(11)-H(11)	108.3
C(19)-C(18)-C(17)	120.2(2)
C(19)-C(18)-H(18)	119.9
C(17)-C(18)-H(18)	119.9
C(5)-C(6)-C(1)	118.8(2)
C(5)-C(6)-H(6)	120.6
C(1)-C(6)-H(6)	120.6
O(1)-C(7)-O(2)	123.8(2)
O(1)-C(7)-C(4)	124.6(2)
O(2)-C(7)-C(4)	111.64(19)
C(22)-C(17)-C(18)	119.2(2)
C(22)-C(17)-C(16)	120.2(2)
C(18)-C(17)-C(16)	120.6(2)
C(8)-C(9)-C(11)	110.9(2)
C(8)-C(9)-C(10)	109.16(19)
C(11)-C(9)-C(10)	113.47(19)
C(8)-C(9)-H(9)	107.7
C(11)-C(9)-H(9)	107.7
C(10)-C(9)-H(9)	107.7
O(4)-C(16)-C(17)	108.28(17)
O(4)-C(16)-H(16A)	110.0
C(17)-C(16)-H(16A)	110.0
O(4)-C(16)-H(16B)	110.0
C(17)-C(16)-H(16B)	110.0
H(16A)-C(16)-H(16B)	108.4
C(14)-C(13)-C(12)	105.04(18)
C(14)-C(13)-H(13A)	110.7

Table A.4.3 (continued).

C(12)-C(13)-H(13A)	110.7
C(14)-C(13)-H(13B)	110.7
C(12)-C(13)-H(13B)	110.7
H(13A)-C(13)-H(13B)	108.8
C(19)-C(20)-C(21)	120.5(2)
C(19)-C(20)-H(20)	119.8
C(21)-C(20)-H(20)	119.8
O(3)-C(14)-C(15)	109.56(19)
O(3)-C(14)-C(13)	103.10(18)
C(15)-C(14)-C(13)	115.2(2)
O(3)-C(14)-H(14)	109.6
C(15)-C(14)-H(14)	109.6
C(13)-C(14)-H(14)	109.6
C(21)-C(22)-C(17)	120.5(2)
C(21)-C(22)-H(22)	119.8
C(17)-C(22)-H(22)	119.8
C(2)-C(3)-C(4)	120.4(2)
C(2)-C(3)-H(3)	119.8
C(4)-C(3)-H(3)	119.8
O(2)-C(8)-C(9)	107.59(18)
O(2)-C(8)-H(8A)	110.2
C(9)-C(8)-H(8A)	110.2
O(2)-C(8)-H(8B)	110.2
C(9)-C(8)-H(8B)	110.2
H(8A)-C(8)-H(8B)	108.5
C(20)-C(19)-C(18)	120.0(2)
C(20)-C(19)-H(19)	120.0
C(18)-C(19)-H(19)	120.0
C(22)-C(21)-C(20)	119.6(2)
C(22)-C(21)-H(21)	120.2
C(20)-C(21)-H(21)	120.2
O(4)-C(12)-C(13)	108.52(18)
O(4)-C(12)-C(11)	112.49(18)

Table A.4.3 (continued).

C(13)-C(12)-C(11)	103.04(18)
O(4)-C(12)-H(12)	110.8
C(13)-C(12)-H(12)	110.8
C(11)-C(12)-H(12)	110.8
C(3)-C(2)-C(1)	118.6(2)
C(3)-C(2)-H(2)	120.7
C(1)-C(2)-H(2)	120.7
C(9)-C(10)-H(10A)	109.5
C(9)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	109.5
C(9)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5
C(14)-C(15)-H(15A)	109.5
C(14)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15B)	109.5
C(14)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15C)	109.5
H(15B)-C(15)-H(15C)	109.5

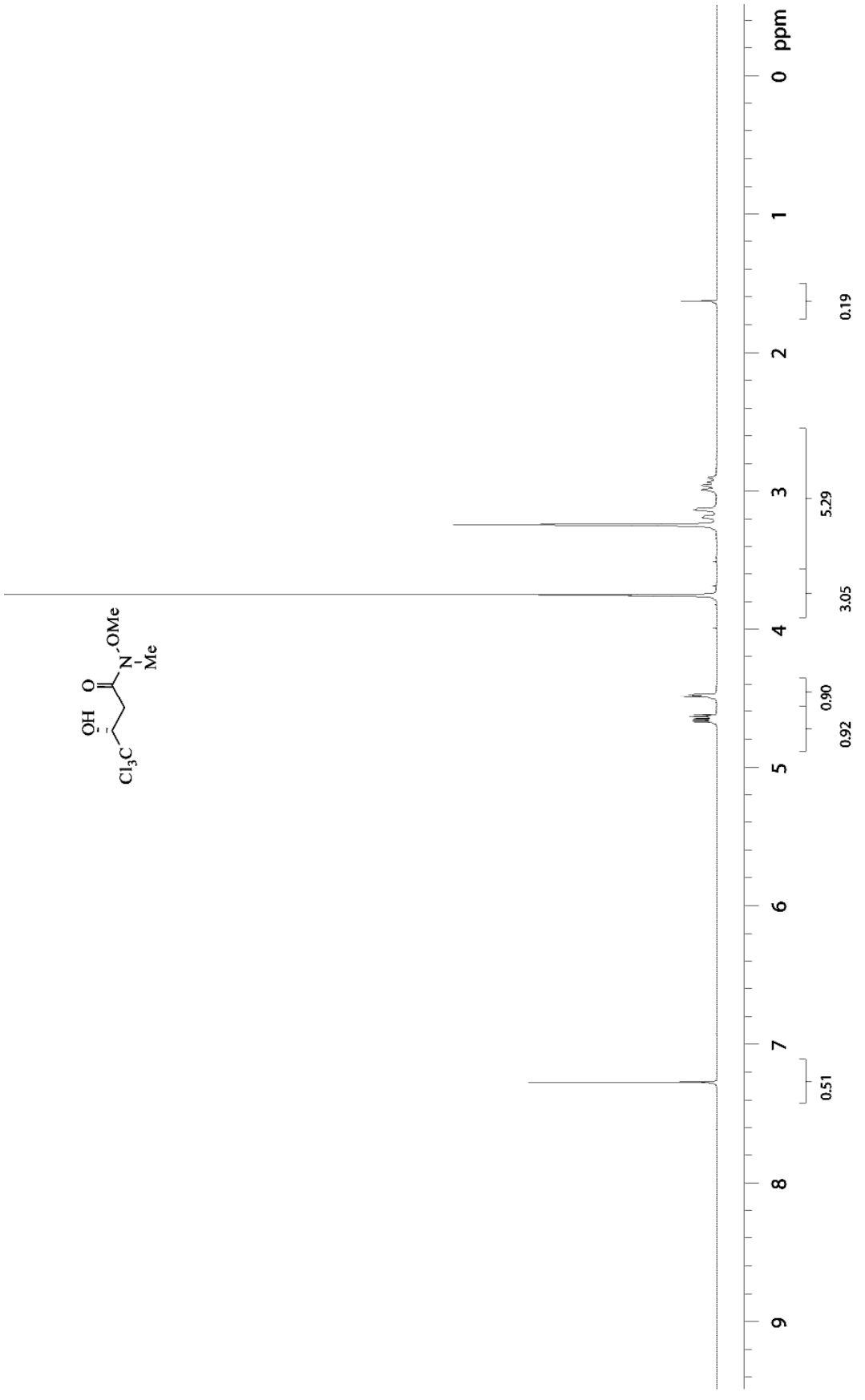
Symmetry transformations used to generate equivalent atoms:

Table A.4.4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for DRB1127b. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

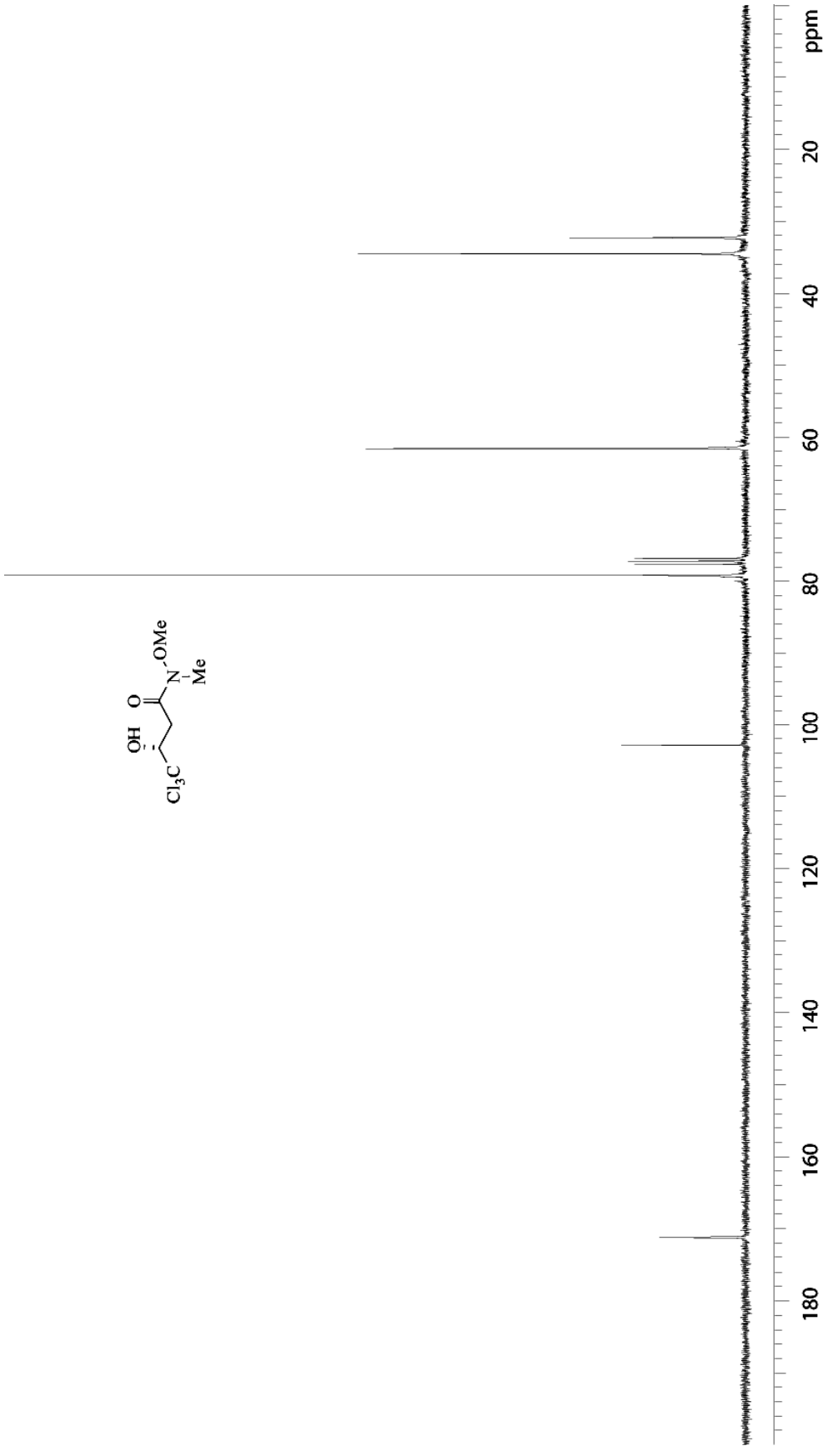
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	31(1)	34(1)	30(1)	6(1)	12(1)	6(1)
O(4)	25(1)	32(1)	19(1)	-5(1)	11(1)	-10(1)
O(2)	23(1)	29(1)	19(1)	-2(1)	9(1)	4(1)
O(3)	32(1)	24(1)	26(1)	-4(1)	20(1)	-5(1)
O(1)	32(1)	32(1)	21(1)	-5(1)	13(1)	-4(1)
C(1)	24(1)	24(1)	27(1)	4(1)	14(1)	-1(1)
C(4)	21(1)	24(1)	22(1)	1(1)	14(1)	-4(1)
C(5)	26(1)	21(1)	25(1)	-1(1)	15(1)	-1(1)
C(11)	20(1)	23(1)	18(1)	0(1)	8(1)	0(1)
C(18)	23(1)	34(2)	26(1)	4(1)	10(1)	1(1)
C(6)	26(1)	25(2)	22(1)	-3(1)	13(1)	-4(1)
C(7)	24(1)	23(1)	27(1)	-1(1)	18(1)	-5(1)
C(17)	23(1)	29(2)	23(1)	1(1)	13(1)	-6(1)
C(9)	24(1)	25(1)	20(1)	3(1)	11(1)	-1(1)
C(16)	28(1)	38(2)	25(1)	-1(1)	14(1)	-7(1)
C(13)	25(1)	35(2)	26(1)	-10(1)	13(1)	-3(1)
C(20)	32(1)	38(2)	23(1)	-4(1)	8(1)	-8(1)
C(14)	27(1)	33(2)	21(1)	1(1)	16(1)	2(1)
C(22)	30(1)	27(2)	28(1)	0(1)	15(1)	-1(1)
C(3)	29(1)	21(1)	26(1)	-3(1)	17(1)	-3(1)
C(8)	25(1)	36(2)	15(1)	3(1)	9(1)	3(1)
C(19)	32(1)	29(2)	31(1)	-4(1)	15(1)	-4(1)
C(21)	27(1)	38(2)	27(1)	5(1)	9(1)	1(1)
C(12)	22(1)	26(2)	19(1)	-2(1)	7(1)	-1(1)
C(2)	28(1)	22(2)	34(1)	1(1)	20(1)	1(1)
C(10)	31(1)	33(2)	23(1)	8(1)	11(1)	5(1)
C(15)	34(1)	32(2)	33(1)	-9(1)	20(1)	-8(1)

Table A.4.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for DRB1127b.

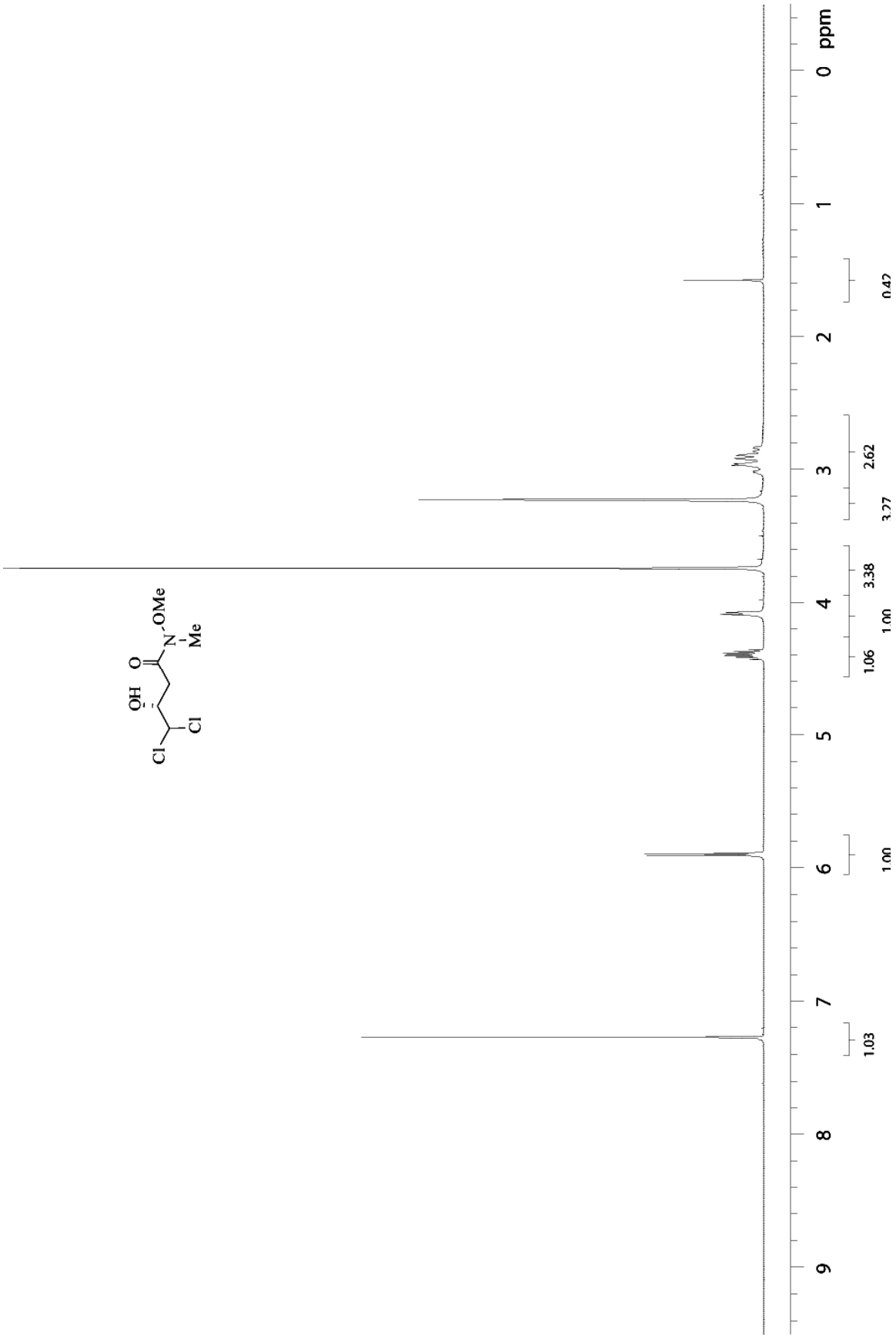
	x	y	z	U(eq)
H(5)	-443	4255	3030	27
H(11)	1345	2845	3538	24
H(18)	848	-5527	2099	33
H(6)	-1461	5816	2007	29
H(9)	1198	39	4326	27
H(16A)	500	-544	2965	35
H(16B)	974	-2966	3121	35
H(13A)	3245	318	3790	33
H(13B)	2719	924	2957	33
H(20)	-909	-4275	146	39
H(14)	2408	4570	3209	30
H(22)	-408	477	1746	32
H(3)	-530	9934	4191	28
H(8A)	1201	2749	5209	30
H(8B)	1721	4527	4992	30
H(19)	101	-6659	910	36
H(21)	-1171	-705	561	38
H(12)	2190	-1410	3802	27
H(2)	-1552	11489	3168	31
H(10A)	2724	1267	5374	43
H(10B)	2520	-1191	4960	43
H(10C)	2143	-518	5498	43
H(15A)	3511	6416	4123	46
H(15B)	3760	4913	3598	46
H(15C)	3913	3910	4374	46



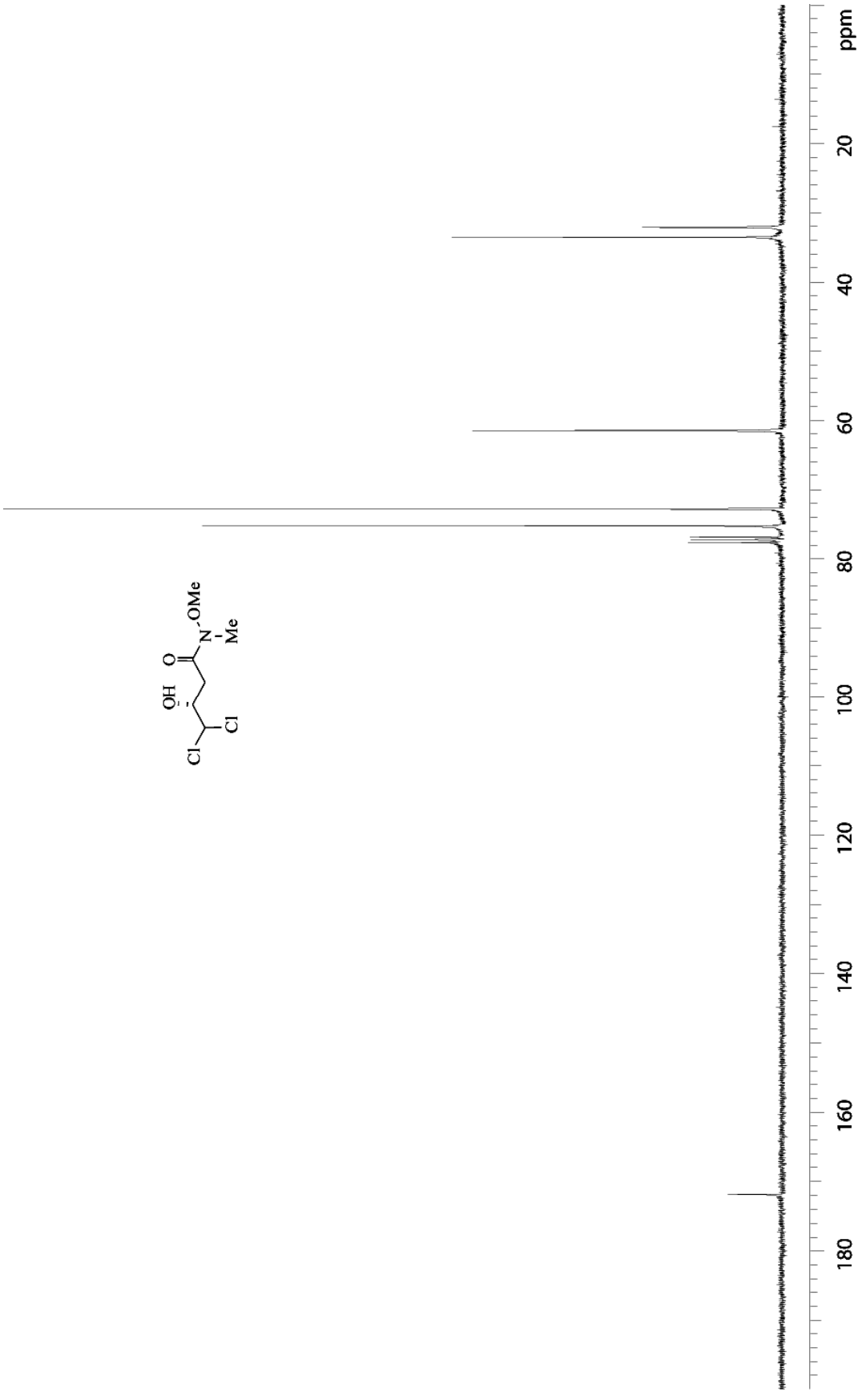
^{1}H NMR (300 MHz) of Trichloro Weinreb Amide **2.16** in $CDCl_3$



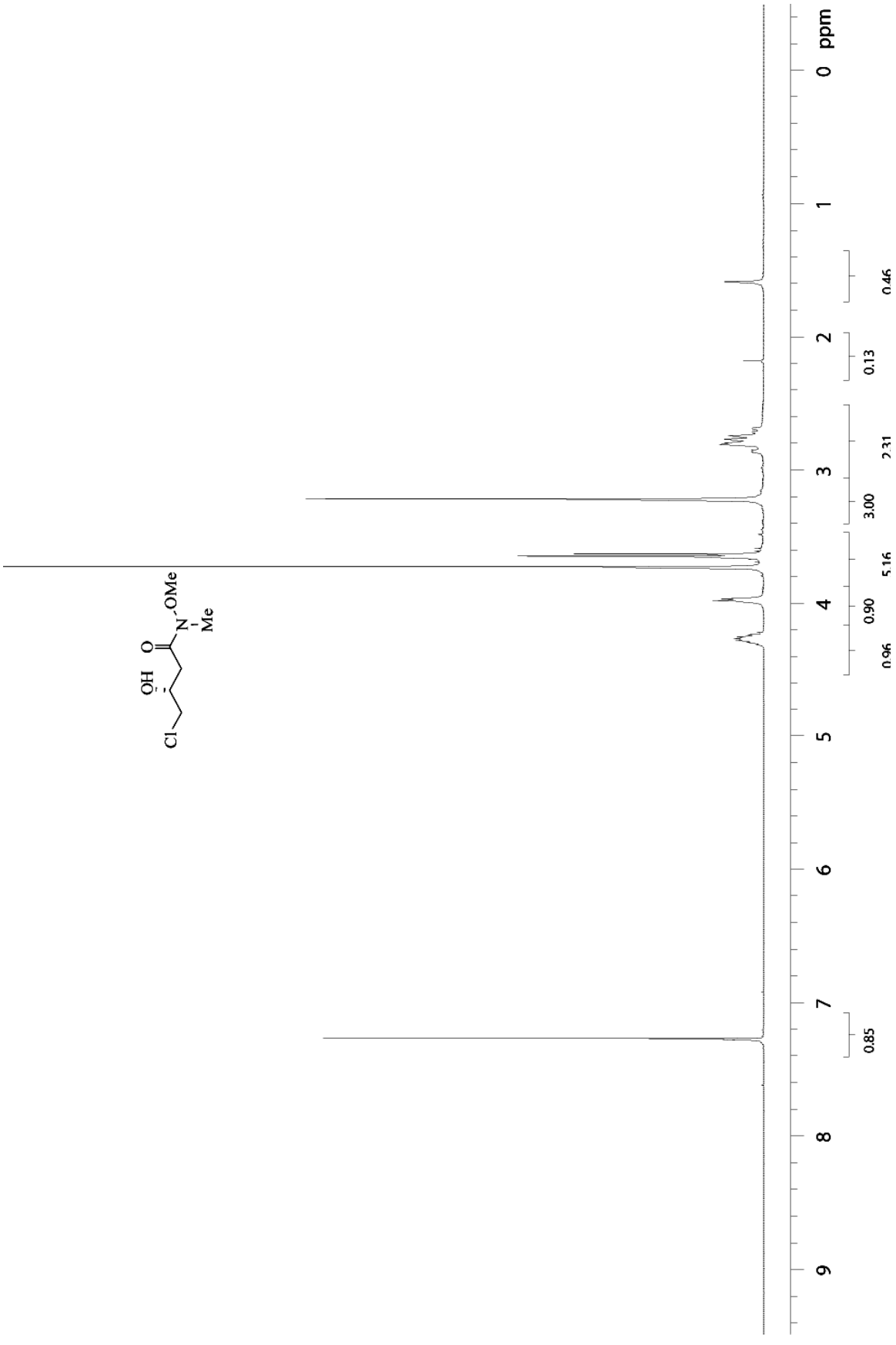
^{13}C NMR (75 MHz) of Trichloro Weinreb Amide **2.16** in $CDCl_3$



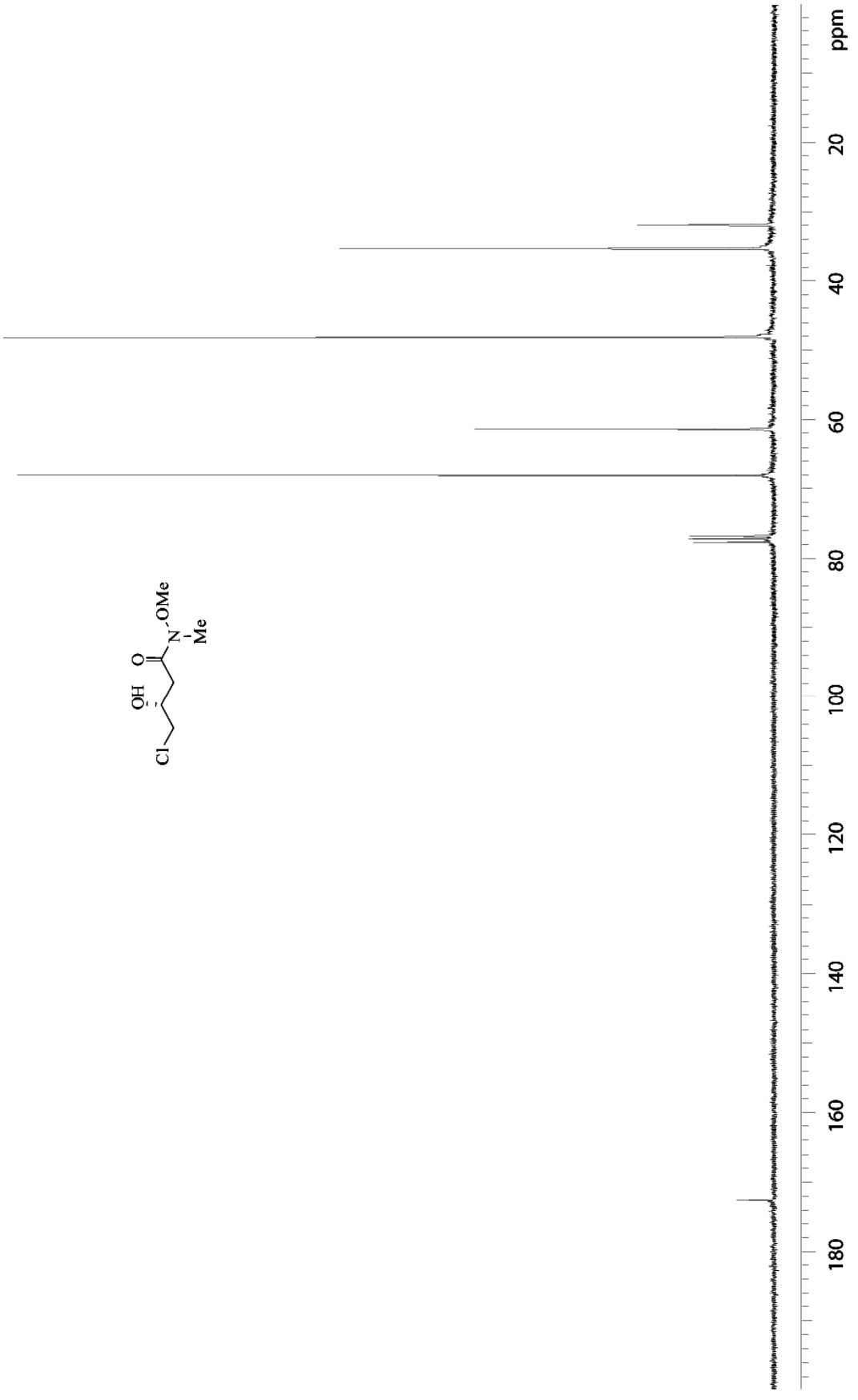
^{1}H NMR (300 MHz) of Dichloro Weinreb Amide **2.22** in $CDCl_3$



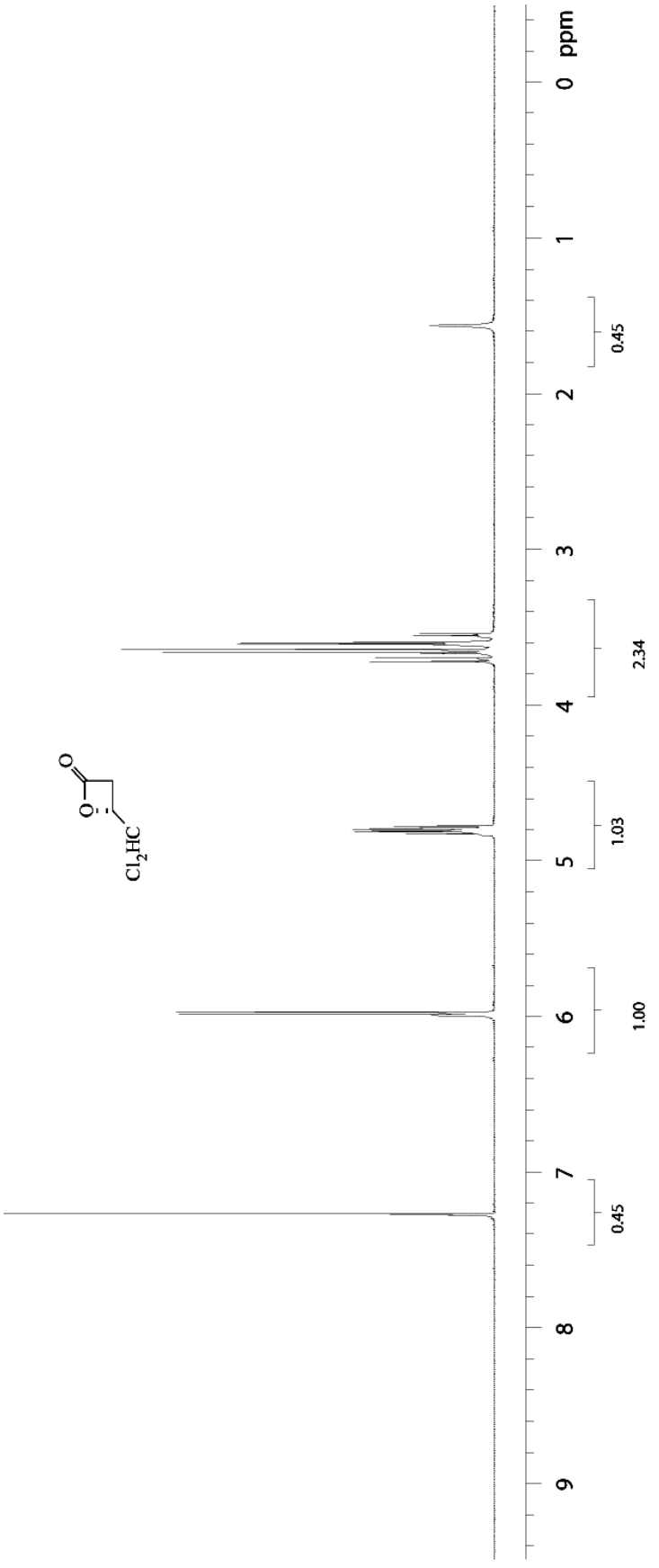
^{13}C NMR (75 MHz) of Dichloro Weinreb Amide **2.22** in $CDCl_3$



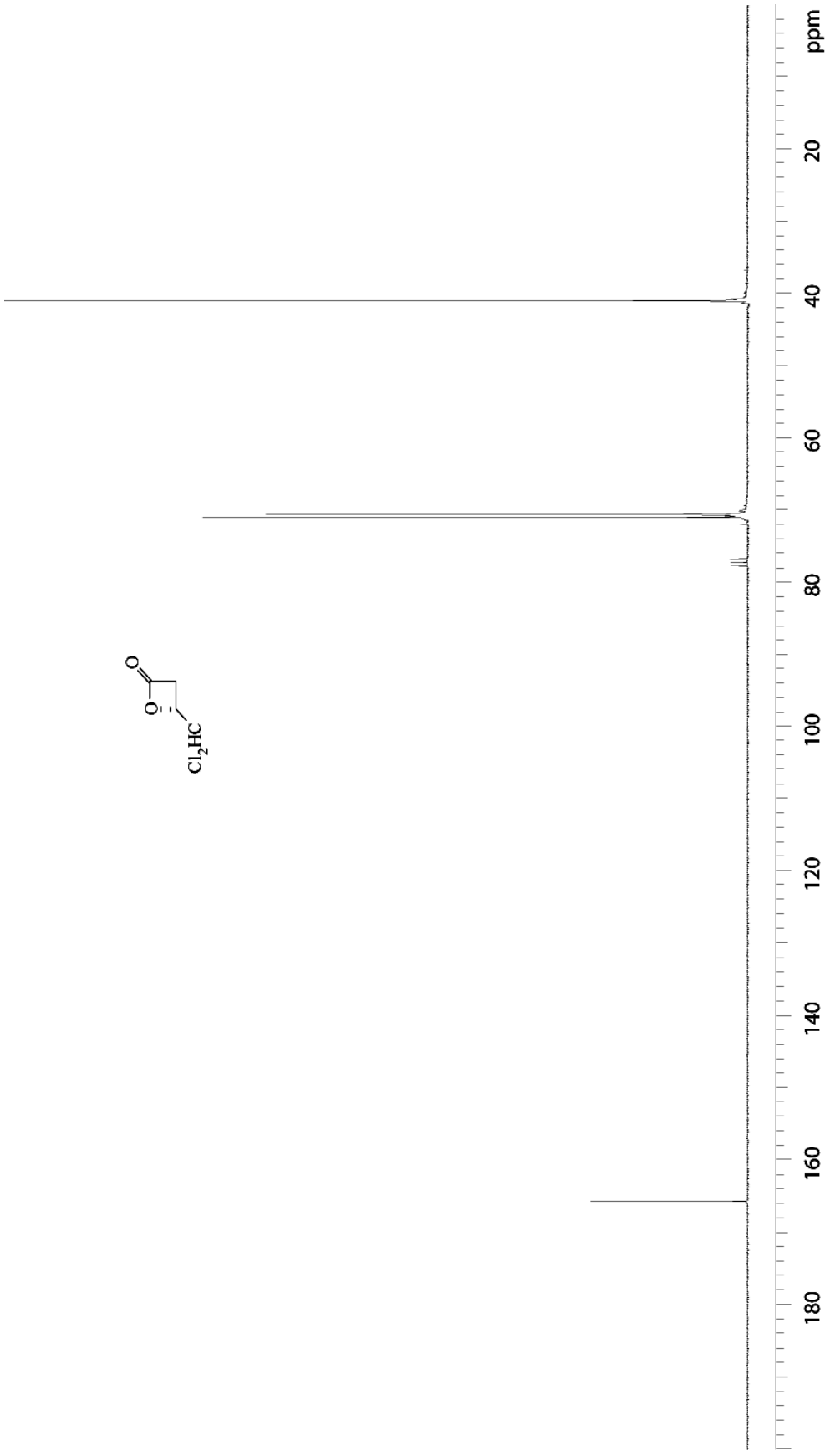
^{1}H NMR (300 MHz) of Chloro Weinreb Amide **2.23** in $CDCl_3$



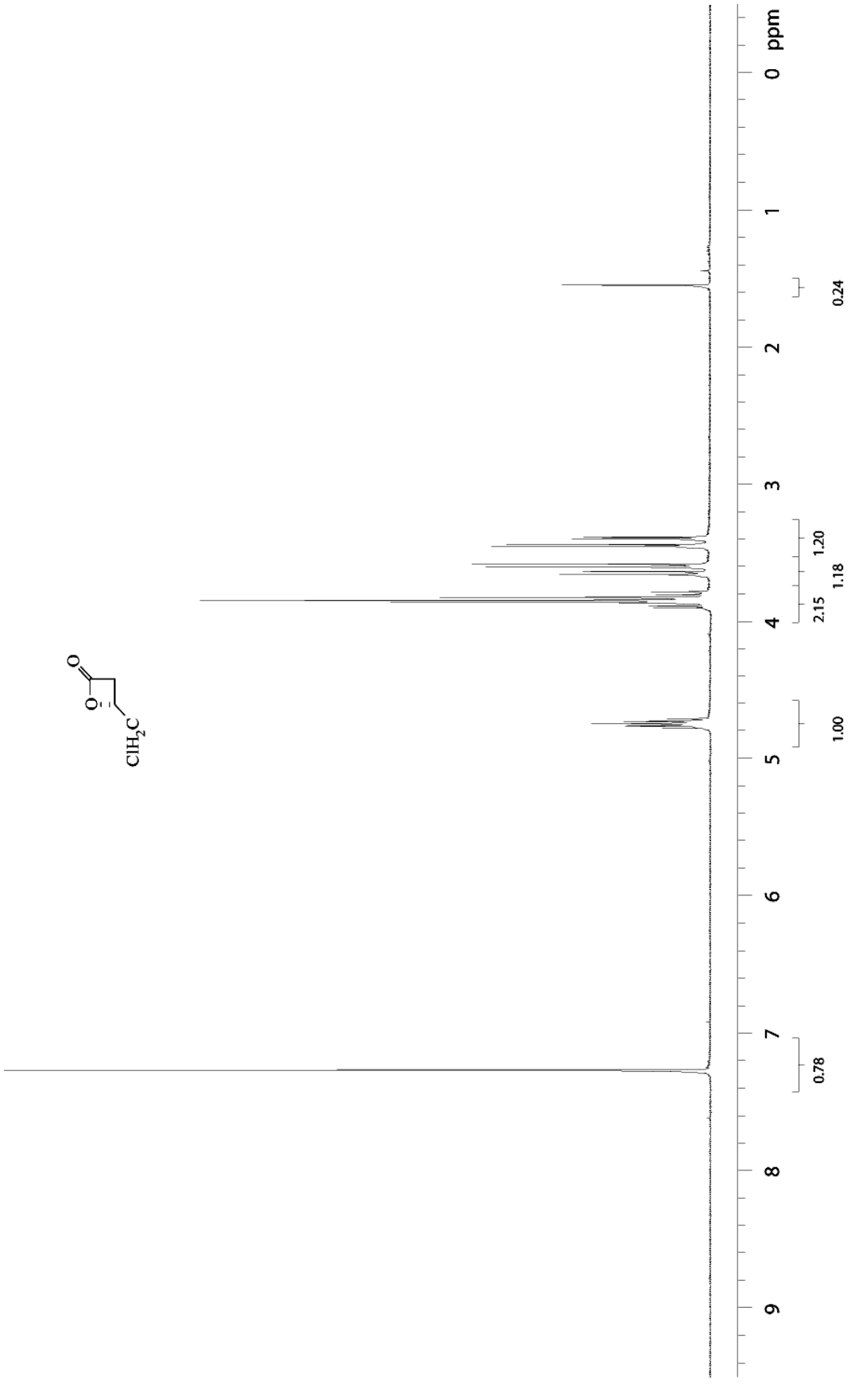
^{13}C NMR (75 MHz) of Chloro Weinreb Amide **2.23** in $CDCl_3$



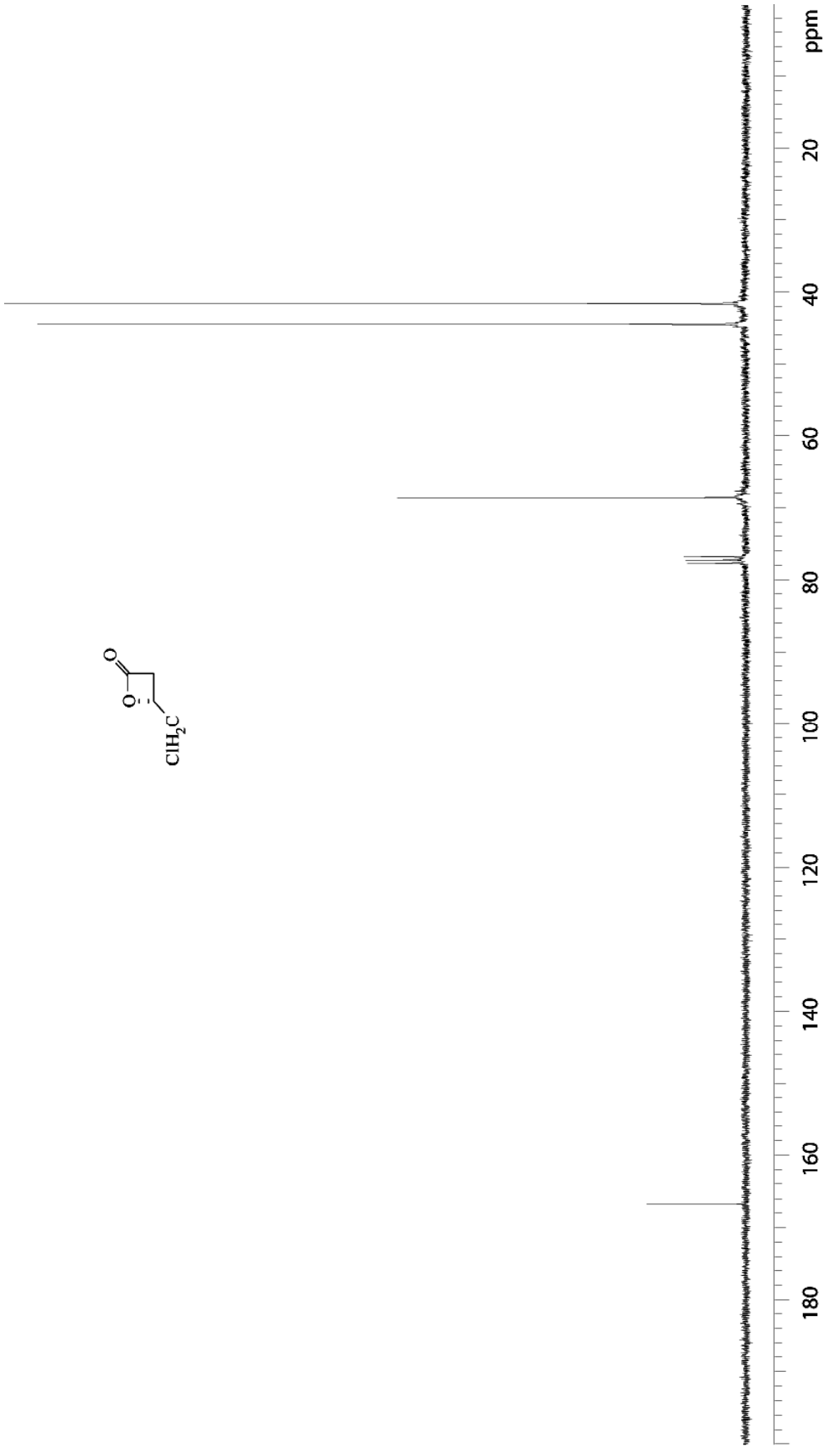
^{1}H NMR (300 MHz) of Dichloromethyl-β-Lactone **2.17a** in $CDCl_3$



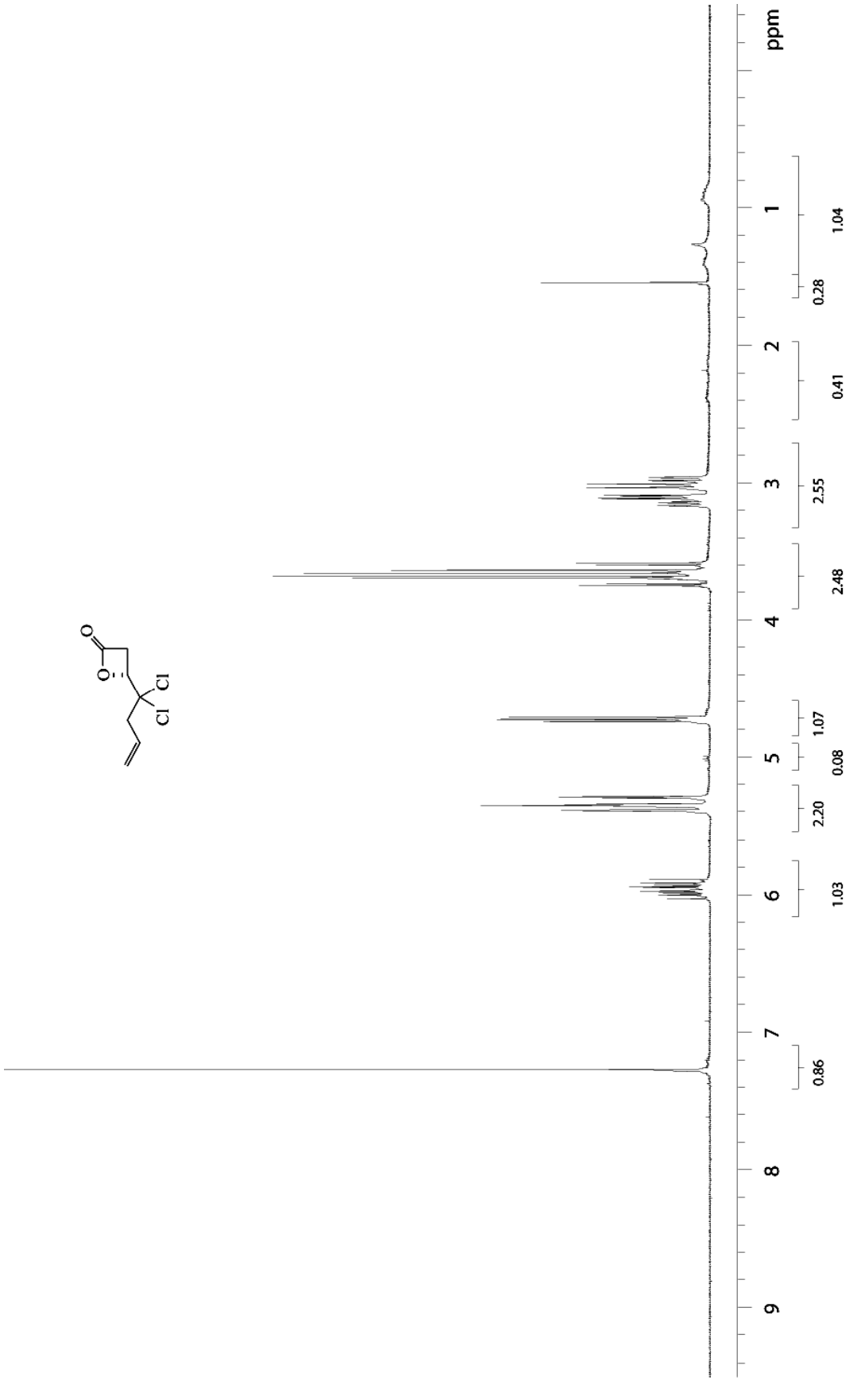
^{13}C NMR (75 MHz) of Dichloromethyl-β-Lactone **2.17a** in $CDCl_3$



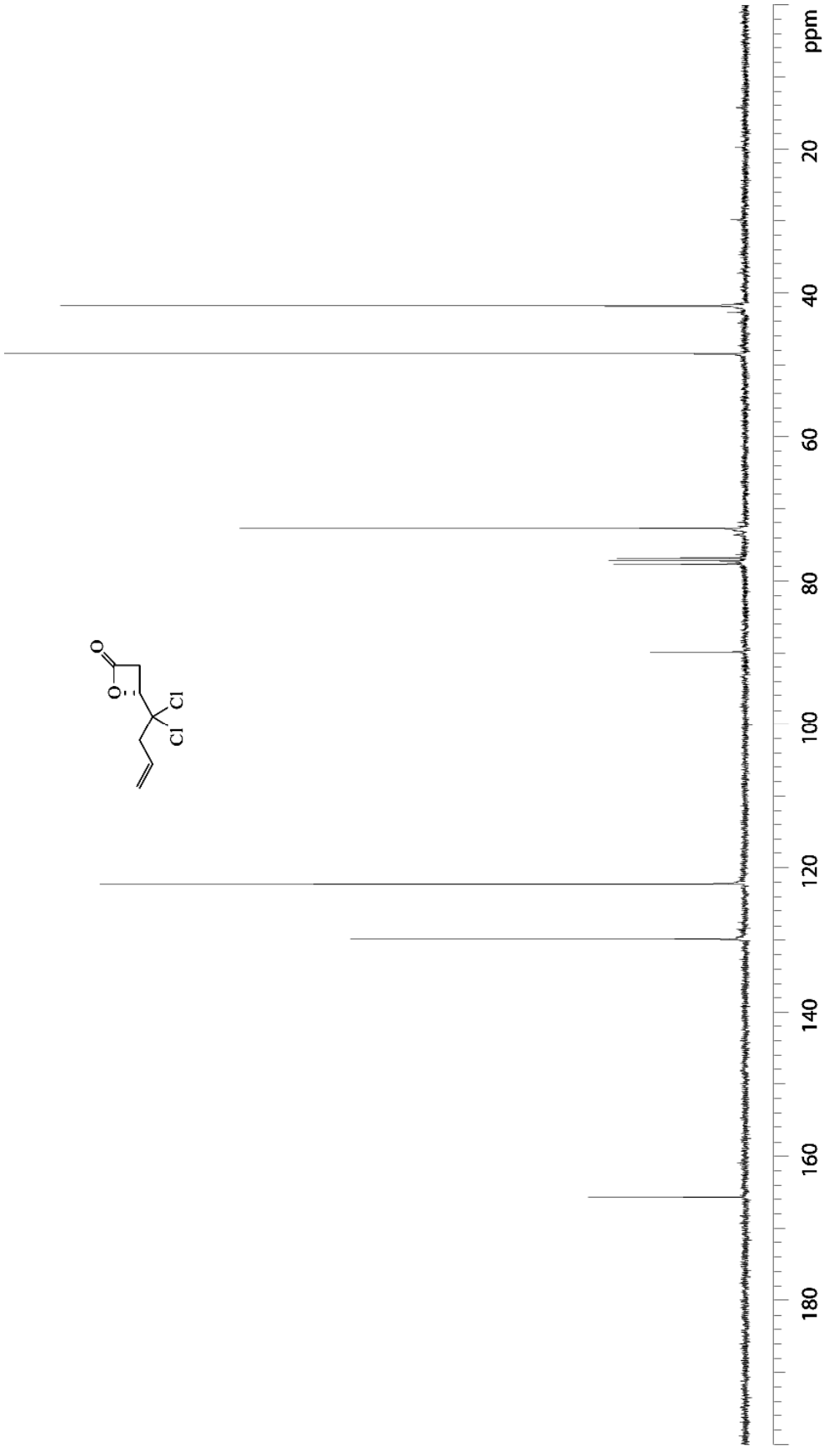
^{1}H NMR (300 MHz) of Chloromethyl-β-Lactone **2.17b** in $CDCl_3$



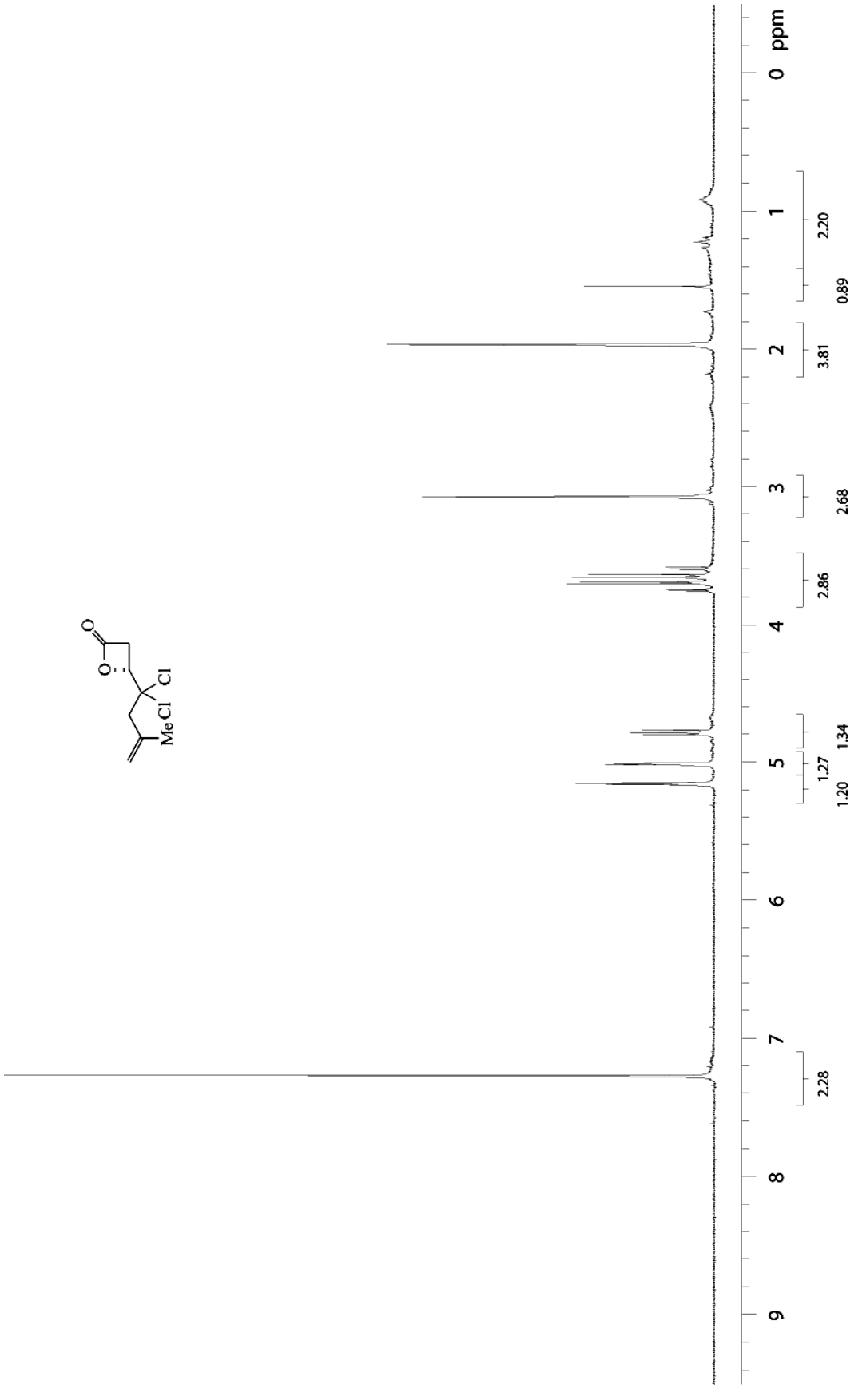
^{13}C NMR (75 MHz) of Chloromethyl-β-Lactone **2.17b** in $CDCl_3$



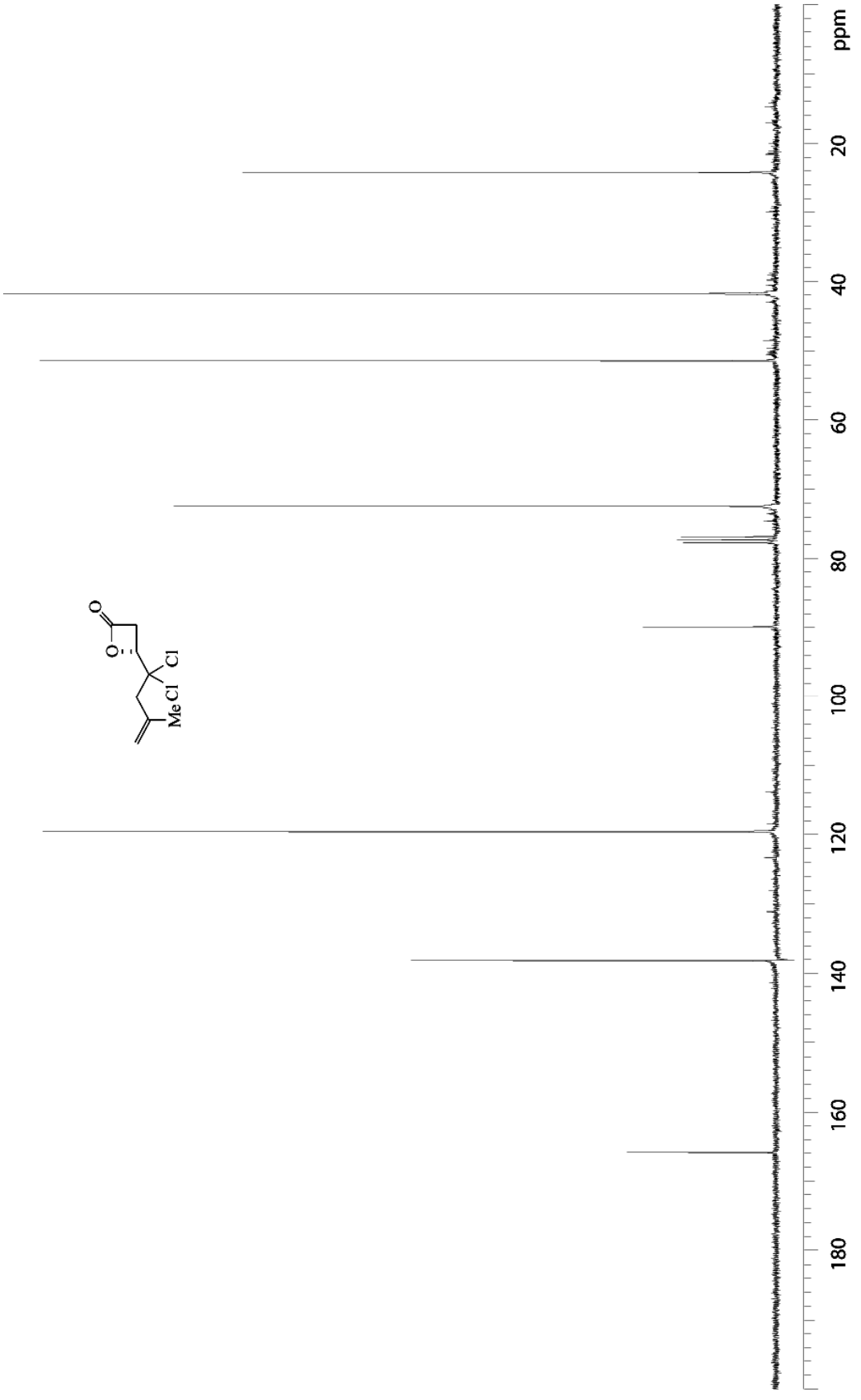
^{1}H NMR (300 MHz) of Allyl-β-Lactone **2.18a** in $CDCl_3$



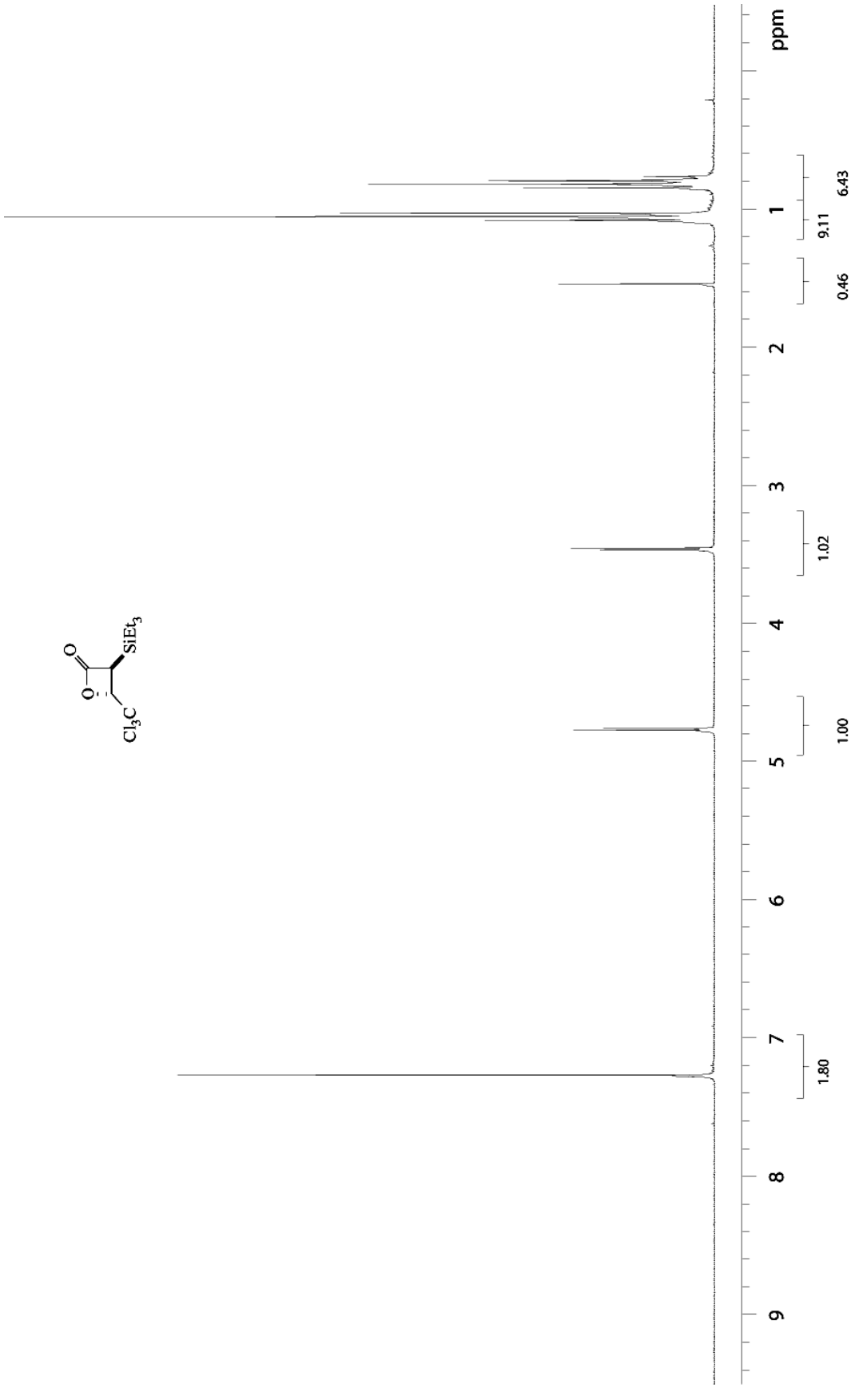
^{13}C NMR (75 MHz) of Allyl-β-Lactone **2.18a** in $CDCl_3$



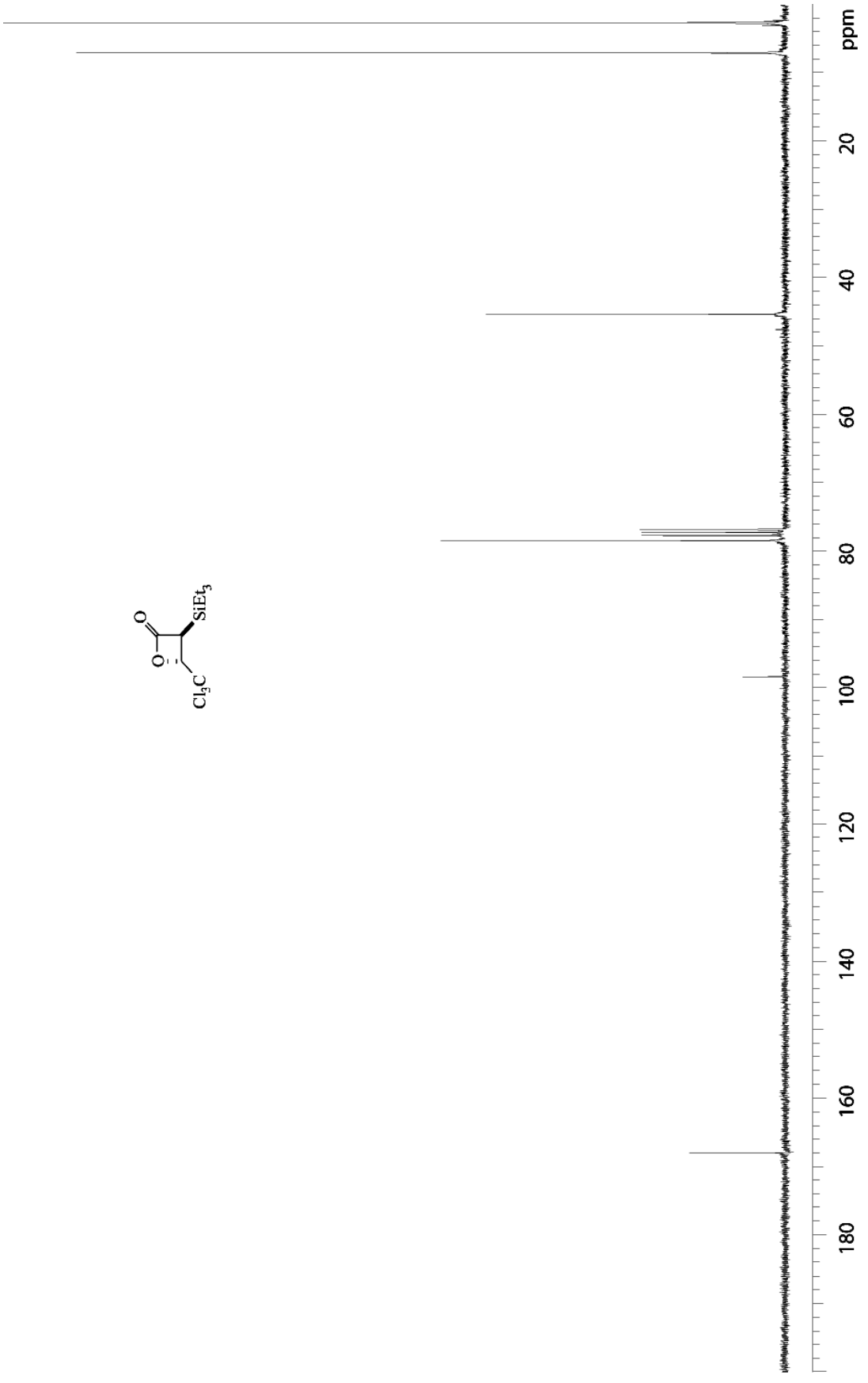
^{1}H NMR (300 MHz) of Methallyl-β-Lactone **2.18b** in $CDCl_3$



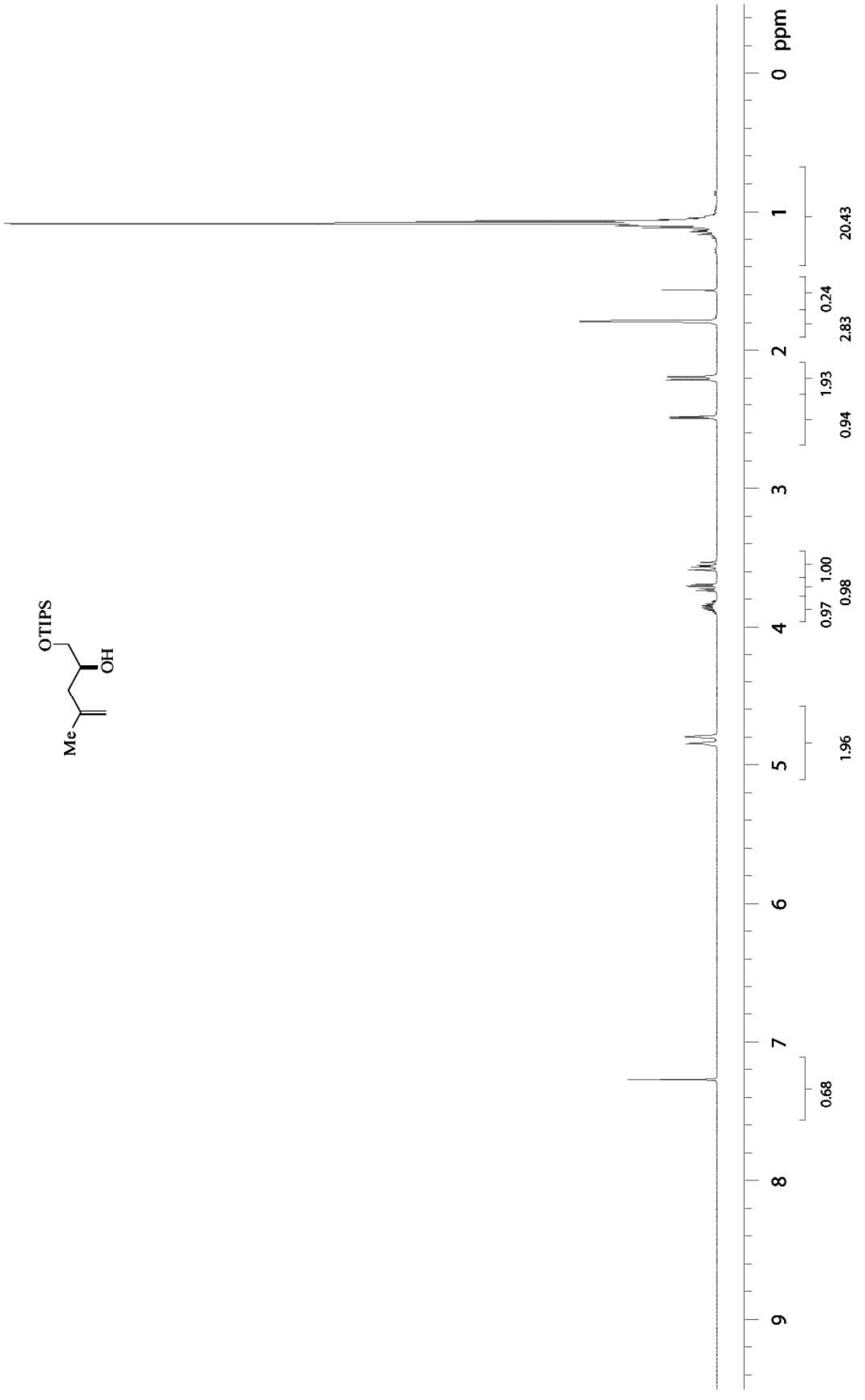
^{1}H NMR (75 MHz) of Methallyl-β-Lactone **2.18b** in $CDCl_3$



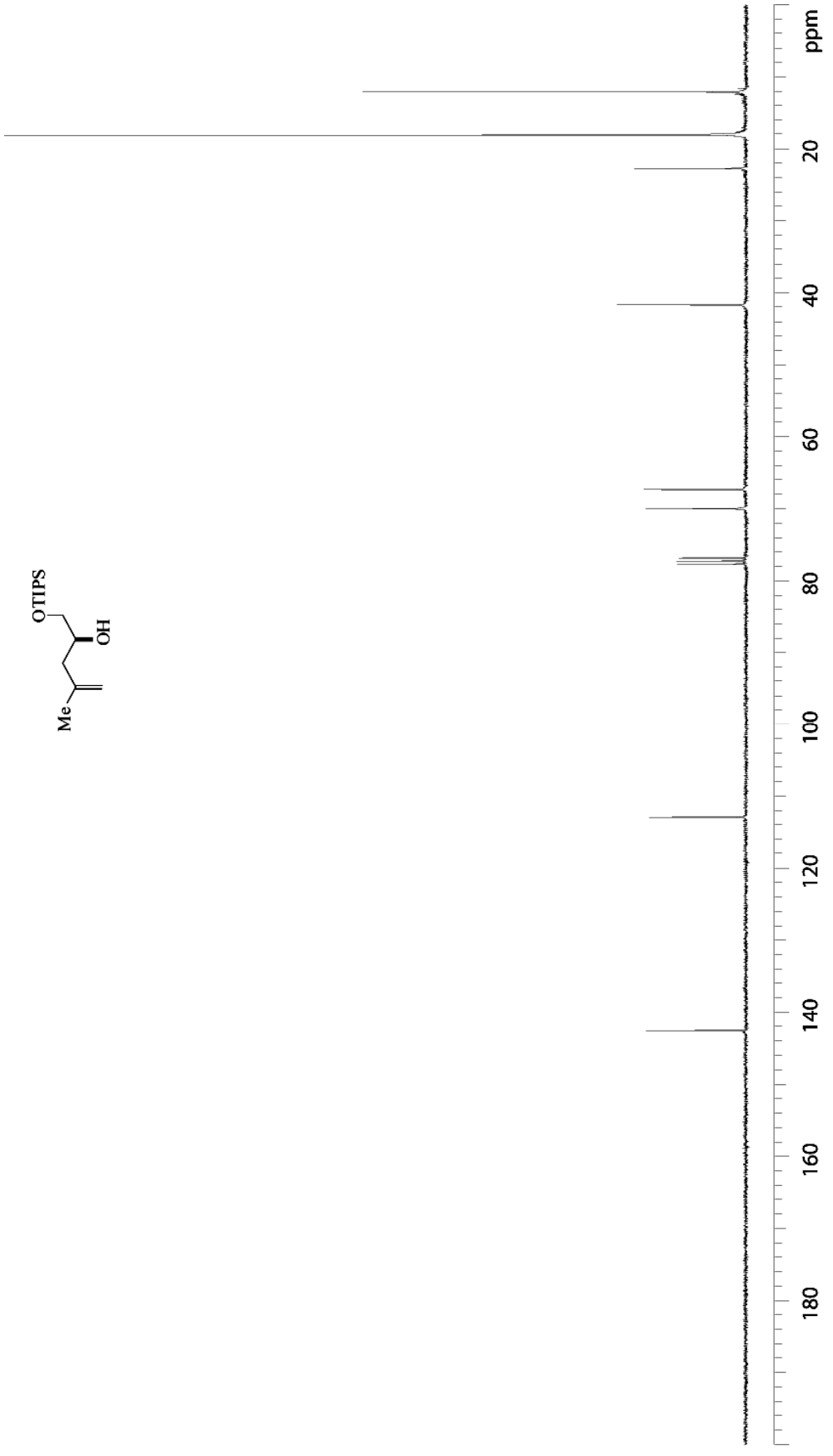
^{1}H NMR (300 MHz) of α-Silyl-β-Lactone **2.19a** in $CDCl_3$



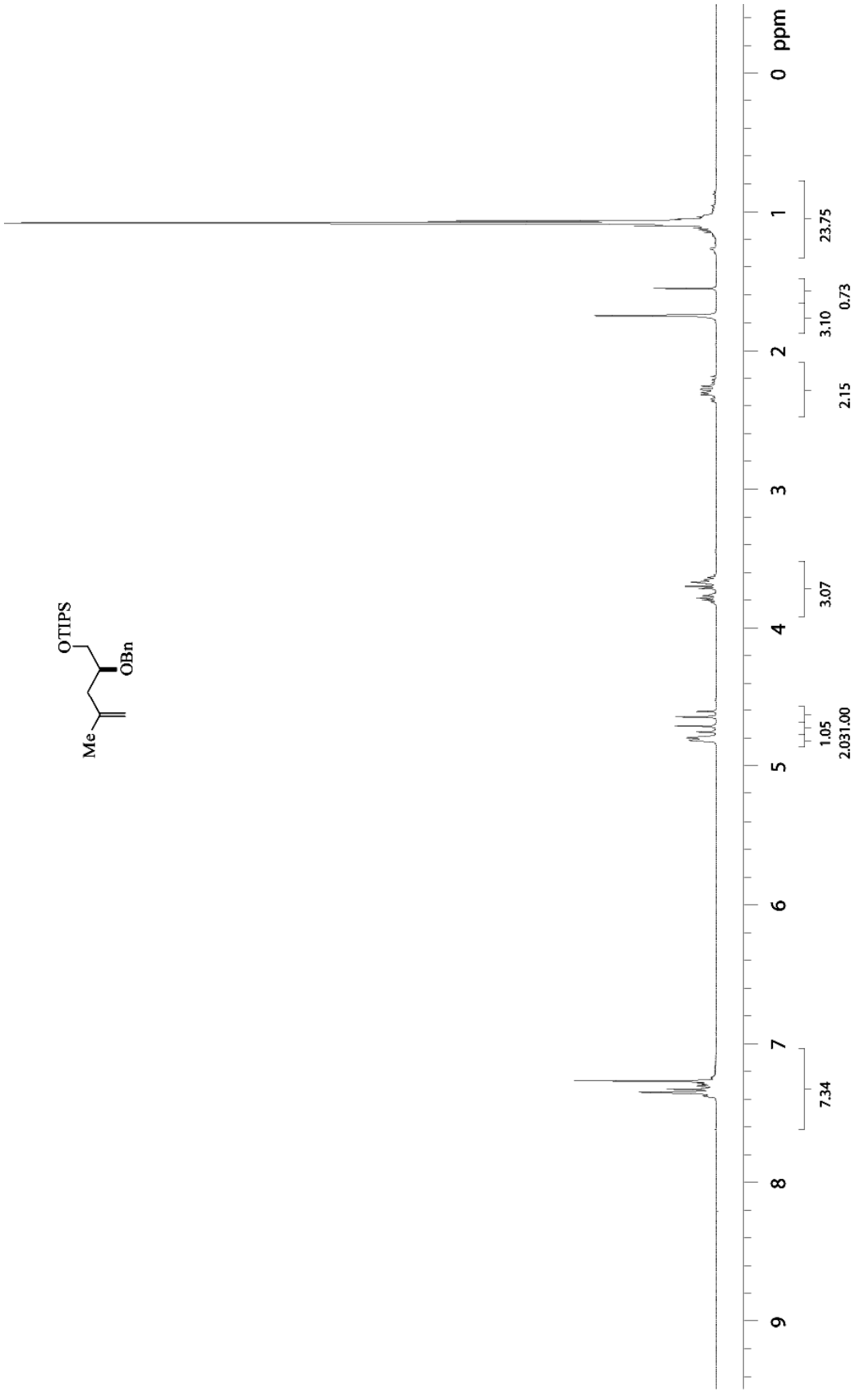
^{13}C NMR (75 MHz) of α-Silyl-β-Lactone **2.19a** in $CDCl_3$



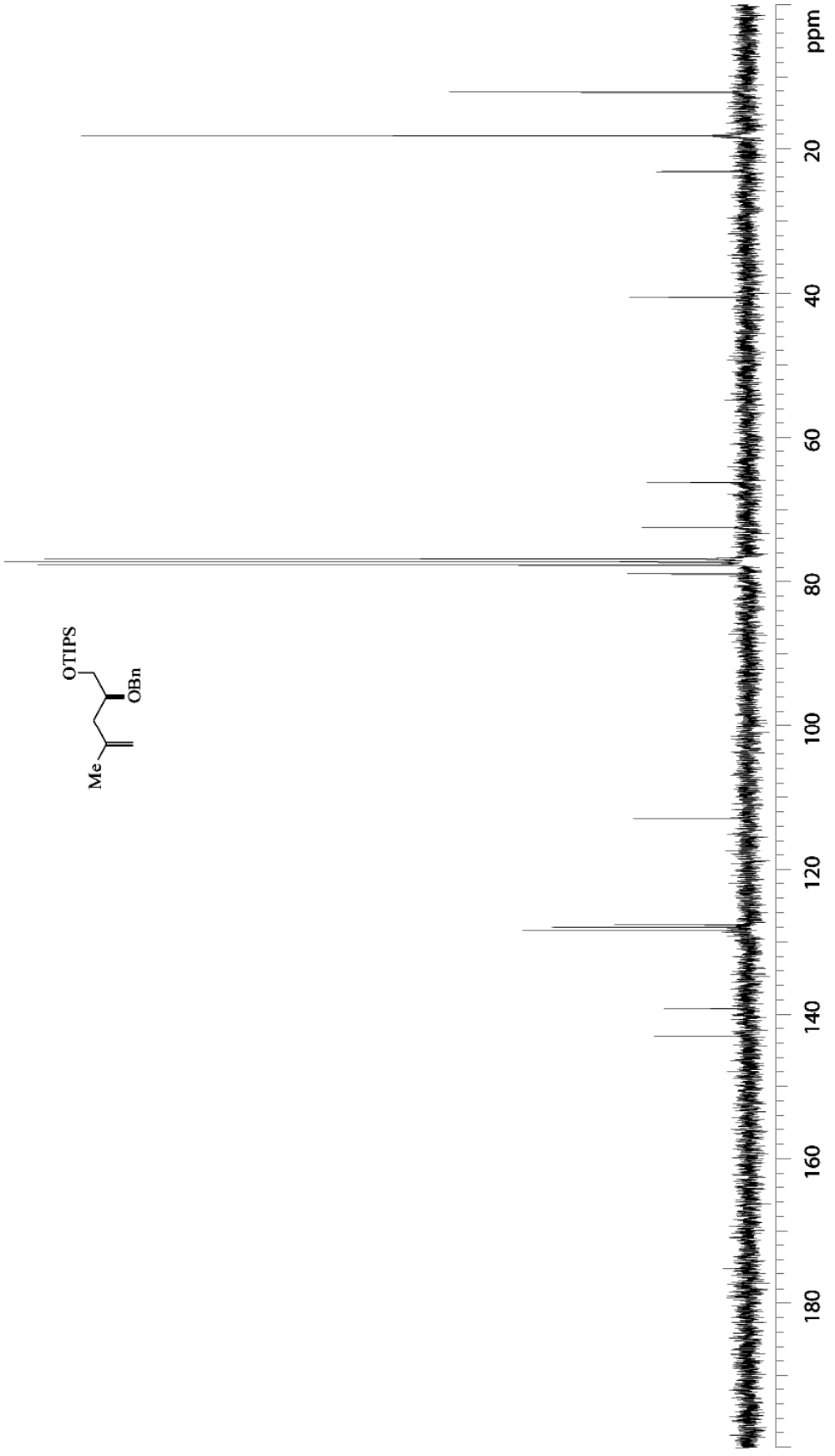
^{1}H NMR (300 MHz) of Secondary Alcohol **S1** in $CDCl_3$



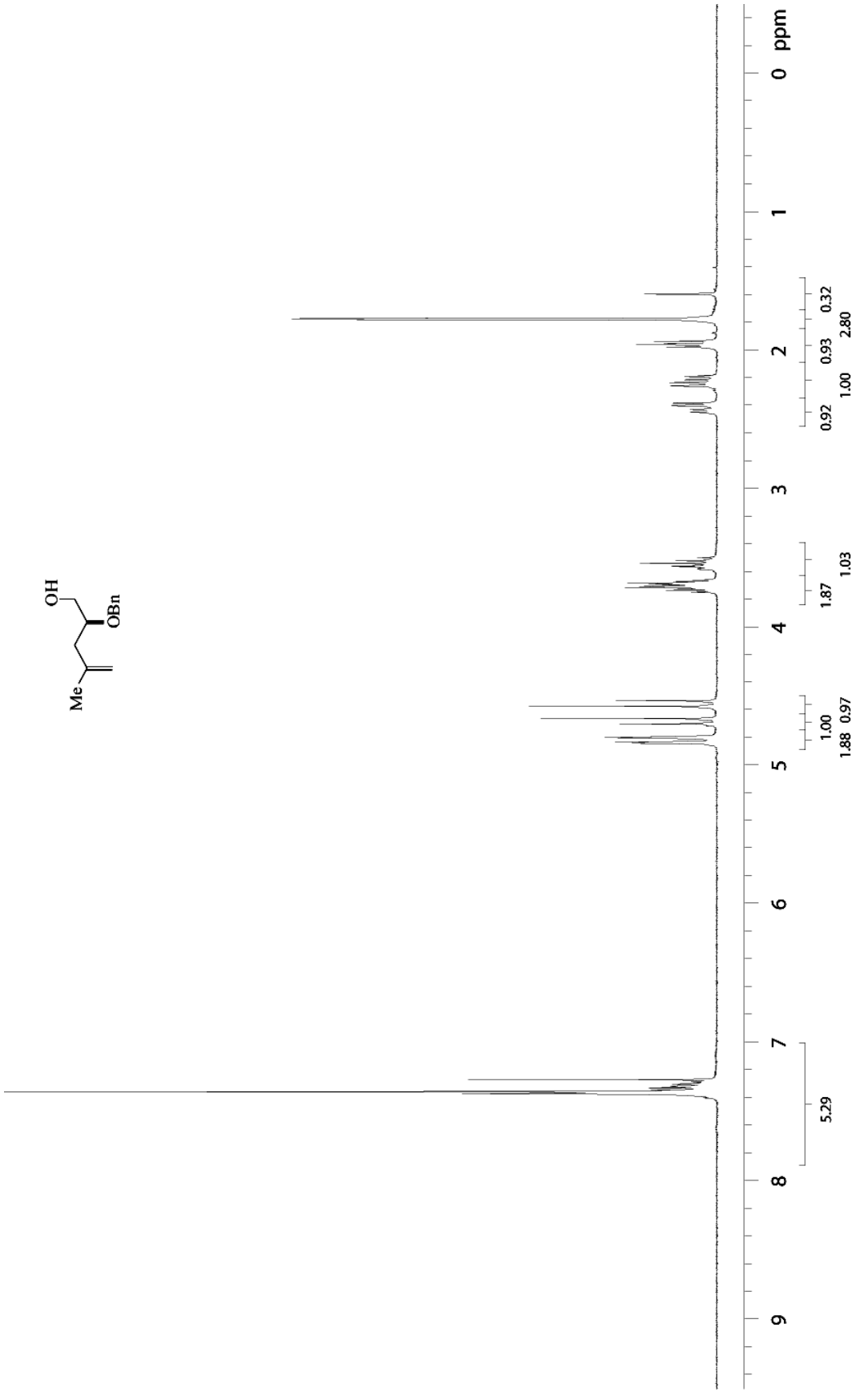
^{13}C NMR (75 MHz) of Secondary Alcohol **S1** in $CDCl_3$



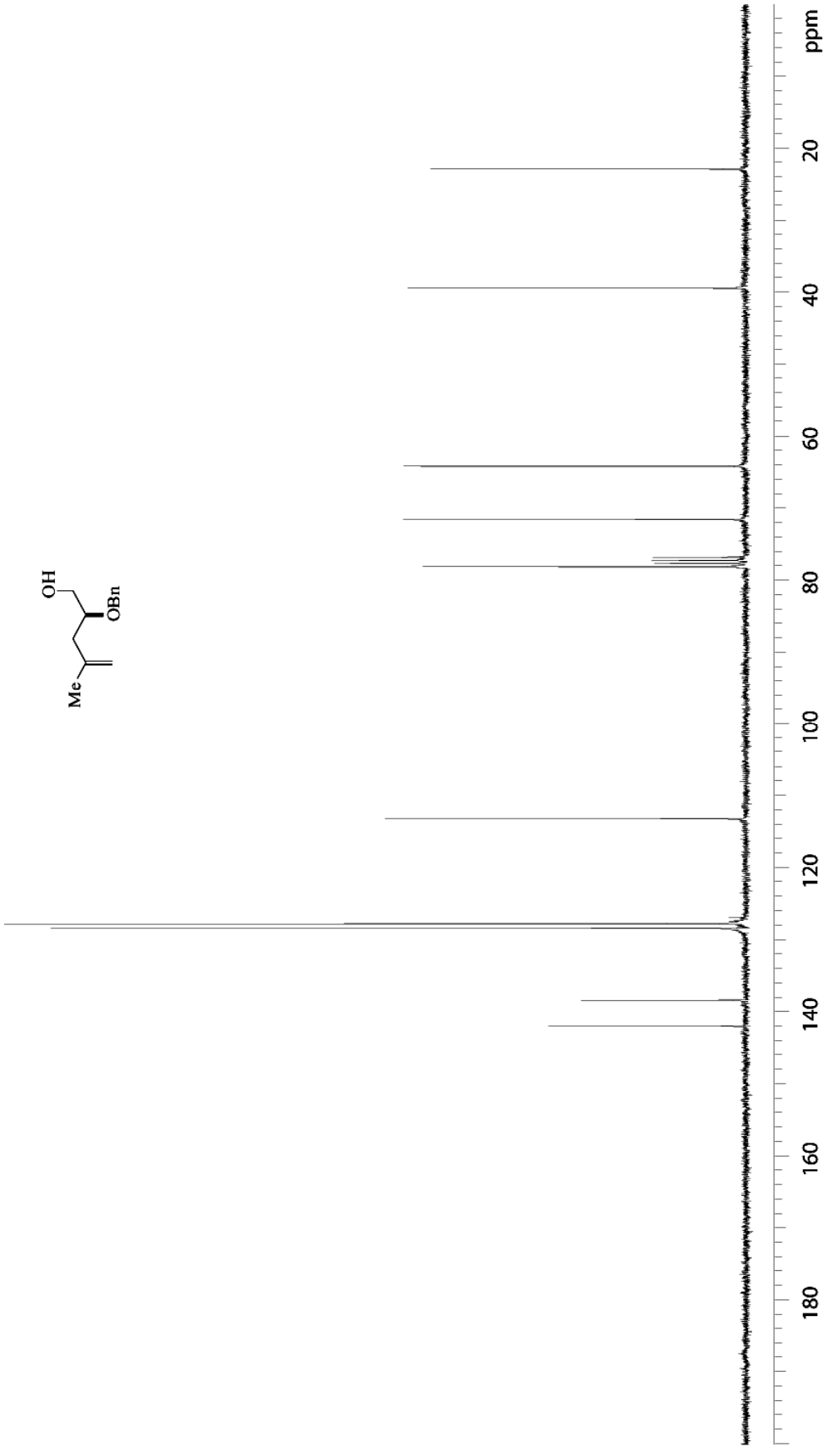
^{1}H NMR (300 MHz) of Benzyl Ether **3.7** in $CDCl_3$



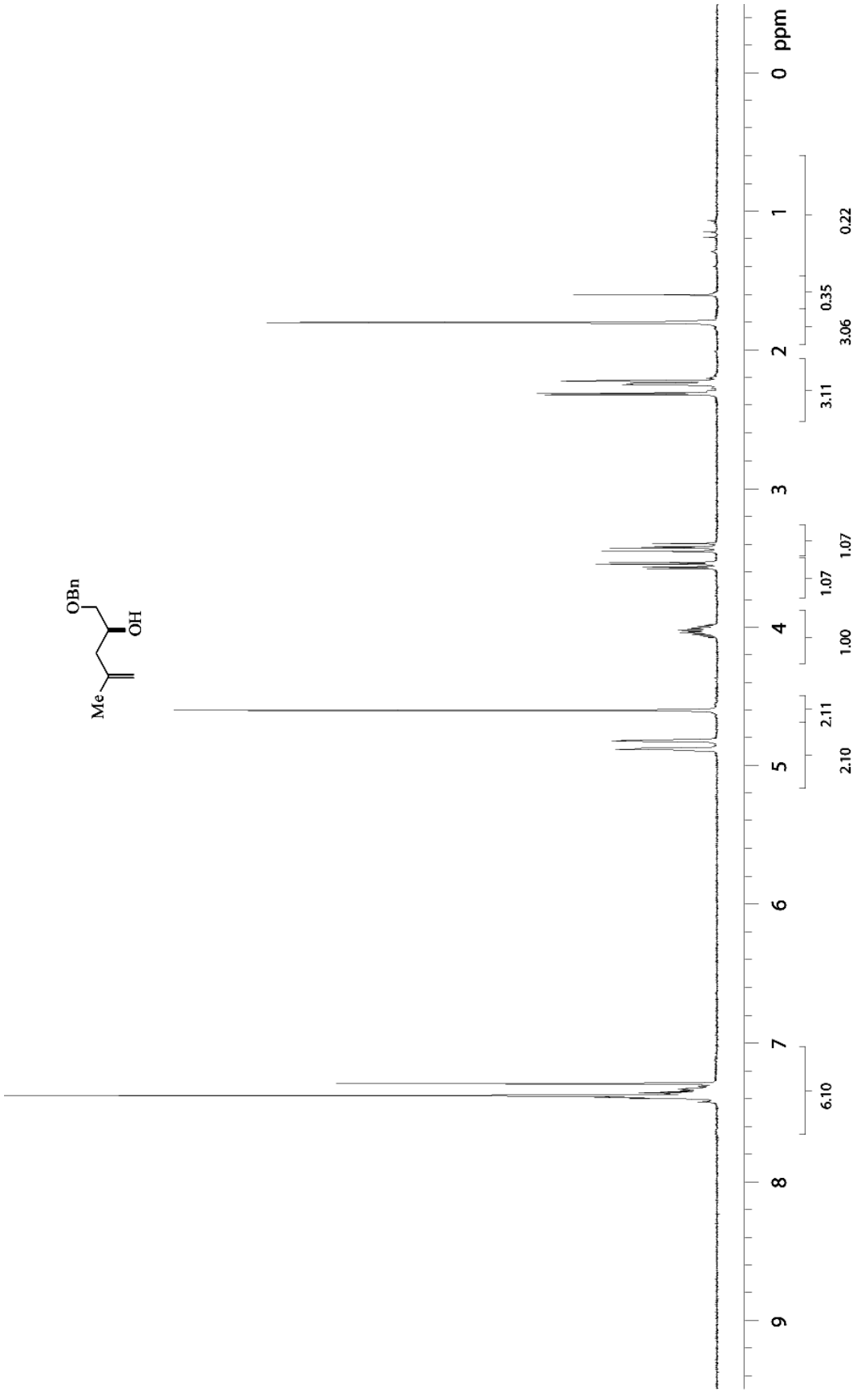
^{13}C NMR (75 MHz) of Benzyl Ether **3.7** in $CDCl_3$



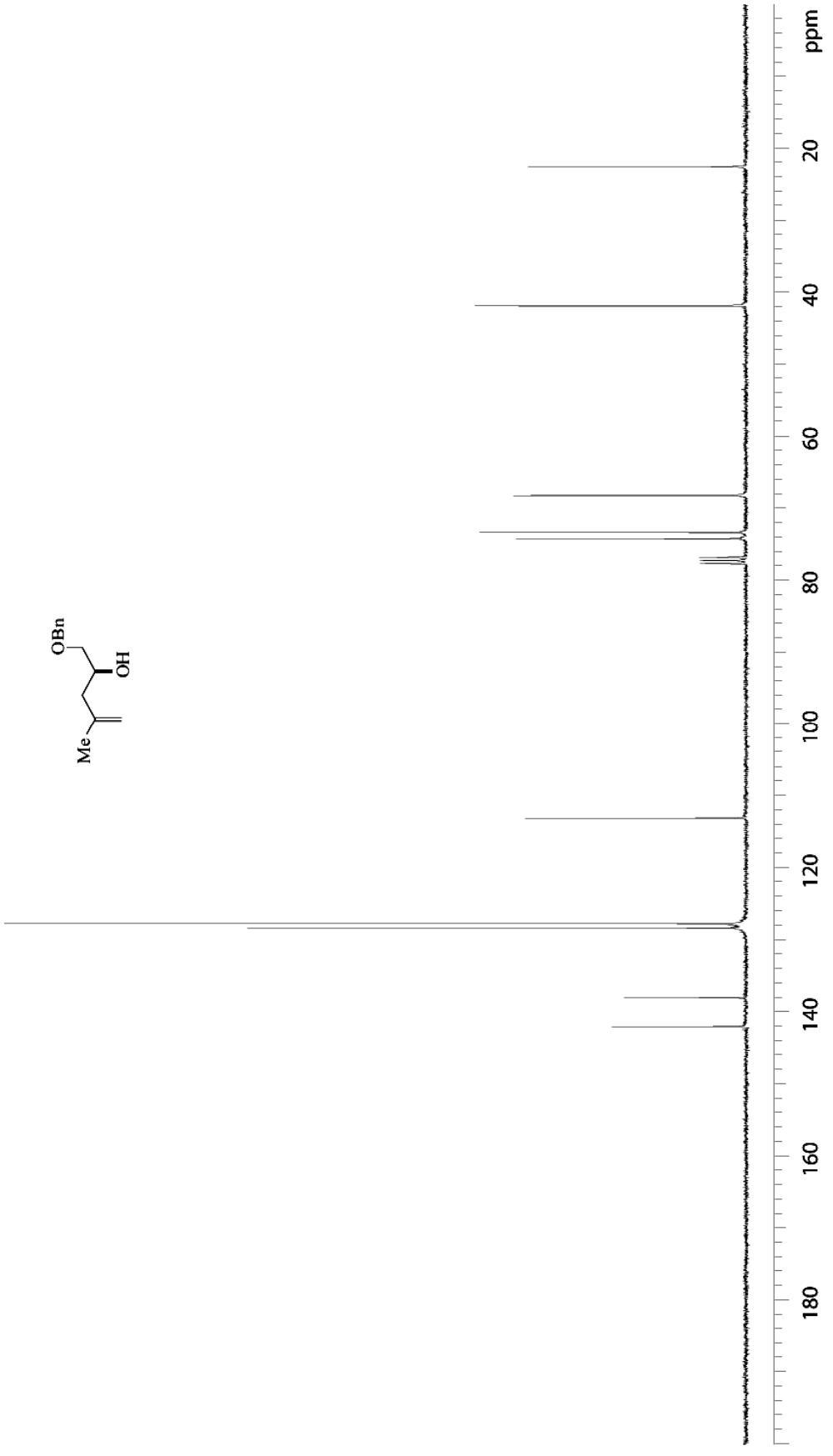
^{1}H NMR (300 MHz) of Primary Alcohol **S2** in $CDCl_3$



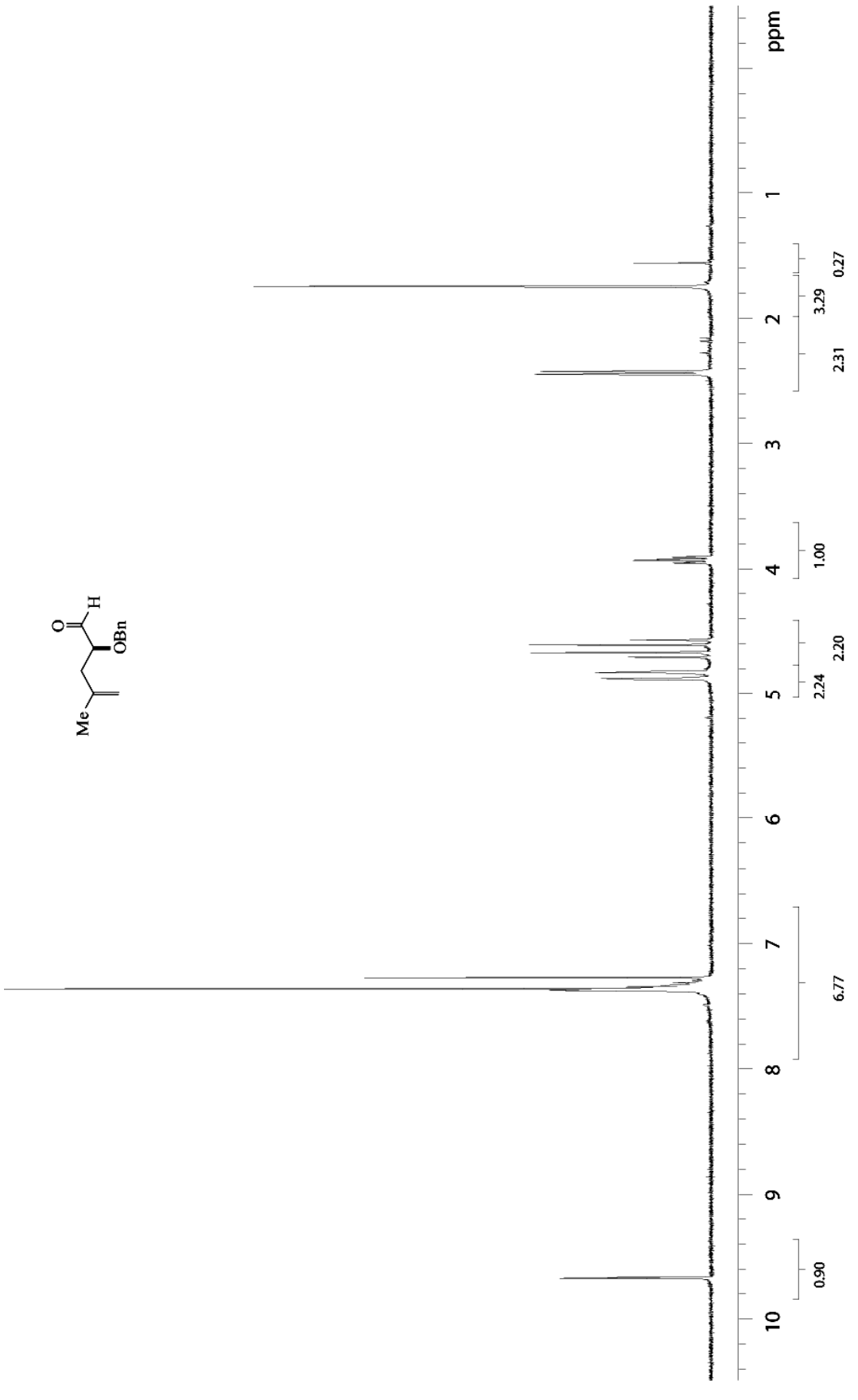
^{13}C NMR (75 MHz) of Primary Alcohol **S2** in $CDCl_3$



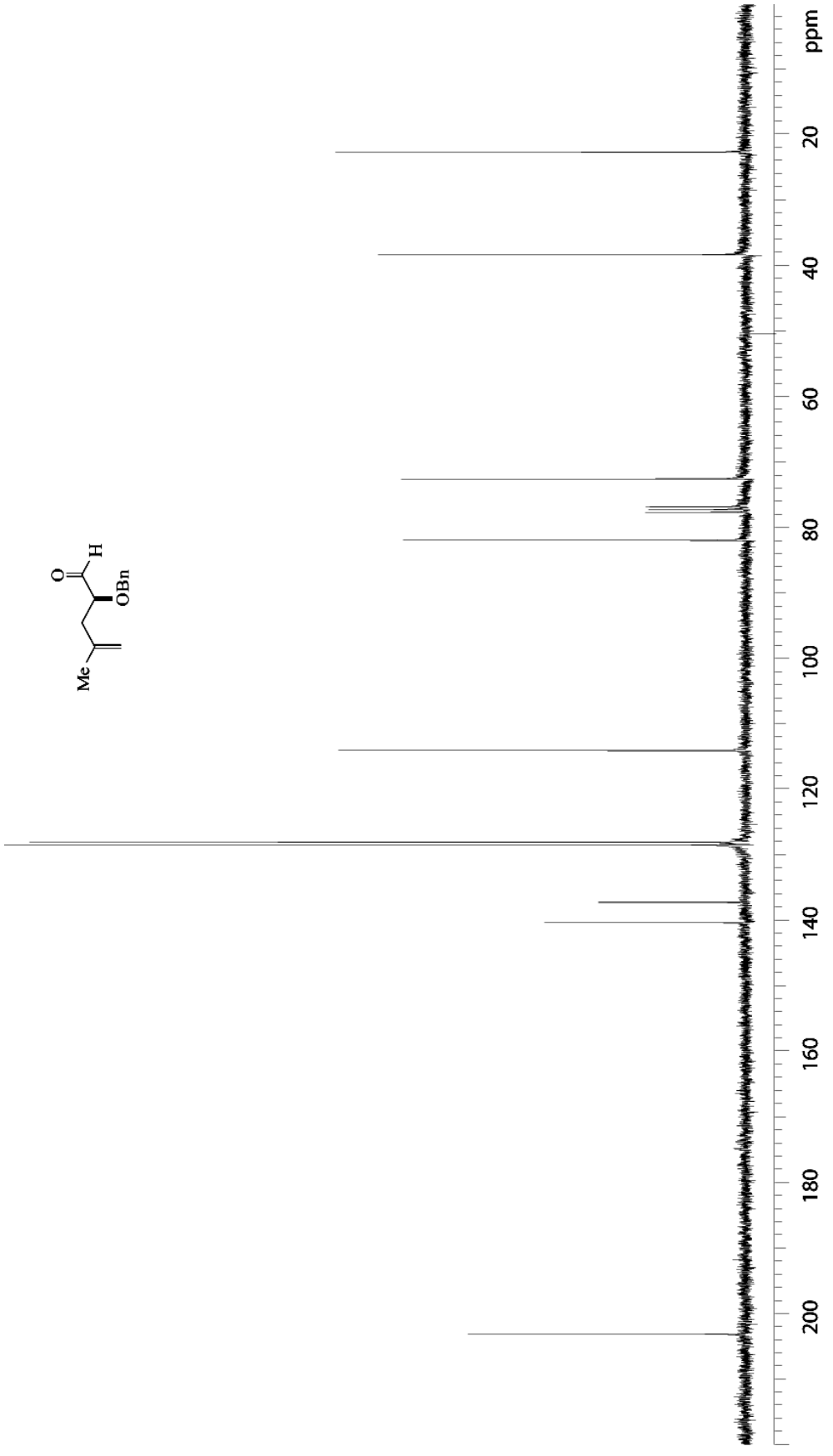
^{1}H NMR (300 MHz) of Secondary Alcohol **S3** in $CDCl_3$



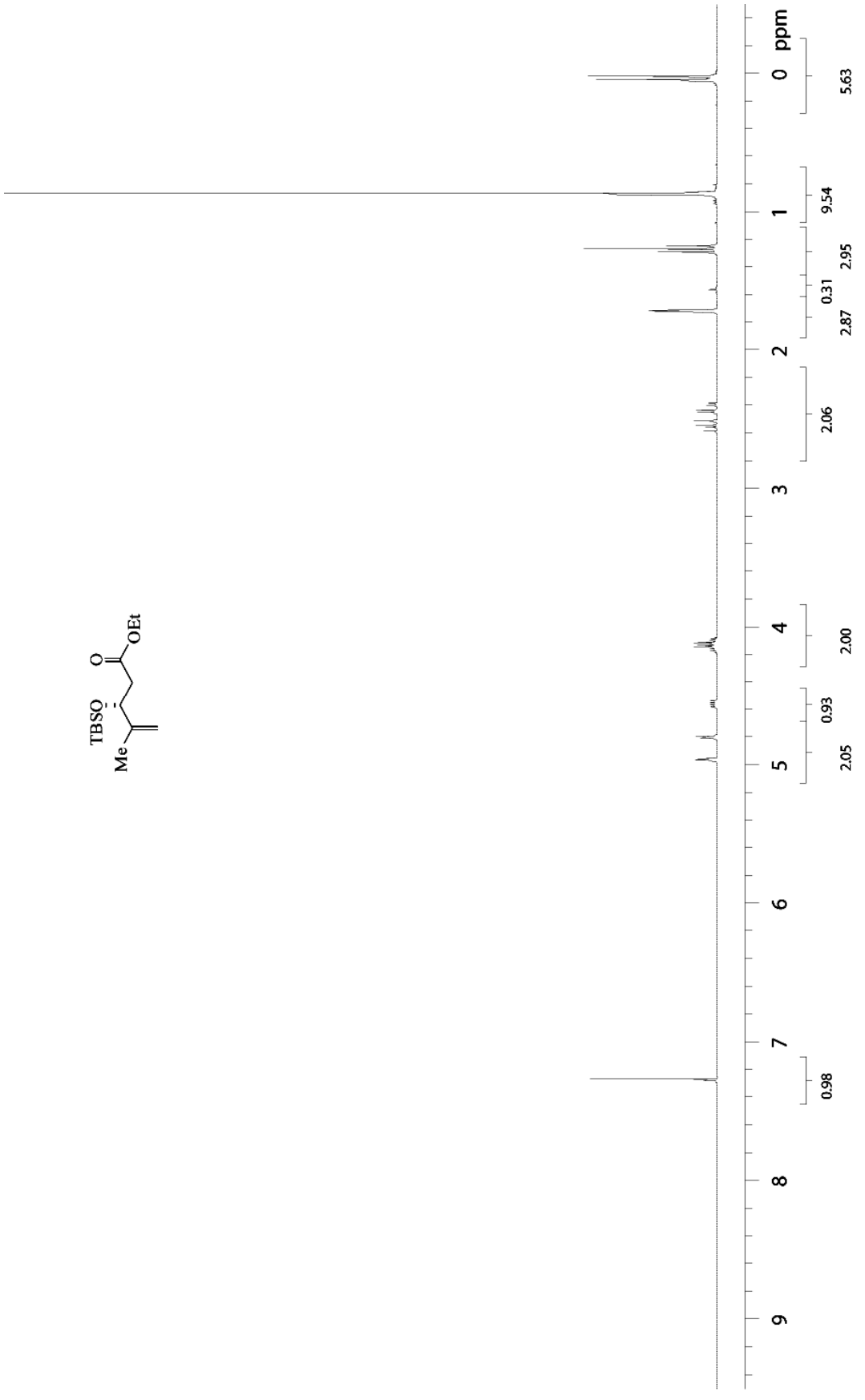
^{13}C NMR (75 MHz) of Secondary Alcohol **S3** in $CDCl_3$



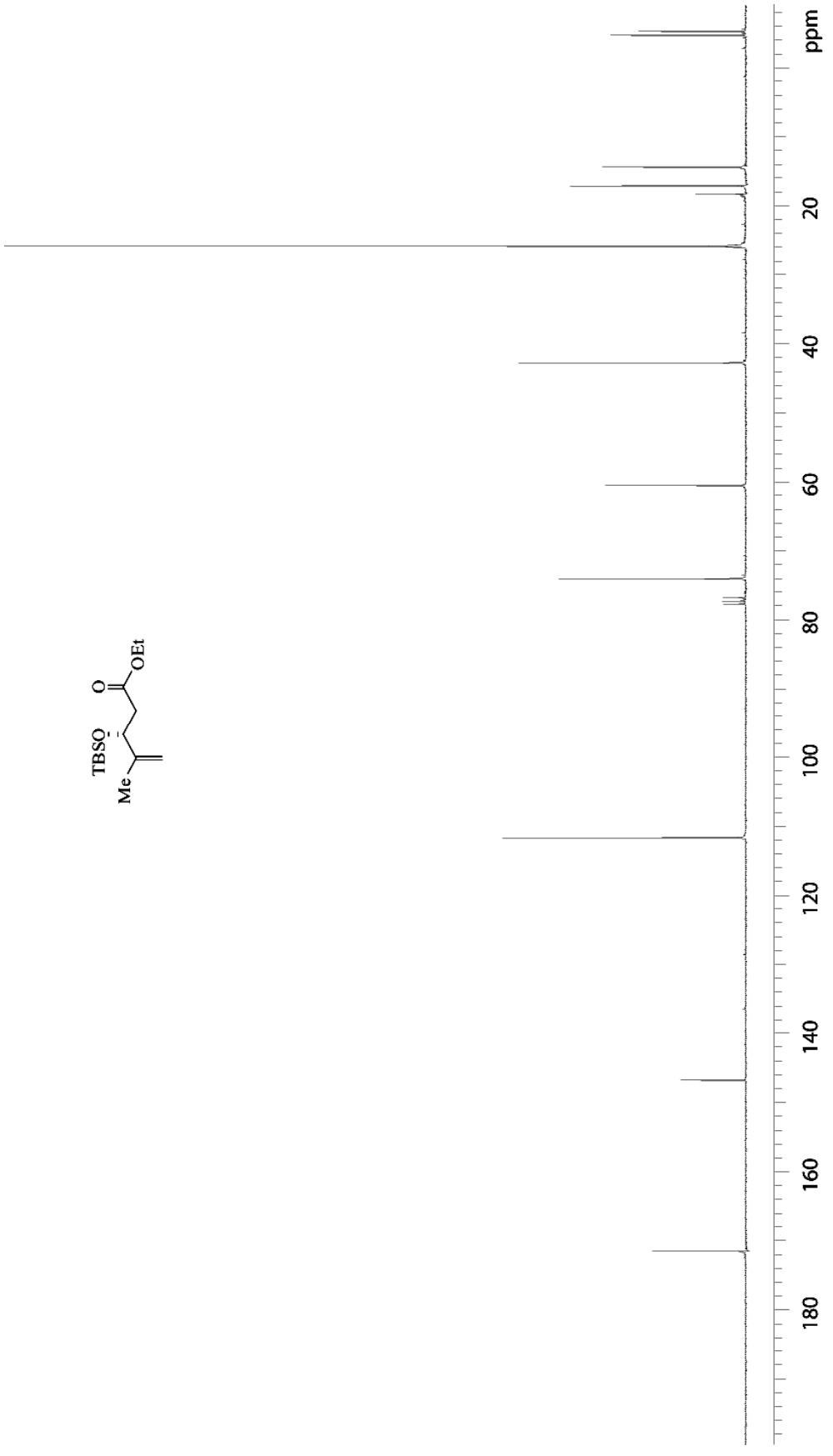
^{1}H NMR (300 MHz) of α-Benzyloxy Aldehyde (±)-**3.1a** in $CDCl_3$



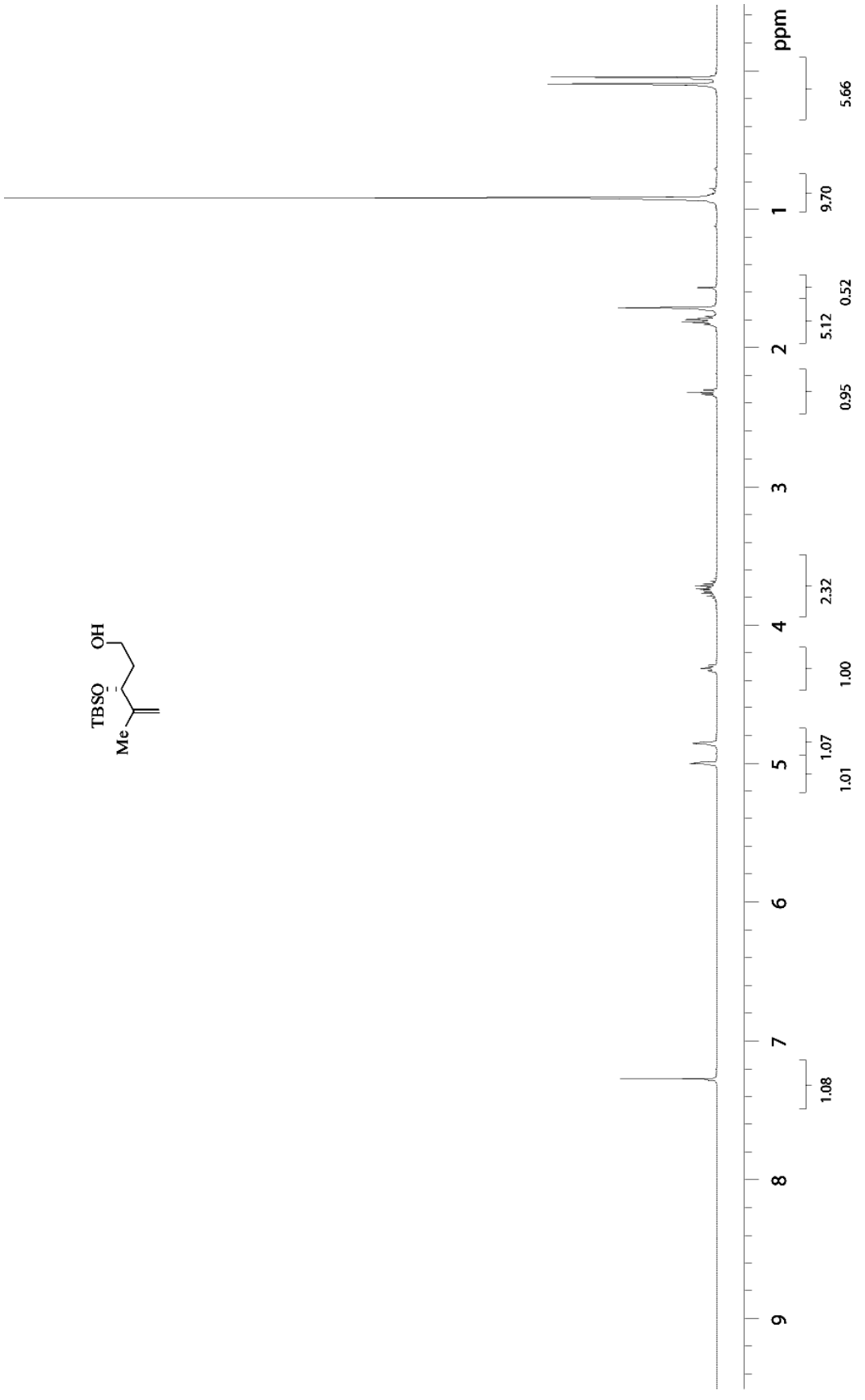
^{13}C NMR (75 MHz) of α-Benzyloxy Aldehyde **(±)-3.1a** in $CDCl_3$



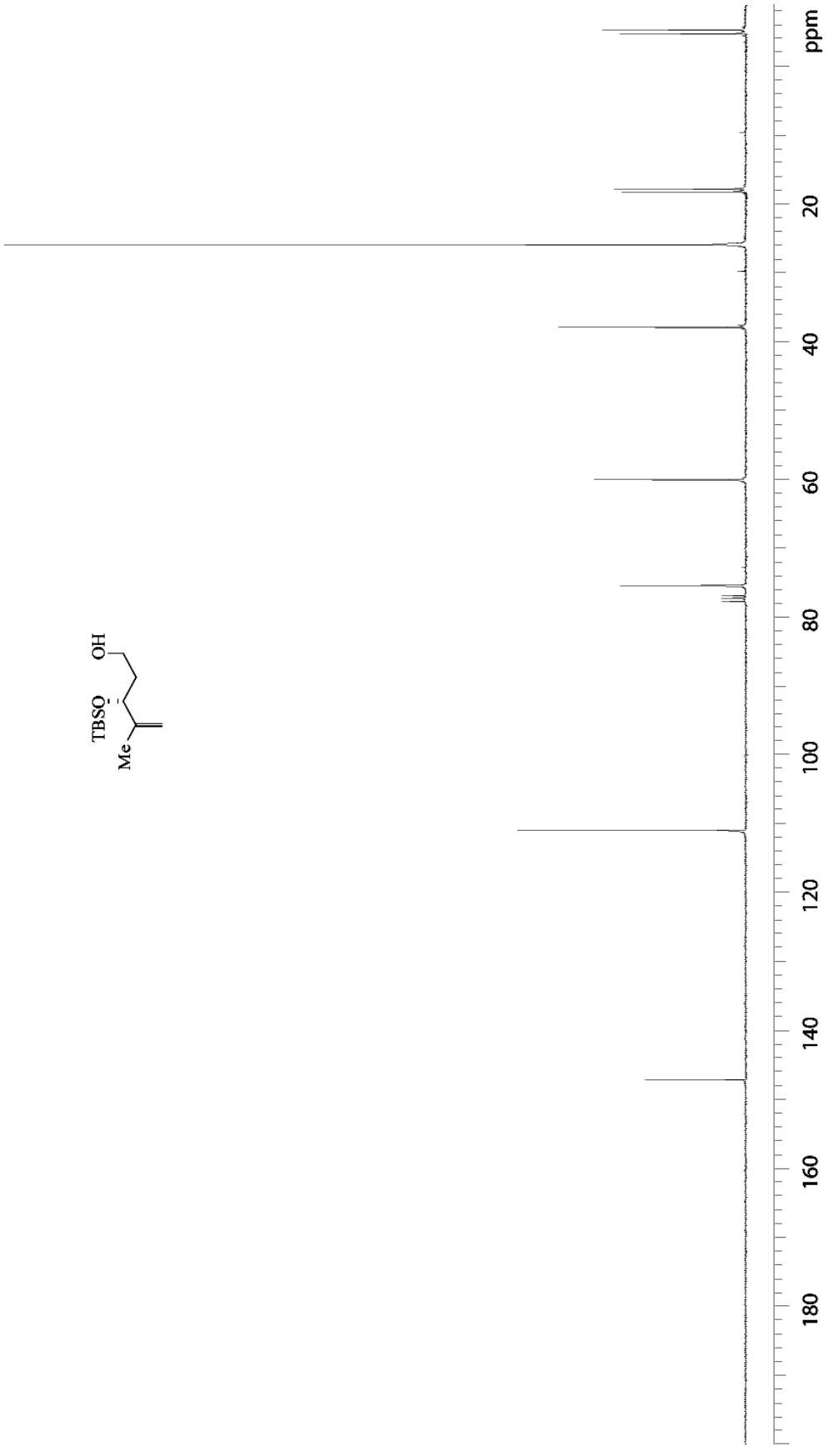
^{1}H NMR (300 MHz) of β-Silyloxy Ester **S4** in $CDCl_3$



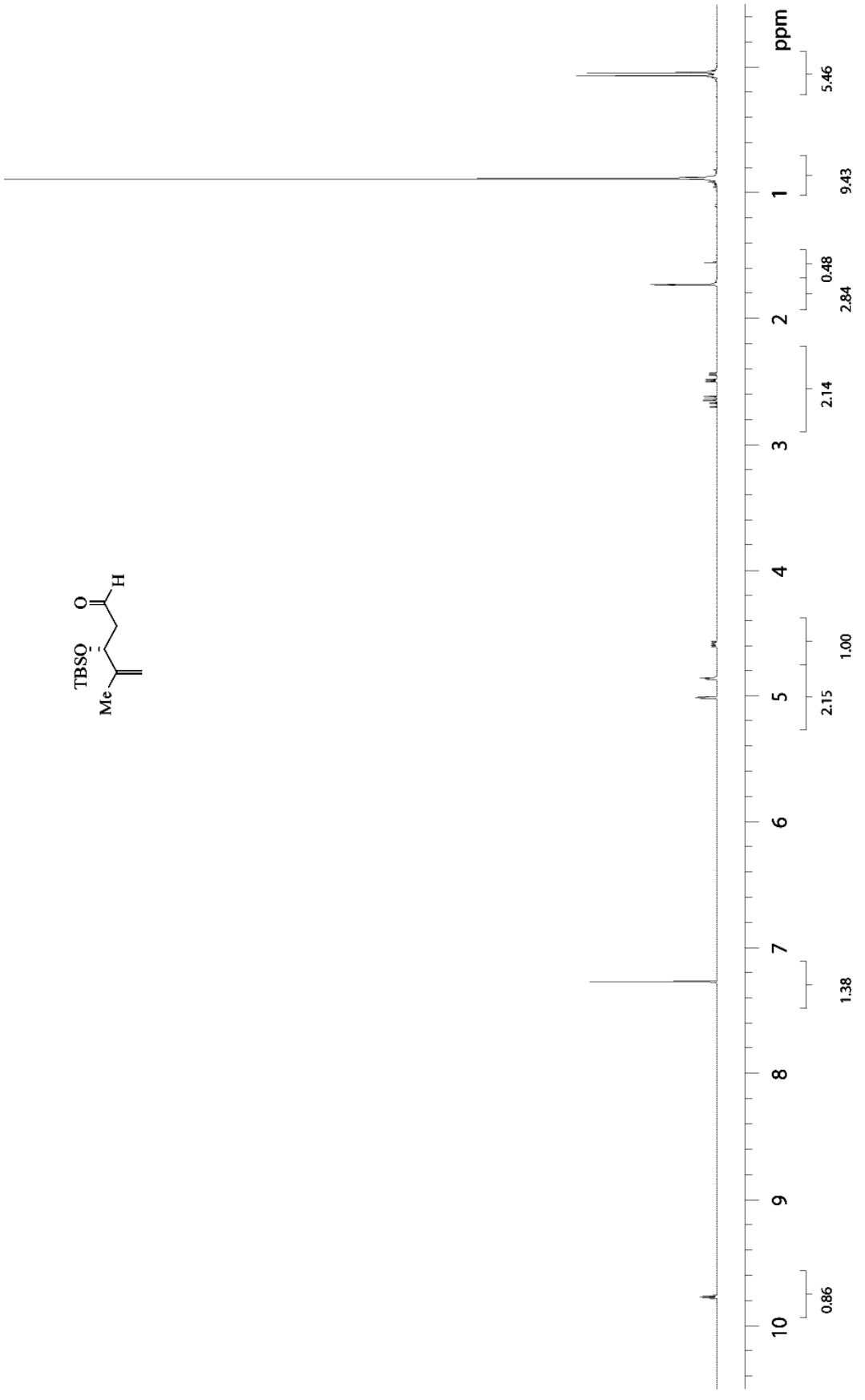
^{13}C NMR (75 MHz) of β-Silyloxy Ester **S4** in $CDCl_3$



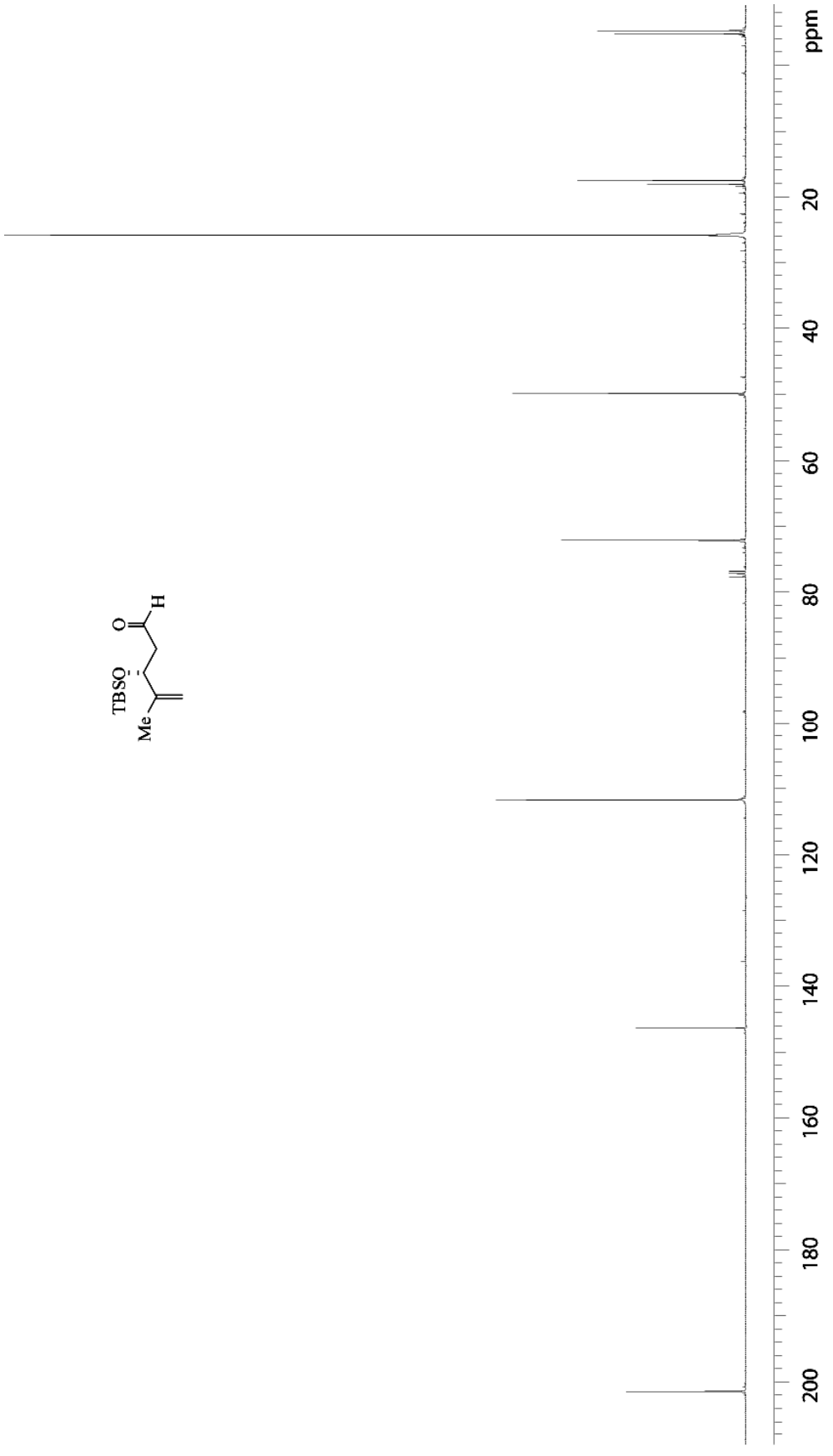
^{1}H NMR (300 MHz) of Primary Alcohol **S5** in $CDCl_3$



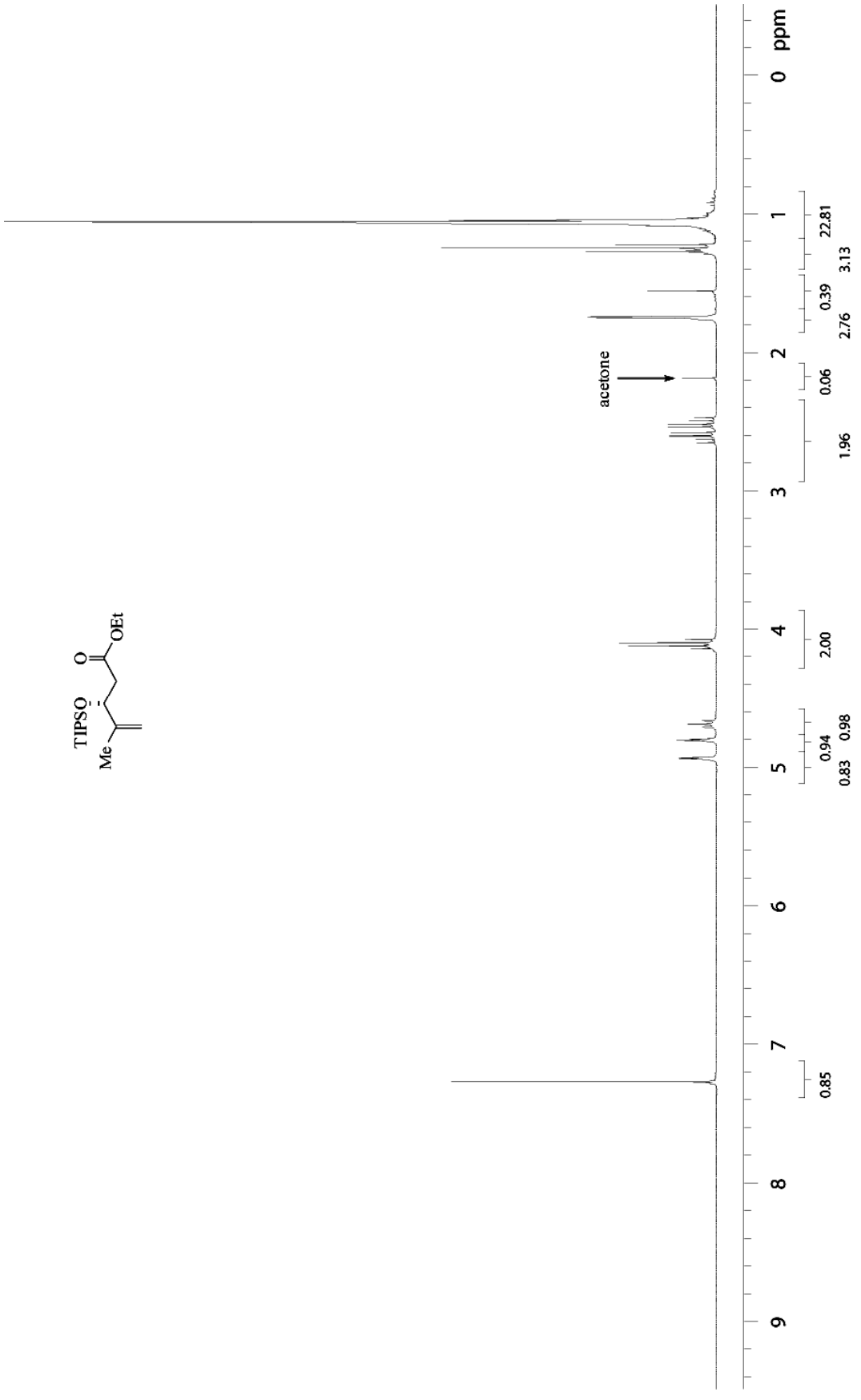
^{13}C NMR (75 MHz) of Primary Alcohol **S5** in $CDCl_3$



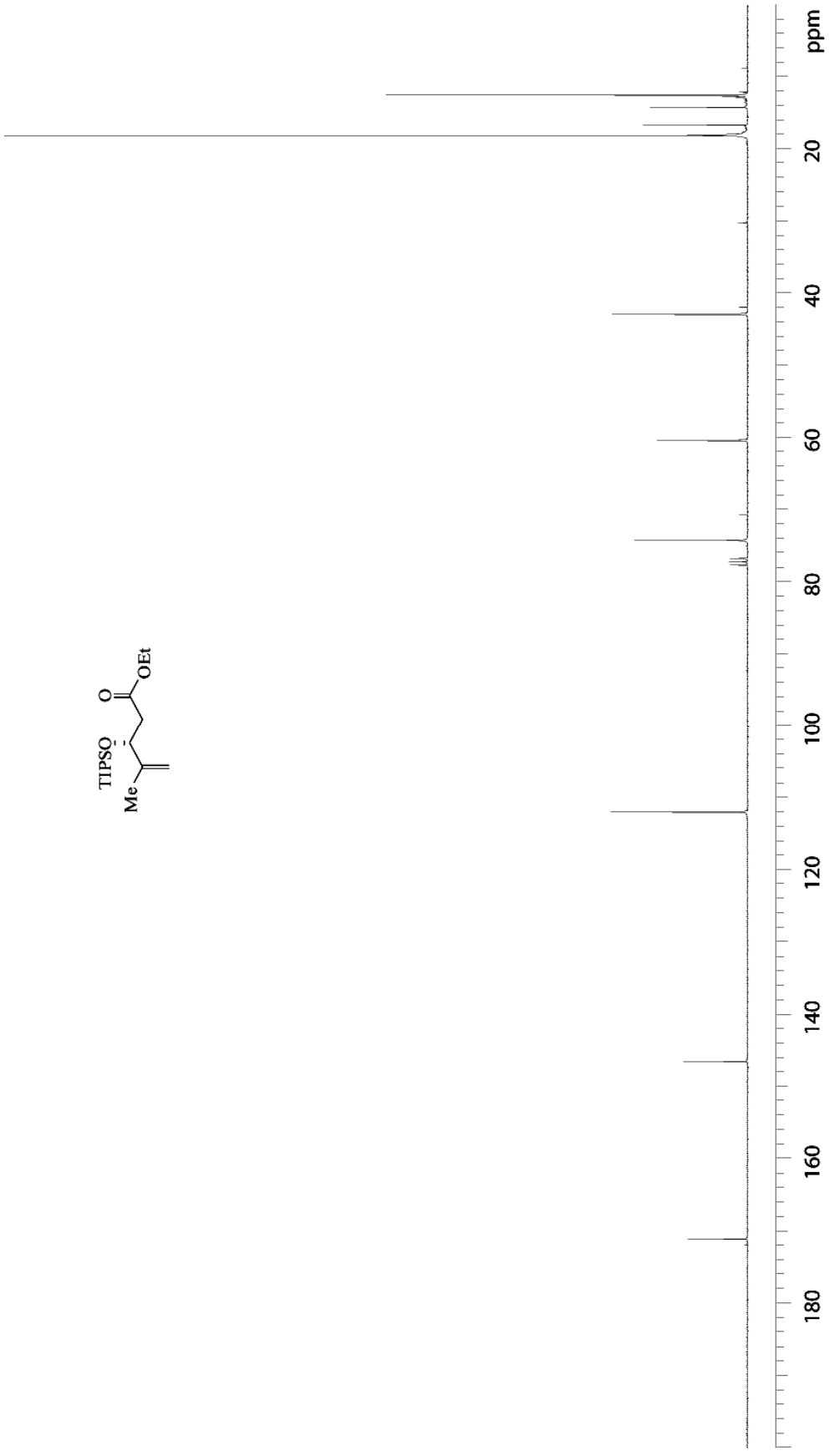
^{1}H NMR (300 MHz) of β-Silyloxy Aldehyde **(±)-3.1b** in $CDCl_3$



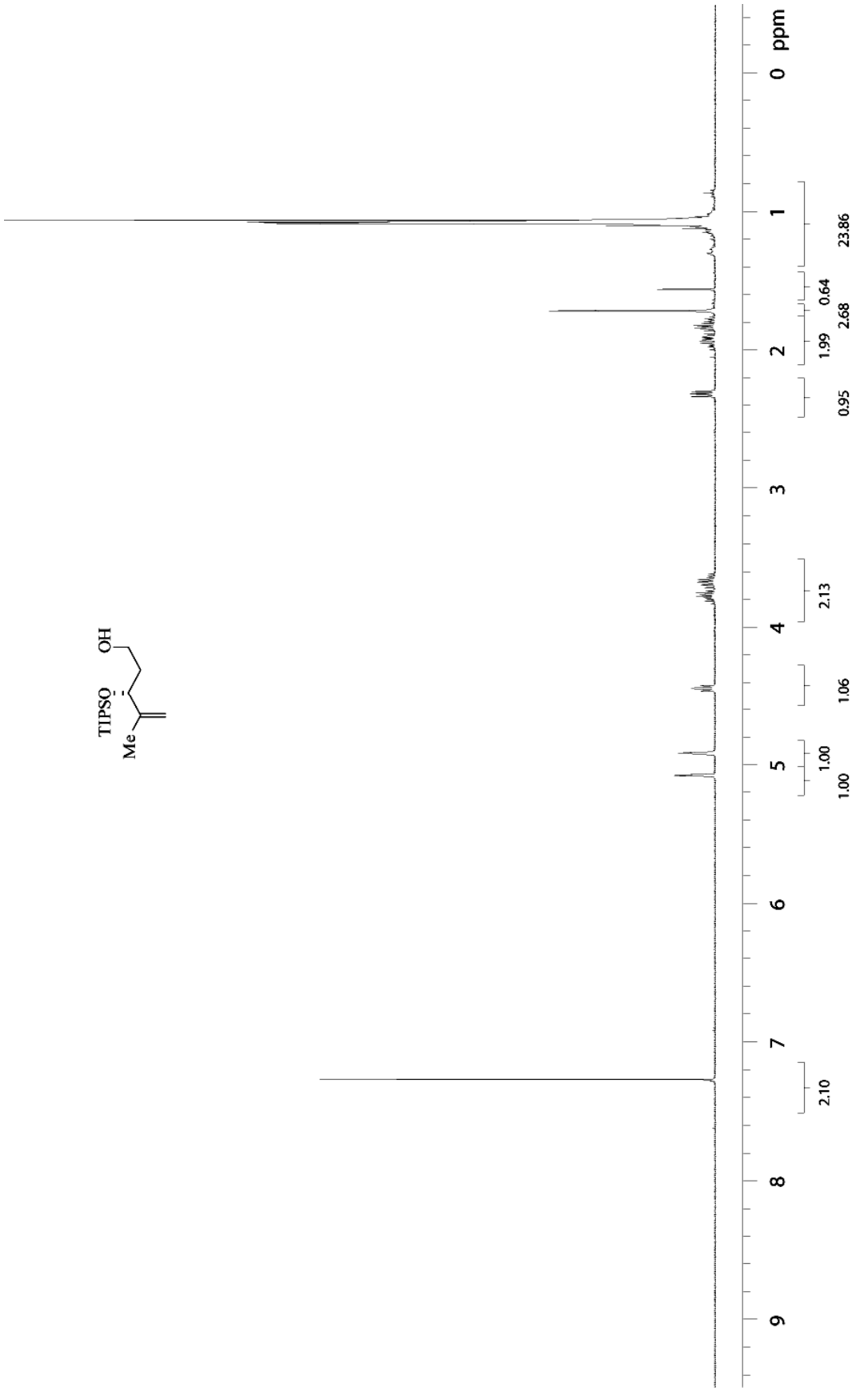
^{13}C NMR (75 MHz) of β-Silyloxy Aldehyde **(±)-3.1b** in $CDCl_3$



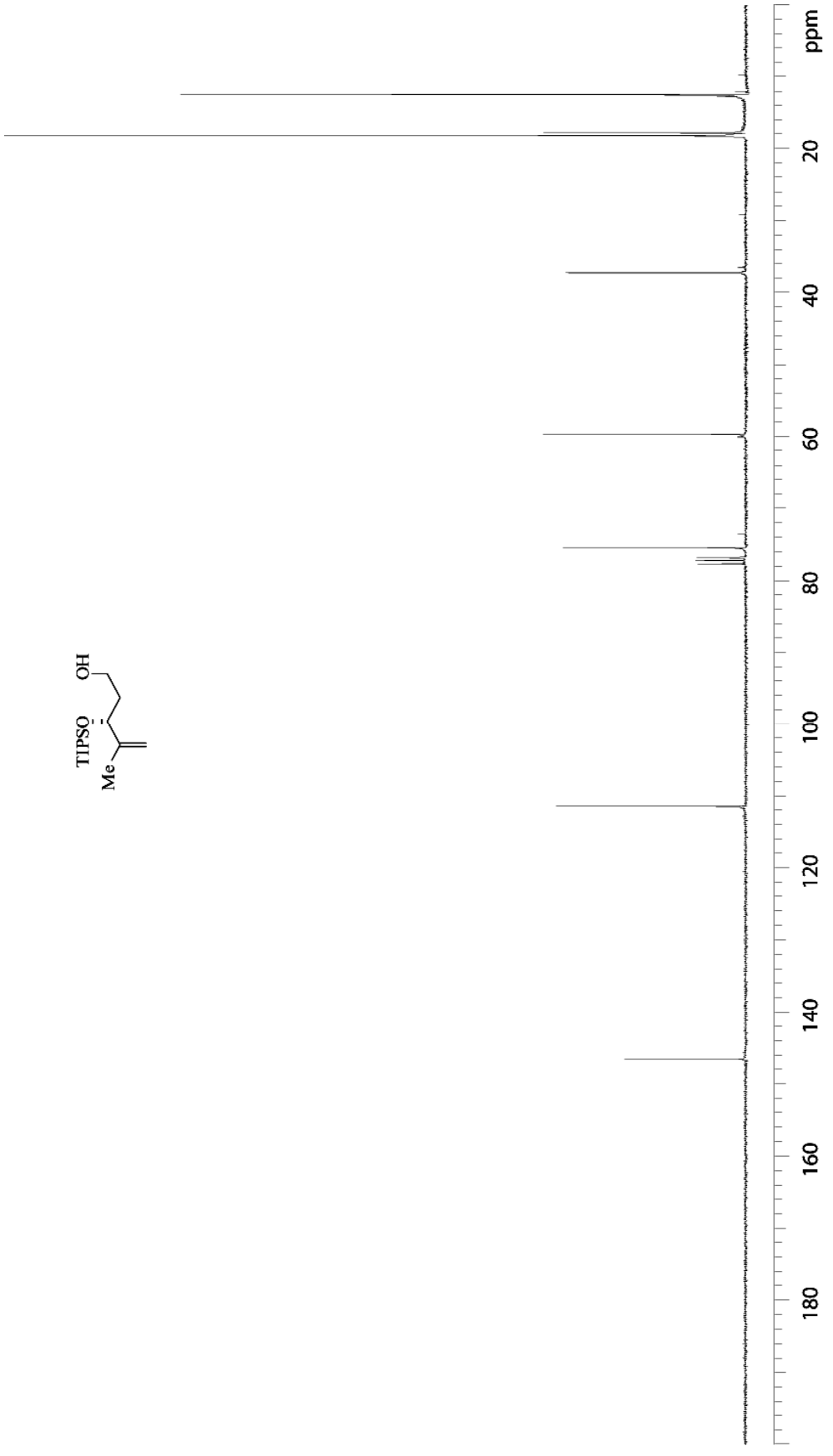
^{1}H NMR (300 MHz) of β-Silyloxy Ester **S6** in $CDCl_3$



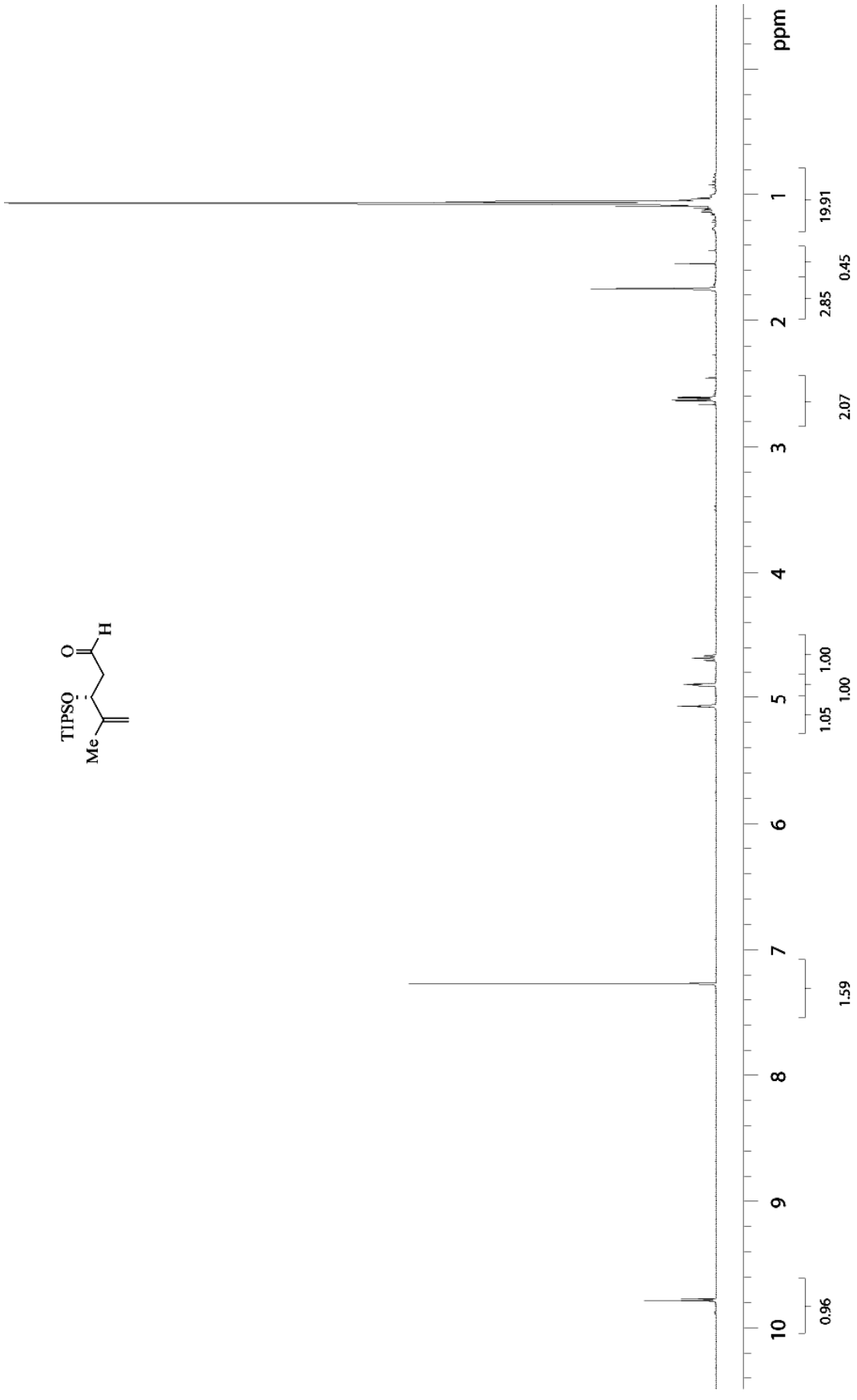
^{13}C NMR (75 MHz) of β-Silyloxy Ester **S6** in $CDCl_3$



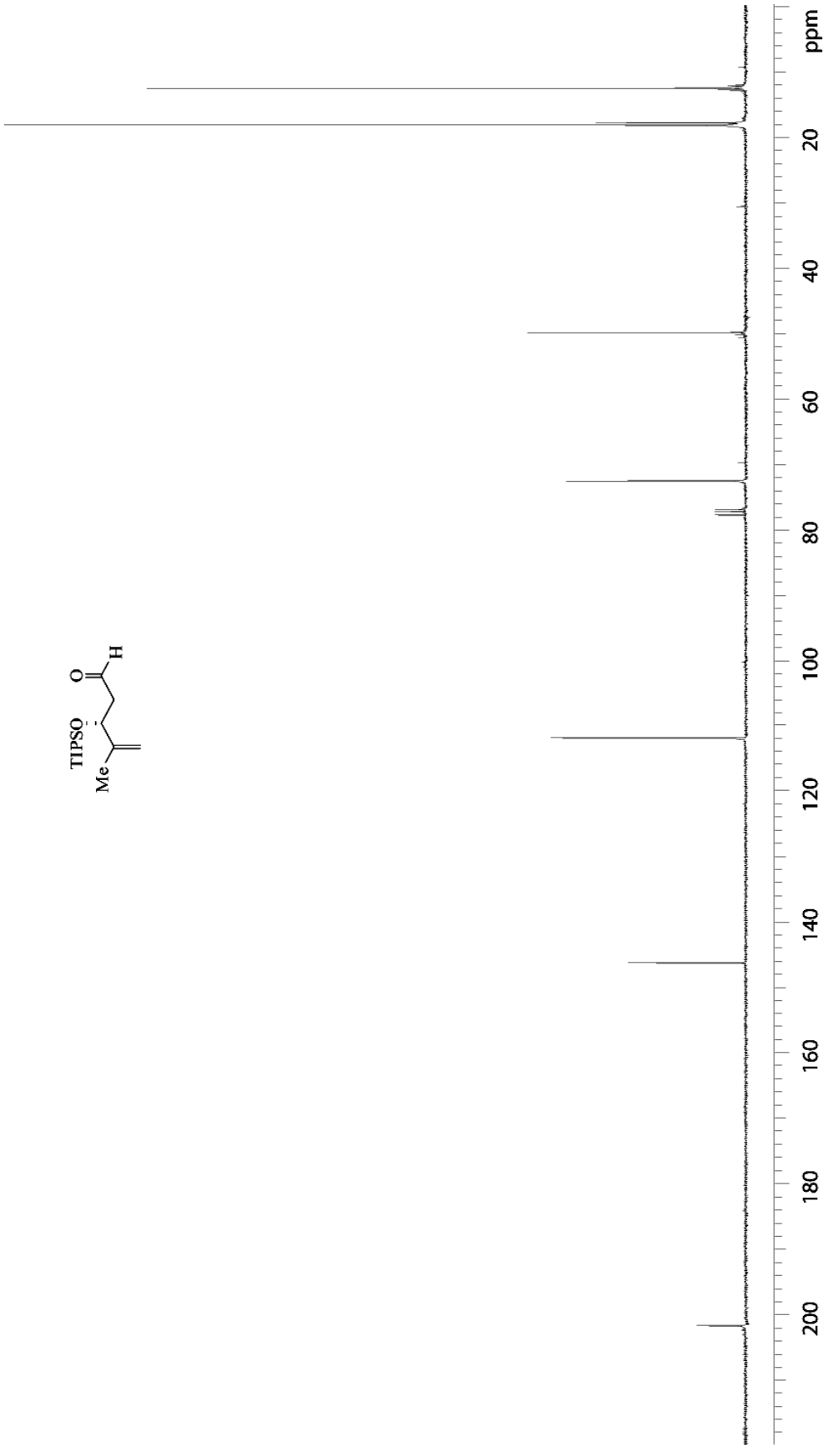
^{1}H NMR (300 MHz) of Primary Alcohol **S7** in $CDCl_3$



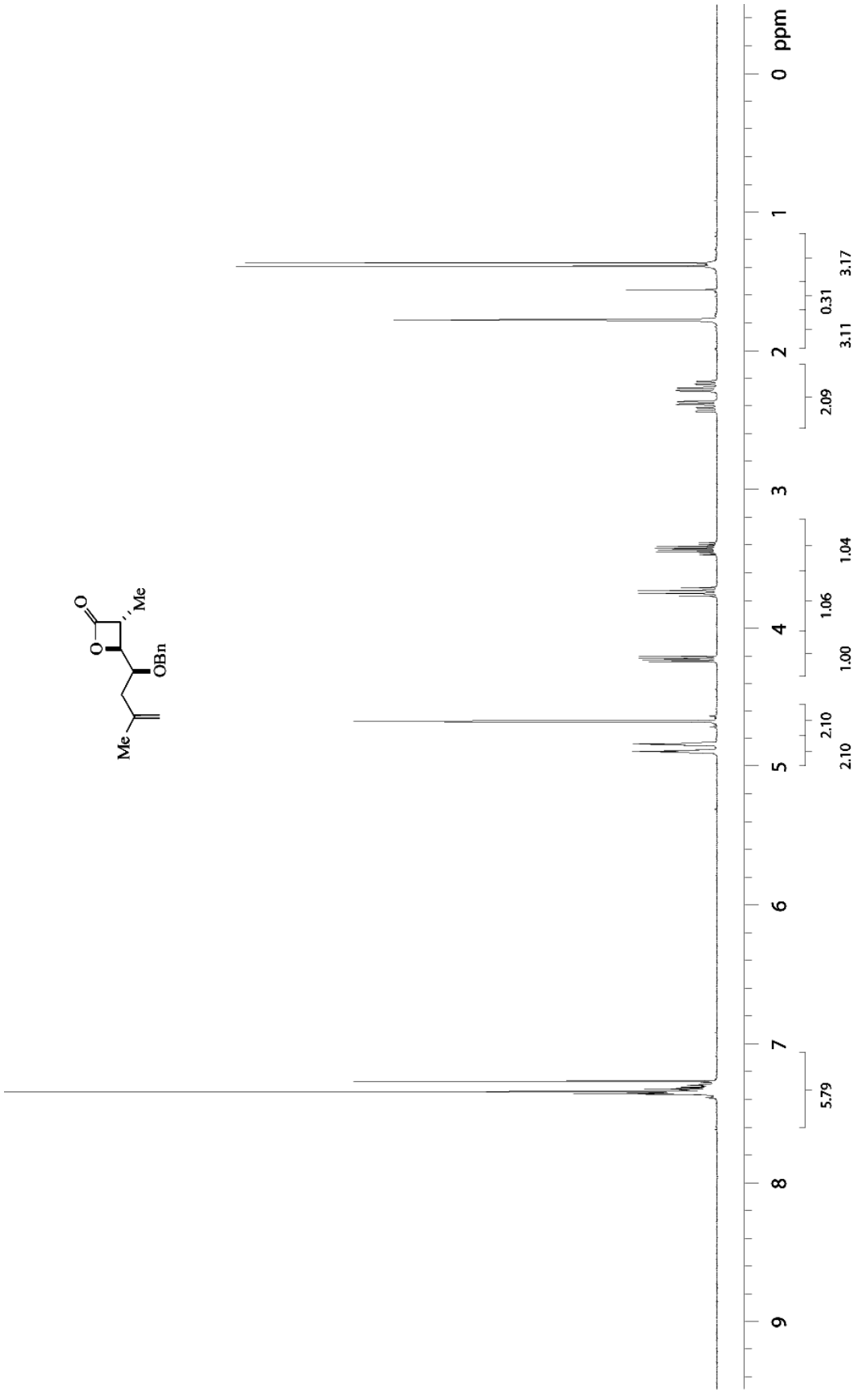
^{13}C NMR (75 MHz) of Primary Alcohol **S7** in $CDCl_3$



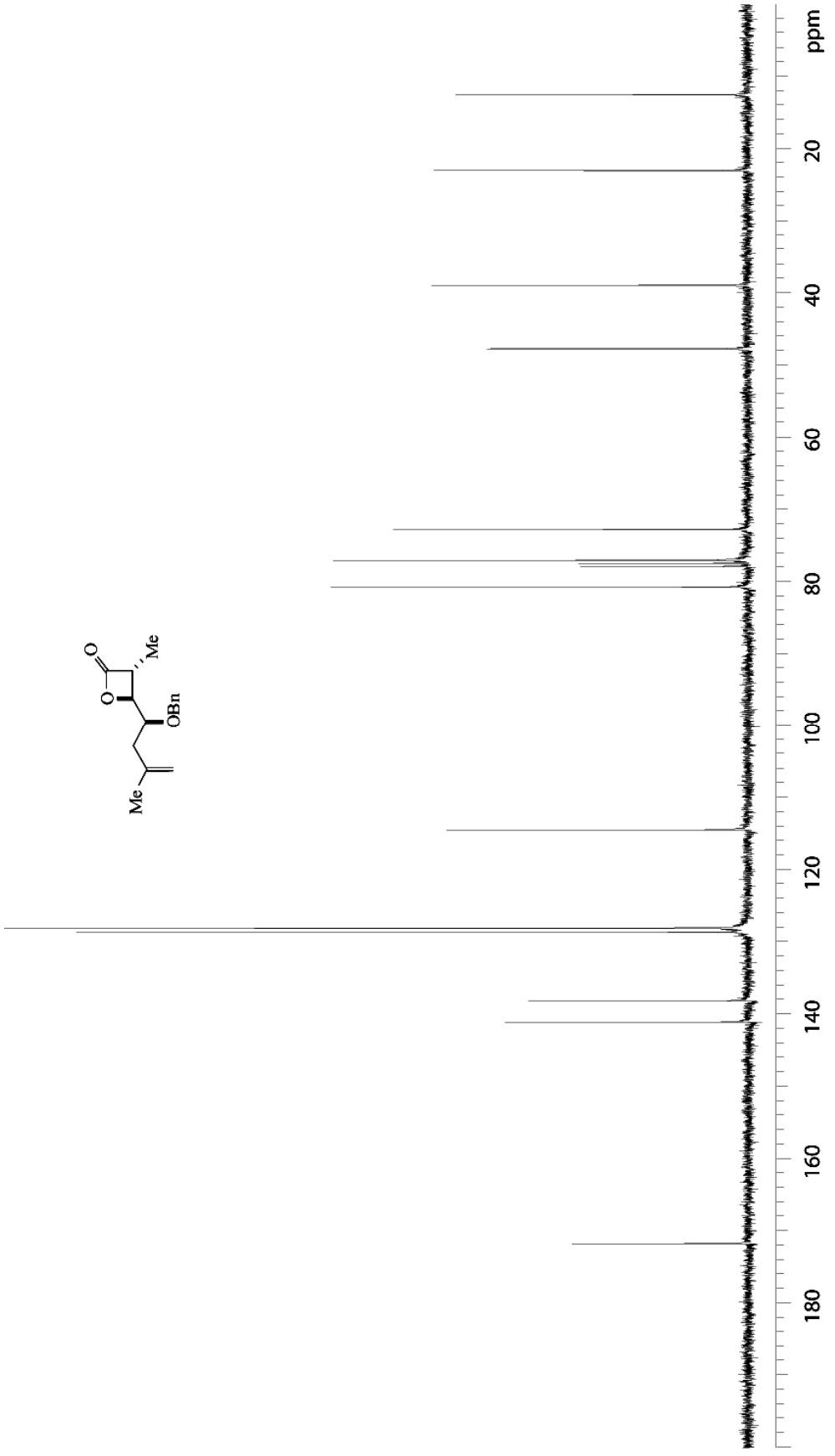
^{1}H NMR (300 MHz) of β-Silyloxy Aldehyde **(±)-3.1c** in $CDCl_3$



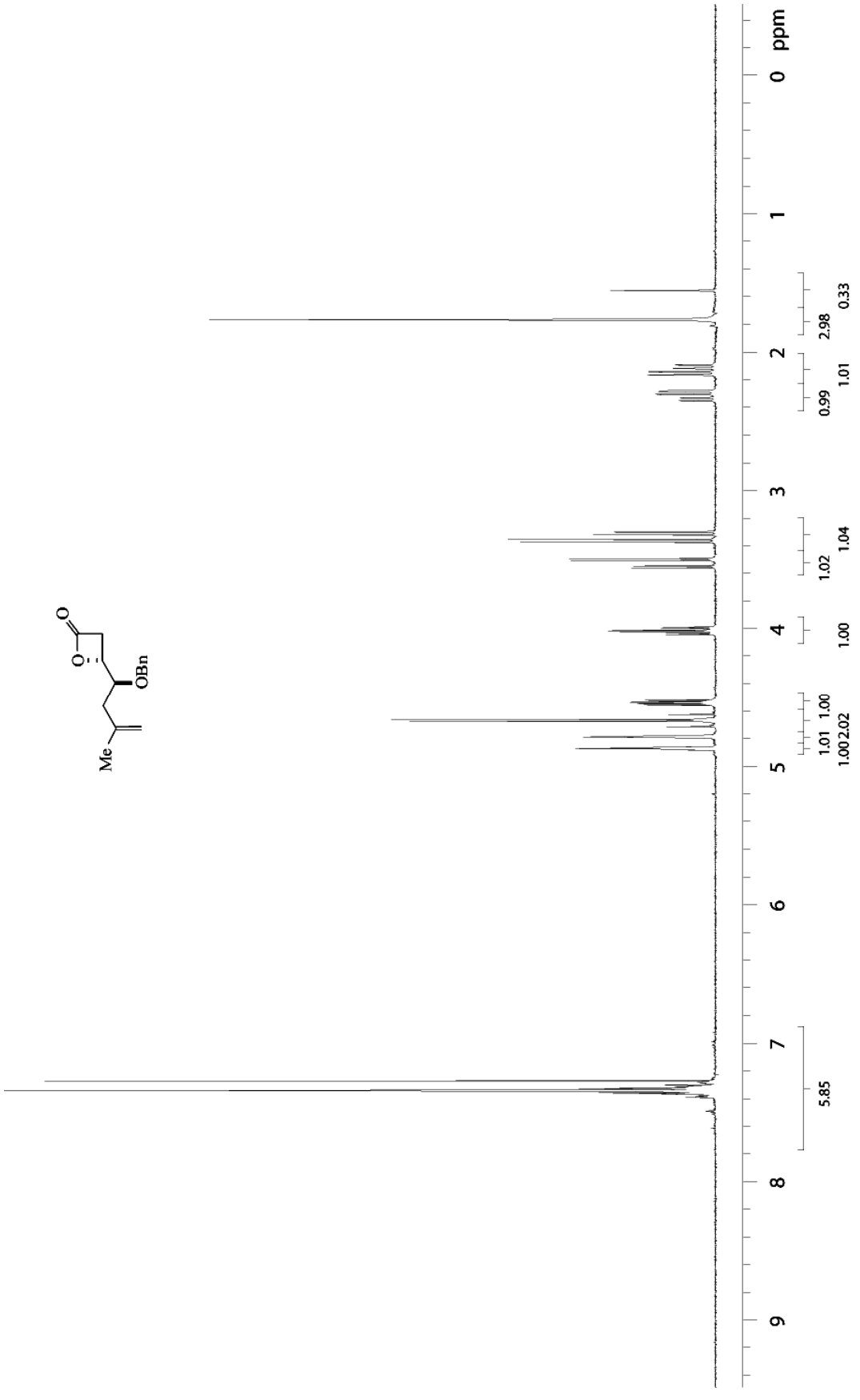
^{13}C NMR (75 MHz) of β-Silyloxy Aldehyde **(±)-3.1c** in $CDCl_3$



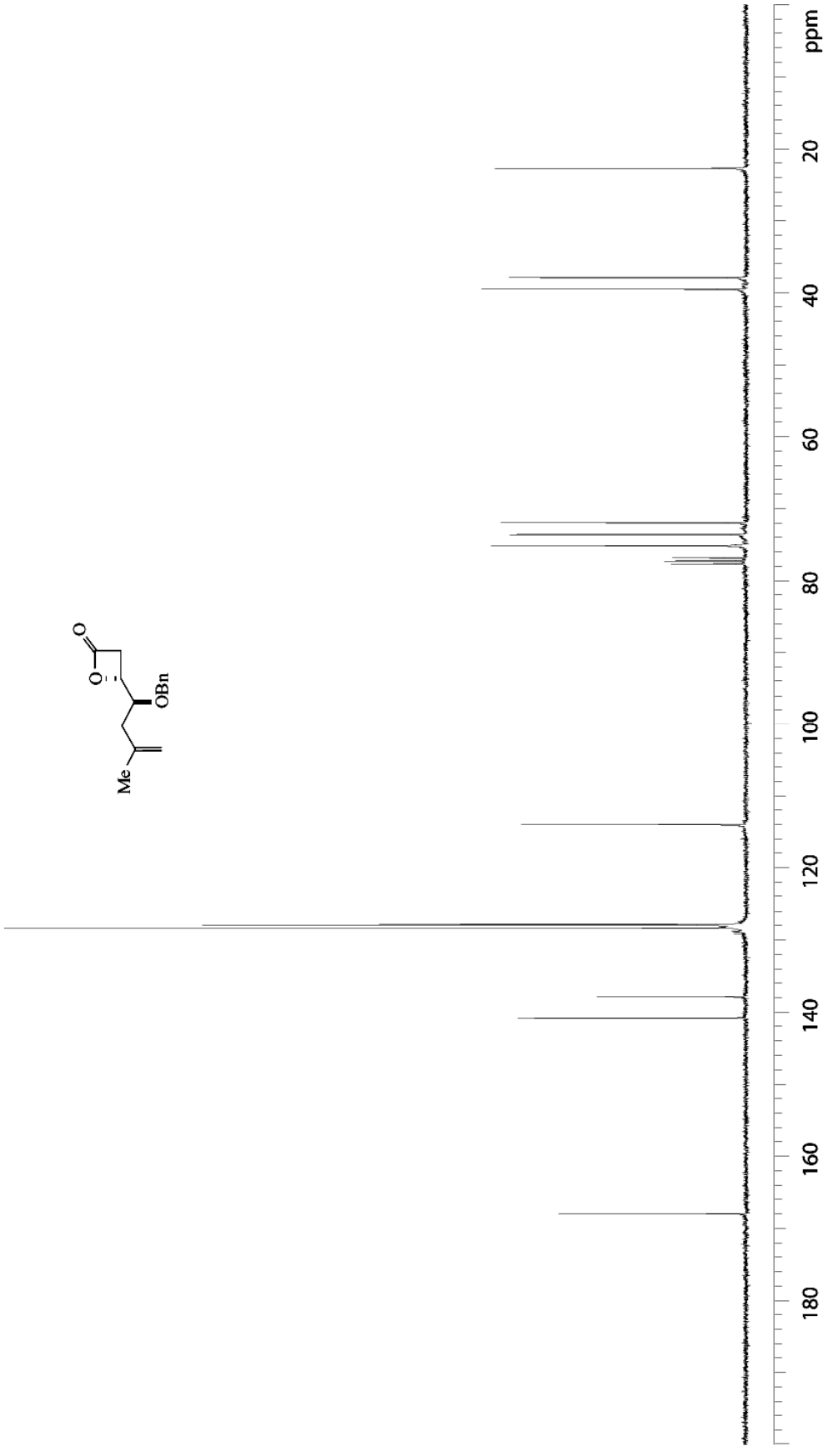
^{1}H NMR (300 MHz) of γ-Benzyloxy-Alkenyl-β-Lactone *syn*-**3.3a** in $CDCl_3$



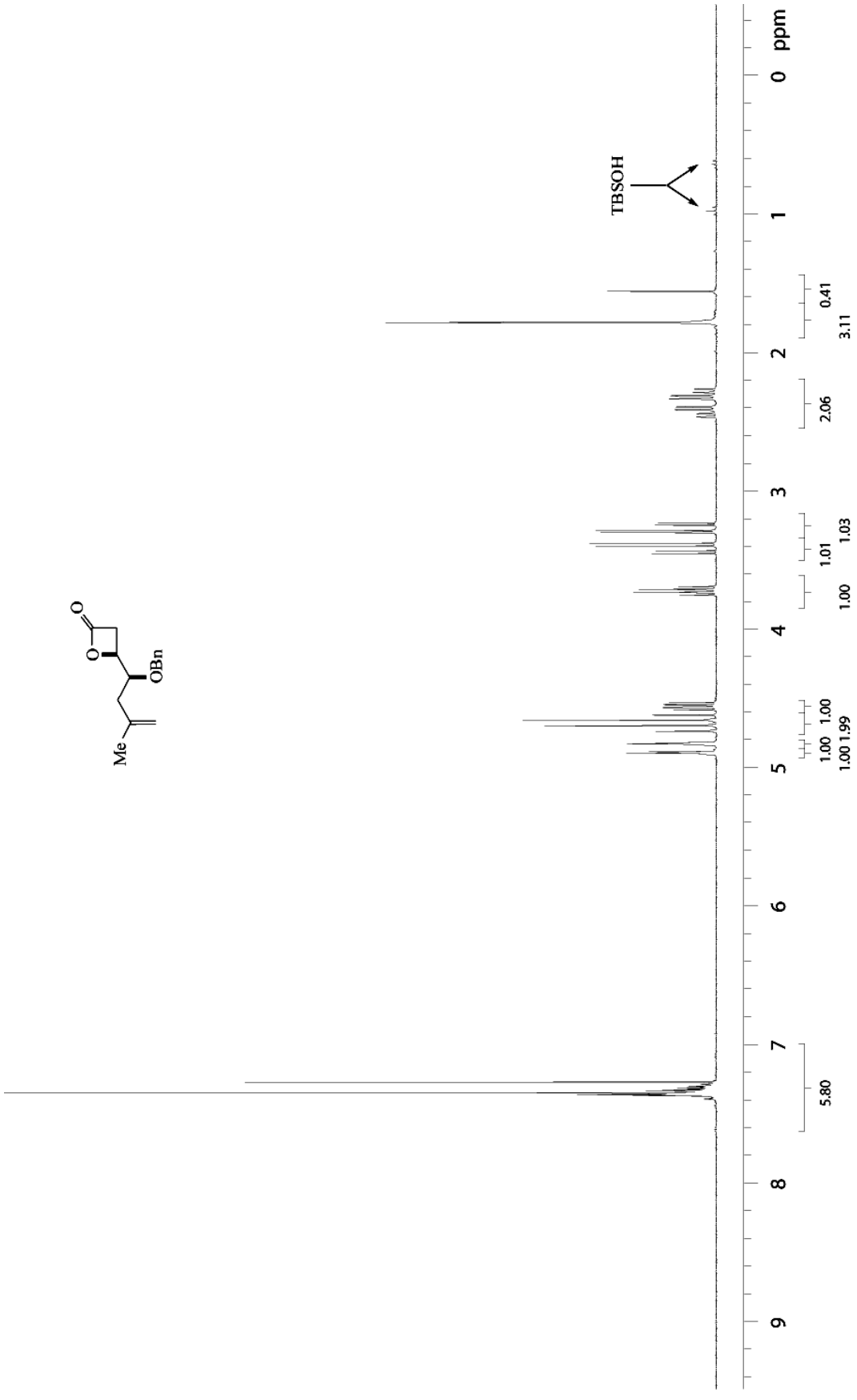
^{13}C NMR (75 MHz) of γ-Benzyloxy-Alkenyl-β-Lactone *syn*-**3.3a** in $CDCl_3$



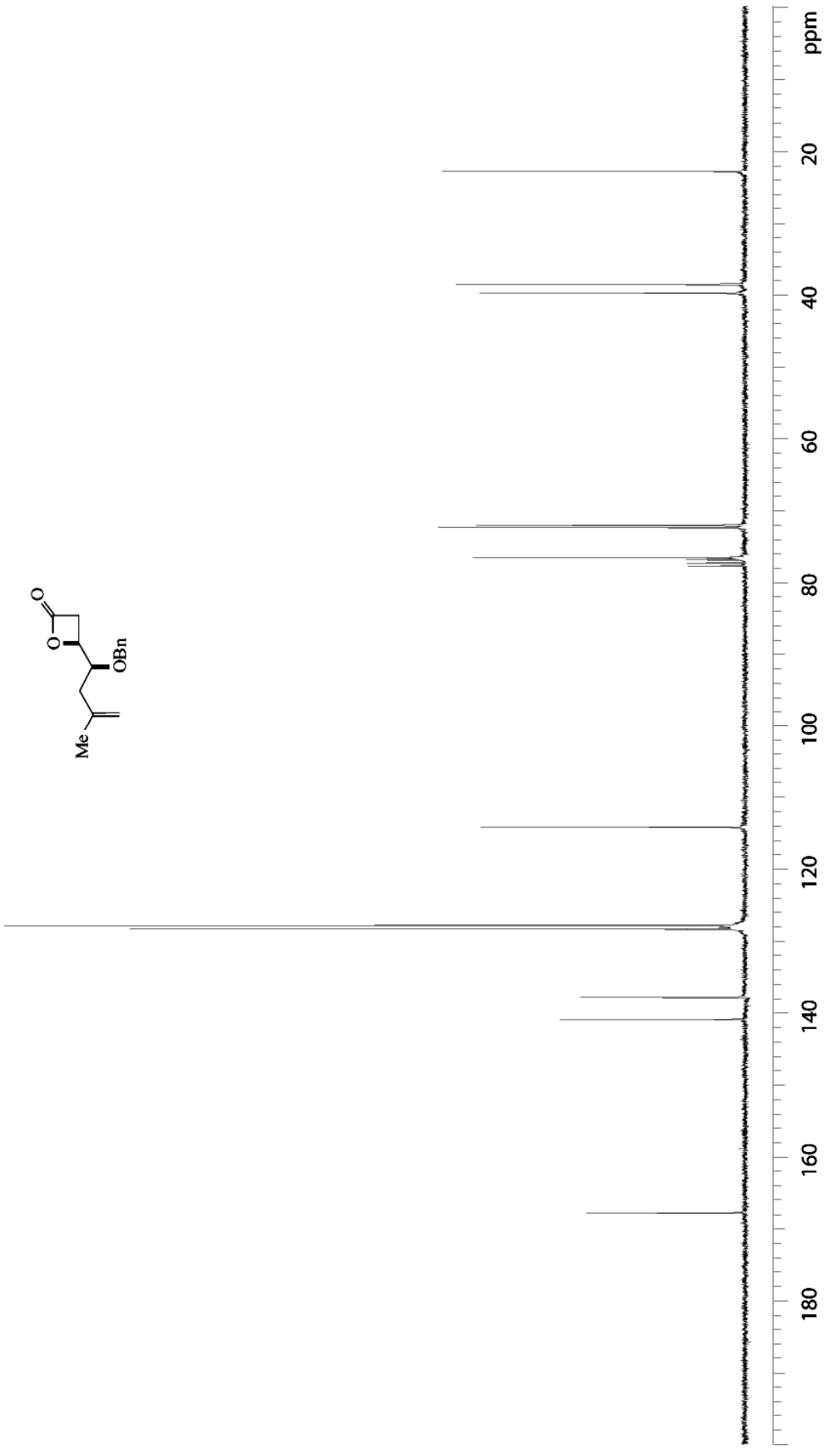
^{1}H NMR (300 MHz) of γ-Benzyloxy-Alkenyl-β-Lactone *anti*-**3.3b** in $CDCl_3$



^{13}C NMR (75 MHz) of γ-Benzyloxy-Alkenyl-β-Lactone *anti*-**3.3b** in $CDCl_3$

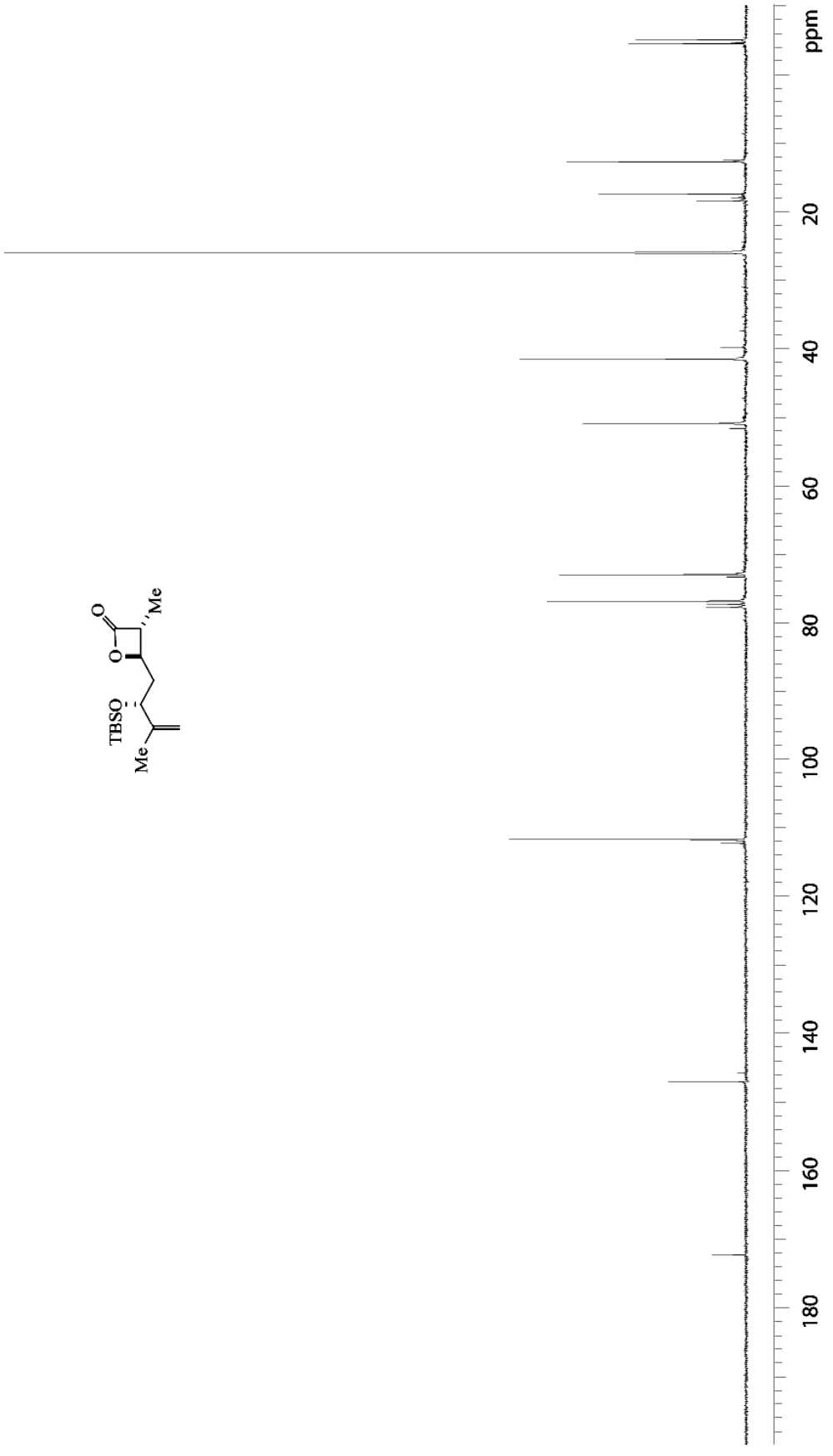


^{1}H NMR (300 MHz) of γ-Benzyloxy-Alkenyl-β-Lactone *syn*-**3.3b** in $CDCl_3$

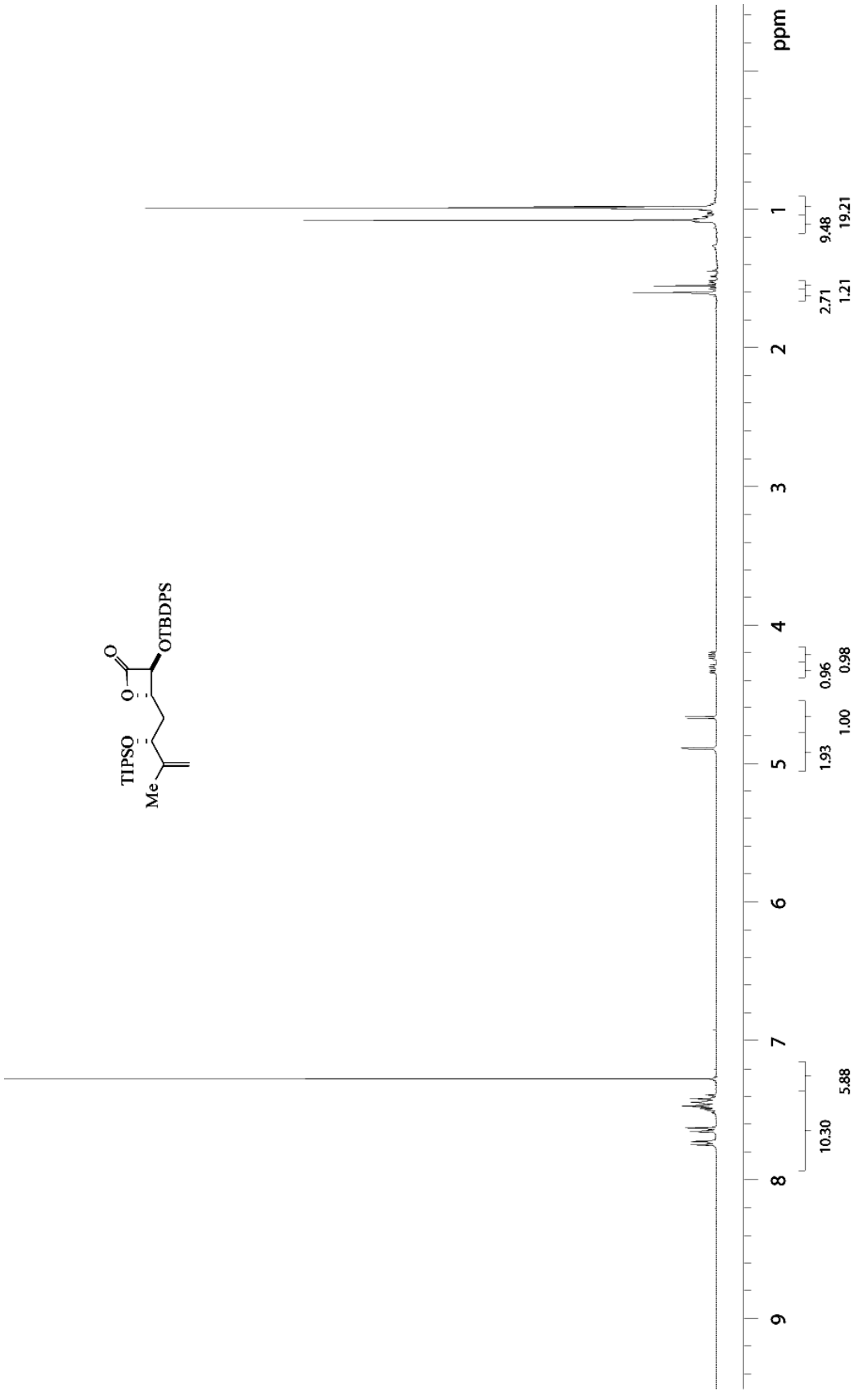


^{13}C NMR (75 MHz) of γ-Benzyloxy-Alkenyl-β-Lactone *syn*-**3.3b** in $CDCl_3$

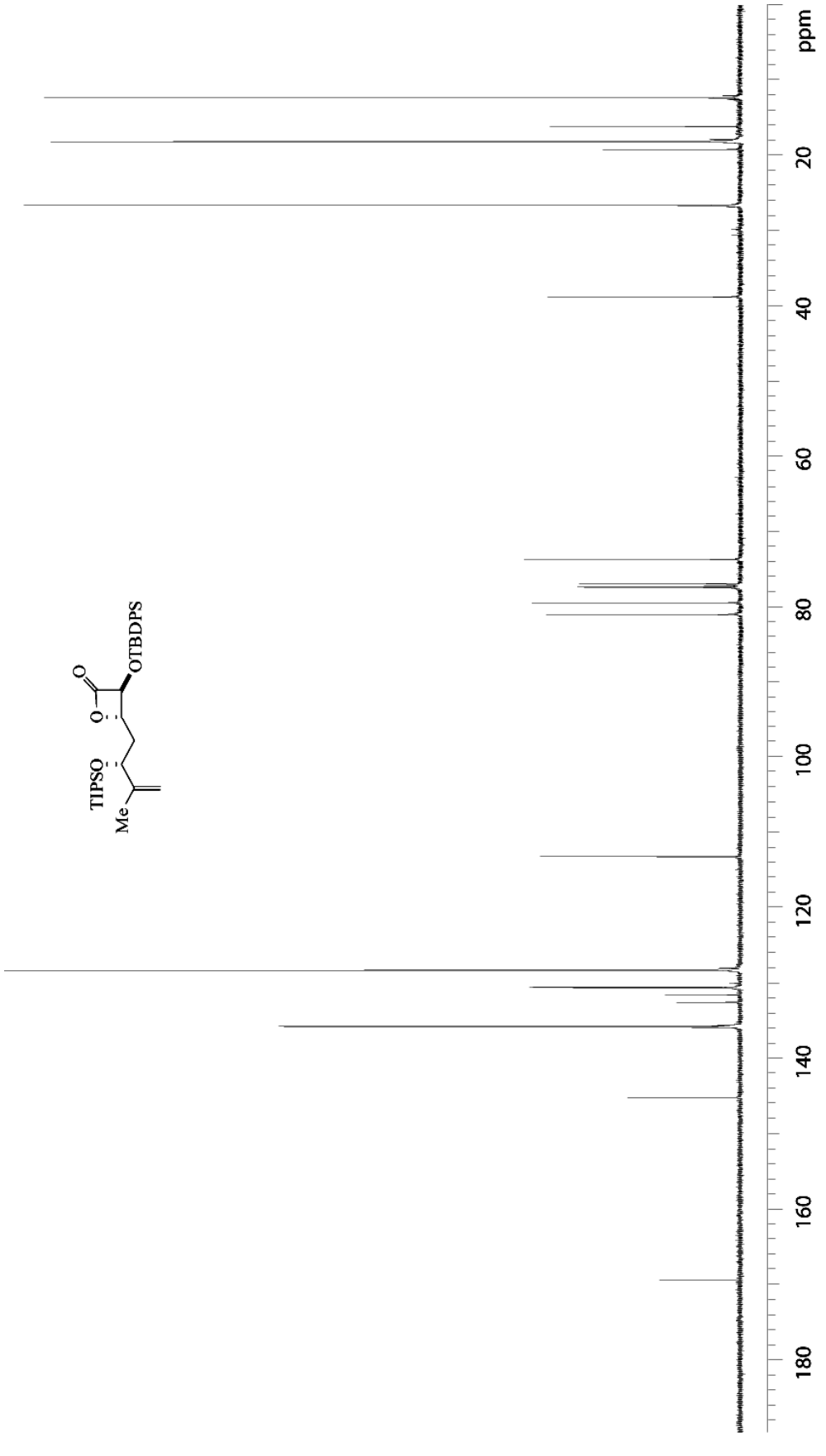
^{1}H NMR (300 MHz) of δ-Silyloxy-Alkenyl-β-Lactone *anti*-**3.3d** in $CDCl_3$



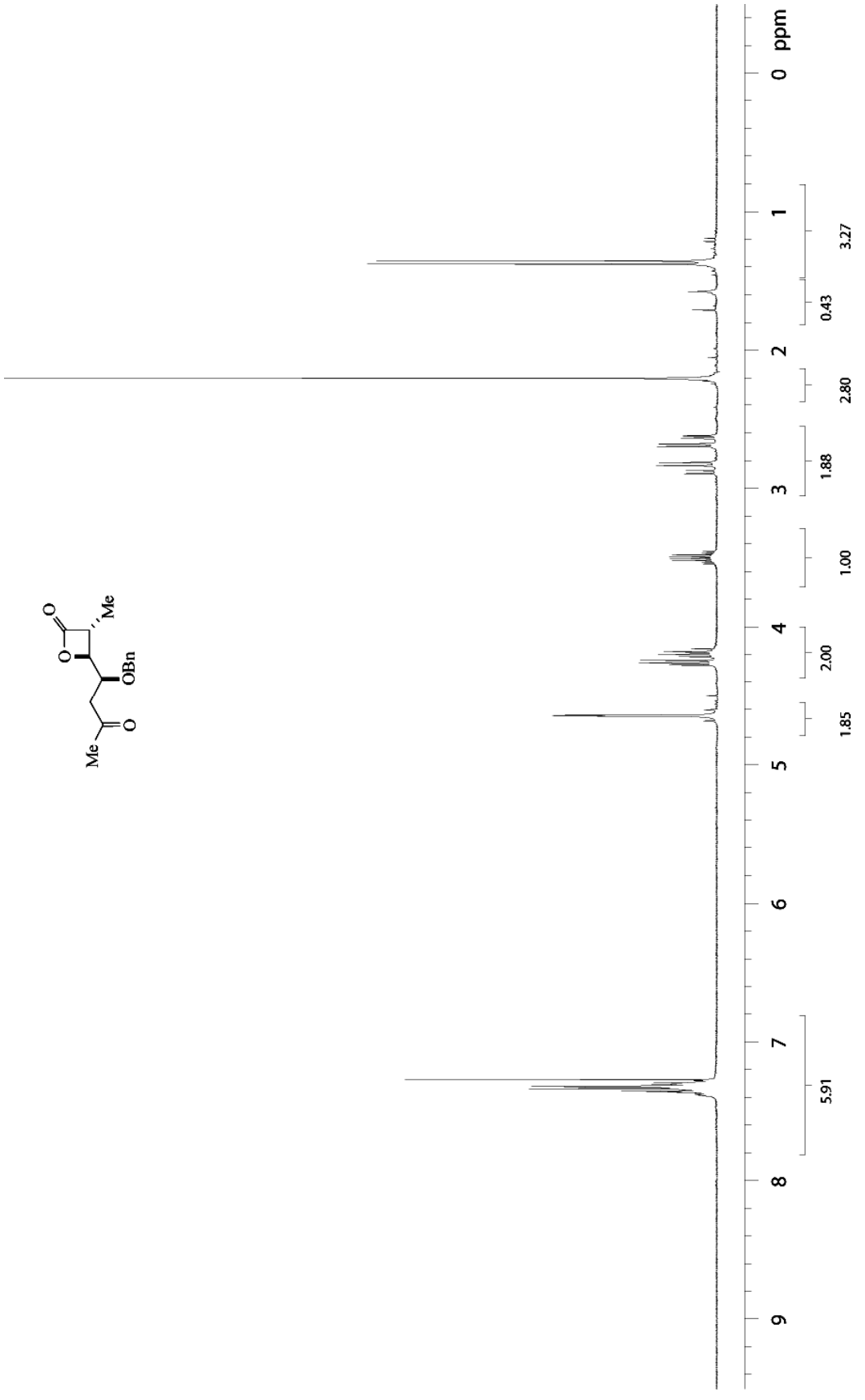
^{13}C NMR (75 MHz) of δ-Silyloxy-Alkenyl-β-Lactone *anti*-**3.3d** in $CDCl_3$



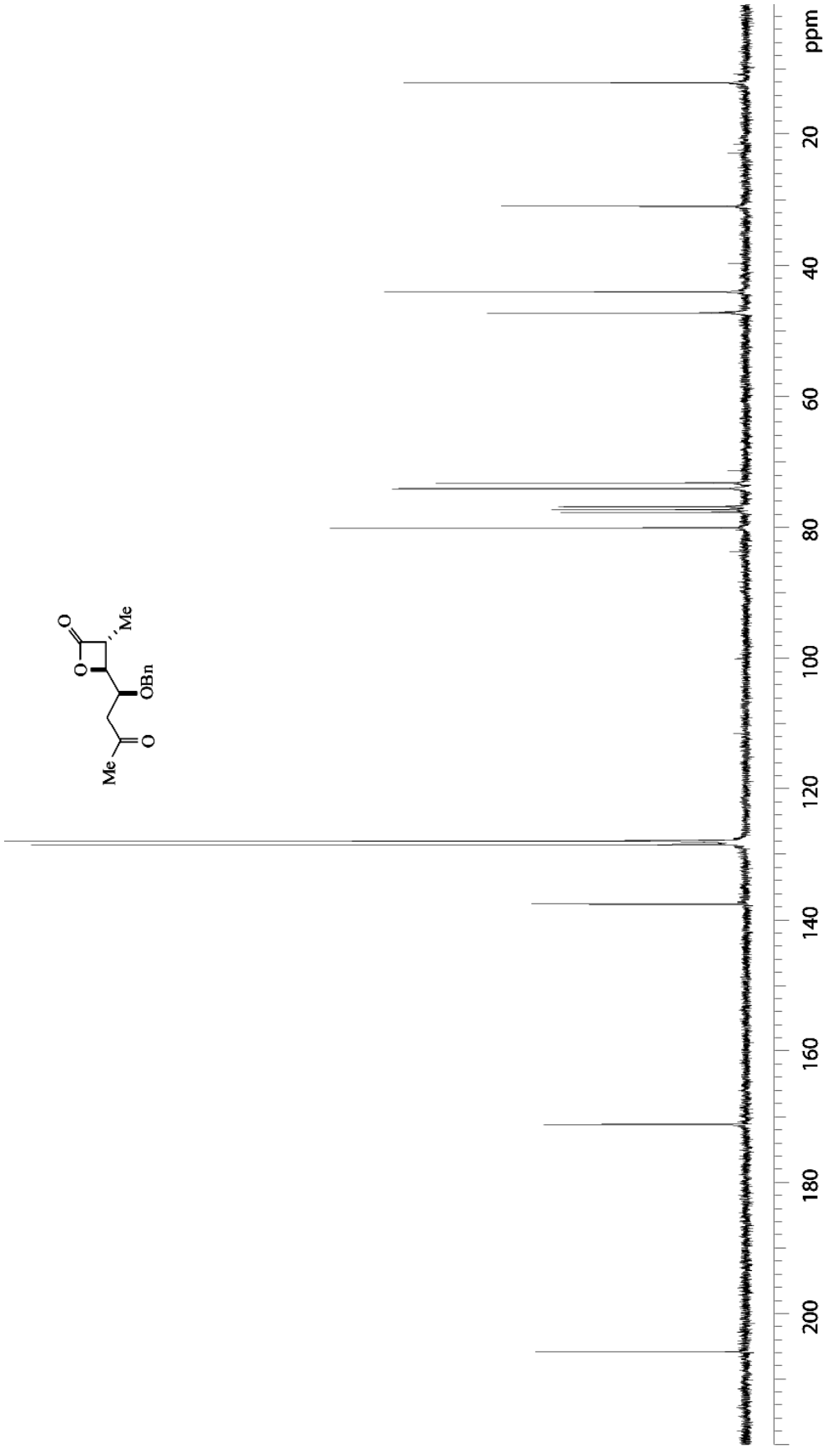
^{1}H NMR (300 MHz) of δ-Silyloxy-Alkenyl-β-Lactone *syn*-**3.3f** in $CDCl_3$



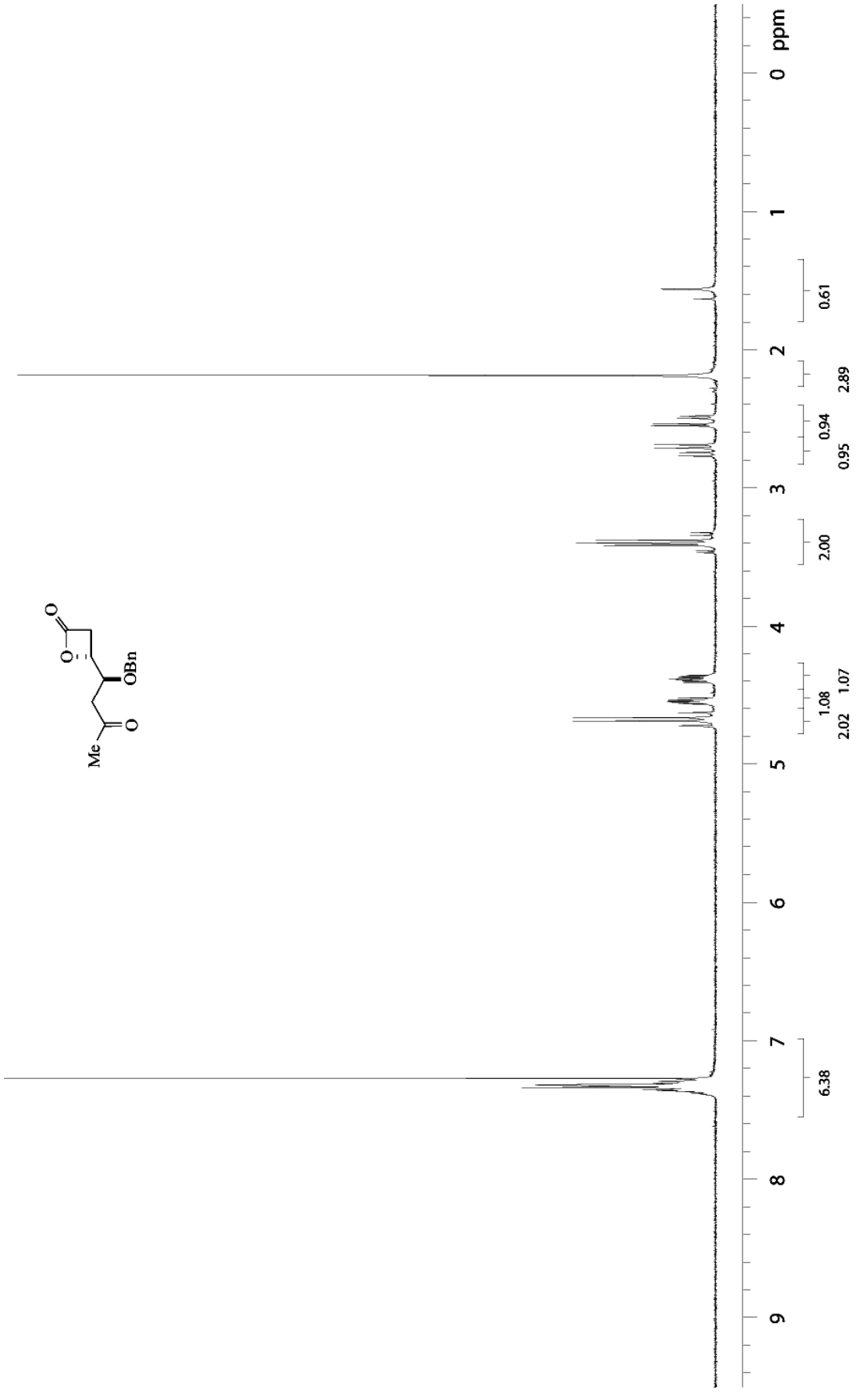
^{13}C NMR (75 MHz) of δ-Silyloxy-Alkenyl-β-Lactone *syn*-**3.3f** in $CDCl_3$



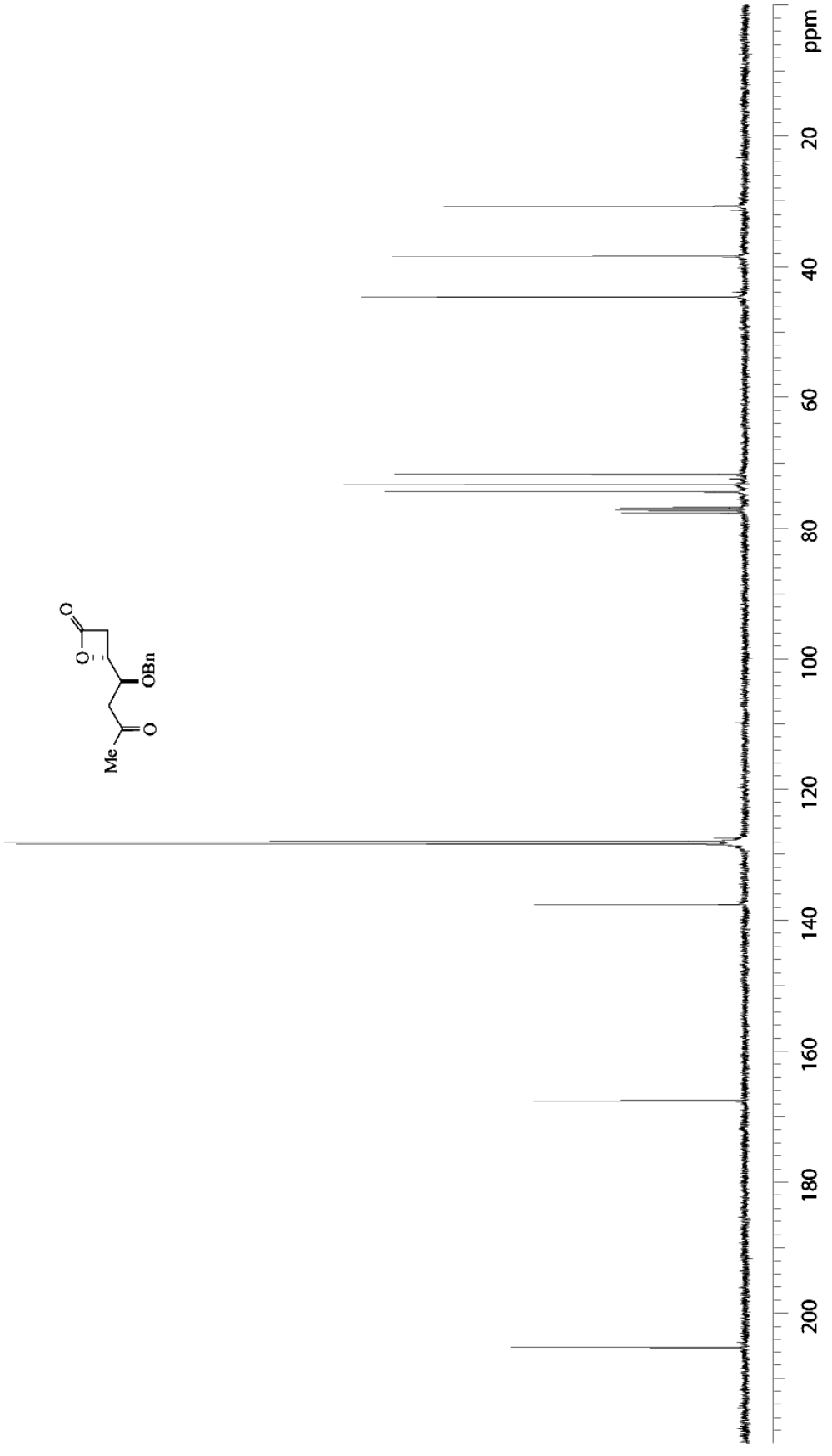
^{1}H NMR (300 MHz) of γ-Benzyloxy-Keto-β-Lactone *syn*-**3.4a** in $CDCl_3$



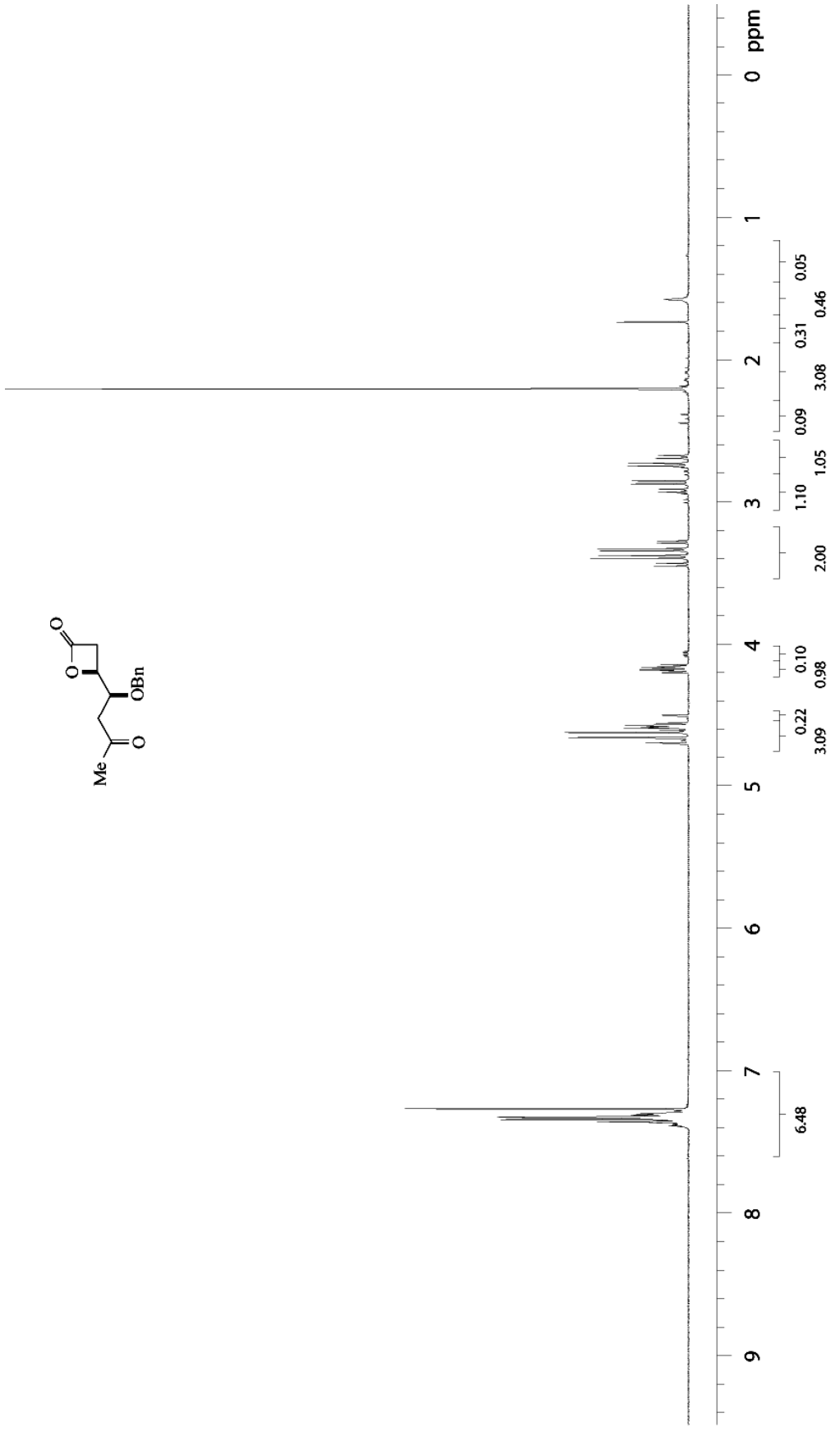
^{13}C NMR (75 MHz) of γ-Benzyloxy-Keto-β-Lactone *syn*-**3.4a** in $CDCl_3$



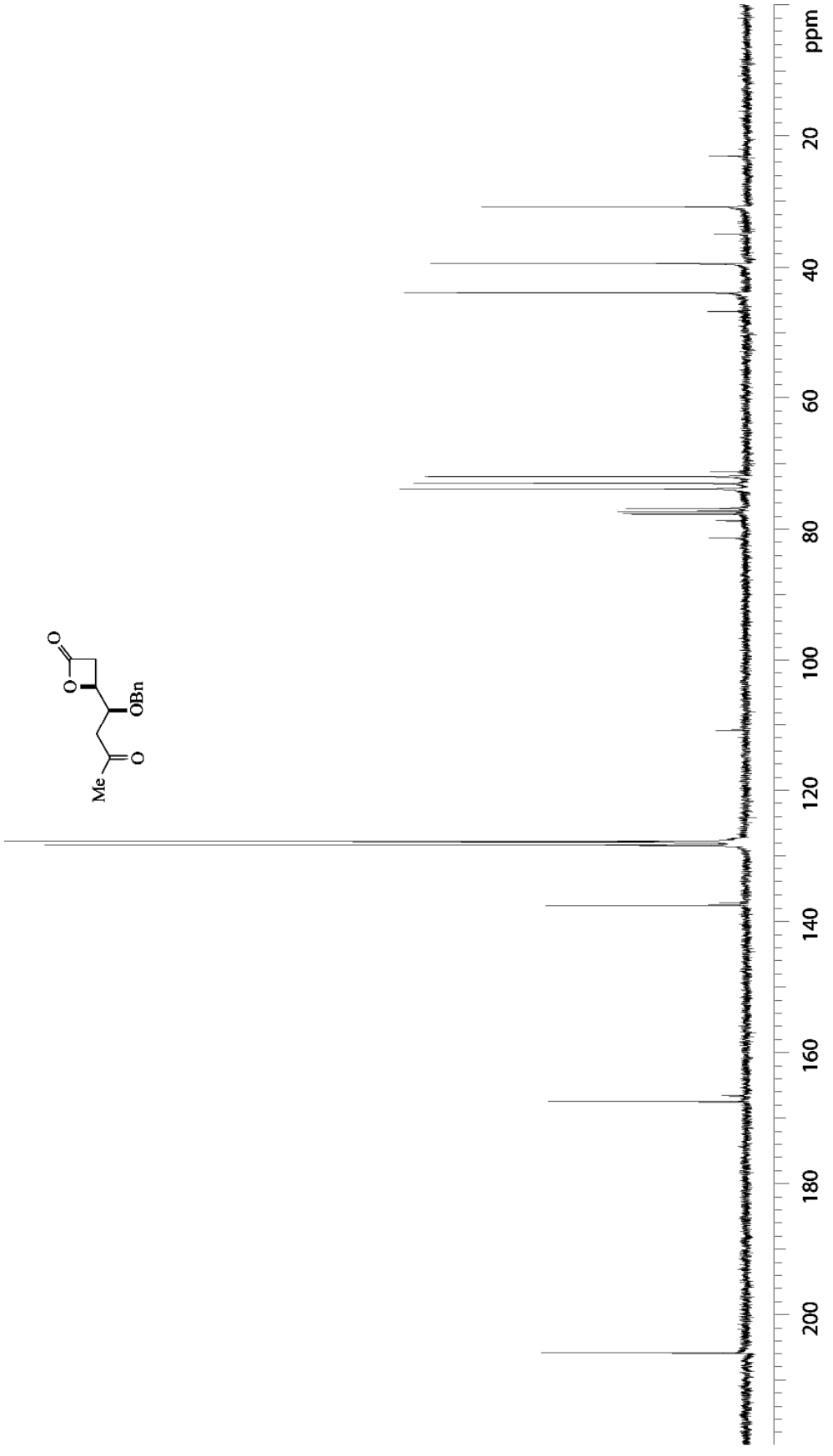
^{1}H NMR (300 MHz) of γ-Benzyloxy-Keto-β-Lactone *anti*-**3.4b** in $CDCl_3$



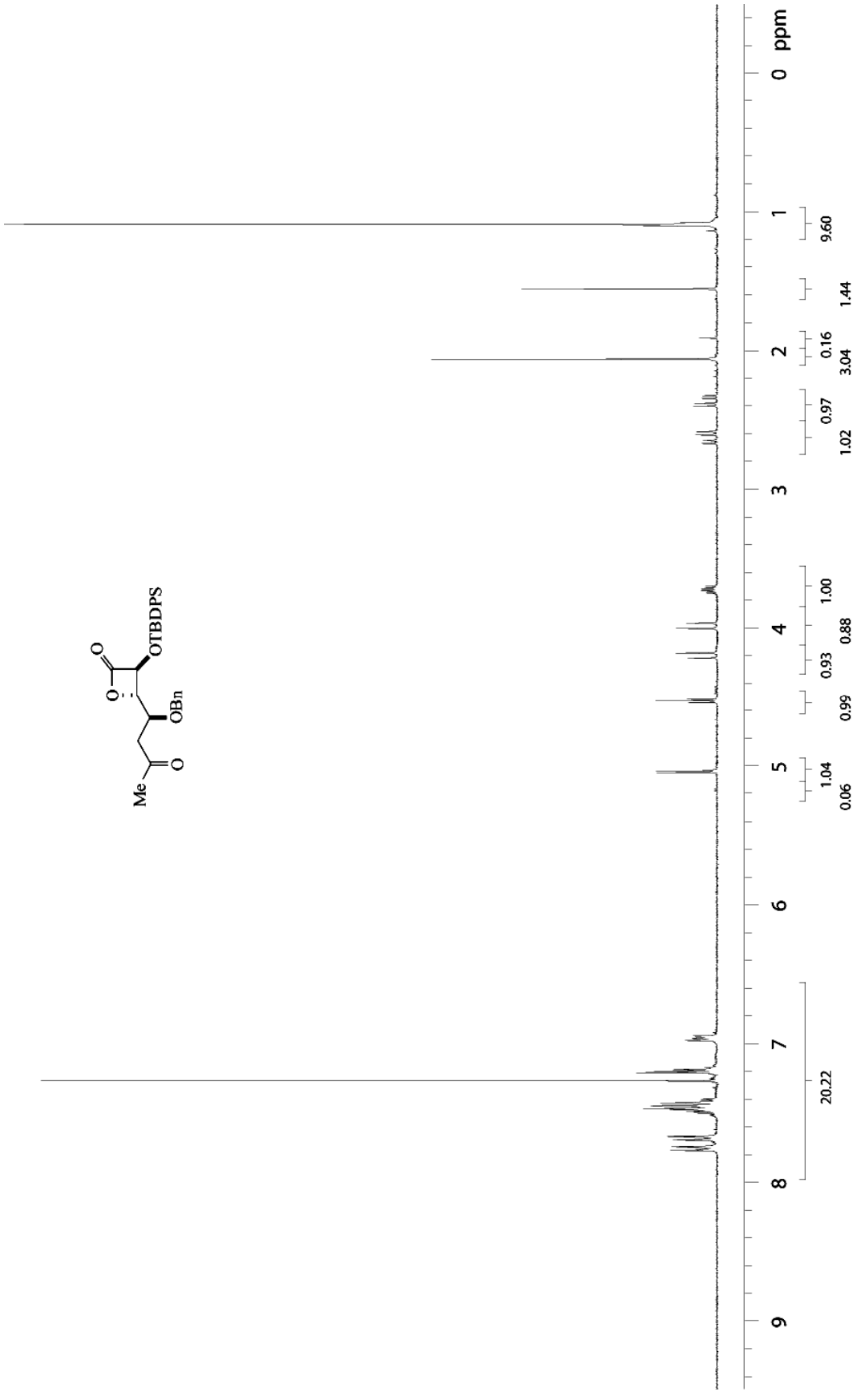
^{13}C NMR (75 MHz) of γ-Benzyloxy-Keto-β-Lactone *anti*-**3.4b** in $CDCl_3$



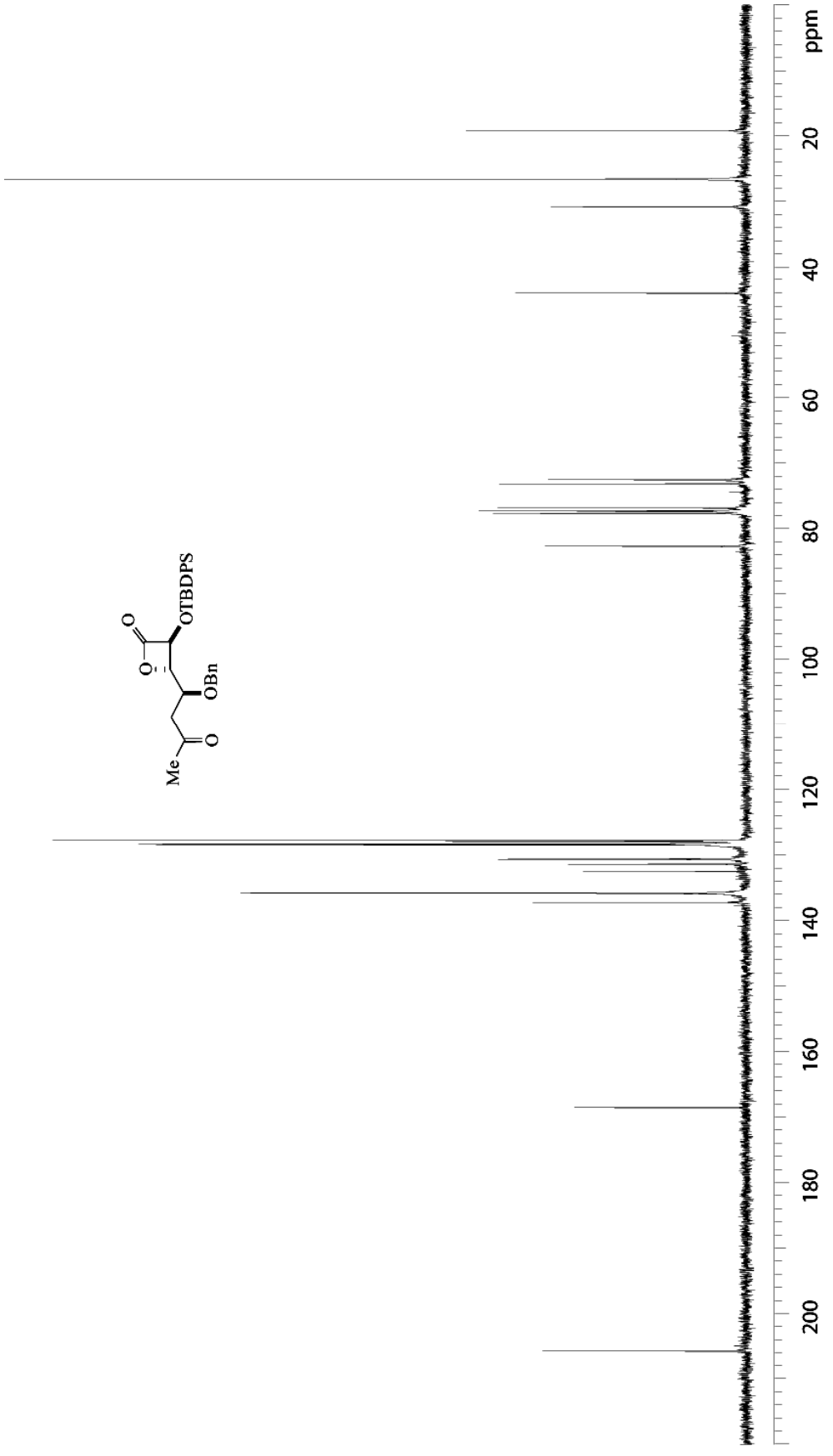
^{1}H NMR (300 MHz) of γ-Benzyloxy-Keto-β-Lactone *syn*-**3.4b** in $CDCl_3$



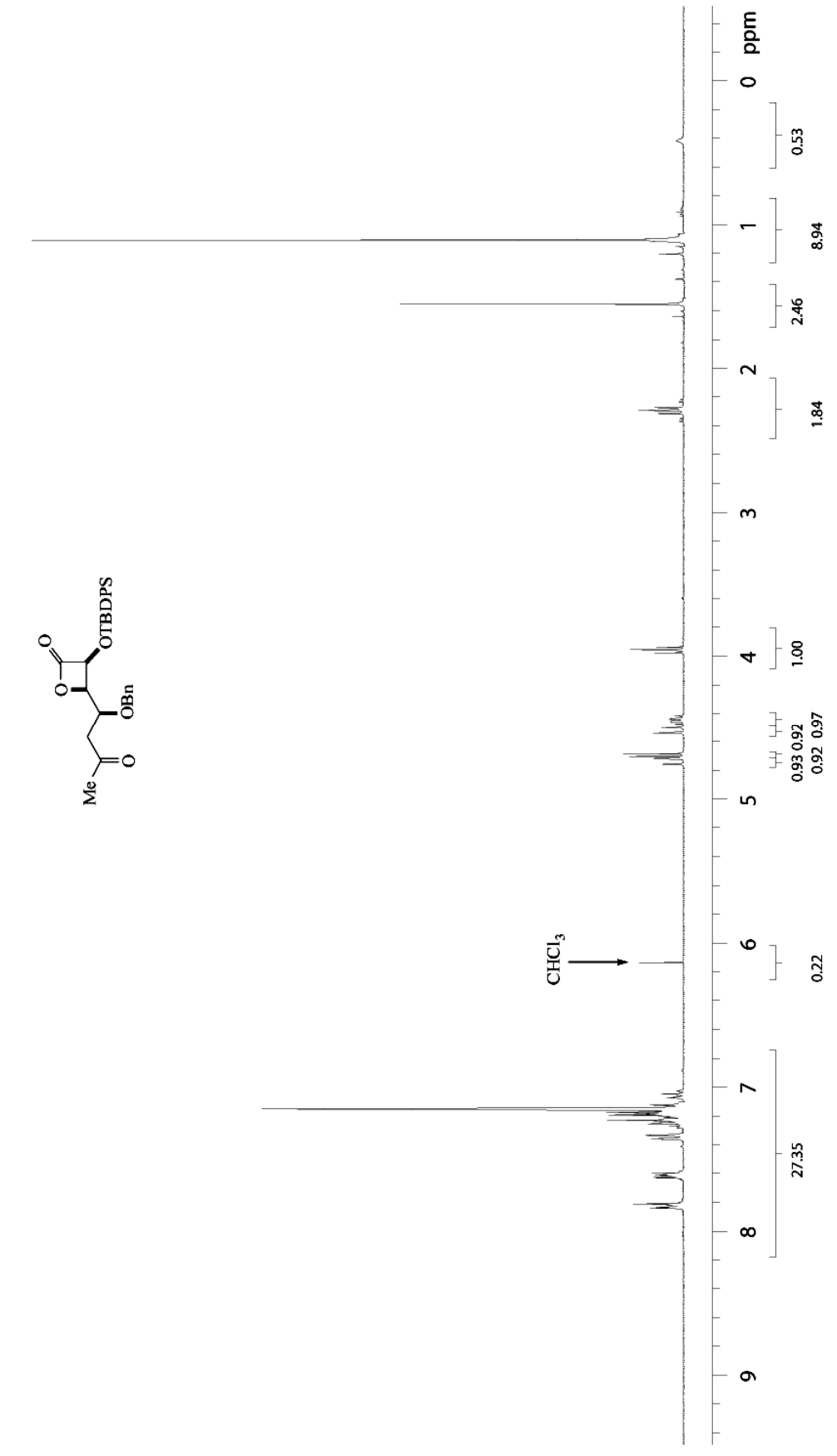
^{13}C NMR (75 MHz) of γ-Benzyloxy-Keto-β-Lactone *syn*-**3.4b** in $CDCl_3$



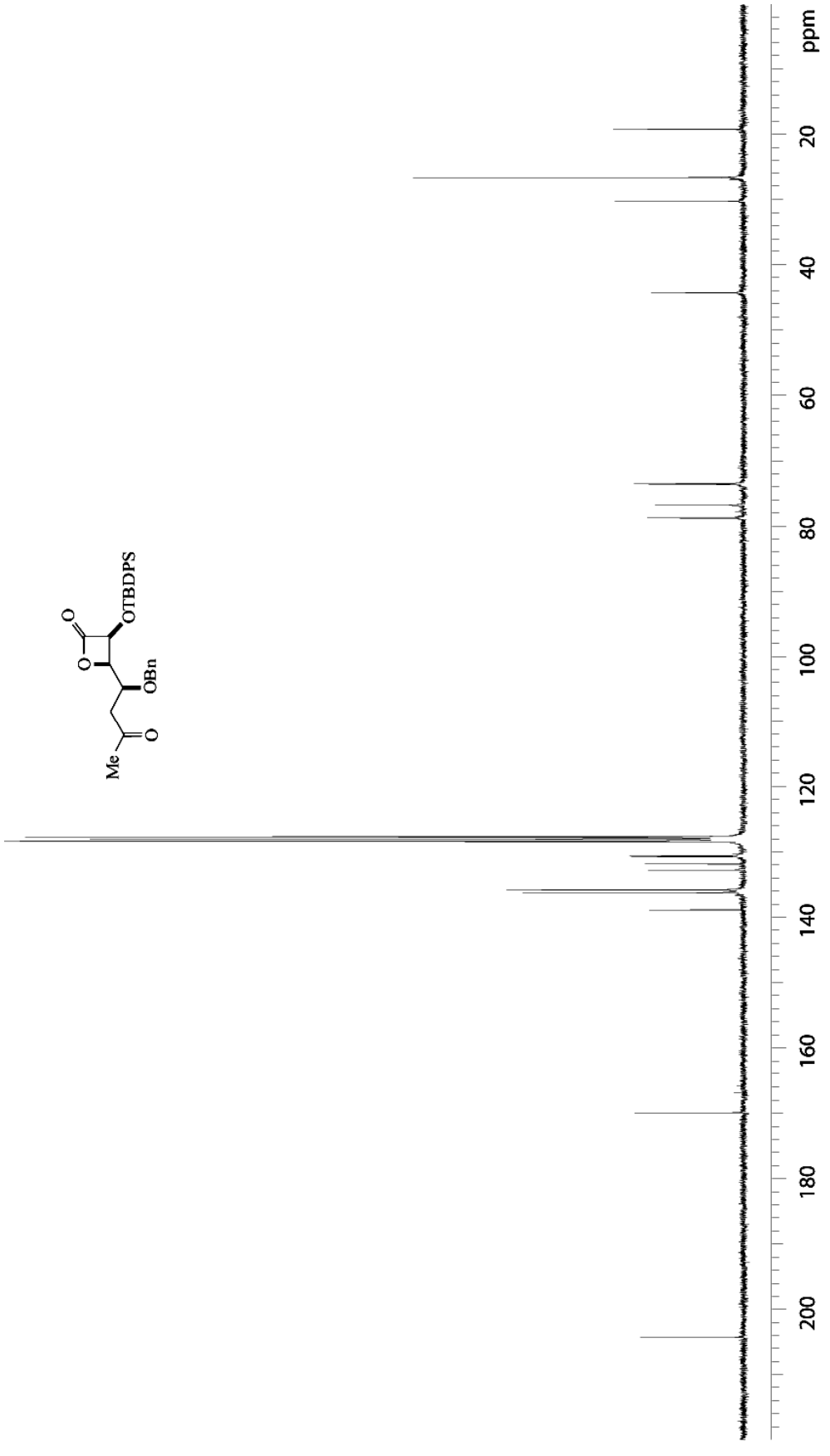
^{1}H NMR (300 MHz) of γ-Benzyloxy-Keto-β-Lactone *anti*-**3.4c** in $CDCl_3$



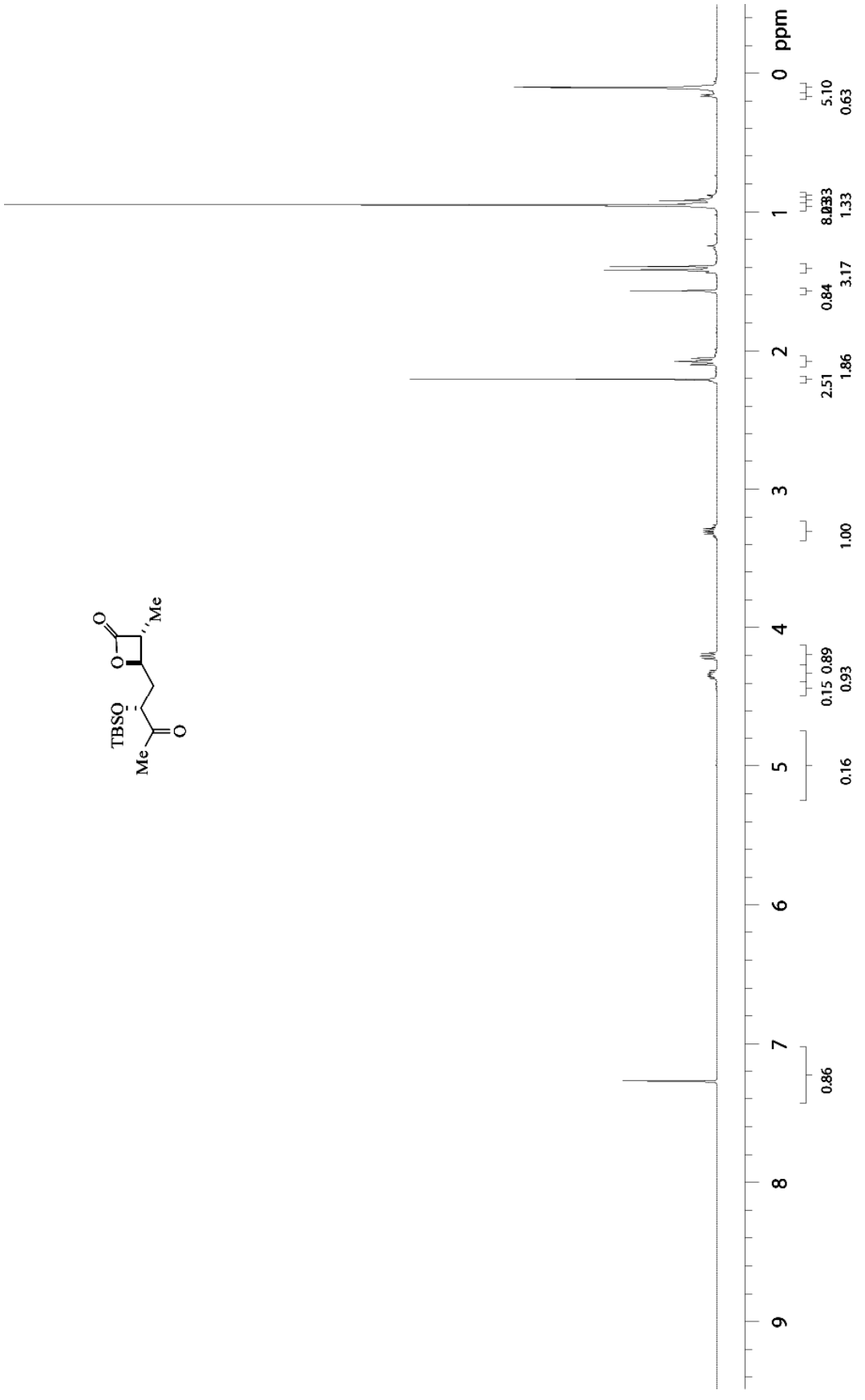
^{13}C NMR (75 MHz) of γ-Benzyloxy-Keto-β-Lactone *anti*-**3.4c** in $CDCl_3$



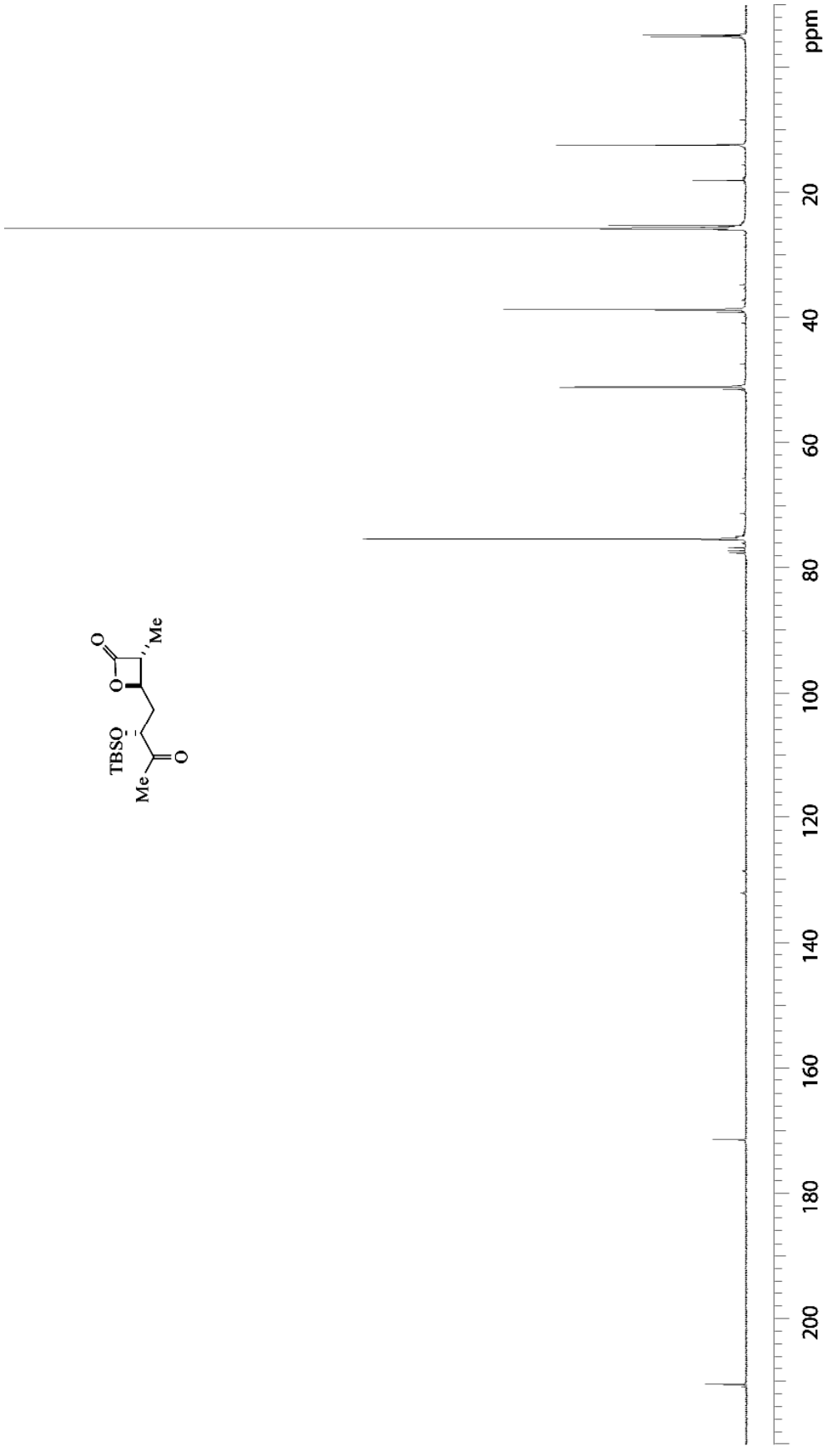
^{1}H NMR (300 MHz) of γ-Benzyloxy-Keto-β-Lactone *syn*-**3.4c** in C_6D_6



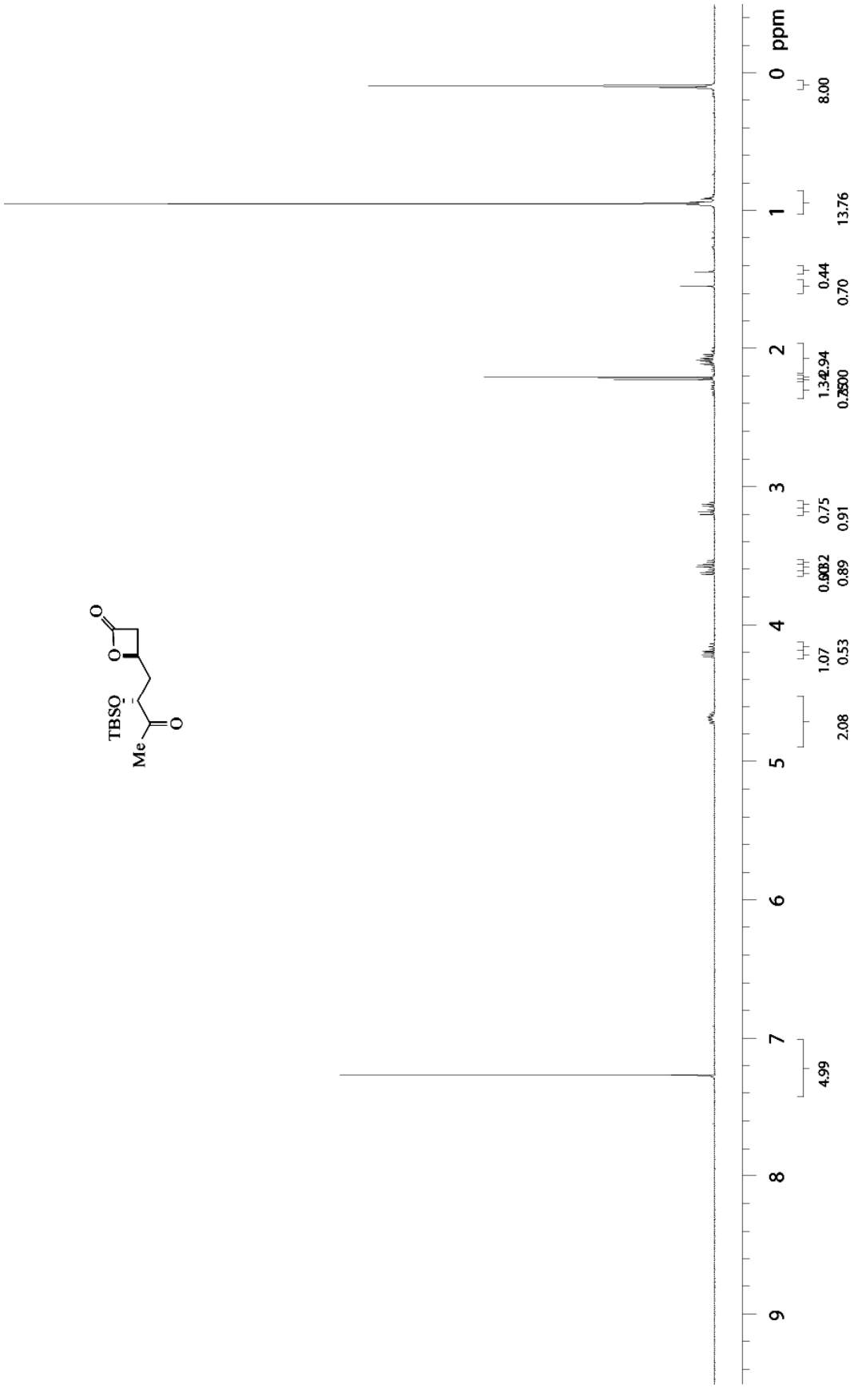
^{13}C NMR (75 MHz) of γ-Benzyloxy-Keto-β-Lactone *syn*-**3.4c** in C_6D_6



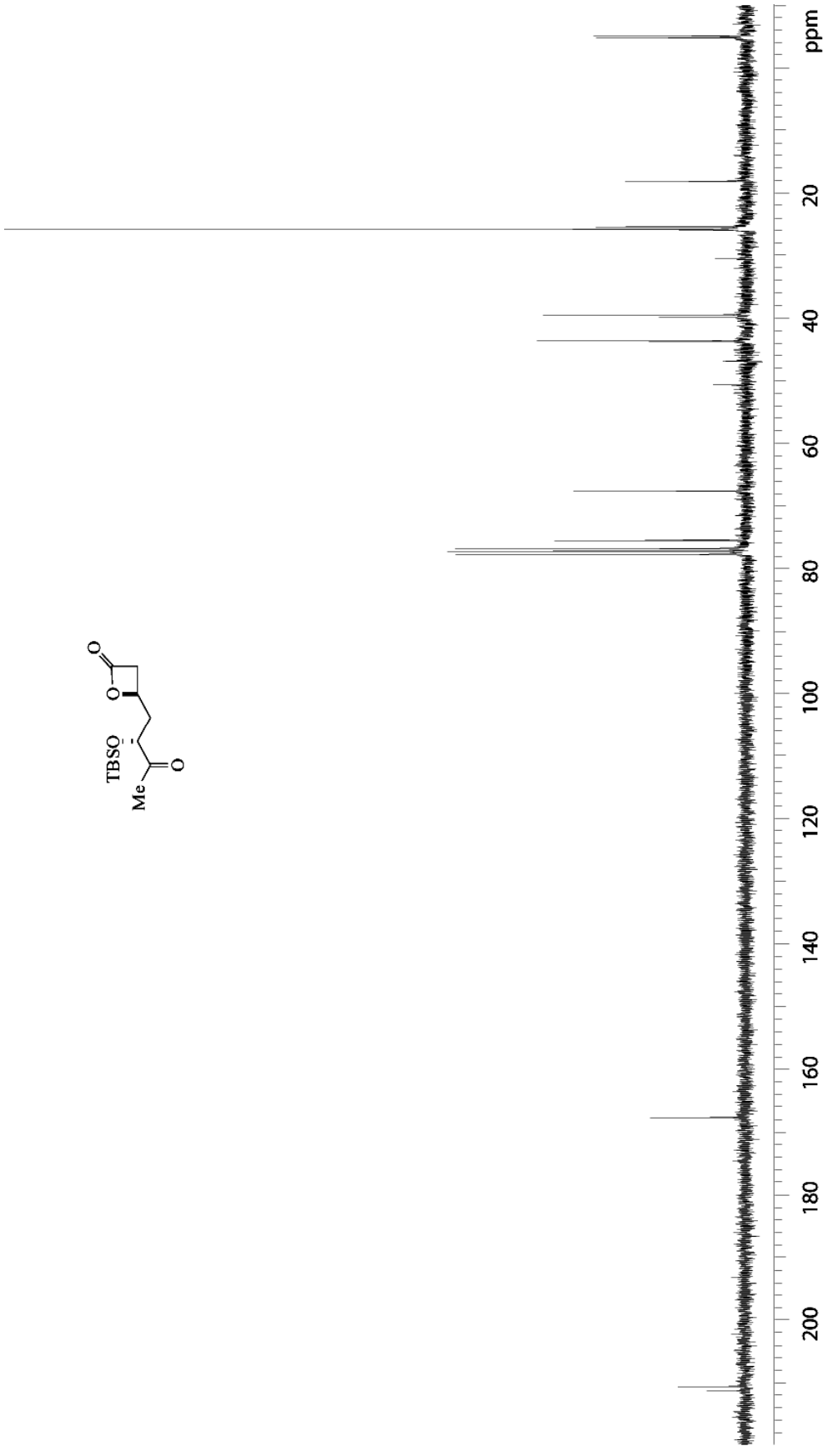
^{1}H NMR (300 MHz) of δ-Silyloxy-Keto-β-Lactone *anti*-**3.4d** in $CDCl_3$



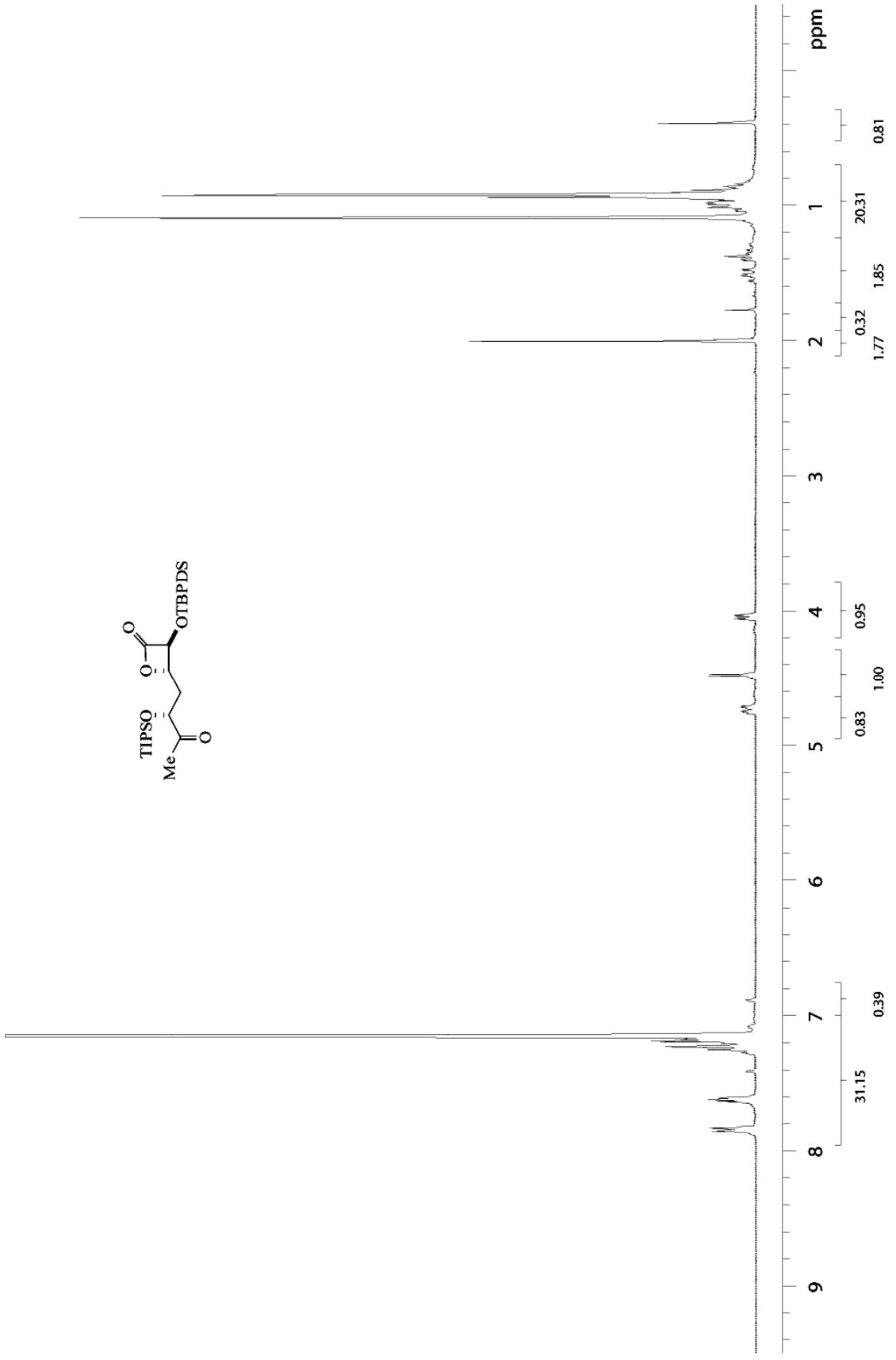
^{13}C NMR (75 MHz) of δ-Silyloxy-Keto-β-Lactone *anti*-**3.4d** in $CDCl_3$



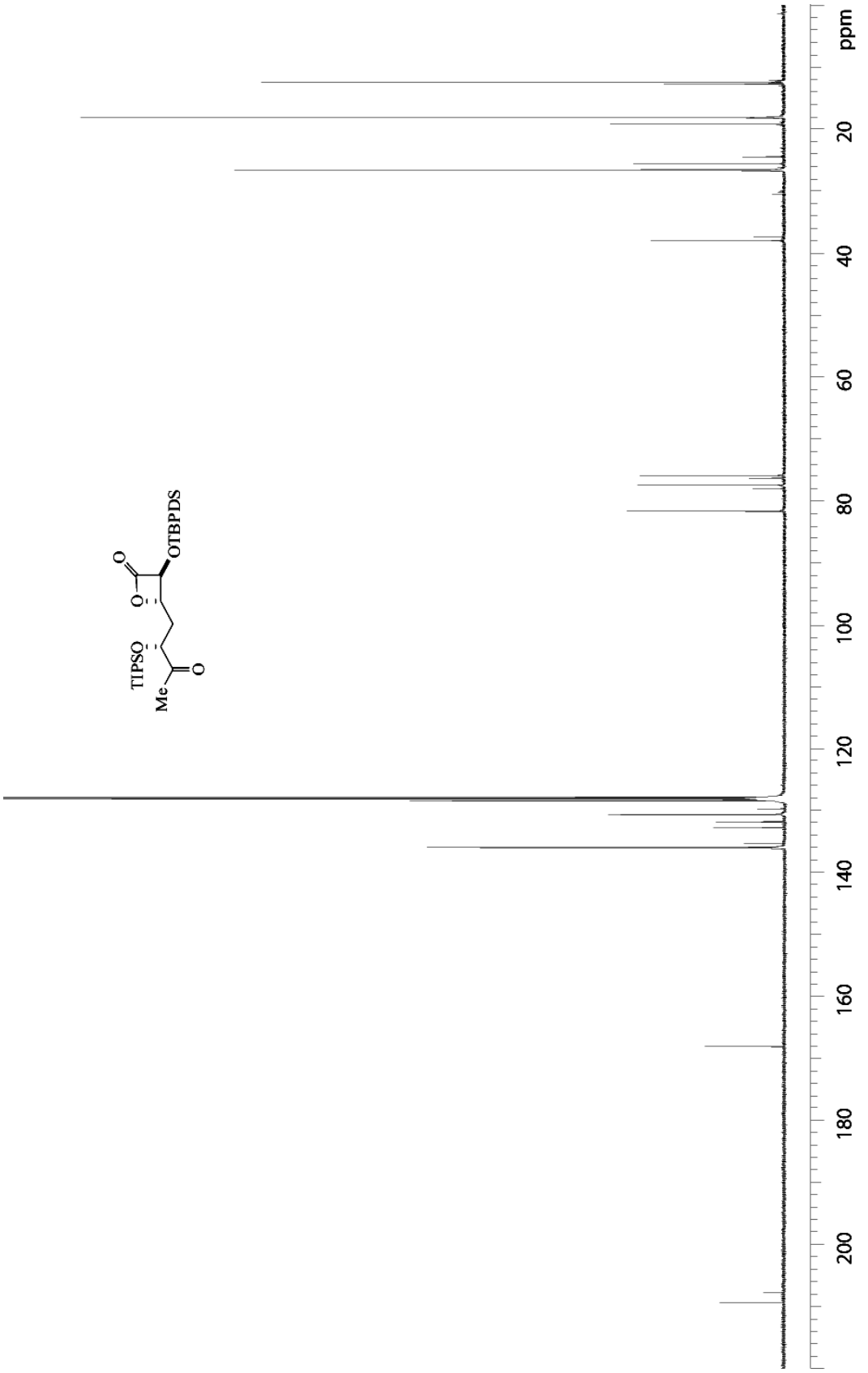
^{1}H NMR (300 MHz) of δ-Silyloxy-Keto-β-Lactone *anti*-**3.4e** in $CDCl_3$



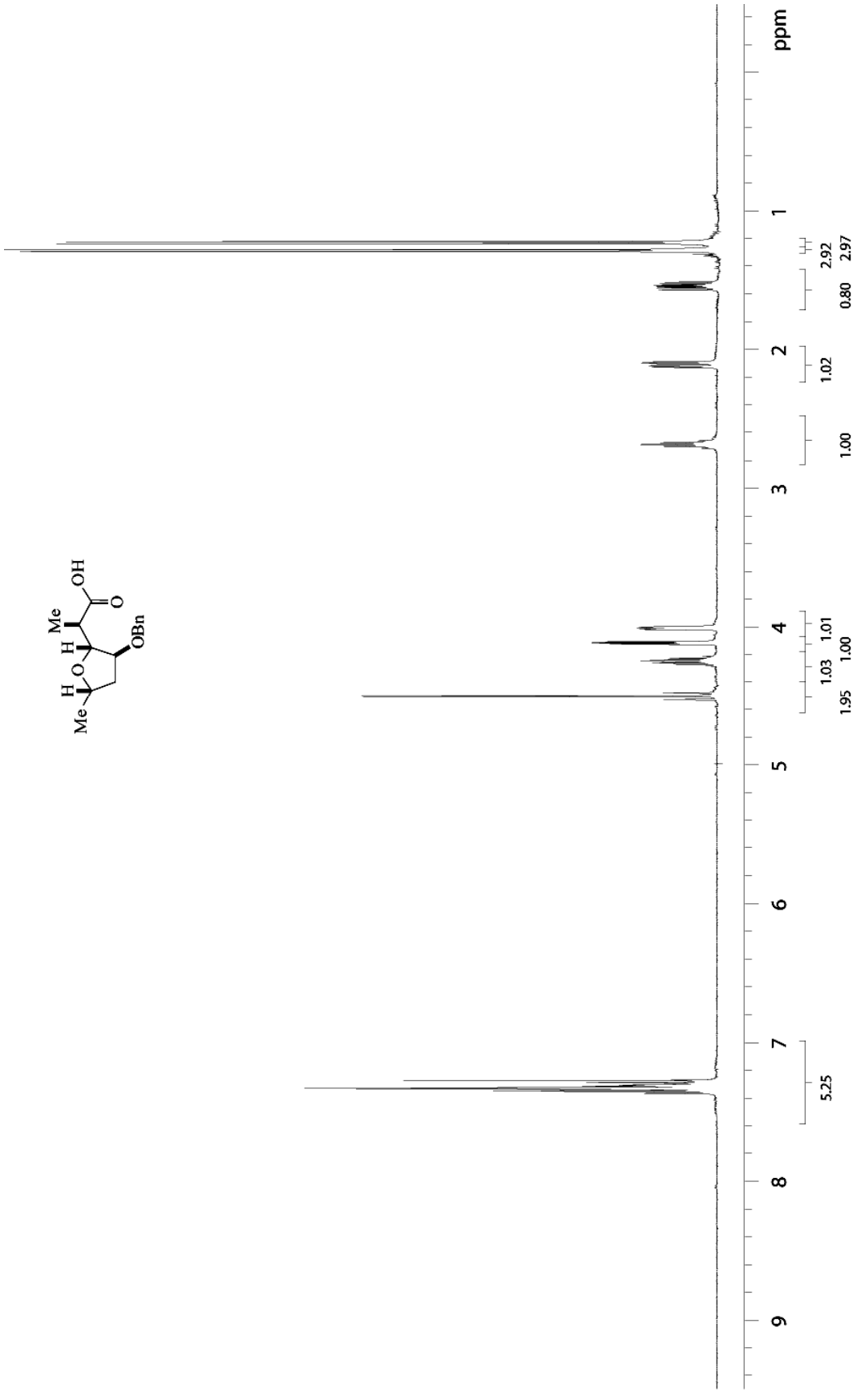
^{13}C NMR (75 MHz) of δ-Silyloxy-Keto-β-Lactone *anti*-**3.4e** in $CDCl_3$



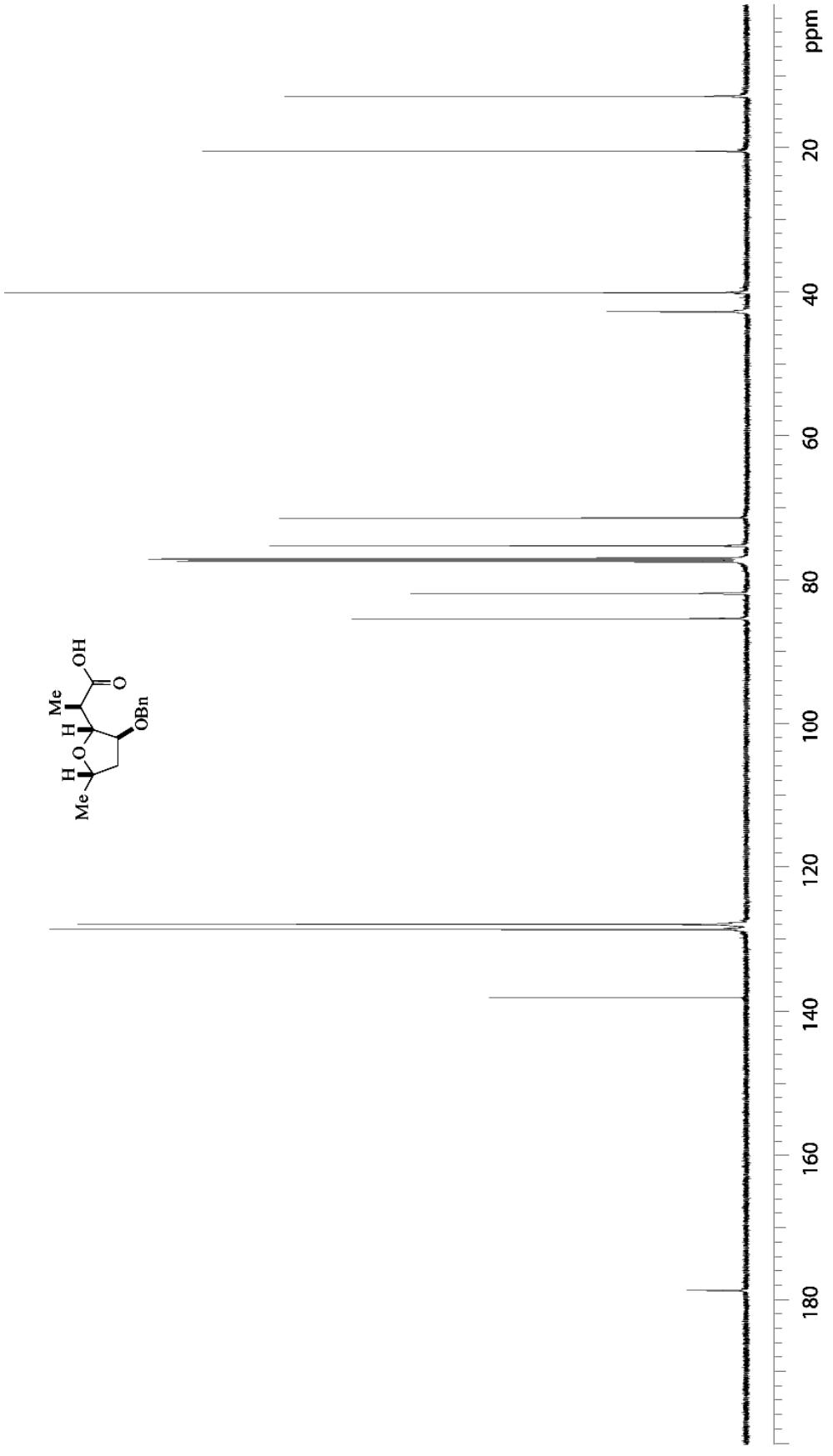
^{1}H NMR (300 MHz) of δ-Silyloxy-Keto-β-Lactone *syn*-**3.4f** in C_6D_6



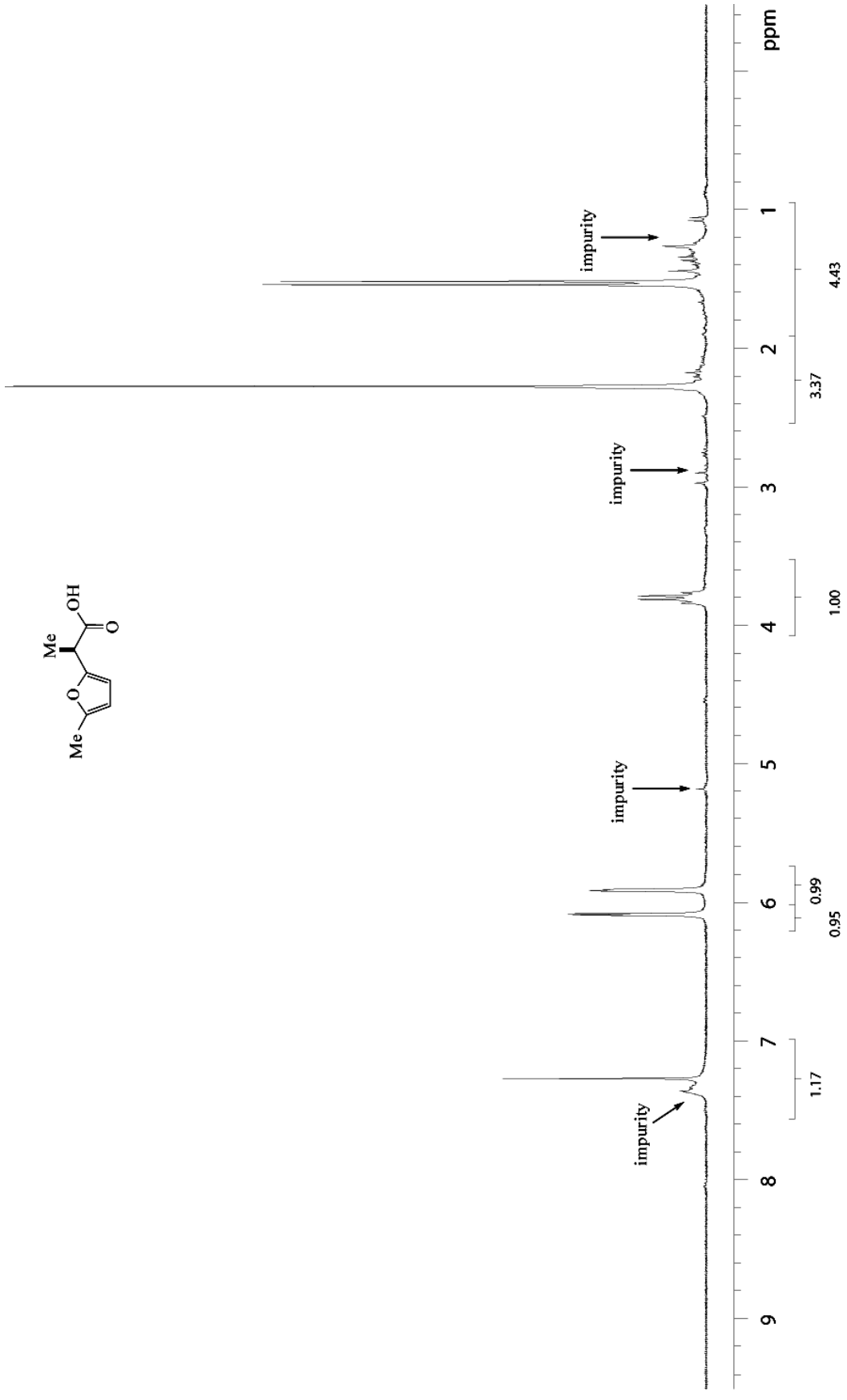
^{13}C NMR (75 MHz) of δ-Silyloxy-Keto-β-Lactone *syn*-**3.4f** in C_6D_6



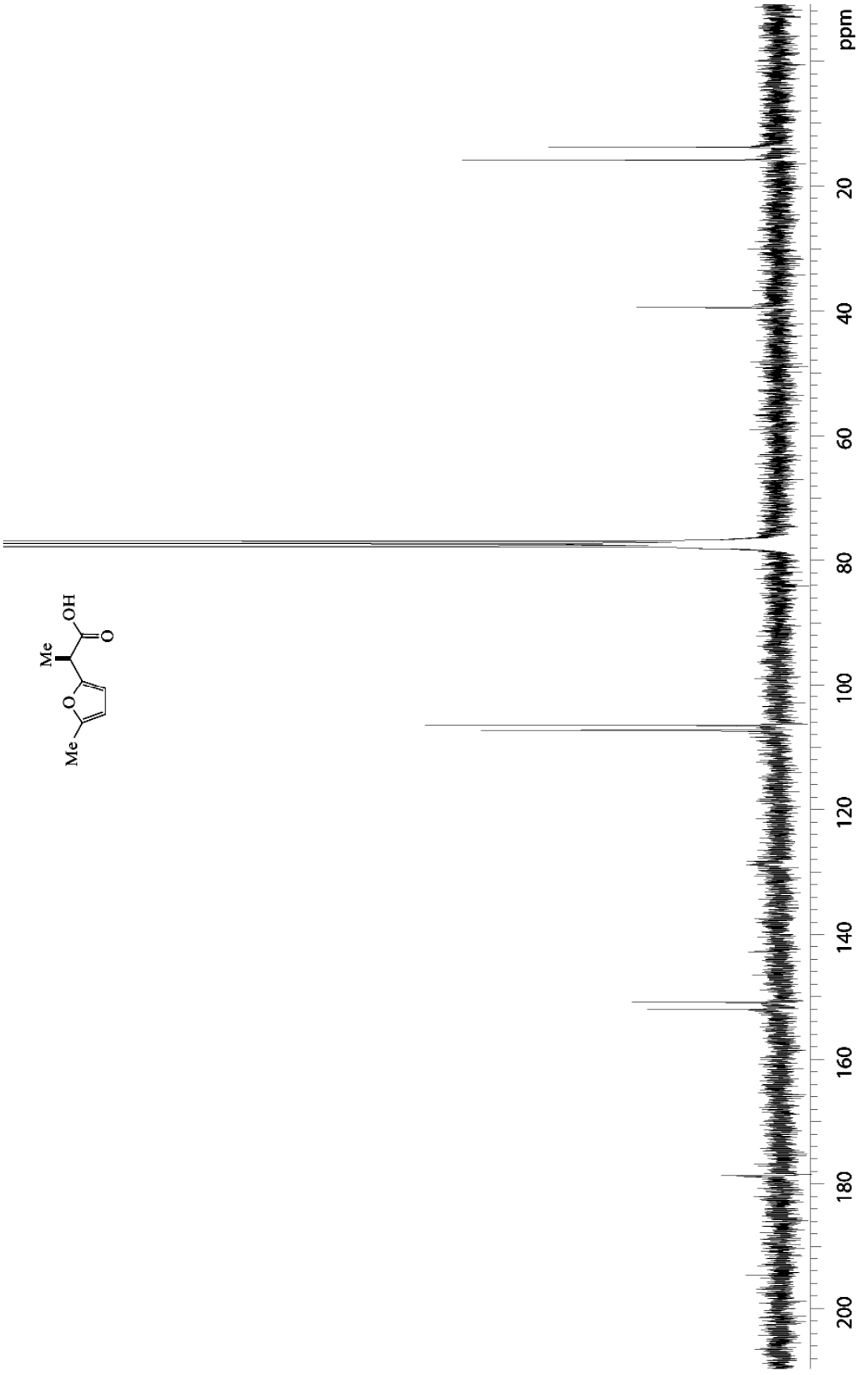
^{1}H NMR (500 MHz) of THF *syn*-**3.5a** in $CDCl_3$



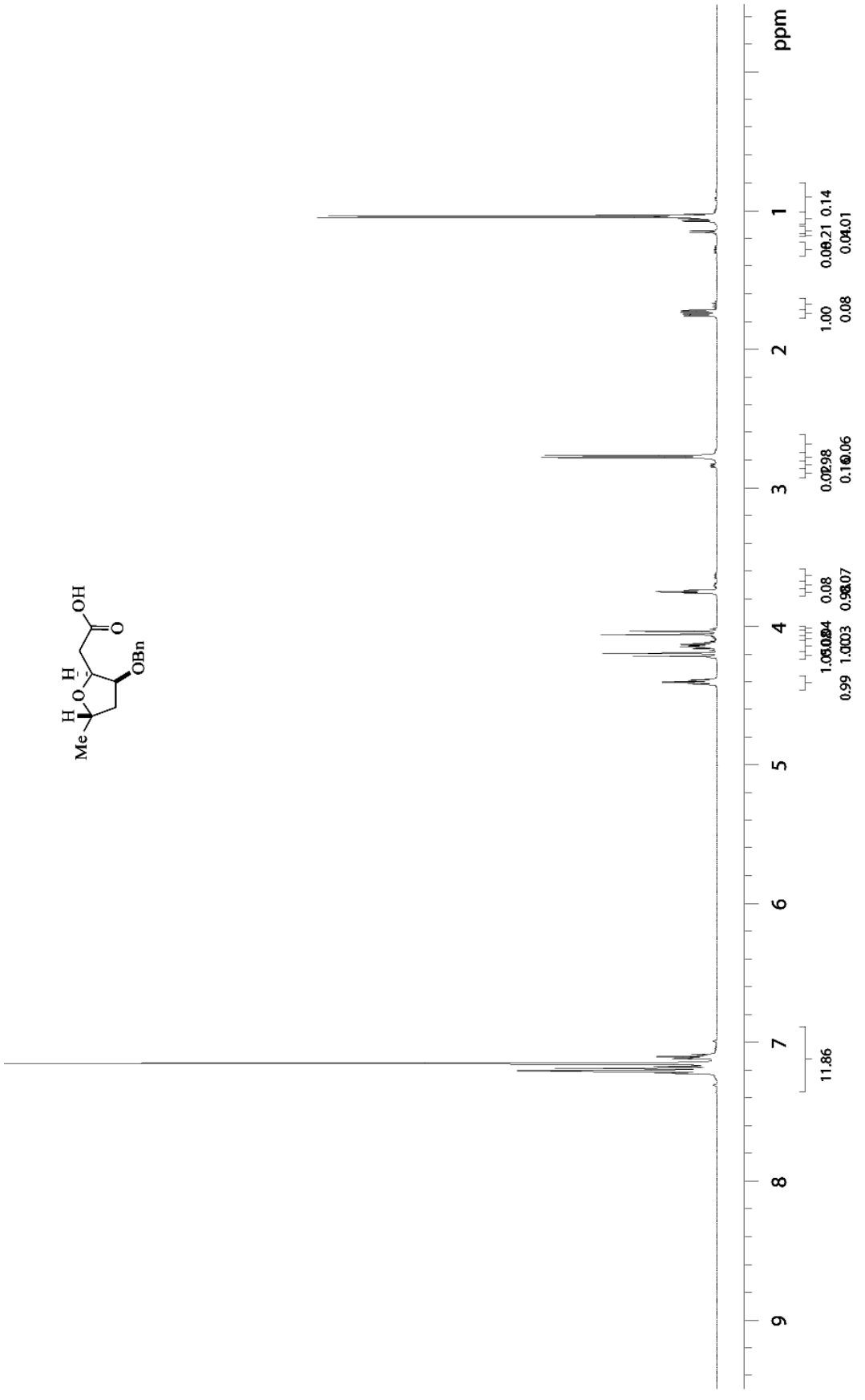
^{13}C NMR (125 MHz) of THF *syn*-**3.5a** in $CDCl_3$



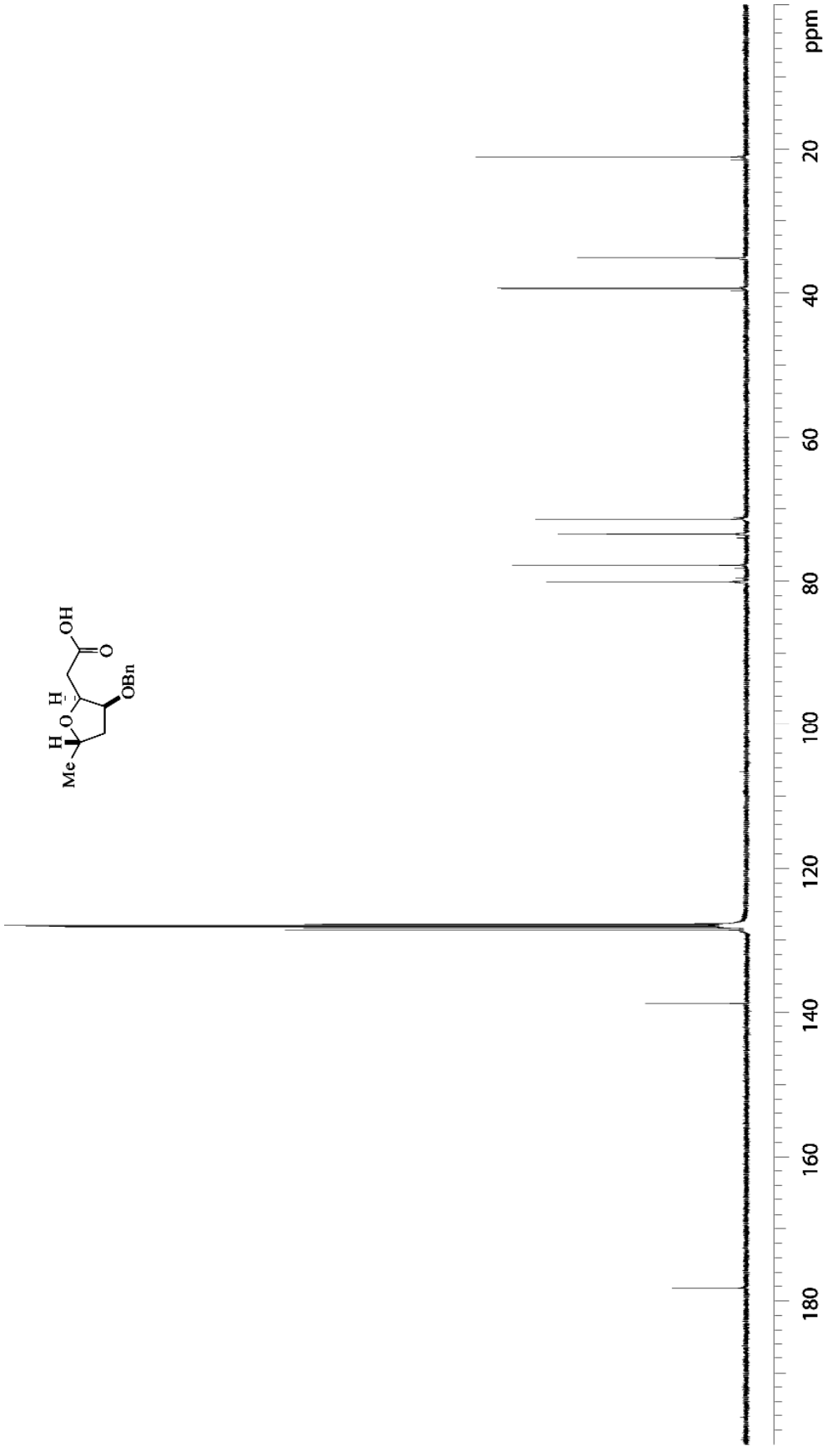
^{1}H NMR (300 MHz) of Furan **3.11** in $CDCl_3$



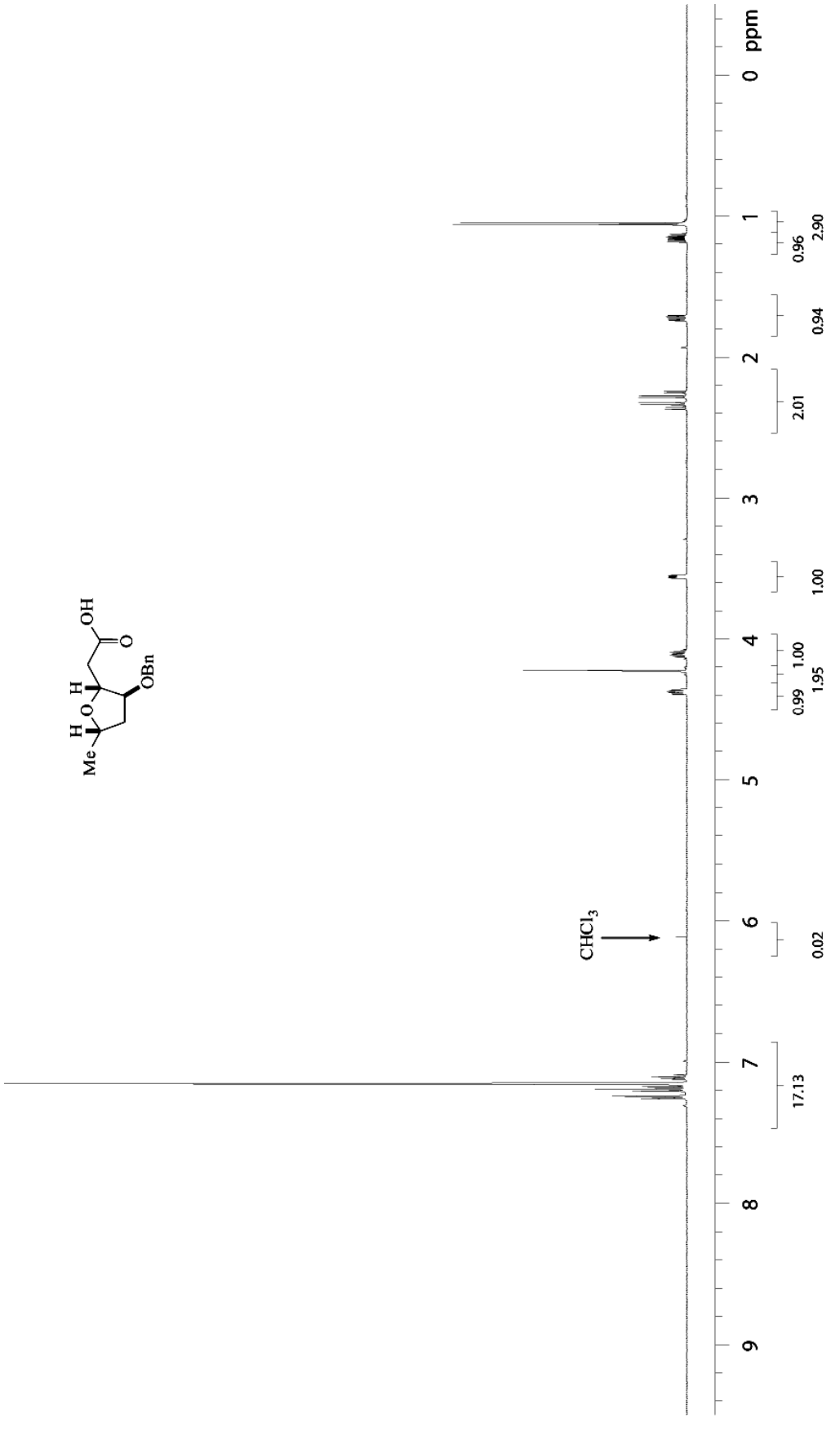
^{13}C NMR (75 MHz) of Furan **3.11** in $CDCl_3$



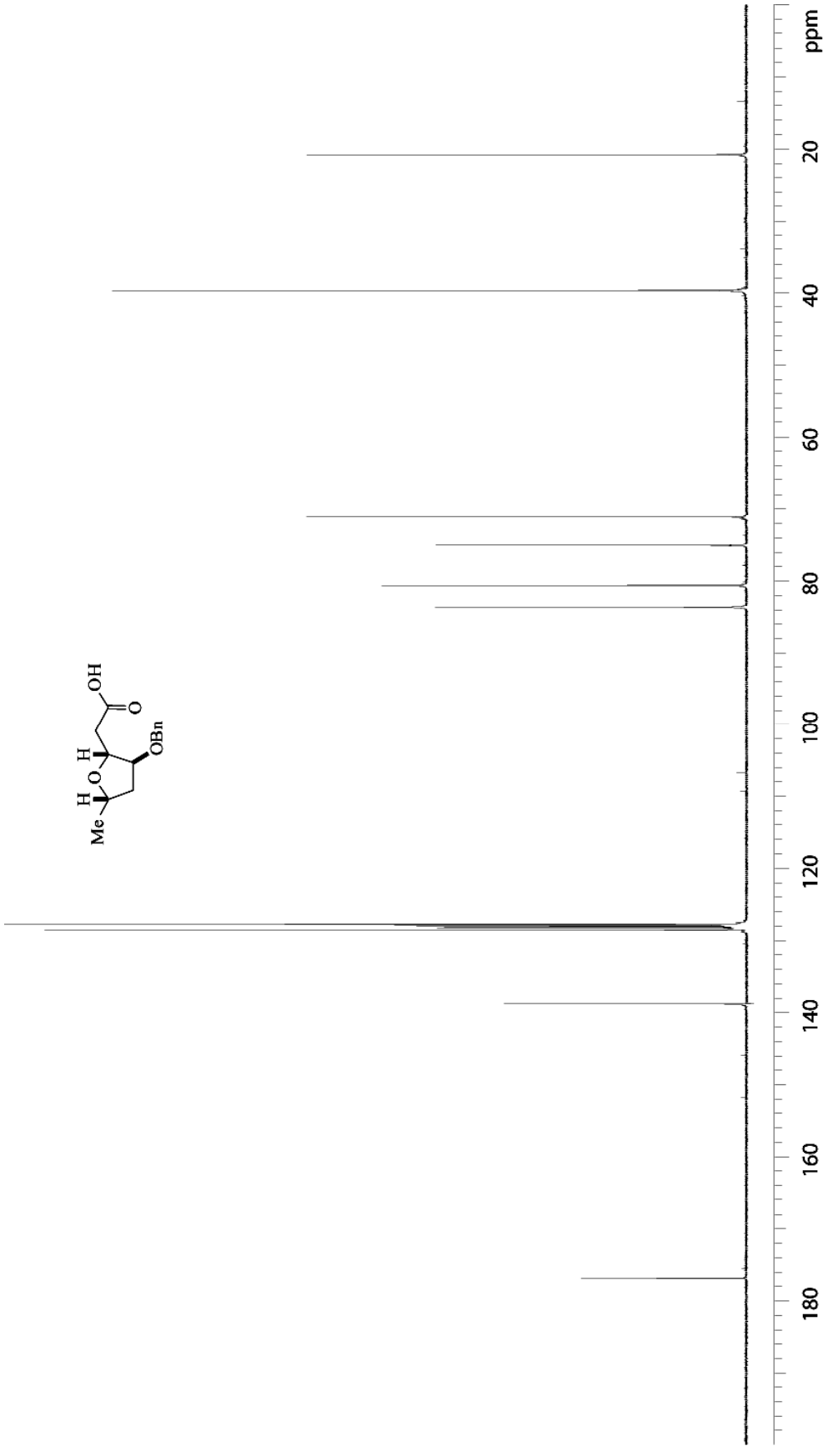
^{1}H NMR (500 MHz) of THF *anti*-**3.5b** in C_6D_6



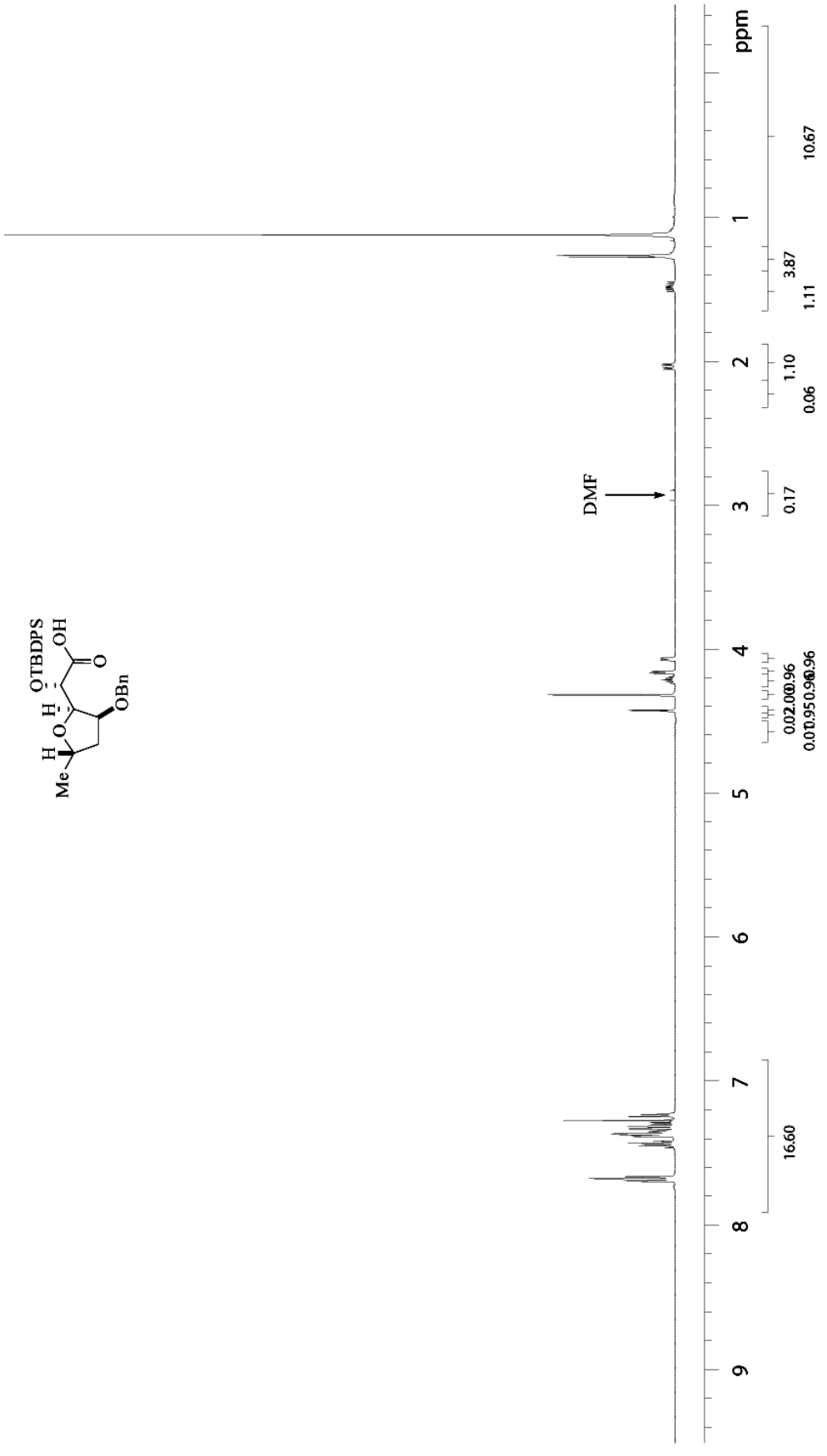
^{13}C NMR (125 MHz) of THF *anti*-**3.5b** in C_6D_6



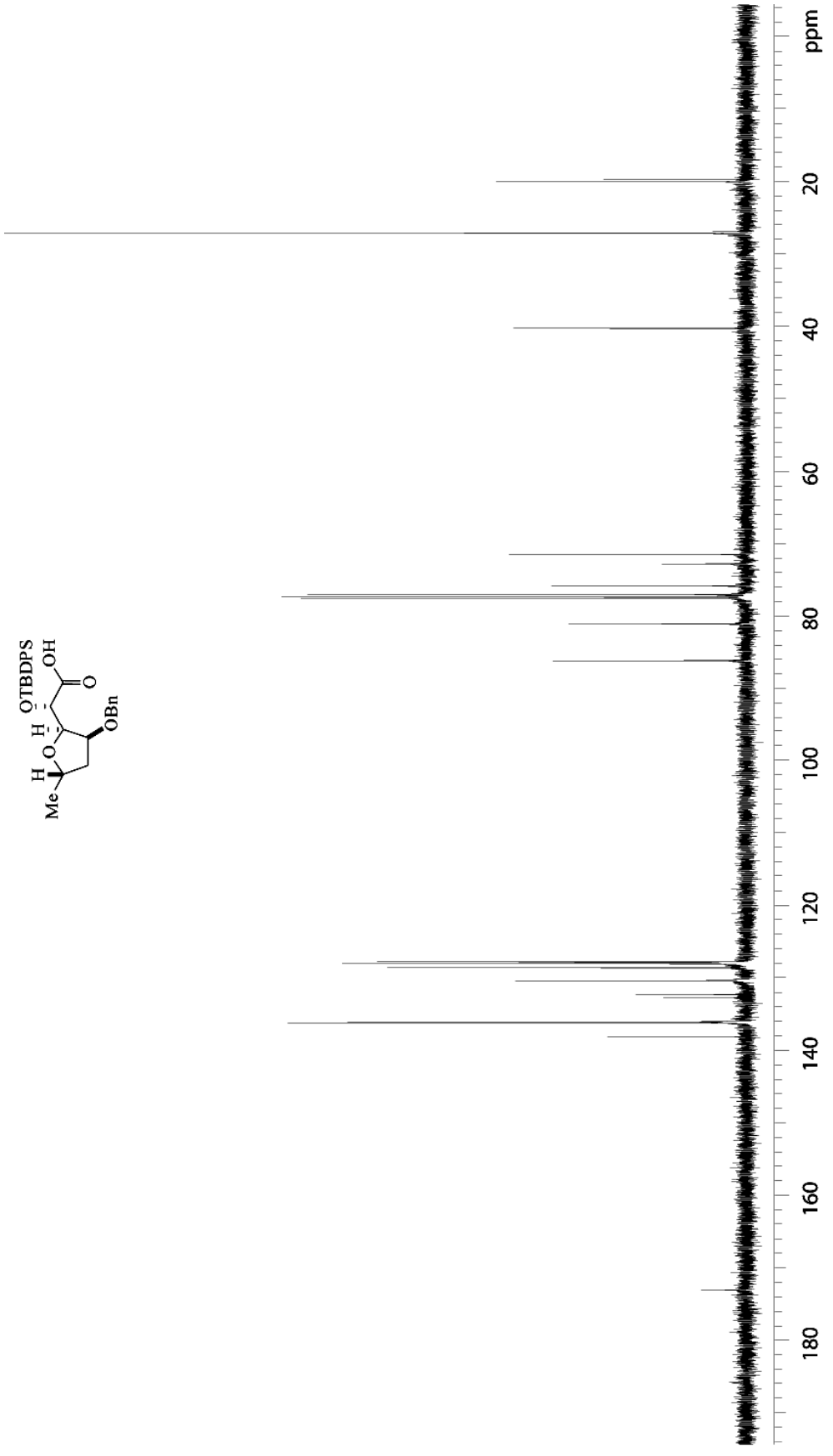
^{1}H NMR (500 MHz) of THF *syn*-**3.5b** in C_6D_6



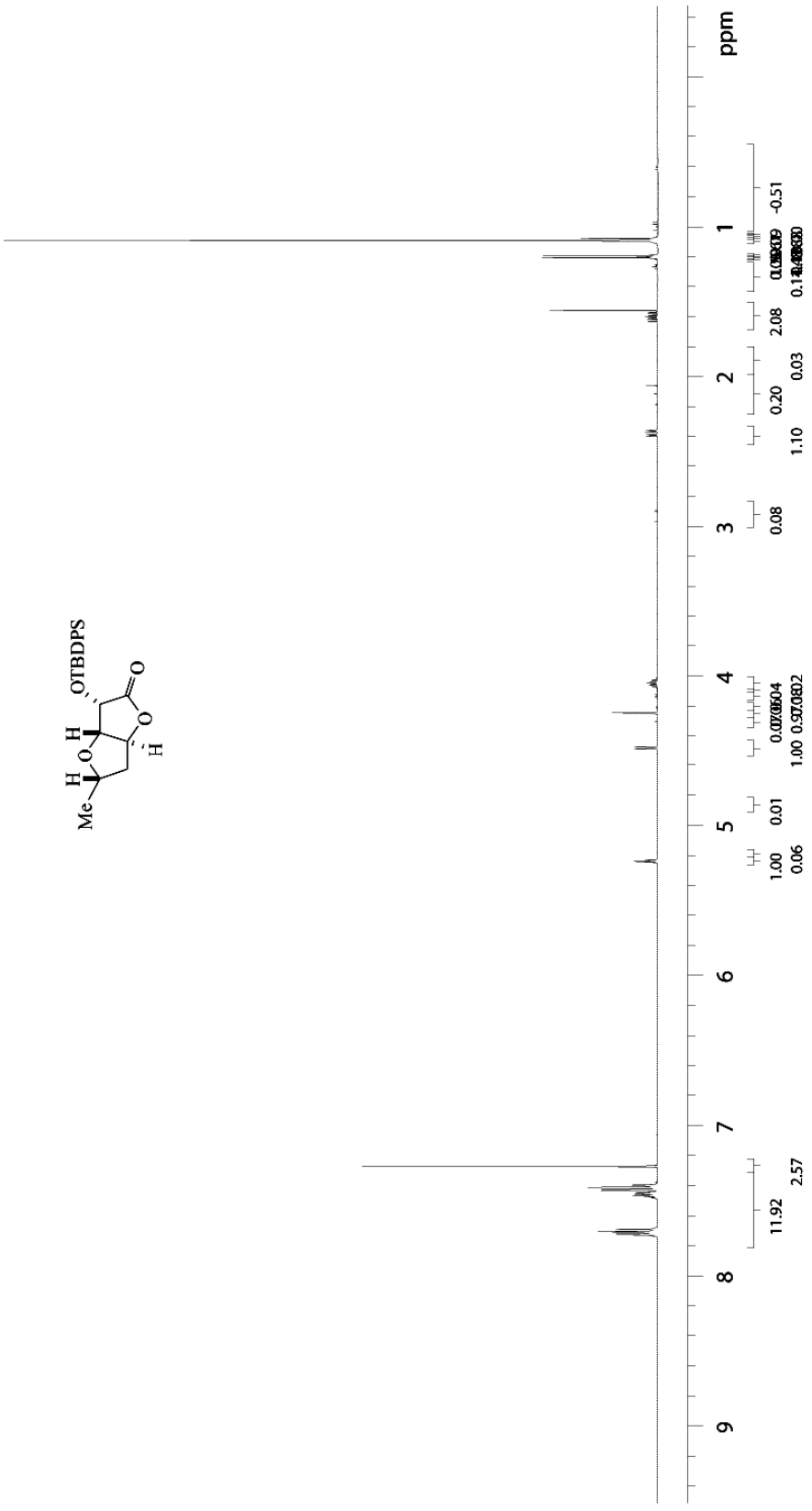
^{13}C NMR (125 MHz) of THF *syn*-**3.5b** in C_6D_6



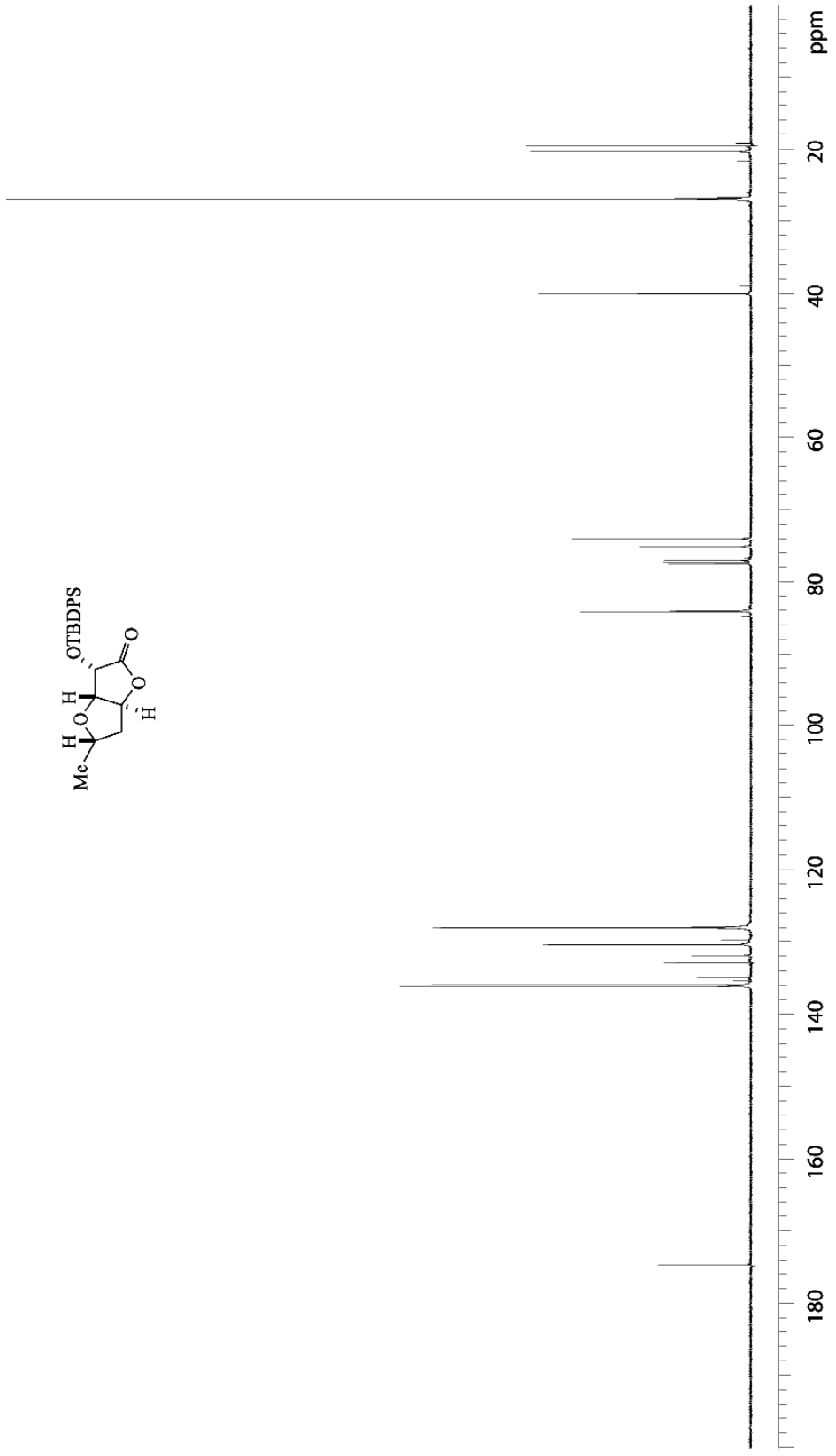
^{1}H NMR (500 MHz) of THF *anti*-**3.5c** in $CDCl_3$



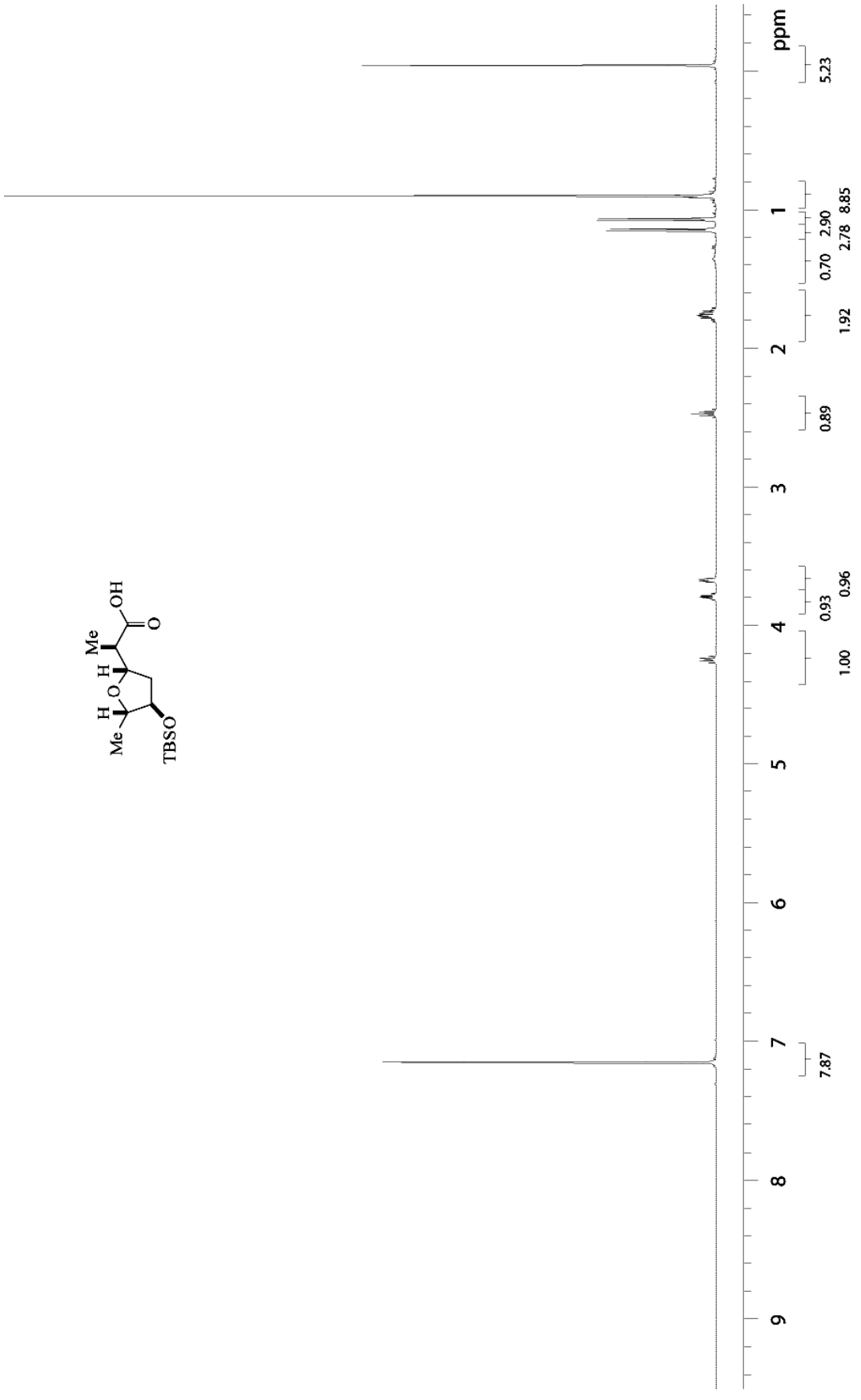
^{13}C NMR (125 MHz) of THF *anti*-**3.5c** in $CDCl_3$



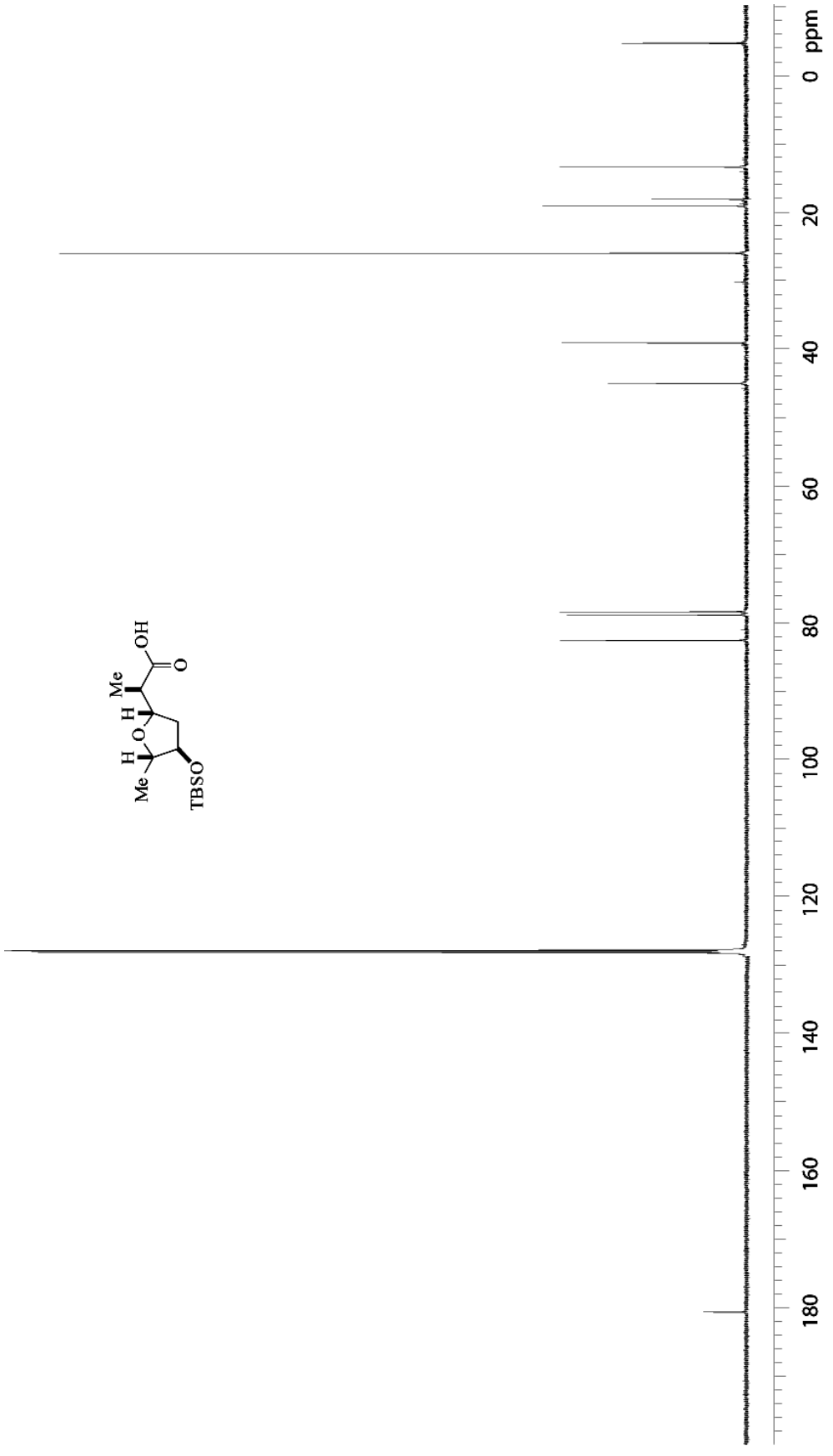
^{1}H NMR (500 MHz) of THF *syn*-**3.5c** in $CDCl_3$



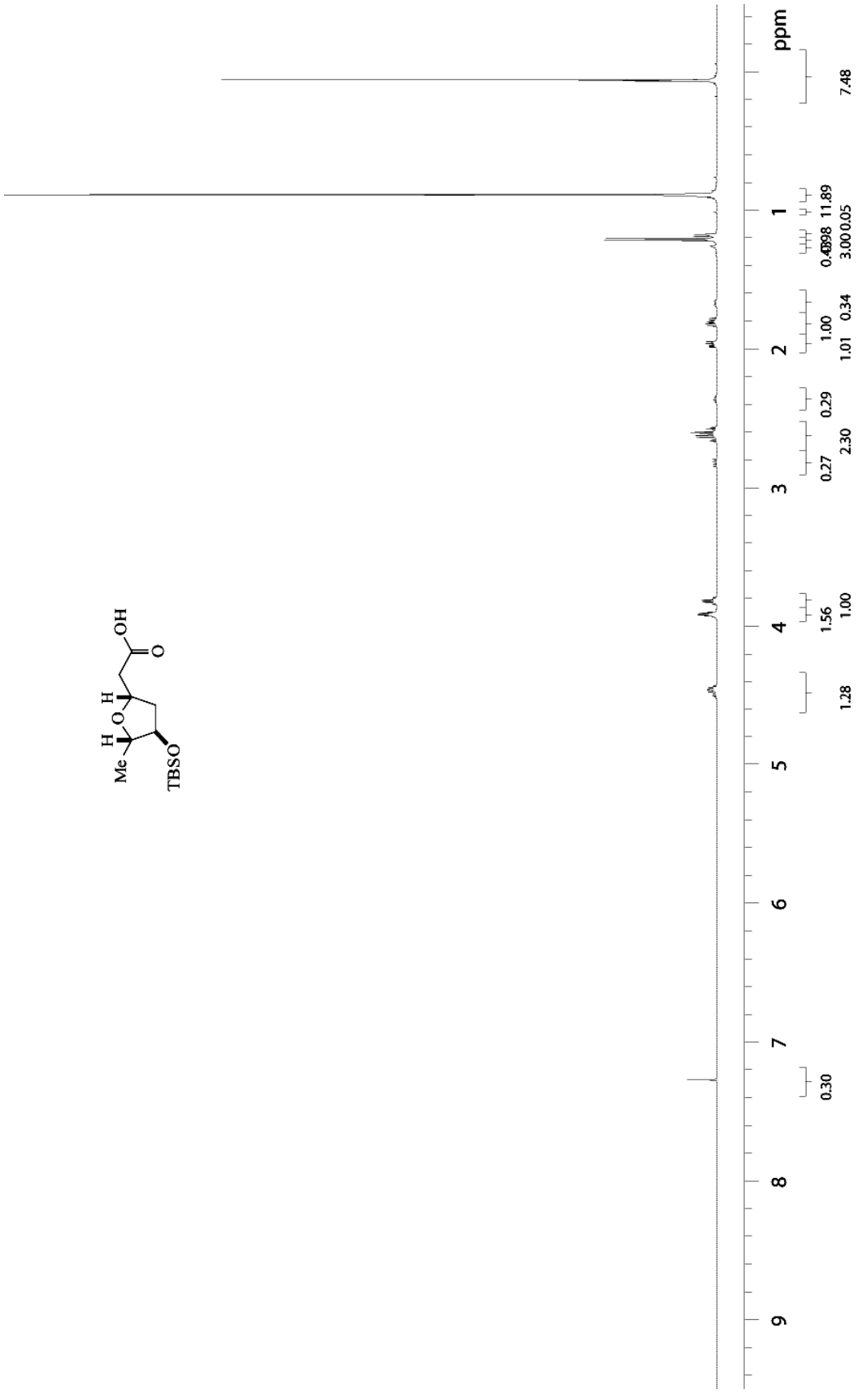
^{13}C NMR (125 MHz) of THF *syn*-**3.5c** in $CDCl_3$



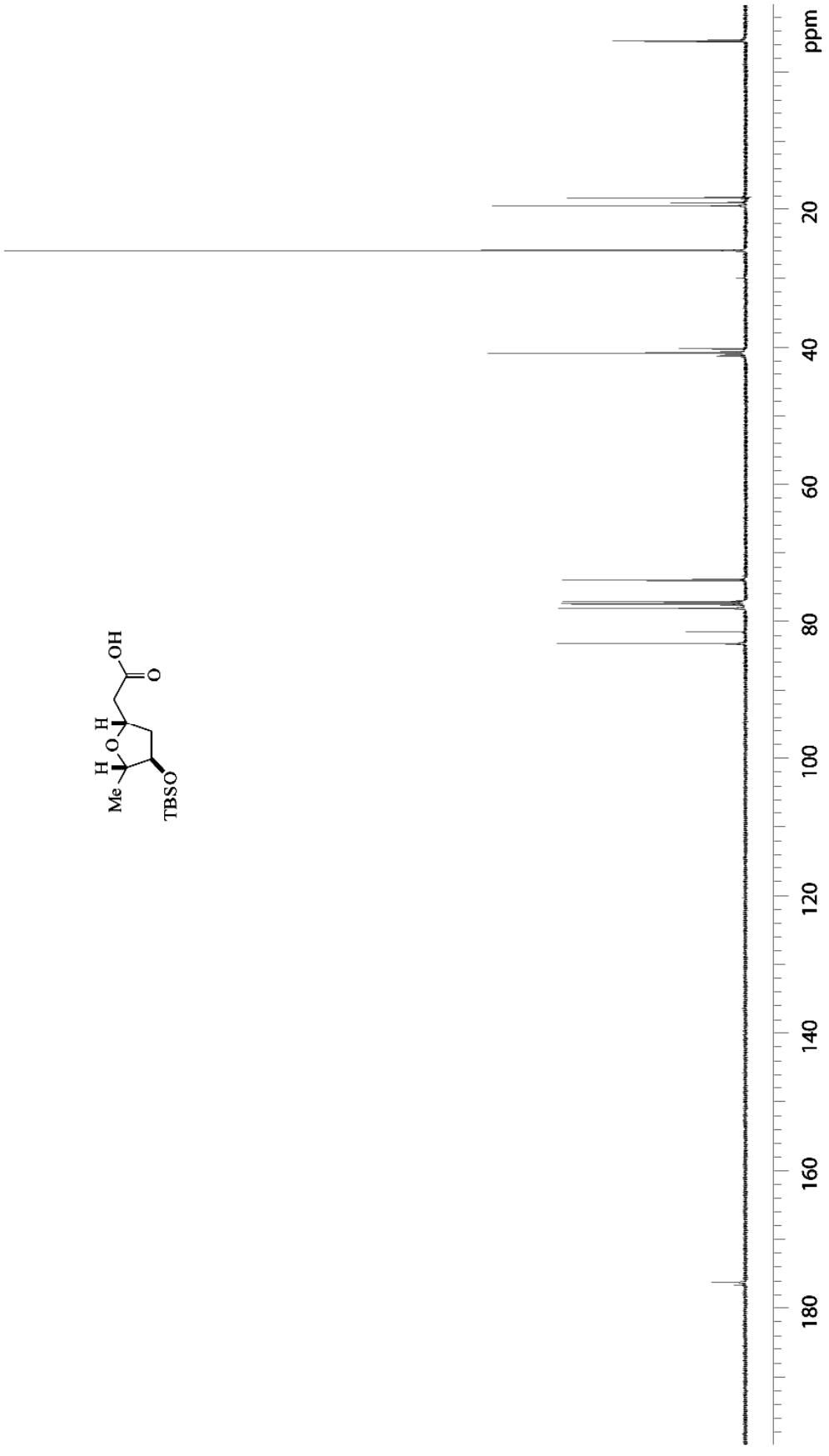
^{1}H NMR (500 MHz) of THF *syn*-**3.5d** in C_6D_6



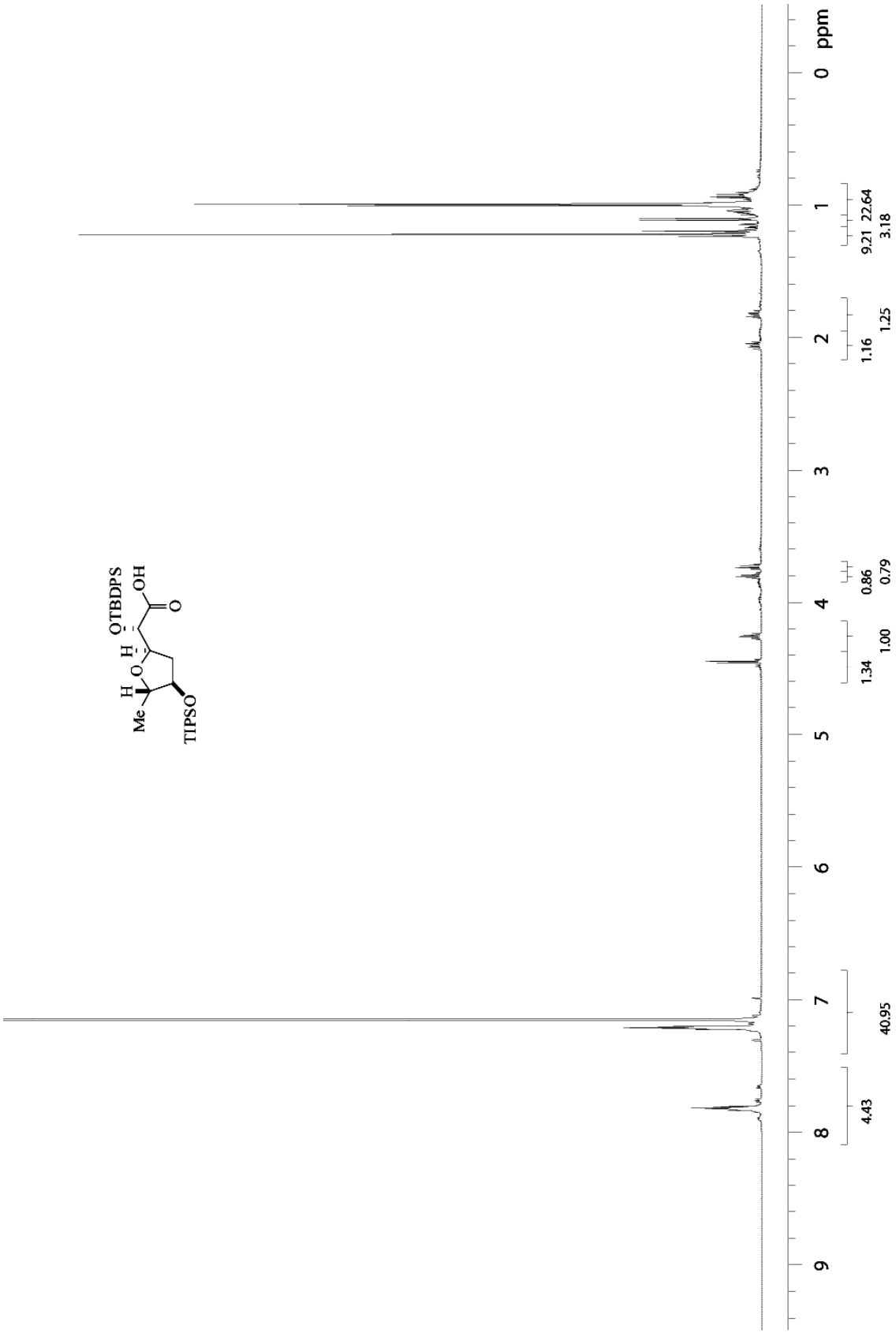
^{13}C NMR (125 MHz) of THF *syn*-**3.5d** in C_6D_6



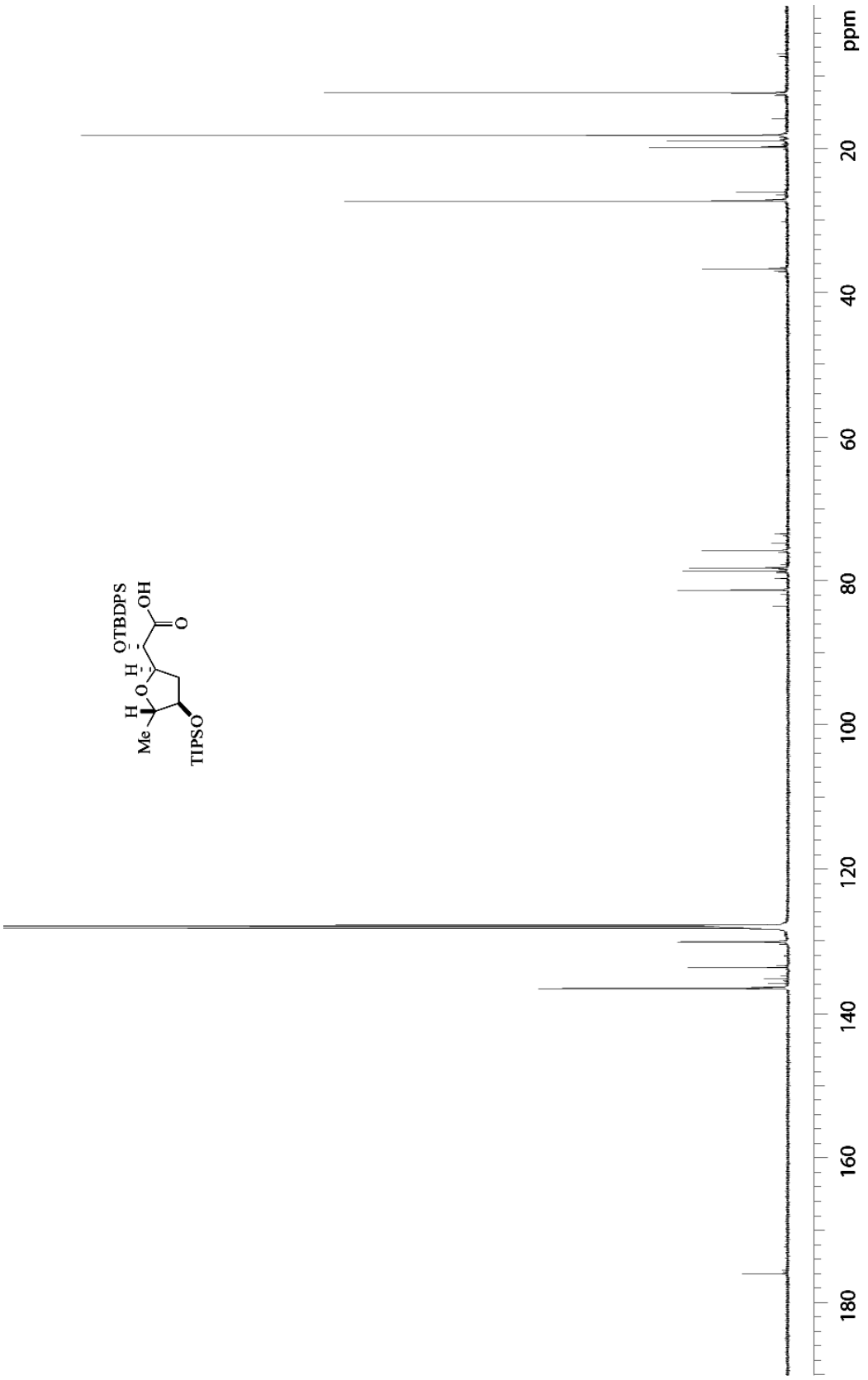
^{1}H NMR (500 MHz) of THF *syn*-**3.5e** in $CDCl_3$



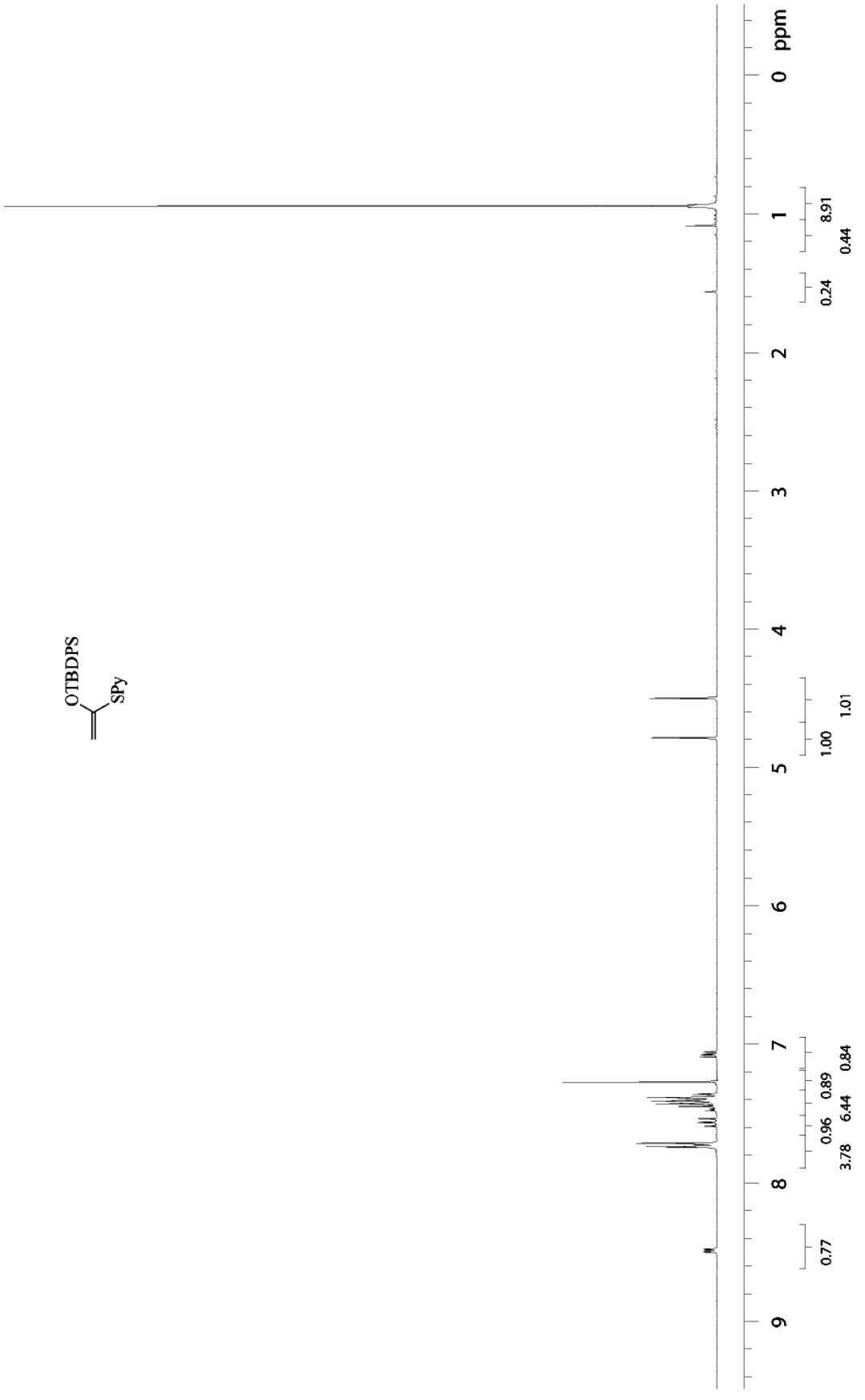
^{13}C NMR (125 MHz) of THF *syn*-**3.5e** in $CDCl_3$



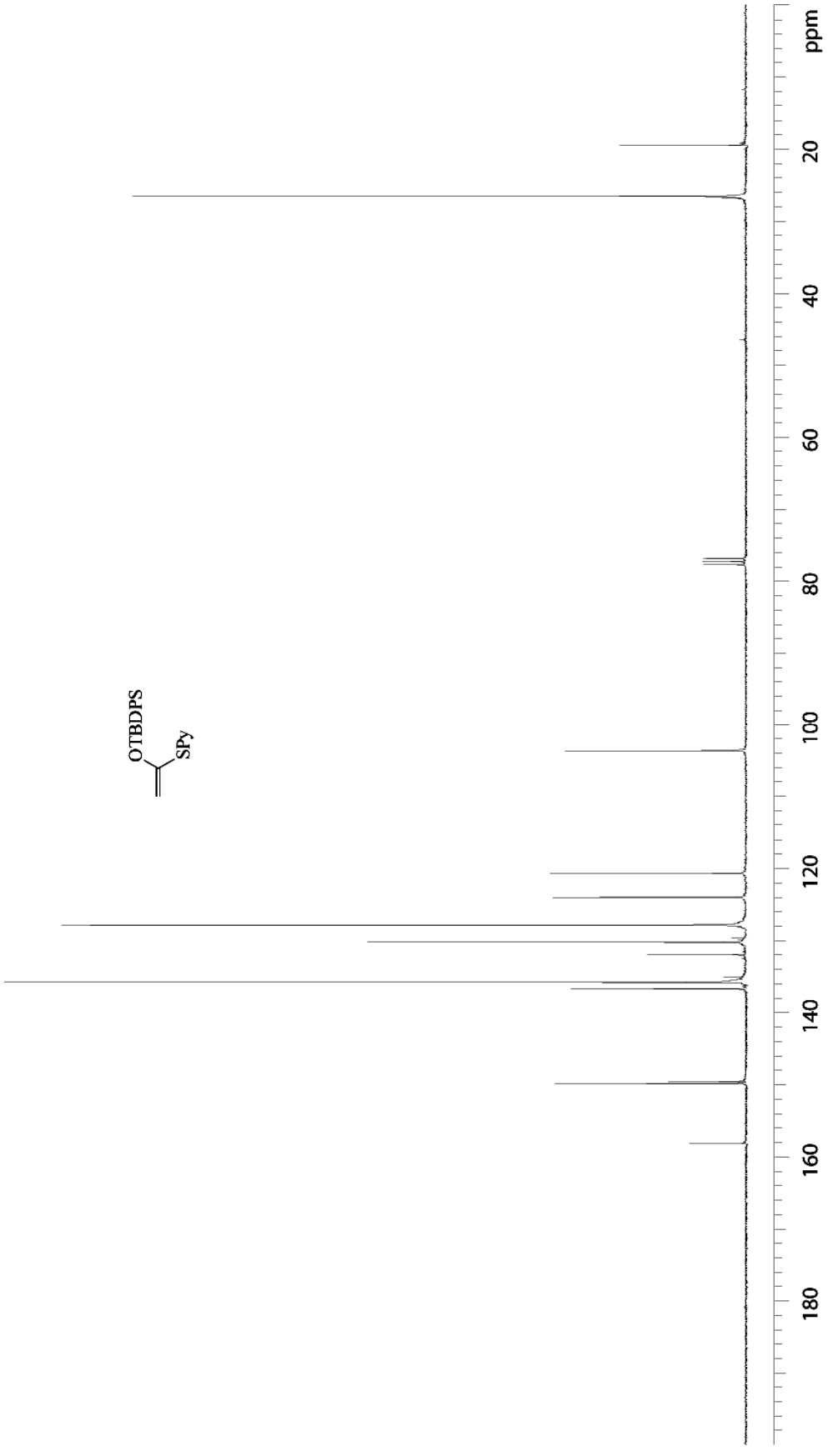
^{1}H NMR (500 MHz) of THF *anti*-**3.5f** in C_6D_6



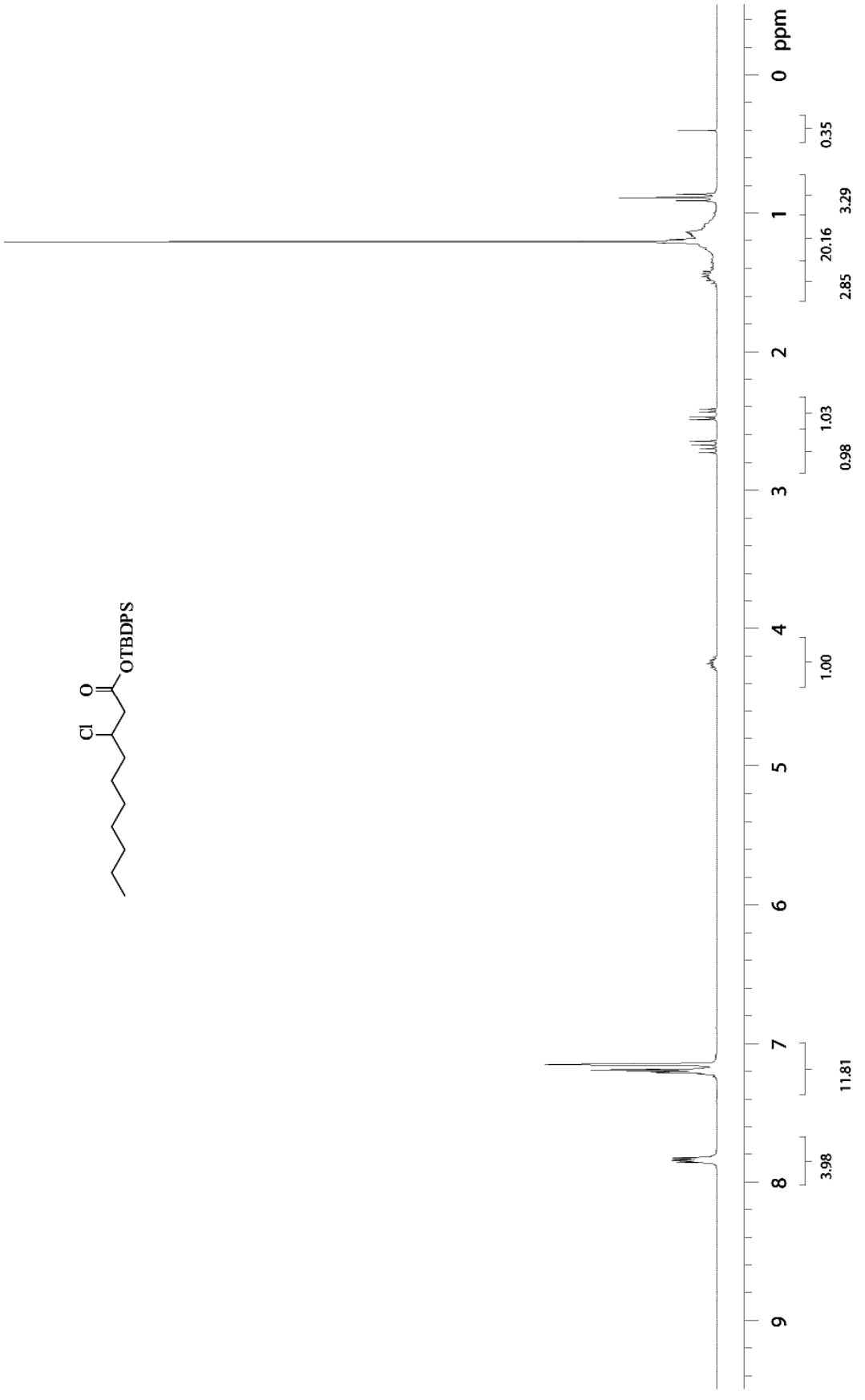
^{13}C NMR (125 MHz) of THF *anti*-**3.5f** in C_6D_6



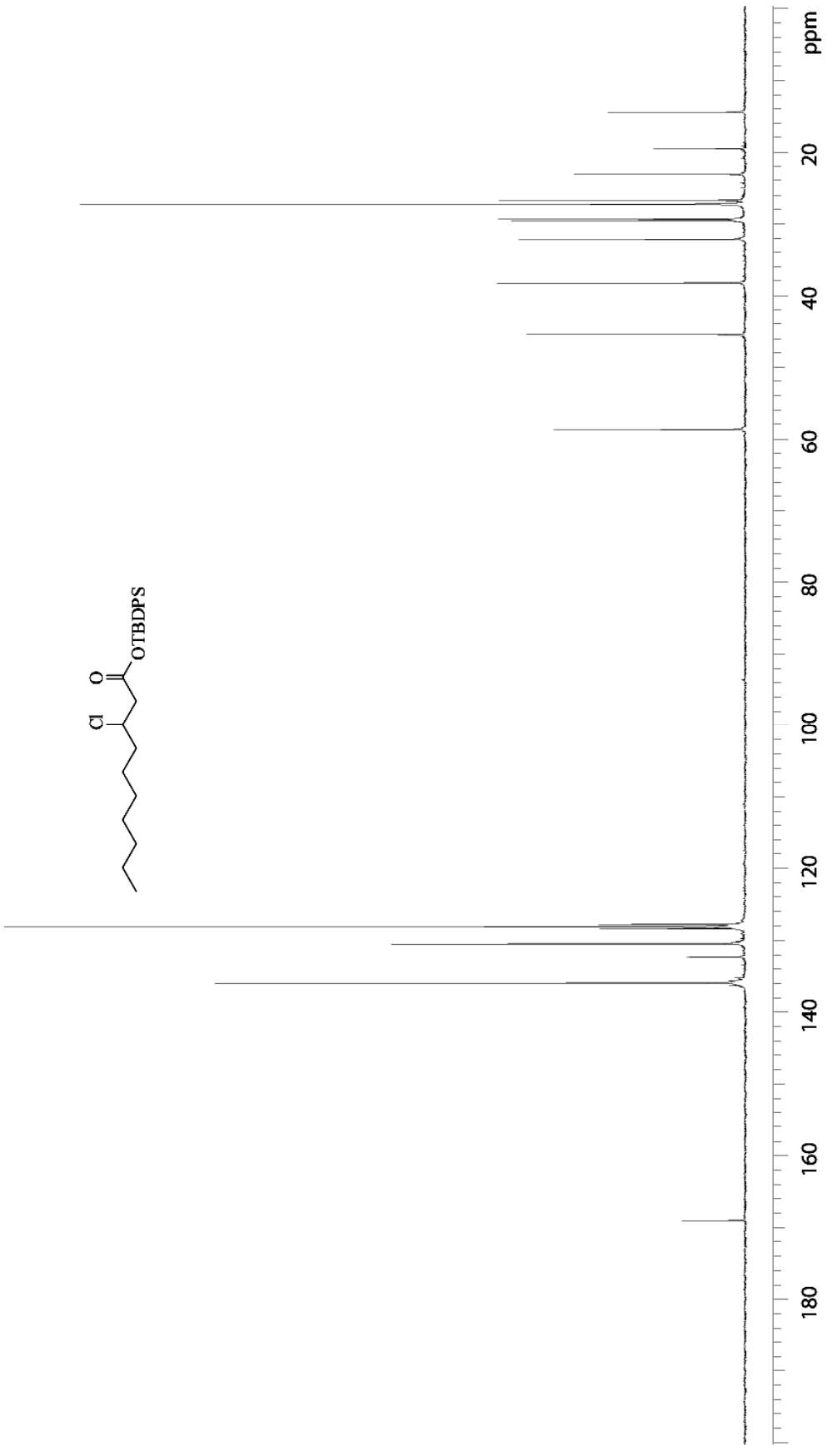
^{1}H NMR (300 MHz) of Ketene Acetal **4.2d** in $CDCl_3$



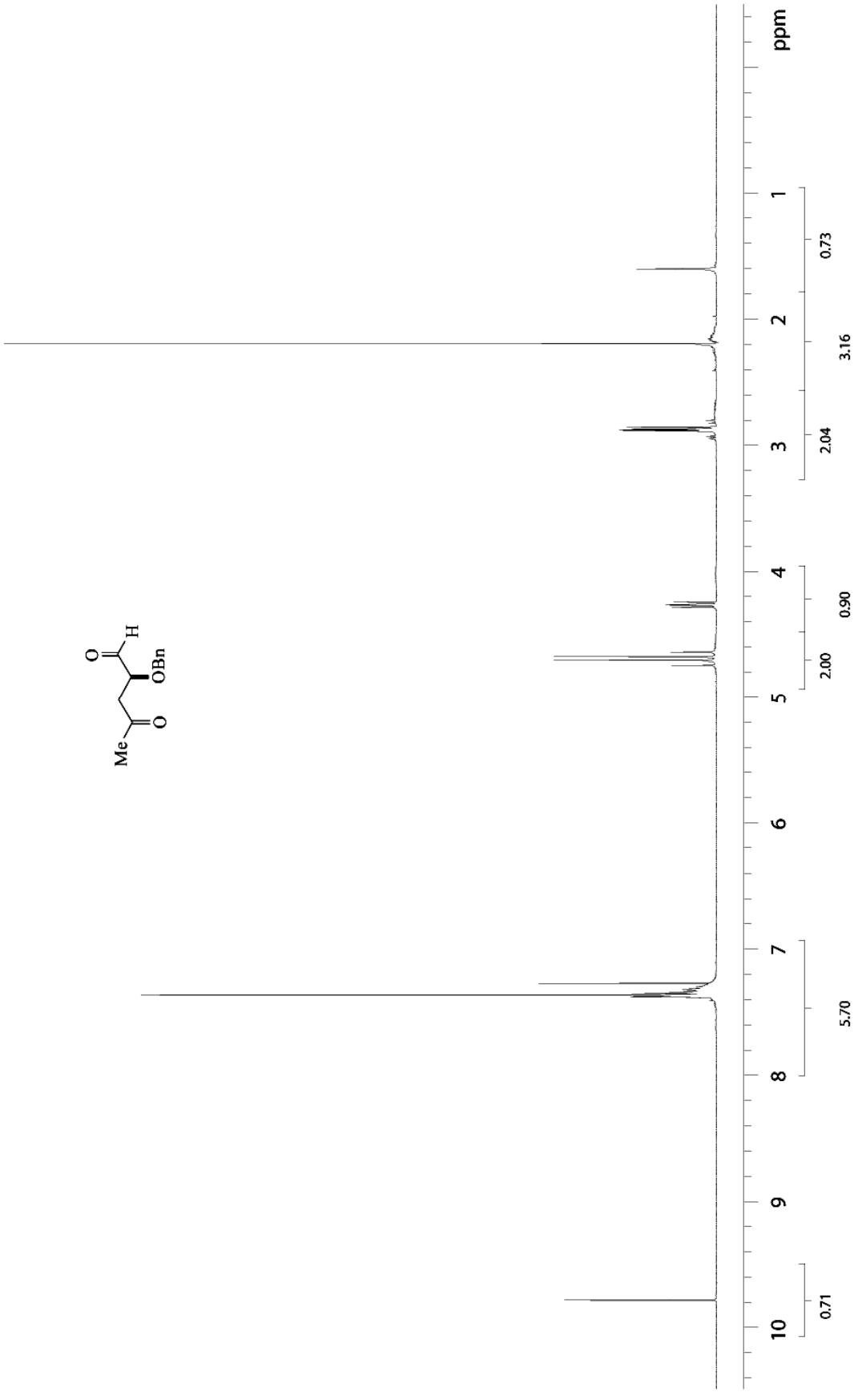
^{13}C NMR (75 MHz) of Ketene Acetal **4.2d** in $CDCl_3$



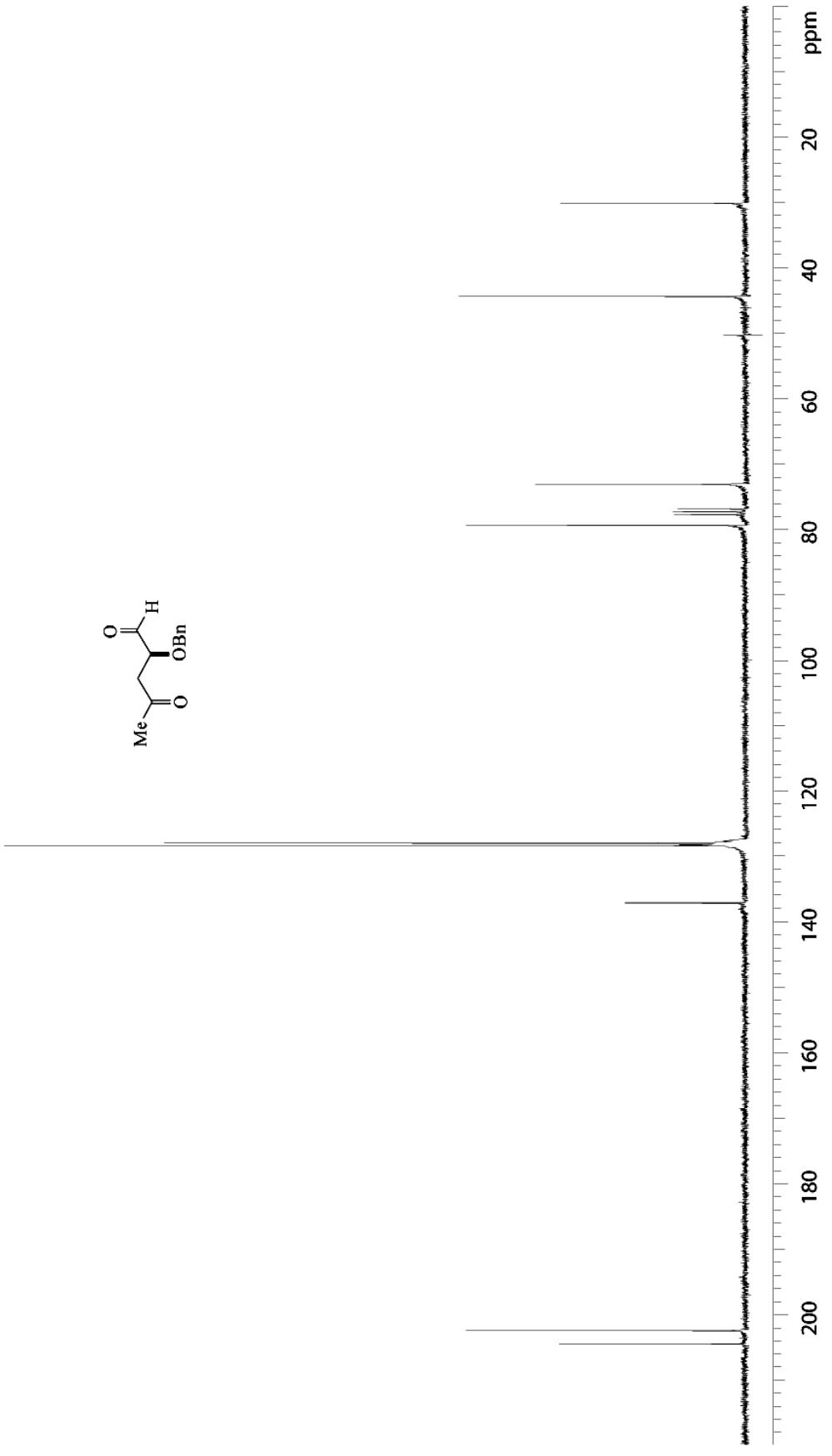
^{1}H NMR (300 MHz) of β-Chlorosilyl Ester **4.7d** in C_6D_6



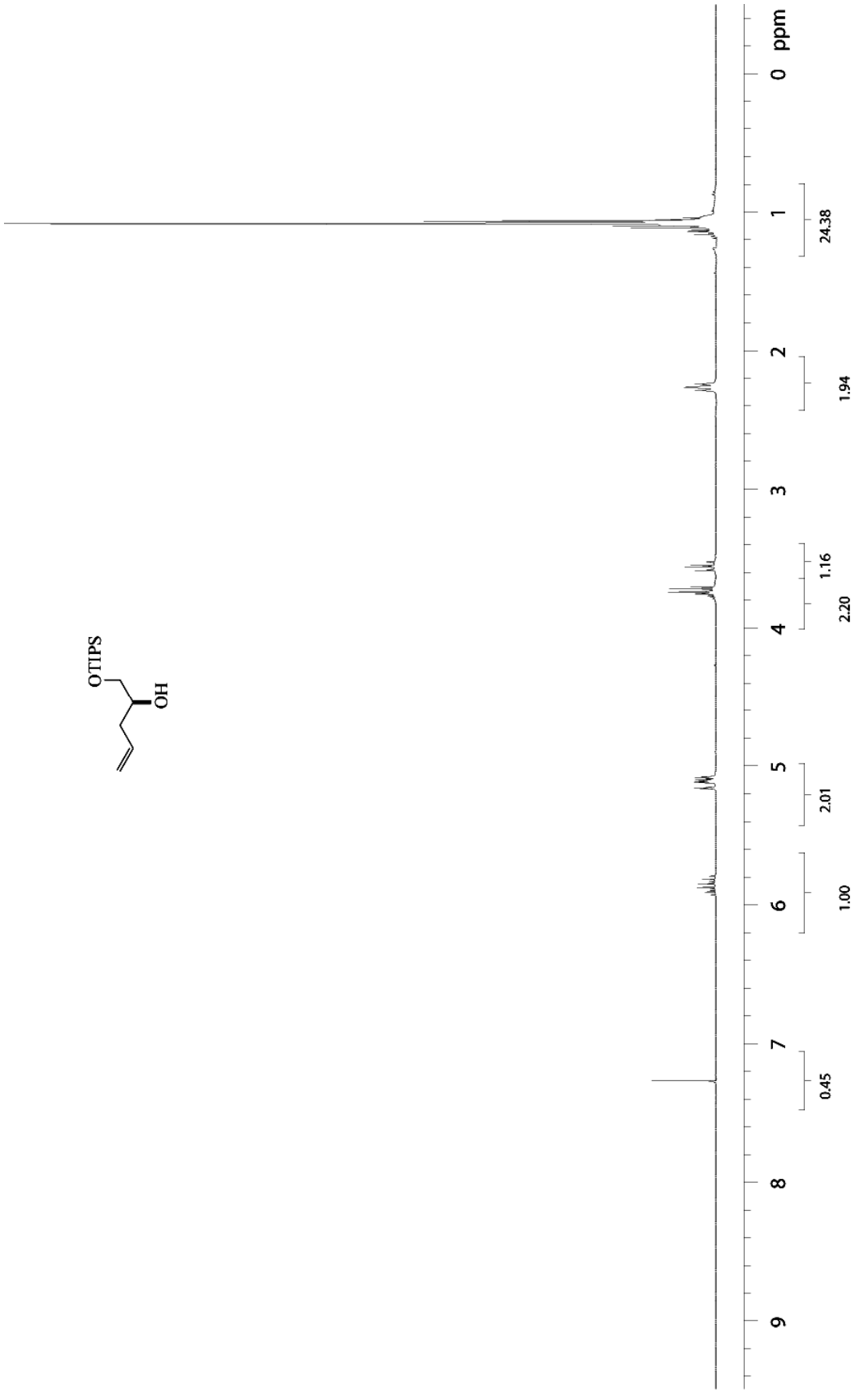
^{13}C NMR (75 MHz) of β-Chlorosilyl Ester **4.7d** in C_6D_6



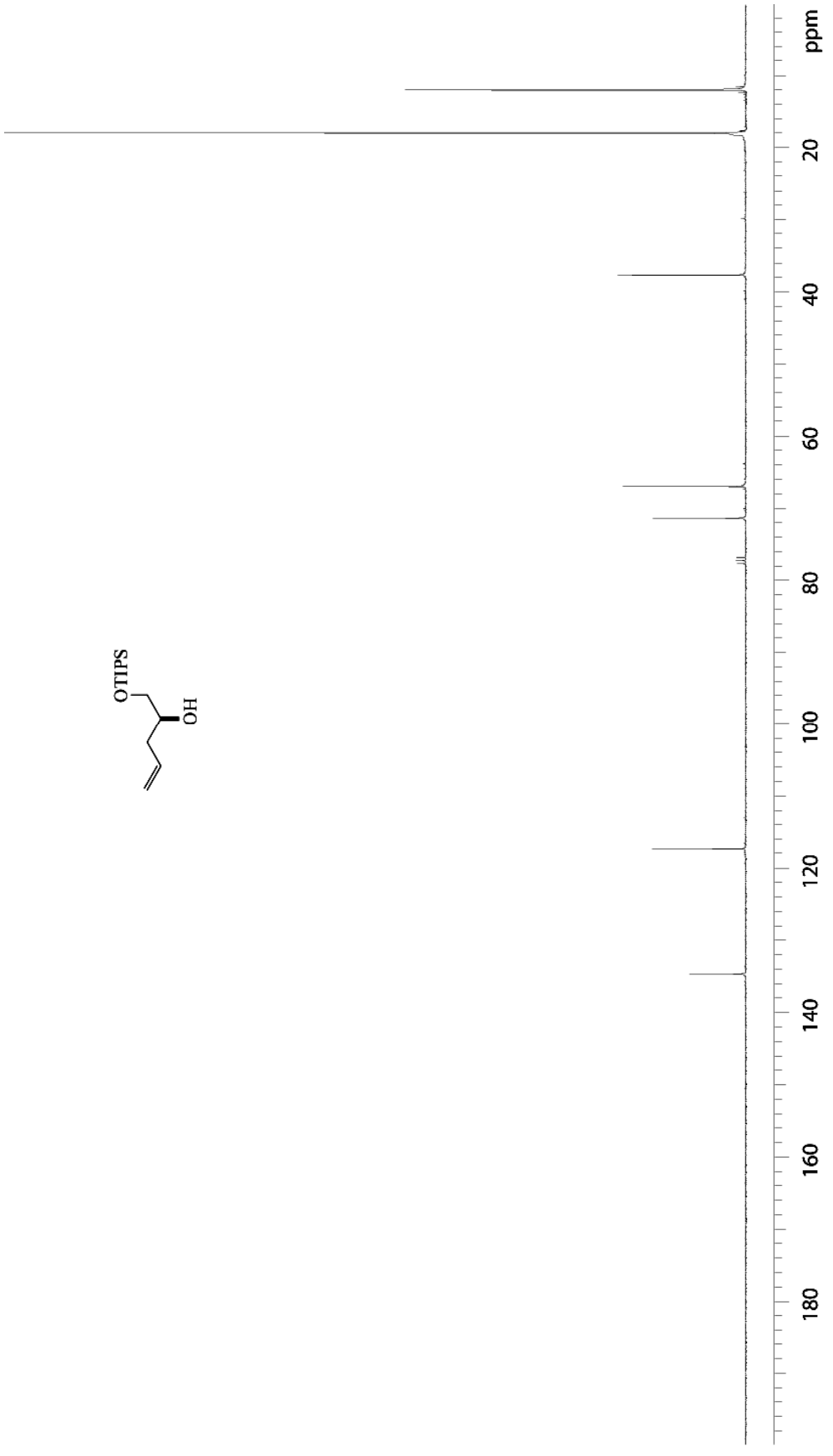
^{1}H NMR (300 MHz) of α-Benzyloxy-γ-Ketoaldehyde (±)-**4.1a** in $CDCl_3$



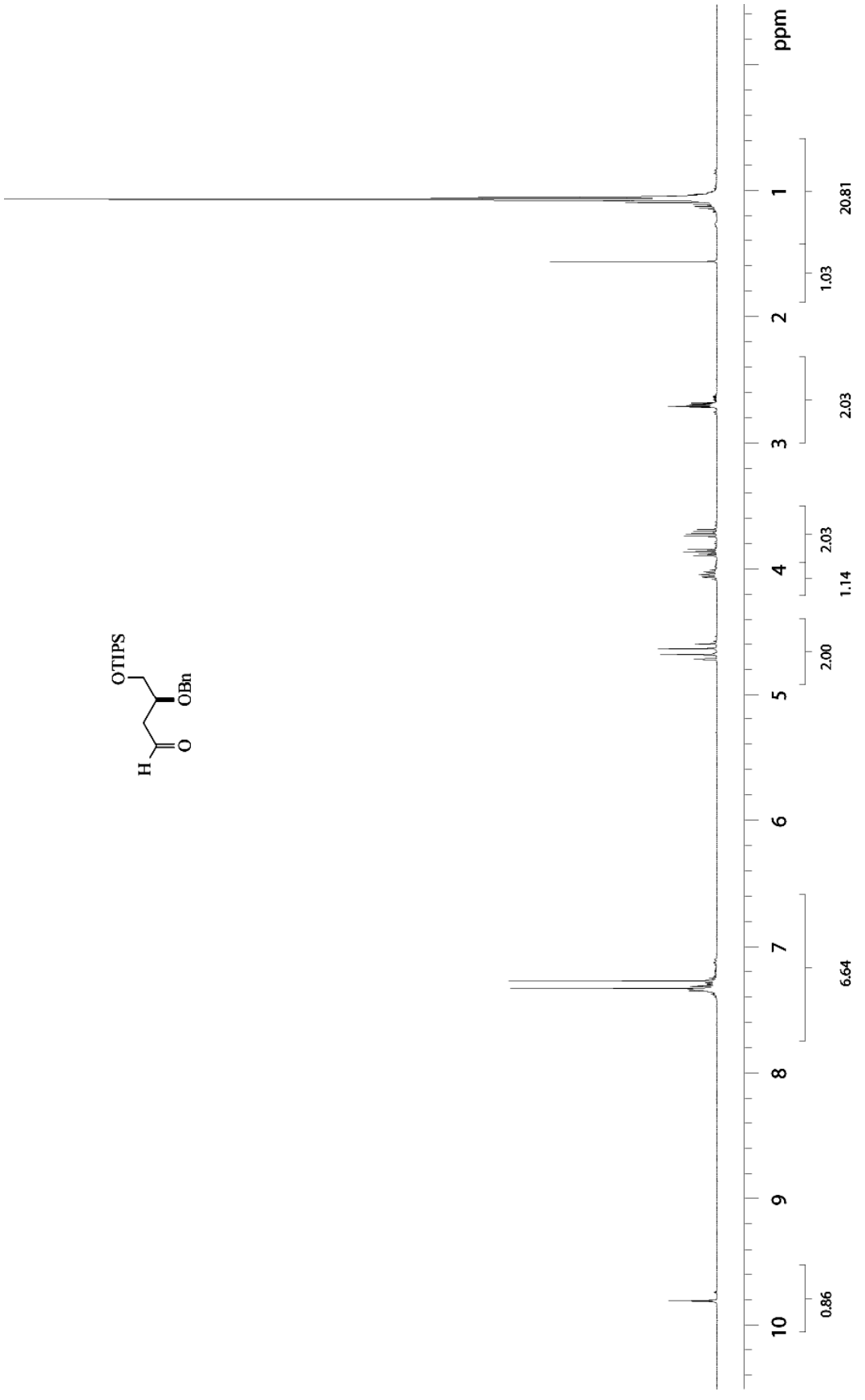
^{13}C NMR (75 MHz) of α-Benzyloxy-γ-Ketoaldehyde **(±)-4.1a** in $CDCl_3$



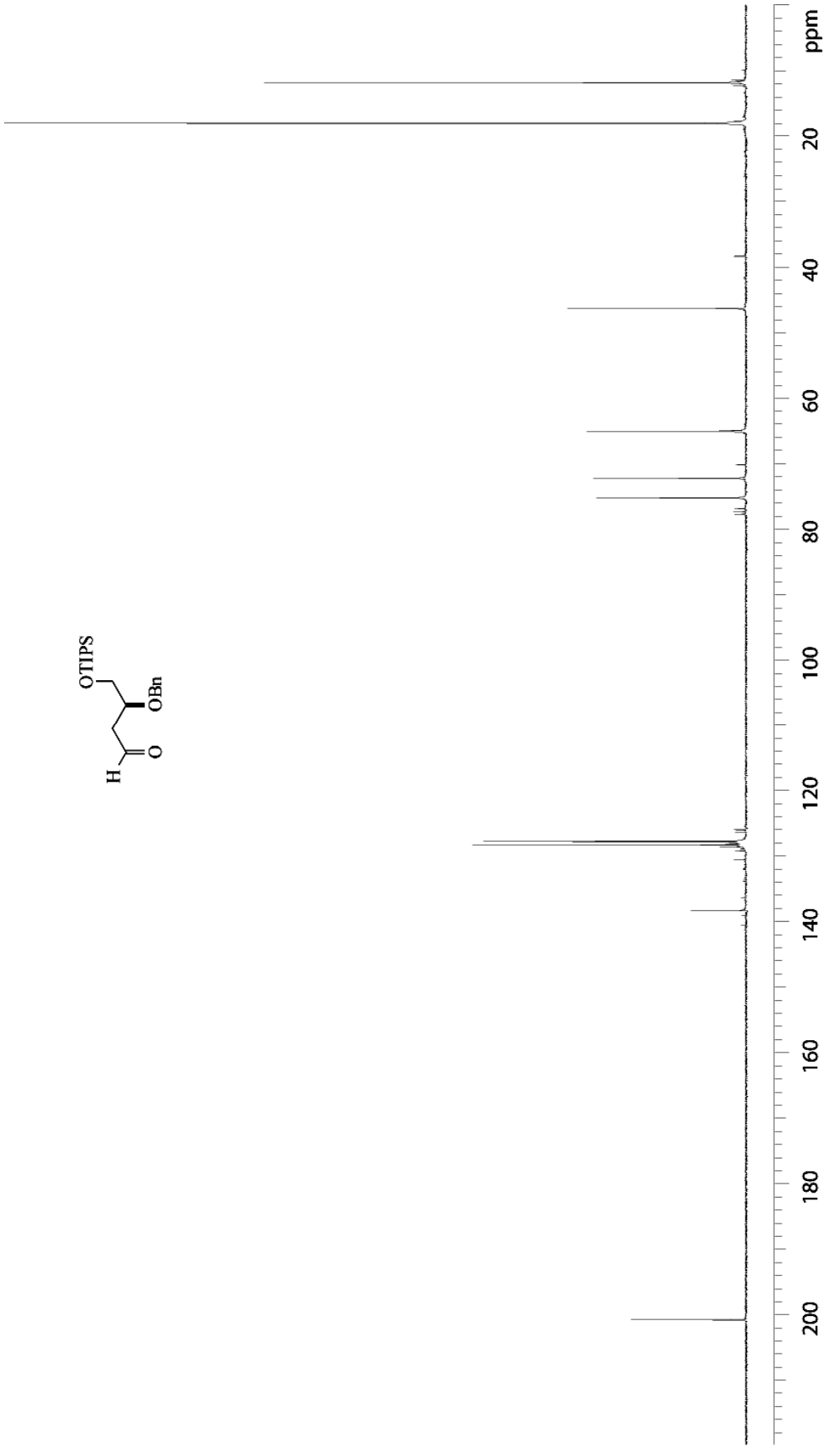
^{1}H NMR (300 MHz) of Secondary Alcohol **S12** in $CDCl_3$



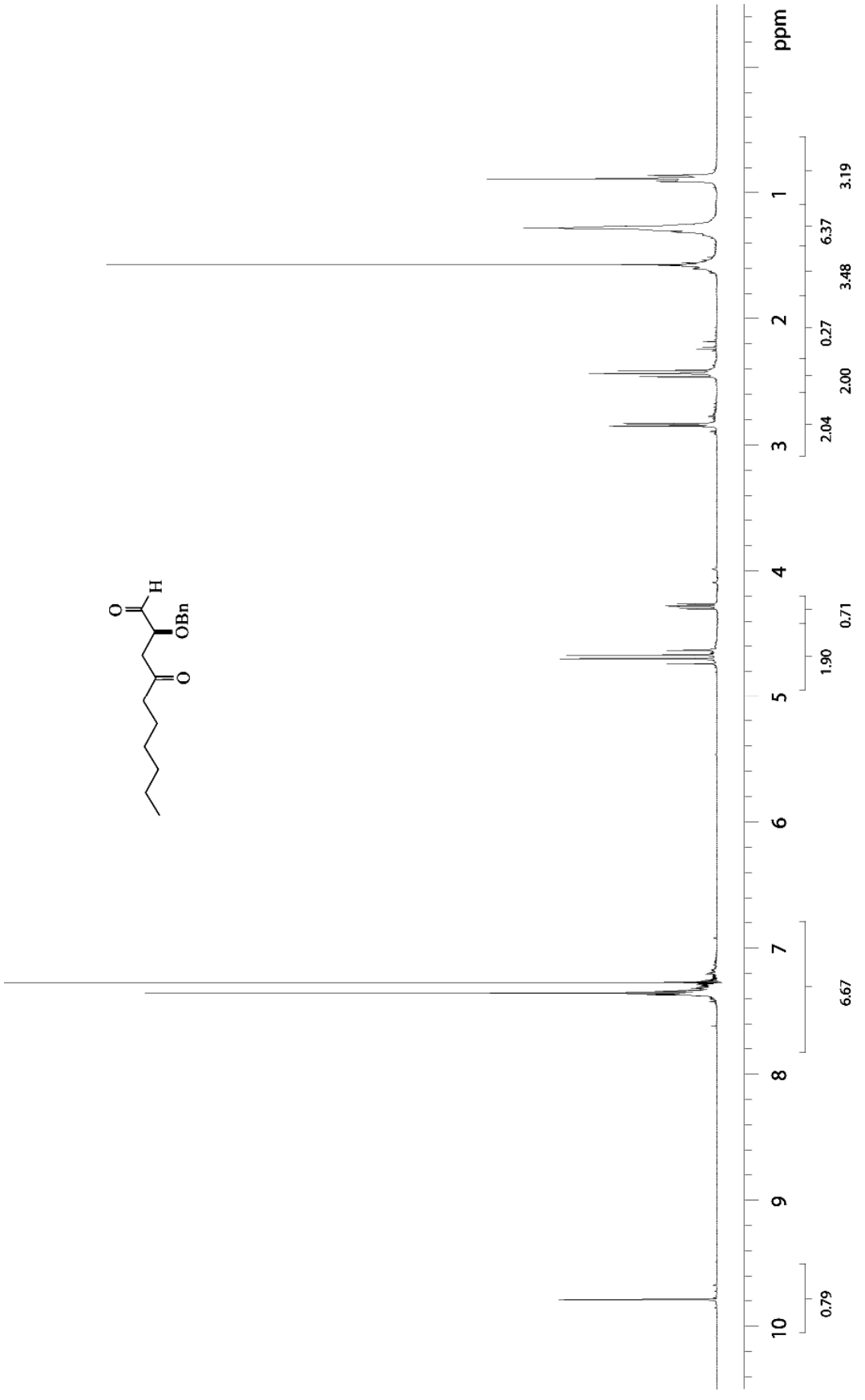
^{13}C NMR (75 MHz) of Secondary Alcohol **S12** in $CDCl_3$



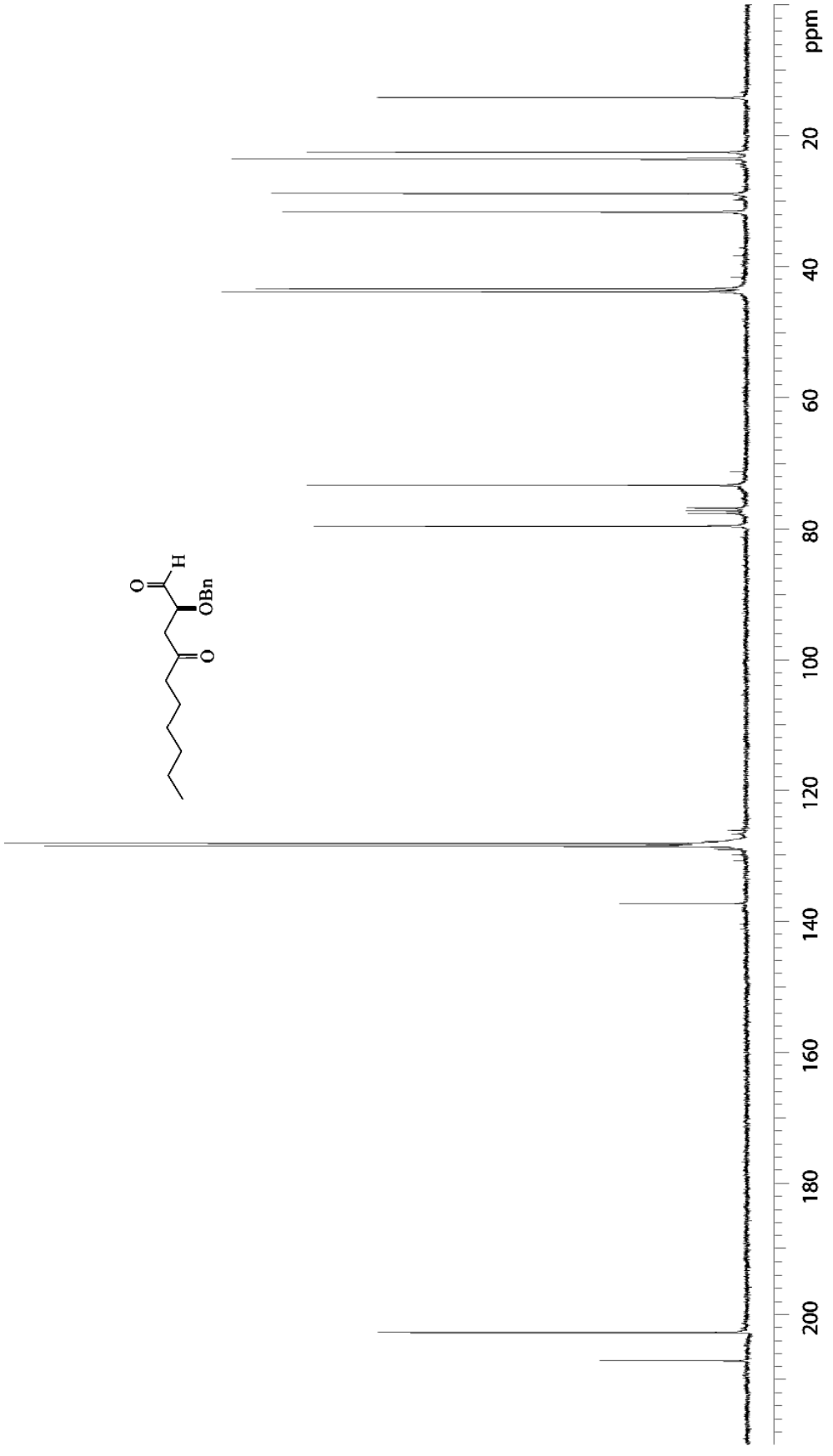
^{1}H NMR (300 MHz) of β-Benzyloxy Aldehyde **4.13** in $CDCl_3$



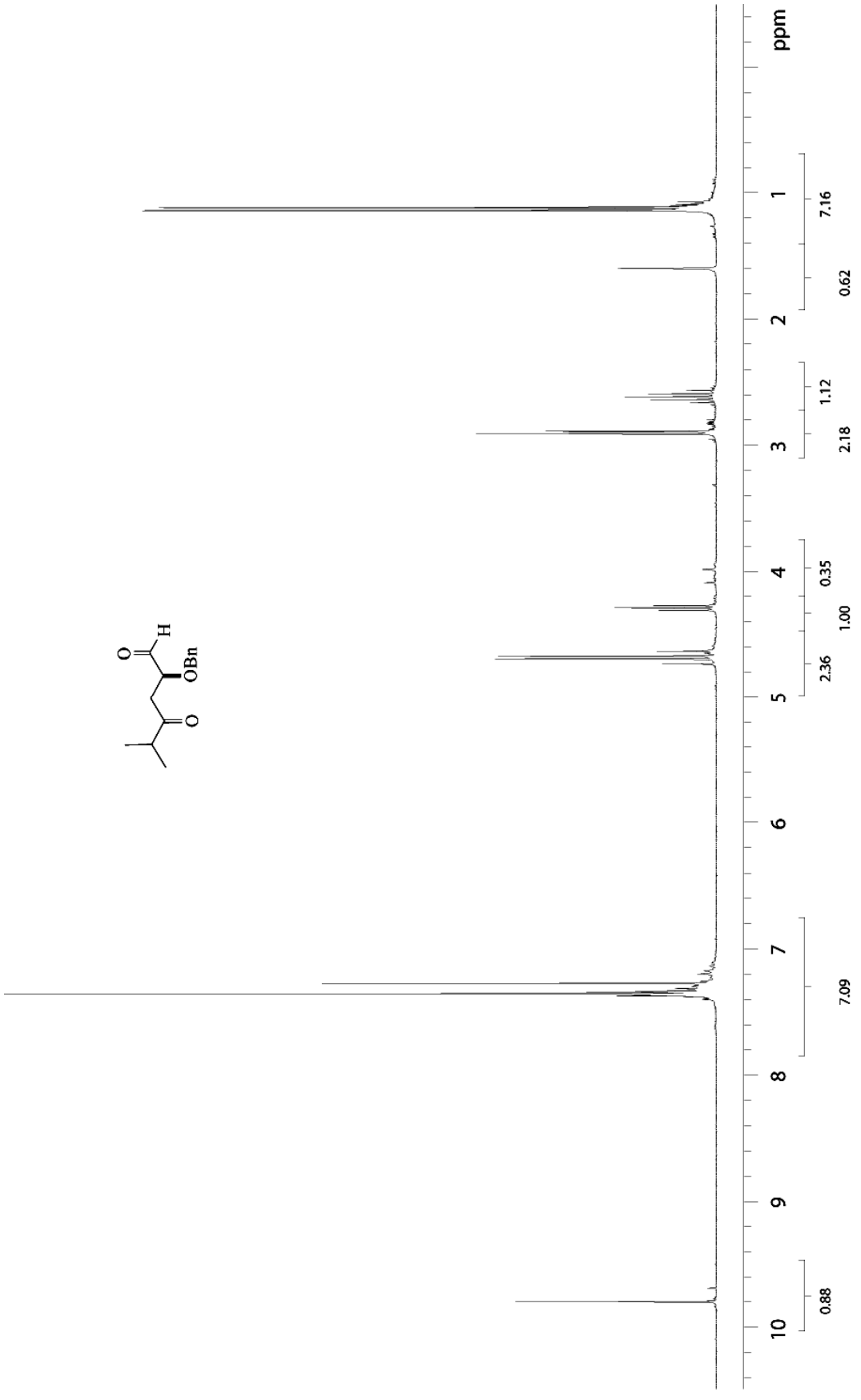
^{13}C NMR (75 MHz) of β-Benzyloxy Aldehyde **4.13** in $CDCl_3$



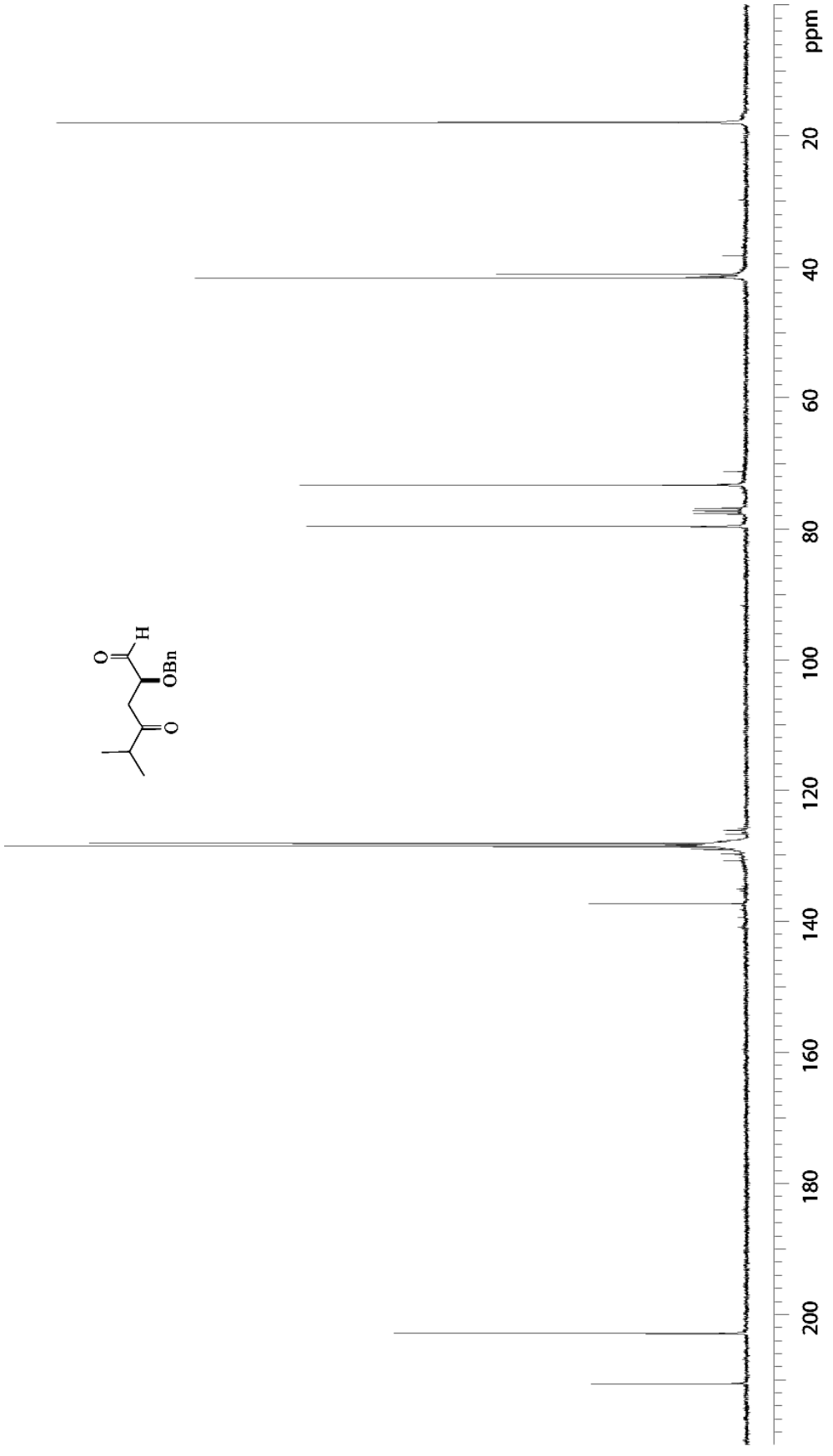
^{1}H NMR (300 MHz) of α-Benzyloxy-γ-Ketoaldehyde **(±)-4.1b** in $CDCl_3$



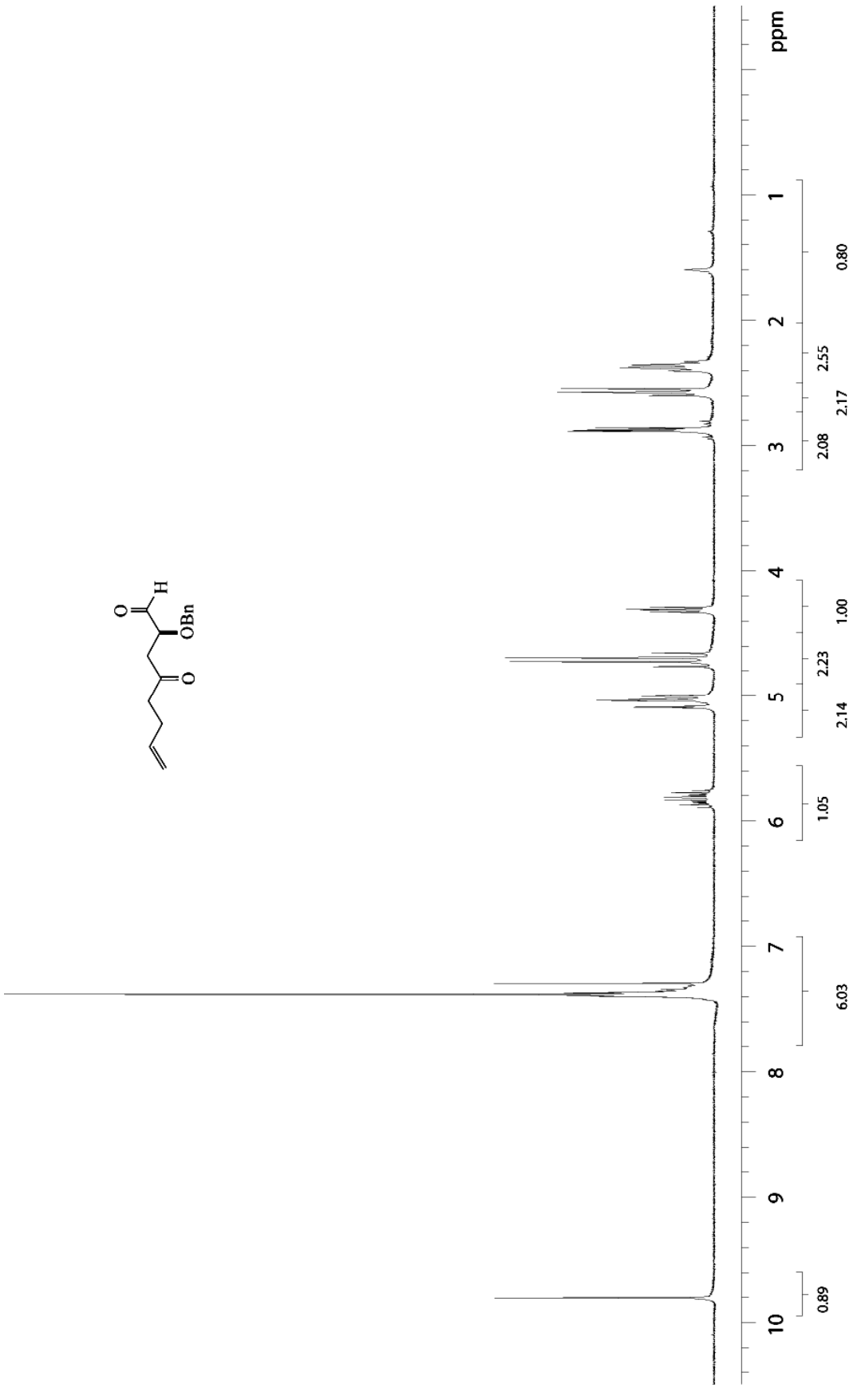
^{13}C NMR (75 MHz) of α-Benzyloxy-γ-Ketoaldehyde (±)-**4.1b** in $CDCl_3$



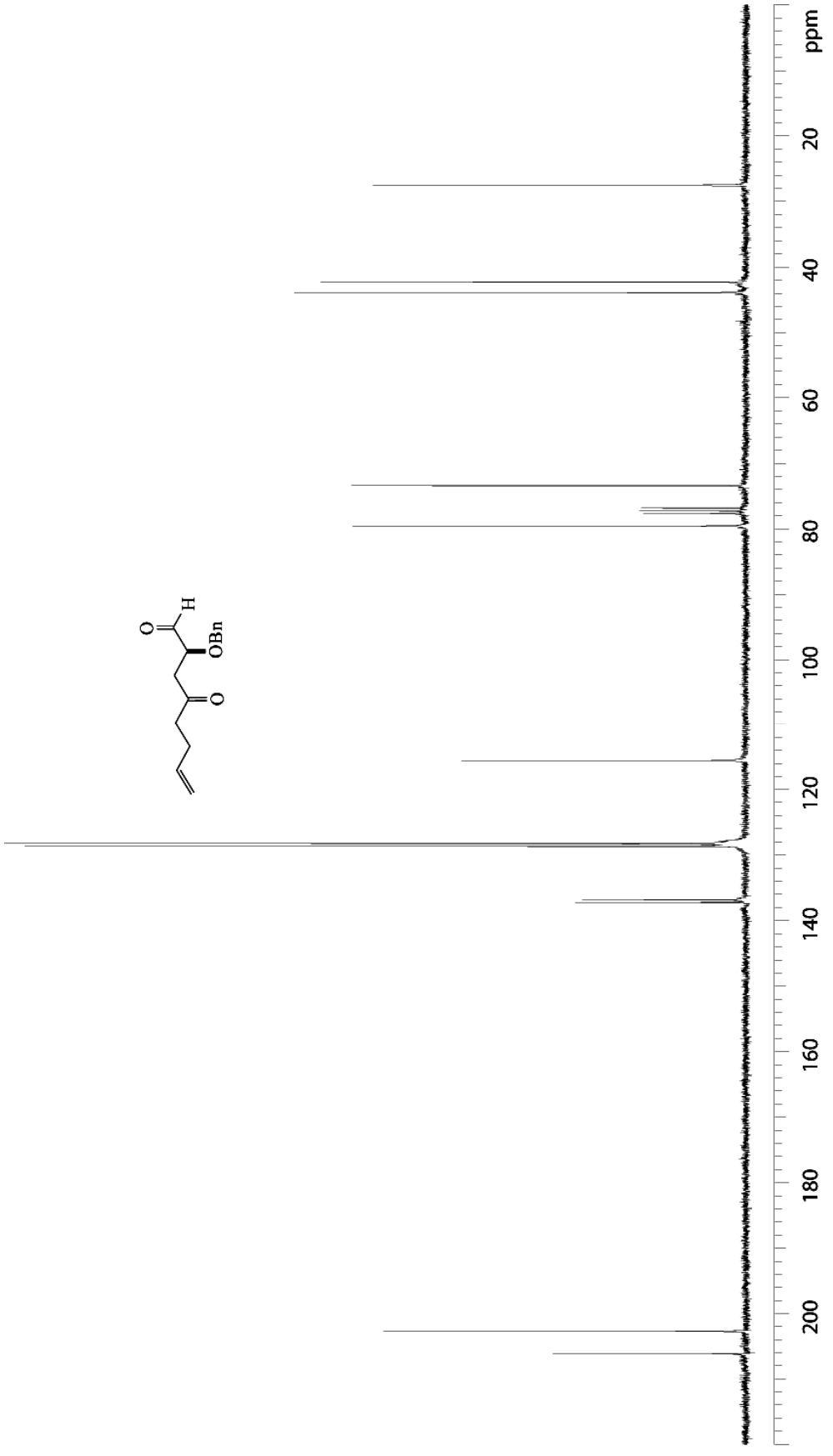
^{1}H NMR (300 MHz) of α-Benzyloxy-γ-Ketoaldehyde **(±)-4.1c** in $CDCl_3$



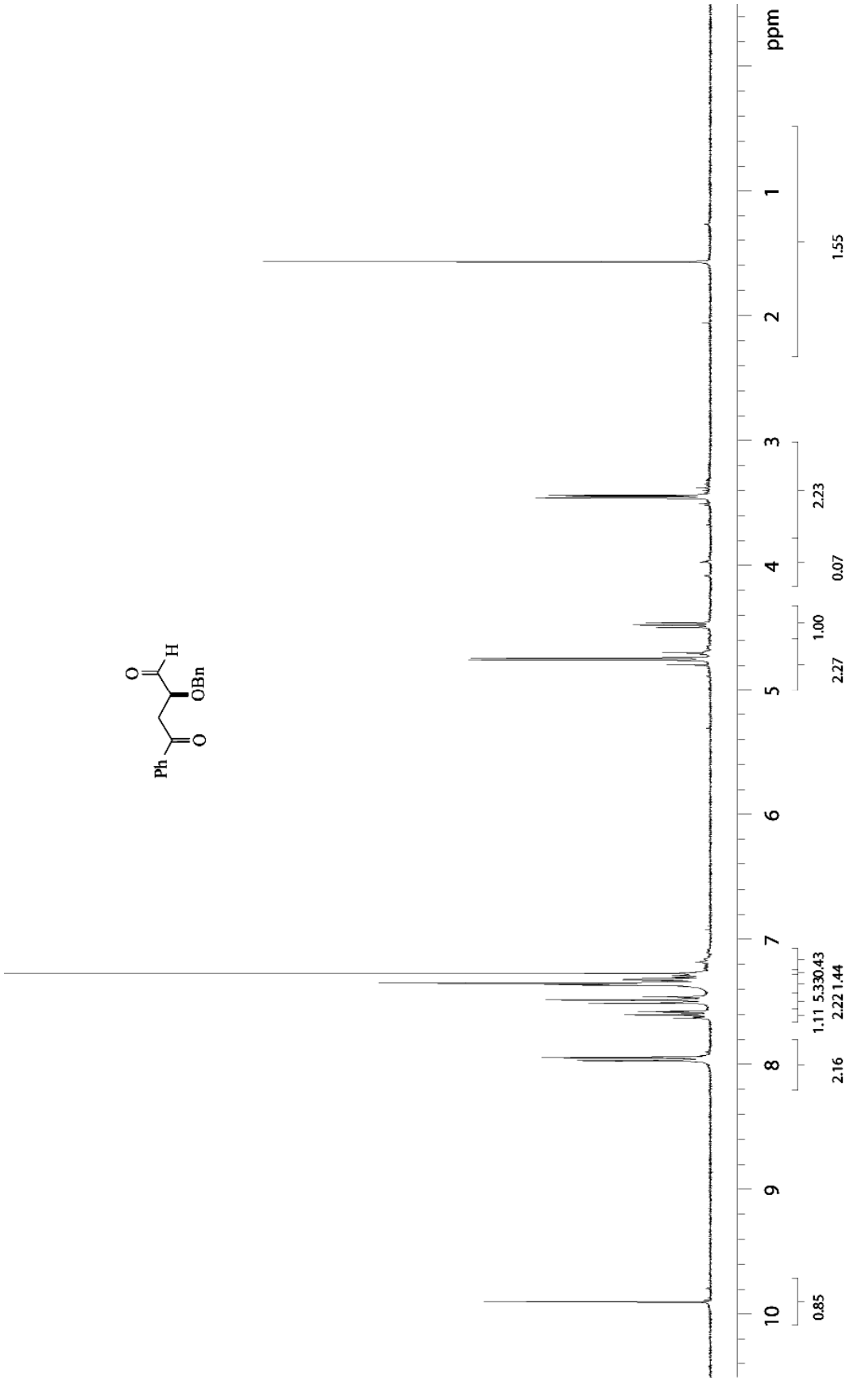
^{13}C NMR (75 MHz) of α-Benzyloxy-γ-Ketoaldehyde (±)-**4.1c** in $CDCl_3$



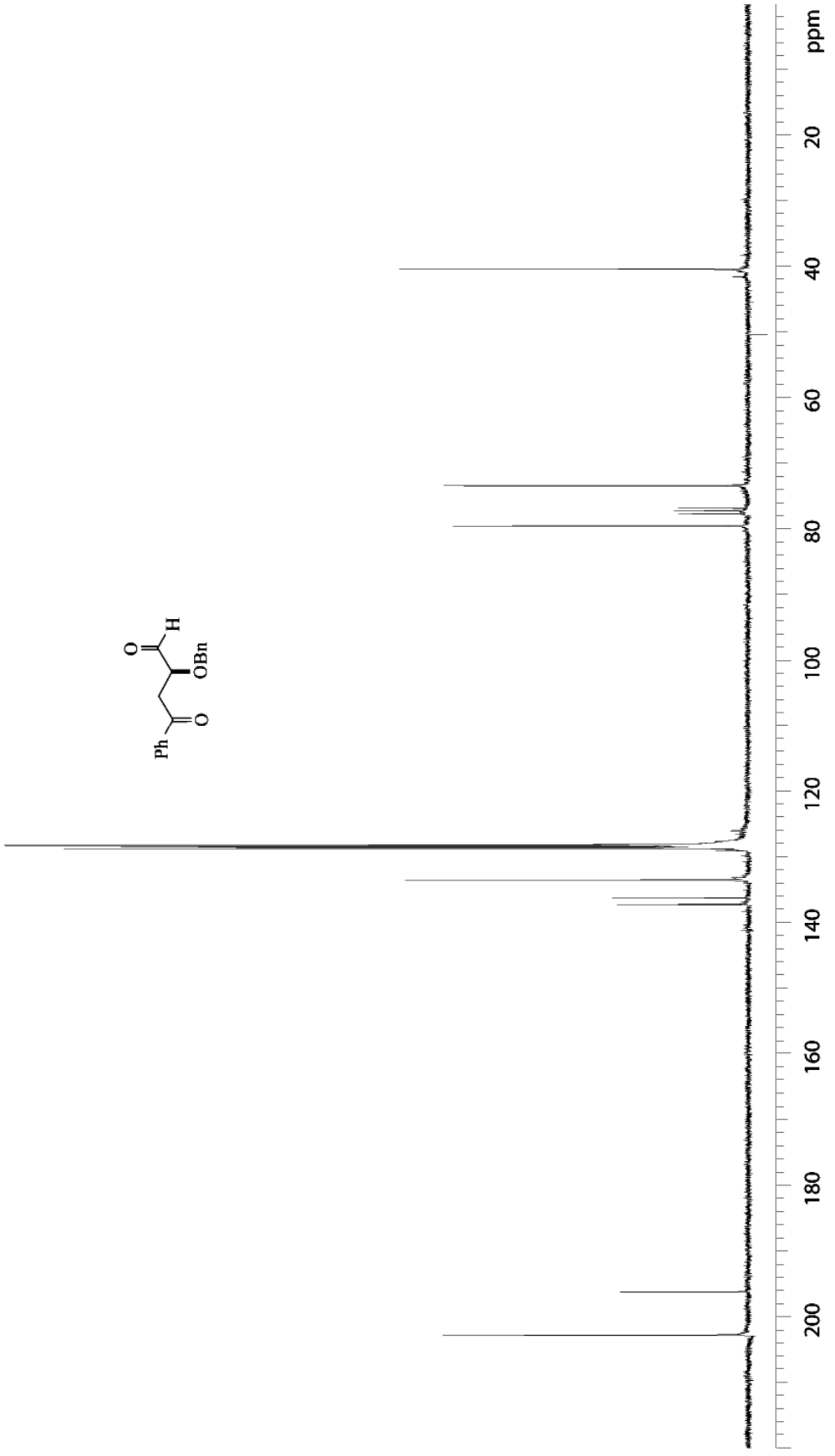
^{1}H NMR (300 MHz) of α-Benzyloxy-γ-Ketoaldehyde **(±)-4.1d** in $CDCl_3$



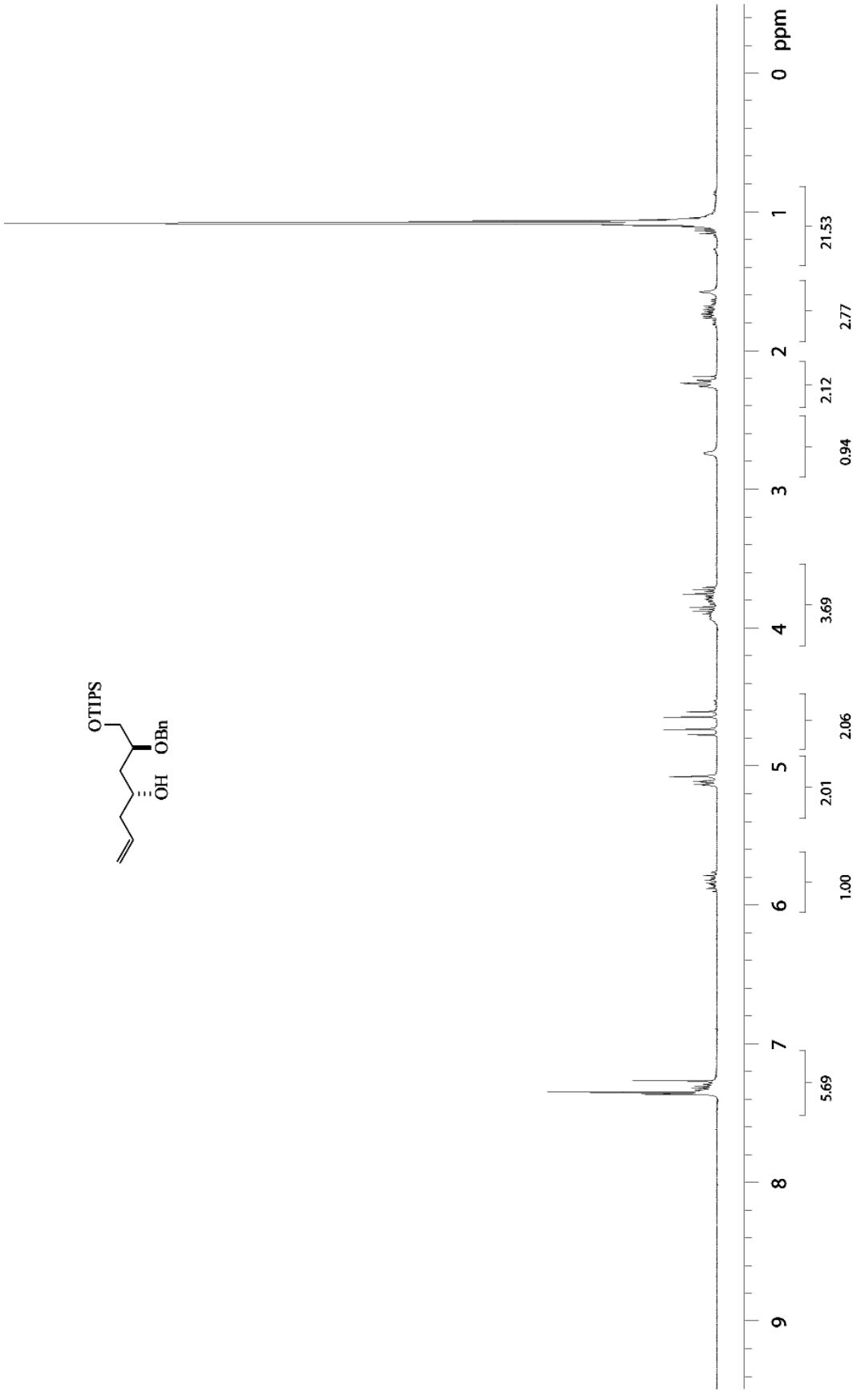
^{13}C NMR (75 MHz) of α-Benzyloxy-γ-Ketoaldehyde **(±)-4.1d** in $CDCl_3$



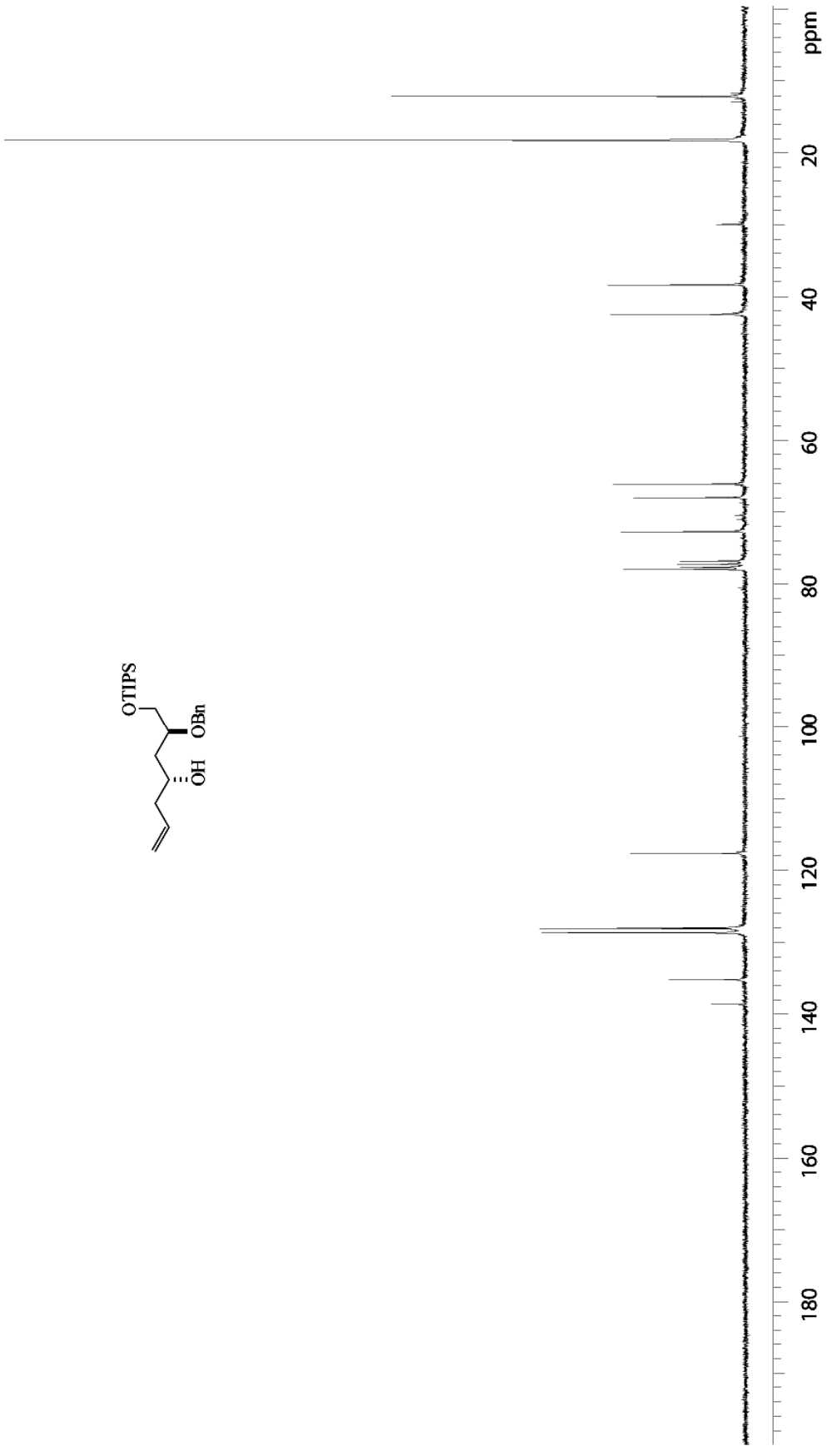
^{1}H NMR (300 MHz) of α-Benzyloxy-γ-Ketoaldehyde **(±)-4.1e** in $CDCl_3$



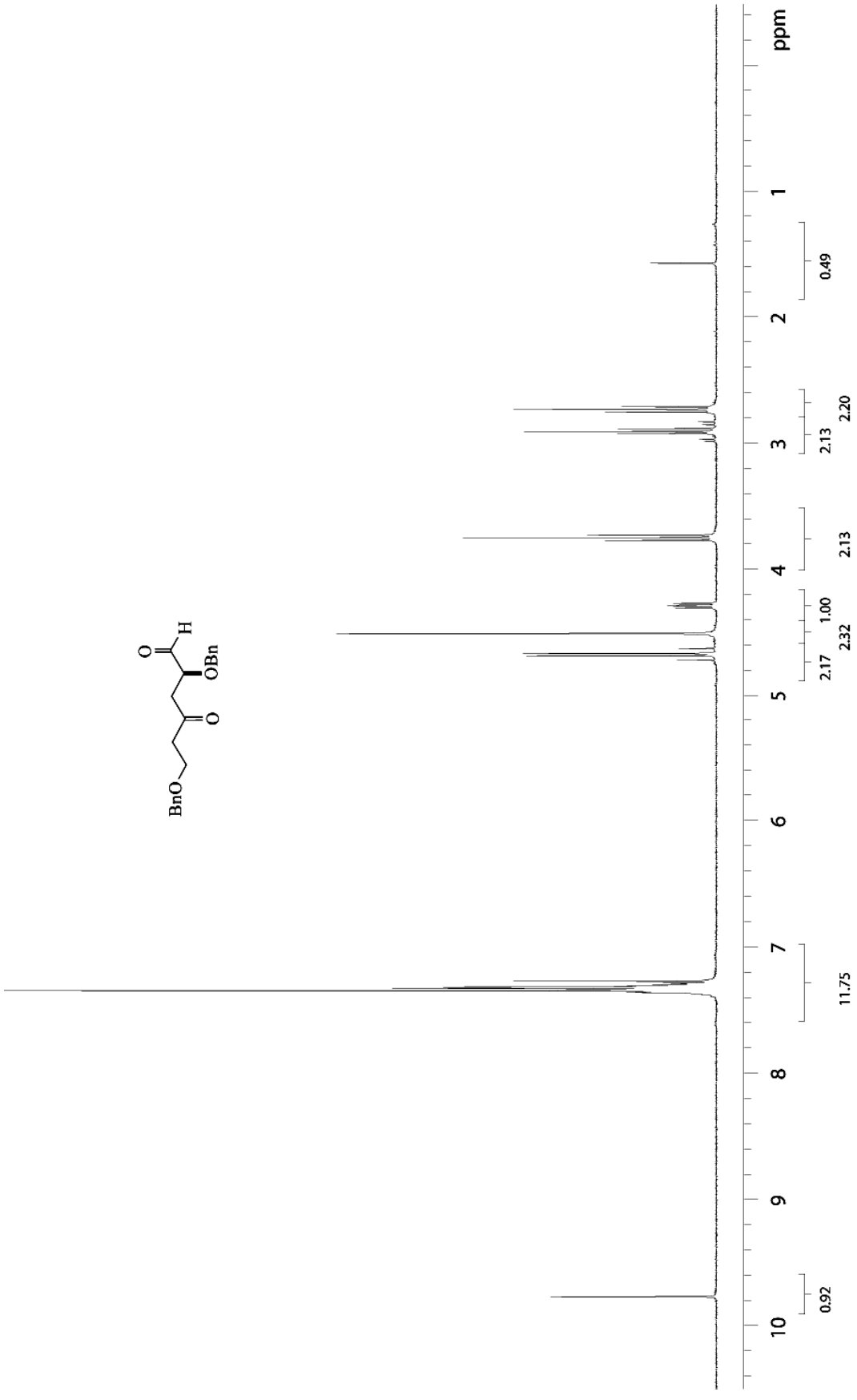
^{13}C NMR (75 MHz) of α-Benzyloxy-γ-Ketoaldehyde **(±)-4.1e** in $CDCl_3$



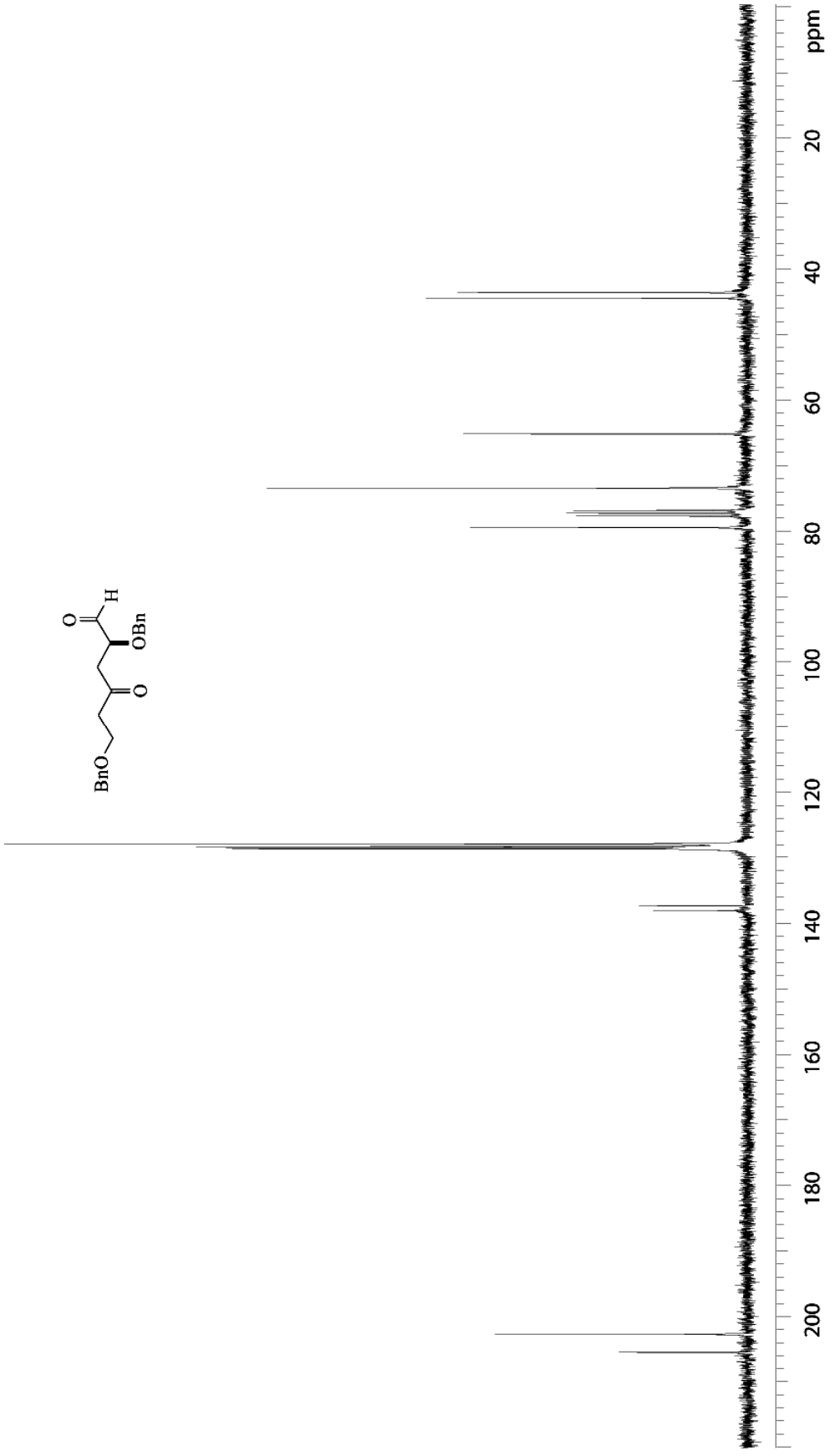
^{1}H NMR (300 MHz) of Secondary Alcohol **S22**in $CDCl_3$



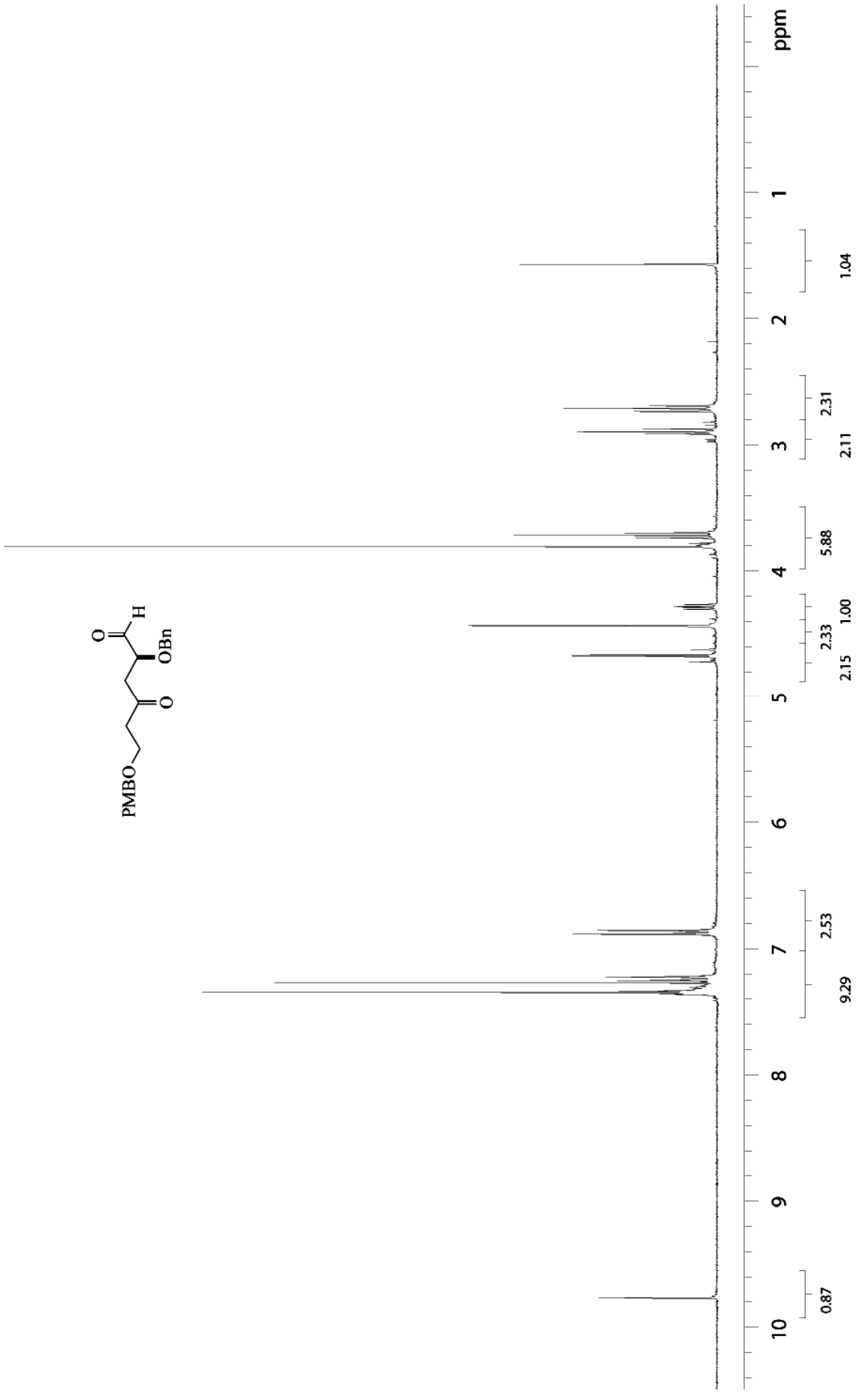
^{13}C NMR (75 MHz) of Secondary Alcohol **S22** in $CDCl_3$



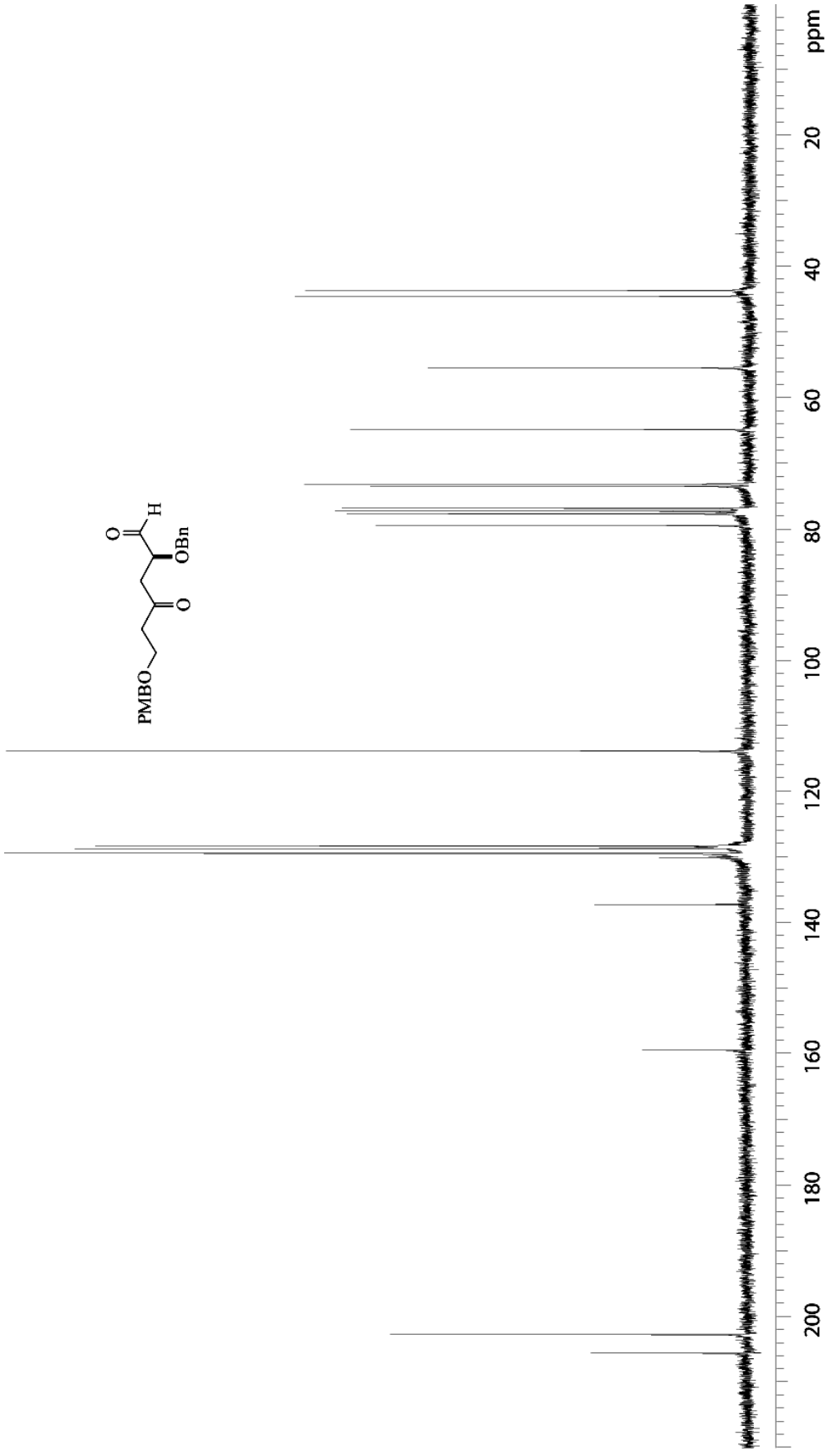
^{1}H NMR (300 MHz) of α-Benzyloxy-γ-Ketoaldehyde (±)-**4.1f** in $CDCl_3$



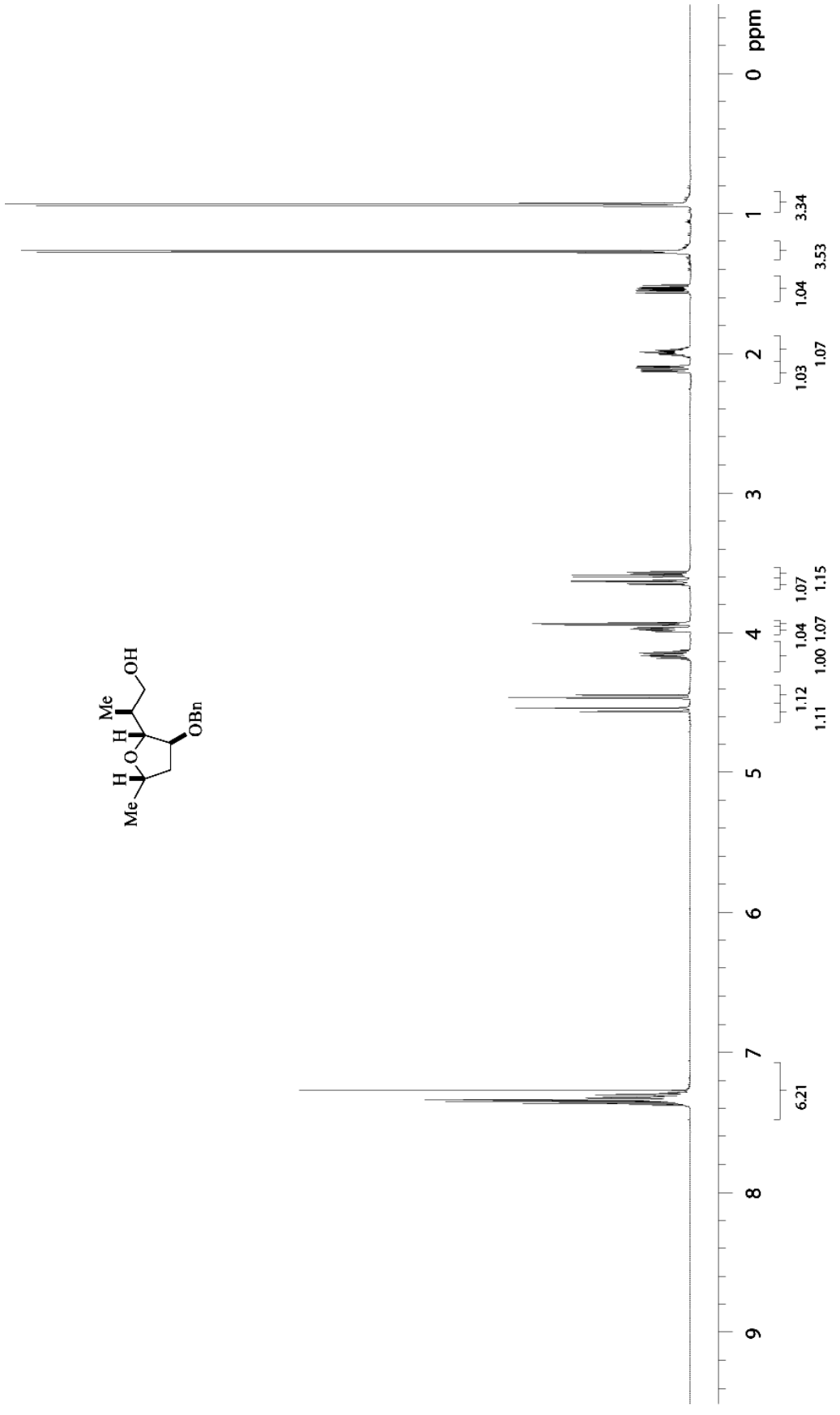
^{13}C NMR (75 MHz) of α-Benzyloxy-γ-Ketoaldehyde **(±)-4.1f** in $CDCl_3$



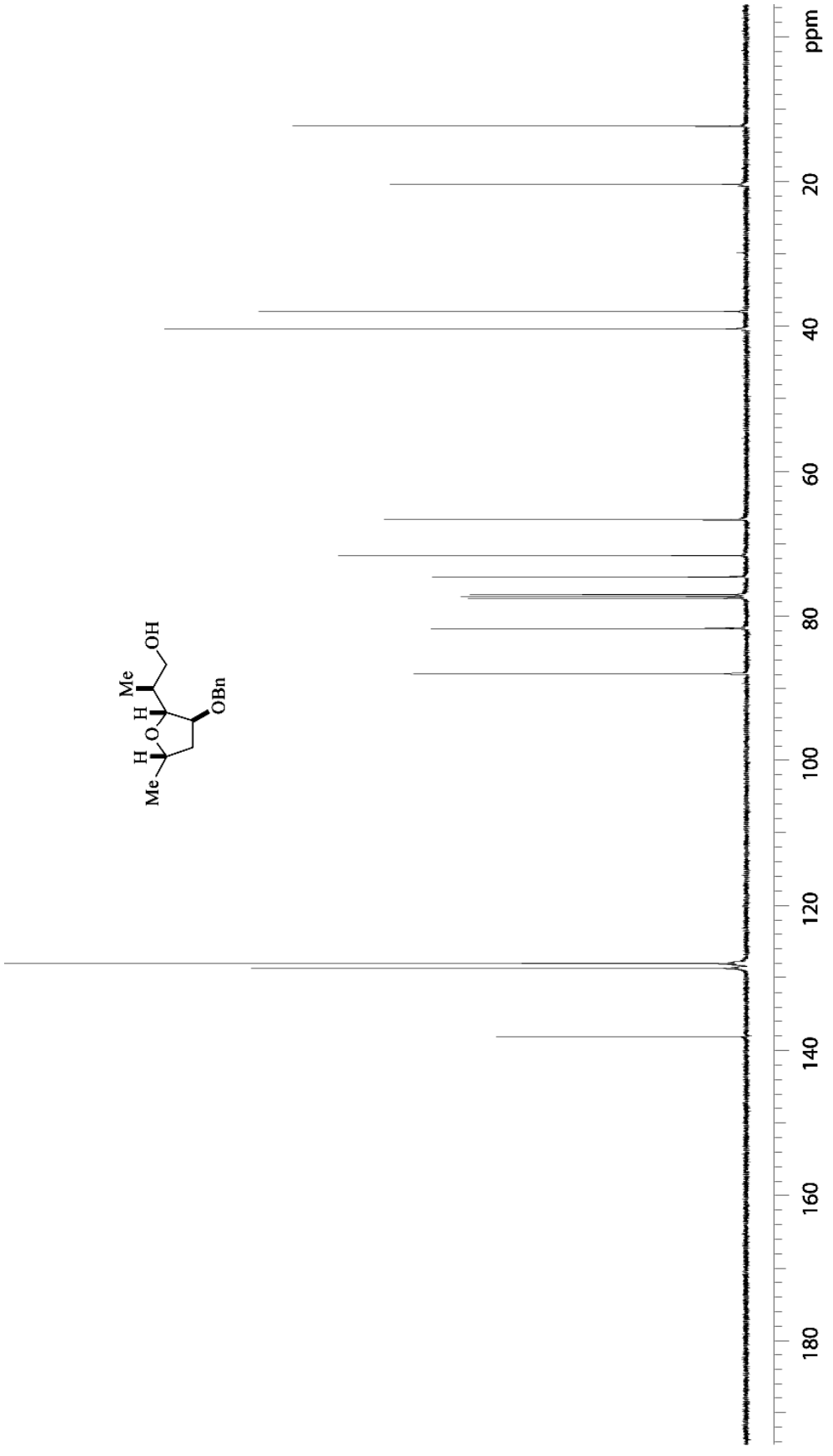
^{1}H NMR (300 MHz) of α-Benzyloxy-γ-Ketoaldehyde (±)-**4.1g** in $CDCl_3$



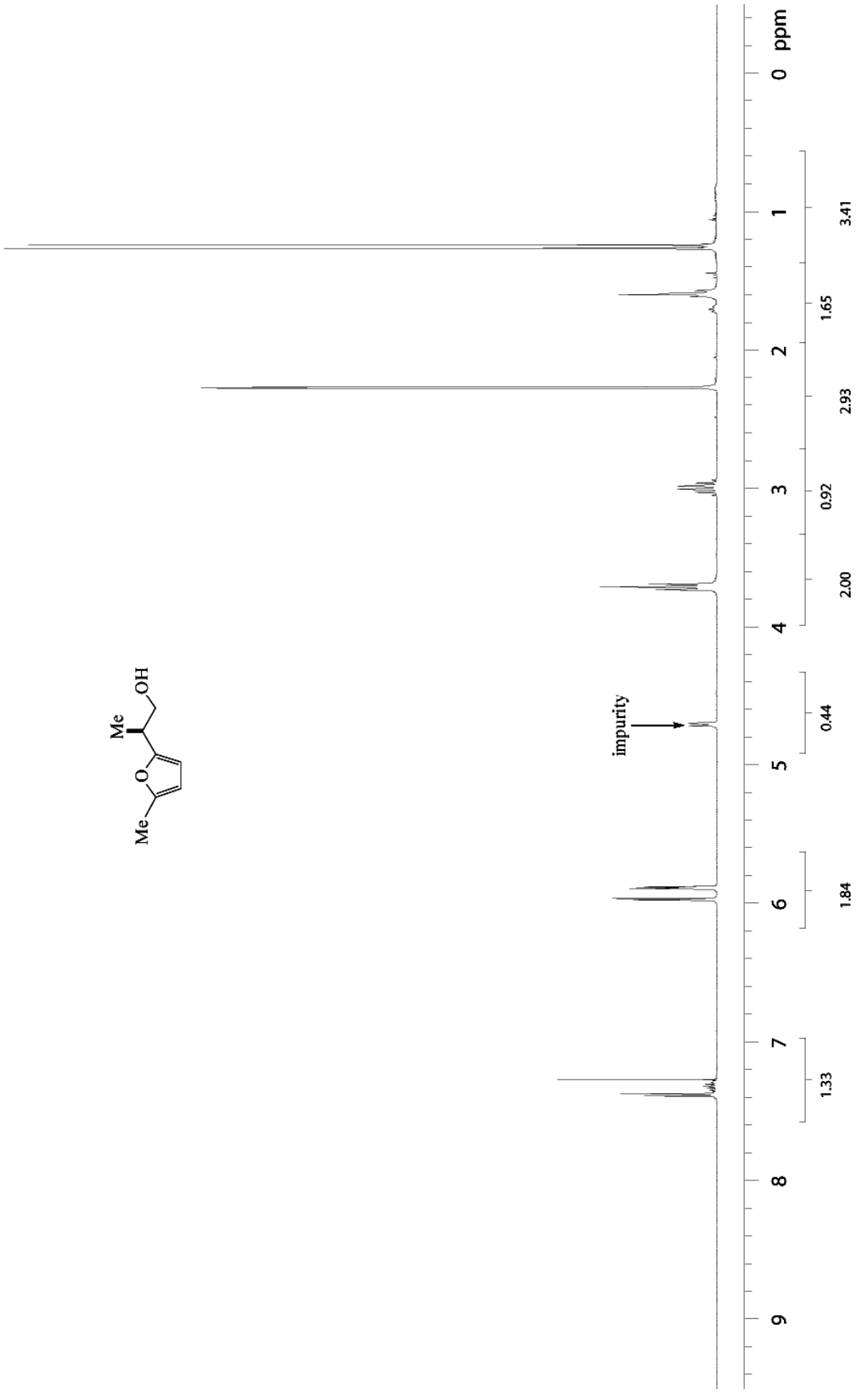
^{13}C NMR (75 MHz) of α-Benzyloxy-γ-Ketoaldehyde **(±)-4.1g** in $CDCl_3$



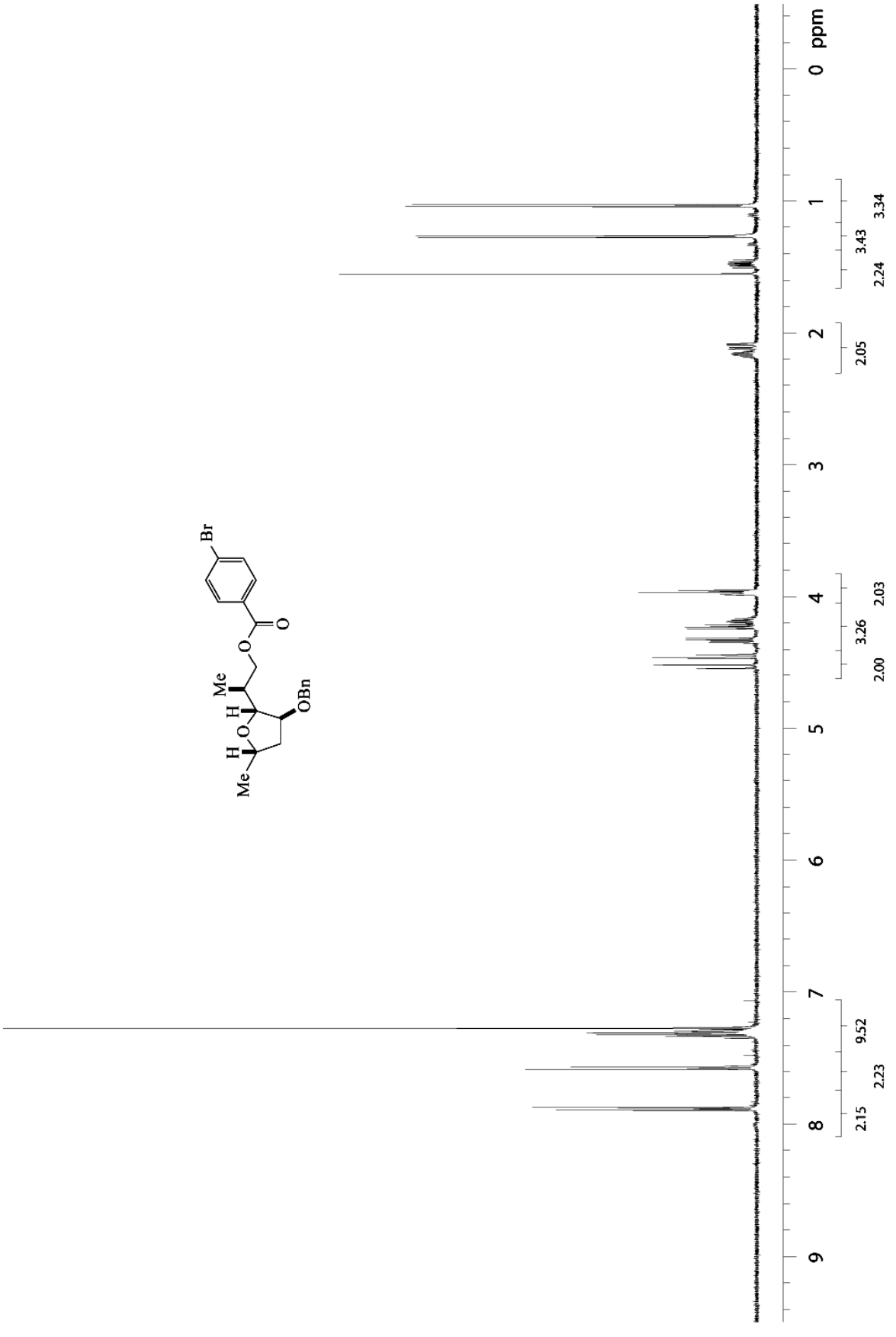
^{1}H NMR (500 MHz) of THF **4.15a** in $CDCl_3$



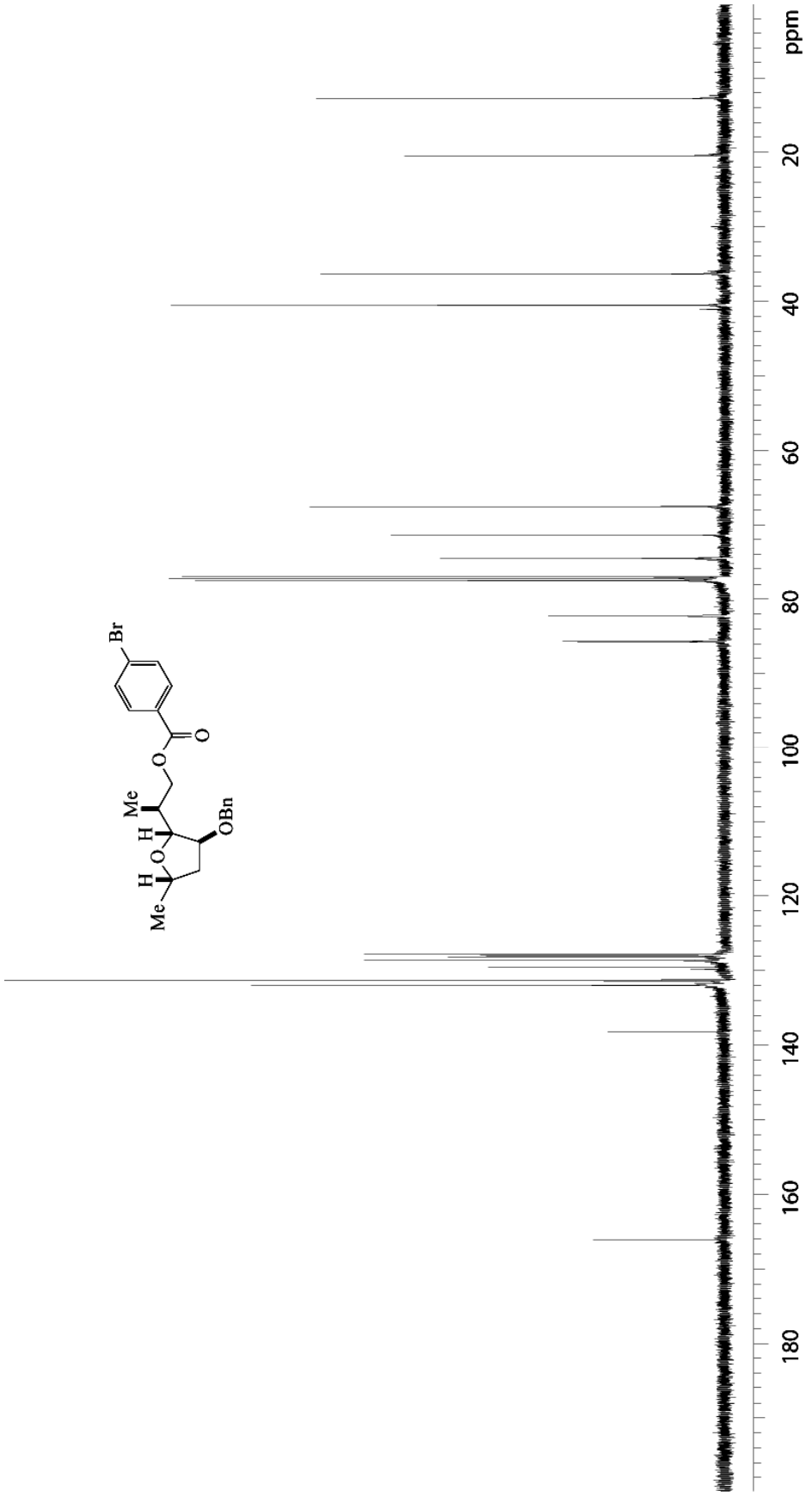
^{13}C NMR (125 MHz) of THF **4.15a** in $CDCl_3$



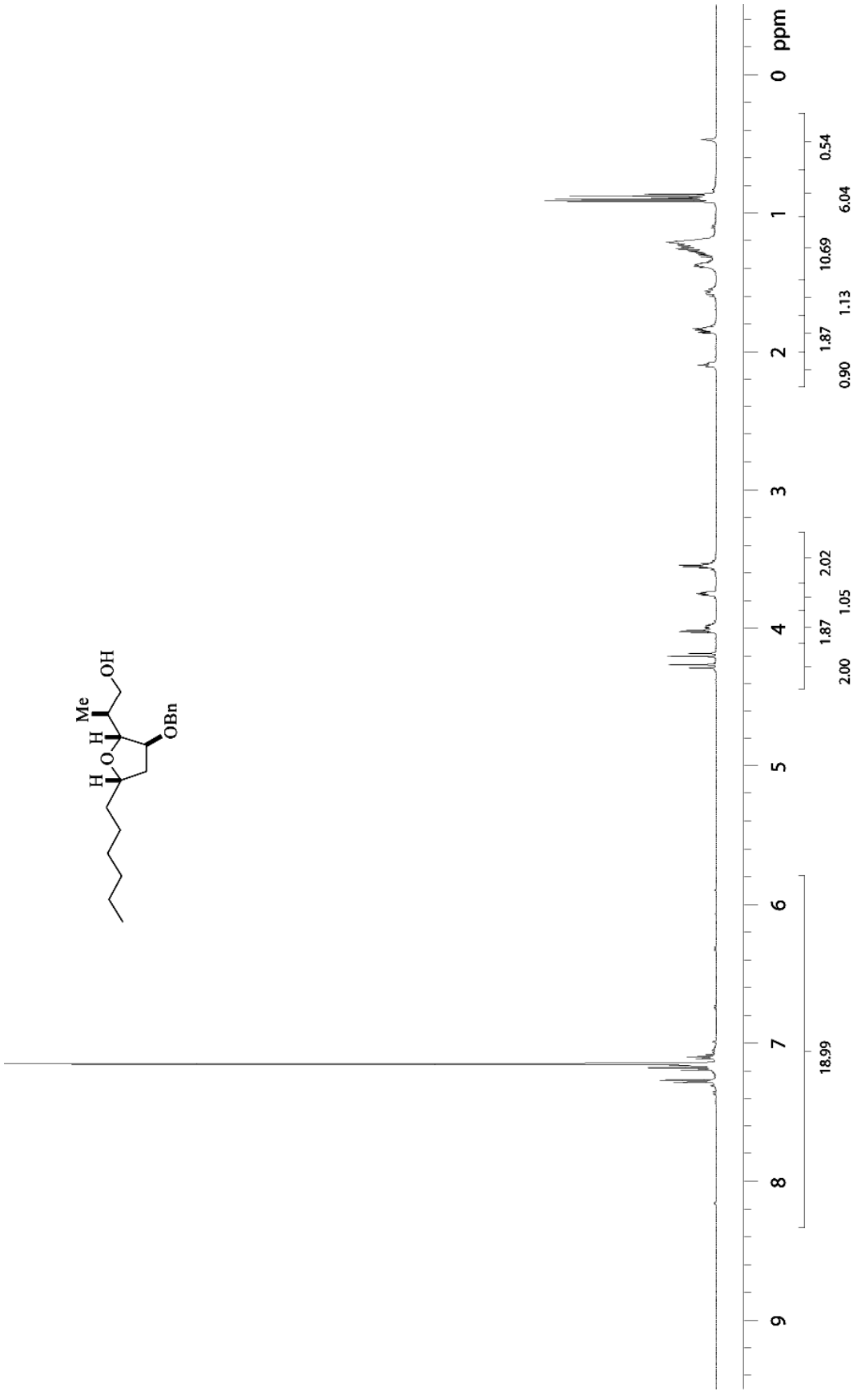
^{1}H NMR of (300 MHz) of Furan **4.16a** in $CDCl_3$



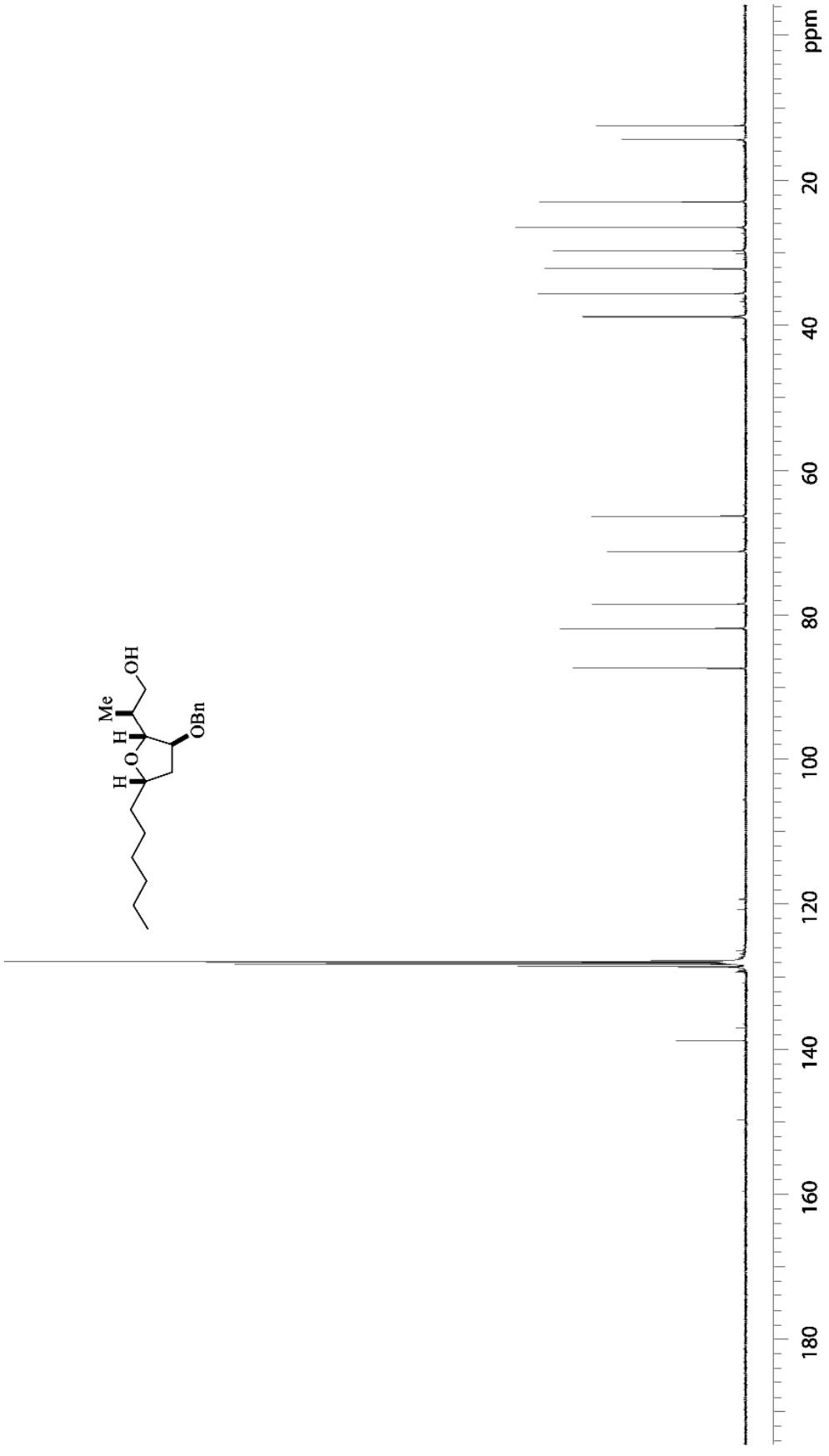
^{1}H NMR (500 MHz) of THF **4.15a'** in $CDCl_3$



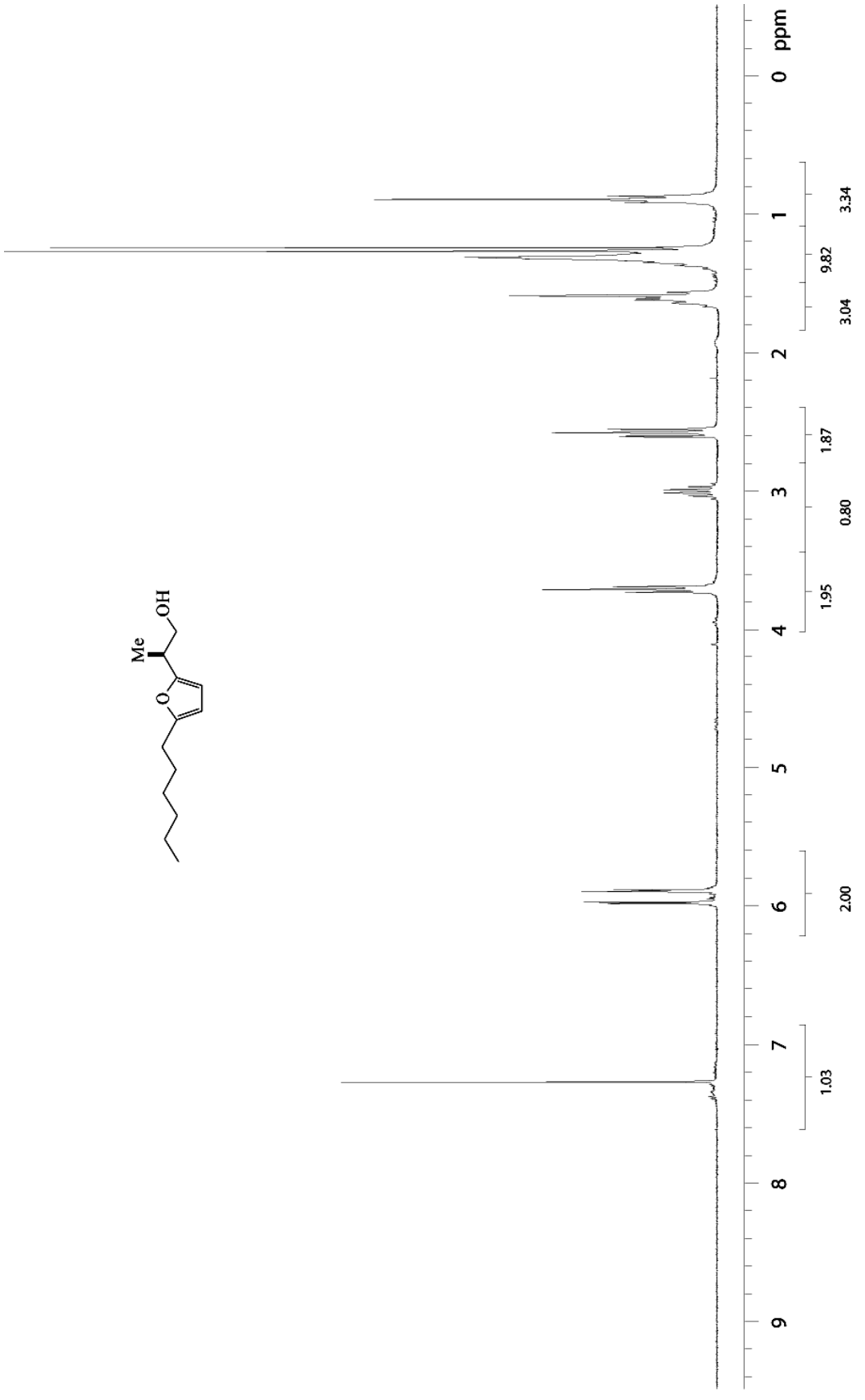
^{13}C NMR (125 MHz) of THF **4.15a'** in $CDCl_3$



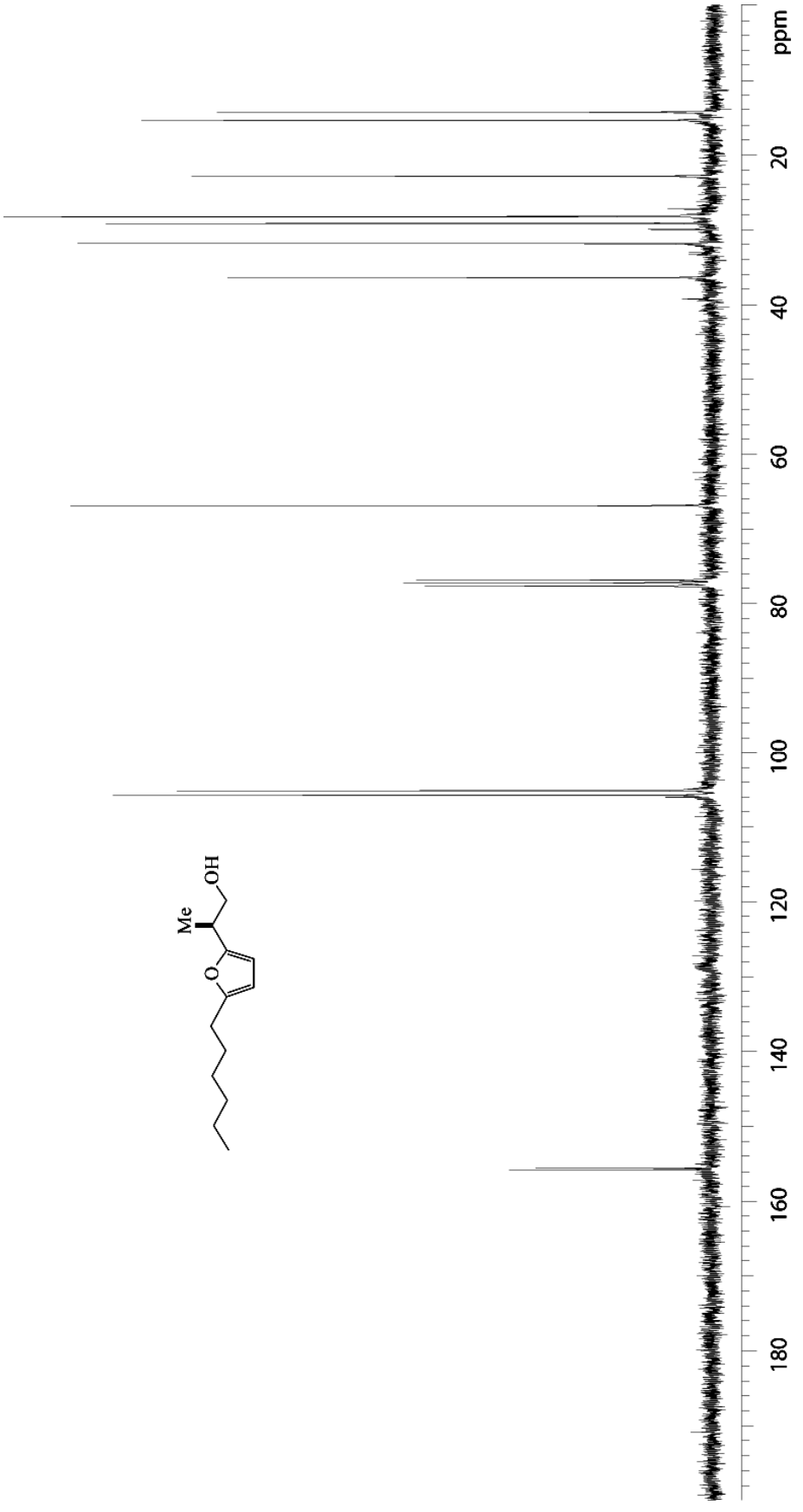
^{1}H NMR (500 MHz) of THF **4.15b** in C_6D_6



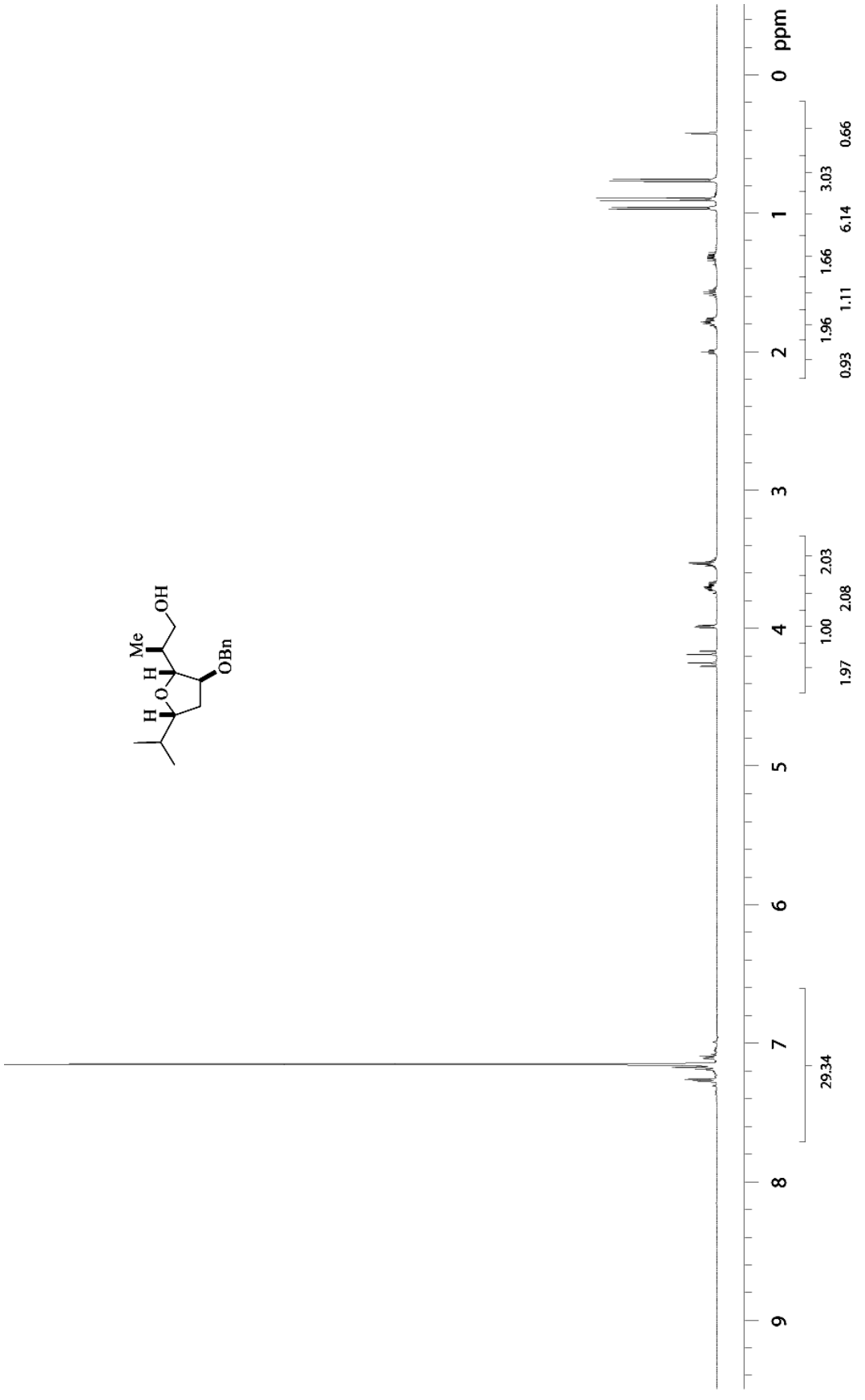
^{13}C NMR (125 MHz) of THF **4.15b** in C_6D_6



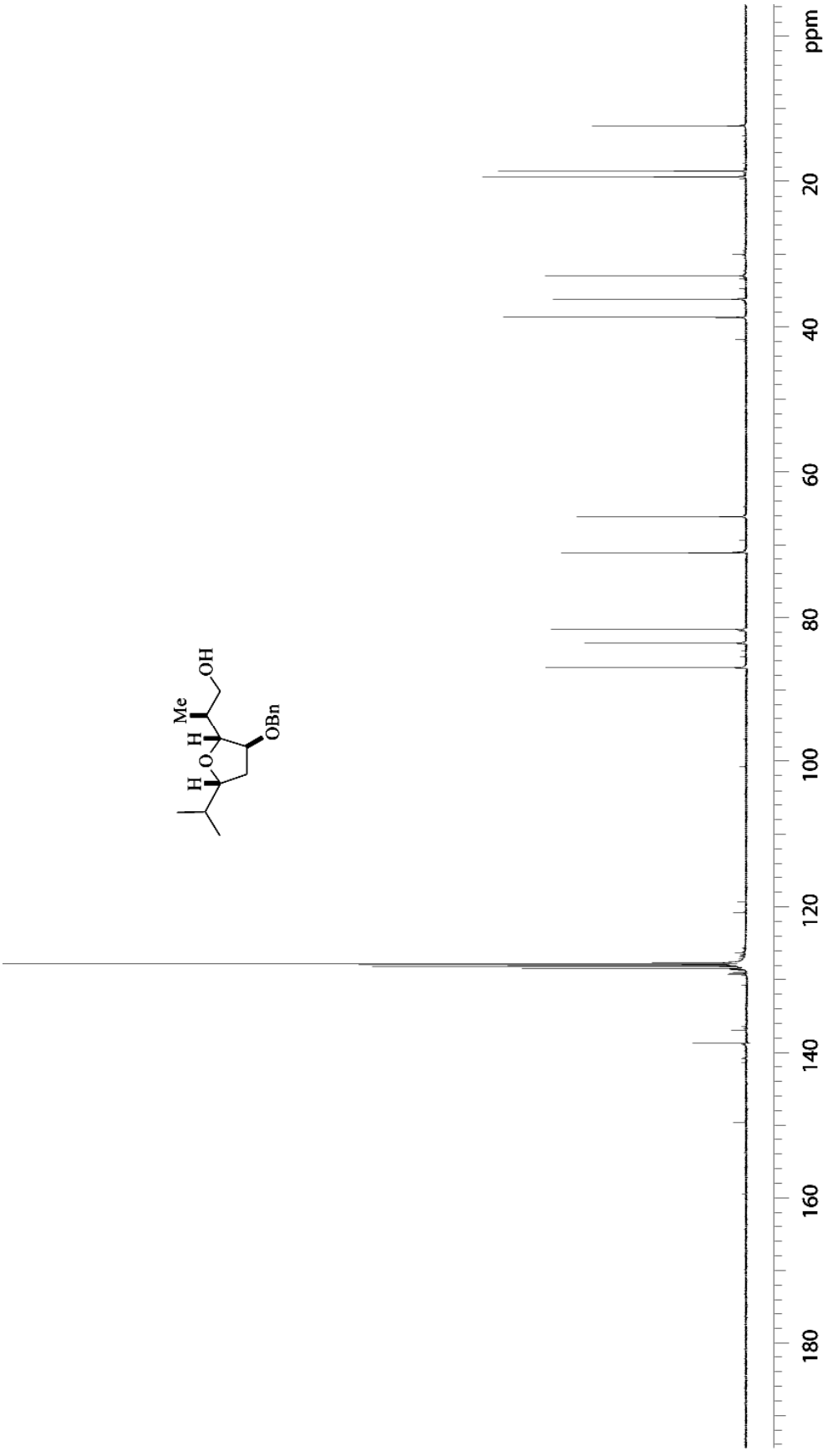
^{1}H NMR (300 MHz) of Furan **4.16b** in $CDCl_3$



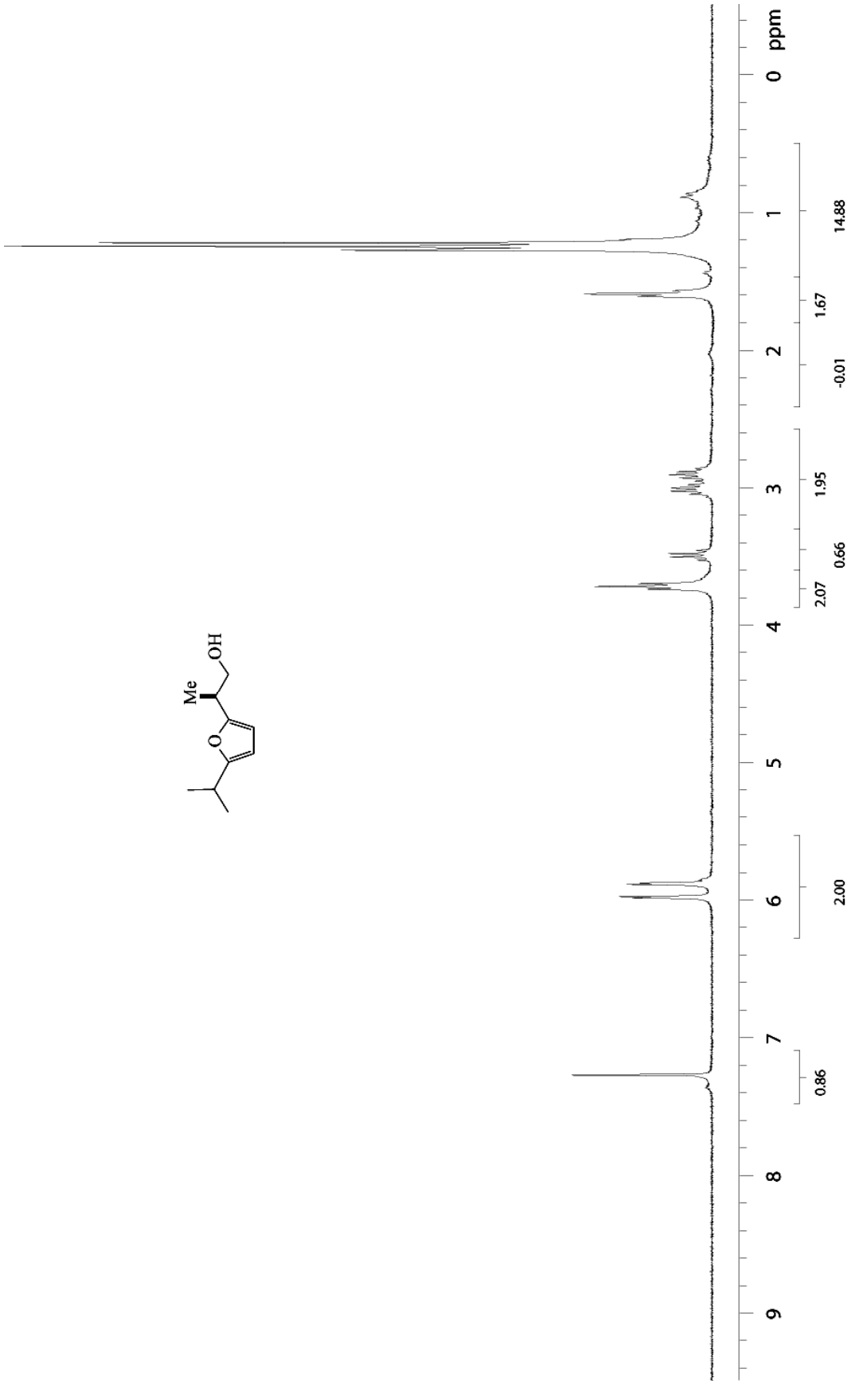
^{13}C NMR (75 MHz) of Furan **4.16b** in $CDCl_3$



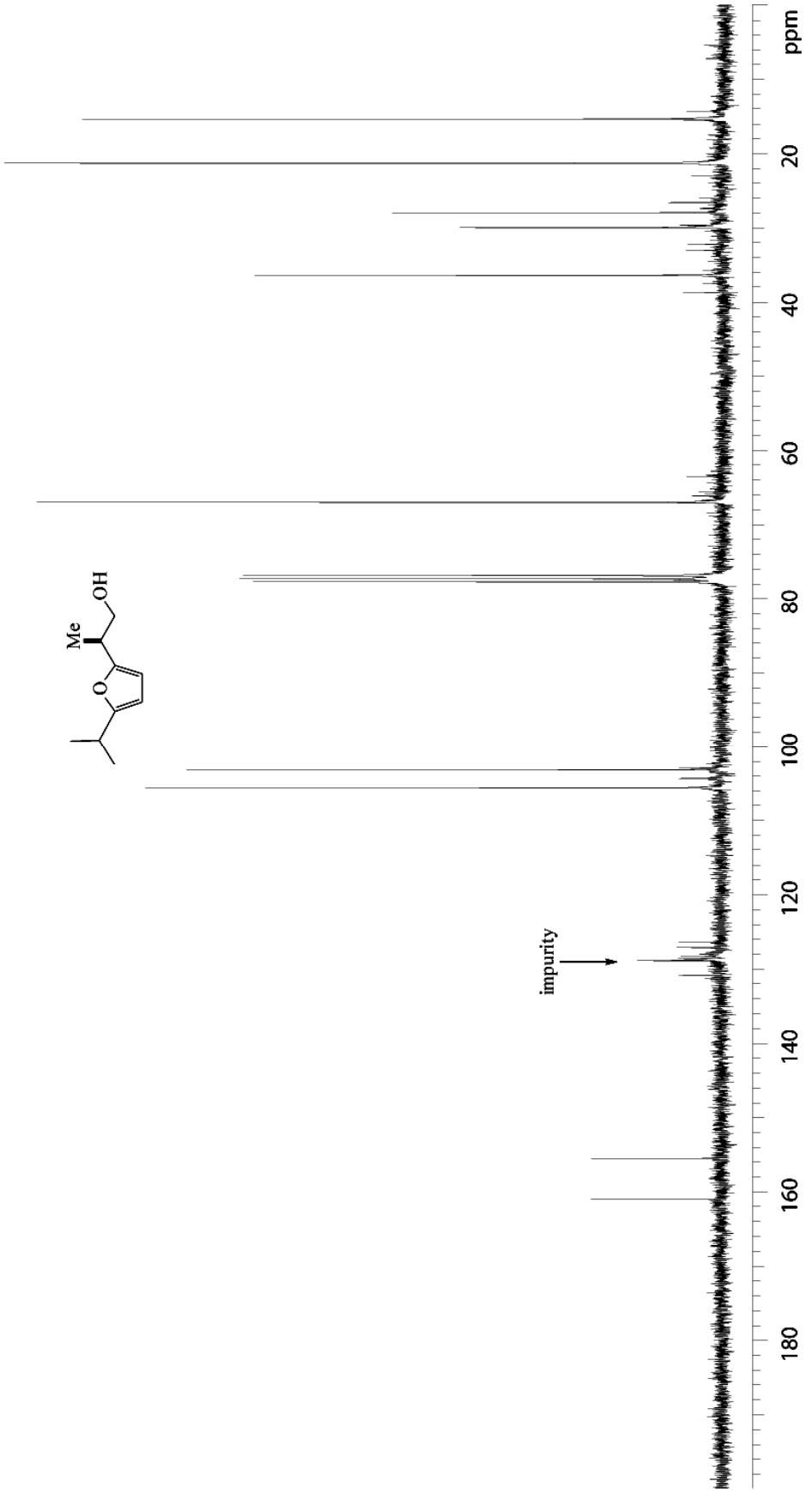
^{1}H NMR (500 MHz) of THF **4.15c** in C_6D_6



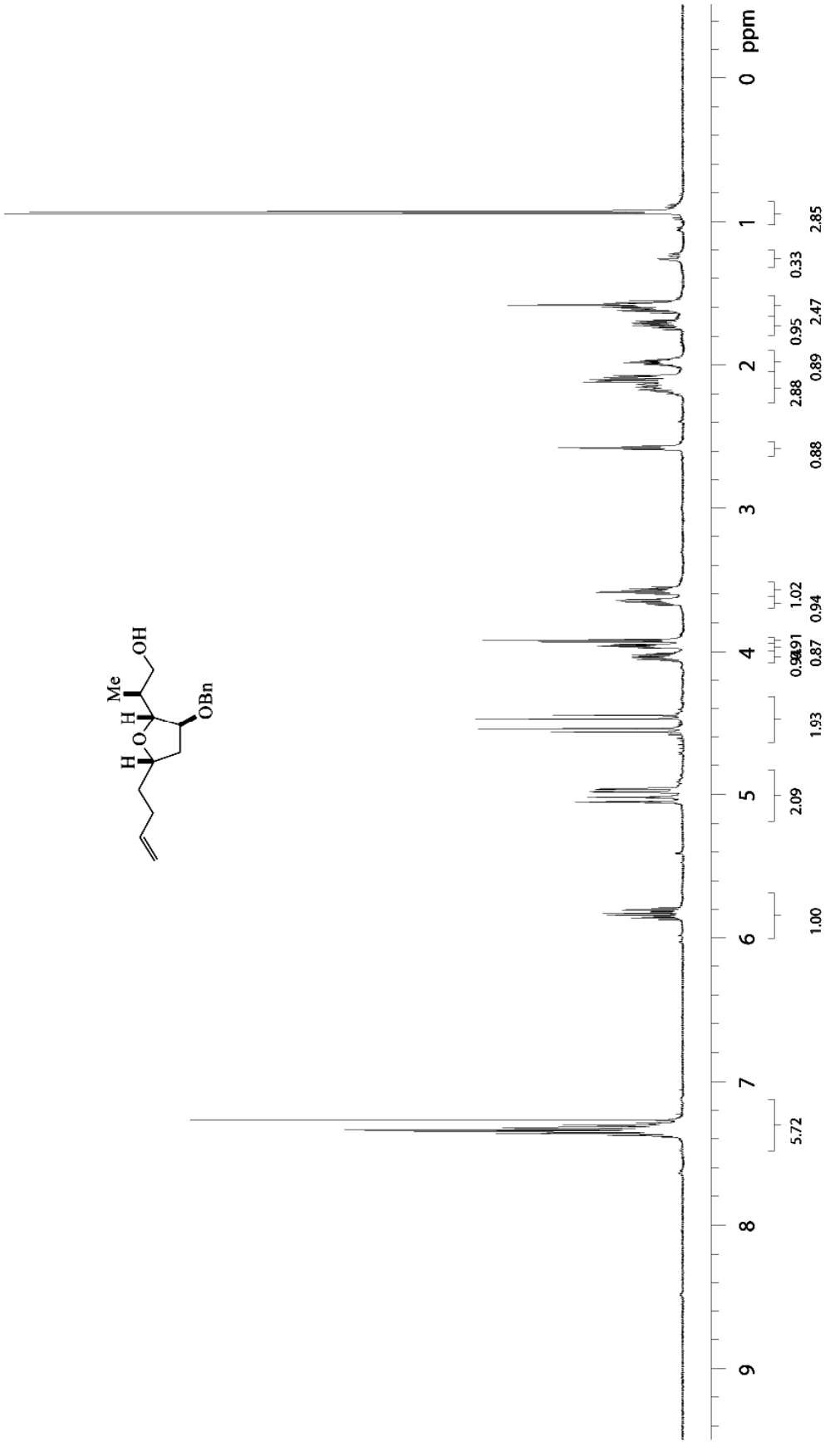
^{13}C NMR (125 MHz) of THF **4.15c** in C_6D_6



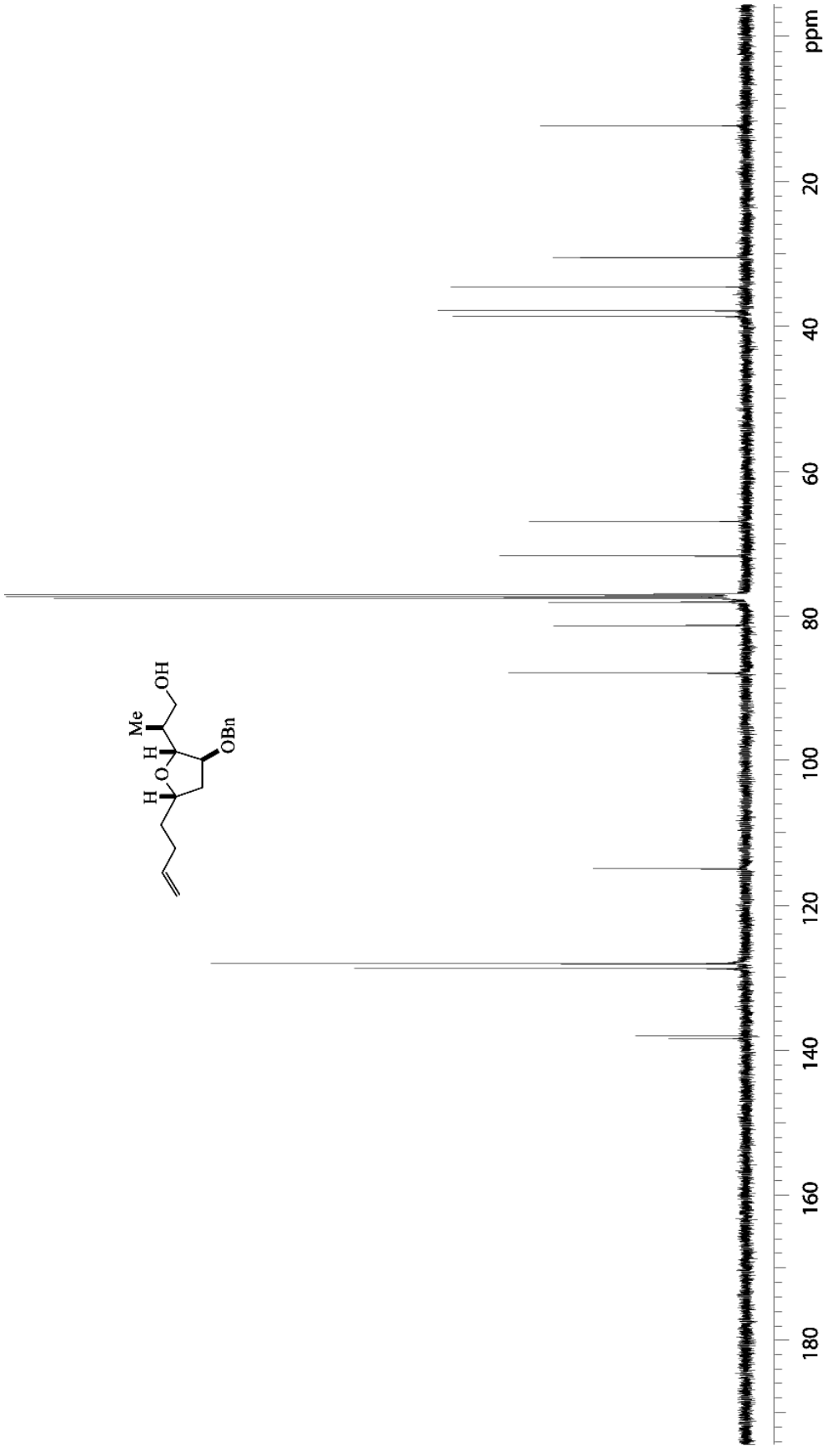
^{1}H NMR (300 MHz) of Furan **4.16c** in $CDCl_3$



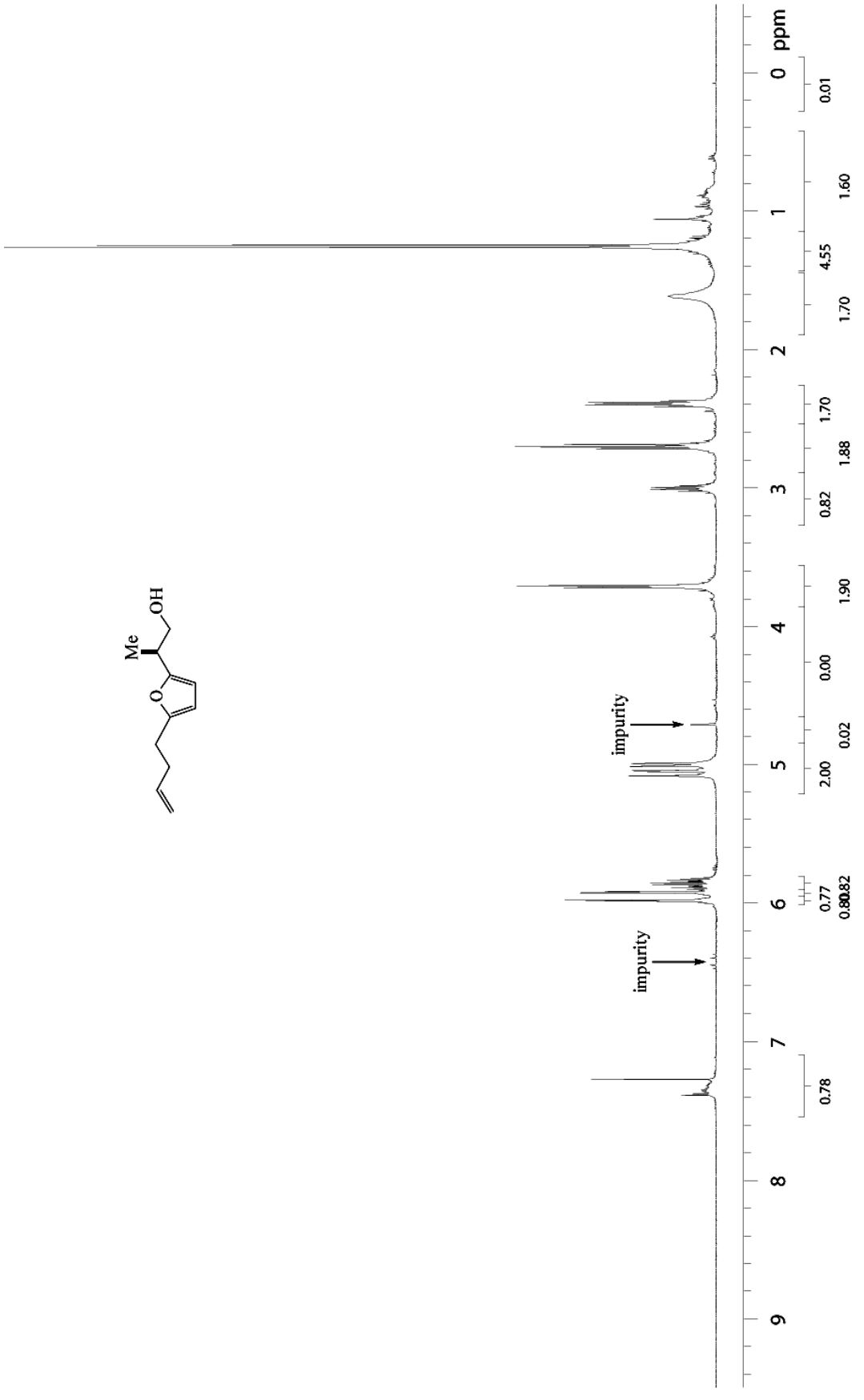
^{13}C NMR (75 MHz) of Furan **4.16c** in $CDCl_3$



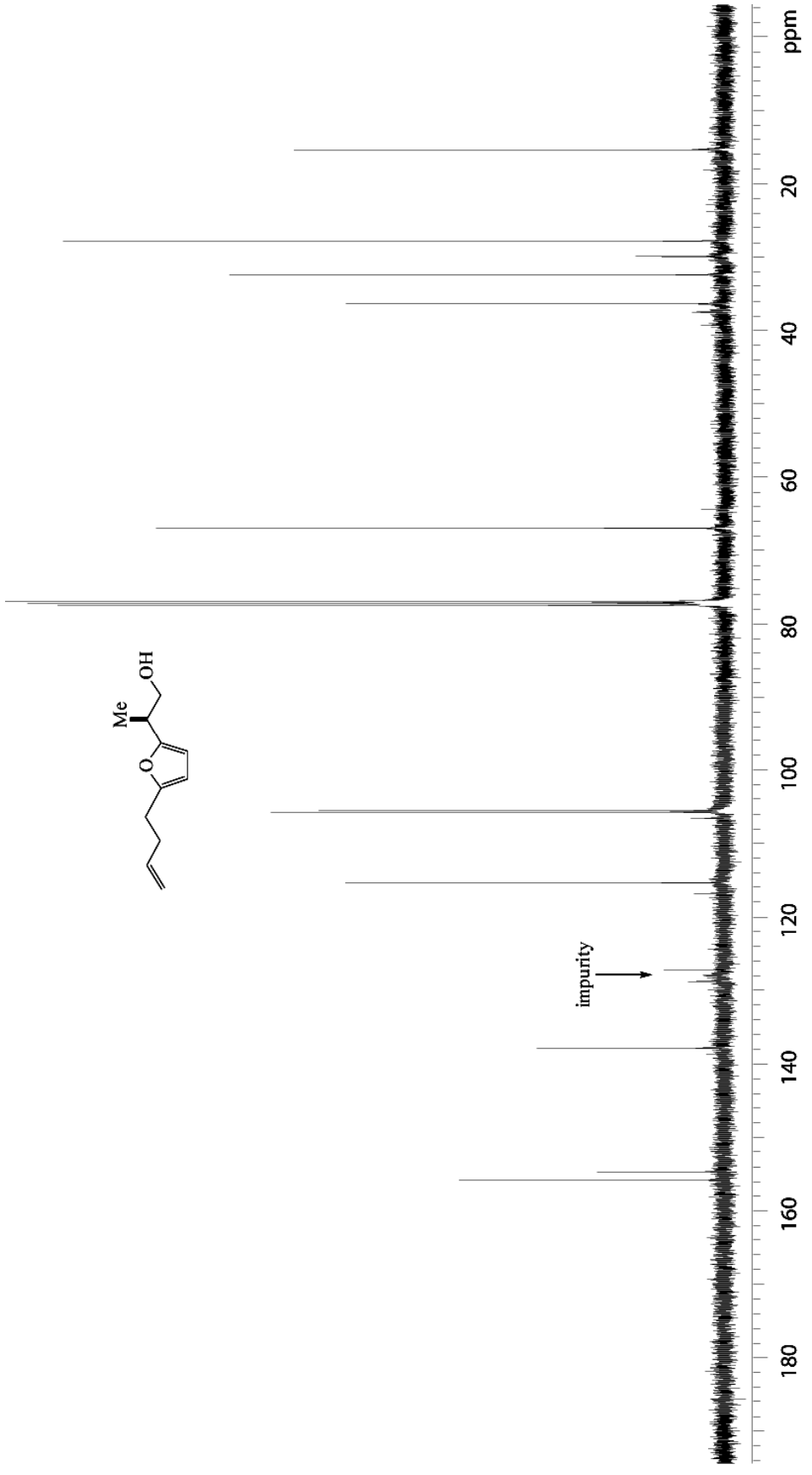
^{1}H NMR (500 MHz) of THF **4.15d** in $CDCl_3$



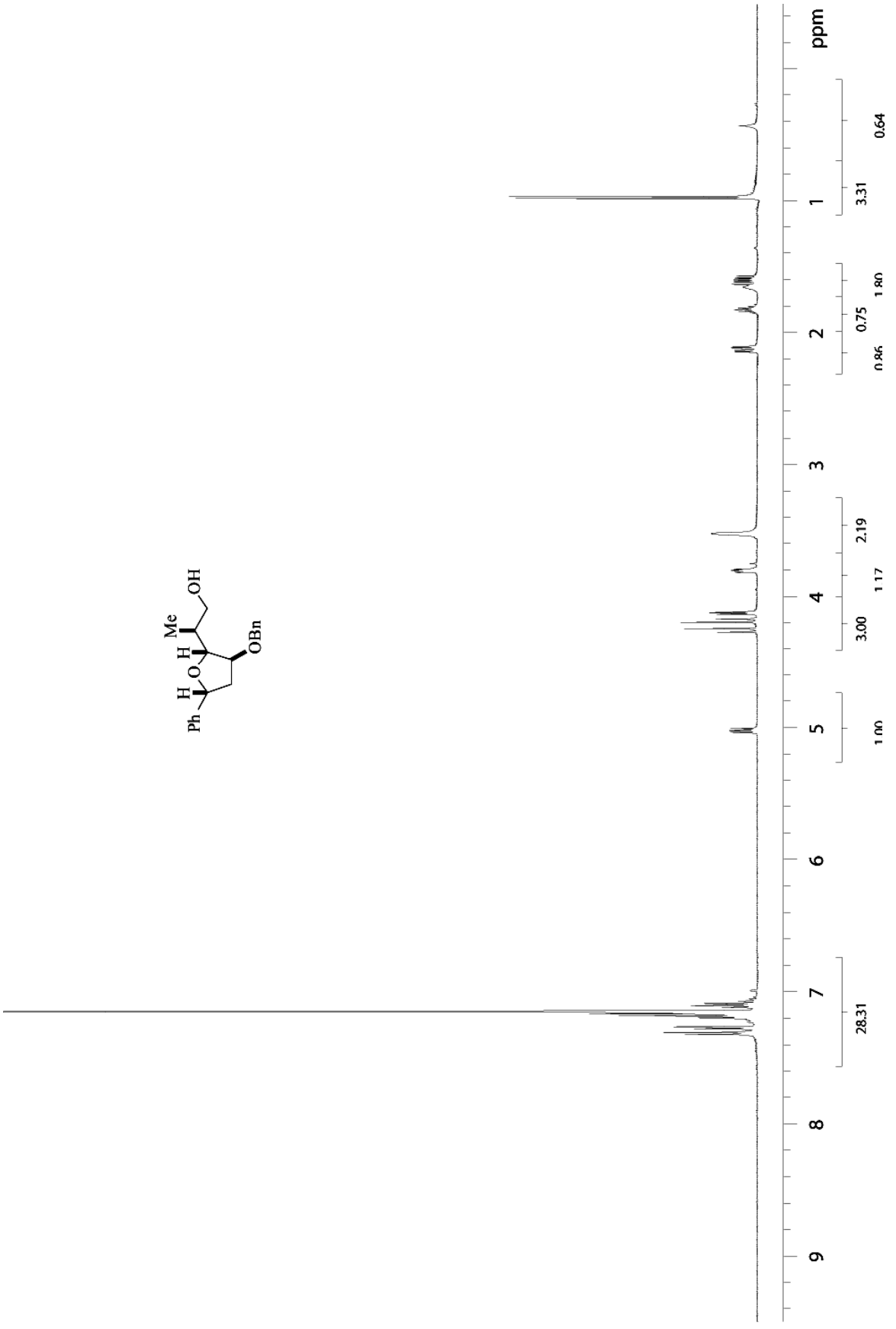
^{13}C NMR (125 MHz) of THF **4.15d** in $CDCl_3$



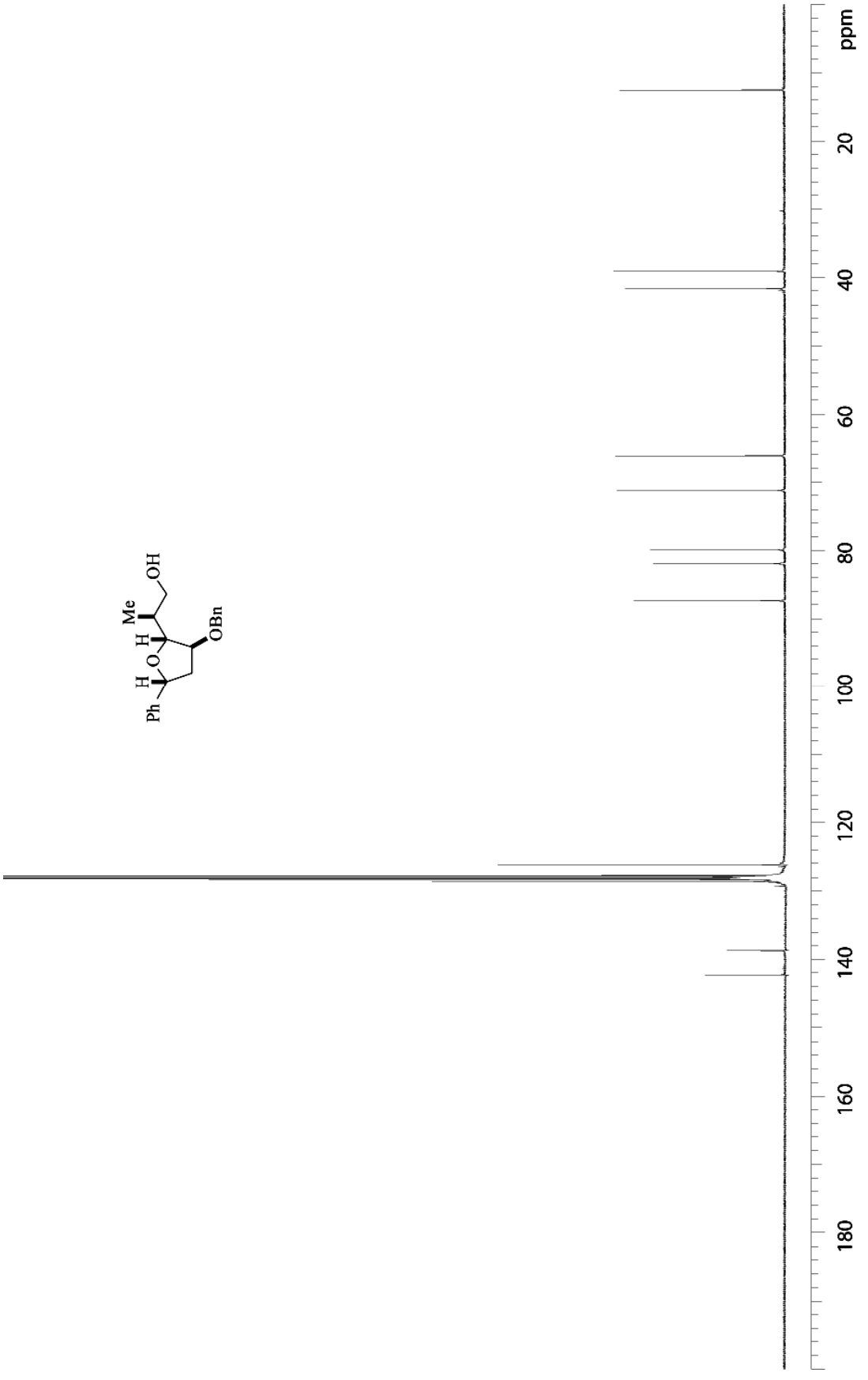
^{1}H NMR (500 MHz) of Furan **4.16d** in $CDCl_3$



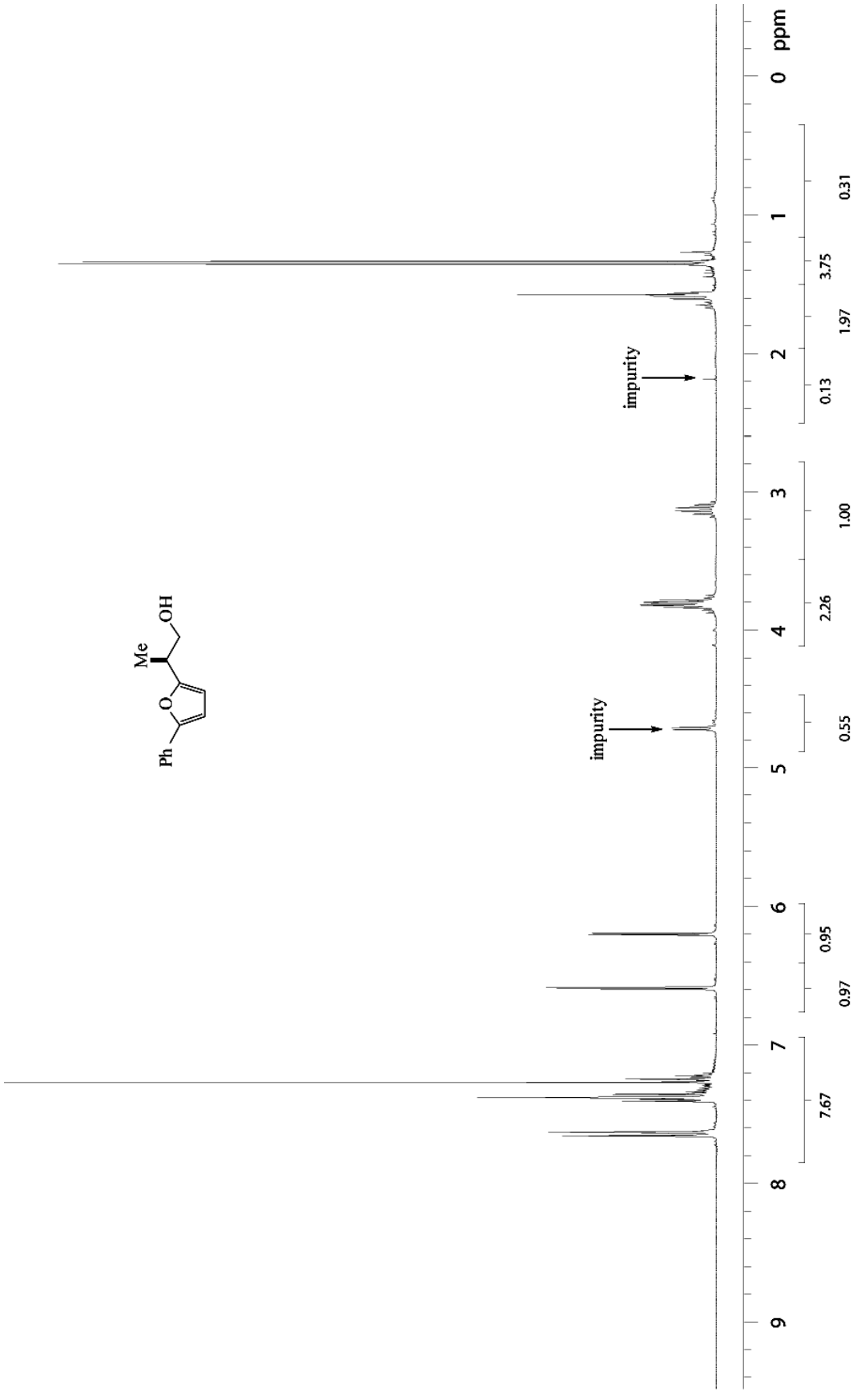
^{13}C NMR (125 MHz) of Furan **4.16d** in $CDCl_3$



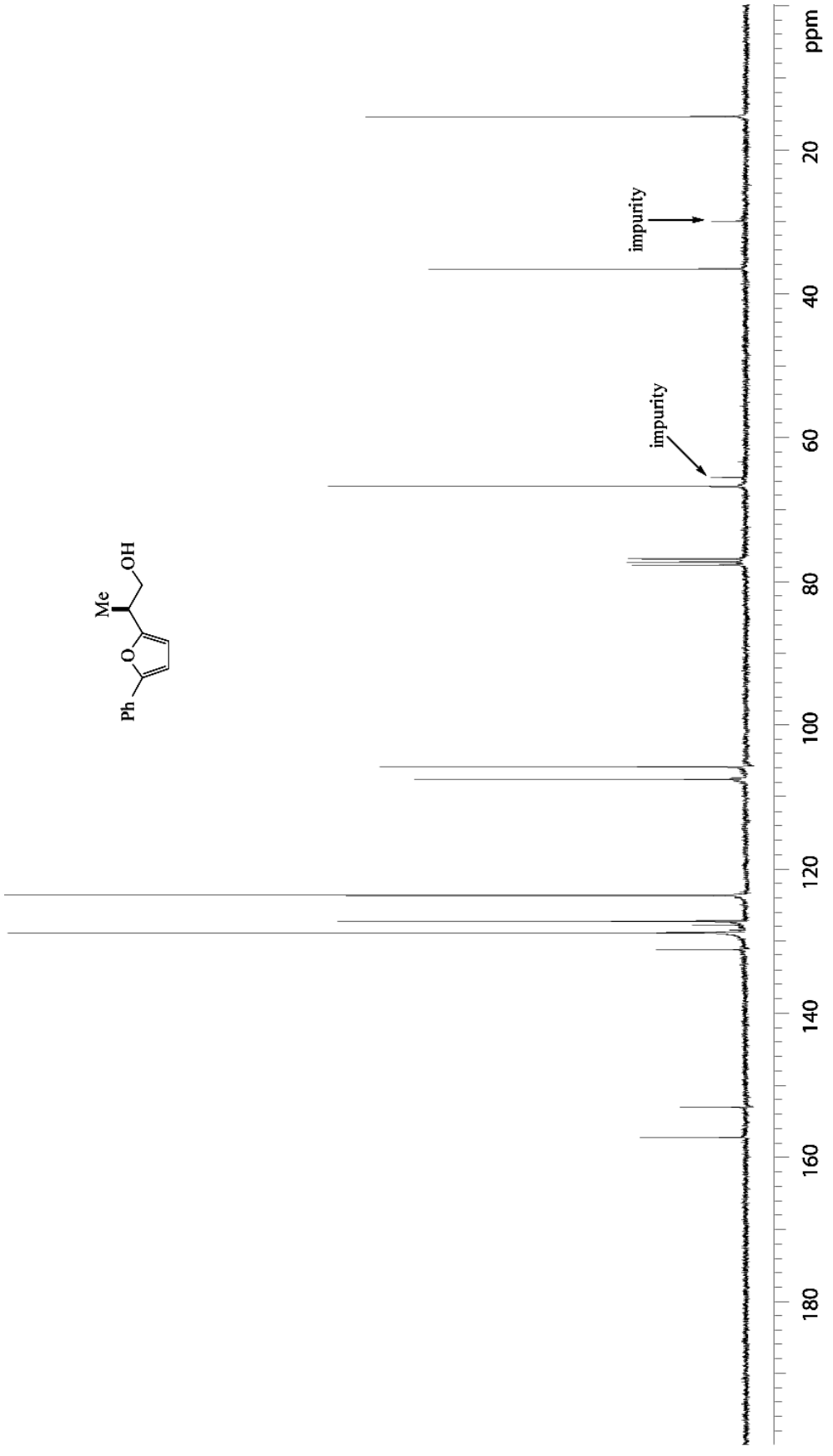
^{1}H NMR (500 MHz) of THF **4.15e** in C_6D_6



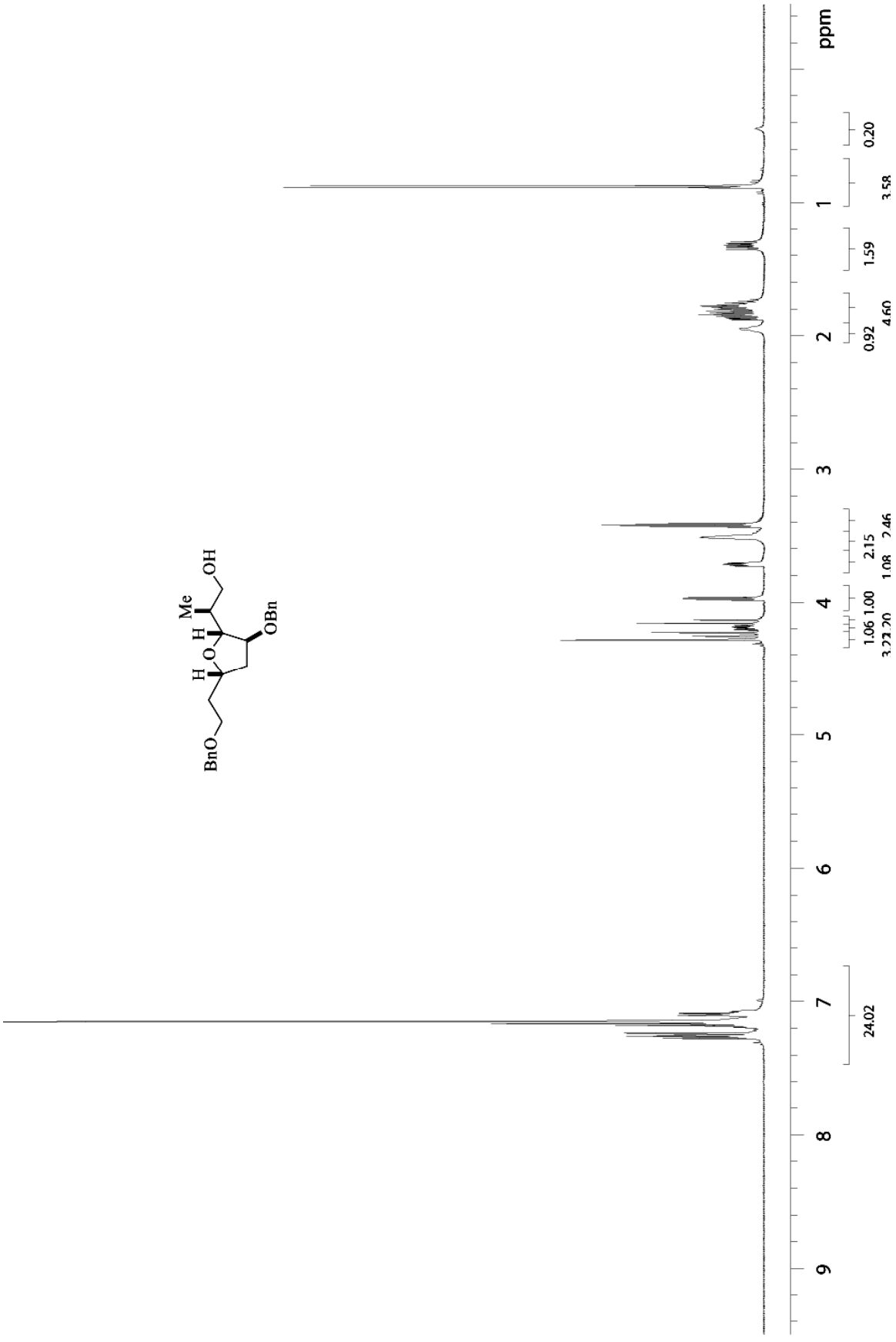
^{13}C NMR (125 MHz) of THF **4.15e** in C_6D_6



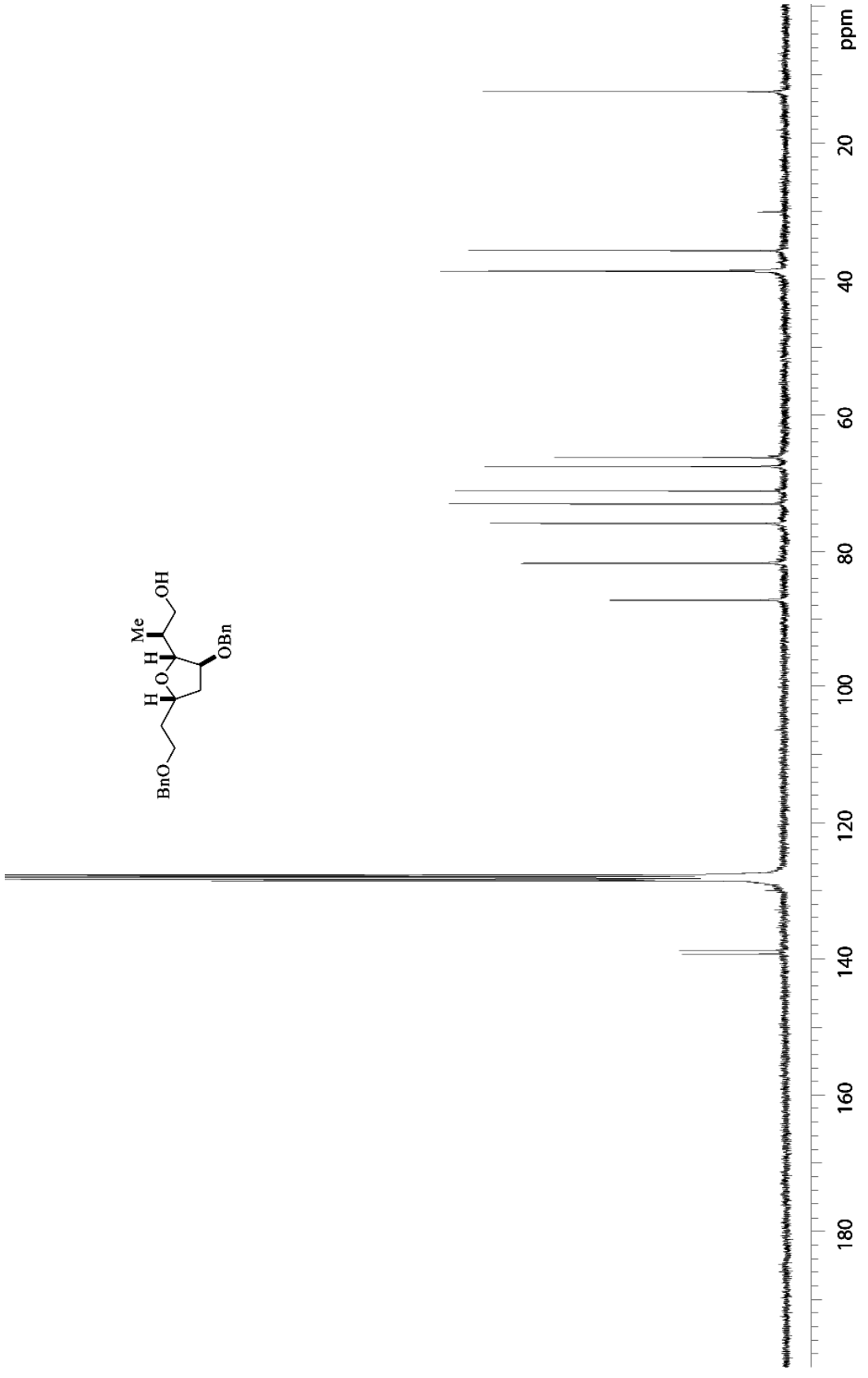
^{1}H NMR (300 MHz) of Furan **4.16e** in $CDCl_3$



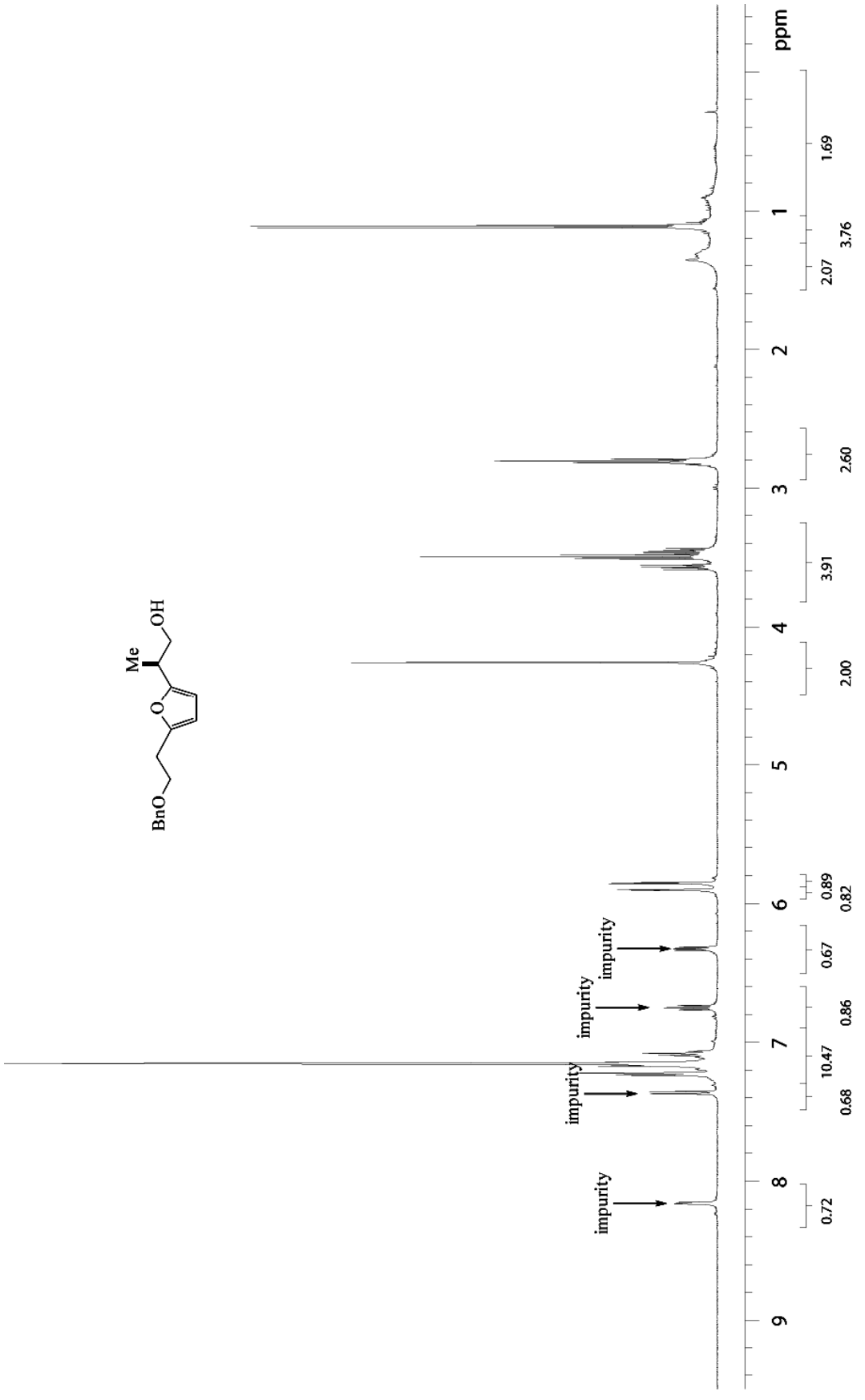
^{13}C NMR (75 MHz) of Furan **4.16e** in $CDCl_3$



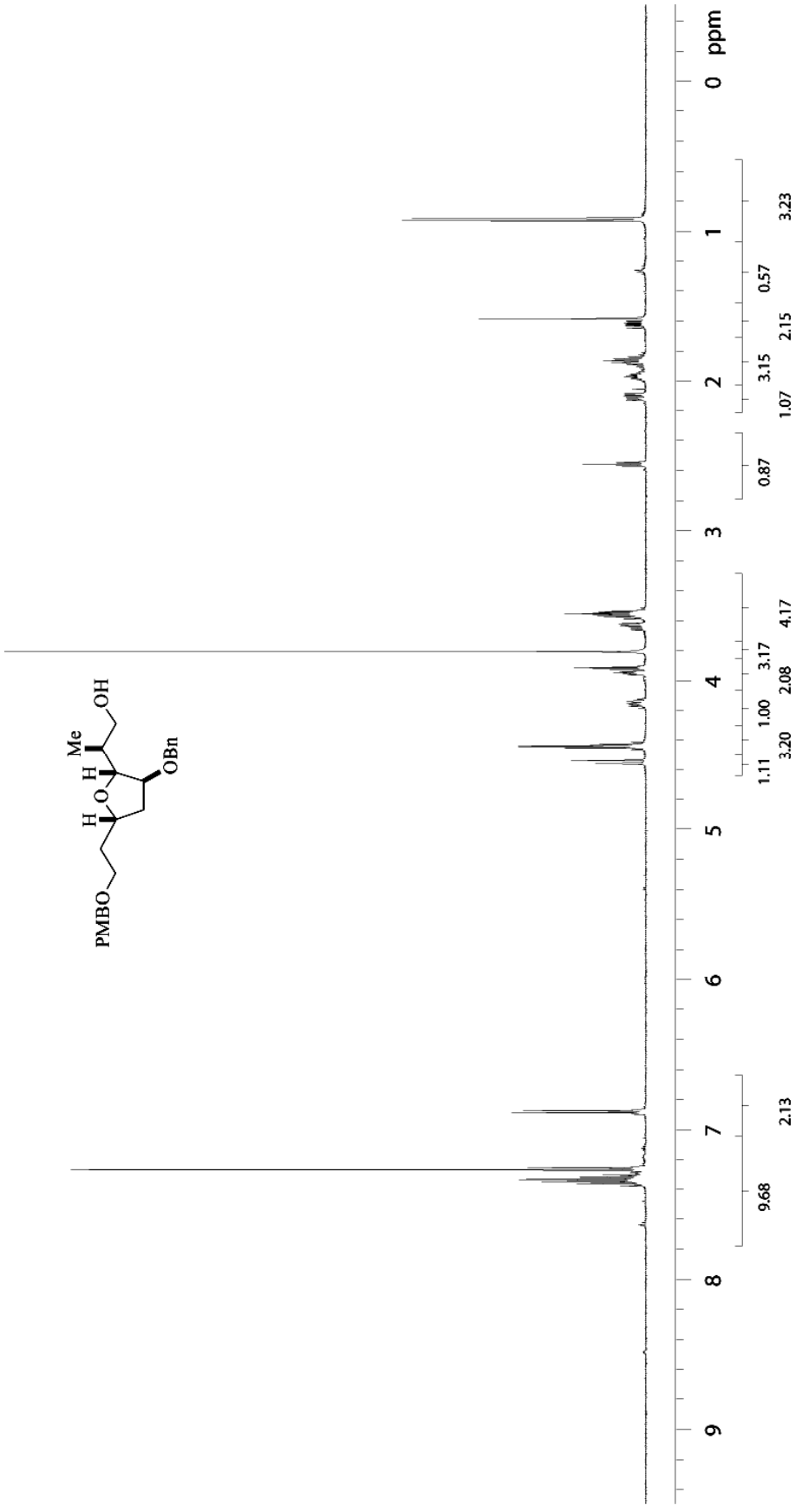
^{1}H NMR (500 MHz) of THF **4.15f** in C_6D_6



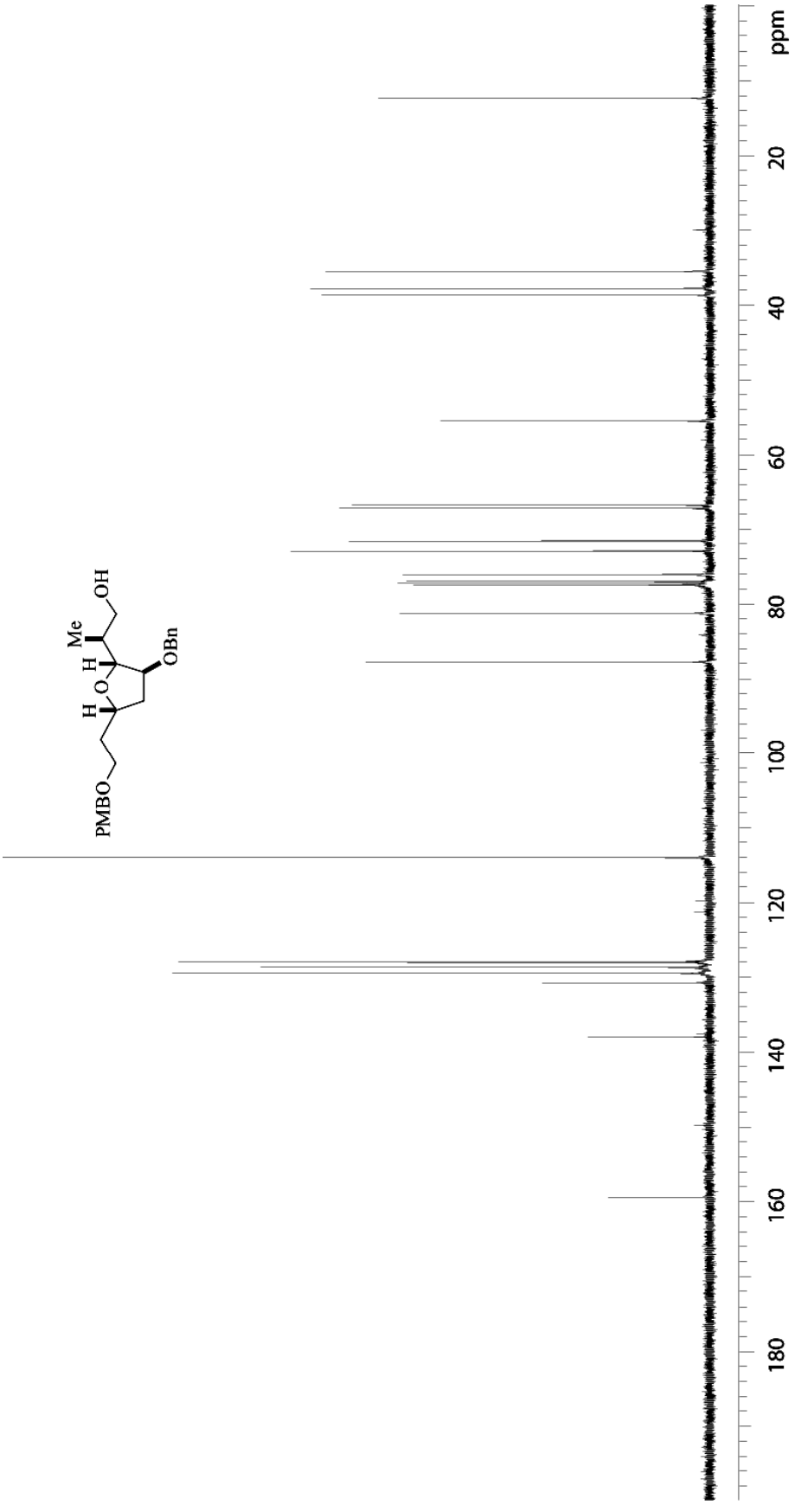
^{13}C NMR (125 MHz) of THF **4.15f** in C_6D_6



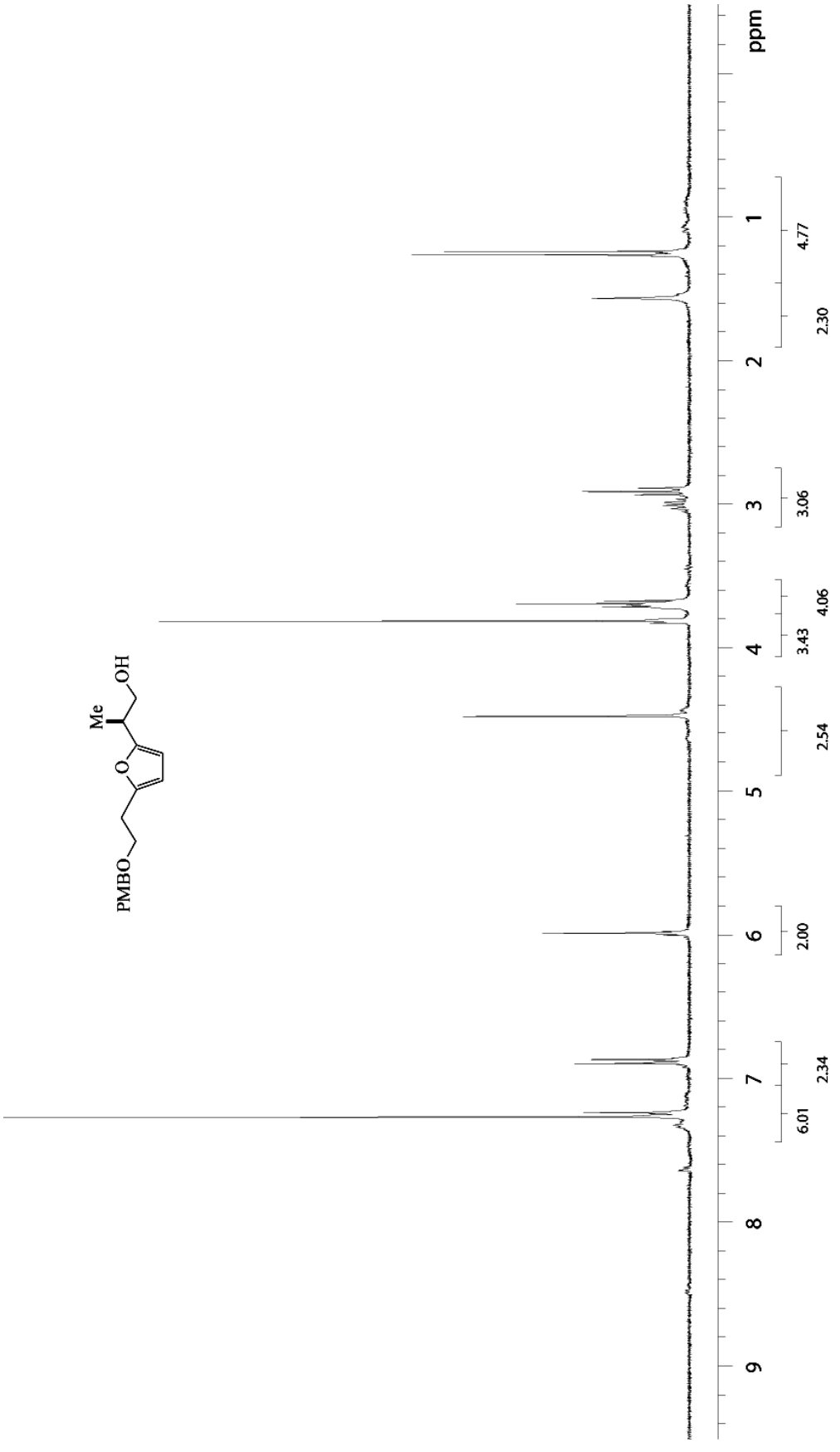
^{1}H NMR (300 MHz) of Furan **4.16f** in C_6D_6



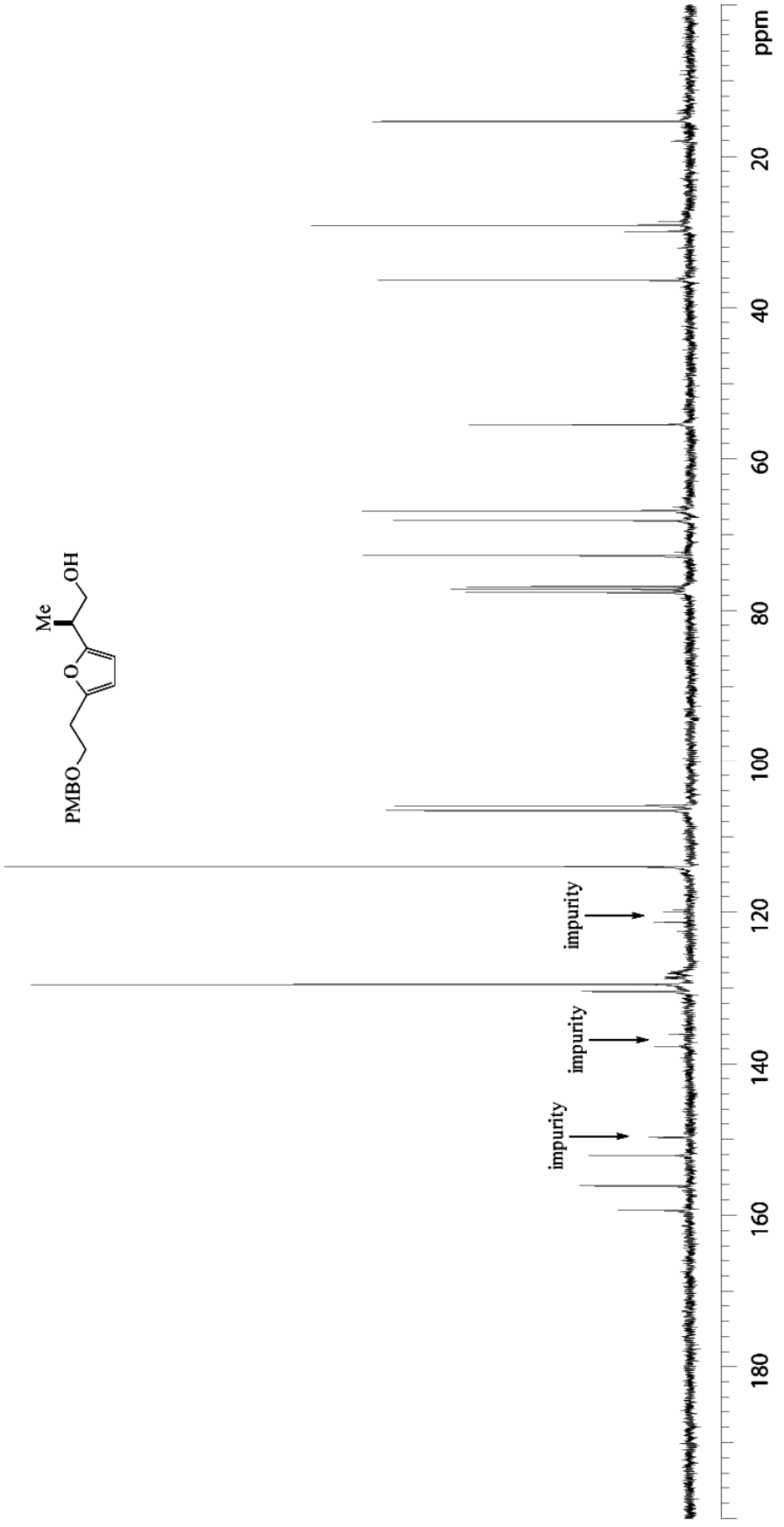
^{1}H NMR (500 MHz) of THF **4.15g** in $CDCl_3$



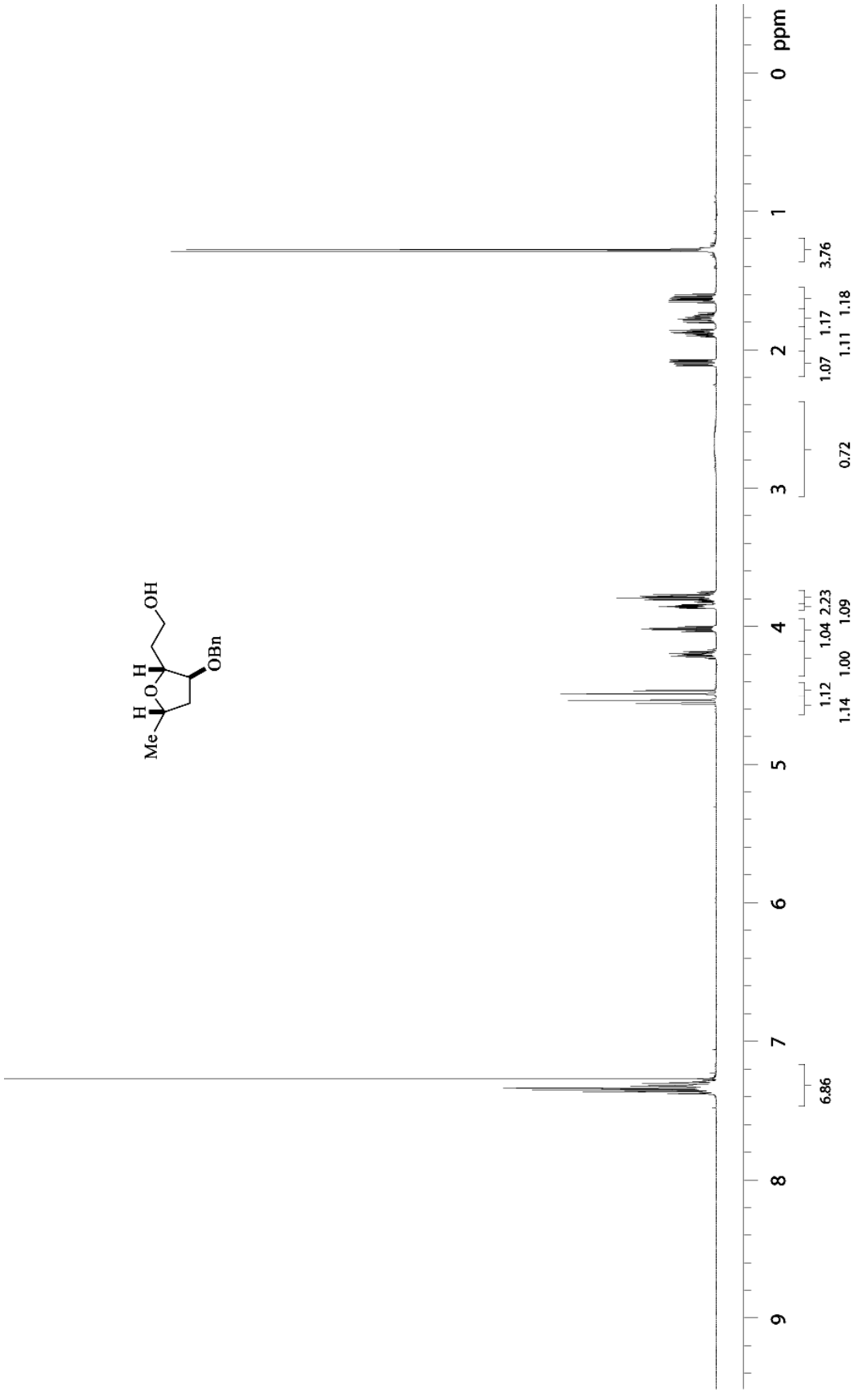
^{13}C NMR (125 MHz) of THF **4.15g** in $CDCl_3$



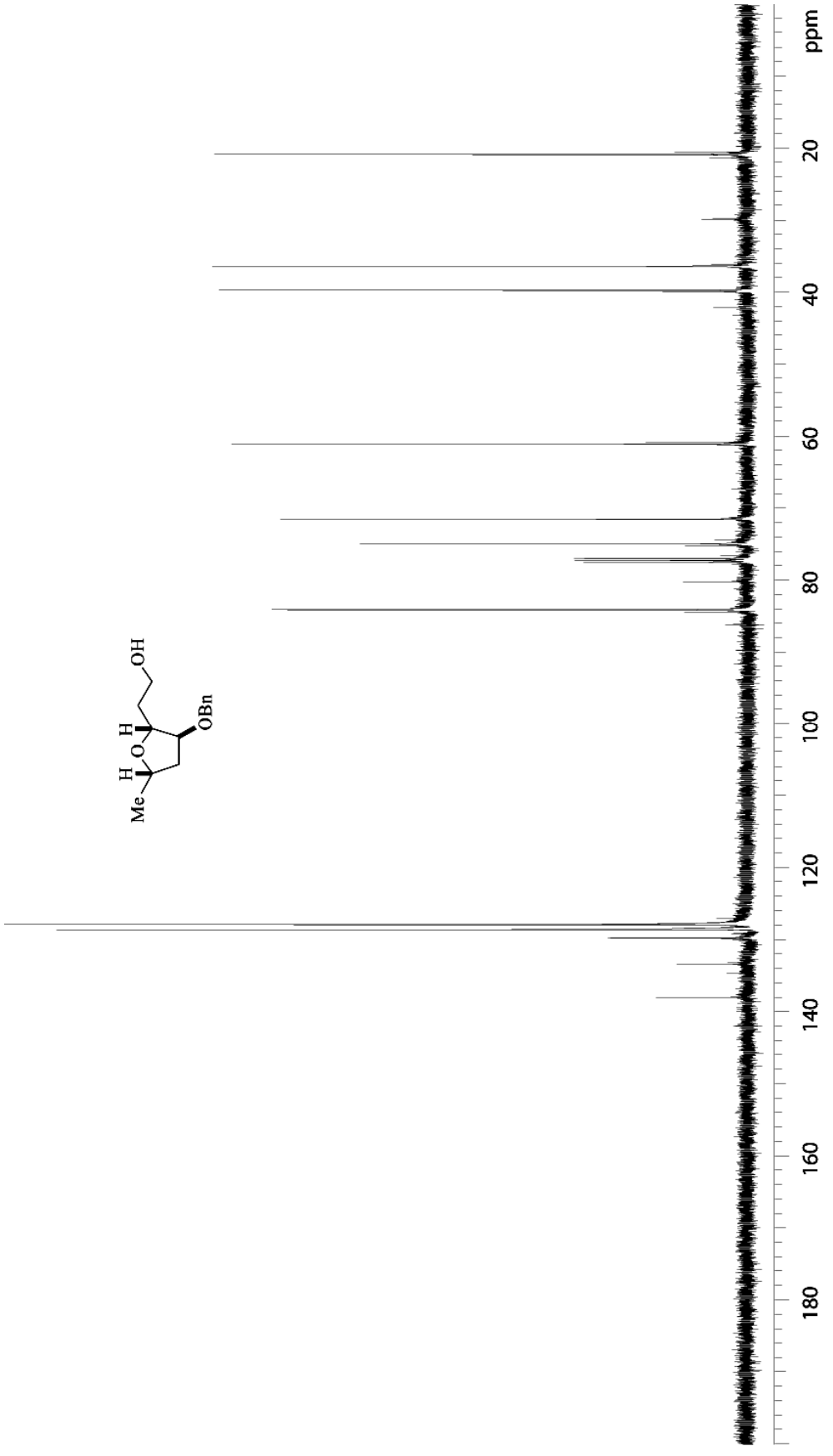
^{1}H NMR (300 MHz) of Furan **4.16g** in $CDCl_3$



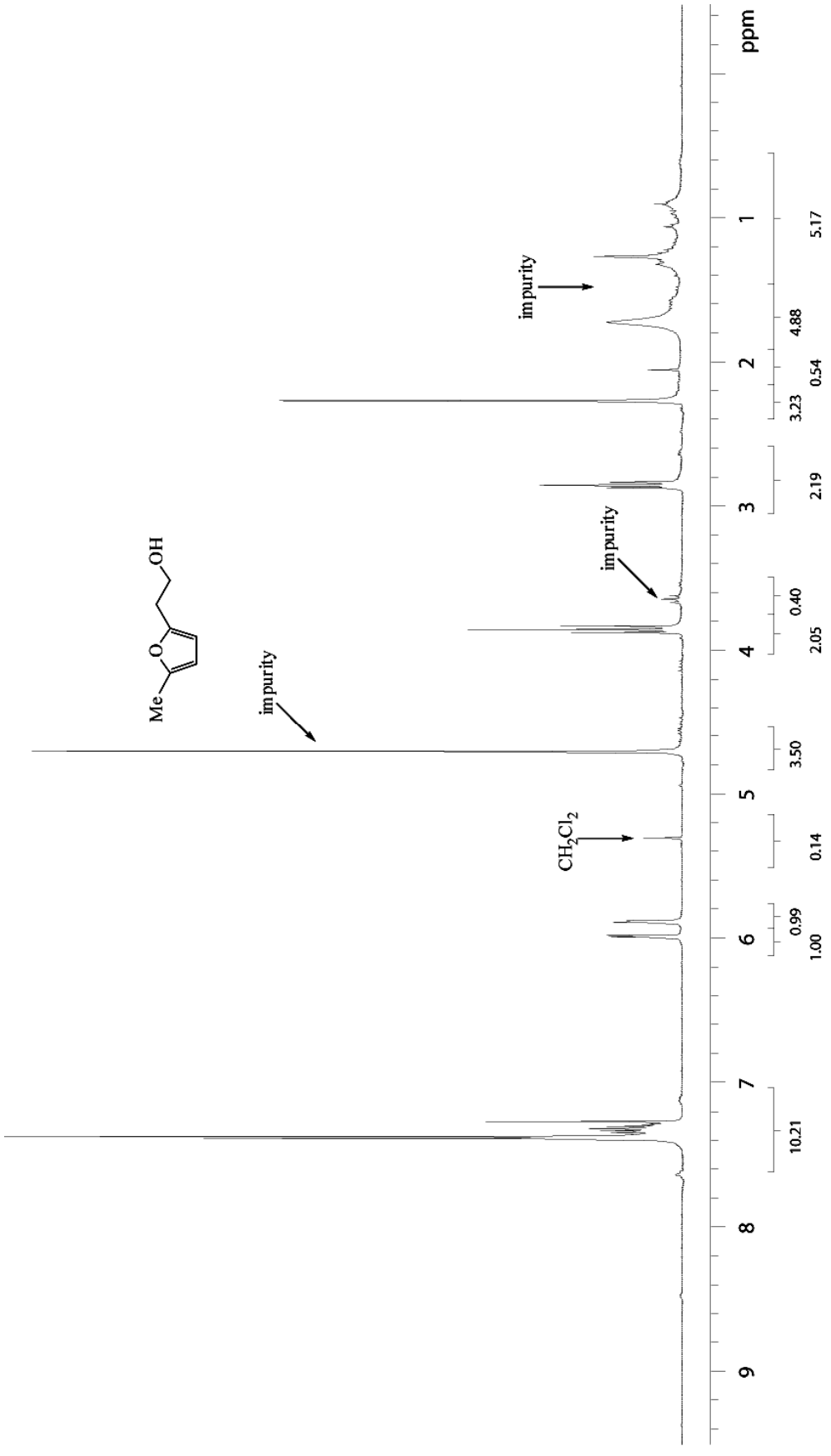
^{13}C NMR (75 MHz) of Furan **4.16g** in $CDCl_3$



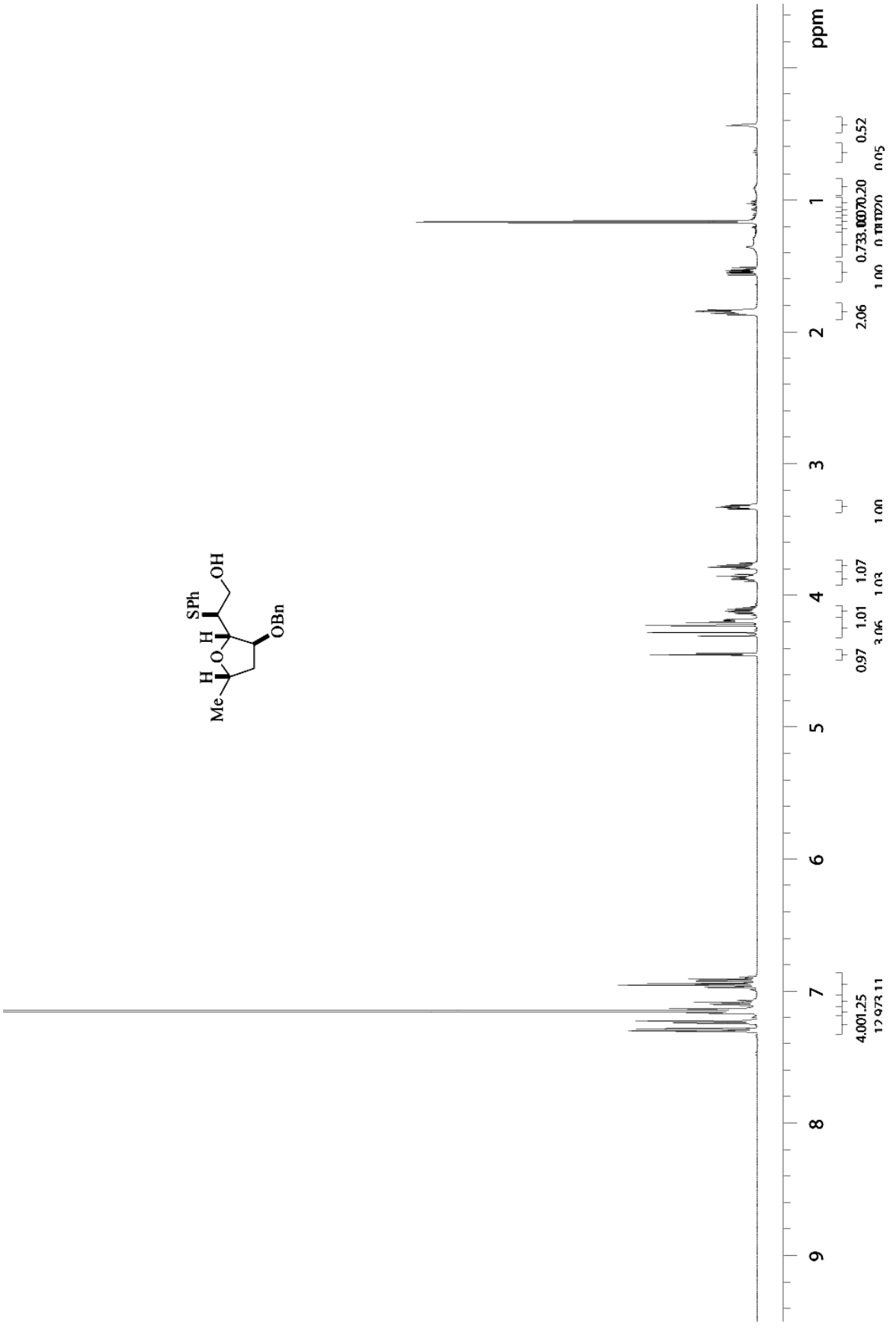
^{1}H NMR (500 MHz) of THF **4.15h** in $CDCl_3$



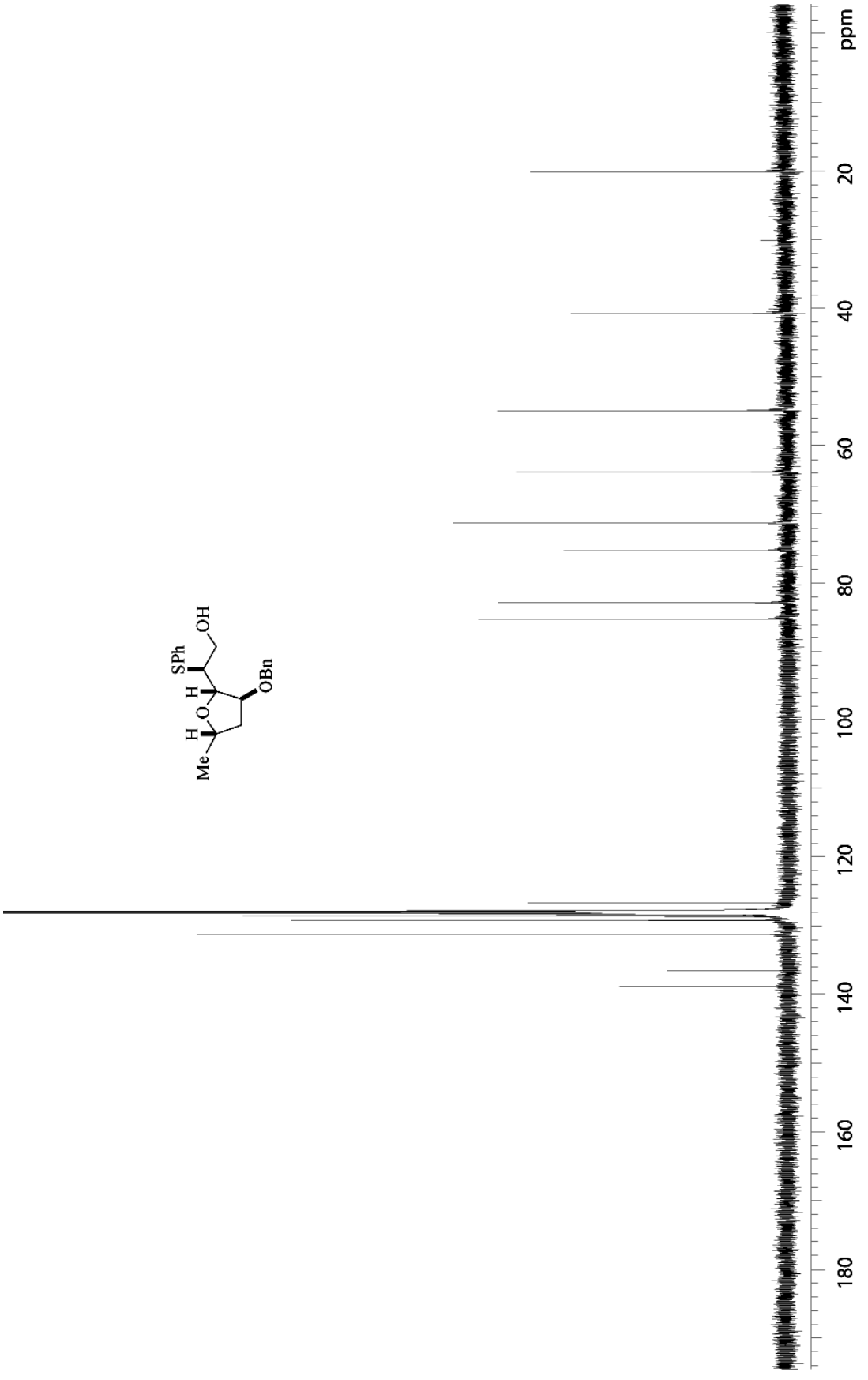
^{13}C NMR (125 MHz) of THF **4.15h** in $CDCl_3$



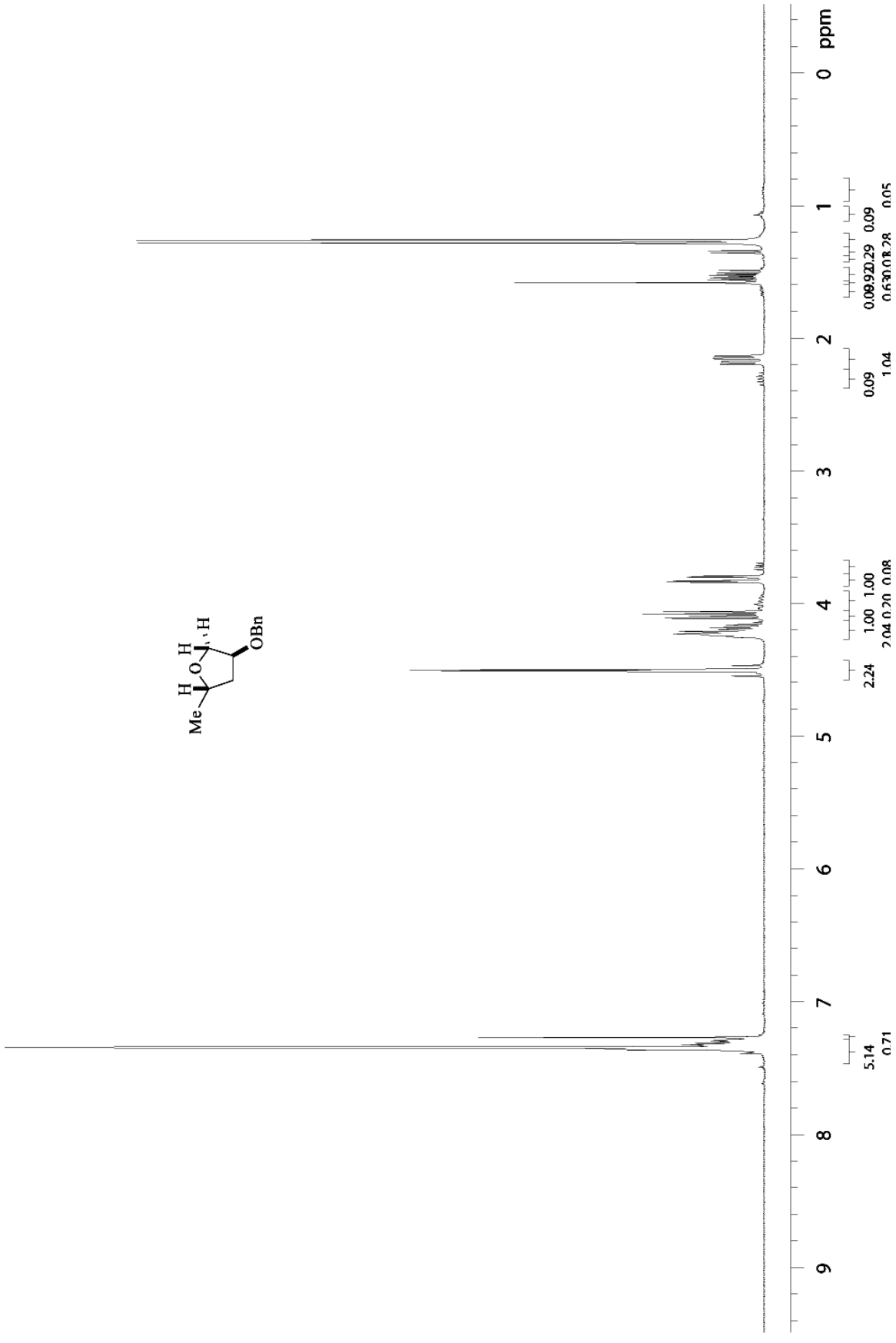
^{1}H NMR (300 MHz) of Furan **4.16h** in $CDCl_3$



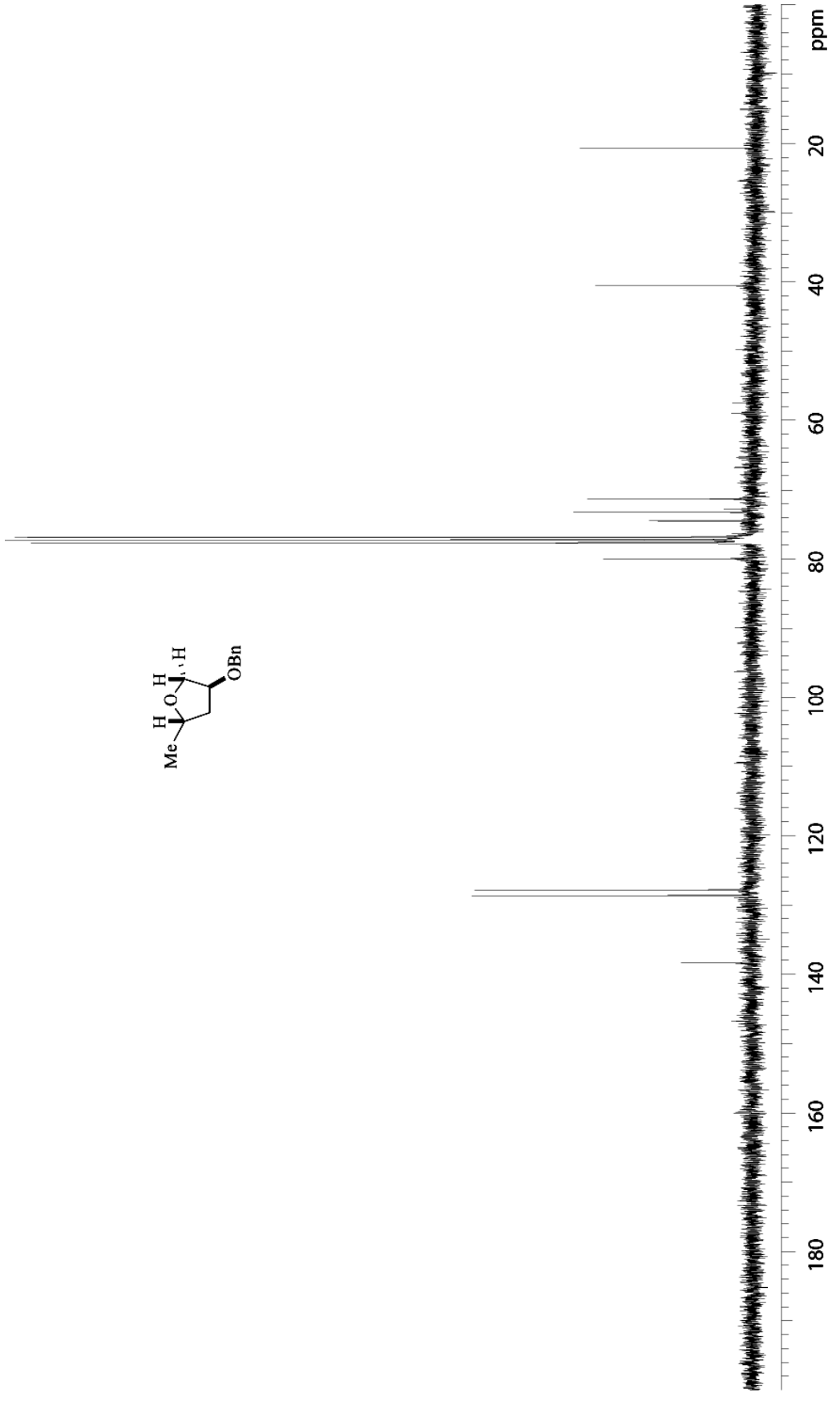
^{1}H NMR (500 MHz) of THF **4.15i** in C_6D_6



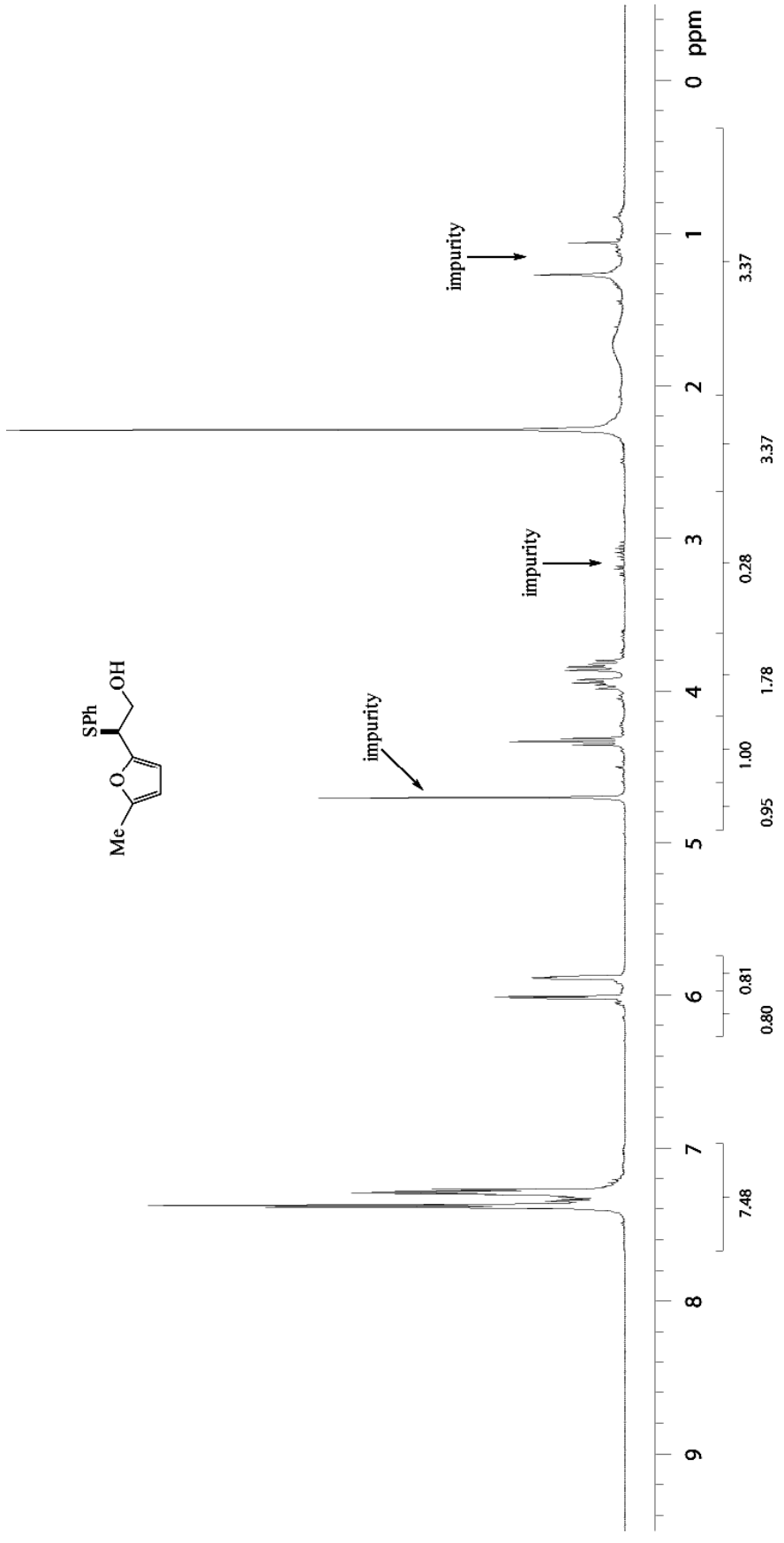
^{13}C NMR (125 MHz) of THF **4.15i** in C_6D_6



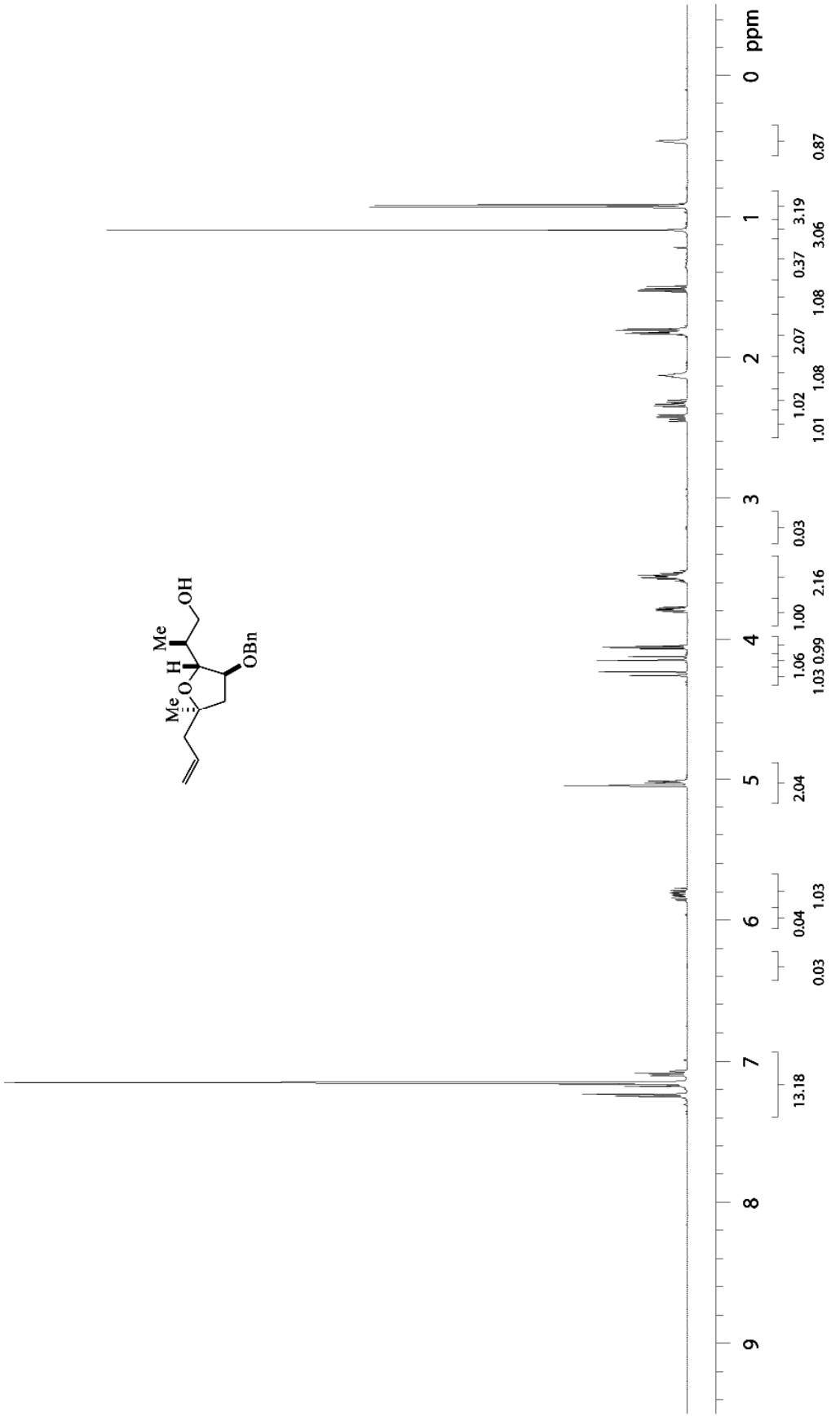
^{1}H NMR (300 MHz) of THF **4.15i'** in $CDCl_3$



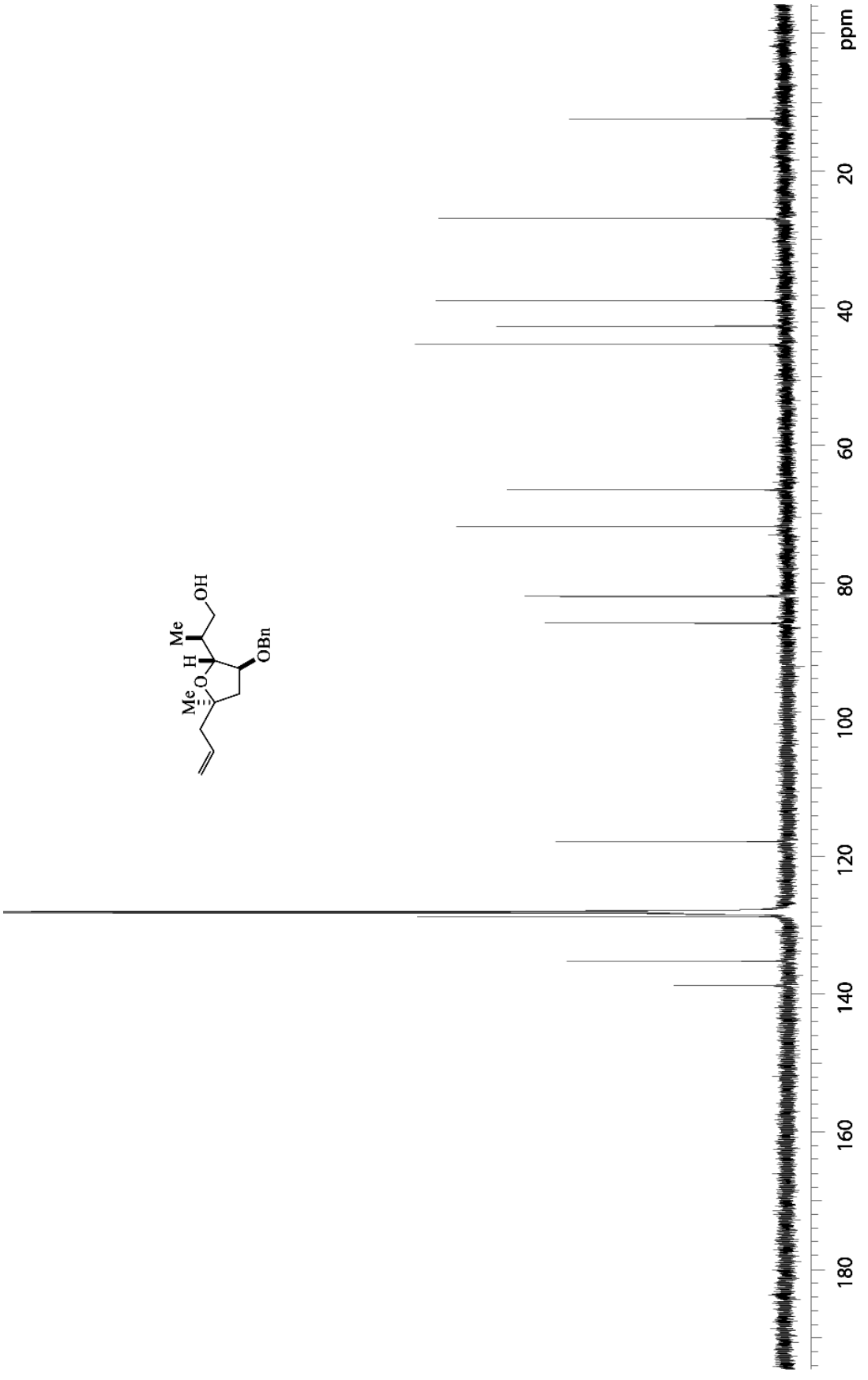
^{13}C NMR (75 MHz) of THF **4.15i'** in $CDCl_3$



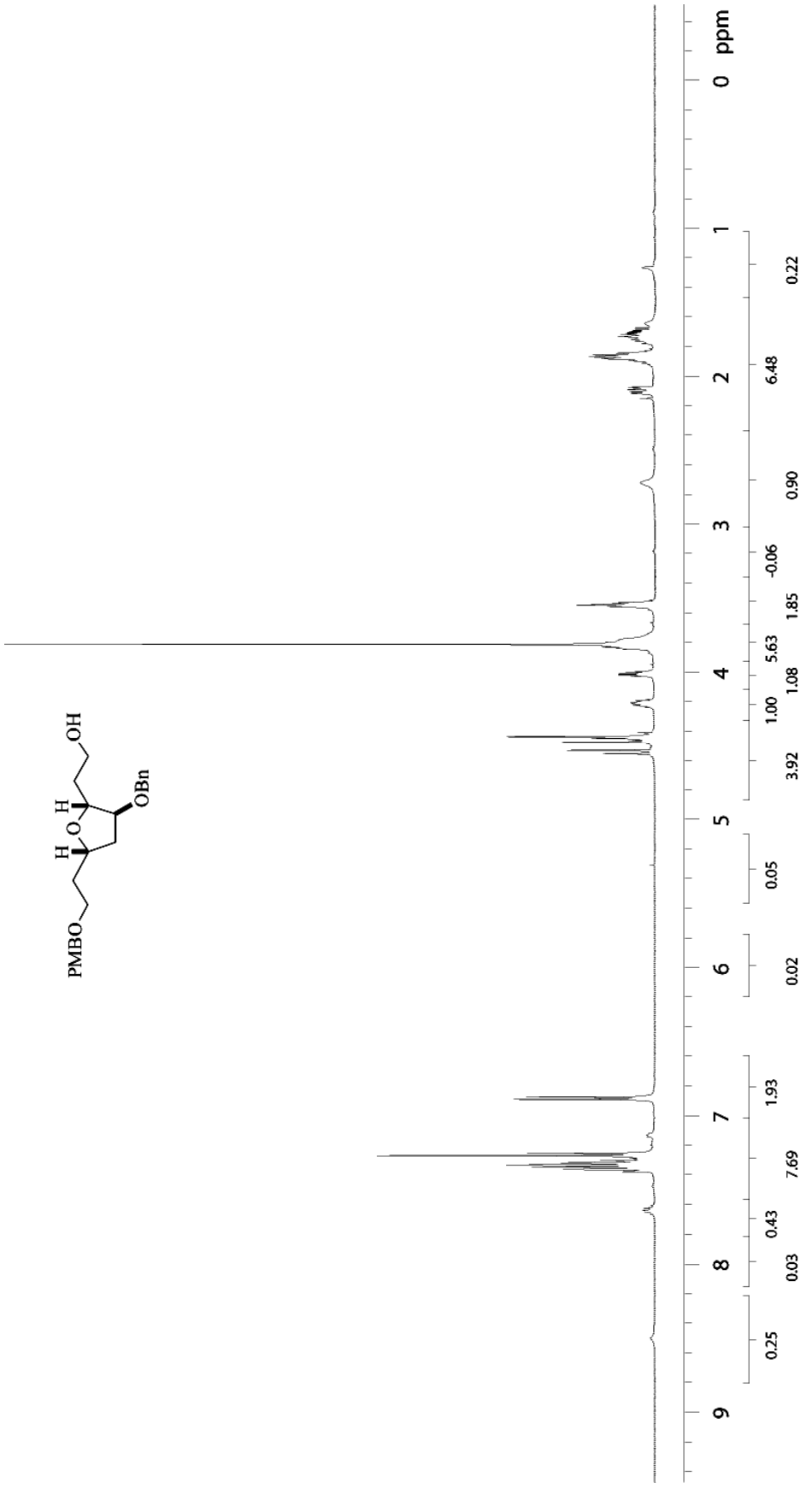
^{1}H NMR (300 MHz) of Furan **4.16i** in $CDCl_3$



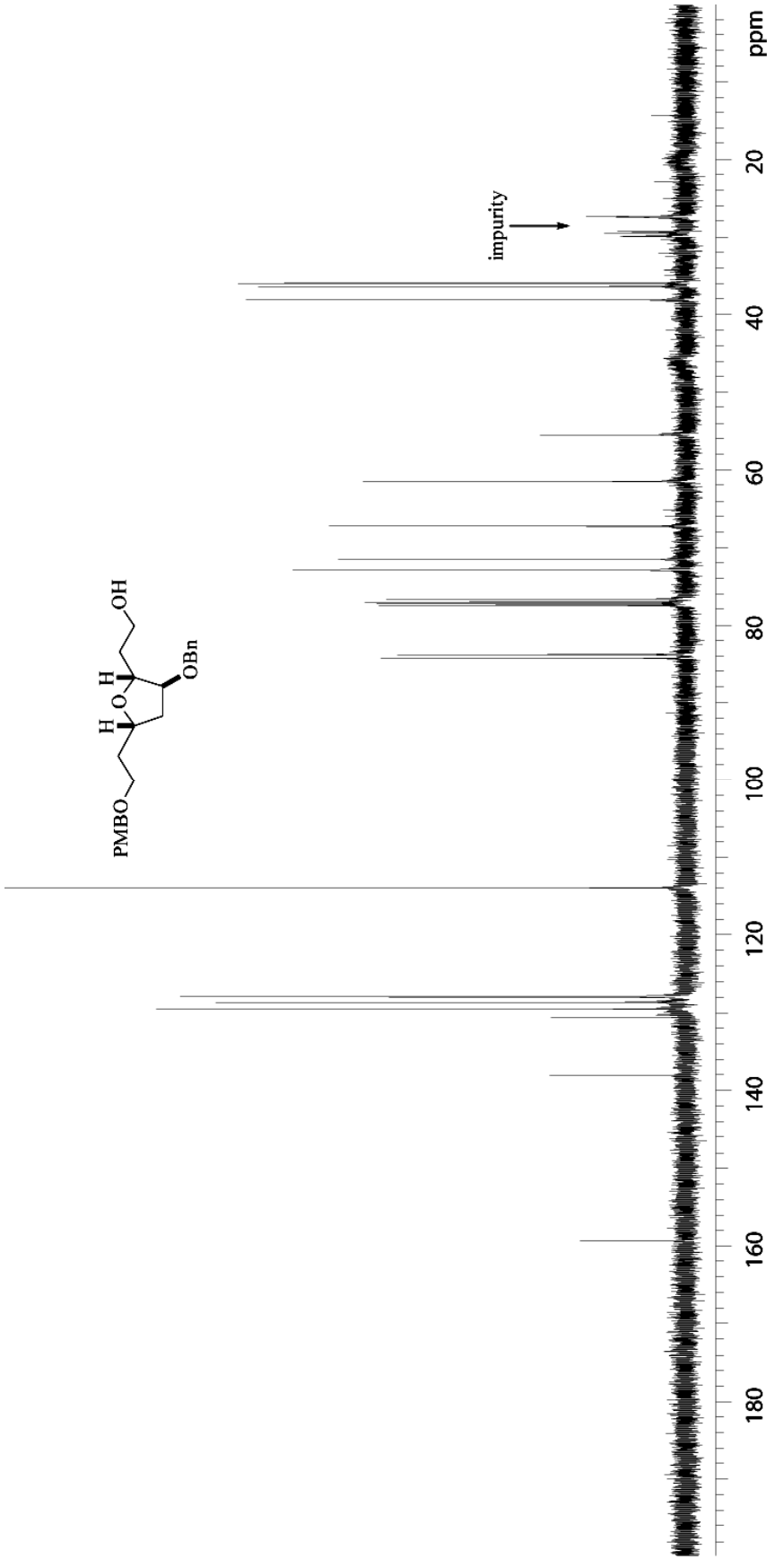
^{1}H NMR (500 MHz) of THF **4.15j** in C_6D_6



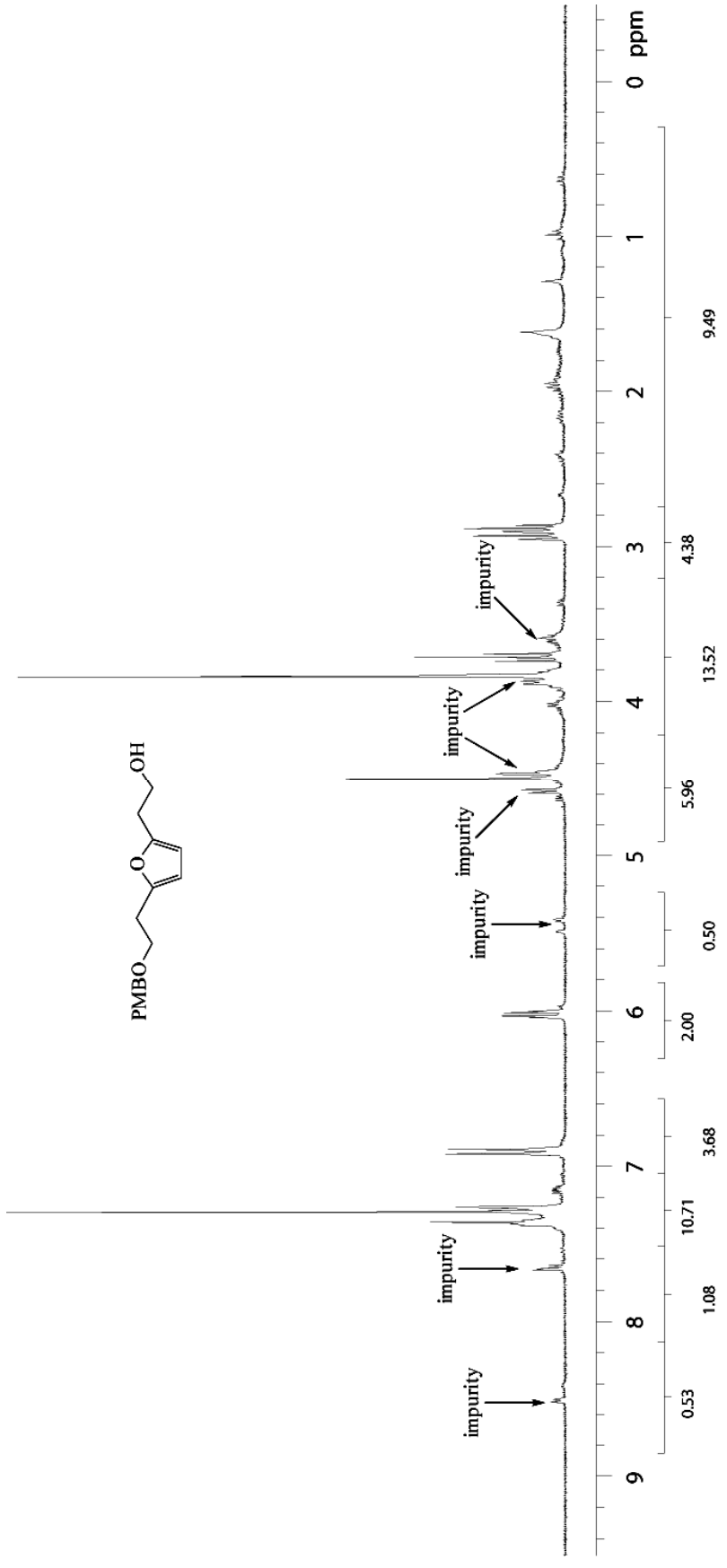
^{13}C NMR (125 MHz) of THF **4.15j** in C_6D_6



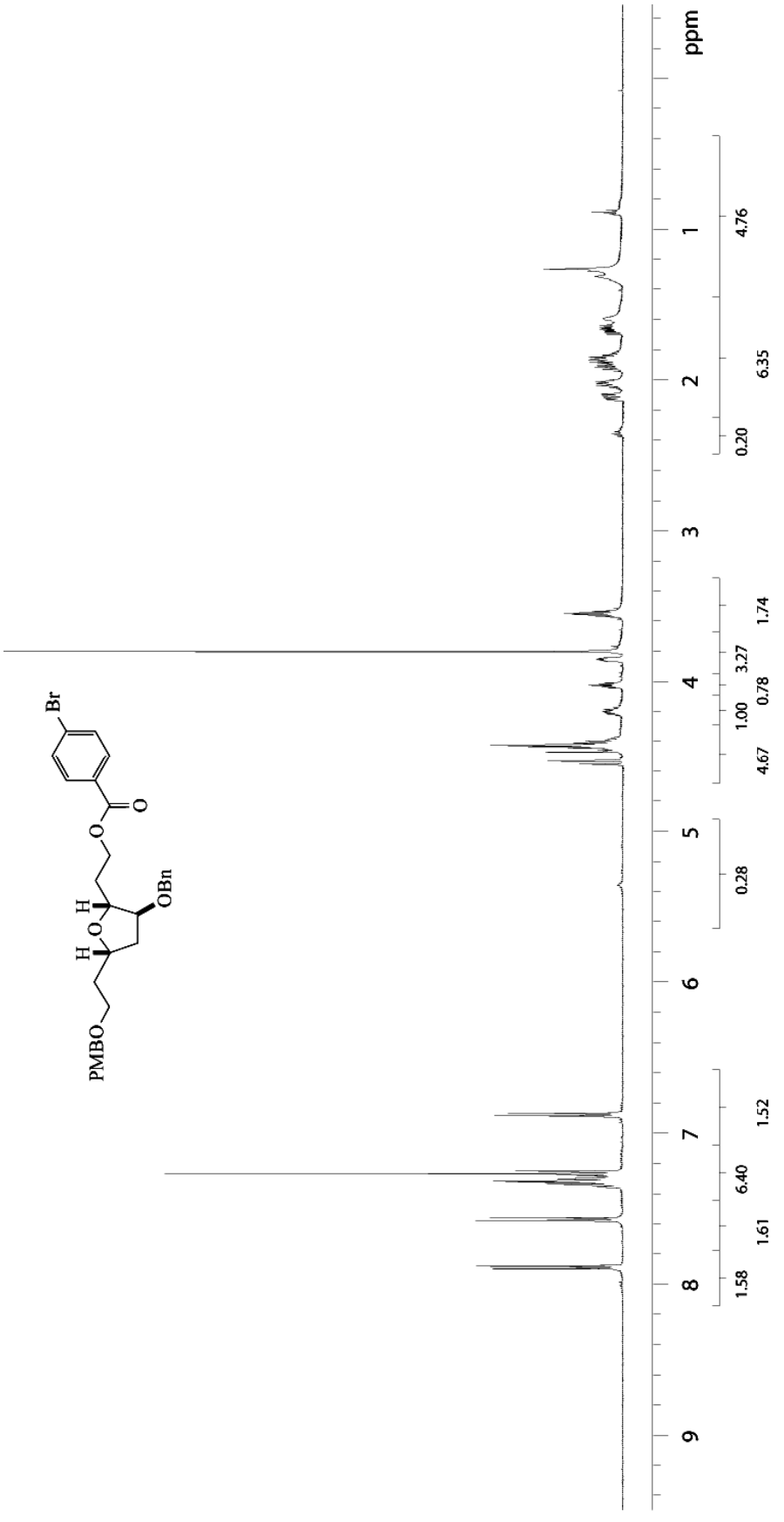
^{1}H NMR (500 MHz) of THF **4.15k** in $CDCl_3$



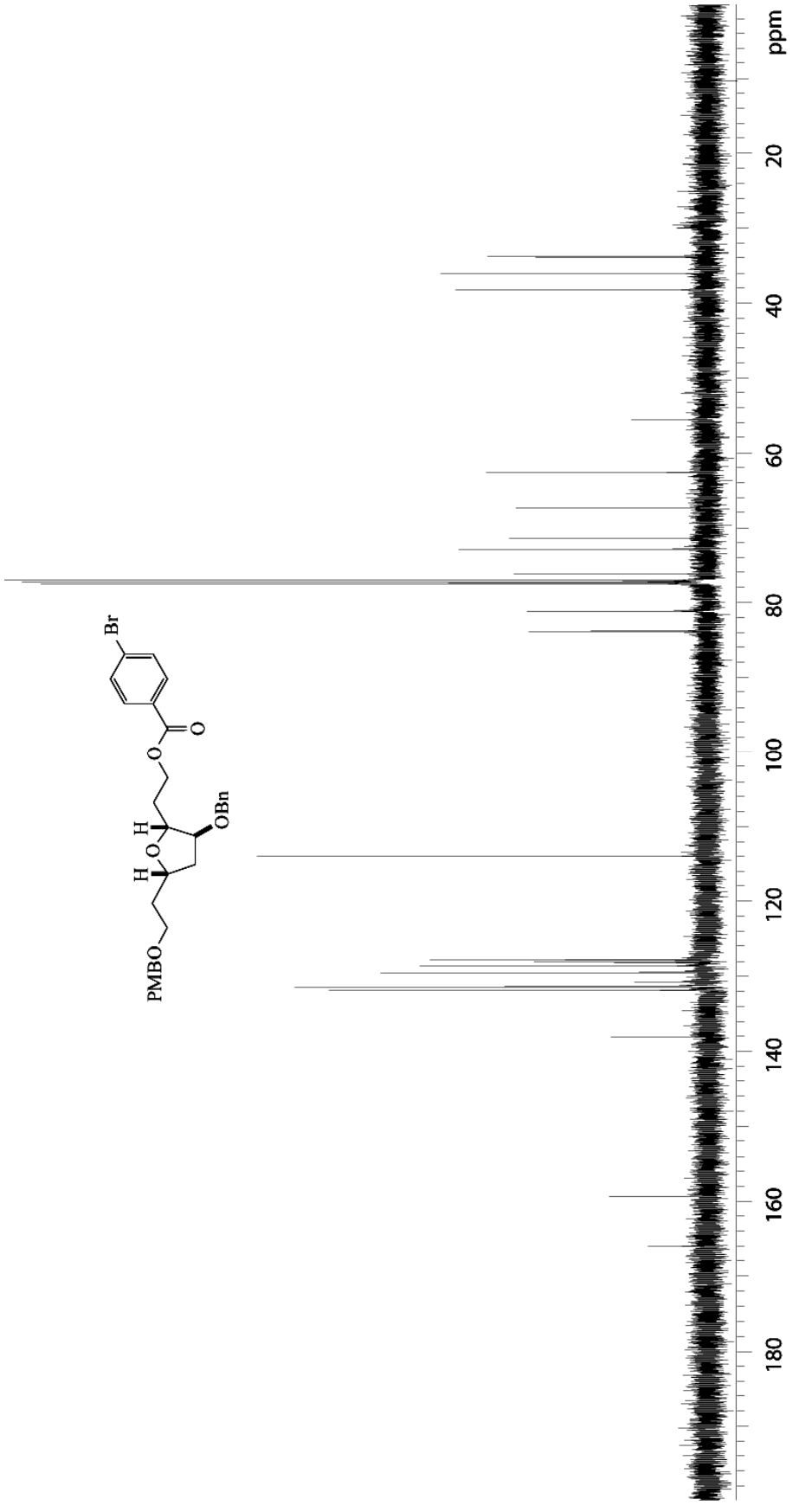
^{13}C NMR (125 MHz) of THF **4.15k** in $CDCl_3$



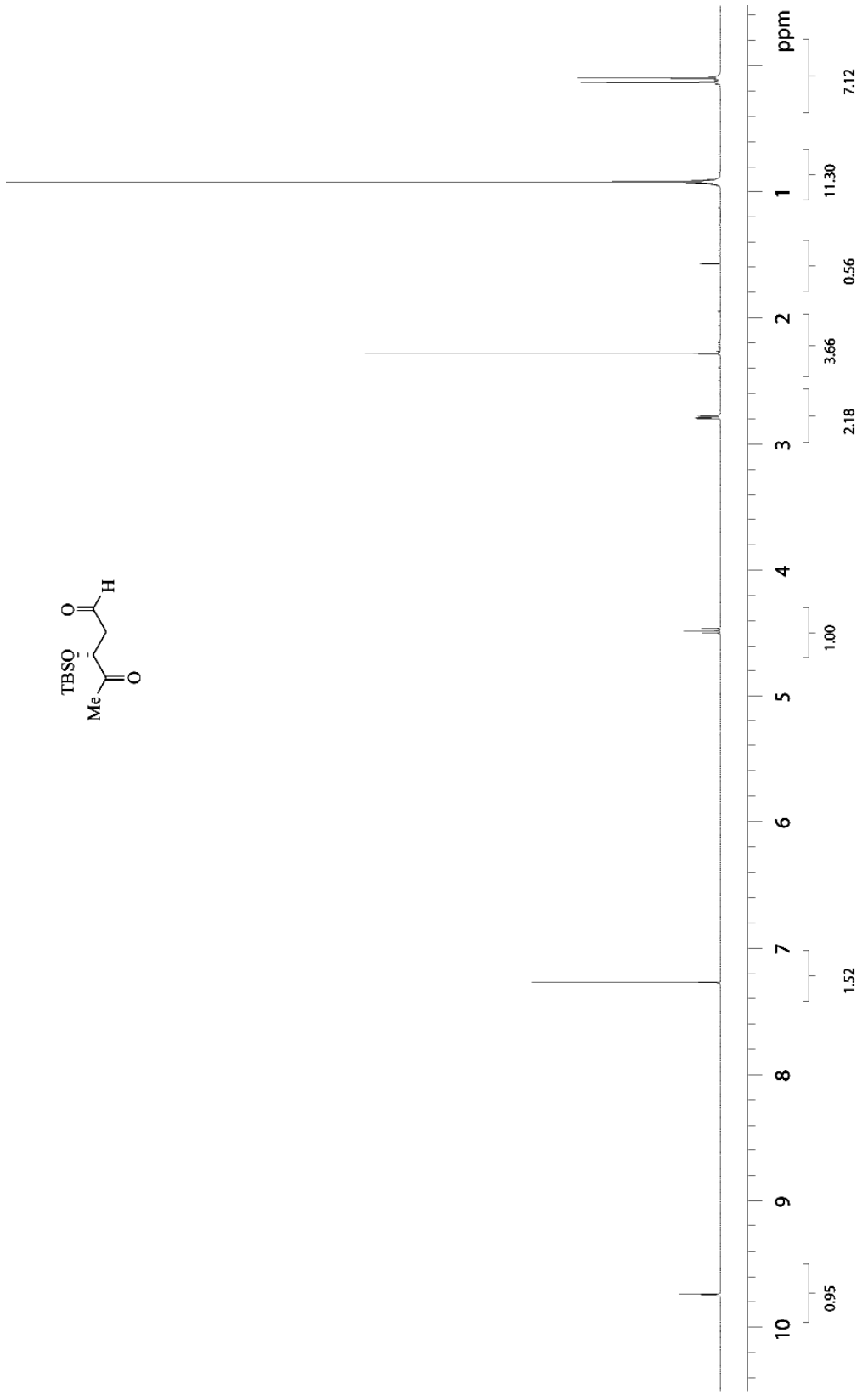
^{1}H NMR (300 MHz) of Furan **4.16k** in $CDCl_3$



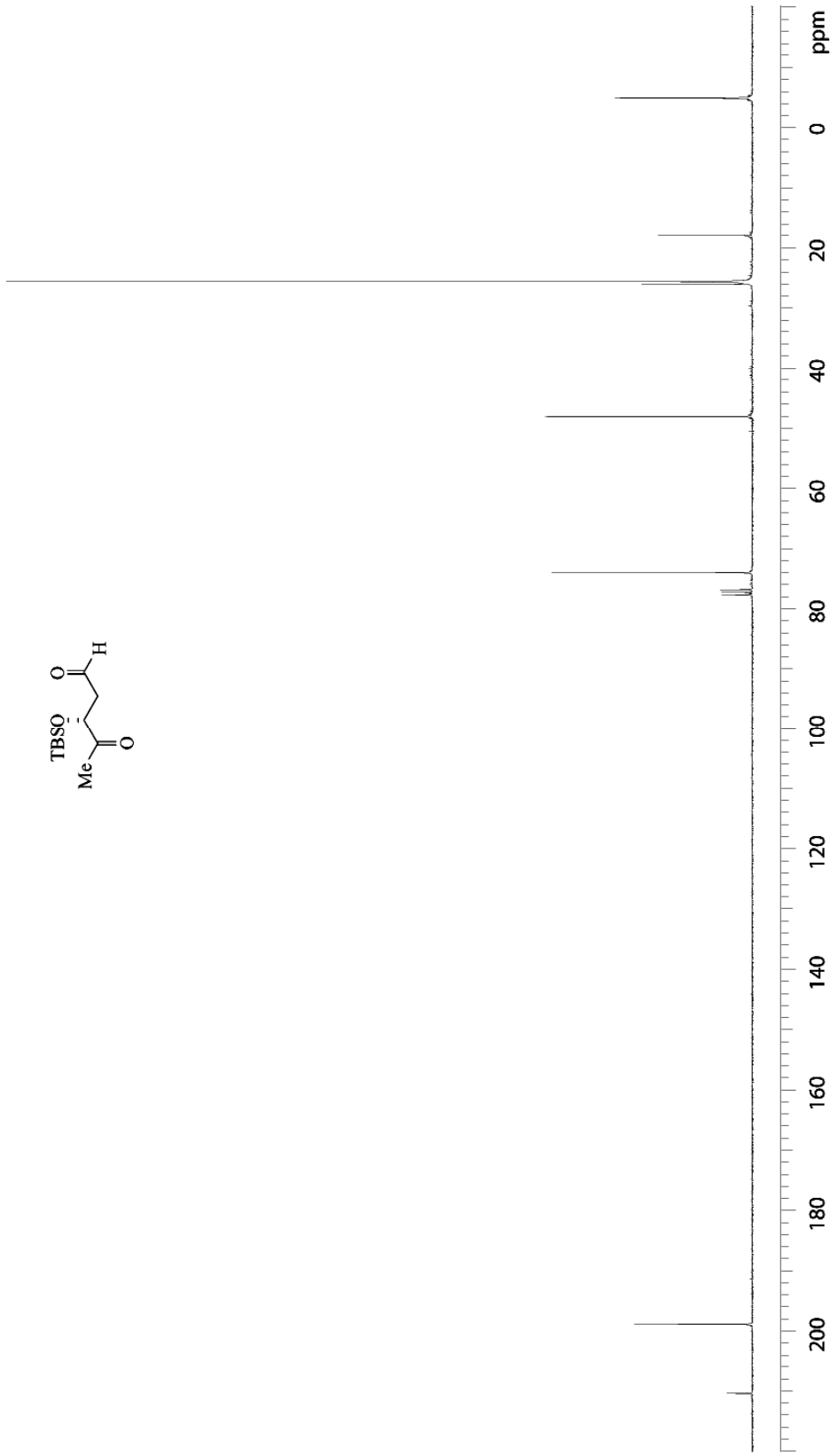
^{1}H NMR (500 MHz) of THF **4.15k'** in $CDCl_3$



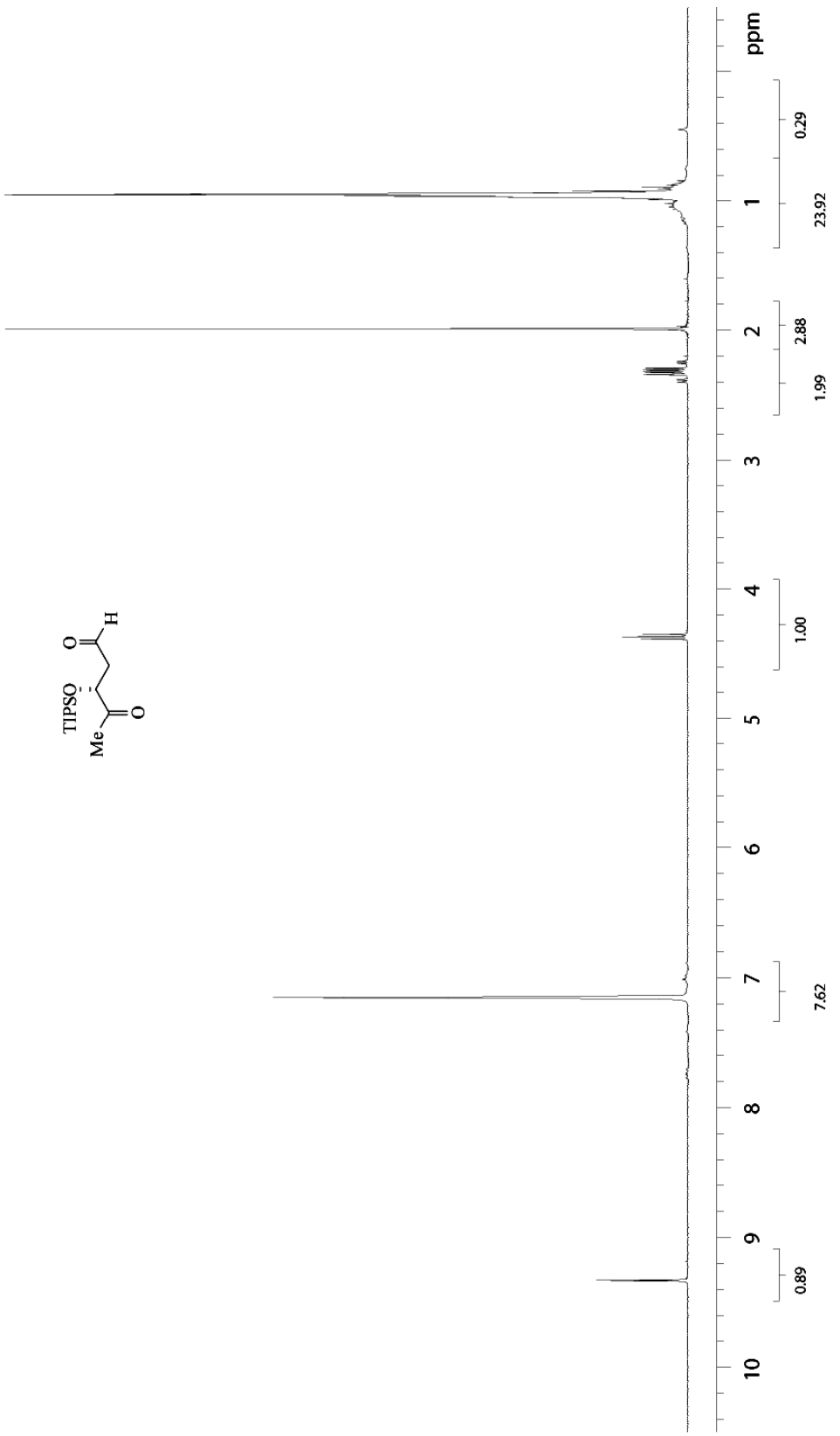
^{13}C NMR (125 MHz) of THF **4.15k'** in $CDCl_3$



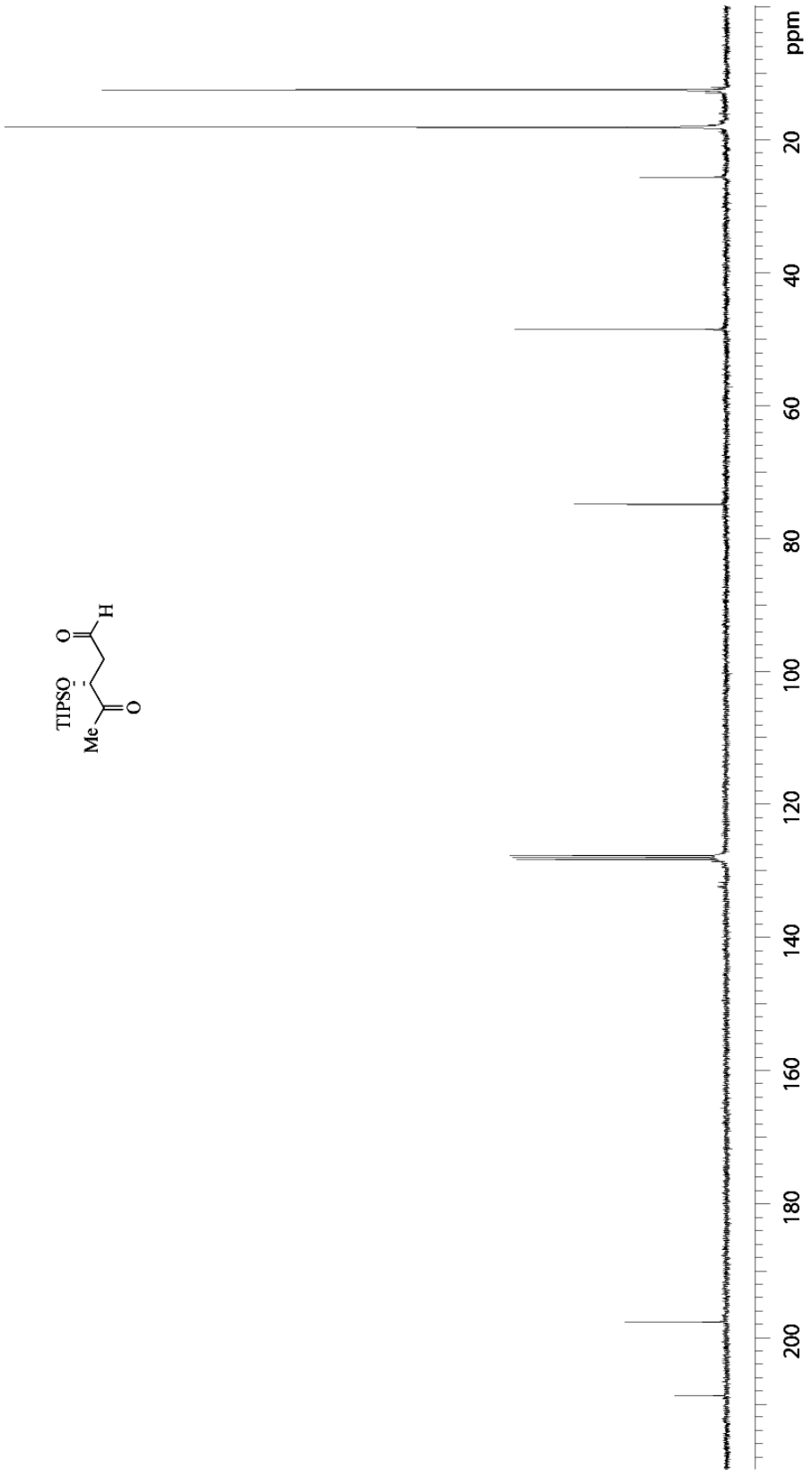
^{1}H NMR (300 MHz) of THF **(±)-4.1m** in $CDCl_3$



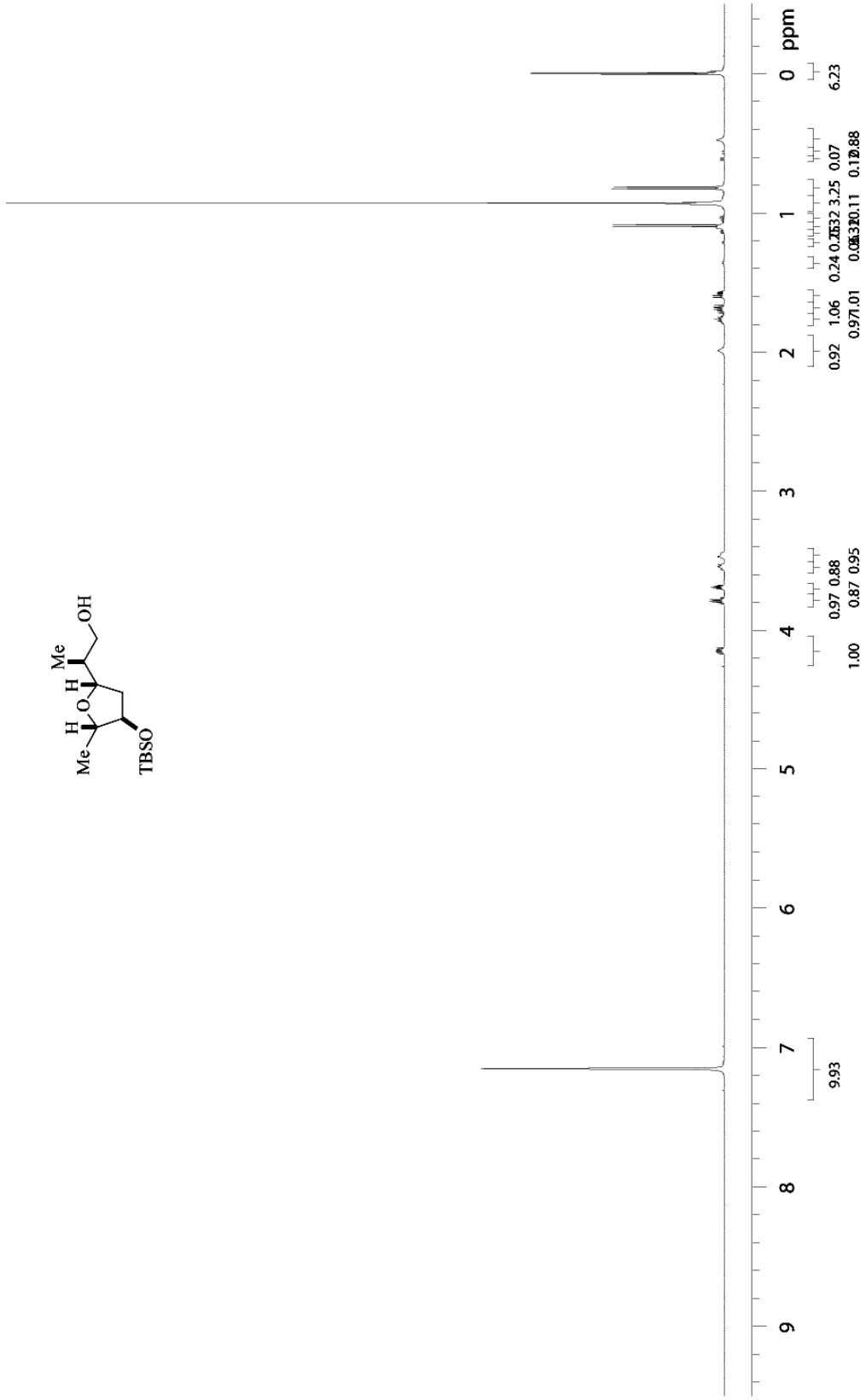
^{13}C NMR (75 MHz) of THF **(±)-4.1m** in $CDCl_3$



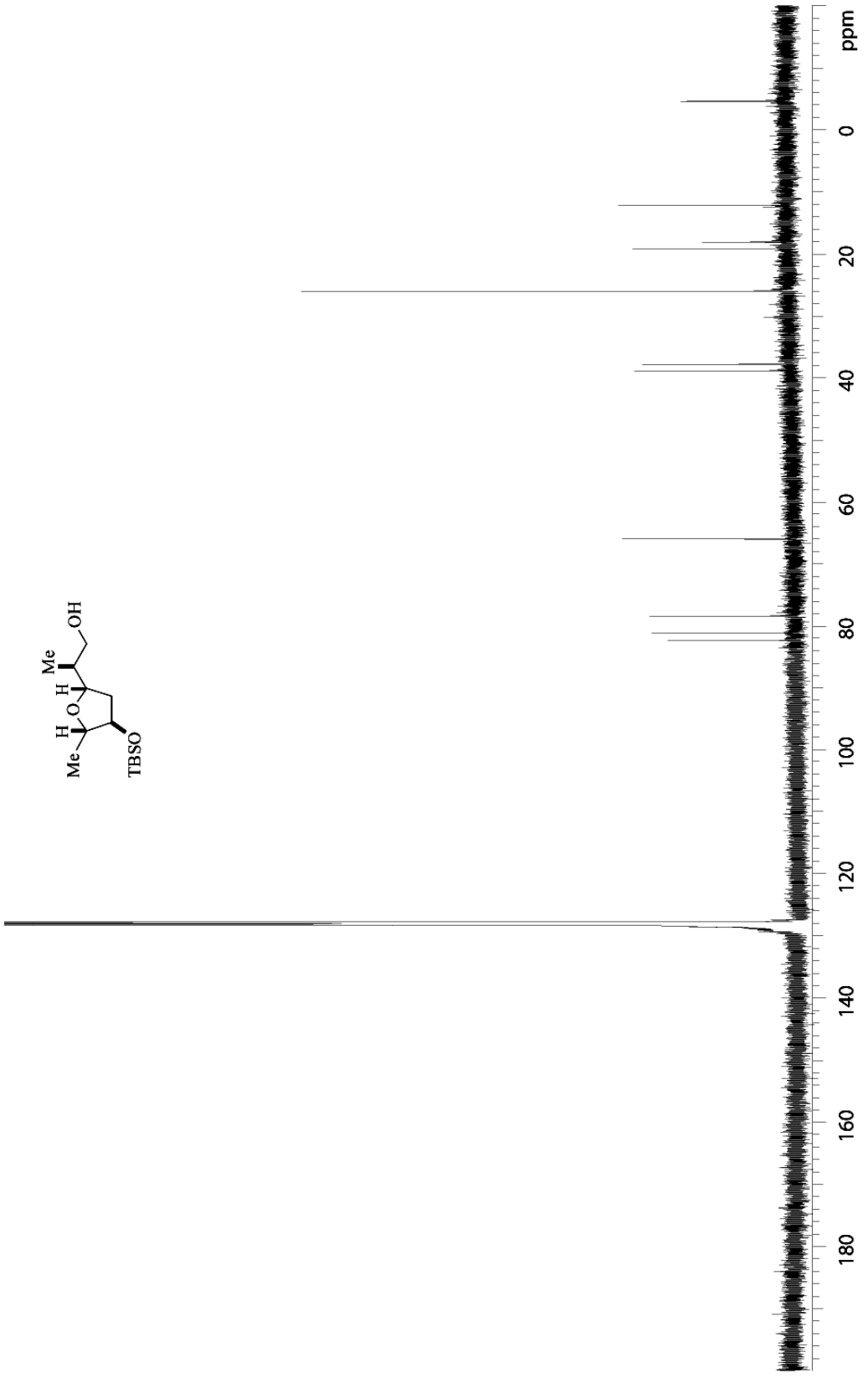
^{1}H NMR (300 MHz) of THF **(±)-4.1n** in C_6D_6



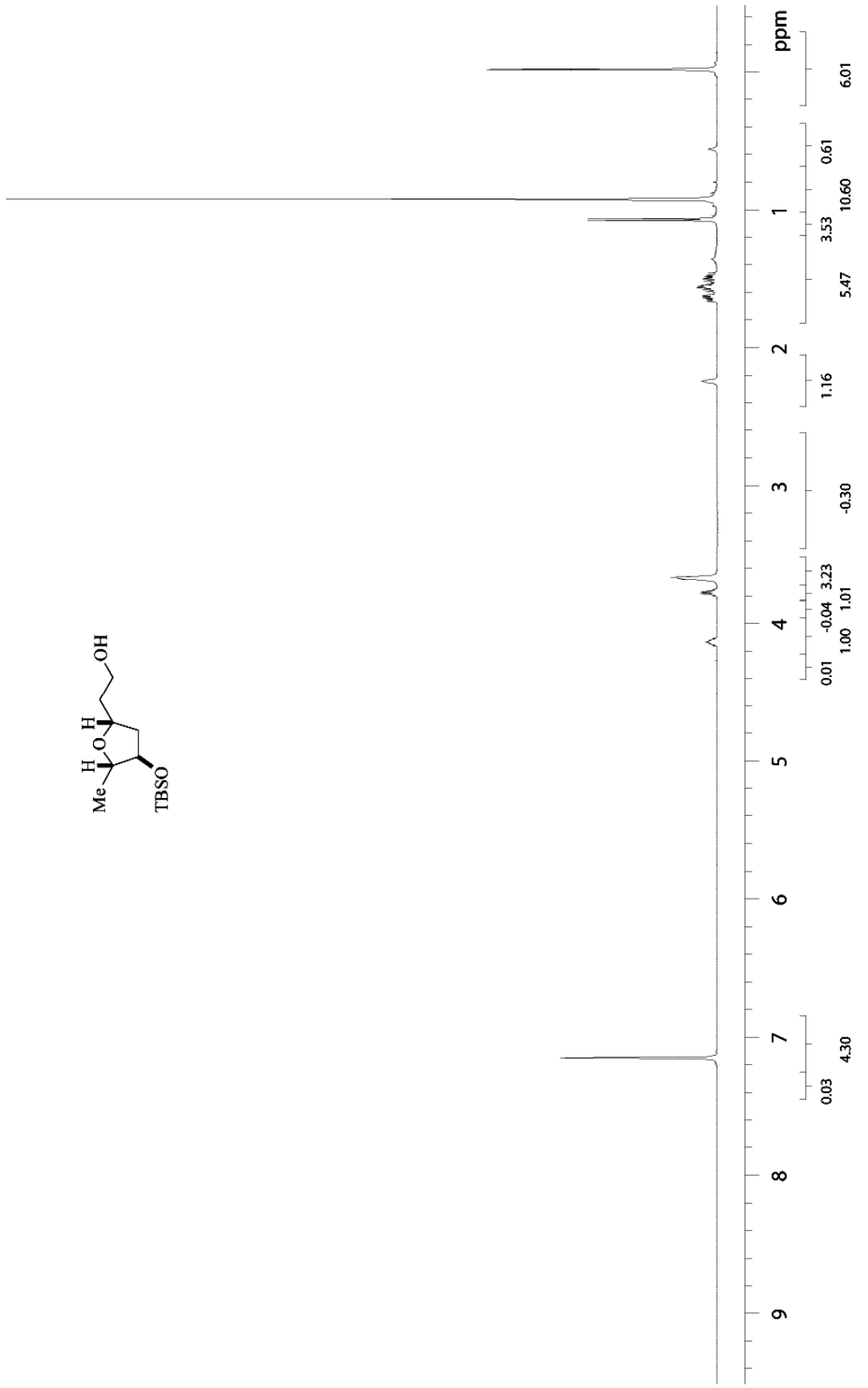
^{13}C NMR (75 MHz) of THF **(±)-4.1n** in C_6D_6



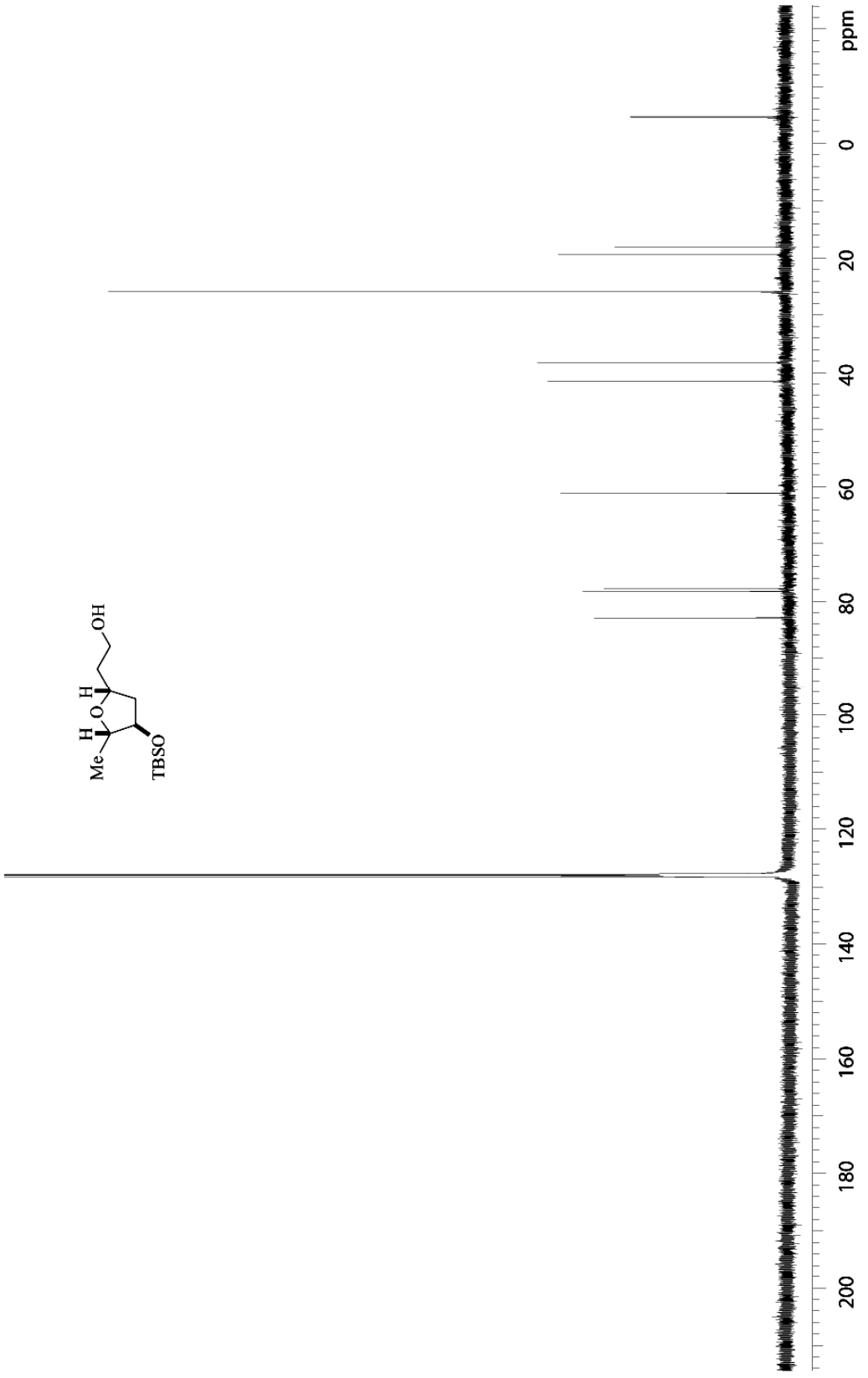
^{1}H NMR (500 MHz) of THF **4.15m** in C_6D_6



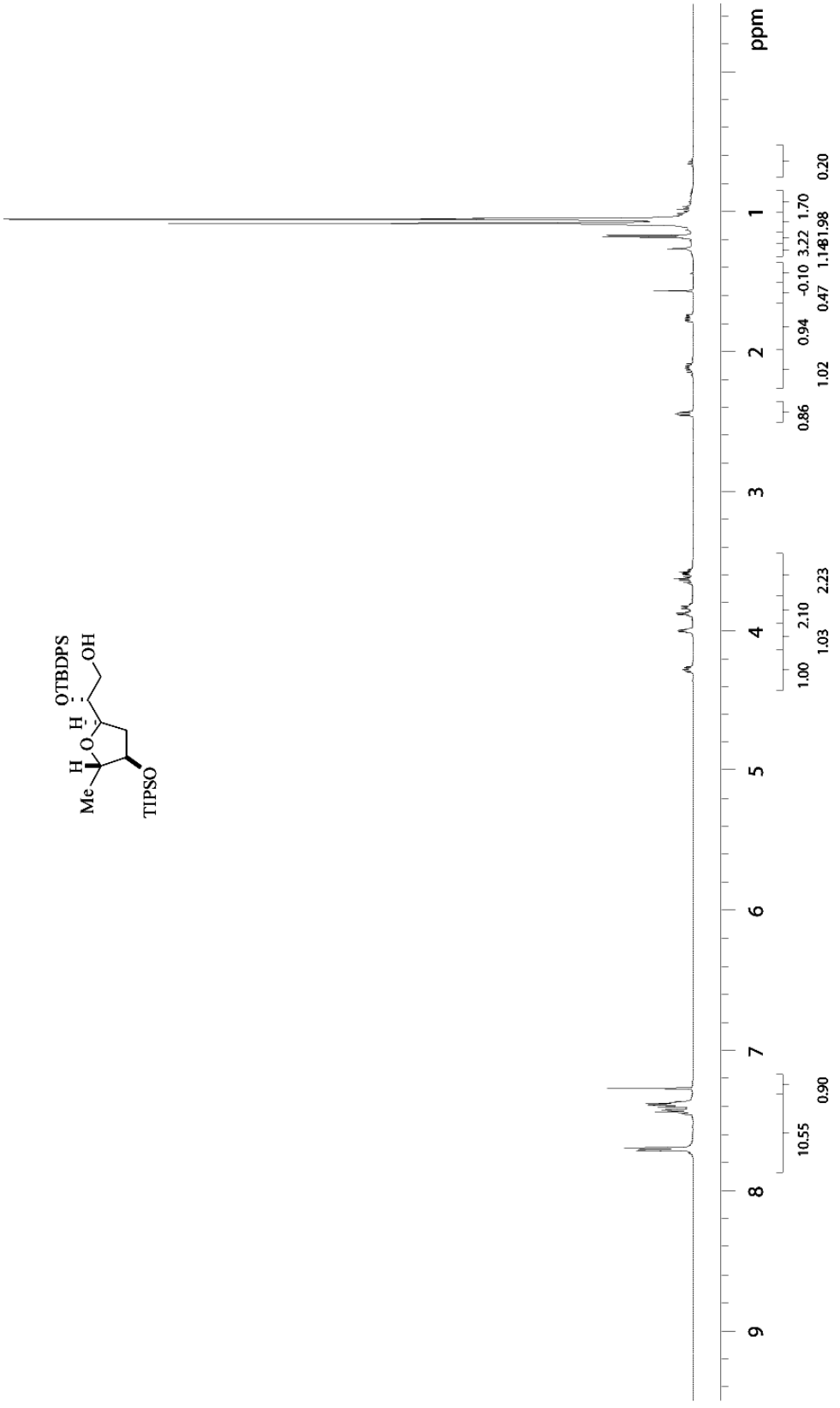
^{13}C NMR (125 MHz) of THF **4.15m** in C_6D_6



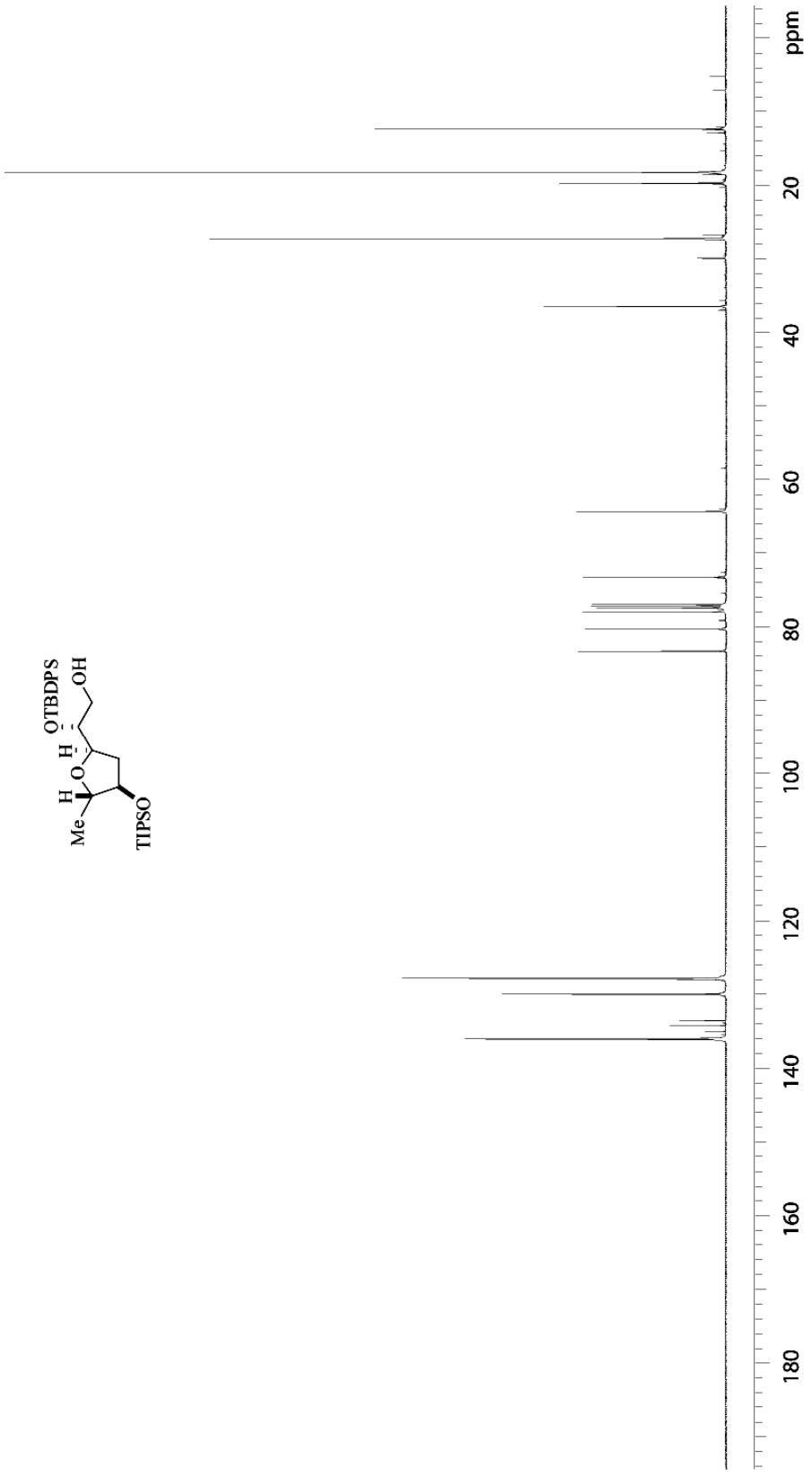
^{1}H NMR (500 MHz) of THF **4.15m'** in C_6D_6



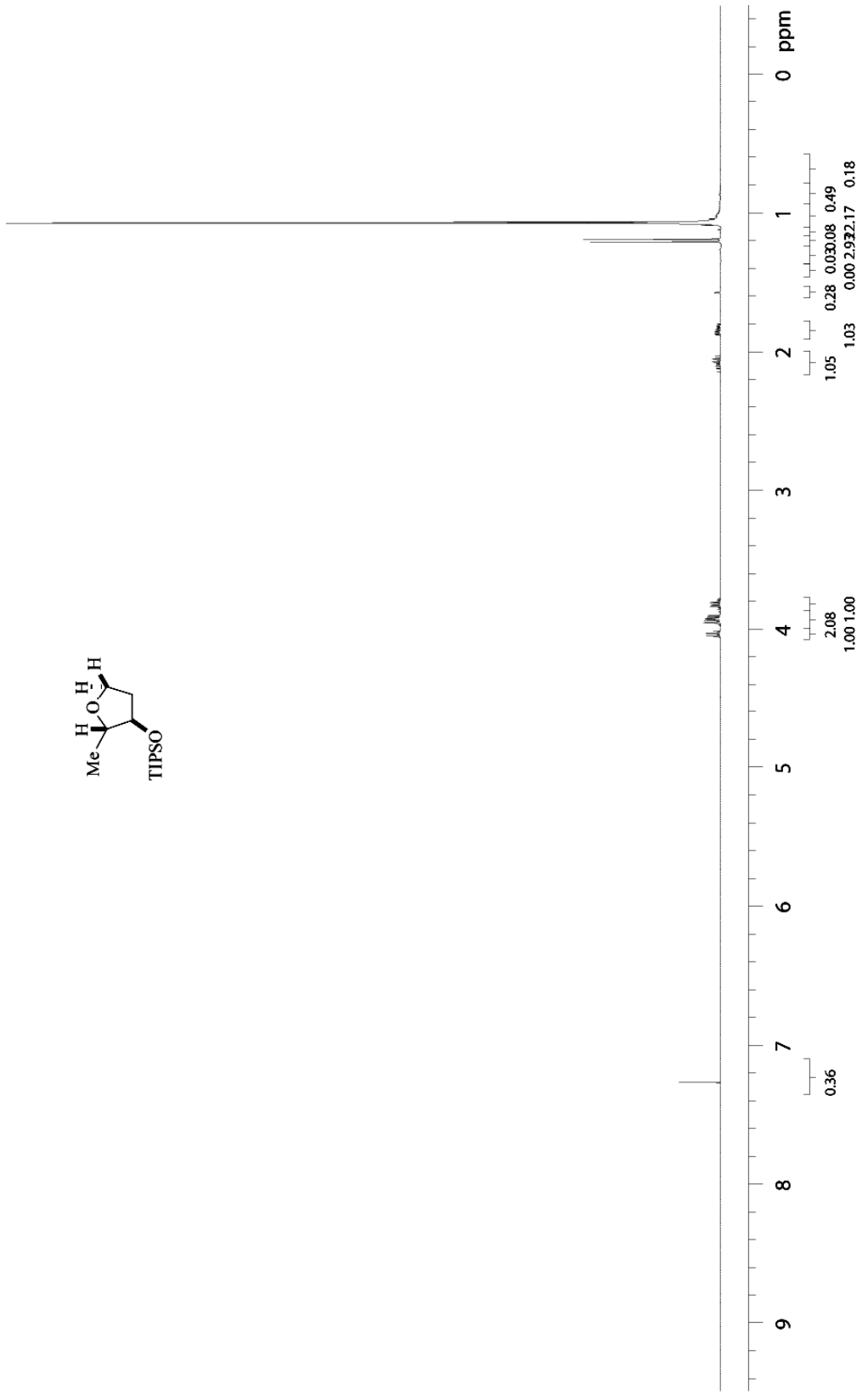
^{13}C NMR (125 MHz) of THF **4.15m'** in C_6D_6



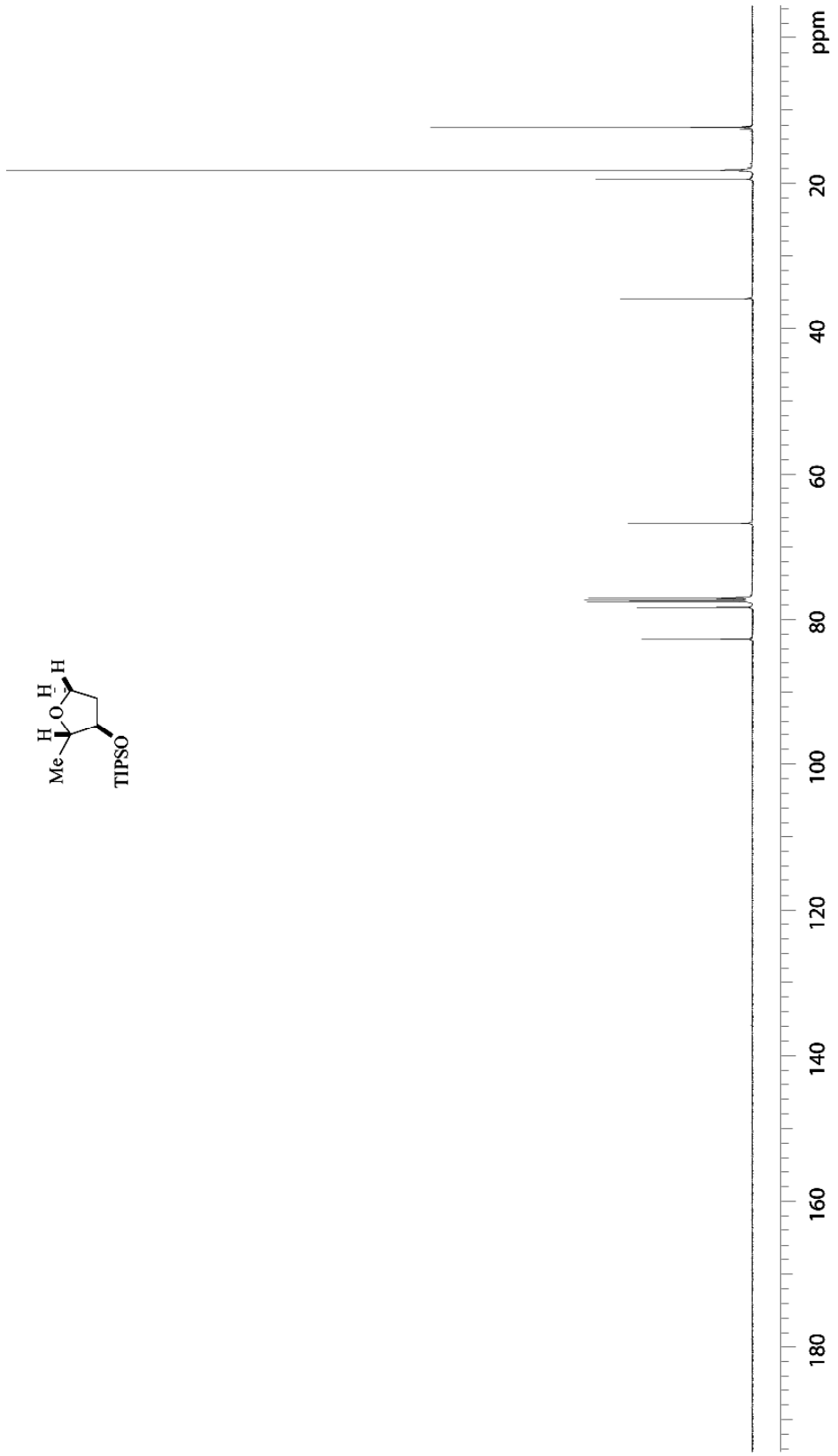
^{1}H NMR (500 MHz) of THF **4.15n** in $CDCl_3$



^{13}C NMR (125 MHz) of THF **4.15n** in $CDCl_3$



^{1}H NMR (300 MHz) of THF **4.15n'** in $CDCl_3$



^{13}C NMR (75 MHz) of THF **4.15n'** in $CDCl_3$

APPENDIX B

LETTERS OF PERMISSION

HETEROCYCLES

The Japan Institute of Heterocyclic Chemistry
1-7-17 Motoakasaka, Minato-ku, Tokyo 107-0051, Japan Tel.+81-3-3404-5019 Fax.+81-3-3497-9370 e-mail: editorial@heterocycles.com URL: http://www.heterocycles.com

February 14, 2008

Dr. Andrew Mitchell
Department of Chemistry,
Texas A & M University,
College Station,
Texas 77843-3255,
U.S.A.

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HETEROCYCLES, 2005, Vol. 66, pp. 627 - 637
"Radical Reactions and α -Silylations of Optically Active 4-Trichloromethyl- β -lactone"
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Sincerely yours

Mr. Koichi Kametani
President of
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This is to confirm that the editorial office of Angewandte Chemie, Int. Ed. permits T. Andrew Mitchell to include the paper, "Highly Diastereoselective, Tandem, Three-Component Synthesis of Tetrahydrofurans from Ketoaldehydes via Silylated β-Lactone Intermediates in the Tandem Mukaiyama Aldol-Lactonization (TMAL) Reaction," (MS
No. Z800235) in his dissertation.

Sincerely yours,
Margitta Schmitt
Business and Production Manager Chemistry Journals

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VITA

Name: T. Andrew Mitchell

Address: 3847 Olentangy Blvd., Columbus, OH 43214

E-mail Address: tandrewmitchell@gmail.com

Education: B.S., Chemistry, Grove City College, 2001

Objective: To obtain an academic appointment with a university that values both pioneering research and exceptional teaching and initiate my own program consisting of studies focused on novel asymmetric routes toward biologically relevant natural products

Publications: Mitchell, T.A.; Zhao, C.; Romo, D. *Angew. Chemie. Int. Ed.* **2008**, *in press*.

Mitchell, T. A.; Romo, D. *J. Org. Chem.* **2007**, *72*, 9053.

Mitchell, T. A.; Romo, D. *Heterocycles*, **2005**, *66*, 627.

Honors: Texas A&M University Department of Chemistry Martin Corera Travel Award: Gordon Conference, Bryant University, RI (2006)

Outstanding Oral Presentation, Industry University Cooperative Chemistry Program (IUCCP): Texas A&M University, Oct. 19, 2005

Texas A&M University College of Science Fellowship: Sept. 2001 – Aug. 2002

Dean's List, Grove City College (1999-2000)