# Synthesis of Heterocycles *via* Chemoselective Geminal Acylation of 2-Methoxyoxazolidines, *E*/*Z* Isomerization in the Metathesis of Allyl Alcohol Derivatives with a First-Generation Ruthenium Catalyst, and Interception of Nazarov Reaction Intermediates of Allenyl Vinyl Ketones with Arenes

by

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## ABSTRACT

Heterocycles were prepared through the geminal acylation of 2-methoxyoxazolidines with 1,2-bis(trimethylsilyloxy)cyclobutene. It was found that when water was excluded from the standard reaction conditions, regioselectivity of the ring expansion step was reversed, resulting in preferential rupturing of the endocyclic C-O bond instead of the C-N bond. Further cyclization resulted in the generation of 6,5-fused ring systems. The aqueous procedure was found to be applicable to 1,2-bis(trimethylsilyloxy)cyclopentene, resulting in the analogous 6,6-fused ring systems, while the anhydrous procedure failed to promote ring expansion. Tricyclic 6,5,6-fused ring systems were obtained with *meso*-7,8-bis(trimethylsilyloxy)bicyclo[4.2.0]oct-7-ene using the anhydrous procedure, while the intermediate generated under aqueous conditions failed to undergo ring closing.

Allylic alcohol derivatives were subjected to homodimerization in the presence of a first-generation ruthenium catalyst. Previous work suggested that thermodynamic equilibration to the *E*-isomer was not a significant process for first-generation catalysts. However, product *E*/*Z* ratios were, in general, observed to increase significantly over time. In addition, an atmosphere of ethylene promoted reversion to the terminal olefins, leading to rapid *E*/*Z* equilibration, albeit at the expense of yield. Brief exposure to ethylene over the course of reaction resulted in a high *E*/*Z* ratio in a moderate yield.

A 6,6,5-fused ring system was synthesized *via* the tandem Nazarov cyclization-intramolecular Friedel-Crafts alkylation of the corresponding allenyl vinyl ketone. The presence of electron donating substituents on the arene, as well as a two-carbon tether linking the arene to the allenyl vinyl ketone, were crucial to the success of the reaction. The intermolecular trapping of an allenyl vinyl ketone with substituted arenes was also investigated. Trapping occurred primarily at the electronically preferred position *a*, while sterically encumbered substrates tended to trap preferentially at the less hindered position *c*. Surprisingly, 1,3,5-trisubstituted arenes trapped almost exclusively at position *a*, having overcome significant steric crowding, demonstrated by hindered rotation about the newly formed carbon-carbon bond.

## LIST OF ABBREVIATIONS AND SYMBOLS USED

| | |
|---|---|
| δ | chemical shift |
| μL | microlitre(s) |
| Ac | acetyl |
| AIBN | azobisisobutyronitrile |
| $BF_3$•$OEt_2$ | boron trifluoride diethyl etherate |
| Bn | benzyl |
| BOC | *tert*-butyloxycarbonyl |
| br | broad |
| *i*Bu | isobutyl |
| *n*Bu | *n*-butyl |
| *t*Bu | *tert*-butyl |
| $cm^{-1}$ | wavenumber(s) |
| COSY | correlation spectroscopy |
| Cy | cyclohexyl |
| d | doublet |
| dd | doublet of doublets |
| DIBAL-H | diisobutylaluminum hydride |
| DMP | Dess-Martin periodinane |
| ESI | electrospray ionization |
| Et | ethyl |
| g | gram(s) |
| h | hour(s) |
| HMBC | heteronuclear multiple-bond correlation |

| | |
|---|---|
| HRMS | high-resolution mass spectrometry |
| HSQC | heteronuclear single quantum correlation |
| Hz | Hertz |
| *i*Pr | isopropyl |
| IR | infrared spectroscopy |
| *J* | coupling constant |
| kcal/mol | kilocalorie(s) per mole |
| L | Lewis acid |
| m | multiplet |
| Me | methyl |
| Mes | mesityl |
| mg | milligram(s) |
| MHz | megahertz |
| min | minute(s) |
| mL | milliliter(s) |
| mp | melting point |
| Ms | methanesulfonyl |
| NMR | nuclear magnetic resonance spectroscopy |
| Nu | nucleophile |
| PCC | pyridinium chlorochromate |
| Ph | phenyl |
| ppm | parts per million |
| rt | room temperature |

| | |
|---|---|
| q | quartet |
| s | singlet |
| t | triplet |
| TBAF | tetrabutylammonium fluoride |
| TBDMS | *tert*-butyldimethylsilyl |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| THP | tetrahydropyranyl |
| TIPS | triisopropylsilyl |
| TMS | trimethylsilyl |
| Ts | *para*-toluenesulfonyl |
| w/v | weight per volume |

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## CHAPTER 1: INTRODUCTION

Organic synthesis involves the assembly of a target organic molecule through a sequence of transformations from relatively simple starting materials, with the ultimate goal of obtaining the final product in high yield over minimal steps. Retrosynthetic analysis of the target molecule enables organic chemists to envision a synthetic pathway to the final product using a series of previously developed reactions.

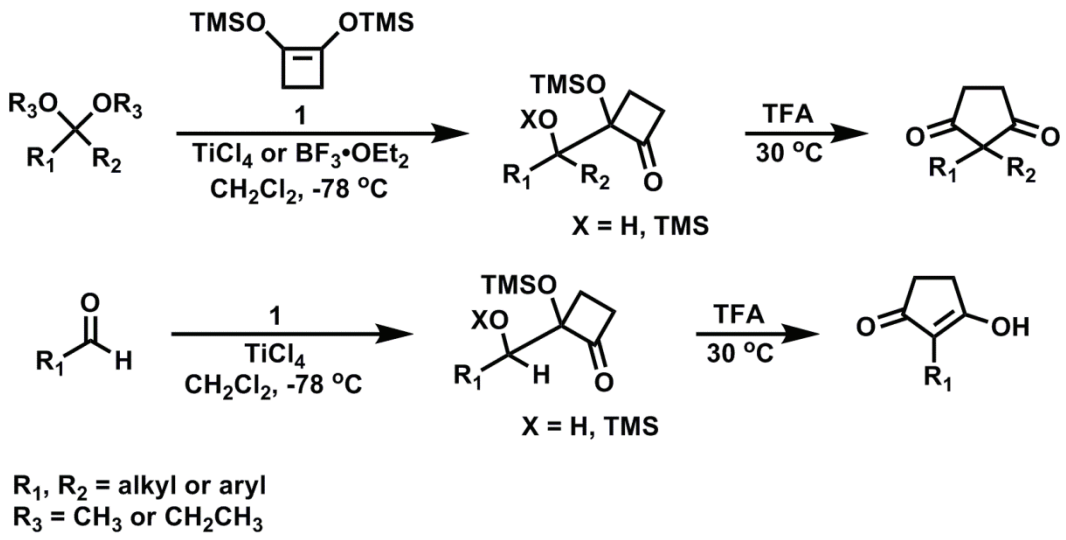
The design and optimization of chemical transformations and the reagents for these transformations falls into the realm of synthetic methodology. The obvious and immediate benefit of methodology studies is a contribution to the body of precedence that allows a chemist to plan syntheses of complex and often useful organic substances. However, the longer term value of methodology studies, where series of related compounds are subjected to similar reaction conditions, stems from the contribution to our fundamental understanding of how chemical reactions really take place.

This thesis presents the results of three studies. These are studies in methodology, and, while the immediate impact might be in terms of how to make particular types of molecules, the more important contribution is a deeper understanding of how three very different types of reaction occur.

# CHAPTER 2: SYNTHESIS OF HETEROCYCLES V*IA* CHEMOSELECTIVE GEMINAL ACYLATION OF 2-METHOXYOXAZOLIDINES

## 2.1 Introduction

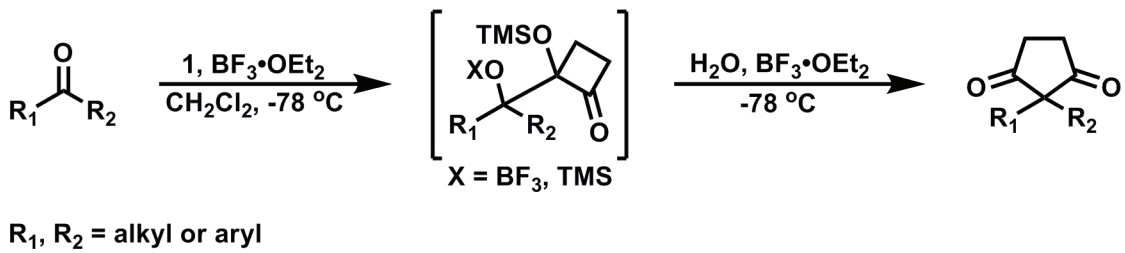
1,3-Cyclopentanediones are useful targets for synthetic chemists due to their amenability to the preparation of a variety of functionalized five-membered ring systems. 2,2-Disubstituted 1,3-cyclopentanediones themselves are useful precursors in the development of natural products containing quaternary carbon centers and spirocyclic frameworks. Prior to 1977, no effective single operation for the generation of 2,2-disubstituted-1,3-cyclopentanediones was known. In 1977, Nakamura and Kuwajima reported a two-step sequence to convert aldehydes, acetals, and ketals to the corresponding 1,3-cyclopentanediones (**Scheme 2.1.1**).[1] In the presence of 1,2-bis(trimethylsilyloxy)cyclobutene[2] **1** these substrates underwent an initial Lewis acid-mediated Mukaiyama-type aldol reaction to generate the corresponding cyclobutanones. Further treatment with trifluoroacetic acid led to a ring-expansion *via* a concerted[3] pinacol rearrangement to the final product. Since overall this resulted in the net replacement of a carbonyl group with two acyl groups, the process was termed geminal acylation.




**Scheme 2.1.1:** Two-step geminal acylation of a ketal and an aldehyde with **1**

Despite the substrate versatility of the geminal acylation process, the reactions of ketones have, in general, been unsuccessful by this process.[3] Although ketones are generally less reactive than aldehydes and their protected counterparts, a significant measure of conversion to cyclobutanone intermediates was found to be achievable. The problem came during the workup stage of the reaction, during which a high degree of retro-aldol reaction, giving back the starting ketone, was observed.[4]

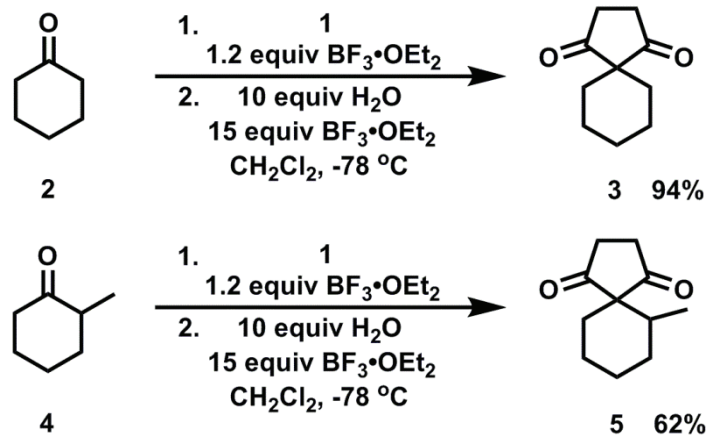
Extensive study of this reaction process by Jenkins and Burnell[4] led to the development of a one-pot geminal acylation procedure (**Scheme 2.1.2**) that circumvented the reversible nature of the Mukaiyama aldol step, particularly in the case of ketones. By adding 10 equivalents of water at the completion of the aldol addition, followed by 15 equivalents of the Lewis acid, Jenkins and Burnell were able to complete the pinacol rearrangement to the geminally acylated product.




**Scheme 2.1.2:** One-pot geminal acylation of ketones with **1**, resulting in the direct formation of 1,3-cyclopentanediones

To date, a number of synthetic endeavors that employ either the one-step or the two-step geminal acylation process as a key transformation have been disclosed in the literature.[5]

The success of geminal acylation has been shown to be highly dependent on the degree of steric hindrance at the position of attack. This can be advantageous, as the resultant 1,3-diketone has been found to resist overreaction. However, as the degree of substitution about the carbonyl group increases, conversion to product has been shown to decrease dramatically. Cyclohexanone **2** underwent geminal acylation with **1** to generate 1,3-diketone **3** in high yield using the one-pot process (**Scheme 2.1.3**). When 2-methylcyclohexanone **4** was subjected to the identical reaction conditions, conversion to 1,3-diketone **5** was significantly lower.[4]




**Scheme 2.1.3:** High conversion of unhindered **2** to **3** and diminished conversion of methyl-substituted **4** to **5**

Cyclohexanones and their dimethoxy ketals that were halide or methoxy substituted at the α-position resisted any significant geminal acylation with **1** under either the Burnell or the Kuwajima conditions. Once again, the problem was in the second, pinacol rearrangement step. Elevated temperatures in the presence of a sulfonic acid resin, Amberlyst-15, and a nonpolar solvent were required to obtain appreciable yields from the rearrangement.[6]

The attractiveness of geminal acylation as a versatile synthetic procedure depends not only on a broad scope of substrate molecules, but also on its amenability to a range of acyloins, varying in both functionalization and ring size. Many natural products contain five-membered rings, including those that are methyl- and geminal dimethyl-substituted. With this in mind, Burnell and co-workers[7] investigated the geminal acylation of ketones and acetals with substituted acyloins **6** and **7** (**Figure 2.1.1**).

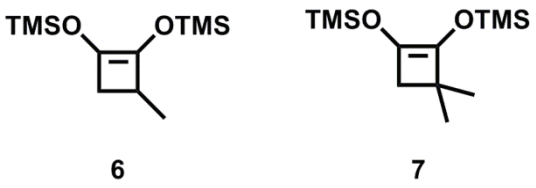
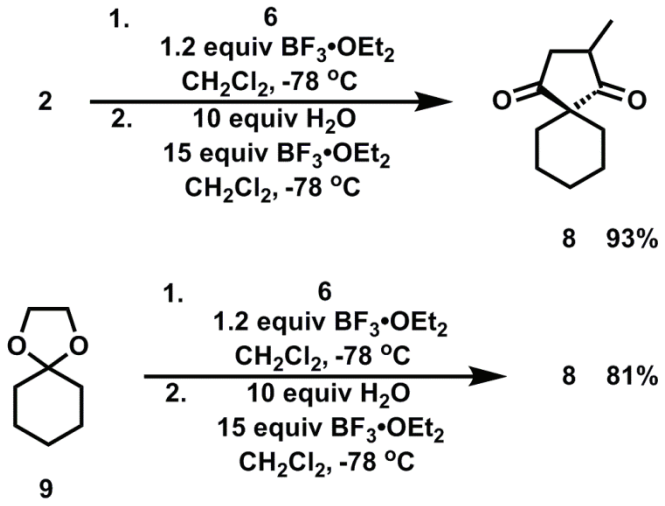



**Figure 2.1.1:** 3-Methyl-1,2-bis[(trimethylsilyl)oxy]cyclobutene **6** and 3,3-dimethyl-1,2-bis[(trimethylsilyl)oxy]cyclobutene **7**

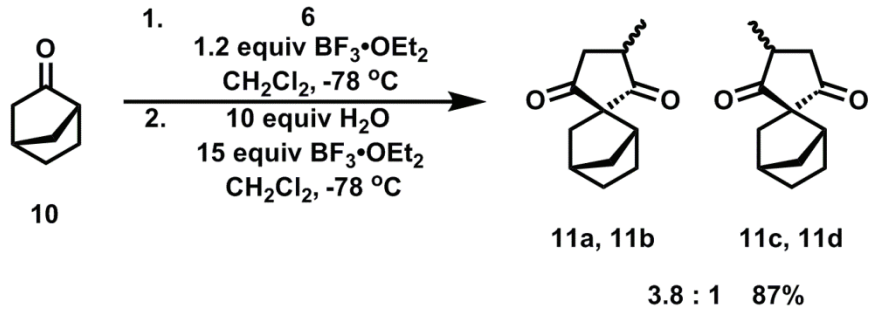
A series of ketones and ethylene glycol-based acetals were subjected to **6** under the standard one-pot procedure developed by Burnell and coworkers. As expected, the acyloin underwent initial Lewis acid-mediated aldol addition primarily from the face *anti* to the methyl substituent. Ring expansion gave rise to the 4-methyl-1,3-cyclopentanediones in moderate to high yields. Overall, the substrates behaved similarly to their reaction with the unhindered **1**. Yields were higher from ketones than from the bulkier corresponding acetals (**Scheme 2.1.4**).[7]




**Scheme 2.1.4:** Geminal acylation of cyclohexanone **2** and its corresponding acetal **9** with **6**, resulting in **8**

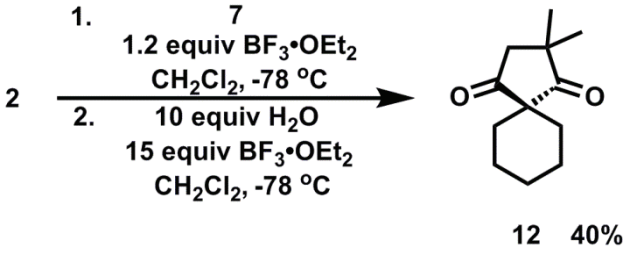
Unlike **1**, reaction with **6** resulted in a diastereomeric mixture of 1,3-cyclopentanediones. While butanone and its acetal demonstrated no selectivity, cyclic

substrates, such as ketone **10**, resulted in mixtures of products with a moderate degree of diastereoselectivity (**Scheme 2.1.5**).




**Scheme 2.1.5:** Geminal acylation of **10** with **6**, resulting in the diastereoselective formation of **11a**,**b** over **11c**,**d**

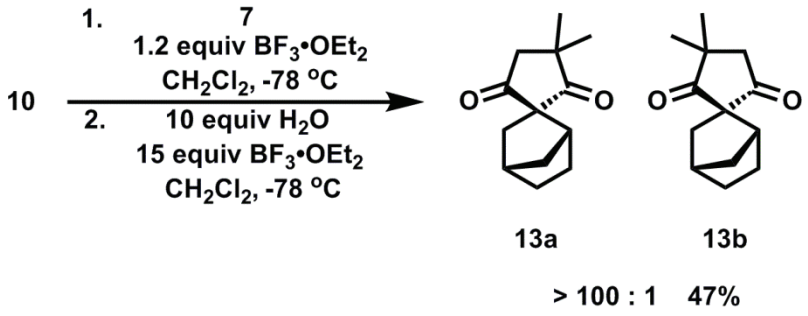
While **6** was observed to add primarily *anti* to the methyl substituent, this was not possible with **7** and the steric consequences of this type of addition were apparent in low to moderate yields of 4,4-dimethyl-1,3-cyclopentanediones (**Scheme 2.1.6**). It was surprising to note that geminal acylation with **7** could also be accomplished without the addition of water and excess $BF_3$•$OEt_2$. Presumably the ring strain of the geminal dimethyl-substituted cyclobutanone intermediates was sufficient to promote the subsequent ring expansion to the 4,4-dimethyl-1,3-cyclopentanedione products.




**Scheme 2.1.6:** Geminal acylation of cyclohexanone **2** with **7** in a single step, resulting in 4,4-dimethyl-1,3-cyclopentanedione **12**

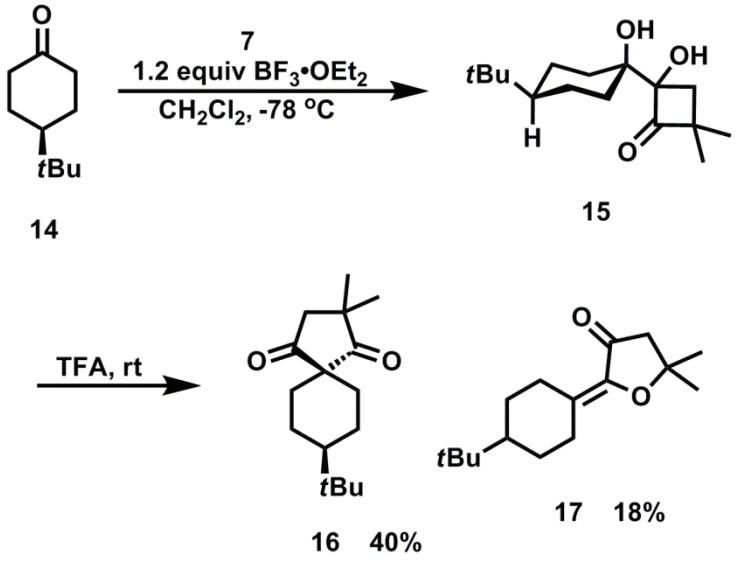
Although reactions with **7** gave rise to lower product yields than with **6**, geminal acylation with the disubstituted acyloin proceeded with a high degree of

diastereoselectivity. For example, cyclohexanone **10** underwent reaction with **7** to give the 4,4-dimethyl-1,3-cyclopentanedione **13a** with minimal formation of **13b** (**Scheme 2.1.7**).



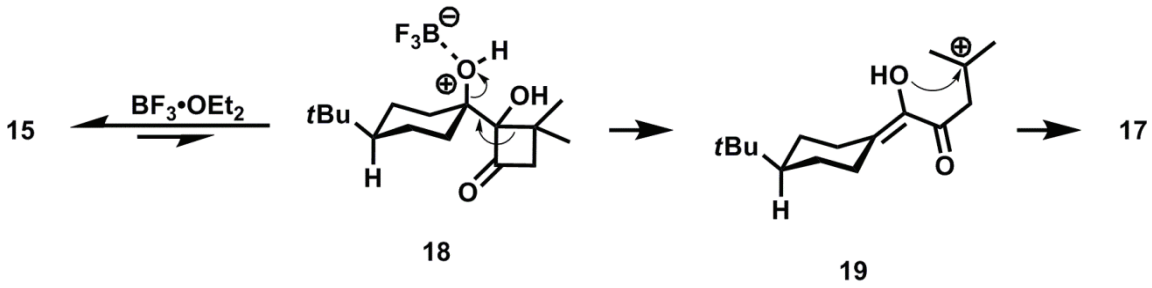

**Scheme 2.1.7:** Geminal acylation of **10** with **7**, resulting in the highly diastereoselective formation of **13a** over **13b**

When 4-*tert*-butylcyclohexanone **14** was reacted with **7**, the 4,4-dimethyl-1,3-cyclopentanedione **16** was obtained in modest yield (**Scheme 2.1.8**). However, in addition to the desired product, a significant amount of furanone **17** had also been formed.



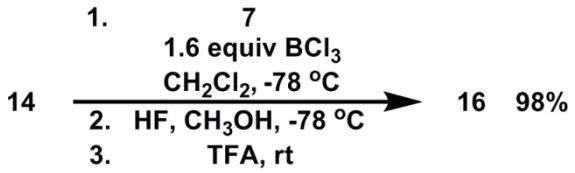

**Scheme 2.1.8:** Geminal acylation of **14** with **7** resulting in the formation of furanone **17** in addition to the desired **16**

It was suggested that the interconversion of the thermodynamically favored aldol intermediate **15** and its diastereomer **18** was being facilitated in the presence of $BF_3$•$OEt_2$ (**Scheme 2.1.9**). Rupturing of the cyclobutanone ring of **18** could give rise to the tertiary carbocationic intermediate **19** which, upon cyclization with the enol oxygen, could result in **17**.



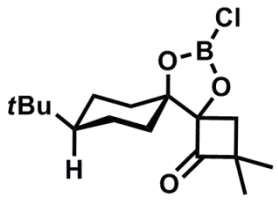

**Scheme 2.1.9:** Suggested pathway for the formation of the furanone by-product **17**

In an effort to prevent isomerisation from **15** to **18**, Crane and Burnell[8] repeated the geminal acylation of **14** with $BCl_3$ as the Lewis acid (**Scheme 2.1.10**). The yield of **16** improved to 98%.




**Scheme 2.1.10:** Improved geminal acylation of **14** with **7** in the presence of $BCl_3$

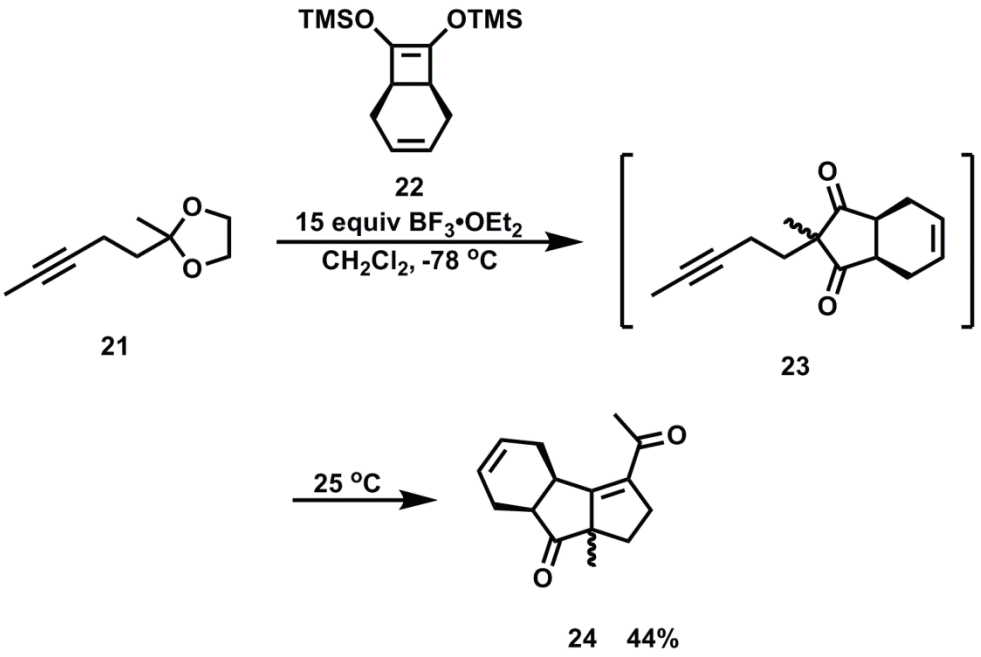
The progress of the reaction was monitored by $^{11}B$ NMR spectroscopy. This study suggested the formation of the intermediate **20** (**Figure 2.1.2**), in which the boron atom was complexed to both hydroxyl groups of **15**, preventing the isomerisation of **15** to **18** and thus the formation of **17**.




**20**

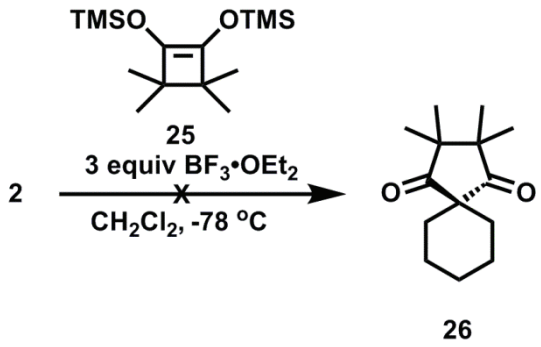
**Figure 2.1.2:** Boron complex **20**

Balog and Curran[5f] reported the $BF_3$•$OEt_2$-mediated reaction of the ω-alkynyl acetal **21** with the vicinally disubstituted acyloin **22** in a tandem geminal acylation-5-*exo*-*dig* cyclization resulting in the formation of a 1:1 diastereomeric mixture of the tricyclic enedione **24** *via* the 4,5-dimethyl-1,3-cyclopentanedione intermediate **23** (**Scheme 2.1.11**).



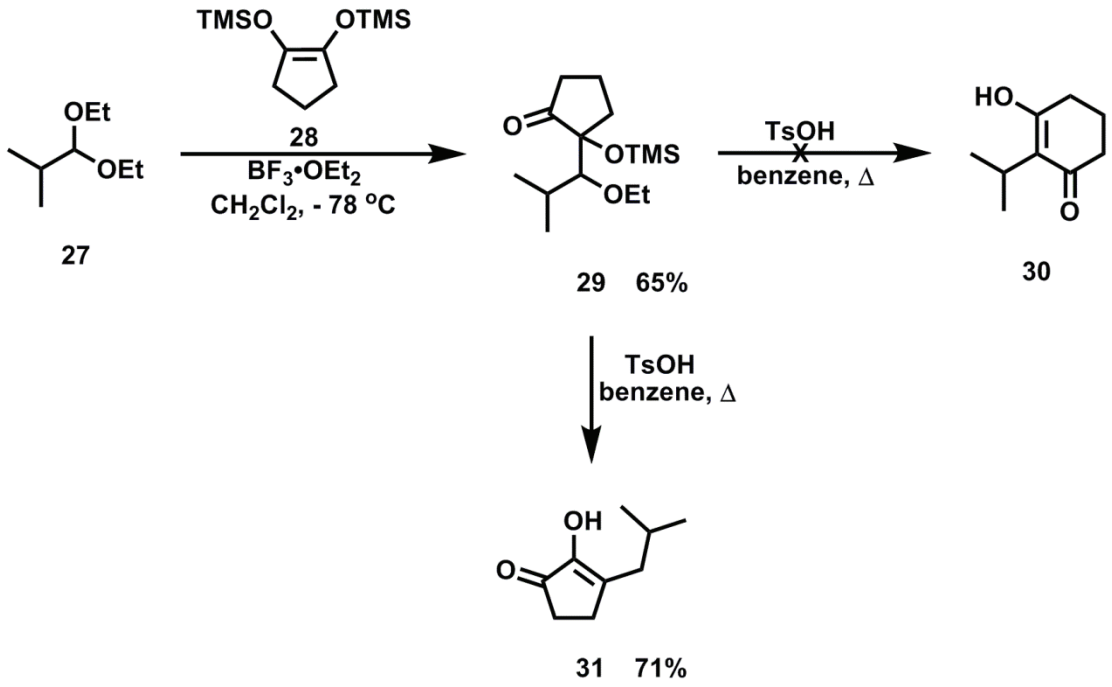

**Scheme 2.1.11:** Tandem geminal acylation-5-*exo*-*dig* cyclization of **21** with **22**, generating the enedione **24** as a 1:1 diastereomeric mixture

To further emphasize the impact of the acyloin's steric bulk on the yield of geminal acylation products, Crane and Burnell[8] demonstrated that tetramethyl-substituted acyloin **25** failed to yield any of the 1,3-diketone **26** from **2** (**Scheme 2.1.12**).



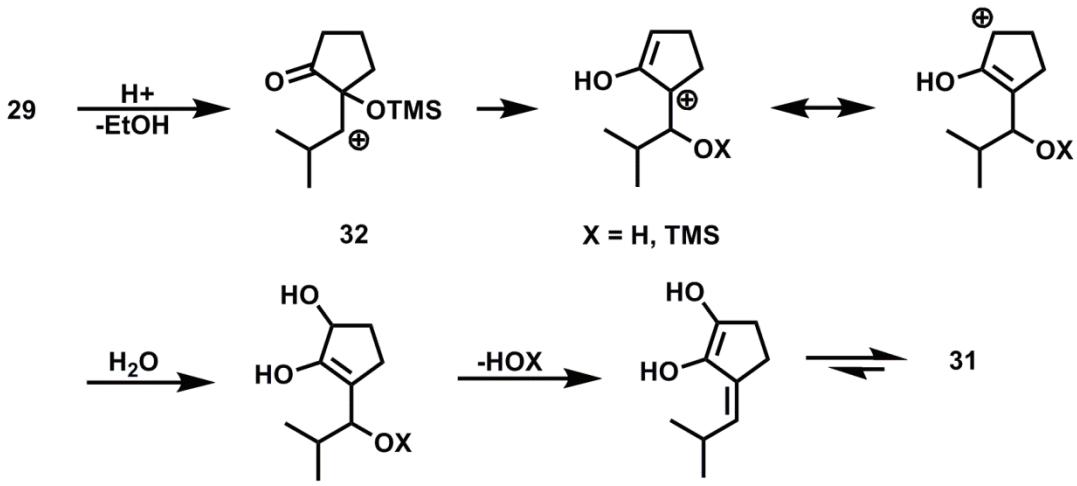

**Scheme 2.1.12:** Unsuccessful geminal acylation of **2** with the tetramethyl-substituted acyloin **25**

In light of the successful geminal acylation of acetals with **1**, Pattenden and Teague[9] investigated the reactivity of the analogous five-membered acyloin **28** (**Scheme 2.1.13**). In the presence of $BF_3$•$OEt_2$, **28** underwent aldol reaction with acetals such as **27**, which resulted in the formation of cyclopentanone intermediate **29**. Similar to the conditions outlined by Nakamura and Kuwajima, the intermediate was subsequently treated with a protic acid in order to promote rearrangement of the pinacol to the desired compound **30**. However, the reaction gave exclusively the enone **31**.



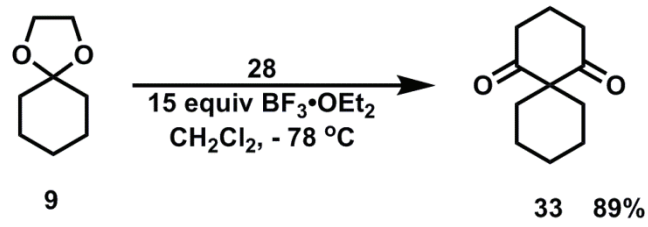

**Scheme 2.1.13:** Attempted geminal acylation of **27** with **28**, resulting instead in the enone **31**

The authors envisioned the product as evolving from carbocation **32** (**Scheme 2.1.14**). It was suggested that this alternate pathway was competitive with the desired ring expansion due to lesser ring strain in cyclopentanone versus cyclobutanone.



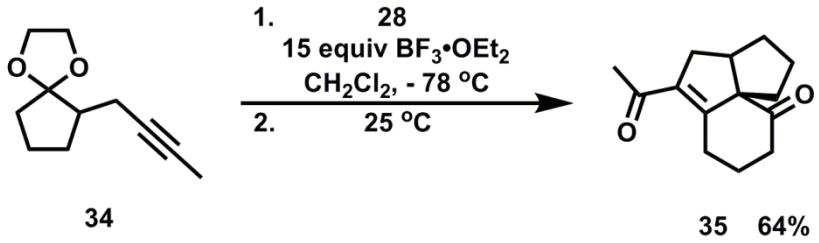

**Scheme 2.1.14:** Suggested pathway for the formation of the enone **31** from the aldol product **29**

Nevertheless, Burnell and Wu[10] observed that in the presence of a large excess of $BF_3$•$OEt_2$, ring expansion of the cyclopentanone aldol product could be achieved to afford the 2,2-disubstituted-1,3-cyclohexanedione in moderate to high yield (**Scheme 2.1.15**). 1,3-Diketone **33** was obtained in 89% yield from the ketal **9**.



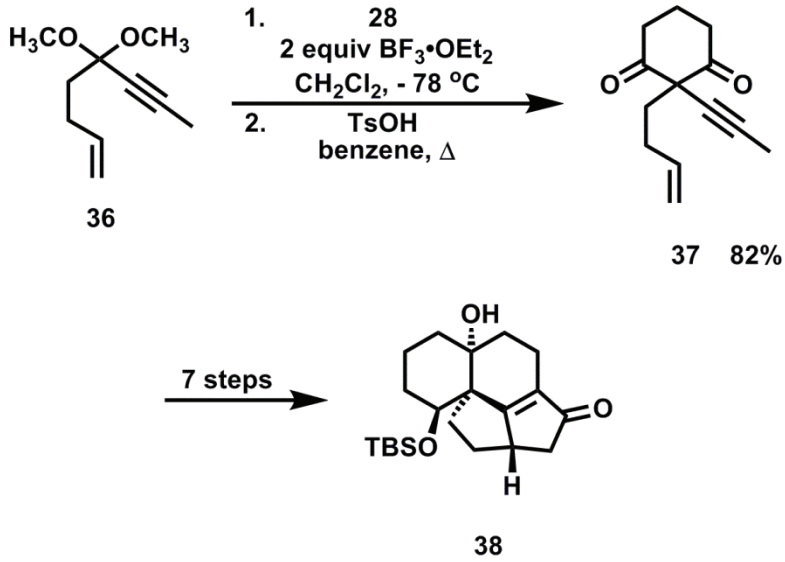

**Scheme 2.1.15:** Geminal acylation of **9** with **28** in the presence of a large excess of $BF_3$•$OEt_2$, giving rise to the 2,2-disubstituted-1,3-cyclohexanedione **33**

Balog and Curran[5f] reported the successful tandem geminal acylation-5-*exo-dig* cyclization of ω-alkynyl acetal **34** with **28**, resulting in the fused tricycle **35** (**Scheme 2.1.16**).



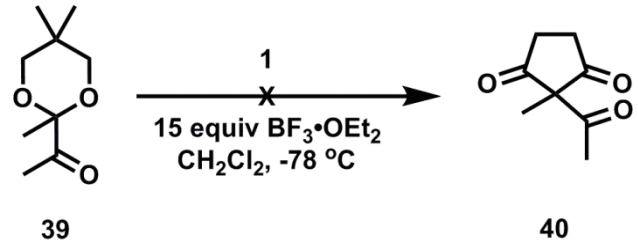

**Scheme 2.1.16:** Tandem geminal acylation-5-*exo-dig* cyclization of **34** with **28**, generating the enedione **35**

Thornton and Burnell[5p] invoked the geminal acylation of ketal **36** with **28** to generate 1,3-diketone **37**, an intermediate to the eventual tetracyclic **38** (**Scheme 2.1.17**).



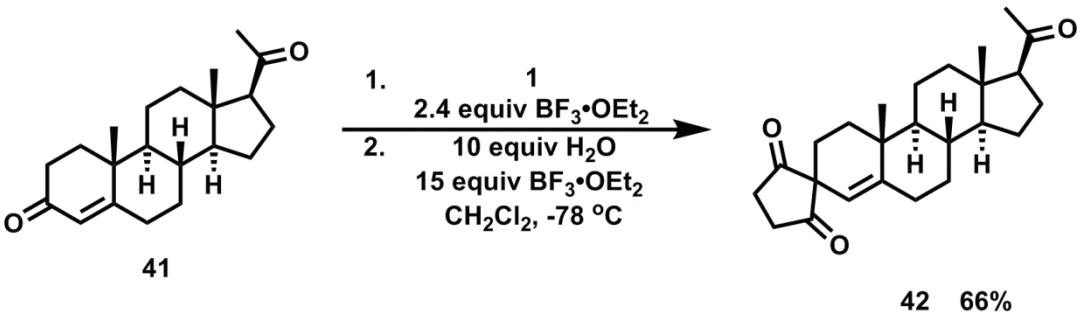

**Scheme 2.1.17:** Geminal acylation of **36** with **28**, resulting in the 2,2-disubstituted-1,3-cyclohexanedione **37**, the precursor to **38**

The success of geminal acylation is also highly dependent on the functionalization surrounding the reactive carbon atom. It has been shown by Burnell and co-workers[11] that substrates bearing a ketone adjacent to the reactive center, such as **39**, will not undergo geminal acylation with **1** to the 1,3-diketone **40** (**Scheme 2.1.18**).



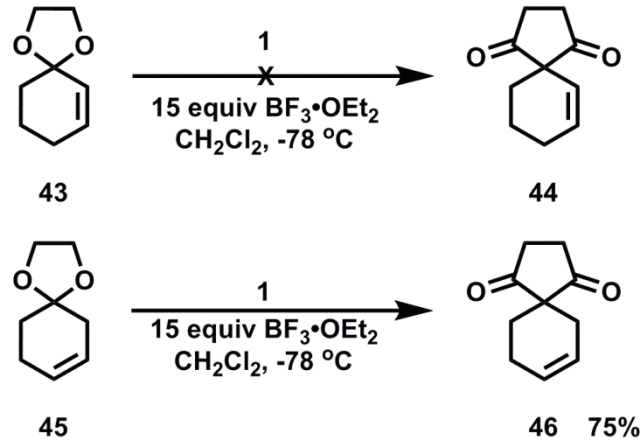

**Scheme 2.1.18:** Unsuccessful geminal acylation of **39**, in which the target carbon atom for reaction is adjacent to a carbonyl group

The geminal acylation of α,β-unsaturated substrates is also problematic. Product yields from ketones were generally found to be poor. However, substrates such as **41**, in which the β-carbon is sterically hindered, underwent geminal acylation in reasonable yield to **42** (**Scheme 2.1.19**).[4]



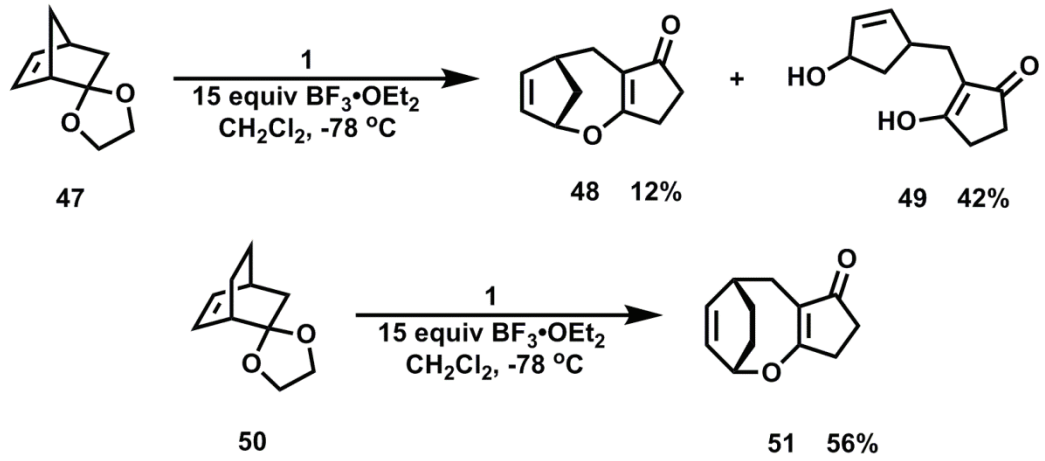

**Scheme 2.1.19:** Successful selective geminal acylation of the α,β-unsaturated ketone of **41**

Reactions with ketals of enones were unsuccessful, although some success was achieved with enones in which the carbon-carbon double bond had migrated to the β,γ-position during the protection step (**Scheme 2.1.20**).[11]




**Scheme 2.1.20:** Unsuccessful geminal acylation of the α,β-unsaturated ketal **43** and the successful reaction of **45**

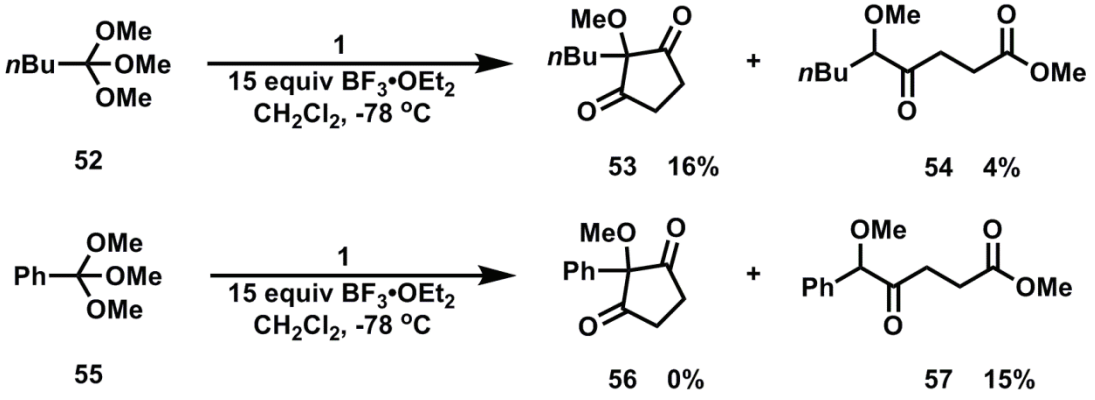
Reaction of bicyclic ketals such as **47** and **50** gave rise to products consistent with cleavage of the bicyclic system following successful geminal acylation (**Scheme 2.1.21**).[11]




**Scheme 2.1.21:** The reaction of bicyclic systems **47** and **50** with **1**, resulting in the rupturing of their bicyclic frameworks

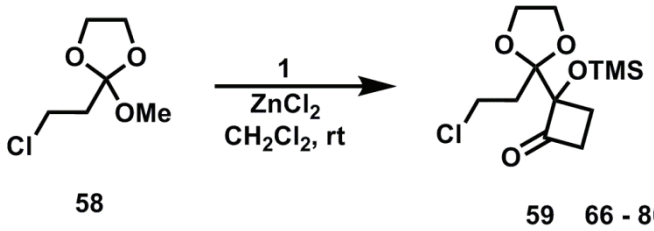
Orthoesters were considered as candidates for geminal acylation as the expected product 1,3-cyclopentanedione would contain functionality at the 2-position amenable to further modification. Orthoesters **52** and **55** were subjected to **1** under the standard

conditions, resulting in only trace quantities of the geminally acylated **53**, whereas no discernable amount of **56** was observed (**Scheme 2.1.22**). Poor reactivity of the orthoesters was evidenced by their degradation to their corresponding esters, likely during workup. In addition, the instability of **53** and **56** was suggested by the appearance of ring-opened products **54** and **57**.[11]




**Scheme 2.1.22:** Geminal acylation of orthoesters **52** and **55** and subsequent ring-opening

In a more recent study, Maulide and Markó[12] accomplished a $ZnCl_2$-mediated Mukaiyama aldol addition of the orthoester **58** with **1** (**Scheme 2.1.23**). The reaction proceeded with exclusive rupturing of the exocyclic carbon-oxygen bond, resulting in the formation of the cyclobutanone **59**. No attempt to subject **59** to conditions that might produce a 1,3-diketone was reported.

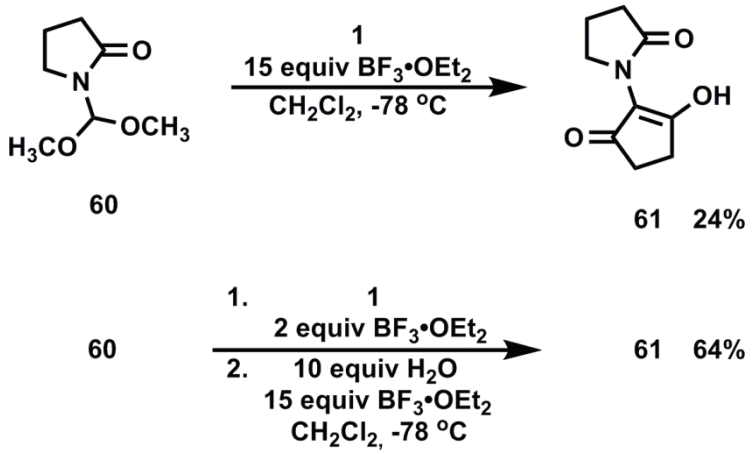



**Scheme 2.1.23:** Mukaiyama aldol addition of **1** to **58** in the presence of $ZnCl_2$ to afford **59**

## 2.2 Results and Discussion

Most biologically active and therapeutically valuable compounds contain a nitrogen atom. Nitrogen-containing products have been produced by a strategy involving Beckman rearrangement of products of geminal acylation, i.e., 1,3-cyclopentanediones.[5j] However, geminal acylation had never been attempted with a substrate that already possessed a nitrogen function, and so, in spite of the synthetically unsatisfactory results from the attempts to geminally acylate orthoesters, the geminal acylation of orthoamides was identified as an attractive target for investigation.

Since the object of the study was to preserve the nitrogen atom of the orthoamide, it seemed prudent to reduce the basicity of the nitrogen. Thus, amide **60** was used as the initial substrate. Compound **60** was subjected to **1** in the presence of an excess of $BF_3$•$OEt_2$ (**Scheme 2.2.1**). The expected product of geminal acylation, the bicyclic **61**, was obtained, albeit in only 24% yield. It was found that by adding 10 equivalents of water, followed by 15 equivalents of $BF_3$•$OEt_2$ after the Mukaiyama aldol reaction, the yield of **61** increased to 64%. The initial aldol reaction had proceeded with the loss of an oxygen substituent from the starting material. The subsequent pinacol rearrangement led to the formation of the product, following the loss of the second oxygen substituent.



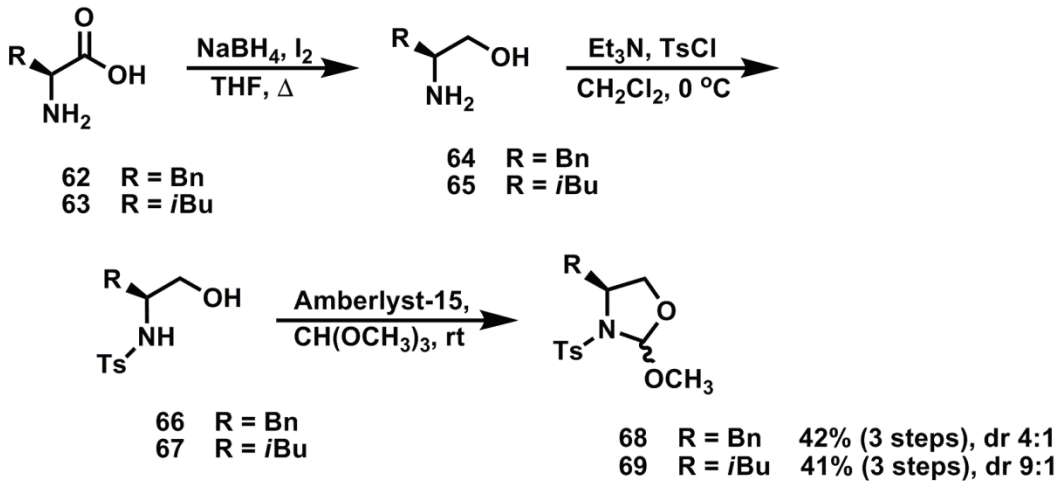

**Scheme 2.2.1:** Geminal acylation of **60** with **1** in a single anhydrous step and using a two-step procedure including the addition of water

Analysis by $^1$H NMR spectroscopy indicated that **61** was completely enolized in $CDCl_3$. It was not surprising that a ring-opened product analogous to **54** and **57** was not detected as the ring-opened products would likely have arisen from a diketo form.

The geminal acylation of **60** proceeded with the loss of two exocyclic oxygen functions. A 2-methoxyoxazolidine might present a greater challenge because the formation of a 1,3-diketone would require the selective cleavage of an annular carbon-oxygen or an annular carbon-nitrogen bond. It was encouraging in this regard that the hydrolysis of oxazolidines is known to proceed very largely by initial cleavage of the carbon-oxygen bond.[13]

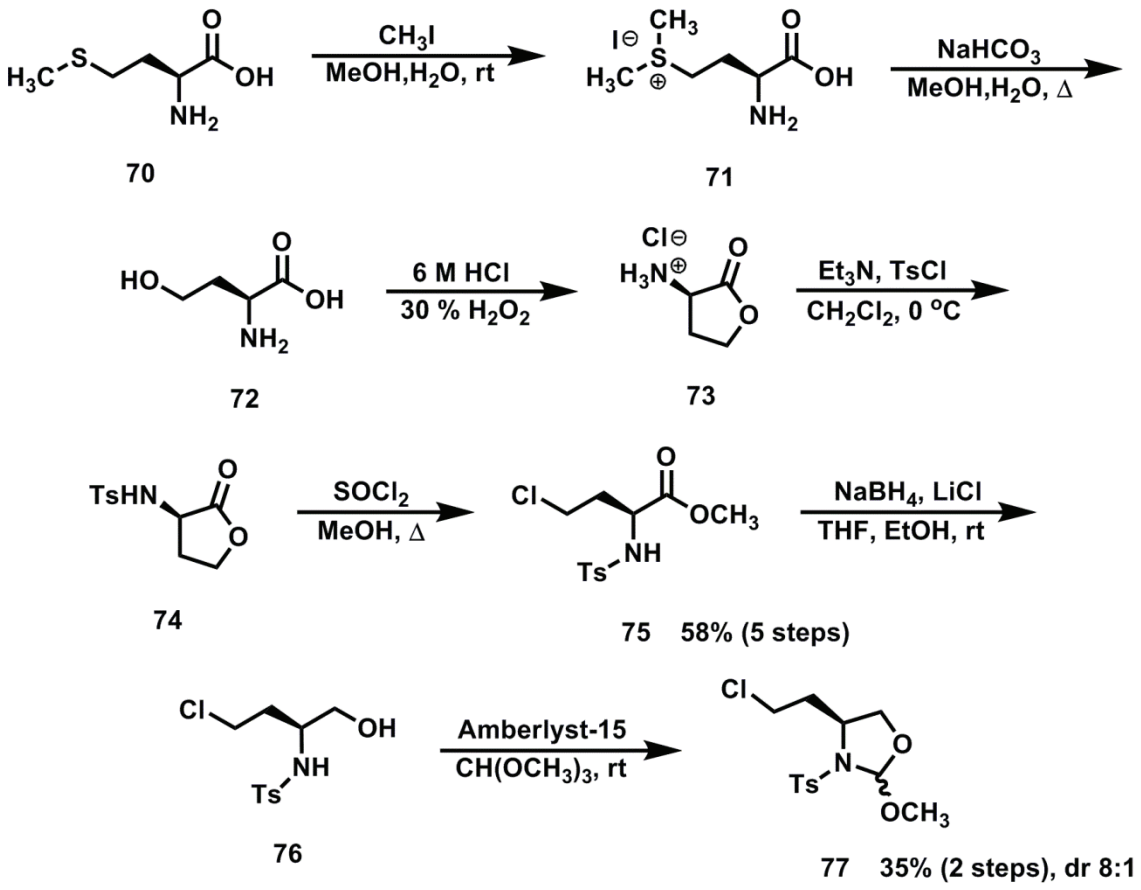
Substituted 2-methoxyoxazolidines **68**, **69**, **77**, and **81** were synthesized over several steps from amino acid starting materials. Compounds **68** and **69** were prepared by initial reduction of L-phenylalanine **62** and L-leucine **63** (**Scheme 2.2.2**), respectively, by sodium borohydride in the presence of iodine,[14] resulting in amino alcohols **64** and **65**. Subsequent $Et_3N$-mediated protection by TsCl gave rise to the *N*-tosylated alcohols **66** and **67**.[15] In neither case was there evidence for significant formation of oxygen-tosylated

products. Ring closure to the 2-methoxyoxazolidines **68** and **69** was then accomplished in overall moderate yields of 42% and 41%, respectively, by treatment of **67** and **68** with an excess of trimethylorthoformate in the presence of Amberlyst-15 over several hours.



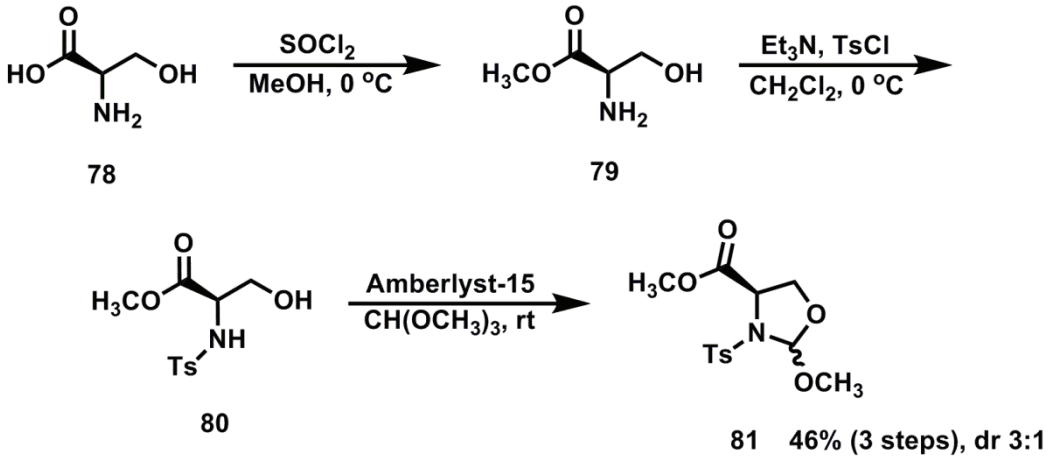

**Scheme 2.2.2:** Preparation of 2-methoxyoxazolidines **68** and **69**

Compound **77** can be envisioned as arising from L-homoserine (**Scheme 2.2.3**), but due to the high cost of that amino acid, a longer synthetic route was followed. α-Amino-γ-butyrolactone **73** was prepared in three steps from L-methionine **70** as described in the literature.[16] Thus, initial treatment of **70** with iodomethane gave rise to sulfonium salt **71** which, upon hydrolysis to amino acid **72** and subsequent lactonization, provided **73**. Protection with TsCl[17] afforded lactone **74** which, upon heating in the presence of thionyl chloride and MeOH,[18] resulted in the chlorinated ester **75**. Reduction of the ester with lithium borohydride[19] gave the *N*-tosylated amino alcohol **76**, which, upon cyclization under the standard conditions yielded the 2-methoxyoxazolidine **77** in a 20% overall yield from **70**.



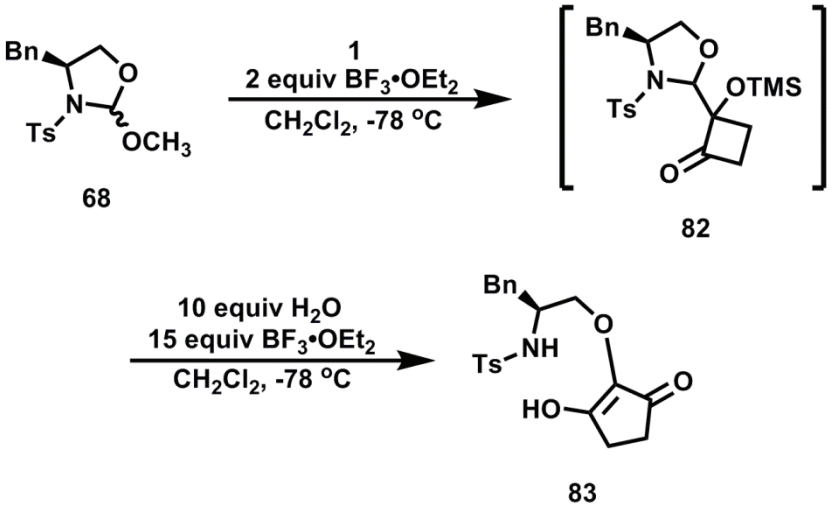

**Scheme 2.2.3:** Preparation of 2-methoxyoxazolidine **77**

Compound **81** was prepared from the D-enantiomer of serine **78** (**Scheme 2.2.4**) as esterification of the carboxylic acid group was expected to result in the formation of amino alcohol **79** with an ester side chain in the L-configuration. This was accomplished by esterification of the amino acid in the presence of thionyl chloride and MeOH.[20] Compound **79** was protected with TsCl[15] to give **80**, which was then cyclized as above, resulting in the 2-methoxyoxazolidine **81** in a 46% overall yield.



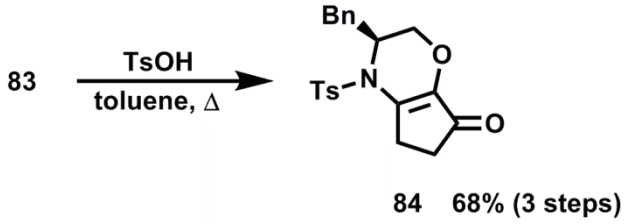

**Scheme 2.2.4:** Preparation of 2-methoxyoxazolidine **81**

Using the same procedure as for the more efficient geminal acylation of **60**, 2-methoxyoxazolidine **68** was reacted with **1** in the presence of two equivalents of $BF_3$•$OEt_2$ (**Scheme 2.2.5**). The initial Mukaiyama aldol reaction proceeded with the breaking of the exocyclic carbon-oxygen bond, giving rise to cyclobutanone **82** as a mixture of diastereomers. Addition of 10 equivalents of water, followed by 15 equivalents of $BF_3$•$OEt_2$ resulted in ring-expansion, by way of a pinacol rearrangement, to the enol **83**. Unlike the geminal acylation of the pyrrolidinone **60**, which had undergone rearrangement with the loss of a carbon-oxygen bond, and unlike the hydrolysis of oxazolidinines, 2-D NMR data indicated that ring-expansion of the cyclobutanone intermediate had proceeded with the exclusive cleavage of the carbon-nitrogen bond to give **83**.




**Scheme 2.2.5:** Geminal acylation of **68** with **1** *via* the two-step procedure including the addition of water to intermediate **82**, resulting in **83**

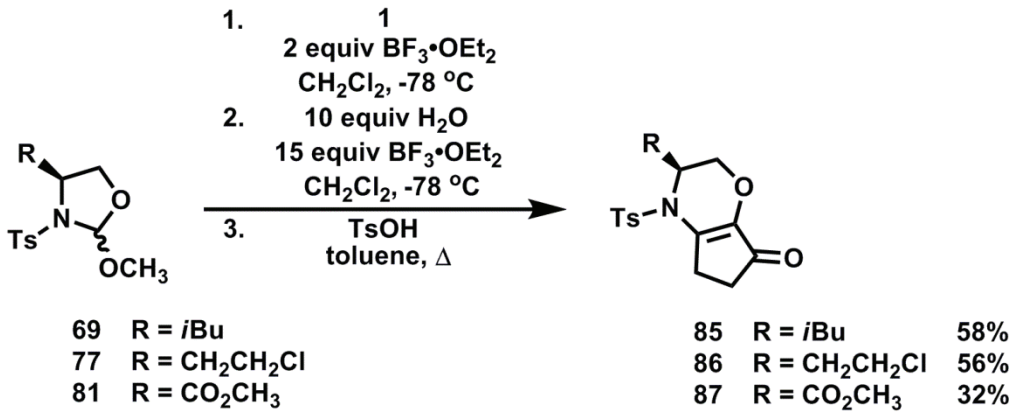
Despite the electron-poor nature of the sulfonamide nitrogen atom, it was found that cyclization, either by 1,2- or 1,4-addition, could be accomplished by treatment of **83** with TsOH at high temperature (**Scheme 2.2.6**). The resulting heterocycle **84** was obtained in 68% yield from **68**.




**Scheme 2.2.6:** TsOH-mediated cyclization of **83** to give the bicyclic heterocycle **84**

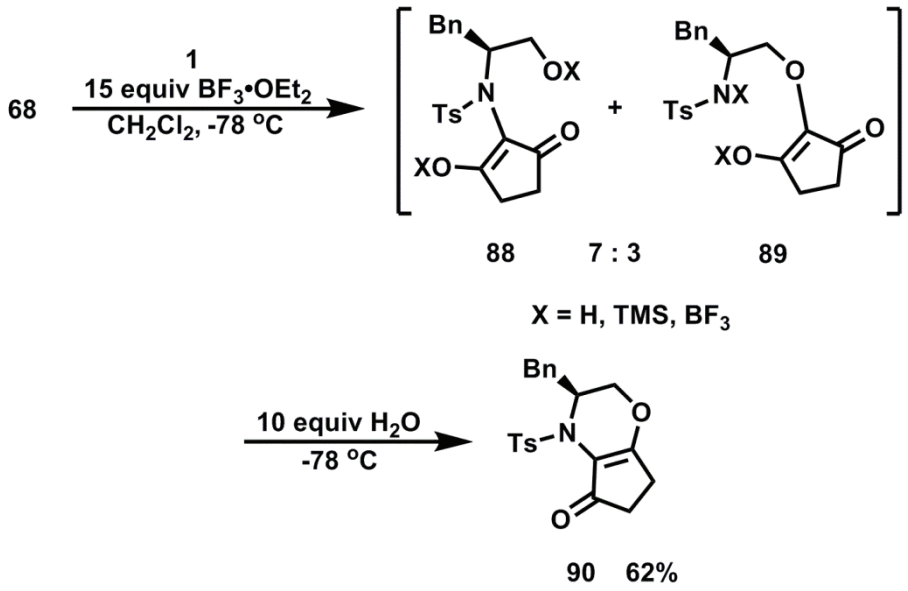
2-Methoxyoxazolidines **69**, **77**, and **81** were subjected to the above geminal acylation reaction conditions (**Scheme 2.2.7**). In each case, the ring-expansion step was accomplished by the exclusive rupture of the carbon-nitrogen bond. The subsequent TsOH-mediated cyclization resulted in moderate to good yields over three steps of the heterocycles **85-87** bearing the same substitution pattern as compound **84**, where the α,β-

unsaturated ketone was oxygen-substituted at the α position and nitrogen-substituted at the β position.




**Scheme 2.2.7:** Geminal acylation of **69**, **77**, and **81** with **1** using the two-step aqueous procedure and the subsequent acid-mediated ring closure to bicyclic heterocycles **85-87**

The geminal acylation of **68** was attempted in a single operation using a large excess of $BF_3$•$OEt_2$ (**Scheme 2.2.8**). Surprisingly, analysis of the product by $^1H$ and 2-D NMR spectroscopy revealed that geminal acylation had proceeded primarily with the rupture of the endocyclic carbon-oxygen bond. Despite an approximately 7:3 mixture of enols **88** and **89**, it was found that compound **88** could be cyclized exclusively through the addition of 10 equivalents of water to the reaction mixture upon completion of the geminal acylation. This resulted in the heterocycle **90**, in which the α,β-unsaturated ketone was nitrogen-substituted at the α position and oxygen-substituted at the β position.

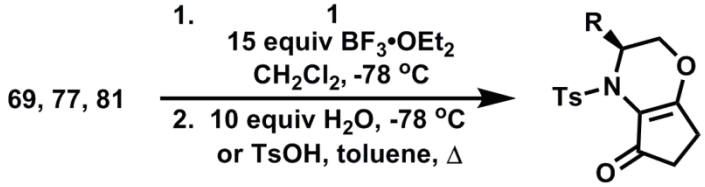



**Scheme 2.2.8:** Geminal acylation of **68** with **1** via anhydrous procedure resulting in a mixture of compounds **88** and **89**, of which only **88** cyclized in the presence of water to give **90**

It seemed paradoxical that the addition of water could promote cyclization to afford **90**, since this would result in the expulsion of water. However, it is possible that the addition of water to a mixture of enols **88** and **89** served to hydrolyze the intermediates (X = H), leading to enhanced nucleophilicity of the primary alcohol and secondary sulfonamide, of which only the alcohol cyclized effectively. It is also possible that water promoted reversible elimination to the final products, which would be favored due to conjugation.

2-Methoxyoxazolidines **69**, **77**, and **81** were similarly subjected to the above one-operation geminal acylation procedure (**Scheme 2.2.9**). An approximately 7:3 mixture of carbon-oxygen to carbon-nitrogen ruptured products were observed in each case. Cyclization to the heterocycles **91** and **92** was accomplished by addition of a small amount of water to the reaction mixture. Compound **93** was not obtained in the presence

of water and required refluxing in toluene in the presence of TsOH, resulting also in a trace amount of **87**. Heterocycles **91-93** were obtained in moderate to good yields.

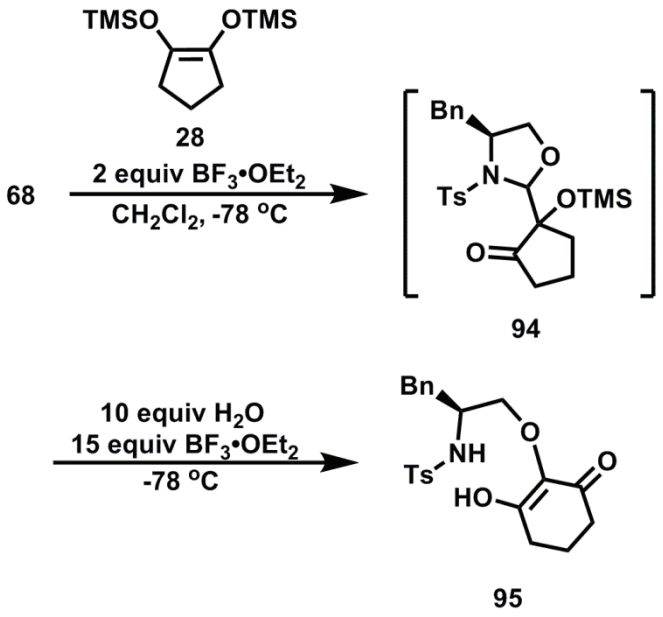



| | | |
|---|---|---|
| **91** | ***i*Bu** | **58%** |
| **92** | **$CH_2CH_2Cl$** | **73%** |
| **93** | **$CO_2CH_3$** | **43%** |

**Scheme 2.2.9:** Geminal acylation of **69**, **77**, and **81** with **1** using the anhydrous procedure and subsequent cyclization to give bicyclic heterocycles **91-93**

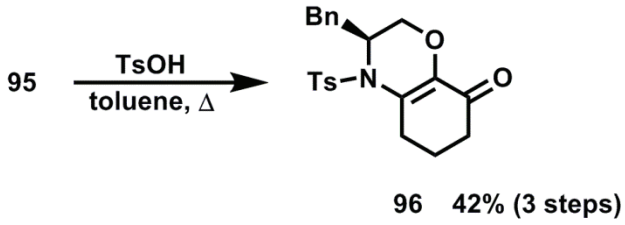
Based on these results, it was evident that the chemoselectivity of the endocyclic bond cleavage during the pinacol rearrangement step could be controlled by judicious choice of procedure for the geminal acylation, that is, whether ring-expansion is carried out in the presence of added water (heterocycles **84-87**) or under anhydrous conditions (heterocycles **90-93**).

In light of these results, the scope of this methodology was expanded with the synthesis of fused 6,6-bicyclic systems through the geminal acylation of 2-methoxyoxazolidines **68**, **69**, **77**, and **81** with 1,2-bis(trimethylsilyloxy)cyclopentene **28**.[21] Compound **68** was treated with the five-membered acyloin in the presence of two equivalents of $BF_3$•$OEt_2$ (**Scheme 2.2.10**). The Mukaiyama aldol step generated cyclopentanone **94** as a mixture of diastereomers. As was observed with **1**, the addition of a small amount of water to the mixture, followed by a large excess of $BF_3$•$OEt_2$, generated a single enol **95**, which was the result of exclusive cleavage of the carbon-nitrogen bond.



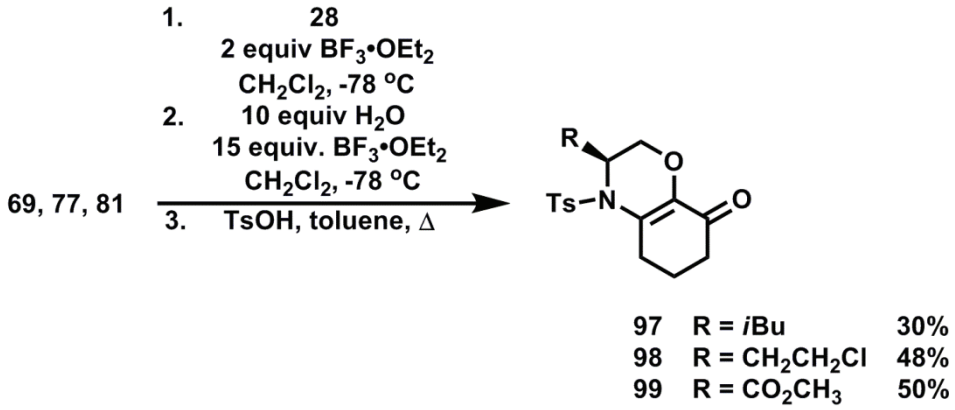

**Scheme 2.2.10:** Geminal acylation of **68** with **28** via the two-operation, aqueous procedure, resulting in **95**

As was previously observed, cyclization required high reaction temperature in the presence of TsOH (**Scheme 2.2.11**). Nonetheless, the heterocycle **96** was obtained in 42% overall yield from the 2-methoxyoxazolidine.



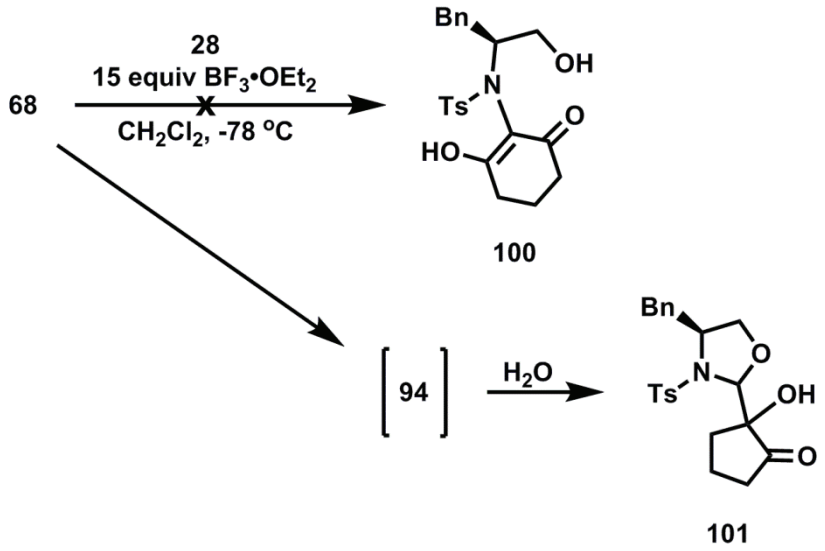

**Scheme 2.2.11:** TsOH-mediated cyclization of **95** to give the bicycle **96**

Using the same procedure, 2-methoxyoxazolidines **69**, **77**, and **81** were subjected to **28** in the presence of $BF_3$•$OEt_2$ (**Scheme 2.2.12**). As was the case with **68**, each substrate underwent ring-expansion with exclusive rupture of the carbon-nitrogen bond. The fused bicyclic structures **97-99** were obtained in moderate yields following TsOH-mediated cyclization.



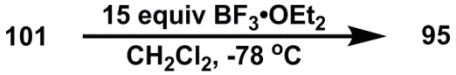

**Scheme 2.2.12:** Geminal acylation of **68**, **77**, and **81** with **28** using the two-step aqueous procedure and the subsequent acid-mediated ring closure to bicyclic heterocycles **97-99**

2-Methoxyoxazolidine **68** was re-subjected to geminal acylation with **28** in the presence of a large excess of $BF_3$•$OEt_2$, with the goal of generating a fused 6,6-bicyclic compound analogous to heterocycles **90-93** (**Scheme 2.2.13**). Instead of the reaction proceeding to the expected enol **100**, the product contained a diastereomeric mixture of alcohols **101**, the desilylated analogue of the expected cyclopentanone intermediate **94**, in addition to intractable material. Likewise, 2-methoxyoxazolidines **69**, **77**, and **81** failed to undergo geminal acylation with **28** using the one-step anhydrous procedure. This observation indicated that ring-expansion likely did not proceed following the completion of the Mukaiyama aldol reaction. The lack of rearrangement to **100** may be a result of the silyl group of intermediate **94** being too tightly bound to the oxygen atom, thereby hindering the ring-expansion to **100**.



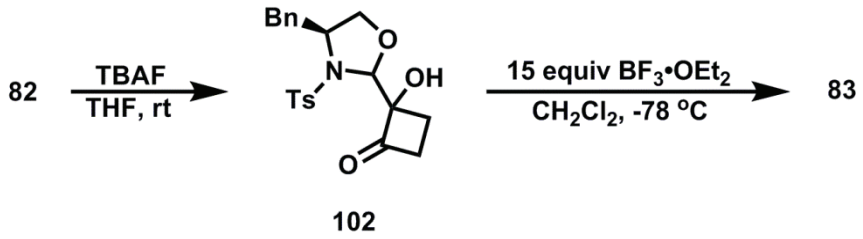

**Scheme 2.2.13:** Unsuccessful geminal acylation of **68** with **28** using the anhydrous procedure, resulting in **101** and intractable material upon aqueous workup

Geminal acylation was found to occur successfully when the cyclopentanone **101** was subjected to a large excess of $BF_3$•$OEt_2$ (**Scheme 2.2.14**). However, instead of ring-expansion proceeding with the expected cleavage of the carbon-oxygen bond, it was the carbon-nitrogen bond that was ruptured, resulting in enol **95**. Based on this result, it was proposed that water influences the chemoselectivity of the ring-expansion step, simply by hydrolyzing the silyl ether of **94**.




**Scheme 2.2.14:** Hydrolyzed aldol product **101** undergoing ring-expansion with exclusive rupturing of the carbon-nitrogen bond to give **95**

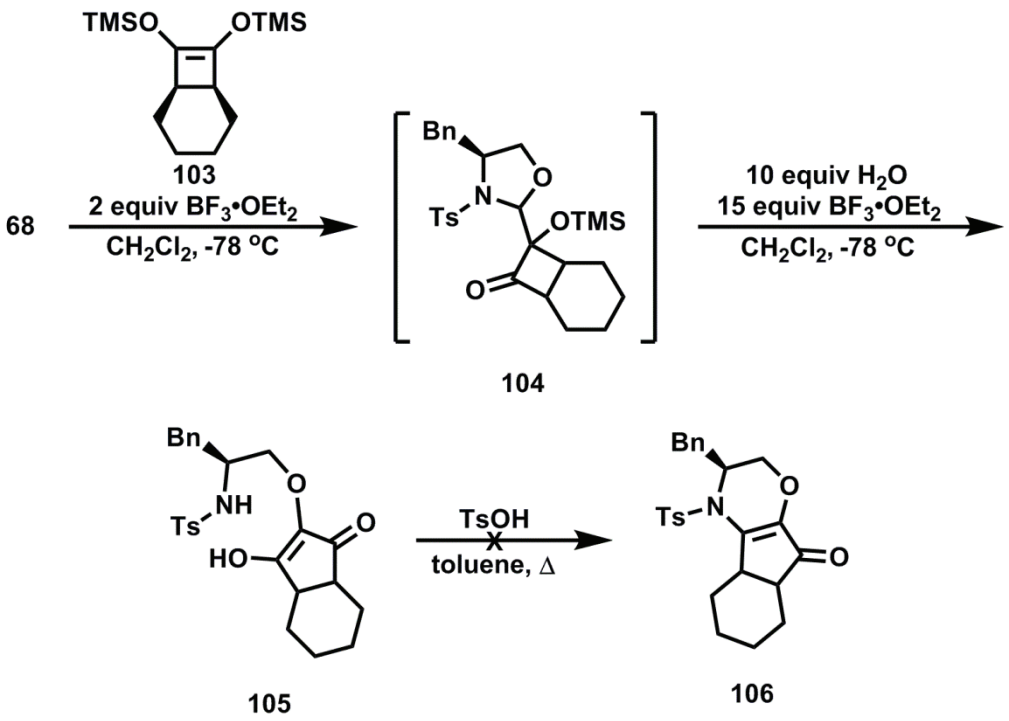
This hypothesis was verified by subjecting **102**, the cyclobutanone analogue of **101**, to an excess of $BF_3$•$OEt_2$ (**Scheme 2.2.15**). Again, geminal acylation resulted in a single compound, enol **83**, resulting from the carbon-nitrogen bond rupturing during ring-expansion.




**Scheme 2.2.15:** Ring-expansion of the hydrolyzed aldol product **102** proceeding with exclusive rupturing of the carbon-nitrogen bond

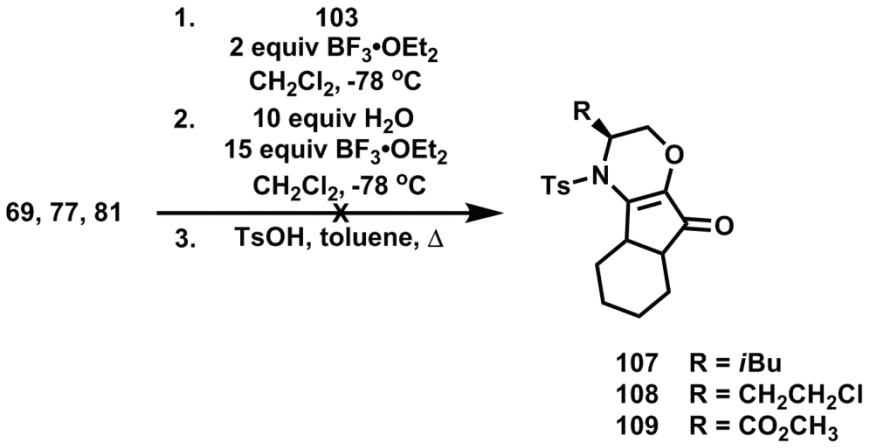
The geminal acylation of 2-methoxyoxazolidines **68**, **69**, **77**, and **81** was further studied with *meso*-7,8-bis(trimethylsilyloxy)bicyclo[4.2.0]oct-7-ene **103**.[22] Reaction with the facially biased, bicyclic acyloin could potentially generate a tricyclic ring structure, following acid-mediated ring closure of the geminal acylation product. Furthermore, it is possible that this ring closure could proceed with facial selectivity in the formation of the tricyclic product.

Compound **68** was subjected to **103** using the two-operation aqueous procedure (**Scheme 2.2.16**). As was observed previously, ring-expansion of the cyclobutanone intermediate **104** proceeded with exclusive rupture of the carbon-nitrogen bond, giving rise to the enol **105** as the only geminal acylation product. Ring closure to tricyclic heterocycle **106** was subsequently attempted under the standard reaction conditions. Unfortunately, reaction of compound **105** instead gave rise to intractable material.



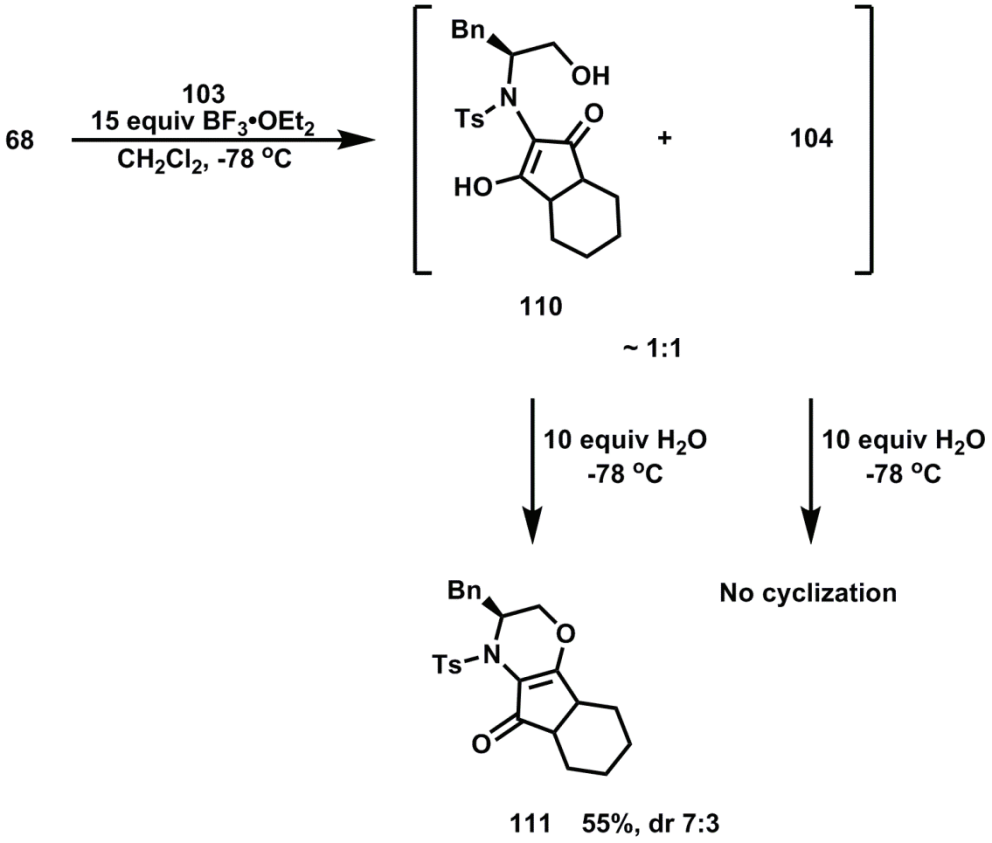

**Scheme 2.2.16:** Geminal acylation of **68** with **103** using the aqueous procedure and the unsuccessful acid-mediated ring closure to tricyclic heterocycle **106**

In a similar fashion, 2-methoxyoxazolidines **69**, **77**, and **81** appeared to undergo successful geminal acylation with **103**, but cyclization to the intended tricyclic molecules **107-109** resulted only in decomposition of the starting material (**Scheme 2.2.17**).



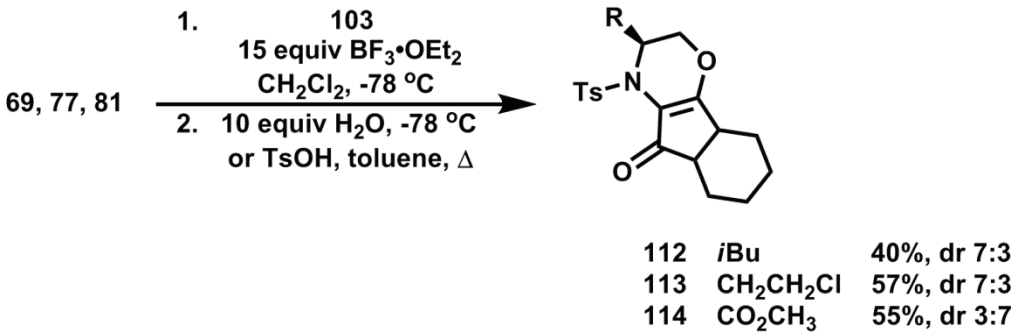

**Scheme 2.2.17:** Geminal acylation of **69, 77, and 81** with **103** using the two-step aqueous procedure and the subsequent unsuccessful acid-mediated ring closure to the tricyclic heterocycles **107-109**

When 2-methoxyoxazolidine **68** was subjected to **103** using the anhydrous procedure for geminal acylation, it was observed that the ring-expansion of the cyclobutanone intermediate proceeded without significant chemoselectivity, resulting in a roughly 1:1 mixture of enols **110** and **104** (**Scheme 2.2.18**). However, the addition of a small amount of water to the reaction mixture gave rise to the tricyclic compound **111** with a high degree of chemoselectivity, but as an approximately 7:3 mixture of diastereomers.



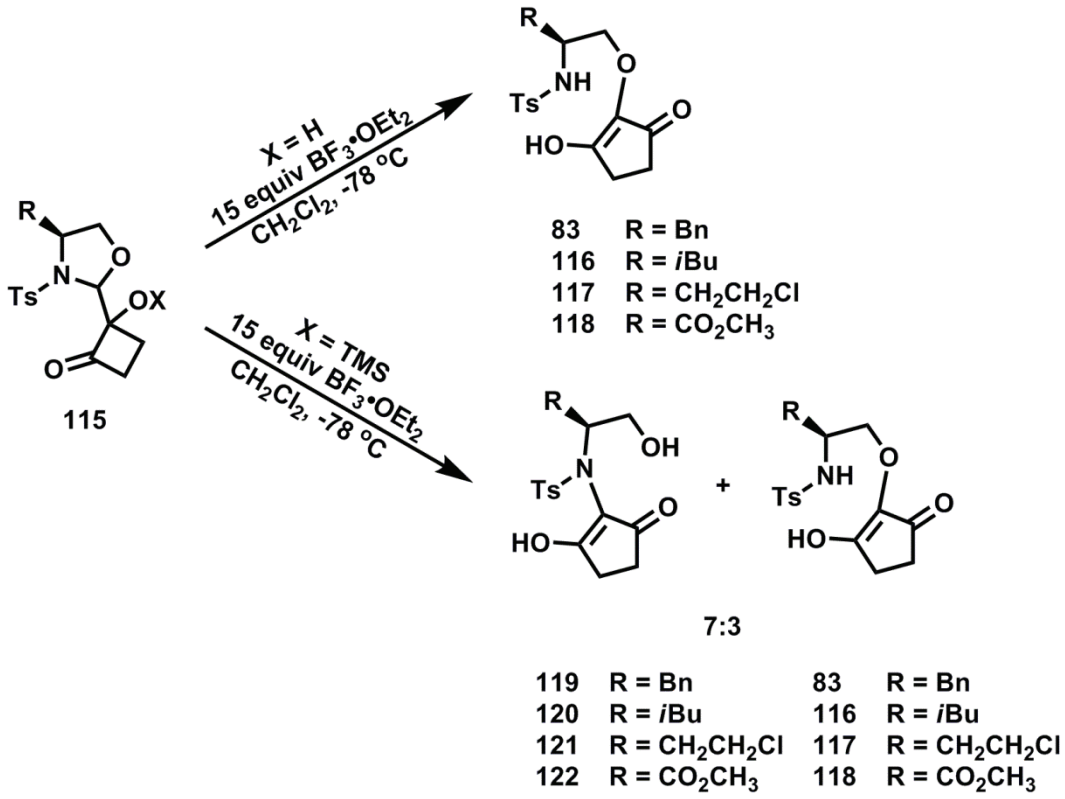

**Scheme 2.2.18:** Geminal acylation of **68** with **103** using the one-step aqueous procedure resulting in **110** and **104**, followed by the exclusive cyclization of **110** to **111** in the presence of water

Using the same procedure, 2-methoxyoxazolidines **69**, **77**, and **81** underwent geminal acylation with **103**, each time giving rise to an approximately 1:1 mixture of enols (**Scheme 2.2.19**). Similarly, the addition of a small amount of water to the reaction mixture produced the tricyclic molecules **112** and **113**. Compound **81**, again, required treatment with TsOH at an elevated temperature to complete its conversion to the heterocycle **114**. Despite the poor chemoselectivity of the pinacol rearrangement, compounds **111-114** were obtained in moderate yields.




**Scheme 2.2.19:** Geminal acylation of **68**, **77**, and **81** with **103** using the aqueous procedure, followed by cyclization to the tricyclic products **112-114**

The reasons for chemoselectivity in the presence or absence of water during ring-expansion are still not clear. However, the role of water appears to involve the desilylation of the cyclobutanone intermediate **115**. Therefore, the chemoselectivity in the ring-expansion step must reside in the identity of X in **115** (**Scheme 2.2.20**). When X = H, the ring expansion takes place with the rupture of the carbon-nitrogen bond to give enols **83**, **116**, **117**, and **118**. When X = TMS, the ring expansion favors the rupture of the carbon-oxygen bond to give enols **119-122**.

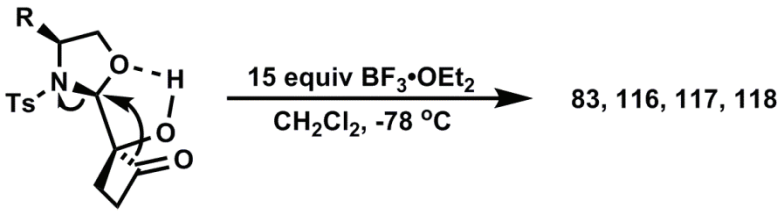



**Scheme 2.2.20:** Chemoselective pinacol rearrangement of **115**, resulting in exclusively **83**, **116**, **117**, and **118** when X = H and predominantly **119-122** when X = TMS

When X = TMS, it could be envisioned that the chemoselectivity in the ring-expansion resided in the relative affinities of the endocyclic nitrogen and oxygen atoms for $BF_3$. With the electron density of the nitrogen atom withdrawn by the adjacent Ts group, it seems possible that the endocyclic oxygen would be the more Lewis basic of the two atoms, resulting in the preferred complexation of $BF_3$ at oxygen and, therefore, cyclobutanone ring-expansion with rupturing of the carbon-oxygen bond.

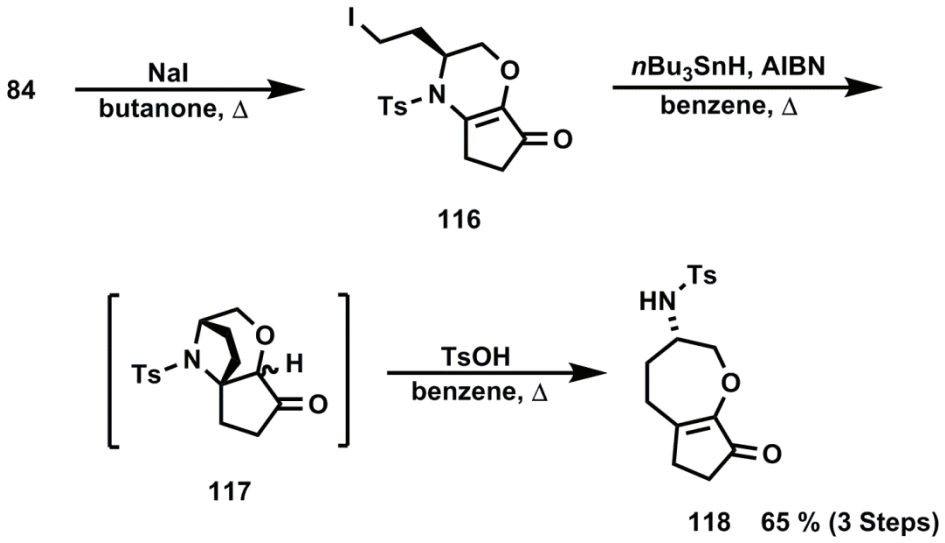
When X = H, the observed chemoselectivity is more difficult to rationalize. However, it is possible that a hydrogen-bonding interaction could result in the two rings being held in a conformation that has the nitrogen atom positioned *anti* to the incoming

acyl group, leading to exclusive rupture of the carbon-nitrogen bond through a concerted ring-expansion (**Scheme 2.2.21**).



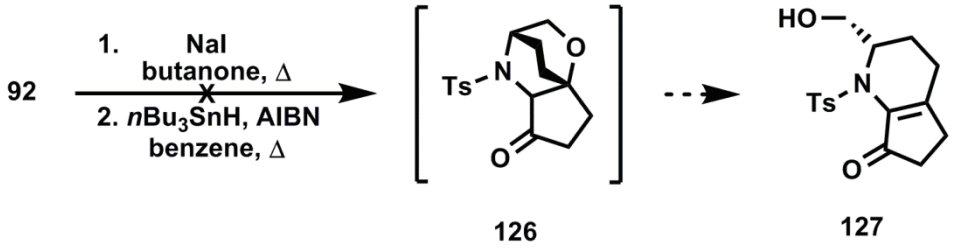

**Scheme 2.2.21:** Possible hydrogen bonding interaction between the hydroxyl group and the endocyclic oxygen atom

With heterocycle **86** in hand, further manipulation was explored by employing the pendant side chain. Halide exchange with NaI resulted in iodide **123**, which subsequently reacted in solution under reflux with *n*$Bu_3SnH$ in the presence of AIBN (**Scheme 2.2.22**). Radical cyclization onto the β-position of the α,β-unsaturated ketone led to the tricyclic compound **124**. Reheating **124** in the presence of TsOH resulted in the elimination of the endocyclic nitrogen to give the fused 7,5-bicyclic system **125** possessing a pendant nitrogen atom.




**Scheme 2.2.22:** Tin-mediated radical cyclization of iodide **123** and subsequent TsOH-mediated elimination to **125**

Heterocycle **92**, which differs only in the position of the carbonyl group, was subjected to the same conditions (**Scheme 2.2.23**). It was predicted that radical conjugate addition might result in tricyclic intermediate **126**, and acid-mediated elimination of the endocyclic oxygen could then provide the heterocycle **127**, bearing a pendant hydroxymethyl group. Unfortunately, this procedure did not work with compound **92**. Iodination, followed by reaction with $Bu_3SnH$ in the presence of AIBN gave rise to intractable material.




**Scheme 2.2.23:** Unsuccessful tin-mediated radical cyclization toward the formation of **127**

## 2.3 Conclusions

Pyrrolidinone **60** was subjected to **1** in the presence of $BF_3$•$OEt_2$, giving rise to the geminally acylated product **61**. It was found that the conversion to product could be enhanced by the addition of a small amount of water following the initial Mukaiyama aldol addition of the acyloin. In any event, it was observed that the ring-expansion to the final product was accompanied by the rupture of the exocyclic carbon-oxygen bond from the cyclobutanone intermediate.

In a similar fashion, **1** underwent $BF_3$•$OEt_2$-mediated geminal acylation with 2-methoxyoxazolidines **68**, **69**, **77**, and **81** which, following cyclization, gave rise to heterocycles **90-93**. It was observed that the preferred endocyclic carbon-oxygen bond rupture during the ring-expansion could be altered by the addition of a small amount of water following the initial step, such that carbon-nitrogen bond rupture was exclusive. Subsequent acid-mediated cyclization yielded heterocycles **84-87**.

The two-step aqueous procedure was found to be applicable to **28**. 2-Methoxyoxazolidines **68**, **69**, **77**, and **81** underwent geminal acylation, followed by cyclization to afford heterocycles **96-99**. As was the case with **1**, this procedure gave rise to ring-expansion of the cyclopentanone intermediates with exclusive rupturing of the carbon-nitrogen bond. Under the anhydrous protocol, **68**, **69**, **77**, and **81** did not appear to progress beyond their respective cyclopentanone intermediates. It is possible that ring-expansion was hindered due to the persistence of the oxygen-silicon bond, which would have been hydrolyzed in the case of the aqueous procedure.

In the case of the bicyclic acyloin **103**, it was observed that 2-methoxyoxazolidines **68**, **69**, **77**, and **81** underwent geminal acylation using the aqueous

procedure. However, the subsequent acid-mediated ring closure to **106-109** was unsuccessful and resulted only in degradation of the starting material. The geminal acylation of **68**, **69**, **77**, and **81** was again accomplished using the anhydrous procedure. However, in contrast with the previous result, little chemoselectivity was observed in the ring-expansion step between the rupturing of the carbon-oxygen bond versus the carbon-nitrogen bond. Despite the poor selectivity, cyclization of the enols gave exclusively heterocycles **111-114** as products.

It was proposed that water influences the chemoselectivity of bond rupturing during the ring-expansion step simply by hydrolyzing the silyl ether of the aldol intermediate. This is because hydrolyzed intermediates **101** and **102** underwent ring-expansion with exclusive rupturing of the carbon-nitrogen bond in the absence of any added water. The resulting enols **95** and **83** were the same products obtained using the two-step procedure including the addition of a small amount of water. Therefore, it was likely that the chemoselectivity of the ring-expansion step was dependent on whether X = H or TMS.

Under the anhydrous protocol, it was believed that the preferred carbon-oxygen bond cleavage could be attributed to the oxygen atom being more Lewis basic than the electron-withdrawn nitrogen atom. Conversely, in the presence of water, a hydrogen bonding interaction with the endocyclic oxygen atom could potentially lock the two rings in a conformation that would favor the rupture of the carbon-nitrogen bond.

2-Methoxyoxazolidine **86** was found to be amenable to further transformation by tin-mediated cyclization of the pendant side chain of iodide **123** to give **124** and, following elimination of the sulfonamide chain, the fused 7,5-ring system **125**, possessing

a pendant nitrogen atom. Despite the success of this transformation, it was not adaptable to heterocycle **92**, which gave rise to intractable material.

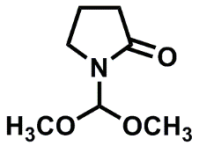
## 2.4 Experimental

### General

Dichloromethane was distilled from calcium hydride. THF was distilled from sodium metal. EtOAc and hexanes were distilled. Commercial reagents were used as received. Column chromatography was carried out on a silica gel (230-400 mesh) stationary phase. Melting points were acquired using a Fisher-Johns apparatus and are uncorrected. IR spectra were recorded as thin films using NaCl plates. High-resolution mass spectra were acquired using a Bruker MicroTOF mass spectrometer *via* electrospray ionization. $^{1}H$ NMR spectra were acquired at 500 MHz, and $^{13}C$ NMR spectra at 125 MHz from $CDCl_3$ sample solutions. Chemical shifts for $^{1}H$ NMR are relative to internal standard tetramethylsilane ($\delta$ 0.00 ppm). Chemical shifts for $^{13}C$ NMR are relative to $CDCl_3$ ($\delta$ 77.16 ppm). Diastereomeric ratios were determined by integration of diagnostic $^{1}H$ NMR signals. Two-dimensional COSY, HSQC, and HMBC data were acquired to establish chemical structure. Single crystal X-ray diffraction data were collected using a Rigaku RAXIS-UNKNOWN diffractometer. All measurements were made with graphite monochromatic Mo-K$\alpha$ radiation (0.71070 Å). An empirical absorption correction was applied which resulted in transmission factors ranging from 0.732 to 0.978. The data were corrected for Lorentz and polarization effects. The structures were solved by direct methods and expanded using Fourier techniques. Hydrogen atoms were refined using the

riding model. Full-matrix least-squares refinement carried out on F was based on the number of reflections and the number of variable parameters. All crystallographic data collection and refinement was performed by Dr. T. Stanley Cameron at Dalhousie University.

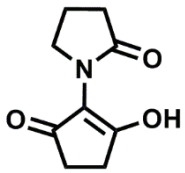
**1-(Dimethoxymethyl)pyrrolidin-2-one (60)**




**60**

2-Pyrrolidone (1.53 mL, 20.0 mmol) was dissolved in $CH(OCH_3)_3$ (50 mL). TsOH (380 mg, 2.00 mmol) was added, and the solution was heated under reflux for 72 h. The solvent was then evaporated under reduced pressure. Column chromatography ($SiO_2$) with 20:1 $CH_2Cl_2$/MeOH provided **60** (2.00 g, 63%) as a yellow oil. $^1$H NMR δ: 5.73 (1H, s), 3.43 (2H, t, $J$ = 7.1 Hz), 3.38 (6H, s), 2.45 (2H, t, $J$ = 8.1 Hz), 2.05 (2H, pentet, $J$ = 7.4 Hz) ppm; $^{13}$C NMR δ: 176.2, 101.7, 54.5, 40.9, 31.9, 18.4 ppm. These data are in accordance with those found in the literature.[23]

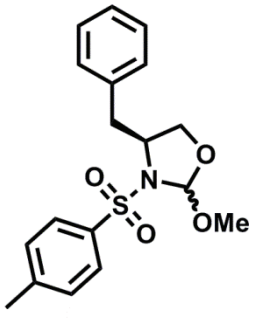
**1-(2-Hydroxy-5-oxocyclopent-1-enyl)pyrrolidin-2-one (61)**




**61**

Compound **60** (159 mg, 1.00 mmol) and **1** (346 mg, 1.50 mmol) were dissolved in $CH_2Cl_2$ (10 mL). The mixture was cooled to -78 °C with stirring. $BF_3$•$OEt_2$ (0.250 mL, 2.00 mmol) was added dropwise, and the reaction mixture was warmed to -20 °C over 3 h. The mixture was re-cooled to -78 °C, and $BF_3$•$OEt_2$ (1.88 mL, 15.0 mmol) and water (0.18 mL, 10 mmol) were added dropwise simultaneously. The mixture was warmed to room temperature overnight and extracted with aqueous 1 M NaOH (3 × 20 mL). The aqueous layer was acidified with concentrated aqueous HCl and extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic fractions were dried with $Na_2SO_4$, and the solvent was evaporated under reduced pressure to afford **61** (115 mg, 64%) as a yellow solid. mp 129-131 $^oC$; IR (film): 3269, 1679, 1629 $cm^{-1}$; $^1H$ NMR δ: 12.58 (1H, br s), 4.18 (2H, t, $J$ = 7.3 Hz), 2.56 (4H, s), 2.51 (2H, t, $J$ = 8.1 Hz), 2.19 (2H, pentet, $J$ = 7.6 Hz) ppm; $^{13}C$ NMR δ: 198.1, 179.4, 177.8, 115.9, 48.0, 33.6, 30.9, 25.8, 20.0 ppm; HRMS (ESI): 204.0624, $[C_9H_{11}NO_3Na]^+$ requires 204.0631.

**(2*R*,4*S*)-4-Benzyl-2-methoxy-3-(4-methylbenzenesulfonyl)-1,3-oxazolidine + (2*S*,4*S*)-4-Benzyl-2-methoxy-3-(4-methylbenzenesulfonyl)-1,3-oxazolidine (68)**



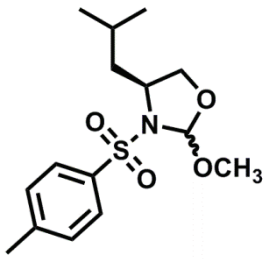

**68**

Compound **62** (16.6 g, 100 mmol) was suspended in THF (250 mL). After cooling to 0 $^oC$, $NaBH_4$ (9.08 g, 240 mmol) was added slowly. A solution of $I_2$ (25.3 g, 100 mmol)

in THF (200 mL) was then added dropwise,[14] and the mixture was stirred for 30 min at 0 °C before being heated under reflux overnight. The mixture was cooled to 0 °C, and MeOH was added dropwise until bubbling ceased and the mixture was clear. The solvent was evaporated under reduced pressure, and 20.0% (w/v) aqueous solution of KOH (200 mL) was added. The mixture was stirred for 3 h before being extracted with $CH_2Cl_2$ (3 × 200 mL). The combined organic layers were dried over $Na_2SO_4$, and the solvent was evaporated under reduced pressure to afford **64**. The product was then redissolved in $CH_2Cl_2$ (200 mL). $Et_3N$ (27.9 mL, 200 mmol) was added, and the solution was cooled to 0 °C. TsCl (17.2 g, 90.0 mmol) was added slowly,[15] and the mixture was warmed to room temperature overnight with stirring. The mixture was washed with an equal volume of aqueous $NH_4Cl$ and extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic layers were dried over $Na_2SO_4$, and the solvent was evaporated under reduced pressure to yield **66**. The product was then dissolved in $CH(OCH_3)_3$ (250 mL). Amberlyst-15 (25.0 g) was pre-dried overnight with heating under vacuum and added to the solution. The mixture was then stirred overnight at room temperature. The acid was removed by vacuum filtration, and the solvent was evaporated under reduced pressure. Column chromatography ($SiO_2$) with 4:1 hexanes/EtOAc gave **68** (15.4 g, 42%) as a white solid in a 4:1 diastereomeric ratio. IR (film): 1356, 1171, 1083 $cm^{-1}$; $^1H$ NMR for major isomer δ: 7.76 (2H, d, *J* = 8.3 Hz), 7.36-7.20 (5H, m), 7.16 (2H, d, *J* = 7.6 Hz), 5.97 (1H, s), 3.92-3.80 (2H, m), 3.71 (1H, dd, *J* = 7.6, 6.3 Hz), 3.43 (3H, s), 3.39 (1H, dd, *J* = 13.5, 3.9 Hz), 2.78 (1H, dd, *J* = 13.9, 10.0 Hz), 2.43 (3H, s) ppm; $^{13}C$ NMR for major isomer δ: 144.4, 137.1, 135.4, 130.1, 129.2, 128.8, 127.7, 127.0, 109.2, 70.6, 59.4, 53.5, 41.1, 21.7 ppm; $^1H$ NMR for minor isomer δ: 7.86 (2H, d, *J* = 8.4 Hz), 7.36-7.20 (7H, m), 5.83 (1H,

s), 3.92-3.80 (2H, m), 3.79-3.73 (1H, m), 3.39-3.34 (1H, m), 3.32 (3H, s), 2.83 (1H, dd, *J* = 13.5, 10.1 Hz), 2.43 (3H, s) ppm; $^{13}$C NMR for minor isomer δ: 143.7, 137.6, 137.4, 129.6, 129.4, 128.8, 128.2, 126.9, 108.2, 67.9, 58.4, 54.1, 40.2, 21.7 ppm; HRMS (ESI): 370.1098, $[C_{18}H_{21}NO_4SNa]^+$ requires 370.1083.

**(2*R*,4*S*)-2-Methoxy-3-(4-methylbenzenesulfonyl)-4-(2-methylpropyl)-1,3-oxazolidine + (2*S*,4*S*)-2-Methoxy-3-(4-methylbenzenesulfonyl)-4-(2-methylpropyl)-1,3-oxazolidine (69)**

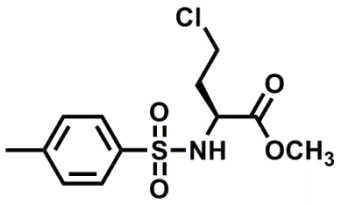



**69**

Compound **63** (13.1 g, 100 mmol) was suspended in THF (250 mL). After cooling to 0 $^{o}$C, $NaBH_4$ (9.08 g, 240 mmol) was added slowly. A solution of $I_2$ (25.3 g, 200 mmol) in THF (200 mL) was then added dropwise,[14] and the mixture was stirred for 30 min at 0 $^{o}$C before being heated under reflux overnight. The mixture was cooled to 0 $^{o}$C, and MeOH was added dropwise until bubbling had ceased and the mixture was clear. The solvent was evaporated under reduced pressure and 20.0% (w/v) aqueous solution of KOH (200 mL) was added. The mixture was stirred for 3 h before being extracted with $CH_2Cl_2$ (3 × 200 mL). The combined organic layers were dried over $Na_2SO_4$, and the solvent was evaporated under reduced pressure to afford **65**. The product was then redissolved in $CH_2Cl_2$ (200 mL). $Et_3N$ (27.9 mL, 200 mmol) was added and the solution was cooled to 0 $^{o}$C. TsCl (17.2 g, 90.0 mmol) was added slowly,[15] and the mixture was warmed to room temperature overnight with stirring. The mixture was washed with an equal volume of

aqueous $NH_4Cl$ and extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic layers were dried over $Na_2SO_4$, and the solvent was evaporated under reduced pressure to afford **67**. The product was then dissolved in $CH(OCH_3)_3$ (250 mL). Amberlyst-15 (25.0 g) was pre-dried with heating under vacuum and added to the solution. The mixture was then stirred overnight at room temperature. The acid was removed by vacuum filtration and the solvent was evaporated under reduced pressure. Column chromatography ($SiO_2$) with 2:1 hexanes/EtOAc provided **69** (13.0 g, 41%) as a white solid in a 9:1 diastereomeric ratio. IR (film): 1356, 1174, 1080 $cm^{-1}$; $^1H$ NMR for major isomer δ: 7.73 (2H, d, *J* = 8.4 Hz), 7.33 (2H, d, *J* = 8.3 Hz), 5.96 (1H, s), 3.88 (1H, dd, *J* = 8.2, 7.4 Hz), 3.74 (1H, dd, *J* = 8.3, 7.1 Hz), 3.71-3.64 (1H, m), 3.41 (3H, s), 2.44 (3H, s), 1.87 (1H, ddd, *J* = 13.5, 8.3, 5.4 Hz), 1.63-1.54 (1H, m), 1.44 (1H, ddd, *J* = 13.5, 8.4, 5.9 Hz), 0.92 (3H, d, *J* = 6.7 Hz), 0.90 (3H, d, *J* = 6.7 Hz) ppm; $^{13}C$ NMR for major isomer δ: 144.2, 135.3, 130.0, 127.7, 109.0, 71.3, 56.7, 53.3, 44.3, 25.4, 23.2, 22.1, 21.7 ppm; $^1H$ NMR for minor isomer δ: 7.79 (2H, d, *J* = 8.4 Hz), 7.28 (2H, d, *J* = 8.4 Hz), 5.83 (1H, s), 4.01-3.96 (1H, m), 3.77 (1H, dd, *J* = 8.3, 1.8 Hz), 3.58-3.51 (1H, m), 3.34 (3H, s), 2.43 (3H, s), 1.87 (1H, ddd, *J* = 13.5, 8.3, 5.4 Hz), 1.63-1.54 (1H, m), 1.44 (1H, ddd, *J* = 13.5, 8.4, 5.9 Hz), 0.94 (3H, d, *J* = 6.7 Hz), 0.93 (3H, dd, *J* = 11.4, 6.7 Hz) ppm; $^{13}C$ NMR for major isomer δ: 143.5, 137.2, 129.2, 128.3, 108.1, 69.3, 55.6, 53.9, 42.9, 25.6, 23.9, 21.7, 21.5 ppm; HRMS (ESI): 336.1229, $[C_{15}H_{23}NO_4SNa]^+$ requires 336.1240.

***(S)*-Methyl 4-chloro-2-(4-methylbenzenesulfonamido)butanoate (75)**

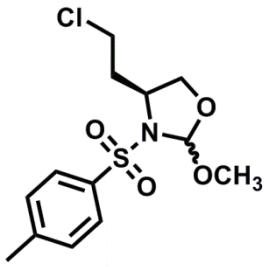


**75**

Compound **70** (7.46 g, 50.0 mmol) was dissolved in water (140 mL) and MeOH (20 mL). Iodomethane (7.47 mL, 120 mmol) was added,[16] and the mixture was stirred at room temperature for 72 h. The solvent was evaporated under reduced pressure, water (100 mL) and $NaHCO_3$ (4.20 g, 50.0 mmol) were added, and the solution was heated under reflux overnight. The solution was cooled to room temperature, and the solvent was evaporated under reduced pressure to afford **72**. Aqueous 6 M HCl (100 mL) and 30.0% (w/v) $H_2O_2$ were added. The mixture was heated until iodine had sublimed, and the reaction mixture was heated under reflux overnight. The solvent was evaporated under reduced pressure, yielding **73**, which was redissolved in $CH_2Cl_2$ (100 mL). $Et_3N$ (20.9 mL, 150 mmol) was added followed by TsCl (11.4 g, 60.0 mmol),[17] and the mixture was stirred at room temperature overnight. The mixture was then washed with aqueous 2 M HCl (2 × 50 mL) and the organic layer was dried over $Na_2SO_4$. The solvent was evaporated to give **74**, which was redissolved in MeOH (250 mL). The solution was cooled to 0 $^oC$, thionyl chloride (36.3 mL, 500 mmol) was added dropwise,[18] and the mixture was heated under reflux for 2 h. Evaporation of volatiles under reduced pressure afforded a brown oil. Column chromatography ($SiO_2$) with 1:1 pentane/ether yielded **75** (8.50 g, 58%) as a white solid. mp 69-72 $^oC$; IR (film): 1751 $cm^{-1}$; $^1H$ NMR δ: 7.74 (2H, d, $J$ = 8.4 Hz), 7.31 (2H, d, $J$ = 8.2 Hz), 5.33 (1H, d, $J$ = 8.9 Hz), 4.09 (1H, ddd, $J$ = 9.0,

8.6, 4.8 Hz) , 3.65-3.60 (2H, m), 3.55 (3H, s), 2.43 (3H, s), 2.25-2.17 (1H, m), 2.12-2.03 (1H, m) ppm; $^{13}$C NMR δ: 171.7, 144.1, 136.3, 129.9, 127.5, 53.3 53.0, 40.2, 36.2, 21.7 ppm; HRMS (ESI): 328.0379, $[C_{12}H_{16}ClNO_4SNa]^+$ requires 328.0381.

**(2*R*,4*R*)- 4-(2-Chloroethyl)-2-methoxy-3-(4-methylbenzenesulfonyl)-1,3-oxazolidine + (2*S*,4*R*)- 4-(2-Chloroethyl)-2-methoxy-3-(4-methylbenzenesulfonyl)-1,3-oxazolidine (77)**

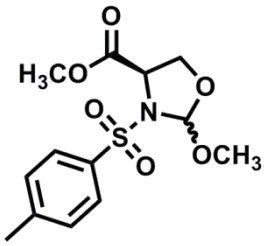



**77**

Compound **75** (8.50 g, 27.8 mmol) was dissolved in a 1:1 mixture of THF and 95% EtOH (280 mL). LiCl (1.18 g, 27.8 mmol) was added, and the mixture was cooled to 0 °C. $NaBH_4$ (1.05 g, 27.8 mmol) was added,[19] and the reaction mixture was stirred to room temperature for 2 h. The solvent was evaporated, and the residue was redissolved in $CH_2Cl_2$. After washing with an equal volume of water and extracting with $CH_2Cl_2$ (2 × 20 mL), the combined organic layers were dried with $Na_2SO_4$ and evaporated to yield **76** as a yellow oil. The residue was then dissolved in $CH(OCH_3)_3$ (50 mL). Amberlyst-15 (3.50 g) was pre-dried with heating under vacuum and added to the solution. The mixture was then stirred overnight at room temperature. The acid was removed by vacuum filtration, and the solvent was evaporated under reduced pressure. Column chromatography with 4:1 hexanes/EtOAc provided **77** (3.13 g, 35%) as a colorless oil in a 8:1 diastereomeric ratio. IR (film): 1353, 1168, 1080 cm$^{-1}$; $^1$H NMR for major isomer

δ: 7.74 (2H, d, *J* = 8.3 Hz), 7.35 (2H, d, *J* = 8.2 Hz), 5.97 (1H, s), 3.91-3.82 (2H, m), 3.81-3.69 (2H, m), 3.65-3.59 (1H, m), 3.41 (3H, s), 2.45 (3H, s), 2.42-2.34 (1H, m), 2.03-1.95 (1H, m) ppm; $^{13}$C NMR for major isomer δ: 144.6, 134.6, 130.2, 127.8, 109.5, 70.7, 55.7, 53.7, 41.6, 37.9, 21.8 ppm; $^{1}$H NMR for minor isomer δ: 7.81 (2H, d, *J* = 8.4 Hz), 7.29 (2H, d, *J* = 8.2 Hz), 5.84 (1H, s), 4.02 (1H, dd, *J* = 8.7, 6.7 Hz), 3.81-3.69 (2H, m), 3.57-3.51 (1H, m), 3.34 (3H, s), 2.46-2.42 (4H, m), 2.42-2.34 (1H, m), 2.22-2.14 (1H, m) ppm; $^{13}$C NMR for minor isomer δ: 143.8, 136.8, 129.4, 128.4, 108.2, 69.0, 54.8, 54.2, 41.3, 36.7, 21.8 ppm; HRMS (ESI): 342.0536, $[C_{13}H_{18}ClNO_4SNa]^+$ requires 342.0537.

**Methyl (2*R*,4*R*)-2-methoxy-3-(4-methylbenzenesulfonyl)-1,3-oxazolidine-4-carboxylate + Methyl (2*S*,4*R*)-2-methoxy-3-(4-methylbenzenesulfonyl)-1,3-oxazolidine-4-carboxylate (81)**

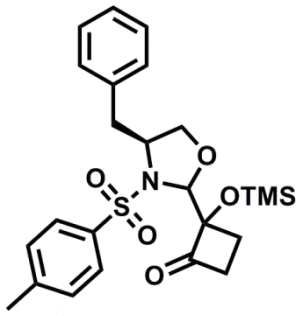



**81**

Thionyl chloride (6.24 mL, 86.0 mmol) was dissolved in MeOH (86 mL). The solution was cooled to 0 $^{o}$C, and **78** (2.52 g, 24.0 mmol) was added.[20] The mixture was warmed to room temperature with stirring overnight. The mixture was concentrated under reduced pressure, and $Et_2O$ was added until **79** precipitated from solution. The precipitate was then dissolved in $CH_2Cl_2$ (50 mL). $Et_3N$ (6.69 mL, 48.0 mmol) was added, and the solution was cooled to 0 $^{o}$C. TsCl (4.19 g, 22.0 mmol) was added slowly,[15] and the mixture was warmed to room temperature overnight with stirring. The mixture was washed with an equal volume of aqueous $NH_4Cl$ and extracted with $CH_2Cl_2$ (3 × 50 mL).

The combined organic layers were dried over $Na_2SO_4$, and the solvent was evaporated under reduced pressure to afford **80**. The product was then dissolved in $CH(OCH_3)_3$ (130 mL). Amberlyst-15 (13.0 g) was pre-dried with heating under vacuum and added to the solution. The mixture was then stirred overnight at room temperature. The acid was removed by vacuum filtration, and the solvent was evaporated under reduced pressure. Column chromatography with 2:1 hexanes/EtOAc gave **81** (3.54 g, 46%) as a white solid in a 3:1 diastereomeric ratio. IR (film): 1353, 1174, 1083 $cm^{-1}$; $^1H$ NMR for major isomer δ: 7.79 (2H, d, *J* = 8.3 Hz), 7.34 (2H, d, *J* = 8.1 Hz), 6.07 (1H, s), 4.47 (1H, dd, *J* = 8.3, 6.5 Hz), 4.26-4.22 (1H, m), 4.16 (1H, t, *J* = 8.4 Hz), 3.72 (3H, s), 3.34 (3H, s), 2.44 (3H, s) ppm; $^{13}C$ NMR for major isomer δ: 170.7, 144.6, 135.6, 129.9, 127.8, 108.8, 68.3, 58.5, 53.0, 52.8, 21.7 ppm; $^1H$ NMR for minor isomer δ: 7.80 (2H, d, *J* = 8.2 Hz), 7.30 (2H, d, *J* = 8.2 Hz), 6.01 (1H, s), 4.26-4.22 (2H, m), 4.13-4.08 (1H, m), 3.79 (3H, s), 3.34 (3H, s), 2.43 (3H, s) ppm; $^{13}C$ NMR for minor isomer δ: 170.7, 144.1, 137.1, 129.5, 128.0, 108, 68.8, 58.3, 54.0, 53.0, 21.7 ppm; HRMS (ESI): 338.0676, $[C_{13}H_{17}NO_6SNa]^+$ requires 338.0669.

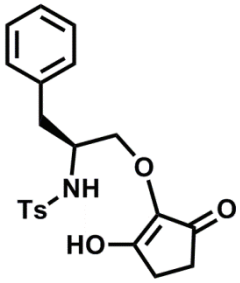
**2-((4*S*)-4-Benzyl-3-tosyloxazolidin-2-yl)-2-(trimethylsilyloxy)cyclobutanones (82)**




**82**

Compound **68** (347 mg, 1.00 mmol) and **1** (346 mg, 1.50 mmol) were dissolved in $CH_2Cl_2$ (10 mL). The reaction mixture was cooled to -78 °C with stirring. $BF_3$•$OEt_2$ (0.25 mL, 2.0 mmol) was added dropwise, and the reaction mixture was warmed to -20 °C over 3 h, after which time the completion of the Mukaiyama aldol reaction was evidenced by TLC. The reaction mixture was warmed to room temperature and then washed with an equal volume of water. The organic fraction was dried with $Na_2SO_4$, and the solvent was evaporated. Column chromatography ($SiO_2$) with 4:1 hexanes/EtOAc provided **82** (170 mg, 71%) as a colorless oil in a 2:1 diastereomeric ratio. IR (film): 1795, 1168 $cm^{-1}$; $^1H$ NMR for major isomer δ: 7.81 (2H, d, *J* = 8.2 Hz), 7.35 (2H, d, *J* = 8.1 Hz), 7.29-7.24 (2H, m), 7.22-7.18 (1H, m), 7.08 (2H, d, *J* = 7.9 Hz), 5.39 (1H, s), 3.91 (1H, dd, *J* = 8.6, 6.9 Hz), 3.84-3.77 (1H, m), 3.54 (1H, dd, *J* = 8.5, 7.1 Hz), 3.17 (1H, dd, *J* = 13.3, 4.0 Hz), 3.14-3.05 (1H, m), 2.88-2.79 (2H, m), 2.69 (1H, dd, *J* = 13.1, 11.2 Hz), 2.43 (3H, s), 2.08-2.00 (1H, m), 0.22 (9H, s) ppm; $^1H$ NMR for minor isomer δ: 7.76 (2H, d, *J* = 8.3 Hz), 7.34 (2H, d, *J* = 8.1 Hz), 7.31-7.26 (2H, m), 7.24-7.20 (2H, m), 7.13 (2H, d, *J* = 7.7 Hz), 5.28 (1H, s), 3.98 (1H, dd, *J* = 8.2, 6.2 Hz), 3.89-3.82 (1H, m), 3.49 (1H, apparent t, *J* = 7.9 Hz), 3.32 (1H, dd, *J* = 13.4, 3.8 Hz), 3.07-2.94 (2H, m), 2.86-2.82 (1H, m), 2.43 (3H, s), 2.11-2.04 (1H, m), 0.27 (9H, s) ppm; $^{13}C$ NMR for major isomer δ: 207.3, 144.8, 137.5, 133.9, 130.2, 129.0, 128.9, 128.5, 126.9, 95.6, 93.7, 71.4, 61.5, 40.8, 40.1, 24.7, 21.8, 1.8 ppm; $^{13}C$ NMR for minor isomer δ: 207.5, 144.7, 137.9, 133.8, 130.2, 129.1, 129.0, 128.2, 126.9, 95.7, 92.6, 72.5, 61.7, 40.7, 39.7, 24.4, 21.7, 1.9 ppm; HRMS (ESI): 496.1575, $[C_{24}H_{31}NO_5SSiNa]^+$ requires 496.1584.

**(*S*)-*N*-(1-(2-Hydroxy-5-oxocyclopent-1-enyloxy)-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (83)**




**83**

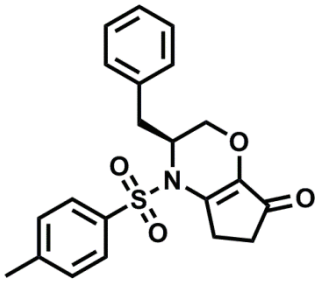
Compound **82** (970 mg, 2.0 mmol) was dissolved in $CH_2Cl_2$ (13 mL). The reaction mixture was cooled to -78 °C with stirring. $BF_3$•$OEt_2$ (3.8 mL, 30 mmol) and water (0.37 mL, 21 mmol) were added dropwise, and the reaction mixture was warmed to room temperature overnight. The mixture was then washed with an equal volume of water. The organic fraction was dried with $Na_2SO_4$, and the solvent was evaporated to afford 83 (750 mg, 92%) as a brown oil, which was used without further purification. IR (film): 3295, 1707, 1610 $cm^{-1}$; $^1H$ NMR δ: 7.58 (2H, d, *J* = 8.3 Hz), 7.21-7.18 (5H, m), 7.04-7.01 (2H, m), 5.65 (1H, d, *J* = 8.1 Hz), 4.02 (1H, dd, *J* = 10.5, 3.2 Hz), 3.93 (1H, dd, *J* = 10.6, 6.4 Hz), 3.71-3.63 (1H, m), 2.80 (1H, dd, *J* = 13.8, 7.1 Hz), 2.69 (1H, dd, *J* = 13.9, 7.1 Hz), 2.43 (4H, s), 2.40 (3H, s) ppm; $^{13}C$ NMR (slow exchange) δ: 143.7, 137.1, 136.8, 134.8, 129.8, 129.5, 128.8, 127.2, 126.9, 72.6, 55.6, 38.1, 21.7 ppm; HRMS (ESI): 402.1372, $[C_{21}H_{24}NO_5SNa]^+$ requires 402.1370.

***General procedure 1:*** **Geminal acylation of 68, 69, 77, and 81 with 1 (aqueous procedure)**

The 2-methoxyoxazolidine (1 equiv.) and **1** (1.5 equiv.) were dissolved in $CH_2Cl_2$ (10 mL/mmol). The reaction mixture was cooled to -78 °C with stirring. $BF_3$•$OEt_2$ (2 equiv)

was added dropwise, and the reaction mixture was warmed to -20 °C over 3 h, after which time the completion of the Mukaiyama aldol reaction was evidenced by TLC. The reaction mixture was re-cooled to -78 °C, and $BF_3$•$OEt_2$ (15 equiv) and water (10 equiv) were added dropwise simultaneously. The reaction mixture was warmed to room temperature overnight and then washed with an equal volume of water. The organic fraction was dried with $Na_2SO_4$, and the solvent was evaporated. The residual oil was dissolved in toluene (50 mL/mmol) and heated under reflux over 24 h in the presence of TsOH (2 equiv) using a Dean-Stark apparatus. The reaction mixture was cooled and washed with an equal volume of saturated aqueous $NaHCO_3$. The organic fraction was dried with $Na_2SO_4$, and the solvent was evaporated. Column chromatography ($SiO_2$) afforded the heterocycle.

**(3*S*)-3-Benzyl-4-(4-methylbenzenesulfonyl)-3,4,6,7-tetrahydro-2*H*-cyclopenta[1,4-*b*] oxazin-7-one (84)**

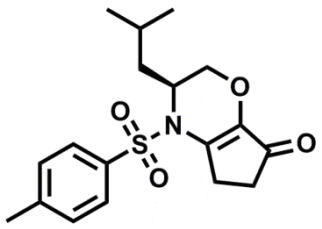


**84**

Following *General procedure 1*, **68** (347 mg, 1.00 mmol) and **1** (346 mg, 1.50 mmol) gave, after column chromatography with 2:1 hexanes/EtOAc, **84** (260 mg, 68%) as a colorless solid. mp 142-143 $^{o}$C; IR (film): 1711, 1632 cm$^{-1}$; $^{1}$H NMR δ: 7.65 (2H, d, *J* = 8.3 Hz), 7.36-7.30 (4H, m), 7.28-7.24 (3H, m), 4.25-4.19 (1H, m), 3.98 (1H, dd, *J* = 11.5, 1.3 Hz), 3.10-2.94 (4H, m), 2.79 (1H, dd, *J* = 13.0, 10.9 Hz), 2.49-2.44 (2H, m), 2.43 (3

H, s) ppm; $^{13}$C NMR δ: 195.6, 145.3, 143.0, 137.9, 136.4, 135.1, 130.5, 129.8, 128.9, 127.3, 127.1, 64.2, 57.0, 37.2, 31.7, 24.8, 21.7 ppm; HRMS (ESI): 406.1076, $[C_{21}H_{21}NO_4SNa]^+$ requires 406.1083.

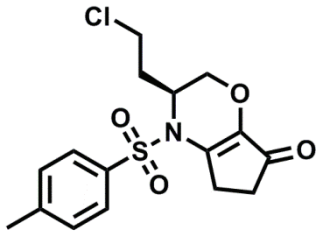
**(3*S*)-4-(4-Methylbenzenesulfonyl)-3-(2-methylpropyl)-3,4,6,7-tetrahydro-2*H*-cyclopenta[1,4-*b*]oxazin-7-one (85)**



**85**

Following *General procedure 1*, **69** (313 mg, 1.00 mmol) and **1** (346 mg, 1.50 mmol) gave, after column chromatography with 2:1 hexanes/EtOAc, **85** (203 mg, 58%) as a colorless solid. mp 180-183 $^{o}$C; IR (film): 1707, 1629 cm$^{-1}$; $^{1}$H NMR δ: 7.64 (2H, d, *J* = 8.4 Hz), 7.36 (2H, dd, *J* = 8.6, 0.7 Hz), 4.10-4.16 (1H, m), 4.03 (1H, dd, *J* = 11.1, 1.4 Hz), 3.08 (1H, ddd, *J* = 18.0, 5.9, 3.2 Hz), 2.98 (1H, dd, *J* = 11.1, 2.3 Hz), 2.93 (1H, ddd, *J* = 18.0, 5.8, 3.1 Hz), 2.47-2.43 (5H, m), 1.80-1.71 (1H, m), 1.45-1.31 (2H, m), 0.99 (3H, d, *J* = 6.5 Hz), 0.96 (3H, d, *J* = 6.7 Hz) ppm; $^{13}$C NMR δ: 196.0, 145.3, 142.6, 138.3, 135.0, 130.5, 127.1, 66.1, 54.0, 39.4, 31.8, 25.2, 24.5, 22.8, 22.4, 21.8; HRMS (ESI): 372.1229, $[C_{18}H_{23}NO_4SNa]^+$ requires 372.1240.

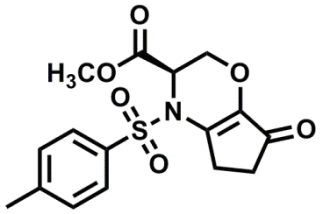
**(3*S*)-3-(2-Chloroethyl)-4-(4-methylbenzenesulfonyl)-3,4,6,7-tetrahydro-2*H*-cyclopenta[1,4-*b*]oxazin-7-one (86)**



**86**

Following *General procedure 1*, **77** (320 mg, 1.00 mmol) and **1** (346 mg, 1.50 mmol) gave, after column chromatography with 1:1 hexanes/EtOAc, **86** (200 mg, 56%) as a yellow oil. IR (film): 1711, 1632 $cm^{-1}$; $^1H$ NMR δ: 7.66 (2H, d, *J* = 8.4 Hz), 7.38 (2H, dd, *J* = 8.6, 0.7 Hz), 4.37-4.32 (1H, m), 4.07 (1H, dd, *J* = 11.4, 1.5 Hz), 3.75 (1H, ddd, *J* = 11.4, 7.4, 5.8 Hz), 3.65 (1H, ddd, *J* = 11.4, 6.8, 5.8 Hz), 3.12 (1H, dt, *J* = 18.1, 4.7 Hz), 3.00-2.92 (2H, m), 2.48-2.45 (5H, m), 2.09-2.00 (1H, m), 1.92-1.84 (1H, m) ppm; $^{13}C$ NMR δ: 195.9, 145.6, 142.2, 138.4, 134.4, 130.7, 127.2, 66.1, 52.9, 40.9, 33.5, 31.8, 25.2, 21.8 ppm; HRMS (ESI): 378.0528, $[C_{16}H_{18}ClNO_4SNa]^+$ requires 378.0537.

**Methyl (3*R*)-4-(4-methylbenzenesulfonyl)-3,4,6,7-tetrahydro-2*H*-cyclopenta[1,4-*b*]oxazin-7-one-3-carboxylate (87)**



**87**

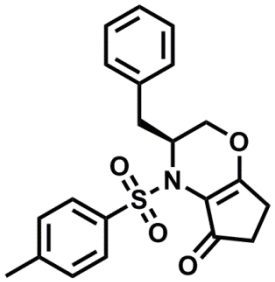
Following *General procedure 1*, **81** (315 mg, 1.00 mmol) and **1** (346 mg, 1.50 mmol) gave, after column chromatography with 1:1 hexanes/EtOAc, **87** (112 mg, 32%) as a

yellow oil. IR (film): 1757, 1707 1635 $cm^{-1}$; $^{1}H$ NMR δ: 7.74 (2H, d, *J* = 8.4 Hz), 7.38 (2H, dd, *J* = 8.5, 0.6 Hz), 5.04 (1H, dd, *J* = 2.9, 1.8 Hz), 4.72 (1H, dd, *J* = 11.2, 1.7 Hz), 3.74 (3H, s), 3.59 (1H, dd, *J* = 11.2, 2.8 Hz), 3.05 (1H, ddd, *J* = 17.8, 5.6, 3.7 Hz), 2.91 (1H, ddd, *J* = 17.8, 5.4, 3.7 Hz), 2.47 (3H, s), 2.42-2.39 (2H, m) ppm; $^{13}C$ NMR δ: 195.0, 167.0, 145.7, 143.9, 137.4, 135.4, 130.5, 127.5, 66.1, 56.9, 53.5, 31.4, 23.8, 21.8 ppm; HRMS (ESI): 374.0681, $[C_{16}H_{17}NO_6SNa]^+$ requires 374.0669.

***General procedure 2:*** **Geminal acylation of 68, 69, 77, and 81 with 1 (anhydrous procedure)**

The 2-methoxyoxazolidine (1 equiv) and **1** (1.5 equiv) were dissolved in $CH_2Cl_2$ (10 mL/mmol). The reaction mixture was cooled to -78 °C with stirring. Distilled $BF_3$•$OEt_2$ (15 equiv) was added dropwise, and the reaction mixture was warmed to room temperature overnight, after which the completion of geminal acylation was evidenced by TLC. The reaction mixture was re-cooled to -78 °C, and water (10 equiv) was added dropwise. The reaction mixture was warmed to room temperature overnight and then washed with an equal volume of water. The organic fraction was dried with $Na_2SO_4$, and the solvent was evaporated. Column chromatography ($SiO_2$) afforded the heterocycle.

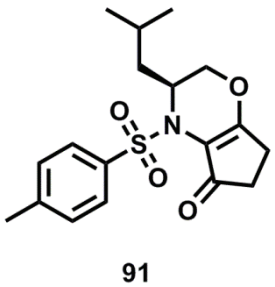
**(*S*)-3-Benzyl-4-(4-methylbenzenesulfonyl)-3,4,6,7-tetrahydro-2*H*-cyclopenta[*b*][1,4] oxazin-5-one (90)**



**90**

Following *General procedure 2*, **68** (347 mg, 1.00 mmol) and **1** (346 mg, 1.50 mmol) gave, after column chromatography with 4:1 hexanes/EtOAc, **90** (240 mg, 63%) as a colorless solid. mp 173-175 $^{o}$C; IR (film): 1711, 1642 cm$^{-1}$; $^{1}$H NMR δ: 7.69 (2H, d, *J* = 8.4 Hz), 7.14-7.06 (5H, m), 6.90 (2H, dd, *J* = 7.8, 1.7 Hz), 4.36 (1H, dd, *J* = 11.3, 1.1 Hz), 4.23 (1H, tdd, *J* = 7.9, 2.9, 1.1 Hz), 4.15 (1H, dd, *J* = 11.0, 2.8 Hz), 2.75-2.57 (3H, m), 2.51 (2H, d, *J* = 7.8 Hz), 2.45 (1H, ddd, *J* = 17.0, 6.9, 2.6 Hz), 2.38 (3H, s) ppm; $^{13}$C NMR δ: 196.8, 172.4, 143.7, 136.6, 136.4, 129.4, 129.3, 128.6, 128.1, 126.7, 115.0, 70.1, 54.2, 36.2, 32.0, 24.4, 21.7 ppm; HRMS (ESI): 406.1075, $[C_{21}H_{21}NO_4SNa]^+$ requires 406.1083.

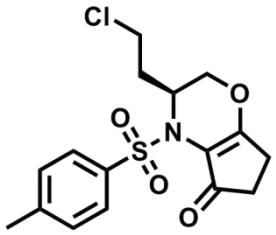
**(*S*)-4-(4-Methylbenzenesulfonyl)-3-(2-methylpropyl)-3,4,6,7-tetrahydro-2*H*-cyclopenta[*b*][1,4]oxazin-5-one (91)**



**91**

Following *General procedure 2*, **69** (313 mg, 1.00 mmol) and **1** (346 mg, 1.50 mmol) gave, after column chromatography with 2:1 hexanes/EtOAc, **91** (203 mg, 58%) as a yellow oil. IR (film): 1717, 1632 $cm^{-1}$; $^{1}H$ NMR δ: 8.01 (2H, d, *J* = 8.5 Hz), 7.32 (2H, dd, *J* = 8.5, 0.6 Hz), 4.23 (1H, dd, *J* = 11.1, 1.1 Hz), 4.09 (1H, dd, *J* = 11.1, 2.9 Hz), 4.05-4.00 (1H, m), 2.70-2.55 (3H, m), 2.46-2.39 (4H, m), 1.39-1.29 (1H, m), 1.22-1.14 (1H, m), 1.01-0.93 (1H, m), 0.73 (3H, d, *J* = 6.6 Hz), 0.61 (3H, d, *J* = 6.6 Hz) ppm; $^{13}C$ NMR δ: 197.1, 172.9, 144.2, 136.4, 129.5, 128.5, 114.5, 70.1, 50.5, 38.5, 31.9, 24.5, 24.3, 23.1, 21.7, 21.4 ppm; HRMS (ESI): 372.1238, $[C_{18}H_{23}NO_4SNa]^+$ requires 372.1240.

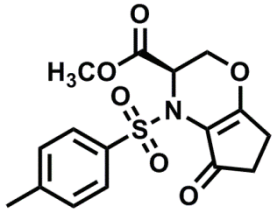
**(*S*)-3-(2-Chloroethyl)-4-(4-methylbenzenesulfonyl)-3,4,6,7-tetrahydro-2*H*-cyclopenta[*b*][1,4]oxazin-5-one (92)**




**92**

Following *General procedure 2*, **77** (320 mg, 1.00 mmol) and **1** (346 mg, 1.50 mmol) gave, after column chromatography with 1:1 hexanes/EtOAc, **92** (261 mg, 73%) as a white solid. mp 140-143 $^{o}C$; IR (film): 1714, 1632 $cm^{-1}$; $^{1}H$ NMR δ: 8.08 (2H, d, *J* = 8.4 Hz), 7.34 (2H, dd, *J* = 8.7, 0.7 Hz), 4.36-4.30 (2H, m), 4.24 (1H, dd, *J* = 11.4, 3.0 Hz), 3.32 (1H, dt, *J* = 11.2, 4.9 Hz), 3.04 (1H, ddd, *J* = 11.2, 9.9, 4.6 Hz), 2.73-2.67 (1H, m), 2.65-2.57 (2H, m), 2.46-2.38 (4H, m), 1.73-1.59 (2H, m) ppm; $^{13}C$ NMR δ: 197.2, 172.5, 144.6, 136.2, 129.7, 128.6, 114.6, 71.0, 49.5, 41.1, 32.5, 31.9, 24.4, 21.8 ppm; HRMS (ESI): 378.0520, $[C_{16}H_{18}ClNO_4SNa]^+$ requires 378.0537.

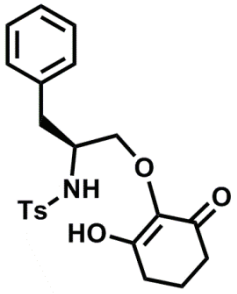
**Methyl (*R*)-4-(4-methylbenzenesulfonyl)-3,4,6,7-tetrahydro-2*H*-cyclopenta[*b*][1,4]oxazin-5-one-3-carboxylate (93)**



**93**

Compound **81** (315 mg, 1.00 mmol) and **1** (346 mg, 1.50 mmol) were dissolved in $CH_2Cl_2$ (10 mL). The reaction mixture was cooled to -78 °C with stirring. Distilled $BF_3$•$OEt_2$ (1.88 mL, 15.0 mmol) was added dropwise, and the reaction mixture was warmed to room temperature overnight, after which the completion of geminal acylation was evidenced by TLC. The reaction mixture was then washed with an equal volume of water. The organic fraction was dried with $Na_2SO_4$, and the solvent was evaporated. The resultant oil was dissolved in toluene (50 mL) and heated under reflux for 24 h in the presence of TsOH (380 mg, 2.00 mmol equiv) using a Dean-Stark apparatus. The reaction mixture was cooled and washed with an equal volume of saturated aqueous $NaHCO_3$. The organic fraction was dried with $Na_2SO_4$ and the solvent was evaporated. Column chromatography ($SiO_2$) with 1:1 hexanes/ EtOAc gave **93** (150 mg, 43%) as a yellow oil. IR (film): 1758, 1717, 1638 $cm^{-1}$; $^1H$ NMR δ: 8.01 (2H, d, *J* = 8.5 Hz), 7.33 (2H, dd, *J* = 8.7, 0.7 Hz), 5.01 (1H, dd, *J* = 3.3, 1.4 Hz), 4.97 (1H, dd, *J* = 11.2, 1.4 Hz), 4.20 (1H, dd, *J* = 11.3, 3.3 Hz), 3.66 (3H, s), 2.67-2.57 (2H, m), 2.52 (1H, ddd, *J* = 17.7, 7.1, 3.3 Hz), 2.43 (3H, s), 2.37 (1H, ddd, *J* = 17.9, 6.8, 2.7 Hz) ppm; $^{13}C$ NMR δ: 195.6, 171.5, 167.4, 144.3, 137.0, 129.5, 128.3, 116.1, 68.6, 54.4, 53.3, 31.8, 24.3, 21.8 ppm; HRMS (ESI): 374.0660, $[C_{16}H_{17}NO_6SNa]^+$ requires 374.0669.

**(*S*)-*N*-(1-(2-Hydroxy-6-oxocyclohex-1-enyloxy)-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (95)**



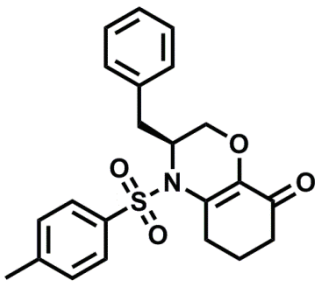

**95**

Compound **68** (347 mg, 1.00 mmol) and **28** (367 mg, 1.50 mmol) were dissolved in $CH_2Cl_2$ (10 mL). The reaction mixture was cooled to -78 °C with stirring. $BF_3$•$OEt_2$ (0.25 mL, 2.0 mmol) was added dropwise, and the reaction mixture was warmed to -20 °C over 3 h, after which time the completion of the Mukaiyama aldol reaction was evidenced by TLC. The reaction mixture was re-cooled to -78 °C, and $BF_3$•$OEt_2$ (1.88 mL, 15.0 mmol) and water (0.18 mL, 10 mmol) were added dropwise simultaneously. The reaction mixture was warmed to room temperature overnight and then extracted with 1 M aqueous NaOH (3 x 50 mL). The aqueous fraction was then acidified with 12 M aqueous HCl. The resulting mixture was then extracted with $CH_2Cl_2$ (3 x 50 mL). The organic fraction was dried with $Na_2SO_4$ and the solvent was evaporated to afford **95** (359 mg, 86 %) as a yellow oil. IR (film): 1737, 1601 $cm^{-1}$; $^1H$ NMR δ: 7.61 (2H, d, $J$ = 8.3 Hz), 7.24-7.17 (5H, m), 7.05-7.00 (2H, m), 5.72 (1H, d, $J$ = 6.0 Hz), 3.96 (1H, dd, $J$ = 9.9, 2.7 Hz), 3.68-3.58 (2H, m), 2.80 (2H, d, $J$ = 6.8 Hz), 2.46 (4H, t, $J$ = 6.3 Hz), 2.41 (3H, s), 1.94 (2H, pentet, $J$ = 6.5 Hz) ppm; $^{13}C$ NMR (slow exchange) δ: 143.5, 136.8, 136.8, 134.1, 129.7, 129.4, 128.9, 127.4, 127.0, 74.1, 55.6, 38.5, 21.7, 20.4 ppm; HRMS (ESI): 438.1329, $[C_{22}H_{25}NO_5SNa]^+$ requires 438.1346.

***General procedure 3:*** **Geminal acylation of 68, 69, 77, and 81 with 28 (aqueous procedure)**

The 2-methoxyoxazolidine (1 equiv) and **28** (1.5 equiv) were dissolved in $CH_2Cl_2$ (10 mL/mmol). The reaction mixture was cooled to -78 °C with stirring. $BF_3$•$OEt_2$ (2 equiv) was added dropwise. The reaction mixture was warmed to -20 °C over 3 h, after which time the completion of the Mukaiyama aldol reaction was evidenced by TLC. The reaction mixture was re-cooled to -78 °C, and $BF_3$•$OEt_2$ (15 equiv) and water (10 equiv) were added dropwise simultaneously. The reaction mixture was warmed to room temperature overnight and then washed with an equal volume of water. The organic fraction was dried with $Na_2SO_4$ and the solvent was evaporated. The residual oil was dissolved in toluene (50 mL/mmol) and heated under reflux for 24 h in the presence of TsOH (2 equiv) using a Dean-Stark apparatus. The reaction mixture was cooled and washed with an equal volume of saturated aqueous $NaHCO_3$. The organic fraction was dried with $Na_2SO_4$ and the solvent was evaporated. Column chromatography ($SiO_2$) afforded the heterocycle.

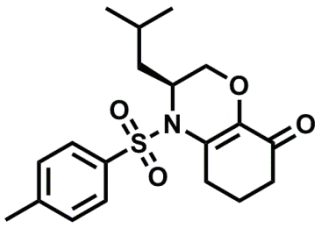
**(3*S*)-3-Benzyl-4-(4-methylbenzenesulfonyl)-3,4,6,7-tetrahydro-2*H*,5*H*-benzo[*b*][1,4] oxazin-8-one (96)**




**96**

Following *General procedure 3*, **68** (347 mg, 1.00 mmol) and **28** (367 mg, 1.50 mmol) gave, after column chromatography with 2:1 hexanes/EtOAc, **96** (165 mg, 42%) as a yellow oil. IR (film): 1683, 1610 $cm^{-1}$; $^1H$ NMR δ: 7.53 (2H, d, *J* = 8.4 Hz), 7.32-7.19 (7H, m), 4.38-4.32 (1H, m), 3.99 (1H, dd, *J* = 11.1, 1.4 Hz), 3.22-3.13 (1H, m), 3.05 (1H, dd, *J* = 11.1, 2.2 Hz), 2.84 (1H, dd, *J* = 13.3, 6.1 Hz), 2.78-2.71 (2H, m), 2.55-2.50 (2H, m), 2.42 (3H, s), 2.08-1.96 (2H, m) ppm; $^{13}C$ NMR δ: 192.1, 144.9, 136.7, 136.2, 135.3, 131.2, 130.3, 129.7, 128.8, 127.1, 127.1, 63.7, 55.5, 37.5, 36.6, 28.8, 22.2, 21.7 ppm; HRMS (ESI): 420.1229, $[C_{22}H_{23}NO_4SNa]^+$ requires 420.1240.

**(3*S*)-4-(4-Methylbenzenesulfonyl)-3-(2-methylpropyl)-3,4,6,7-tetrahydro-2*H*,5*H*-benzo[*b*][1,4]oxazin-8-one (97)**

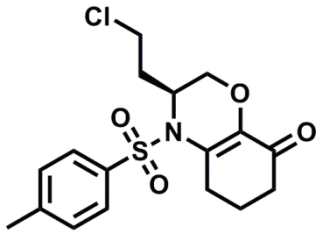


**97**

Following *General procedure 3*, **69** (313 mg, 1.00 mmol) and **28** (367 mg, 1.50 mmol) gave, after column chromatography with 2:1 hexanes/EtOAc, **97** (110 mg, 30%) as a yellow oil. IR (film): 1682, 1607 $cm^{-1}$; $^1H$ NMR δ: 7.63 (2H, d, *J* = 8.5 Hz), 7.35 (2H, dd, *J* = 8.5, 0.7 Hz), 4.20-4.15 (2H, m), 3.94 (1H, dd, *J* = 11.1, 1.5 Hz), 3.22 (1H, ddd, *J* = 17.6, 7.4, 5.9 Hz), 3.00 (1H, dd, *J* = 11.1, 2.7 Hz), 2.74 (1H, ddd, *J* = 17.7, 6.1, 5.6 Hz), 2.51 (2H, m), 2.45 (3H, s), 2.04-1.96 (1H, m), 1.77-1.67 (1H, m), 1.36 (1H, ddd, *J* = 14.1, 7.8, 6.5 Hz), 1.24 (1H, ddd, *J* = 14.1, 7.3, 6.6 Hz), 0.97 (3H, d, *J* = 6.6 Hz), 0.93 (3H, d, *J* = 6.7 Hz) ppm; $^{13}C$ NMR δ: 192.4, 145.0, 136.6, 134.9, 130.8, 130.4, 127.3,

65.3, 52.2, 39.0, 37.6, 29.3, 24.7, 22.8, 22.5, 22.4, 21.7 ppm; HRMS (ESI): 386.1401, $[C_{19}H_{25}NO_4SNa]^+$ requires 386.1397.

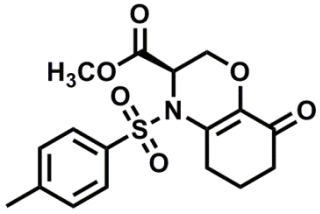
**(3*S*)-3-(2-Chloroethyl)-4-(4-methylbenzenesulfonyl)-3,4,6,7-tetrahydro-2*H*,5*H*-benzo[*b*][1,4]oxazin-8-one (98)**




**98**

Following *General procedure 3*, **77** (320 mg, 1.00 mmol) and **28** (367 mg, 1.50 mmol) gave, after column chromatography with 1:1 hexanes/EtOAc, **98** (179 mg, 48%) as a yellow oil. IR (film): 1682, 1601 $cm^{-1}$; $^1H$ NMR δ: 7.65 (2H, d, *J* = 8.4 Hz), 7.37 (2H, dd, *J* = 8.5, 0.7 Hz), 4.41-4.36 (1H, m), 4.00 (1H, dd, *J* = 11.4, 1.5 Hz), 3.69-3.58 (2H, m), 3.26 (1H, dt, *J* = 17.6, 6.7 Hz), 3.01 (1H, dd, *J* = 11.3, 2.5 Hz), 2.75 (1H, dt, *J* = 17.8, 5.6 Hz), 2.51 (2H, dd, *J* = 7.6, 5.9 Hz), 2.46 (3H, s), 2.05-1.91 (3H, m), 1.86-1.78 (1H, m) ppm; $^{13}C$ NMR δ: 192.2, 145.3, 136.4, 134.5, 130.6, 130.5, 127.4, 65.0, 51.4, 41.0, 37.5, 33.0, 29.1, 22.3, 21.8 ppm; HRMS (ESI): 392.0686, $[C_{17}H_{20}ClNO_4SNa]^+$ requires 392.0694.

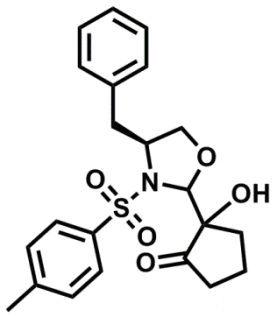
**Methyl (3*R*)-4-(4-methylbenzenesulfonyl)-3,4,6,7-tetrahydro-2*H*,5*H*-benzo[*b*][1,4]oxazin-8-one-3-carboxylate (99)**



**99**

Following *General procedure 3*, **81** (315 mg, 1.00 mmol) and **28** (367 mg, 1.50 mmol) gave, after column chromatography with 1:1 hexanes/EtOAc, **99** (183 mg, 50%) as a yellow oil. IR (film): 1760, 1675, 1610 $cm^{-1}$; $^{1}H$ NMR δ: 7.76 (2H, d, *J* = 8.4 Hz), 7.38 (2H, d, *J* = 8.2 Hz), 5.21 (1H, dd, *J* = 2.9, 1.8 Hz), 4.73 (1H, dd, *J* = 11.1, 1.8 Hz), 3.77 (3H, s), 3.61 (1H, dd, *J* = 11.2, 3.0 Hz), 3.10 (1H, ddd, *J* = 17.3, 7.0, 4.9 Hz), 2.61 (1H, ddd, *J* = 17.2, 8.3, 4.7 Hz), 2.49-2.40 (5H, m), 2.01-1.86 (2H, m) ppm; $^{13}C$ NMR δ: 191.7, 167.4, 145.3, 136.4, 135.6, 132.7, 130.4, 127.3, 65.4, 56.5, 53.3, 37.1, 27.5, 21. 8, 21.5 ppm; HRMS (ESI): 388.0823, $[C_{17}H_{19}NO_6SNa]^+$ requires 388.0825.

**2-((4*S*)-4-Benzyl-3-tosyloxazolidin-2-yl)-2-hydroxycyclopentanone (101)**



**101**

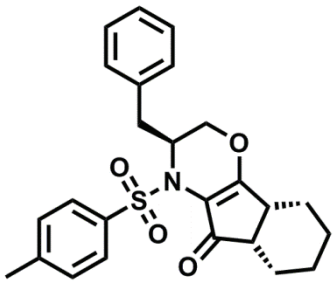
Compound **68** (347 mg, 1.00 mmol) and **28** (367 mg, 1.50 mmol) were dissolved in $CH_2Cl_2$ (10 mL). The reaction mixture was cooled to -78 °C with stirring. $BF_3$•$OEt_2$ (0.25

mL, 2.0 mmol) was added dropwise, and the reaction mixture was warmed to -20 °C over 3 h, after which time the completion of the Mukaiyama aldol reaction was evidenced by TLC. The reaction mixture was warmed to room temperature and then washed with an equal volume of water. The organic fraction was dried with $Na_2SO_4$, and the solvent was evaporated. The residue was then dissolved in THF (50 mL). A 1.0 M solution of TBAF (2.0 mL, 2.0 mmol) was then added and the mixture was stirred at room temperature until complete desilylation was evidenced by TLC. Column chromatography ($SiO_2$) with 2:1 pentane/$Et_2O$ provided **101** (294 mg, 71%) as a colorless solid in a 5:1 diastereomeric ratio. mp 45-48 $^oC$; IR (film): 1750 $cm^{-1}$; $^1H$ NMR for major isomer δ: 7.79 (2H, d, *J* = 8.3 Hz), 7.36 (2H, d, *J* = 8.3 Hz), 7.32-7.20 (3H, m), 7.15 (2H, d, *J* = 8.3 Hz), 5.14 (1H, s), 3.89-3.83 (3H, m), 3.30-3.25 (1H, m), 3.12 (1H, dd, *J* = 13.0, 3.1 Hz), 2.83 (1H, dd, *J* = 13.4, 10.3 Hz), 2.57-2.38 (6H, m), 2.12-1.94 (3H, m) ppm; $^1H$ NMR for minor isomer δ: 7.75 (2H, d, *J* = 8.2 Hz), 7.33 (2H, d, *J* = 8.3 Hz), 7.32-7.20 (3H, m), 7.17-7.12 (2H, m), 5.17 (1H, s), 3.96-3.90 (1H, m), 3.89-3.83 (1H, m), 3.81 (1H, dd, *J* = 8.6, 3.5 Hz), 3.19 (1H, dd, *J* = 13.5, 4.3 Hz), 2.91 (1H, dd, *J* = 13.5, 10.7 Hz), 2.72-2.66 (1H, m), 2.57-2.38 (6H, m), 2.12-1.94 (3H, m) ppm; $^{13}C$ NMR for major isomer δ: 215.7, 145.1, 137.3, 133.4, 130.3, 129.4, 129.0, 128.4, 127.1, 92.8, 80.0, 70.3, 61.8, 40.9, 36.0, 32.7, 21.8, 17.3 ppm; $^{13}C$ NMR for minor isomer δ: 216.8, 144.9, 137.7, 133.8, 130.3, 129.4, 128.9, 128.3, 126.9, 92.1, 80.4, 70.9, 61.9, 40.6, 35.8, 33.4, 21.8, 17.0 ppm; HRMS (ESI): 438.1357, $[C_{22}H_{25}NO_5SNa]^+$ requires 438.1346.

***General procedure 4:*** **Geminal acylation of 68, 69, 77, and 81 with 103 (anhydrous procedure)**

The 2-methoxyoxazolidine (1 equiv) and **103** (1.5 equiv) were dissolved in $CH_2Cl_2$ (10 mL/mmol). The reaction mixture was cooled to -78 °C with stirring. Distilled $BF_3$•$OEt_2$ (15 equiv) was added dropwise, and the reaction mixture was warmed to room temperature overnight, after which the completion of geminal acylation was evidenced by TLC. The reaction mixture was re-cooled to -78 °C, and water (10 equiv) was added dropwise. The reaction mixture was warmed to room temperature overnight and then washed with an equal volume of water. The organic fraction was dried with $Na_2SO_4$, and the solvent was evaporated. Column chromatography ($SiO_2$) afforded the heterocycle.

**(3*S*,5a*S*,9a*R*)-3-Benzyl-4-(4-methylbenzenesulfonate)-3,4,5a,6,7,8,9,9a-octahydroindeno[1,2-*b*][1,4]oxazin-5(2*H*)-one (111a)**

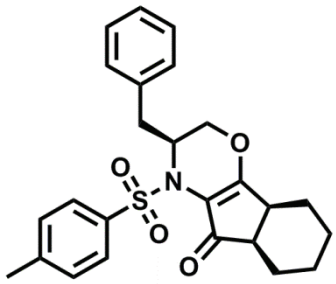


**111a**

Following *General procedure 4*, **68** (347 mg, 1.00 mmol) and **103** (427 mg, 1.50 mmol) gave, after column chromatography with 4:1 hexanes/EtOAc, **111a** (169 mg, 39%) as a yellow solid. mp 141-144 $^oC$; IR (film): 1715, 1634 $cm^{-1}$; $^1H$ NMR δ: 7.71 (2H, d, $J$ = 8.4 Hz), 7.15-7.08 (5H, m), 6.92 (2H, d, $J$ = 7.3 Hz), 4.35 (1H, d, $J$ = 11.2 Hz), 4.22 (1H, dd, $J$ = 8.7, 7.8 Hz), 4.06 (1H, dd, $J$ = 11.2, 2.8 Hz), 3.01 (1H, dd, $J$ = 12.9, 6.2 Hz), 2.60-2.47 (3H, m), 2.39 (3H, s), 2.00-1.91 (1H, m), 1.82-1.63 (4H, m), 1.58-1.50 (1H, m),

1.49-1.39 (2H, m) ppm; $^{13}$C NMR δ: 220.2, 173.7, 143.7, 136.7, 136.4, 129.4, 129.3, 128.6, 128.1, 126.7, 113.8, 70.0, 54.3, 43.6, 36.2, 36.1, 24.3, 23.2, 21.7, 20.5, 19.9 ppm; HRMS (ESI): 460.1561, $[C_{25}H_{27}NO_4SNa]^+$ requires 460.1553.

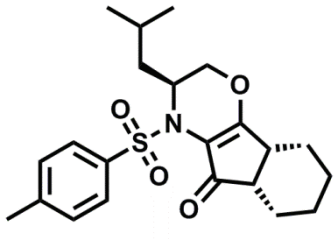
**(3*S*,5a*R*,9a*S*)-3-Benzyl-4-(4-methylbenzenesulfonate)-3,4,5a,6,7,8,9,9a-octahydroindeno[1,2-*b*][1,4]oxazin-5(2*H*)-one (111b)**



**111b**

Following *General procedure 4*, **68** (347 mg, 1.00 mmol) and **103** (427 mg, 1.50 mmol) gave, after column chromatography with 4:1 hexanes/EtOAc, **111b** (72 mg, 16%) as a yellow solid. mp 126-128 $^{o}$C; IR (film): 1715, 1634 cm$^{-1}$; $^1$H NMR δ: 7.67 (2H, d, *J* = 8.3 Hz), 7.13-7.07 (5H, m), 6.88 (2H, d, *J* = 7.5 Hz), 4.35 (1H, d, *J* = 10.9 Hz), 4.22 (1H, dd, *J* = 8.7, 7.8 Hz), 4.16 (1H, dd, *J* = 11.1, 2.8 Hz), 3.02-2.96 (1H, dd, *J* = 15.1, 6.5 Hz), 2.78-2.72 (1H, m), 2.50 (2H, d, *J* = 7.8 Hz), 2.38 (3H, s), 2.26-2.18 (2H, m), 1.68-1.56 (2H, m), 1.42-1.21 (4H, m) ppm; $^{13}$C NMR δ: 199.3, 174.7, 143.7, 136.6, 136.4, 129.4, 129.3, 128.7, 128.0, 126.7, 113.3, 70.0, 54.5, 42.5, 36.6, 36.1, 27.7, 21.7, 21.3, 21.3, 21.1 ppm; HRMS (ESI): 460.1540, $[C_{25}H_{27}NO_4SNa]^+$ requires 460.1553.

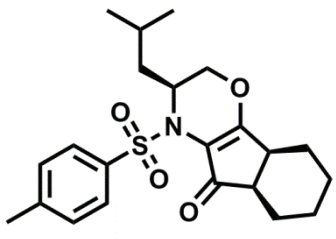
**(3*S*,5a*S*,9a*R*)-4-(4-methylbenzenesulfonate)-3-(2-methylpropyl)-3,4,5a,6,7,8,9,9a-octahydroindeno[1,2-*b*][1,4]oxazin-5(2*H*)-one (112a)**



**112a**

Following *General procedure 4*, **69** (313 mg, 1.00 mmol) and **103** (427 mg, 1.50 mmol) gave, after column chromatography with 10:1 hexanes/EtOAc, **112a** (165 mg, 28%) as a yellow solid. mp 138-141 $^{o}$C; IR (film): 1711, 1630 cm$^{-1}$; $^{1}$H NMR δ: 8.00 (2H, d, *J* = 8.1 Hz), 7.31 (2H, d, *J* = 8.2 Hz), 4.23 (1H, d, *J* = 10.4 Hz), 4.06-3.99 (2H, m), 2.94 (1H, dd, *J* = 13.1, 6.1 Hz), 2.53 (1H, dd, *J* = 15.9, 7.0 Hz), 2.43 (3H, s), 1.99-1.91 (1H, m), 1.80-1.60 (4H, m), 1.57-1.48 (1H, m), 1.47-1.32 (3H, m), 1.23-1.15 (1H, m), 1.00-0.92 (1H, m), 0.74 (3H, d, *J* = 6.6 Hz), 0.64 (3H, d, *J* = 6.6 Hz) ppm; $^{13}$C NMR δ: 200.5, 174.0, 144.3, 136.5, 129.6, 128.6, 113.4, 71.1, 50.7, 43.5, 38.7, 35.9, 24.5, 24.4, 23.2, 23.1, 21.8, 21.5, 20.6, 19.9 ppm; HRMS (ESI): 426.1698, $[C_{22}H_{29}NO_4SNa]^+$ requires 426.1710.

**(3*S*,5a*R*,9a*S*)-4-(4-Methylbenzenesulfonate)-3-(2-methylpropyl)-3,4,5a,6,7,8,9,9a-octahydroindeno[1,2-*b*][1,4]oxazin-5(2*H*)-one (112b)**

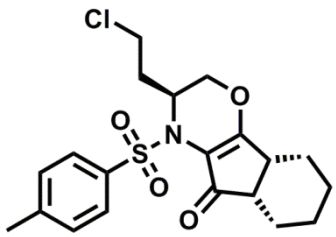


**112b**

Following *General procedure 4*, **69** (313 mg, 1.00 mmol) and **103** (427 mg, 1.50 mmol) gave, after column chromatography with 10:1 hexanes/EtOAc, **112b** (48 mg, 12%) as a

yellow oil. IR (film): 1711, 1629 $cm^{-1}$; $^1H$ NMR δ: 8.03 (2H, d, *J* = 8.3 Hz), 7.31 (2H, d, *J* = 8.1 Hz), 4.24 (1H, d, *J* = 11.2 Hz), 4.14 (1H, dd, *J* = 11.1, 2.7 Hz), 4.06-3.99 (1H, m), 2.93 (1H, dd, *J* = 15.4, 6.5 Hz), 2.73-2.67 (1H, m), 2.43 (3H, s), 2.20-2.13 (1H, m), 2.13-2.05 (1H, m), 1.65-1.47 (3H, m), 1.37-1.27 (2H, m), 1.23-1.13 (3H, m), 0.98-0.89 (1H, m), 0.71 (3H, d, *J* = 6.6 Hz), 0.58 (3H, d, *J* = 6.6 Hz) ppm; $^{13}C$ NMR δ: 199.5, 175.1, 144.2, 136.6, 129.6, 128.6, 112.9, 71.1, 50.7, 42.4, 38.6, 36.4, 27.1, 24.5, 23.3, 21.8, 21.5, 21.0, 21.0, 20.9 ppm; HRMS (ESI): 426.1709, $[C_{22}H_{29}NO_4SNa]^+$ requires 426.1710.

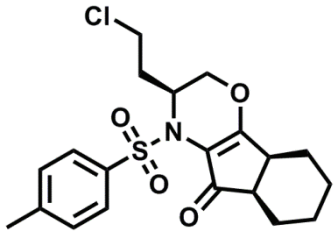
**(3*S*,5a*S*,9a*R*)-3-(2-Chloroethyl)-4-(4-methylbenzenesulfonate)-3,4,5a,6,7,8,9,9a-octahydroindeno[1,2-*b*][1,4]oxazin-5(2*H*)-one (113a)**




**113a**

Following *General procedure 4*, **77** (320 mg, 1.00 mmol) and **103** (427 mg, 1.50 mmol) gave, after column chromatography with 2:1 hexanes/EtOAc, **113a** (170 mg, 40%) as a colorless solid. mp 190-193 $^oC$; IR (film): 1704, 1626 $cm^{-1}$; $^1H$ NMR δ: 8.06 (2H, d, *J* = 8.3 Hz), 7.33 (2H, d, *J* = 8.3 Hz), 4.36-4.30 (2H, m), 4.16 (1H, dd, *J* = 11.3, 2.9 Hz), 3.33 (1H, apparent dt, *J* = 11.2, 4.9 Hz), 3.08 (1H, apparent td, *J* = 10.8, 4.5 Hz), 2.94 (1H, dd, *J* = 13.4, 6.2 Hz), 2.52 (1H, dd, *J* = 15.3, 6.9 Hz), 2.44 (3H, s), 1.99-1.91 (1H, m), 1.83-1.49 (7H, m), 1.48-1.37 (2H, m); $^{13}C$ NMR δ: 200.5, 173.6, 144.5, 136.3, 129.7, 128.6, 113.4, 71.0, 49.7, 43.6, 41.2, 36.1, 32.6, 24.4, 23.0, 21.8, 20.5, 19.8 ppm; HRMS (ESI): 432.1006, $[C_{20}H_{24}ClNO_4SNa]^+$ requires 432.1007.

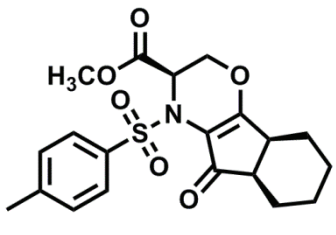
**(3*S*,5a*R*,9a*S*)-3-(2-Chloroethyl)-4-(4-methylbenzenesulfonate)-3,4,5a,6,7,8,9,9a-octahydroindeno[1,2-*b*][1,4]oxazin-5(2*H*)-one (113b)**



**113b**

Following *General procedure 4*, **77** (320 mg, 1.00 mmol) and **103** (427 mg, 1.50 mmol) gave, after column chromatography with 2:1 hexanes/EtOAc, **113b** (70 mg, 17%) as a colorless solid. mp 141-145 $^{o}$C; IR (film): 1720, 1629 cm$^{-1}$; $^{1}$H NMR δ: 8.08 (2H, d, *J* = 8.3 Hz), 7.33 (2H, d, *J* = 8.1 Hz), 4.32 (2H, d, *J* = 11.0 Hz), 4.23 (1H, dd, *J* = 11.5, 2.9 Hz), 3.35-2.98 (1H, m), 3.04 (1H, ddd, *J* = 11.3, 7.3, 5.3 Hz), 2.93 (1H, apparent dt, *J* = 9.1, 6.4 Hz), 2.75-2.70 (1H, m), 2.44 (3H, s), 2.21-2.09 (2H, m), 1.66-1.47 (5H, m), 1.35-1.03 (3H, m) ppm; $^{13}$C NMR δ: 199.5, 174.7, 144.5, 136.3, 129.7, 128.6, 112.8, 70.9, 49.7, 42.5, 41.2, 36.5, 32.7, 27.8, 21.8, 21.3, 21.2, 21.0 ppm; HRMS (ESI): 432.1010, $[C_{20}H_{24}ClNO_4SNa]^+$ requires 432.1007.

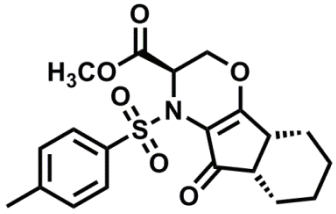
**Methyl (3*R*,5a*S*,9a*R*)-4-(4-methylbenzenesulfonate)-5-oxo-2,3,4,5,5a,6,7,8,9,9a-decahydroindeno[1,2-*b*][1,4]oxazine-3-carboxylate (114a)**



**114a**

Compound **81** (315 mg, 1.00 mmol) and **103** (427 mg, 1.50 mmol) were dissolved in $CH_2Cl_2$ (10 mL). The reaction mixture was cooled to -78 °C with stirring. Distilled $BF_3$•$OEt_2$ (1.88 mL, 15.0 mmol) was added dropwise, and the reaction mixture was warmed to room temperature overnight, after which the completion of geminal acylation was evidenced by TLC. The reaction mixture was then washed with an equal volume of water. The organic fraction was dried with $Na_2SO_4$, and the solvent was evaporated. The resultant oil was dissolved in toluene (50 mL) and heated under reflux for 24 h in the presence of TsOH (380 mg, 2.00 mmol equiv) using a Dean-Stark apparatus. The reaction mixture was cooled and washed with an equal volume of saturated aqueous $NaHCO_3$. The organic fraction was dried with $Na_2SO_4$ and the solvent was evaporated. Column chromatography ($SiO_2$) with 2:1 hexanes/ EtOAc gave **114a** (160 mg, 39%) as a colorless solid. mp 156-159 $^oC$; IR (film): 1756, 1715, 1638 $cm^{-1}$; $^1H$ NMR δ: 8.02 (2H, d, *J* = 8.3 Hz), 7.33 (2H, d, *J* = 8.2 Hz), 4.94 (2H, d, *J* = 10.9 Hz), 4.21 (2H, dd, *J* = 11.7, 3.5 Hz), 3.63 (3H, s), 2.91 (1H, dd, *J* = 15.4, 6.9 Hz), 2.68-2.63 (1H, m), 2.43 (3H, s), 2.15-2.08 (1H, m), 2.03 -1.96 (1H, m), 1.60-1.46 (2H, m), 1.45-1.36 (1H, m), 1.31-1.21 (1H, m), 1.21-1.11 (1H, m) ppm; $^{13}C$ NMR δ: 198.0, 174.1, 167.4, 144.3, 136.9, 129.5, 128.2, 114.4, 68.8, 54.6, 53.1, 42.3, 36.3, 26.6, 21.8, 21.0, 20.6, 20.4 ppm; HRMS (ESI): 428.1140, $[C_{20}H_{23}NO_6SNa]^+$ requires 428.1138.

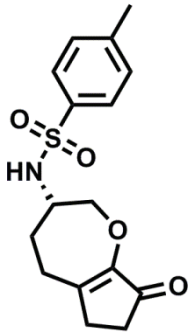
**Methyl (3*R*,5a*R*,9a*S*)-4-(4-methylbenzenesulfonate)-5-oxo-2,3,4,5,5a,6,7,8,9,9a-decahydroindeno[1,2-*b*][1,4]oxazine-3-carboxylate (114b)**



**114b**

Compound **81** (315 mg, 1.00 mmol) and **103** (427 mg, 1.50 mmol) were dissolved in $CH_2Cl_2$ (10 mL). The reaction mixture was cooled to -78 °C with stirring. Distilled $BF_3$•$OEt_2$ (1.88 mL, 15.0 mmol) was added dropwise, and the reaction mixture was warmed to room temperature overnight, after which the completion of geminal acylation was evidenced by TLC. The reaction mixture was then washed with an equal volume of water. The organic fraction was dried with $Na_2SO_4$, and the solvent was evaporated. The resultant oil was dissolved in toluene (50 mL) and heated under reflux for 24 h in the presence of TsOH (380 mg, 2.00 mmol equiv) using a Dean-Stark apparatus. The reaction mixture was cooled and washed with an equal volume of saturated aqueous $NaHCO_3$. The organic fraction was dried with $Na_2SO_4$ and the solvent was evaporated. Column chromatography ($SiO_2$) with 2:1 hexanes/ EtOAc gave **114b** (67 mg, 16%) as a yellow oil. IR (film): 1755, 1714, 1632 $cm^{-1}$; $^1H$ NMR δ: 8.01 (2H, d, *J* = 8.3 Hz), 7.32 (2H, d, *J* = 8.3 Hz), 5.00 (1H, d, *J* = 3.2 Hz), 4.97 (1H, d, *J* = 11.6 Hz), 4.15 (1H, dd, *J* = 11.4, 3.2 Hz), 3.66 (3H, s), 2.92 (1H, dd, *J* = 13.6, 6.2 Hz), 2.48 (1H, dd, *J* = 15.2, 7.1 Hz), 2.43 (3H, s), 1.92-1.84 (1H, m), 1.78 -1.61 (4H, m), 1.54-1.36 (3H, m) ppm; $^{13}C$ NMR δ: 198.8, 172.8, 167.5, 144.2, 137.1, 129.5, 128.3, 114.9, 68.7, 54.6, 53.3, 43.3, 36.0, 24.0, 23.2, 21.8, 20.4, 19.8 ppm; HRMS (ESI): 428.1140, $[C_{20}H_{23}NO_6SNa]^+$ requires 428.1138.

**(*S*)-4-Methyl-*N*-(8-oxo-3,4,5,6,7,8-hexahydro-2*H*-cyclopenta[*b*]oxepin-3-yl)-benzenesulfonamide (125)**



**125**

Compound **86** (220 mg, 0.618 mmol) was dissolved in butanone (3.09 mL). NaI (929 mg, 6.18 mmol) was added, and the mixture was heated under reflux for 3 h. The solvent was removed under reduced pressure, and the solid was dissolved in $CH_2Cl_2$ (50 mL). The organic layer was washed with equal volumes of water and saturated aqueous $Na_2SO_3$, and finally dried over $Na_2SO_4$. The organic layer was then evaporated under reduced pressure to afford **123** as a colorless oil. The product was then dissolved in benzene (250 mL). AIBN (100 mg, 0.618 mmol) was added, and the mixture was heated under reflux. A solution of $Bu_3SnH$ (728 mg, 2.50 mmol) in benzene (50 mL) was added over 48 h. After no starting material was apparent by TLC, TsOH (476 mg, 2.5 mmol) was added, and the mixture was heated under reflux for an additional 24 h. The organic layer was washed with an equal volume of water, dried over $Na_2SO_4$, and concentrated under reduced pressure. Column chromatography ($SiO_2$) with 2:1 hexanes/EtOAc provided **125** (130 mg, 65%) as a colorless solid. mp 171-173 $^oC$; IR (film): 1707, 1645 $cm^{-1}$; $^1H$ NMR δ: 7.77 (2H, d, $J$ = 8.3 Hz), 7.31 (2H, d, $J$ = 8.5 Hz), 5.18 (1H, d, $J$ = 8.2 Hz), 3.85-3.79 (1H, m), 3.78-3.71 (1H, m), 3.71-3.67 (1H, m), 2.65-2.55 (1H, m), 2.47-2.42 (5H, m), 2.42-2.34 (3H, m), 2.10-2.01 (1H, m), 1.86-1.78 (1H, m) ppm; $^{13}C$ NMR δ: 202.0, 154.3,

153.4, 143.9, 137.6, 130.0, 127.0, 74.6, 53.3, 32.8, 31.4, 27.3, 26.4, 21.7 ppm; HRMS (ESI): 344.0925, $[C_{16}H_{19}NO_4SNa]^+$ requires 344.0927.

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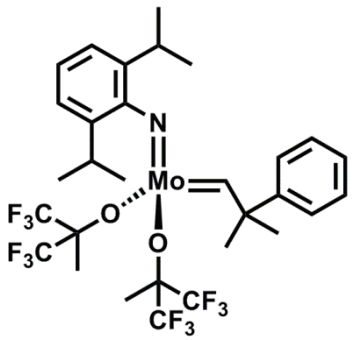
# CHAPTER 3: *E*/*Z* ISOMERIZATION IN THE METATHESIS OF ALLYL ALCOHOL DERIVATIVES WITH A FIRST-GENERATION RUTHENIUM CATALYST

## 3.1 Introduction

Olefin metathesis has evolved into a standard reaction in organic and polymer chemistry for the systematic cleavage and reformation of carbon-carbon double bonds.[1] The procedure was first observed in the realm of polymer chemistry in 1955 where Anderson and Merckling[2] observed carbon-carbon double bond rearrangement in the polymerization of norbornene with a titanium-based catalyst. Shortly thereafter, rudimentary olefin metathesis catalysts emerged based on early transition metals combined with an alkylating agent co-catalyst or grafted onto a chromatographic medium.[1b,c] Catalytic systems such as $WCl_2/EtAlCl_2$, $WCl_2/n Bu_4Sn$, $WOCl_4/EtAlCl_2$, $Re_2O_7/Al_2O_3$, and $MoO_3/SiO_2$ were shown to carry out olefin metathesis, but their utility was hampered by long initiation periods and harsh reaction conditions.[1b]

By the late 1970s, metathesis-active early transition metal complexes based on titanium,[3] tantalum,[4] and tungsten[5] were reported. Although these systems demonstrated high catalytic activity, they suffered from high sensitivity to oxygen and moisture, and they had a narrow range of functional group tolerance.[6] A decade later, Schrock and co-workers[7] developed a series of more functional group-tolerant molybdenum alkylidene-based catalysts, such as **128** (**Figure 3.1.1**). Despite their utility to this day, molybdenum-based catalysts require strict oxygen- and moisture-free conditions.[1]

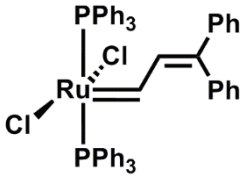



**128**

**Figure 3.1.1:** Schrock's molybdenum-alkylidene **128**

Metathesis-active ruthenium-based catalysts of the form $RuCl_3(H_2O)_n$ had been known since the 1960s and had demonstrated significant air, moisture, and functional group tolerance. Although the reactions mediated by these systems were poorly defined mechanistically, it was believed that a ruthenium alkylidene was the propagating species.[8] It would not be until the late 1980s that ruthenium-based complexes re-emerged as viable metathesis catalysts.[9]

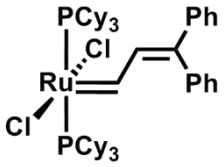
In 1992, Grubbs and co-workers[10] synthesized **129** (**Figure 3.1.2**), the first known ruthenium alkylidene to carry out olefin metathesis. The catalyst demonstrated only modest activity, and its utility was essentially limited to the ring-opening metathesis polymerization of strained olefins, such as norbornadiene.[1b,c] Despite its low reactivity, **129** was the first ruthenium-based metathesis catalyst, the active species of which was identifiable throughout the course of the reaction.[1b]




**129**

**Figure 3.1.2:** Grubbs' ruthenium-alkylidene **129**

Grubbs and co-workers addressed the low reactivity of **129** by substituting the phosphine ligands with larger and more basic phosphines. If a dissociative mechanism were assumed, catalyst initiation should be enhanced by the accelerated dissociation of larger phosphines from the pre-catalyst. Furthermore, the incorporation of more basic phosphines should stabilize the formation of metallacyclobutanes, as the postulated [2+2] cycloaddition is accompanied by oxidation of the ruthenium center. As a result, an increase in activity was observed in the following order: $PPh_3 < P(i\text{Pr})_3 << PCy_3$.[11] The increased stability and reactivity of **130** (**Figure 3.1.3**) expanded on the scope of **129** to include unstrained and acyclic olefins and accomplished, for the first time, ring-closing metathesis in the presence of a broad range of functional groups.[1b]

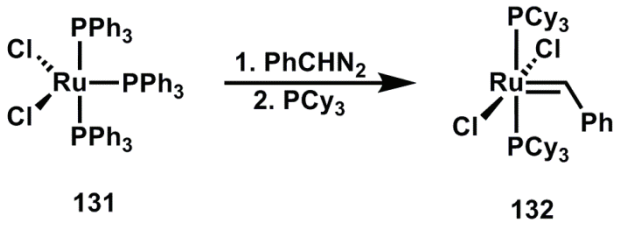



**130**

**Figure 3.1.3:** Grubbs' ruthenium-alkylidene **130**, bearing the more basic $PCy_3$ ligands

During the mid-1990s, in an attempt to meet the growing demand for catalyst, Grubbs and co-workers[1a] encountered difficulty in preparing **130** on a large scale *via* the standard method. It was determined that ruthenium alkylidenes could be prepared

efficiently using diazoalkanes. Treatment of **131** with phenyldiazomethane followed by phosphine ligand exchange afforded the ruthenium benzylidene complex **132** (**Scheme 3.1.1**), which was observed to be a faster-initiating, more active and more functional group tolerant catalyst.[12] Its versatility has made it a standard tool in organic synthesis, even to this day. Known as the "first-generation" of Grubbs' ruthenium benzylidene catalysts, its structure has served as the foundation for future developments in ruthenium-mediated olefin metathesis catalysts.[1a,b]

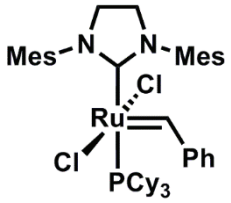



**131** **132**

**Scheme 3.1.1:** Preparation of Grubbs' first-generation metathesis catalyst **132**

Although Grubbs-type metathesis catalysts have evolved significantly since the development of **129**, the general framework of the complexes has remained largely unchanged: a ruthenium alkylidene surrounded by two halogens and two *trans* L-type ligands.[1]

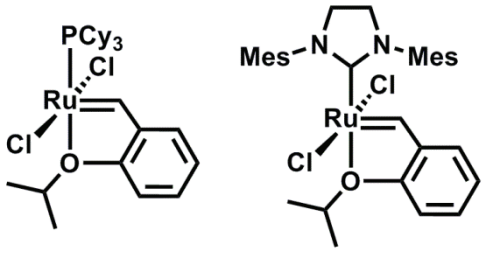
It was later envisioned that the incorporation of a stronger σ-donating L-type ligand could increase catalytic activity by further stabilizing the metal center of the active species.[13] The substitution of a single phosphine ligand with a non-labile *N*-heterocyclic carbene resulted in **133** (**Figure 3.1.4**).[14] Forming the basis for Grubbs' "second generation" metathesis catalysts, **133** demonstrated activity reminiscent of early transition-metal systems[1b,c] while at the same time maintaining the stability and expanding the scope of the previous ruthenium-based systems to include a number of challenging substrates.[14,15]




133

**Figure 3.1.4:** Grubbs' second-generation metathesis catalyst **133**

Since this establishment of **133** as a versatile metathesis-active catalyst, development in the field of ruthenium-mediated olefin metathesis has continued. In the late-1990s, Grubbs and Hoveyda[16] reported the synthesis of bidentate alkylidene-containing structures, such as **134** and **135** (**Figure 3.1.5**), which resulted in a marked increase in the catalysts' lifetime.

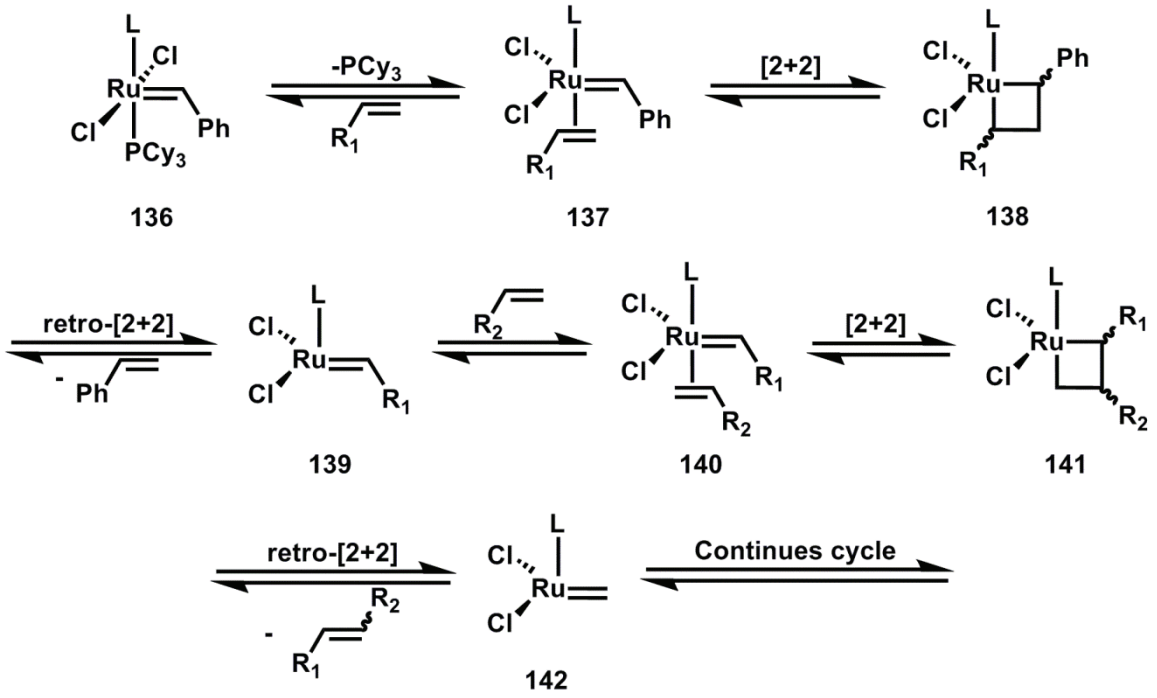



134 135

**Figure 3.1.5:** Grubbs-Hoveyda metathesis catalysts **134** and **135**

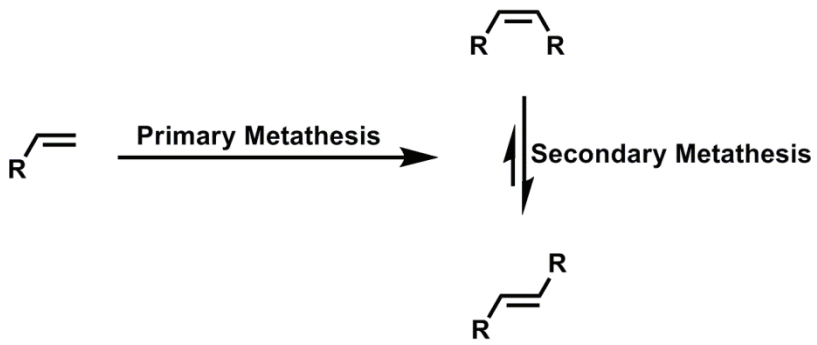
The mechanism of ruthenium-mediated olefin metathesis (**Scheme 3.1.2**) has been investigated rigorously since the emergence of Grubbs' first-generation catalyst, **132**.[11,17] Initial dissociation of a phosphine ligand from **136** results in a 14-electron catalytically active species, which, upon coordination of a π-acidic terminal olefin, gives **137**. The complex undergoes a [2+2] cyclization with oxidation of the ruthenium center to give the ruthenacyclobutane **138**. A [2+2] cycloreversion in the opposite sense, followed by the dissociation of styrene, regenerates a catalytically active species **139**.

Coordination of a second terminal olefin results in **140**, which upon [2+2] cyclization generates **141**. Again, [2+2] cycloreversion in the opposite sense, followed by the dissociation of the newly formed internal olefin, affords the ruthenium-methylidene **142**, which continues the catalytic cycle.




**Scheme 3.1.2:** Proposed mechanism for ruthenium-alkylidine mediated olefin metathesis

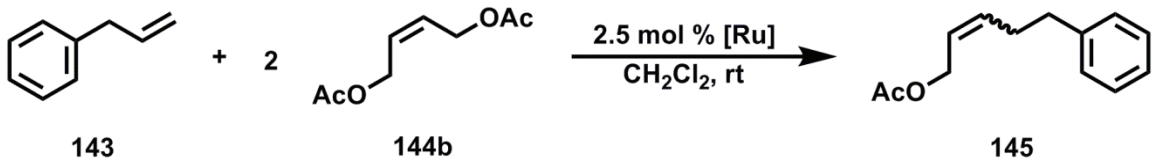
The catalytic sequence by which terminal olefins undergo transformation to generate internal olefins is known as primary olefin metathesis (**Scheme 3.1.3**). However, since internal olefins are often metathesis-reactive themselves, there exists a secondary metathesis pathway in which internal olefins are cleaved by ruthenium-alkylidenes, thereby re-entering the primary metathesis cycle.[18] Therefore, while *E*/*Z*-selectivity can be somewhat controlled kinetically by the direction of approach by a terminal olefin to the ruthenium-alkylidene,[19] it is often a thermodynamic equilibration of the isomers by secondary metathesis that controls the overall product ratio.[20]




**Scheme 3.1.3:** Primary metathesis of a terminal olefin, yielding a kinetic mixture of internal olefins, which equilibrates to a thermodynamic mixture by secondary metathesis

While ring-opening metathesis polymerization is driven by the release of ring strain and ring-closing metathesis is favored entropically, cross metathesis lacks such driving forces and, without control over the reacting partners, gives a statistical mixture of cross products.[1c] As a result, the use of cross metathesis has been relatively underreported.[1a] Significant development in this area was achieved in a study by Grubbs and co-workers,[20a] which was based on the idea that sterically congested olefins ("Type 2 and 3") will participate in cross metathesis with unhindered olefins ("Type 1") more readily than they will undergo homodimerization. This enables one to circumvent the statistical product mixture associated with the cross metathesis of two unhindered olefins. When cross metathesis is carried out between a Type 1 and a Type 2 or 3 olefin, the more sterically hindered partner is typically used in excess in order to maximize the rate of cross product formation.

In 2006, Grubbs and co-workers devised a series of six experiments with which to evaluate a metathesis catalyst's selectivity, activity and stability.[21] In one of these tests, the authors investigated the abilities of several catalysts to promote the cross metathesis of allyl benzene **143** with *cis*-1,4-diacetoxy-2-butene **144b** (**Scheme 3.1.4**).




143 144b 145

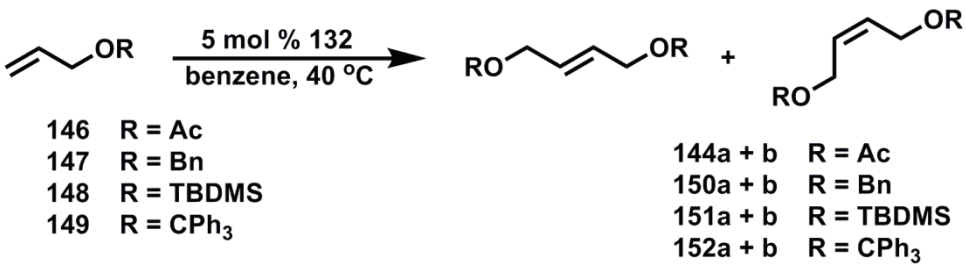
**Scheme 3.1.4:** Cross metathesis of **143** and **144b** mediated by first- and second-generation ruthenium-alkylidene catalysts

As expected, second-generation catalysts bearing an *N*-heterocyclic carbene ligand exhibited higher catalytic activity and efficiency over the phosphine-substituted first-generation catalysts. The authors further noted that, while the second-generation catalysts demonstrated significant thermodynamic equilibration of the heterocoupled product, *E*/*Z* ratios remained essentially unchanged in the presence of first-generation catalysts. From this study, the authors concluded that for the first-generation catalysts explored, secondary metathesis did not take place to a significant degree.

## 3.2 Results and Discussion

During the course of a metathesis experiment involving the homodimerization of an allyl alcohol derivative in the presence of **132**,[22] it was observed that the product underwent significant thermodynamic equilibration during the course of the reaction, resulting in an increase in the product *E*/*Z* ratio over time. This finding seemed contradictory to the findings of Grubbs and co-workers,[21] who previously suggested that first-generation metathesis catalysts did not demonstrate significant secondary-metathesis.

Based on this finding, the homodimerization of a series of allyl alcohol derivatives **146-149** in the presence of **132** was investigated (**Scheme 3.2.1**), while the product *E*/*Z* ratio was monitored over the course of the reaction (**Table 3.2.1**).[22]




**Scheme 3.2.1:** Homodimerization of allyl alcohol derivatives **146-149** in the presence of **132**

| | Yield of Metathesis Products (%), ***E*/*Z* Ratio** | | | |
|---|---|---|---|---|
| **Alkene** | **5 min** | **30 min** | **4 h** | **24 h** |
| **146** | 16, **4.4** | 27, **4.6** | 34, **5.3** | 58, **5.7** |
| **147** | 68, **4.4** | 66, **6.4** | 69, **7.2** | 62, **7.6** |
| **148** | 35, **7.7** | 46, **9.7** | 59, **16** | 51, **18** |
| **149** | 23, **1.9** | 41, **3.0** | 66, **6.4** | 61, **7.9** |

**Table 3.2.1:** Product yields and *E*/*Z* ratios for the homodimerization of allyl alcohol derivatives **146-149**

The acetylated derivative **146** reacted slowly and required several hours of reaction time before an appreciable yield of **144a** and **144b** was obtained. However, over the course of 24 hours, the *E*/*Z* distribution increased only slightly. The benzylated derivative **147** appeared to undergo primary metathesis to **150a** and **150b** rapidly, as the yield of metathesis products did not change significantly beyond the first 5 minutes of reaction. *E*/*Z* isomerisation, on the other hand, continued steadily up to 4 hours before tapering off. The silylated and tritylated compounds **148**and **149** both reacted slowly and achieved the highest product yield after 4 hours. Although **148** appeared to rapidly favour the *E*-homodimer **151a** significantly within minutes, isomerisation continued over 24

hours until virtually none of the *Z*-isomer **151b** remained. The bulkier tritylated derivative **149** had the lowest observed *E*/*Z* distribution in the early stages of the reaction. This was not surprising as the *Z*-isomer **152b** was likely favoured kinetically. Nonetheless, the relative thermodynamic stabilities of the *E*- and *Z*-isomers were apparent as the product mixture underwent significant isomerization, particularly within the first 4 hours.

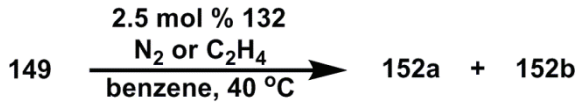
It was also postulated[22] that the gradual increase in *E*/*Z* ratio might be caused by an unknown product of catalyst decomposition. In light of this hypothesis, the homodimerization of **149** was repeated, however this time the substrate was introduced to a benzene solution of **132** that had been stirring at 40 $^{o}$C for 5 hours. After 30 minutes of reaction, the product yield was only 29% and the *E*/*Z* ratio was 2.2. The "aged" catalyst therefore resulted in a diminished product yield, in comparison to the 41% yield with "fresh" catalyst. Furthermore, it appeared that aging the catalyst did not result in an increased *E*/*Z* distribution, but rather had the opposite effect. It however remained unclear whether *E*/*Z* isomerization was promoted by side products of the catalyst and **149**.

The possibility that increases in *E*/*Z* distribution over time were a result of *Z*-isomer degradation was considered unlikely, as *E*/*Z* enhancement generally proceeded with an increase in product yield. It was, however, believed that some decomposition was taking place with prolonged reaction times as the yields did not exceed 70%. For substrates **147-149**, reaction beyond 4 hours resulted in diminished yields of product olefins.

In an effort to improve the product yield and the *E*/*Z* ratio, two parallel experiments were conducted in which **149** underwent homodimerization over 48 hours.

In one experiment, 2.5 mol% of **132** was added incrementally, every 12 hours, to a benzene solution of **149**, and the mixture was heated to 40 $^{o}$C. In the other, 2.5 mol% of **132** was introduced in a single addition to the mixture, under otherwise identical reaction conditions. The periodic addition of fresh catalyst to the reaction mixture resulted in a 67% yield and an *E*/*Z* ratio of 11:1, in comparison to a 49% yield and *E*/*Z* ratio of 8.4:1 for the other experiment. Although the observed yield for the first experiment was similar to that of the 4 hour reaction, the *E*/*Z* distribution had increased to 11:1. In an effort to maintain the solutions' concentrations over the prolonged reaction times, these parallel experiments were conducted in sealed vials. While the sequential addition of catalyst may have contributed to an enhancement of *E*/*Z* distribution, it is possible that this increased stereoselectivity was a result of ethylene, a by-product of the reaction, being retained within the initial 12 hour period of reaction. Previous work in enyne metathesis has suggested that an atmosphere of ethylene can enhance the reversion of internal olefins to terminal olefins, resulting in an increased driving force toward a thermodynamic product mixture.[23]

This phenomenon was therefore investigated by repeating the homodimerization of **149** under a stream of ethylene (**Scheme 3.2.2**). It was observed that after only 2 hours, the *E*/*Z* ratio had improved to 11:1 (**Table 3.2.2**). Despite the enhanced stereoselectivity, the product conversion was diminished, even after 24 hours, owing to a shift in equilibrium toward **149**. It was later found that product yield could be somewhat improved by reducing the exposure time to ethylene.



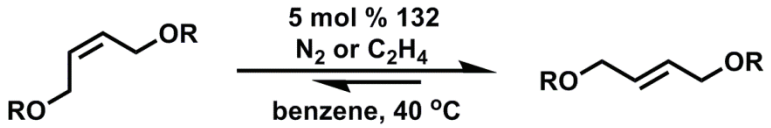

**Scheme 3.2.2:** Homodimerization of **149** under an atmospheres of $N_2$ and $C_2H_4$, resulting in a mixture of **152a** and **152b**

| Atmosphere, Time | Yield (%) | *E*/*Z* |
|---|---|---|
| $C_2H_4$, 2 h | 27 | 11:1 |
| $C_2H_4$, 24 h | 32 | 11:1 |
| $N_2$, 3 h then $C_2H_4$, 1 h | 45 | 11:1 |

**Table 3.2.2:** Product yields and *E*/*Z* ratios for the homodimerization of **149** under atmospheres of $N_2$ and $C_2H_4$

The ability for **132** to promote secondary metathesis was further evaluated by subjecting *Z*-enriched but-2-enediol derivatives under the standard reaction conditions (**Scheme 3.2.3**). After only 10 minutes, compounds **144b**, **150b**, **151b**, and **152b** showed significant equilibration toward the more thermodynamically favourable *E*-isomer, with the silylated product mixture **151a** and **151b** already possessing an *E*/*Z* ratio greater than 1:1 (**Table 3.2.3**).

In light of the previous success in enhancing secondary metathesis with ethylene, the reactions of *Z*-enhanced olefins were repeated under a stream of ethylene. In the majority of cases, isomerization to the *E*-olefins increased in the presence of ethylene, which again suggested that secondary metathesis was enhanced by equilibrating the internal olefins with their corresponding terminal olefins. Again, *E*/*Z* ratio enhancement came at the expense of overall product yield as the reaction equilibrium was shifted significantly toward the terminal alkenes.




**144b** R = Ac
**150b** R = Bn
**151b** R = TBDMS
**152b** R = $CPh_3$

**144a** R = Ac
**150a** R = Bn
**151a** R = TBDMS
**152a** R = $CPh_3$

**Scheme 3.2.3:** Thermodynamic equilibration of **144b**, **150b**, **151b**, and **152b** to **144a**, **150a**, **151a**, and **152a** under atmospheres of $N_2$ and $C_2H_4$

| Alkene | Initial *E*/*Z* Ratio | Yield of Metathesis Products, *E*/*Z* Ratio | |
|---|---|---|---|
| | | $N_2$ | $C_2H_4$ |
| **144b** | < 0.05:1 | 90%, **0.2:1** | 48%, **0.1:1** |
| **150b** | < 0.05:1 | 83%, **0.3:1** | 33%, **3.3:1** |
| **151b** | 0.08:1 | 96%, **1.2:1** | 20%, **2.6:1** |
| **151b** | < 0.05:1 | 86%, **< 0.05:1** | 21%, **0.2:1** |

**Table 3.2.3:** Product yields and *E*/*Z* ratios for the equilibration of **144b**, **150b**, **151b**, and **151b** under atmospheres of $N_2$ and $C_2H_4$ (10 minute reactions)

Unlike the other substrates, however, the acetylated substrate **144b** underwent a greater degree of isomerisation in the presence of nitrogen. It has been reported by Grubbs and co-workers[24] that **144b** tends to react with greater *E*-selectivity in the presence of **132** than its more reactive terminal olefin counterpart. It is possible, based on these results, that the bulkier substrates **150b**, **151b**, and **152b** were more reactive than their corresponding terminal olefins and, therefore, less *E*-selective.

## 3.3 Conclusions

It has been found that derivatives of allyl alcohol undergo homodimerization in the presence of the first-generation Grubbs metathesis catalyst **132** with gradual

isomerisation to an equilibrium mixture of *E*- and *Z*- olefins. These results contradicted earlier findings by Grubbs and co-workers,[21] which suggested first-generation metathesis catalysts were not efficient in the secondary metathesis of internal olefins. Although higher *E*/*Z* ratios were achievable with longer reaction times, this also resulted in some loss of the desired products due to unwanted side reactions.

Enhancement of the *E*/*Z* distributions of homodimers **150b**, **151b**, and **152b** could be accomplished by carrying out the metathesis reaction under an atmosphere of ethylene, which served to equilibrate the homodimers with the corresponding terminal alkenes. However, this also often resulted in reduced yields of metathesis products. By limiting the exposure of **149** to ethylene, it was found that a compromise between thermodynamic equilibration and product yield could be achieved.

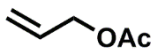
## 3.4 Experimental

### General

Benzene and dichloromethane were distilled from calcium hydride. THF was distilled from sodium metal. EtOAc and hexanes were distilled. Commercial reagents were used as received. Column chromatography was carried out on a silica gel (230-400 mesh) stationary phase. High-resolution mass spectra were acquired using a Bruker MicroTOF mass spectrometer *via* electrospray ionization. $^{1}$H NMR spectra were acquired at 500 MHz and $^{13}$C NMR spectra at 125 MHz from $CDCl_3$ sample solutions. Chemical shifts for $^{1}$H NMR are relative to internal standard tetramethylsilane ($\delta$ 0.00 ppm). Chemical

shifts for $^{13}C$ NMR are relative to $CDCl_3$ (δ 77.16 ppm). E/Z values were determined by integration of diagnostic $^{1}H$ NMR signals.

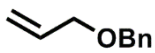
**Allyl acetate (146)**




**146**

According to the literature,[25] allyl alcohol (5.85 mL, 86.0 mmol) was dissolved in $CH_2Cl_2$ (50 mL). The mixture was cooled to 0 $^{o}C$ and AcCl (9.17 mL, 129 mmol) was added dropwise. After warming to room temperature and stirring for 24 h, the mixture was washed with an equal volume of aqueous $NaHCO_3$, which was re-extracted with $CH_2Cl_2$ (2 × 20 mL). The combined organic layers were dried over $Na_2SO_4$, and the solvent was evaporated under reduced pressure to afford **146** (8.24 g, 96%) as a colorless oil, which was used without further purification. $^{1}H$ NMR δ: 5.97-5.88 (1H, m), 5.32 (1H, apparent dq, $J$ = 17.2, 1.5 Hz), 5.24 (1H, apparent dq, $J$ = 10.4, 1.3 Hz), 4.57 (2H, apparent dt, $J$ = 5.8, 1.4 Hz), 2.08 (3H, s) ppm; $^{13}C$ NMR δ: 170.8, 132.3, 118.3, 65.2, 20.1 ppm; HRMS (ESI): 123.0420, $[C_5H_8O_2Na]^+$ requires 123.0417.

**Allyloxymethylbenzene (147)**

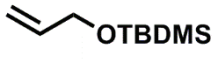



**147**

According to the literature,[26] allyl alcohol (5.44 mL, 80.0 mmol) was dissolved in THF (20 mL). The mixture was cooled to 0 $^{o}C$, and 60% NaH in mineral oil (2.08 g, 52.0 mmol) was added slowly. After stirring for 1 h at 0 $^{o}C$, BnBr (4.76 mL, 40.0 mmol) was

added dropwise, and the mixture was heated under reflux for 1 h. After cooling to room temperature, the solvent was evaporated under reduced pressure and $CH_2Cl_2$ (20 mL) was added. The mixture was washed with an equal volume of aqueous $NH_4Cl$, which was re-extracted with $CH_2Cl_2$ (2 × 20 mL). The combined organic layers were dried over $Na_2SO_4$, and the solvent was evaporated under reduced pressure. Column chromatography ($SiO_2$) with 40:1 hexanes/EtOAc gave **147** (5.86 g, 99%) as a colorless oil. $^1$H NMR δ: 7.35-7.29 (4H, m), 7.27-7.22 (1H, m), 5.98-5.89 (1H, m), 5.29 (1H, br dd, $J$ = 17.2, 1.7 Hz), 5.18 (1H, br dd, $J$ = 10.5, 1.5 Hz), 4.49 (2H, s), 4.00 (2H, br d, $J$ = 5.6 Hz) ppm; $^{13}$C NMR δ: 138.3, 134.8, 128.4, 127.7, 127.6, 117.0, 72.1, 71.1 ppm. These data are in agreement with those found in the literature.[26]

**Allyloxy-*tert*-butyldimethylsilane (148)**

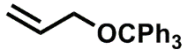



**148**

According to the literature,[27] allyl alcohol (2.15 mL, 31.9 mmol) was dissolved in THF (50 mL). The mixture was cooled to 0 $^o$C, and imidazole (5.15 g, 75.5 mmol) was added slowly, followed by TBDMSCl (5.80 g, 38.5 mmol). After warming to room temperature and stirring for 24 h, the solvent was evaporated under reduced pressure and $CH_2Cl_2$ (50 mL) was added. The mixture was washed with an equal volume of aqueous $NH_4Cl$, which was re-extracted with hexanes (2 × 50 mL). The combined organic layers were dried over $Na_2SO_4$, and the solvent was evaporated under reduced pressure. Column chromatography ($SiO_2$) with 20:1 hexanes/EtOAc gave **148** (2.98 g, 54%) as a colorless oil. $^1$H NMR δ: 5.97-5.88 (1H, m), 5.27 (1H, apparent dq, $J$ = 17.1, 1.9 Hz), 5.09 (1H,

apparent dq, $J$ = 10.4, 1.8 Hz), 4.18 (2H, apparent dt, $J$ = 4.6, 1.8 Hz), 0.92 (9H, s), 0.08 (6H, s) ppm; $^{13}$C NMR δ: 137.6, 114.1, 64.2, 26.1, 18.6, -5.1 ppm. These data are in agreement with those found in the literature.[27]

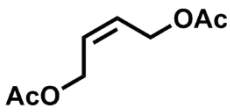
**Allyloxytriphenylmethane (149)**




**149**

Triphenylmethanol (15.1 g, 58.0 mmol) was dissolved in DMF (60 mL). The mixture was cooled to 0 $^{o}$C and 60% NaH in mineral oil (2.56 g, 64.0 mmol) was added slowly, followed by allyl chloride (8.10 mL, 99.4 mmol). After warming to room temperature and stirring for 24 h, the mixture was diluted with an equal volume of $CH_2Cl_2$ and washed with water (5 × 500 mL). The organic layer was dried over $Na_2SO_4$, and the solvent was evaporated under reduced pressure to afford **149** (16.7 g, 96%) as a pale yellow solid, which was used without further purification. $^{1}$H NMR δ: 7.46 (6H, d, $J$ = 8.2 Hz), 7.29 (6H, dd, $J$ = 8.1, 7.5 Hz), 7.22 (3H, t, $J$ = 7.3 Hz), 5.98-5.89 (1H, m), 5.43 (1H, apparent dq, $J$ = 17.3, 1.9 Hz), 5.16 (1H, apparent dq, $J$ = 10.6, 1.7 Hz), 3.61 (2H, apparent dt, $J$ = 4.8, 1.8 Hz) ppm; $^{13}$C NMR δ: 144.3, 135.2, 128.8, 128.0, 127.1, 115.4, 86.9, 65.2 ppm. These data are in agreement with those found in the literature.[28]

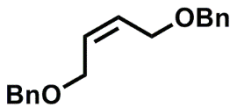
**(*Z*)-1,4-Diacetoxy-2-butene (144b)**




**144b**

According to the literature,[29] 1,4-dihydroxy-2-butene (97% *Z*) (1.87 mL, 22.7 mmol) was dissolved in $CH_2Cl_2$ (20 mL). $Ac_2O$ (7.37 mL, 78.0 mmol) was added, and the mixture was cooled to 0 $^oC$. Pyridine (5.53 mL, 70.0 mmol) was then added dropwise. After warming to room temperature with stirring overnight, the mixture was washed with an equal volume of 1M aqueous HCl, which was re-extracted with $CH_2Cl_2$ (2 × 20 mL). The combined organic layers were dried over $Na_2SO_4$, and the solvent was evaporated to afford a yellow oil. Column chromatography ($SiO_2$) with 4:1 hexanes/EtOAc gave **144b** (3.43 g, 85%) (*E*/*Z* < 0.05) as a colorless oil. $^1H$ NMR δ: 5.76 (2H, t, *J* = 4.4 Hz), 4.68 (4H, d, *J* = 4.2 Hz), 2.07 (6H, s) ppm; $^{13}C$ NMR δ: 170.9, 128.2, 60.1, 21.1 ppm. These data are in agreement with those found in the literature.[29]

**(*Z*)-1,4-Bis(benzyloxy)but-2-ene (150b)**

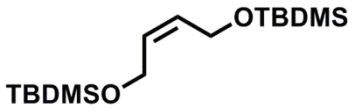



**150b**

According to the literature,[30] 1,4-dihydroxy-2-butene (97% *Z*) (1.87 mL, 22.7 mmol) was dissolved in THF (20 mL). The mixture was cooled to 0 $^oC$, and 60% NaH in mineral oil (2.56 g, 64.0 mmol) was added slowly, followed by BnBr (8.21 mL, 69.0 mmol). After warming to room temperature with stirring overnight, the solvent was evaporated under reduced pressure and $CH_2Cl_2$ (20 mL) was added. The mixture was washed with an equal volume of aqueous $NH_4Cl$, which was re-extracted with $CH_2Cl_2$ (2 × 20 mL). The combined organic layers were dried over $Na_2SO_4$, and the solvent was evaporated under reduced pressure to afford a yellow oil. Column chromatography ($SiO_2$) with 20:1

hexanes/EtOAc gave **150b** (3.18 g, 52%) (*E*/*Z* < 0.05) as a colorless oil. $^{1}$H NMR δ: 7.37-7.27 (10H, m), 5.79 (2H, br t), 4.49 (4H, s), 4.07 (4H, d, *J* = 3.4 Hz) ppm; $^{13}$C NMR δ: 138.2, 129.6, 128.5, 127.9, 127.8, 72.4, 65.9 ppm. These data are in agreement with those found in the literature.[30]

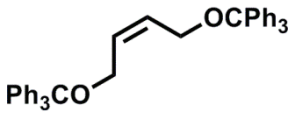
**(*Z*)-2,2,3,3,10,10,11,11-Octamethyl-4,9-dioxa-3,10-disiladodec-6-ene (151b)**




**151b**

According to the literature,[31] 1,4-dihydroxy-2-butene (97% *Z*) (1.87 mL, 22.7 mmol) was dissolved in $CH_2Cl_2$ (50 mL). After cooling to 0 $^{o}$C, $Et_3N$ (6.97 mL, 50.0 mmol), DMAP (0.220 g, 1.80 mmol), and TBDMSCl (7.54 g, 50.0 mmol) were added. After warming to room temperature and stirring overnight, the mixture was washed with an equal volume of aqueous $NaHCO_3$, which was re-extracted with $CH_2Cl_2$ (2 × 20 mL). The combined organic layers were dried over $Na_2SO_4$, and the solvent was evaporated to afford a yellow oil. Column chromatography ($SiO_2$) with 4:1 hexanes/EtOAc gave **151b** (5.50 g, 76%) (*E*/*Z* < 0.05) as a colorless oil. $^{1}$H NMR δ: 5.55 (2H, t, *J* = 3.7 Hz), 4.23 (4H, d, *J* = 3.8 Hz), 0.90 (18H, s), 0.07 (12H, s) ppm; $^{13}$C NMR δ: 130.3, 59.8, 26.1, 18.5, -5.0 ppm. These data are in agreement with those found in the literature.[32]

**(*Z*)-1,4-Bis(triphenylmethoxy)but-2-ene (152b)**



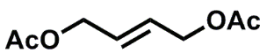

**152b**

According to the literature,[33] triphenylmethanol (20.0 g, 77.0 mmol) was dissolved in benzene (7.0 mL). The mixture was heated and AcCl (12.1 mL, 170 mmol) was added dropwise. After heating for 1 h, the mixture was cooled to 0 $^{o}$C. Hexanes (20 mL) and petroleum ether (10.0 mL) were added, and the mixture was left to crystallize at 0 $^{o}$C for 1 h. The resulting solid was isolated by vacuum filtration and washed with petroleum ether. Evaporation of residual solvent under reduced pressure afforded a white solid, which was redissolved in $CH_2Cl_2$ (50 mL) in a separate flask. 1,4-Dihydroxy-2-butene (97% *Z*) (1.87 mL, 22.7 mmol) was then added. After cooling to 0 $^{o}$C, $Et_3N$ (6.42 mL, 46.0 mmol) was added. After warming to room temperature and stirring overnight, the mixture was washed with an equal volume of aqueous $NH_4Cl$, which was re-extracted with $CH_2Cl_2$ (2 × 20 mL). The combined organic layers were dried over $Na_2SO_4$, and the solvent was evaporated. Column chromatography ($SiO_2$) with 10:1 hexanes/EtOAc gave **152b** (7.51 g, 57%) (*E*/*Z* < 0.05) as a white solid. $^{1}$H NMR δ: 7.37-7.33 (12H, m), 7.24-7.17 (18H, m), 5.74 (2H, t, *J* = 3.8 Hz), 3.50 (4H, d, *J* = 3.7 Hz) ppm; $^{13}$C NMR δ: 144.2, 128.9, 128.7, 127.9, 127.0, 86.9, 60.7 ppm. These data are in agreement with those found in the literature.[34]

***General procedure 1:*** **Homodimerization of Allyl Alcohol Derivatives 146-149**

The allyl alcohol derivative (1 equiv) was dissolved in benzene (10 mL/mmol). The solution was heated to 40 $^{o}$C and **132** (0.05 or 0.025 equiv) was added. The reaction mixture was stirred for the requisite time under a gentle flow of $N_2$ or $C_2H_4$. The solvent was evaporated to afford the product.

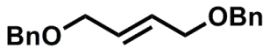
**(*E*)-1,4-Diacetoxy-2-butene (144a)**




**137a**

Following *General procedure 1*, **146** (67 mg, 0.67 mmol) gave, without purification, **144a** (with **144b**) as a brown oil. $^{1}$H NMR δ: 5.88-5.85 (2H, m), 4.60-4.57 (4H, m), 2.09 (6H, s) ppm; $^{13}$C NMR δ: 170.6, 128.0, 63.9, 20.9 ppm. These data are in agreement with those found in the literature.[35]

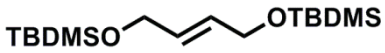
**(*E*)-1,4-Bis(benzyloxy)but-2-ene (150a)**




**150a**

Following *General procedure 1*, **147** (99 mg, 0.67 mmol) gave, after column chromatography with 20:1 hexanes/EtOAc, **150a** (with **150b**) as a colorless oil. $^{1}$H NMR δ: 7.36-7.31 (8H, m), 7.30-7.25 (2H, m), 5.89-5.87 (2H, m), 4.52 (4H, s), 4.05-4.03 (4H, m) ppm; $^{13}$C NMR δ: 138.3, 129.6, 128.5, 127.8, 127.7, 72.3, 70.2 ppm; HRMS (ESI): 291.1357, $[C_{18}H_{20}O_2Na]^+$ requires 291.1356.

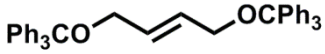
**(*E*)-2,2,3,3,10,10,11,11-Octamethyl-4,9-dioxa-3,10-disiladodec-6-ene (151a)**




**151a**

Following *General procedure 1*, **148** (115 mg, 0.670 mmol) gave, without purification, **151a** (with **151b**) as a brown oil. $^{1}$H NMR δ: 5.76 (2H, t, *J* = 2.2 Hz), 4.18 (4H, d, *J* = 2.2 Hz), 0.91 (18H, s), 0.07 (12H, s) ppm; $^{13}$C NMR δ: 129.3, 63.3, 26.0, 18.4, -5.2 ppm; HRMS (ESI): 339.2136, $[C_{16}H_{36}O_2Si_2Na]^+$ requires 339.2146.

**(*E*)-1,4-*Bis*(triphenylmethoxy)but-2-ene (152a)**




**152a**

Following *General procedure 1*, **150** (201 mg, 0.670 mmol) gave, after column chromatography with 20:1 $CH_2Cl_2$/MeOH, **152a** (with **152b**) as a white solid. $^{1}$H NMR δ: 7.49–7.44 (12H, m), 7.31-7.26 (12H, m), 7.24-7.21 (6H, m), 5.94 (2H, t, *J* = 2.3 Hz), 3.65 (4H, d, *J* = 2.3 Hz) ppm; $^{13}$C NMR δ: 144.3, 128.8, 128.7, 127.9, 127.1, 87.0, 64.5 ppm; HRMS (ESI): 595.2588, $[C_{42}H_{36}O_2Na]^+$ requires 595.2608.

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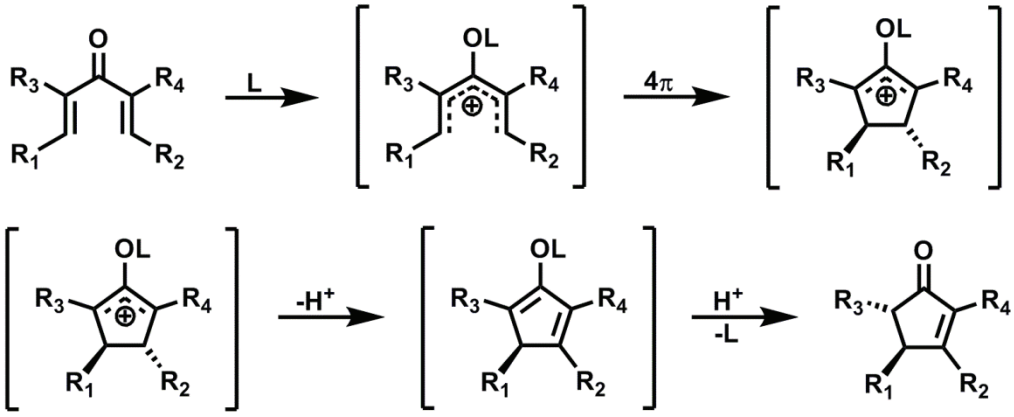
## CHAPTER 4: INTERCEPTION OF NAZAROV REACTION INTERMEDIATES OF ALLENYL VINYL KETONES WITH ARENES

### 4.1 Introduction

The acid-mediated cyclization that is now called the Nazarov reaction was initially described in 1941.[1] The reaction is an acid-mediated 4π electrocyclization which converts divinyl ketones to their corresponding cyclopentenones (**Scheme 4.1.1**). Initial coordination of a proton or, much more commonly nowadays, a Lewis acid to the carbonyl oxygen gives rise to a pentadienyl cation. Electrocyclization results in the formation of an oxyallyl cation intermediate, which undergoes loss of a proton generating an enol or the Lewis acid-enolate. Tautomerization, or protonation of the Lewis acid-enolate and then tautomerization, yields the product, the cyclopentenone.[2]




**Scheme 4.1.1:** Lewis acid-mediated Nazarov cyclization of a divinyl ketone resulting in a cyclopentenone

In order for orbital symmetry to be maintained, electrocyclization must take place by conrotation of the termini of the pentadienyl cation (**Figure 4.1.1**), as dictated by the Woodward-Hoffman rules.[3] This gives rise to a cyclopentenone in which $R_1$ and $R_2$ substituents are exclusively *anti* to one another.

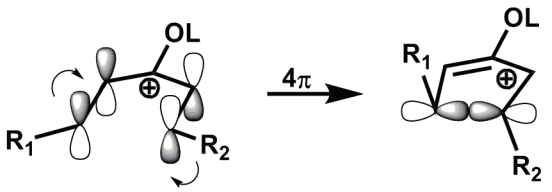



**Figure 4.1.1:** Conrotatory 4π electrocyclization of a pentadienyl cation resulting in an oxyallyl cation with $R_1$ and $R_2$ *anti* to one another

Historically, the scope and utility of the Nazarov cyclization were limited for several reasons. Unactivated substrates often required initiation by strong protic or Lewis acids in stoichiometric amounts. Upon formation of the oxyallyl cationic intermediate, the proton elimination step suffered from poor regioselectivity and, in any event, resulted in the loss of a stereogenic center. Furthermore, re-protonation in the tautomerization step also lacked regioselectivity. Extensive research has led to the development of "activated" divinyl ketones in order to circumvent some of these challenges.[4]

Unsubstituted divinyl ketones tend to preferentially adopt the lower energy s-*cis*/s-*cis* conformation over the s-*trans*/s-*trans* geometry necessary for Nazarov cyclization to occur (**Figure 4.1.2**).

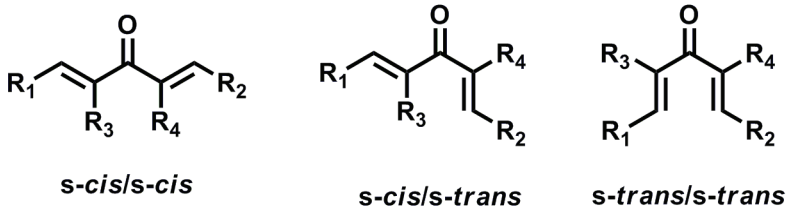



**Figure 4.1.2:** s-*Cis*/s-*cis*, s-*cis*/s-*trans*, and s-*trans*/s-*trans* conformations of a divinyl ketone

In general, substitution at the α positions has been shown to assist in electrocyclization by lowering the energy of the s-*trans*/s-*trans* conformation. Divinyl ketones bearing bulky substituents minimize steric repulsion by adopting the s-*trans*/s-

*trans* conformation, resulting in activation of the substrate toward cyclization.[5] Furthermore, the incorporation of an α substituent capable of complexing a Lewis acid in a bidentate fashion with the carbonyl oxygen can assist in positioning the divinyl ketone in the reactive conformation (**Figure 4.1.3**).[6]

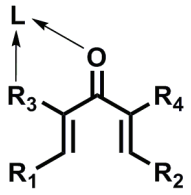
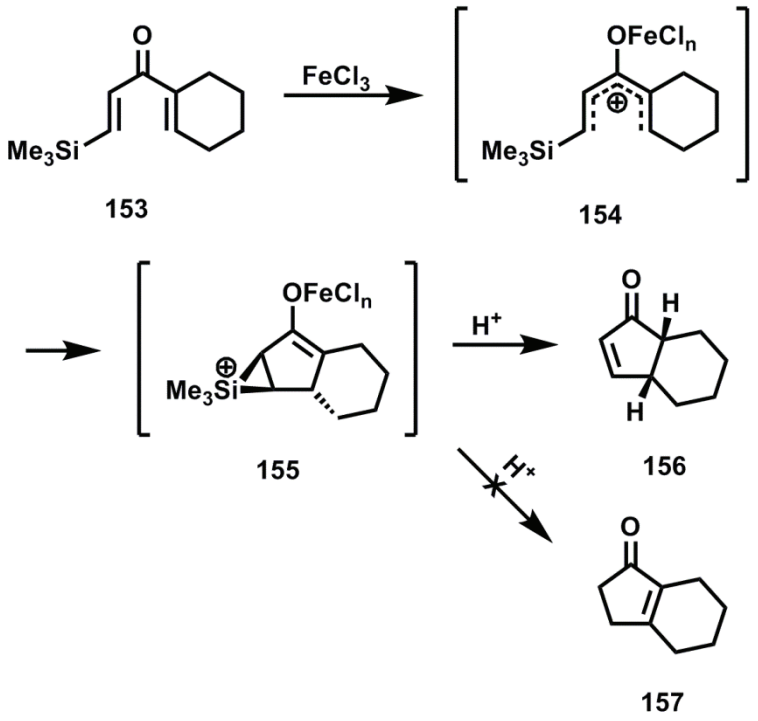



**Figure 4.1.3:** Bidentate coordination to a Lewis acid, resulting in an increase in the population of the s-*trans*/s-*trans* conformation

Substitution at the α positions with electron-donating groups can also enhance Nazarov cyclization, not only by increasing electron density at the termini of the pentadienyl cation to drive electrocyclization, but also by stabilizing the oxyallyl cationic intermediate following electrocyclization.[5b] In addition, substitution of a divinyl ketone by a single electron donating group can lead to regioselective proton elimination through stabilization of the carbocation.

On the other hand, substitution at the β-positions has typically been shown to inhibit electrocyclization, largely due to stabilization of the pentadienyl cation.[5b] However, Denmark and Jones[7] demonstrated that β-substitution with a silyl group could serve to localize the positive charge of the oxyallyl cation and effectively promote regioselective elimination (**Scheme 4.1.2**). In addition to minimizing rearrangement of the intermediate, the β-silyl substituent can also promote elimination at the thermodynamically less favored position in the case of α'-substituted divinyl ketones. This is especially useful in the synthesis of fused bicyclic systems, such as **156**. The silyl

substituent promotes regioselective elimination to give **156**, instead of the more thermodynamically favored **157**, which would have resulted in loss of both stereocenters at the ring junction.[5b]



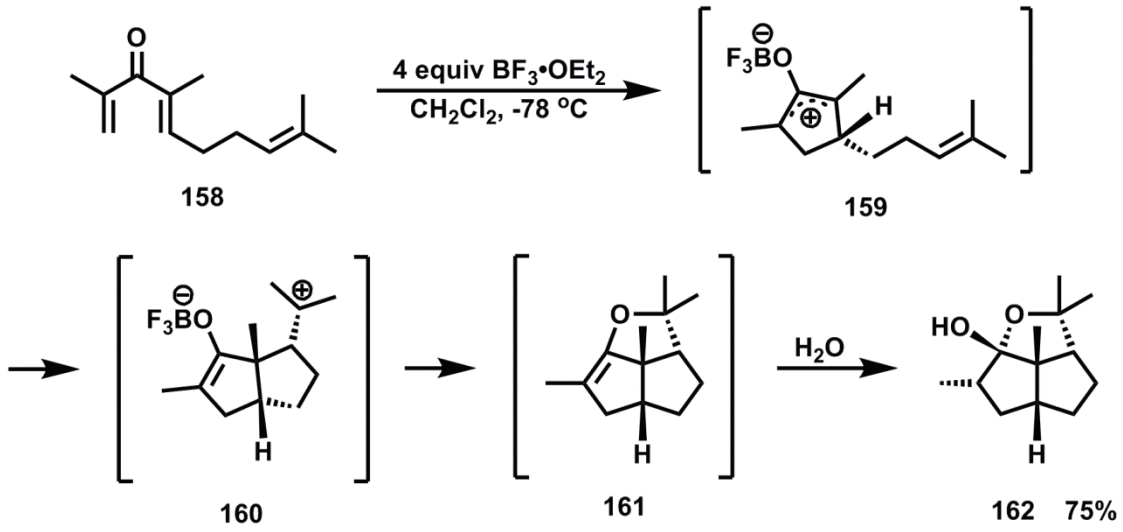

**Scheme 4.1.2:** β-Silane-promoted regioselective elimination of oxyallyl cation **155**

Despite the extensive developments in enhancing the reactivity of divinyl ketones and in controlling the regioselectivity of proton elimination, it remains that elimination results in the loss of a stereogenic center formed during the electrocyclization.

Efficient synthetic chemistry relies on the generation of multiple bonds in high yield and high stereoselectivity, over minimal steps.[8] Fused polycycles containing six-membered rings have been derived readily from the cascade cationic cyclization of polyolefinic starting materials.[9] On the other hand, the construction of polycycles of five-membered rings under cationic conditions has been under-represented.[10] If the reaction

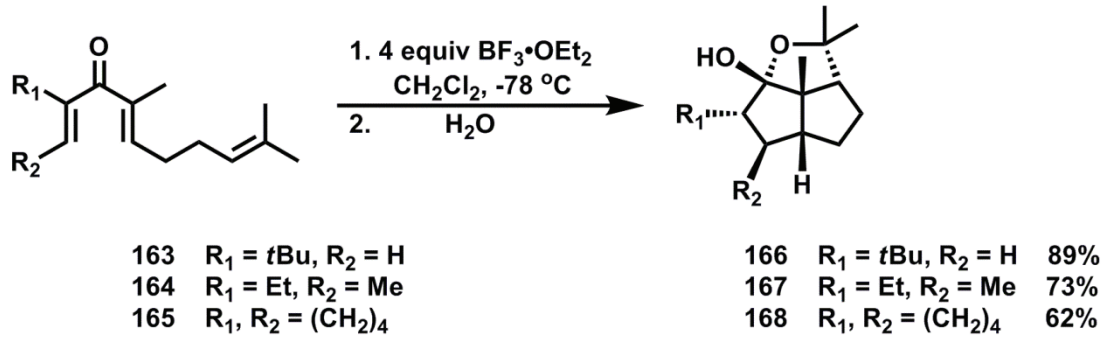
were carried out in the presence of a nucleophile, such that the rate of nucleophilic attack on the oxyallyl cationic intermediate were competitive with the rate of proton elimination, this "interrupted" Nazarov reaction would result in a molecule of increased complexity, without the loss of a stereogenic center that has plagued the traditional elimination pathway.

Examples of nucleophilc interception of oxyallyl cations had only been observed by solvent molecules[11] until 1998, when West and co-workers[5d] investigated the intramolecular trapping of divinyl ketones bearing tethered olefins. In the presence of $BF_3$•$OEt_2$, trienone **158** underwent cascade cyclization to afford the diquinane **162** (**Scheme 4.1.3**). This represented the conversion of an acyclic, achiral polyolefin into a tricyclic product through the formation of two new carbon-carbon bonds and five contiguous stereocenters in good yield and with complete diastereoselectivity. According to the proposed mechanism, following electrocyclization to oxyallyl cation **159**, the pendant olefin underwent a 5-*exo* cyclization to generate the tertiary carbocation **160**. Attack by the enolate oxygen resulted in **161**, which finally underwent hydration during work-up to give **162**.



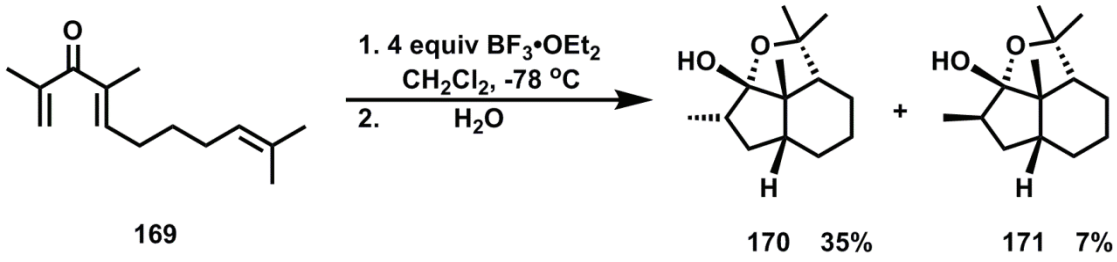

**Scheme 4.1.3:** Intramolecular interception of the oxyallyl cation **159**, resulting ultimately in diquinane **162**

Diquinanes **166-168** were similarly prepared from the corresponding trienones **163**–**165** (**Scheme 4.1.4**). In each case, the authors obtained the product as a single diastereomer in moderate to good yield.



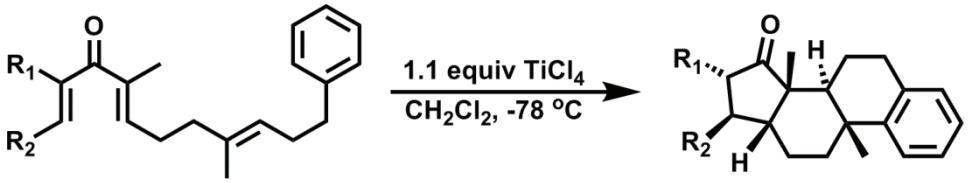

**Scheme 4.1.4:** Formation of diquinanes **166-168** via the intramolecular interrupted Nazarov cyclization of trienones **163-165**

Reaction of trienone **169**, in which the tether was extended to three carbon atoms, resulted in a decrease in yield as well as a 5:1 diastereomeric mixture of products **170** and **171** (**Scheme 4.1.5**).




**Scheme 4.1.5:** Intramolecularly interrupted Nazarov cyclization of **169** bearing a three carbon tether, resulting in diquinanes **170** and **171**

Shortly thereafter, West and co-workers[12] demonstrated that trienones **172–175** containing a pendant olefins and a terminal arene could undergo a domino-type reaction to generate tetra- and pentacyclic structures **176–179**, which possess carbon skeletons akin to numerous steroidal targets (**Scheme 4.1.6**). Reactions mediated by $BF_3$•$OEt_2$ required elevated temperatures and led to unwanted elimination products. However, treatment of **172–175** with $TiCl_4$ enabled the cascade reaction to proceed at low temperature giving rise to **176–179** in good to high yields and generating six contiguous stereocenters with complete diastereoselectivity.

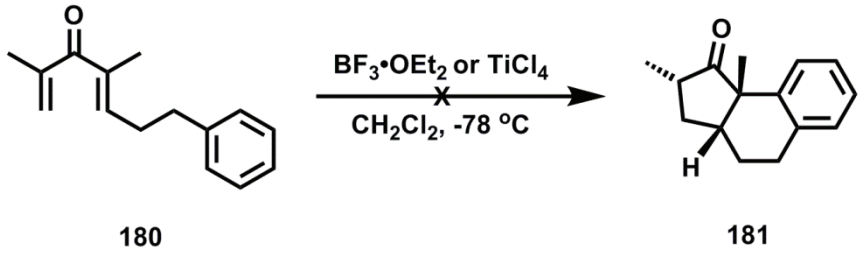



| | | | |
|---|---|---|---|
| **172** | $R_1$ = Me, $R_2$ = H | **176** | $R_1$ = Me, $R_2$ = H 99% |
| **173** | $R_1$ = Me, $R_2$ = Et | **177** | $R_1$ = Me, $R_2$ = Et 73% |
| **174** | $R_1$, $R_2$ = $(CH_2)_4$ | **178** | $R_1$, $R_2$ = $(CH_2)_4$ 98% |
| **175** | $R_1$, $R_2$ = $(CH_2)_5$ | **179** | $R_1$, $R_2$ = $(CH_2)_5$ 74% |

**Scheme 4.1.6:** Formation of **176–179** via the cascade cyclization of the oxyallyl cations derived from **172–175**

In light of these results, the West group began to pursue the trapping of oxyallyl cationic intermediates directly by pendant arenes through *via* Friedel-Crafts reaction.[13]

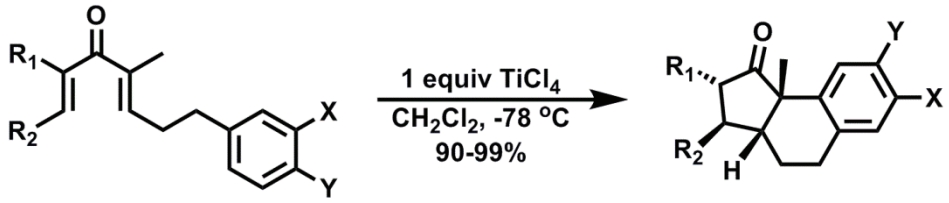
The procedure was initially tested with divinyl ketone **180** (**Scheme 4.1.7**), which was substituted at the β-position by a two-carbon tether with a terminal phenyl substituent. Treatment with either $BF_3$•$OEt_2$ or $TiCl_4$ failed to give the desired tricyclic product **181**.




**180** **181**

**Scheme 4.1.7:** Unsuccessful intramolecular Friedel-Crafts trapping of the oxyallyl cation of **180** with a pendant unsubstituted phenyl group

The reaction with $BF_3$•$OEt_2$ did, however, afford a significant amount of product consistent with elimination of the oxyallyl cationic intermediate. It was therefore surmised that the unsubstituted aryl moiety lacked the reactivity necessary to promote Friedel-Crafts alkylation at a rate that was competitive with the alternative elimination pathway. Divinyl ketones **182**–**187**, bearing electron-donating substituents, were subsequently prepared and subjected to the same reaction conditions as for **180**. Treatment with $BF_3$•$OEt_2$ resulted in a mixture of products stemming from both oxyallyl cation trapping and elimination. Reaction with $TiCl_4$, on the other hand, afforded the desired tricyclic products **188**–**193** in excellent yields (**Scheme 4.1.8**). In each case, trapping occurred at the proximal α position of the oxyallyl cation. On the aromatic ring, Friedel-Crafts alkylation occurred at the less sterically hindered position *para* to the methoxy substituent in **188**–**190** and at the *meta/para* position in **191**–**193**.



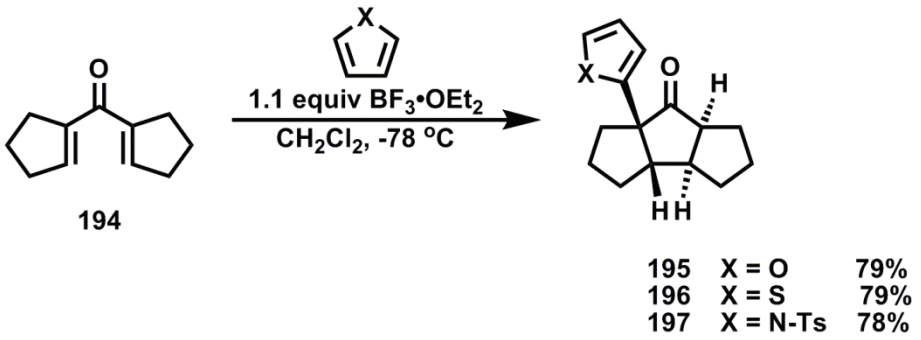

**182** $R_1$ = Me, $R_2$ = H, X = OMe, Y = H
**183** $R_1$ = Et, $R_2$ = Me, X = OMe, Y = H
**184** $R_1$, $R_2$ = $(CH_2)_4$, X = OMe, Y = H
**185** $R_1$ = Me, $R_2$ = H, X, Y = $OCH_2O$
**186** $R_1$ = Et, $R_2$ = Me, X, Y = $OCH_2O$
**187** $R_1$, $R_2$ = $(CH_2)_4$, X, Y = $OCH_2O$

**188** $R_1$ = Me, $R_2$ = H, X = OMe, Y = H
**189** $R_1$ = Et, $R_2$ = Me, X = OMe, Y = H
**190** $R_1$, $R_2$ = $(CH_2)_4$, X = OMe, Y = H
**191** $R_1$ = Me, $R_2$ = H, X, Y = $OCH_2$
**192** $R_1$ = Et, $R_2$ = Me, X, Y = $OCH_2$
**193** $R_1$, $R_2$ = $(CH_2)_4$, X, Y = $OCH_2$

**Scheme 4.1.8:** $TiCl_4$-mediated intramolecular trapping of the oxyallyl cation of **182–187** with pendant electron-rich arenes

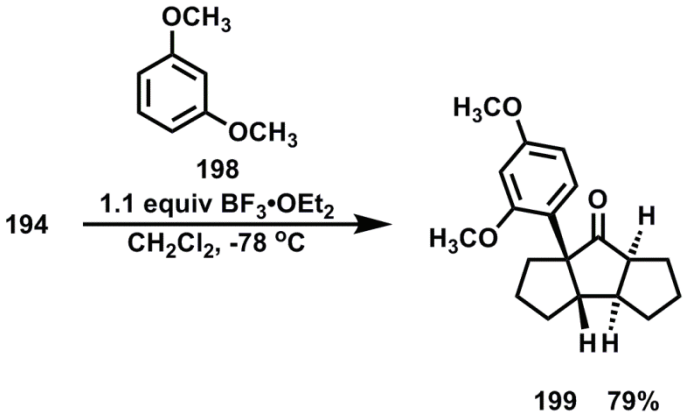
Since these initial studies, West and co-workers have demonstrated that the oxyallyl cationic intermediates of divinyl ketones can be intercepted both intramolecularly and intermolecularly by a range of nucleophiles including dienes by cycloaddition,[14] halides,[15] hydride,[16] and alkyl groups.[17]

When proton elimination from the oxyallyl cation was sufficiently inhibited, West and co-workers[18] discovered that it was possible to intercept oxyallyl cations intermolecularly by electron-rich arenes, so long as the nucleophile was present in a large excess. In the case of the dicyclopentenyl ketone **194**, Nazarov cyclization would give rise to a fused tricyclic oxyallyl cation, whose elimination might be sterically hindered. Compound **194** was subjected to $BF_3$•$OEt_2$ in the presence of a series of heterocycles (**Scheme 4.1.9**). In each case, the product was consistent with Friedel-Crafts alkylation of the oxyallyl cation generated by Nazarov cyclization.




**Scheme 4.1.9:** Intermolecular interception of the oxyallyl cationic intermediate of **194** with heterocycles, resulting in the formation of **195–197**

For compounds **195–197**, the heterocycles were substituted exclusively at the 2-positions in good yield. When the reaction was carried out in the presence of 1,3-dimethoxybenzene **198**, the authors again observed a single product **199** consistent with nucleophilic attack of the Nazarov intermediate (**Scheme 4.1.10**). For compound **199**, substitution on the aromatic ring occurred at the position *ortho*/*para* to the methoxy substituents.



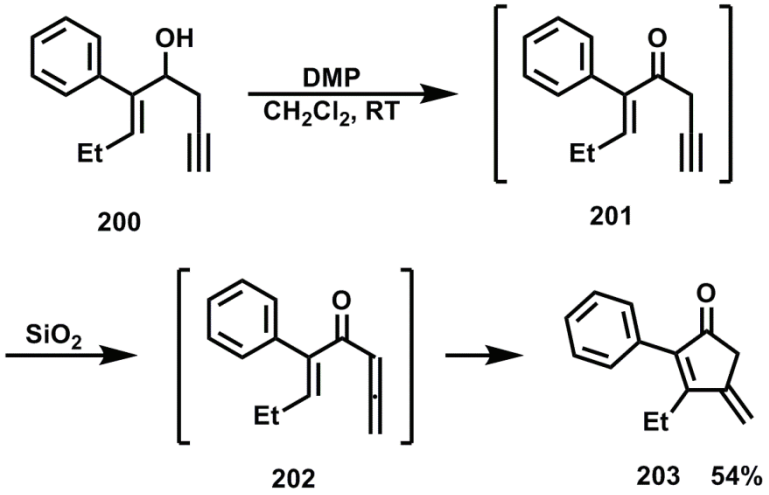

**Scheme 4.1.10:** Intermolecular interception of the oxyallyl cationic intermediate of **194** with **198**, resulting in the formation of **199**

This result was particularly surprising as the authors determined that an electron-rich heterocycle was not necessary to trap the oxyallyl cation. It was determined,

however, that multiple electron-donating substituents on the arene were required as anisole failed to undergo reaction.

From these results, it was apparent that preorganization of the oxyallyl cation and the nucleophile by way of a carbon tether was not necessary for trapping to occur.

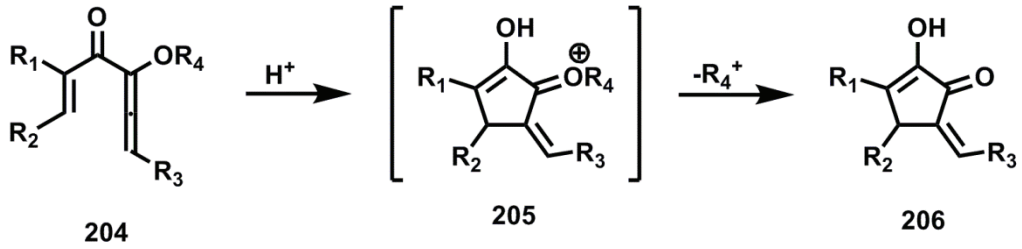
Substrates containing an allenyl moiety have been shown to be particularly active toward Nazarov cyclization. This high reactivity was first demonstrated by Hashmi and co-workers[19] during their attempted synthesis of allenyl vinyl ketones such as **202** (**Scheme 4.1.11**). Oxidation of the homopropargyl alcohol **200** with DMP afforded the propargyl ketone **201**. Subsequent purification on silica gel was expected to incite isomerization to the target **202**. Instead, chromatography resulted in the exclusive formation of the dienone **203**, which was believed to have originated from the Nazarov cyclization of **202**, generated *in situ*.




**Scheme 4.1.11:** Preparation of allenyl vinyl ketone **202** which, upon purification, afforded the Nazarov-cyclized product **203**

Tius[5e] reported that allenyl vinyl ketones of the form **204** underwent Nazarov cyclization in the presence of a protic acid to generate oxyallyl cations **205** (**Scheme**

**4.1.12**). Subsequent loss of stabilized carbocations $R_4^+$ resulted in the formation of the corresponding 2-hydroxycyclopentenones **206**.

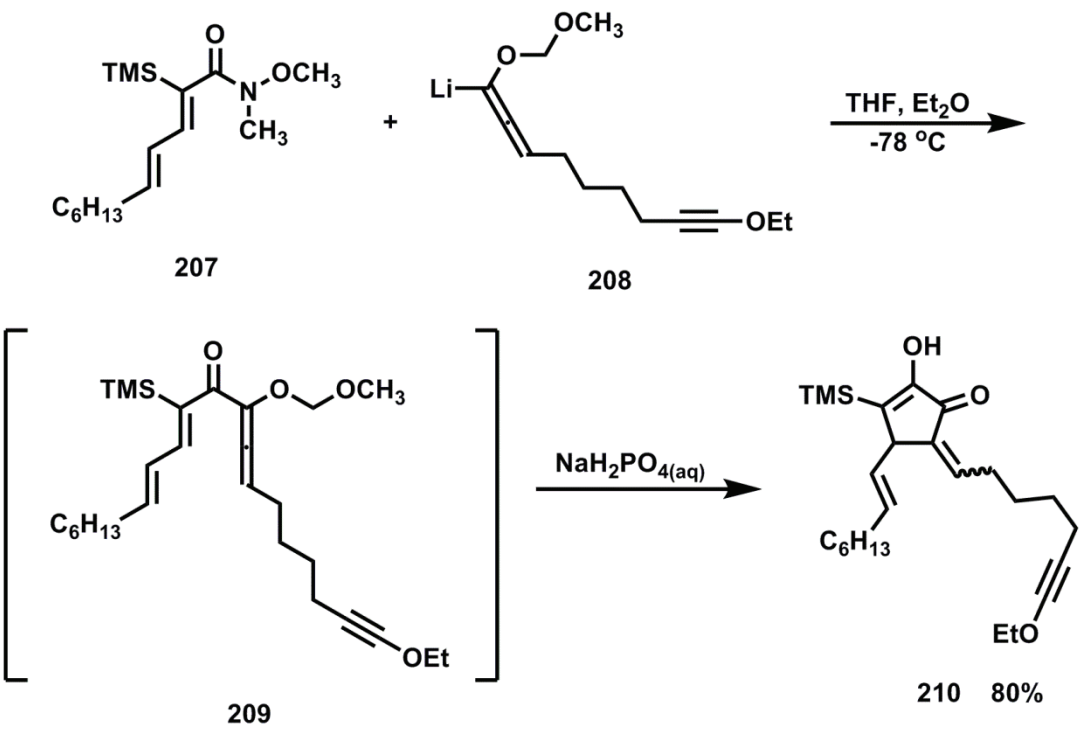



**204** **205** **206**

**$R_1$, $R_2$, $R_3$ = alkyl**
**$R_4$ = $CH_2OMe$, $CH_2CH_2OEt$, $CH_2SCH_3$, 2-THP**

**Scheme 4.1.12:** Acid mediated Nazarov cyclization of allenyl vinyl ketones **204**, giving rise to 2-hydroxycyclopentenones **206**

The reaction has functioned as a key step toward the synthesis of natural products such as the prostaglandin analogue **210** (**Scheme 4.1.13**). Reaction of the Weinreb amide **207** with the lithioallene **208** gave the allenyl vinyl ketone **209** which was treated directly with monosodium phosphate to afford the product **210**. This represents a Nazarov cyclization carried out under mild reaction conditions. The steric implications of an allene substituent conrotating into the plane of the molecule were evident with the product being isolated in an *E*/*Z* ratio of 1:6.




**Scheme 4.1.13:** Synthesis of the prostaglandin analogue **210** *via* the Nazarov cyclization of **209**, generated *in situ*

The increase in reactivity of allenyl vinyl ketones over divinyl ketones toward Nazarov cyclization is believed to be a result of two primary factors. First, the lack of β-substituent interactions in allenyl vinyl ketones results in an increase in the population of the s-*trans*/s-*trans* conformation (**Figure 4.1.4**). The less sterically encumbered allenyl moiety facilitates the approach of β-carbons in order for electrocyclization to occur.[20]

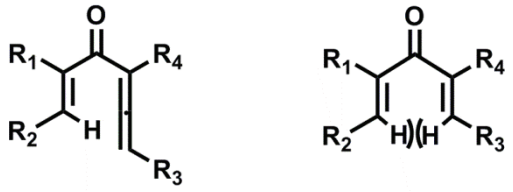



**Figure 4.1.4:** Absence of steric repulsions of β-substituents in allenyl vinyl ketones

In addition, while oxyallyl cations of divinyl ketones are stabilized by two resonance structures, those of allenyl vinyl ketones have an added resonance contributor (**Figure 4.1.5**), resulting in an increased lifetime of these species. Furthermore, the normal elimination pathway is thought to be disfavored, as this would result in the formation of a high-energy fulvene. This combination results in an increased lifetime of the oxyallyl cation, thereby promoting the pathway of nucleophilic attack.

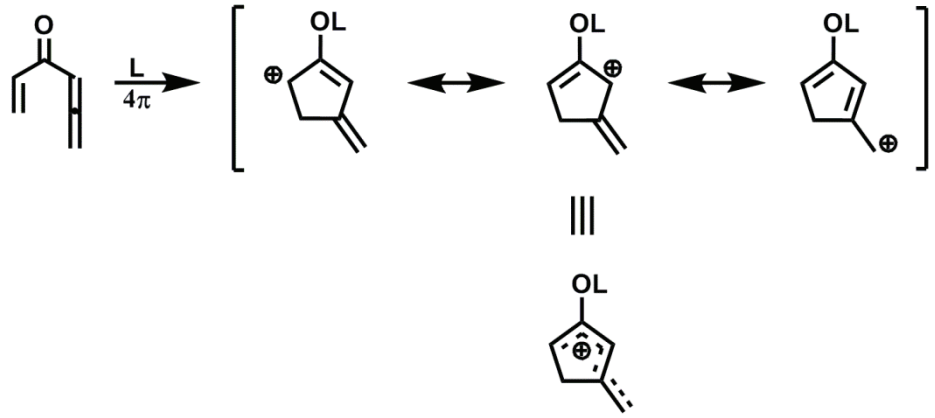



**Figure 4.1.5:** Resonance stabilization of the oxyallyl cationic intermediate of allenyl vinyl ketones

A joint experimental and computational study by Burnell and co-workers[21] into the regioselectivity of the interrupted Nazarov cyclization of allenyl vinyl ketones determined that for substrates of the form **211**, trapping occurred primarily at position *a* as a result of an electronic bias (**Figure 4.1.6**). For sterically encumbered nucleophiles, the least hindered position *c* was the preferred trapping site. No significant trapping was observed at position *b*, regardless of substitution. It was, however, concluded that alkyl substitution at this position was essential in circumventing unwanted side reactions of the allene.

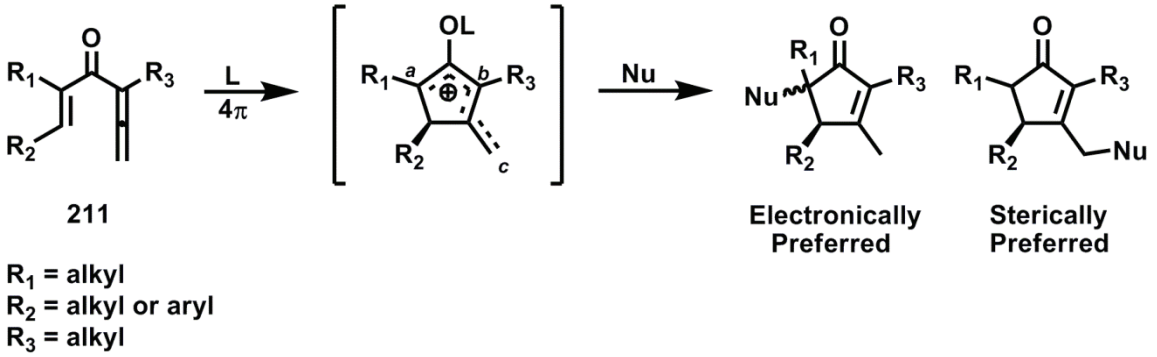
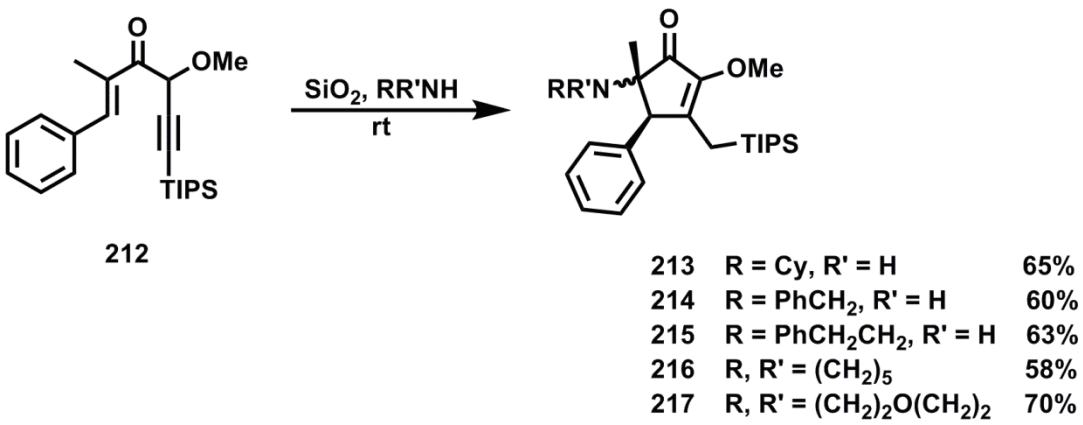



**Figure 4.1.6:** Positions for nucleophilic trapping by nucleophiles with allenyl vinyl ketones of type **211**

In 2005, Dhoro and Tius[22] reported the first interrupted Nazarov cyclization of an allenyl vinyl ketone with amines. Products **213**–**217** represented the first known formation of a carbon-nitrogen bond *via* the interrupted pathway (**Scheme 4.1.14**). The authors observed that the competitive elimination pathway could be minimized if the reactions were carried out under solvent-free conditions. Furthermore, while Nazarov reactions in the presence of sterically encumbered tertiary amines underwent elimination preferentially, primary and secondary amines were sufficiently nucleophilic to trapping the oxyallyl cation. In each case, trapping occurred on the face of the oxylallyl cation opposite the adjacent phenyl substituent.




212

| | | |
|---|---|---|
| 213 | R = Cy, R' = H | 65% |
| 214 | R = $PhCH_2$, R' = H | 60% |
| 215 | R = $PhCH_2CH_2$, R' = H | 63% |
| 216 | R, R' = $(CH_2)_5$ | 58% |
| 217 | R, R' = $(CH_2)_2O(CH_2)_2$ | 70% |

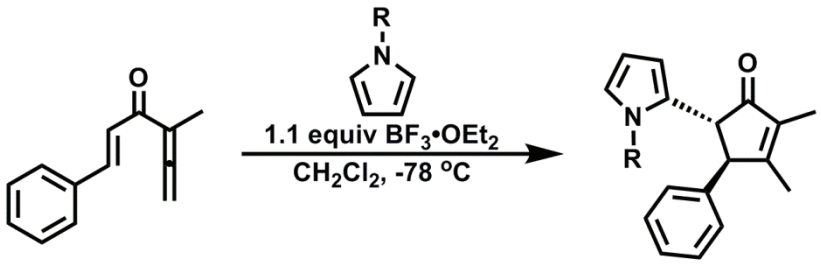
**Scheme 4.1.14:** Interrupted Nazarov cyclization of **212** with amines, resulting in compounds **213-217**

When the reaction was carried out in the presence of aromatic amines, the result was a mixture of products resulting from nucleophilic attack by nitrogen as well as by the aromatic rings through Friedel-Crafts alkylation. Trapping with indoles by this method was later shown to be successful; however, the lower basicities of indoles required reaction in acetonitrile to promote isomerization to the allenyl vinyl ketone prior to cyclization.[23]

Burnell and co-workers have demonstrated the interception Nazarov reactions of allenyl vinyl ketones such as **218** by numerous nucleophiles, including dienes[24] and halides.[25] Furthermore, nucleophilic attack by trifluoroacetate, followed by hydrolysis of the resultant ester during chromatography, was found to be an efficient manner to install a hydroxyl group at position *a*.[26]

Following the successful trapping of **212** with indoles by Dhoro and Tius,[22] Burnell and coworkers[27] investigated the trapping abilities of nitrogen-containing heterocycles on less sterically encumbered allenyl vinyl ketones, such as **218** (**Scheme 4.1.15**). The authors observed modest trapping with *N*-substituted pyrroles, resulting from

competitive Michael addition to the allenyl carbon atom. Trapping occurred primarily at position *a* for *N*-alkylated, arylated, and silylated pyrroles **219**–**224**.

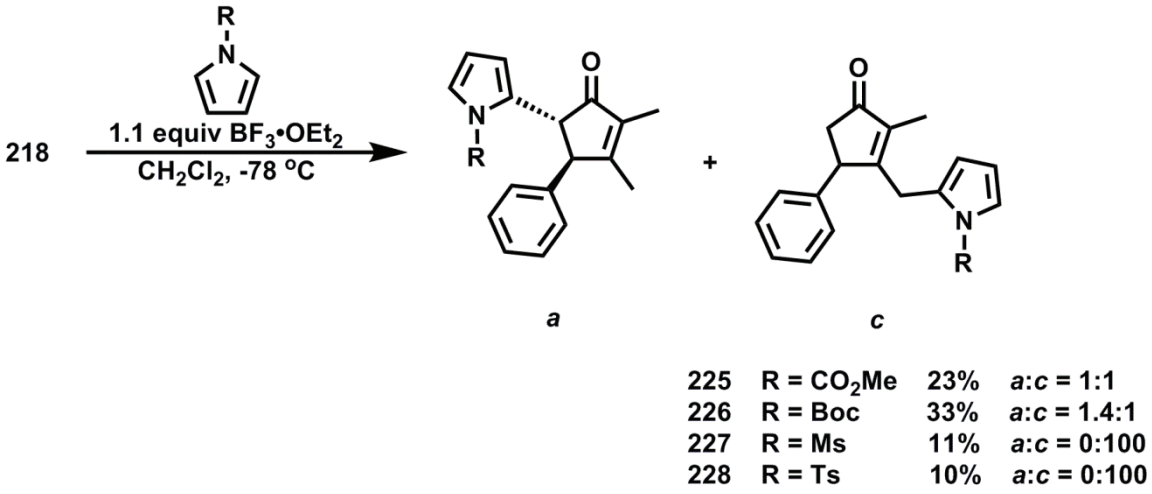



**218**

| | | |
|---|---|---|
| **219** | **R = H** | **54%** |
| **220** | **R = Me** | **32%** |
| **221** | **R = Bn** | **50%** |
| **222** | **R = Ph** | **67%** |
| **223** | **R = $CH_2OCH_3$** | **41%** |
| **224** | **R = TIPS** | **31%** |

**Scheme 4.1.15:** Interrupted Nazarov cyclization of **218** with *N*-alkylated, arylated, and silylated pyrroles

Substitution of the pyrrole with electron-withdrawing groups served to minimize the side reaction. In these cases, trapping regioselectivity shifted toward position *c*, with **227** and **228** resulting in exclusive trapping at position *c* (**Scheme 4.1.16**). In all cases, however, the overall yields were reduced significantly in comparison to those for **219**–**224**.




**Scheme 4.1.16:** Interrupted Nazarov cyclization of **218** with electron withdrawing group-substituted pyrroles

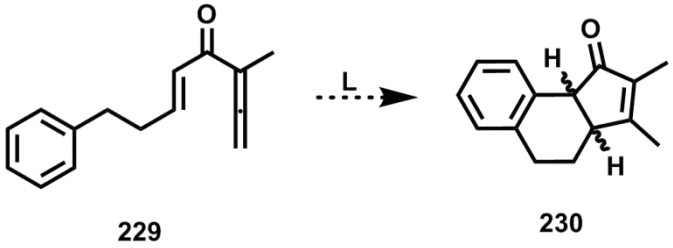
Reaction of **218** in the presence of indoles gave rise to significantly higher yields of trapped products. Regioselectivity of the trapping was less pronounced than in the case of pyrroles, and steadily decreased with increased substitution of the allenyl vinyl ketone as well as the indole. These results supported the earlier computational studies that suggested position *a* was the electronically preferred trapping site, while position *c* was favored in the case of sterically encumbered heterocycles.

While it has been shown that allenyl vinyl ketones are good substrates for interrupted Nazarov cyclization with a range of nucleophiles, few examples of trapping by non-heterocyclic arenes have been reported in the literature. In particular, no examples of intramolecular trapping of allenyl vinyl ketones *en route* to complex polycyclic molecules, analogous to the studies by West and coworkers, had been disclosed.

## 4.2 Results and Discussion

West and co-workers[13] had demonstrated the ability of divinyl ketones **182-187**, bearing pendant aryl moieties, to undergo tandem Nazarov cyclization-intramolecular Friedel-Crafts alkylation to generate tricyclic products **188-193**. However, the authors noted that the unsubstituted phenyl group in **180** was not sufficiently activated to undergo trapping at a rate that was competitive with the lifetime of the oxyallyl cation. Since the oxyallyl cations stemming from allenyl vinyl ketones should be more stable than those from divinyl ketones, it was proposed that the lifetime of the reactive intermediate might be sufficient to allow efficient trapping of an unsubstituted pendant phenyl group.

Allenyl vinyl ketone **229** was envisioned as the substrate to fulfill this goal (**Scheme 4.2.1**). The incorporation of a two-carbon tether bearing a terminal phenyl group should effect Friedel-Crafts alkylation of the oxyallyl cationic intermediate following Nazarov cyclization. Successful trapping at the electronically preferred position *a* would ultimately result in tricyclic molecule **230**.

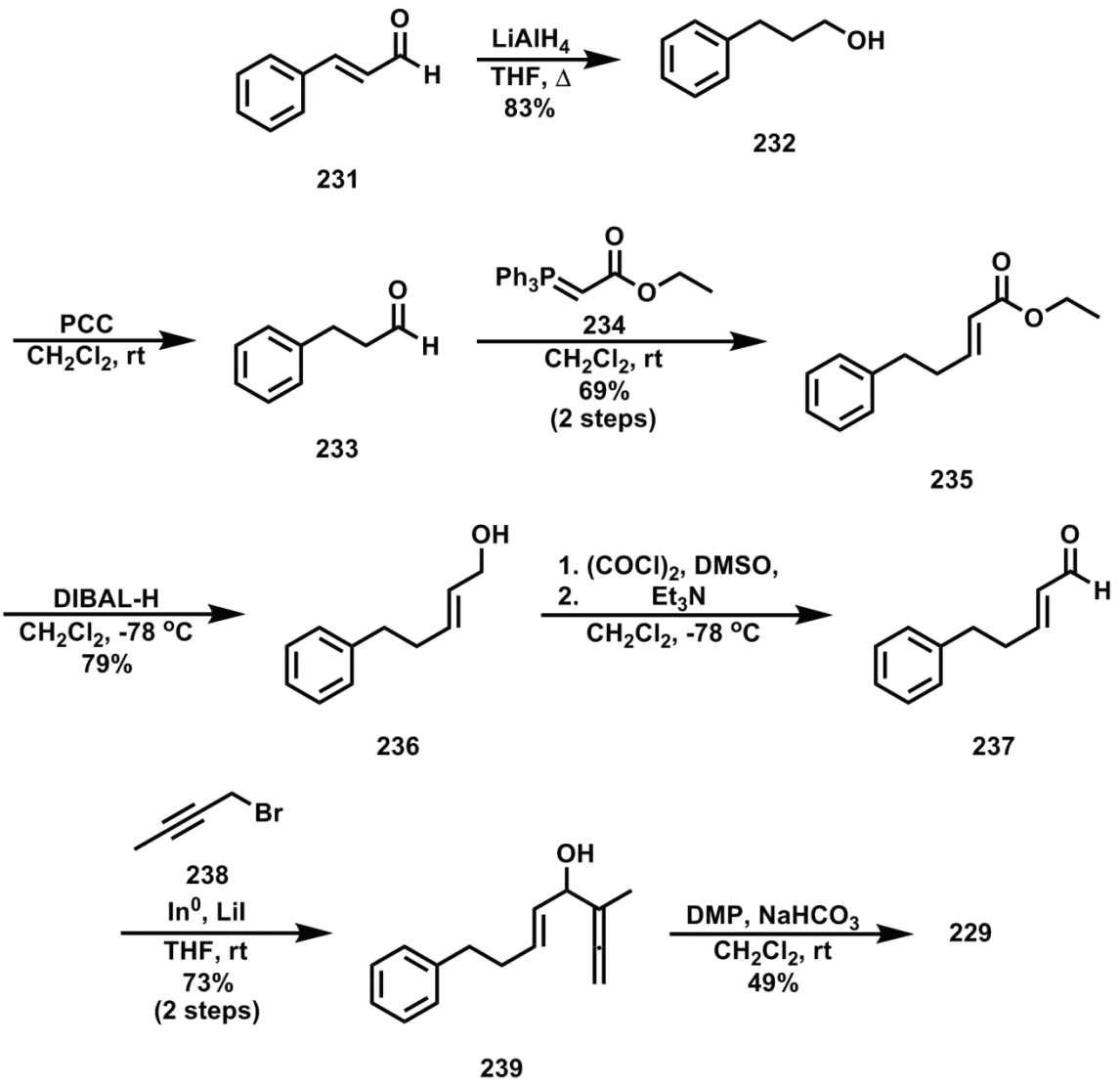



**229** **230**

**Scheme 4.2.1:** Proposed interrupted Nazarov cyclization of **229** by intramolecular Friedel-Crafts alkylation to give the tricyclic product **230**

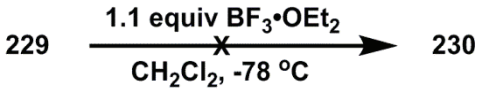
Compound **229** was prepared over several steps from *trans*-cinnamaldehyde **231** (**Scheme 4.2.2**). Initial treatment with $LiAlH_4$[28] resulted in reduction of the carbon-carbon double bond in addition to the aldehyde yielding **232**. The alcohol was then

oxidized to the aldehyde **233** with PCC.[29] Treatment with the Horner-Wadsworth-Emmons stabilized ylide **234**[29] resulted in the α,β-unsaturated ester **235**, which existed in the *E*-geometry exclusively. Attempts to reduce **235** directly to the desired α,β-unsaturated aldehyde **237** in the presence of DIBAL-H were thwarted by over-reduction to the corresponding alcohol **236**.[30] Therefore, the alcohol was re-oxidized under Swern conditions[31] to give aldehyde **237**. Conversion to the allenyl alcohol **239** was then accomplished by an indium-mediated Barbier-type coupling[26] with 1-bromo-2-butyne **238**.[32] Subsequent oxidation by DMP[21] afforded **229**.




**Scheme 4.2.2:** Preparation of allenyl vinyl ketone **229**

The tandem Nazarov, Friedel-Crafts cyclization of **229** was then attempted by subjecting the substrate to 1.1 equivalents of $BF_3$•$OEt_2$ (**Scheme 4.2.3**). Instead of proceeding to the desired tricyclic product **230**, the reaction resulted in degradation of the starting material.

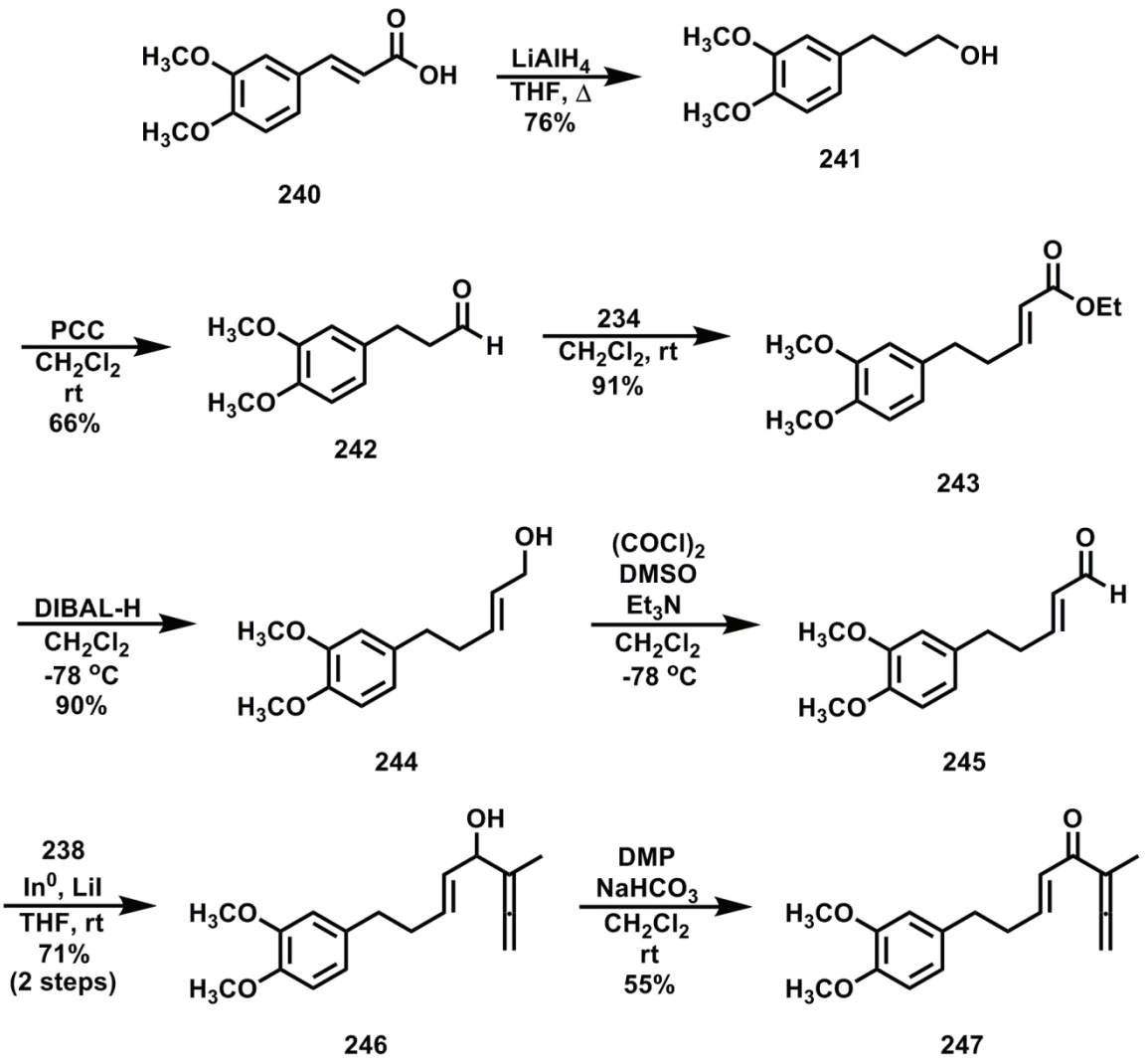



**Scheme 4.2.3:** Unsuccessful tandem Nazarov cyclization-intramolecular Friedel-Crafts alkylation of **229**

As had been observed by West and co-workers, the unsubstituted phenyl group did not appear to be sufficiently electron-rich to promote intramolecular trapping of the oxyallyl cationic intermediate. It was reported,[13] however, that the incorporation of electron-donating methoxy substituents on the aromatic ring dramatically improved the intramolecular trapping of oxyallyl cationic intermediates.

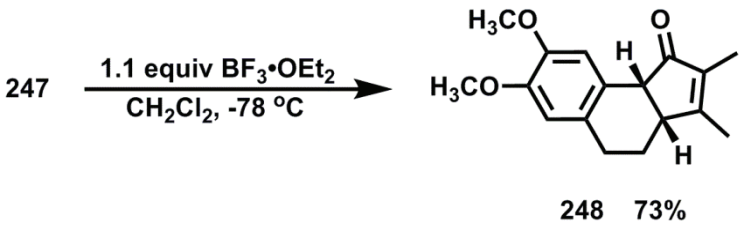
An allenyl vinyl ketone containing a pendant electron-rich arene was therefore envisioned with the goal of carrying out tandem Nazarov cyclization-intramolecular Friedel-Crafts cyclizations in the presence of $BF_3$•$OEt_2$.

Allenyl vinyl ketone **247** was prepared over several steps from *trans*-3,4-dimethoxycinnamic acid **240** (**Scheme 4.2.4**), which was initially reduced to the alcohol **241** in the presence of $LiAlH_4$. Oxidation of the alcohol with PCC afforded the aldehyde **242**. Reaction with ylide **234** resulted in the α,β-unsaturated ester **243**, exclusively in the *E*-geometry. Compound **243** was reduced to the alcohol **244** by DIBAL-H and then re-oxidized to the aldehyde **245** under Swern conditions. Indium-mediated coupling with **238** generated the allenyl alcohol **246**, which was then oxidized by DMP to afford the ketone **247**.




**Scheme 4.2.4:** Preparation of allenyl vinyl ketone **247**

When compound **247** was treated with 1.1 equivalents of $BF_3$•$OEt_2$, the reaction gave rise to the tricyclic compound **248** (**Scheme 4.2.5**), the structure of which was consistent with the intramolecular trapping of the oxyallyl cationic intermediate stemming from the Nazarov cyclization of **247**.

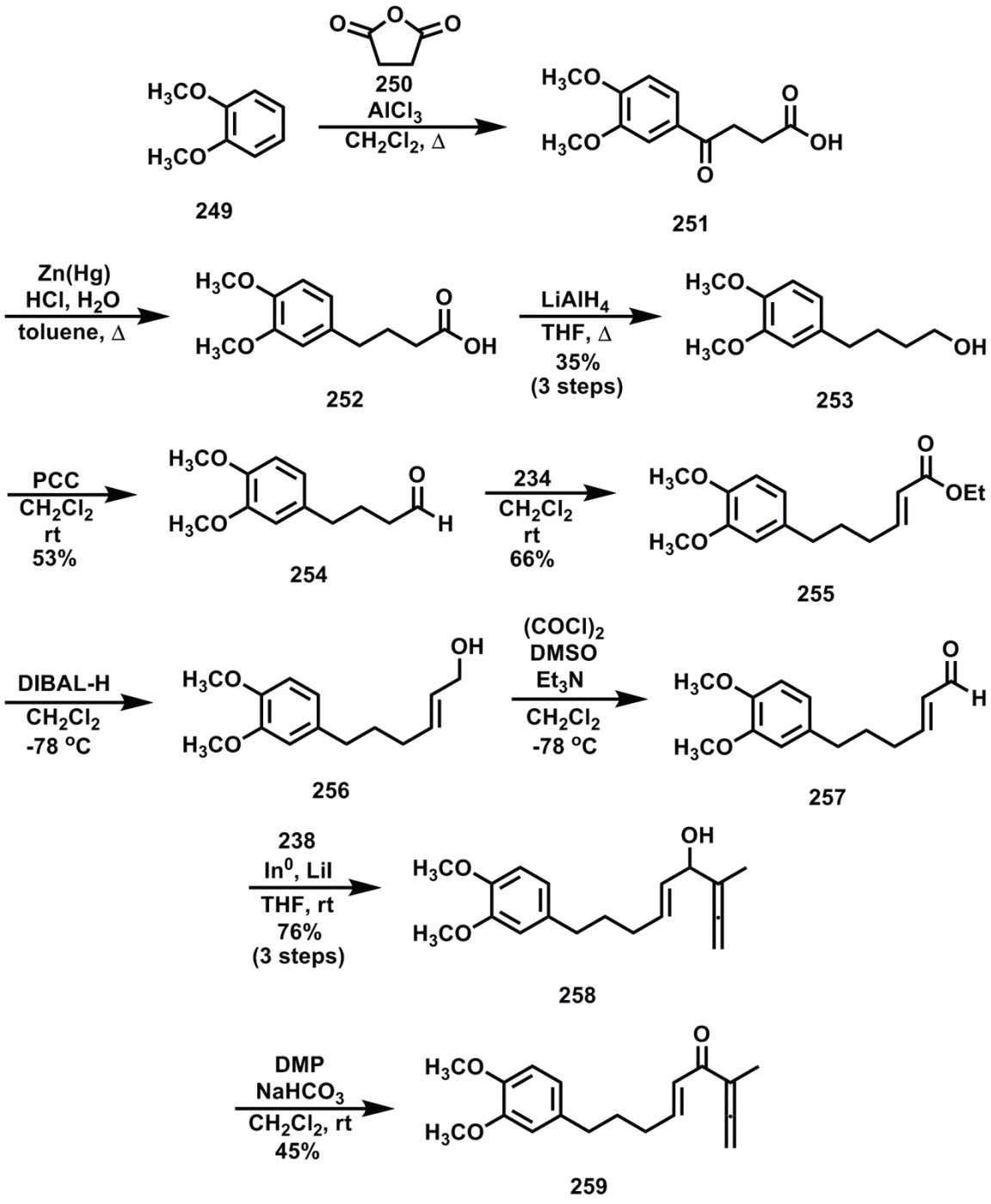



**Scheme 4.2.5:** Interrupted Nazarov cyclization by intramolecular Friedel-Crafts alkylation of **247**, resulting in the tricyclic **248**

Analysis of the product by $^{1}$H NMR indicated that Friedel-Crafts alkylation had occurred, as expected, at position *a*. Trapping had also taken place exclusively at the position *meta*/*para* to the methoxy substituents as evidenced in its $^{1}$H NMR spectrum by the presence of a pair of singlets at 7.20 and 6.55 ppm. The preference for trapping at this position over the position *ortho/meta* to the methoxy substituents was most likely steric in nature. Based on a $^{3}J$ proton coupling constant of 6.4 Hz and nuclear Overhauser enhancement experiments, it appeared that the relative stereochemistry at the ring junction was *cis*.

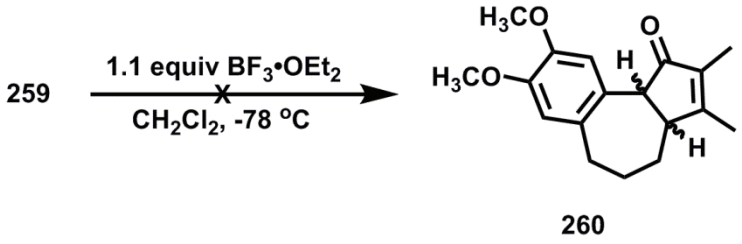
With the successful intramolecular interception of the Nazarov intermediate of **247**, the generality of this methodology was investigated by expanding the tether length to a three-carbon chain. Following the procedure developed for the syntheses of **229** and **247**, the preparation of allenyl vinyl ketone **259** required the initial formation of butanol **253** (**Scheme 4.2.6**). This was accomplished through the Friedel-Crafts acylation of 1,2-dimethoxybenzene **249** with succinic anhydride **250**.[33] This resulted in almost exclusive formation of the mono-acylated product **251**. Clemmensen reduction of the ketone gave rise to the carboxylic acid **252**,[34] which was further reduced to **253** by $LiAlH_4$. Oxidation with PCC afforded aldehyde **254**, which when reacted with ylide **234**, gave the α,β-unsaturated ester **255**, exclusively in the *E*-geometry. DIBAL-H-mediated reduction

yielded the allylic alcohol **256**, which was then oxidized to the aldehyde **257** under Swern conditions. Indium-mediated coupling with **238** generated the allenyl alcohol **258**, which was then oxidized by DMP to afford the allenyl vinyl ketone **259**.




**Scheme 4.2.6:** Preparation of allenyl vinyl ketone **259**

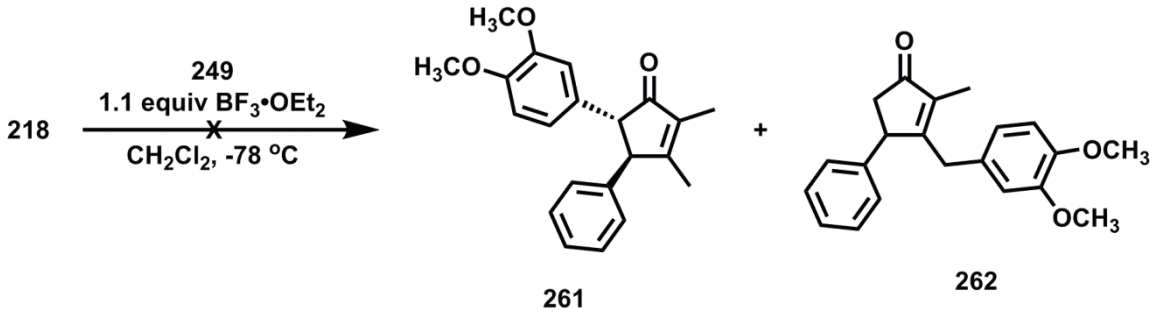
Unfortunately, treatment of **259** with $BF_3$•$OEt_2$ failed to yield any of the desired tricyclic compound **260** (**Scheme 4.2.7**). It was deemed unlikely that a longer tether would obstruct the formation of a seven-membered ring for steric reasons. However, it might be that the degrees of rotational freedom associated with a longer tether may have prevented the electron-rich arene from capturing the oxyallyl cation at a rate that was competitive with the decomposition of the intermediate.




**260**

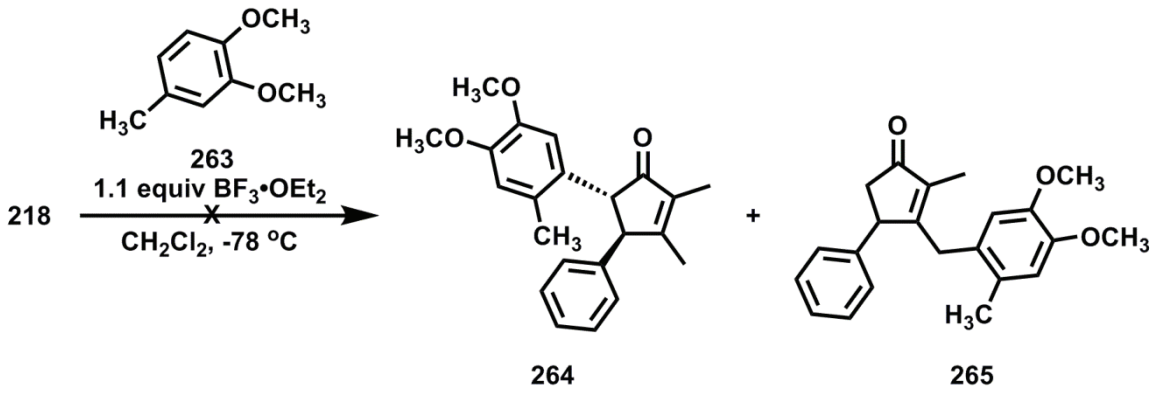
**Scheme 4.2.7:** Unsuccessful tandem Nazarov cyclization-intramolecular Friedel-Crafts alkylation of **259**

If the three-carbon tether did not effectively position the arene in sufficient proximity to the reactive center, the reaction would have been essentially intermolecular in nature. It was therefore anticipated that the intermolecular trapping of the oxyallyl cation with a generic allenyl vinyl ketone **218**[26] with **249** would be unsuccessful. As expected, when **218** was subjected to $BF_3$•$OEt_2$ in the presence of 5 equivalents of **249**, the reaction did not give rise to any significant formation of **261** or **262**. This indicated that the two-carbon tether of **247** was essential in positioning the arene sufficiently close to the reactive center to promote efficient trapping (**Scheme 4.2.8**).




**Scheme 4.2.8:** Unsuccessful interrupted Nazarov cyclization of **218** with **249**

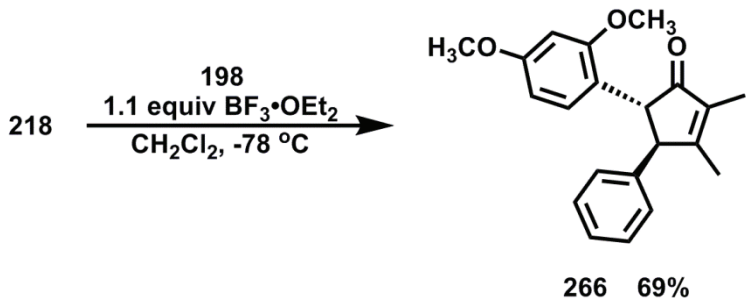
It was questioned whether the role of the tether was to pre-organize the substrate prior to Friedel-Crafts alkylation or simply to serve as an additional electron-donating group on the aromatic ring. The latter idea was deemed unlikely as 3,4-dimethoxytoluene **263**, mimicking the electron richness of the pendant arene of **247**, failed to undergo intermolecular trapping in the presence of **218** and $BF_3$•$OEt_2$ (**Scheme 4.2.9**).




**Scheme 4.2.9:** Unsuccessful interrupted Nazarov cyclization of **218** with **263**

As was previously demonstrated by West and co-workers,[18] **198** was sufficiently activated to undergo intermolecular trapping of an oxyallyl cation originating from a divinyl ketone. Allenyl vinyl ketone **218** was treated with $BF_3$•$OEt_2$ in the presence of **198** (**Scheme 4.2.10**). The reaction resulted in the successful trapping of the oxyallyl cationic intermediate exclusively at position *a* to give **266** with the arene being alkylated

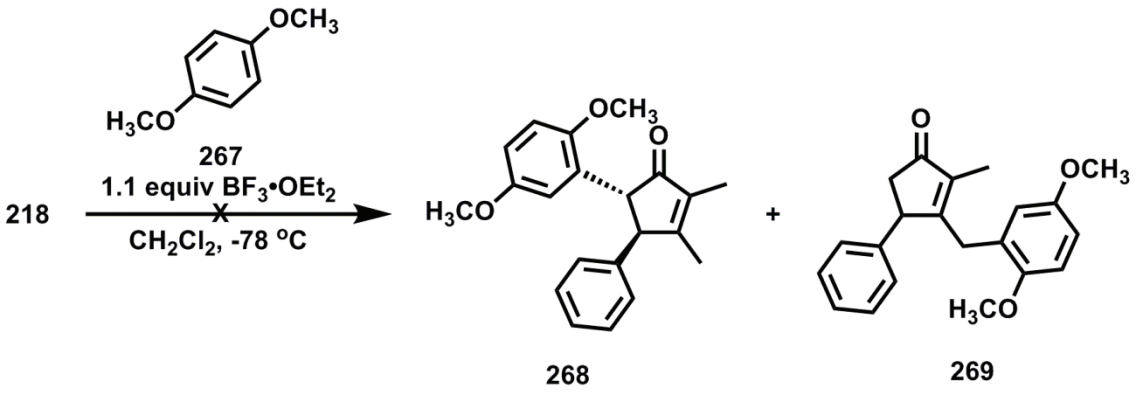
at *ortho/para* to the methoxy substituents. The improved reactivity of **198** over **249** was not surprising since the position of trapping was activated through resonance by both methoxy substituents.




**266** **69%**

**Scheme 4.2.10:** Interrupted Nazarov cyclization of **218** with **198**, resulting in **266**

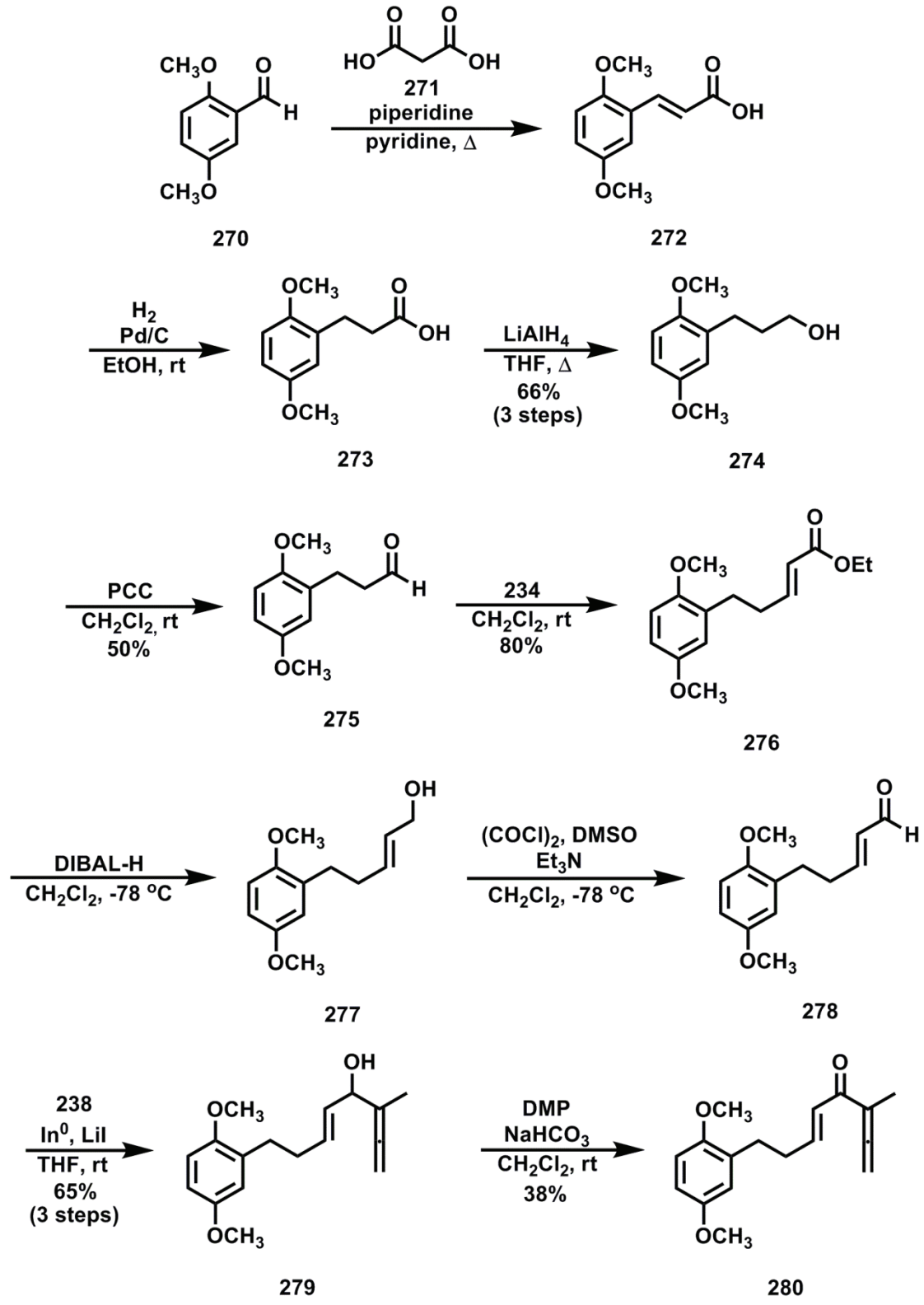
It was anticipated that 1,4-dimethoxybenzene **267** would not be as active as **198** toward Friedel-Crafts alkylation due to the fact that each of the four equivalent positions for attack would be activated through resonance by one methoxy substituent instead of two. Furthermore, trapping would require substitution *ortho* to one of the methoxy substituents, which might be sterically unfavorable. Nazarov cyclization of **218** in the presence of **267** did not give rise to any significant formation **268** or **269** (**Scheme 4.2.11**).




**268** **269**

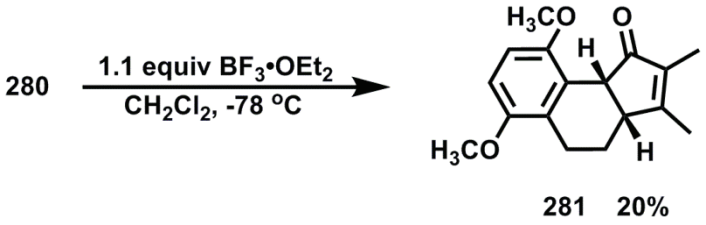
**Scheme 4.2.11:** Unsuccessful interrupted Nazarov cyclization of **218** with **267**

The reactivity of **249** was enhanced significantly when it was joined to the allenyl vinyl ketone with a two-carbon tether. Thus, it was suggested that the trapping of a 1,4-dimethoxy-substituted arene might be possible if carried out intramolecularly. Allenyl vinyl ketone **280** was prepared over several steps from 2,5-dimethoxybenzaldehyde **270** (**Scheme 4.2.12**). Reaction with malonic acid **271** in the presence of piperidine gave rise to the cinnamic acid derivative **272**.[35] Catalytic hydrogenation resulted in carboxylic acid **273**,[36] which was reduced with $LiAlH_4$ to afford alcohol **274**. Following the standard procedure, **274** was oxidized with PCC, generating the aldehyde **275**. Reaction with **234** gave the *E* isomer of the α,β-unsubstituted ester **276**, which was then reduced to the alcohol **277** with DIBAL-H. Swern oxidation yielded aldehyde **278**, which was converted to the allenyl alcohol **279** *via* indium-mediated coupling with **238**. Finally, DMP-mediated oxidation afforded **280**.




**Scheme 4.2.12:** Preparation of allenyl vinyl ketone **280**

When compound **280** was subjected to 1.1 equivalents of $BF_3$•$OEt_2$, the reaction gave rise to **281**, albeit it significantly lower yield than in the case of allenyl vinyl ketone **247** (**Scheme 4.1.13**). Once again, $^1$H NMR data indicated that intramolecular trapping occurred exclusively at position *a*. Furthermore, it was observed that trapping had also taken place exclusively *ortho* to the two-carbon tether as evidenced by the presence of a pair of doublets at 6.77 and 6.68 ppm. A *cis* relative stereochemistry was again inferred at the ring junction, based on a $^3J$ proton coupling constant of 6.6 Hz.



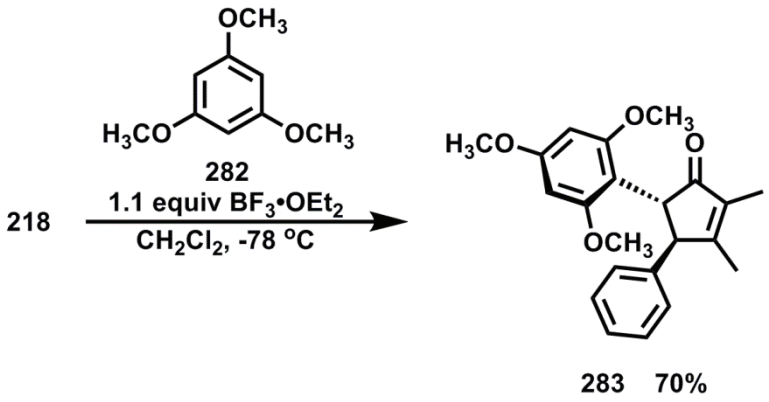

**Scheme 4.2.13:** Interrupted Nazarov cyclization by intramolecular Friedel-Crafts alkylation of **280**, resulting in the tricyclic **281**

Despite the low conversion to product, it was again apparent that the presence of a two-carbon tether promoted intramolecular trapping of an oxyallyl cationic intermediate while the analogous intermolecular reaction did not take place.

With the successful intermolecular interception of the oxyallyl cationic intermediate of **218** with **198**, it became obvious that improving the intermolecular trapping of **218** with arenes would require significant electron-donation.

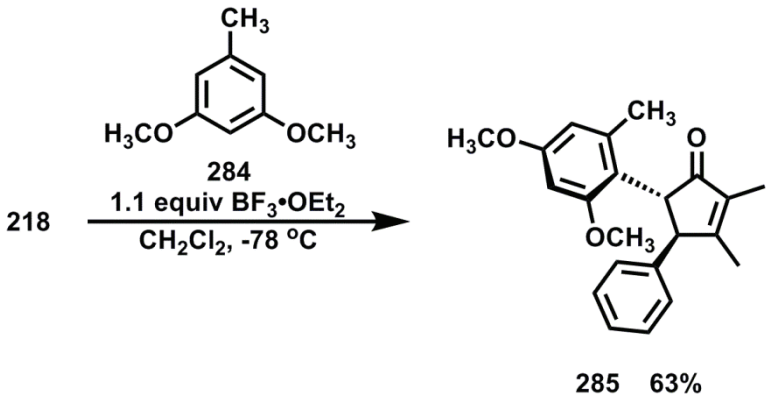
Reaction of **218** with $BF_3$•$OEt_2$ in the presence of 1,3,5-trimethoxybenzene **282** resulted in successful trapping of the oxyallyl cationic intermediate in an improved yield over the reaction with **198** (**Scheme 4.2.14**). This was surprising since the reaction required the trapping of the oxyallyl cation *ortho* to two methoxy substituents. Furthermore, $^1$H NMR data indicated that trapping had taken place at the sterically less

favorable position *a*. The steric demand of substitution at this position was evidenced by the appearance of three distinct chemical shifts pertaining to the methoxy substituents. The data were consistent with hindered rotation about the newly formed C-Nu bond in **283**. From variable temperature NMR analysis,[37] the barrier to rotation was estimated at 9.4 kcal/mol.



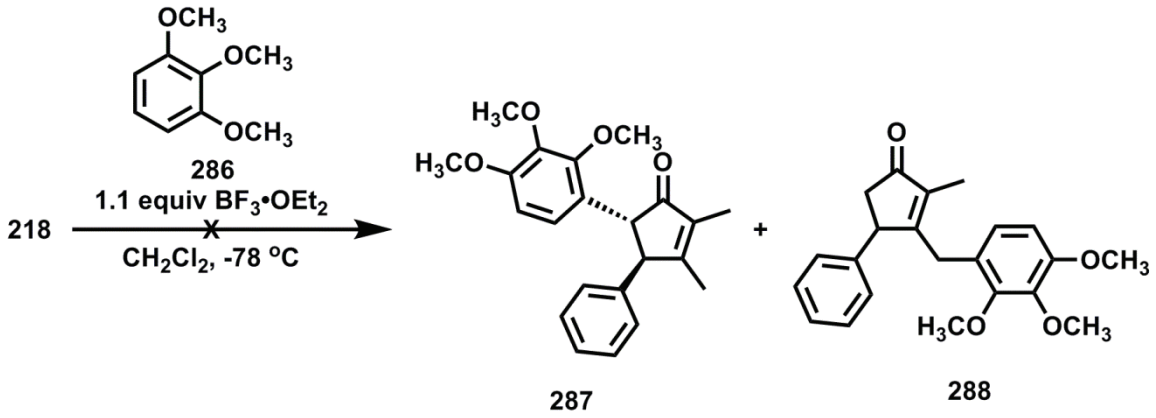

**Scheme 4.2.14:** Interrupted Nazarov cyclization of **218** with **282**, resulting in **283**

When the reaction was repeated in the presence of 3,5-dimethoxytoluene **284**, trapping occurred exclusively at position *a*, with the arene substituted *ortho* to the methyl substituent (**Scheme 4.2.15**). Analysis of the $^{1}$H NMR spectrum indicated that hindered rotation about the carbon-Nu bond gave rise to **285** as the major atropisomer in a product ratio >10:1. The barrier to rotation could not be approximated by variable temperature NMR due to overlapping of chemical shifts and a coalescence temperature that exceeded the high-temperature limit of the spectrometer. The orientation of the nucleophile in **285** could not be ascertained by nuclear Overhauser enhancement experiments. However, the structure was assigned tentatively such that the more sterically encumbered methyl substituent was oriented away from the hydrogen atom at the β-position.



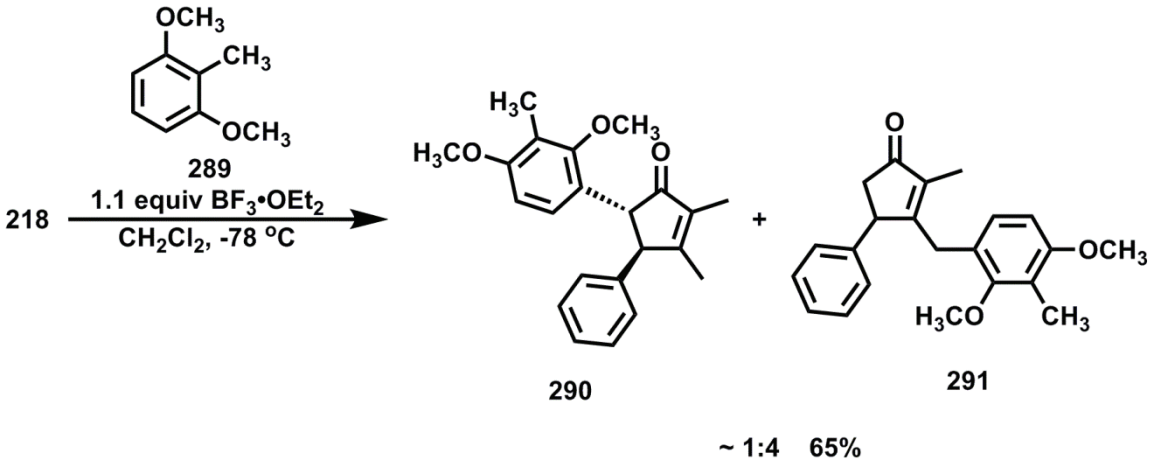

**Scheme 4.2.15:** Interrupted Nazarov cyclization of **218** with **284**, resulting in atropisomer **285**

1,2,3-Trimethoxybenzene **286** was anticipated to exhibit similar reactivity to compounds **198** and **282**. However, reaction of **218** with **286** resulted in no significant formation of **287** or **288** (**Scheme 4.1.16**). These results were unexpected as, unlike the case of **282**, trapping with **286** required substitution *ortho* to only one methoxy substituent, not two. It was hypothesized that, in the case of **282**, the methoxy substituents could orient themselves away from the incoming electrophile. On the other hand, the presence of the central methoxy substituent in compound **286** might force the adjacent methoxy substituents to orient themselves toward the opposite face of the arene. The positioning of methoxy substituents on both faces of the arene could result in a more sterically encumbered nucleophile, resulting in less efficient trapping.




**Scheme 4.2.16:** Unsuccessful interrupted Nazarov cyclization of **218** with **286**

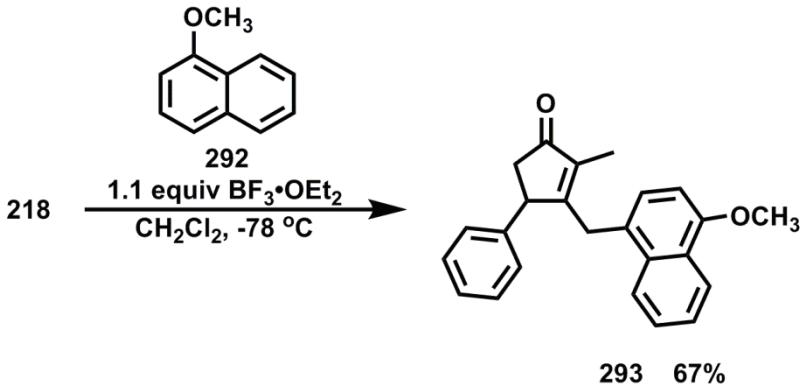
On the other hand, it is possible that the methoxy substituents in 2,6-dimethoxytoluene **289** might possess greater flexibility in the absence of a central methoxy group. This could result in one face of the arene being more accessible by the electrophile in order for trapping to occur. Compound **218** was thus subjected to $BF_3$•$OEt_2$ in the presence of **289** (**Scheme 4.2.17**). Surprisingly, trapping efficiency was enhanced significantly, with a product yield comparable to **198** and **282**. Unlike the previous case, however, trapping appeared to occur preferentially at position *c*.




**Scheme 4.2.17:** Interrupted Nazarov cyclization of **218** with **289**, resulting in **290** and **291**

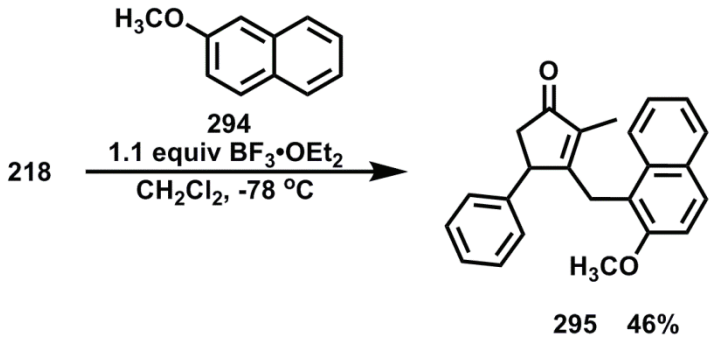
While the interception of Nazarov intermediates with indoles has been successful,[25,27] no examples of trapping by larger non-heterocyclic arenes has been reported. Naphthalenes are particularly well suited for Friedel-Crafts alkylation by virtue of additional resonance stabilization of the carbocationic intermediate provided by the additional aromatic ring.

Compound **218** was treated with $BF_3$•$OEt_2$ in the presence of 1-methoxynaphthalene **292** (**Scheme 4.2.18**). The resultant product **293** was obtained in a yield comparable to activated benzenes, and its structure was consistent with Friedel-Crafts alkylation *para* to the methoxy substituent. Trapping by the naphthalene was observed to occur exclusively at position *c*.



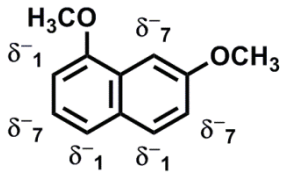

**Scheme 4.2.18:** Interrupted Nazarov cyclization of **218** with **292**, resulting in **293**

The reaction was repeated in the presence of the 2-methoxynaphthalene **294** (**Scheme 4.2.19**). Again the reaction proceeded with trapping occurring exclusively at the sterically preferred site to give **295**. This time, however, the product yield was considerably lower, owing to the most nucleophilic site being *ortho* to the methoxy substituent at the *peri*-position.




**Scheme 4.2.19:** Interrupted Nazarov cyclization of **218** with **294**, resulting in **295**

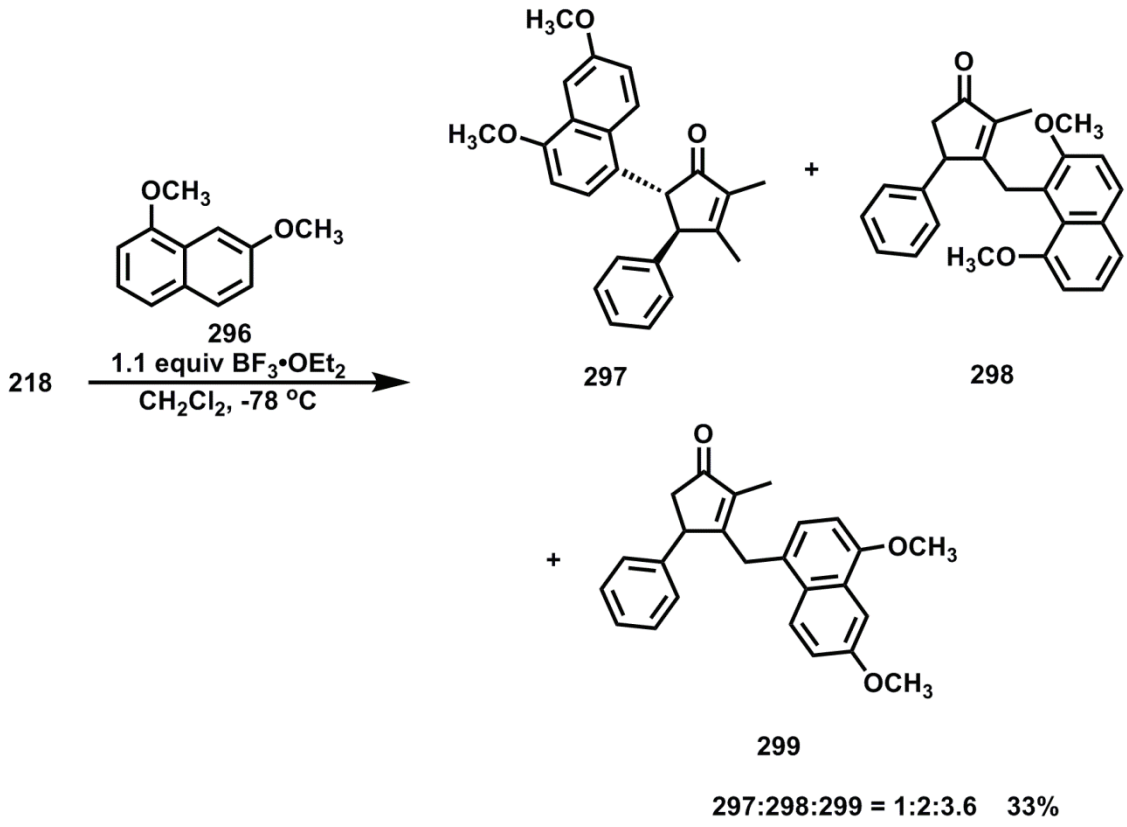
1,7-Dimethoxynaphthalene **296** is substituted such that each potential trapping site is activated through resonance by a single substituent (**Figure 4.2.1**).




**296**

**Figure 4.2.1:** Activation of potential trapping sites of **296** through resonance from methoxy substituents at the 1- and 7-positions

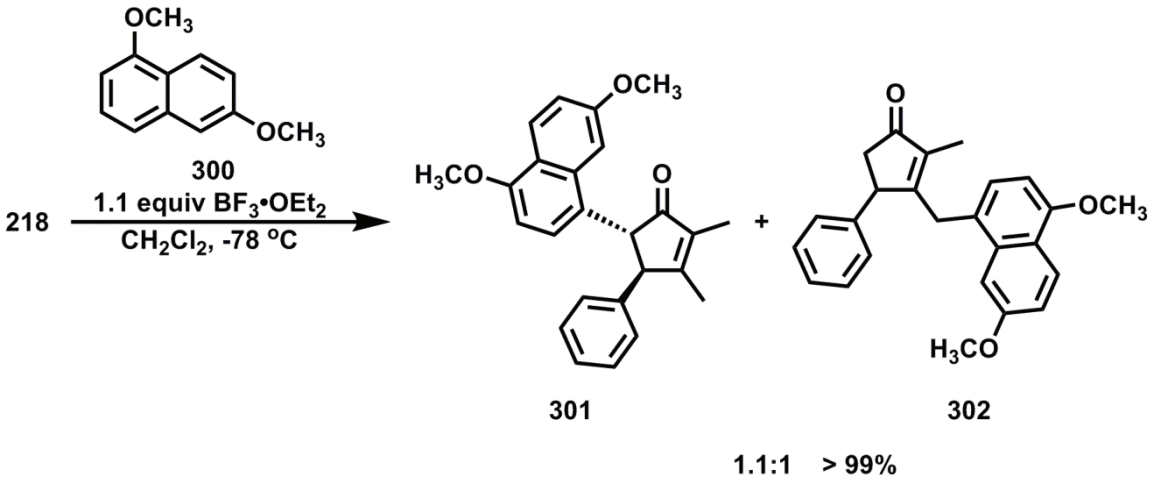
By carrying out Nazarov cyclization in the presence of **296**, one could potentially determine the relative degrees to which each methoxy substituent directs Friedel-Crafts alkylation. As such, **218** was subjected to $BF_3$•$OEt_2$ in the presence of **296** (**Scheme 4.2.20**). This resulted in a mixture of products **297**, **298**, and **299**, albeit in an overall modest yield. As expected, trapping of the oxyallyl cation occurred primarily at position *c*. However, it was evident that the majority of the product stemmed from Friedel-Crafts alkylation at the 4-position. This result indicated that the methoxy substituent at the 1-position was significantly more effective in the activation of **296** toward the trapping of the oxyallyl cation.




**Scheme 4.2.20:** Interrupted Nazarov cyclization of **218** with **296**, resulting in **297**, **298**, and **299**

From these results, it was apparent that substituted naphthalenes could participate in the trapping of oxyallyl cationic intermediates with fewer activating groups than were required by substituted benzenes. Furthermore, the presence of the second aromatic ring in naphthalenes offers the opportunity for additional activation, without encumbering the nucleophilic center to the same degree as the benzenes. 1,6-Dimethoxynaphthalene **300** is substituted such that each potential trapping site is activated through resonance by both methoxy substituent. This should make **300** an ideal trap for oxyallyl cations. The $BF_3$•$OEt_2$-mediated cyclization of **218** in the presence of **300** gave rise to a roughly equimolar mixture of products **301** and **302** trapped at positions *a* and *c*, respectively, with the naphthalenes undergoing substitution *para* to 1-methoxy substituent (**Scheme**

**4.2.21**). The simultaneous activation of the 4-position by the methoxy substituents was evident by the formation of products in an overall quantitative yield. It is possible that the lack of regioselectivity was a direct result of the high degree of activation of **300**.




**Scheme 4.2.21:** Interrupted Nazarov cyclization of **218** with **300**, resulting in **301** and **302**

## 4.3 Conclusions

The Nazarov reaction intermediates of allenyl vinyl ketones have been shown to be efficiently interrupted both intramolecularly and intermolecularly by electron-rich arenes. Despite the increased resonance stabilization of the oxyallyl cationic intermediate of allenyl vinyl ketones over divinyl ketones, the pendant phenyl substituent of allenyl vinyl ketone **229** was insufficiently activated to undergo efficient intramolecular Friedel-Crafts alkylation to afford the desired product **230**. Substitution of the aromatic ring with electron-donating groups was found to promote intramolecular interception of the oxyallyl cation of **247** in the presence of $BF_3$•$OEt_2$ to give the tricyclic product **248**.

With the successful reaction of **247**, the tether length was expanded from two carbon atoms to three in an effort to generate a tricyclic system **260** containing a seven-membered ring. Allenyl vinyl ketone **259** was prepared and subjected to reaction conditions identical with those of **247**. Rather than proceeding to **260**, the reaction instead gave rise to intractable material. This result suggested that the length of the alkyl tether is critical in positioning the arene in proximity to the oxyallyl cation such that Friedel-Crafts alkylation is competitive with alternative reaction pathways. The added tether length in **259** may result in diminished pre-organization of the arene and oxyallyl cation, rendering the reaction essentially intermolecular. This idea was supported by the fact that **249** and **263** did not undergo trapping of the oxyallyl cation of **218** intermolecularly. While the intermolecular reaction of **218** with **267** was similarly unsuccessful, it was found that trapping was possible when the arene was joined to the allenyl vinyl ketone by a two-carbon tether as **280**.

The intermolecular trapping of the Nazarov intermediate of **218** was found to rely upon significant activation by electron-donating substituents about the arenes. Trapping occurred primarily at the electronically preferred position *a*, while sterically encumbered arenes trapped more readily at the sterically less hindered position *c*. This did not appear to be the case for 1,3,5-trisubstituted arenes **282** and **284**, which reacted with high regioselectivity at position *a*. It was suggested that the alternating substitution pattern in these arenes may have provided the substituents the steric freedom to rotate away from the site of reaction, thereby accommodating the incoming electrophile. The steric encumbrance of the resulting products **283** and **285** was evidenced by hindered

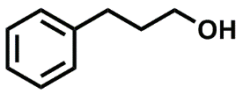
rotation of the arene. In particular, the reaction of **218** with **284** appeared to result in almost exclusive formation of one atropisomer.

## 4.4 Experimental

### General

Dichloromethane was distilled from calcium hydride. THF was distilled from sodium metal. EtOAc and hexanes were distilled. Commercial reagents were used as received. Column chromatography was carried out on a silica gel (230-400 mesh) stationary phase. Melting points were acquired using a Fisher-Johns apparatus and are uncorrected. High-resolution mass spectra were acquired using a Bruker MicroTOF mass spectrometer *via* electrospray ionization. $^{1}$H NMR spectra were acquired at 500 MHz, and $^{13}$C NMR spectra at 125 MHz from $CDCl_3$ sample solutions. Chemical shifts for $^{1}$H NMR are relative to internal standard tetramethylsilane (δ 0.00 ppm). Chemical shifts for $^{13}$C NMR are relative to residual chloroform (δ 77.16 ppm). Two-dimensional COSY, HSQC, and HMBC data were acquired to establish chemical structure.

### 3-Phenylpropan-1-ol (232)

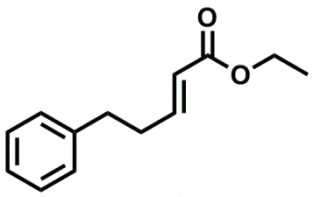



**232**

According to the literature,[28] **231** (10.0 g, 76.0 mmol) was dissolved in THF (750 mL). After the mixture was cooled to 0 $^{o}$C, $LiAlH_4$ (3.45 g, 91.0 mmol) was added slowly, and the mixture was warmed to room temperature before heating to reflux overnight. The

mixture was cooled to room temperature and diluted with $Et_2O$ (200 mL) and then cooled to 0 $^oC$. Water (3.5 mL) was added cautiously, followed by 15% (w/v) aqueous NaOH (3.5 mL), and then additional water (11 mL). The mixture was warmed to room temperature and $MgSO_4$ was added. After stirring 15 min, the solid material was removed by vacuum filtration and the solvent was evaporated under reduced pressure. Column chromatography ($SiO_2$) with 4:1 hexanes/EtOAc afforded **232** (8.58 g, 83%) as a colorless oil. $^1H$ NMR δ: 7.31-7.26 (2H, m), 7.22-7.17 (3H, m), 3.68 (2H, t, $J$ = 6.4 Hz), 2.71 (2H, t, $J$ = 7.7 Hz), 1.93-1.87 (2H, m), 1.36 (1H, br s) ppm; $^{13}C$ NMR δ: 142.0, 128.6, 128.5, 126.0, 62.5, 34.4, 32.2 ppm. These data are in accordance with those found in the literature.[38]

**Ethyl (*E*)-5-phenylpent-2-enoate (235)**

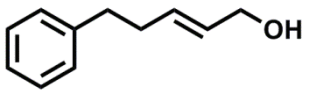


**235**

According to the literature,[29] PCC (15.6 g, 72.4 mmol) was dissolved in $CH_2Cl_2$ (400 mL). After the mixture was cooled to 0 $^oC$, a solution of **232** (6.58 g, 48.3 mmol) in $CH_2Cl_2$ (100 mL) was added dropwise. The mixture was protected from light and warmed to room temperature with stirring overnight. The mixture was filtered through a pad of silica gel and washed with $Et_2O$ (2 x 100 mL). The organic layer was dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure to afford **233** as a colorless oil which was redissolved in $CH_2Cl_2$ (500 mL). Compound **234** (21.5 g, 62.0

mmol) was added and the reaction mixture was stirred at room temperature for 6 h. The solvent was then evaporated under reduced pressure. Column chromatography ($SiO_2$) with 10:1 hexanes/EtOAc afforded **235** (6.74 g, 69%) as a colorless oil. $^1$H NMR δ: 7.31-7.26 (2H, m), 7.22-7.16 (3H, m), 7.00 (1H, dt, *J* = 15.6, 6.7 Hz), 5.84 (1H, dt, *J* = 15.6, 1.6 Hz), 4.17 (2H, q, *J* = 7.0 Hz), 2.77 (2H, t, *J* = 8.2 Hz), 2.52 (2H, apparent q, *J* = 7.6 Hz), 1.28 (3H, t, *J* = 7.1 Hz) ppm; $^{13}$C NMR δ: 166.6, 148.0, 140.8, 128.5, 128.3, 126.2, 121.8, 60.2, 34.3, 33.9, 14.3 ppm. These data are in accordance with those found in the literature.[39]

**(*E*)-5-Phenylpent-2-en-1-ol (236)**

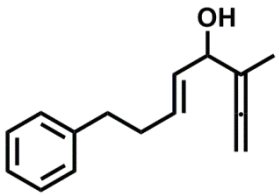



**236**

According to the literature,[30] compound **235** (400 mg, 1.96 mmol) was dissolved in $CH_2Cl_2$ (5.0 mL). After cooling to -78 $^o$C, DIBAL-H (1.0 M in toluene) (2.9 mL, 2.9 mmol) was added dropwise and the mixture was warmed to room temperature over 6 h. MeOH (1.0 mL) was added dropwise, followed by saturated aqueous sodium potassium tartrate (3.0 mL). After stirring for 20 min, the mixture was extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic fractions were dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. Column chromatography ($SiO_2$) with 2:1 hexanes/EtOAc afforded **236** (252 mg, 79%) as a colorless oil. $^1$H NMR δ: 7.31-7.26 (2H, m), 7.22-7.15 (3H, m), 5.78-5.62 (2H, m), 4.08 (2H, dd, *J* = 5.6, 1.1 Hz), 2.71 (2H, t, *J* = 6.9 Hz), 2.40-2.34 (2H, m), 1.41 (1H, br s) ppm; $^{13}$C NMR δ: 141.7, 132.3, 129.6,

128.4, 128.3, 125.9, 63.7, 35.5, 34.0 ppm. These data are in accordance with those found in the literature.[30]

**(*E*)-3-Methyl-8-phenylocta-1,2,5-trien-4-ol (239)**

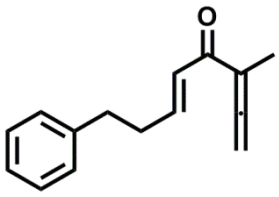



**239**

According to the literature,[31] oxalyl chloride (0.476 mL, 5.46 mmol) was dissolved in $CH_2Cl_2$ (18 mL). After cooling to -78 $^oC$, DMSO (0.517 g, 7.27 mmol) was added dropwise and the mixture was stirred for 15 min. A solution of compound **236** (295 mg, 1.82 mmol) in $CH_2Cl_2$ (3.6 mL) was added, and the mixture was stirred for 30 min at -78 $^oC$. $Et_3N$ (2.54 mL, 18.2 mmol) was then added and stirring was continued for 5 min at -78 $^oC$ before warming to 0 $^oC$ and stirring an additional 20 min. An equal volume of saturated aqueous $NH_4Cl$ was added, and the mixture was extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic fractions were dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure to afford **237** as a yellow oil, which was used in the subsequent step without further purification. According to the literature,[26] in a separate flask, compound **238** (177 mg, 1.33 mmol) was added to a stirring mixture of LiI (178 mg, 1.33 mmol) and indium powder (132 mg, 1.15 mmol) in THF (4.4 mL). The mixture was stirred for 30 min before compound **237** (146 mg, 0.911 mmol) in THF (4.4 mL) was added. After stirring overnight at room temperature, LiI (59 mg, 0.44 mmol) was added and the mixure was stirred an additional 3 h. The mixture was filtered through a plug of Celite and washed with $Et_2O$. After washing with saturated aqueous $NaHCO_3$, and

extracting with $Et_2O$ (3 x 20 mL), the combined organic fractions were dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. Column chromatography ($SiO_2$) with 20:1 hexanes/EtOAc afforded **239** (138 mg, 73%) as a pale yellow oil. $^1$H NMR δ: 7.30-7.25 (2H, m), 7.21-7.16 (3H, m), 5.76 (1H, dt, *J* = 15.4, 6.8 Hz), 5.49 (1H, ddt, *J* = 15.4, 7.2, 1.4 Hz), 4.85-4.81 (2H, m), 4.42 (1H, d, *J* = 7.1 Hz), 2.72 (2H, m), 2.42-2.36 (2H, m), 1.79-1.76 (1H, m), 1.63 (3H, t, *J* = 3.1 Hz) ppm; $^{13}$C NMR δ: 204.4, 141.9, 132.6, 131.1, 128.7, 128.5, 126.1, 102.2, 78.0, 73.4, 35.7, 34.1, 15.0 ppm; HRMS (ESI): 237.1250, $[C_{15}H_{18}ONa]^+$ requires 237.1250.

**(*E*)-3-Methyl-8-phenylocta-1,2,5-trien-4-one (229)**

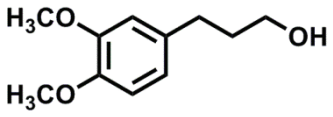


**229**

According to the literature,[21] compound **239** (138 mg, 0.644 mmol) and $NaHCO_3$ (541 mg, 6.44 mmol) were combined in $CH_2Cl_2$ (6.4 mL). DMP (355 mg, 0.837 mmol) was added and the mixture was stirred at room temperature for 1 h. An equal volume of saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$ solutions were added, and the mixture was stirred until both layers were clear. The mixture was extracted with $CH_2Cl_2$ (3 x 20 mL) and the combined organic fractions were dried over $Na_2SO_4$. The solvent was then evaporated under reduced pressure. Column chromatography ($SiO_2$) with 20:1 hexanes/EtOAc afforded **229** (67 mg, 49%) as a pale yellow oil. $^1$H NMR δ: 7.31-7.26 (2H, m), 7.22-7.16 (3H, m), 6.93 (1H, dt, *J* = 15.4, 6.9 Hz), 6.77 (1H, dt, *J* = 15.4, 1.5

Hz), 5.14 (2H, q, $J$ = 3.0 Hz), 2.77 (2H, t, $J$ = 7.8 Hz), 2.55-2.49 (2H, m), 1.84 (3H, t, $J$ = 2.9 Hz) ppm; $^{13}$C NMR δ: 216.4, 189.8, 145.3, 141.1, 128.6, 128.5, 126.2, 125.7, 104.5, 78.9, 34.6, 34.1, 13.5 ppm. These data are in accordance with those found in the literature.[40]

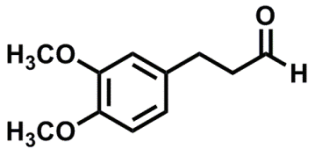
**3-(3,4-Dimethoxyphenyl)propan-1-ol (241)**




**241**

As with **231**, compound **240** (11.0 g, 52.8 mmol) was dissolved in THF (550 mL). After the mixture was cooled to 0 $^{o}$C, $LiAlH_4$ (6.02 g, 158 mmol) was added slowly, and the mixture was warmed to room temperature before heating to reflux overnight. The mixture was cooled to room temperature and diluted with $Et_2O$ (200 mL) and then cooled to 0 $^{o}$C. Water (6.0 mL) was added cautiously, followed by 15% (w/v) aqueous NaOH (6.0 mL), and then additional water (18 mL). The mixture was warmed to room temperature and $MgSO_4$ was added. After stirring 15 min, the solid material was removed by vacuum filtration and the solvent was evaporated under reduced pressure. Column chromatography ($SiO_2$) with 1:1 hexanes/EtOAc afforded **241** (7.88 g, 76%) as a colorless oil. $^1$H NMR δ: 6.80 (1H, d, $J$ = 8.3 Hz), 6.76-6.72 (2H, m), 3.87 (3H, s), 3.86 (3H, s), 3.68 (2H, t, $J$ = 6.3 Hz), 2.66 (2H, t, $J$ = 7.6 Hz), 1.92-1.84 (2H, m), 1.45 (1H, br s) ppm; $^{13}$C NMR δ: 148.8, 147.2, 134.4, 120.2, 111.7, 111.2, 62.3, 55.9, 55.8, 34.4, 31.7 ppm. These data are in accordance with those found in the literature.[41]

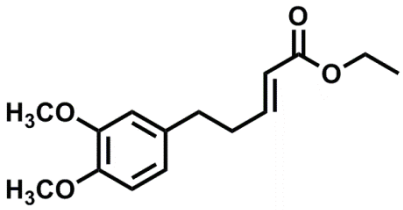
**3-(3,4-Dimethoxyphenyl)propanal (242)**



242

As with **232**, PCC (13.0 g, 60.3 mmol) was dissolved in $CH_2Cl_2$ (250 mL). After the mixture was cooled to 0 $^oC$, a solution of **241** (7.88 g, 40.2 mmol) in $CH_2Cl_2$ (150 mL) was added dropwise. The mixture was protected from light and warmed to room temperature with stirring overnight. The mixture was filtered through a pad of silica gel and washed with $Et_2O$ (3 x 100 mL). The organic layer was dried over $Na_2SO_4$, and the solvent was evaporated under reduced pressure to afford a **242** (5.16 g, 66%) as a colorless oil which was used without further purification. $^1H$ NMR δ: 9.82 (1H, t, $J$ = 1.5 Hz), 6.80 (1H, d, $J$ = 8.3 Hz), 6.75-6.71 (2H, m), 3.87 (3H, s), 3.86 (3H, s), 2.91 (2H, t, $J$ = 7.4 Hz), 2.77 (2H, t, $J$ = 7.4 Hz) ppm; $^{13}C$ NMR δ: 201.7, 148.9, 147.5, 132.9, 120.1, 111.6, 111.3, 55.9, 55.8, 45.5, 27.7 ppm. These data are in accordance with those found in the literature.[42]

**Ethyl (*E*)-5-(3,4-dimethoxyphenyl)pent-2-enoate (243)**

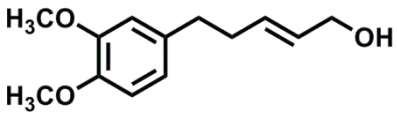


243

According to the literature,[29] compound **242** (2.58 g, 13.3 mmol) and **234** (5.54 g, 15.9 mmol) were dissolved in $CH_2Cl_2$ (140 mL). After stirring at room temperature for 6 h, the

solvent was evaporated under reduced pressure. Column chromatography ($SiO_2$) with 4:1 hexanes/EtOAc afforded **243** (3.03 g, 91%) as a colorless oil. $^1$H NMR δ: 7.00 (1H, dt, *J* = 15.7, 6.9 Hz), 6.80 (1H, d, *J* = 8.1 Hz), 6.74-6.68 (2H, m), 5.84 (1H, dt, *J* = 15.7, 1.5 Hz), 4.18 (2H, q, *J* = 7.2 Hz), 3.87 (3H, s), 3.86 (3H, s), 2.73 (2H, t, *J* = 7.3 Hz), 2.50 (2H, apparent q, *J* = 7.4 Hz), 1.28 (3H, t, *J* = 7.2 Hz) ppm; $^{13}$C NMR δ: 166.6, 148.8, 148.1, 147.4, 133.4, 121.8, 120.1, 111.6, 111.2, 60.2, 55.9, 55.8, 34.1, 34.0, 14.2 ppm; HRMS (ESI): 287.1254, $[C_{15}H_{20}O_4Na]^+$ requires 287.1254.

**(*E*)-5-(3,4-Dimethyoxyphenyl)pent-2-en-1-ol (244)**

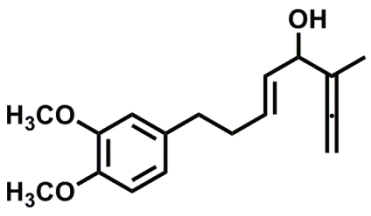



**244**

As with **235**, compound **243** (3.03 g, 12.1 mmol) was dissolved in $CH_2Cl_2$ (60 mL). After cooling to -78 $^o$C, DIBAL-H (1.0 M in toluene) (27 mL, 27 mmol) was added dropwise, and the mixture was warmed to room temperature over 6 h. MeOH (15 mL) was added dropwise, followed by saturated aqueous sodium potassium tartrate (40 mL). After stirring for 20 min, the mixture was extracted with $CH_2Cl_2$ (3 x 100 mL). The combined organic fractions were dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. Column chromatography ($SiO_2$) with 1:1 hexanes/EtOAc afforded **244** (2.41 g, 90%) as a colorless oil. $^1$H NMR δ: 6.80 (1H, d, *J* = 8.0 Hz), 6.74-6.69 (2H, m), 5.78-5.63 (2H, m), 4.12-4.06 (2H, m), 3.87 (3H, s), 3.86 (3H, s), 2.65 (2H, t, *J* = 7.9 Hz), 2.39-2.32 (2H, m), 1.34 (1H, br s) ppm; $^{13}$C NMR δ: 148.7, 147.2, 134.3, 132.2, 129.5, 120.2,

111.7, 111.1, 63.7, 55.9, 55.8, 35.1, 34.2 ppm. These data are in accordance with those found in the literature.[43]

**(*E*)-8-(3,4-Dimethoxyphenyl)-3-methylocta-1,2,5-trien-4-ol (246)**

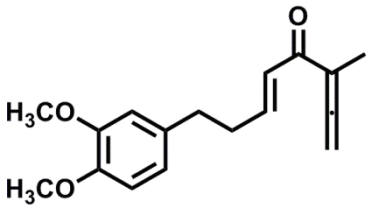



**246**

As with **236**, oxalyl chloride (2.84 mL, 32.6 mmol) was dissolved in $CH_2Cl_2$ (110 mL). After cooling to -78 $^oC$, DMSO (3.09 mL, 43.4 mmol) was added dropwise and the mixture was stirred for 15 min. A solution of compound **244** (2.41 g, 10.9 mmol) in $CH_2Cl_2$ (22 mL) was added, and the mixture was stirred for 30 min at -78 $^oC$. $Et_3N$ (15.2 mL, 109 mmol) was then added, and stirring was continued for 5 min at -78 $^oC$ before warming to 0 $^oC$ and stirring an additional 20 min. An equal volume of saturated aqueous $NH_4Cl$ was added, and the mixture was extracted with $CH_2Cl_2$ (3 x 100 mL). The combined organic fractions were dried over $Na_2SO_4$, and the solvent was evaporated under reduced pressure to afford **245** as a yellow oil which was used in the subsequent step without further purification. In a separate flask, compound **238** (1.78 g, 13.4 mmol) was added to a stirring mixture of LiI (1.79 g, 13.4 mmol) and indium powder (1.10 g, 9.61 mmol) in THF (27 mL). The mixture was stirred for 30 min and half of a stock solution of aldehyde **245**, dissolved in THF (27 mL) was added. After stirring overnight at room temperature, the mixture was filtered through a plug of Celite and washed with $Et_2O$. After washing with saturated aqueous $NaHCO_3$ and extracting with $Et_2O$ (3 x 100

mL), the combined organic fractions were dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. Column chromatography ($SiO_2$) with 4:1 hexanes/EtOAc afforded **246** (1.06 g, 71%) as a pale yellow oil. $^1$H NMR δ: 6.79 (1H, d, *J* = 8.1 Hz), 6.74-6.69 (2H, m), 5.76 (1H, dt, *J* = 15.3, 7.5 Hz), 5.50 (1H, br dd, *J* = 15.5, 7.2 Hz), 4.84 (2H, q, *J* = 2.6 Hz), 4.42 (1H, br s), 3.87 (3H, s), 3.86 (3H, s), 2.66 (2H, td, *J* = 7.8, 2.6 Hz), 2.41-2.33 (2H, m), 1.77 (1H, d, *J* = 4.7 Hz), 1.65 (3H, t, *J* = 3.2 Hz) ppm; $^{13}$C NMR δ: 204.2, 148.8, 147.2, 134.3, 132.4, 130.8, 120.2, 111.7, 111.1, 102.0, 77.8, 73.2, 55.9, 55.8, 35.1, 34.2, 14.8 ppm; HRMS (ESI): 297.1460, $[C_{17}H_{22}O_3Na]^+$ requires 297.1461.

**(*E*)-8-(3,4-Dimethoxyphenyl)-3-methylocta-1,2,5-trien-4-one (247)**

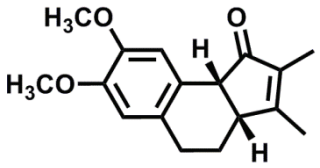



**247**

As with **239**, compound **246** (500 mg, 1.82 mmol) and $NaHCO_3$ (1.53 g, 18.2 mmol) were combined in $CH_2Cl_2$ (20 mL). DMP (1.01 g, 2.37 mmol) was added and the mixture was stirred at room temperature for 30 min. Saturated aqueous $NaHCO_3$ (20 mL) and $Na_2S_2O_3$ (20 mL) solutions were added, and the mixture was stirred until both layers were clear. The mixture was extracted with $CH_2Cl_2$ (3 x 50 mL) and the combined organic fractions were dried over $Na_2SO_4$. The solvent was then evaporated under reduced pressure. Column chromatography ($SiO_2$) with 10:1 hexanes/EtOAc afforded **247** (277 mg, 55%) as a pale yellow oil. $^1$H NMR δ: 6.93 (1H, dt, *J* = 15.4, 6.9 Hz), 6.79

(1H, d, *J* = 8.1 Hz), 6.76 (1H, *J* = 15.6, 1.5 Hz), 6.72 (1H, dd, *J* = 8.0, 2.0 Hz), 6.69 (1H, d, *J* = 2.0 Hz), 5.15 (2H, q, *J* = 2.9 Hz), 3.87 (3H, s), 3.86 (3H, s), 2.72 (2H, t, *J* = 7.6 Hz), 2.53-2.47 (2H, m), 1.85 (3H, t, *J* = 2.9 Hz) ppm; $^{13}$C NMR δ: 216.3, 189.6, 148.8, 147.3, 145.3, 133.6, 125.6, 120.2, 111.7, 111.2, 104.4, 78.8, 55.9, 55.8, 34.3, 34.1, 13.4 ppm; HRMS (ESI): 295.1303, $[C_{17}H_{20}O_3Na]^+$ requires 295.1305.

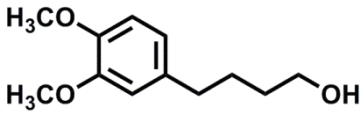
**(3a*R*,9b*R*)-7,8-Dimethoxy-2,3-dimethyl-3a,4,5,9b-tetrahydro-1*H*-cyclopenta[*a*]naphthalene-1-one (248)**




**248**

Compound **247** (100 mg, 0.367 mmol) was dissolved in $CH_2Cl_2$ (37 mL). After cooling to -78 $^{o}$C, $BF_3$•$OEt_2$ (45 μL, 0.37 mmol) was added dropwise, and the solution was stirred for 20 min. Water (20 mL) was added and the mixture was extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic fractions were dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. Column chromatography ($SiO_2$) with 4:1 hexanes : EtOAc afforded **248** (73 mg, 73%) as a colorless oil. $^1$H NMR δ: 7.20 (1H, s), 6.55 (1H, s), 3.93 (3H, s), 3.83 (3H, s), 3.48 (1H, d, *J* = 6.4 Hz), 3.14 (1H, br dd, *J* = 12.4, 5.6 Hz), 2.53 (1H, ddd, *J* = 15.3, 6.5, 3.6 Hz), 2.35 (1H, ddd, *J* = 15.2, 10.8, 3.7 Hz), 2.09 (3H, s), 1.98-1.90 (1H, m), 1.86-1.79 (1H, m), 1.71 (3H, s) ppm; $^{13}$C NMR δ: 206.9, 170.9, 147.8, 147.4, 136.8, 129.9, 124.9, 112.8, 111.1, 56.2, 56.1, 48.4, 43.3, 26.8, 26.63, 15.3, 8.5 ppm; HRMS (ESI): 295.1306, $[C_{17}H_{20}O_3Na]^+$ requires 295.1305.

**4-(3,4-Dimethoxyphenyl)butan-1-ol (253)**

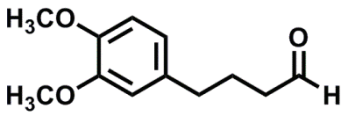



**253**

According to the literature,[33] aluminum chloride (8.00 g, 60.0 mmol) was suspended in $CH_2Cl_2$ (60 mL). After the mixture was cooled to 0 $^oC$, **249** (6.37 mL, 50.0 mmol) and **250** (6.00 g, 60.0 mmol) were added. The mixture was then heated to reflux with stirring overnight. After cooling to room temperature, the mixture was poured over ice and subsequently dried over $Na_2SO_4$. The solution was then evaporated to dryness under reduced pressure to afford **251**, which was used without further purification. According to the literature,[34] in a separate flask, mossy zinc (21.4 g, 327 mmol) was treated with $HgCl_2$ (2.14 g, 7.88 mmol) in distilled water (36 mL). After shaking for 5 min, the supernatant was discarded and distilled water (13 mL), concentrated HCl (31 mL) and toluene (18 mL) were added to the flask, followed by **251**. The mixture was heated to reflux overnight, during which time concentrated HCl (27 mL) was added intermittently. The mixture was cooled to room temperature and extracted with $Et_2O$ (3 x 100 mL). The organic layer was dried over $Na_2SO_4$, and the solvent was evaporated to afford **252**, which was used directly in the following step. As with **231**, in a separate flask, $LiAlH_4$ (2.31 g, 61.0 mmol) was added to THF (110 mL). After the mixture was cooled to 0 $^oC$, **252** was added dropwise, and the mixture was warmed to room temperature overnight. The mixture was cooled to room temperature and diluted with an equal volume of $Et_2O$. After cooling to 0 $^oC$, distilled water (2.3 mL) was added dropwise, followed by 15% (w/v) aqueous NaOH (2.3 mL), and additional distilled water (6.9 mL). The mixture was warmed to room temperature and $MgSO_4$ was added. After stirring 15 min, the solid

material was removed by vacuum filtration, and the solvent was evaporated under reduced pressure to afford **253** (3.71 g, 35%) as an orange oil that was used without further purification. $^{1}$H NMR δ: 6.79 (1H, d, *J* = 7.8 Hz), 6.74-6.70 (2H, m), 3.88 (3H, s), 3.86 (3H, s), 3.66 (2H, t, *J* = 6.5 Hz), 2.60 (2H, t, *J* = 7.3 Hz), 2.13 (1H, br s), 1.72-1.65 (2H, m), 1.65-1.58 (2H, m) ppm; $^{13}$C NMR δ: 148.8, 147.1, 135.1, 120.2, 111.9, 111.3, 62.6, 55.9, 55.8, 35.2, 32.2, 27.7 ppm; HRMS (ESI): 233.1138, $[C_{12}H_{18}O_3Na]^+$ requires 233.1148.

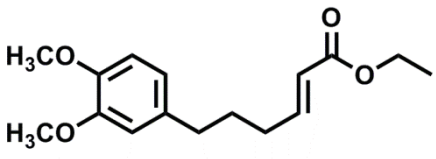
**4-(3,4-Dimethoxyphenyl)butanal (254)**




**254**

As with **232**, PCC (2.80 g, 13.0 mmol) was dissolved in $CH_2Cl_2$ (18 mL). After the mixture was cooled to 0 $^{o}$C, a solution of **253** (1.35 g, 6.42 mmol) in $CH_2Cl_2$ (18 mL) was added dropwise. The mixture was protected from light and warmed to room temperature with stirring overnight. The mixture was filtered through a pad of silica gel and washed with $Et_2O$. The organic layer was dried over $Na_2SO_4$, and the solvent was evaporated under reduced pressure to afford **254** (712 mg, 53%) as an orange oil that was used without further purification. $^{1}$H NMR δ: 9.77 (1H, br s), 6.80 (1H, d, *J* = 8.0 Hz), 6.73-6.69 (2H, m), 3.88 (3H, s), 3.86 (3H, s), 2.61 (2H, t, *J* = 7.6 Hz), 2.46 (2H, t, *J* = 7.2 Hz), 1.95 (2H, pentet, *J* = 7.5 Hz) ppm; $^{13}$C NMR δ: 202.6, 149.0, 147.5, 133.9, 120.4, 111.8, 111.3, 56.0, 56.0, 43.3, 34.7, 24.0 ppm; HRMS (ESI): 231.0989, $[C_{12}H_{16}O_3Na]^+$ requires 231.0992.

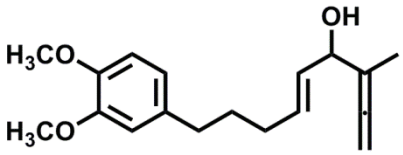
**Ethyl (*E*)-6-(3,4-dimethoxyphenyl)hex-2-enoate (255)**



**255**

As with **233**, compound **254** (712 mg, 3.42 mmol) was dissolved in $CH_2Cl_2$ (50 mL). Compound **234** (1.43 g, 4.10 mmol) was added and the mixture was stirred at room temperature overnight. The solvent was then evaporated under reduced pressure. Column chromatography ($SiO_2$) with 4:1 hexanes/EtOAc afforded **255** (630 mg, 66%) as a colorless oil. $^1$H NMR δ: 6.98 (1H, dt, *J* = 15.6, 7.0 Hz), 6.80 (1H, d, *J* = 8.0 Hz), 6.73-6.68 (2H, m), 5.83 (1H, d, *J* = 15.6 Hz), 4.19 (2H, q, *J* = 7.1 Hz), 3.88 (3H, s), 3.86 (3H, s), 2.59 (2H, t, *J* = 7.6 Hz), 2.23 (2H, apparent q, *J* = 7.2 Hz), 1.78 (2H, pentet, *J* = 7.6 Hz), 1.29 (3H, t, *J* = 7.2 Hz) ppm; $^{13}$C NMR δ: 166.9, 149.0, 148.9, 147.3, 134.5, 121.8, 120.3, 111.8, 111.3, 60.3, 56.0, 55.9, 35.0, 31.7, 29.9, 14.4 ppm; HRMS (ESI): 301.1418, $[C_{16}H_{22}O_4Na]^+$ requires 301.1410.

**(*E*)-9-(3,4-Dimethoxyphenyl)-3-methylnona-1,2,5-trien-4-ol (258)**



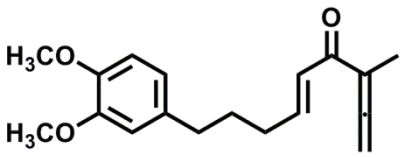
**258**

As with **235**, compound **255** (630 mg, 2.26 mmol) was dissolved in $CH_2Cl_2$ (12 mL). After cooling to -78 $^o$C, DIBAL-H (1.0 M in toluene) (5.0 mL, 5.0 mmol) was added dropwise, and the mixture was warmed to room temperature over 6 h. MeOH (3.0 mL)

was added dropwise, followed by saturated aqueous sodium potassium tartrate (7.5 mL). After stirring for 20 min, the mixture was extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic fractions were dried over $Na_2SO_4$, and the solvent was evaporated under reduced pressure to afford alcohol **256**. As with **236**, in a separate flask, oxalyl chloride (0.58 mL, 6.8 mmol) was dissolved in $CH_2Cl_2$ (23 mL). After cooling to -78 $^oC$, DMSO (0.64 ml, 9.0 mmol) was added dropwise and the mixture was stirred for 15 min. Alcohol **256** was added as a solution in $CH_2Cl_2$ (5.0 mL), and the mixture was stirred for 30 min at -78 $^oC$. $Et_3N$ (3.15 mL, 22.6 mmol) was then added, and stirring was continued for 5 min at -78 $^oC$ before warming to 0 $^oC$ and stirring an additional 20 min. An equal volume of saturated aqueous $NH_4Cl$ was added and the mixture was extracted with $CH_2Cl_2$ (3 x 50 mL). The combined organic fractions were dried over $Na_2SO_4$, and the solvent was evaporated under reduced pressure to afford aldehyde **257**. In a separate flask, compound **238** (300 mg, 2.3 mmol) was added to a stirring mixture of LiI (402 mg, 3.00 mmol) and indium powder (259 mg, 2.26 mmol) in THF (5.6 mL). The mixture was stirred for 30 min and aldehyde **257**, dissolved in THF (5.6 mL), was added. After stirring overnight at room temperature, the mixture was filtered through a plug of Celite and washed with $Et_2O$. After washing with saturated aqueous $NaHCO_3$ and extracting with $Et_2O$ (3 x 20 mL), the combined organic fractions were dried over $Na_2SO_4$, and the solvent was evaporated under reduced pressure to afford **258** (504 mg, 76%) as an orange oil which was used without further purification. $^1H$ NMR δ: 6.79 (1H, d, $J$ = 7.8 Hz), 6.73-6.69 (2H, m), 5.75 (1H, dt, $J$ = 15.4, 6.8 Hz), 5.49 (1H, br dd, $J$ = 15.3, 7.1 Hz), 4.88-4.81 (2H, m), 4.47-4.42 (1H, m), 3.87 (3H, s), 3.86 (3H, s), 2.57 (2H, t, $J$ = 7.6 Hz), 2.11 (2H, q, $J$ = 7.2 Hz), 1.75-1.67 (5H, m) ppm; $^{13}C$ NMR δ: 204.4, 148.9, 147.2, 135.1,

133.1, 130.8, 120.3, 118.9, 111.3, 102.2, 78.0, 73.4, 56.1, 55.9, 35.1, 31.8, 31.1, 15.0 ppm; HRMS (ESI): 311.1608, $[C_{18}H_{24}O_3Na]^+$ requires 311.1618.

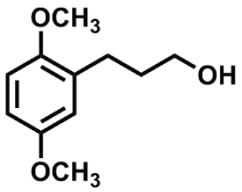
**(*E*)-9-(3,4-Dimethoxyphenyl)-3-methylnona-1,2,5-trien-4-one (259)**




**259**

As with **239**, compound **258** (252 mg, 0.874 mmol) and $NaHCO_3$ (735 mg, 8.74 mmol) were combined in $CH_2Cl_2$ (10 mL). DMP (484 mg, 1.14 mmol) was added, and the mixture was stirred at room temperature for 30 min. Saturated aqueous $NaHCO_3$ (10 mL) and $Na_2S_2O_3$ (10 mL) solutions were added, and the mixture was stirred until both layers were clear. The mixture was extracted with $CH_2Cl_2$ (3 x 20 mL), and the combined organic fractions were dried over $Na_2SO_4$. The solvent was then evaporated under reduced pressure. Column chromatography ($SiO_2$) with 4:1 hexanes : EtOAc afforded **259** (112 mg, 45%) as a colorless oil. $^1$H NMR δ: 6.92 (1H, dt, *J* = 15.3, 7.0 Hz), 6.81-6.74 (2H, m), 6.72-6.68 (2H, m), 5.17 (2H, q, *J* = 3.0 Hz), 3.87 (3H, s), 3.86 (3H, s), 2.58 (2H, t, *J* = 7.7 Hz), 2.24 (2H, q, *J* = 7.3 Hz), 1.85 (3H, t, *J* = 3.0 Hz), 1.77 (2H, pentet, *J* = 7.6 Hz) ppm; $^{13}$C NMR δ: 216.4, 189.8, 148.9, 147.3, 146.2, 134.6, 125.6, 120.4, 111.9, 111.3, 104.5, 78.8, 56.1, 56.0, 35.0, 31.9, 30.2, 13.5 ppm; HRMS (ESI): 309.1469, $[C_{18}H_{22}O_3Na]^+$ requires 309.1461.

**3-(2,5-Dimethoxyphenyl)propan-1-ol (274)**

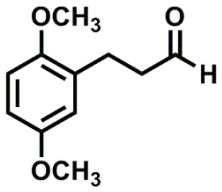



**274**

According to the literature,[35] compound **270** (10.2 g, 98.0 mmol) and **271** (7.98 g, 48.0 mmol) were dissolved in pyridine (20 mL). Piperidine (0.70 mL) was added and the solution was heated under reflux overnight. After cooling to room temperature, the solution was poured over water (200 mL) and acidified with 12 M aqueous HCl. The solid material was isolated by suction filtration and subsequently dissolved in 10% w/v aqueous NaOH. The remaining solid material was removed by suction filtration and the filtrate was acidified with 12 M aqueous HCl. The solid was again isolated by suction filtration, washed with water, and dried under reduced pressure. The resulting **272** was obtained as a yellow solid, which, according to the literature,[36] was dissolved in EtOH (100 mL). 10% w/w Pd/C (2.00 g) was added, and the mixture was stirred overnight under a static atmosphere of $H_2$. The mixture was passed through a plug of Celite and washed with $Et_2O$. The solvent was then evaporated under reduced pressure to afford **273** as a colorless oil. As with **231**, compound **273** was then added slowly to a stirring suspension of $LiAlH_4$ (1.71 g, 45.0 mmol) in THF (100 mL), and the mixture was warmed to room temperature before heating to reflux overnight. The mixture was cooled to room temperature, and diluted with $Et_2O$ (200 mL) and then cooled to 0 $^oC$. Water (1.7 mL) was added, followed by 15% (w/v) aqueous NaOH (1.7 mL), and then additional water (5.1 mL). The mixture was warmed to room temperature and $MgSO_4$ was added. After stirring 15 min, the solid material was removed by vacuum filtration. Evaporation

of the solvent resulted in **274** (6.21 g, 66%) as a colorless oil. $^{1}$H NMR δ: 6.79 (1H, d, *J* = 8.8 Hz), 6.74 (1H, d, *J* = 3.1 Hz), 6.71 (1H, dd, *J* = 8.6, 3.1 Hz), 3.80 (3H, s), 3.76 (3H, s), 3.59 (2H, t, *J* = 6.1 Hz), 2.70 (2H, t, *J* = 7.3 Hz), 1.98-1.88 (1H, br s), 1.84 (2H, pentet, *J* = 6.7 Hz) ppm; $^{13}$C NMR δ: 153.8, 151.8, 131.3, 116.6, 111.4, 111.2, 61.8, 56.2, 55.8, 33.1, 26.1 ppm. These data are in accordance with those found in the literature.[44]

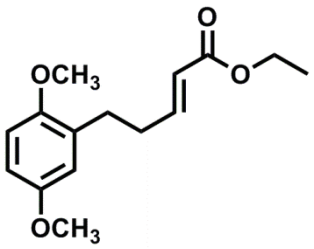
**3-(2,5-Dimethoxyphenyl)propanal (275)**




**275**

As with **232**, PCC (3.75 g, 17.4 mmol) was dissolved in $CH_2Cl_2$ (100 mL). After the mixture was cooled to 0 $^{o}$C, a solution of **274** (1.71 g, 8.70 mmol) in $CH_2Cl_2$ (50 mL) was added dropwise. The mixture was protected from light and warmed to room temperature with stirring overnight. The mixture was filtered through a pad of silica gel and washed with $Et_2O$ (3 x 50 mL). The organic layer was dried over $Na_2SO_4$, and the solvent was evaporated under reduced pressure to afford **275** (852 mg, 50%) as a colorless oil, which was used without further purification. $^{1}$H NMR δ: 9.80 (1H, t, *J* = 1.6 Hz), 6.77 (1H, d, *J* = 8.6 Hz), 6.74-6.71 (2H, m), 3.78 (3H, s), 3.76 (3H, s), 2.92 (2H, t, *J* = 7.4 Hz), 2.72 (2H, td, *J* = 7.5, 1.5 Hz) ppm; $^{13}$C NMR δ: 202.5, 153.6, 151.7, 129.9, 116.5, 111.6, 111.2, 55.8 (2 x $OCH_3$), 44.0, 23.8 ppm. These data are in accordance with those found in the literature.[45]

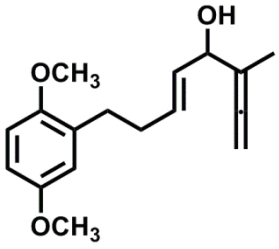
**Ethyl (*E*)-5-(2,5-dimethoxyphenyl)pent-2-enoate (276)**



**276**

As with **233**, compound **275** (1.10 g, 5.66 mmol) was dissolved in $CH_2Cl_2$ (60 mL). Compound **234** (2.30 g, 6.60 mmol) was added, and the mixture was stirred at room temperature overnight. The solvent was then evaporated under reduced pressure. Column chromatography ($SiO_2$) with 2:1 hexanes/EtOAc afforded **276** (1.15 g, 80%) as a colorless oil. $^1$H NMR δ: 7.02 (1H, dt, *J* = 15.7, 6.9 Hz), 6.77 (1H, d, *J* = 9.7 Hz), 6.72-6.69 (2H, m), 5.83 (1H, dt, *J* = 15.7, 1.5 Hz), 4.18 (2H, q, *J* = 7.1 Hz), 3.77 (3H, s), 3.75 (3H, s), 2.74 (2H, t, *J* = 7.7 Hz), 2.48 (2H, apparent q, *J* = 7.6 Hz), 1.28 (3H, t, *J* = 7.2 Hz) ppm; $^{13}$C NMR δ: 166.9, 153.6, 151.9, 148.9, 130.7, 121.6, 116.4, 111.5, 111.4, 60.3, 56.0, 55.9, 32.6, 29.3, 14.4 ppm; HRMS (ESI): 287.1248, $[C_{15}H_{20}O_4Na]^+$ requires 287.1254.

**(*E*)-8-(2,5-Dimethoxyphenyl)-3-methylocta-1,2,5-trien-4-ol (279)**

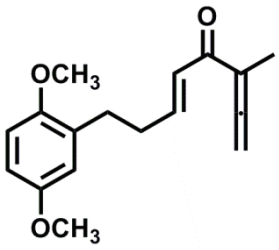


**279**

As with **235**, Compound **276** (1.13 g, 4.28 mmol) was dissolved in $CH_2Cl_2$ (12 mL). After cooling to -78 $^oC$, DIBAL-H (1.0 M in toluene) (8.6 mL, 8.6 mmol) was added dropwise, and the mixture was warmed to room temperature over 6 h. MeOH (6.0 mL) was added dropwise, followed by saturated aqueous sodium potassium tartrate (15 mL). After stirring for 20 min, the mixture was extracted with $CH_2Cl_2$ (3 x 50 mL). The combined organic fractions were dried over $Na_2SO_4$, and the solvent was evaporated under reduced pressure to afford the allylic alcohol **277**. As with **236**, in a separate flask, oxalyl chloride (1.09 mL, 12.8 mmol) was dissolved in $CH_2Cl_2$ (44 mL). After cooling to -78 $^oC$, DMSO (1.22 ml, 17.1 mmol) was added dropwise, and the mixture was stirred for 15 min. Alcohol **277** was added as a solution in $CH_2Cl_2$ (10 mL), and the mixture was stirred for 30 min at -78 $^oC$. $Et_3N$ (5.97 mL, 42.8 mmol) was then added, and stirring was continued for 5 min at -78 $^oC$ before warming to 0 $^oC$ and stirring an additional 20 min. An equal volume of saturated aqueous $NH_4Cl$ was added, and the mixture was extracted with $CH_2Cl_2$ (3 x 100 mL). The combined organic fractions were dried over $Na_2SO_4$, and the solvent was evaporated under reduced pressure to afford aldehyde **278**. In a separate flask, compound **238** (569 mg, 4.28 mmol) was added to a stirring mixture of LiI (670 mg, 5.01 mmol) and indium powder (458 mg, 4.00 mmol) in THF (12 mL). The mixture was stirred for 30 min and aldehyde **278**, dissolved in THF (12 mL), was added. After stirring overnight at room temperature, the mixture was filtered through a plug of Celite and washed with $Et_2O$. After washing with saturated aqueous $NaHCO_3$ and extracting with $Et_2O$ (3 x 50 mL), the combined organic fractions were dried over $Na_2SO_4$, and the solvent was evaporated under reduced pressure. Column chromatography ($SiO_2$) with 4:1 hexanes/EtOAc resulted in **279** (769 mg, 65%) as an yellow oil. $^1H$ NMR $\delta$: 6.76 (1H, d,

*J* = 8.6 Hz), 6.72-6.67 (2H, m), 5.78 (1H, dtd, *J* = 15.4, 6.7, 0.9 Hz), 5.48 (1H, ddt, *J* = 15.5, 7.3, 1.4 Hz), 4.86-4.80 (1H, m), 4.44-4.40 (1H, m), 3.77 (3H, s), 3.76 (3H, s), 2.71-2.66 (2H, m), 2.35 (2H, dq, *J* = 7.3, 1.4 Hz), 1.65 (3H, t, *J* = 3.1 Hz) ppm; $^{13}$C NMR δ: 204.4, 153.5, 151.9, 133.1, 131.5, 130.6, 116.5, 111.3, 111.0, 102.1, 77.8, 73.4, 56.0, 55.8, 32.4, 30.2, 14.9 ppm; HRMS (ESI): 297.1466, $[C_{17}H_{22}O_3Na]^+$ requires 297.1461.

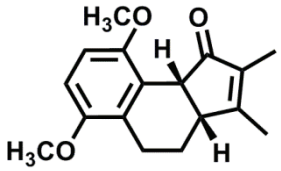
**(*E*)-8-(2,5-Dimethoxyphenyl)-3-methylocta-1,2,5-trien-4-one (280)**




**280**

As with **239**, compound **279** (100 mg, 0.364 mmol) and $NaHCO_3$ (310 mg, 3.6 mmol) were combined in $CH_2Cl_2$ (10 mL). DMP (256 mg, 0.600 mmol) was added, and the mixture was stirred at room temperature for 30 min. Saturated aqueous $NaHCO_3$ (10 mL) and $Na_2S_2O_3$ (10 mL) solutions were added, and the mixture was stirred until both layers were clear. The mixture was extracted with $CH_2Cl_2$ (3 x 25 mL), and the combined organic fractions were dried over $Na_2SO_4$. The solvent was then evaporated under reduced pressure. Column chromatography ($SiO_2$) with 10:1 hexanes/EtOAc afforded **280** (38 mg, 38%) as a pale yellow oil. $^1$H NMR δ: 6.95 (1H, dt, *J* = 15.4, 6.9 Hz), 6.78-6.74 (2H, m), 7.73-7.69 (2H, m), 5.15 (2H, q, *J* = 3.0 Hz), 3.77 (3H, s), 3.75 (3H, s), 2.74 (2H, t, *J* = 7.7 Hz), 2.51-2.45 (2H, m), 1.84 (3H, t, *J* = 3.0 Hz) ppm; $^{13}$C NMR δ: 216.4, 189.9, 153.6, 151.9, 146.2, 130.8, 125.4, 116.4, 111.3, 111.3, 104.5, 78.9, 56.0, 55.8, 32.7, 29.4, 13.5 ppm; HRMS (ESI): 295.1306, $[C_{17}H_{20}O_3Na]^+$ requires 295.1305.

**(3a*R**,9b*R**)-6,9-Dimethoxy-2,3-dimethyl-3a,4,5,9b-tetrahydro-1*H*-cyclopenta[*a*]naphthalen-1-one (281)**




**281**

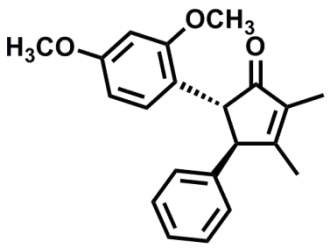
Compound **280** (56 mg, 0.21 mmol) was dissolved in $CH_2Cl_2$ (21 mL). After cooling to -78 $^oC$, $BF_3$•$OEt_2$ (26 μL, 0.21 mmol) was added dropwise, and the solution was stirred for 20 min. Water (20 mL) was added and the mixture was extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic fractions were dried over $Na_2SO_4$, and the solvent was evaporated under reduced pressure. Column chromatography ($SiO_2$) with 2:1 hexanes/EtOAc afforded **281** (11 mg, 20%) as a colorless solid. mp 109-112 $^oC$; $^1H$ NMR δ: 6.77 (1H, d, *J* = 8.9 Hz), 6.68 (1H, d, *J* = 8.9 Hz), 4.21 (1H, d, *J* = 6.5 Hz), 3.87 (3H, s), 3.73 (3H, s), 3.17 (1H, apparent t, *J* = 6.6 Hz), 2.87 (1H, apparent dt, *J* = 15.5, 3.4 Hz), 2.08 (3H, s), 2.05-1.99 (1H, m), 1.79-1.68 (4H, m), 1.65-1.57 (1H, m) ppm; $^{13}C$ NMR δ: 206.5, 170.0, 152.8, 150.2, 137.9, 129.2, 125.1, 109.4, 109.0, 56.9, 56.2, 44.4, 42.9, 25.8, 18.0, 15.6, 8.5 ppm; HRMS (ESI): 295.1294, $[C_{17}H_{20}O_3Na]^+$ requires 295.1305.

***General procedure 1:*** **Intermolecular Trapping of the Oxyallyl Cation Derived from 218 with Arenes**

The arene (5 equiv) and **218** (1 equiv) were dissolved in $CH_2Cl_2$ (10 mL/mmol). The reaction mixture was cooled to -78 °C with stirring. Distilled $BF_3$•$OEt_2$ (1.1 equiv) was added dropwise, and the reaction mixture was stirred at -78 $^oC$ for 15 min, after which the reaction was complete by TLC. The reaction mixture was washed with saturated aqueous

$NaHCO_3$ (75 mL/mmol). The organic fraction was dried with $Na_2SO_4$, and the solvent was evaporated. Column chromatography ($SiO_2$) afforded the product.

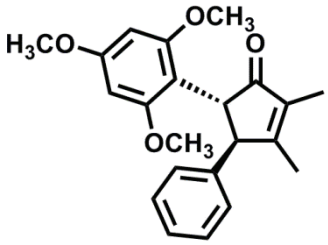
**(4*R**, 5*R**)-5-(2,4-Dimethoxyphenyl)-2,3-dimethyl-4-phenylcyclopent-2-enone (266)**




**266**

Following *General procedure 1*, **198** (0.18 mL, 1.4 mmol) and **218** (50 mg, 0.27 mmol) gave, after column chromatography with 10:1 hexanes/EtOAc, **266** (60 mg, 69%) as a colorless oil. $^1$H NMR δ: 7.32-7.27 (2H, m), 7.26-7.22 (1H, m), 7.07-7.02 (2H, m), 6.78 (1H, d, $J$ = 8.3 Hz), 6.43 (1H, d, $J$ = 2.4 Hz), 6.37 (1H, dd, $J$ = 8.3, 2.4 Hz), 3.76 (3H, s), 3.74 (1H, br s), 3.61 (3H, s), 3.44 (1H, d, $J$ = 3.2 Hz), 1.87 (3H, s), 1.85 (3H, s) ppm; $^{13}$C NMR δ: 209.1, 168.5, 160.1, 158.3, 142.0, 136.5, 130.9, 128.8, 127.8, 126.9, 120.4, 104.3, 99.3, 58.8, 58.4, 55.5, 55.4, 15.5, 8.7 ppm; HRMS (ESI): 345.1446, $[C_{21}H_{22}O_3Na]^+$ requires 345.1461.

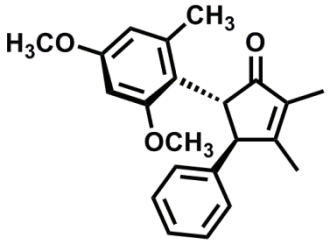
**(4*R**, 5*R**)-2,3-Dimethyl-4-phenyl-5-(2,4,6-trimethoxyphenyl)cyclopent-2-enone (283)**



**283**

Following *General procedure 1*, **282** (227 mg, 1.35 mmol) and **218** (50 mg, 0.27 mmol) gave, after column chromatography with 2:1 hexanes/ EtOAc, **283** (67 mg, 70%) as a colorless oil. $^{1}$H NMR δ: 7.30-7.25 (2H, m), 7.23-7.19 (1H, m), 7.07-7.03 (2H, m), 6.11 (1H, d, *J* = 2.0 Hz), 6.05 (1H, d, *J* = 2.0 Hz), 3.95 (1H, d, *J* = 3.6 Hz), 3.78 (3H, s), 3.71 (1H, br s), 3.66 (3H, s), 3.40 (3H, s), 1.86 (3H, s), 1.83 (3H, s) ppm; $^{13}$C NMR δ: 209.3, 167.1, 160.3, 159.8, 158.9, 142.3, 136.2, 128.6, 128.0, 126.6, 109.1, 91.9, 91.6, 57.6, 56.1, 55.9, 55.4, 52.2, 15.3, 8.8 ppm; HRMS (ESI): 375.1571, $[C_{22}H_{24}O_4Na]^+$ requires 375.1567.

**(4*R**, 5*R**)-5-(2,4-Dimethoxy-6-methylphenyl)-2,3-dimethyl-4-phenylcyclopent-2-enone (285)**

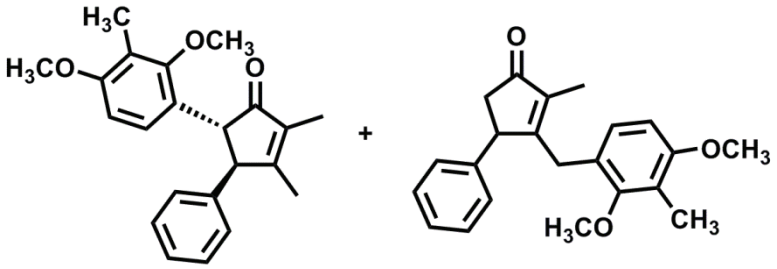


**285**

Following *General procedure 1*, **284** (0.20 mL, 1.4 mmol) and **218** (50 mg, 0.27 mmol) gave, after column chromatography with 2:1 hexanes/EtOAc, **285** (57 mg, 63%) as a

colorless oil. $^1$H NMR δ: 7.32-7.21 (3H, m), 7.08-7.03 (2H, m), 6.31 (1H, d, *J* = 2.4 Hz), 6.24 (1H, d, *J* = 2.4 Hz), 3.75 (3H, s), 3.72 (1H, br s), 3.64 (3H, s), 3.48 (1H, d, *J* = 3.7 Hz), 1.88 (3H, s), 1.85 (3H, s), 1.74 (3H, s) ppm; $^{13}$C NMR δ: 209.0, 166.6, 159.2, 158.3, 142.3, 139.5, 136.2, 128.9, 127.8, 126.9, 119.0, 107.2, 97.3, 57.7, 56.5, 55.7, 55.3, 20.4, 15.1, 8.7 ppm; HRMS (ESI): 359.1612, $[C_{22}H_{24}O_3Na]^+$ requires 359.1618.

**(4*R**, 5*R**)-5-(2,4-Dimethoxy-3-methylphenyl)-2,3-dimethyl-4-phenylcyclopent-2-enone (290) + 3-(2,4-dimethoxy-3-methylbenzyl)-2-methyl-4-phenylcyclopent-2-enone (291)**

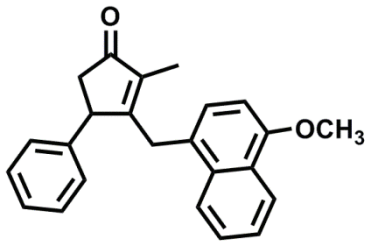



**290** **291**

Following *General procedure 1*, **289** (205 mg, 1.35 mmol) and **218** (50 mg, 0.27 mmol) gave, after column chromatography with 4:1 hexanes/EtOAc, **290** and **291** as a 1:4 mixture (59 mg, 65%) as a colorless oil. $^1$H NMR for **290** δ: 7.33-7.27 (2H, m), 7.27-7.21 (1H, m), 7.06 (2H, d, *J* = 7.8 Hz), 6.72 (1H, d, *J* = 8.4 Hz), 6.55 (1H, d, *J* = 8.2 Hz), 3.80-3.77 (4H, m), 3.59 (1H, d, *J* = 2.9 Hz), 3.44 (3H, s), 2.12 (3H, s), 1.89 (6H, br s); $^{13}$C NMR for **290** δ: 209.4, 169.9, 158.1, 157.7, 141.7, 136.4, 127.8, 127.1, 127.1, 126.7, 122.1, 119.8, 106.3, 60.1, 59.8, 58.1, 58.1, 15.6, 9.8, 8.8 ppm; $^1$H NMR for **291** δ: 7.33-7.27 (2H, m), 7.27-7.21 (1H, m), 7.03 (2H, d, *J* = 7.7 Hz), 6.67 (1H, d, *J* = 8.4 Hz), 6.54 (1H, d, *J* = 8.4 Hz), 3.84 (1H, d, *J* = 6.9 Hz), 3.81 (3H, s), 3.77 (1H, d, *J* = 15.2 Hz), 3.52 (3H, s), 3.16 (1H, d, *J* = 14.9 Hz), 2.84 (1H, dd, *J* = 19.0, 7.2 Hz), 2.32 (1H, dd, *J* = 19.0,

2.0 Hz), 2.14 (3H, s), 1.89 (3H, br s) ppm; $^{13}$C NMR for **291** δ: 209.8, 173.7, 158.0, 157.7, 142.4, 137.7, 128.9, 127.8, 127.7, 127.0, 122.1, 120.0, 106.0, 60.3, 55.8, 46.6, 44.9, 29.9, 9.4, 8.7 ppm; HRMS (ESI): 359.1610, $[C_{22}H_{24}O_3Na]^+$ requires 359.1618.

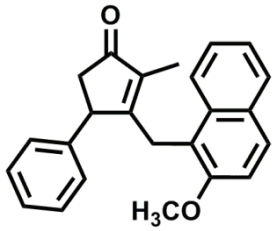
**3-((4-Methoxynaphthalen-1-yl)methyl)-2-methyl-4-phenylcyclopent-2-enone (293)**




**293**

Following *General procedure 1*, **292** (0.20 mL, 1.4 mmol) and **218** (50 mg, 0.27 mmol) gave, after column chromatography with 4:1 hexanes/EtOAc, **293** (61 mg, 67%) as a colorless oil. $^1$H NMR δ: 8.32-8.29 (1H, m), 7.61-7.58 (1H, m), 7.50-7.43 (2H, m), 7.31-7.23 (3H, m), 6.95-6.92 (2H, m), 6.80 (1H, d, *J* = 7.8 Hz), 6.65 (1H, d, *J* = 7.8 Hz), 4.21 (1H, d, *J* = 15.7 Hz), 3.99 (3H, s), 3.62 (1H, d, *J* = 7.1 Hz), 3.55 (1H, d, *J* = 15.7 Hz), 2.78 (1H, dd, *J* = 19.0, 7.2 Hz), 2.30 (1H, dd, *J* = 19.0, 2.0 Hz), 1.97 (3H, s) ppm; $^{13}$C NMR δ: 209.6, 173.6, 155.0, 142.3, 137.7, 132.9, 128.9, 127.7, 127.6, 127.1, 126.9, 126.0, 125.2, 124.7, 123.3, 122.8, 103.2, 55.6, 46.7, 44.9, 32.8, 8.8 ppm; HRMS (ESI): 365.1516, $[C_{24}H_{22}O_2Na]^+$ requires 365.1512.

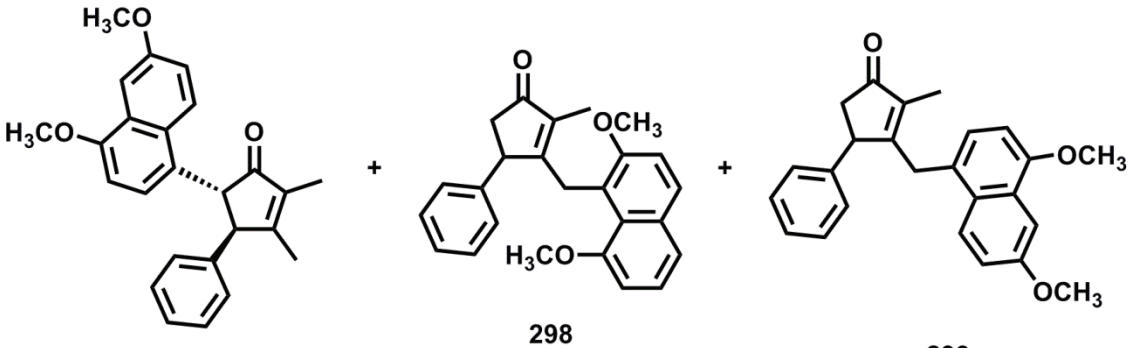
**3-((2-Methoxynaphthalen-1-yl)methyl)-2-methyl-4-phenylcyclopent-2-enone (295)**



**295**

Following *General procedure 1*, **294** (0.20 mL, 1.4 mmol) and **218** (50 mg, 0.27 mmol) gave, after column chromatography with 4:1 hexanes/EtOAc, **295** (42 mg, 46%) as a colorless oil. $^{1}$H NMR δ: 7.77 (1H, d, *J* = 7.6 Hz), 7.75 (1H, d, *J* = 8.8 Hz), 7.41 (1H, d, *J* = 7.5 Hz), 7.35-7.29 (2H, m), 7.20-7.16 (3H, m), 7.11 (1H, d, *J* = 9.0 Hz), 6.79 (1H, d, *J* = 7.6 Hz), 6.78 (1H, d, *J* = 7.0 Hz), 4.07 (2H, br s), 3.61 (3H, s), 3.54 (1H, d, *J* = 7.2 Hz), 2.74 (1H, dd, *J* = 18.9, 7.2 Hz), 2.20 (1H, dd, *J* = 18.9, 2.0 Hz), 1.90 (3H, s) ppm; $^{13}$C NMR δ: 209.7, 174.2, 155.0, 142.6, 137.7, 133.5, 129.1, 129.0, 128.7, 128.6, 127.6, 126.8, 126.8, 123.4, 123.1, 117.8, 112.5, 55.8, 47.0, 45.3, 26.2, 8.6 ppm; HRMS (ESI): 365.1510, $[C_{24}H_{22}O_2Na]^+$ requires 365.1512.

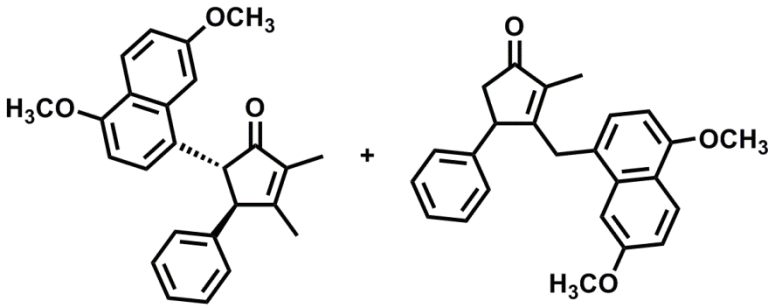
**(4*R**, 5*R**)-5-(4,6-Dimethoxynaphthalen-1-yl)-2,3-dimethyl-4-phenylcyclopent-2-enone (297) + 3-((4,6-dimethoxynaphthalen-2-yl)methyl)-2-methyl-4-phenylcyclopent-2-enone (298) + 3-((4,6-dimethoxynaphthalen-1-yl)methyl)-2-methyl-4-phenylcyclopent-2-enone (299)**



**297** **298** **299**

Following *General procedure 1*, **296** (0.22 mL, 1.4 mmol) and **218** (50 mg, 0.27 mmol) gave, after column chromatography with 4:1 hexanes/EtOAc, **297**, **298**, and **299** as a 1:2:3.6 mixture (33 mg, 33%) as a colorless oil. $^{1}$H NMR for **297** δ: 7.58 (1H, d, *J* = 2.6 Hz), 7.35-7.24 (3H, m), 7.22 (1H, d, *J* = 9.3 Hz), 7.06 (2H, d, *J* = 7.4 Hz), 6.97 (1H, dd, *J* = 9.2, 2.4 Hz), 6.83 (1H, d, *J* = 7.9 Hz), 6.70 (1H, d, *J* = 7.7 Hz), 3.97 (3H, s), 3.91 (3H, s), 3.92-3.89 (1H, m), 3.81 (1H, br s), 1.96 (3H, s), 1.89 (3H, s) ppm; $^{13}$C NMR for **297** δ: 209.6, 173.7, 157.2, 154.0, 141.7, 137.3, 129.1, 128.2, 127.9, 127.9, 127.4, 127.3, 125.5, 124.9, 119.0, 104.2, 101.2, 55.6, 55.5, 55.4, 46.7, 15.8, 8.8 ppm; $^{1}$H NMR for **298** δ: 7.65 (1H, d, *J* = 9.0 Hz), 7.34 (1H, d, *J* = 8.0 Hz), 7.20 (1H, apparent t, *J* = 7.9 Hz), 7.04-7.00 (3H, m), 6.97 (1H, d, *J* = 9.0 Hz), 6.72 (1H, d, *J* = 7.9 Hz), 6.57-6.54 (2H, m), 4.48 (1H, d, *J* = 17.9 Hz), 4.40 (1H, d, *J* = 17.8 Hz), 3.67 (3H, s), 3.57 (1H, d, *J* = 6.7 Hz), 3.48 (3H, s), 2.75 (1H, dd, *J* = 19.2, 6.9 Hz), 2.18 (1H, d, *J* = 19.0 Hz), 1.80 (3H, s) ppm; $^{13}$C NMR for **298** δ: 209.9, 178.3, 156.6, 155.5, 142.6, 135.1, 131.0, 128.7, 128.0, 127.7, 127.2, 125.2, 123.2, 121.5, 118.3, 112.6, 105.7, 55.9, 55.1, 47.4, 45.5, 29.5, 8.3 ppm; $^{1}$H NMR for **299** δ: 7.59 (1H, d, *J* = 2.6 Hz), 7.49 (1H, d, *J* = 7.5 Hz), 7.35-7.24 (3H, m), 7.10 (1H, dd, *J* = 9.1, 2.7 Hz), 6.93 (2H, d, *J* = 7.5 Hz), 6.68 (1H, d, *J* = 7.6 Hz), 6.65 (1H, d, *J* = 7.8 Hz), 4.17 (1H, d, *J* = 15.8 Hz), 3.99 (3H, s), 3.94 (3H, s), 3.62 (1H, d, *J* = 7.2 Hz), 3.52 (1H, d, *J* = 15.9 Hz), 2.78 (1H, dd, *J* = 19.4, 6.9 Hz), 2.30 (1H, dd, *J* = 19.1, 1.6 Hz), 1.96 (3H, s) ppm; $^{13}$C NMR for **299** δ: 209.6, 173.7, 157.4, 154.0, 142.3, 137.6, 128.9, 128.2, 127.7, 127.7, 127.1, 127.0, 125.0, 124.9, 119.2, 103.9, 101.2, 55.6 (2 x $CH_3$), 46.7, 44.9, 32.7, 8.8 ppm; HRMS (ESI): 395.1601, $[C_{25}H_{24}O_3Na]^+$ requires 395.1618.

**(4*R**, 5*R**)-5-(4,7-Dimethoxynaphthalen-1-yl)-2,3-dimethyl-4-phenylcyclopent-2-enone (301) + 3-((4,7-dimethoxynaphthalen-1-yl)methyl)-2-methyl-4-phenylcyclopent-2-enone (302)**




**301** **302**

Following *General procedure 1*, **300** (254 mg, 1.35 mmol) and **218** (50 mg, 0.27 mmol) gave, after column chromatography with 4:1 hexanes/EtOAc, **301** and **302** as a 1.1:1 mixture (100 mg, > 99%) as a colorless oil. $^{1}$H NMR for **301** δ: 8.21 (1H, d, *J* = 9.2 Hz), 7.31-7.24 (3H, m), 7.12 (1H, dd, *J* = 9.2, 2.5 Hz), 6.93 (2H, dd, *J* = 8.2, 2.9 Hz), 6.76 (1H, d, *J* = 7.9 Hz), 6.55-6.51 (2H, m), 3.97 (3H, s), 3.94 (3H, s), 3.75 (1H, br s), 3.60 (1H, d, *J* = 7.0 Hz), 2.01 (3H, s), 1.87 (3H, s) ppm; $^{13}$C NMR for **301** δ: 209.5, 173.7, 158.4, 155.2, 142.3, 137.5, 134.4, 128.9, 128.7, 127.7, 127.1, 124.6, 123.5, 121.0, 117.0, 102.3, 101.4, 55.6 (2 x $CH_3$), 55.3, 46.5, 15.7, 8.8 ppm; $^{1}$H NMR for **302** δ: 8.17 (1H, d, *J* = 9.2 Hz), 7.33 (2H, dd, *J* = 7.6, 7.3 Hz), 7.31-7.24 (1H, m), 7.12 (2H, d, *J* = 7.6 Hz), 7.03 (1H dd, *J* = 9.2, 2.4 Hz), 6.93 (1H, d, *J* = 7.8 Hz), 6.86 (1H, d, *J* = 2.5 Hz), 6.59 (1H, d, *J* = 8.0 Hz), 4.18 (1H, d, *J* = 15.7 Hz), 3.78 (3H, s), 3.78-3.72 (1H, m), 3.50 (1H, d, *J* = 15.8 Hz), 3.34 (3H, br s), 2.79 (1H, dd, *J* = 19.0, 7.1 Hz), 2.30 (1H, dd, *J* = 19.0, 2.0 Hz), 1.97 (3H, s) ppm; $^{13}$C NMR for **302** δ: 209.5, 173.7, 158.2, 155.1, 142.1, 137.4, 134.4, 129.2, 128.7, 128.0, 127.4, 124.5, 123.5, 121.3, 117.6, 102.4, 101.8, 55.3, 54.5, 46.5, 44.9, 33.0, 8.7 ppm; HRMS (ESI): 395.1604, $[C_{25}H_{24}O_3Na]^+$ requires 395.1618.

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## CHAPTER 5: CONCLUSION

The immediate benefit of methodology studies is an expansion of the library of reactions and reagents used in the development of synthetic pathways to complex organic molecules. Evolution of the methodology of geminal acylation has led to a procedure that allows for the development of heterocycles with the ability to control the position at which the endocyclic carbonyl group is installed. The long-term benefit from these studies is a greater understanding of the mechanism of germinal acylation, and particularly, the previously unappreciated role played by water, which may be to control the conformation of the cyclobutanone intermediate. This provides further evidence for a concerted mechanism for the pinacol rearrangement step.

While the investigation into the *E*/*Z* equilibration of allyl alcohol derivatives does not necessarily provide an advantage to the synthesis of complex molecules, it was evident that secondary metathesis by first-generation ruthenium catalysts was indeed a significant process for the substrates investigated. In addition, the introduction of a small amount of ethylene gas into the reaction medium may assist in the accelerated establishment of a thermodynamic mixture of olefins. These studies provided a contribution to the understanding of the behaviour of ruthenium-alkylidene catalysts in the interest of increasing their utility to carry out olefin metathesis.

The interrupted Nazarov cyclization of allenyl vinyl ketones with arenes provides the opportunity for the diastereoselective creation of complex polycyclic structures in a single transformation from relatively simple achiral starting materials. This type of methodology is attractive in the synthesis of polycyclic natural products. The long-term benefit from this investigation is an expansion of the precedence of the interrupted

Nazarov cyclization of allenyl vinyl ketones to intramolecular reaction pathways. In addition, this study provides a contribution to the understanding of the regioselectivity with which sterically encumbered nucleophiles undergo trapping of the oxyallyl cationic intermediate.

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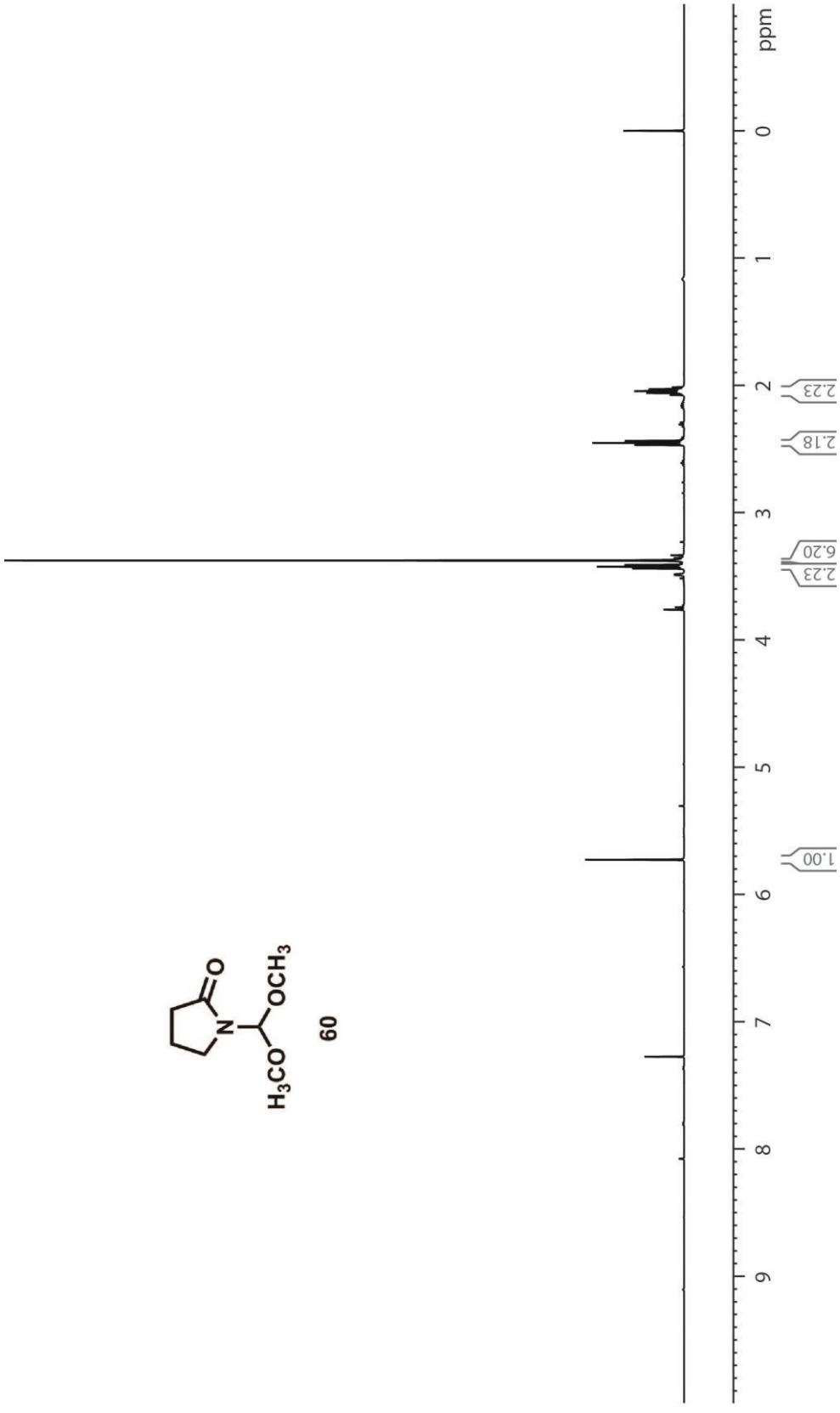
## APPENDIX I: $^{1}H$, $^{13}C$ NMR SPECTRA AND X-RAY STRUCTURES FOR CHAPTER 2

$^{1}H$ NMR and $^{13}C$ NMR spectra for compounds **60**, **61**, **68**, **69**, **75**, **77**, **81**, **82**, **84**, **85**, **86**, **87**, **90**, **91**, **92**, **93**, **95**, **96**, **97**, **98**, **99**, **101**, **111a**, **111b**, **112a**, **112b**, **113a**, **113b**, **114a**, **114b**, and **125**.

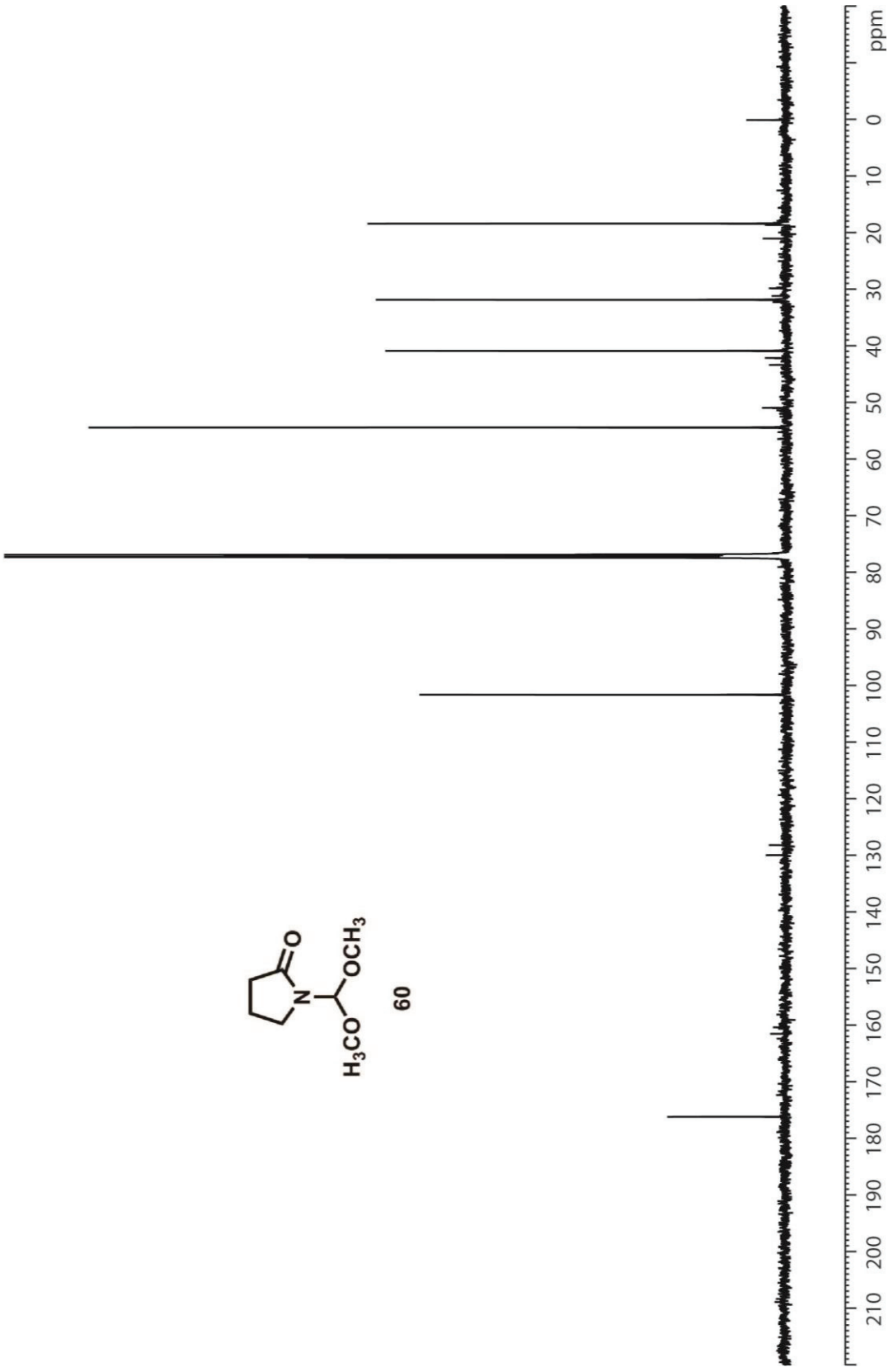
X-ray structures for compounds **113a** and **113b**.

**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of 1-(dimethoxymethyl)pyrrolidin-2-one (60)**



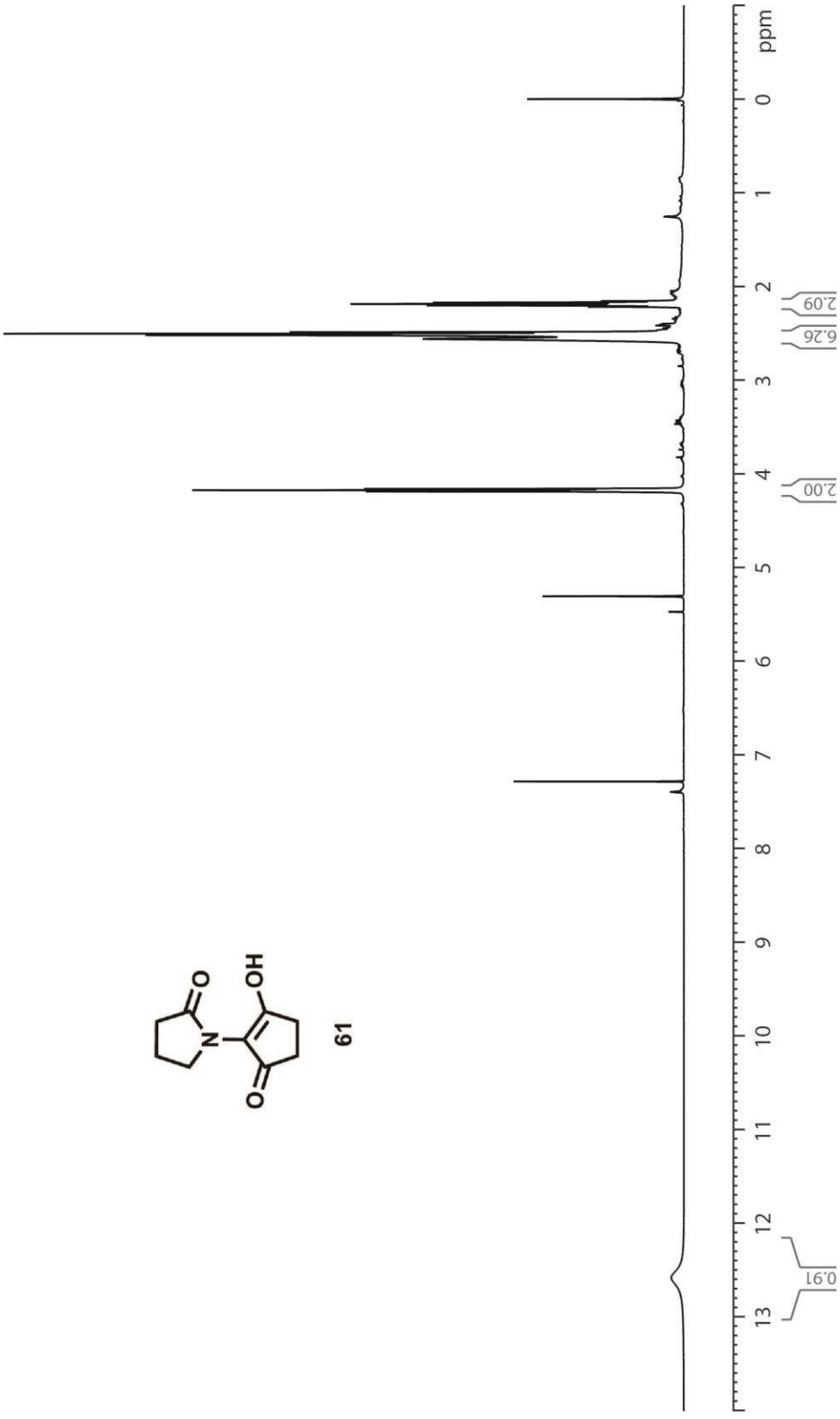

60

**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of 1-(dimethoxymethyl)pyrrolidin-2-one (60)**

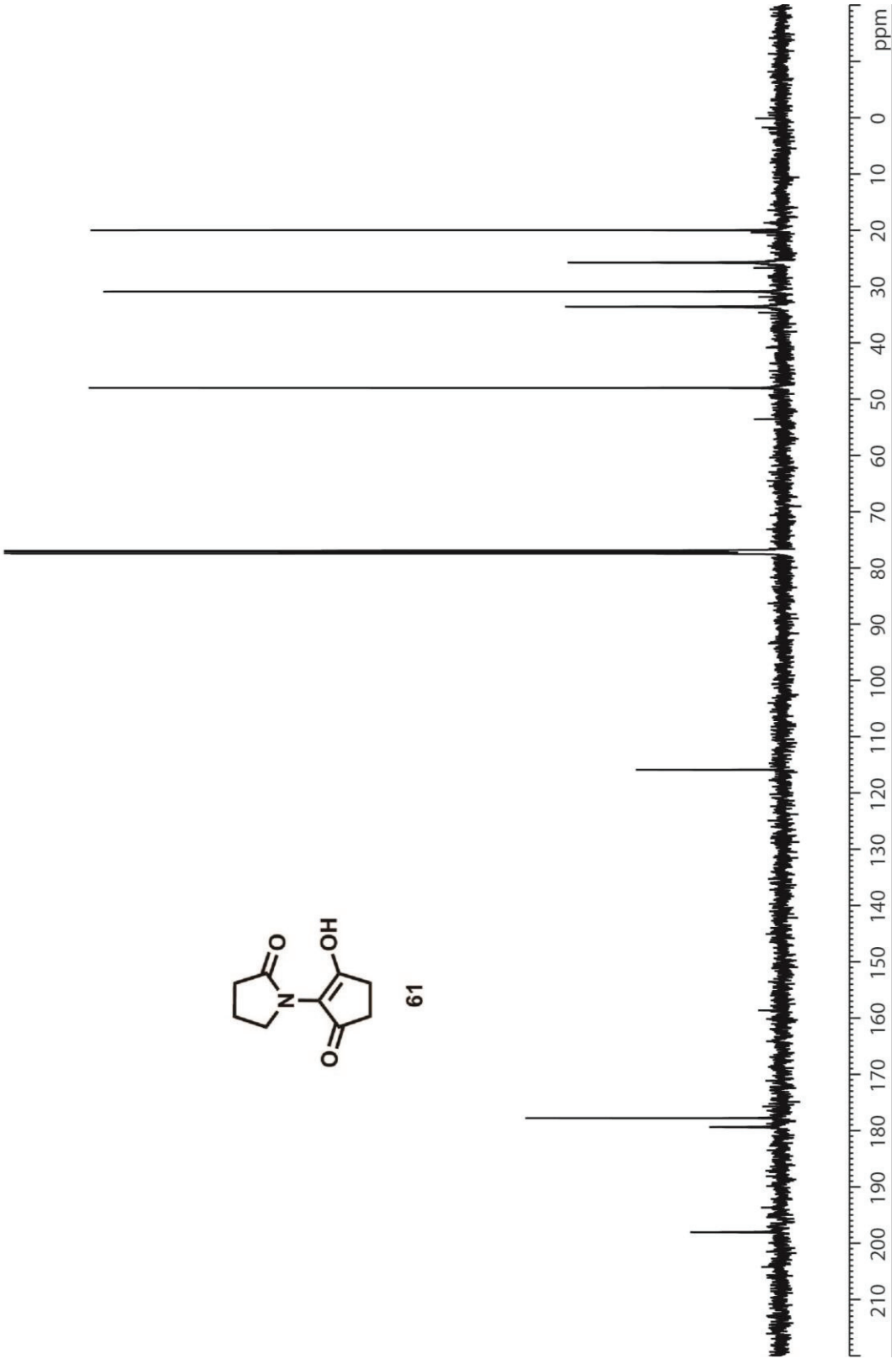



60

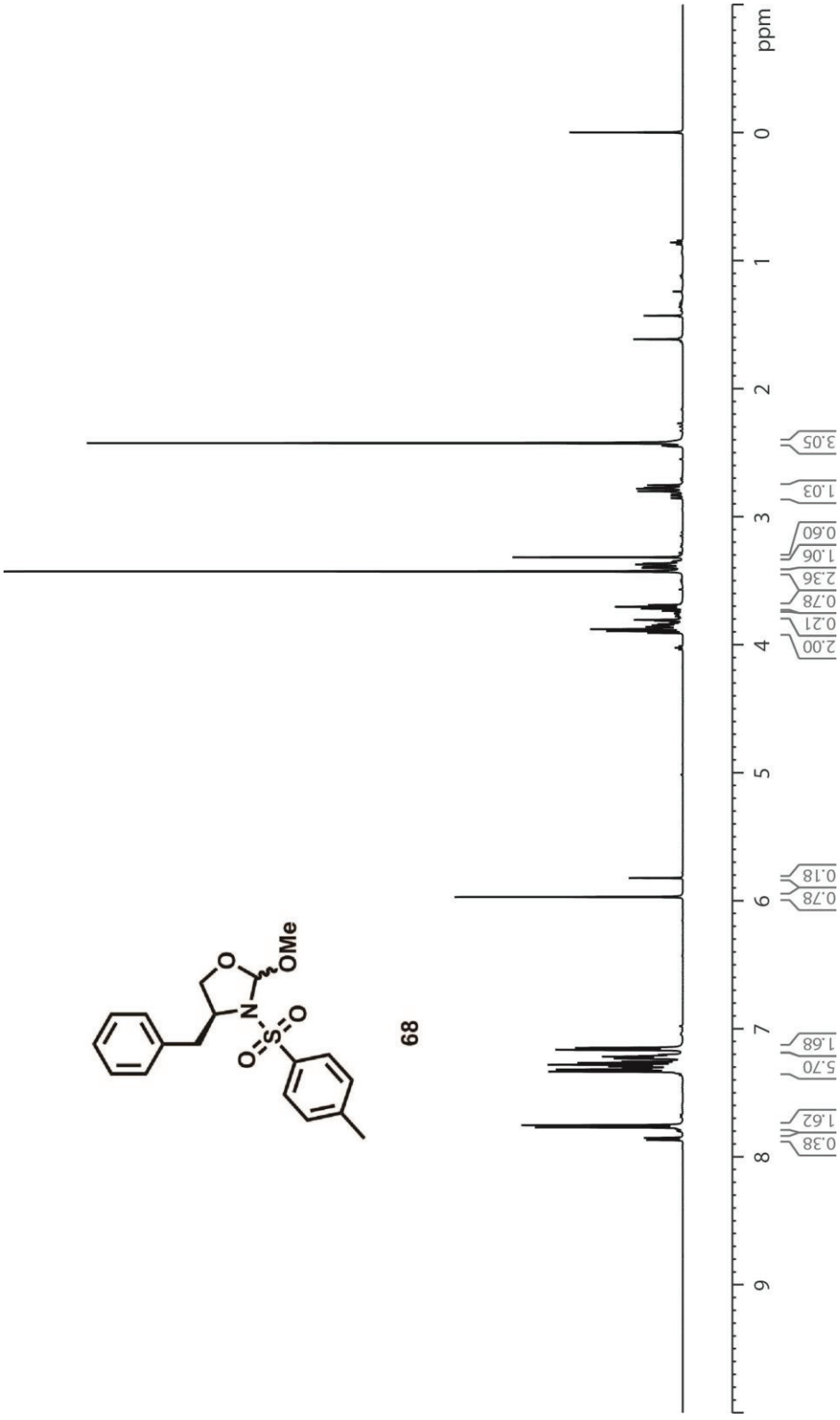
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of 1-(2-hydroxy-5-oxocyclopent-1-enyl)pyrrolidin-2-one (61)**



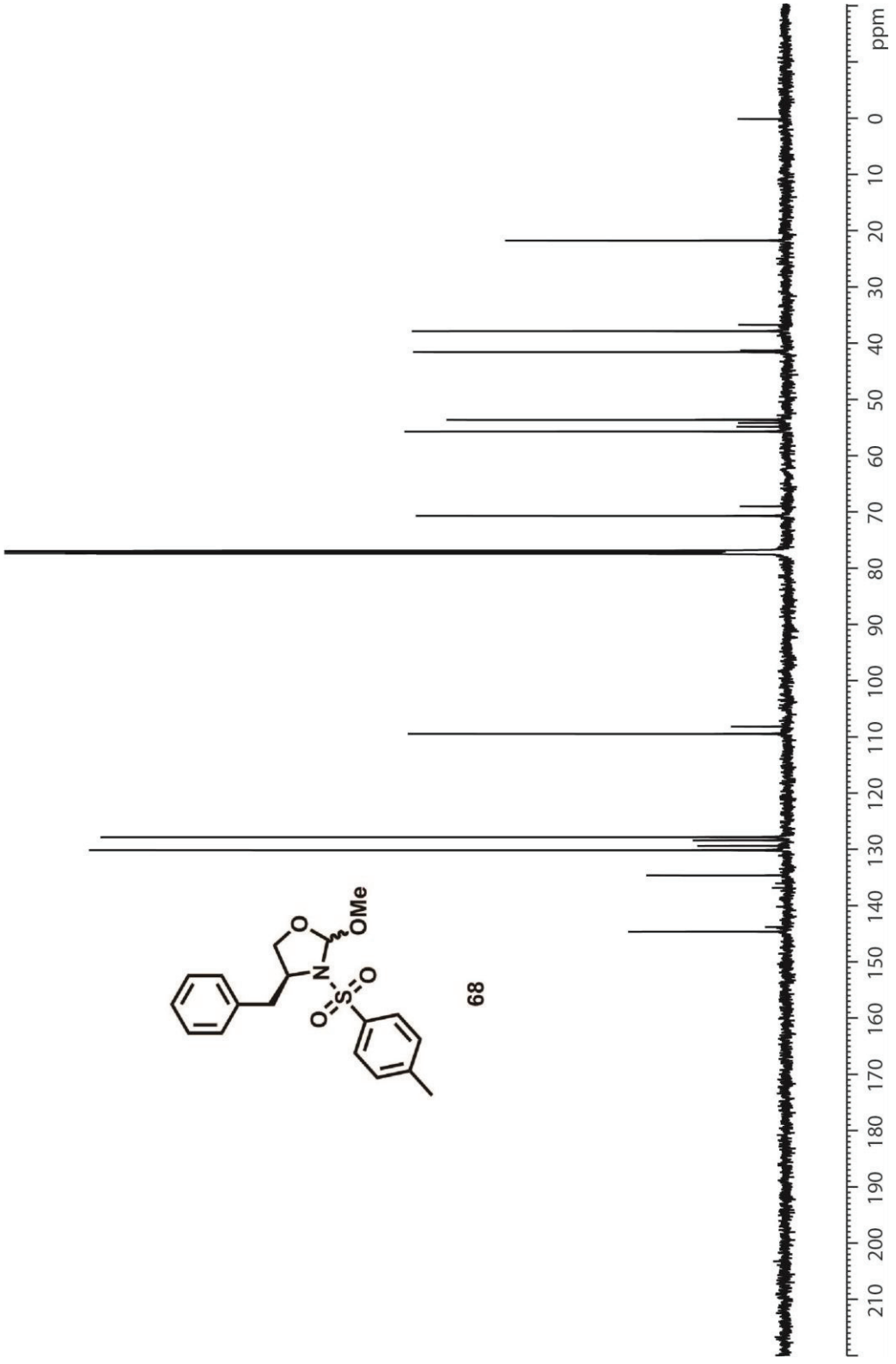
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of 1-(2-hydroxy-5-oxocyclopent-1-enyl)pyrrolidin-2-one (61)**



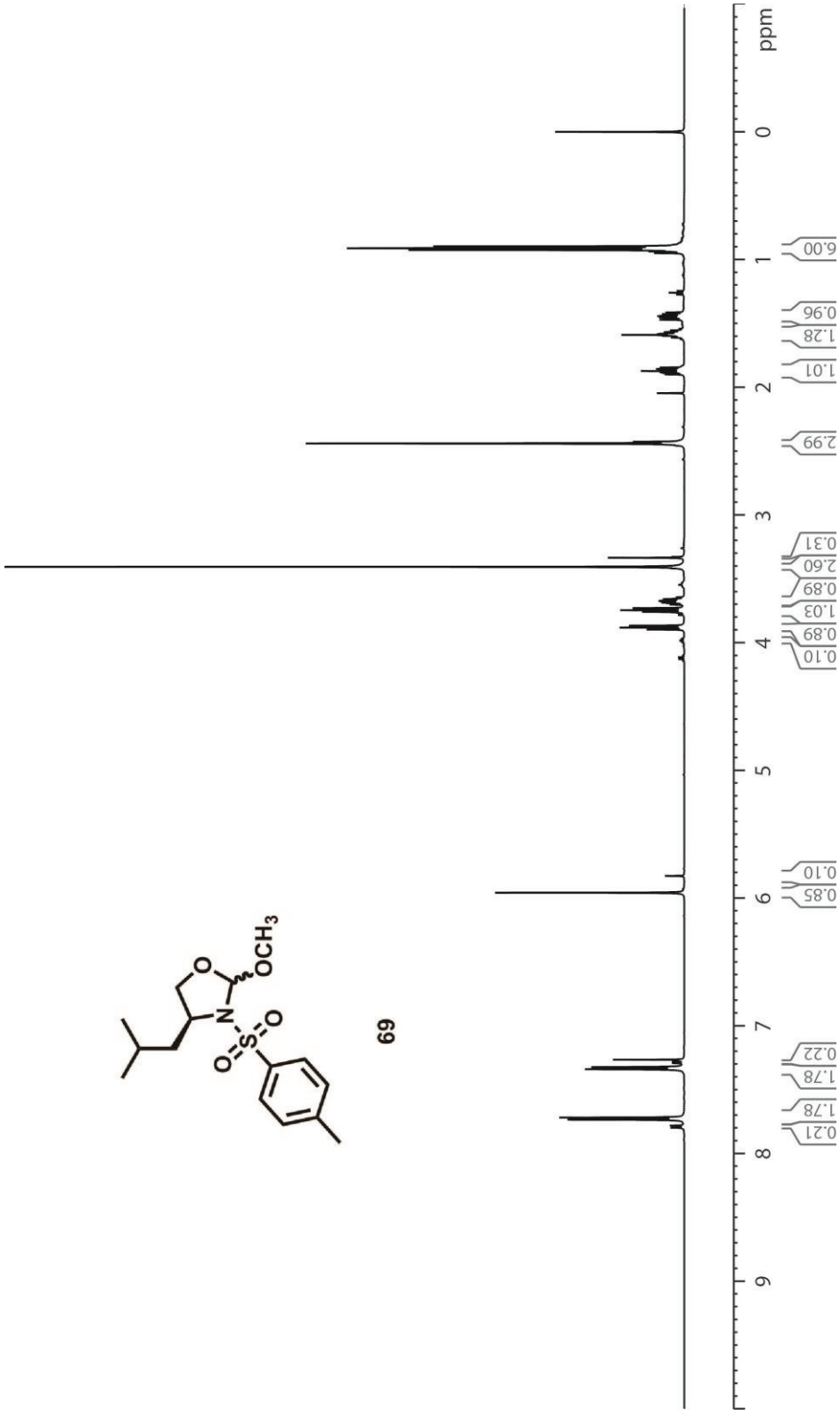
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (2*R*,4*S*)-4-benzyl-2-methoxy-3-(4-methylbenzenesulfonyl)-1,3-oxazolidine + (2*S*,4*S*)-4-benzyl-2-methoxy-3-(4-methylbenzenesulfonyl)-1,3-oxazolidine (68)**



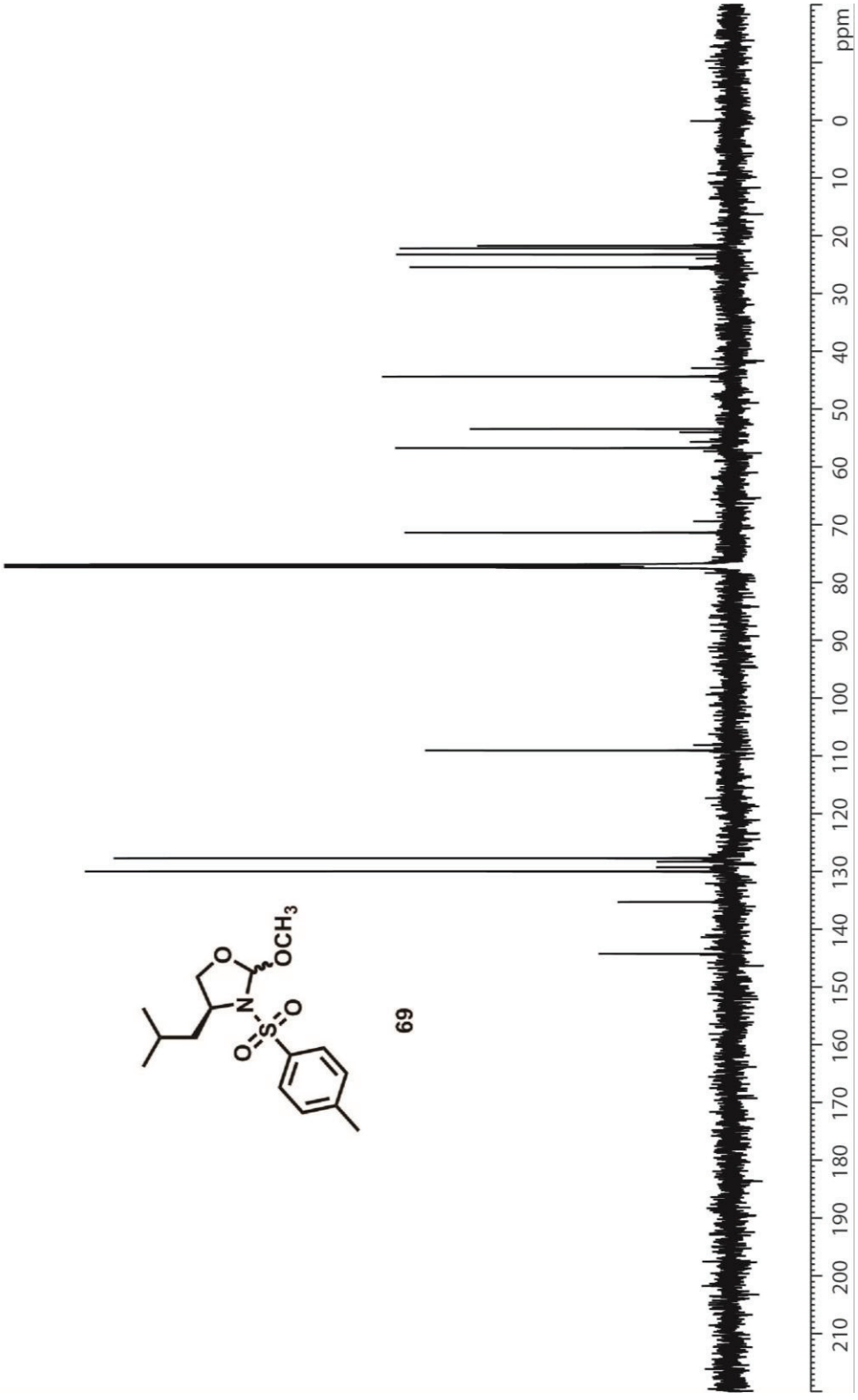
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (2*R*,4*S*)-4-benzyl-2-methoxy-3-(4-methylbenzenesulfonyl)-1,3-oxazolidine + (2*S*,4*S*)-4-benzyl-2-methoxy-3-(4-methylbenzenesulfonyl)-1,3-oxazolidine (68)**



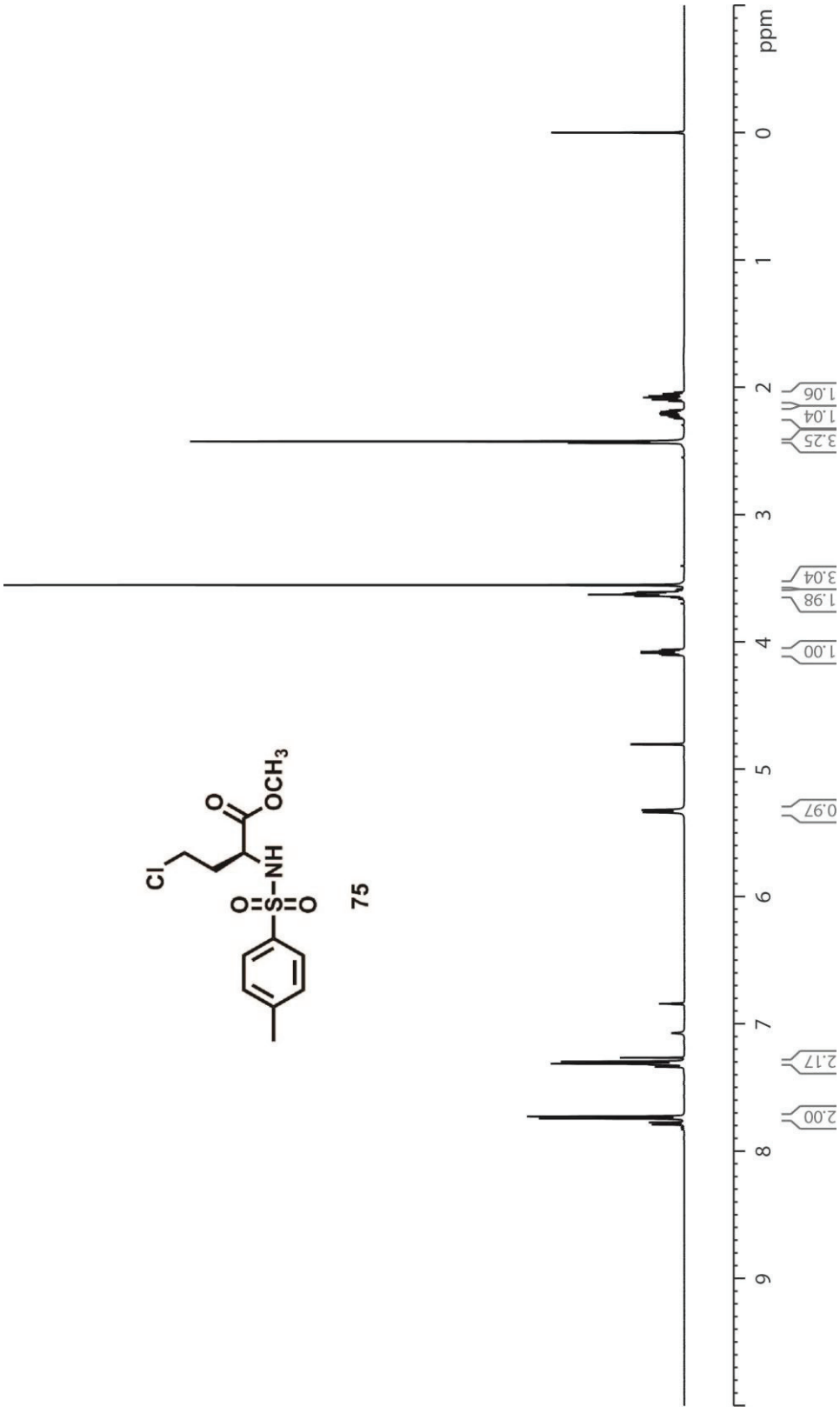
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (2*R*,4*S*)-2-methoxy-3-(4-methylbenzenesulfonyl)-4-(2-methylpropyl)-1,3-oxazolidine + (2*S*,4*S*)-2-methoxy-3-(4-methylbenzenesulfonyl)-4-(2-methylpropyl)-1,3-oxazolidine (69)**



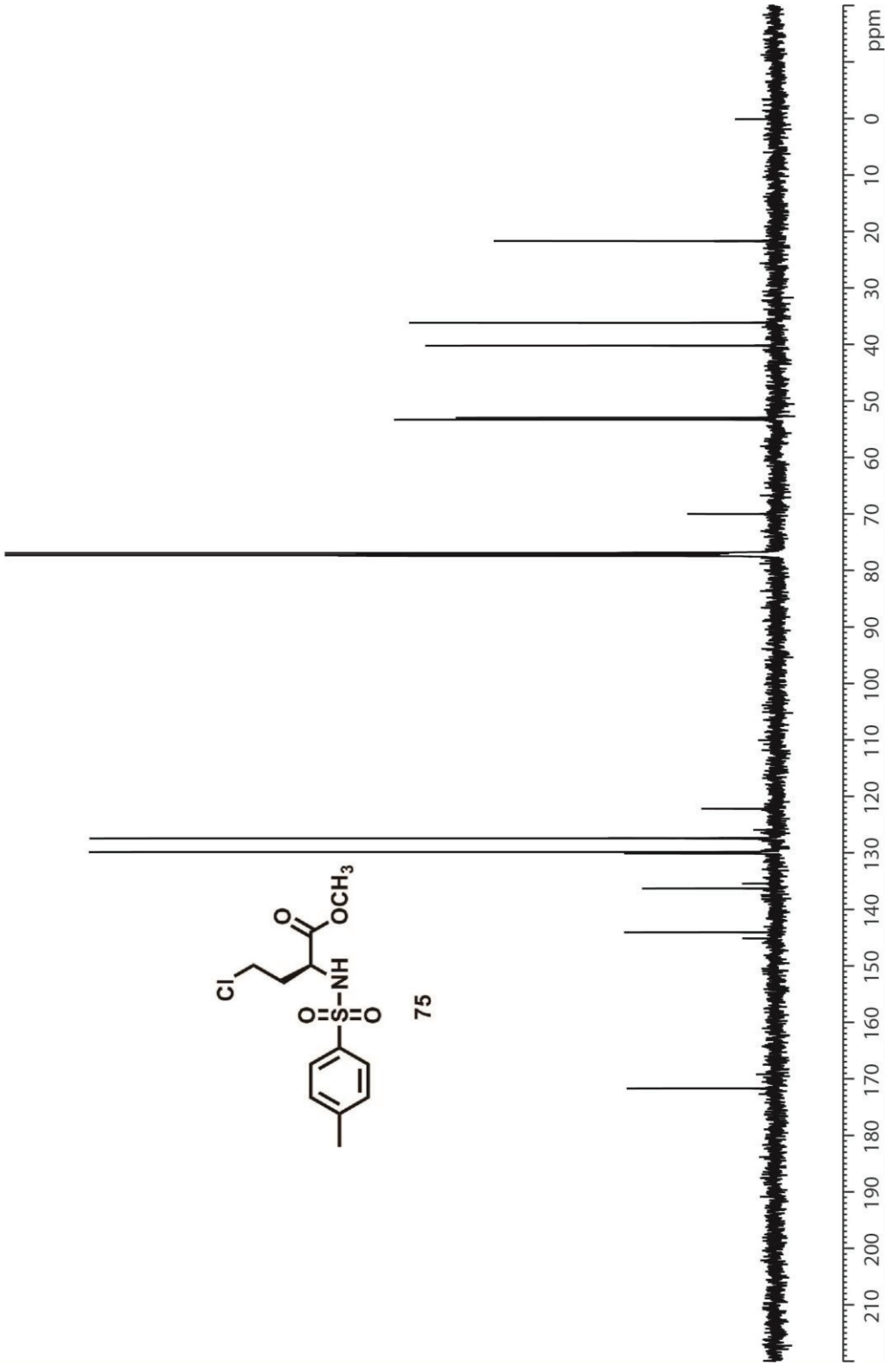
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (2*R*,4*S*)-2-methoxy-3-(4-methylbenzenesulfonyl)-4-(2-methylpropyl)-1,3-oxazolidine + (2*S*,4*S*)-2-methoxy-3-(4-methylbenzenesulfonyl)-4-(2-methylpropyl)-1,3-oxazolidine (69)**



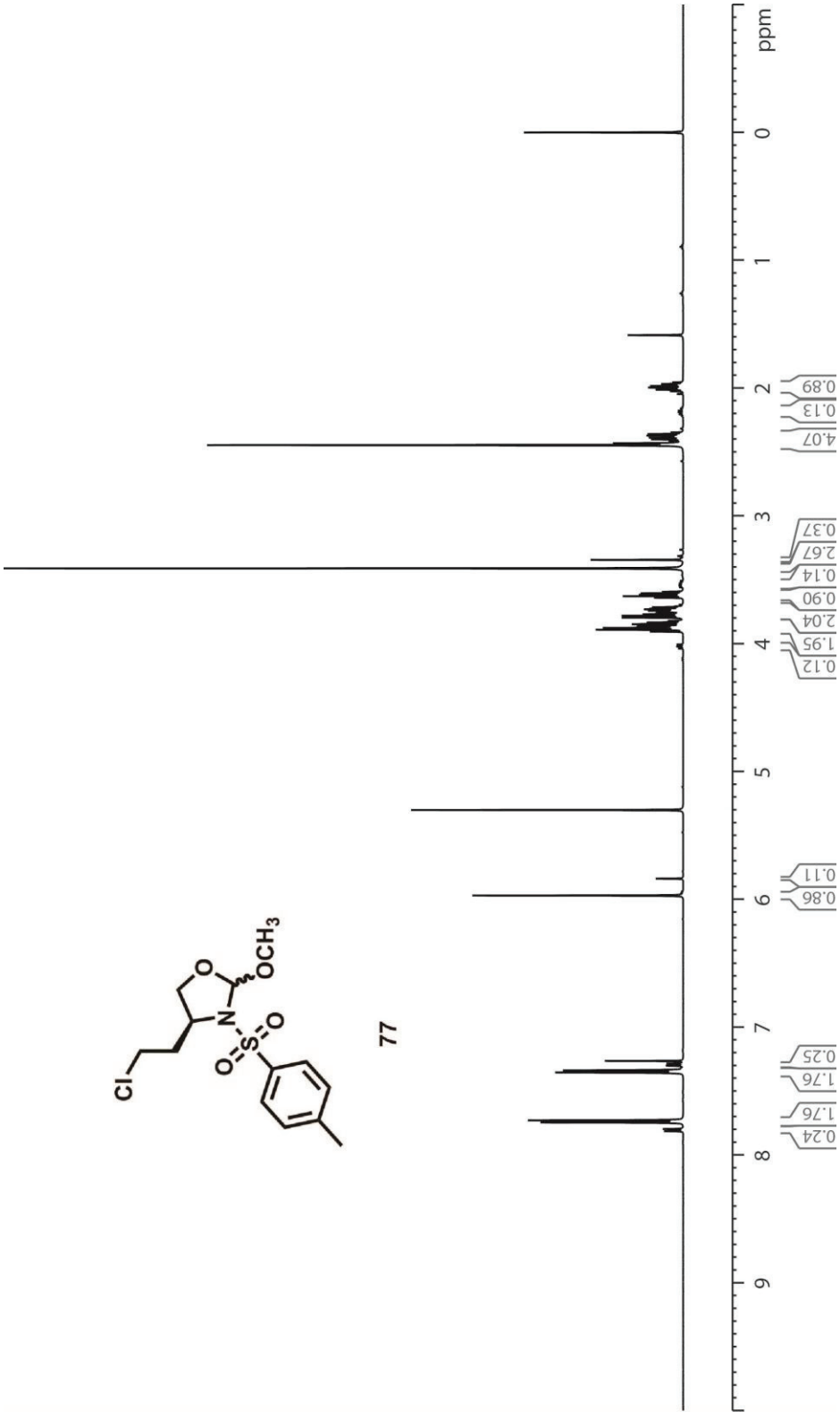
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of *(S)*-methyl 4-chloro-2-(4-methylbenzenesulfonamido)butanoate (75)**



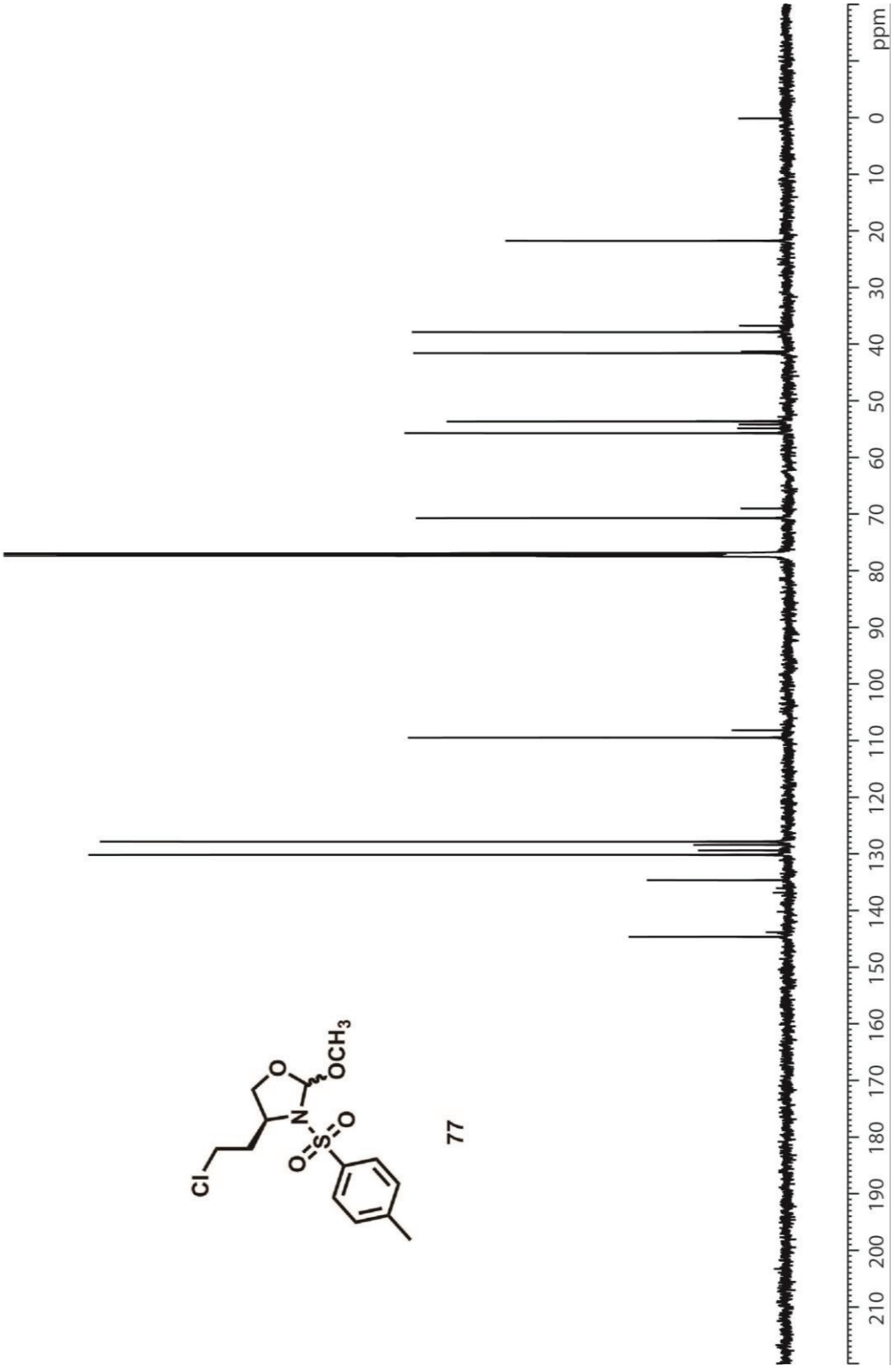
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of *(S)*-methyl 4-chloro-2-(4-methylbenzenesulfonamido)butanoate (75)**



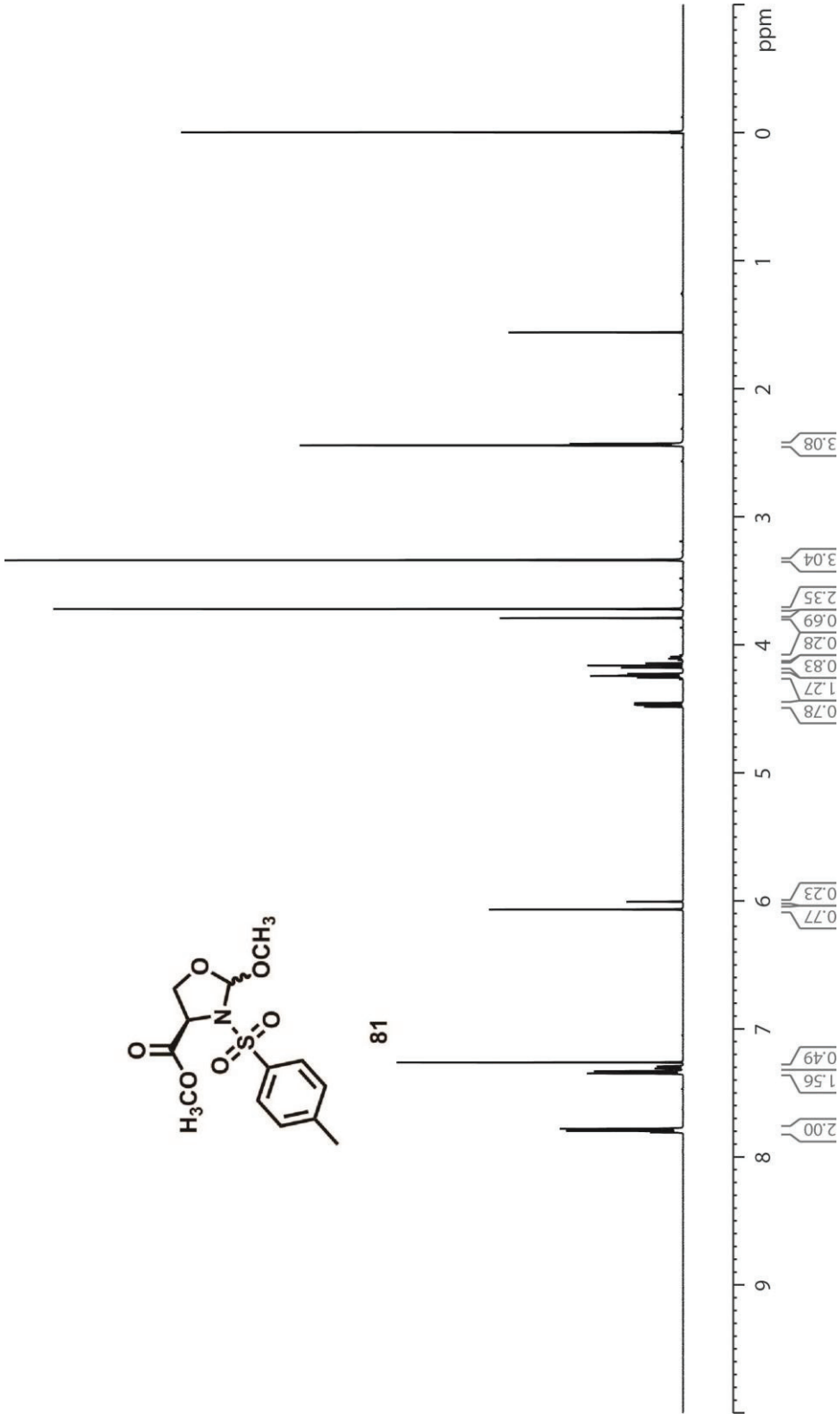
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (2*R*,4*R*)- 4-(2-chloroethyl)-2-methoxy-3-(4-methylbenzenesulfonyl)-1,3-oxazolidine + (2*S*,4*R*)- 4-(2-chloroethyl)-2-methoxy-3-(4-methylbenzenesulfonyl)-1,3-oxazolidine (77)**



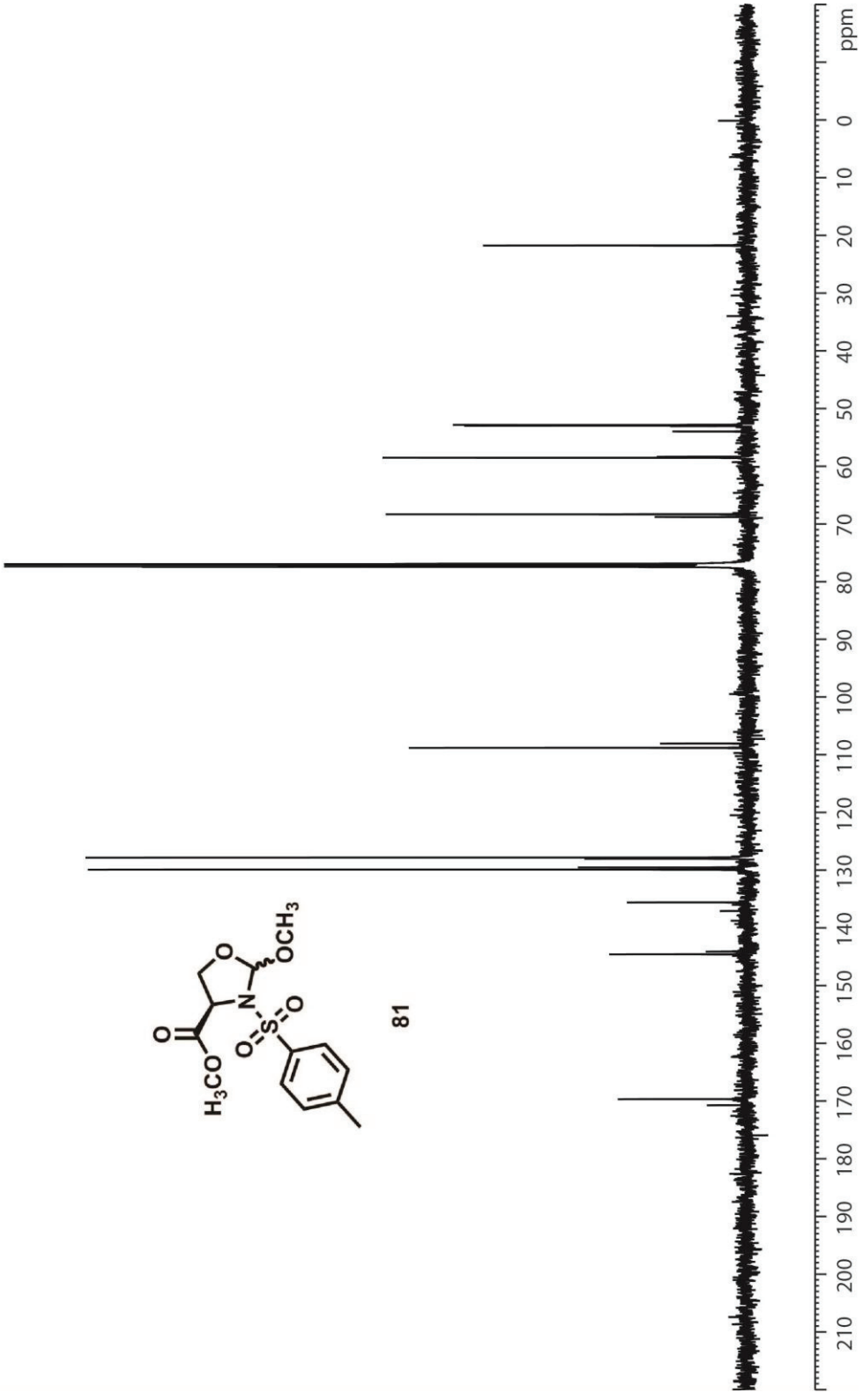
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (2*R*,4*R*)- 4-(2-chloroethyl)-2-methoxy-3-(4-methylbenzenesulfonyl)-1,3-oxazolidine + (2*S*,4*R*)- 4-(2-chloroethyl)-2-methoxy-3-(4-methylbenzenesulfonyl)-1,3-oxazolidine (77)**



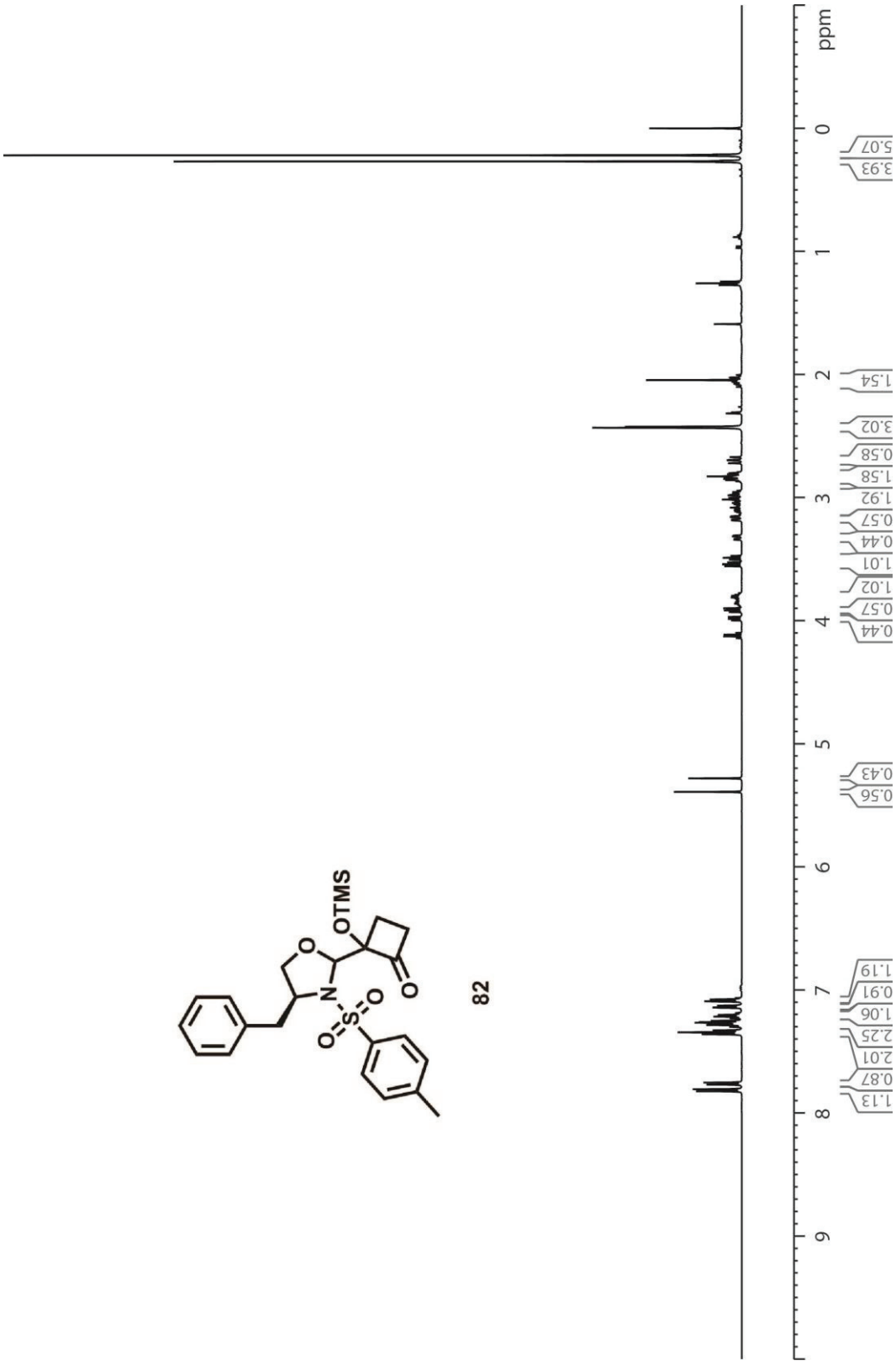
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of methyl (2*R*,4*R*)-2-methoxy-3-(4-methylbenzenesulfonyl)-1,3-oxazolidine-4-carboxylate + methyl (2*S*,4*R*)-2-methoxy-3-(4-methylbenzenesulfonyl)-1,3-oxazolidine-4-carboxylate (81)**



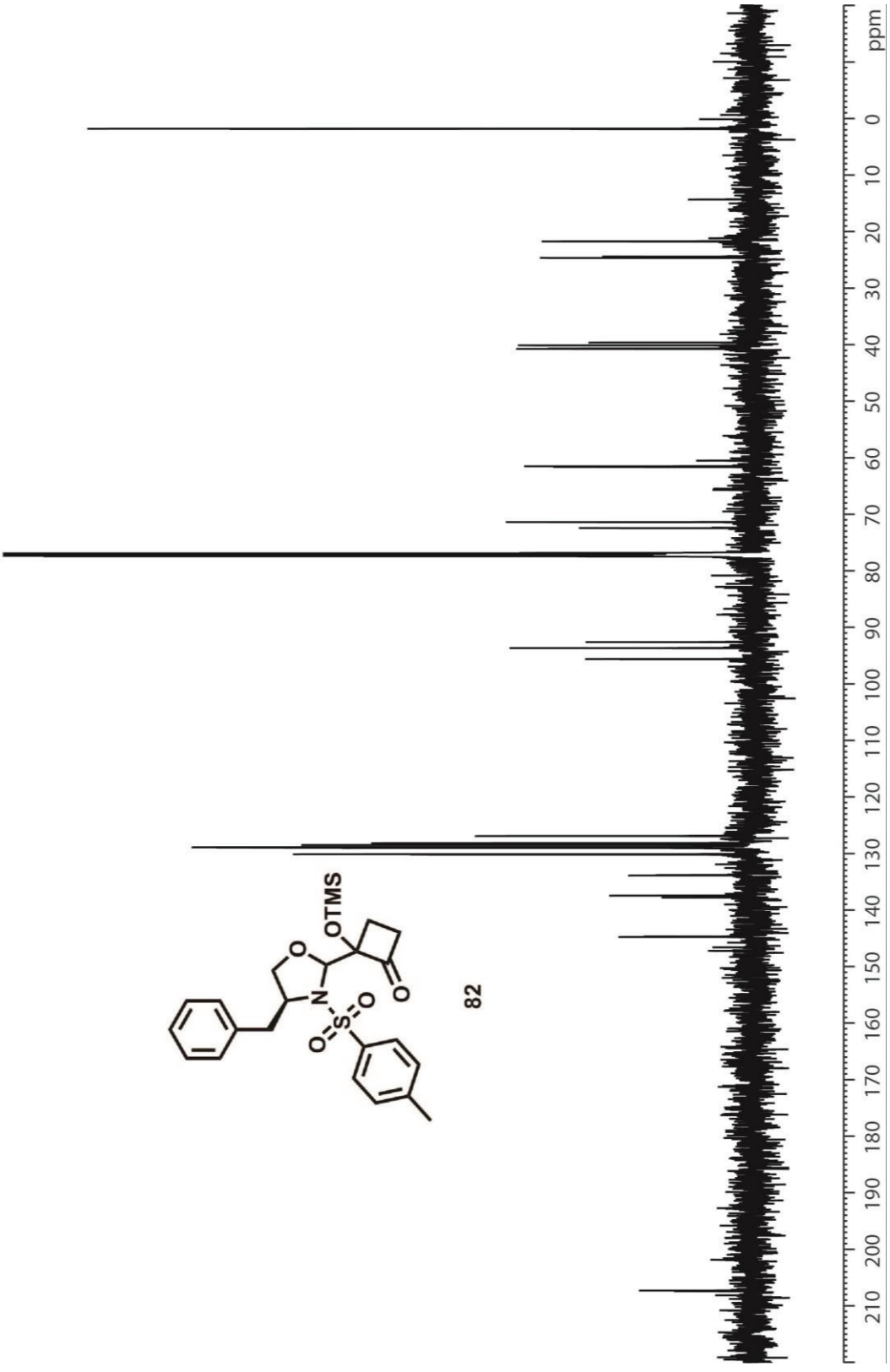
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of methyl (2*R*,4*R*)-2-methoxy-3-(4-methylbenzenesulfonyl)-1,3-oxazolidine-4-carboxylate + methyl (2*S*,4*R*)-2-methoxy-3-(4-methylbenzenesulfonyl)-1,3-oxazolidine-4-carboxylate (81)**



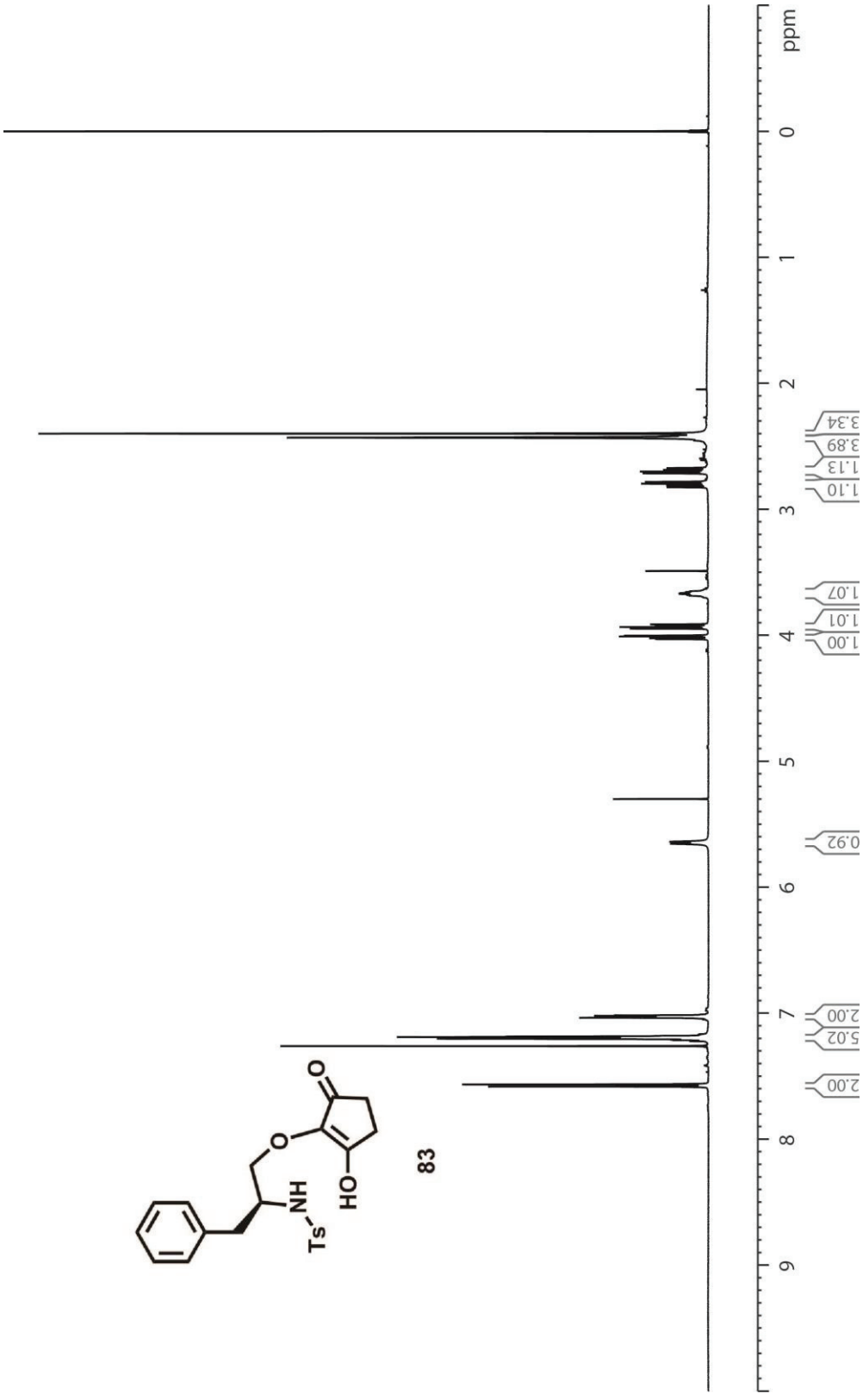
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of 2-((4*S*)-4-benzyl-3-tosyloxazolidin-2-yl)-2-(trimethylsilyloxy)cyclobutanones (82)**



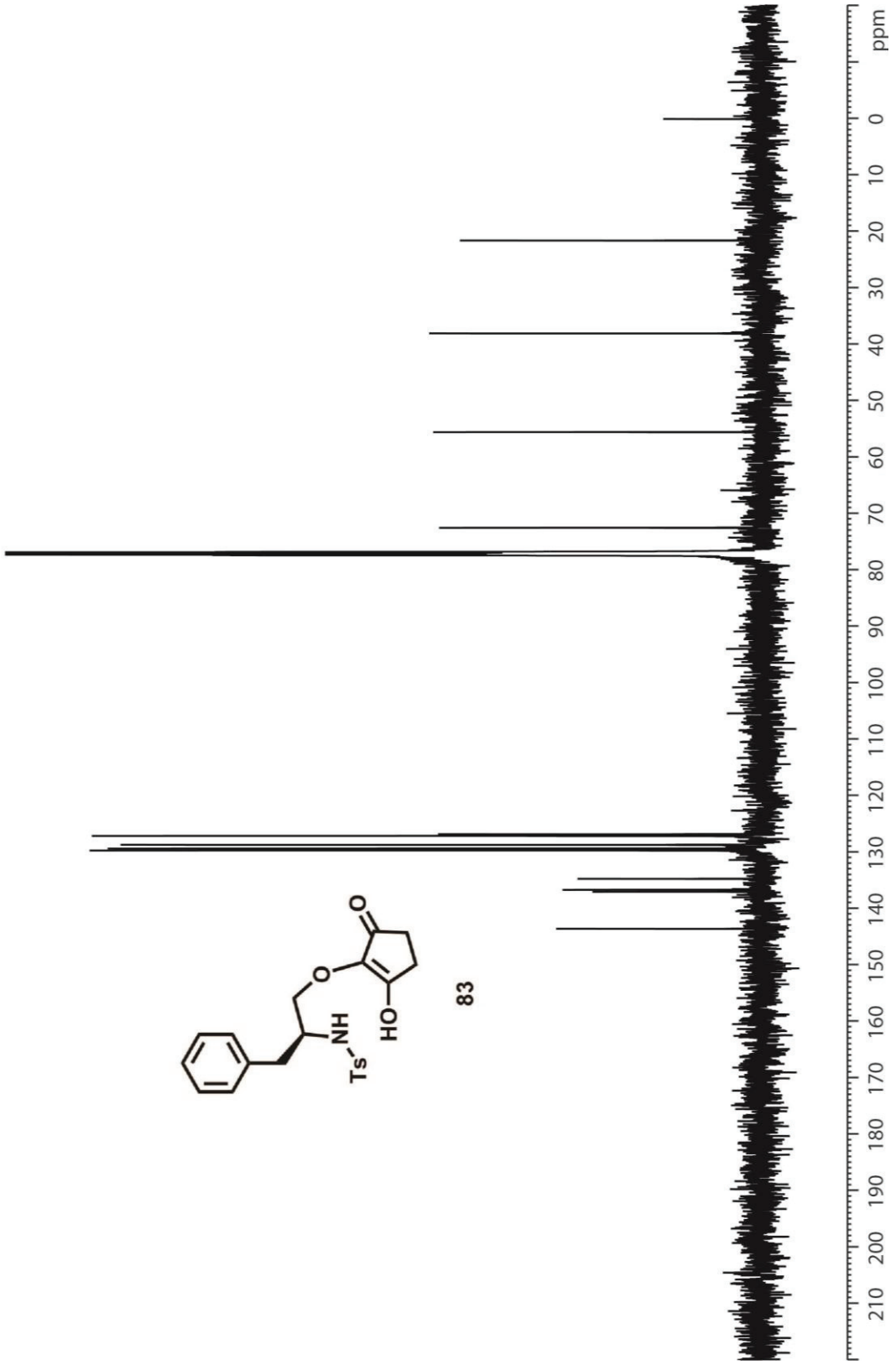
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of 2-((4*S*)-4-benzyl-3-tosyloxazolidin-2-yl)-2-(trimethylsilyloxy)cyclobutanones (82)**



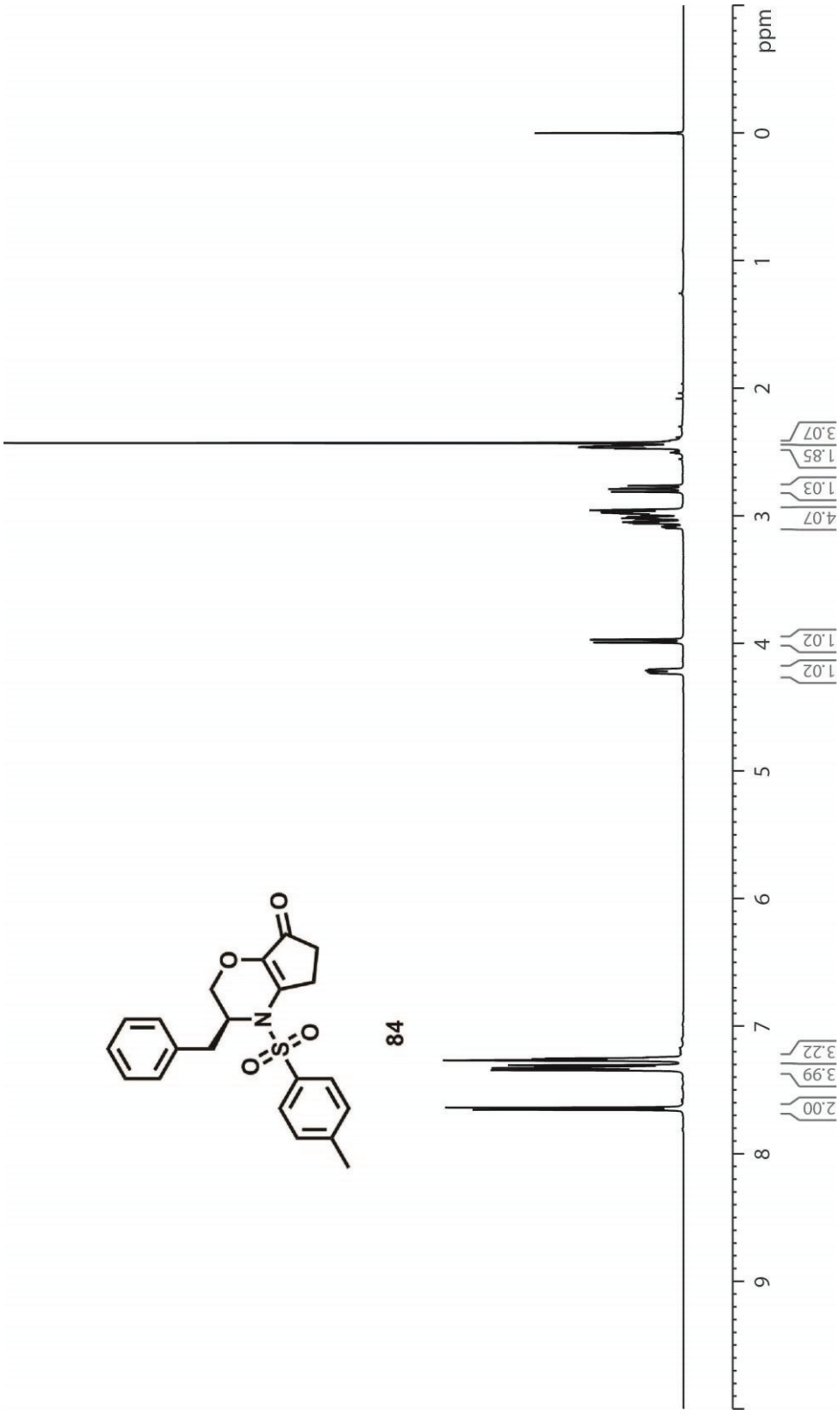
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (*S*)-*N*-(1-(2-hydroxy-5-oxocyclopent-1-enyloxy)-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (83)**



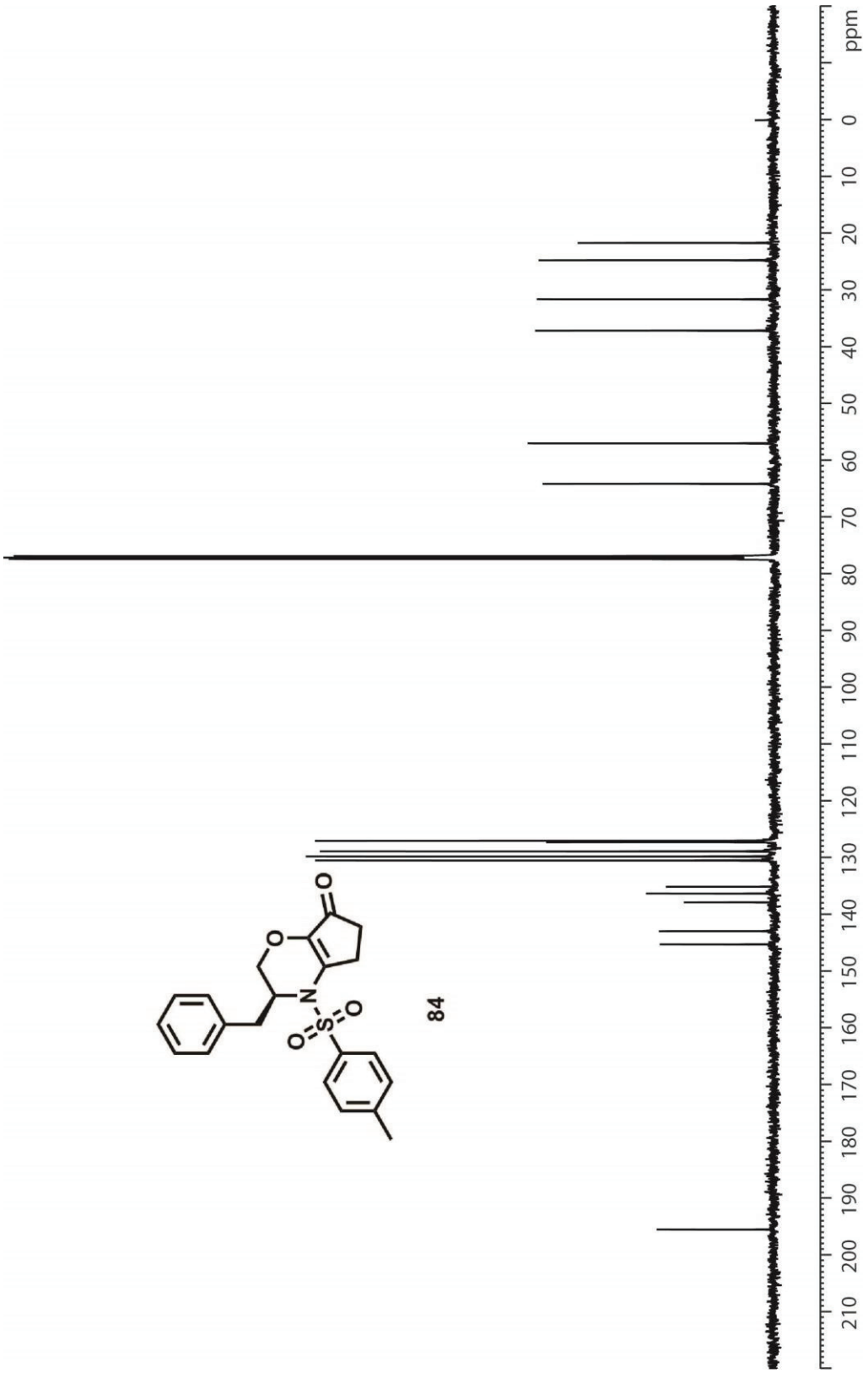
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (*S*)-*N*-(1-(2-hydroxy-5-oxocyclopent-1-enyloxy)-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (83)**



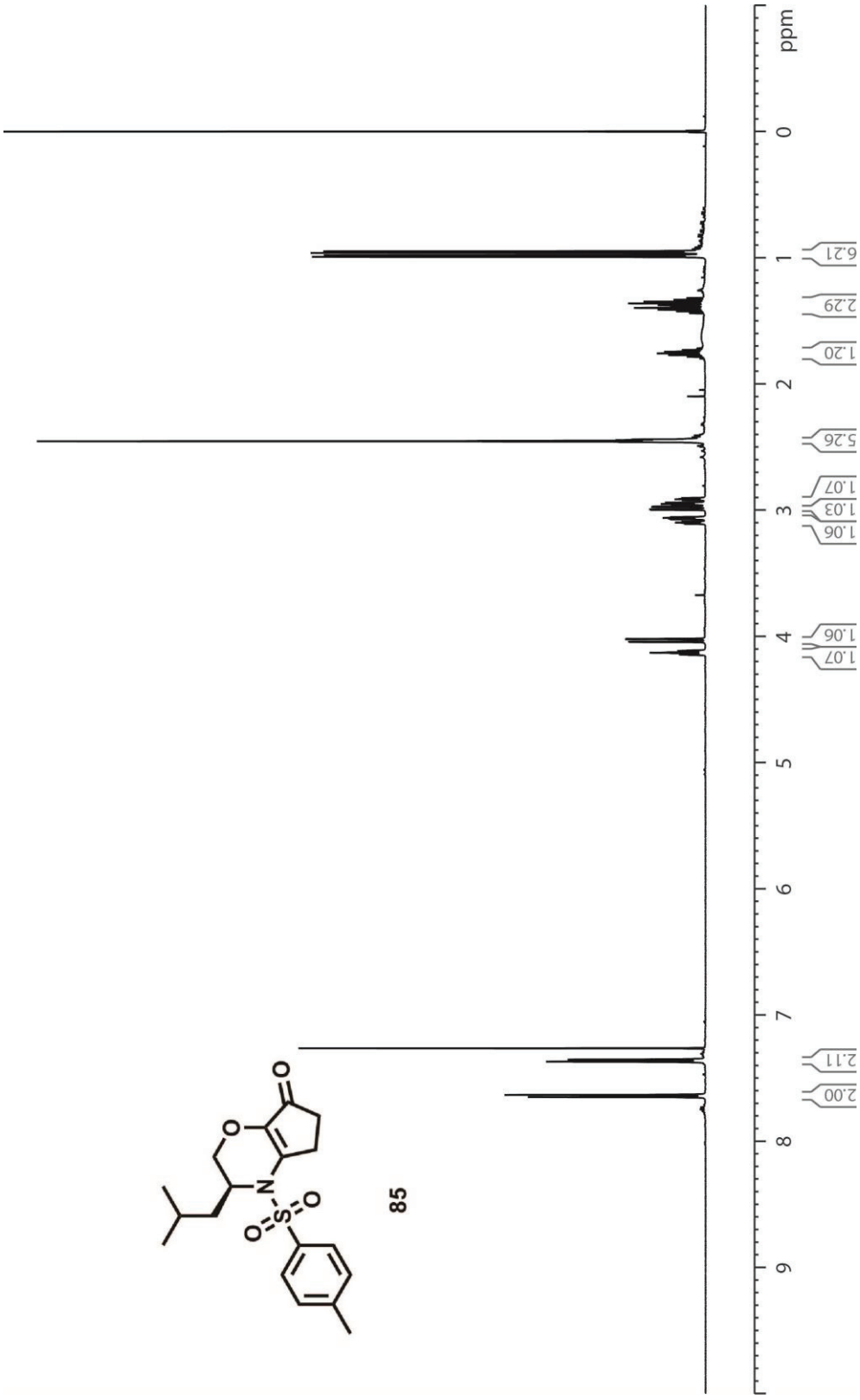
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (3*S*)-3-benzyl-4-(4-methylbenzenesulfonyl)-3,4,6,7-tetrahydro-2*H*-cyclopenta[1,4-*b*]oxazin-7-one (84)**



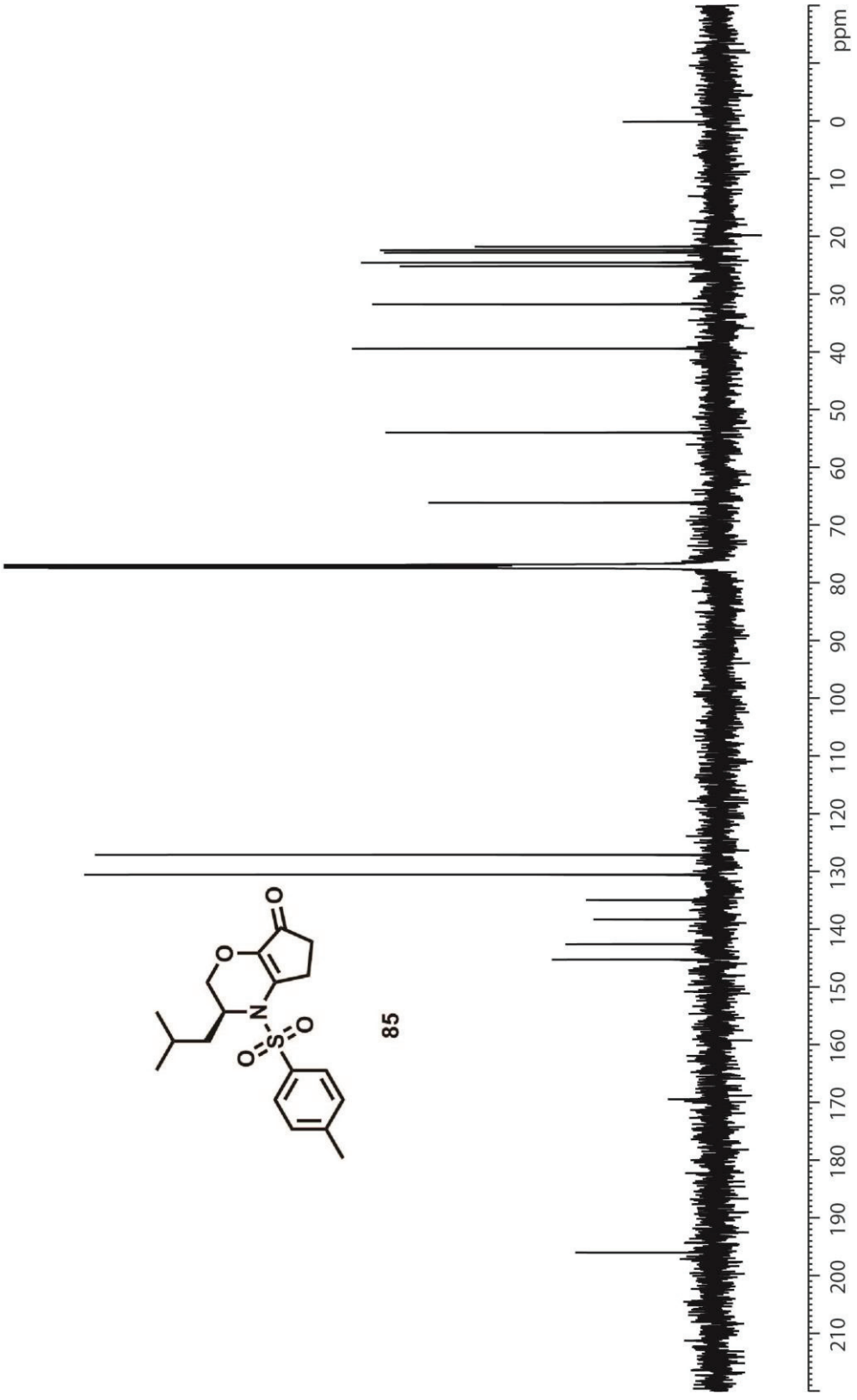
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (3*S*)-3-benzyl-4-(4-methylbenzenesulfonyl)-3,4,6,7-tetrahydro-2*H*-cyclopenta[1,4-*b*]oxazin-7-one (84)**



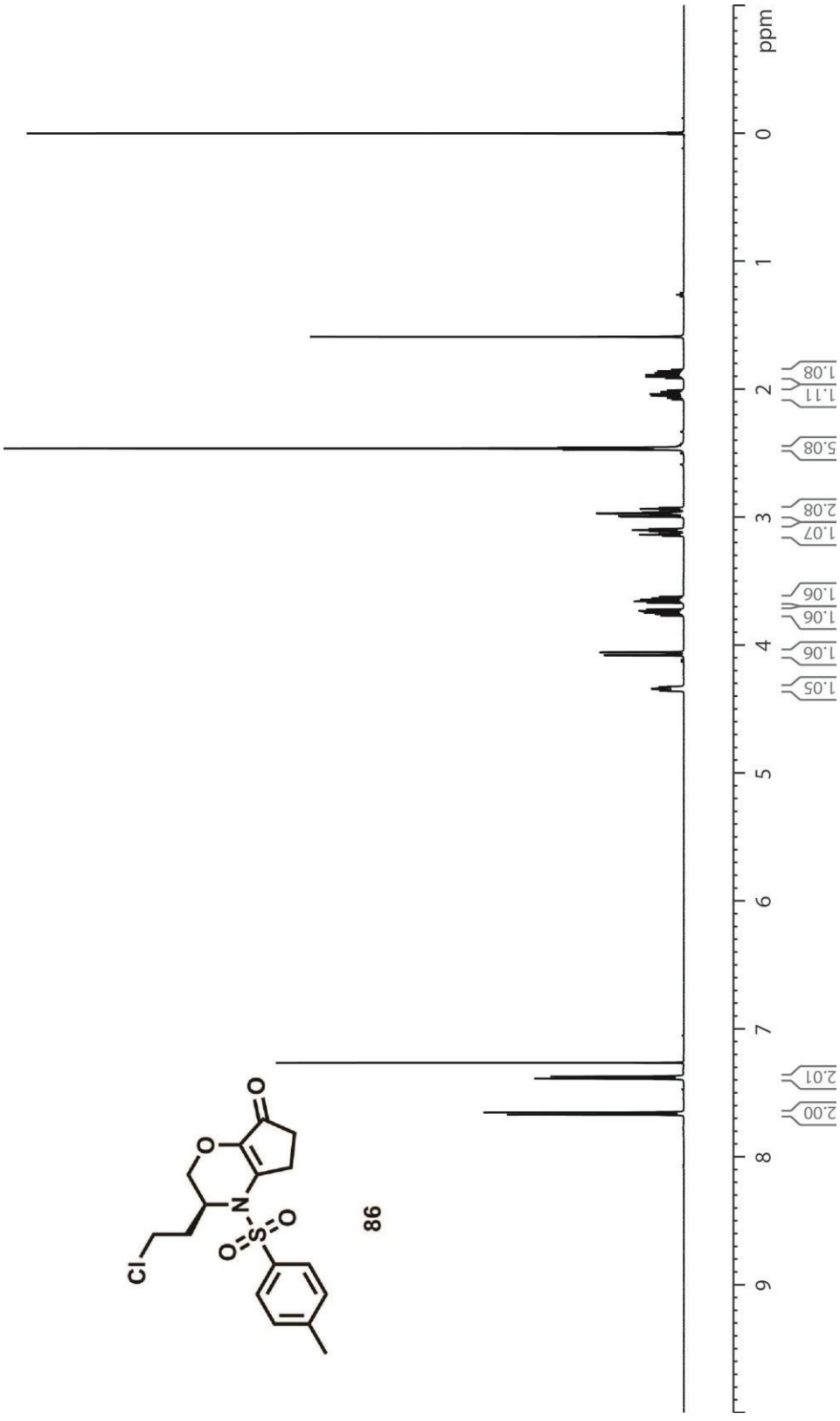
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (3*S*)-4-(4-methylbenzenesulfonyl)-3-(2-methylpropyl)-3,4,6,7-tetrahydro-2*H*-cyclopenta[1,4-*b*]oxazin-7-one (85)**



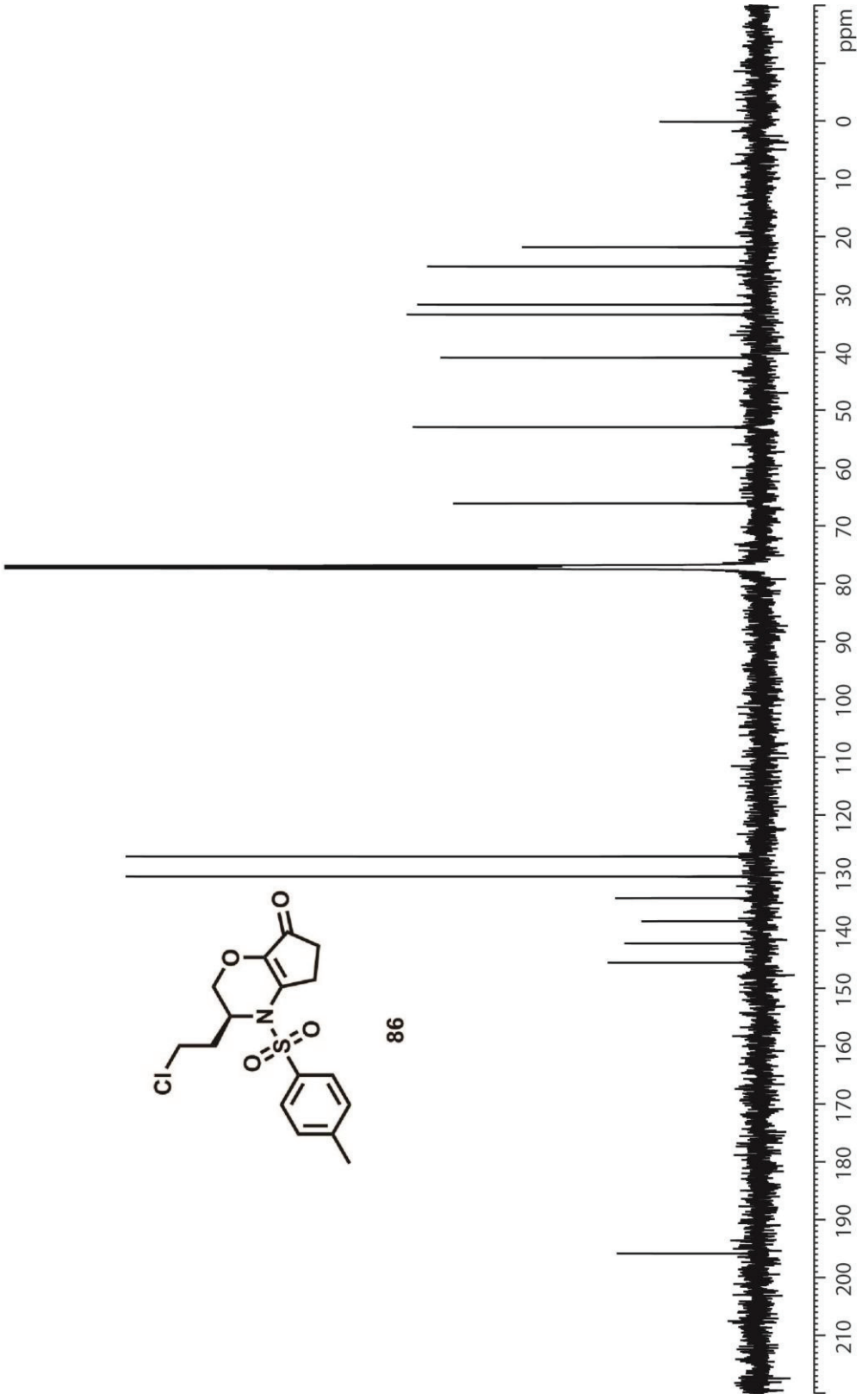
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (3*S*)-4-(4-methylbenzenesulfonyl)-3-(2-methylpropyl)-3,4,6,7-tetrahydro-2*H*-cyclopenta[1,4-*b*]oxazin-7-one (85)**



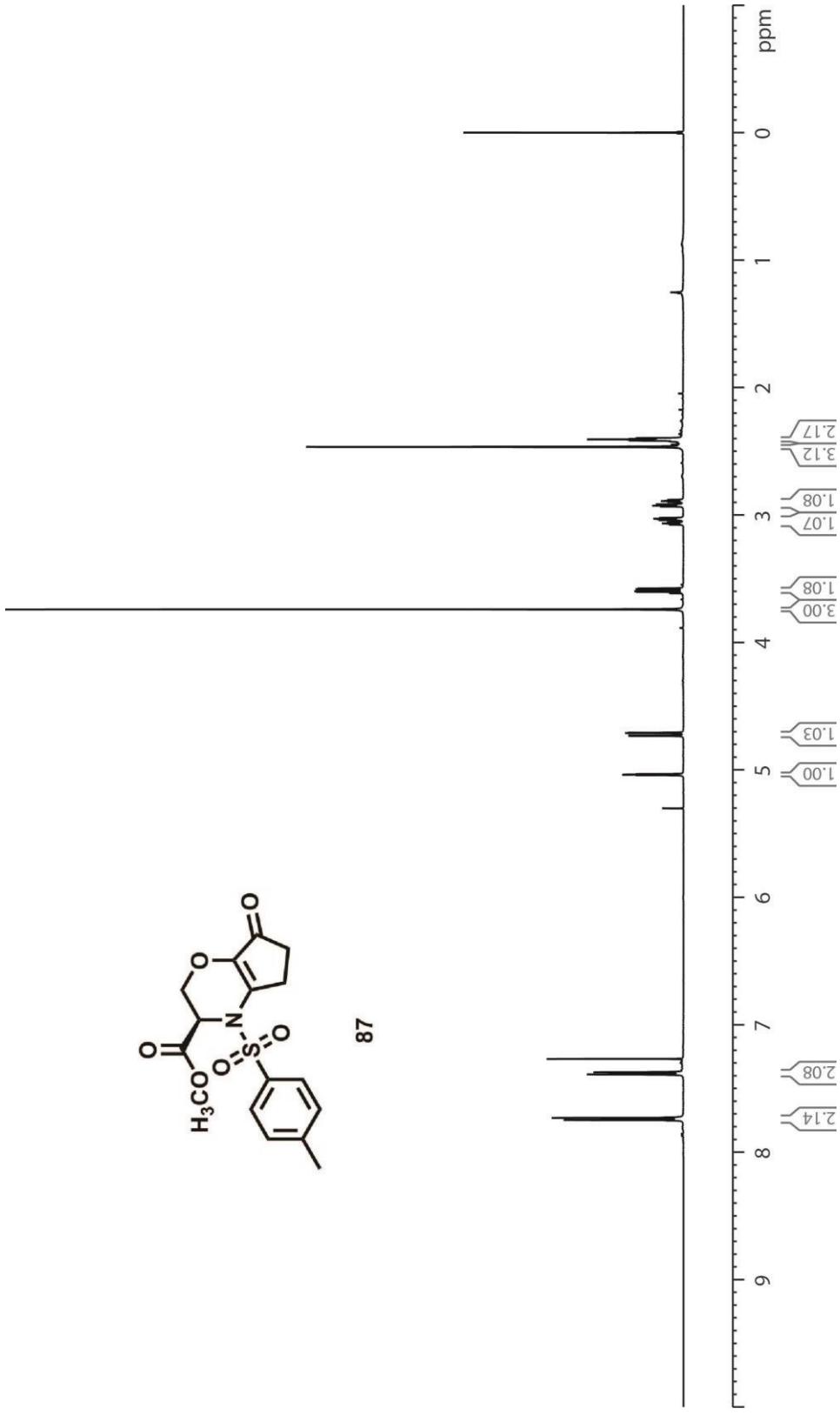
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (3*S*)-3-(2-chloroethyl)-4-(4-methylbenzenesulfonyl)-3,4,6,7-tetrahydro-2*H*-cyclopenta[1,4-*b*]oxazin-7-one (86)**



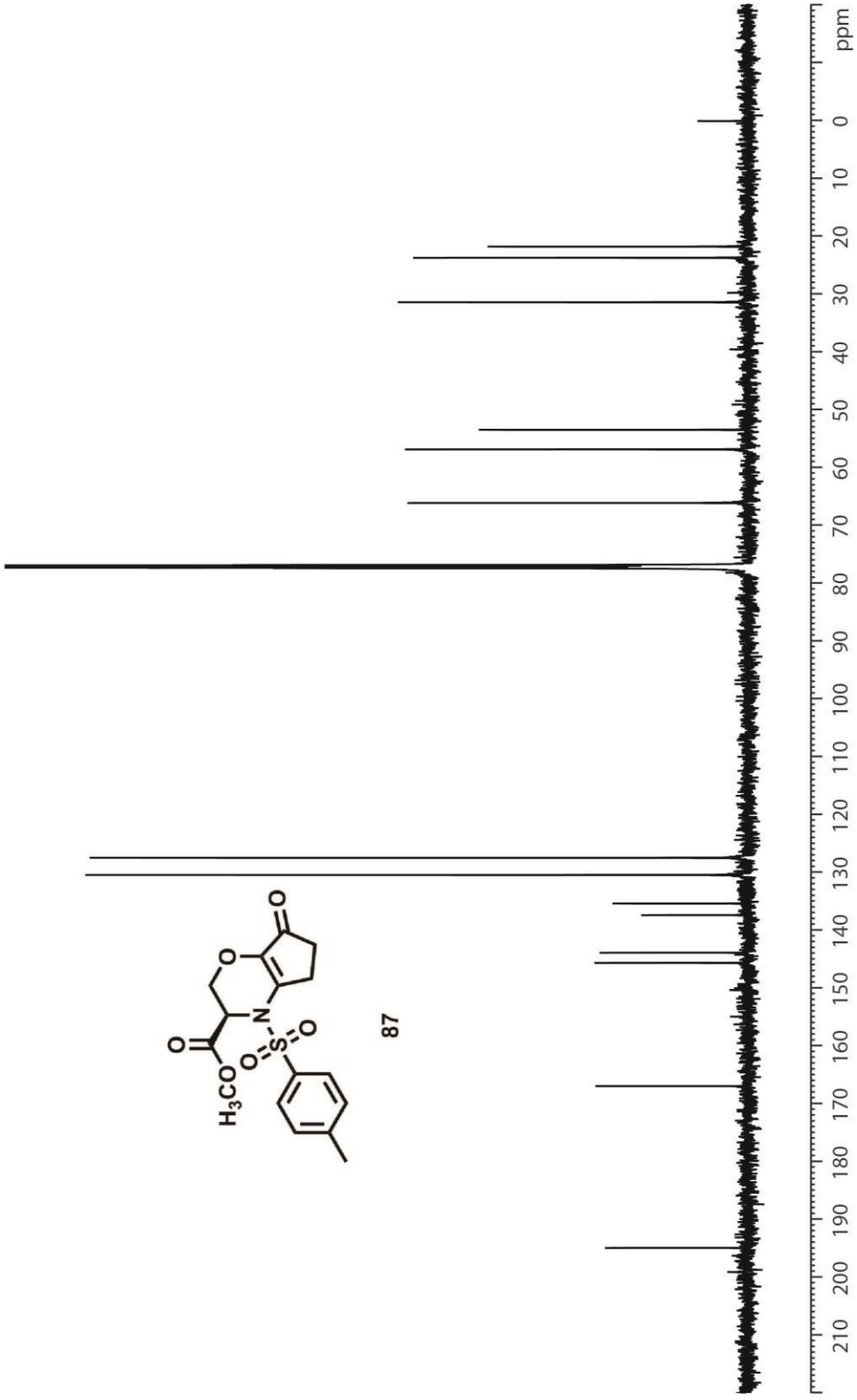
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (3*S*)-3-(2-chloroethyl)-4-(4-methylbenzenesulfonyl)-3,4,6,7-tetrahydro-2*H*-cyclopenta[1,4-*b*]oxazin-7-one (86)**



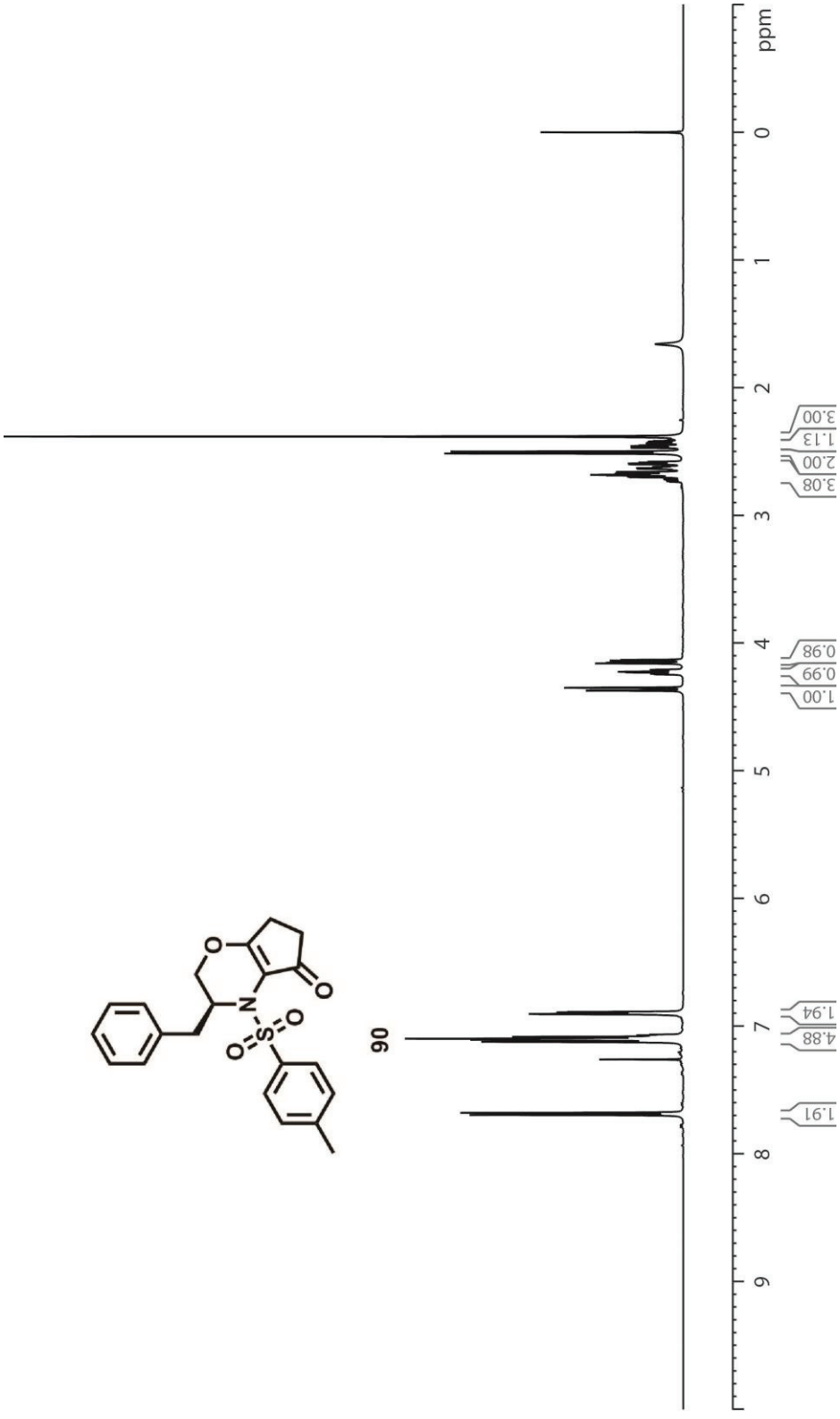
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of methyl (3*R*)-4-(4-methylbenzenesulfonyl)-3,4,6,7-tetrahydro-2*H*-cyclopenta[1,4-*b*]oxazin-7-one-3-carboxylate (87)**



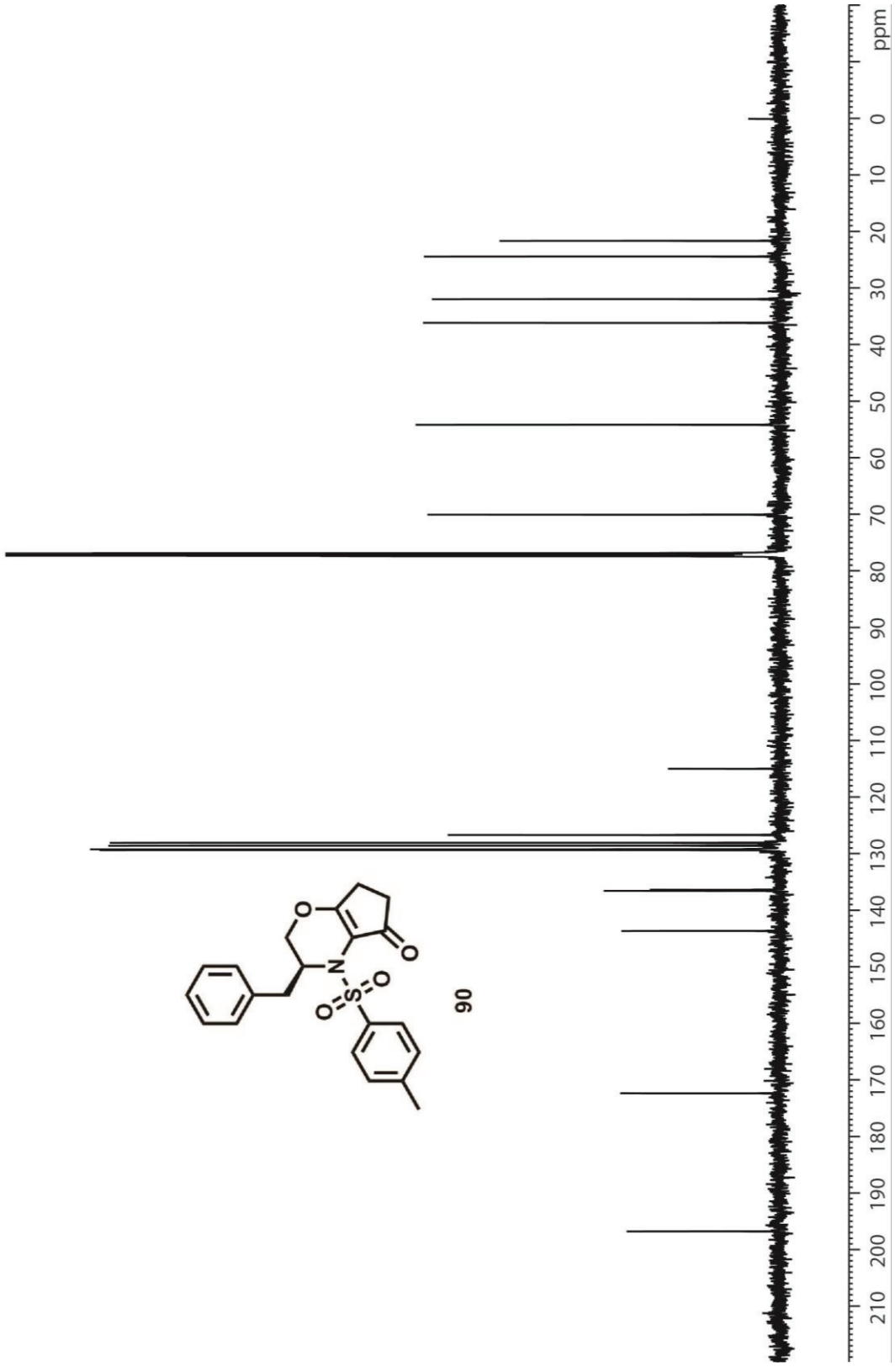
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of methyl (3*R*)-4-(4-methylbenzenesulfonyl)-3,4,6,7-tetrahydro-2*H*-cyclopenta[1,4-*b*]oxazin-7-one-3-carboxylate (87)**



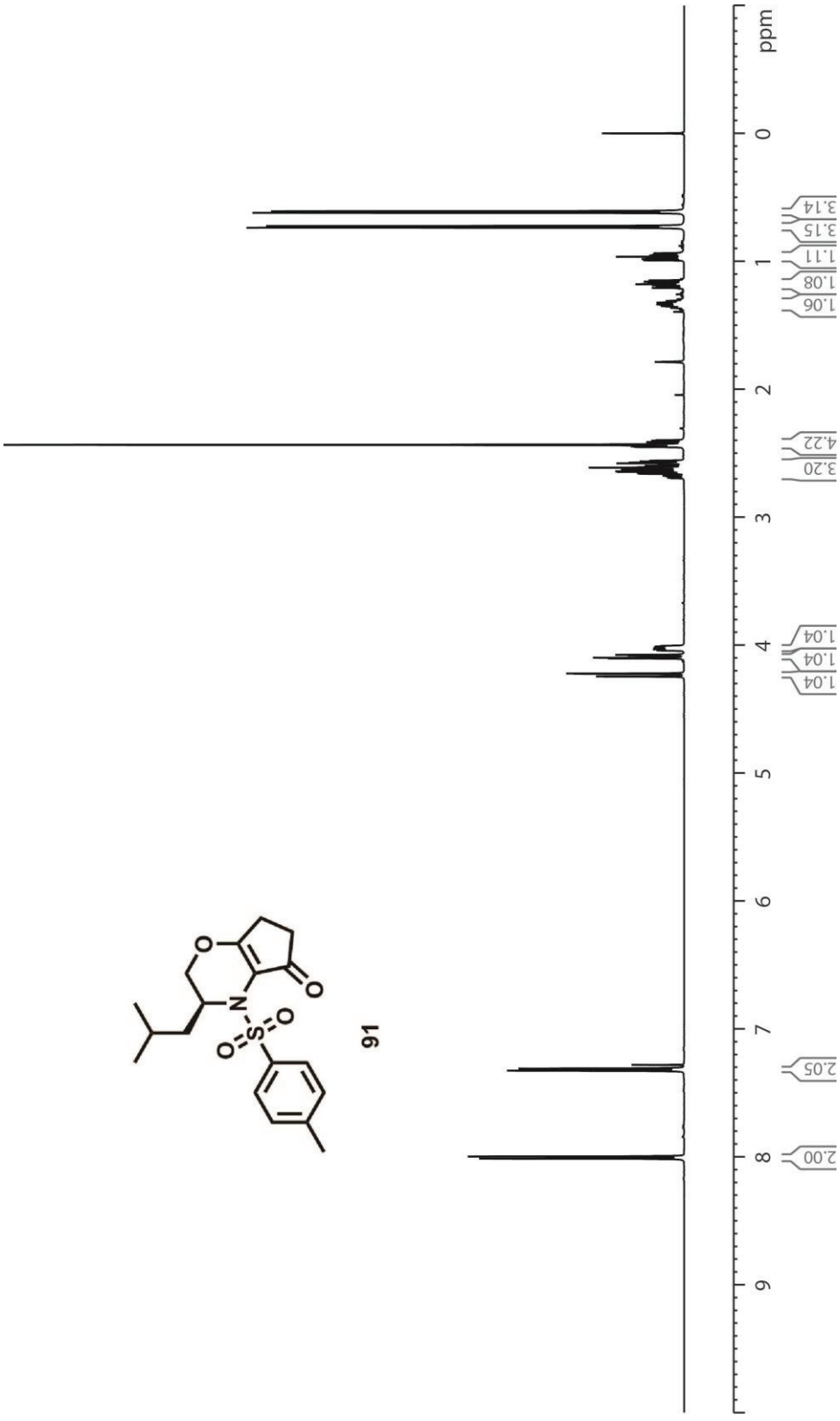
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (*S*)-3-benzyl-4-(4-methylbenzenesulfonyl)-3,4,6,7-tetrahydro-2*H*-cyclopenta[*b*][1,4]oxazin-5-one (90)**



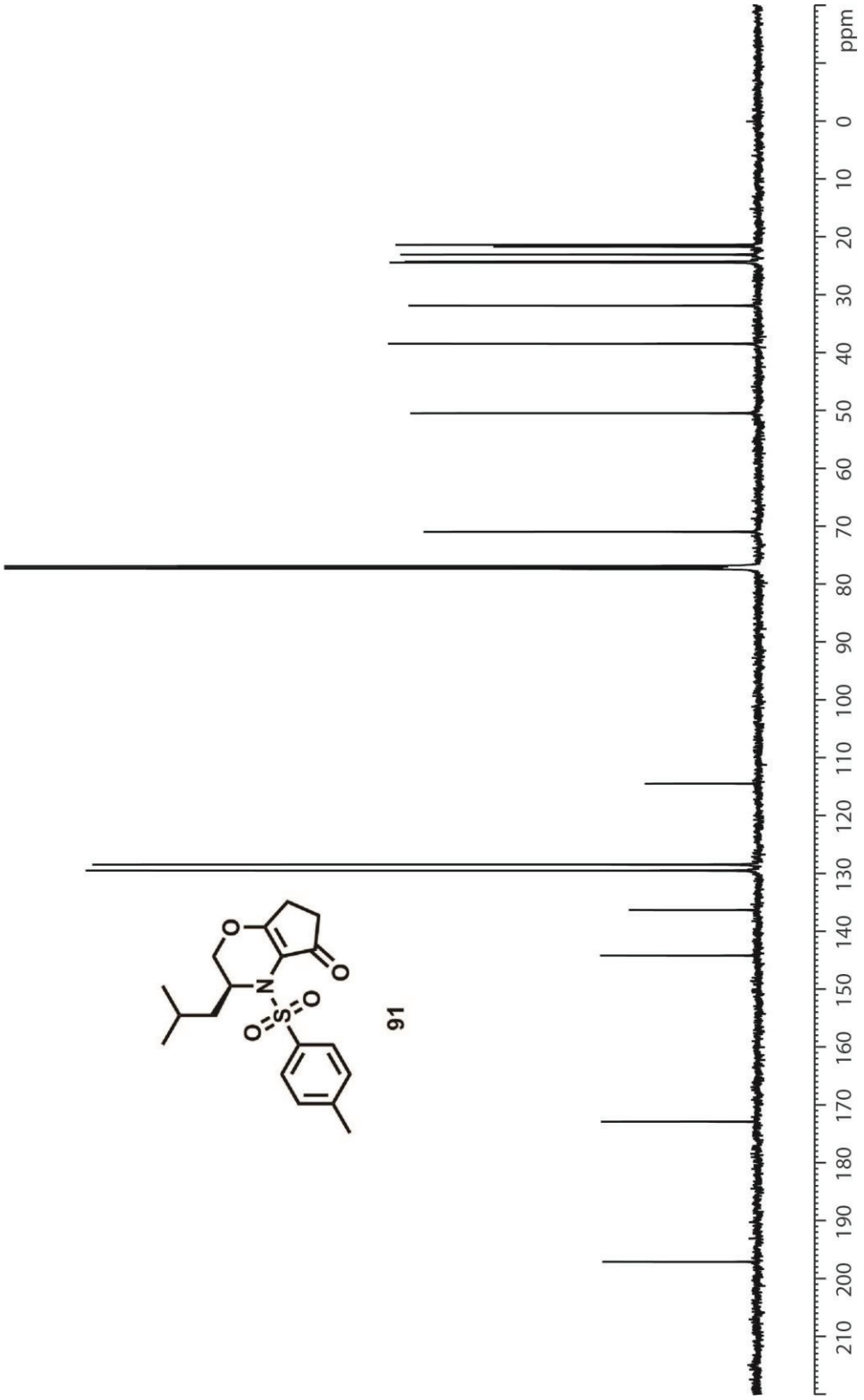
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (*S*)-3-benzyl-4-(4-methylbenzenesulfonyl)-3,4,6,7-tetrahydro-2*H*-cyclopenta[*b*][1,4]oxazin-5-one (90)**



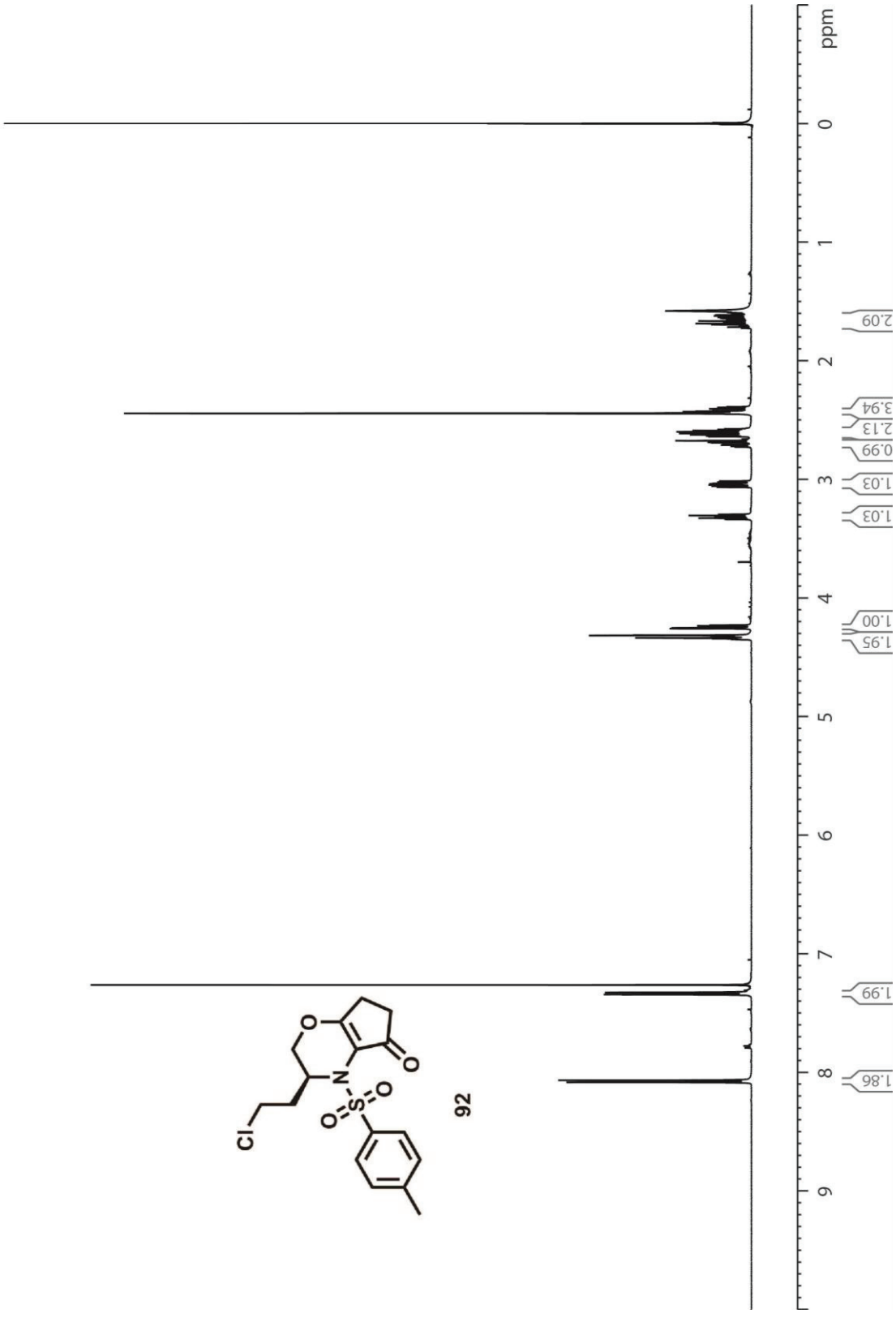
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (*S*)-4-(4-methylbenzenesulfonyl)-3-(2-methylpropyl)-3,4,6,7-tetrahydro-2*H*-cyclopenta[*b*][1,4]oxazin-5-one (91)**



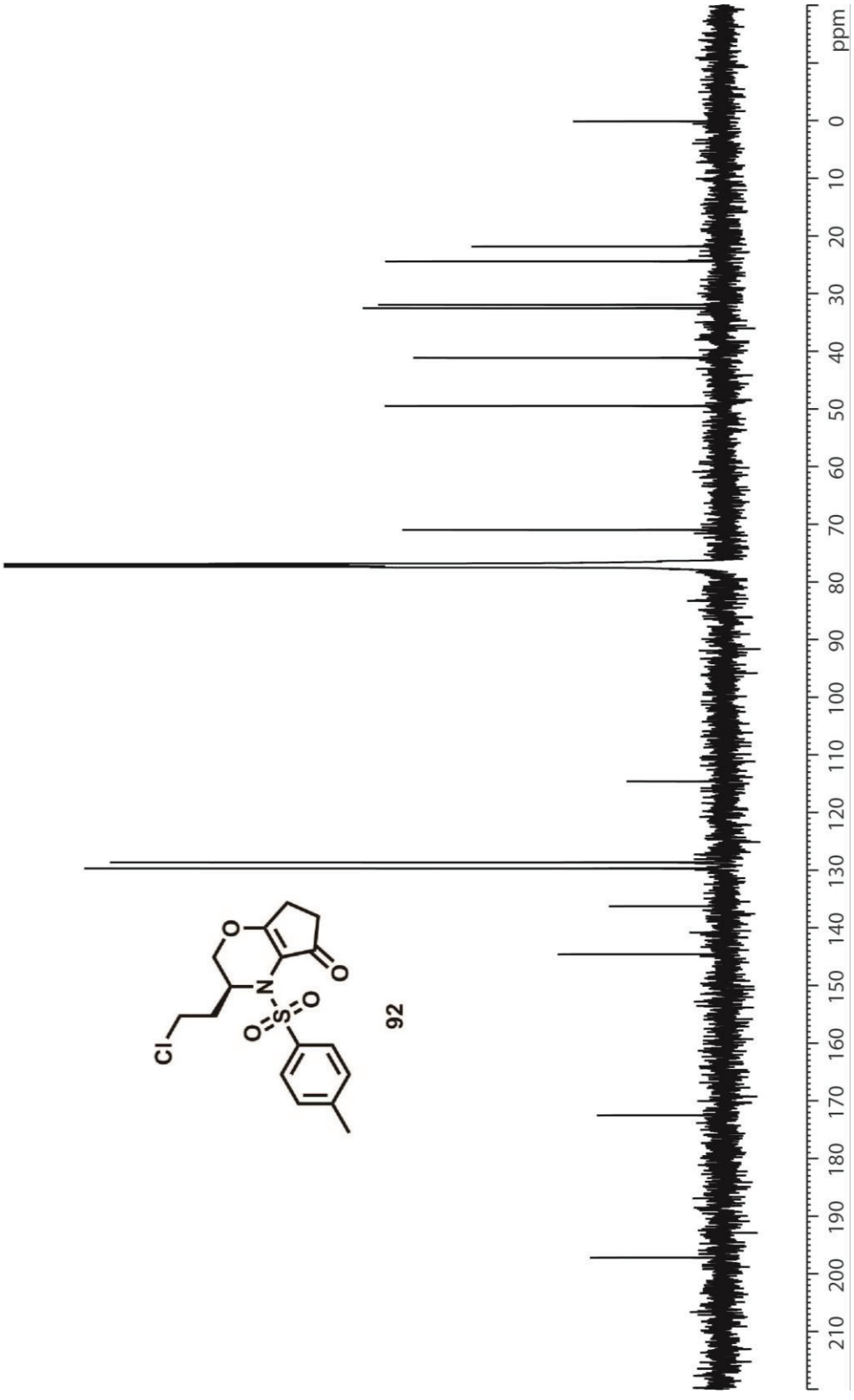
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (*S*)-4-(4-methylbenzenesulfonyl)-3-(2-methylpropyl)-3,4,6,7-tetrahydro-2*H*-cyclopenta[*b*][1,4]oxazin-5-one (91)**



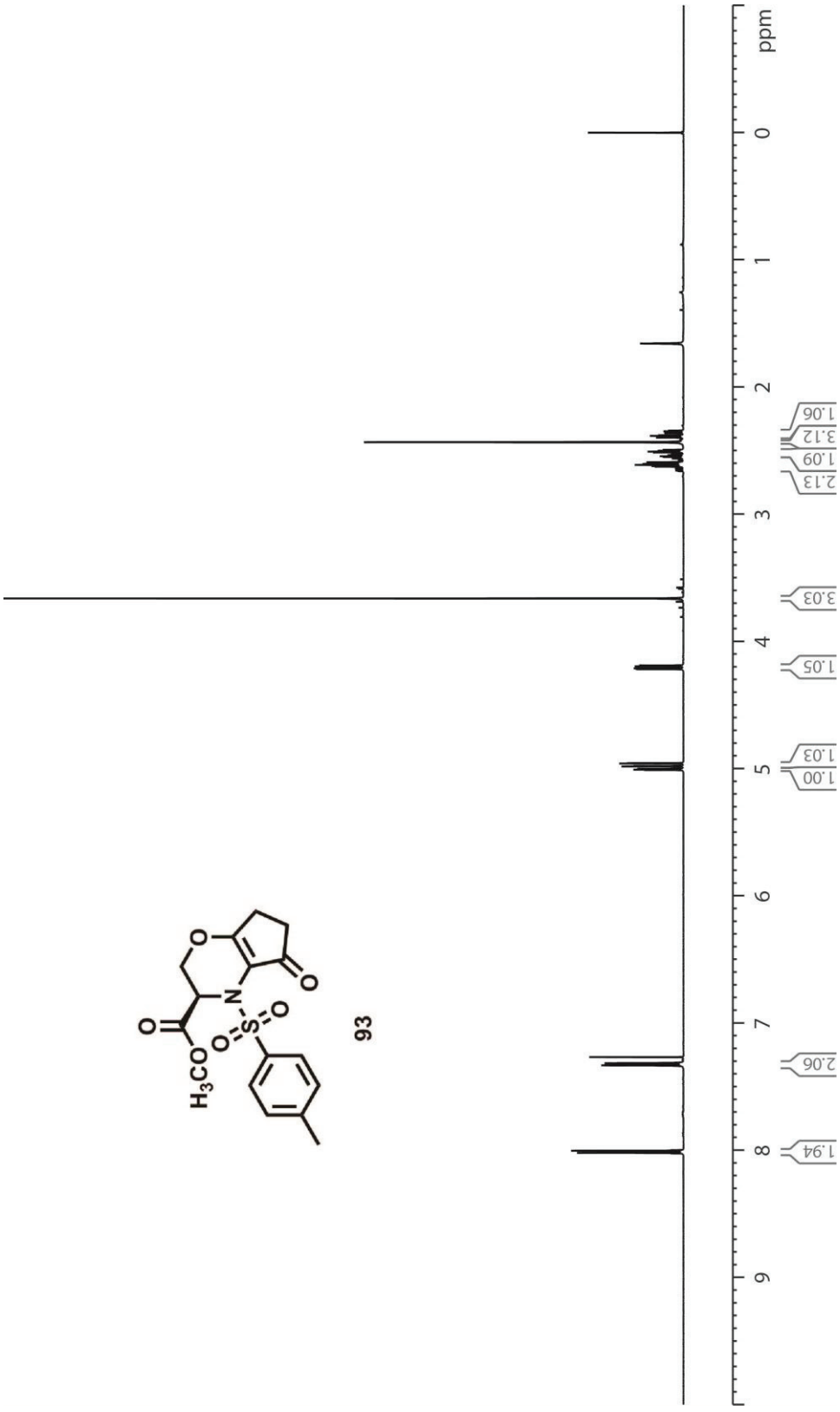
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (*S*)-3-(2-chloroethyl)-4-(4-methylbenzenesulfonyl)-3,4,6,7-tetrahydro-2*H*-cyclopenta[*b*][1,4]oxazin-5-one (92)**



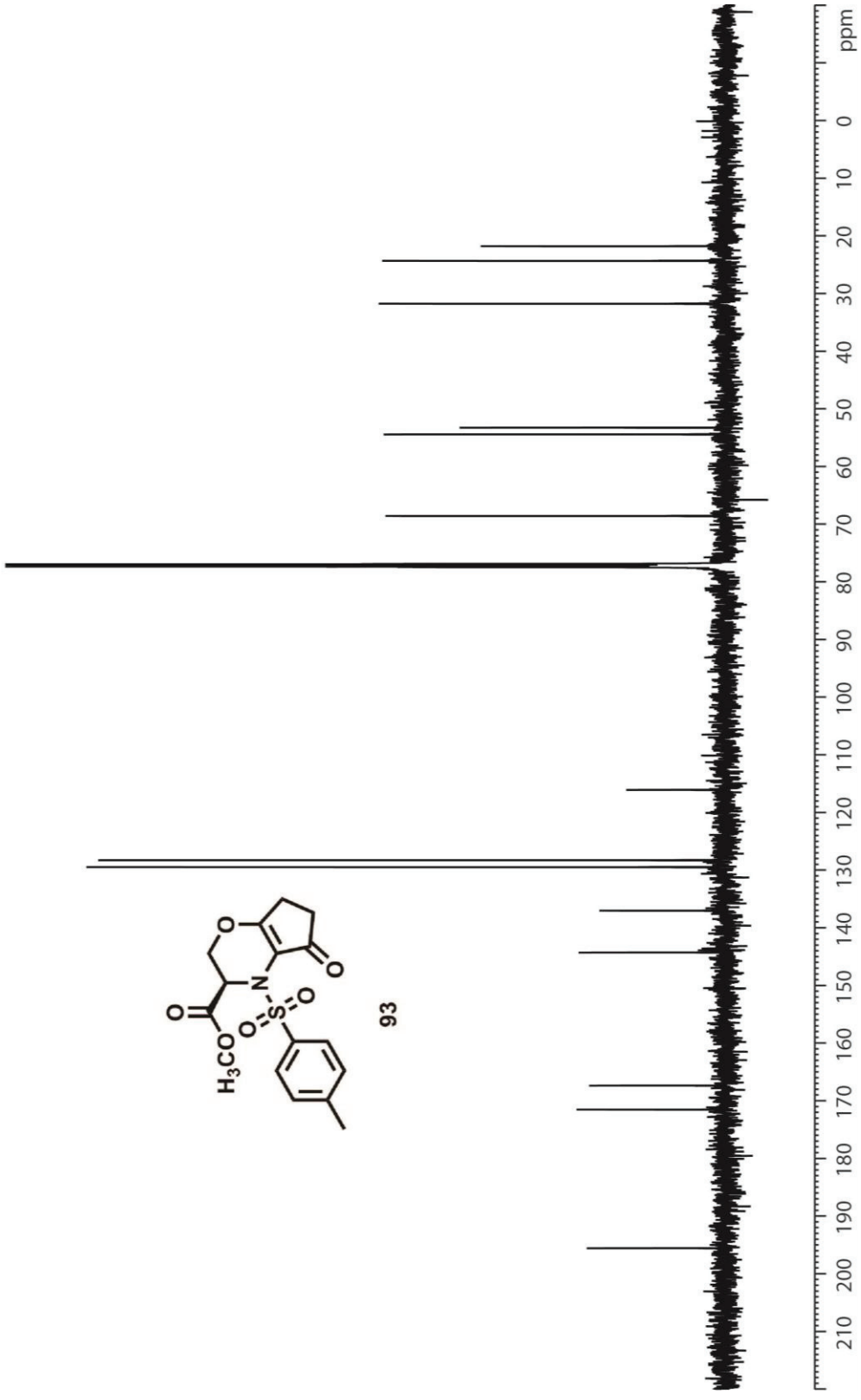
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (*S*)-3-(2-chloroethyl)-4-(4-methylbenzenesulfonyl)-3,4,6,7-tetrahydro-2*H*-cyclopenta[*b*][1,4]oxazin-5-one (92)**



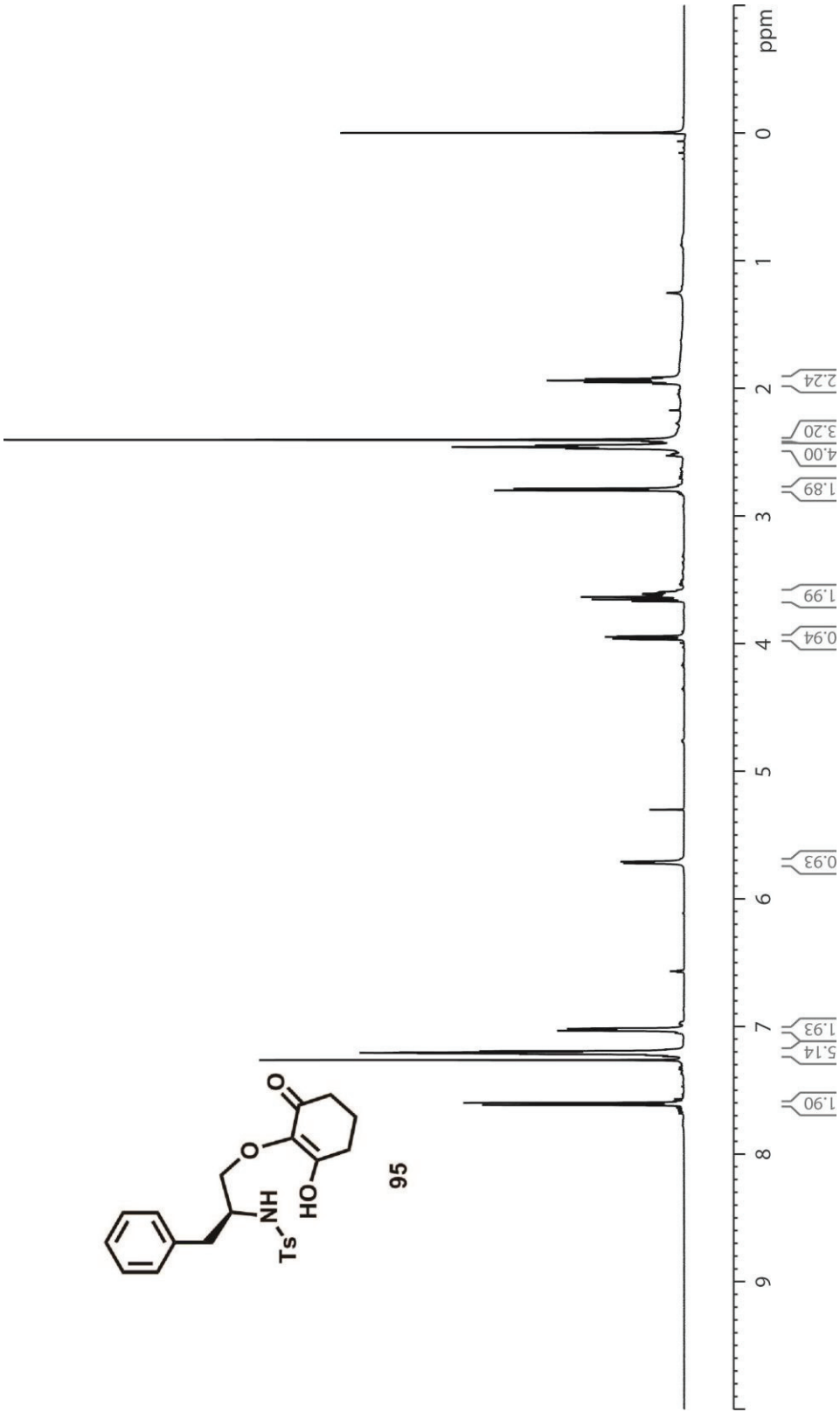
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of methyl (*R*)-4-(4-methylbenzenesulfonyl)-3,4,6,7-tetrahydro-2*H*-cyclopenta[*b*][1,4]oxazin-5-one-3-carboxylate (93)**



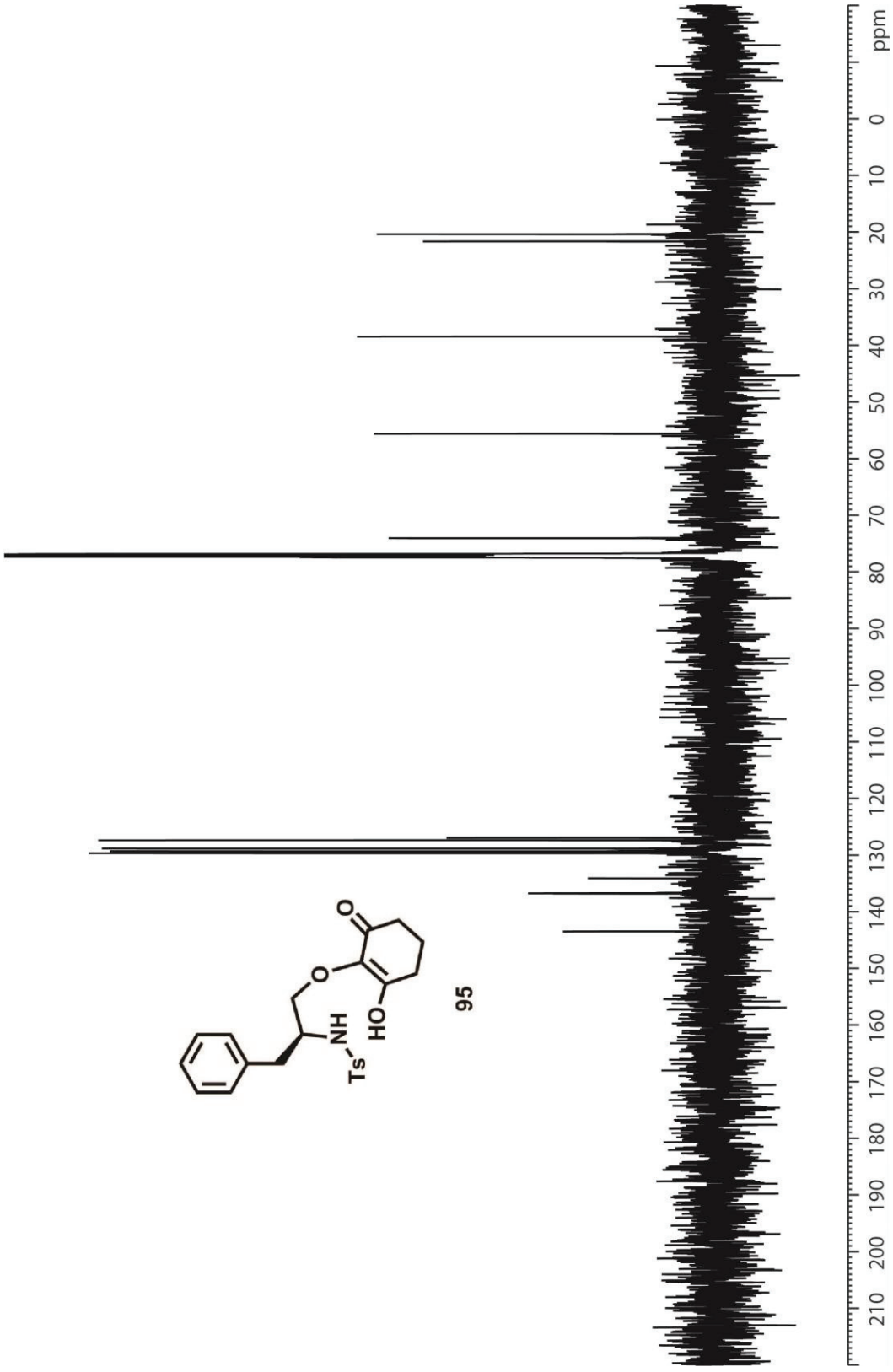
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of methyl (*R*)-4-(4-methylbenzenesulfonyl)-3,4,6,7-tetrahydro-2*H*-cyclopenta[*b*][1,4]oxazin-5-one-3-carboxylate (93)**



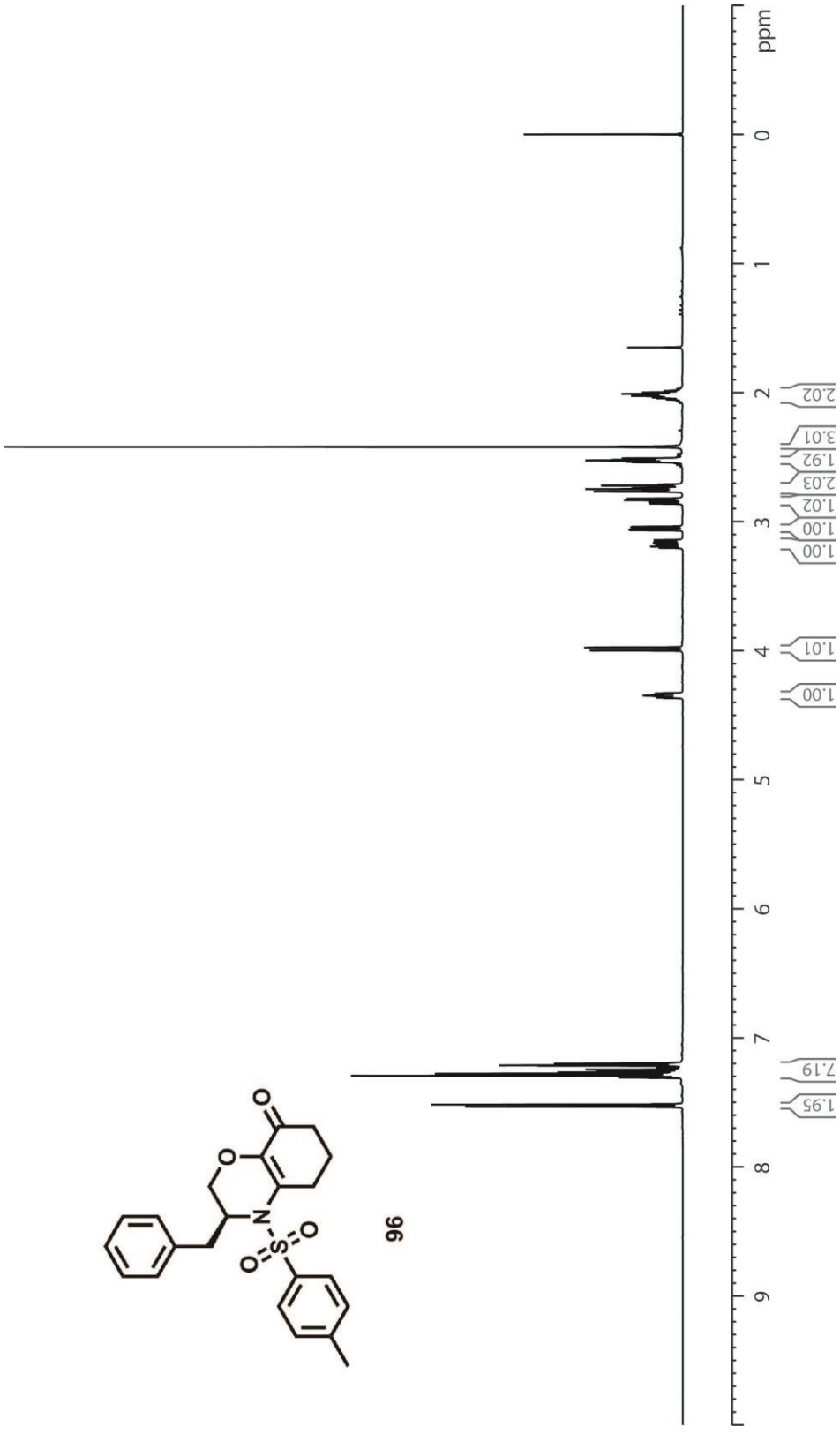
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (*S*)-*N*-(1-(2-hydroxy-6-oxocyclohex-1-enyloxy)-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (95)**



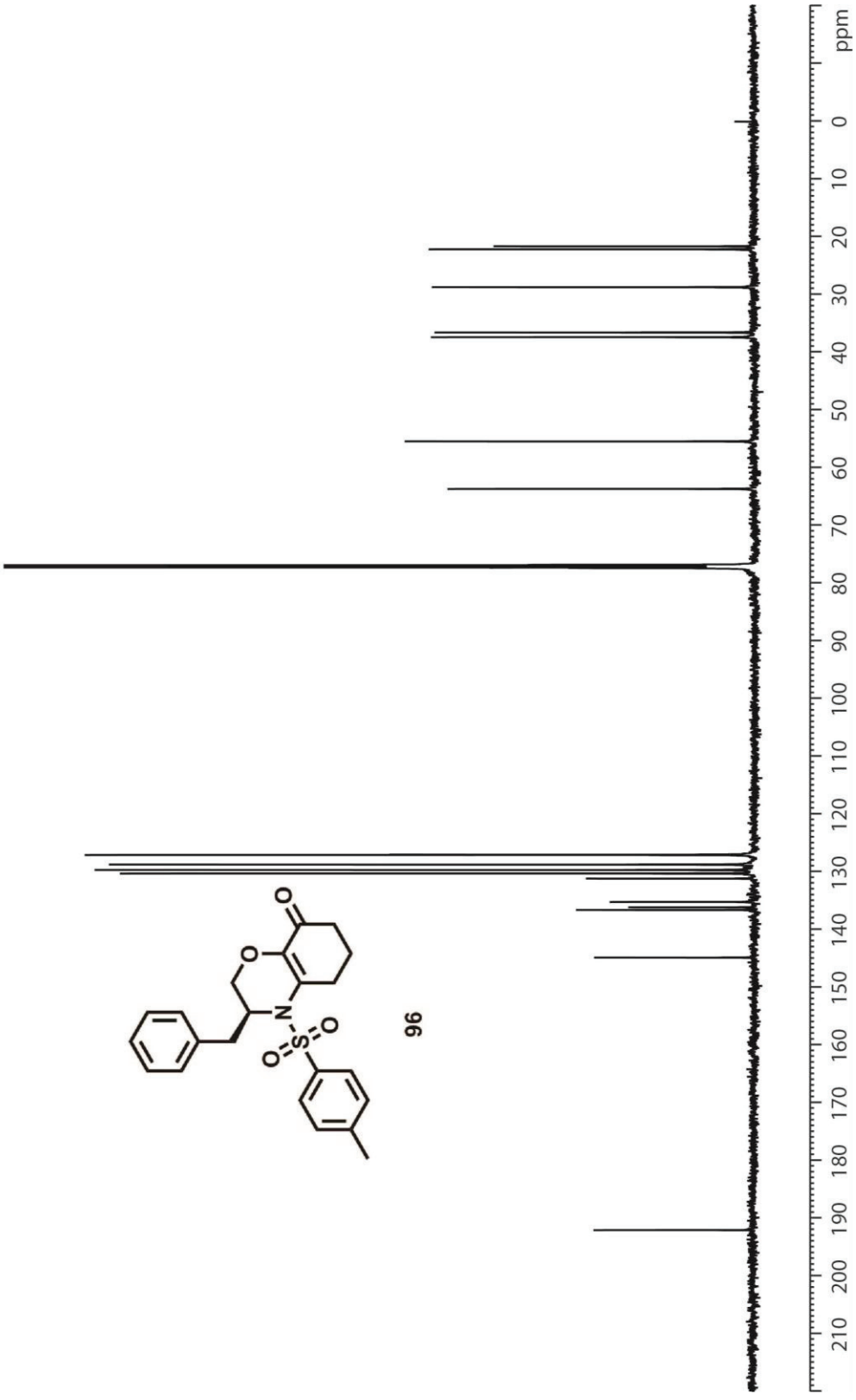
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (*S*)-*N*-(1-(2-hydroxy-6-oxocyclohex-1-enyloxy)-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (95)**



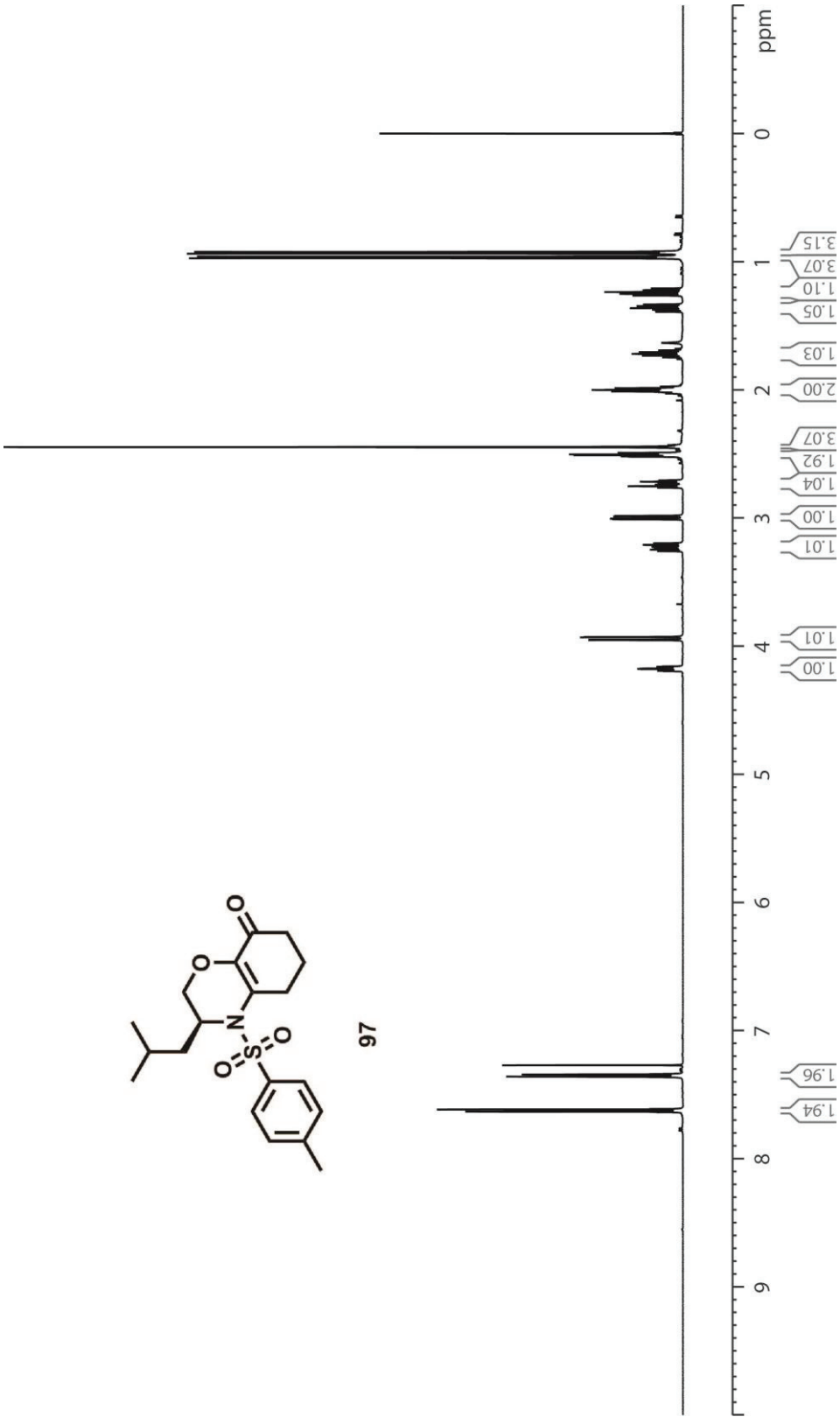
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (3*S*)-3-benzyl-4-(4-methylbenzenesulfonyl)-3,4,6,7-tetrahydro-2*H*,5*H*-benzo[*b*][1,4]oxazin-8-one (96)**



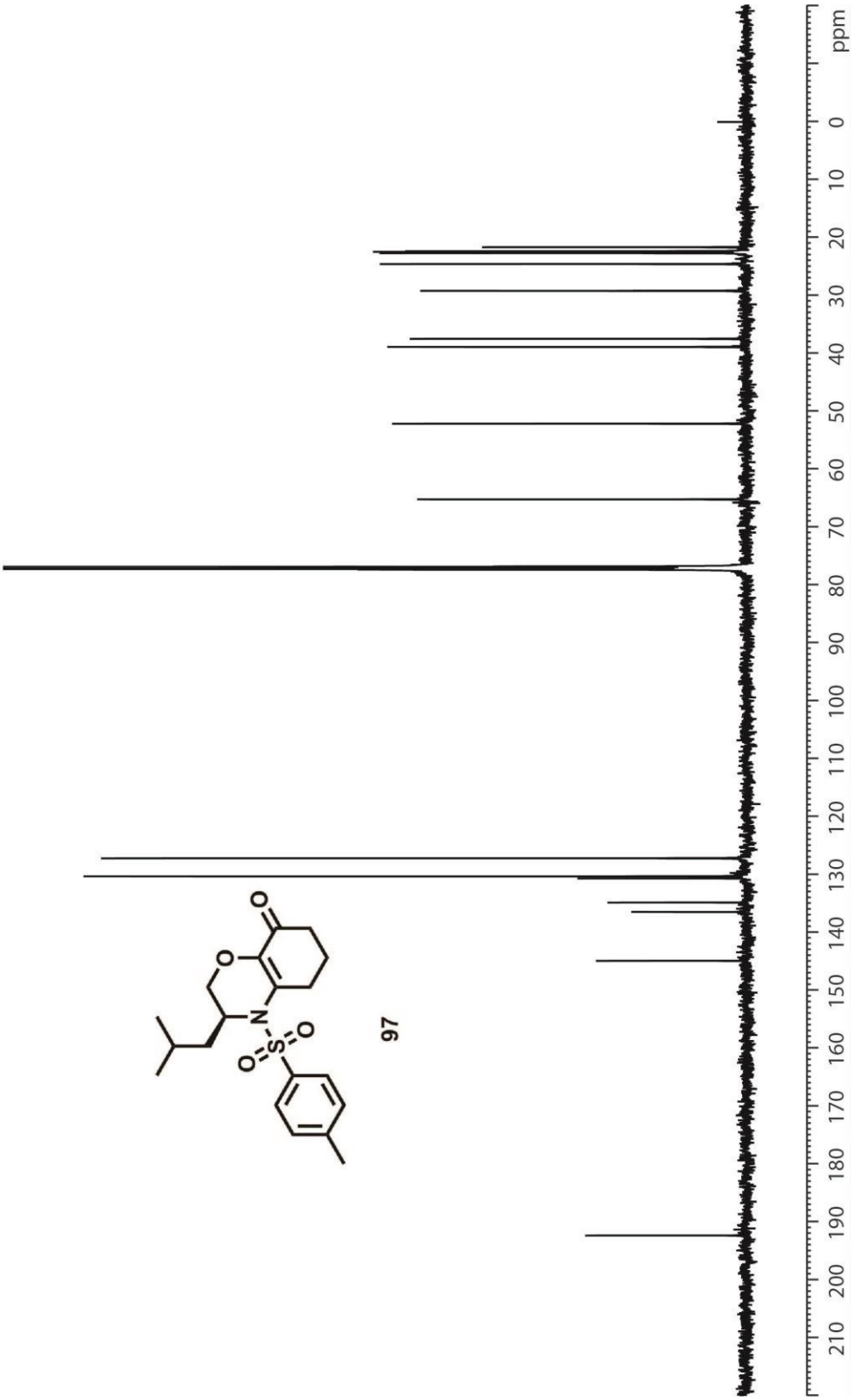
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (3*S*)-3-benzyl-4-(4-methylbenzenesulfonyl)-3,4,6,7-tetrahydro-2*H*,5*H*-benzo[*b*][1,4]oxazin-8-one (96)**



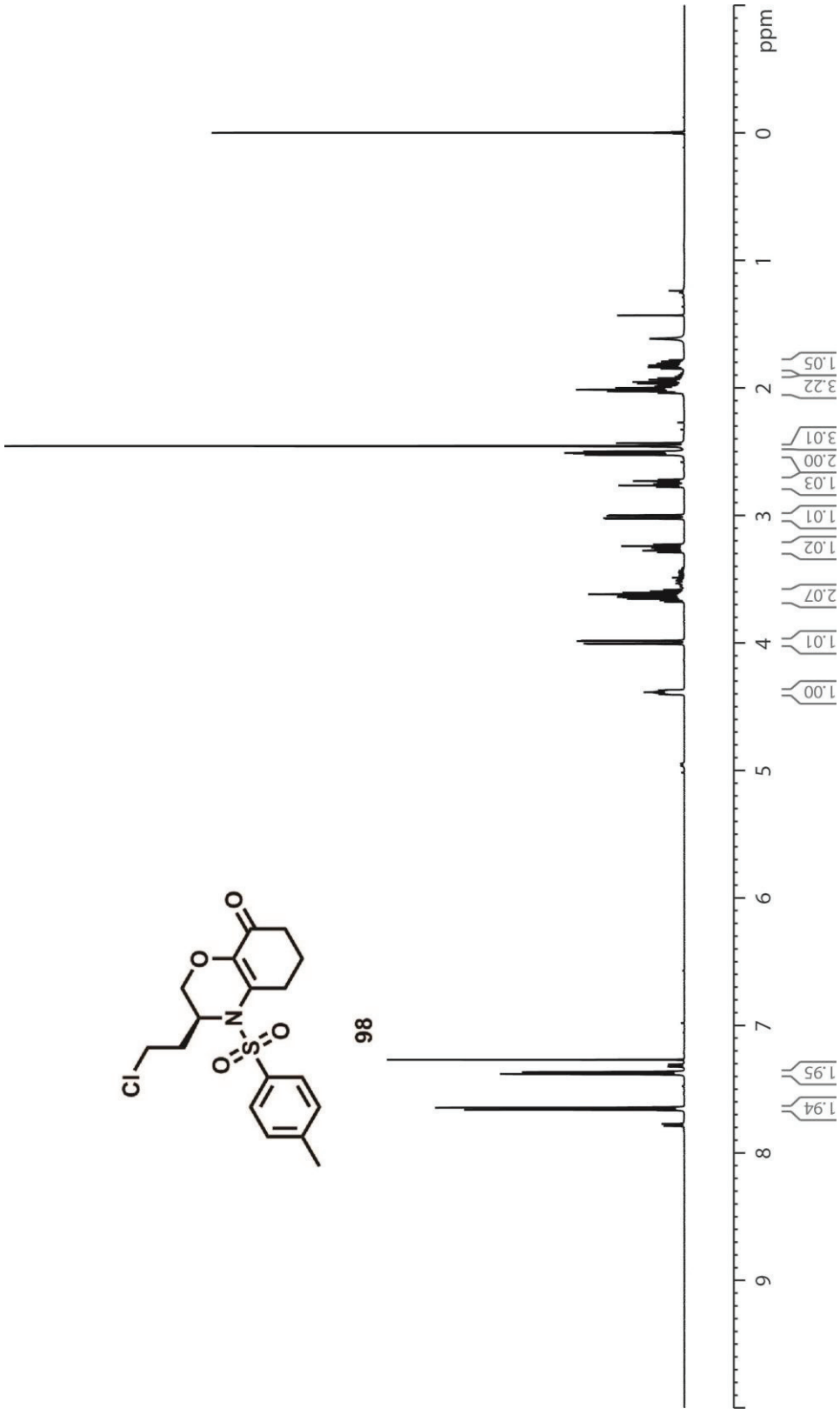
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (3*S*)-4-(4-methylbenzenesulfonyl)-3-(2-methylpropyl)-3,4,6,7-tetrahydro-2*H*,5*H*-benzo[*b*][1,4]oxazin-8-one (97)**



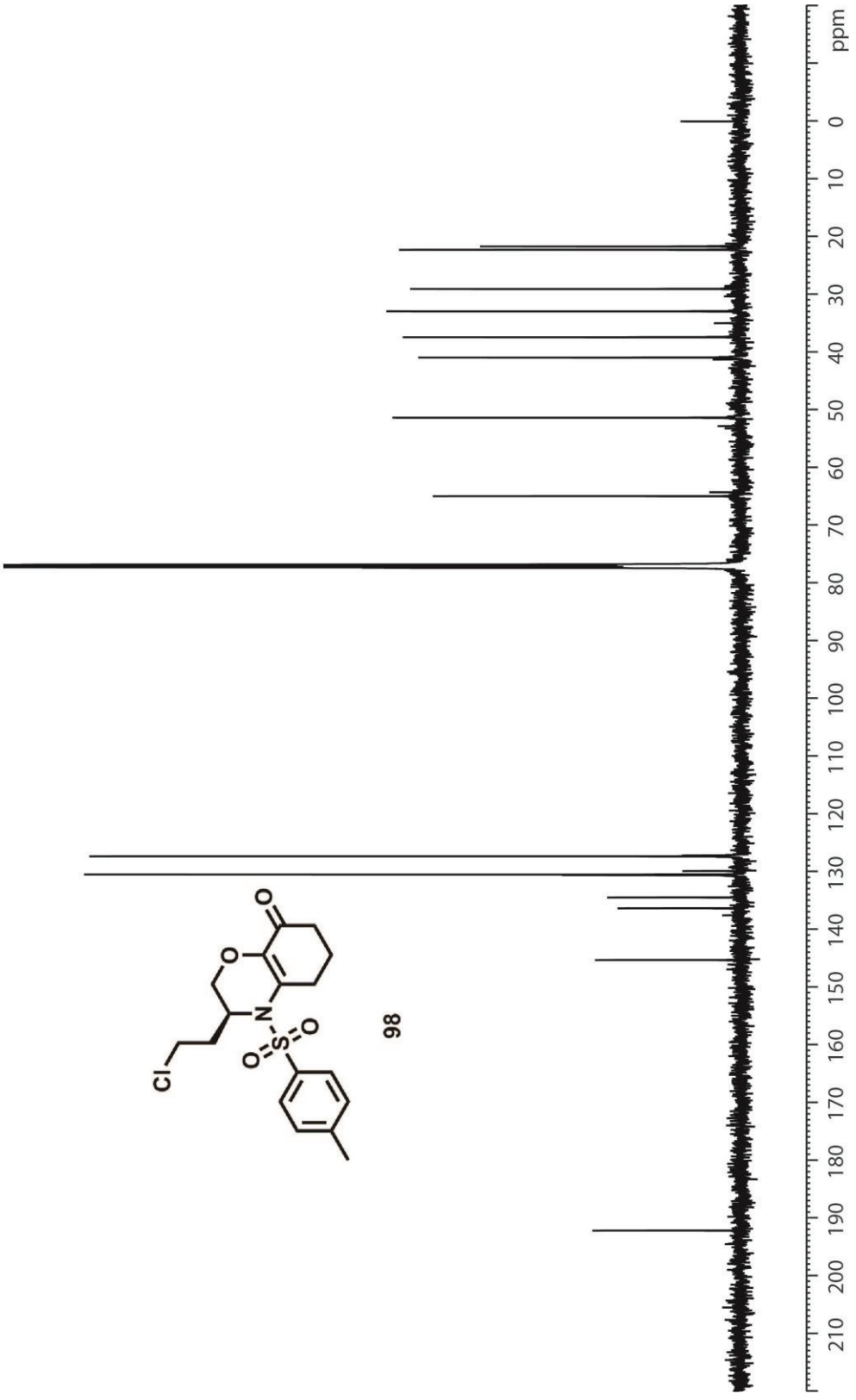
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (3*S*)-4-(4-methylbenzenesulfonyl)-3-(2-methylpropyl)-3,4,6,7-tetrahydro-2*H*,5*H*-benzo[*b*][1,4]oxazin-8-one (97)**



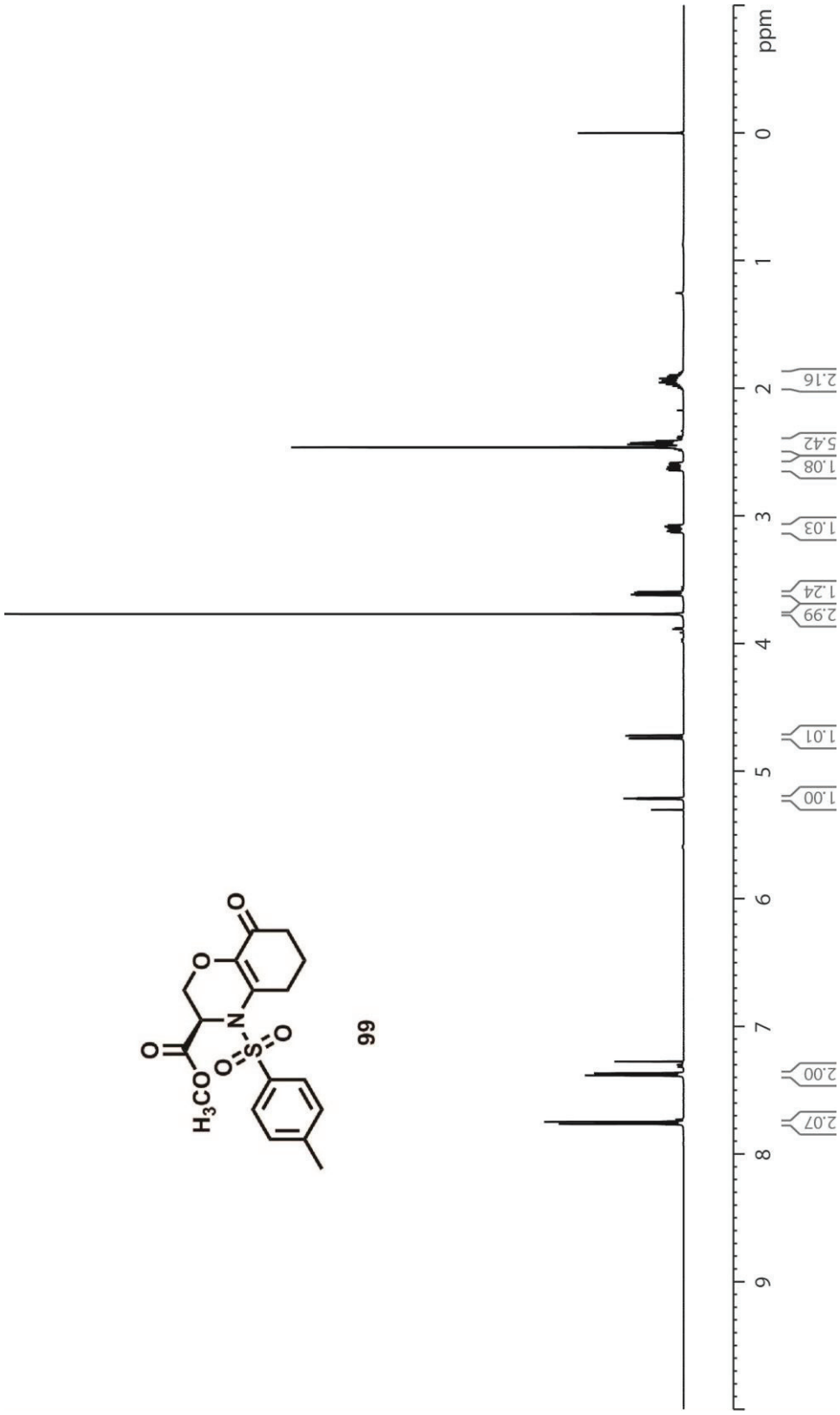
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (3*S*)-3-(2-chloroethyl)-4-(4-methylbenzenesulfonyl)-3,4,6,7-tetrahydro-2*H*,5*H*-benzo[*b*][1,4]oxazin-8-one (98)**



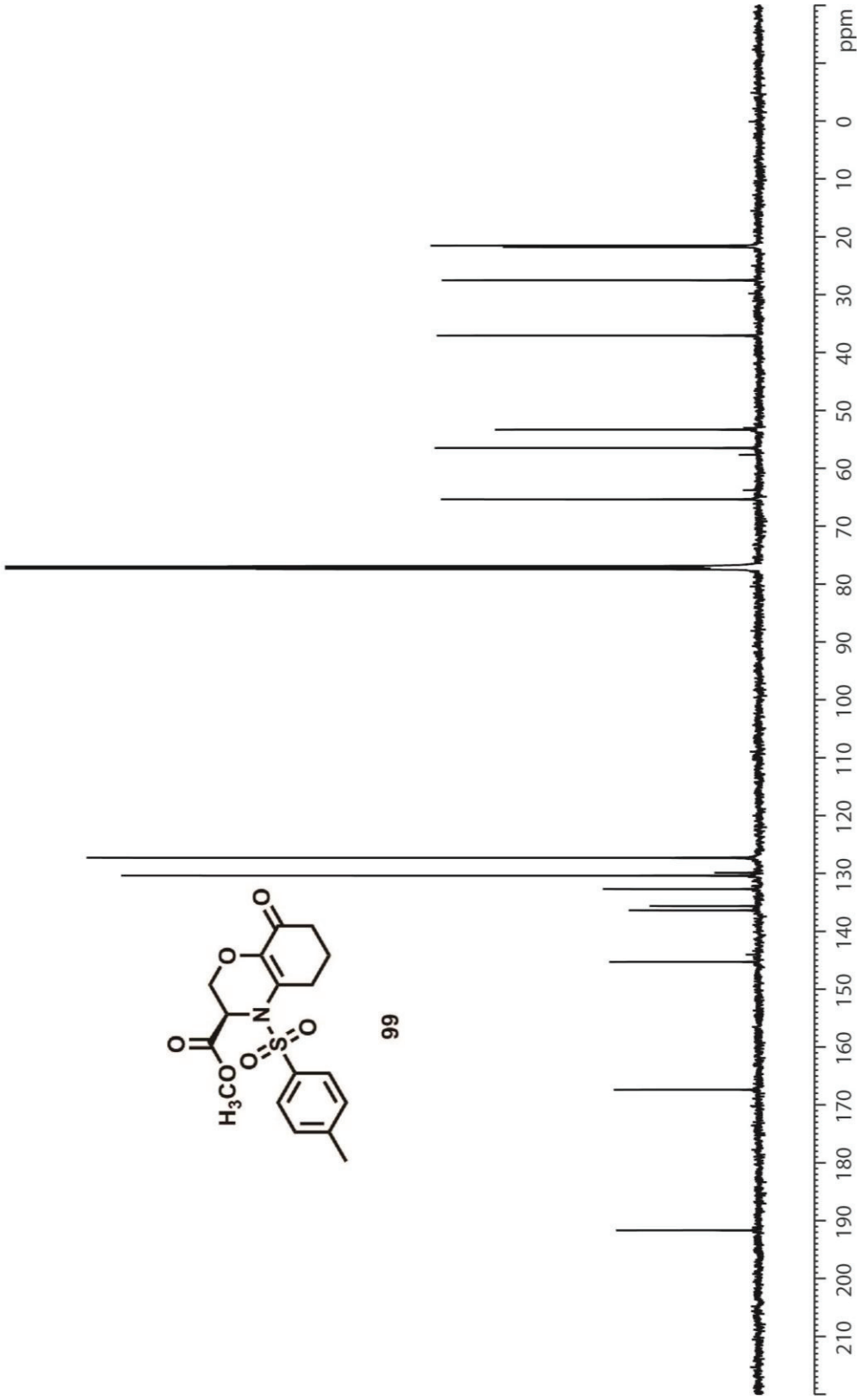
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (3*S*)-3-(2-chloroethyl)-4-(4-methylbenzenesulfonyl)-3,4,6,7-tetrahydro-2*H*,5*H*-benzo[*b*][1,4]oxazin-8-one (98)**



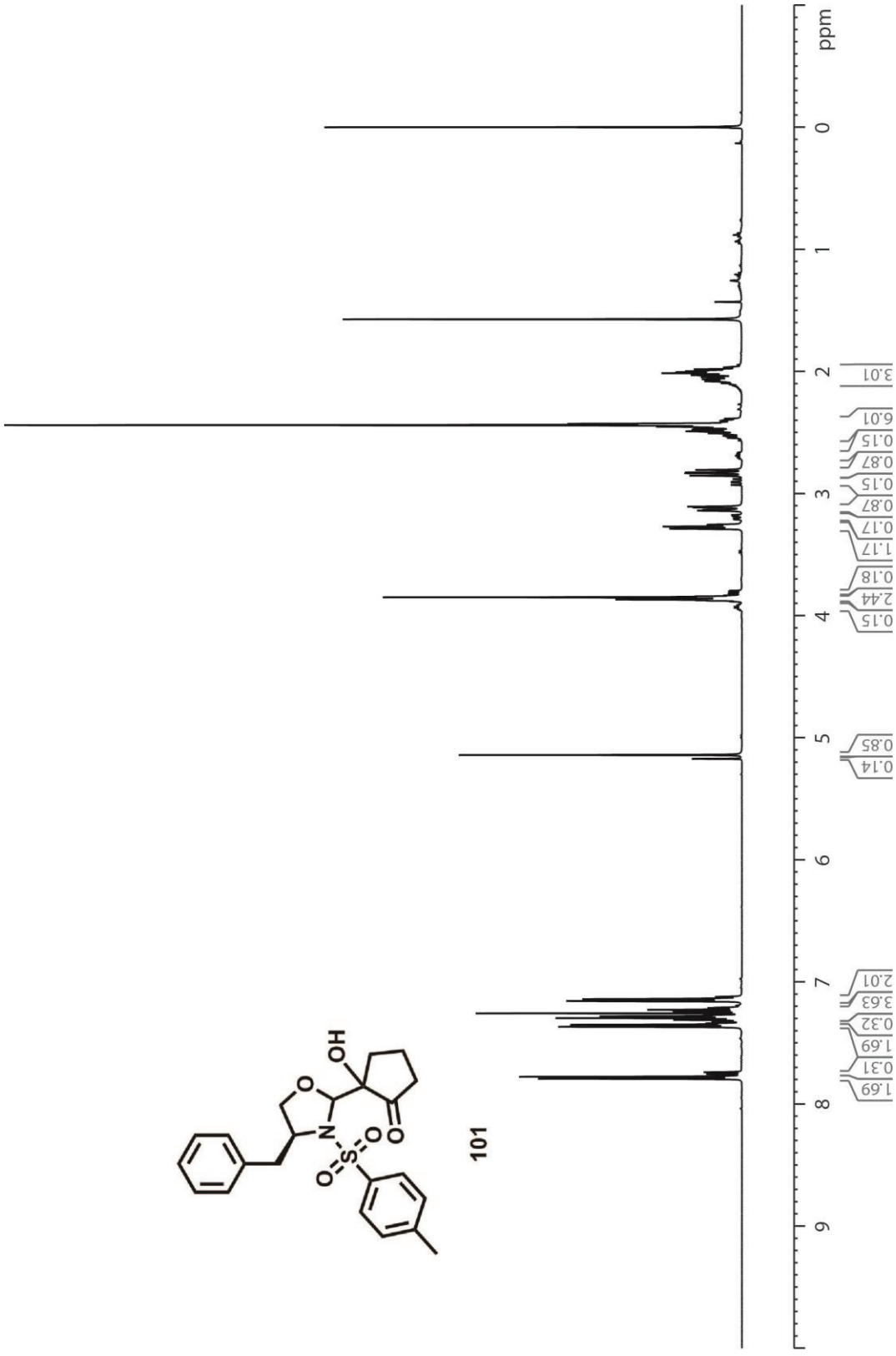
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of methyl (3*R*)-4-(4-methylbenzenesulfonyl)-3,4,6,7-tetrahydro-2*H*,5*H*-benzo[*b*][1,4]oxazin-8-one-3-carboxylate (99)**



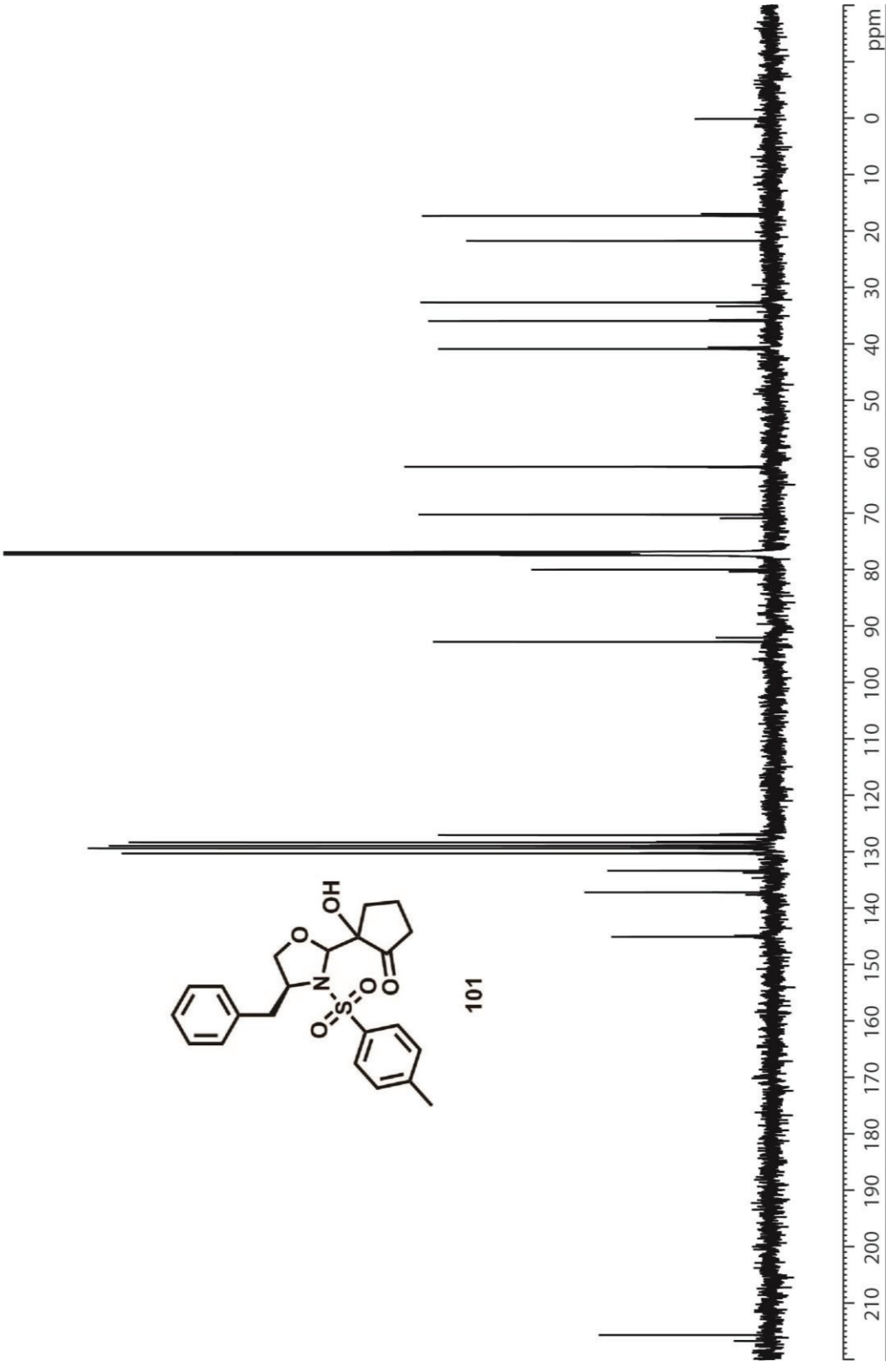
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of methyl (3*R*)-4-(4-methylbenzenesulfonyl)-3,4,6,7-tetrahydro-2*H*,5*H*-benzo[*b*][1,4]oxazin-8-one-3-carboxylate (99)**



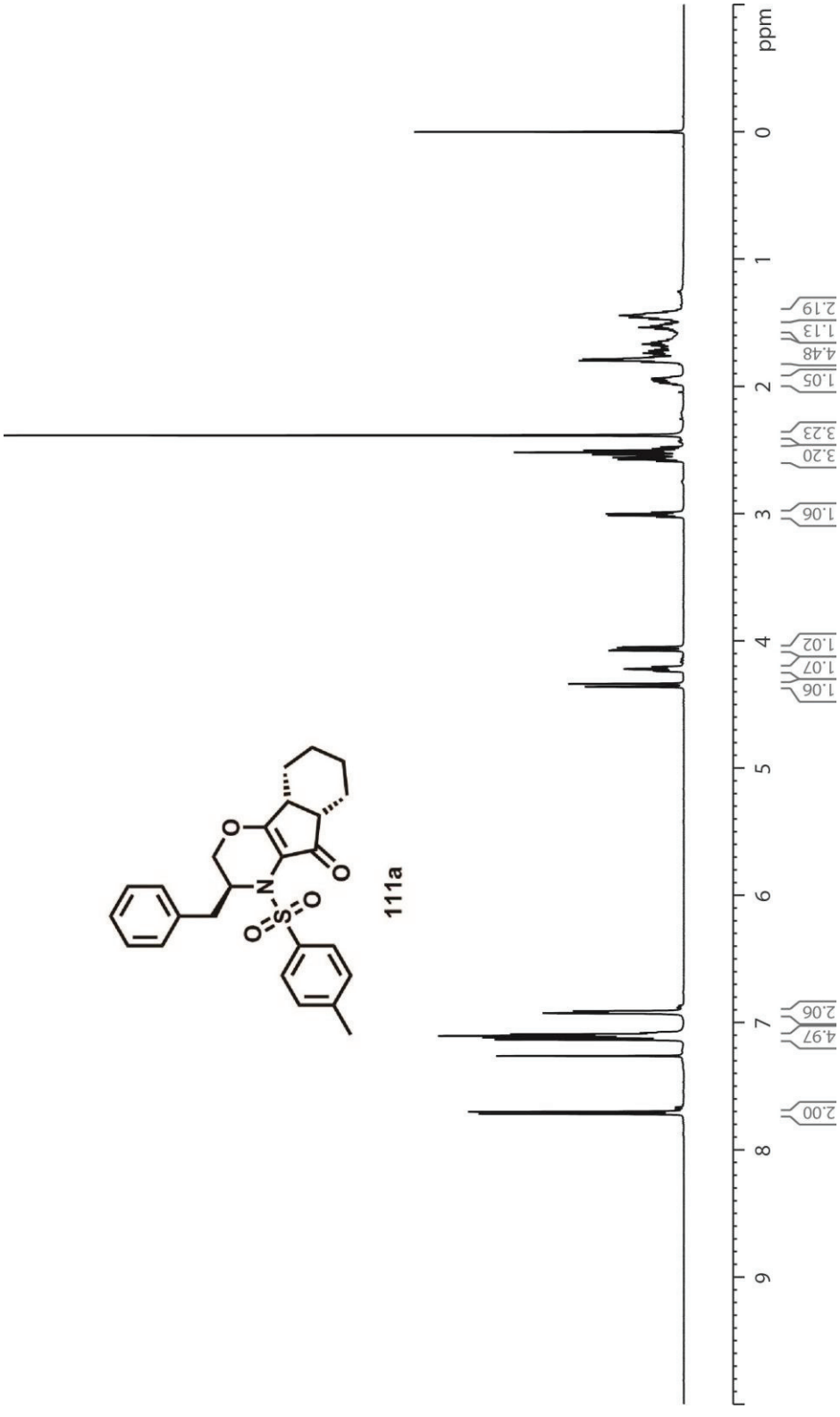
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of 2-((4*S*)-4-benzyl-3-tosyloxazolidin-2-yl)-2-hydroxycyclopentanone (101)**



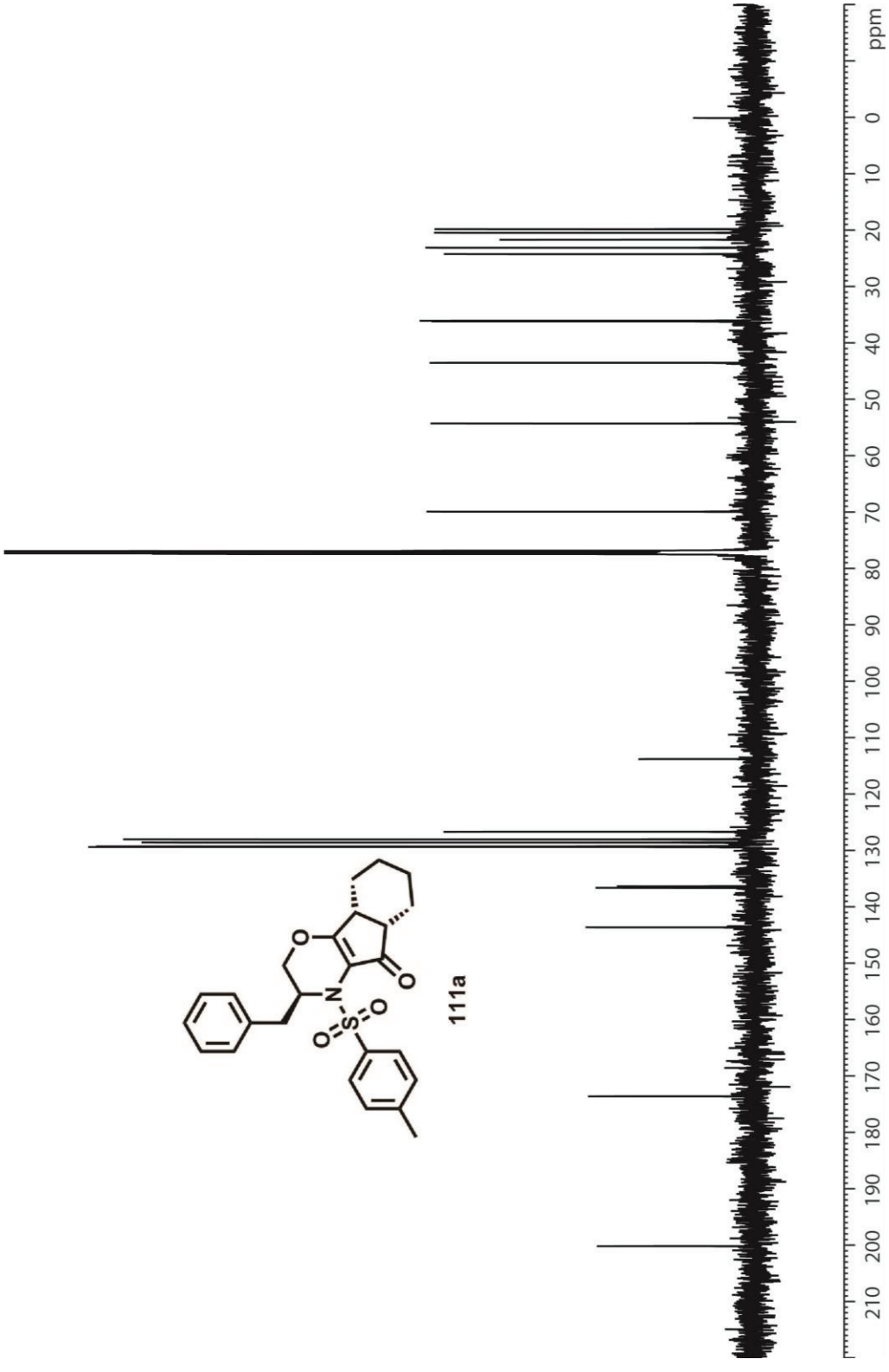
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of 2-((4*S*)-4-benzyl-3-tosyloxazolidin-2-yl)-2-hydroxycyclopentanone (101)**



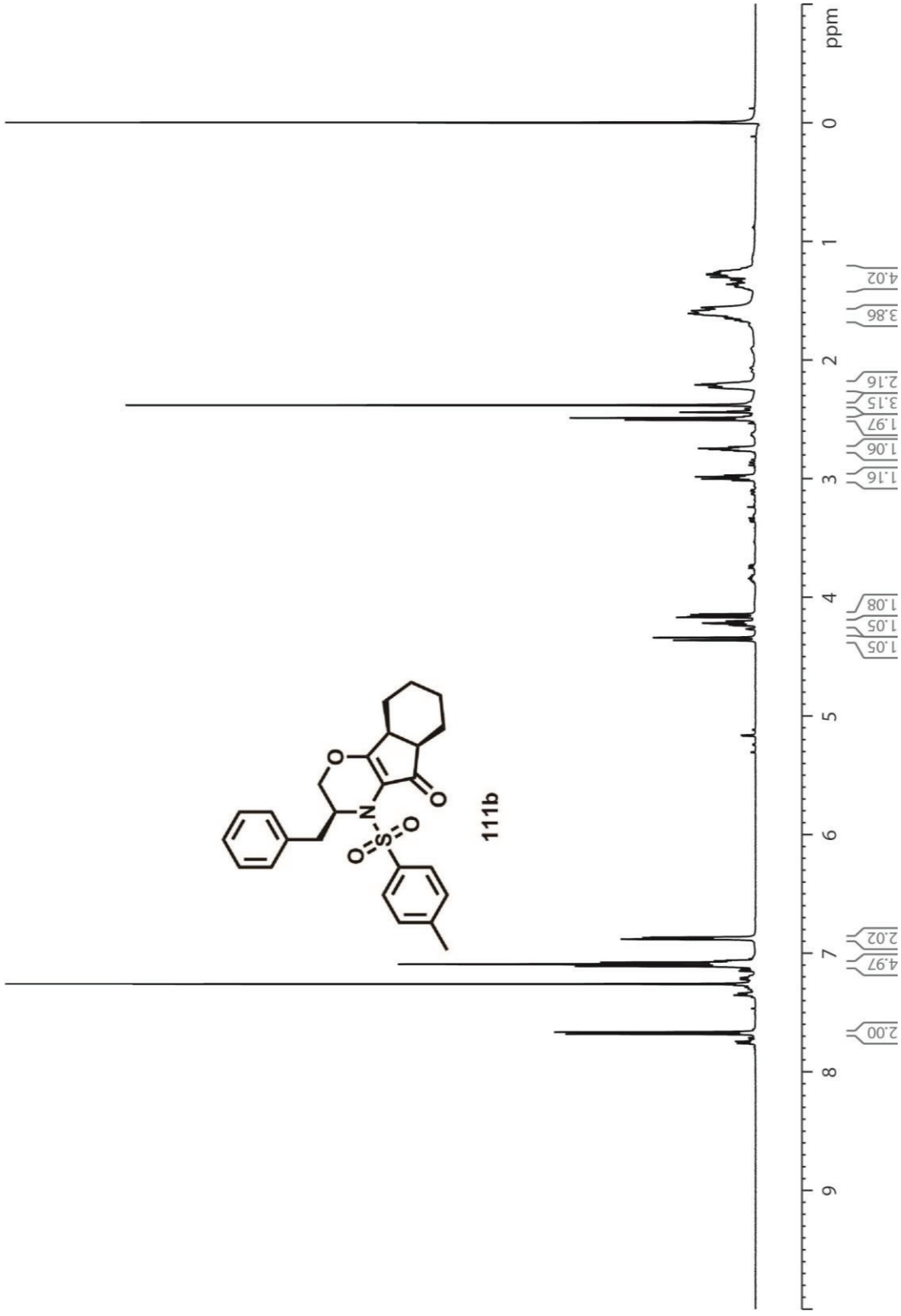
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (3*S*,5a*S*,9a*R*)-3-benzyl-4-(4-methylbenzenesulfonate)-3,4,5a,6,7,8,9,9a-octahydroindeno[1,2-*b*][1,4]oxazin-5(2*H*)-one (111a)**



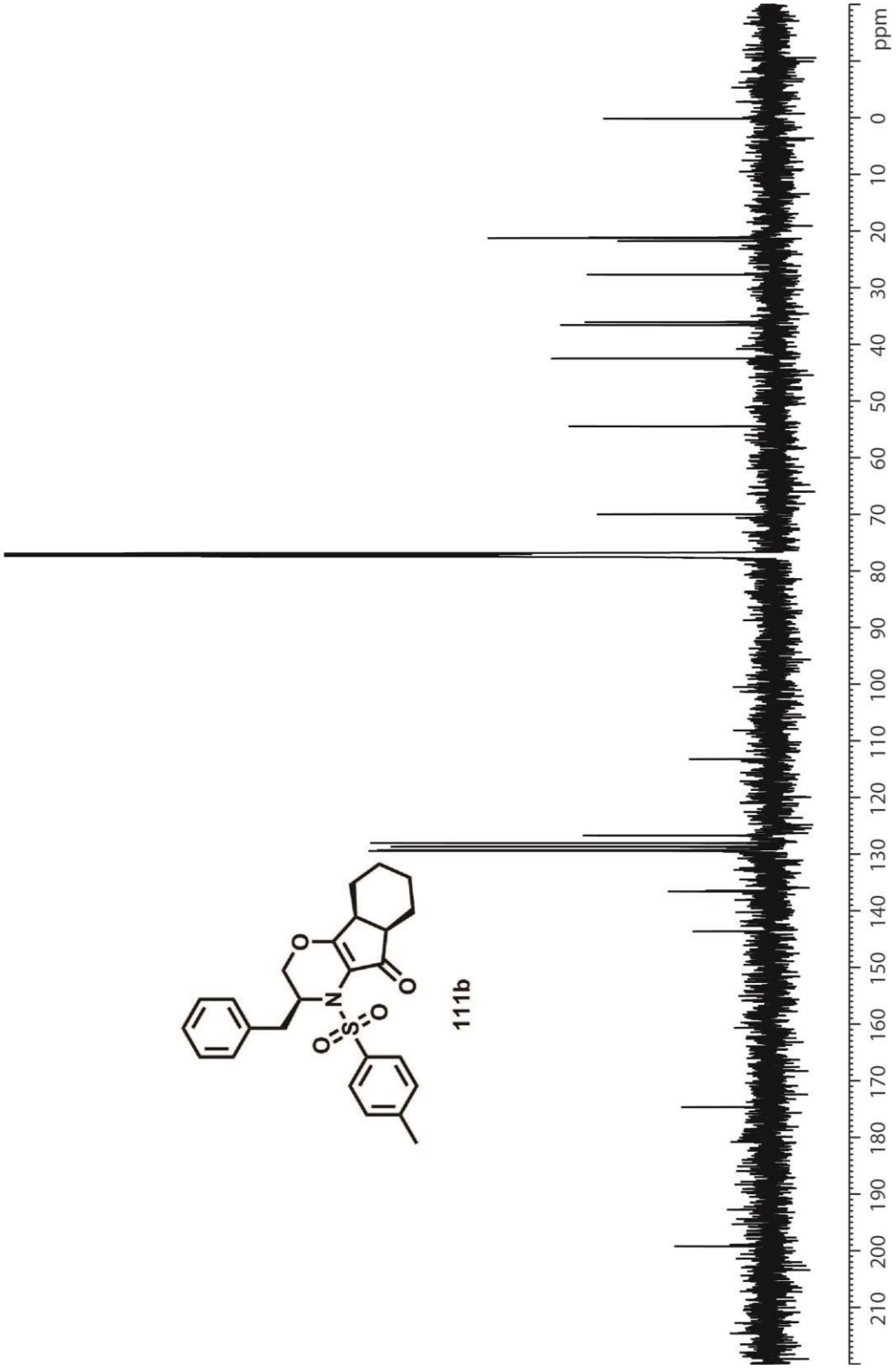
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (3*S*,5a*S*,9a*R*)-3-benzyl-4-(4-methylbenzenesulfonate)-3,4,5a,6,7,8,9,9a-octahydroindeno[1,2-*b*][1,4]oxazin-5(2*H*)-one (111a)**



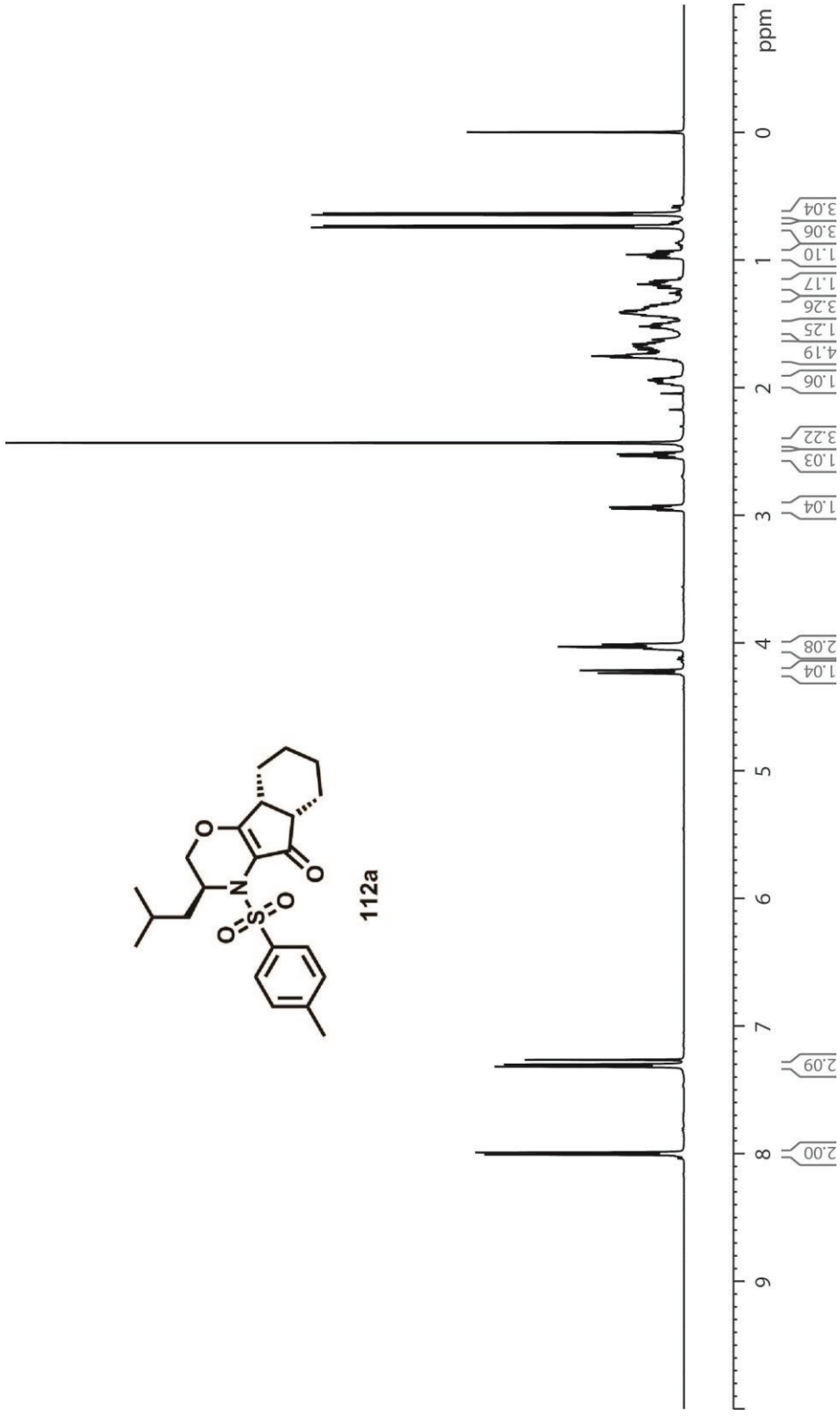
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (3*S*,5a*R*,9a*S*)-3-benzyl-4-(4-methylbenzenesulfonate)-3,4,5a,6,7,8,9,9a-octahydroindeno[1,2-*b*][1,4]oxazin-5(2*H*)-one (111b)**



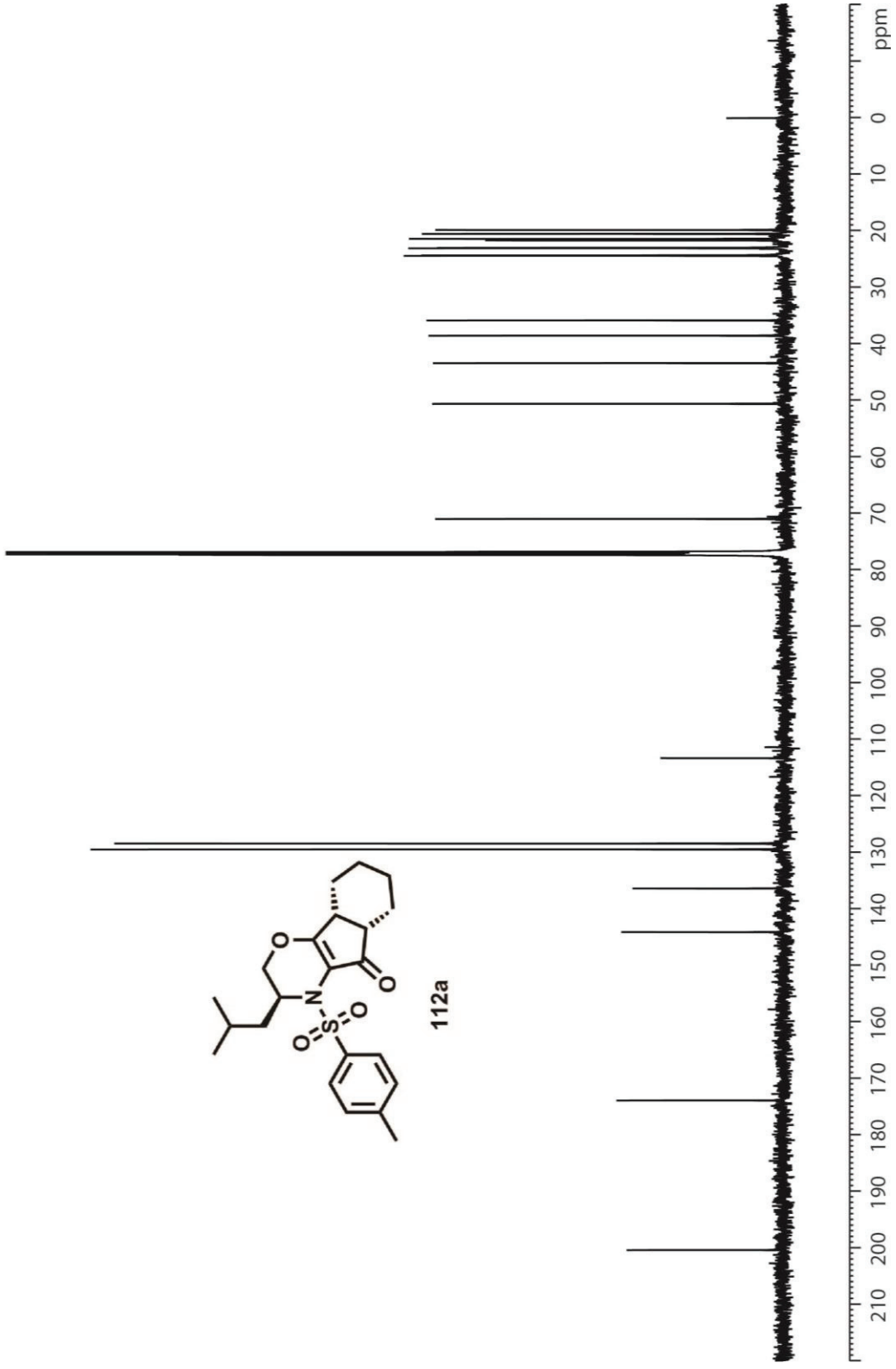
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (3*S*,5a*R*,9a*S*)-3-benzyl-4-(4-methylbenzenesulfonate)-3,4,5a,6,7,8,9,9a-octahydroindeno[1,2-*b*][1,4]oxazin-5(2*H*)-one (111b)**



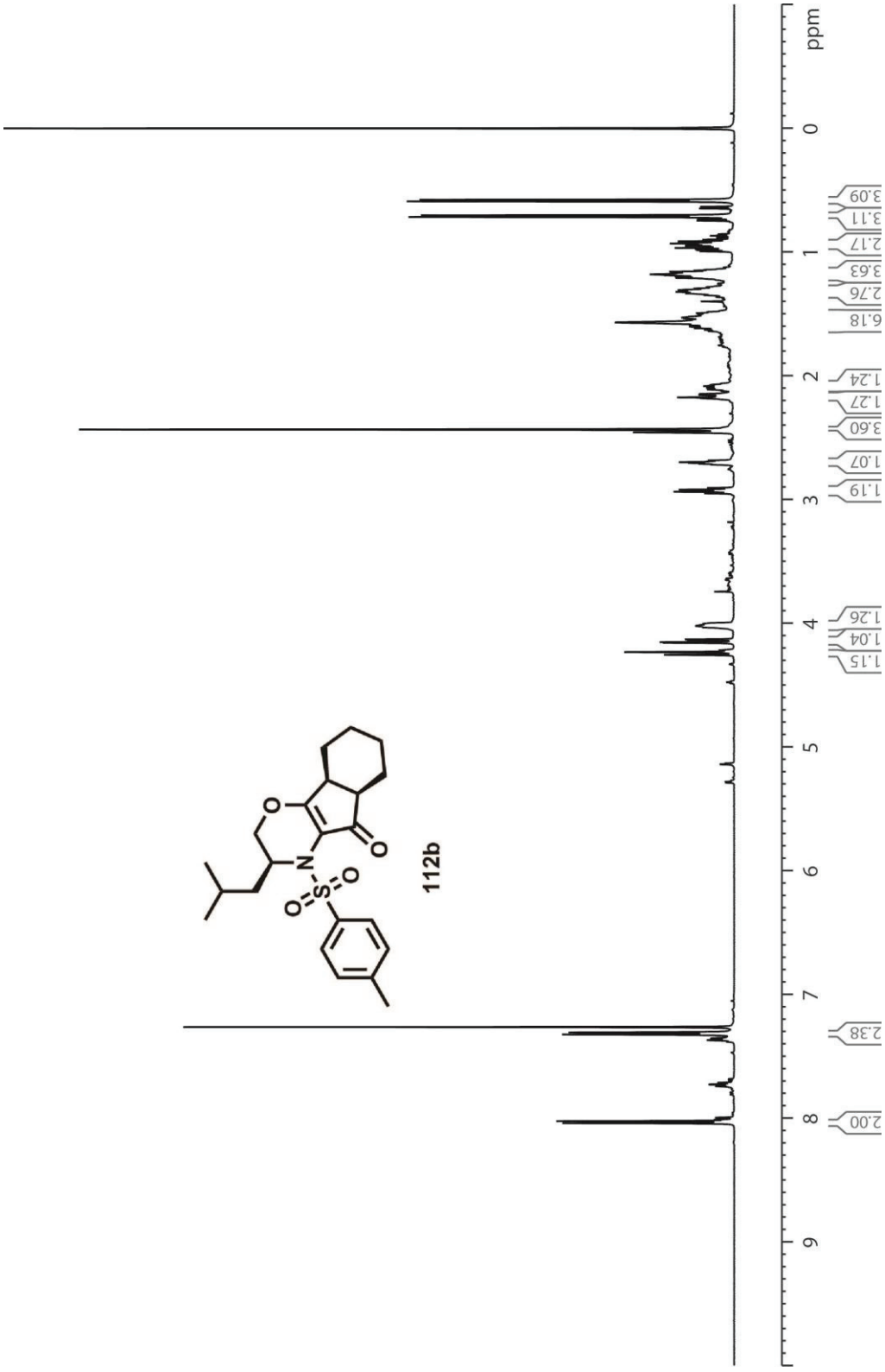
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (3*S*,5a*S*,9a*R*)-4-(4-methylbenzenesulfonate)-3-(2-methylpropyl)-3,4,5a,6,7,8,9,9a-octahydroindeno[1,2-b][1,4]oxazin-5(2*H*)-one (112a)**



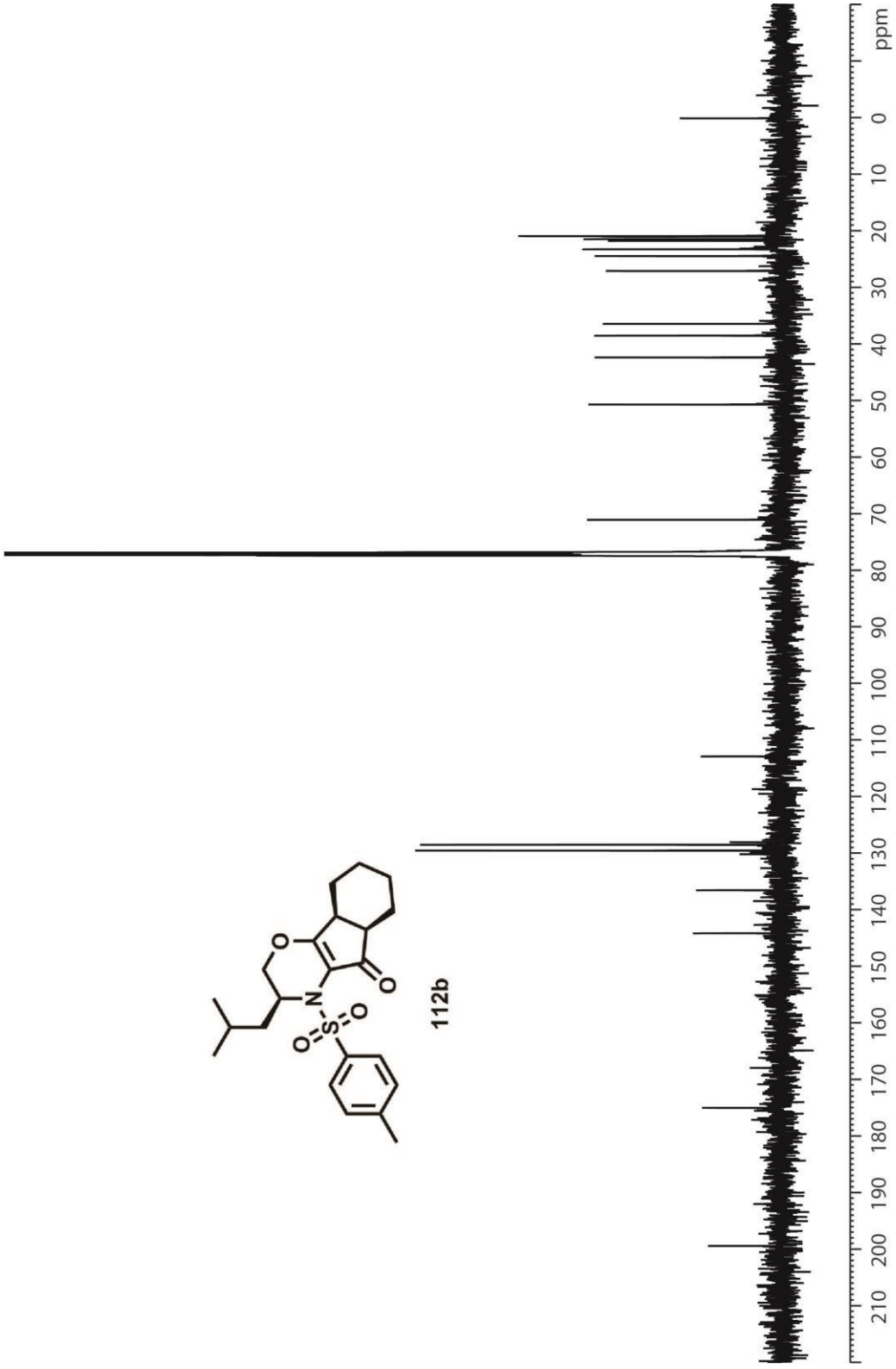
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (3*S*,5a*S*,9a*R*)-4-(4-methylbenzenesulfonate)-3-(2-methylpropyl)-3,4,5a,6,7,8,9,9a-octahydroindeno[1,2-b][1,4]oxazin-5(2*H*)-one (112a)**



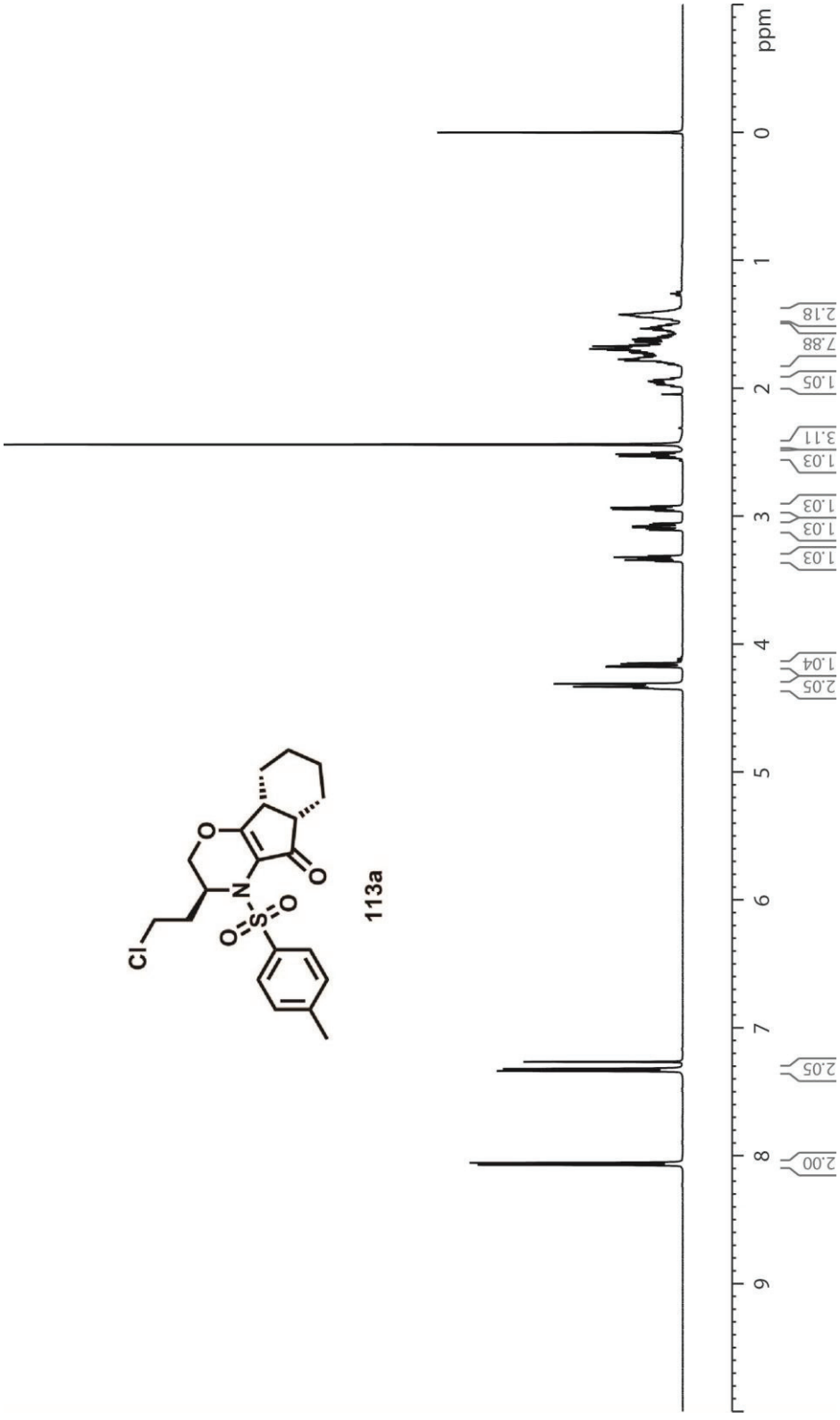
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (3*S*,5a*R*,9a*S*)-4-(4-methylbenzenesulfonate)-3-(2-methylpropyl)-3,4,5a,6,7,8,9,9a-octahydroindeno[1,2-*b*][1,4]oxazin-5(2*H*)-one (112b)**



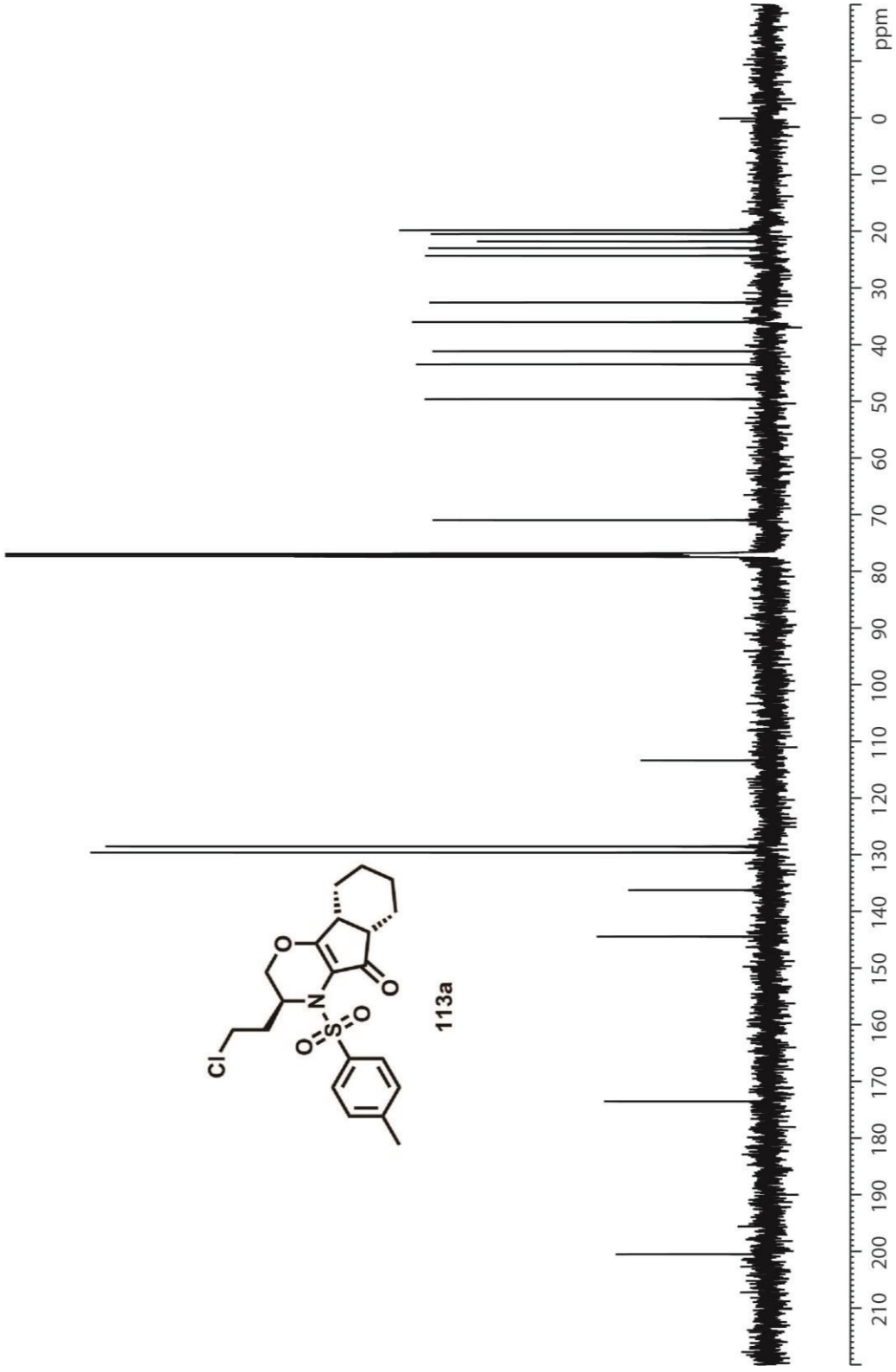
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (3*S*,5a*R*,9a*S*)-4-(4-methylbenzenesulfonate)-3-(2-methylpropyl)-3,4,5a,6,7,8,9,9a-octahydroindeno[1,2-*b*][1,4]oxazin-5(2*H*)-one (112b)**



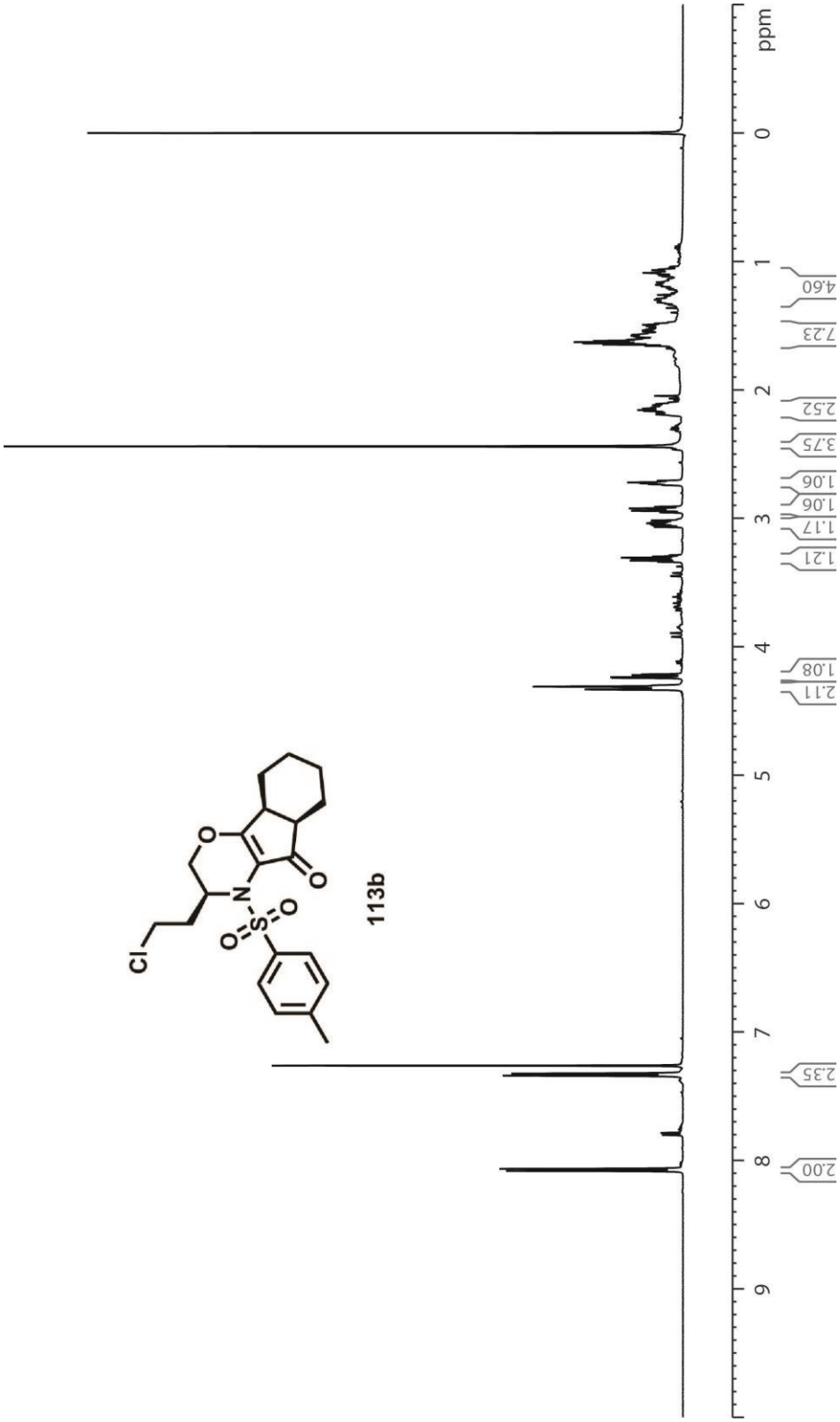
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (3*S*,5a*S*,9a*R*)-3-(2-chloroethyl)-4-(4-methylbenzenesulfonate)-3,4,5a,6,7,8,9,9a-octahydroindeno[1,2-*b*][1,4]oxazin-5(2*H*)-one (113a)**



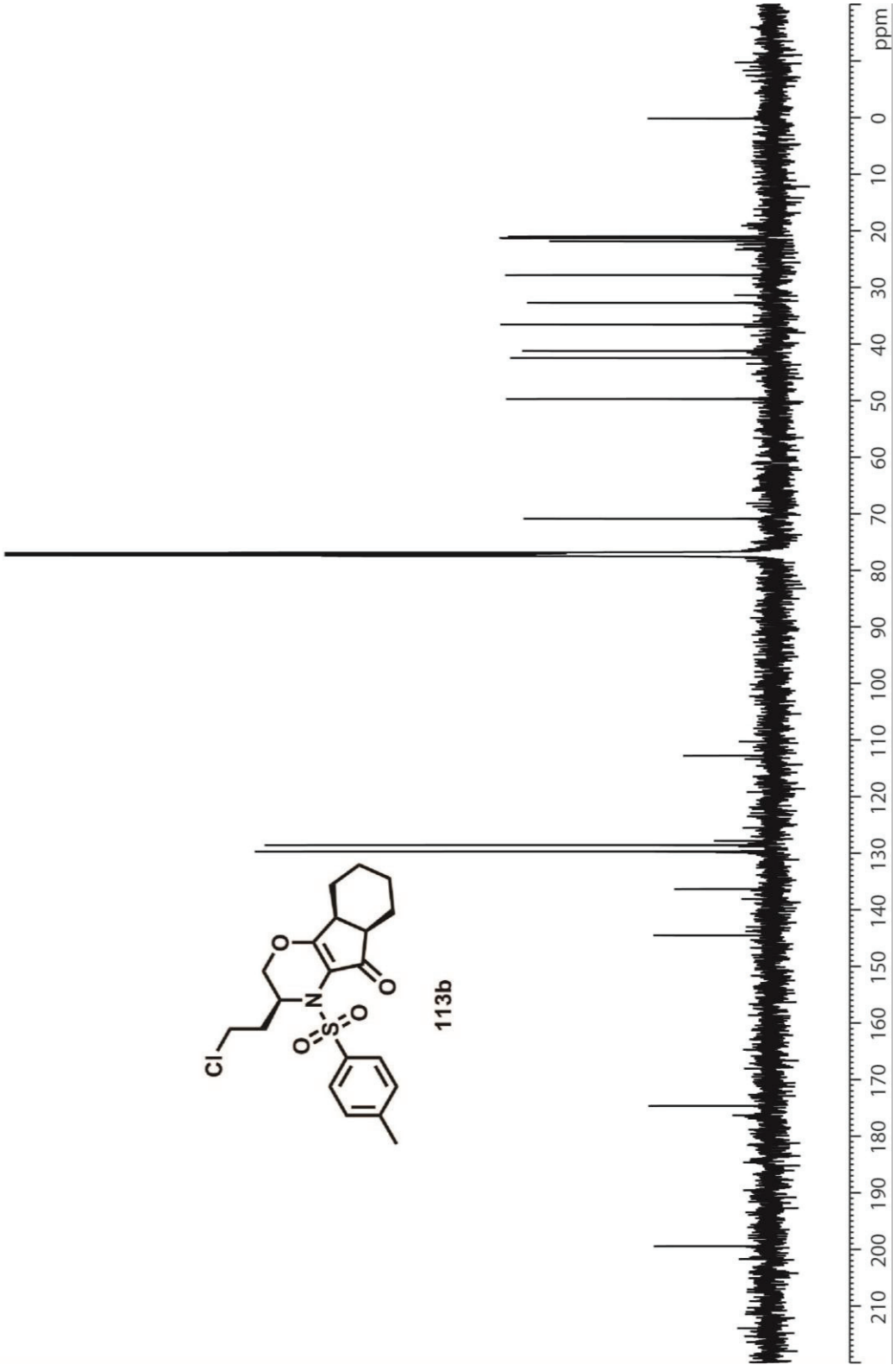
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (3*S*,5a*S*,9a*R*)-3-(2-chloroethyl)-4-(4-methylbenzenesulfonate)-3,4,5a,6,7,8,9,9a-octahydroindeno[1,2-*b*][1,4]oxazin-5(2*H*)-one (113a)**



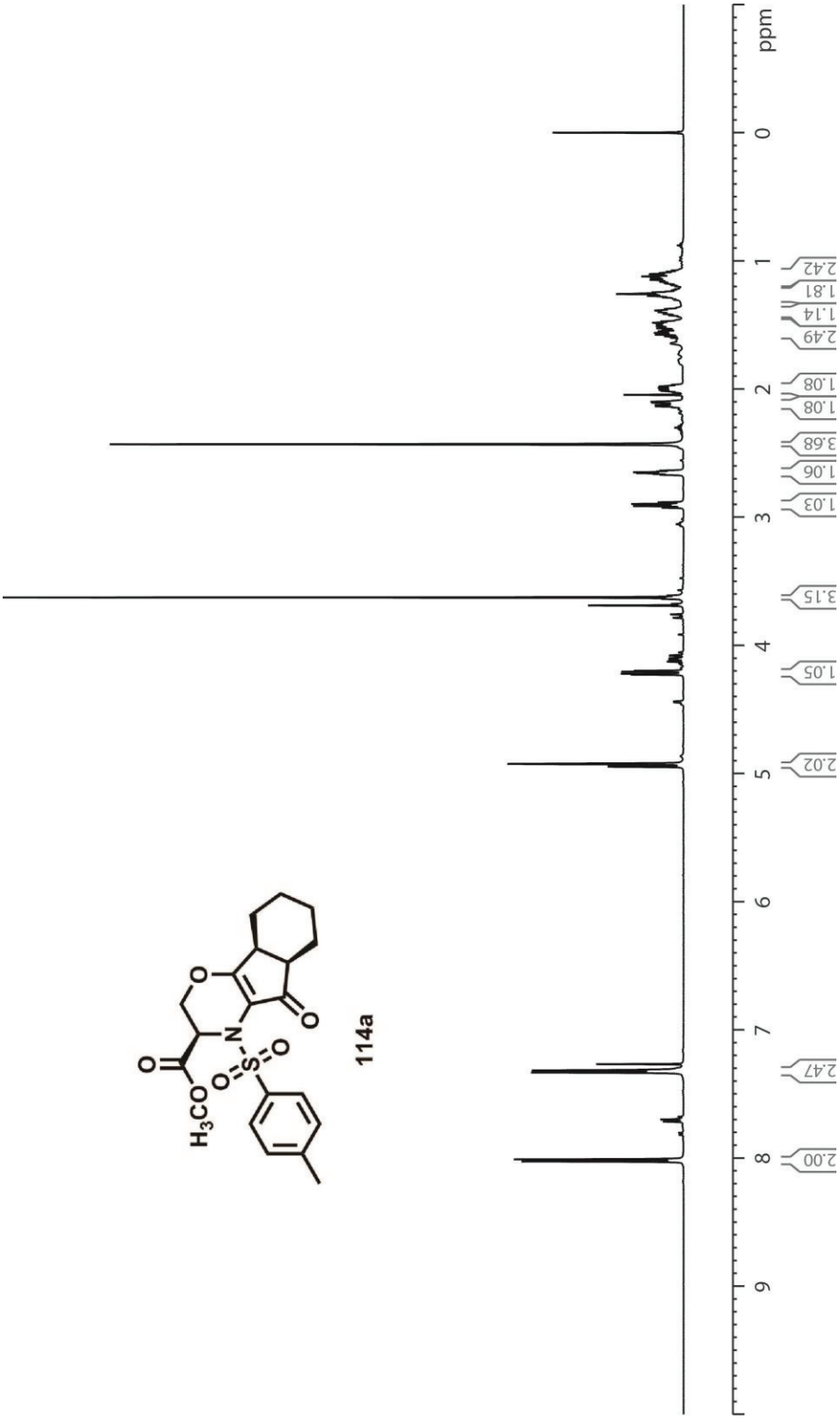
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (3*S*,5a*R*,9a*S*)-3-(2-chloroethyl)-4-(4-methylbenzenesulfonate)-3,4,5a,6,7,8,9,9a-octahydroindeno[1,2-*b*][1,4]oxazin-5(2*H*)-one (113b)**



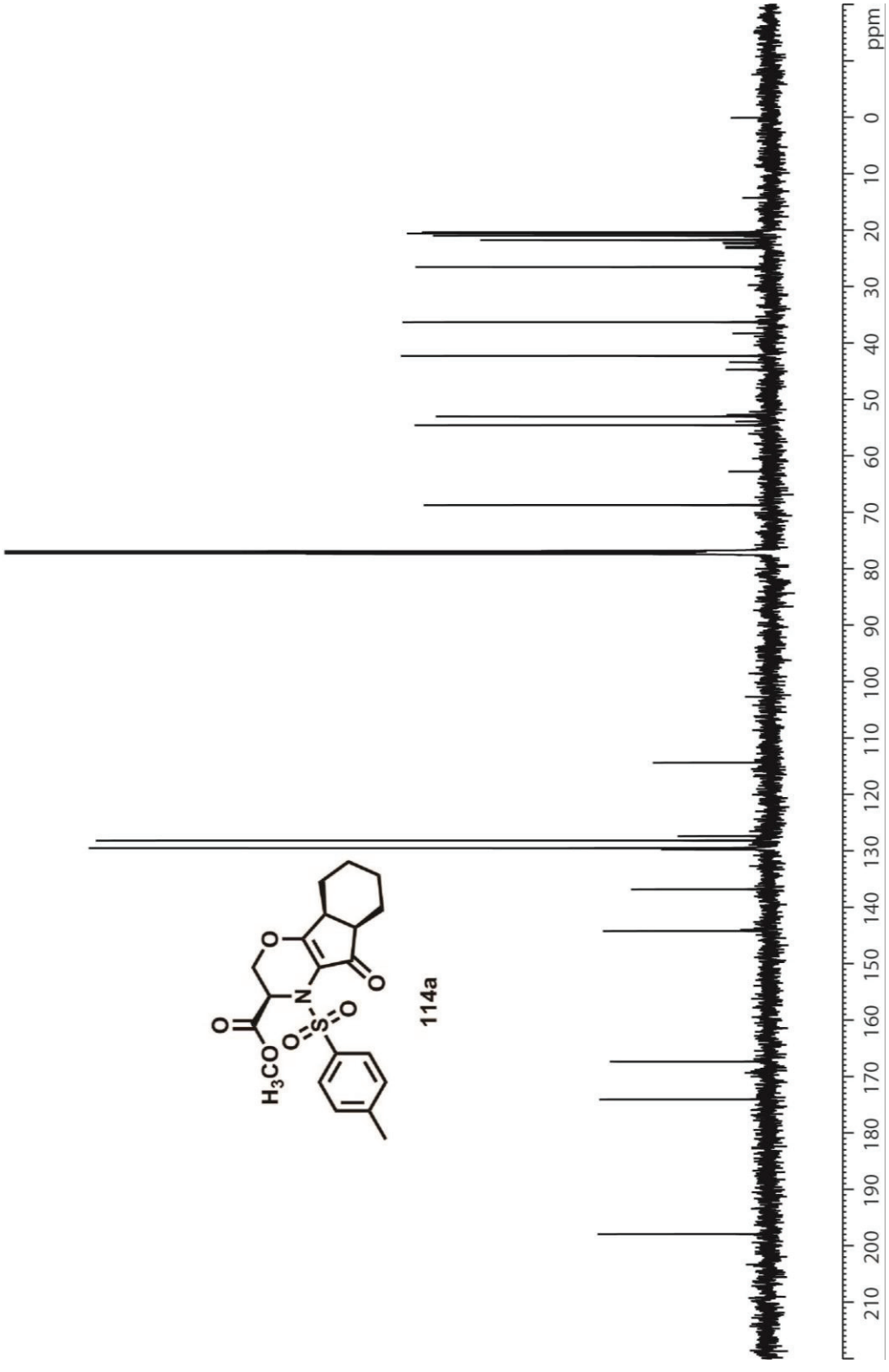
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (3*S*,5a*R*,9a*S*)-3-(2-chloroethyl)-4-(4-methylbenzenesulfonate)-3,4,5a,6,7,8,9,9a-octahydroindeno[1,2-*b*][1,4]oxazin-5(2*H*)-one (113b)**



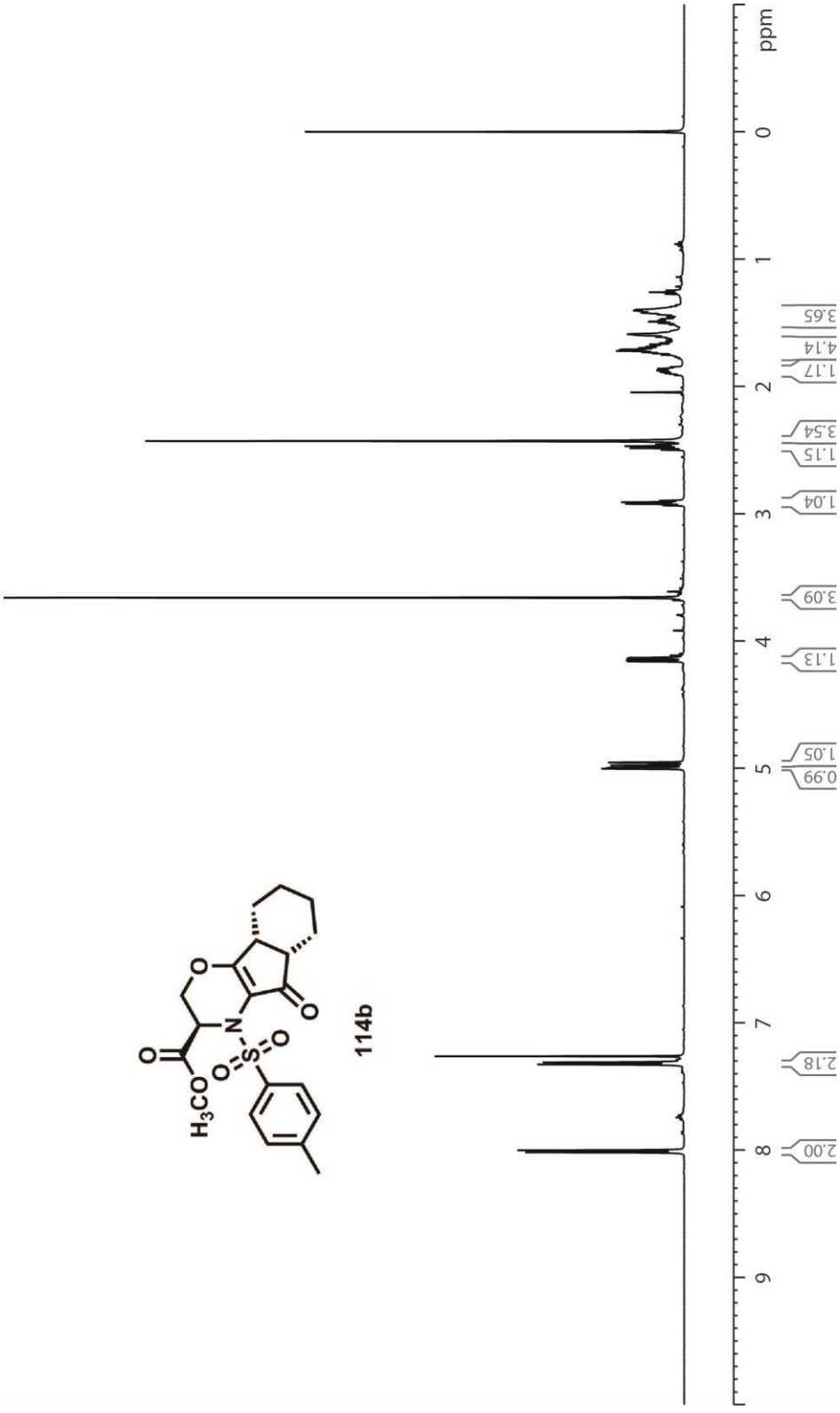
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of methyl (3*R*,5a*R*,9a*S*)-4-(4-methylbenzenesulfonate)-5-oxo-2,3,4,5,5a,6,7,8,9,9a-decahydroindeno[1,2-*b*][1,4]oxazine-3-carboxylate (114a)**



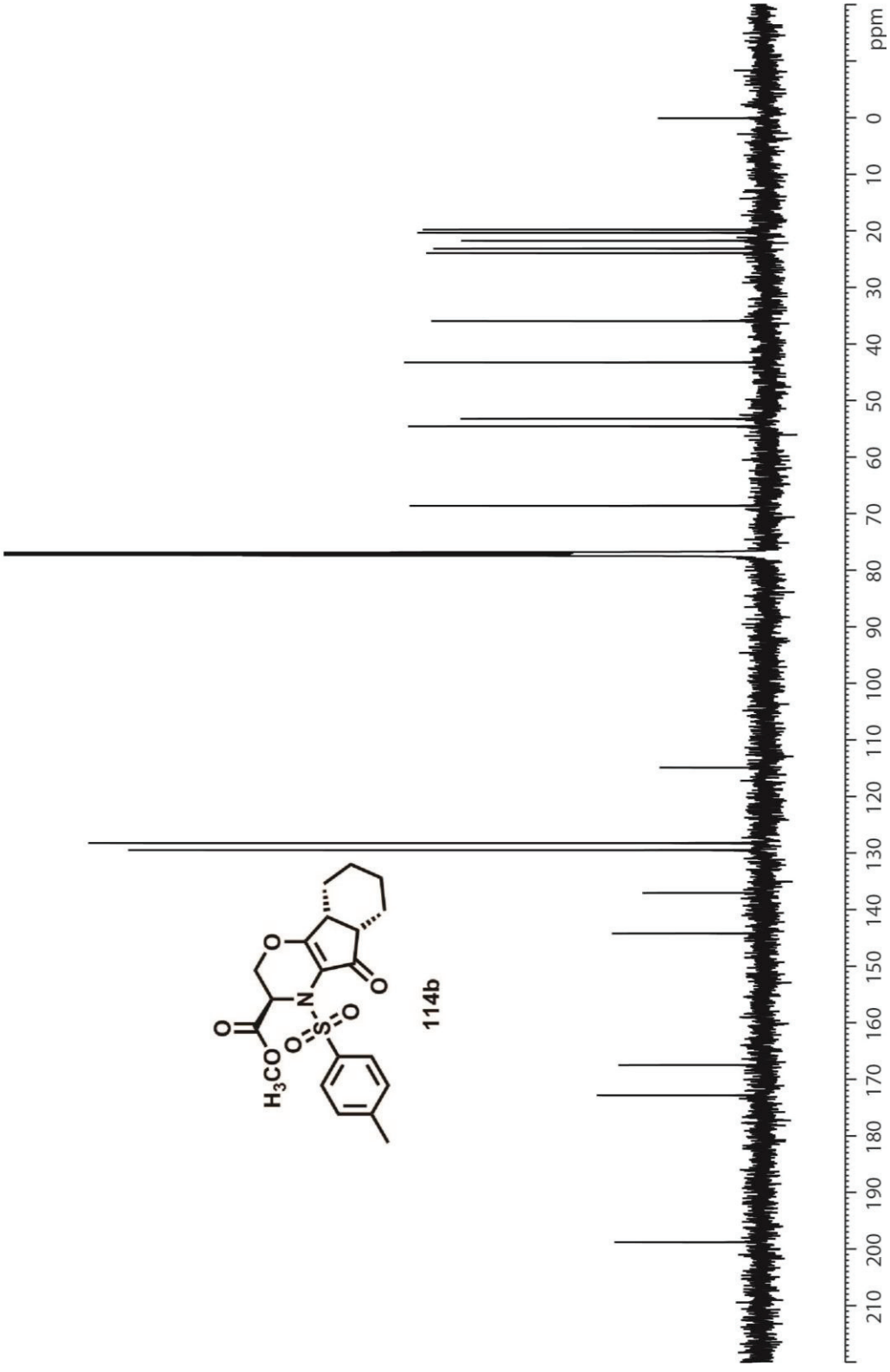
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of methyl (3*R*,5a*R*,9a*S*)-4-(4-methylbenzenesulfonate)-5-oxo-2,3,4,5,5a,6,7,8,9,9a-decahydroindeno[1,2-*b*][1,4]oxazine-3-carboxylate (114a)**



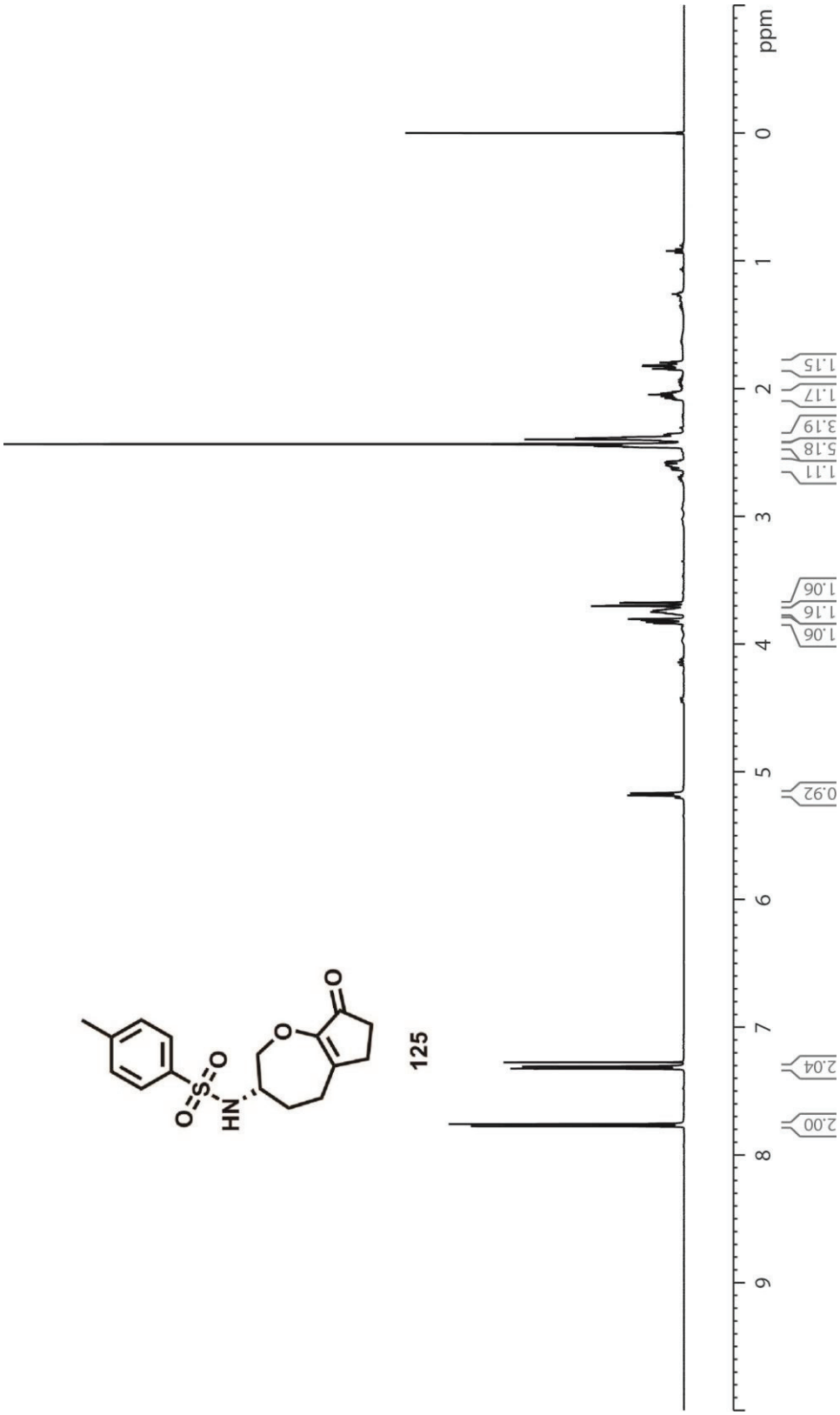
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of methyl (3*R*,5a*S*,9a*R*)-4-(4-methylbenzenesulfonate)-5-oxo-2,3,4,5,5a,6,7,8,9,9a-decahydroindeno[1,2-*b*][1,4]oxazine-3-carboxylate (114b)**



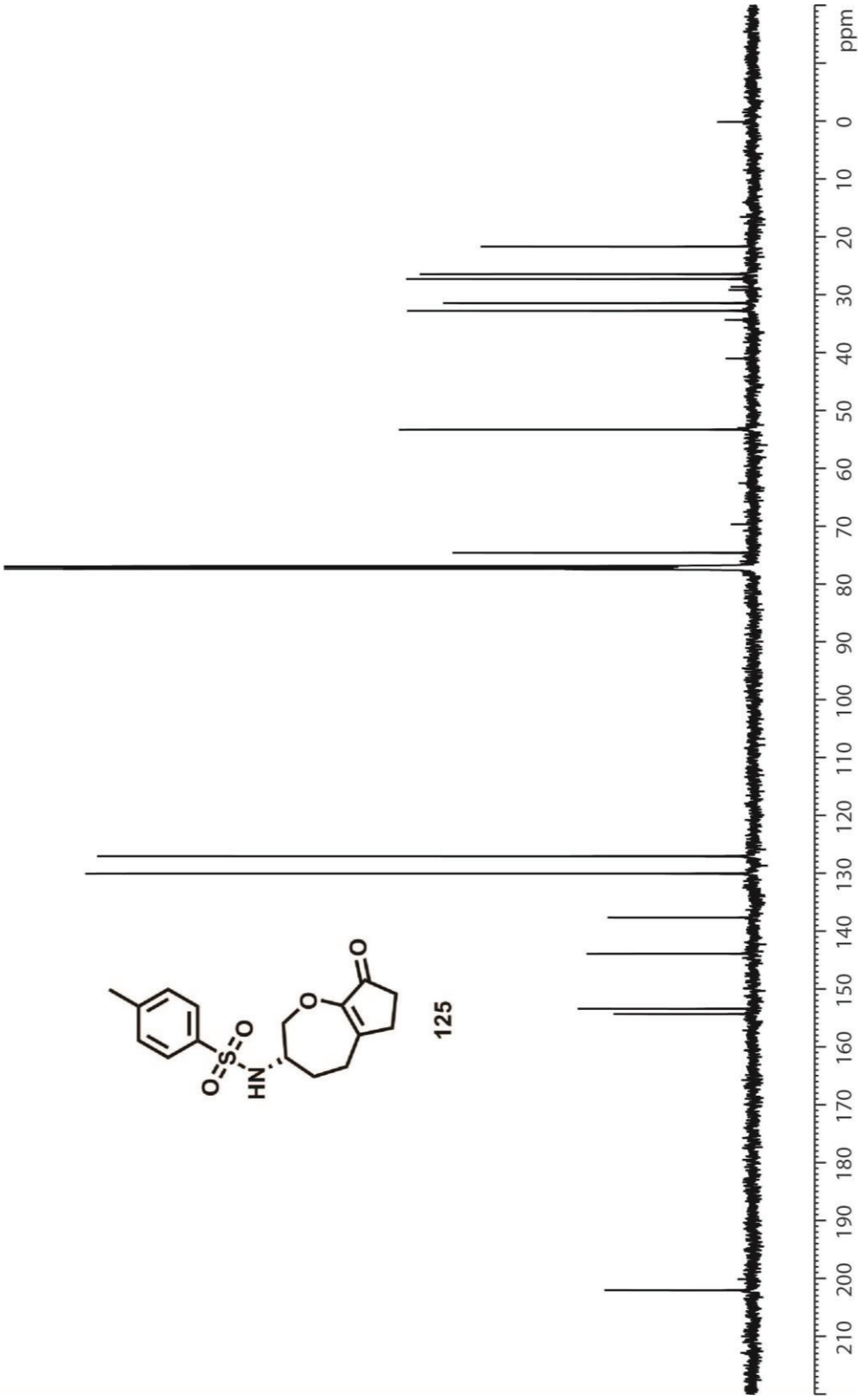
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of methyl (3*R*,5a*S*,9a*R*)-4-(4-methylbenzenesulfonate)-5-oxo-2,3,4,5,5a,6,7,8,9,9a-decahydroindeno[1,2-*b*][1,4]oxazine-3-carboxylate (114b)**

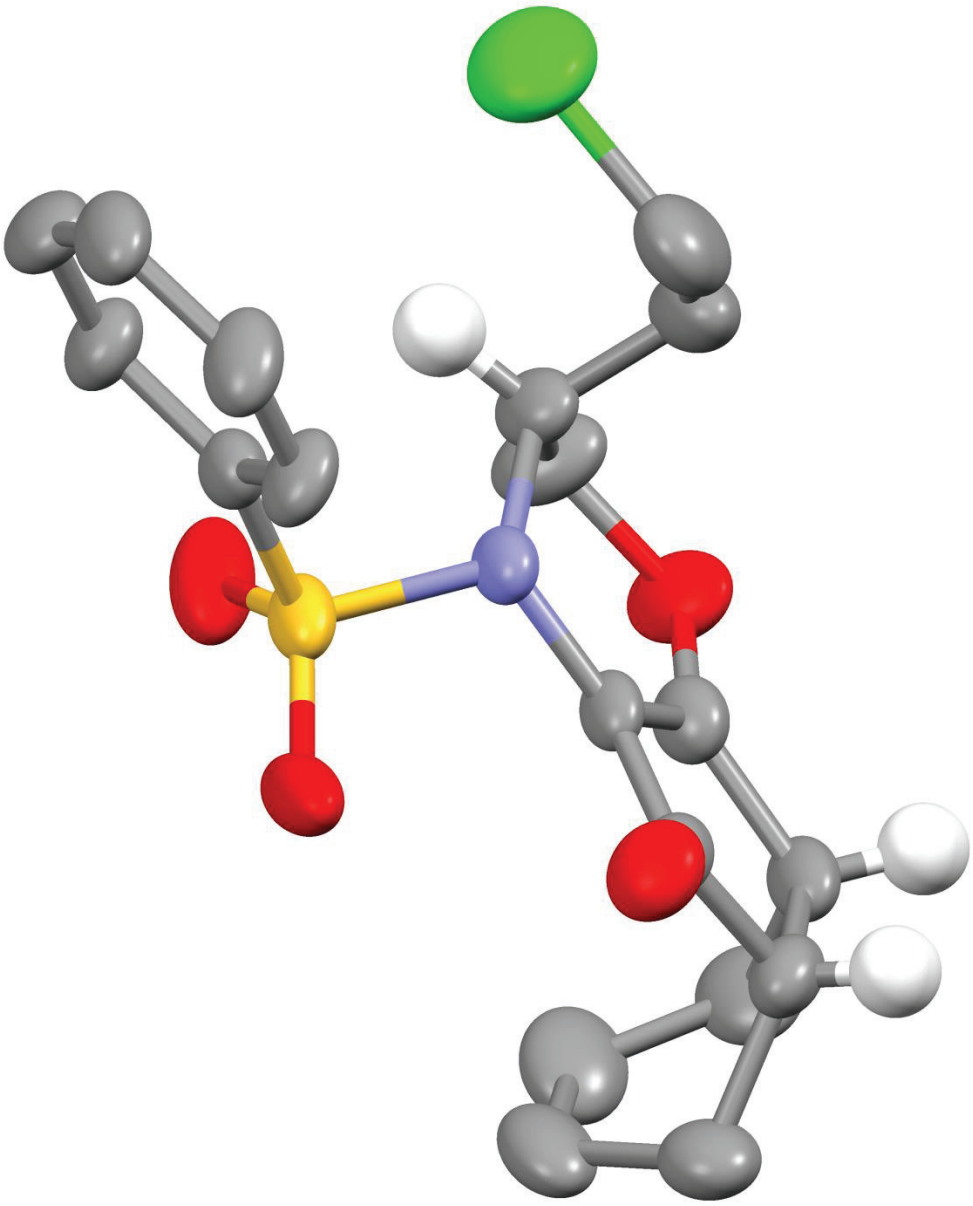


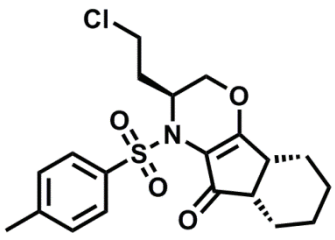
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (*S*)-4-methyl-*N*-(8-oxo-3,4,5,6,7,8-hexahydro-2*H*-cyclopenta[*b*]oxepin-3-yl)-benzenesulfonamide (125)**



**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (*S*)-4-methyl-*N*-(8-oxo-3,4,5,6,7,8-hexahydro-2*H*-cyclopenta[*b*]oxepin-3-yl)-benzenesulfonamide (125)**

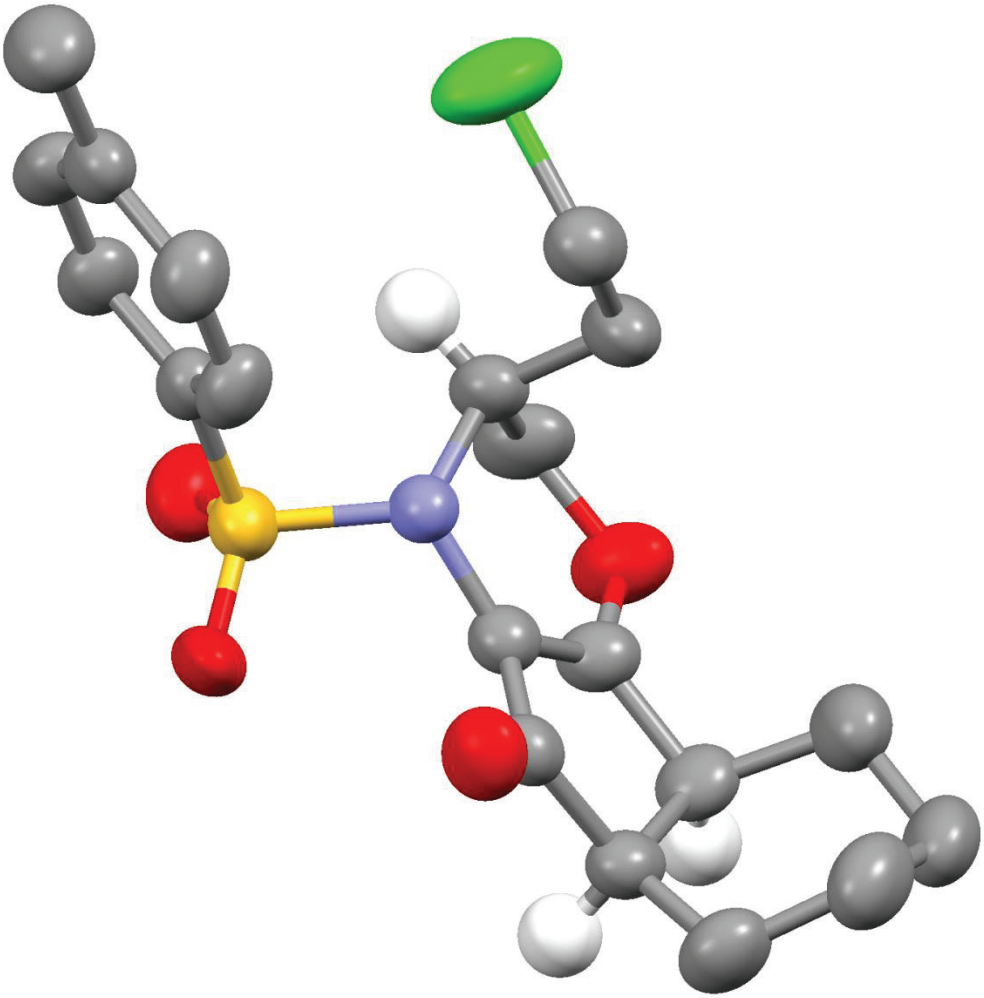


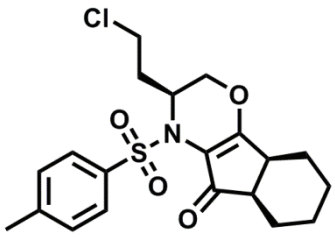





**113a**

X-ray crystal structure of **113a** (selected hydrogen atoms omitted for clarity)






**113b**

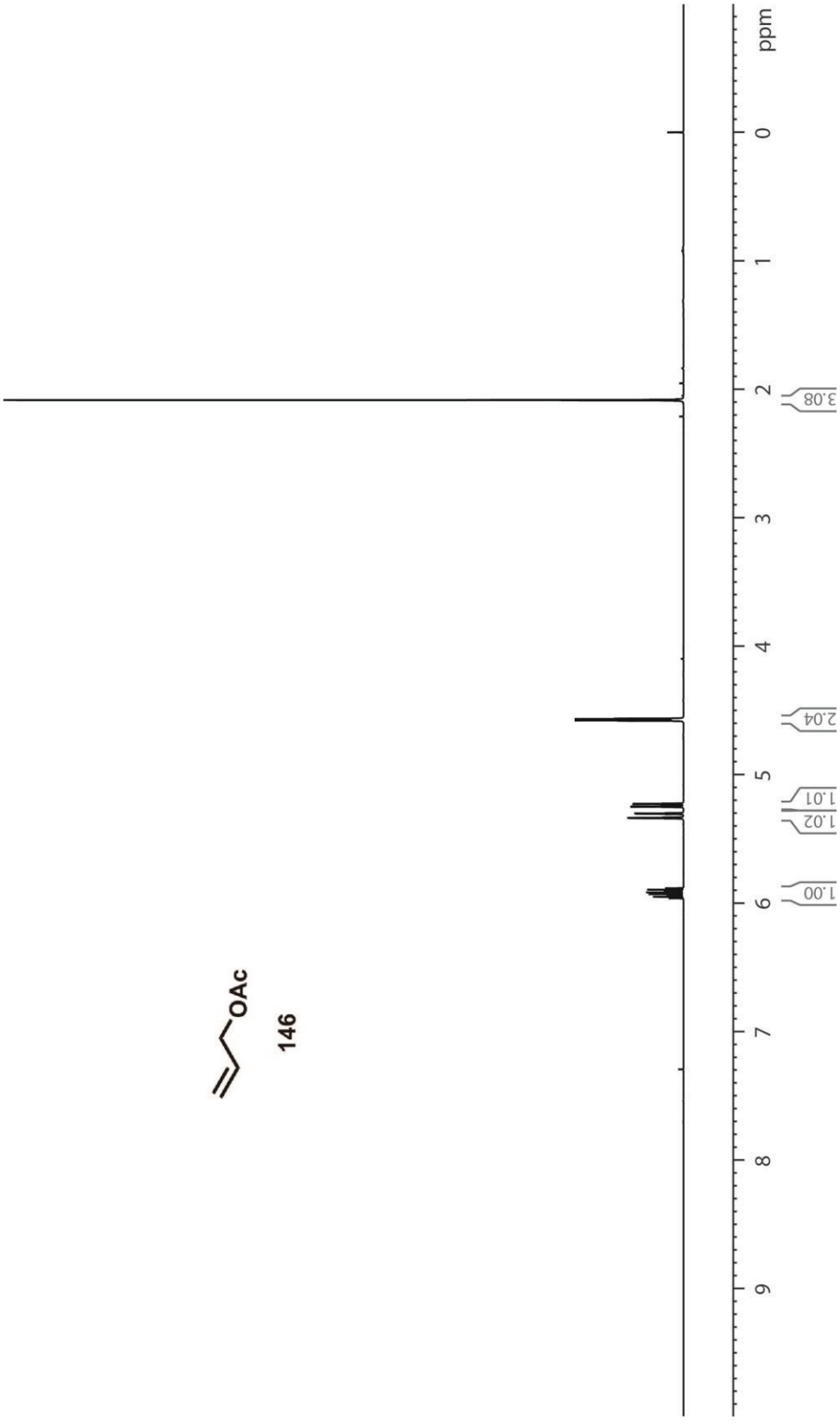
X-ray crystal structure of **113a** (selected hydrogen atoms omitted for clarity)

| | **113a** | **113b** |
|---|---|---|
| Empirical formula | $C_{20}H_{24}NO_4ClS$ | $C_{20}H_{24}NO_4SCl$ |
| T (K) | 296 | 296 |
| λ (Mo Ka) (Å) | 0.71070 | 0.71070 |
| Color and habit | colourless, needle | colourless, needle |
| Crystal system | triclinic | orthorhombic |
| Space group | P1 | $P2_12_12_1$ |
| a (Å) | 8.1043(4) | 23.5288(7) |
| b (Å) | 7.4922(3) | 7.4859(3) |
| c (Å) | 16.4678(7) | 11.1461(4) |
| α (°) | 90.027(3) | 90 |
| β (°) | 100.842(3) | 90 |
| γ (°) | 89.954(3) | 90 |
| V (Å$^3$) | 982.06(8) | 1963.21(12) |
| Z | 2 | 4 |
| Crystal size (mm$^3$) | 0.43 x 0.15 x 0.09 | 0.38 x 0.26 x 0.08 |
| Absorption coefficient (cm-$^1$) | 3.264 | 3.266 |
| Reflections | 6722 | 14732 |
| Independent reflections | 6640 | 5802 |
| $R_{int}$ | 0.025 | 0.053 |
| $2\theta_{max}$ (°) | 84.3 | 71.3 |
| GOF | 1.126 | 1.078 |
| $R_1$ (I>3.00σ(I)) | 0.0466 | 0.0345 |
| $wR_2$ (I>3.00σ(I)) | 0.0561 | 0.0404 |
| Largest differential peak and hole (e$^-$/Å$^3$) | 0.37 and -0.27 | 0.25 and -0.27 |

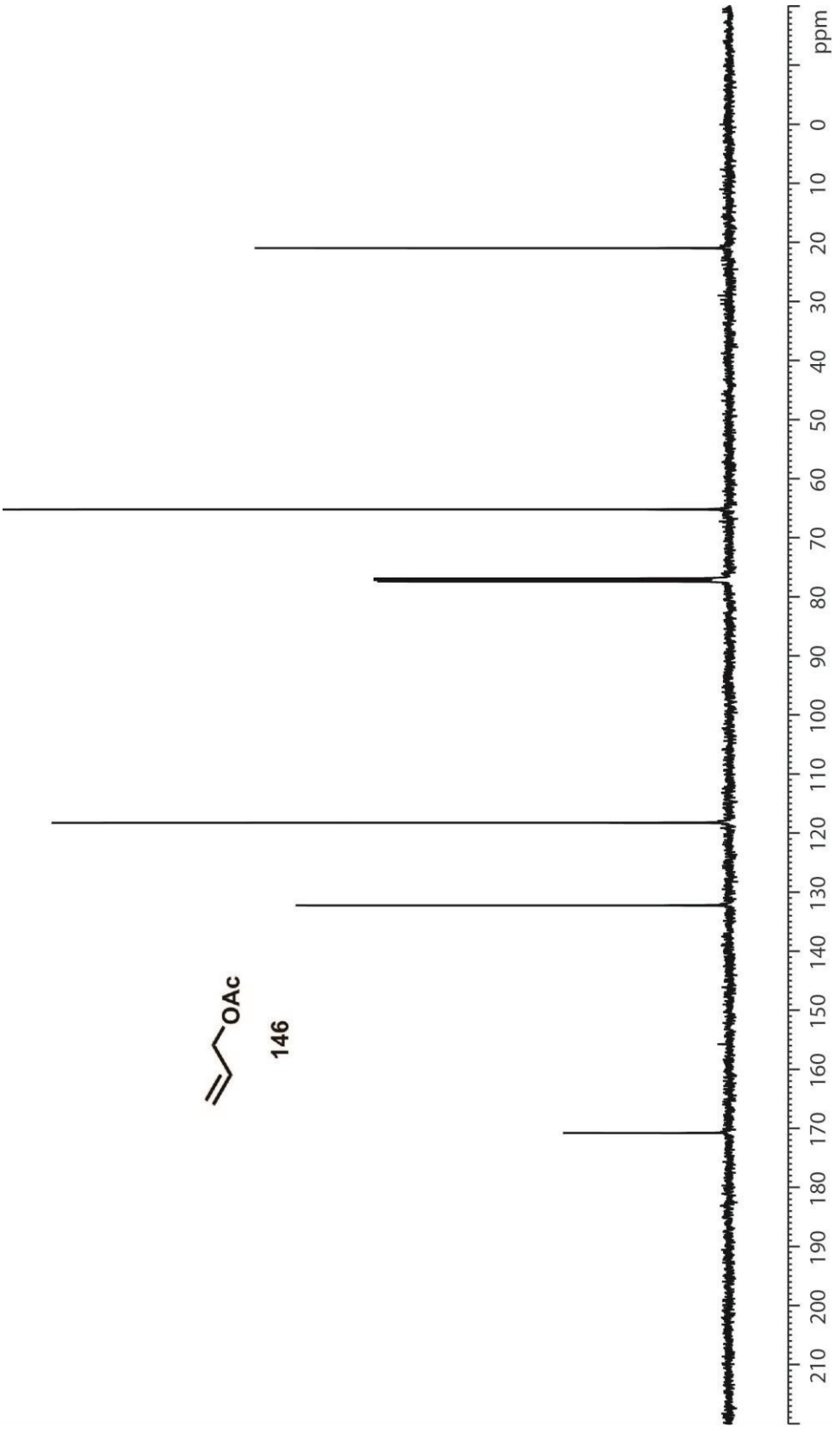
## APPENDIX II: $^{1}H$ AND $^{13}C$ NMR SPECTRA FOR CHAPTER 3

$^{1}H$ NMR and $^{13}C$ NMR spectra for compounds **146**, **147**, **148**, **149**, **144a**, **144b**, **150a**, **150b**, **151a**, **151b**, **152a**, and **152b**.

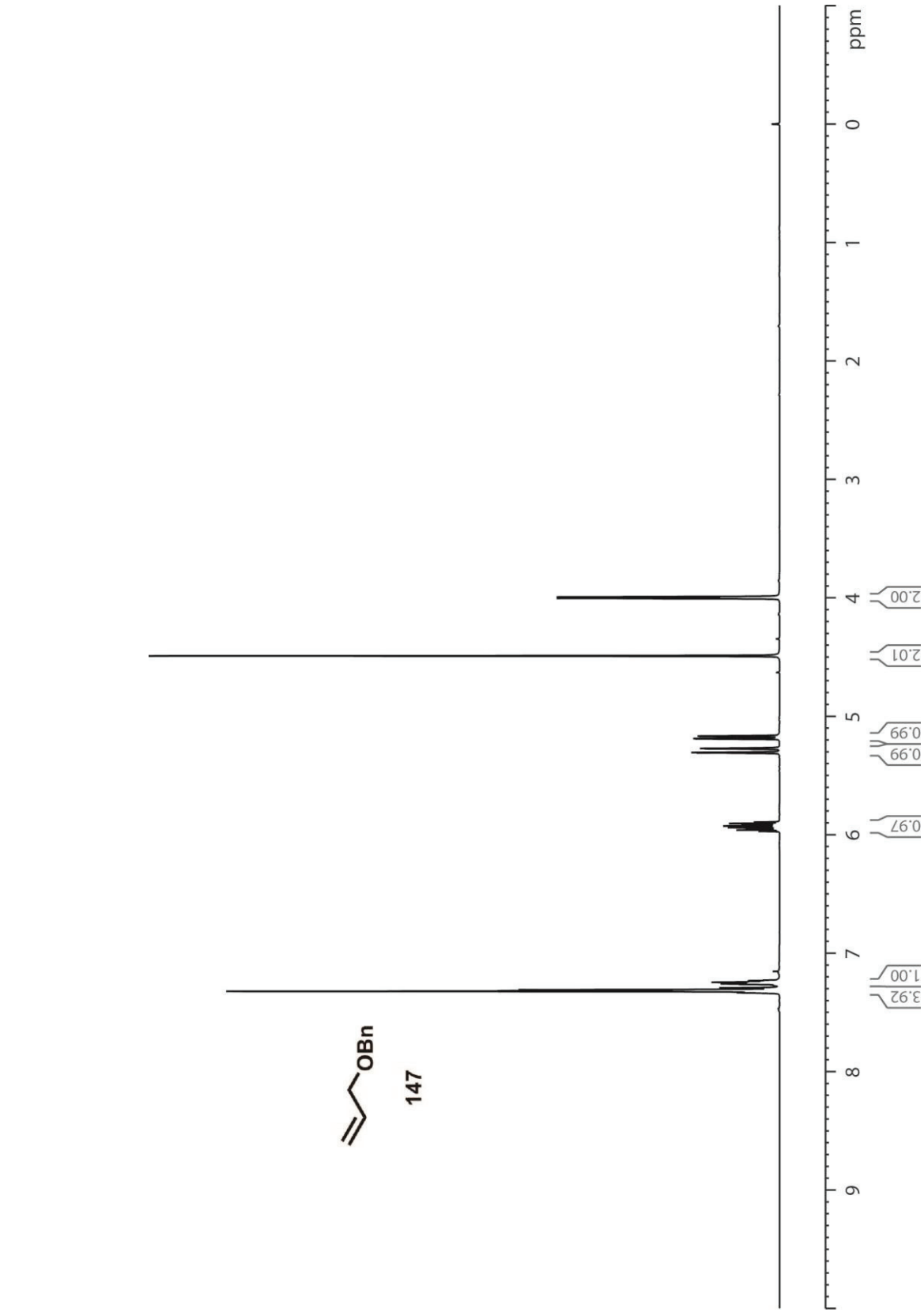
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of allyl acetate (146)**



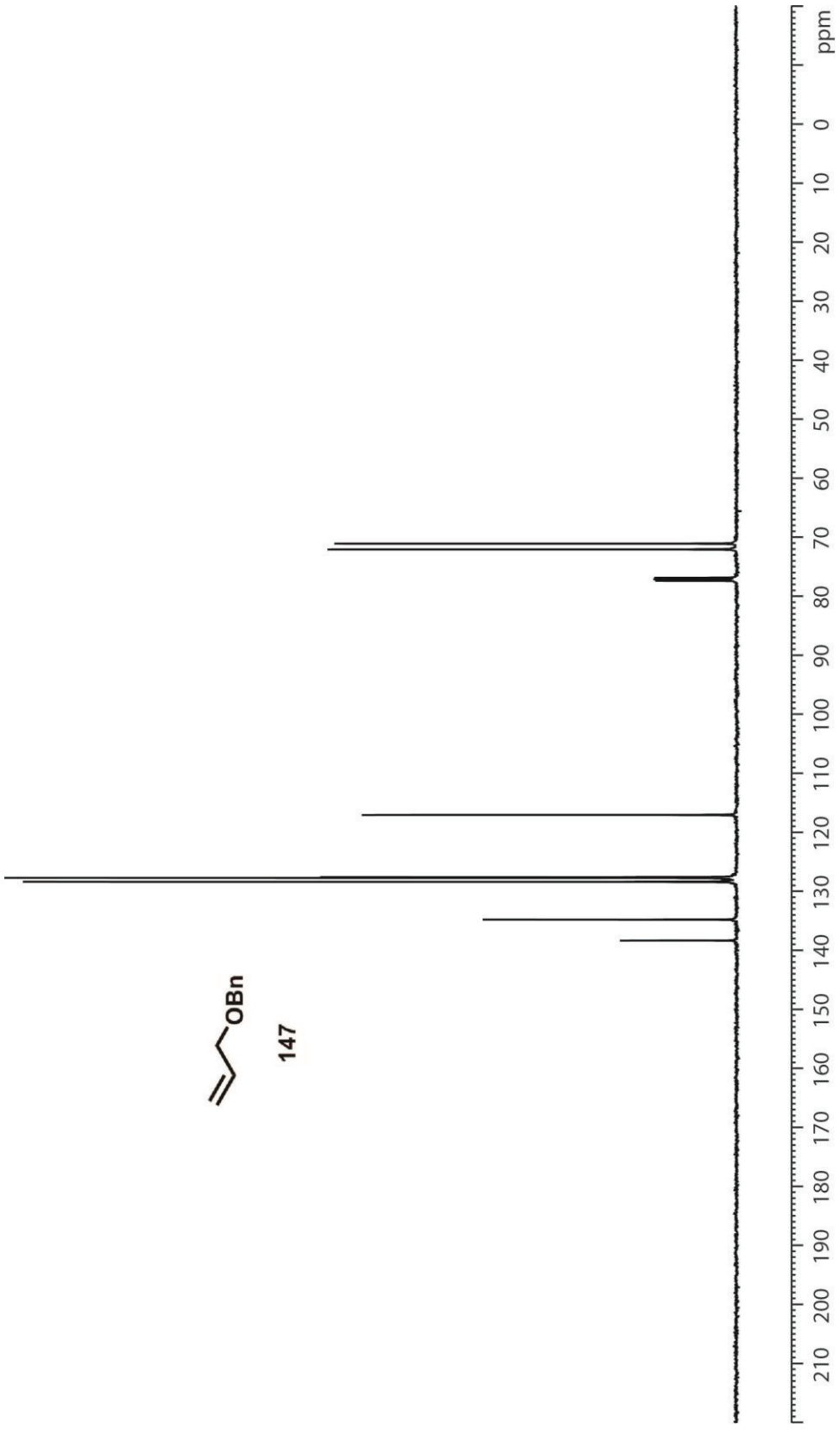
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of allyl acetate (146)**



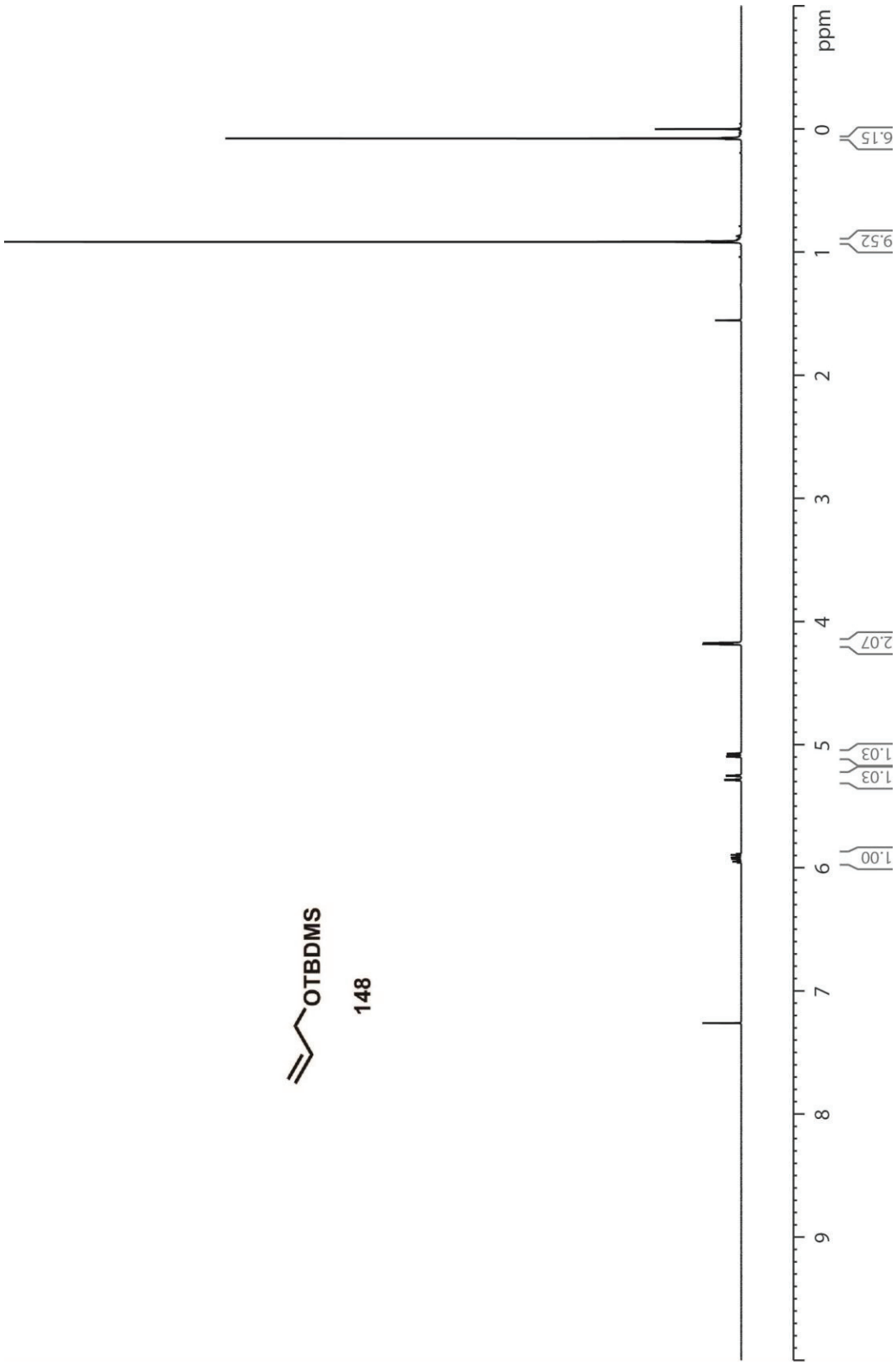
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of allyloxymethylbenzene (147)**



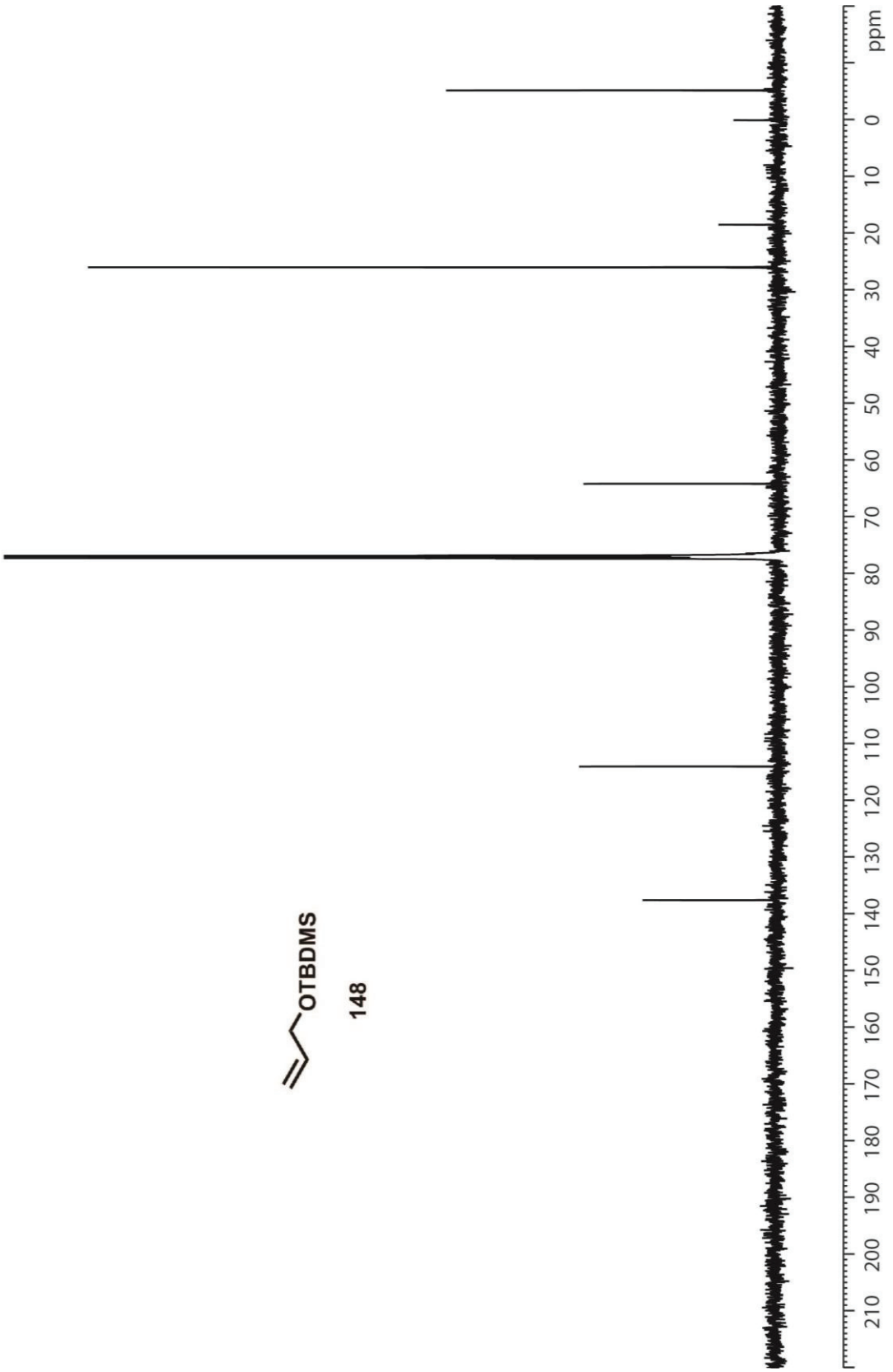
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of allyloxymethylbenzene (147)**



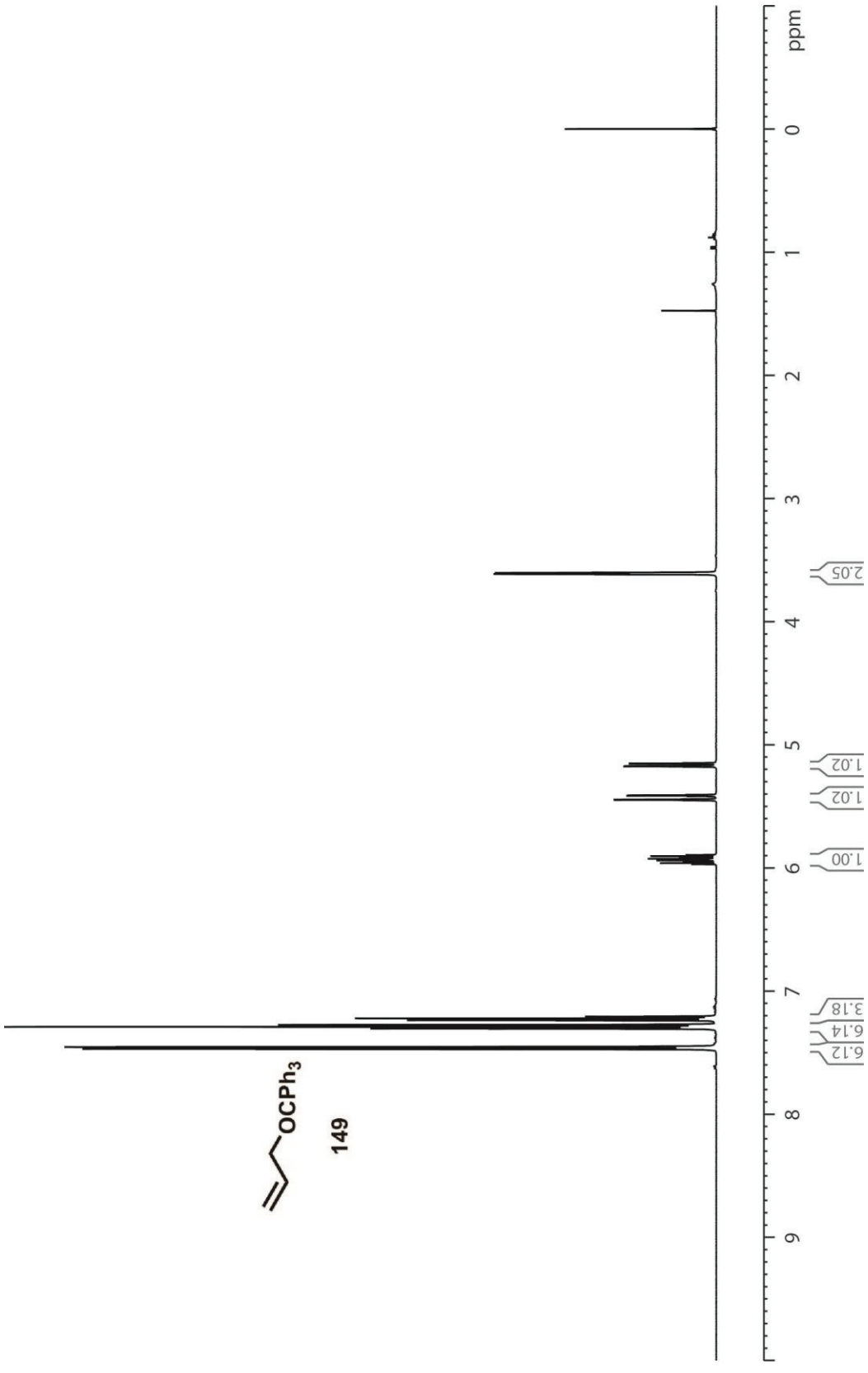
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of allyloxy-*tert*-butyldimethylsilane (148)**



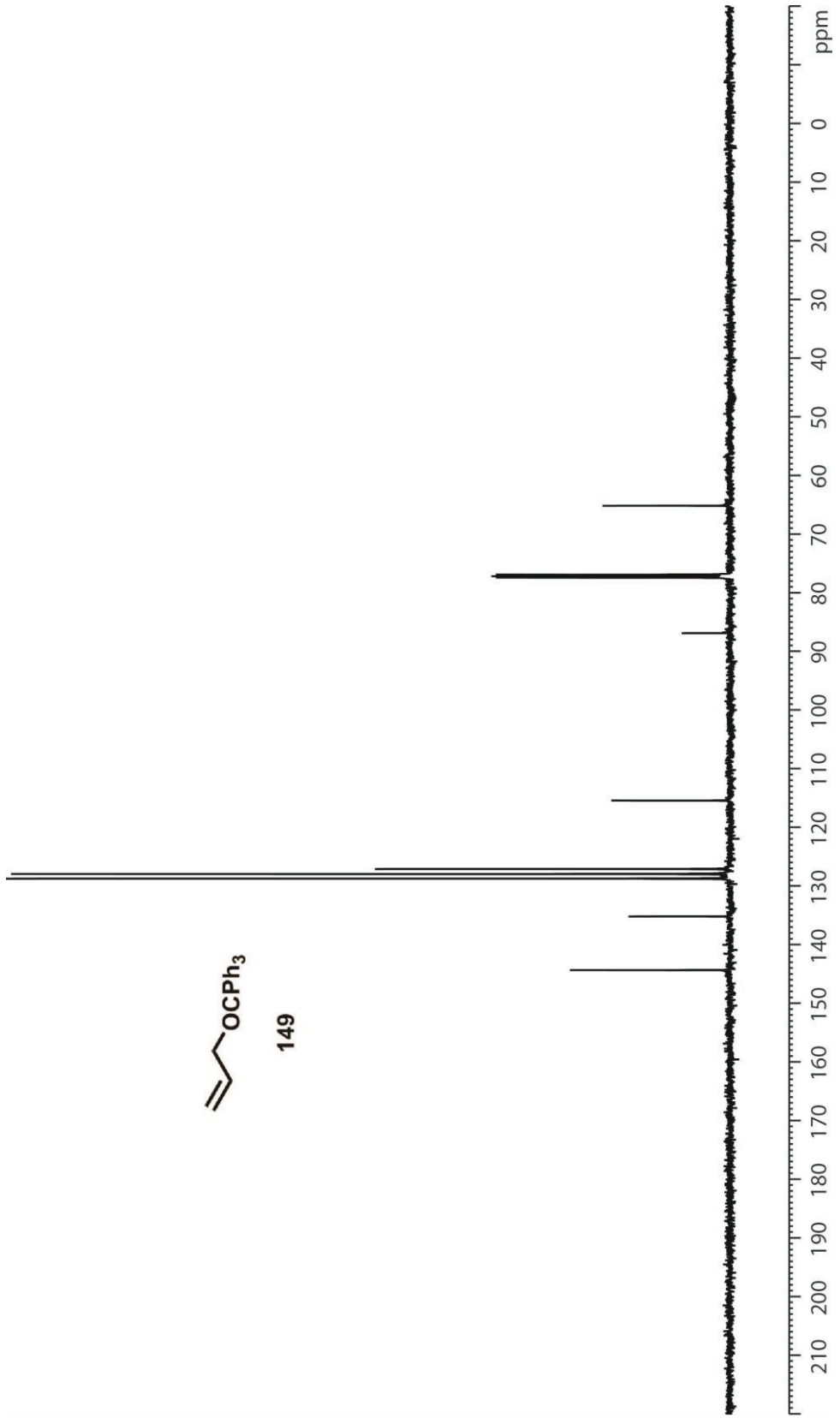
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of allyloxy-*tert*-butyldimethylsilane (148)**



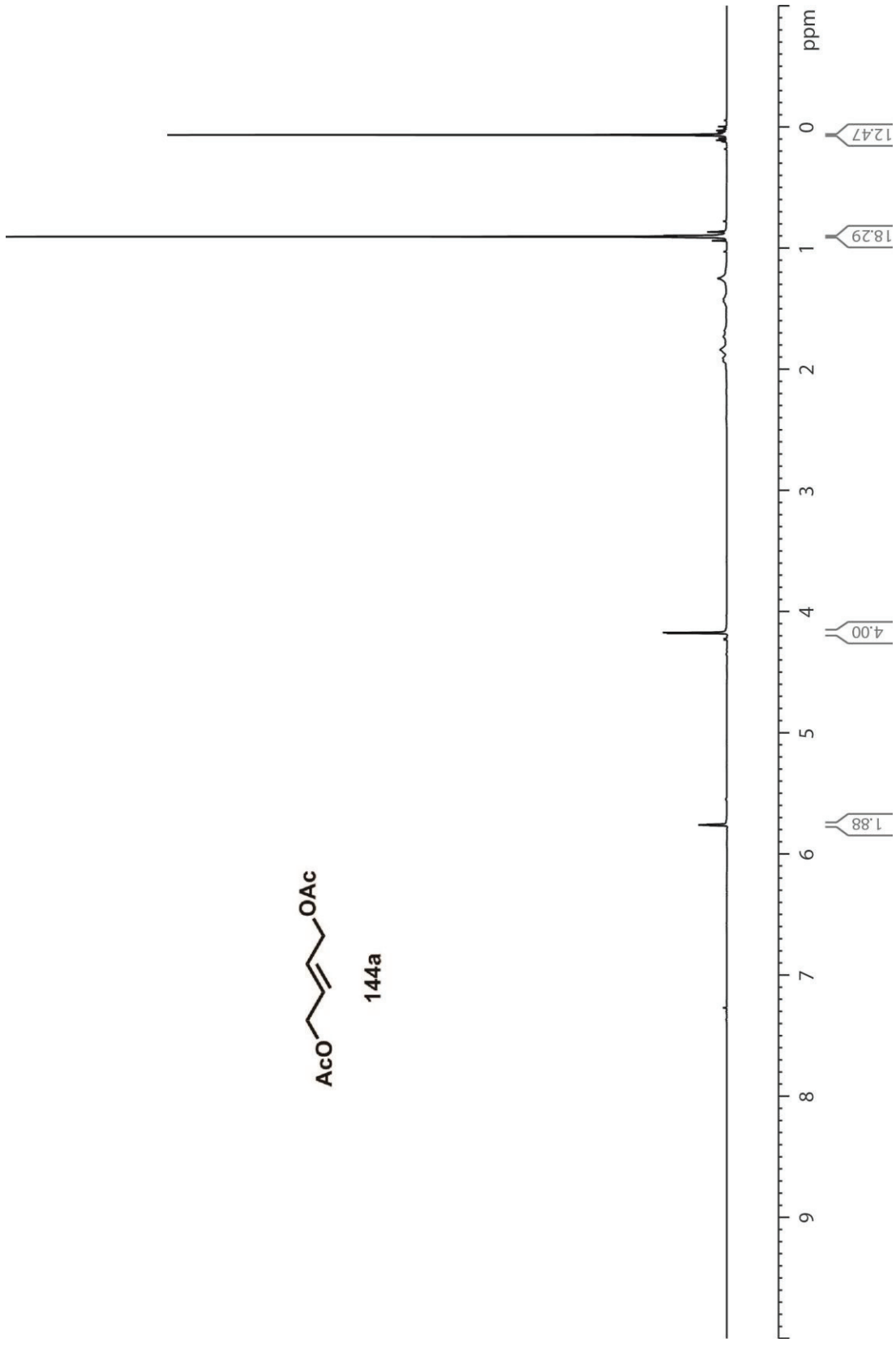
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of allyloxytriphenylmethane (149)**



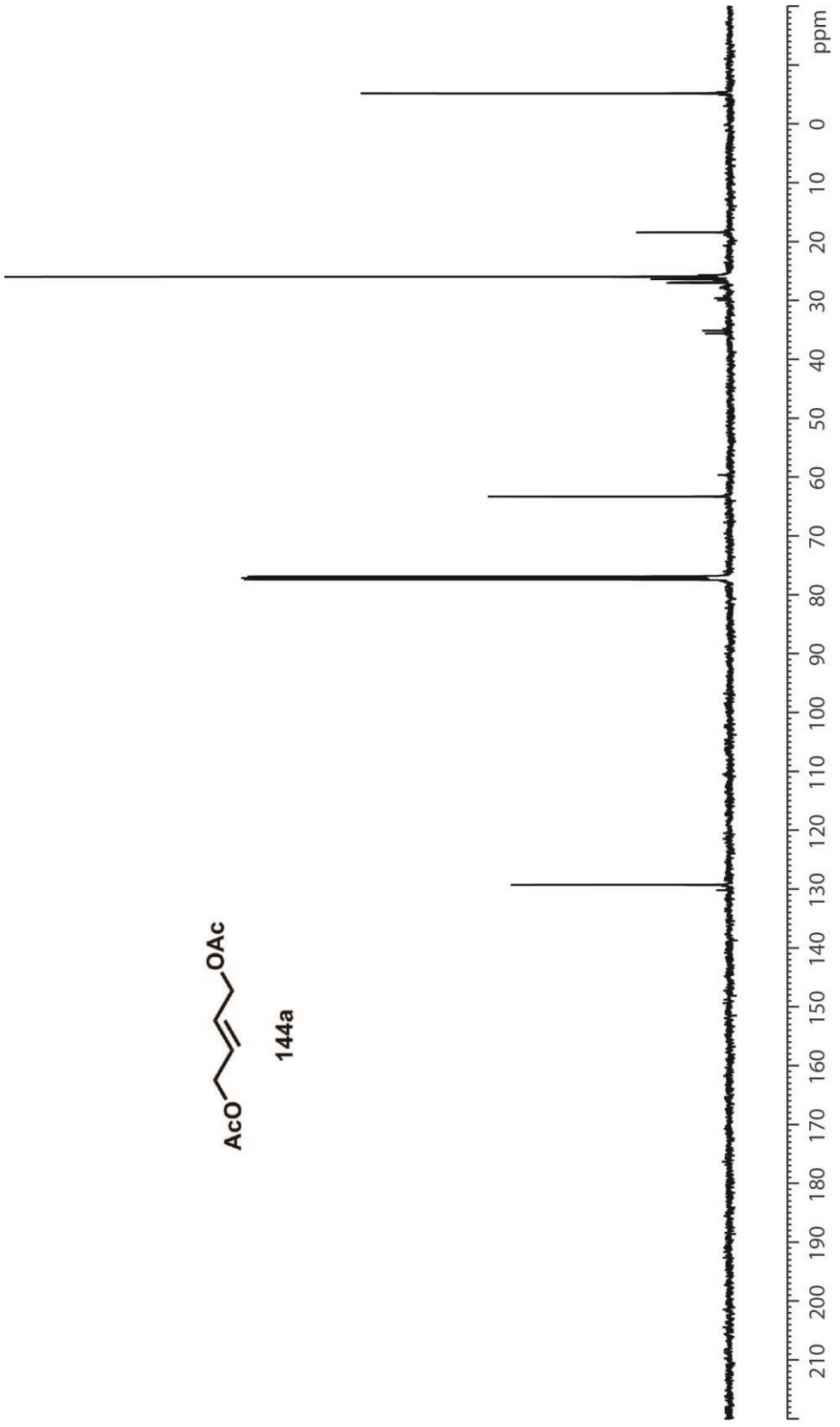
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of allyloxytriphenylmethane (149)**



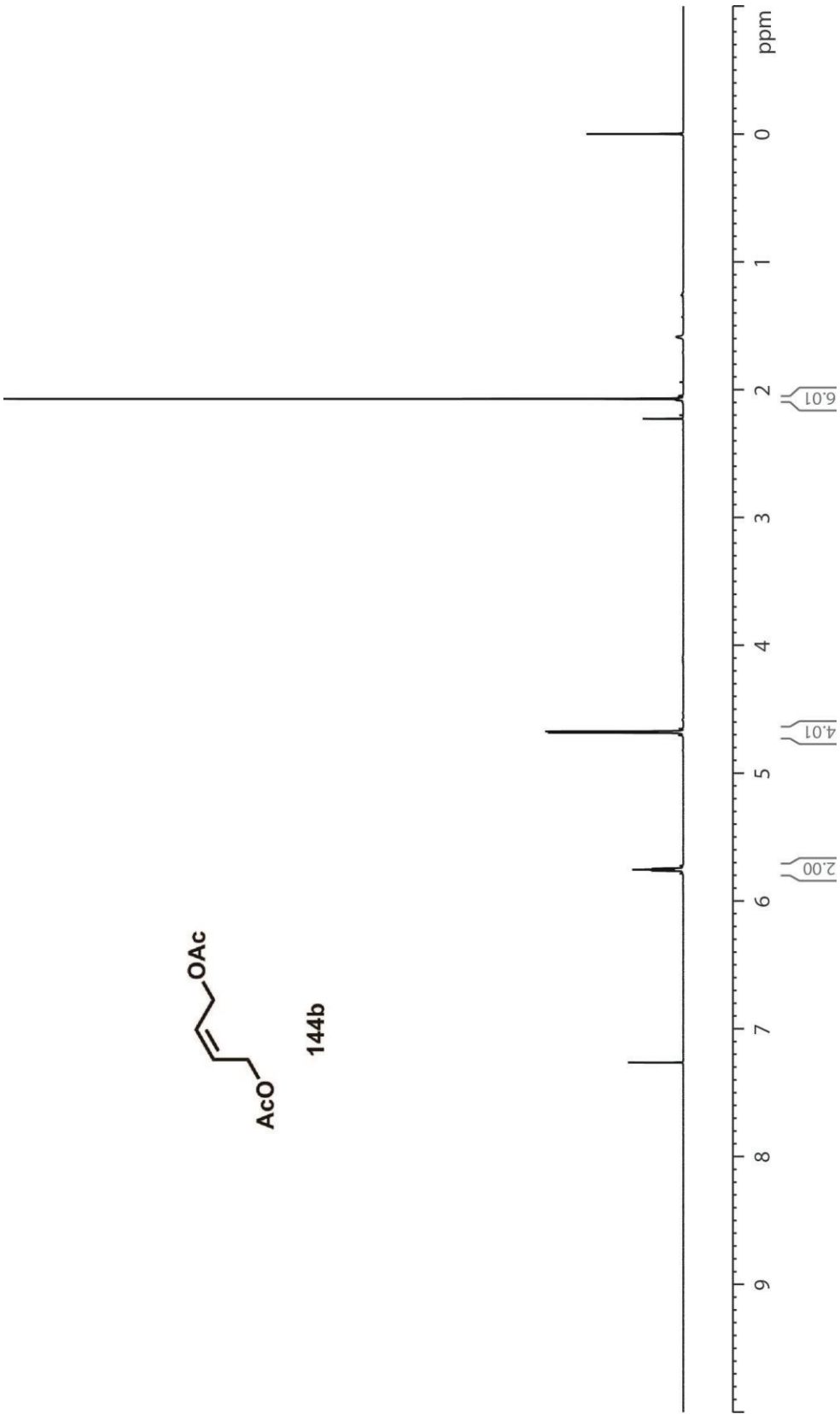
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (*E*)-1,4-diacetoxy-2-butene (144a)**



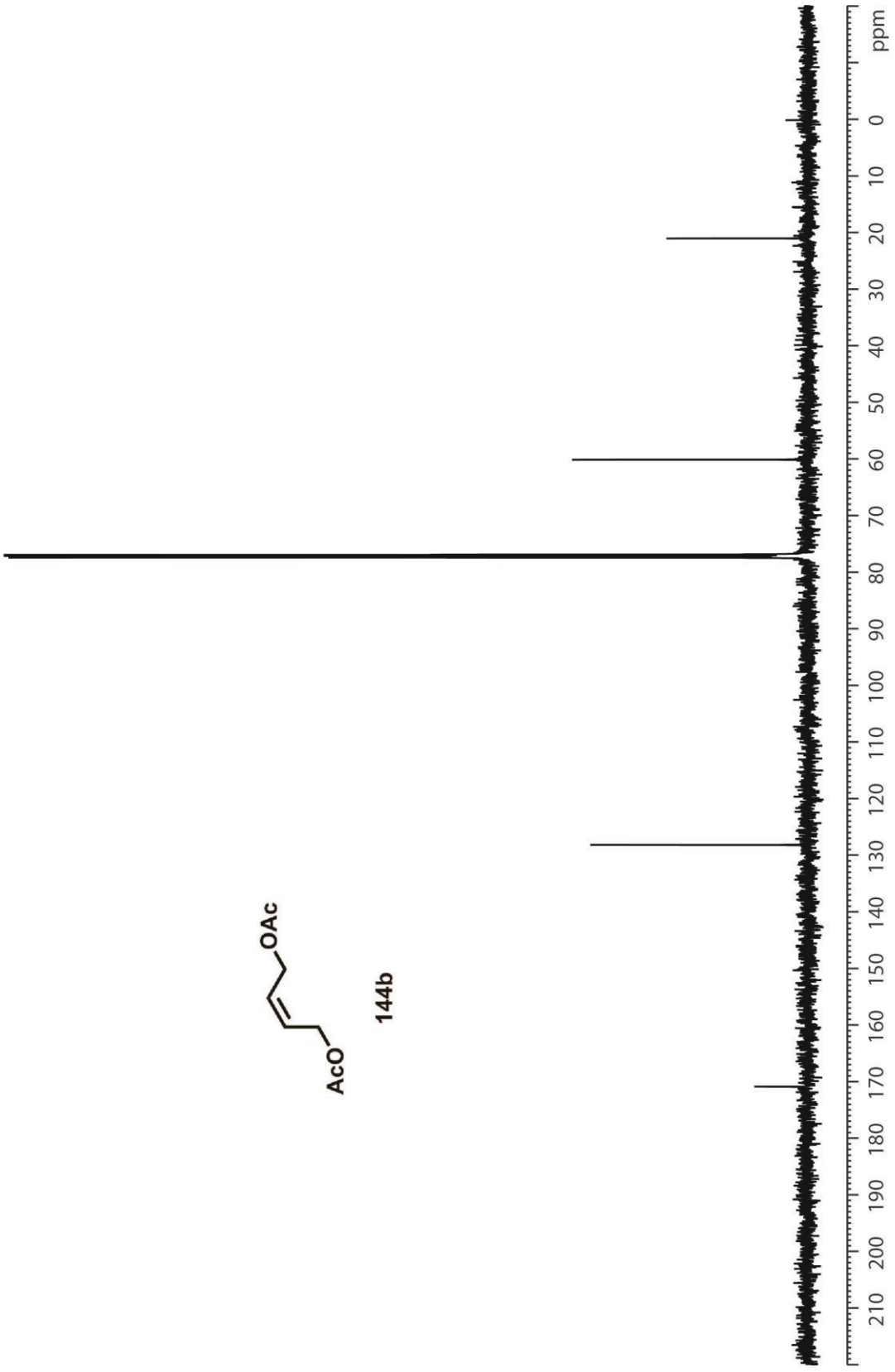
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (*E*)-1,4-diacetoxy-2-butene (144a)**



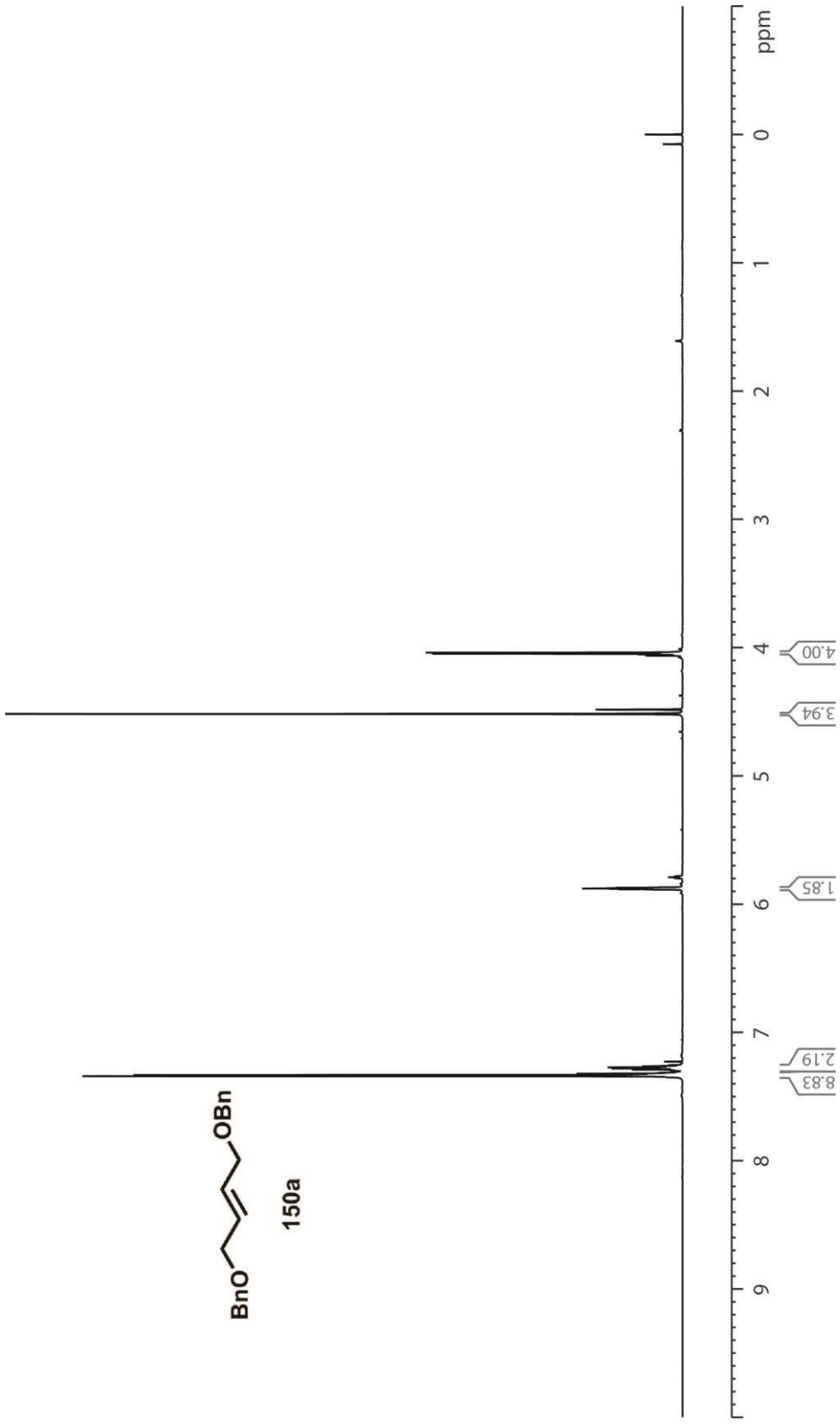
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (*Z*)-1,4-diacetoxy-2-butene (144b)**



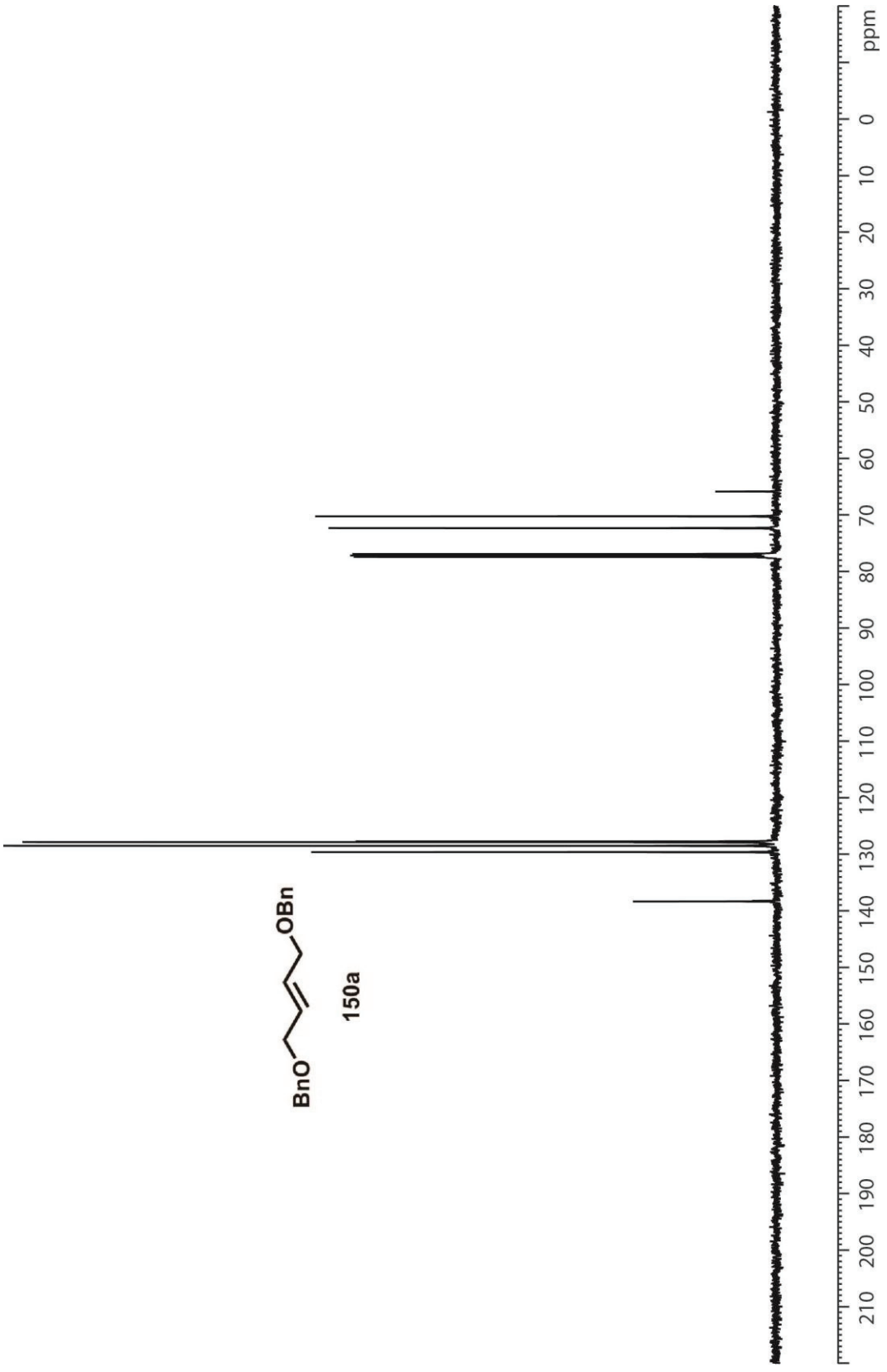
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (*Z*)-1,4-diacetoxy-2-butene (144b)**



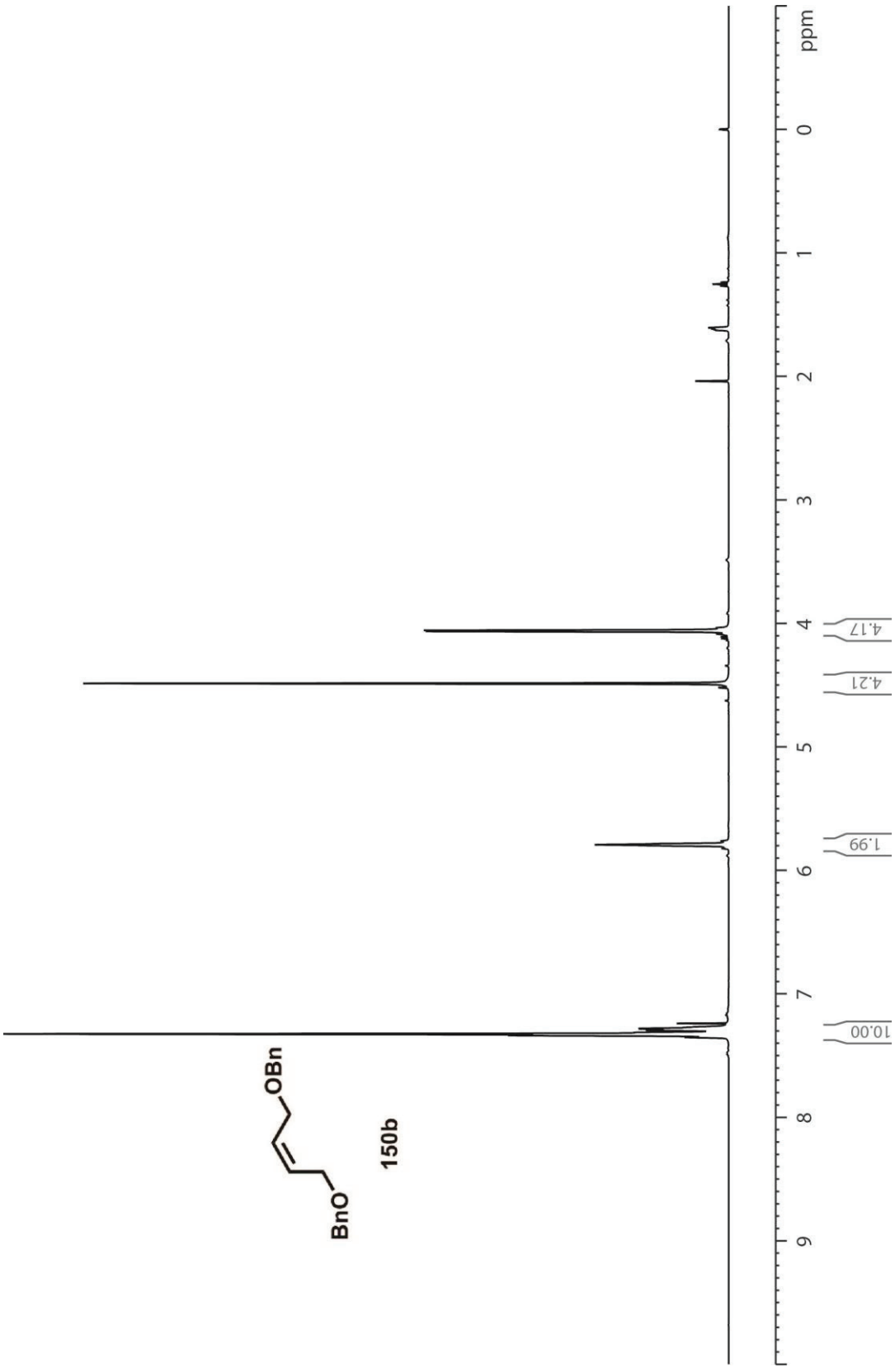
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (*E*)-1,4-bis(benzyloxy)but-2-ene (150a)**



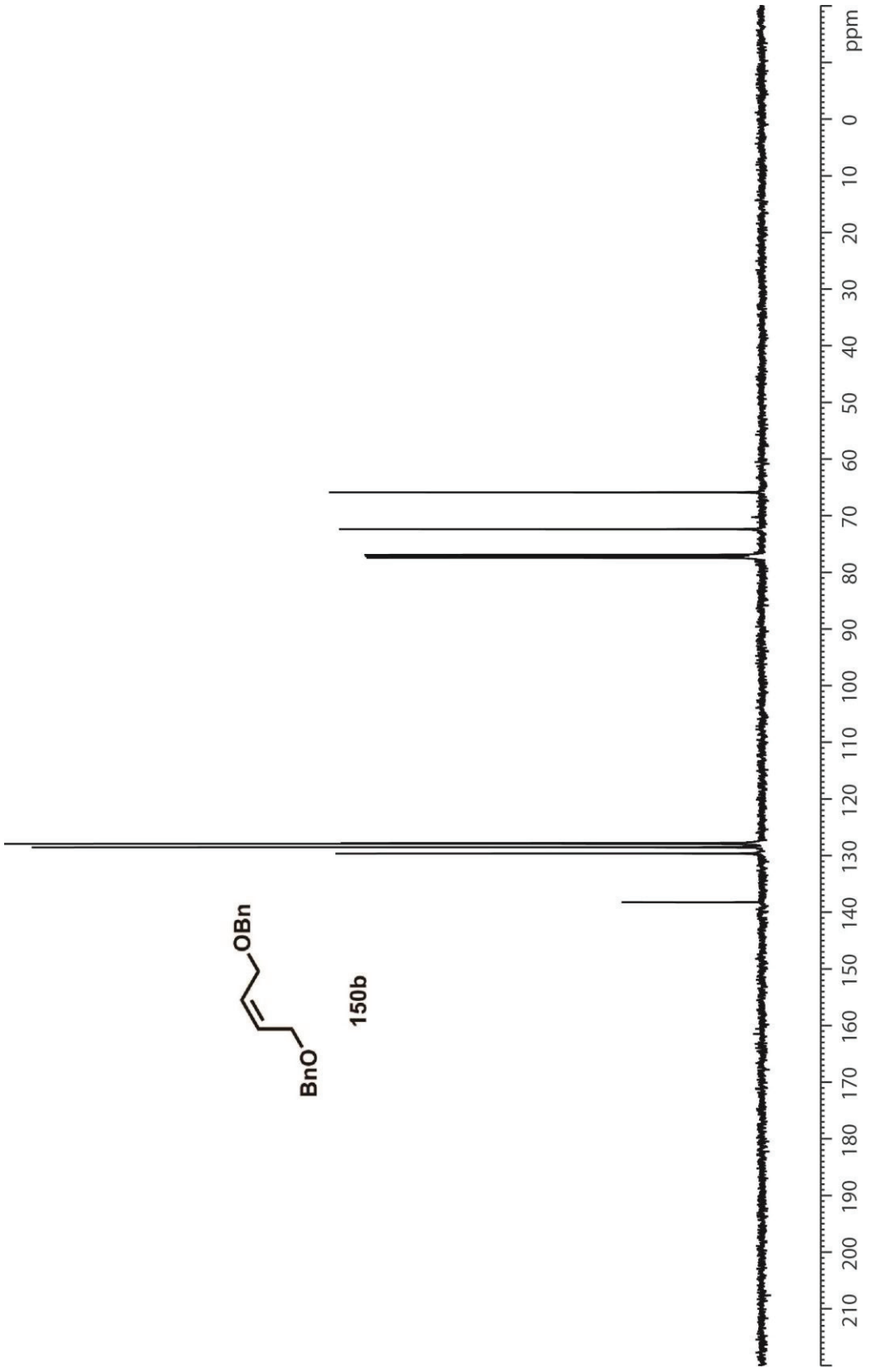
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (*E*)-1,4-bis(benzyloxy)but-2-ene (150a)**



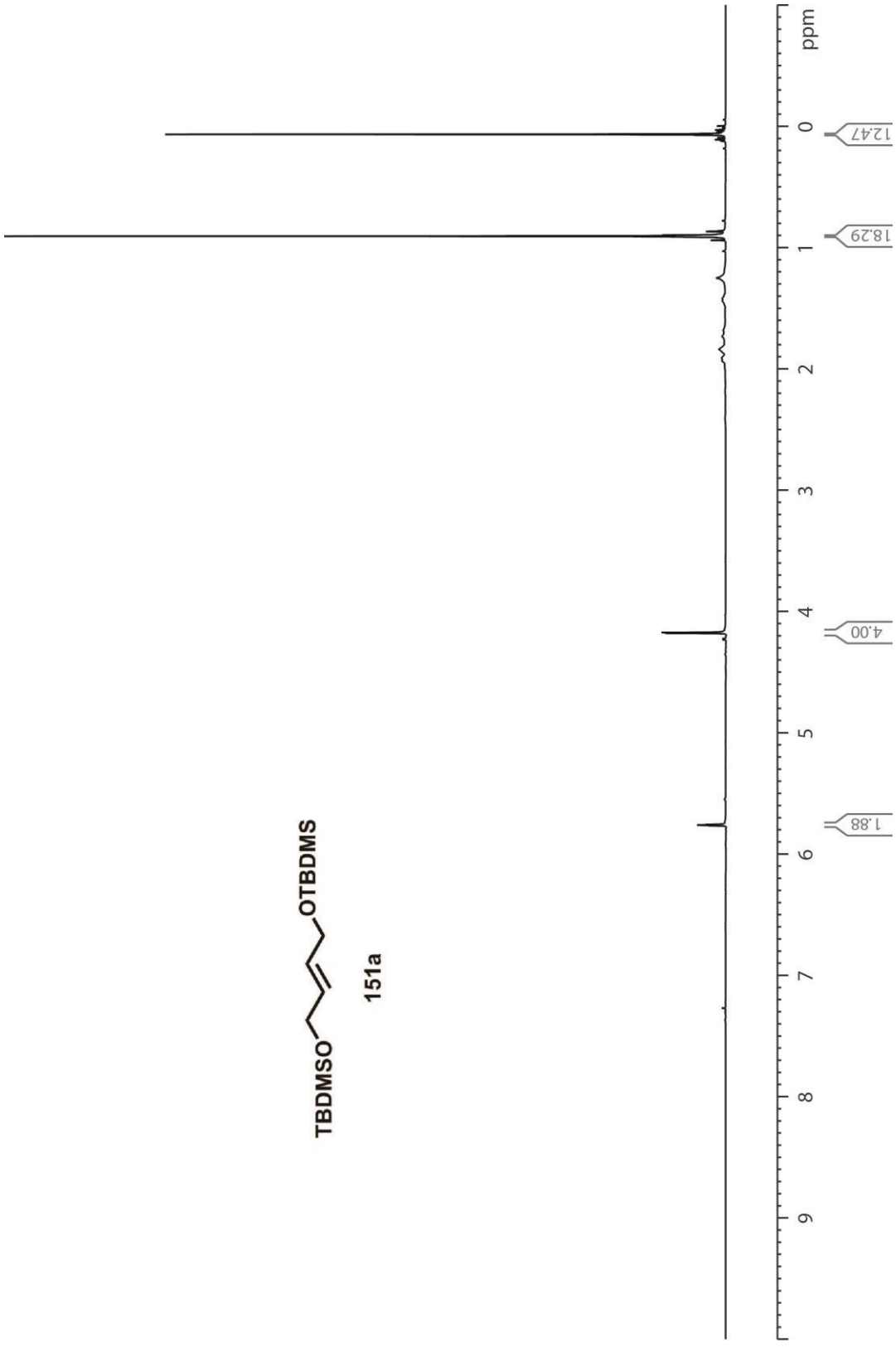
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (*Z*)-1,4-bis(benzyloxy)but-2-ene (150b)**



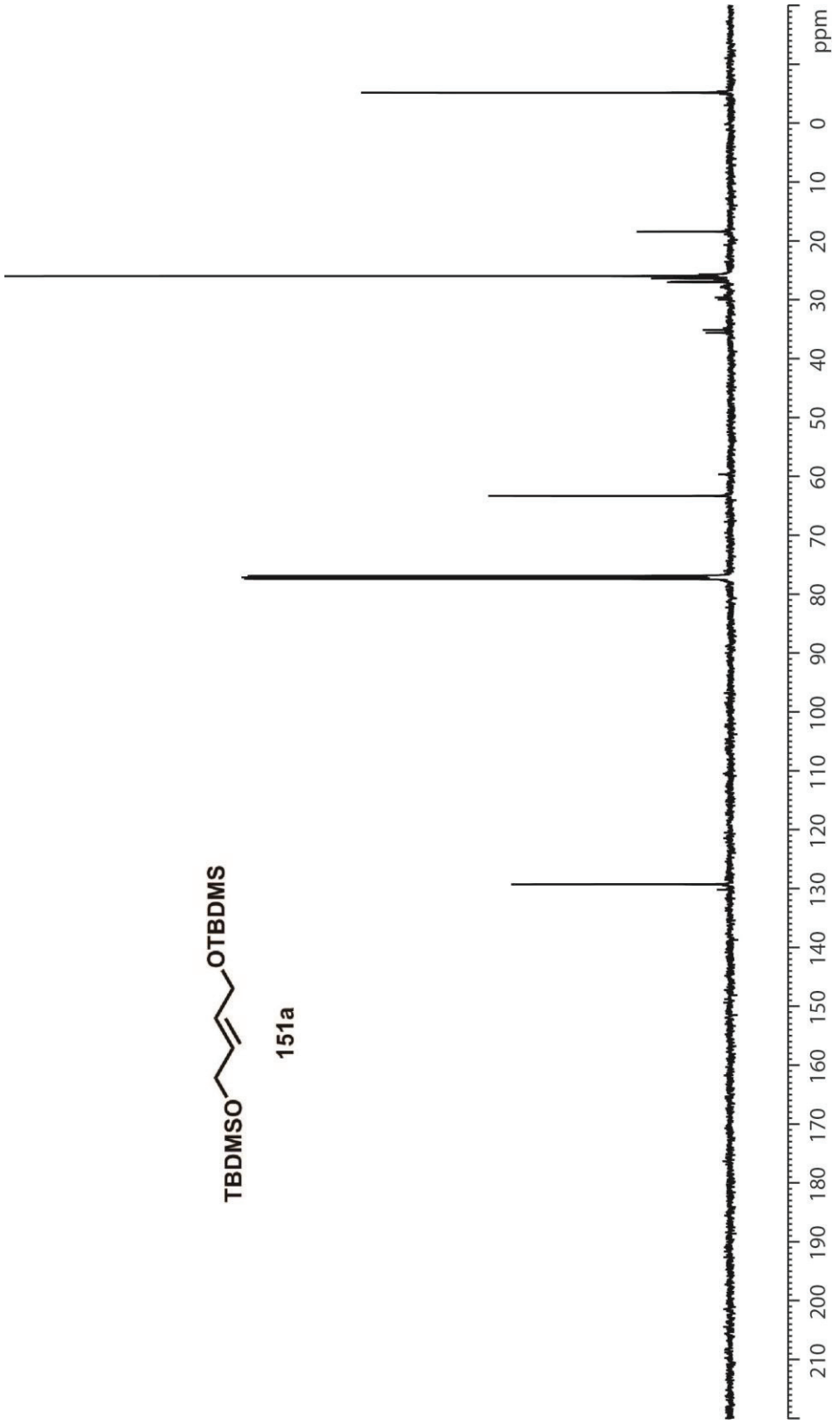
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (*Z*)-1,4-bis(benzyloxy)but-2-ene (150b)**



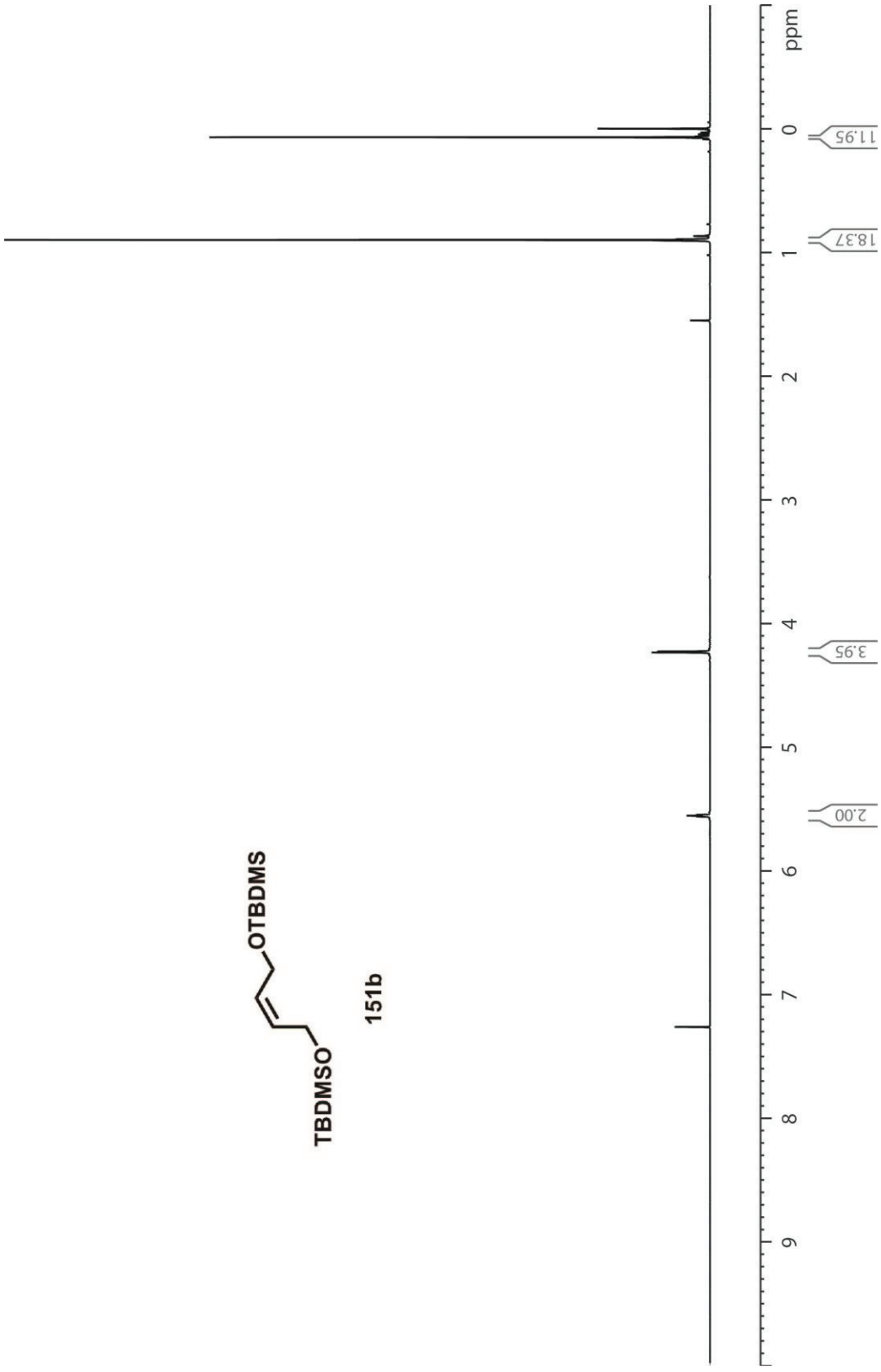
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (*E*)-2,2,3,3,10,10,11,11-octamethyl-4,9-dioxa-3,10-disiladodec-6-ene (151a)**



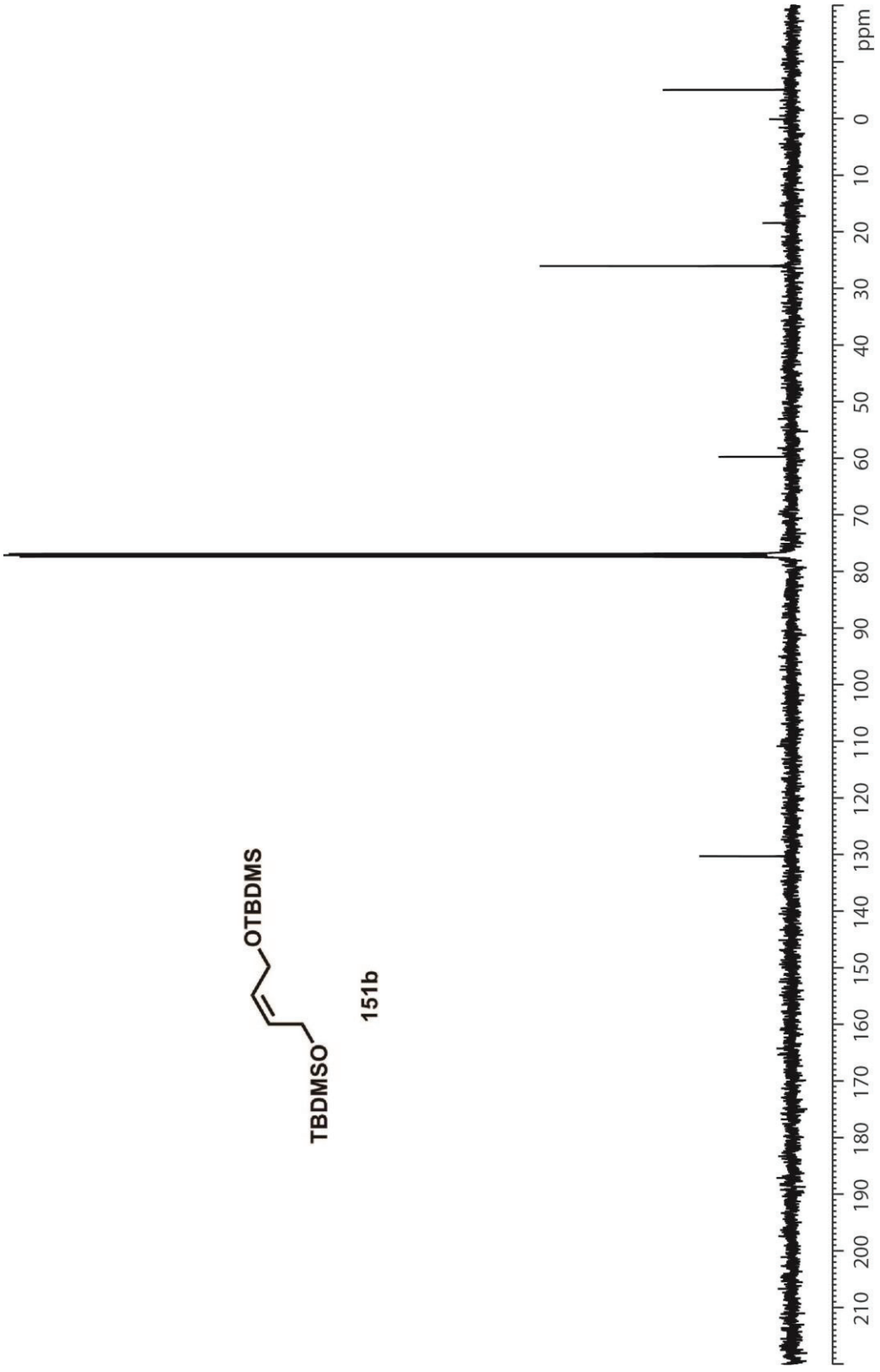
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (*E*)-2,2,3,3,10,10,11,11-octamethyl-4,9-dioxa-3,10-disiladodec-6-ene (151a)**



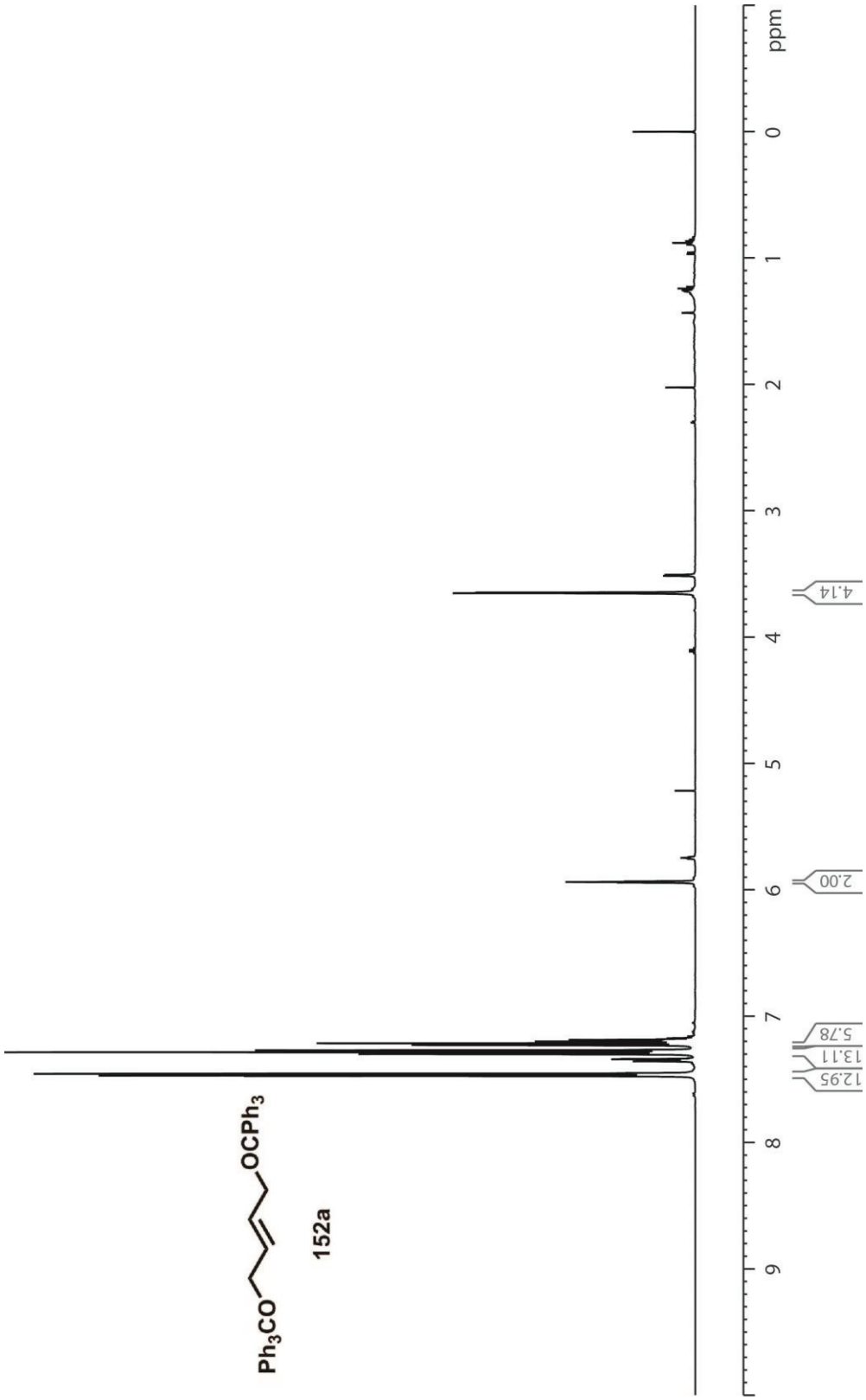
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (*Z*)-2,2,3,3,10,10,11,11-octamethyl-4,9-dioxa-3,10-disiladodec-6-ene (151b)**



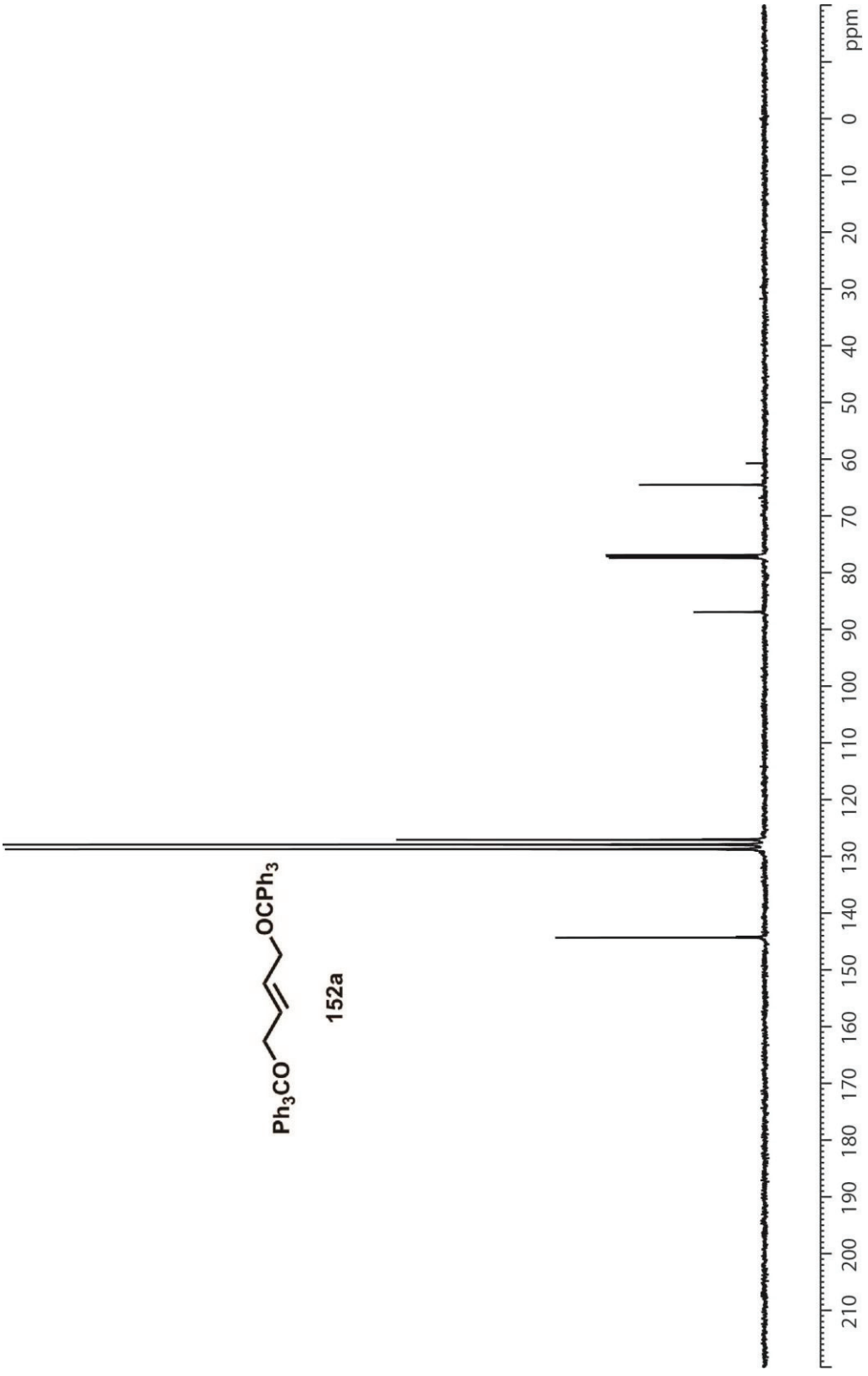
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (*Z*)-2,2,3,3,10,10,11,11-octamethyl-4,9-dioxa-3,10-disiladodec-6-ene (151b)**



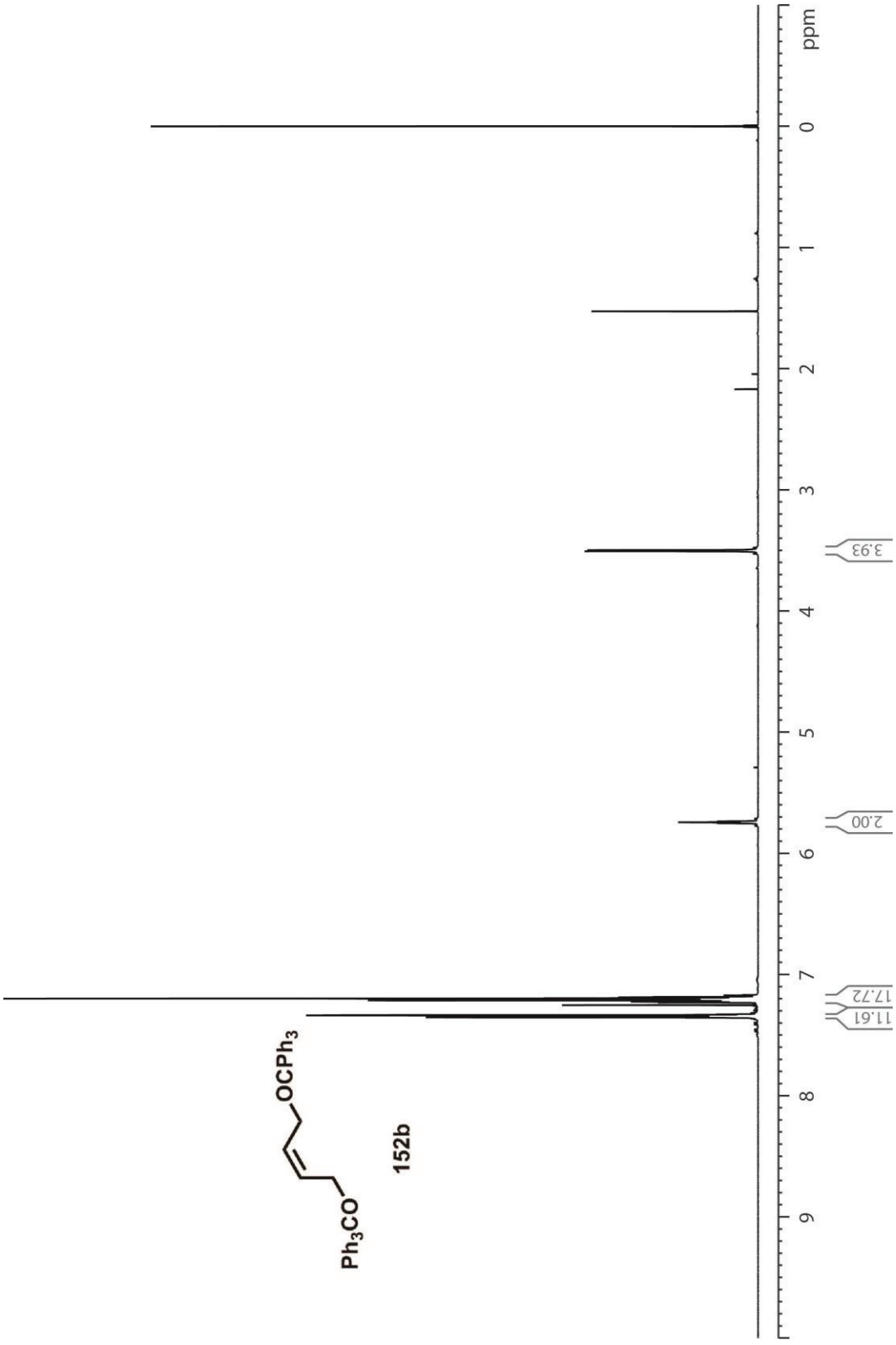
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (*E*)-1,4-bis(triphenylmethoxy)but-2-ene (152a)**



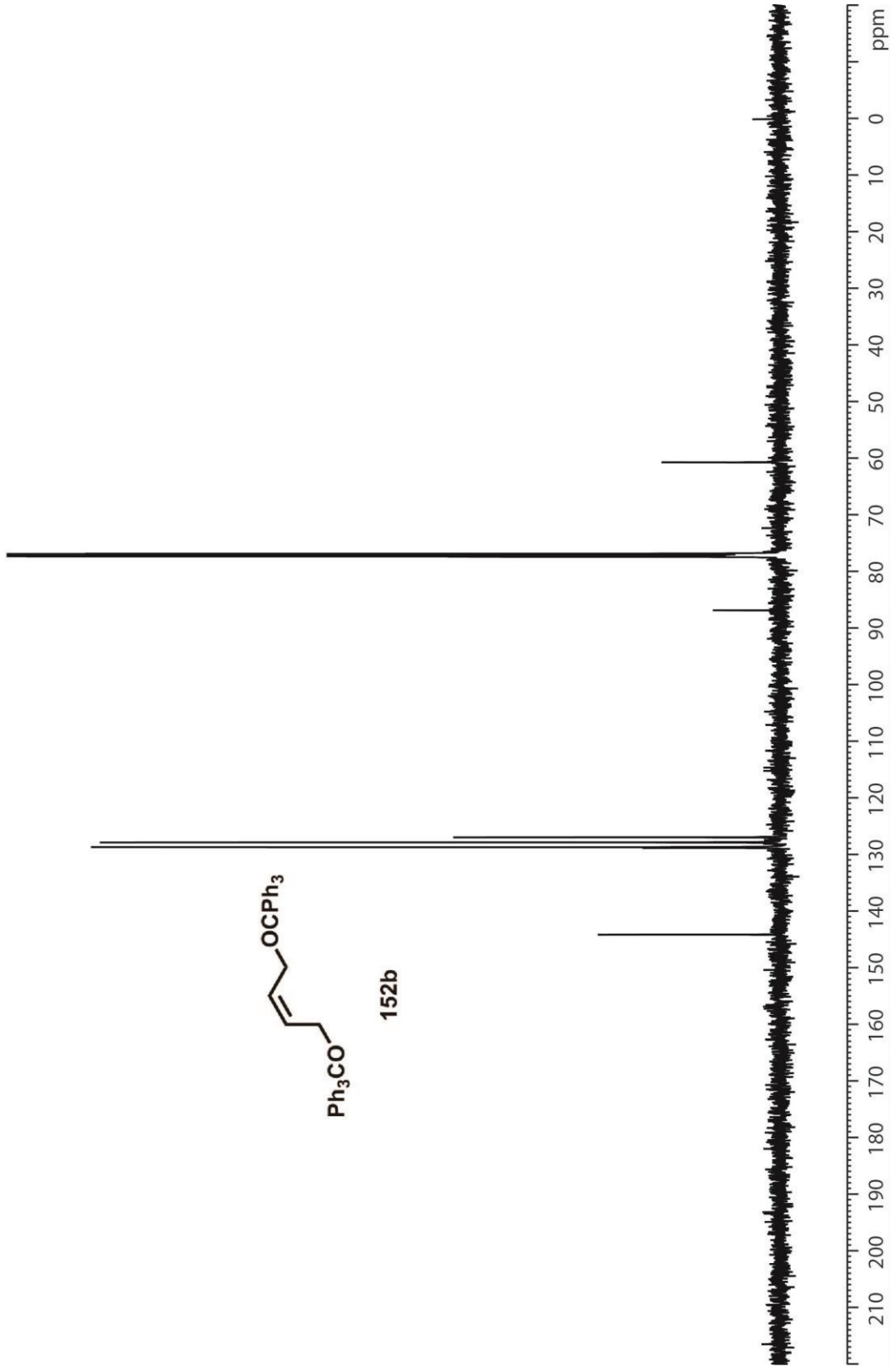
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (*E*)-1,4-bis(triphenylmethoxy)but-2-ene (152a)**



**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (*Z*)-1,4-bis(triphenylmethoxy)but-2-ene (152b)**



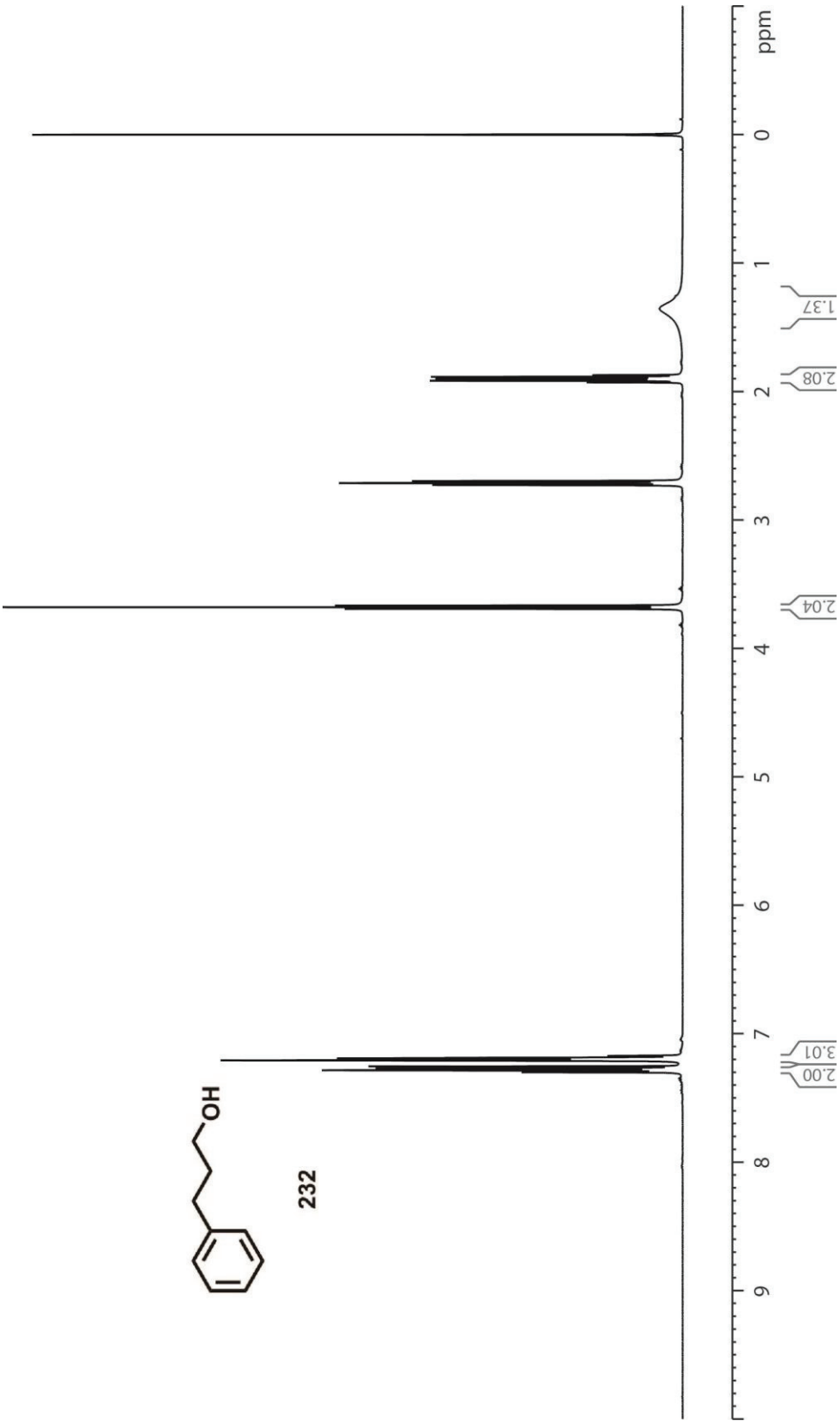
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (*Z*)-1,4-bis(triphenylmethoxy)but-2-ene (152b)**



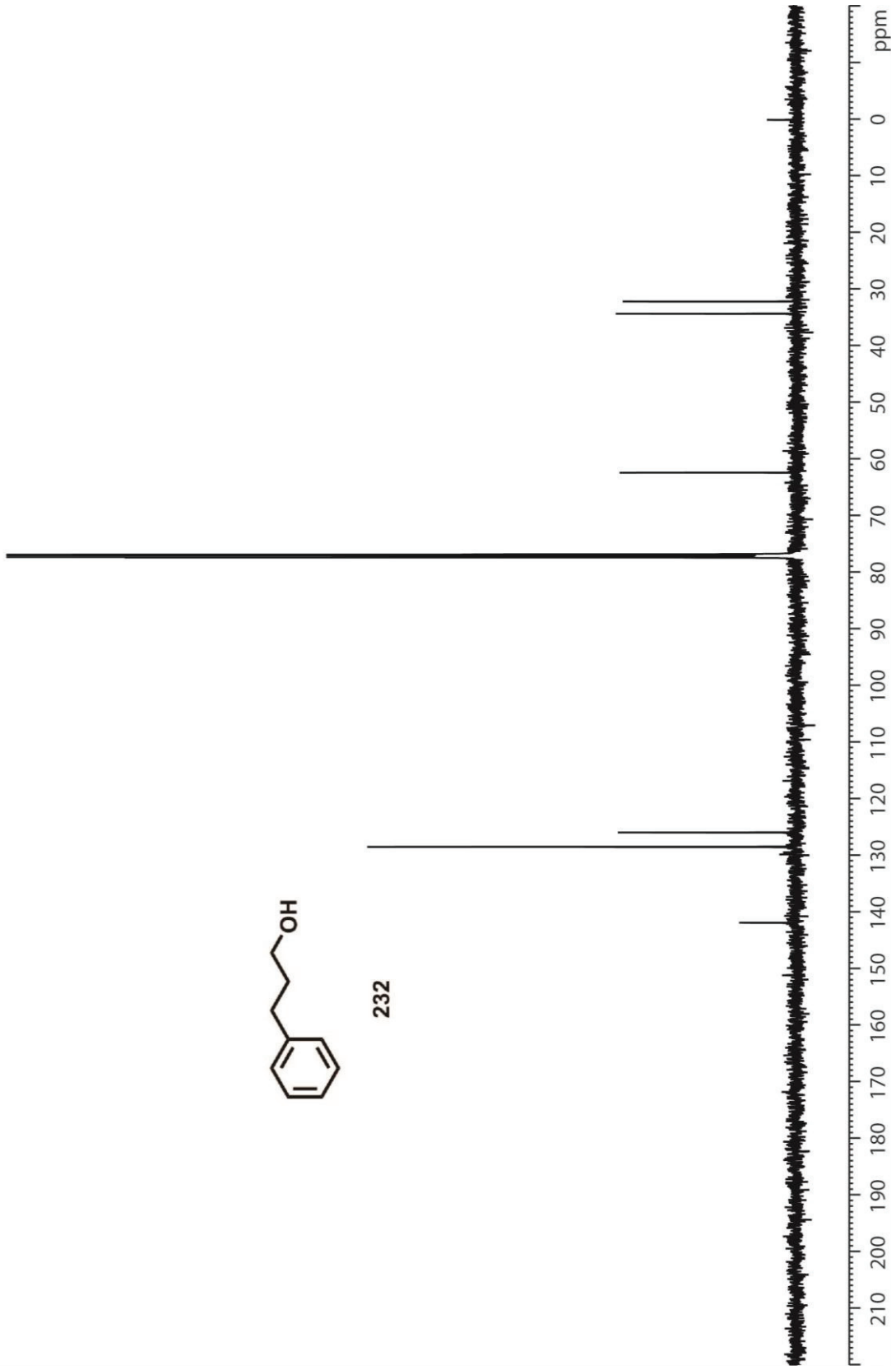
## APPENDIX III: $^{1}$H AND $^{13}$C NMR SPECTRA FOR CHAPTER 4

$^{1}$H NMR and $^{13}$C NMR spectra for compounds **232**, **235**, **236**, **239**, **229**, **241**, **242**, **243**, **244**, **246**, **247**, **248**, **253**, **254**, **255**, **258**, **259**, **274**, **275**, **276**, **279**, **280**, **281**, **266**, **283**, **285**, **290** + **291**, **293**, **295**, **297** + **298** + **299**, **297** + **299**, and **301** + **302**.

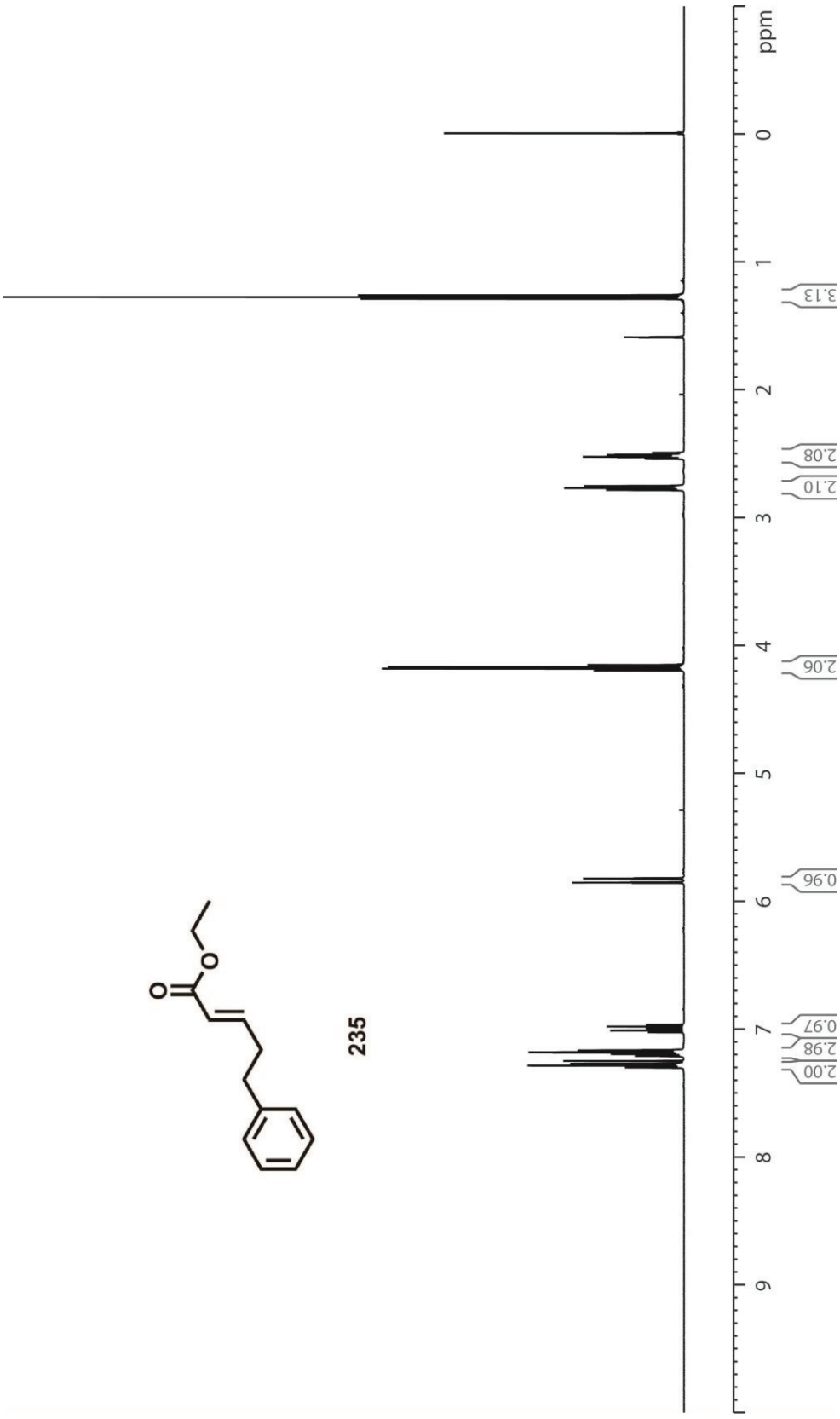
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of 3-phenylpropan-1-ol (232)**



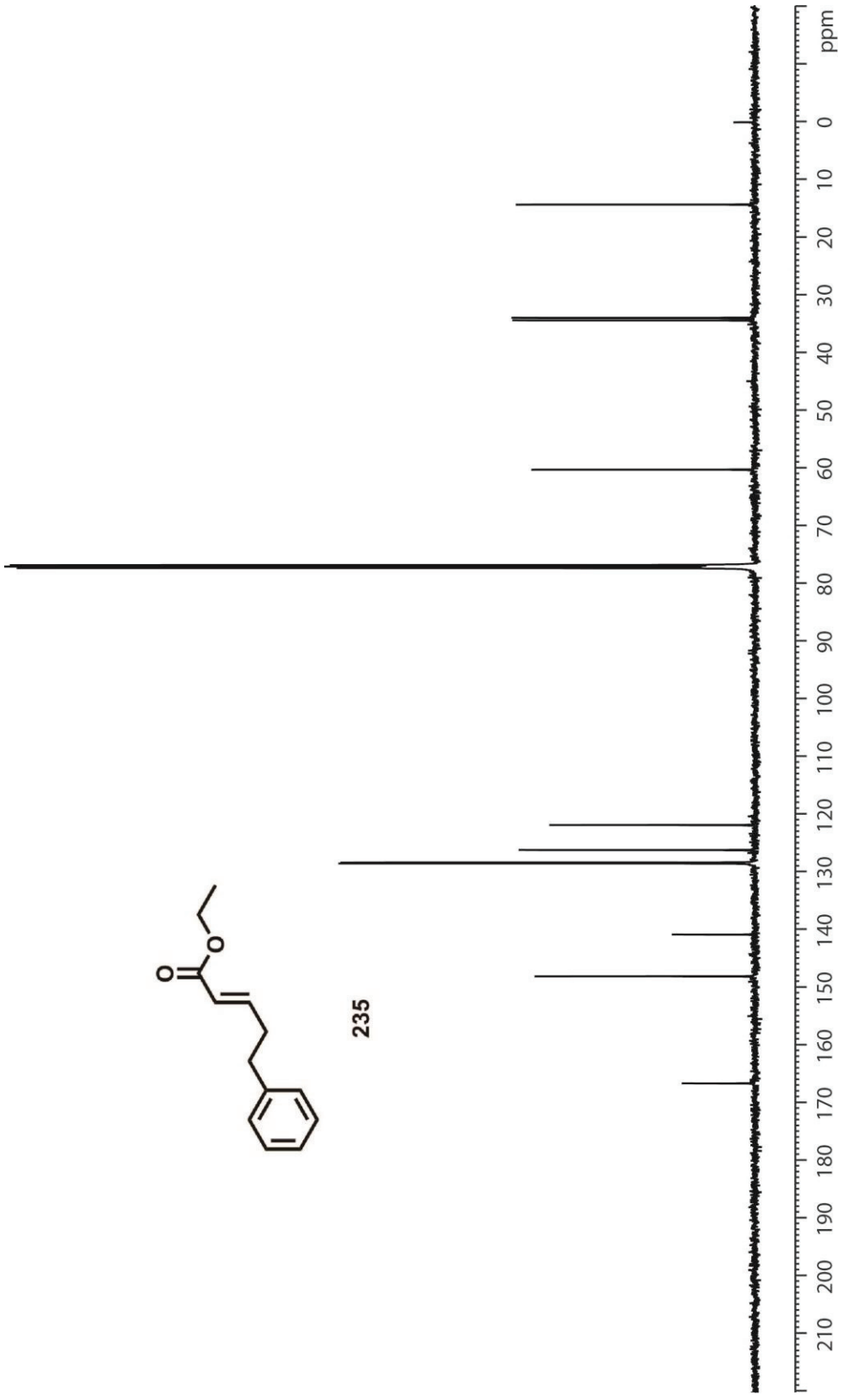
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of 3-phenylpropan-1-ol (232)**



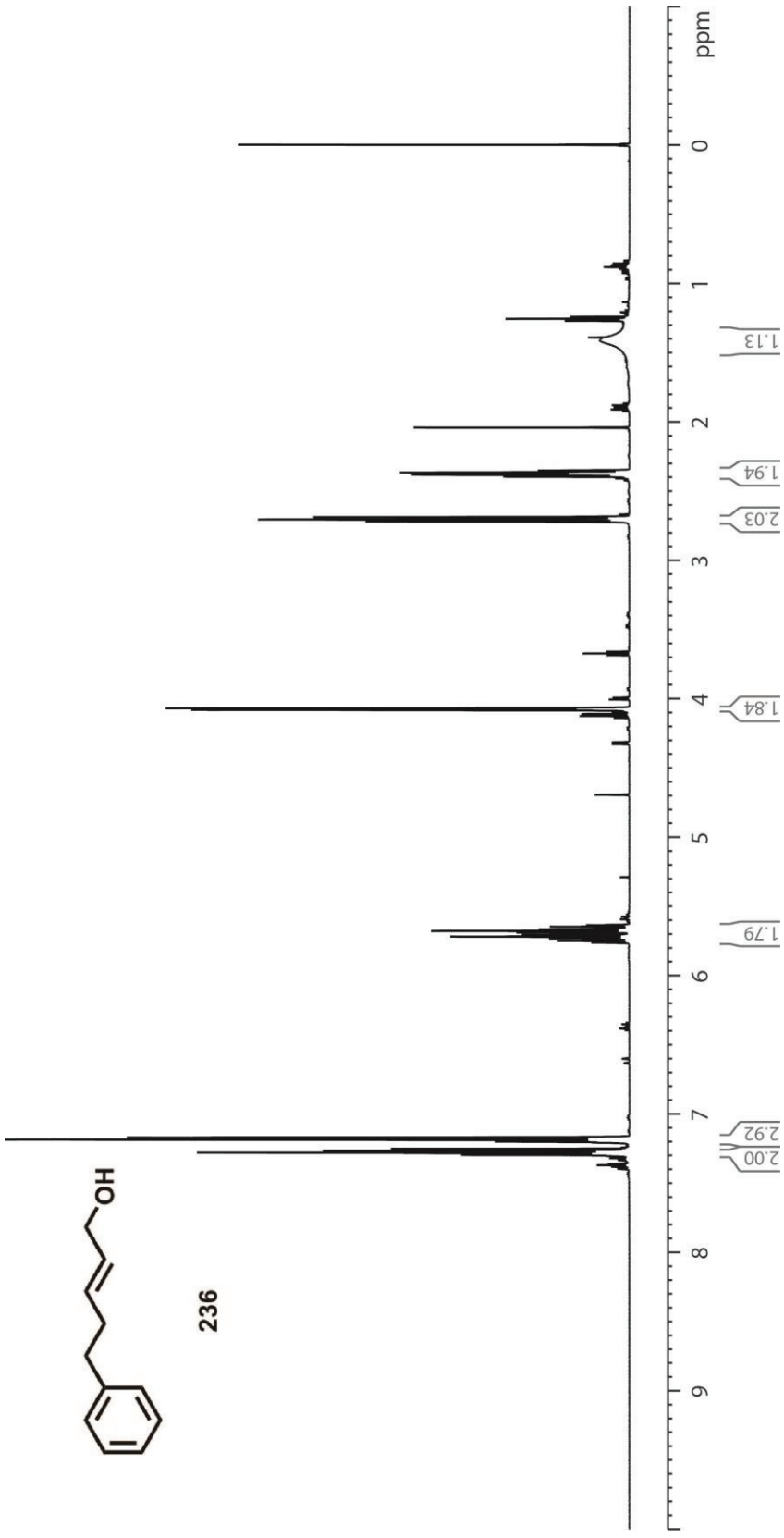
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of ethyl (*E*)-5-phenylpent-2-enoate (235)**



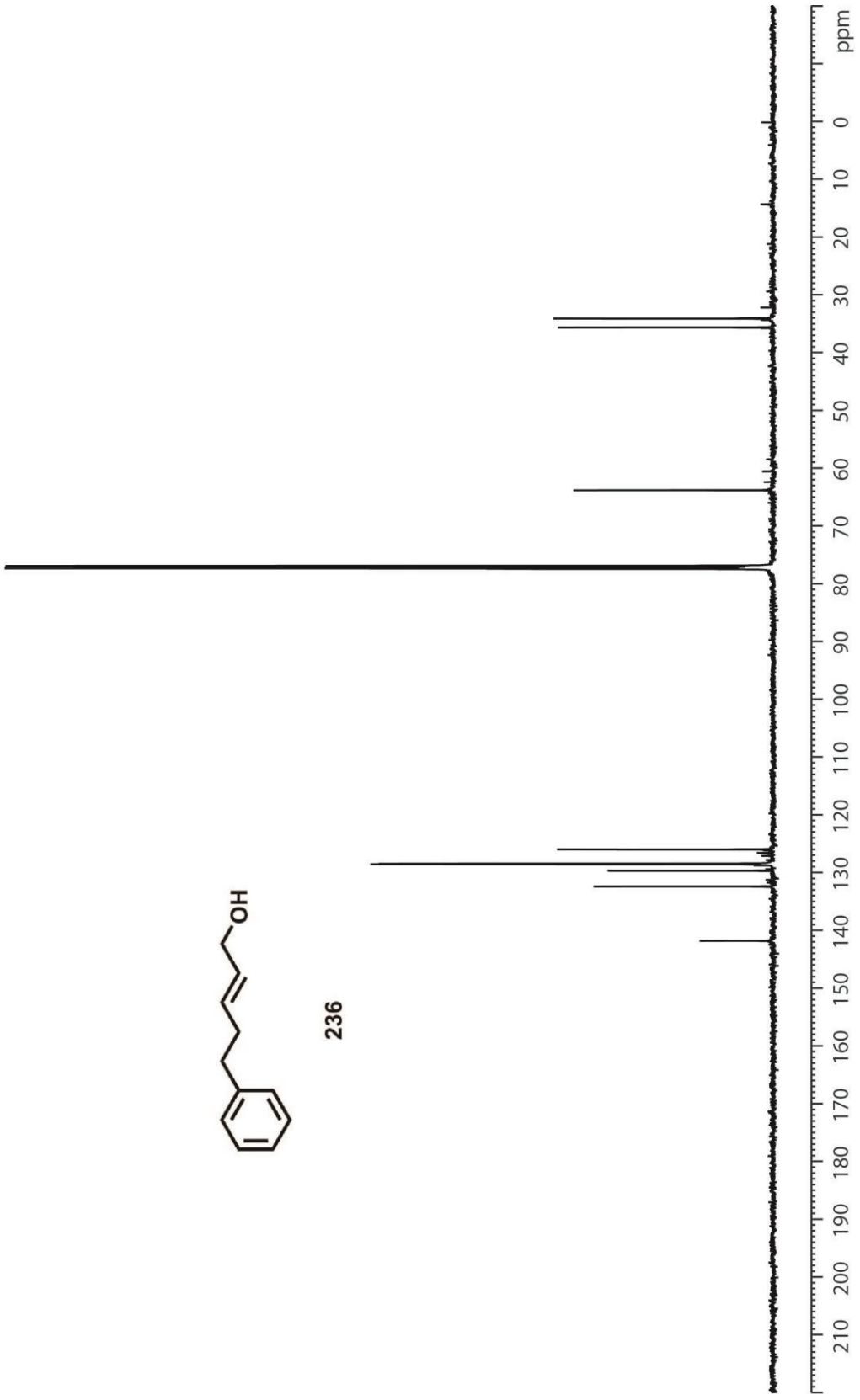
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of ethyl (*E*)-5-phenylpent-2-enoate (235)**



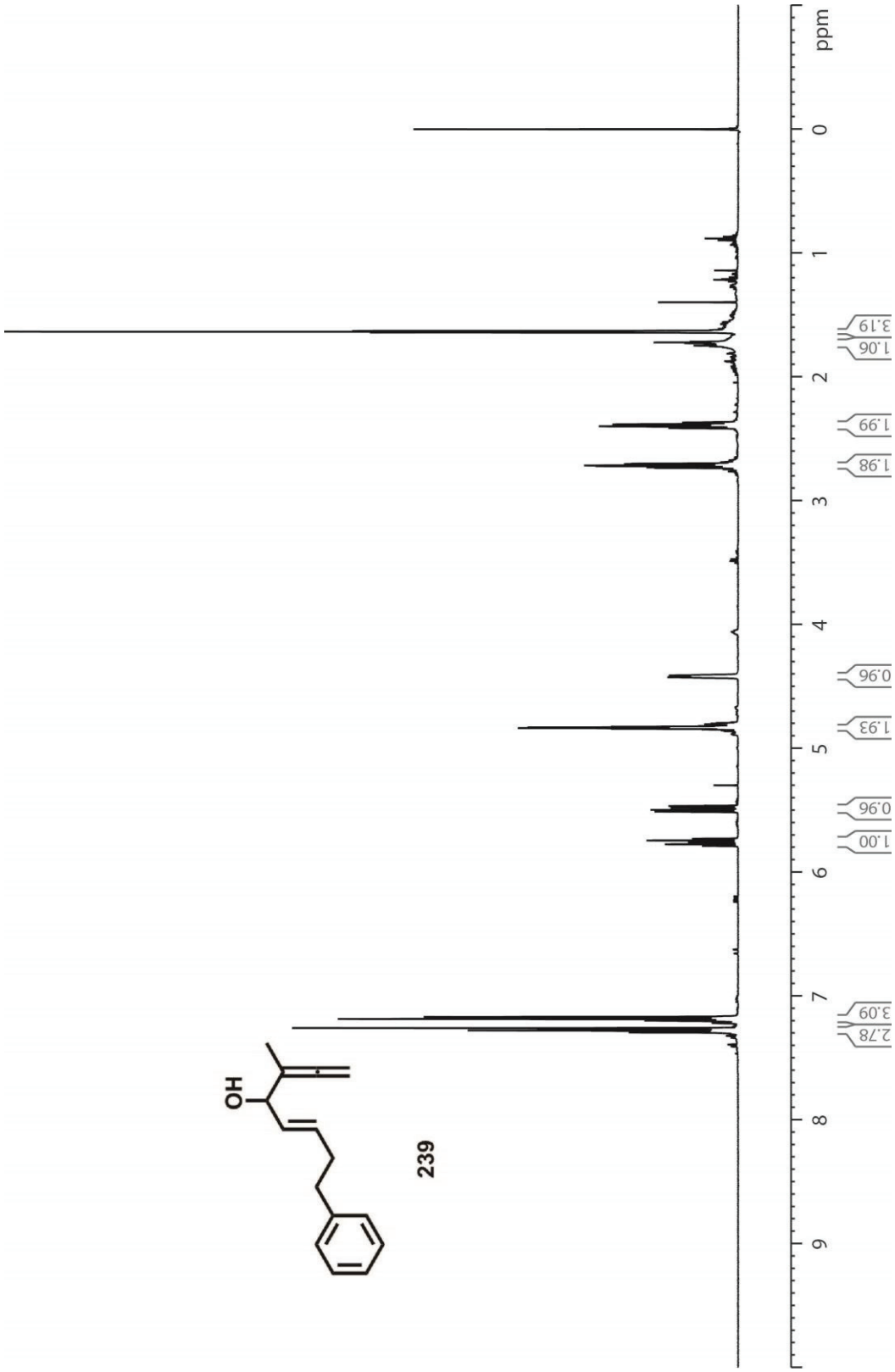
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (*E*)-5-phenylpent-2-en-1-ol (236)**



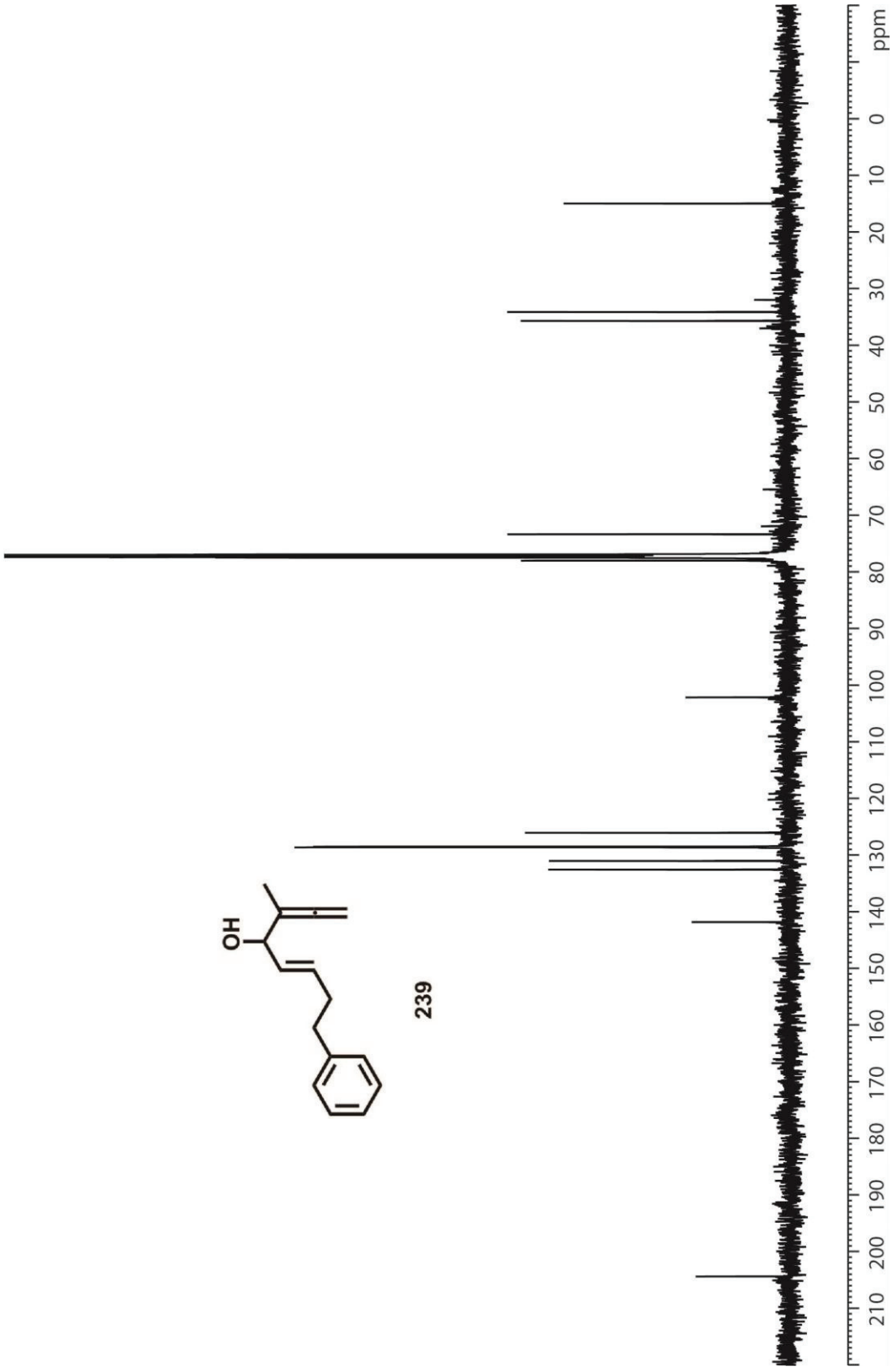
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (*E*)-5-phenylpent-2-en-1-ol (236)**



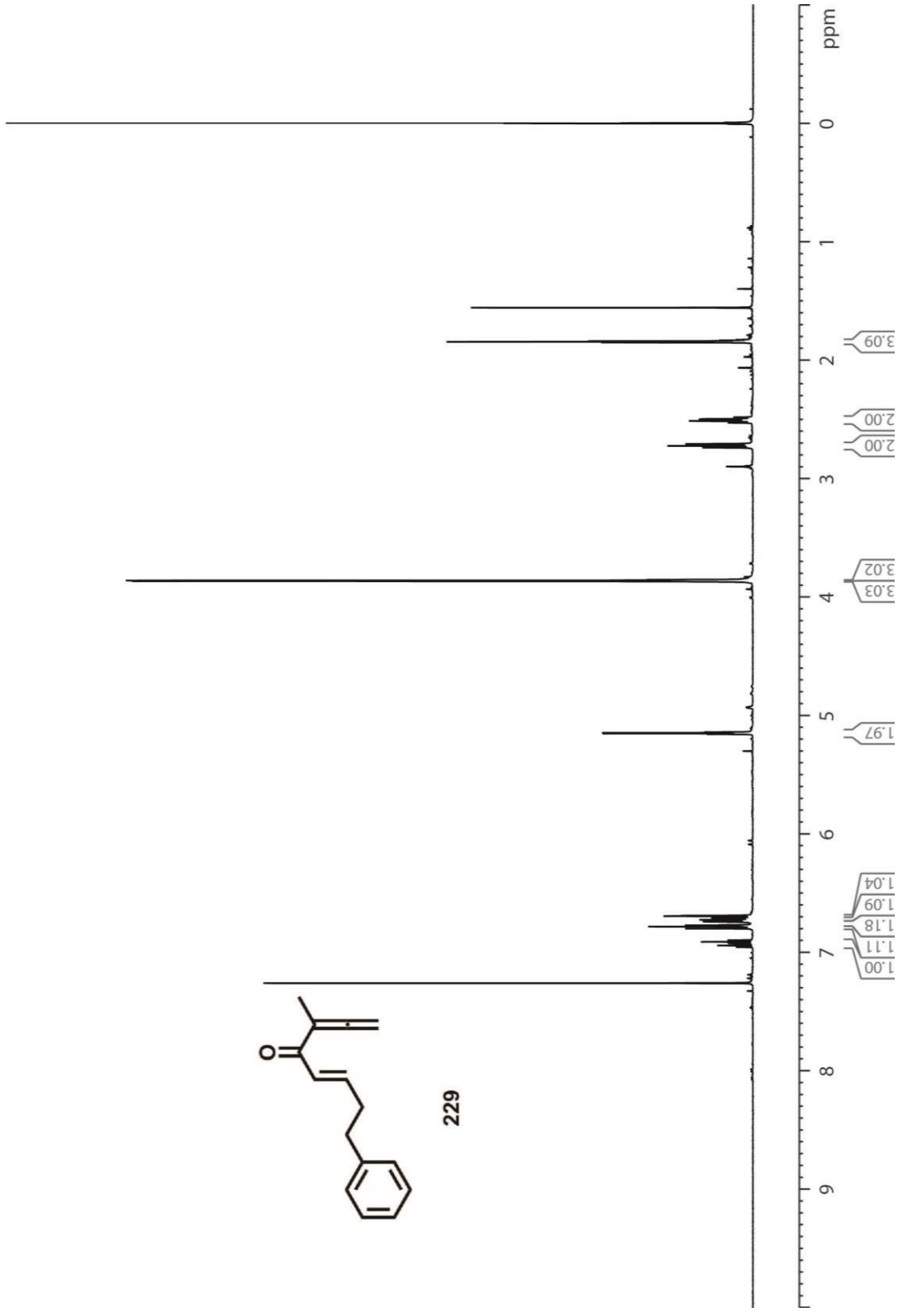
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (*E*)-3-methyl-8-phenylocta-1,2,5-trien-4-ol (239)**



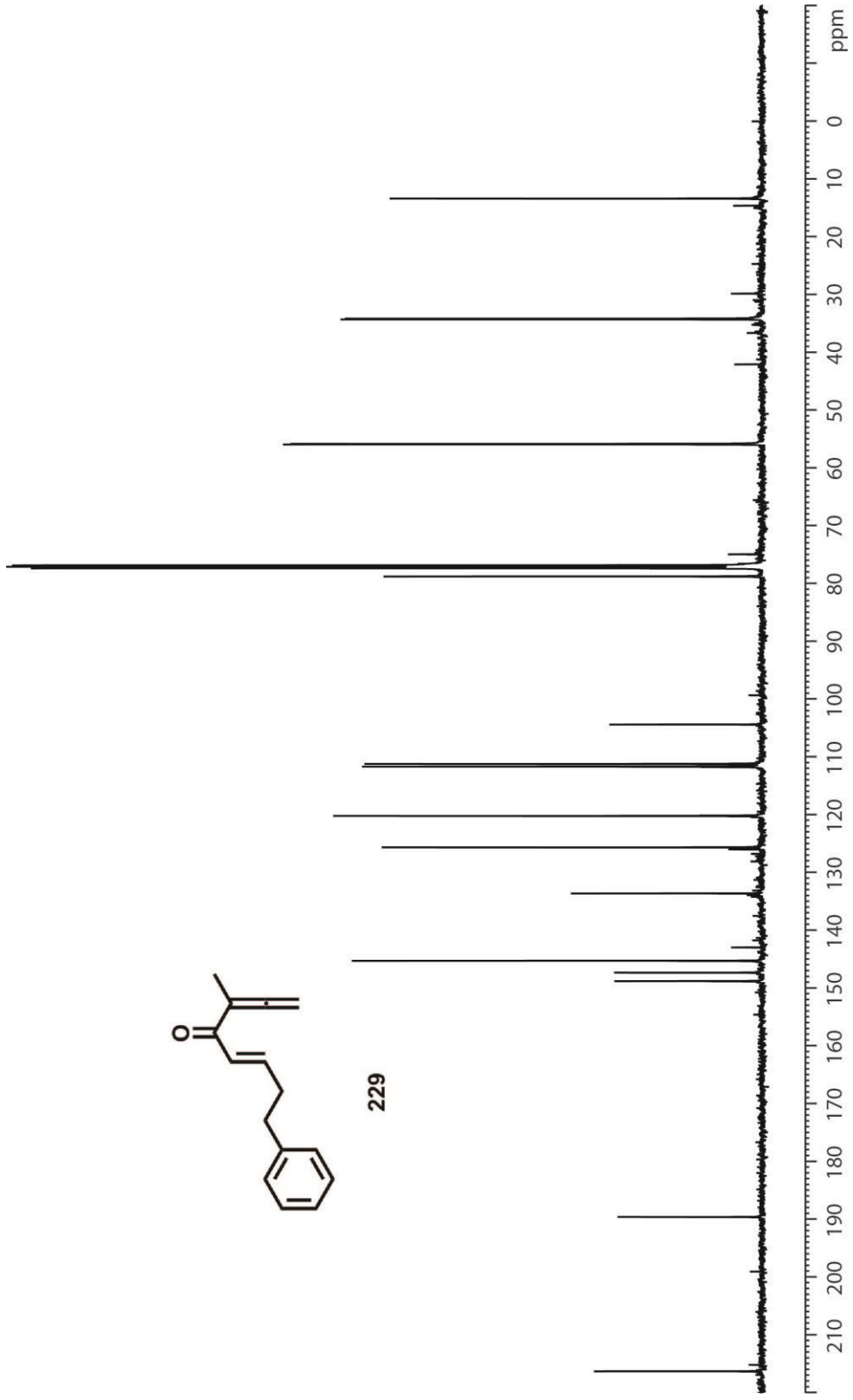
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (*E*)-3-methyl-8-phenylocta-1,2,5-trien-4-ol (239)**



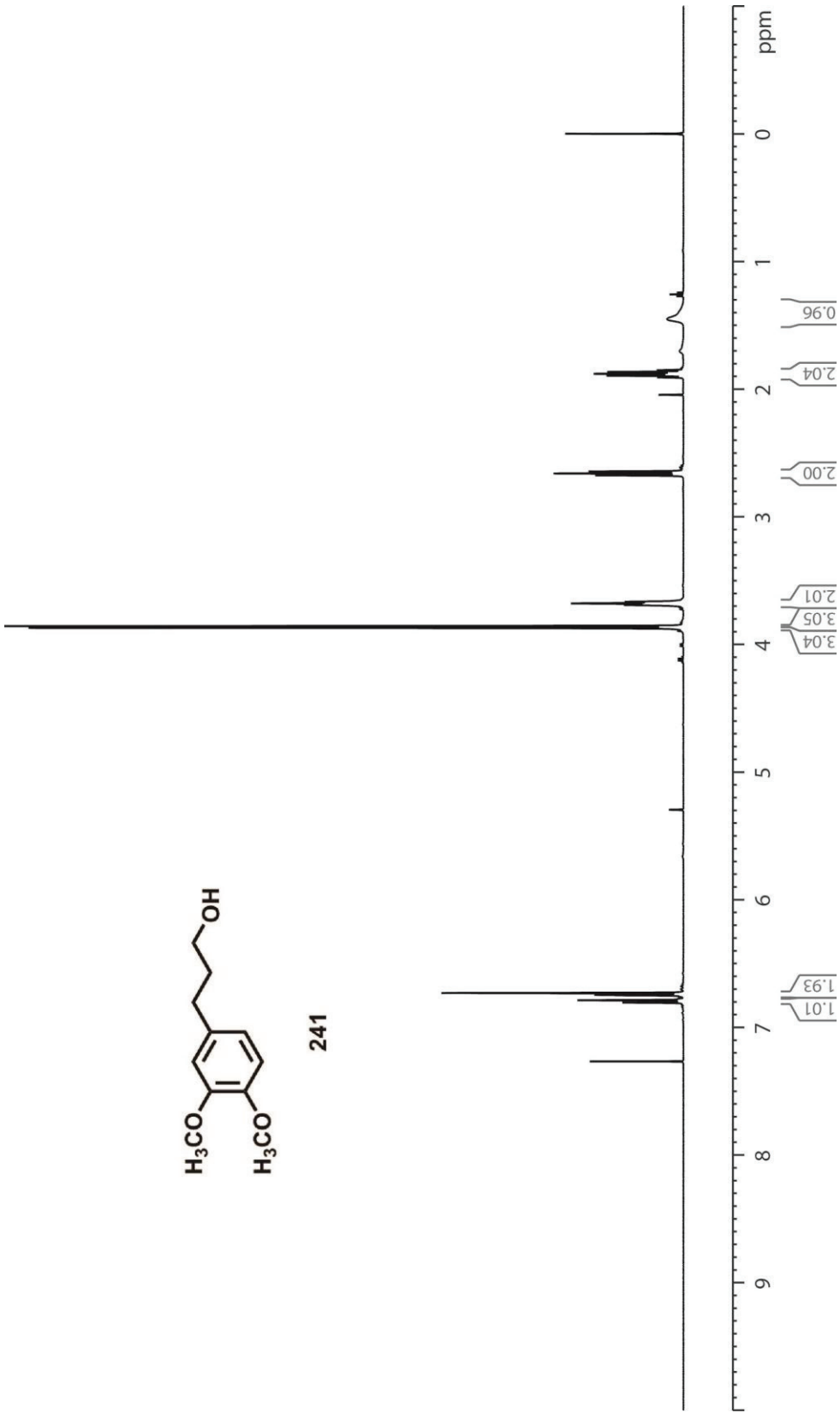
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (*E*)-3-methyl-8-phenylocta-1,2,5-trien-4-one (229)**



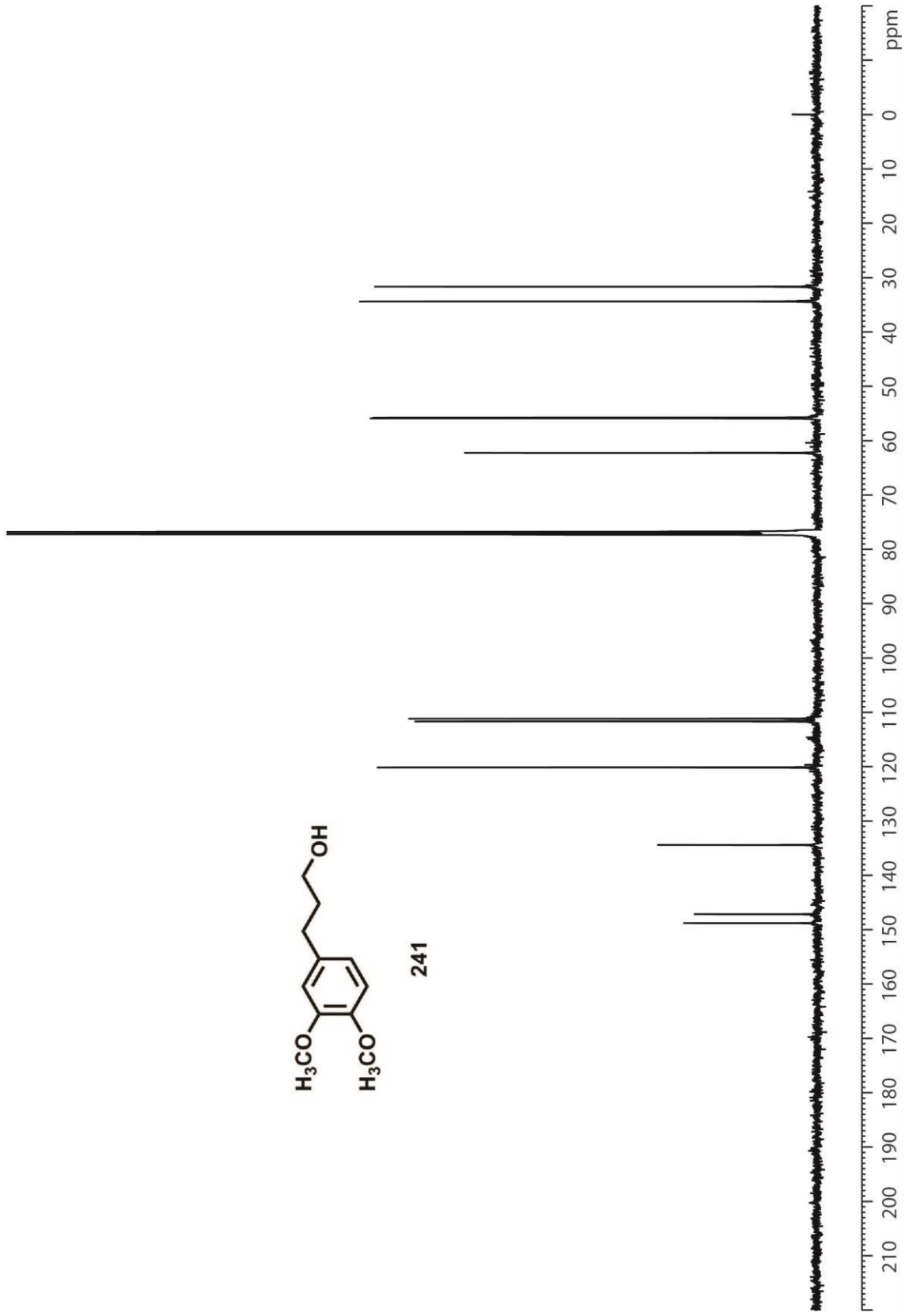
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (*E*)-3-methyl-8-phenylocta-1,2,5-trien-4-one (229)**



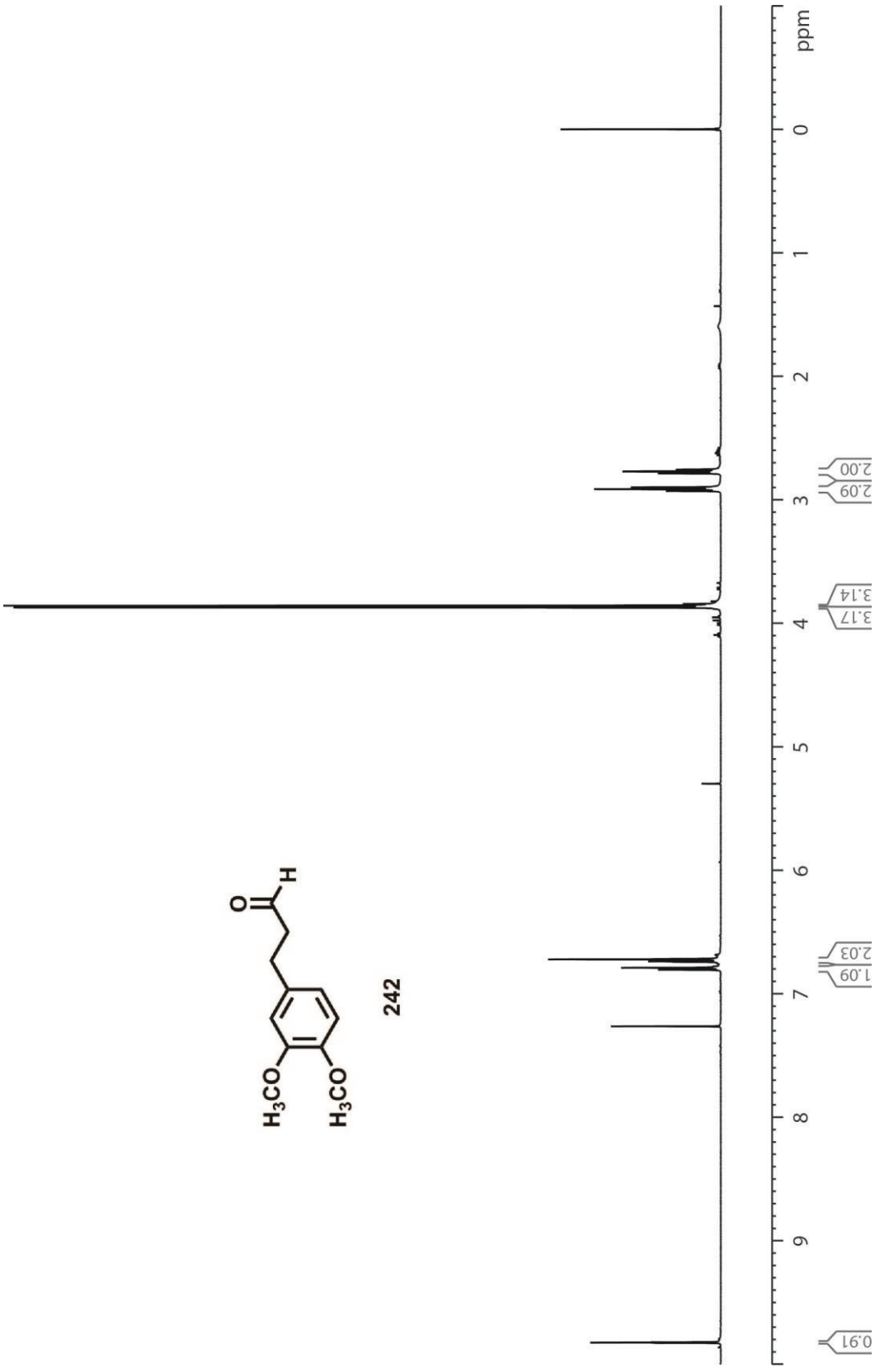
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of 3-(3,4-dimethoxyphenyl)propan-1-ol (241)**



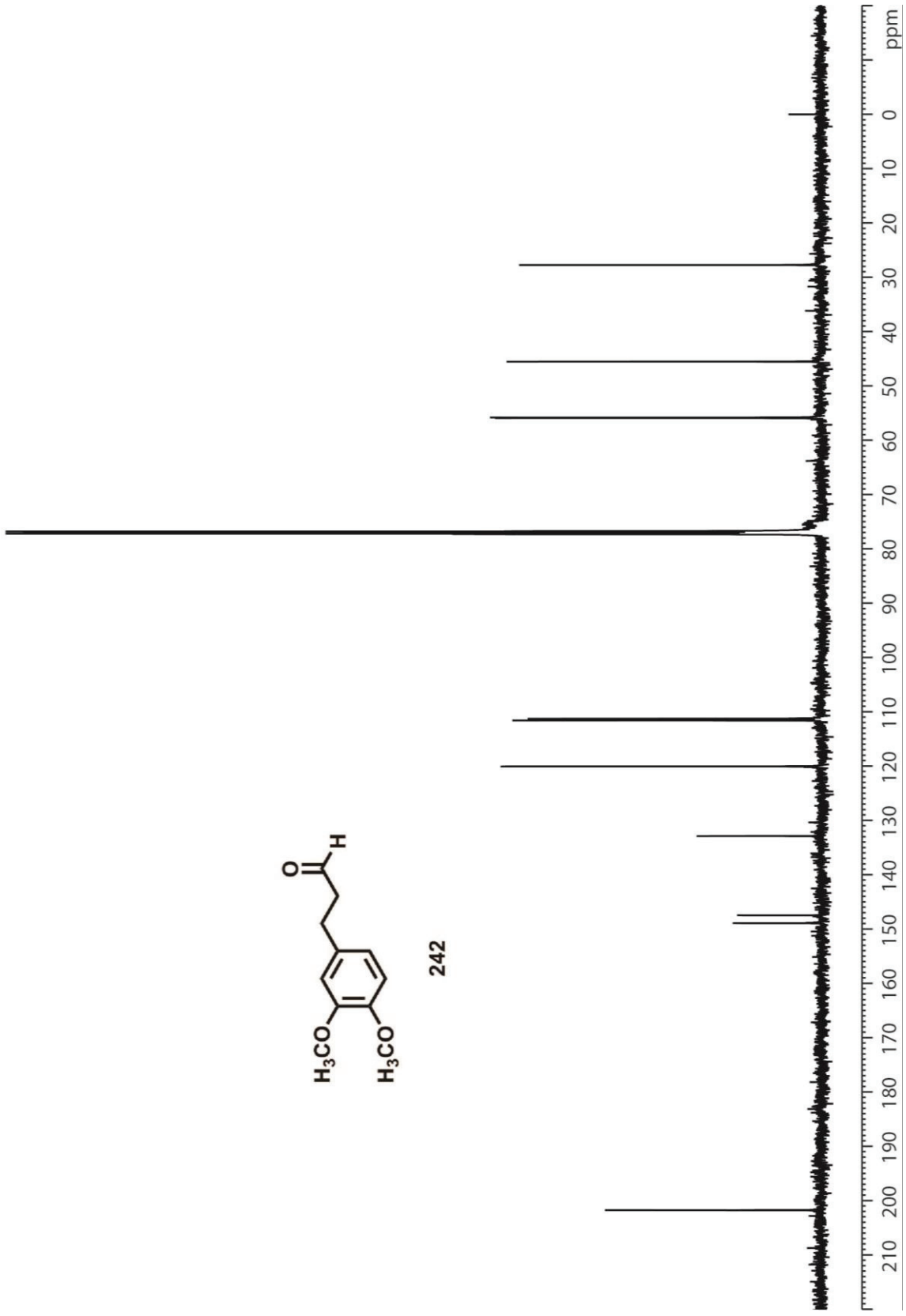
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of 3-(3,4-dimethoxyphenyl)propan-1-ol (241)**



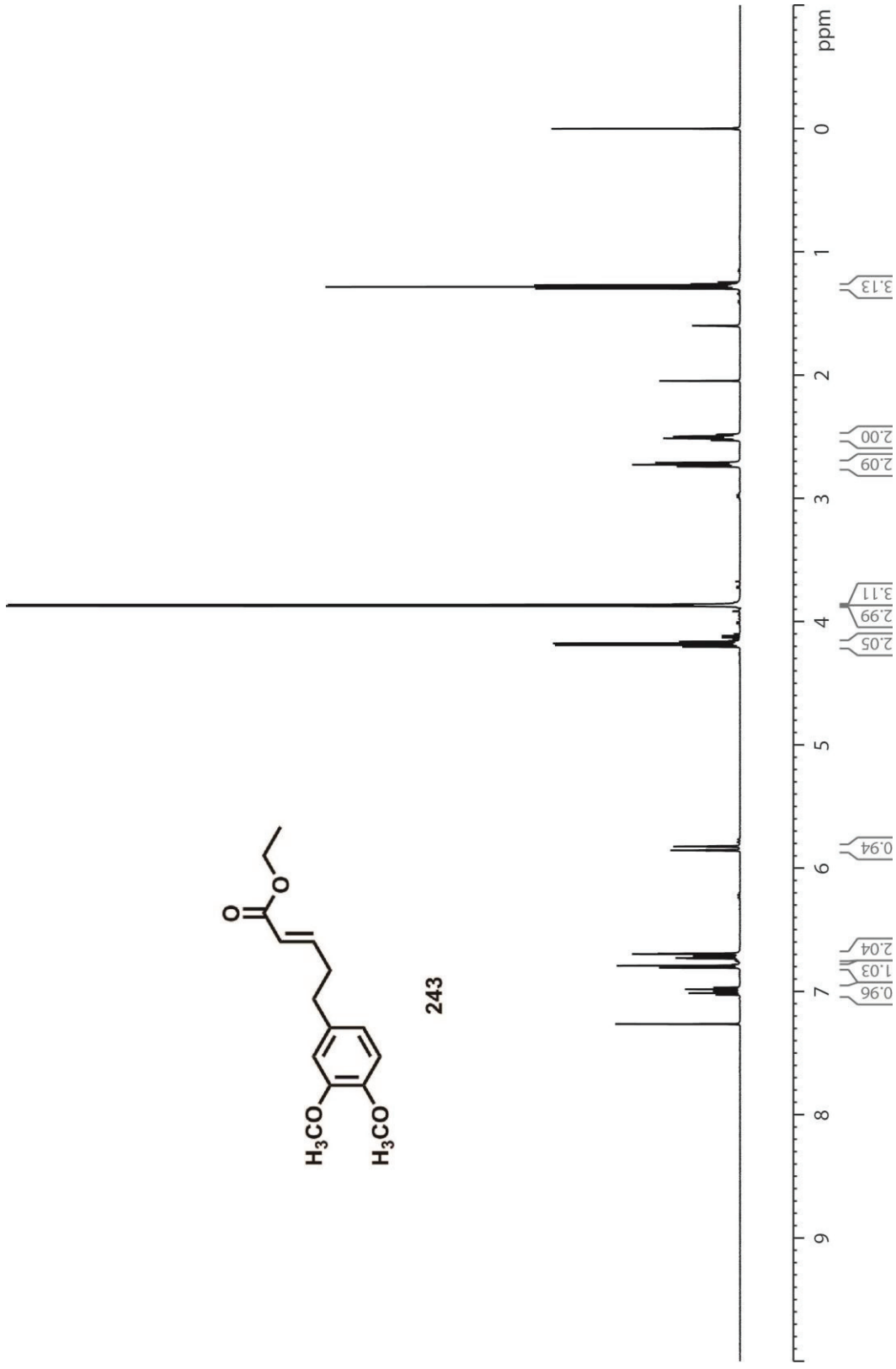
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of 3-(3,4-dimethoxyphenyl)propanal (242)**



**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of 3-(3,4-dimethoxyphenyl)propanal (242)**

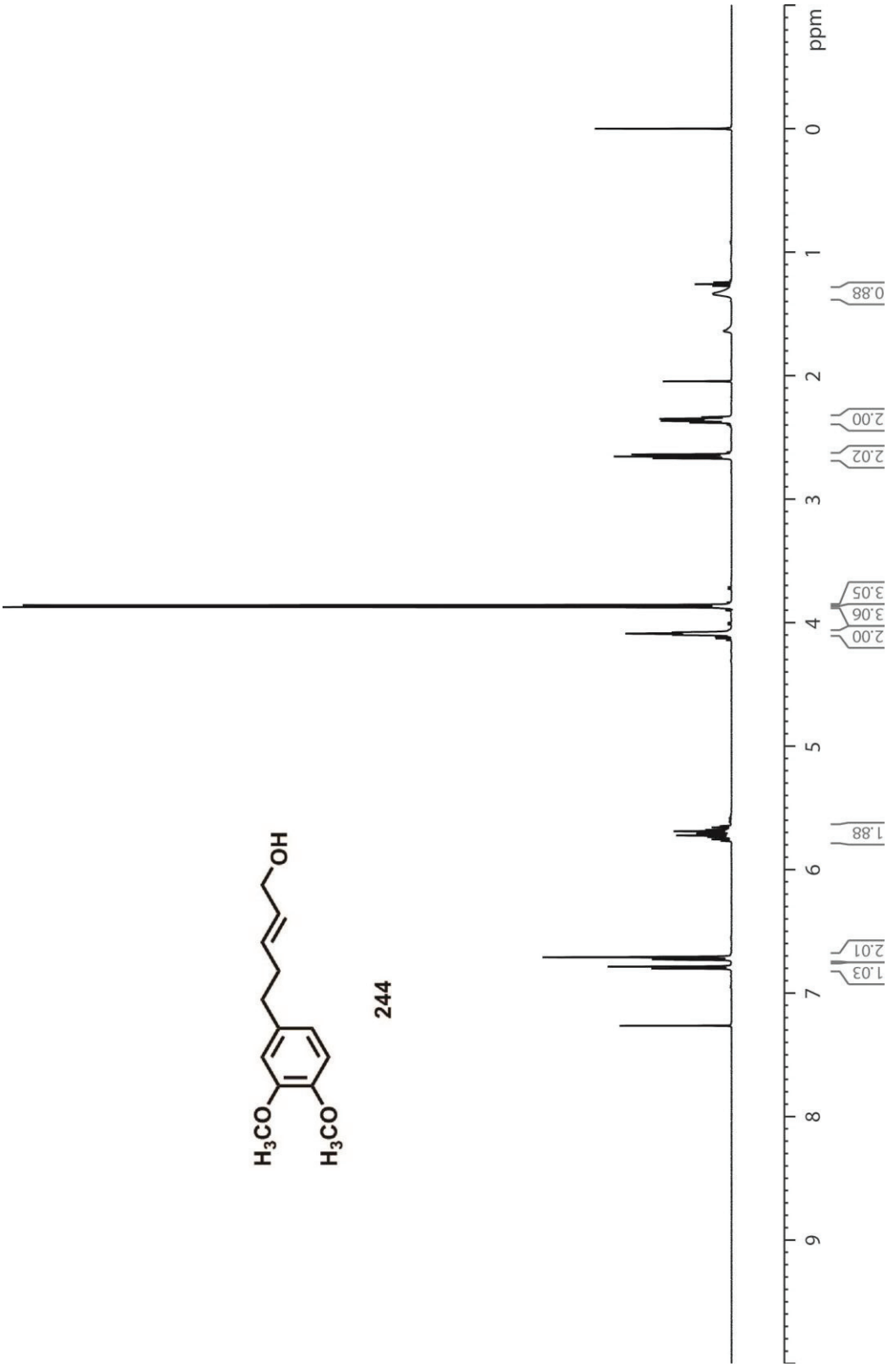


**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of ethyl (*E*)-5-(3,4-dimethoxyphenyl)pent-2-enoate (243)**

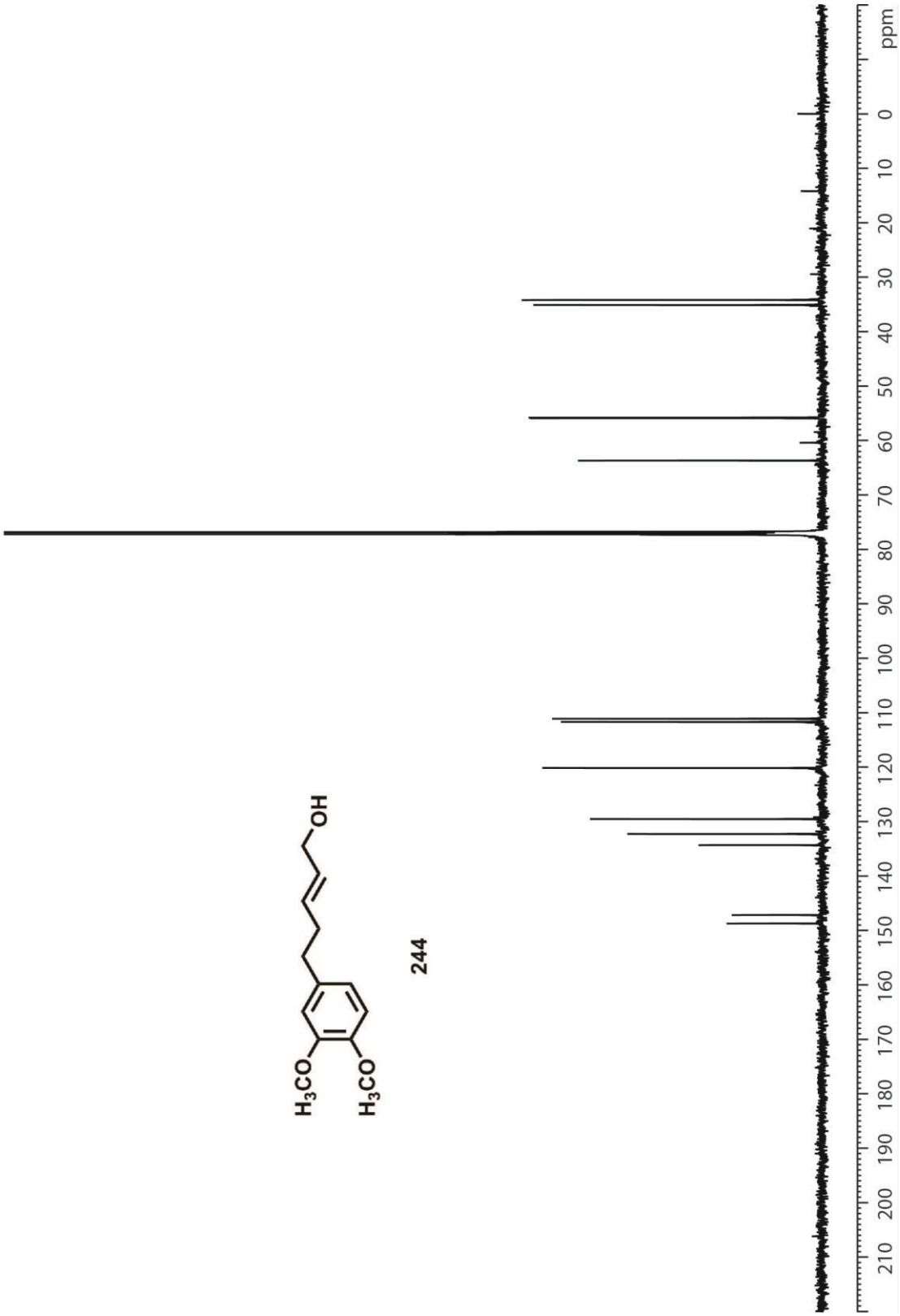


**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of ethyl (*E*)-5-(3,4-dimethoxyphenyl)pent-2-enoate (243)**

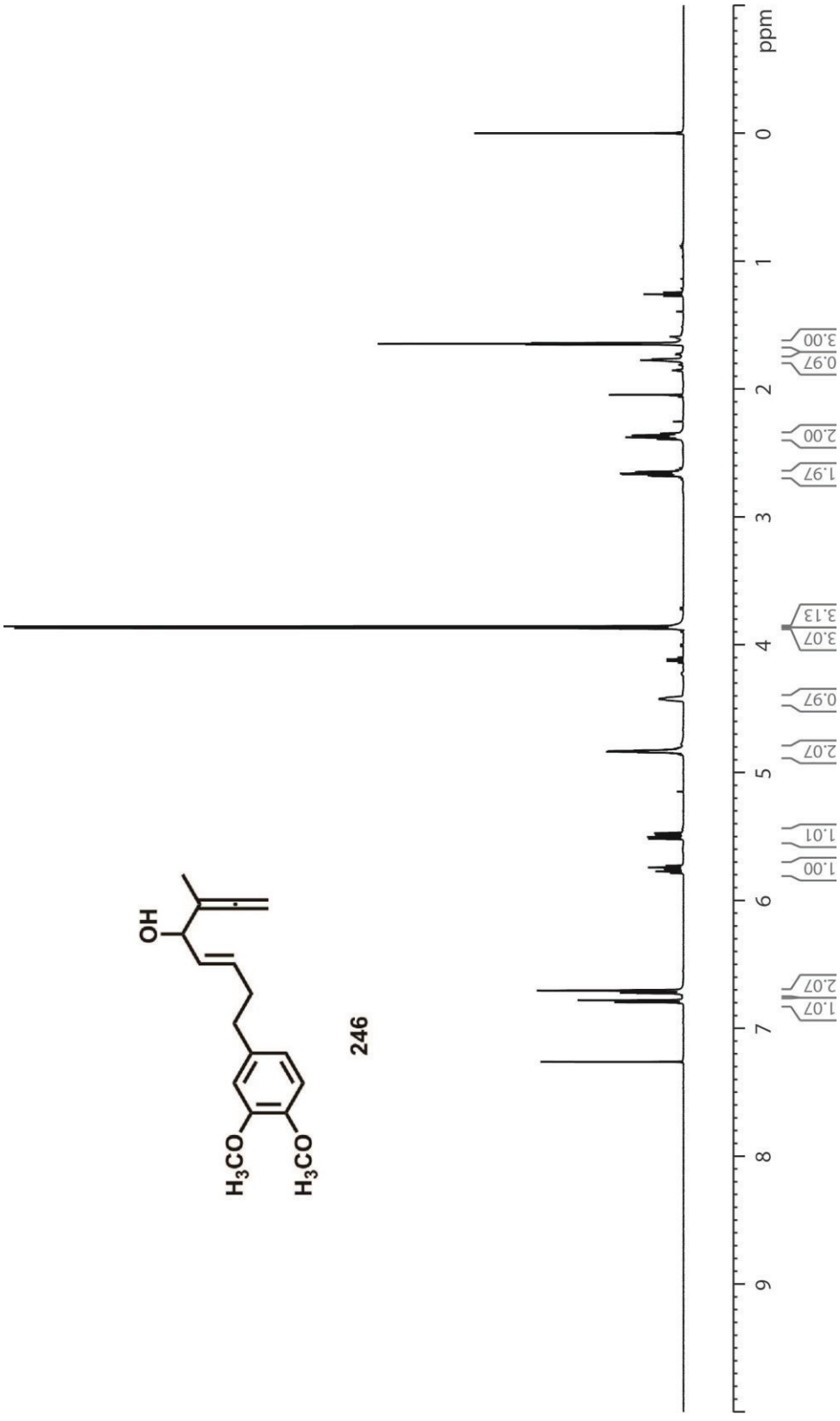
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (*E*)-5-(3,4-dimethyoxyphenyl)pent-2-en-1-ol (244)**



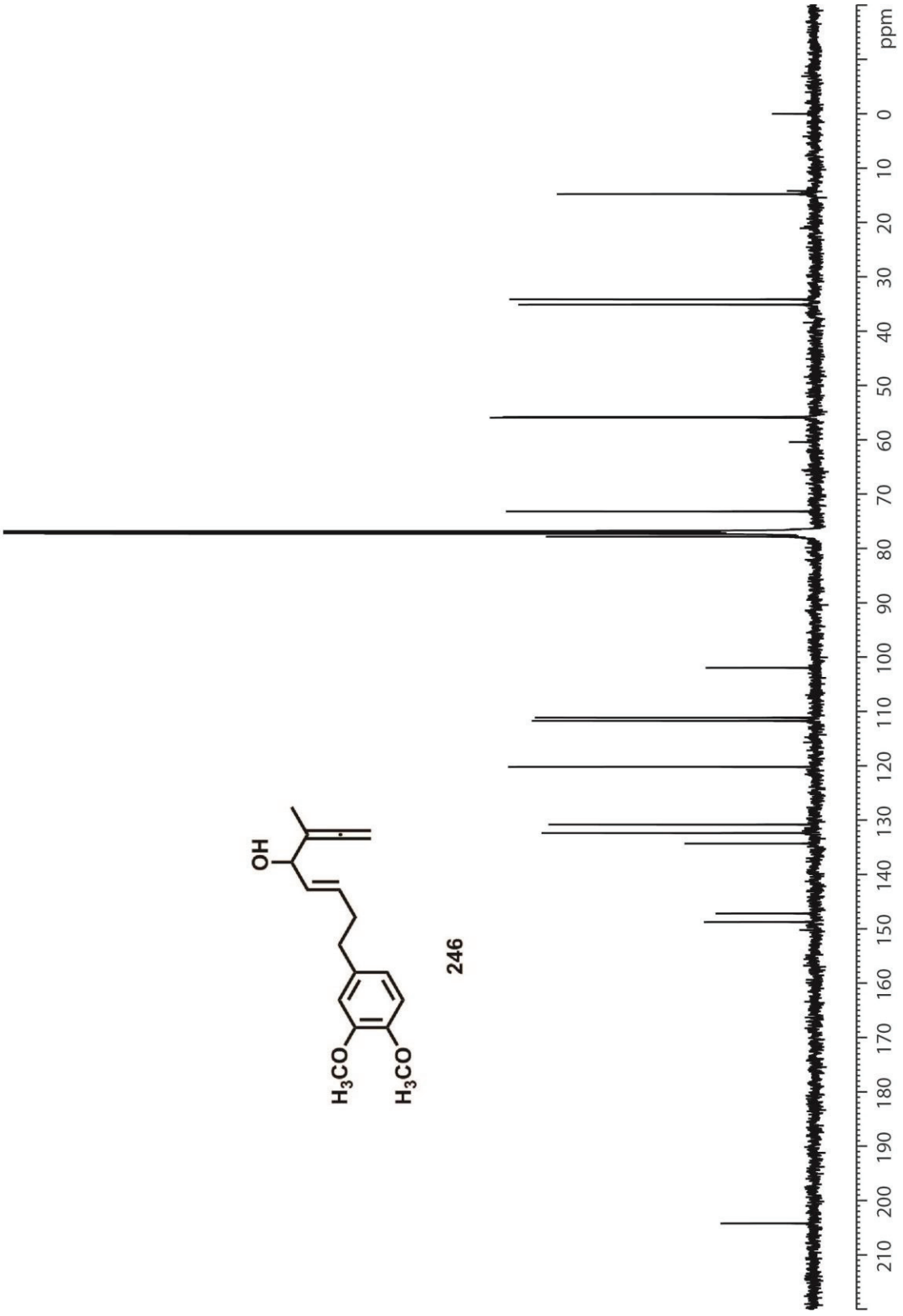
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (*E*)-5-(3,4-dimethyoxyphenyl)pent-2-en-1-ol (244)**



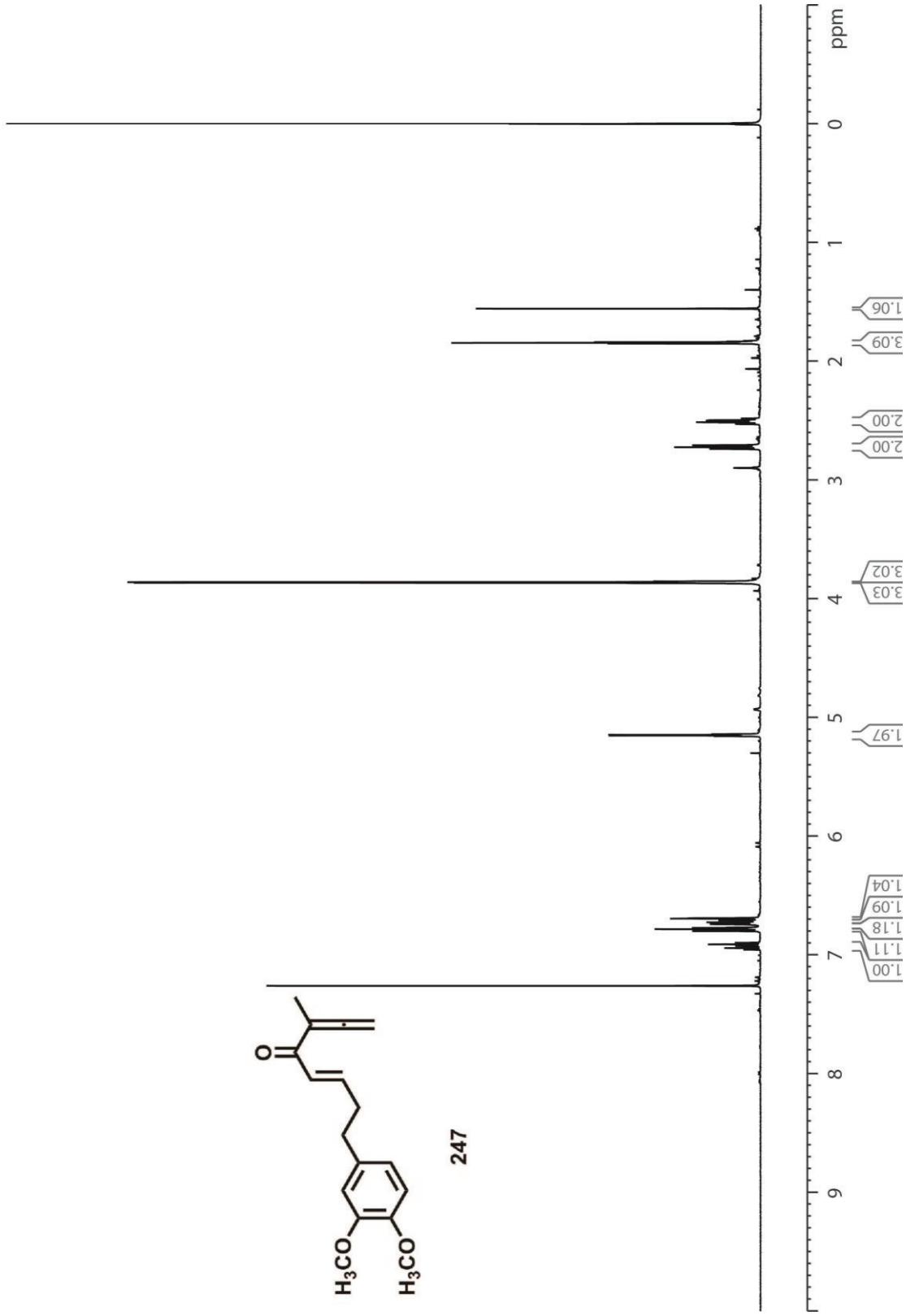
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (*E*)-8-(3,4-dimethoxyphenyl)-3-methylocta-1,2,5-trien-4-ol (246)**



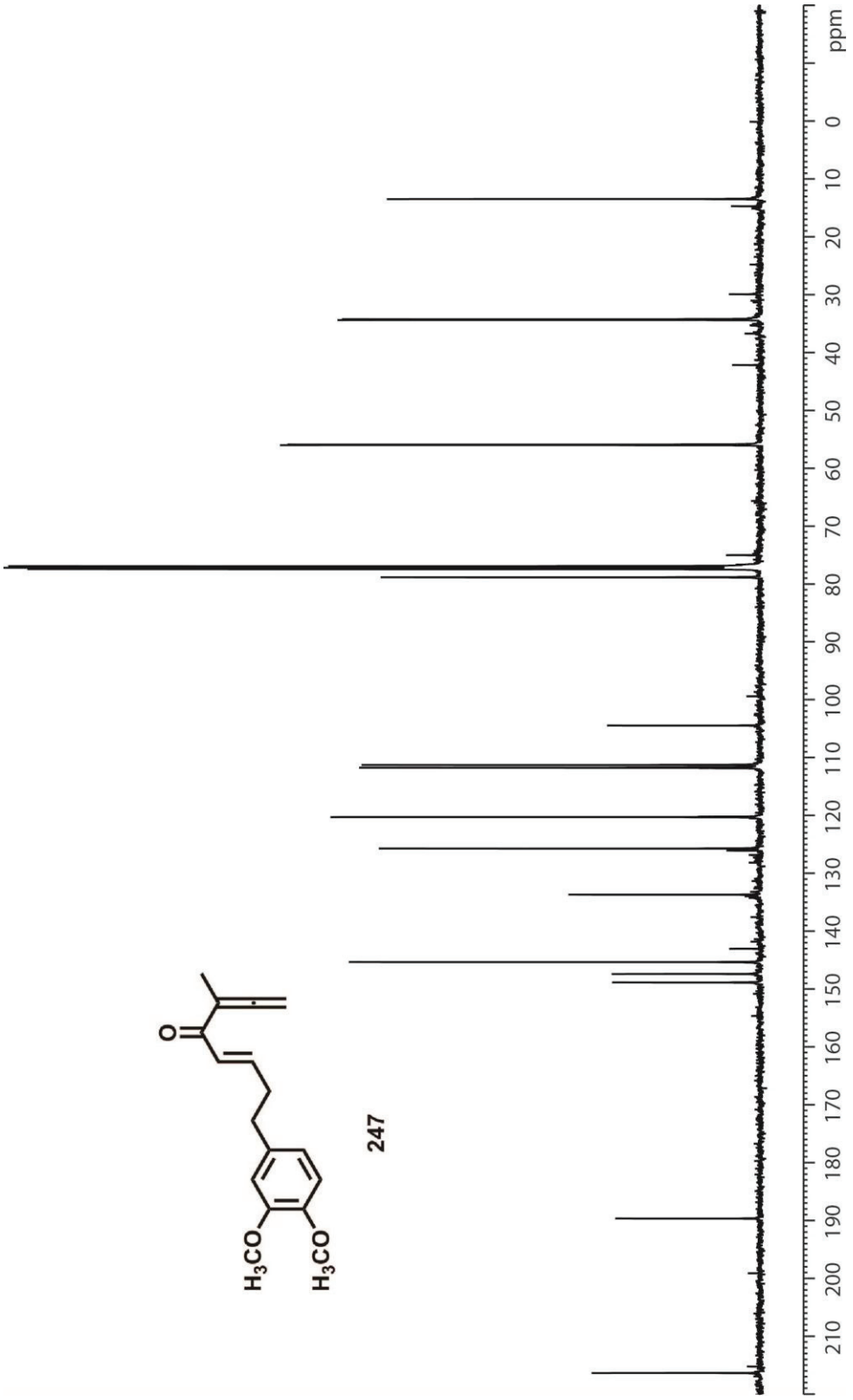
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (*E*)-8-(3,4-dimethoxyphenyl)-3-methylocta-1,2,5-trien-4-ol (246)**



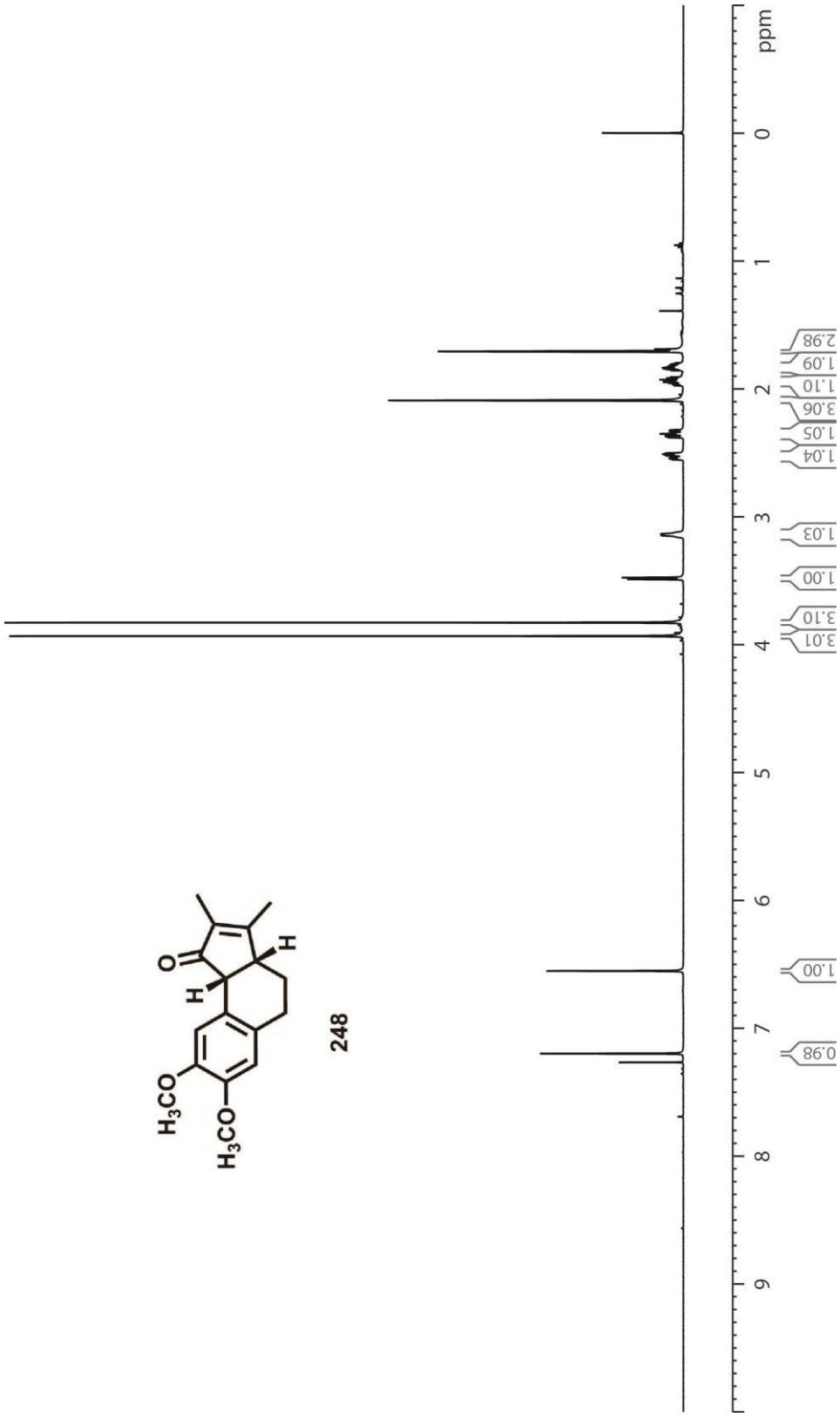
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (*E*)-8-(3,4-dimethoxyphenyl)-3-methylocta-1,2,5-trien-4-one (247)**



**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (*E*)-8-(3,4-dimethoxyphenyl)-3-methylocta-1,2,5-trien-4-one (247)**

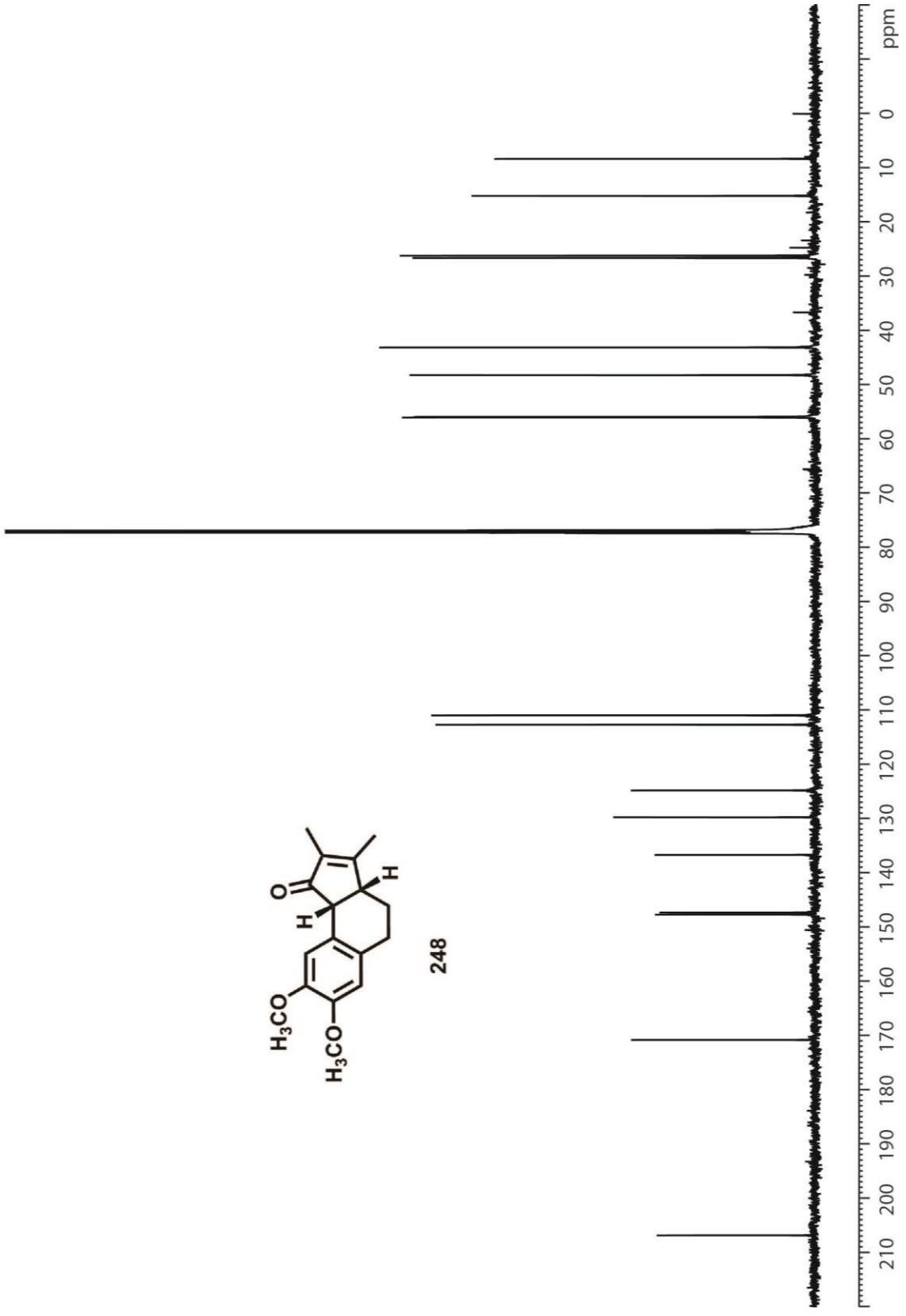


**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (3a*R*,9b*R*)-7,8-dimethoxy-2,3-dimethyl-3a,4,5,9b-tetrahydro-1*H*-cyclopenta[*a*]naphthalene-1-one (248)**




248

**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (3a*R*,9b*R*)-7,8-dimethoxy-2,3-dimethyl-3a,4,5,9b-tetrahydro-1*H*-cyclopenta[*a*]naphthalene-1-one (248)**

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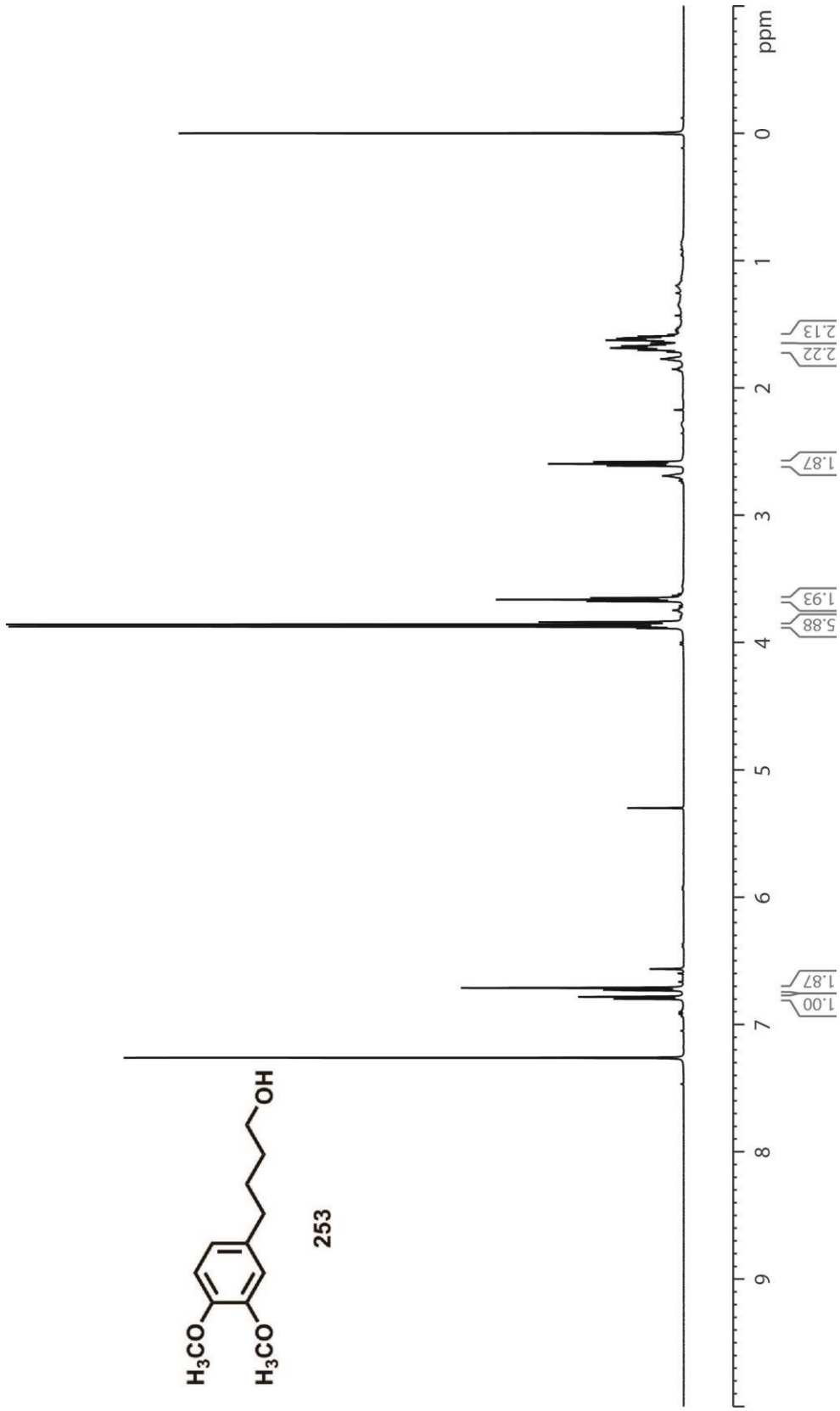
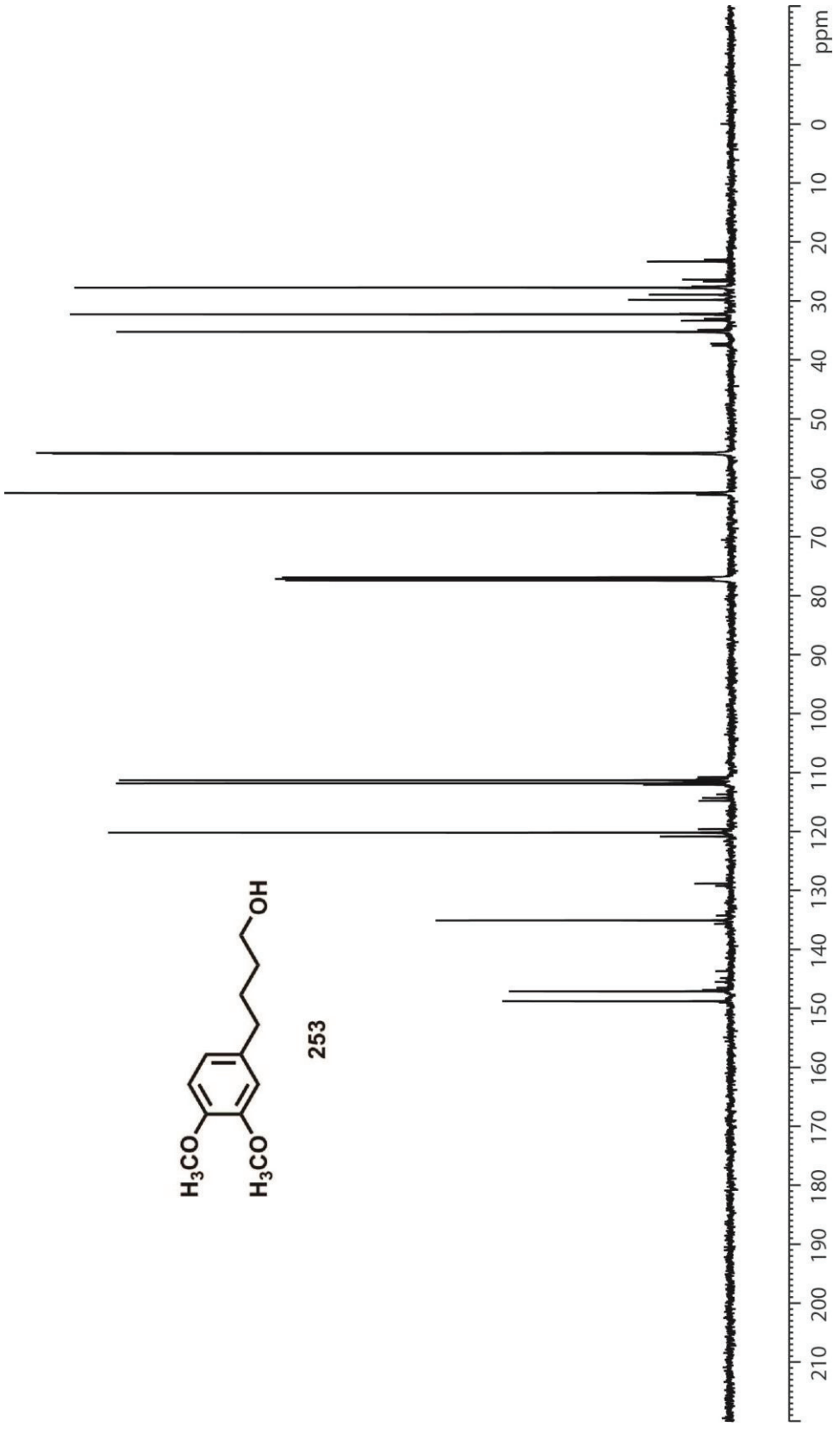
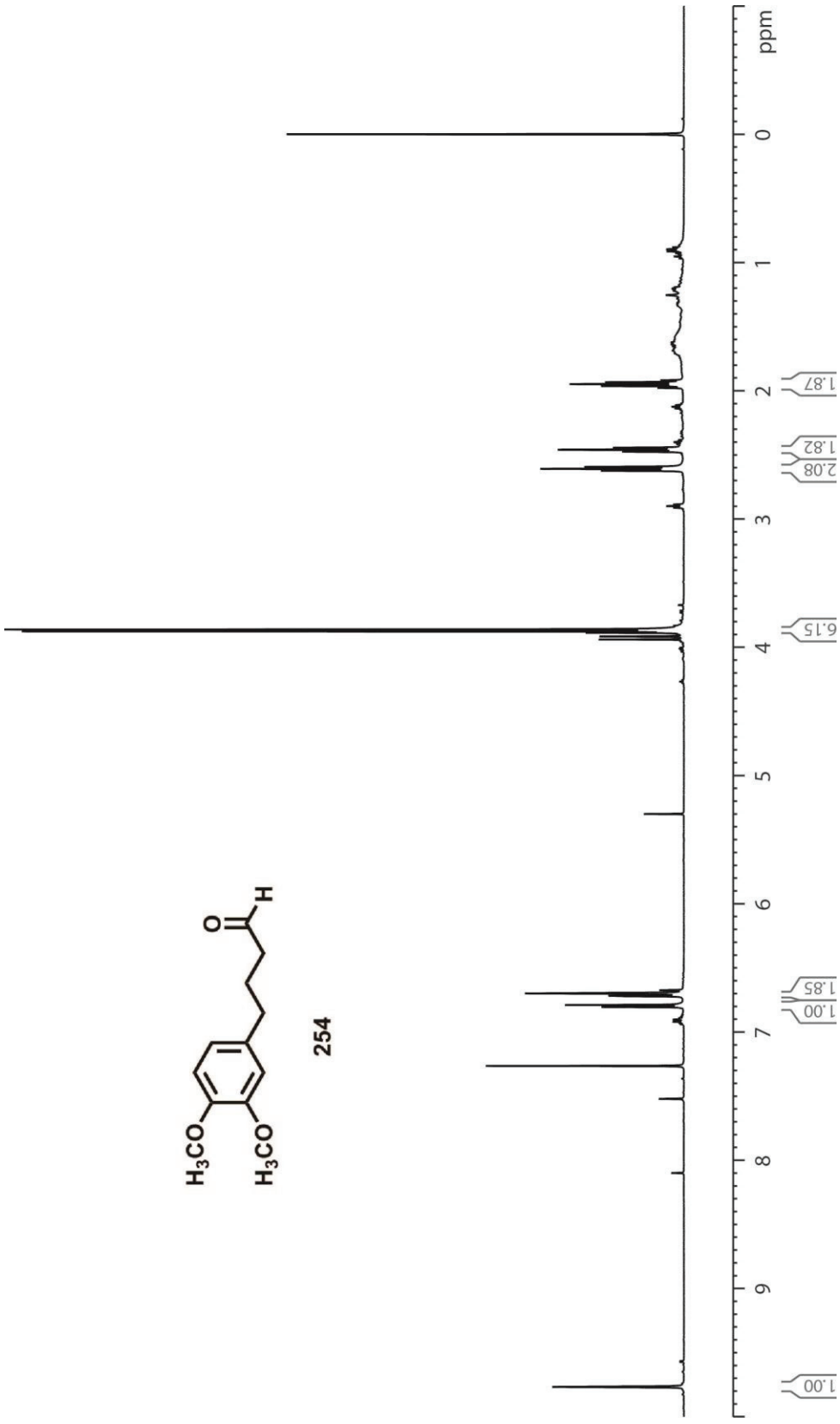
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of 4-(3,4-dimethoxyphenyl)butan-1-ol (253)**



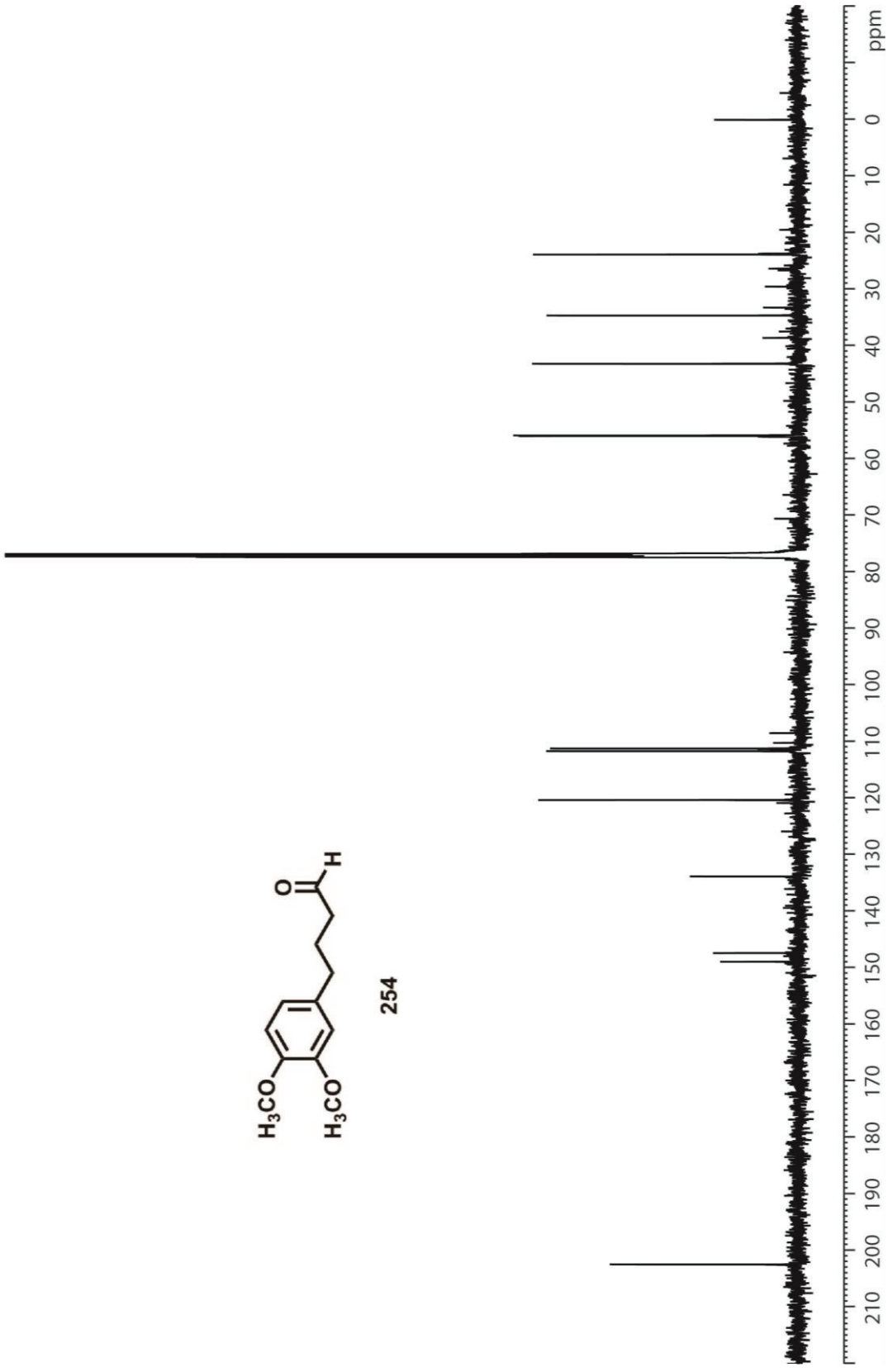
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of 4-(3,4-dimethoxyphenyl)butan-1-ol (253)**



**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of 4-(3,4-Dimethoxyphenyl)butanal (254)**

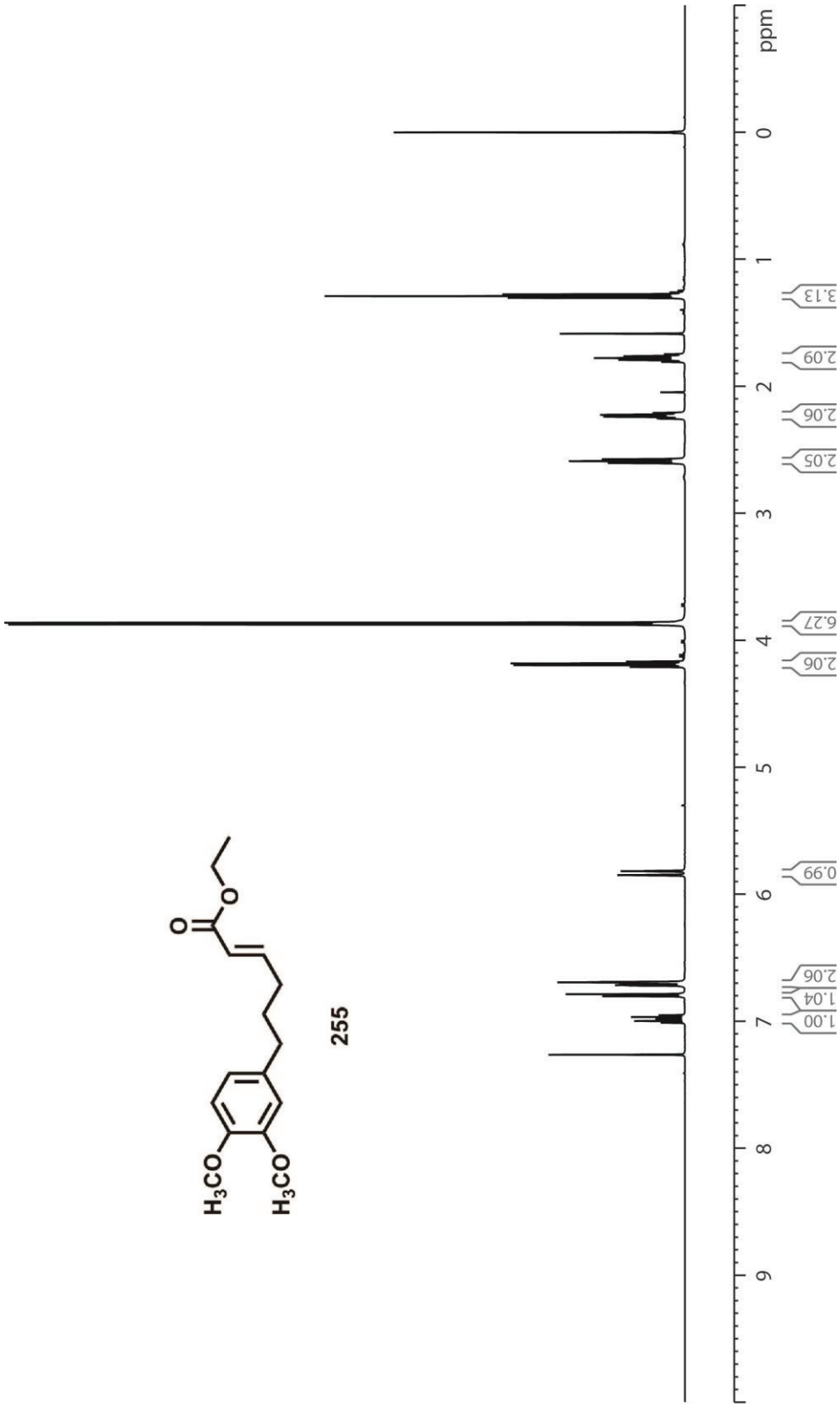


**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of 4-(3,4-Dimethoxyphenyl)butanal (254)**

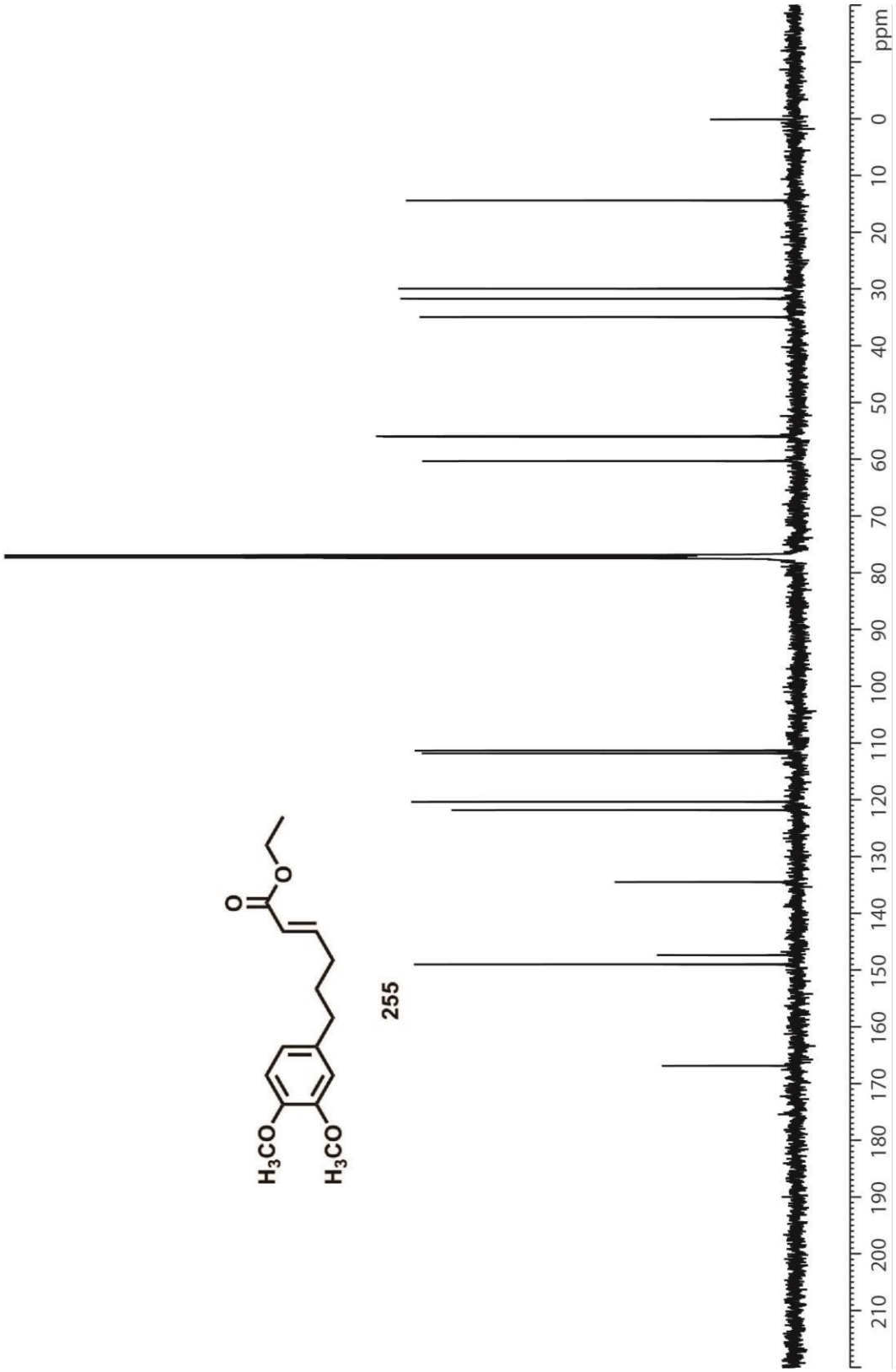



254

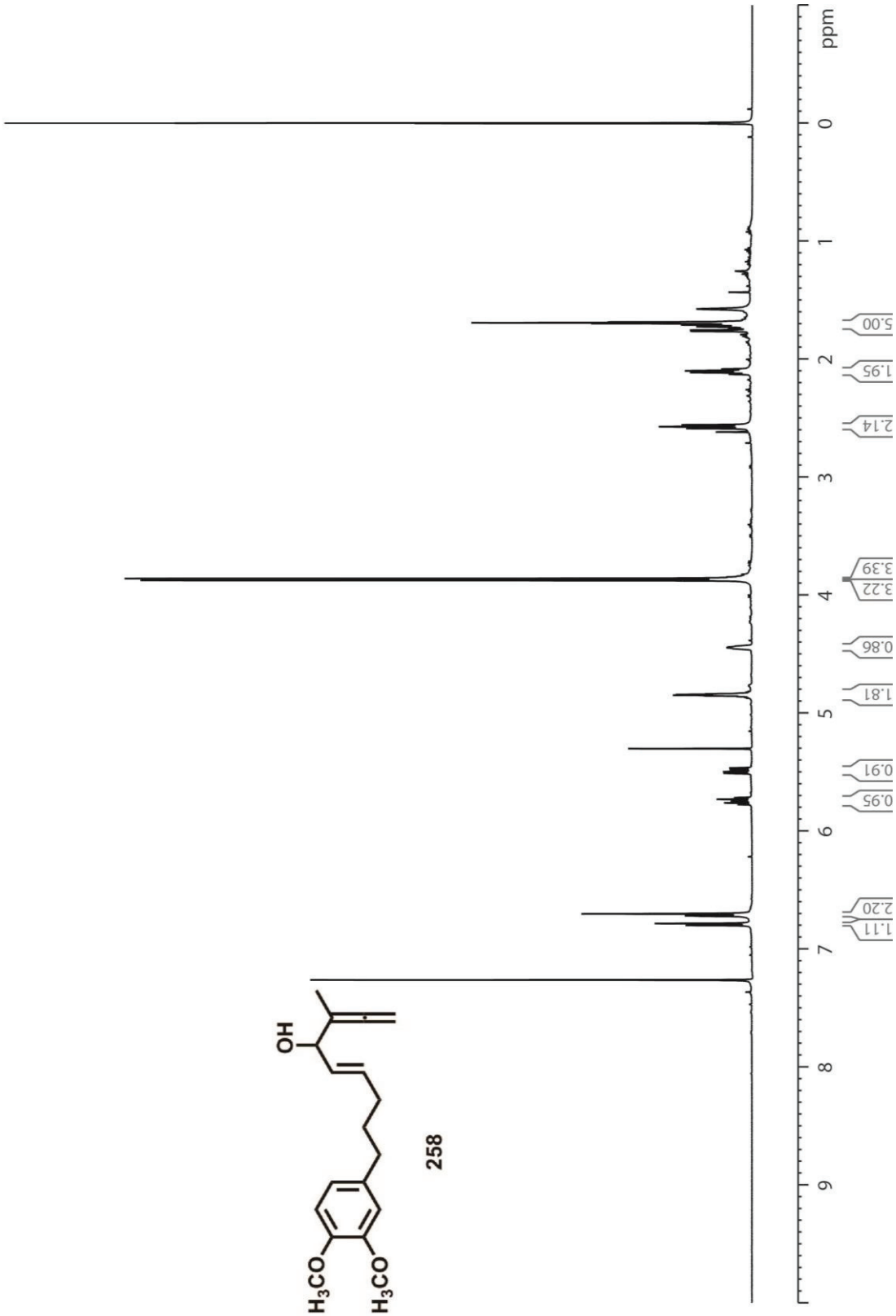
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (*E*)-ethyl 6-(3,4-dimethoxyphenyl)hex-2-enoate (255)**



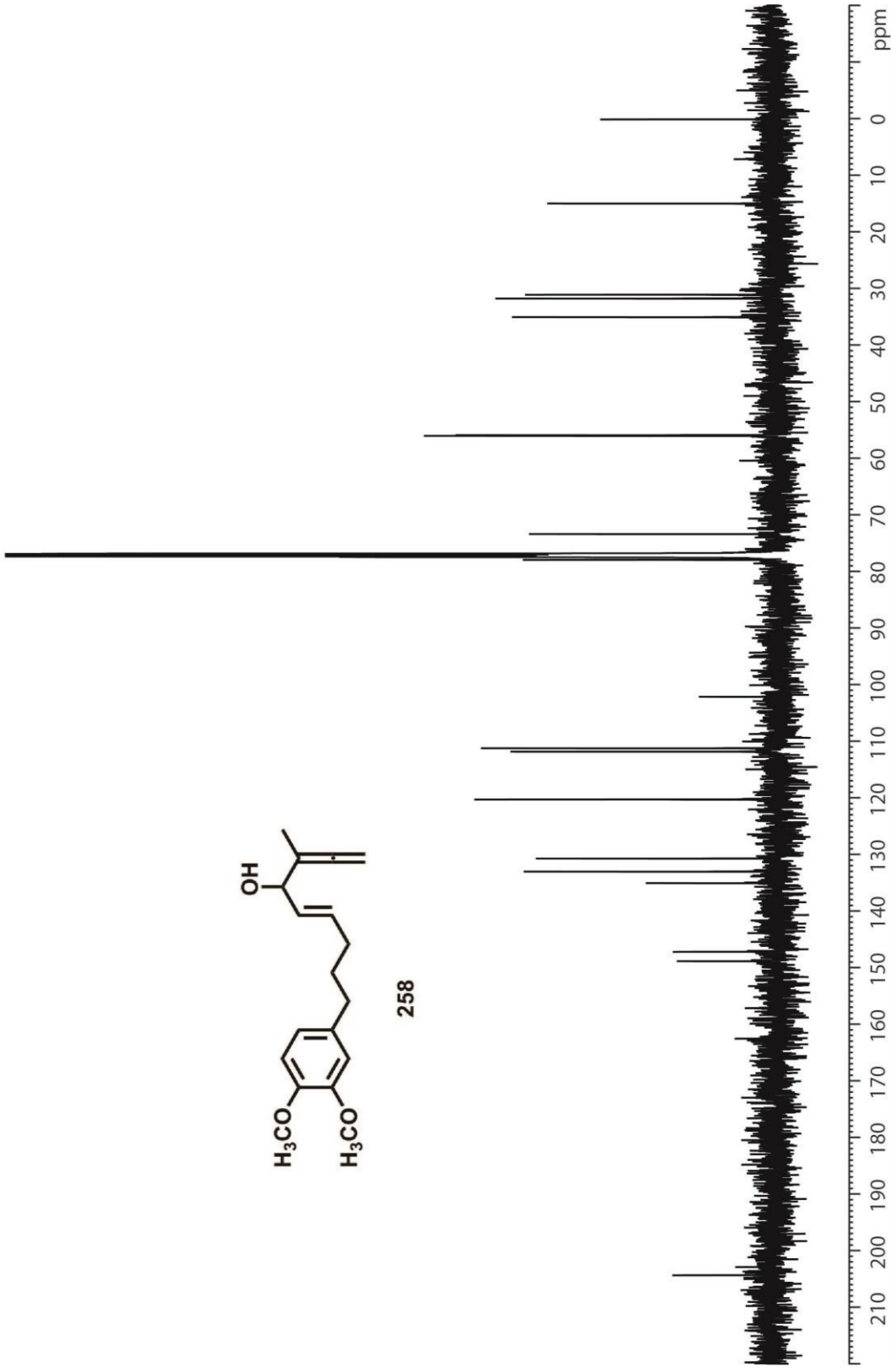
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (*E*)-ethyl 6-(3,4-dimethoxyphenyl)hex-2-enoate (255)**



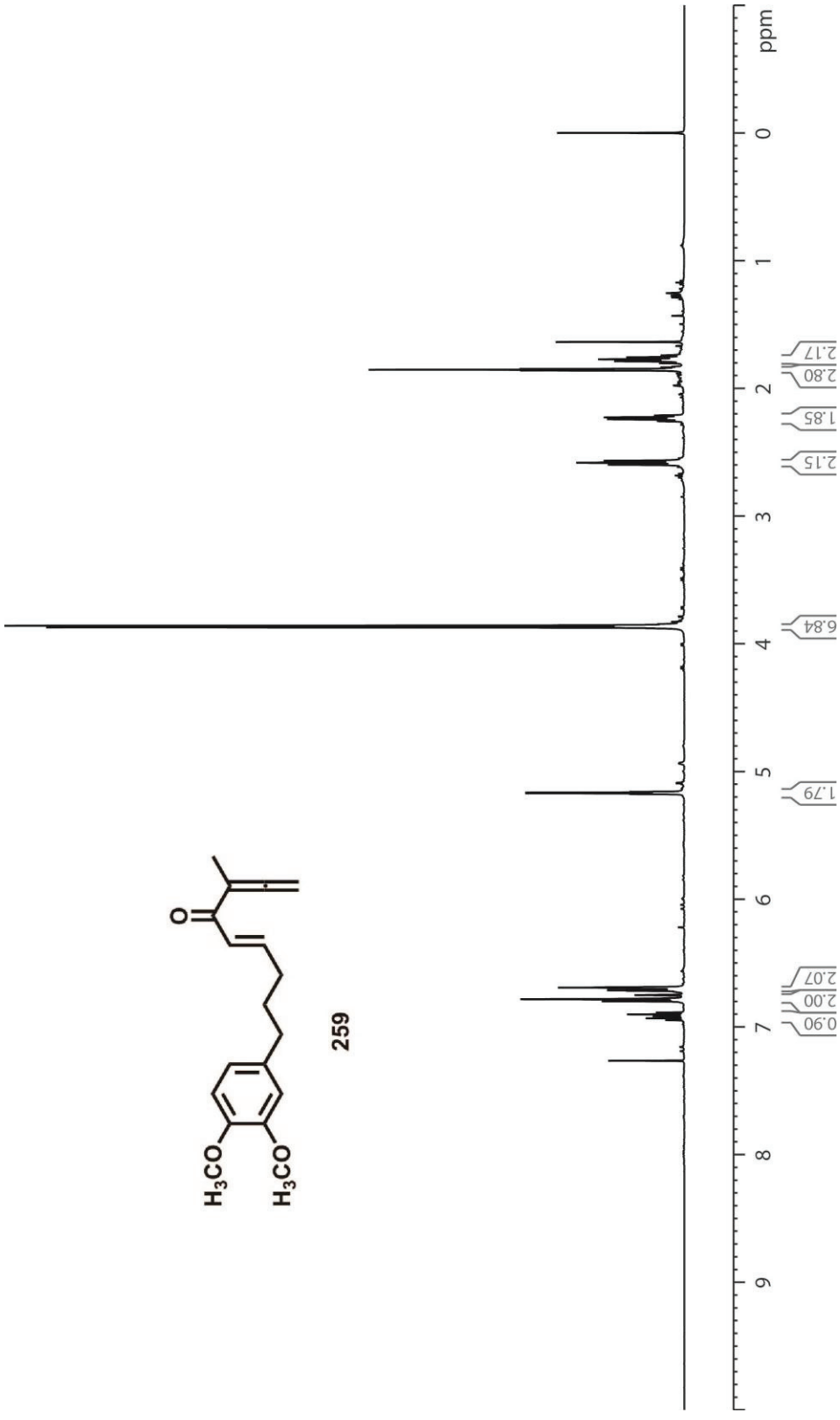
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (*E*)-9-(3,4-dimethoxyphenyl)-3-methylnona-1,2,5-trien-4-ol (258)**



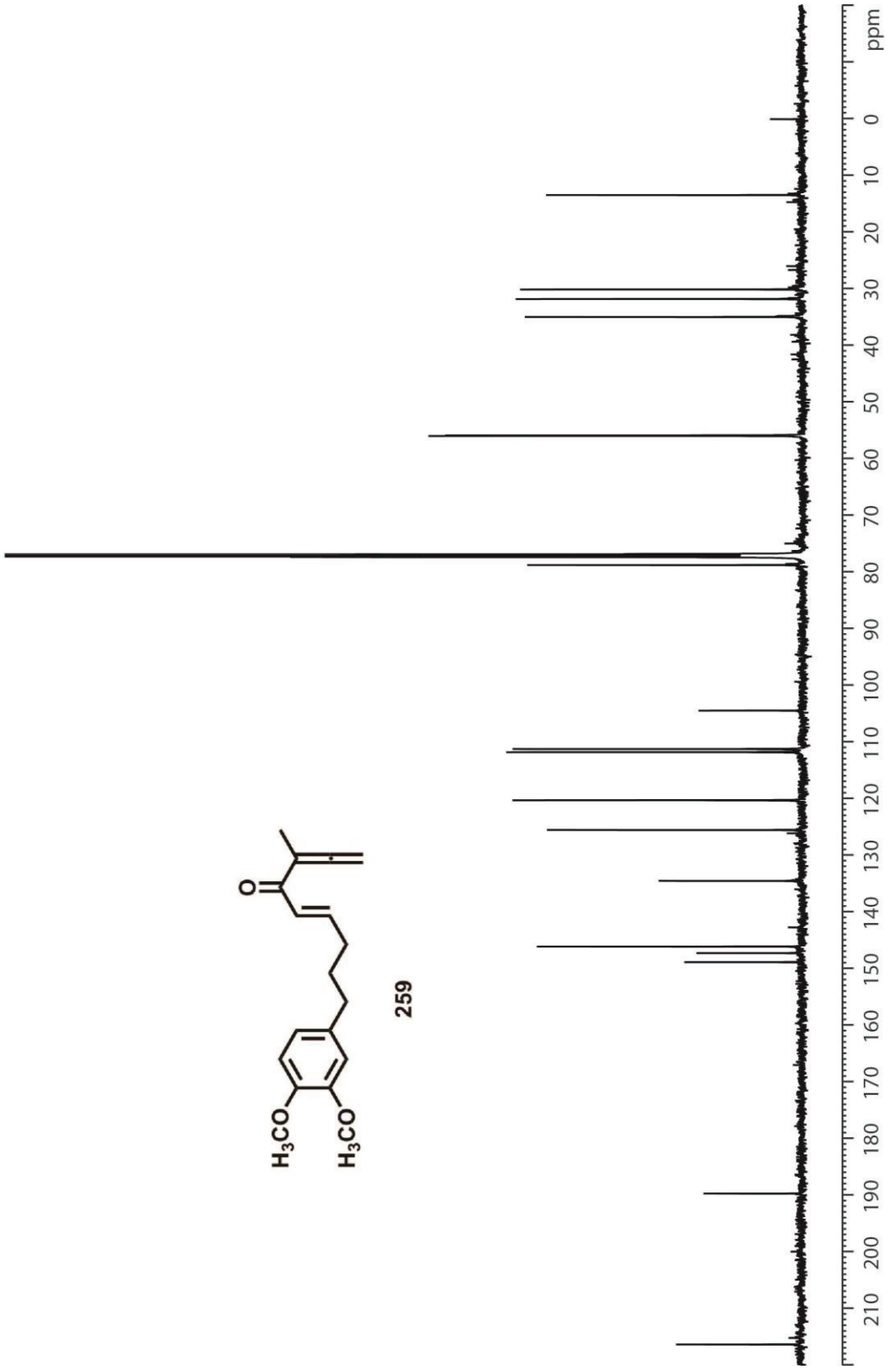
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (*E*)-9-(3,4-dimethoxyphenyl)-3-methylnona-1,2,5-trien-4-ol (258)**



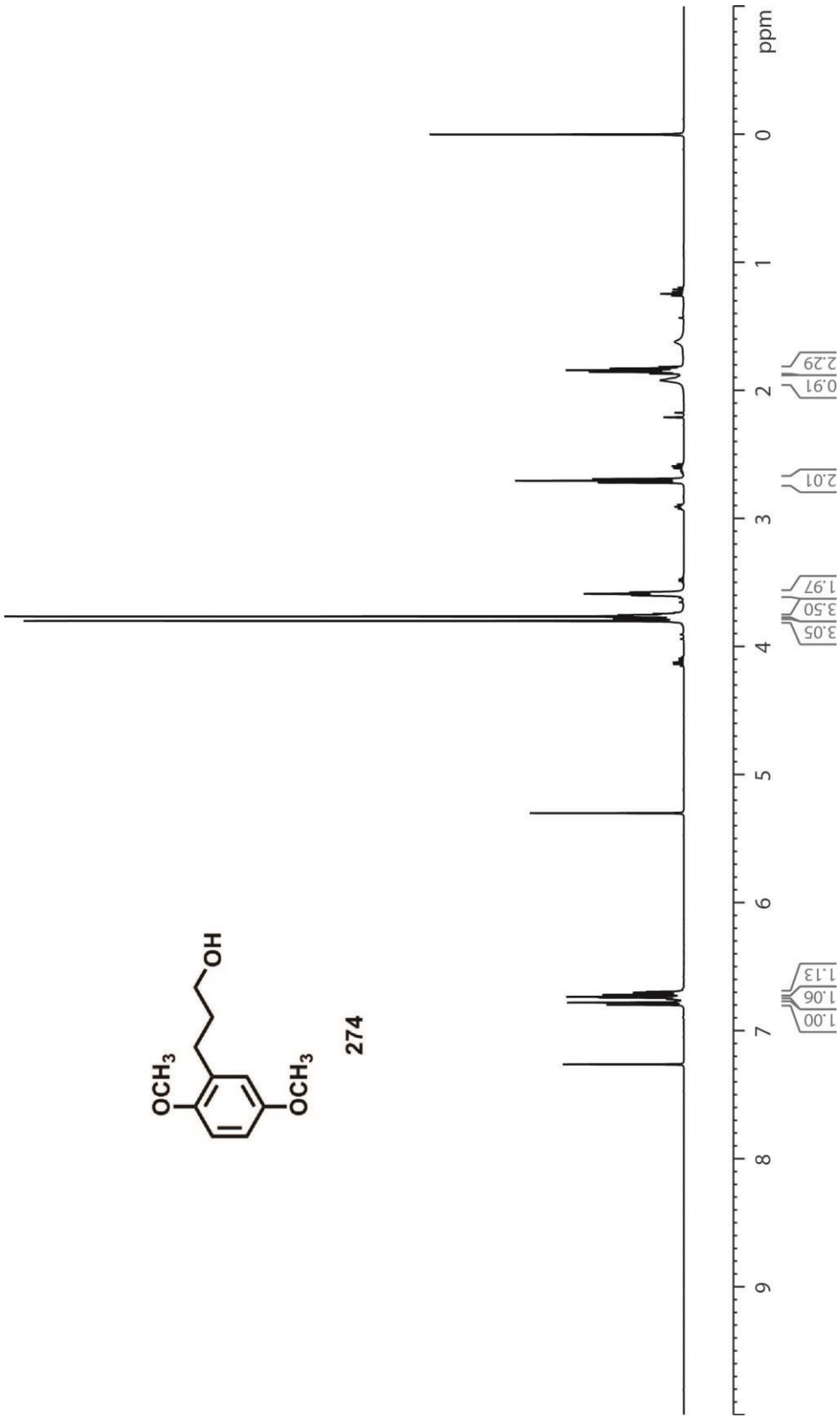
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (*E*)-9-(3,4-dimethoxyphenyl)-3-methylnona-1,2,5-trien-4-one (259)**



**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (*E*)-9-(3,4-dimethoxyphenyl)-3-methylnona-1,2,5-trien-4-one (259)**

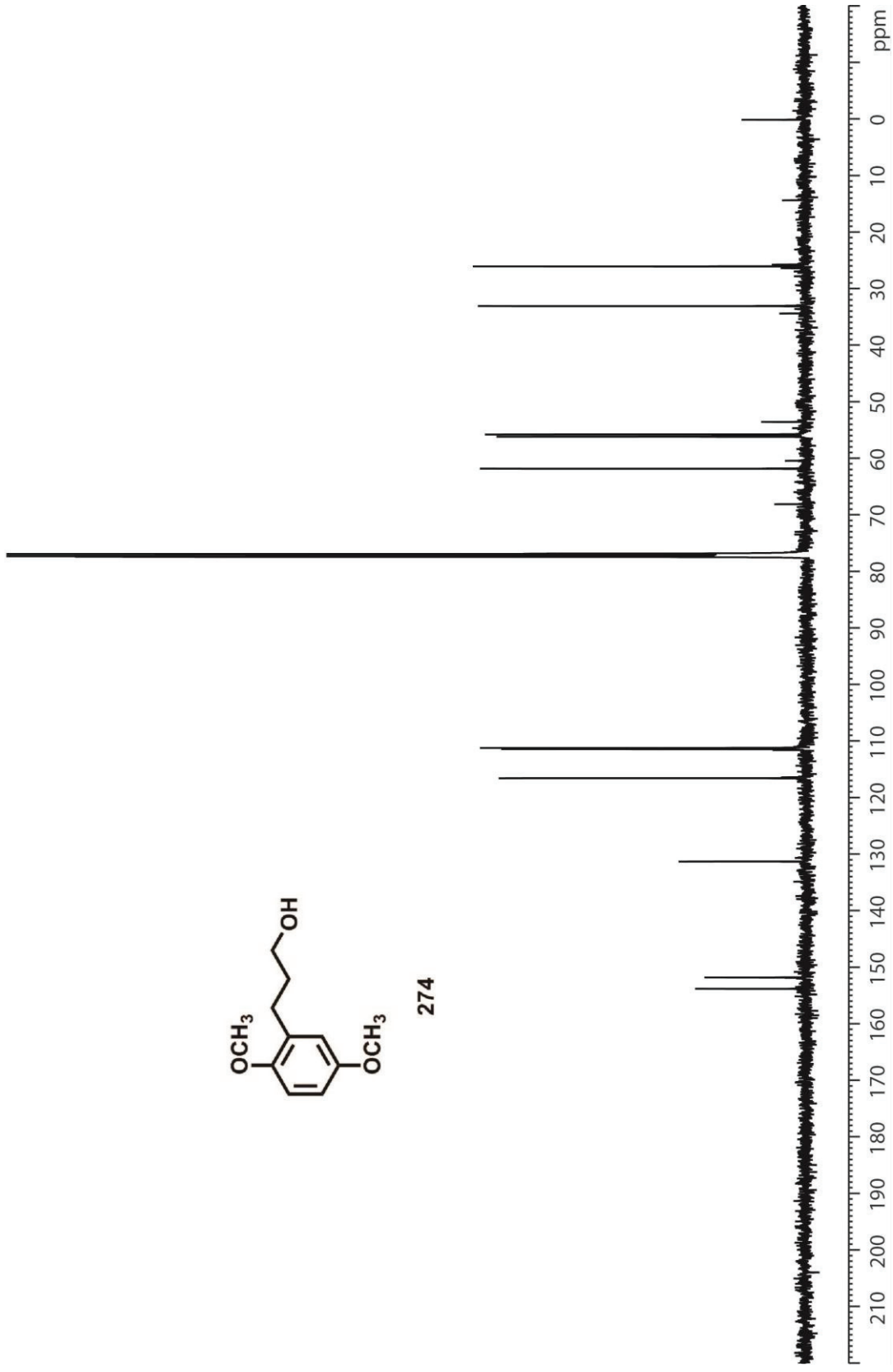


**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of 3-(2,5-dimethoxyphenyl)propan-1-ol (274)**

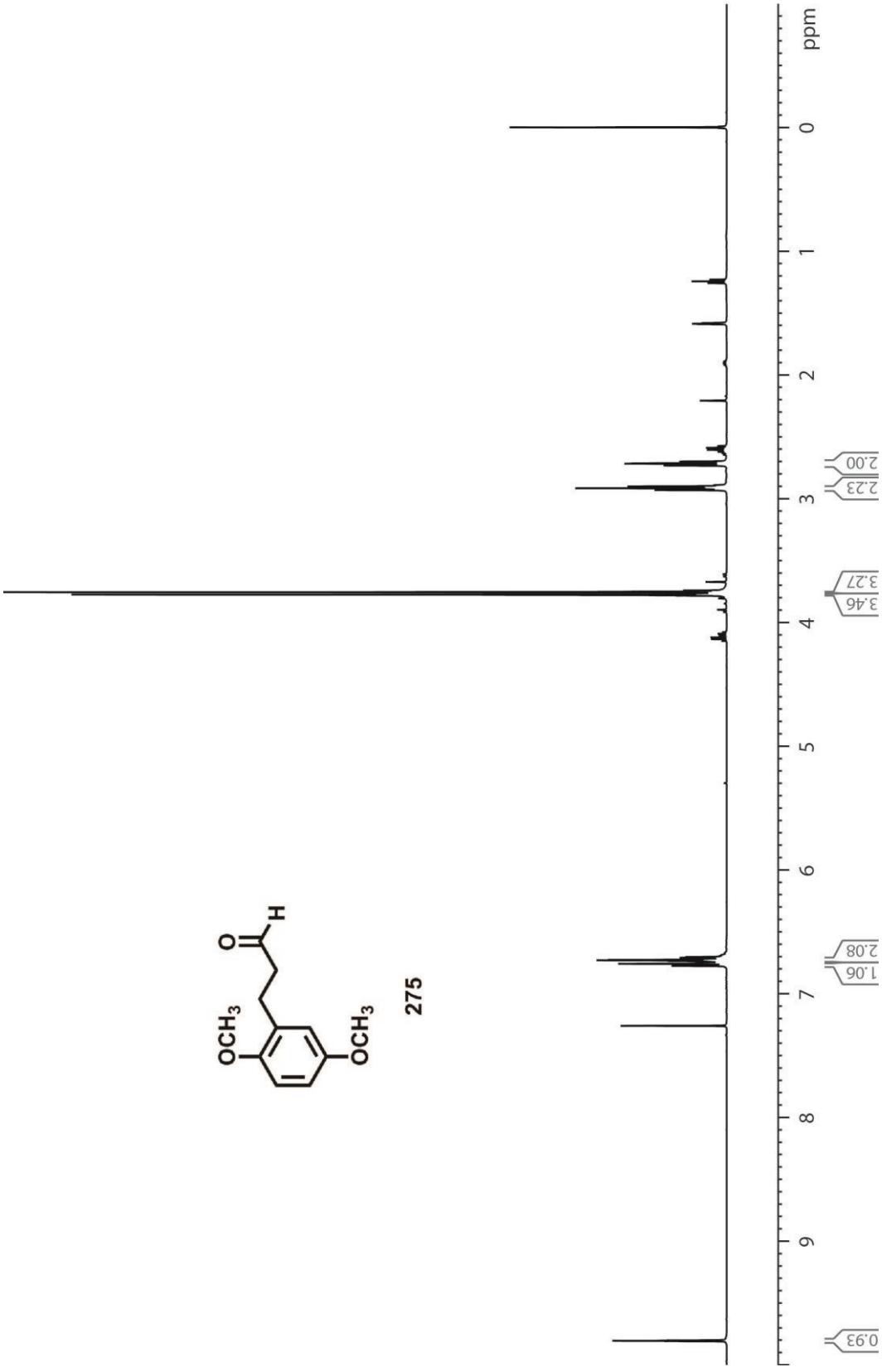



274

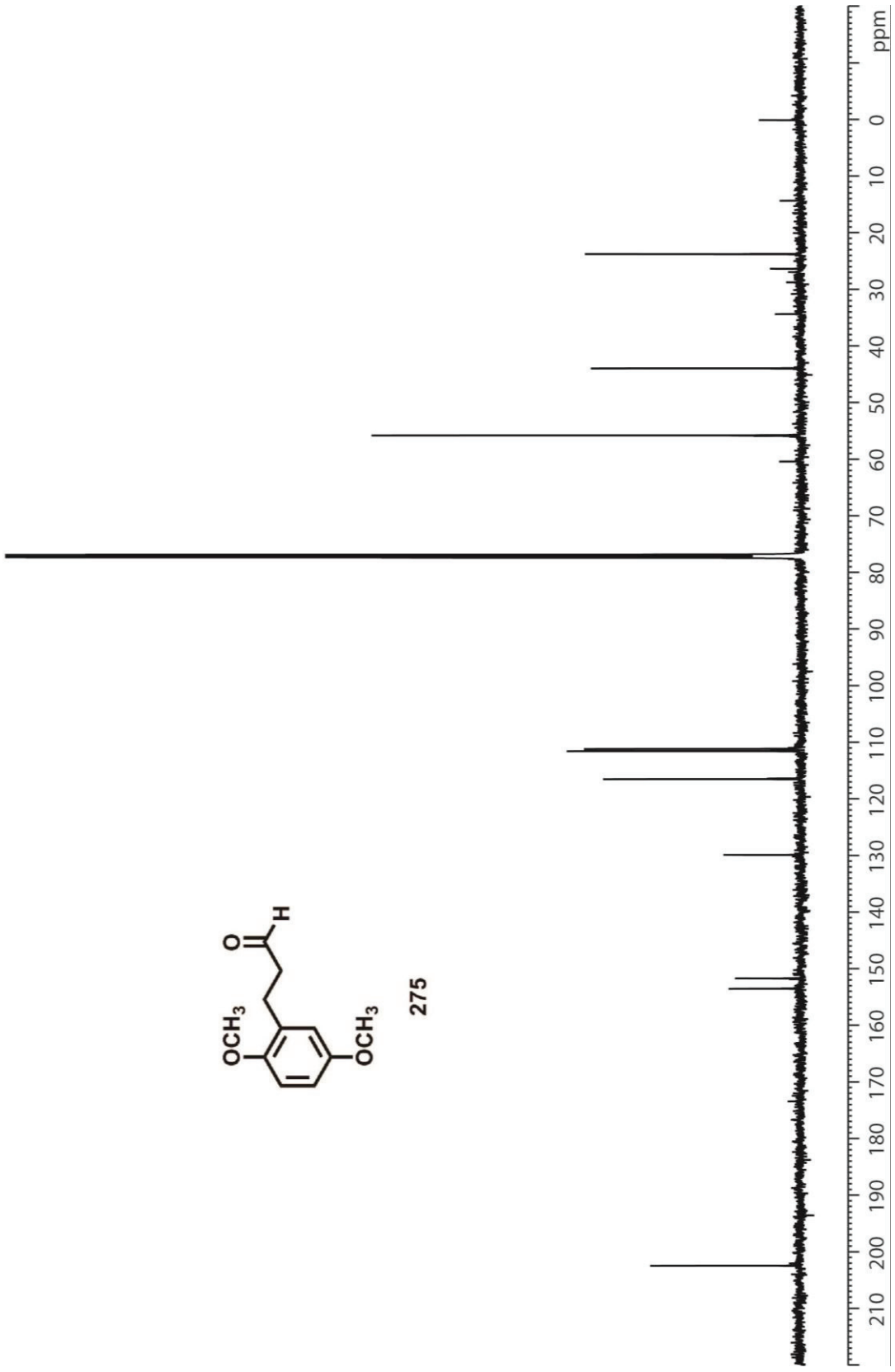
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of 3-(2,5-dimethoxyphenyl)propan-1-ol (274)**



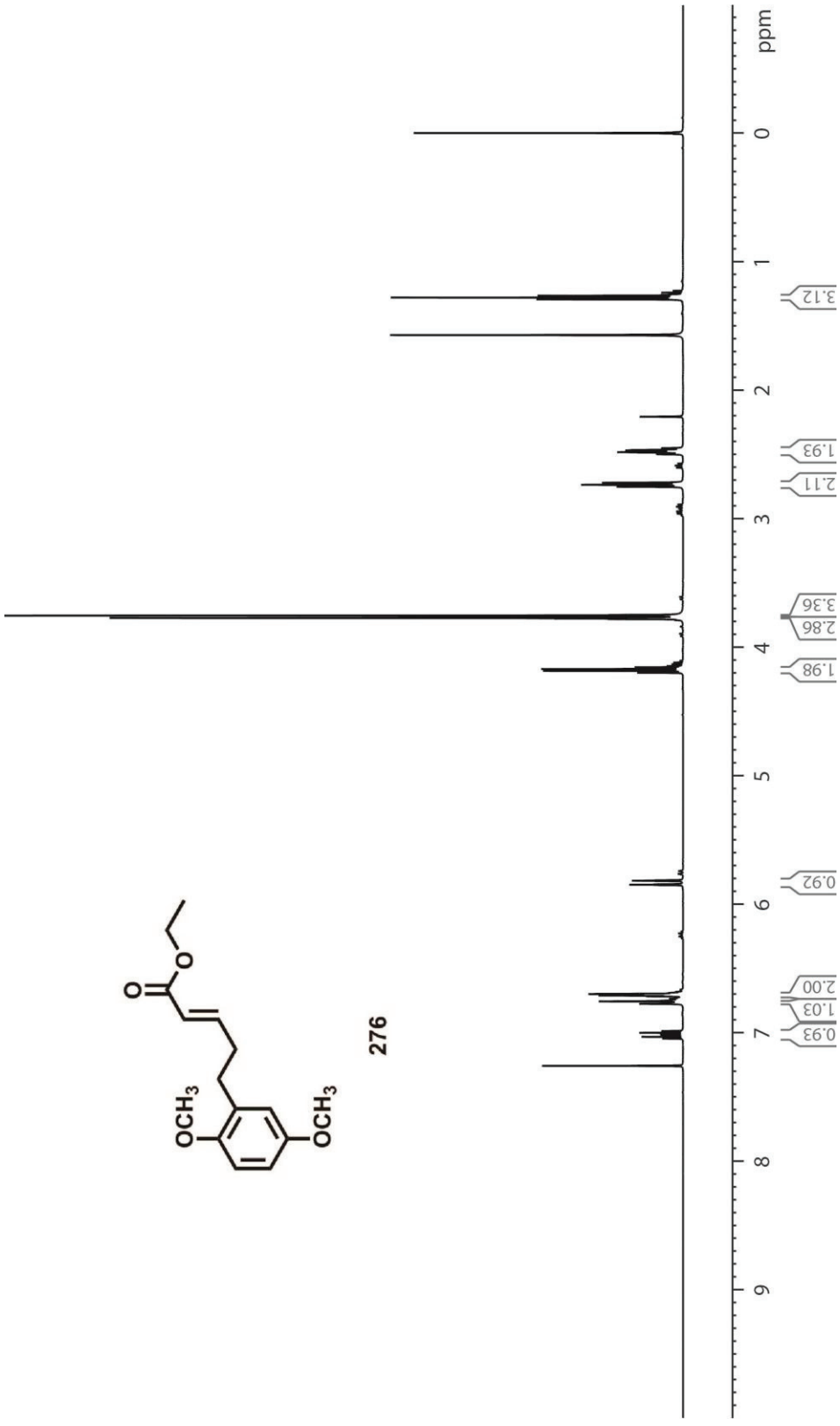
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of 3-(2,5-dimethoxyphenyl)propanal (275)**



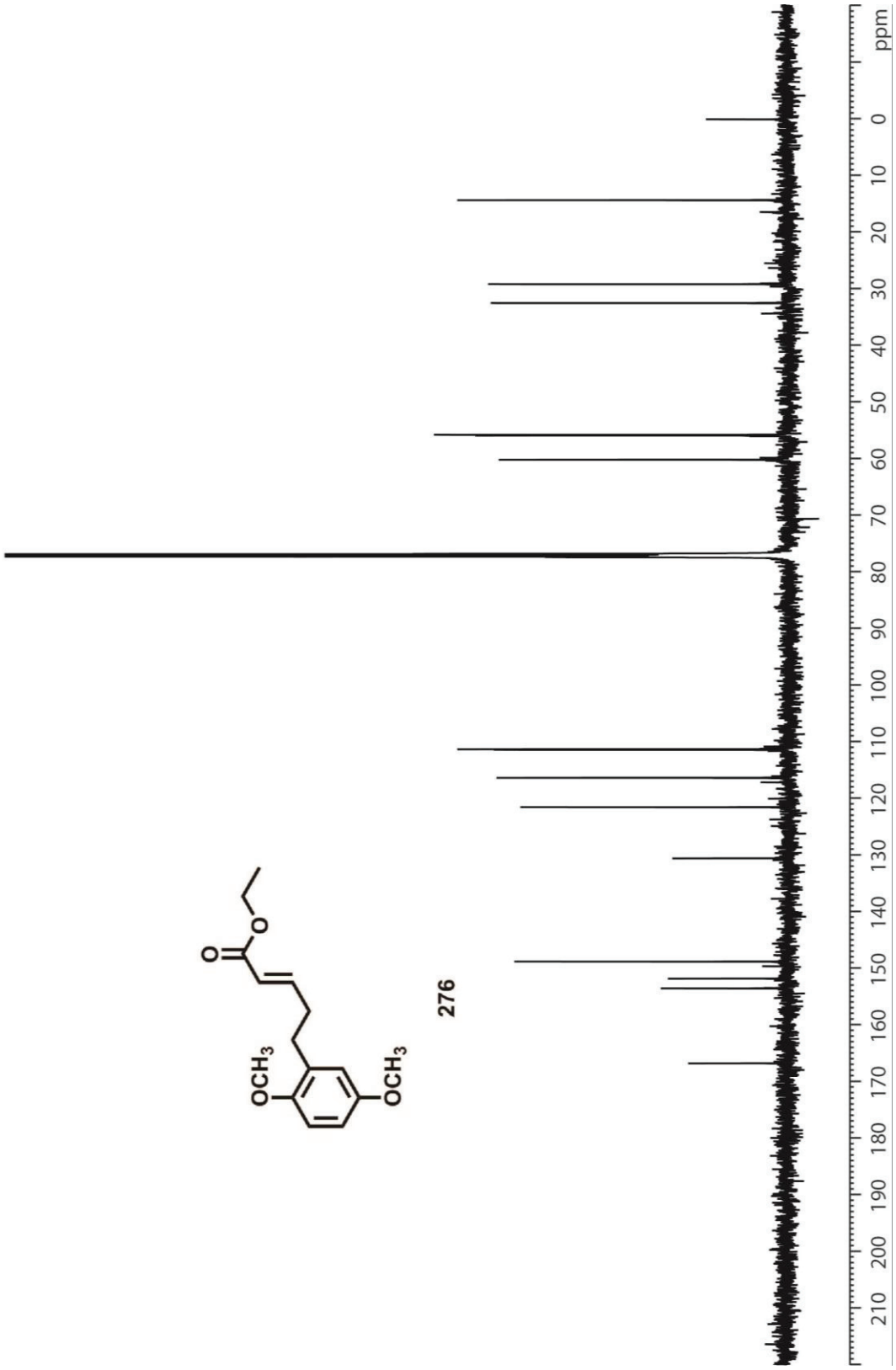
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of 3-(2,5-dimethoxyphenyl)propanal (275)**



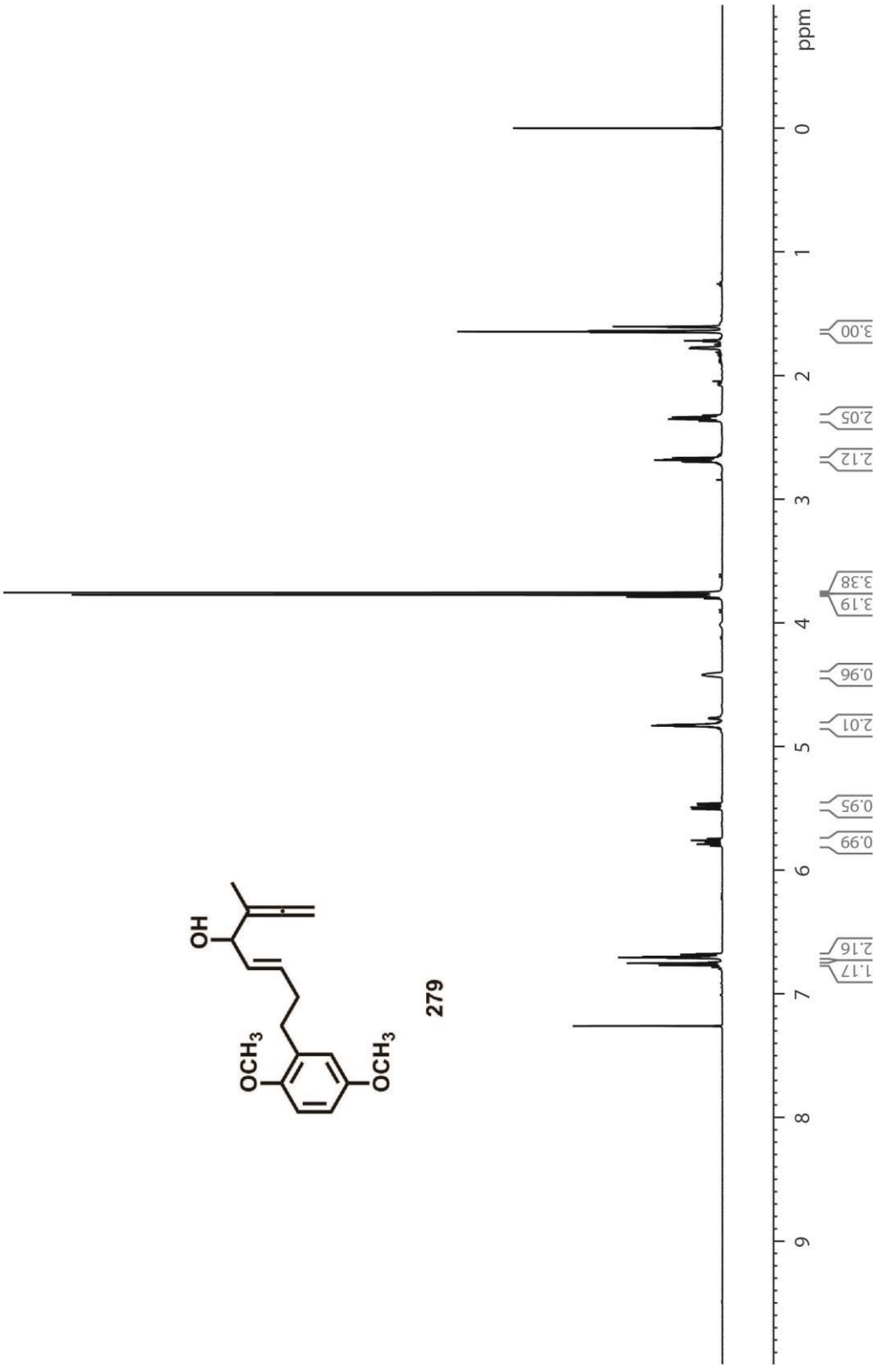
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of ethyl (*E*)-5-(2,5-dimethoxyphenyl)pent-2-enoate (276)**



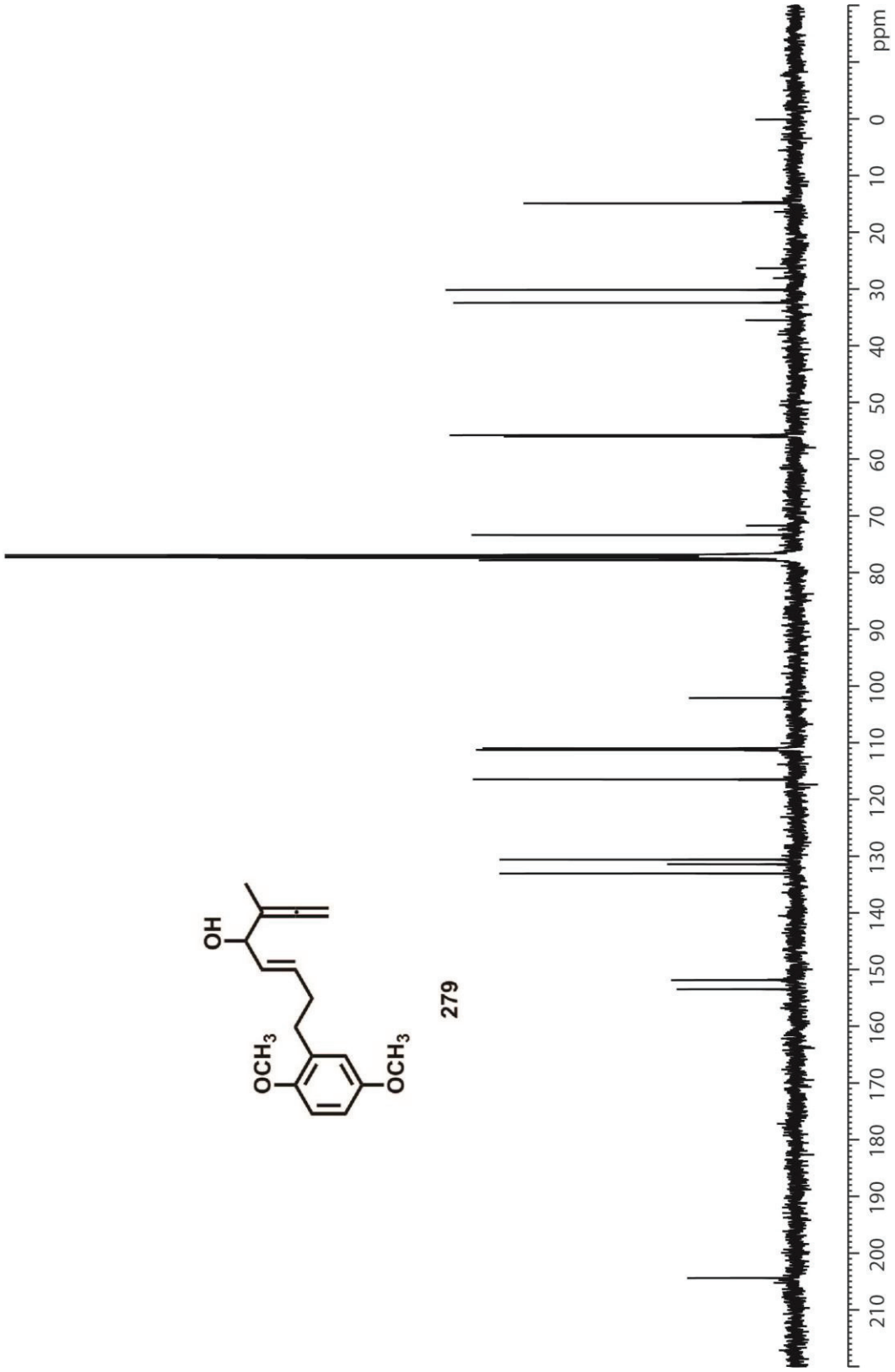
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of ethyl (*E*)-5-(2,5-dimethoxyphenyl)pent-2-enoate (276)**



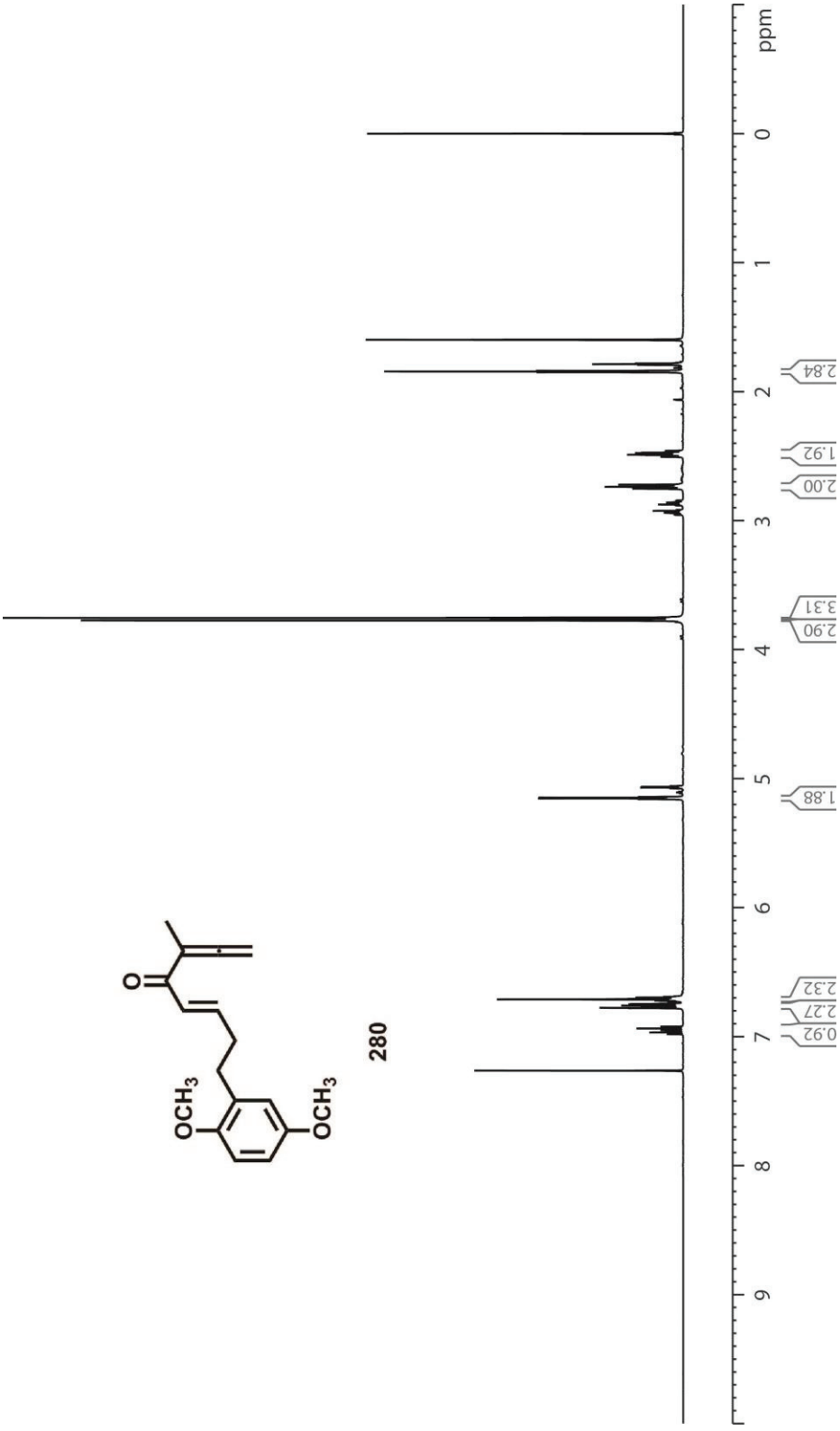
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (*E*)-8-(2,5-dimethoxyphenyl)-3-methylocta-1,2,5-trien-4-ol (279)**



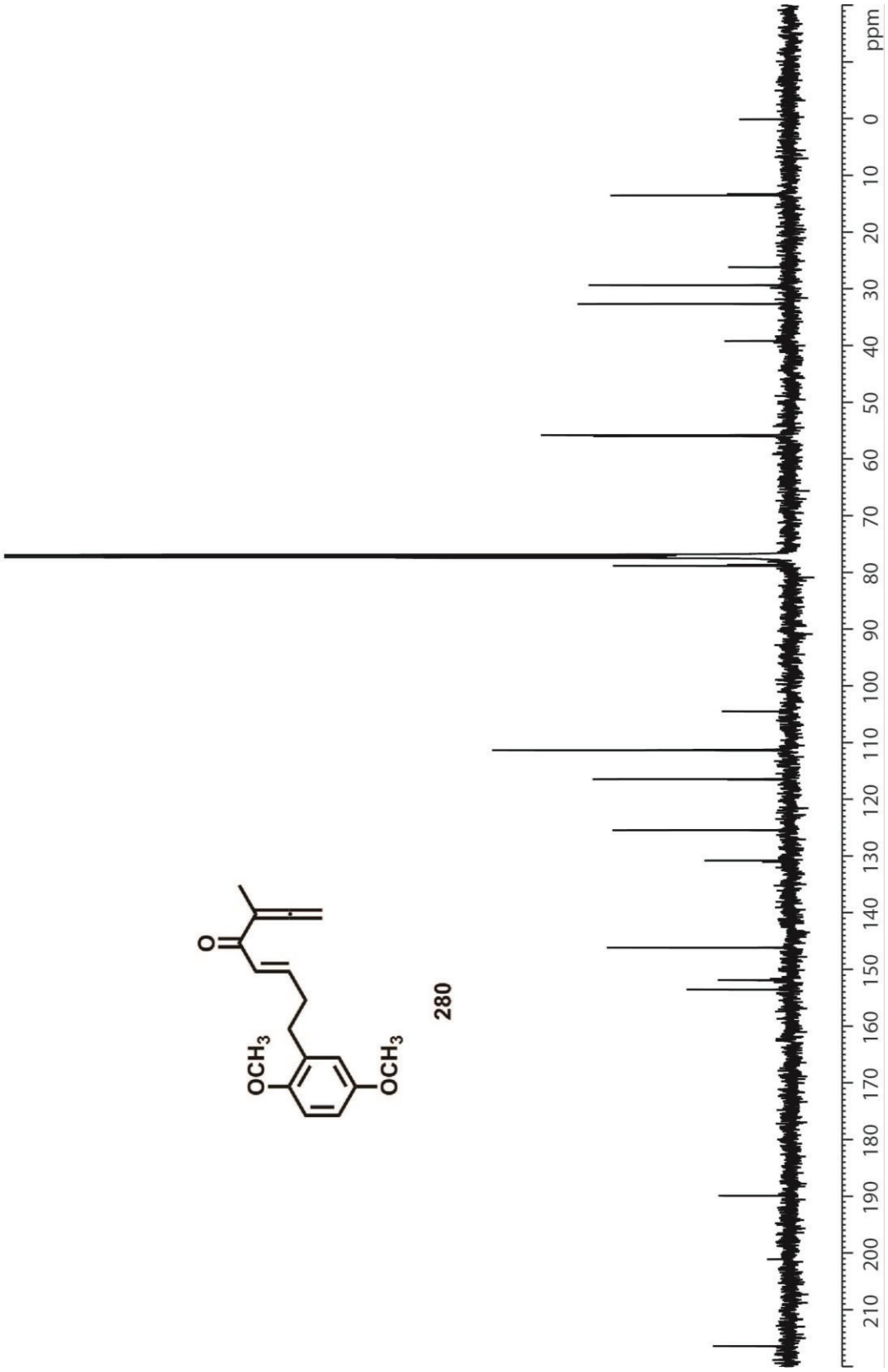
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (*E*)-8-(2,5-dimethoxyphenyl)-3-methylocta-1,2,5-trien-4-ol (279)**



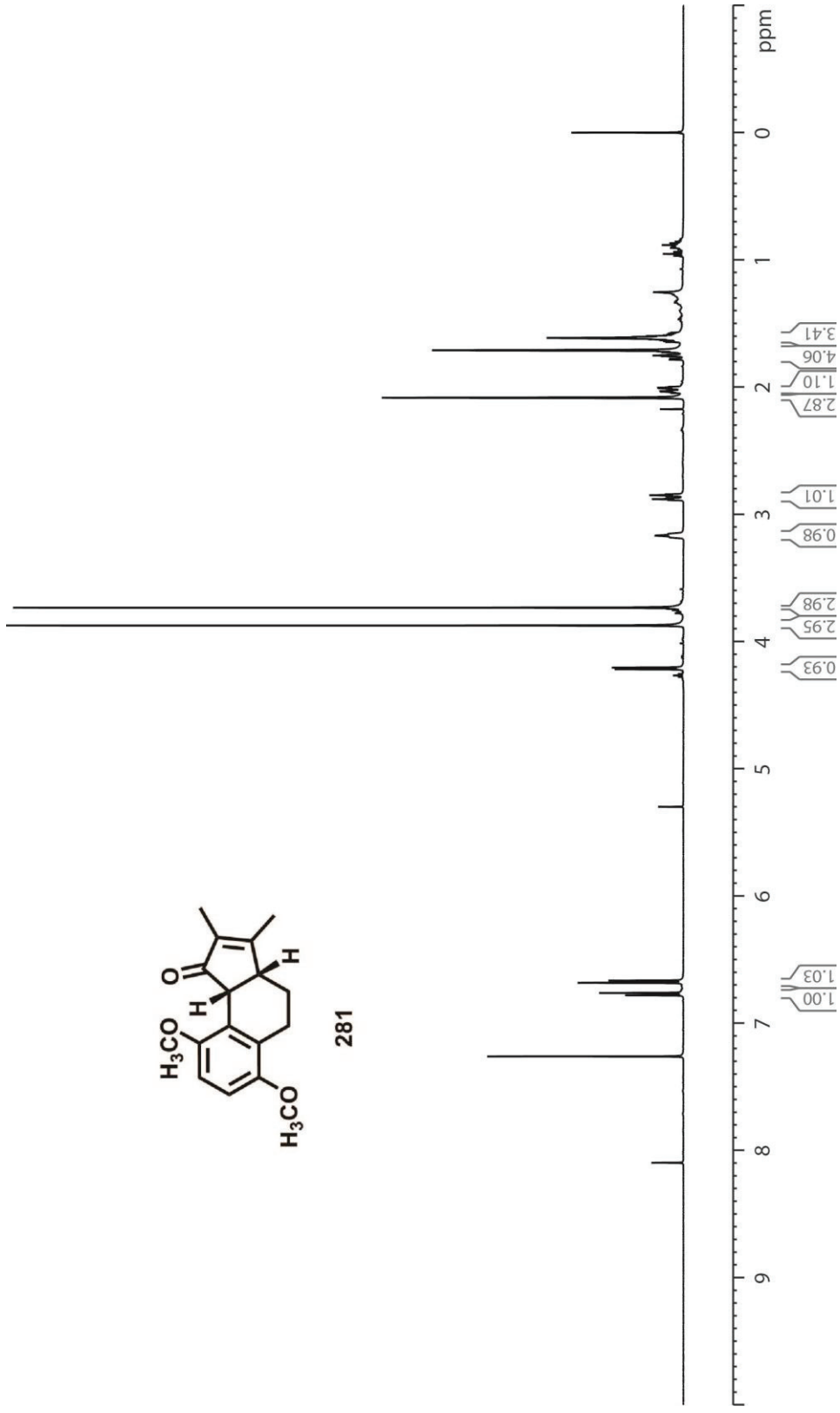
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (*E*)-8-(2,5-dimethoxyphenyl)-3-methylocta-1,2,5-trien-4-one (280)**



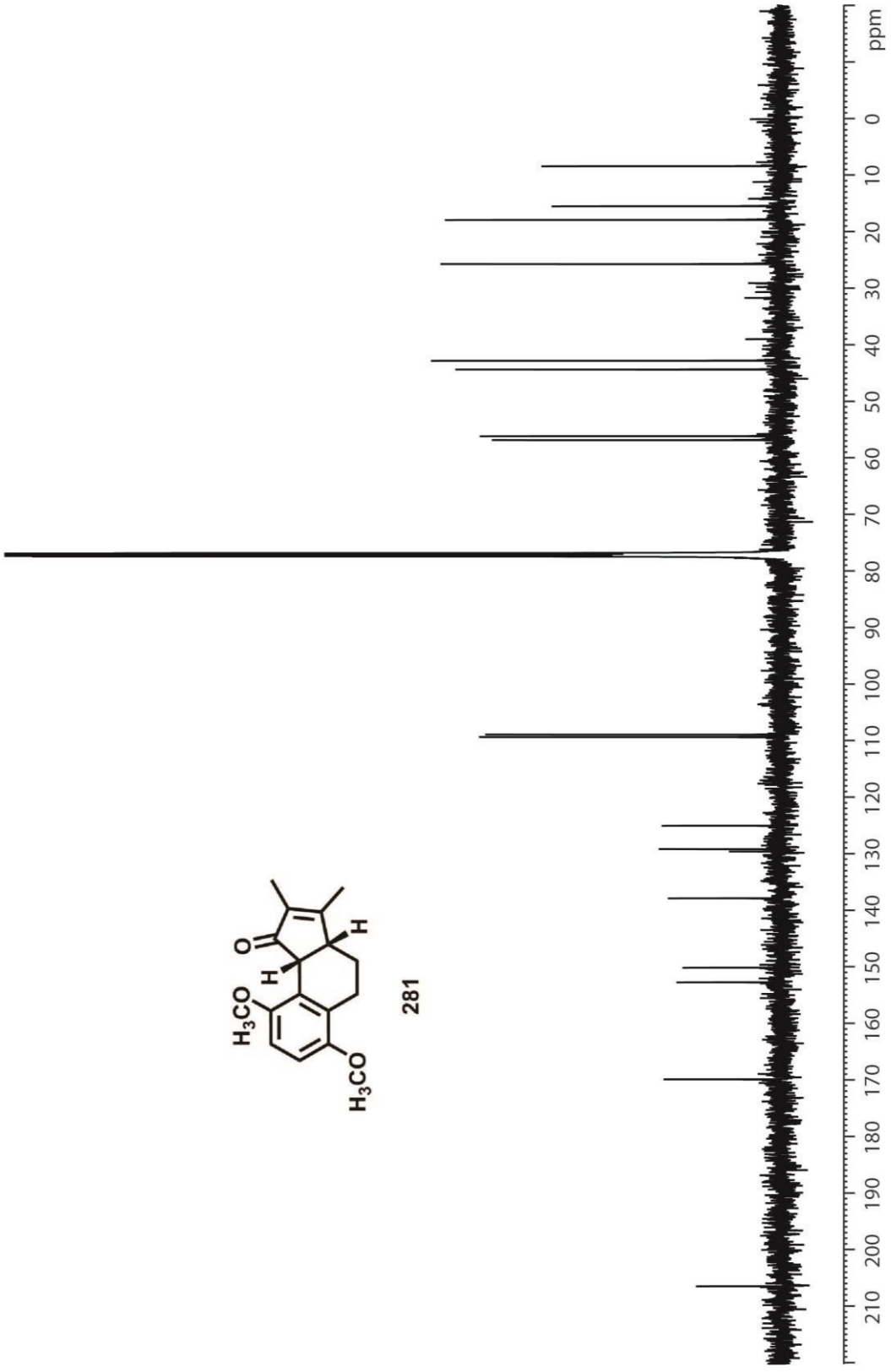
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (*E*)-8-(2,5-dimethoxyphenyl)-3-methylocta-1,2,5-trien-4-one (280)**



**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (3a*R**,9b*R**)-6,9-dimethoxy-2,3-dimethyl-3a,4,5,9b-tetrahydro-1*H*-cyclopenta[*a*]naphthalen-1-one (281)**



**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (3a*R**,9b*R**)-6,9-dimethoxy-2,3-dimethyl-3a,4,5,9b-tetrahydro-1*H*-cyclopenta[*a*]naphthalen-1-one (281)**

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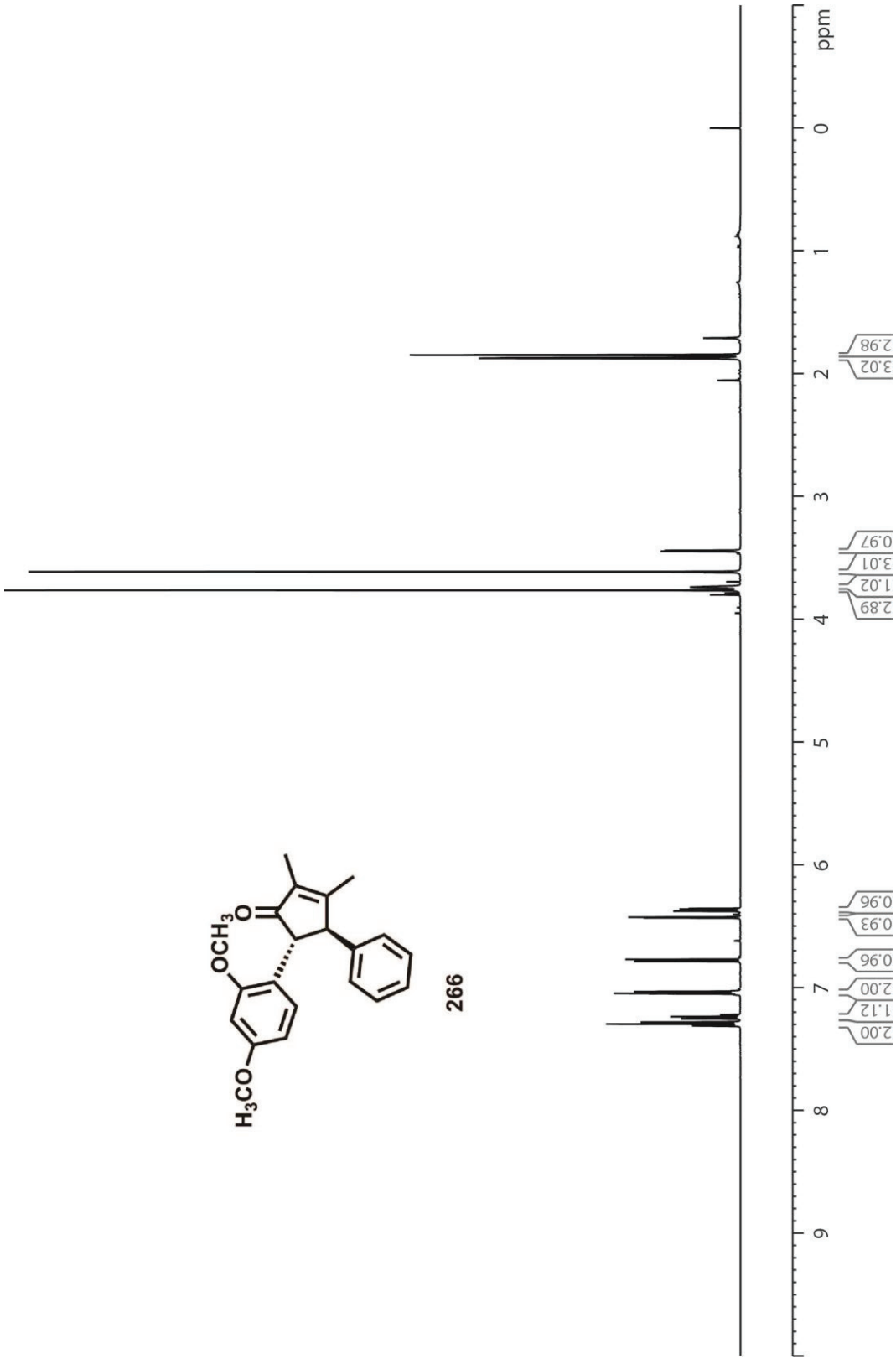
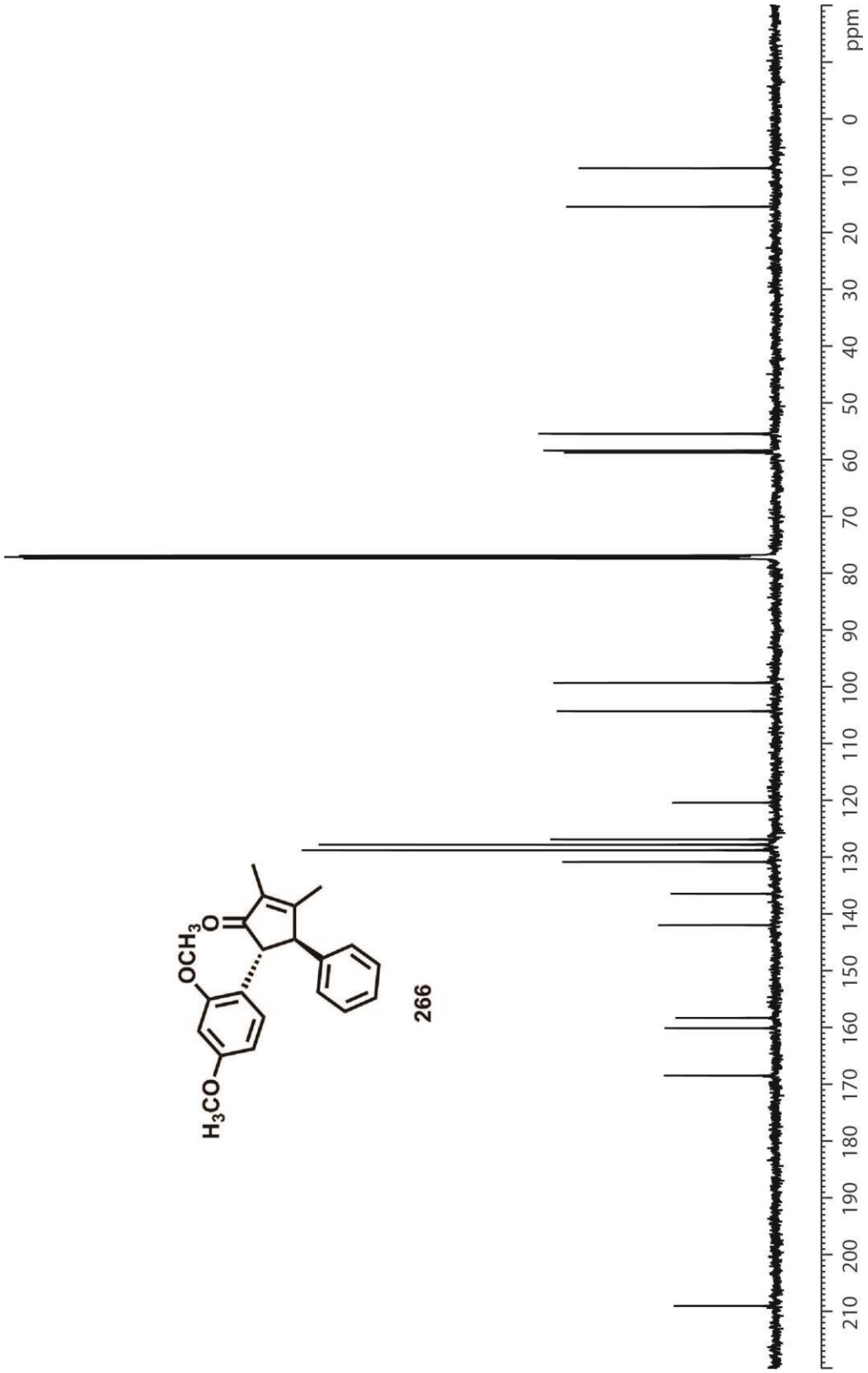
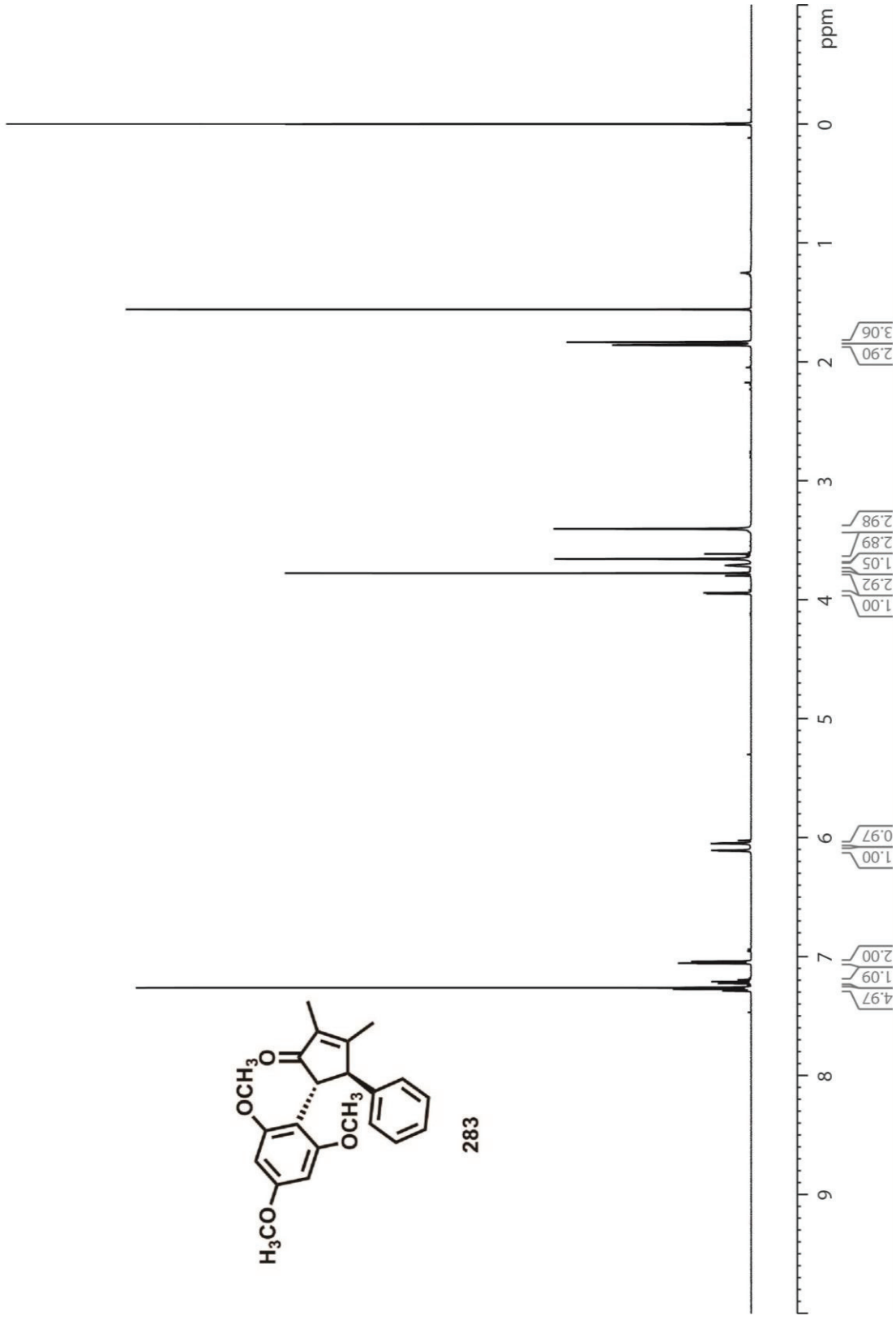
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (4*R**, 5*R**)-5-(2,4-dimethoxyphenyl)-2,3-dimethyl-4-phenylcyclopent-2-enone (266)**



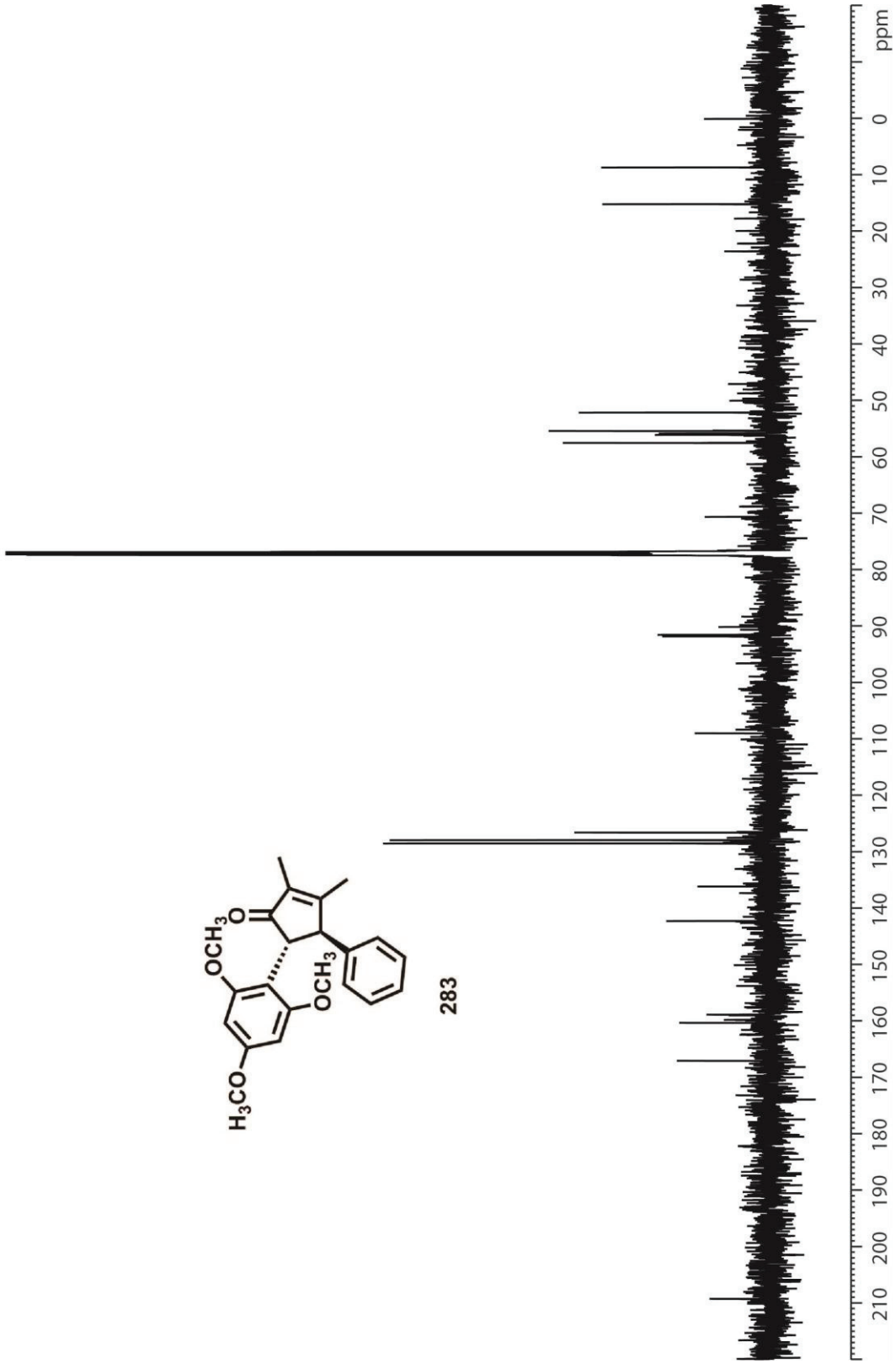
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (4*R**, 5*R**)-5-(2,4-dimethoxyphenyl)-2,3-dimethyl-4-phenylcyclopent-2-enone (266)**



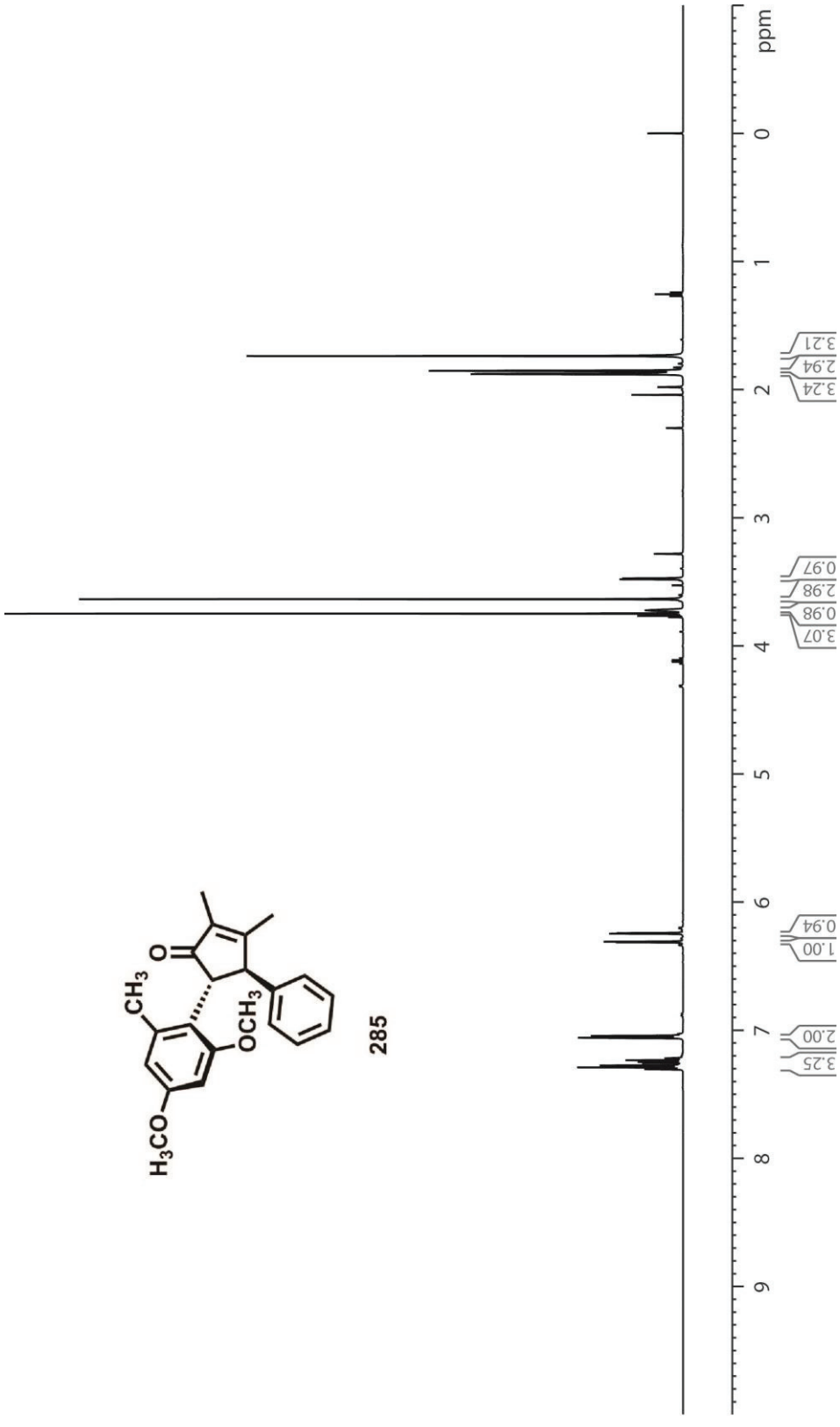
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (4*R**, 5*R**)-2,3-dimethyl-4-phenyl-5-(2,4,6-trimethoxyphenyl)cyclopent-2-enone (283)**



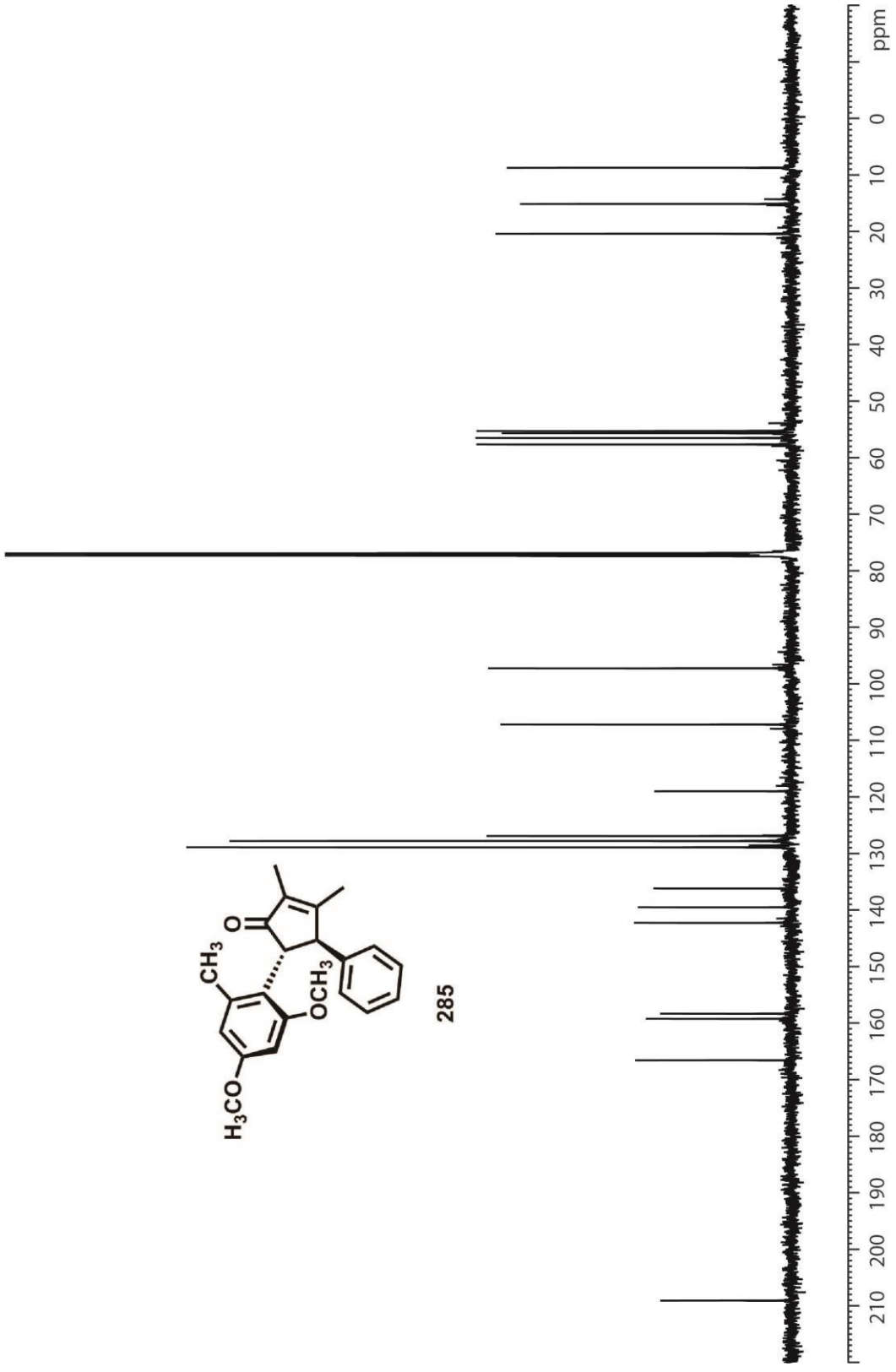
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (4*R**, 5*R**)-2,3-dimethyl-4-phenyl-5-(2,4,6-trimethoxyphenyl)cyclopent-2-enone (283)**



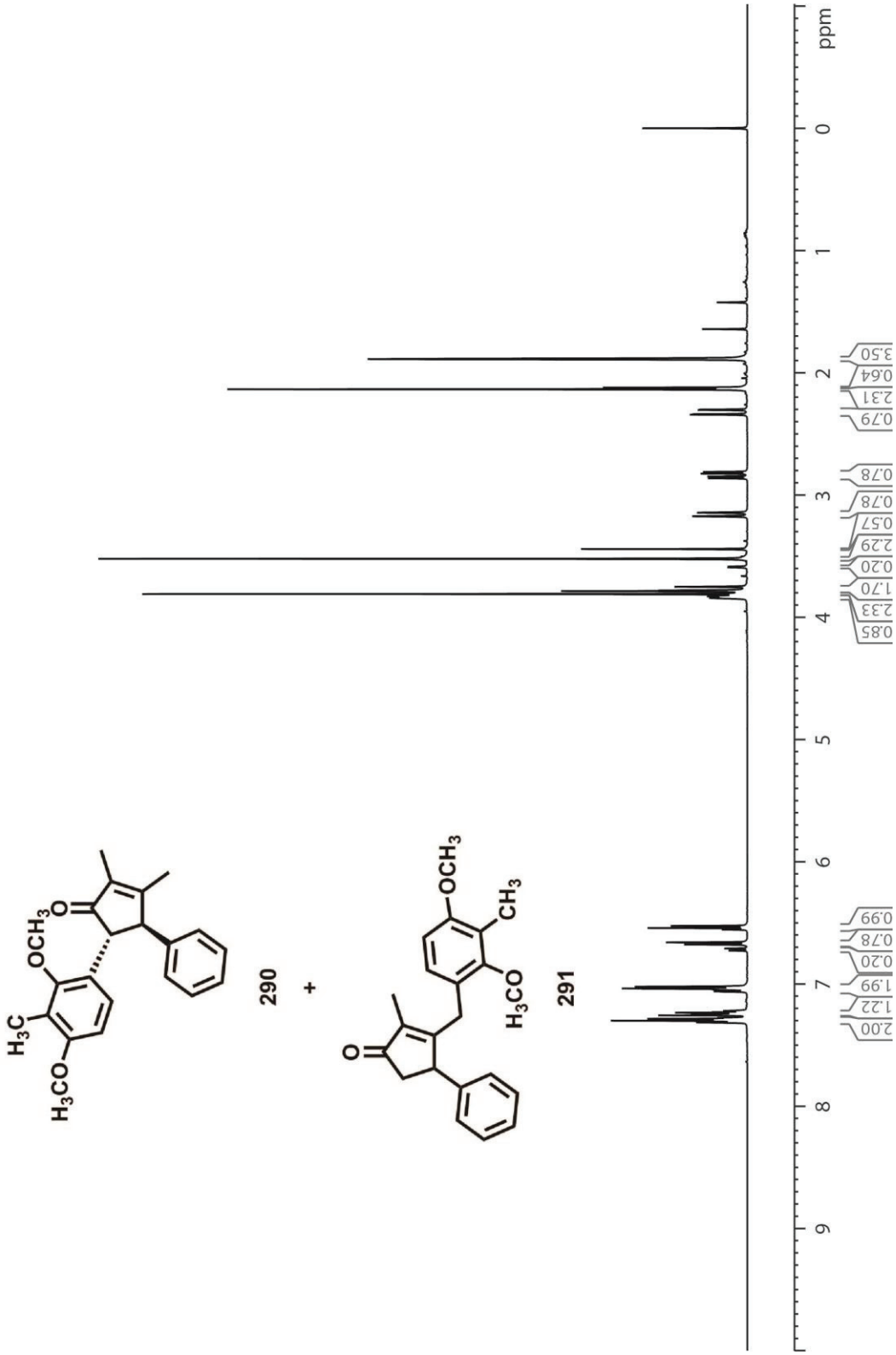
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (4*R**, 5*R**)-5-(2,4-dimethoxy-6-methylphenyl)-2,3-dimethyl-4-phenylcyclopent-2-enone (285)**



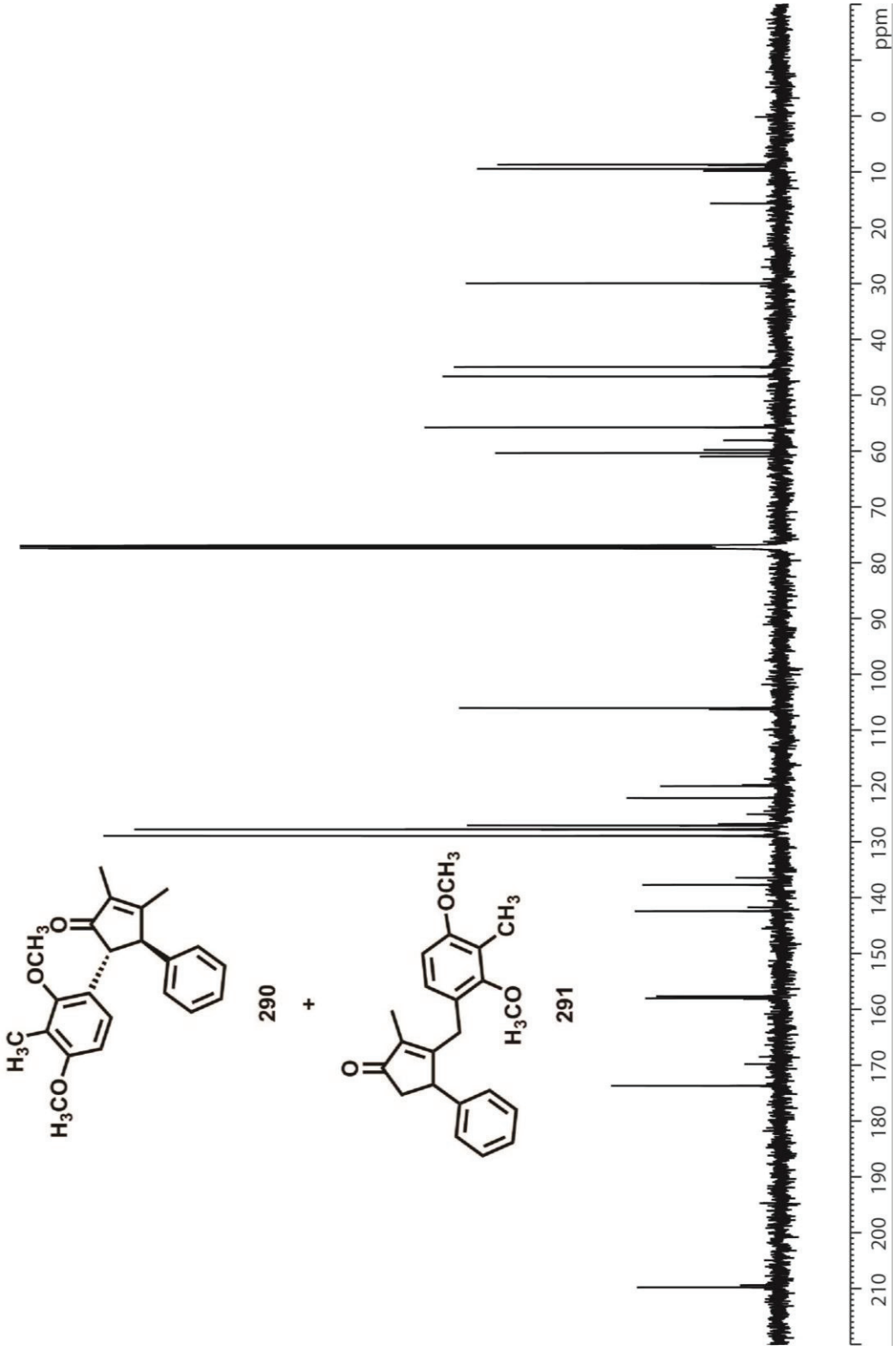
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (4*R**, 5*R**)-5-(2,4-dimethoxy-6-methylphenyl)-2,3-dimethyl-4-phenylcyclopent-2-enone (285)**



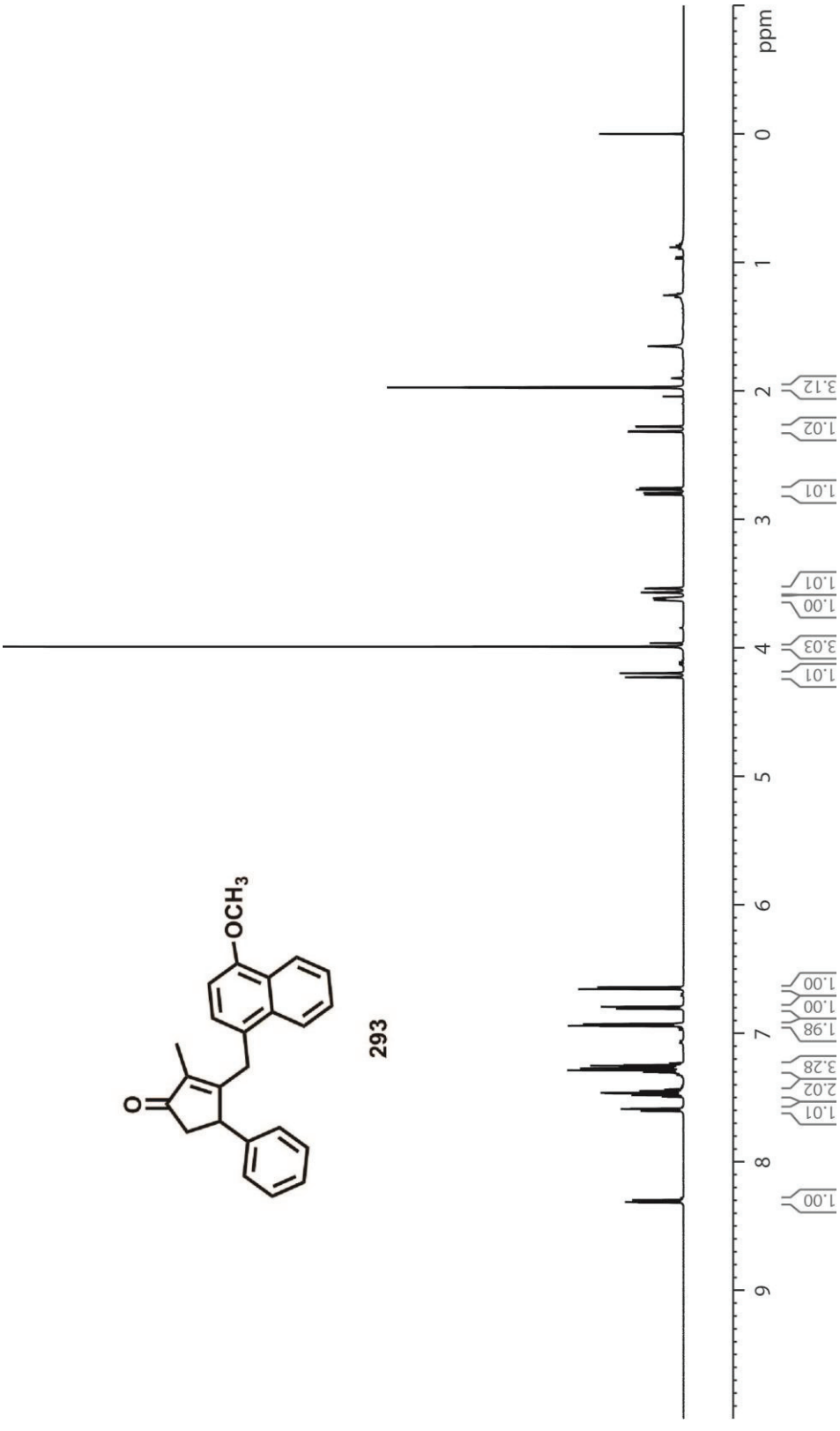
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (4*R**, 5*R**)-5-(2,4-dimethoxy-3-methylphenyl)-2,3-dimethyl-4-phenylcyclopent-2-enone (290) + 3-(2,4-dimethoxy-3-methylbenzyl)-2-methyl-4-phenylcyclopent-2-enone (291)**



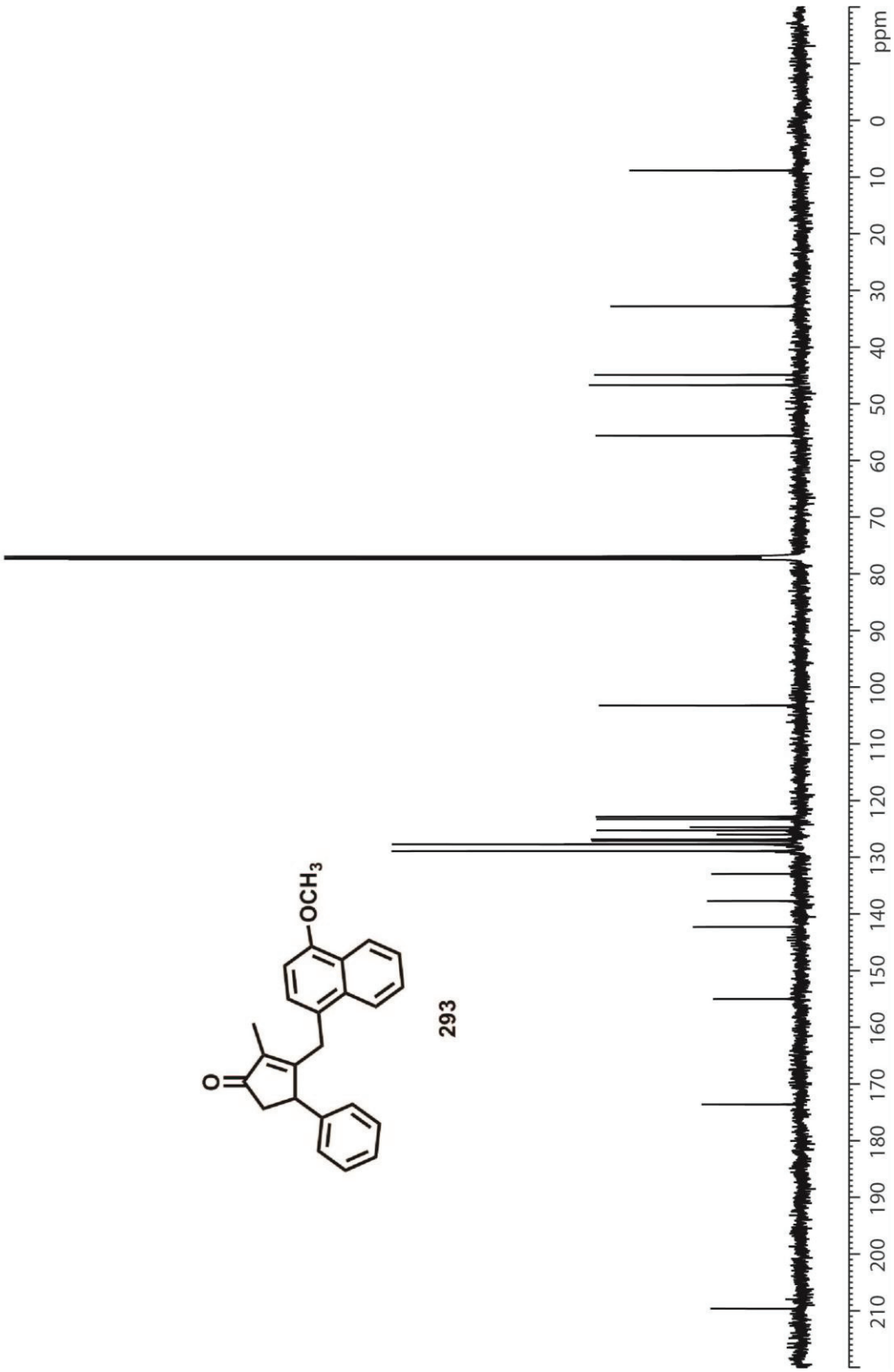
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (4*R**, 5*R**)-5-(2,4-dimethoxy-3-methylphenyl)-2,3-dimethyl-4-phenylcyclopent-2-enone (290) + 3-(2,4-dimethoxy-3-methylbenzyl)-2-methyl-4-phenylcyclopent-2-enone (291)**



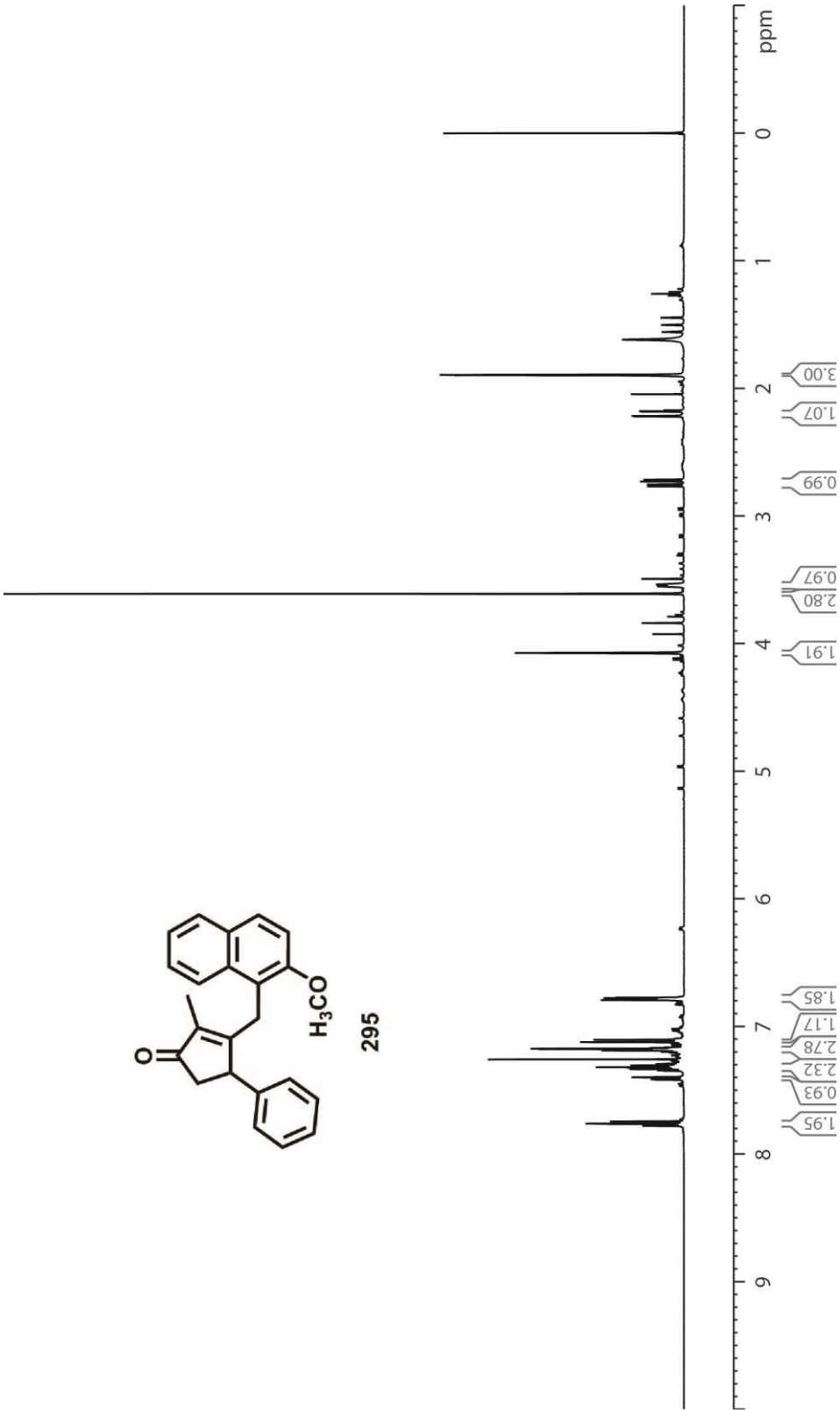
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of 3-((4-methoxynaphthalen-1-yl)methyl)-2-methyl-4-phenylcyclopent-2-enone (293)**



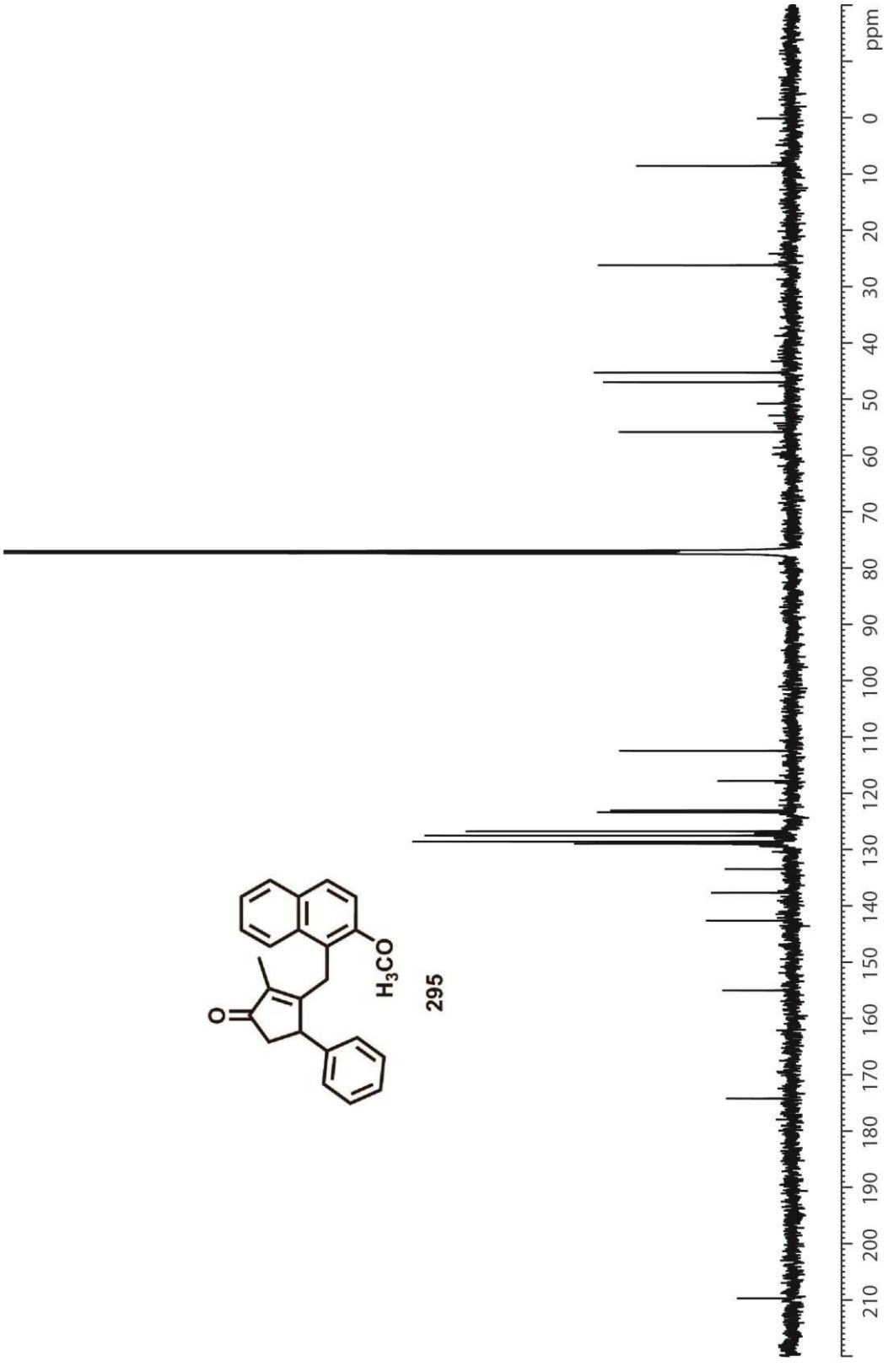
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of 3-((4-methoxynaphthalen-1-yl)methyl)-2-methyl-4-phenylcyclopent-2-enone (293)**



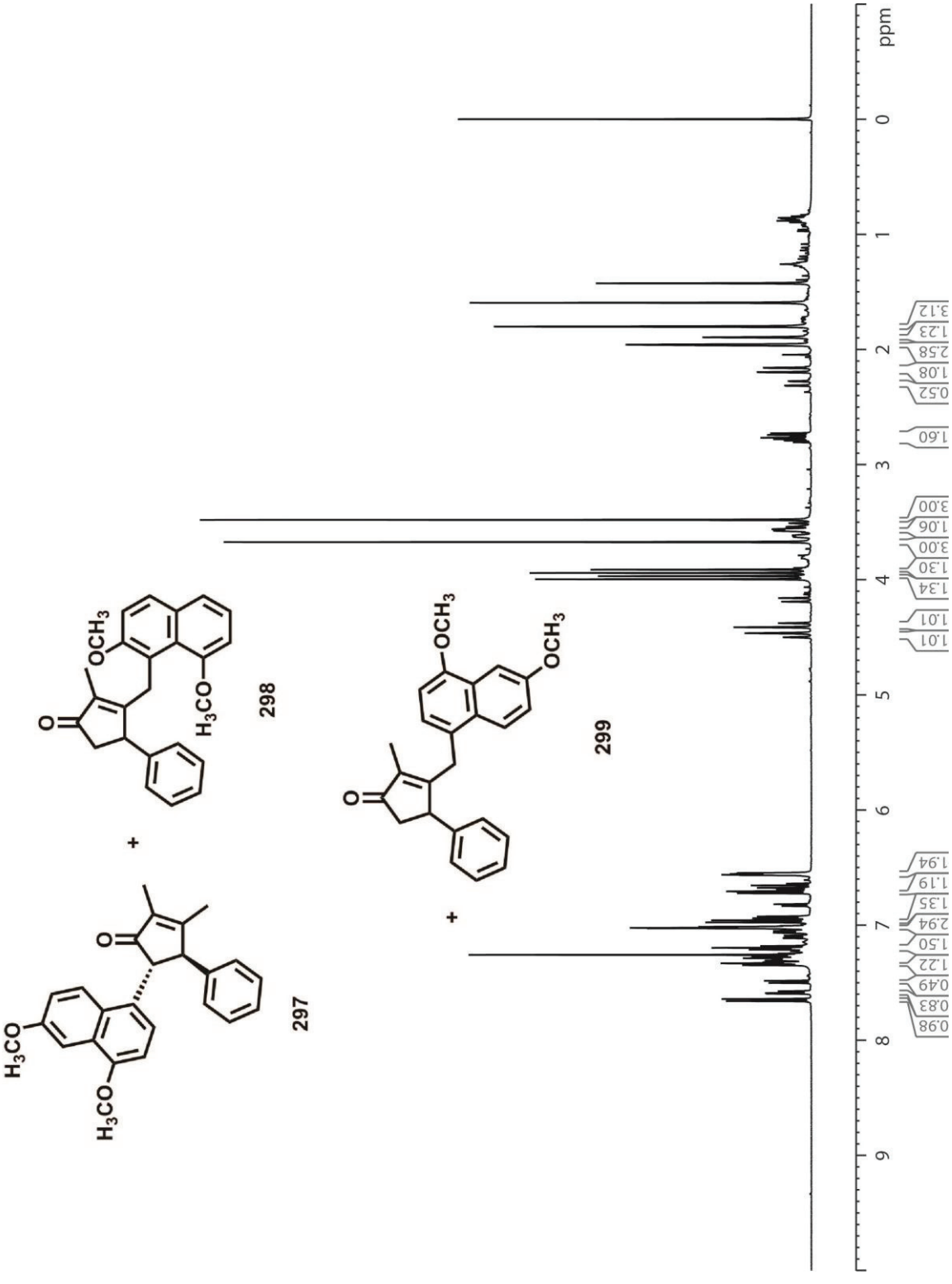
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of 3-((2-methoxynaphthalen-1-yl)methyl)-2-methyl-4-phenylcyclopent-2-enone (295)**



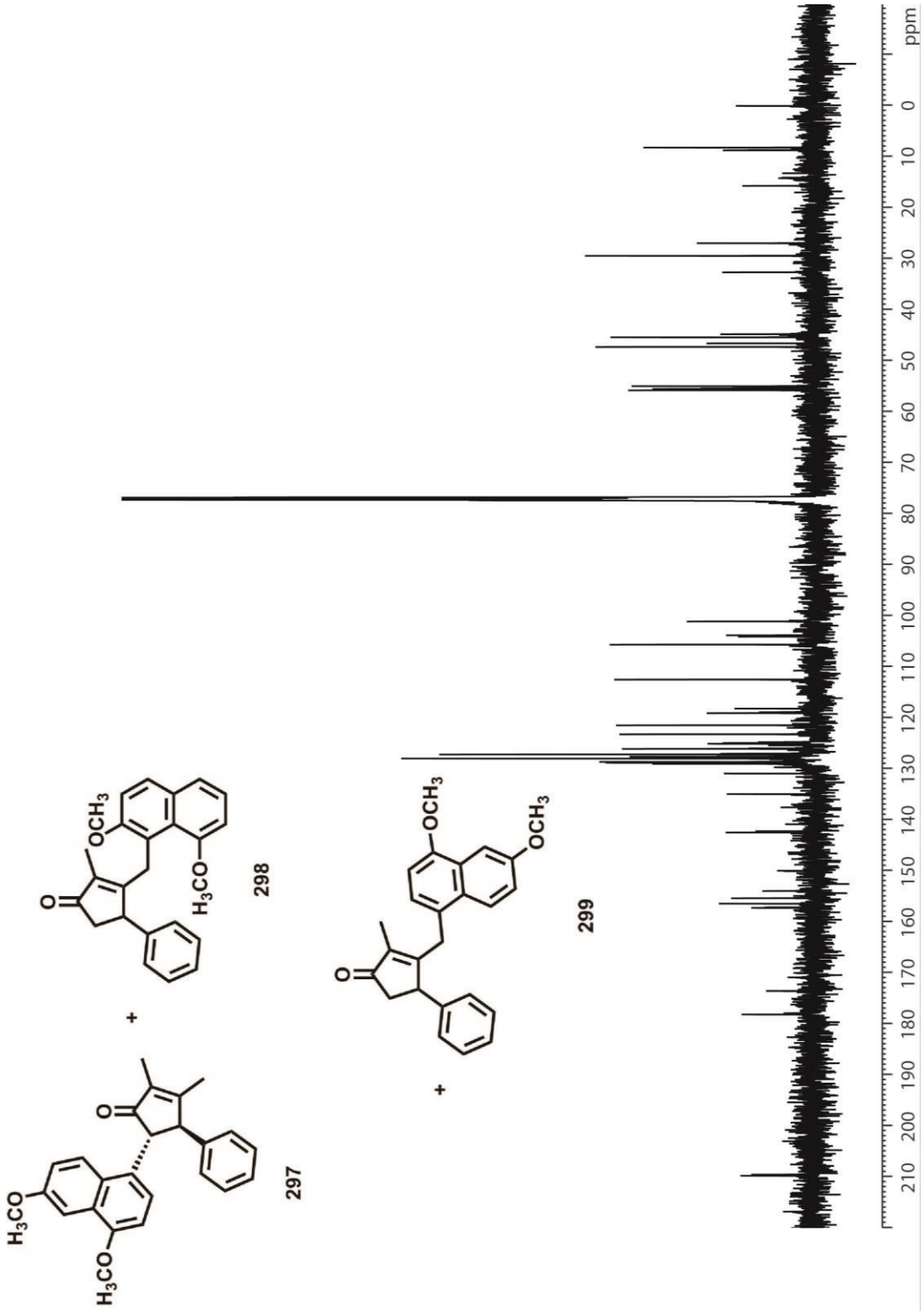
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of 3-((2-methoxynaphthalen-1-yl)methyl)-2-methyl-4-phenylcyclopent-2-enone (295)**



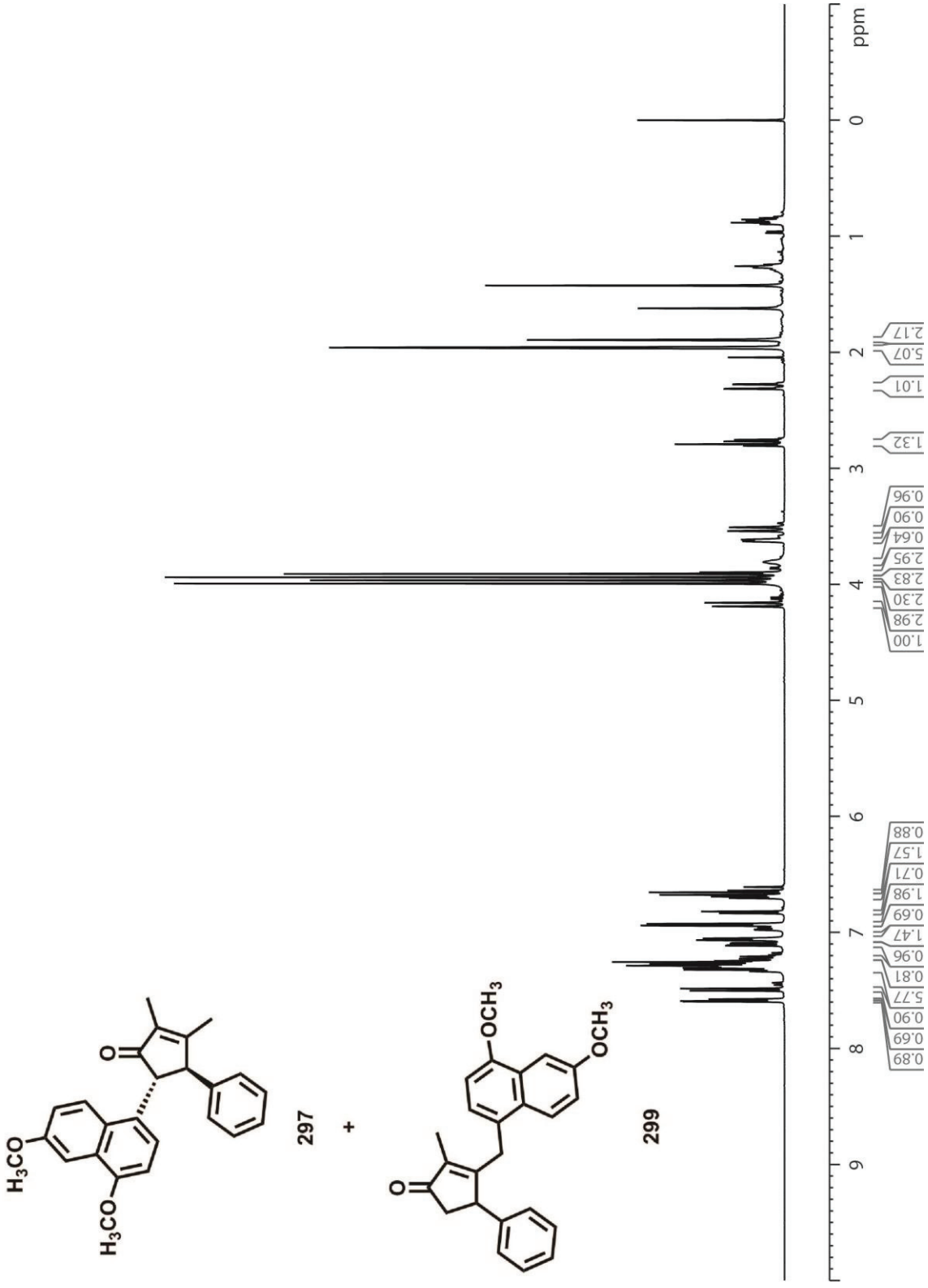
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (4*R**, 5*R**)-5-(4,6-dimethoxynaphthalen-1-yl)-2,3-dimethyl-4-phenylcyclopent-2-enone (297) + 3-((4,6-dimethoxynaphthalen-2-yl)methyl)-2-methyl-4-phenylcyclopent-2-enone (298) + 3-((4,6-dimethoxynaphthalen-1-yl)methyl)-2-methyl-4-phenylcyclopent-2-enone (299)**



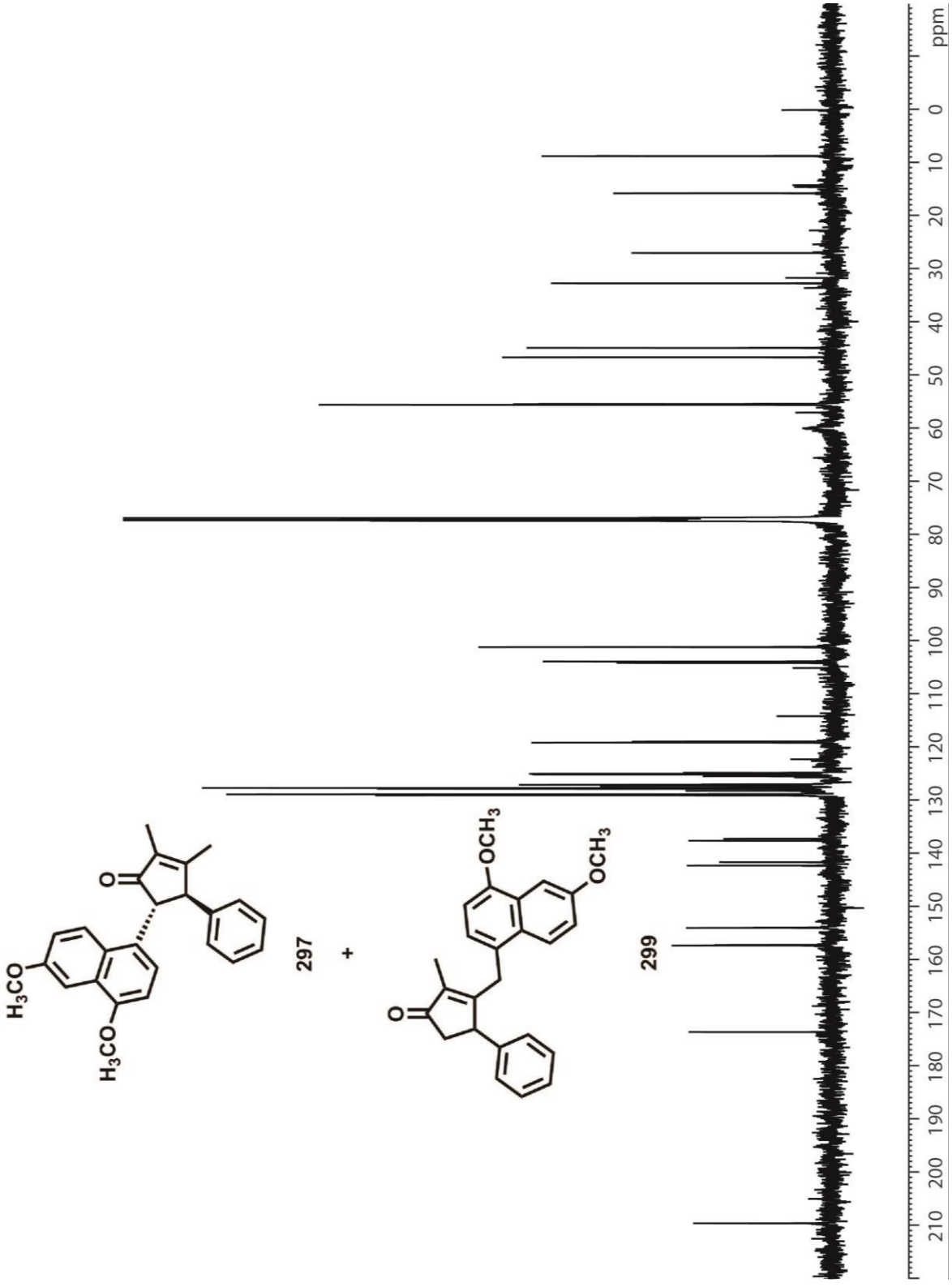
**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (4*R**, 5*R**)-5-(4,6-dimethoxynaphthalen-1-yl)-2,3-dimethyl-4-phenylcyclopent-2-enone (297) + 3-((4,6-dimethoxynaphthalen-2-yl)methyl)-2-methyl-4-phenylcyclopent-2-enone (298) + 3-((4,6-dimethoxynaphthalen-1-yl)methyl)-2-methyl-4-phenylcyclopent-2-enone (299)**



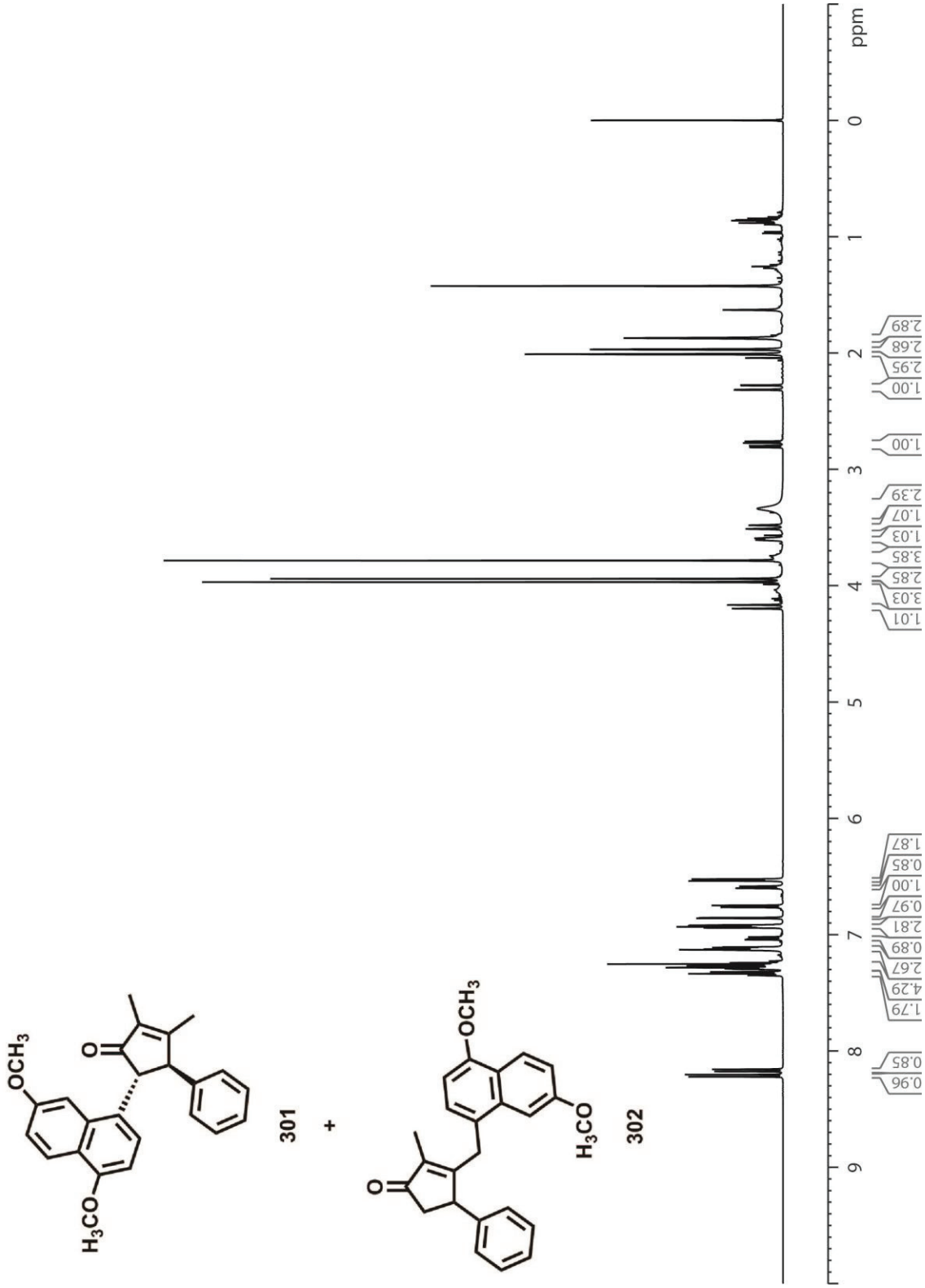
**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (4*R**, 5*R**)-5-(4,6-dimethoxynaphthalen-1-yl)-2,3-dimethyl-4-phenylcyclopent-2-enone (297) + 3-((4,6-dimethoxynaphthalen-1-yl)methyl)-2-methyl-4-phenylcyclopent-2-enone (299)**



**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (4*R**, 5*R**)-5-(4,6-dimethoxynaphthalen-1-yl)-2,3-dimethyl-4-phenylcyclopent-2-enone (297) + 3-((4,6-dimethoxynaphthalen-1-yl)methyl)-2-methyl-4-phenylcyclopent-2-enone (299)**



**$^1$H NMR ($CDCl_3$, 500 MHz) spectrum of (4*R**, 5*R**)-5-(4,7-dimethoxynaphthalen-1-yl)-2,3-dimethyl-4-phenylcyclopent-2-enone (301) + 3-((4,7-dimethoxynaphthalen-1-yl)methyl)-2-methyl-4-phenylcyclopent-2-enone (302)**



**$^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of (4*R**, 5*R**)-5-(4,7-dimethoxynaphthalen-1-yl)-2,3-dimethyl-4-phenylcyclopent-2-enone (301) + 3-((4,7-dimethoxynaphthalen-1-yl)methyl)-2-methyl-4-phenylcyclopent-2-enone (302)**