AN ABSTRACT OF THE DISSERTATION OF

Christopher M. Lincoln for the degree of Doctor of Philosophy in Chemistry presented on March 7, 2005.

Title: Asymmetric Synthesis of Cyclopropanes *via* a "Zipper Reaction"

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James D. White

The rearrangement of a homoallyl cation to a cyclopropylcarbinyl cation is thought to play a role in the biogenesis of a variety of cyclopropane-containing natural products,[1] a hypothesis which has previously led to the design of successful biomimetic syntheses of several natural products.[2] The strategy underlying this approach to cyclopropane synthesis[3] can be applied more broadly and would be particularly valuable if it could be extended to a set of contiguous cyclopropanes.

This concept has led us to examine the rearrangement of certain homoallylic systems bearing a leaving group (triflate) at one terminus and a cation-stabilizing metal (tin) at the other. The effects of protecting groups of varying steric demand and of olefin geometry on the stereochemical outcome of the cyclization were examined. "Zipper" cyclization of (8*R*,5*E*,2*Z*)-1-tri-*n*-butylstannyl-9-trityloxy-nona-2,5-dien-8-ol (**117**) led to the stereoselective formation of three distinct bicyclopropane stereoisomers (**110**,**111**,**112**). The major diastereomer was isolated through derivatization and the absolute stereochemistry was verified by X-ray crystallography.

The *trans,syn,trans*-bicyclopropane **118** was carried forward to complete a formal synthesis of the antifungal agent FR-900848 (**49**).

The synthesis of a key precursor to halicholactone (**188**), neohalicholactone (**189**), and the solandelactones A-H (**190-197**) constructed around a *trans*-cyclopropane core is also described. The key steps in this synthesis are the stereoselective synthesis of *trans*-vinylcyclopropane **79**, followed by a highly diastereoselective acetate aldol reaction leading to compound **269**.

Asymmetric Synthesis of Cyclopropanes *via* a "Zipper Reaction"

by

Christopher M. Lincoln

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Christopher M. Lincoln, Author

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Asymmetric Synthesis of Cyclopropanes *via* a "Zipper Reaction"

GENERAL INTRODUCTION

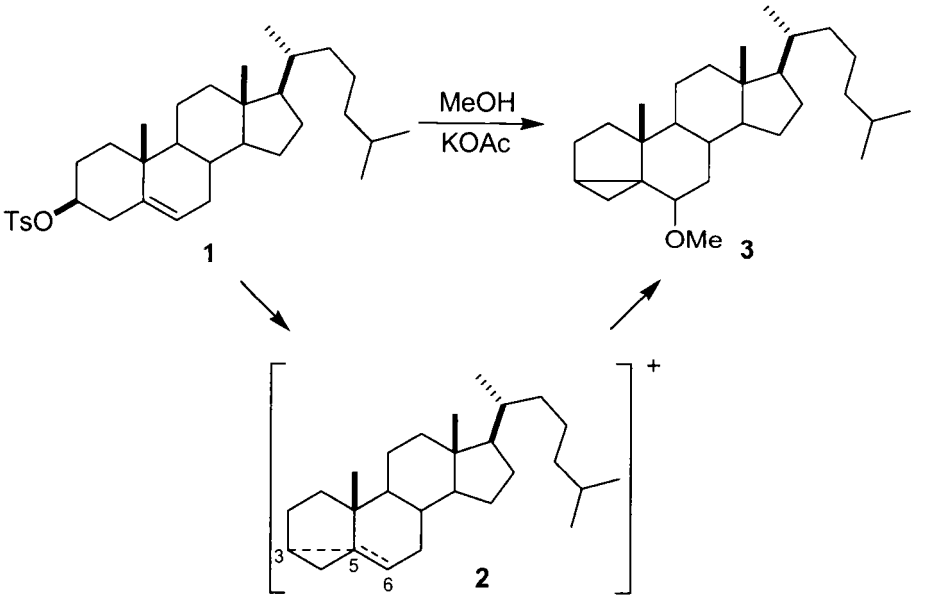
The rearrangement of a homoallyl cation to a cyclopropylcarbinyl cation is thought to play a role in the biogenesis of a variety of cyclopropane-containing natural products,[1] a hypothesis which previously led to the design successful biomimetic syntheses of eicosanoids such as the constanolactones.[2b,c] The strategy underlying this approach to cyclopropane synthesis can be applied more broadly and would be particularly valuable if it could be extended to a set of contiguous cyclopropanes such as that present in the fungal metabolite FR-900848.[4]

We have examined the rearrangement of homoallylic systems bearing a leaving group (triflate) at one terminus and a cation stabilizing metal (tin) at the other to clarify the role of double bond geometry in the cyclization process as well as elucidate the absolute stereochemistry associated with this reaction.

CHAPTER ONE: BACKGROUND

1.1 HISTORICAL BACKGROUND OF THE HOMOALLYL-CYCLOPROPYLCARBINYL-CYCLOBUTYL CATION INTERCHANGE

Early interest in the interconversion of cyclobutyl, cyclopropylcarbinyl and homoallyl cations arose from Demjanov's 1907 observation,[5] whereby both cyclobutyl amine and cyclopropylcarbinyl amine react with nitrous acid to give mixtures of cyclobutanol and cyclopropylcarbinol. Until 1948, no clear explanation for this interconversion had been presented. At that time, two independent mechanistic proposals began to develop based upon observations of the stereospecific cholesteryl-*i*-cholesteryl rearrangement of **1** to **3** (Scheme 1).[6] Weinstein and Adams[6a] showed the kinetics of acetolysis of **1** to be first order, thus supporting a stepwise mechanism. The reaction was postulated to proceed *via* nonclassical cation **2**, which then could react with methanol at either C-3 or C-6.



Scheme 1: The Cholesteryl-*i*-Cholesteryl Rearrangement

Dodson and Riegel[6b] further explored the structure of the intermediate cation **2** in order to explain the stereospecificity of the cholesteryl-*i*-cholesteryl transformation (Figure 1). They portrayed ion **4** as having a greatly distorted sigma bond between C-3 and C-5 and a partially distorted sigma bond between C-5 and C-6. This postulate dictates that the orbitals from C-3 and C-6 are overlapping the orbital at C-5. In this nonclassical representation, C-4 is in a *cis* relationship to the methyl group at C-10 and maximum electron density is on the α-face at C-3, forcing nucleophilic attack to occur from the more sterically hindered β-face. In practice, nucleophilic attack occurs almost exclusively at the less sterically encumbered C-6, providing strong evidence for significant delocalization as depicted by nonclassical cation **4**.

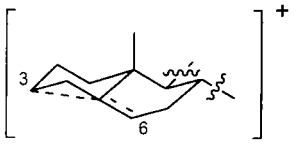


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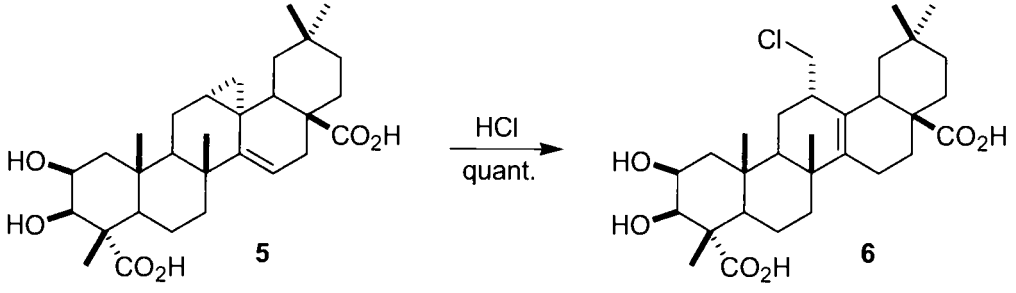
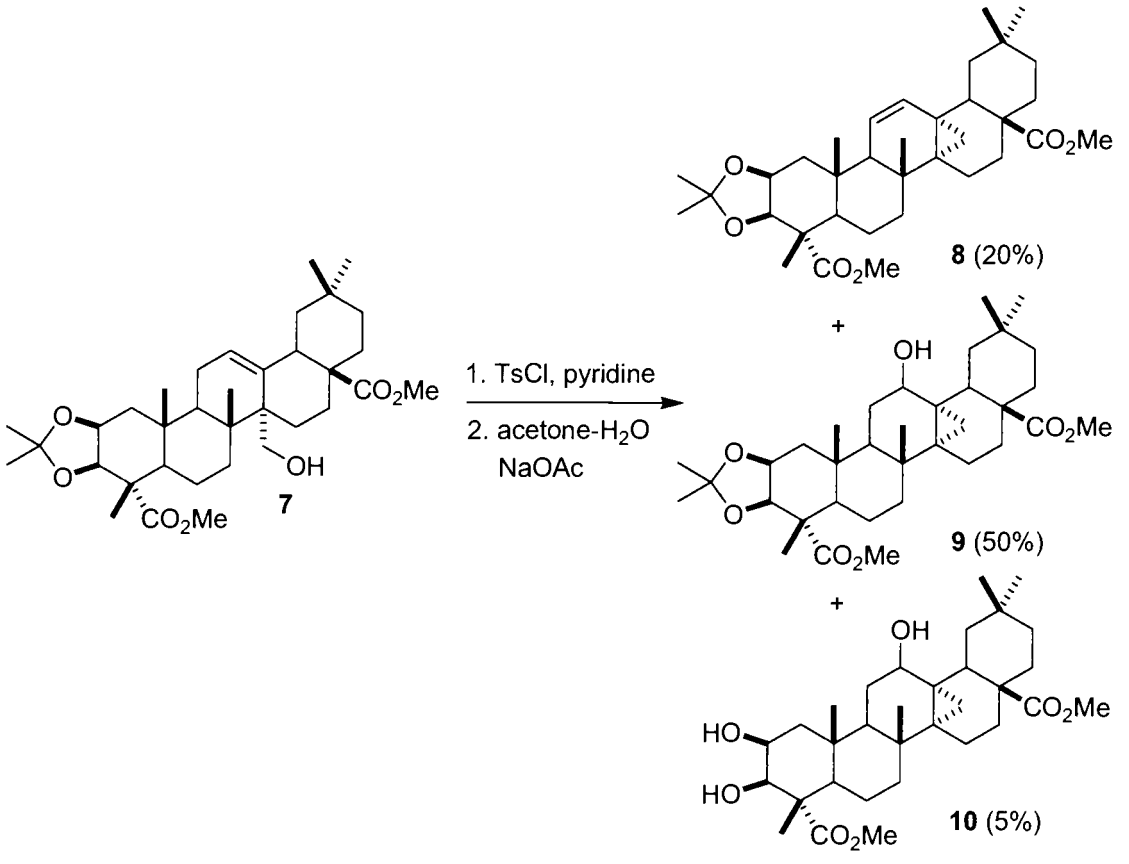
Figure 1: Proposed Nonclassical Structure of the Cation in the Cholesteryl-*i*-Cholesteryl Rearrangement

In 1966, Pelletier and co-workers suggested participation by a homoallylic cation in the conversion of cyclosenegenin **5** into senenegin **6** upon treatment with hydrochloric acid (Scheme 2).[7]



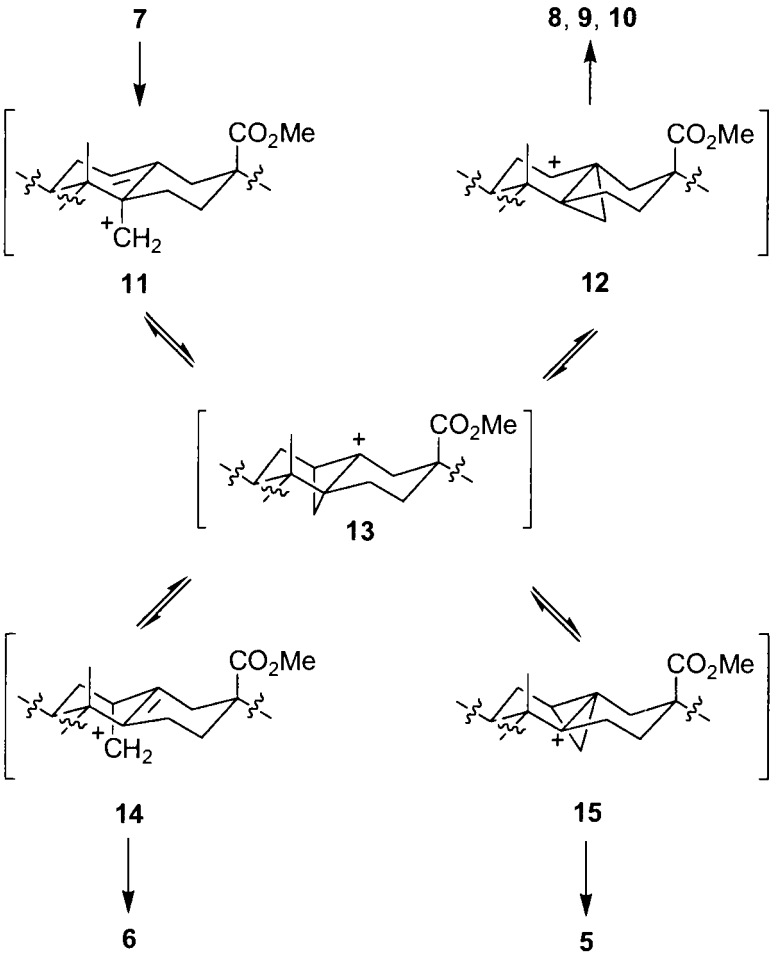
Scheme 2: Conversion of Cyclosenegenin to Senenegin

To evaluate the role of a homoallylic cation in the above transformation, homoallylic tosylate **7** was treated with sodium acetate in aqueous acetone to yield a mixture of cyclopropanes **8**, **9** and **10** (Scheme 3).



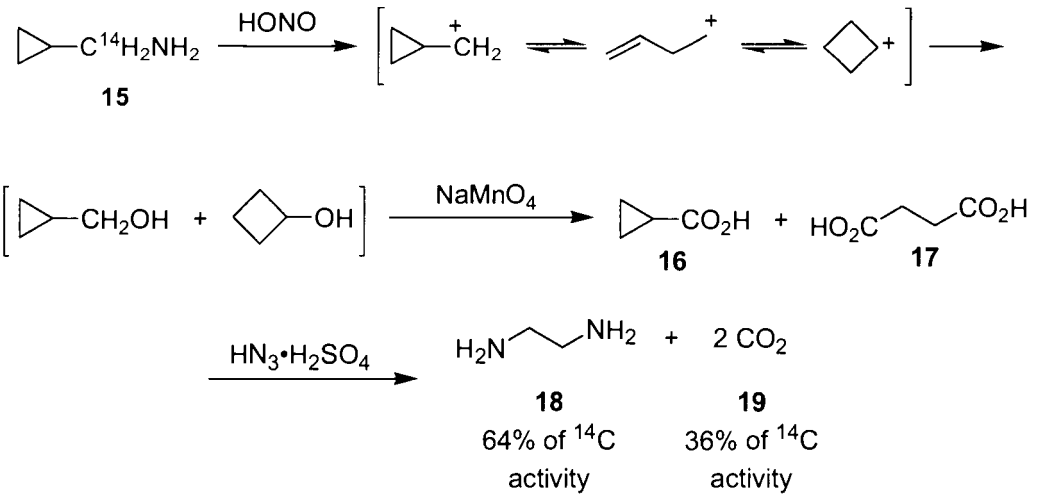
Scheme 3: Solvolysis of Homoallylic Tosylate **7**

The experimental results outlined in schemes 2 and 3 were explained through the proposed interconversion of two homoallylic cations **13** and **15**, which are interconnected through cyclobutonium ion **14** (Scheme 4).



Scheme 4: Homoallyl- Cyclopropylcarbinyl-Cyclobutyl Cation Interchange in the Conversion of **7** to **8**, **9**, and **10**

The abnormally large solvolytic reactivities of cyclobutyl, cyclopropylcarbinyl and homoallylic halides[8] and sulfonate esters led Roberts and co-workers to investigate the nature of the intermediates in the homoallyl-cyclobutyl-cyclopropylcarbinyl cation interchange. A study of the diazotization of ^{14}C-labeled cyclopropylmethylamine revealed that the three methylene groups in this structure achieved a degree of equivalence along the reaction pathway (Scheme 5).[9]



Scheme 5: ^{14}C Incorporation Study of the Homoallyl-Cyclopropylcarbinyl-Cyclobutyl Cation Interchange

From the experimental data, the authors concluded that all four of the carbon atoms of the cyclopropylcarbinyl cation formed from **15** are sp^3 hybridized and that the methynyl carbon is attached to the three methylene carbons by sigma bonds. The three extra orbitals of the methylene groups are then positioned in such a way as to allow overlap as shown in Figure 2, forming one stable three-center molecular orbital holding two electrons and two vacant orbitals of considerably higher energy.

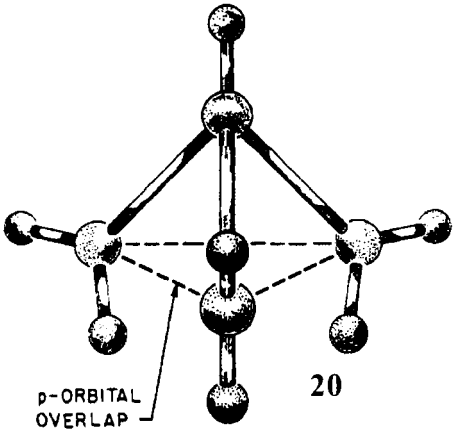
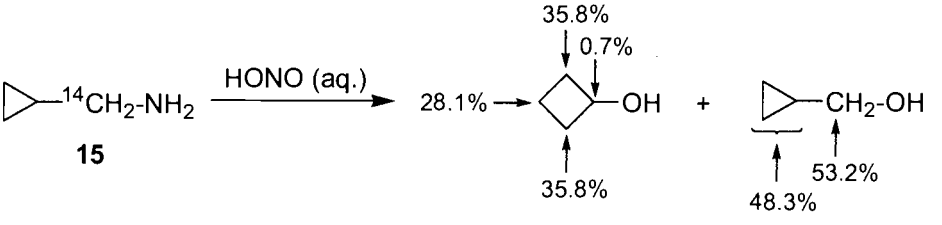


Figure 2: Initially Proposed Symmetrical Structure of the C_4H_7 Cation

Further labeling studies performed by Roberts and co-workers concluded that a more accurate description of the cationic intermediates involved in the cyclobutyl-

cyclopropylcarbinyl interchange was required. In order to differentiate between two possible pathways for the interconversion, the authors sought to irreversibly trap intermediate cations with a highly nucleophilic solvent. If the cations do not interconvert faster than they react with solvent, then the degree of equivalence of the methylene carbons would be less than that depicted by **20**. The deamination of cyclopropylcarbinylamine-α-^{14}C **15** under aqueous conditions afforded a mixture of products typical for this family of compounds (48% cyclopropylcarbinol, 47% cyclobutanol, 5% allylcarbinol). The unequal distribution of the ^{14}C label in the product alcohols (Scheme 6) ruled out the symmetrical intermediate **20** (Figure 2). [10]



Scheme 6: ^{14}C Isotope-Distribution in the Homoallyl-Cyclopropylcarbinyl-Cyclobutyl Cation Interchange of [^{14}C]-Cyclopropylmethylamine **15**

The most geometrically favorable conformation for the unsymmetrical cation from **15** based upon the experimental results was proposed to be that of **21**, where the charge on the cation is fairly evenly distributed between positions 1, 2, and 4 (Figure 3). Reaction of **21** with a nucleophile at positions 1, 2, and 4 would lead to cyclopropylcarbinyl, cyclobutyl or homoallyl derivatives respectively.

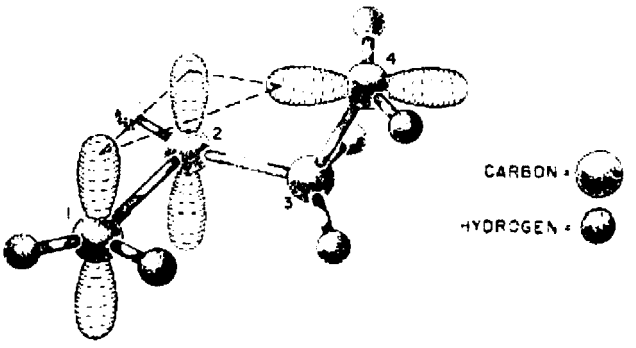


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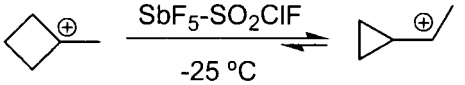
Figure 3: Revised Unsymmetrical Structure of the C_4H_7 Cation

NMR studies of the secondary cyclopropylcarbinyl-tertiary cyclobutyl cation equilibrium provided supporting evidence for the increased stability of cyclopropylcarbinyl cations. At -25 °C, **22** or **23** isomerize to an equilibrium mixture containing approximately 2% of **22** and 98% of **23**, showing that the secondary cyclopropylcarbinyl cation is more stable than the tertiary cyclobutyl cation by *ca* 2 kcal/mol (Figure 4).[11]



22 **23**

Figure 4: Secondary Cyclopropylcarbinyl-Tertiary Cyclobutyl Cation Equilibrium

A rationale for the increased stability of the secondary cyclopropyl carbinyl cation can be deduced from NMR studies of stable dimethylcyclopropylcarbinyl salts, eg **24**. The methyl groups of this cation were shown to be non-equivalent, offering strong evidence that the cyclopropyl ring is not coplanar with the plane of the cation. In the orientation shown, the cyclopropyl ring lies *cis* to one methyl group and *trans* to the other, allowing the *cis*-methyl group to experience the diamagnetic anisotropic shielding of the cyclopropyl ring and thus accounting for the upfield shift of this signal (0.54 ppm). The bisected orientation shown in Figure 5 allows the empty *p* orbital to

achieve maximum overlap with the carbon-carbon σ-bonds of the cyclopropane ring.[12] No rotation of the cyclopropyl ring in this cation was observed upon warming **24** to -35 °C, at which temperature the ion rapidly decomposed with no coalescence of the methyl signals.

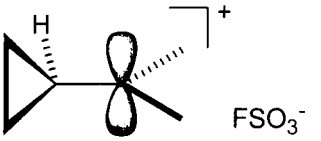


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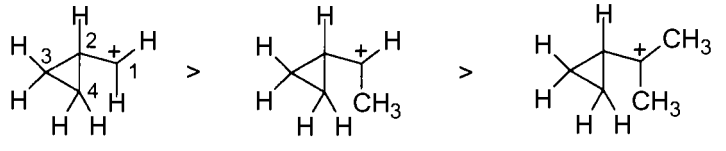
Figure 5: Bisected Conformation of the Dimethylcyclopropylcarbinyl Cation

Olah and co-workers subsequently showed by ^{1}H NMR and ^{13}C NMR studies that cyclopropylcarbinyl, methylcyclopropylcarbinyl and dimethylcyclopropylcarbinyl cations exhibit a high degree of delocalization of the positive charge into the cyclopropyl ring.[13] The ^{13}C NMR data of **25**, **26**, and **27** displayed a dramatic increase in the sigma delocalization of the cation in the order dimethylcyclopropyl < methylcyclopropyl < cyclopropylcarbinyl (Figure 6).



25 **26** **27**

	δ(^{1}H)				δ(^{13}C)			
	Alkyl		Cyclopropyl					
Ion	CH_3	^{+}CH	CH_2	CH	CH_3	CH_2	>CH	^{+}C
25			4.21 4.64	6.50		137.90	84.70	137.90
26	3.34	9.60	4.32 4.45	4.58	160.00	136.60	126.50	-59.10
27	2.70		3.57	3.83	153.90	140.40	133.80	-86.80

Table 1: ^{1}H and ^{13}C NMR Data Showing the Chemical Shifts of Protons and Carbons in Cyclopropylcarbinyl Cations

Kabakoff and Namanworth estimated the barrier to interconversion between the bisected conformation and the corresponding perpendicular conformation of the dimethylcyclopropyl cation (Figure 6). Utilizing nuclear magnetic double resonance, the activation energy was experimentally determined to be 13.7 ± 0.4 kcal/mol.[14] This large energy of activation supports the previously reported high degree of delocalization of the positive charge into the cyclopropyl ring.

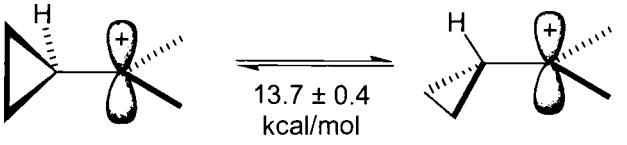


Figure 6: Energy of Activation for Rotation Between Bisected and Perpendicular Conformations of the Dimethylcyclopropylcarbinyl Cation

This ground breaking early work elucidating the nature of the intermediates and the role of the cyclopropyl ring in the homoallyl-cyclopropylcarbinyl-cyclobutyl cation interchange laid an important foundation for the use of homoallylic systems in the stereoselective synthesis of cyclopropanes. A few examples drawn primarily from the area of natural product synthesis are discussed in the section which follows.

1.2 STEREOSELECTIVE SYNTHESIS OF CYCLOPROPANES *VIA* A HOMOALLYL-TO-CYCLOPROPYLCARBINYL CYCLIZATION

The cyclization of homoallyl systems to cyclopropanes is a commonly observed rearrangement in the biosynthesis of isoprenoids. For example, formation of the cyclopropyl group present in the thujane family of bicyclic monoterpenes starts from cyclization of geranyl diphosphate **28** (Scheme 7). The presence of homoallyl cation **31** in this process and the mechanism of its cyclization to α-thujene (**32**) are supported by labeling studies of several terpenoids derived *via* a similar pathway.[15]

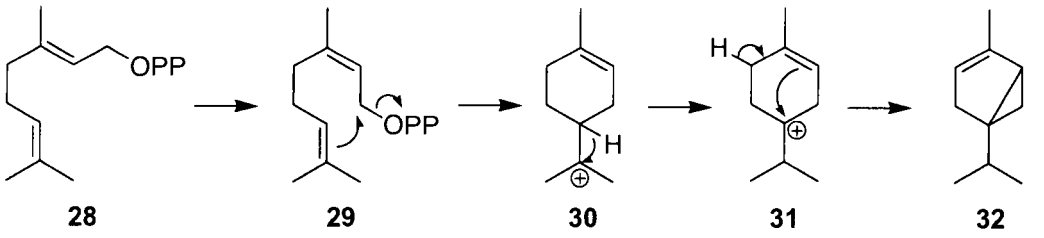
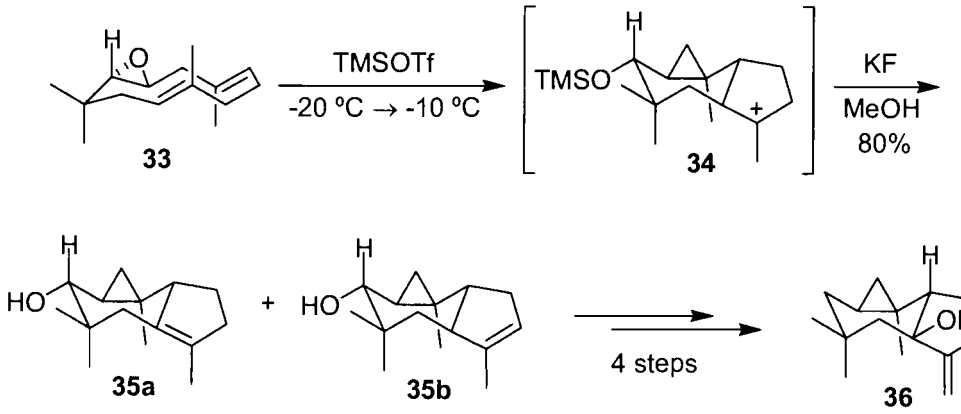


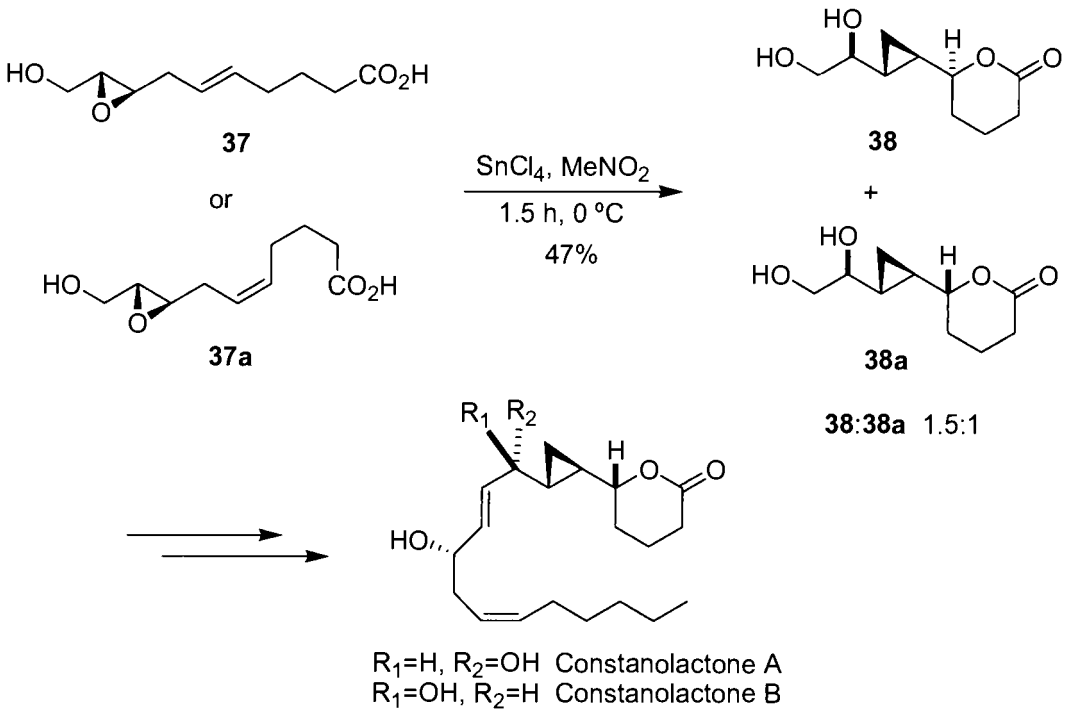
Figure 7: Mechanism of Homoallyl-Cyclopropylcarbinyl Cyclization in the Biosynthesis of α-Thujene (**32**)

In 1980, Shirahama and co-workers developed a conformationally selective transannular cyclization of humulene-9,10-epoxide (**33**) to afford the tricyclic core of africen-10-ol (**36**) *via* cation **34** (Scheme 8).[2a]



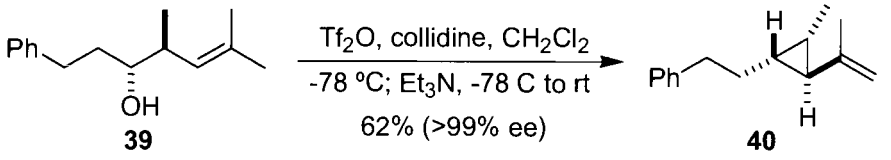
Scheme 8: Cyclization of an Activated Homoallylic Epoxide in the Synthesis of Africen-10-ol (**36**)

White and Jensen similarly utilized an activated homoallylic epoxide for the key construction of a *trans*-disubstituted cyclopropane in their biomimetic synthesis of constanolactones A and B (Scheme 9).[2b,2c,16]



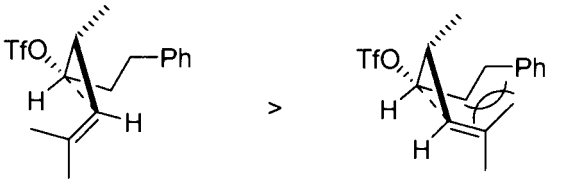
Scheme 9: Cyclization of an Activated Homoallylic Epoxide in the Synthesis of Constanolactones A and B

Suzuki and co-workers later devised a facile method for synthesizing *trans*-disubstituted cyclopropanes from activated homoallylic triflates.[3b] The authors took advantage of the stability of the *tertiary*-cyclopropylcarbinyl cation, which enabled trapping without skeletal rearrangement of the intermediate cyclopropylcarbinyl cation. This strategy afforded the first practical asymmetric synthesis of cyclopropylcarbinyl compounds *via* homoallylic displacement of an activated alcohol (Scheme 10).



Scheme 10: Stereoselective Synthesis of a Cyclopropane *via* Cyclization of a Homoallylic Triflate

Displacement of the intermediate homoallylic triflate occurs with clean inversion at the stereogenic alcohol center in this reaction. The high degree of diastereoselectivity observed in the formation of cyclopropane **40** was rationalized by the preferred transition state **41** (Figure 7). A second possible transition state **42**, leading to a *cis*-isomer was believed to be highly disfavored due to steric repulsion between the olefinic moiety and the alkyl substituent at the reacting center.[3c]

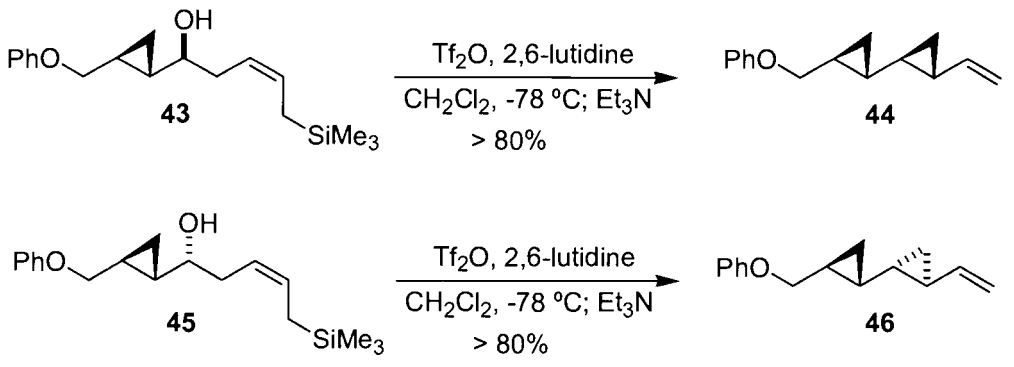


41
Favored

42
Disfavored

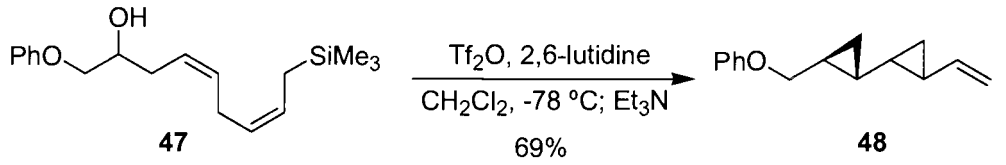
Figure 8: Proposed Transition States for the Cyclization of Activated Homoallylic Alcohol **39**

Taylor extended the work of Suzuki by incorporating a silyl group which could stabilize the cation formed after cyclization. He was successful in synthesizing both *syn,trans*-bicyclopropane **44** from **43** and *anti,trans*-bicyclopropane **46** from **45**. These stepwise cyclizations conform to the Suzuki transition state model in terms of the stereochemical outcome at the second cyclopropane, but shed no light on the role of the double bond geometry in the cyclization process (Scheme 11).[3f,3g]



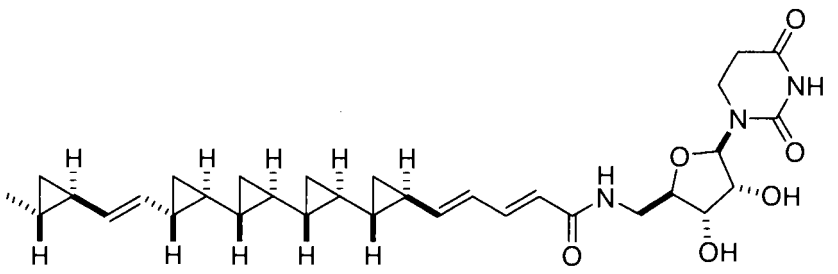
Scheme 11: Taylor's Stepwise Cyclization Leading to Stereocontrolled Bicyclopropane Synthesis

Attempts by Taylor and co-workers to construct a bicyclopropane *via* a cascade cyclization process, starting from **47**, afforded a mixture of stereoisomeric bicyclopropanes **48** (Scheme 12).[3f,3g]

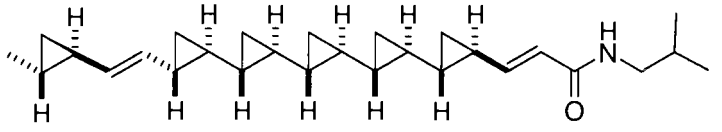


Scheme 12: Taylor's Cascade Cyclization of a Skipped Dienyl Homoallylic Triflate

This dissertation describes an investigation that led to the first stereoselective cascade cyclization of a skipped dienyl homoallylic triflate resulting in a diastereomerically pure *trans,syn,trans* contiguous bicyclopropane in good yield. Our results differ significantly from those of Taylor. They clarify the role of double bond geometry in the cyclization process and they address other stereochemical issues, such as that of absolute configuration, associated with this approach to contiguous cyclopropane synthesis. Our method produces differentiated terminal functional groups attached to a bicyclopropane, a feature which lends itself to the synthesis of all-*syn,trans*-polycyclopropane motifs in natural products such as FR-900848[4] (**49**) and U-106305[17] (**50**) (Figure 9).



FR-900848 (**49**)



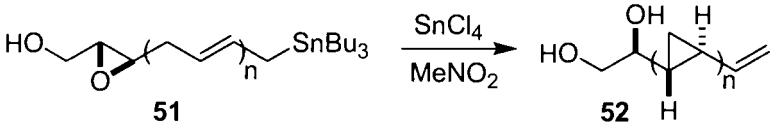
U-106305 (**50**)

Figure 9: Naturally Occurring All-*syn*,*trans*-Oligocyclopropanes

CHAPTER TWO: CYCLOPROPANE SYNTHESIS *VIA* A TIN STABILIZED HOMOALLYLIC-TO-CYCLOPROPYLCARBINYL CYCLIZATION

2.1 INITIAL SYNTHETIC STRATEGY FOR CYCLOPROPANE SYNTHESIS

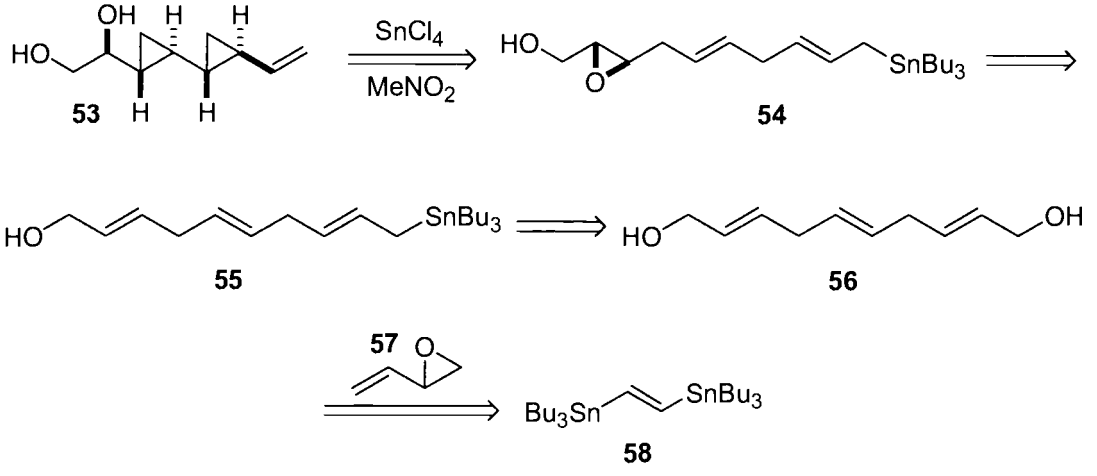
A reexamination of the synthesis of the constanolactones by White and Jensen led to the concept of a cyclopropane synthesis from the cyclization of a homoallylic epoxide bearing a β-cation stabilizing group (**51**). Our initial approach to cyclopropane synthesis envisioned a cascade cyclization triggered by an epoxide opening in which absolute configuration would be derived from an enantiomerically pure homoallylic epoxide arising from a Sharpless asymmetric epoxidation (Scheme 13).



Scheme 13: Initial Strategy for Cyclopropane Synthesis

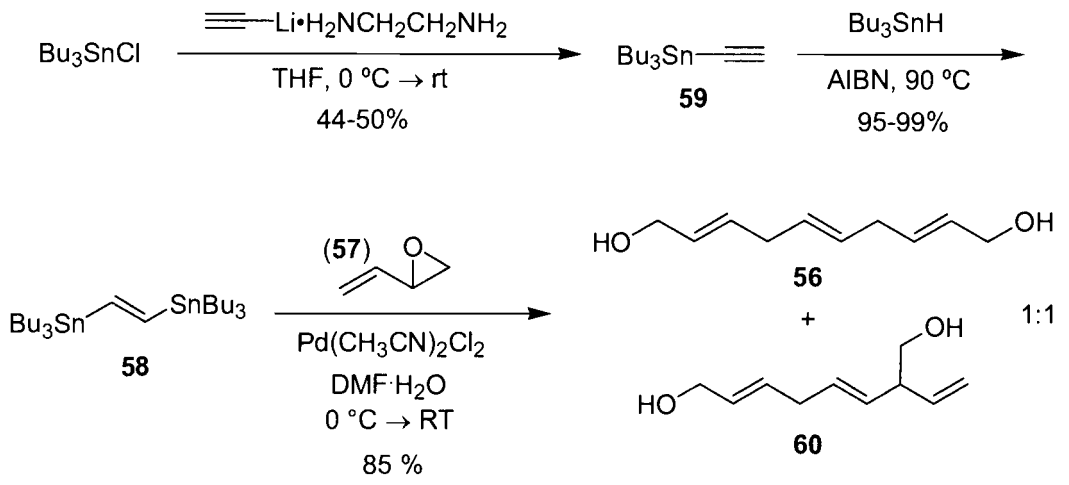
Following the precedent of White and Jensen,[16] the synthetic approach to skipped dienyl homoallylic epoxide **54** was designed around skipped decatriene diol

56, readily available from a bis-Heck coupling of bis(tributylstannyl)ethylene (**58**) and butadiene monoepoxide (**57**).[18] Desymmetrization of **56** followed by Sharpless asymmetric epoxidation of **55** would then afford quick entry into the cyclization precursor **54** necessary for an attempt at a cascade cyclization (Scheme 14).



Scheme 14: Retrosynthetic Analysis Based Upon White and Jensen's Approach to Homoallylic Epoxide **37**

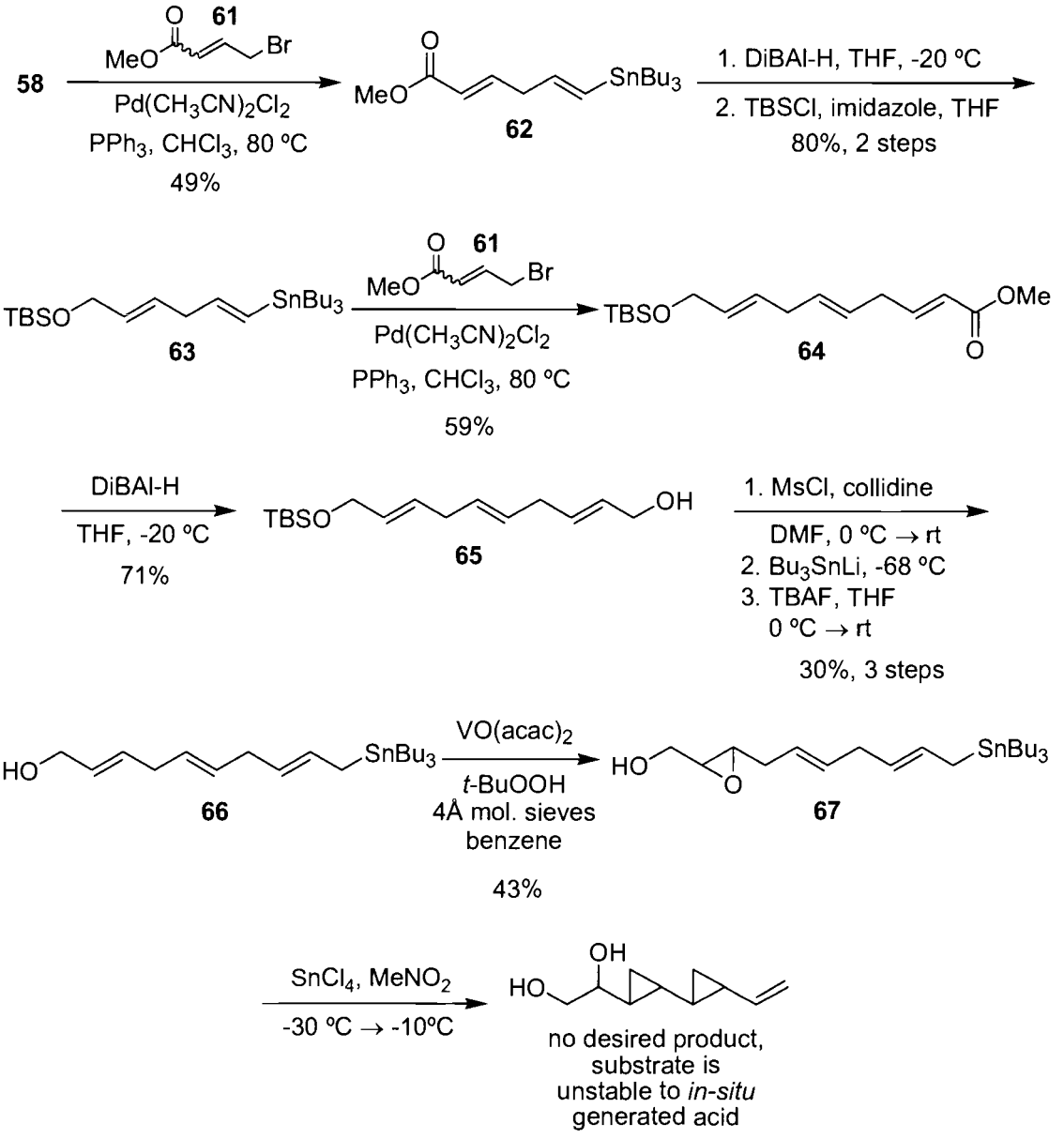
(*E*)-Bis(tri-*n*-butylstannyl)ethylene (**58**), a compound previously reported by Stille and co-workers,[19] was prepared in two steps from commercially available tributyltin chloride and lithium acetylide-ethylenediamine complex. Coupling of **58** with butadiene monoepoxide **57** under conditions previously reported by White and Jensen afforded an inseparable 1:1 mixture of regioisomeric diols **56** and **60** (Scheme 15).



Scheme 15: Mixture of Regioisomeric Diols from the bis-Heck Coupling of (*E*)-Bis(tributylstannyl)ethylene (**58**) and Butadiene Monoepoxide (**57**)

The synthetic strategy was revised in order to more effectively control the regio- and stereoselectivity in the formation of the decatrienediol core **56** (Scheme 16). Following literature precedent,[20] mono-Stille coupling of bis(tri-n-butylstannyl)ethylene (**58**) with methyl 4-bromo-2-butenoate (**61**, 1:1 *cis*:*trans*) at elevated temperature proceeded with complete isomerization of the *cis-trans* mixture to yield the *trans,trans*-hexadienoate **62**. Subsequent reduction of the ester and protection of the primary alcohol afforded all-*trans* vinylstannane **63**. A second coupling of **63** with 4-bromo-2-butenoate (**61**, 1:1 *cis*:*trans*) afforded, after reduction with diisobutylaluminum hydride, mono-protected *trans*-decatrienediol **65**. Allylic alcohol **65** was converted to the allylic chloride without rearrangement[21] and then to the allylstannane, and the silyl protecting group was removed to yield allylic alcohol **66**. In order to test the proposed cyclization, racemic epoxide **67** was prepared and subjected to the cyclization conditions reported by White and Jensen.[16] Several attempts at this cyclization resulted in recovery of highly polar products, but in no case were cyclopropyl signals observed in the ^{1}H-NMR spectra of the mixtures obtained

from the reaction. The instability of the skipped diene precursor **67** and the absence of cyclopropane products under White and Jensen's optimized cyclization conditions led us to reevaluate our approach to contiguous cyclopropane synthesis.

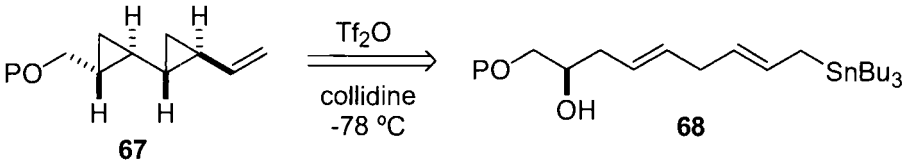


Scheme 16: Initial Approach to Contiguous Cyclopropane Synthesis

2.2 MONOCYCLOPROPANE SYNTHESIS

With the work reported by Suzuki[3b,c] and Taylor[3f,g] on homoallylic triflate cyclizations as a precedent, we set forth to construct a different cyclization precursor,

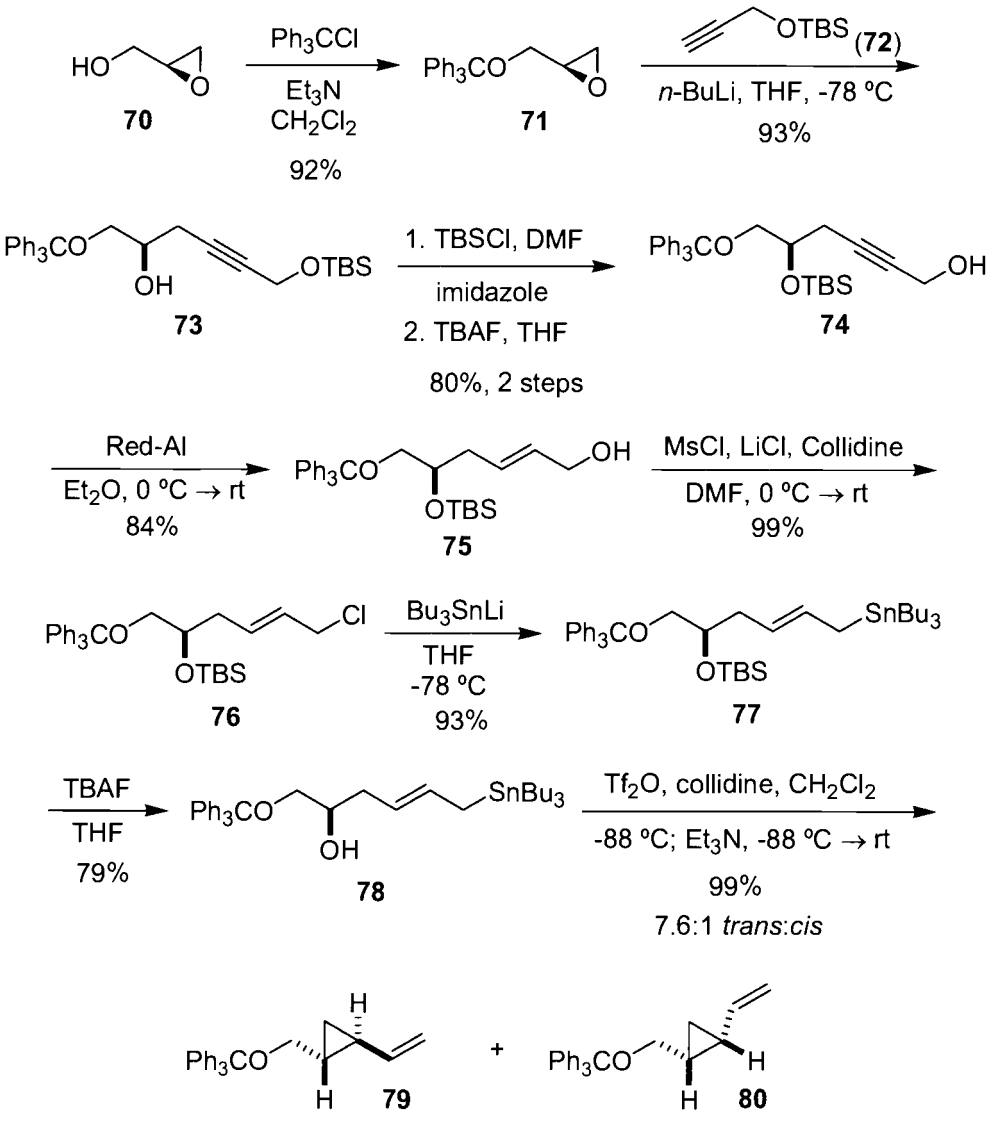
in which the homoallylic epoxide was replaced by a homoallylic alcohol that could be derivatized as a triflate. We decided to retain the allylstannane moiety as a β-cation stabilizer (Scheme 17).



Scheme 17: Revised Cyclization Strategy Based Upon Suzuki's Asymmetric Homoallylic Triflate-Vinylcyclopropane Approach

2.2.1 SYNTHESIS AND SOLVOLYSIS OF A *TRANS* HOMOALLYLIC TRIFLATE

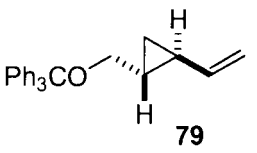
We first studied the reaction of an enantiopure *trans* homoallylic triflate bearing a tri-*n*-butylstannyl residue at the distal terminus. Synthesis of the requisite homoallylic alcohol began from (*S*)-(–)-glycidol (**70**) which was protected as its trityl ether before conversion to alkynol **73** with lithiated alkyne **72** (Scheme 18). Protection of the secondary alcohol followed by unmasking of the primary hydroxyl group gave **74** which was reduced with Red-Al to a *trans* allylic alcohol. The derived allylic chloride **76** underwent displacement with lithio tri-*n*-butylstannane,[22] and subsequent cleavage of the silyl ether afforded **78**. Exposure of **78** to triflic anhydride in base at low temperature resulted in rapid solvolysis of the transient homoallylic triflate to produce a mixture of two cyclopropanes in quantitative yield. Although these cyclopropanes were not separable, the ratio of products was readily identified by ^{13}C NMR as *trans* and *cis* vinylcyclopropanes **79** and **80**, formed in the ratio 7.6:1 respectively.



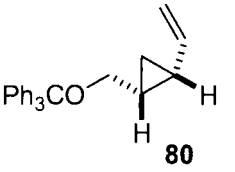
Scheme 18: Synthesis and Solvolysis of a *Trans* Homoallylic Triflate

Analysis of the product mixture *via* the ^{1}H-^{1}H couplings of the cyclopropane peaks proved difficult due to a high degree of overlap of the signals. Alternatively, the ^{13}C NMR of the mixture of cyclopropanes displayed an upfield chemical shift of the alkoxy methylene carbon for the minor isomer (3.1 ppm, Figure 10). Analysis of ^{13}C NMR spectral data for structurally similar *cis* and *trans* vinylcyclopropanes reported by Taylor[3e] showed an upfield shift of 3 ppm for the *cis* isomer in relation to the *trans*

isomer. This upfield chemical shift can be rationalized by the increased shielding of the alkoxy methylene carbon by the pi cloud of the *cis* vinyl group. HPLC analysis on stationary chiral phase verified the product ratio as 7.6:1 and showed **79** and **80** to be enantiomerically pure through comparison with the mixture obtained from the cyclization of *ent*-**78**.



79

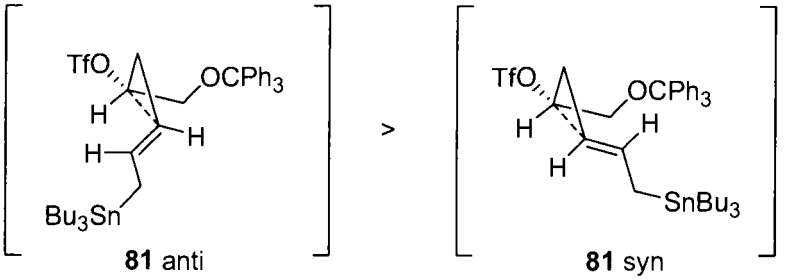


80

	δ(^{13}C)				
	Alkyl	Vinyl		Cyclopropyl	
	CH_2	CH	CH_2	CH	CH_2
79	66.7	141.2	114.3	20.4 20.6	11.9
80	63.6	137.5	111.9	18.4 19.6	10.5

Figure 10: ^{13}C NMR Shifts for Vinylcyclopropanes **79** and **80**

The modest degree of selectivity in favor of *trans* cyclopropane **79** observed in the cyclization arises from a steric interaction of the trityl protecting group and the allyl stannane in the transition state **81** syn leading to *cis* cyclopropane **80** (Figure 11). This interaction is absent in transition state **81** anti. It was reasoned that a modification to the synthesis which incorporated a *cis*-allylstannane would increase selectivity in the cyclization of the activated homoallylic triflate in favor of **79** by enhancing the unfavorable steric interaction of the stannane with the trityl protecting group.

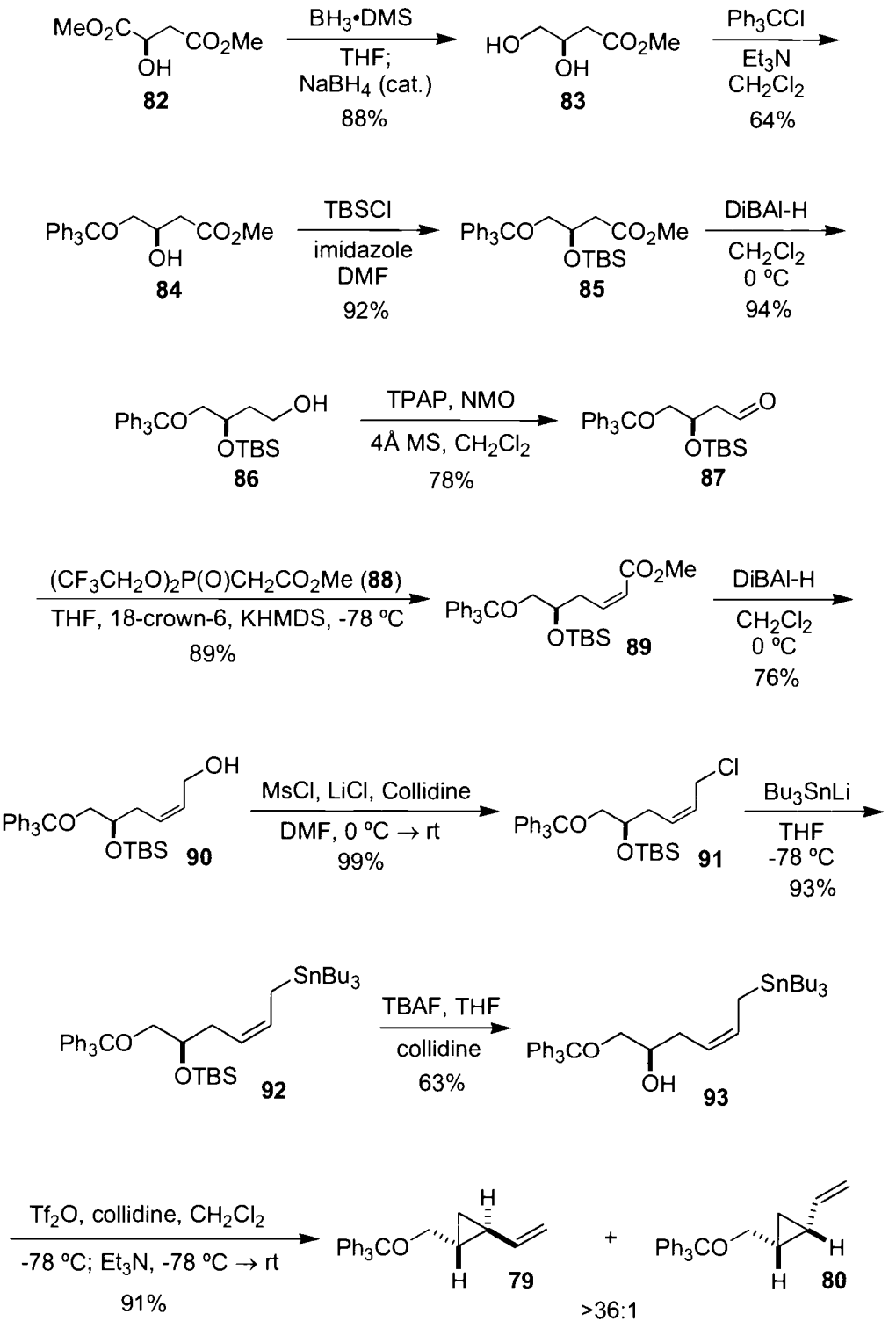


81 anti (favored) > **81** syn (disfavored)

Figure 11: Rationale for Stereoselectivity in the Cyclization of *trans*-Homoallylic Triflate **78**

2.2.2 INFLUENCE OF DOUBLE BOND GEOMETRY AND PROTECTING GROUPS ON STEREOSELECTIVITY

In order to test our hypothesis, the *cis* isomer of **78** was synthesized from (*R*)-(+)-dimethyl malate (**82**), as shown in Scheme 19. Selective reduction of this diester,[23] masking of the resultant primary alcohol **83** as its trityl ether **84**, and protection of the remaining secondary alcohol proceeded smoothly to yield **85**. This ester was converted *via* alcohol **86** to the corresponding aldehyde **87** which was condensed with the Gennari-Still phosphonate **88**[24] to give a *cis* α,β-unsaturated ester **89**. The ester was reduced and alcohol **90** was converted to allylic chloride **91**. Displacement with lithio tri-*n*-butylstannane[22] and cleavage of the silyl ether from **92** furnished *cis* homoallylic alcohol **93**. Treatment of **93** with triflic anhydride under the same conditions used for **78** yielded *trans* cyclopropane **79** as virtually the sole product by ^{13}C NMR and stationary phase chiral HPLC analysis (**79**:**80** >36:1).



Scheme 19: Synthesis and Solvolysis of a *Cis* Homoallylic Triflate

A rationale for the improved stereoselectivity seen in the cyclization of **93** as compared with **78** is shown in Figure 12, and conforms to the explanation put forward

by Suzuki for the stereoselectivity observed in the cyclization of his substrates.[3b,c] Thus, the **79**:**80** product ratio from **78** reflects the more favorable "*anti*" transition state for cyclization, the "**81** *syn*" transition state being disfavored due to the trityl-hydrogen interaction. The steric interaction between trityl and tin groups in the "**94** *syn*" transition state is much more severe, so that cyclization proceeds almost completely through the "**94** *anti*" pathway in this case.

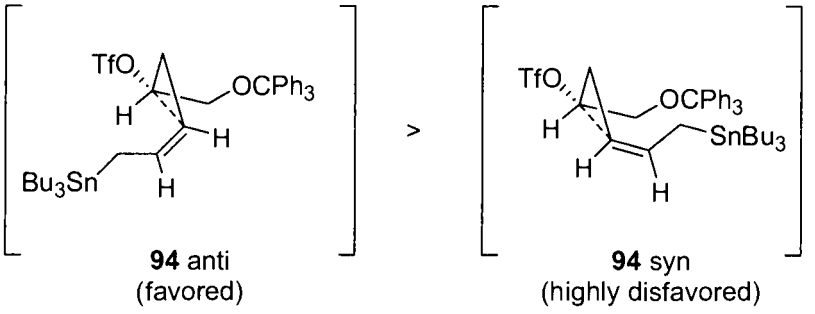
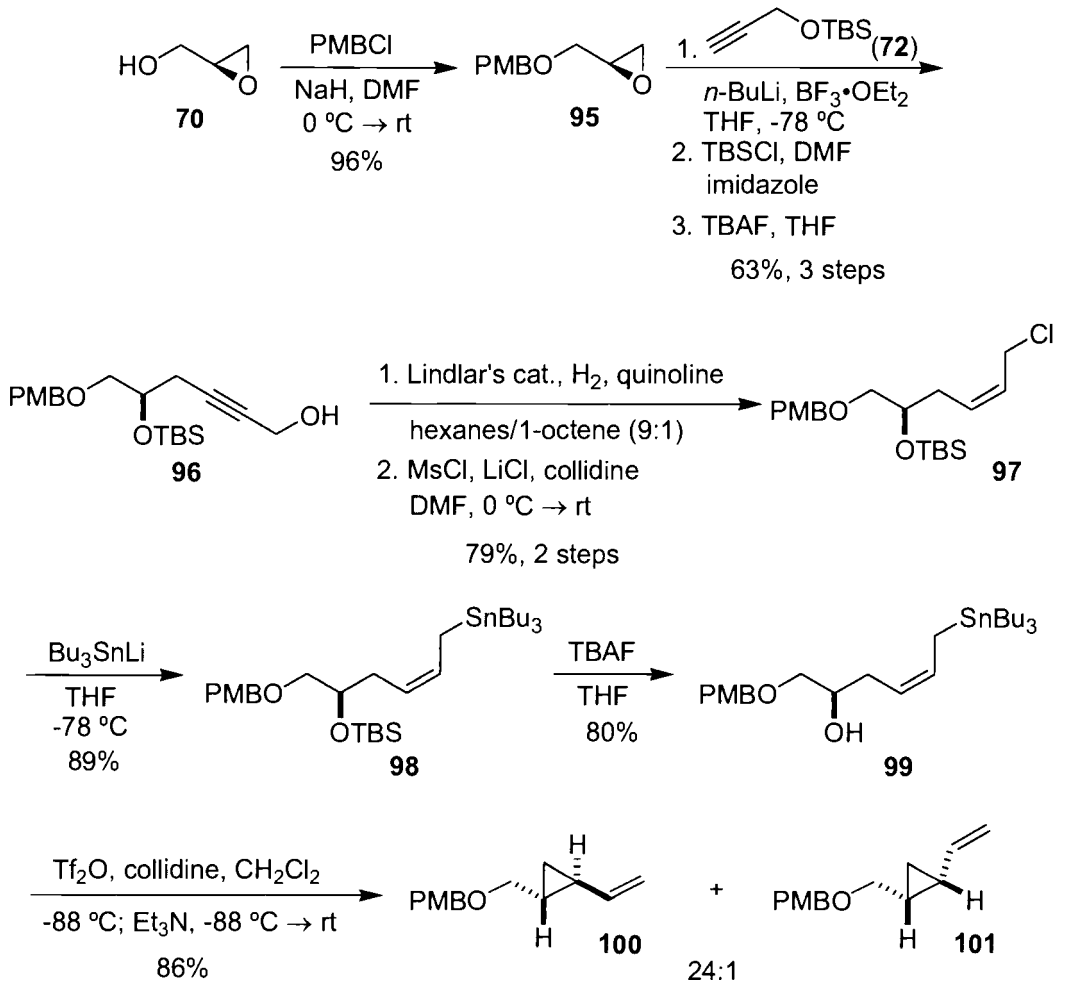


Figure 12: Rationale for Increased Stereoselectivity in the Cyclization of *cis*-Homoallylic Triflate **93**

Attempts to remove the trityl group from vinylcyclopropane **79** under mildly acidic conditions proved problematic, so an alternative protecting group was chosen. (*S*)-(–)-glycidol (**70**) was first protected as its *p*-methoxybenzyl ether **95** before conversion to a homopropargylic alcohol with lithiated alkyne **72** (Scheme 20). Protection of the secondary alcohol followed by unmasking of the primary hydroxyl group gave **96** which was hydrogenated in the presence of Lindlar's catalyst to a *cis* allylic alcohol. Addition of 1-octene as a co-solvent was critical in this reaction in order to inhibit over reduction of the propargylic alcohol. The derived allylic chloride **97** underwent displacement with lithio tri-*n*-butylstannane,[22] and subsequent cleavage of the silyl ether from **98** afforded homoallylic alcohol **99**. Exposure of **99** to cyclization conditions identical to those used for **78** afforded a 24:1 mixture of *trans*

(**100**) and *cis* (**101**) cyclopropanes. The lower degree of *trans* selectivity in this cyclization as compared to **93** was attributed to a smaller steric contribution from the *p*-methoxybenzyl group than the trityl group in destabilizing the transition state analogous to **94** syn.

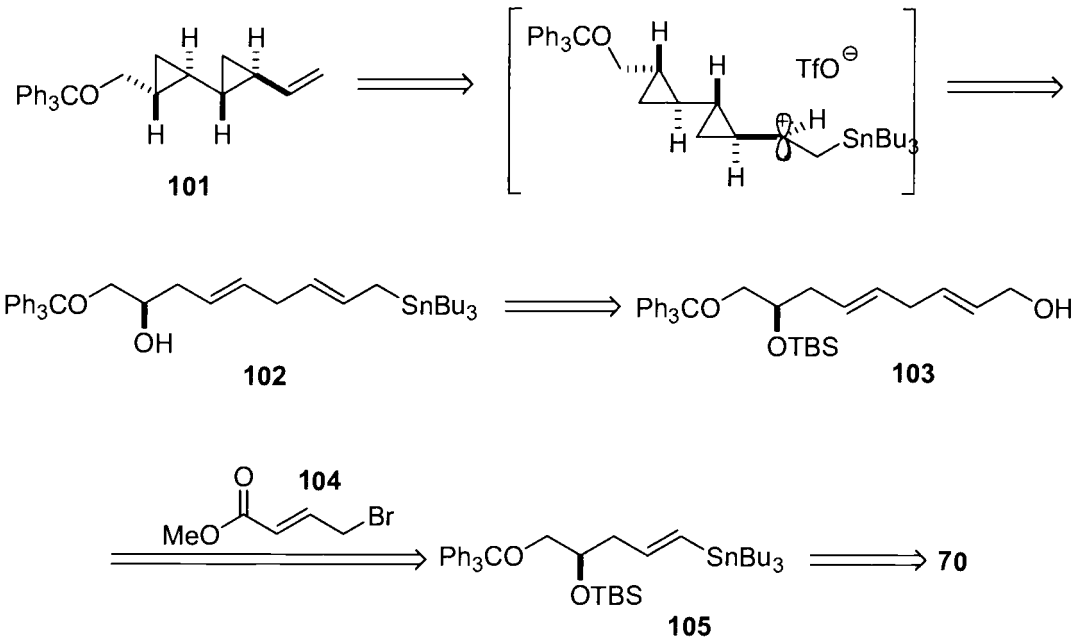


Scheme 20: Synthesis and Solvolysis of a *Cis* Homoallylic Triflate: The Influence of the Protecting Group on Selectivity

2.3 BICYCLOPROPANE SYNTHESIS

The efficient cyclization of homoallylic alcohol **93** to cyclopropane **79** suggested an extension of this study to a system containing a skipped diene, where a second contiguous cyclopropane (**101**) could be formed in a cascade process. The skipped

diene cyclization precursor **102** would be readily available from all-*trans* allylic alcohol **103** *via* synthetic transformations developed for the synthesis of allylic stannane **78**. Allylic alcohol **103** would result from a Stille coupling of methyl *trans*-4-bromo-2-butenoate **104** and vinylstannane **105**, which in turn would be available from (*S*)-(–)-glycidol (**70**, Scheme 21).

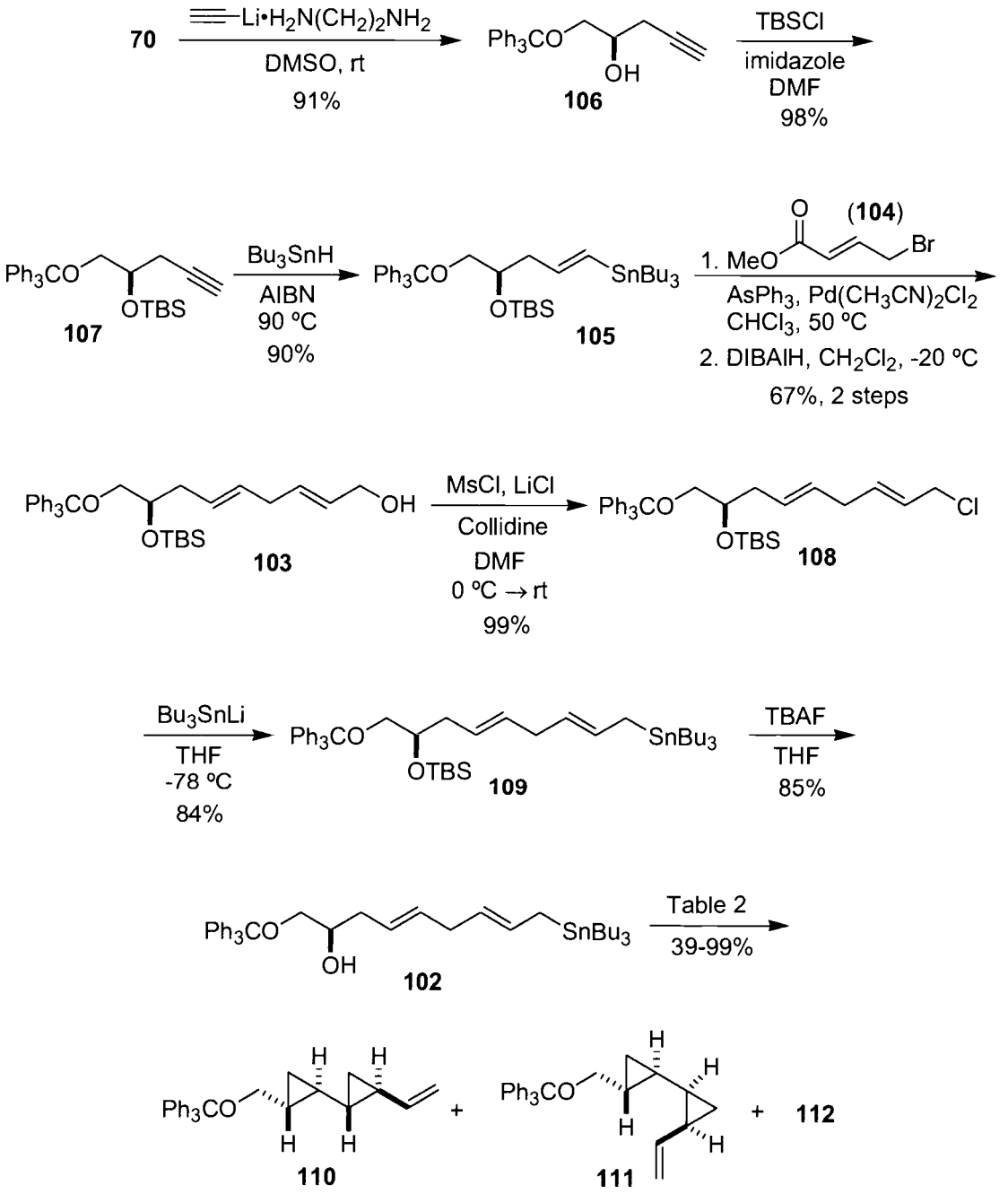


Scheme 21: Retrosynthetic Approach Towards Bicyclopropane Synthesis

2.3.1 SYNTHESIS AND SOLVOLYSIS OF AN ALL-*TRANS* HOMOALLYLIC TRIFLATE

S-(–)-Glycidol was treated with lithium acetylide ethylenediamine complex and the resulting secondary alcohol **106** was protected as its *tert*-butyldimethylsilyl ether **107**. Hydrostannylation[19] of terminal alkyne **107** afforded vinyl stannane **105**, which in turn was coupled with methyl *trans*-4-bromo-2-butenoate (**104**). Reduction of the resulting ester with diisobutylaluminum hydride afforded the all-*trans* allylic alcohol **103**. Clean conversion to allylic chloride **108** was followed by treatment with tri-*n*-butylstannyl lithium[22] and deprotection of the resultant allylstannane **109**

afforded the cyclization precursor **102** (Scheme 22). Homoallylic alcohol **102** was exposed to triflic anhydride and collidine at low temperature under a variety of solvent conditions to afford a mixture of three bicyclopropanes (**110**, **111**, and **112**). The structural assignments made to **110** and **111** are discussed in section 2.3.2.



Scheme 22: Synthesis and Solvolysis of a *trans,trans* Homoallylic Triflate

The ratio of the three cyclopropanes observed in the product mixture from **102** was independent of the reaction conditions (Table 2). Optimized conditions were identical to those utilized for the cyclization of **93** to **79** and afforded a quantitative recovery of **110**, **111**, and **112** as a 2.3:1:1 mixture.

Leaving Group	Solvent Conditions	Temp.	Reaction Time	Product Ratio 110:111:112	Yield
OTf	THF	-78 °C	1 hour	n.d.	39%
OTf	CH_2Cl_2:hexanes (1:1)	-78 °C	1 hour	2.3:1.3:1	81%
OTf	CH_2Cl_2:hexanes (5:1)	-78 °C	1 hour	2.2:1.2:1	72%
OTf	CH_2Cl_2	-78 °C	20 minutes	2.3:1:1	99%
OTf	$CHCl_3$: CH_2Cl_2 (1.25:1)	-78 °C	15 minutes	2.2:1.2:1	86%

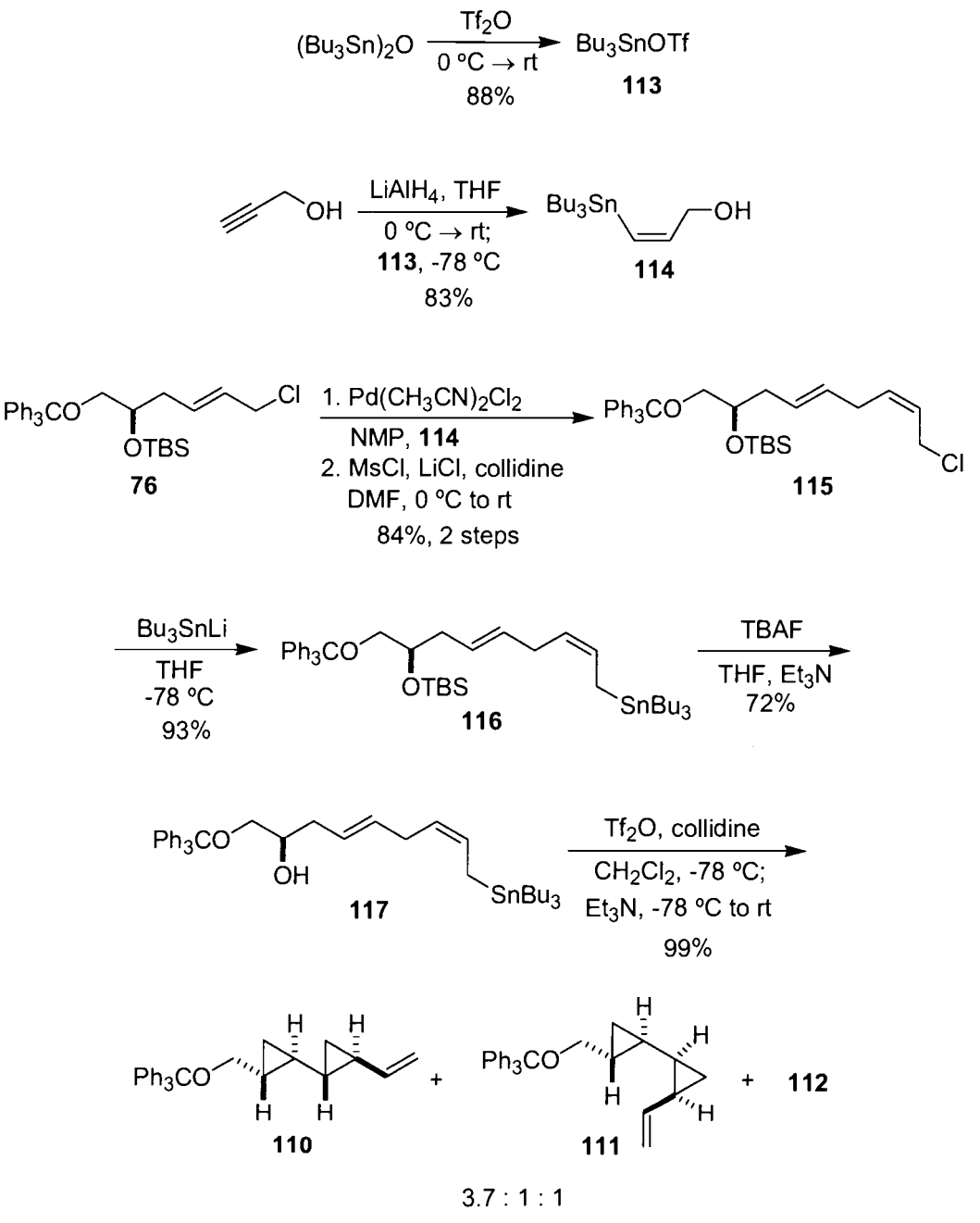
Table 2: Product Ratios Determined by Chiral HPLC

The ratio of products was initially determined by the three sets of bicyclopropane signals in the ^{13}C NMR spectrum of the mixture. HPLC analysis on stationary phase chiral HPLC confirmed the ratio of products as 2.3:1:1 and showed the products to be enantiomerically pure within the limit of detection. This latter observation establishes that no racemization of the triflate from **102** occurs prior to cyclopropane formation.

2.3.2 INFLUENCE OF DOUBLE BOND GEOMETRY ON DIASTEREOSELECTIVITY

The increased efficiency in the cyclization of *cis*-homoallylic alcohol **93** to cyclopropane **79** suggested that incorporation of a *trans,cis* skipped diene would allow for a more stereoselective cascade process. For this purpose, we prepared *cis*-3-(tri-*n*-butylstannyl)-2-propenol **114**[25] from propargyl alcohol and tri-*n*-butyltin triflate **113** and coupled this stannane in a Stille reaction[26] with *trans* allylic chloride **76** (Scheme 23). Conversion of the resulting alcohol to allylic chloride **115** was followed by

displacement with lithio tri-*n*-butylstannane[22] to afford allylstannane **116**. In contrast to the *trans,trans* skipped diene **109**, cleavage of the silyl ether from **116** proved to be problematic. A roughly 50:50 mixture of both the desired alcohol **117** and destannylated material was recovered from this reaction. Addition of an excess of triethylamine to the reaction mixture prior to the addition of tetra-*n*-butylammonium fluoride resulted in a two-fold increase in yield, with only a minor amount of proto-destannylation observed. Treatment of **117** with triflic anhydride in collidine resulted in the formation of three inseparable biclopropane products identical to those obtained from the cyclization of **102**. The yield was again quantitative but there was only a modest increase in stereoselectivity to 3.7:1:1

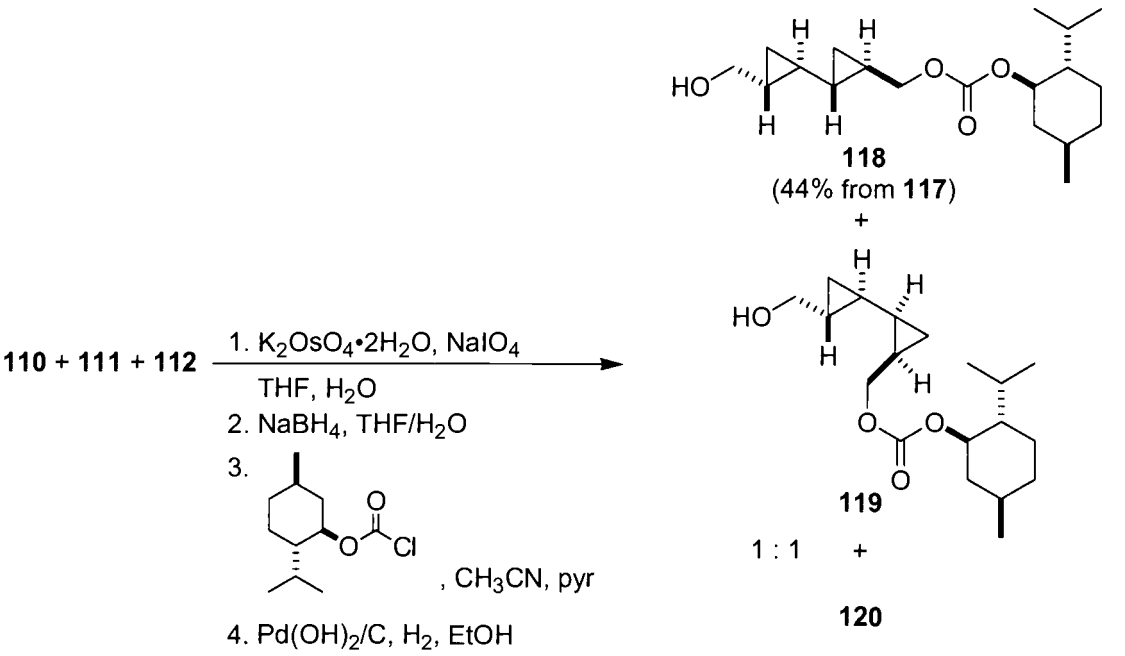


Scheme 23: Synthesis and Solvolysis of a *trans,cis* Homoallylic Triflate

2.3.3 ISOLATION AND STRUCTURAL DETERMINATION OF REACTION PRODUCTS

In order to determine the configuration of the major isomer **110** from the cyclization of **117**, the mixture of bicyclopropanes was oxidized with potassium osmate and sodium periodate and the resultant aldehydes were reduced to primary

alcohols (Scheme 24). These alcohols were then reacted with (–)-menthyl chloroformate and the trityl group was removed by hydrogenolysis to give a mixture from which the major stereoisomer was separated by chromatography and was crystallized. This compound was shown by X-ray crystallographic analysis to possess the relative configuration of *trans,syn,trans*-bicyclopropane **118**, the absolute configuration being defined by the configuration of (–)-menthol (Figure 13).



Scheme 24: Isolation and Characterization of the Major Diastereomer **118** from the Cyclization of **117**

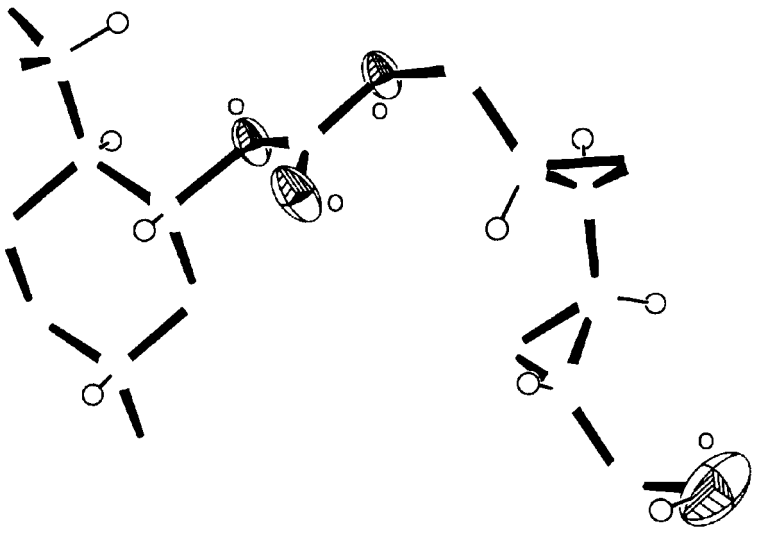
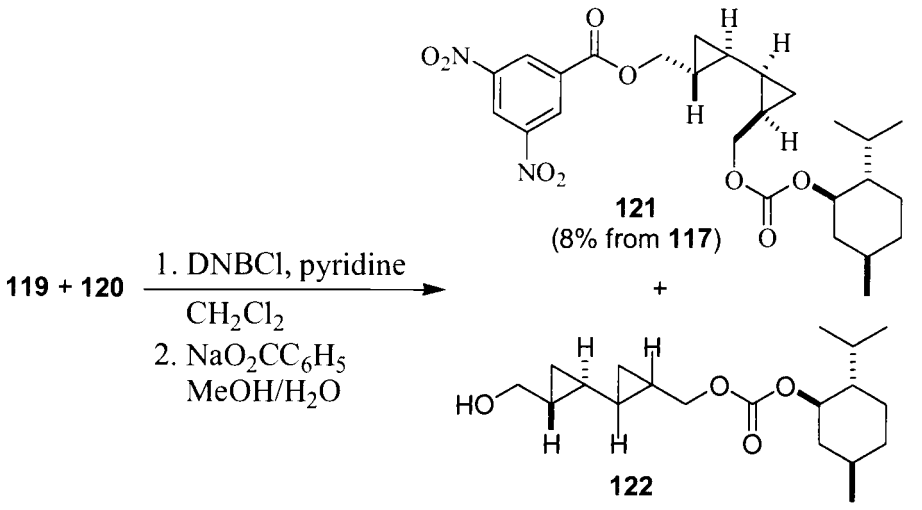


Figure 13: ORTEP of the X-ray Crystal Structure of **118** showing the *trans,syn,trans* Stereochemical Relationship of Cyclopropanes

The inseparable mixture of alcohols **119** and **120** was subsequently transformed into the corresponding 3,5-dinitrobenzoate derivatives. The chromatographically inseparable mixture of 3,5-dinitrobenzoate esters was then treated with sodium benzoate in aqueous methanol (Scheme 25). After 52 h at ambient temperature, TLC analysis indicated ~50% consumption of the starting material. The compound corresponding to starting material (**121**) was isolated as well as a new, more polar compound corresponding to the free alcohol (**122**). Analysis of the ^{1}H NMR and ^{13}C NMR spectra of **121** and **122** showed both compounds to be diastereomerically pure. Dinitrobenzoate **121** also yielded to X-ray crystallographic analysis and was found to have the *trans,anti,cis* configuration (Figure 14). The bicyclopropanes from which **118** and **121** originate are therefore **110** and **111**, respectively, and their structural identification confirms that in each case inversion took place at the hydroxyl-bearing carbon of **117** as the first cyclopropane was formed.



Scheme 25: Conversion of Bicyclopropane **119** to Crystalline Derivative **121**

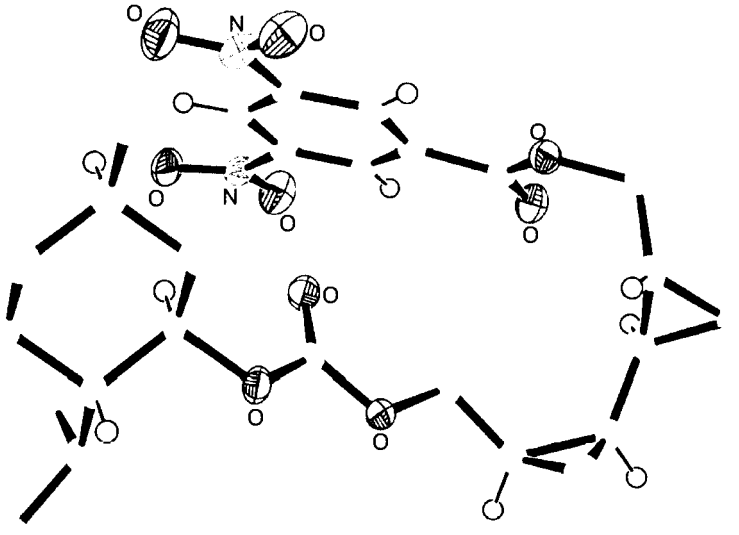
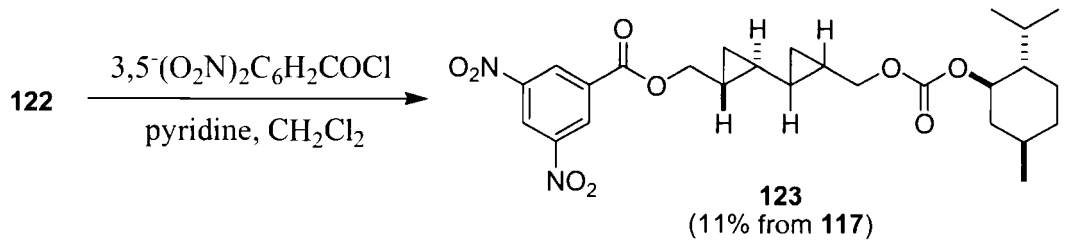


Figure 14: ORTEP of the X-ray Crystal Structure of **121** Showing the *trans,anti,cis* Stereochemical Relationship of Cyclopropanes

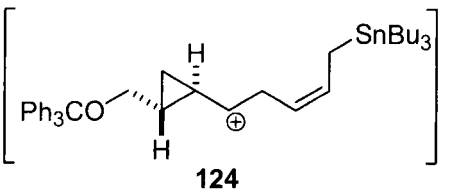
Alcohol **122** was transformed to its crystalline 3,5-dinitrobenzoate derivate **123** (Scheme 26). Unfortunately, the crystals of this third diastereomeric bicyclopropane from the cyclization were of low quality and have not yet yielded to X-ray crystallographic analysis.



123
(11% from **117**)

Scheme 26: Conversion of Bicyclopropane **122** to Crystalline Derivative **123**

From these results, it is proposed that the first cyclization is rapid and stereoselective, and that the diastereomeric mixture of bicyclopropanes arises from a cascade cyclization which is interrupted at monocyclopropylcarbinyl cation **124** (Figure 15). The consequent loss of stereocontrol in the second cyclization event would explain the formation of **111** and perhaps **112**. As previously reported,[12] the cyclopropylcarbinyl cation is highly stabilized due to the empty *p* orbital achieving maximum overlap with the carbon-carbon σ-bonds of the cyclopropane ring. This delocalizes the positive charge originating at the cationic center into the cyclopropane ring. A partially interrupted cyclization in which cyclopropylcarbinyl cation **124** has a discrete lifetime allows for the formation of four possible diastereomers, and it is the only cyclization pathway that would allow both *syn* and *anti* bicyclopropanes to form. The reason for formation of only three of the four possible stereoisomers is not clearly understood, but the absence of a fourth stereoisomer could be due to the destabilization of one of the transition states leading to bicyclopropane formation. The precise course of the cyclization pathway and the absence of a fourth diastereomeric bicyclopropane is difficult to model until compound **123** yields to X-ray crystallographic analysis.



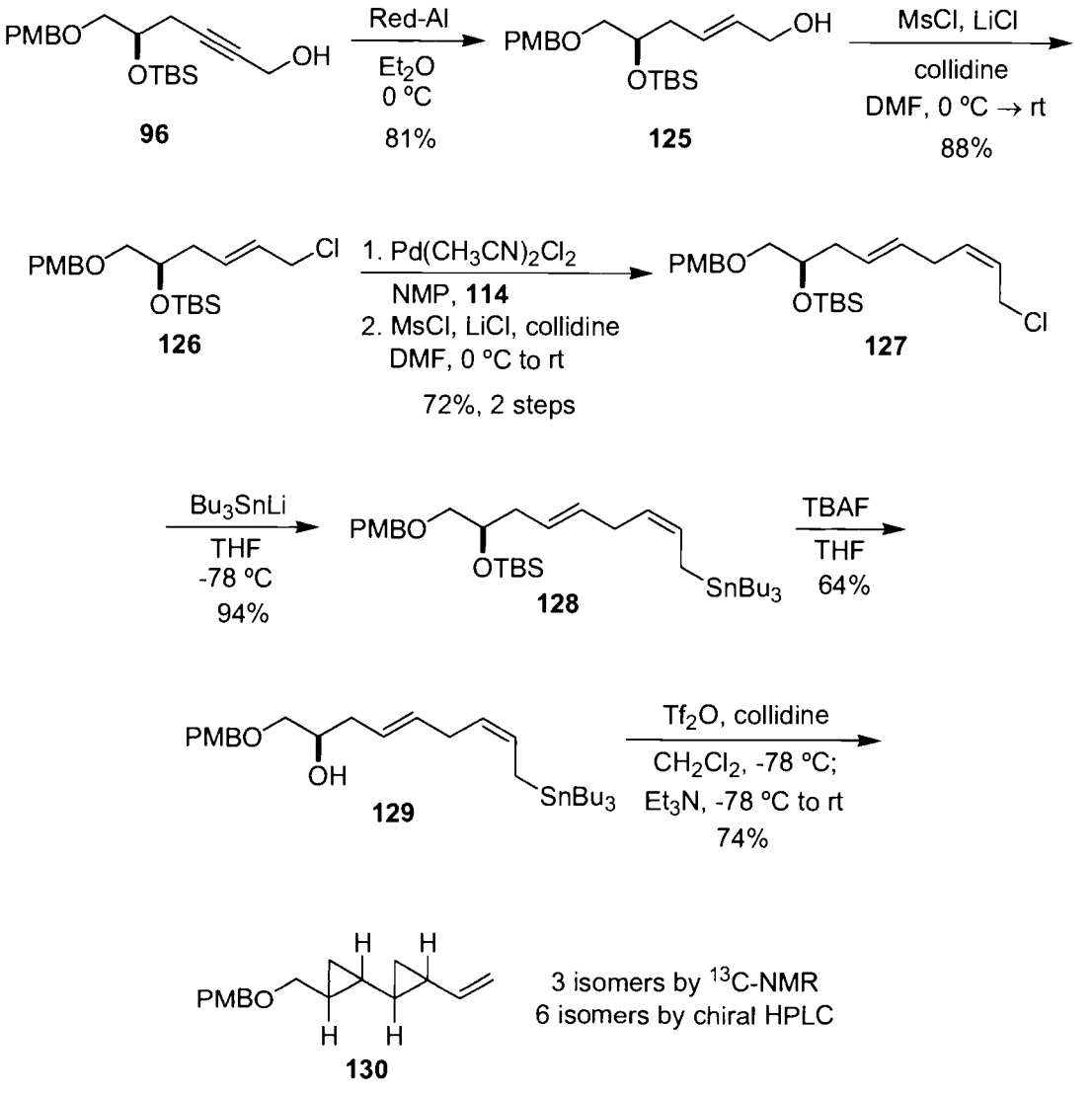
124

Figure 15: Intermediate Cyclopropylcarbinyl Cation **124** in the Interrupted Cyclization of **117**

2.3.4 INFLUENCE OF A PRIMARY *P*-METHOXYBENZYL PROTECTING GROUP ON THE SOLVOLYSIS OF A *TRANS,CIS* HOMOALLYLIC TRIFLATE

Removal of the trityl protecting group under mildly acidic conditions (acetic acid in ethyl acetate) in an attempt to separate and identify the cyclization products resulted in a complex mixture of decomposition products. In order to bypass this problematic deprotection, the synthetic strategy was revised to incorporate a *p*-methoxybenzyl protecting group for the primary alcohol. Propargylic alcohol **96**, an intermediate used for the synthesis of monocyclopropane **79**, was treated with sodium bis(2-methoxyethoxy)aluminum hydride and the resultant alcohol **125** was converted to allylic chloride **126**. A Stille reaction with *cis*-3-(tri-*n*-butylstannyl)-2-propenol **114**, was followed by conversion of the resulting alcohol to allylic chloride **127**. Displacement of **127** with lithio tri-*n*-butylstannane[22] afforded allylstannane **128**, and liberation of the secondary alcohol then gave cyclization precursor **129**. It was observed that the cyclization of the *p*-methoxybenzyl protected skipped diene, under conditions identical to those used for the cyclization of **117**, was extremely sluggish and did not proceed until the reaction was warmed to – 50 °C. Analysis of the ^{13}C NMR spectrum of the product mixture indicated three bicyclopropane stereoisomers in a ratio comparable to that observed for the cyclization of **102** and **116**. However, stationary phase chiral HPLC showed the presence of six stereoisomeric

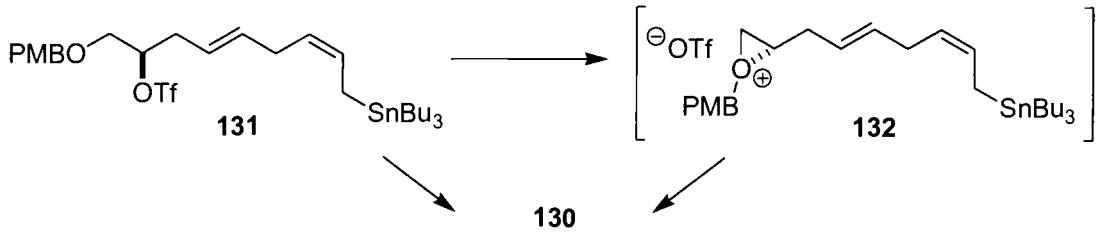
bicyclopropanes (Scheme 27). From the latter analysis, it was clear that a degree of racemization had occurred during the cyclization of **129**.



Scheme 27: Synthesis and Solvolysis of a *p*-Methoxybenzyl Protected *trans,cis* Homoallylic Triflate

Since the enantiomeric mixture of bicyclopropanes seen from this reaction must arise from stereochemical randomization at the reacting chiral center, a possible explanation is that at -50 °C, the *p*-methoxybenzyl ether internally displaces the in-situ generated triflate (**131**) competitively with "zipper" cyclization. This would afford six

products arising from both inversion at the triflate bearing carbon through direct displacement and a double inversion, *ie* overall retention, due to neighboring group participation (Scheme 28).



Scheme 28: Rationale for the Stereochemical Randomization in the Cyclization of **129**

2.4 SYNTHESIS AND SOLVOLYSIS OF AN ALL-*TRANS* SKIPPED TETRAENE HOMOALLYLIC TRIFLATE

The successful synthesis and isolation of *trans,syn,trans*-bicyclopropane **118** led us to attempt the synthesis of an all-*trans* skipped tetraene **133**. Upon treatment under conditions identical to those used for the cyclization of **117**, **133** could potentially yield a quatercyclopropane (Figure 16).

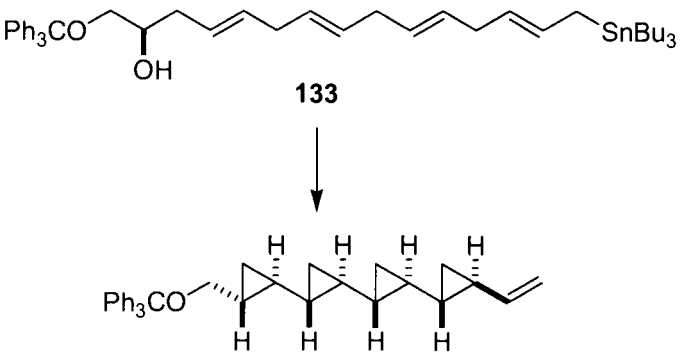
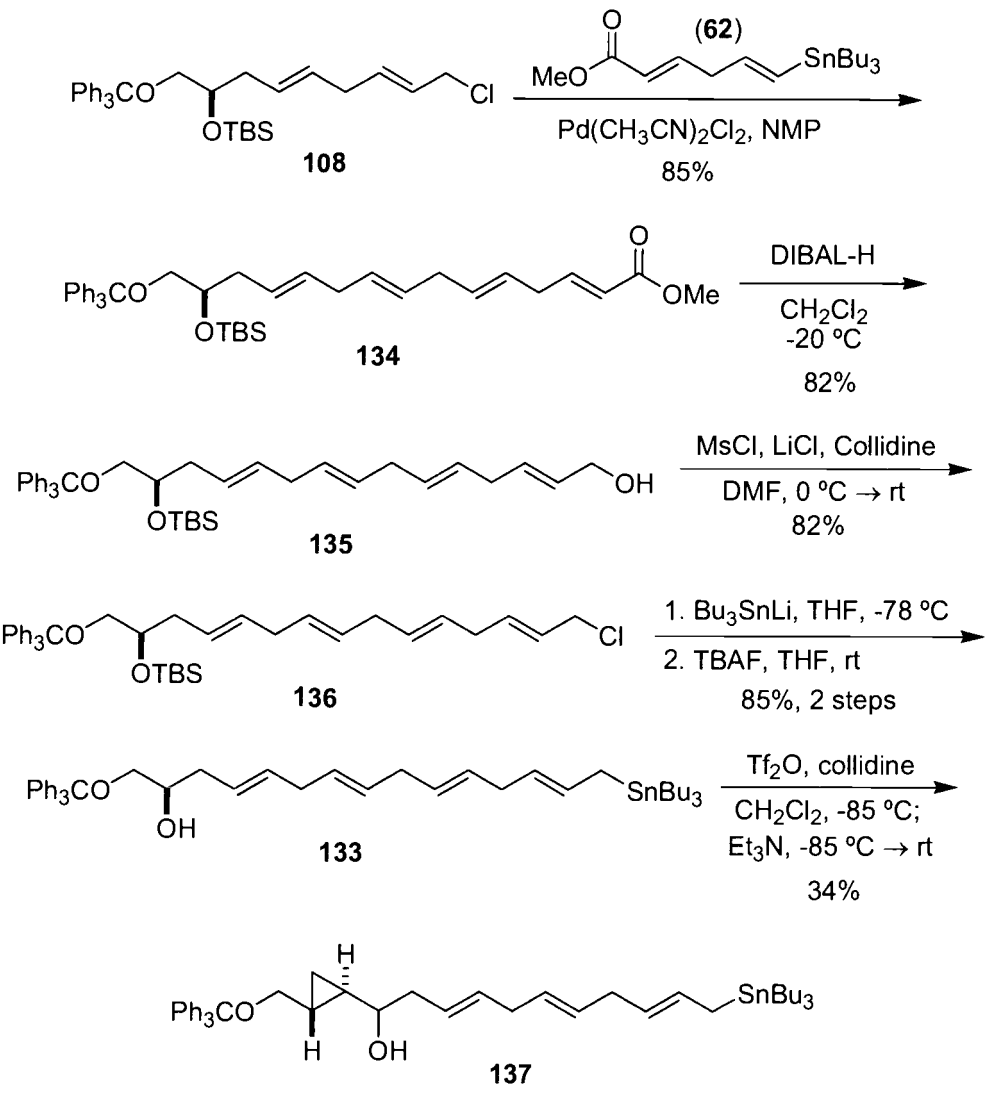


Figure 16: Desired Quatercyclopropane Cyclization Precursor

The synthesis of **133** commenced from a Stille coupling of *trans,trans*-allylic alcohol **108** and *trans,trans*-vinylstannane **62** to yield the all-*trans*-skipped tetraene **134**. Reduction of ester **134** with diisobutylaluminum hydride afforded allylic alcohol **135** which was transformed into allylic chloride **136**. Displacement of the chloride

with tri-*n*-butylstannyl lithium,[22] followed by liberation of the secondary alcohol yielded cyclization precursor **133**. Exposure of **133** to triflic anhydride at low temperature followed by addition of triethylamine, warming to ambient temperature and an aqueous workup resulted in the formation of no less than eight products by TLC. Analysis of the ^{1}H NMR spectrum of one of the more polar products, showed the presence of cyclopropyl protons at δ 0.43 (dt, J = 5.0, 8.5 Hz, 1H) and 0.57 (dt, J = 5.0, 8.5 Hz, 1H). Further analysis of the ^{1}H NMR and ^{13}C NMR spectra of this product indicated that it contained a single cyclopropane and that three of the four alkenes had been retained. An IR spectrum and HRMS helped to confirm the formation of α-hydroxycyclopropane **137** as a single diasteomer in which the allylstannane terminus was still present (Scheme 29). The configuration of the alcohol in **137** was not determined.



Scheme 29: Synthesis and Solvolysis of an all-*trans* Skipped Tetraene Homoallylic Triflate

The formation of **137** provides further support for an interrupted cyclization pathway where the cyclopropylcarbinyl cation **138** fails to cyclize further and is trapped by water upon aqueous workup (Figure 17). Since subsequent cyclization of **138** would not result in the formation of a more stable carbocation, the reaction stalls at monocyclopropylcarbinyl cation **138**. Unlike the formation of bicyclopropanes **110**, **111**, and **112**, in which the cyclization is terminated at a β-stannyl stabilized

cyclopropylcarbinyl cation, the stannane moiety is too far removed from the reacting center to allow the cyclization to progress past **138**.

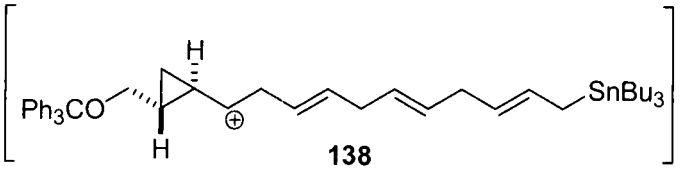


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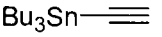
Figure 17: Terminating Cyclopropylcarbinyl Cation in the Cyclization of **133**

2.5 EXPERIMENTAL SECTION

General techniques: All reactions requiring anhydrous conditions were conducted in flame-dried glass apparatus under an atmosphere of argon. THF and Et_2O were freshly distilled from sodium benzophenone ketyl prior to use. DMSO and DMF were distilled from CaH_2 at 15 mm Hg. CH_2Cl_2 was freshly distilled from CaH_2, and PhMe was distilled from molten sodium metal. Anhydrous MeOH was obtained by distillation from magnesium alkoxide and stored under argon over activated 4Å molecular sieves. Preparative chromatographic separations were performed on silica gel (35-75 μm); reactions were followed by TLC analysis using silica plates with fluorescent indicator (254 nm) and visualized with UV, phosphomolybdic acid or 4-hydroxy-3-methoxybenzaldehyde. All commercially available reagents were purchased from Aldrich and were typically used as supplied.

Melting points were recorded using open capillary tubes on a Büchi melting point apparatus and are uncorrected. Optical rotations were measured at ambient temperature (22 °C) on $CHCl_3$ solutions with a polarimeter using a 1 mL capacity cell with 1 dm path length. Infrared spectra were recorded on a Nicolet 5DXB spectrometer using a thin film supported between NaCl plates or KBr discs. ^1H and ^{13}C NMR spectra were recorded in Fourier transform mode at the field strength specified either on a Bruker AC300 or AM400 spectrometer. Spectra were obtained on $CDCl_3$ solutions in 5 mm diameter tubes, and the chemical shift in ppm is quoted relative to the residual signals of chloroform (δ_H 7.25 ppm, or δ_C 77.0 ppm). Multiplicities in the ^1H NMR spectra are described as: s = singlet, d = doublet, t = triplet, q= quartet, m = multiplet, br = broad; coupling constants are reported in Hz.

Low (MS) and high (HRMS) resolution mass spectra were measured on a Kratos MS50 spectrometer. Ion mass/charge (*m/z*) ratios are reported as values in atomic mass units.



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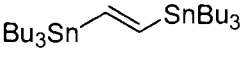
Tri-*n*-butyl(ethynyl)stannane. Lithium acetylide, ethylene diamine complex (75 g, 25 wt% in toluene, 204 mmol) was taken up in THF (450 mL) and cooled to 0 °C under argon. Tributyltin chloride (57.5 g, 96%, 48.0 mL, 170 mmol) was added dropwise *via* syringe over a period of 1.5 h and the mixture was warmed to ambient temperarture. After 80 h, the reaction was quenched with H_2O (29 mL), concentrated under reduced pressure, and the resulting viscous oil was extracted with hexanes (3 x 250 mL). The organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified *via* distillation (80-90 °C, 0.10 mmHg) to yield 26.9 g (50%) of tri-*n*-butyl(ethynyl)stannane as a clear colorless oil: IR (film) 3284, 3265, 2956, 2925, 2870, 2852, 2003, 1463, 1418, 1378 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.21 0.92 (t, J = 7.2 Hz, 9H), 0.99-1.05 (m, 6H), 1.29-1.41 (m, 6H), (s, 1H), 1.53-1.61 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.0, 13.6, 26.9, 28.8, 88.9, 96.8.



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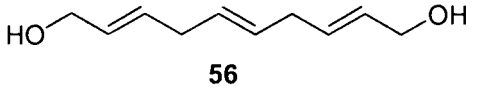
(*E*)-1,2-Bis(tri-*n*-butylstannyl)ethylene. Tri-*n*-butyl(ethynyl)stannane (8.79 g, 27.9 mmol) was added to a stirred suspension of tri-*n*-butyltin hydride (10.04 g, 97%, 33.5 mmol) and AIBN (117 mg, 0.70 mmol, 2.5 mol%) under argon and the mixture was heated slowly to 90 °C. After 17 h, the reaction mixture was allowed to cool to

ambient temperature, and stannyl impurities were removed *via* short path distillation (60-65 °C, 0.075 mmHg). The remaining material was purified on a short column of silica gel (50% EtOAc in hexanes) to afford 16.9 g (99%) of (*E*)-1,2-bis(tri-*n*-butylstannyl)ethylene as a clear colorless oil: IR (film) 2950, 2920, 2870, 2852, 1465, 1372 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.08-1.00 (m, 30H), 1.27-1.39 (m, 12H), 1.47-1.61 (m, 12H), 6.90 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.8, 14.0, 27.5, 29.4, 153.2.



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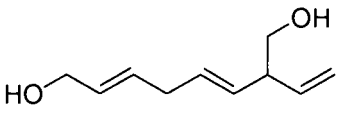
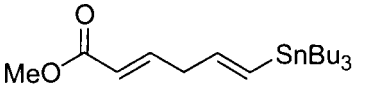


60

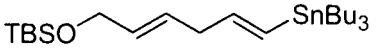
(2*E*,5*E*,8*E*)-Deca-2,5,8-triene-1,10-diol and (2*E*,5*E*)-7-Vinylocta-2,5-diene-1,8-diol. A solution of bis(acetonitrile)palladium(II) chloride (170 mg, 10 mol%) in DMF (20 mL) was cooled to 0 °C under argon and H_2O (20 mL) was added. Butadiene monoxide (1.14 mL, 98%, 13.9 mmol) was added drowise *via* syringe, the mixture was stirred 20 min, (*E*)-1,2-bis(tri-*n*-butylstannyl)ethylene (4.00 g, 6.60 mmol) was added over 20 min and the reaction was allowed to warm to ambient temperature. After 20 h, the suspension was filtered through a pad of Celite (50% EtOAc in hexane) and the filtrate was concentrated under reduced pressure. The residue was purified on a column of silica gel (10-100% EtOAc in hexane) to yield 843 mg (76%) of (2*E*,5*E*,8*E*)-deca-2,5,8-triene-1,10-diol and (2*E*,5*E*)-7-vinylocta-2,5-diene-1,8-diol as a 1:1 mixture of regioisomeric products: IR (film) 3336, 3077, 3023, 3003, 2974, 2920, 2867, 1421, 1367, 1308, 1225 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.88 (brs, 2H), 2.72-2.99 (m, 4H), 3.52 (d, J = 6.9 Hz, 1H), 4.05-4.19 (m, 4H), 5.08-5.17 (m, 1H), 5.33-5.80 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.1, 35.2, 49.6, 63.4,

65.1, 116.7, 129.0, 129.7, 129.9, 130.5, 130.6, 131.0, 137.8; MS (CI) *m/z* 151 (M-OH)$^+$, 133, 121, 107, 97, 91, 89, 79, 71, 67; HRMS (CI) *m/z* 151.1123 (calcd for $C_{10}H_{15}O$ (M-OH)$^+$: 151.1120).



62

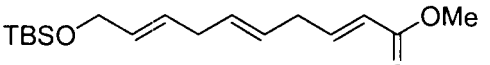
(2*E*,5*E*)-6-(Tri-*n*-butylstannyl)-hexa-2,5-dienoic acid Methyl Ester. (*E*)-1,2-Bis(tri-*n*-butylstannyl)ethylene (20.0 g, 33.0 mmol), methyl (*E*)-4-bromo2-butenoate (4.15 g, 95%, 22.0 mmol), bis(acetonitrile)palladium(II) chloride (101 mg, 2 mol%), and $AsPh_3$ (66.7 mg, 1 mol%) were taken up in dry $CHCl_3$ (75 mL), degassed with an argon bubbler for 30 min, and heated to 50 °C. After 5 days, the reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was purified on a short column of silica gel (0-40% EtOAc in hexane) to give 3.91 g (43%) of (2*E*,5*E*)-6-(tri-*n*-butylstannyl)-hexa-2,5-dienoic acid methyl ester as a colorless oil: IR (film) 2952, 2924, 2870, 2849, 1728, 1656, 1591, 1462, 1434, 1332 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75-1.00 (m, 15H), 1.20-1.70 (m, 12H), 3.03 (t, *J* = 5.8 Hz, 2H), 3.73 (s, 3H), 5.78-6.10 (m, 3H), 6.99 (dt, *J* = 6.7, 6.9, 15.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.4, 13.7, 27.3, 29.1, 40.2, 51.4, 121.4, 131.8, 143.3, 147.2, 167.1; MS (CI) *m/z* 359 (M-C_4H_9)$^+$, 303, 247, 213, 179, 151, 149, 121; HRMS (CI) m/*z* 417.1809 (calcd for $C_{19}H_{37}O_2{}^{120}Sn$ (M+H)$^+$: 417.1816).



63

(2*E*,5*E*)-1-(*tert*-Butyldimethylsilyloxy)-6-tri-*n*-butylstannylhexa-2,5-diene. (2*E*,5*E*)-6-(Tri-*n*-butylstannyl)-hexa-2,5-dienoic acid methyl ester (1.31 g, 3.15 mmol) was taken up in THF (20 mL) and cooled to -20 °C under argon. DIBAl-H (1.24 mL,

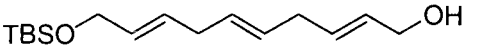
6.94 mmol) was added slowly, and the mixture was stirred for 10 min and then quenched with saturated aqueous Na^+/K^+ tartrate (20 mL). After 4 h of vigorous stirring, the organic phase was washed with brine (10 mL) and the combined aqueous fractions were extracted with Et_2O (10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, concentrated under reduced pressure. The resulting crude product, TBSCl (1.04 mL, 50 wt% in toluene, 1.21 mmol) and imidazole (214 mg, 3.13 mmol) were taken up in THF (20 mL) and the reaction flask was evacuated with argon. After 14 h at ambient temperature, the entire reaction mixture was added to a separatory funnel containing H_2O (10 mL) and extracted with Et_2O (15 mL). The organic fraction was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification on a column of silica gel (5-15% EtOAc in hexane) afforded 1.27 g (80%, 2 steps) of (2*E*,5*E*)-1-(*tert*-butyldimethylsilyloxy)-6-(tri-*n*-butylstannyl)-hexa-2,5-diene: IR (neat) 3014, 2956, 2927, 2856, 1596, 1463, 1419, 1377, 1361, 1255 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.75-1.00 (m, 25H), 1.23-1.38 (m, 6H), 1.40-1.62 (m, 6H), 2.75-3.00 (m, 2H), 4.16 (dd, J = 1.2, 5.1 Hz, 2H), 5.50-6.15 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.1, 9.4, 13.7, 18.4, 26.0, 27.7, 29.1, 40.4, 64.0, 128.8, 129.0, 130.2, 146.6; MS (CI) *m/z* 445 $(M-C_4H_9)^+$, 437, 389, 365, 309, 291, 235, 209, 193, 147, 105; HRMS (CI) *m/z* 501.2582 (calcd for $C_{24}H_{49}OSi^{120}Sn$ $(M-H)^+$: 501.2575).



64

(2*E*,5*E*,8*E*)-10-(*tert*-Butyldimethylsiloxy)-deca-2,5,8-trienoic acid Methyl Ester. (2*E*,5*E*)-1-(*tert*-butyldimethylsilyloxy)-6-(tri-*n*-butylstannyl)-hexa-2,5-diene (1.23 g, 2.45 mmol), methyl 4-bromo2-butenoate (620 mg, 85% tech, 2.94 mmol),

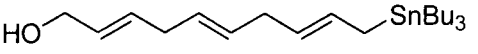
bis(acetonitrile)palladium(II) chloride (25.5 mg, 4 mol%), and PPh_3 (12.9 mg, 2 mol%) were taken up in $CHCl_3$ (5 mL), degassed with an argon bubbler for 20 min, and heated to 80 °C. After 60 h, the mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was purified on a short column of silica gelplug (0-10% EtOAc in hexane containing 1% Et_3N) to afford 374 mg (57%) of (2*E*,5*E*,8*E*)-10-(*tert*-butyldimethylsiloxy)-deca-2,5,8-trienoic acid methyl ester as a colorless oil: IR (film) 3021, 2954, 2930, 2895, 2857, 1728, 1656, 1472, 1463, 1328, 1272, 1210 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.91 (s, 9H), 2.72-2.80 (m, 2H), 2.86-2.95 (m, 2H), 3.73 (s, 3H), 4.11-4.16 (m, 2H), 5.38-5.70 (m, 4H), 5.83 (dt, J = 1.7, 15.7 Hz, 1H), 6.97 (dt, J = 6.5, 15.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.2, 18.4, 26.0, 35.0, 35.1, 51.4, 63.8, 121.3, 126.2, 128.7, 130.3, 131.2, 147.5, 167.0; MS (CI) *m/z* 279 $(M-C_2H_6)^+$, 253, 167, 149, 132, 117, 89, 75; HRMS (CI) m/*z* 309.1879 (calcd for $C_{17}H_{29}O_3Si$ $(M-H)^+$: 309.1886).



65

(2*E*,5*E*,8*E*)-10-(*tert*-Butyldimethylsiloxy)-deca-2,5,8-trien-1-ol. (2*E*,5*E*,8*E*)-10-(*tert*-Butyldimethylsiloxy)-deca-2,5,8-trienoic acid methyl ester (1.88 g, 6.05 mmol) was taken up in CH_2Cl_2 (100 mL) and cooled to -20 °C under argon. DIBAl-H (2.37 mL, 13.3 mmol) was added slowly, the mixture was stirred for 10 min and then quenched with saturated aqueous Na^+/K^+ tartrate (100 mL). After 4 h of vigorous stirring, the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL), and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (5-40% EtOAc in hexane containing 1% Et_3N) to yield 1.34 g (78%) of (2*E*,5*E*,8*E*)-10-(*tert*-

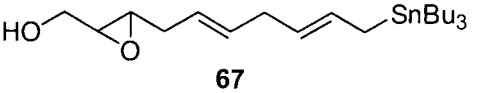
butyldimethylsiloxy)-deca-2,5,8-trien-1-ol as a colorless oil: IR (neat) 3336, 3077, 2959, 2930, 2896, 2857, 2739, 2710, 1670, 1641, 1469, 1430, 1377, 1362, 1259, 1098 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.91 (s, 9H), 1.39 (brs, 1H), 2.69-2.85 (m, 4H), 4.11 (d, J = 4.4 Hz, 2H), 4.14 (dd, J = 1.1, 4.9 Hz, 2H), 5.38-5.77 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.3, 18.4, 26.0, 35.1, 38.9, 63.6, 63.9, 128.7, 129.2, 129.4, 129.6, 130.0, 131.3; MS (CI) *m/z* 281 $(M-H)^+$, 265, 225, 209, 171, 157, 151, 145, 133, 119, 115; HRMS (CI) *m/z* 283.2093 (calcd for $C_{16}H_{31}O_2Si$ $(M+H)^+$: 283.2096).



66

(2*E*,5*E*,8*E*)-10-(Tri-*n*-butylstannyl)-deca-2,5,8-trien-1-ol. Methanesulfonyl chloride (20.6 μL, 0.27 mmol) was added dropwise *via* syringe to a stirred suspension of (2*E*,5*E*,8*E*)-10-(*tert*-butyldimethylsiloxy)-deca-2,5,8-triene-1-ol (50 mg, 0.18 mmol), collidine (117 μL, 0.90 mmol) and LiCl (7.5 mg, 0.20 mmol) in DMF (1.5 mL) at 0 °C under argon. The resulting mixture was allowed to warm to ambient temperature and was stirred for 20 h. The mixture was placed in a separatory funnel containing Et_2O/pentane (1:1, 15 mL) and saturated aqueous $NaHCO_3$ (10 mL). The aqueous phase was extracted with Et_2O/pentane (1:1, 5 mL) and the combined organic fractions were washed with saturated aqueous $Cu(NO_3)_2$ (2 x 20 mL), dried (Na_2SO_4), filtered, concentrated under reduced pressure and dried *in vacuo*. *n*-BuLi (51.2 μL, 3.46 M in hexanes) was added slowly to a stirred solution of hexa-*n*-butylditin (224 μL , 256.5 mg) in THF (1.5 mL) 0 °C under argon, and the mixture was cooled to -68 °C. After 1.5 h, a solution of the crude allylic alcohol in THF (2 mL) was added

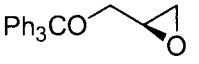
slowly. After 3 h, the mixture was diluted with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (10 mL). The organic extract was washed with saturated aqueous NH_4Cl, dried (Na_2SO_4), filtered, concentrated under reduced pressure and dried *in vacuo*. TBAF (77 μL, 1 M in THF) was added dropwise *via* syringe to a stirred solution of the crude allylic stannane in THF (1 mL) under argon. After 13 h, the mixture was placed in a separatory funnel containing EtOAc (20 mL) and saturated aqueous NH_4Cl (20 mL), and the aqueous phase was extracted with EtOAc (10 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified on a short column of silica gel (0-20% EtOAc in hexane containing 1% Et_3N) to afford 21.0 mg (27%, 3 steps) of (2*E*,5*E*,8*E*)-10-(tri-*n*-butylstannyl)-deca-2,5,8-trien-1-ol: IR (neat) 3350, 3010, 2954, 2923, 2870, 2853, 1465, 1455, 1428, 1418; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82-0.94 (m, 15H), 1.22-1.35 (m, 6H), 1.42-1.55 (m, 6H), 1.73 (d, J = 5.3 Hz, 2H), 2.61-2.82 (m, 4H), 4.11 (d, J = 4.4 Hz, 2H), 5.14-5.26 (m, 1H), 5.39-5.45 (m, 2H), 5.46-5.63 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.2, 13.7, 14.2, 27.3, 29.1, 35.2, 35.7, 63.7, 123.4, 127.6, 129.5, 130.2, 130.9, 131.6; MS (CI) *m/z* 442 $(M)^+$, 385, 367, 327, 291, 251, 235, 179, 121, 91, 79; HRMS (CI) *m/z* 442.2259 (calcd $C_{22}H_{42}O^{120}Sn$ 442.2258).



67

(5*E*,8*E*)-2,3-Epoxy-10-(tri-*n*-butylstannyl)-deca-5,8-dien-1-ol. (2*E*,5*E*,8*E*)-10-(Tri-*n*-butylstannyl)-deca-2,5,8-trien-1-ol (18 mg, 4.08 x 10^{-5} mol) was taken up in dry benzene (1 mL) containing powdered 4Å molecular sieves. The flask was evacuated with argon and the mixture was treated with vanadyl acetylacetonate (1.6 mg (95%),

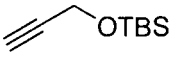
5.71 x 10^{-6} mol) followed by *tert*-butyl hydroperoxide (27.3 μL of a 2.99 M solution in toluene). After 1 hr, the reaction mixture was quenched with 10% aqueous $Na_2S_2O_3$, and the mixture was added to a separatory funnel containing brine (10 mL) and EtOAc (20 mL). The aqueous phase was extracted with EtOAc (5 mL), and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification on a column of silica gel (10-20% EtOAc in hexanes containing 1% Et_3N) gave 8.0 mg (43%) of (5*E*,8*E*)-2,3-epoxy-10-(tri-*n*-butylstannyl)-deca-5,8-dien-1-ol: IR (neat) 3417, 3011, 2956, 2924, 2871, 2853, 1650, 1463, 1376, 1260, 1073; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82-0.94 (m, 15H), 1.21-1.37 (m, 6H), 1.45-1.53 (m, 6H), 1.67-1.75 (m, 2H), 2.17-2.40 (m, 2H), 2.65-2.76 (m, 2H), 2.93-2.98 (m, 1H), 3.02 (td, J = 2.4, 5.4 Hz, 1H), 3.59-3.71 (m, 1H), 3.88-3.98 (m, 1H), 5.13-5.26 (m, 1H), 5.34-5.64 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.2, 13.7, 14.3, 27.3, 29.1, 34.5, 133.1, 35.8, 55.2, 57.9, 61.6, 123.1, 123.9, 130.5; MS (CI) *m/z* 458 $(M)^+$, 416, 401, 383, 291, 251, 235, 179, 121; HRMS (CI) *m/z* 458.2209 (calcd $C_{22}H_{42}O_2{}^{120}Sn$ 458.2207).



71

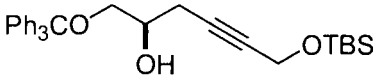
(*R*)-Glycidol Trityl Ether. *S*-(–)-Glycidol (4.98 g, 97%, 98% *ee*, 65.3 mmol) was added dropwise *via* syringe to a stirred solution of triphenylmethyl chloride (20.0 g, 72.5 mmol) and Et_3N (10.0 mL, 71.8 mmol) in CH_2Cl_2 (46 mL) at 0 °C under argon. After complete addition, the mixture was allowed to warm to ambient temperature. After 18.5 h, the entire mixture was added to a separatory funnel containing saturated aqueous NH_4Cl (20 mL). The organic phase was washed with saturated aqueous NH_4Cl (1 mL) and the combined aqueous phases were extracted with CH_2Cl_2 (20 mL).

The organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Recrystallization from hot isopropyl alcohol afforded 19.0 g (92%) of (*R*)-glycidol trityl ether: $[\alpha]_D^{23}$ + 11.2 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.63 (dd, *J* = 2.4, 5.1 Hz, 1H), 2.76-2.82 (m, 1H), 3.10-3.20 (m, 2H), 3.29-3.38 (m, 1H), 7.21-7.36 (m, 9H), 7.44-7.51 (m, 6H); ^{13}C NMR (75 MHz, acetone-d6) δ 44.6, 51.0, 64.8, 86.7, 127.1, 127.8, 128.7, 143.8.



72

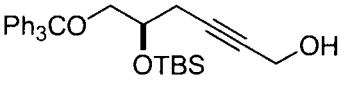
1-(*tert*-Butyldimethylsilyloxy)-prop-2-yne. TBSCl (14.98 g, 98%, 97.1 mmol) and imidazole (6.62 g, 99%, 97.1 mmol) were taken up in DMF (150 mL) under argon. Propargyl alcohol (5.19 g, 99%, 91.7 mmol) was added dropwise *via* syringe, and the mixture was stirred at ambient temperature under argon. After 22 h, the entire reaction mixture was added to a separatory funnel containing H_2O (200 mL) and was extracted with Et_2O (200, then 2 x 100 mL). The combined extracts were washed with H_2O (20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue on a short column of silica gel (20% EtOAc in hexane) afforded 14.9 g (95%) of 1-(*tert*-butyldimethylsilyloxy)-prop-2-yne: ^1H NMR (300 MHz, $CDCl_3$) δ 0.11 (s, 6H), 0.90 (s, 9H), 2.38 (t, *J* = 2.4 Hz, 1H), 4.29 (d, *J* = 2.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.3, 18.2, 25.7, 51.4, 72.8, 82.3.



73

(2*R*)-6-(*tert*-Butyldimethylsilyloxy)-1-trityloxy-hex-4-yn-2-ol. *n*-BuLi (2.19 mL, 2.5 M in hexanes) was added to a stirred suspension of 1-(*tert*-butyldimethylsilyloxy)-prop-2-yne (931 mg, 5.47 mmol) in THF (15 mL) at -78 °C under argon. After 30

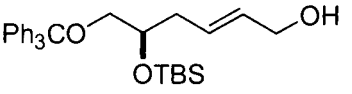
min, (*R*)-glycidyl trityl ether (1.13 g, 3.63 mmol) in THF (2 mL) was added slowly. After an additional 20 min at -78 °C, BF_3•OEt_2 (726 μL, 5.10 mmol) was added slowly, the resulting mixture was stirred at -78 °C for 2 h, then allowed to warm to ambient temperature. After 22 h, the reaction mixture was placed in a separatory funnel containing saturated aqueous NH_4Cl (15 mL) and CH_2Cl_2 (50 mL, 2 x 20 mL). The organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (5-20% EtOAc in hexane) to yield 1.64 g (93%) of (2*R*)-6-(*tert*-butyldimethylsilyloxy)-1-trityloxy-hex-4-yn-2-ol as a colorless oil: $[\alpha]_D^{23}$ -6.70 (c 0.75, $CHCl_3$); IR (neat) 3453, 3086, 3059, 3033, 2953, 2928, 2883, 2857, 1597, 1491, 1471, 1443, 1371, 1254, 1219, 1141, 1076 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.88 (s, 9H), 2.44 (ddt, *J* = 2.1, 6.0, 16.6 Hz, 1H), 2.54 (ddt, *J* = 2.1, 6.4, 16.6 Hz, 1H), 3.17 (dd, *J* = 5.4, 9.2 Hz, 1H), 3.20 (dd, *J* = 5.0, 9.2 Hz, 1H), 3.91 (quintet, *J* = 5.9 Hz, 1H), 4.11 (d, *J* = 5.4 Hz, 1H), 4.23 (t, *J* = 2.1 Hz, 2H), 7.21-7.36 (m, 9H), 7.47-7.53 (m, 6H); ^{13}C NMR (75 MHz, acetone-d_6) δ -4.8, 18.8, 25.1, 52.4, 67.6, 70.1, 81.1, 82.6, 87.3, 127.8, 128.6, 129.6, 1475.2; MS (CI) *m/z* 487 $(M)^+$, 485, 443, 423, 409, 342, 243, 165; HRMS (CI) *m/z* 486.2590 (calcd for $C_{31}H_{38}O_3Si$: 486.2590).



74

(2*R*)-2-(*tert*-Butyldimethylsilyloxy)-1-trityloxy-hex-4-yn-6-ol. (2*R*)-6-(*tert*-Butyldimethylsilyloxy)-1-trityloxy-hex-4-yn-2-ol (1.57 g, 3.22 mmol), TBSCl (531 mg, 97%, 3.42 mmol) and imidazole (233 mg, 3.42 mmol) were taken up in DMF (7 mL) and the reaction flask was purged with argon. After 26 h, the mixture was placed

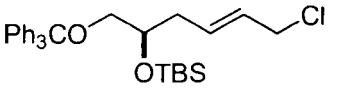
in a separatory funnel containing H_2O (10 mL) and EtOAc (25 mL). The separated organic phase was washed with H_2O (5 mL), dried (Na_2SO_4), filtered, concentrated under reduced pressure, and dried *in vacuo*. TBAF (2.61 mL, 1.0M in THF) was added to a solution of the crude bis-silyl ether in THF (20 mL) under argon. After 1 h, the mixture was placed in a separatory funnel containing saturated aqueous NH_4Cl (10 mL) and CH_2Cl_2 (20 mL). The separated aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified on a short column of silica gel (5-40% EtOAc in hexane) to yield 1.25 g (80%, 2 steps) of (2*R*)-2-(*tert*-butyldimethylsilyloxy)-1-trityloxy-hex-4-yn-6-ol as a colorless oil: $[\alpha]_D^{23}$ - 6.6 (c 1.45, $CHCl_3$); IR (neat) 3362, 3086, 3059, 3033, 2949, 2928, 2883, 2856, 1662, 1597, 1491, 1471, 1448, 1388, 1361, 1255, 1126, 1001 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 1.42 (t, J = 5.8 Hz, 1H), 2.42 (ddt, J = 2.1, 6.2, 16.6 Hz, 1H), 2.62 (ddt, J = 2.1, 6.2, 16.6 Hz, 1H), 3.14 (dd, J = 5.0, 9.3 Hz, 1H), 3.17 (dd, J = 5.3, 9.3 Hz, 1H), 3.88-3.97 (m, 1H), 4.14 (brt, J = 2.6 Hz, 2H), 7.21-7.34 (m, 9H), 7.46-7.51 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.6, -4.8, 18.1, 25.1, 25.8, 51.3, 66.7, 70.6, 83.5, 86.4, 126.9, 127.7, 127.9, 128.7, 144.0; MS (CI) *m/z* 485 $(M+H)^+$, 468, 409, 357, 354, 295, 243, 228, 165; HRMS (CI) *m/z* 486.2579 (calcd for $C_{31}H_{38}O_3Si$: 486.2590).



75

(2*R*,4*E*)-2-(*tert*-Butyldimethylsilyloxy)-1-trityloxy-hex-4-en-6-ol. Red-Al (2.00 mL, 70 wt % in toluene, 6.91 mmol) was added to a stirred solution of (2*R*)-2-(*tert*-

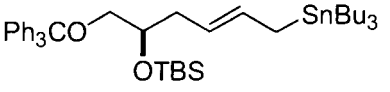
butyldimethylsilyloxy)-1-trityloxy-hex-4-yn-6-ol (1.21 g, 2.49 mmol) in Et_2O (45 mL) at 0 °C under argon. The cooling bath was removed and the reaction mixture was stirred at ambient temperature. After 24 h, the reaction was quenched with saturated aqueous Na^+/K^+ tartrate (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (20% EtOAc in hexane) to yield 1.02 g (84%) of (2*R*,4*E*)-2-(*tert*-butyldimethylsilyloxy)-1-trityloxy-hex-4-en-6-ol as a clear colorless oil: $[\alpha]_D^{23}$ + 2.8 (c 1.0, $CHCl_3$); IR (neat) 3357, 3086, 3059, 3023, 2954, 2928, 2856, 1597, 1491, 1471, 1448, 1388, 1361, 1325, 1254, 1222, 1184, 1154 cm^{-1}; ^1H NMR (300 MHz, acetone-d6) δ -0.01 (s, 3H), 0.02 (s, 3H), (s, 9H), 2.38-2.51 (m, 1H), 2.80-2.86 (m, 1H), 3.04 (dd, *J* = 5.6, 9.3 Hz, 1H), 3.06 (dd, *J* = 5.1, 9.3 Hz, 1H), 3.51 (dt, *J* = 1.6, 5.5 Hz, 1H), 3.88 (quintet, *J* = 5.6 Hz, 1H), 3.91-3.97 (m, 2H), 5.59 (dt, *J* = 1.6, 4.1 Hz, 1H), 7.23-7.37 (m, 9H), 7.46-7.54 (m, 6H); ^{13}C NMR (75 MHz, acetone-d6) δ -3.9, -3.7, 19.2, 26.8, 39.2, 63.6, 63.7, 68.4, 73.0, 87.8, 127.6, 128.4, 129.1, 130.1, 134.4, 145.8; MS (CI) *m/z* 488 $(M)^+$, 470, 411, 271, 243, 215, 165, 117, 79; HRMS (CI) *m/z* 488.2760 (calcd for $C_{31}H_{40}O_3Si$: 488.2747).



76

(2*E*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-1-chloro-6-trityloxy-hex-2-ene. Methanesulfonyl chloride (243.5 μL, 3.14 mmol) was added dropwise *via* syringe to a stirred suspension of (2*R*,4*E*)-2-(*tert*-butyldimethylsilyloxy)-1-trityloxy-hex-4-en-6-ol (1.02 g, 2.09 mmol), collidine (1.37 mL, 10.5 mmol) and LiCl (87.4 mg, 2.30 mmol) in DMF (30 mL) at 0 °C under argon. The resulting mixture was allowed to warm to

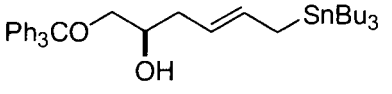
ambient temperature and was stirred for 21 h. The mixture was placed in a separatory funnel containing Et_2O/pentane (1:1, 125 mL) and saturated aqueous $NaHCO_3$ (40 mL). The aqueous phase was extracted with Et_2O/pentane (1:1,10 mL) and the combined organic extracts were washed with saturated aqueous $Cu(NO_3)_2$ (2 x 75 mL). The combined aqueous fractions were extracted with Et_2O/pentane (1:1, 25 mL), and the combined extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified on a short column of silica gel (20% Et_2O in pentane) to yield 1.05 g (99%) of (2*E*,5*R*)-5-(*tert*-butyldimethylsilyloxy)-1-chloro-6-trityloxy-hex-2-ene as a colorless oil: $[\alpha]_D^{23}$ + 1.9 (c 1.0, $CHCl_3$); IR (neat) 3086, 3059, 3033, 2954, 2928, 2883, 2856, 1597, 1491, 1471, 1448, 1361, 1320, 1253, 1220, 1154 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ -0.030 (s, 3H), 0.014 (s, 3H), 0.86 (s, 9H), 2.28 (dt, *J* = 6.3, 14.3 Hz, 1H), 2.99 (dt, *J* = 6.3, 14.3 Hz, 1H), 3.07 (td, *J* = 4.9, 9.3 Hz, 1H), 3.82 (quintet, *J* = 5.6 Hz, 1H), 3.96 (d, *J* = 6.3 Hz, 2H), 5.54-5.76 (m, 2H), 7.20-7.34 (m, 9H), 7.43-7.48 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.8, -4.5, 18.1, 25.8, 37.7, 45.2, 66.9, 71.2, 86.5, 126.9, 127.7, 128.2, 128.7, 132.0, 144.1; MS (CI) *m/z* 506 $(M)^+$, 471, 429, 365, 243, 165, 117; HRMS (CI) *m/z* 506.2402 (calcd for $C_{31}H_{39}O_2Si^{35}Cl$: 506.2408).



77

(2*R*,4*E*)-2-(*tert*-Butyldimethylsilyloxy)-6-(tri-*n*-butylstannyl)-1-trityloxy-hex-2-ene. Tri-*n*-butyltin chloride (11.6 mL, 17.3 g, 96%, 50.5 mmol) was added to finely cut lithium wire (3.51 g) at ambient temperature under argon. THF (45 mL) was added and the mixture was stirred for 7 h. The resulting dark green suspension was

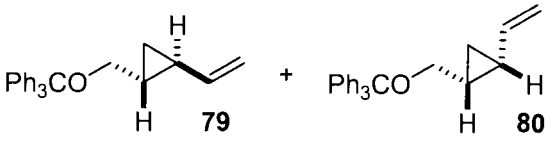
transferred *via* cannula to a 200 mL flask under argon and was cooled to –78 °C. A solution of (2*E*,5*R*)-5-(*tert*-butyldimethylsilyloxy)-1-chloro-6-trityloxy-hex-2-ene (5.12 g, 10.1 mmol) in THF (30 mL) was added dropwise during 1 h, and the mixture was stirred for 13 h at –78 °C. The mixture was diluted with saturated aqueous NH_4Cl (50 mL) and was extracted with Et_2O (100 mL, then 50 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified on a short column of silica gel (hexane, then 20% Et_2O in hexane) to yield 7.17 g (93%) of (2*R*,4*E*)-2-(*tert*-butyldimethylsilyloxy)-6-(tri-*n*-butylstannyl)-1-trityloxy-hex-2-ene as a colorless oil: $[\alpha]_D^{23}$ -1.5 (c 1.0, $CHCl_3$); IR (neat) 3087, 3060, 3022, 2955, 2927, 2871, 2855, 1491, 1463, 1449, 1376, 1361, 1254, 1219 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.05 (s, 3H), 0.79-0.93 (m, 24H), 1.20-1.35 (m, 6H), 1.41-1.53 (m, 6H), 1.63 (d, J = 8.4 Hz, 2H), 2.14 (dt, J = 5.5, 14.1 Hz, 1H), 2.35 (dt, J = 5.5, 14.1 Hz, 1H), 3.03 (dd, J = 5.3, 9.2 Hz, 1H), 3.04 (dd, J = 5.3, 11.9 Hz, 1H), 3.74 (quintet, J = 5.5 Hz, 1H), 5.11 (dt, J = 7.3, 15 Hz, 1H), 5.51 (dt, J = 8.4, 15 Hz, 1H), 7.19-7.33 (m, 9H), 7.45-7.51 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.7, -4.5, 9.1, 11.1, 13.7, 14.2, 18.2, 25.9, 27.3, 29.0, 38.4, 67.3, 72.5, 86.3, 121.4, 126.8, 127.6, 128.8, 131.6, 144.3; MS (CI) *m/z* 519 $(M-[Ph_3C])^+$, 291, 243, 167, 117, 75; HRMS (CI) *m/z* 758.3847 (calcd for $C_{43}H_{66}O_2Si^{116}Sn$: 758.3850).



78

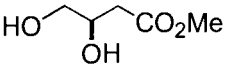
(2*R*,4*E*)-6-(Tri-*n*-butylstannyl)-1-trityloxy-hex-4-en-2-ol. TBAF (9.40 mL, 1.0 M in THF) was added dropwise *via* syringe to a stirred solution of (2*R*,4*E*)-2-(*tert*-butyldimethylsilyloxy)-6-(tri-*n*-butylstannyl)-1-trityloxy-hex-2-ene (7.16 g, 9.40

mmol) in THF (100 mL) at ambient temperature under argon. After 45 h, the mixture was placed in a separatory funnel with CH_2Cl_2 (150 mL) and saturated aqueous NH_4Cl (50 mL), and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified on a short column of silica gel (5-20% Et_2O in hexane) to yield 4.79 g (79%) of (2*R*,4*E*)-6-(tri-*n*-butylstannyl)-1-trityloxy-hex-4-en-2-ol as a colorlesss oil: $[\alpha]_D^{23}$ - 3.4 (c 1.0, $CHCl_3$); IR (neat) 3468, 3090, 3059, 3022, 2955, 2924, 2870, 2852, 1597, 1490, 1448, 1418, 1220, 1184, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.80-0.94 (m, 15H), 1.22-1.36 (m, 6H), 1.41-1.54 (m, 6H), 1.68 (d, J = 8.5 Hz, 2H), 2.08-2.24 (m, 2H), 3.05-3.24 (m, 1H), 5.12 (dt, J = 7.1, 14.7 Hz, 1H), 5.54-5.68 (m, 1H), 7.21-7.35 (m, 9H), 7.42-7.48 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.1, 13.7, 14.4, 27.3, 29.1, 37.2, 67.1, 70.9, 86.6, 120.3, 127.0, 127.8, 128.7, 133.2, 144.0; HRMS (CI) *m/z* 609.2034 (calcd for $C_{32}H_{41}O_4{}^{120}Sn$: 609.2027).



(1*R*,2*S*)-1-(Trityloxymethyl)-2-vinylcyclopropane (79) and (1*R*,2*R*)-1-(Trityloxymethyl)-2-vinylcyclopropane (80). Triflic anhydride (2.42 mL, 14.4 mmol) was added dropwise *via* syringe to a stirred solution of (2*R*,4*E*)-6-(tri-*n*-butylstannyl)-1-trityloxy-hex-2-en-1-ol (6.20 g, 9.58 mmol) and collidine (1.89 mL, 14.4 mmol) in CH_2Cl_2 (120 mL) at -88 °C under argon, and the mixture was stirred for 30 min. Et_3N (4.38 mL, 33.5 mmol) was added dropwise *via* syringe, and the mixture was allowed to warm to ambient temperature during 3 h. The mixture was placed in a

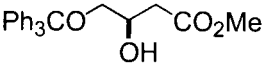
separatory funnel containing saturated aqueous $NaHCO_3$ (100 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified on a short column of silica gel (20% EtOAc in hexane) to yield 3.23 g (99%) of 1-(trityloxymethyl)-2-vinylcyclopropane as a 7.6:1 mixture **79** and **80** respectively (Chiral OD, 0.85 mL/min, 100% hexanes): IR (neat) 3468, 3090, 3059, 3022, 2955, 2924, 2870, 2852, 1597, 1490, 1448, 1418, 1220, 1184, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) for **79** δ 0.66 (t, J = 6.9 Hz, 2H), 1.11-1.22 (m, 1H), 1.23-1.34 (m, 1H), 2.94 (dd, J = 6.6, 9.6 Hz, 1H), 3.06 (dd, J = 6.0, 9.6 Hz, 1H), 4.88 (ddd, J = 0.5, 1.9, 10.2 Hz, 1H), 5.05 (ddd, J = 0.5, 1.9, 17.0 Hz, 1H), 5.44 (ddd, J = 8.5, 10.2, 17.0 Hz, 1H), 7.19-7.34 (m, 9H), 7.43-7.50 (m, 6H); ^1H NMR (300 MHz, $CDCl_3$) for **80** δ 0.62 (q, J = 5.5 Hz, 1H), 0.86-0.95 (m, 2H), 1.58-1.66 (m, 1H), 2.95 (dd, J = 7.7, 9.9 Hz, 1H), 3.19 (dd, J = 6.3, 9.9 Hz, 1H), 4.89 (ddd, J = 0.6, 1.9, 10.2 Hz, 1H), 5.06 (ddd, J = 0.6, 1.9, 17.0 Hz, 1H), 5.46 (ddd, J = 8.5, 10.2, 17.0 Hz, 1H), 7.19-7.34 (m, 9H), 7.43-7.50 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) for **79** δ 11.9, 20.4, 20.6, 66.7, 86.2, 111.9, 126.9, 127.7, 128.7, 141.2, 144.3; ^{13}C NMR (75 MHz, $CDCl_3$) for **80** δ 10.5, 18.4, 19.6, 63.6, 86.3, 114.2, 126.8, 127.7, 128.7, 137.5, 144.3; MS (CI) m/z 340 $(M)^+$, 271, 263, 243, 183, 165, 158, 105, 91; HRMS (CI) m/z 340.1828 (calcd for $C_{25}H_{24}O$: 340.1827).



83

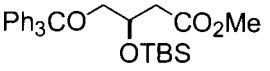
Methyl (3*R*)-3,4-Dihydroxybutyrate. BH_3•DMS (2.59 mL, 2.0 M in THF, 5.16 mmol) was added to a stirred solution of dimethyl (*R*)-(+)-malate (824 mg, 98%, 5.08

mmol) in THF (10 mL) at ambient temperature under argon. After 30 min, $NaBH_4$ (8.5 mg, 5 mol%) was added and the reaction flask was evacuated with argon. After an additional 30 min, anhydrous MeOH (3.25 mL) was added slowly, the reaction mixture was stirred 30 min and then concentrated under reduced pressure. Purification on a short column of silica gel (10% MeOH/EtOAc), afforded 603 mg (88%) of methyl (3*R*)-3,4-dihydroxybutyrate: ^{1}H NMR (300 MHz, acetone-d_6) δ 2.35 (dd, J = 8.5, 15.4 Hz, 1H), 2.54 (dd, J = 4.4, 15.4 Hz, 1H), 3.42-3.49 (m, 2H), 3.61 (s, 3H), 3.86 (brs, 2H), 3.96-4.07 (m, 1H); ^{13}C NMR (75 MHz, acetone-d_6) δ 39.7, 52.0, 66.9, 70.1, 173.1.



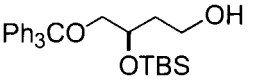
84

Methyl (3*R*)-3-Hydroxy-4-trityloxybutyrate. Et_3N (1.66 mL, 12.0 mmol) was added to a stirred solution of methyl (3*R*)-3,4-dihydroxybutyrate (1.45 g, 10.8 mmol) and triphenylmethyl chloride (3.30 g, 12.0 mmol) in CH_2Cl_2 (10 mL) under argon. After 20 h, the mixture was added to a separatory funnel containing saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (2 x10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification on a column of silica gel (5-40% EtOAc in hexane), afforded 2.61 g (64%) of methyl (3*R*)-3-hydroxy-4-trityloxybutyrate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.56 (dd, J =8.1, 16.1 Hz, 1H), 2.62 (dd, J = 4.8, 16.1 Hz, 1H), 3.21 (d, J = 5.5 Hz, 2H), 3.72 (s, 3H), 4.23-4.32 (m, 1H), 7.25-7.31 (m, 3H), 7.32-7.37 (m, 6H), 7.45-7.49 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.3, 51.7, 66.5, 67.6, 86.7, 127.1, 127.8, 128.6, 143.7, 172.6.



85

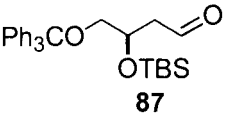
Methyl (3*R*)-3-(*tert*-Butyldimethylsiloxy)-4-trityloxybutyrate. Methyl (3*R*)-3-hydroxy-4-trityloxybutyrate (2.61 g, 6.93 mmol), TBSCl (1.14 g, 97%, 7.35 mmol) and imidazole (502 mg, 7.35 mmol) were taken up in DMF (25 mL) and the reaction flask was evacuated with argon. After 16 h at ambient temperature, the mixture was added to a separatory funnel containing 50% aqueous NH_4Cl (30 mL) and extracted with EtOAc (30 mL). The organic fraction was washed with H_2O (20 mL) and the combined aqueous fractions were extracted with EtOAc (5 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification on a column of silica gel (2-20% EtOAc in hexane) afforded 3.14 g (92%) of methyl (3*R*)-3-(*tert*-butyldimethylsiloxy)-4-trityloxybutyrate: ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.03 (s, 3H), 0.02 (s, 3 H), 0.84 (s, 9H), 2.52 (dd, J = 8.1, 15.0 Hz, 1H), 2.79 (dd, J = 4.4, 15.0 Hz, 1H), 3.05 (dd, J = 7.0, 9.1 Hz, 1H), 3.17 (dd, J = 4.4, 9.5 Hz, 1H), 3.67 (s, 3H), 4.25-4.32 (m, 1H), 7.24-7.30 (m, 3H), 7.31-7.37 (m, 6H), 7.45-7.49 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.2, -4.6, 17.9, 25.6, 40.7, 51.4, 67.2, 68.9, 86.6, 127.0, 127.7, 128.7, 143.9, 172.2.



86

(2*R*)-2-(*tert*-Butyldimethylsiloxy)-1-trityloxy-butan-4-ol. Methyl (3*R*)-3-(*tert*-butyldimethylsilyloxy)-4-trityloxybutyrate (3.14 g, 6.41 mmol), was taken up in CH_2Cl_2 (60 mL) and the solution was cooled to 0 °C under argon. DIBAl-H (2.51 mL,

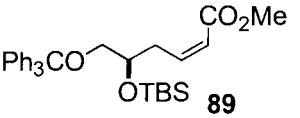
14.1 mmol) was added slowly, the mixture was stirred for 30 min and then quenched with saturated aqueous Na^+/K^+ tartrate (60 mL). After 1 h of vigorous stirring, the aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL), and the combined organic fractions were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (20% EtOAc in hexane) to yield 2.79 g (94%) of (2*R*)-2-(*tert*-butyldimethylsiloxy)-1-trityloxy-butan-4-ol: $[\alpha]_D^{23}$ + 16.2 (c 1.0, $CHCl_3$); IR (neat) 3419, 3086, 3059, 3032, 2947, 2928, 2889, 2856, 1597, 1491, 1471, 1448, 1388, 1361, 1320, 1256, 1184 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ -0.04 (s, 3H), 0.04 (s, 3H) 0.85 (s, 9H), 1.77-1.89 (m, 1H), 1.96-2.08 (m, 1H), 2.36 (t, *J* = 5.4 Hz, 1H), 3.09 (dd, *J* = 7.1, 9.3 Hz, 1H), 3.17 (dd, *J* = 4.9, 9.3 Hz, 1H), 3.65-3.82 (m, 2H), 3.98-4.07 (m, 1H), 7.21-7.34 (m, 9H), 7.43-7.48 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.1, -4.6, 17.9, 25.8, 36.6, 59.9, 66.7, 70.8, 86.7, 127.0, 127.8, 128.6, 143.9; MS (CI) *m/z* 385 $(M-C_6H_5)^+$, 333, 319, 297, 243, 189, 165; HRMS (CI) *m/z* 385.2191 (calcd for $C_{23}H_{33}O_3Si$ $(M-C_6H_5)^+$: 385.2199).



87

(3*R*)-3-(*tert*-Butyldimethylsilyloxy)-4-trityloxybutyraldehyde. (2*R*)-2-(*tert*-Butyldimethylsiloxy)-1-trityloxy-butan-4-ol (11.1 g, 5.25 mmol), was taken up in CH_2Cl_2 (20 mL) along with 4Å molecular sieves (2.43 g, powdered) at ambient temperature under argon. NMO (861 mg, 7.34 mmol) and TPAP (126 mg, 5 mol%) were sequentially added, the reaction flask was purged with argon and the mixture was stirred for 1h at ambient temperature. The mixture was diluted with hexane (20 mL) and filtered through a short column of silica gel (20% EtOAc in hexane) to yield 1.88

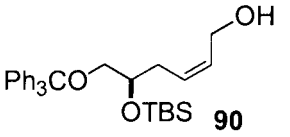
g (78%) of (3*R*)-3-(*tert*-butyldimethylsilyloxy)-4-trityloxybutyraldehyde as a colorless oil: $[\alpha]_D^{23}$ + 8.51 (c 2.4, $CHCl_3$); IR (neat) 3086, 3059, 3032, 2954, 2928, 2884, 2856, 2721, 1728, 1597, 1491, 1475, 1448, 1254, 1219 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ -0.03 (s, 3H), 0.03 (s, 3H), 0.85 (s, 9H), 2.61 (ddd, *J* = 2.7, 6.6, 15.9 Hz, 1H), 2.76 (ddd, *J* = 1.9, 4.9, 15.9 Hz, 1H), 3.12 (dd, *J* = 6.6, 9.3 Hz, 1H), 3.21 (dd, *J* = 4.7, 9.3 Hz, 1H), 4.28 (tt, *J* = 4.9, 6.6 Hz, 1H), 7.22-7.36 (m, 9H), 7.43-7.48 (m, 6H), 9.81 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.1, -4.6, 17.9, 25.7, 49.1, 67.2, 67.5, 86.9, 127.0, 127.8, 128.3, 128.6, 143.8, 201.8; MS (CI) *m/z* 383 $(M-C_6H_5)^+$, 333, 271, 243, 165; HRMS (CI) *m/z* 383.2048 (calcd for $C_{23}H_{31}O_3Si$ $(M-C_6H_5)^+$: 383.2043).



89

Methyl (2*Z*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-6-trityloxy-hex-2-enoate. Methyl (bis-1,1,1-trifluoroethoxy)phosphonylacetate (1.30 g, 4.08 mmol) and 18-crown-6 (5.40 g, 20.4 mmol) were taken up in THF (60 mL) and the solution was cooled to -78 °C under argon. KHMDS (6.81 mL, 0.60 M in toluene) was added slowly. After 30 min, (3*R*)-3-(*tert*-butyldimethylsilyloxy)-4-trityloxy-butyraldehyde (1.88 g, 4.08 mmol) in THF (5 mL) was added slowly, the mixture was stirred for 1 h, then was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with Et_2O (2 x 25 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (2-10% EtOAc in hexane) to yield 1.88 g (89%) of methyl (2*Z*,5*R*)-5-(*tert*-butyldimethylsilyloxy)-6-trityloxy-hex-2-enoate as a colorless oil: $[\alpha]_D^{23}$ - 5.8 (c 1.0, $CHCl_3$); IR (neat) 3.86, 3059, 3033, 2953, 2928, 2884, 2856, 1724, 1647, 1597, 1491,

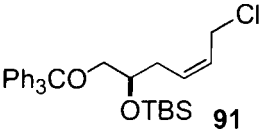
1471, 1448, 1407, 1361, 1323, 1255, 1174 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ -0.01 (s, 3H), 0.03 (s, 3H), 0.80-0.95 (m, 9H), 2.96-3.05 (m, 1H), 3.06-3.13 (m, 1H), 3.69 (s, 3H), 3.83-3.99 (m, 1H), 5.78-5.83 (m, 1H), 5.78-5.83 (m, 1H), 7.19-7.34 (m, 9H), 7.42-7.49 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.9, -4.6, 18.0, 25.8, 34.5, 51.0, 67.1, 70.8, 86.5, 120.6, 126.9, 127.7, 128.3, 128.6, 128.7, 144.1, 146.4, 166.7; MS (CI) *m/z* 485 $(M-[OCH_3])^+$, 473, 439, 407, 333, 327, 291, 277, 271, 257; HRMS (CI) *m/z* 485.2503 (calcd for $C_{31}H_{37}O_3Si$ $(M-[OCH_3])^+$: 485.2512).



90

(2*R*,4*Z*)-2-(*tert*-Butyldimethylsilyloxy)-1-trityloxy-hex-4-en-6-ol. A solution of methyl (2*Z*,5*R*)-5-(*tert*-butyldimethylsilyloxy)-6-trityloxy-hex-2-enoate (1.85 g, 3.58 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C under argon and DiBAl-H (1.40 mL, 7.88 mmol) was added slowly. The mixture was stirred for 45 min, then quenched with saturated aqueous Na^+/K^+ tartrate (20 mL). After 1 h of vigorous stirring, the aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL), and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (5-40% EtOAc in hexane) to yield 1.33 g (76%) of (2*R*,4*Z*)-2-(*tert*-butyldimethylsilyloxy)-1-trityloxy-hex-4-en-6-ol as a colorless oil: $[\alpha]_D^{23}$ + 2.8 (c 1.0, $CHCl_3$); IR (neat) 3348, 3086, 3059, 3023, 2958, 2928, 2883, 2856, 1597, 1491, 1471, 1448, 1388, 1361, 1322, 1255, 1220, 1184, 1154 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ -0.026 (s, 3H), 0.017 (s, 3H), 0.85 (s, 9H), 1.56 (brs, 1H), 2.32-2.54 (m, 2H), 2.98 (dd, *J* = 6.6, 9.1 Hz, 1H), 3.10 (dd, *J* = 4.9, 9.1 Hz, 1H), 3.79-3.89 (m, 1H), 4.04-4.17 (m, 2H), 5.64-5.74 (m, 1H), 5.47-5.58 (m, 1H),

7.20-7.34 (m, 9H), 7.42-7.49 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.7, -4.6, 18.1, 25.8, 33.0, 58.5, 67.0, 71.1, 86.6, 127.0, 127.7, 128.7, 128.8, 130.6, 144.0; MS (CI) *m/z* 488 $(M-H)^+$, 484, 471, 411, 333, 297, 271, 257; HRMS (CI) *m/z* 411.2360 (calcd for $C_{25}H_{35}O_3Si$ $(M-[C_6H_5])^+$: 411.2356).

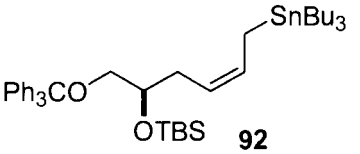


91

(2*Z*,5*R*)-1-Chloro-5-(*tert*-butyldimethylsilyloxy)-6-trityloxy-hex-2-ene.

Methanesulfonyl chloride (311 μL, 3.99 mmol, 1.5 eq) was added dropwise *via* syringe to a stirred solution of (2*R*,4*Z*)-2-(*tert*-butyldimethylsilyloxy)-1-trityloxy-hex-4-en-6-ol (1.30 g, 2.66 mmol), LiCl (112 mg) and collidine (1.75 mL) in DMF (16 mL) at 0 °C under argon. The mixture was allowed to warm to ambient temperature and was stirred for 18 h. The mixture was added to a separatory funnel containing Et_2O/pentane (1:1, 40 mL) and saturated aqueous $NaHCO_3$ (10 mL), and the separated aqueous phase was extracted with Et_2O/pentane (1:1, 10 mL). The combined organic extracts were washed with saturated aqueous $CuSO_4$ (4 x 20 mL), dried (Na_2SO_4), filtered, concentrated under reduced pressure, and the residue was purified on a short column of silica gel (20% EtOAc in hexane) to yield 1.34 g (99%) of (2*Z*,5*R*)-1-chloro-5-(*tert*-butyldimethylsilyloxy)-6-trityloxy-hex-2-ene as a colorless oil: $[\alpha]_D^{23}$ -15.3 (c 1.0, $CHCl_3$); IR (neat) 3086, 3057, 3023, 2952, 2927, 2891, 2855, 1491, 1470, 1448, 1360, 1251, 1178, 1154 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.1 (s, 3H), 0.03 (s, 3H), 0.85 (s, 9H), 2.31-2.42 (m, 1H), 2.47-2.57 (m, 1H), 3.00 (dd, *J* = 6.3, 9.3 Hz, 1H), 3.11 (dd, *J* = 4.9, 9.3 Hz, 1H), 3.85 (tt, *J* = 5.2, 6.0 Hz, 1H), 3.95-4.12 (m, 2H), 5.58-5.73 (m, 2H), 7.21-7.35 (m, 9H), 7.43-7.51 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$)

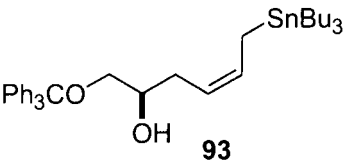
δ -4.8, -4.6, 18.0, 25.8, 32.6, 39.5, 67.0, 71.1, 86.6, 126.9, 127.7, 128.7, 131.1, 144.0; MS (CI) *m/z* 507 $(M)^+$, 471, 451, 429, 333, 297, 283, 271, 257; HRMS (CI) *m/z* 429.2020 (calcd for $C_{25}H_{34}O_3Si^{35}Cl(M-[C_6H_5])^+$: 429.2017).



92

(2*R*,4*Z*)-2-(*tert*-Butyldimethylsilyloxy)-6-(tri-*n*-butylstannyl)-1-trityloxy-hex-4-ene. Bu_3SnCl (3.02 mL, 4.51 g, 96%, 13.3 mmol) was added to finely cut lithium wire (1.04 g) under argon, after which THF (16 mL) was added, and the mixture was stirred for 20 h at ambient temperature. The resulting dark green suspension was transferred *via* cannula to a 50 mL flask under argon and the mixture was cooled to –78 °C. A solution of (2*Z*,5*R*)-1-chloro-5-(*tert*-butyldimethylsilyloxy)-6-trityloxy-hex-2-ene (1.33 g, 2.62 mmol) in THF (4 mL) was added dropwise during 15 min, and the mixture was stirred for 6 h. The mixture was placed in a separatory funnel with 50% aqueous NH_4Cl (30 mL) and CH_2Cl_2 (40 mL), and the separated aqueous phase was extracted with CH_2Cl_2 (2 x 40 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified on a short column of silica gel (hexane, then 20% EtOAc in hexane) to yield 1.86 g (93%) of (2*R*,4*Z*)-2-(*tert*-butyldimethylsilyloxy)-6-(tri-*n*-butylstannyl)-1-trityloxy-hex-4-ene as a colorless oil: $[\alpha]_D^{23}$ - 4.1 (c 1.0, $CHCl_3$); IR (neat) 3086, 3060, 3022, 2955, 2927, 2873, 2855, 1637, 1598, 1491, 1463, 1449, 1418, 1377, 1254, 1219, 1182 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.10 (s, 3H), 0.86-0.95 (m, 24 H), 1.27-1.37 (m, 6H), 1.46-1.56 (m, 6H), 1.71 (dd, *J* = 3.7, 9.1 Hz, 2H), 2.18-2.27 (m, 1H), 2.36-2.45 (m, 1H), 3.06 (dd, *J* = 5.3, 9.2 Hz, 1H), 3.10 (dd, *J* = 5.3, 9.2 Hz, 1H)

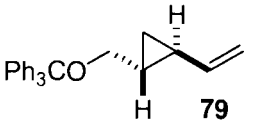
3.86 (septet, J = 5.7 Hz, 1H), 5.00-5.09 (m, 1H), 5.55-5.63 (m, 1H), 7.23-7.35 (m, 9H), 7.48-7.54 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.7, -4.4, 9.3, 10.7, 13.7, 18.1, 25.9, 27.3, 29.2, 32.6, 67.5, 72.1, 119.7, 126.8, 127.6, 128.8, 130.0, 144.3; MS (CI) *m/z* 762 $(M)^+$, 717, 685, 519, 405, 291, 243, 165; HRMS (CI) *m/z* 762.3853 (calcd for $C_{43}H_{66}O_2Si^{120}Sn$: 762.3854).



93

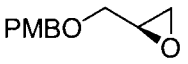
(2*R*,4*Z*)-6-(Tri-*n*-butylstannyl)-1-trityloxy-hex-4-en-2-ol. TBAF (2.43 mL, 1.0 M in THF) was added dropwise *via* syringe to a stirred solution of (2*R*,4*Z*)-2-(*tert*-butyldimethylsilyloxy)-6-(tri-*n*-butylstannyl)-1-trityloxy-hex-4-ene (906 mg, 1.18 mmol) and collidine (227 μL) in THF (18 mL) at 0 °C under argon, and the mixture was stirred at ambient temperature for 21 h. The mixture was placed in a separatory funnel containing CH_2Cl_2 (50 mL) and saturated aqueous NH_4Cl (20 mL) and the separated aqueous phase was extracted with CH_2Cl_2 (4 x 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure, and the residue was purified by column chromatography (2-10% EtOAc in hexane) to yield 516 mg (63%) of (2*R*,4*Z*)-6-(tri-*n*-butylstannyl)-1-trityloxy-hex-4-en-2-ol as a colorless oil: $[\alpha]_D^{23}$ - 2.4 (c 1.0, $CHCl_3$); IR (neat) 3460, 3086, 3059, 3022, 2955, 2924, 2870, 2853, 1637, 1597, 1491, 1448, 1418, 1376, 1220, 1183, 1153 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82-0.92 (m, 15H), 1.22-1.36 (m, 6H), 1.42-1.54 (m, 6H), 1.69 (d, J = 9.2 Hz, 2H), 2.18-2.27 (m, 2H), 2.30 (d, J = 3.8 Hz, 1H), 3.11 (dd, J = 6.9, 9.3 Hz, 1H), 3.22 (dd, J = 3.8, 9.3 Hz, 1H), 3.77-3.88 (m, 1H), 4.97-5.07 (m, 1H), 5.59-5.72 (m, 1H), 7.22-7.35 (m, 9H), 7.43-7.49 (m, 6H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 9.3, 10.7, 13.7, 27.3, 29.1, 31.2, 67.3, 71.0, 86.6, 118.6, 127.0, 127.8, 128.7, 131.4, 143.9; MS (CI) *m/z* 648 $(M)^+$, 603, 523, 467, 405, 349, 291, 257; HRMS (CI) *m/z* 648.2973 (calcd for $C_{37}H_{52}O_2{}^{120}Sn$: 648.2989).



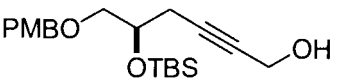
79

(1*R*,2*S*)-1-(Trityloxymethyl)-2-vinylcyclopropane. Triflic anhydride (246 μL, 1.46 mmol) was added dropwise *via* syringe to a stirred solution of (2*R*,4*Z*)-6-(tri-*n*-butylstannyl)-1-trityloxy-hex-4-en-2-ol (630 mg, 0.973 mmol) and collidine (192 μL, 1.46 mmol) in CH_2Cl_2 (10 mL) at -78 °C under argon, and the mixture was stirred for 1 h. Et_3N (443 μL, 3.42 mmol) was added dropwise *via* syringe, and the mixture was stirred for an additional 19 h at -78 °C. The mixture was allowed to warm to ambient temperature and concentrated under reduced pressure. The residue was purified by column chromatography (2-4% EtOAc in hexane, containing 1% Et_3N) to yield 302 mg (91%) of (1*R*,2*S*)-1-(trityloxymethyl)-2-vinylcyclopropane as a >36:1 mixture of *trans* and *cis* vinylcyclopropanes (Chiral OD, 0.85 mL/min, 100% hexanes): $[\alpha]_D^{23}$ -45.3 (c 1.0, $CHCl_3$); IR (neat) 3083, 3059, 3021, 2993, 2955, 2915, 2868, 1635, 1597, 1491, 1448, 1402, 1317, 1218, 1182, 1153 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.66 (t, *J* = 6.9 Hz, 2H), 1.07-1.23 (m, 1H), 1.24-1.34 (m, 1H), 2.94 (dd, *J* = 6.5, 9.6 Hz, 1H), 3.07 (dd, *J* = 6.1, 9.6 Hz, 1H), 4.88 (dd, *J* = 1.7, 10.3 Hz, 1H), 5.06 (ddd, *J* = 0.5, 1.7, 17.1 Hz, 1H), 5.45 (ddt, *J* = 8.5, 10.2, 17.1 Hz, 2H), 7.20-7.34 (m, 9H), 7.44-7.49 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.9, 20.4, 20.6, 66.7, 86.2, 111.9, 126.9, 127.7, 128.7, 141.2, 144.3; MS (CI) *m/z* 340 $(M)^+$, 263, 243, 228, 183, 165, 143, 105, 91; HRMS (CI) *m/z* 340.1827 (calcd for $C_{25}H_{24}O$: 340.1827).



95

(*R*)-Glycidyl 4-Methoxybenzyl Ether. *p*-Methoxybenzyl chloride (19.95 mL, 22.58 g, 144.2 mmol) was added slowly to a stirred suspension of NaH (5.76 g, 60% dispersion in mineral oil, 144.2 mmol) in DMF (250 mL) at 0 °C under argon. After 25 min, *S*-(–)-glicydol (9.70 g, 97%, 98% *ee*, 131 mmol) was added dropwise *via* syringe during 45 min and the mixture was allowed to warm to ambient temperature. After 20 h, the mixture was added to a separatory funnel containing saturated aqueous NH_4Cl (100 mL) and EtOAc (250 mL). The organic phase was washed with 10% aqueous $NaHCO_3$ (100 mL) and H_2O (150 mL) and the combined aqueous phases were extracted with EtOAc (100 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification on a column of silica gel (10-40% EtOAc in hexane) afforded 24.5 g (96%) of (*R*)-glycidyl 4-methoxybenzyl ether: $[\alpha]_D^{23}$ + 3.5 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.60 (dd, J = 2.7, 5.0 Hz, 1H), 2.75-2.81 (m, 1H), 3.13-3.20 (m, 2H), 3.41 (dd, J = 5.9, 11.4 Hz, 1H), 3.72 (dd, J = 3.2, 11.4 Hz, 1H), 3.79 (s, 3H), 4.44-4.57 (m, 2H), 6.84-6.91 (m, 2H), 7.24-7.30 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.2, 50.8, 55.1, 70.4, 72.8, 113.7, 129.3, 129.9, 159.2.

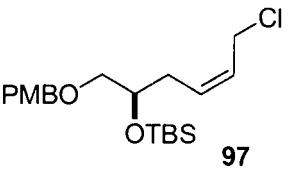


96

(2*R*)-2-(*tert*-Butyldimethylsilyloxy)-1-(4'-methoxybenzyloxy)-hex-4-yn-6-ol. *n*-BuLi (7.64 M in hexane, 5.67 mL) was added during 20 min to a stirred solution of 1-(*tert*-butyldimethylsilyloxy)-prop-2-yne (7.40 g, 43.4 mmol) in THF (125 mL) at -78 °C under argon. After 1 h, a solution of (*R*)-glycidyl 4-methoxybenzyl ether (5.65 g,

28.9 mmol) in THF (15 mL) was added slowly. After 20 min, BF_3•OEt_2 (5.77 mL, 40.5 mmol) was added slowly, the resulting mixture was stirred at -78 °C for 2.5 h, then allowed to warm to ambient temperature. After 19 h, the reaction mixture was placed in a separatory funnel containing saturated aqueous NH_4Cl (50 mL) and CH_2Cl_2 (100 mL, 2 x 25 mL). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified on a short column of silica gel (5-50% EtOAc in hexanes) to afford 8.82 g of (5*R*)-1-(*tert*-butyldimethylsilyloxy)-6-(4'-methoxybenzyloxy)-hex-2-yn-5-ol. A solution of the propargyllic alcohol (8.82 g, 24.2 mmol) in CH_2Cl_2 (10mL) was added to a stirred solution of TBSCl (3.96 g, 98%, 25.7 mmol) and imidazole (1.75 g, 25.7 mmol) in CH_2Cl_2 (30 mL) under argon. After 40 h, TBAF (24.2 mL, 1.0M in THF) was added, the reaction was stirred an additional 23 h, then the mixture was added to a separatory funnel containing saturated aqueous NH_4Cl (50 mL) and CH_2Cl_2 (40 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL) and the combined organic fractions were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification on a short column of silica gel (5-40% EtOAc in hexane) gave 6.42 g (61%, 3 steps) of (2*R*)-2-(*tert*-butyldimethylsilyloxy)-1-(4'-methoxybenzyloxy)-hex-4-yn-6-ol: $[\alpha]_D^{23}$ + 0.7 (c 1.0, $CHCl_3$); IR (neat) 3422, 3000, 2953, 2929, 2856, 1613, 1586, 1514, 1464, 1362, 1302, 1249, 1173, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.10 (s, 3H), 0.12 (s, 3H), 0.93 (s, 9H), 1.96 (brs, 1H), 2.41 (ddt, J = 2.2, 6.1, 16.8 Hz, 1H), 2.53 (ddt, J = 2.2, 6.1, 16.8 Hz, 1H), 3.44-3.53 (m, 2H), 3.83 (s, 3H), 3.94-4.01 (m, 1H), 4.23 (s, 2H), 4.51 (s, 2H), 6.88-6.93 (m, 2H), 7.26-7.31 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.8, -4.7, 18.1, 24.9, 25.7, 51.2, 55.2, 70.4, 72.9, 73.2, 79.9,

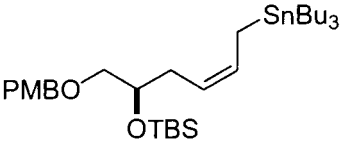
83.2, 113.6, 113.8, 129.2, 130.3, 159.1; MS (CI) *m/z* 363 $(M-H)^+$, 347, 295, 241, 215, 121; HRMS (CI) *m/z* 364.2048 (calcd for $C_{20}H_{32}O_4Si$: 364.2070).



97

(2*Z*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-1-chloro-6-(4'-methoxybenzyloxy)-hex-2-ene. A solution of (2*R*)-2-(*tert*-butyldimethylsilyloxy)-1-(4'-methoxybenzyloxy)-hex-4-yn-6-ol (5.27 g, 14.5 mmol) in hexane/1-octene (9:1, 10 mL) was added to a stirred suspension of Lindlar catalyst (1.86 g, 6 mol%) and quinoline (2.45 g, 98%, 19.0 mmol) in hexane/1-octene (9:1, 130 mL) under argon. The reaction flask was evacuated with H_2 gas, and the reaction mixture was stirred under 1 atm of H_2. After 4 h, the entire reaction mixture was filtered through Celite, the filter cake was washed with EtOAc (50 mL), and the eluent was concentrated under reduced pressure. Purification *via* distillation (165-170 °C. 0.150 mmHg) afforded product contaminated with over reduced alcohol. Methanesulfonyl chloride (1.80 mL, 23.2 mmol) was added dropwise *via* syringe to a stirred solution of the crude product, collidine (10.21 mL, 78.3 mmol) and LiCl (650 mg, 2.30 mmol) in DMF (130 mL) at 0 °C under argon. The resulting mixture was allowed to warm to room temperature and was stirred for 22 h. The mixture was placed in a separatory funnel containing Et_2O/pentane (1:1, 100 mL) and saturated aqueous $NaHCO_3$ (50 mL). The aqueous phase was extracted with Et_2O/pentane (1:1, 25 mL) and the combined organic fractions were washed with saturated aqueous $CuSO_4$ (3 x 100 mL). The combined aqueous fractions were extracted with Et_2O/pentane (1:1, 50 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced

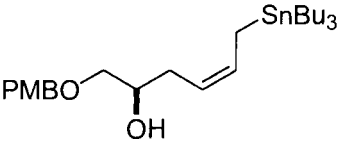
pressure. Purification on a silica gel column (2-15% EtOAc/hexane) afforded 3.91 g (79%, 2 steps) of (2*Z*,5*R*)-5-(*tert*-butyldimethylsilyloxy)-1-chloro-6-(4'-methoxy-benzyloxy)-hex-2-ene: $[\alpha]_D^{23}$ - 12.2 (c 1.0, $CHCl_3$); IR (neat) 3031, 3000, 2954, 2929, 2897, 2856, 1613, 1586, 1514, 1463, 1362, 1249, 1097 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.88 (s, 9H), 2.15-2.45 (m, 2H), 3.33 (dd, *J* = 6.0, 9.6 Hz, 1H), 3.37 (dd, *J* = 5.2, 9.6 Hz, 1H), 3.81-3.91 (m, 4H), 3.99-4.16 (m, 2H), 4.45 (brs, 2H) 5.60-5.77 (m, 2H), 6.85-6.91 (m, 2H), 7.22-7.28 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.7, -4.6, 18.1, 25.8, 32.4, 39.6, 55.2, 70.7, 73.0, 73.6, 113.7, 127.1, 129.2, 130.4, 131.0, 159.2; MS (CI) *m/z* 383 $(M-H)^+$, 349, 295, 277, 247, 233, 223, 197, 121, 93; HRMS (CI) *m/z* 383.1811 (calcd for $C_{20}H_{32}O_3SiCl$ $(M-H)^+$: 383.1809).



98

(2*R*,4*E*)-2-(*tert*-Butyldimethylsilyloxy)-6-(tri-*n*-butylstannyl)-1-(4'-methoxy-benzyloxy)-hex-4-ene. Tri-*n*-butyltin chloride (13.81 mL, 20.6 g, 96%, 55.9 mmol) was added to finely cut lithium wire (1.64 g,) under argon at ambient temperature. THF (90 mL) was added and the mixture was stirred for 21 h. The resulting dark green suspension was transferred *via* cannula to a 250 mL flask under argon and was cooled to –78 °C. A solution of (2*Z*,5*R*)-5-(*tert*-butyldimethylsilyloxy)-1-chloro-6-(4'-methoxy-benzyloxy)-hex-2-ene (3.66 g, 9.51 mmol) in THF (15 mL) was added dropwise during 15 min, and the mixture was stirred for 20 h at –78 °C. The mixture was diluted with saturated aqueous NH_4Cl (75 mL) and was extracted with CH_2Cl_2 (75 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated under

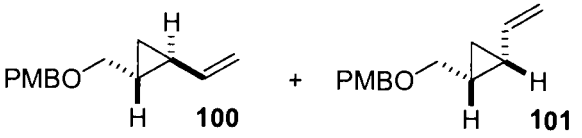
reduced pressure. The residue was purified on a short column of silica gel (0-20% Et_2O in hexane) to yield 5.39 g (89%) of (2*R*,4*E*)-2-(*tert*-butyldimethylsilyloxy)-6-(tri-*n*-butylstannyl)-1-(4'-methoxy-benzyloxy)-hex-4-ene: $[\alpha]_D^{23}$ - 9.9 (c 1.0, $CHCl_3$); IR (neat) 3002, 2955, 2927, 2855, 1614, 1588, 1514, 1463, 1249, 1109, 1087 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.11 (s, 6H), 0.86-0.96 (m, 24H), 1.29-1.39 (m, 6H), 1.48-1.56 (m, 6H), 1.70-1.82 (m, 2H), 2.16-2.35 (m ,2H), 3.40 (dd, *J* = 5.9, 9.5 Hz, 1H), 3.43 (dd, *J* = 5.1, 9.5 Hz, 1H), 3.84 (s, 3H), 3.85-3.93 (m, 1H), 4.47-4.51 (m, 2H), 5.10-5.19 (m, 1H), 5.60-5.71 (m, 1H), 6.88-6.93 (m, 2H), 7.27-7.32 (m, 2H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.7, -4.4, 9.1, 10.7, 13.7, 18.2, 25.9, 27.4, 29.2, 32.4, 55.2, 71.9, 72.9, 74.3, 113.6, 119.7, 129.1, 130.1, 130.7, 159.0; MS (CI) *m/z* 640 $(M)^+$, 583, 365, 291, 235, 179, 121, 91; HRMS (CI) *m/z* 640.3323 (calcd for $C_{32}H_{60}O_3SiSn$: 640.3333).



99

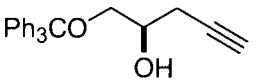
(2*R*,4*E*)-6-(Tri-*n*-butylstannyl)-1-(4'-methoxybenzyloxy)-hex-4-en-2-ol. TBAF (9.32 mL, 1.0 M in THF) was added dropwise *via* syringe to a stirred solution of (2*R*,4*E*)-2-(*tert*-butyldimethylsilyloxy)-6-(tri-*n*-butylstannyl)-1-(4'-methoxy-benzyloxy)-hex-4-ene (5.38 g, 8.41 mmol) in THF (60 mL) under argon, and the mixture was stirred at ambient temperature for 5 h. The mixture was placed in a separatory funnel with CH_2Cl_2 (60 mL) and saturated aqueous NH_4Cl (40 mL) and the separated aqueous phase was extracted with CH_2Cl_2 (25 mL). The combined organic extracts were dried (Na_2SO_4), filtered, concentrated under reduced pressure, and the

residue was purified on a column of silica gel (5-20% EtOAc in hexane) to afford 3.53 g (80%) of (2*R*,4*E*)-6-(tri-*n*-butylstannyl)-1-(4'-methoxybenzyloxy)-hex-4-en-2-ol: $[\alpha]_D^{23}$ - 2.4 (c 1.0, $CHCl_3$); IR (neat) 3457, 3004, 2955, 2925, 2867, 2853, 1613, 1587, 1514, 1464, 1248, 1173 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.80-0.96 (m, 15H), 1.28-1.37 (m, 6H), 1.46-1.56 (m, 6H), 1.76 (d, *J* = 9.1 Hz, 2H), 2.17-2.32 (m, 2H), 2.38 (dd, *J* = 3.3, 7.7 Hz, 1H), 3.29-3.41 (m, 1H), 3.49-3.58 (m, 1H), 3.78-3.91 (m, 4H), 4.50-4.54 (m, 2H), 5.06-5.16 (m, 1H), 5.66-5.78 (m, 1H), 6.89-6.94 (m, 2H), 7.27-7.32 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.1, 9.3, 10.7, 13.6, 27.3, 29.1, 31.0, 55.1, 70.4, 72.9, 73.8, 113.7, 118.6, 129.3, 130.1, 131.3, 159.2; MS (CI) *m/z* 525 $(M)^+$, 469, 409, 347, 291, 235, 179, 121; HRMS (CI) *m/z* 526.2461 (calcd for $C_{26}H_{46}O_3Sn$: 526.2469).



(1*R*,2*S*)-1-(4'-Methoxybenzyloxymethyl)-2-vinylcyclopropane. Triflic anhydride (1.14 mL, 6.75 mmol) was added dropwise *via* syringe to a stirred solution of (2*R*,4*E*)-6-(tri-*n*-butylstannyl)-1-(4'-methoxybenzyloxy)-hex-4-en-2-ol (2.37g, 4.50 mmol) and collidine (889 μL, 6.75 mmol) in CH_2Cl_2 (25 mL) at -88 °C under argon, and the mixture was stirred for 1 h. Et_3N (2.05 mL, 15.8 mmol) was added dropwise *via* syringe, and the mixture was stirred for an additional 22 h at -88 °C. The mixture was allowed to warm to ambient temperature and concentrated under reduced pressure and the residue was purified by column chromatography (CH_2Cl_2) to yield 844 mg (86%) of (1*R*,2*S*)-1-(4'-methoxybenzyloxymethyl)-2-vinyl cyclopropane as a 96:4 mixture of

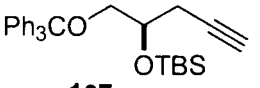
trans and *cis* vinylcyclopropanes (Chiral OD, 0.85 mL/min, 100% hexanes): $[\alpha]_D^{23}$ -46.9 (c 1.0, $CHCl_3$); IR (neat) 3076, 3001, 2948, 2933, 2906, 2854, 2835, 1636, 1613, 1513, 1464, 1302, 1248, 1089 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.64-0.70 (m, 2H), 1.10-1.22 (m, 1H), 1.26-1.38 (m, 1H), 3.31 (ddd, J = 0.82, 6.9, 10.4 Hz, 1H), 3.39 (dd, J = 6.9, 10.4 Hz, 1H), 3.80 (s, 3H), 4.42-4.51 (m, 2H), 5.03-5.11 (m, 1H), 5.35-5.49 (m, 1H), 6.86-6.91 (m, 2H), 7.24-7.29 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.9, 20.2, 20.8, 55.2, 72.1, 72.9, 112.2, 113.7, 129.2, 130.5, 140.7, 159.1; MS (CI) *m/z* 218 $(M)^+$, 188, 176, 163, 134, 121, 91; HRMS (CI) *m/z* 218.1300 (calcd for $C_{14}H_{18}O_2$: 218.1307).



106

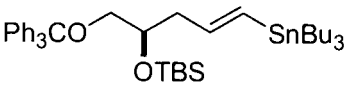
(2*R*)-1-Trityloxy-pent-4-yn-2-ol. (*R*)-Glycidol trityl ether (5.00 g, 15.8 mmol) was added to a stiring suspension of lithium acetylide, ethylenediamine complex (2.42 g, 90%, 23.7 mmol) in DMSO (20 mL) at ambient temperature under argon. After 7 h, the reaction was quenched with saturated aqueous NH_4Cl (2 mL), then the mixture was added to a separatory funnel containing saturated aqueous NH_4Cl (25 mL) and Et_2O (40 mL). The organic phase was washed with brine (30 mL) and the combined aqueous phases were extracted with Et_2O (30 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification on a column of silica gel (20-40% EtOAc/hexanes) gave 4.94 g (91%) of (2*R*)-1-trityloxy-pent-4-yn-2-ol: $[\alpha]_D^{23}$ -5.40 (c 1.0, $CHCl_3$) IR (neat) 3441, 3300, 3086, 3058, 3033, 2927, 2876, 1597, 1491, 1448, 1221, 1074 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.99 (t, J = 2.7 Hz, 1H), 2.44 (brs, 1H), 2.49 (dd, J = 1.5, 2.7 Hz, 1H), 2.51 (dd, J =

1.3, 2.7 Hz, 1H), 3.27 (d, J = 2.7 Hz, 1H), 3.95 (quintet, J = 5.7 Hz, 1H), 7.23-7.38 (m, 9H), 7.44-7.51 (m, 6H); ^{13}CNMR (75 MHz, acetone-d6) δ 23.8, 66.0, 69.2, 70.5, 86.8, 127.1, 127.8, 128.6, 143.7; MS (CI) *m/z* 342 $(M)^+$, 260, 243, 183, 165, 105, 69; HRMS (CI) *m/z* 342.1615 (calcd for $C_{24}H_{22}O_2$: 342.1620).



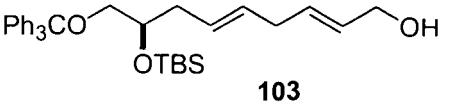
107

(2*R*)-2-(*tert*-Butyldimethylsilyloxy)-1-trityloxy-pent-4-yne. (2*R*)-1-Trityloxy-pent-4-yn-2-ol (2.61 g, 6.93 mmol), TBSCl (450 mg, 98%, 2.92 mmol) and imidazole (199 mg, 2.9 mmol) were taken up in DMF (5 mL) and the reaction flask was evacuated with argon. After 24 h at ambient temperature, the mixture was added to a separatory funnel containing saturated aqueous NH_4Cl (20 mL) and extracted with Et_2O (20 mL, 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification on a column of silica gel (1% EtOAc in hexane containing 1% Et_3N) afforded 1.19 g (98%) of (2*R*)-2-(*tert*-butyldimethylsilyloxy)-1-trityloxy-pent-4-yne: $[\alpha]_D^{23}$ -3.30 (c 1.0, $CHCl_3$) IR (neat) 3311, 3087, 3059, 3033, 2954, 2928, 2884, 2857, 1597, 1491, 1449, 1361, 1256, 1220, 1121 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.01 (s, 3H), 0.03 (s, 3H), 0.88 (s, 9H), 1.90 (t, J = 2.7 Hz, 1H), 2.39 (ddd, J = 2.7, 6.2, 16.7 Hz, 1H), 2.61 (ddd, J = 2.7, 5.7, 16.7 Hz, 1H), 3.16 (d, J = 5.3 Hz, 2H), 3.92 (quintet, J = 5.7 Hz, 1H), 7.20-7.34 (m, 9H), 7.44-7.51 (m, 6H); ^{13}C NMR (75 MHz, acetone-d6) δ -4.8, -4.6, 18.1, 25.0, 25.8, 66.7, 69.7, 70.5, 81.6, 86.5, 126.9, 127.7, 128.7, 144.1; MS (CI) *m/z* 457 $(M+H)^+$, 456 $(M)^+$, 379, 297, 271, 257, 243, 165, 117, 73; HRMS (CI) *m/z* 456.2482 (cacld for $C_{30}H_{36}O_2Si$: 456.2485).



105

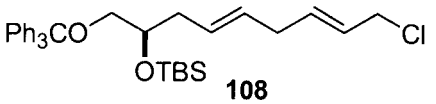
(2*R*,4*E*)-2-(*tert*-Butyldimethylsilyloxy)-1-trityloxy-5-(tri-*n*-butylstannyl)-pent-4-ene. A suspension of tri-*n*-butyltin hydride (4.53 mL, 4.90 g (97%), 16.3 mmol), AIBN (57.5 mg, 0.34 mmol, 2.5 mol%) and (2*R*)-2-(*tert*-butyldimethylsilyloxy)-1-trityloxy-pent-4-yne (6.22 g, 13.6 mmol) was heated slowly to 90 °C under argon. After 20 h, the reaction mixture was cooled to ambient temperature and purified on a column of silica gel (hexane containing 1% Et_3N) to yield 9.20 g (90%) of (2*R*,4*E*)-2-(*tert*-butyldimethylsilyloxy)-1-trityloxy-5-(tri-*n*-butylstannyl)-pent-4-ene: $[\alpha]_D^{23}$ -0.40 (c 1.0, $CHCl_3$); IR (neat) 3087, 3060, 3033, 2955, 2927, 2855, 1598, 1491, 1471, 1463, 1449, 1376, 1360, 1252, 1220, 1183 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ -0.02 (s, 3H), 0.05 (s, 3H), 0.79-0.92 (m, 24H), 1.21-1.36 (m, 6H), 1.40-1.53 (m, 6H), 2.27-2.38 (m, 1H), 2.50-2.59 (m, 1H), 2.94-3.10 (m, 2H), 3.84 (quintet, J = 5.7 Hz, 1H), 5.89-5.93 (m, 2H), 7.19-7.34 (m, 9H), 7.44-7.50 (m, 6H); ^{13}C NMR (75 MHz, acetone-d6) δ -4.7, -4.4, 9.3, 13.7, 18.0, 25.9, 27.3, 29.1, 43.7, 67.3, 71.6, 86.4, 126.8, 127.7, 128.8, 130.5, 144.2, 145.5; MS (CI) *m/z* 747 $(M)^+$, 691, 391, 291, 243, 165; HRMS (CI) *m/z* 747.3632 (calcd for $C_{42}H_{63}O_2{}^{120}SnSi$: 747.3619).



103

(2*R*,4*E*,7*E*)-2-(*tert*-Butyldimethylsilyloxy)-1-trityloxy-nona-4,7-dien-9-ol. (2*R*,4*E*)-2-(*tert*-Butyldimethylsilyloxy)-1-trityloxy-5-(tri-*n*-butylstannyl)-pent-4-ene (1.55 g, 2.07 mmol), methyl (*E*)-4-bromo-2-butenoate (508.7 mg, 95%, 338 μL, 2.69 mmol), bis(acetonitrile)palladium(II) chloride (10.9 mg, 2 mol%), and $AsPh_3$ (6.6 mg, 1

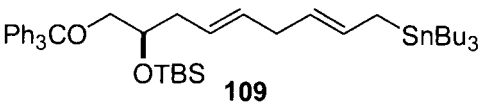
mol%) were taken up in dry $CHCl_3$ (7 mL), degassed with an argon bubbler for 20 min, and heated to 50 °C. After 20 h, the reaction mixture was cooled to ambient temperature and concentrated under reduced pressure, and the residue was purified on a short column of silica gel (1-5% EtOAc in hexane). DIBAl-H (726 μL, neat, 4.1 mmol) was added dropwise *via* syringe to a stirred solution of the purified ester in CH_2Cl_2 (27 mL) at –20 °C under argon. After 10 min, the reaction was quenched with saturated aqueous Na^+/K^+ tartrate (27 mL) and stirred vigorously for 20 h. The aqueous layer was extracted with Et_2O (2 x 20 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification on a column of silica gel (5-20% EtOAc in hexane containing 1% Et_3N) gave 759 mg (67%, 2 steps) of (2*R*,4*E*,7*E*)-2-(*tert*-butyldimethylsilyloxy)-1-trityloxy-nona-4,7-dien-9-ol: $[\alpha]_D^{23}$ + 1.30 (c 1.0, $CHCl_3$); IR (neat) 3334, 3086, 3059, 3023, 2954, 2928, 2883, 2856, 1491, 1471, 1449, 1361, 1254, 1221, 1077 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.11 (s, 3H), 0.89 (s, 9H), 2.15-2.27 (m, 1H), 2.35-2.46 (m, 1H), 3.00-3.13 (m, 2H), 3.55 (t, J = 5.6 Hz, 1H), 3.87 (quintet, J = 5.7 Hz, 1H), 3.97-4.03 (m, 2H), 5.37-5.44 (m, 2H), 5.55-5.59 (m, 2H), 7.22-7.37 (m, 9H), 7.45-7.53 (m, 6H); ^{13}C NMR (75 MHz, acetone-d6) δ -4.4, -4.1, 18.7, 26.4, 36.0, 39.1, 63.2, 68.1, 72.7, 87.3, 127.9, 128.7, 129.5, 129.6, 131.6, 132.0, 145.3; MS (CI) *m/z* 528 $(M)^+$, 456, 319, 297, 243, 211, 175, 159, 117, 84; HRMS (CI) *m/z* 528.3052 (calcd for $C_{34}H_{44}O_3Si$: 528.3060).



108

(2*E*,5*E*,8*R*)-8-(*tert*-Butyldimethylsilyloxy)-1-chloro-9-trityloxy-nona-2,5-diene. Methanesulfonyl chloride (336 μL, 4.31 mmol) was added dropwise *via* syringe to a stirred suspension of (2*R*,4*E*,7*E*)-2-(*tert*-butyldimethylsilyloxy)-1-trityloxy-nona-4,7-dien-9-ol (1.52 g, 2.87 mmol), collidine (1.90 mL, 14.4 mmol) and LiCl (121.5 mg, 3.16 mmol) in DMF (15 mL) at 0 °C under argon. The resulting mixture was allowed to warm to ambient temperature and was stirred for 21 h. The mixture was placed in a separatory funnel containing Et_2O/pentane (1:1, 50 mL) and saturated aqueous $NaHCO_3$ (50 mL). The aqueous phase was extracted with Et_2O/pentane (1:1,10 mL) and the combined organic fractions were washed with saturated aqueous $Cu(NO_3)_2$ (4 x 10 mL). The combined aqueous fractions were extracted with Et_2O/pentane (1:1, 10 mL), and the combined extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified on a short column of silica gel (20% Et_2O in pentane) to yield 1.56 g (99%) of (2*E*,5*E*,8*R*)-8-(*tert*-butyldimethylsilyloxy)-1-chloro-9-trityloxy-nona-2,5-diene: $[\alpha]_D^{23}$ + 2.30 (c 1.0, $CHCl_3$) IR (neat) 3086, 3059, 3033, 2954, 2928, 2884, 2856, 1491, 1471, 1463, 1449, 1361, 1252, 1076 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ -0.01 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 2.13-2.24 (m, 1H), 2.34-2.48 (m, 1H), 2.66-2.82 (m, 2H), 2.95-3.12 (m, 2H), 3.80 (quintet, J = 5.7 Hz, 1H), 4.03 (d, J = 7.1 Hz, 2H), 5.36-5.42 (m, 2H), 5.52-5.78 (m, 2H), 7.20-7.35 (m, 9H), 7.44-7.51 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.7, -4.5, 18.1, 25.9, 35.0, 38.3, 45.2, 67.1, 71.7, 86.4, 126.4, 126.9, 127.7, 128.2, 128.7, 129.3, 134.1, 144.2; MS

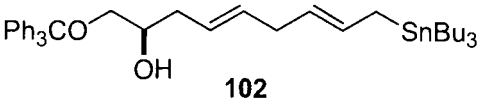
(CI) *m/z* 546 $(M)^+$, 511, 469, 417, 333, 243, 165, 117, 73; HRMS (CI) *m/z* 546.2715 (calcd for $C_{34}H_{43}O_2Si^{35}Cl$: 546.2721).



109

(2*R*,4*E*,7*E*)-2-(*tert*-Butyldimethylsilyloxy)-9-(tri-*n*-butylstannyl)-1-trityloxy-nona-4,7-diene. Tri-*n*-butyltin chloride (2.70 mL, 4.02 g, 96%, 10.9 mmol) was added to finely cut lithium wire (930 mg,) under argon at ambient temperature. THF (12.5 mL) was added and the mixture was stirred for 22 h. The resulting dark green suspension was transferred *via* cannula to a 50 mL flask under argon and was cooled to –78 °C. A solution of (2*E*,5*E*,8*R*)-8-(*tert*-butyldimethylsilyloxy)-1-chloro-9-trityloxy-nona-2,5-diene (1.19 g, 2.17 mmol) in THF (2 mL) was added dropwise during 20 min, and the mixture was stirred for 6.5 h at –78 °C. The mixture was diluted with saturated aqueous NH_4Cl (10 mL) and was extracted with Et_2O (20 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified on a short column of silica gel (0-20% Et_2O in hexane containing 1% Et_3N) to yield 1.46 g (84%) of (2*R*,4*E*,7*E*)-2-(*tert*-butyldimethylsilyloxy)-9-(tri-*n*-butylstannyl)-1-trityloxy-nona-4,7-diene: $[\alpha]_D^{23}$ +0.80 (c 1.0, $CHCl_3$); IR (neat) 3086, 3059, 3022, 2955, 2927, 2871, 2855, 1491, 1463, 1449, 1376, 1361, 1254, 1220, 1183 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ -0.01 (s, 3H), 0.05 (s, 3H), 0.80-0.97 (m, 24H), 1.22-1.38 (m, 6H), 1.43-1.57 (m, 6H), 1.71 (d, *J* = 8.4 Hz, 2H), 2.12-2.23 (m, 1H), 2.34-2.43 (m, 1H), 2.61 (t, *J* = 6.1 Hz, 2H), 3.00 (d, *J* = 1.9 Hz, 1H), 3.02 (d, *J* = 2.4 Hz, 1H), 3.79 (quintet, *J* = 5.7 Hz, 1H), 5.08-5.20 (m, 1H), 5.25-5.44 (m, 2H), 5.45-5.58 (m, 1H), 7.19-7.34 (m, 9H), 7.44-7.52 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -

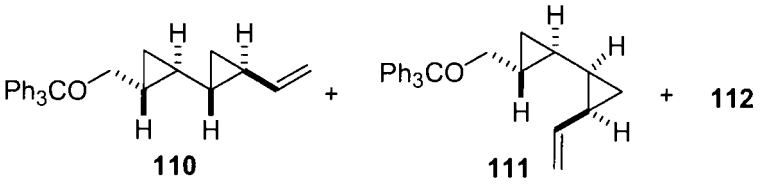
4.7, -4.5, 9.2, 13.7, 14.2, 18.1, 25.9, 27.3, 29.1, 35.9, 38.4, 67.3, 72.0, 86.4, 123.7, 126.4, 126.8, 127.6, 128.8, 129.9, 131.9, 144.3; MS (CI) *m/z* 802 $(M)^+$,745, 675, 559, 501, 445, 365, 291, 243, 165, 117, 75; HRMS (CI) *m/z* 802.4179 (calcd for $C_{46}H_{70}O_2Si^{120}Sn$: 802.4167).



102

(2*R*,4*E*,7*E*)-9-(Tri-*n*-butylstannyl)-1-trityloxy-nona-4,7-dien-2-ol. TBAF (199 μL, 1.0 M in THF) was added dropwise *via* syringe to a stirred solution of (2*R*,4*E*,7*E*)-2-(*tert*-butyldimethylsilyloxy)-9-(tri-*n*-butylstannyl)-1-trityloxy-nona-4,7-diene (145 mg, 0.18 mmol) in THF (2.5 mL) under argon, and the mixture was stirred at ambient temperature for 20 h. The mixture was placed in a separatory funnel containing CH_2Cl_2 (20 mL) and saturated aqueous NH_4Cl (10 mL) and the separated aqueous phase was extracted with CH_2Cl_2 (5 mL). The combined organic extracts were dried (Na_2SO_4), filtered, concentrated under reduced pressure, and the residue was purified on a column of silica gel (5-15% EtOAc in hexane containing 1% Et_3N) to afford 106 mg (85%) of (2*R*,4*E*,7*E*)-9-(tri-*n*-butylstannyl)-1-trityloxy-nona-4,7-dien-2-ol: $[\alpha]_D^{23}$ -0.80 (c 1.0, $CHCl_3$); IR (neat) 3458, 3086, 3059, 3022, 2955, 2925, 2871, 2853, 1490, 1449, 1376, 1220, 1183, 1154 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.78-1.04 (m, 15H), 1.23-1.38 (m, 6H), 1.45-1.59 (m, 6H), 1.72 (d, *J* = 6.9 Hz, 2H), 2.11-2.45 (m, 2H), 2.53-2.70 (m, 2H), 3.06 (d, *J* = 5.1 Hz, 2H), 3.71-3.88 (m, 2H), 5.09-5.24 (m, 1H), 5.30-5.47 (m, 2H), 5.48-5.64 (m, 1H), 7.21-7.37 (m, 9H), 7.47-7.54 (m, 6H); $^{13}CNMR$ (75 MHz, $CDCl_3$) δ 9.2, 13.7, 14.3, 27.3, 29.1, 29.7, 35.8, 37.0, 67.0, 70.6, 86.6, 123.3, 125.5, 127.0, 127.6, 128.7, 130.2, 133.0, 143.9; MS (CI) *m/z* 711

$(M+Na)^+$, 637, 543, 527, 421, 387, 339, 291, 244, 205, 167, 97, 71; HRMS (CI) *m/z* 711.3198 (calcd for $C_{40}H_{56}O_2{}^{120}SnNa$ $(M+Na)^+$: 711.3200).



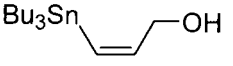
(1*R*)-1-(Trityloxymethyl)-6-vinylbicyclopropane. Triflic anhydride (44 μL, 0.26 mmol) was added dropwise *via* syringe to a solution of (2*R*,4*E*,7*E*)-9-(tri-*n*-butylstannyl)-1-trityloxy-nona-4,7-dien-2-ol (150 mg, 0.22 mmol) and 2,6-lutidine (38 μL, 0.33 mmol) in CH_2Cl_2 (3 mL) at -78 °C under argon, and the mixture was stirred for 20 min. Et_3N (76 μL, 0.55 mmol) was added dropwise *via* syringe, the mixture was stirred for an additional 20 min at -78 °C, then warmed to ambient temperature. After 20 min, the mixture was concentrated under reduced pressure, and the residue was purified by column chromatography (2-5% $CHCl_3$ in hexane containing 1% Et_3N) to yield 82.3 mg (99%) of a mixture of three bicyclopropanes in the ratio 2.3:1:1 (Chiral OD, 0.85 mL/min, 100% hexanes): ^1H NMR (300 MHz, $CDCl_3$) δ 0.22-0.48 (m, 2H), 0.48-1.12 (m, 5H), 1.16-1.38 (m, 1H), 1.42-1.66 (m, 1H), 2.77 (dd, *J* = 7.7, 9.6 Hz, 0.2H), 2.82-2.94 (m, 0.8H), 2.94-3.06 (m, 0.8H), 3.11 (dd, *J* = 5.8, 9.6 Hz, 0.2H), 4.86 (dt, *J* = 1.6, 10.2 Hz, 0.5 H), 4.95 (d, *J* = 2.2, 0.1H), 4.98 (t, *J* = 2.5Hz, 0.2H), 5.00-5.04 (m, 0.3H), 5.07-5.10 (m, 0.3H), 5.18 (dd, *J* = 2.2, 17.0 Hz, 0.4H), 5.42 (dt, *J* = 9.6, 17.0 Hz, 0.5H), 5.70 (dt, *J* = 9.6, 17.0 Hz, 0.3 H), 5.90 (dt, *J* = 10.2, 17.0 Hz, 0.2H), 7.20-7.37 (m, 9H), 7.42-7.55 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.4, 9.3, 10.4, 12.0, 12.4, 16.1, 16.2, 16.7, 17.6, 18.5, 18.9, 21.5, 21.7, 21.8, 22.5, 67.8, 68.0, 86.5, 111.7, 113.9, 114.0, 127.3, 128.1, 129.1, 139.6, 139.9, 142.2, 144.9;

MS (CI) *m/z* 380 $(M)^+$, 371, 362, 339, 303, 271, 243, 183, 165, 129, 105, 79; HRMS (CI) *m/z* 380.2146 (calcd for $C_{28}H_{28}O$: 380.2140).

Bu_3SnOTf

113

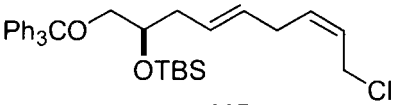
Tri-*n*-butylstannyl Triflate. Triflic anhydride (4.33 mL, 98%, 25.2 mmol) was added slowly to a round bottom flask containing bis(tri-*n*-butyltin)oxide (13.35 mL, 96%, 25.2 mmol) at 0 °C under argon, and the mixture was allowed to warm to ambient temperature. After 3 h, the mixture was purified *via* distillation (173.5-174.5 °C, 0.150 mmHg) to afford 15.4 g (70%) of tri-*n*-butylstannyl triflate: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, J = 7.4 Hz, 9H), 1.30-1.46 (m, 12H), 1.62-1.74 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.4, 21.2, 26.7, 27.3.



114

(*Z*)-3-Tri-*n*-butylstannyl-prop-2-en-1-ol. Propargyl alcohol (6.86 g, 7.13 mL, 123 mmol) was added slowly to a stirred suspension of $LiAlH_4$ (2.45 g, 95%, 61.2 mmol) in THF (230 mL) at 0 °C under argon and the mixture was warmed to ambient temperature over 1.5 h. After 19 h, the mixture was cooled to -78 °C and a solution of tri-*n*-butylstannyl triflate (15.42 g, 35.1 mmol) in THF (15 mL) was added slowly. After 4 h, the reaction was quenched with NH_3 gas (10 min, bubbler), then MeOH (10 mL) and saturated aqueous Na^+/K^+ tartrate (150 mL) were added, the aqueous fraction was extracted with CH_2Cl_2 (2 x 75 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification *via* distillation (125-127 °C, 0.15 mmHg) afforded 7.04 g (58%) of (*Z*)-3-tri-*n*-butylstannyl-prop-2-en-1-ol: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80-1.04 (m, 15H), 1.24-

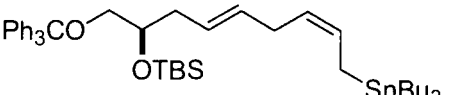
1.38 (m, 6H), 1.40-1.56 (m, 6H), 4.11 (td, J = 1.1, 5.8 Hz, 2H), 6.08 (dt, J = 1.1, 12.9 Hz, 1H), 6.69 (dt, J = 5.8, 12.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.6, 13.7, 27.3, 29.1, 66.1, 131.7, 146.2.



115

(2*Z*,5*E*,8*R*)-8-(*tert*-Butyldimethylsilyloxy)-1-chloro-9-trityloxy-nona-2,5-diene. (2*E*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-1-chloro-6-trityloxy-hex-2-ene (1.05 g, 2.07 mmol) and (*Z*)-3-tri-*n*-butylstannyl-prop-2-en-1-ol (794 mg, 2.29 mmol) were taken up in *N*-methyl-2-pyrrolidinone (11 mL) and degassed with an argon bubbler for 10 min. A solution of bis(acetonitrile)palladium(II) chloride (12.0 mg, 10 mol%) in *N*-methyl-2-pyrrolidinone (1.5 mL) was then added the mixture was degassed with an argon bubbler an additional 5 min. After 21 h, the mixture was added to a separatory funnel containing saturated aqueous NH_4Cl (30 mL) and CH_2Cl_2 (75 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL) and the organic extracts were dried (Na_2SO_4), filtered, concentrated under reduced pressure and dried *in vacuo*. Methanesulfonyl chloride (241 μL, 3.11 mmol) was added dropwise *via* syringe to a stirred solution of the crude alcohol, collidine (1.37 mL, 10.4 mmol) and LiCl (87.5 mg, 2.28 mmol) in DMF (22 mL) at 0 °C under argon, and the mixture was allowed to warm to ambient temperature. After 23 h, the mixture was added to a separatory funnel containing Et_2O/pentane (1:1, 75 mL) and saturated aqueous $NaHCO_3$ (25 mL). The aqueous phase was extracted with Et_2O/pentane (1:1, 10 mL) and the combined organic extracts were washed with saturated aqueous $Cu(NO_3)_2$ (3 x 40 mL). The combined aqueous $Cu(NO_3)_2$ washes were extracted with Et_2O/pentane (1:1, 10 mL),

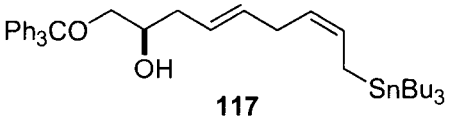
and the combined extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification on a short column of silica gel (2-10% EtOAc/hexane) afforded 762 mg (84%, 2 steps) of (2*Z*,5*E*,8*R*)-8-(*tert*-butyldimethylsilyloxy)-1-chloro-9-trityloxy-nona-2,5-diene: $[\alpha]_D^{23}$ + 0.71 (c 1.41, $CHCl_3$); IR (neat) 3086, 3059, 3025, 2954, 2928, 2883, 2856, 1597, 1491, 1471, 1449, 1361, 1253, 1220, 1076 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ -0.01 (m, 3H), 0.02 (m, 3H), 0.87 (s, 9H), 2.14-2.25 (m, 1H), 2.34-2.45 (m, 1H), 2.75 (brdd, *J* = 3.1, 7.1 Hz 2H), 2.99 (dd, *J* 5.8, 9.3 Hz, 1H), 3.03 (dd, *J* = 5.1, 9.3 Hz, 1H), 3.79 (quintet, *J* = 5.7 Hz, 1H), 4.04 (d, *J* = 7.5 Hz, 2H), 5.34-5.39 (m, 2H), 5.49-5.69 (m, 2H), 7.20-7.33 (m, 9H), 7.44-7.49 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.7, -4.5, 18.1, 25.8, 30.1, 38.2, 39.3, 67.0, 71.6, 86.3, 125.6, 126.9, 127.7, 128.7, 129.3, 132.9, 144.2; MS (CI) *m/z* 547 $(M+H)^+$, 512, 489, 469, 417, 407, 243, 165; HRMS (CI) *m/z* 546.2740 (calcd for $C_{34}H_{43}O_2{}^{35}ClSi$: 546.2721).



116

(2*R*,4*E*,7*Z*)-2-(*tert*-Butyldimethylsilyloxy)-9-(tri-*n*-butylstannyl)-1-trityloxy-nona-4,7-diene. Tri-*n*-butyltin chloride (2.02 mL, 96%, 8.90 mmol) was added to finely cut lithium wire (692 mg) under argon at ambient temperature. THF (10 mL) was added and the mixture was stirred for 21 h. The resulting dark green suspension was transferred *via* cannula to a 50 mL flask under argon and was cooled to –78 °C. A solution of (2*Z*,5*E*,8*R*)-8-(*tert*-butyldimethylsilyloxy)-1-chloro-9-trityloxy-nona-2,5-diene (762 mg, 1.39 mmol) in THF (3 mL) was added dropwise during 20 min, and the mixture was stirred for 22 h at –78 °C. The mixture was diluted with 50% aqueous

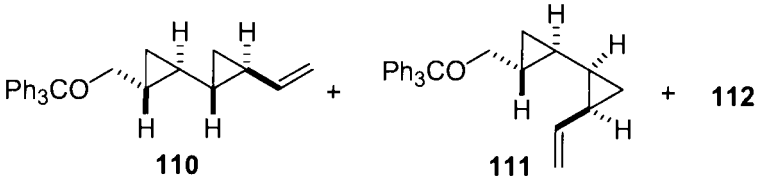
NH_4Cl (25 mL) and was extracted with CH_2Cl_2 (50 mL, 2 x 10 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified on a short column of silica gel (0-20% EtOAc in hexane) to yield 1.50 g (93%) of (2*R*,4*E*,7*Z*)-2-(*tert*-butyldimethylsilyloxy)-9-(tri-*n*-butylstannyl)-1-trityloxy-nona-4,7-diene as a colorless oil: $[\alpha]_D^{23}$ + 0.91 (c 1.1, $CHCl_3$); IR (neat) 3086, 3060, 3023, 2955, 2927, 2855, 1598, 1491, 1463, 1449, 1376, 1361, 1254, 1220, 1183, 1076 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.04 (s, 3H), 0.86-0.94 (m, 24H), 1.27-1.39 (m, 6H), 1.42-1.56 (m, 6H), 1.71 (d, *J* = 8.4 Hz, 2H), 2.14-2.24 (m, 1H), 2.36-2.45 (m ,1H), 2.61 (t, *J* = 6.2 Hz, 1H), 2.63-2.70 (m, 1H), 3.01-3.05 (m, 2H), 3.76-3.82 (m, 1H), 5.11-5.20 (m, 1H), 5.27-5.43 (m, 2H), 5.47-5.62 (m, 1H), 7.21-7.33 (m, 10H), 7.47-7.50 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.5, -4.7, 9.2, 9.3, 10.4, 13.7, 14.2, 18.1, 25.9, 27.1, 27.3, 27.6, 29.1, 30.2, 35.9, 38.3, 67.2, 72.0, 86.3, 122.0, 123.7, 126.4, 126.8, 127.6, 128.3, 129.4, 131.4, 131.9, 144.3; MS (CI) *m/z* 802 $(M)^+$, 800, 745, 662, 655, 291, 243, 235, 165; HRMS (CI) *m/z* 802.4176 (calcd for $C_{46}H_{70}O_2{}^{120}SnSi$: 802.4167).



117

(2*R*,4*E*,7*Z*)-9-(Tri-*n*-butylstannyl)-1-trityloxy-nona-4,7-dien-2-ol. TBAF (1.89 mL, 1.0 M in THF) was added dropwise *via* syringe to a stirred solution of (2*R*,4*E*,7*Z*)-2-(*tert*-butyldimethylsilyloxy)-9-(tri-*n*-butylstannyl)-1-trityloxy-nona-4,7-diene (960 mg, 1.20 mmol) and Et_3N (836 μL) in THF (10 mL) at ambient temperature under argon. After 7 h, the mixture was concentrated under reduced pressure and the residue was purified by column chromatography to yield 595 mg

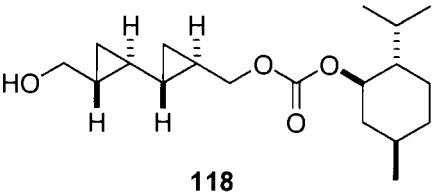
(72%) of (2*R*,4*E*,7*Z*)-9-(tri-*n*-butylstannyl)-1-trityloxy-nona-4,7-dien-2-ol: $[\alpha]_D^{23}$ - 0.60 (c 1.0, $CHCl_3$); IR (neat) 3454, 3086, 3059, 3022, 2955, 2924, 2870, 2852, 1597, 1491, 1448, 1418, 1376, 1120, 1183, 1154, 1074 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.80-0.94 (m, 15H), 1.23-1.38 (m, 6H), 1.42-1.56 (m, 6H), 1.70 (d, *J* = 8.6 Hz, 2H), 2.13-2.32 (m, 2H), 2.65 (quintet, *J* = 6.7 Hz, 2H), 3.09 (dd, *J* = 6.7, 9.3 Hz, 1H), 3.17 (dd, *J* = 4.0, 9.3 Hz, 1H), 3.74-3.84 (m, 1H), 5.09-5.21 (m, 1H), 5.27-5.64 (m, 3H), 7.22-7.35 (m, 9H), 7.43-7.47 (m, 6H); ^{13}C NMR (75 MHz, acetone-d_6) δ 9.2, 9.3, 13.7, 14.2, 27.3, 29.1, 35.8, 36.9, 67.0, 70.6, 86.6, 123.3, 125.5, 127.0, 127.8, 128.7, 130.2, 133.0, 143.9; MS (CI) *m/z* 688 (M+H)+, 611, 483, 445, 387, 331, 291, 243, 183, 165, 105; HRMS (CI) *m/z* 688.3314 (calcd for $C_{40}H_{56}O_2{}^{120}Sn$: 688.3302).



110 111

Triflation and Solvolysis of (2*R*,4*E*,7*Z*)-9-(Tri-*n*-butylstannyl)-1-trityloxy-nona-4,7-dien-2-ol. Triflic anhydride (757 μL, 4.49 mmol) was added dropwise *via* syringe to a stirred solution of (2*R*,4*E*,7*Z*)-9-(tri-*n*-butylstannyl)-1-trityloxy-nona-4,7-dien-2-ol (2.51 g, 3.65 mmol) and collidine (593 μL, 4.49 mmol) in CH_2Cl_2 (40 mL) at -78 °C under argon, and the mixture was stirred for 2 h. Et_3N (1.43 mL, 11.0 mmol) was added dropwise *via* syringe during 30 min, and the mixture was stirred for an additional 22 h at -78 °C. The mixture was concentrated under reduced pressure, and the residue was purified by column chromatography (5% EtOAc in hexane) to yield 1.37 g (99%) of a mixture of three bicyclopropanes in the ratio 3.7:1:1 (Chiral OD, 0.85 mL/min, 100% hexanes): ^1H NMR (300 MHz, $CDCl_3$) δ 0.22-0.48 (m, 2H), 0.48-

1.12 (m, 5H), 1.16-1.38 (m, 1H), 1.42-1.66 (m, 1H), 2.77 (dd, *J* = 7.7, 9.6 Hz, 0.2H), 2.82-2.94 (m, 0.8H), 2.94-3.06 (m, 0.8H), 3.11 (dd, *J* = 5.8, 9.6 Hz, 0.2H), 4.86 (dt, *J* = 1.6, 10.2 Hz, 0.5 H), 4.95 (d, *J* = 2.2, 0.1H), 4.98 (t, *J* = 2.5Hz, 0.2H), 5.00-5.04 (m, 0.3H), 5.07-5.10 (m, 0.3H), 5.18 (dd, *J* = 2.2, 17.0 Hz, 0.4H), 5.42 (dt, *J* = 9.6, 17.0 Hz, 0.5H), 5.70 (dt, *J* = 9.6, 17.0 Hz, 0.3 H), 5.90 (dt, *J* = 10.2, 17.0 Hz, 0.2H), 7.20-7.37 (m, 9H), 7.42-7.55 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.4, 9.3, 10.4, 12.0, 12.4, 16.1, 16.2, 16.7, 17.6, 18.5, 18.9, 21.5, 21.7, 21.8, 22.5, 67.8, 68.0, 86.5, 111.7, 113.9, 114.0, 127.3, 128.1, 129.1, 139.6, 139.9, 142.2, 144.9; MS (CI) *m/z* 380 $(M)^+$, 371, 362, 339, 303, 271, 243, 183, 165, 129, 105, 79; HRMS (CI) *m/z* 380.2146 (calcd for $C_{28}H_{28}O$: 380.2140).

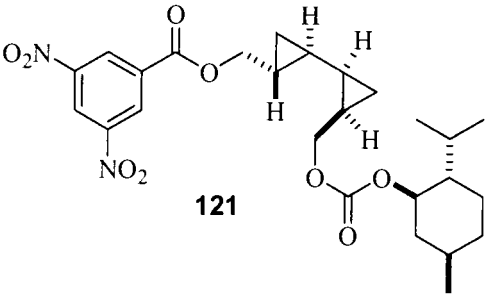


118

(1*R*,2*S*,4*S*,5*R*)-1-Hydroxymethyl-6-[hydroxymethyl-(1'*R*,2'*S*,5'*R*)-menthyl-carbonyloxymethyl]bicyclopropane. $K_2OsO_4 \cdot 2H_2O$ (49.4 mg, 5 mol%) and $NaIO_4$ (571 mg, 2.68 mmol) were added to a stirred solution containing **110** and **111** and **112** (1.02 g, 2.68 mmol) in THF (30 mL) and H_2O (25 mL). After 1 h, an additional quantity of $NaIO_4$ was added (1.71 g, 8.04 mmol) and the reaction was stirred for 21 h. Saturated aqueous $Na_2S_2O_3$ (15 mL) was added and, after 30 min, the mixture was extracted with 75% EtOAc in hexane (3 x 25 mL). The combined extracts were dried (Na_2SO_4), filtered, concentrated under reduced pressure and dried *in vacuo* to give a crude mixture of aldehydes. To this mixture in THF (40 mL) was added $NaBH_4$ (102.1 mg, 2.68 mmol) and the reaction flask was purged with argon. After 20 h, the

reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL), and filtered through Celite. The filter cake was washed with CH_2Cl_2 (200 mL) and the combined filtrate was dried (Na_2SO_4), concentrated under reduced pressure and then dried *in vacuo* to give a mixture of primary alcohols. To a solution of this mixture (1.03 g) and pyridine (649 μL) in CH_3CN (20 mL) was added (*R*)-(−)-menthyl chloroformate (624 μL, 643 mg, 2.94 mmol). The reaction flask was purged with argon and the mixture was stirred for 46 h. The mixture was placed in a separatory funnel containing saturated aqueous NH_4Cl (25 mL) and EtOAc (75 mL, 2 x 25 mL), and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (2-20% EtOAc in hexane) to yield 1.11 g of a 3.7:1:1 mixture of stereoisomeric menthyl carbonates. The mixture (943 mg, 1.66 mmol) was taken up in EtOH (180 mL), $Pd(OH)_2/C$ (109 mg, 20 wt%) was added, and the reaction flask was placed under an atmosphere of hydrogen gas. After 18 h, the mixture was filtered through Celite, the filter cake was washed with EtOAc (3 x 15 mL), and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (10-60% Et_2O in petroleum ether) to yield 326 mg (61%, 45% from **110**) of (1*R*,2*S*,4*S*,5*R*)-1-hydroxymethyl-6-[hydroxymethyl-(1'*R*,2'*S*,5'*R*)-menthylcarbonyloxymethyl]bicyclopropane as a crystalline solid: mp 58-59 °C; $[\alpha]_D^{23}$ - 40.2 (c 1.0, $CHCl_3$); IR (film) 3394, 3063, 2995, 2956, 2921, 2867, 2849, 1738, 1458, 1386, 1263, 1182 cm^{-1}; ^1H NMR (300 MHz, CDCl3) δ 0.32 (dd, *J* = 6.3, 13.4 Hz, 2H), 0.34-0.46 (m, 2H), 0.78 (dd, *J* = 1.5, 7.0 Hz, 4H), 0.86-0.94 (m, 8H), 0.95-1.11 (m, 3H), 1.34-1.53 (m, 3H), 1.62-1.72 (m, 2H), 1.91-2.10 (m, 2H), 3.34-3.48 (m, 2H), 3.89 (dd, *J* = 7.4, 11.3 Hz, 1H), 3.92 (dd, *J* = 7.1, 11.3 Hz, 1H),

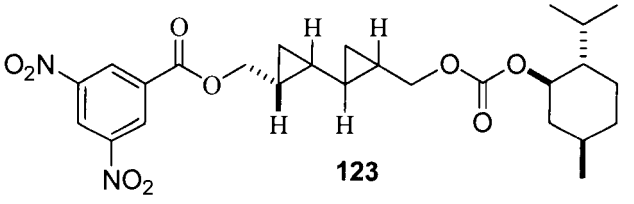
4.49 (td, J = 4.4, 11.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.0, 8.5, 8.6, 15.9, 16.0, 16.2, 17.7, 17.8, 18.4, 18.6, 19.5, 19.7, 20.7, 21.9, 23.2, 26.0, 31.3, 34.1, 40.7, 46.9, 66.6, 71.5, 76.6, 78.1, 155.0; MS (CI) *m/z* 325(M+H)$^+$, 307, 281, 239, 227, 187, 168, 138; HRMS (CI) *m/z* 325.2377 (M+H)$^+$ (calcd for $C_{19}H_{33}O_4$: 325.2378).



121

(1*R*,2S,4*R*,5*R*)-1-(3,5-Dinitrobenzoyloxymethyl)-6-[(1'*R*,2'*S*,5'*R*)-menthyl-carbonyloxymethyl]bicyclopropane. A solution containing the 1:1 mixture of stereoisomers obtained above (95 mg, 0.29 mmol), 3,5-dinitrobenzoyl chloride (82.7 mg, 98%, 0.35 mmol) and pyridine (71 μl, 0.88 mmol) in $CHCl_2$ (1 mL) was stirred at ambient temperature for 30 min. The mixture was placed in a separatory funnel containing 50% aqueous NH_4Cl (10 mL) and EtOAc (20 mL), and the separated organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (50-100% $CHCl_3$ in petroleum ether) to yield 151.4 mg of a mixture of two 3,5-dinitrobenzoates which was taken up in MeOH/H_2O (4 mL, 9:1). Sodium benzoate (42.1 mg, 0.29 mmol) was added and the mixture was stirred at ambient temperature under argon. After 52 h, the mixture was placed in a separatory funnel containing saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure, and the residue was purified by column chromatography (10-40% EtOAc in hexane) to yield 53.5 mg

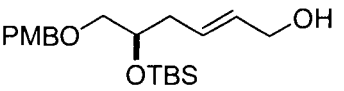
(35%, 8% from **111**) of (1*R*,2S,4*R*,5*R*)-1-3,5-dinitrobenzoyloxymethyl]-6-[(1'*R*,2'*S*,5'*R*)-menthylcarbonyloxymethyl]bicyclopropane as a crystalline solid: mp 108-109 °C; $[\alpha]_D^{23}$ (c - 27.6, $CHCl_3$); IR (film) 3104, 3001, 2956, 2928, 2871, 1733, 1630, 1598, 1547, 1459, 1345, 1284, 1260, 1161, 1076 (film) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.24 (q, *J* = 5.4 Hz, 1H), 0.65 (dd, *J* = 6.5, 7.2 Hz, 2 H), 0.75 (dd, *J* = 5.3, 8.4 Hz, 1H), 0.78 (d, *J* = 7.0 Hz, 3H), 0.81-0.87 (m, 1H), 0.88-0.93 (m, 8H), 0.94-1.11 (m, 2H), 1.20-1.31 (m, 2H), 1.33-1.42 (m, 1H), 1.42-1.54 (m, 1H),1.64-1.71 (m, 2H), 1.91-2.03 (m, 2H), 4.11 (dd, *J* = 8.0, 11.3 Hz, 1H), 4.23 (dd, *J* = 7.5, 11.3 Hz, 1H), 4.27 (dd, *J* = 7.7, 11.5 Hz, 1H), 4.34 (dd, *J* = 7.3, 11.5 Hz, 1H), 4.45 (dd, *J* = 4.4, 10.9 Hz, 1H), 9.19 (d, *J* = 2.1 Hz, 2H), 9.23 (t, *J* = 2.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.8, 11.0, 14.9, 16.0, 16.2, 18.0, 20.7, 22.0, 23.3, 26.0, 31.4, 34.1, 40.7, 47.0, 68.6, 71.0, 78.2, 122.2, 129.6, 134.1, 148.6, 155.0, 162.6; MS (CI) *m/z* 519 $(M+H)^+$, 488, 458, 319, 289, 168, 139; HRMS (CI) *m/z* 519.2328 $(M+H)^+$ (calcd for $C_{26}H_{34}N_2O_9$: 519.2343).



123

(1*R*,2S,4*R*,5*R*)-1-(3,5-Dinitrobenzoyloxymethyl)-6-[(1'*R*,2'*S*,5'*R*)-menthyl-carbonyloxymethyl]bicyclopropane. There was obtained from above a fraction containing 1-hydroxymethyl-6-[(1'*R*,2'*S*,5'*R*)-menthylcarbonyloxy]bicyclopropane as a viscous oil. This was taken taken up in CH_2Cl_2 (500 μL), 3,5-dinitrobenzoyl chloride (41.4 mg, 98%, 0.18 mmol) and pyridine (35 μl, 0.44 mmol, 3 eq) were added, and the mixture was stirred at ambient temperature for 30 min. The mixture was placed in a

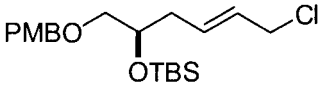
separatory funnel containing 50% aqueous NH_4Cl (5 mL) and EtOAc (10 mL), and the organic phase was separated, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (2-10% EtOAc/hexane) to yield 72.3 mg (48%, 11% from **112**) of 1-(3,5-dinitrobenzoyloxymethyl)-6-[(1'*R*,2'*S*,5'*R*)-menthylcarbonyloxy]bicyclopropane as a pure crystalline compound: mp 76-78 °C; $[\alpha]_D^{23}$ - 6.12 (c 1.88, $CHCl_3$); IR (film) 3105, 2998, 2956, 2925, 2871, 1732, 1630, 1599, 1548, 1460, 1345, 1283, 1260, 1162, 1076 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.20 (q, *J* = 5.4 Hz, 1H), 0.62-0.73 (m, 2H), 0.73-0.76 (m, 4H), 0.77-0.86 (m, 1H), 0.86-0.89 (m, 4H), 0.90-0.94 (m, 4H), 0.95-1.10 (m, 3H), 1.14-1.32 (m, 2H), 1.33-1.42 (m, 1H), 1.43-1.53 (m, 1H), 1.64-1.71 (m, 2H), 1.91 (quintd, *J* = 2.6, 6.9 Hz, 1H), 1.98-2.05 (m, 1H), 4.09-4.25 (m, 2H), 4.28 (dd, *J* = 7.3, 11.3 Hz, 1H), 4.35 (dd, *J* = 6.9, 11.4 Hz, 1H), 4.43 (td, *J* = 4.3, 10.9 Hz, 1H), 9.18 (dd, *J* = 2.1, 4.5 Hz, 1H), 9.22 (t, *J* = 2.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.8, 10.5, 15.1, 15.9, 16.2, 16.9, 17.8, 20.6, 22.0, 23.3, 26.1, 31.4, 34.1, 40.7, 46.9, 68.4, 70.8, 78.2, 122.2, 129.6, 133.9, 148.6, 154.9, 162.6; MS (CI) *m/z* 519 $(M+H)^+$,488, 319, 289, 168, 139; HRMS (CI) *m/z* $(M+H)^+$ 519.2347 (calcd for $C_{26}H_{35}N_2O_9$: 519.2343). The configuration of this bicyclopropane has not been determined.



125

(2*R*,4*E*)-2-(*tert*-Butyldimethylsilyloxy)-1-(4'-methoxybenzyloxy)-hex-4-en-6-ol. Red-Al (70 wt% in toluene, 221 μL, 0.76 mmol) was added slowly to a stirred solution of (2*R*)-2-(*tert*-butyldimethylsilyloxy)-1-(4'-methoxybenzyloxy)-hex-4-yn-6-ol (100 mg, 0.274 mmol) in Et_2O (5 mL) at 0 °C under argon. The cooling bath was removed

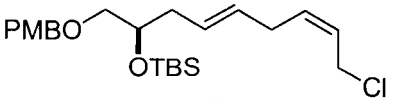
and the reaction mixture was stirred at ambient temperature for 3 h. Saturated aqueous Na^+/K^+ tartrate (5 mL) was then added and the biphasic mixture was stirred vigorously. The aqueous layer was extracted with CH_2Cl_2 (10 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification on a short column of silica gel (5-50% EtOAc/hexane) afforded 81 mg (81%) of (2*R*,4*E*)-2-(*tert*-butyldimethylsilyloxy)-1-(4'-methoxybenzyloxy)-hex-4-en-6-ol: $[\alpha]_D^{23}$ + 3.8 (c 1.0, $CHCl_3$); IR (neat) 3405, 3000, 2954, 2929, 2898, 2856, 1613, 1586, 1514, 1463, 1362, 1302, 1249, 1102 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.88 (s, 9H), 1.29 (brs, 1H), 2.15-2.26 (m, 1H), 2.28-2.38 (m, 1H), 3.34 (d, *J* = 1.6 Hz, 1H), 3.36 (d, *J* = 1.1 Hz, 1H), 3.80-3.90 (m, 4H), 4.05-4.09 (m, 2H), 4.45 (s, 2H), 5.60-5.76 (m, 2H), 6.84-6.91 (m, 2H), 7.21-7.28 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.7, -4.5, 18.2, 25.8, 37.6, 55.2, 63.7, 71.1, 72.9, 73.8, 113.7, 129.0, 129.2, 130.5, 131.5, 159.1; MS (CI) *m/z* 365 $(M)^+$, 295, 291, 241, 215, 199, 180, 159, 121; HRMS (CI) *m/z* 365.2158 (calcd for $C_{20}H_{33}O_4Si$ $(M-H)^+$: 365.2148).



126

(2*E*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-1-chloro-6-(4'-methoxybenzyloxy)-hex-2-ene. Methanesulfonyl chloride (678 μL, 8.72 mmol) was added dropwise *via* syringe to a stirred solution of (2*R*,4*E*)-2-(*tert*-butyldimethylsilyloxy)-1-(4'-methoxybenzyloxy)-hex-4-en-6-ol (2.13 g, 5.81 mmol), collidine (3.85 mL, 29.1 mmol) and LiCl (245 mg, 6.38 mmol) in DMF (50 mL) at 0 °C under argon, and the mixture was allowed to warm to ambient temperature. After 20 h, the mixture was added to a separatory funnel containing Et_2O/pentane (1:1, 100 mL) and saturated

aqueous $NaHCO_3$ (50 mL). The aqueous phase was extracted with Et_2O/pentane (1:1, 15 mL) and the combined organic extracts were washed with saturated aqueous $Cu(NO_3)_2$ (3 x 25 mL). The combined aqueous $Cu(NO_3)_2$ washes were extracted with Et_2O/pentane (1:1, 25 mL), and the combined extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification on a short column of silica gel (20% EtOAc/hexane) afforded 1.96 g (88%) of (2*E*,5*R*)-5-(*tert*-butyl-dimethylsilyloxy)-1-chloro-6-(4'-methoxybenzyloxy)-hex-2-ene: $[\alpha]_D^{23}$ + 7.9 (c 1.0, $CHCl_3$); IR (neat) 3033, 3001, 2954, 2929, 2897, 2856, 1613, 1585, 1514, 1463, 1362, 1249, 1173 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.88 (s, 9H), 2.16-2.28 (m, 1H), 2.30-2.41 (m, 1H), 3.32 (dd, *J* = 6.0, 9.6 Hz, 1H), 3.37 (dd, *J* = 5.5, 9.6 Hz, 1H), 3.81-3.90 (m, 4H), 3.99-4.04 (m, 2H), 4.45 (s, 2H), 5.58-5.69 (m, 1H), 5.73-5.84 (m, 1H), 6.85-6.91 (m, 2H), 7.22-7.28 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.8, -4.5, 18.1, 25.8, 37.5, 45.2, 55.2, 70.9, 73.0, 73.7, 113.7, 128.3, 129.2, 130.4, 132.0, 159.1; MS (CI) *m/z* 383 $(M-H)^+$, 295, 277, 247, 233, 197, 121, 117; HRMS (CI) *m/z* 383.1815 (calcd for $C_{20}H_{32}O_3SiCl$ $(M-H)^+$: 383.1809).



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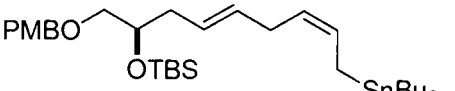
(2*Z*,5*E*,8*R*)-8-(*tert*-Butyldimethylsilyloxy)-1-chloro-9-(4'-methoxybenzyloxy)-nona-2,5-diene. (2*E*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-1-chloro-6-(4'-methoxy-benzyloxy)-hex-2-ene (1.76 g, 4.57 mmol) and (*Z*)-3-(tri-*n*-butylstannyl)-prop-2-en-1-ol (1.75 g, 5.02 mmol) were taken up in *N*-methyl-2-pyrrolidinone (20 mL) and degassed with an argon bubbler for 20 min. A solution of bis(acetonitrile)palladium(II) chloride (26.4 mg, 10 mol%) in *N*-methyl-2-

pyrrolidinone (2 mL) was then added the mixture was degassed with an argon bubbler an additional 10 min. After 21 h, the mixture was added to a separatory funnel containing brine (25 mL) and CH_2Cl_2 (75 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 15 mL) and the organic extracts were dried (Na_2SO_4), filtered, concentrated under reduced pressure and dried *in vacuo*. Methanesulfonyl chloride (476 μL, 6.14 mmol) was added dropwise *via* syringe to a stirred solution of the crude alcohol, collidine (2.70 mL, 20.5 mmol) and LiCl (172 mg, 4.48 mmol) in DMF (40 mL) at 0 °C under argon, and the mixture was allowed to warm to ambient temperature. After 22 h, the mixture was added to a separatory funnel containing Et_2O/pentane (1:1, 100 mL) and saturated aqueous $NaHCO_3$ (100 mL). The aqueous phase was extracted with Et_2O/pentane (1:1, 20 mL) and the combined organic extracts were washed with saturated aqueous $Cu(NO_3)_2$ (3 x 50 mL). The combined aqueous $Cu(NO_3)_2$ washes were extracted with Et_2O/pentane (1:1, 2 x 20 mL), and the combined extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification on a short column of silica gel (5-10% EtOAc/hexane) afforded 1.39 g (72%, 2 steps) of (2*Z*,5*E*,8*R*)-8-(*tert*-butyldimethylsilyloxy)-1-chloro-9-(4'-methoxybenzyloxy)-nona-2,5-diene: $[\alpha]_D^{23}$ + 6.2 (C 1.0, $CHCl_3$); IR (neat) 3028, 3001, 2954, 2929, 2898, 2856, 1613, 1513, 1471, 1362, 1249, 1173, 1101 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.92 (s, 9H), 2.14-2.23 (m, 1H), 2.28-2.36 (m, 1H), 2.82-2.88 (m, 2H), 3.38 (dd, *J* = 1.8, 5.5 Hz, 2H), 3.85 (s, 3H), 3.82-3.92 (m, 1H), 4.12 (d, *J* = 7.3 Hz, 2H), 4.45-4.52 (m, 2H), 5.41-5.55 (m, 2H), 5.61-5.75 (m, 2H), 6.89-6.94 (m, 2H), 7.27-7.31 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.7, -4.5, 18.2, 25.8, 30.2, 38.0, 39.3, 55.2, 71.4, 72.9, 73.9, 113.7, 125.7, 127.9, 129.2, 129.3, 130.5,

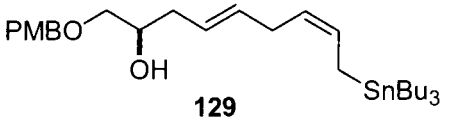
132.9, 159.1; MS (CI) *m/z* 424 $(M)^+$, 423, 389, 317, 295, 273, 241, 201, 185, 121; HRMS (CI) *m/z* 423.2126 (calcd for $C_{23}H_{36}O_3SiCl$ $(M-H)^+$: 423.2122).



128

(2*R*,4*E*,7*Z*)-2-(*tert*-Butyldimethylsilyloxy)-9-(tri-*n*-butylstannyl)-1-(4'-methoxy-benzyloxy)-nona-4,7-diene. Tri-*n*-butyltin chloride (4.65 mL, 96%, 18.8 mmol) was added to finely cut lithium wire (1.59 g) under argon at ambient temperature. THF (20 mL) was added and the mixture was stirred for 20 h. The resulting dark green suspension was transferred *via* cannula to a 100 mL flask under argon and was cooled to –78 °C. A solution of (2*Z*,5*E*,8*R*)-8-(*tert*-butyldimethylsilyloxy)-1-chloro-9-(4'-methoxybenzyloxy)-nona-2,5-diene (1.36 g, 3.20 mmol) in THF (15 mL) was added dropwise during 15 min, and the mixture was stirred for 21 h at –78 °C. The mixture was diluted with saturated aqueous NH_4Cl (50 mL) and was extracted with CH_2Cl_2 (50 mL, 3 x 15 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified on a short column of silica gel (0-20% EtOAc in hexane) to yield 2.05 g (94%) of (2*R*,4*E*,7*Z*)-2-(*tert*-butyldimethylsilyloxy)-9-(tri-*n*-butylstannyl)-1-(4'-methoxy-benzyloxy)-nona-4,7-diene: $[\alpha]_D^{23}$ + 1.8 (c 1.0, $CHCl_3$); IR (neat) 3007, 2956, 2927, 2855, 1613, 1587, 1514, 1463, 1376, 1249, 1172, 1097 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.84-0.94 (m, 24H), 1.25-1.38 (m, 6H), 1.44-1.56 (m, 6H), 1.73 (d, *J* = 9.1 Hz, 2H), 2.09-2.21 (m, 1H), 2.23-2.34 (m, 1H), 2.65-2.80 (m, 2H), 3.36 (d, *J* = 5.2 Hz, 2H), 3.79-3.86 (m, 4H), 4.46 (brs, 2H), 4.85-5.14 (m, 1H), 5.38-5.48 (m, 2H), 5.50-5.68 (m, 1H), 6.84-6.91 (m, 2H), 7.23-7.29 (m, 2H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.7, -4.5, 9.3,

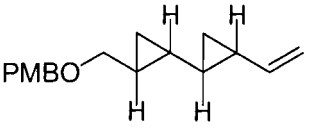
10.4, 13.7, 18.2, 25.9, 27.4, 29.2, 30.3, 38.1, 55.2, 71.7, 72.9, 74.1, 113.7, 121.9, 126.4, 128.9, 129.1, 130.7, 131.4, 159.1; MS (CI) *m/z* 679 $(M)^+$, 622, 500, 490, 365, 291, 235, 231, 179; HRMS (CI) *m/z* 680.3642 (calcd for $C_{35}H_{64}O_3SnSi$: 680.3647).



129

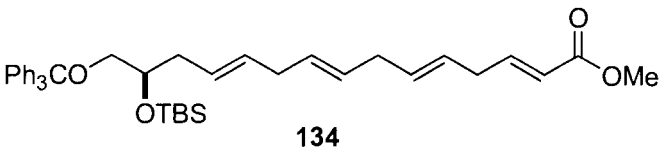
(2*R*,4*E*,7*Z*)-9-(tri-*n*-butylstannyl)-1-(4'-methoxybenzyloxy)-nona-4,7-dien-2-ol. TBAF (4.48 mL, 1.0 M in THF) was added dropwise *via* syringe to a stirred solution of (2*R*,4*E*,7*Z*)-2-(*tert*-butyldimethylsilyloxy)-9-(tri-*n*-butylstannyl)-1-(4'-methoxybenzyloxy)-nona-4,7-diene (2.03 g, 2.99 mmol) in THF (30 mL) at ambient temperature under argon. After 16 h, the mixture was added to a separatory funnel containing saturated aqueous NH_4Cl (25 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification of the residue on a short column of silica gel (5-30% Et_2O in hexane) gave 1.07 g (64%) of (2*R*,4*E*,7*Z*)-9-(tri-*n*-butylstannyl)-1-(4'-methoxybenzyloxy)-nona-4,7-dien-2-ol: $[\alpha]_D^{23}$ - 0.2 (c 1.0, $CHCl_3$); IR (neat) 3454, 3007, 2955, 2925, 2870, 2853, 1634, 1613, 1587, 1514, 1464, 1248, 1087 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.83-0.93 (m, 15H), 1.24-1.37 (m, 6H), 1.43-1.55 (m, 6H), 1.72 (d, *J* = 9.3 Hz, 2H), 2.17-2.24 (m, 2H), 2.34 (d, *J* = 3.3 Hz, 1H), 2.73 (t, *J* = 6.6, 2H), 3.34 (dd, *J* = 7.4, 9.3 Hz), 3.48 (dd, *J* = 3.3, 9.3 Hz, 1 H), 3.76-3.87 (m, 4H), 4.48 (s, 2H), 5.00-5.10 (m, 1H), 5.38-5.66 (m, 3H), 6.85-6.91 (m, 2H), 7.23-7.28 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.3, 10.4, 13.7, 27.3, 29.1, 30.2, 36.7, 55.2, 70.0, 73.0, 73.6, 113.8, 121.5, 125.3, 129.1, 129.3, 130.1, 132.4,

159.2; MS (CI) *m/z* 565 $(M)^+$, 509, 291, 269, 235, 179, 121, 91; HRMS (CI) *m/z* 564.2787 (calcd for $C_{29}H_{50}O_3Sn$: 564.2776).



130

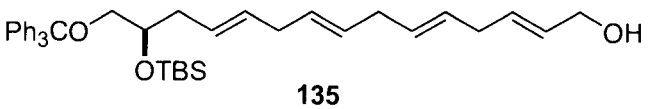
Triflation and Solvolysis of (2*R*,4*E*,7*Z*)-9-(Tri-*n*-butylstannyl)-1-(4'-methoxybenzyloxy)-nona-4,7-dien-2-ol. Triflic anhydride (90 μL, 0.53 mmol) was added dropwise *via* syringe to a solution of (2*R*,4*E*,7*Z*)-9-(tri-*n*-butylstannyl)-1-(4'-methoxybenzyloxy)-nona-4,7-dien-2-ol (200 mg, 0.35 mmol) and collidine (70 μL, 0.53 mmol) in CH_2Cl_2 (45 mL) at -78 °C under argon, and the mixture was stirred for 15 h. Et_3N (1.43 mL, 11.0 mmol) was added dropwise *via* syringe, the mixture was stirred for an additional 4 h at -78 °C, then at ambient temperature for 4 h. The mixture was concentrated under reduced pressure, and the residue was purified by column chromatography (2-10% EtOAc in hexane) to yield 68 mg (74%) of a mixture of six stereoisomeric bicyclopropanes (Chiral OD, 0.85 mL/min, 100% hexanes): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01-0.18 (m, 0.1H), 0.21-0.70 (m, 3.5H), 0.71-1.04 (m, 2.9H), 1.05-1.61 (m, 1.5H), 3.18-3.65 (m, 2H), 3.80 (s, 3H), 4.46 (s, 2H), 4.78-4.88 (m, 0.6H), 4.92-5.06 (m, 1H), 5.08-5.19 (m, 0.4H), 5.26-5.47 (m, 0.6H), 5.52-5.77 (m, 0.4H), 6.88 (d, J = 8.6 Hz, 1H), 7.26 (d, J = 8.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.0, 8.9, 11.4, 11.6, 12.2, 15.7, 16.4, 17.1, 18.2, 18.3, 20.9, 21.0, 21.3, 21.8, 22.0, 55.2, 70.4, 72.0, 73.6, 73.7, 111.3, 113.7, 129.2, 130.7, 138.9, 141.6, 159.1.



134

Methyl (2*E*,5*E*,8*E*,11*E*,14*R*)-14-(*tert*-Butyldimethylsilyloxy)-15-trityloxy-pentadeca-2,5,8,11-tetraenoate. (2*E*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-1-chloro-6-trityloxy-hex-2-ene (100 mg, 0.18 mmol) and (2*E*,5*E*)-6-(tri-*n*-butylstannyl)-hexa-2,5-dienoic acid methyl ester (83.5 mg, 0.20 mmol) were taken up in *N*-methyl-2-pyrrolidinone (500 μL), and degassed with an argon bubbler for 10 min. A solution of bis(acetonitrile)palladium(II) chloride (4.8 mg, 10 mol%) in *N*-methyl-2-pyrrolidinone (500 μL) was then added the mixture was degassed with an argon bubbler an additional 5 min. After 26 h, the mixture was added to a separatory funnel containing H_2O (5 mL) and Et_2O (20 mL). The aqueous phase was extracted with Et_2O (2 x 5 mL) and the organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified on a short column of silica gel (5-20% EtOAc in hexane) to afford 99 mg (85%) of methyl (2*E*,5*E*,8*E*,11*E*,14*R*)-14-(*tert*-butyldimethylsilyloxy)-15-trityloxy-pentadeca-2,5,8,11-tetraenoate: $[\alpha]_D^{23}$ + 1.2 (c 1.0, $CHCl_3$); IR (neat) 3059, 3024, 2952, 2928, 2894, 2856, 1726, 1654, 1491, 1462, 1449, 1271, 1256, 1158 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ -0.04-0.05 (m, 6H), 1.14 (s, 9H), 2.19 (dt, *J* = 6.2, 13.2 Hz, 1H), 2.39 (dt, *J* = 6.2, 13.2 Hz, 1H), 2.61-2.74 (m, 4H), 2.89 (q, *J* = 6.2 Hz, 2H), 2.99 (dd, *J* = 5.9, 9.5 Hz, 1H), 3.02-3.09 (m, 1H), 3.73 (s, 3H), 3.78 (quintet, *J* = 5.9 Hz, 1H), 5.29-5.55 (m, 6H), 5.83 (dt, *J* = 1.8, 15.4 Hz, 1H), 6.97 (dtd, *J* = 2.6, 6.6, 13.2 Hz, 1H), 7.19-7.32 (m, 9H), 7.43-7.49 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.7, -4.5, 18.1, 25.9, 32.8, 35.0, 35.5, 35.6, 38.3, 67.2, 71.8, 86.4, 121.3, 125.8, 126.8, 127.1, 127.7, 128.6, 128.8, 129.6, 130.8, 131.7, 144.2,

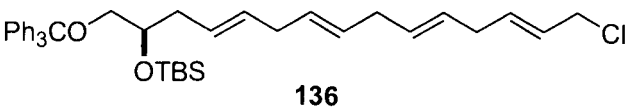
147.6, 167.0; MS (CI) *m/z* 635 $(M-H)^+$, 243, 215, 165, 105, 91; HRMS (CI) *m/z* 636.3637 (calcd for $C_{41}H_{52}O_4Si$: 636.3635).



135

(2*R*,4*E*,7*E*,10*E*,13*E*)-2-(*tert*-Butyldimethylsilyloxy)-1-trityloxy-pentadeca-4,7,10,13-tetraen-15-ol. A solution of methyl (2*E*,5*E*,8*E*,11*E*,14*R*)-14-(*tert*-butyldimethylsilyloxy)-15-trityloxy-pentadeca-2,5,8,11-tetraenoate (1.02 g, 1.60 mmol) in CH_2Cl_2 (25 mL) was cooled to -20 °C under argon and DiBAl-H (627 μL, neat, 3.53 mmol) was added slowly. The mixture was stirred for 10 min, then quenched with saturated aqueous Na^+/K^+ tartrate (25 mL). After 15 h of vigorous stirred, the aqueous phase was extracted with CH_2Cl_2 (2 x 15 mL), and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (10-50% EtOAc in hexane containing 1% Et_3N) to afford 795 mg (82%) of (2*R*,4*E*,7*E*,10*E*,13*E*)-2-(*tert*-butyldimethylsilyloxy)-1-trityloxy-pentadeca-4,7,10,13-tetraen-15-ol: $[\alpha]_D^{23}$ + 0.7 (c 1.0, $CHCl_3$); IR (neat) 3343, 3086, 3059, 3024, 2956, 2928, 2885, 2856, 1597, 1491, 1471, 1462, 1448, 1428, 1387, 1361, 1254, 1219, 1184 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ -0.03-0.05 (m, 6H), 0.85 (s, 9H), 2.18 (dt, *J* = 6.6, 13.7 Hz, 1H), 2.39 (dt, *J* = 1.9, 6.6, 13.7 Hz, 1H), 2.54 (q, *J* = 7.2 Hz, 1H), 2.60-2.79 (m, 6H), 2.95-3.10 (m, 2H), 3.73-3.83 (m, 1H), 4.10 (brs, 2H), 5.32-5.46 (m, 6H), 5.64-5.72 (m, 2H), 7.18-7.32 (m, 9H), 7.44-7.49 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.7, -4.5, 18.1, 25.9, 35.2, 35.6, 35.7, .8.3, 46.2, 67.2, 71.8, 86.4, 126.8, 127.1, 127.7, 128.3, 128.8, 129.0,

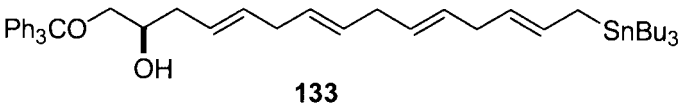
129.6, 130.0, 130.9, 131.4, 144.2; MS (CI) *m/z* 484 $(M-C_8H_{12}O)^+$, 378, 315, 302, 243, 215, 165.



136

(2*E*,5*E*,8*E*,11*E*,14*R*)-14-(*tert*-Butyldimethylsilyloxy)-1-chloro-15-trityloxy-pentadeca-2,5,8,11-tetraene. Methanesulfonyl chloride (140 μL, 1.80 mmol) was added dropwise *via* syringe to a stirred solution of (2*R*,4*E*,7*E*,10*E*,13*E*)-2-(*tert*-butyldimethylsilyloxy)-1-trityloxy-pentadeca-4,7,10,13-tetraen-15-ol (730 mg, 1.20 mmol), collidine (793 μL, 6.00 mmol) and LiCl (50.5 mg, 1.32 mmol) in DMF (10 mL) at 0 °C under argon, and the mixture was allowed to warm to ambient temperature. After 7 h, the mixture was added to a separatory funnel containing Et_2O/petroleum ether (1:1, 50 mL) and saturated aqueous $NaHCO_3$ (25 mL). The aqueous phase was extracted with Et_2O/petroleum ether (5 mL) and the combined organic extracts were washed with saturated aqueous $Cu(NO_3)_2$ (2 x 25 mL). The combined aqueous $Cu(NO_3)_2$ washes were extracted with Et_2O/petroleum ether (1:1, 5 mL), and the combined extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification on a short column of silica gel (20% EtOAc/hexane) afforded 620 mg (82%) of (2*E*,5*E*,8*E*,11*E*,14*R*)-14-(*tert*-butyldimethylsilyloxy)-1-chloro-15-trityloxy-pentadeca-2,5,8,11-tetraene: $[\alpha]_D^{23}$ + 1.3 (c 1.0, $CHCl_3$); IR (neat) 3086, 3059, 3031, 2954, 2928, 2886, 2856, 1597, 1491, 1471, 1448, 1361, 1252, 1220, 1154 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ -0.03-0.02 (m, 6H), 0.86 (s, 9H), 2.19 (dt, *J* = 6.0, 13.2 Hz, 1H), 2.40 (dt, *J* = 6.0, 13.2 Hz, 1H), 2.60-2.81 (m, 6H), 2.95-3.10 (m, 2H), 5.33-5.47 (m, 6H), 5.61-5.69 (m, 1H), 5.72-5.84 (m, 1H), 7.19-7.33 (m, 9H),

7.44-7.49 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.7, -4.5, 18.1, 25.9, 35.0, 35.5, 35.6, 38.3, 45.2, 67.2, 71.8, 86.4, 126.5, 126.8, 127.1, 127.7, 128.8, 129.4, 130.4, 130.9, 134.2, 144.2; MS (CI) *m/z* 498 $(M\text{-}C_7H_{10}O)^+$, 484, 426, 259, 243, 165.



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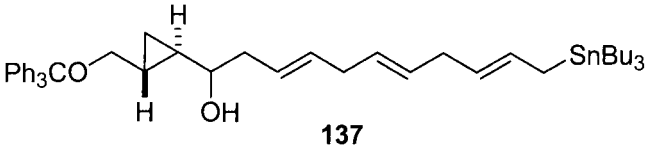
(2*R*,4*E*,7*E*,10*E*,13*E*)-15-(Tri-*n*-butylstannyl)-1-trityloxy-pentadeca-4,7,10,13-tetraen-2-ol. Tri-*n*-butyltin chloride (1.38 mL, 96%, 5.88 mmol) was added to finely cut lithium wire (417 mg) under argon at ambient temperature. THF (5 mL) was added and the mixture was stirred for 16 h. The resulting dark green suspension was transferred *via* cannula to a 25 mL flask under argon and was cooled to –78 °C. A solution of (2*R*,4*E*,7*E*,10*E*,13*E*)-2-(*tert*-butyldimethylsilyloxy)-15-chloro-1-trityloxy-pentadeca-4,7,10,13-tetraene (615 mg, 0.98 mmol) in THF (3 mL) was added dropwise during 30 min, and the mixture was stirred for 6 h at –78 °C. The mixture was diluted with saturated aqueous NH_4Cl (10 mL) and was extracted with CH_2Cl_2 (15 mL, 2 x 5 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified on a short column of silica gel (0-20% EtOAc/hexane) to yield 917 mg of (2*R*,4*E*,7*E*,10*E*,13*E*)-2-(*tert*-butyldimethylsilyloxy)-15-(tri-*n*-butylstannyl)-1-trityloxy-pentadeca-4,7,10,13-tetraene containing slight stannyl impurities. TBAF (1.95 mL, 1.0 M in THF) was added dropwise *via* syringe to a stirred solution of the crude product from above in THF (7 mL) at ambient temperature under argon. After 12 h, the mixture was added to a separatory funnel containing saturated aqueous NH_4Cl (15 mL) and the aqueous phase was extracted with CH_2Cl_2 (25, 2 x 10 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification of the

residue on a short column of silica gel (5-15% EtOAc in hexane) gave 483 mg (85%) of (2*R*,4*E*,7*E*,10*E*,13*E*)-15-(tri-*n*-butylstannyl)-1-trityloxy-pentadeca-4,7,10,13-tetraen-2-ol: $[\alpha]_D^{23}$ - 1.1 (c 1.0, $CHCl_3$); IR (neat) 3461, 3086, 3059, 3022, 2955, 2924, 2871, 2853, 1597, 1491, 1448, 1376, 1220, 1183, 1154 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.82-0.95 (m, 15H), 1.24-1.39 (m, 6H), 1.44-1.58 (m, 6H), 1.73 (d, J = 8.5 Hz, 6H), 2.18-2.31 (m, 3H), 2.69 (brs, 2H), 3.06-3.24 (m, 2H), 3.75-3.87 (m, 1H), 5.16-5.64 (m, 8H), 7.21-7.36 (m, 9H), 7.42-7.49 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.2, 13.7, 14.2, 27.3, 29.1, 30.4, 35.6, 36.9, 67.0, 70.5, 86.6, 123.6, 126.1, 127.0, 127.8, 128.5, 128.6, 128.8, 129.3, 129.5, 130.0, 130.2, 130.5, 132.0, 143.9; MS (CI) *m/z* 653 $(M-(C_4H_9)_2)^+$, 599, 548, 481, 423, 291, 243, 177, 121.



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(1*R*,2*R*,3'*E*,6'*E*,9'*E*)-1-[11'-(Tri-*n*-butylstannanyl)-undeca-3',6',9'-trien-1-ol]-2-(2'-trityloxymethyl)cyclopropane. Triflic anhydride (33.5 μL, 0.20 mmol) was added dropwise *via* syringe to a solution of (2*R*,4*E*,7*E*,10*E*,13*E*)-15-(tri-*n*-butylstannyl)-1-trityloxy-pentadeca-4,7,10,13-tetraen-2-ol (110 mg, 0.14 mmol) and collidine (26.3 μL, 0.20 mmol) in CH_2Cl_2 (1.5 mL) at -85 °C under argon, and the mixture was stirred for 19 h. Et_3N (60.4 μL, 0.47 mmol) was added dropwise *via* syringe, the mixture was stirred for an additional 2 h at -85 °C, then warmed to 0 °C over 4 h. After 20 min, the mixture was quenched with saturated aqueous NH_4Cl (1 mL), extracted with CH_2Cl_2 (2 x 10 mL) and the combined extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification of the residue on a short column of silica gel (1-15% EtOAc in hexane) to yield 34 mg (31%)

of (1*R*,2*R*,3'*E*,6'*E*,9'*E*)-1-[11'-(tri-*n*-butylstannanyl)-undeca-3',6',9'-trien-1-ol]-2-(2'-trityloxymethyl)cyclopropane: IR (neat) 3392, 3059, 3021, 3006, 2955, 2924, 2870, 2853, 1490, 1448, 1419, 1376 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.43 (dt, *J* = 5.0, 8.5 Hz, 1H), 0.57 (dt, *J* = 5.0, 8.5 Hz, 1H), 0.81-0.93 (m, 17H), 1.22-1.36 (m, 6H), 1.42-1.56 (m, 6H), 1.66 (brs, 1H), 1.72 (d, *J* = 2.8 Hz, 2H), 2.34 (t, *J* = 1.2 Hz, 1H), 2.47 (dt, *J* = 0.7, 2.2 Hz, 1H), 2.62-2.74 (m, 4H), 2.85 (dd, *J* = 7.1, 9.5 Hz, 1H), 2.96-3.03 (m, 1H), 3.08 (dd, *J* = 5.9, 9.5 Hz, 1H), 5.21 (dt, *J* = 7.1, 15.0 Hz, 1H), 5.40 (q, *J* = 2.5 Hz, 2H), 5.48-5.62 (m, 3H), 7.19-7.34 (m, 9H), 7.42-7.48 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.2, 9.2, 13.7, 14.2, 16.5, 23.2, 27.0, 27.3, 29.1, 35.7, 40.6, 66.6, 75.0, 86.2, 123.6, 126.5, 126.9, 127.7, 128.2, 128.6, 130.1, 130.4, 132.5, 144.3; MS (CI) *m/z* 768 $(M)^+$, 619, 526, 451, 364, 342, 291, 243, 183, 165, 105, 91; HRMS (CI) *m/z* 768.3945 (calcd for $C_{46}H_{62}O_2{}^{120}Sn$: 768.3928).

CHAPTER THREE: APPLICATION TOWARDS THE SYNTHESIS OF ANTIFUNGAL AGENT FR-900848

3.1 BACKGROUND

There is considerable concern in the medical community with regards to fungal disease. Dermatophyte infections such as *Tinea pedia* and *Cadidiasis*, though rarely fatal, are common and widespread throughout the world.[27] Other fungi, such as *Candida albicans*, *Crytococcus neoformans*, *Pneumocystis carinii* and *Aspergillus fumigatus* are the cause of serious illness in immuno compromised patients. Current therapies for serious fungal disease and for the management of legions of topical fungal infections are deficient and there is a need for novel and potent therapies to treat these illnesses. Pharmaceutical companies worldwide, as a consequence, are looking to microbial fermentation broths as sources of leads for superior therapeutic agents.

3.1.1 ISOLATION AND BIOLOGICAL ACTIVITY OF FR-900848

FR-900848 is a natural product isolated from the fermentation broth of the bacterium *Streptoverticillium fervens* HP-891. The bacterium was obtained from soil samples taken in Tsukuba city, Japan by scientists from the Fujisawa company.[4] The antimicrobial spectrum of FR-900848 is shown in Table 3. The compound was found to have a high specific activity against filamentous fungi at concentrations of 0.05~0.5 μg/mL, causing the hyphae of the fungi to branch frequently and the filaments to swell. By contrast, FR-900848 was shown to have relatively poor activity against yeasts and Gram-negative or Gram–positive bacteria (Table 3).[4]

Test Organisms	MIC (mg/mL)
Aspergillus niger	0.05
Mucor rouxianus	0.05
Aureobasidium pullulans	0.05
Penicillium chrysogenum	0.1
Trichophyton metagrophytes	0.2
Trichophyton asteroides	0.5
Trichophyton rubrum	0.5
Fusarium oxysporum	0.1
Sclerotinia arachidis	0.1
Candida albicans	100
Candida tropicalis	100
Candida guilliermondii	0.2
Crytococcus albidus	100
Saccharomyces cerevisiiae	100
Staphylcoccus aureus 209 P	100
Escherichia coli NIHJ	100

Table 3: Antimicrobial Spectrum of FR-900848

This activity makes FR-900848 an attractive lead for novel therapeutic agents against fungal infections from pathogens such as *Aspergillus fumigatus*, commonly found growing in compost and in building dust. *Aspergillus fumigatus* is responsible for serious systematic fungal infections in AIDS patients, immuno-compromised patients and those with genetically impaired immune systems.[27]

3.1.2 STRUCTURAL DETERMINATION

Although initial degradation studies on FR-900848 at Fujisawa laboratories determined its constitution, there remained elements of ambiguity in the stereochemistry of the isolated cyclopropane ring as well as the quatercyclopropane core of the molecule (Figure 18).[27]

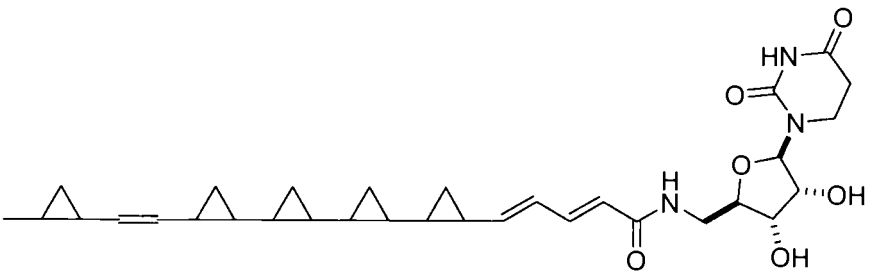
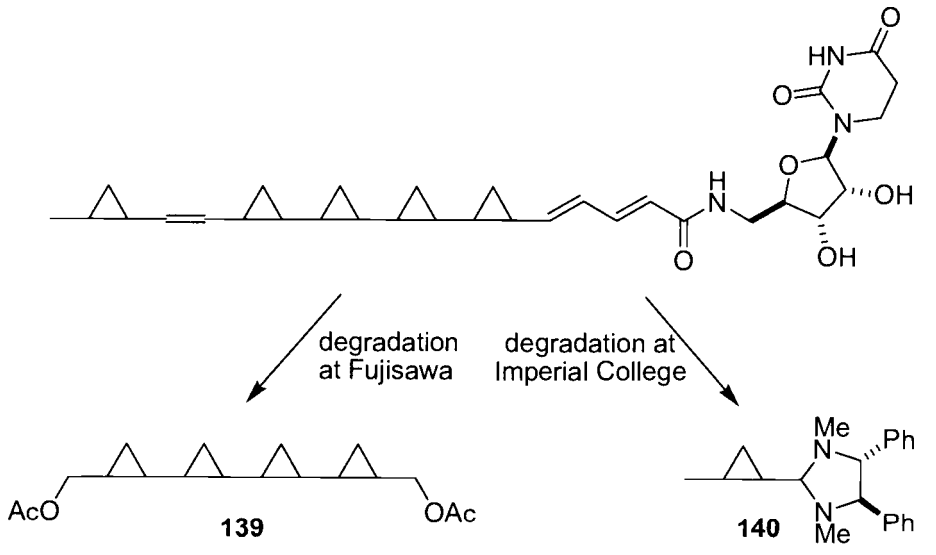


Figure 18: Unrefined Structure of FR-900848 from Initial Degradation Studies

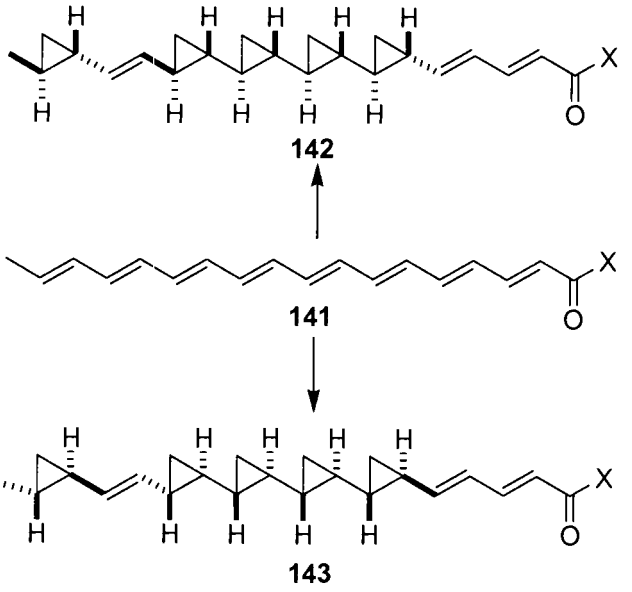
Yoshida and co-workers at Fujisawa established that the central quatercyclopropane unit **139**, obtained by ozonolysis followed by a sodium borohydride workup and acetylation, was C_2-symmetric by analysis of the ^{1}H NMR and ^{13}C NMR spectra (Scheme 30).



Scheme 30: Structural Assignment of the Quatercyclopropane Core of FR-900848

Barrett and co-workers at Imperial College, London, postulated that the methylene units of all five cyclopropanes were introduced from a C_1 source such as *S*-adenosylmethionine, leading to a C_{18} polyene precursor **141** as a key biosynthetic intermediate (Scheme 31).[28] These authors further postulated that the polyene backbone would most likely be *all-trans* since double bonds $\Delta^{2,4}$ were shown by Yoshida to be *trans*. Barrett therefore proposed that FR-900848 should be represented

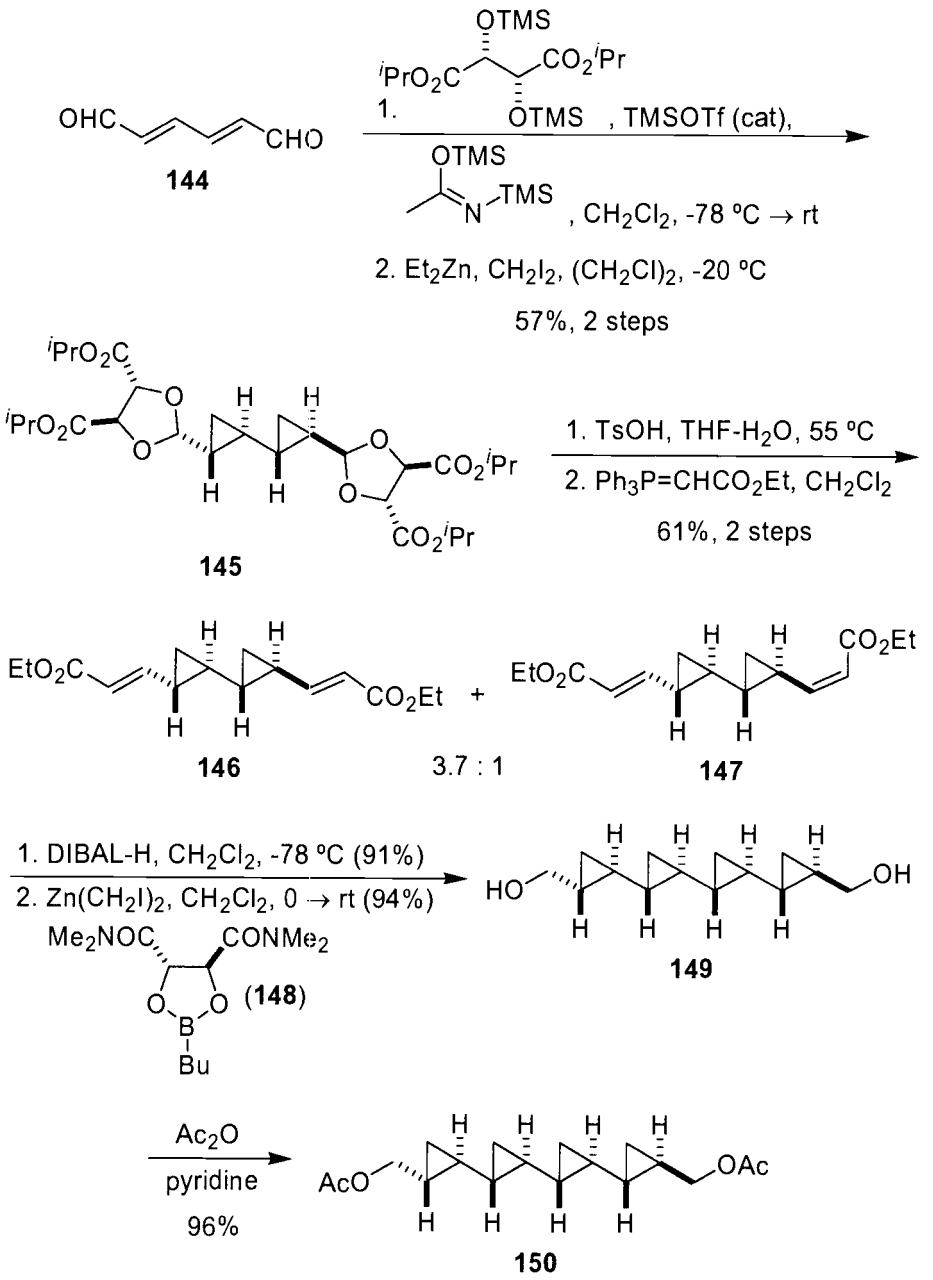
by structure **142** or **143**, since an enzymatic cyclopropanation of **141** would be expected to retain alkene geometry and show the same absolute stereochemical bias for each cyclopropane.



Scheme 31: Postulated all-*Trans* Stereochemical Pentacyclopropane Representing the Relative and Absolute Stereochemistry of FR-900848

In order to elucidate the relative and absolute configuration of the natural product, Barrett and co-workers set forth to independently synthesize both the quatercyclopropane core and the isolated cyclopropane. Synthesis of the quatercyclopropane subunit commenced with Noyori acetylation[29] of muconaldehyde (**144**) followed by Yamamoto's modified Simmons-Smith cyclopropanation[30] to provide bicyclopropane **145** (Scheme 32). Single crystal X-ray analysis of **145** confirmed both the relative and absolute stereochemistry to be as shown. Acid catalyzed deprotection of diacetal **145** followed by direct homologation using a double Wittig reaction afforded a chromatographically separable 3.7:1 mixture of diesters **146** and **147**. Diester **146** was subsequently reduced with diisobutylaluminum hydride and the resulting diol was subjected to Charette asymmetric cyclopropanation[31] in the

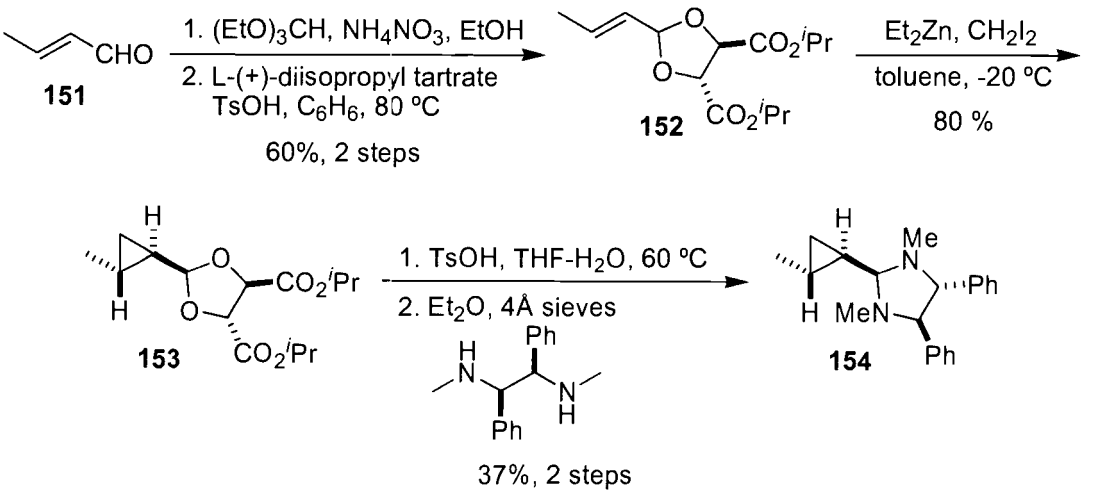
presence of (*S*,*S*)-dioxaborolane **148** to afford C_2 symmetric quatercyclopropane **149**. The relative and absolute stereochemistry of **149** was proven through single crystal X-ray analysis of its bis-*p*-bromobenzoate ester. Conversion of **149** to diacetate **150** afforded an intermediate for comparison with degradation product **139**.[28]



Scheme 32: Synthesis of the Quatercyclopropane Core of FR-900848

Comparison of the optical rotation and the ^{13}C NMR spectra of **150** with the degradation sample **139** obtained from Fujisawa laboratories showed that the diacetates were identical, therefore establishing the absolute stereochemistry of the quatercyclopropane core of the side chain of FR-900848 to be as shown for **150**.

Having conclusively proven the relative and absolute stereochemistry of the core of FR-900848, Barrett and co-workers established the configuration of the remaining isolated cyclopropane through the independent synthesis of degradation product **140** (Scheme 30).[32] Tartaric acetal **152**, which was prepared from crotonaldehyde (**151**), underwent Yamamoto asymmetric cyclopropanation[30] and was purified by chromatography to afford cyclopropane **153**. The aldehyde obtained from acidic deprotection of the tartaric acetal was directly condensed with (1*R*,2*R*)-*N*,*N*'-dimethyl-1,2-diphenylethanediamine[33] to provide imidazolidine **154** (Scheme 33).



Scheme 33: Independent Synthesis of Degradation Product **140**

The spectroscopic data and optical rotation of imidazolidine **154** were compared to data obtained for **140**. The ^{1}H NMR and ^{13}C NMR spectra, mp and the optical rotation showed these derivatives to be identical, therefore establishing the absolute

stereochemistry of the terminal cyclopropane of the side chain of FR-900848 to be as shown for **154**. From the results obtained by Barrett and co-workers, the complete structure of FR-900848 is that depicted by **143**, where all five cyclopropanes are *trans*-substituted and have an all-*syn* relationship.

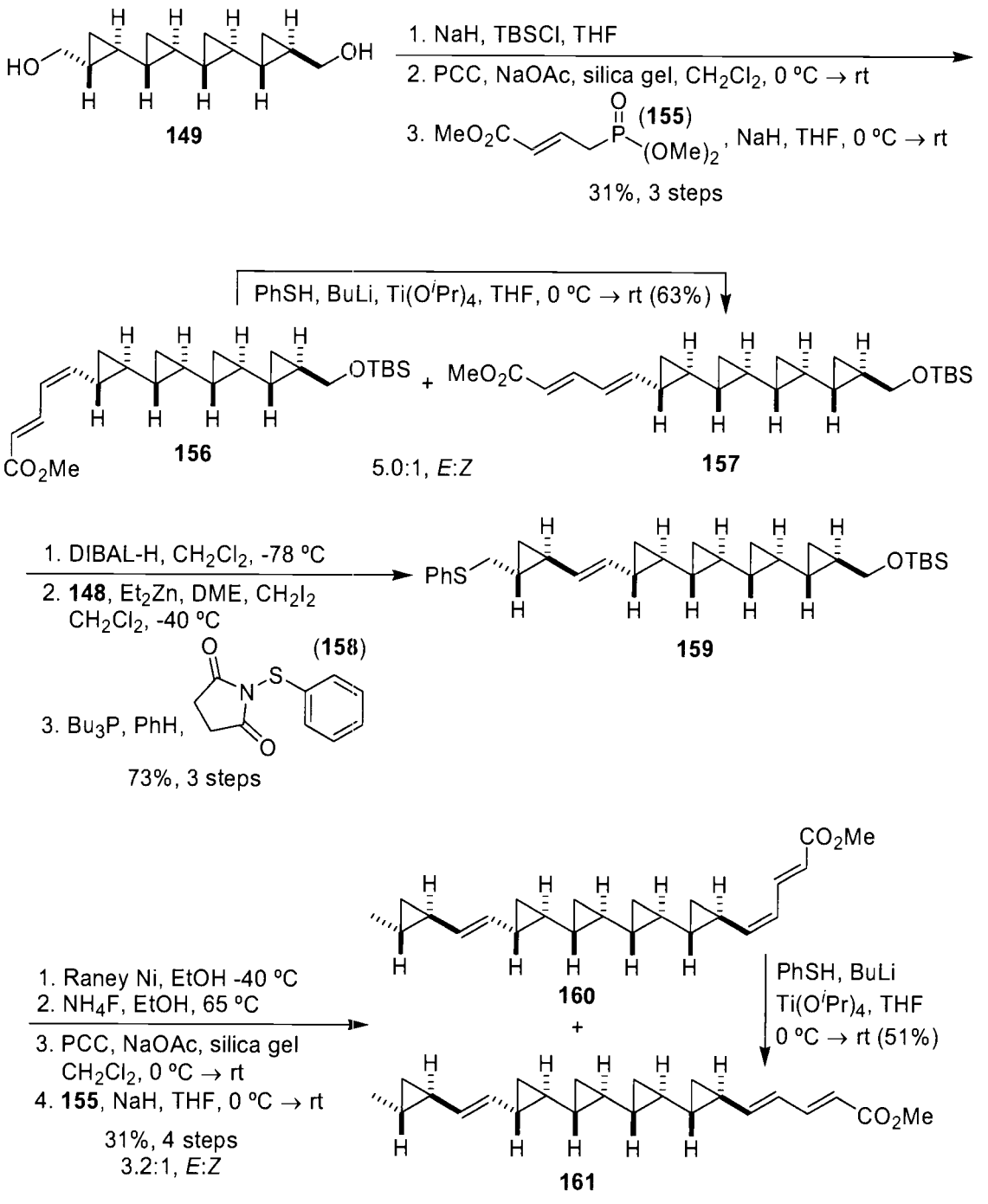
3.2 PREVIOUS SYNTHETIC WORK

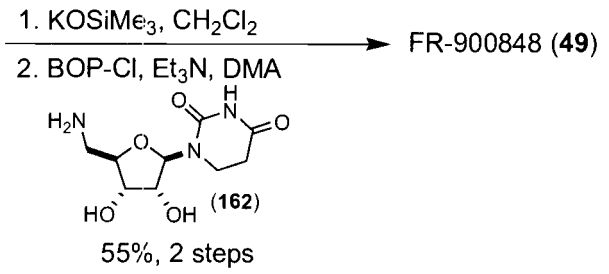
Since the isolation, the reported antimicrobial spectrum of FR-900848 in 1990 by Yoshida and co-workers,[4] and the structural elucidation work performed by Barrett and co-workers,[28,32] much synthetic interest has been focused on this structurally intriguing pentacyclopropane nucleoside. This has culminated in two total syntheses of FR-900848 and one formal synthesis.

3.2.1 TOTAL SYNTHESIS OF FR-900848: A. G. M. BARRETT

Barrett and co-workers proceeded to assemble the natural product around the quatercyclopropane core prepared in the course of the structural elucidation[28] of FR-900848. Mono-*tert*-butyldimethylsilylation of diol **149**, oxidation of the free hydroxyl group and Horner-Emmons hornologation gave a 5 to 1 mixture of esters **156** and **157** (Scheme 34). The undesired isomer **156** was isomerized to the desired isomer **157** using $LiTi(O^iPr)_4(SPh)$, a reagent introduced by Hunter and co-workers[34] for the isomerization of α,β-unsaturated esters. Reduction of ester **157** with diisobutylaluminum hydride was followed by a Charette asymmetric cyclopropanation[31] and conversion of the resultant alcohol to its corresponding phenyl sulfide[35] **159**. Treatment of **159** with Raney nickel was followed by exposure to ammonium fluoride to liberate the primary alcohol. Pyridinium chlorochromate oxidation of this alcohol to the aldehyde and Horner-Emmons homologation afforded a 3.2:1 mixture of *E,Z* (**160**) and *E,E* (**161**) esters. Hunter isomerization[34] of unwanted *E,Z*-ester **160**, potassium trimethylsilanolate[36] mediated hydrolysis and a final bis(2-

oxo-3-oxazolidinyl)phosphinic chloride[37] mediated coupling with nucleoside amine **162** furnished FR-900848.[38]





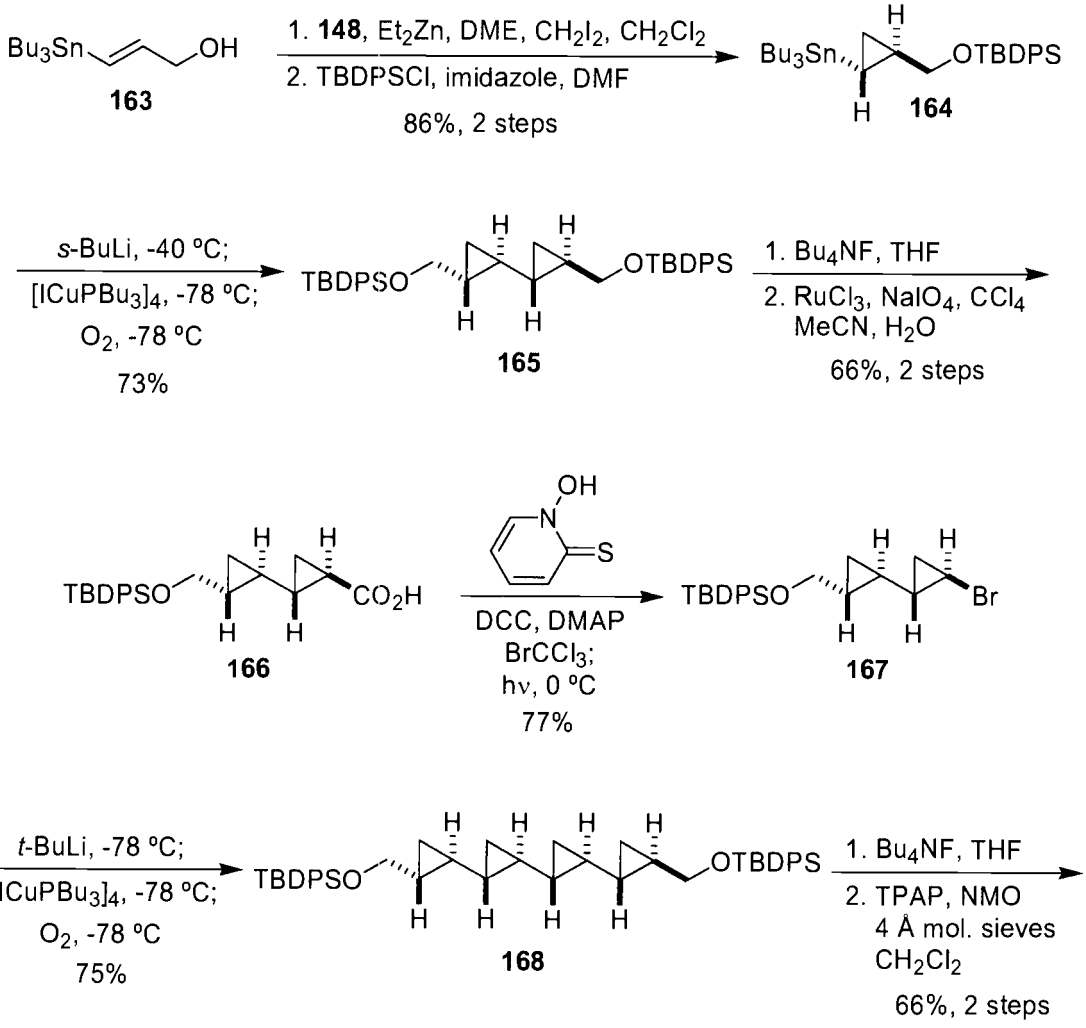
Scheme 34: Total Synthesis of Antifungal Agent FR-900848

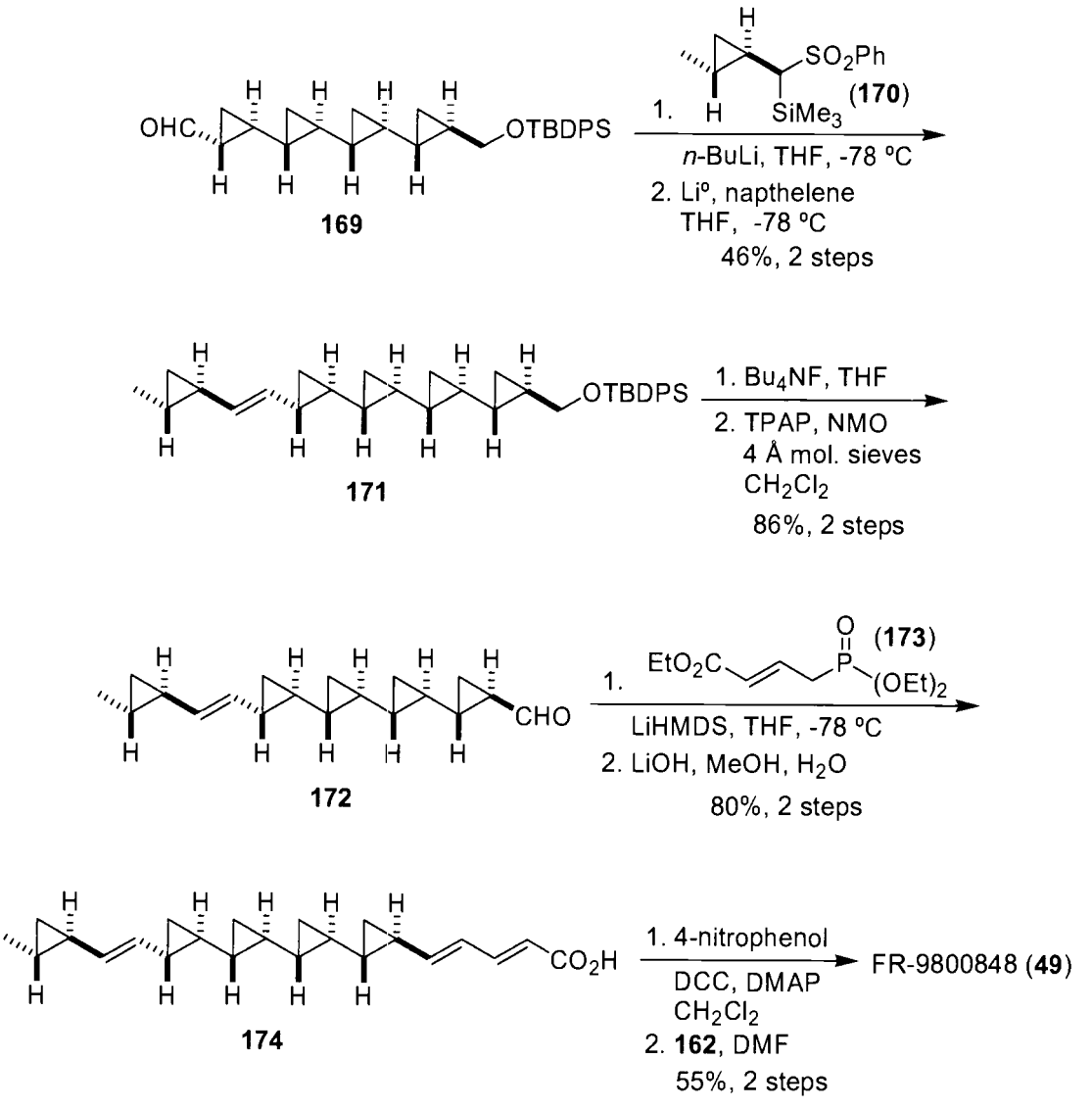
3.2.2 TOTAL SYNTHESIS OF FR-900848: J. R. FALCK

Falck and co-workers reported a total synthesis of FR-900848[39] which utilizes a reiterative dimerization strategy to construct the quatercyclopropane core of the molecule. Falck's synthesis commenced with a moderately stereospecific (88-90% ee) Charette[40] asymmetric cyclopropanation of *trans*-allylic alcohol **163**.[41] Silylation furnished stannane **164** which was transmetalated with *sec*-BuLi. The lithium anion was added to $[ICuPBu_3]_4$[42] and the intermediate copper species was then subjected to an oxidative[43] dimerization[44] at low temperature to afford *trans,syn,trans*-bicyclopropane **165**. The *ee* of this compound was found to be 98%. The enrichment in enantiomeric composition is a manifestation of the statistical distribution of products and represents a variant of the Horeau amplification principle.[45]

Bicyclopropane **165** was subsequently converted to carboxylic acid **166** *via* selective fluoride cleavage of one of the silyl ethers and $RuCl_3$-catalyzed oxidation of the liberated alcohol. The one-pot preparation and photolytic decarboxylation of the corresponding Barton thiohydroxamic ester[46] in $BrCCl_3$ at 0 °C resulted in a 14:1 mixture of bromide **167** and its chromatographically separable *cis*-isomer. Repetition of the dimerization sequence, using *tert*-BuLi for anion generation, stereospecifically transformed **167** into quatercyclopropane **168** (>99.9% ee) in good yield. Partial deprotection of **168** followed by catalytic tetrapropylammonium perruthenate (TPAP)

oxidation afforded aldehyde **169**. Julia coupling of this aldehyde with sulfone **170**[40,41] followed by a Peterson-type olefination yielded the vinyl sulfone and a variable amount (10-20%) of chromatographically separable *cis*-isomer. Reductive sulfone removal with lithium naphthalenide followed by silyl deprotection and catalytic TPAP oxidation afforded aldehyde **172**. Horner-Emmons homologation gave the *all-trans* adduct **174** as the sole product. Saponification, condensation with 4-nitrophenol and coupling with nucleoside amine **162** furnished FR-900848 (**49**).



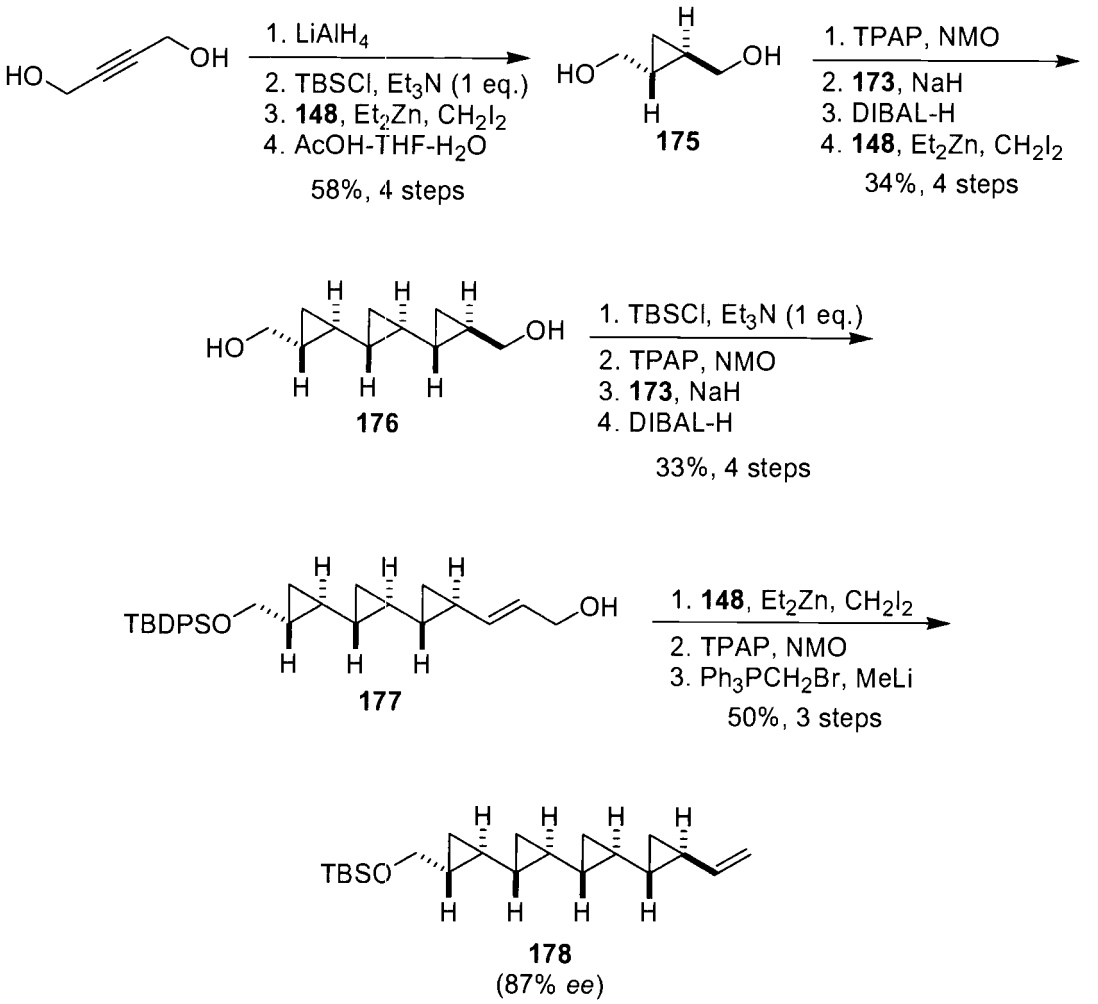


Scheme 35: Falck's Total Synthesis of FR-900848 *via* the Horeau Gambit

3.2.3 FORMAL SYNTHESIS OF FR-900848: C. K. ZERCHER

Zercher and co-workers' synthetic effort commenced with the lithium aluminum hydride reduction of butyne-1,4-diol, followed by monoprotection, Charette asymmetric cyclopropanation[40] and deprotection to afford monocyclopropane **175** (Scheme 36). Oxidation to the dialdehyde, a bidirectional Horner-Emmons homologation and reduction to the corresponding bis-allylic alcohol afforded a substrate which was again subjected to Charette asymmetric cyclopropanation[40] to

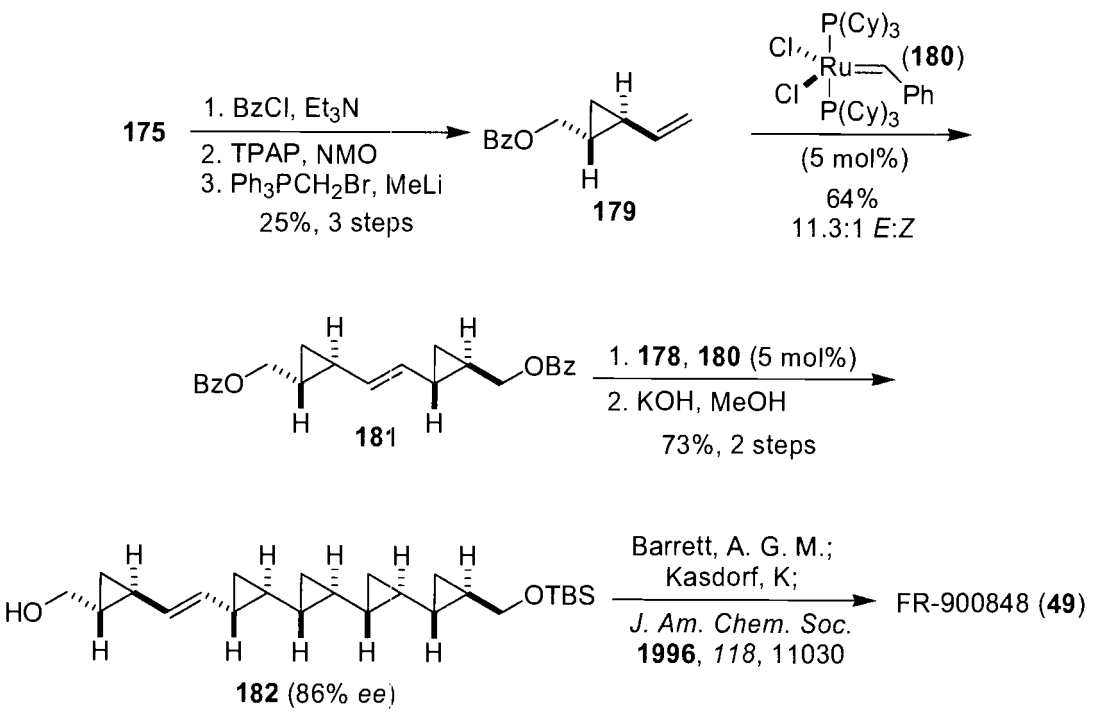
furnish tricyclopropane **176**. Monoprotection of **176**, oxidation with TPAP, Horner-Emmons homologation and reduction gave allylic alcohol **177**. A third Charette asymmetric cyclopropanation[40] followed by TPAP oxidation and homologation afforded the vinyl substituted quatercyclopropane **178** in 87% *ee*.[47]



Scheme 36: Synthesis of Olefin-Metathesis Coupling Partner **178**

Monoprotection of diol **175** with benzoyl chloride, followed by oxidation and olefination provided vinyl cyclopropane **179** for this purpose (Scheme 37). Exposure of **179** to Grubbs' catalyst **180**[48] yielded homodimer **181** as a chromatographically separable 11.3:1 mixture of *E* and *Z* isomers. When **178** and **181** were combined and exposed to Grubbs' catalyst, the cross coupled product **182** was obtained in good yield

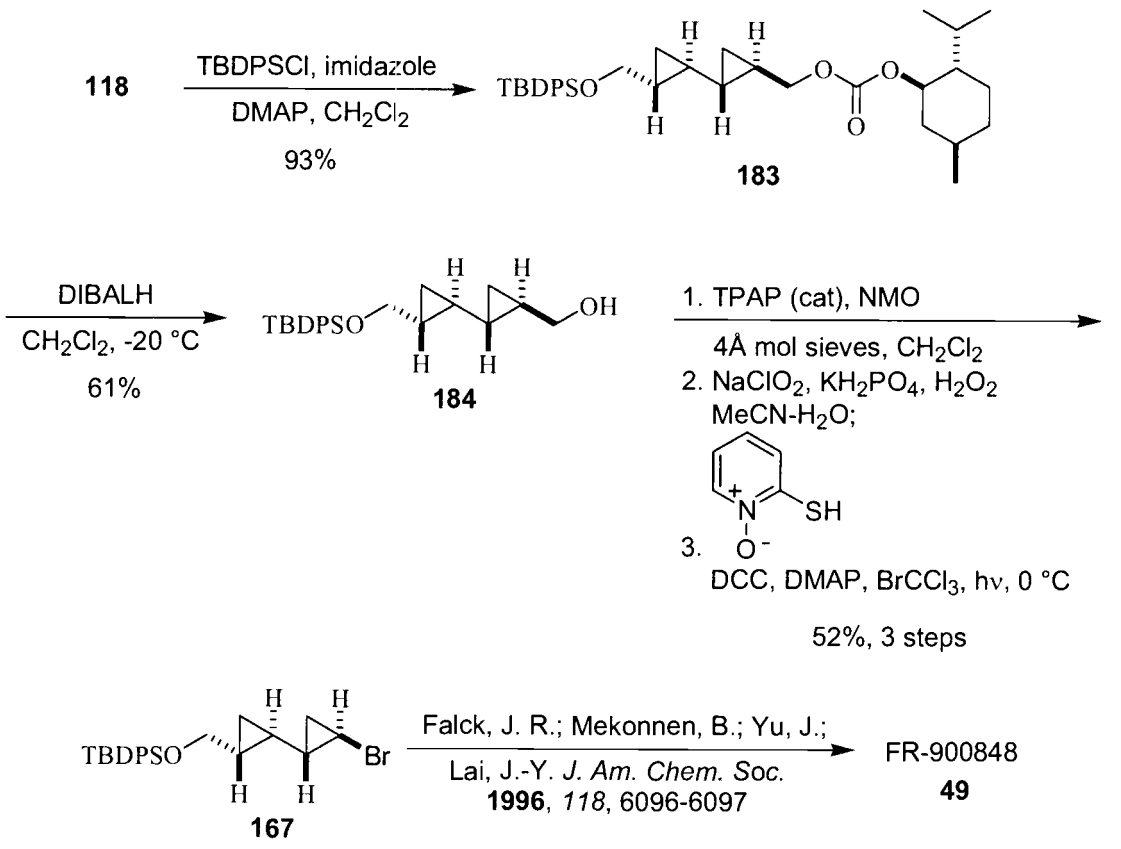
with modest olefin selectivity (>5:1; *E*:*Z*). Pentacyclopropane **182** was shown to be identical to an intermediate in Barrett's[49] total synthesis of FR-900848 (**49**).



Scheme 37: Zercher's Formal Synthesis of FR-900848

3.3 SYNTHESIS OF A KEY PRECURSOR TO FR-900848

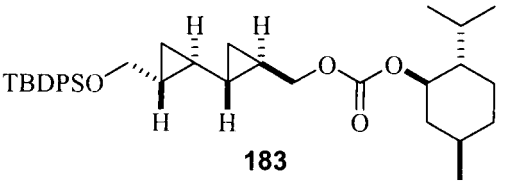
The utility of our bicyclopropane synthesis was demonstrated by the conversion of **118** to an intermediate employed by Falck in his synthesis of FR-900848.[39] Thus, protection of alcohol **118** as a silyl ether was followed by reduction of the menthyl carbonate to yield alcohol **183**. Oxidation of **183** to the corresponding carboxylic acid and brominative decarboxylation under photolytic conditions[39] afforded the bromobicyclopropane **167**. Falck has shown that a copper catalyzed homocoupling of **167** yields a tetracyclopropane[39] which can be further elaborated to FR-900848 (**49**).



Scheme 38: Conversion of **118** to Falck's Bicyclopropane (**167**) in the Synthesis of FR-900848 (**49**)

3.4 EXPERIMENTAL SECTION

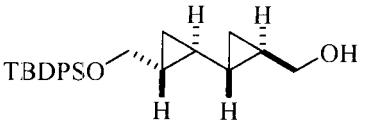
General experimental techniques and instrumentation used in this work are described in section 2.5.



183

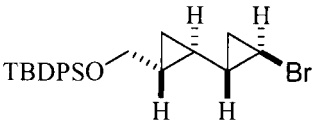
(1*R*,3S,4*S*,6*R*)-1-(*tert*-Butyldimethylsiloxymethyl)-6-[hydroxymethyl-(1'*R*,2'*S*,5'*R*)-menthylcarbonyloxymethyl]-bicyclopropane. (1*R*,3*S*,4*S*,6*R*)-1-Hydroxymethyl-5-[hydroxymethyl-(1'*R*,2'*S*,5'*R*)-menthylcarbonyloxymethyl]-bicyclopropane (28.4 mg, 8.75 x10^{-5} mol), TBDPSCl (25.6 mg, 98%, 9.63 x10^{-5} mol), imidazole (6.5 mg, 9.63 x10^{-5} mol) and 4-DMAP (0.20 mg, 5 mol%) were taken up in CH_2Cl_2 (1 mL) and the reaction flask was purged with argon. After 2.5 h, the mixture was concentrated under reduced pressure and the residue was purified by PTLC (5 EtOAc in cyclohexane) to yield 45.8 mg (93%) of (1*R*,3S,4*S*,6*R*)-1-(*tert*-butyldimethylsiloxymethyl)-6-[hydroxymethyl-(1'*R*,2'*S*,5'*R*)-menthylcarbonyl-oxymethyl]-bicyclopropane as a colorless oil: $[\alpha]_D^{23}$ - 46.2 (c 1.00, $CHCl_3$); IR (neat) 3071, 3050, 2999, 2956, 2932, 2858, 1739, 1589, 1456, 1428, 1388, 1371, 1259, 1182, 1112, 1078 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.18-0.32 (m, 2H), 0.34-0.45 (m, 2H), 0.60-0.83 (m, 2H), 0.81 (dd, *J* = 2.3, 7.0 Hz, 3H), 0.84-0.96 (m, 3H), 0.89-0.95 (m, 9H), 1.06 (s, 9H), 1.05-1.09 (m, 2H), 1.36-1.57 (m, 2H), 1.64-1.75 (m, 2H), 1.89-2.04 (m, 1H), 2.04-2.14 (m, 1H), 3.45 (ddd, *J* = 2.7, 6.5, 10.7 Hz, 1H), 3.59 (ddd, *J* = 3.0, 5.8, 10.7 Hz, 1H), 3.87-4.02 (m, 2H), 4.53 (dt, *J* = 4.4, 10.9 Hz, 1H), 7.34-7.47 (m, 6H), 7.64-7.74 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.8, 8.7, 8.9, 15.9, 15.8,

16.2, 17.3, 17.5, 18.5, 19.0, 19.2, 20.7, 22.0, 23.3, 26.0, 26.9, 31.4, 34.1, 40.8, 47.0, 66.9, 71.7, 78.1, 127.6, 129.5, 134.0, 135.6, 155.1; MS (CI) *m/z* 563 $(M+H)^+$, 505, 455, 367, 323, 305, 243, 199, 139; HRMS (CI) *m/z* 563.3559 (calcd for $C_{35}H_{51}O_4Si$: 563.3557).



184

(1*R*,3*S*,4*S*,6*R*)-1-(*tert*-Butyldimethylsiloxymethyl)-6-hydroxymethyl-bicyclopropane. A solution of (1*R*,2*S*,4*S*,5*R*)-1-hydroxymethyl-6-[hydroxymethyl-(1'*R*,2'*S*,5'*R*)-menthylcarbonyloxymethyl]bicyclopropane (45.8 mg, 8.13 $x10^{-5}$ mol) in CH_2Cl_2 (1.5 mL) was cooled to -20 °C under argon and DIBAl-H (29.0 μL, 0.163 mmol) was added slowly. The mixture was stirred for 10 min, then quenched with saturated aqueous Na^+/K^+ tartrate (500 μL) and concentrated under reduced pressure. The residue was purified by PTLC (30% EtOAc in cyclohexane) to yield 19.0 mg (61%) of (1*R*,3*S*,4*S*,6*R*)-1-(*tert*-butyldimethylsiloxymethyl)-6-hydroxymethyl-bicyclopropane as a colorless oil: $[\alpha]_D^{23}$ - 27.3 (c 1.00, EtOH); IR (neat) 3344, 3070, 2998, 2957, 2931, 2893, 2857, 1472, 1428, 1390, 1361, 1189, 1112, 1085, 1029 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.20-0.36 (m, 4H), 0.63-0.78 (m, 2H), 0.78-0.96 (m, 2H), 1.06 (s, 9H), 3.39 (dd, *J* = 6.5, 10.6 Hz, 1H), 3.40-3.48 (m, 2H), 3.61 (ddd, *J* = 3.2, 5.8, 10.6 Hz, 1H), 7.34-7.47 (m, 6H), 7.64-7.73 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$ δ 8.0, 8.3, 17.7, 18.1, 19.2, 19.4, 19.7, 26.9, 66.9, 67.1, 127.6, 129.5, 134.0, 135.6; MS (CI) *m/z* 379 $(M-H)^+$, 363, 323, 305, 281, 269, 239, 229, 199, 183, 139; HRMS (CI) *m/z* 379.2095 (calcd for $C_{24}H_{31}O_2Si$: 379.2093).



167

(1*R*,3*S*,4*R*,6*R*)-1-Bromo-6-(*tert*-butyldimethylsiloxymethyl)-bicyclopropane.

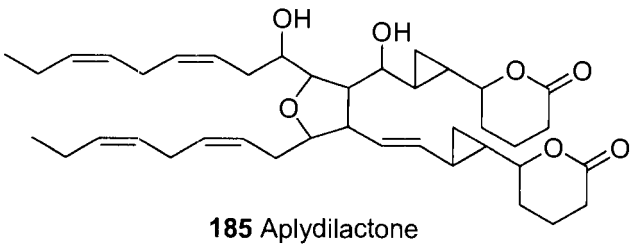
(1*R*,3S,4*S*,6*R*)-1-*tert*-Butyldimethylsiloxymethyl-6-hydroxymethyl-bicyclopropane (19.0 mg, 8.13 x10^{-5} mol) was taken up in CH_2Cl_2 (500 μL) along with 4Å molecular sieves (23.0 mg, powdered) at ambient temperature under argon. NMO (8.2 mg, 6.99 x10^{-5} mol) and TPAP (1.2 mg, 5 mol%) were sequentially added, the reaction flask was purged with argon and the mixture was stirred for 30 min at ambient temperature. The mixture was diluted with hexane (500 μL) and filtered through a short column of silica gel (50% EtOAc in hexane), concentrated under reduced pressure and dried in *vacuo*. The crude aldehyde was taken up in CH_3CN (300 μL), and a solution of KH_2PO_4 (8.2 mg) and H_2O_2 (9.6 μl, 30%) in H_2O (85 μL) was added. $NaClO_2$ (20.5 mg, 80% tech) in H_2O (200 μL) was then added and the reaction was stirred for 5 h at ambient temperature. $Na_2S_2O_3$ (10.2 mg) was added, then after 20 min at ambient temperature 1M $KHSO_4$ (250 μL) was added. The mixture was dried over Na_2SO_4, filtered, concentrated under reduced pressure and dried in *vacuo*. The crude acid, 4-DMAP (9.1 mg, 7.5 x10^{-5}) and 2-mercaptopyridine-*N*-oxide (19.0 mg, 0.150 mmol) were taken up in $BrCCl_3$ (1.25 mL) in the dark. DCC (150 μL, 1.0M in CH_2Cl_2) was added, the reaction was stirred at ambient temperature for 14h, then cooled to 0 °C and irradiated with a 300W lamp. After 1.5 h, the mixture was concentrated and the residue was purified by PTLC (CH_2Cl_2) to yield 11.2 mg (52%, 3 steps) of (1*R*,3*S*,4*R*,6*R*)-1-bromo-6-(*tert*-butyldimethylsiloxymethyl)-bicyclopropane as a

colorless oil: $[\alpha]_D^{23}$ - 47.1 (c 0.35, EtOH); IR (neat) 3070, 3044, 2999, 2958, 2930, 2894, 2857, 1472, 1428, 1390, 1361, 1261, 1235, 1112, 1085, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.19-0.39 (m, 2H), 0.64-0.77 (m, 2H), 0.78-0.94 (m, 2H), 1.06 (s, 9H), 1.25-1.38 (m, 1H), 2.60 (ddd, *J* = 3.7, 6.9, 13.9 Hz, 1H), 3.40 (ddd, *J* = 6.6, 10.7, 13.6 Hz, 1H), 3.64 (ddd, J=3.0, 5.6, 10.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$ δ 7.4, 14.1, 16.7, 18.8, 19.2, 19.3, 23.8, 26.9, 66.5, 127.6, 129.6, 133.9, 135.6; MS (CI) *m/z* 429 $(M+H)^+$, 427, 373, 291, 263, 239, 199, 197, 169, 135; HRMS (CI) *m/z* 427.1083 (calcd for $C_{23}H_{28}O^{79}BrSi$: 427.1093).

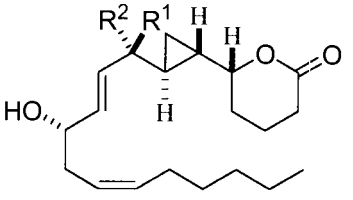
CHAPTER FOUR: APPLICATION TOWARDS THE SYNTHESIS OF A KEY PRECURSOR OF HALICHOLACTONE, NEOHALICHOLACTONE AND SOLANDELACTONES A-H

4.1 BACKGROUND

Oxylipins are fatty acid metabolites isolated from marine invertebrates and algae. Of particular interest are the *trans*-disubstituted cyclopropane-containing oxylipins bearing an adjacent lactone ring, proposed to form biosynthetically *via* a homoallyl cation-cyclopropylcarbinyl cation interchange.[1b,c,d] To date, 15 members of this class have been reported. Aplydilactone (**185**), isolated from the sea hare *Aplysia kurodia*[50] and constanolactones A (**186**) and B (**187**), isolated from the red alga *Constantinea simplex*[1d,51] harvested off the Oregon coast at Seal Rock, contain functional cores similar to the other members of this class of marine natural products. Yamada and co-workers reported the structures of halicholactone (**188**) and neohalicholactone (**189**) in 1989; both compounds were isolated from the marine sponge *Halichondria okadai*.[52] In 1996, Shin and co-workers isolated and characterized solandelactones A-H (**190-197**) from the hydroid *Solanderia secunda*, and showed that solandelactones E (**194**), F (**195**), G (**196**) and H (**197**) contain a novel eight-membered unsaturated lactone (Figure 19).[53] Halicholactone, neohalicholactone and solanedelactones A-H share the same absolute configuration about the cyclopropane ring, which is opposite to that of the constanolactones. However the solandelactones differ in configuration at the lactone carbinol center alpha to the cyclopropane ring from that of halicholactone and neohalicholactone.



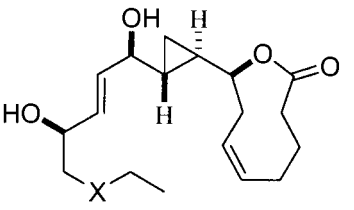
185 Aplydilactone



Constanolactones

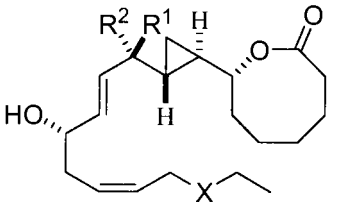
186 A (R^1 = H, R^2 = OH)

187 B (R^1 = OH, R^2 = H)



188 Halicholactone (X = CH_2CH_2)

189 Neohalicholactone (X = *cis*-CH=CH)



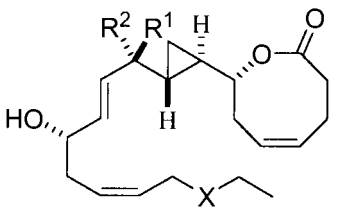
Solandelactones

190 A (R^1 = OH, R^2 = H, X = CH_2CH_2)

191 B (R^1 = H, R^2 = OH, X = CH_2CH_2)

192 C (R^1 = OH, R^2 = H, X = *cis*-CH=CH)

193 D (R^1 = H, R^2 = OH, X = *cis*-CH=CH)



Solandelactones

194 E (R^1 = OH, R^2 = H, X = CH_2CH_2)

195 F (R^1 = H, R^2 = OH, X = CH_2CH_2)

196 G (R^1 = OH, R^2 = H, X = *cis*-CH=CH)

197 H (R^1 = H, R^2 = OH, X = *cis*-CH=CH)

Figure 19: *Trans*-cyclopropane Containing Marine Oxylipins

4.1.1 PROPOSED BIOSYNTHETIC PATHWAY TO CYCLOPROPYL-LACTONE CONTAINING MARINE OXYLIPINS

Gerwick has proposed a pathway for the biosynthesis of the constanolactones through the oxidation and rearrangement of arachidonic acid (**198**, Figure 20).[1d] The key intermediate in the biosynthesis of the constanolactones is 12-hydroperoxyicosatetraenoic acid (**201**). Halicholactone, neohalicholactone and solandelactones A-H are likely formed from related oxidative rearrangements of arachidonic, eicosapentaenoic acid and docosahexaenoic acid respectively.

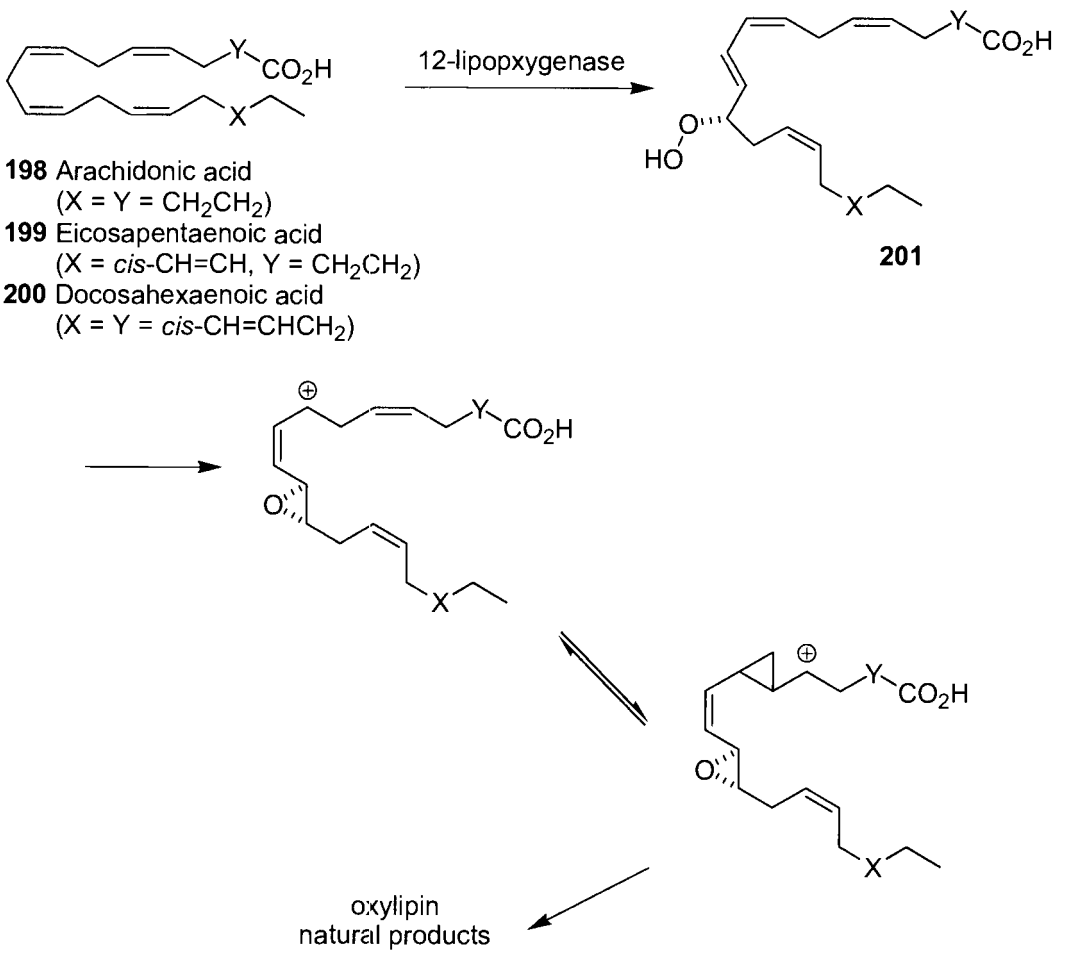
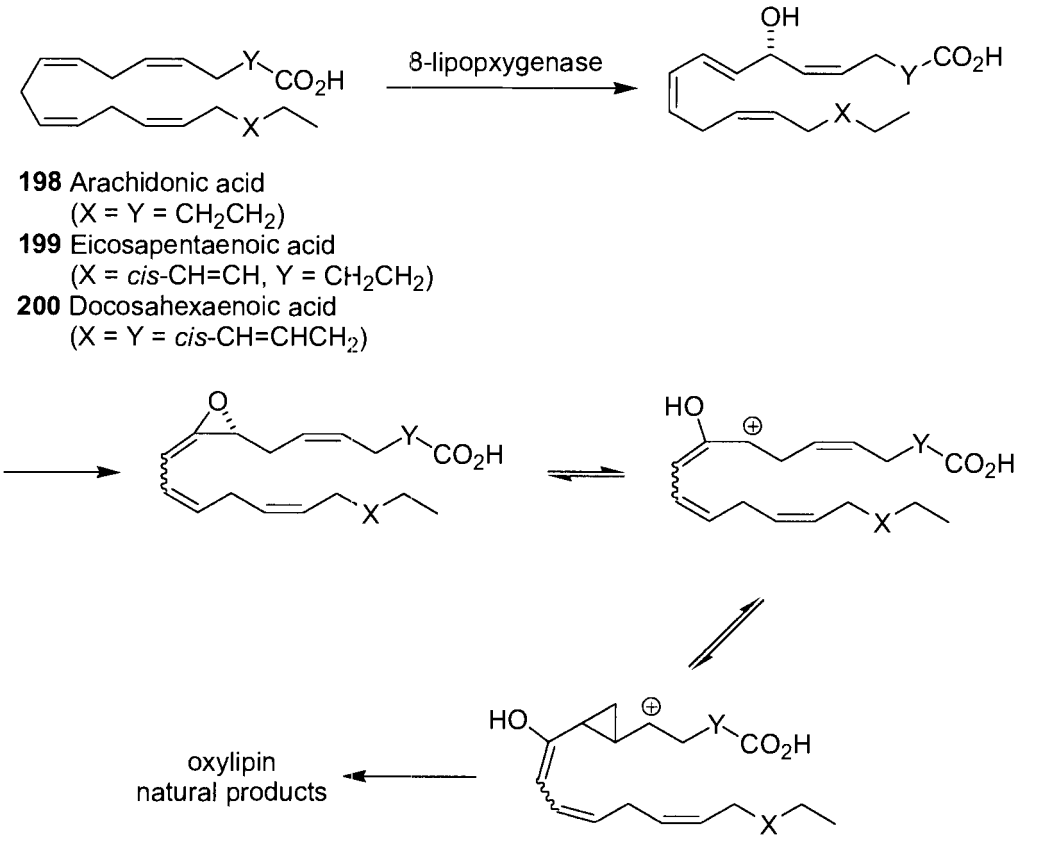


Figure 20: Gerwick's Proposed Biosynthetic Route to Cyclopropane-containing Oxylipin Marine Natural Products

Brash has proposed an alternative biosynthetic route involving formation of an allene oxide intermediate (Figure 21).[1b,c] The feature common to both of these proposed synthetic pathways is the cyclopropane-forming step, which holds precedent in the homoallyl-cyclopropyl carbinyl cation equilibrium.



198 Arachidonic acid
(X = Y = CH_2CH_2)
199 Eicosapentaenoic acid
(X = *cis*-CH=CH, Y = CH_2CH_2)
200 Docosahexaenoic acid
(X = Y = *cis*-CH=$CHCH_2$)

Figure 21: Brash's Proposed Biosynthesis of Cyclopropane-containing Oxylipin Marine Natural Products

Although both of these hypotheses appear reasonable, none of the proposed biosynthetic intermediates in these routes have been converted to oxylipin natural products.

4.2 HALICHOLACTONE AND NEOHALICHOLACTONE

4.2.1 ISOLATION AND BIOLOGICAL ACTIVITY

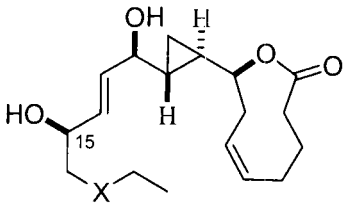
The marine metabolites halicholactone **185** and neohalicholactone **186** were isolated from the marine sponge *Halichondria okadai*, collected at Daiozaki, Mie Prefecture, Japan in 1989.[52] Halicholactone has exhibited inhibitory activity against 5-lipoxygenase of guinea pig polymorphonuclear leukocytes (IC_{50} = 630 μM).

5-Lipoxygenase, which is selectively expressed in bone marrow–derived cells such as neutrophils, monocytes, macrophages, dendritic cells, and mast cells, is pivotally involved in the production of leukotrienes from arachidonic acid.[54] Leukotrienes may contribute to atherosclerosis by promoting nonspecific leukocyte chemotaxis (leukotriene B_4) and by increasing vascular permeability (cysteinyl leukotrienes C_4, D_4, and E_4). The activation and gene expression of 5-lipoxygenase, can be increased by various cytokines in inflammatory conditions. Resident macrophages perpetuate a vicious cycle of local inflammation by releasing inflammatory cytokines, matrix-degrading metalloproteinases (contributing to plaque rupture), and tissue factor (increasing plaque thrombogenicity), as well as by producing more leukotrienes.[55] New synthetic targets for drug therapy which inhibit 5-lipoxygenase would be significant leads for the treatment of inflammation and atherosclerosis.

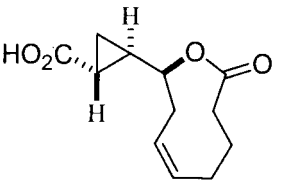
4.2.2 STRUCTURAL DETERMINATION AND SYNTHESIS

Though the planar structures of halicholactone and neohalicholactone were elucidated through chemical degradation and NMR analysis,[52] their relative and absolute stereochemistries remained elusive. In 1995, Wills and co-workers reported the structure and synthesis of the right-hand hemisphere of halicholactone and neohalicholactone (Scheme 39).[56] The relative stereochemistry of **202** was established by an X-ray crystallographic study, while the absolute configuration of the C15 carbinol was confirmed by degradation of halicholactone to a derivative of known absolute configuration (**203**, Figure 22).[52] Wills predicted the absolute

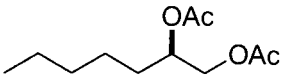
stereochemistry of neohalicholactone to be as shown, with the assumption that both **188** and **189** form *via* similar biosynthetic pathways.



188 Halicholactone (X = CH_2CH_2)
189 Neohalicholactone (X = *cis*-CH=CH)



202

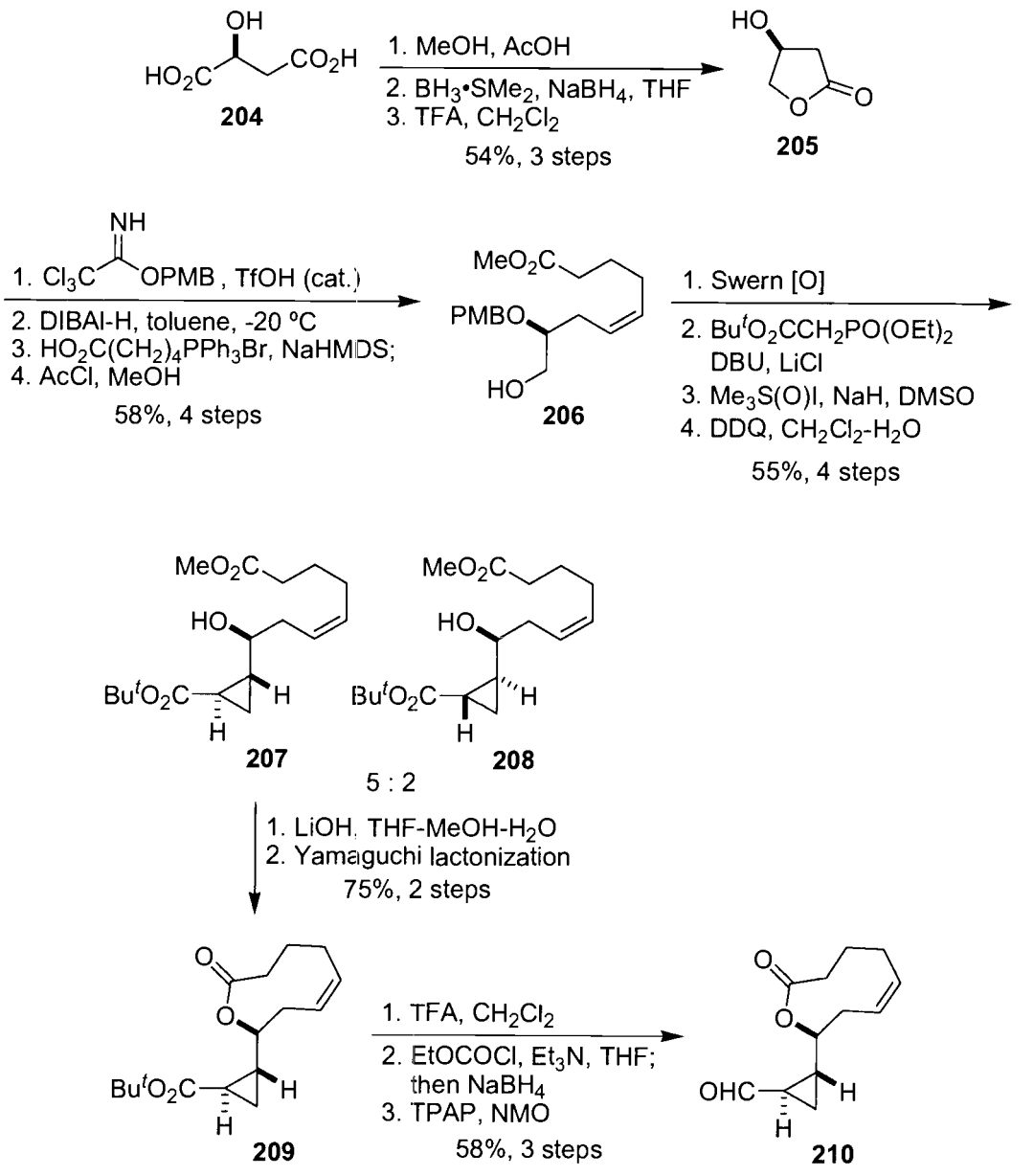


203

Figure 22: Structural Determination of Halicholactone and Neohalicholactone

The absolute stereochemistry of halicholactone and neohalicholactone was unambiguously confirmed *via* enantioselective total synthesis undertaken by Wills and co-workers.[57] Their convergent strategy commenced with the synthesis of the right hand hemisphere of the halicholactones (Scheme 39). (*S*)-Malic acid (**204**) was converted to 3-hydroxy-γ-lactone **205** *via* esterification, selective reduction and lactonization. *p*-Methoxybenzyl protection, reduction to the corresponding lactol, Wittig olefination and esterification of the resultant acid afforded unsaturated ester **206**. Swern oxidation of **206** followed by olefination furnished a suitable substrate for cyclopropanation. Treatment with dimethylsulfoxonium ylide (prepared from trimethylsulfoxonium iodide and NaH) afforded an inseparable 5:2 mixture of diastereomeric cyclopropanes, which, after deprotection, yielded to chromatographic separation. An X-ray crystal structure of the derived acid from **207** confirmed the presence of a *trans*-cyclopropane which had the correct relative stereochemistry required for the synthesis. Yamaguchi lactonization[58] of this acid, followed by

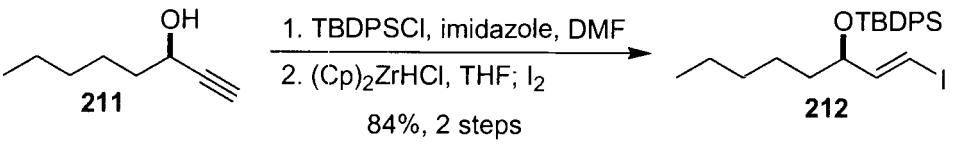
saponification and reduction through the corresponding carbonic-carboxylic anhydride afforded enantiomerically pure 8*S*,9*R*,11*R*-aldehyde **210.**



Scheme 39: Synthesis of the Right Hand Hemisphere of Halicholactone and Neohalicholactone

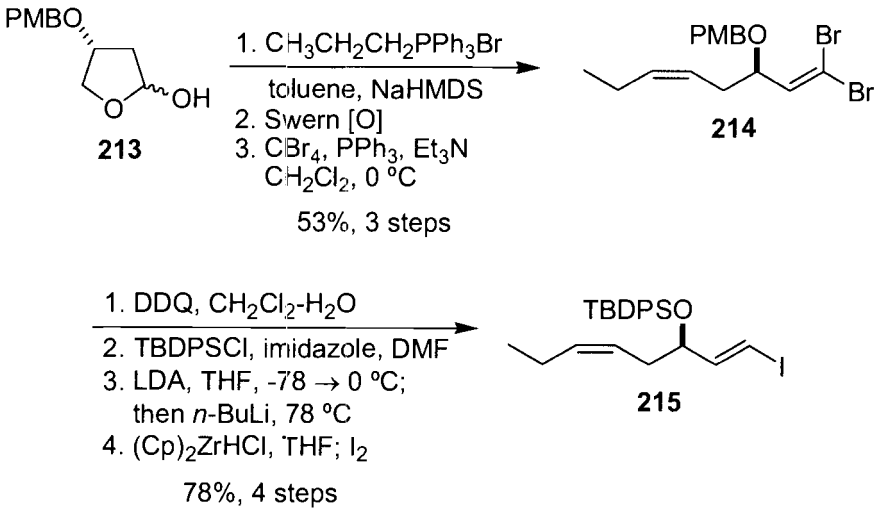
A suitable left hemisphere substrate for the synthesis of halicholactone was obtained from commercially available (*R*)-1-octyn-3-ol (**211**, Scheme 40). Protection

of the secondary alcohol of **211** as its silyl ether was followed by a hydrozirconation-iodination procedure as first reported by Schwartz,[59] to give vinyl iodide **212**.



Scheme 40: Synthesis of the Left Hand Portion of Halicholactone

Synthesis of the corresponding fragment of neohalicholactone commenced from protected hydroxy lactol **213** (Scheme 41). Wittig extension, oxidation of the primary alcohol and conversion of the resultant aldehyde utilizing a modified Corey-Fuchs procedure[60] afforded dibromide **214**. Protecting group exchange, conversion of the dibromide to the corresponding alkyne and subsequent hydrozirconation-iodination[59] yielded vinyl iodide **215**.

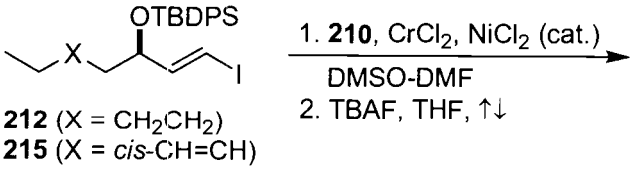


Scheme 41: Synthesis of the Left Hand Portion of Neohalicholactone

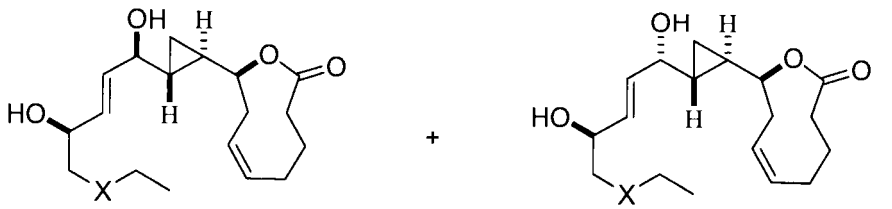
To complete the asymmetric total synthesis of halicholactone, Wills reacted vinyl iodide **212** with aldehyde **210** utilizing the chromium(II) chloride/nickel(II) chloride methodology developed by Kishi[61] and Takai[62] (Scheme 42). The major

isomer was partially separated from the 2:1 diastereomeric mixture of products and the silyl group was removed under vigorous deprotection conditions to afford halicholactone (**188**) as a single diastereomer. The ^{1}H NMR and ^{13}C NMR spectra of **188** exactly matched the data reported for natural halicholactone, and the optical rotation of the synthesized material, $[\alpha]_D^{23}$ -91.7 (c 0.29, $CHCl_3$), corresponded well with the literature value for the natural product, $[\alpha]_D^{23}$ -85.4 (c 1.16, $CHCl_3$).

The asymmetric total synthesis of neohalicholactone was achieved using similar conditions to those reported above for halicholactone. After coupling of vinyl iodide **215** with aldehyde **210**, deprotection and chromatographic separation of the major isomer from the 2:1 mixture of diastereomers provided diastereomerically pure neohalicholactone (**189**). The ^{1}H NMR and ^{13}C NMR spectra for **189** exactly matched the data reported for natural neohalicholactone, and the optical rotation of the synthesized material, $[\alpha]_D^{23}$ -54.6 (c 0.76, $CHCl_3$), was virtually identical to the literature value, $[\alpha]_D^{23}$ -54.2 (c 0.73, $CHCl_3$).



212 (X = CH_2CH_2)
215 (X = *cis*-CH=CH)



188 Halicholactone (X = CH_2CH_2)
189 Neohalicholactone (X = *cis*-CH=CH)

216 12-*epi*-Halicholactone (X = CH_2CH_2)
217 12-*epi*-Neohalicholactone (X = *cis*-CH=CH)

188:**216**, 2:1 (72%, 2 steps)
189:**217**, 2:1 (57%, 2 steps)

Scheme 42: Completion of the Total Syntheses of Halicholactone and Neohalicholactone

The total synthesis of halicholactone (**188**) and neohalicholactone (**189**) served to unambiguously confirm the original assignment of absolute configuration which was made by Yamada and Clardy.[63]

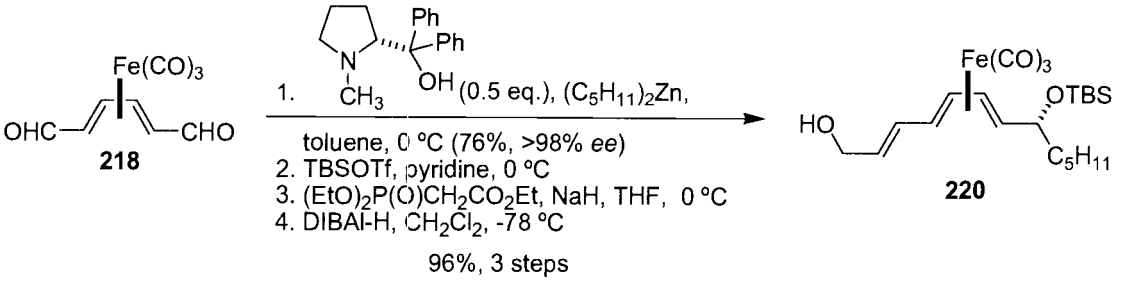
4.2.3 OTHER SYNTHETIC WORK

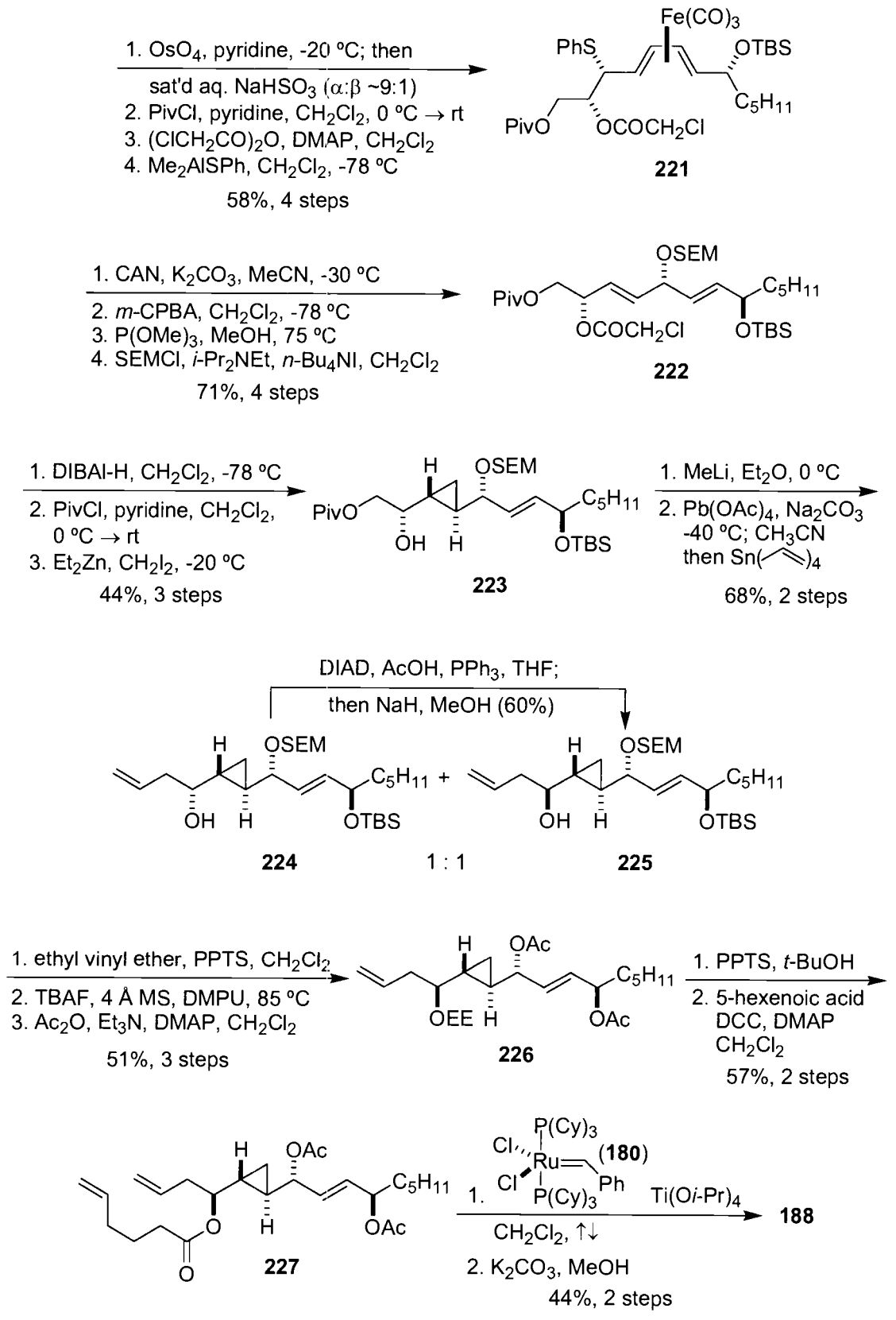
In addition to the synthetic efforts of Wills and co-workers on the confirmation of the absolute stereochemistry of halicholactone and neohalicholactone,[56,57] there have been two total syntheses of halicholactone,[64] and two synthetic approaches to a key precursor[65] of both natural products.

4.2.3.1 TOTAL SYNTHESIS OF HALICHOLACTONE: Y. TAKEMOTO

Takemoto and co-workers reported a synthesis of halicholactone[64a] which utilizes the chirality of an $Fe(CO)_3$ complex to prepare a stereochemically pure cyclopropanation substrate bearing all the functionality of the left hand portion of halicholactone. The synthesis commenced from known chiral dialdehyde **218**[66] which was initially converted *via* an asymmetric alkylation/protection protocol to its TBS ether,[66] then condensed with ethyl diethylphosphonoacetate and reduced with diisobutylaluminum hydride to give allylic alcohol **220** (Scheme 43). Dihydroxylation of **220** afforded an inseparable mixture of triols which was subjected to primary hydroxyl protection and conversion of the remaining secondary diols to their bis-chloroacetoxy esters to give a chromatographically separable mixture of diastereomers. Reaction of the major diastereomer with Me_2AlSPh[67] afforded phenyl sulfide **221** as a single isomer. Decomplexation of **221** with ceric(IV) ammonium nitrate, followed by successive treatment of the sulfide with *m*-CPBA and $P(OMe)_3$ in

methanol provided the desired bisallylic alcohol functionality *via* a [2,3]-sigmatropic rearrangement. Protection of the resultant alcohol as a SEM ether yielded the differentiated tetrol **222**. A two-step protocol to liberate the chloroacetoxy protected alcohol afforded a substrate for a directed Simmons-Smith cyclopropanation, which gave **223** as a single product. Removal of the pivaloyl group, cleavage of the 1,2-diol with $Pb(OAc)_4$ and introduction of an allyl group yielded a 1:1 mixture of diastereomers **224** and **225**. The undersired diastereomer **224** was converted to **225** *via* a standard Mitsonubu protocol.[68] Treatment of alcohol **225** with ethyl vinyl ether in the presence of PPTS was followed by removal of the the TBS and SEM protecting groups with TBAF and protection of the resulting diol provided diacetate **226**. Acid catalyzed deprotection of the ethoxyethyl group and DCC-mediated esterification afforded ester **227,** a substrate intended for ring closing metathesis. After many experiments on the ring closing metathesis of **227**, it was discovered that reaction with catalyst **180**[48] in the presence of a catalytic amount of $Ti(O^iPr)_4$[69] under high dilution gave the desired product as a single olefin isomer along with about 11% of the corresponding dimer. Methanolysis of the acetyl groups afforded **188**, which was identical (^1H NMR, ^{13}C NMR, IR, MS, and optical rotation) in all aspects to the reported data for natural halicholactone.[52,63]

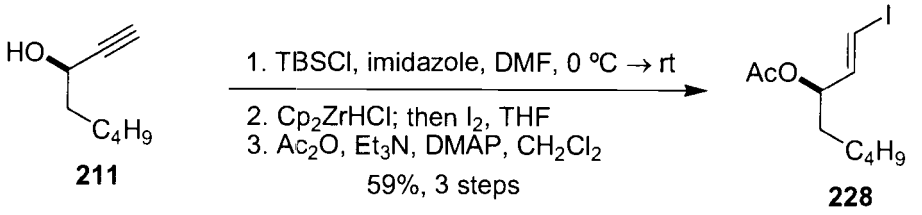




Scheme 43: Total Synthesis of Halicholactone - Y. Takemoto

4.2.3.2 TOTAL SYNTHESIS OF HALICHOLACTONE: T. KITAHARA

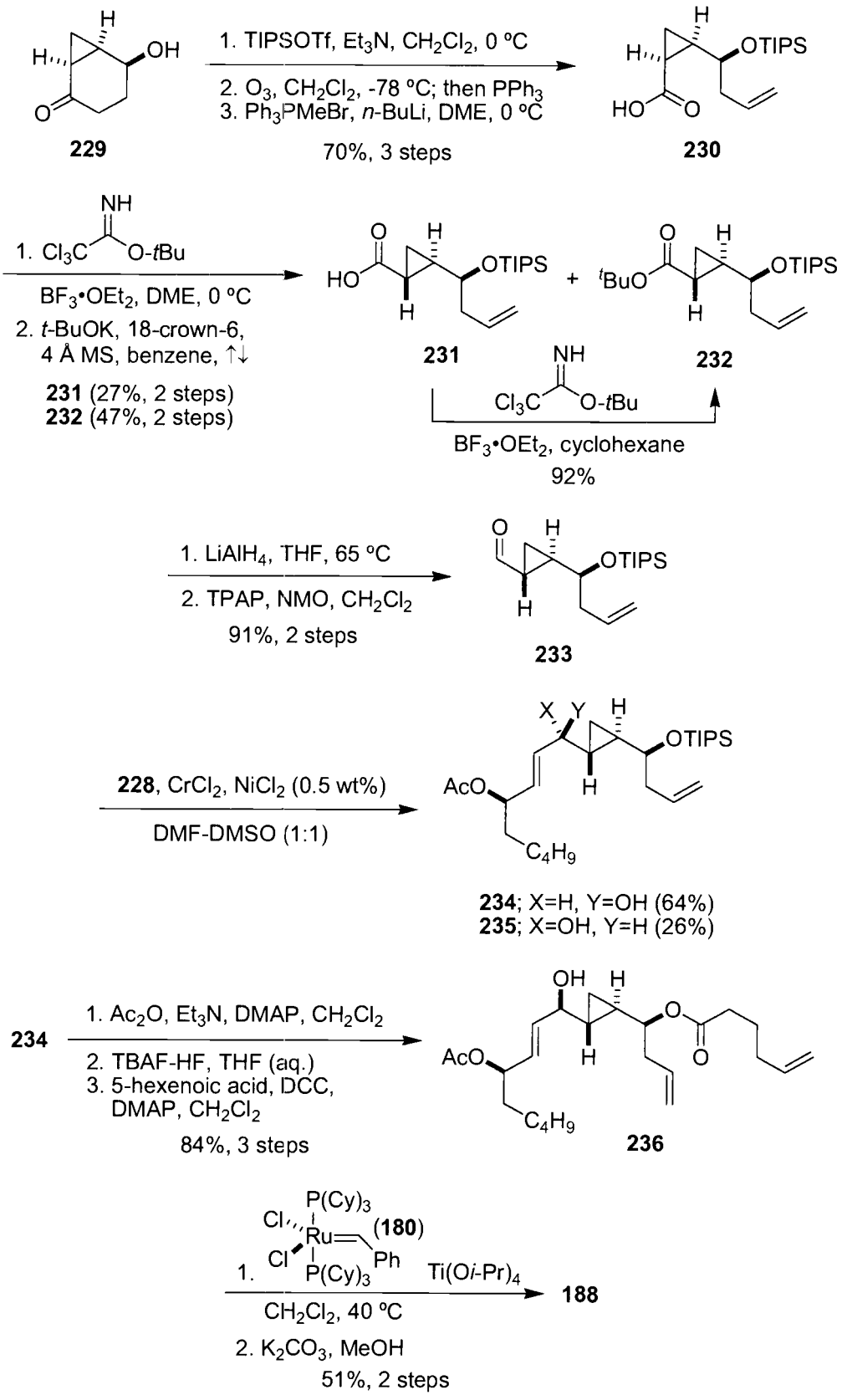
Kitihara and co-workers reported the total synthesis of halicholactone[64c] incorporating a ring closing metathesis to produce a 9-membered lactone similar to that utilized by Takemoto,[64a,b] and a Nozaki-Hiyama-Kishi (NHK) reaction on a substrate slightly modified from that reported by Wills[57] to install the left hand portion of the molecule. Vinyl iodide **228**, the left hand coupling partner for the NHK reaction, was prepared in three steps from commercially available (*R*)-1-octyn-3-ol (**211**, Scheme 44).



Scheme 44: Synthesis of the NHK Coupling Partner

Ozonolytic cleavage of the corresponding TIPS protected silyl enol ether of **229** followed by Wittig olefination gave carboxylic acid **230**. In order to obtain the desired *trans*-cyclopropane needed for halicholactone, efforts were undertaken to isomerize the *cis*-cyclopropane **230** under basic conditions. Transformation of the acid to the corresponding *t*-butyl ester utilizing potassium *tert*-butoxide, 18-crown-6 and molecular sieves in refluxing benzene afforded the desired *trans*-cylclopropyl *t*-butyl ester **232** and *trans*-cyclopropyl carboxylic acid **231**. Conversion of the free acid to the *t*-butyl ester gave an overall yield of 72% for the cyclopropyl isomerization. Reduction of **232** with lithium aluminum hydride followed by oxidation with TPAP afforded the right hand coupling partner aldehyde (**233**) for the NHK reaction. Vinyl iodide **228** was reacted with the previously prepared aldehyde **233** utilizing

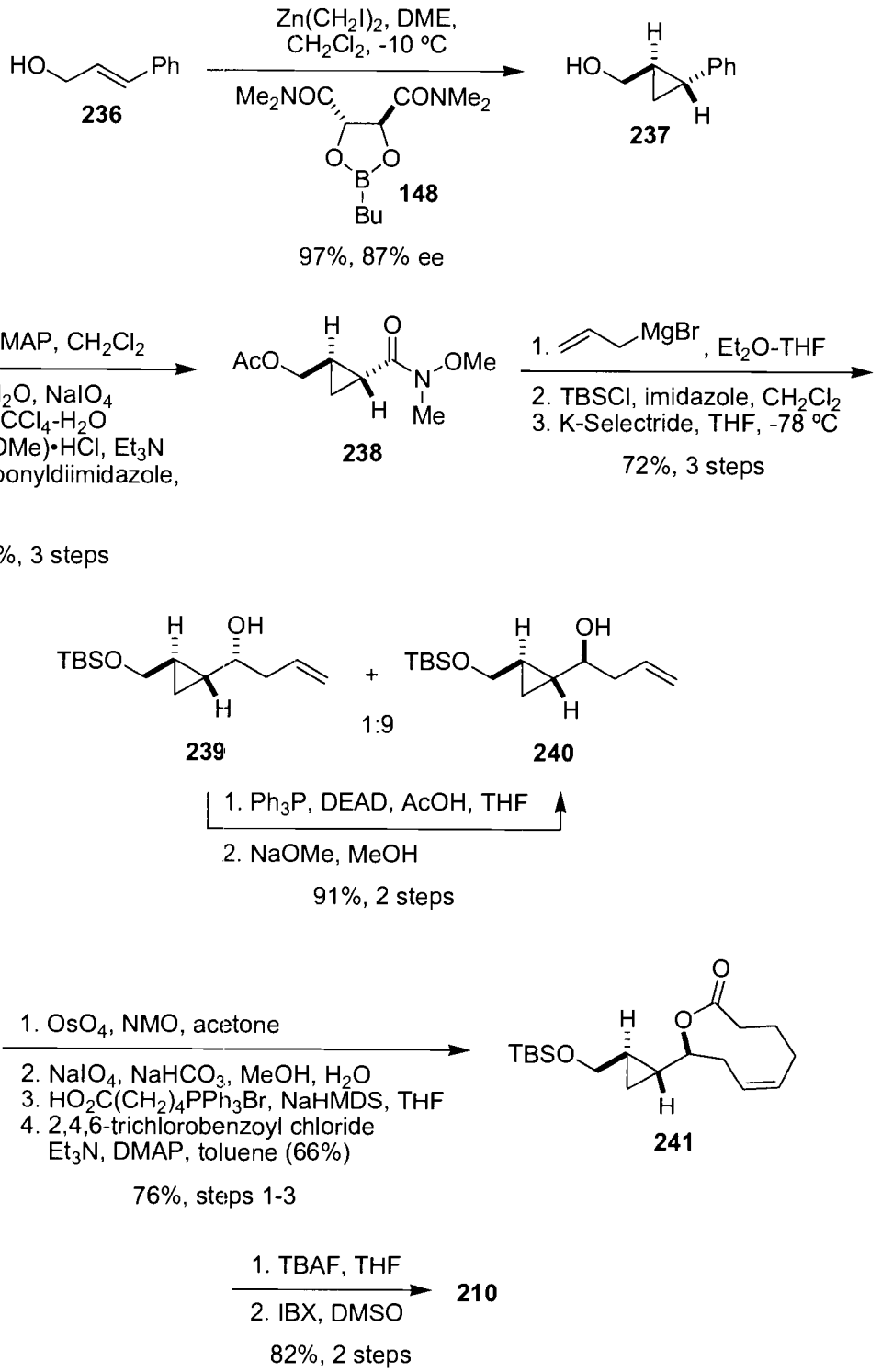
chromium(II) chloride/nickel(II) chloride methodology developed by Kishi[61] and Takai[62] (Scheme 45). The major isomer **234** was separated from the 2.5:1 diastereomeric mixture of products containing **235** and the stereochemistry of **234** was confirmed by Mosher's modified method[70] to be the desired (*R*)-isomer at the newly formed chiral center. Protection of the secondary hydroxyl group as an acetate, removal of the silyl group using TBAF-HF and esterification with 5-hexenoic acid gave the RCM substrate **236**. Reaction of **236** with catalyst **180**[48] in the presence of a catalytic amount of $Ti(O^iPr)$[52,63] under high dilution gave the desired product as a single olefin isomer with about 3% of the corresponding dimer. Methanolysis of the acetyl groups afforded **188**, which was identical (^1H NMR, ^{13}C NMR, IR, MS, and optical rotation) in all aspects to the reported data for natural halicholactone.[52,63]



Scheme 45: Total Synthesis of Halicholactone – T. Kitahara

4.2.3.3 SYNTHESIS OF A KEY PRECURSOR OF HALICHOLACTONE AND NEOHALICHOLACTONE: A. DATTA

Datta and Mohaptra[65a] pursued a strategy involving the stereoselective synthesis of a pivotal *trans*-disubstituted bifunctional cyclopropane, a known precursor to both halicholactone and neohalicholactone (Scheme 46). Cyclopropanation of *trans*-cinnamyl alcohol according to Charette's protocol[31] in the presence of dioxaborolane chiral ligand **148** afforded *trans*-cyclopropyl alcohol **237** with good enantioselectivity and high yield. Acetylation, oxidative degradation of the phenyl group and conversion of the resultant aldehyde to the corresponding Weinreb amide gave protected alcohol **238**. Exposure of the Weinreb amide to allylmagnesium bromide, protection of the primary alcohol as its silyl ether and stereoselective reduction using K-Selectride afforded a 9:1 mixture of diastereomeric alcohols which were easily separated by column chromatography. Having found the major diasteomer (**240**) to be of appropriate stereochemistry by the modified Mosher method,[70] the minor isomer (**239**) was converted to the required isomer *via* a Mitsonobu inversion. Oxidative cleavage of the terminal olefin, *cis*-selective Wittig[56] reaction of the resultant aldehyde and lactonization under Yamaguchi conditions[58] afforded the nine-membered lactone **241** in good yield. Deprotection of the silyl ether and oxidation[71] of the resulting alcohol to aldehyde **210**, a known precursor of halicholactone (**188**) and neohalicholactone (**189**), resulted in a formal synthesis of the natural products.



Scheme 46: Synthesis of a Key Precursor of Halicholactone and Neohalicholactone - A. Datta

4.3 SOLANDELACTONES A-H

4.3.1 ISOLATION AND BIOLOGICAL ACTIVITY

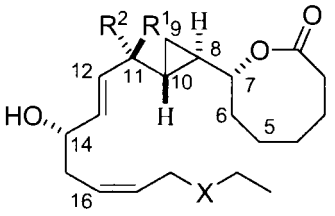
Solandelactones A-H are cyclopropyl and lactone containing novel docosanoids isolated from the hydroid *Solanderia secunda* by Shin and co-workers off the shore of Jaeju Island in Korea.[53] The chemistry of the hydroids (class Hydrazoa) remains largely unexplored. As a result, besides a few common steroids and phospholipids, aromatic polyketides and β-carbolines are the only secondary metabolites ever isolated from these organisms.[72]

Cyclopropyl containing oxylipins have been reported to inhibit 5-lipoxygenase or PLA_2. Considering that these compounds possess a biogenetic origin similar to that of prostaglandins (Figure 21, 22), bioactivities against enzymes participating in the arachidonic acid cascade would be expected.[50,52] In the authors' studies, however, solandelactones exhibited none of these activities. This was postulated to be due to the presence of an additional C_2 unit in solandelactones. On the other hand solandelactones C (**192**), D (**193**), and G (**196**) inhibited Farnesyl Protein Transferase by 69, 89 and 61% respectively at a concentration of 100 μg/mL.

4.3.2 STRUCTURAL DETERMINATION

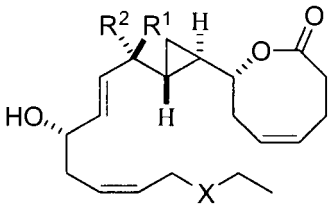
The gross structure of solandelactone A (**190**), including double bond geometry at C-12 and C-16 and the geometry of the cyclopropyl ring, was determined by a combination of HMQC and ^{1}H COSY NMR experiments along with chemical degradation experiments. Careful examination of a three-dimensional model based upon NOESY experiments showed that the C-9 methylene group was facing the oxygen of the lactone ring in the solandelactones, while the same methylene group in

both the constalactones[51] and halicholactone[57] was facing the C-6 methylene group. This indicated that the center at C-7 was inverted from that of halicholactone and neohalicholactone. The relative and absolute configurations of asymmetric carbon centers C-7, C-8, C-10, C-11 and C-14 were determined following methods developed by Gerwick and Nagle for the structural determination of constanolactones A (**186**) and B (**187**), related oxylipins isolated from the red alga *Constantinea simplex*.[51] The absolute configuration of these centers in the constanolactones were determined by chemical transformation and CD measurements to be 7*R*, 8*R*, 10*R*, 11*R* (or 11*S*), and 14*S*. Similar chemical transformation and CD measurements resulted in the assignment of stereochemistry for the solandelactones as shown in Figure 23.



Solandelactones

190 A (R^1 = OH, R^2 = H, X = CH_2CH_2)
191 B (R^1 = H, R^2 = OH, X = CH_2CH_2)
192 C (R^1 = OH, R^2 = H, X = *cis*-CH=CH)
193 D (R^1 = H, R^2 = OH, X = *cis*-CH=CH)



Solandelactones

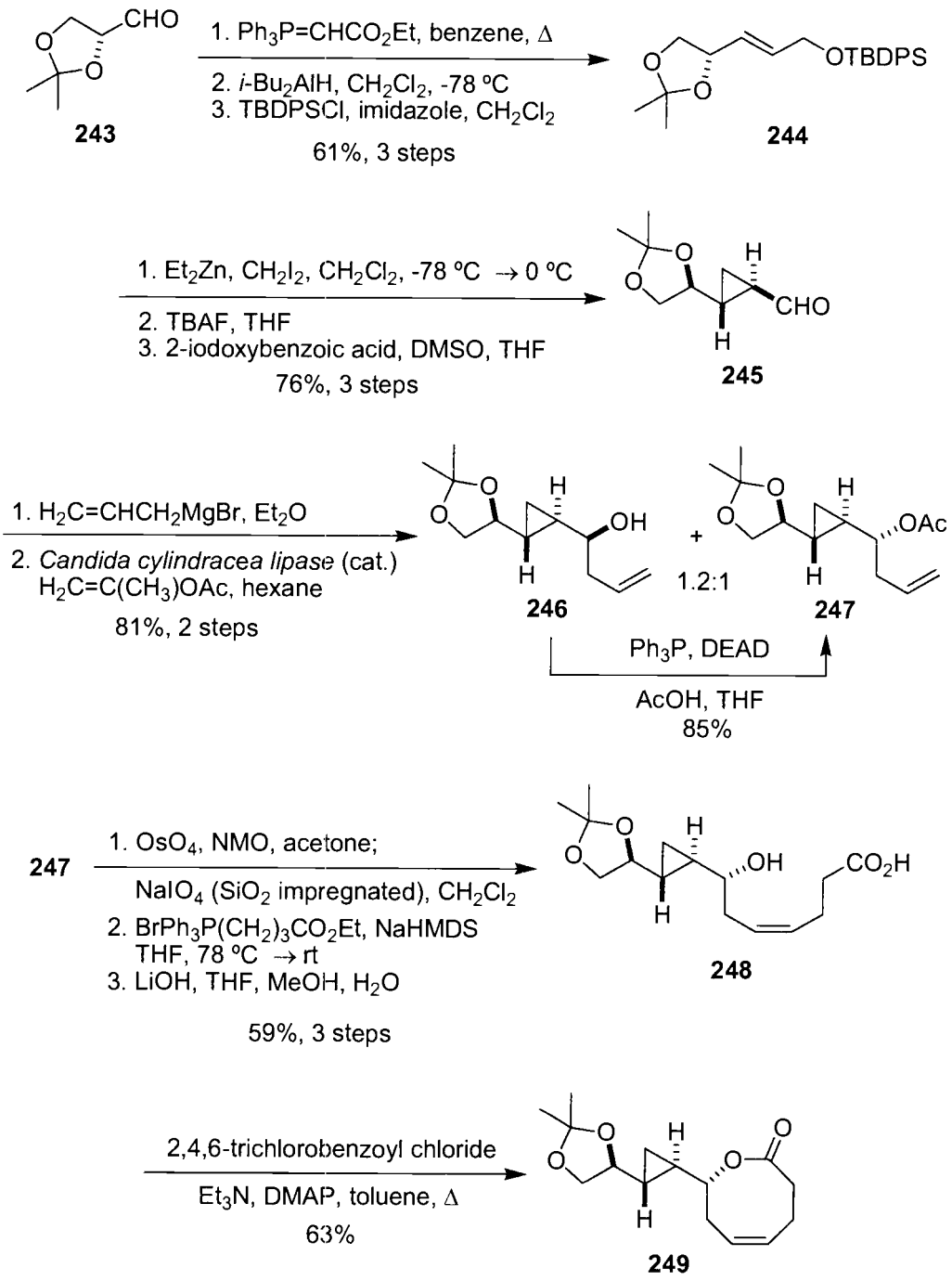
194 E (R^1 = OH, R^2 = H, X = CH_2CH_2)
195 F (R^1 = H, R^2 = OH, X = CH_2CH_2)
196 G (R^1 = OH, R^2 = H, X = *cis*-CH=CH)
197 H (R^1 = H, R^2 = OH, X = *cis*-CH=CH)

Figure 23: Marine Oxylipins Solandelactones A-H

4.3.3 SYNTHESIS OF THE CYCLOPROPYL-LACTONE SEGMENT OF SOLANDELACTONES A-H: A. DATTA

Datta and co-workers reported a concise stereoselective route to the right hand fragment of solandelactones A-H, whereby the initial preparation of a key bifunctional cyclopropane intermediate was followed by construction of the eight-membered lactone ring (Schem 46).[73] The synthesis commenced with (*R*)-2,3-*O*-isopropylidene glyceraldehyde (**243**)[74] which was converted to the silyl protected *E*-allylic alcohol

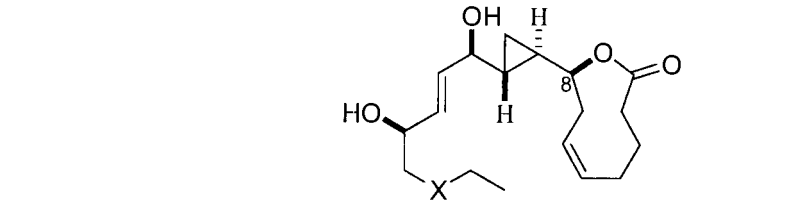
244 under standard reaction conditions.[75] The cyclopropane moiety was installed following a reported procedure,[75] the silyl group was removed with TBAF, and oxidation of the resultant primary alcohol with IBX[71] afforded the key bifunctional cyclopropane **245** in good yield. Exposure of the aldehyde **245** to allylmagnesium bromide resulted in an inseparable mixture of diastereomeric alcohols. The alcohol mixture was subjected to *Candida cylindracea lipase* (CCL) catalyzed enzymatic resolution,[76] yielding the corresponding alcohol **246** (55%) and acetate **247** (45%) with high optical purity (>95%). Stereochemical assignment of the hydroxyl bearing center was determined by Mosher's modified method.[70] The undesired isomer **246** was readily converted to the required acetate **247** *via* a standard Mitsonobu[68] protocol. Degradative oxidation of the terminal olefin followed by a *cis*-selective Wittig reaction with 4-carboethoxybutyl triphenylphosphonium bromide in the presence of NaHMDS at -78 °C[77] and saponification of the resultant ester afforded hydroxy acid **248**. Lactonization of acid **248** under Yamaguchi conditions[58] cleanly gave the eight membered lactone **249**, a key precursor for the synthesis of solandelactones A-H.



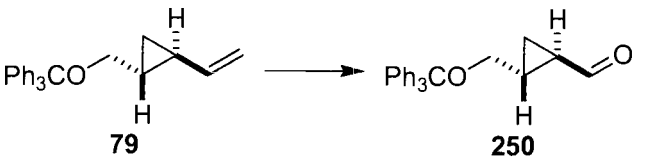
Scheme 47: Synthesis of the Cyclopropyl Lactone Segment of the Solandelactones - A. Datta

4.4 VINYLCYCLOPROPANE 79 AS A SYNTHETIC PRECURSOR TO THE MARINE OXYLIPINS HALICHOLACTONE, NEOHALICHOLACTONE AND SOLANDELACTONES A-H

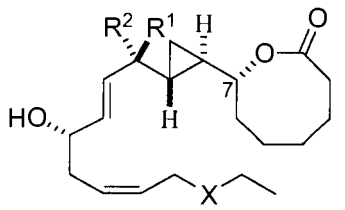
Stereoselective formation of *trans*-vinylcyclopropane **79**, as described in section 2.2.1, afforded an entry into a key precursor of halicholactone (**188**), neohalicholactone (**189**) and solandelactones A-H (**190-197**, Figure 24).



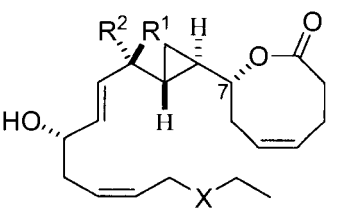
188 Halicholactone (X = CH_2CH_2)
189 Neohalicholactone (X = *cis*-CH=CH)



79 **250**



Solandelactones
190 A (R^1 = OH, R^2 = H, X = CH_2CH_2)
191 B (R^1 = H, R^2 = OH, X = CH_2CH_2)
192 C (R^1 = OH, R^2 = H, X = *cis*-CH=CH)
193 D (R^1 = H, R^2 = OH, X = *cis*-CH=CH)



Solandelactones
194 E (R^1 = OH, R^2 = H, X = CH_2CH_2)
195 F (R^1 = H, R^2 = OH, X = CH_2CH_2)
196 G (R^1 = OH, R^2 = H, X = *cis*-CH=CH)
197 H (R^1 = H, R^2 = OH, X = *cis*-CH=CH)

Figure 24: Cyclopropyl Aldehyde **250** Affording Entry into Two Classes of Marine Oxylipins

Utilization of an asymmetric acetate aldol addition, developed by Phillips and co-worker,[78] to set the desired secondary carbinol asymmetric center at C8 of

halicholactone and neohalicholactone and C7 of the solandelactones allows for entry into either of the two families of natural products, which at the core of their structures differ only at the configuration of the carbinol of the lactone ring.

Although there have been significant advances in catalytic asymmetric auxilliary-based aldol reactions, many of the auxilliaries that work well for propionate aldol reactions give minimal diastereoselection for the synthesis of acetate aldol adducts. Phillips has developed a highly diastereoselective oxazolidinethione based acetate aldol[78] reaction with aliphatic aldehydes utilizing conditions reported by Crimmins and co-workers[79] for a non-Evans syn selective propionate aldol (Figure 25).

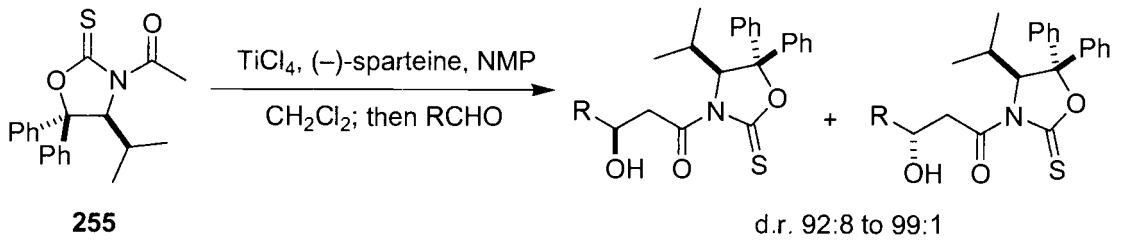
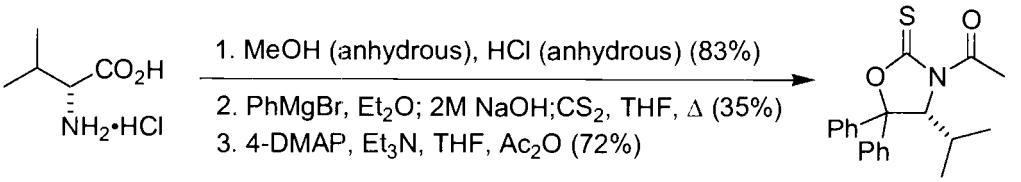


Figure 25: Phillips' Highly Selective Acetate Aldol Reaction of *N*-Acyl-oxazolidinethione **255**

4.4.1 INVESTIGATION OF AN ASYMMETRIC *N*-ACYL-OXAZOLIDINETHIONE BASED ACETATE ALDOL REACTON

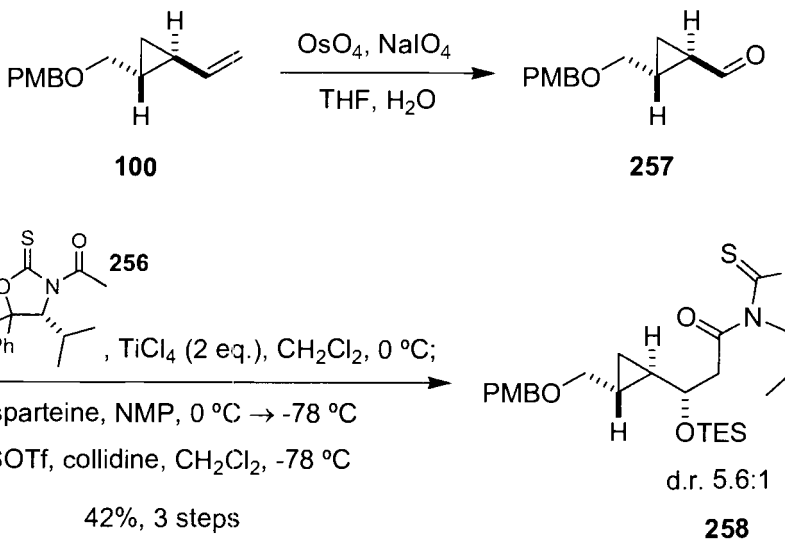
The previously prepared *p*-methoxybenyl protected vinylcyclopropane **100**, (section 2.2.2), was utilized as a model substrate to test the compatability of Phillips' auxilliary with our α-chiral cyclopropyl aldehyde. In an attempt to construct the core structure leading to halicholactone (**188**) and neohalicholactone (**189**), oxazolidinethione **256** was prepared in three steps following a protocol reported by Phillips (Scheme 48).[78]



256

Scheme 48: Preparation of Oxazolidinethione **256**

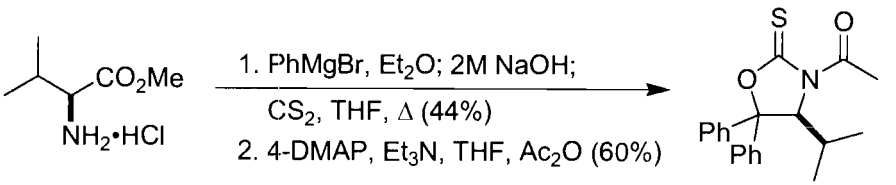
The protected vinylcyclopropane **100** was first converted to the corresponding aldehyde **257** by treatment with osmium tetroxide in the presence of excess sodium periodate. Oxazolidinethione **256** was treated with titanium tetrachloride, followed by (–)-sparteine and *N*-methyl pyrrolidinone, and the aldehyde **257** was added to the mixture at low temperature under argon. The aldol reaction was extremely sluggish and required more than 48 h to completely consume the aldehyde. The unstable aldol adduct was immediately protected as its silyl ether **258** for which the diastereomeric ratio was determined to be 5.6:1 based upon NMR integration of the methine proton of the oxazolidinethione ring (Scheme 49).[80]



Scheme 49: A Non-Diastereoselective Phillips' Acetate Aldol Reaction

With the poor diastereoselectivity observed in this acetate aldol reaction, the enantiomeric oxazolidinethione **255**, prepared according to the protocol developed by

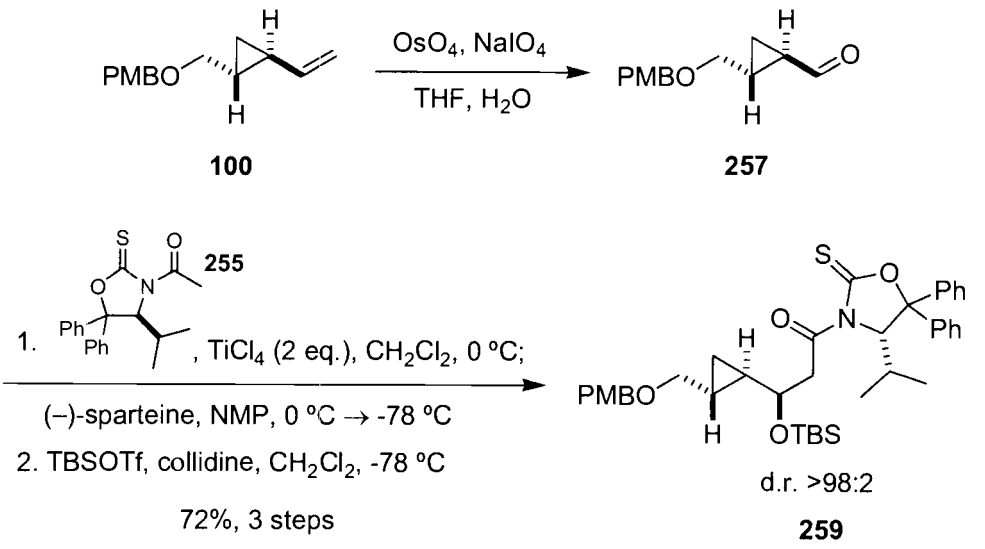
Phillips (Scheme 50),[78] was utilized to set the stereochemistry of the carbinol necessary for the synthesis of solandelactones A-H (**190-197**).



255

Scheme 50: Preparation of Oxazolidinethione **255**

The protected vinylcyclopropane **100** was first converted to the corresponding aldehyde **257** by treatment with potassium osmate in the presence of excess sodium periodate. Oxazolidinethione **255** was treated with titanium tetrachloride, followed by (–)-sparteine and *N*-methyl pyrrolidinone, and the aldehyde **257** was added to this mixture at low temperature under argon. As with **256**, this aldol reaction was extremely sluggish and required 60 h to completely consume the aldehyde. Again, the unstable aldol adduct was immediately protected as its silyl ether **259** and the diastereomeric ratio in this case was determined to be >98:2 based upon integration of the methine proton of the oxazolidinethione ring (Scheme 51).[81]



Scheme 51: A Highly Diastereoselective Phillips' Acetate Aldol Reaction

The high degree of diastereoselectivity in the aldol reaction of oxazolidinethione **255** can be explained by application of a model developed by Yan and co-workers[82] for the titanium mediated camphor based *N*-propionyloxazolidinethione aldol reaction (Figure 26). Coordination of aldehyde **257** to chelate **260** may result in a 1:1 chlorotitanium enolate/aldehyde complex with an octahedrally hexacoordinated titanium atom.[83] Unlike corresponding oxazolidinones, which adopt a dipole minimized transition state structure analogous to **262**, aldolizations of *N*-acyloxazolidinethiones proceed *via* chelated complexes resulting from displacement of chloride ion from titanium (**261**). Yan rationalized the preference for transition state **261** through the strong affinity of thiocarbonyl toward association with chlorotitanium and through the relatively small dipole moment of thioketones[84] compared to the corresonding ketones which suggests that the dipolar repulsion between aldehyde carbonyl and thiocarbonyl is relatively unimportant.

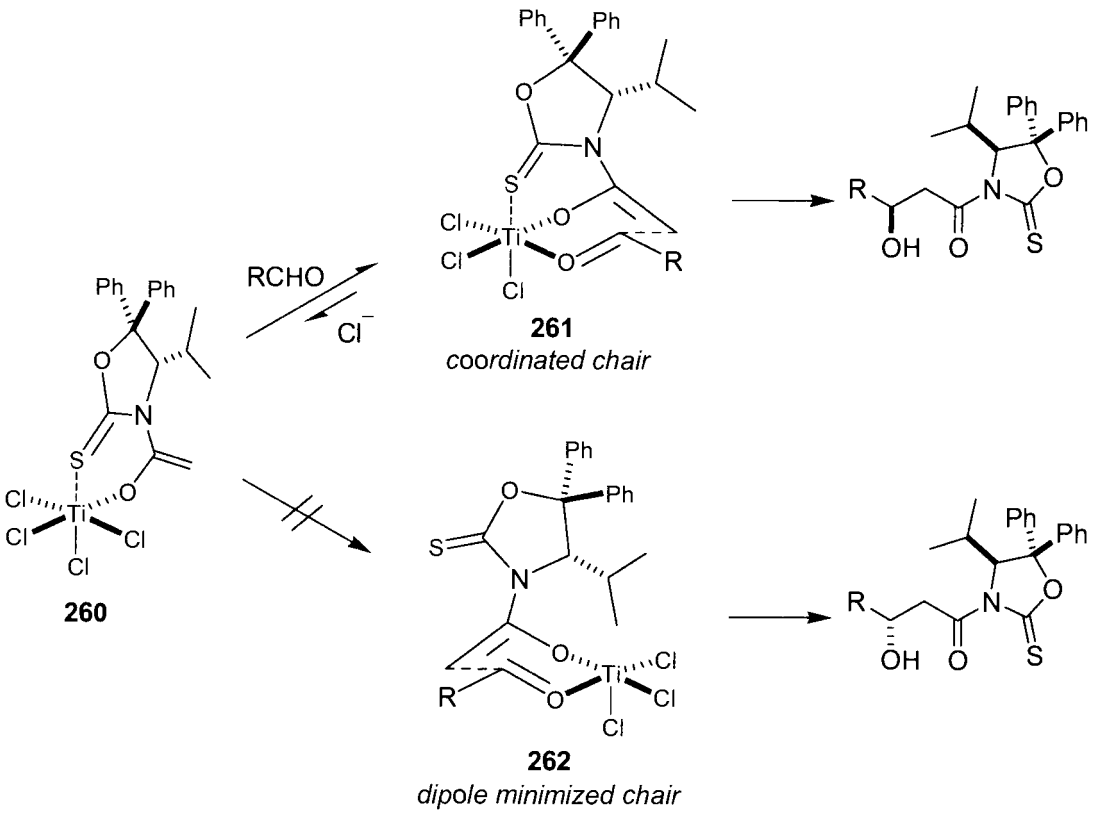
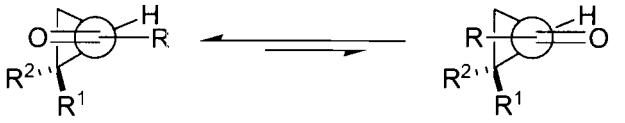


Figure 26: Preferred Coordinated Chair Transition State **261** in the Chlorotitanium Mediated *N*-Acyloxazolidinethione-Based Acetate Aldol Reaction

In order to understand the difference in diastereoselectivity observed between the two oxazolidinethiones **255** and **256** in the acetate aldol transformation of **257**, the conformation of the cyclopropyl aldehyde in the transition state structure must be taken into consideration. It has been previously reported that delocalization of electrons of cyclopropyl aldehydes is possible *via* overlap between the cyclopropyl C-C bonds and the carbonyl π-orbitals,[85] and is maximized when the cyclopropane and the carbonyl group are oriented orthogonally in a bisected conformation. Both the *s-cis* (**263**) and the *s-trans* (**264**) conformations provide this stabilization,[86] but computational studies indicate that the *s*-(*cis*)-conformation **263** is favored by approximately 1.6 kcal/mol over the *s*-(*trans*)-conformation **264** (Figure 27).[86b]



263 **264**

s-cis preferred conformation

s-trans disfavoured conformation

Figure 27: Bisected Conformations of Cyclopropyl Aldehydes and Ketones

Using the *s*-(*cis*)-conformation **263** as a model for the preferred conformation of the *trans*-cyclopropyl aldehyde **257** in transition state structure **261**, we can propose a pathway which accounts for the lower degree of selectivity observed with chiral auxilliary **256**. The more stable *s*-(*cis*)-conformation as shown in coordinated chair transition state structure **265** produces steric interaction between the *p*-methoxybenzyl ether on the aldehyde and chlorotitanium chelate. The 5.6:1 diastereoselectivity observed in the reaction of **257** with **256** can be rationalized through the higher energy of the coordinated chair **265**, making the coordinated boat transition state **266** an energetically competitive transition state for the reaction (Figure 28).

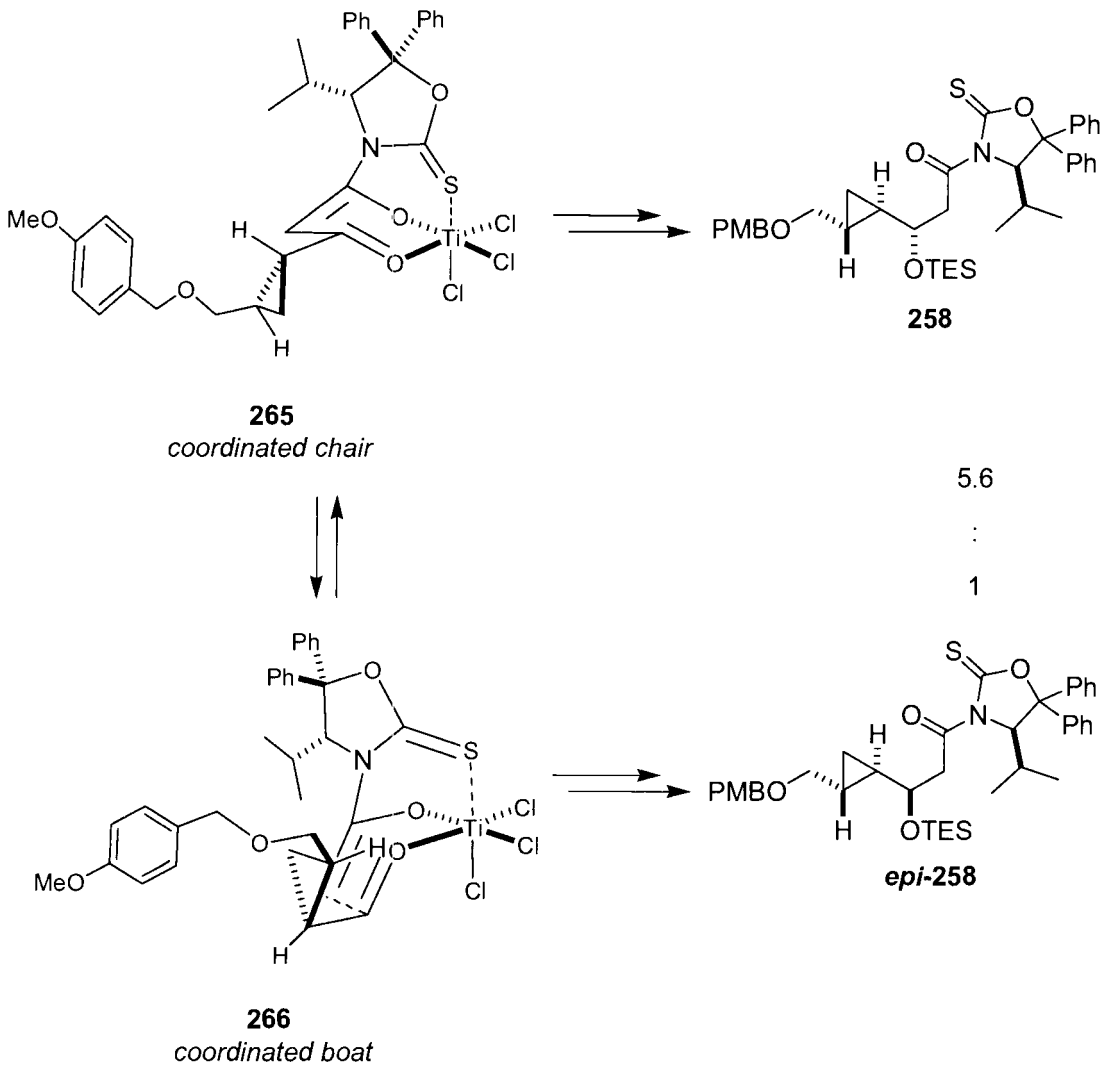


Figure 28: Competitive Coordinated and Boat Transition States in the *N*-Acyl-oxazolidinethione Based Asymmetric Acetate Aldol Reaction

The absence of any steric interaction in the coordinated chair **267** leading to the highly diastereoselective formation of **258** helps to support this hypothesis (Figure 29).

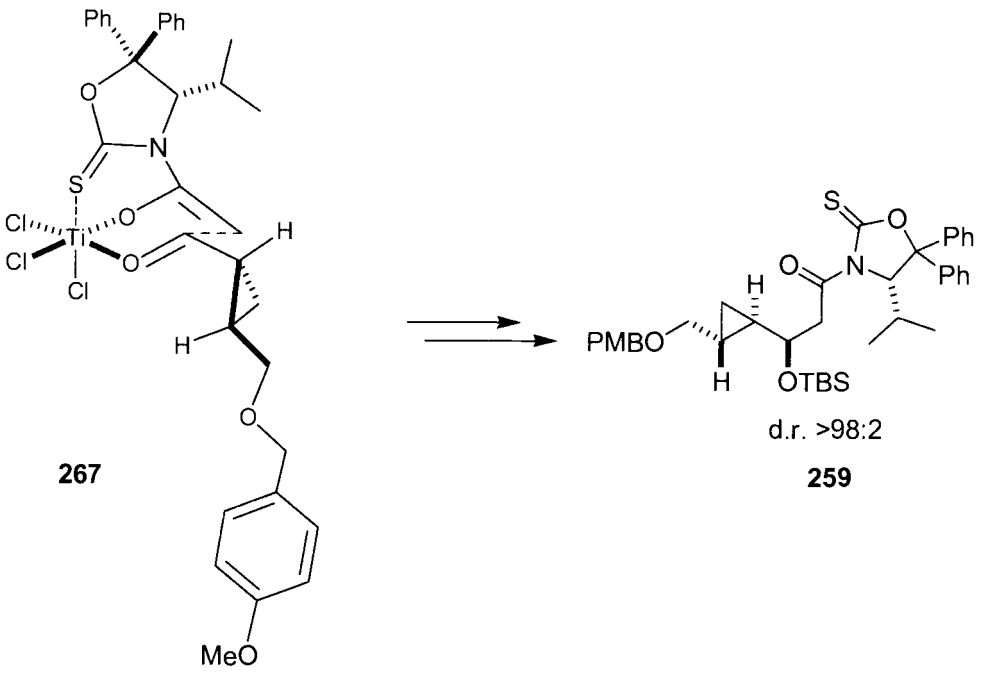
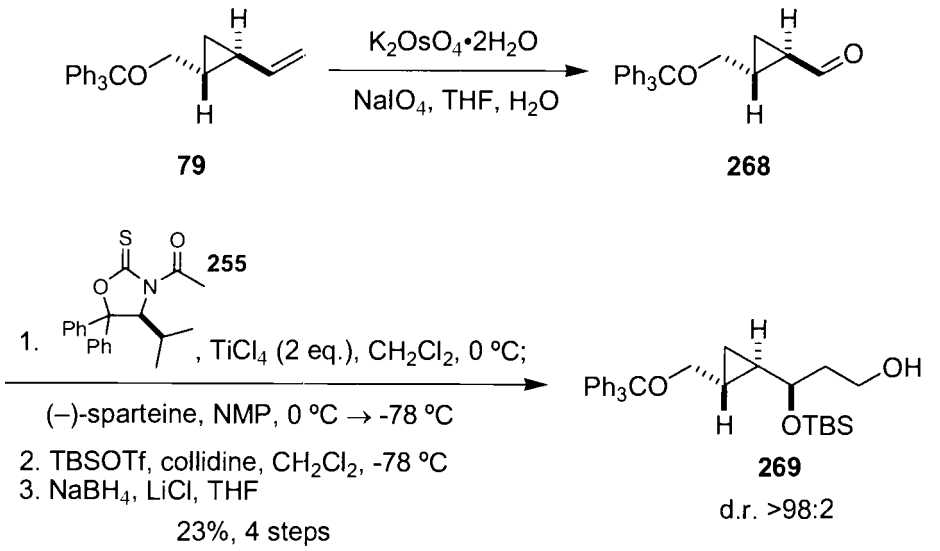


Figure 29: Influence of the Bisected Conformation of *trans*-Cyclopropyl Aldehydes in the *N*-Acyloxazolidinethione Based Asymmetric Acetate Aldol Reaction

4.4.2 SYNTHESIS OF A KEY PRECURSOR OF HALICHOLACTONE, NEOHALICHOLACTONE AND SOLANDELACTONES A-H

From the above results, it was determined that the diastereoselective acetate aldol[78] reaction between *N*-acyloxazolidinethione **255** and the aldehyde derived from the more diastereopure vinylcyclopropane **79** could be used to supply a direct synthetic precursor to solandelactones A-H, and which would also allow entry into halicholactone and neohalicholactone *via* an inversion of the newly formed cyclopropyl carbinol (Scheme 50). The protected vinylcyclopropane **79** was first converted to the corresponding aldehyde **268** by treatment with potassium osmate in the presence of excess sodium periodate. Oxazolidinethione **255** was then treated with titanium tetrachloride, followed by (–)-sparteine and *N*-methyl pyrrolidinone, and the aldehyde **268** was added at low temperature under argon. As before, the aldol reaction was extremely sluggish and required more than 48 h to completely consume the

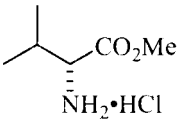
aldehyde. The unstable aldol adduct was immediately protected as its silyl ether and the auxilliary was cleaved with *in situ* generated lithium borohydride to afford the primary alcohol **269** with greater than 98:2 diastereoselectivity for the newly installed secondary alcohol. Alcohol **269** now stands ready for further elaboration at each of the three oxygen-bearing centers in a manner which can lead to solandelactones on the one hand or to halicholactone and neohalicholactone on the other.



Scheme 50: Synthesis of a Key Precursor to Halicholactone, Neohalicholatone and Solandelactones A-H

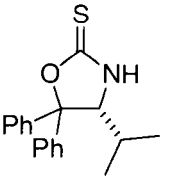
4.5 EXPERIMENTAL SECTION

General experimental techniques and instrumentation used in this work are described in section 2.5.



270

(2*R*)-2-Amino-3-methylbutyric Acid Methyl Ester Hydrochloride Salt. A stirred solution of D-valine (5.00 g, 98%, 99% e.e., 41.8 mmol) in anhydrous methanol (100 mL) was degassed with an argon bubbler for 10 min, then cooled to 0 °C. HCl gas (anhydrous) was bubbled through the suspension for 1 h and the solution was allowed to warm to ambient temperature. After 4 h, the solution was degassed with argon and concentrated under reduced pressure. The crude residue was crystallized from acetone-Et_2O (1:10) to afford 5.80 g (83%) of (2*R*)-2-amino-3-methylbutyric acid methyl ester, hydrochloride salt: ^{1}H NMR (300 MHz, DMSO-d6/acetone-d6) δ 0.93 (d, J = 6.9 Hz, 3H), 0.99 (d, J = 7.0 Hz, 3H), 2.20-2.32 (m, 1H), 3.72 (s, 3H), 8.9 (brs, 2H); ^{13}C NMR (75 MHz, DMSO-d6/acetone-d6) δ 17.4, 18.6, 52.3, 57.5, 169.2.

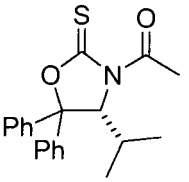


271

(4*R*)-4-Isopropyl-5,5-diphenyloxazolidine-2-thione. Bromobenzene (570 μL, 5.13 mmol) was added to a stirred suspension of magnesium turnings (4.12 g, 170 mmol) and a crystal of I_2 in Et_2O (25 mL). The reaction mixture was slowly heated to initiate the Grignard reaction, the heating bath was removed and a solution of bromobenzene

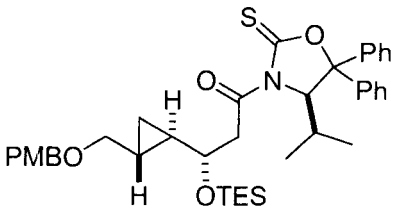
(17.32 mL, 164 mmol) in Et_2O (250 mL) was added slowly to maintain a gentle reflux. Upon completion of addition, the solution was stirred for an additional 30 min, after which (2*R*)-2-amino-3-methylbutyric acid methyl ester hydrochloride salt (5.69 g, 33.9 mmol) was added slowly and the mixture was stirred for 21 h at ambient temperature. The reaction was quenched by pouring the mixture into 2 M NaOH (50 mL), the solution was filtered through Celite and the filter cake was washed with CH_2Cl_2 (3 x 100 mL). The organic extract was dried (Na_2SO_4), filtered, and concentrated under reduced pressure.

To the crude material obtained above in triethylamine (18.9 mL, 135.5 mmol) in THF (170 mL) was added CS_2 (10.2 mL, 170 mmol) and the mixture was gently refluxed for 21 h. The reaction mixture was added to a separatory funnel containing saturated aqueous NH_4Cl (75 mL) and EtOAc (170 mL), and the separated organic solution was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude solid was triturated with hot Et_2O and crystallized from acetone-petroleum ether to afford 3.53 g (35%, 2 steps) of (4*R*)-4-isopropyl-5,5-diphenyloxazolidine-2-thione: ^{1}H NMR (300 MHz, DMSO-d6) δ 0.47 (d, *J* = 6.6 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H), 1.89 (dtd, *J* = 1.9, 6.5, 13.2 Hz, 1H), 4.63 (s, 1H), 7.24-7.32 (m, 2H), 7.37 (td, *J* = 3.3, 7.3 Hz, 4H), 7.47 (d, *J* = 7.5 Hz, 2H), 7.65 (d, *J* = 7.5 Hz, 2H), 10.47 (brs, 1H); ^{13}C NMR (75 MHz, DMSO-d6) δ 14.8, 20.0, 29.3, 68.2, 93.5, 125.0, 125.6, 127.5, 128.0, 128.2, 128.5, 138.7, 144.1, 186.6.



256

1-[(4*R*)-Isopropyl-5,5-diphenyl-2-thioxooxazolidin-3-yl]-ethanone. Acetic anhydride (1.36 mL, 14.0 mmol) was added to a stirred solution of (4*R*)-4-isopropyl-5,5-diphenyloxazolidine-2-thione (3.47 g, 11.7 mmol), Et_3N (4.16 mL, 29.3 mmol) and 4-DMAP (286 mg, 20 mol%) in THF (125 mL) under argon. After 19 h at ambient temperature, the reaction mixture was added to a separatory funnel containing saturated aqueous NH_4Cl (50 mL) and Et_2O (75 mL) and the aqueous fraction was extracted with Et_2O (2 x 20 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure to leave a crude solid which was crystallized from hot ethanol to afford 2.87 g (72%) of 1-[(4*R*)-isopropyl-5,5-diphenyl-2-thioxooxazolidin-3-yl]-ethanone: mp 96-97 °C; $[\alpha]_D^{23}$ + 218.1 (c 1.0, $CHCl_3$); IR (neat) 3061, 3033, 2966, 2933, 2871, 1703, 1465, 1450, 1414, 1375, 1335, 1308, 1221, 1171 cm^{-1}; ^1H NMR (300 MHz, DMSO-d6) δ 0.47 (d, *J* = 6.6 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H), 1.89 (dtd, *J* = 1.9, 6.5, 13.2 Hz, 1H), 2.69 (s, 3H), 5.61 (d, *J* = 3.9 Hz, 1H), 7.29-7.38 (m, 6H), 7.41-7.50 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d6) δ 16.9, 21.5, 25.7, 30.0, 67.9, 93.2, 125.4, 126.1, 128.1, 128.4, 128.6, 128.8, 137.4, 141.6, 171.0, 185.3; MS (CI) *m/z* 339 $(M)^+$, 296, 279, 254, 220, 205, 198, 165, 152, 105, 97; HRMS (CI) *m/z* 339.1295 (calcd for $C_{20}H_{21}O_2NS$: 339.1293).



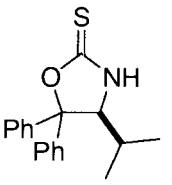
258

(1*R*,2*R*)-1-(4'-Methoxybenzyloxymethyl)-2-[(1*S*)-triethylsilyloxy-4-[(4*R*)-isopropyl-5,5-diphenyl-2-thioxooxazolidin-3-yl]cyclopropane. OsO_4 (228 μL, 0.04 M in H_2O, 5 mol%) and $NaIO_4$ (39 mg, 0.183 mmol) were sequentially added to a stirred solution of (1*R*,2*S*)-1-(4'-methoxybenzyloxymethyl)-2-vinylcyclopropane (40 mg, 0.183 mmol) in THF (1.9 mL) and H_2O (1.6 mL). After 1 h at ambient temperature, $NaIO_4$ (117 mg, 549 mmol) was added and after 21 h at ambient temperature, saturated aqueous $Na_2S_2O_3$ (5 mL) was added. The mixture was stirred for 30 min, then the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure.

$TiCl_4$ (238 μL, 1.0 M in CH_2Cl_2, 0.238 mmol) was added dropwise *via* syringe to a stirred solution of (4*R*)-4-isopropyl-5,5-diphenyloxazolidine-2-thione (68.3 mg, 0.201 mmol) in CH_2Cl_2 (940 μL) at 0 °C under argon. After 10 min, (–)-sparteine (55 μL, 0.238 mmol) and *N*-methylpyrrolidone (23 μL, 0.238 mmol) were added dropwise *via* syringe and the deep red solution was stirred for 20 min at ambient temperature. The solution was cooled to -82 °C and a solution of the crude aldehyde obtained above in CH_2Cl_2 (500 μL) was added dropwise under argon. After 50 h, the reaction mixture was quenched with 50% aqueous NH_4Cl and extracted with CH_2Cl_2 (15 mL, 3 x 5

mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure.

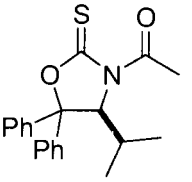
TESOTf (29.4 μL, 0.129 mmol) and collidine (17.0 μL, 0.129 mmol) were added sequentially to a stirred solution of the crude aldol adduct obtained above in CH_2Cl_2 (1.5 mL) at 0 °C under argon. After 20 min, the cooling bath was removed and the mixture was stirred for an additional 21 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (2 mL) and extracted with CH_2Cl_2 (5 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified on a column of silica gel (5-20% EtOAc in hexane) to afford 49 mg (42%, 3 steps) of (1*R*,2*R*)-1-(4'-methoxybenzyloxymethyl)-2-[(1*S*)-triethylsilyloxy-4-[(4*R*)-isopropyl-5,5-diphenyl-2-thioxooxazolidin-3-yl]cyclopropane as a 5.6:1 mixture of diastereomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.37 (td, *J* = 4.9, 9.0 Hz, 1H), 0.47 (td, *J* = 5.0, 8.5 Hz, 1H), 0.51-0.65 (m, 6H), 0.80 (d, *J* = 6.8 Hz, 4H), 0.87-0.98 (m, 9 H), 1.13 (dq, *J* = 5.1, 9.8 Hz, 2H), 2.08 (dtd, *J* = 3.8, 6.9, 13.8 Hz, 1H), 3.03 (dd, *J* = 8.2, 10.2 Hz, 1H), 3.46 (d, *J* = 5.6 Hz, 1H), 3.54 (d, *J* = 6.3 Hz, 1H), 3.57-3.63 (m, 1H), 3.84 (s, 3H), 3.82-3.86 (m, 1H), 4.48 (d, *J* = 3.7 Hz, 2H), 5.60 (d, *J* = 3.8 Hz, 1H), 6.88-6.93 (m, 2H), 7.27-7.40 (m, 10H), 7.47-7.53 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.0, 6.9, 8.2, 16.3, 17.0, 21.5, 22.9, 30.1, 55.2, 68.5, 69.9, 72.0, 73.1, 93.0, 113.7, 125.3, 126.1, 128.0, 128.4, 128.6, 128.9, 129.2, 130.7, 137.4, 141.7, 159.0, 171.4, 184.7.



272

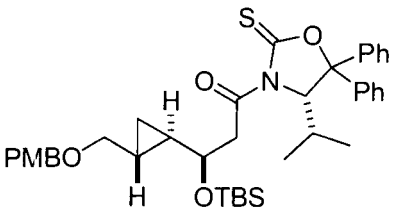
(*S*)-4-Isopropyl-5,5-diphenyloxazolidine-2-thione. A stirred suspension of bromobenzene (842 μL, 7.58 mmol), magnesium turnings (6.09 g, 2.51 mmol) and a crystal of iodine in anhydrous Et_2O (40 mL) was gently heated to reflux under argon. The heating bath was removed and a solution of bromobenzene (25.60 mL, 242 mmol) in Et_2O (350 mL) was added slowly to maintain a gentle reflux. The mixture was stirred for an additional 30 min at ambient temperature, and then L-valine methyl ester hydrochloride (8.40 g, 50.1 mmol) was added portionwise over 10 min. After 13 h, the mixture was added to a stirred solution of 2M NaOH (50 mL), the resulting slurry was filtered through Celite and the filter cake was washed with Et_2O (3 x 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude solid was taken up in THF (250 mL), Et_3N (27.9 mL, 200 mmol) and CS_2 (15.1 mL, 250 mmol) and the reaction mixture was refluxed for 12 h. A further quantity of CS_2 (10.0 mL, 165 mmol) was added, the solution was stirred for an additional 16 h, and the reflux condenser was replaced with a distillation head. The volume of the solution was reduced to 75 mL and the concentrated mixture was added to a separatory funnel containing saturated aqueous NH_4Cl (25 mL) and EtOAc (100 mL). The aqueous layer was extracted with EtOAc (25 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude solid was triturated with hot Et_2O and crystallized from acetone-petroleum ether (10:1) to afford 6.58 g (44%, 2 steps) of (*S*)-4-isopropyl-5,5-

diphenyloxazolidine-2-thione. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.68 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.9 Hz, 3H), 1.79-1.95 (m, 1H), 4.50 (dd, J = 0.96, 4.0 Hz, 1H), 7.24-7.38 (m, 8H), 7.47-7.52 (m, 2H), 8.79 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.2, 21.0, 29.6, 69.6, 95.5, 125.7, 126.5, 128.0, 128.1, 128.5, 128.6, 138.0, 142.4, 187.6.



255

1-((*S*)-4-Isopropyl-5,5-diphenyl-2-thioxooxazolidin-3-yl)ethanone. Ac_2O (2.56 mL, 1.2 eq) was added to a stirred solution of (*S*)-4-isopropyl-5,5-diphenyloxazolidine-2-thione (6.50 g, 21.9 mmol), 4-DMAP (534 mg, 20 mol%) and Et_3N (7.82 mL, 2.5 eq) in THF (150 mL) at ambient temperature under argon. After 14 h, the mixture was added to a separatory funnel containing 50% aqueous NH_4Cl (40 mL) and EtOAc (150 mL). The separated aqueous layer was extracted with EtOAc (25 mL) and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified on a column of silica gel (20% Et_2O in petroleum ether) followed by crystallization from hot cyclohexane-pentane (1:1) to afford 4.44 g (60%) of 1-((*S*)-4-isopropyl-5,5-diphenyl-2-thioxooxazolidin-3-yl)ethanone: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.9 Hz, 3H), 1.96-2.12 (m, 1H), 2.69 (s, 3H), 5.60 (d, J = 3.9 Hz, 1H), 7.25-7.38 (m, 6H), 7.41-7.50 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.9, 21.5, 25.7, 30.0, 68.0, 93.2, 125.4, 126.1, 128.1, 128.4, 128.6, 128.9, 137.4, 141.6, 171.0, 185.3.



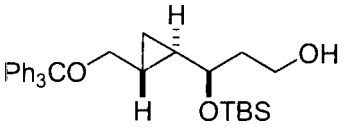
259

(1*R*,2*R*)-1-(4'-Methoxybenzyloxymethyl)-2-[(1*R*)-triethylsilyloxy-4-((4*S*)-isopropyl-5,5-diphenyl-2-thioxo-oxazolidin-3-yl)]cyclopropane. OsO_4 (2.53 mL, 0.04 M in H_2O, 5 mol%) and $NaIO_4$ (430 mg, 2.02 mmol) were sequentially added to a stirred solution of (1*R*,2*S*)-1-(4'-methoxybenzyloxymethyl)-2-vinylcyclopropane (442 mg, 2.02 mmol) in THF (20.75 mL) and H_2O (17.50 mL). After 1 h at ambient temperature, a further quantity of $NaIO_4$ (1.29 g, 6.06 mmol) was added. After 22 h at ambient temperature, saturated aqueous $Na_2S_2O_3$ (11 mL) was added, the mixture was stirred for 30 min, then the aqueous layer was extracted with 25% hexane in EtOAc (3 x 50 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give the crude aldehyde.

$TiCl_4$ (4.04 mL, 1.0 M in CH_2Cl_2) was added dropwise *via* syringe to a stirred solution of (4*S*)-4-isopropyl-5,5-diphenyloxazolidine-2-thione (1.37 g, 4.04 mmol) in CH_2Cl_2 (10 mL) at 0 °C under argon. After 10 min, (–)-sparteine (933 μL, 4.04 mmol) and *N*-methylpyrrolidone (390 μL, 4.04 mmol) were added dropwise *via* syringe and the deep red solution was stirred for 20 min at ambient temperature. The solution was cooled to -78 °C and a solution of the crude aldehyde obtained above in CH_2Cl_2 (4.5 mL) was added dropwise under argon. After 50 h, the reaction mixture was quenched with 50% aqueous NH_4Cl (6 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The

combined extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give the crude aldol product.

TBSOTf (572 μL, 98%, 2.44 mmol) and collidine (321 μL, 2.44 mmol) were added sequentially to a stirred solution of the crude aldol adduct obtained above in CH_2Cl_2 (25 mL) at -78 °C under argon. After 20 min, the cooling bath was removed and the mixture was stirred for an additional 21 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried (Na_2SO_4), filtered, concentrated under reduced pressure and the residue was purified on column of silica gel (5-20% EtOAc in hexane) to afford 974 mg (72%, 3 steps) of (1*R*,2*R*)-1-(4'-methoxybenzyloxymethyl)-2-[(1*R*)-triethylsilyloxy-4-((4*S*)-isopropyl-5,5-diphenyl-2-thioxo-oxazolidin-3-yl)]cyclopropane: $[\alpha]_D^{23}$ - 108.8 (c 1.4, $CHCl_3$); IR (neat) 3063, 3028, 2994, 2956, 2930, 2883, 2855, 1705, 1613, 1586, 1513, 1494, 1464, 1450, 1396, 1366, 1335, 1310, 1248, 1204, 1171 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ - 0.56 (s, 3H), 0.36 (s, 3H), 0.43 (dt, *J* = 4.8, 8.6 Hz, 1H), 0.59 (dt, *J* = 5.0, 8.4 Hz, 1H), 2.69 (s, 1H), 3.19 (dd, *J* = 7.2, 10.2 Hz, 1H), 3.34 (dd, *J* = 6.2, 10.2 Hz, 1H), 3.40 (d, *J* = 4.3 Hz, 1H) 3.42-3.63 (m, 1H), 3.71 (td, *J* = 4.5, 7.1 Hz, 1H), 3.80 (s, 3H), 4.44 (s, 2H), 5.54 (d, *J* = 3.8 Hz, 1H), 6.85-6.91 (m, 2H), 7.21-7.38 (m, 10H), 7.41-7.50 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.6, -4.3, 9.6, 14.2, 15.8, 17.0, 18.0, 21.0, 21.5, 23.5, 25.6, 25.8, 30.0, 45.7, 55.2, 60.3, 67.9, 68.6, 70.5, 72.1, 73.0, 93.0, 113.7, 125.2, 125.4, 126.1, 128.0, 128.3, 128.5, 128.9, 129.1, 130.6, 137.5, 141.7, 159.0, 171.3, 184.7; MS (CI) *m/z* 674 $(M+H)^+$, 658, 616, 556, 405, 316, 222, 207, 121; HRMS (CI) *m/z* 674.3321 (calcd for $C_{39}H_{52}O_5NSiS$ $(M+H)^+$: 674.3336).



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(1*R*,2*R*)-1-(Trityloxymethyl)-2-[1-(*R*)-*tert*-butyldimethylsiloxy-4-hydroxy-propyl]cyclopropane. $K_2OsO_4 \cdot 2H_2O$ (49.4 mg, 5 mol%) and $NaIO_4$ (341 mg, 1.60 mmol) were added to a stirred solution of (1*R*,2*S*)-1-(trityloxymethyl)-2-vinylcyclopropane (545 mg, 1.60 mmol) in THF (17 mL) and H_2O (14 mL). After 1 h, an additional quantity of $NaIO_4$ was added (1.02 g, 4.80 mmol) and the reaction was stirred for 17 h. Saturated aqueous $Na_2S_2O_3$ (8.8 mL) was added and, after 30 min, the mixture was extracted with 75% EtOAc in hexane (3 x 50 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated under reduced to give crude aldehyde.

$TiCl_4$ (3.20 mL, 1.0 M in CH_2Cl_2, 2 eq) was added slowly to a stirred solution of 1-((*S*)-4-isopropyl-5,5-diphenyl-2-thioxooxazolidin-3-yl)ethanone (1.09 g, 3.20 mmol, 2 eq) in CH_2Cl_2 (7.75 mL) at 0 °C under argon. After 10 min, (-)-sparteine (739 μL, 3.20 mmol, 2 eq) and *N*-methylpyrrolidone (309 μL, 3.20 mmol, 2 eq) were added and the mixture was stirred an additional 30 min at 0 °C. The solution was cooled to -78 °C and a solution of the crude aldehyde obtained above in CH_2Cl_2 (3.5 mL) was added dropwise over 10 min under argon. After 49 h at -78 °C, the reaction was quenched with saturated aqueous NH_4Cl (15 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give crude aldol product.

TBSOTf (1.13 mL, 98%, 4.80 mmol) and collidine (632 μL, 4.80 mmol) were added sequentially to a stirred solution of the crude aldol product obtained above in CH_2Cl_2 (28 mL) at -78 °C under argon. After 16 h at -78 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered, concentrated under reduced pressure and dried in vacuo.

A suspension of LiCl (813 mg, 19.2 mmol) and $NaBH_4$ (365 mg, 9.6 mmol) in THF (17 mL) was stirred at ambient temperature under argon for 1 h, and a solution of the crude TBS protected aldol product obtained above in THF (10 mL) was added slowly. After 18 h, the reaction mixture was added to a separatory funnel containing saturated aqueous $NaHCO_3$ (25 mL) and was extracted with CH_2Cl_2 (4 x 25 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified on a column of silica gel (2-50% EtOAc in cyclohexane) to afford 186 mg (23%, 4 steps) of (1*R*,2*R*)-1-(trityloxymethyl)-2-[1-(*R*)-*tert*-butyldimethylsiloxy-4-hydroxy-propyl]cyclopropane: $[\alpha]_D^{23}$ - 23.2 (c 1.0, $CHCl_3$); IR (neat) 3440, 3085, 3060, 3023, 3000, 2954, 2928, 2884, 2856, 1491, 1471, 1449, 1377, 1360, 1255, 1217, 1173, 1154 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 0.09 (s, 3H), 0.11 (s, 3H), 0.36 (td, *J* = 4.8, 8.4 Hz, 1H), 0.54 (td, *J* = 4.9, 8.6 Hz, 1H), 0.73-0.88 (m, 1H), 0.91 (s, 9H), 0.96-1.12 (m, 1H), 1.81 (dd, *J* = 6.3Hz, 13.4 Hz, 1H), 1.93 (ddd, *J* = 5.1, 6.8, 13.4 Hz, 1H), 2.80 (dd, *J* = 7.4, 9.6 Hz, 1H), 3.11 (dd, *J* = 5.8, 9.6 Hz, 1H), 3.45 (ddd, *J* = 5.0, 7.9, 13.6 Hz, 2H), 3.69-3.80 (m, 2H), 7.20-7.27 (m, 3H), 7.28-7.35 (m, 6H), 7.44-7.50 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.7, -3.9, 9.7, 16.2, 18.0, 23.3, 25.8, 39.3, 60.3, 67.0, 75.3, 86.3, 126.9, 127.7, 128.6, 144.3; MS

(CI) *m/z* 501 $(M-H)^+$, 484, 457, 352, 293, 243, 165; HRMS (CI) *m/z* 501.2823 (calcd for $C_{32}H_{41}O_3Si$: 501.2823).

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80 ^{1}H NMR (400 MHz) d 5.60 (d, J = 3.8Hz, 1H) and 5.63 (d, J = 3.8Hz, 1H) in a ratio of 5.6:1 respectively.

81 ^{1}H NMR (300 MHz) d 5.49 (d, J = 3.8Hz, 1H) and 5.44 (d, J = 3.8Hz, 1H) in a ratio of >98:2 respectively.

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CHAPTER FIVE: GENERAL CONCLUSION

We have shown that there is a pathway in the solvolytic displacement of homoallylic triflates which can lead to polycyclopropane formation. There appears to be partial interruption of the process at a monocyclopropylcarbinyl cation and which can be used to generate a *trans,syn,trans* bicyclopropane with control of both relative and absolute stereochemistry. The method produces contiguous cyclopropanes with differentiated terminal functional groups and, by extension, may lend itself to the synthesis of extended *trans,syn,trans* polycyclopropane motifs.

The isolation of a diastereomerically pure bis-functionalized *trans,syn,trans* bicyclopropane afforded a valuable synthetic precursor for the synthesis of an intermediate previously utilized in the total synthesis of the antifungal agent FR-900848.

The synthesis of a key precursor to halicholactone, neohalicholactone, and solandelactones A-H was designed around a *trans*-disubstituted cyclopropane core and utilized a modified auxilliary based acetate aldol reaction to intall the desired secondary carbinol configuration in a highly diastereoselective process.

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APPENDICES

A 1: Crystal data and structure refinement for 118

Identification code	**118**	
Empirical formula	$C_{19}H_{32}O_4$	
Formula weight	324.45	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 9.2830(7) Å	α= 90°.
	b = 5.5489(5) Å	β= 90.844(6)°.
	c = 18.4252(14) Å	γ = 90°.
Volume	948.99(13) $Å^3$	
Z	2	
Density (calculated)	1.132 Mg/m^3	
Absorption coefficient	0.621 mm^{-1}	
F(000)	354	
Crystal size	0.1 x 0.1 x 0.1 mm^3	
Theta range for data collection	4.76 to 59.99°.	
Index ranges	-10<=h<=10, -4<=k<=6, -20<=l<=20	
Reflections collected	6021	
Independent reflections	2220 [R(int) = 0.0895]	
Completeness to theta = 59.99°	97.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.0000 and 0.6894	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2220 / 8 / 219	
Goodness-of-fit on F^2	1.031	
Final R indices [I>2sigma(I)]	R1 = 0.0784, wR2 = 0.1933	
R indices (all data)	R1 = 0.0818, wR2 = 0.1972	
Absolute structure parameter	0.4(6)	
Largest diff. peak and hole	0.242 and -0.305 $e.Å^{-3}$	

A 2: Atomic coordinates (x 104) and equivalent isotropic displacement parameters (Å2x 103) for 118. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1A)	-200(40)	7350(70)	5270(7)	114(7)
C(1A)	-34(8)	7407(18)	6040(3)	89(2)
O(1B)	-290(40)	8090(70)	5303(7)	111(7)
C(1B)	-34(8)	7407(18)	6040(3)	89(2)
O(2)	6500(4)	7208(6)	7796(2)	43(1)
O(3)	6408(4)	9764(6)	6926(2)	42(1)
O(4)	6168(4)	5834(7)	6648(2)	56(1)
C(2)	1509(6)	7846(14)	6260(3)	65(2)
C(3)	1860(6)	8431(12)	7039(3)	61(2)
C(4)	1984(6)	10355(13)	6455(3)	62(2)
C(5)	3430(7)	11406(12)	6276(3)	60(2)
C(6)	3805(6)	11745(11)	5494(3)	59(2)
C(7)	4572(5)	9951(11)	5959(2)	48(1)
C(8)	6109(5)	10375(9)	6167(2)	42(1)
C(9)	6331(5)	7404(10)	7090(3)	42(1)
C(10)	6436(6)	4742(9)	8099(2)	41(1)
C(11)	4932(5)	4297(9)	8363(3)	42(1)
C(12)	4795(5)	1796(9)	8711(3)	45(1)
C(13)	5948(5)	1530(9)	9305(3)	47(1)
C(14)	7462(5)	2071(9)	9039(2)	42(1)
C(15)	7575(5)	4599(9)	8694(2)	39(1)
C(16)	3296(6)	1295(11)	8978(3)	57(2)
C(17)	9093(6)	5244(9)	8437(3)	44(1)
C(18)	9728(6)	3369(11)	7927(3)	56(2)
C(19)	10102(6)	5753(11)	9073(3)	54(1)

A 3: Bond lengths [Å] and angles [°] for **118**

O(1A)-C(1A)	1.426(13)	C(1A)-C(2)-C(3)	119.0(5)
C(1A)-C(2)	1.502(9)	C(2)-C(3)-C(4)	59.5(4)
O(2)-C(9)	1.313(5)	C(2)-C(4)-C(5)	124.5(5)
O(2)-C(10)	1.479(6)	C(2)-C(4)-C(3)	59.6(4)
O(3)-C(9)	1.346(6)	C(5)-C(4)-C(3)	120.2(5)
O(3)-C(8)	1.461(5)	C(7)-C(5)-C(6)	60.4(3)
O(4)-C(9)	1.201(6)	C(7)-C(5)-C(4)	121.9(6)
C(2)-C(4)	1.502(10)	C(6)-C(5)-C(4)	118.6(5)
C(2)-C(3)	1.503(7)	C(7)-C(6)-C(5)	58.5(3)
C(3)-C(4)	1.522(8)	C(5)-C(7)-C(6)	61.1(4)
C(4)-C(5)	1.505(8)	C(5)-C(7)-C(8)	120.5(5)
C(5)-C(7)	1.461(7)	C(6)-C(7)-C(8)	119.4(5)
C(5)-C(6)	1.500(7)	O(3)-C(8)-C(7)	112.1(4)
C(6)-C(7)	1.489(7)	O(4)-C(9)-O(2)	128.6(5)
C(7)-C(8)	1.490(7)	O(4)-C(9)-O(3)	124.0(4)
C(10)-C(11)	1.505(7)	O(2)-C(9)-O(3)	107.3(4)
C(10)-C(15)	1.514(6)	O(2)-C(10)-C(11)	108.4(4)
C(11)-C(12)	1.535(7)	O(2)-C(10)-C(15)	106.8(4)
C(12)-C(16)	1.508(7)	C(11)-C(10)-C(15)	113.5(4)
C(12)-C(13)	1.526(7)	C(10)-C(11)-C(12)	111.5(4)
C(13)-C(14)	1.525(7)	C(16)-C(12)-C(13)	112.9(4)
C(14)-C(15)	1.545(7)	C(16)-C(12)-C(11)	112.7(4)
C(15)-C(17)	1.535(7)	C(13)-C(12)-C(11)	109.0(4)
C(17)-C(19)	1.516(7)	C(14)-C(13)-C(12)	113.0(4)
C(17)-C(18)	1.527(7)	C(13)-C(14)-C(15)	112.3(4)
O(1A)-C(1A)-C(2)	111.1(15)	C(10)-C(15)-C(17)	113.5(4)
		C(10)-C(15)-C(14)	107.2(4)
C(9)-O(2)-C(10)	116.4(4)	C(17)-C(15)-C(14)	114.0(4)
C(9)-O(3)-C(8)	115.6(4)	C(19)-C(17)-C(18)	111.3(4)
C(4)-C(2)-C(1A)	119.3(6)	C(19)-C(17)-C(15)	111.4(4)
C(4)-C(2)-C(3)	60.9(4)	C(18)-C(17)-C(15)	113.3(4)

A 4: Anisotropic displacement parameters ($Å^2 x\ 10^3$)for 118. 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}
O(1A)	94(7)	180(20)	72(6)	-10(7)	-32(6)	-7(10)
C(1A)	79(4)	124(7)	63(4)	7(5)	-13(3)	4(5)
O(1B)	86(7)	180(20)	64(5)	-4(7)	-22(5)	-9(11)
C(1B)	79(4)	124(7)	63(4)	7(5)	-13(3)	4(5)
O(2)	69(2)	24(2)	36(2)	-3(2)	-8(2)	6(2)
O(3)	65(2)	24(2)	35(2)	-3(1)	-5(2)	3(2)
O(4)	99(3)	25(2)	43(2)	-7(2)	-7(2)	-2(2)
C(2)	55(3)	84(5)	56(3)	-5(3)	-5(3)	8(4)
C(3)	56(3)	82(5)	45(3)	9(3)	8(3)	3(3)
C(4)	54(3)	80(5)	52(3)	16(3)	15(3)	23(3)
C(5)	77(4)	66(4)	39(3)	7(3)	7(3)	15(3)
C(6)	62(3)	63(4)	50(3)	19(3)	-1(3)	8(3)
C(7)	55(3)	52(4)	37(2)	2(3)	-1(2)	11(3)
C(8)	56(3)	34(3)	36(2)	0(2)	2(2)	5(3)
C(9)	54(3)	32(3)	41(3)	-1(2)	-6(2)	1(3)
C(10)	60(3)	22(2)	42(3)	-1(2)	2(2)	8(3)
C(11)	50(3)	35(3)	42(3)	-4(2)	-3(2)	6(2)
C(12)	54(3)	35(3)	45(3)	-5(2)	1(2)	6(3)
C(13)	55(3)	35(3)	51(3)	3(2)	4(2)	7(3)
C(14)	56(3)	32(3)	38(2)	1(2)	-1(2)	6(2)
C(15)	50(3)	27(3)	41(2)	-2(2)	-6(2)	11(2)
C(16)	51(3)	50(4)	69(3)	-1(3)	-1(3)	3(3)
C(17)	61(3)	28(3)	44(3)	-2(2)	3(2)	9(3)
C(18)	64(3)	57(4)	48(3)	-7(3)	12(3)	10(3)
C(19)	56(3)	45(3)	62(3)	-11(3)	0(3)	0(3)

A 5: Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 118

	x	y	z	U(eq)
H(1A)	355	6355	5101	171
H(1A1)	-352	5884	6241	107
H(1A2)	-634	8673	6236	107
H(1B)	-457	9540	5283	166
H(1B1)	-258	5712	6100	107
H(1B2)	-661	8324	6353	107
H(2)	2223	6861	6010	78
H(3A)	2745	7782	7247	73
H(3B)	1067	8554	7374	73
H(4)	1200	11538	6455	74
H(5)	3764	12691	6602	72
H(6A)	3133	11145	5128	70
H(6B)	4318	13198	5361	70
H(7)	4318	8265	5865	58
H(8A)	6721	9412	5858	50
H(8B)	6343	12057	6087	50
H(10)	6660	3575	7717	50
H(11A)	4257	4425	7958	51
H(11B)	4686	5521	8716	51
H(12)	5003	601	8335	54
H(13A)	5727	2616	9701	57
H(13B)	5923	-102	9493	57
H(14A)	7730	867	8684	51
H(14B)	8136	1961	9445	51
H(15)	7316	5774	9066	47
H(16A)	3044	2476	9335	85
H(16B)	3267	-282	9192	85
H(16C)	2624	1372	8578	85
H(17)	9005	6747	8161	53
H(18A)	9045	3016	7545	84
H(18B)	9942	1923	8193	84

H(18C)	10597	3990	7721	84
H(19A)	10194	4333	9368	81
H(19B)	9720	7044	9359	81
H(19C)	11031	6203	8896	81

A 6: Torsion angles [°] for 118

O(1A)-C(1A)-C(2)-C(4)		C(8)-O(3)-C(9)-O(4)	7.0(7)
O(1A)-C(1A)-C(2)-C(3)	168.5(18)	C(8)-O(3)-C(9)-O(2)	-174.5(4)
C(1A)-C(2)-C(3)-C(4)	-109.4(7)	C(9)-O(2)-C(10)-C(11)	-96.4(4)
C(1A)-C(2)-C(4)-C(5)	-143.4(6)	C(9)-O(2)-C(10)-C(15)	140.9(4)
C(3)-C(2)-C(4)-C(5)	107.7(6)	O(2)-C(10)-C(11)-C(12)	-177.9(3)
C(1A)-C(2)-C(4)-C(3)	108.9(6)	C(15)-C(10)-C(11)-C(12)	-59.4(5)
C(2)-C(3)-C(4)-C(5)	-114.8(6)	C(10)-C(11)-C(12)-C(16)	-179.7(4)
C(2)-C(4)-C(5)-C(7)	-6.8(8)	C(10)-C(11)-C(12)-C(13)	54.2(5)
C(3)-C(4)-C(5)-C(7)	65.2(7)	C(16)-C(12)-C(13)-C(14)	-179.2(4)
C(2)-C(4)-C(5)-C(6)	64.3(8)	C(11)-C(12)-C(13)-C(14)	-53.2(5)
C(3)-C(4)-C(5)-C(6)	136.3(6)	C(12)-C(13)-C(14)-C(15)	55.7(5)
C(4)-C(5)-C(6)-C(7)	-112.5(6)	O(2)-C(10)-C(15)-C(17)	-56.1(5)
C(4)-C(5)-C(7)-C(6)	107.1(6)	C(11)-C(10)-C(15)-C(17)	-175.5(4)
C(6)-C(5)-C(7)-C(8)	109.0(6)	O(2)-C(10)-C(15)-C(14)	177.1(3)
C(4)-C(5)-C(7)-C(8)	-143.9(5)	C(11)-C(10)-C(15)-C(14)	57.7(5)
C(5)-C(6)-C(7)-C(8)	-110.8(6)	C(13)-C(14)-C(15)-C(10)	-55.0(5)
C(9)-O(3)-C(8)-C(7)	68.1(5)	C(13)-C(14)-C(15)-C(17)	178.4(4)
C(5)-C(7)-C(8)-O(3)	66.6(6)	C(10)-C(15)-C(17)-C(19)	164.2(4)
C(6)-C(7)-C(8)-O(3)	138.5(5)	C(14)-C(15)-C(17)-C(19)	-72.7(5)
C(10)-O(2)-C(9)-O(4)	-2.3(8)	C(10)-C(15)-C(17)-C(18)	-69.4(5)
C(10)-O(2)-C(9)-O(3)	179.3(4)	C(14)-C(15)-C(17)-C(18)	53.7(5)

A 7: Hydrogen bonds for 118 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1A)-H(1A)...O(1A)#1	0.82	2.33	2.972(14)	136.0
O(1B)-H(1B)...O(1B)#2	0.82	2.36	3.044(17)	141.8

Symmetry transformations used to generate equivalent atoms:
#1 -x,y-1/2,-z+1 #2 -x,y+1/2,-z+1

A 8: Crystal data and structure refinement for 121

Identification code	**121**	
Empirical formula	$C_{26}H_{34}N_2O_9$	
Formula weight	518.55	
Temperature	100(2) K	
Wavelength	1.54060 Å	
Crystal system	orthorhombic	
Space group	$P2_12_12_1$ #19	
Unit cell dimensions	a = 7.5080(3) Å	α= 90°.
	b = 8.6340(3) Å	β= 90°.
	c = 40.4790(15) Å	γ = 90°.
Volume	2624.01(17) $Å^3$	
Z	4	
Density (calculated)	1.313 Mg/m^3	
Absorption coefficient	0.830 mm^{-1}	
F(000)	1104	
Crystal size	0.30 x 0.30 x 0.10 mm^3	
Theta range for data collection	4.37 to 67.48°.	
Index ranges	0<=h<=7, 0<=k<=10, -48<=l<=48	
Reflections collected	27905	
Independent reflections	3925 [R(int) = 0.0150]	
Completeness to theta = 67.48°	85.8 %	
Max. and min. transmission	1.0000 and 0.5340	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3925 / 0 / 337	
Goodness-of-fit on F^2	1.087	
Final R indices [I>2sigma(I)]	R1 = 0.0470, wR2 = 0.1180	
R indices (all data)	R1 = 0.0483, wR2 = 0.1190	
Absolute structure parameter	0.0(3)	
Largest diff. peak and hole	0.310 and -0.216 $e.Å^{-3}$	

A 9: Atomic coordinates (x 104) and equivalent isotropic displacement parameters (Å2x 103) for 121. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	5265(5)	4383(4)	1864(1)	28(1)
C(2)	4730(5)	3216(4)	2115(1)	30(1)
C(3)	3172(5)	2189(4)	2047(1)	36(1)
C(4)	3009(5)	3409(4)	2307(1)	32(1)
C(5)	1764(5)	4752(4)	2278(1)	28(1)
C(6)	-202(5)	4488(4)	2290(1)	32(1)
C(7)	623(5)	5122(4)	1979(1)	29(1)
C(8)	234(5)	6761(4)	1893(1)	28(1)
N(21)	8863(4)	10461(3)	1658(1)	31(1)
N(22)	5387(5)	8863(3)	698(1)	37(1)
O(21)	1635(3)	7421(2)	1682(1)	29(1)
O(22)	3141(4)	8242(3)	2131(1)	34(1)
O(23)	10145(4)	10658(3)	1472(1)	42(1)
O(24)	8902(4)	10723(3)	1956(1)	46(1)
O(25)	6604(4)	9344(4)	524(1)	54(1)
O(26)	4034(4)	8210(3)	593(1)	45(1)
C(21)	2998(5)	8114(3)	1835(1)	26(1)
C(22)	4350(5)	8704(3)	1597(1)	25(1)
C(23)	4153(5)	8562(3)	1258(1)	26(1)
C(24)	5534(5)	9060(3)	1057(1)	27(1)
C(25)	7100(5)	9688(3)	1179(1)	28(1)
C(26)	7224(5)	9824(3)	1518(1)	26(1)
C(27)	5887(5)	9363(3)	1730(1)	26(1)
C(31)	6719(4)	4490(3)	1349(1)	22(1)
C(32)	7999(5)	4413(4)	809(1)	27(1)
C(33)	6490(5)	4515(4)	560(1)	33(1)
C(34)	7121(5)	5233(4)	234(1)	37(1)
C(35)	5581(6)	5337(5)	-15(1)	52(1)
C(36)	8668(5)	4290(5)	103(1)	39(1)
C(37)	10188(5)	4220(4)	356(1)	32(1)
C(38)	9572(5)	3498(4)	685(1)	27(1)

C(39)	11067(5)	3370(4)	946(1)	29(1)
C(310)	11941(5)	4923(4)	1024(1)	38(1)
C(311)	12453(5)	2153(4)	849(1)	38(1)
O(31)	6098(3)	3558(2)	1587(1)	28(1)
O(32)	6753(3)	5877(2)	1360(1)	30(1)
O(33)	7314(3)	3604(2)	1105(1)	30(1)

A 10: Bond lengths [Å] and angles [°] for 121

C(1)-O(31)	1.469(3)	C(34)-C(35)	1.538(5)
C(1)-C(2)	1.487(4)	C(36)-C(37)	1.532(5)
C(2)-C(3)	1.493(5)	C(37)-C(38)	1.542(4)
C(2)-C(4)	1.516(5)	C(38)-C(39)	1.545(5)
C(3)-C(4)	1.493(5)	C(39)-C(310)	1.527(5)
C(4)-C(5)	1.494(5)	C(39)-C(311)	1.529(5)
C(5)-C(6)	1.494(5)		
C(5)-C(7)	1.517(5)	O(31)-C(1)-C(2)	108.0(2)
C(6)-C(7)	1.507(4)	C(1)-C(2)-C(3)	119.2(3)
C(7)-C(8)	1.487(4)	C(1)-C(2)-C(4)	120.4(3)
C(8)-O(21)	1.469(4)	C(3)-C(2)-C(4)	59.5(2)
N(21)-O(24)	1.225(3)	C(4)-C(3)-C(2)	61.0(2)
N(21)-O(23)	1.234(4)	C(3)-C(4)-C(5)	123.0(3)
N(21)-C(26)	1.463(4)	C(3)-C(4)-C(2)	59.5(2)
N(22)-O(25)	1.227(4)	C(5)-C(4)-C(2)	125.4(3)
N(22)-O(26)	1.236(4)	C(6)-C(5)-C(4)	119.8(3)
N(22)-C(24)	1.467(4)	C(6)-C(5)-C(7)	60.0(2)
O(21)-C(21)	1.338(4)	C(4)-C(5)-C(7)	125.3(3)
O(22)-C(21)	1.207(4)	C(5)-C(6)-C(7)	60.7(2)
C(21)-C(22)	1.489(4)	C(8)-C(7)-C(6)	117.5(3)
C(22)-C(23)	1.388(4)	C(8)-C(7)-C(5)	119.9(3)
C(22)-C(27)	1.393(5)	C(6)-C(7)-C(5)	59.2(2)
C(23)-C(24)	1.386(5)	O(21)-C(8)-C(7)	111.4(3)
C(24)-C(25)	1.386(5)	O(24)-N(21)-O(23)	123.8(3)
C(25)-C(26)	1.381(4)	O(24)-N(21)-C(26)	118.1(3)
C(26)-C(27)	1.378(5)	O(23)-N(21)-C(26)	118.1(3)
C(31)-O(32)	1.199(4)	O(25)-N(22)-O(26)	124.7(3)
C(31)-O(33)	1.328(3)	O(25)-N(22)-C(24)	118.3(3)
C(31)-O(31)	1.337(4)	O(26)-N(22)-C(24)	117.0(3)
C(32)-O(33)	1.478(3)	C(21)-O(21)-C(8)	116.8(2)
C(32)-C(38)	1.508(5)	O(22)-C(21)-O(21)	124.7(3)
C(32)-C(33)	1.520(5)	O(22)-C(21)-C(22)	123.3(3)
C(33)-C(34)	1.531(5)	O(21)-C(21)-C(22)	112.0(3)
C(34)-C(36)	1.514(5)	C(23)-C(22)-C(27)	120.3(3)

C(23)-C(22)-C(21)	122.5(3)	C(38)-C(32)-C(33)	113.0(3)
C(27)-C(22)-C(21)	117.1(3)	C(32)-C(33)-C(34)	111.4(3)
C(24)-C(23)-C(22)	118.3(3)	C(36)-C(34)-C(33)	108.7(3)
C(23)-C(24)-C(25)	123.1(3)	C(36)-C(34)-C(35)	112.3(3)
C(23)-C(24)-N(22)	119.3(3)	C(33)-C(34)-C(35)	110.9(3)
C(25)-C(24)-N(22)	117.6(3)	C(34)-C(36)-C(37)	111.1(3)
C(26)-C(25)-C(24)	116.4(3)	C(36)-C(37)-C(38)	111.6(3)
C(27)-C(26)-C(25)	122.9(3)	C(32)-C(38)-C(37)	108.2(3)
C(27)-C(26)-N(21)	118.7(3)	C(32)-C(38)-C(39)	112.2(3)
C(25)-C(26)-N(21)	118.3(3)	C(37)-C(38)-C(39)	113.7(3)
C(26)-C(27)-C(22)	118.8(3)	C(310)-C(39)-C(311)	111.4(3)
O(32)-C(31)-O(33)	126.5(3)	C(310)-C(39)-C(38)	113.1(3)
O(32)-C(31)-O(31)	125.7(3)	C(311)-C(39)-C(38)	111.7(3)
O(33)-C(31)-O(31)	107.8(2)	C(31)-O(31)-C(1)	113.9(2)
O(33)-C(32)-C(38)	107.2(2)	C(31)-O(33)-C(32)	116.6(2)
O(33)-C(32)-C(33)	107.8(3)		

A 11: Anisotropic displacement parameters ($Å^2 x\ 10^3$)for 121. 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}
C(1)	24(2)	31(2)	28(2)	-3(1)	6(1)	2(1)
C(2)	27(2)	32(2)	32(2)	0(1)	6(1)	1(2)
C(3)	39(3)	27(2)	41(2)	0(1)	7(2)	-2(2)
C(4)	32(2)	30(2)	33(2)	3(1)	12(2)	2(2)
C(5)	26(2)	31(2)	28(2)	-1(1)	8(1)	2(1)
C(6)	27(2)	31(2)	38(2)	0(1)	9(2)	0(2)
C(7)	26(2)	31(2)	29(2)	-6(1)	4(1)	-1(1)
C(8)	19(2)	26(2)	39(2)	0(1)	3(1)	0(1)
N(21)	28(2)	27(1)	40(2)	8(1)	-2(1)	-6(1)
N(22)	45(2)	32(2)	33(1)	7(1)	-2(2)	-1(1)
O(21)	25(2)	26(1)	35(1)	1(1)	1(1)	-3(1)
O(22)	35(2)	35(1)	30(1)	-4(1)	3(1)	-8(1)
O(23)	27(2)	47(2)	51(1)	13(1)	3(1)	-10(1)
O(24)	44(2)	56(2)	39(1)	-1(1)	-4(1)	-16(1)
O(25)	51(2)	74(2)	35(1)	9(1)	9(1)	-7(2)
O(26)	56(2)	46(2)	35(1)	2(1)	-7(1)	-13(1)
C(21)	25(2)	18(1)	34(2)	-2(1)	2(1)	0(1)
C(22)	26(2)	19(1)	31(2)	-2(1)	0(1)	0(1)
C(23)	25(2)	19(1)	36(2)	1(1)	-2(2)	3(1)
C(24)	30(2)	20(1)	30(2)	4(1)	3(1)	2(1)
C(25)	29(2)	20(2)	35(2)	7(1)	8(1)	5(1)
C(26)	23(2)	21(2)	35(2)	3(1)	-1(1)	-2(1)
C(27)	32(2)	17(1)	30(2)	0(1)	3(1)	0(1)
C(31)	16(2)	21(2)	30(2)	1(1)	3(1)	2(1)
C(32)	23(2)	26(2)	32(2)	2(1)	11(1)	-3(1)
C(33)	24(2)	31(2)	44(2)	0(2)	5(2)	7(2)
C(34)	33(3)	44(2)	34(2)	4(2)	1(2)	4(2)
C(35)	44(3)	63(3)	48(2)	1(2)	-7(2)	7(2)
C(36)	37(3)	51(2)	28(2)	3(2)	4(2)	4(2)
C(37)	27(2)	38(2)	30(2)	2(1)	9(1)	-3(2)

C(38)	24(2)	29(2)	29(2)	0(1)	6(1)	-3(1)
C(39)	25(2)	31(2)	32(2)	3(1)	4(1)	-2(2)
C(310)	33(3)	39(2)	41(2)	-7(2)	2(2)	0(2)
C(311)	31(3)	36(2)	47(2)	4(2)	2(2)	6(2)
O(31)	29(1)	23(1)	30(1)	4(1)	10(1)	5(1)
O(32)	33(2)	24(1)	34(1)	0(1)	9(1)	1(1)
O(33)	34(2)	22(1)	34(1)	1(1)	16(1)	-1(1)

A 12: Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 121

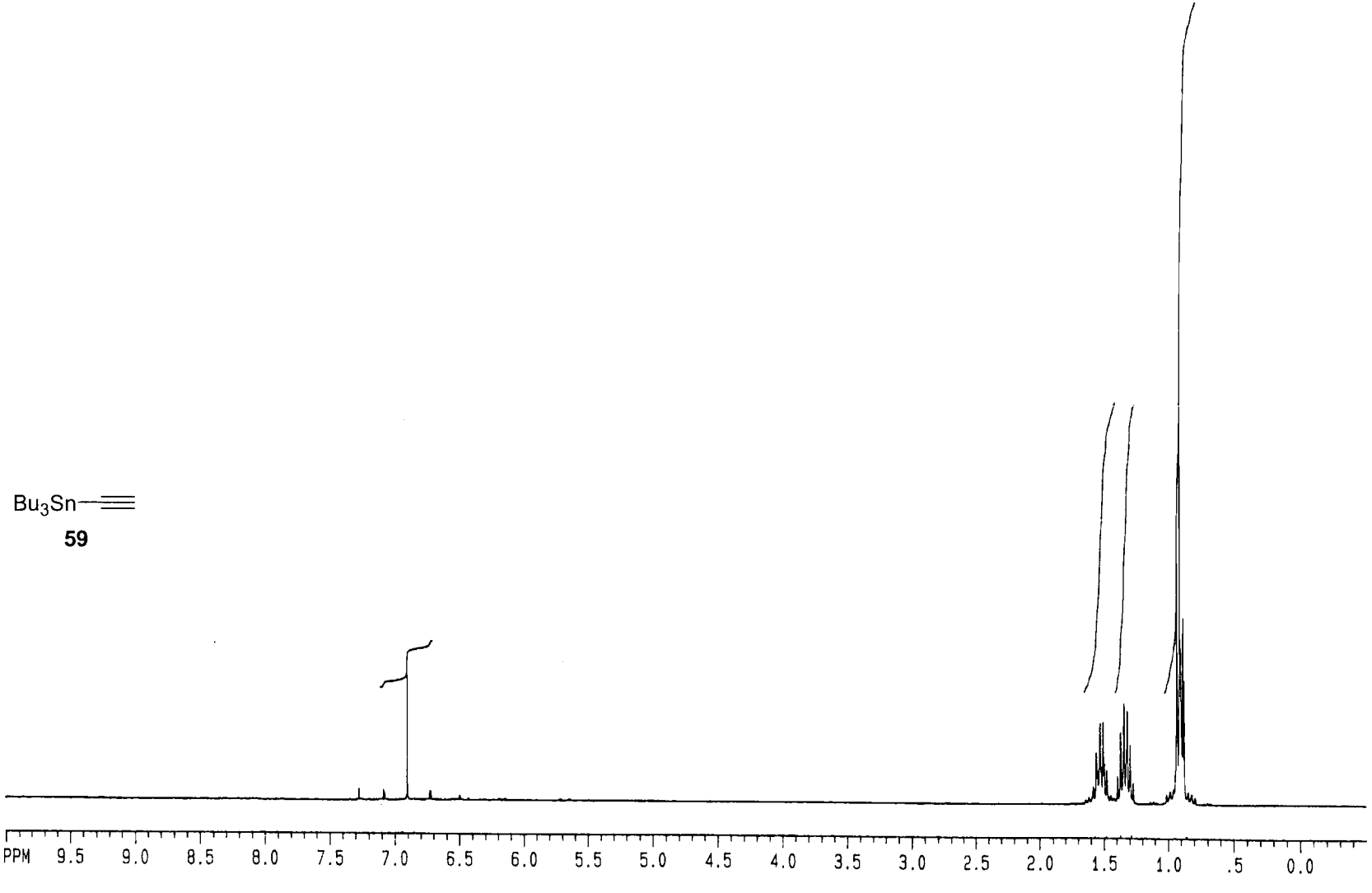
	x	y	z	U(eq)
H(1A)	4207	4963	1786	33
H(1B)	6118	5129	1961	33
H(2)	5731	2724	2240	36
H(3A)	2517	2349	1837	43
H(3B)	3248	1098	2121	43
H(4)	3079	2983	2536	38
H(5)	2162	5689	2403	34
H(6A)	-926	5203	2426	38
H(6B)	-631	3404	2287	38
H(7)	717	4384	1789	34
H(8A)	-922	6816	1776	34
H(8B)	134	7380	2098	34
H(23)	3098	8135	1166	32
H(25)	8039	10006	1037	34
H(27)	6011	9492	1962	32
H(32)	8394	5480	872	32
H(33A)	5514	5150	653	40
H(33B)	6017	3464	517	40
H(34)	7555	6307	281	44
H(35A)	6006	5824	-219	78
H(35B)	4615	5960	79	78
H(35C)	5141	4294	-64	78
H(36A)	9108	4760	-104	46
H(36B)	8257	3226	53	46
H(37A)	10640	5280	397	38
H(37B)	11179	3597	264	38
H(38)	9146	2424	636	33
H(39)	10495	3000	1154	35
H(31D)	12850	4776	1195	56
H(31E)	11035	5650	1104	56
H(31F)	12498	5340	824	56

H(31A)	13053	2474	645	57
H(31B)	11863	1155	814	57
H(31C)	13333	2051	1027	57

A 13: Torsion angles [°] for 121

O(31)-C(1)-C(2)-C(3)	-72.8(4)	C(23)-C(24)-C(25)-C(26)	-1.0(5)
O(31)-C(1)-C(2)-C(4)	-142.5(3)	N(22)-C(24)-C(25)-C(26)	-178.4(3)
C(1)-C(2)-C(3)-C(4)	-110.1(3)	C(24)-C(25)-C(26)-C(27)	0.4(5)
C(2)-C(3)-C(4)-C(5)	114.8(4)	C(24)-C(25)-C(26)-N(21)	179.2(3)
C(1)-C(2)-C(4)-C(3)	108.1(4)	O(24)-N(21)-C(26)-C(27)	-8.3(4)
C(1)-C(2)-C(4)-C(5)	-2.9(5)	O(23)-N(21)-C(26)-C(27)	169.6(3)
C(3)-C(2)-C(4)-C(5)	-110.9(4)	O(24)-N(21)-C(26)-C(25)	172.9(3)
C(3)-C(4)-C(5)-C(6)	67.8(4)	O(23)-N(21)-C(26)-C(25)	-9.3(4)
C(2)-C(4)-C(5)-C(6)	141.5(3)	C(25)-C(26)-C(27)-C(22)	1.1(5)
C(3)-C(4)-C(5)-C(7)	-4.8(5)	N(21)-C(26)-C(27)-C(22)	-177.7(3)
C(2)-C(4)-C(5)-C(7)	68.9(5)	C(23)-C(22)-C(27)-C(26)	-2.0(4)
C(4)-C(5)-C(6)-C(7)	-116.0(3)	C(21)-C(22)-C(27)-C(26)	175.5(3)
C(5)-C(6)-C(7)-C(8)	-110.2(3)	O(33)-C(32)-C(33)-C(34)	-175.8(3)
C(6)-C(5)-C(7)-C(8)	106.1(3)	C(38)-C(32)-C(33)-C(34)	-57.5(4)
C(4)-C(5)-C(7)-C(8)	-146.7(3)	C(32)-C(33)-C(34)-C(36)	56.5(4)
C(4)-C(5)-C(7)-C(6)	107.2(4)	C(32)-C(33)-C(34)-C(35)	-179.7(3)
C(6)-C(7)-C(8)-O(21)	155.6(3)	C(33)-C(34)-C(36)-C(37)	-57.6(4)
C(5)-C(7)-C(8)-O(21)	87.1(3)	C(35)-C(34)-C(36)-C(37)	179.4(3)
C(7)-C(8)-O(21)-C(21)	-90.1(3)	C(34)-C(36)-C(37)-C(38)	59.0(4)
C(8)-O(21)-C(21)-O(22)	-0.7(4)	O(33)-C(32)-C(38)-C(37)	174.1(3)
C(8)-O(21)-C(21)-C(22)	178.7(2)	C(33)-C(32)-C(38)-C(37)	55.4(4)
O(22)-C(21)-C(22)-C(23)	-179.2(3)	O(33)-C(32)-C(38)-C(39)	-59.7(3)
O(21)-C(21)-C(22)-C(23)	1.4(4)	C(33)-C(32)-C(38)-C(39)	-178.4(3)
O(22)-C(21)-C(22)-C(27)	3.3(5)	C(36)-C(37)-C(38)-C(32)	-55.8(4)
O(21)-C(21)-C(22)-C(27)	-176.1(3)	C(36)-C(37)-C(38)-C(39)	178.9(3)
C(27)-C(22)-C(23)-C(24)	1.4(5)	C(32)-C(38)-C(39)-C(310)	-66.3(4)
C(21)-C(22)-C(23)-C(24)	-176.0(3)	C(37)-C(38)-C(39)-C(310)	56.8(4)
C(22)-C(23)-C(24)-C(25)	0.2(5)	C(32)-C(38)-C(39)-C(311)	167.1(3)
C(22)-C(23)-C(24)-N(22)	177.5(3)	C(37)-C(38)-C(39)-C(311)	-69.7(4)
O(25)-N(22)-C(24)-C(23)	178.3(3)	O(32)-C(31)-O(31)-C(1)	5.6(5)
O(26)-N(22)-C(24)-C(23)	-2.1(4)	O(33)-C(31)-O(31)-C(1)	-175.5(3)
O(25)-N(22)-C(24)-C(25)	-4.2(5)	C(2)-C(1)-O(31)-C(31)	-177.0(3)
O(26)-N(22)-C(24)-C(25)	175.4(3)	O(32)-C(31)-O(33)-C(32)	-3.4(5)

O(31)-C(31)-O(33)-C(32)	177.7(3)	C(33)-C(32)-O(33)-C(31)	-95.0(3)
C(38)-C(32)-O(33)-C(31)	143.0(3)		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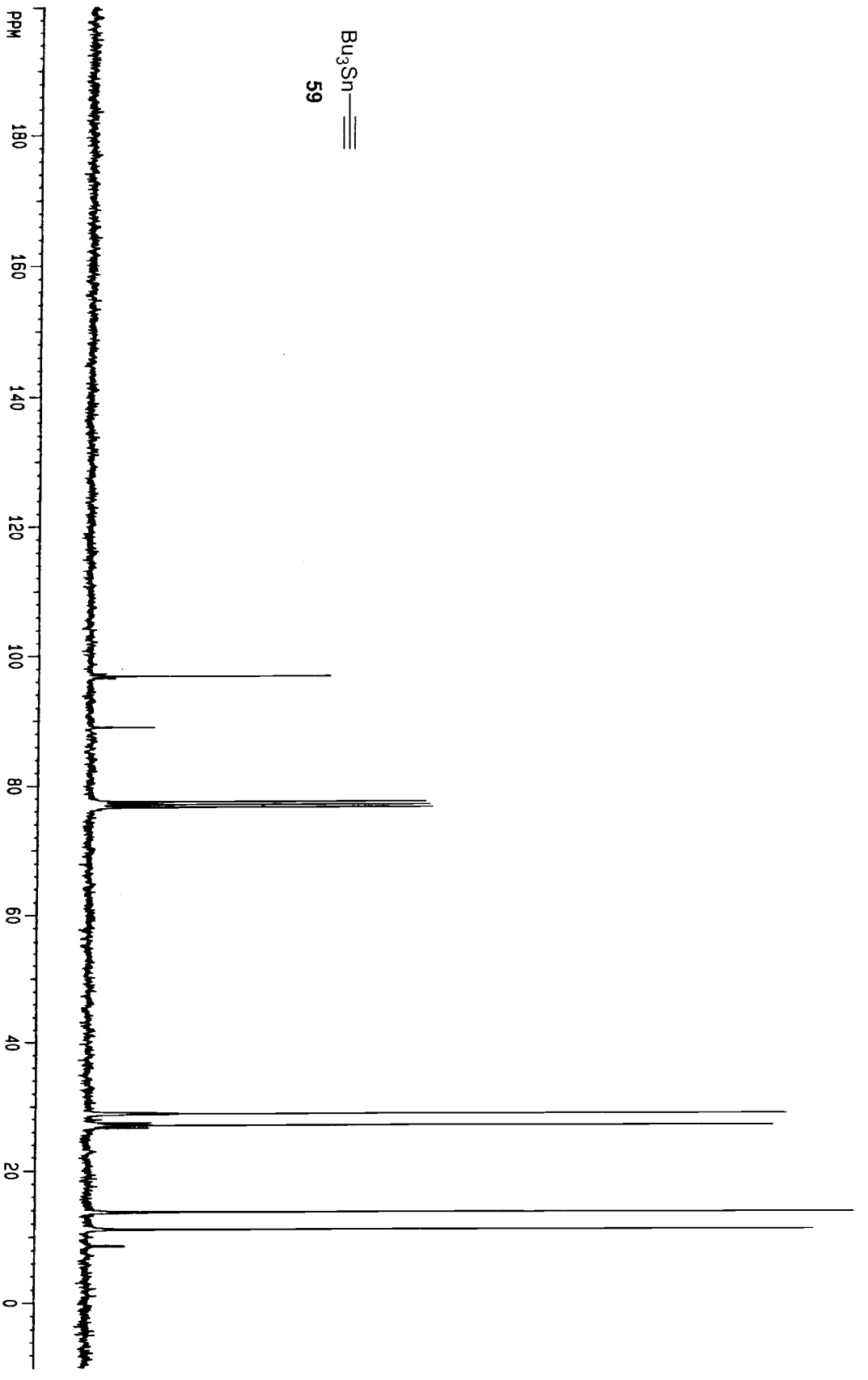
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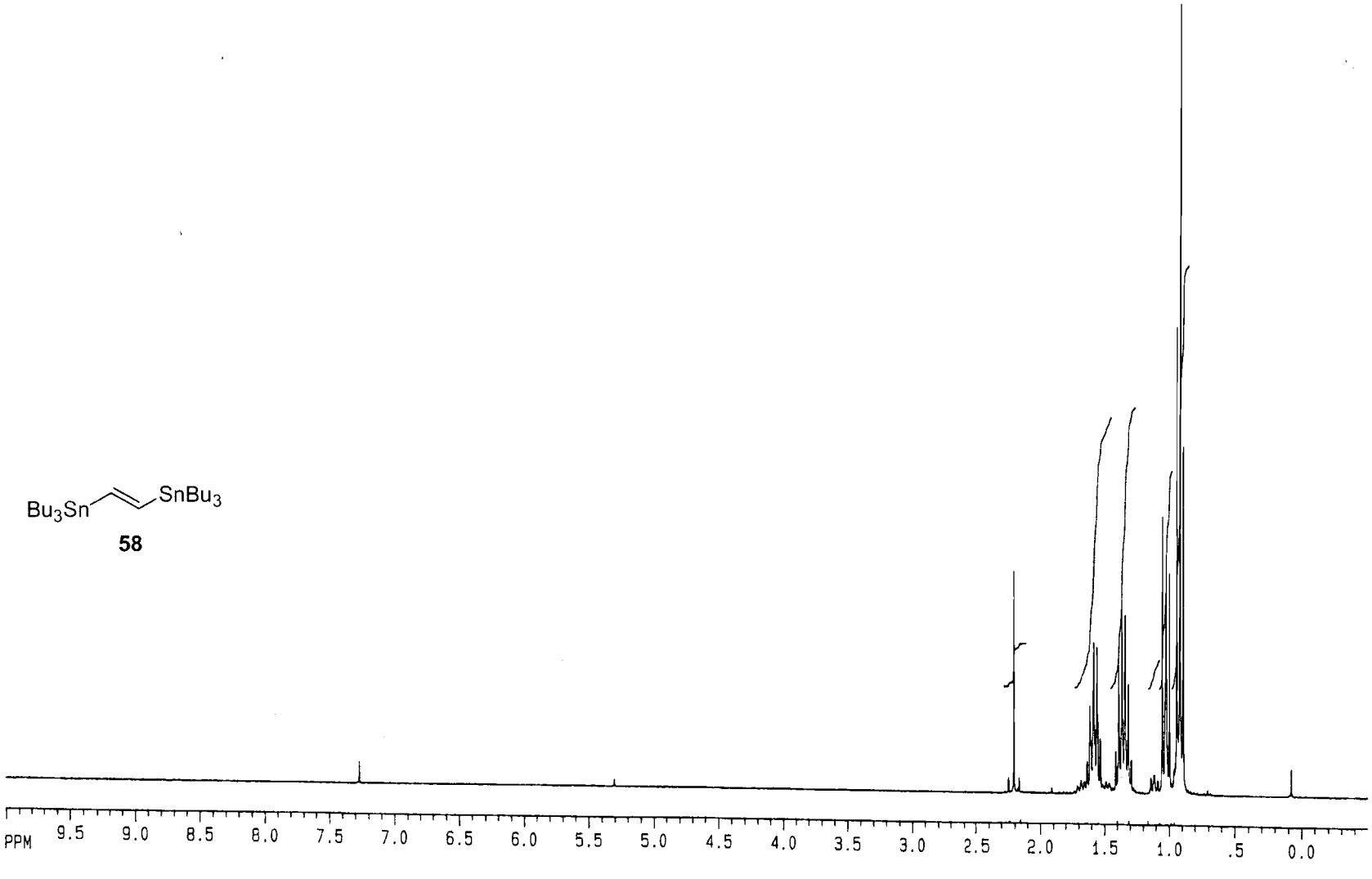
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1.5
1.0
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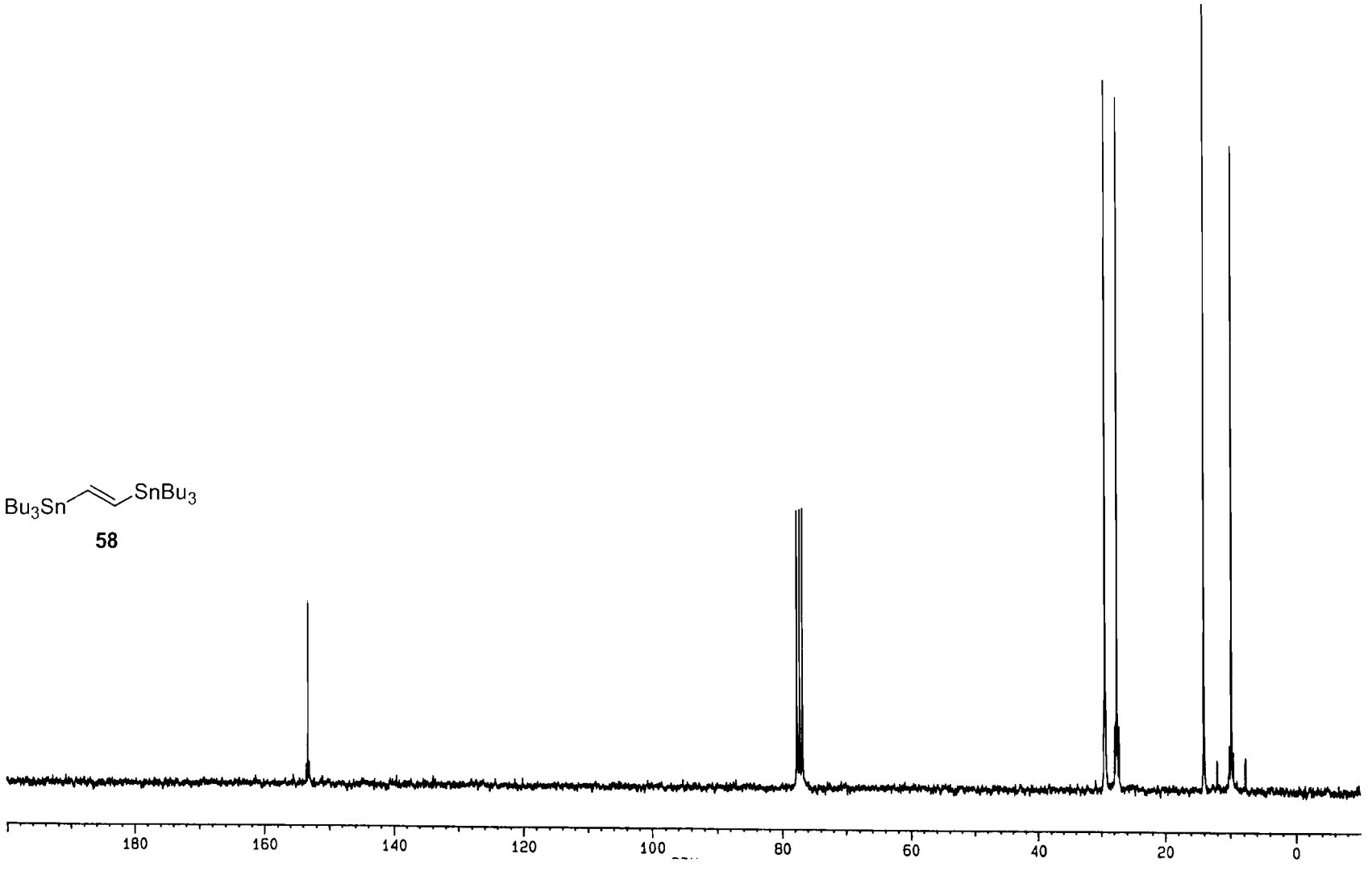
0.0

58



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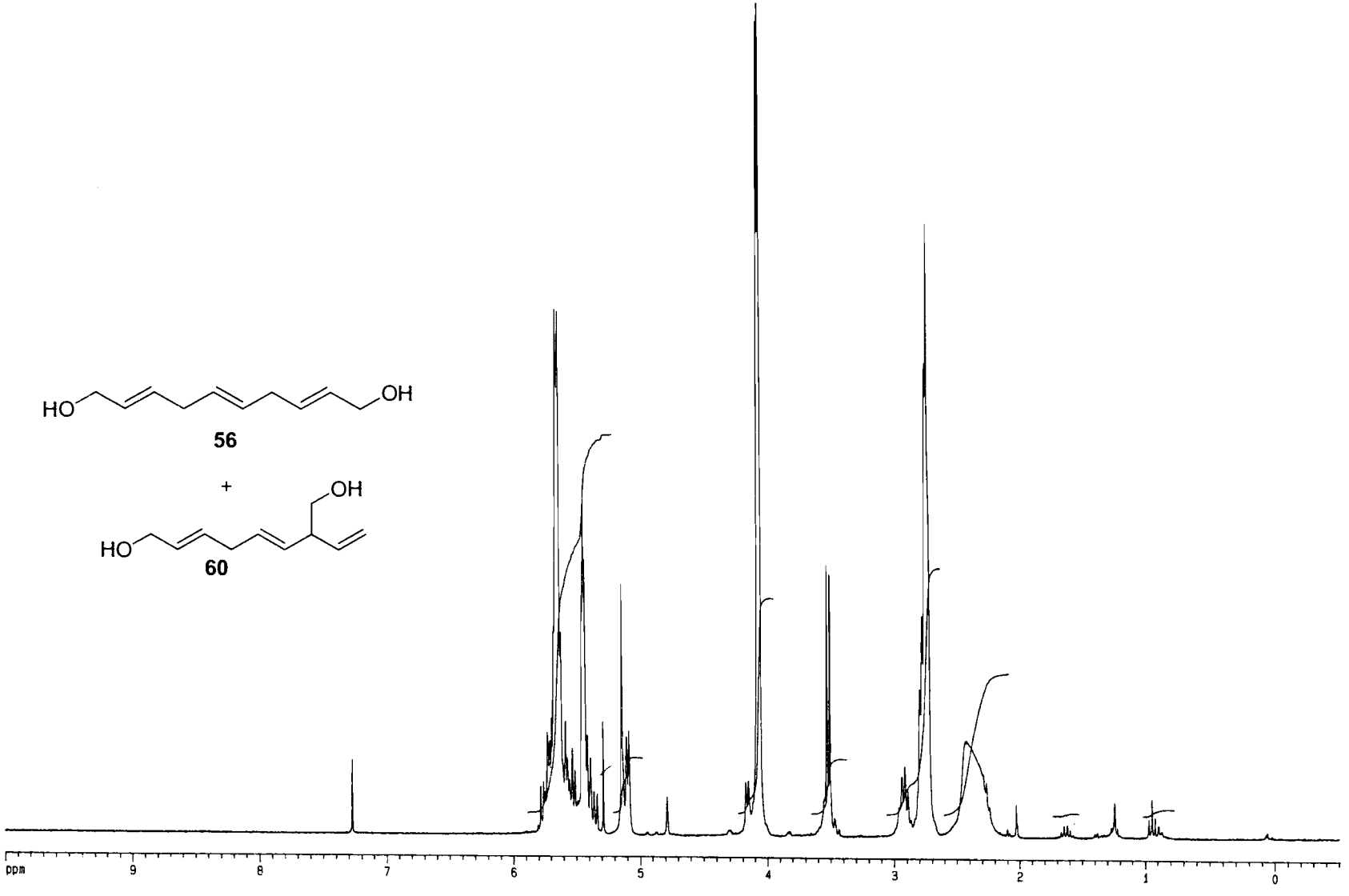
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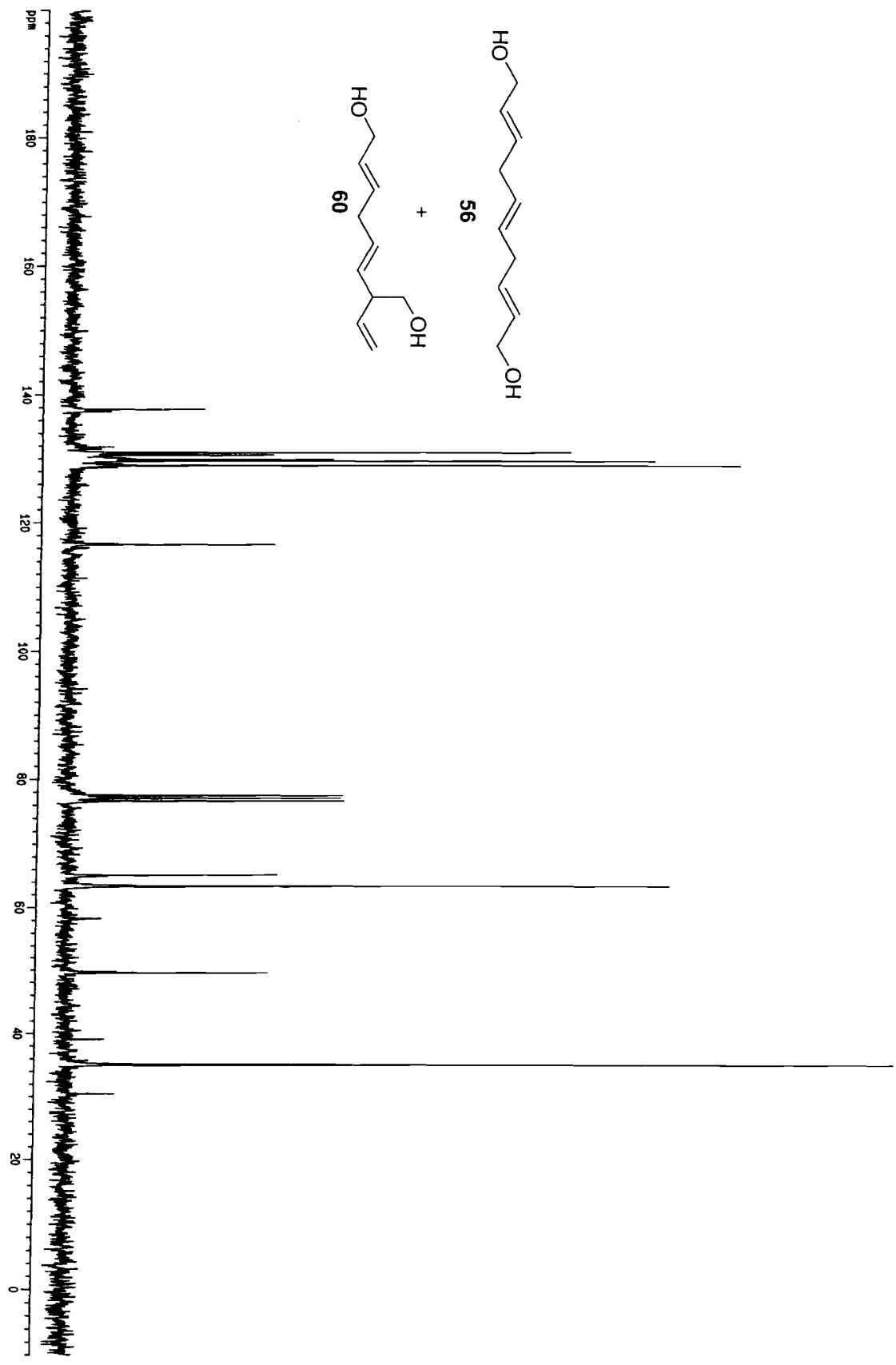
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HO
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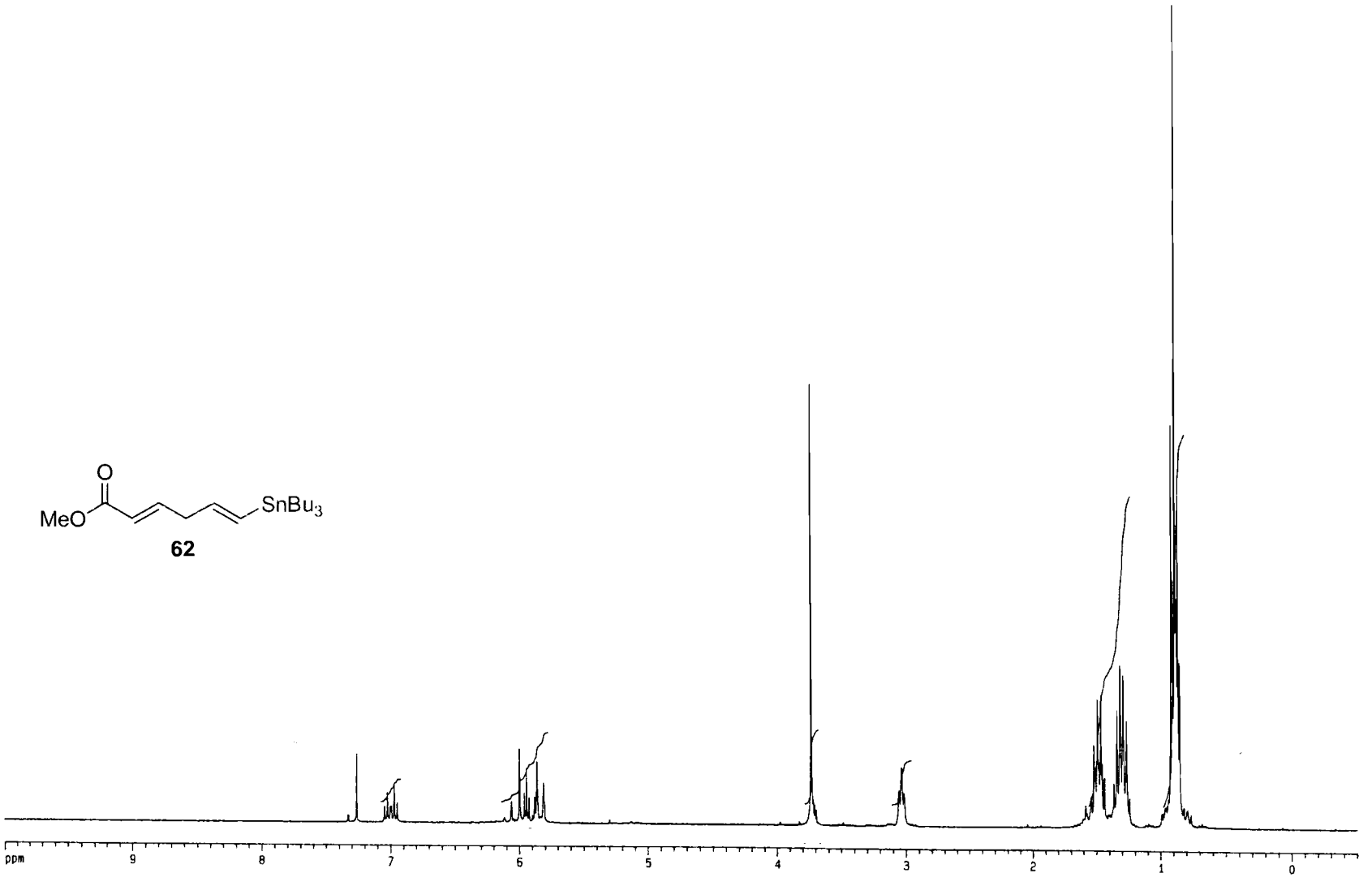
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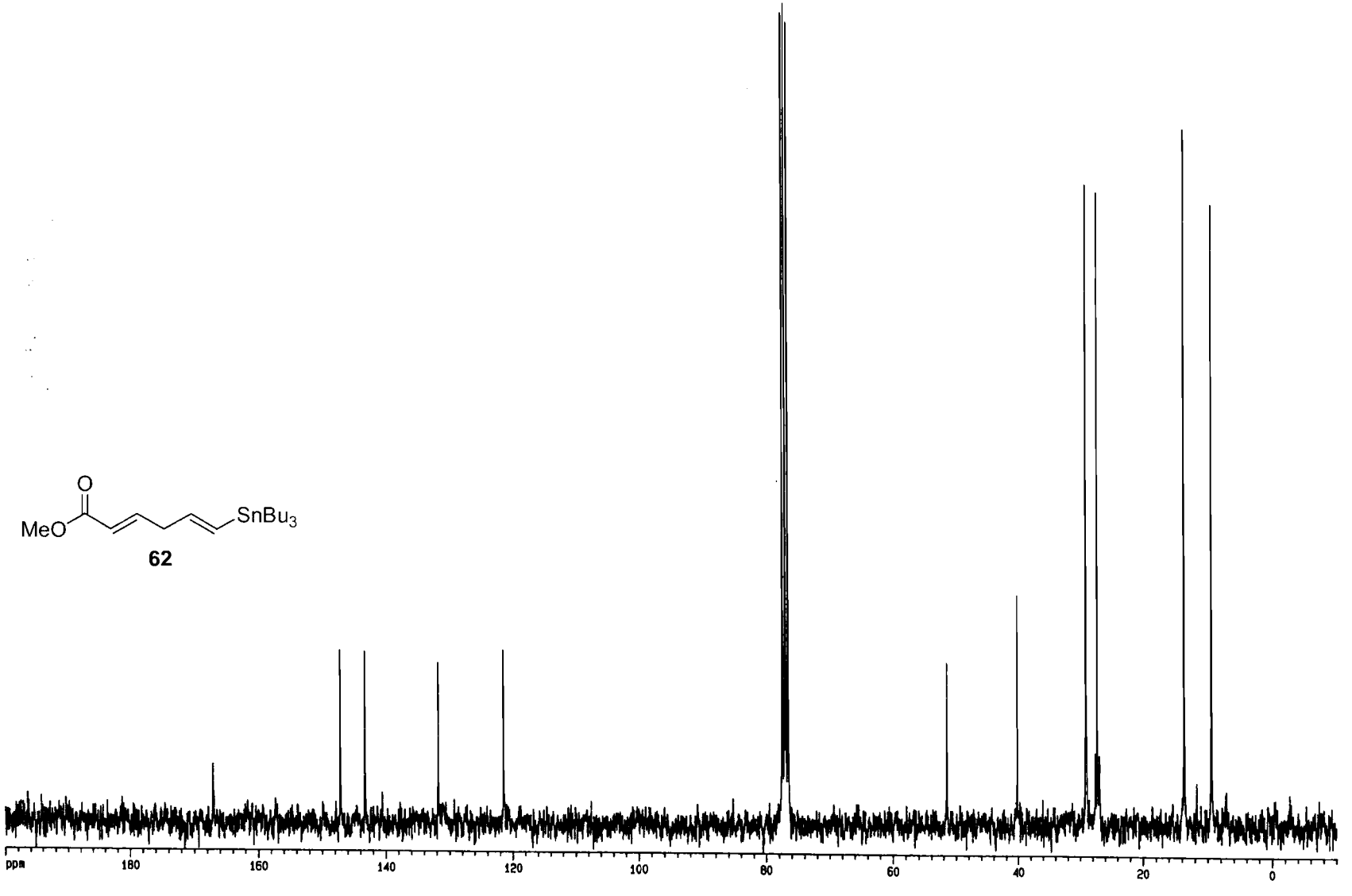
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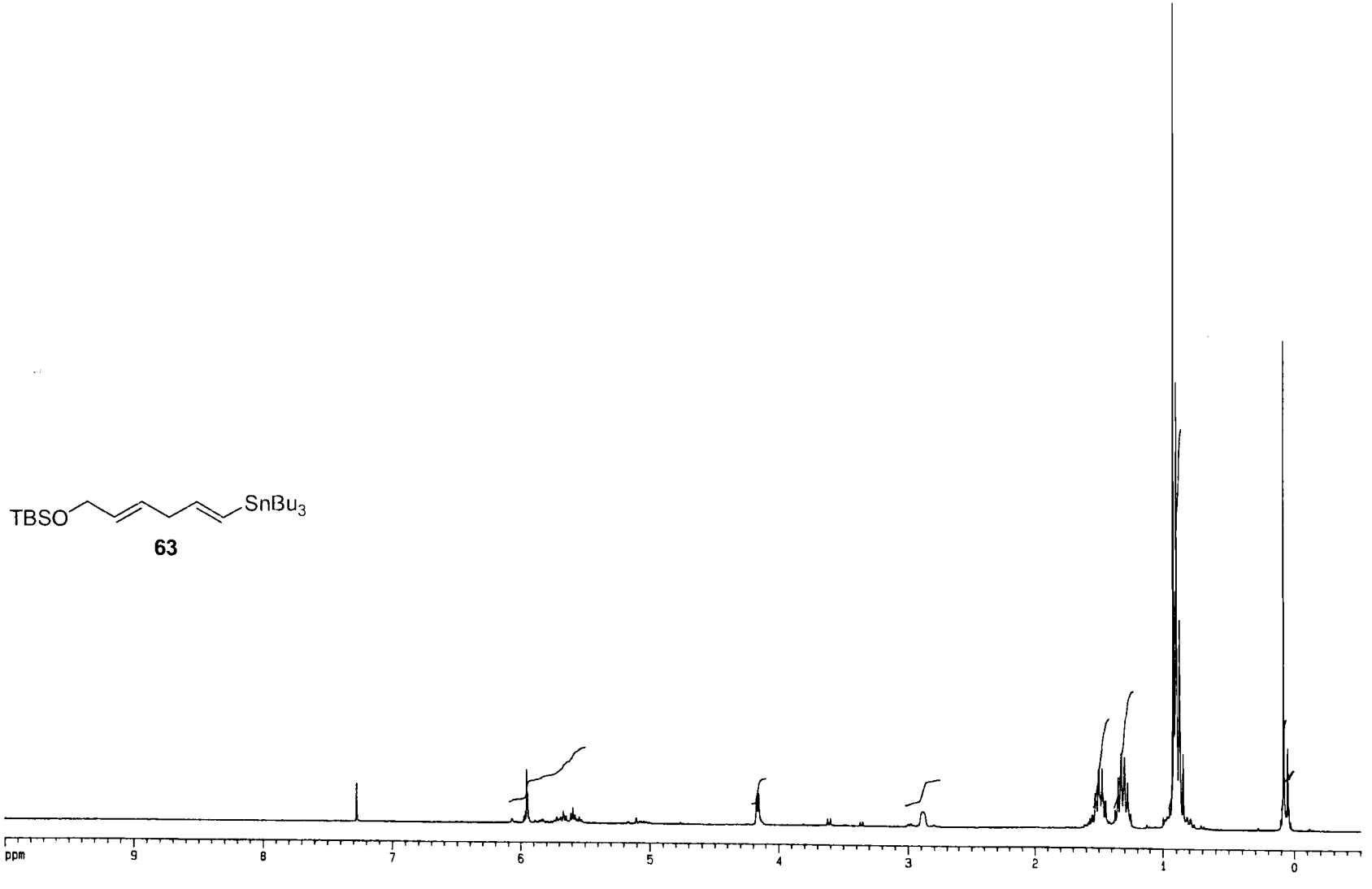
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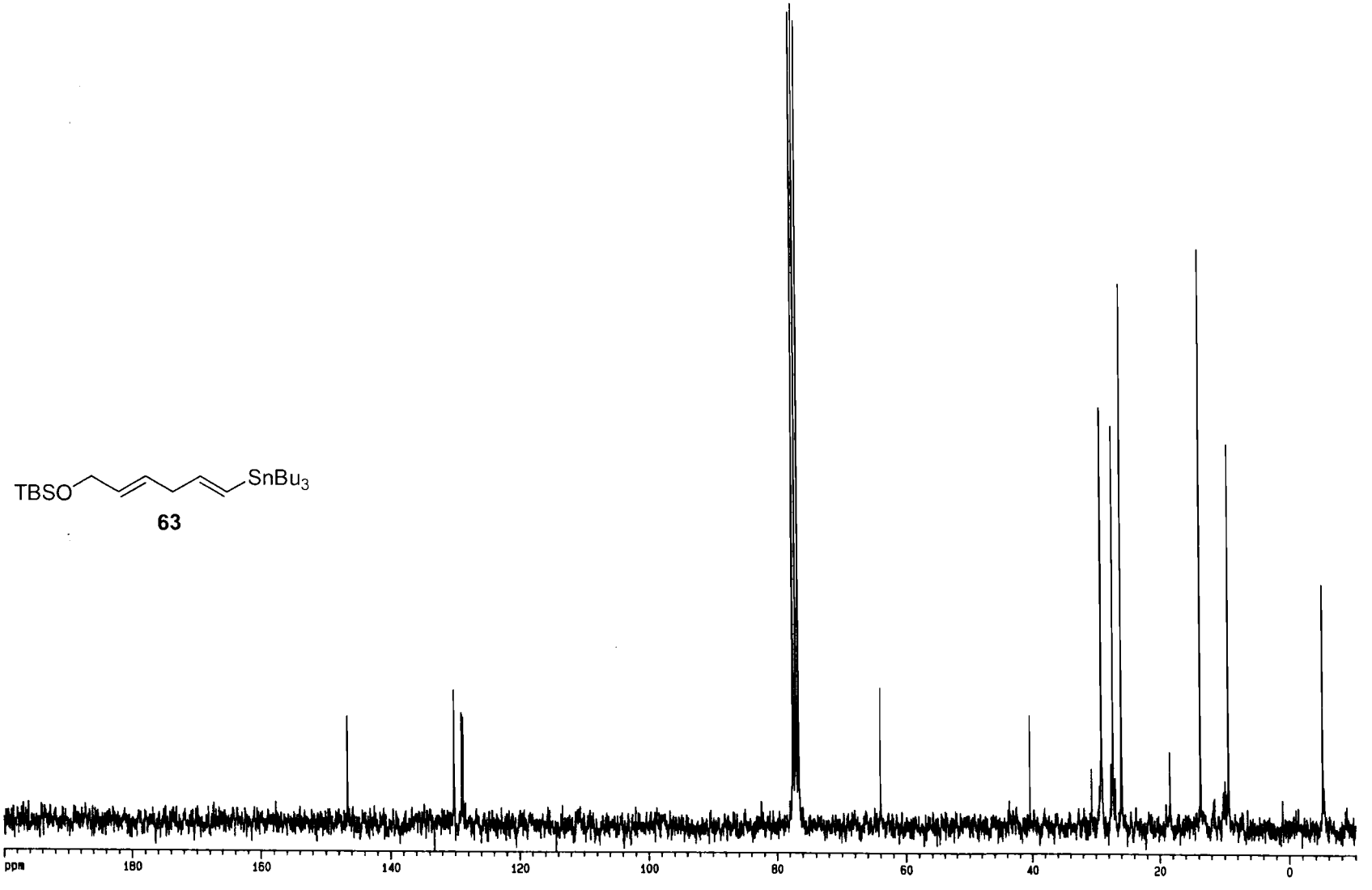
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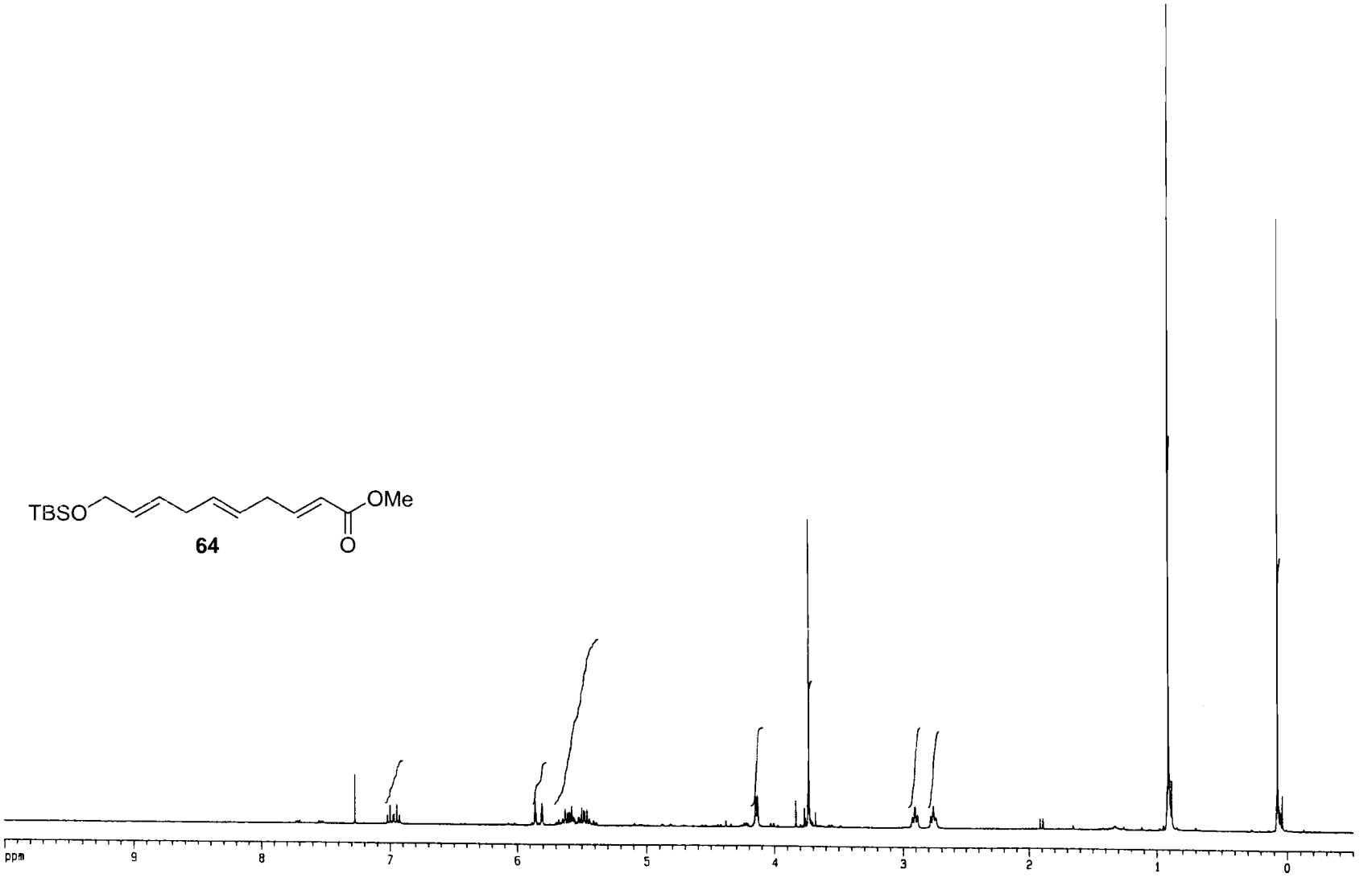
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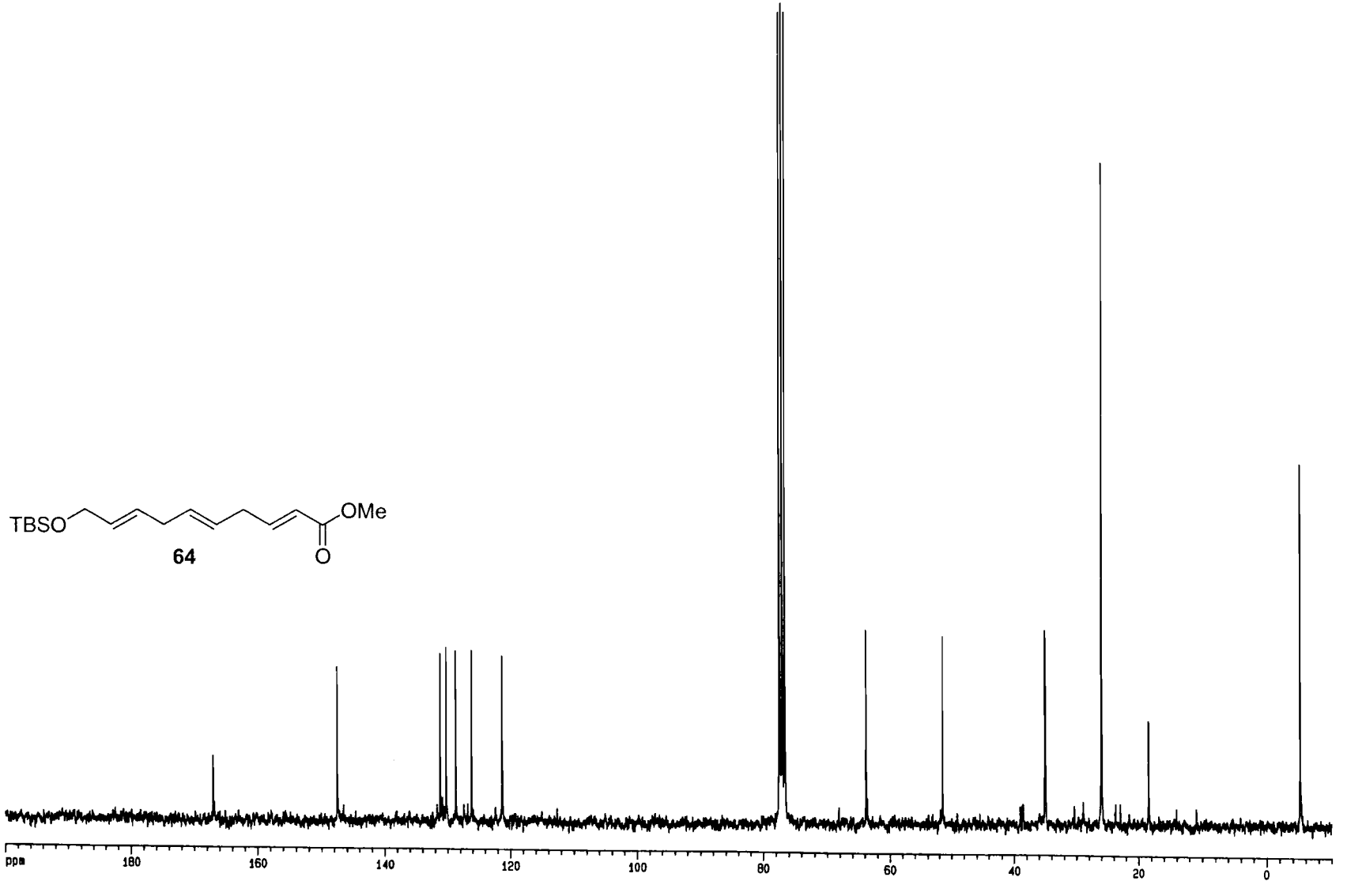
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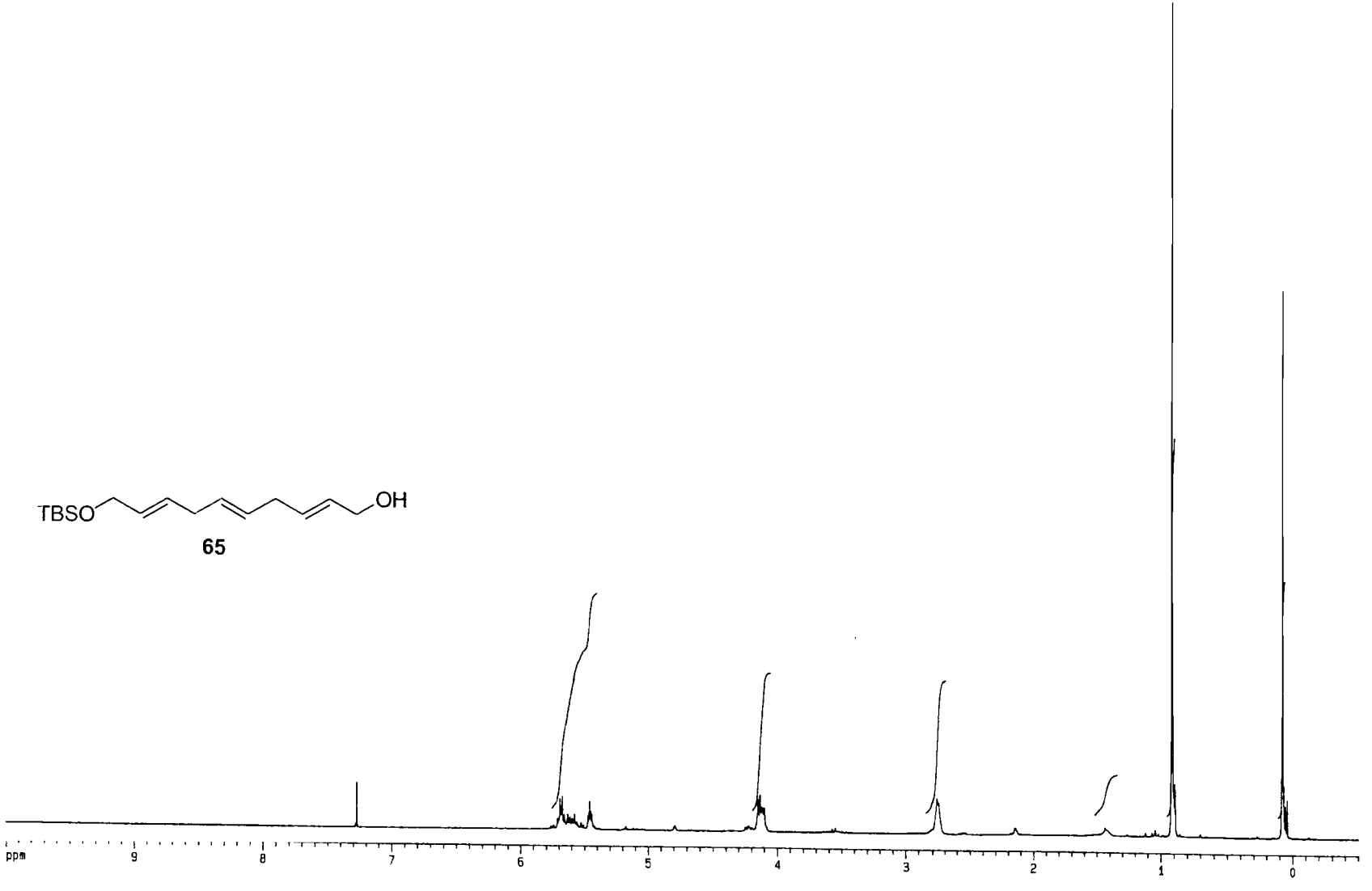
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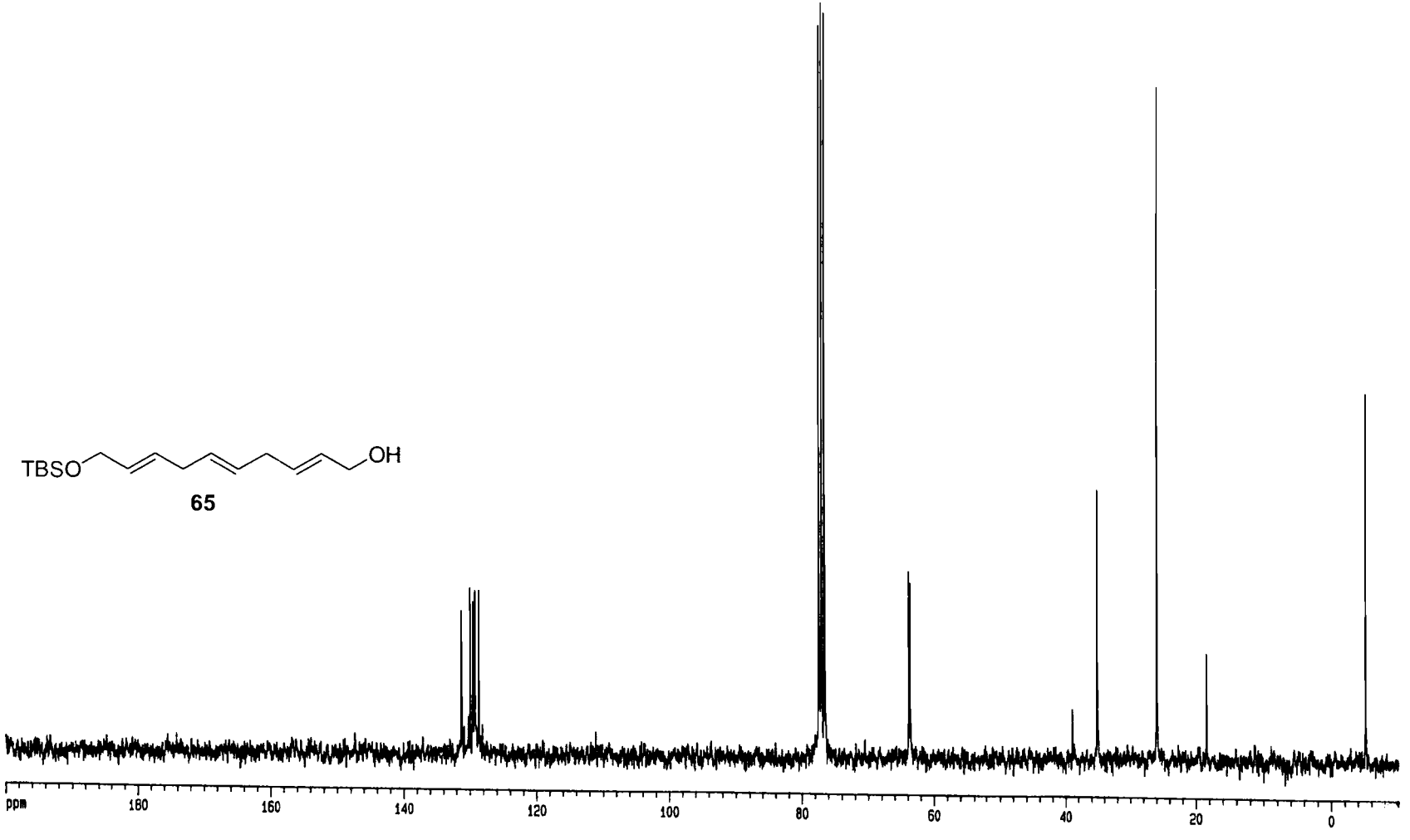
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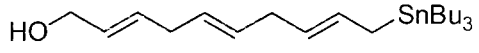

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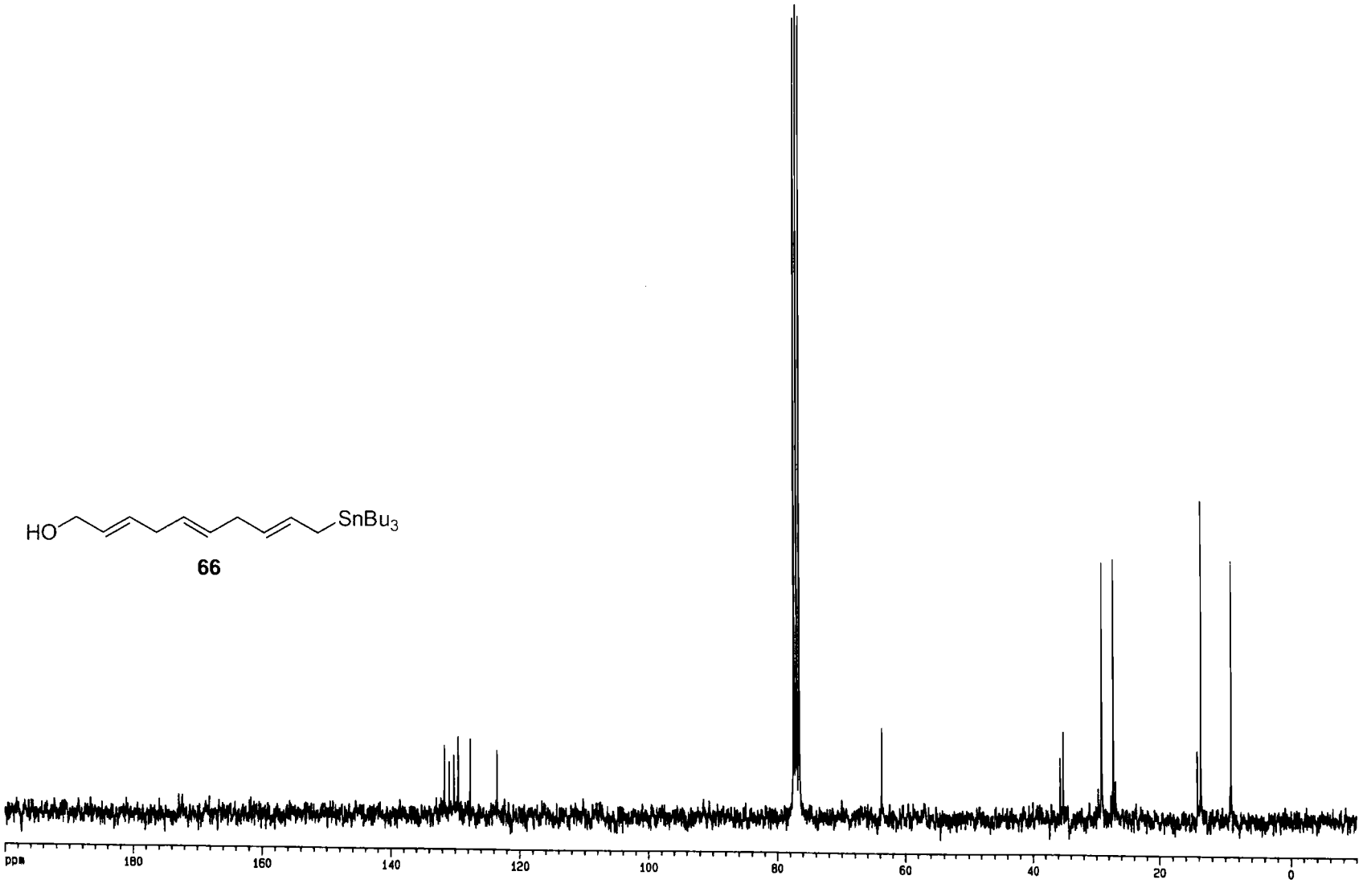
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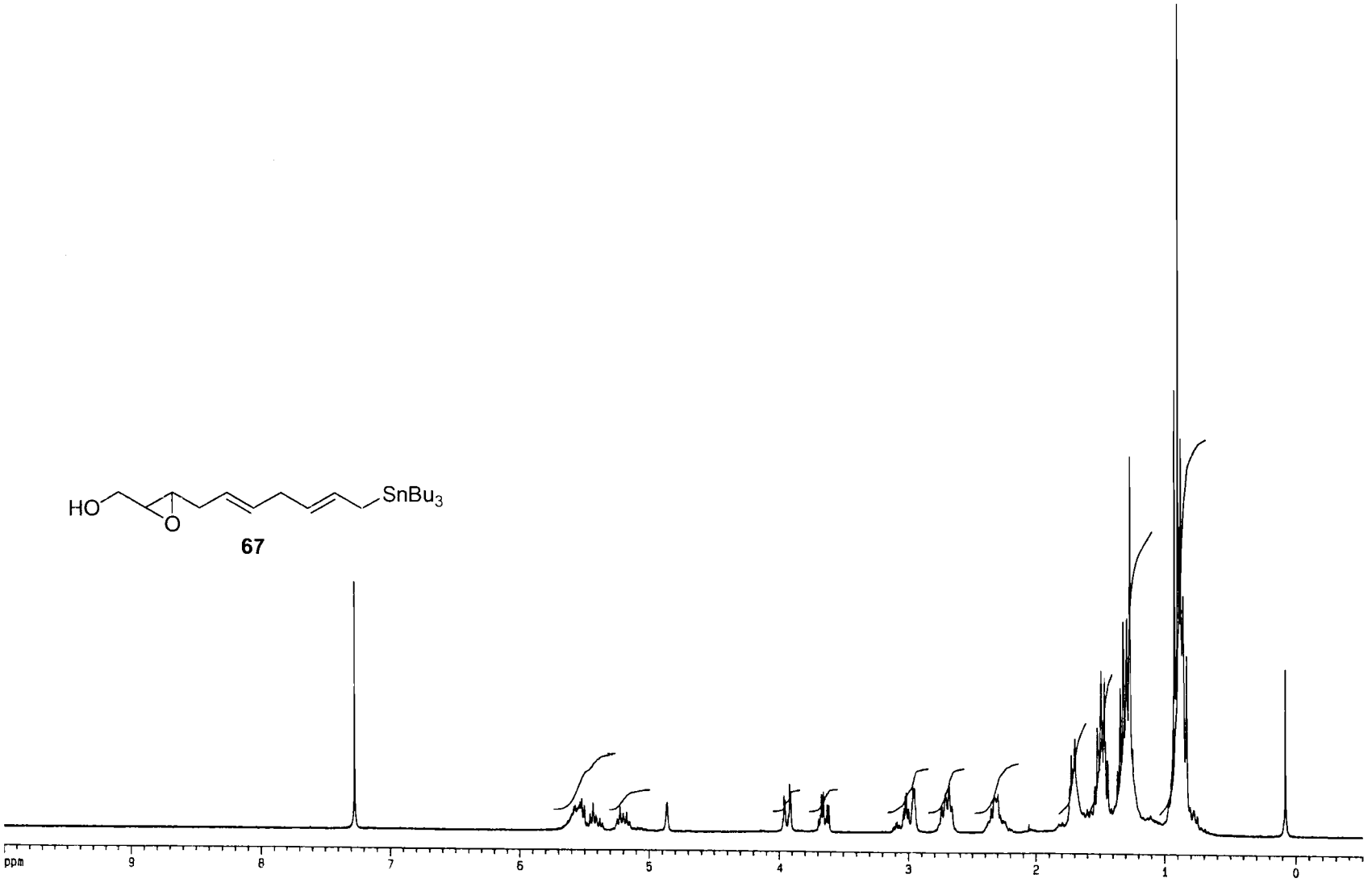

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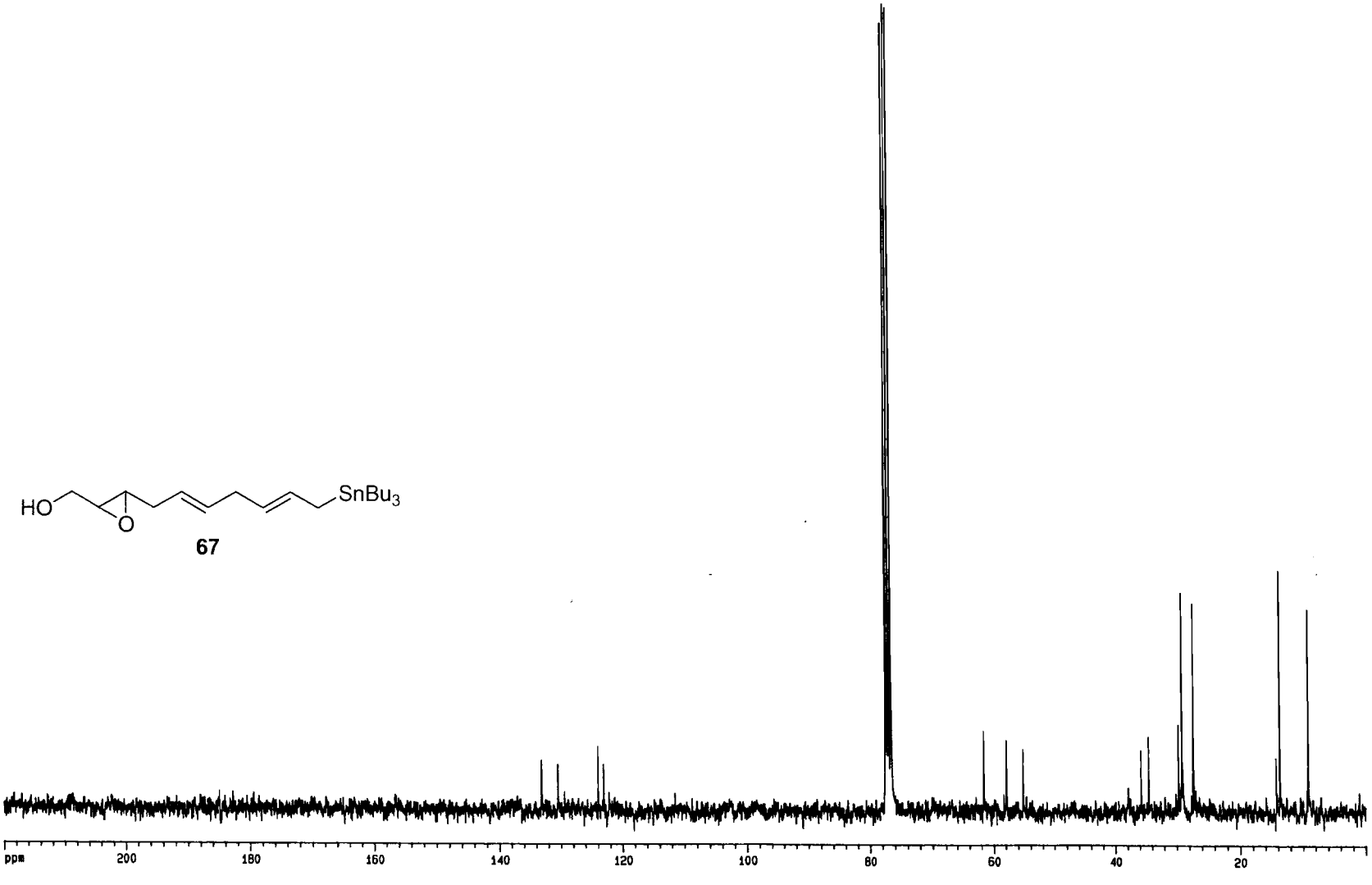

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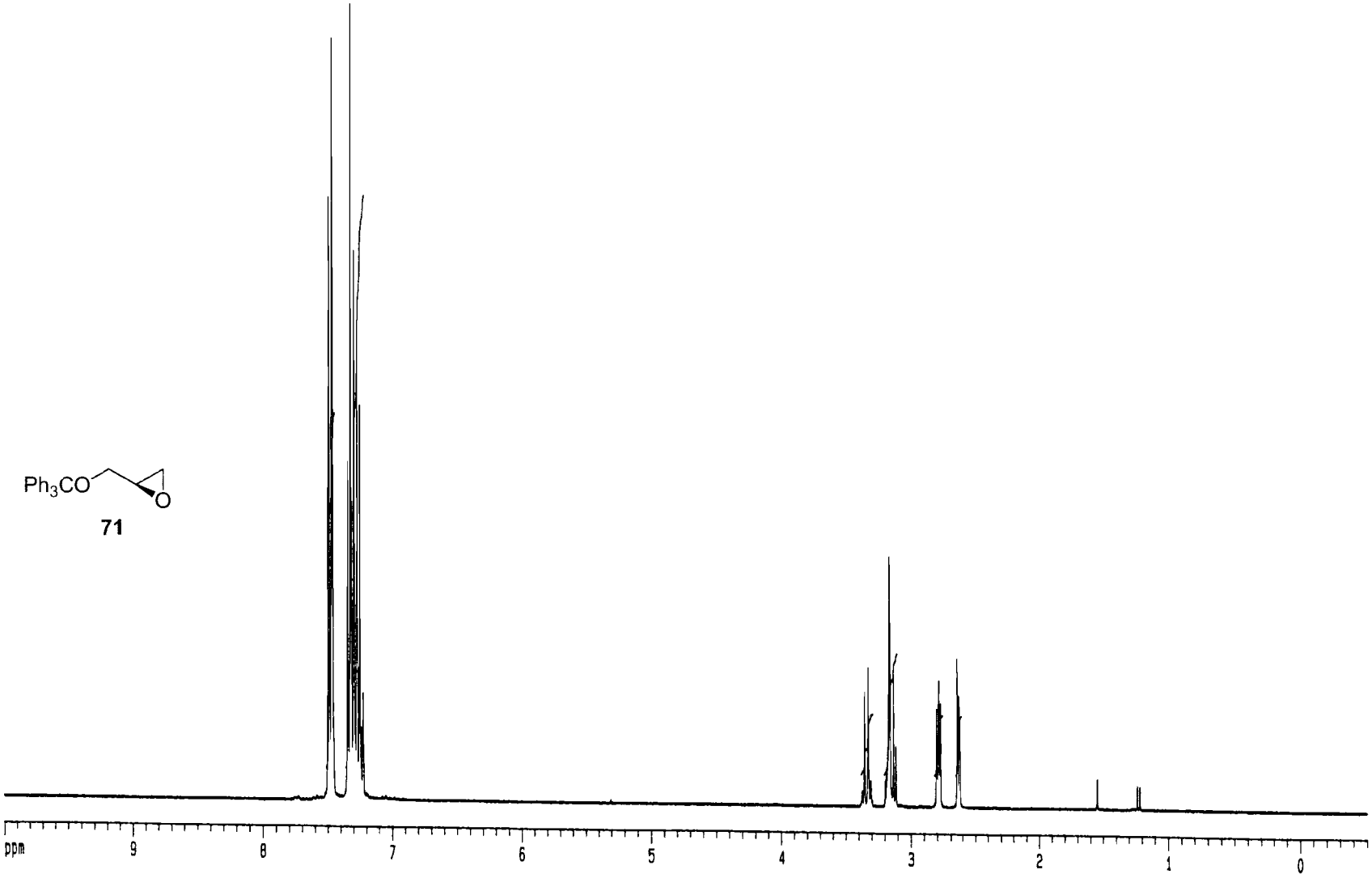
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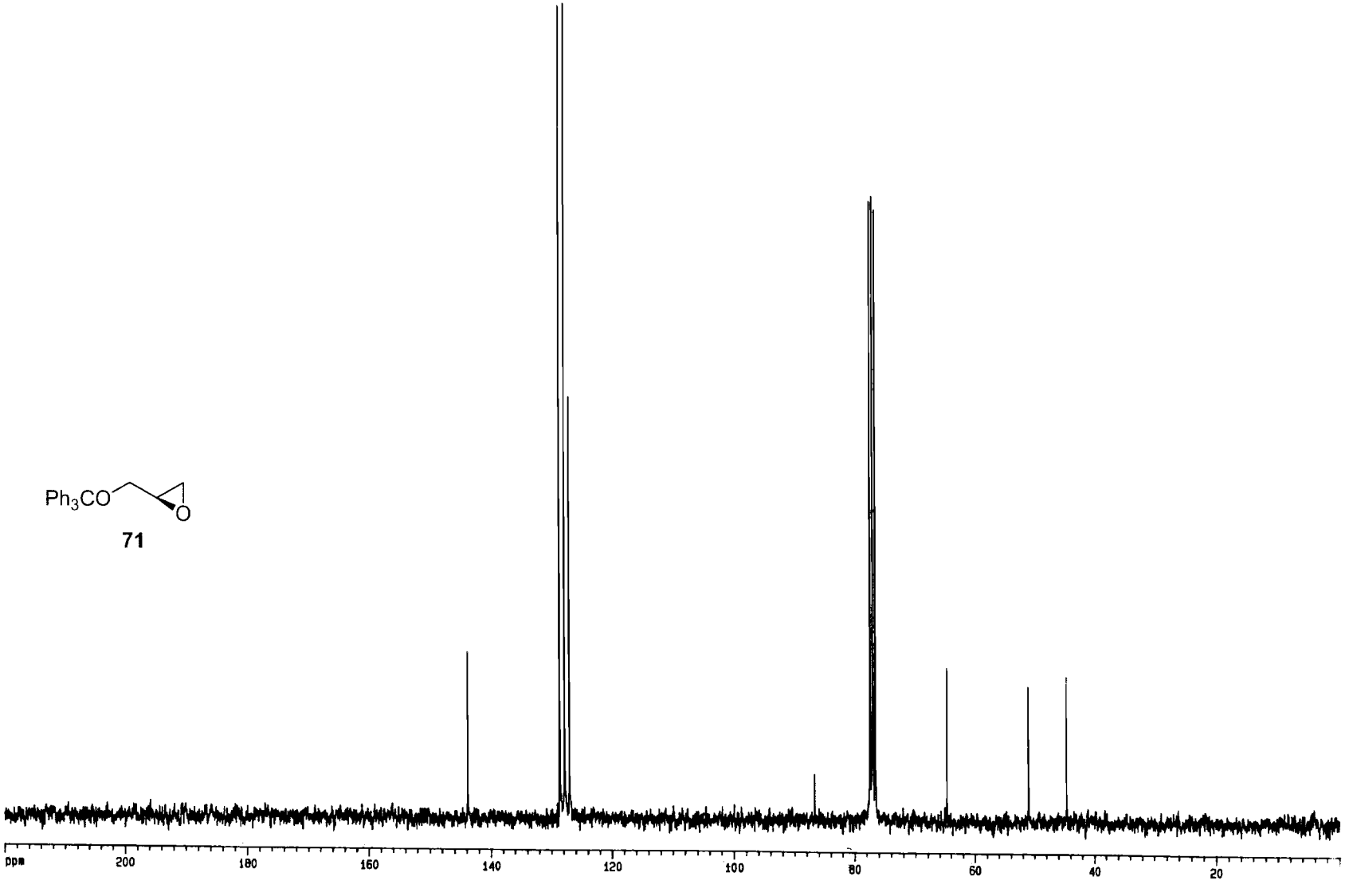
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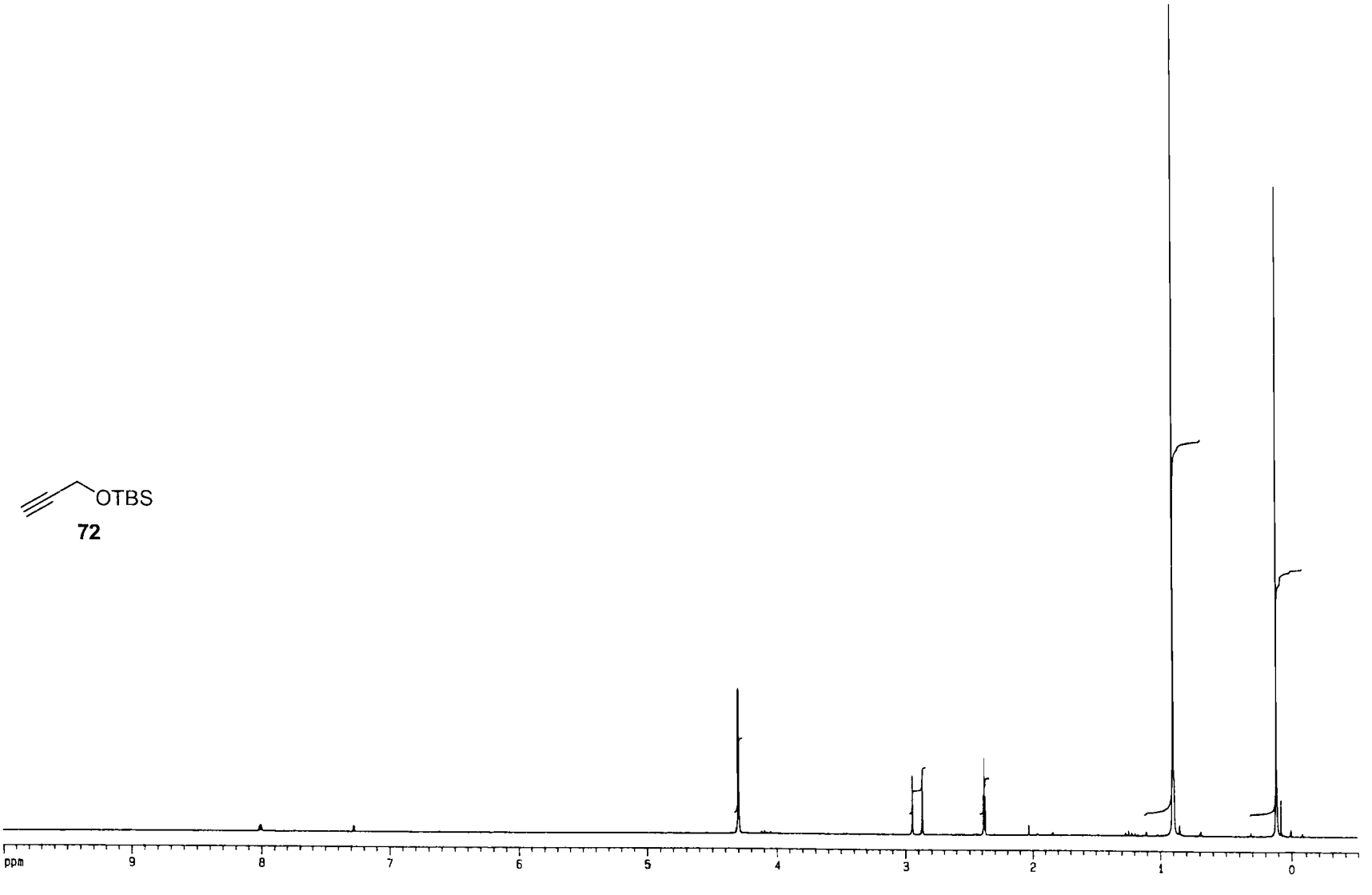
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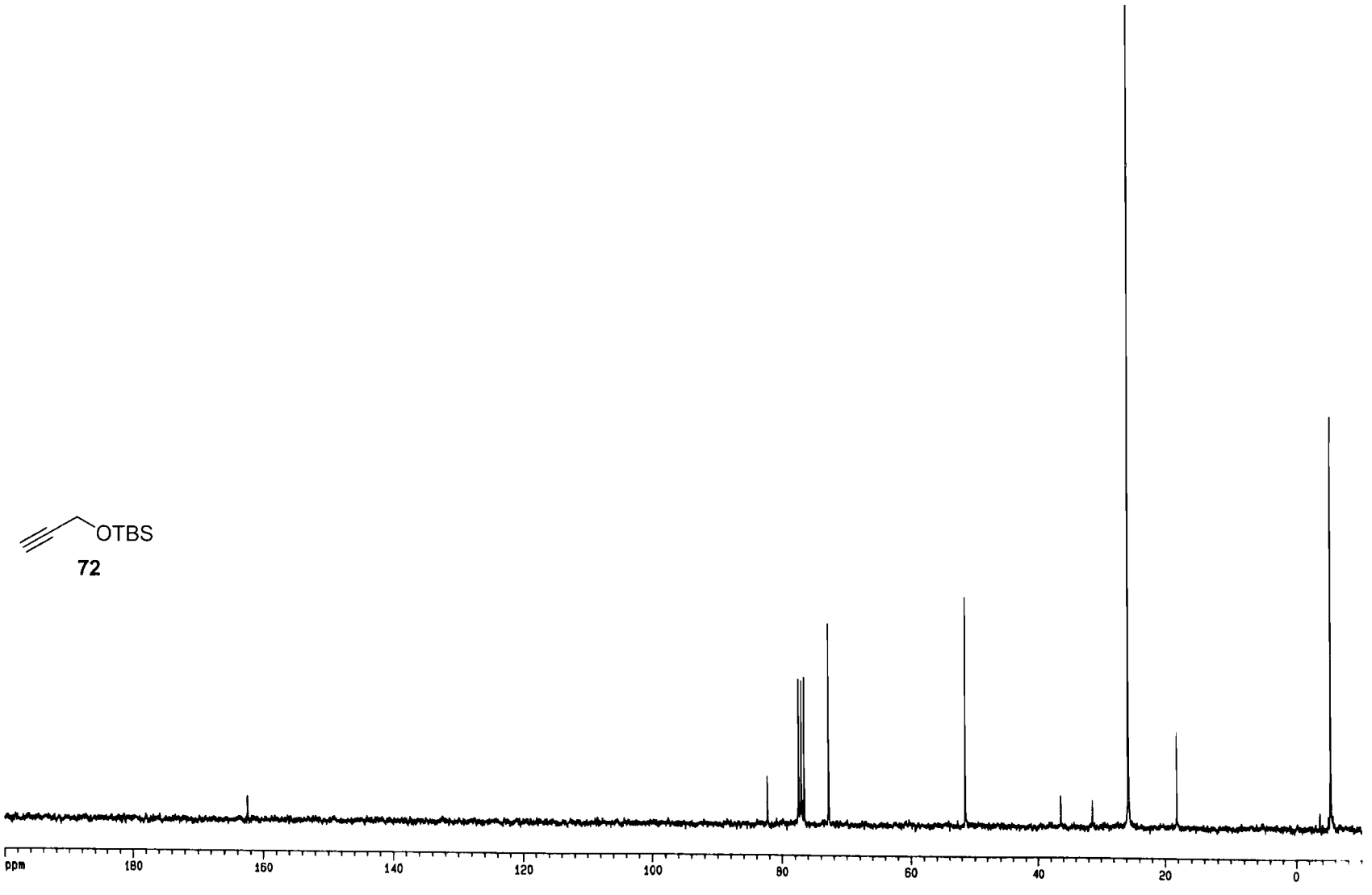
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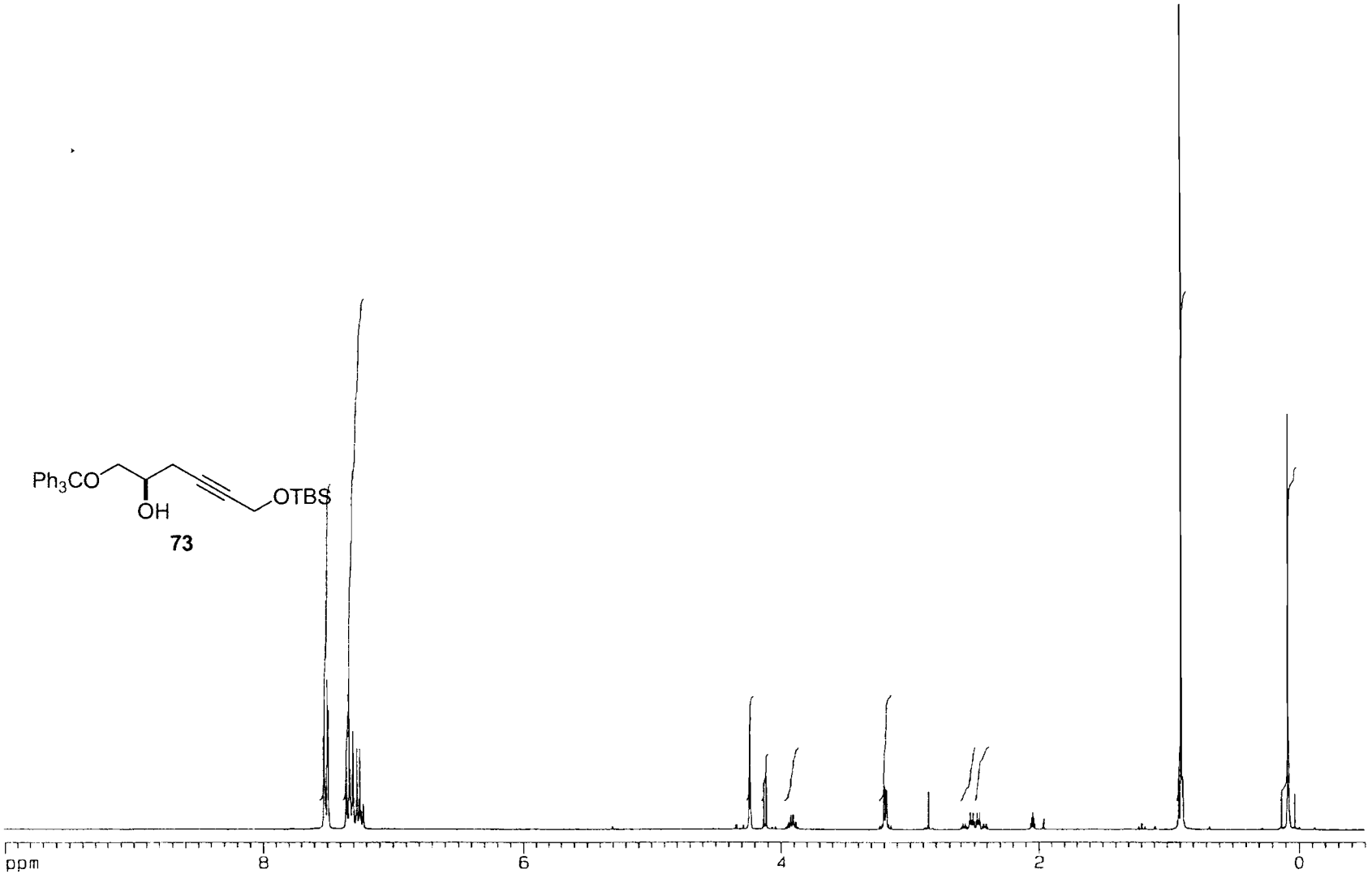
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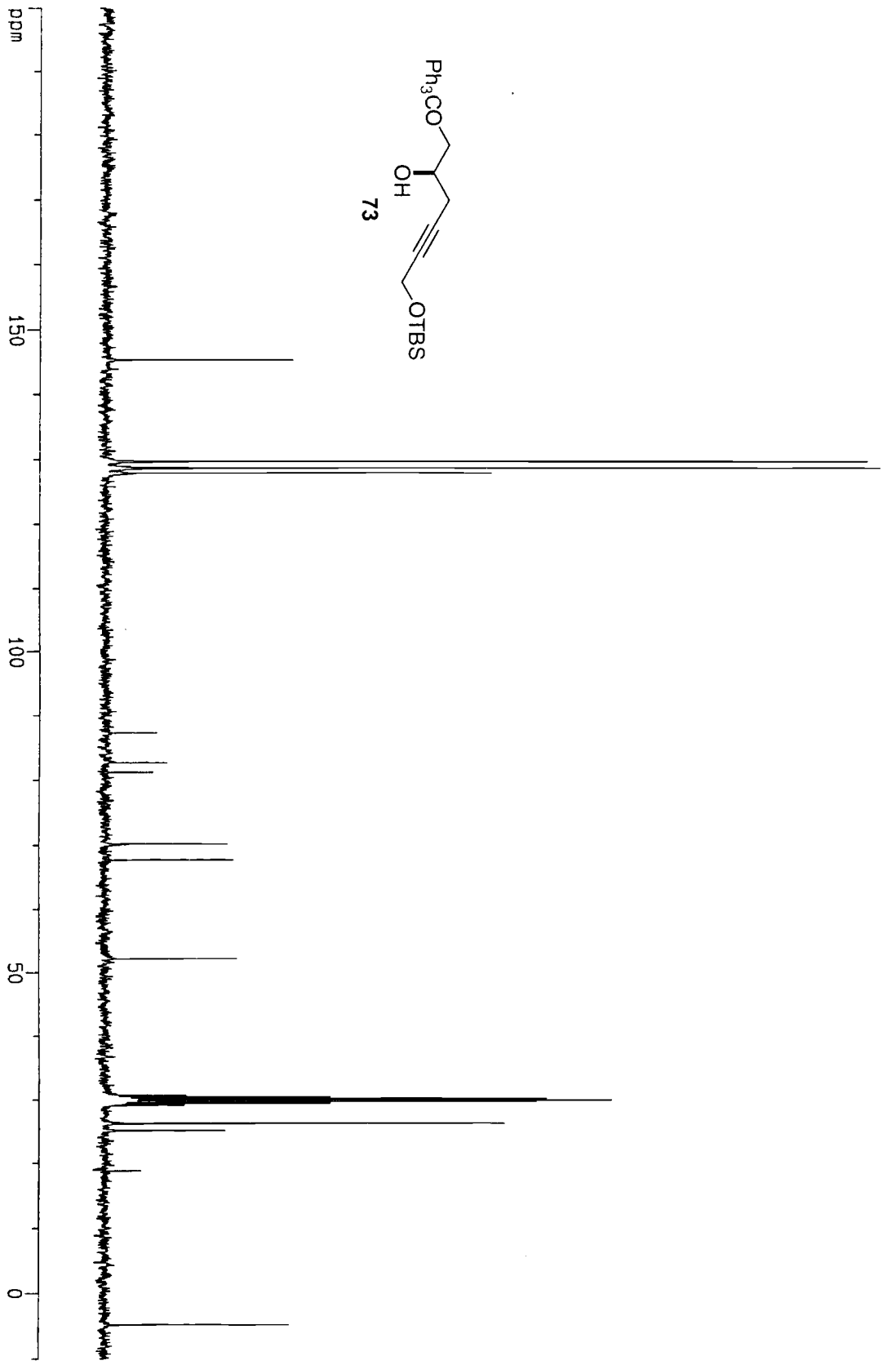
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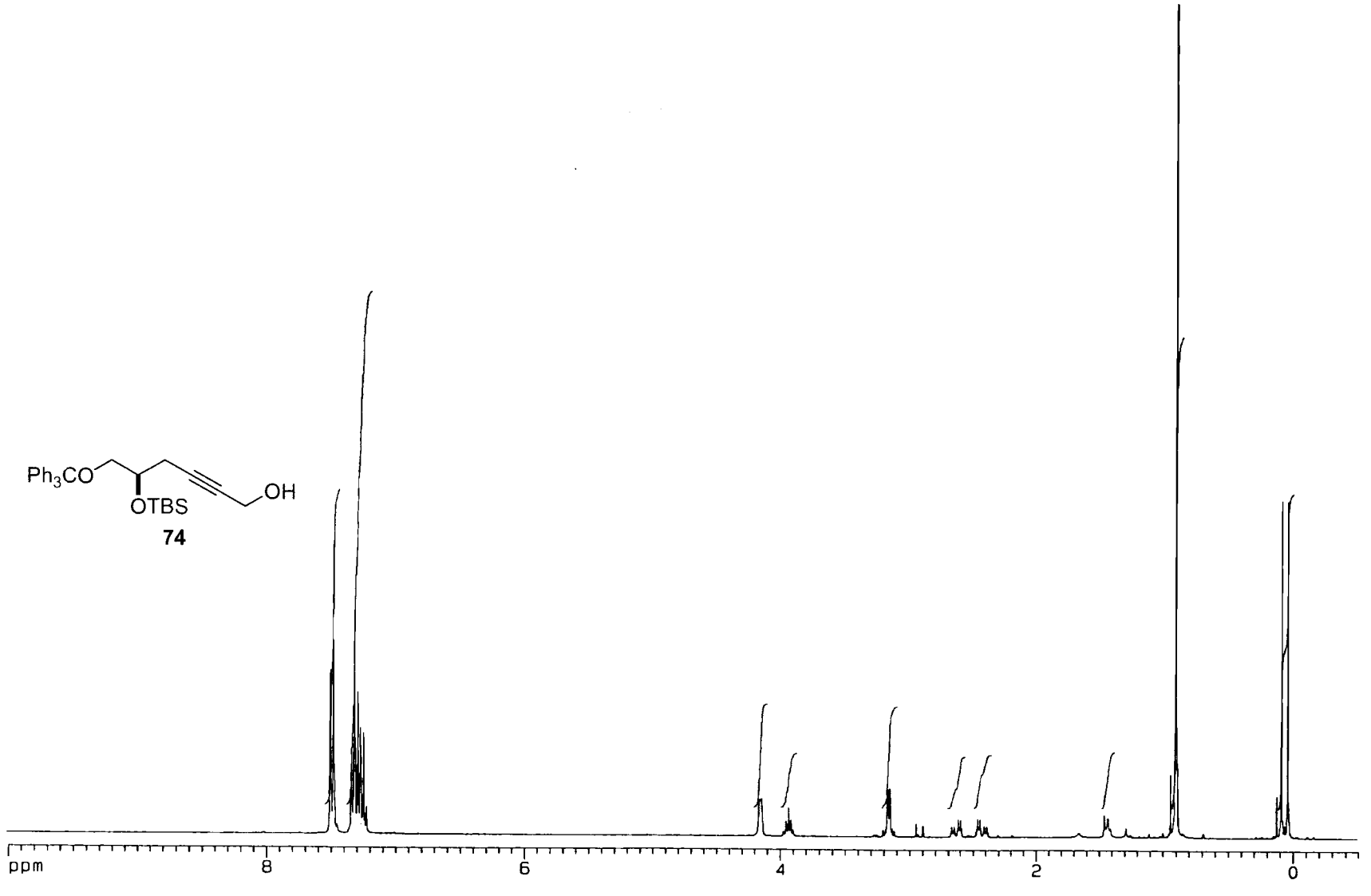
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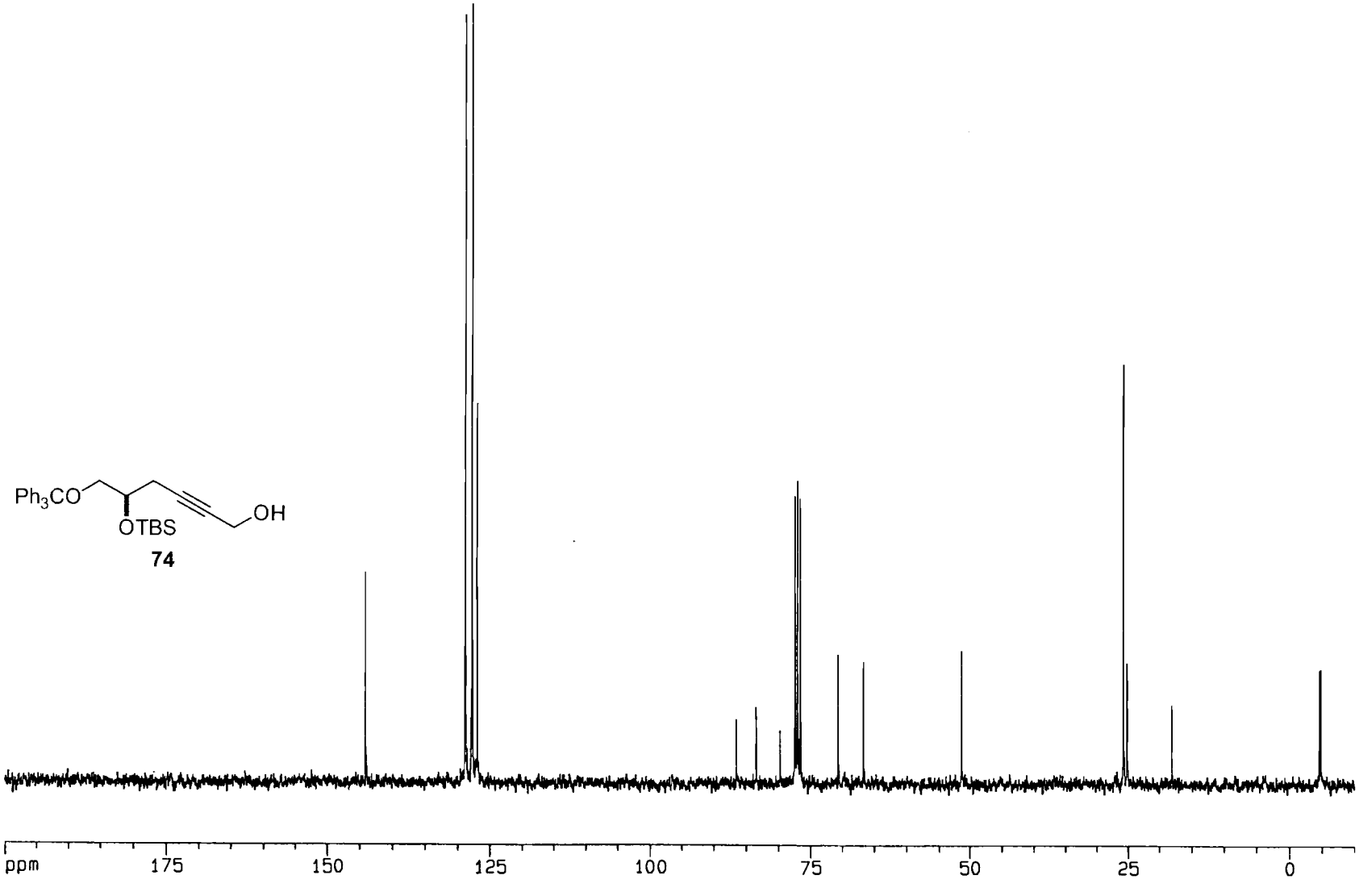
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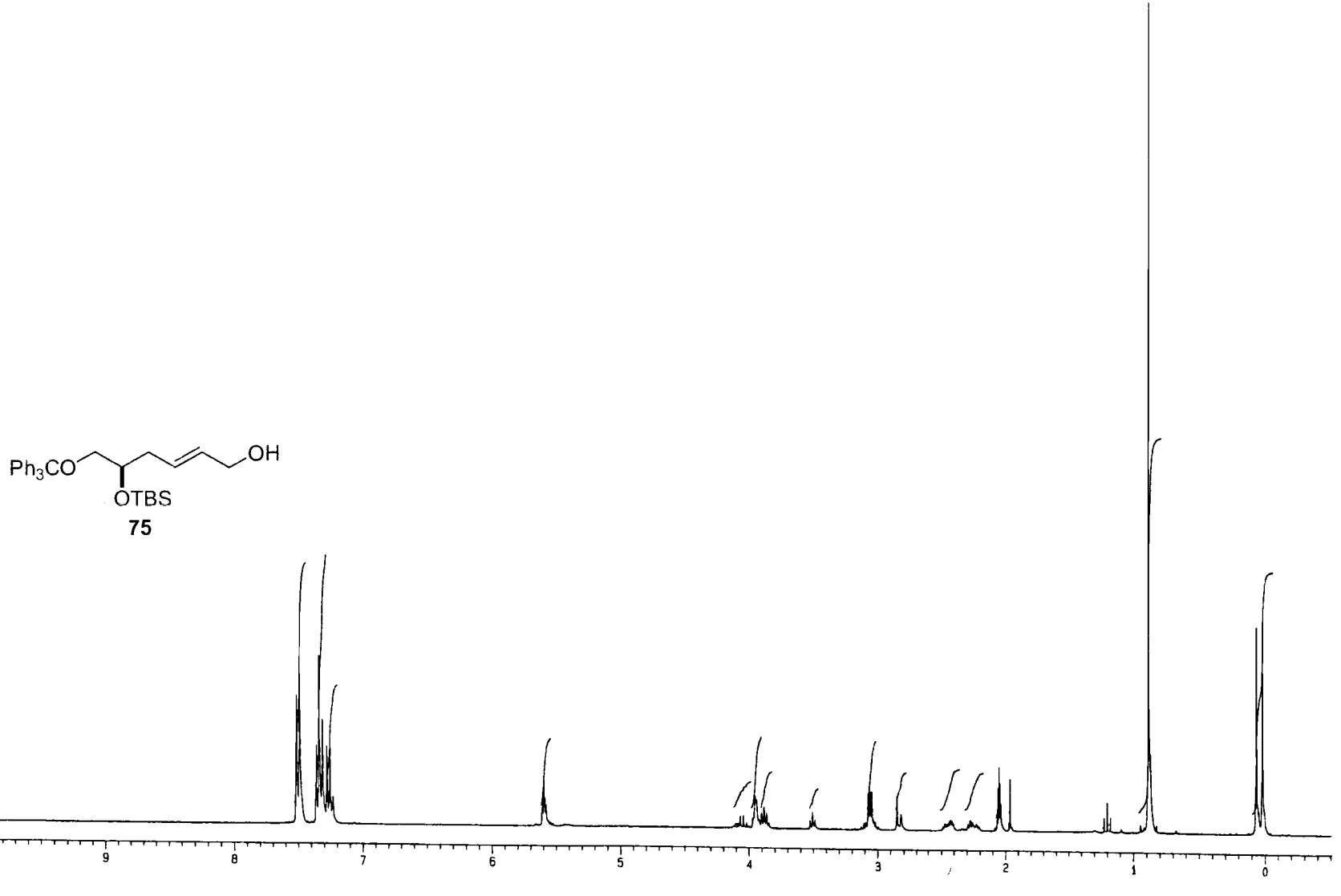
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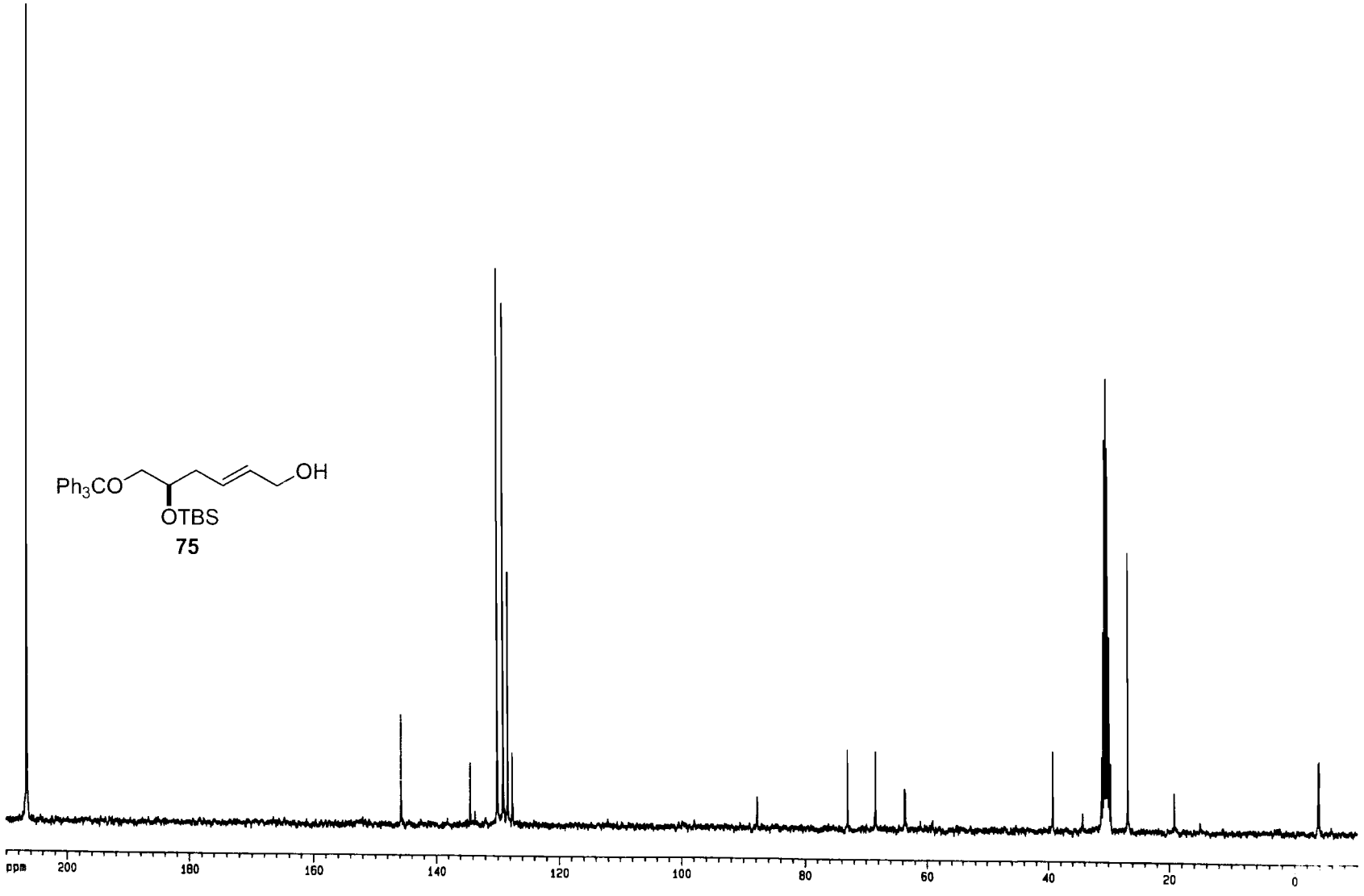
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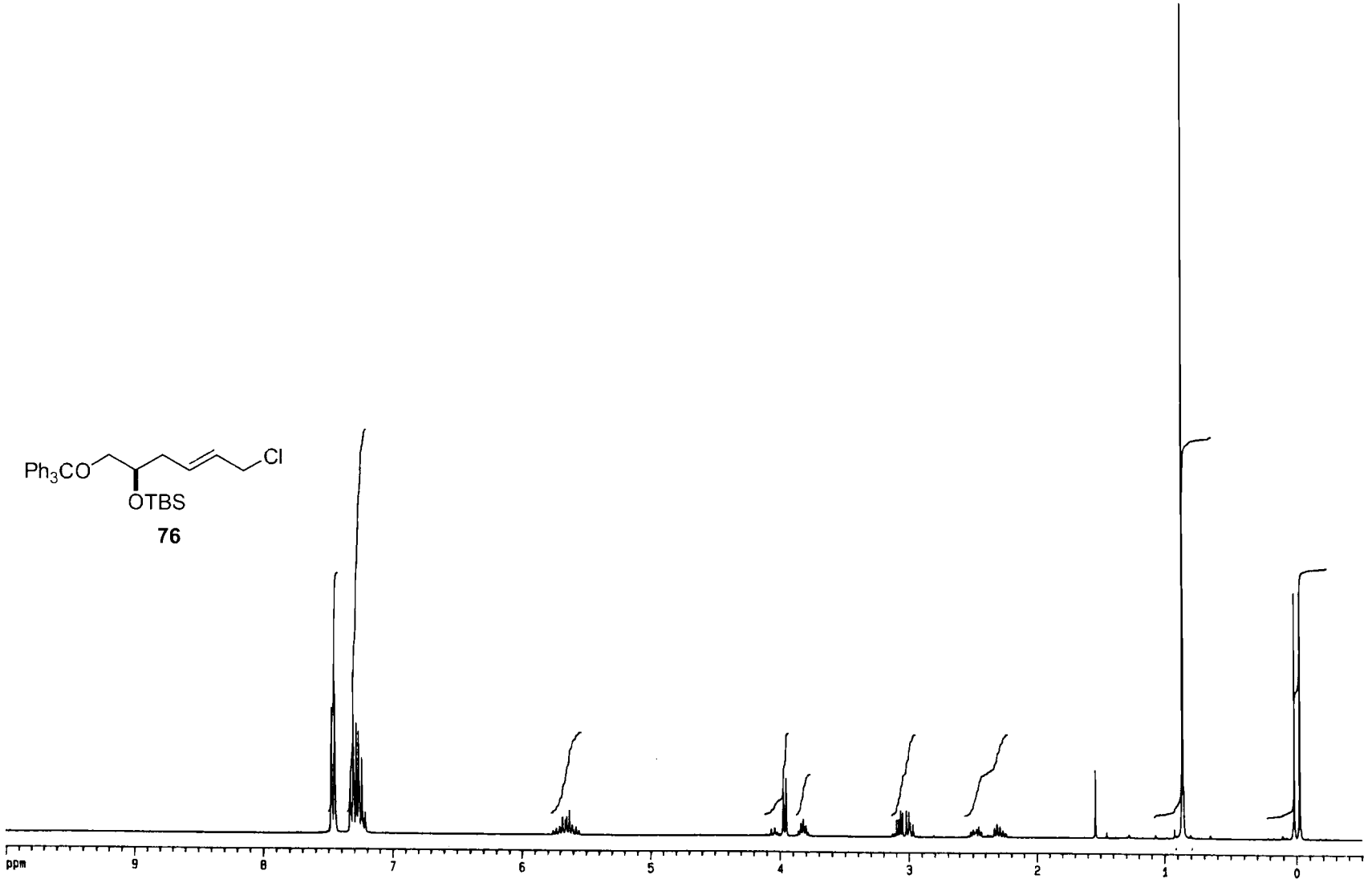
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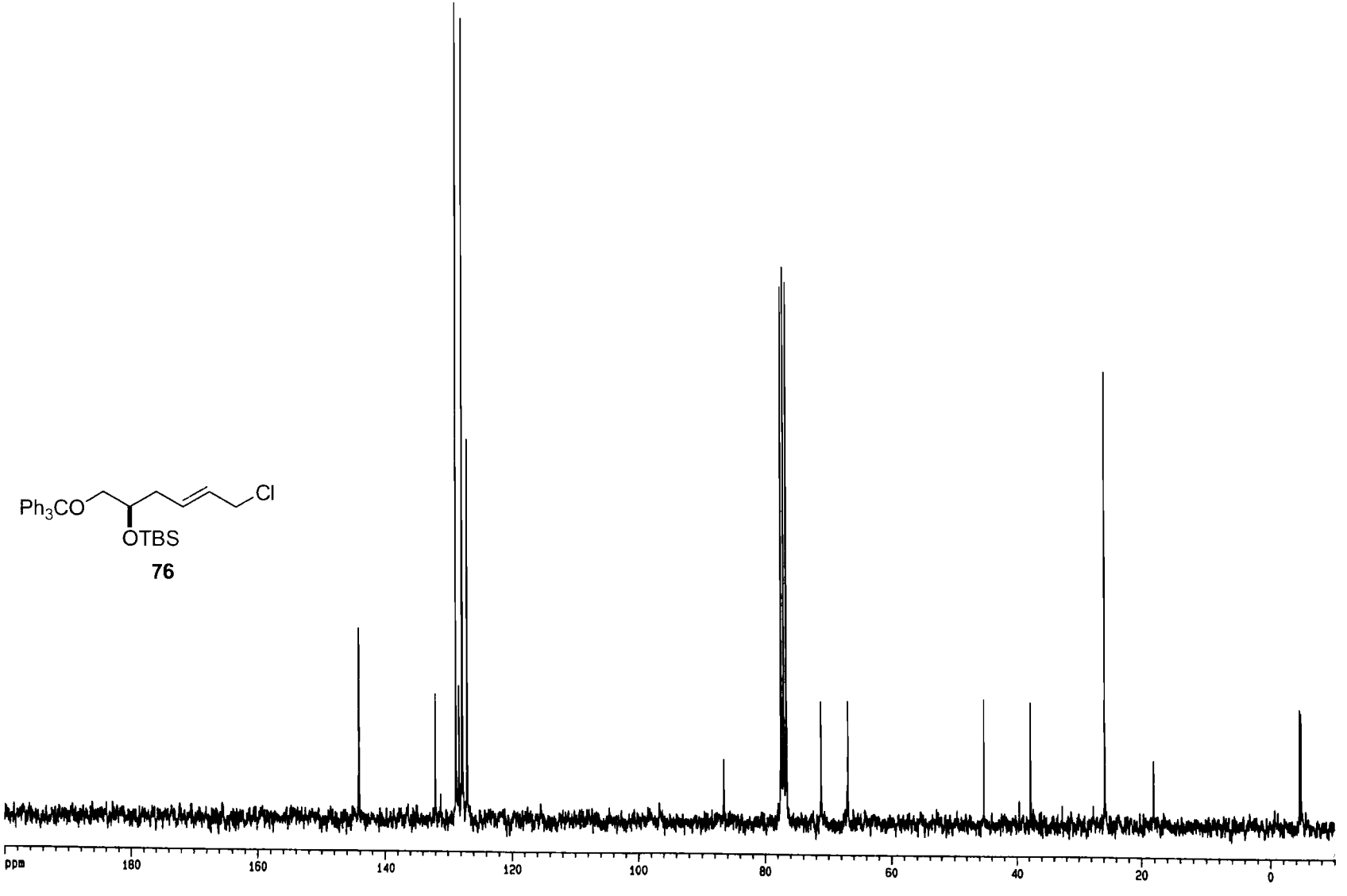

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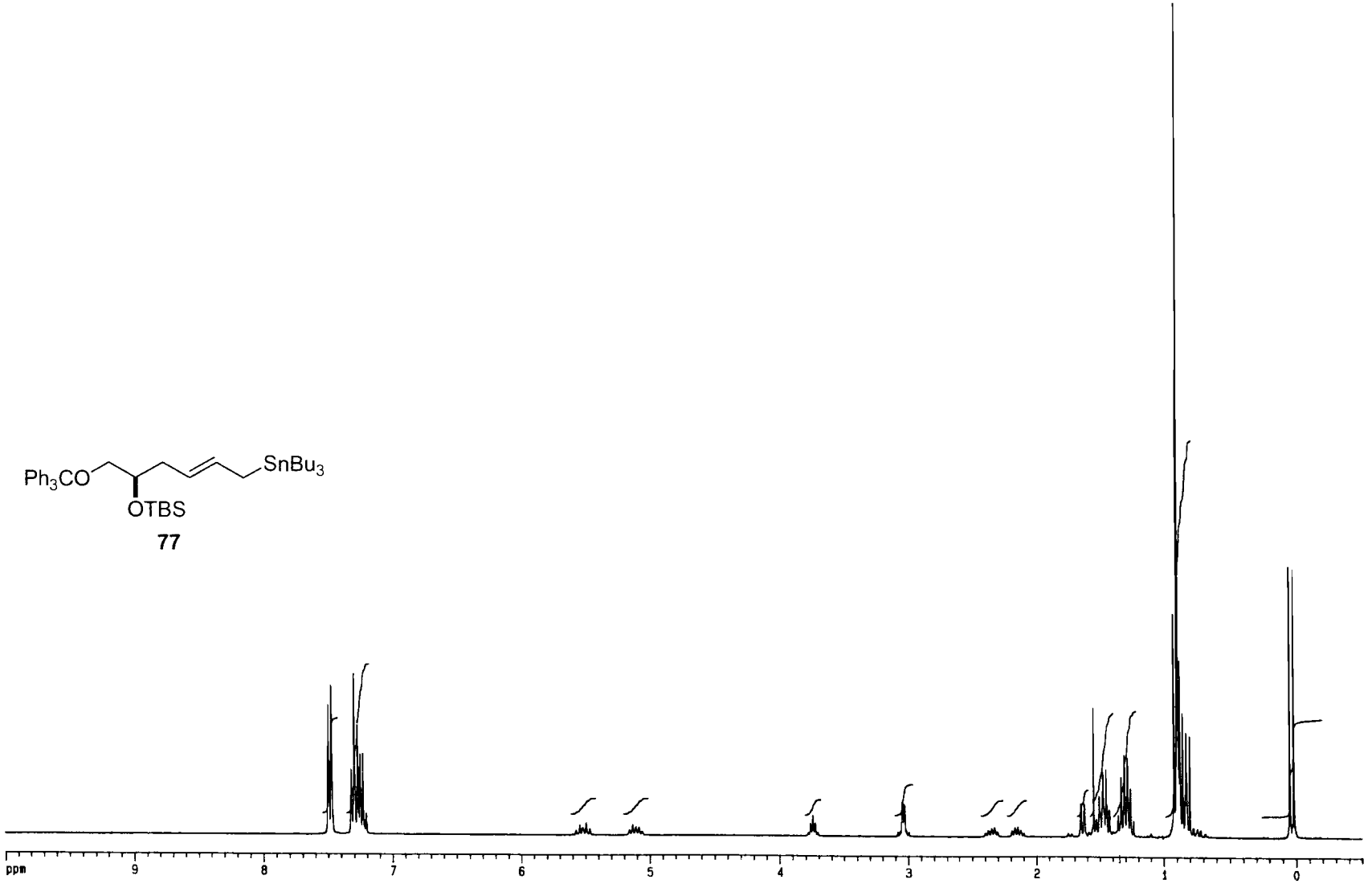

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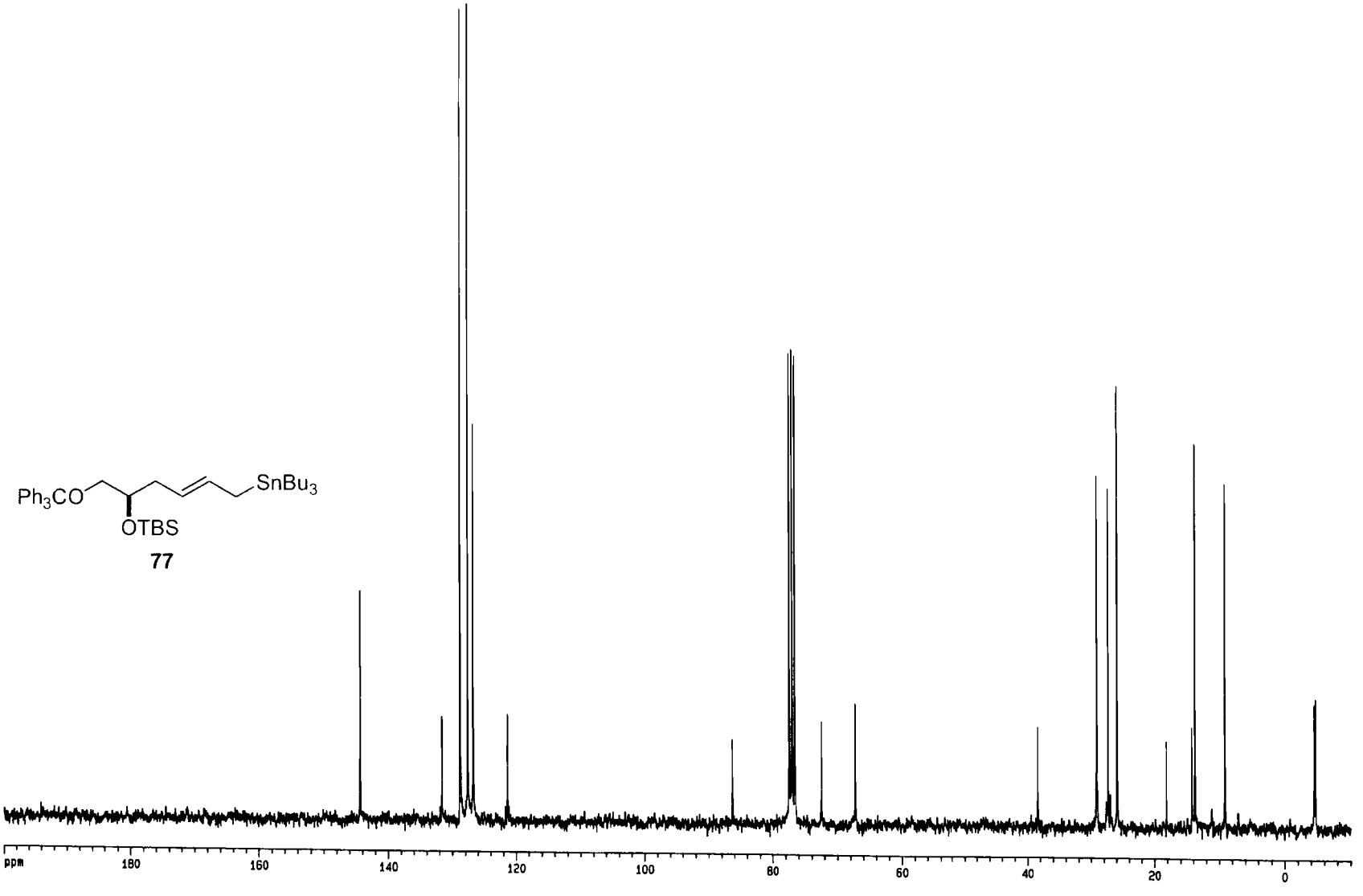
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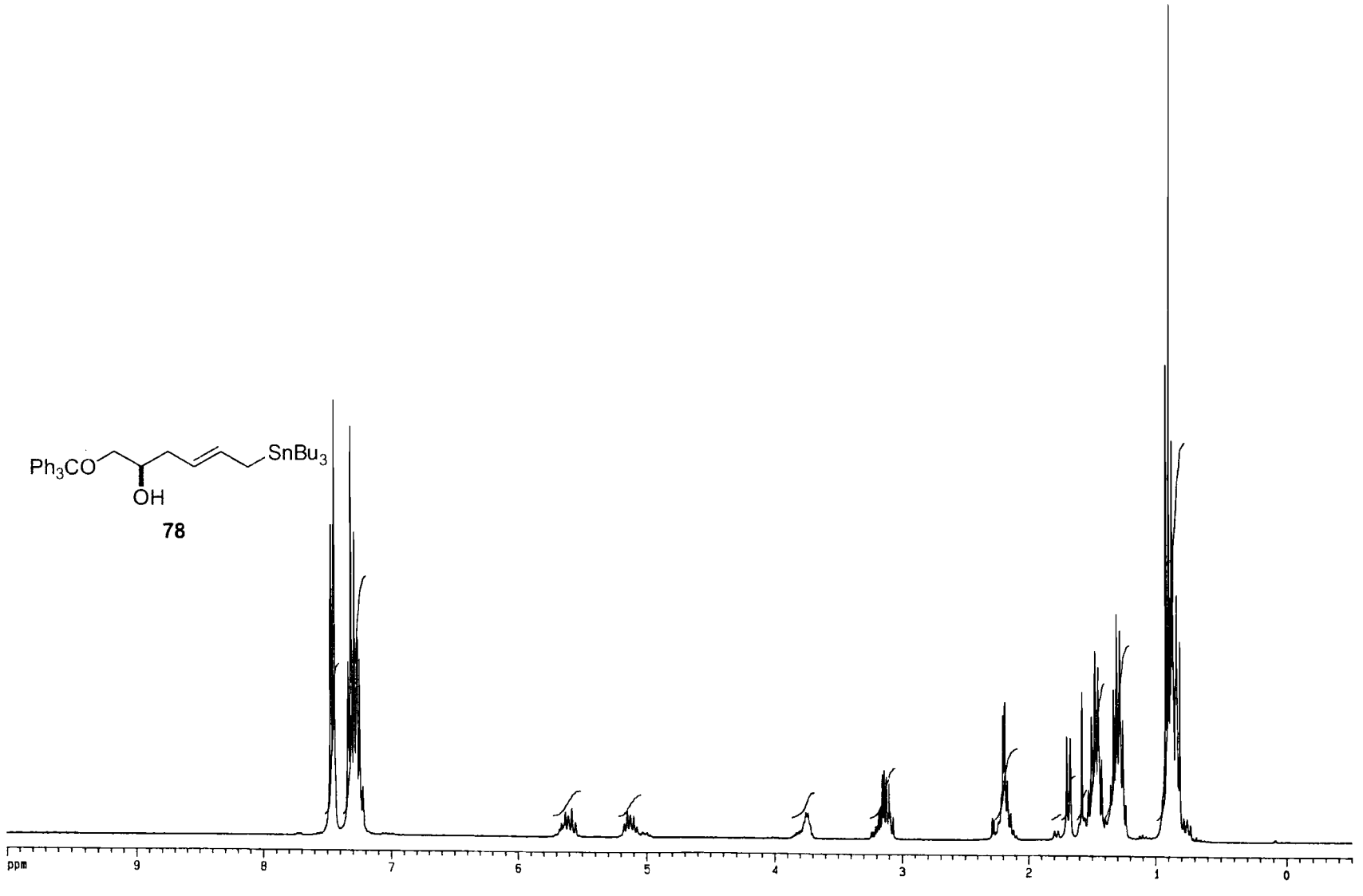
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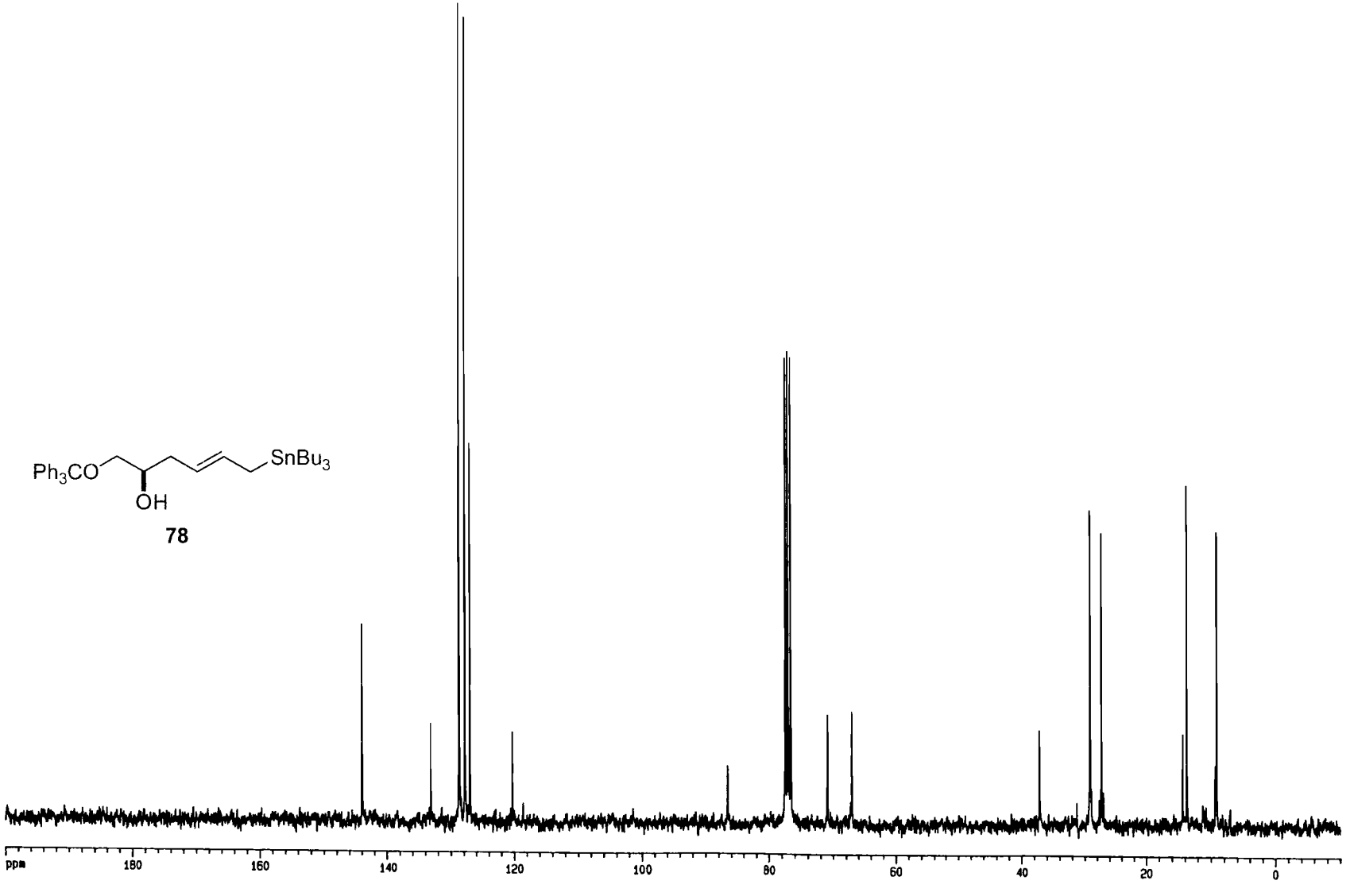
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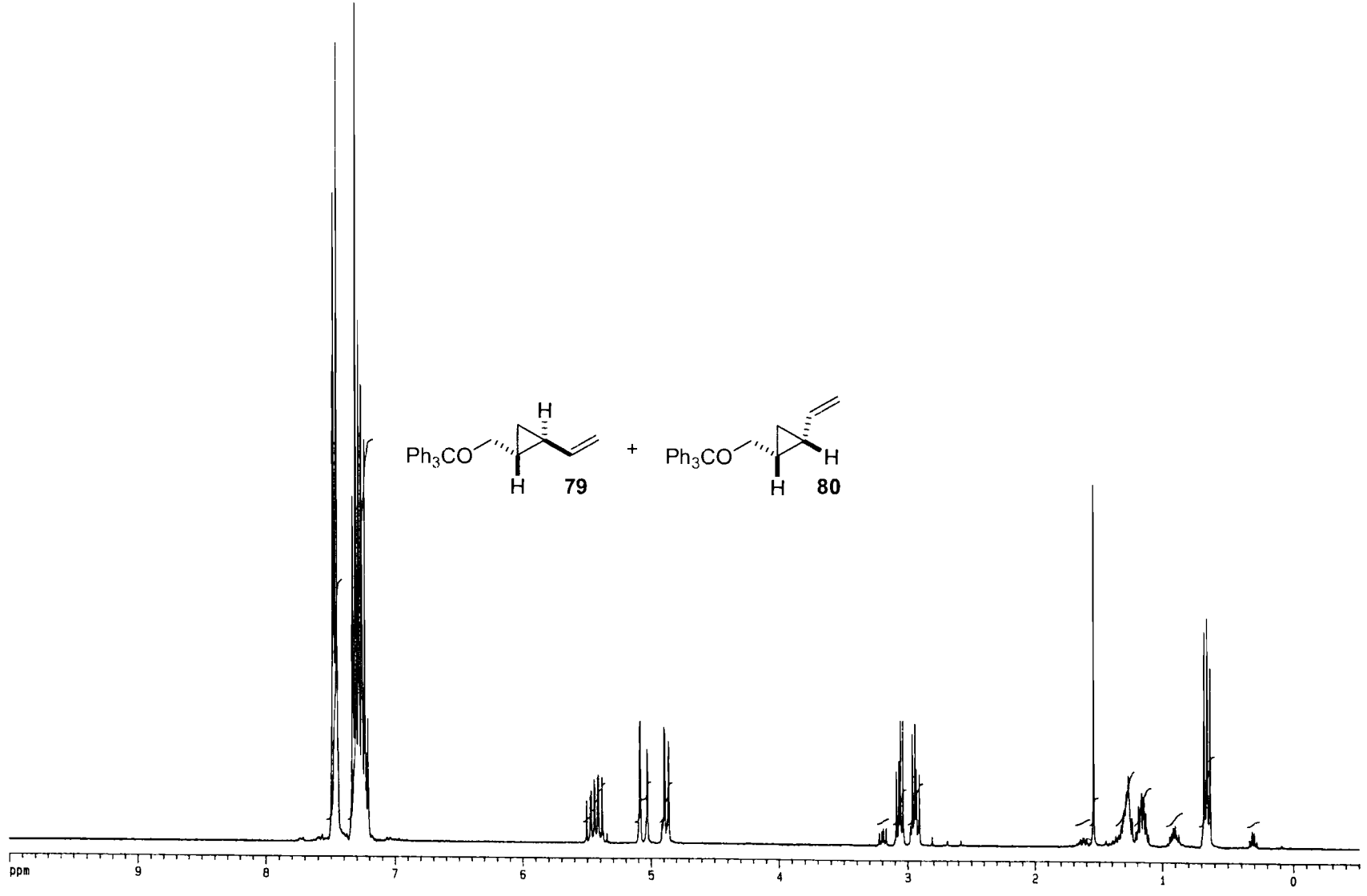
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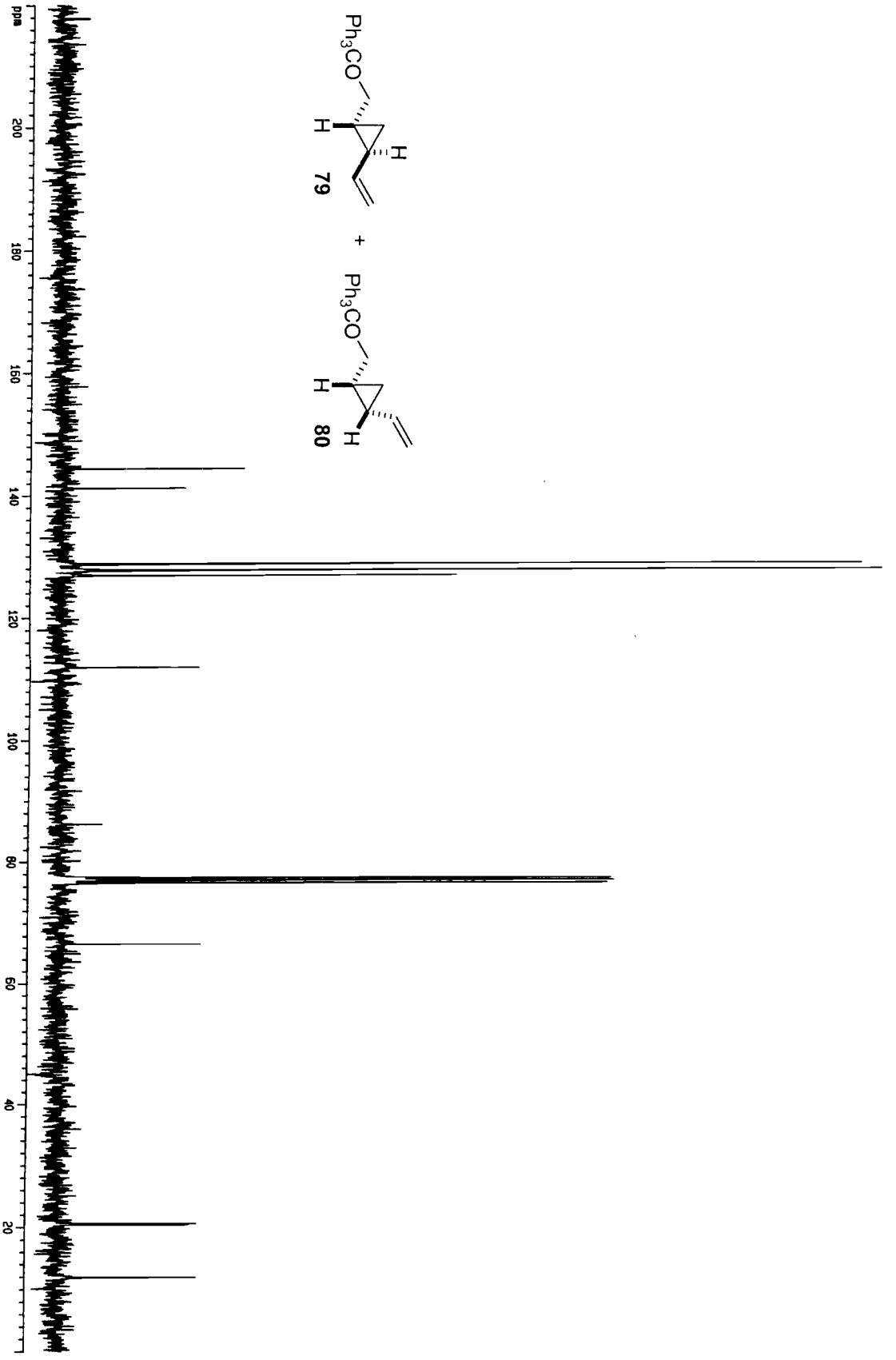
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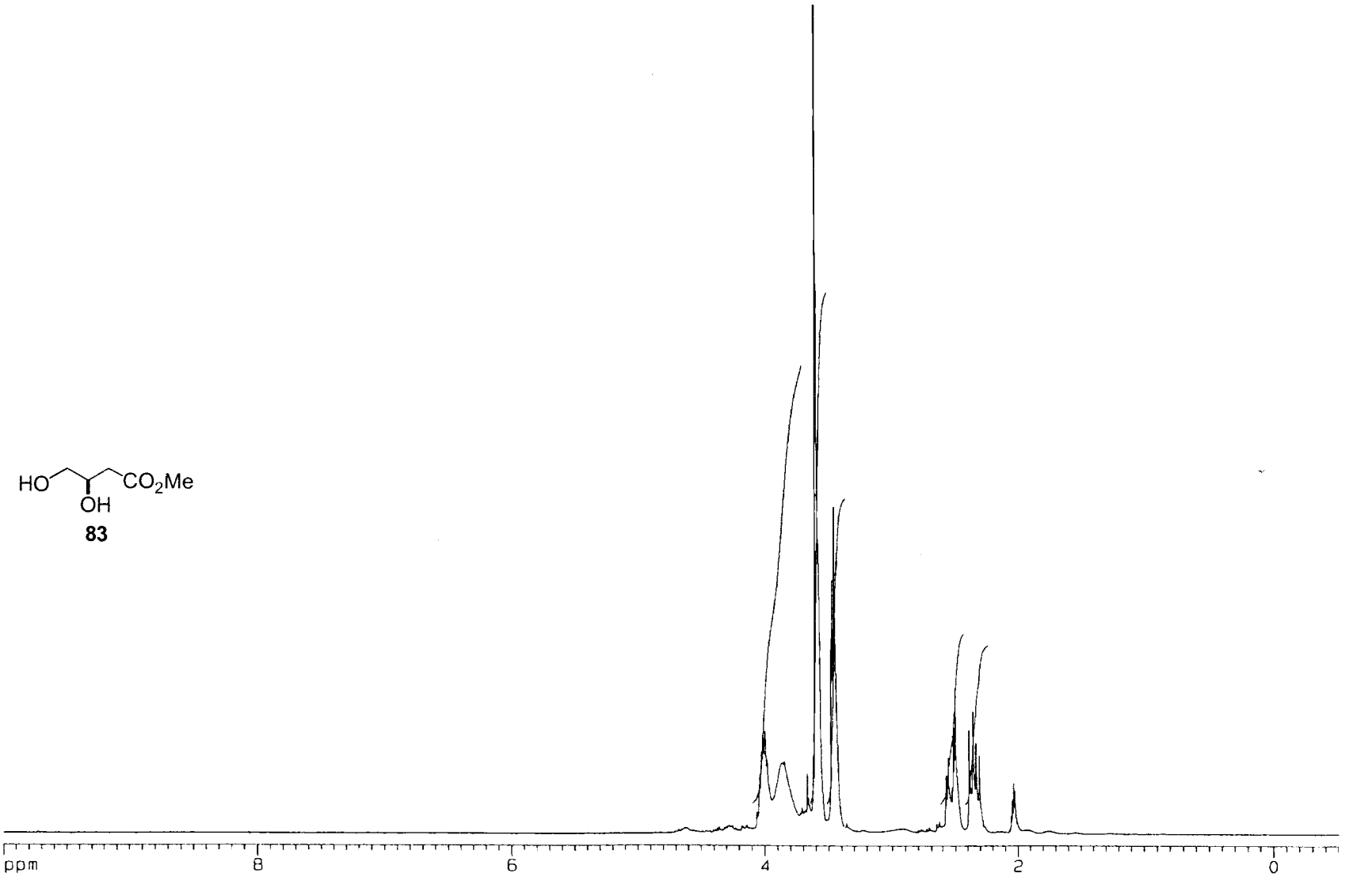

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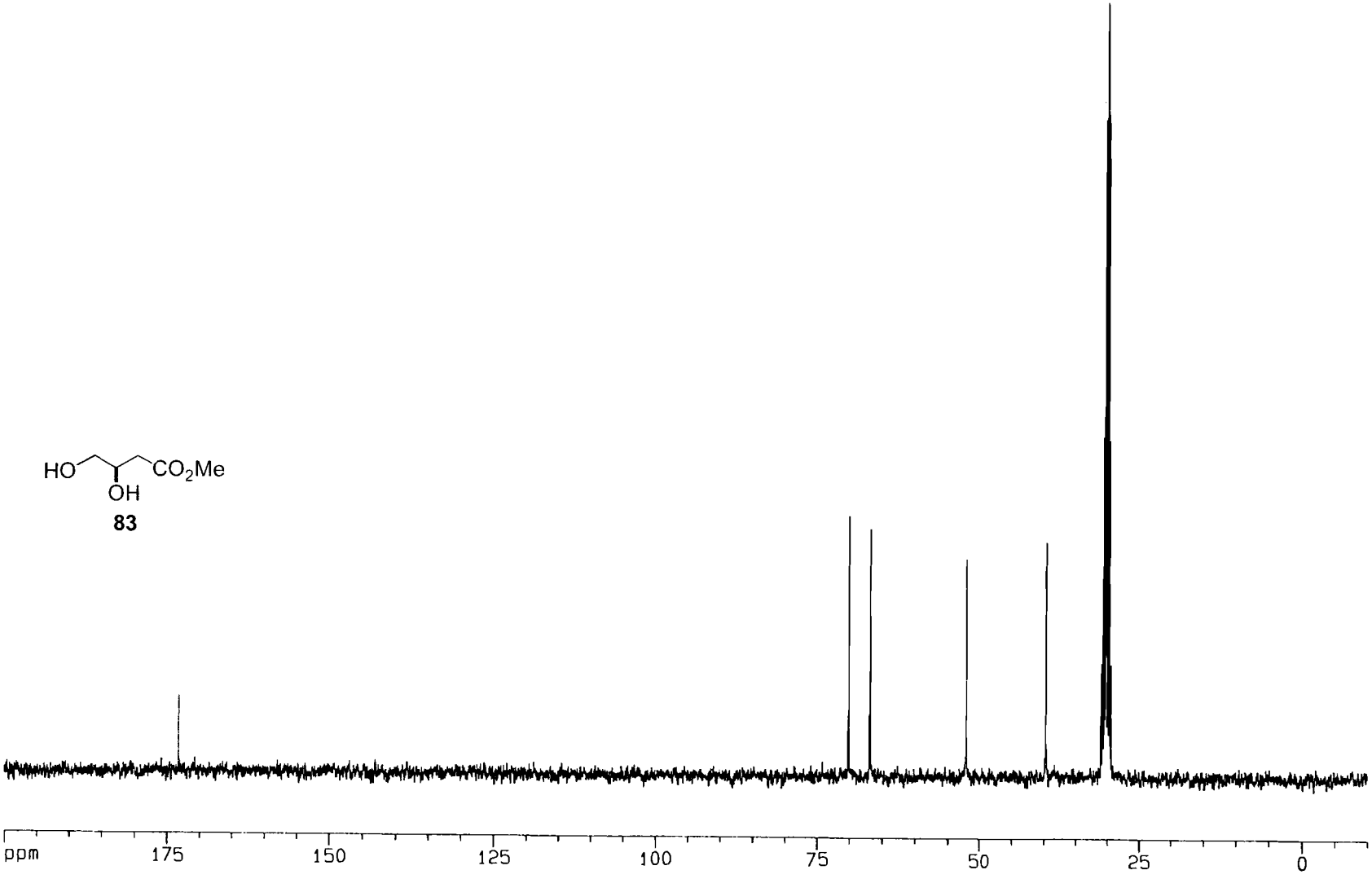

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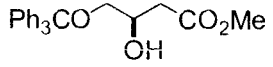

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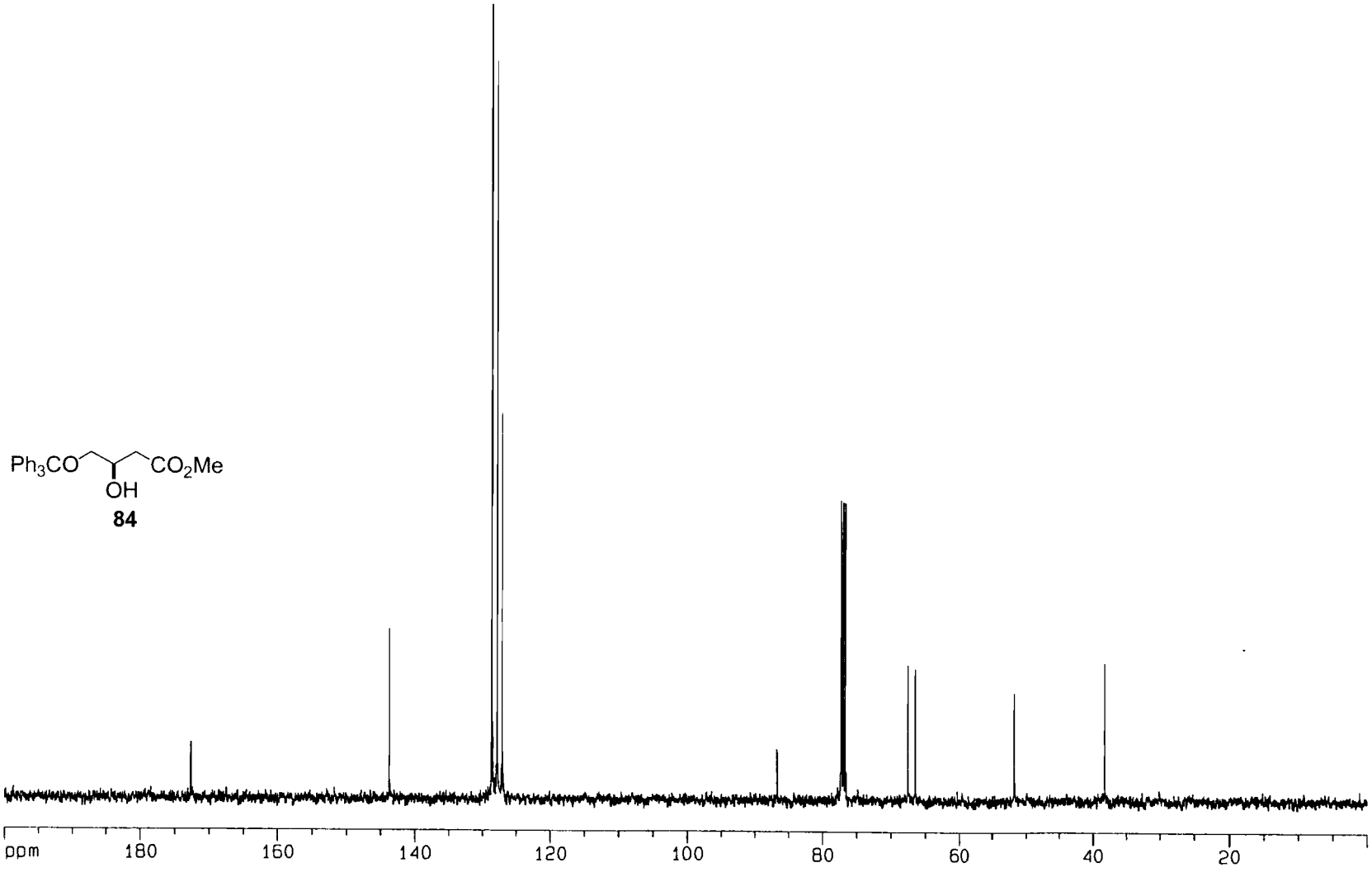
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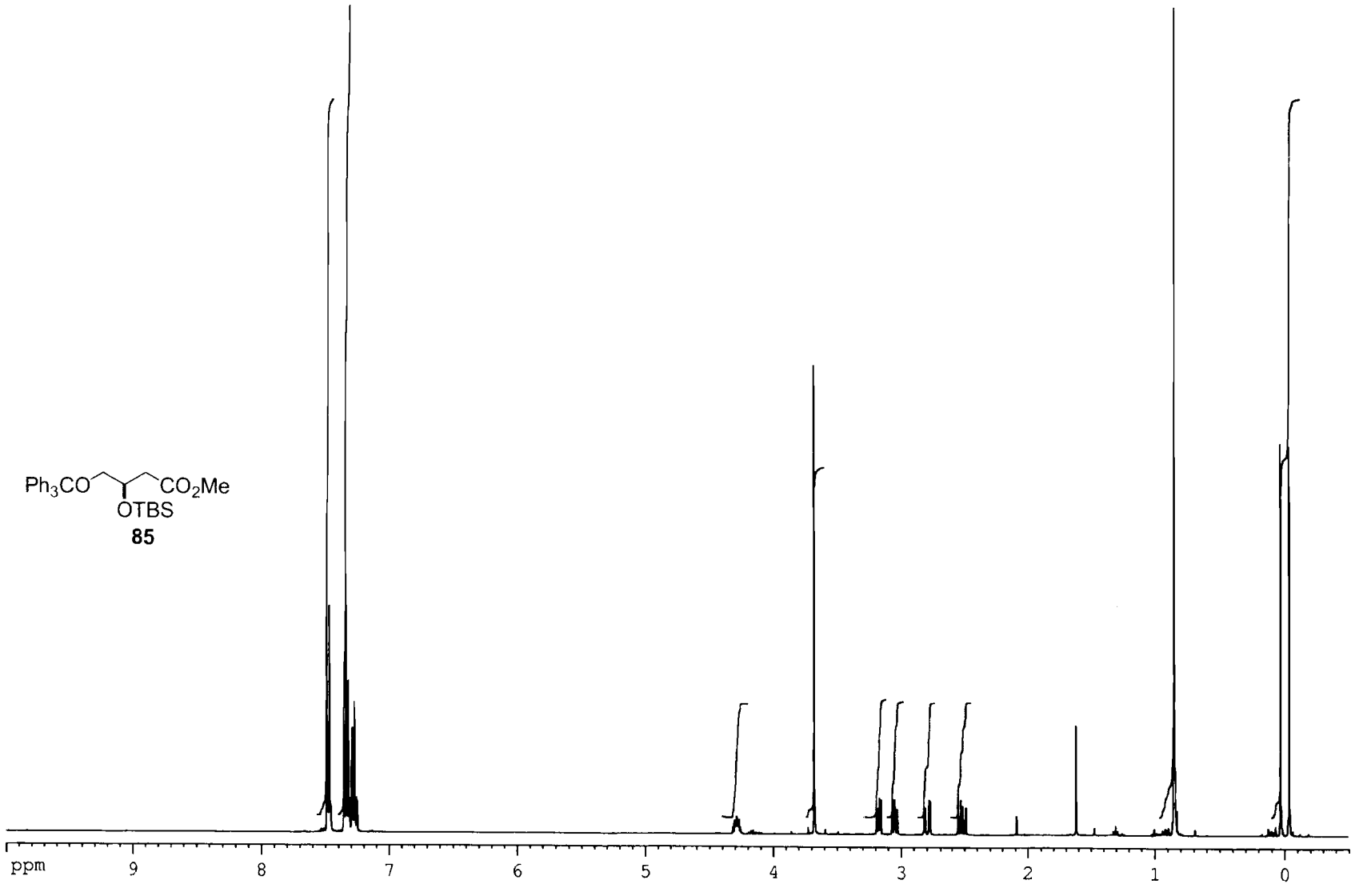
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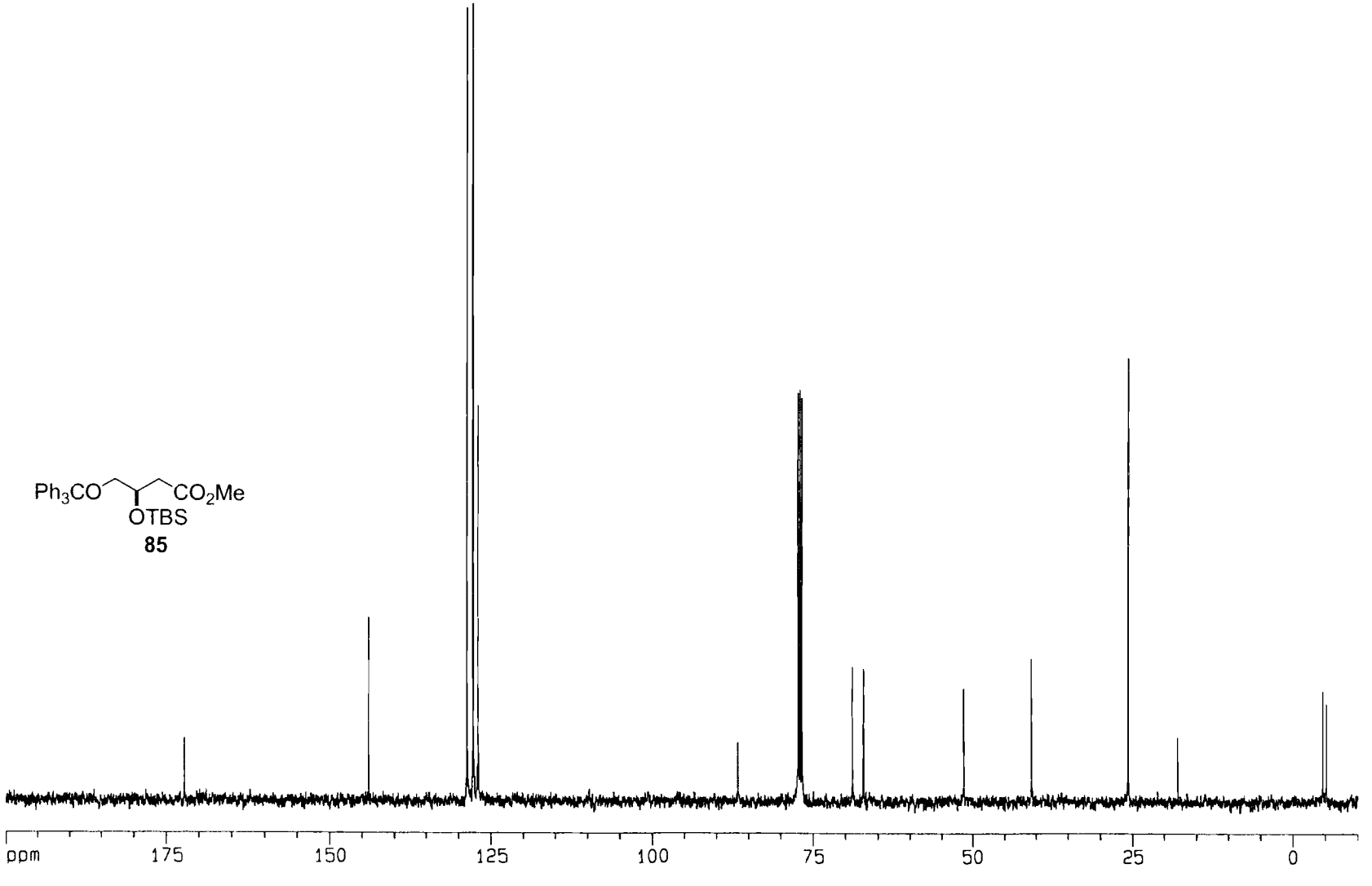
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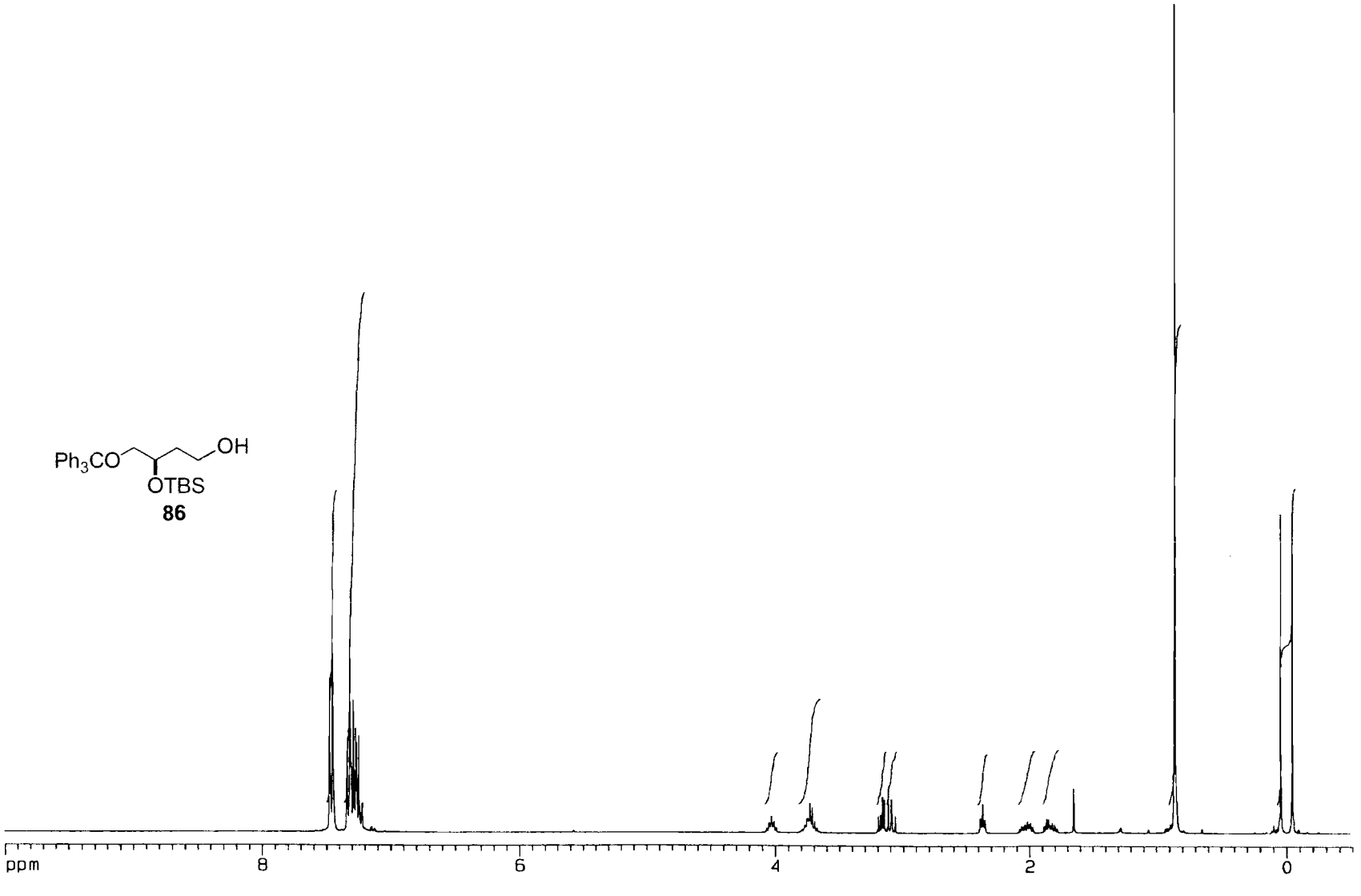
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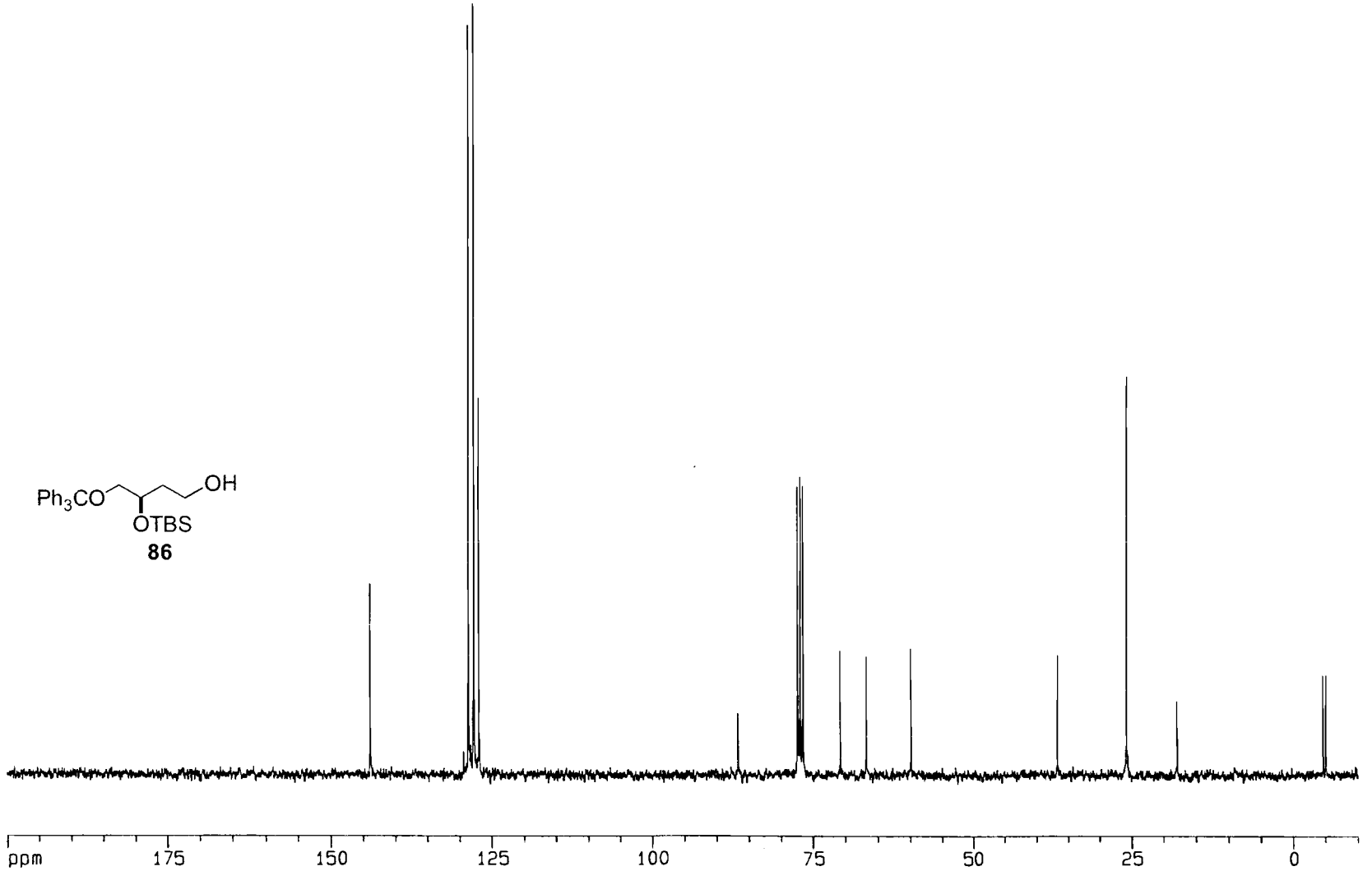
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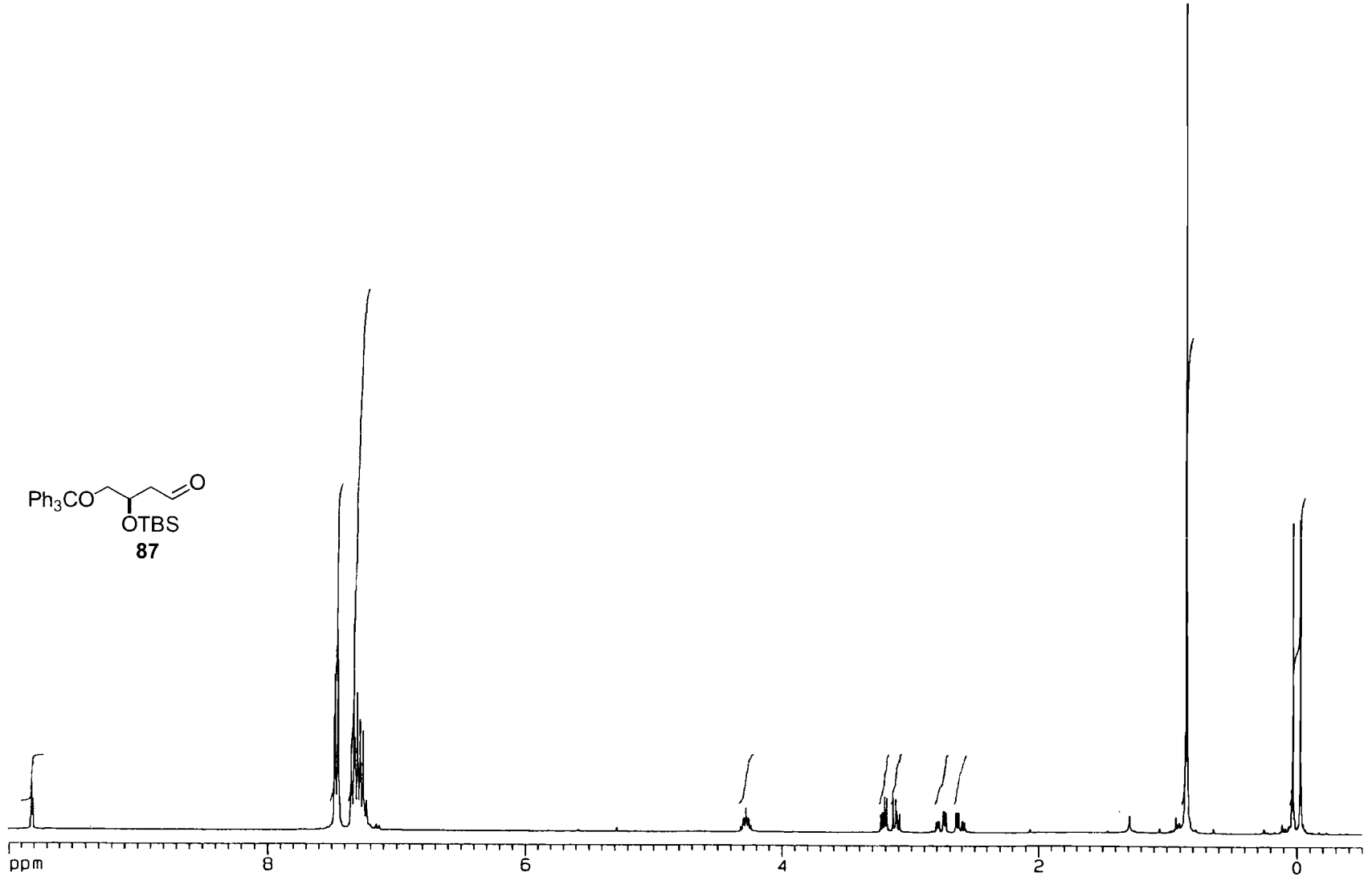
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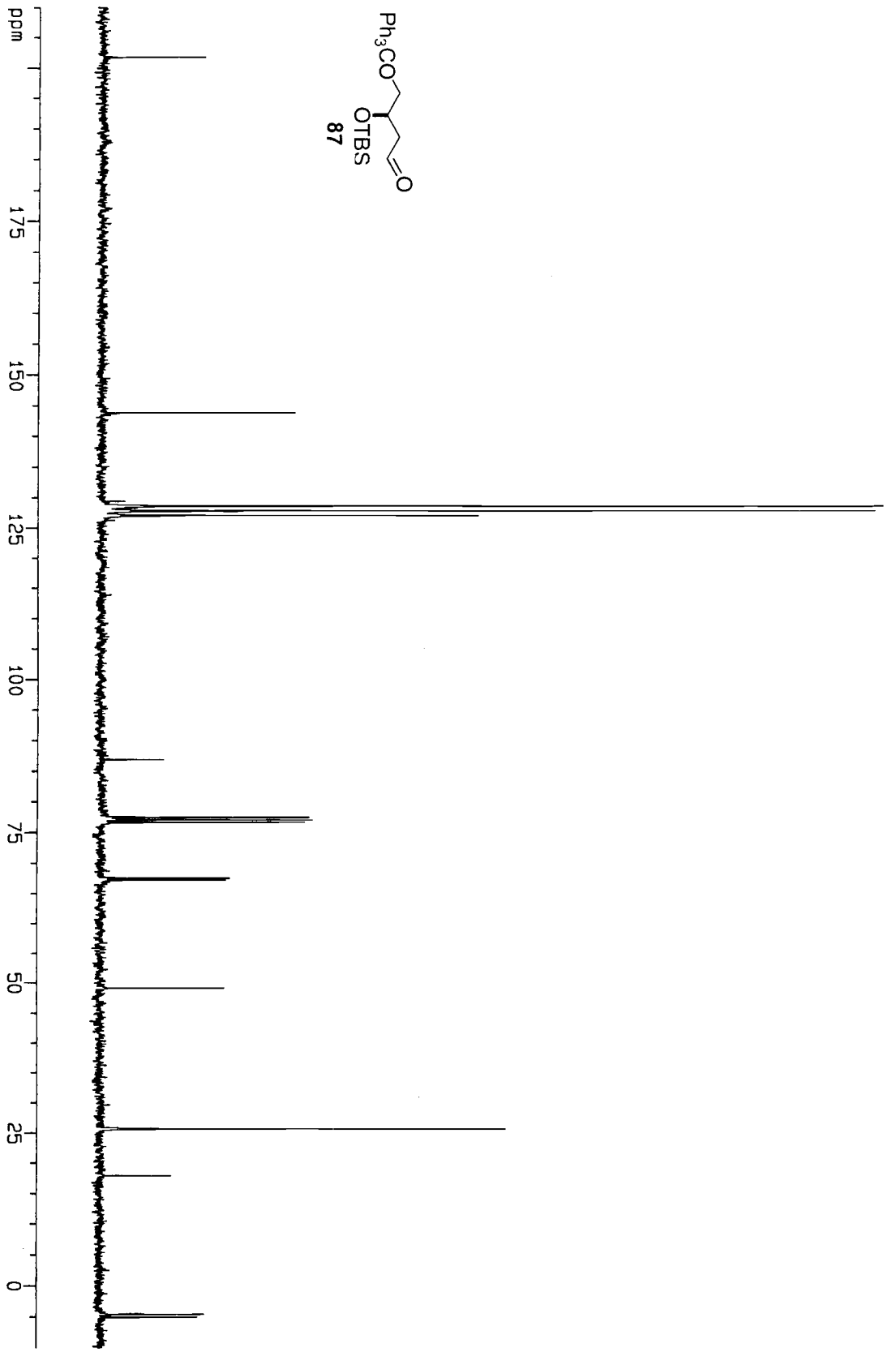
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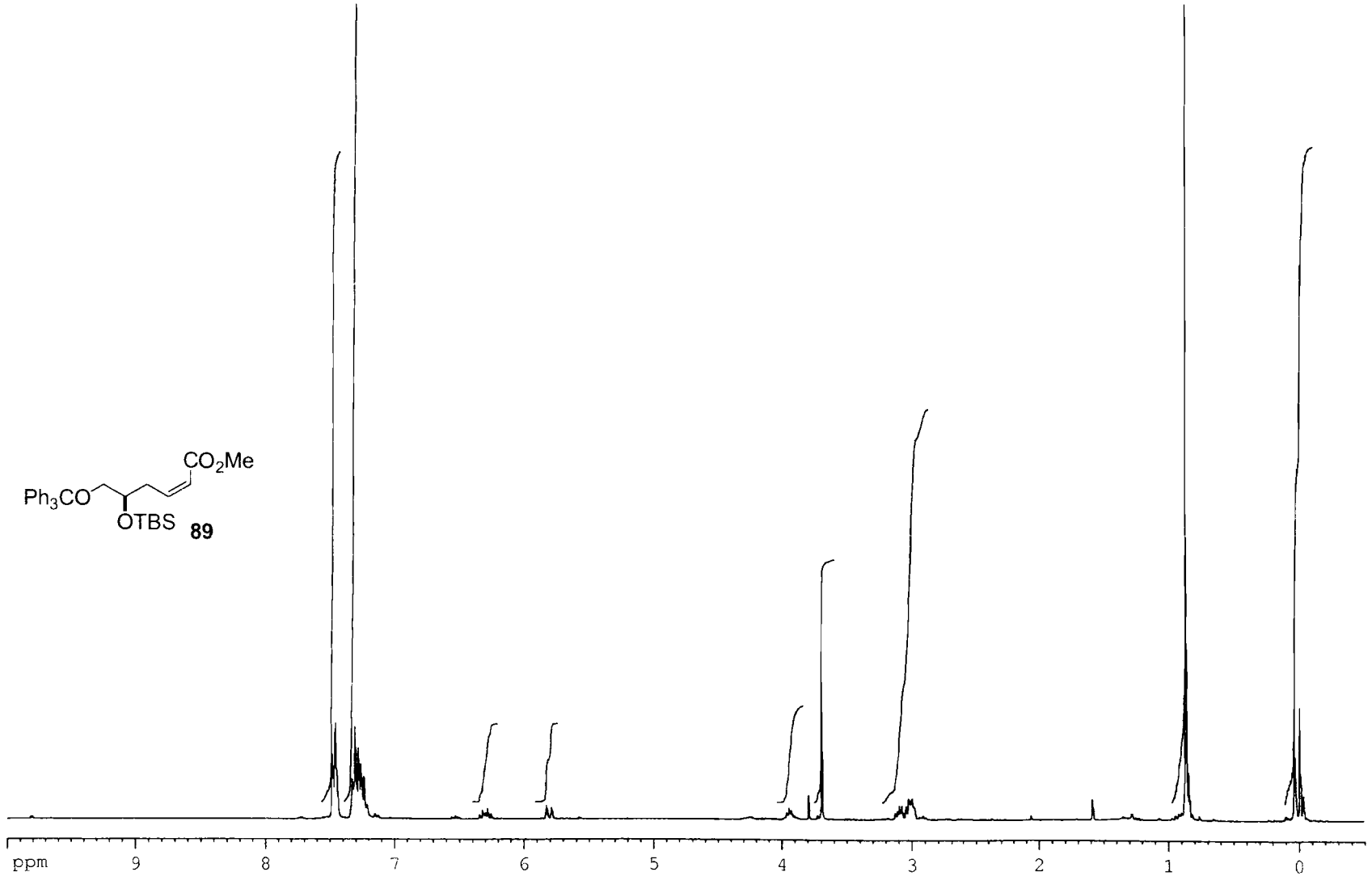
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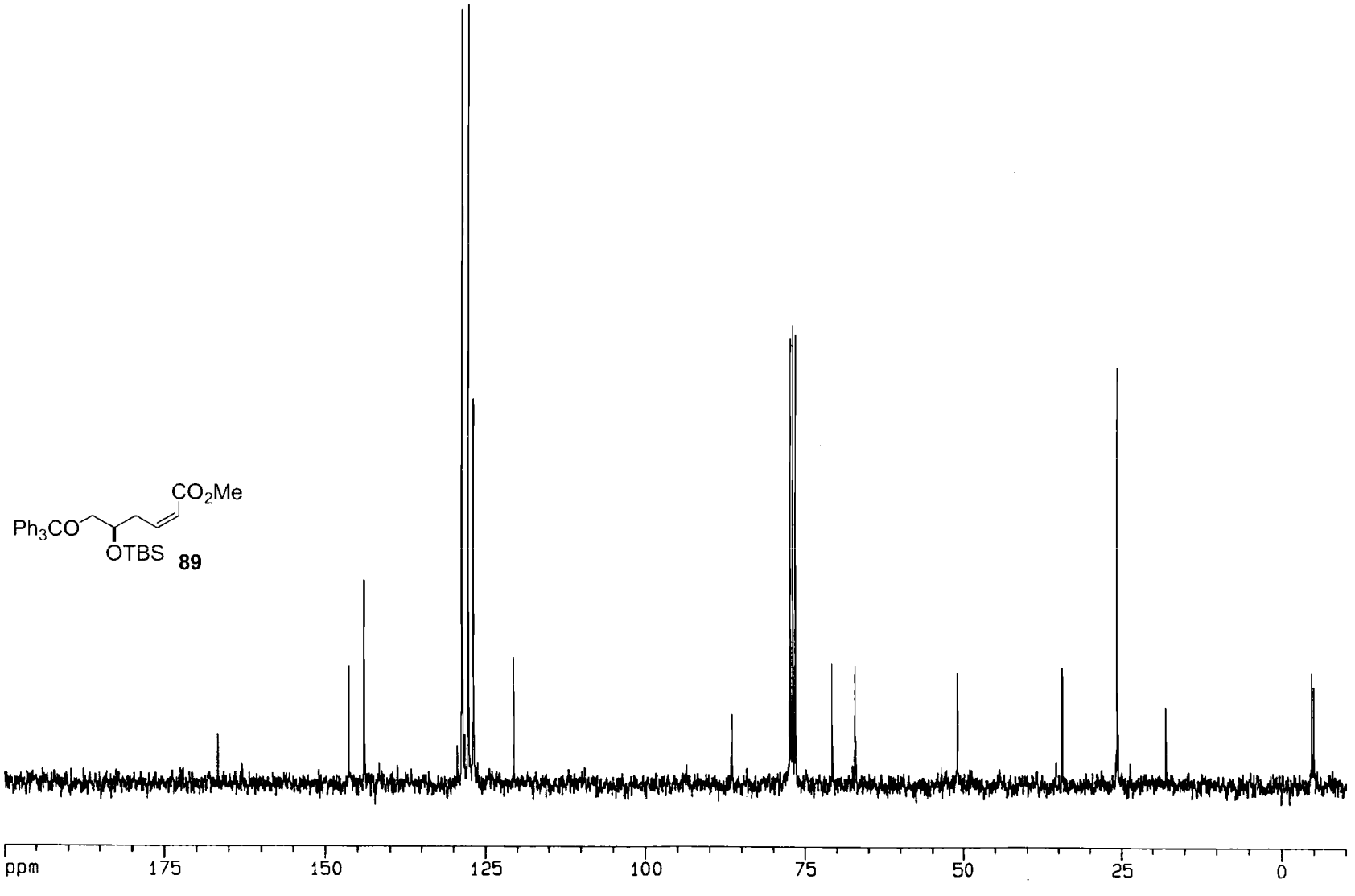
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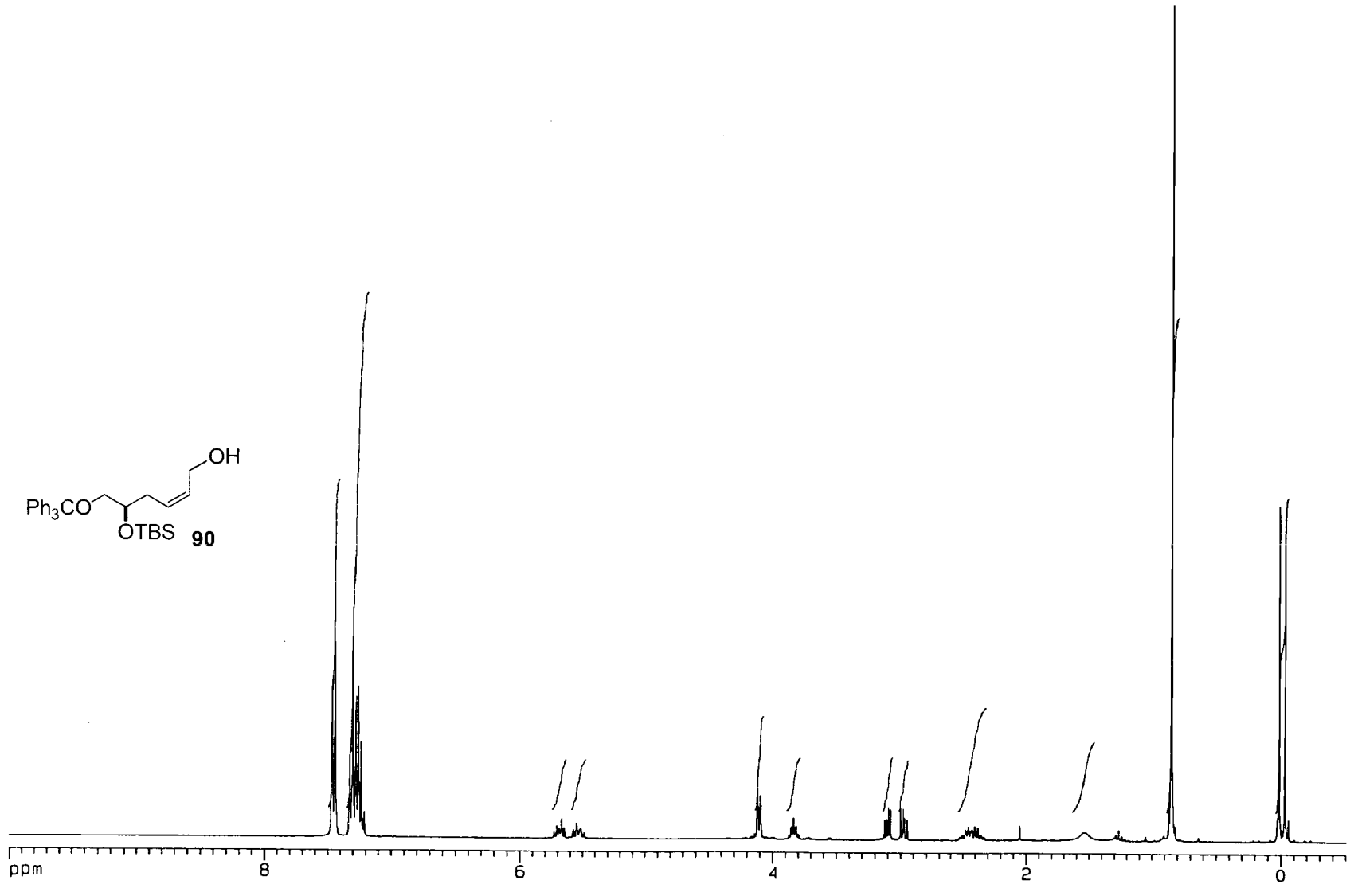
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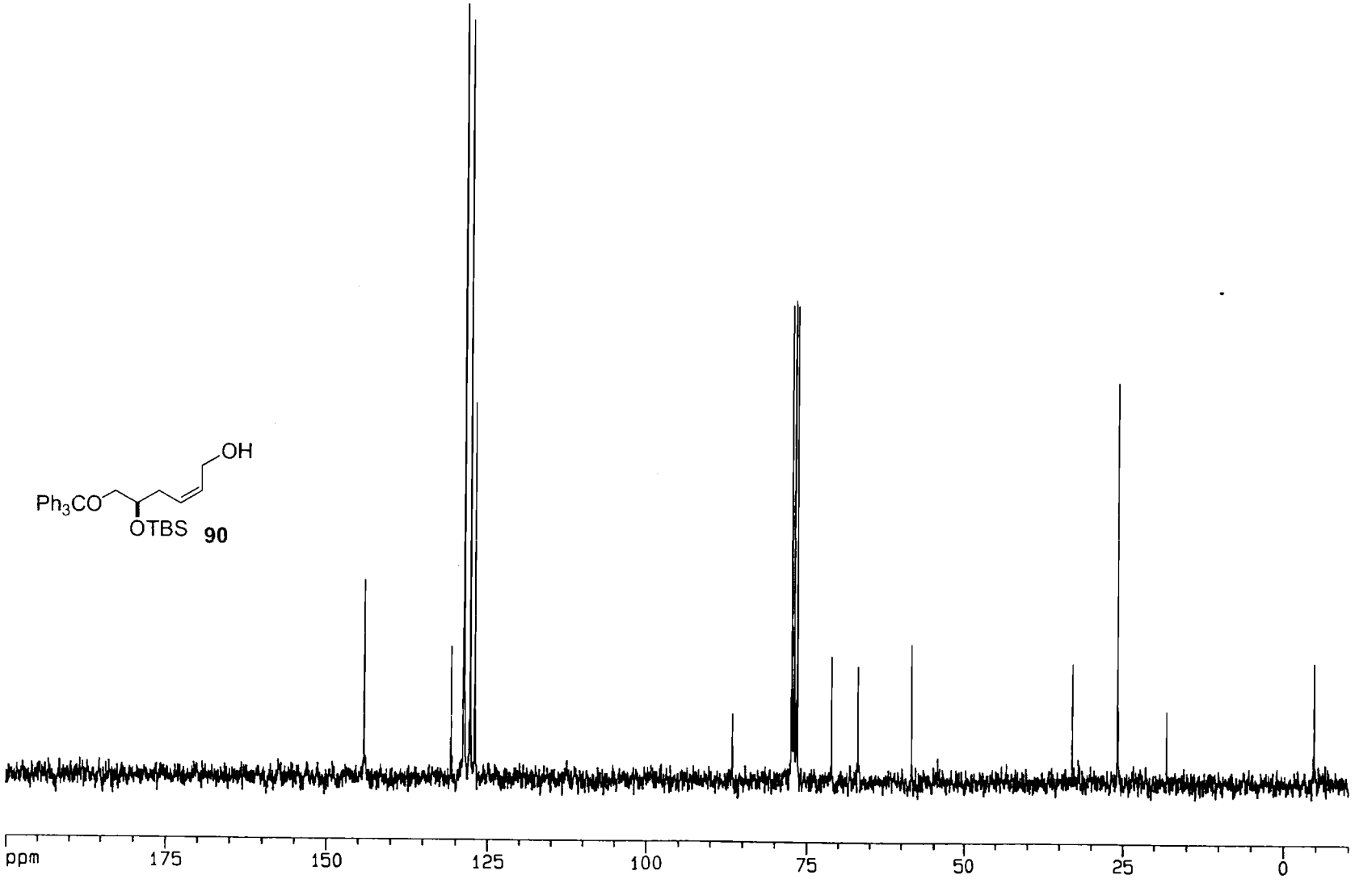
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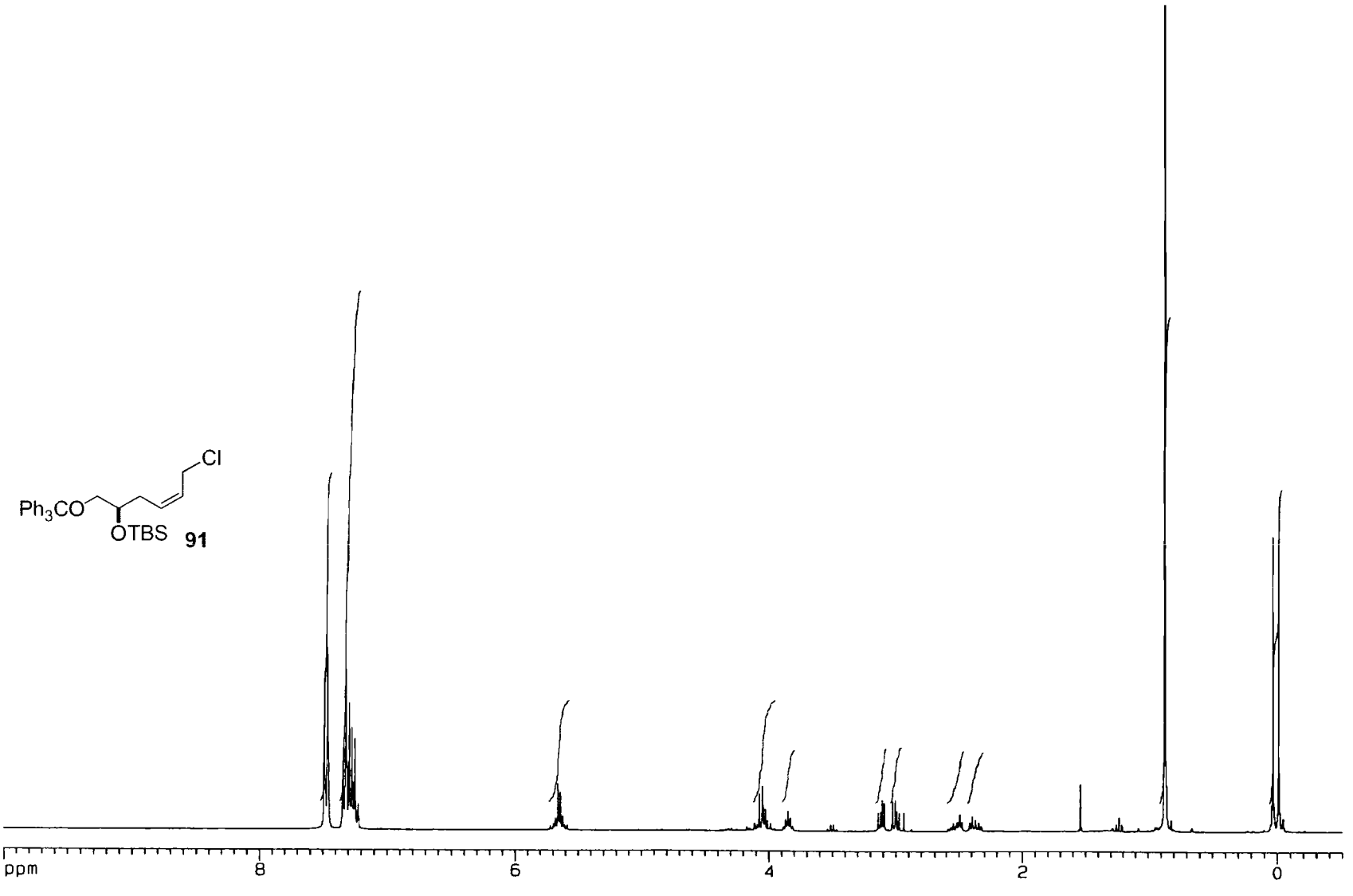
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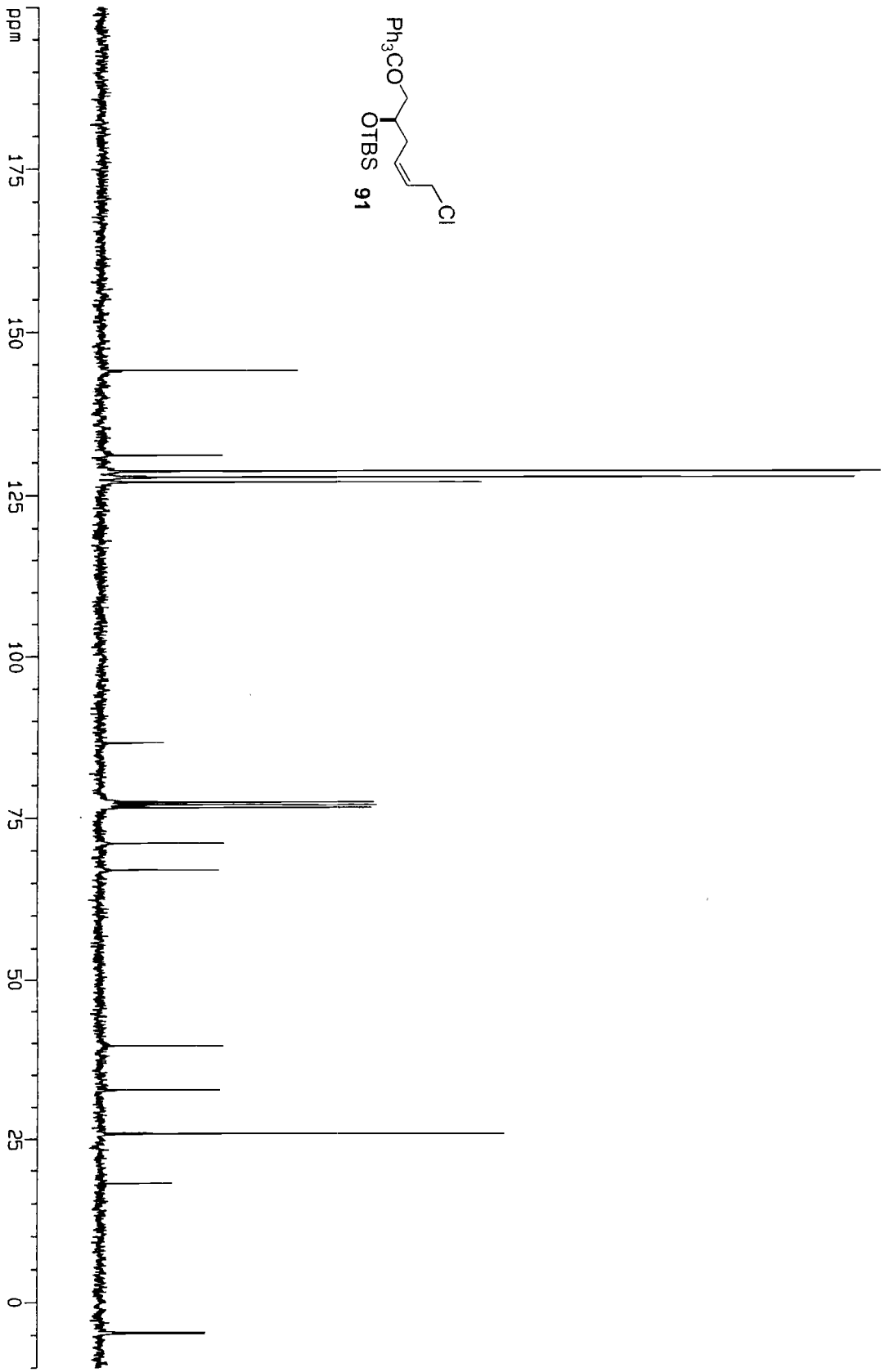
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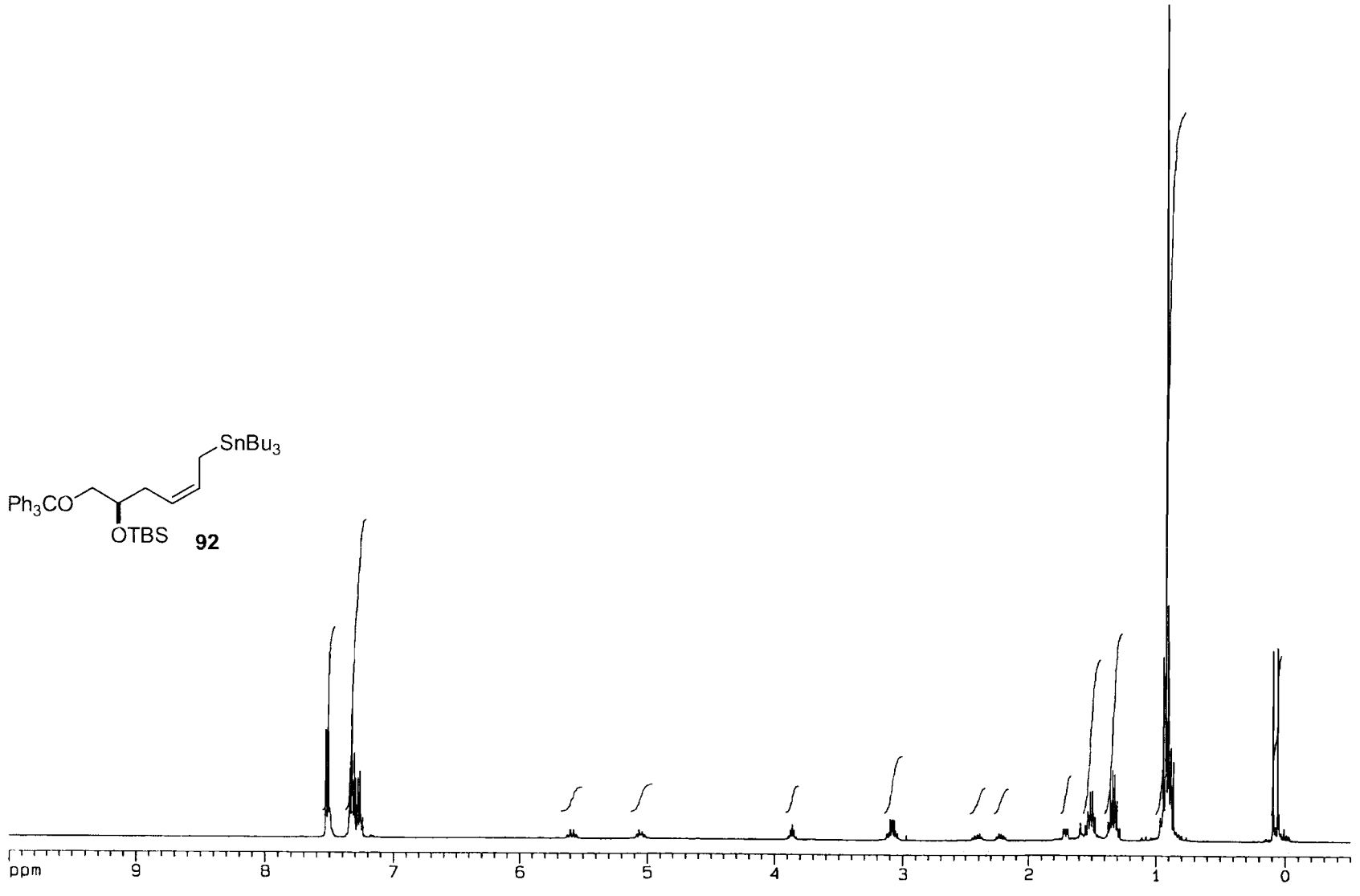
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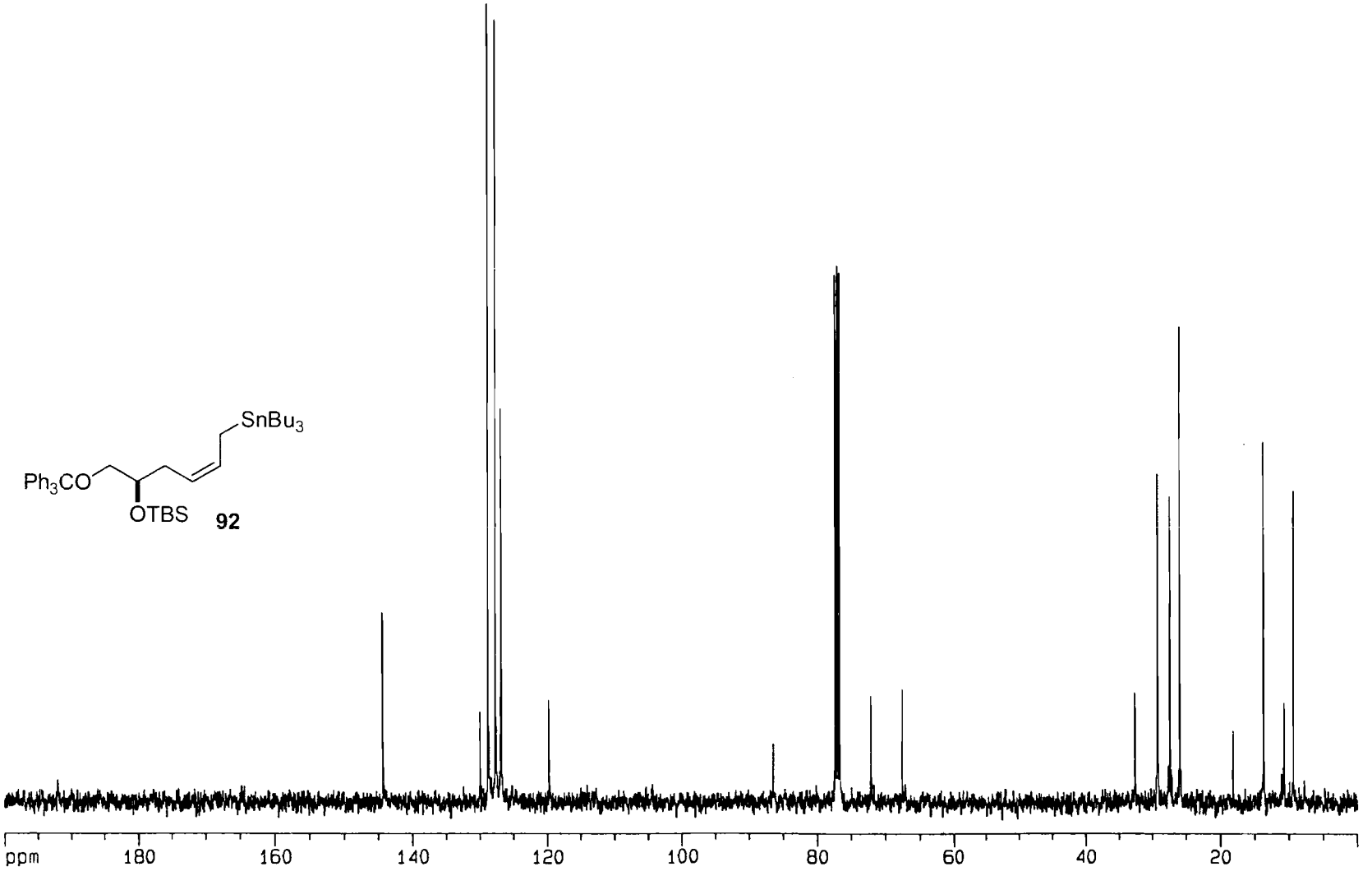
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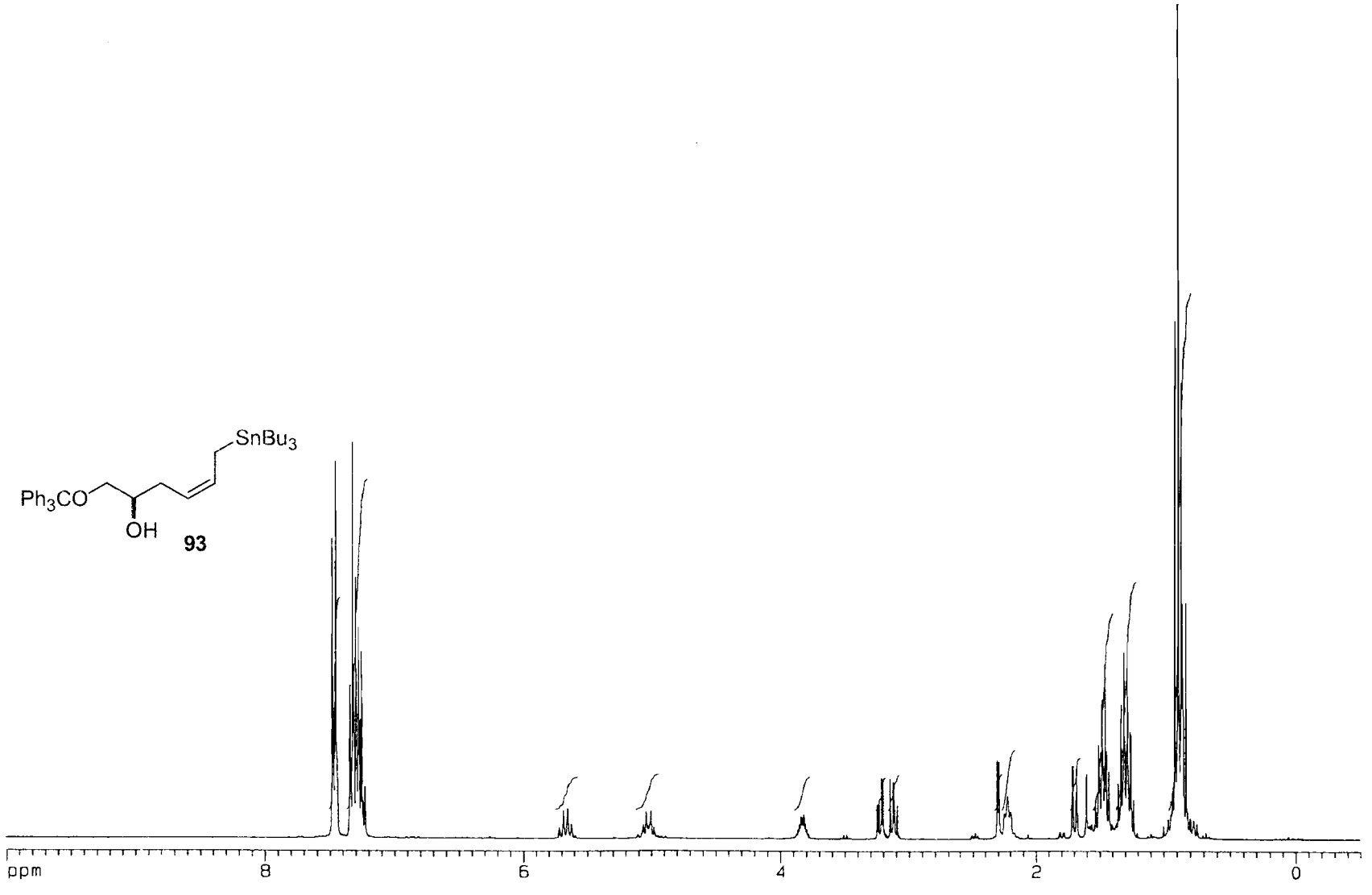
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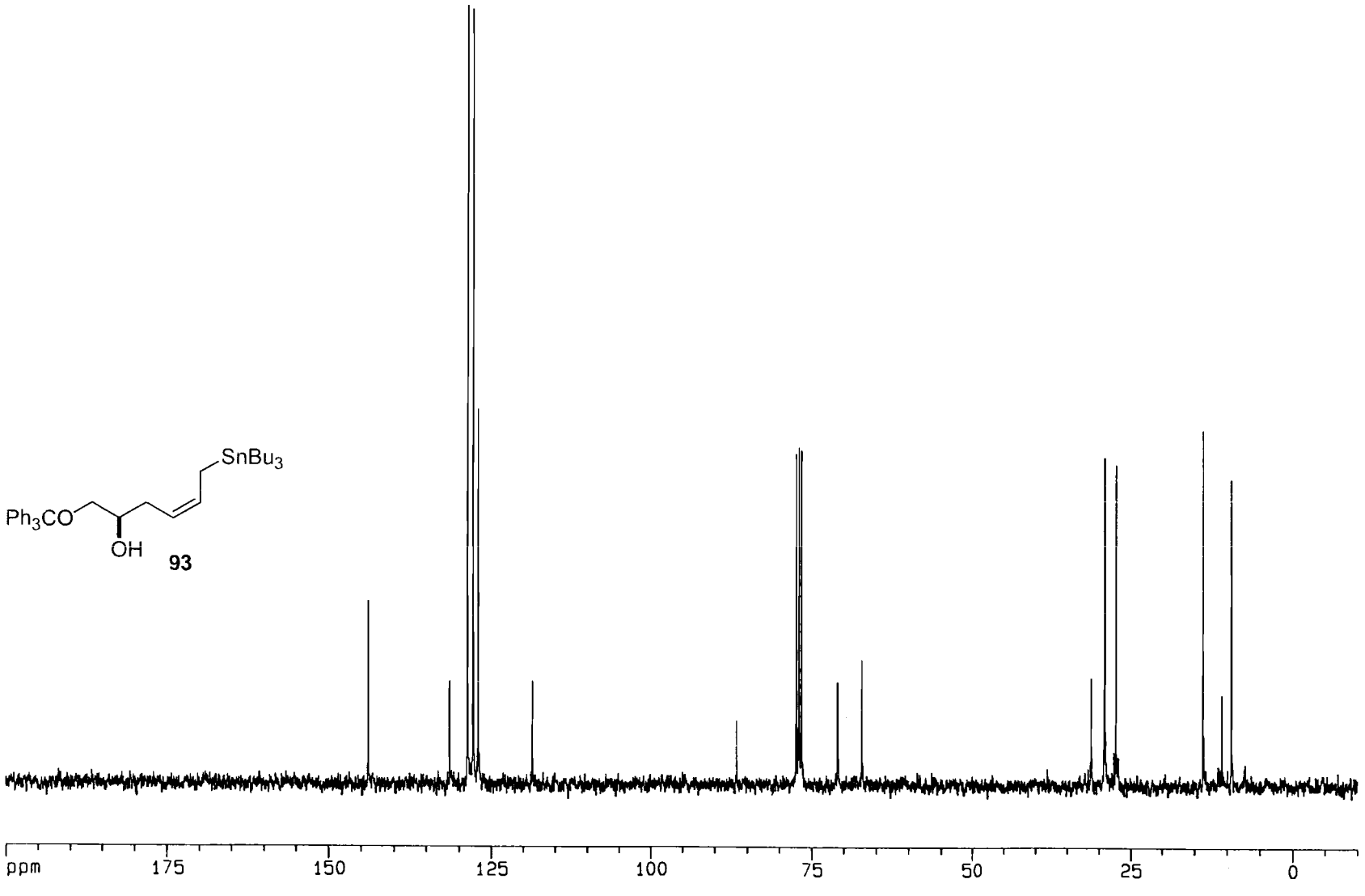
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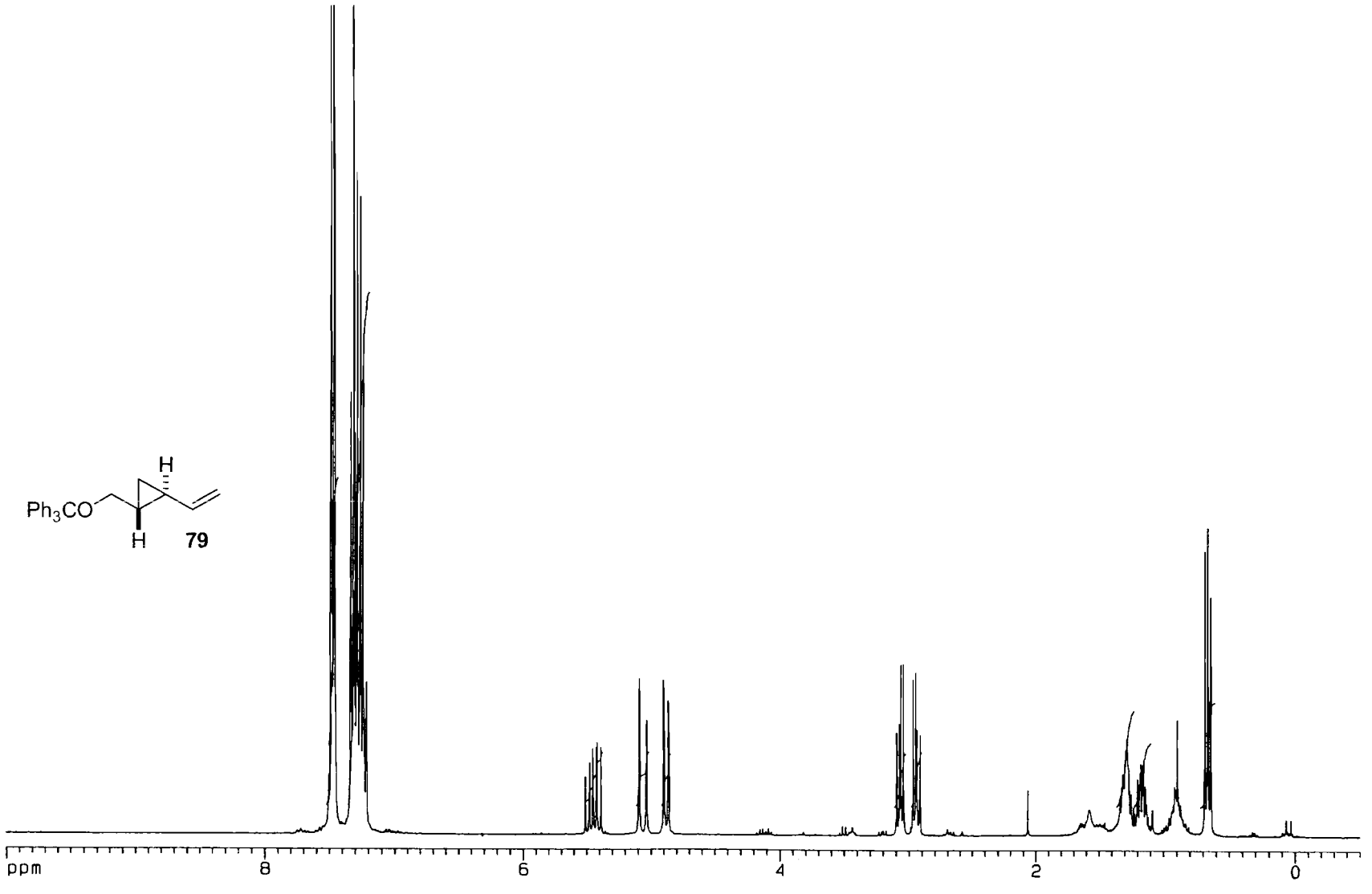
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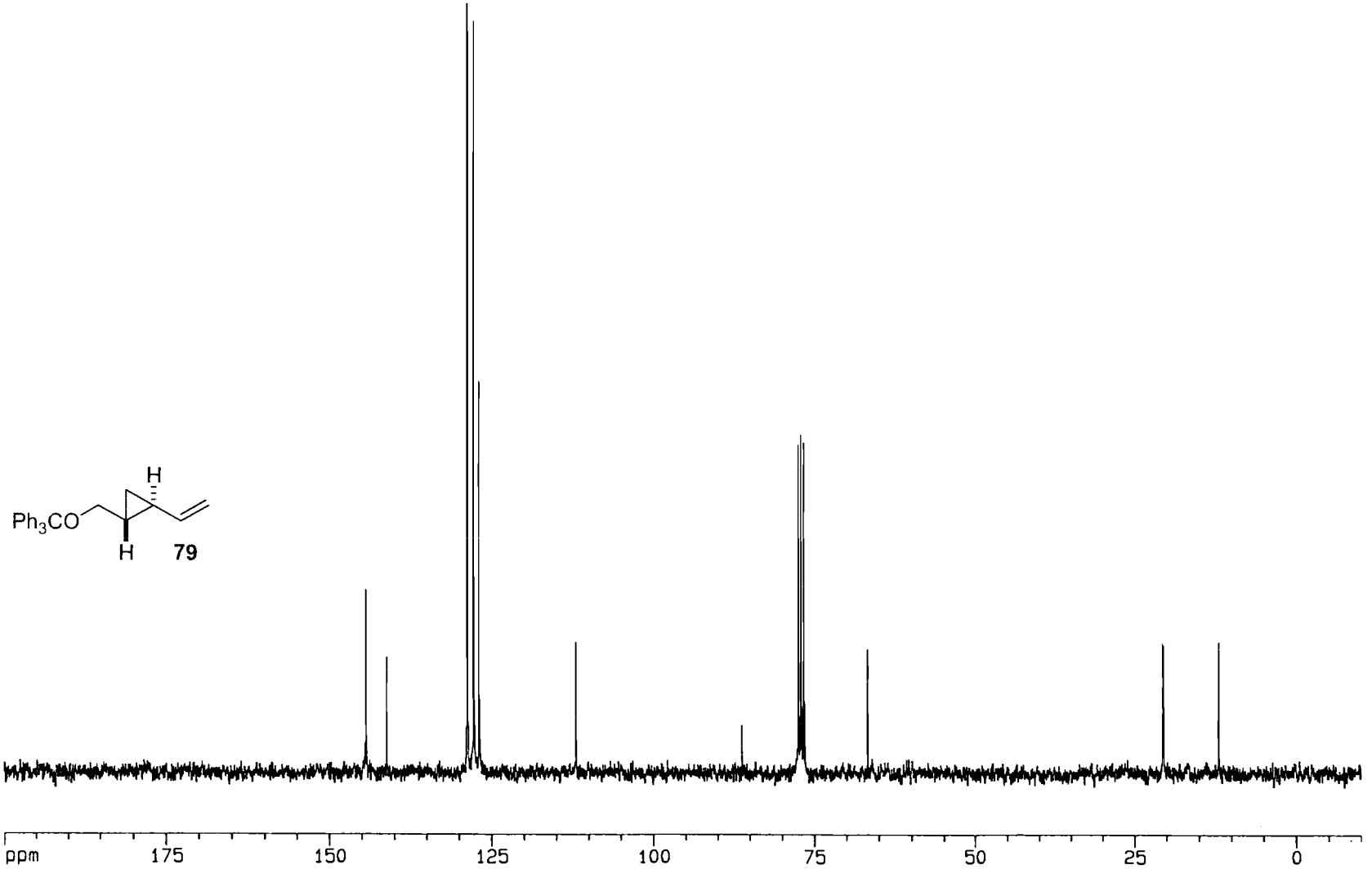
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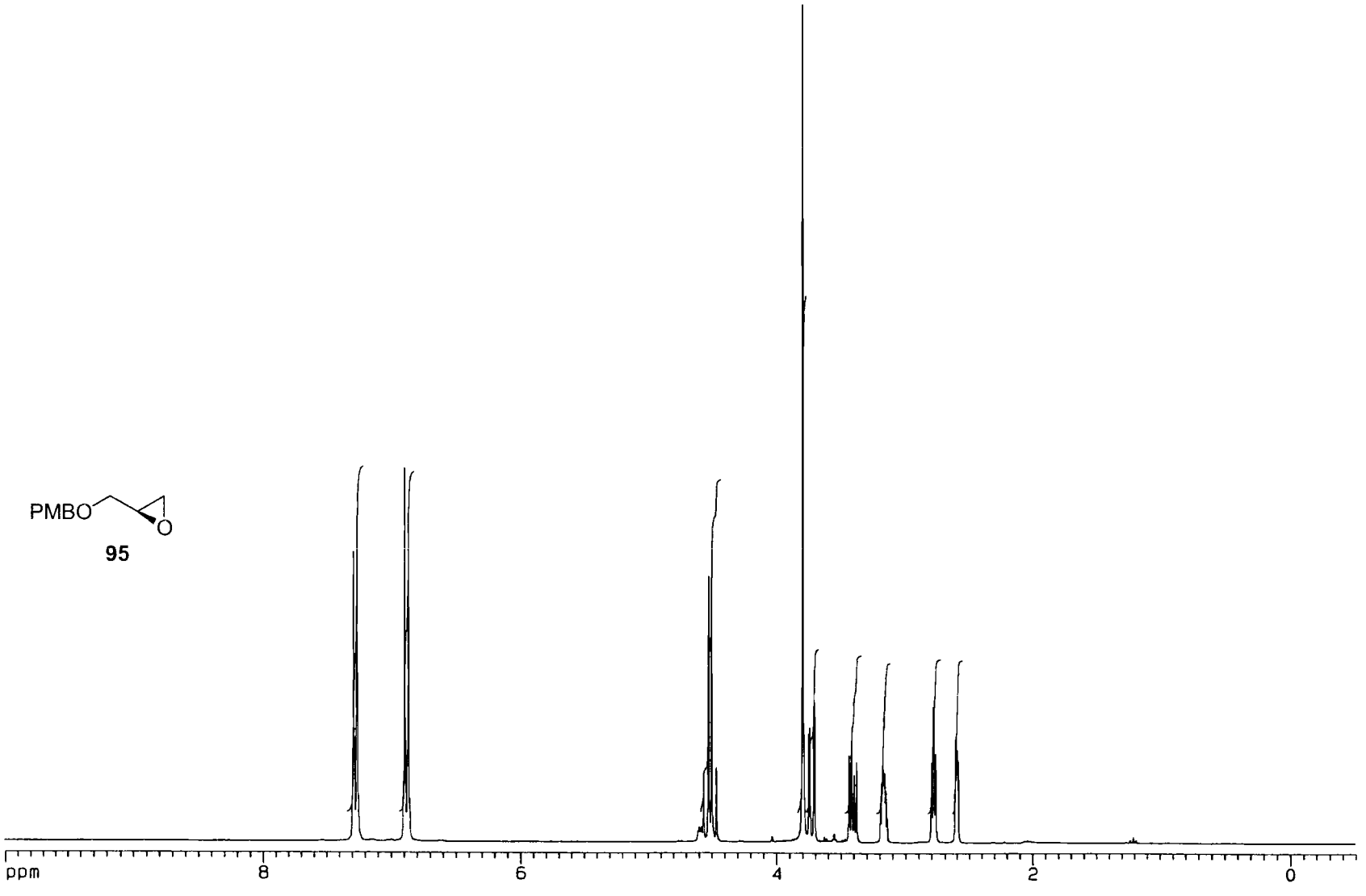
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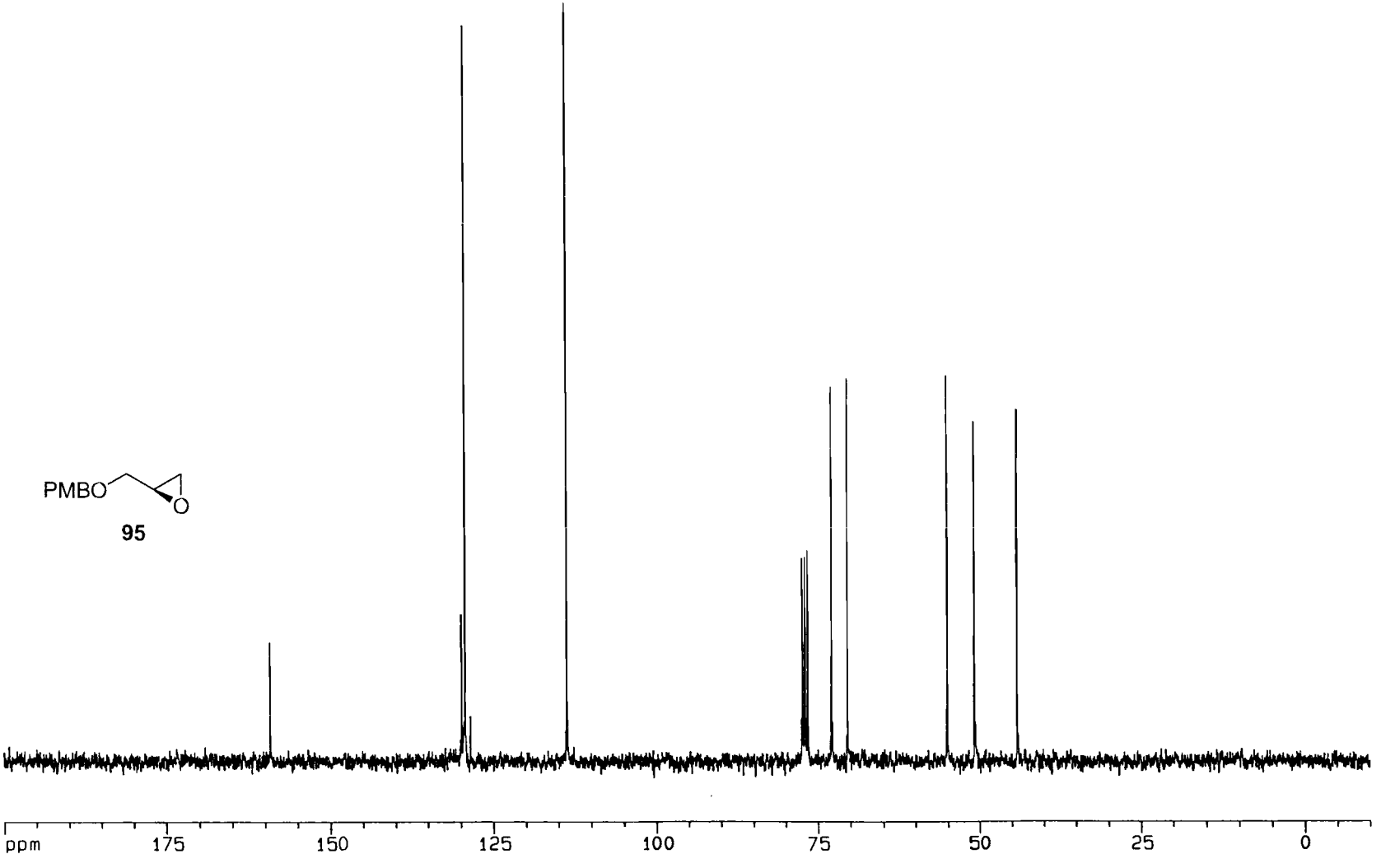
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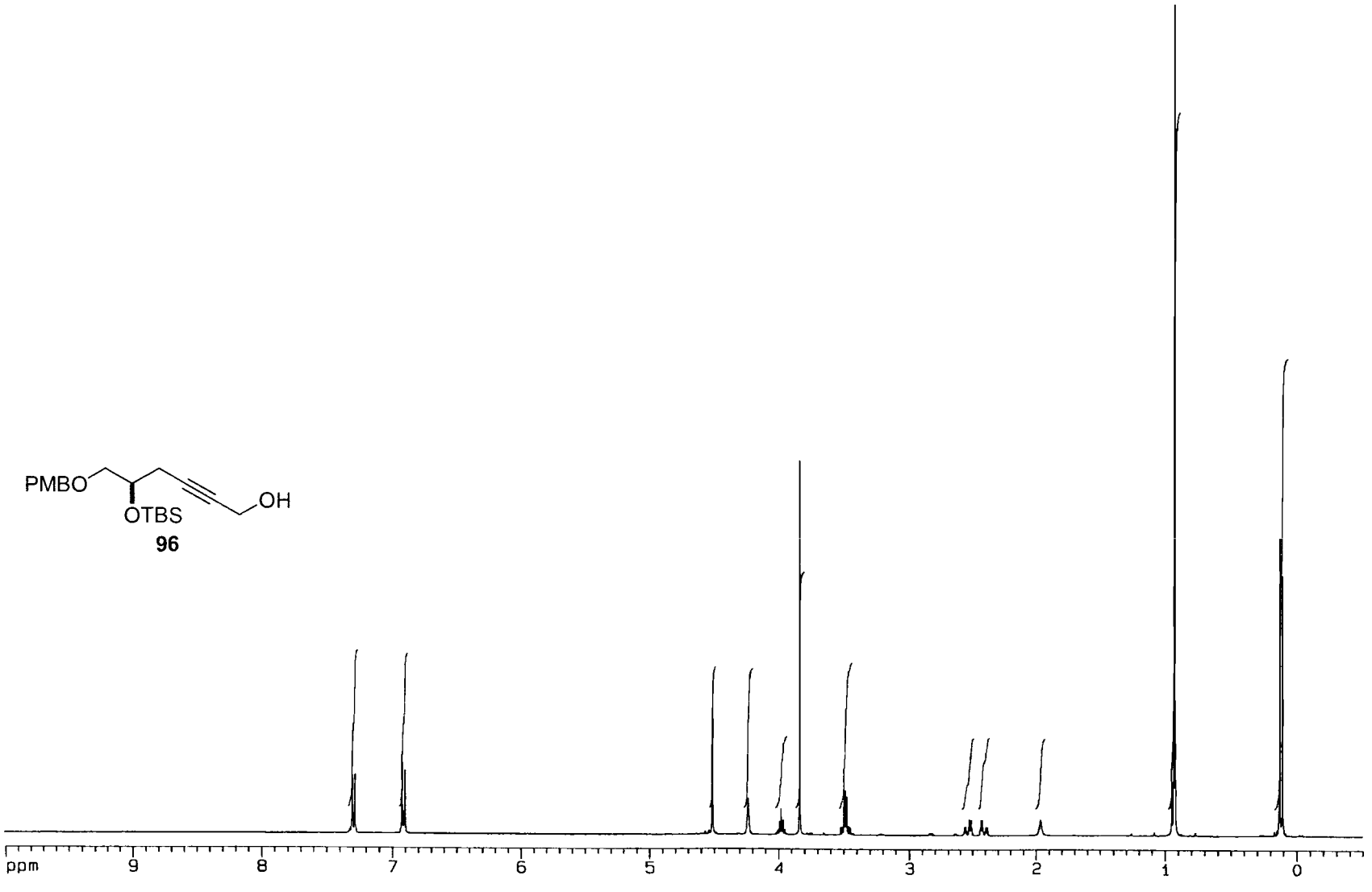
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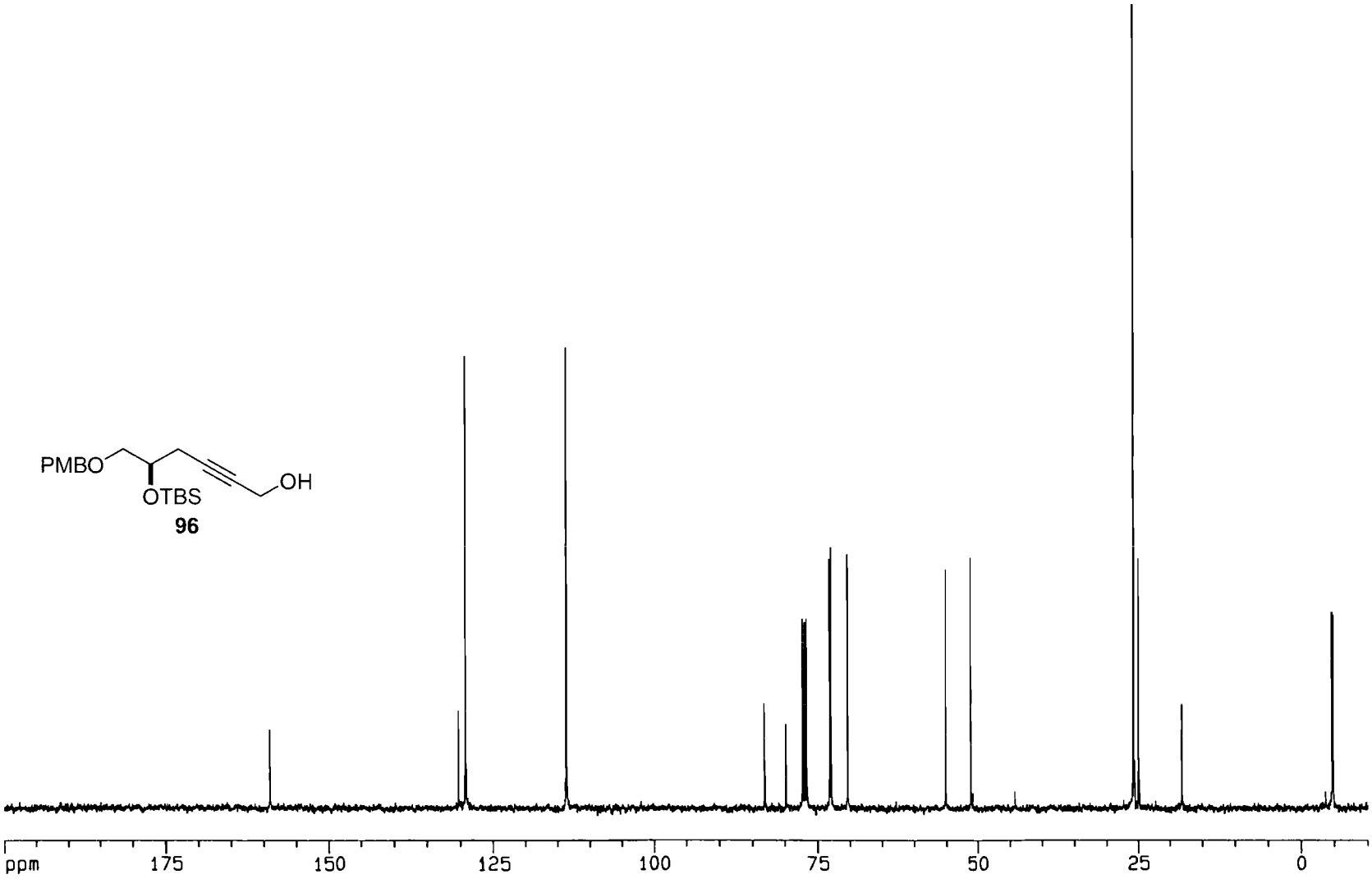
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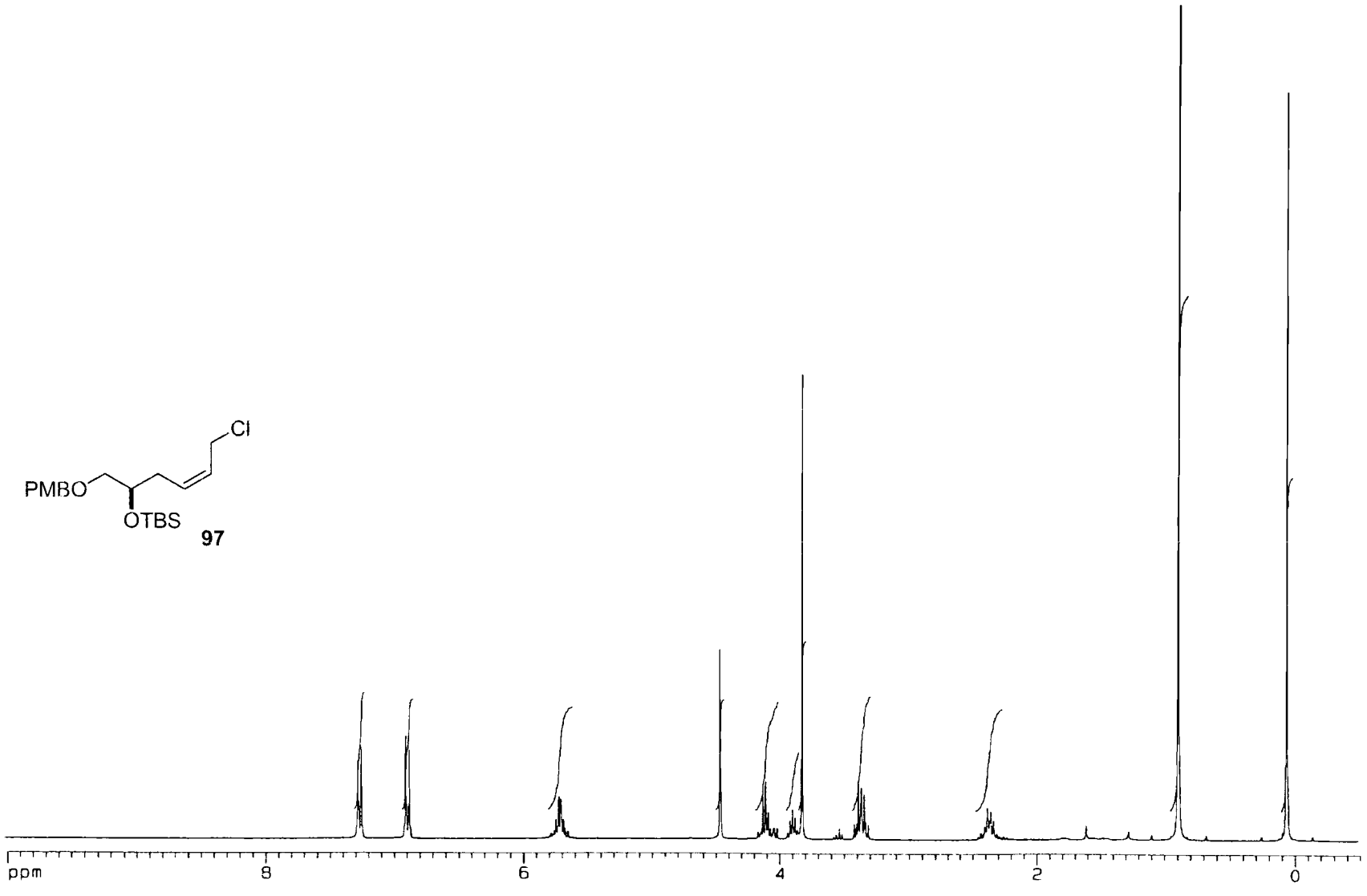
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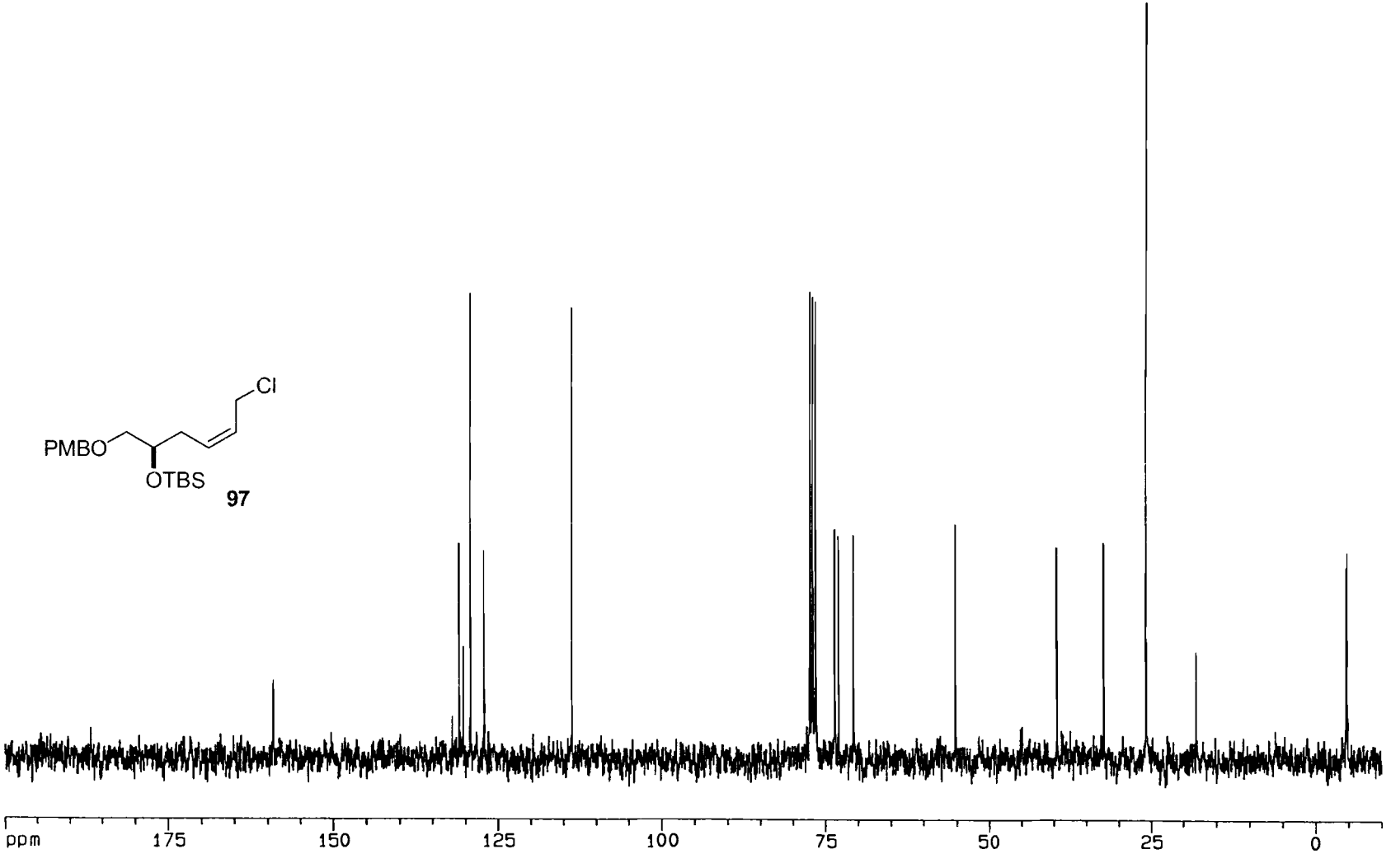
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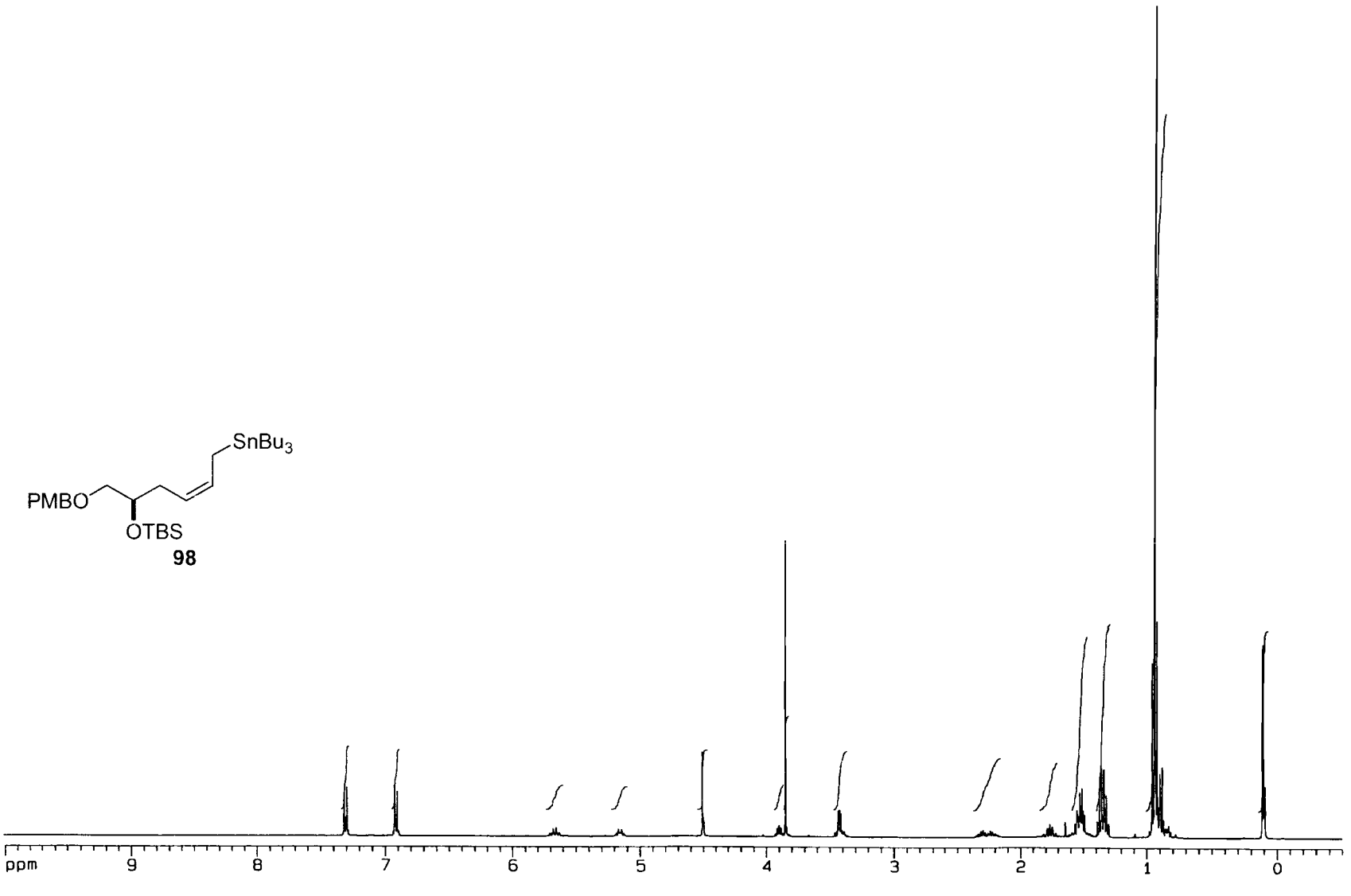
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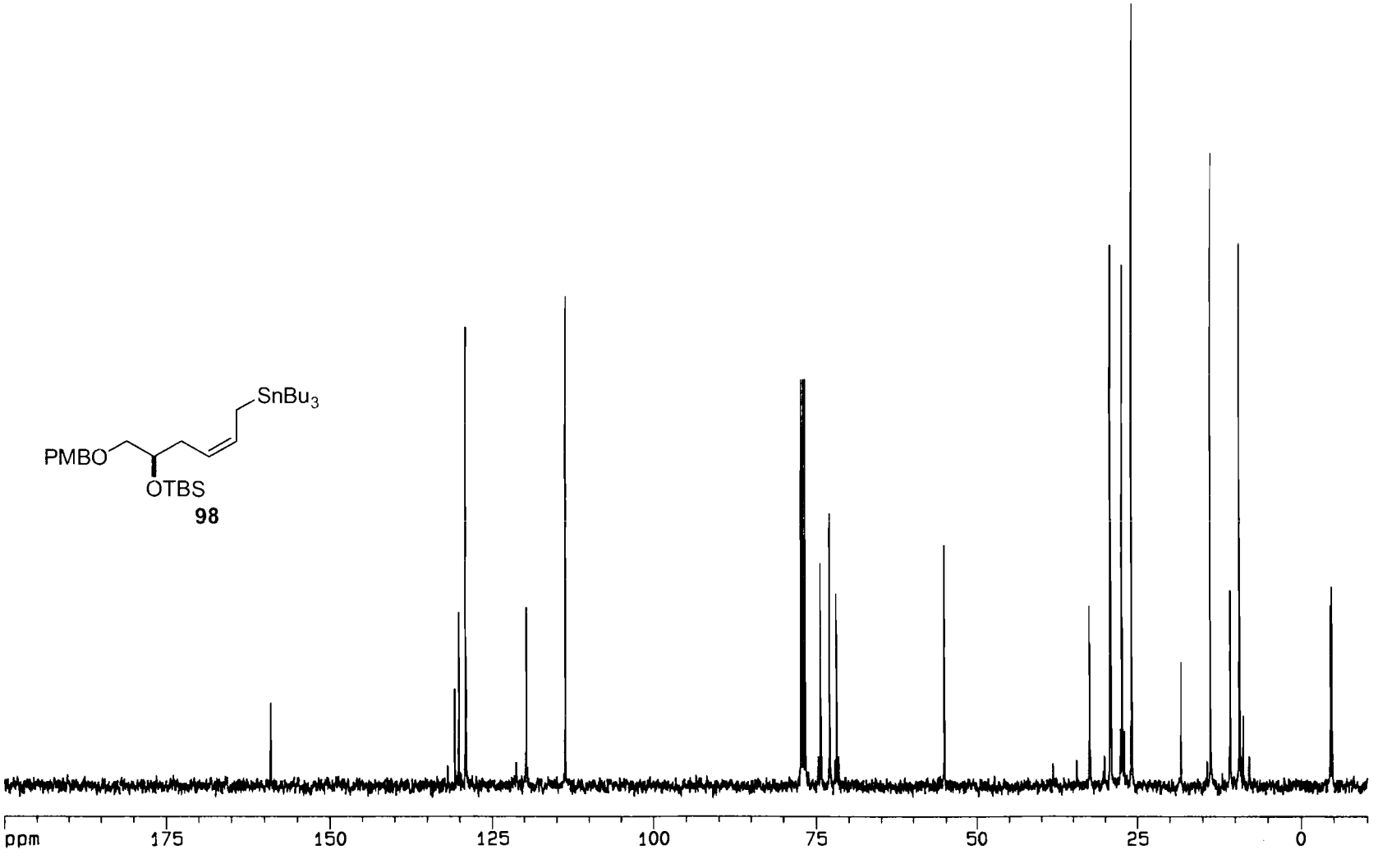
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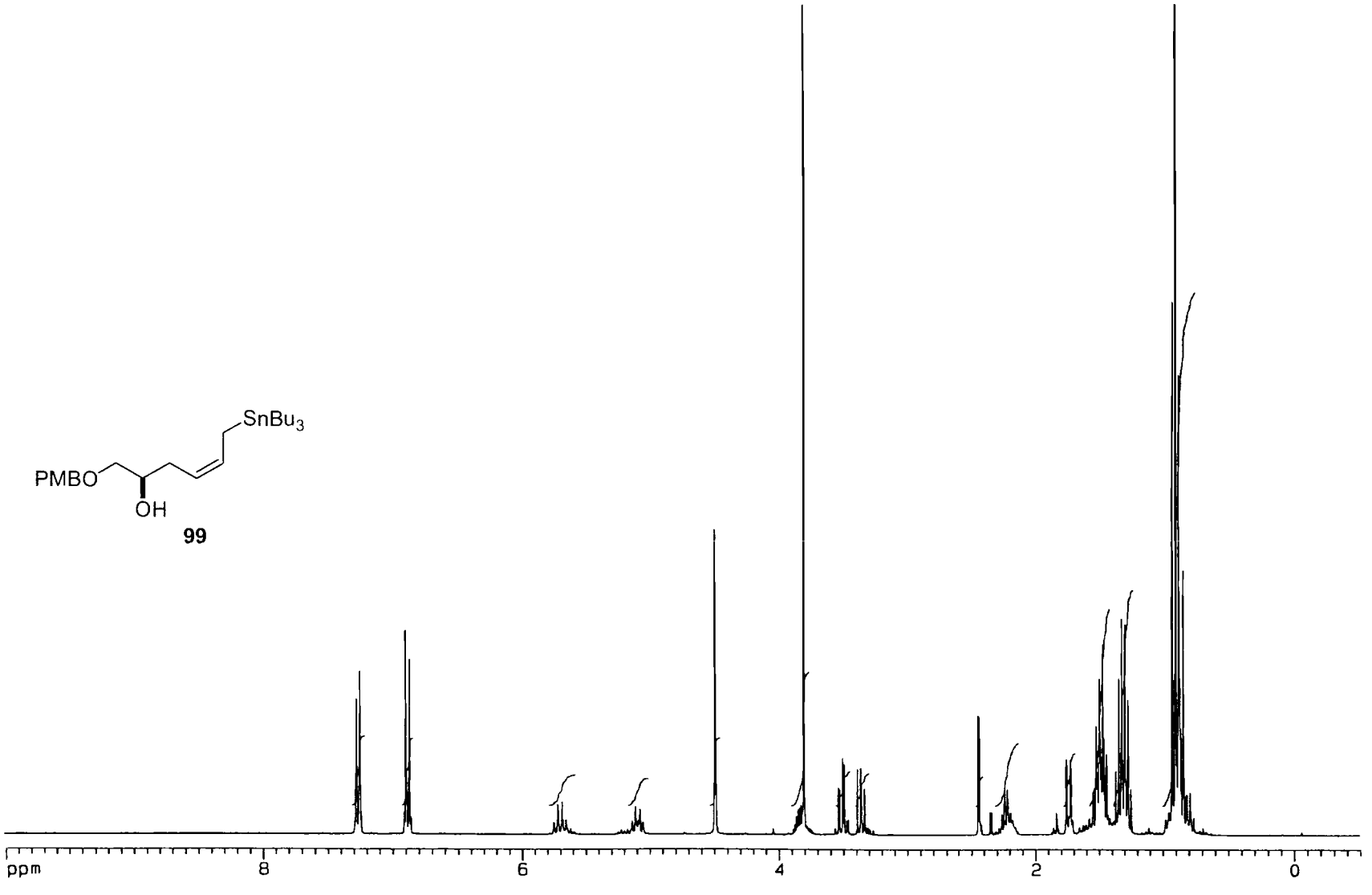
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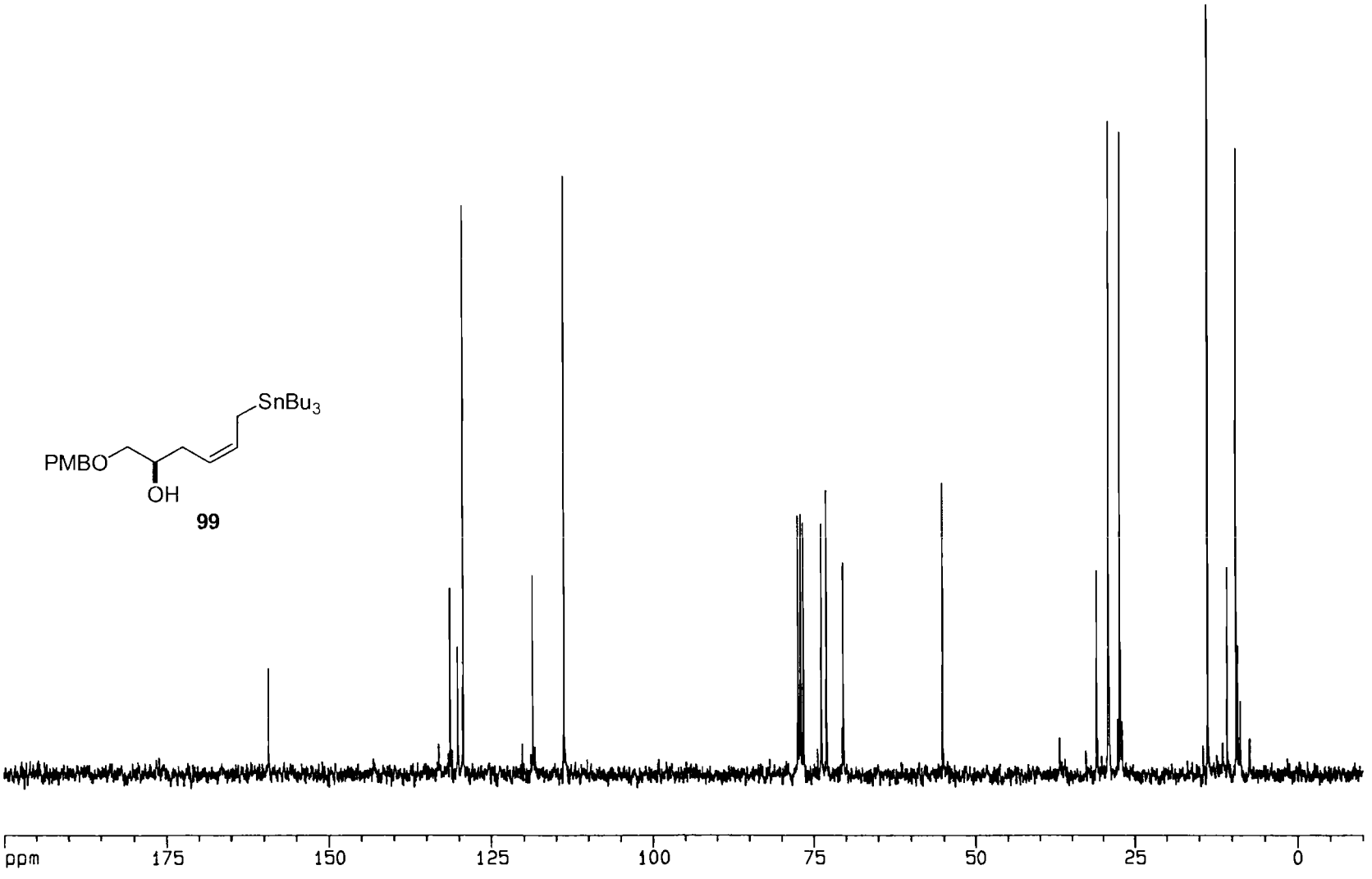
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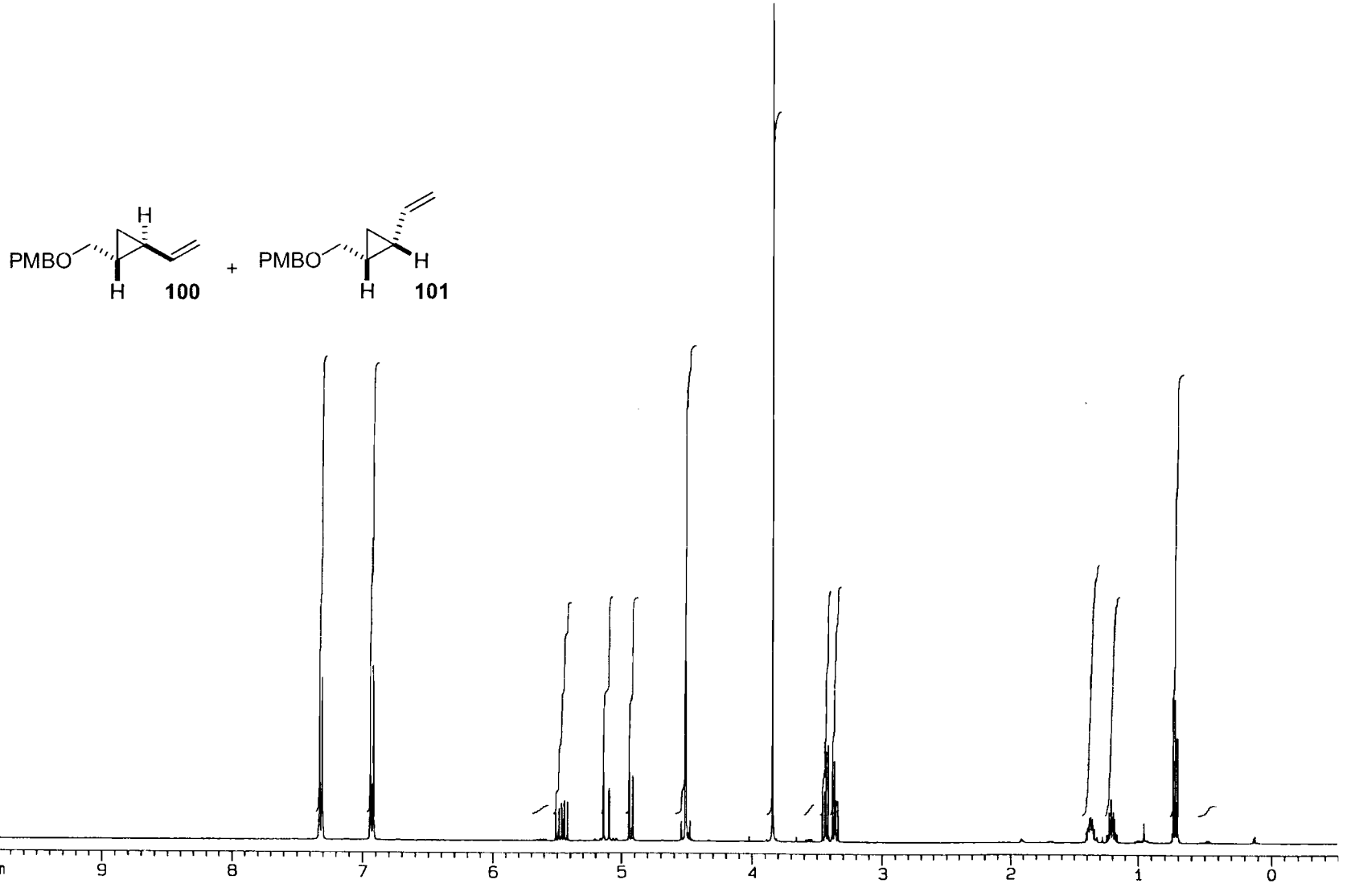
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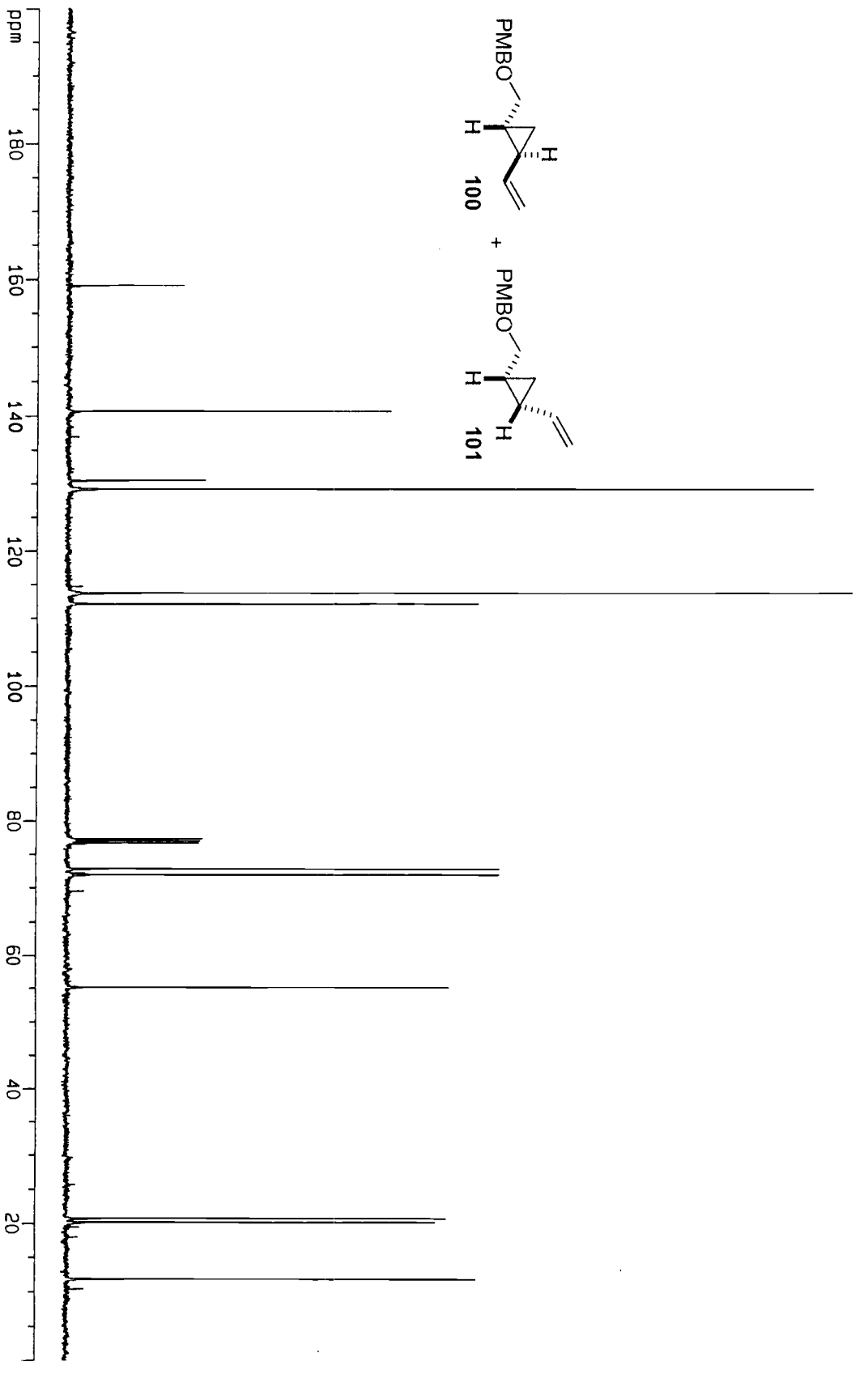
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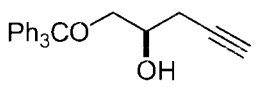

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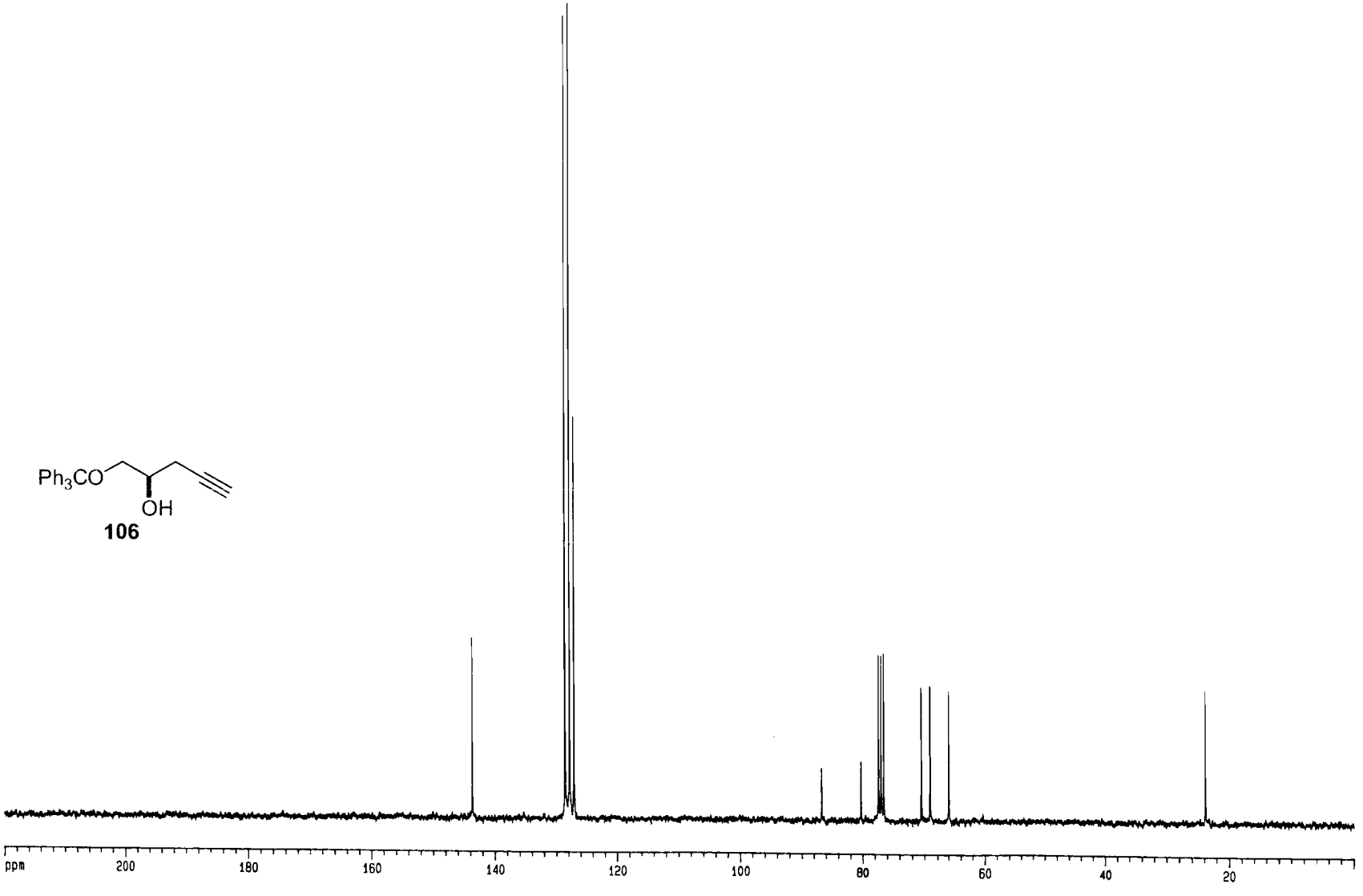
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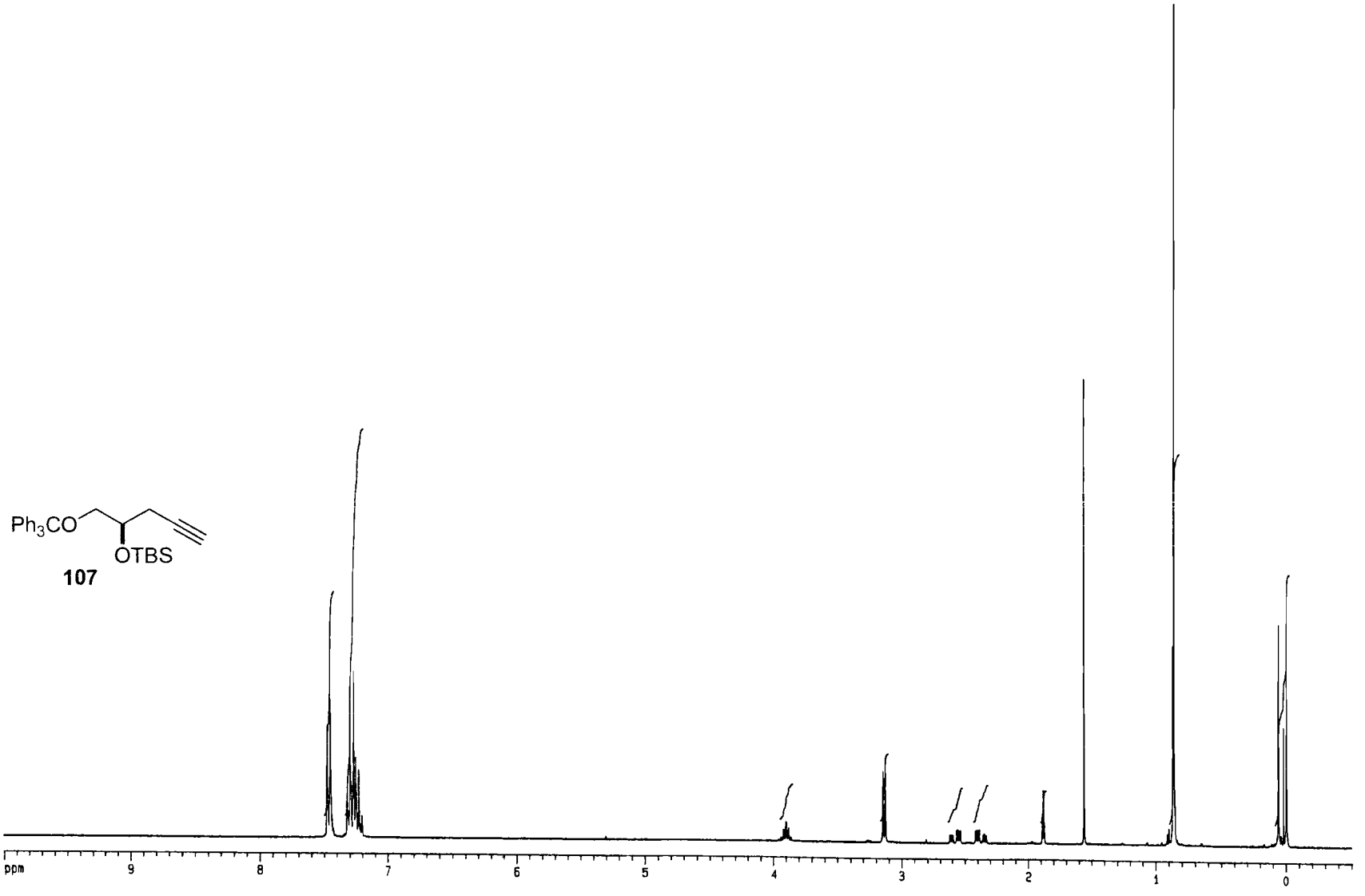
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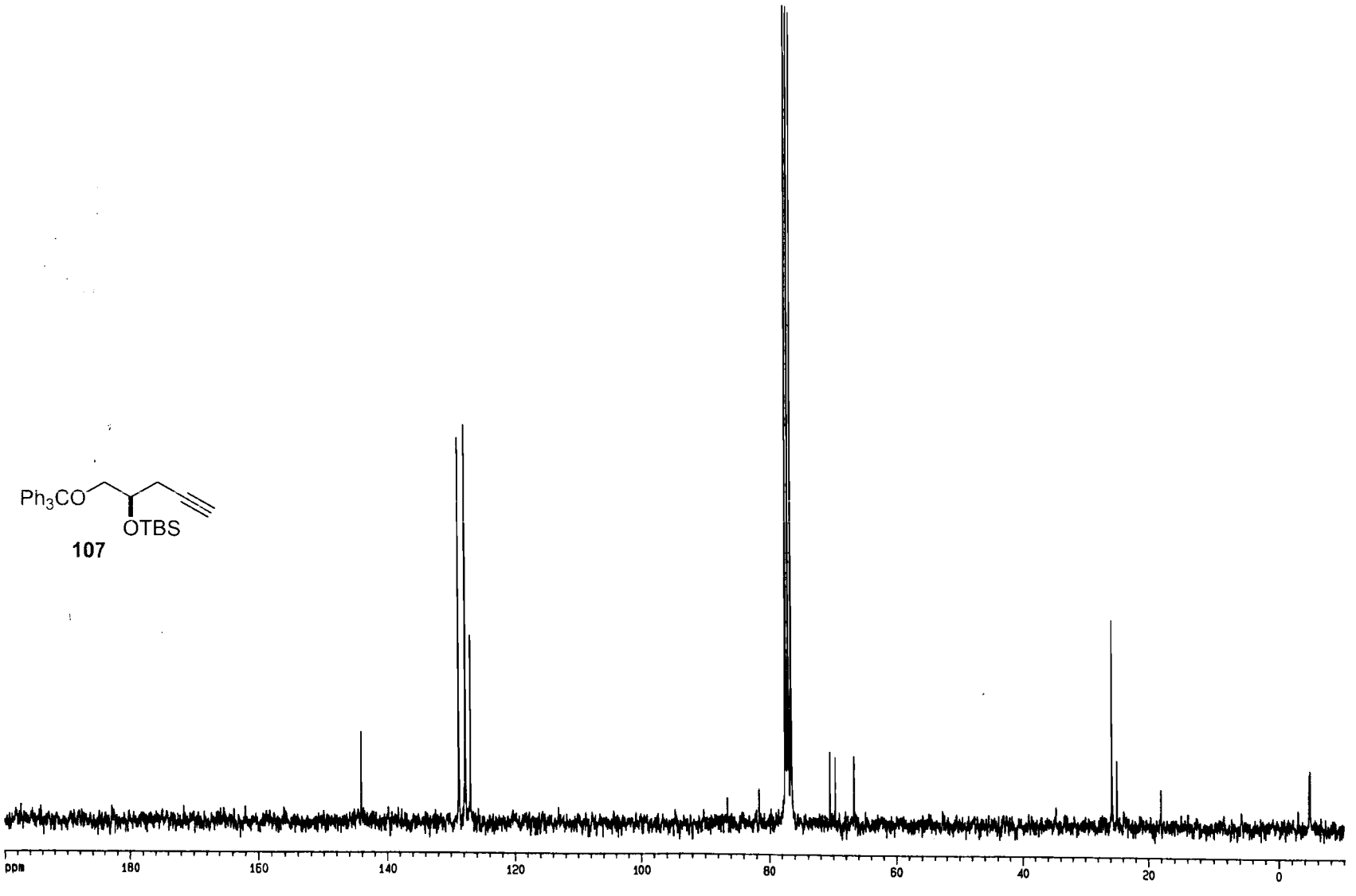
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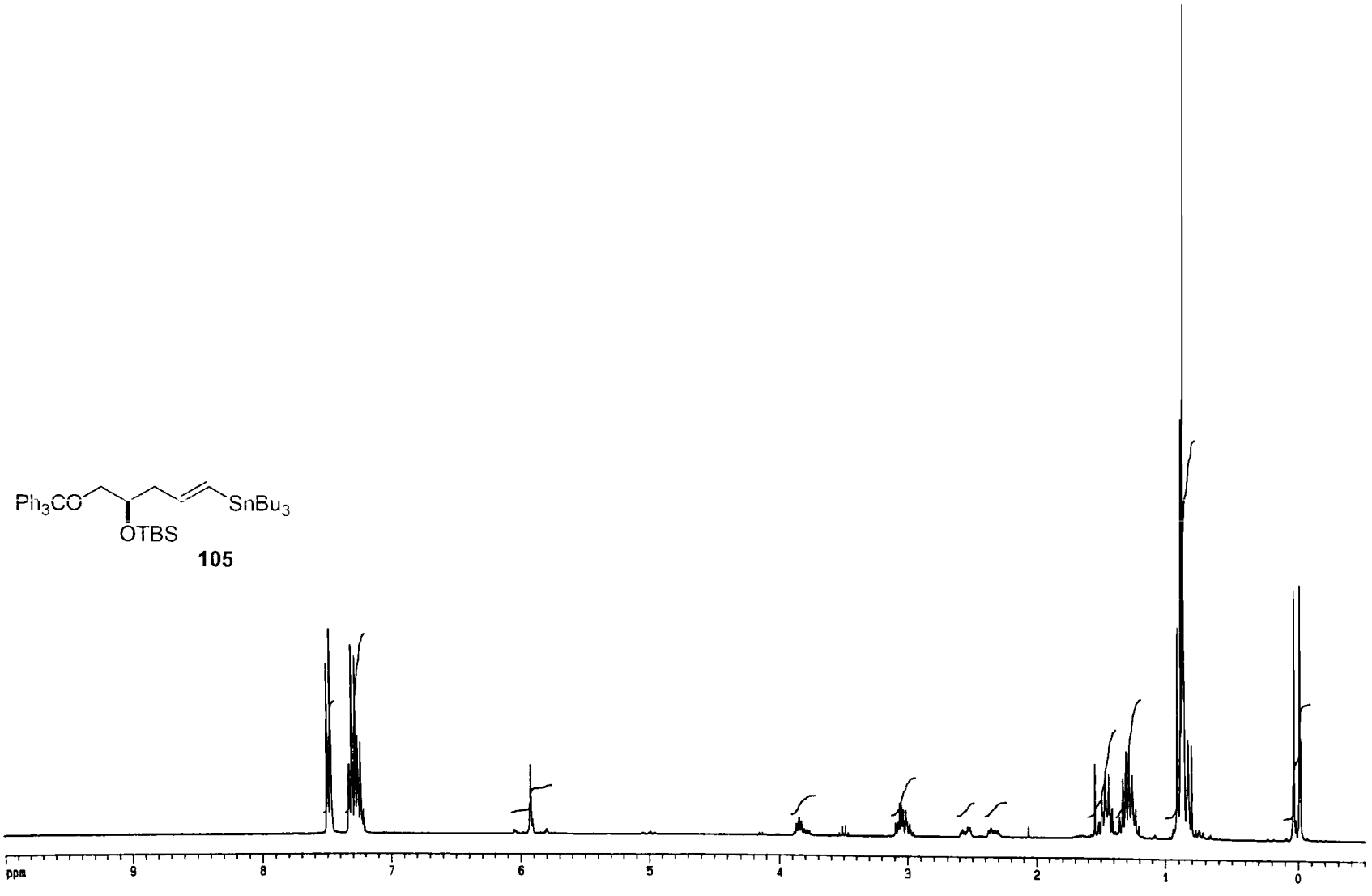
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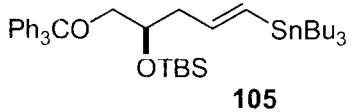

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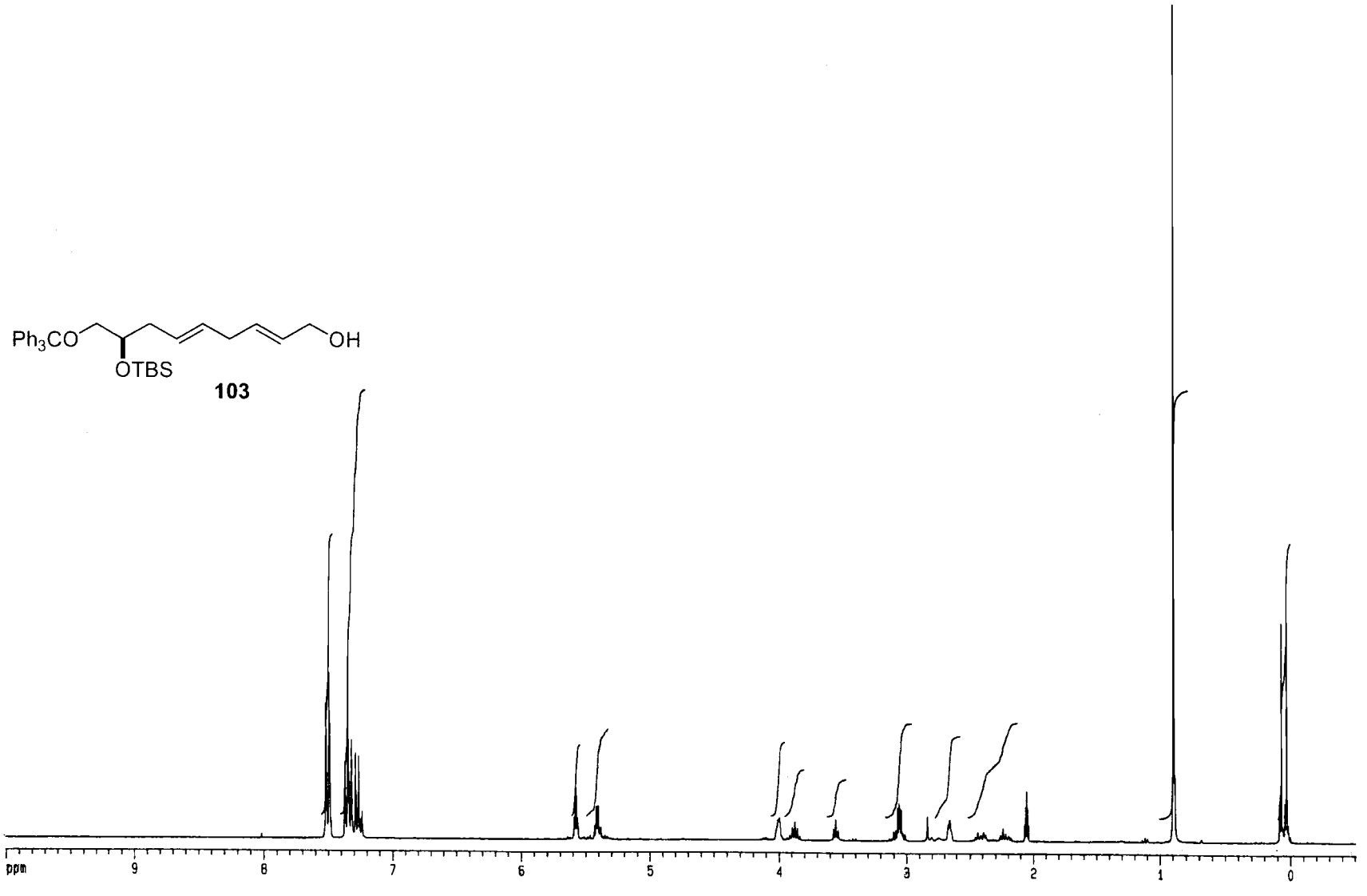
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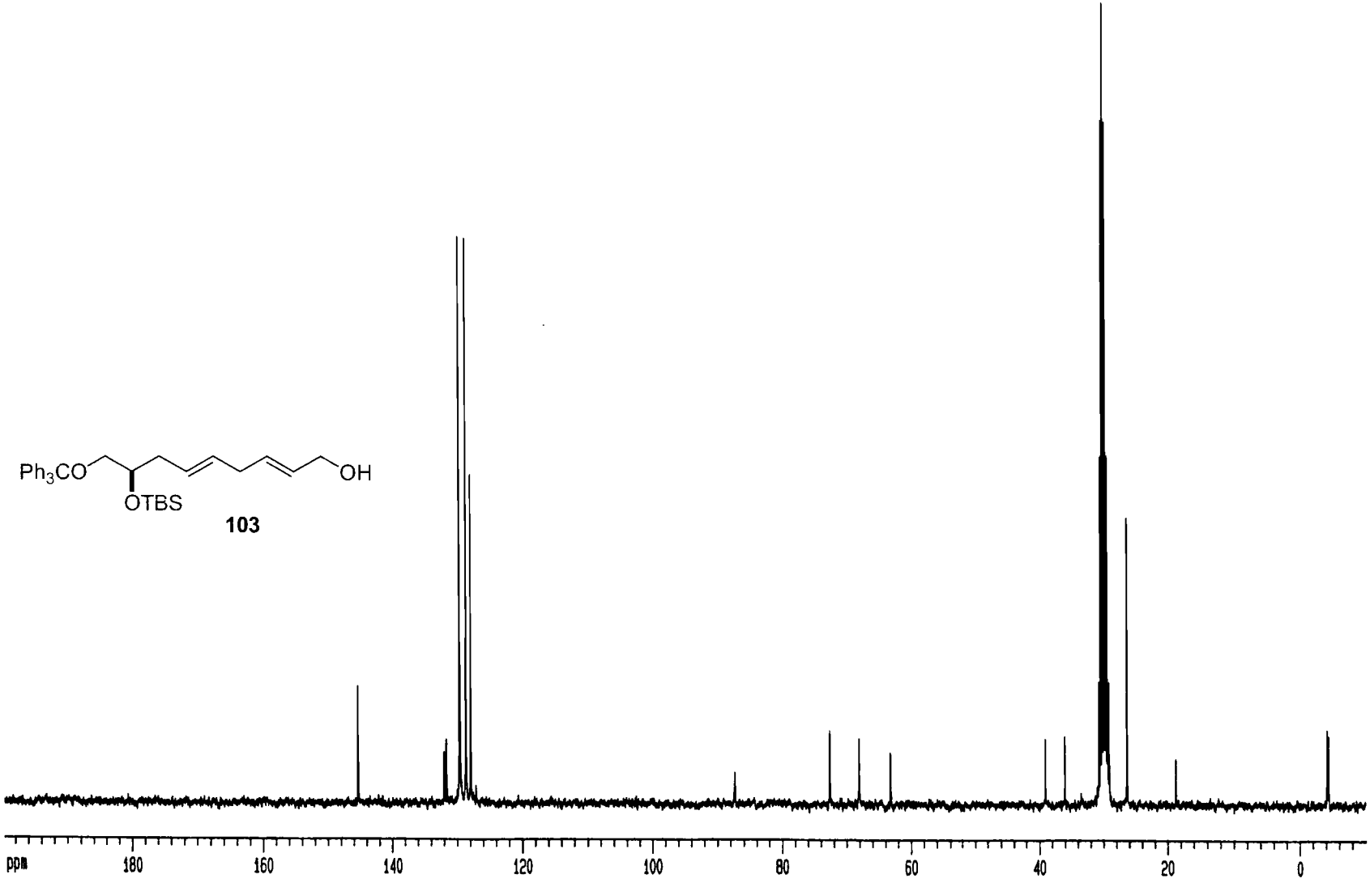
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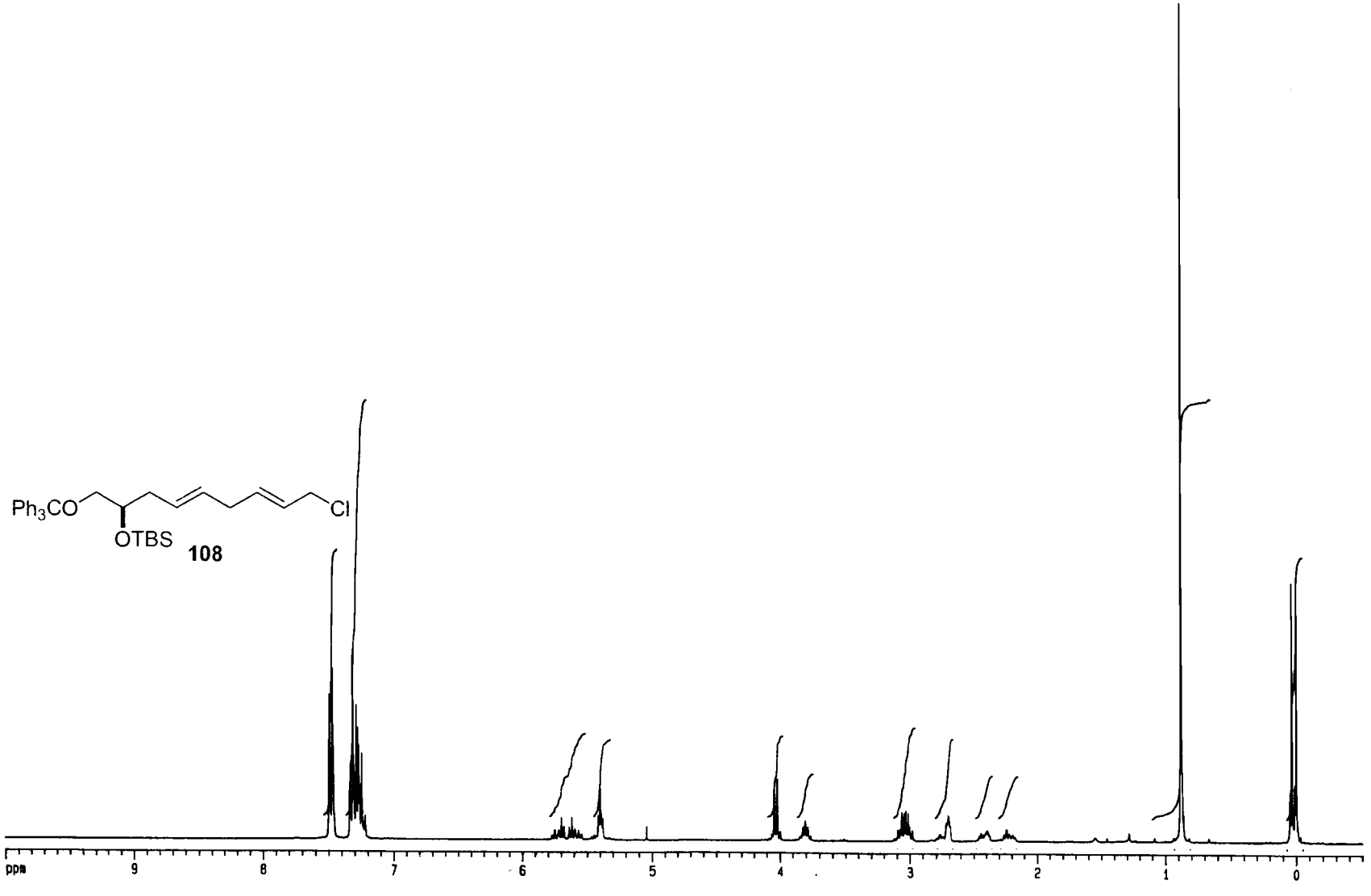
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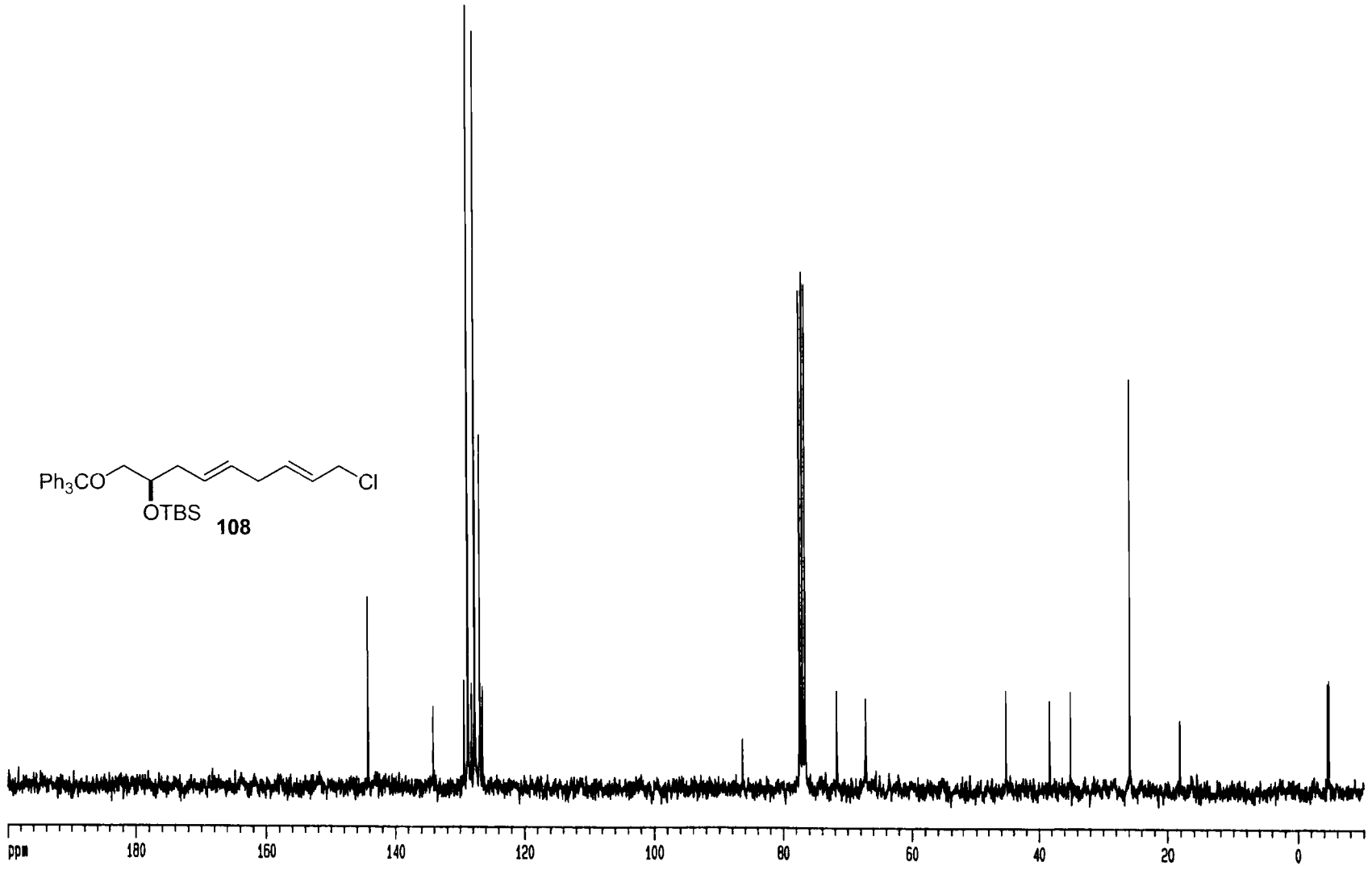
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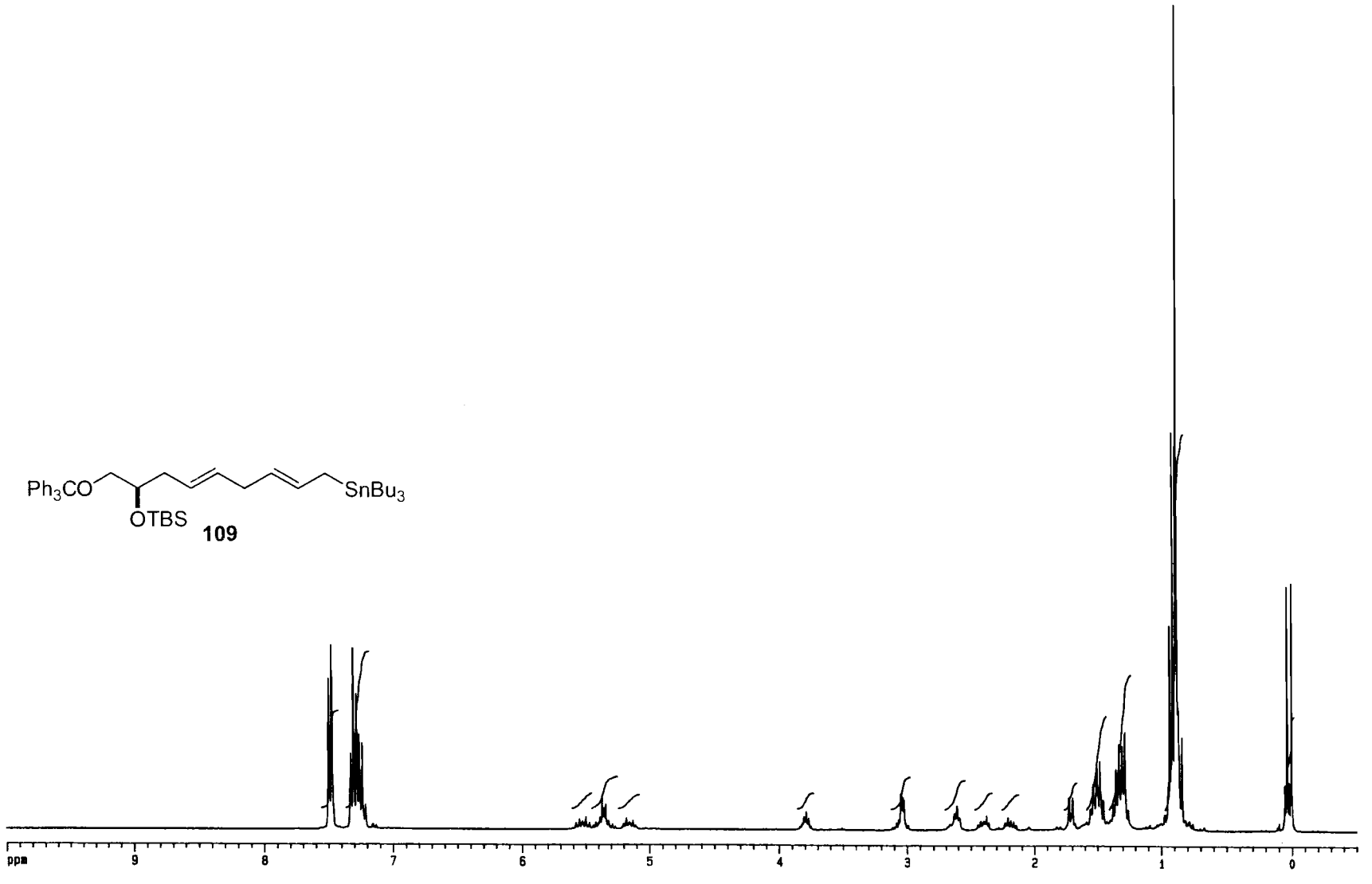
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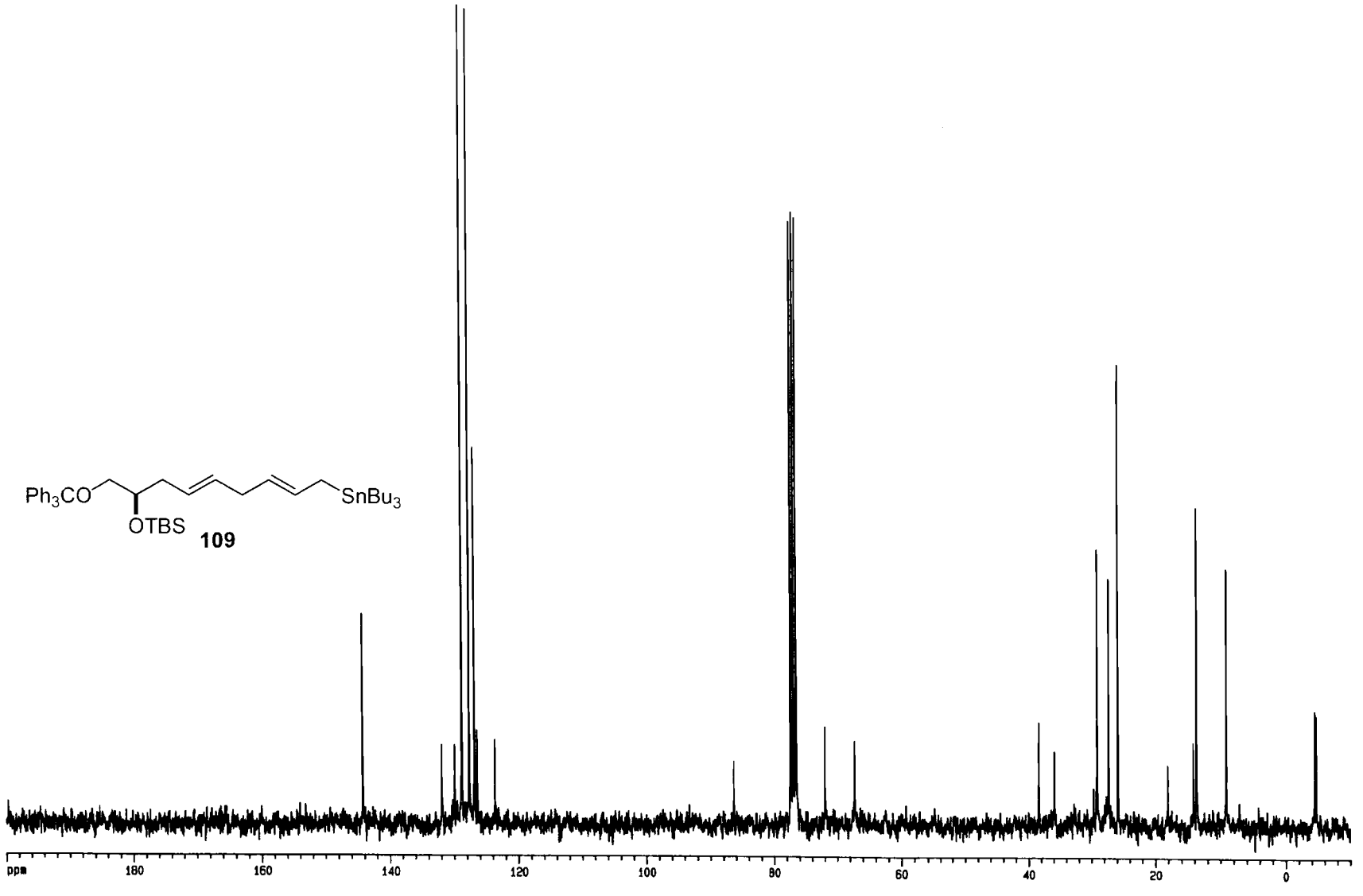
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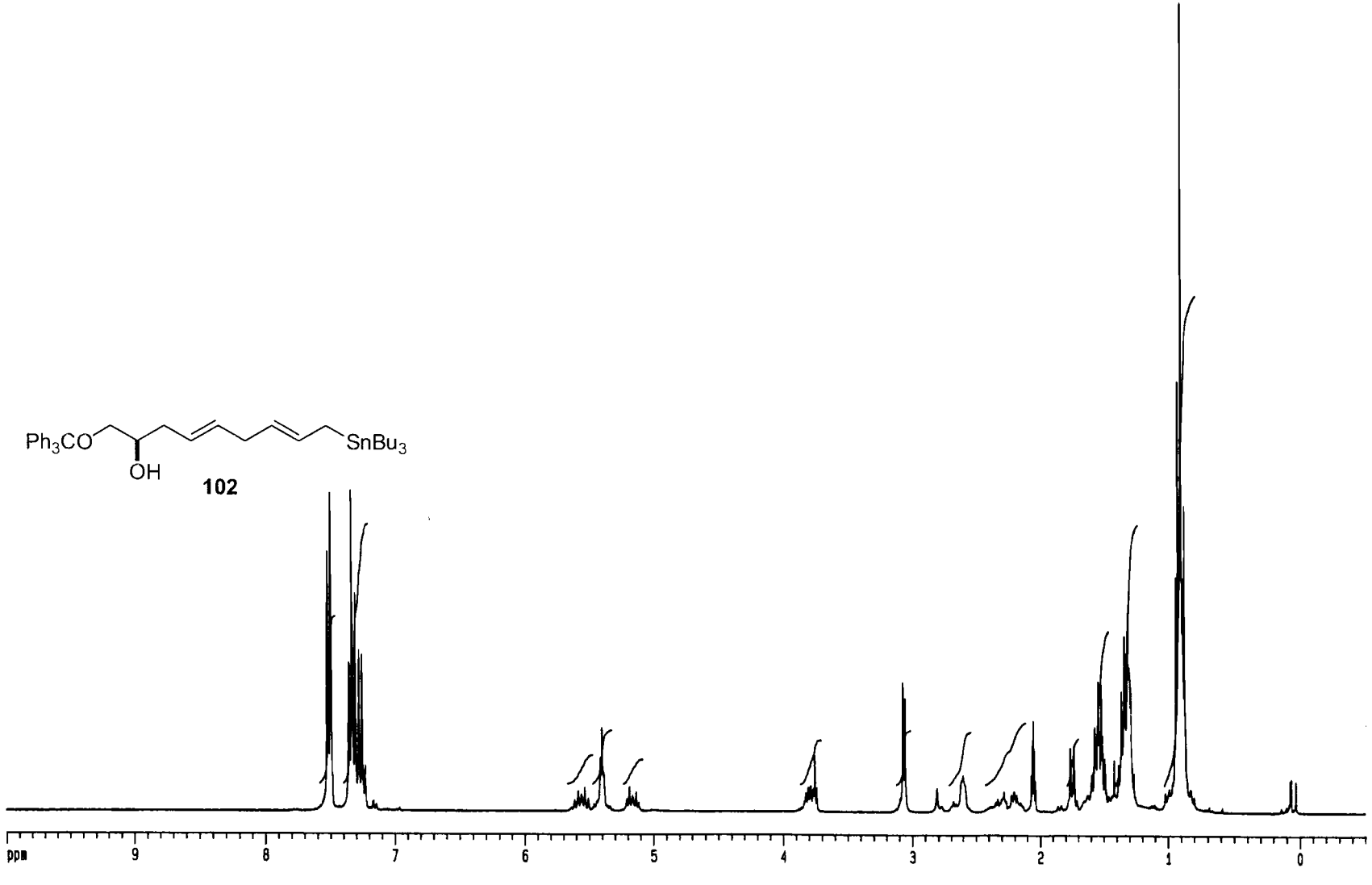
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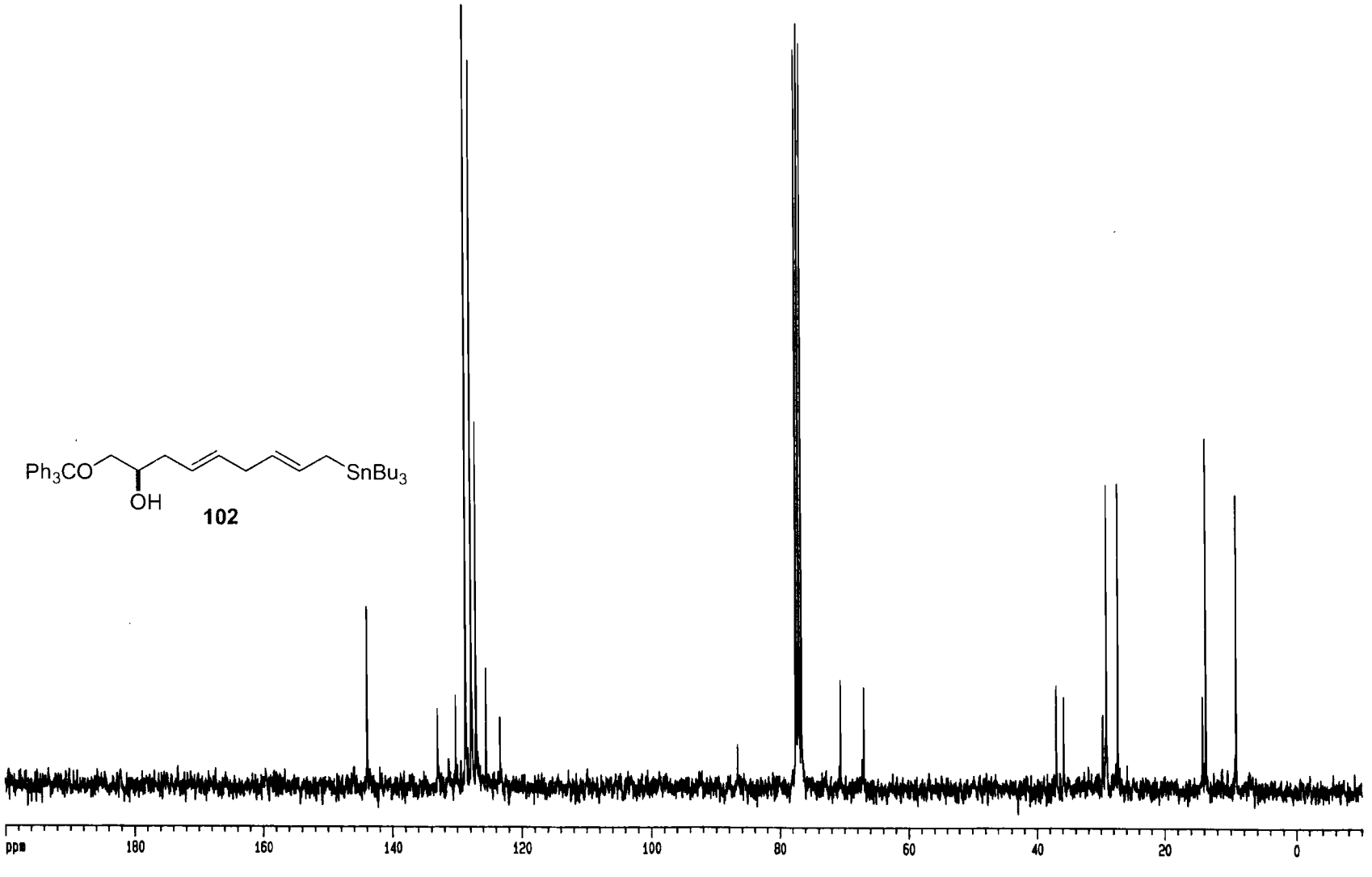
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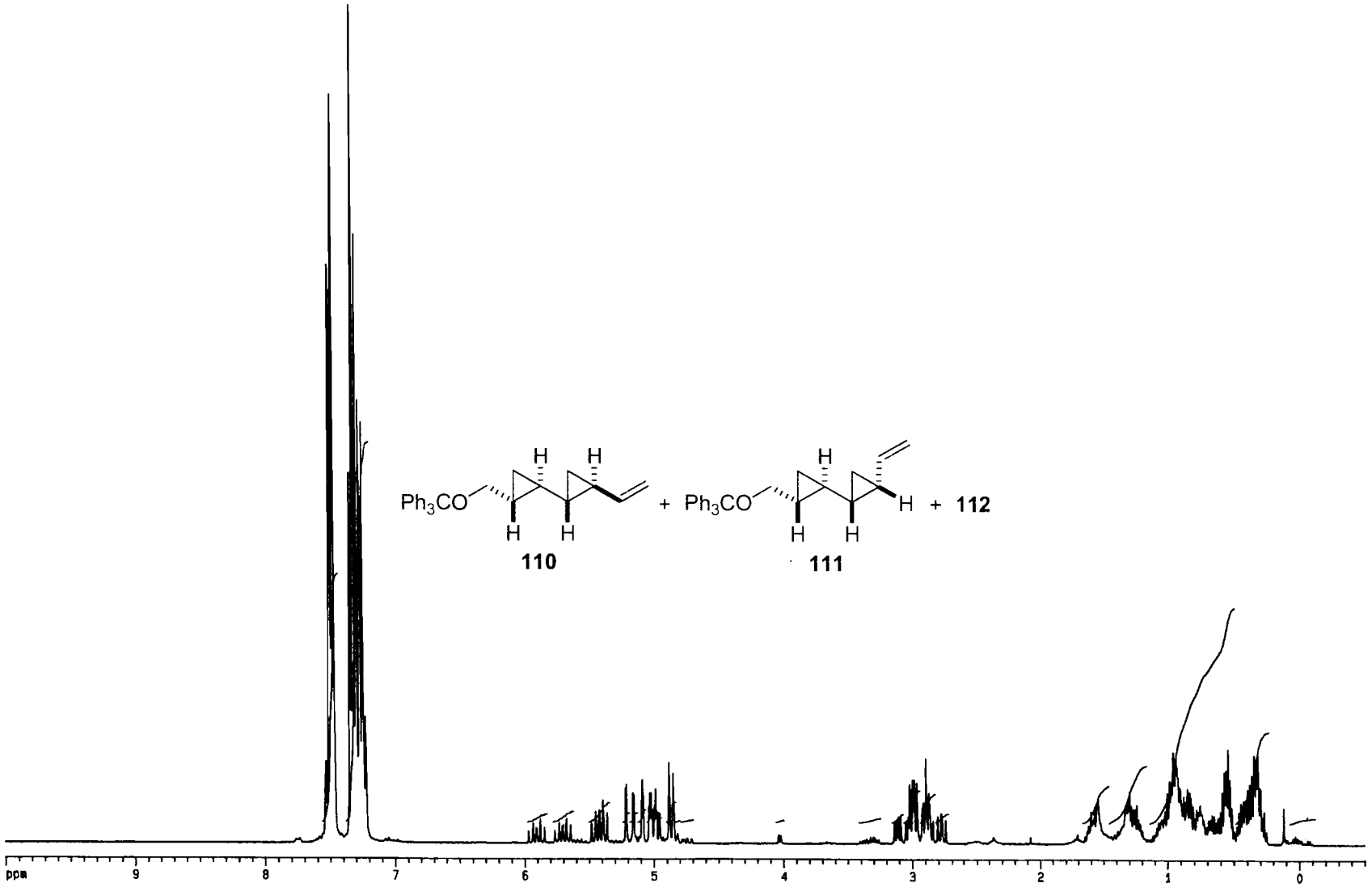
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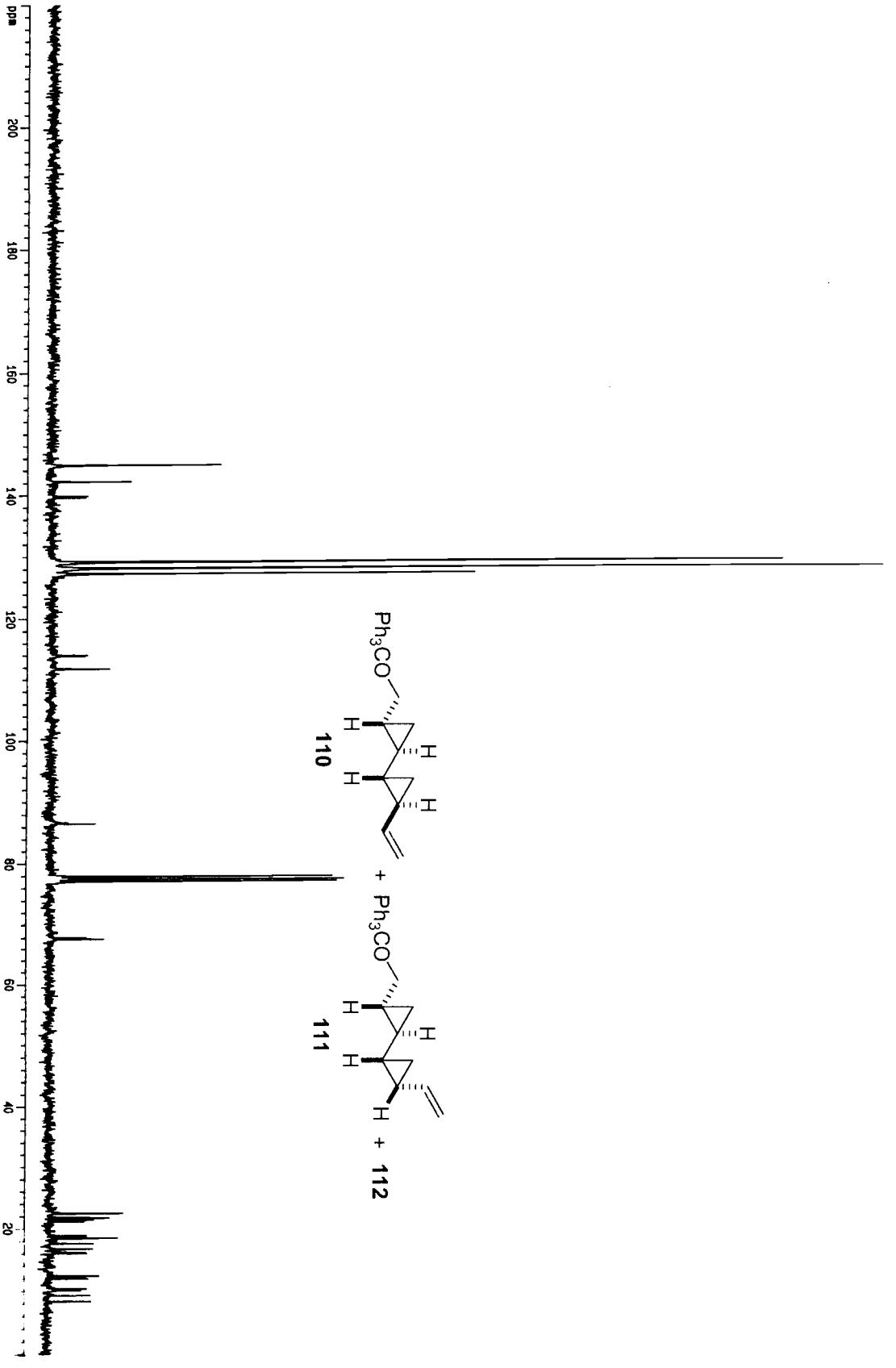
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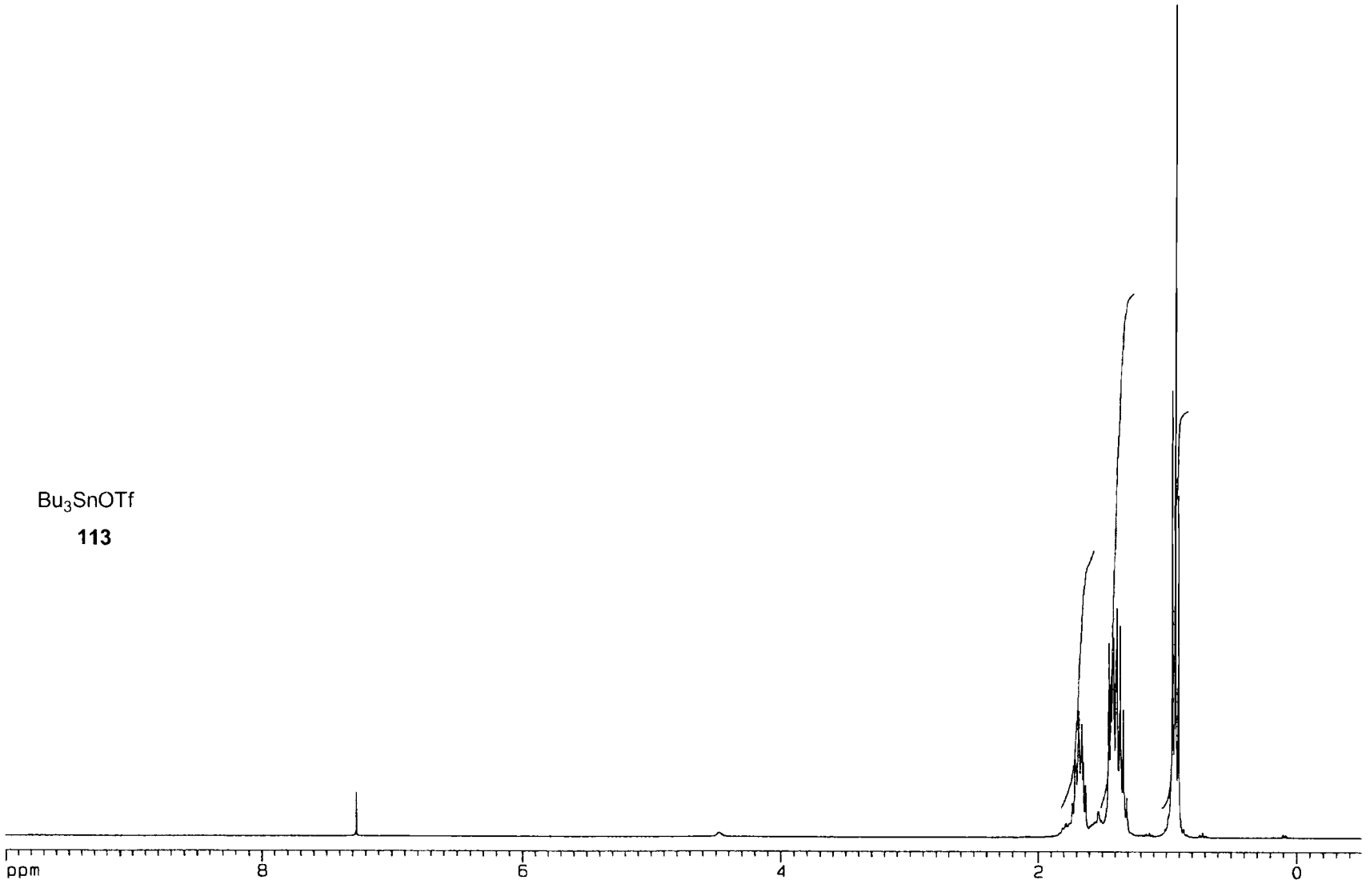
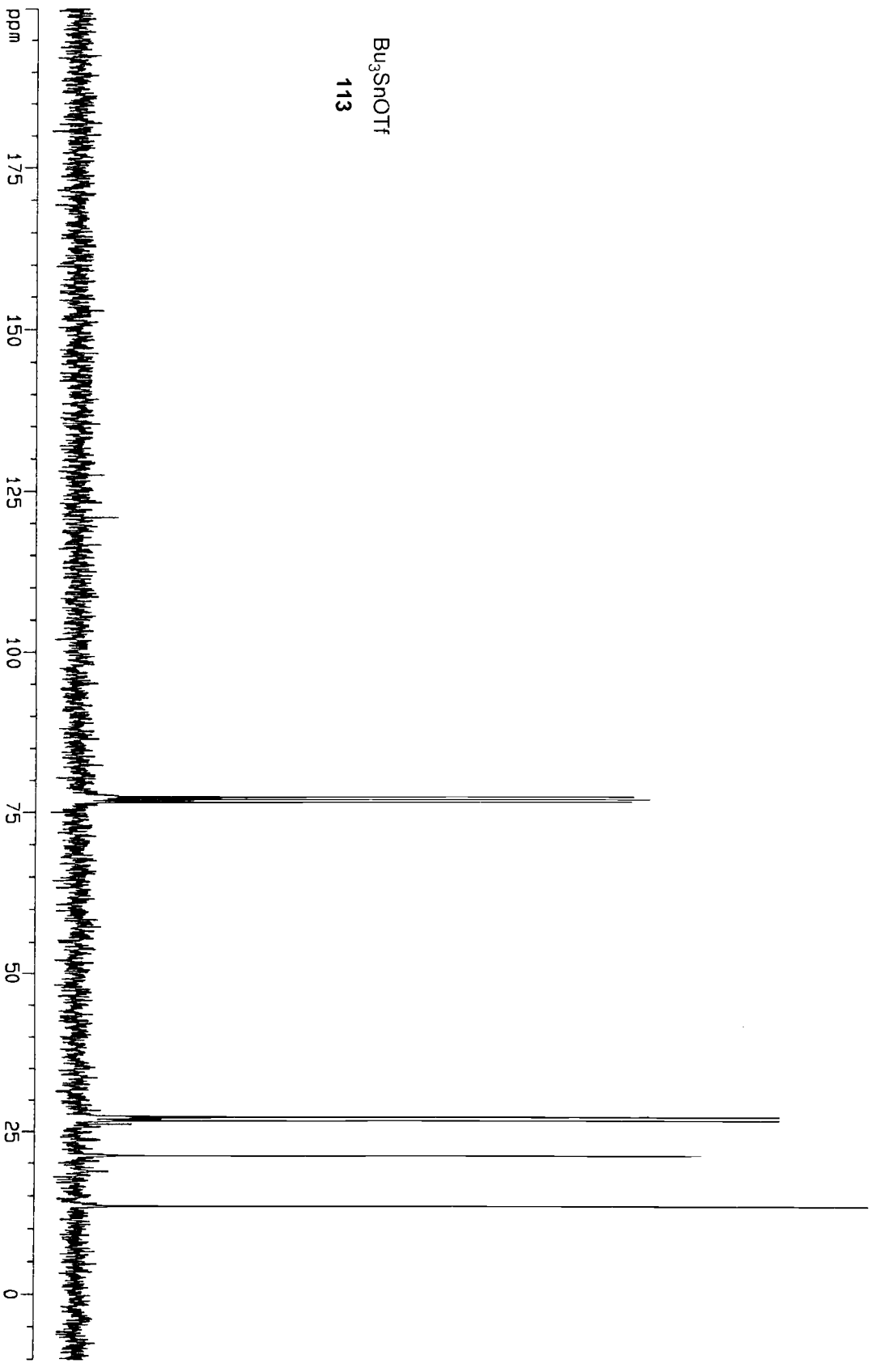
H
H
H
111
+ 112

Bu_3SnOTf

113

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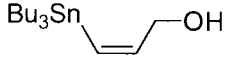

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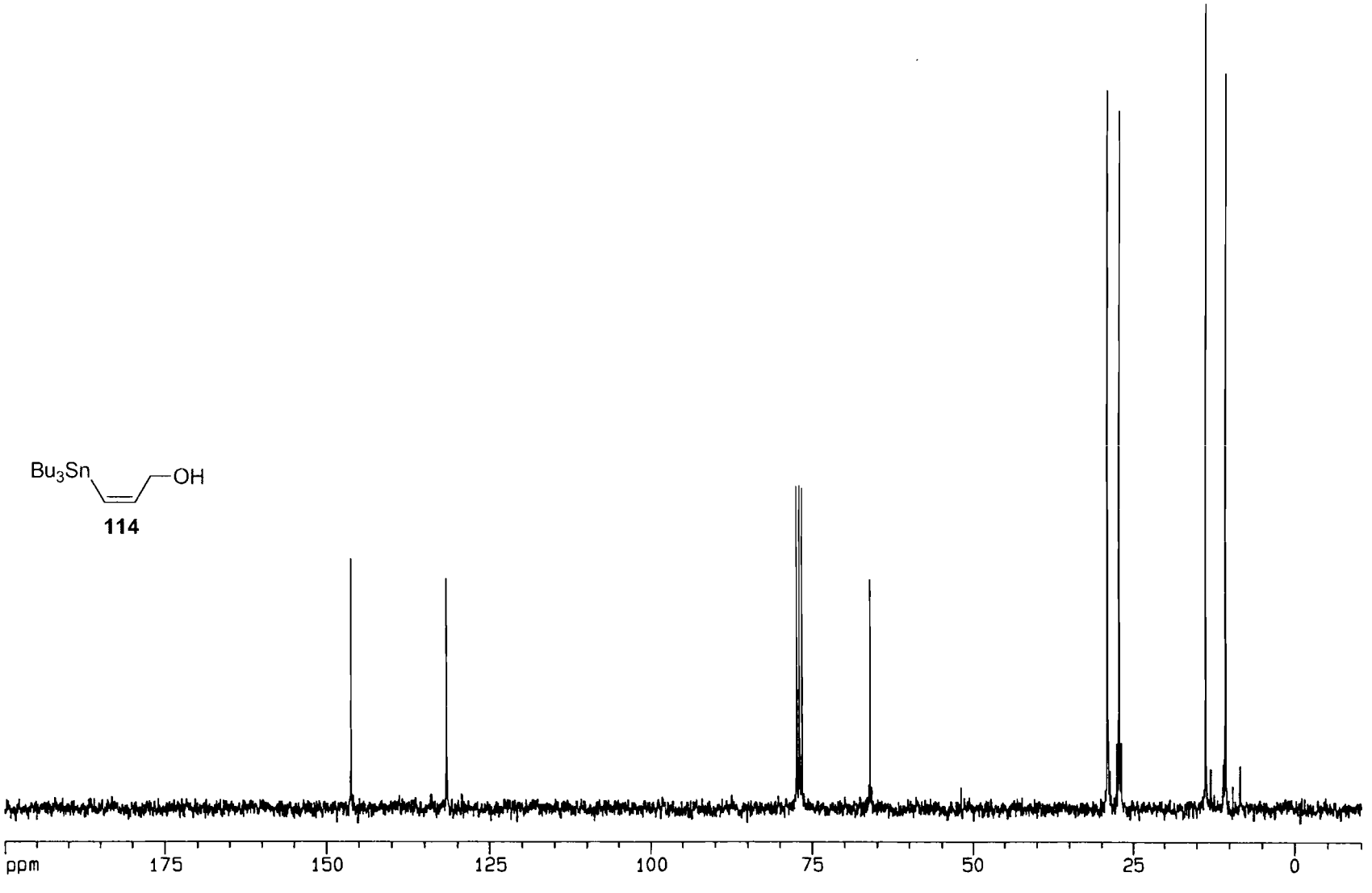
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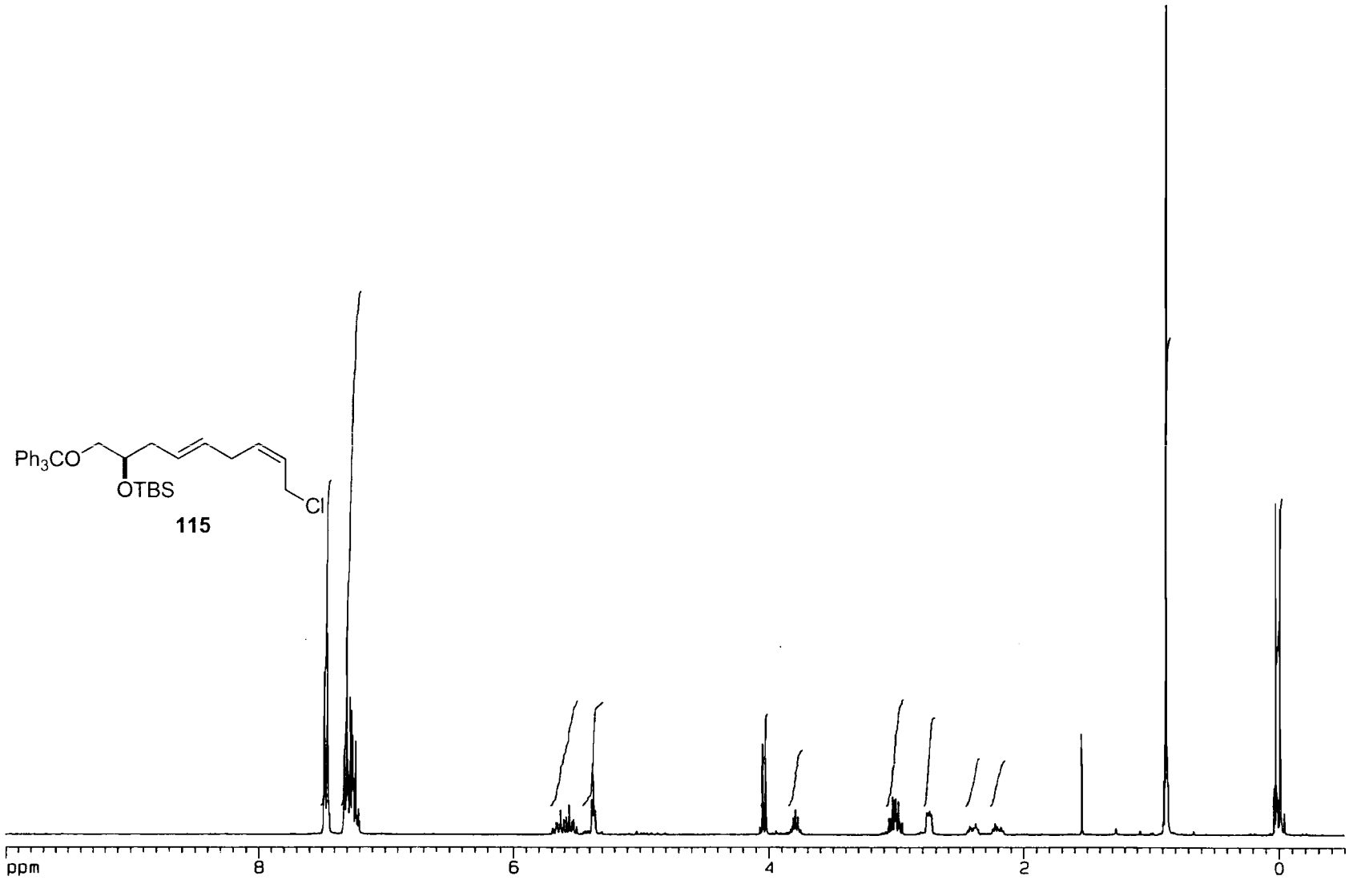
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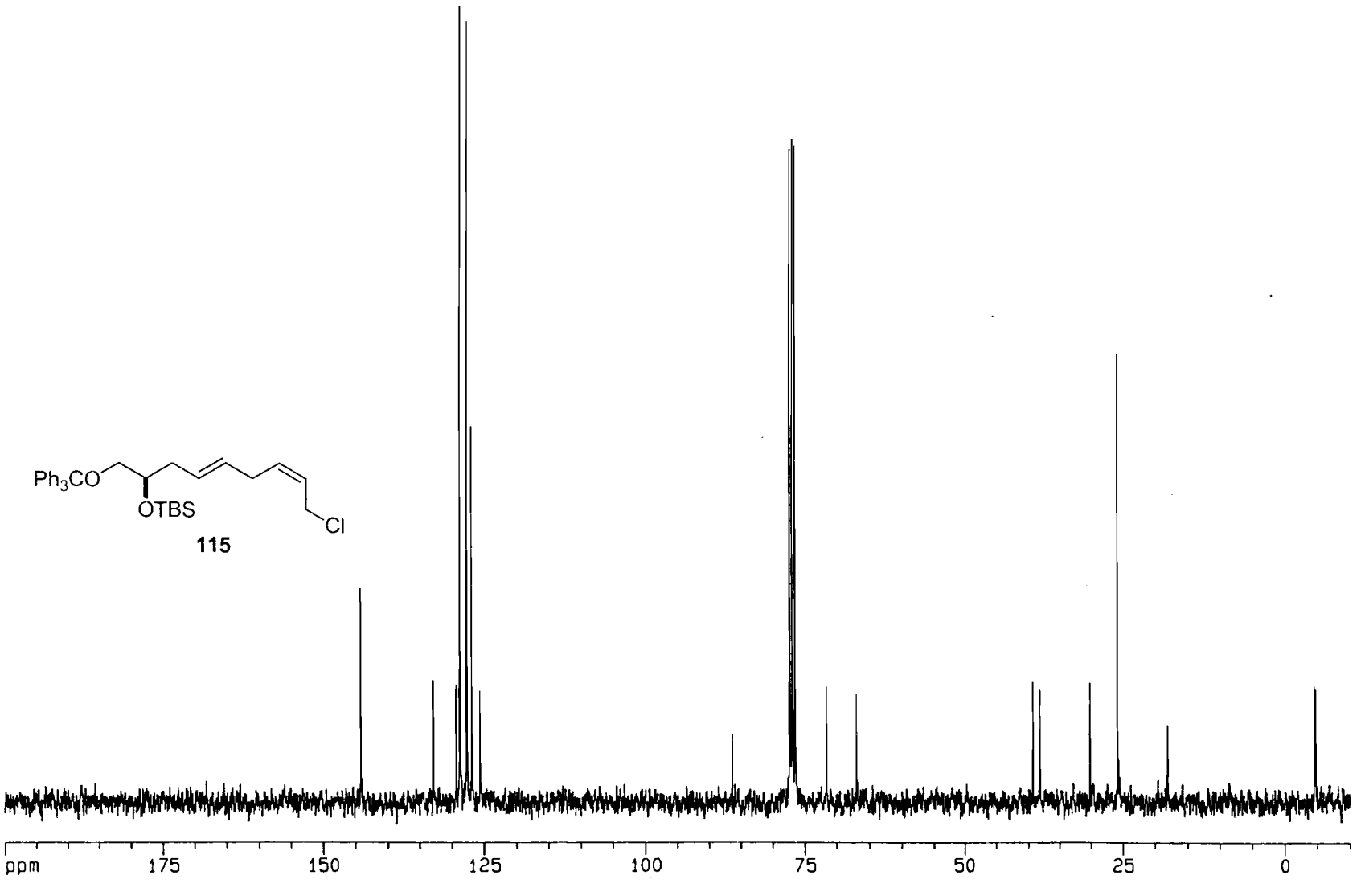
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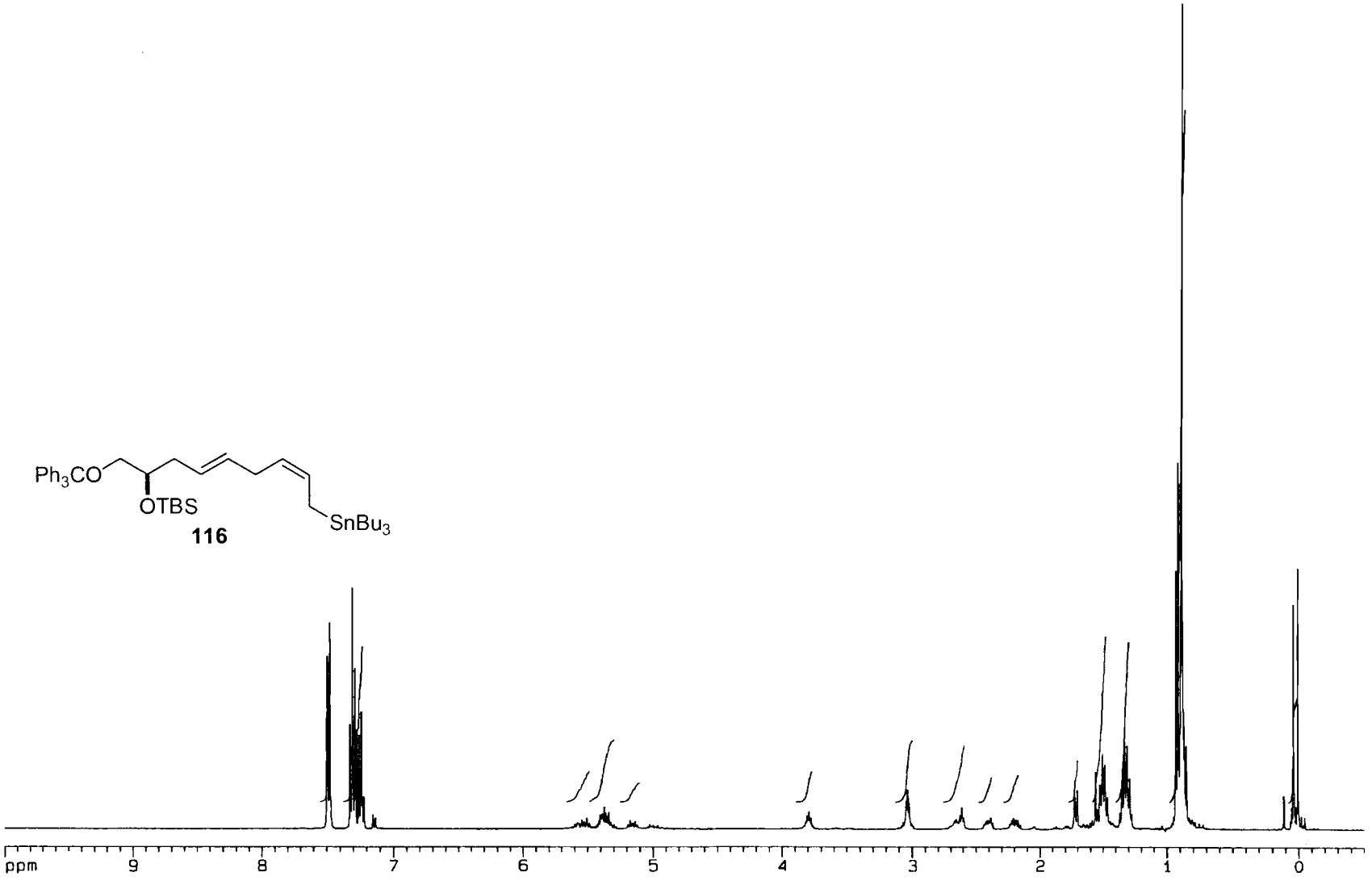
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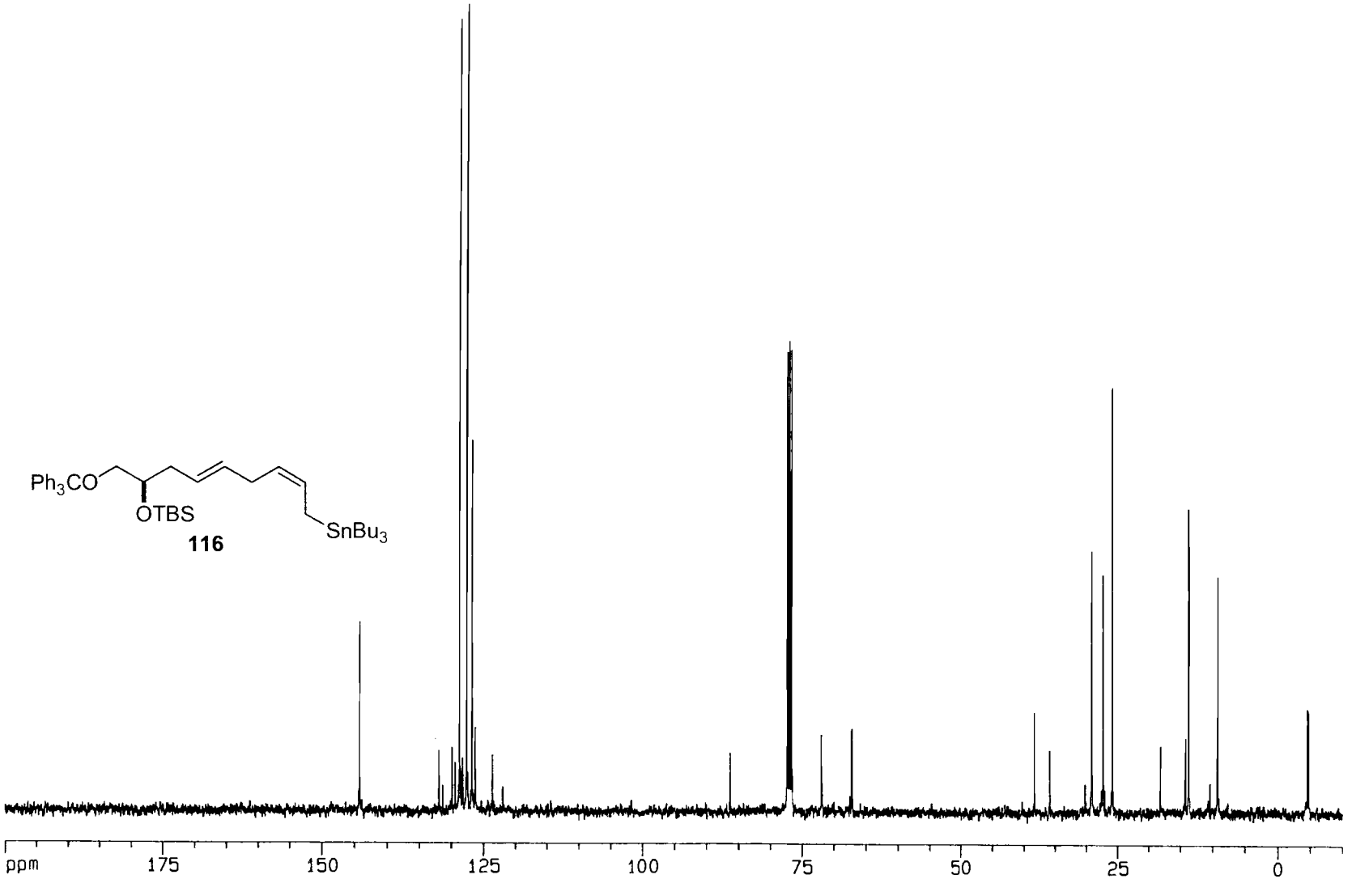
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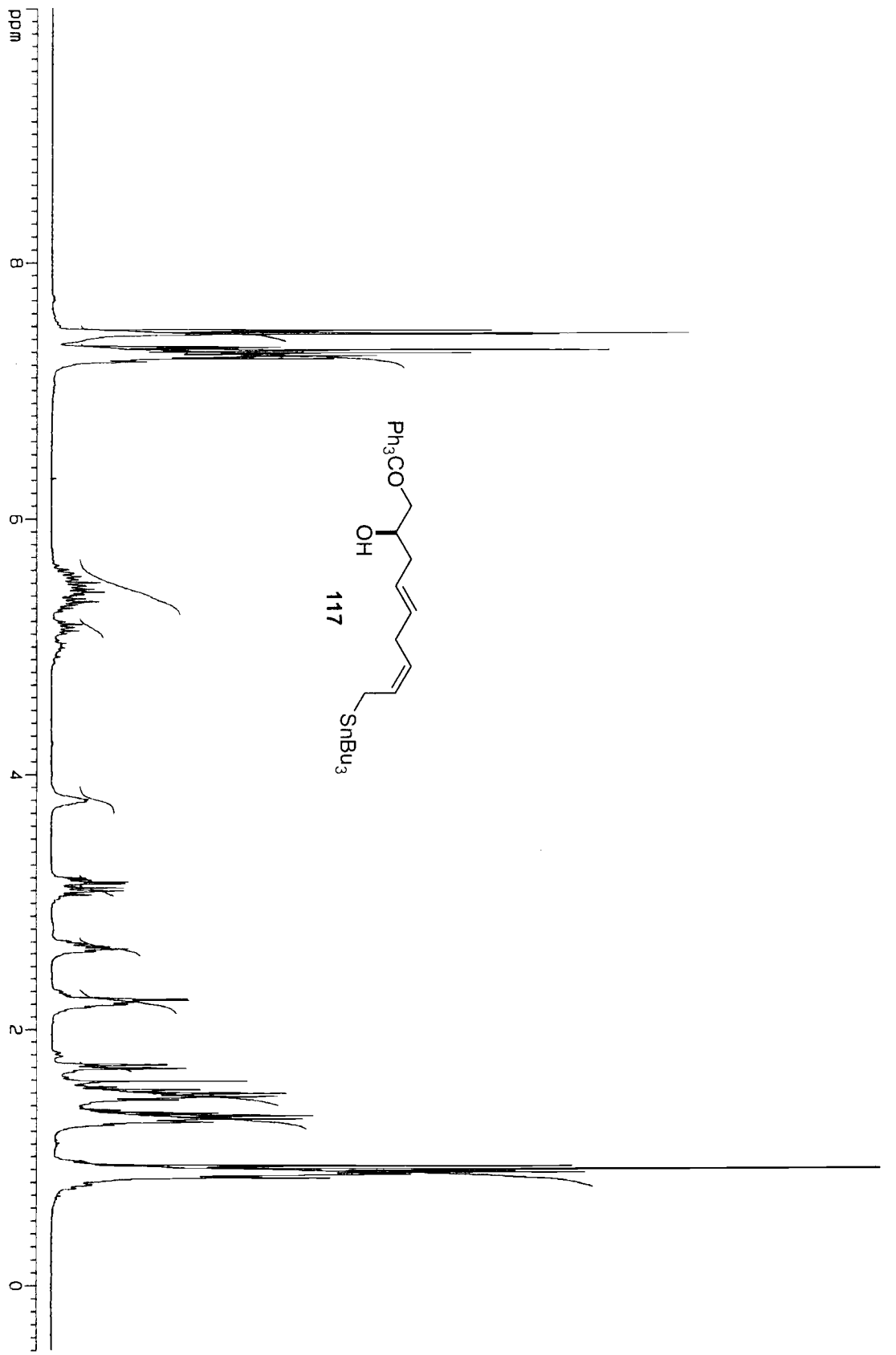
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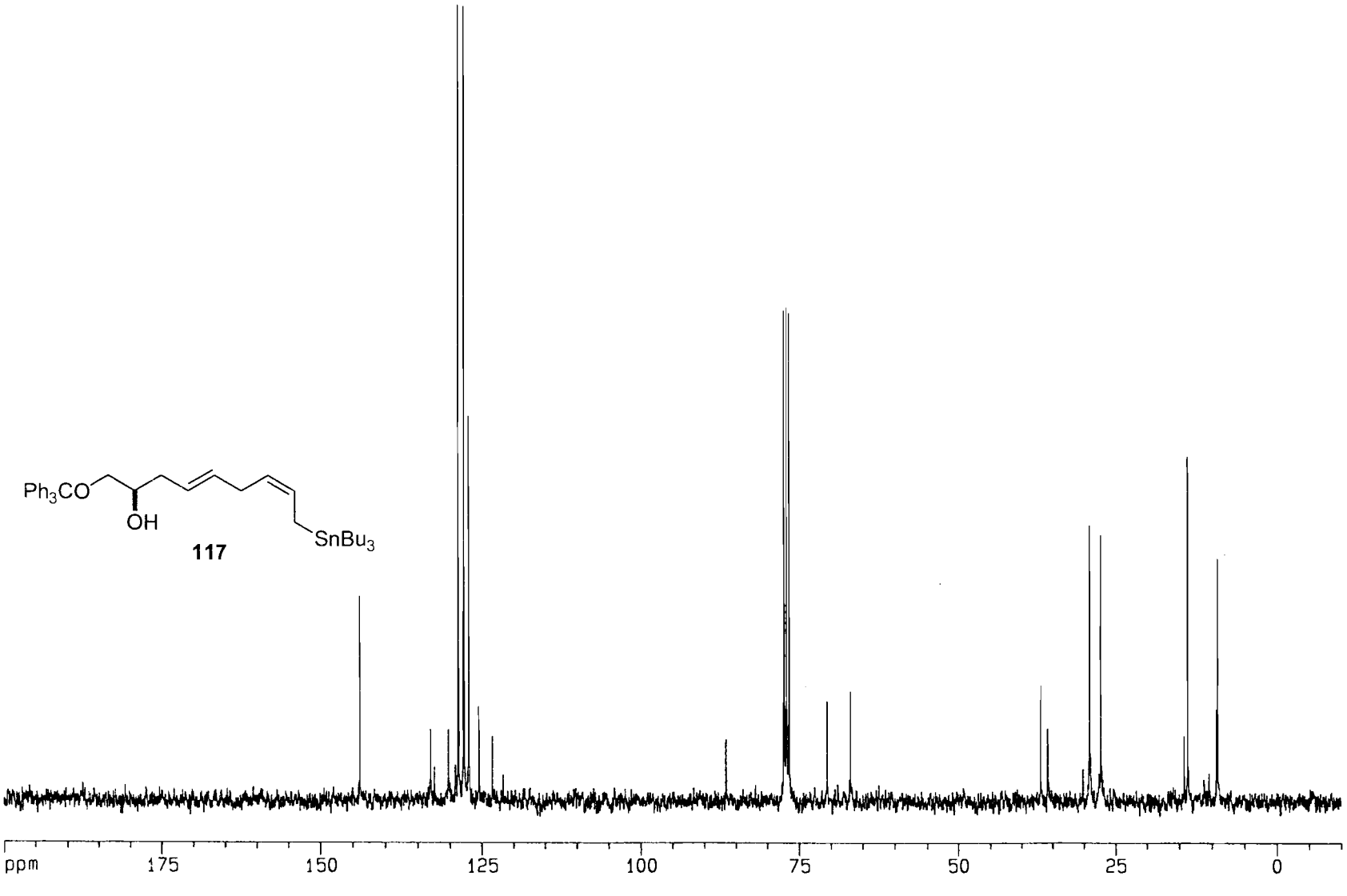
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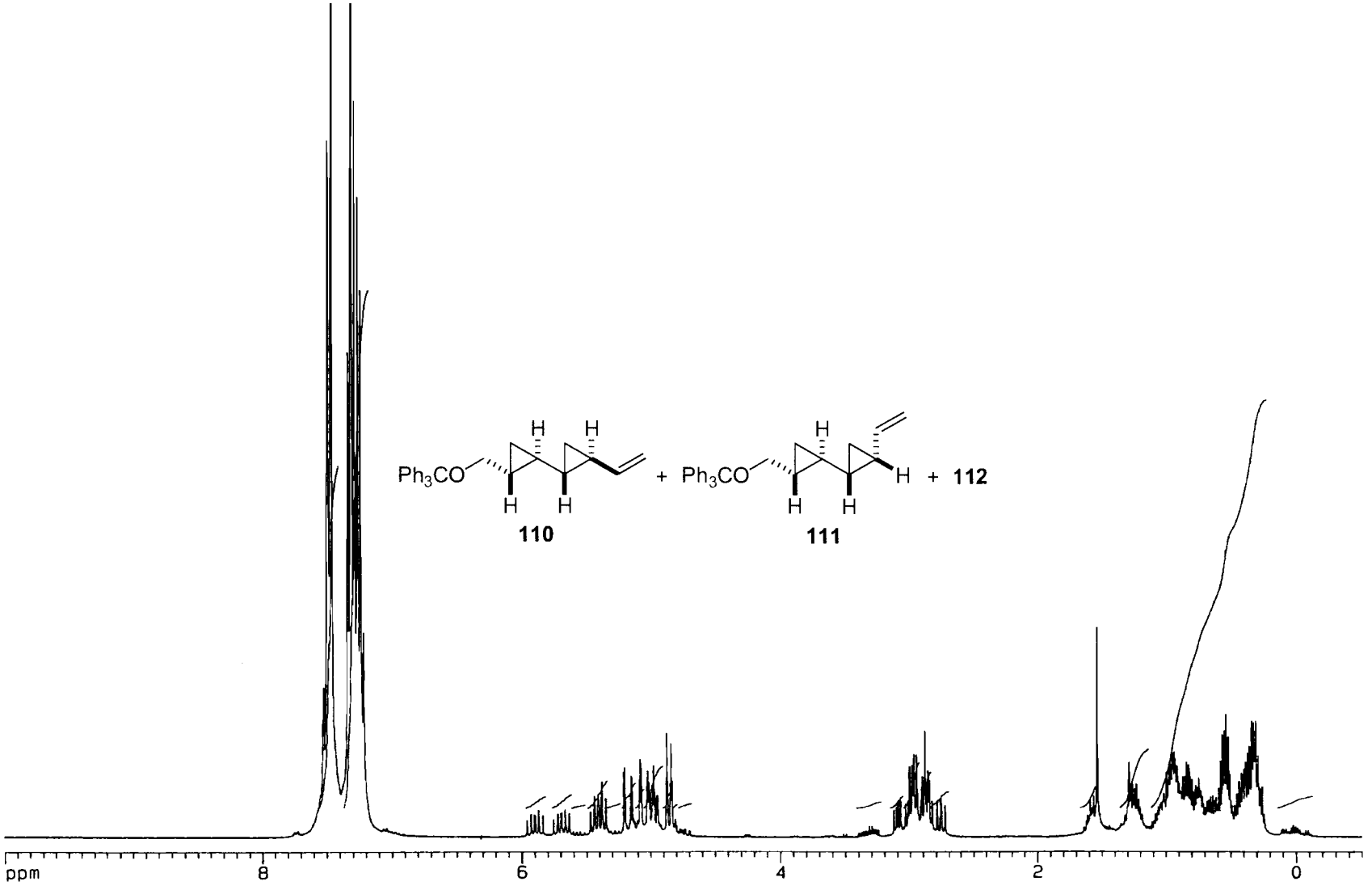
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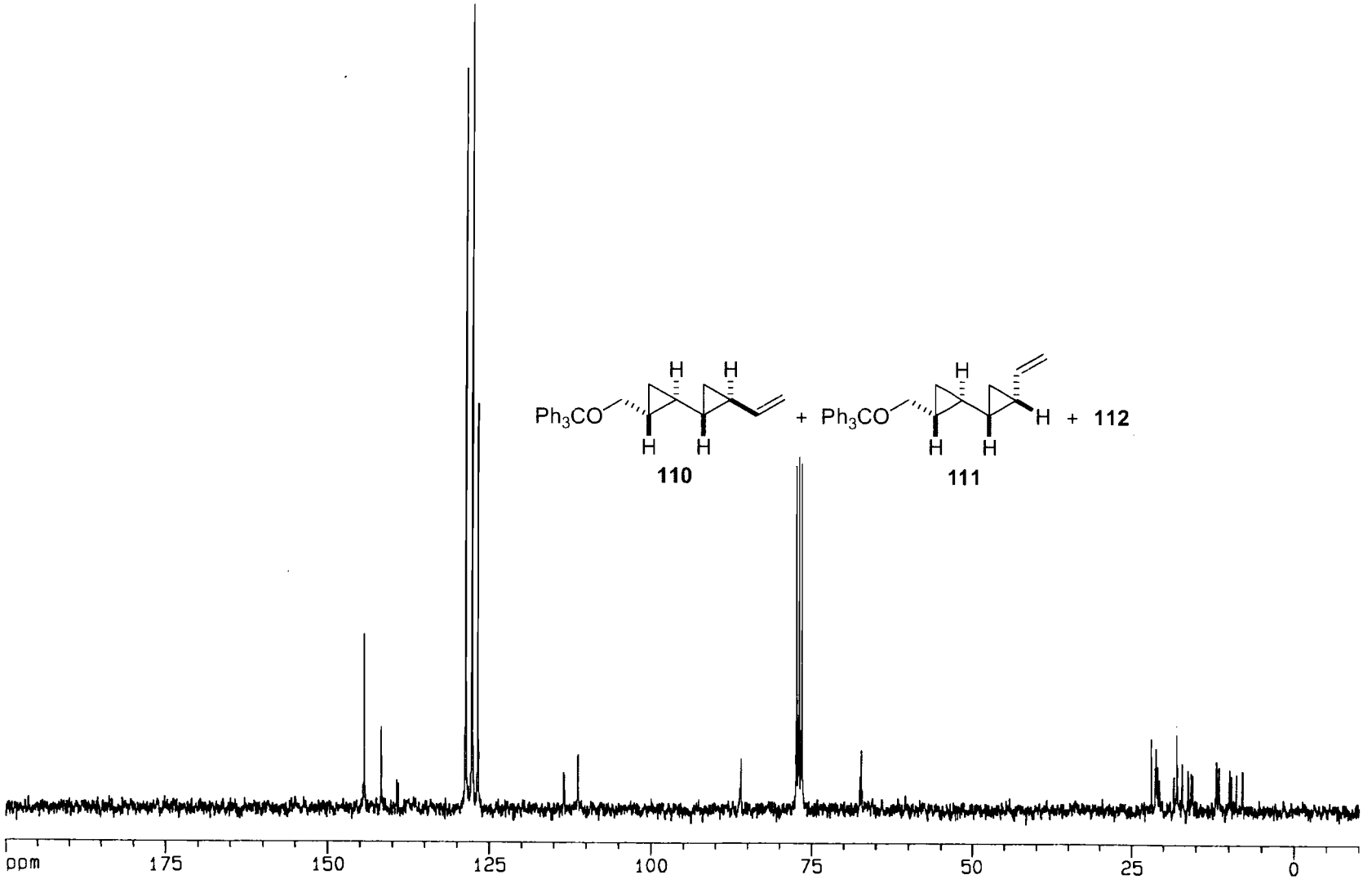
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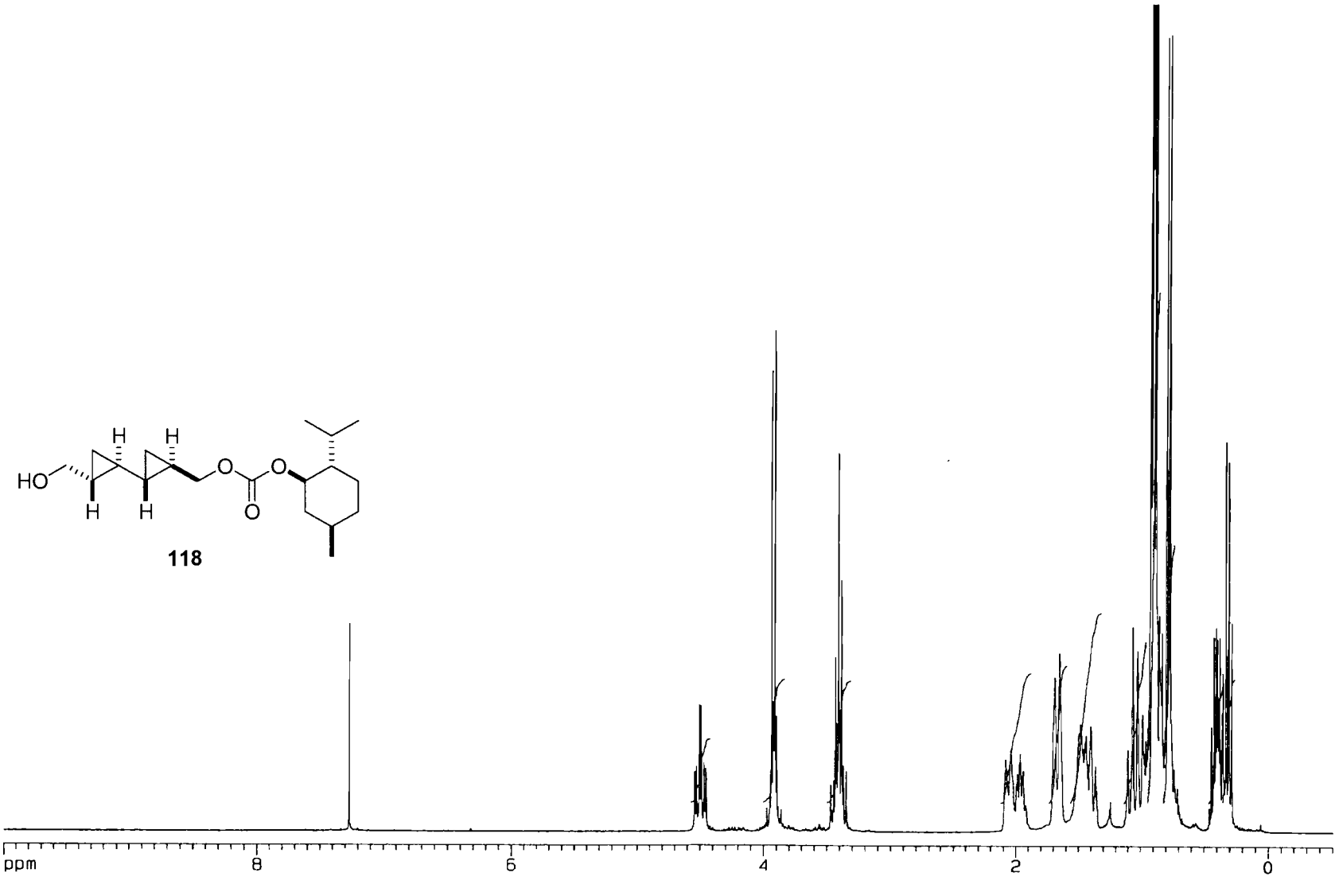

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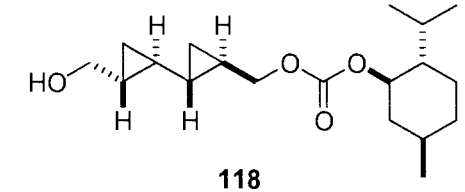

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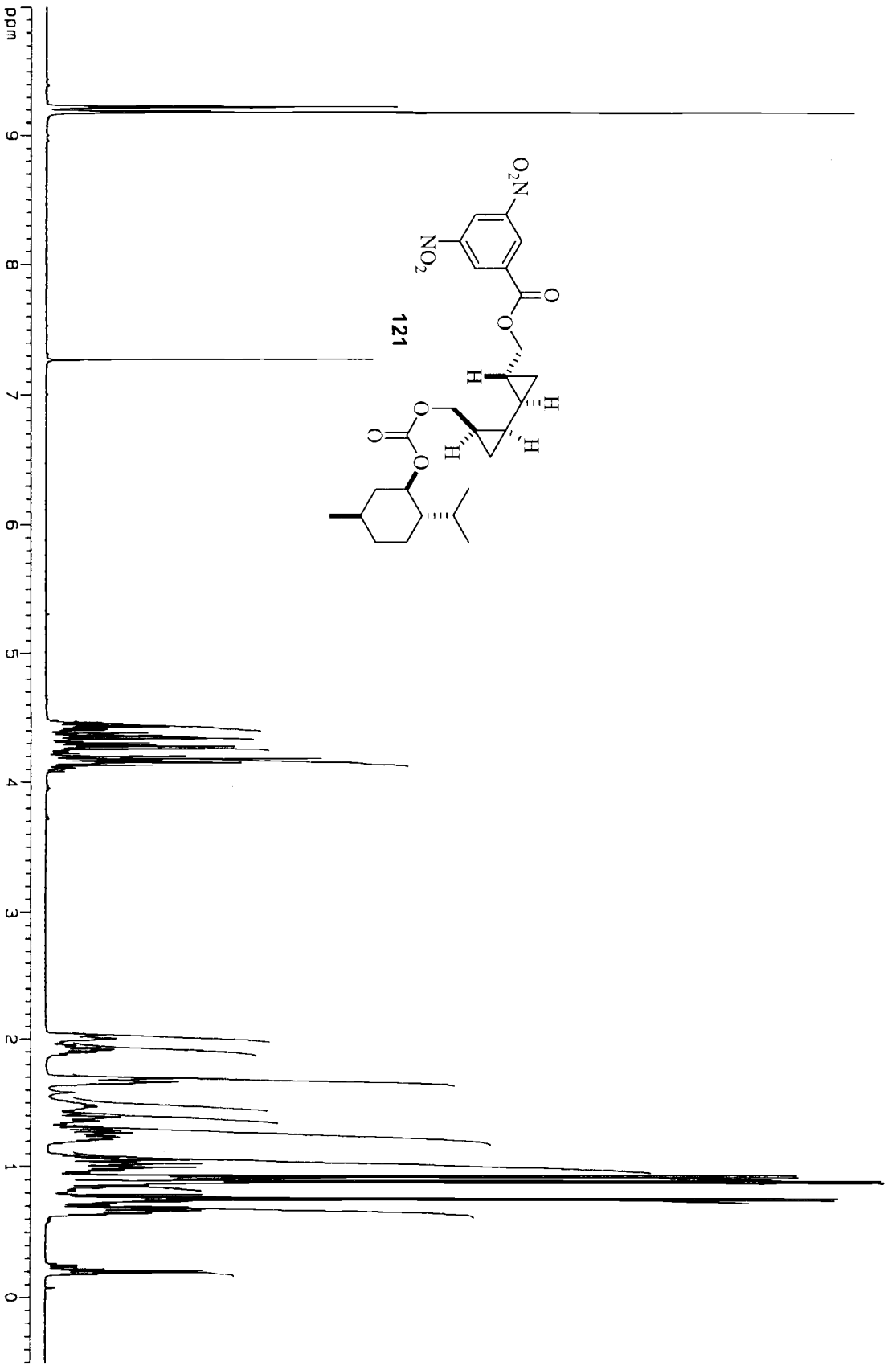
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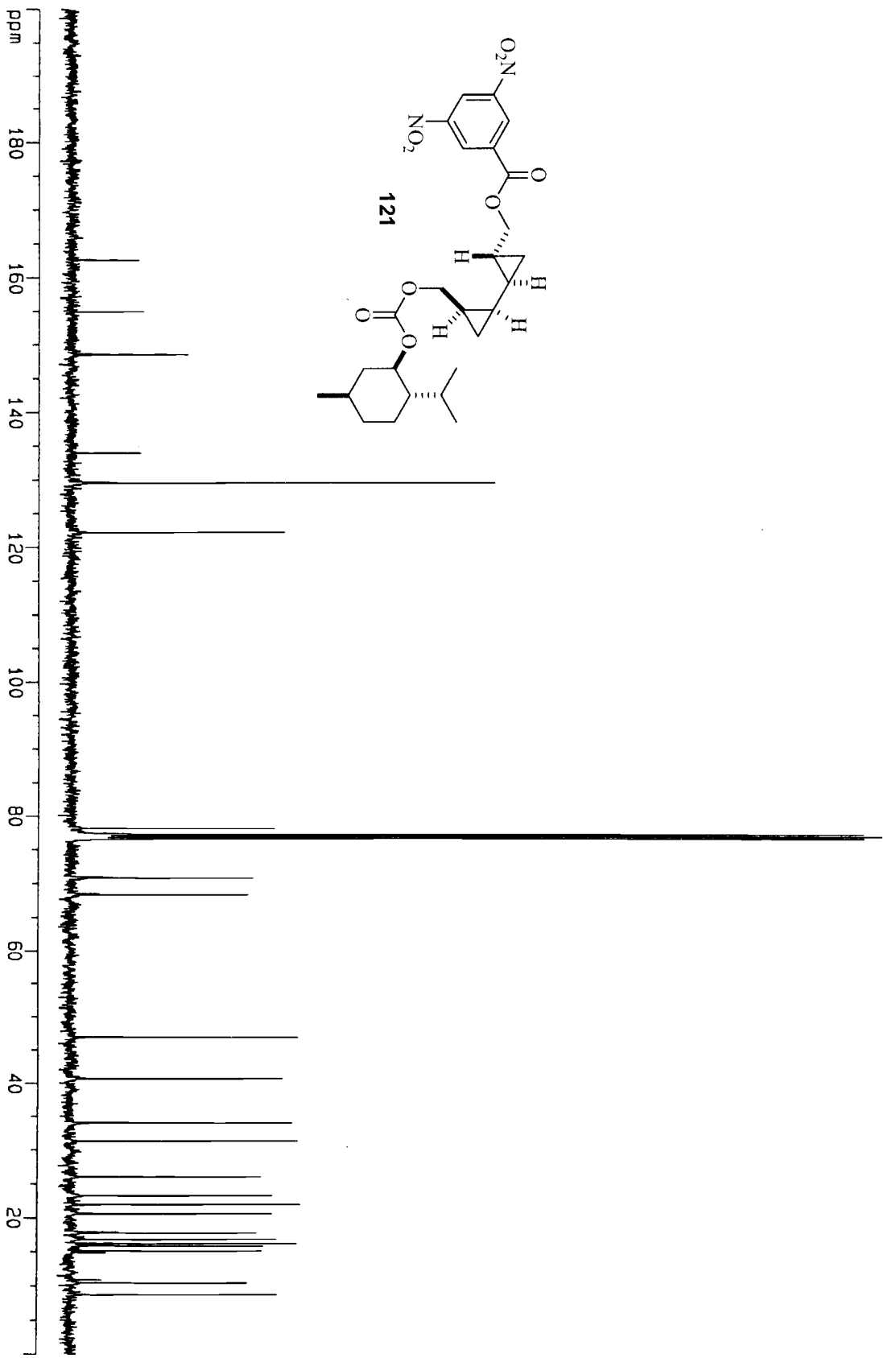
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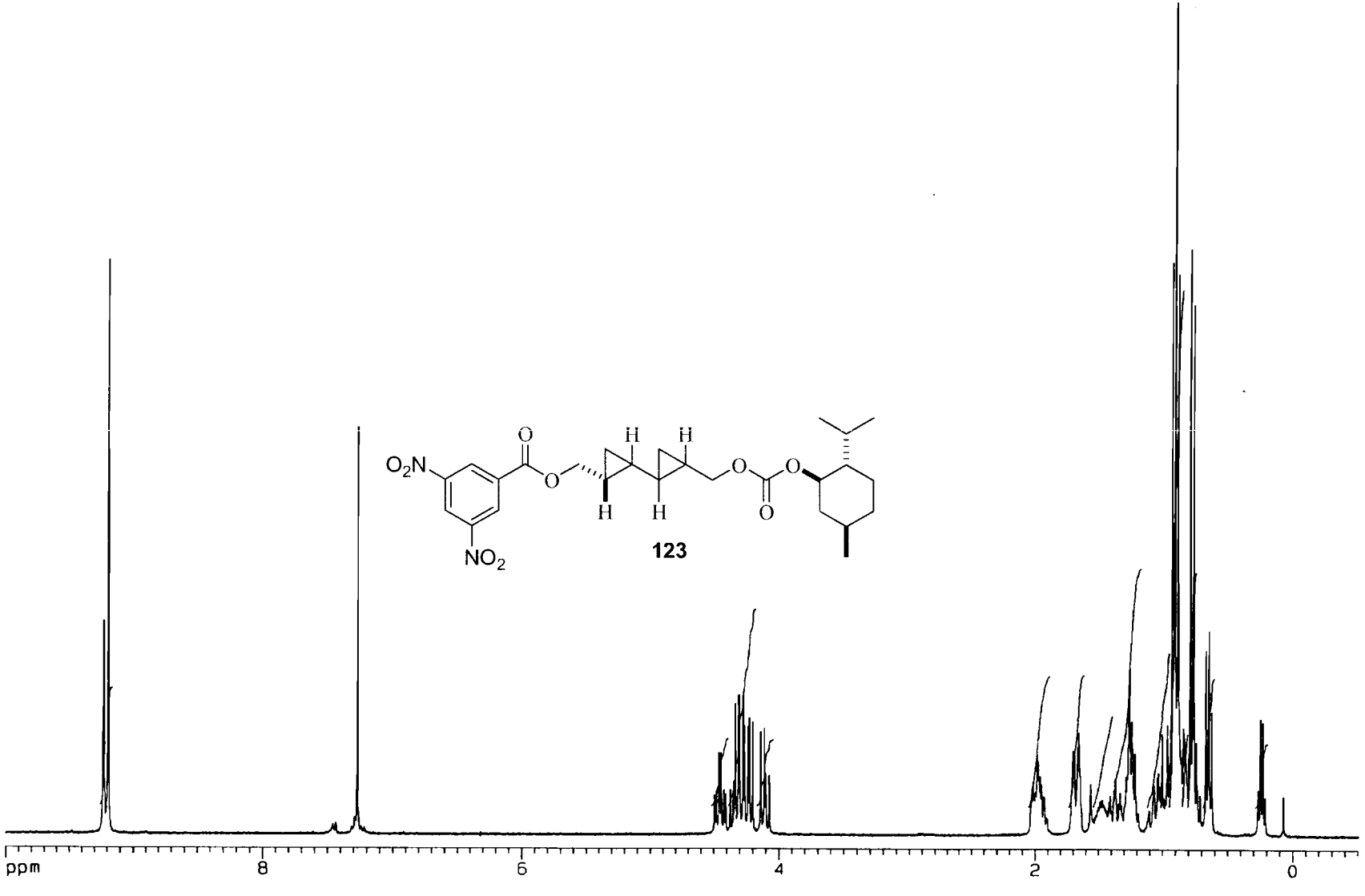

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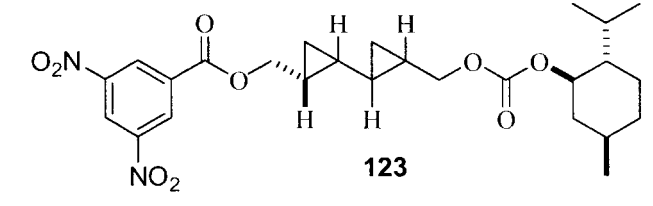

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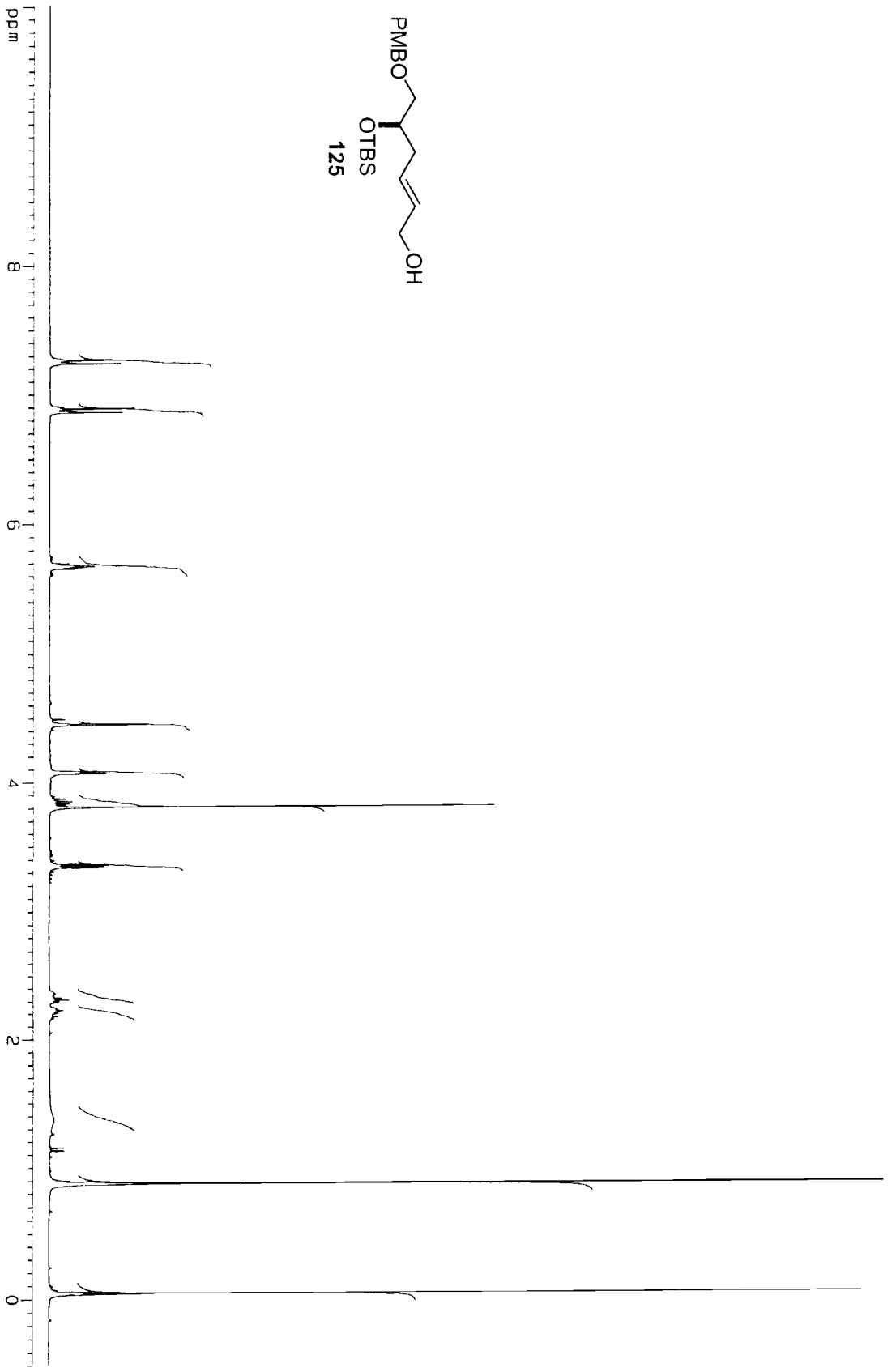
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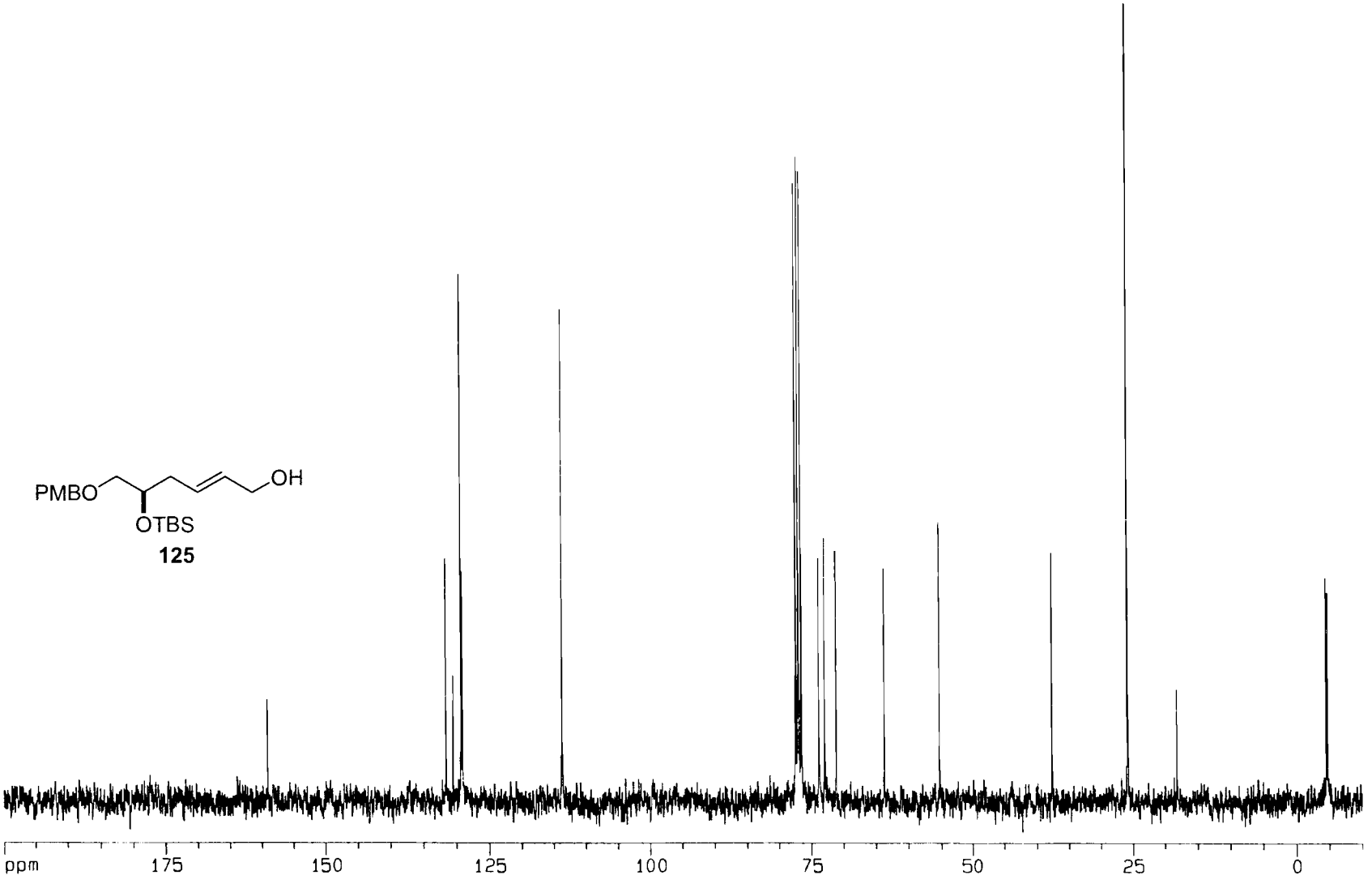
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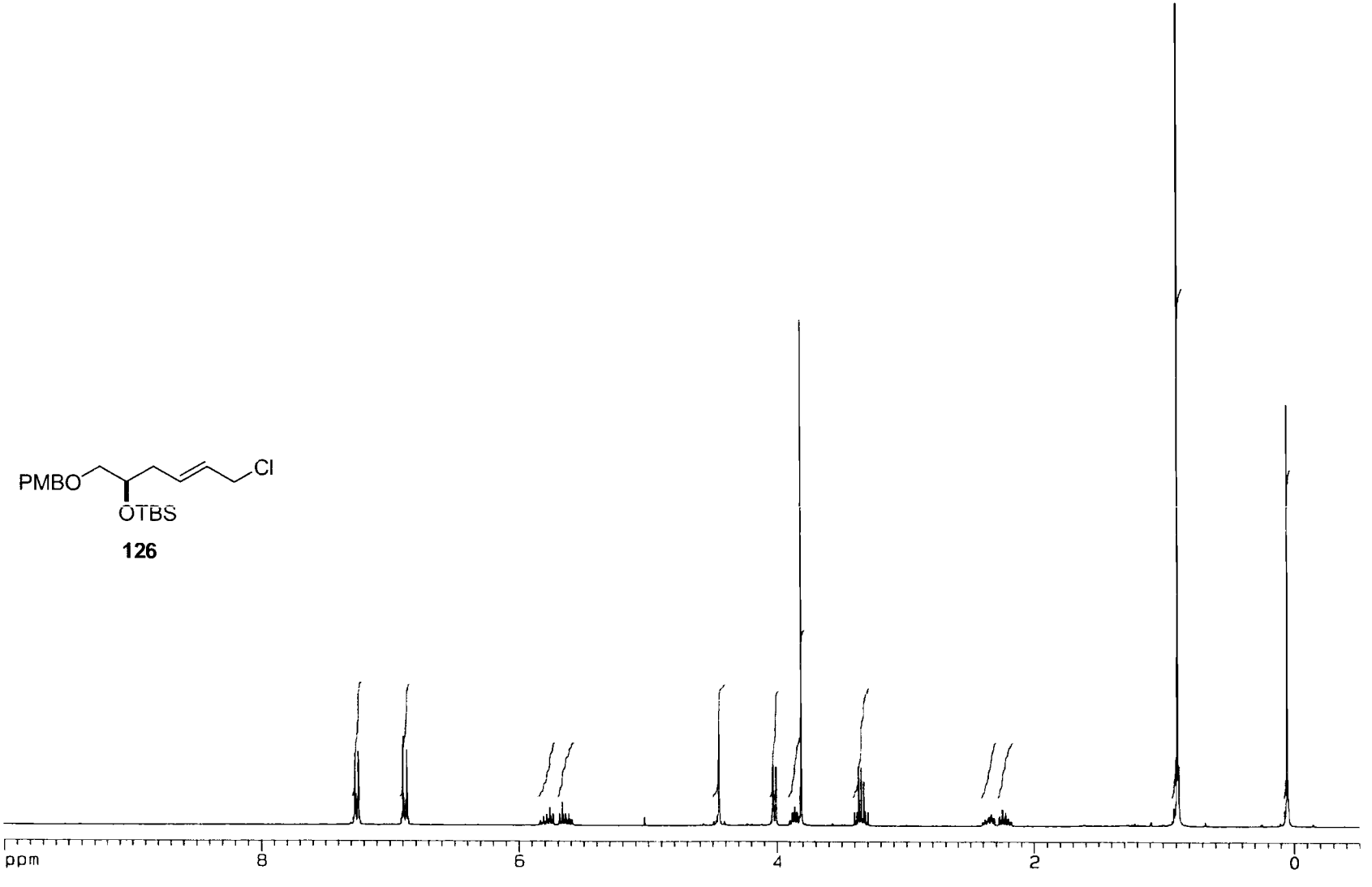

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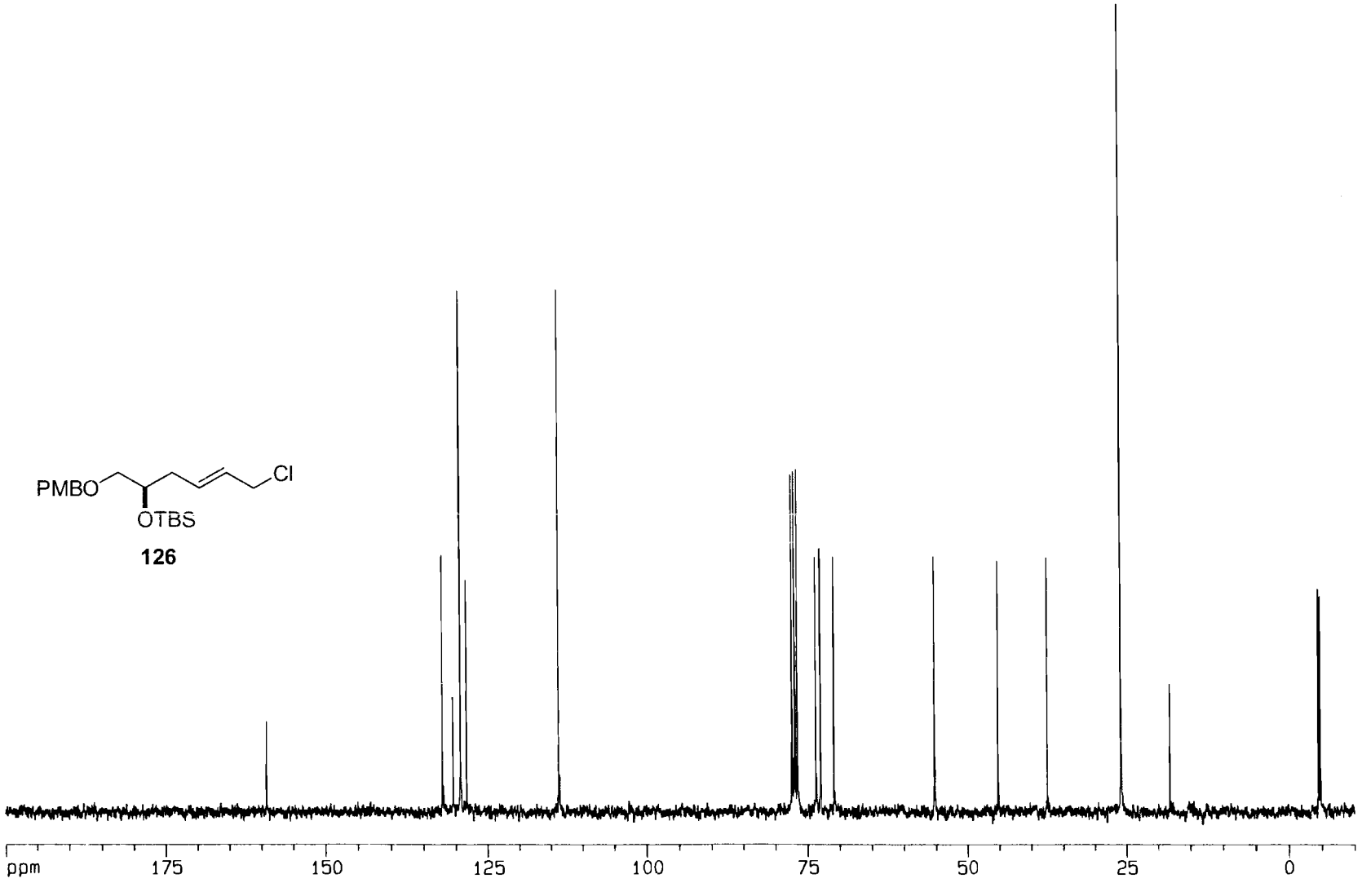
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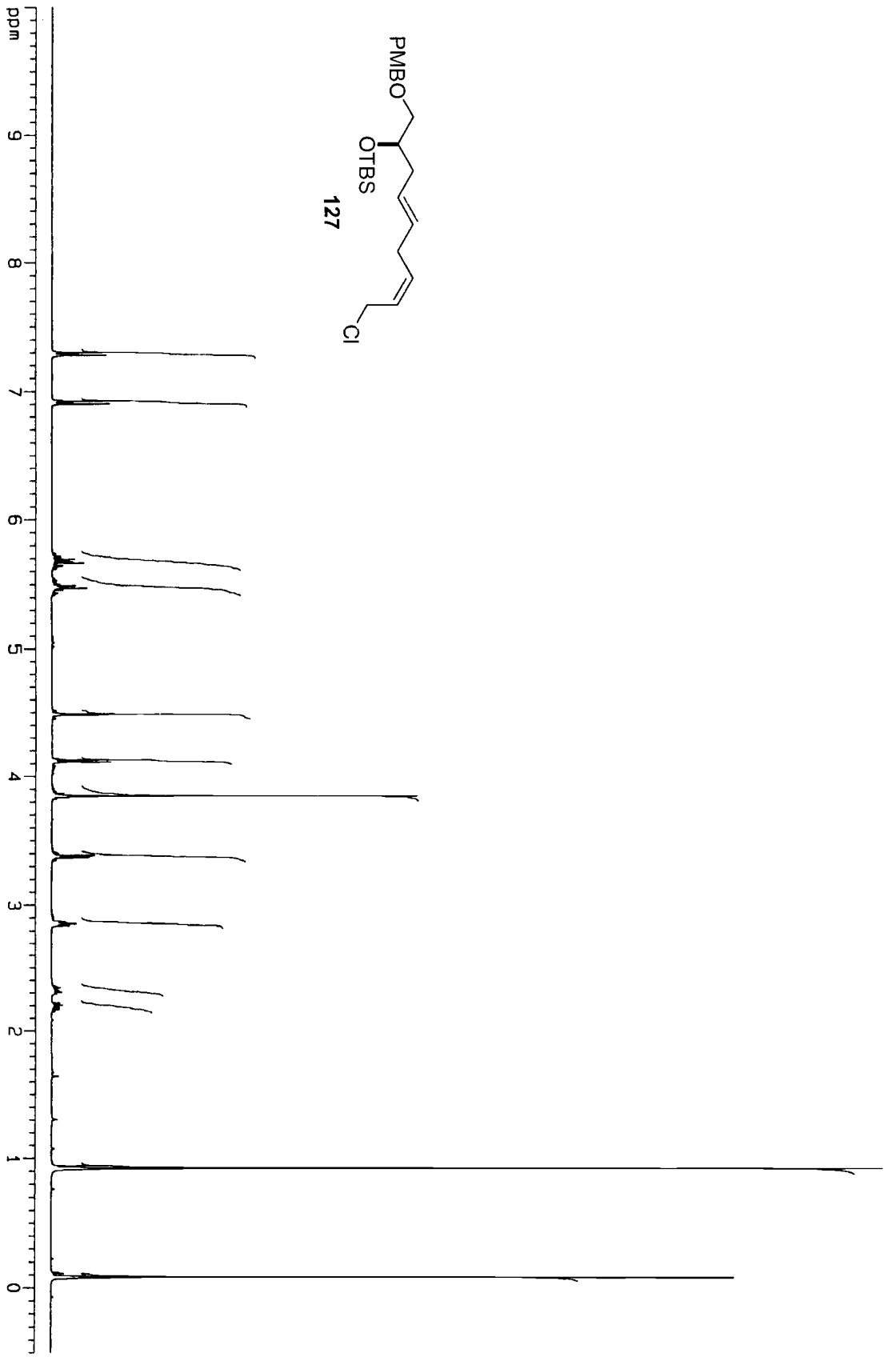
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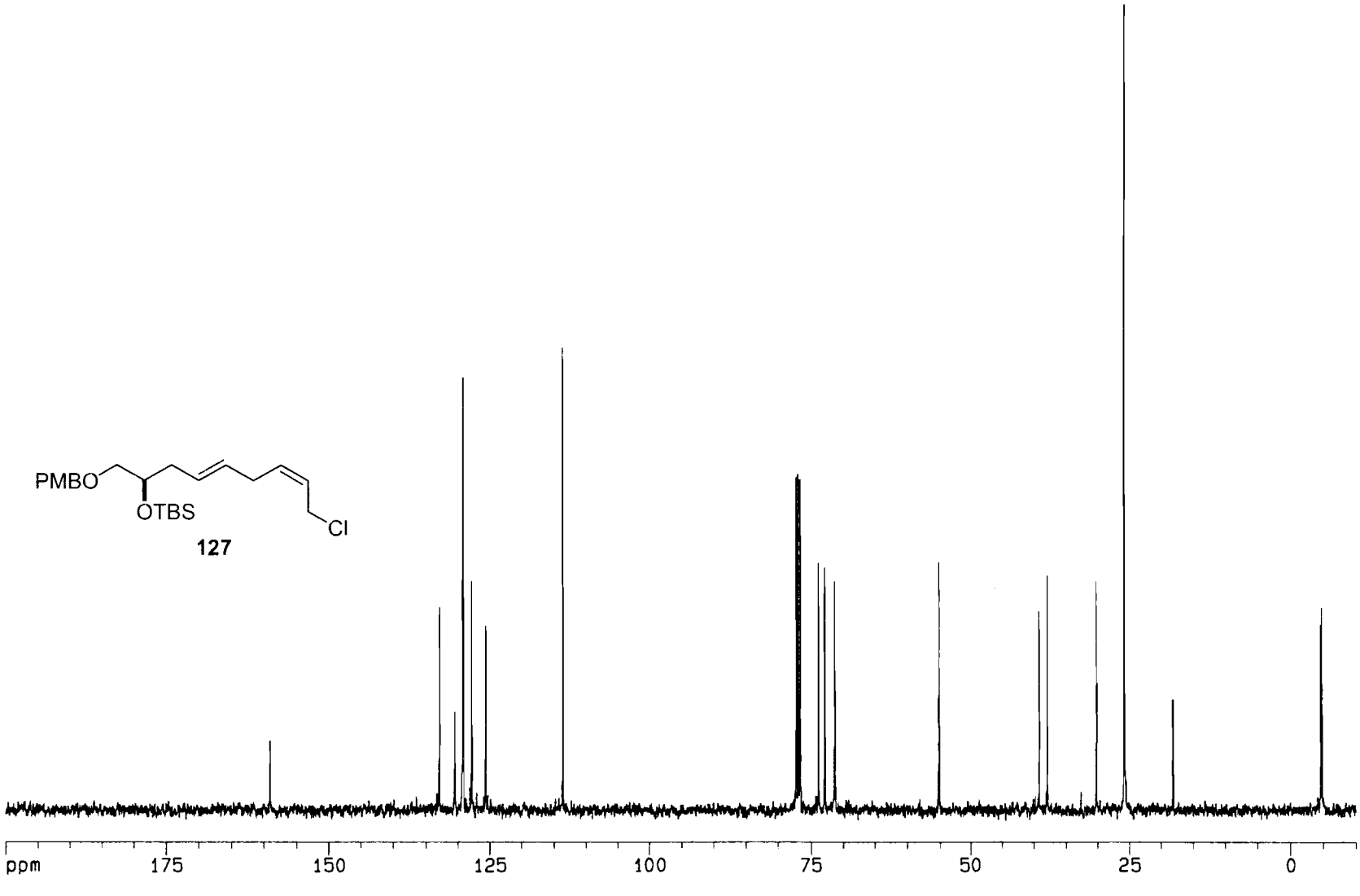
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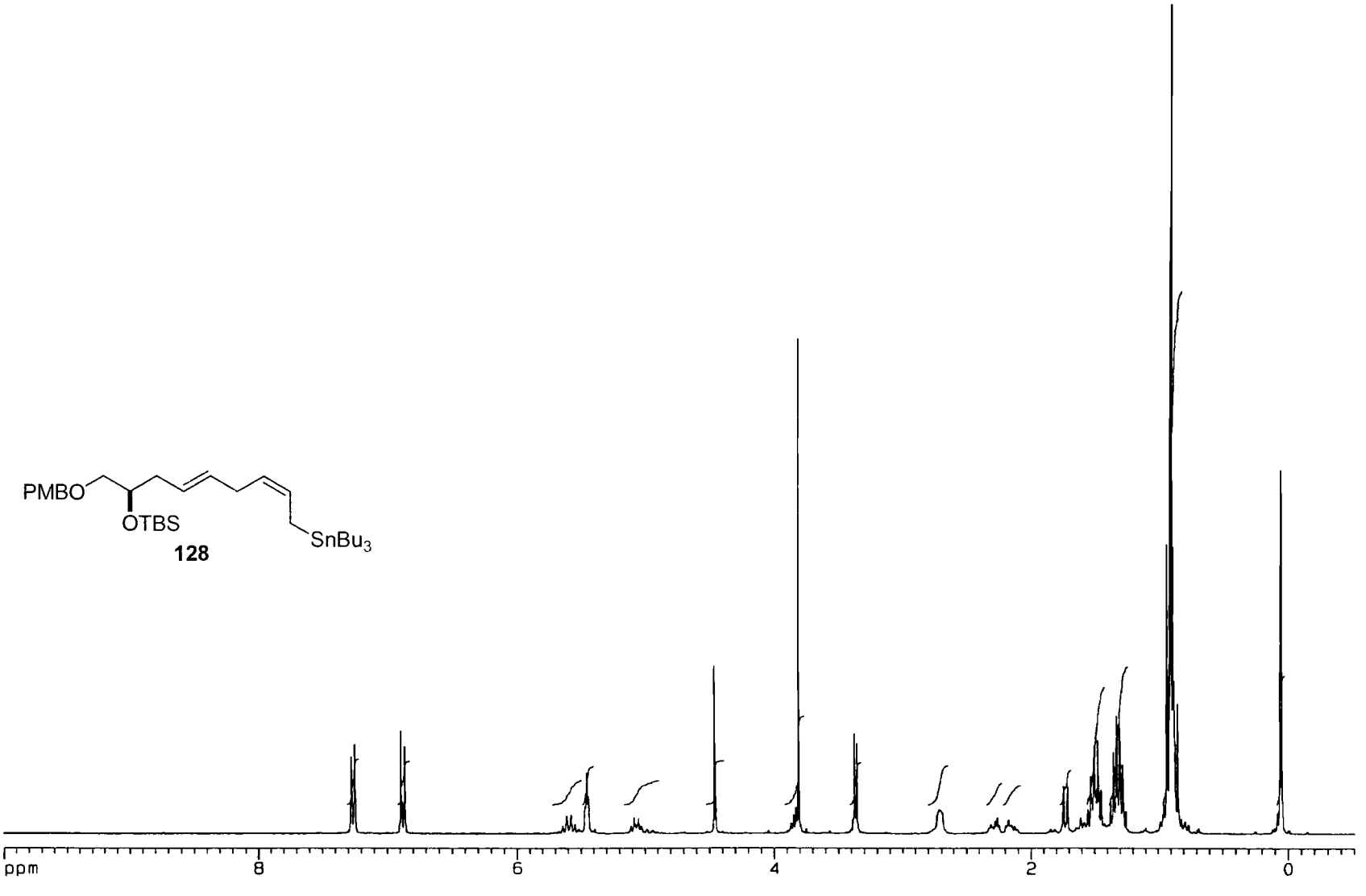
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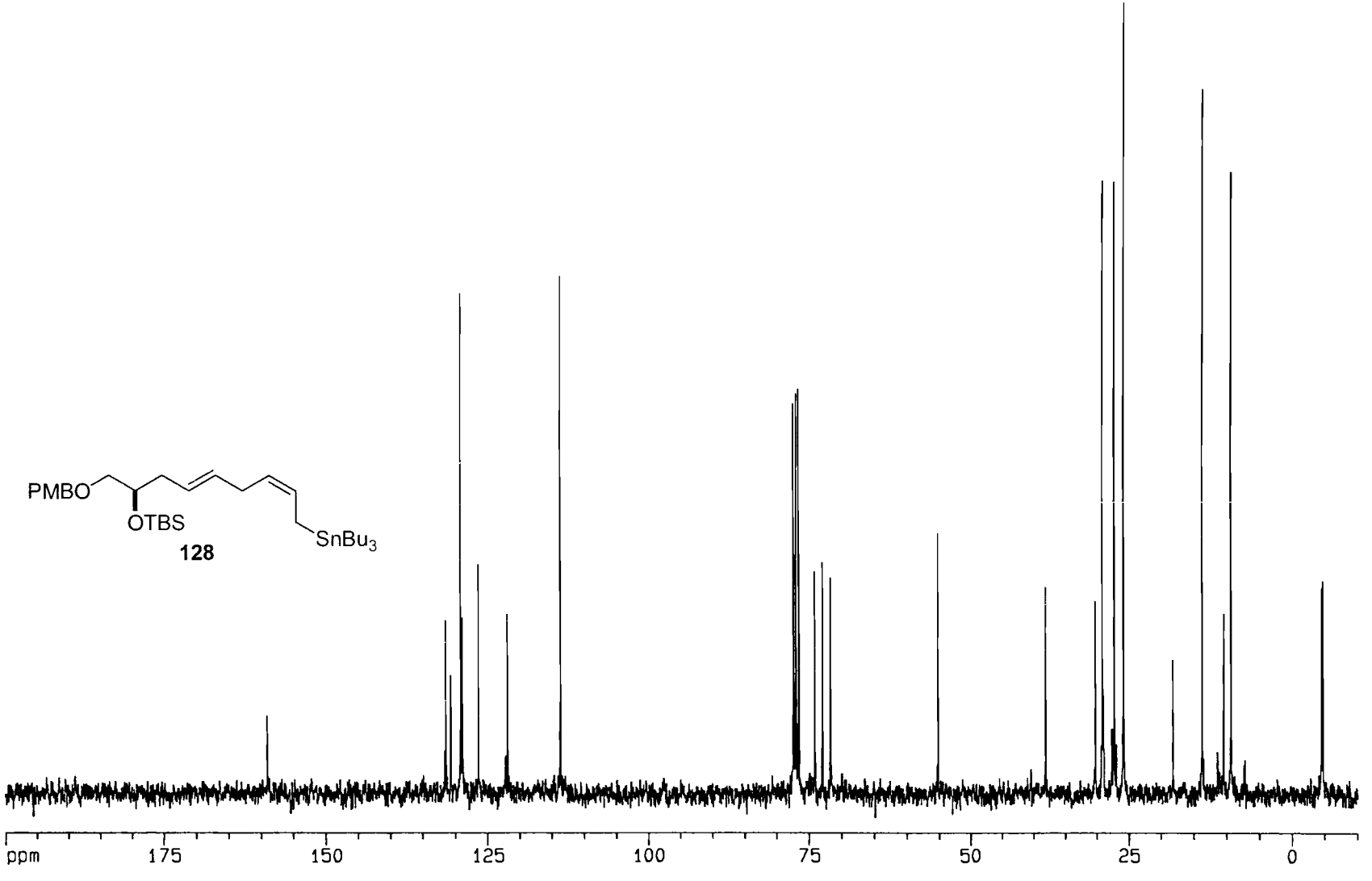
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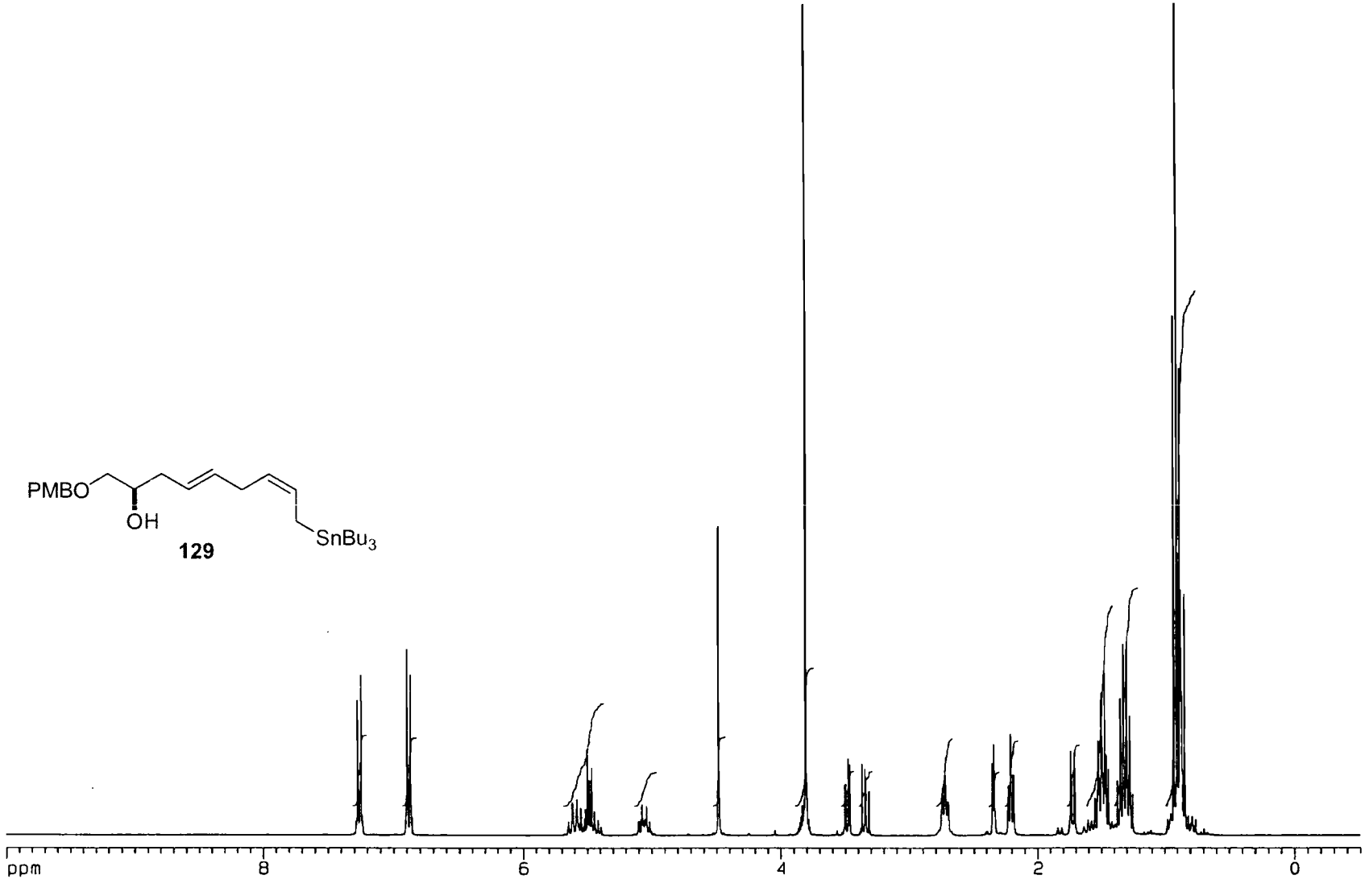
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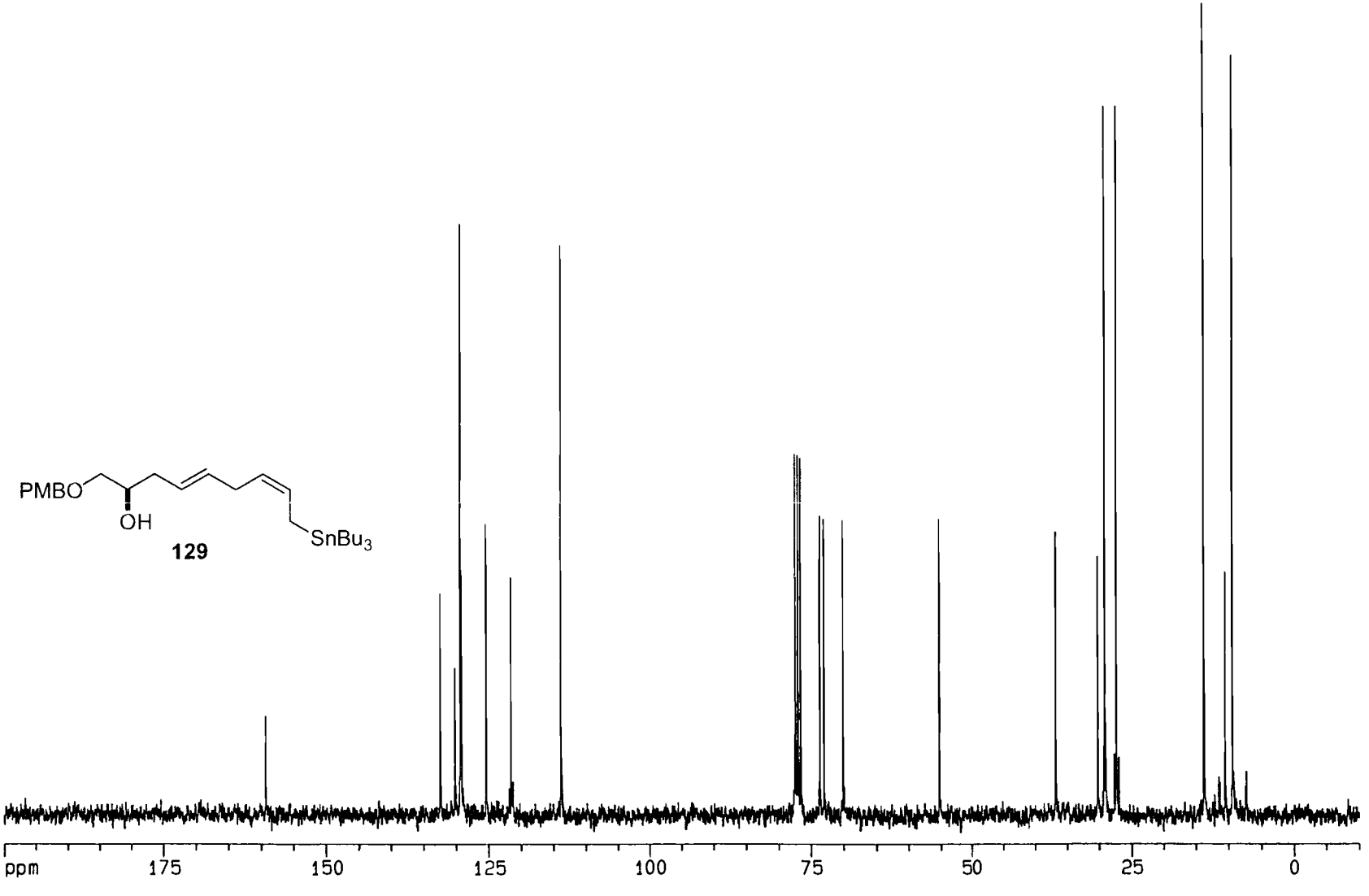
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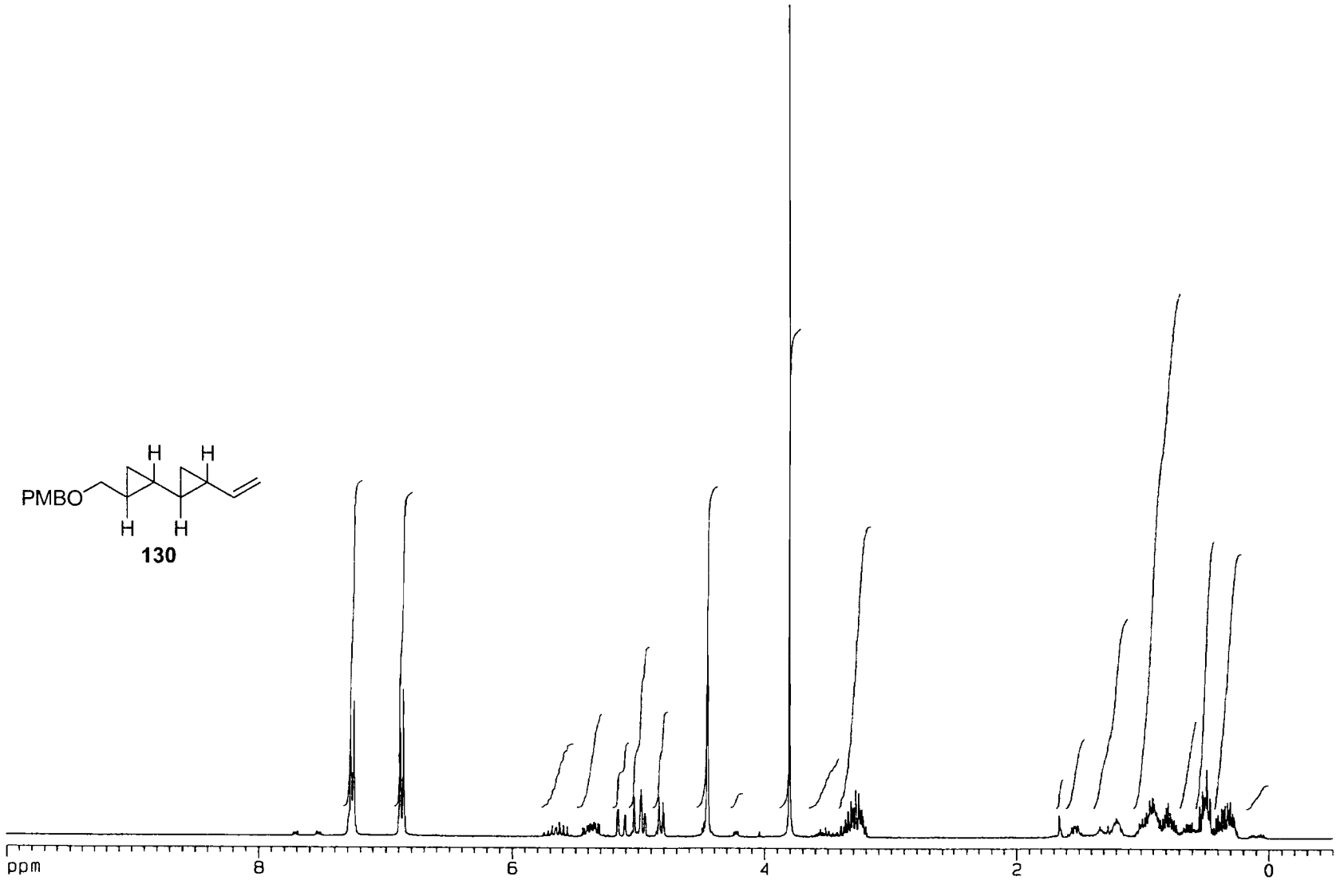

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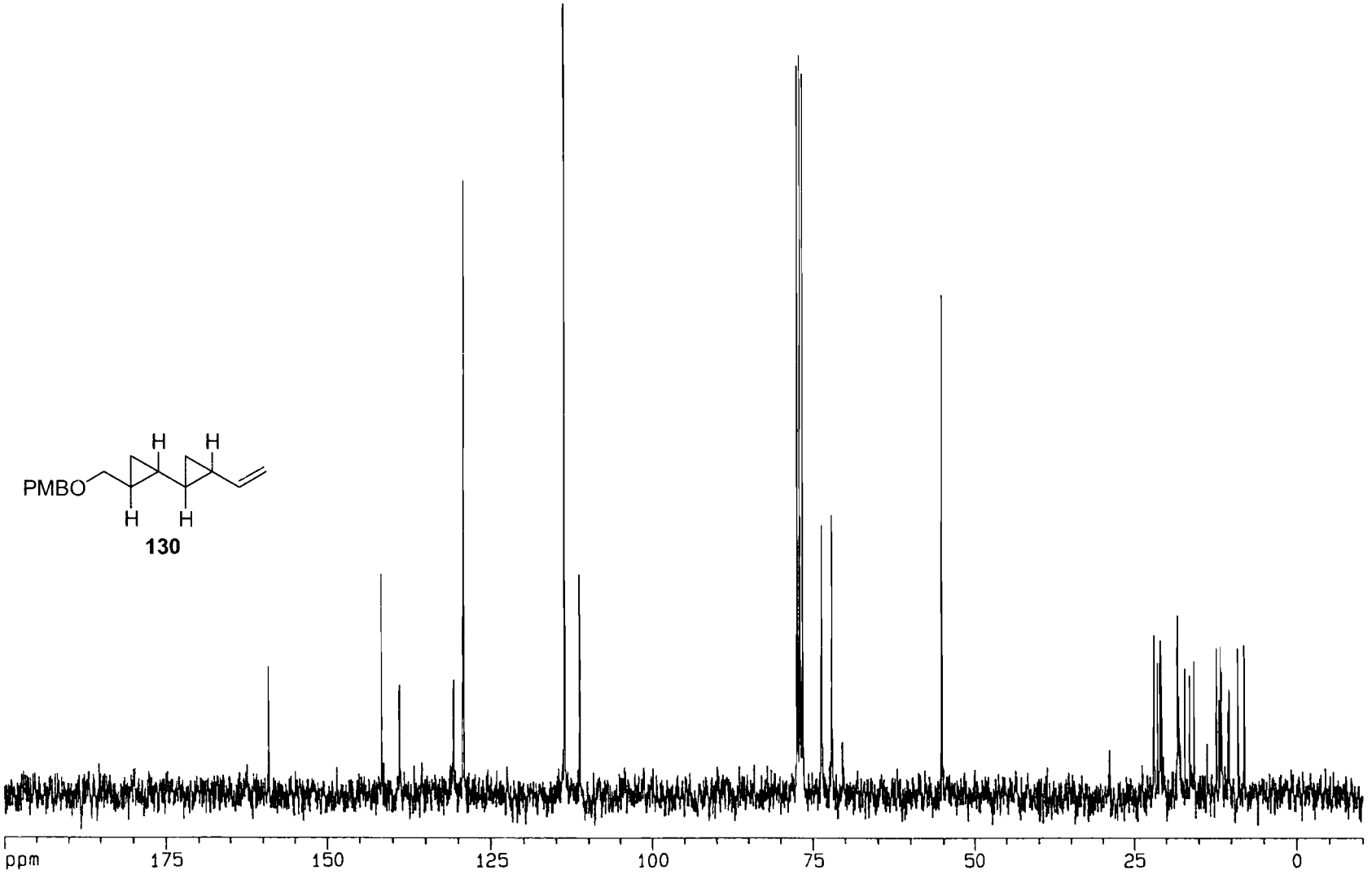

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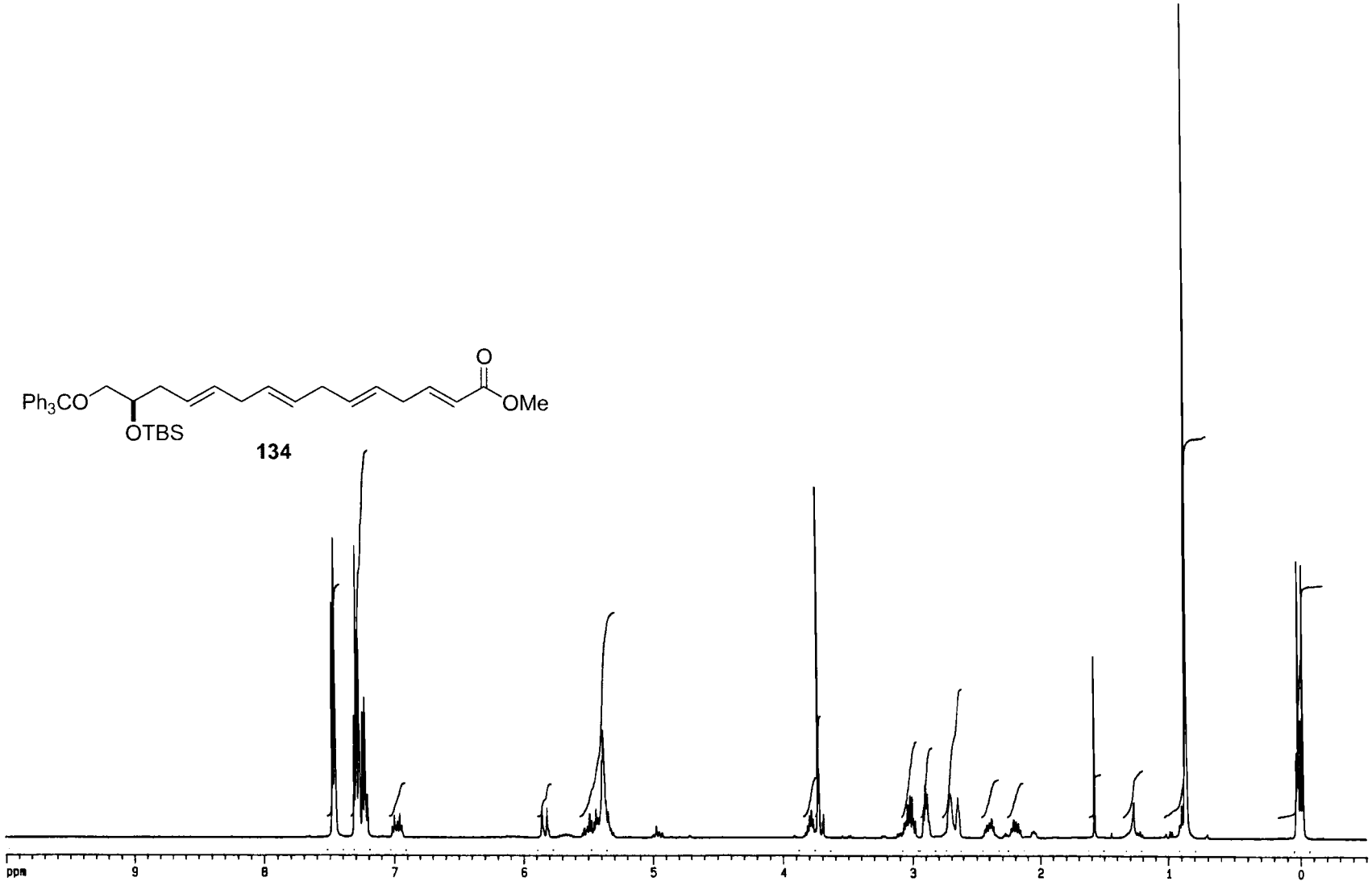

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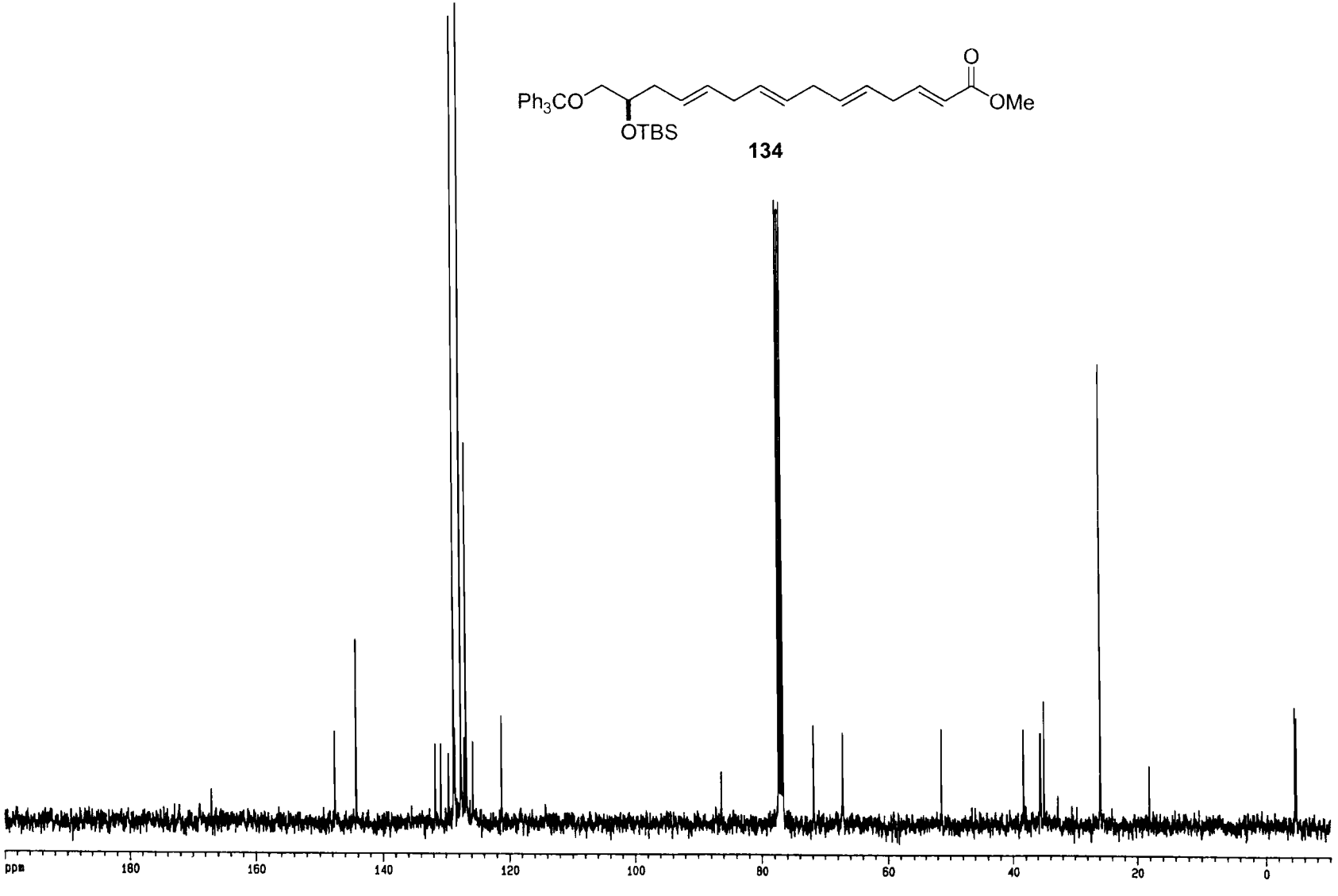
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20
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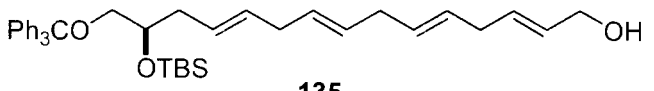

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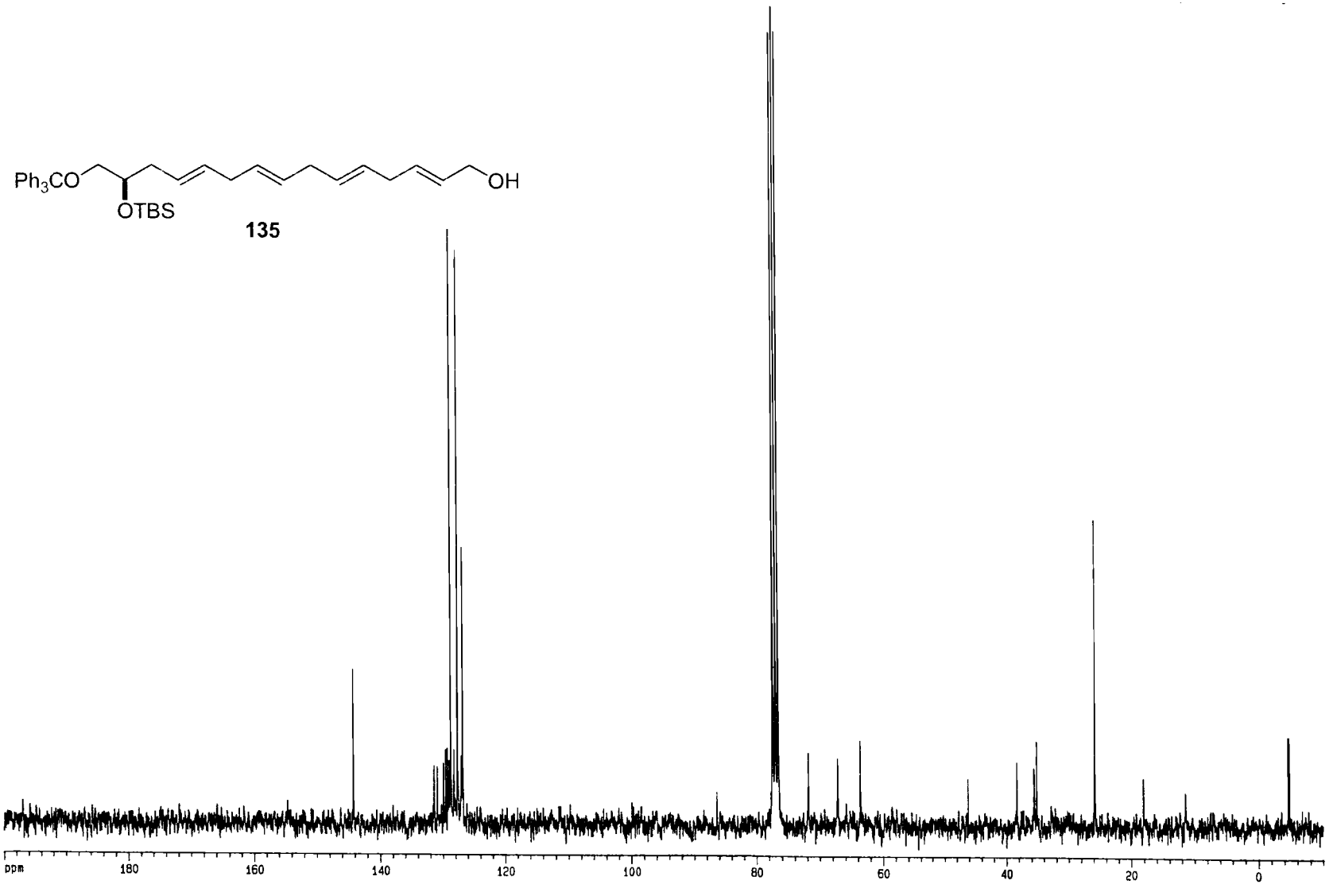
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60
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20
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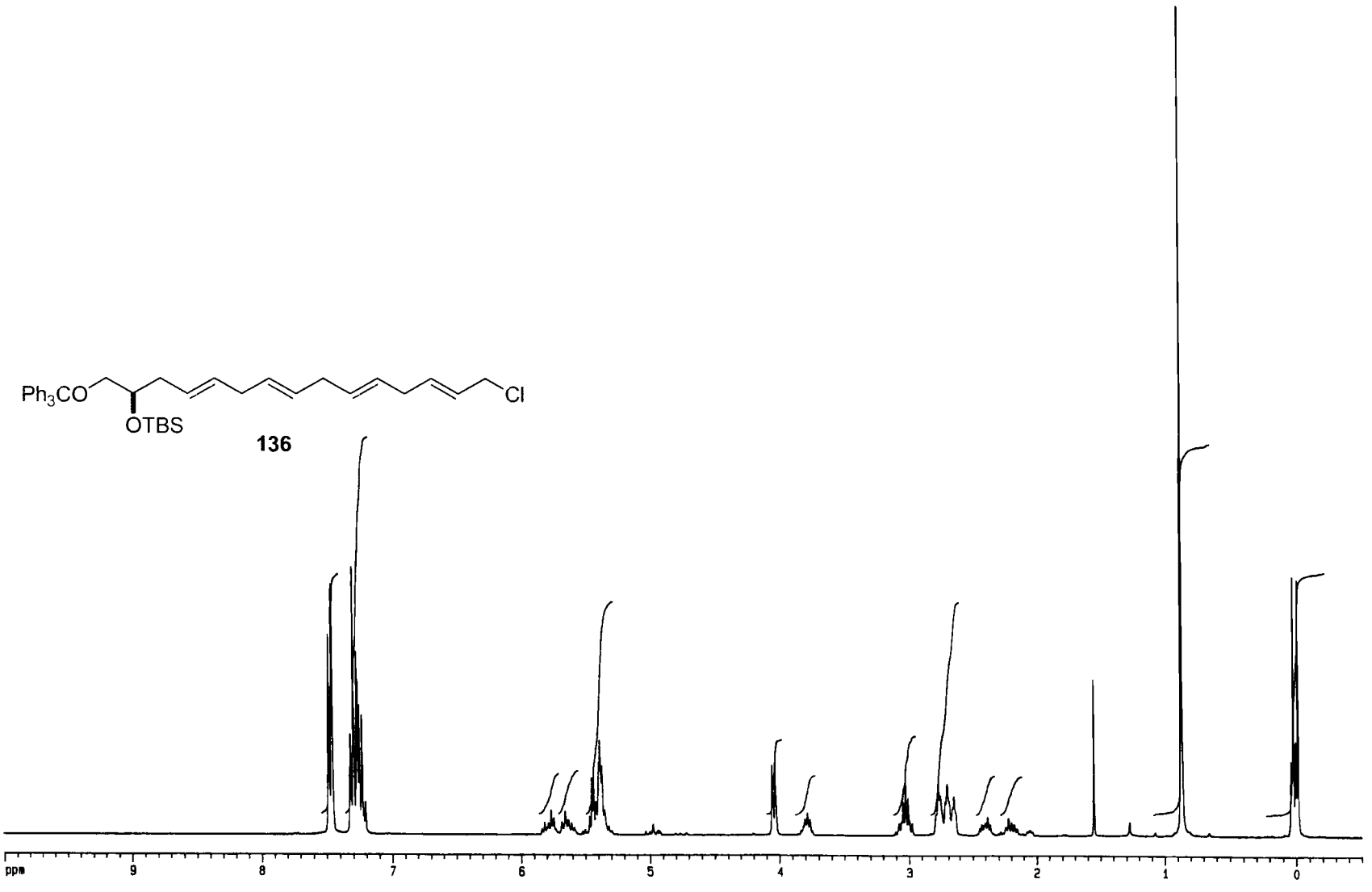
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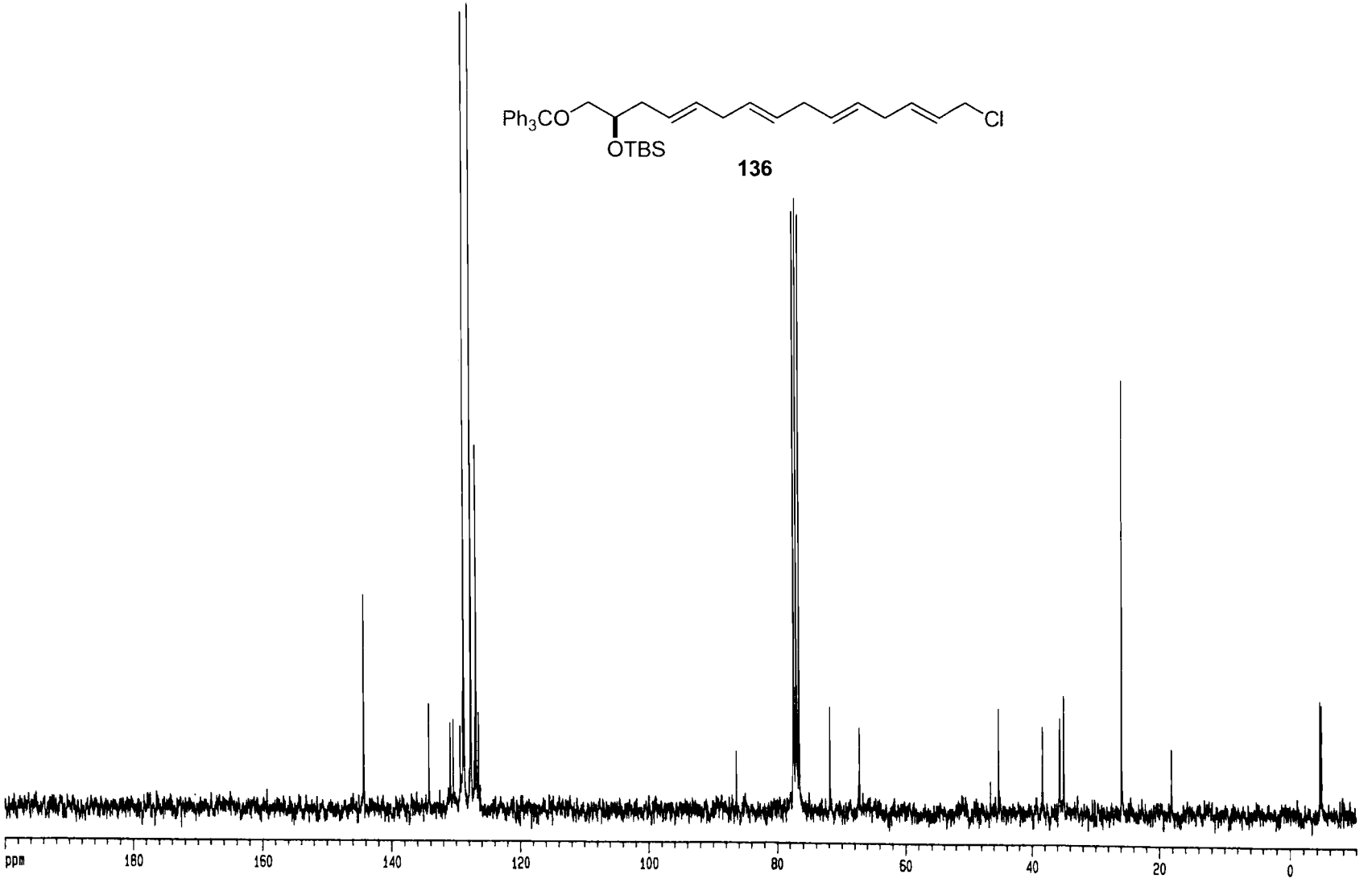

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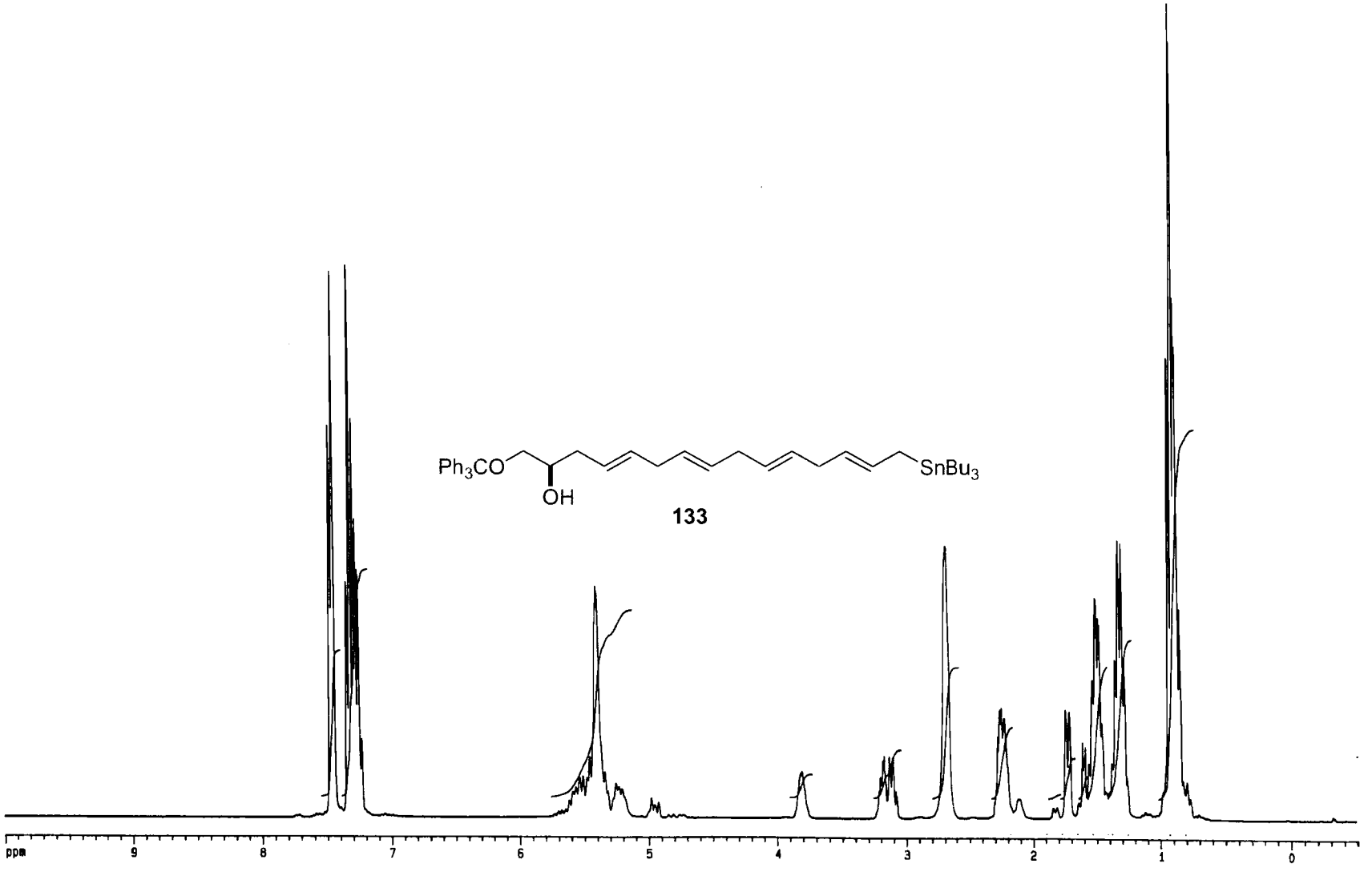

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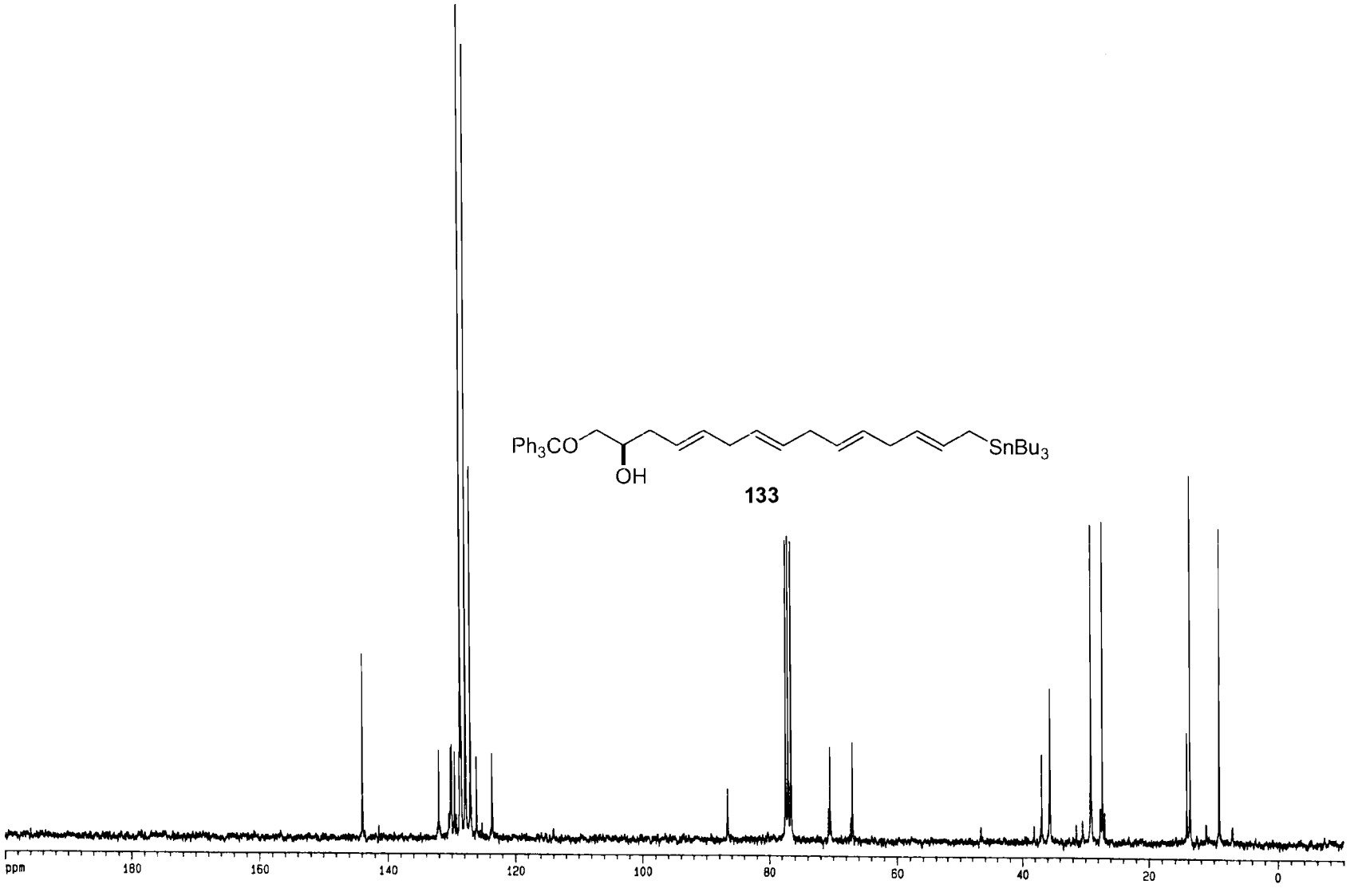

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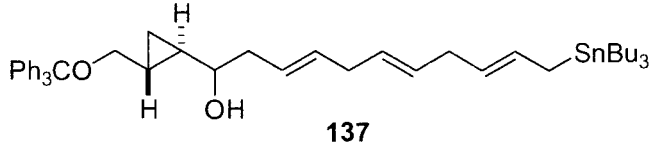

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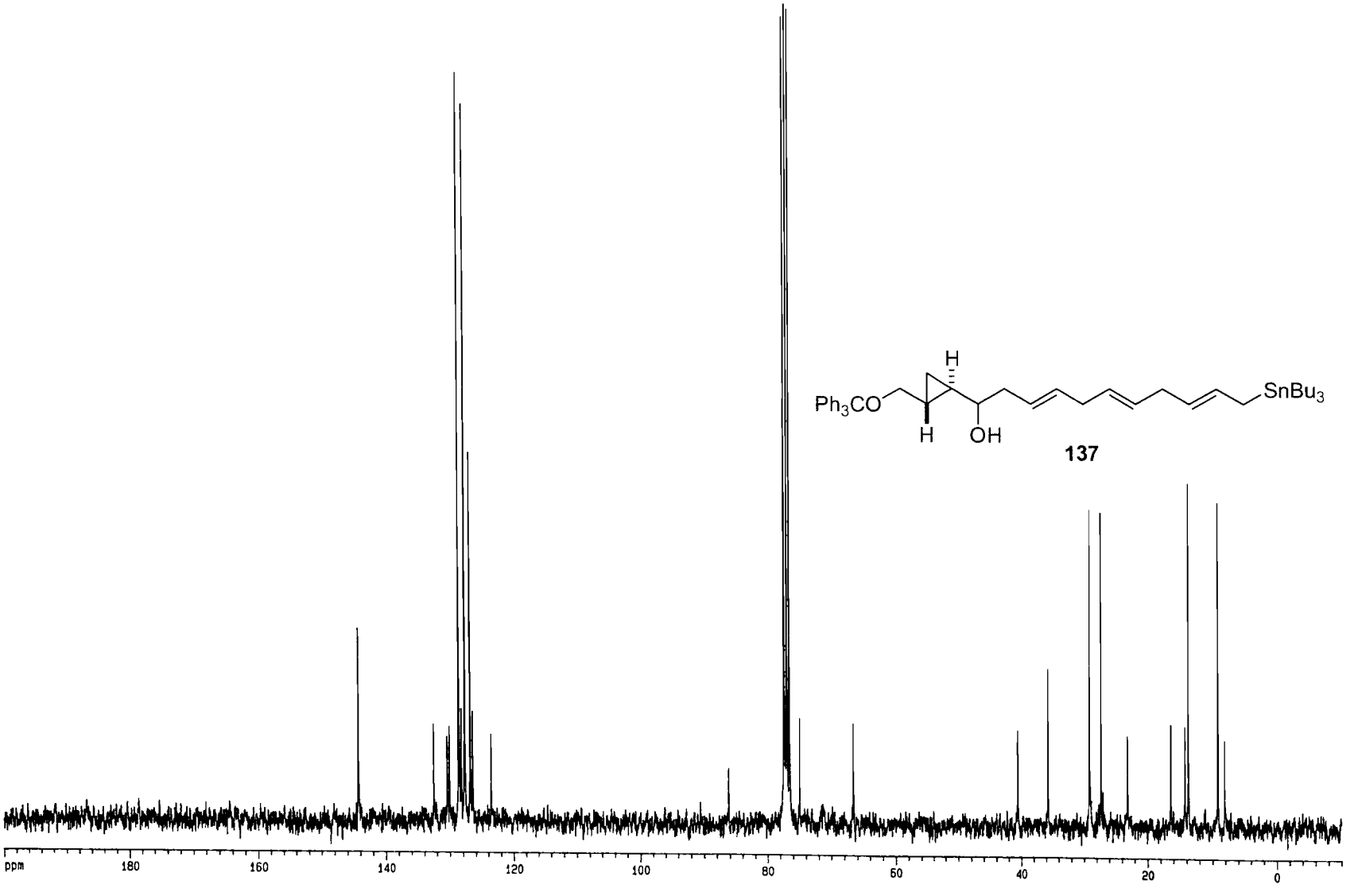
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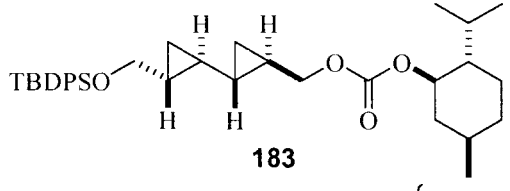

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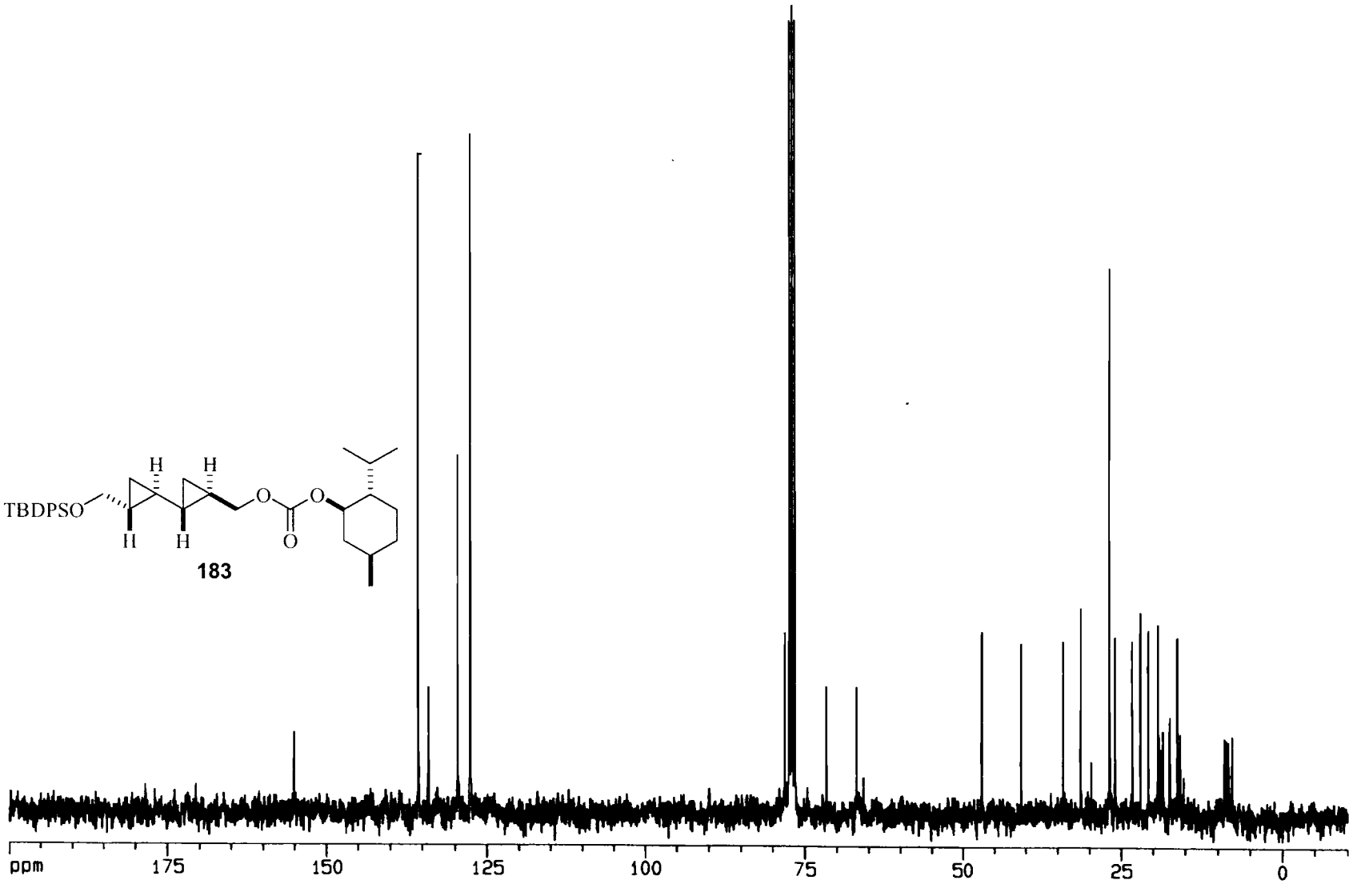
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75
50
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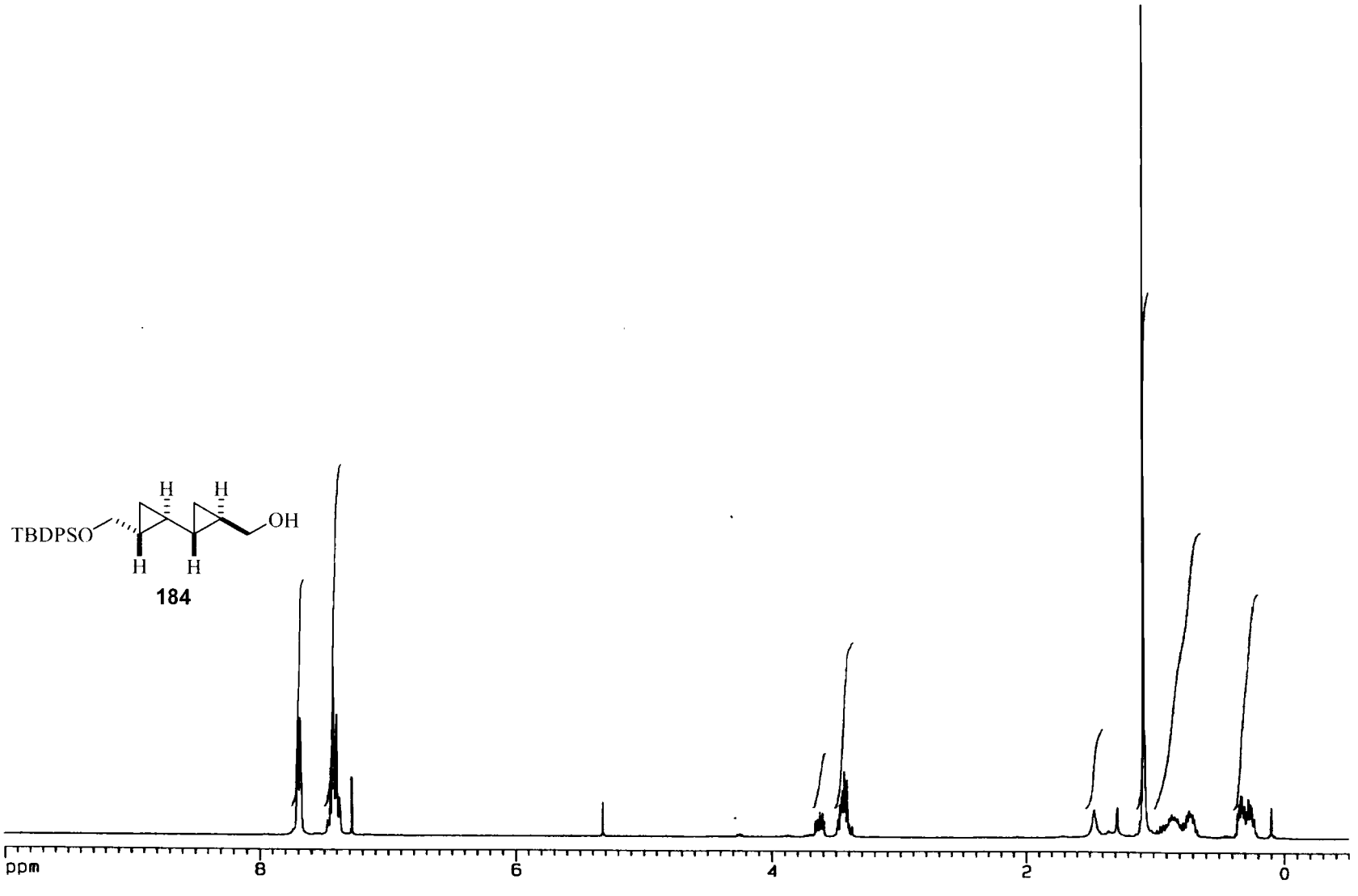

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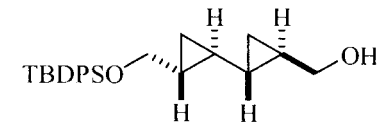

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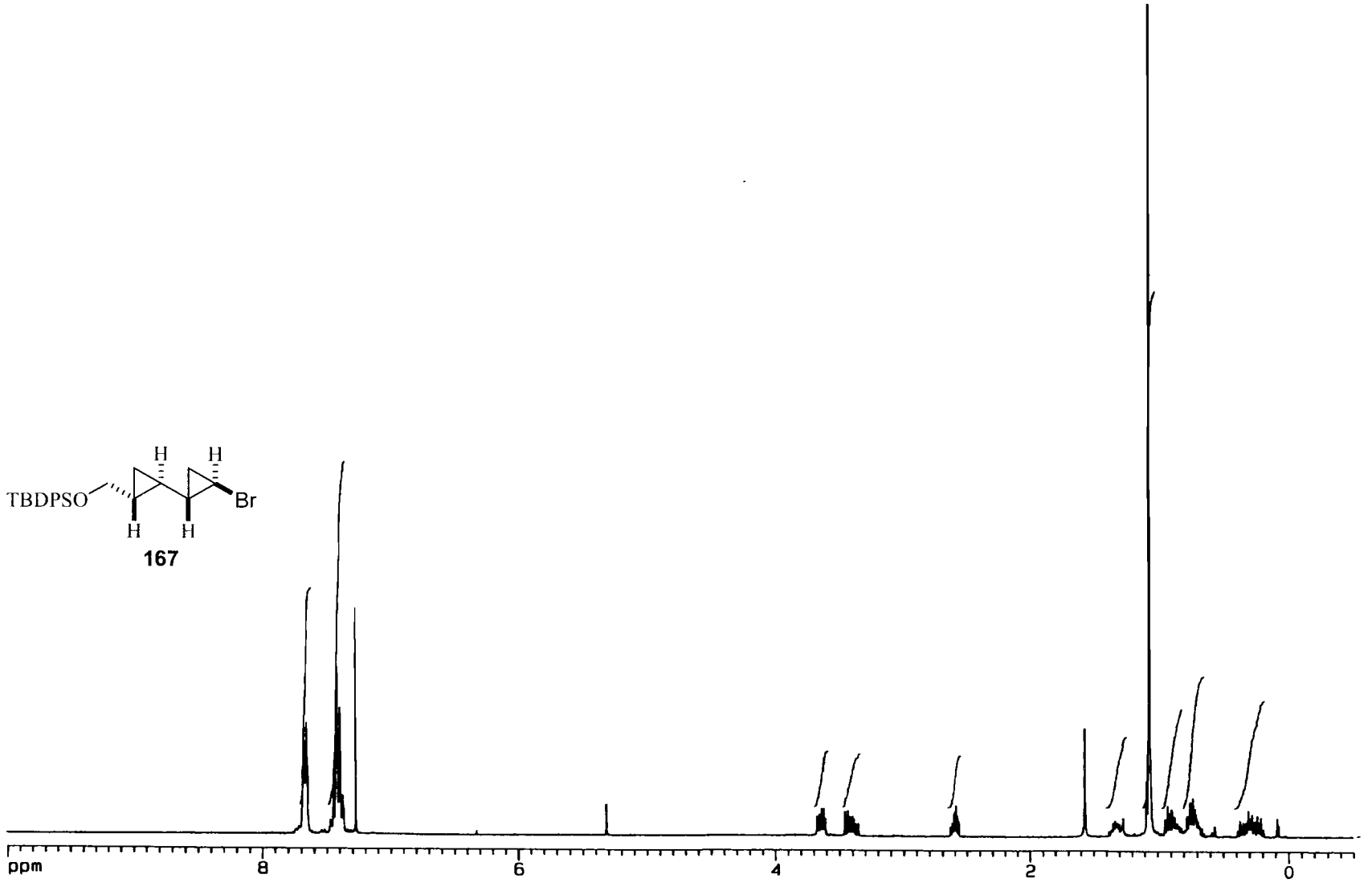

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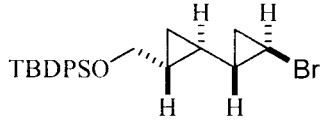

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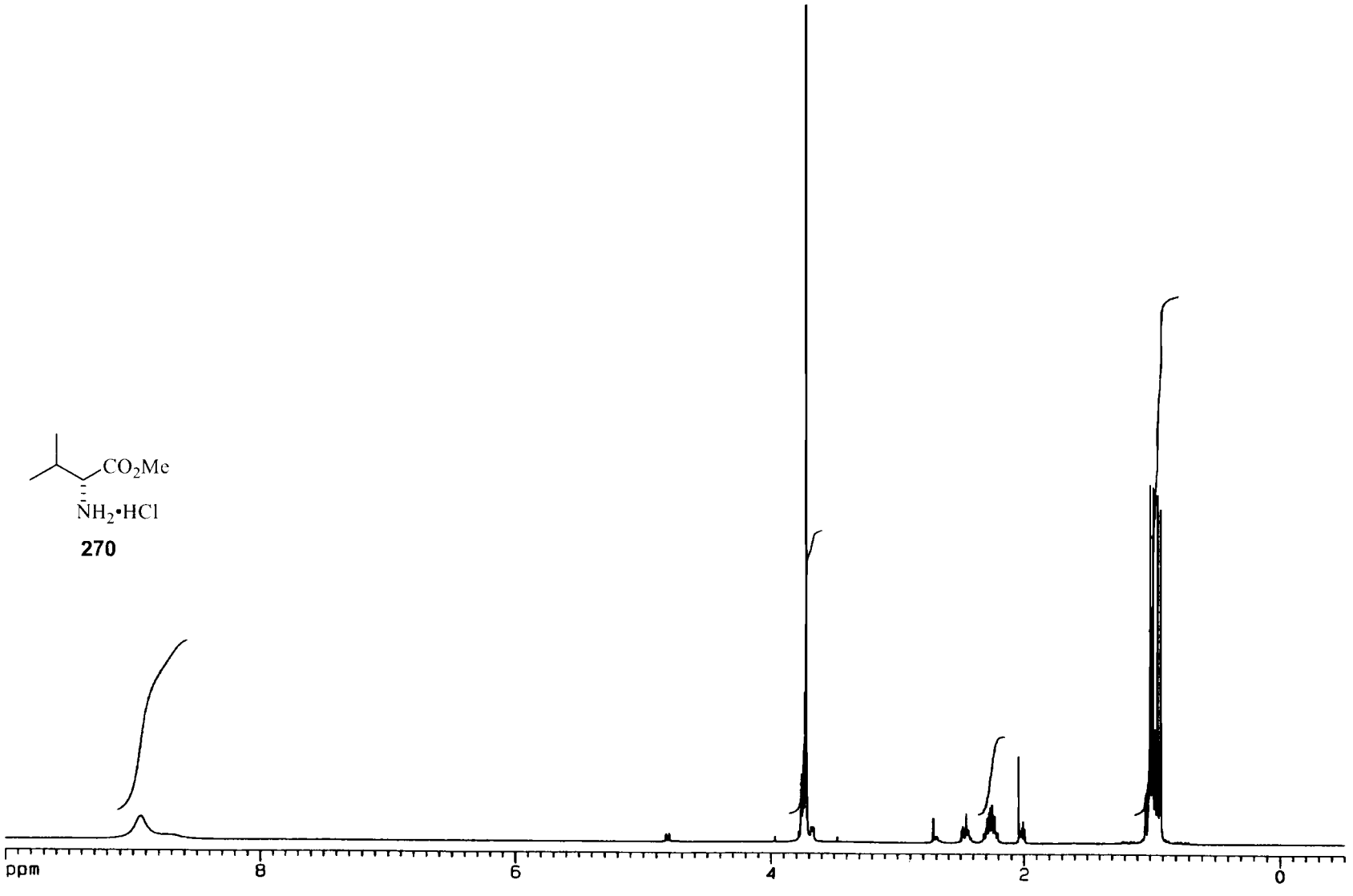

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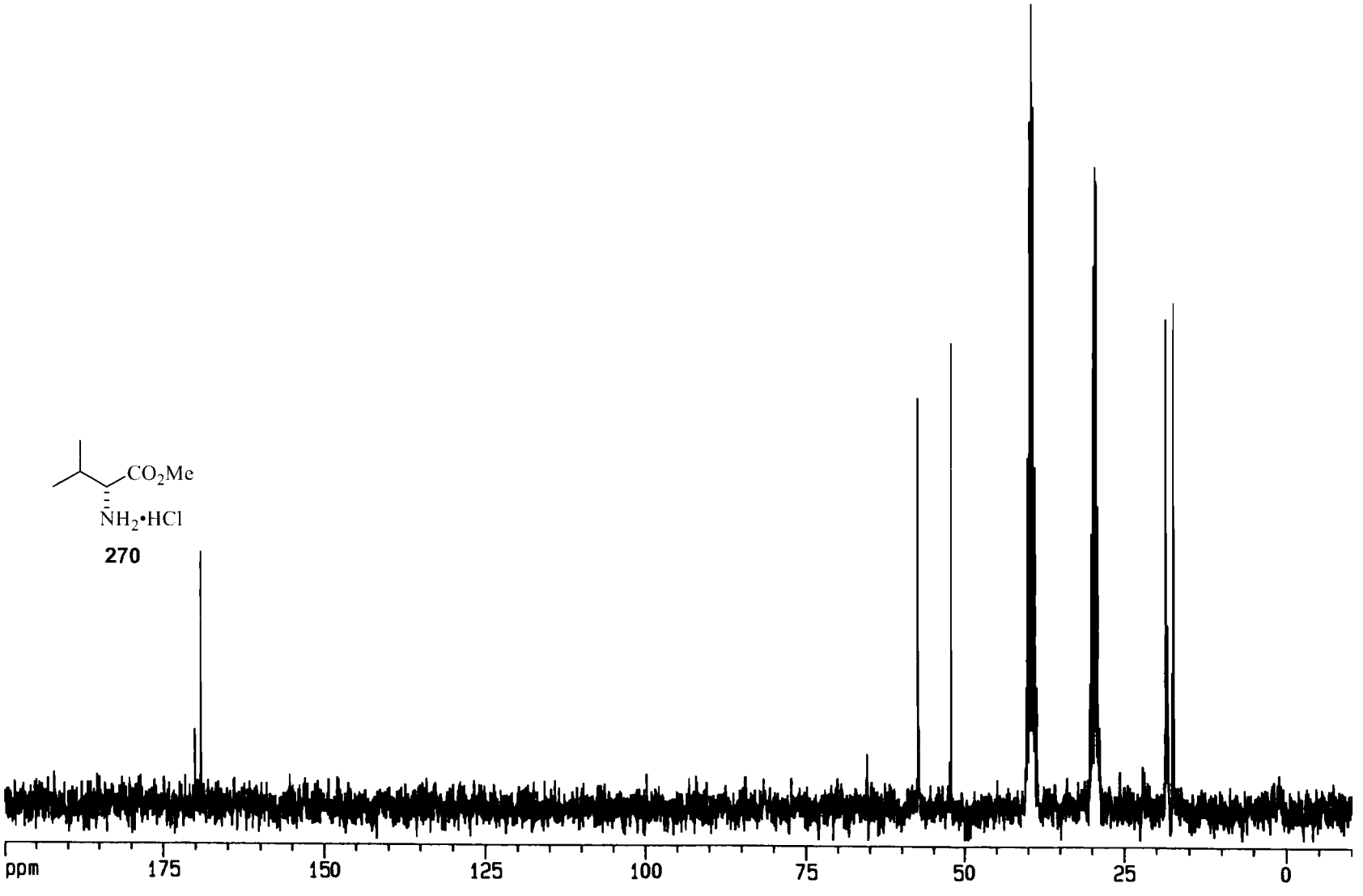
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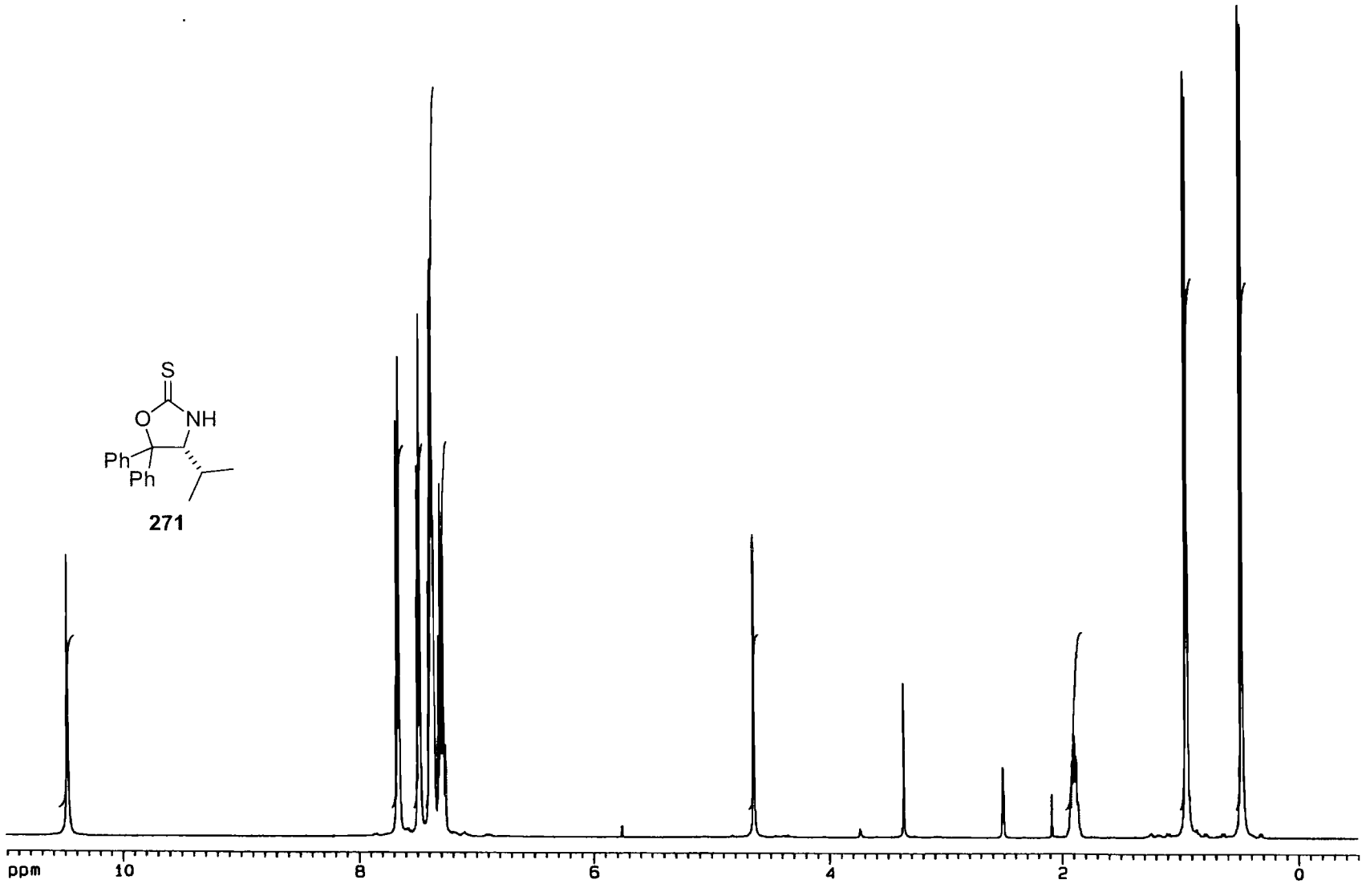

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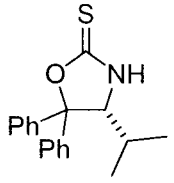

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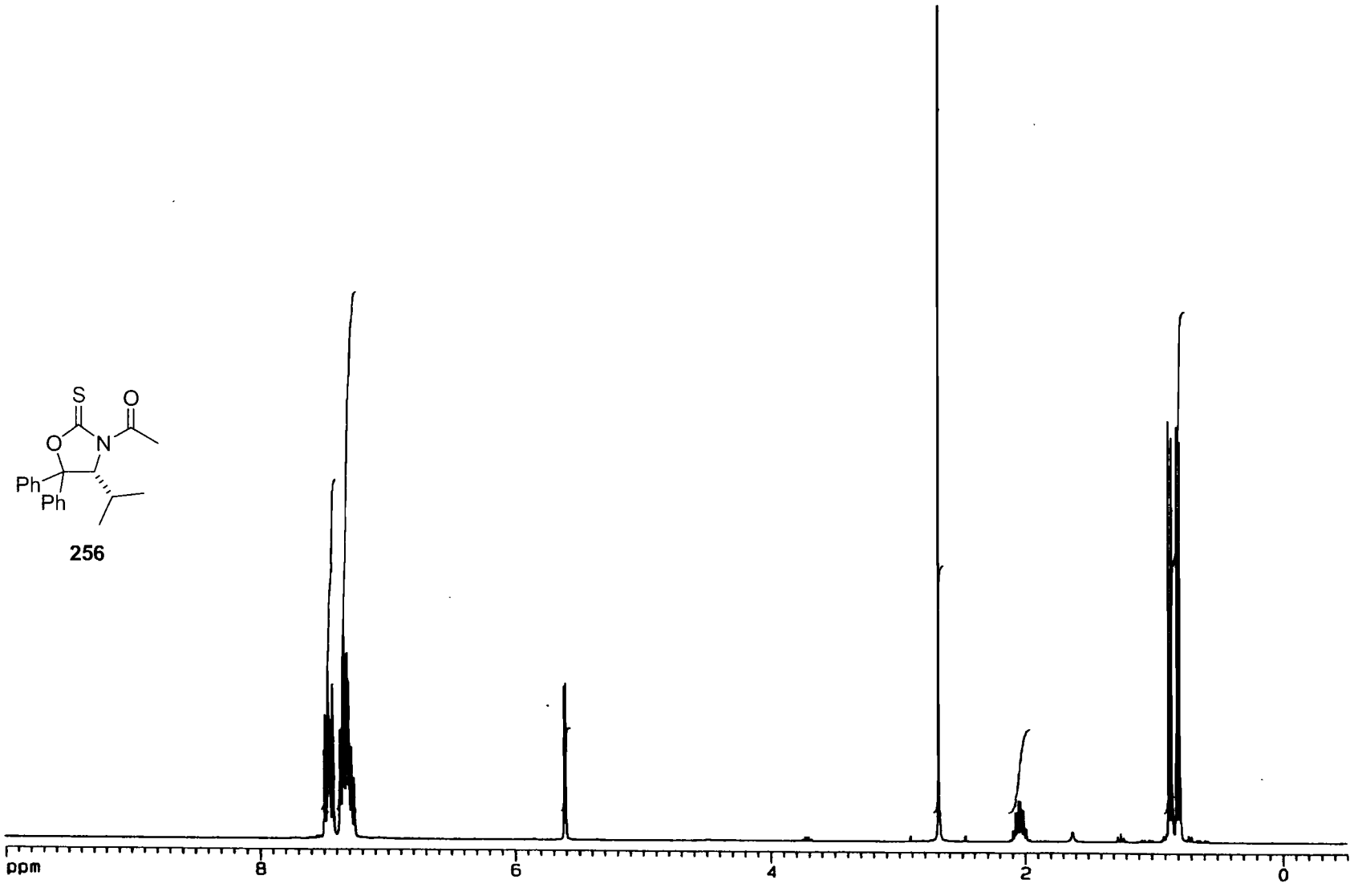

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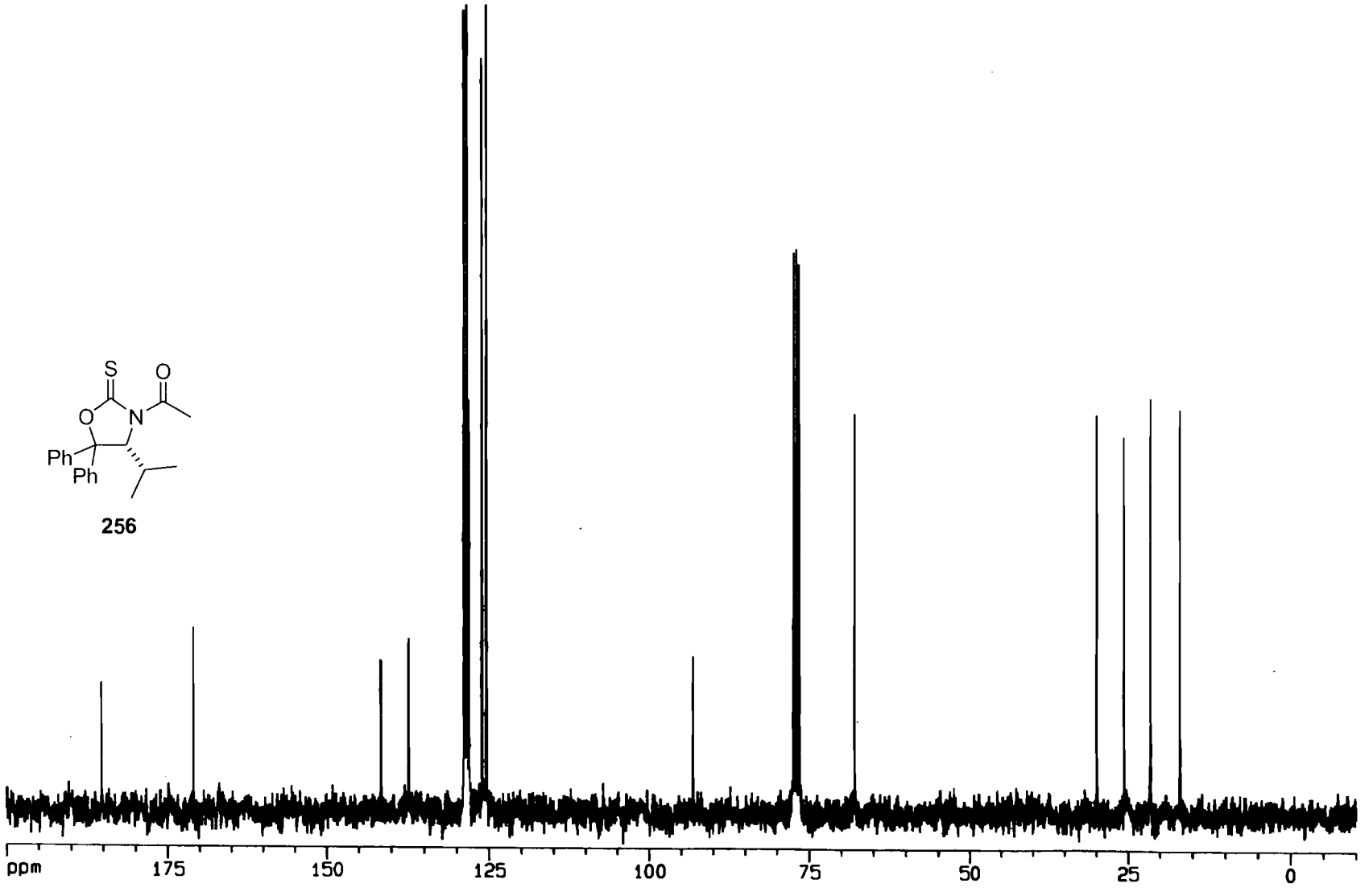

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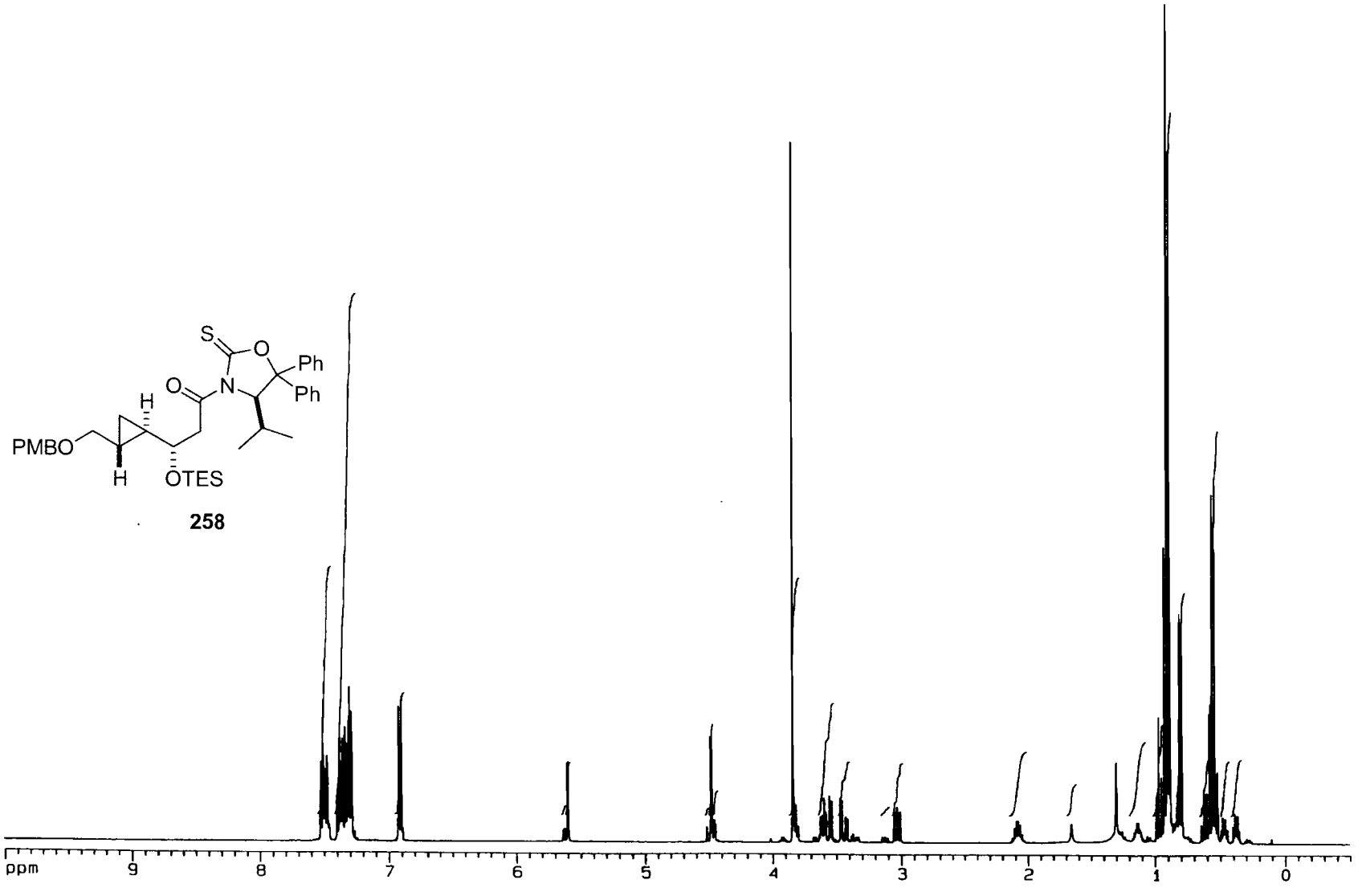

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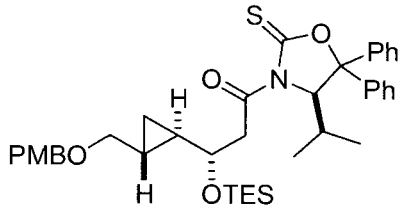

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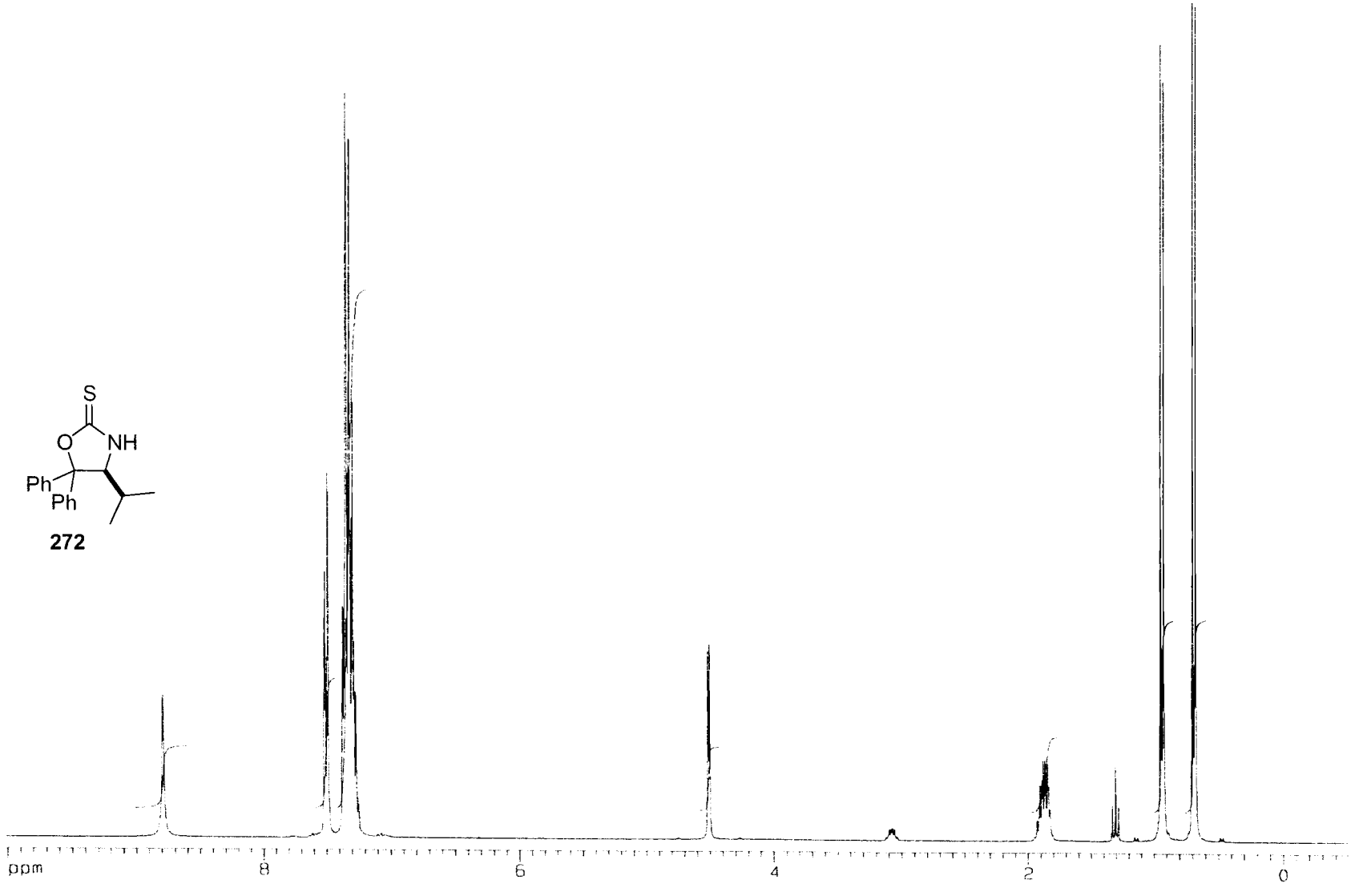

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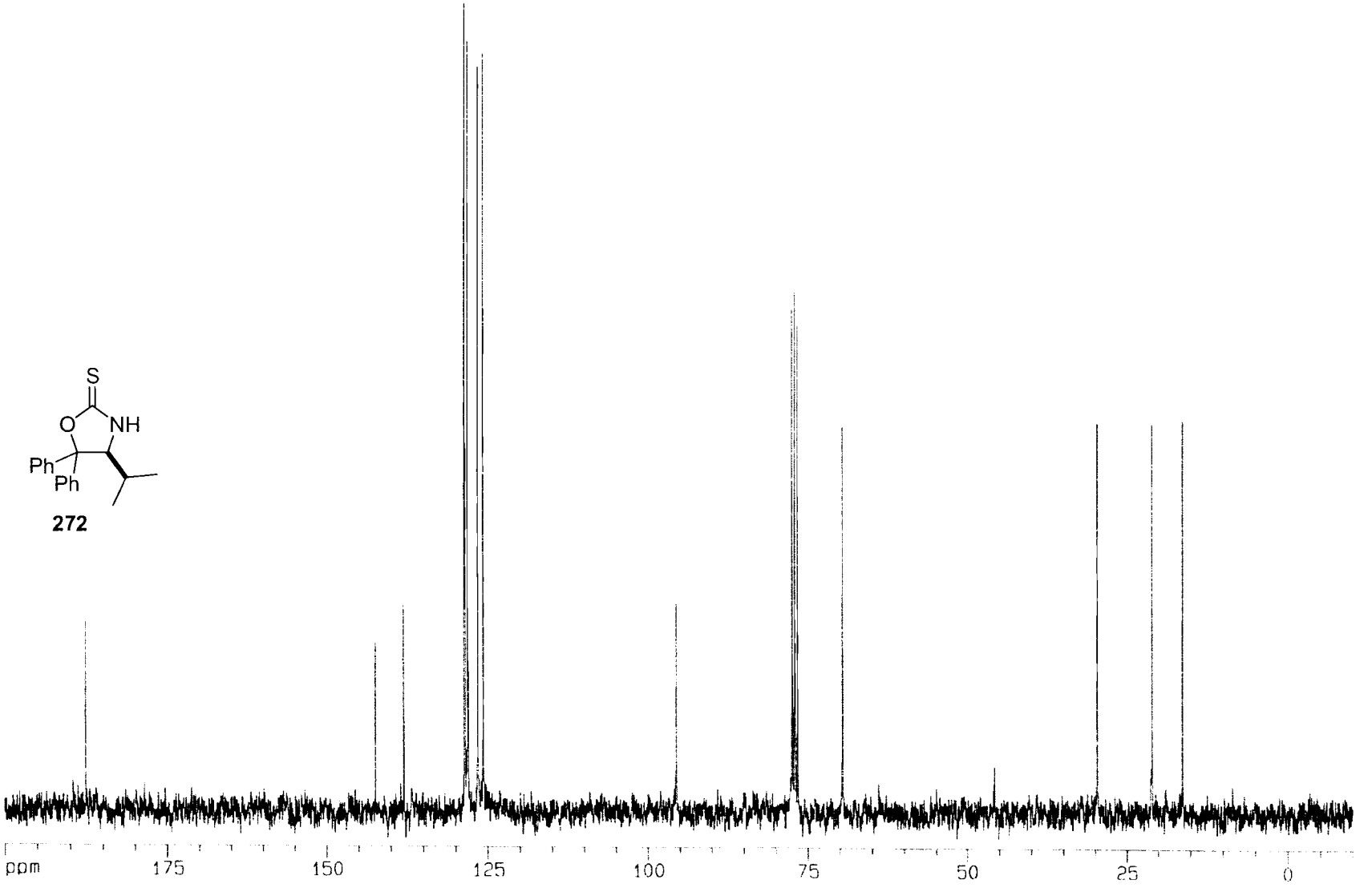

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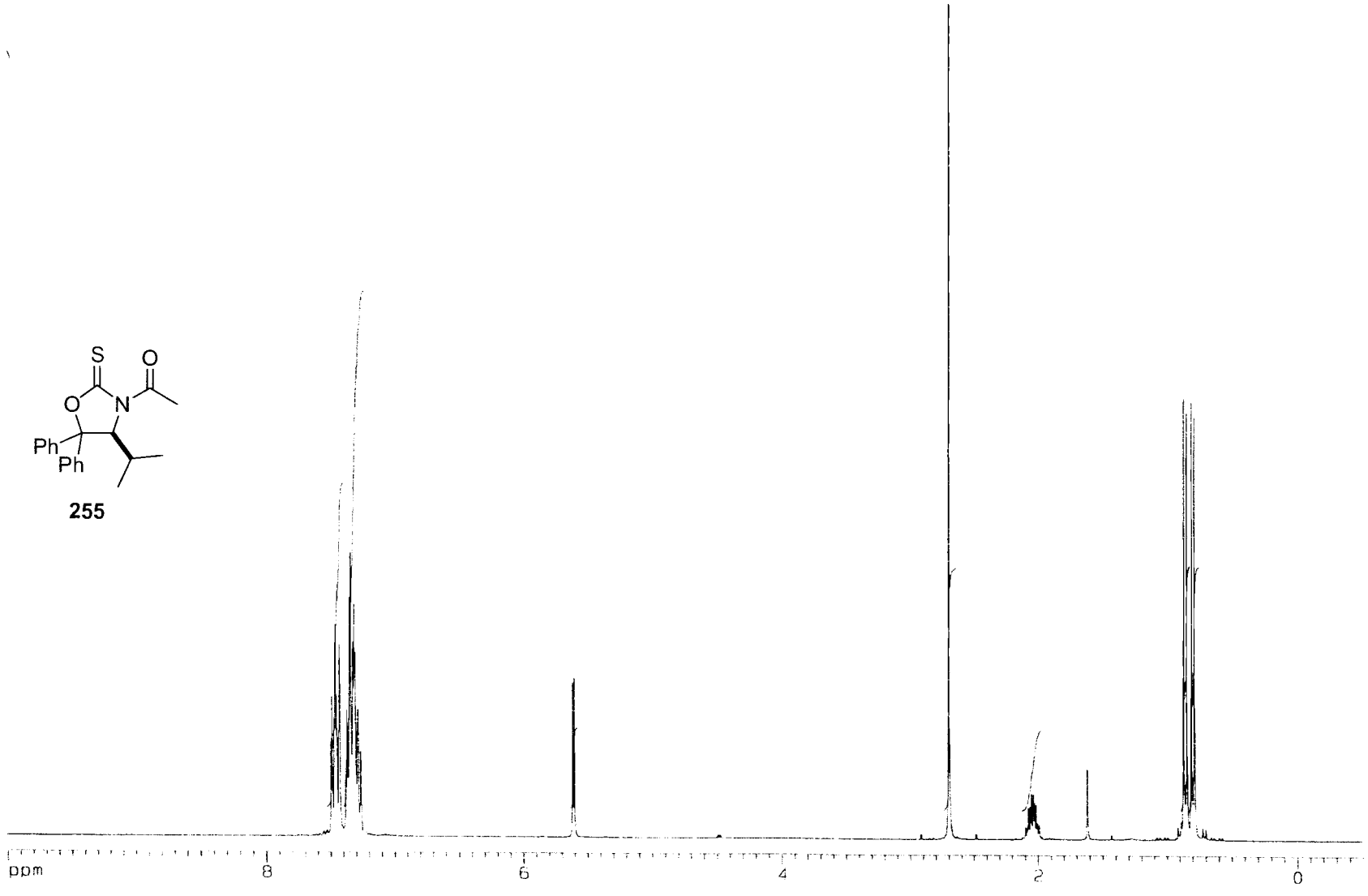

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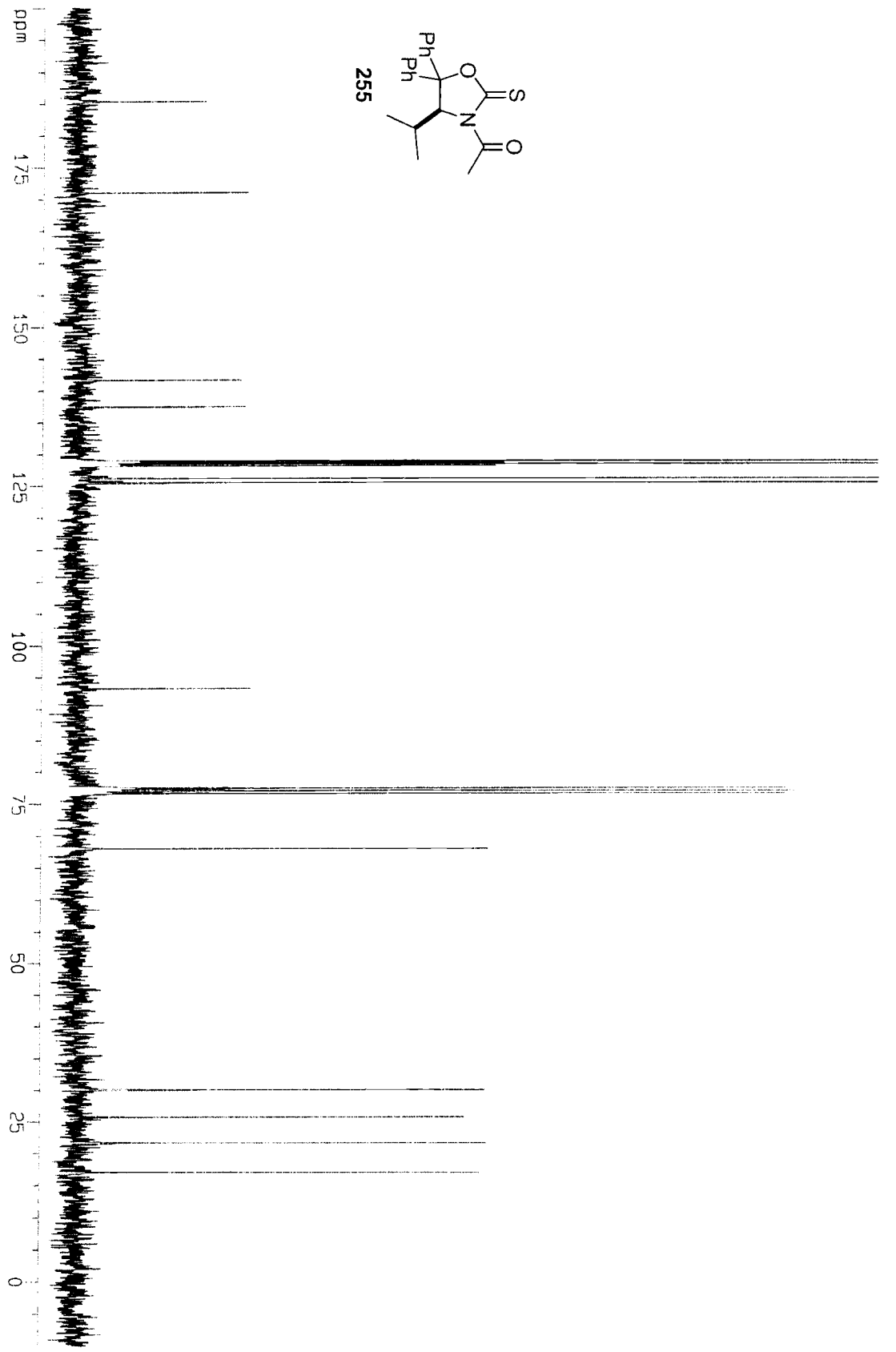

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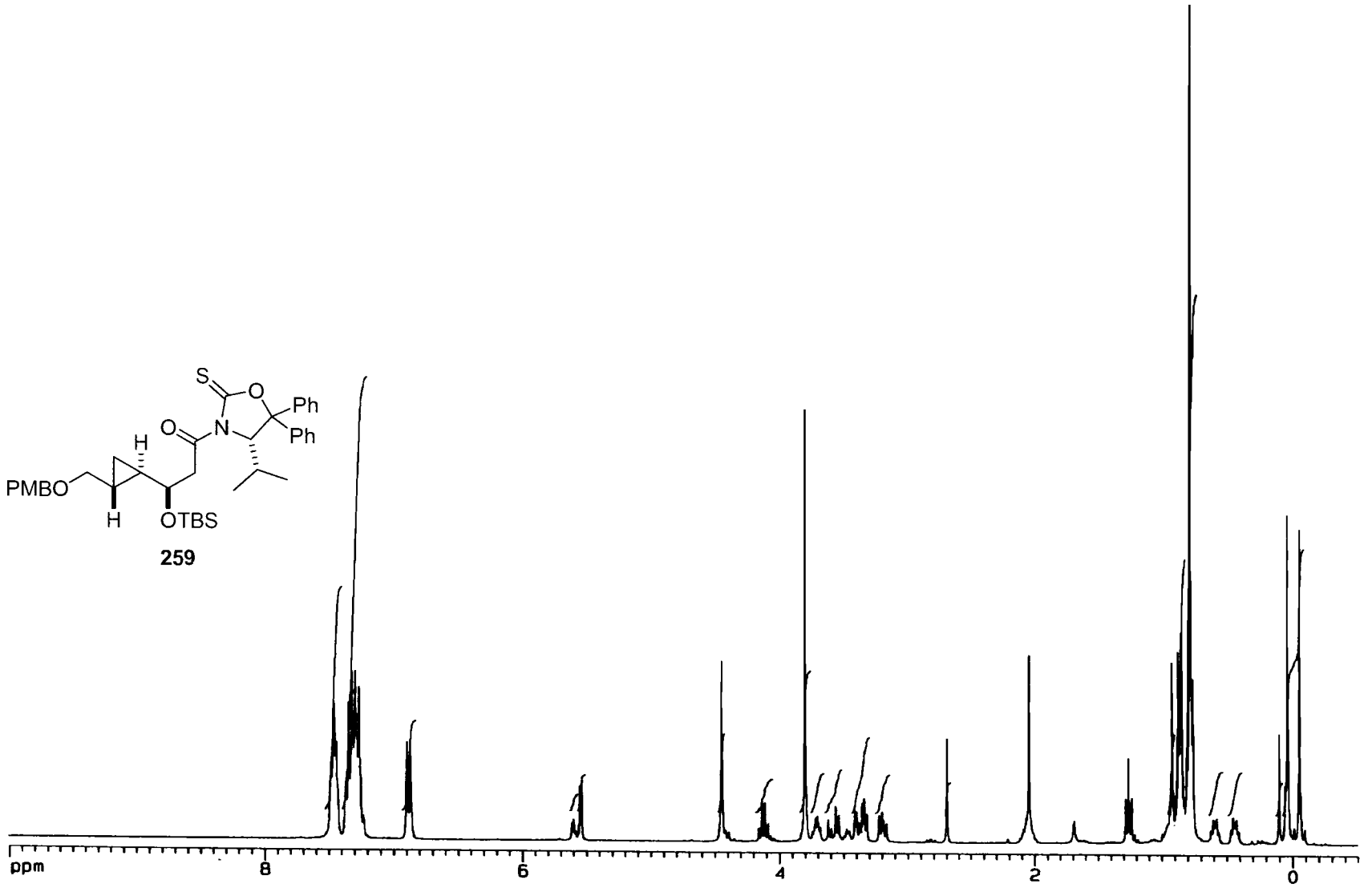

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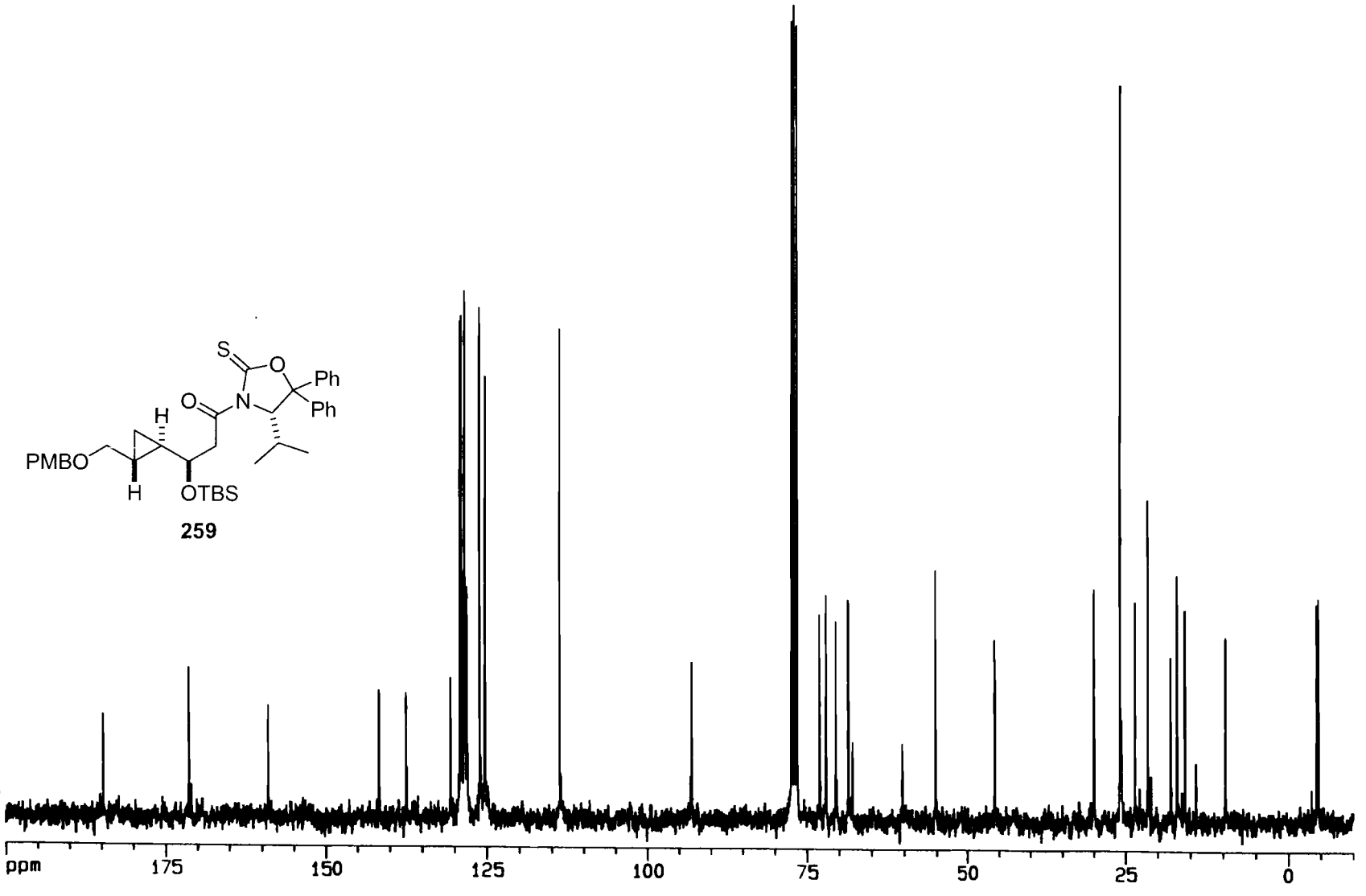

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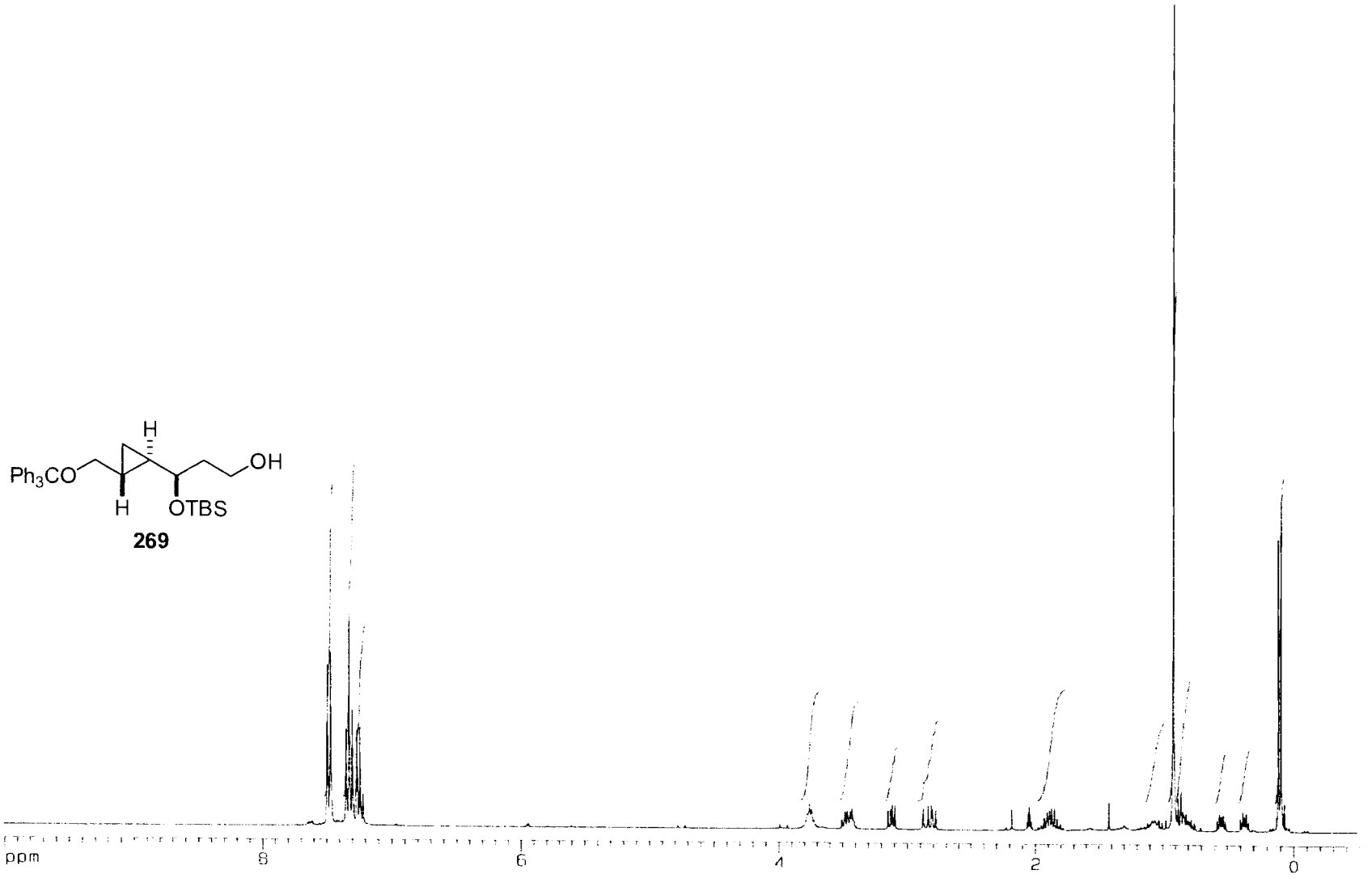

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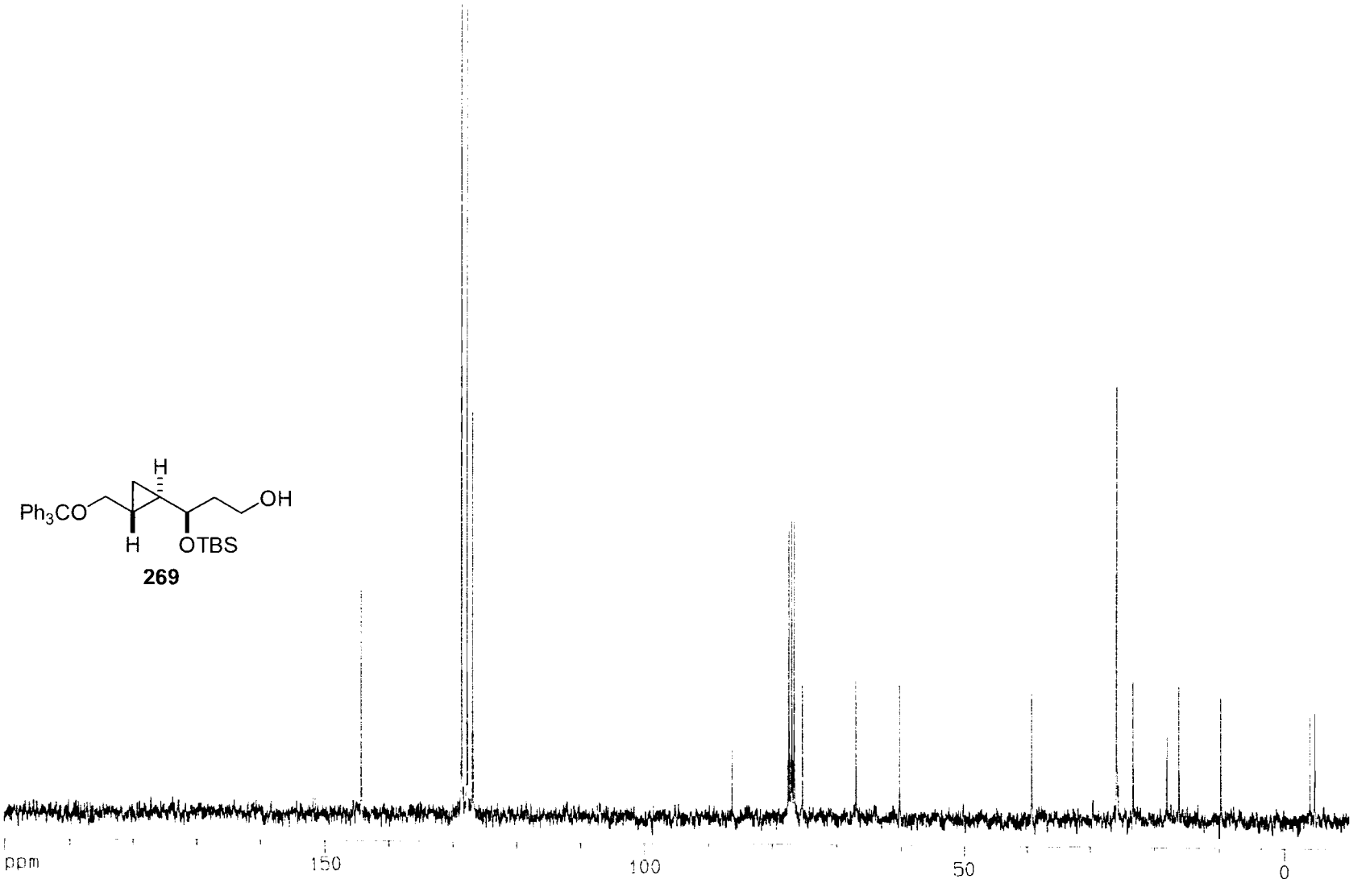

269