Halonium-Induced Reactions for the Synthesis of Diverse Molecular Scaffolds

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ABSTRACT

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Chapter 1. Introduction

A vast number of halogenated natural products have been isolated to date that contain unique structural and electronic characteristics due to the installed halogen. These properties not only aid in their bioactivity, but also put into question nature's biosynthesis of these complex molecules. Nature's ability to install halogens in a direct and concise manner has inspired our group to seek out chemical transformations that accomplish the same efficiency in the context of synthesizing complex natural products. Specifically, our group has targeted challenges in the areas of halonium-induced polyene cyclization, asymmetric halonium addition to alkenes, and medium-sized bromoether formation, as having access to such transformations would further facilitate total syntheses of these halogenated isolates.

Chapter 2. Discovery of IDSI and Iodonium- and Chloronium-Induced Polyene Cyclizations

Only a few electrophilic iodonium reagents have proven capable of inducing polyene cyclization of linear terpene precursors, though, to date, these only include substrates with electron rich functional groups. Due to this, we targeted development of a new iodonium reagent, IDSI. This easily synthesized, isolable solid has promoted cyclization of both electron rich and poor linear polyene precursors in good yields and

diastereoselectivities. The produced iodinated cores allow for further diversification as demonstrated in the formal synthesis of loliolide, stemodin, and K-76. In general, the use of IDSI in previous routes decreases step count, increases overall yields, and avoids the use of stoichiometric amounts of toxic metals. In addition, the chloronium variant, CDSC, completed the first polyene cyclization ever to be initiated by a chloronium electrophile.

Chapter 3. Enantioselective Iodohydrin Formation using Simple Alkenes

With the development of our halonium reagents, BDSB (the bromonium variant), IDSI, and CDSC, we next varied the synthesis of each reagent to include an asymmetric component. While their use in polyene cyclization only produced racemic materials, the iodohydroxylation of simple alkenes provided up to 63% ee with only a select substrate. Yet, this chiral IDSI reagent is one of only a handful of strategies capable of transferring an iodonium electrophile with moderate enantioselectivity (above 50% ee).

Chapter 4. Discovery and Development of a Bromonium-Induced Ring Expansion to Rapidly Produce *Laurencia* Medium-Sized Bromoethers

By analyzing the hypothesized biosynthesis of the *Laurencia* natural isolates, we realized the proposed direct 8-membered bromoetherification from a linear precursor was most likely an unfavorable event, leading us to investigate an alternative idea. Discovery of a unique bromonium-induced ring expansion method generated 8-membered bromoethers diastereoselectively in a single step in good yields. From easily prepared tetrahydrofuran precursors, a variety of diastereomers of 8-*endo* and 8-*exo* bromoethers

were generated selectively, modeling the cores of over half of the medium-sized isolates. This method was then expanded to include diastereoselective synthesis of 9-membered bromoethers, also found in the *Laurencia* family.

Chapter 5. Formal Total Synthesis of Laurefucin and Evaluation of the Proposed Biosynthesis of Medium-Sized *Laurencia* Bromoethers

The BDSB-induced ring expansion strategy was then used as the key step in the completed formal total synthesis of laurefucin, an 8-*endo* bromoether in the *Laurencia* natural products. By utilizing this method, we have developed the shortest synthesis of any 8-membered bromoether isolate in the family to date. Due to the breadth of products this transformation has generated, we believe this bromonium-induced ring expansion may have biosynthetic relevance. Our proposed biosynthesis could account for generation of not only the 8-membered bromoethers, but also additional 5-, 7- and 9-membered ethers found in the family. Additional experiments were completed to support this pathway, including mimicking enzymatic conditions as well as intercepting the proposed intermediates.

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Chapter 5. Formal Total Synthesis of Laurefucin and Evaluation of the Proposed Biosynthesis of Medium-Sized *Laurencia* Bromoethers

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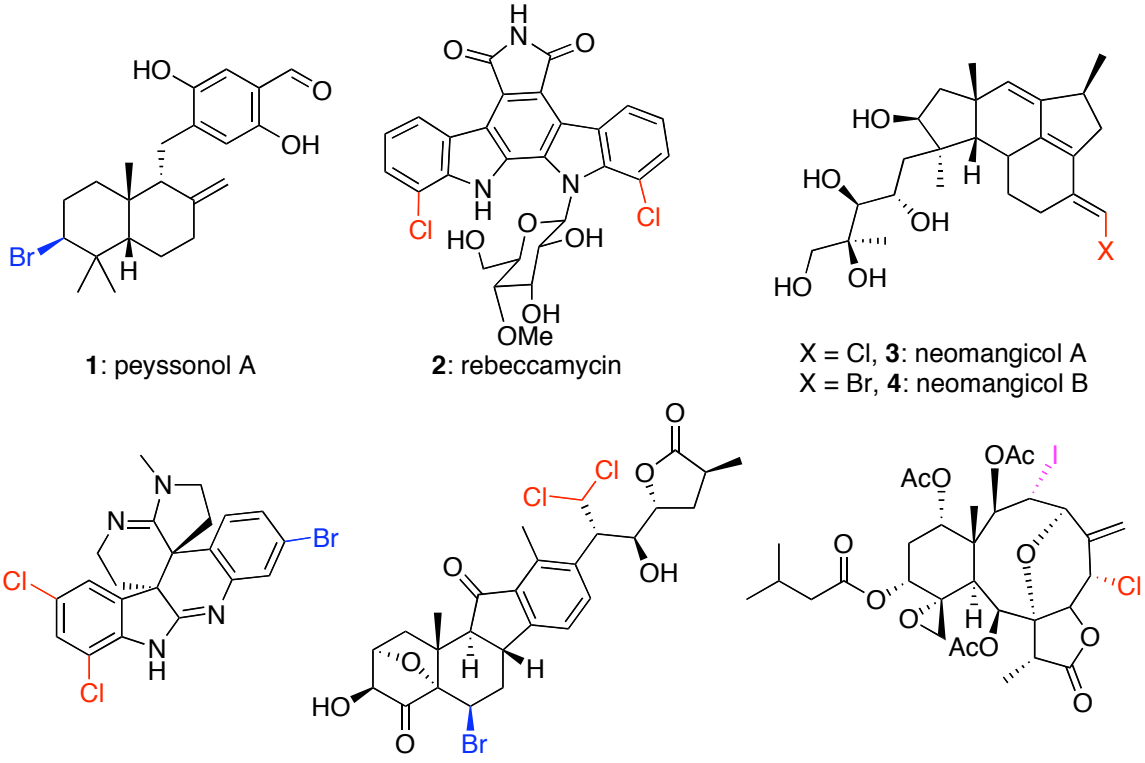
CHAPTER 1

Introduction

1.1 Halogenated Natural Products

To date, there are over 4,500 isolated natural products that contain at least one halogen atom.[1] Moreover, their positioning within these frameworks is quite diverse, alpha to carbonyls, or attached to arenes, sp^3 rings, or even linear precursors, with some examples shown in Figure 1.[2] Chlorine and bromine are the most abundant overall, present in over 98% of these halogen-containing isolates. There are a few examples of iodine- and fluorine-containing natural products, though comparatively they are few and far between. These isolates typically contain a broad range of biological activity, and in general the installed halogen is responsible for the unique structural and electronic characteristics of these compounds, potentially even including elements of their bioactivity.



1: peyssonol A

2: rebeccamycin

X = Cl, **3**: neomangicol A
X = Br, **4**: neomangicol B

5: (+)-perophoramidine

6: nakiterpiosinone

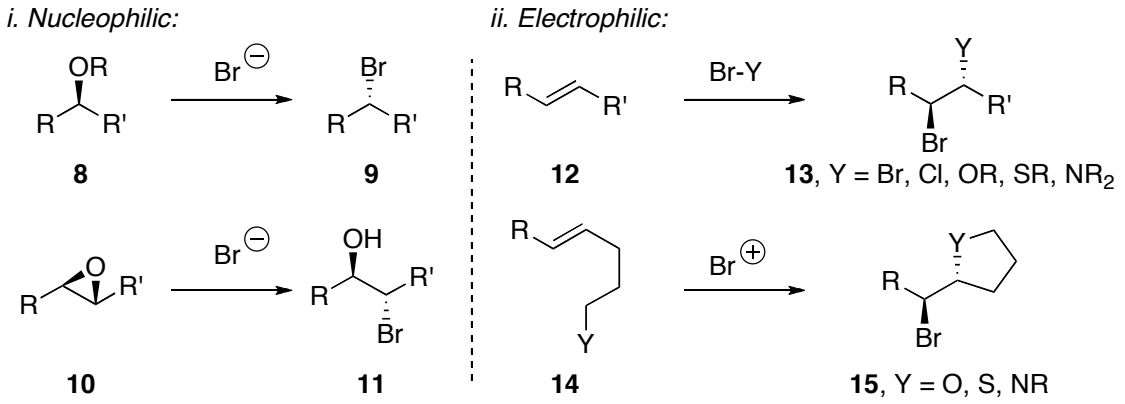
7: dichotellides A

Figure 1: Selected Natural Products Containing a Halogen

As one example of this halogen-dependent bioactivity, rebeccamycin (**2**) requires its chloride substituents to display its potent cytotoxicity against melanoma and leukemia lines; synthesized derivatives that lack these halogens are magnitudes less active and, in some cases where additional structural changes have been made, completely inactive in the same assay.[3] Likewise, neomangicol A and B (**3** and **4**), the first examples of halogenated sesterterpenoid natural products, show cytotoxicity against human colon tumor cell lines.[4] Yet, this effect was lost when the non-halogenated derivative of these natural products was tested, demonstrating the unique and important properties that these functional groups possess.

Critically, in these cases, the non-halogenated derivatives could not have been accessed without the power of total synthesis; in addition, total synthesis allows for the preparation of larger quantities of a given molecule of interest for testing. Overall, for most halogenated targets, their synthesis requires the addition of the halogen atom via an S_N2 reaction (Scheme 1). Nucleophilic bromide (or other halide) displacement of a leaving group or an epoxide thus incorporates the desired halide with stereoinversion (**8** to **9** and **10** to **11**). Typically, the presence of a bromide, chloride, or iodide atom is considered a reactive handle, allowing for further diversification of complex molecules; yet, when this halide is desired in the final product, late stage installation is often required, a task that can be accomplished by nucleophilic addition through careful planning. An alternate mode of halogen inclusion is electrophilic halonium addition to an alkene. In this case, following halonium addition to an olefin, the reactive intermediate could be quenched by an intermolecular halide or heteroatom to yield derivatives of **13**,

or instead by an intramolecular nucleophile in a net halonium-induced cyclization reaction (i.e. **14** to **15**), the topic of discussion for Chapters 2, 4, and 5.



Scheme 1: Synthetic Methods for Halogenation

While in a laboratory flask halides are great nucleophiles, in nature, there are few carbon electrophiles, making nucleophilic halogenation a rare event.[5] Instead, nature turns to a two-electron oxidation of these halide anions to the corresponding electrophilic halonium ions, accounting for the abundant halonium-induced cyclizations found in biosynthetic hypotheses via nucleophilic attack of substrates onto these materials.[6] My work in Prof. Scott Snyder's research group at Columbia University has been focused on the discovery of novel reagents and transformations to access halogenated motifs found in natural products, with the main topics:

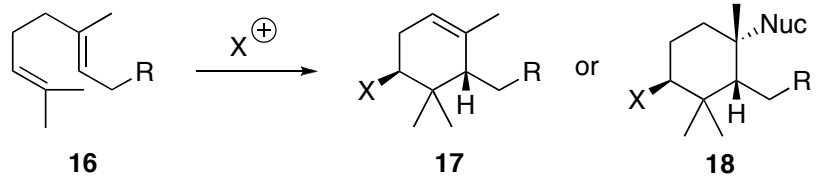
- Halonium-induced polyene cyclizations
- Asymmetric halonium addition to unfunctionalized alkenes
- Formation of *Laurencia* medium-sized haloethers

The main objectives have been to develop robust reactions with high regio- and stereocontrol which are capable of completing total syntheses of complex molecules in a concise and efficient manner, often mimicking nature's biogenesis of these materials, but making use of the first approaches that have proven broadly successful.

1.2 Halonium-Induced Polyene Cyclization

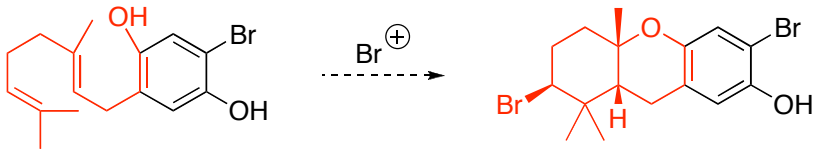
The intramolecular cyclization example shown in Scheme 1 in Section 1.1 uses a heteroatom as the nucleophile to generate final products such as lactones, lactams, ethers, and cyclic amines (i.e. **14** to **15**). These processes, in general, are well-studied with numerous comprehensive reviews covering these halonium-induced cyclization reactions.[7] However, when the internal nucleophile is an alkene, a new C-C bond could be formed (i.e. **16** to **17** or **18**, Scheme 2i). The generation of this newly formed carbocycle is termed polyene cyclization, a reaction that allows multiple stereocenters to be constructed at once in a controlled fashion.[8] While polyene cyclizations initiated by epoxides or Brønsted acids are well known in multiple formats, little success has been achieved in the halonium-induced variant of the process.[9] If this technology were available, chemists would have access to the over 200 isolates derived from, or believed to arise via, a halonium-induced polyene cyclization in nature (Scheme 2ii).[10]

i. General Reaction

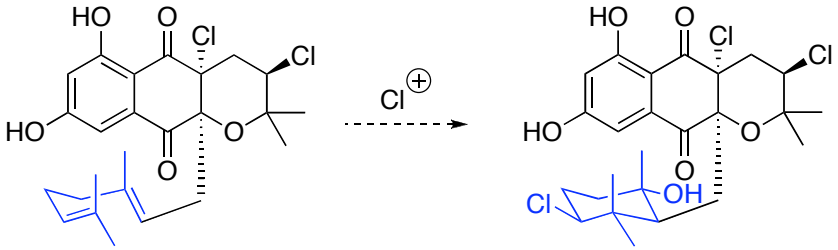


16 **17** **18**

ii. Polyene Cyclization in Nature



19: cymopol **20:** 4-isocymobarbatol



21: napyradiomycin A1 **22:** napyradiomycin B4

Scheme 2: A Representative Example of Polyene Cyclization and Natural Isolates Derived from a Halonium-Induced Polyene Cyclization

While total syntheses of these halogen-containing isolates have been completed, very few generate the core carbocycle via a direct halonium-induced cyclization reaction; instead, cyclization with stoichiometric Hg(II), followed by stereoretentive replacement, has afforded these substrates.[11] The reason for this is due to poor yields and selectivities using known halonium reagents, a topic that will be discussed further in Chapter 2. Additionally, while bromonium-[12] or iodonium-initiated[13] cyclizations are known (though only when using electron rich alkenes), there has yet to be a reported example of a direct chloronium-induced polyene cyclization.[14] As such, no general solution exists in which each halonium variant (Cl, Br, and I) is capable of generating carbocycles diastereoselectively in good yields. The targeted goal in this project was to develop a new halonium reagent class with the ability to induce polyene cyclization reactions for

both electron rich and poor linear polyene precursors, thereby affording more efficient access to an array of bioactive natural products and analogs.

1.3 Enantioselective Halonium Addition

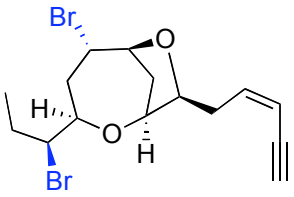
When analyzing the collection of known halonium-induced polyene cyclization discussed in the previous section, only a single example generates enantioselective products in any level of ee.[13a] Nevertheless, most of the isolated halogen-containing natural products are chiral; suggesting that nature installs these halogens asymmetrically since the rest of the structure is produced following halonium introduction. More generally, while X_2 addition to alkenes was discovered over 100 years ago,[15] chemists are still challenged by achieving asymmetry in this process.[16] Even if chiral halonium sources are developed, there are major factors that can erode enantioselectivity in ways not typical for other electrophiles, a topic to be discussed in further detail in Chapter 3. Chemists have solved this problem in some instances through the use of a bifunctional chiral catalyst that coordinates both the nucleophile and electrophile. Although high asymmetry can be achieved, only modest substrate scopes and a single halogen atom typically can be used for each given set of conditions. Additionally, the substrates generally need a nearby functional group for chelation to the chiral catalyst; only one example of enantioselective X_2 addition with high ee to an unfunctionalized alkene is known.[17] Due to the lack of successful literature precedent on this topic, we pursued approaches for the asymmetric halogenation with the hope that new classes of highly reactive halonium reagents would be unique in their ability to add X_2 to a variety of

alkenes and generate enantiopure 1,2-dihalides and/or related materials such as halohydrins.

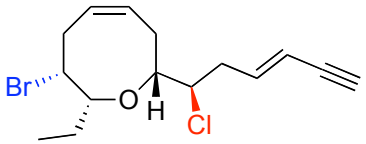
1.4 *Laurencia* Medium-Sized Bromoether Cores

While the direct asymmetric halogenation of alkenes is noticeably absent in the literature, numerous methods exist to generate halolactones and haloethers with synthetically useful enantioselectivities.[16] These halocyclization reactions may have utility in synthesis of the *Laurencia* medium-sized bromoethers. The *Laurencia* C15 acetogenins are one of the largest groups of halogenated natural products comprising of over 100 compounds.[18] Within this family, the medium-sized rings (i.e. 7-, 8-, and 9-membered ethers) make up over half of these molecules, with the 8-membered ethers encompassing at least 50 substrates itself (Scheme 3i).

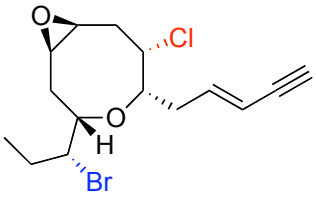
i. Natural Products



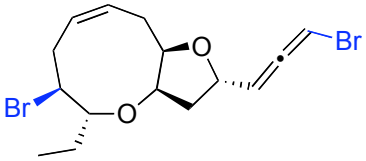
22: neoisoprelaurefucin



23: laurepinnacin

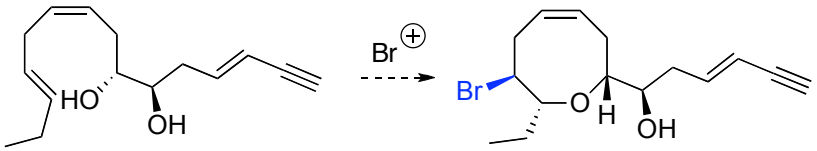


24: epoxy-*trans*-isodihydrorhodophytin



25: neolaurallene

ii. Proposed Biosynthesis



26: *R*,*R*-laurediol

27: deacyllaurencin

Scheme 3: Selected Natural Products from the *Laurencia* Family and Proposed Biosynthesis

The proposed biosynthesis for these compounds in nature involves a direct bromoetherification of a linear precursor to a medium-sized bromoether (Scheme 3ii);[19] yet in the over 30 total syntheses of these isolates, none generate the core via the same direct process.[20] The challenge here lies in the formation of medium-sized rings, difficult because of both entropic and enthalpic barriers;[21] only a small number of haloetherifications to generate medium-sized rings exist in the literature.[22] Additionally, that halogen electrophile must add regioselectively to a substrate with multiple nucleophilic sites (such as in **26**). We hoped to follow nature's lead in using a direct bromonium-induced cyclization event to complete a more expedient synthesis of these isolates. If we could effect this transformation, an entire class of halogenated natural products would be readily accessible. Additionally, the synthesis of these natural

products via a direct bromonium-induced reaction may provide further support for their biosynthesis as well as new biogenetic hypotheses. And, given the role that halogens have on biological activity, as discussed above in Section 1.1, their biosynthesis has been a topic of interest for numerous decades.

1.5 Conclusion

Whether it is polyene cyclization, asymmetric halonium addition, or the general synthesis of *Laurencia* medium-sized bromoethers, each of these separate topics in halogenation chemistry has been a challenge that chemists have yet to solve in an efficient manner. The multiple step routes used to circumvent each problem led us to believe that there is a more direct pathway towards each of these motifs made smoothly in nature. Our goal was to match nature's selectivity using newly developed tools and concepts focused on polyene cyclization as well as medium-sized bromoether formation.

This thesis will cover the discovery of a new class of highly reactive halonium reagents, materials that are isolable, air stable solids.[23] These unique halonium reagents have allowed us to synthesize previously unobtainable isolates as well as streamline the synthesis of multiple additional compounds. Specifically, we have been able to complete seven different total and formal syntheses using halonium-induced polyene cyclization.[23] The transformation of these halonium reagents into enantiopure derivatives has allowed the asymmetric addition of X_2 to certain unfunctionalized alkenes.[24] Lastly, studies focused on the *Laurencia* natural products have uncovered a powerful halonium-induced ring expansion transformation capable of synthesizing the isolated medium-sized haloether cores; we believe this process may have biogenetic relevance.[25] Using nature's

biosynthetic pathway as inspiration, we have been able to mimic halonium-induced transformations which nature can complete in a regio- and stereoselective manner in a laboratory setting.

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CHAPTER 2

Discovery of IDSI and Iodonium- and Chloronium-Induced Polyene Cyclizations

2.1 Introduction

The polyene cyclization reaction of linear terpenes is a transformation with great power in its ability to rapidly assemble molecular complexity. To date, there have been numerous variants of polyene cyclizations with multiple reagent and substrate classes in both racemic and enantioselective formats,[1] though the use of halonium electrophiles to promote such cascades has shown little progress until recently. Such a reaction would be of great value considering there are over 135 bromine-containing cores and over 35 isolates that possess a chlorine.[2] Figure 1 provides four examples of these materials, compounds known to derive biosynthetically from a polyene cyclization.

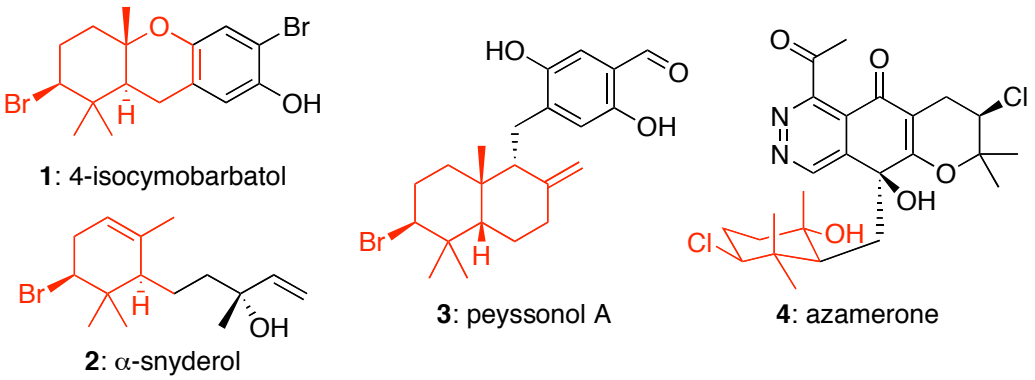
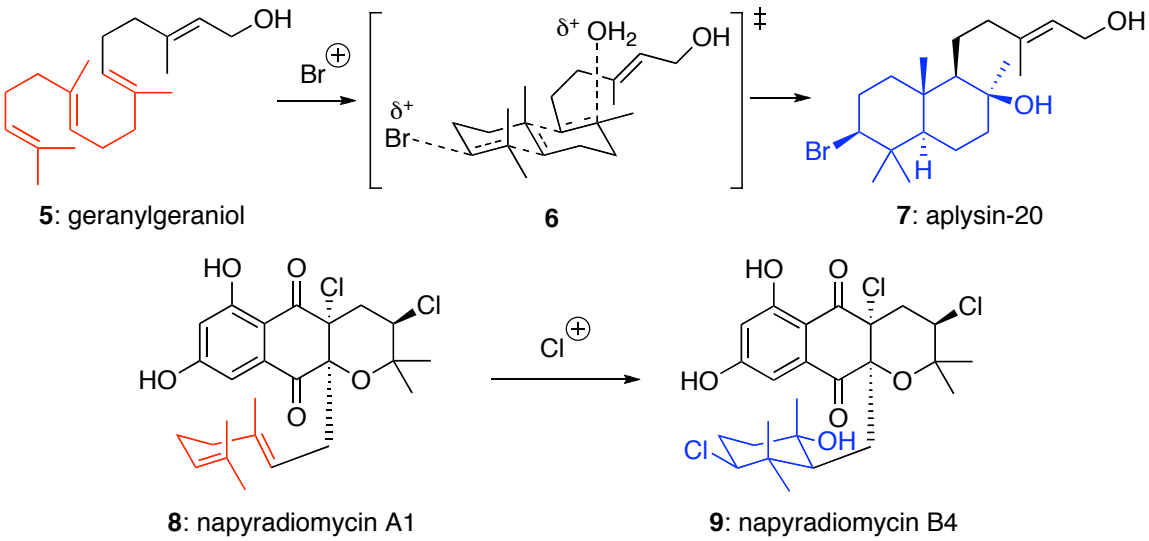


Figure 1: Selected Polyene Cyclization Products Containing a Bromine or Chlorine Atom

Scheme 1 presents two mechanistic examples of halonium-induced polyene cyclization reactions, one accomplished in nature with chemo- and facial-selectivity using either vanadium- or heme-based haloperoxidases.[3] The first displays a bromonium electrophile, while the second is activated by a chloronium ion. Based on Stork and Eschenmoser's original hypothesis for the stereocontrol observed in polyene cyclization,[4] the stereoselectivity probably results from a preorganized all-chair like transition state represented by **6** in the aplysin-20 example.

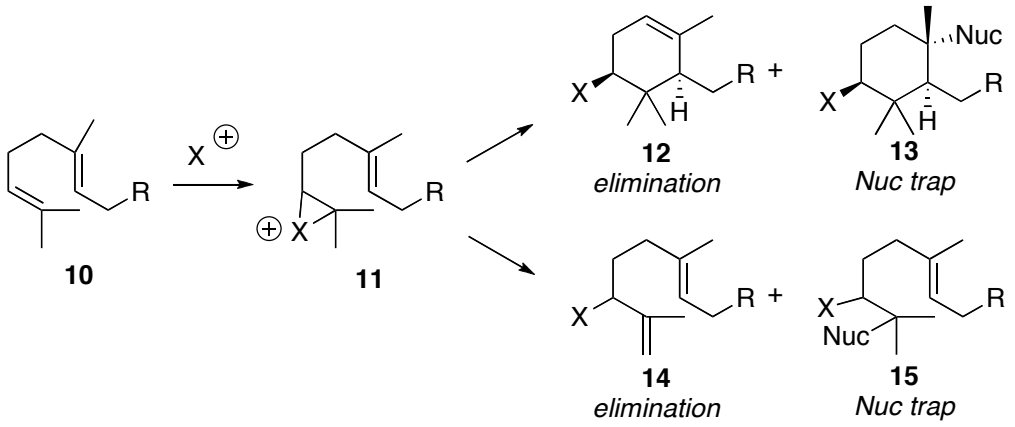


5: geranylgeraniol **6** **7**: aplysin-20

8: napyradiomycin A1 **9**: napyradiomycin B4

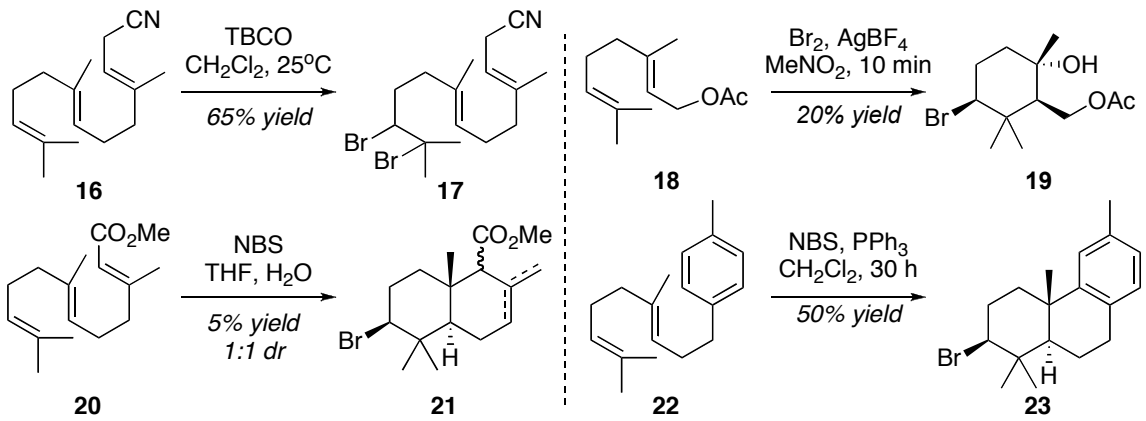
Scheme 1: Nature's Synthesis of Aplysin-20 and Napyradiomycin B4 uisng Enzymes

While nature can synthesize these compounds selectively, mimicking this reaction in a laboratory setting has proven quite challenging. Examining a simpler system in Scheme 2, treatment of this linear precursor (**10**) with a halonium source should generate **11**. Here, an intramolecular cyclization would generate **12** and/or **13** based on whether the process is terminated by an elimination or external nucleophilic attack. Alternatively, if the internal alkene is relatively non-nucleophilic or a competing nucleophile/base is available in solution, **14** and/or **15** could potentially form alongside **12** and/or **13**, again via direct elimination or nucleophilic attack. Because of these multiple possible pathways, in addition to the potential for further reactions of the alkenes within **12**, **14**, and **15** with additional electrophile in solution, attempts to control this collection of reactivity have proven particularly challenging with available halogen electrophile sources.



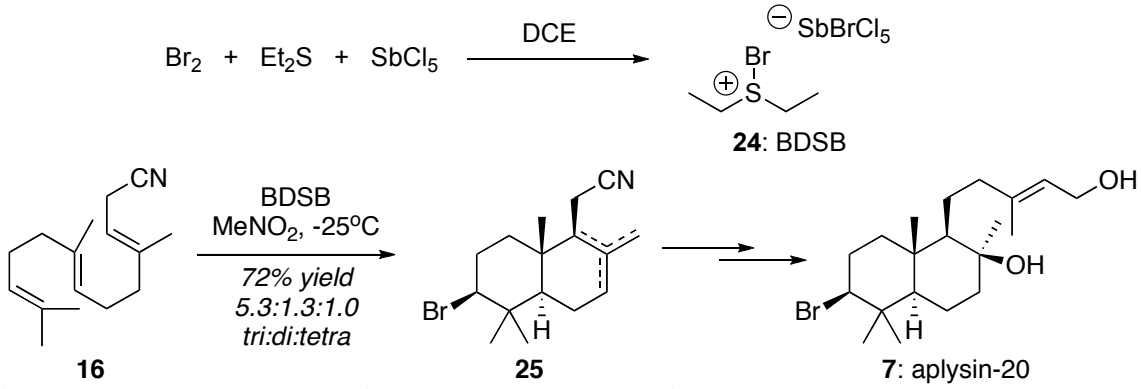
Scheme 2: Polyene Cyclization Intermediate and Possible Products

Bromine is the most common halogen found within these natural products and therefore has attracted the most attention from the synthetic community. Despite much effort, yields and selectivity are poor at best.[5] Scheme 3 provides a few representative examples of common bromonium sources being deployed for this transformation, including TBCO (2,4,4,6-tetrabromo-2,5-cyclohexadienone),[5f] NBS (N-bromosuccinimide),[5a] Br_2/Ag (I),[5c] and NBS/Lewis base.[9c] In the case of Br_2/Ag(I), the bromide counterion is removed from solution due to the formation of AgBr. While these bromonium sources typically are competent at providing the needed electrophilic bromine atom, the counterion used to stabilize that electrophile is typically also highly nucleophilic and/or basic, leading primarily to the low yields and unwanted byproducts such as those described above (i.e. **14** or **15**, Scheme 2). Outside of the bromide, to the best of our knowledge there are no known chloronium sources capable of inducing polyene cyclization in any yield, highlighting an even greater challenge in accessing appropriate reactivity, let alone selectivity.[6]



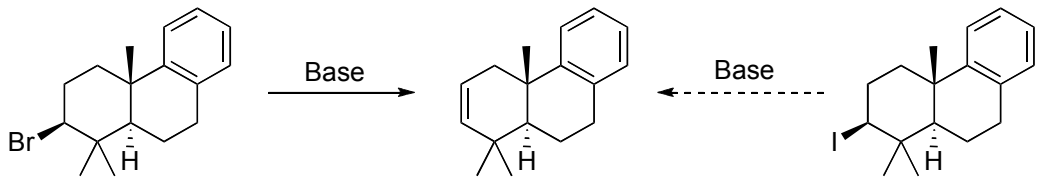
Scheme 3: Previous Attempts with Bromonium-Induced Polyene Cyclizations

The first significant breakthrough in this field came from the Snyder group in 2009 in the form of a new reagent developed by my colleague, Dr. Daniel Treitler.[7] He set out to create new bromonium sources, trying to stabilize the bromonium electrophile with a Lewis base as well as to add a Lewis acid to sequester the potentially nucleophilic bromide counterion. A thorough search of the literature, combined with an array of pilot experiments, led to the ideal combination of molecular bromine, diethyl sulfide, and $SbCl_5$ (Scheme 4). This orange crystalline solid was called BDSB, an acronym for bromodiethylsulfonium bromopentachloroantimonate. Its utility in polyene cyclization was quickly realized, as a variety of geraniol, nerol, and farnesol derivatives were cyclized in good to excellent yields as single diastereomers. A single example is shown in Scheme 4 in which farnesol cyanide (**16**) was cyclized in a 72% yield to the desired product **25**, an intermediate previously used to accomplish a total synthesis of aplysin-20.[7b] This same intermediate (i.e. **25**) was accessed by the Murai group starting from the same linear precursor, though a three step sequence of bromohydrin formation, acylation, and Lewis acid promoted polyene cyclization was required (generating the same product in a diminished yield) because direct bromonium cyclization of this electron deficient system was not possible with other bromonium sources.[8]



Scheme 4: Development of BDSB and its use in Polyene Cyclization

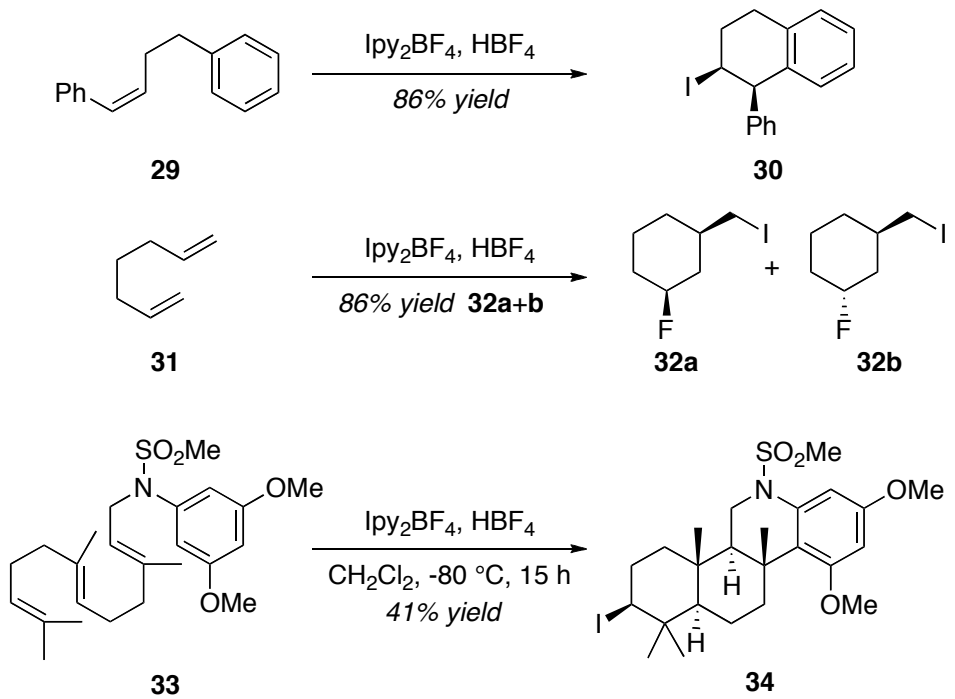
With BDSB's capability of cyclizing both electron rich and poor linear polyene precursors established, we hoped to use this installed bromide as a functional handle to access an even greater array of natural products via elimination, substitution, or coupling. Unfortunately, the elimination of this installed equatorial bromine proved quite challenging. Numerous conditions were varied to attempt the transformation of **26** (Scheme 5) into alkene **27**, though typically only trace elimination to **27**, recovered starting material, and/or decomposition occurred. As such, we wanted to see if the elimination could be achieved with its iodinated counterpart (**28**) since its larger size might make it more readily manipulated. To accomplish this goal, however, a method to synthesize compound **28** would be required.



Scheme 5: Attempts to Access Eliminated Product **27**

While iodinated natural products derived from polyene cyclizations do not occur in nature, there are several iodonium sources known to be capable of performing this transformation.[9] In 1988, Barluenga and co-workers were the first to show that

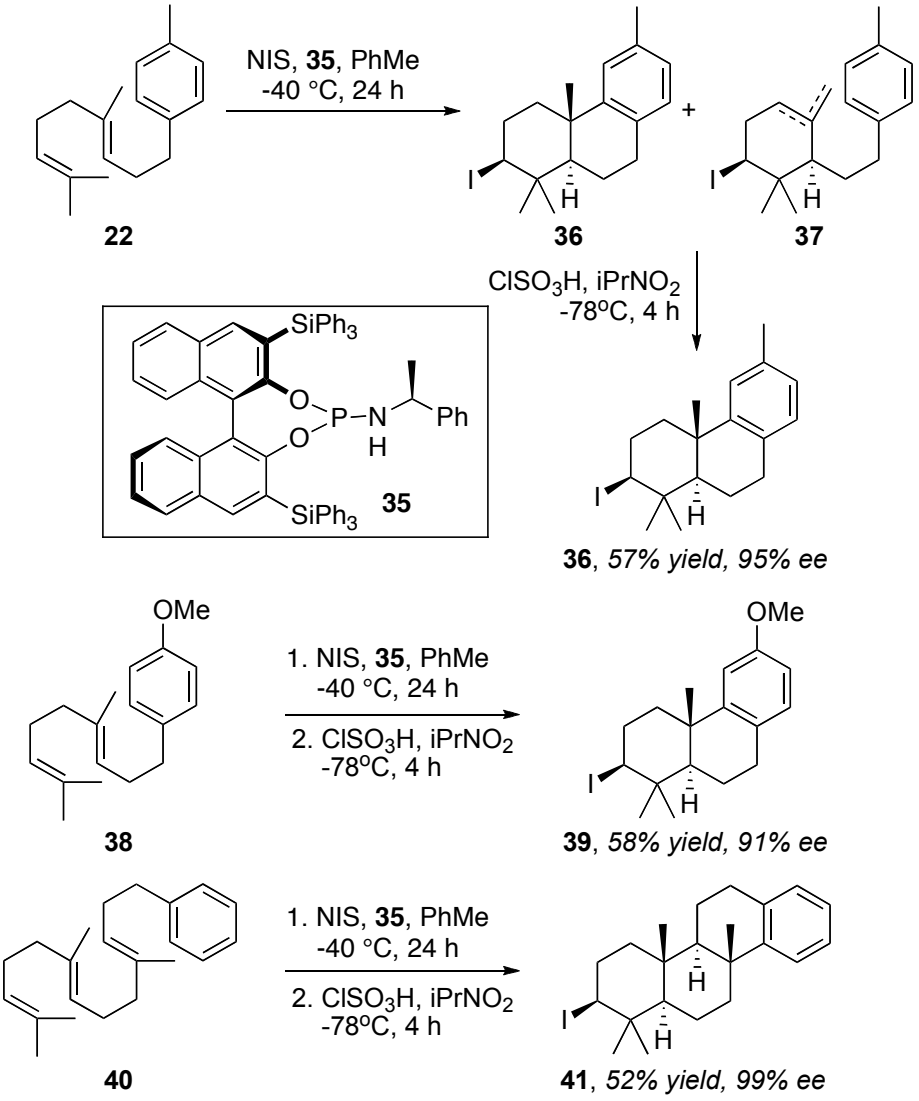
bis(pyridine)iodonium tetrafluoroborate (Ipy_2BF_4), in combination with HBF_4, was capable of performing a similar reaction, though initially not based on a terpene structure (**29** to **30** and **31** to **32**, Scheme 6).[9b] This preliminary finding was expanded in a follow up publication in 2004 to include linear polyene precursors such as **33**.[9a] In the drawn example, it is quite impressive that **34** was generated in 41% yield as a single diastereomer (74% yield per ring formation), though drawbacks of this methodology include the need for long reaction times at cryogenic temperatures. However, to date it is worth noting that only electron rich terpene precursors have been shown to undergo the desired transformation, revealing that room for additional solutions exists.



Scheme 6: Barluenga and Co-workers Iodonium Reagent Results

Shortly thereafter, in 2007, the Ishihara group developed an iodonium-induced polyene cyclization reaction using NIS and a Lewis base (Scheme 7).[9c] The Lewis base chosen was a chiral phosphoramidite (**35**), now able to render this reaction enantioselective. Treatment of **22** with stoichiometric amounts of both NIS and **35** at

-40°C for 24 h yielded both fully cyclized and partially cyclized products. This mixture then underwent a second acid promoted step to complete the final cyclization of **37**, overall producing **36** in 57% yield with 95% ee. While this transformation is remarkable, only three substrates are proven to work using these conditions, all of which are electron rich arenes as displayed in Scheme 7.



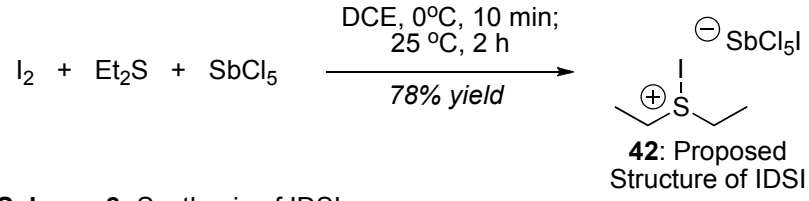
Scheme 7: Ishihara and Co-workers' Iodonium Reagent Results

Looking globally at these two developed methodologies, both enable the cyclization of electron rich polyene precursors, though require the use of cryogenic temperatures for extended periods of time, and, in the case of Ishihara's work, a second

step to complete the cyclization. The lack of general methodology to cyclize a variety of linear polyene precursors with halonium electrophiles has encouraged us to pursue this topic, with the main goals of my project being the development of reagents and/or strategies capable of cyclizing both electron rich and poor linear precursors using a single iodonium source. The installation of this iodide would not be for the purpose of residing in a final product, but rather in the ability to use that iodine atom as a functional handle for further transformations. Additionally, since there have been no reported polyene cyclizations induced by a chloronium electrophile, we also wished to see if any successful designs with the iodine could extend to this system as well, to afford a global solution to halonium-induced polyene cyclizations.

2.2 Discovery of IDSI

Although the synthesis of BDSB was readily achieved, direct extension of that procedure for the synthesis of the iodinated variant proved to be far from trivial, particularly in terms of generating a crystalline material.[7b] To begin, I_2 was dissolved in DCE and Et_2S was added; at this point, a color change was observed, suggesting the probable formation of iodosulfonium iodide intermediate. Next, $SbCl_5$ was added and further stirring at 25°C for 2 h yielded a dark reddish brown solution. If the reaction was placed in the freezer, only excess I_2 crystallized from the solution. However, addition of a small layer of hexanes (a solvent I_2 is soluble in) allowed for crystallization of the desired product as dark reddish orange crystals. Typically these were grown overnight, then quickly filtered and rinsed with hexanes to afford IDSI.



Scheme 8: Synthesis of IDSI

At the onset, we named these crystals IDSI in the hope that they would react like BDSB, though the actual name of solid **42** based on IUPAC rules would be diethyliodosulfonium pentachloroiodoantimonate. These crystals had to be stored at -20°C, as IDSI is stable for only a short period of time at 25°C. Yet, IDSI is stable enough at 25°C for the crystals to be isolated and weighed out in air. IDSI is soluble in $MeNO_2$, $EtNO_2$, MeCN, CH_2Cl_2, DMSO, DMF, acetone, and EtOAc; slightly soluble in dioxane and $CHCl_3$; and insoluble in benzene, toluene, and hexanes. The dimethyl variant of **42** was prepared by Minkwitz and Prenzel, though only IR analysis of this structure had been previously completed.[10]

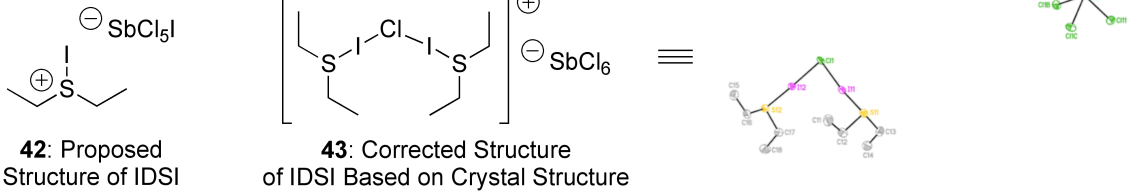


Figure 2: Corrected Structure of IDSI

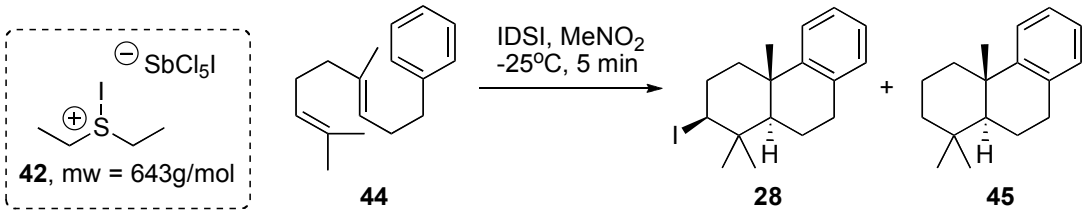
However, it was in obtaining a crystal structure of this material that we discovered that IDSI actually exists as a chloride linked dimer in the solid state. This dimer moiety could possibly be contributing to its instability, since ICl could be lost upon warming. Structurally, the I-Cl bond lengths in **43** are 2.814 and 2.714 Å, values much larger than that of molecular I-Cl at 2.553 Å.[11] Because of this, we expect a more reactive iodonium electrophile due to the increased bond length. Additionally, a NIS chloride-linked dimer has also been prepared which displays similar bond lengths at 2.845 and 2.910 Å and this

dimer has shown to previously behave as an equivalent of ICl.[12] This was a characteristic we were hesitant about on the onset of the project, as hopefully our reagent would not quench the reaction with the chloride ion prior to ring formation. As will be shown in the following section, IDSI once dissociated seems to behave as a source of one equiv each of I^+, ICl, $SbCl_6^-$, and 2 equiv of Et_2S.

2.3 Iodonium-Induced Polyene Cyclization

With our iodonium source in hand, our next efforts were to examine whether IDSI was capable of promoting polyene cyclization of a variety of terpenes. Pleasingly, simple treatment of homogeranyl benzene (**44**) with IDSI in nitromethane (0.05 M) for 5 min at -25°C yielded the *trans*-decalin core of **28** (Table 1), although these initial results were obtained prior to the crystal structure analysis of IDSI (thus at this point, Entry 2 of Table 1 was considered 1 equivalent of **42**). While a 73% yield of product was observed, the remainder of the material balance was H-cyclized byproduct **45**. Mechanistically, the reaction terminates by regaining aromaticity via loss of a proton, a species that could initiate a proton-induced polyene cyclization of any residual **44** to generate **45**. However, once receiving the corrected structure of IDSI, use of an appropriate amount of the reagent led to the ability to form **28** cleanly in 93% yield (Table 1, Entry 4) without any observed **45**.

Table 1: Equivalents of IDSI Used for Polyene Cyclization

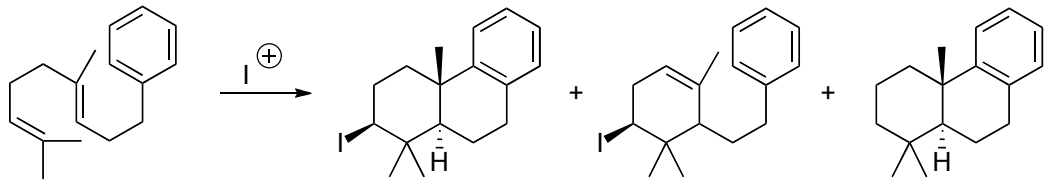


Entry	Equiv IDSI	Results
1	40.2 mg = 0.5 equiv	1.6:1 **28**:**45**, 4:1 **28**+**45**:**44**
2	64.3 mg = 0.8 equiv	73% **28**, 4:1 **28**:**45**
3	80.4 mg = 1.0 equiv	87% **28**
4	96.5 mg = 1.2 equiv	93% **28**

Not only was IDSI capable of performing this desired transformation, it also does so with greater efficiency than other known iodonium sources, namely those used by Barluenga and co-workers (Ipy_2BF_4, HBF_4)[9a] and the Ishihara group (NIS, PPh_3)[9c] (Table 2). Under Barluenga's standard conditions (Entry 1), compound **28** was obtained in 41% yield along with 14% of partially cyclized **46**. The excess pyridine (from the Ipy_2BF_4 reagent) present in the reaction mixture most likely quenched the proton generated from regaining aromaticity, removing the acid which could further catalyze the cyclization of **46** to **28**. With this idea in hand, the conditions of Entry 2 were designed with excess acid present to aid in completing the final cyclization. Here, unfortunately, too much acid was present; generating byproduct **45** in approx 15% yield with no improvement on the yield of **28**. When decreasing the temperature, multiple inseparable diastereomers of **28** were produced. Interestingly, the use of Ipy_2BF_4 without HBF_4 typically yielded unreacted starting material (Entry 4). We hypothesize that the need for HBF_4 is to help activate the iodonium species, likely by protonating one of the pyridine rings to facilitate its departure and generate the "active" iodonium reagent *in situ* as the monopyridine iodonium complex.

Under Ishihara's conditions (Entry 5),[9c] only 50% conversion was observed after 24 h at -40°C. And, in our hands, none of the fully cyclized material was produced; only partially cyclized **46** was observed. This product again can be taken forward to desired **28** in a second acidic step, an additional step that IDSI does not require. When using NIS/PPh_3, the proton lost is most likely quenched by the succinimide anion. IDSI differs from both conditions, as the most basic atom in solution is likely the sulfur of diethyl sulfide, a compound much less basic and therefore more easily deprotonated. In fact treatment of diethylsulfide with HCl and $SbCl_5$ makes the protonated variant of IDSI ($Et_2SH{\bullet}SbCl_6$), a crystalline solid capable of transforming **44** into **45** in quantitative yield (Entry 6).

Table 2: Alternative Iodonium Sources used for Polyene Cyclization

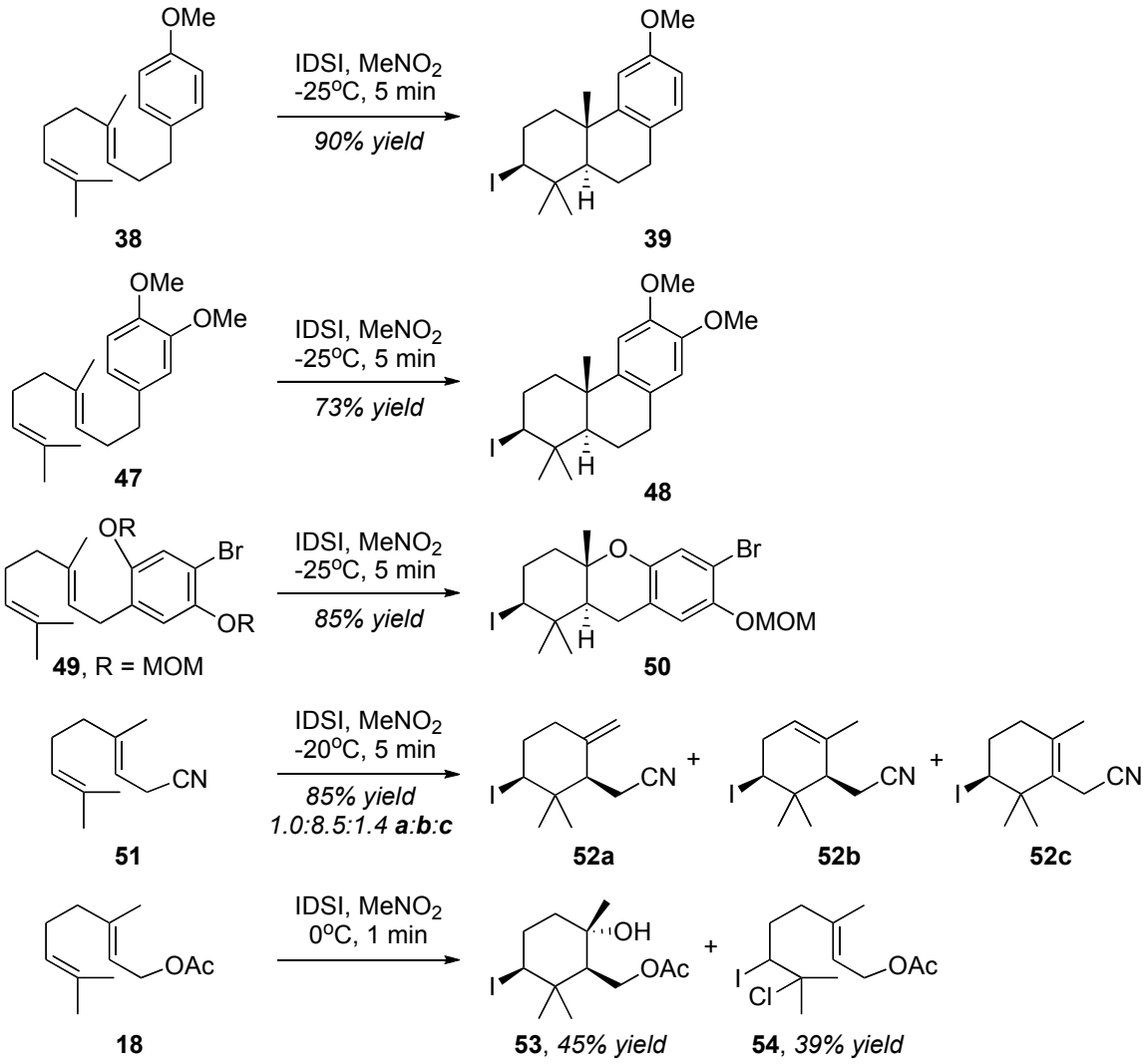


44 **28** **46** **45**

Entry	Reagents	Solvent/Temp	Results
1	Ipy_2BF_4, HBF_4 (1eq)	CH_2Cl_2, -40°C	41% **28**, 14% **46**
2	Ipy_2BF_4, HBF_4 (3eq)	CH_2Cl_2, -40°C	~40% **28**, ~15% **45**
3	Ipy_2BF_4, HBF_4 (1eq)	CH_2Cl_2, -78°C	multiple diast of **28**
4	Ipy_2BF_4	CH_2Cl_2, -78°C	only **44**
5	NIS, PPh_3	CH_2Cl_2, -78 to -40°C	<50% **46**, 50% **44**
6	$Et_2SH{\bullet}SbCl_6$	$MeNO_2$, -25°C	only **45**

Given that these initial results looked promising, IDSI was explored next for its ability to cyclize both electron rich and poor linear polyene precursors. Scheme 9 shows numerous substrates that IDSI successfully transformed into cyclized adduct. Electron rich arenes such as **38** and **47** both underwent full cyclization in good yields. Interestingly, the extremely electron rich aromatic ring in **47** was not iodinated under the

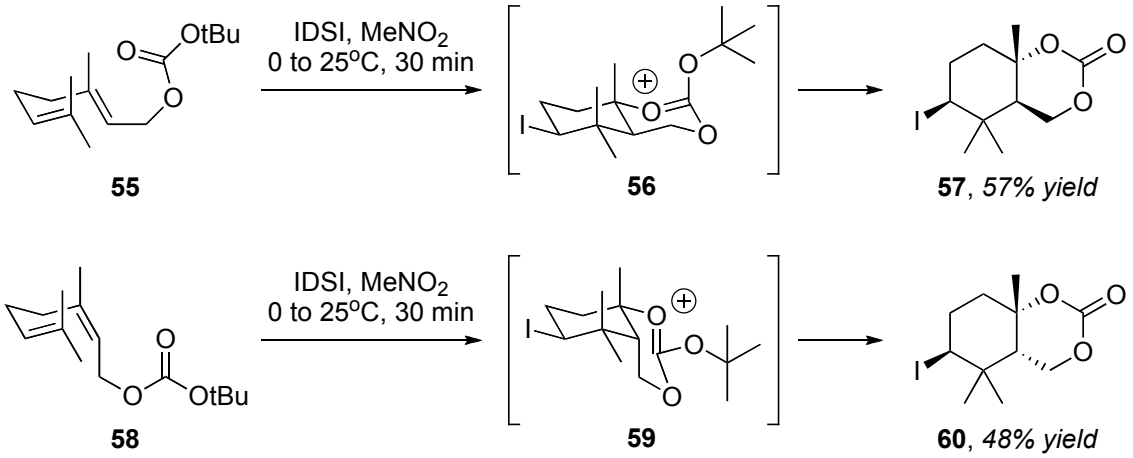
reaction conditions; **47** instead reacted chemoselectively only at the desired alkene. Substrate **49** shows oxygen trapping the resultant carbocation, here losing the MOM group during the termination of the reaction to afford **50** in an 85% yield. While these examples show slight diversity in functional groups, addition of a nitrogen in the context of a nitrile can be used as well. Compound **51** generated three different regioisomeric alkenes in good yields, as there is no nucleophilic trapping group in this example. Additionally, differentially protected alcohols in the form of **53** were produced in 45% yield starting from linear acetate **18**. The yield in this particular case was moderate, as the competing side product was the iodochloride **54**. This unwanted by product was not especially surprising considering that IDSI structurally is a chloride linked dimer, now showing that IDSI can behave as a source of ICl if the competing intramolecular nucleophile is only modest in overall quality (in this example due to the sigma withdrawing capability of the acetate).



Scheme 9: Substrate Scope of Polyene Cyclization using IDSI

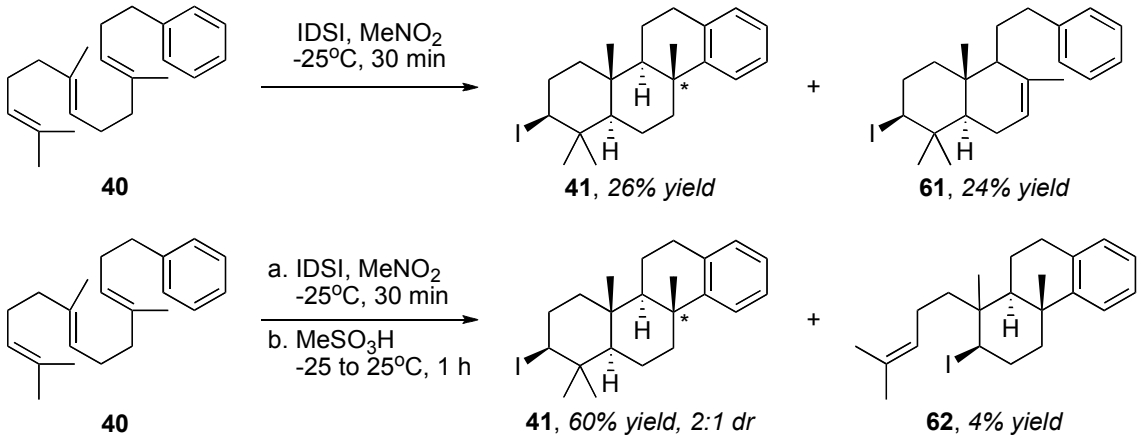
This pathway of halogen addition proved to be a general trend for most electron deficient linear polyenes. As shown in Scheme 10, the *tert*-butyl carbonate terminated polyenes **55** and **58** were cyclized in 57% and 48% yields respectively, with the major byproduct resulting again from ICl addition to the most electron rich alkene. Nevertheless, what is key to note from these successful cyclizations is that these examples differ in their alkene geometry, with **55** being synthesized from geraniol and **58** being a nerol derivative. This stereochemical information was then relayed into the products; overall, compound **55** afforded the *trans*-bicyclic junction, whereas **58**

generated the *cis*-disposed alternative. Based on the established mechanism for polyene cyclization, these results suggest the intermediacy of chair-chair intermediates **56** or **59** in leading to the single diastereomer observed for each product. Critically, substrates **18**, **55**, and **58** are the first examples of any electron deficient linear terpene precursor undergoing polyene cyclization initiated by an iodonium source, illustrating the unique power of IDSI.



Scheme 10: Stereochemistry Transferred from Geometrically Differentiated Starting Materials

The substrates shown thus far have afforded only bicyclic products; however, if an additional terpene unit is included in the starting material, tricyclic cores can be produced as well. As shown in Scheme 11, farnesol derivative **40** was treated with IDSI at -25°C for a longer period of time (30 min) to generate tricycle **41** in 26% yield. The major by product was the partially cyclized material **61**. Here, IDSI was not able to fully cyclize the linear precursor, but by the addition of $MeSO_3H$ into the reaction mixture after 30 min, a greater mass balance of the desired product was achieved. Most likely the added acid was capable of completing the final cyclization, transforming **61** into **41** *in situ*, similar to the conditions used by Ishihara and co-workers in Scheme 7,[9c] though the reason it is required for this particular substrate is, at present, unclear.



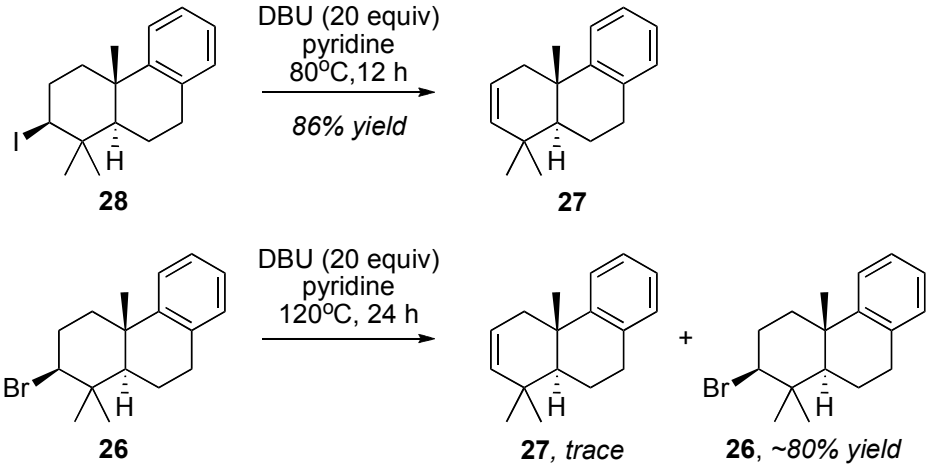
Scheme 11: Synthesis of Tricyclic Cores from a Linear Precursor

This section has outlined the utility of IDSI to cyclize linear polyenes in a single step in good yields to a single diastereomer. While a diverse array of cyclized products can be produced, the utility of these iodinated substrates lies principally in their ability to be easily manipulated as, to the best of our knowledge, there are no natural products that contain an iodinated decalin core. The next section will describe the value of these products in context of several total syntheses.

2.4 Formal Syntheses of K-76, Stemodin, and Loliolide

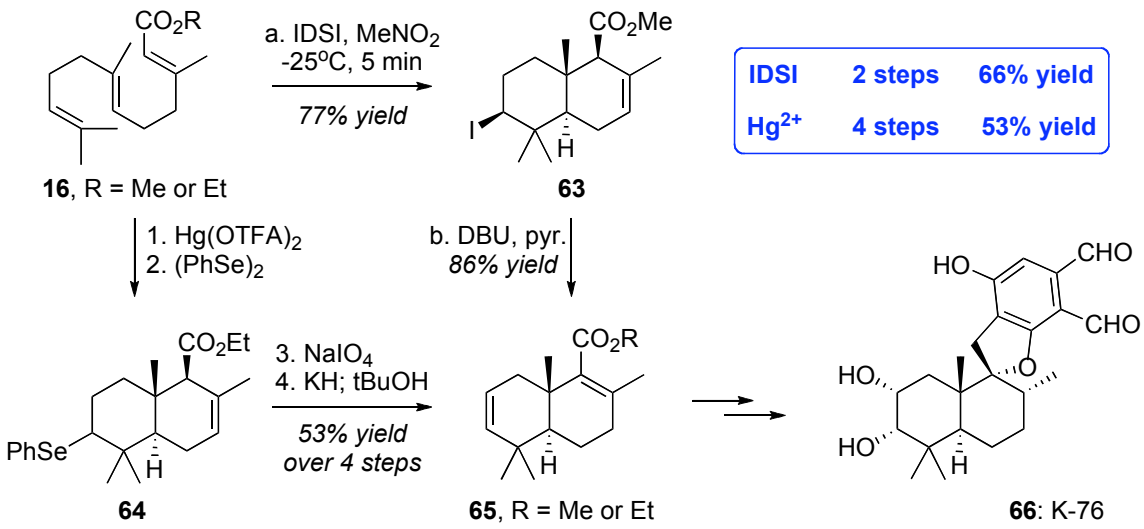
As noted in the introduction to this chapter, the real advantage of the installed iodide is that it can be eliminated, coupled, or substituted. As one example, treatment of **28** with DBU in pyridine at 80°C yielded the eliminated product in 86% yield. The elevated temperatures are likely required because the installed iodide atom is equatorial, rendering E2 elimination much more challenging to achieve.[13] Under the same conditions, the brominated variant of this material (i.e. **26**) gave largely recovered starting material with a trace amount of eliminated product. Since this transformation was quite facile with the iodinated starting material, the eliminated intermediate was

targeted to determine if this new two step approach could afford decreased step counts and increased yields, overall streamlining synthetic efforts with non-toxic and readily handled reagents.



Scheme 12: Eliminiation of the Halogen Derived from the Polyene Cyclization

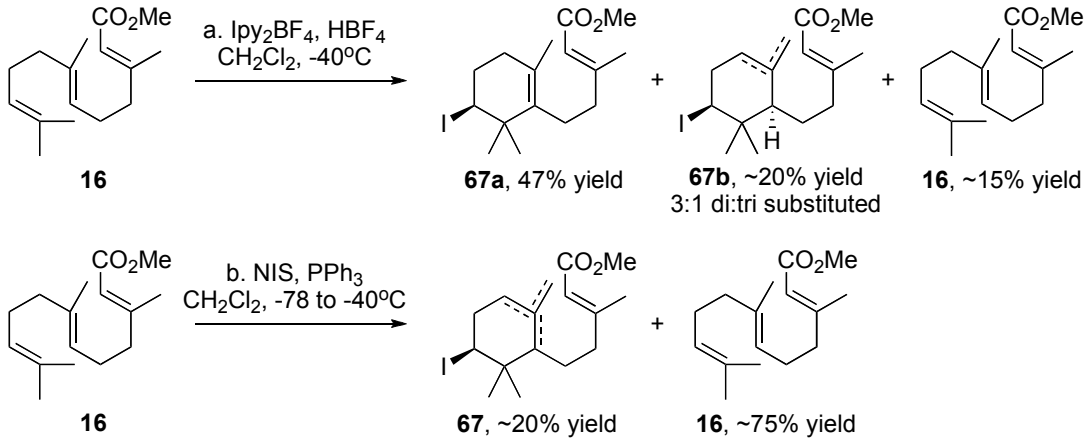
As one example, K-76[14] was synthesized by McMurry and Erion in 1985 with the *trans*-decalin core deriving from a mercury(II)-promoted polyene cyclization of a linear terpene precursor.[15] As shown in Scheme 13, α,β-unsaturated ester **16** (R = Et) was cyclized with stoichiometric $Hg(OTFA)_2$, with the resultant organomercurial then treated with stoichiometric $(PhSe)_2$ to generate intermediate **64**. After oxidation and double bond migration, the desired diene intermediate **65** was generated in four steps and overall 53% yield.



Reagents and Conditions: a. IDSI (1.2 equiv), $MeNO_2$, -25°C, 5 min, 77%; b. DBU (20 equiv), pyridine, 120°C, 12 h, 86%.

Scheme 13: McMurry and Erion's Synthesis of K-76 and Comparison to IDSI Alternative

Using the same starting material (varied only in the ester, though this should have no effect on the transformation shown), **16** (R = Me) was treated with IDSI under standard conditions to afford the desired bicycle **63** in 77% yield. It is quite remarkable that IDSI performed this desired transformation, as, to the best of our knowledge, the only electrophiles capable of generating the desired bicycle are Hg(II) salts. As shown in Scheme 14, other iodonium sources such as Ipy_2BF_4/HBF_4 and NIS/PPh_3 produced only partially cyclized material **67**; the decreased nucleophilicity of the α,β-unsaturated alkene probably disfavors the desired transformation from occurring with these reagents.

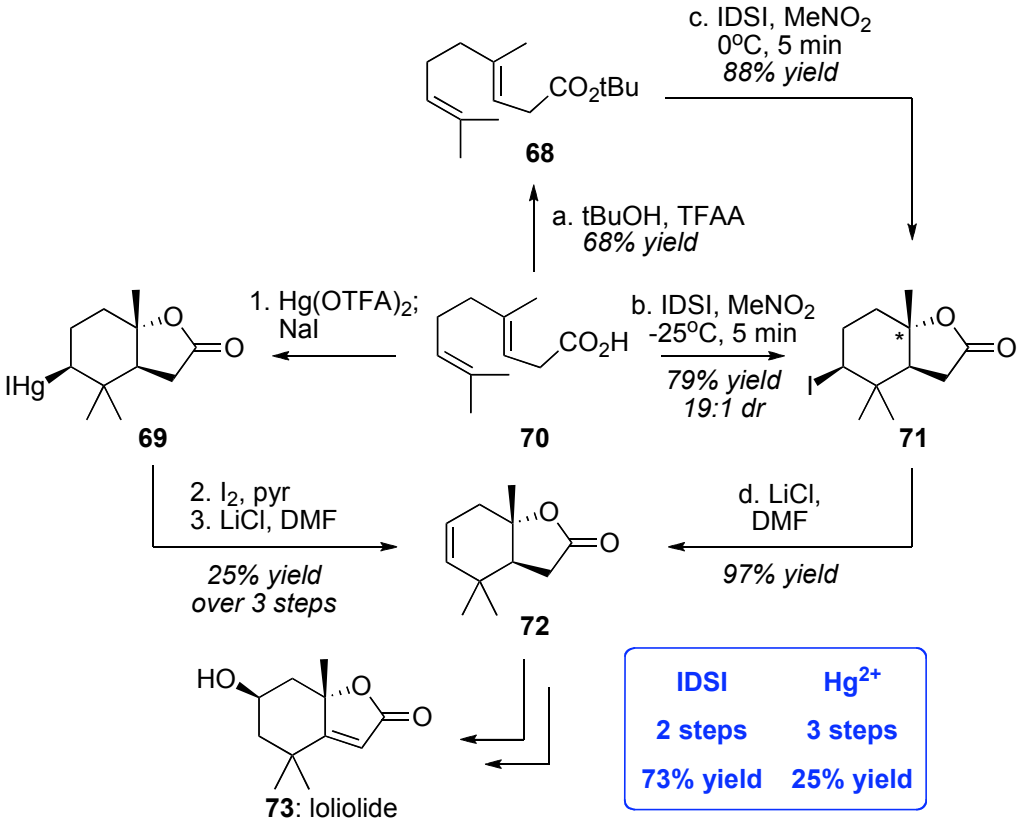


Reagents and Conditions: a. Ipy_2BF_4 (1 equiv), HBF_4 (1 equiv), CH_2Cl_2, -40°C, 30 min; b. NIS (1 equiv), PPh_3 (0.1 equiv), CH_2Cl_2, -78 for 30 min then -40°C for 24 h.

Scheme 14: Cyclization Attempts of **16** using Alternative Iodonium Sources

BDSB proved incapable of fully cyclizing the desired linear precursor, producing only partially cyclized material (a brominated variant of **67**, not shown). The ability of IDSI to complete this transformation, whereas BDSB cannot, must lie in the iodonium atom itself. Iodine is soft and easily polarizable, making it quite similar to Hg(II), features that can facilitate complete cyclization. A higher energy transition state was likely seen with the bromonium case, not allowing the final electron deficient alkene to organize and react before termination occurred. Additionally, IDSI contains an equivalent of ICl, which, under the reaction conditions, could lead to the generation of HI or HCl, materials which may have the capability of cyclizing **67** to **16**.

To complete the formal synthesis of K-76, the iodine atom within **63** was eliminated in 86% yield using the previously developed conditions to generate the same bicyclic diene synthesized by McMurry and Erion (Scheme 13). Overall, IDSI avoids the use of stoichiometric amounts of mercury and selenium reagents and generates the same desired compound in two steps with a 66% yield, thereby streamlining the synthesis of this particular natural product.

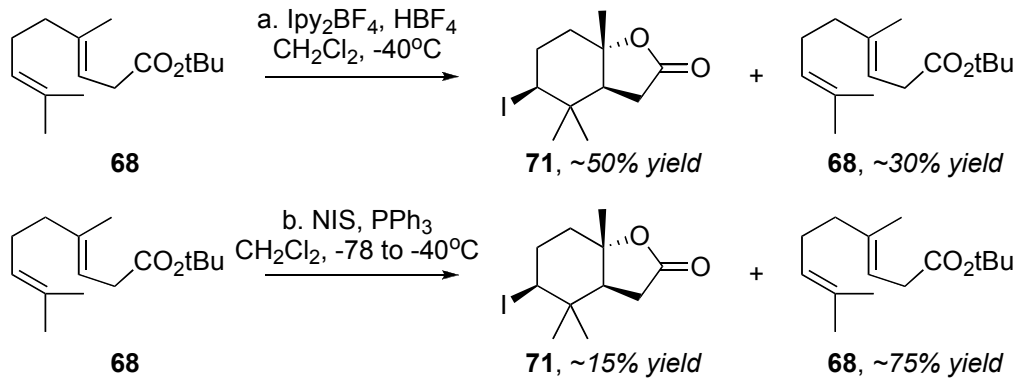


Reagents and Conditions: a. TFAA (5 equiv), tBuOH, 0 to 25°C, 20 min, 68%; b. IDSI (1.2 equiv), $MeNO_2$, -25°C, 5 min, 79%; c. IDSI (1.2 equiv), $MeNO_2$, 0°C, 5 min, 88%; d. LiCl (50 equiv), DMF, 80°C, 12 h, 97%.

Scheme 15: Formal Synthesis of Loliolide Inspired by Rouessac and Co-workers

As a second example shown in Scheme 15, loliolide[16] was synthesized by Rouessac and coworkers in 1983, with the key step in the synthesis being a cyclization of acid **70** using $Hg(OTFA)_2$.[17] The so-produced organomercurial **69** was then transformed into the corresponding iodide and eliminated with LiCl in DMF. Overall, Rouessac's sequence from **70** to **72** was three steps and produced **72** in 25% yield. Avoiding the use of mercury, IDSI transformed the same starting carboxylic acid into **71** in 79% yield (with a 19:1 dr at the methyl bridgehead). An additional step circumvented this modest erosion in dr by cyclizing instead the *tert*-butyl ester derivative (**68**). This reaction led to **71** in 88% yield as a single diastereomer. Again, comparing the mercury (II)-induced

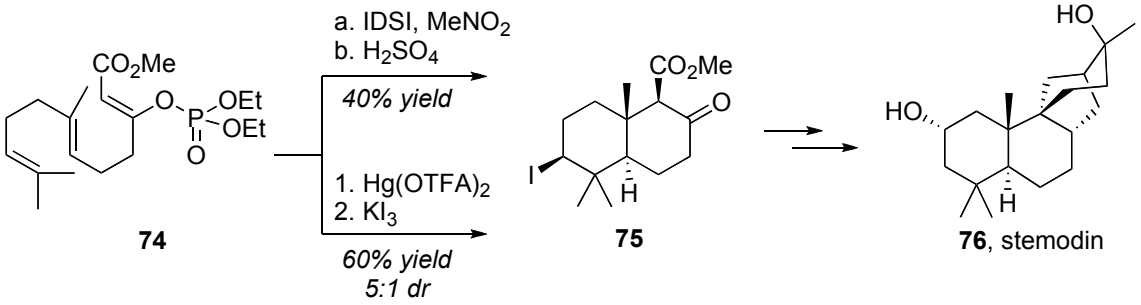
route to the use of IDSI, the synthesis was shortened by a step with a three-fold boost in yield using IDSI.



Reagents and Conditions: a. Ipy_2BF_4 (1 equiv), HBF_4 (1 equiv), CH_2Cl_2, -40°C, 30 min; b. NIS (1 equiv), PPh_3 (0.1 equiv), CH_2Cl_2, -78 for 30 min then -40°C for 24 h.

Scheme 16: Cyclization Attempts of Ester **68** using Alternative Iodonium Sources

Using the *tert*-butyl ester derivative **68**, the desired iodinated bicycle **71** could be produced using other iodonium sources, though in decreased yields (Scheme 16). Use of Ipy_2BF_4 with HBF_4 yielded approximately 50% of the desired product with an additional 30% yield of unreacted starting material. Similarly, NIS and catalytic PPh_3 were lower yielding, though they produced **71** in 15% yield; here, the majority of the mass balance was recovered starting material. Although we must note that the shown procedures for these reagents were clearly not optimized for this direct transformation, since only starting material remained in both cases.

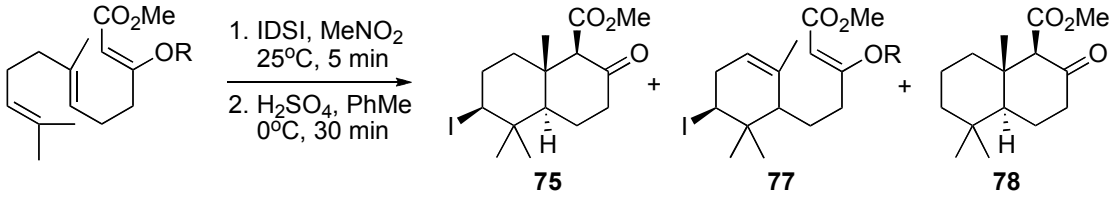


Reagents and Conditions: a. IDSI (1.2 equiv), $MeNO_2$, 25°C, 5 min; b. H_2SO_4 (15 equiv), PhMe, 0°C, 30 min, 40% over 2 steps.

Scheme 17: Formal Synthesis of Stemodin Inspired by Corey and Co-workers

As a final cationic cyclization, the total synthesis of stemodin[18] was accomplished in 1980 by Corey and co-workers (Scheme 17).[19] Enol phosphate **74** was cyclized using $Hg(OTFA)_2$, after which the intermediate organomercurial was then displaced with iodine in 60% yield (with a 5:1 dr at the iodine center). Access to the same intermediate could also be achieved using IDSI, though treatment of enol phosphate **74** with IDSI typically produced only partially cyclized material. Here, a second acid-promoted step proved necessary to facilitate complete cyclization. Overall, IDSI provided **75** over two steps in 40% yield as a single diastereomer, where the mercury (II) variant also two steps but with a higher 60% overall yield. While IDSI was not able to increase the yield here, it still avoids the need to use stoichiometric amounts of mercury.

Table 3: Optimization Attempts at Cyclization of Derivatives of Enol **74**

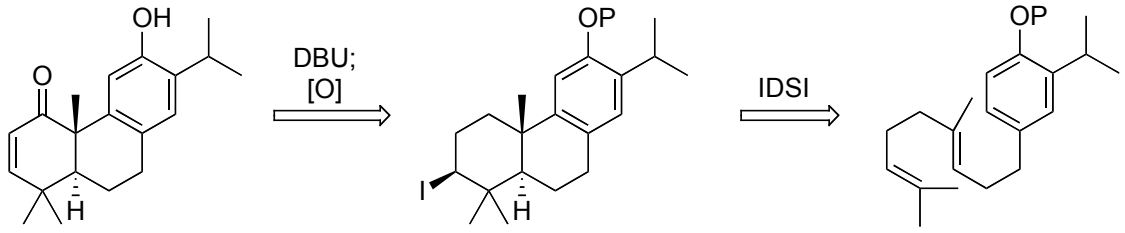


75 **77** **78**

Entry	*R*	*Conditions*	*Results*
1	-P(O)(OEt)$_2$	Step 1 only	5% **75** + 53% **77**
2	-P(O)(OEt)$_2$	Step 1 and add H_2SO_4	27% **75** + 64% **78**
3	-P(O)(OEt)$_2$	Step 1, concentrate, Step 2	<10% **75**
4	-P(O)(OEt)$_2$	Step 2: HCl/dioxane	5% **75** + 53% **77**
5	-P(O)(OEt)$_2$	Step 2: $ClSO_3H$/PhMe	decomp
6	-P(O)(OEt)$_2$	Step 2: at -78°C	decomp
7	-P(O)(OEt)$_2$	I_2/PPh_3 in DCM	**RSM**
8	-TIPS	above	loss of TIPS
9	-TBS	above	24% combined 1:1.5 **75**:**77**
10	-TBDPS	above	25% combined 1:1.5 **75**:**77**
11	-MOM	above	decomp
12	-Me	above	decomp

Looking more closely at this cyclization reaction, Entry 1 of Table 3 demonstrates that cyclization of phosphate **74** without the acidic step afforded only 5% of the desired product and 53% of partially cyclized **77**. Use of H_2SO_4 at the same time as IDSI

resulted in a large amount of proton-induced polyene cyclized product **78** (Entry 2). Without a workup in between the reactions (i.e. if they were done as a "single step"), mostly decomposition resulted (Entry 3). Entries 4 and 5 illustrate that other acids yielded only partially cyclized product and/or decomposition. Additionally, the reaction temperature appeared to play a critical role, as performing the reaction at -78°C also yielded decomposition (Entry 6). Other iodonium sources such as I_2/PPh_3 only afforded unreacted starting material (Entry 7). With the highest yield achieved at 40% over two steps, another approach was targeted (was the enol phosphate was too deactivated to participate in the full cyclization?). Therefore, other enol derivatives were prepared. Entries 8-10 demonstrate that silyl enol ethers had similar problems, typically affording poor mass recovery with the major product being partially cyclized **77**. Additionally, the MOM- and methyl-enol ethers both led to decomposition under the reaction conditions (Entries 11 and 12). Thus, while several efforts were taken to increase the yield of the desired transformation, none of these alternative conditions or approaches actually increased the overall yield of the produced **75** above 40%.



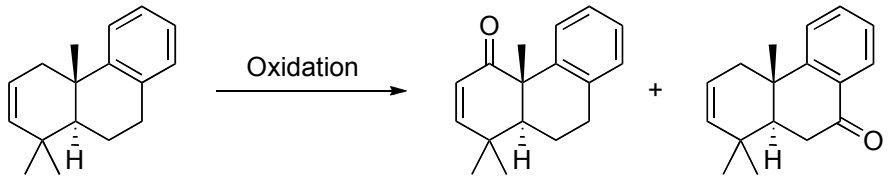
79: (+)-shonanol **80** **81**

Scheme 18: Reterosynthesis of (+)-Shonanol

Other cyclized natural products retain the alkene motif, including (+)-shonanol (**79**, Scheme 18).[20] This compound was isolated in 1965 and has only been synthesized from derivatization of a similar natural product.[20c] Looking at our proposed retrosynthesis of shonanol, a late-stage elimination and allylic oxidation would generate

the α,β-unsaturated ketone from **80**, a compound that we believed could derive from polyene cyclization of **81** with IDSI. Here, because we believed strongly that IDSI would prove capable of performing the polyene cyclization, we focused our efforts on the requisite allylic oxidation of the alkene needed post-cyclization.

Table 4: Attempts at Allylic Oxidation of Model Compound **27**



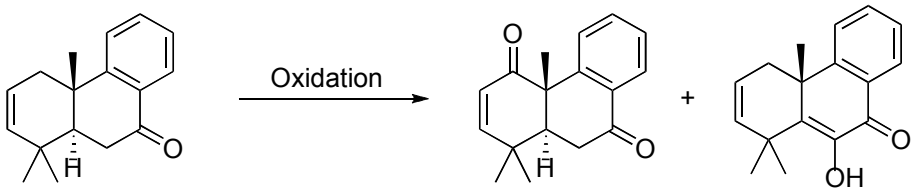
27 **82** **83**

Entry	Oxidant	Solvent/Temp	Results
1	CuI, TBHP	MeCN, 50°C	3:1 **83**:**82**
2	$Mn(OAc)_2$•$2H_2O$, TBHP	EtOAc, 25°C	only **83**
3	SeO_2, TBHP	CH_2Cl_2, 70°C	**27** and **83**
4	$Pd(OH)_2$/C, O_2	CH_2Cl_2, 25°C	mostly **83**
5	$RuCl_3$•H_2O, TBHP	hexanes/H_2O, 25°C	mostly **83**
6	$MgCl_2$•$6H_2O$, TBHP	MeCN, 60°C	**27** and **83**
7	MnO_2	CH_2Cl_2	**27**
8	PCC	CH_2Cl_2	**27** and **83**

Table 4 provides a subset of examples of oxidations attempted to achieve the desired transformation to the α,β-unsaturated ketone **82**. All entries favored benzylic oxidation to **83** over allylic oxidation to **82**, likely due to both steric and electronic factors. When each of these conditions was varied to favor allylic oxidation based on published procedures,[21] the only case where the desired oxidation was observed was in Entry 1, using CuI and *tert*-butylhydrogen peroxide (TBHP). Interestingly, Entry 2 was quite clean, a great method to generate **83**. Because the desired product was never formed in a good yield, we pursued further oxidation of **83**, hoping it would undergo a second oxidation to generate diketone **84** (Table 5). At this point, the installed allylic ketone would be more hindered than the benzylic position and selective reduction would

hopefully be an easier transformation. While this task seemed achievable, unfortunately no allylic ketone was ever observed. As shown in Entries 1 and 2, only recovered unreacted **83** was observed, and using more forcing conditions generated ketoenol **85**. Since the desired allylic oxidation was a challenge at this point and benzylic oxidation was an easier task, we shifted our focus to a new target molecule.

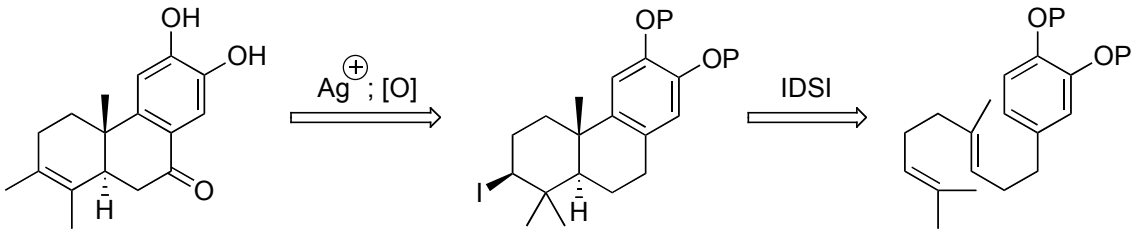
Table 5: Attempts at Allylic Oxidation of **83**



83 **84** **85**

Entry	Oxidant	Solvent/Temp	Results
1	CuI, TBHP	MeCN, 50°C	only **83**
2	$Mn(OAc)_2 \cdot 2H_2O$, TBHP	EtOAc, 25°C	only **83**
3	SeO_2, TBHP	CH_2Cl_2, 70°C	only **85**

Specifically, that target was celahypodiol (**86**),[22] a molecule which has a uniquely substituted ring system, containing two vinyl methyl groups and a benzylic ketone (Scheme 19).[23] Based on our previous oxidation work, the benzylic ketone should be easily prepared. Thus, retrosynthetically, **86** could be derived from a methyl migration and oxidation of substrate **87**. In turn, compound **87** would derive from IDSI cyclization of the corresponding linear precursor, an example shown previously in Scheme 9 (though the methyl ether protecting group would likely need to be altered for ease of late-stage target delivery). At the onset of this total synthesis endeavor, the only undeveloped step was the methyl shift, a reaction we targeted for our initial studies.

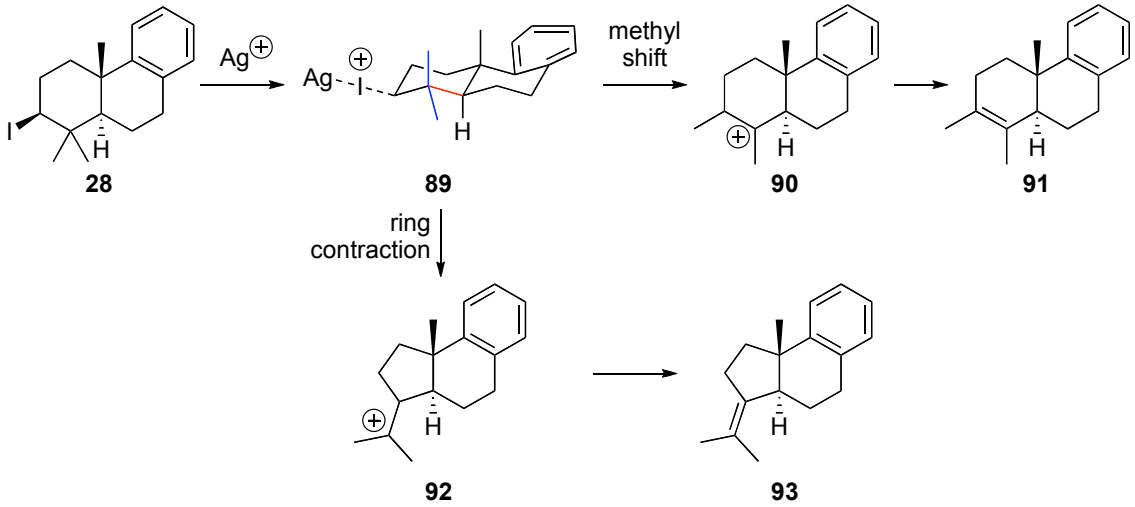


86: celahypodiol **87** **88**

Scheme 19: Retrosynthesis of Celahypodiol Featuring IDSI-Promoted Polyene Cyclization

Table 6 shows initial efforts towards this proposed rearrangement. The general idea was to treat the iodinated polyene cyclized product with a silver (I) source, inducing a methyl shift following carbocation formation (i.e. **90**), which upon loss of a proton would then generate the desired substitution in **91**. While the desired group for migration should be one of the two methyls, a ring contraction is possibility, funneling material to the now exocyclic alkene **93**. The listed silver salts in different solvents typically led to decomposition (Entries 2, 5, 10) or unreacted starting material (Entries 3, 4, and 9). However, under the conditions detailed in Entries 1, 6, and 7, a new product was observed, one that had a promising ^{1}H NMR spectrum revealing loss of the *ipso*-I proton and shift of the methyl peaks downfield due to their allylic or benzylic positioning. Both **91** and **93** showed these key ^{1}H NMR peaks, so derivatization was preformed to determine the exact structure. Oxidative cleavage of this new compound produced a new material that lacked the two methyl groups, confirming the structure as **93**. While this product was not the desired one, this ring contraction most likely occurs due to the alignment of the highlighted C-C sigma bond with the antibonding I-C.[24] In the chair-chair conformation of the decalin framework, the methyl groups are not properly aligned and cannot rotate to achieve the position necessary to shift.

Table 6: Attempts to Generate the Core Structure **91**

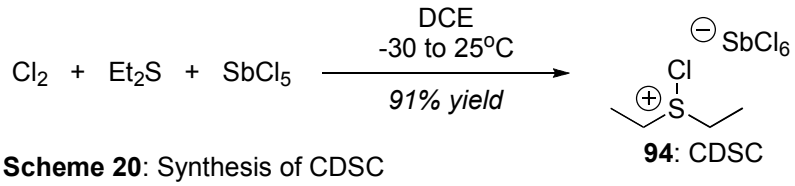


Entry	Ag^+	Solvent	Results
1	AgOAc	CH_2Cl_2	**28** and **93**
2	$AgBF_4$	CH_2Cl_2	decomp
3	$AgNO_3$	CH_2Cl_2	**28**
4	Ag_2SO_4	CH_2Cl_2	**28**
5	AgF_2	CH_2Cl_2	decomp
6	AgTFA	CH_2Cl_2	**93** and decomp
7	AgOAc	AcOH	41% **93**
8	AgOAc	MeOH	elimination product
9	AgOAc	MeCN	**28**
10	AgOAc	$MeNO_2$	decomp

2.5 Chloronium-Induced Polyene Cyclization

While BDSB and IDSI were the first halonium reagents developed by our group, the chloronium variant also has great merit as numerous natural products are derived from a chloronium-induced polyene cyclization as described in Section 2.1. Synthesis of the chloronium reagent followed a similar experimental protocol, now using chlorine gas as the halogen source, and was readily crystallized like BDSB. The isolated white crystalline solid was termed CDSC (**94**), following the same naming scheme as the other XDSX reagents. CDSC shows similar stability to BDSB; both could be handled in air at

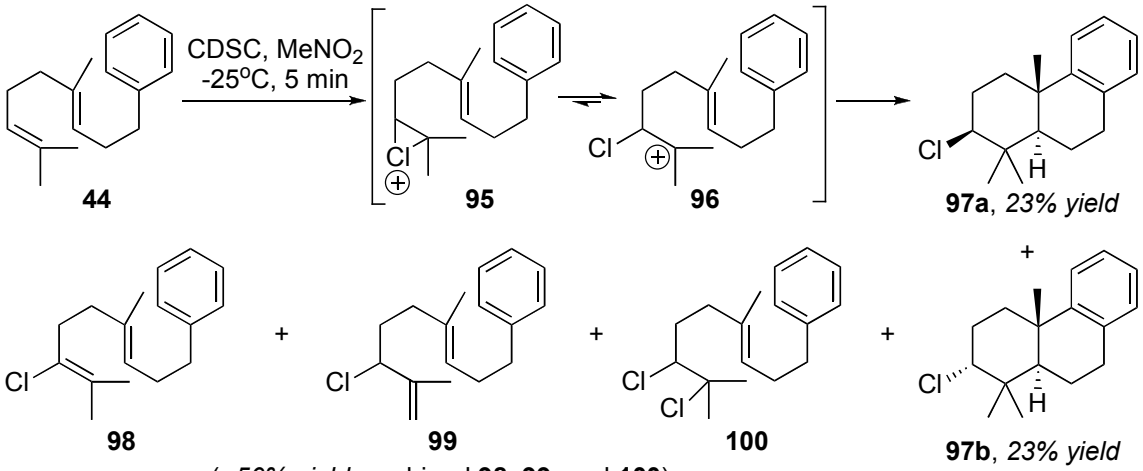
25°C and stored at -20°C to prevent decomposition. The dimethyl sulfide variant of CDSC had been previously synthesized.[25]



94: CDSC

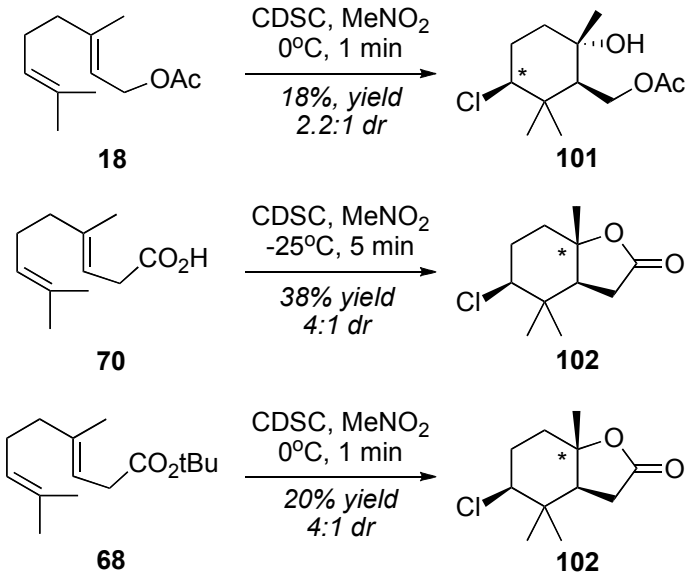
Scheme 20: Synthesis of CDSC

With the new reagent in hand, a variety of polyene cyclizations were examined. As shown in Scheme 21, treatment of homogeranyl benzene (**44**) with 1 equiv of CDSC in nitromethane at -25°C for 5 min yielded a mixture of products. The major product was the desired **97**, but the reaction was not diastereoselective as previously observed with the other two XDSX reagents. This outcome may reflect the propensity for the 3-membered chloronium intermediate **95** to preferentially exist in the open tertiary carbocation form (i.e. **96**).[26] Because of this preference, intramolecular attack from the remaining alkene occurs through an open transition state, allowing attack from either face of the carbocation and producing both diastereomers of the product at the chlorine center. In support of such an intermediate (**96**), a number of byproducts, including **98**, **99**, and **100**, were observed which would likely be formed if such a species had been generated.



Scheme 21: Initial Exploration of CDSC-Promoted Polyene Cyclization

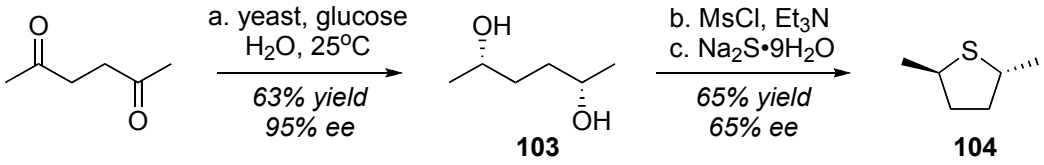
Looking at additional substrates, CDSC proved capable of cyclizing **18**, **70**, and **68** (Scheme 22). Though, similar to the previous example, poor yields and diastereoselectivity were observed. While substrate **101** was diastereomeric about the chloride, the cyclic lactone **102** had two products about the bridgehead methyl. Diastereomers of each product about the other chiral centers are possible, as the low yields observed may be due to additional diastereomers that were difficult to isolate and purify after work-up. Overall, CDSC is the first chloronium reagent that generates to some degree polyene cyclized products; yet, the alternative mechanism occurring for chloronium cyclizations causes loss of stereocontrol.



Scheme 22: Substrate Scope of Polyene Cyclization Using CDSC

2.6 Enantioselective Polyene Cyclization

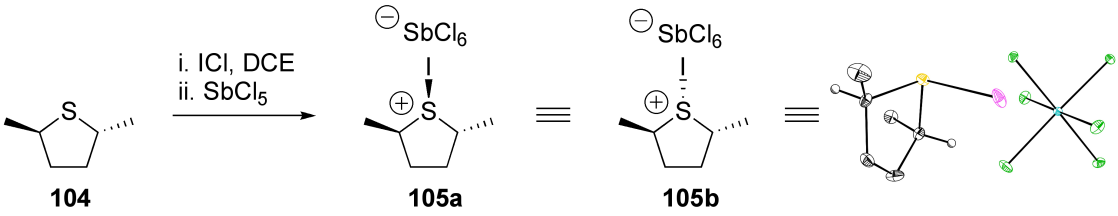
With such success in polyene cyclization using our developed BDSB, IDSI, and CDSC halonium reagents, we hoped to be able to translate these findings into an asymmetric variant (work done in collaboration with coworker Dr. Daniel Treitler).[27] For instance, replacement of the diethyl sulfide backbone of the XDSX reagents with a chiral sulfide could potentially generate a chiral XDSX variant.[28] At the onset of this work, we focused on synthesizing simple chiral sulfides, such as dimethyl thiolane **104** (Scheme 23). 2,5-Hexadione was enzymatically reduced in an asymmetric manner to produce diol **103** in a 63% yield and 95% ee.[29] This chiral diol was bismesylated and treated with Na_2S, which underwent two S_N2 substitutions, to afford thiolane **104** in a 65% yield. The enantiomeric excess of this prepared thiolane was only 65% (measured by optical rotation), implying that racimazation had occurred during this sequence; potentially an S_N1 reaction occurred at some point.



Reagents and Conditons: a. yeast, glucose, water, 35°C, 12 h, 63%; b. MsCl (4 equiv), Et_3N (6 equiv), CH_2Cl_2, -20 to 0°C, 1 h; c. $Na_2S•9H_2O$ (2 equiv), EtOH, 25°C, 30 min, 65%.

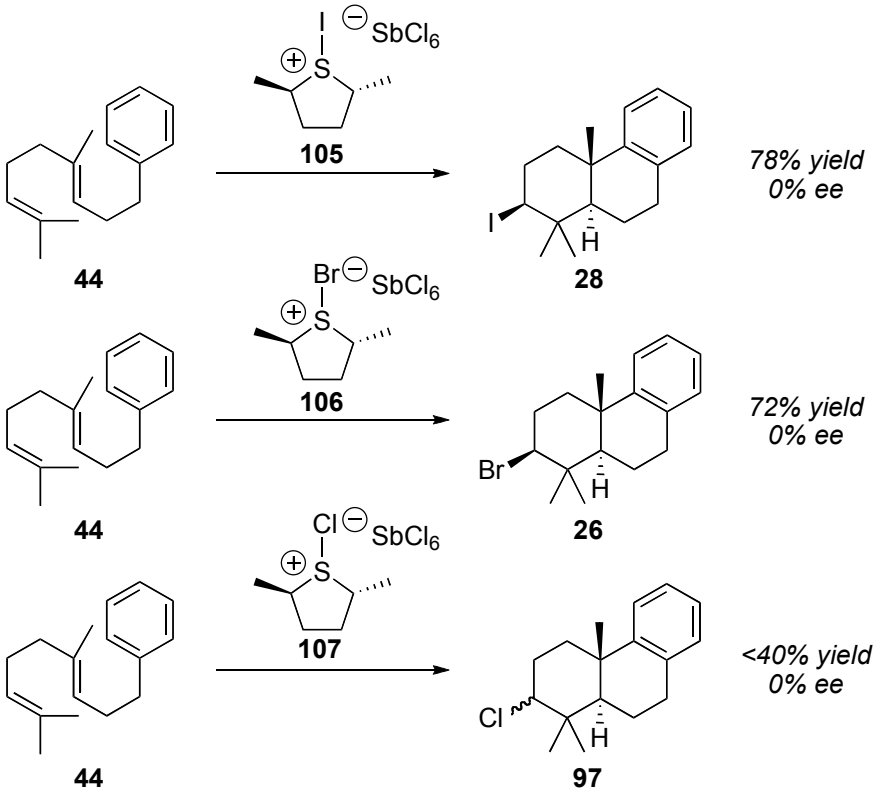
Scheme 23: Synthesis of Chiral Thiolane **104**

Nevertheless, despite the loss of some ee, we continued to push forward. Upon iodonium formation under standard conditions as shown in Scheme 24; though these reagents **105a** and **105b** are identical because of the C_2-symmetry of the thiolane.[30] Crystallographic analysis of compound **105** confirmed a monomeric structure in the solid state, differing from achiral IDSI crystals.



Scheme 24: Synthesis of Chiral Iodonium Reagent and Crystal Structure to Verify Structure

With the chiral iodonium reagent in hand, polyene cyclization using homogeranyl benzene was again tested (Scheme 25). While the linear polyene underwent cyclization quite smoothly to generate the iodinated bicycle **28** in 78% yield, unfortunately the product was racemic. Work done by my colleague, Dr. Daniel Treilter, proved that the other reagents containing bromine and chlorine also underwent polyene cyclization, but without any induced chirality. However, while polyene cyclization was not rendered enantioselective, as will be described in the next chapter, these chiral halonium reagents are capable of transferring X^+ asymmetrically to a simpler substrate, containing only a single alkene.[27]



Scheme 25: Attempts at Asymmetric Polyene Cyclizations Using Chiral XDSX Reagents

2.7 Conclusion

The discovery of IDSI, a new iodonium reagent, has enabled the first cyclization reactions of electron rich and poor linear polyene precursors in good yield, typically affording only a single product diastereomer. While the utility of the installed iodine is not necessarily in the atom itself, it does afford a new handle capable of being converted into new functionality. The benefit of the installation of an iodine atom was highlighted in its ability to streamline total syntheses of K-76, loliolide, and stemodin by decreasing step count and boosting yields of previous technologies. Moreover, IDSI has proven a suitable alternative for the mercury (II) salts, thereby offering a green replacement for the use of stoichiometric amounts of highly toxic reagents. While I have discovered IDSI and its use as an iodonium electrophile, we were pleased to learn this reagent also has

unique features highlighted in the total synthesis of a member of the resveratrol family of polyphenols[31] as well as in stereoselective polyketide synthesis.[32] The chloronium reagent, CDSC, was developed and similarly used to perform the first reported polyene cyclization of both electron rich and deficient alkenes. These XDSX reagents (BDSB, IDSI, and CDSC) appear unique in their ability to act as a "naked" halonium sources without a nucleophilic or basic counterion present in solution. This property could lead to further advancements in organic chemistry outside of direct polyene cyclizations.

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2.9 Experimental Section

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry methylene chloride (CH_2Cl_2), benzene, toluene, diethyl ether (Et_2O) and tetrahydrofuran (THF) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns; acetonitrile (MeCN) was dried over 3 Å molecular sieves, distilled, and stored over 3 Å molecular sieves; pyridine was distilled from CaH_2 and stored over 3 Å molecular sieves; triethylamine (Et_3N) was distilled from KOH; N,N-dimethylformamide (DMF) was stored over 3 Å molecular sieves; 1,2-dichloroethane, acetone, and methanol (MeOH) were purchased in anhydrous form from Sigma-Aldrich and used as received. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an aqueous solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. Preparative thin-layer chromatography was carried out on 0.50 mm E. Merck silica gel plates (60F-254). SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. NMR spectra were recorded on Bruker DRX-300 and DRX-400 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, AB = AB quartet, br = broad,

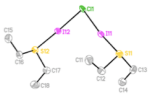
app = apparent. IR spectra were recorded on a Nicolet Avatar 370 DTGS series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded in the Columbia University Mass Spectral Core facility on a JOEL HX110 mass spectrometer using FAB (Fast Atom Bombardment) and EI (Electron Ionization) techniques. All enantiomeric excess (*e.e.*) values were obtained by HPLC using a Daicel CHIRALCEL OD column.

Abbreviations. AcOH = acetic acid, AgOAc = silver (I) acetate, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, EtOH = ethanol, Et2S, diethyl sulfide, HBF_4•Et_2O = tetrafluoroboric acid diethyl ether complex, MeLi = methyl lithium, Me_3OBF_4 = trimethyloxonium tetrafluoroborate, $Mn(OAc)_3$•$2H_2O$ = manganese (III) acetate dihydrate, MOMCl = chloromethyl methyl ether, MsCl = methanesulfonyl chloride, *n*-BuLi = *n*-butyl lithium, TBDPSCl = *tert*-butyldiphenylsilyl chloride, TBHP = *tert*-butyl hydrogen peroxide, TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate, *t*-BuLi = *tert*-butyl lithium.

Note. Synthetic procedures, complete characterization, and ^{1}H and ^{13}C NMR spectra of **18**, **38**, **40**, **44**, **49**, **51**, **55**, **68**, and **70** are available in the preliminary publication on polyene cyclization using BDSB: Snyder, S. A.; Treitler, D. S. *Angew. Chem. Int. Ed.* **2009**, *48*, 7899–7903.

IDSI (43). Et_2S (0.54 mL, 5.0 mmol, 2.0 equiv) was added dropwise to a solution of I_2 (0.64 g, 2.5 mmol, 1.0 equiv) in 1,2-dichloroethane (15 mL) at 0 °C. The mixture was stirred for 5 min at 0 °C. $SbCl_5$ (1.0 M in CH_2Cl_2, 5.0 mL, 5.0 mmol, 2.0 equiv) was then added dropwise, and the resultant solution was allowed to slowly warm to 25 °C

over 30 min, then stirred for an additional 2 h at 25 °C. Upon completion, and in order to collect IDSI crystals, hexanes (4 mL) was carefully pipetted onto the top of the solution and the layered solution was cooled to –20 °C for 24 h. The resulting orange crystals were isolated by decanting off the liquid, rinsing with hexanes (2 x 1 mL), and then drying under vacuum prior to use in cation-p cyclizations (1.26 g, 78% yield).



[Note from crystallographer: The iodine thermal parameters are elongated in the direction of the bond, and this implies that there may be a chlorine impurity. This can therefore artificially change the observed bond lengths and angles. The atoms have been assigned based on the information of the synthetic chemists].

28. A solution of IDSI (0.097 g, 0.120 mmol, 1.2 equiv) in nitromethane (0.5 mL) was quickly added via syringe to a solution of homogeranylbenzene (**44**, 0.023 g, 0.100 mmol, 1.0 equiv) in nitromethane (1.5 mL) at –25 °C. After stirring for 5 min at –25 °C, the resulting mixture was poured into a solution of saturated aqueous $NaHCO_3$:5% aqueous Na_2SO_3 (1:1, 10 mL) and the resultant biphasic mixture was stirred vigorously for 15 min at 25 °C. The reaction contents were then extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes: CH_2Cl_2, 9:1) to afford tricycle **28** (0.034 g, 93% yield) as a colorless amorphous solid.

28: R_f = 0.49 (silica gel, hexanes: CH_2Cl_2, 9:1); IR (film) ν_{max} 3058, 2965, 2945, 1488, 1475, 1377, 762, 723, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20–7.03 (m, 4 H), 4.28 (dd, *J* = 13.2, 4.0 Hz, 1 H), 2.92–2.87 (m, 2 H), 2.57 (dq, *J* = 3.6, 13.6 Hz, 1 H), 2.45 (dq, *J* = 14.0, 3.6 Hz, 1 H), 2.17 (dt, *J* = 13.2, 3.6 Hz, 1 H), 2.00 (m, 1 H), 1.82 (m, 1 H), 1.62–1.54 (m, 2 H), 1.25 (s, 3 H), 1.13 (s, 3 H), 1.09 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.8, 134.8, 129.2, 126.0, 125.7, 124.6, 53.5, 50.0, 41.9, 39.7, 38.3, 34.5, 33.2, 31.0, 25.0, 21.8, 21.3; HRMS (EI) calcd for $C_{17}H_{23}I$ $[M]^+$ 354.0845, found 354.0840.

Polyene Cyclization of 44 Using Ipy_2BF_4/HBF_4. Prepared according to: Barluenga, J.; Trincado, M.; Rubio, E.; González, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 3416–3417. A suspension of bis(pyridine)iodonium tetrafluoroborate (0.037 g, 0.100 mmol, 1.0 equiv) in CH_2Cl_2 (0.1 mL) was stirred for 5 min at 25 °C until the solid dissolved. The reaction contents were then cooled to –40 °C and HBF_4•Et_2O (0.014 mL, 0.100 mmol, 1.0 equiv) was added. After stirring for 10 min at –40 °C, homogeranylbenzene (**44**, 0.023 g, 0.100 mmol, 1.0 equiv) was added as a solution in CH_2Cl_2 (0.8 mL). The reaction mixture was kept at –40 °C for 3 h with constant stirring. Upon completion, the reaction contents were quenched with ice-cold water (10 mL), $Na_2S_2O_3$ (0.100 g) was added, and the materials were extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (10 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant brown oil was purified by flash column chromatography (silica gel, hexanes:CH_2Cl_2, 9:1) to afford bicycle **28** (0.015 g, 41% yield) as a colorless amorphous solid. [**Note**: Since the partially-cyclized compounds are difficult to isolate, we calculated 7% yield partially-cyclized material and 6% proton-cyclized product based

on ^{1}H NMR ratios of diagnostic signals. The remaining mass balance was divided between incorrect diastereomers and other unknown products. The proton-cyclized product **45** was spectroscopically identical to previously reported material: (a) Rosales, V.; Zambrano, J. L.; Demuth, M. *J. Org. Chem.* **2002**, *67*, 1167–1170. (b) Banick, B. K.; Chakraborti, A. K.; Ghatak, U. R. *J. Chem. Res. Miniprint* **1986**, 3391.]

Using the above conditions with substrate **16** afforded 47% isolated yield of the tetra-substituted partially-cyclized product **67a**. The remaining mass was assigned as a mixture of di- and tri-substituted alkene isomers (partially-cyclized material), as well as trace starting material. Product **63** was not observed under these conditions.

Using the above conditions with substrate **68** afforded approx a 50% isolated yield of the cyclized product **71**. The remaining mass was starting material.

Polyene Cyclization of 44 Using PPh_3/NIS. Prepared according to: Sakakura, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900–903. A solution of homogeranylbenzene (**44**, 0.023 g, 0.100 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) was added to a solution of triphenylphosphine (7.9 mg, 0.0030 mmol, 30 mol %) in CH_2Cl_2 (0.5 mL) at -78 °C. *N*-Iodosuccinimide (0.023 g, 0.100 mmol, 1.0 equiv) was added to the reaction mixture, which was kept at -78 °C for 24 h. The reaction mixture was then warmed to –40 °C and kept at -40 °C for 6 h with constant stirring. The reaction contents were then quenched with 20% aqueous $Na_2S_2O_3$ (5 mL) and the materials were extracted with hexanes (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. Since the partially-cyclized compounds are difficult to isolate, we calculated a 1.8:1.0 ratio of partially-cyclized material:starting

material based on ^{1}H NMR ratios of diagnostic signals. The desired product **45** was observed in trace amounts.

Using the above conditions with substrate **16** afforded a 3.5:1.0 starting material:partially-cyclized material based on the crude ^{1}H NMR. The desired product **63** was not observed under these conditions.

Using the above conditions with substrate **68** afforded approx 15% yield of the desired cyclized product **71** with the remainder of the mass balance being recovered starting material.

Preparation of Polyene Cyclization Precursors

47. Procedure adapted from: Pouységu, L.; Chassaing, S.; Dejugnac, D.; Lamidey, A.-M.; Miqueu, K.; Sotiropoulos, J.-M.; Quideau, S. *Angew. Chem.* **2008**, *47*, 3552–3555. First, *t*-BuLi (1.7 M in pentane, 0.690 mL, 1.17 mmol, 3.0 equiv) was added dropwise to solution of **38** (0.100 g, 0.390 mmol, 1.0 equiv) in THF (1.5 mL) at –40 °C. The reaction mixture was then stirred at –40 °C for 1 h. Next, trimethylborate (0.135 mL, 1.17 mmol, 3.0 equiv) was added in a single portion at –40 °C, and the reaction mixture was then allowed to warm to 0 °C over the course of 1 h. A solution of 1 M NaOH: aqueous 30% H_2O_2 (1:1, 0.6 mL) was then carefully added at 0 °C and the reaction mixture was stirred for an additional 30 min at 0 °C. The reaction contents were then quenched with saturated aqueous Na_2SO_3 (5 mL) and the resultant biphasic mixture was stirred for 10 min at 25 °C. The mixture was then extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with water (50 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant colorless oil was purified by flash column

chromatography (silica gel, hexanes:EtOAc, 9:1) to give the desired phenol (0.096 g, 90% yield) as a colorless oil. Next, to a solution of a portion of the newly prepared phenol (0.063 g, 0.230 mmol, 1.0 equiv) and methanesulfonic acid (0.044 mL, 0.260 mmol, 2.0 equiv) in THF (1 mL) at 0 °C was slowly added NaH (60% dispersion in mineral oil, 0.040 g, 1.00 mmol, 4.3 equiv). The resulting suspension was allowed to warm to 25 °C and stirred for 3 h. Upon completion, the reaction contents were poured into water (10 mL) and extracted with Et_2O (5 × 15 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. The resulting yellow oil was purified by flash column chromatography (silica gel, hexanes:EtOAc, 20:1) to afford cyclization precursor **47** (0.063 g, 95% yield) as a light yellow oil. **47:** R_f = 0.29 (silica gel, hexanes:EtOAc, 9:1); IR (film) ν_{max} 2928, 2854, 1516, 1464, 1263, 1236, 1156, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.79 (dd, *J* = 6.4, 2.0 Hz, 1 H), 6.73 (dd, *J* = 6.8, 2.0 Hz, 2 H), 5.18 (tt, *J* = 7.2, 1.2 Hz, 1 H), 5.09 (tt, *J* = 6.8, 1.2 Hz, 1 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 2.59 (t, *J* = 7.2 Hz, 2 H), 2.29 (q, *J* = 7.6 Hz, 2 H), 2.11–1.94 (m, 4 H), 1.69 (s, 3 H), 1.60 (s, 3 H), 1.57 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.9, 147.3, 135.8, 135.3, 131.4, 124.5, 123.8, 120.4, 112.0, 111.4, 56.1, 55.9, 39.8, 35.8, 30.2, 26.9, 25.8, 17.8, 16.2; HRMS (EI) calcd for $C_{19}H_{28}O_2$ $[M]^+$ 288.2094, found 288.2089.

58. Prepared according to: Alonso, E.; Guijarro, D.; Martínez, P.; Ramón, D. J.; Yus, M. *Tetrahedron* **1999**, *55*, 11027–11038. 0.546 g (85% yield) as a yellow viscous oil. **58:** R_f = 0.66 (silica gel, hexanes:EtOAc, 19:1); IR (film) ν_{max} 2972, 2933, 1739, 1369, 1277, 1254, 1166 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.37 (dt, *J* = 1.2, 6.8 Hz, 1 H), 5.08 (tt, *J* = 6.8, 1.2 Hz, 1 H), 4.55 (dd, *J* = 7.2, 0.8 Hz, 2 H), 2.14–2.04 (m, 4 H),

1.75 (s, 3 H), 1.68 (s, 3 H), 1.59 (s, 3 H), 1.47 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 142.8, 132.3, 123.7, 119.1, 81.9, 63.6, 32.3, 27.9 (3 C), 26.8, 25.8, 23.6, 17.8; HRMS (FAB) calcd for $C_{15}H_{25}O_3$ $[M-H]^+$ 253.1804, found 253.1794.

Standard Procedure for Small-Scale Polyene Cyclizations with IDSI

A solution of IDSI (0.0965 g, 0.120 mmol, 1.2 equiv) in nitromethane (0.5 mL) was quickly added to a solution of the substrate (0.100 mmol, 1.0 equiv) in nitromethane (1.5 mL) at the temperature indicated. After stirring the reaction contents for the indicated time, the mixture was poured into a solution of saturated aqueous $NaHCO_3$:5% aqueous Na_2SO_3 (1:1, 10 mL) and the resultant biphasic mixture was vigorously stirred for an additional 15 min at 25 °C. Upon completion, the reaction contents were extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified either by flash column chromatography or preparative TLC to yield the desired cation-π cyclization products in the amount and yields indicated below.

39. White crystalline solid, 0.035 g, 90% yield; R_f = 0.35 (silica gel, hexanes:EtOAc, 19:1); IR (film) ν_{max} 2949, 2924, 2851, 1609, 1502, 1463, 1264, 1044, 870, 669 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, *J* = 8.4 Hz, 1 H), 6.72 (d, *J* = 2.4 Hz, 1 H), 6.67 (dd, *J* = 8.0, 2.4 Hz, 1 H), 4.27 (dd, *J* = 12.8, 4.0 Hz, 1 H), 3.77 (s, 3 H), 2.90–2.77 (m, 2 H), 2.54 (dq, *J* = 3.6, 13.4 Hz, 1 H), 2.44 (dq, *J* = 14.0, 4.0 Hz, 1 H), 2.11 (dt, *J* = 13.2, 3.6 Hz, 1 H), 1.98 (m, 1 H), 1.79 (m, 1 H), 1.60 (dd, *J* = 13.2, 4.0 Hz, 1 H), 1.53 (m, 1 H), 1.25 (s, 3 H), 1.13 (s, 3 H), 1.08 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 150.4, 130.2, 127.3, 111.5, 110.6, 55.7, 53.8, 50.3, 42.2, 39.9, 38.7, 34.8, 33.5,

30.4, 25.2, 22.2, 21.6; HRMS (EI) calcd for $C_{18}H_{25}IO$ $[M]^+$ 384.0950, found 384.0952.

48. Yellow amorphous solid, 0.030 g, 73% yield; R_f = 0.29 (silica gel, hexanes:EtOAc, 9:1); IR (film) ν_{max} 2947, 2847, 1510, 1463, 1256, 1146 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.67 (s, 1 H), 6.51 (s, 1 H), 4.28 (dd, *J* = 13.2, 4.4 Hz, 1 H), 3.83 (s, 6 H), 2.82 (dd, *J* = 8.8, 4.4 Hz, 2 H), 2.56 (dq, *J* = 3.2, 13.2 Hz, 1 H), 2.44 (dq, *J* = 14.0, 4.0 Hz, 1 H), 2.10 (dt, *J* = 13.2, 3.6 Hz, 1 H), 1.98 (m, 1 H), 1.80 (m, 1 H), 1.62–1.51 (m, 2 H), 1.24 (s, 3 H), 1.13 (s, 3 H), 1.07 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4, 147.2, 140.9, 127.0, 111.6, 111.5, 50.3 (2 C), 42.2, 39.6, 38.0, 34.5, 33.2 (2 C), 30.8, 25.0, 24.9, 21.9, 21.3; HRMS (EI) calcd for $C_{19}H_{27}IO_2$ $[M]^+$ 414.1056, found 414.1068.

50. Yellow crystalline solid, 0.042 g, 85% yield; R_f = 0.64 (silica gel, hexanes: EtOAc, 4:1); IR (film) ν_{max} 2946, 2866, 2825, 1482, 1388, 1195, 1151, 1134, 1011, 964, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.96 (s, 1 H), 6.86 (s, 1 H), 5.13 (s, 2 H), 4.23 (dd, *J* = 12.8, 4.0 Hz, 1 H), 3.53 (s, 3 H), 2.77 (dd, *J* = 16.8, 5.6 Hz, 1 H), 2.67 (dd, *J* = 16.4, 12.8 Hz, 1 H), 2.45 (dq, *J* = 14.0, 4.0 Hz, 1 H), 2.29 (dq, *J* = 3.6, 13.6 Hz, 1 H), 1.87–1.69 (m, 3 H), 1.21 (s, 3 H), 1.12 (s, 3 H), 1.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 147.4, 122.0, 121.4, 117.8, 111.4, 96.2, 76.3, 56.5, 49.1, 46.5, 42.4, 39.0, 34.3, 32.2, 25.8, 19.9, 19.7; HRMS (FAB) calcd for $C_{18}H_{24}BrIO_3$ $[M]^+$ 493.9954, found 493.9931.

52. Colorless viscous oil, 0.025 g of a 8.5:1.4:1.0 mixture of alkene isomers (trisubstituted:tetrasubstituted:disubstituted), 85% combined yield; Major alkene isomer of **52b**: R_f = 0.33 (silica gel, hexanes:EtOAc, 4:1); IR (film) ν_{max} 2969, 2935, 2858, 2246, 1445, 1372, 1139, 844 cm^{-1}; Diagnostic ^1H NMR signals (400 MHz, $CDCl_3$) δ 5.32 (br s, 1 H), 4.33 (dd, *J* = 10.8, 5.6 Hz, 1 H), 2.72 (dd, *J* = 17.6, 4.8 Hz, 1 H), 2.47 (dd, *J* =

17.2, 5.6 Hz, 1 H), 1.80 (s, 3 H), 1.19 (s, 3 H), 1.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.7, 125.2, 119.9, 46.9, 45.4, 37.7, 34.1, 28.0, 21.6, 18.1, 18.0; HRMS (EI) calcd for $C_{11}H_{16}IN$ $[M]^+$ 289.0328, found 289.0315. [Diagnostic ^{1}H NMR signals for other isomers: tetrasubstituted δ 4.41 (dd, *J* = 9.6, 4.4 Hz, 1 H), 3.07 (AB, *J* = 44.4, 17.6 Hz, 2 H), 1.74 (s, 3 H), 1.26 (s, 3 H), 1.23 (s, 3 H); disubstituted δ 5.06 (s, 1 H), 4.78 (s, 1 H), 1.22 (s, 3 H), 0.88 (s, 3 H)].

53. White crystalline solid, 0.015 g, 45% yield; R_f = 0.42 (silica gel, hexanes: EtOAc, 1:1); IR (film) ν_{max} 3394 (br), 2971, 2947, 1736, 1372, 1244, 1140, 1028, 913 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.45 (dd, *J* = 12.0, 4.8 Hz, 1 H), 4.31 (dd, *J* = 12.0, 5.2 Hz, 1 H), 4.16 (dd, *J* = 12.8, 4.0 Hz, 1 H), 2.53 (br s, 1 H), 2.36 (dq, *J* = 14.0, 4.0 Hz, 1 H), 2.20 (dq, *J* = 4.0, 13.6 Hz, 1 H), 2.06 (s, 3 H), 1.77 (t, *J* = 5.2 Hz, 1 H), 1.66 (dt, *J* = 13.2, 3.6 Hz, 1 H), 1.56 (dt, *J* = 4.0, 13.6 Hz, 1 H), 1.23 (s, 3 H), 1.14 (s, 3 H), 1.02 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 72.0, 64.1, 54.3, 49.5, 44.9, 39.6, 34.9, 32.9, 23.8, 21.3, 20.5; HRMS (EI) calcd for $C_{12}H_{21}IO_3$ $[M]^+$ 340.0535, found 340.0540.

54. Colorless viscous oil, 0.014 g, 39% yield, contaminated with ~15% of an inseparable, unidentified impurity; R_f = 0.28 (silica gel, hexanes: EtOAc, 20:1); IR (film) ν_{max} 2980, 2934, 1784, 1370, 1232, 1023 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47 (t, *J* = 7.2 Hz, 1 H), 4.63 (d, *J* = 6.8 Hz, 2 H), 4.16 (dd, *J* = 11.2, 1.2 Hz, 1 H), 2.40 (m, 1 H), 2.28 (m, 1 H), 2.15 (m, 1 H), 2.08 (s, 3 H), 1.92 (m, 1 H), 1.88 (s, 3 H), 1.75 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 140.1, 120.2, 72.5, 61.3, 48.6, 39.4, 35.6, 34.2, 28.4, 21.2, 16.5; HRMS (FAB) calcd for $C_{12}H_{19}ClIO_2$ $[M-H]^+$ 357.0118, found 357.0135.

57. Light yellow crystalline solid, 0.018 g, 57% yield; R_f = 0.26 (silica gel, hexanes: EtOAc, 3:2); IR (film) ν_{max} 2932, 1732, 1223, 1135, 1081 cm^{-1}; ^{1}H NMR (400

MHz, $CDCl_3$) δ 4.51 (dd, *J* = 10.8, 5.6 Hz, 1 H), 4.42 (dd, *J* = 12.7, 10.8 Hz, 1 H), 4.14 (dd, *J* = 12.8, 4.0 Hz, 1 H), 2.47 (dq, *J* = 14.4, 4.0, 1 H), 2.21 (m, 1 H), 2.11 (dd, *J* = 12.8, 5.6 Hz, 1 H), 1.85 (dt, *J* = 13.2, 3.6 Hz, 1 H), 1.75 (dt, *J* = 4.4, 0.8 Hz, 1 H), 1.52 (s, 3 H), 1.11 (s, 3 H), 1.01 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 81.0, 68.4, 45.7, 45.1, 41.2, 37.8, 33.8, 31.2, 20.9, 20.1; HRMS (FAB) calcd for $C_{11}H_{18}IO_3$ $[M+H]^+$ 325.0301, found 325.0290.

60. White amorphous solid, 0.016 g, 48% yield; R_f = 0.26 (silica gel, hexanes: EtOAc, 3:2); IR (film) ν_{max} 2971, 2946, 1742, 1214, 1112 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 (dd, *J* = 12.4, 6.0 Hz, 1 H), 4.52 (br s, 1 H), 4.47 (d, *J* = 12.0 Hz, 1 H), 2.28–2.11 (m, 2 H), 2.01 (m, 1 H), 1.94–1.88 (m, 2 H), 1.55 (s, 3 H), 1.28 (s, 3 H), 1.19 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 80.7, 66.4, 50.7, 40.1, 37.1, 35.5, 35.1, 28.8, 28.1, 20.1; HRMS (EI) calcd for $C_{11}H_{17}IO_3$ $[M]^+$ 324.0222, found 324.0205.

41. In order to ensure completion in the final cyclization leading to tetracycle **41**, methanesulfonic acid (0.100 mL, 1.50 mmol, 15 equiv) was added to the reaction mixture at –25 °C after the initial 5 min IDSI-cyclization period, and the resultant solution was stirred for 60 min at –25 °C prior to the standard reaction quench described above. **41:** white amorphous solid, 0.025 g, 60% yield; R_f = 0.47 (silica gel, hexanes: CH_2Cl_2, 9:1); IR (film) ν_{max} 3059, 2941, 2868, 1451, 1386, 1145, 758 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (m, 1 H), 7.16–7.00 (m, 3 H), 4.26 (dd, *J* = 13.2, 4.4 Hz, 1 H), 2.98–2.78 (m, 2 H), 2.49 (dq, *J* = 4.0, 13.6 Hz, 1 H), 2.38 (dt, *J* = 12.4, 3.2 Hz, 1 H), 2.31 (dq, *J* = 13.6, 3.6 Hz, 1 H), 1.88–1.63 (m, 5 H), 1.58–1.49 (m, 2 H), 1.28 (dd, *J* = 12.0, 2.4 Hz, 1 H), 1.20 (s, 3 H), 1.10 (dd, *J* = 11.6, 2.0 Hz, 1 H), 1.06 (s, 3 H), 1.02 (s, 3 H), 0.99 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9, 134.9, 128.9, 125.9, 125.4, 124.6, 55.5, 55.2,

55.0, 43.2, 40.8, 39.6, 38.2, 37.9, 34.0, 33.2, 30.8, 26.1, 21.8, 21.0, 18.2, 16.3; HRMS (EI) calcd for $C_{22}H_{31}I$ $[M]^+$ 422.1471, found 422.1471.

Alkene 27. DBU (0.25 mL, 1.70 mmol, 20 equiv) was added to a solution of **28** (0.030 g, 0.085 mmol, 1.0 equiv) in pyridine (1 mL) at 25 °C. The resultant solution was then heated with stirring at 120 °C for 12 h. Upon completion, the reaction contents were cooled to 25 °C, quenched with saturated aqueous NH_4Cl (10 mL), and extracted with Et_2O (3 × 10 mL). The combined organic layers were then washed with water (10 mL), dried ($MgSO_4$), filtered, and concentrated. The resulting brown oil was purified by flash column chromatography (silica gel, hexanes:CH_2Cl_2, 9:1) to afford alkene **27** (0.160 g, 83% yield) as a white amorphous solid. **27:** R_f = 0.68 (silica gel, hexanes: CH_2Cl_2, 9:1); IR (film) ν_{max} 3011, 2959, 2936, 2838, 1489, 1447, 1373, 1044, 758, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 1 H), 7.18–7.02 (m, 3 H), 5.62 (ddd, *J* = 10.0, 6.0, 2.0 Hz, 1 H), 5.50 (dd, *J* = 10.0, 2.8 Hz, 1 H), 2.96–2.80 (m, 2 H), 2.55 (dd, *J* = 16.8, 6.0 Hz, 1 H), 2.13 (d, *J* = 16.4 Hz, 1 H), 1.87 (m, 1 H), 1.76–1.65 (m, 2 H), 1.27 (s, 3 H), 1.06 (s, 3 H), 1.00 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.1,138.3, 135.6, 129.0, 126.2, 126.1, 125.4, 122.0, 48.3, 39.9, 37.2, 35.2, 32.0, 31.3, 25.4, 22.5, 20.1; HRMS (EI) calcd for $C_{17}H_{22}$ $[M]^+$ 226.1722, found 226.1716.

Formal Synthesis of K-76

16. Procedure adapted from: Brown, R. C. D.; Bataille, C. J.; Hughes, R. M.; Kenney, A.; Luker, T. J. *J. Org. Chem.* **2002**, *67*, 8079–8085. To a solution of CuI (0.24 g, 1.3 mmol, 1.5 equiv) in Et_2O (15 mL) at 0 °C was added MeLi (1.6 M in Et_2O, 1.6 mL,

2.6 mmol, 3.0 equiv) dropwise. After 5 min at 0 °C, the reaction mixture was cooled to –78 °C and a solution of **74** (0.345 g, 0.859 mmol, 1.0 equiv) in Et_2O (2 mL) was added. The reaction mixture was allowed to slowly warm to –30 °C over the course of 2 h, then quenched with saturated aqueous NH_4Cl (10 mL). The reaction mixture was poured into water (5 mL), and extracted with hexanes:EtOAc (2:1, 3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. The crude yellow viscous oil was purified by careful column flash column chromatography (silica gel, hexanes:CH_2Cl_2, 9:1→5:2) to afford **16** (0.175 g, 77% yield) as a light yellow viscous oil, spectroscopically identical to previously synthesized material.

63. Following the above procedure for the poylene cyclizations with IDSI at –25 °C for 5 min using substrate **16**, cyclization product **63** (0.013 g, 77% yield) was obtained as a colorless viscous oil. **63:** R_f = 0.43 (silica gel, hexanes:EtOAc, 9:1); IR (film) ν_{max} 2971, 2947, 2852, 1735, 1440, 1164, 1132 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.51 (br s, 1 H), 4.25 (dd, *J* = 12.8, 4.4 Hz, 1 H), 3.67 (s, 3 H), 2.90 (br s, 1 H), 2.42–2.25 (m, 2 H), 2.20–2.02 (m, 2 H), 1.60 (br s, 3 H), 1.51 (q, *J* = 4.0 Hz, 1 H), 1.46 (m, 1 H), 1.43 (dd, *J* = 11.4, 5.6 Hz, 1 H), 1.09 (s, 3 H), 1.04 (s, 3 H), 0.99 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 129.1, 124.0, 61.9, 53.0, 51.3, 48.7, 43.3, 39.2, 36.5, 33.8, 33.3, 26.2, 21.3, 21.1, 15.0; HRMS (FAB) calcd for $C_{16}H_{26}IO_2$ $[M+H]^+$ 377.0978, found 377.0977.

Alkene 65. DBU (0.160 mL, 1.00 mmol, 20 equiv) was added to a solution of **63** (0.020 g, 0.048 mmol, 1.0 equiv) in pyridine (1 mL) at 25 °C. The resulting solution was heated with stirring at 80 °C for 12 h. Upon completion, the reaction contents were quenched with saturated aqueous NH_4Cl (10 mL) and then extracted with Et_2O (3 × 10

mL). The combined organic layers were washed with water (10 mL), dried ($MgSO_4$), filtered, and concentrated. The resulting light yellow oil was purified by flash column chromatography (silica gel, hexanes:CH_2Cl_2, 4:1) to afford alkene **65** (0.010 g, 86% yield) as a colorless viscous oil. **65:** R_f = 0.43 (silica gel, hexanes:EtOAc, 9:1); IR (film) ν_{max} 3011, 2955, 1722, 1431, 1281, 1211, 1021, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.46 (ddd, *J* = 10.0, 5.6, 1.6 Hz, 1 H), 5.41 (dd, *J* = 10.4, 2.8 Hz, 1 H), 3.74 (s, 3 H), 2.13–1.97 (m, 2 H), 2.04 (d, *J* = 16.8 Hz, 1 H), 1.78 (dd, *J* = 16.4, 5.6 Hz, 1 H), 1.68 (m, 1 H), 1.64 (s, 3 H), 1.60–1.42 (m, 2 H), 1.18 (s, 3 H), 0.98 (s, 3 H), 0.92 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 138.1, 136.6, 133.5, 121.3, 51.2, 47.6, 37.2, 36.0, 34.9, 32.4, 31.8, 22.5, 21.3, 20.2, 19.5; HRMS (EI) calcd for $C_{16}H_{24}O_2$ $[M]^+$ 248.1776, found 248.1761.

Formal Synthesis of Loliolide

71. Following the above procedure for the polyene cyclizations with IDSI at –25 °C or 0 °C for 5 min using **70** or **68** respectively, cyclization product **71** (0.024 g, 79% yield, 19:1 inseparable diastereomers from **70** or 0.027 g, 88% yield from **68**) was obtained as a white crystalline solid. **71:** R_f = 0.53 (silica gel, hexanes: EtOAc, 4:1); IR (film) ν_{max} 2957, 2871, 1774, 1457, 1188, 1126, 920 cm^{-1}; *Major diastereomer:* ^1H NMR (400 MHz, $CDCl_3$) δ 4.08 (dd, *J* = 13.2, 4.8 Hz, 1 H), 2.59–2.48 (m, 2 H), 2.40 (dd, *J* = 16.4, 6.8 Hz, 1 H), 2.29 (m, 1 H), 2.11 (dd, *J* = 14.4, 6.8 Hz, 1 H), 1.89–1.74 (m, 2 H) 1.37 (s, 3 H), 1.03 (s, 3 H), 1.02 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 84.9, 52.9, 44.9, 40.0, 38.3, 35.0, 32.1, 30.9, 20.5, 19.8; HRMS (EI) calcd for $C_{11}H_{17}IO_2$ $[M]^+$ 308.0273, found 308.0275.

Alkene 72. Dry LiCl (0.125 g, 2.95 mmol, 50 equiv) was added to a solution of iodide **71** (0.018 g, 0.060 mmol, 1.0 equiv) in DMF (2 mL) at 25 °C. The resulting solution was heated with stirring at 80 °C for 12 h. Upon completion, the reaction contents were quenched with saturated aqueous NH_4Cl (10 mL). Water (3 mL) was then added and the reaction mixture was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resulting yellow oil was purified by flash column chromatography (silica gel, hexanes:EtOAc, 4:1) to afford alkene **72** (0.010 g, 97% yield) as a colorless amorphous solid. **72:** R_f = 0.56 (silica gel, hexanes: EtOAc, 4:1); IR (film) ν_{max} 2958, 2871, 1786, 1771, 1227, 1053, 952 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.55 (ddd, *J* = 10.0, 5.2, 2.0 Hz, 1 H), 5.50 (dd, *J* = 10.0, 2.8 Hz, 1 H), 2.53–2.27 (m, 5 H), 1.33 (s, 3 H), 1.07 (s, 3 H), 1.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 138.2, 121.9, 85.0, 52.3, 38.6, 35.4, 31.8, 28.8, 20.7, 20.6; HRMS (EI) calcd for $C_{11}H_{16}O_2$ $[M]^+$ 180.1150, found 180.1146.

Formal Synthesis of Stemodin

74. Procedure adapted from: Brown, R. C. D.; Bataille, C. J.; Hughes, R. M.; Kenney, A.; Luker, T. J. *J. Org. Chem.* **2002**, *67*, 8079. Methyl acetoacetate (0.30 mL, 2.8 mmol, 1.2 equiv) was added dropwise under constant flow of argon to a suspension of NaH (60% dispersion in mineral oil, 0.12 g, 3.0 mmol, 1.3 equiv) in THF (4 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C, then a solution of *n*-BuLi (1.6 M in hexanes, 1.7 mL, 2.8 mmol, 1.2 equiv) was added slowly and the resultant light orange solution was stirred an additional 10 min at 0 °C. This dianion solution was cannulated slowly into a solution of geranyl bromide (0.50 g, 2.3 mmol, 1.0 equiv) in THF (4 mL) at

0 °C. After 15 min at 0 °C, diethyl chlorophosphate (0.67 mL, 4.6 mmol, 2.0 equiv) was then added dropwise at 0 °C. The reaction mixture was allowed to warm slowly to 25 °C over the course of 90 min, then the reaction mixture was quenched with 0.25 M HCl (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL), dried ($MgSO_4$), filtered, and concentrated. The crude yellow oil was purified by flash column chromatography (silica gel, hexanes:EtOAc, 9:1→5:2) to afford **74** (0.67 g, 72% yield) as a light yellow viscous oil, spectroscopically identical to previously synthesized material. To synthesize derivatives of **74** found in Table 3, in place of the chlorophosphate, the same equivalents of either TIPSCl, TBSOTf, TBDPSCl, MOMCl, or Me_3OBF_4 were used.

75. A solution of IDSI (0.097 g, 0.120 mmol, 1.2 equiv) in nitromethane (0.5 mL) was added quickly via syringe to a solution of enol phosphate **74** (0.039 g, 0.100 mmol, 1.0 equiv) in nitromethane (3.5 mL) at 25 °C. After stirring for 5 min at 25 °C, the resulting mixture was poured into a solution of saturated aqueous $NaHCO_3$:5% aqueous Na_2SO_3 (1:1, 10 mL) and stirred for an additional 15 min at 25 °C. The reaction contents were then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were concentrated and the crude partially cyclized material was then dissolved in toluene (2 mL) and cooled to 0 °C. Concentrated H_2SO_4 (0.080 mL, 1.5 mmol, 15 equiv) was added dropwise to the solution and the resultant mixture was stirred for 30 min at 0 °C. Upon completion, the reaction contents were slowly quenched with saturated aqueous $NaHCO_3$ (10 mL), and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resulting brown oil was purified by flash column chromatography (silica gel, hexanes:EtOAc, 5:1) to afford cyclization

adduct **75** (0.015 g, 40% yield) as a white crystalline solid. **75:** R_f = 0.34 (silica gel, hexanes: EtOAc, 4:1); IR (film) ν_{max} 2949, 1748, 1715, 1434, 1263, 1170, 1135 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.25 (dd, *J* = 12.8, 4.4 Hz, 1 H), 3.67 (s, 3 H), 3.21 (s, 1 H), 2.53–2.28 (m, 4 H), 2.14 (m, 1 H), 1.90 (dq, *J* = 5.2, 12.8 Hz, 1 H), 1.65 (dd, *J* = 12.4, 3.2 Hz, 1 H), 1.60 (dt, *J* = 13.2, 3.6 Hz, 1 H), 1.43 (dt, *J* = 4.4, 13.2 Hz, 1 H), 1.21 (s, 3 H), 1.14 (s, 3 H), 1.07 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.4, 168.3, 69.4, 52.1, 51.7, 51.0, 42.1, 41.9, 41.2, 39.6, 33.6, 33.5, 25.5, 21.2, 14.9; HRMS (FAB) calcd for $C_{15}H_{24}IO_3$ $[M+H]^+$ 379.0770, found 379.0772.

Model System Towards the Formal Synthesis of Shonanol

83. Procedure adapted from: Shing, T. K. M.; Yeung, Y.-Y.; Su, P. L. *Org. Lett.* **2006**, *8*, 3149. To a solution of alkene **27** (5 mg, 0.022 mmol, 1.0 equiv) in EtOAc (0.18 mL) was added TBHP (5.5 M in decane, 20.5 μL, 0.11 mmol, 5.0 equiv) and 3Å molecular sieves (8 mg), and the reaction mixture was allowed to stir for 30 min at 25 °C. Next $Mn(OAc)_3•2H_2O$ (0.6 mg, 0.0022 mmol, 0.1 equiv) was added and the solution was allowed to stir at 25 °C for 48 h. Upon completion, the reaction contents were filtered through a pad of Celite with EtOAc (2 mL) and concentrated. The crude benzylic oxidation adduct **83** was a resulting brown oil which was only tentatively characterized by ^1H NMR.

85. Prepared adapted from: Brown, H. C.; Dhokte, U. P. *J. Org. Chem.* **1994**, *59*, 2025. To a stirred suspension of SeO_2 (small spatula tip) and AcOH (0.05 μL, 0.0014 mmol, 0.2 equiv) in 1,2-dichloroethane (50 μL) was added TBHP (5.5 M in decane, 3.8 μL, 0.021 mmol, 3.0 equiv) and the suspension was stirred 30 min at 25 °C. Next, a

solution of alkene **83** (2 mg, 0.007 mmol, 1.0 equiv) in 1,2-dichloroethane (50 μL) was added and the reaction mixture was heated to 70 °C and stirred at this temperature for 12 h. Upon completion, the reaction contents were slowly quenched with saturated aqueous $NaHCO_3$ (1 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude oxidation adduct **85** was only tentatively characterized by ^1H NMR.

Model System Towards the Formal Synthesis of Celahypodiol

93. To a solution of **28** (0.030 g, 0.085 mmol, 1.0 equiv) in AcOH (15 mL) was added AgOAc (0.017 g, 0.10 mmol, 1.2 equiv) at 25 °C and the reaction was allowed to stir for 12 h at 25 °C. Upon completion, the reaction contents were slowly quenched with water (20 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resulting oil was purified by flash column chromatography (silica gel, hexanes:CH_2Cl_2, 9:1) to afford rearranged product **93** (8 mg, 41% yield), only tentatively characterized by ^1H NMR.

Investigations Using CDSC

Chlorodiethylsulfonium hexachloroantimonate (94, CDSC). A flask containing a stir bar and 1,2-dichloroethane (10 mL) was cooled to –30 °C. Chlorine gas was then bubbled through the solvent for 1 min, yielding a transparent yellow solution. At this point the amount of Cl_2 was measured in solution (~0.25 g, 3.5 mmol, 1.0 equiv). Et_2S (0.41 mL, 3.9 mmol, 1.1 equiv) was then added dropwise to this solution at –30 °C and the resultant mixture was stirred for 5 min at –30 °C. $SbCl_5$ (1.0 M in CH_2Cl_2, 4.2

mL, 4.2 mmol, 1.2 equiv) was then slowly added via syringe. The resultant mixture was allowed to warm to 0 °C over the course of 30 min (precipitate dissolved). To collect CDSC, hexanes (4 mL) was carefully pipetted onto the top of the solution and the layered solution was cooled to –20 °C for 12 h. The resulting off-white powder was isolated by decanting off the liquid, rinsing with hexanes (2 x 1 mL), then drying under vacuum prior to use in cation-p cyclizations (1.45 g, 91% yield).

Standard Procedure for Small-Scale Polyene Cyclizations with CDSC

A solution of CDSC (**94**, 0.050 g, 0.110 mmol, 1.1 equiv) in nitromethane (0.5 mL) was added to a solution of the substrate (0.100 mmol, 1.0 equiv) in nitromethane (1.5 mL) at the temperature indicated. After stirring for the indicated, the resulting mixture was poured into a solution of saturated aqueous $NaHCO_3$:5% aqueous Na_2SO_3 (1:1, 10 mL) and vigorously stirred for an additional 15 min at 25 °C. The reaction contents were then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography or preparative TLC to yield the desired cation-p cyclization products in the amount and yields shown below.

97. Colorless viscous oil, 0.012 g of a mixture of 1.0:1.0 inseparable diastereomers, 46% combined yield; R_f = 0.56 (silica gel, hexanes: CH_2Cl_2, 9:1); IR (film) ν_{max} 2945, 1452, 1262, 1027, 766, 726 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{23}Cl$ $[M]^+$ 262.1488, found 262.1490; *Equatorial chlorine diastereomer* (**97a**): ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (m, 1 H), 7.15–7.04 (m, 3 H), 3.81 (dd, *J* = 12.0, 4.8 Hz, 1 H), 3.02–2.88 (m, 2 H), 2.36 (m, 1 H), 2.22–2.03 (m, 2 H), 1.95 (m, 1 H), 1.81 (m, 1 H), 1.58 (dt, *J* =

4.2, 11.7 Hz, 1 H), 1.42 (dd, *J* = 12.0, 2.4 Hz, 1 H), 1.24 (s, 3 H), 1.15 (s, 3 H), 1.03 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.9, 134.9, 129.1, 126.0, 125.7, 124.5, 72.8, 51.4, 40.1, 38.9, 37.8, 30.8, 30.3, 29.3, 25.0, 20.0, 16.8. *Axial chlorine diastereomer* (**97b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 1 H), 7.17–7.03 (m, 3 H), 4.13 (t, *J* = 2.8 Hz, 1 H), 3.01–2.83 (m, 2 H), 2.38 (m, 1 H), 2.20–2.06 (m, 2 H), 2.01 (m, 1 H), 1.87–1.79 (m, 2 H), 1.28 (dd, *J* = 10.0, 2.4 Hz, 1 H), 1.22 (s, 3 H), 1.11 (s, 3 H), 1.09 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5, 135.1, 129.1, 125.9, 125.5, 124.3, 71.9, 43.1, 38.6, 37.6, 32.0, 31.0, 30.1, 27.8, 25.4, 23.0, 18.5. [Note: Though the above diastereomers are inseparable, characterization was accomplished by comparing our experimental spectra to that of previously synthesized equatorial diastereomers. For instance, the equatorial diastereomer of **97** can be generated using our previously reported Hg(II)-based polyene cyclization of homogeranylbenzene: Snyder, S. A.; Treitler, D. S.; Schall, A. *Tetrahedron*, **2010**, *66*, 4796].

101. 5.3 mg of a 2.2:1.0 mixture of separable diastereomers, 18% combined yield; *Major diastereomer:* White crystalline solid; R_f = 0.14 (silica gel, hexanes: EtOAc, 7:3); IR (film) ν_{max} 3419 (br), 2974, 1736, 1369, 1245, 1030 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42 (dd, *J* = 12.0, 5.2 Hz, 1 H), 4.33 (dd, *J* = 12.0, 5.2 Hz, 1 H), 3.78 (dd, *J* = 12.0, 4.0 Hz, 1 H), 2.48 (br s, 1 H), 2.07 (s, 3 H), 2.03 (m, 1 H), 1.91–1.80 (m, 2 H), 1.69 (t, *J* = 5.2 Hz, 1 H), 1.59 (dt, *J* = 4.0, 13.6 Hz, 1 H), 1.24 (s, 3 H), 1.17 (s, 3 H), 0.96 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 71.9, 70.7, 63.2, 55.8, 41.8, 40.0, 30.9, 29.1, 24.0, 21.3, 16.4; HRMS (FAB) calcd for $C_{12}H_{22}ClO_3$ $[M+H]^+$ 249.1257, found 249.1261. *Minor diastereomer:* White crystalline solid; R_f = 0.21 (silica gel, hexanes: EtOAc, 7:3); IR (film) ν_{max} 3421 (br), 2925, 1732, 1367, 1238, 1029 cm^{-1}; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 4.38 (dd, *J* = 12.0, 5.2 Hz, 1 H), 4.27 (dd, *J* = 11.6, 5.2 Hz, 1 H), 4.00 (m, 1 H), 2.14 (br s, 1 H), 2.07 (s, 3 H), 2.07–1.92 (m, 3 H), 1.67 (m, 1 H), 1.26 (br s, 1 H), 1.24 (s, 3 H), 1.18 (s, 3 H), 1.07 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 72.2, 70.4, 62.8, 39.5, 36.3, 29.8, 29.5, 28.6, 25.4, 23.8, 21.3; HRMS (FAB) calcd for $C_{12}H_{22}ClO_3$ $[M+H]^+$ 249.1257, found 249.1263.

102. White solid, 8.2 mg of a 4.0:1.0 mixture of separable diastereomers, 38% combined yield from **70**, 4.4 mg of a 4.0:1.0 mixture of separable diastereomers, 20% combined yield from **68**; *Major diastereomer:* R_f = 0.43 (silica gel, hexanes: EtOAc, 4:1); IR (film) ν_{max} 2947, 1776, 922, 670 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (dd, *J* = 12.0, 4.8 Hz, 1 H), 2.52 (dd, *J* = 16.4, 14.4 Hz, 1 H), 2.37 (dd, *J* = 16.4, 6.8 Hz, 1 H), 2.25 (m, 1 H), 2.05 (dt, *J* = 12.0, 3.6 Hz, 1 H), 2.01–1.87 (m, 2 H), 1.80 (dt, *J* = 4.0, 12.8 Hz, 1 H), 1.37 (s, 3 H), 1.09 (s, 3 H), 0.99 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 84.7, 68.8, 54.9, 38.5, 37.6, 31.4, 29.9, 29.1, 20.6, 15.8; HRMS (FAB) calcd for $C_{11}H_{18}ClO_2$ $[M+H]^+$ 217.0995, found 217.1007.

Chiral Polyene Cyclization

(2*S*,5*S*)-Hexanediol (**103**) was in turn produced by a yeast reduction of 2,5-hexanedione according to the procedure in: Braun, W.; Calmuschi, B.; Haberland, J.; Hummel, W.; Liese, A.; Nickel, T.; Stelzer, O.; Salzer, A. *Eur. J. Inorg. Chem.* **2004**, *11*, 2235.

(2*R*,5*R*)-Dimethylthiolane (104). To a solution of (2*S*,5*S*)-hexanediol (**103**, 3.00 g, 25.3 mmol, 1.0 equiv) and Et_3N (21.2 mL, 152 mmol, 6.0 equiv) in CH_2Cl_2 (50 mL) at –20 °C was added MsCl (7.83 mL, 101 mmol, 4.0 equiv) dropwise. The reaction

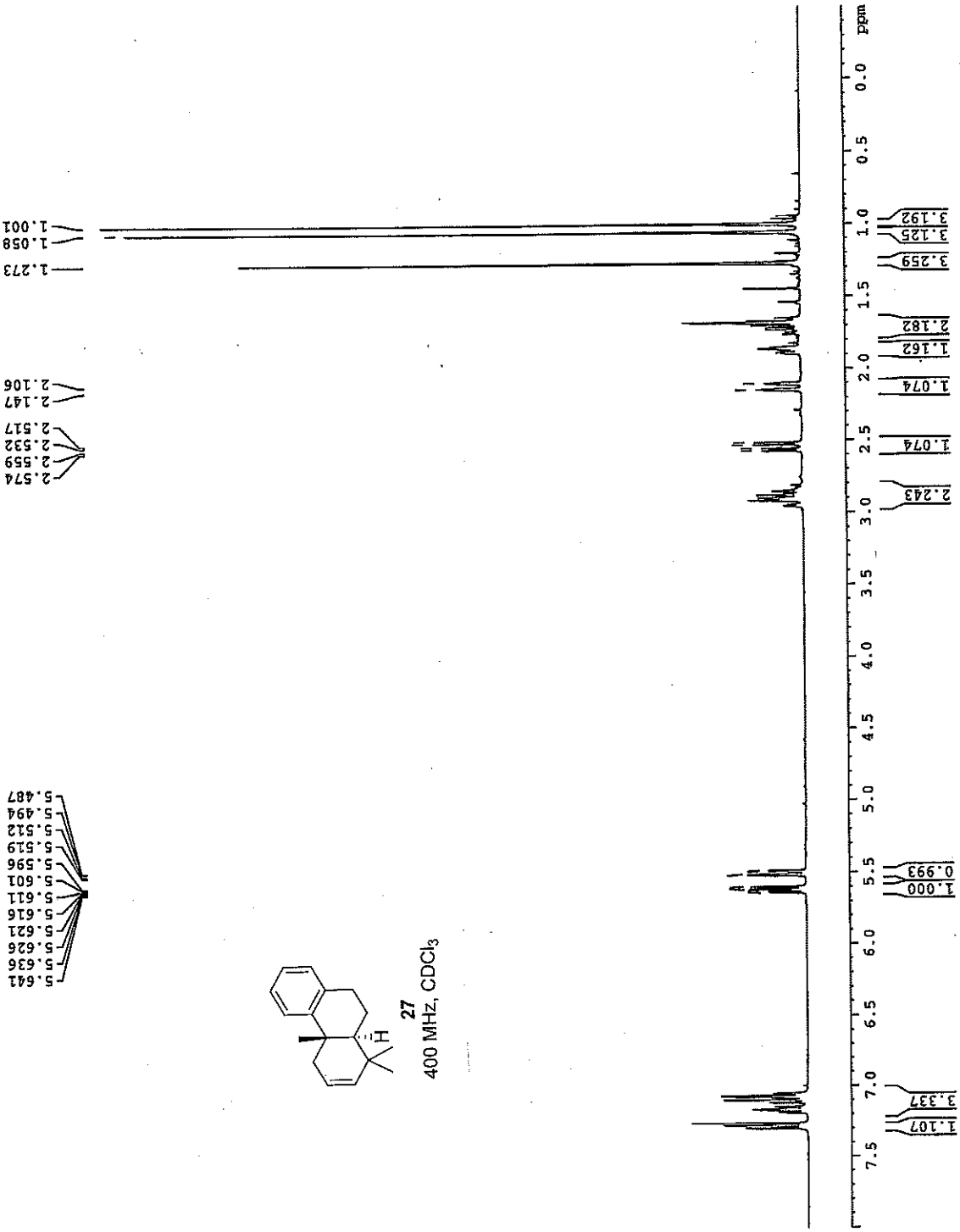
solution was then allowed to warm to 0 °C over 1 h before being quenched with 1 M HCl (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated to provide the desired bis-mesylated intermediate as a viscous oil that was used immediately without further purification. Next, powdered $Na_2S•9H_2O$ (12.2 g, 50.6 mmol, 2.0 equiv) was dissolved in EtOH (200 proof, 80 mL) and the resultant solution was cooled to 0 °C. The crude bis-mesylate (25.3 mmol assumed, 1.0 equiv) was then added and the reaction contents were stirred at 0 °C for 4 h before being warmed slowly to 25 °C over the course of 4 h. Next, the reaction mixture was stirred at 25 °C for an additional 36 h. Upon completion, the reaction mixture was quenched with water (150 mL) and extracted with pentane (4 × 150 mL). The combined organic layers were then washed with H_2O (3 × 100 mL) and brine (2 × 100 mL), dried ($MgSO_4$), filtered, concentrated, and purified by vacuum distillation (→120 °C at 100 torr) to afford (2*R*,5*R*)-dimethylthiolane as a colorless liquid (**104**, 2.70 mL, contaminated with pentane, 65% yield) whose spectral properties matched: Julienne, K.; Metzner, P. *J. Org. Chem.* **1998**, *63*, 4532. **104**: $[\alpha]_D^{23}$ = 109.1 (c = 1.74, Et_2O); 65% e.e.

105 ("Chiral IDSI"). To a solution of thiolane **104** (3.30 g, 28.4 mmol, 1.0 equiv) in 1,2-dichloroethane (370 mL) at –25 °C was added ICl (1.42 mL, 28.4 mmol, 1.0 equiv) and $SbCl_5$ (1.0 M in CH_2Cl_2, 29.5 mL, 29.5 mmol, 1.1 equiv). After the reaction contents were stirred at –25 °C for 30 min, it was then allowed to warm to 25 °C. The reaction contents were then layered with hexanes (600 mL) and cooled to –20 °C for 1 week. The filtrate was decanted and the resultant crystals were washed with cold CH_2Cl_2

(2 × 10 mL) and dried under vacuum to afford **105** (12.4 g, 76% yield) as an orange crystalline solid.

Asymmetric Cyclization Attempts of Homogeranylbenzene:

A solution of **105** (0.053 g, 0.110 mmol, 1.1 equiv) in nitromethane (0.5 mL) was quickly added via syringe to a solution of homogeranylbenzene (**44**, 0.023 g, 0.100 mmol, 1.0 equiv) in nitromethane (1.5 mL) at –25 °C. After stirring for 5 min at –25 °C, the resulting mixture was poured into a solution of saturated aqueous $NaHCO_3$:5% aqueous Na_2SO_3 (1:1, 10 mL) and the resultant biphasic mixture was stirred vigorously for 15 min at 25 °C. The reaction contents were then extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes: CH_2Cl_2, 9:1) to afford bicycle **28** (0.028 g; 78% yield) as a white crystalline solid. HPLC (OD column, 1.0 mL/min, 99:1 hex:IPA, 30 °C, 265 nm, t_R = 7.54 min, 10.99 min): 0% e.e.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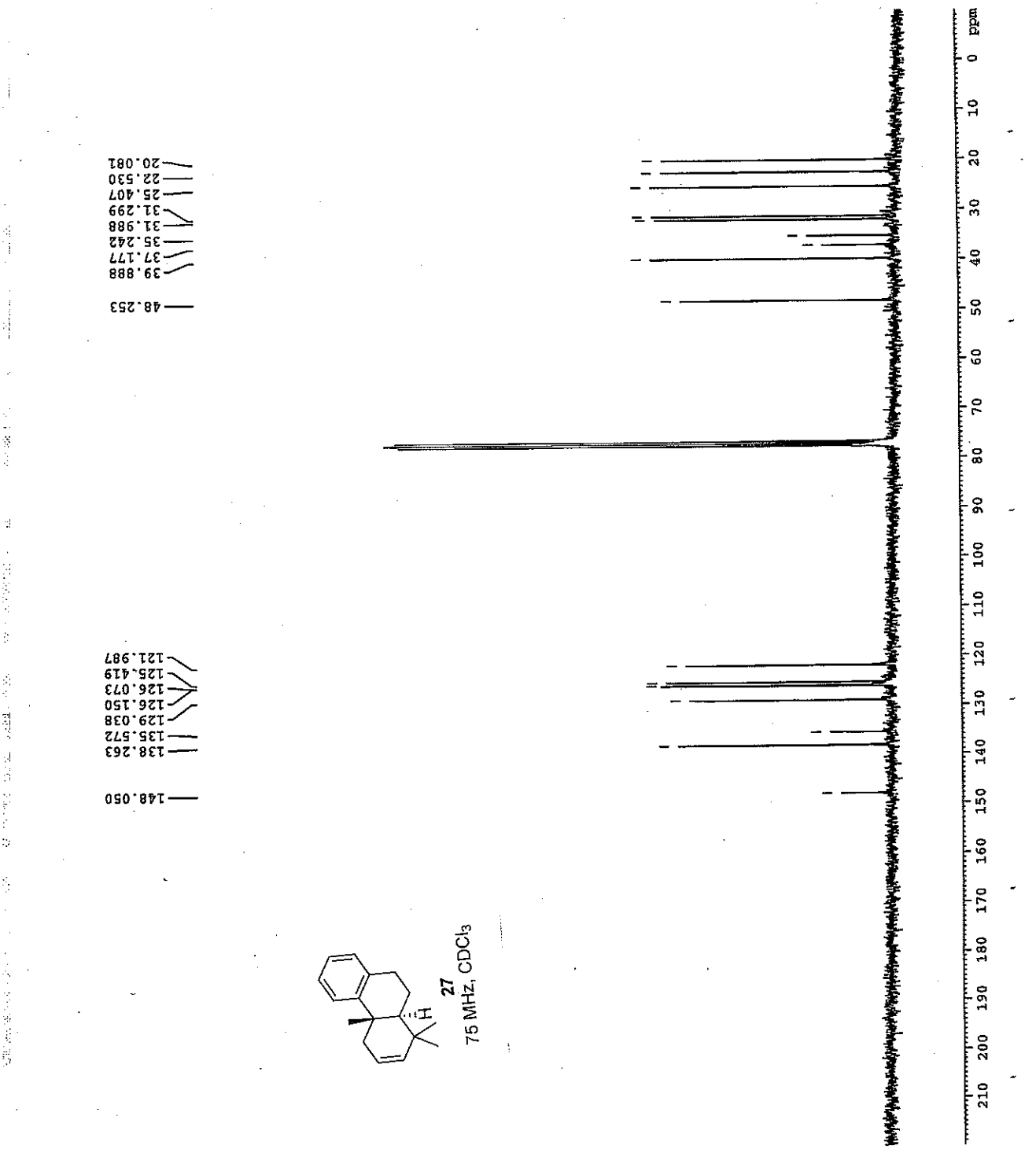
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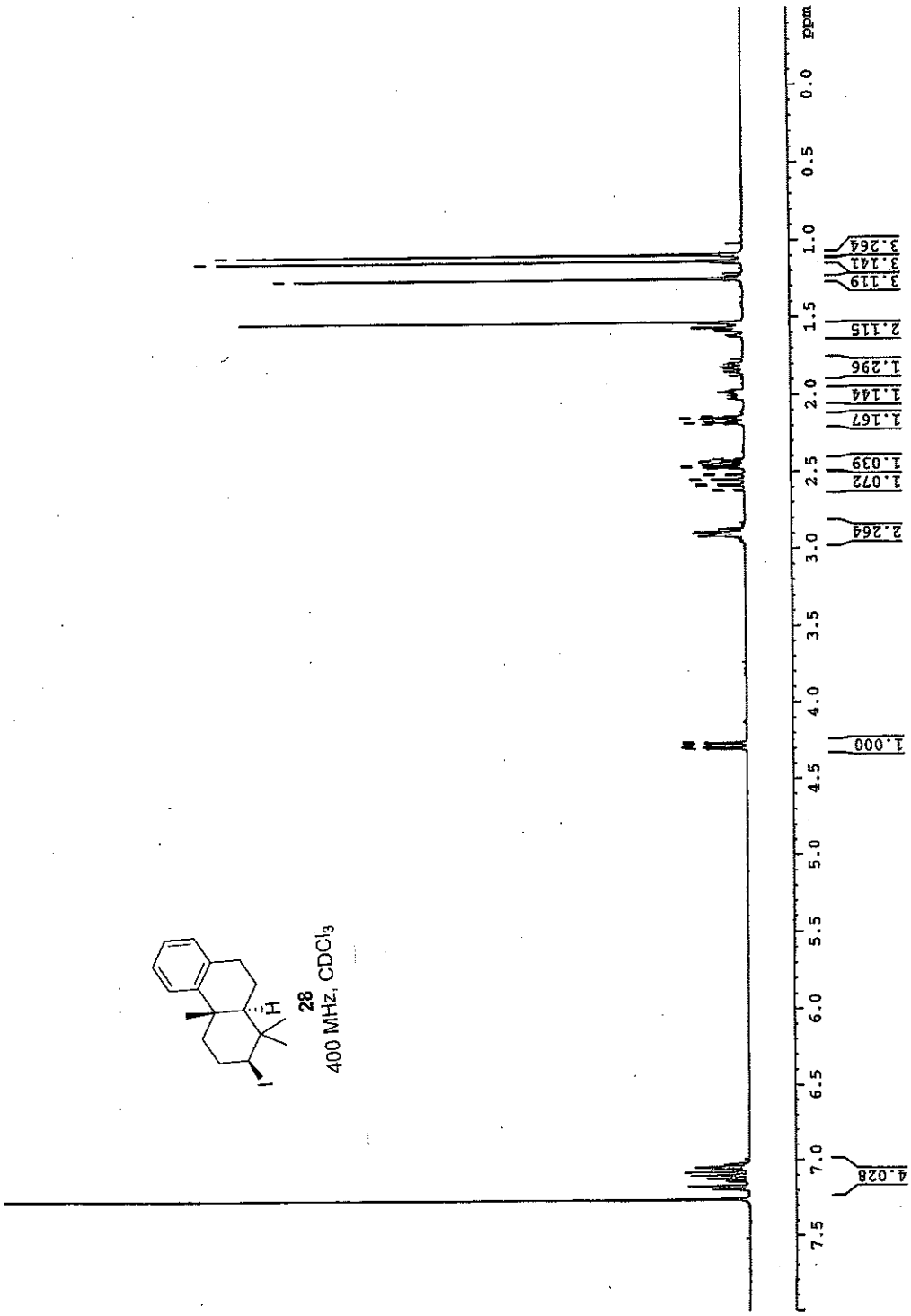
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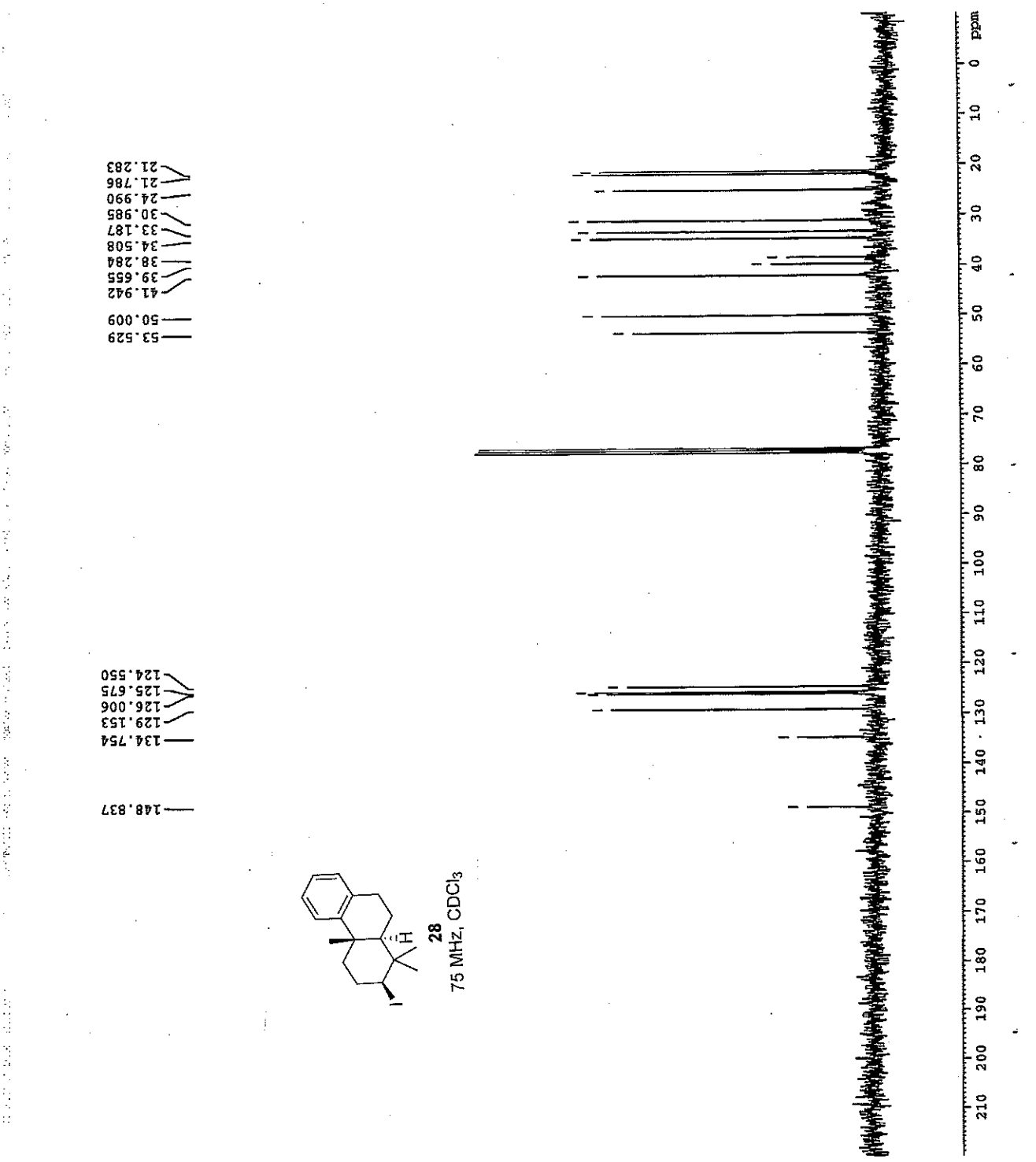
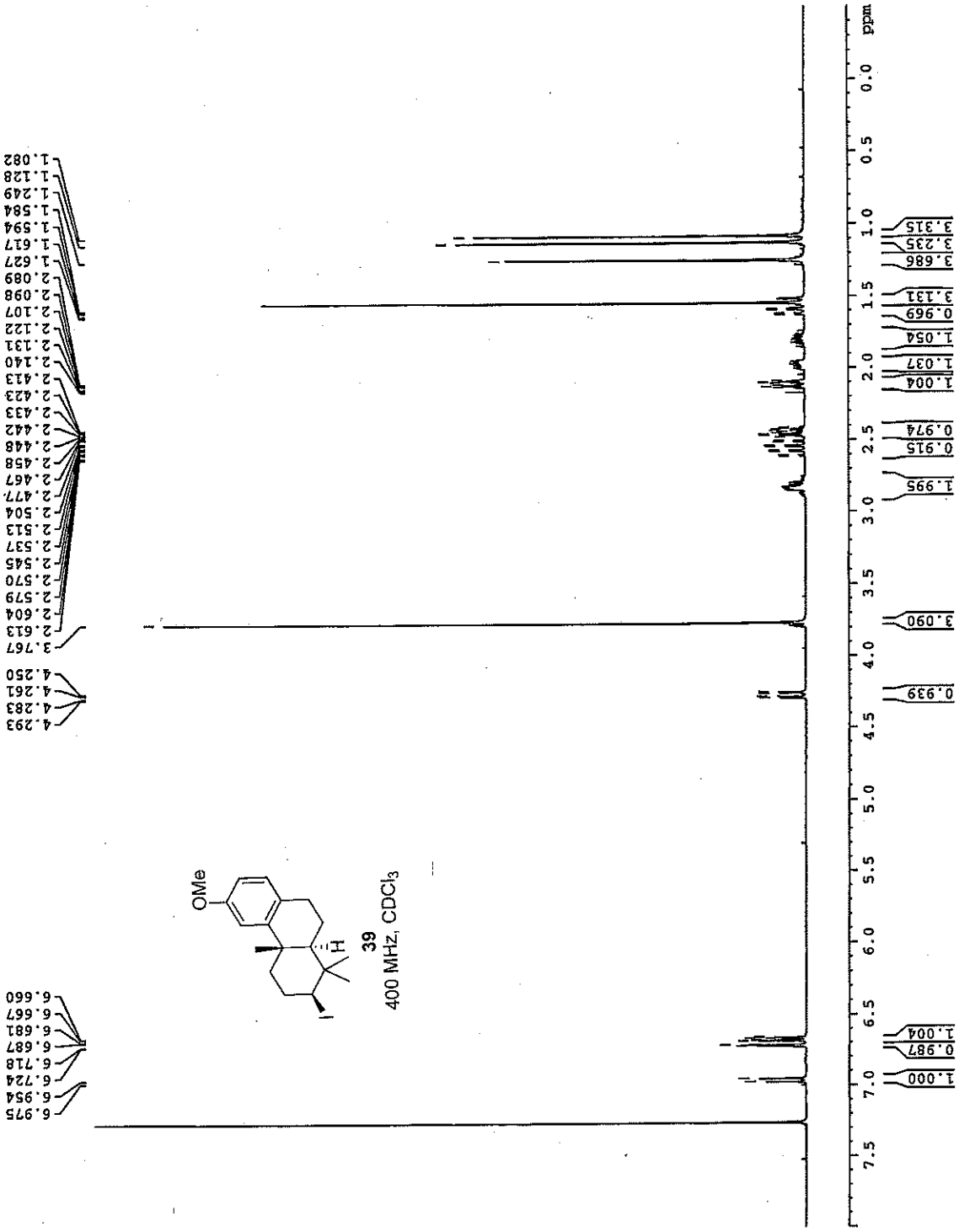
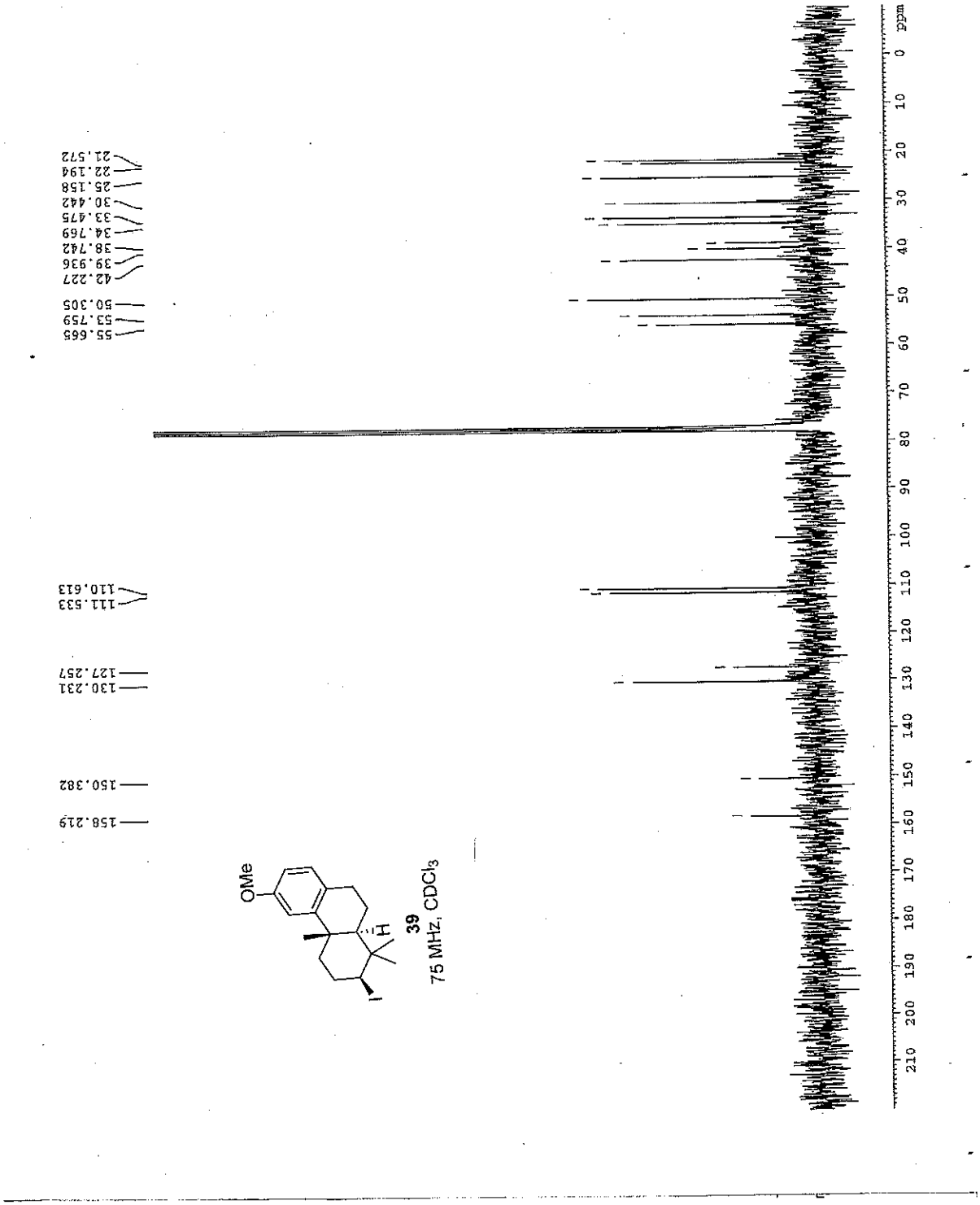
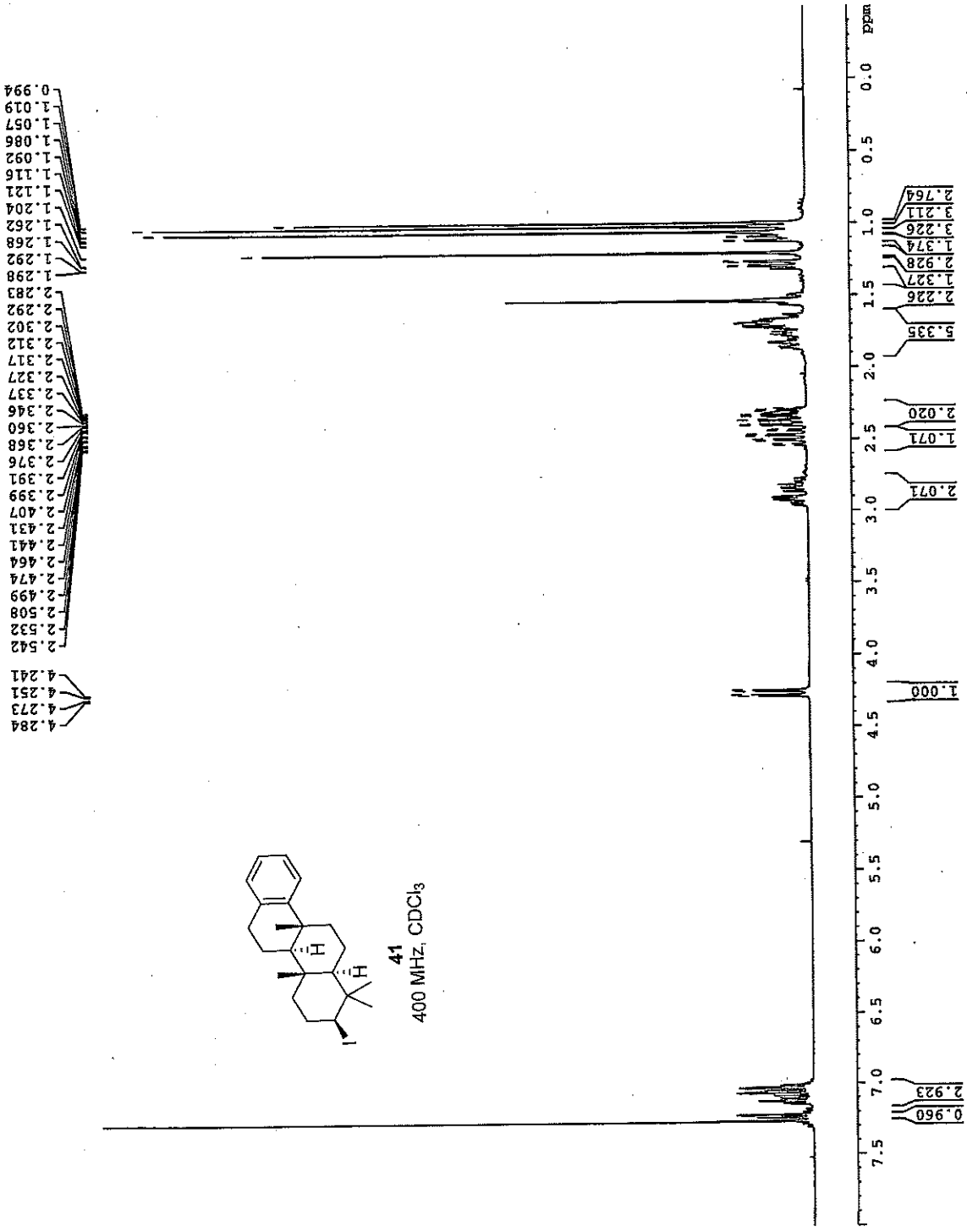
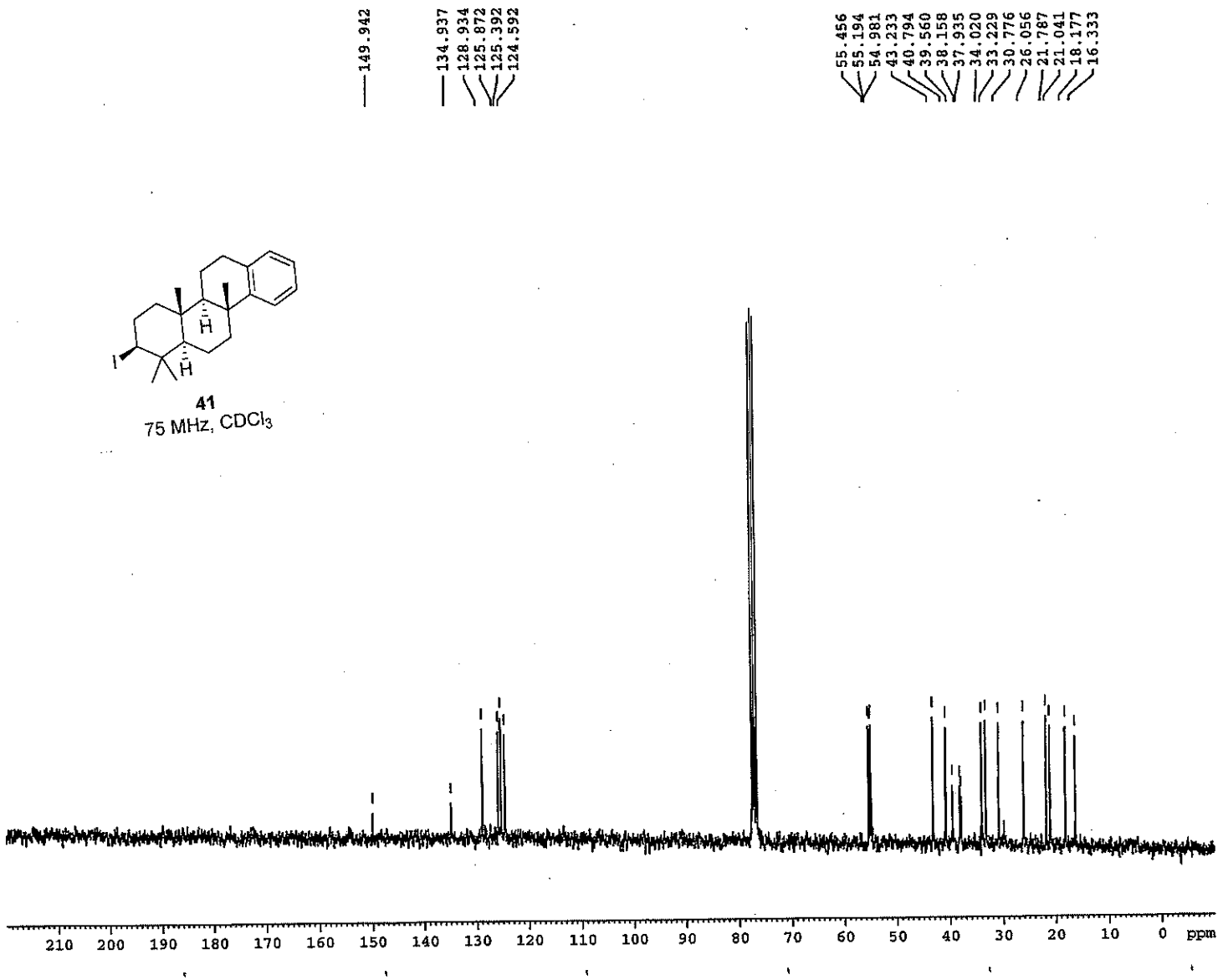
2.524
2.515
2.482
2.473
2.463
2.453
2.447
2.438
2.428
2.418
2.192
2.183
2.175
2.159
2.150
2.141
1.249
1.133
1.091


148.837
134.754
129.153
126.006
125.675
124.550
53.529
50.009
41.942
39.655
38.284
34.508
33.187
30.985
24.990
21.786
21.283
H
I
28
75 MHz, CDCl3
ppm


OMe
H
39
400 MHz, CDCl3
ppm

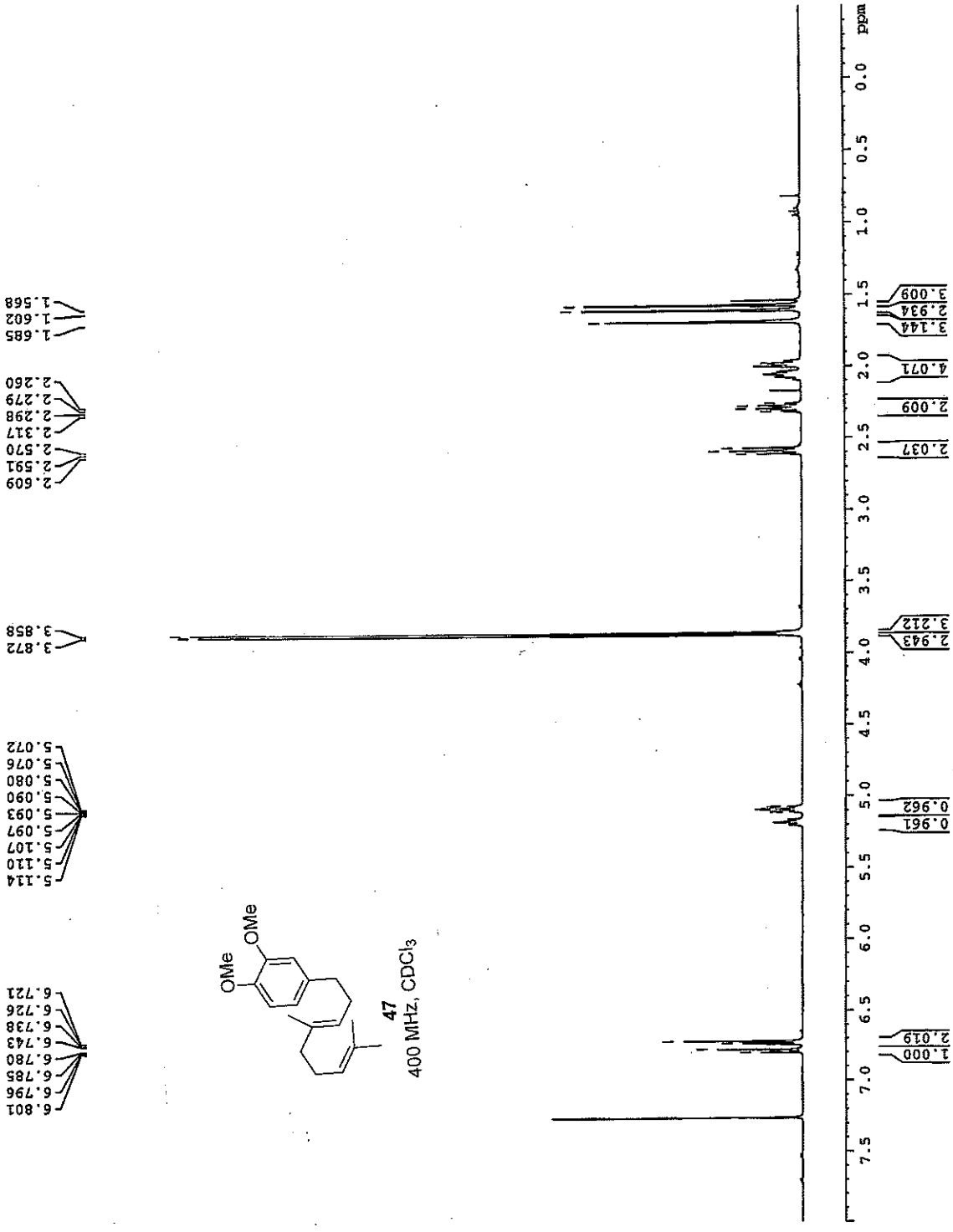

158.219
150.382
130.231
127.257
111.533
110.613
55.665
53.759
50.305
42.227
39.936
38.742
34.769
33.475
30.442
25.158
22.194
21.572
OMe
H
39
75 MHz, CDCl3
ppm

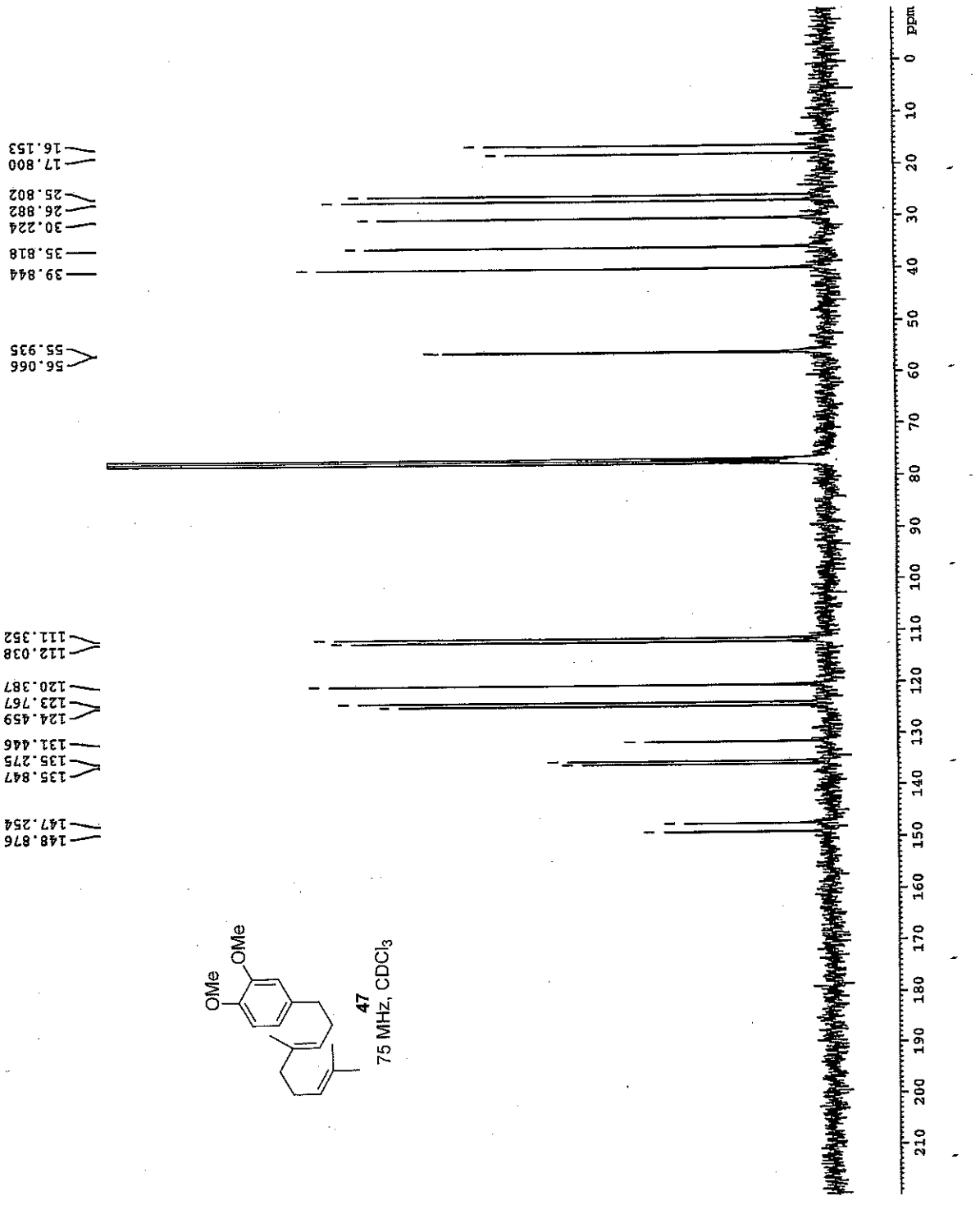

41
400 MHz, CDCl3
ppm
0.994
1.019
1.057
1.086
1.092
1.116
1.121
1.204
1.262
1.268
1.292
1.298
2.283
2.292
2.302
2.312
2.317
2.327
2.337
2.346
2.360
2.368
2.376
2.391
2.399
2.407
2.431
2.441
2.464
2.474
2.499
2.508
2.532
2.542
4.241
4.251
4.273
4.284
0.960
2.923
1.000
2.071
1.071
2.020
5.335
2.226
1.327
2.928
1.374
3.226
3.211
2.764

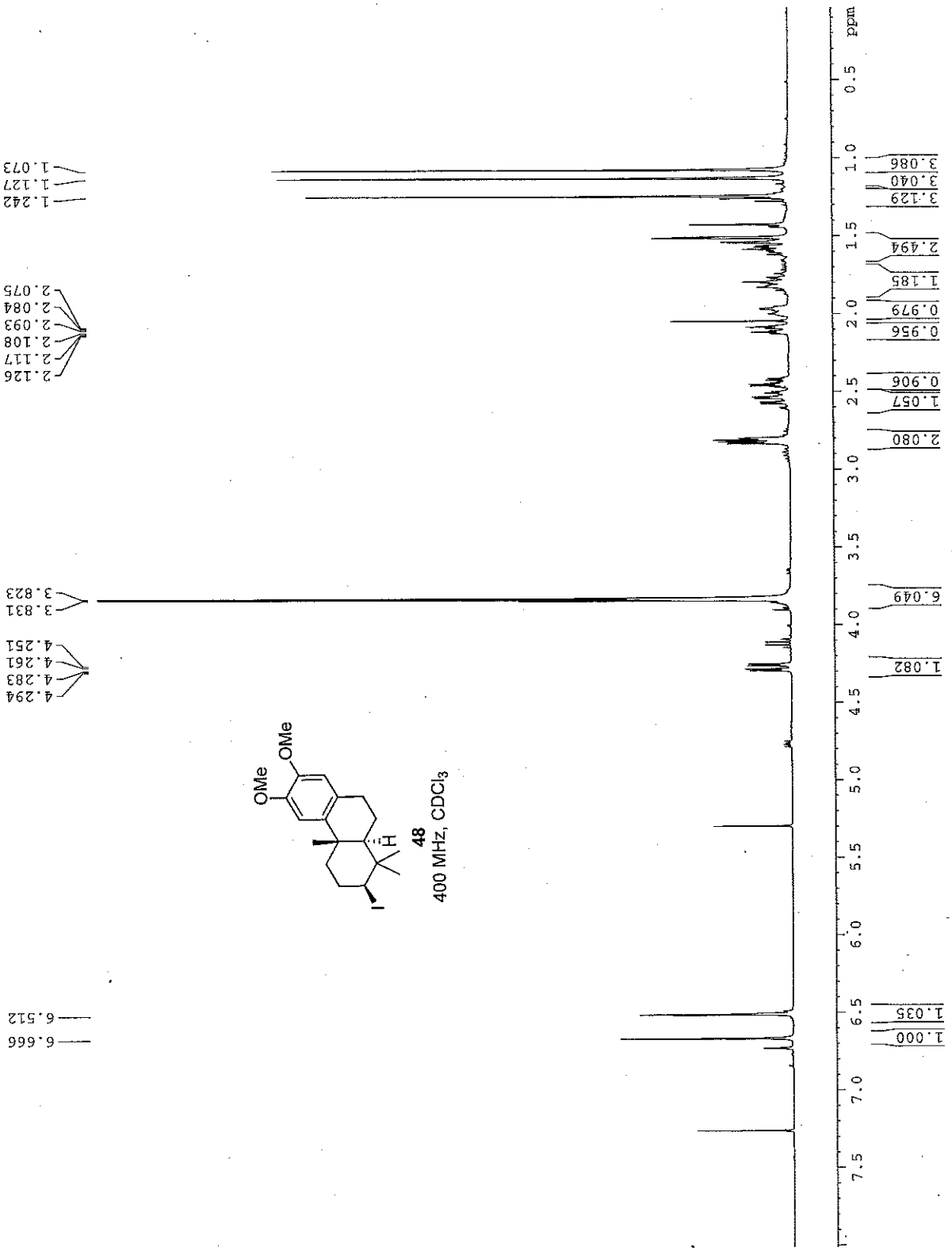


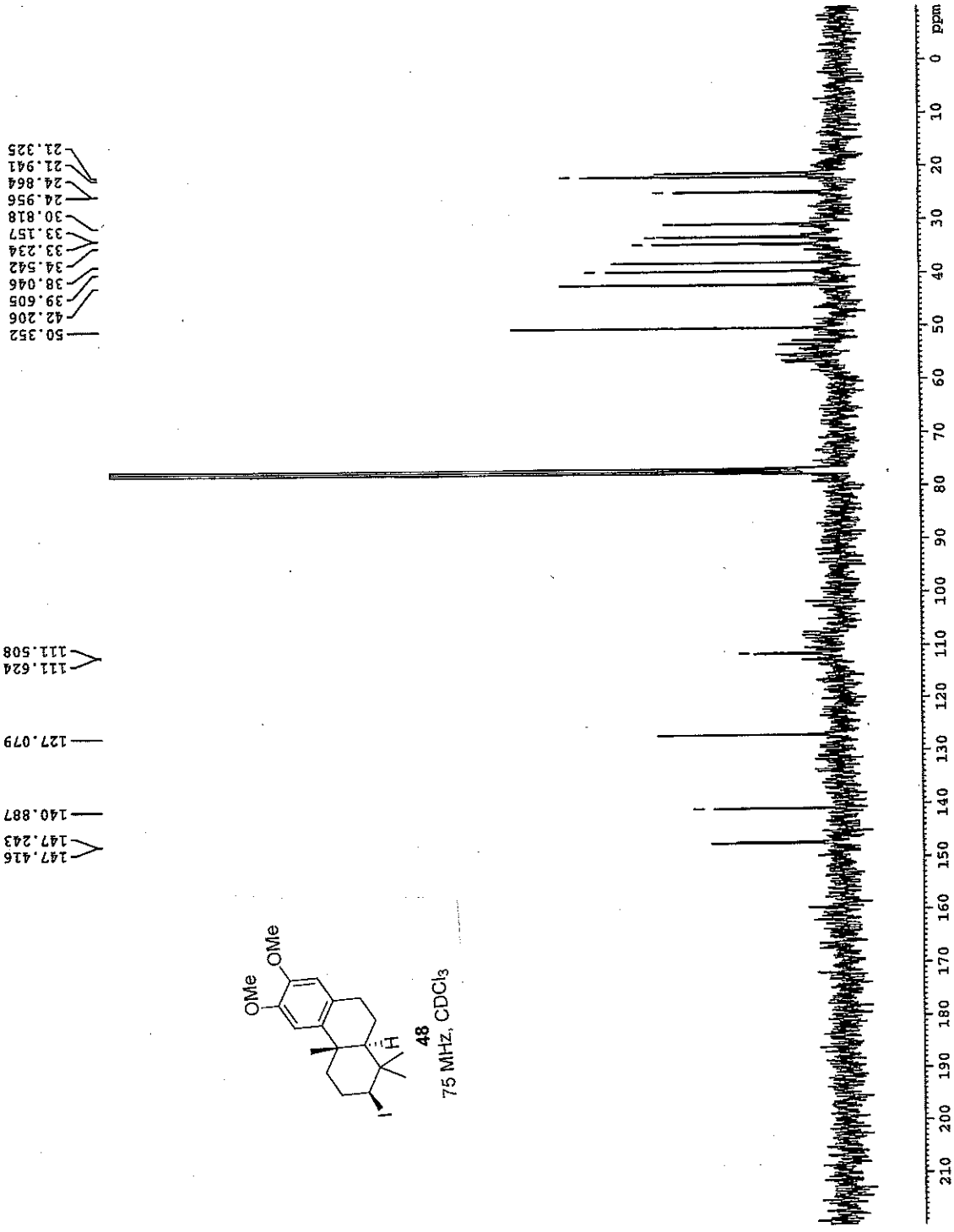
41

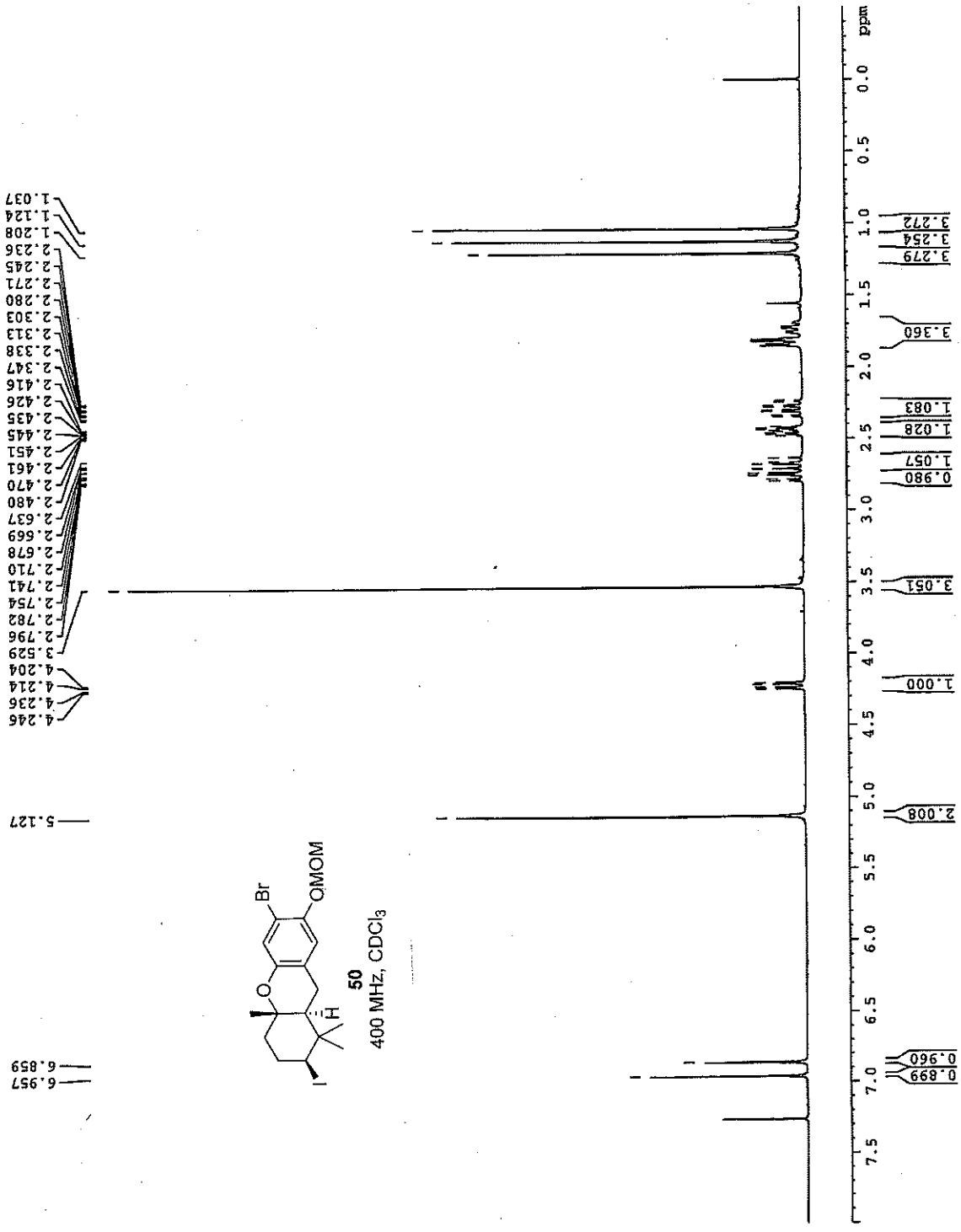
75 MHz, $CDCl_3$

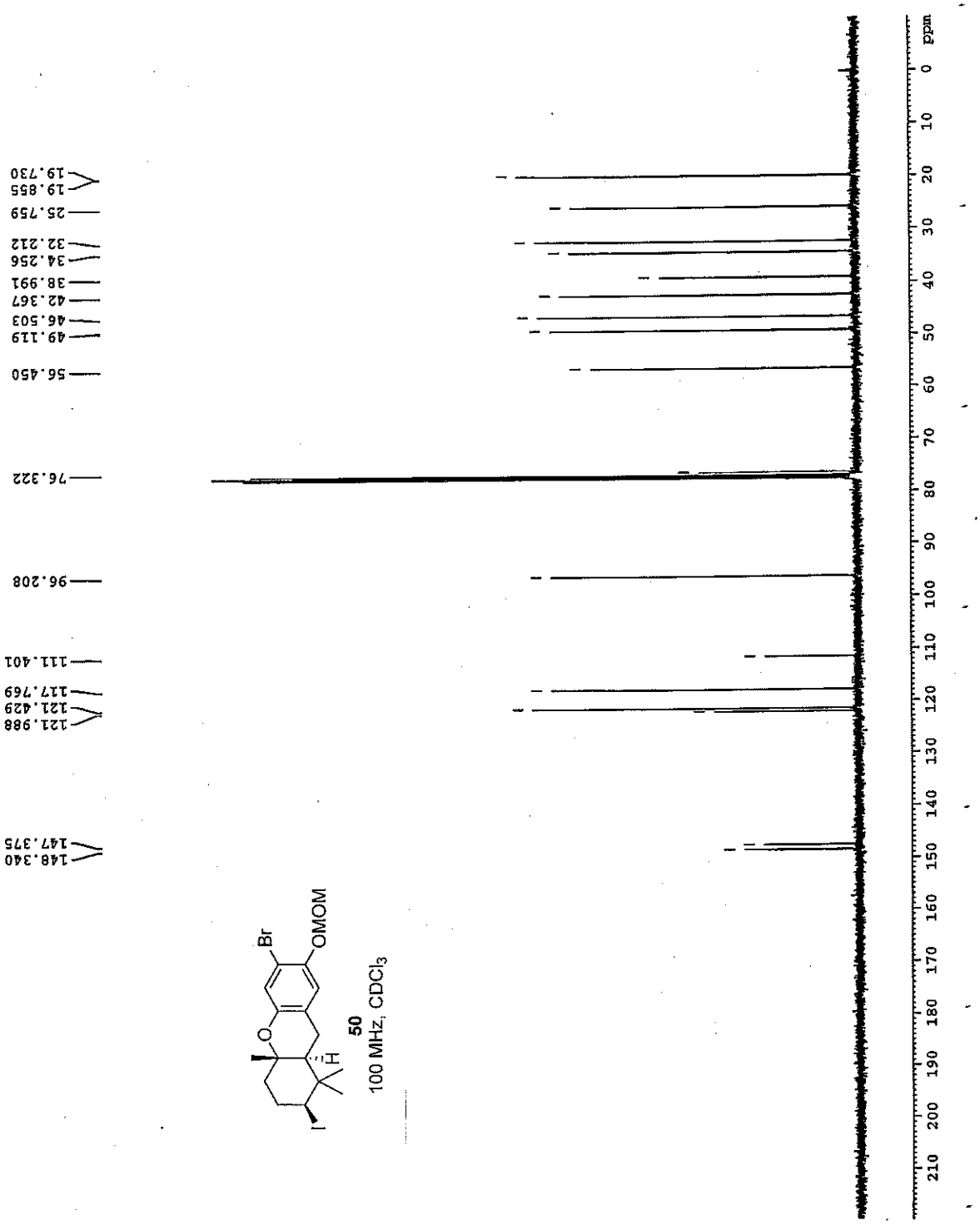

OMe
OMe
47
400 MHz, CDCl3
6.801
6.796
6.785
6.780
6.743
6.738
6.726
6.721
5.114
5.110
5.107
5.097
5.093
5.090
5.080
5.076
5.072
3.872
3.858
2.609
2.591
2.570
2.317
2.298
2.279
2.260
1.685
1.602
1.568
1.000
2.019
0.962
0.961
2.943
3.212
2.037
2.009
4.071
3.144
2.934
3.009
ppm

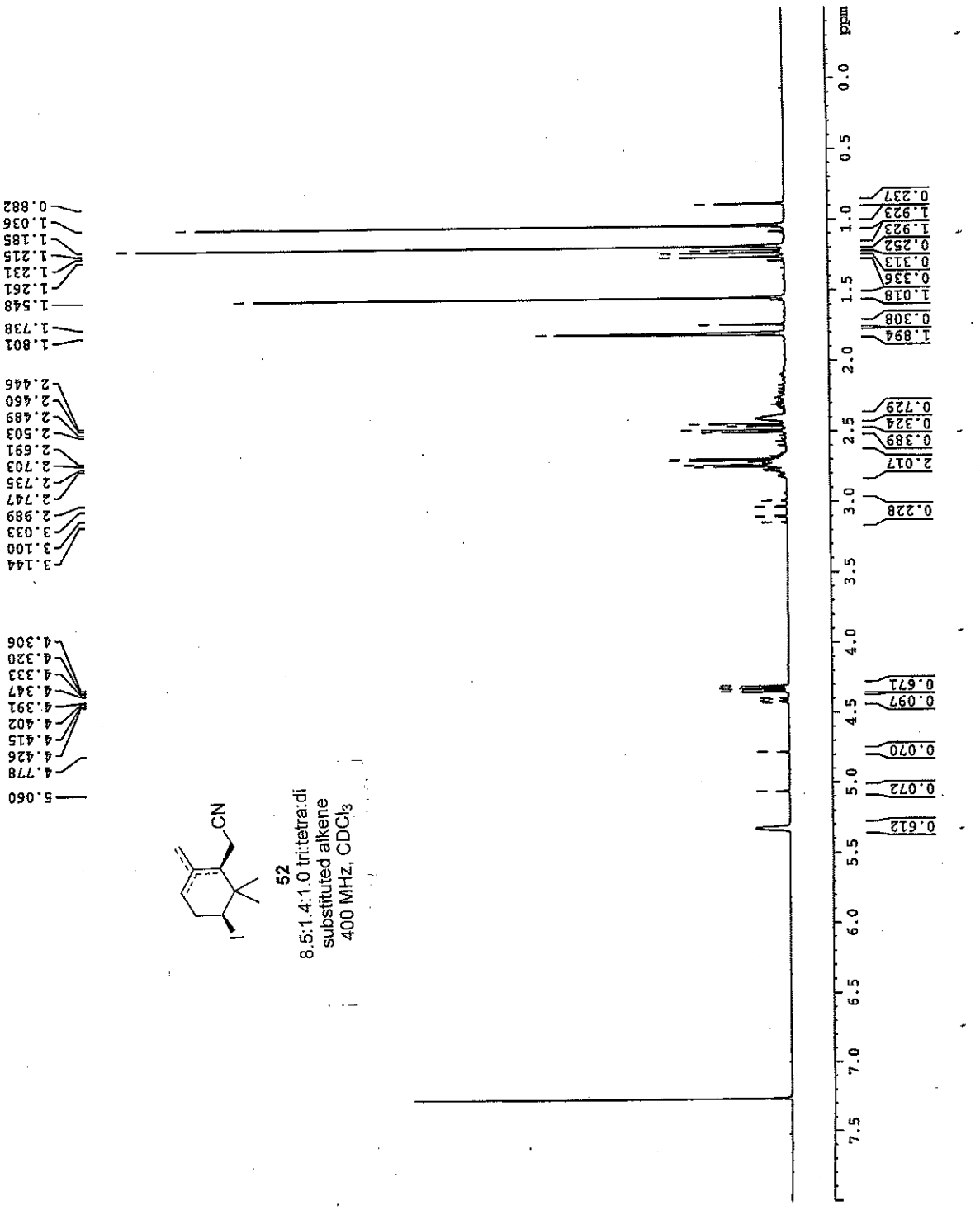

148.876
147.254
135.847
135.275
131.446
124.459
123.767
120.387
112.038
111.352
56.066
55.935
39.844
35.818
30.224
26.882
25.802
17.800
16.153
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
OMe
OMe
47
75 MHz, CDCl3

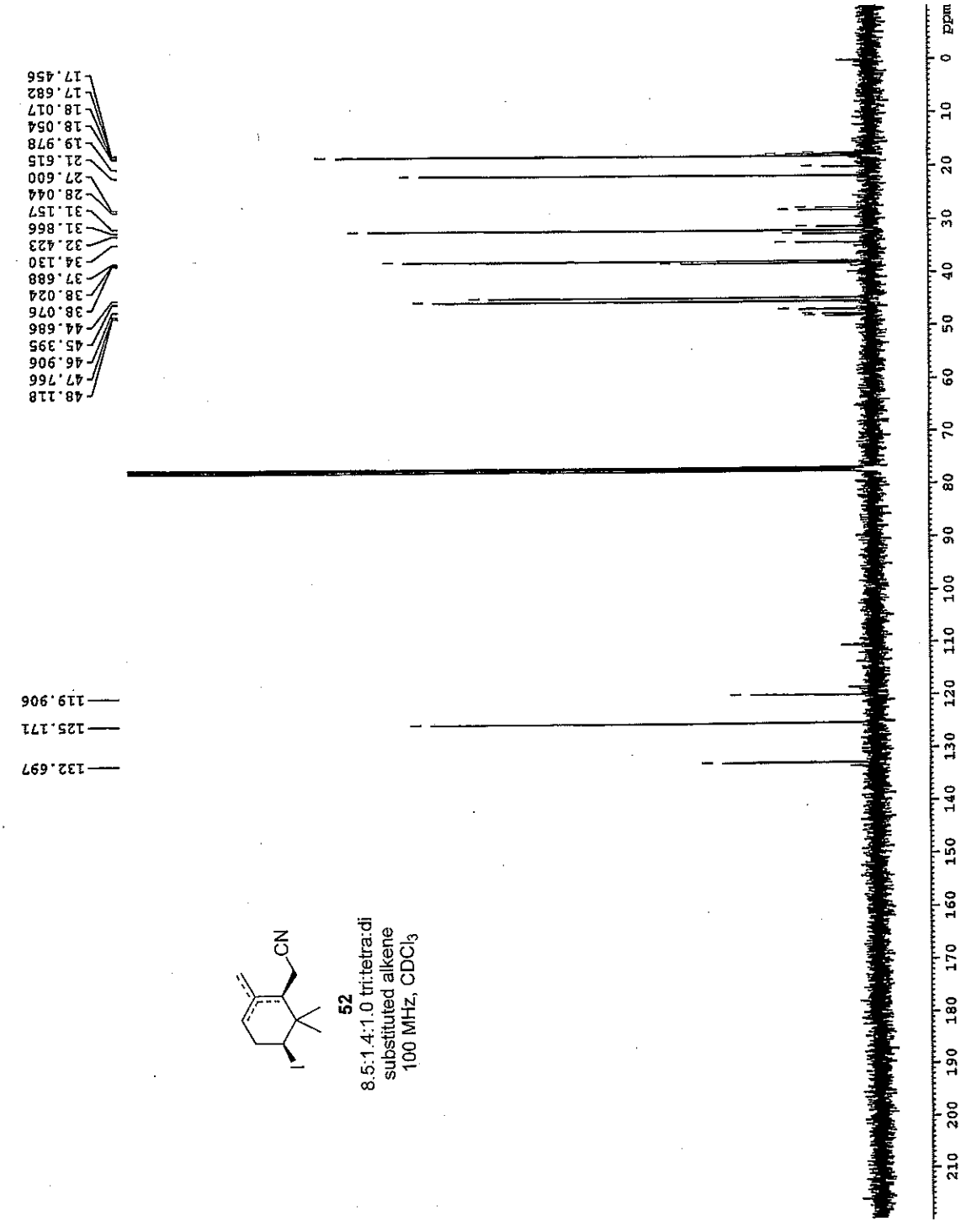

OMe
OMe
H
I
48
400 MHz, CDCl3
6.666
6.512
4.294
4.283
4.261
4.251
3.831
3.823
2.126
2.117
2.108
2.093
2.084
2.075
1.242
1.127
1.073
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
1.000
1.035
1.082
6.049
2.080
1.057
0.906
0.956
0.979
1.185
2.494
3.129
3.040
3.086

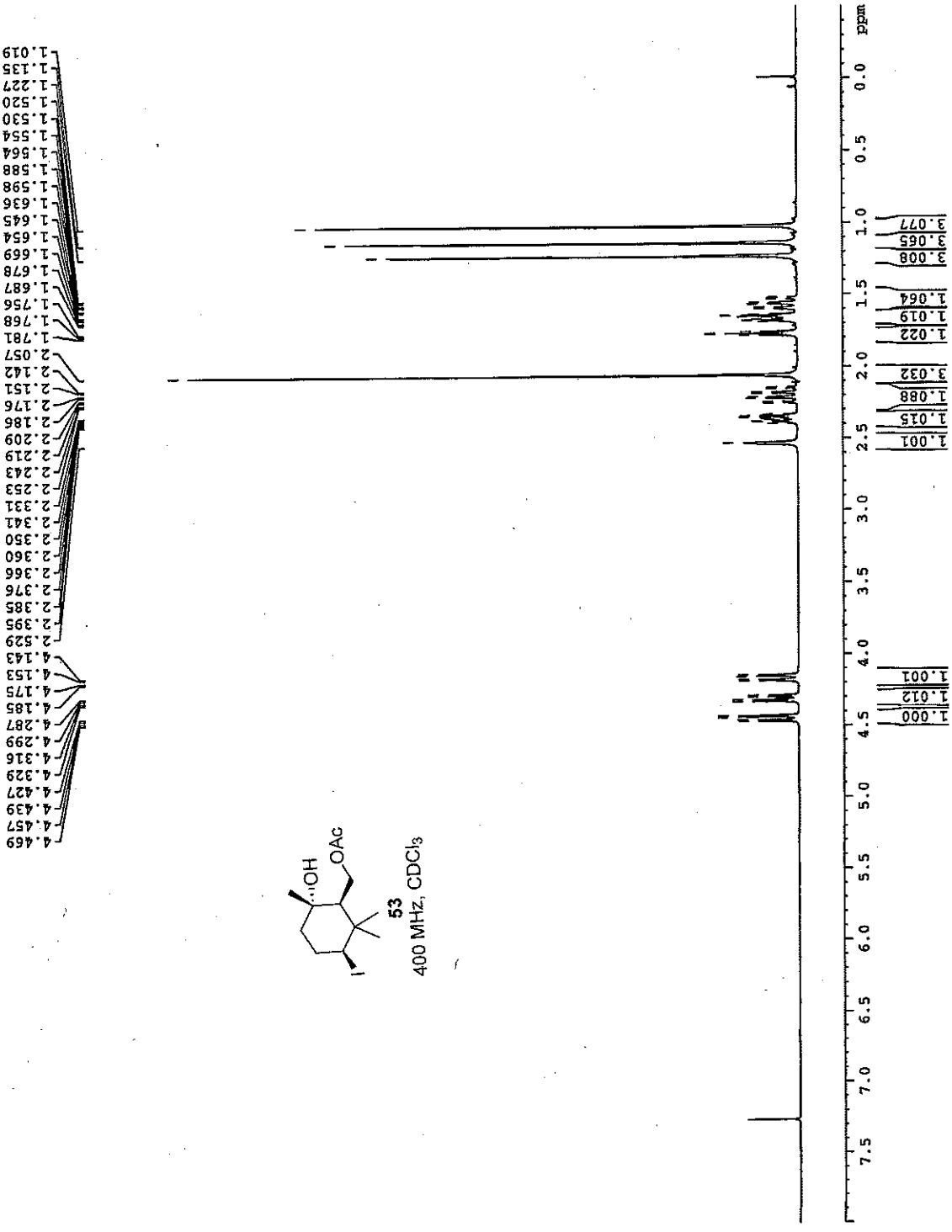

147.416
147.243
140.887
127.079
111.624
111.508
50.352
42.206
39.605
38.046
34.542
33.234
33.157
30.818
24.956
24.864
21.941
21.325
OMe
OMe
H
I
48
75 MHz, CDCl3
ppm

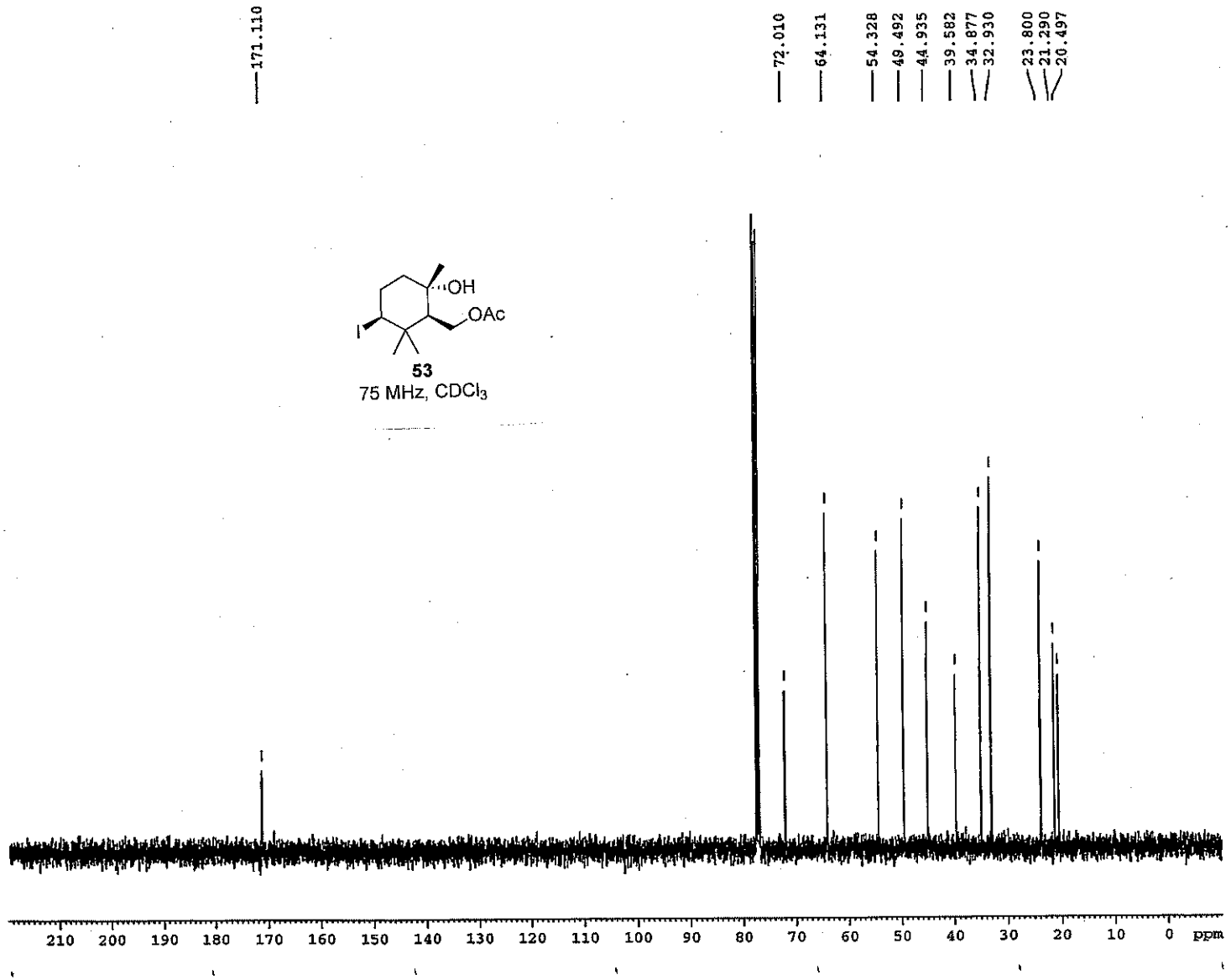

Br
OMOM
O
H
50
400 MHz, CDCl3
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
3.272
3.254
3.279
3.360
1.083
1.028
1.057
0.980
3.051
1.000
2.008
0.899
0.960
1.037
1.124
1.208
2.236
2.245
2.271
2.280
2.303
2.313
2.338
2.347
2.416
2.426
2.435
2.445
2.451
2.461
2.470
2.480
2.637
2.669
2.678
2.710
2.741
2.754
2.782
2.796
3.529
4.204
4.214
4.236
4.246
5.127
6.857
6.859

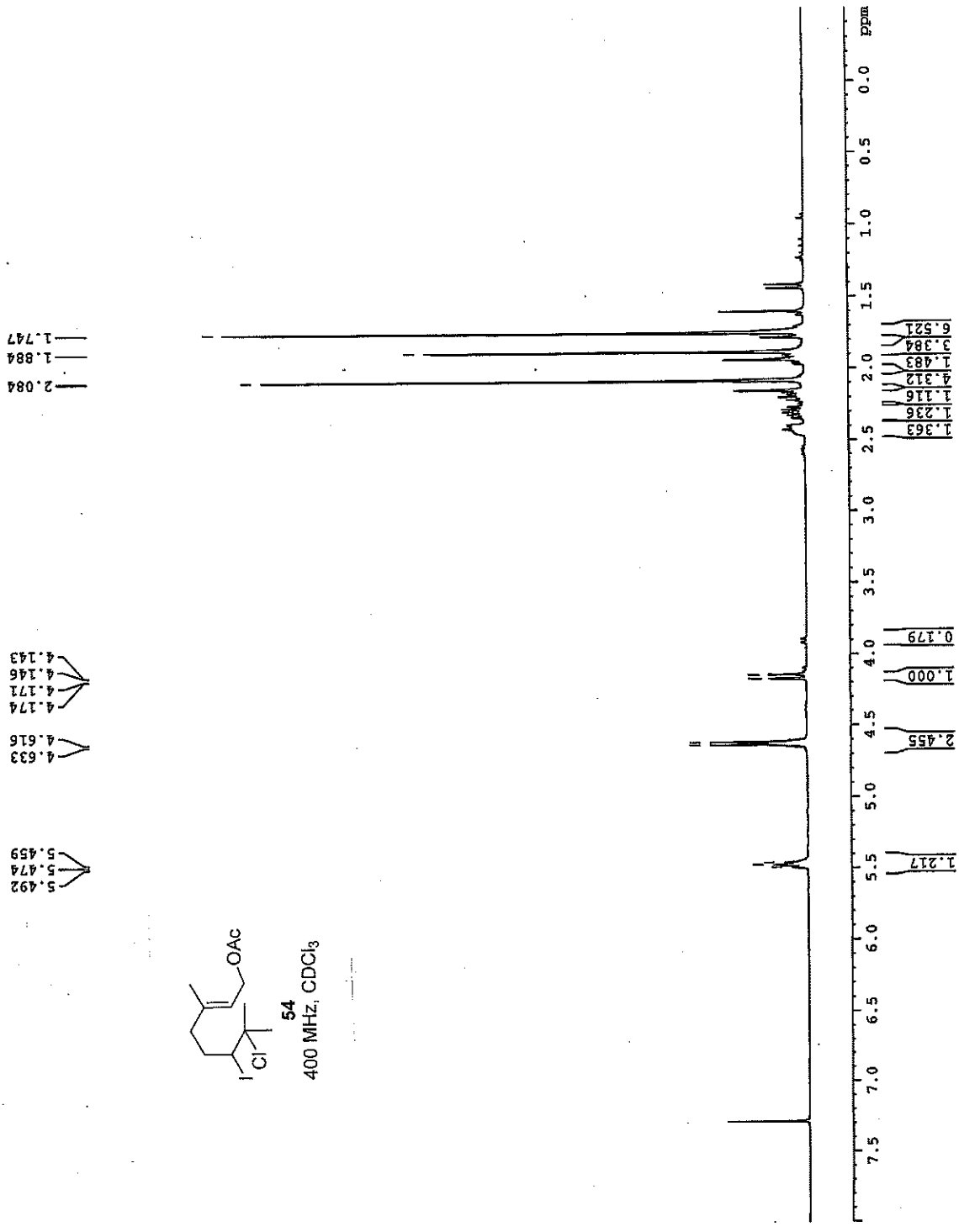

148.340
147.375
121.988
121.429
117.769
111.401
96.208
76.322
56.450
49.119
46.503
42.367
38.991
34.256
32.212
25.759
19.855
19.730
Br
OMOM
O
H
I
50
100 MHz, CDCl3
ppm

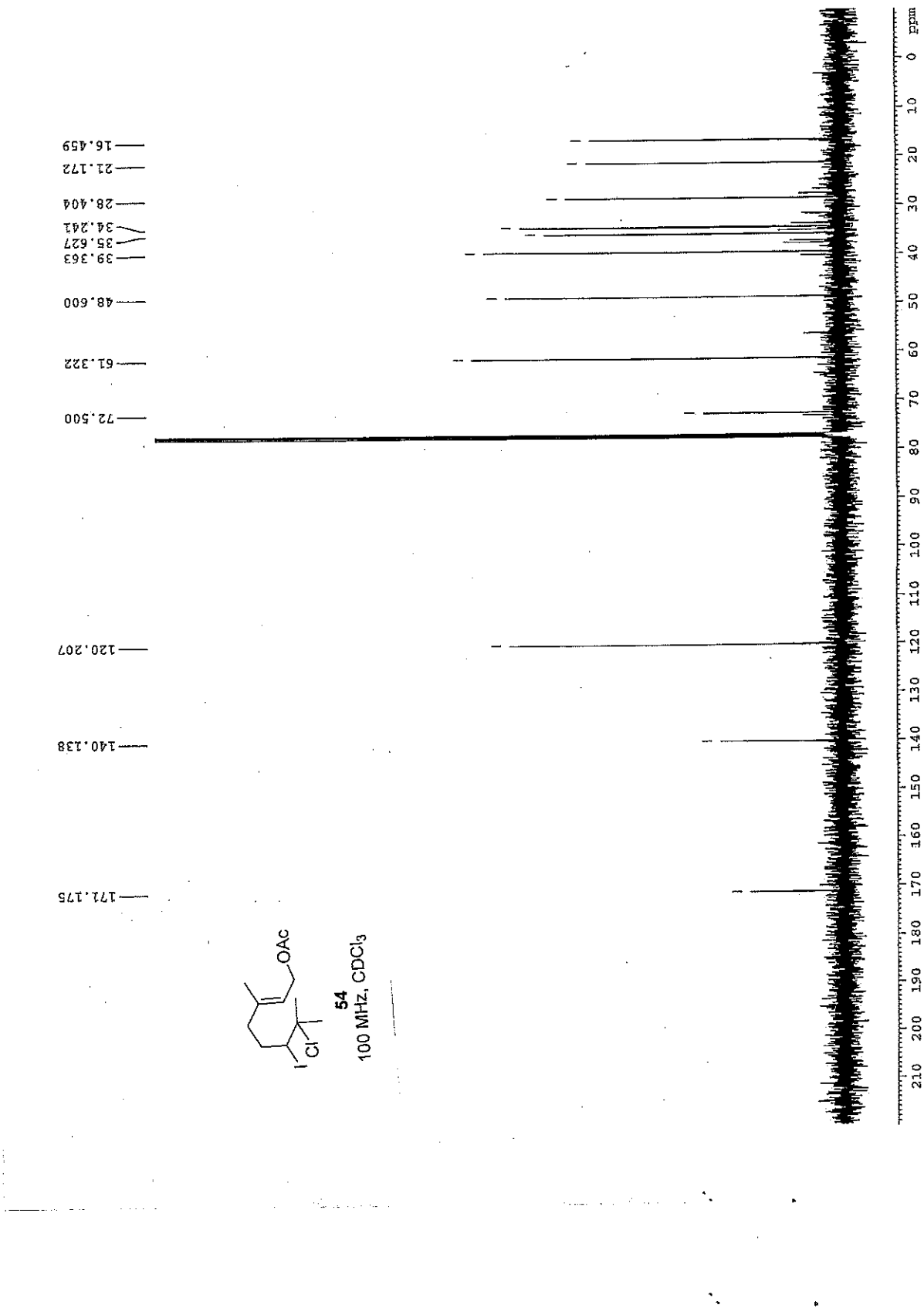

CN
I
52
8.5:1.4:1.0 tri:tetra:di
substituted alkene
400 MHz, CDCl3
ppm

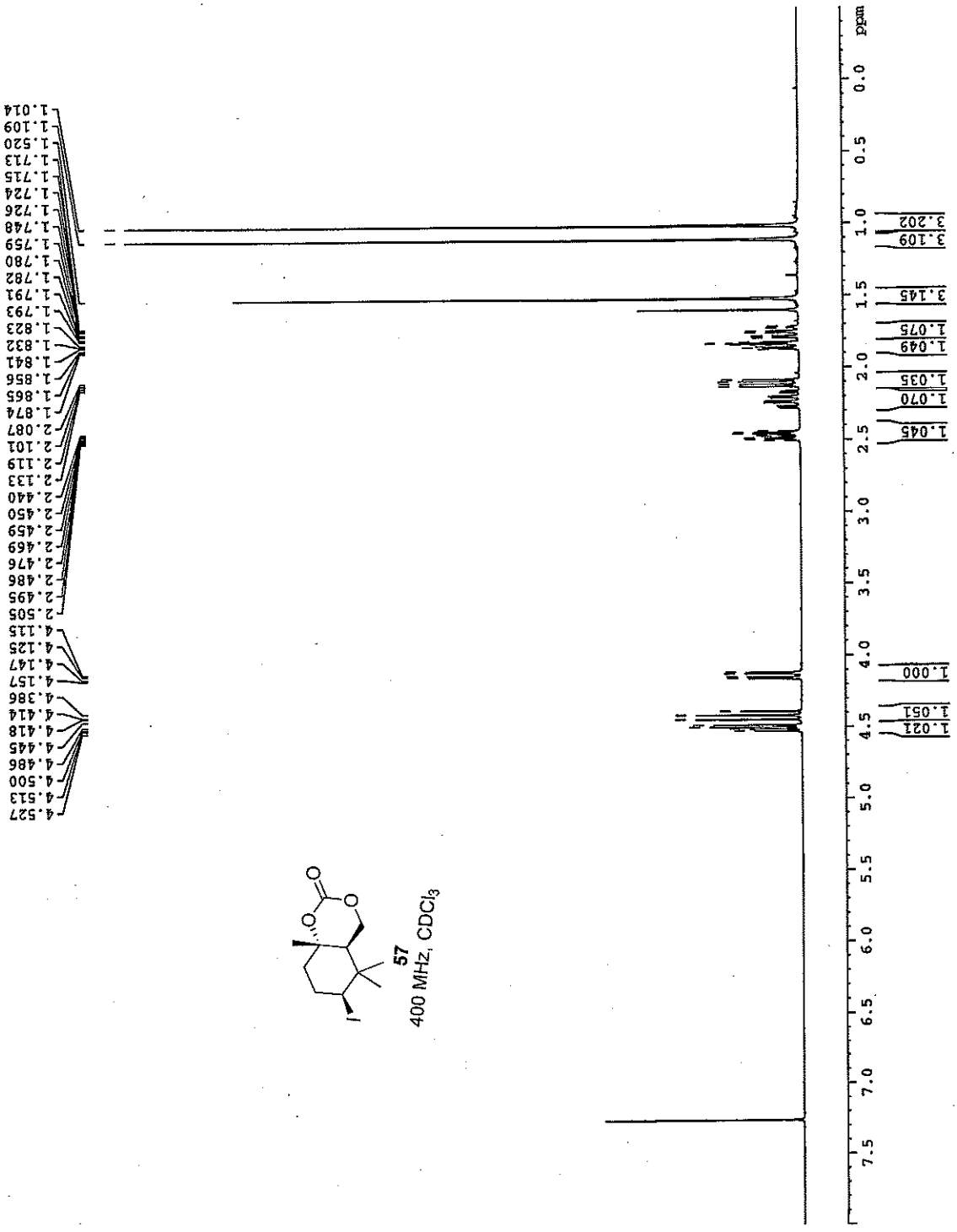

CN
I
52
8.5:1.4:1.0 tri:tetra:di
substituted alkene
100 MHz, CDCl3
17.456
17.682
18.017
18.054
19.978
21.615
27.600
28.044
31.157
31.866
32.423
34.130
37.688
38.024
38.076
44.686
45.395
46.906
47.766
48.118
119.906
125.171
132.697
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

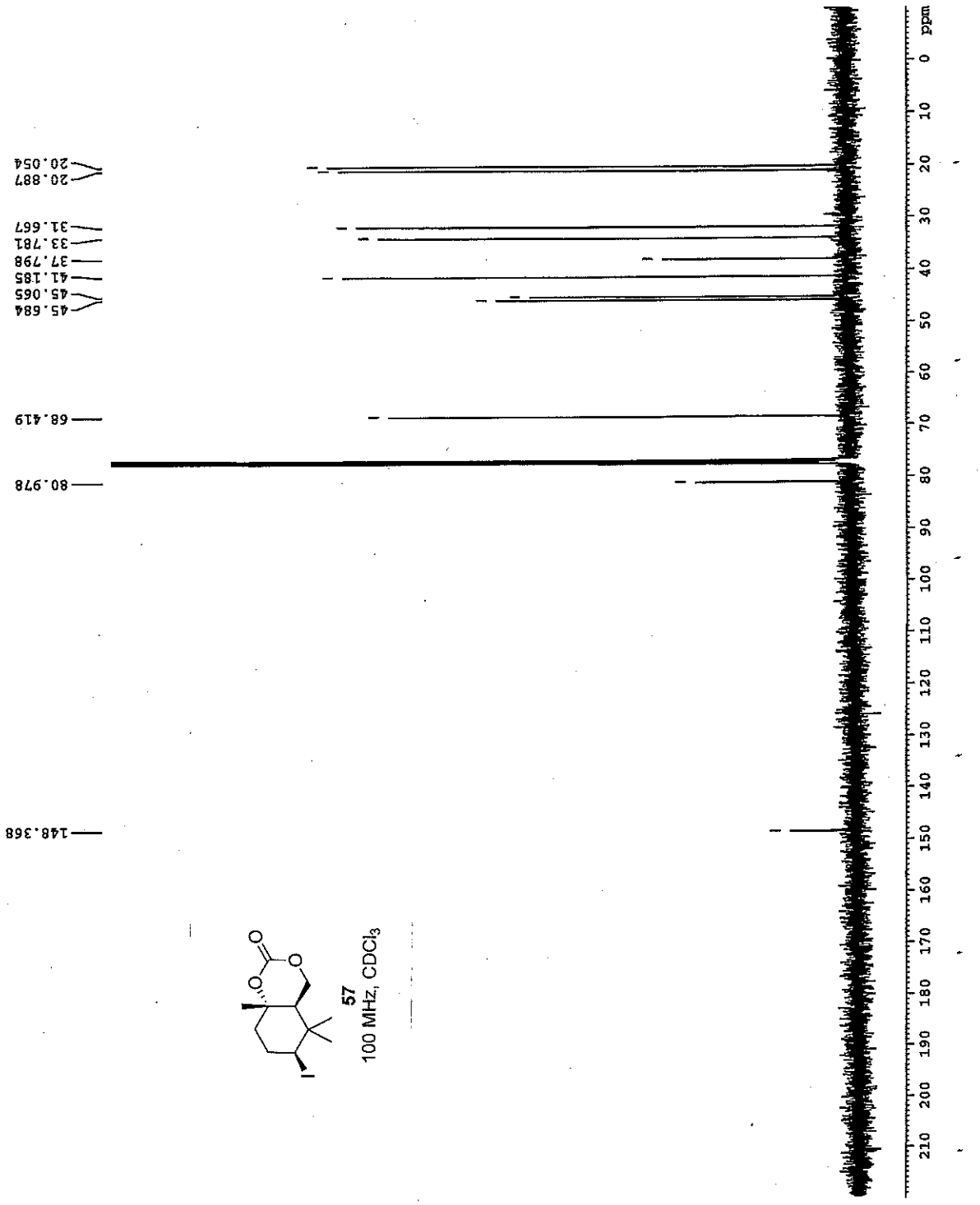

OAc
OH
I
53
400 MHz, CDCl3
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.001
1.012
1.000
1.001
1.015
1.088
3.032
1.022
1.019
1.064
3.008
3.065
3.077
4.469
4.457
4.439
4.427
4.329
4.316
4.299
4.287
4.185
4.175
4.153
4.143
2.529
2.395
2.385
2.376
2.366
2.360
2.350
2.341
2.331
2.253
2.243
2.219
2.209
2.186
2.176
2.151
2.142
2.057
1.781
1.768
1.756
1.687
1.678
1.669
1.654
1.645
1.636
1.598
1.588
1.564
1.554
1.530
1.520
1.227
1.135
1.019


171.110
72.010
64.131
54.328
49.492
44.935
39.582
34.877
32.930
23.800
21.290
20.497
OH
OAc
I
53
75 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

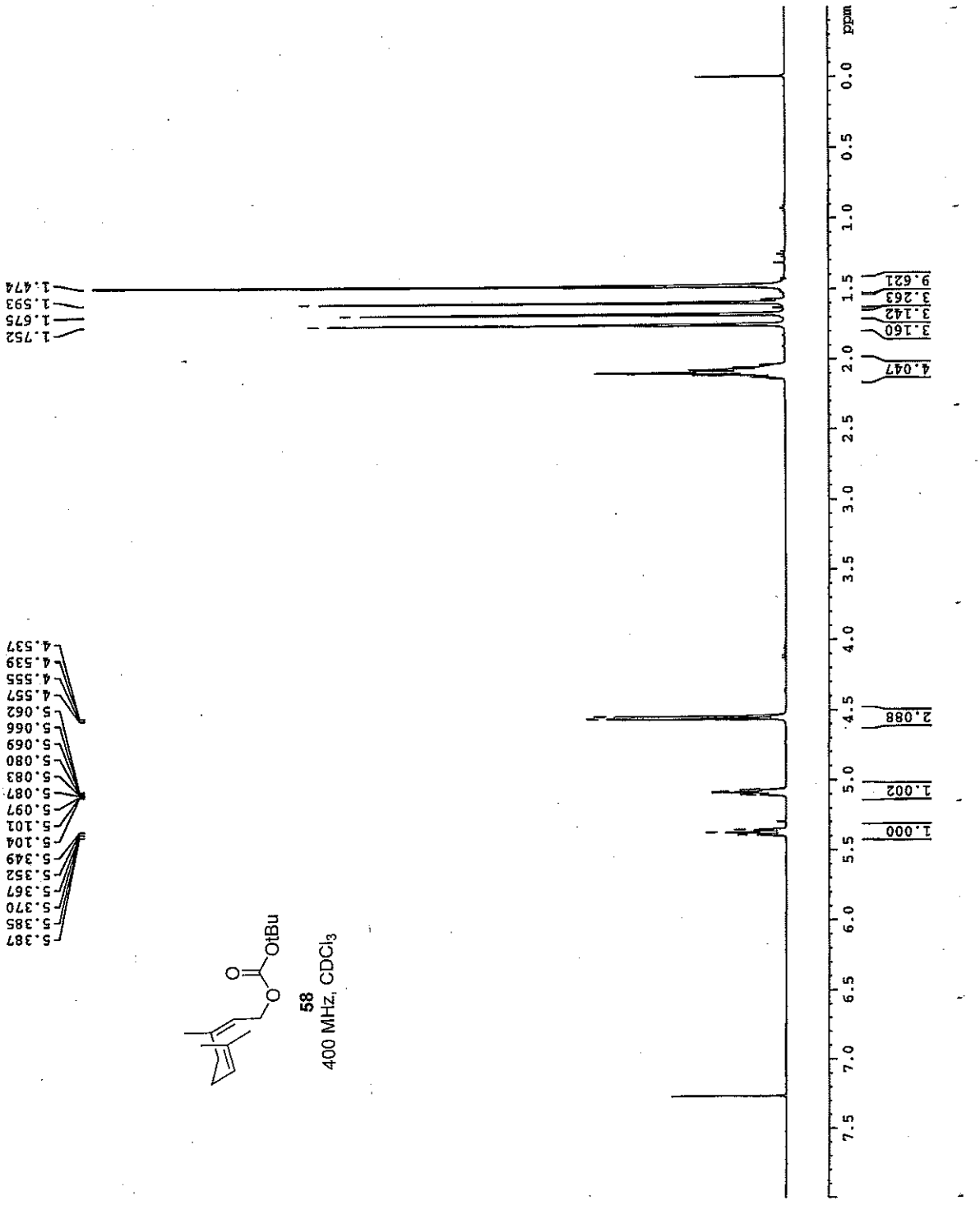

OAc
Cl
54
400 MHz, CDCl3
5.492
5.474
5.459
4.633
4.616
4.174
4.171
4.146
4.143
2.084
1.884
1.747
1.217
2.455
1.000
0.179
1.363
1.236
1.116
4.312
1.483
3.384
6.521
ppm

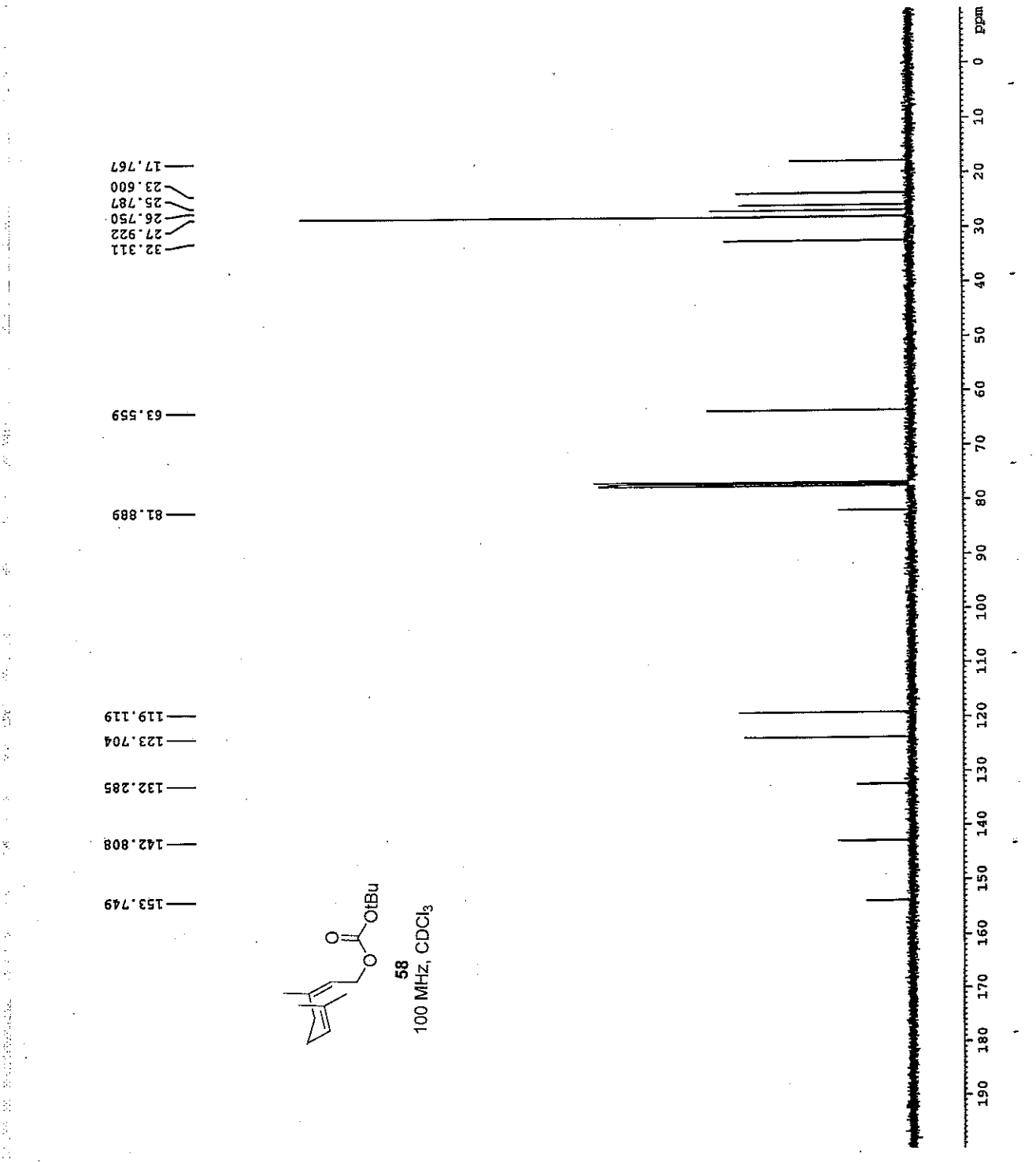

OAc
Cl
54
100 MHz, CDCl3
16.459
21.172
28.404
34.241
35.627
39.363
48.600
61.322
72.500
120.207
140.138
171.175
ppm

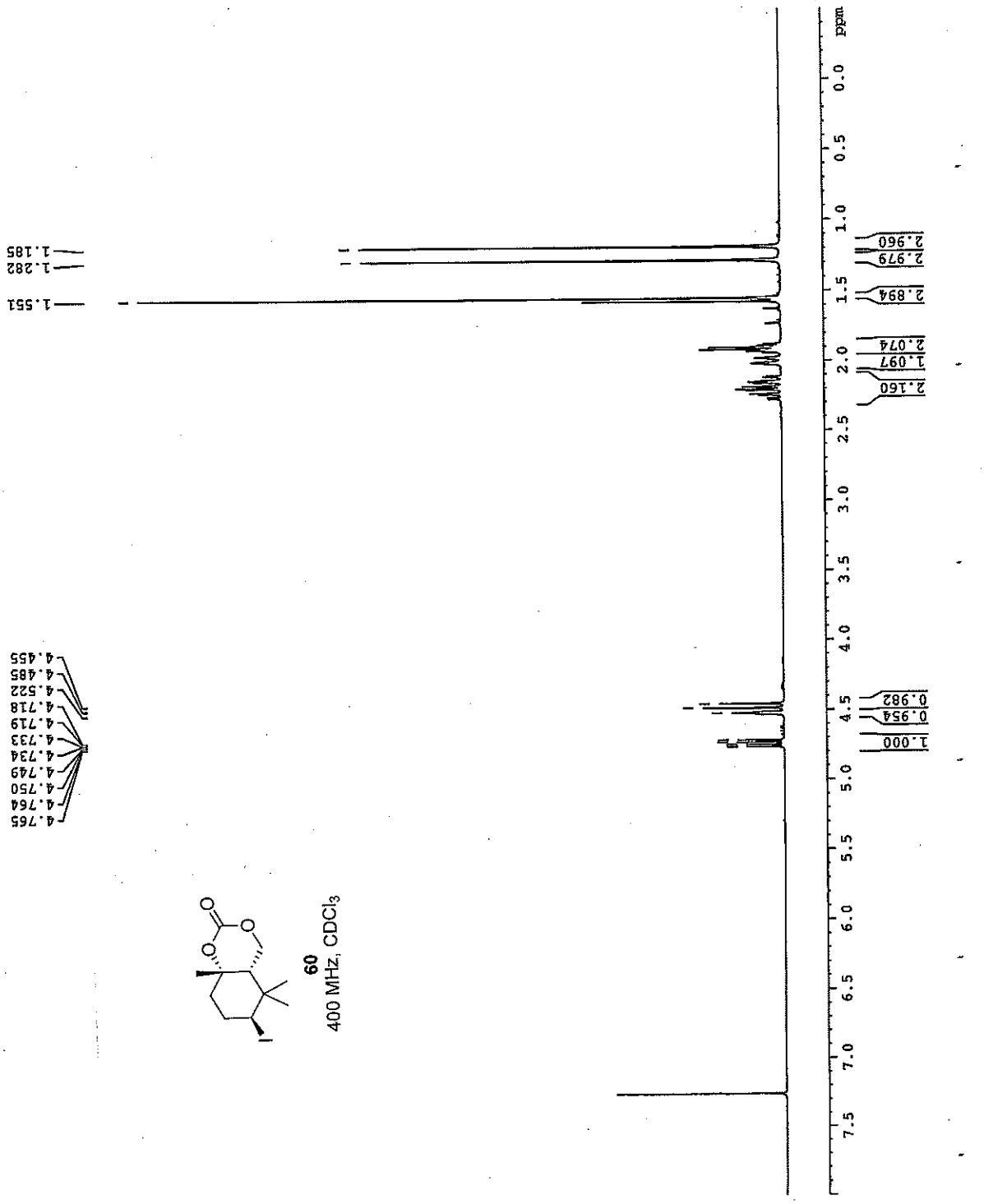

1.014
1.109
1.520
1.713
1.715
1.724
1.726
1.748
1.759
1.780
1.782
1.791
1.793
1.823
1.832
1.841
1.856
1.865
1.874
2.087
2.101
2.119
2.133
2.440
2.450
2.459
2.469
2.476
2.486
2.495
2.505
4.115
4.125
4.147
4.157
4.386
4.414
4.418
4.445
4.486
4.500
4.513
4.527
3.202
3.109
3.145
1.075
1.049
1.035
1.070
1.045
1.000
1.051
1.021
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
O
O
O
I
57
400 MHz, CDCl3

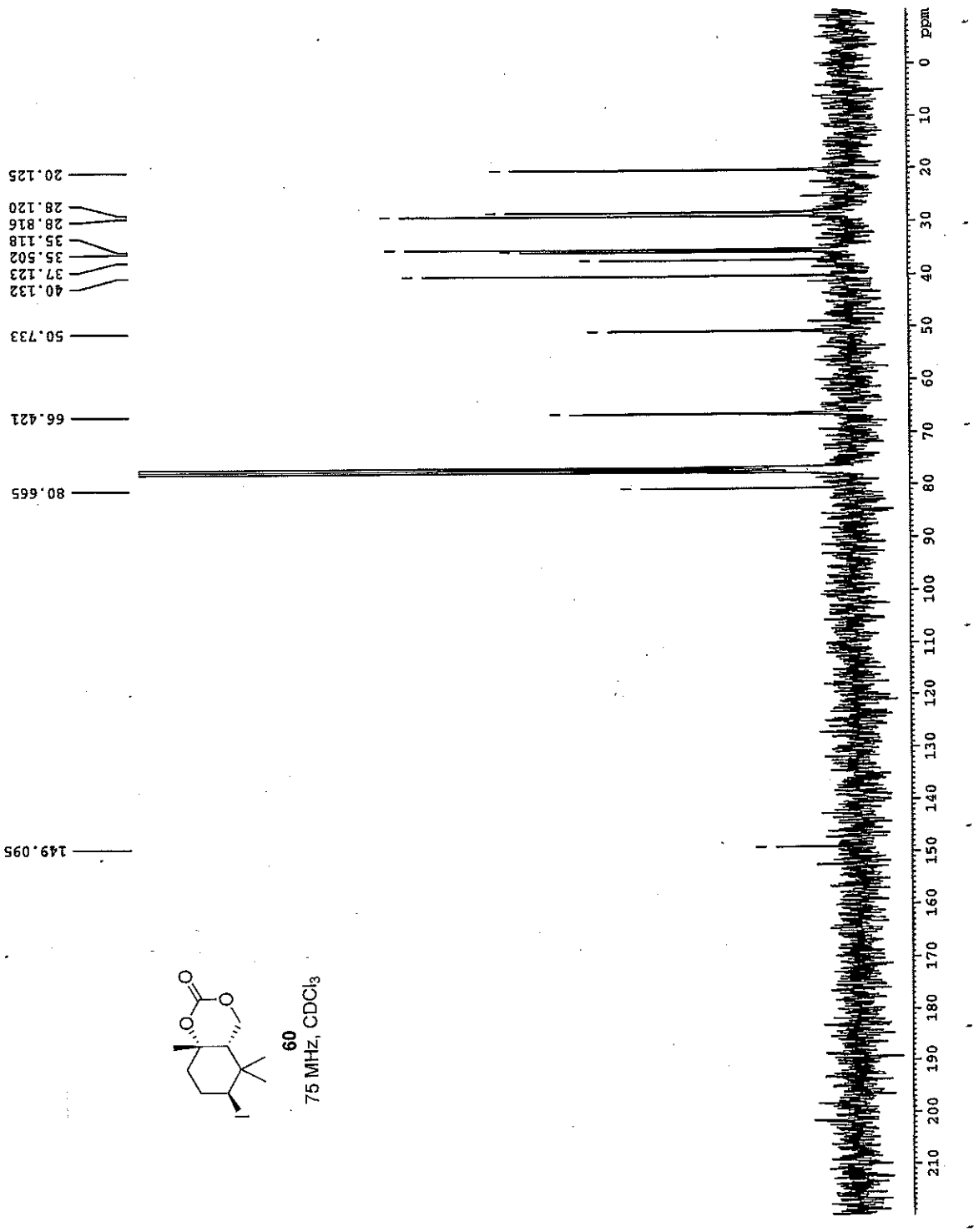


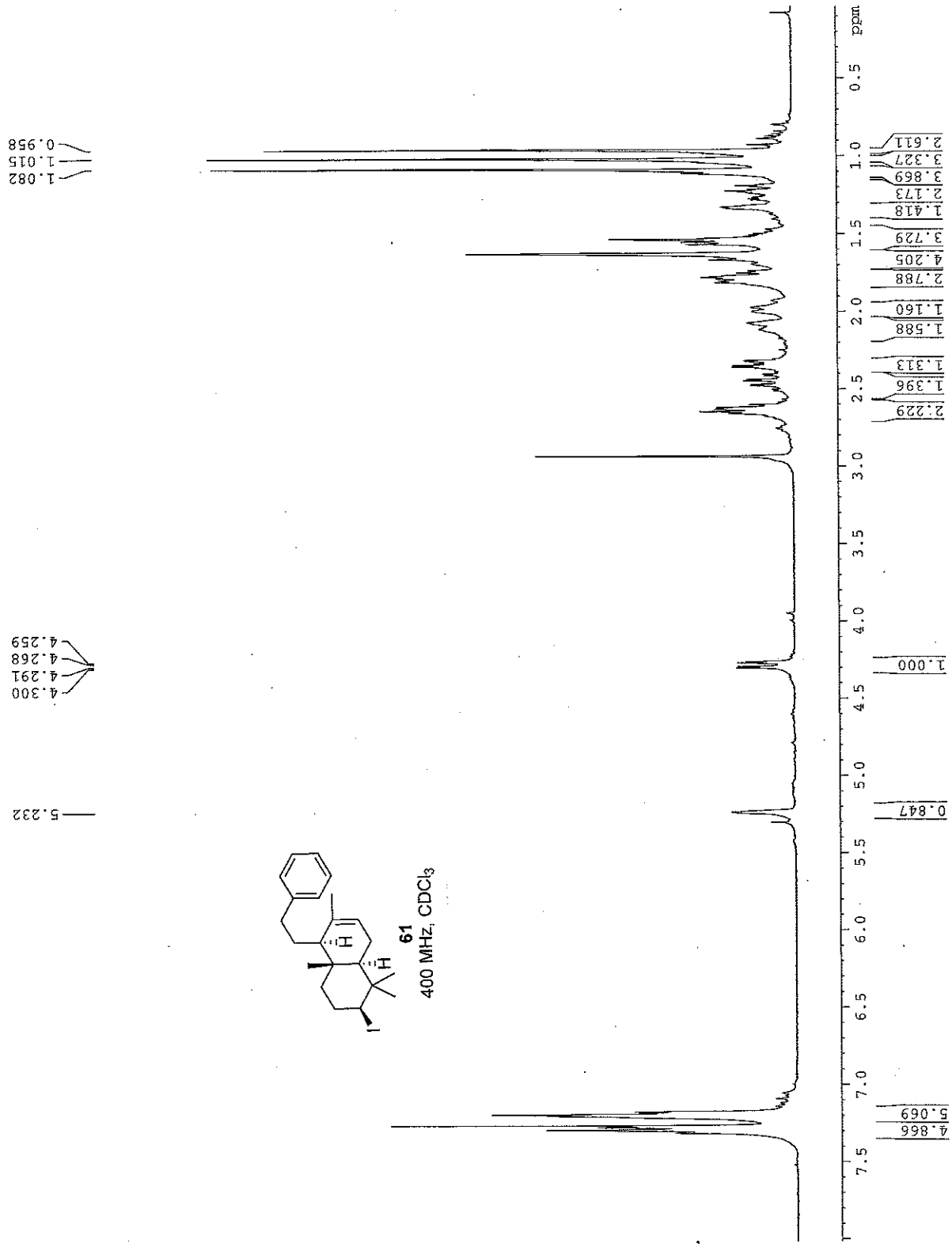
57
100 MHz, $CDCl_3$

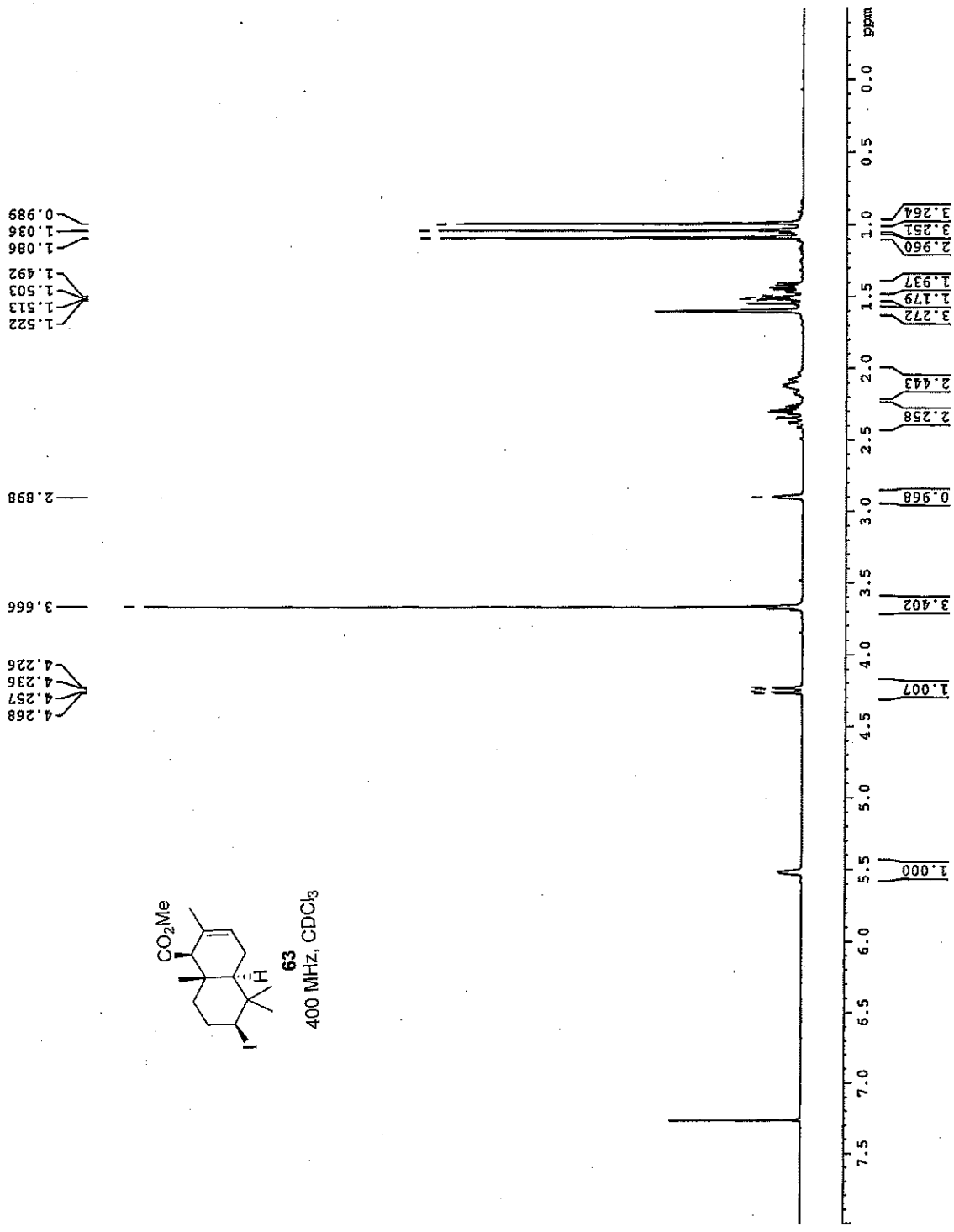

1.474
1.593
1.675
1.752
4.537
4.539
4.555
4.557
5.062
5.066
5.069
5.080
5.083
5.087
5.097
5.101
5.104
5.349
5.352
5.367
5.370
5.385
5.387
OtBu
O
O
58
400 MHz, CDCl3
9.621
3.263
3.142
3.160
4.047
2.088
1.002
1.000
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

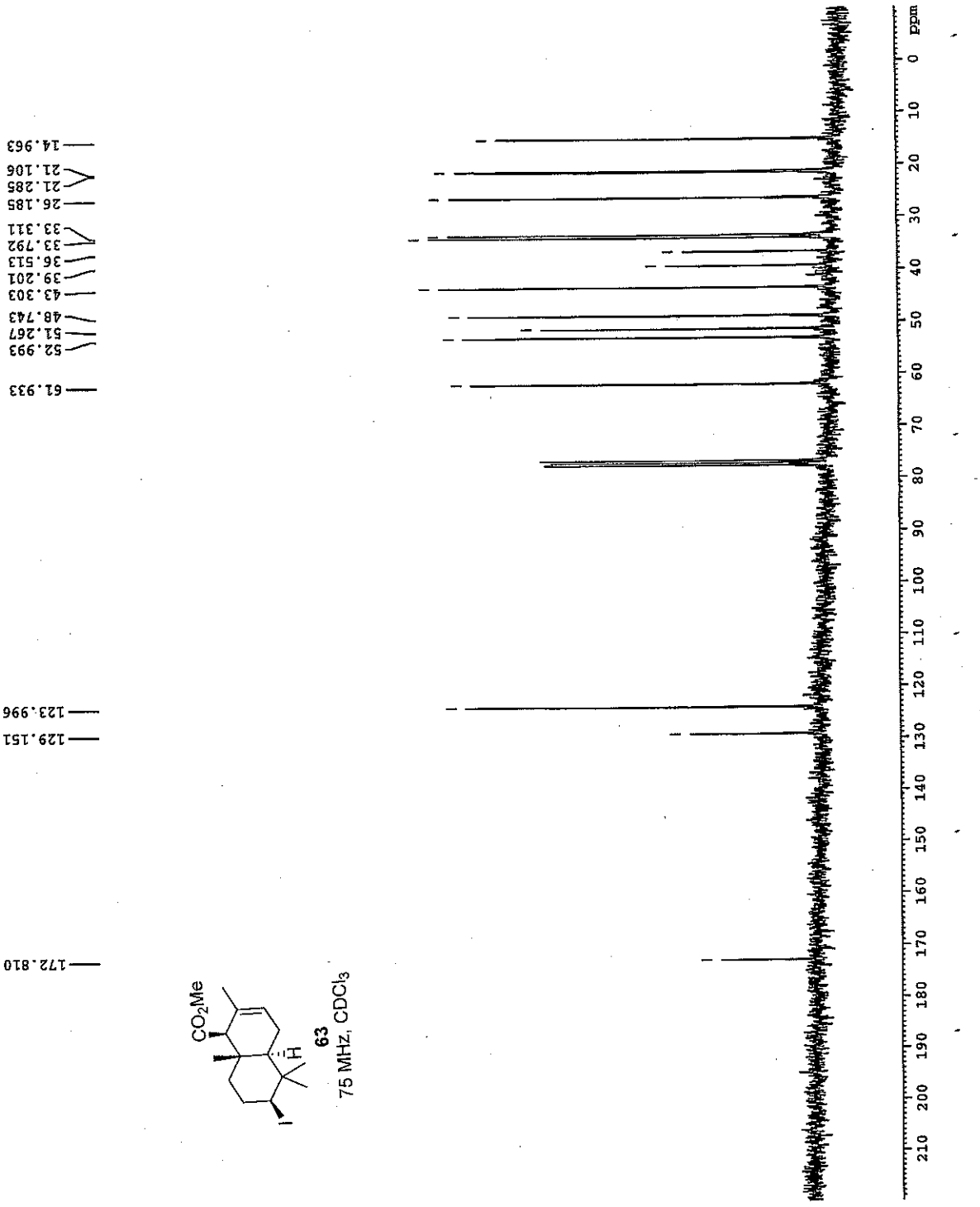

153.749
142.808
132.285
123.704
119.119
81.889
63.559
32.311
27.922
26.750
25.787
23.600
17.767
OtBu
O
O
58
100 MHz, CDCl3
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190

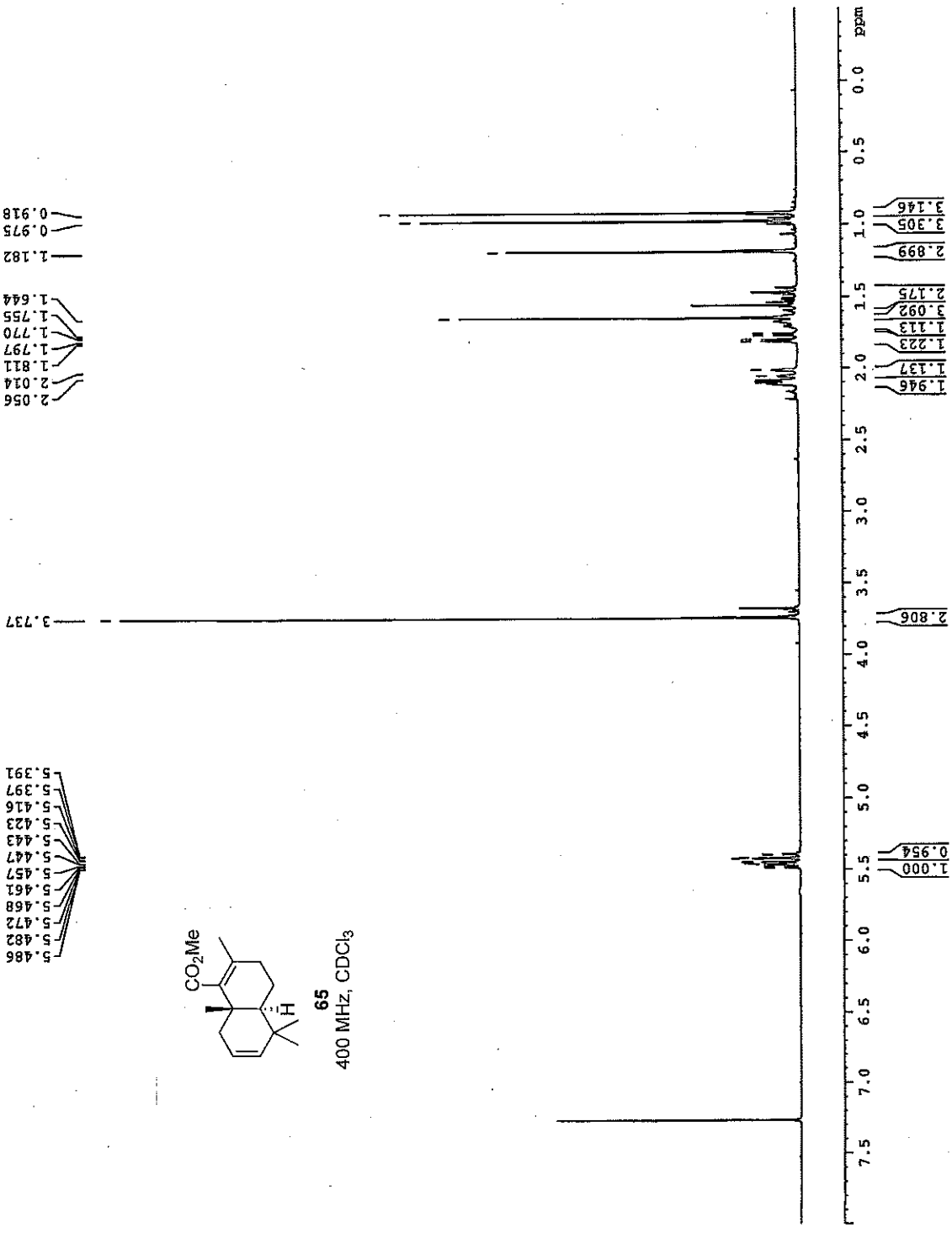

4.765
4.764
4.750
4.749
4.734
4.733
4.719
4.718
4.522
4.485
4.455
1.551
1.282
1.185
2.960
2.979
2.894
2.074
1.097
2.160
1.000
0.954
0.982
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
60
400 MHz, CDCl3

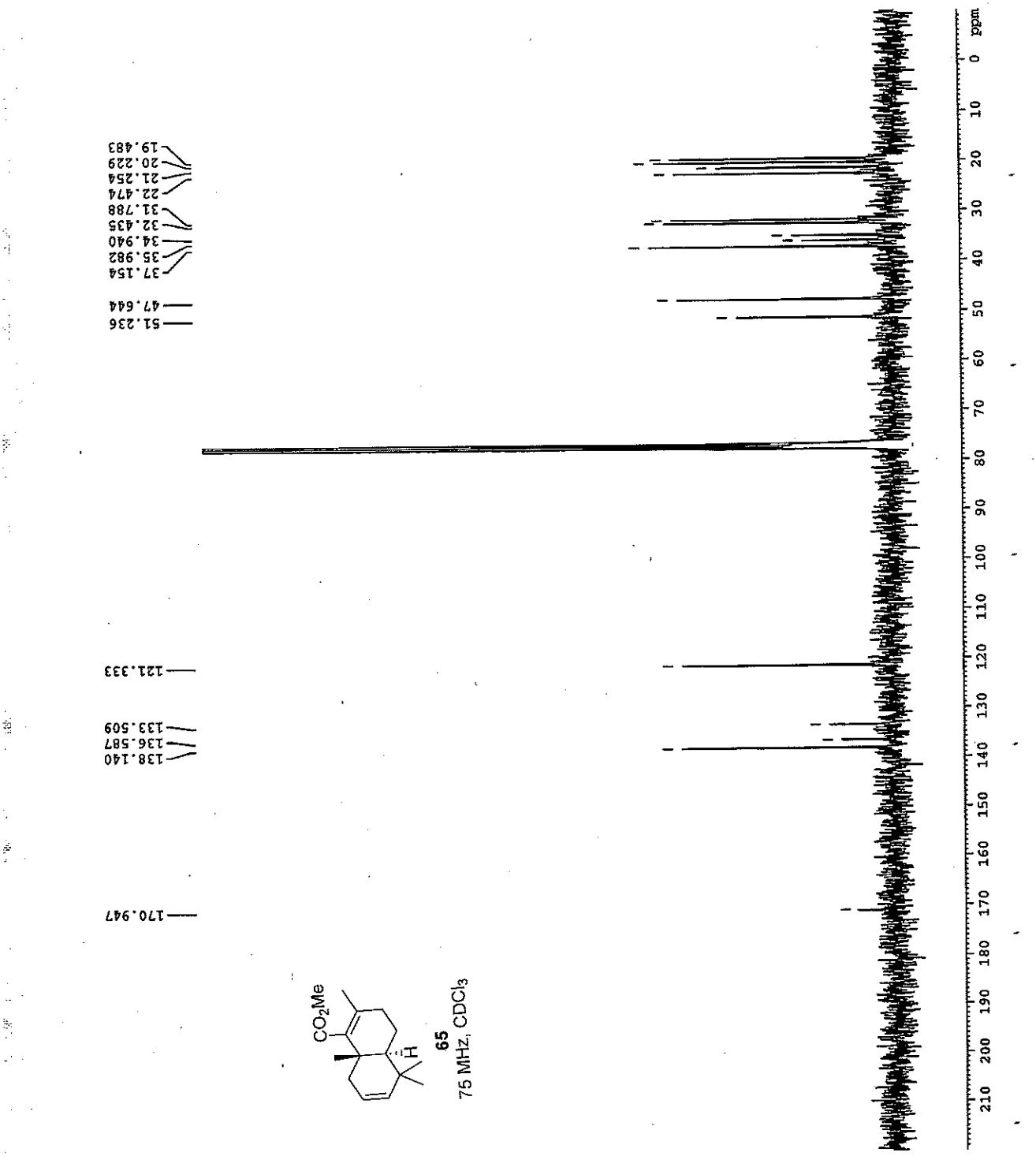

149.095
80.665
66.421
50.733
40.132
37.123
35.502
35.118
28.816
28.120
20.125
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
60
75 MHz, $CDCl_3$

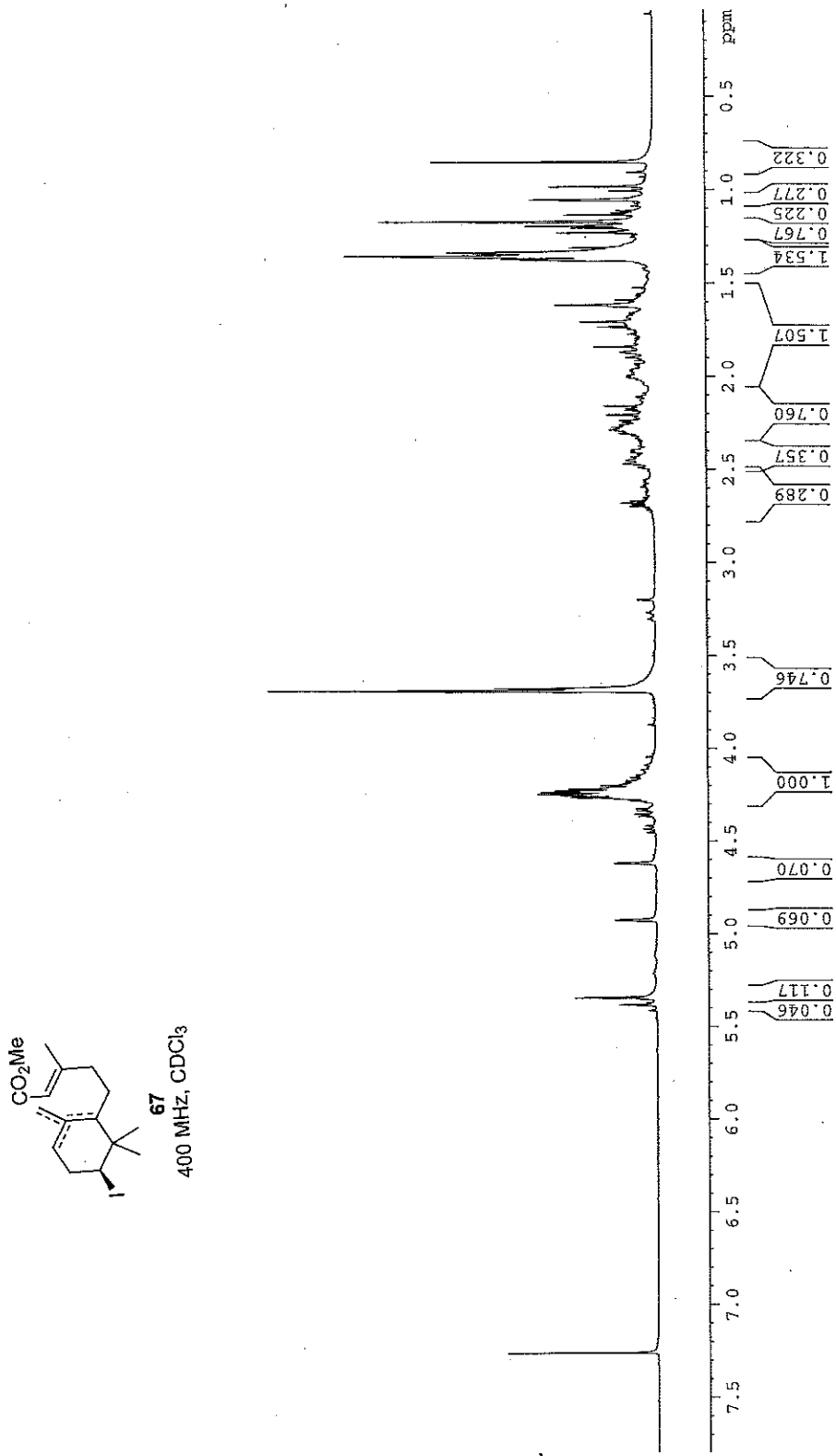

61
400 MHz, CDCl3
5.232
4.300
4.291
4.268
4.259
1.082
1.015
0.958
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
4.866
5.069
0.847
1.000
2.229
1.396
1.313
1.588
1.160
2.788
4.205
3.729
1.418
2.173
3.869
3.327
2.611

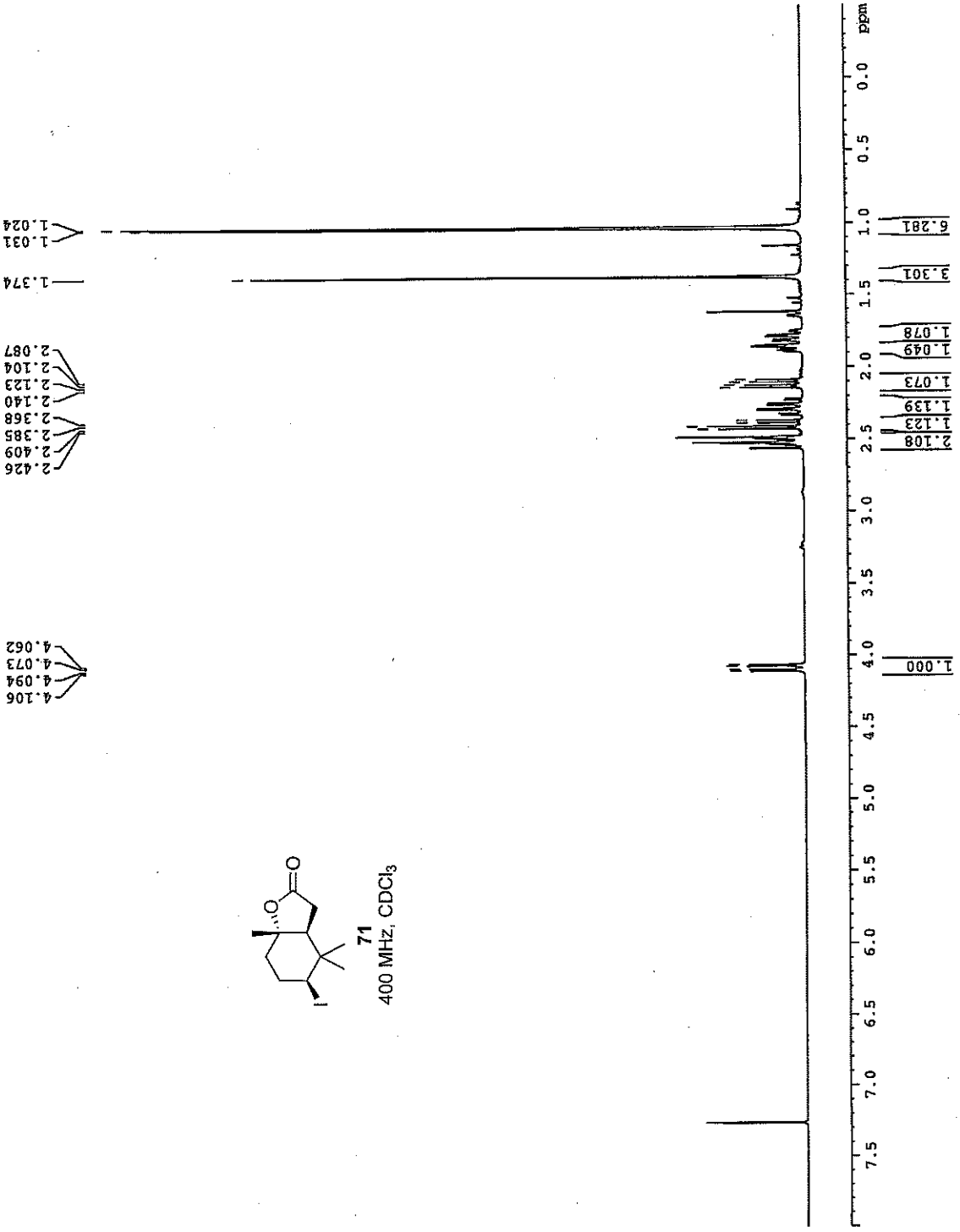

CO2Me
H
63
400 MHz, CDCl3
4.268
4.257
4.236
4.226
3.666
2.898
1.522
1.513
1.503
1.492
1.086
1.036
0.989
1.000
3.402
1.007
0.968
2.443
2.258
3.272
1.179
1.937
2.960
3.251
3.264
ppm

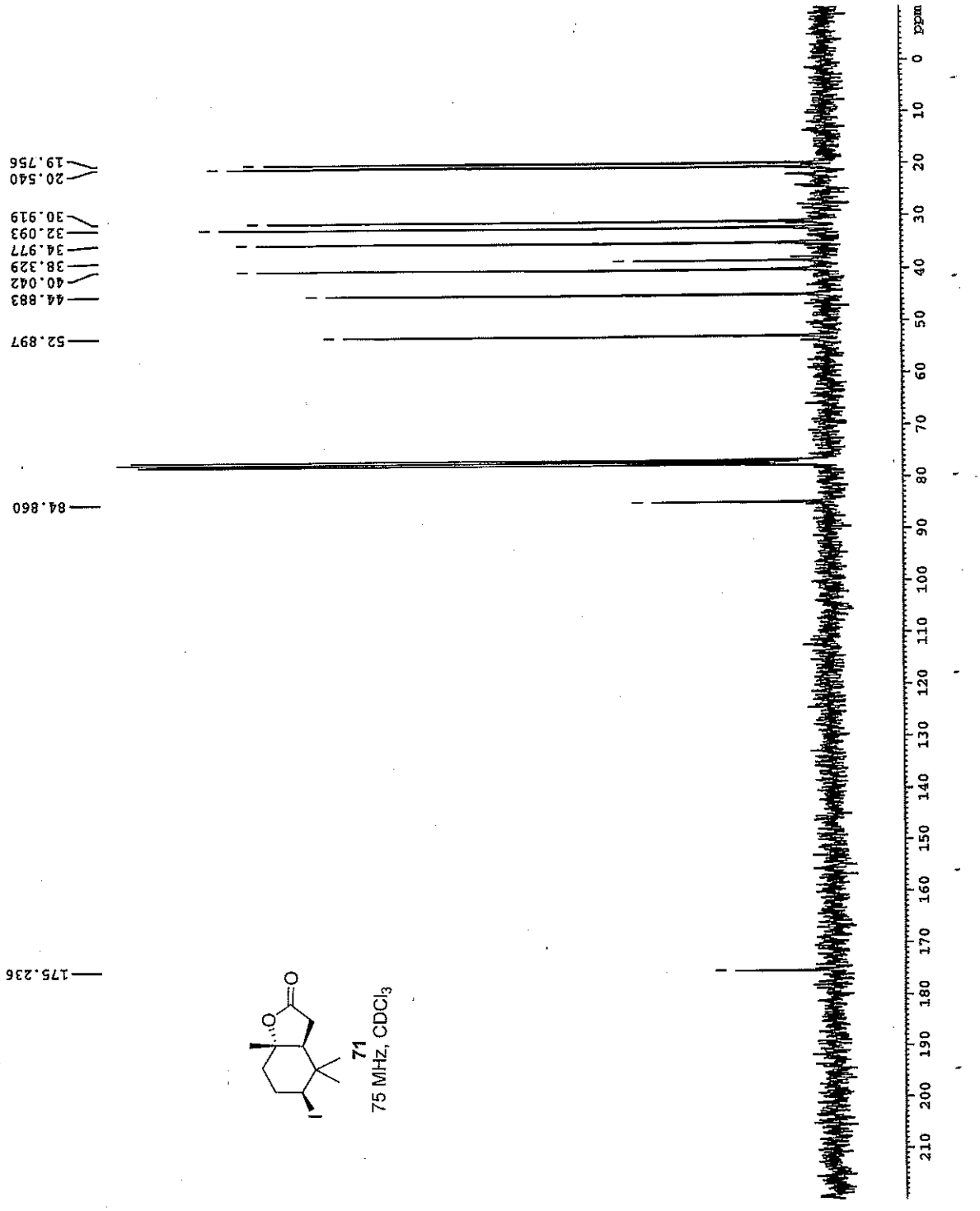

172.810
129.151
123.996
61.933
52.993
51.267
48.743
43.303
39.201
36.513
33.792
33.311
26.185
21.285
21.106
14.963
CO2Me
H
63
75 MHz, CDCl3
ppm


CO2Me
H
65
400 MHz, CDCl3
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
1.000
0.954
2.806
1.946
1.137
1.223
1.113
3.092
2.175
2.899
3.305
3.146
0.918
0.975
1.182
1.644
1.755
1.770
1.797
1.811
2.014
2.056
3.737
5.391
5.397
5.416
5.423
5.443
5.447
5.457
5.461
5.468
5.472
5.482
5.486

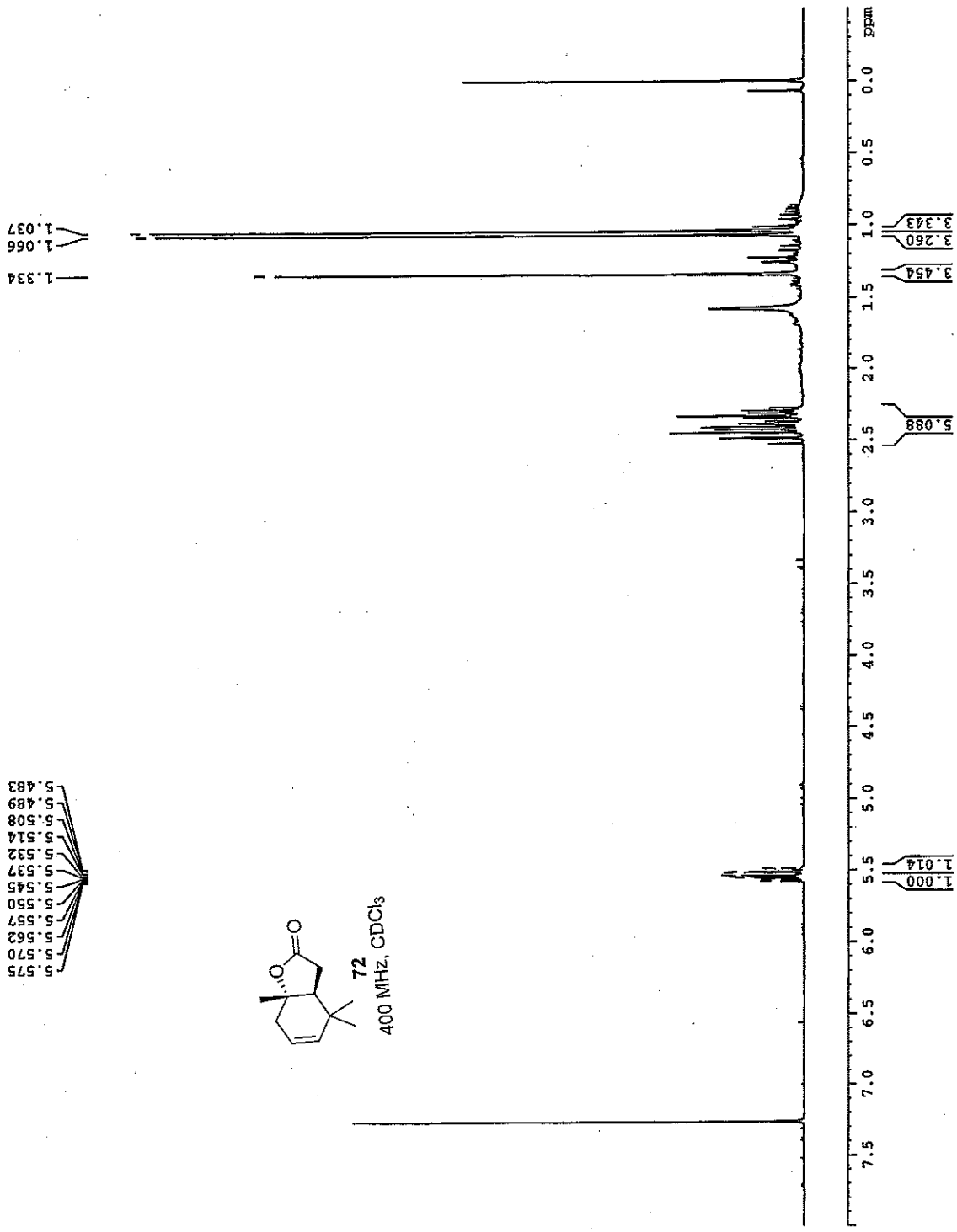

170.947
138.140
136.587
133.509
121.333
51.236
47.644
37.154
35.982
34.940
32.435
31.788
22.474
21.254
20.229
19.483
CO2Me
H
65
75 MHz, CDCl3
ppm

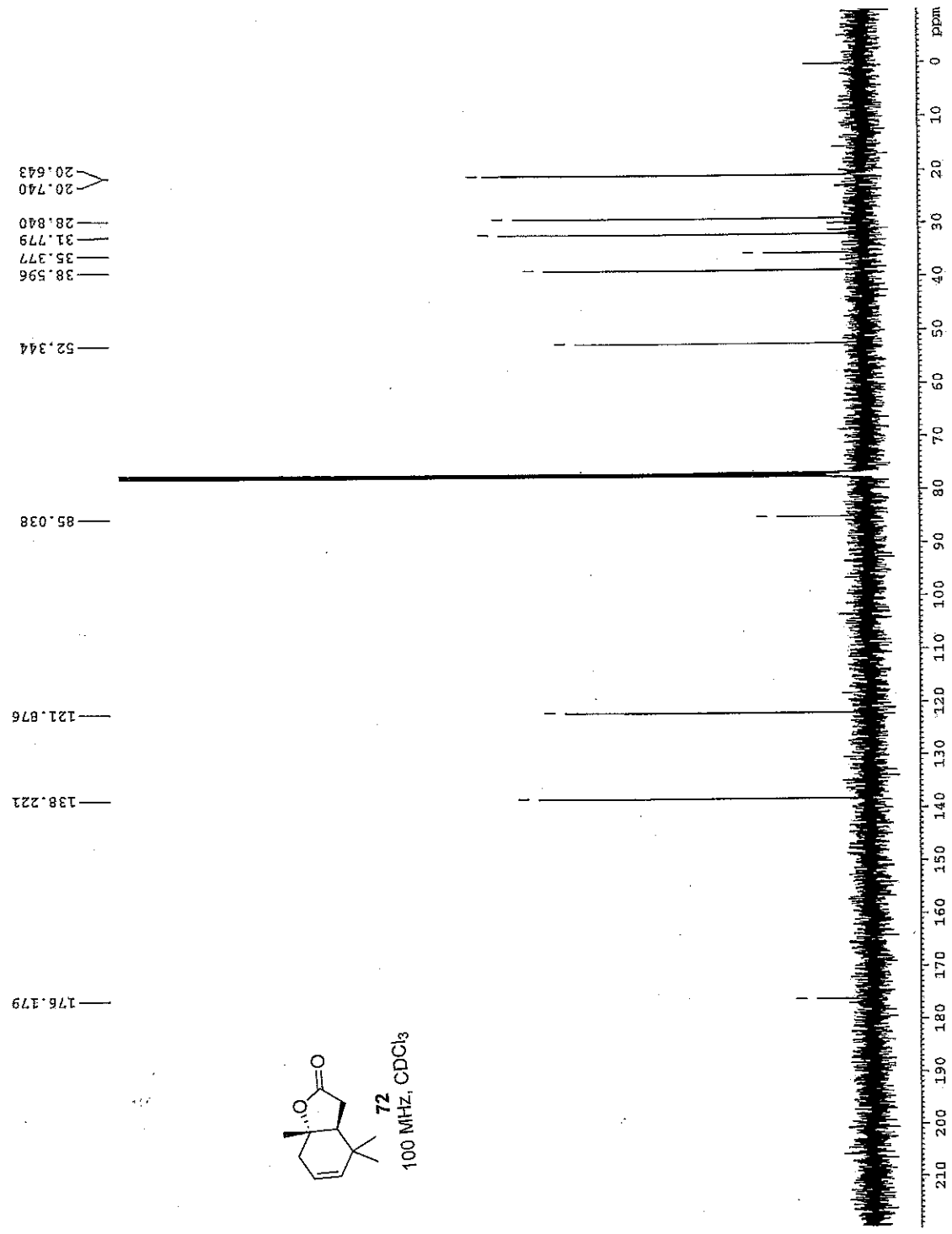

CO2Me
I
67
400 MHz, CDCl3
ppm
0.322
0.277
0.225
0.767
1.534
1.507
0.760
0.357
0.289
0.746
1.000
0.070
0.069
0.117
0.046

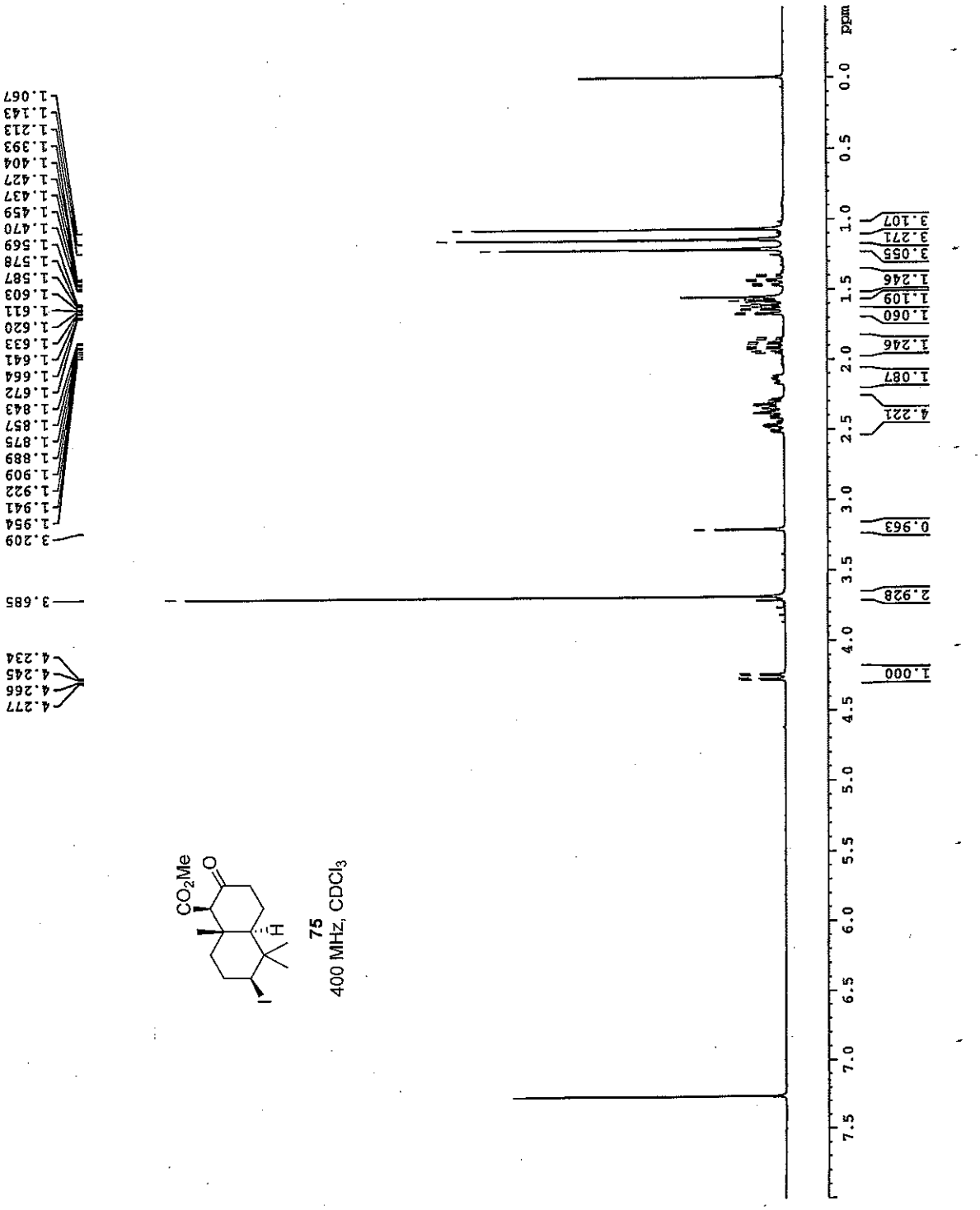

1.024
1.031
1.374
2.087
2.104
2.123
2.140
2.368
2.385
2.409
2.426
4.062
4.073
4.094
4.106
6.281
3.301
1.078
1.049
1.073
1.139
1.123
2.108
1.000
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
71
400 MHz, CDCl3

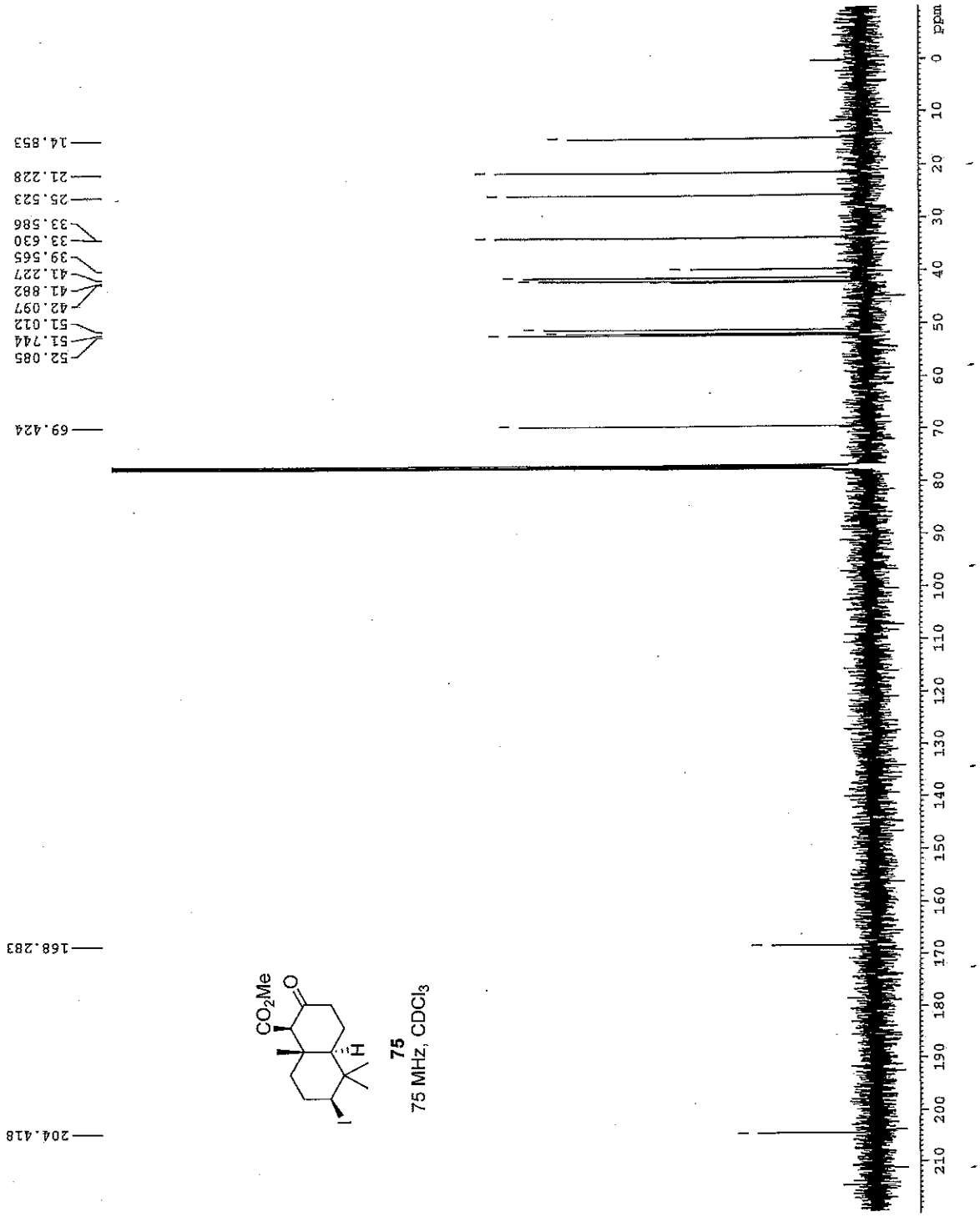


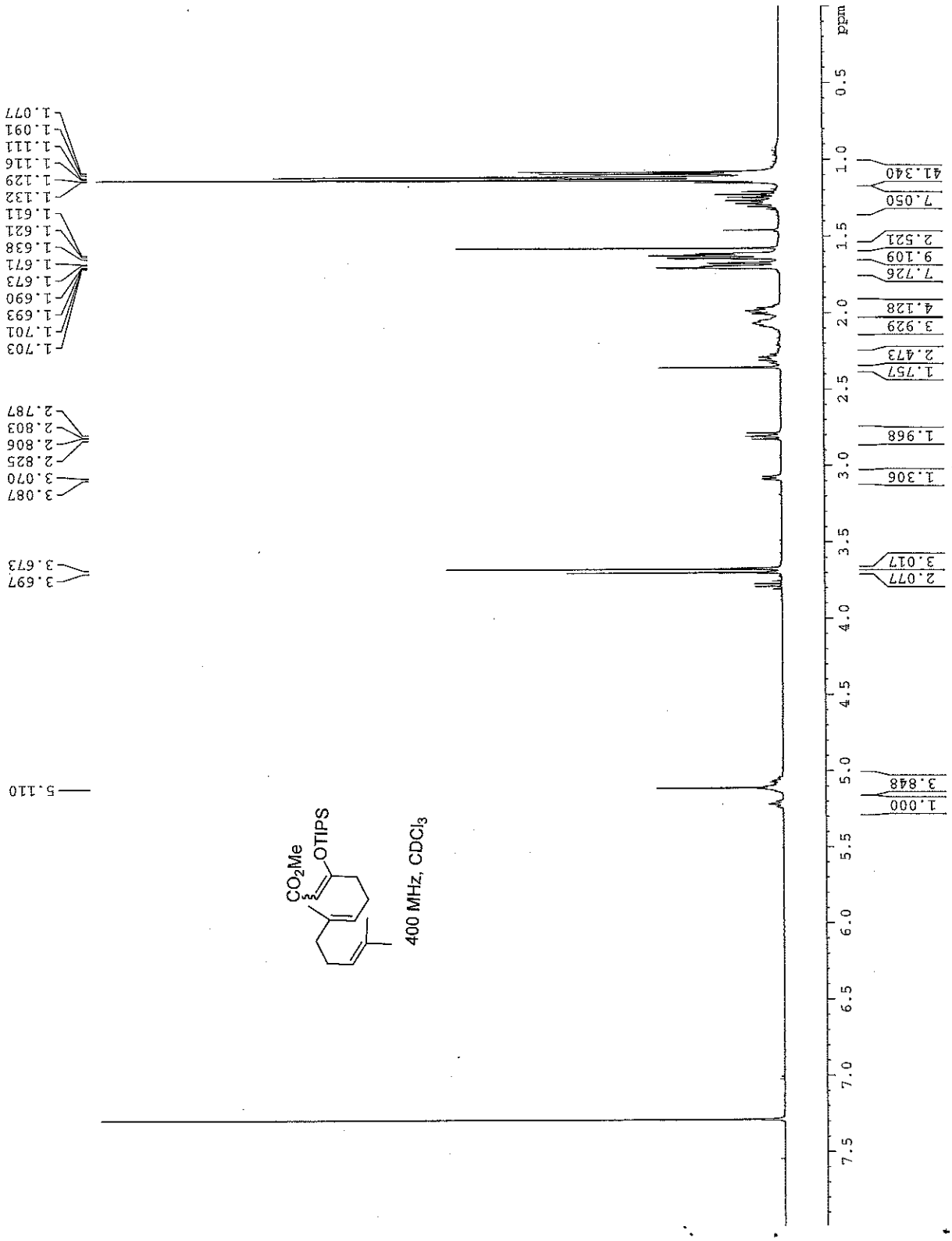
71
75 MHz, $CDCl_3$

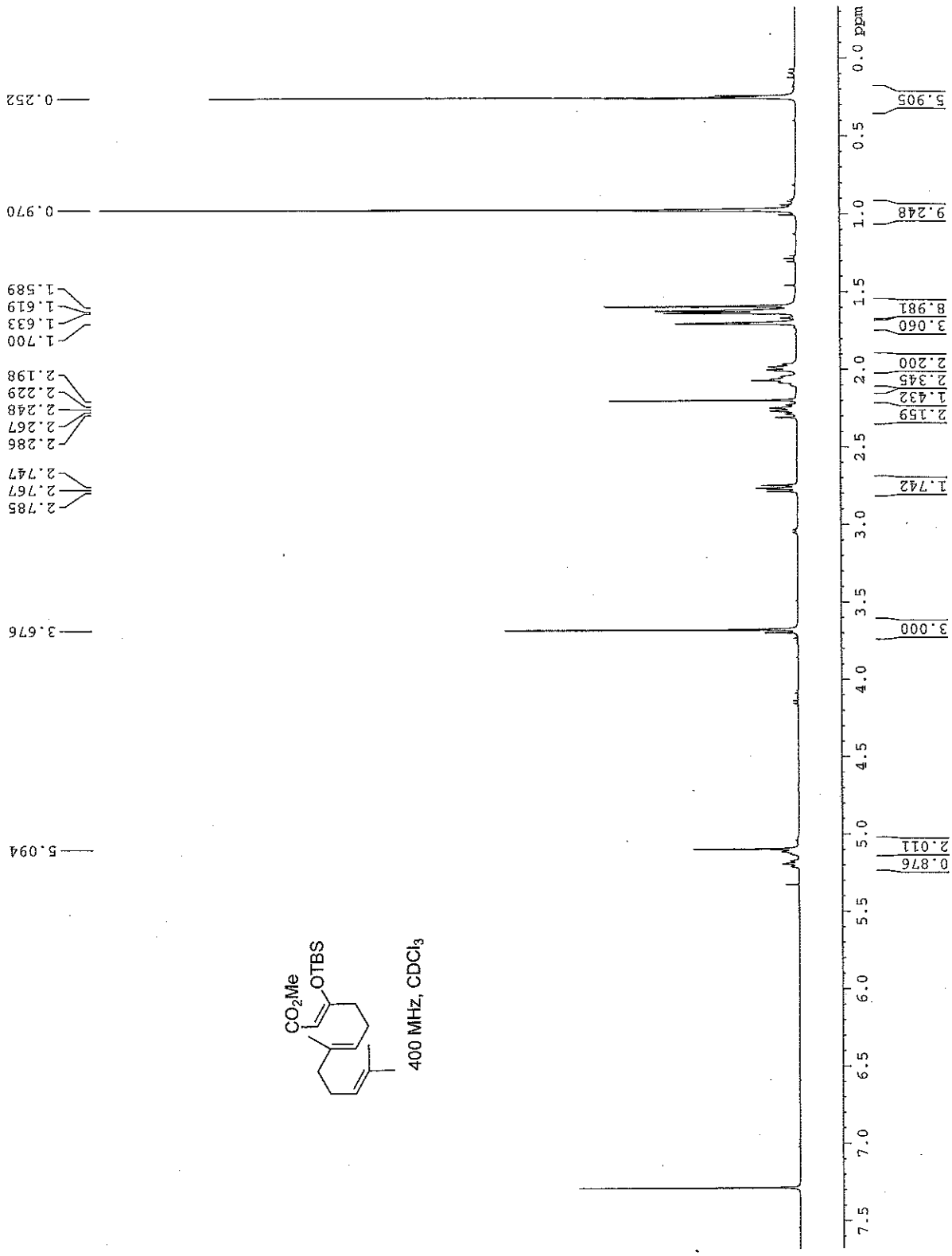

72
400 MHz, CDCl3
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
1.000
1.014
3.260
3.343
3.454
5.088
1.037
1.066
1.334
5.483
5.489
5.508
5.514
5.532
5.537
5.545
5.550
5.557
5.562
5.570
5.575

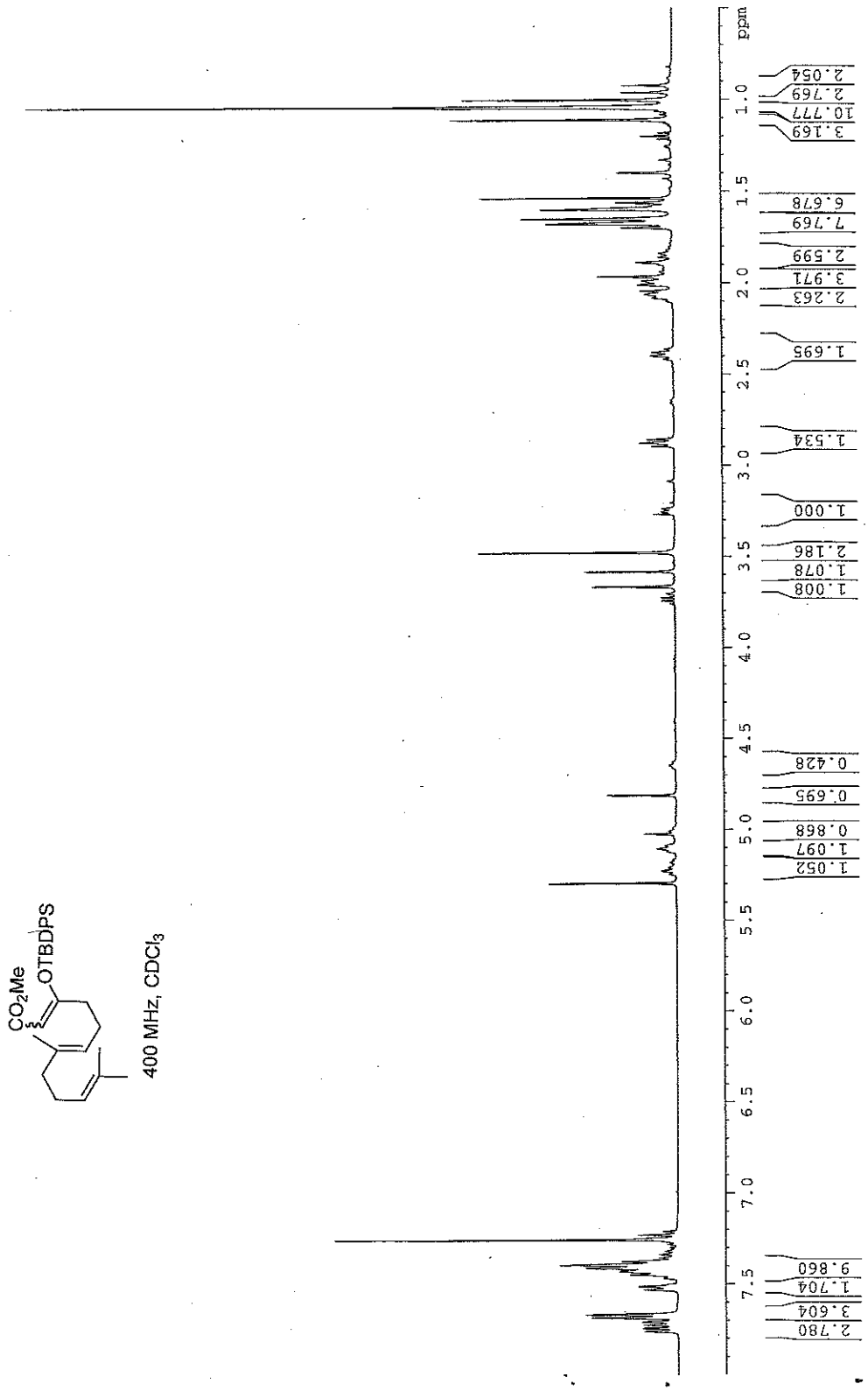

72
100 MHz, CDCl3
176.179
138.221
121.876
85.038
52.344
38.596
35.377
31.779
28.840
20.740
20.643
ppm

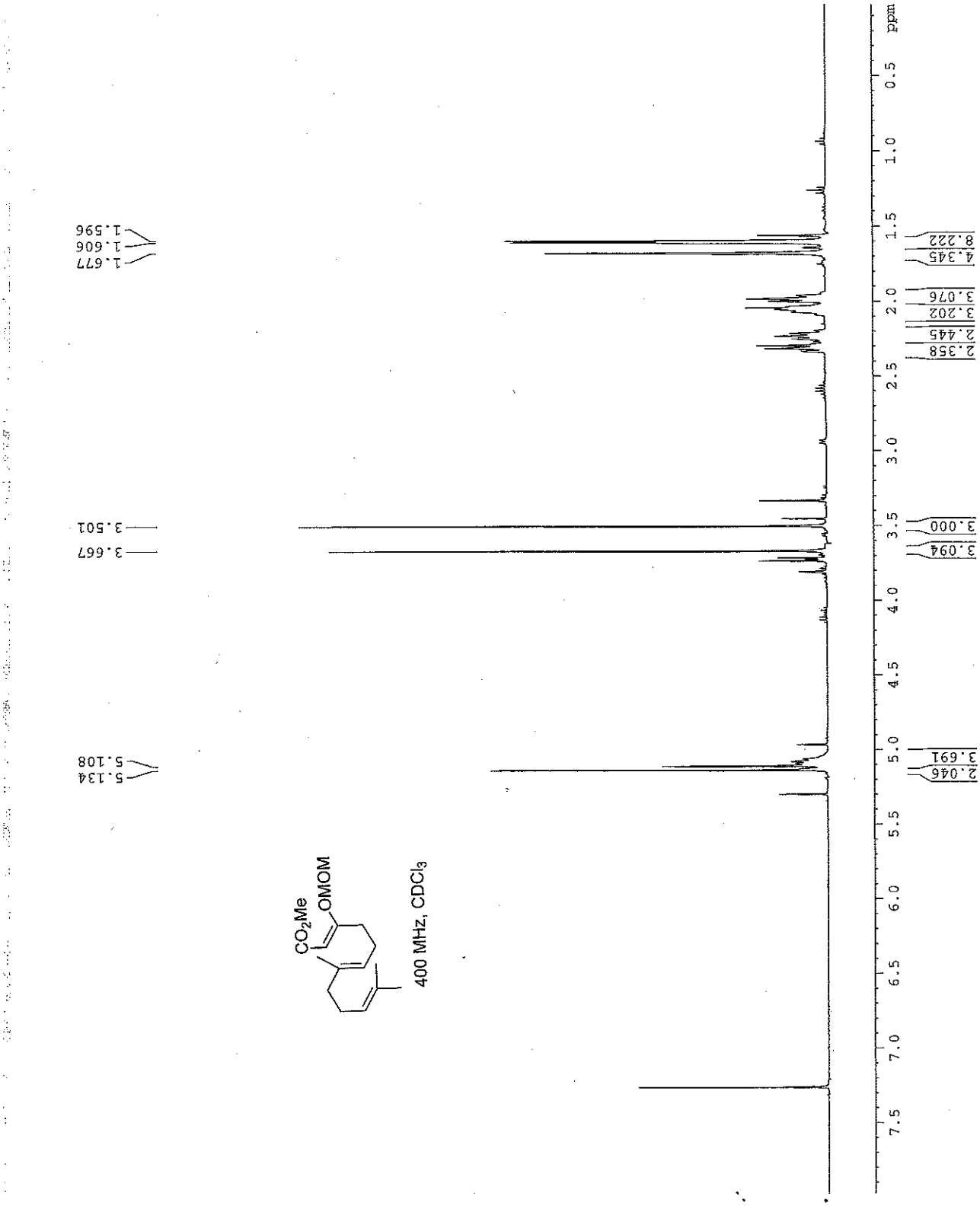

CO2Me
O
H
75
400 MHz, CDCl3
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.000
2.928
0.963
4.221
1.087
1.246
1.060
1.109
1.246
3.055
3.271
3.107
4.277
4.266
4.245
4.234
3.685
3.209
1.954
1.941
1.922
1.909
1.889
1.875
1.857
1.843
1.672
1.664
1.641
1.633
1.620
1.611
1.603
1.587
1.578
1.569
1.470
1.459
1.437
1.427
1.404
1.393
1.213
1.143
1.067

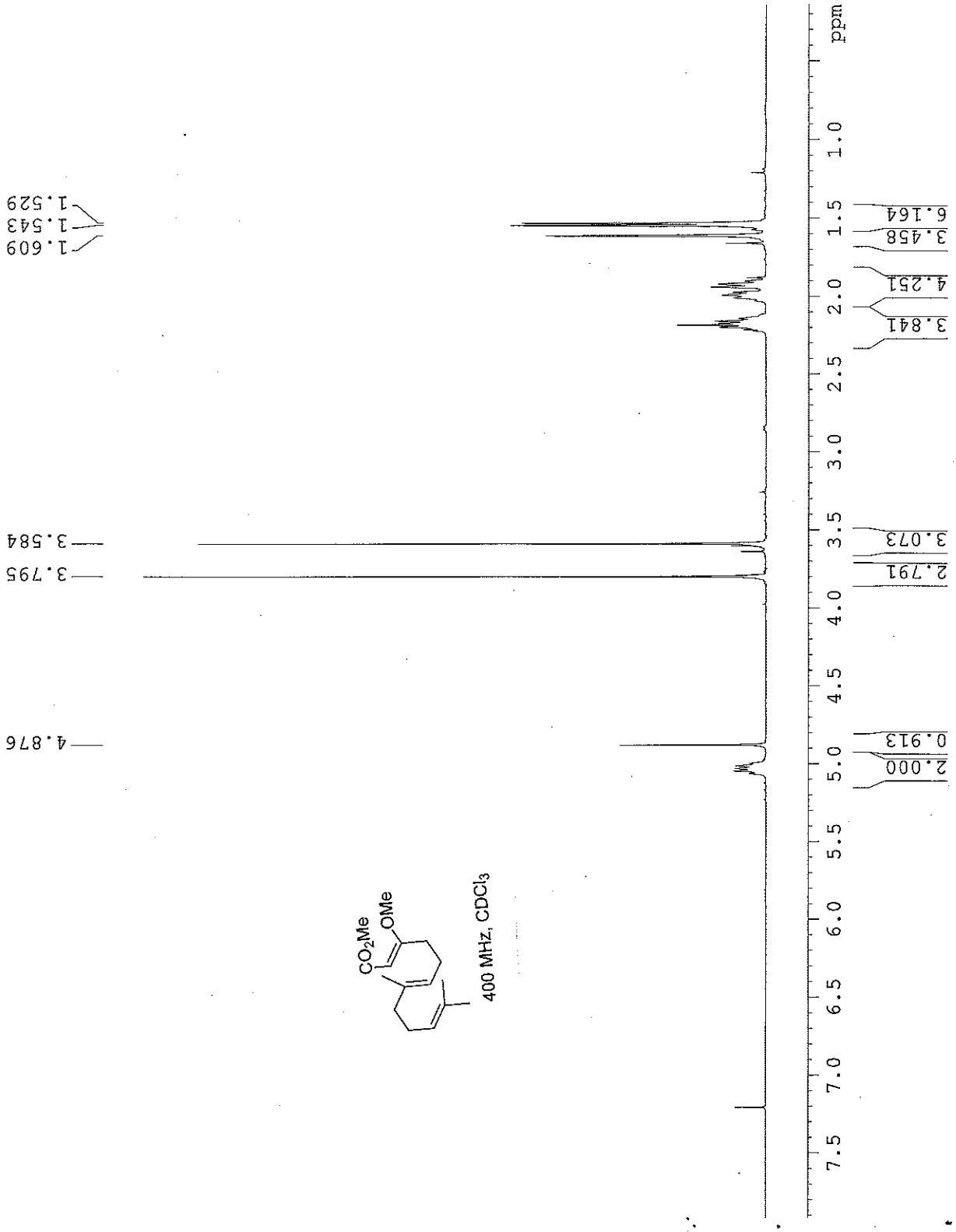

204.418
168.283
69.424
52.085
51.744
51.012
42.097
41.882
41.227
39.565
33.630
33.586
25.523
21.228
14.853
CO2Me
O
H
75
75 MHz, CDCl3
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

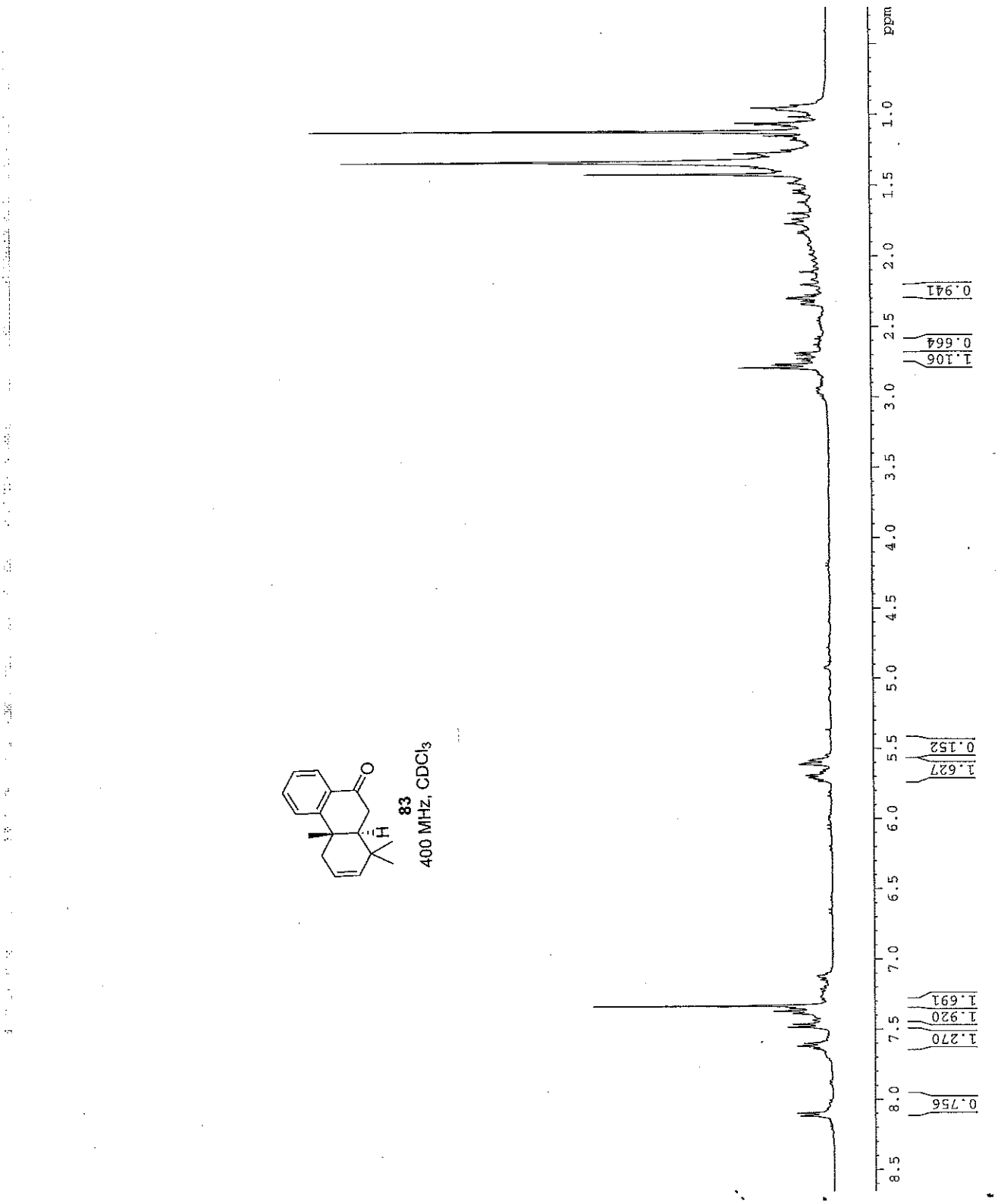

1.077
1.091
1.111
1.116
1.129
1.132
1.611
1.621
1.638
1.671
1.673
1.690
1.693
1.701
1.703
2.787
2.803
2.806
2.825
3.070
3.087
3.673
3.697
5.110
CO2Me
OTIPS
400 MHz, CDCl3
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
41.340
7.050
2.521
9.109
7.726
4.128
3.929
2.473
1.757
1.968
1.306
3.017
2.077
3.848
1.000

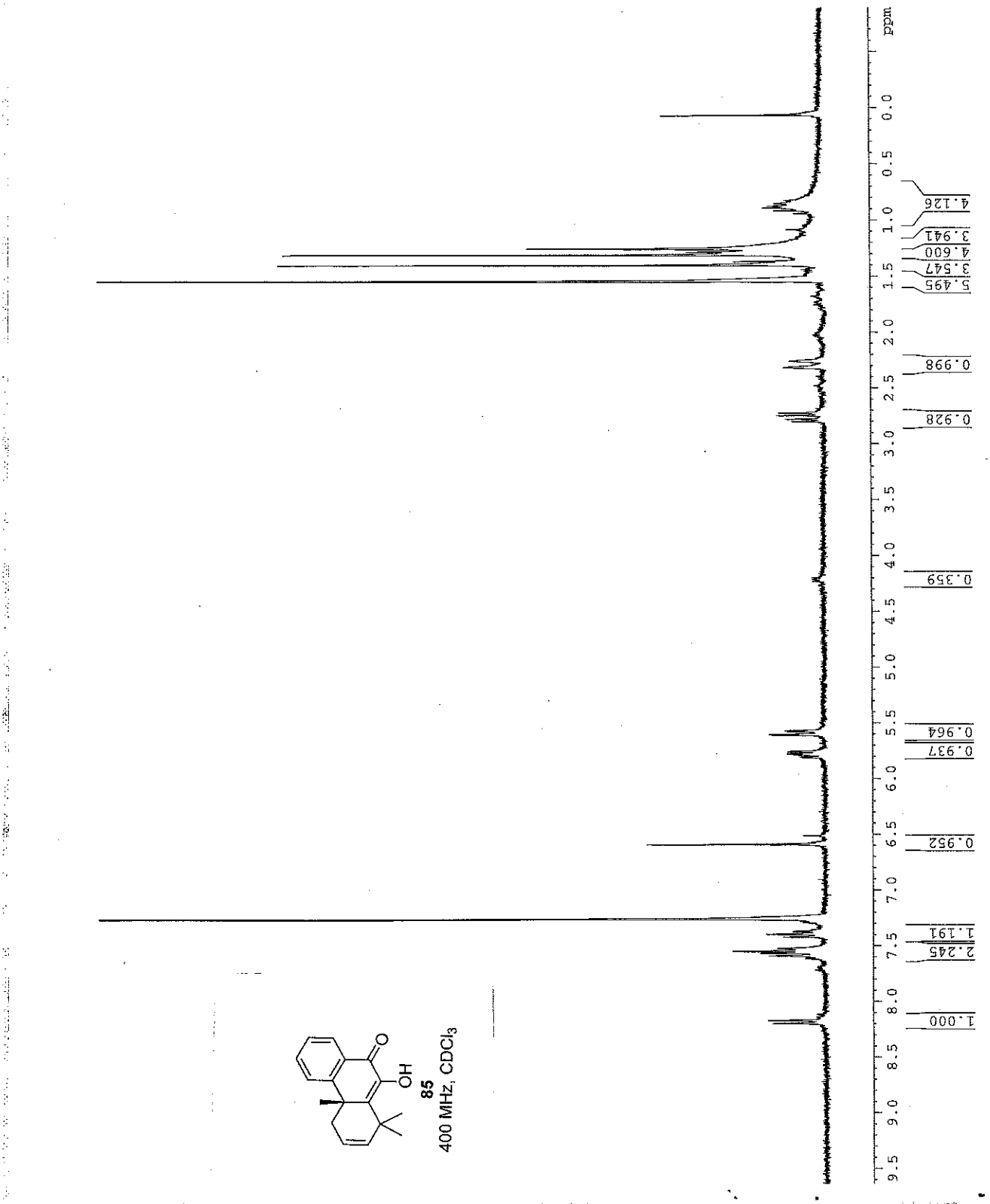

CO2Me
OTBS
400 MHz, CDCl3
0.252
0.970
1.589
1.619
1.633
1.700
2.198
2.229
2.248
2.267
2.286
2.747
2.767
2.785
3.676
5.094
5.905
9.248
8.981
3.060
2.200
2.345
1.432
2.159
1.742
3.000
0.876
2.011
0.0 ppm

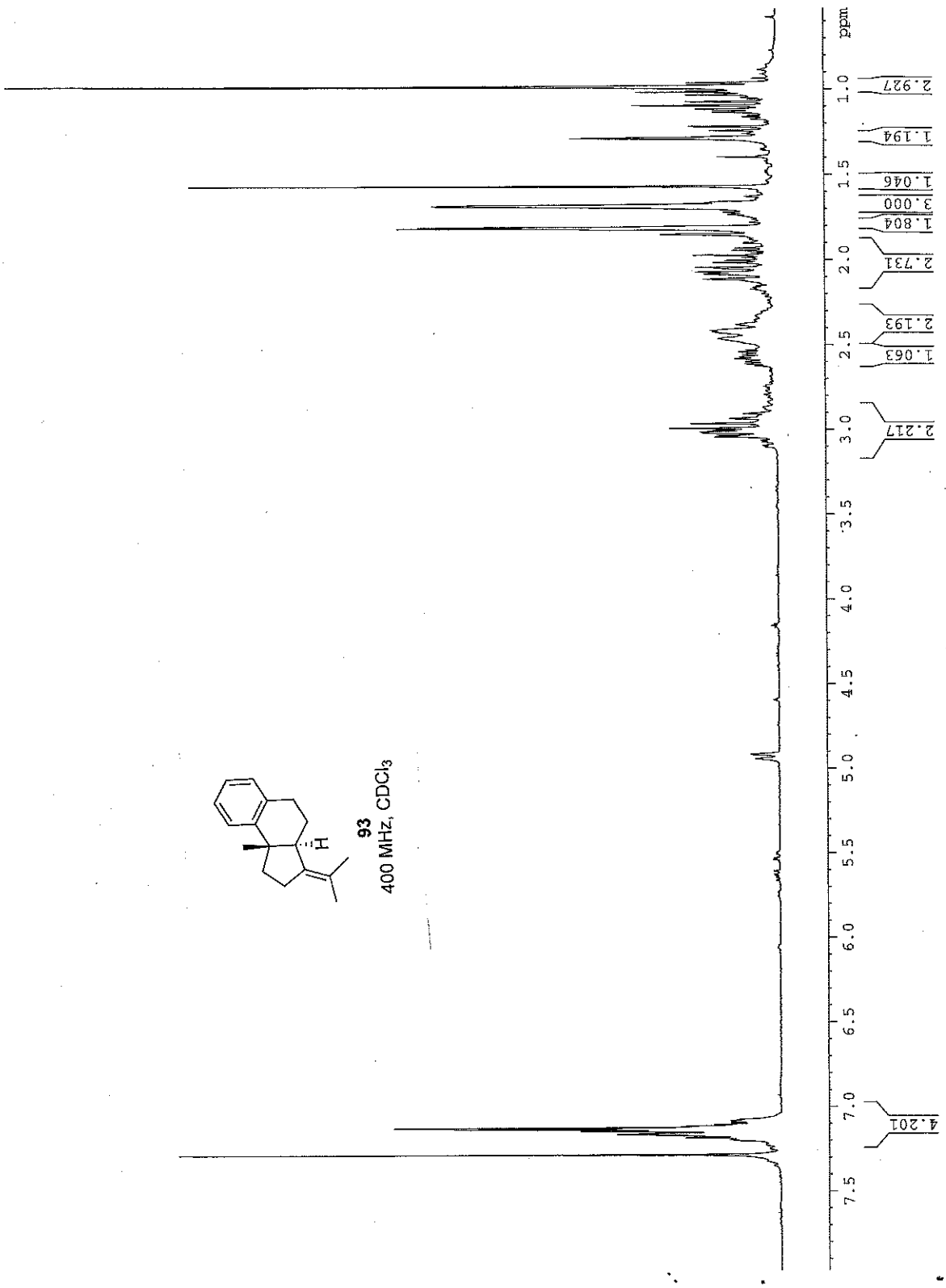

CO2Me
OTBDPS
400 MHz, CDCl3
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
2.780
3.604
1.704
9.860
0.428
0.695
0.868
1.097
1.052
1.008
1.078
2.186
1.000
1.534
1.695
2.263
3.971
2.599
7.769
6.678
3.169
10.777
2.769
2.054

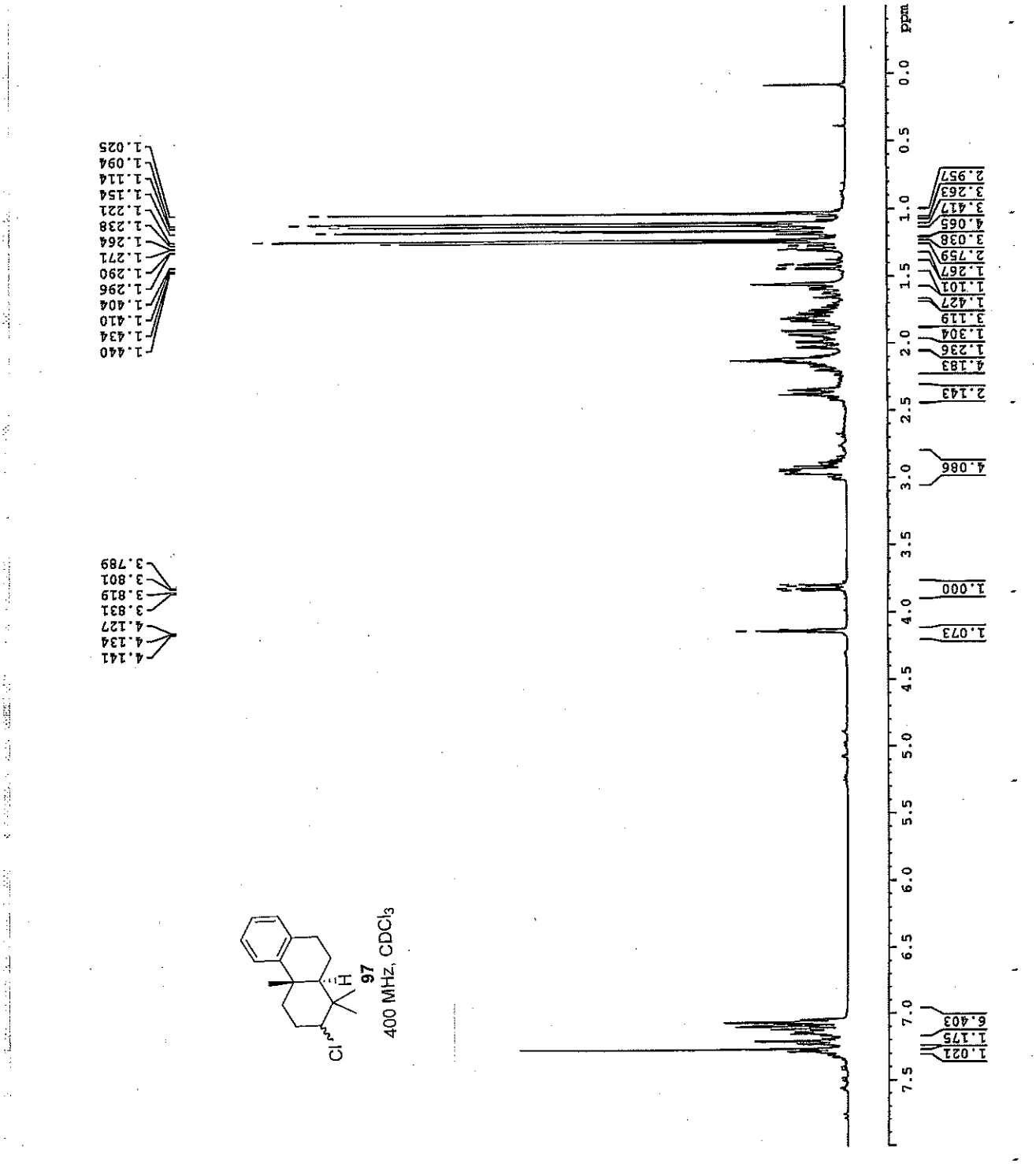

400 MHz, CDCl3
CO2Me
OMOM
5.134
5.108
3.667
3.501
1.677
1.606
1.596
2.046
3.691
3.094
3.000
2.358
2.445
3.202
3.076
4.345
8.222
ppm

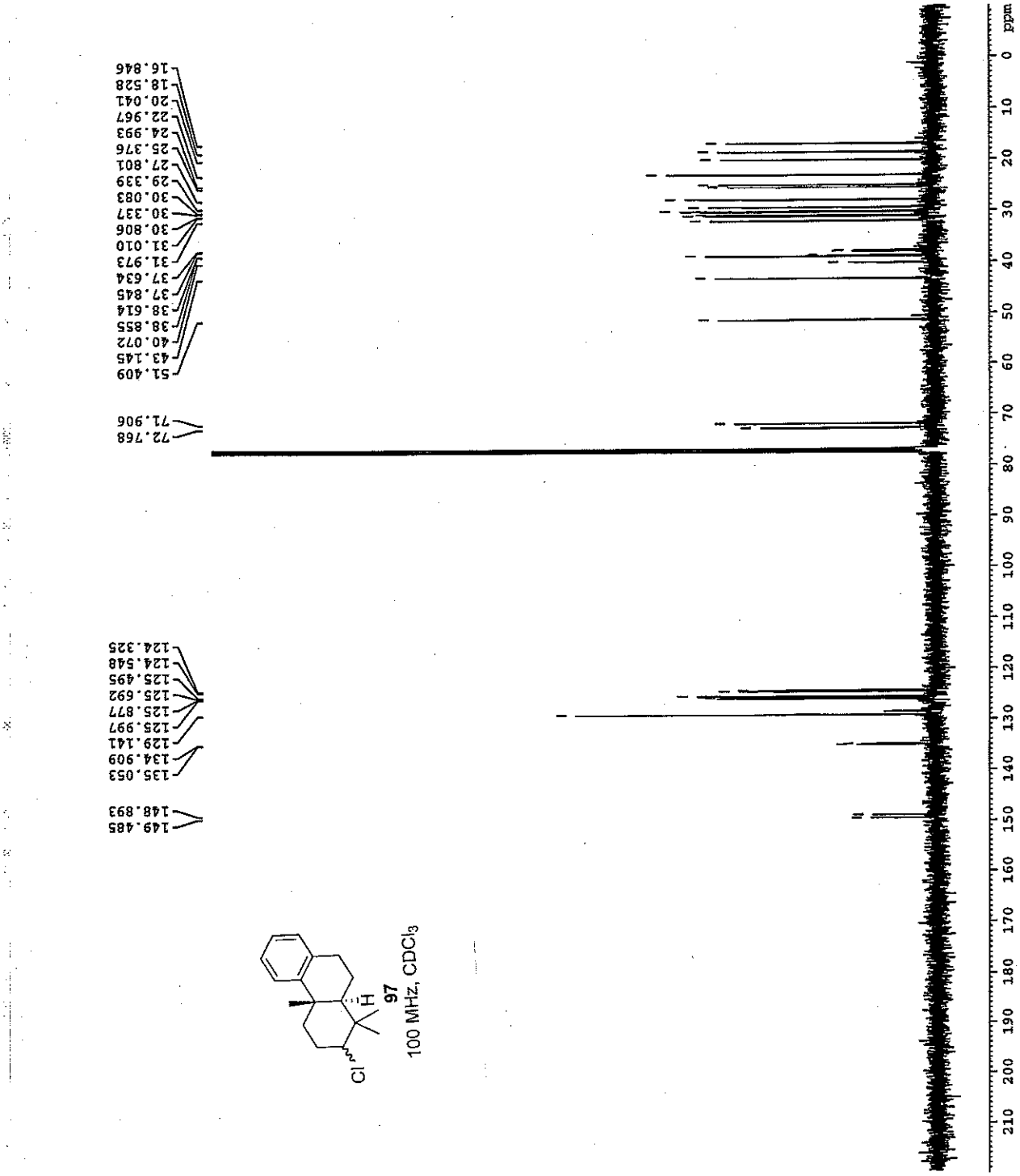

400 MHz, CDCl3
CO2Me
OMe
4.876
3.795
3.584
1.609
1.543
1.529
2.000
0.913
3.073
2.791
6.164
3.458
4.251
3.841
ppm

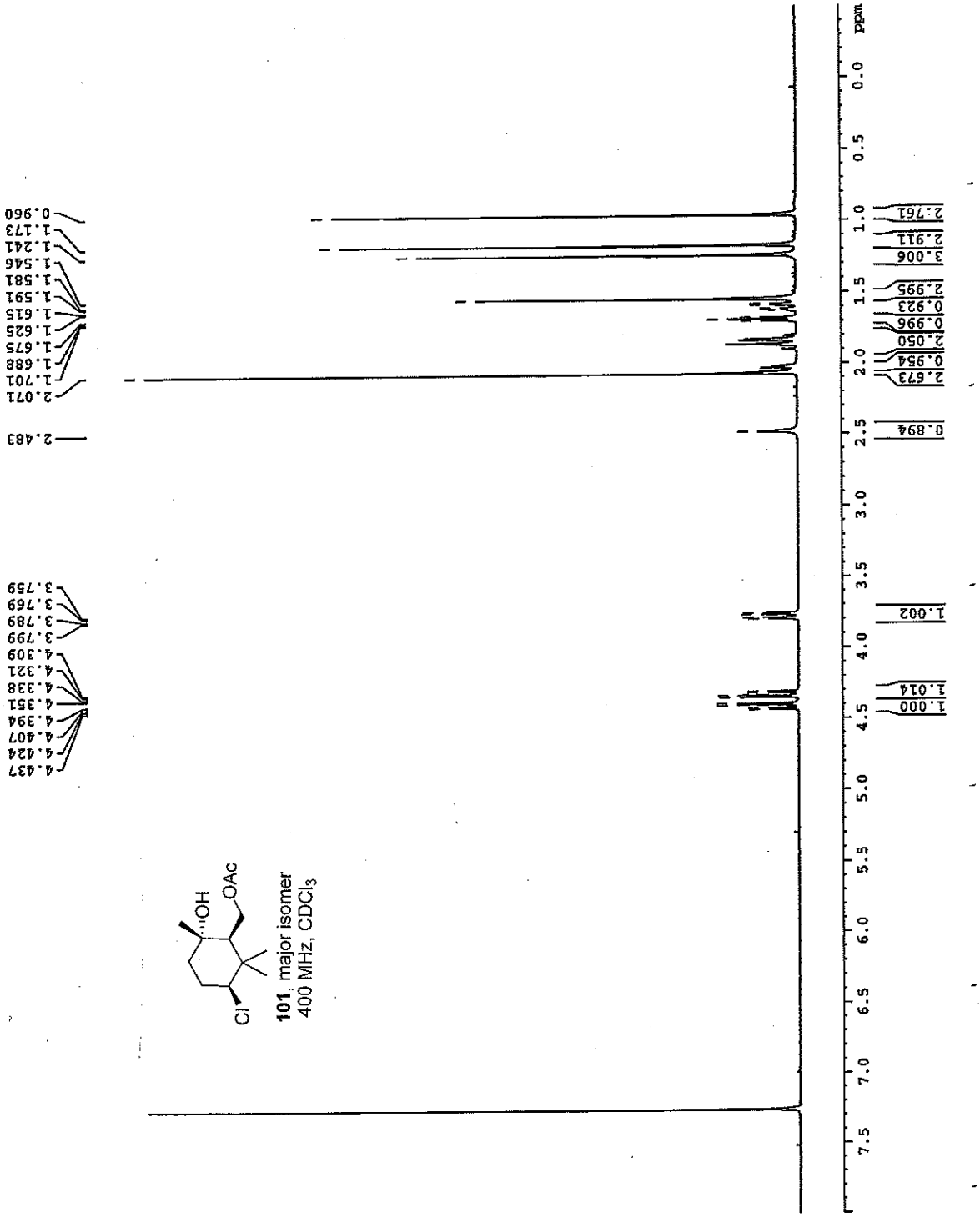

83
400 MHz, CDCl3
ppm
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.756
1.691
1.920
1.270
1.627
0.152
1.106
0.664
0.941

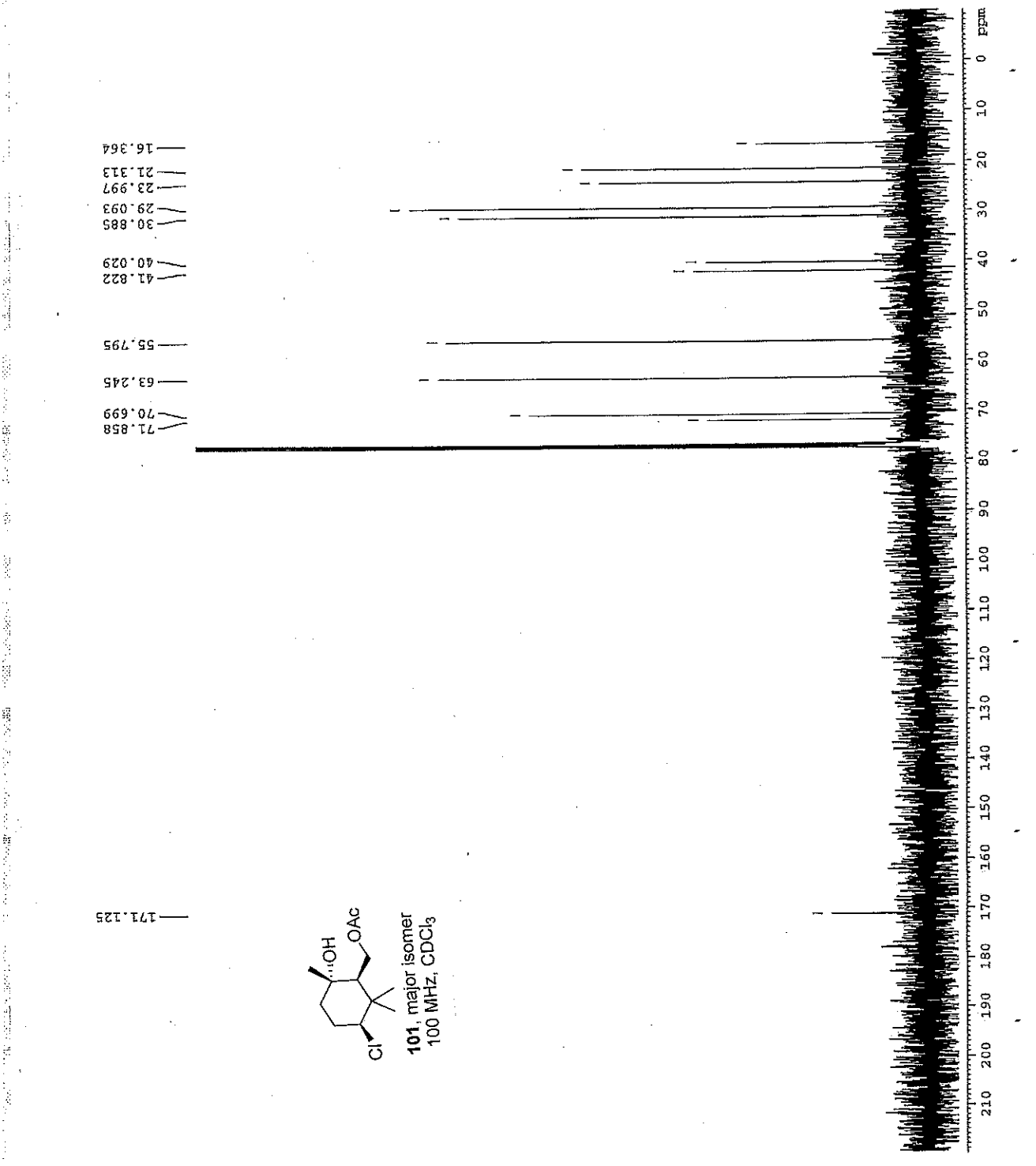

O
OH
85
400 MHz, CDCl3
ppm
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.000
2.245
1.191
0.952
0.937
0.964
0.359
0.928
0.998
5.495
3.547
4.600
3.941
4.126


93
400 MHz, $CDCl_3$
H
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
2.927
1.194
1.046
3.000
1.804
2.731
2.193
1.063
2.217
4.201

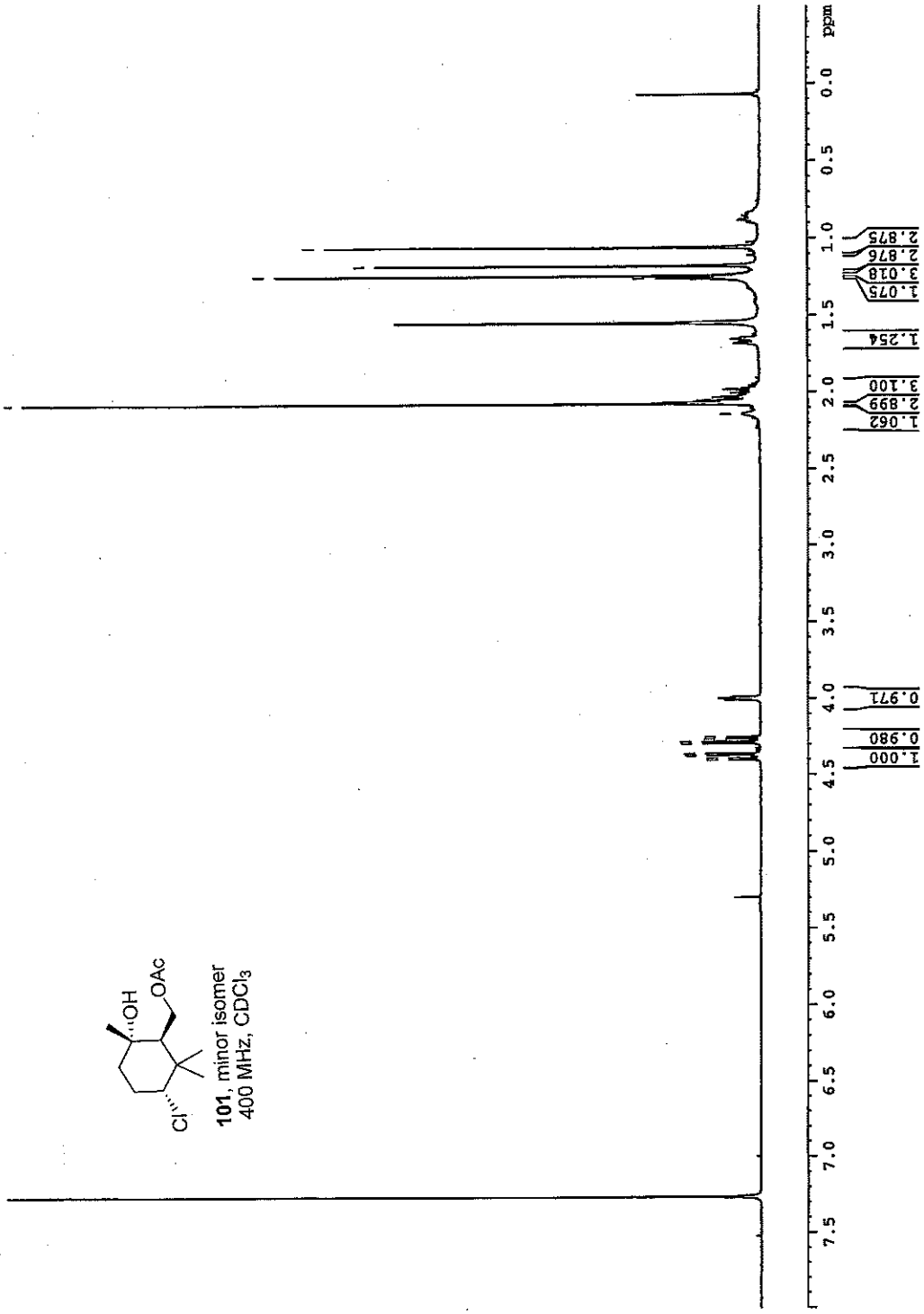

97
400 MHz, CDCl3
Cl
H
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.021
1.175
6.403
1.000
1.073
4.086
2.143
4.183
1.236
1.304
3.119
1.427
1.101
1.267
2.759
3.038
4.065
3.417
3.263
2.957
4.141
4.134
4.127
3.831
3.819
3.801
3.789
1.440
1.434
1.410
1.404
1.296
1.290
1.271
1.264
1.238
1.221
1.154
1.114
1.094
1.025

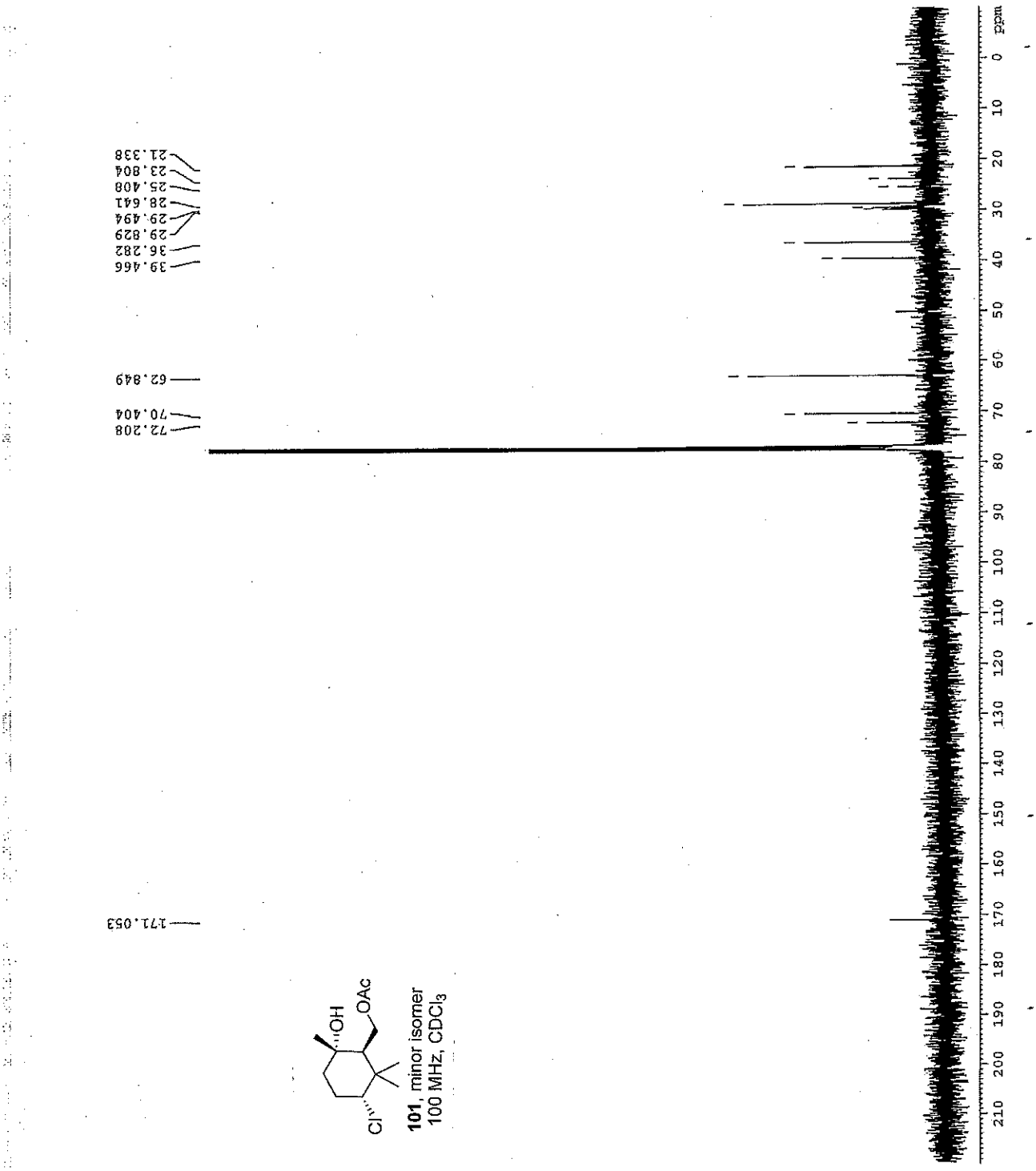

16.846
18.528
20.041
22.967
24.993
25.376
27.801
29.339
30.083
30.337
30.806
31.010
31.973
37.634
37.845
38.614
38.855
40.072
43.145
51.409
72.768
71.906
124.325
124.548
125.495
125.692
125.877
125.997
129.141
134.909
135.053
148.893
149.485
97
100 MHz, CDCl3
Cl
H
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 ppm


OAc
OH
Cl
101, major isomer
400 MHz, CDCl3
ppm

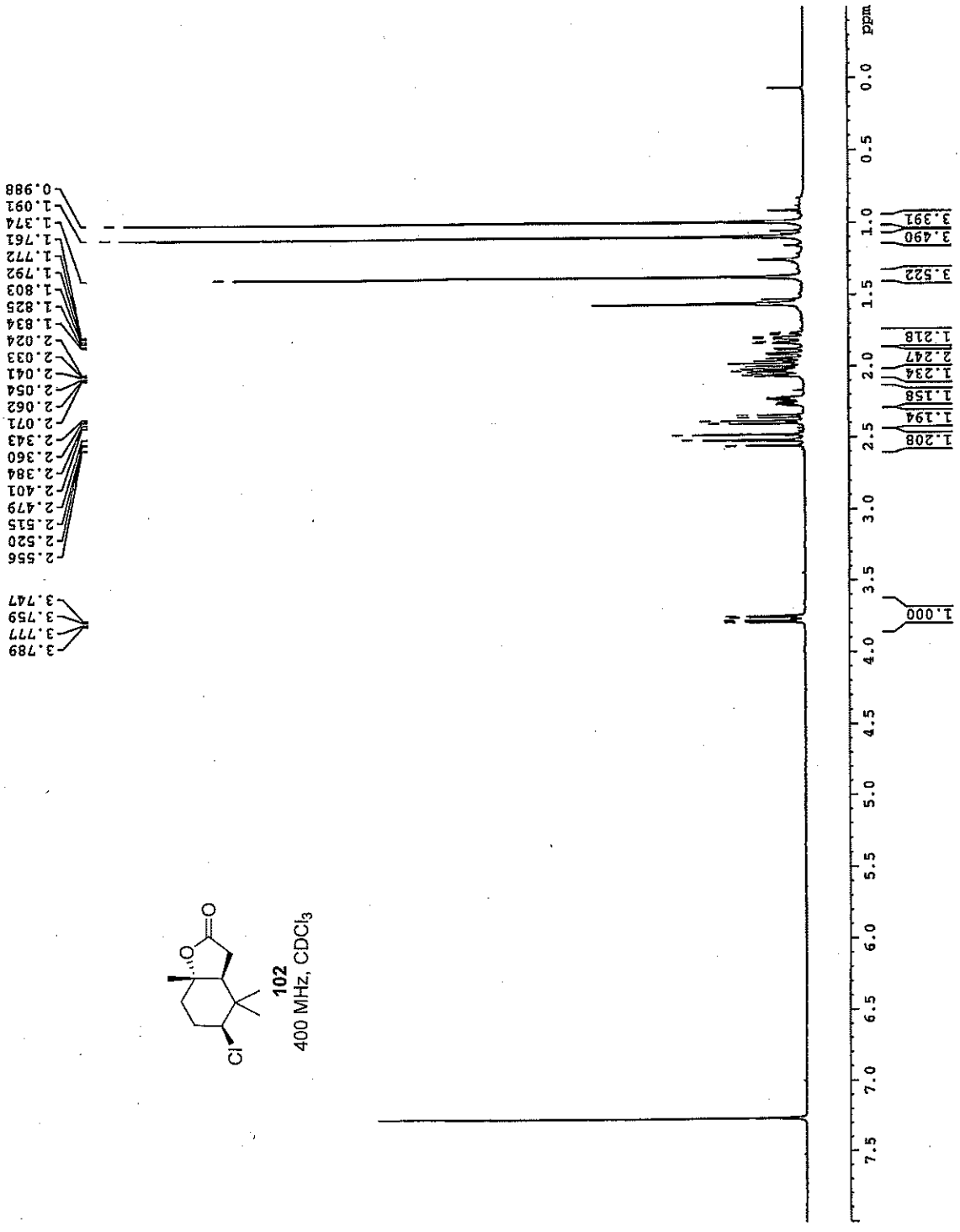


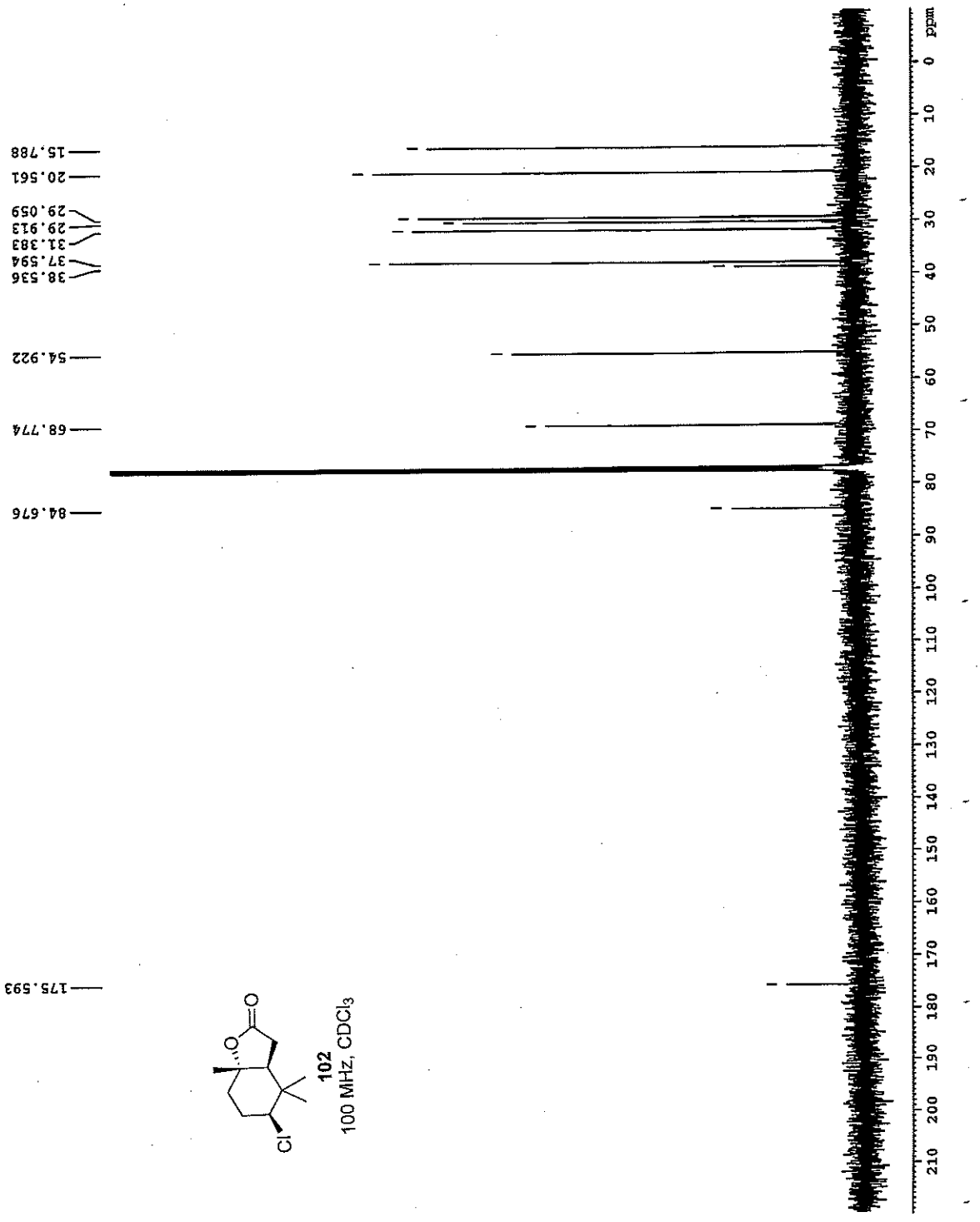
101, major isomer
100 MHz, $CDCl_3$


OAc
OH
Cl
101, minor isomer
400 MHz, CDCl3
4.403
4.390
4.373
4.361
4.293
4.280
4.264
4.251
2.143
2.072
1.256
1.241
1.175
1.056
ppm
0.971
1.000
0.980
1.062
2.899
3.100
1.254
4.075
3.018
2.876
2.875



101, minor isomer
100 MHz, $CDCl_3$


102
400 MHz, CDCl3
Cl
O
O
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
0.988
1.091
1.374
1.761
1.772
1.792
1.803
1.825
1.834
2.024
2.033
2.041
2.054
2.062
2.071
2.343
2.360
2.384
2.401
2.479
2.515
2.520
2.556
3.747
3.759
3.777
3.789
1.000
1.208
1.194
1.158
1.234
2.247
1.218
3.522
3.490
3.391



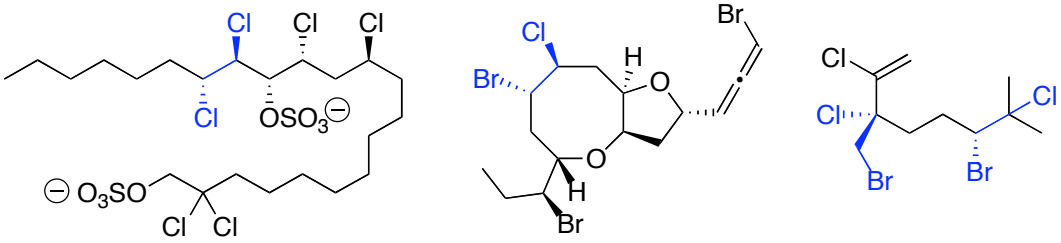
102
100 MHz, $CDCl_3$

CHAPTER 3

Enantioselective Iodohydrin Formation using Simple Alkenes

3.1 Introduction

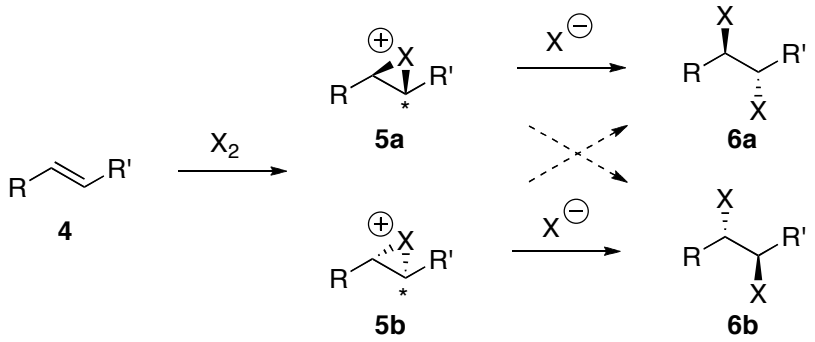
Over 100 years ago, the halogenation of alkenes was first discovered, and this reaction has remained a well-studied topic in the entering century.[1] While consisting of a motif commonly found in nature, the chemical synthesis of enantiopure dihalides has proven quite challenging.[2] Examining just a few naturally occurring 1,2-dihalides, a variety of combinations exist including the 1,2-dichloride found in the chlorosulfolipid family (such as **1**)[3] as well as the 1,2-bromochlorides present in *Laurencia* natural isolates (**2**)[4] and halomon (**3**)[5]. While multiple syntheses of each of these natural products exist, none are generated directly via enantiospecific halogenation of the corresponding alkene. Indeed, no real solution for any asymmetric halogenation has been provided prior to a few selected examples from just the past few years.



1: (-)-danicalipin A **2** **3**: halomon

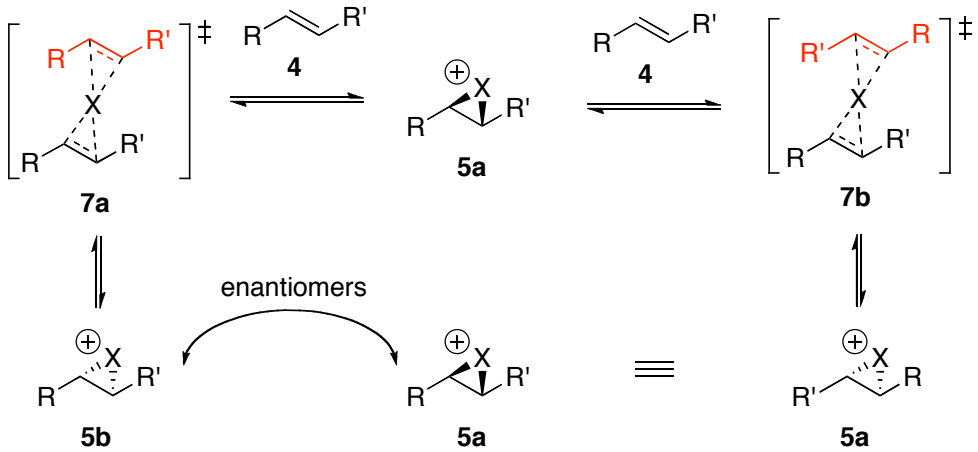
Figure 1: Natural Products Contaning Dihalides

To approach the challenge of enantioselective halogenation, there are two major concerns that must be addressed. The first, and easier problem, is that the opening of the generated halonium intermediate must be fully regioselective (Scheme 1). Opening of the chiral halonium **5a** at the starred carbon yields **6a**, though a regioisomeric opening of **5a** would yield **6b**, the enantiomer of **6a**. In order for an enantiopure product to be produced, opening at a single side of the cyclic halonium has to occur, or both **6a** and **6b** would be generated leading to an overall loss of asymmetry.



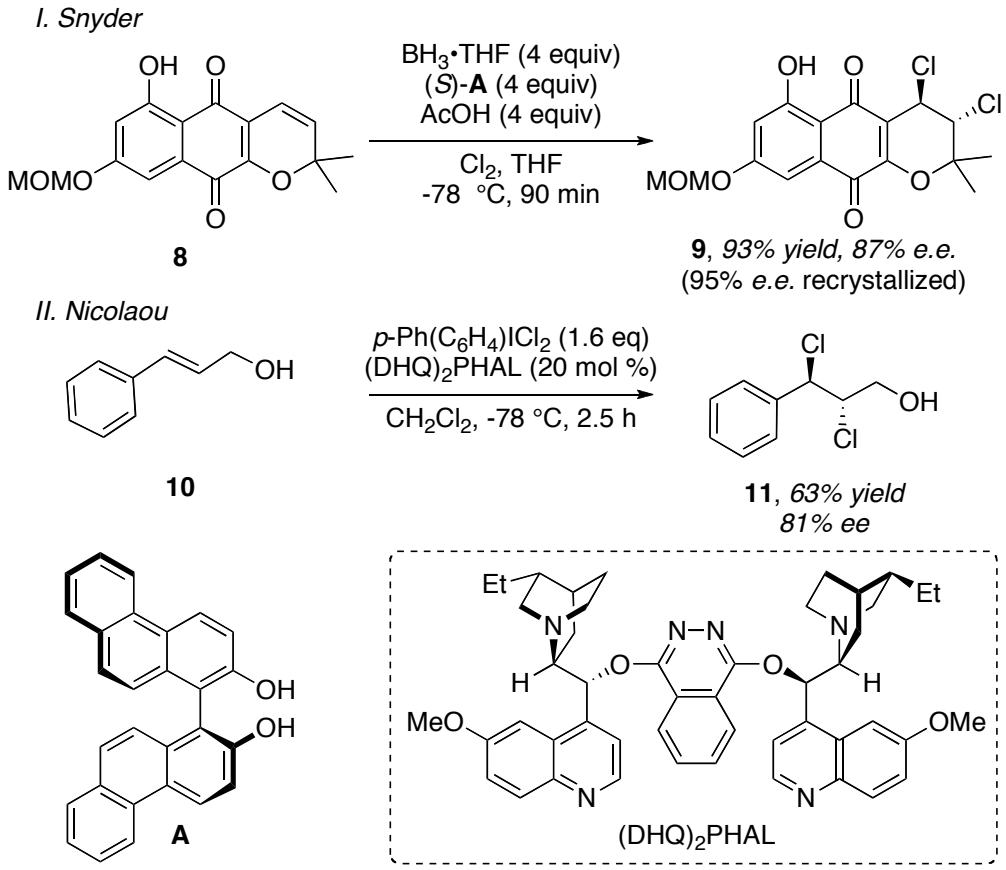
Scheme 1: General Mechanism of Dihalogenation

The second, and more challenging problem, rests in the generation of the chiral halonium intermediate. Not only does a 3-membered halonium have to form on a single face of an alkene (i.e. **5a** or **5b**), it is well known that halonium transfer to unreacted alkenes can erode enantioselectivity.[6] As shown in Scheme 2, transfer of a chiral halonium **5a** to alkene **4** would lead to both enantiomers of the halonium, **5a** and **5b**, dependent on the approach of the nucleophilic alkene, overall eroding any enantioselectivity of the initial halonium. It is also important to note that the rates at which these different haloniums transfer follows the stability of each halonium, with the most stable ion, iodonium, transferring at the fastest rate[6c,d] and chloronium transfer being the slowest.[6g]



Scheme 2: Mechanism of Halonium Transfer to an Unreacted Alkene

There have been a few examples in the literature that are able to overcome these obstacles and generate enantiopure dihalides, two of which have shown some substrate generality. The seminal example which produced synthetically useful enantiomeric excess was completed in our group as a key step in the total synthesis of napyradiomycin A1.[7] Intermediate **8** was dichlorinated in 93% yield using Cl_2 and ligand **A** to block a single face of the alkene. While initially 87% ee was obtained, recrystallization allowed for an increase in this asymmetry.

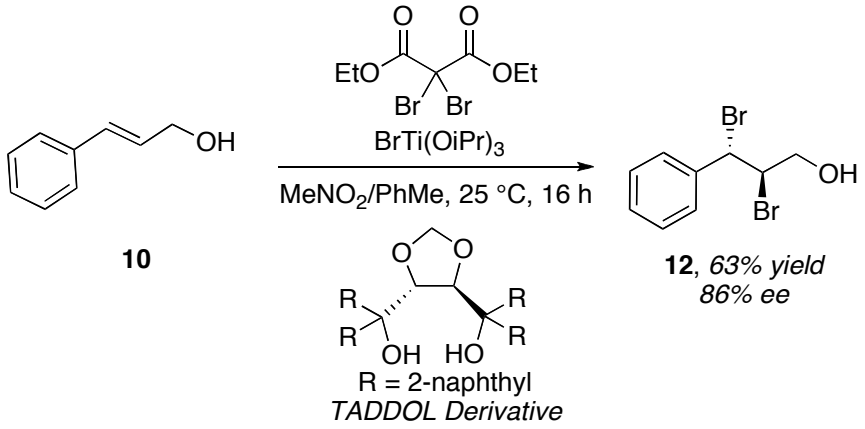


Scheme 3: Examples of Enantioselective Dichlorination

Next, Nicolaou and co-workers were able to expand dichlorination to a group of similar substrates in modest to good enantioselectivity (Scheme 3).[8] Allylic alcohols, a common precursor in syntheses of the chlorosulfolipids, were chlorinated through the use of a $PhICl_2$ derivative in combination with the chiral catalyst $(DHQ)_2PHAL$, a dimeric

cinchona alkaloid derivative. This catalyst/substrate combination was key as the hydrogen-bonding between the alcohol of the substrate and phthalazine moiety of the catalyst likely is the reason for the high enantioselectivity. In support of this observation, both triethylsilane protection of **10** or the use of naphthalene core derivative of $(DHQ)_2PHAL$ led to low asymmetric induction.

Beyond dichlorination, dibromides have also been synthesized in high enantioselectivites by two groups.[9] First, the Henry group expanded upon their chiral chlorohydrin synthesis[9a-d] to include generation of 1,2-dibromides under modified Wacker conditions.[9e] A more recent example comes from Burns and co-workers in an effort to synthesize enantiopure dibromides (Scheme 4).[9f] Here, enantioselective dibromination of cinnamyl alcohol (**10**) and its derivatives was achieved with the use of diethyldibromomalonate as the bromonium source, $BrTi(OiPr)_3$ as the Lewis base, and a TADDOL derivative to induce asymmetry. The authors propose that the titanium-derived Lewis base allowed for chelation to each component of the reaction mixture, enabling overall delivery of the bromonium electrophile and bromide nucleophile via an inner-sphere-type mechanism. Under these conditions, a larger array of substitutions (both of electron rich and poor) as well as differently substituted arenes are tolerated compared to the previous precedent.



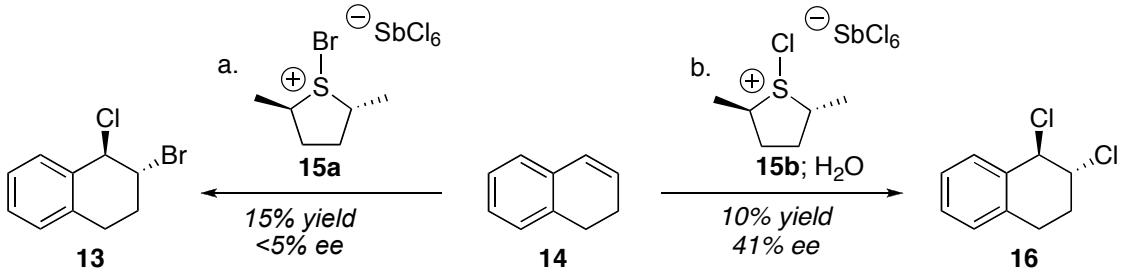
Scheme 4: Burns and Coworkers' Enantioselective Dibromination

Given that there are just these few methods available for asymmetric dihalogenation, clearly there is room for additional approaches; due to the overall difficulty of both asymmetric halonium generation and regioselective opening, any new results would help chemists understand how to better solve these difficult problems since the field as a whole is underdeveloped. At the onset of the discovery of the halonium reagents, BDSB, IDSI, and CDSC, it was quickly surmised that the diethyl sulfide backbone could be replaced with alternative Lewis bases, including chiral sulfide derivatives. Thus, we hoped to develop an additional method to generate this valuable 1,2-dihalogen motif enantioselectively with the use of chiral XDSX variants.

3.2 Initial Results with Chiral Halonium Reagents

Having achieved little success in enantioselective polyene cyclization in Chapter 2, we turned to an alternative substrate class with a smaller array of challenges. In particular using a substrate with only a single alkene, such as 1,2-dihydronaphthalene (**14**), would reduce halonium transfer to unreacted olefins relative to the two alkenes found in homogeranyl benzene. Additionally, the chosen substrate should not have regioisomeric issues, as halide ring opening should be favored at the benzylic position.

At the onset of exploring this variant of asymmetric halogenation, we desired that the XDSX halonium reagents could access a variety of 1,2-dihalide combinations. Initial results using chiral BDSB and CDSC were obtained by my colleague Dr. Daniel Treitler (Scheme 5).[10] He discovered that treatment of **14** with chiral BDSB (**15a**) produced bromochloride **13**, though only in trace enantioselectivity and yield; the $SbCl_6^-$ counterion is the source of the chloride used here to quench the formed bromonium intermediate. Using chiral CDSC (**15b**), dichloride **16** was observed with 41% ee, though a poor yield was obtained as multiple other by-products were produced. Optimization of both of these reactions was attempted, though further improvement in yields and enantioselectivities proved unattainable. We predicted that the chloronium variant (**15b**) should produce higher enantioselectivities, as chloronium transfer to unreacted alkenes is a slower process than its bromonium counterpart.[6g]

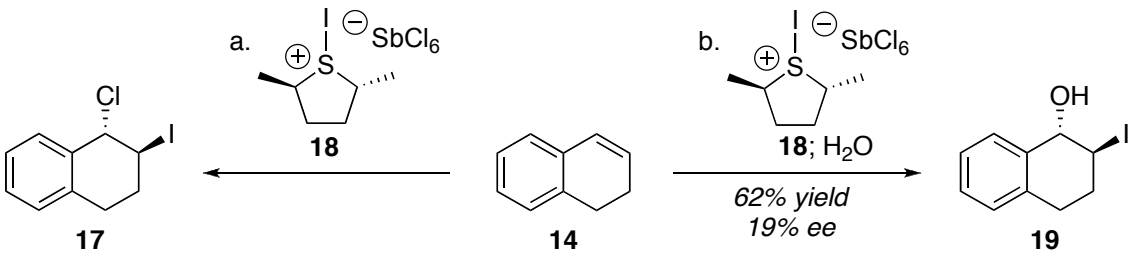


Reagents and Conditions: a. **15a** (1 equiv), $MeNO_2/CH_2Cl_2$, -30°C, 10 min, 15% yield, <5% ee; b. **15b** (1 equiv), $EtNO_2$, -78 to 0°C, 2 h, 10% yield, 41% ee.

Scheme 5: Chiral BDSB and CDSC Results with 1,2-Dihydronaphthalene

With these initial results using the chiral bromonium and chloronium reagents producing poor yields and enantioselectivities, we next turned to our attention to chiral iodonium derivatives. Following conditions similar to those used in successful polyene cyclizations, 1,2-dihydronaphthalene (**14**) was treated with chiral IDSI (**18**) in $MeNO_2$ at -30°C for 10 min, yielding the chloroiodide **17** (Scheme 6). Attempted purification of this compound led to decomposition, possibly due to the loss of chloride and subsequent

iodonium reformation, a reactive intermediate that we believe readily decomposes. Synthesis and isolation of chloroidide **17** was completed previously with the use of solid supported ICl reagents, therefore no chromatography was needed to for purification.[11] Interestingly, when the reaction mixture was stirred for a longer period of time with water present, iodohydrin **19** was obtained instead in an isolated 62% yield. Mechanistically, the initially installed chloride must be replaced with retention in the aqueous quench to give the *trans*-iodohydrin, presumably via iodonium reformation. To our delight, iodohydrin **19** was generated in this reaction in 19% ee. The absolute configuration of the iodohydrin was derived based on Mosher's ester analysis as discussed in the Experimental Section (Section 3.7).[12] Given the marked yield generated, we were hopeful this initial enantioselectivity could be improved by varying a number of conditions in the reaction mixture. These efforts are discussed further in Sections 3.3 and 3.4.



Reagents and Conditions: a. **18** (1 equiv), $MeNO_2/CH_2Cl_2$, -30°C, 10 min; b. **18** (1 equiv), $MeNO_2/CH_2Cl_2$, -30°C, 10 min; H_2O, 25°C, 10 min, 62%.

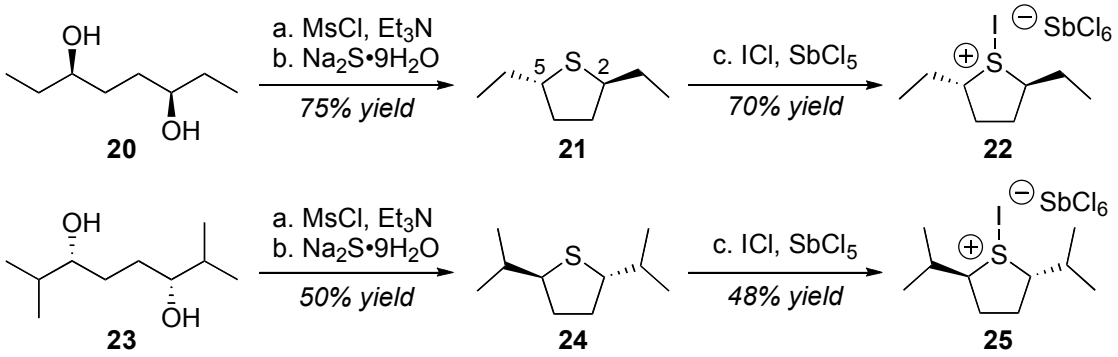
Scheme 6: Initial Results with Chiral IDSI Reagent **18**

3.3 Synthesis of Chiral Variants of IDSI

Outside of the standard variations in solvent, temperature, and time, another major factor in obtaining optimal results was altering the chiral source. Prior to discussing the reaction conditions and given the success with sulfides, we elected to prepare a number

of chiral thiolanes for our optimization studies. Of note is the design of these compounds, as the general XDSX reagent class is incompatible with electron-rich aromatic rings, carbonyls, alkenes, and alcohols.

The first variations we attempted were substituents at the C2 and C5 of the potential core thiolane ring with different alkyl groups. Preparation of the ethyl or *iso*-propyl derivatives was completed using the appropriate chiral alcohol as shown in Scheme 7. From the diol precursors, dimesylation and Na_2S displacement yielded chiral thiolanes **21** and **24**.[13] Due to the larger groups at the C2 and C5 positions, we hypothesized that the thiolane may have racemized upon cyclization. Indeed, Connon and co-workers synthesized the *iso*-propyl derivative (**24**) following the same reaction conditions and measured only 18% ee of the product **24**. Nevertheless, pushing forward, the isolable, solid chiral iodonium reagents were prepared by treatment with ICl and $SbCl_5$.

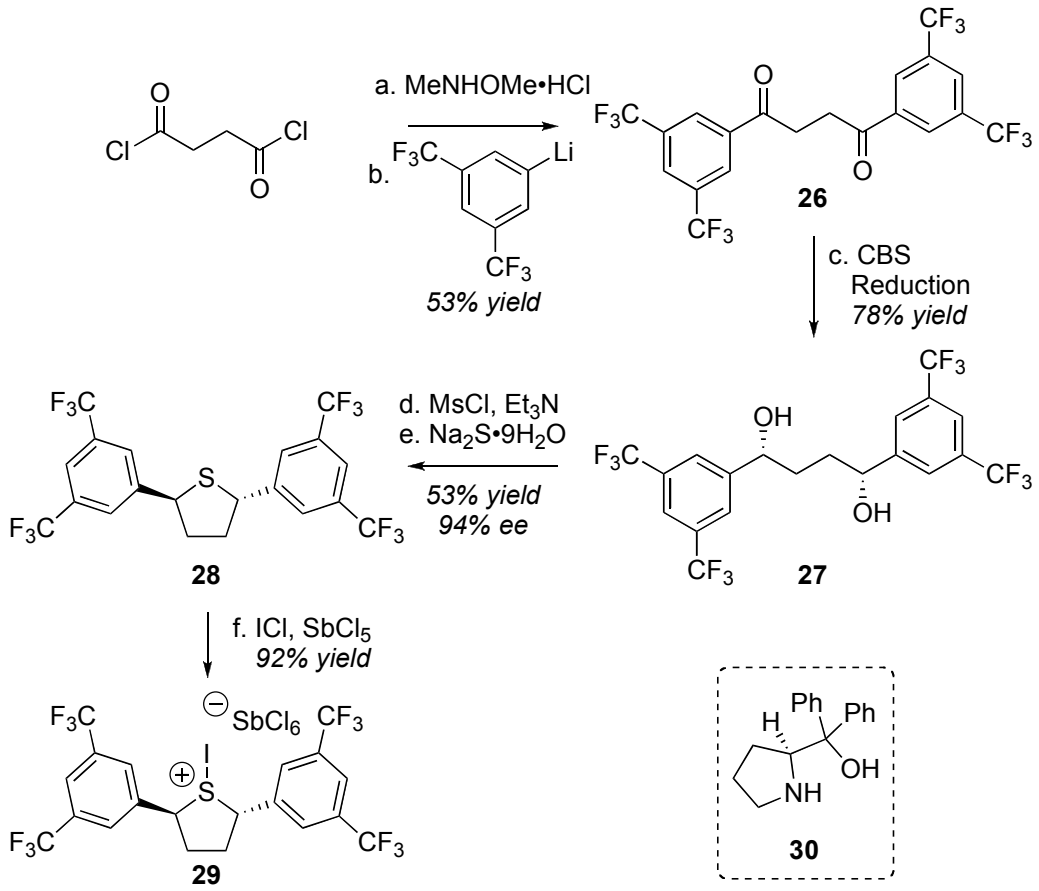


Reagents and Conditions: a. MsCl (4 equiv), Et_3N (6 equiv), CH_2Cl_2, -20 to 0°C, 1 h; c. $Na_2S•9H_2O$ (2 equiv), EtOH, 25°C; c. ICl (1 equiv), $SbCl_5$ (1.1 equiv), DCE.

Scheme 7: Synthesis of Ethyl and *iso*-Propyl Chiral Thiolane Iodonium Reagents

To increase the overall steric bulk and allow π-stacking between the substrate and the halonium source, a diaryl thiolane was also synthesized as shown in Scheme 8. The aryl ring chosen was 3,5-bis(trifluoromethyl)benzene, as its withdrawing groups were expected to deactivate the aromatic ring to a degree that the synthesized reagent would

not iodinate itself. This synthesis began with double Weinreb amide formation[14] and arylation[15] of succinyl chloride to produce diketone **26**. A Corey-Bakshi-Shibata (CBS) reduction then allowed for the synthesis of enantiopure **27** in 78% yield.[16] Typically, CBS reductions are performed between -10 and 25 $^{\circ}$C; here the reaction had to be heated to 40°C (due to the insolubility of starting diketone **26** in THF) for productive reaction to occur.[17] Subsequent dimesylation and cyclization with $Na_2S\bullet 9H_2O$ yielded the diaryl thiolane **28** in good yield. Comparison of this asymmetric material (**28**) to its racemic variant through chiral HPLC revealed the desired thiolane was prepared in 94% ee. Pleasingly, final transformation to the solid chiral iodonium reagent proceeded smoothly, generating **29** in a 92% yield.

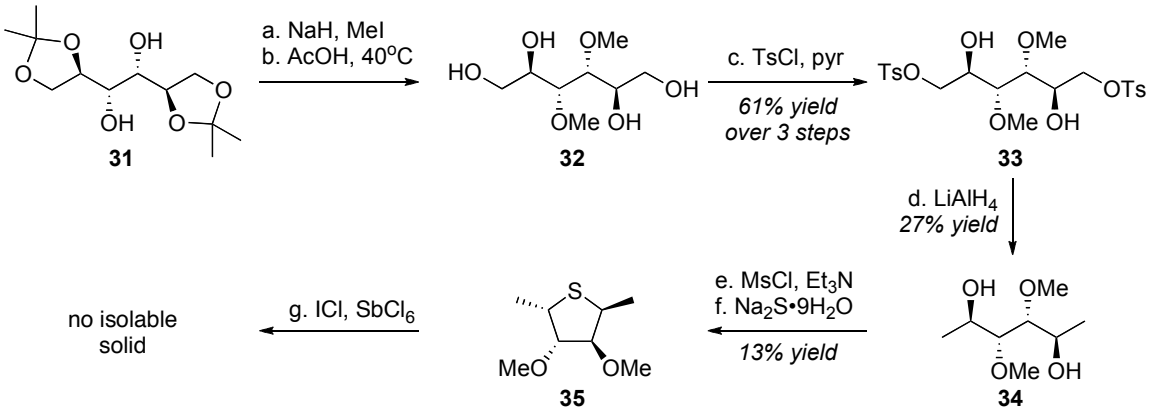


Reagents and Conditions: a. MeNHOMe•HCl (3 equiv), Et_3N (4 equiv), CH_2Cl_2, 25°C, 3 h; b. 1-bromo-3,5-bis(trifluoromethyl)benzene (3 equiv), nBuLi (3 equiv), Et_2O, -78 to 25°C, 4 h, 53%; c. **30** (0.15 equiv), $B(OMe)_3$ (0.2 equiv), BH_3•SMe_2 (2.2 equiv), THF, 40°C, 30 min, 78%; d. MsCl (4 equiv), Et_3N (6 equiv), CH_2Cl_2, -20 to 0°C, 1 h; e. Na_2S•$9H_2O$ (2 equiv), EtOH, 25°C, 30 min, 53%; f. ICl (1 equiv), $SbCl_5$ (1.1 equiv), DCE, -25°C, 30 min, 92%.

Scheme 8: Synthesis of Diaryl Thiolane Iodonium Reagent **29**

Lastly, a reagent with additional substitution on the thiolane backbone was also synthesized, by substrate **35** (Scheme 9). Derived from D-mannitol, all chirality in this reagent was purchased, meaning that only manipulation of each functional group had to be completed to transform commercially-available **31** into the desired dimethoxy dimethyl thiolane (**35**).[18] As shown, initial dimethylation of **31**, ketal cleavage, and bistosylation produced intermediate **33** in 61% yield. Next, treatment with $LiAlH_4$ displaced each of the primary leaving groups. Mechanistically, this process occurs via deprotonation of the alcohol, epoxide formation, and hydride opening at the terminal

position of the generated epoxide. With chiral diol **34** in hand, bismesylation and substitution then produced **35** in 13% overall yield. Throughput here likely reflects the additional steric bulk provided by the methyl ethers since their positing in a ring requires that at least two groups sit pseudo-axially. Attempts to generate an isolable solid iodonium reagent from **35** were unsuccessful and *in situ* generation of the reagent was deployed instead for all subsequent reactions with this chiral sulfide.



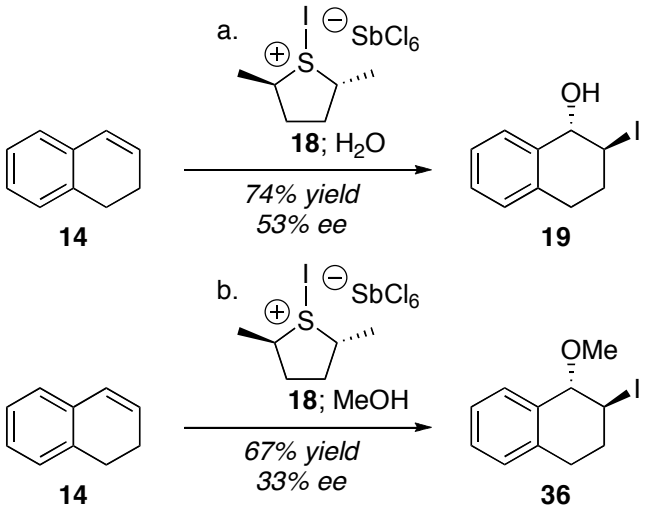
Reagents and Conditions: a. NaH (4 equiv), MeI (3 equiv), THF, 25°C, 1 h b. 70% aq AcOH, 40°C, 2 h; TsCl (2.2 equiv), pyridine, 0°C, 4 h, 61%; c. $LiAlH_4$ (2.5 equiv), THF, 25°C, 12 h, 27%; e. MsCl (4 equiv), Et_3N (6 equiv), CH_2Cl_2, -20 to 0°C, 1 h; f. $Na_2S•9H_2O$ (2 equiv), EtOH, 25°C, 30 min, 13%; g. ICl (1 equiv), $SbCl_5$ (1.1 equiv), DCE, -25°C, 30 min.

Scheme 9: Synthesis of Chiral Thiolane **35**

3.4 Enantioselective Iodohydrin Formation

With the synthesis of these chiral iodonium reagents completed, we next studied their effectiveness at transferring an iodonium electrophile asymmetrically. Initial optimization was performed by my colleague, Dr. Daniel Treitler, and was focused on solvent, temperature, and time, overall leading to the major improvements displayed in Scheme 10. Interestingly, 2.2 equivalents of the chiral reagent proved to be optimal, possibly suggesting the aggregation of at least two monomers in solution. The change of solvent from $MeNO_2$ to an $MeCN/CH_2Cl_2$ mixture allowed the temperature to be

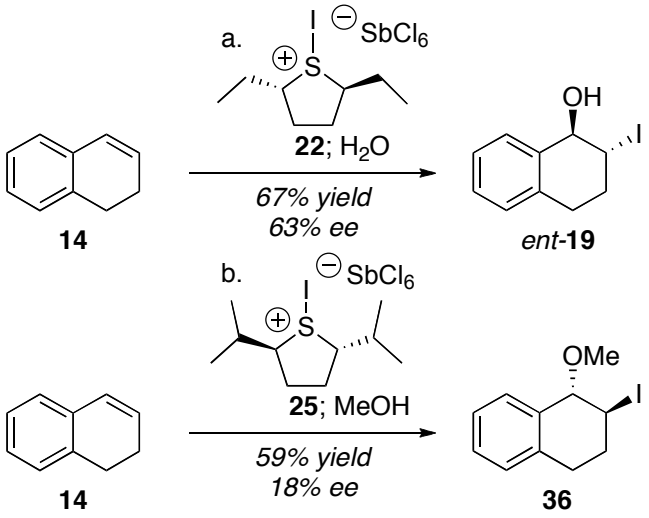
reduced, while achieving greater enantioselectivities, though longer reaction times were needed to drive the process to completion. The solvent choice may have had additional effects on the reaction success that are less obvious.



Reagents and Conditions: a. **18** (2.2 equiv), $MeCN/CH_2Cl_2$, -78 to -20°C, 1 h; H_2O, 25°C, 30 min, 74% yield, 53% ee; b. **18** (2.2 equiv), $MeCN/CH_2Cl_2$, -78 to -20°C, 1 h; MeOH, 25°C, 30 min, 67% yield, 33% ee;

Scheme 10: Optimizaition Results to Generate Iodohydrin **19** and Methyl Ether **36**

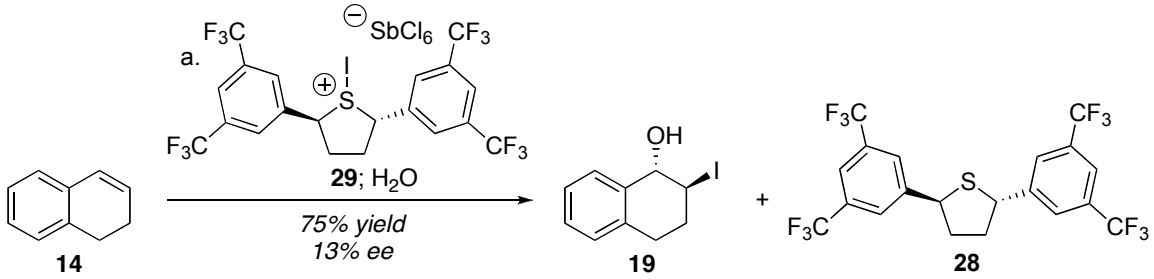
For instance, it has been shown that MeCN is a more coordinating solvent than nitromethane [DN ($MeNO_2$) = 2.7 kcal/mol vs DN (MeCN) = 14.1 kcal/mol; DN = donicity value calculated as $-\Delta H$ of the electron pair donor to $SbCl_5$].[19] Thus overall, the presence of MeCN may have increased coordination to the 3-membered iodonium intermediate (by its own solvation) thereby decreasing the likelihood of iodonium transfer to unreacted alkenes.[6] Collectively, putting these reaction alterations in practice allowed for the generation of iodohydrin **19** in 74% yield and 53% ee. By quenching the reaction with MeOH instead of water, methyl ether **36** could be isolated instead in 67% yield, though with reduced enantioselectivity (33% ee).



Reagents and Conditions: a. **22** (2.2 equiv), $MeCN/CH_2Cl_2$, -78 to -20°C, 1 h; H_2O, 25°C, 30 min, 67% yield, 63% ee; b. **25** (2.2 equiv), $MeCN/CH_2Cl_2$, -78 to -20°C, 1 h; MeOH, 25°C, 30 min, 59% yield, 18% ee.

Scheme 11: Results using Reagents **22** and **25**

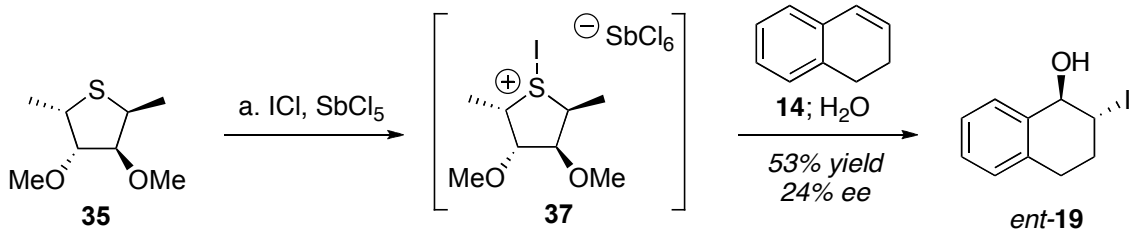
Next, we explored the alternative chiral halonium sources in the newly found iodohydrin formation reaction. Use of the synthesized iodonium reagent **22** produced the desired iodohydrin **19** in 67% yield with increased enantioselectivity at 63% ee (Scheme 11). Interestingly, however, use of the *iso*-propyl derivative produced methyl ether **36** with only 18% ee. Yet examining the aryl thiolane iodonium reagent **29**, the iodohydrin was obtained with only 13% ee (Scheme 12); this was the first case in which the reduced thiolane **28** was re-isolated after the reaction completion. Further analysis of **28** revealed the thiolane had retained 93% ee, implying that no erosion of the thiolane occurred under the reaction conditions. Increasing the steric bulk of the thiolane initiator (from Me < Et < iPr < Aryl), decreases the ee, possibly making it difficult for the substrate to properly approach the iodonium electrophile.



Reagents and Conditions: a. **29** (2.2 equiv), MeCN, -78 to -20°C, 1 h; H_2O, 25°C, 30 min.

Scheme 12: Iodohydrin Generation using Iodonium Reagent **29**

The final examination of the chiral thiolane with substitution along the C3 and C4 positions was a bit more challenging. As previously stated, isolation of a solid iodonium reagent was difficult, so the reagent was generated *in situ*. Treatment of thiolane **35** with ICl and $SbCl_5$ in CH_2Cl_2 yielded the desired iodonium intermediate **37** (Scheme 13). Addition of the alkene **14** under the standard reaction conditions produced the desired iodohydrin in 53% yield with 24% ee.

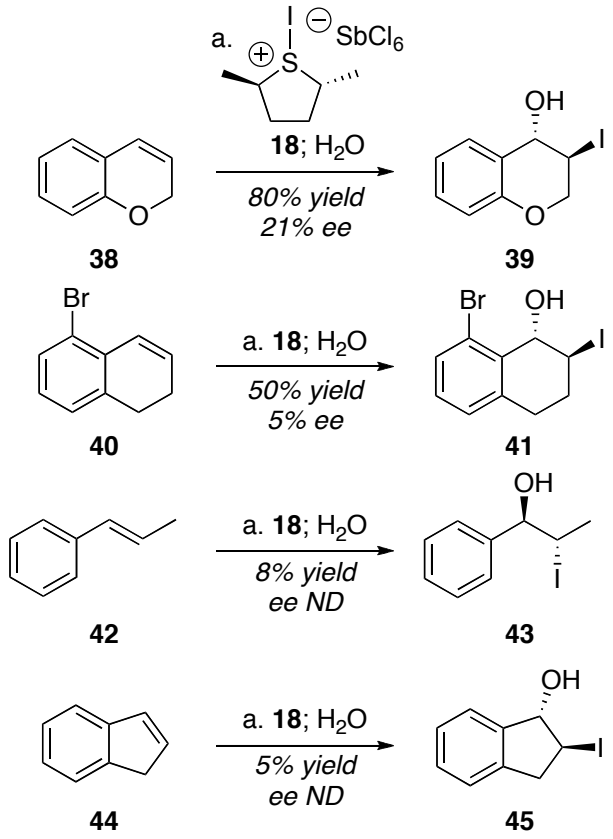


Reagents and Conditions: a. ICl (2.2 equiv), $SbCl_5$ (2.2 equiv), CH_2Cl_2, -25 to 0°C, 1 h then **14** (1 equiv), MeCN, -78 to -20°C, 1 h; H_2O, 25°C, 30 min.

Scheme 13: Use of Initiating Reagent **37** for Asymmetric Iodohydrin Formation

Globally, analysis of all the synthesized thiolane derivatives revealed the ethyl thiolane **22** to be superior, generating **19** in 67% yield with 63% ee. With an increased yield and enantioselectivity in hand, we next examined 1,2-dihydronaphthalene derivatives in hopes of revealing a substrate scope for the developed protocol, as well as a potentially better substrate/halonium initiator match (Scheme 14). The initial idea was to increase the stability of the benzylic position to either a) increase electrophilicity, which might quicken the rate of the nucleophilic attack and/or b) help stabilize the iodonium

intermediate to decrease potential transfer to unreacted alkenes. This task could easily be performed by installing an electron donating group onto the aryl ring at the *ortho*- or *para*-positions. Substrate **38** was presumed to have this effect, though the final results were less than desirable, with iodohydrin **39** obtained in an increased yield (80%) but with only 21% ee. Addition of steric bulk on the arene in the form of a bromine (substrate **40**) produced **41** in a 50% yield with little enantioselectivity (5% ee) upon treatment with chiral iodonium reagent **18**. Larger modifications to the substrate, including acyclic *trans*-β-methylstyrene (**42**) or indene (**44**), both led to very low yields of the corresponding iodohydrin, with mostly decomposition in both cases.



Reagents and Conditions: a. **18** (2.2 equiv), MeCN, -78 to -20°C, 1 h; H_2O, 25°C, 30 min.

Scheme 14: Substrate Scope of Asymmetric Iodohydrin Formation

3.5 Conclusion

The development of a method to achieve the asymmetric iodohydrin of 1,2-dihydronaphthalene was accomplished using a chiral IDSI derivative. With the synthesis of numerous chiral thiolane analogs and reaction optimization, the desired iodohydrin was produced in 67% yield with 63% ee. Remarkably this example is one of only a handful which has afforded a chiral iodonium in >50% ee. This result is proof of concept that these chiral reagents are capable of transferring an iodonium atom asymmetrically. Incomplete transfer of the enantioselectivity could be due to a) poor catalyst/substrate match leading to incomplete transfer of asymmetry or b) iodonium transfer to unreacted alkenes in solution. While both of these processes are possible, it is unclear at this time which one (or both) might be the underlying factor in preventing production of enantiopure products. As mentioned, this developed method seems to be highly substrate specific, as substrates with only slight modifications underwent iodohydrin formation largely in racemic fashion. Additionally, the overall approach has room for further improvement, as use of 2.2 equivalents of the chiral reagent is not ideal, especially if a multiple step synthesis of the needed reagent is necessary. Nevertheless, the synthesized chiral XDSX reagents are the first class of isolable asymmetric halonium reagents capable of producing products with promising enantioselectivity and path the way for future explorations along these lines. These results were also highlighted in a review encompassing the current enantioselective halogenations of alkenes.[2b]

3.6 References

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3.7 Experimental Section

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry methylene chloride (CH_2Cl_2), benzene, toluene, diethyl ether (Et_2O) and tetrahydrofuran (THF) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns; acetonitrile (MeCN) was dried over 3 Å molecular sieves, distilled, and stored over 3 Å molecular sieves; pyridine was distilled from CaH_2 and stored over 3 Å molecular sieves; triethylamine (Et_3N) was distilled from KOH; N,N-dimethylformamide (DMF) was stored over 3 Å molecular sieves; 1,2-dichloroethane, acetone, ethanol (EtOH) and methanol (MeOH) were purchased in anhydrous form from Sigma-Aldrich and used as received. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an aqueous solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. Preparative thin-layer chromatography was carried out on 0.50 mm E. Merck silica gel plates (60F-254). SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. NMR spectra were recorded on Bruker DRX-300 and DRX-400 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, AB = AB quartet, br = broad,

app = apparent. IR spectra were recorded on a Nicolet Avatar 370 DTGS series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded in the Columbia University Mass Spectral Core facility on a JOEL HX110 mass spectrometer using FAB (Fast Atom Bombardment) and EI (Electron Ionization) techniques. All enantiomeric excess (*e.e.*) values were obtained by HPLC using a Daicel CHIRALCEL OD column.

Abbreviations. AcOH = acetic acid, BH_3•Me_2S = borane dimethyl sulfide complex, *n*-BuLi = *n*-butyl lithium, *t*-BuLi = *tert*-butyl lithium, 4-DMAP = 4-(dimethylamino)pyridine, EtOAc = ethyl acetate, EtOH = ethanol, IPA = *iso*-propanol, MeI = iodomethane, MsCl = methanesulfonyl chloride, *p*-TsCl = *para*-toluenesulfonyl chloride.

(2*R*,5*R*)-Dimethylthiolane (Precursor to 18). To a solution of (2*S*, 5*S*)-hexandiol (3.00 g, 25.3 mmol, 1.0 equiv) and Et_3N (21.2 mL, 152 mmol, 6.0 equiv) in CH_2Cl_2 (50 mL) at –20 °C was added MsCl (7.83 mL, 101 mmol, 4.0 equiv) dropwise. The reaction solution was then allowed to warm to 0 °C over 1 h before being quenched with 1 M HCl (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated to provide the desired bis-mesylated intermediate as a viscous oil that was used immediately without further purification. Next, powdered Na_2S•$9H_2O$ (12.2 g, 50.6 mmol, 2.0 equiv) was dissolved in EtOH (200 proof, 80 mL) and the resultant solution was cooled to 0 °C. The crude bis-mesylate (25.3 mmol assumed, 1.0 equiv) was then added and the reaction contents were stirred at 0 °C for 4 h before being warmed slowly to 25 °C over the course of 4 h. Next, the reaction mixture was stirred at 25 °C for an additional 36 h. Upon

completion, the reaction mixture was quenched with water (150 mL) and extracted with pentane (4 × 150 mL). The combined organic layers were then washed with H_2O (3 × 100 mL) and brine (2 × 100 mL), dried ($MgSO_4$), filtered, concentrated, and purified by vacuum distillation (→120 °C at 100 torr) to afford (2*R*,5*R*)-dimethylthiolane as a colorless liquid (2.70 mL, contaminated with pentane, 65% yield) whose spectral properties matched: Julienne, K.; Metzner, P. *J. Org. Chem.* **1998**, *63*, 4532. $[\alpha]_D^{23}$ = 109.1 (c = 1.74, Et_2O); 65% e.e.

18 ("Chiral IDSI"). To a solution of (2*R*,5*R*)-dimethylthiolane (3.30 g, 28.4 mmol, 1.0 equiv) in 1,2-dichloroethane (370 mL) at –25 °C was added ICl (1.42 mL, 28.4 mmol, 1.0 equiv) and $SbCl_5$ (1.0 M in CH_2Cl_2, 29.5 mL, 29.5 mmol, 1.1 equiv). After the reaction contents were stirred at –25 °C for 30 min, it was then allowed to warm to 25 °C. The reaction contents were then layered with hexanes (600 mL) and cooled to –20 °C for 1 week. The filtrate was decanted and the resultant crystals were washed with cold CH_2Cl_2 (2 × 10 mL) and dried under vacuum to afford **18** (12.4 g, 76% yield) as an orange crystalline solid.

***trans*-1-Hydroxy-2-iodotetralin (19).** A solution of 1,2-dihydronaphthalene (**14**, 5.0 mg, 0.038 mmol, 1.0 equiv) in MeCN (0.2 mL) and CH_2Cl_2 (0.5 mL) was cooled to –78 °C. A separate solution of chiral reagent **18** (48 mg, 0.084 mmol, 2.2 equiv) in MeCN (0.3 mL) was added to the substrate slowly down the side of the flask. The resultant reaction solution was then allowed to warm slowly from –78 °C to –20 °C over the course of 1 h before being quenched by the sequential and rapid addition of MeCN (1.0 mL) and H_2O (1.0 mL). The cold bath was removed, and the resultant solution was stirred at 25 °C for 1 h. Upon completion, 5% aqueous Na_2SO_3 (1 mL) and saturated

aqueous $NaHCO_3$ (1 mL) were added, and this heterogeneous mixture was then stirred vigorously at 25 °C for 20 min before being poured into H_2O (2 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were then dried ($MgSO_4$), filtered, concentrated, and purified by column chromatography (silica gel, hexanes:EtOAc, 9:1→7:3) to afford **19** (8 mg, 74% yield) as a white crystalline solid. **19**: R_f= 0.46 (silica gel, hexanes:EtOAc, 7:3); IR (film) ν_{max} 3243 (br), 2903, 1419, 1203, 979, 774, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (m, 1 H), 7.30–7.24 (m, 2 H), 7.14 (m, 1 H), 5.03 (t, *J* = 5.6 Hz, 1 H), 4.52 (td, *J* = 6.8, 3.2 Hz, 1 H), 2.94 (t, *J* = 6.4 Hz, 2 H), 2.54–2.45 (m, 2 H), 2.36 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.2, 135.1, 128.7, 128.5, 128.1, 126.7, 75.1, 36.0, 30.8, 29.3; HRMS (EI) calcd for $C_{10}H_{11}IO$ $[M]^+$ 273.9855, found 273.9858; HPLC (OD column, 1.0 mL/min, 50:1 hex:IPA, 30 °C, 265 nm, t_R (major) = 9.94 min, t_R (minor) = 12.31 min): 53% e.e. The absolute configuration of **19** was determined based on Mosher's ester analysis: Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nature Protocols* **2007**, *2*, 2451. This reaction was performed with both (*R*)- and (*S*)-Mosher's acid separately, and the major diastereomer produced in each case was then characterized by ^1H NMR. Specifically, to a solution of methoxy-α-trifluoromethylphenylacetic acid (39.8 mg, 0.17 mmol, 2.0 equiv) in hexane (2.3 mL) at 25 °C was sequentially added DMF (4.5 mL, 0.058 mmol, 1.0 equiv) and oxalyl chloride (25 mL, 0.29 mmol, 5.0 equiv). The reaction solution was then stirred at 25 °C for 1 h, filtered through Celite, rinsed with hexanes (2 × 1 mL), and concentrated. Next, a solution of the resultant crude acid chloride (0.17 mmol assumed) and iodohydrin **19** (16 mg, 0.058 mmol, 1.0 equiv) in CH_2Cl_2 (0.12 mL) was cooled to 0 °C and 4-DMAP (0.07 mg, 0.0006 mmol, 0.01 equiv) and Et_3N (40 mL, 0.29 mmol, 5.0 equiv) were added

sequentially. The reaction contents were then allowed to warm slowly to 25 °C over the course 2 h, quenched with 1 M HCl (1 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by column chromatography (silica gel, hexanes:EtOAc, 9:1) to afford the major diastereomer ester as a white crystalline solid. *(R)-Mosher's ester:* (5.0 mg, 17% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.5 Hz, 2 H), 7.41–7.28 (m, 5 H), 7.22 (t, *J* = 7.0 Hz, 1 H), 7.17 (d, *J* = 7.5 Hz, 1 H), 6.41 (d, *J* = 3.0 Hz, 1 H), 4.60 (q, *J* = 3.5 Hz, 1 H), 3.49 (s, 3 H), 3.01 (dt, *J* = 17.0, 6.0 Hz, 1 H), 2.83 (dq, *J* = 17.5, 3.0 Hz, 1 H), 2.08–1.93 (m, 2 H). *(S)-Mosher's ester:* (5.6 mg, 20% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.0 Hz, 2 H), 7.41–7.34 (m, 3 H), 7.26 (m, 1 H), 7.19–7.12 (m, 3 H), 6.40 (d, *J* = 3.5 Hz, 1 H), 4.68 (q, *J* = 4.0 Hz, 1 H), 3.49 (s, 3 H), 3.01 (dt, *J* = 17.0, 8.0 Hz, 1 H), 2.85 (dt, *J* = 17.5, 4.5 Hz, 1 H), 2.15 (quintet, *J* = 4.5 Hz, 1 H).

(2*S*,5*S*)-Diethylthiolane (21). Prepared according to the procedure used to synthesize (2*R*,5*R*)-dimethylthiolane. The cyclization with $Na_2S•9H_2O$ was performed at 25 °C for 22 h. (2*S*,5*S*)-Diethylthiolane (0.28 g, contaminated with pentane, 75% yield) was obtained as a colorless liquid. R_f = 0.62 (silica gel, hexanes:CH_2Cl_2, 9:1); IR (film) ν_{max} 2939, 1275, 1266, 767, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.36–3.28 (m, 2 H), 2.23–2.14 (m, 2 H), 1.71–1.60 (m, 2 H), 1.60–1.48 (m, 4 H), 0.95 (t, *J* = 7.2 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.4 (2 C), 36.9 (2 C), 30.6 (2 C), 13.4 (2 C); HRMS: no molecular ion peak was observed; $[a]_D^{23}$ = -38.4 (c = 0.65, $CHCl_3$).

22. Prepared according to the procedure used to synthesize **18**. Compound **22** (0.58 g, 70%) was obtained as an orange crystalline solid.

(2*R*,5*R*)-Di-*iso*-propylthiolane (24). Prepared according to the procedure used to synthesize (2*R*,5*R*)-dimethylthiolane. The cyclization with $Na_2S•9H_2O$ was performed at 25 °C for 7 d. (2*R*,5*R*)-Di-*iso*-propylthiolane (0.60 g, contaminated with pentane, 50% yield) was obtained as a colorless liquid whose spectral properties that matched literature data: Piccinini, A.; Kavanaugh, S. A.; Connon, P. B.; Connon, S. J. *Org. Lett.* **2010**, *12*, 608.

25. Prepared according to the procedure used to synthesize **18**. Compound **25** (0.15 g, 48%) was obtained as an orange crystalline solid.

26. Prepared according to a procedure adapted from: (a) Déziel, R.; Goulet, S.; Grenier, L.; Bordeleau, J.; Bernier, J. *J. Org. Chem.* **1993**, *58*, 3619; (b) Prasad, K. R. K.; Joshi, N. N. *J. Org. Chem.* **1996**, *61*, 3888; (c) Kumar, G. D. K.; Chavarria, G. E.; Charlton-Sevcik, A. K.; Arispe, W. M.; MacDonough, M. T.; Strecker, T. E.; Chen, S.-E.; Siim, B. G.; Chaplin, D. J.; Trawick, M. L.; Pinney, K. G. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1415. *N,O*-Dimethylhydroxylamine hydrochloride (4.10 g, 42.0 mmol, 3.0 equiv) was azeotroped with toluene, sealed under argon, and cooled to 0 °C. CH_2Cl_2 (32.6 mL) and Et_3N (7.8 mL, 56 mmol, 4.0 equiv) were then added sequentially at 0 °C. The resultant suspension was then stirred for 10 min at 0 °C before a solution of succinyl chloride (1.54 mL, 14.0 mmol, 1.0 equiv) in CH_2Cl_2 (10.7 mL) was added at 0 °C. The reaction solution was then allowed to warm to 25 °C over the course of 3 h. Upon completion, the reaction contents were quenched with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated to afford the crude bis-Weinreb amide (only a portion of which was carried forward in the next operation). Next, a solution of 3,5-bis(trifluoromethyl)bromobenzene

(0.75 mL, 4.5 mmol, 3.0 equiv) was dissolved in Et_2O (5.0 mL), cooled to –78 °C and *n*-BuLi (1.6 M in Et_2O, 2.8 mL, 4.5 mmol, 3.0 equiv) was added dropwise to produce the desired aryl lithium species following an additional 1 h of stirring at –78 °C. In a separate flask, a suspension of crude bis-Weinreb amide (0.31 g, 1.5 mmol, 1.0 equiv) in Et_2O (5.0 mL) was cooled to –78 °C. The so-prepared aryllithium solution was then added to this suspension of diamide at –78 °C, and the resultant reaction mixture was allowed to warm to 25 °C over the course of 3 h and stirred for an additional 1 h at 25 °C. Upon completion, the reaction contents were quenched with 1 M HCl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were then dried ($MgSO_4$), filtered, concentrated, and purified by recrystallization by dissolving the crude solid in hot EtOAc (4 mL), cooling the resultant solution to 25 °C, and then layering it with hexanes (1 mL) and cooling it to –20 °C for 12 h; the filtrate was decanted and the resultant crystals were washed with cold hexanes (2 × 1 mL) and dried under vacuum to afford the diaryl ketone intermediate **26** (0.40 g, 53% yield over 2 steps) as a shiny orange/yellow crystalline solid.

27. (*S*)-α,α-Diphenyl-2-pyrrolidinemethanol (7.7 mg, 0.030 mmol, 0.15 equiv) was azeotroped with toluene (1.0 mL), sealed under argon, and then dissolved in THF (0.3 mL). Trimethylborate (4.5 mL, 0.040 mmol, 0.20 equiv) was added at 25 °C and the reaction contents were stirred at 25 °C for 1 h, at which time BH_3•Me_2S (42 mL, 0.44 mmol, 2.2 equiv) was added. After stirring at 25 °C for 10 min, THF (0.5 mL) was added followed by solid diaryl ketone (0.10 g, 0.20 mmol, 1.0 equiv). The reaction solution was then heated at 40 °C for 30 min before being re-cooled to 25 °C, quenched with 1 M HCl (4 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were

then dried ($MgSO_4$), filtered, concentrated, and purified by column chromatography (silica gel, hexanes:EtOAc 9:1→1:1) to afford the diaryl diol **27** (0.080 g, 78% yield) as a white crystalline solid. **27**: R_f = 0.53 (silica gel, hexanes:EtOAc, 7:3); IR (film) ν_{max} 3384 (br), 3283 (br), 2927, 1275, 1167, 1122, 898, 682 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ 8.03 (s, 4 H), 7.90 (s, 2 H), 5.08–4.97 (m, 2 H), 4.90 (br d, *J* = 18.4 Hz, 2 H), 2.05–1.94 (m, 3 H), 1.85 (m, 1 H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 150.6, 150.6, 131.9 (q, *J* = 32.6 Hz, 4 C), 127.3 (4 C), 124.6 (q, *J* = 270.3 Hz, 4 C), 121.4 (t, *J* = 3.6 Hz, 2 C), 72.8, 72.6, 36.4, 36.3; HRMS: no molecular ion peak was observed.

28. The diaryl thiolane **28** was prepared according to the procedure used to synthesize (2*R*,5*R*)-dimethylthiolane. The cyclization with $Na_2S•9H_2O$ was performed at 25 °C for 30 min. The diaryl thiolane **28** (0.068 g, 53% yield) was obtained as a white crystalline solid. R_f = 0.27 (silica gel, hexanes:CH_2Cl_2, 9:1); IR (film) ν_{max} 2934, 2859, 1376, 1275, 1123, 681 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 4 H), 7.80 (s, 2 H), 5.02–4.96 (m, 2 H), 2.77–2.67 (m, 2 H), 2.21–2.09 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5 (2 C), 132.0 (q, *J* = 33.2 Hz, 4 C), 128.0 (4 C), 123.2 (q, *J* = 271.1 Hz, 4 C), 121.6 (quintet, *J* = 3.8 Hz, 2 C), 53.6 (2 C), 41.2 (2 C); HRMS (FAB) calcd for $C_{20}H_{11}F_{12}S$ $[M–H]^+$ 511.0390, found 511.0373; HPLC (OD column, 1.0 mL/min, 50:1 hex:IPA, 30 °C, 200 nm, t_R (major) = 4.11 min, t_R (minor) = 4.63 min): 94% e.e.

29. Prepared according to the procedure used to synthesize **18**. Compound **29** (0.17 g, 92%) was obtained as a yellow crystalline solid.

33. Prepared according to a procedure adapted from: Hanaya, T.; Nakamura, Y.; Yamamoto, H. *Heterocycles* **2007**, *74*, 983. To a stirred suspension of NaH (60% dispersion in mineral oil, 1.28 g, 38.1 mmol, 4.0 equiv) in THF (6.5 mL) at 0 °C was

added slowly a solution of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**31**, 2.50 g, 9.53 mmol, 1.0 equiv) in THF (2.0 mL). The resultant suspension was then stirred at 0 °C for 30 min. MeI (1.78 mL, 28.6 mmol, 3.0 equiv) was then added dropwise, and the reaction contents were stirred for 1 h at 25 °C. Upon completion, the solution was cooled to 0 °C, quenched by the slow addition of H_2O (10 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated to afford the desired crude bis-methylated mannitol derivative. Moving forward without any additional purification, this crude intermediate was dissolved in 70% aqueous AcOH (25 mL) and heated to 40 °C for 2 h. The reaction contents were then cooled to 25 °C, and concentrated directly with toluene coevaporations (6 × 25 mL) to remove all of the AcOH and H_2O. The resultant crude tetraol was then dissolved in dry pyridine (28 mL), cooled to 0 °C, and *p*-TsCl (4.09 g, 21.4 mmol, 2.25 equiv) was added. The resultant solution was then stirred at 0 °C for 4 h. Upon completion, the reaction contents were quenched by the addition of H_2O (3 mL) and directly concentrated using toluene coevaporations (3 × 10 mL) to remove any residual pyridine. The resultant crude mixture was then redissolved in CH_2Cl_2 (10 mL) and washed with H_2O (2 × 10 mL). The organic layer was then dried ($MgSO_4$), filtered, concentrated, and purified by column chromatography (silica gel, hexanes:EtOAc 7:3→1:4) to afford the desired bis-tosylated intermediate **33** (3.0 g, 61% yield over 3 steps) as a yellow amorphous solid.

34. The bis-tosylate **33** (3.0 g, 5.78 mmol, 1.0 equiv) was dissolved in THF (27 mL), cooled to 0 °C, and solid $LiAlH_4$ (0.548 g, 14.5 mmol, 2.5 equiv) was added in five separate portions over the course of 30 min. The resultant slurry was then stirred at 25 °C for 12 h, cooled to 0 °C, and quenched slowly with H_2O (10 drops). The resultant

suspension was then filtered through Celite and rinsed with MeOH (5 mL). The filtrate was then concentrated and purified by column chromatography (silica gel, CH_2Cl_2:MeOH, 9:1) to afford (2*R*,3*R*,4*R*,5*R*)-3,4-dimethoxyhexane-2,5-diol (**34**, 0.044 g, 27% yield over 4 steps) as a white crystalline solid. **34:** R_f = 0.58 (silica gel, CH_2Cl_2:MeOH, 9:1); IR (film) ν_{max} 3443 (br), 3378 (br), 2969, 2839, 1111, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.07 (t, *J* = 5.2 Hz, 2 H), 3.50 (s, 6 H), 3.32–3.28 (m, 2 H), 2.98 (br s, 2 H), 1.26 (d, *J* = 6.4 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.2 (2 C), 66.8 (2 C), 58.7 (2 C), 19.9 (2 C); HRMS (FAB) calcd for $C_8H_{19}O_4$ $[M+H]^+$ 179.1283, found 179.1293.

(2*S*,3*S*,4*S*,5*S*)-3,4-Dimethoxy-2,5-dimethylthiolane (35). Prepared according to the procedure used to synthesize (2*R*,5*R*)-dimethylthiolane. The cyclization with $Na_2S•9H_2O$ was performed at 50 °C for 24 h. Compound **35** (11.5 mg, 13% yield) was obtained as a light yellow volatile oil. **35:** R_f = 0.81 (silica gel, hexanes:EtOAc, 4:1); IR (film) ν_{max} 2934, 1451, 1121, 752, 474 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.74–3.70 (m, 2 H), 3.64–3.55 (m, 2 H), 3.43 (s, 6 H), 1.27 (d, *J* = 6.8 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 86.0 (2 C), 58.3 (2 C), 40.6 (2 C), 16.6 (2 C); HRMS: no molecular ion peak was observed; $[a]_D^{23}$ = -48.3 (c = 0.44, $CHCl_3$).

***trans*-2-Iodo-1-methoxytetralin (36).** Prepared according to the procedure used to synthesize **19**, quenching with MeOH. Compound **36** (7.3 mg, 67% yield) was obtained as a white crystalline solid. **36**: R_f = 0.52 (silica gel, hexanes:EtOAc, 19:1); IR (film) ν_{max} 2924, 2818, 1455, 1203,1070, 768, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.18 (m, 3 H), 7.14 (d, *J* = 6.8 Hz, 1 H), 4.75 (m, 1 H), 4.57 (d, *J* = 3.6 Hz, 1 H), 3.50 (s, 3 H), 2.97 (dq, *J* = 16.8, 5.6 Hz, 1 H), 2.85 (dq, *J* = 17.2, 3.6 Hz, 1 H), 2.29 (m, 1

H), 2.10 (m, 1 H); ^{13}C NMR (100 MHz, ($CDCl_3$) δ 135.7, 133.0, 130.4, 129.1, 128.5, 126.3, 83.0, 57.3, 29.4, 27.9, 27.8; HRMS (EI) calcd for $C_{11}H_{13}IO$ $[M]^+$ 288.0011, found 288.0000; HPLC (AD-H column, 1.0 mL/min, 99:1 hex:IPA, 30 °C, 263 nm, t_R (major) = 5.94 min, t_R (minor) = 6.46 min): 33% e.e.

***trans*-3-Iodochroman-4-ol (39).** Prepared according to the procedure used to synthesize **19**. Compound **39** (9 mg, 80% yield) was obtained as a white crystalline solid. **39**: R_f = 0.47 (silica gel, hexanes:EtOAc, 7:3); IR (film) ν_{max} 3344 (br), 2859, 1486, 1223, 1981, 757 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.26 (td, *J* = 7.8, 1.6 Hz, 1 H), 6.99 (td, *J* = 7.2, 0.8 Hz, 1 H), 6.89 (dd, *J* = 8.4, 1.2 Hz, 1 H), 5.00 (t, *J* = 5.2 Hz, 1 H), 4.45–4.39 (m, 2 H), 4.32 (m, 1 H), 2.43 (d, *J* = 5.2 Hz, 1 H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 153.3, 130.4, 129.2, 122.4, 120.7, 116.3, 70.2, 66.9, 28.0; HRMS (EI) calcd for $C_9H_9IO_2$ $[M]^+$ 275.9647, found 275.9640; HPLC (AD-H column, 1.0 mL/min, 9:1 hex:IPA, 30 °C, 280 nm, t_R (major) = 8.14 min, t_R (minor) = 7.68 min): 21% e.e.

5-bromo-1,2-dihydronaphthalene (40). Prepared according to a procedure adapted from: Izmer, V. V.; Lebedev, A. Y.; Nikulin, M. V.; Ryabov, A. N.; Asachenko, A. F.; Lygin, A. V.; Sorokin, D. A.; Voskoboynikov, A. Z. *Organometallics* **2006**, *25*, 1217. To a solution of 1,2,3,4-tetrahydro-1-naphthol (0.74 g, 5.0 mmol, 1.0 equiv) in hexanes (10 mL) at 0 °C was added *t*-BuLi (1.7 M in pentane, 8.8 mL, 15 mmol, 3.0 equiv) dropwise. The reaction contents were then heated at 40 °C for 1 h. Once complete, the solution was cooled to –78 °C and $BrCl_2CCCl_2Br$ (3.42 g, 10.5 mmol, 2.1 equiv) was added quickly in a single portion. The reaction contents were then allowed to warm to 25 °C over the course of 4 h. Upon completion, the solution was quenched with

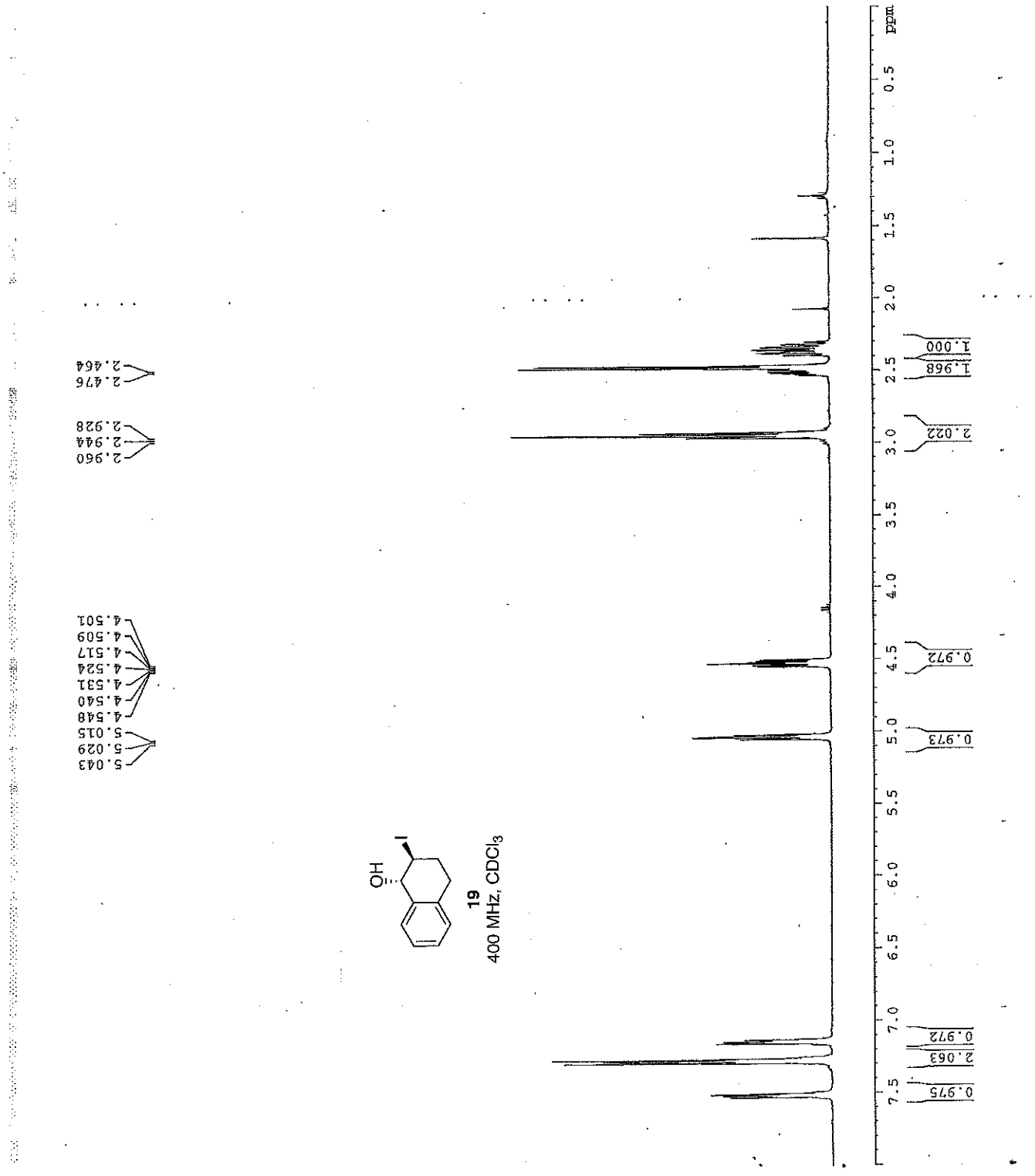
saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by column chromatography (silica gel, hexanes:EtOAc 9:1→4:1) to afford 8-bromo-1,2,3,4-tetrahydro-1-naphthol (0.42 g, 37% yield) as a light brown, crystalline solid. Next, a portion of the newly synthesized alcohol (0.10 g, 0.44 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (2.2 mL) and cooled to 0 °C. MsCl (68 mL, 0.88 mml, 2.0 equiv) and Et_3N (0.245 mL, 1.76 mmol, 4.0 equiv) were then added sequentially and the resultant solution was allowed to warm to 25 °C over the course of 3 h. Upon completion, the reaction contents were quenched with 1 M HCl (3 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were then dried ($MgSO_4$), filtered, concentrated, and purified by column chromatography (silica gel, hexanes:CH_2Cl_2, 9:1) to afford **40** (21 mg, 23% yield) as a colorless viscous oil. **40**: R_f = 0.90 (silica gel, hexanes:CH_2Cl_2, 9:1); IR (film) n_{max} 3054, 2935, 2829, 1552, 1442, 1012, 763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.38 (d, *J* = 7.6 Hz, 1 H), 7.04 (d, *J* = 7.2 Hz, 1 H), 6.96 (t, *J* = 8.0 Hz, 1 H), 6.85 (dq, *J* = 10.0, 1.6 Hz, 1 H), 6.18 (dt, *J* = 9.2, 4.4 Hz, 1 H), 2.79 (t, *J* = 8.0 Hz, 2 H), 2.34–2.27 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) d 138.0, 133.0, 130.9, 130.7, 127.8, 126.7, 126.4, 121.9, 28.2, 22.8; HRMS (EI) calcd for $C_{10}H_9Br$ $[M]^+$ 207.9888, found 207.9877.

***trans*-8-Bromo-1-hydroxy-2-iodotetralin (41).** Prepared according to the procedure used to synthesize **19**. Compound **41** (4 mg, 50%) was obtained as a white crystalline solid. **41**: R_f = 0.42 (silica gel, hexanes:EtOAc, 7:3); IR (film) ν_{max} 3289 (br), 2929, 2854, 1566, 1446, 1261, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (m, 1 H), 7.17–7.10 (m, 2 H), 5.31 (t, *J* = 3.2 Hz, 1 H), 4.72 (q, *J* = 2.8 Hz, 1 H), 3.09 (ddd, *J* =

17.6, 11.6, 5.6 Hz, 1 H), 2.86 (m, 1 H), 2.56 (d, *J* = 4.4 Hz, 1 H), 2.21 (m, 1 H), 2.06 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 133.7, 131.0, 129.6, 128.6, 126.2, 72.7, 31.2, 27.8, 25.8; HRMS (EI) calcd for $C_{10}H_{10}BrIO$ $[M]^+$ 351.8960, found 351.8972; HPLC (AD-H column, 1.0 mL/min, 9:1 hex:IPA, 30 °C, 220 nm, t_R (major) = 11.58 min, t_R (minor) = 10.80 min): 5% e.e.

***trans*-2-Iodo-1-phenylpropan-1-ol (43).** Prepared according to the procedure used to synthesize **19**. Compound **43** (7 mg, 8%) was obtained as a white crystalline solid. **43**: R_f = 0.67 (silica gel, hexanes:EtOAc, 7:3); IR (film) ν_{max} 3431 (br), 2969, 2922, 1451, 1165, 1014, 751, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.29 (m, 5 H), 4.96 (t, *J* = 3.2 Hz, 1 H), 4.53 (ddd, *J* = 14.0, 6.8, 3.6 Hz, 1 H), 2.35 (d, *J* = 3.2 Hz, 1 H), 1.74 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 128.4 (2 C), 128.0, 126.4 (2 C), 78.5, 35.9, 21.2; HRMS (EI) calcd for $C_9H_{11}IO$ $[M]^+$ 261.9855, found 261.9845.

***trans*-1-Hydroxy-2-iodoindane (45).** Prepared according to the procedure used to synthesize **19**. Compound **43** (2 mg, 5%) was obtained as a white crystalline solid whose spectral properties matched literature data: (a) Stavber, G.; Iskra, J.; Zupan, M.; Stavber, S. *Adv. Synth. Catal.* **2008**, *350*, 2921. (b) Pandit, P.; Gayen, K. S.; Khamarui, S.; Chatterjee, N.; Maiti, D. K. *Chem. Commun.* **2011**, *47*, 6933.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0.973
0.973
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2.476
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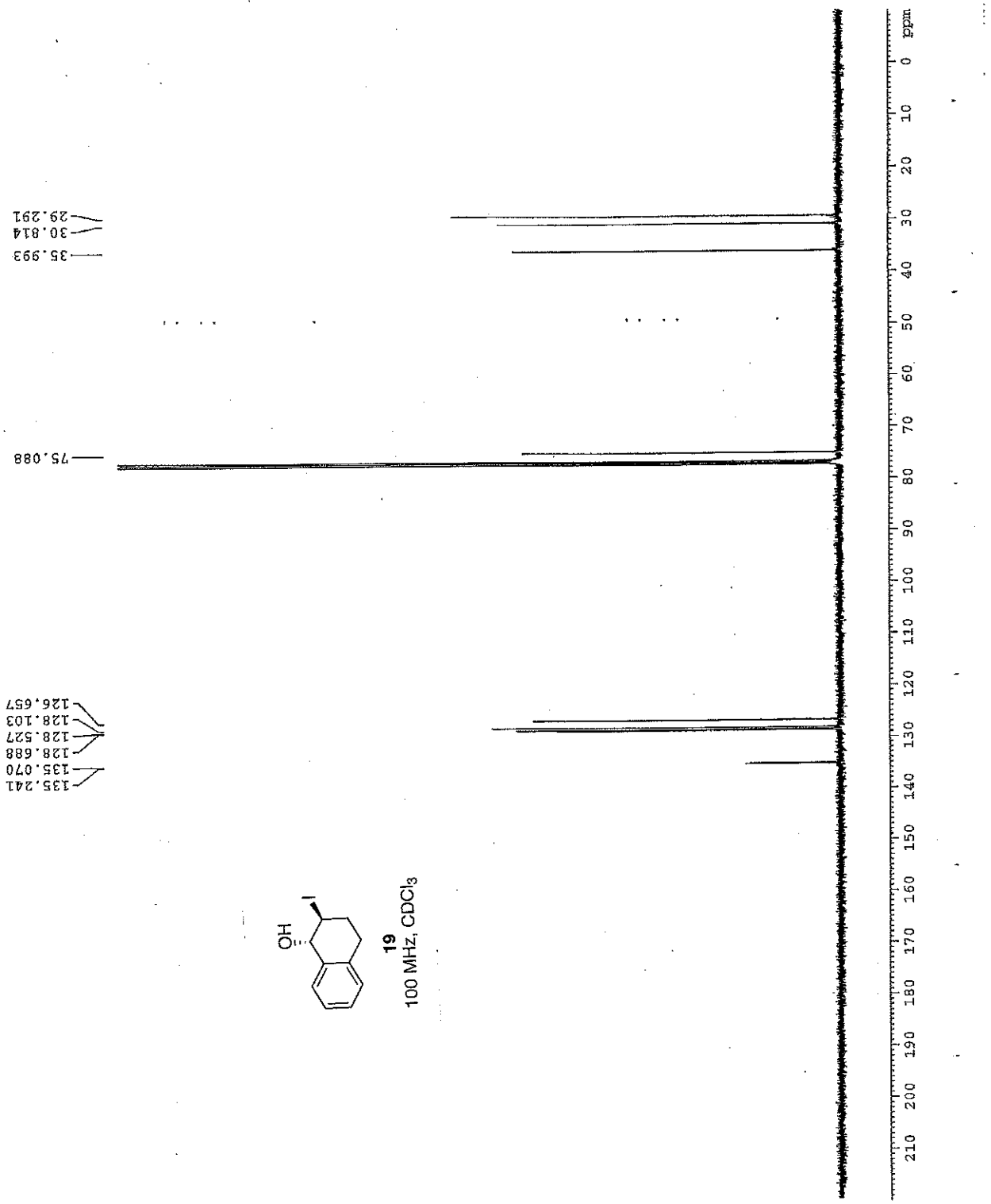
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135.241
OH
19
100 MHz, CDCl3
ppm

5/28/2013 09:56:25 1 / 1

trans-2-Iodo-1,2,3,4-tetrahydronaphthalene-1-ol

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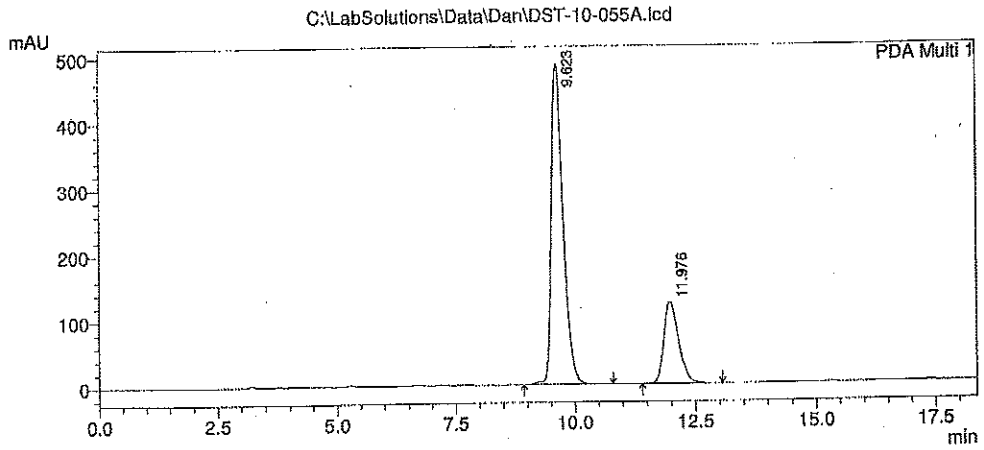

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5/28/2013 11:42:55 1 / 1

Racemic trans-2-Iodo-1,2,3,4-tetrahydronaphthalen-1-ol

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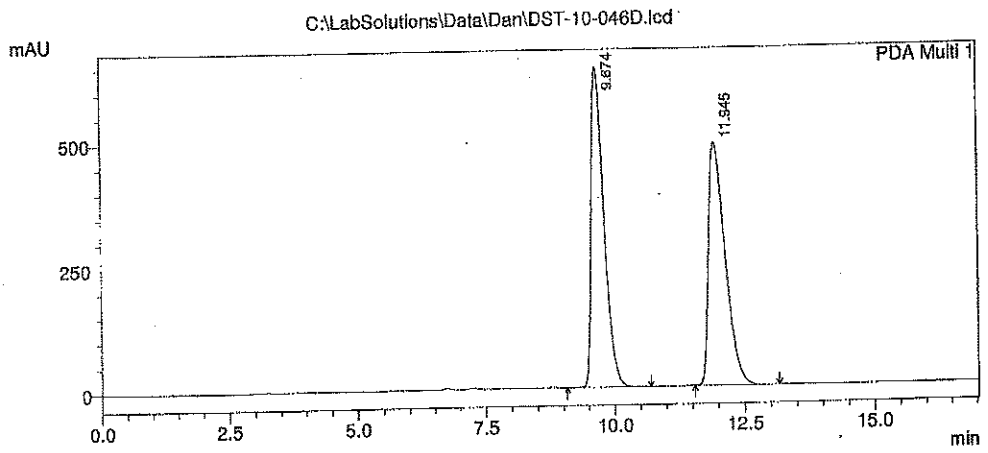
30 oC
265 nm

<Chromatogram>



1 PDA Multi 1/265nm 4nm

PeakTable

PDA Ch1 265nm 4nm

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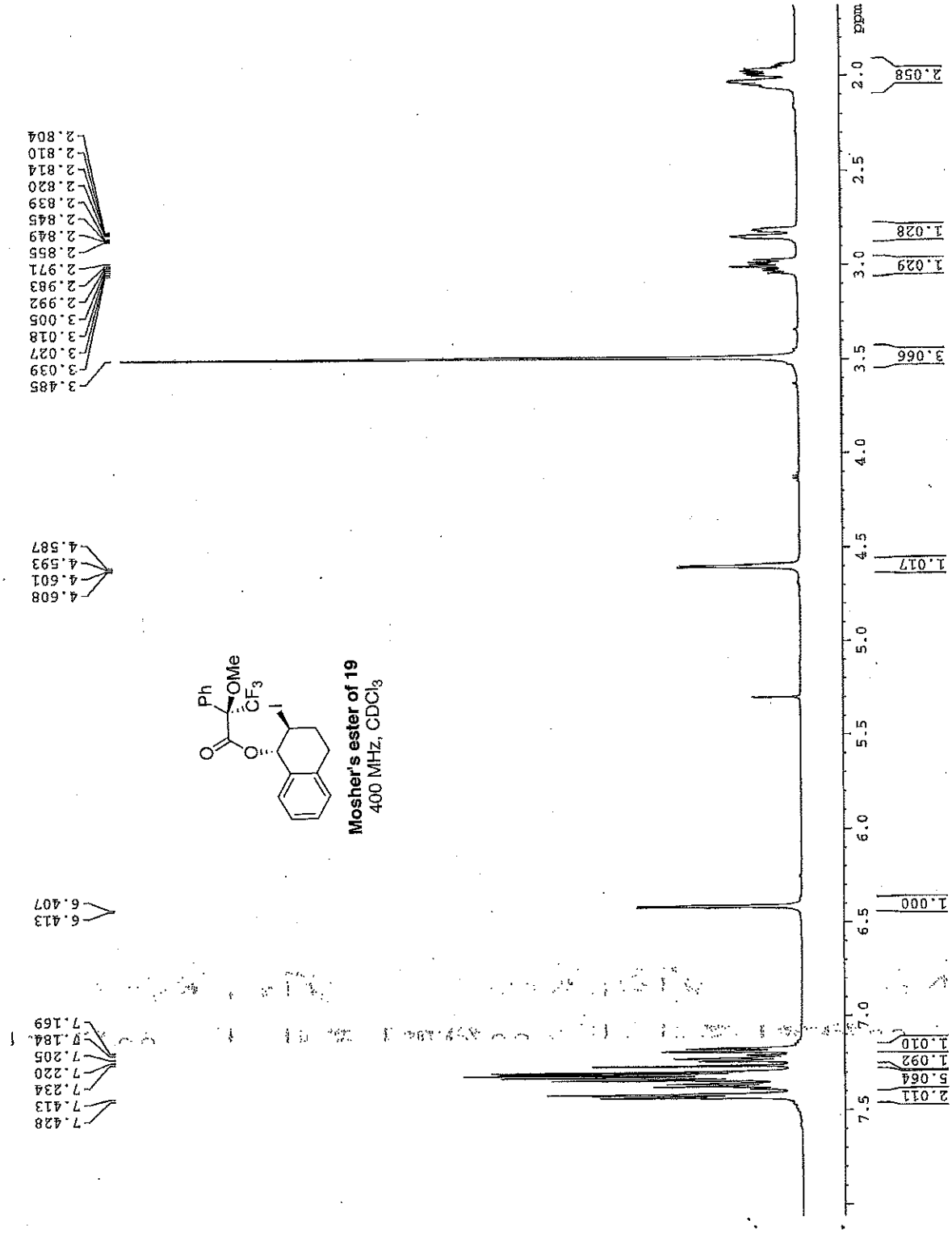
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CF3
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O
O
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4.5
5.0
5.5
6.0
6.5
7.0
7.5
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1.028
1.029
3.066
1.017
1.000
1.010
1.092
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2.971
2.855
2.849
2.845
2.839
2.820
2.814
2.810
2.804
4.608
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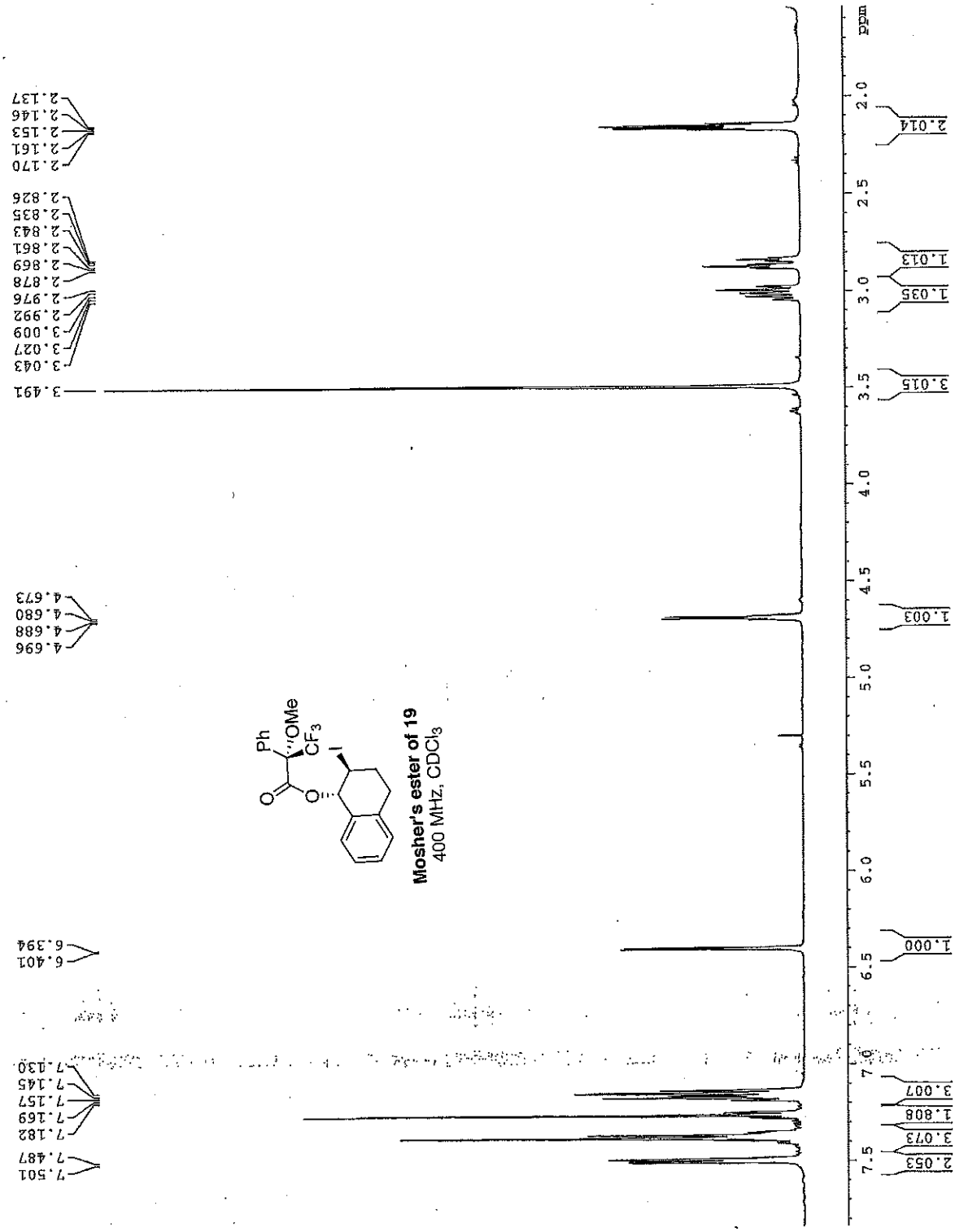
Mosher's ester of 19
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CF3
O
O
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4.696
6.394
6.401
7.130
7.145
7.157
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7.182
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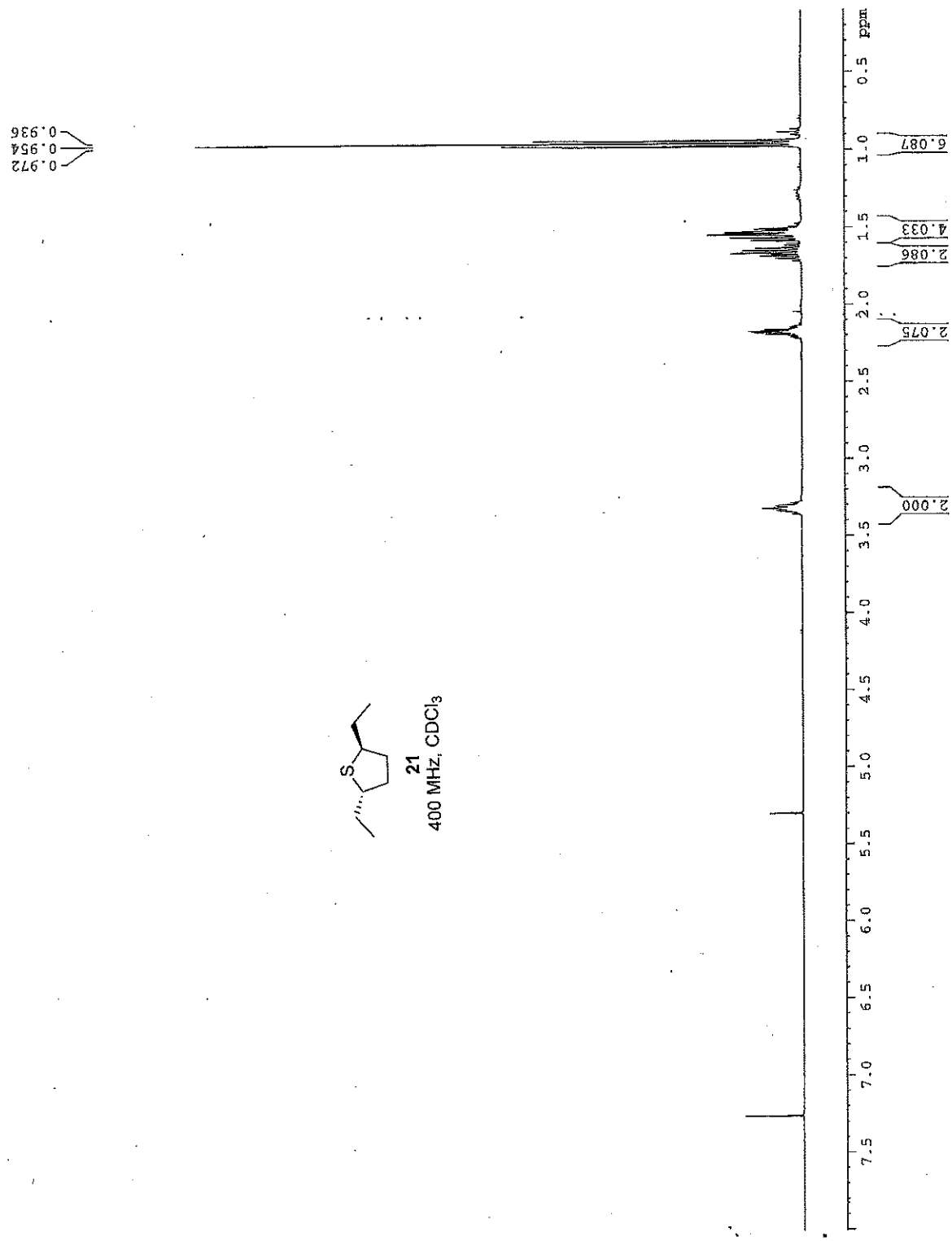
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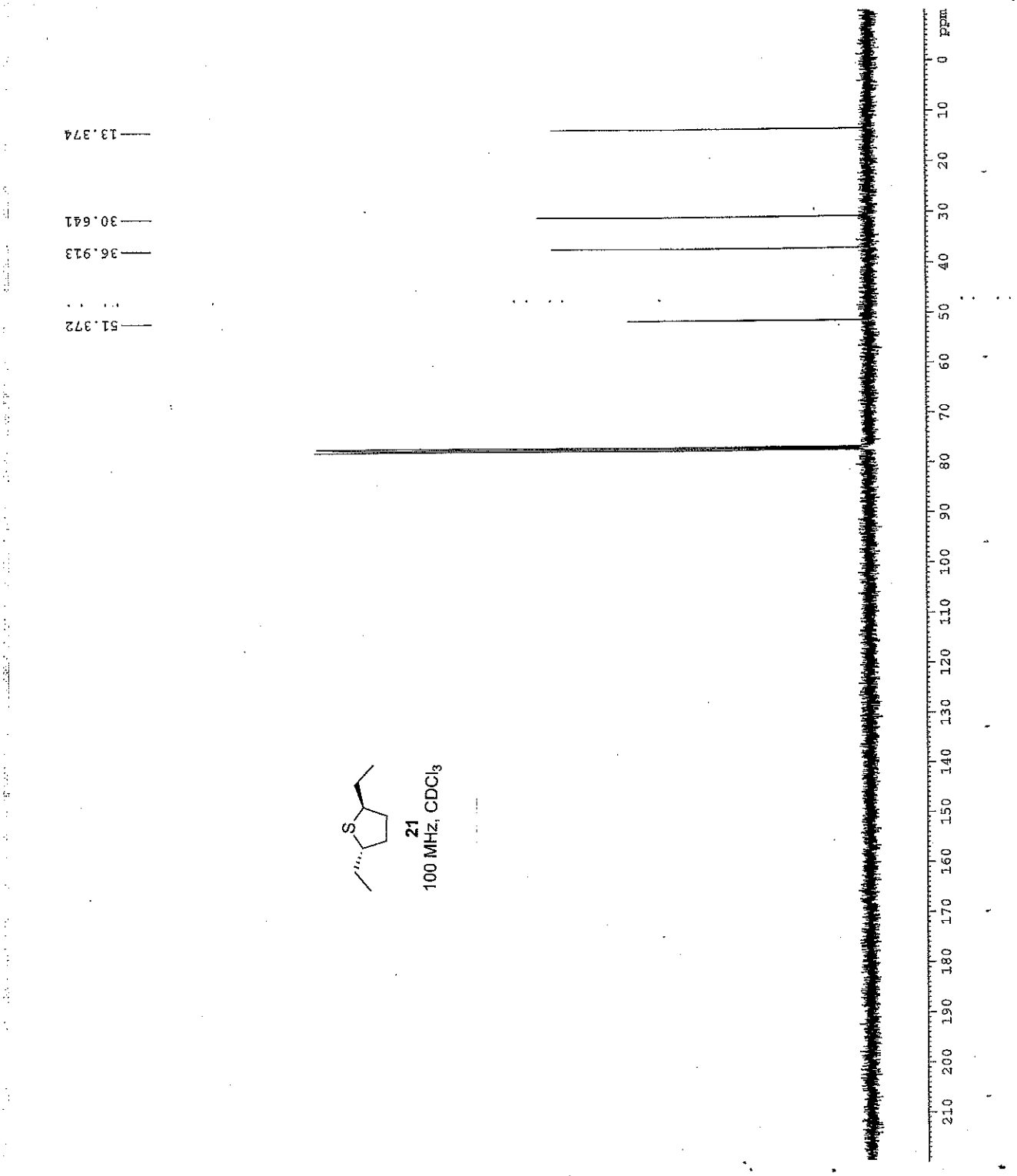
400 MHz, CDCl3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100 MHz, CDCl3
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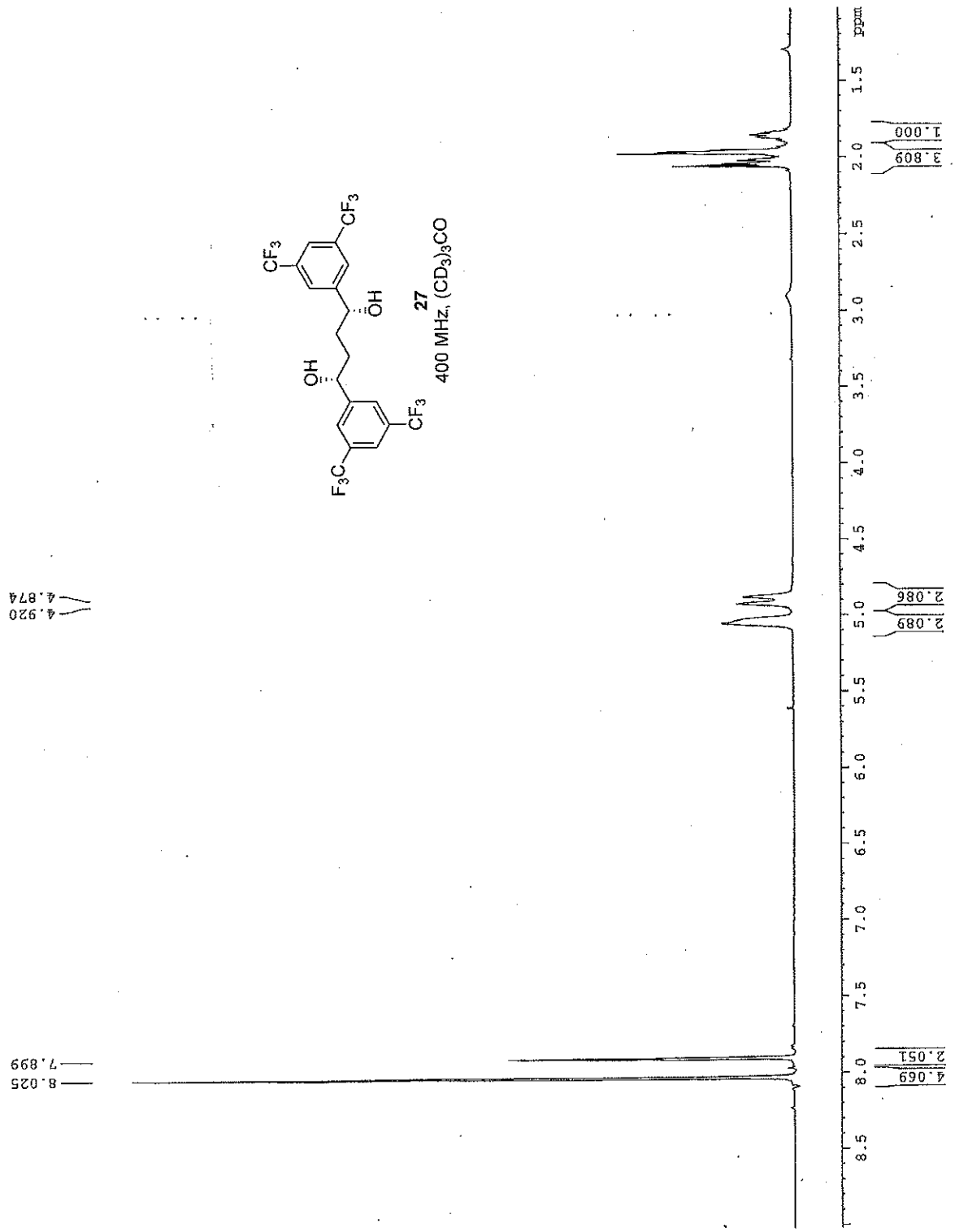
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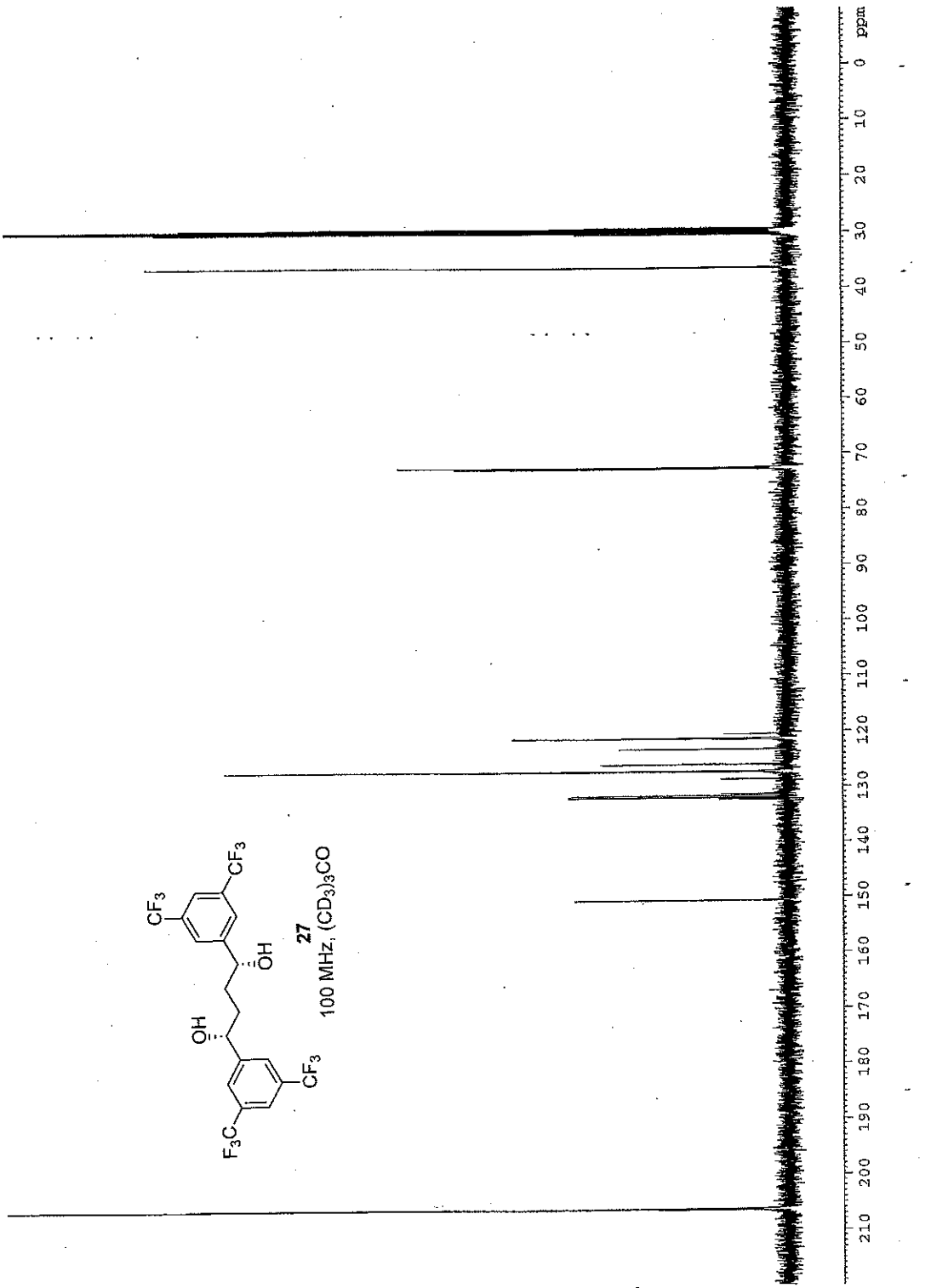
ppm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OH
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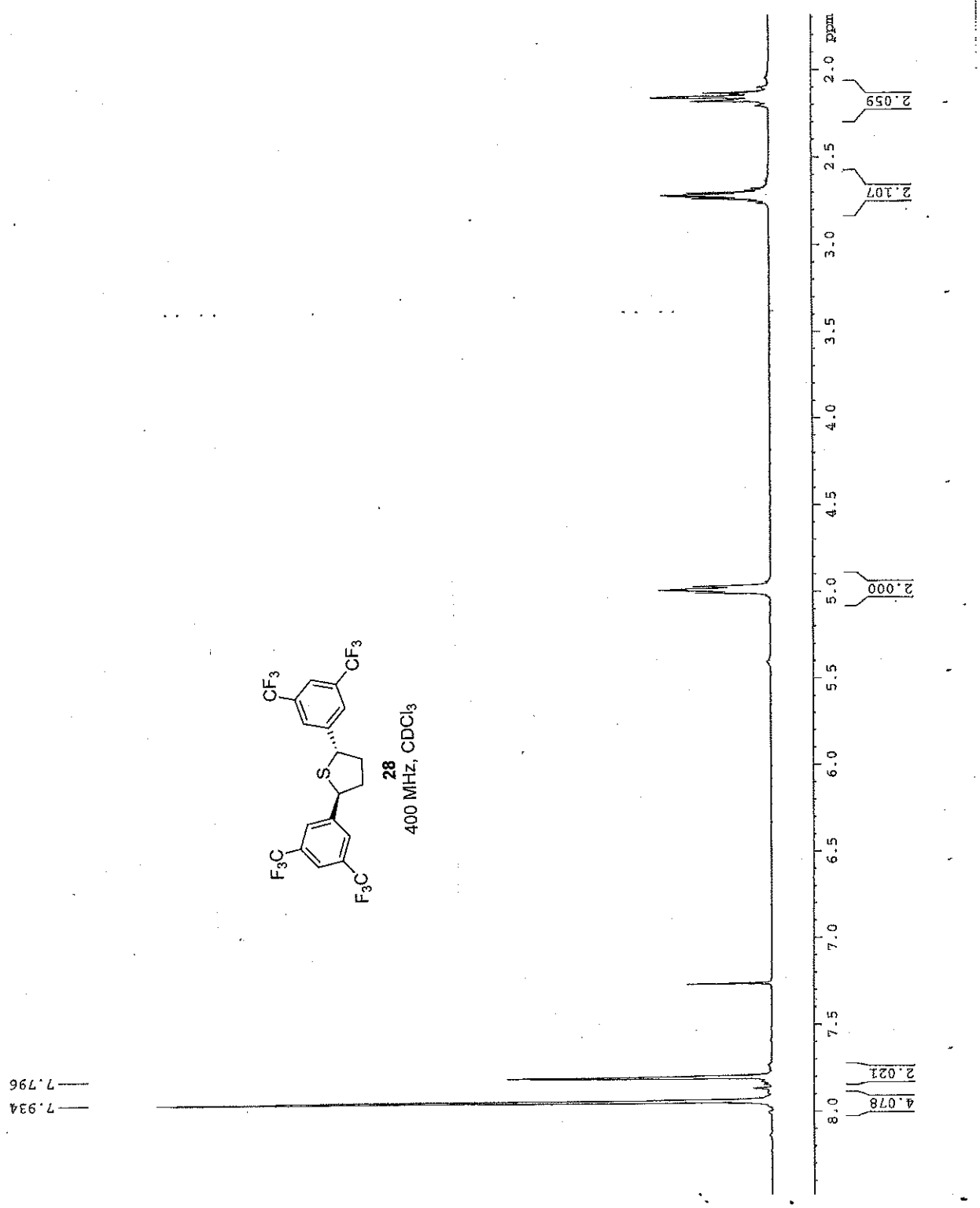
ppm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2.5
2.0
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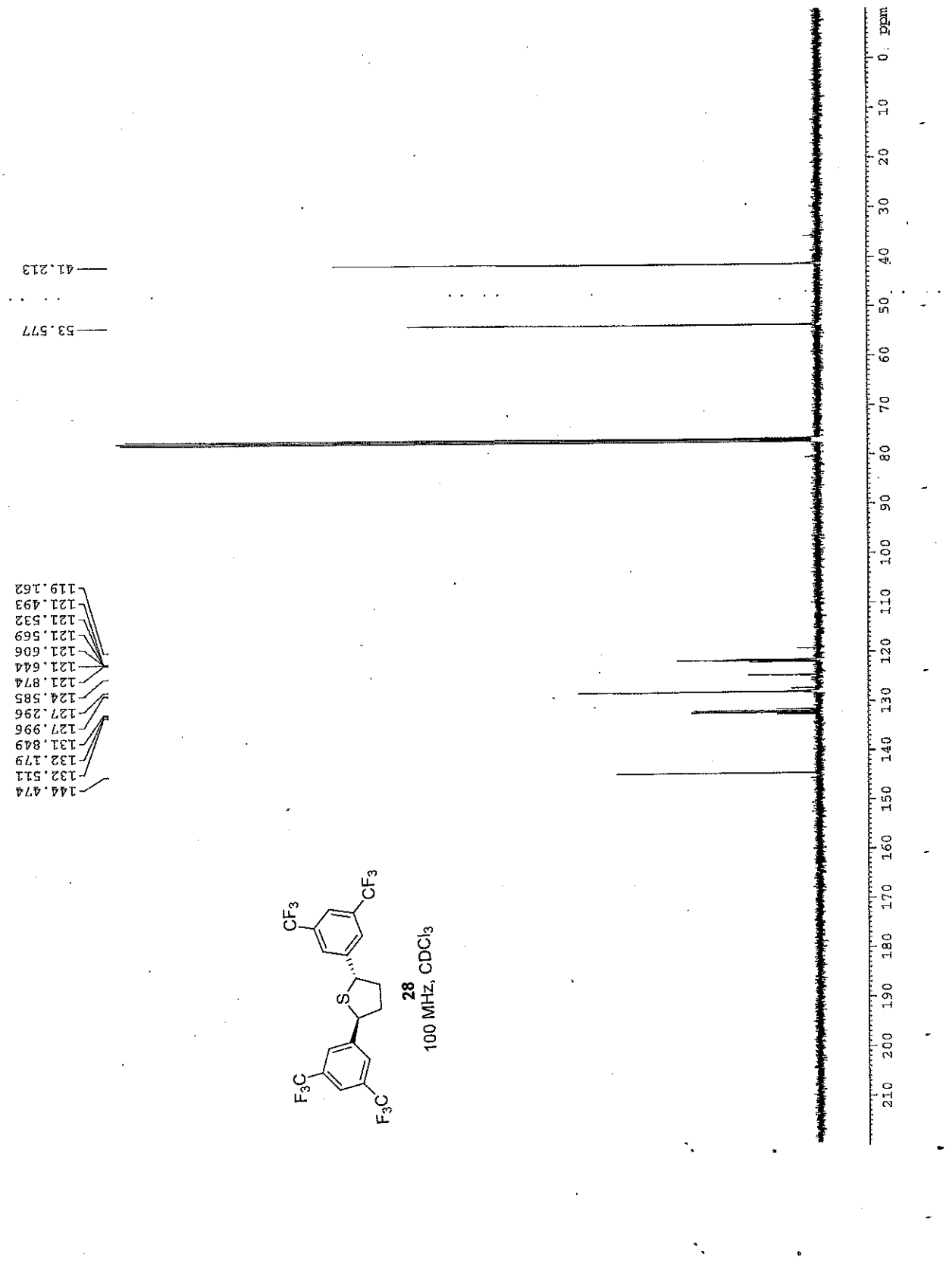
CF3
S
F3C
F3C
28
400 MHz, CDCl3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132.179
132.511
144.474
CF3
CF3
S
F3C
F3C
28
100 MHz, CDCl3
ppm

5/28/2013 10:01:11 1 / 1

2R,5S)-2,5-Bis[3,5-bis(trifluoromethyl)phenyl]tetrahydrothiophen

OD column
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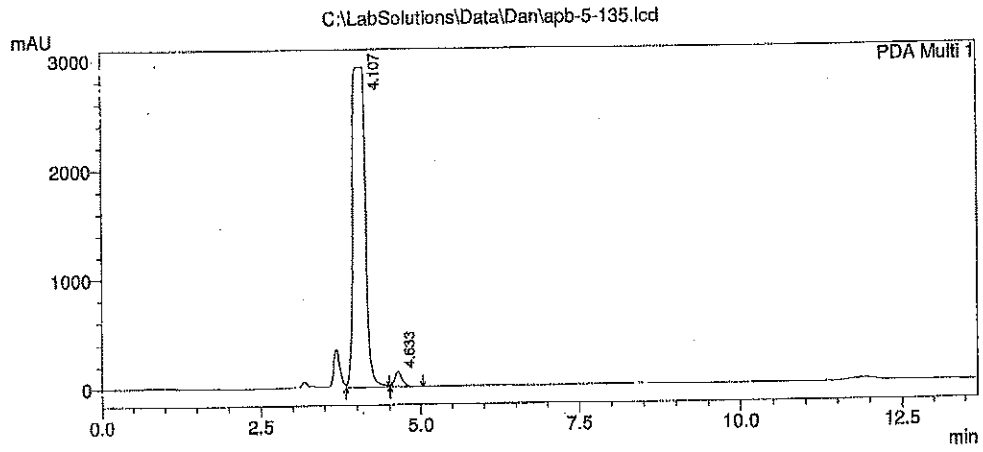
30 oC
200 nm

<Chromatogram>



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5/28/2013 10:09:04 1 / 1

lacemic 2,5-Bis[3,5-bis(trifluoromethyl)phenyl]tetrahydrothiophen

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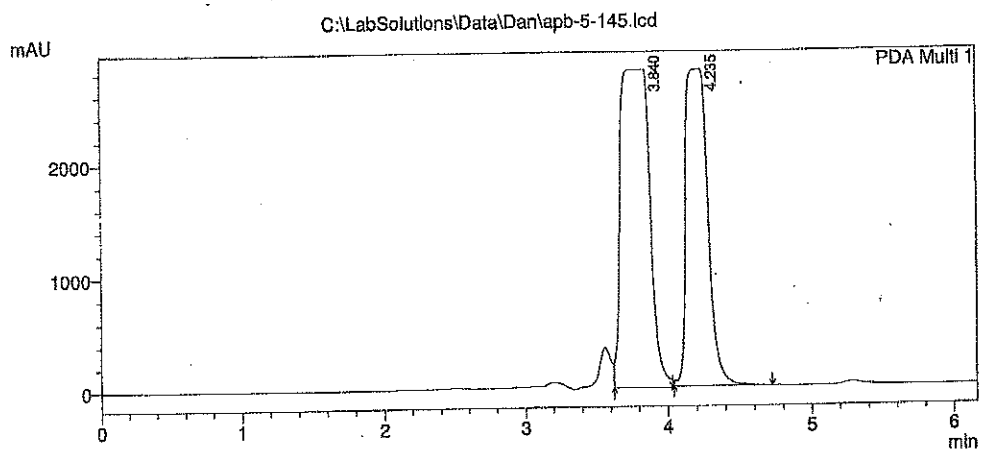
30 oC
200 nm

<Chromatogram>



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PeakTable

PDA Ch1 200nm 4nm

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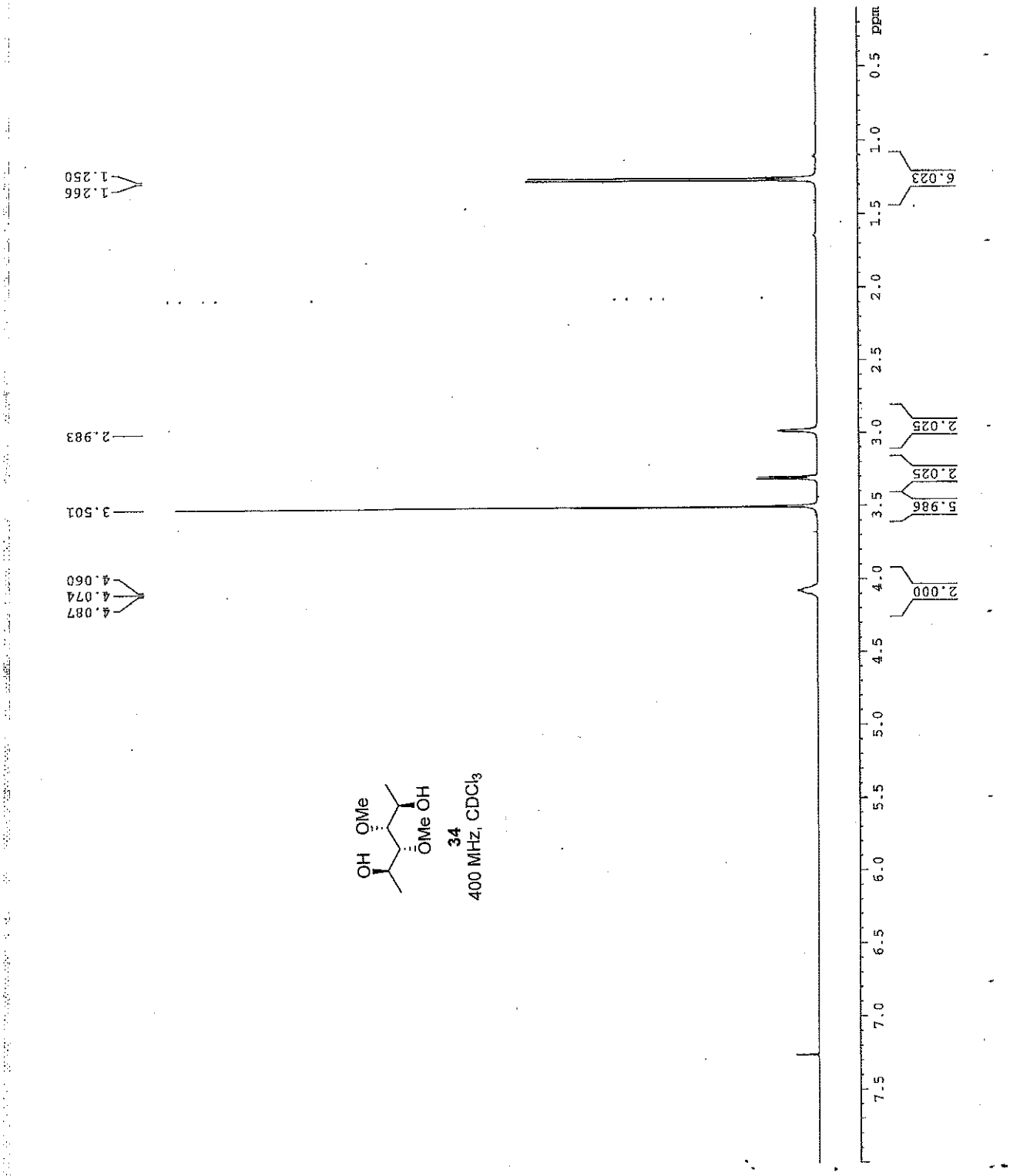
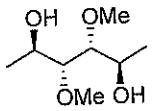
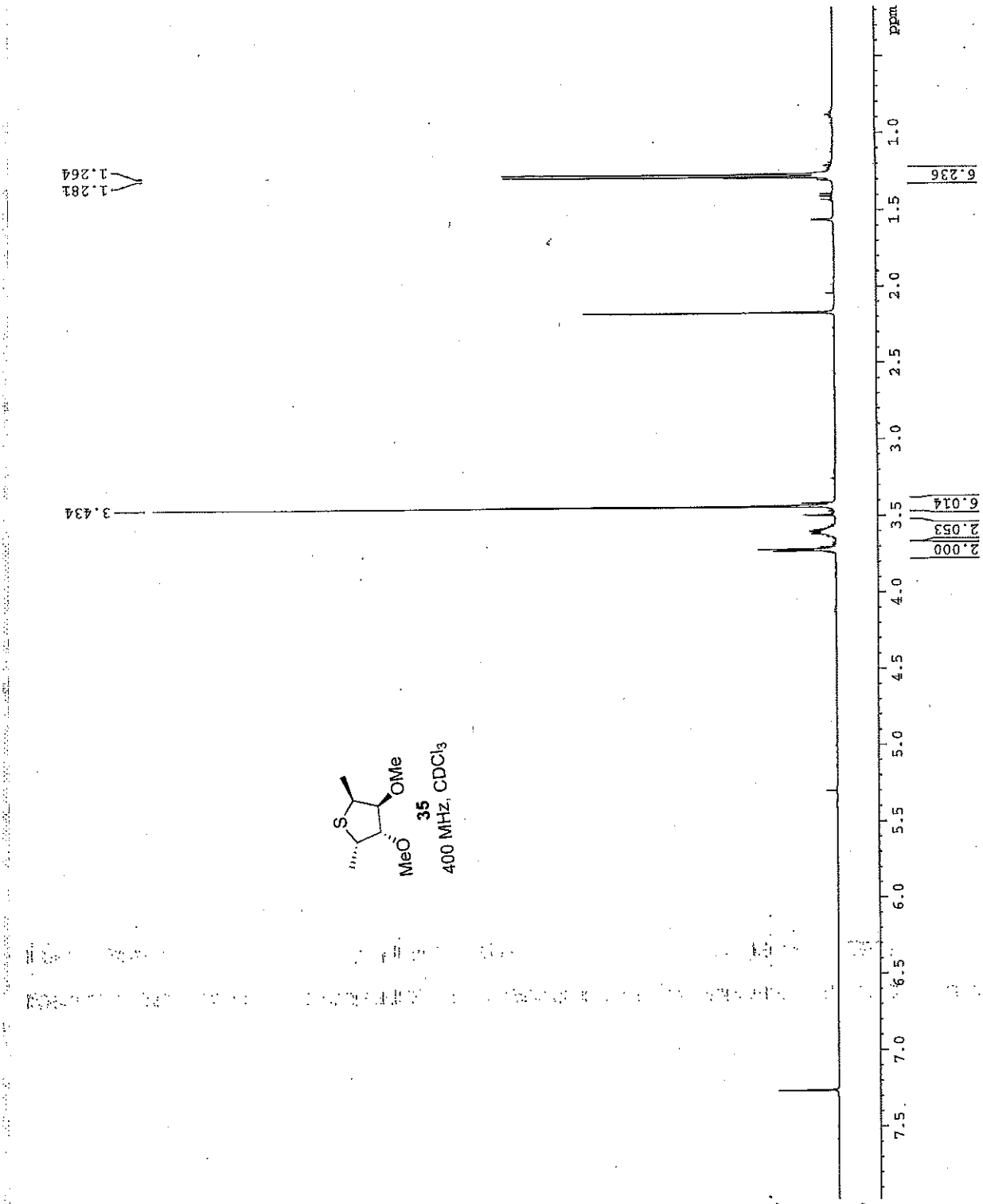
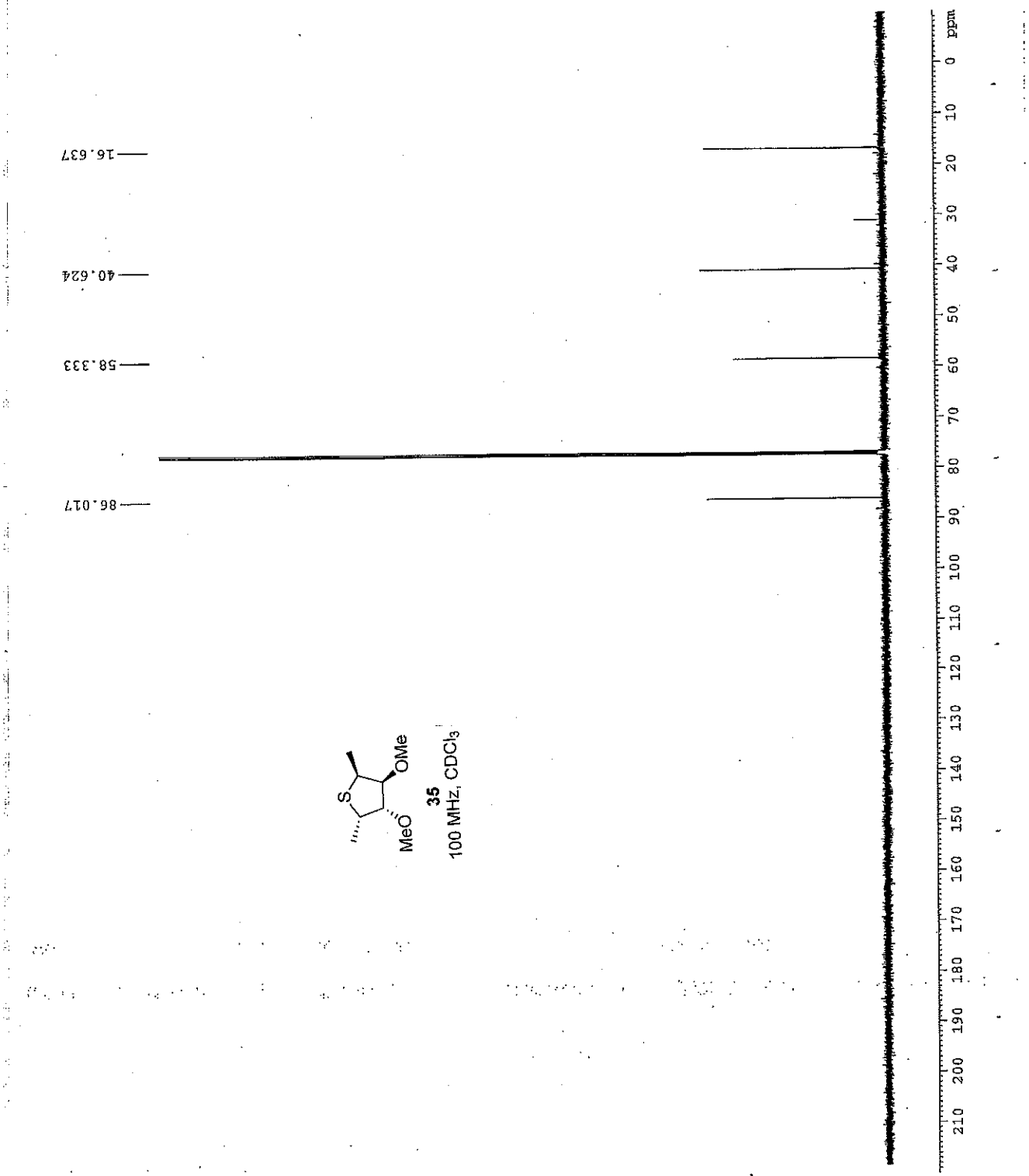
Total		68427185	5606651	100.000	100.000

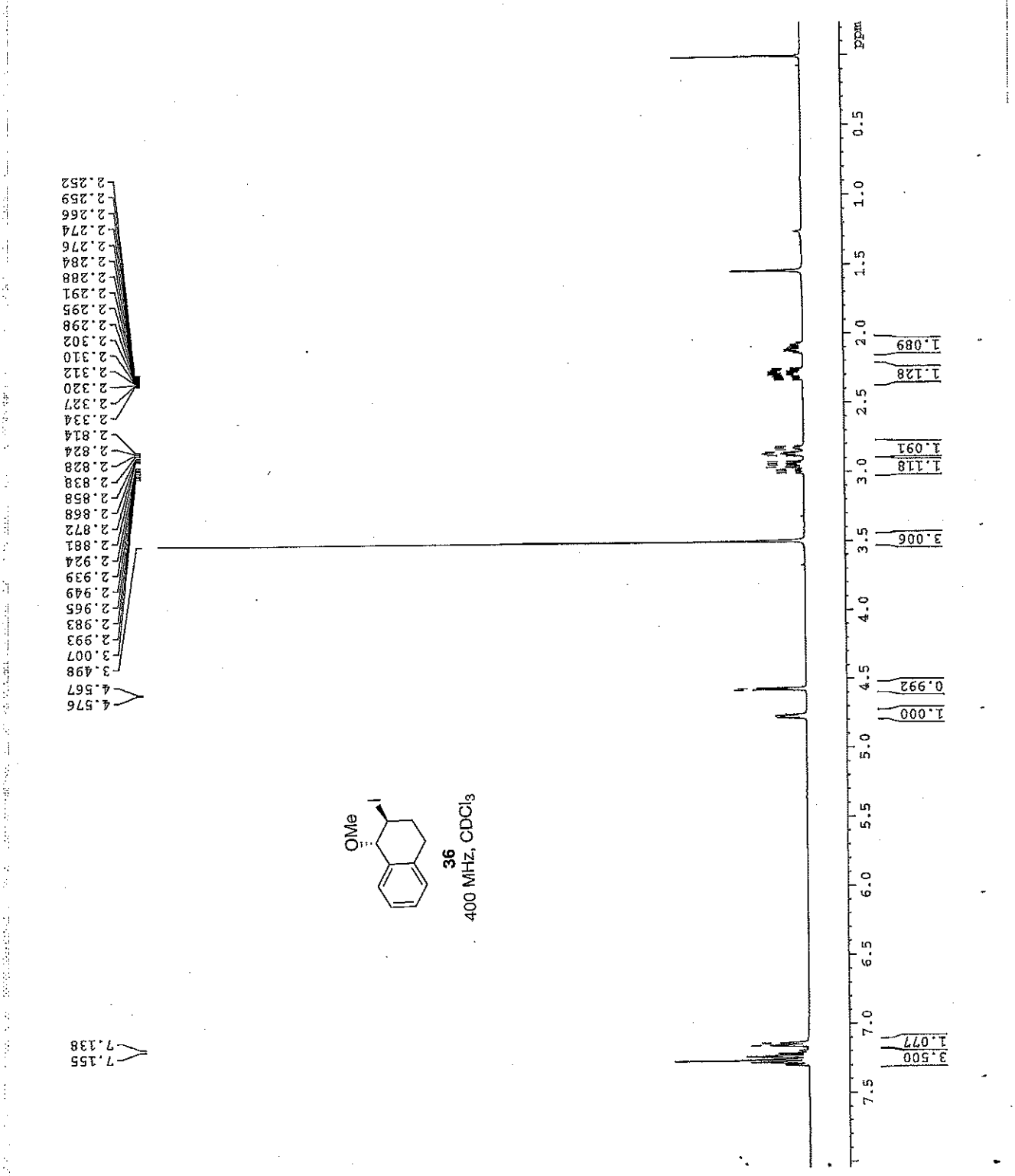

1.250
1.266
2.983
3.501
4.060
4.074
4.087
6.023
2.025
2.025
5.986
2.000
ppm
OH
OMe
OMe
OH
34
400 MHz, CDCl3

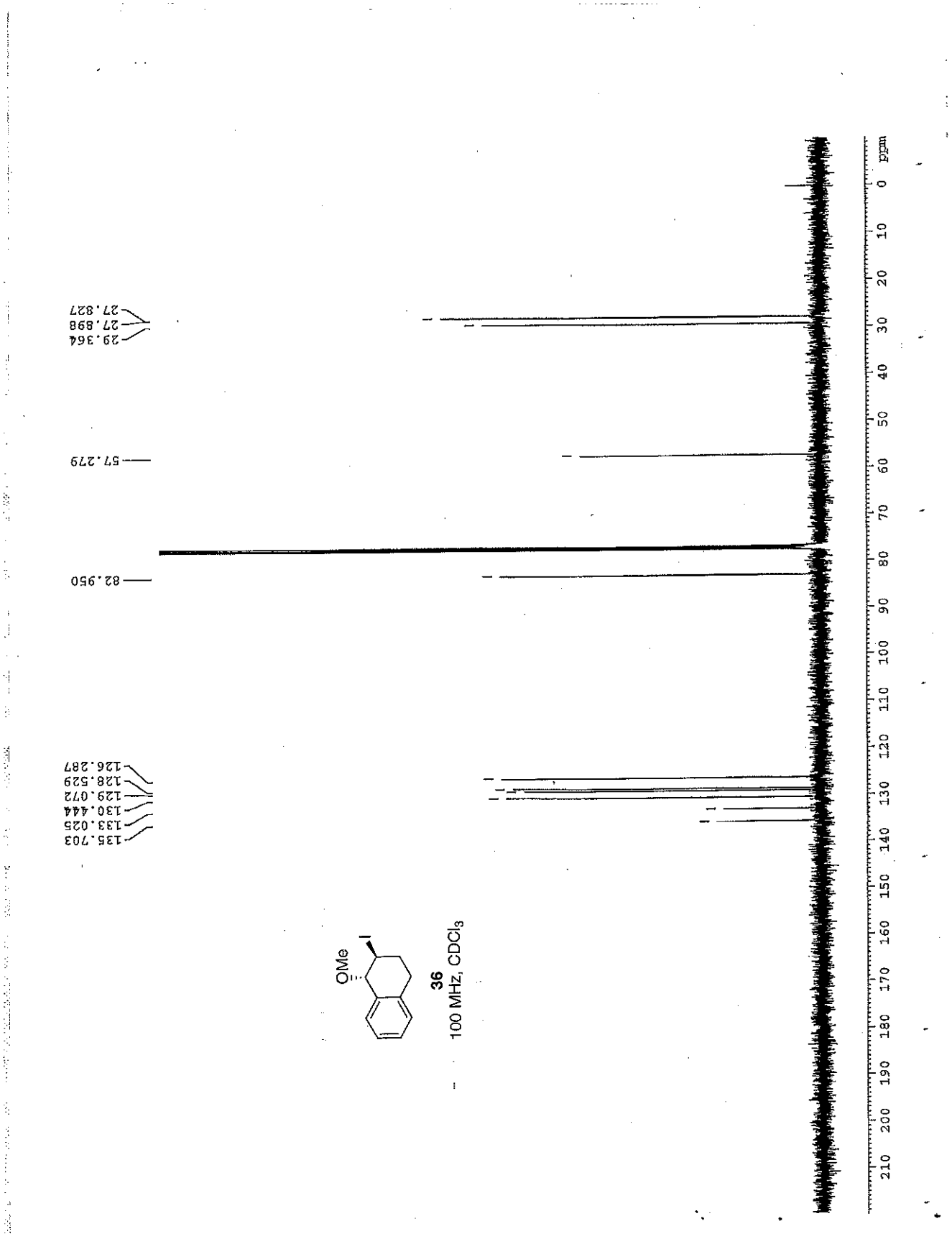


34
100 MHz, $CDCl_3$


35
400 MHz, $CDCl_3$
OMe
MeO
S
1.264
1.281
3.434
6.236
6.014
2.053
2.000
ppm


16.637
40.624
58.333
86.017
MeO
OMe
S
35
100 MHz, CDCl3
ppm


OMe
I
36
400 MHz, CDCl3
ppm
7.155
7.138
4.576
4.567
3.498
3.007
2.993
2.983
2.965
2.949
2.939
2.924
2.881
2.872
2.868
2.858
2.838
2.828
2.824
2.814
2.334
2.327
2.320
2.312
2.310
2.302
2.298
2.295
2.291
2.288
2.284
2.276
2.274
2.266
2.259
2.252
3.500
1.077
1.000
0.992
3.006
1.118
1.091
1.128
1.089

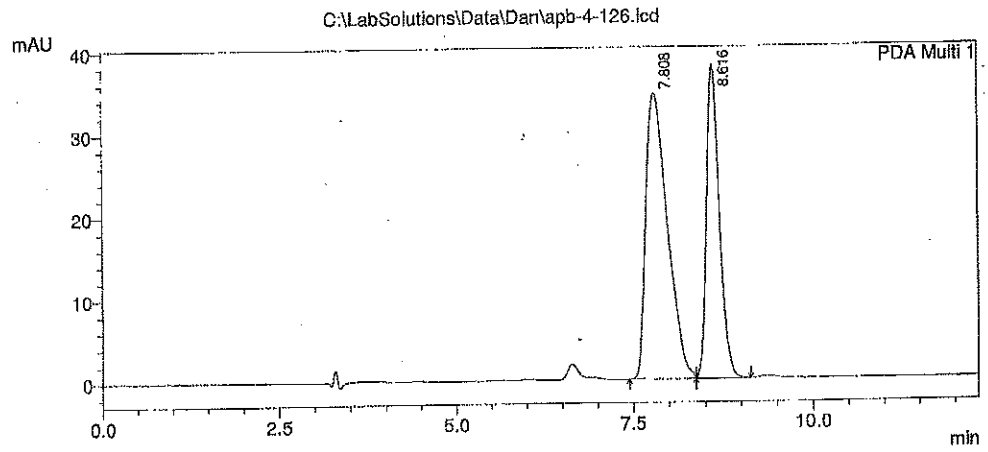

135.703
133.025
130.444
129.072
128.529
126.287
82.950
57.279
29.364
27.898
27.827
OMe
I
36
100 MHz, CDCl3
ppm

5/28/2013 12:11:47 1 / 1

trans-2-Iodo-1-methoxy-1,2,3,4-tetrahydronaphthalene

AD-H column
1.0 mL/min
99:1 hexane:iPrOH
30 oC
263 nm

<Chromatogram>



1 PDA Multi 1/263nm 4nm

PeakTable

PDA Ch1 263nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
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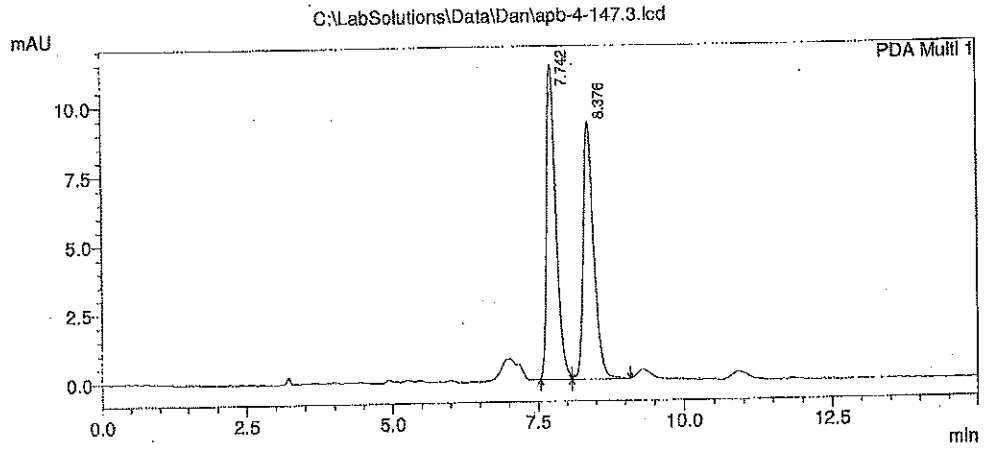
2	8.616	472309	38038	39.701	52.370
Total		1189673	72634	100.000	100.000

5/28/2013 12:10:08 1 / 1

racemic trans-2-Iodo-1-methoxy-1,2,3,4-tetrahydronaphthalene

AD-H column
1.0 mL/min
99:1 hexane:iPrOH
30 oC
263 nm

<Chromatogram>

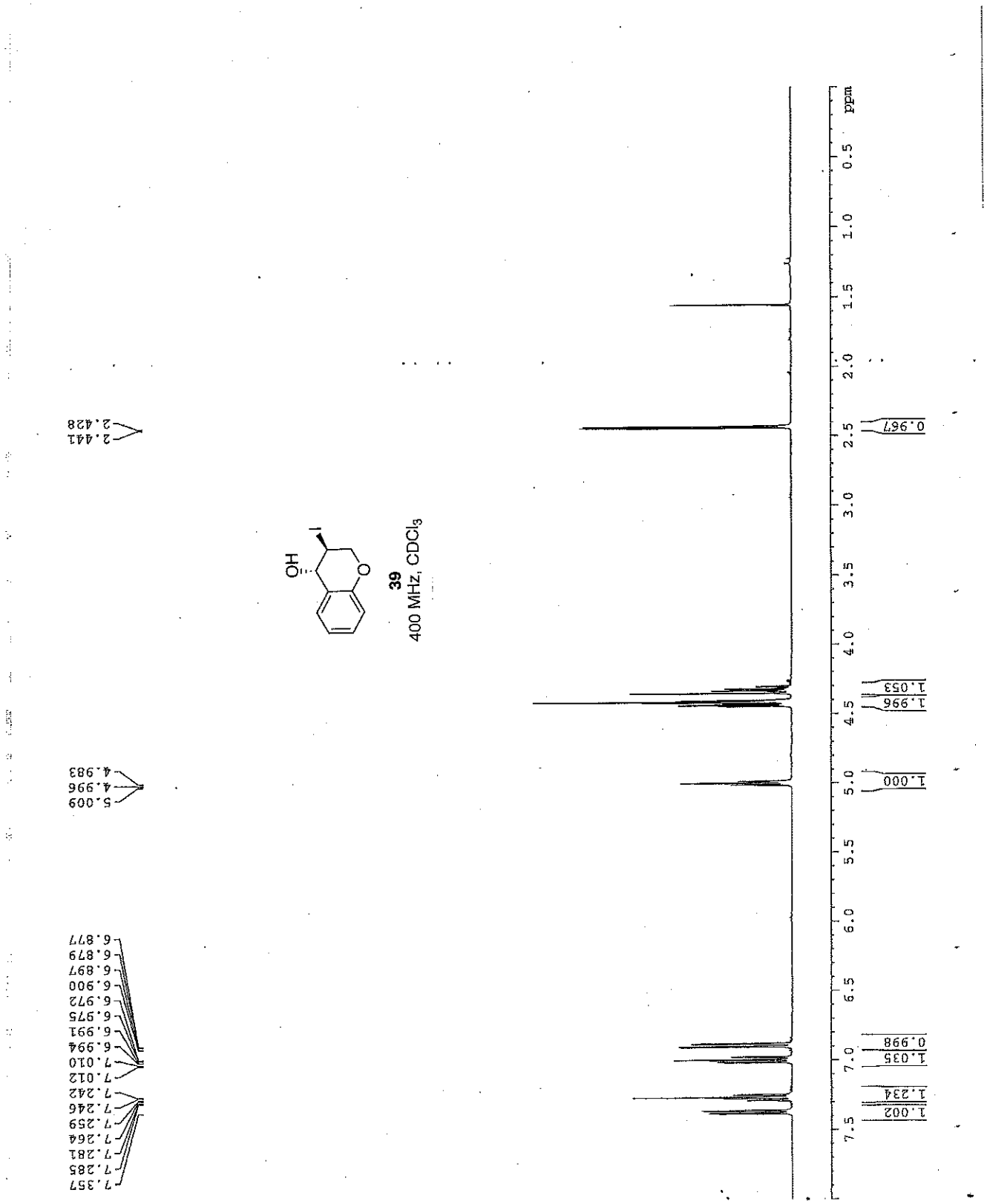


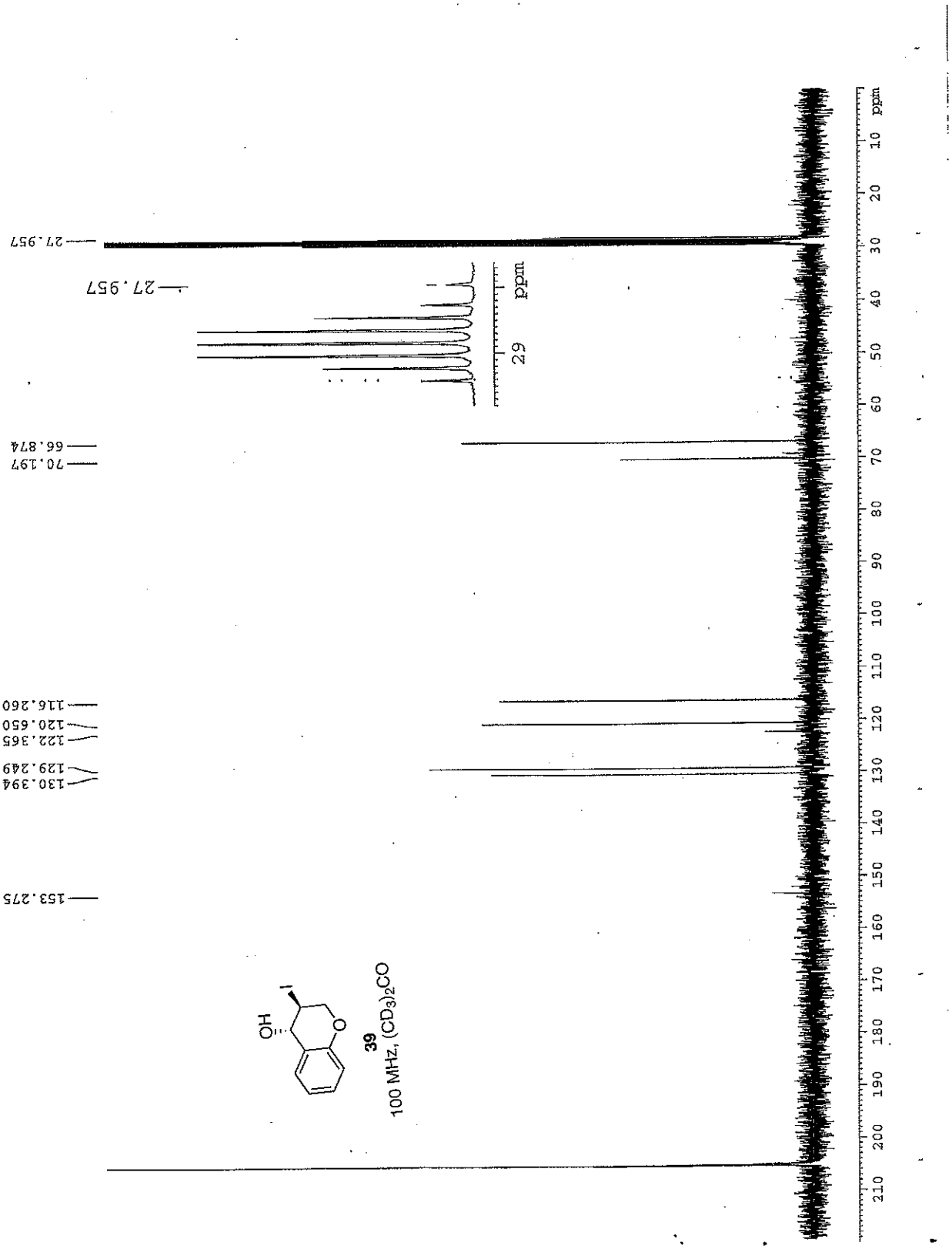
1 PDA Multi 1/263nm 4nm

PeakTable

PDA Ch1 263nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.742	127571	11420	51.895	55.090
2	8.376	118254	9309	48.105	44.910
Total		245825	20729	100.000	100.000


39
400 MHz, CDCl3
OH
I
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
0.967
1.053
1.996
1.000
0.998
1.035
1.234
1.002
2.428
2.441
5.009
4.996
4.983
7.357
7.285
7.281
7.264
7.259
7.246
7.242
7.012
7.010
6.994
6.991
6.975
6.972
6.900
6.897
6.879
6.877

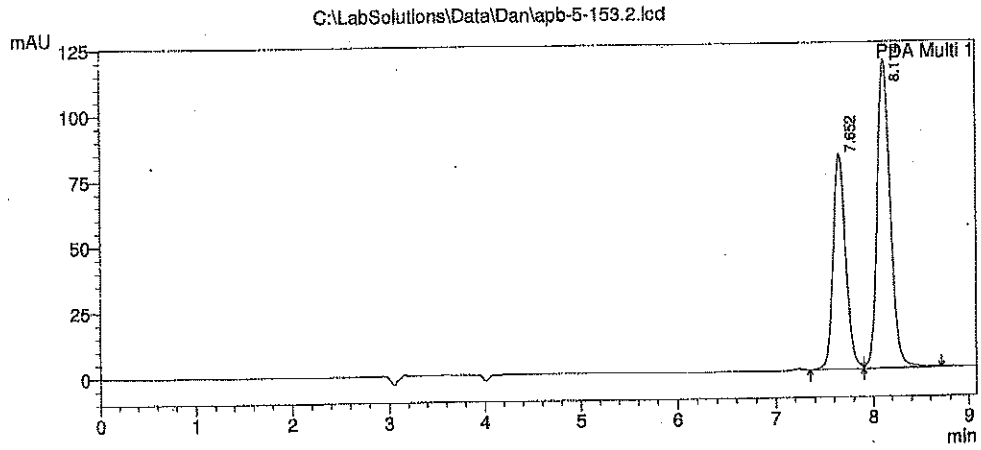

27.957
66.874
70.197
116.260
120.650
122.365
129.249
130.394
153.275
OH
O
39
100 MHz, (CD3)2CO
27.957
29
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
ppm

5/28/2013 10:14:14 1 / 1

trans-3-Iodochroman-4-ol

AD-H column
1.0 mL/min
9:1 hexane:iPrOH
30 oC
280 nm

<Chromatogram>



1 PDA Multi 1/280nm 4nm

PeakTable

PDA Ch1 280nm 4nm

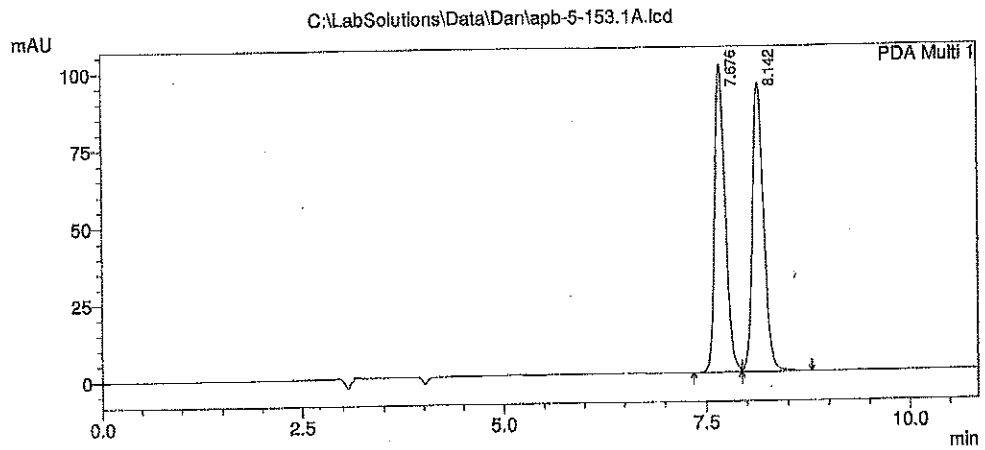
Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.652	731850	82331	39.562	41.149
2	8.114	1118030	117749	60.438	58.851
Total		1849880	200080	100.000	100.000

5/28/2013 10:12:35 1 / 1

Racemic trans-3-Iodochroman-4-ol

AD-H column
1.0 mL/min
9:1 hexane:iPrOH
30 oC
280 nm

<Chromatogram>

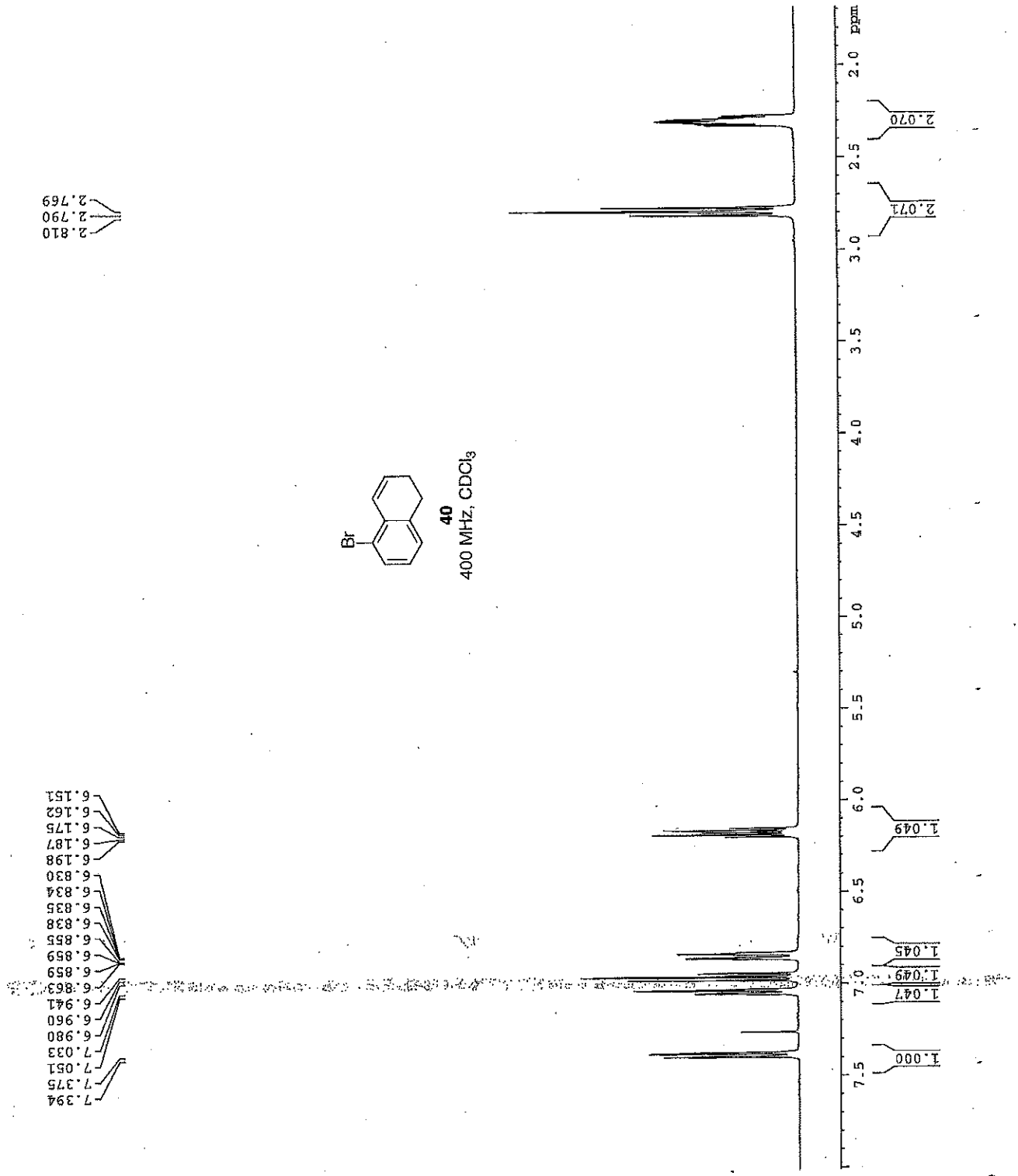


1 PDA Multi 1/280nm 4nm

PeakTable

PDA Ch1 280nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.676	883186	100026	49.839	51.611
2	8.142	888888	93782	50.161	48.389
Total		1772074	193808	100.000	100.000


Br
40
400 MHz, CDCl3
2.769
2.790
2.810
6.151
6.162
6.175
6.187
6.198
6.830
6.834
6.835
6.838
6.855
6.859
6.859
6.863
6.941
6.960
6.980
7.033
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7.375
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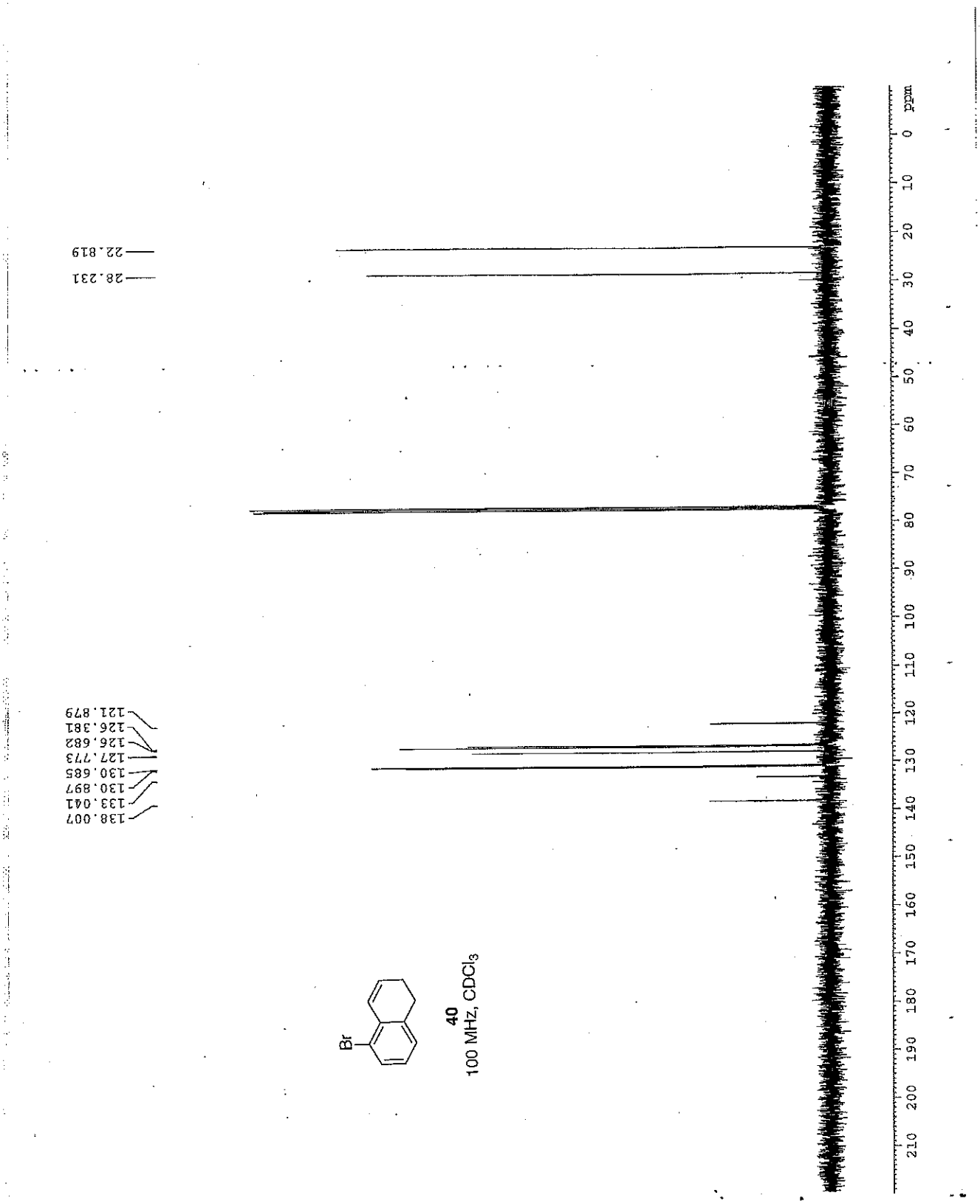
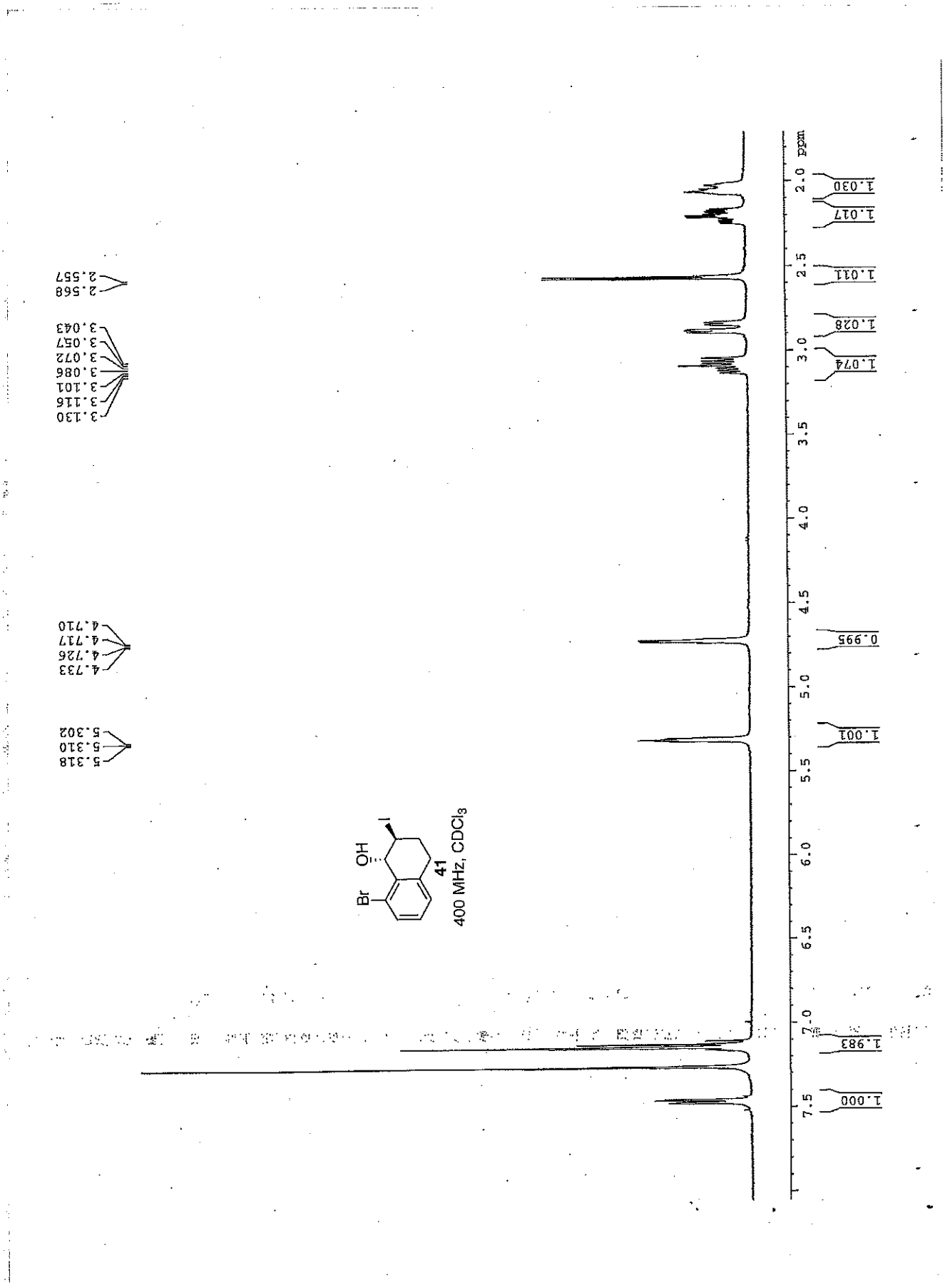
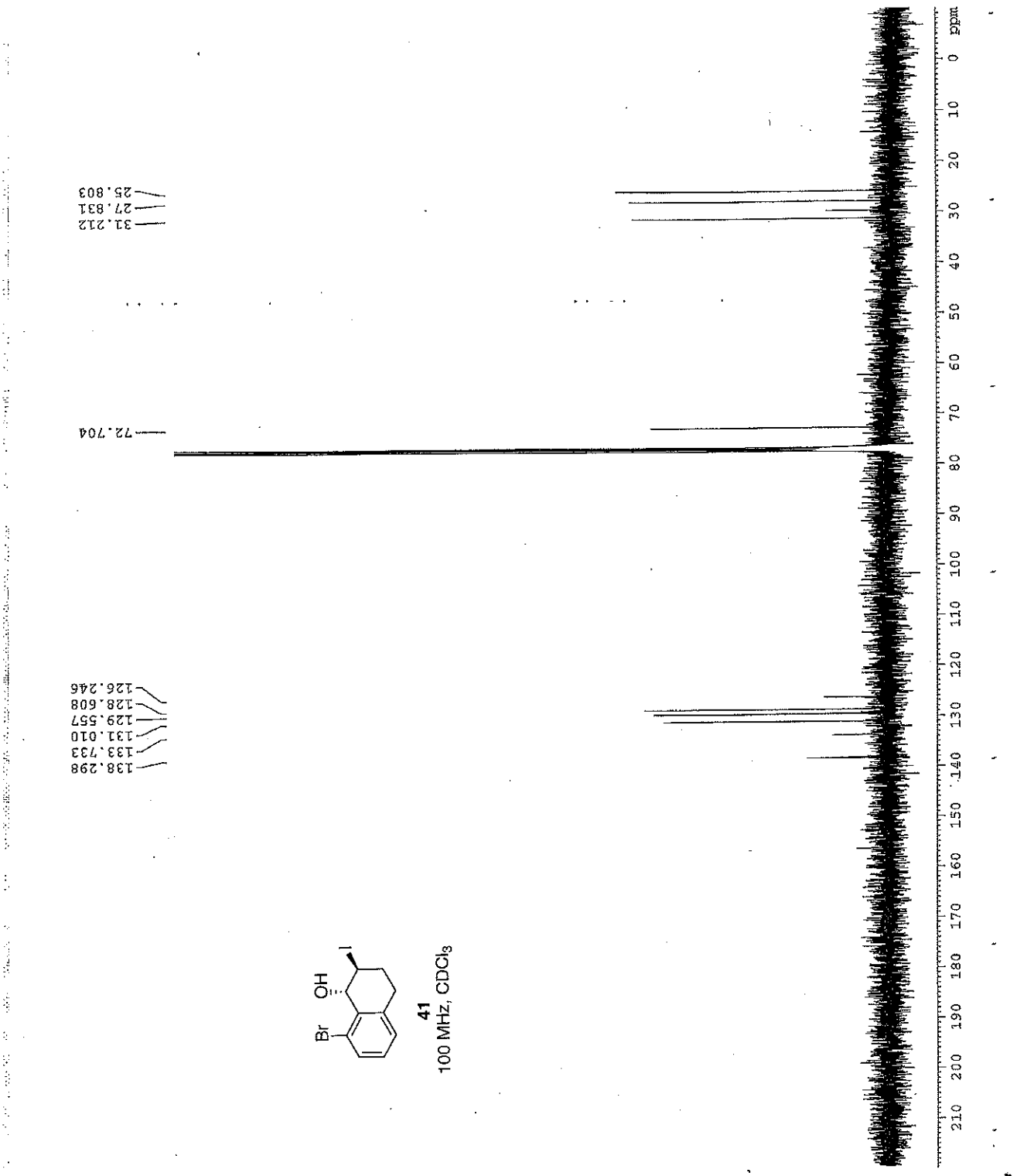
1.049
1.045
1.049
1.047
1.000
ppm


22.819
28.231
121.879
126.381
126.682
127.773
130.685
130.897
133.041
138.007
Br
40
100 MHz, CDCl3
ppm


41
400 MHz, CDCl3
Br
OH
I
2.568
2.557
3.130
3.116
3.101
3.086
3.072
3.057
3.043
4.733
4.726
4.717
4.710
5.318
5.310
5.302
1.030
1.017
1.011
1.028
1.074
0.995
1.001
1.983
1.000
ppm



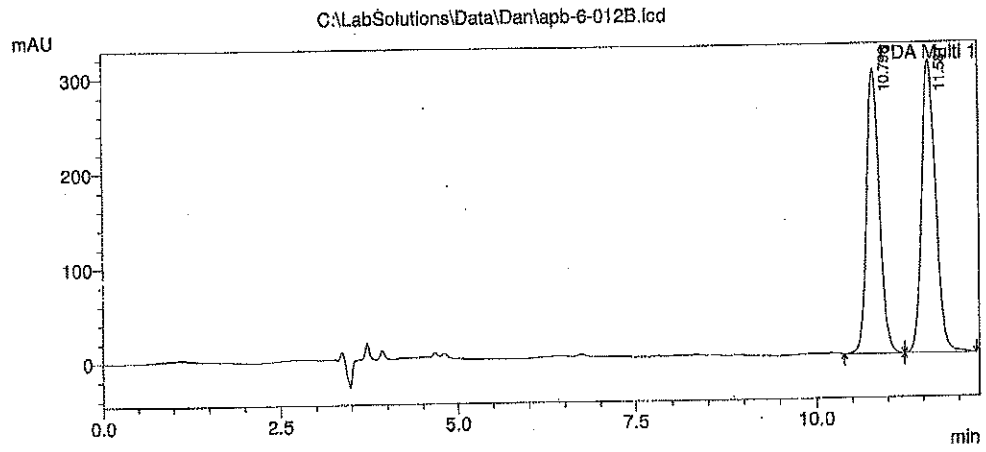
41
100 MHz, $CDCl_3$

5/28/2013 10:58:21 1 / 1

trans-8-Bromo-2-iodo-1,2,3,4-tetrahydronaphthalen-1-ol

AD-H column
1.0 mL/min
9:1 hexane:iPrOH
30 oC
220 nm

<Chromatogram>



1 PDA Multi 1/220nm 4nm

PeakTable

PDA Ch1 220nm 4nm

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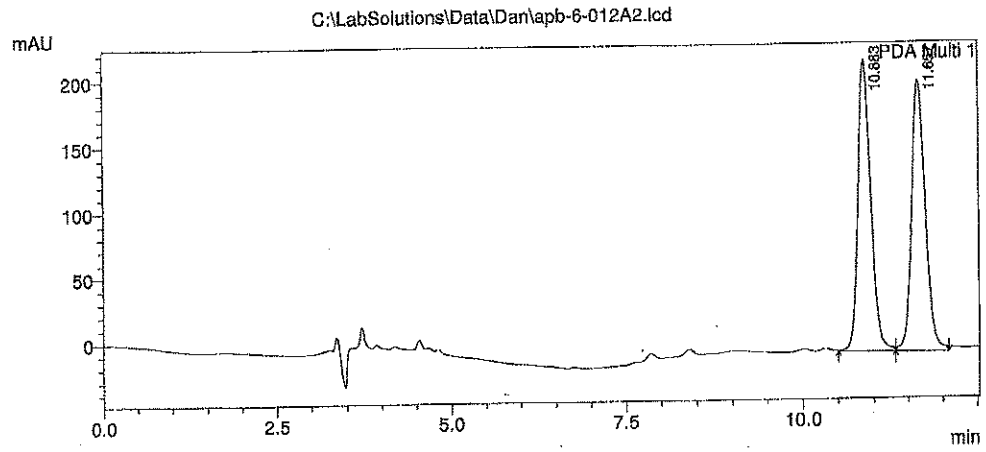
1	10.798	3787021	301404	47.376	49.326
2	11.581	4206576	309641	52.624	50.674
Total		7993597	611045	100.000	100.000

5/28/2013 10:57:06 1 / 1

acemic trans-8-Bromo-2-iodo-1,2,3,4-tetrahydronaphthalen-1-ol

AD-H column
1.0 mL/min
9:1 hexane:iPrOH
30 oC
220 nm

<Chromatogram>

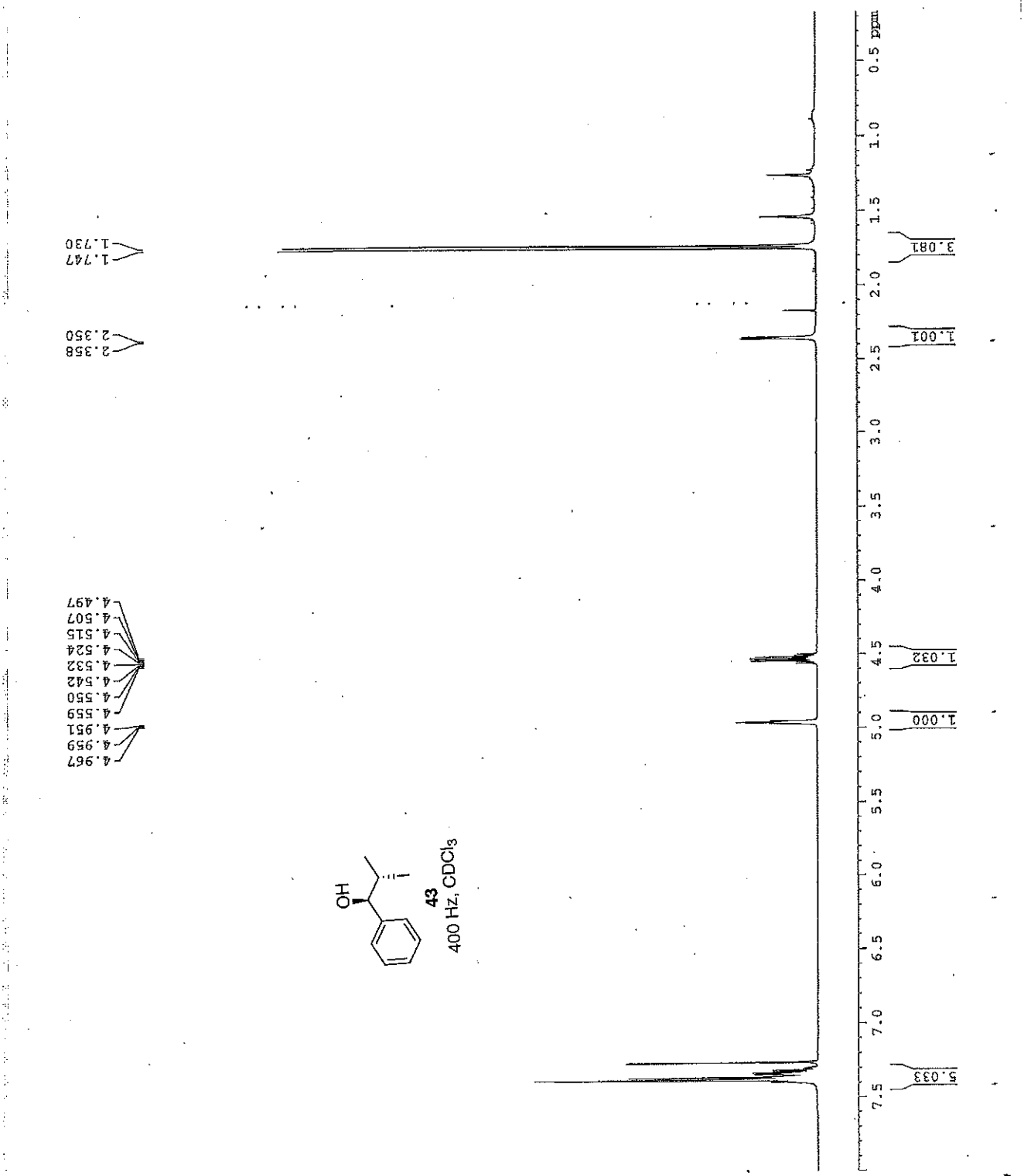


1 PDA Multi 1/220nm 4nm

PeakTable

PDA Ch1 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.883	2823540	222755	49.773	51.774
2	11.657	2849285	207493	50.227	48.226
Total		5672825	430248	100.000	100.000


OH
43
400 Hz, CDCl3
1.730
1.747
2.350
2.358
4.497
4.507
4.515
4.524
4.532
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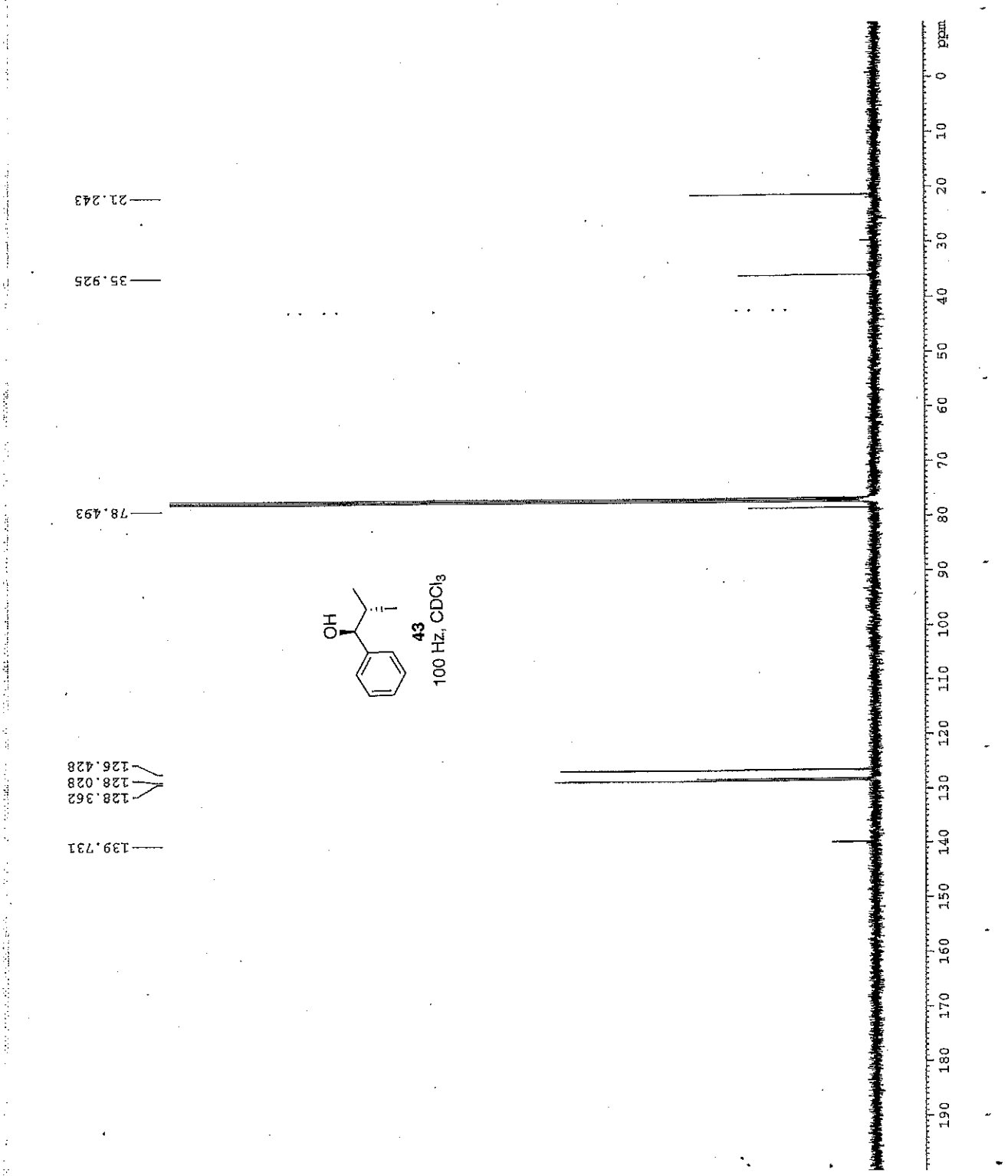
5.033
1.000
1.032
1.001
3.081
ppm

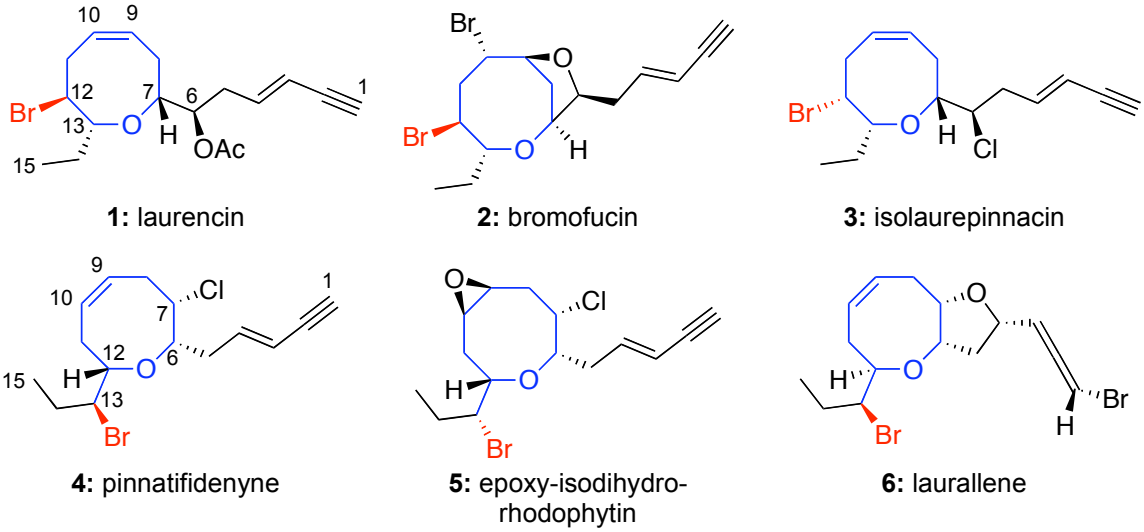

21.243
35.925
78.493
128.362
128.028
128.428
139.731
OH
43
100 Hz, CDCl3
ppm

CHAPTER 4

Discovery and Development of a Bromonium-Induced Ring Expansion to Rapidly Produce *Laurencia* Medium-Sized Bromoethers

4.1 Introduction

The first natural products from the *Laurencia* red algae were isolated in 1965, specifically, when Irie and co-workers discovered and characterized laurencin (**1**).[1] Since then, over 150 members have been isolated in total, all containing a 15 carbon framework that includes an enyne or bromoallene unit at one end.[2] A majority of the isolates also contain a cyclic ether ranging in size between 3 and 12 atoms, with the largest subset of the family containing 8-membered bromoethers. That subset comprises over 50 natural products, a small number of which are drawn in Figure 1.[3] These 8-membered rings encompass both 8-*endo* and 8-*exo* bromoether systems, i.e. ones where the bromine is attached directly to a carbon in the ring (**1**, **2**, or **3**) or a carbon outside of it (**4**, **5**, or **6**). Additionally, this family has also been classified in the literature as the lauroxocane (8-membered ether ring) class, and more specifically as lauthisan-like (8-*endo*) or laurenan-like (8-*exo*) materials based on the positioning of their bromine atoms.[3] Globally, over the past 50 years, the lauroxocanes have attracted a deal of attention, particularly recently, whether it is synthetic efforts as discussed in this chapter[5] or the elucidation of their biosynthesis (a topic we will discuss in depth in Chapter 5).[6]

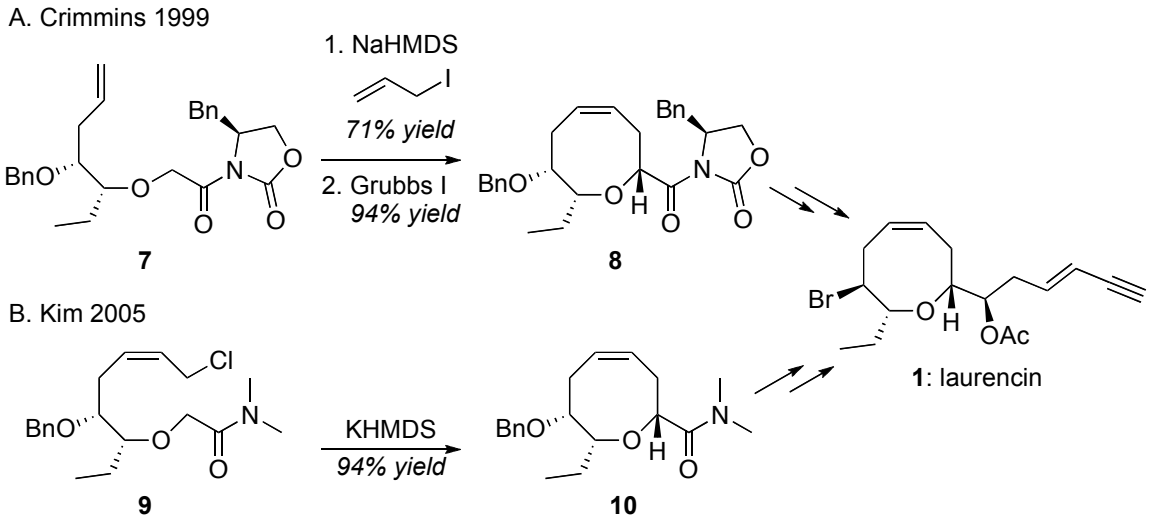


1: laurencin **2:** bromofucin **3:** isolaurepinnacin

4: pinnatifidenyne **5:** epoxy-isodihydro-rhodophytin **6:** laurallene

Figure 1: Selected Natural Products from the *Laurencia* Family

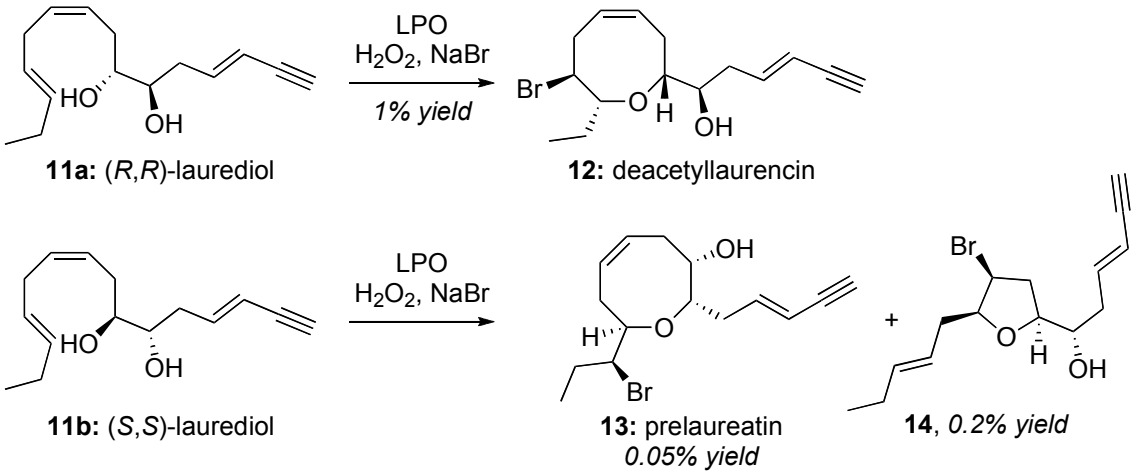
Based on the array of previous total syntheses of these 8-membered bromoethers, reviewed in a detailed fashion by Fujiwara in 2006,[5] there are numerous approaches toward a single target core, but only a small number of solutions capable of achieving a potentially global solution for the diversity of cores found in the family. Using one strategy, Crimmins and co-workers have synthesized six natural products in the class with the key sequence being an aldol reaction/ring closing metathesis to generate the medium-sized ether ring (Scheme 1);[7] targets prepared include 7-, 8-, and 9-membered ring cores, including the natural products laurencin and laurallene (**1** and **6**, Figure 1). As a second example, the Kim group developed an alkylation-based strategy to synthesize multiple natural products with medium-sized bromoether cores, including pinnatifidenyne (**4**) and laurencin (**1**), as shown in Scheme 1b.[8] While both described approaches are impressive in terms of generating a single diastereomer of the desired medium-sized ring in good yields, on average, the complete step count of these (and other) syntheses of the lauroxocane family is 25 linear steps.



Scheme 1: General Strategies of the Crimmins Group and Kim Group

Equally interesting, to note as indicated for the work in Scheme 1 as well as the over 30 additional syntheses of 8-membered bromoethers, every route has installed the bromide atom late stage, typically though displacement of an alcohol;[5] none generate the 8-membered bromoether core directly via a bromoetherification, a strategy which is the original biosynthetic proposal for the formation of these medium-sized rings in Nature. Indeed, Murai and co-workers have studied this idea extensively through use of enzymatic conditions in a laboratory setting.[9] As shown in Scheme 2, (*R*,*R*)-laurediol (**11a**) was transformed into deacyllaurencin (**12**) using lactoperoxidase (LPO) via what is presumed to be a direct 8-*endo* bromoetherification. LPO, the enzyme isolated from the same producing species as these natural products were discovered, in combination with hydrogen peroxide and bromide ion, is known to produce Br_2 or BrOH, species which can serve as the active bromonium source in these proposed transformations.[10] Interestingly, use of the enantiomer, (*S*,*S*)-laurediol (**11b**), led to prelaureatin (**13**)[11], an 8-*exo* bromoether, in 0.05% yield along with 5-membered bromoether **14** in 0.2% yield as the major cyclized product. Whether the enzyme plays a role in stereoselection is

unclear. A larger question, given the poor yields, is whether this direct bromoetherification of a linear precursor to a medium-sized ring is plausible for the biosynthesis of these natural products, even in the confines of an enzymatic pocket, which contains additional factors that could assist to overcome the enthalpic and entropic penalties associated with such a closure.

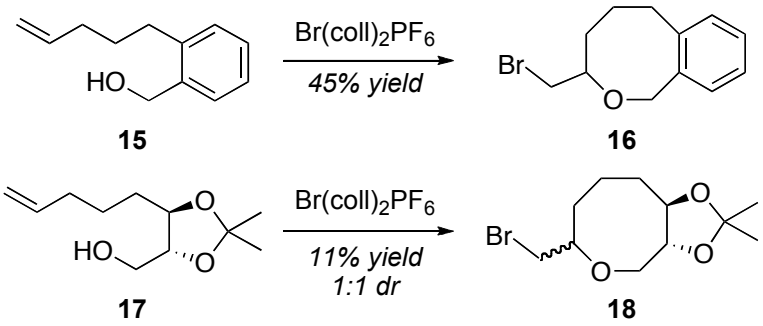


Scheme 2: Muria and Co-workers' Results for Cyclization of Linear Laurediol

Since the direct bromoetherification to generate the 8-membered core of these *Laurencia* isolates had never been attempted in a purely chemical setting (with the exception of enzymatically promoted processes), we hoped to develop a method capable of effecting this direct transformation. Similar to our approach in polyene cyclizations, we wanted to use the proposed biosynthesis to ideally decrease step count, thereby streamlining the synthesis of these medium-sized cyclic bromoethers through a more expediant process. As discussed below, we targeted the lauroxocanes, the largest class as well as the most difficult medium-sized ring to synthesize, as the focus of our efforts.[12]

4.2 Discovery of Ring-Expansion Methodology

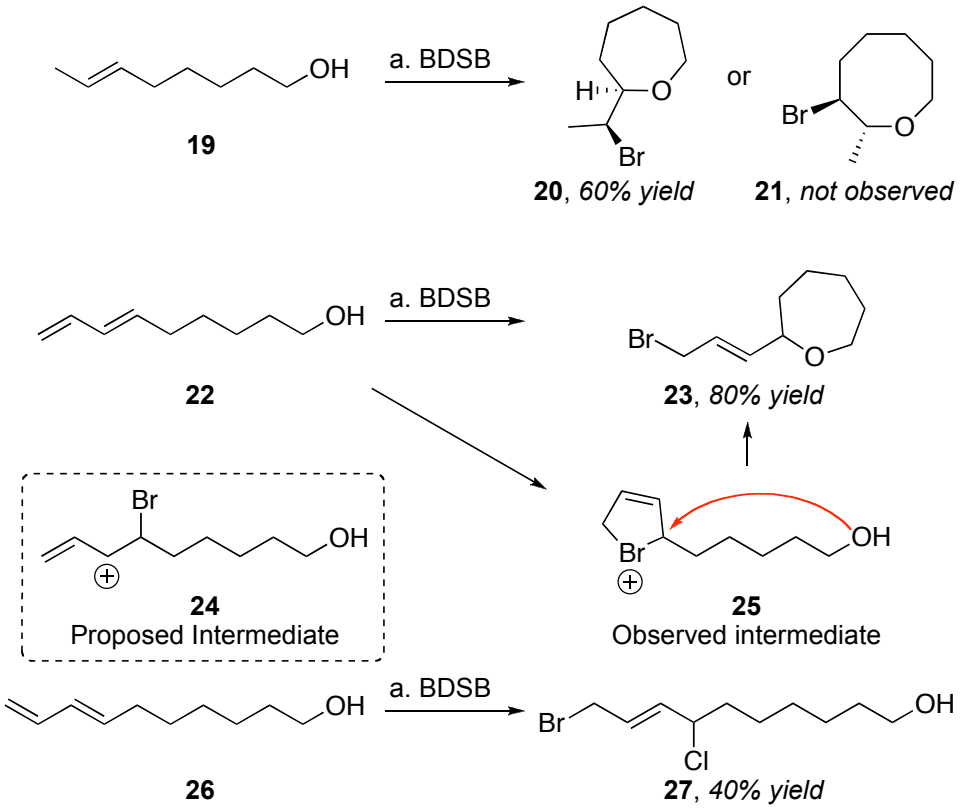
Rousseau and co-workers previously generated cyclic medium-sized bromoethers via bromonium-induced etherifications of linear precursors.[13] As shown in Scheme 3 with some selected examples, treatment of linear precursor **15** with a bis(collidine) bromonium salt yielded 8-*exo* bromoether **16** in 45% yield. Using the same conditions, 8-*exo* bromoether **18** was produced in only 11% yield from **17** with no diastereocontrol about the newly generated stereocenter. Both examples shown produce 8-*exo* bromoethers, with no examples of the 8-*endo* alternative described in this study; additionally, the use of a conformational constraint (i.e. aromatic ring or cyclic ketal) was necessary to generate the desired medium-sized rings. The Rousseau group propose that this requirement is due to a decrease in the activation entropy of the reaction, thereby allowing for greater yields of the bromoethers to be produced in lieu of alternative reaction pathways.



Scheme 3: Rousseau and Co-workers Bromoetherification to Generate Medium Sized Rings

While this report is the only example of using a bromonium source to directly cyclize a linear alcohol precursor to an 8-membered ring, the requirement for such conformational constraint and the observed low levels of diastereoselectivity were discouraging for its potential use in the synthesis of the *Laurencia* bromoethers. Thus, we next turned to our own bromonium reagent, BDSB, hoping its unique reactivity would

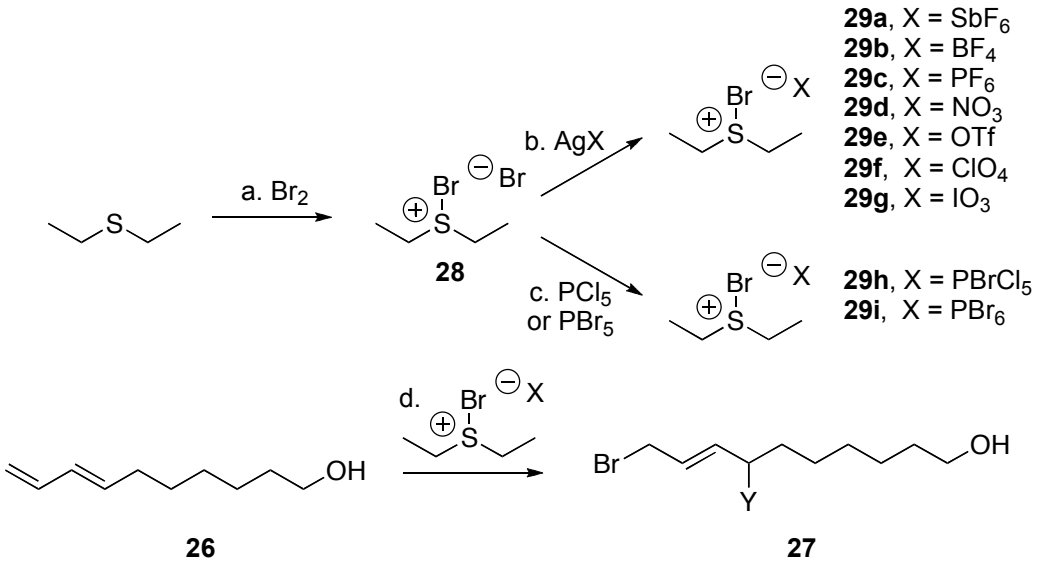
be capable of effecting the desired transformation without some of the same substrate requirements and issues of diastereocontrol. As shown in Scheme 4, initial tests through cyclization of linear alcohol **19** with BDSB yielded the 7-*exo* bromoether **20** in 60% yield without any trace of the alternative 8-*endo* bromoether **21** observed. Next, in an attempt to favor 8-membered ring formation via added stabilization through an allylic carbocation intermediate (i.e. **24**), substrate **22** was synthesized and again treated with BDSB. In this case, only 7-membered allylic bromide **23** was obtained in 80% yield. Mechanistically, this reaction most likely generated a 5-membered bromonium intermediate (**25**)[14] that underwent simple displacement to the final 7-membered ether (**23**). Since 7-membered rings are easier to produce than any medium-sized ring,[12] we then elongated the chain to potentially disallow this process. Thus, compound **26** was synthesized and then treated with BDSB; here, however, only bromochloride **27** was produced with no ring formation observed. In this case, because the direct generation of the 8-membered ring is energetically disfavored, we surmise that intermolecular attack by a chloride (likely from the $SbCl_6^-$ counterion) was a faster and more favorable process.



Reagents and Conditions: a. BDSB (1.1 equiv), $MeNO_2$, -25°C, 15 min.

Scheme 4: Attempts at Cyclization of a Linear Precursor Using BDSB

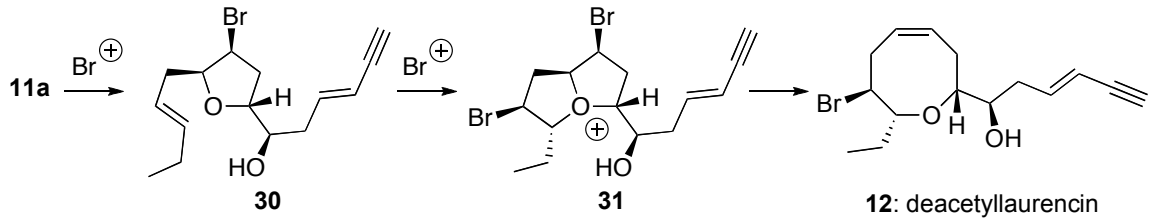
In an attempt to avoid the observed intermolecular chloride addition, we then wondered if better sequestration of the chloride nucleophile could favor intramolecular cyclization. Such a switching of the $SbCl_6^-$ ion for an alternate counterion was performed either by the addition of a silver (I) salt or a Lewis base to the initially generated bromodiethylsulfonium bromide (**28**, Scheme 5). Out of the numerous variations attempted, only **29h** and **29i** proved to be isolable solids; all the other derivatives were generated *in situ* prior to evaluation. However, even with these alternative stabilizing anions, no intramolecular cyclization to a medium-sized ring was detected for any linear precursor probed; typically, addition of a halide from the counterion or decomposition was observed instead.



Reagents and Conditions: a. Et_2S (1.0 equiv), Br_2 (1.1 equiv), CH_2Cl_2, -30°C, 10 min; b. AgX (1.2 equiv), -30 to 25°C, 30 min; c. PCl_5 (1.2 equiv) or PBr_5 (1.2 equiv), -30 to 25°C, 30 min; d. **29a-i** (1.6 equiv), $MeNO_2$, -25°C, 15 min.

Scheme 5: Attempts at Alternate Counterion Cyclization

Since all of these efforts to achieve a direct bromoetherification to form medium-sized rings from a linear precursor were unsuccessful, we re-examined the precedent from Murai and co-workers using enzymes, the only successful attempt at this transformation (albeit in only trace yield, Scheme 2).[9] Upon further analysis, we noted that the major cyclized product in each case was a 5-membered bromoether. This discovery led us to wonder whether this type of compound could actually be an intermediate en route to the larger 8-membered ethers of the family. In particular, we believed that this idea could have biogenetic merit since it is both thermodynamically and kinetically more favorable in general to generate 5-membered rings over the 8-membered alternative.

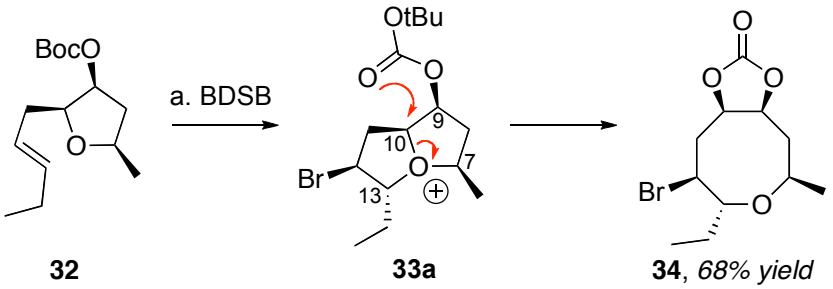


Scheme 6: Hypothesis on Generation of 8-Membered Bromoethers via Two 5-Membered Cyclizations

Scheme 6 presents our new proposal on the biogenesis of these natural isolates based on 5-membered ring formation. As shown, instead of the unfavorable, direct 8-membered bromoetherification, what if an initial 5-*endo* bromoetherification occurred to generate **30**? Then, treatment with a second equivalent of a bromonium electrophile and nucleophilic attack from the tetrahydrofuran oxygen could produce bicycle **31**,[15] an intermediate that upon opening at C10 (via loss of a bromonium from C9) could yield deacyllaurencin (**12**). While the direct loss of a bromine atom is not a common idea in a laboratory setting, in nature perhaps a residual cysteine or the metal center of the enzyme itself could accept this electrophile. Globally though, we quickly realized that this overall idea of ring expansion via a series of smaller ring forming events could lead to a variety of different 7-, 8-, and 9-membered isolates from the *Laurencia* family. This biosynthetic hypothesis will be further discussed in Chapter 5, including synthetic results to confirm these proposed intermediates.

With initial explorations to achieve this goal completed in work that will not be shown here (see Dr. Daniel Treitler's Ph.D. thesis),[16] we learned that in order to open the proposed oxonium (**31**) at C10, a trapping group needed to be installed at C9 to facilitate the production of the desired 8-membered ring.[17,18] Without this intramolecular trapping group, opening at the C7 or C13 of **31** was observed instead to form new tetrahydrofuran derivatives. Thus, as the key initial successful experiment, tetrahydrofuran **32** containing

a *tert*-butyl carbonate instead of a free C9 alcohol was synthesized (to be described in Section 4.3, Scheme 7). Upon treatment of **32** with 1.5 equivalents of BDSB in $MeNO_2$ for 20 min, the desired 8-*endo* bromoether **34** was observed in 68% yield. We propose that the desired product was generated via oxonium intermediate **33a**, derived from a 5-*endo* bromocyclization of starting tetrahydrofuran **32**.

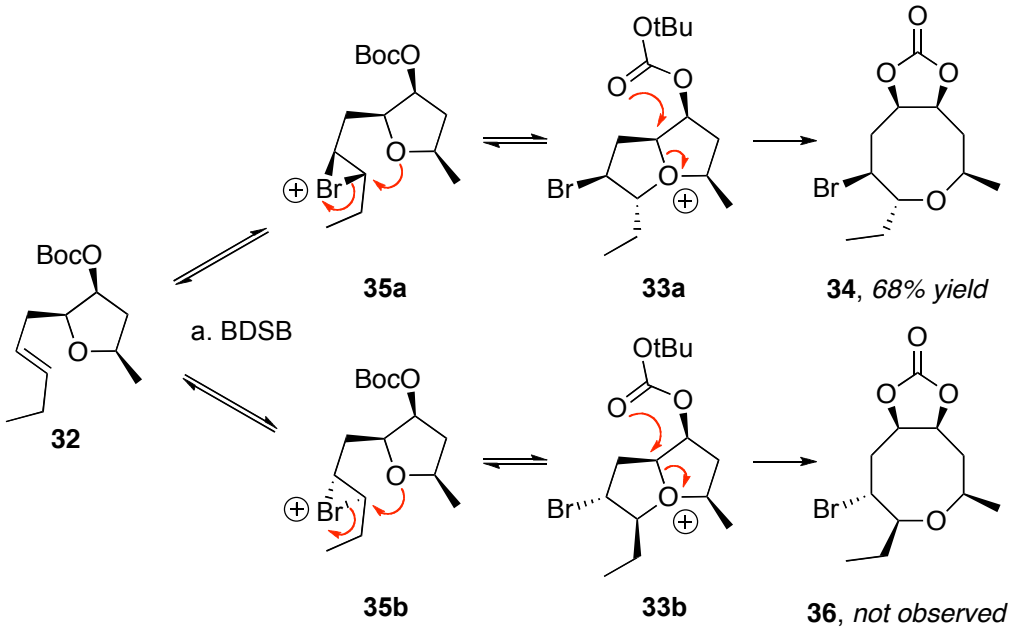


32 **33a** **34**, *68% yield*

Reagents and Conditions: a. BDSB (1.5 equiv), $MeNO_2$, -25 to 25°C, 20 min.

Scheme 7: First Formation of an 8-Membered Ring

Upon further consideration, however, it was remarkable that only a single diastereomer of the 8-membered ring was generated in this reaction. This observed selectivity could be derived from either a) an initial diastereoselective bromonium generation or b) a reversible process that favors an intermediate on the path to the observed diastereomer. We believe the stereochemistry of the tetrahydrofuran is far enough removed from the alkene to not favor bromonium formation on only a single face of the olefin, so that both bromonium intermediates are being produced (i.e. **35a** and **35b**, Scheme 8). Yet these two generated bromonium intermediates should be in equilibrium through bromonium transfer to unreacted alkenes, a feature we believe could make the overall process reversible.[19] From **35a** and **35b**, nucleophilic attack with the tetrahydrofuran oxygen would yield oxoniums **33a** and **33b**, followed by opening with the pendent carbonate to give 8-*endo* products **34** and/or **36**.[20]



Reagents and Conditions: a. BDSB (1.5 equiv), $MeNO_2$, -25 to 25°C, 20 min.

Scheme 8: Mechanism for Formation of a Single Diastereomer of 8-*endo* Bromoether **34**

If both bromonium diastereomers (**35a** and **35b**) are indeed formed, then one of the intermediates must be favored on a single product-determining pathway in this reversible process. We propose that oxoniums **33a** and **33b** have a large energy difference, which upon analysis of the side view becomes more apparent (Figure 2). Opening of **33a** produced the observed product, an intermediate we believe is favored over alternative **33b**. Here, steric repulsion between the ethyl and methyl groups on the concave face of **33b** is disfavored, funneling material overall to the less sterically encumbered oxonium **33a**, where the ethyl substituent is located on the less hindered convex face.

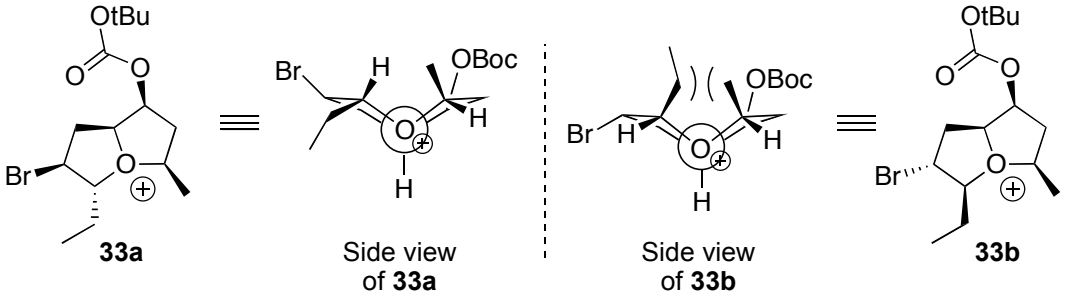


Figure 2: Analysis of Intermediates **33a** and **b**

With the ring expansion of the tetrahydrofuran into an 8-membered bromoether achieved diastereoselectively, we hoped this approach would translate to other derivatives. If so, it could allow for the synthesis of a variety of *Laurencia* natural product cores, including the 8-*exo* alternatives. Quite interestingly, the synthesized 8-*endo* **34** correlates stereochemically to at least five natural isolates from the *Laurencia* family, including bromofucin (**2**, Figure 1 is shown again on the next page with a different emphasis). Upon comparison of 8-*endo* bromoethers **1**, **2**, and **3**, we realized that multiple diastereomers of each bromoether core would need to be synthesized as the relationship between the three stereocenters containing the bromide (C12) and both sides of the cyclic ether (C7 and C13) differ in these examples. A similar pattern of variability is observed in the 8-*exo* examples (i.e. **4**, **5**, and **6**) with C6, C12, and C13 differing stereochemically. Our goal was to install these three stereocenters in the correct orientation in the cyclization itself, as attempts to vary them late stage in the synthesis would most likely be a lengthy process; thus, since the bromonium-induced ring expansion developed is diastereoselective, the starting tetrahydrofuran stereochemistry would need to be altered to provide the correct diastereomer of each 8-membered ring. The following section will discuss the selective synthesis of each diastereomeric tetrahydrofuran starting material needed for a general appraoch. After which, Section 4.4

will then analyze their use in generating laurosocane cores which specifically correlate to the *Laurencia* natural isolates.

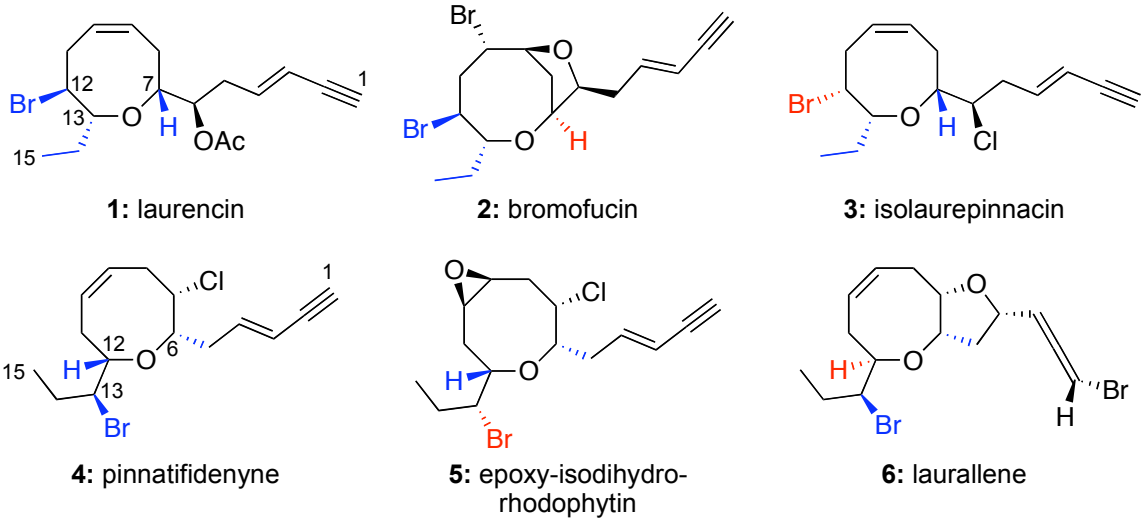
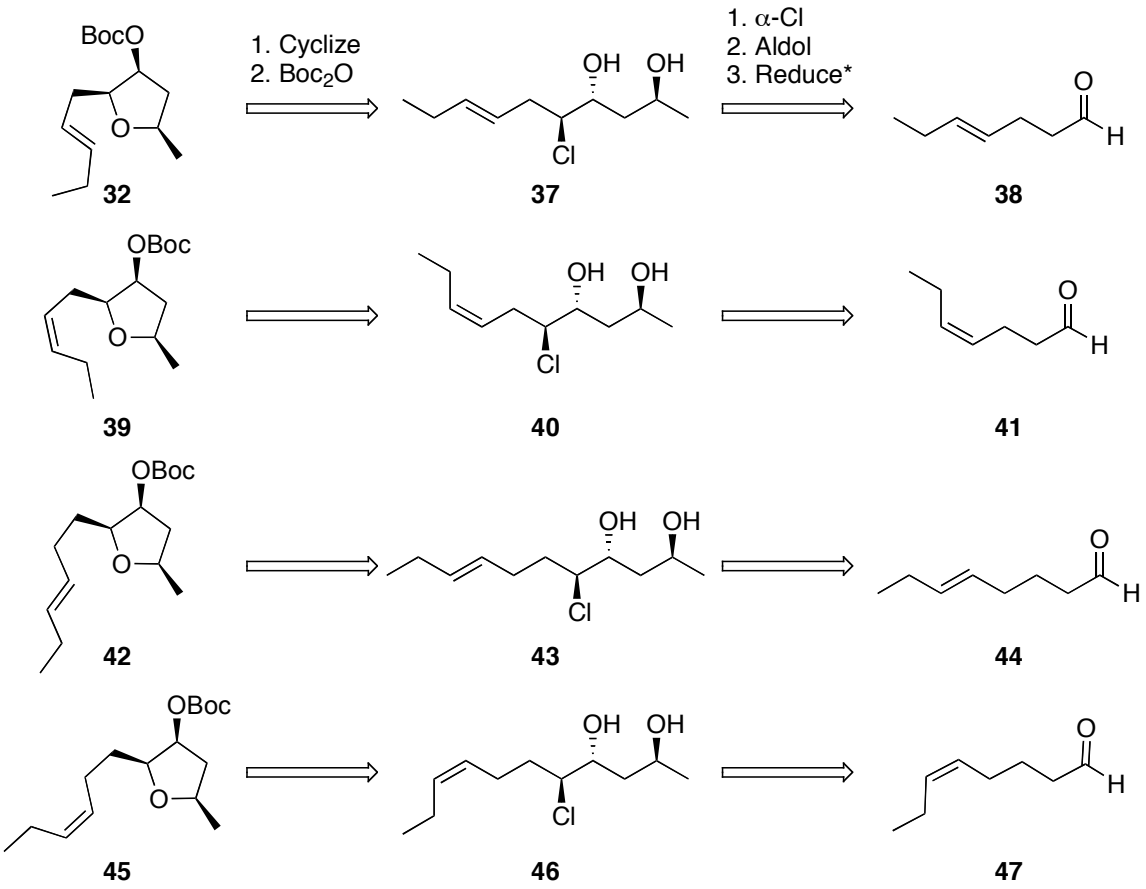


Figure 1: Selected Natural Products Highlighting the Stereochemical Differences

4.3 Synthesis of Tetrahydrofuran Precursors

As discussed earlier, a variety of diastereomeric tetrahydrofurans needed to be synthesized selectively (work done in collaboration with undergraduate Ioana Moga). In terms of the previously utilized tetrahydrofuran starting material **32**, cyclization and *tert*-butyl carbonate formation of **37** led to the desired compound (Scheme 9). Diol **37** could be accessed from a three step route of α-chlorination, an aldol (with the enolate of acetone), and reduction to the *trans*-diol starting from aldehyde **38**. This overall synthetic sequence was first developed by Britton and co-workers for the synthesis of a varied tetrahydrofuran.[21] For additional analogs, adjustment of the starting aldehyde chain length and/or stereochemistry of alkene would be needed (i.e. **38**, **41**, **44**, and **47**). In this fashion we hoped that the same sequence, could lead to multiple tetrahydrofuran derivatives (i.e. **32**, **39**, **42**, and **45**). In addition, the starred ketone reduction (Step 3)

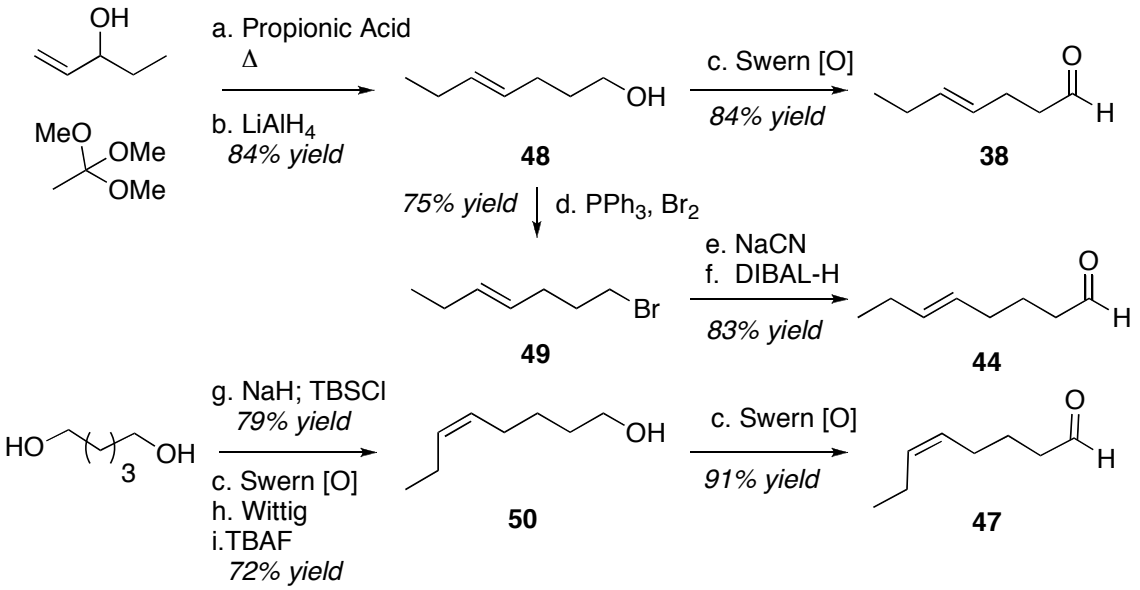
step could afford either the *cis*- or *trans*-diol (only *trans*-diol shown), thereby producing two diastereomers at the terminal methyl position of each derivative.



Scheme 9: Retrosynthesis of Starting Tetrohydrofurans

In the forward direction, aldehydes **38**, **44**, and **47** required syntheses, with **41** being commercially available (Scheme 10). Synthesis of the *trans*-alkene derivative **38** commenced with a Johnson-Claisen reaction catalyzed by propionic acid followed by $LiAlH_4$ reduction. These steps generated alcohol **48** in 84% yield. Next, simple oxidation of **48** using standard Swern conditions produced aldehyde **38** in 84% yield. Pleasingly, if **48** was transformed instead into bromide **49** followed by NaCN displacement, reduction, and hydrolysis, then the homologated aldehyde **44** was obtained in good yield. Finally, the synthesis of aldehyde **47** began with 1,5-hexanediol, which

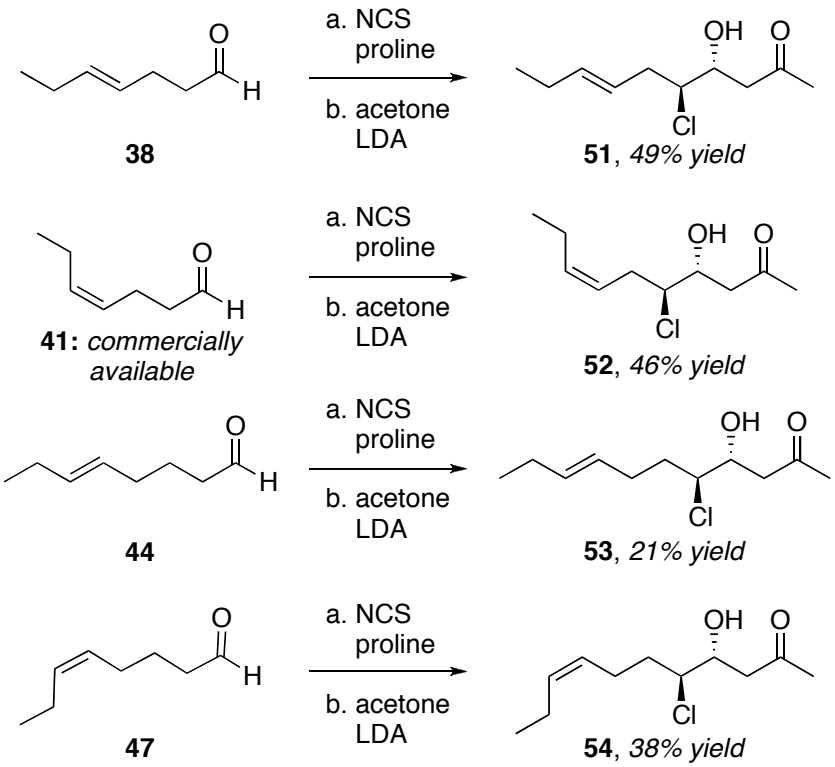
after mono-TBS protection, oxidation, Wittig olefination, and deprotection, yielded alcohol **50**. Oxidation of this alcohol, again using Swern conditions, produced the desired aldehyde (**47**) in 91% yield.



Reagents and Conditions: a. propionic acid (0.05 equiv), 120°C, 12 h; b. $LiAlH_4$ (1 equiv), Et_2O, 0°C, 1 h; c. oxalyl chloride (1.2 equiv), DMSO (2 equiv), Et_3N (4 equiv), CH_2Cl_2, -78 to -20°C, 2 h; d. Br_2 (1.05 equiv), PPh_3 (1.2 equiv), CH_2Cl_2, -20 to 25°C, 2 h; e. NaCN (1.5 equiv), DMSO, 25°C, 3 h; f. DIBAL-H (1.2 equiv), CH_2Cl_2, -78 to -50°C, 1.5 h; g. NaH (1 equiv), THF, 25°C, 45 min; TBSCl (1 equiv), 25°C, 2 h, 79%; h. Propyl-PPh_3Br (1.2 equiv), KOtBu (1.1 equiv), THF, 0°C, 1 h; i. TBAF (1.2 equiv), THF, 0 to 25°C, 2 h.

Scheme 10: Synthesis of Aldehyde Products on Route to Tetrahydrofuran Precursors

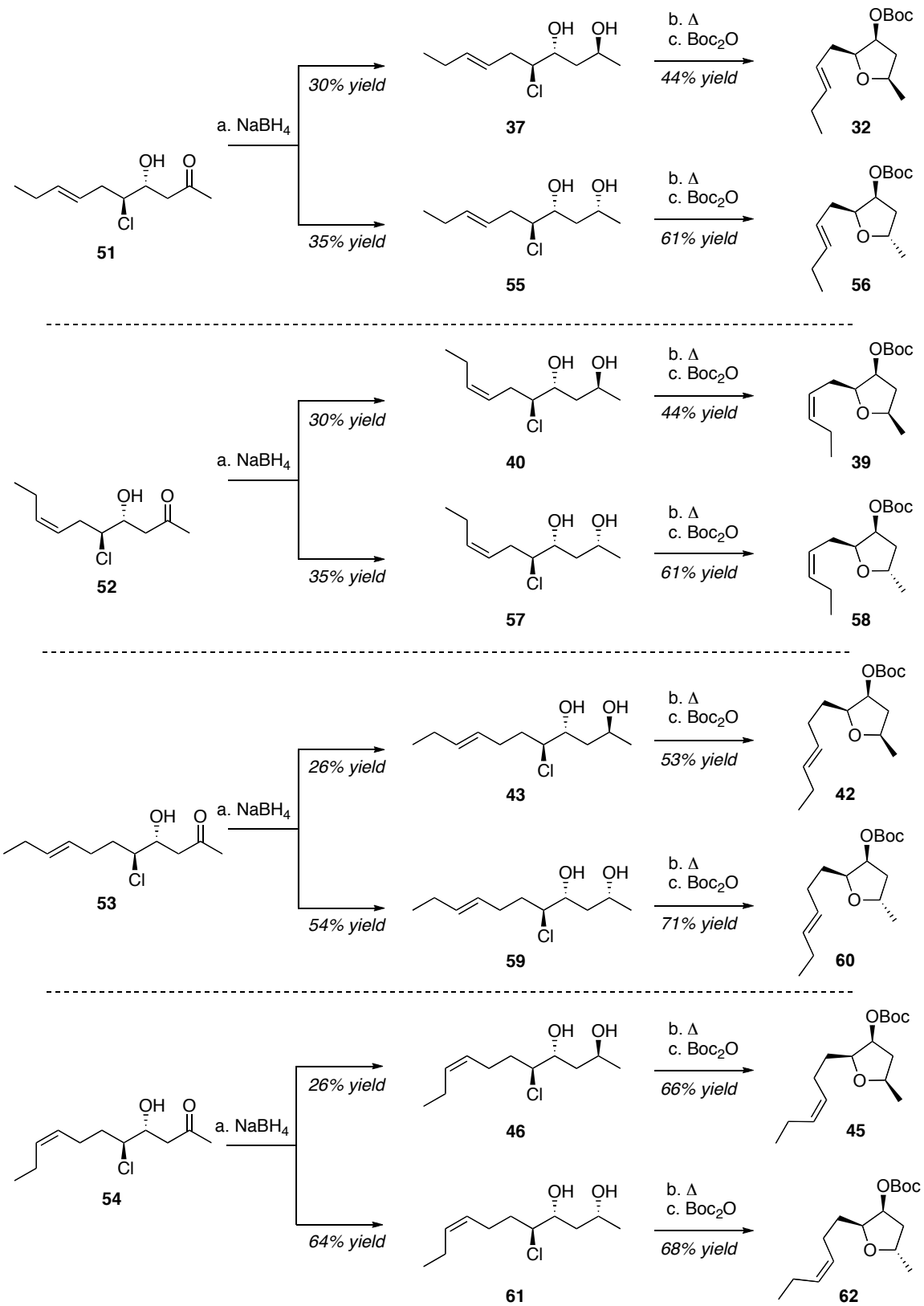
Pushing forward, α-chlorination using NCS and proline as a catalyst provided the desired α-chlorinated aldehyde derivatives (Scheme 11). This reaction was sensitive to both time and temperature as reflected in part by the low yields initially obtained, as dichlorination was a common by-product; its formation could be avoided or minimized by slow addition of NCS to the reaction mixture as well as keeping the reaction temperature at 0ºC throughout this addition. An aldol reaction with the enolate of acetone then resulted in the production of only *trans*-chlorohydrin derivatives due to Felkin-Ahn control in the addition of the enolate to the aldehyde precursor.



Reagents and Conditions: a. NCS (1.3 equiv), L-proline (0.1 equiv), CH_2Cl_2, 0 to 25°C; b. LDA (1 equiv), acetone (1 equiv), THF, -78°C, 1 h.

Scheme 11: Synthesis of Ketone Products on Route to Tetrahydrofuran Precursors

With the desired ketones in hand, reduction with $NaBH_4$ led to a mixture of separable *cis*- and *trans*-diol derivatives (Scheme 12). These diols were then heated in a polar protic solvent to undergo cyclization to the tetrahydrofuran. Finally, the addition of a *tert*-butyl carbonate generated the desired tetrahydrofuran precursors for the key BDSB-promoted cyclization. As shown in Scheme 12, eight derivatives of the tetrahydrofuran starting material were produced selectively in good yield dependent on the starting ketone derivative (i.e. **51 – 54**) and selected reduction adduct (*cis*- or *trans*-diols).

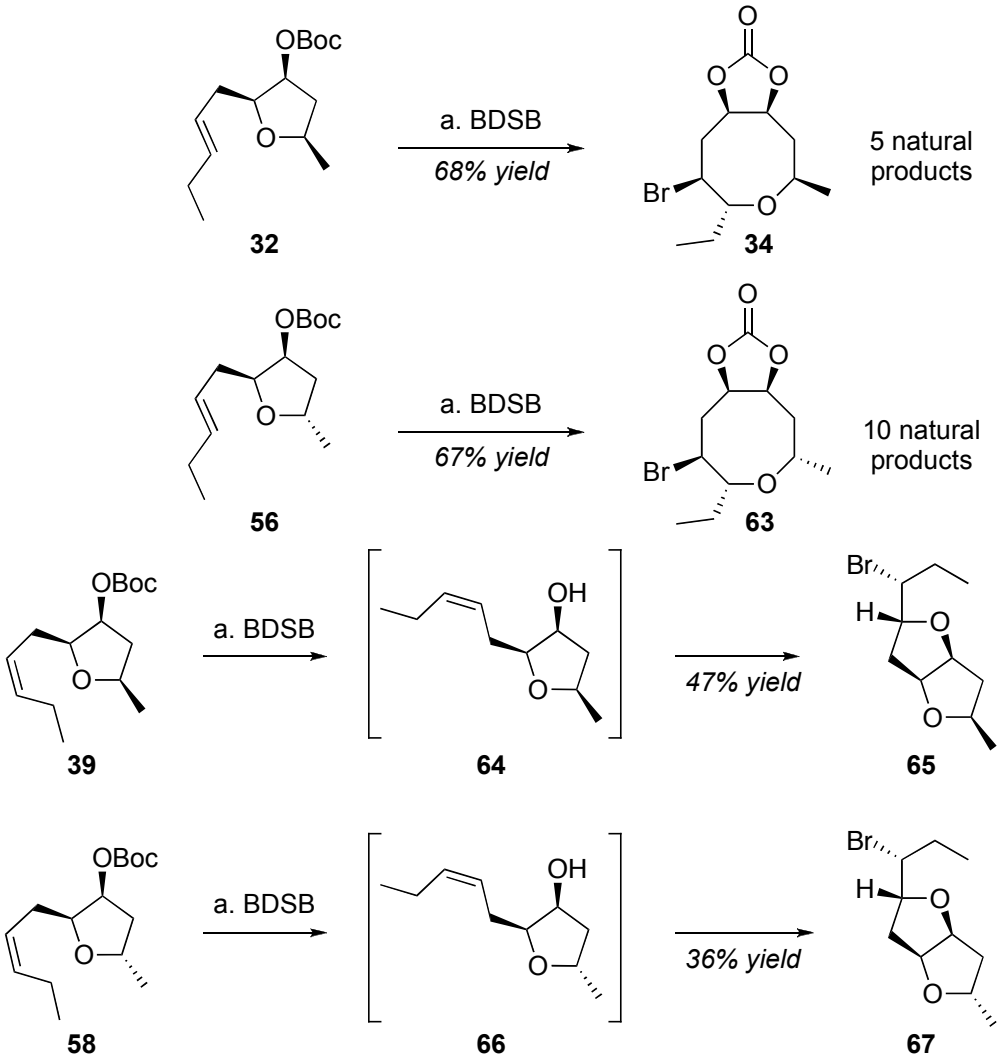


Reagents and Conditions: a. $NaBH_4$ (1.2 equiv), MeOH, -20°C, 15 min; b. MeOH/H_2O, 130°C, 4 h; c. nBuLi (1 equiv), Boc_2O (1 equiv), THF, 0 to 25°C, 1 h.

Scheme 12: Synthesis of Various Tetrahydrofuran Precursors

4.4 8-Membered Bromoether Cores

With several analogs of the origional tetrahydrofuran system synthesized, the next goal was to test each in the bromonium-induced ring expansion, with the hope that a single diastereomer would be produced in good yields in each case. Scheme 13 displays attempts to generate all four diastereomers of the 8-*endo* bromoether cores. Starting tetrahydrofurans containing the *trans*-alkene (i.e. **32** and **56**) underwent the ring expansion to generate **34** and **63** in good yields. When using the *cis*-disposed olefins (i.e. **39** and **58**), however, the desired 8-membered rings were not observed. Instead, it appears that the *tert*-butyl carbonate was cleaved first, which then allowed the resultant pendant alcohol to undergo a 5-*exo* bromoetherification to generate **65** or **67**. BDSB is most likely assisting in carbonate cleavage with its Lewis acidic properties at both sulfur and bromine, and upon reacting with trace water that could form HBr and Et_2SOH^+ *in situ*. Yet, this reaction manifold is known to be challenging, as in general 5-*endo* bromoetherificiations are slower with *cis*-alkenes.[22] In spite of that, the two synthesized 8-*endo* bromoether cores (i.e. **34** and **63**) have the same stereochemical relationship as at least 15 natural isolates, whereas the two cores derived from the unsuccessful ring expansion of starting tetrahydrofurans **39** or **58**, match only one of the known natural products.

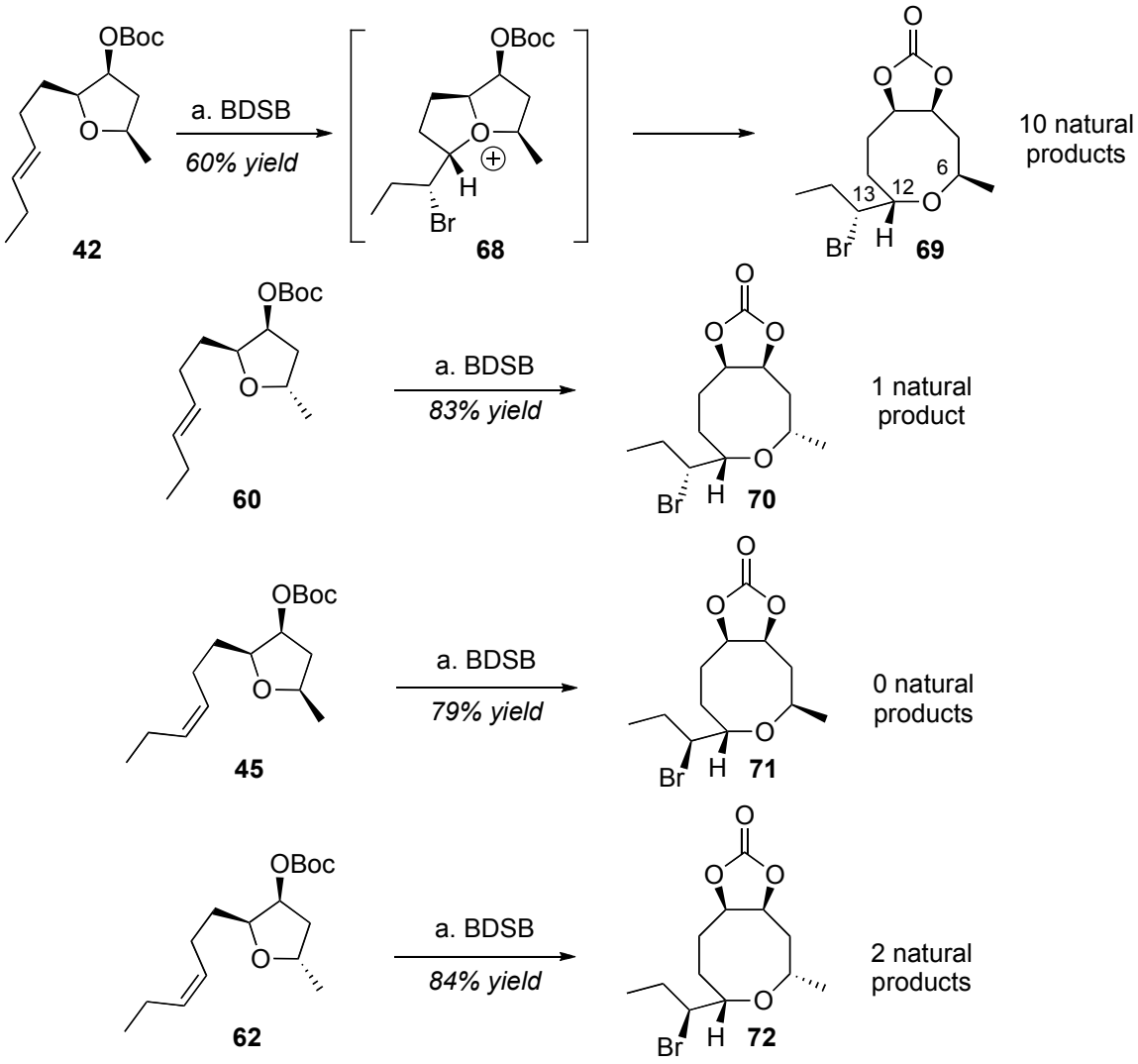


Reagents and Conditions: a. BDSB (1.5 equiv), $MeNO_2$, 20 min, -25 to 25°C.

Scheme 13: Generation of 8-*endo* Bromoether Cores

Beyond 8-*endo* products, the 8-*exo* alternatives were also explored using our bromonium-induced ring expansion method (Scheme 14). Now, the starting materials contain an additional methylene between the tetrahydrofuran and alkene to generate 8-*exo* products via a 5-*exo* bromocyclization. As shown, each diastereomeric tetrahydrofuran underwent the reaction smoothly, producing **69 - 72** in good yields. When using the *trans*-alkene containing starting material (i.e. **42** and **60**), the *trans*-Br/H at C12/C13 was observed in the product, whereas use of the *cis*-disposed olefin generated

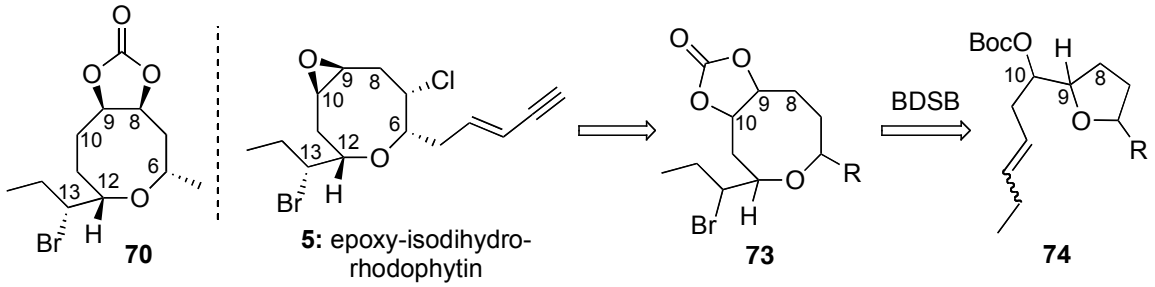
the *cis*-Br/H relationship. Additionally, the methyl stereochemistry at C6 appears to have no effect on the overall transformation as both the α- and β-methyl underwent the desired ring expansion transformation. The bromonoium source used in these cyclizations proved key, as BDSB provided the optimal results in synthesis of these lauroxocane cores. The use of alternative bromonium sources, such as TBCO or $Br(coll)_2OTf$, generated the 8-*exo* bromoether (**71**) in decreased yields (62% and 52% yield respectively), while NBS produced only trace amounts of compound **71** (<10% yield).



Reagents and Conditions: a. BDSB (1.2 equiv), $MeNO_2$, 10 min, -25 to 25°C.

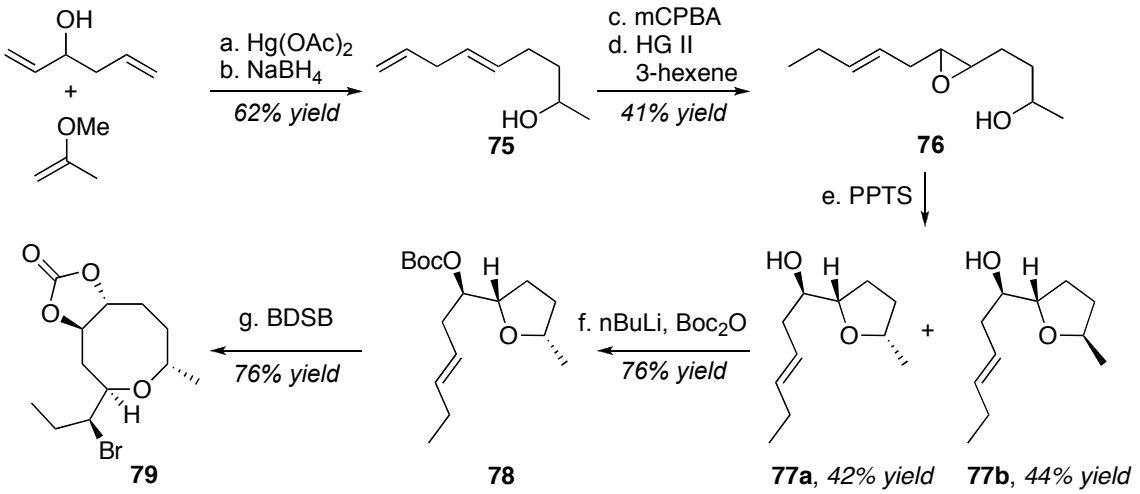
Scheme 14: Generation of 8-*exo* Diasteromeric Bromoethers

Comparing these successful model systems to the natural product derivatives reveals that the produced six diastereomers of the 8-membered bromoethers have the same stereochemical relationship at approximately 60% of the natural product isolates (over 28 of the 50 total 8-membered isolates). In addition, using the developed method, we have been able to produce a non-natural core (**71**), potentially one that has yet to be isolated. Structurally, all of the synthesized 8-membered rings were confirmed using crystallographic analysis of the diol derivatives, performed by Dr. Wesley Sattler of the Parkin group. Additionaly, the installed carbonate functionality is not unwanted, as it can be used for further diversification since the natural products that correspond to each core differ at the positions where the oxygen atoms are attached to the cores. Specifically, while the carbonate backbone of the 8-*endo* cores are correctly positioned to match the functionality of the natural product backbone, the 8-*exo* alternatives have the carbonate incorrectly substituted. As shown in Scheme 15, model compound **70** has the same stereochemical array at C6, C12, and C13 as epoxy-isodihydrorhodophytin (**5**), yet the carbonate at C8/C9 of **70** should to be located in the same position as the epoxide at C9/C10 of **5**. Since movement of this functionality would require multiple steps, installation of the carbonate at C9/C10 could provide a more direct approach to **5**. With that notion in place, the synthesis of a model system similar to **73** was approached, where the precursor of the ring expansion step would now be tetrahydrofuran **74** containing the *tert*-butyl carbonate outside of the ring.



Scheme 15: Moving of Produced Cyclic Carbonate to C9/C10

The synthesis of tetrahydrofuran **74** was completed following the route outlined in Scheme 16. As shown, initial Hg(II)-promoted Claisen rearrangement[23] and subsequent reduction generated alcohol **75** in 62% yield. Epoxidation and cross metathesis initiated by the Hoveyda-Grubbs second generation catalyst[24] yielded compound **76**, which upon treatment with acid produced two separable diastereomers of the tetrahydrofuran core (**77a** and **77b**). Carrying only **77a** forward (since it can be separated from **77b** by silica gel column chromatography), *tert*-butyl carbonate formation produced the required precursor for the ring expansion step (i.e. **78**). Next, in the key step, treatment of **78** with 1.2 equiv of BDSB yielded the desired 8-*exo* bromoether **79** in 76% yield as a single diastereomer. Compound **79** now contains the correct positioning at the cyclic carbonate on the backbone, with stereochemistry correlating to over 10 natural product isolates.



Reagents and Conditions: a. $Hg(OAc)_2$ (0.02 equiv), 120°C, 24 h; b. $NaBH_4$ (2 equiv), MeOH, 0°C, 30 min; c. mCPBA (1 equiv), CH_2Cl_2, 25°C, 2 h; d. *trans*-3-hexene (5 equiv), Hoveyda-Grubbs second generation (0.1 equiv), CH_2Cl_2, 25°C, 2 h, 41% yield; e. PPTS (1.4 equiv), CH_2Cl_2, 25°C, 1 h; f. nBuLi (1.05 equiv), Boc_2O (1 equiv), THF, 0 to 25°C, 2 h, 76%; g. BDSB (1.2 equiv), $MeNO_2$, -25 to 25°C, 10 min, 76%.

Scheme 16: Synthesis of 8-*exo* Bromoether **79** with Carbonate at Alternate Position

4.5 9-Membered Bromoether Cores

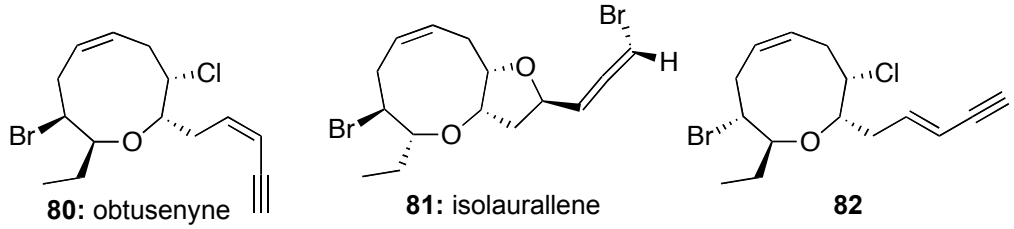
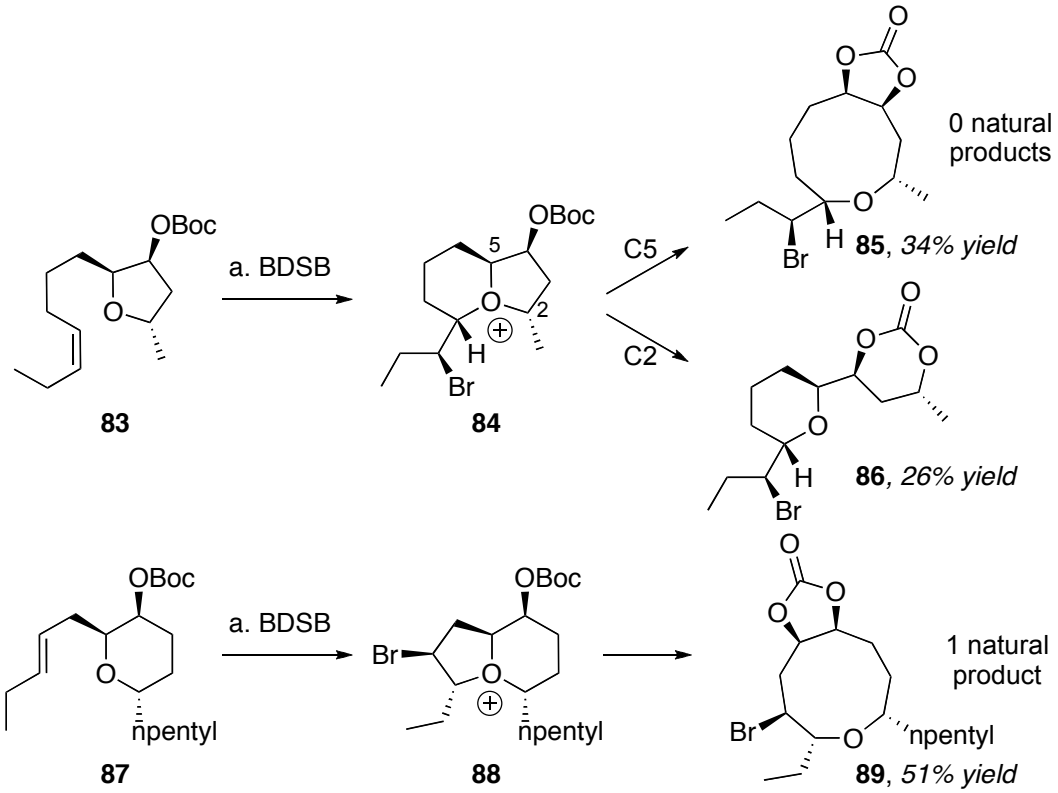


Figure 3: Selected 9-Membered Bromoether Natural Products from the *Laurencia* Family

Having developed a model system to generate various 8-*endo* and 8-*exo* bromoethers diastereoselectively in good yields, we hoped this method would extend to syntheses of other medium-sized ring systems, specifically 9-membered bromoethers. There are at least 10 natural products containing a 9-membered bromoether core, termed lauroxonane in the context of the *Laurencia* isolates (Figure 3).[25,26] Having just discussed our success with generation of 8-membered rings, in this section, we will first discuss results in formation of 9-membered bromoethers followed by syntheses of the starting materials used. As shown in Scheme 17, substrate **83** now contains three

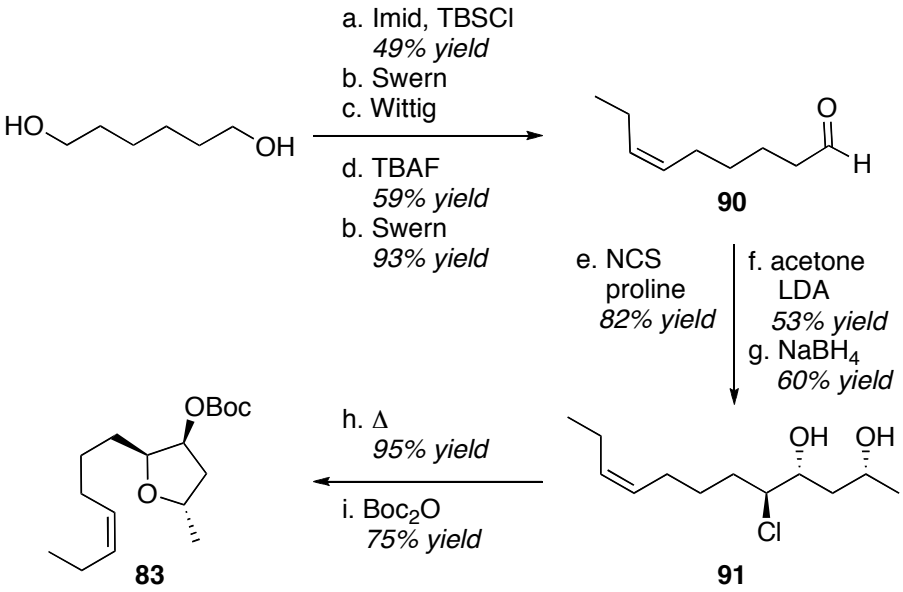
methylenes between the tetrahydrofuran and alkene. Treatment of **83** with 1.2 equiv of BDSB in $MeNO_2$ for 10 min generated the 9-*exo* bromoether **85**, via a 6-*exo* bromocyclization to the proposed intermediate **84**. In addition to the desired product, the tetrahydropyran **86** was also producted; the connectivity of **86** was confirmed by COSY 2D NMR, though full characterization of each stereocenter of the product was derived only based on the proposed intermediate. Intercepting a similar oxonium intermediate, the 9-*endo* bromoether **89** was generated from instead the tetrahydropyran **87**. In this case, a 5-*endo* bromocyclization transformed **87** into oxonium intermediate **88**, which opened to the desired 9-membered bromoether. While the 9-*endo* product **89** corresponds specifically to only one natural product of the ten isolated 9-membered rings, it is worth noting that all the natural products in the class contain 9-*endo* bromoether cores; the 9-*exo* derivative **85** is non-natural, as there are no 9-*exo* cores isolates in the *Laurencia* family.



Reagents and Conditions: a. BDSB (1.2 equiv), $MeNO_2$, 10 min, -25 to 25°C.

Scheme 17: Generation of 9-*exo* and 9-*endo* Bromoethers

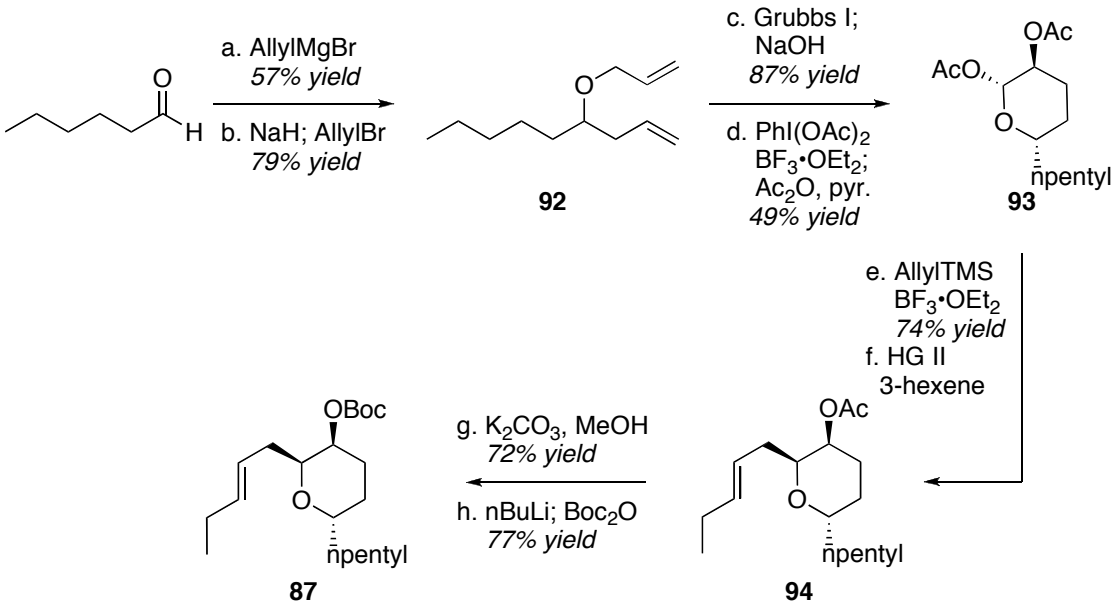
The synthesis of tetrahydrofuran precursor **83** followed the same sequence as described for previous furan derivatives.[21] As shown in Scheme 18, 1,6-hexanediol was first transformed to aldehyde **90** in five steps, using simple modifications of the previously delineated route. From aldehyde **90**, α-chlorination, an aldol reaction with the enolate of acetone, and reduction generated the separable *cis*- and *trans*-diol products (*cis*-diol **91** with *trans*-diol not drawn). Cyclization and *tert*-butyl carbonate formation from **91** produced the desired tetrahydrofuran (**83**).



Reagents and Conditions: a. imidazole (1 equiv), TBSCl (1 equiv), THF, 25°C, 12 h, 49%; b. oxalyl chloride (1.2 equiv), DMSO (2 equiv), Et_3N (4 equiv), CH_2Cl_2, -78 to -20°C, 2 h; c. Propyl-PPh_3Br (1.2 equiv), KOtBu (1.1 equiv), THF, 0°C, 1 h; d. TBAF (1.2 equiv), THF, 0 to 25°C, 2 h; 59% over 3 steps; e. NCS (1.3 equiv), L-proline (0.1 equiv), CH_2Cl_2, 0 to 25°C, 82% yield; f. LDA (1 equiv), acetone (1 equiv), THF, -78°C, 1 h, 53% yield; g. $NaBH_4$ (1.2 equiv), MeOH, -20°C, 15 min, 60% yield (+ 20% yield *trans*-diol); h. MeOH/H_2O, 130°C, 4 h, 95% yield; i. nBuLi (1 equiv), Boc_2O (1 equiv), THF, 0 to 25°C, 1 h, 75% yield.

Scheme 18: Synthesis of Tetrahydrofuran Derivative **83**

While the tetrahydrofuran synthesis followed closely to previous routes, tetrahydropyran derivative **87** was synthesized using transformations based strongly on sugar chemistry (Scheme 19). In this case, starting from hexanal, nucleophilic allylation and subsequent treatment with NaH and allyl bromide yielded bisalkene **92**. Ring-closing metathesis initiated by the Grubbs first generation initiator, double bond migration,[27] oxidation, and bis-acylation generated tetrahydropyran **93**. Compound **94** was then synthesized by introduction of its allyl group using a Lewis acid and allyl trimethylsilane[28] followed by a cross metathesis to generate the internal alkene. Lastly, acyl cleavage and *tert*-butyl carbonate formation produced the desired tetrahydropyran **87** in 55% overall yield.



Reagents and Conditions: a. allylMgBr (1.2 equiv), Et_2O, 0°C, 30 min, 57% yield; b. NaH (2 equiv), allyl bromide (2 equiv), THF, reflux, 45 min, 79% yield; c. Grubbs first generation (0.05 equiv), PhMe, 25°C, 30 min; NaOH (0.25 equiv), 2-propanol, reflux, 12 h, 87% yield; d. $PhI(OAc)_2$ (1.2 equiv), BF_3•OEt_2 (0.2 equiv), CH_2Cl_2, -40°C, 4 h; Ac_2O (16 equiv), pyridine, -40 to 25°C, 12 h, 49% yield; e. AllylTMS (3 equiv), BF_3•OEt_2 (5 equiv), CH_2Cl_2, -78 to 25°C, 12 h, 74% yield; f. Hoveyda Grubbs second generation catalyst (0.03 equiv), *trans*-3-hexene, 25°C, 12 h; g. K_2CO_3 (10 equiv), MeOH, 0°C, 1 h, 72% yield; h. nBuLi (1 equiv), Boc_2O (1 equiv), THF, 0 to 25°C, 1 h, 77% yield.

Scheme 19: Synthesis of Tetrahydropyran Starting Material **87**

4.6 Conclusion

Using the developed ring expansion methodology promoted by BDSB, we have been able to synthesize two 8-*endo* and five 8-*exo* bromoethers diastereoselectively using easily prepared tetrahydrofuran precursors. These generated lauroxacanes correspond to over 28 of the 50 naturally occurring 8-membered bromoethers of the *Laurencia* C15 acetogenins. In addition, the developed transformation was expanded to include the synthesis of 9-membered bromoethers as well. Currently, this method is the only one capable of preparing a single diastereomer of a medium-sized bromoether initiated by a bromonium-induced cyclization event, and does so in a general and predictable way. The power of this transformation lies in its ability to install the desired bromide and ether

stereocenters in a direct and efficient manner from a single easily prepared tetrahydrofuran. In addition, this idea was highlighted in two reviews on tetrahydrofuran[29] and medium-sized ether[30] formation as well as in an article featuring *Laurencia* natural isolates.[5j] While this chapter delineated results on a model system, synthesis of a natural product using this robust method was also completed, to be discussed further in Chapter 5.

4.7 References

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4.8 Experimental Section

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry methylene chloride (CH_2Cl_2), benzene, toluene, diethyl ether (Et_2O) and tetrahydrofuran (THF) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns; pyridine was distilled from CaH_2 and stored over 3 Å molecular sieves; triethylamine (Et_3N) was distilled from KOH; N,N-dimethylformamide (DMF), acetonitrile (MeCN), and nitromethane ($MeNO_2$) were stored over 3 Å molecular sieves; 1,2-dichloroethane, acetone, ethyl acetate (EtOAc), and methanol (MeOH) were purchased in anhydrous form from Sigma-Aldrich and used as received. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an aqueous solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. Preparative thin-layer chromatography was carried out on 0.50 mm E. Merck silica gel plates (60F-254). SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. NMR spectra were recorded on Bruker DRX-300 and DRX-400 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, AB = AB quartet, br = broad, app = apparent. IR spectra were recorded on a Nicolet Avatar 370

DTGS series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded in the Columbia University Mass Spectral Core facility on a JOEL HX110 mass spectrometer using FAB (Fast Atom Bombardment) and EI (Electron Ionization) techniques. All enantiomeric excess (*e.e.*) values were obtained by HPLC using a Daicel CHIRALCEL OD column.

Abbreviations. Ac_2O = acetic anhydride, BF3•OEt2 = boron trifuloride diethyl etherate, Boc_2O = di-*tert*-butyl dicarbonate, *n*-BuLi = *n*-butyllithium, DIBAL-H = di-*iso*-butylaluminum hydride, 4-DMAP = 4-dimethylaminopyridine, DMSO = dimethylsulfoxide, $Hg(OAc)_2$ = mercury (II) acetate, *i*Pr_2NH = diisopropyl amine, KO*t*-Bu = potassium *tert*-butoxide, LDA = lithium diisopropylamide, mCPBA = *meta*-chloroperoxybenzoic acid, *n*-BuLi = *n*-butyl lithium, NCS = *N*-chlorosuccinimide, $PhI(OAc)_2$ = (diacetoxyiodo)benzene, PPTS = pyridinium *p*-toluenesulfonate, TBAF = tetra-*n*-butyl ammonium fluoride, TBSCl = *tert*-butylchlorodimethylsilane.

Attempts at Cyclizing Linear Precursors with BDSB

19. Prepared according to a procedue adapted from the work of Warren and co-workers: Buss, A. D.; Greeves, N.; Mason, R.; Warren, S. *J. Chem. Soc. Perkin Trans. 1* **1987**, 2569. To a solution of ethyl diphenylphosphine oxide (1.0 g, 4.3 mmol, 1.0 equiv) in THF (12.9 mL) was added *n*-BuLi (1.5 M in hexanes, 2.87 mL, 4.3 mmol, 1.0 equiv) dropwise at 0 °C and the reaction was allowed to strir for 15 min at 0 °C. The mixture was then cooled to –78 °C and ε-caprolactone (0.48 mL, 4.3 mmol, 1.0 equiv) was added. The reaction was stirred at –78 °C for 10 min. Upon completion, the reaction contents were quenched by the careful addition of saturated aqueous NH_4C1 (5 mL) and extracted

with CH_2Cl_2 (3 × 5 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. The resultant oil was purified by flash column chromatography (silica gel, CH_2Cl_2:MeOH, 9:1) to afford the ketophosphate (0.84 g, 72% yield) as a colorless viscous oil. Next, the freshly prepared ketophosphate (0.84 g, 3.1 mmol, 1.0 equiv) was dissolved in EtOH (17 mL) and $NaBH_4$ (0.117 g, 3.1 mmol, 1.0 equiv) was added. The reaction was then refluxed for 3 h. Upon completion, the reaction contents were quenched by the careful addition of saturated aqueous NH_4C1 (5 mL) and the EtOH was removed by concentration. To the remaining contents, 1 M HCl (3 drops) and brine (5 mL) were added and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. The resultant oil was purified by flash column chromatography (silica gel, hexanes:acetone, 1:1) to afford the alcohol (0.28 g, 32% yield isolated pure, along with more fractions containing both *cis*- and *trans*-isomers) as a white foam. Lastly, this alcohol (0.28 g, 1.0 mmol, 1.0 equiv) was dissolved in DMF (24 mL) at 25 °C. To this solution, NaH (60% dispersion in mineral oil, 0.080 g, 2.0 mmol, 2.0 equiv) was added and the reaction mixture was heated to 50 °C for 30 min. Upon completion, the reaction contents were quenched by the careful addition of water (20 mL) and brine (5 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were then washed with water (5 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant oil was purified by flash column chromatography (silica gel, pentane:Et2O, 1:0 to 1:1) to afford the alkenol **19** (0.064 g, 60% yield) as a colorless viscous oil whose spectral properties matched: Waizumi, N.; Itoh, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2000**, *122*, 7825.

20. A solution of BDSB (0.056 g, 0.11 mmol, 1.1 equiv) in $MeNO_2$ (0.5 mL) was added rapidly via syringe to a solution of alcohol **19** (0.013 g, 0.100 mmol, 1.0 equiv) in $MeNO_2$ (1.5 mL) at –25 °C. The resultant yellow solution was stirred for 15 min at –25 °C. Upon completion, the reaction mixture was quenched by the addition of a combination of saturated aqueous $NaHCO_3$ and 5% aqueous Na_2SO_3 (1:1, 5 mL), and the resultant biphasic mixture was stirred vigorously for 20 min at 25 °C. The reaction contents were added to brine (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 19:1 to 3:2) to afford the 7-*exo* bromoether **20** (0.012 g, 60% yield). Only ^1H NMR was completed for characterization of compound **20**.

22. To a solution of 1,6-hexandiol (5.0 g, 42 mmol, 1.0 equiv) in THF (100 mL) was added NaH (60% dispersion in mineral oil, 1.41 g, 42 mmol, 1.0 equiv) slowly at 0 °C. The suspension was stirred at 25 °C for 30 min, followed by the addition of TBSCl (6.96 g, 46.2 mmol, 1.1 equiv). The reaction was allowed to stir at 25 °C for 12 h. Upon completion, the reaction contents were quenched by the careful addition of saturated aqueous NH_4Cl (30 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were then washed with water (5 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant oil was purified by flash column chromatography (silica gel, hexanes:EtOAc, 4:1) to afford the monoTBS alcohol (5.0 g, 50% yield) as a colorless viscous oil. Next, the monoTBS alcohol (5.0 g, 21.5 mmol, 1.0 equiv) was dissolved in DMSO (50 mL) and Et_3N (30.0 mL, 215 mmol, 10. equiv) was added followed by a solution of pyridine sulfur trioxide (11.4 g, 70.0 mmol, 3.3 equiv) in DMSO (50 mL).

The reation mixture was stirred at 25 °C for 10 mn. Upon completion, the reaction contents were quenched by the careful addition of water (100 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were then washed with $CuSO_4$ (3 × 10 mL), water (5 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant oil was purified by flash column chromatography (silica gel, hexanes:EtOAc, 19:1 to 17:3) to afford the aldehyde (3.5 g, 71% yield) as a colorless viscous oil. To a stirred solution of this freshly prepared aldehyde (3.5 g, 15.2 mmol, 1.0 equiv) in CH_2Cl_2 (35 mL) was added a solution of (carbethoxymethylene)-triphenylphosphorane (7.41 g, 21.3 mmol, 1.4 equiv) in CH_2Cl_2 (35 mL) at 25 °C. The reaction was stirred for 24 h at 25 °C. Upon completion, the reaction contents concentrated to a resultant oil which was purified by flash column chromatography (silica gel, hexanes:EtOAc, 19:1 to 9:1) to afford the α,β-unsaturated ester product (4.33 g, 94% yield) as a light yellow viscous oil. Subsequently, the freshly prepared α,β-unsaturated ester (4.33 g, 14.3 mmol, 1.0 equiv) was dissolved in toluene (75 mL) and cooled to –78 °C. DIBAL-H (1.0 M in toluene, 43 mL, 43 mmol, 3.0 equiv) was added to the reaction mixture dropwise. And the reaction was stirred at –78 °C for 30 min. Upon completion, the reaction contents were quenched by the careful dropwise addition of water (17 mL) over 30 min and the reaction was stirred for an additional 10 min at 25 °C. The biphasic solution was then diluted with EtOAc (25 mL) and solid $NaHCO_3$ (2 g) was added. The solid was filtered off, washed with EtOAc (2 × 10 mL), and the filtrate was concentrated. The resultant oil was purified by flash column chromatography (silica gel, hexanes:EtOAc, 9:1 to 4:1) to afford the allylic alcohol (2.87 g, 78% yield) as a colorless viscous oil. Next, to a slurry of MnO_2 (7.7 g, 89 mmol, 8 equiv) in CH_2Cl_2 (30 mL) was added a solution of the freshly prepared allylic alcohol

(2.87 g, 11.1 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL). The reaction was stirred at 25 °C for 24 h. Upon completion, the slurry was filtered through a pad of Celite and washed with CH_2Cl_2 (2 × 10 mL). The filtrate was concentrated and the resultant oil was purified by flash column chromatography (silica gel, hexanes:EtOAc, 19:1 to 4:1) to afford the aldehyde (2.25 g, 79% yield) as a colorless viscous oil. Subsequently, the Wittig reagent was prepared by first dissolving methyltriphenylphosphonium bromide (4.71 g, 13.2 mmol, 1.5 equiv) in THF (30 mL) at 0 °C. To this solution, *n*-BuLi (1.6 M in hexanes, 7.70 mL, 12.3 mmol, 1.4 equiv) was added dropwise and the reaction mixture was allowed to stir at 25 °C for 30 min. The reaction was cooled to –78 °C and a solution of the freshly prepared aldehyde (2.25 g, 8.80 mmol, 1.0 equiv) in THF (10 mL) was added. The reaction mixture was allowed to warm to 25 °C over the course of 4 h. Upon completion, the reaction contents were quenched by the careful addition of saturated aqueous NH_4Cl (30 mL) and extracted with hexanes (3 × 20 mL). The combined organic layers were then washed with water (5 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant oil was purified by flash column chromatography (silica gel, hexanes:CH_2Cl_2, 9:1 to 3:1) to afford the diene (0.270 g, 12% yield) as a colorless viscous oil. Lastly, the TBS group was removed by dissolving a portion of the freshly prepared diene (50 mg, 0.20 mmol, 1.0 equiv) in THF (2 mL). To this solution, TBAF (1.0 M in THF, 0.22 mmol, 1.1 equiv) was added at 0 °C and the reaction was stirred at 0 °C for 2 h. Upon completion, the reaction contents were quenched by the careful addition of water (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. The resultant oil was purified by flash column chromatography (silica gel, hexanes:EtOAc, 9:1 to 3:1) to afford the

alcohol **22** (0.020 g, 72% yield) as a colorless viscous oil. Only ^{1}H NMR was completed for characterization of compound **22**.

23. A solution of BDSB (0.040 g, 0.079 mmol, 1.1 equiv) in $MeNO_2$ (0.5 mL) was added rapidly via syringe to a solution of alcohol **22** (0.010 g, 0.072 mmol, 1.0 equiv) in $MeNO_2$ (1.5 mL) at –25 °C. The resultant yellow solution was stirred for 15 min at –25 °C. Upon completion, the reaction mixture was quenched by the addition of a combination of saturated aqueous $NaHCO_3$ and 5% aqueous Na_2SO_3 (1:1, 5 mL), and the resultant biphasic mixture was stirred vigorously for 20 min at 25 °C. The reaction contents were added to brine (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 99:1 to 9:1) to afford the 7-*exo* ether **23** (0.013 g, 80% yield). Only ^{1}H NMR was completed for characterization of compound **23**.

26. Prepared according to the seven step route described in the synthesis of compound **22**, now transforming 1,7-heptanediol into diene **26** in a 20% overall yield. Only ^{1}H NMR was completed for characterization of compound **26**.

27. Prepared according to the procedure outlined in the synthesis of **23**. The bromochloride product **27** was isolated as a colorless viscous oil and was only characterized by ^{1}H NMR.

Alternation of Counterion in the BDSB Reagent

29a-g. Et_2S (0.037 mL, 0.35 mmol, 1.8 equiv) was added slowly to a solution of Br_2 (0.016 mL, 0.32 mmol, 1.6 equiv) in CH_2Cl_2 (0.9 mL) at –30 °C. The solution was

allowed to stir for 10 min at –30 °C, at which point, solid AgX (0.38 mmol, 1.9 equiv) was added. The reaction miture was allowed to warm to 25 °C and stirred at this temperature for 1 h. This newly formed bromonium reagent was then syringed into a solution of dienol **26** (0.028 g, 0.2 mmol, 1.0 equiv) in $MeNO_2$ (3 mL) at –30 °C. The resultant yellow solution was stirred for 15 min at –25 °C. Upon completion, the reaction mixture was quenched by the addition of a combination of saturated aqueous $NaHCO_3$ and 5% aqueous Na_2SO_3 (1:1, 5 mL), and the resultant biphasic mixture was stirred vigorously for 20 min at 25 °C. The reaction contents were added to brine (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 99:1 to 9:1) to afford **27** in various yields.

29h or **29i.** Et_2S (0.297 mL, 2.75 mmol, 1.1 equiv) was added slowly to a solution of Br_2 (0.128 mL, 2.50 mmol, 1.0 equiv) in 1,2-dichloroethane (6 mL) at –30 °C. Next, PCl_5 (0.688 g, 3.0 mmol, 1.2 equiv) [or PBr_5 for synthesis of **29i**] was added and the solution was warmed to 25 °C. The reaction mixture was stirred for 30 min at 25 °C. At this time, the reaction flask was cooled to 0 °C and stored at that temperature for 4 h before then being cooled to –20 °C and stored for an additional 12 h, during which time large orange needles crystallized from the reaction solution. The solvent was decanted, and the crystals were rinsed with cold CH_2Cl_2 (2 × 5 mL) and dried under vacuum to afford **29h** or **29i**.

Preparation of Unsaturated Aldehydes

(4*E*)-Heptenal (38).

48. Prepared according to a procedure adapted from the work of Shayakhmetova and co-workers: Shakhmaev, R. N.; Ishbaeva, A. U.; Shayakhmetova, I. S. *Russ. J. Gen. Chem.* **2009**, *79*, 1171–1174. 1-Penten-3-ol (10.0 g, 116 mmol, 1.0 equiv), propionic acid (0.435 mL, 5.80 mmol, 0.05 equiv), and trimethyl orthoacetate (43.6 mL, 348 mmol, 3.0 equiv) were added to a high-pressure sealed tube. The reaction vessel was then sealed and heated at 120 °C for 12 h. Upon completion, the reaction contents were cooled to 25 °C, the cap was removed, and the reaction contents were reheated to 120 °C for 2 h, open to the atmosphere, to distill off the MeOH byproduct. The resultant yellow oil was then dissolved in Et_2O (20 mL) and cannulated dropwise into a suspension of $LiAlH_4$ (4.41 g, 116 mmol, 1.0 equiv) in Et_2O (440 mL) at 0 °C. The resultant slurry was stirred at 0 °C for 60 min and then quenched by the careful dropwise addition of saturated aqueous NH_4Cl (20 mL), followed by 1 M sodium potassium tartrate solution (300 mL). The resultant biphasic mixture was stirred vigorously for 16 h at 25 °C. The layers were then allowed to separate and the aqueous layer was extracted with additional Et_2O (2 × 200 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$), filtered, and concentrated (→100 mm Hg at 20 °C). The resultant crude oil was purified by flash column chromatography (silica gel, hexanes:Et_2O, 1:0→4:1) to afford (4*E*)-hepten-1-ol (**48**, 11.1 g, 84% yield) as a moderately volatile colorless oil. **48**: R_f = 0.28 (silica gel, hexanes:EtOAc, 4:1); IR (film) ν_{max} 3335 (br), 2962, 2934, 2874, 1454, 1058, 966 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.49 (m, 1 H), 5.41 (m, 1 H), 3.65 (t, *J* = 6.4 Hz, 2 H), 2.12–1.96 (m, 4 H), 1.64 (quintet, *J* = 6.8 Hz, 2 H), 1.40 (br s, 1 H),

0.97 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.9, 128.6, 62.8, 32.6, 29.0, 25.7, 14.0; HRMS (EI) calcd for $C_7H_{14}O$ $[M]^+$ 114.1045, found 114.1041.

38. Prepared according to the general Swern procedure described in the synthesis of **50**. (4*E*)-hepten-1-ol (**48**, 3.34 g, 29.2 mmol) was oxidized to (4*E*)-heptenal (**38**, 2.36 g, 72% yield) as a volatile light yellow oil which was carried forward without any additional purification. [Note: this product proved unstable to silica gel exposure, rendering column purification impractical]. **38**: IR (film) ν_{max} 2963, 2719, 1726, 1441, 1243, 968 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (t, J = 2.0 Hz, 1 H), 5.51 (m, 1 H), 5.39 (m, 1 H), 2.49 (m, 2 H), 2.33 (m, 2 H), 1.99 (m, 2 H), 0.96 (t, J = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6, 133.7, 126.8, 43.7, 25.6, 25.3, 13.9; HRMS: No molecular ion peak could be observed.

(4*Z*)-Heptenal (41). Purchased from TCI America.

(5*E*)-Octenal (44). Prepared according to a procedure adapted from the work of Shayakhmetova and co-workers: Shakhmaev, R. N.; Ishbaeva, A. U.; Shayakhmetova, I. S. *Russ. J. Gen. Chem.* **2009**, *79*, 1171–1174. Bromine (1.08 mL, 21.0 mmol, 1.05 equiv) was added dropwise to a solution of Ph_3P (6.30 g, 24.0 mmol, 1.2 equiv) in CH_2Cl_2 (120 mL) at 0 °C, and the resultant colorless solution was stirred for 5 min. The reaction mixture was then cooled to –20 °C and *trans*-4-hepten-1-ol (**48** [vide infra], 2.28 g, 20.0 mmol, 1.0 equiv) was added dropwise. The resultant reaction solution was allowed to warm slowly over 2 h to 25 °C. Upon completion, the reaction contents were concentrated by rotary evaporation to a volume of ~20 mL, and the resultant residue was purified directly by flash column chromatography (silica gel, pentane:Et_2O, 19:1) to afford bromide **49** (2.82 g, 75% yield) as a colorless volatile oil. **49**: R_f = 0.81 (silica gel,

hexanes); IR (film) ν_{max} 2962, 2930, 2848, 1438, 1239, 967 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.47 (m, 1 H), 5.29 (m, 1 H), 3.35 (t, *J* = 6.8 Hz, 2 H), 2.08 (q, *J* = 6.8 Hz, 2 H), 1.95 (m, 2 H), 1.85 (quintet, *J* = 6.8 Hz, 2 H), 0.91 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.9, 127.1, 33.5, 32.6, 31.0, 25.7, 14.0; HRMS (FAB) calcd for $C_8H_{13}O$ $[M–H]^+$ 125.0966, found 125.0962. Next, a portion of bromide **49** (2.15 g, 12.1 mmol, 1.0 equiv) was added to a suspension of NaCN (0.892 g, 18.2 mmol, 1.5 equiv) in DMSO (18 mL) at 25 °C, and the resultant reaction mixture was stirred vigorously for 3 h. Upon completion, the reaction contents were quenched with water (150 mL) and extracted with hexanes:Et_2O (1:1, 3 × 75 mL). The combined organic layers were then washed with water (3 × 50 mL), then brine (50 mL), dried ($MgSO_4$), filtered, and concentrated to afford the desired nitrile, which was carried forward without additional purification. Lastly, prepared according to a procedure adapted from the work of Ishihara and co-workers: Uyanik, M.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2006**, *8*, 5649–5652. DIBAL-H (1.0 M in toluene, 14.6 mL, 14.6 mmol, 1.2 equiv) was added dropwise over the course of 10 min to a solution of the crude nitrile produced above (12.1 mmol assumed, 1.0 equiv) in CH_2Cl_2 (61 mL) at –78 °C. The resultant colorless solution was allowed to warm slowly to –50 °C over 90 min. Upon completion, the reaction contents were quenched by the sequential addition of acetone (120 mL), saturated aqueous NH_4Cl (10 mL), and 1 M sodium potassium tartrate (30 mL); the resultant biphasic mixture was stirred vigorously for 12 h at 25 °C. The reaction contents were then poured into brine (200 mL) and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$), filtered, and concentrated to afford (5*E*)-octenal (**44**, 1.26 g, 83% yield) as a light yellow viscous oil which was carried forward

without additional purification. [Note: this product proved unstable to silica gel exposure, rendering column purification impractical]. **44**: IR (film) ν_{max} 2958, 2918, 2850, 1724, 1460, 968 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.76 (t, *J* = 2.0 Hz, 1 H), 5.47 (m, 1 H), 5.34 (m, 1 H), 2.42 (td, *J* = 7.2, 1.6 Hz, 2 H), 2.07–1.95 (m, 4 H), 1.70 (quintet, *J* = 7.2 Hz, 2 H), 0.96 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 133.6, 127.9, 43.3, 31.9, 25.7, 22.1, 14.0; HRMS (FAB) calcd for $C_8H_{13}O$ $[M–H]^+$ 125.0966, found 125.0962.

(5*Z*)-Octenal (47).

50. Prepared according to a procedure adapted from the work of Condon and co-workers: McDougal, P. G.; Rico, J. G.; Oh, Y.-I.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388–3390. 1,5-Pentanediol (6.3 mL, 60. mmol, 1.0 equiv) was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 2.4 g, 60. mmol, 1.0 equiv) in THF (120 mL) at 25 °C (while venting the H_2 produced). The resultant reaction mixture was stirred vigorously for 45 min at 25 °C, after which TBSCl (9.0 g, 60. mmol, 1.0 equiv) was added in a single portion. The reaction mixture was then stirred for an additional 2 h at 25 °C. Upon completion, the reaction contents were quenched by the careful addition of saturated aqueous $NaHCO_3$ (100 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. The resultant colorless oil was purified by flash column chromatography (silica gel, hexanes:EtOAc, 4:1) to afford desymmetrized alcohol (10.3 g, 79% yield) as a colorless viscous oil. R_f = 0.42 (silica gel, hexanes:EtOAc, 4:1); IR (film) ν_{max} 3351 (br), 2933, 2859, 1470, 1388, 1254, 1101 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.65 (t, *J* = 6.4 Hz, 2 H), 3.62 (t, *J* = 6.4 Hz, 2 H), 1.63–1.51 (m, 4 H), 1.46–1.37 (m, 2 H), 0.89 (s, 9 H), 0.05

(s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 63.5, 63.3, 32.9 (2 C), 26.3 (3 C), 22.4, 18.7, –4.9 (2 C); HRMS (FAB) calcd for $C_{11}H_{27}O_2Si$ $[M+H]^+$ 219.1780, found 219.1779.

General Swern Procedure: DMSO (3.75 mL, 52.8 mmol, 2.0 equiv) was added dropwise over the course of 5 min to a solution of oxalyl chloride (2.76 mL, 31.7 mmol, 1.2 equiv) in CH_2Cl_2 (264 mL) at –78 °C, and the resultant colorless solution was stirred at –78 °C for 5 min. A solution of the freshly prepared monoTBS alcohol (5.77 g, 26.4 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) was then added slowly over the course of 10 min, and the resultant colorless solution was stirred for an additional 5 min at –78 °C. Finally, Et_3N (14.6 mL, 106 mmol, 4.0 equiv) was added slowly via syringe, and the reaction contents were allowed to warm slowly to –40 °C over the course of 2 h. Upon completion, the reaction contents were quenched by the addition of water (200 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were then washed with 1 M HCl (100 mL), dried ($MgSO_4$), filtered, and concentrated to afford the desired aldehyde as a light yellow oil, which was carried forward without any additional purification.

Next, KO*t*-Bu (1.0 M in THF, 29.0 mL, 29.0 mmol, 1.1 equiv) was added slowly to a suspension of propyltriphenylphosphonium bromide (12.2 g, 31.7 mmol, 1.2 equiv) in THF (86 mL) at 0 °C. The resultant orange solution was allowed to warm to 25 °C and stirred for an additional 30 min, then re-cooled to 0 °C. A solution of the aldehyde produced above (26.4 mmol assumed, 1.0 equiv) in THF (20 mL) was added slowly into the ylid solution via cannula. After stirring for 1 h at 0 °C, the reaction contents were quenched by the sequential addition of saturated aqueous NH_4Cl (50 mL) and water (50 mL), and extracted with Et_2O (3 × 100 mL). The combined organic layers were then

washed with brine (200 mL), dried ($MgSO_4$), filtered, and concentrated. The bulk of the triphenylphosphine oxide byproduct was removed by slowly concentrating the resultant crude product from a solution of CH_2Cl_2:hexanes (1:1, 200 mL) until approximately 50 mL solvent remained. The resultant slurry was filtered, and the precipitate was rinsed with hexanes (2 × 30 mL); the combined filtrate and rinses were concentrated to afford the internal alkene product as a light yellow oil, which was carried forward without any additional purification. [Note: The Wittig reaction was not entirely stereospecific; the desired *Z*-alkene was contaminated with, and inseparable from, about 8% of the undesired *E*-alkene. This undesired isomer was carried through all steps, at no stage being separable by chromatography, as such resulting in a slight impurity in bromoetherification substrates]. Lastly, a solution of TBAF (1.0 M in THF, 31.7 mL, 31.7 mmol, 1.2 equiv) was added to a solution of crude prepared internal alkene (26.4 mmol assumed, 1.0 equiv) in THF (94 mL) at 0 °C, and the resultant reaction mixture was stirred at 0 °C for 1 h before being warmed to 25 °C. After an additional 3 h at 25 °C, the reaction contents were quenched by the sequential addition of saturated aqueous NH_4Cl (50 mL) and water (50 mL) and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant light brown oil was purified by flash column chromatography (silica gel, hexanes:EtOAc, 19:1→4:1) to afford **50** (2.44 g, 72% yield over 3 steps) as a colorless viscous oil. **50**: R_f = 0.44 (silica gel, hexanes:EtOAc, 4:1); IR (film) ν_{max} 3332 (br), 3005, 2934, 1458, 1276, 1261, 1062, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.42–5.28 (m, 2 H), 3.65 (t, *J* = 6.8 Hz, 2 H), 2.10–2.00 (m, 4 H), 1.58 (m, 2 H), 1.44 (m, 2 H), 1.35 (br s, 1 H), 0.96 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 132.2, 128.9, 63.1, 32.5, 26.9, 26.0, 20.7, 14.5; HRMS (EI) calcd for $C_8H_{16}O$ $[M]^+$ 128.1201, found 128.1199.

47. Prepared according to the general Swern procedure described above in the synthesis of **50**. **50** (2.44 g, 19.0 mmol) was subjected to oxidation followed by purification by flash column chromatography (silica gel, hexanes:EtOAc, 1:0→19:1) to afford (5*Z*)-octenal (**47**, 2.18 g, 91% yield) as a light yellow oil. **47**: R_f = 0.36 (silica gel, hexanes:EtOAc, 19:1); IR (film) ν_{max} 3005, 2962, 2934, 1748, 1242 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.77 (t, *J* = 2.0 Hz, 1 H), 5.42 (m, 1 H), 5.27 (m, 1 H), 2.43 (td, *J* = 7.2, 2.0 Hz, 2 H), 2.12–1.97 (m, 4 H), 1.70 (quintet, *J* = 7.2 Hz, 2 H), 0.96 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.8, 133.1, 127.8, 43.4, 26.5, 22.2, 20.7, 14.4; HRMS (FAB) calcd for $C_8H_{13}O$ $[M–H]^+$ 125.0966, found 125.0965.

Alpha-Chlorination/Aldol Addition:

51. Prepared according to the procedure described below for the synthesis of **54.** (4*E*)-Heptenal (**38**, 1.82 g, 16.2 mmol) was α-chlorinated to yield (4*E*)-2-chloro-4-heptenal (1.88 g, 79% yield – no vacuum distillation necessary) as a fragrant colorless oil. The aldol addition with acetone was performed immediately to yield **51** (1.35 g, 62% yield) as a colorless viscous oil after purification by careful flash column chromatography (silica gel, hexanes:EtOAc, 1:0→7:3).

52. Prepared according to the procedure described below for the synthesis of **54.** (4*Z*)-Heptenal (**41**, 2.24 g, 20.0 mmol) was α-chlorinated to yield (4*Z*)-2-chloro-4-heptenal (2.23 g, 76% yield after vacuum distillation: 2 mm Hg at 50 °C) as a fragrant colorless oil. The aldol addition with acetone was performed immediately to yield **52**

(1.56 g, 60% yield) as a colorless viscous oil after purification by careful flash column chromatography (silica gel, hexanes:EtOAc, 1:0→7:3).

53. Prepared according to the procedure described below for the synthesis of **54.** (5*E*)-Octenal (**44**, 1.26 g, 10.0 mmol) was α-chlorinated to yield the highly unstable (5*E*)-2-chloro-5-octenal (0.600 g, 37% yield after vacuum distillation: 2 mm Hg at 60 °C) as a fragrant colorless oil. The aldol addition with acetone was performed immediately to yield **53** (0.383 g, 56% yield) as a colorless viscous oil after purification by careful flash column chromatography (silica gel, hexanes:EtOAc, 1:0→7:3).

54. Prepared according to a procedure adapted from the work of Britton and co-workers: Kang, B.; Mowat, J.; Pinter, T.; Britton, R. *Org. Lett.* **2009**, *11*, 1717–1720. A suspension of NCS (3.47 g, 26.0 mmol, 1.3 equiv) and L-proline (0.230 g, 2.00 mmol, 0.10 equiv) in CH_2Cl_2 (60 mL) was cooled to 0 °C, and (5*Z*)-octenal (**47**, 2.52 g, 20.0 mmol, 1.0 equiv) was added. The resultant reaction mixture was allowed to warm very slowly, approaching 25 °C. Once the reaction had reached ~50% conversion as judged by NMR analysis of reaction aliquots (~3 h, 9 °C), a second portion of L-proline (0.230 g, 2.00 mmol, 0.10 equiv) was added and the reaction was stirred for an additional 3 h with continued slow warming. Upon completion (final reaction temperature: 18 °C), the reaction contents were diluted with hexanes (120 mL) and cooled to –78 °C. The resultant slurry was filtered (precipitate was rinsed with 2 × 15 mL of cold hexanes) and the combined filtrate and rinses were concentrated (→150 mm Hg at 20 °C) to a total volume of ~20 mL. The reaction contents were then cooled to –20 °C for 16 h, during which time more precipitate formed. The filtrate was decanted and concentrated (→100 mm Hg at 20 °C). The resultant yellow oil was purified by distillation under reduced

pressure (2 mm Hg at 60 °C) to afford (5*Z*)-2-chloro-5-octenal (2.01 g, 63% yield) as a fragrant colorless viscous oil. [Note: this unsaturated a-chloro aldehyde, as with all others produced by this procedure, was rather unstable and was used immediately]. Pressing forward, *n*-BuLi (1.5 M in hexane, 7.28 mL, 10.9 mmol, 1.05 equiv) was added dropwise to a solution of *i*Pr_2NH (1.76 mL, 12.5 mmol, 1.2 equiv) in THF (52 mL) at –78 °C. The resultant colorless solution was removed from the cold bath and allowed to warm (to ~0 °C) over 15 min, then re-cooled to –78 °C. Acetone (0.766 mL, 10.4 mmol, 1.0 equiv) was added dropwise to the resultant LDA solution and the reaction contents were stirred for 30 min at –78 °C. The aldehyde produced above, (5*Z*)-2-chloro-5-octenal (2.01 g, 12.5 mmol, 1.2 equiv), was then added dropwise and the resultant colorless solution was stirred for an additional 60 min at –78 °C. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (30 mL) and water (30 mL) and extracted with hexanes:EtOAc (1:1, 3 × 80 mL). The combined organic layers were then washed with brine (150 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant crude yellow oil was purified by careful flash column chromatography (silica gel, hexanes:EtOAc, 1:0→7:3) to afford **54** (1.38 g, 61% yield) as a colorless viscous oil. [Note: although stable to silica gel, the aldol products tended to decompose over time and as such were used immediately].

Production of Both c*is*- and *trans*-Diols:

37/55. Prepared according to the procedure described for the synthesis of **46/61**. Reduction of **51** (1.30 g, 6.35 mmol) afforded mostly pure *cis*-diol **55** (0.635 g) as a white solid along with the separable *trans*-diol **37** (0.397 g, 30% yield). Analytically pure **55**

was obtained by recrystallization (10 mL boiling hexanes) to afford 0.460 g (35% yield) white needles. **37**: R_f = 0.39 (silica gel, hexanes:EtOAc, 1:1); IR (film) ν_{max} 3363 (br), 2965, 2932, 2874, 1459, 1376, 1067, 967 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.60 (m, 1 H), 5.45 (m, 1 H), 4.18 (m, 1 H), 4.02 (m, 1 H), 3.95 (m, 1 H), 2.97 (d, *J* = 6.0 Hz, 1 H), 2.56 (m, 1 H), 2.42 (m, 1 H), 2.14 (br s, 1 H), 2.04 (quintet, *J* = 7.2 Hz, 2 H), 1.81 (ddd, *J* = 14.4, 8.8, 2.8 Hz, 1 H), 1.67 (ddd, *J* = 14.4, 8.4, 2.8 Hz, 1 H), 1.26 (d, *J* = 6.0 Hz, 3 H), 0.98 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 124.3, 71.5, 67.0, 65.5, 40.0, 37.0, 25.7, 23.9, 13.8; HRMS (FAB) calcd for $C_{10}H_{20}ClO_2$ $[M+H]^+$ 207.1152, found 207.1160. **55**: R_f = 0.43 (silica gel, hexanes:EtOAc, 1:1); IR (film) ν_{max} 3363 (br), 2966, 2933, 1458, 1429, 1133, 1080, 968 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.60 (m, 1 H), 5.45 (m, 1 H), 4.07 (m, 1 H), 3.98 (m, 1 H), 3.87 (m, 1 H), 3.12 (br s, 2 H), 2.58–2.39 (m, 2 H), 2.04 (quintet, *J* = 7.2 Hz, 2 H), 1.80 (dt, *J* = 14.4, 2.4 Hz, 1 H), 1.62 (m, 1 H), 1.24 (d, *J* = 6.4 Hz, 3 H), 0.98 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 124.2, 75.2, 68.8, 67.0, 40.4, 36.6, 25.7, 24.3, 13.8; HRMS (FAB) calcd for $C_{10}H_{20}ClO_2$ $[M+H]^+$ 207.1152, found 207.1154.

40/57. Prepared according to the procedure described for the synthesis of **46/61**. Reduction of **52** (0.435 g) afforded *cis*-diol **57** (0.232 g, 53% yield) as a colorless amorphous solid, along with the separable *trans*-diol **40** (0.153 g, 35% yield). **40**: R_f = 0.36 (silica gel, hexanes:EtOAc, 1:1); IR (film) ν_{max} 3372 (br), 2966, 2934, 2876, 1458, 1376, 1069 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.51 (m, 1 H), 5.39 (m, 1 H), 4.18 (m, 1 H), 4.05–3.89 (m, 2 H), 2.74 (br s, 2 H), 2.65–2.41 (m, 2 H), 2.06 (quintet, *J* = 7.6 Hz, 2 H), 1.81 (ddd, *J* = 14.4, 8.8, 2.8 Hz, 1 H), 1.66 (ddd, *J* = 14.4, 8.8, 2.4 Hz, 1 H), 1.26 (d, *J* = 6.4 Hz, 3 H), 0.97 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.9, 124.2,

71.7, 67.0, 65.4, 40.1, 31.5, 23.9, 20.9, 14.2; HRMS (FAB) calcd for $C_{10}H_{20}ClO_2$ $[M+H]^+$ 207.1152, found 207.1143. **57**: R_f = 0.46 (silica gel, hexanes:EtOAc, 1:1); IR (film) ν_{max} 3362 (br), 2967, 2933, 2875, 1457, 1134, 1074 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.55 (m, 1 H), 5.41 (m, 1 H), 4.09 (m, 1 H), 3.99 (ddd, *J* = 10.0, 4.8, 2.0 Hz, 1 H), 3.90 (m, 1 H), 2.82 (br s, 2 H), 2.65–2.45 (m, 2 H), 2.06 (quintet, *J* = 7.6 Hz, 2 H), 1.81 (dt, *J* = 14.4, 2.4 Hz, 1 H), 1.63 (m, 1 H), 1.25 (d, *J* = 6.0 Hz, 3 H), 0.98 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.0, 124.1, 75.4, 68.9, 67.0, 40.5, 31.1, 24.4, 21.0, 14.2; HRMS (FAB) calcd for $C_{10}H_{20}ClO_2$ $[M+H]^+$ 207.1152, found 207.1157.

43/59. Prepared according to the procedure described for the synthesis of **46/61**. Reduction of **53** (0.233 g, 1.07 mmol) afforded *cis*-diol **59** (0.128 g, 54% yield) as a colorless amorphous solid, along with the separable *trans*-diol **43** (0.062 g, 26% yield). **43**: R_f = 0.35 (silica gel, hexanes:EtOAc, 1:1); IR (film) ν_{max} 3368 (br), 2964, 2931, 1451, 1376, 1065, 968 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.54 (m, 1 H), 5.35 (m, 1 H), 4.19 (m, 1 H), 4.06–3.97 (m, 2 H), 2.72 (br s, 1 H), 2.29 (m, 1 H), 2.11 (sextet, *J* = 7.6 Hz, 1 H), 2.00 (quintet, *J* = 7.2 Hz, 2 H), 1.93–1.72 (m, 3 H), 1.62 (ddd, *J* = 14.4, 8.4, 2.4 Hz, 1 H), 1.58 (br s, 1 H), 1.28 (d, *J* = 6.4 Hz, 3 H), 0.97 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.8, 127.3, 72.0, 67.5, 65.5, 40.2, 33.3, 29.5, 25.7, 24.0, 14.0; HRMS (FAB) calcd for $C_{11}H_{22}ClO_2$ $[M+H]^+$ 221.1308, found 221.1306. **59**: R_f = 0.42 (silica gel, hexanes:EtOAc, 1:1); IR (film) ν_{max} 3367 (br), 2964, 2931, 1449, 1076, 968 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.53 (m, 1 H), 5.35 (m, 1 H), 4.07 (m, 1 H), 4.01–3.88 (m, 2 H), 2.86 (br s, 2 H), 2.29 (m, 1 H), 2.10 (sextet, *J* = 7.2 Hz, 1 H), 2.00 (quintet, *J* = 7.2 Hz, 2 H), 1.90–1.59 (m, 4 H), 1.24 (d, *J* = 6.0 Hz, 3 H), 0.97 (t, *J* = 7.6 Hz, 3 H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 133.9, 127.3, 75.8, 68.9, 67.3, 40.5, 32.9, 29.5, 25.7, 24.3, 14.0; HRMS (FAB) calcd for $C_{11}H_{22}ClO_2$ $[M+H]^+$ 221.1308, found 221.1300.

46/61. Prepared according to a procedure adapted from the work of Britton and co-workers: Kang, B.; Mowat, J.; Pinter, T.; Britton, R. *Org. Lett.* **2009**, *11*, 1717–1720. $NaBH_4$ (0.195 g, 5.16 mmol, 1.2 equiv) was added in a single portion to a solution of ketone **54** (0.940 g, 4.30 mmol, 1.0 equiv) in MeOH (43 mL) at –20 °C. After 15 min at –20 °C, the clear solution was quenched by the careful addition of saturated aqueous NH_4Cl (40 mL) and water (40 mL) and extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant crude oil was purified by flash column chromatography (silica gel, hexanes:EtOAc, 1:0→1:1) to afford *cis*-diol **61** (0.604 g, 64% yield, contaminated with minor inseparable impurities) as a colorless amorphous solid, along with the separable *trans*-diol **46** (0.247 g, 26% yield). **46**: R_f = 0.36 (silica gel, hexanes:EtOAc, 1:1); IR (Film) ν_{max} 3362 (br), 2965, 2933, 2874, 1455, 1069 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.44 (m, 1 H), 5.28 (m, 1 H), 4.19 (m, 1 H), 4.06–3.95 (m, 2 H), 2.82 (d, *J* = 6.4 Hz, 1 H), 2.34–2.18 (m, 2 H), 2.07 (quintet, *J* = 7.2 Hz, 2 H), 1.95 (d, *J* = 4.4 Hz, 1 H), 1.93–1.70 (m, 3 H), 1.63 (ddd, *J* = 14.8, 8.8, 2.4 Hz, 1 H), 1.27 (d, *J* = 6.4 Hz, 3 H), 0.97 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.5, 127.2, 72.0, 67.5, 65.5, 40.2, 33.4, 24.2, 24.0, 20.7, 14.5; HRMS (FAB) calcd for $C_{11}H_{22}ClO_2$ $[M+H]^+$ 221.1308, found 221.1307. **61**: R_f = 0.46 (silica gel, hexanes:EtOAc, 1:1); IR (film) ν_{max} 3363 (br), 2965, 2933, 2874, 1455, 1136, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.43 (m, 1 H), 5.28 (m, 1 H), 4.06 (m, 1 H), 3.97 (m, 1 H), 3.90 (ddd, *J* = 10.4, 4.8, 3.2 Hz, 1 H), 3.40 (d, *J* = 4.0 Hz, 1 H), 2.87 (d, *J* = 2.4 Hz, 1 H), 2.34–2.18 (m, 2 H), 2.07 (quintet

of doublets, J = 7.6, 0.8 Hz, 2 H), 1.89–1.58 (m, 4 H), 1.24 (d, J = 6.4 Hz, 3 H), 0.97 (t, J = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.6, 127.2, 75.8, 68.8, 67.3, 40.5, 32.9, 24.3, 24.1, 20.7, 14.5; HRMS (FAB) calcd for $C_{11}H_{22}ClO_2$ $[M+H]^+$ 221.1308, found 221.1306.

Cyclization/Carbonate Formation to Form Bromoetherification Substrates:

32. Prepared according to the procedures described for the synthesis of **45**. Cyclization of *trans*-diol **37** (0.260 g, 1.26 mmol) at 130 °C for 2 h afforded the desired hydroxytetrahydrofuran intermediate (0.122 g, 57% yield) as a colorless viscous oil. Carbonate formation on 0.50 mmol scale afforded **32** (0.104 g, 77% yield) as a colorless viscous oil. **32**: R_f = 0.44 (silica gel, hexanes:EtOAc, 9:1); IR (film) ν_{max} 2974, 2934, 2873, 1739, 1369, 1281, 1256, 1167 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55 (m, 1 H), 5.39 (m, 1 H), 5.08 (m, 1 H), 3.92 (m, 1 H), 3.68 (td, J = 6.8, 4.0 Hz, 1 H), 2.47 (quintet, J = 7.2 Hz, 1 H), 2.41–2.29 (m, 2 H), 2.00 (m, 2 H), 1.58 (ddd, J = 14.0, 7.6, 2.8 Hz, 1 H), 1.47 (s, 9 H), 1.31 (d, J = 6.4 Hz, 3 H), 0.95 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 134.9, 124.7, 82.1, 82.0, 77.9, 73.7, 40.8, 32.4, 27.9 (3 C), 25.7, 21.5, 13.8; HRMS (FAB) calcd for $C_{15}H_{27}O_4$ $[M+H]^+$ 271.1909, found 271.1912.

56. Prepared according to the procedures described for the synthesis of **45**. Cyclization of *cis*-diol **55** (0.460 g, 2.23 mmol) at 130 °C for 2 h afforded the desired hydroxytetrahydrofuran intermediate (0.316 g, 83% yield) as a colorless viscous oil. Carbonate formation on 0.50 mmol scale afforded **56** (0.100 g, 74% yield) as a colorless viscous oil. **56**: R_f = 0.46 (silica gel, hexanes:EtOAc, 9:1); IR (film) ν_{max} 2969, 2931, 2874, 1740, 1369, 1280, 1254, 1166 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55 (m, 1 H),

5.37 (m, 1 H), 5.15 (t, *J* = 4.0 Hz, 1 H), 4.32 (m, 1 H), 4.01 (td, *J* = 7.2, 3.6 Hz, 1 H), 2.37–2.21 (m, 2 H), 2.17 (ddd, *J* = 14.0, 6.0, 1.2 Hz, 1 H), 1.99 (m, 2 H), 1.76 (ddd, *J* = 14.0, 9.2, 5.2 Hz, 1 H), 1.47 (s, 9 H), 1.23 (d, *J* = 6.0 Hz, 3 H), 0.94 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 134.9, 124.7, 82.2, 80.8, 78.3, 73.4, 41.1, 32.8, 27.9 (3 C), 25.7, 21.5, 13.8; HRMS (FAB) calcd for $C_{15}H_{27}O_4$ $[M+H]^+$ 271.1909, found 271.1901.

39. Prepared according to the procedures described for the synthesis of **45**. Cyclization of *trans*-diol **40** (0.263 g, 1.27 mmol) at 130 °C for 4 h afforded the desired hydroxytetrahydrofuran intermediate (0.155 g, 72% yield) as a colorless viscous oil. Carbonate formation on 0.30 mmol scale afforded **39** (0.068 g, 84% yield) as a colorless viscous oil. **39**: R_f = 0.34 (silica gel, hexanes:EtOAc, 9:1); IR (film) ν_{max} 2975, 2934, 2873, 1739, 1282, 1256, 1166 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48 (m, 1 H), 5.36 (m, 1 H), 5.08 (m, 1 H), 3.93 (m, 1 H), 3.70 (td, *J* = 7.2, 4.4 Hz, 1 H), 2.48 (quintet, *J* = 7.2 Hz, 1 H), 2.41 (t, *J* = 7.2 Hz, 2 H), 2.11–2.00 (m, 2 H), 1.60 (ddd, *J* = 14.0, 7.2, 2.8 Hz, 1 H), 1.47 (s, 9 H), 1.31 (d, *J* = 6.0 Hz, 3 H), 0.95 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 134.1, 124.4, 82.2, 81.7, 77.9, 73.7, 40.9, 27.9 (3 C), 27.2, 21.4, 20.8, 14.3; HRMS (FAB) calcd for $C_{15}H_{27}O_4$ $[M+H]^+$ 271.1909, found 271.1899.

58. Prepared according to the procedures described for the synthesis of **45**. Cyclization of *cis*-diol **57** (0.216 g, 1.04 mmol) at 130 °C for 5 h afforded the desired hydroxytetrahydrofuran intermediate (0.153 g, 86% yield) as a colorless viscous oil. Carbonate formation on 0.30 mmol scale afforded **58** (0.067 g, 83% yield) as a colorless viscous oil. **58**: R_f = 0.34 (silica gel, hexanes:EtOAc, 9:1); IR (film) ν_{max} 2973, 2932, 2874, 1740, 1281, 1254, 1165 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48 (m, 1 H), 5.31

(m, 1 H), 5.14 (t, *J* = 4.4 Hz, 1 H), 4.32 (m, 1 H), 4.03 (td, *J* = 7.2, 4.0 Hz, 1 H), 2.42–2.28 (m, 2 H), 2.19 (dd, *J* = 13.6, 5.6 Hz, 1 H), 2.11–1.98 (m, 2 H), 1.77 (ddd, *J* = 14.4, 9.6, 5.2 Hz, 1 H), 1.48 (s, 9 H), 1.24 (d, *J* = 6.4 Hz, 3 H), 0.95 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 134.1, 124.3, 82.3, 80.6, 78.3, 73.3, 41.1, 27.9 (3 C), 27.5, 21.5, 20.8, 14.3; HRMS (FAB) calcd for $C_{15}H_{27}O_4$ $[M+H]^+$ 271.1909, found 271.1900.

42. Prepared according to the procedures described for the synthesis of **45**. Cyclization of *trans*-diol **43** (0.198 g, 0.898 mmol) at 130 °C for 8 h afforded the desired hydroxytetrahydrofuran intermediate (0.118 g, 72% yield) as a colorless viscous oil. Carbonate formation on 0.50 mmol scale afforded **42** (0.105 g, 74% yield) as a colorless viscous oil. **42**: R_f = 0.39 (silica gel, hexanes:EtOAc, 9:1); IR (film) ν_{max} 2977, 2934, 2872, 1739, 1369, 1280, 1255, 1167 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52–5.34 (m, 2 H), 5.07 (ddd, *J* = 7.2, 4.0, 2.8 Hz, 1 H), 3.89 (m, 1 H), 3.66 (ddd, *J* = 10.0, 5.6, 3.6 Hz, 1 H), 2.47 (quintet, *J* = 7.2 Hz, 1 H), 2.19–1.93 (m, 4 H), 1.79–1.63 (m, 2 H), 1.58 (ddd, *J* = 14.0, 7.6, 2.8 Hz, 1 H), 1.47 (s, 9 H), 1.30 (d, *J* = 6.4 Hz, 3 H), 0.94 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 132.7, 128.5, 82.1, 81.4, 78.2, 73.5, 40.9, 29.4, 28.8, 27.9 (3 C), 25.7, 21.4, 14.0; HRMS (FAB) calcd for $C_{16}H_{29}O_4$ $[M+H]^+$ 285.2066, found 285.2063.

60. Prepared according to the procedures described for the synthesis of **45**. Cyclization of *cis*-diol **59** (0.128 g, 0.580 mmol) at 130 °C for 2 h afforded the desired hydroxytetrahydrofuran intermediate (0.101 g, 94% yield) as a colorless viscous oil. Carbonate formation on 0.50 mmol scale afforded **60** (0.108 g, 76% yield) as a colorless viscous oil. **60**: R_f = 0.39 (silica gel, hexanes:EtOAc, 9:1); IR (film) ν_{max} 2967, 2932,

2873, 1739, 1369, 1279, 1255, 1166 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.51–5.33 (m, 2 H), 5.15 (t, *J* = 4.0 Hz, 1 H), 4.29 (m, 1 H), 4.00 (ddd, *J* = 9.6, 6.0, 4.0 Hz, 1 H), 2.21–1.94 (m, 5 H), 1.77 (ddd, *J* = 14.0, 9.2, 5.2 Hz, 1 H), 1.71–1.51 (m, 2 H), 1.47 (s, 9 H), 1.22 (d, *J* = 6.4 Hz, 3 H), 0.94 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 132.7, 128.5, 82.2, 80.2, 78.6, 73.0, 41.1, 29.3, 29.1, 27.9 (3 C), 25.7, 21.5, 14.0; HRMS (FAB) calcd for $C_{16}H_{29}O_4$ $[M+H]^+$ 285.2066, found 285.2073.

45. Prepared according to a procedure adapted from the work of Britton and co-workers: Kang, B.; Chang, S.; Decker, S.; Britton, R. *Org. Lett.* **2010**, *12*, 1716–1719. *trans*-Diol **46** (0.274 g, 1.24 mmol, 1.0 equiv) was dissolved in MeOH (24 mL) and water (12 mL) in a high-pressure sealed tube. The reaction vessel was then sealed and heated at 130 °C for 4 h. Upon completion, the reaction mixture was allowed to cool to 25 °C, quenched by the addition of saturated aqueous $NaHCO_3$ (30 mL) and water (30 mL), and extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant yellow oil was purified by flash column chromatography (silica gel, hexanes:EtOAc, 1:0→7:3) to afford the hydroxytetrahydrofuran intermediate (0.183 g, 80% yield) as a colorless viscous oil. R_f = 0.46 (silica gel, hexanes:EtOAc, 3:2); IR (film) ν_{max} 3419 (br), 3004, 2965, 2933, 2870, 1453, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.45–5.31 (m, 2 H), 4.16 (m, 1 H), 3.90 (sextet, *J* = 6.4 Hz, 1 H), 3.52 (td, *J* = 6.8, 3.6 Hz, 1 H), 2.41 (m, 1 H), 2.22–2.10 (m, 2 H), 2.05 (quintet, *J* = 7.2 Hz, 2 H), 1.81–1.62 (m, 2 H), 1.53 (d, *J* = 7.6 Hz, 1 H), 1.48 (ddd, *J* = 14.0, 6.8, 2.0 Hz, 1 H), 1.33 (d, *J* = 6.4 Hz, 3 H), 0.95 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.6, 128.5, 83.0, 73.5, 73.4, 43.7, 28.9, 24.0, 22.3, 20.7, 14.4; HRMS (FAB) calcd for $C_{11}H_{21}O_2$ $[M+H]^+$ 185.1542, found 185.1549. Next, a

solution of *n*-BuLi (1.5 M in hexanes, 0.662 mL, 0.993 mmol, 1.0 equiv) was added to a solution of the freshly prepared hydroxytetrahydrofuran (0.183 g, 0.993 mmol, 1.0 equiv) in THF (8 mL) at 0 °C. After stirring for 5 min at 0 °C, a solution of Boc_2O (0.217 g, 0.993 mmol, 1.0 equiv) in THF (2 mL) was added slowly, and the resultant colorless solution was warmed to 25 °C and stirred for 1 h. Upon completion, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (10 mL) and water (10 mL). The crude product was extracted into Et_2O (3 × 15 mL), and the combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the resultant yellow oil by flash column chromatography (silica gel, hexanes:EtOAc, 19:1) afforded **45** (0.232 g, 82% yield) as a colorless viscous oil [Note: as mentioned above, the previous Wittig reaction was not entirely stereoselective, as such **45** was contaminated with approximately 8% of undesired *E*-alkene **42**]. **45**: R_f = 0.43 (silica gel, hexanes:EtOAc, 9:1); IR (film) ν_{max} 2973, 2935, 2872, 1738, 1280, 1256, 1167 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.42–5.28 (m, 2 H), 5.07 (m, 1 H), 3.90 (sextet, *J* = 6.4 Hz, 1 H), 3.67 (m, 1 H), 2.48 (app quintet, 1 H), 2.20–2.10 (m, 2 H), 2.04 (quintet, *J* = 7.2 Hz, 2 H), 1.79–1.55 (m, 3 H), 1.47 (s, 9 H), 1.31 (d, *J* = 6.0 Hz, 3 H), 0.94 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 132.5, 128.4, 82.1, 81.4, 78.2, 73.6, 41.0, 29.0, 27.9 (3 C), 24.1, 21.4, 20.6, 14.5; HRMS (FAB) calcd for $C_{16}H_{29}O_4$ $[M+H]^+$ 285.2066, found 285.2065.

62. Prepared according to the procedures described for the synthesis of **45**. Cyclization of *cis*-diol **61** (0.590 g, 2.67 mmol) at 130 °C for 1 h afforded the desired hydroxytetrahydrofuran intermediate (0.430 g, 87% yield) as a colorless viscous oil. Carbonate formation on 0.50 mmol scale afforded **62** (0.111 g, 78% yield) as a colorless

viscous oil [Note: as mentioned above, the previous Wittig reaction was not entirely stereoselective, as such **62** was contaminated with approximately 8% of undesired *E*-alkene **60**]. **62**: R_f = 0.44 (silica gel, hexanes:EtOAc, 9:1); IR (film) ν_{max} 2969, 2933, 2872, 1739, 1369, 1280, 1254, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.41–5.27 (m, 2 H), 5.15 (t, *J* = 4.0 Hz, 1 H), 4.31 (m, 1 H), 4.00 (ddd, *J* = 9.6, 5.6, 3.6 Hz, 1 H), 2.23–1.96 (m, 5 H), 1.78 (ddd, *J* = 14.4, 9.2, 5.2 Hz, 1 H), 1.74–1.50 (m, 2 H), 1.48 (s, 9 H), 1.23 (d, *J* = 6.4 Hz, 3 H), 0.94 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 132.5, 128.4, 82.3, 80.2, 78.6, 73.0, 41.1, 29.3, 27.9 (3 C), 24.0, 21.5, 20.6, 14.5; HRMS (FAB) calcd for $C_{16}H_{29}O_4$ $[M+H]^+$ 285.2066, found 285.2055.

BDSB Cyclizations:

General Cyclization Procedure A. A cold (–25 °C) solution of BDSB (0.0659 g, 0.120 mmol, 1.2 equiv) in $MeNO_2$ (0.5 mL) was added rapidly via syringe to a solution of the cyclization precursor (0.100 mmol, 1.0 equiv) in $MeNO_2$ (4.5 mL) at –25 °C. After stirring the resultant yellow solution for 5 min at –25 °C, the flask was removed from the cold bath and stirred for an additional 5 min. Upon completion, the reaction mixture was quenched by the addition of a combination of saturated aqueous $NaHCO_3$ and 5% aqueous Na_2SO_3 (1:1, 5 mL), and the resultant biphasic mixture was stirred vigorously for 20 min at 25 °C. The reaction contents were added to brine (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes:EtOAc) to afford the desired products as detailed below.

General Cyclization Procedure B. Identical to cyclization Procedure A, except that 1.5 equivalents of BDSB was utilized and the reaction was stirred for 15 min at –25 °C before being removed from the cold bath and stirred for an additional 5 min prior to quench. This procedure proved ideal for the more sluggish reactions forming the 8-*endo* products.

General Cyclization Procedure C. Identical to cyclization Procedure A, except that the reaction was quenched immediately after 5 min at –25 °C without allowing any warming of the reaction mixture. This procedure was utilized for all non-carbonate substrates.

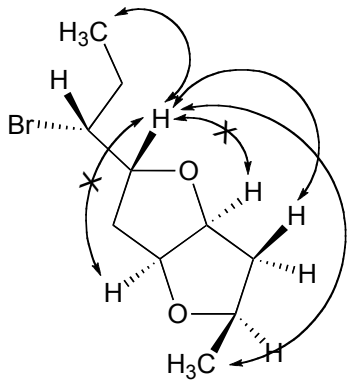
8-*endo* Bromoethers:

34. Cyclization of **32** utilizing General Cyclization Procedure B afforded **34** (0.0198 g, 68% yield) as a colorless amorphous solid. **34**: R_f = 0.49 (silica gel, hexanes:EtOAc, 3:2); IR (film) ν_{max} 2971, 2939, 2881, 1805, 1192, 1041 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.86–4.77 (m, 2 H), 4.02 (sextet of doublets, *J* = 6.4, 2.8 Hz, 1 H), 3.81 (m, 1 H), 3.62 (td, *J* = 10.8, 4.0 Hz, 1 H), 2.60–2.47 (m, 2 H), 2.19 (m, 1 H), 2.06 (dt, *J* = 14.4, 3.2 Hz, 1 H), 1.91 (sextet of doublets, *J* = 7.2, 4.0 Hz, 1 H), 1.70 (sextet of doublets, *J* = 7.2, 3.6 Hz, 1 H), 1.27 (d, *J* = 6.8 Hz, 3 H), 0.89 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 79.7, 78.8, 74.1, 70.6, 48.1, 39.3, 34.1, 27.6, 18.7, 6.9; HRMS (FAB) calcd for $C_{11}H_{18}BrO_4$ $[M+H]^+$ 293.0388, found 293.0395.

63. Cyclization of **56** utilizing General Cyclization Procedure B afforded **63** (0.0195 g, 67% yield) as a white crystalline solid. **63**: R_f = 0.54 (silica gel, hexanes:EtOAc, 3:2); IR (film) ν_{max} 2973, 2939, 2881, 1807, 1188, 1052, 1034 cm^{-1}; ^1H

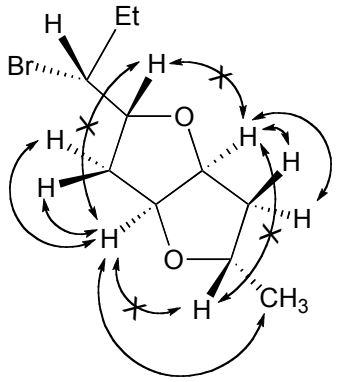
NMR (400 MHz, $CDCl_3$) δ 4.98 (ddd, *J* = 12.4, 7.2, 3.6 Hz, 1 H), 4.83 (ddd, *J* = 10.8, 7.2, 1.2 Hz, 1 H), 3.79 (quintet, *J* = 6.4 Hz, 1 H), 3.72 (m, 1 H), 3.26 (m, 1 H), 2.59 (m, 1 H), 2.52–2.42 (m, 2 H), 2.12 (sextet of doublets, *J* = 7.2, 2.4 Hz, 1 H), 2.02 (dd, *J* = 14.4, 3.6 Hz, 1 H), 1.44 (m, 1 H), 1.29 (d, *J* = 6.4 Hz, 3 H), 0.94 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 84.4, 80.0, 75.6, 73.4, 49.3, 39.1, 32.5, 28.0, 20.1, 9.3; HRMS (FAB) calcd for $C_{11}H_{18}BrO_4$ $[M+H]^+$ 293.0388, found 293.0395.

65. Attempted cyclization of **39** utilizing General Cyclization Procedure B afforded **65** (0.0116 g, 47% yield) as a colorless amorphous solid (as the predominant product of a complex mixture of products). Connectivity and stereochemistry were determined by COSY and NOESY NMR experiments (see attached spectra). As additional evidence for the structure of **65**, cyclization of the alcohol precursor to **64** using BDSB was undertaken using Procedure C, and **65** was produced in >90% yield. **65**: R_f = 0.40 (silica gel, hexanes:EtOAc, 4:1); IR (film) ν_{max} 2970, 2934, 2877, 1384, 1117, 1083 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.79 (quintet, *J* = 4.0 Hz, 1 H), 4.46 (t, *J* = 4.8 Hz, 1 H), 4.22 (quintet, *J* = 5.2 Hz, 1 H), 3.92–3.84 (m, 2 H), 2.35 (m, 1 H), 2.17 (dd, *J* = 13.2, 5.2 Hz, 1 H), 1.98–1.73 (m, 3 H), 1.55 (ddd, *J* = 13.2, 9.6, 4.0 Hz, 1 H), 1.30 (d, *J* = 6.0 Hz, 3 H), 1.09 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 85.0, 83.8, 80.4, 76.0, 60.8, 42.0, 37.5, 28.9, 20.6, 12.6; HRMS (EI) calcd for $C_{10}H_{16}BrO_2$ $[M–H]^+$ 247.0334, found 247.0328.



65
NOESY
($CDCl_3$, 500 MHz)

67. Attempted cyclization of **58** utilizing General Cyclization Procedure B above afforded **67** (8.9 mg, 36% yield) as a colorless amorphous solid (as the predominant product of a complex mixture of products). Connectivity and stereochemistry were determined by COSY and NOESY NMR experiments (see attached spectra). As additional evidence for the structure of **67**, cyclization of the alcohol precursor to **66** using BDSB was undertaken using Procedure C, and **67** was produced in >90% yield. **67**: R_f = 0.40 (silica gel, hexanes:EtOAc, 4:1); IR (film) ν_{max} 2969, 2933, 2875, 1381, 1123, 1089, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.80–4.72 (m, 2 H), 4.26–4.13 (m, 2 H), 3.86 (quintet, *J* = 4.4 Hz, 1 H), 2.27–2.15 (m, 2 H), 1.96–1.78 (m, 3 H), 1.54 (ddd, *J* = 14.8, 10.0, 4.4 Hz, 1 H), 1.24 (d, *J* = 6.0 Hz, 3 H), 1.08 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 85.4, 83.6, 82.6, 75.9, 61.7, 43.0, 39.3, 28.7, 20.8, 12.6; HRMS (EI) calcd for $C_{10}H_{16}BrO_2$ $[M–H]^+$ 247.0334, found 247.0327.



67
NOESY
($CDCl_3$, 500 MHz)

8-*exo* Bromoethers:

69. Cyclization of **42** utilizing General Cyclization Procedure A afforded **69** (0.0183 g, 60% yield) as a white crystalline solid. **69**: R_f = 0.44 (silica gel, hexanes:EtOAc, 3:2); IR (film) ν_{max} 2969, 2937, 2877, 1797, 1192, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.89–4.80 (m, 2 H), 4.11 (sextet of doublets, *J* = 6.8, 3.2 Hz, 1 H), 3.84 (ddd, *J* = 10.0, 4.4, 3.6 Hz, 1 H), 3.43 (dt, *J* = 10.4, 2.8 Hz, 1 H), 2.22–1.94 (m, 4 H), 1.89–1.68 (m, 4 H), 1.27 (d, *J* = 6.8 Hz, 3 H), 1.08 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 82.0, 78.9, 72.9, 70.5, 64.8, 34.3, 29.4, 28.3, 27.4, 19.0, 13.1; HRMS (FAB) calcd for $C_{12}H_{20}BrO_4$ $[M+H]^+$ 307.0545, found 307.0545.

70. Cyclization of **60** utilizing General Cyclization Procedure A afforded **70** (0.0254 g, 83% yield) as a colorless amorphous solid. **70**: R_f = 0.53 (silica gel, hexanes:EtOAc, 3:2); IR (film) ν_{max} 2973, 2938, 2878, 1804, 1188, 1050, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.98 (ddd, *J* = 12.4, 7.6, 3.2 Hz, 1 H), 4.79 (ddd, *J* = 10.8, 7.2, 1.2 Hz, 1 H), 3.91 (quintet, *J* = 6.4 Hz, 1 H), 3.72 (ddd, *J* = 10.4, 6.4, 2.8 Hz, 1 H), 3.45 (ddd, *J* = 11.6, 6.4, 2.0 Hz, 1 H), 2.45 (ddd, *J* = 18.4, 12.4, 5.6 Hz, 1 H), 2.22–1.90 (m, 5 H), 1.68 (m, 1 H), 1.51 (m, 1 H), 1.29 (d, *J* = 6.8 Hz, 3 H), 1.07 (t, *J* = 7.2 Hz, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 82.5, 82.3, 75.6, 73.0, 61.8, 32.6, 30.9, 27.5, 26.8, 19.8, 12.8; HRMS (FAB) calcd for $C_{12}H_{20}BrO_4$ $[M+H]^+$ 307.0545, found 307.0556.

71. Cyclization of **45** utilizing General Cyclization Procedure A [Note: 0.0108 mmol of starting material and 0.130 mmol BDSB were utilized, since 8% was the undesired *E*-alkene isomer], followed by purification by flash column chromatography (silica gel, hexanes:EtOAc, 4:1), afforded **71** (0.0283 g) as a colorless amorphous solid (contaminated with a small impurity, likely the product derived from the *E*-alkene contaminant in the starting material, ~85% yield). **71**: R_f = 0.52 (silica gel, hexanes:EtOAc, 3:2); IR (film) ν_{max} 2970, 2933, 1805, 1210, 1076, 1055 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.57 (td, *J* = 10.4, 5.6 Hz, 1 H), 4.36 (m, 1 H), 4.09 (septet, *J* = 5.6 Hz, 1 H), 3.86–3.78 (m, 2 H), 2.45 (ddt, *J* = 14.0, 7.6, 2.0 Hz, 1 H), 2.28 (ddd, *J* = 15.6, 10.0, 5.2 Hz, 1 H), 2.12 (m, 1 H), 1.99–1.72 (m, 5 H), 1.37 (d, *J* = 6.4 Hz, 3 H), 1.06 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 83.4, 81.6, 79.6, 64.3, 63.0, 39.6, 30.8, 28.6, 27.2, 22.6, 12.4; HRMS (FAB) calcd for $C_{12}H_{20}BrO_4$ $[M+H]^+$ 307.0545, found 307.0530.

72. Cyclization of **62** utilizing General Cyclization Procedure A [Note: 0.0108 mmol of starting material and 0.130 mmol BDSB were utilized, since 8% was the undesired *E*-alkene isomer] afforded **72** (0.0257 g, 84% yield) as a white crystalline solid. **72**: R_f = 0.46 (silica gel, hexanes:EtOAc, 3:2); IR (film) ν_{max} 2972, 2940, 2879, 1802, 1188, 1048, 1029 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.00 (ddd, *J* = 12.4, 7.2, 3.2 Hz, 1 H), 4.81 (ddd, *J* = 10.8, 7.2, 1.2 Hz, 1 H), 3.91 (quintet, *J* = 6.4 Hz, 1 H), 3.83 (m, 1 H), 3.40 (ddd, *J* = 11.6, 5.2, 2.0 Hz, 1 H), 2.44 (ddd, *J* = 18.0, 12.4, 5.6 Hz, 1 H), 2.13–1.84 (m, 5 H), 1.68–1.54 (m, 2 H), 1.31 (d, *J* = 6.4 Hz, 3 H), 1.07 (t, *J* = 7.2 Hz, 3 H); ^{13}C

NMR (100 MHz, $CDCl_3$) d 154.3, 82.3, 81.7, 75.7, 72.7, 62.1, 32.6, 29.7, 27.6, 27.4, 19.9, 12.5; HRMS (FAB) calcd for $C_{12}H_{20}BrO_4$ $[M+H]^+$ 307.0545, found 307.0545

Alterative Bromonium Source Cyclizations:

Bis(collidine)bromonium Triflate. A solution of $(coll)_2BrOTf$ (0.0566 g, 0.120 mmol, 1.2 equiv) in $MeNO_2$ (0.5 mL) was syringed into a solution of **45** (0.0284 g, 0.100 mmol, 1.0 equiv) in $MeNO_2$ (4.5 mL) at 0 °C. After 5 min at 0 °C, the reaction mixture was removed from the ice bath and stirred at 25 °C for an additional 5 min. Upon completion, the reaction mixture was quenched by the addition of 5% aqueous Na_2SO_3 (5 mL). The reaction contents were added to water (5 mL) and then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 1:0→7:3) to afford 0.0199 g of **71** contaminated by two minor, inseparable, impurities (calculated yield of pure **71** is 0.0159 g, 52% yield).

TBCO. TBCO (0.0492 g, 0.120 mmol, 1.2 equiv) was added in one portion to a solution of **45** (0.0284 g, 0.100 mmol, 1.0 equiv) in MeCN (5 mL) at 25 °C. After 10 min at 25 °C, the reaction mixture was quenched by the addition of a mixture of saturated aqueous $NaHCO_3$ and 5% aqueous Na_2SO_3 (1:1, 5 mL). The reaction contents were added to water (5 mL) and then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 1:0→7:3) to afford 0.0190 g (62% yield) of pure **71**.

NBS. NBS (0.0214 g, 0.120 mmol, 1.2 equiv) was added in one portion to a

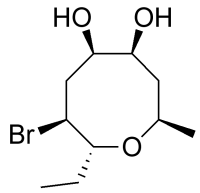
solution of **45** (0.0284 g, 0.100 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) at 25 °C. After 48 h, the solvent was removed under vacuum and the residue subjected to flash column chromatography (silica gel, hexanes:EtOAc, 1:0→1:1) to afford 3.6 mg of **71** that was approximately 75% pure by NMR (2.8 mg pure **71**, 9% yield). The remaining mass balance contained approximately 50% starting material in addition to numerous unidentified byproducts. Performing the reaction at lower temperatures or higher dilution led to only recovered starting material. Utilizing excess NBS or 3 equivalents of *N,N*-dimethylacetamide as a nucleophilic promoter resulted in faster reactions, but with increased side product formation such that even less desired product was formed. More polar solvents such as THF and DMF resulted in an increased rate of consumption of starting material, but with no product formation at all.

Post-cyclization Modification of 8-Membered Rings:

General Procedure for Acetate/Carbonate Hydrolysis. K_2CO_3 (0.069 g, 0.50 mmol, 10 equiv) was added in a single portion to a solution of the cyclic carbonate or acetate (0.050 mmol, 1.0 equiv) in MeOH (1.8 mL) and water (0.2 mL) at 0 °C. The reaction mixture was allowed to warm slowly to 25 °C and was monitored by TLC. Upon completion (~0.5 to 2 h), the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (5 mL) and water (5 mL), and the crude product was extracted into EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by flash column chromatography (silica gel, hexanes:EtOAc) afforded the desired diols as white crystalline solids (in all but one case – derivative of **70**). Recrystallization was performed by slow evaporation

from a hexanes:CH_2Cl_2 mixture to afford single crystals suitable for X-ray diffraction.

Diol Derivative of 36: White crystalline solid. R_f = 0.31 (silica gel, hexanes:EtOAc, 1:2); IR (film) ν_{max} 3357 (br), 2963, 2930, 2879, 1460, 1375, 1062, 1044 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.23 (td, *J* = 7.2, 3.6 Hz, 1 H), 4.01–3.90 (m, 3 H), 3.63 (ddd, *J* = 10.4, 5.6, 3.6 Hz, 1 H), 2.61 (ddd, *J* = 20.4, 12.4, 8.0 Hz, 1 H), 2.44 (d, *J* = 2.8 Hz, 1 H), 2.35 (br s, 1 H), 2.21 (dd, *J* = 14.8, 4.4 Hz, 1 H), 1.95–1.72 (m, 4 H), 1.18 (d, *J* = 6.8 Hz, 3 H), 0.92 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 74.8 (br), 71.8 (2 C), 69.4, 51.7, 42.2, 38.1, 27.8, 20.9, 8.1; HRMS (FAB) calcd for $C_{10}H_{20}BrO_3$ $[M+H]^+$ 267.0596, found 267.0592; structure confirmed by single crystal X-Ray diffraction. [Note: Owing to the appearance of the strangely broad carbon peak, an HSQC spectrum is also attached, establishing that the peak at 74.8 ppm is real].



Diol Derivative of 36

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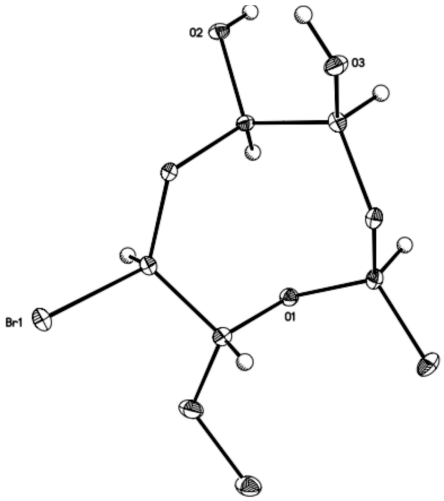
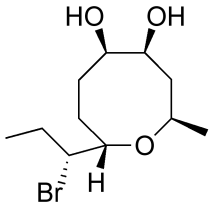


Diol Derivative of 63: White crystalline solid. R_f = 0.37 (silica gel, hexanes:EtOAc, 1:2); IR (film) ν_{max} 3372 (br), 2969, 2933, 2877, 1101, 1064, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.27 (dd, *J* = 7.6, 2.8 Hz, 1 H), 4.13 (quintet, *J* = 4.4 Hz, 1 H), 3.90 (ddd, *J* = 14.4, 10.4, 4.0 Hz, 1 H), 3.80 (m, 1 H), 3.34 (td, *J* = 9.6, 2.4 Hz, 1 H), 2.78 (ddd, *J* = 20.4, 12.4, 10.4 Hz, 1 H), 2.28 (br s, 1 H), 2.20–2.08 (m, 2 H), 2.02 (m, 1

H), 1.83 (dt, J = 14.8, 4.4 Hz, 1 H), 1.58 (br s, 1 H), 1.39 (m, 1 H), 1.21 (d, J = 6.4 Hz, 3 H), 0.94 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.3, 73.2, 72.2, 70.0, 53.5, 41.8, 37.8, 28.4, 20.9, 9.8; HRMS (FAB) calcd for $C_{10}H_{20}BrO_3$ $[M+H]^+$ 267.0596, found 267.0607; structure could not be fully solved by single crystal X-Ray diffraction, although the crystallographer (W. S.) is confident it matches the assigned structure.

Diol Derivative of 69: White crystalline solid. R_f = 0.22 (silica gel, hexanes:EtOAc, 1:2); IR (film) ν_{max} 3391 (br), 2965, 2935, 1459, 1376, 1144, 1059 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (app d, 1 H), 4.07 (sextet of doublets, J = 6.4, 2.4 Hz, 1 H), 3.93 (m, 1 H), 3.85 (m, 1 H), 3.57 (m, 1 H), 2.31 (br s, 2 H), 2.10–1.68 (m, 7 H), 1.63 (dt, J = 15.2, 4.0 Hz, 1 H), 1.19 (d, J = 6.4 Hz, 3 H), 1.06 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.7, 73.4, 72.3, 69.2, 65.0, 38.3, 29.3 (2 C), 28.3, 21.3, 13.0; HRMS (FAB) calcd for $C_{11}H_{22}BrO_3$ $[M+H]^+$ 281.0752, found 281.0767; structure confirmed by single crystal X-Ray diffraction.



Diol Derivative of 69

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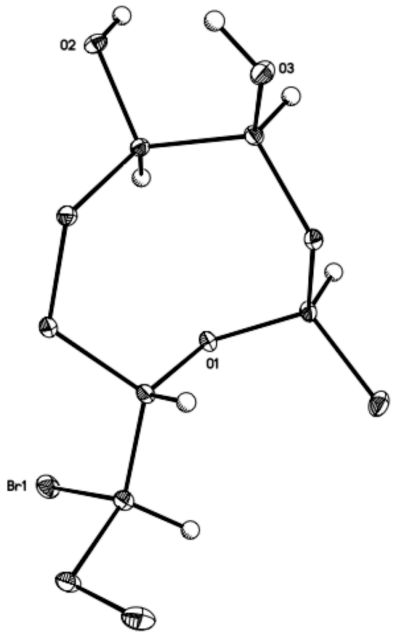
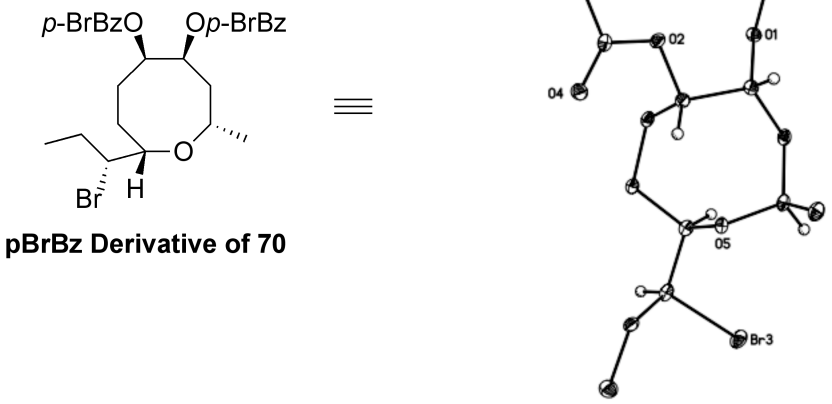


Diol Derivative of 70: Colorless amorphous solid. R_f = 0.29 (silica gel,

hexanes:EtOAc, 1:2); IR (film) ν_{max} 3373 (br), 2969, 2935, 2876, 1460, 1110, 1047, 1027, 1006 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.22 (app d, 1 H), 4.13 (dt, *J* = 10.4, 4.0 Hz, 1 H), 3.85 (m, 1 H), 3.74 (m, 1 H), 3.53 (m, 1 H), 2.24 (br s, 2 H), 2.18–1.98 (m, 4 H), 1.80–1.54 (m, 4 H), 1.23 (d, *J* = 6.4 Hz, 3 H), 1.06 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.0, 73.3, 72.7, 69.4, 63.0, 36.9, 31.4, 29.3, 27.1, 20.8, 12.7; HRMS (FAB) calcd for $C_{11}H_{20}BrO_2$ $[M\text{-}OH]^+$ 263.0647, found 263.0661.

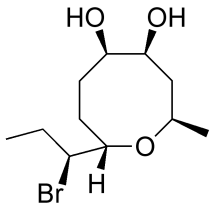
pBrBz Derivative of 70. 4-Bromobenzoyl chloride (0.059 g, 0.27 mmol, 4.0 equiv) was added to a solution of diol derivative of **70** (0.019 g, 0.067 mmol, 1.0 equiv), 4-DMAP (8.2 mg, 0.067 mmol, 1.0 equiv), and Et_3N (0.075 mL, 0.54 mmol, 8.0 equiv) in CH_2Cl_2 (1 mL) at 0 °C. The resultant colorless solution was then allowed to warm to 25 °C and was stirred at that temperature for 3 h. Upon completion, the light orange heterogeneous reaction mixture was quenched by the addition of water (8 mL) and 1 M HCl (2 mL). The crude product was then extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 19:1 + 2% Et_3N) afforded bis-bromobenzoate derivative of **70** (0.037 g, 85% yield) as a white crystalline solid. Recrystallization from boiling MeOH (8 mL) afforded single crystals suitable for X-ray diffraction. R_f = 0.44 (silica gel, hexanes:EtOAc, 9:1); IR (film) ν_{max} 2968, 2930, 2875, 2851, 1718, 1590, 1265, 1101, 1012, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.4 Hz, 2 H), 7.76 (d, *J* = 8.4 Hz, 2 H), 7.62 (d, *J* = 8.8 Hz, 2 H), 7.50 (d, *J* = 8.4 Hz, 2 H), 5.75–5.66 (m, 2 H), 3.95 (m, 1 H), 3.85 (ddd, *J* = 9.6, 6.8, 2.4 Hz, 1 H), 3.72 (m, 1 H), 2.41–2.22 (m, 3 H), 2.11 (sextet of doublets, *J* = 7.2, 2.8 Hz, 1 H), 2.05–1.85

(m, 3 H), 1.78 (m, 1 H), 1.32 (d, J = 6.4 Hz, 3 H), 1.09 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 165.1, 132.1 (2 C), 131.8 (2 C), 131.2 (4 C), 129.3 (2 C), 128.5, 128.2, 82.0, 76.2, 72.6 (2 C), 61.8, 37.1, 30.7, 27.3, 27.1, 21.4, 12.5; HRMS: No molecular ion peak could be observed; structure confirmed by single crystal X-Ray diffraction.



pBrBz Derivative of 70

Diol Derivative of 71: White crystalline solid. R_f = 0.28 (silica gel, hexanes:EtOAc, 1:2); IR (film) ν_{max} 3380 (br), 2965, 2934, 2875, 1459, 1376, 1052 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (m, 1 H), 4.07–3.90 (m, 2 H), 3.69–3.62 (app d, 2 H), 2.53 (d, J = 2.8 Hz, 1 H), 2.21 (d, J = 6.0 Hz, 1 H), 2.10–1.82 (m, 4 H), 1.79–1.57 (m, 4 H), 1.19 (d, J = 6.8 Hz, 3 H), 1.05 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 74.3, 73.5, 72.1, 69.4, 62.3, 37.9, 29.6, 27.3, 26.5, 21.3, 13.2; HRMS (FAB) calcd for $C_{11}H_{22}BrO_3$ $[M+H]^+$ 281.0752, found 281.0746; structure confirmed by single crystal X-Ray diffraction.



Diol Derivative of 71

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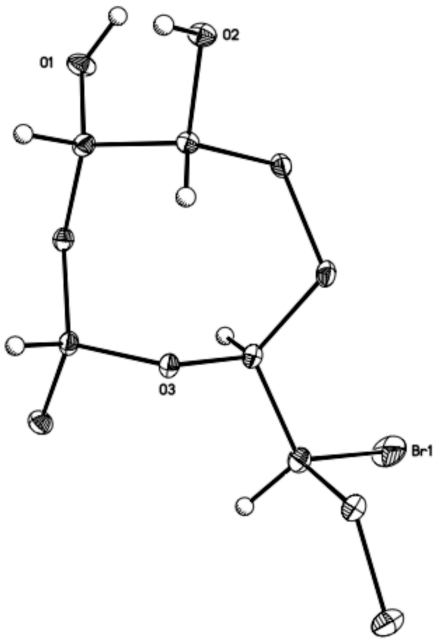
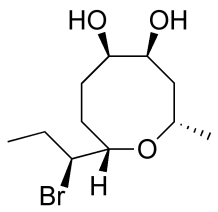


Diol Derivative of 72: White crystalline solid; R_f = 0.29 (silica gel, hexanes:EtOAc, 1:2); IR (film) ν_{max} 3394 (br), 2969, 2936, 2876, 1462, 1113, 1062, 1039, 1009 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.23 (m, 1 H), 4.14 (m, 1 H), 3.91–3.82 (m, 2 H), 3.50 (ddd, *J* = 10.8, 5.2, 2.4 Hz, 1 H), 2.40 (d, *J* = 2.4 Hz, 1 H), 2.18–1.99 (m, 3 H), 1.92 (sextet of doublets, *J* = 7.2, 3.6 Hz, 1 H), 1.85–1.55 (m, 5 H), 1.23 (d, *J* = 6.8 Hz, 3 H), 1.06 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 80.3, 73.4, 72.6, 69.4, 63.4, 37.1, 30.4, 29.3, 27.9, 20.9, 12.5; HRMS (FAB) calcd for $C_{11}H_{20}BrO_2$ $[M\text{-}OH]^+$ 263.0647, found 263.0658; structure confirmed by single crystal X-Ray diffraction.



Diol Derivative of 72

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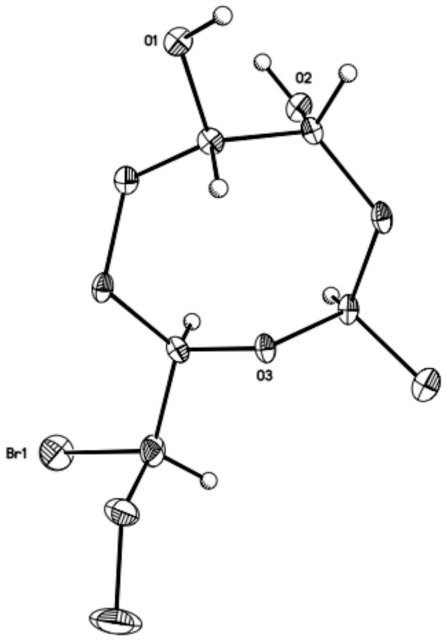


Synthesis of 8-*Exo* Bromoether 79:

75. Prepared according to a procedure adapted from the work of Reddy: Reddy, D. S. *Org. Lett.* **2004**, *6*, 3345–3347. 1,5-hexadiene-3-ol (1.34 mL, 12.0 mmol, 1.0 equiv) and 2-methoxypropene (5.77 mL, 60.0 mmol, 5.0 equiv) were added to a thick-walled reaction tube. Next, $Hg(OAc)_2$ (0.0769 g, 0.240 mmol, 0.020 equiv) was added, the tube was sealed, and the resultant mixture was heated at 120 °C for 24 h. Upon completion (as monitored by ^1H NMR of small reaction aliquots), the reaction contents were quenched by the addition of water (50 mL) and extracted with Et_2O (3 × 15 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and carefully concentrated (the desired ketone is volatile). Pressing forward without any additional purification, the crude ketone (12.0 mmol assumed, 1.0 equiv) was dissolved in MeOH (6 mL) and cooled to 0 °C. $NaBH_4$ (0.908 g, 24.0 mmol, 2.0 equiv) was then added slowly

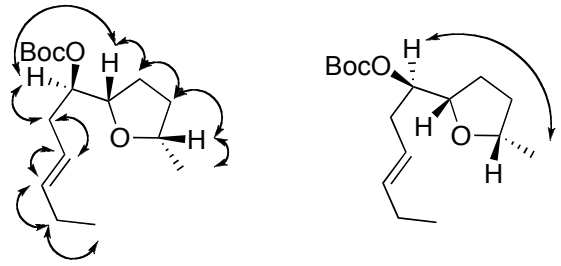
at 0 °C, and the resultant reaction mixture was stirred for 30 min at 0 °C. Upon completion, the reaction mixture was quenched at 0 °C by the slow addition of water (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and carefully concentrated. The resultant crude residue was purified by flash column chromatography (silica gel, pentane:Et_2O, 9:1→7:3) to afford **75** (3.20 g, 62% yield over 2 steps) as colorless oil. **75**: R_f = 0.43 (silica gel, hexanes:EtOAc, 7:3); IR (film) ν_{max} 3337 (br), 2968, 2925, 1429, 1374, 1128, 969, 911 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.82 (m, 1 H), 5.52–5.42 (m, 2 H), 5.06–4.95 (m, 2 H), 3.81 (sextet, *J* = 6.0 Hz, 1 H), 2.74 (m, 2 H), 2.19–2.05 (m, 2 H), 1.60–1.48 (m, 2 H), 1.19 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.2, 131.0, 128.2, 114.9, 67.7, 38.8, 36.7, 28.9, 23.4; HRMS: No molecular ion peak was observed.

76. To a solution of diene **75** (0.240 g, 1.71 mmol, 1.0 equiv) in CH_2Cl_2 (17 mL) at 25 °C was added mCPBA (0.363 g, 1.71 mmol, 1.0 equiv), and the resultant reaction mixture was stirred for 2 h at 25 °C. Upon completion, the reaction contents were quenched by the addition of saturated aqueous Na_2SO_3 (10 mL). After vigorously stirring the resultant biphasic mixture for 15 min at 25 °C, the organic layer was separated and washed with saturated aqueous $NaHCO_3$ (10 mL) and water (10 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. Pressing forward without any additional purification, the crude epoxide products (1.71 mmol assumed, 1.0 equiv) were dissolved in CH_2Cl_2 (17 mL). *Trans*-3-hexene (1.06 mL, 8.53 mmol, 5.0 equiv) and Hoveyda-Grubbs second generation catalyst (0.011 g, 0.017 mmol, 0.10 equiv) were added sequentially at 25 °C, and the reaction mixture was then stirred for 2 h at 25 °C. Upon completion (as monitored by ^1H NMR analysis of small reaction

aliquots), the reaction contents were concentrated and purified directly by flash column chromatography (silica gel, hexanes:EtOAc, 9:1→1:1) to afford **76** (0.132 g, 41% yield over 2 steps, contaminated with ~5% of an unknown side product) as a light brown viscous oil. **76**: R_f = 0.52 (silica gel, hexanes:EtOAc, 1:1); IR (film) ν_{max} 3417 (br), 2966, 2927, 1457, 1071, 968, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$; Note: although there are two diastereomers, the ^1H NMR spectrum appears to be one compound) δ 5.58 (m, 1 H), 5.39 (m, 1 H), 3.84 (m, 1 H), 2.78–2.71 (m, 2 H), 2.30–2.16 (m, 2 H), 2.02 (quintet, *J* = 7.2 Hz, 2 H), 1.88–1.67 (m, 2 H), 1.63–1.48 (m, 3 H), 1.19 (d, *J* = 6.0 Hz, 3 H), 0.97 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.2 (2 C), 123.2 (2 C), 67.6, 67.3, 58.5, 58.4, 58.2, 58.1, 35.5, 35.3, 35.0 (2 C), 28.4, 28.2, 25.6 (2 C), 23.5, 23.4, 13.6 (2 C); HRMS (EI) calcd for $C_{11}H_{20}O_2$ $[M]^+$ 184.1463, found 184.1472.

78. To a solution of epoxide **76** (0.132 g, 0.717 mmol, 1.0 equiv) in CH_2Cl_2 (25 mL) at 25 °C was added PPTS (0.255 g, 1.01 mmol, 1.4 equiv), and the resultant solution was stirred for 1 h at 25 °C. Upon completion, the reaction contents were quenched with water (10 mL). The organic layer was then separated and washed with saturated aqueous $NaHCO_3$ (10 mL) and 1 M HCl (10 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant crude residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 9:1→7:3) to afford the desired tetrahydrofuran products as a 1:1 mixture of separable diastereomers (less polar diastereomer, **77a**, 0.055 g, 42% yield; more polar diastereomer, **77b**, 0.057 g, 44% yield), both as light yellow viscous oils. The reaction was repeated and the combined less polar diastereomer (**77a**, 0.062 g, 0.34 mmol, 1.0 equiv) was then dissolved in THF (1.3 mL) and *n*-BuLi (1.6 M in hexanes, 0.223 mL, 0.357 mmol, 1.05 equiv) was added at 0 °C. The reaction was removed from the ice bath

and stirred for 10 min at 25 °C before being recooled to 0 °C. At this time, a solution of Boc_2O (0.074 g, 0.34 mmol, 1.0 equiv) in THF (0.34 mL) was added and then the reaction mixture was allowed to warm to 25 °C over 2 h with stirring. Upon completion, the reaction contents were quenched with water (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were then concentrated and purified by flash column chromatography (silica gel, hexanes:EtOAc, 99:1→9:1) to afford **78** (0.073 g, 76% yield) as a light yellow viscous oil. **78**: R_f = 0.48 (silica gel, hexanes:EtOAc, 9:1); IR (film) ν_{max} 2969, 1740, 1274, 1254, 1164, 1094, 850 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.56 (dt, *J* = 15.0, 6.5 Hz, 1 H), 5.37 (m, 1 H), 4.70 (dt, *J* = 8.0, 5.0 Hz, 1 H), 4.00 (m, 1 H), 3.92 (q, *J* = 6.0 Hz, 1 H), 2.36 (dt, *J* = 14.0, 6.0 Hz, 1 H), 2.27 (m, 1 H), 2.02–1.80 (m, 6 H), 1.47 (s, 9 H), 1.20 (d, *J* = 6.0 Hz, 3 H), 0.95 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.4, 135.4, 123.7, 81.6, 79.6, 77.6, 76.0, 34.5, 32.7, 27.8 (3 C), 27.1, 25.6, 21.2, 13.7; HRMS (FAB) calcd for $C_{16}H_{29}O_4$ $[M+H]^+$ 285.2058, found 285.2066.

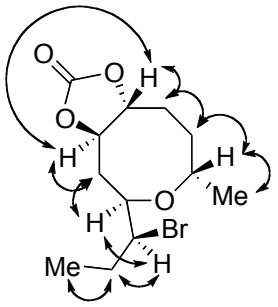


78
COSY

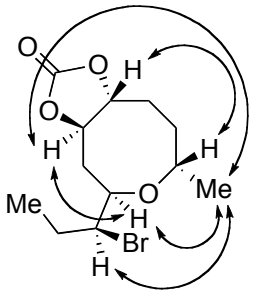
78
NOESY

79. A solution of BDSB (0.066 g, 0.12 mmol, 1.2 equiv) in $MeNO_2$ (0.5 mL) was added quickly via syringe to a solution of **78** (0.028 g, 0.10 mmol, 1.0 equiv) in $MeNO_2$ (4.5 mL) at –25 °C. After stirring for 5 min at –25 °C, the reaction flask was removed from the cooling bath and the reaction contents were stirred at 25 °C for 5 min. At that time, the reaction mixture was quenched by the addition of 5% aqueous Na_2SO_3 (3 mL)

and saturated aqueous $NaHCO_3$ (3 mL). After vigorously stirring the resultant biphasic mixture for 5 min at 25 °C, the reaction contents were extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. The resultant crude residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 9:1→1:1) to afford **79** (0.023 g, 76% yield, contaminated with ~5% of an unknown side product) as a colorless viscous oil. **79**: R_f = 0.36 (silica gel, hexanes:EtOAc, 7:3); IR (film) ν_{max} 2968, 1799, 1382, 1206, 1064, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.03 (td, *J* = 9.6, 6.4 Hz, 1 H), 4.49 (ddd, *J* = 13.2, 9.6, 3.6 Hz, 1 H), 4.03 (m, 1 H), 3.85 (dt, *J* = 10.0, 4.0 Hz, 1 H), 3.63 (m, 1 H), 2.37–2.24 (m, 2 H), 2.10 (m, 1 H), 1.93–1.68 (m, 4 H), 1.63 (m, 1 H), 1.19 (d, *J* = 6.4 Hz, 3 H), 1.09 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.0, 81.5, 79.3, 73.9, 68.7, 63.8, 34.9, 29.7, 29.0, 28.5, 20.1, 12.9; HRMS (FAB) calcd for $C_{12}H_{20}BrO_4$ $[M+H]^+$ 307.0545, found 307.0539.



79
COSY



79
NOESY

Synthesis of 83 and Cyclization to 9-*exo* Product 85:

(6*Z*)-Nonenal (90). TBSCl (9.0 g, 60. mmol, 1.0 equiv) and imidazole (4.9 g, 60. mmol, 1.0 equiv) were added sequentially to a solution of 1,6-hexanediol (7.1 g, 60. mmol, 1.0 equiv) in CH_2Cl_2 (300 mL) at 25 °C. After 12 h at 25 °C, the reaction contents

were quenched by the addition of saturated aqueous NH_4Cl (100 mL) and water (50 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL); the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resultant oil was purified by flash column chromatography (silica gel, hexanes:EtOAc, 1:0→4:1) to afford the mono-TBS protected alcohol (6.8 g, 49% yield) as a colorless viscous oil. R_f = 0.31 (silica gel, hexanes:EtOAc, 4:1); IR (film) ν_{max} 3407 (br), 2932, 2858, 1640, 1254, 1097, 835, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.64 (t, *J* = 6.8 Hz, 2 H), 3.61 (t, *J* = 6.4 Hz, 2 H), 1.62–1.48 (m, 4 H), 1.42–1.32 (m, 4 H), 1.22 (br s, 1 H), 0.89 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 63.2, 63.0, 32.8 (2 C), 26.0 (3 C), 25.6, 25.5, 18.4, –5.3 (2 C); HRMS (FAB) calcd for $C_{12}H_{29}O_2Si$ $[M+H]^+$ 233.1937, found 233.1940. The next sequence was prepared according to the procedures described above for the transformation to **50**. The freshly prepared mono-TBS protected alcohol (5.11 g, 22.0 mmol) was subject to Swern oxidation, Wittig olefination, and deprotection followed by purification by flash column chromatography (silica gel, hexanes:EtOAc, 1:0→4:1) to afford alcohol intermediate (1.47 g, 59% yield over 3 steps) as a colorless viscous oil. R_f = 0.25 (silica gel, hexanes:EtOAc, 4:1); IR (film) ν_{max} 3377 (br), 3005, 2962, 2932, 2858, 1649, 1460, 1054 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.41–5.28 (m, 2 H), 3.64 (t, *J* = 6.4 Hz, 2 H), 2.08–1.97 (m, 4 H), 1.58 (m, 2 H), 1.41–1.33 (m, 4 H), 1.24 (br s, 1 H), 0.95 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.8, 129.0, 63.0, 32.7, 29.5, 27.0, 25.4, 20.5, 14.4; HRMS (EI) calcd for $C_9H_{18}O$ $[M]^+$ 142.1358, found 142.1360. The next procedure was prepared according to the general Swern procedure for the oxidation of **50**. Oxidation of the freshly prepared alcohol (1.47 g, 12.9 mmol) afforded the desired aldehyde **90** (1.35 g, 93% yield) as a light yellow oil

that was used directly without purification. **90**: R_f = 0.48 (silica gel, hexanes:EtOAc, 9:1); IR (film) ν_{max} 3005, 2962, 2934, 2861, 2718, 1727, 1460 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.76 (t, *J* = 2.0 Hz, 1 H), 5.43–5.25 (m, 2 H), 2.43 (td, *J* = 7.2, 2.0 Hz, 2 H), 2.09–1.98 (m, 4 H), 1.65 (quintet, *J* = 7.6 Hz, 2 H), 1.39 (quintet, *J* = 7.6 Hz, 2 H), 0.95 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 132.2, 128.3, 43.8, 29.2, 26.7, 21.7, 20.5, 14.3; HRMS (FAB) calcd for $C_9H_{15}O$ $[M–H]^+$ 139.1123, found 139.1118.

91. Prepared according to the procedure described above for the synthesis of **54**. (6*Z*)-Nonenal (**90**, 1.35 g) was α-chlorinated to yield (6*Z*)-2-chloro-6-nonenal (1.99 g, 82% yield) as a colorless viscous oil that was used directly without purification. The aldol addition with acetone was performed immediately, followed by purification by careful flash column chromatography (silica gel, hexanes:EtOAc, 1:0→4:1) to afford the desired ketone (0.963 g, 53% yield) as a colorless viscous oil. R_f = 0.28 (silica gel, hexanes:EtOAc, 4:1); IR (film) ν_{max} 3435 (br), 3005, 2962, 2934, 2872, 1714, 1362, 1165, 1080 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.38 (m, 1 H), 5.30 (m, 1 H), 4.10 (m, 1 H), 3.92 (ddd, *J* = 9.6, 6.0, 3.2 Hz, 1 H), 3.24 (d, *J* = 5.2 Hz, 1 H), 2.89–2.74 (m, 2 H), 2.22 (s, 3 H), 2.12–1.98 (m, 4 H), 1.90 (m, 1 H), 1.73–1.58 (m, 2 H), 1.46 (m, 1 H), 0.96 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3, 132.4, 128.2, 70.8, 65.8, 45.9, 33.3, 30.9, 26.4 (2 C), 20.5, 14.3; HRMS (FAB) calcd for $C_{12}H_{22}ClO_2$ $[M+H]^+$ 233.1308, found 233.1308. The next procedure was prepared according to the procedure described above for the synthesis of **46/61**. $NaBH_4$ reduction of the freshly prepared ketone (0.421 g, 1.81 mmol) followed by purification by flash column chromatography (silica gel, hexanes:EtOAc, 4:1→1:1) afforded *cis*-diol **91** (0.282 g, 60% yield) [along with the corresponding *trans*-diol (0.097 g, 20% yield)] as a colorless amorphous solid. **91**: R_f =

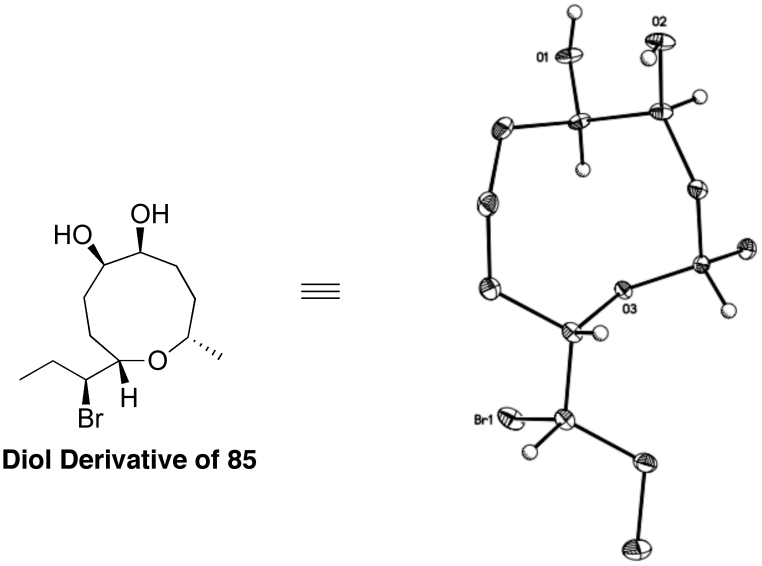
0.29 (silica gel, hexanes:EtOAc, 7:3); IR (film) ν_{max} 3369 (br), 3005, 2965, 2933, 2873, 1457, 1137, 1076 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.43–5.25 (m, 2 H), 4.06 (m, 1 H), 3.95 (m, 1 H), 3.88 (m, 1 H), 3.51 (d, *J* = 4.0 Hz, 1 H), 3.00 (d, *J* = 2.0 Hz, 1 H), 2.11–1.96 (m, 4 H), 1.87–1.38 (m, 6 H), 1.23 (d, *J* = 6.0 Hz, 3 H), 0.95 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.3, 128.2, 75.6, 68.7, 67.7, 40.2, 32.4, 26.6, 26.4, 24.1, 20.5, 14.3; HRMS (FAB) calcd for $C_{12}H_{24}ClO_2$ $[M+H]^+$ 235.1465, found 235.1466.

83. Prepared according to the procedures described above for the synthesis of **45**. Cyclization of **91** (0.150 g, 0.64 mmol) at 130 °C for 12 h followed by flash column chromatography (silica gel, hexanes:EtOAc, 9:1→1:1) afforded the desired hydroxytetrahydrofuran (0.120 g, 95% yield) as a colorless viscous oil. A portion of the cyclized product (0.060 g, 0.30 mmol) was taken forward to afford carbonate **83** (0.065 g, 75% yield) after flash column chromatography (silica gel, hexanes:EtOAc, 19:1→4:1) as a colorless viscous oil. **83**: R_f = 0.35 (silica gel, hexanes:EtOAc, 9:1); IR (film) ν_{max} 2966, 2933, 2871, 1739, 1369, 1280, 1255, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.40–5.26 (m, 2 H), 5.16 (t, *J* = 4.0 Hz, 1 H), 4.31 (m, 1 H), 4.00 (m, 1 H), 2.18 (ddd, *J* = 13.6, 6.0, 1.2 Hz, 1 H), 2.09–1.97 (m, 4 H), 1.77 (ddd, *J* = 14.4, 9.6, 5.2 Hz, 1 H), 1.65–1.47 (m, 3 H), 1.48 (s, 9 H), 1.36 (m, 1 H), 1.23 (d, *J* = 6.0 Hz, 3 H), 0.94 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 131.9, 128.7, 82.1, 80.7, 78.5, 72.9, 40.9, 28.8, 27.8 (3 C), 27.1, 26.4, 21.3, 20.5, 14.3; HRMS (FAB) calcd for $C_{17}H_{31}O_4$ $[M+H]^+$ 299.2222, found 299.2217.

85. Prepared according to General Cyclization Procedure A described above. BDSB cyclization of **83** (0.0298 g, 0.100 mmol) followed by flash column chromatography (silica gel, hexanes:EtOAc, 1:0→1:1) afforded **85** (0.0110 g, 34% yield)

as a colorless amorphous solid. **85**: R_f = 0.48 (silica gel, hexanes:EtOAc, 7:3); IR (film) ν_{max} 2969, 2939, 2876, 1799, 1748, 1379, 1243, 1199, 1121 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.97 (ddd, *J* = 11.6, 6.4, 2.4 Hz, 1 H), 4.82 (q, *J* = 6.8 Hz, 1 H), 3.94–3.83 (m, 2 H), 3.53 (m, 1 H), 2.60 (ddd, *J* = 18.0, 11.6, 6.4 Hz, 1 H), 2.02–1.78 (m, 5 H), 1.75–1.60 (m, 4 H), 1.34 (d, *J* = 6.4 Hz, 3 H), 1.06 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 83.3, 80.9, 76.7, 73.9, 60.7, 33.9, 28.1, 27.1, 26.8, 21.7, 20.1, 12.5; HRMS (FAB) calcd for $C_{13}H_{22}BrO_4$ $[M+H]^+$ 321.0701, found 321.0704.

Diol Derivative of 85. Prepared according to the procedure described above for general acetate/carbonate hydrolysis. Hydrolysis of **85** (0.011 g, 0.034 mmol) followed by purification by flash column chromatography (silica gel, hexanes:EtOAc, 4:1→0:1) afforded the diol derivative of **85** (7.4 mg, 74% yield) as a white crystalline solid. Crystals suitable for X-ray diffraction were grown by slow evaporation from a CH_2Cl_2:toluene mixture. R_f = 0.20 (silica gel, hexanes:EtOAc, 1:1); IR (film) ν_{max} 3375 (br), 2966, 2926, 1461, 1331, 1076, 995 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.27 (m, 1 H), 4.18 (m, 1 H), 3.92–3.83 (m, 2 H), 3.49 (ddd, *J* = 10.4, 4.4, 2.0 Hz, 1 H), 2.26 (ddd, *J* = 14.8, 9.6, 4.4 Hz, 1 H), 2.12 (br s, 1 H), 2.01–1.49 (m, 10 H), 1.28 (d, *J* = 6.8 Hz, 3 H), 1.06 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.1, 73.5, 71.9, 70.7, 62.6, 36.5, 30.9, 29.5, 270, 21.4, 20.4, 12.8; HRMS (FAB) calcd for $C_{12}H_{23}BrNaO_3$ $[M+Na]^+$ 317.0728, found 317.0734; structure confirmed by single crystal x-ray diffraction.



Diol Derivative of 85

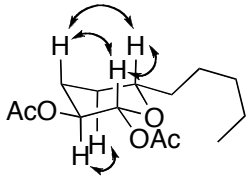
Synthesis of 87 and Cyclization to 9-*endo* Product 89

92. Prepared according to a procedure adapted from Schmidt: Schmidt, B. *J. Org. Chem.* **2004**, *69*, 7672–7687. A solution of allylmagnesium bromide (1.0 M in Et_2O, 12.0 mL, 12.0 mmol, 1.2 equiv) was added to a solution of hexanal (1.30 mL, 10.0 mmol, 1.0 equiv) in Et_2O (4.0 mL) at 0 °C. After 30 min at 0 °C, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (5 mL) and water (5 mL). The layers were separated and the aqueous layer was extracted with additional Et_2O (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to yield a light yellow residue that was purified by flash column chromatography (silica gel, pentane:Et_2O, 49:1→9:1) to afford 1-nonen-4-ol (0.81 g, 57% yield) as a colorless oil. Next, NaH (60% dispersion in mineral oil, 0.456 g, 11.4 mmol, 2.0 equiv) was added slowly to a solution of the newly formed 1-nonen-4-ol (0.810 g, 5.69 mmol, 1.0 equiv) in THF (19 mL) at 25 °C. The mixture was carefully heated to reflux for 30 min, then cooled to 25 °C. Allyl bromide (0.975 mL, 11.4 mmol, 2.0 equiv) was added, and the reaction contents were again heated to reflux for 45 min. Upon completion, the colorless

solution was cooled to 25 °C, quenched by the addition of saturated aqueous NH_4Cl (10 mL) and water (10 mL), and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to afford a light yellow residue that was purified by flash column chromatography (silica gel, hexanes:CH_2Cl_2, 9:1) to afford **92** (0.820 g, 79% yield) as a colorless viscous oil. **92**: R_f = 0.28 (silica gel, hexanes:CH_2Cl_2, 9:1); IR (film) ν_{max} 3078, 2957, 2931, 2859, 1642, 1460, 1084, 916 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.97–5.77 (m, 2 H), 5.26 (dq, *J* = 17.2, 1.6 Hz, 1 H), 5.14 (dq, *J* = 10.4, 1.2 Hz, 1 H), 5.11–5.02 (m, 2 H), 4.00 (qdt, *J* = 12.8, 5.6, 1.2 Hz, 2 H), 3.35 (quintet, *J* = 5.6 Hz, 1 H), 2.32–2.21 (m, 2 H), 1.53–1.21 (m, 8 H), 0.88 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 135.3, 116.9, 116.6, 78.7, 70.1, 38.5, 33.9, 32.1, 25.2, 22.8, 14.2; HRMS (FAB) calcd for $C_{12}H_{21}O$ $[M–H]^+$ 181.1592, found 181.1599.

93. Prepared according to a procedure adapted from Schmidt: Schmidt, B. *J. Org. Chem.* **2004**, *69*, 7672–7687. Grubbs catalyst (1st generation, 0.135 g, 0.163 mmol, 0.05 equiv) was added to a solution of **92** (0.600 g, 3.29 mmol, 1.0 equiv) in toluene (13.2 mL) at 25 °C. After consumption of **92** was observed by TLC analysis (~30 min), 2-propanol (3.3 mL) and NaOH (0.0330 g, 0.823 mmol, 0.25 equiv) were added sequentially in single portions. The resultant brown solution was heated to reflux for 12 h, then cooled to 25 °C and quenched with water (5 mL). The crude product was extracted into Et_2O (3 × 5 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resultant brown residue was purified by flash column chromatography (silica gel, hexanes:CH_2Cl_2, 2:1) to afford the desired enol ether product (0.442 g, 87% yield) as a colorless viscous oil. Next, $PhI(OAc)_2$ (1.19 g, 3.40 mmol, 1.2

equiv) and BF_3•OEt_2 (0.088 mL, 0.570 mmol, 0.20 equiv) were added sequentially in single portions to a solution of the enol ether produced above (0.442 g, 2.90 mmol, 1.0 equiv) in CH_2Cl_2 (22 mL) at –40 °C. The reaction contents were stirred at –40 °C for 4 h, then pyridine (9 mL) and Ac_2O (4.50 mL, 47.6 mmol, 16.4 equiv) were then added, and the reaction contents were warmed to 25 °C and stirred at that temperature for 12 h. Upon completion, the reaction mixture was quenched by the addition of water (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (20 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant brown residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 2:1) to afford diacetate **93** as a colorless viscous oil contaminated with small amounts of inseparable impurities (estimated pure yield = 0.380 g, 49% yield). Stereochemistry was determined by COSY and NOESY NMR experiments (see attached spectra). **93:** R_f = 0.44 (silica gel, hexanes:EtOAc, 4:1); IR (film) ν_{max} 2932, 2861, 1747, 1371, 1241, 1060, 949 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.61 (d, J = 8.4 Hz, 1 H), 4.69 (m, 1 H), 3.54 (m, 1 H), 2.21 (m, 1 H), 2.10 (s, 3 H), 2.03 (s, 3 H), 1.72 (m, 1 H), 1.63–1.20 (m, 10 H), 0.86 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 169.5, 94.0, 77.0, 70.1, 35.1, 31.7, 29.6, 27.9, 25.2, 22.5, 21.1, 21.0, 14.0; HRMS (FAB) calcd for $C_{14}H_{23}O_5$ $[M–H]^+$ 271.1545, found 271.1535.

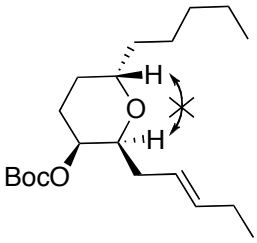


93
NOESY

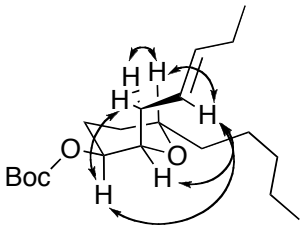
94. Prepared according to a procedure adapted from Danishefsky and co-workers: Wang, P.; Zhu, J.; Yuan, Y.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2009**, *131*, 16669–16671. Allyltrimethylsilane (0.66 mL, 4.2 mmol, 3.0 equiv) was added to a solution of diacetate **93** (0.38 g, 1.4 mmol, 1.0 equiv) in CH_2Cl_2 (3.8 mL), at –78 °C. Next, BF_3•OEt_2 (0.98 mL, 7.0 mmol, 5.0 equiv) was added dropwise over 5 min, and the resultant light yellow solution was allowed to slowly warm from –78 °C to 25 °C over the course of 12 h. Upon completion, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL), and the reaction mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to yield a brown residue that was purified by flash column chromatography (silica gel, hexanes:EtOAc, 9:1) to afford the desired allylated product (0.26 g, 74% yield) as a colorless viscous oil. Next, the Hoveyda–Grubbs catalyst (2nd generation, 0.0195 g, 0.31 mmol, 0.03 equiv) was added to a solution of the allylated product generated above (0.264 g, 1.04 mmol, 1.0 equiv) in *trans*-3-hexene (5.00 g, 59.0 mmol, 57 equiv) at 25 °C. The resultant brown solution was stirred for 12 h at 25 °C, then filtered through a small plug of silica gel with hexanes:EtOAc (3:1, 100 mL) to generate the crude acetate **94**.

87. This crude acetate **94** was concentrated and the resultant oil was dissolved in MeOH (50 mL) and cooled to 0 °C. K_2CO_3 (1.44 g, 10.4 mmol, 10.0 equiv) was then added and the reaction mixture was stirred for 1 h at 0 °C. Upon completion, the solution was quenched by the addition of saturated aqueous NH_4Cl (10 mL) and water (50 mL), and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to yield an oil that was purified by flash column

chromatography (silica gel, hexanes:EtOAc, 1:0→4:1) to afford the alcohol derivative of **94** (0.180 g, 72% yield over two steps) as a colorless viscous oil. R_f = 0.33 (silica gel, hexanes:EtOAc, 4:1); IR (film) ν_{max} 3403 (br), 2933, 2860, 1460, 1376, 1080, 966 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.57 (m, 1 H), 5.43 (m, 1 H), 3.77–3.69 (m, 2 H), 3.66 (m, 1 H), 2.32 (m, 1 H), 2.22 (m, 1 H), 2.07–1.89 (m, 3 H), 1.85–1.64 (m, 4 H), 1.42–1.24 (m, 8 H), 0.97 (t, *J* = 7.6 Hz, 3 H), 0.90 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.7, 125.2, 73.0, 71.3, 67.3, 32.5, 31.9, 31.8, 26.9, 25.9, 25.8, 25.4, 22.8, 14.2, 13.9; HRMS (FAB) calcd for $C_{15}H_{29}O_2$ $[M+H]^+$ 241.2168, found 241.2172. The next procedure was prepared according to the procedure described above for the synthesis of carbonate **45**. Carbonate formation on 0.36 mmol scale followed by flash column chromatography (silica gel, hexanes:EtOAc, 19:1→17:3) afforded **87** (0.095 g, 77% yield) as a colorless viscous oil. Stereochemistry was determined by COSY and NOESY NMR experiments (see attached spectra). **87**: R_f = 0.58 (silica gel, hexanes:EtOAc, 9:1); IR (film) ν_{max} 2958, 2933, 2859, 1739, 1369, 1278, 1255, 1165, 1086 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.52 (m, 1 H), 5.39 (m, 1 H), 4.69 (quintet, *J* = 4.0 Hz, 1 H), 3.85 (quintet, *J* = 4.4 Hz, 1 H), 3.66 (m, 1 H), 2.39 (m, 1 H), 2.14 (m, 1 H), 2.01 (quintet, *J* = 7.2 Hz, 2 H), 1.92–1.75 (m, 3 H), 1.58 (m, 1 H), 1.47 (s, 9 H), 1.40–1.20 (m, 8 H), 0.96 (t, *J* = 7.6 Hz, 3 H), 0.88 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 134.7, 124.8, 82.0, 72.5, 72.0, 70.0, 33.2, 32.0, 31.2, 28.0 (3 C), 27.6, 27.4, 25.8, 24.0, 22.8, 14.2, 13.9; HRMS (FAB) calcd for $C_{20}H_{37}O_4$ $[M+H]^+$ 341.2692, found 341.2678.



87
NOESY

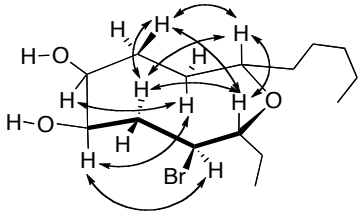


87
NOESY

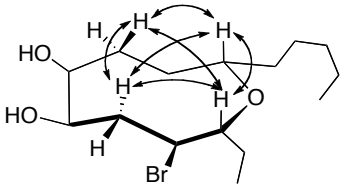
89. Prepared according to General Cyclization Procedure A. BDSB cyclization of **87** (0.0341 g, 0.100 mmol) afforded **89** (0.0185 g, 51% yield) after flash column chromatography (silica gel, hexanes:EtOAc, 19:1→17:3) as a colorless viscous oil. **89**: R_f = 0.23 (silica gel, hexanes:EtOAc, 9:1); IR (film) ν_{max} 2934, 2861, 1805, 1363, 1186, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.89 (m, 1 H), 4.75 (ddd, *J* = 9.2, 7.2, 1.6 Hz, 1 H), 3.90 (ddd, *J* = 11.6, 9.2, 2.4 Hz, 1 H), 3.50 (quintet, *J* = 4.8 Hz, 1 H), 3.43 (m, 1 H), 2.70 (m, 1 H), 2.56 (dt, *J* = 15.2, 2.0 Hz, 1 H), 2.10–1.94 (m, 4 H), 1.84–1.67 (m, 2 H), 1.58 (m, 1 H), 1.44–1.20 (m, 7 H), 0.92 (t, *J* = 7.2 Hz, 3 H), 0.89 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 84.7, 82.8, 82.1, 81.4, 49.6, 37.4, 34.5, 31.9, 30.3, 26.4, 26.2, 24.8, 22.6, 14.0, 7.8; HRMS (FAB) calcd for $C_{16}H_{28}BrO_4$ $[M+H]^+$ 363.1171, found 363.1163.

Diol Derivative of 89. Prepared according to the procedure described above for general acetate/carbonate hydrolysis. Hydrolysis of **89** (0.0153 g, 0.0423 mmol) followed by purification by flash column chromatography (silica gel, hexanes:EtOAc, 9:1→1:1) afforded diol derivative of **89** (0.0115 g, 81% yield) as a white crystalline solid. Connectivity and stereochemistry were confirmed by COSY and NOESY NMR experiments (see attached spectra). R_f = 0.20 (silica gel, hexanes:EtOAc, 7:3); IR (film) ν_{max} 3391 (br), 2929, 2857, 1459, 1066, 914, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ

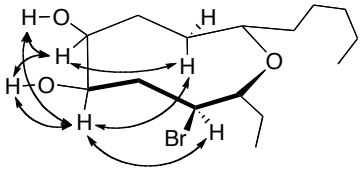
4.27 (br s, 1 H), 4.04–3.92 (m, 2 H), 3.48 (dt, *J* = 10.0, 4.0 Hz, 1 H), 3.35 (m, 1 H), 2.58 (ddd, *J* = 17.2, 11.2, 6.0 Hz, 1 H), 2.25 (ddd, *J* = 15.2, 3.6, 2.0 Hz, 1 H), 2.18–2.07 (m, 2 H), 1.94–1.63 (m, 5 H), 1.55–1.35 (m, 3 H), 1.34–1.19 (m, 6 H), 0.91 (t, *J* = 7.6 Hz, 3 H), 0.88 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 87.2, 85.1, 74.9, 73.3, 50.4, 42.2, 36.6, 32.0, 30.6, 29.8, 26.5, 24.7, 22.6, 14.0, 7.1; HRMS (FAB) calcd for $C_{15}H_{29}BrNaO_3$ $[M+Na]^+$ 359.1198, found 359.1181.



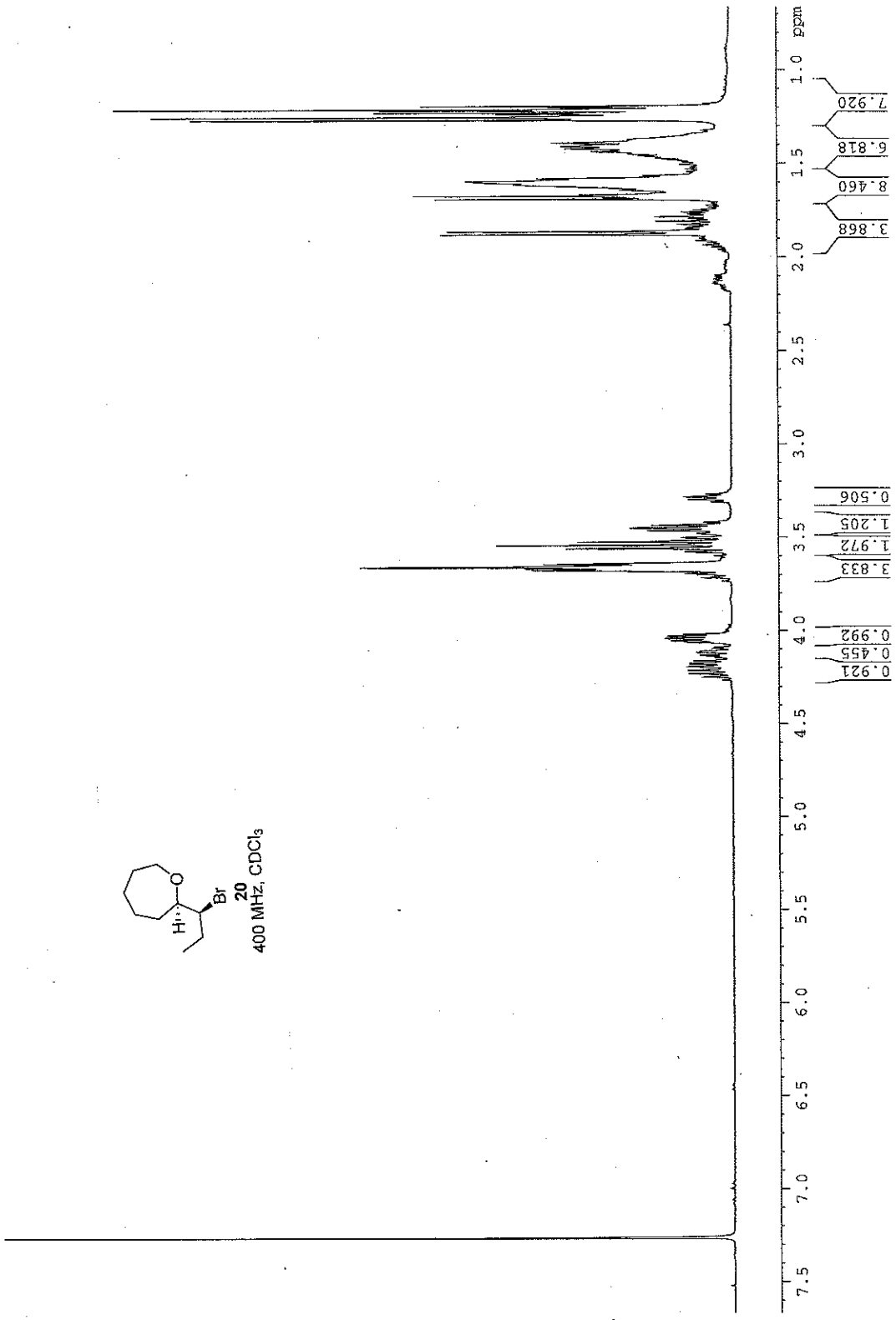
Diol Derivative of 89
NOESY

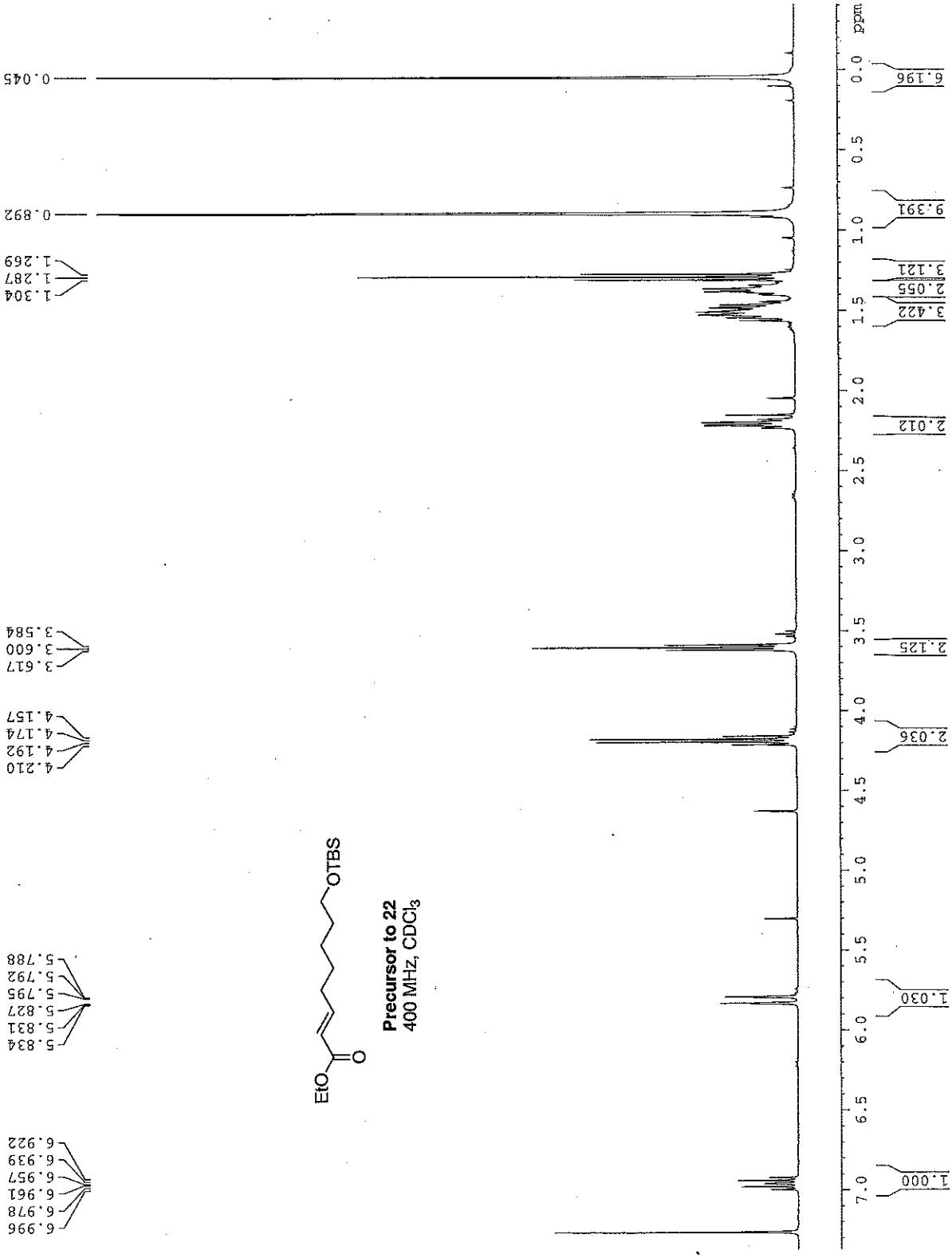


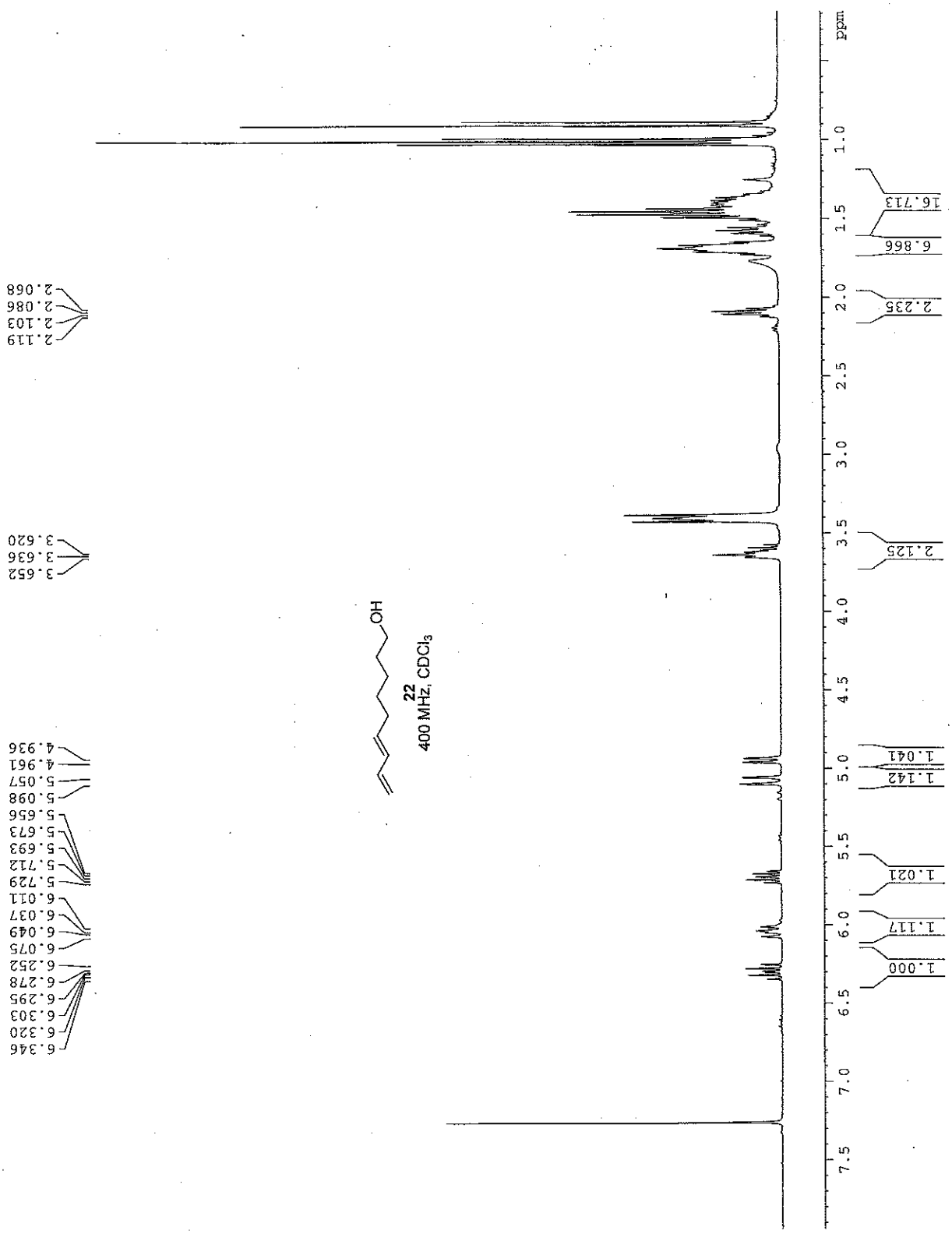
Top Proton
nOe Signals

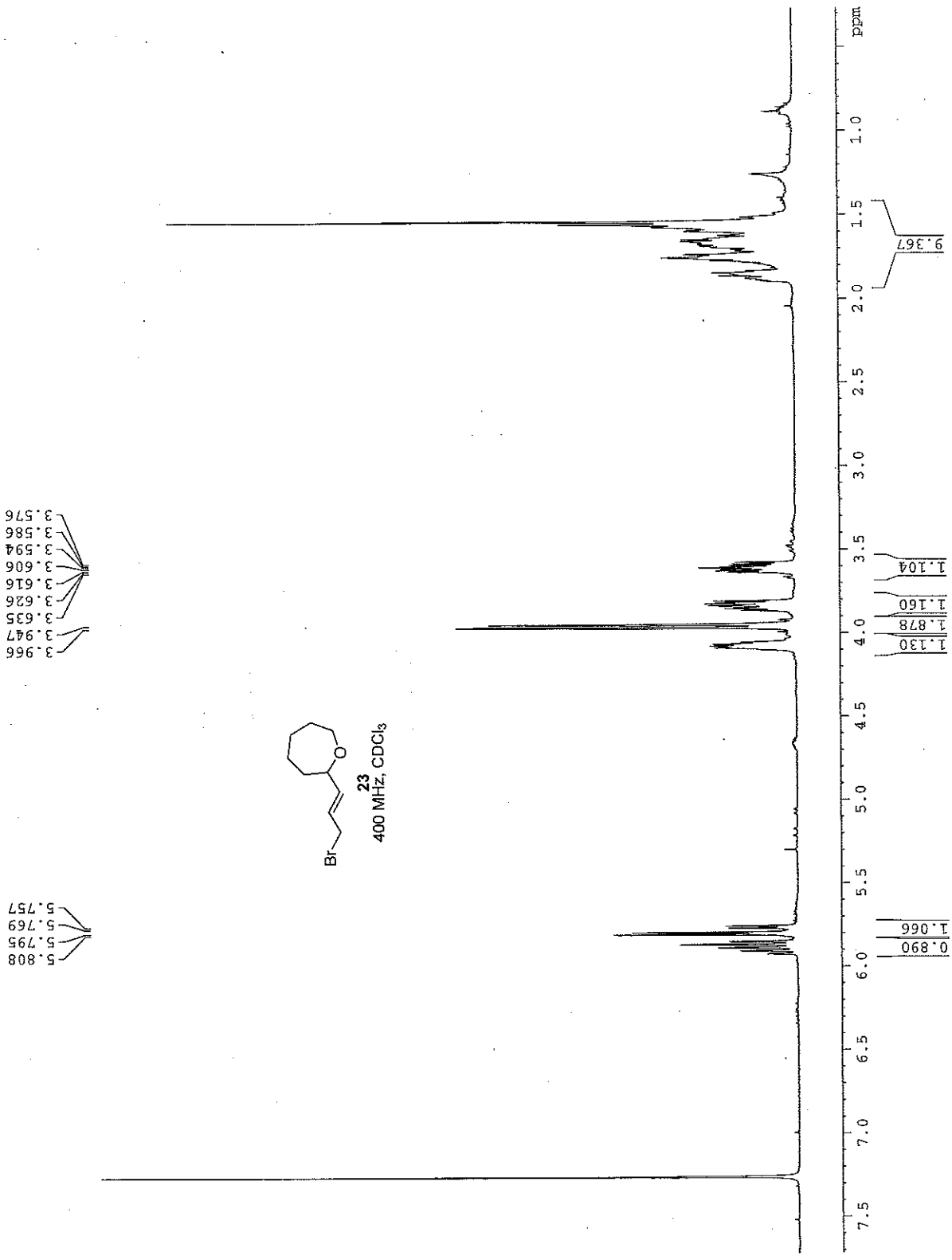


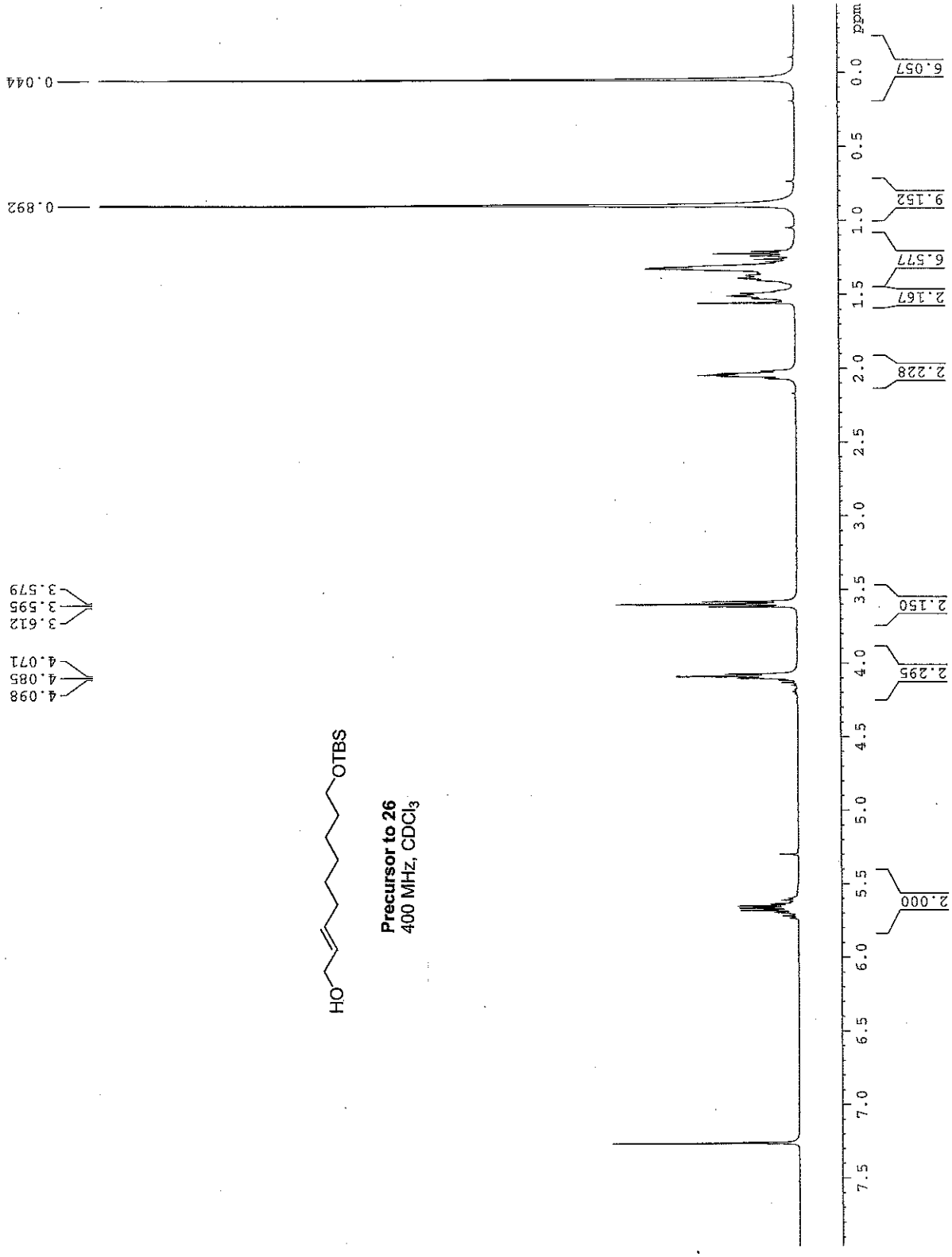
Bottom Proton
nOe Signals

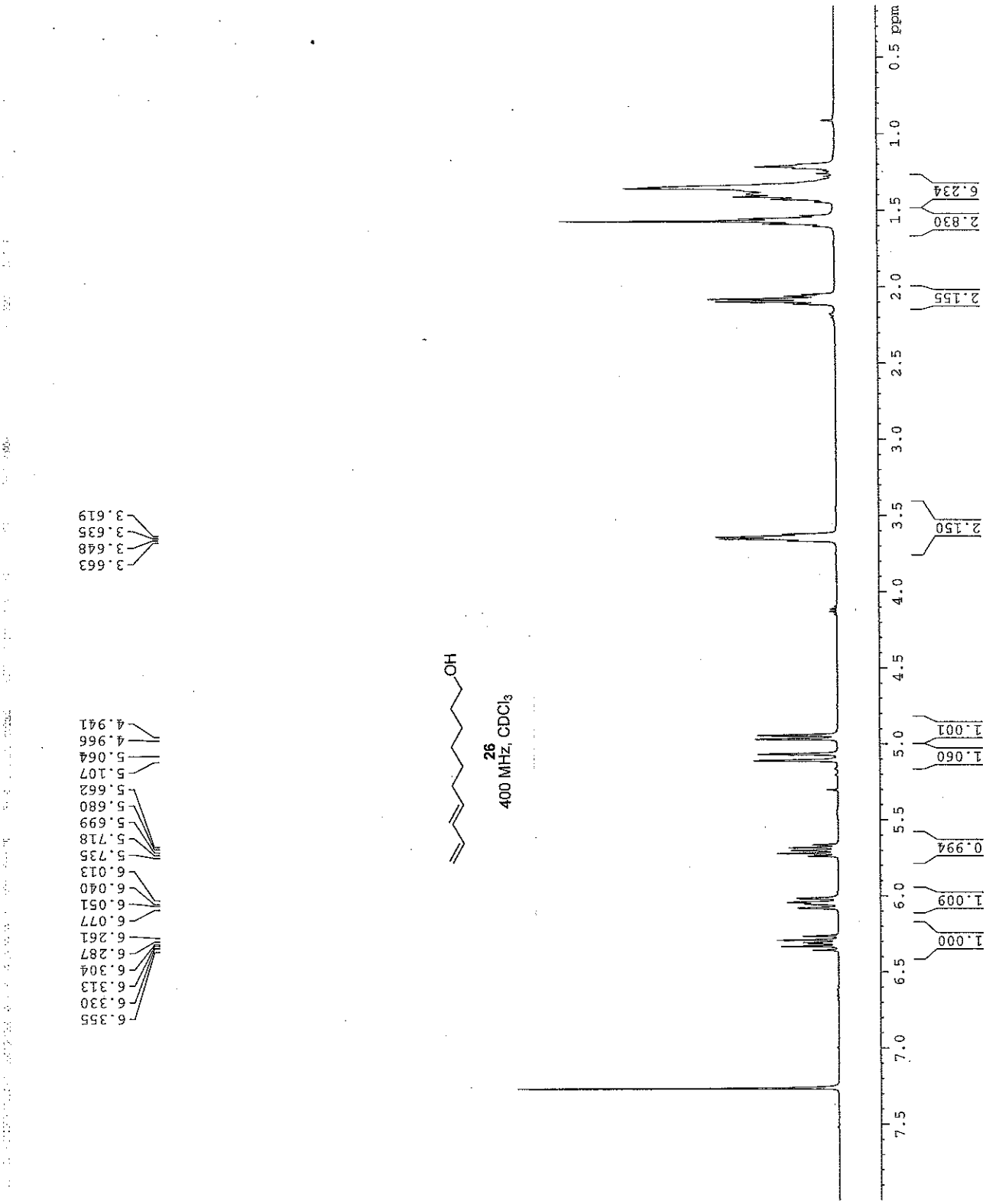

Br
H
20
400 MHz, CDCl3
7.920
6.818
8.460
3.868
0.506
1.205
1.972
3.833
0.921
0.455
0.992
ppm

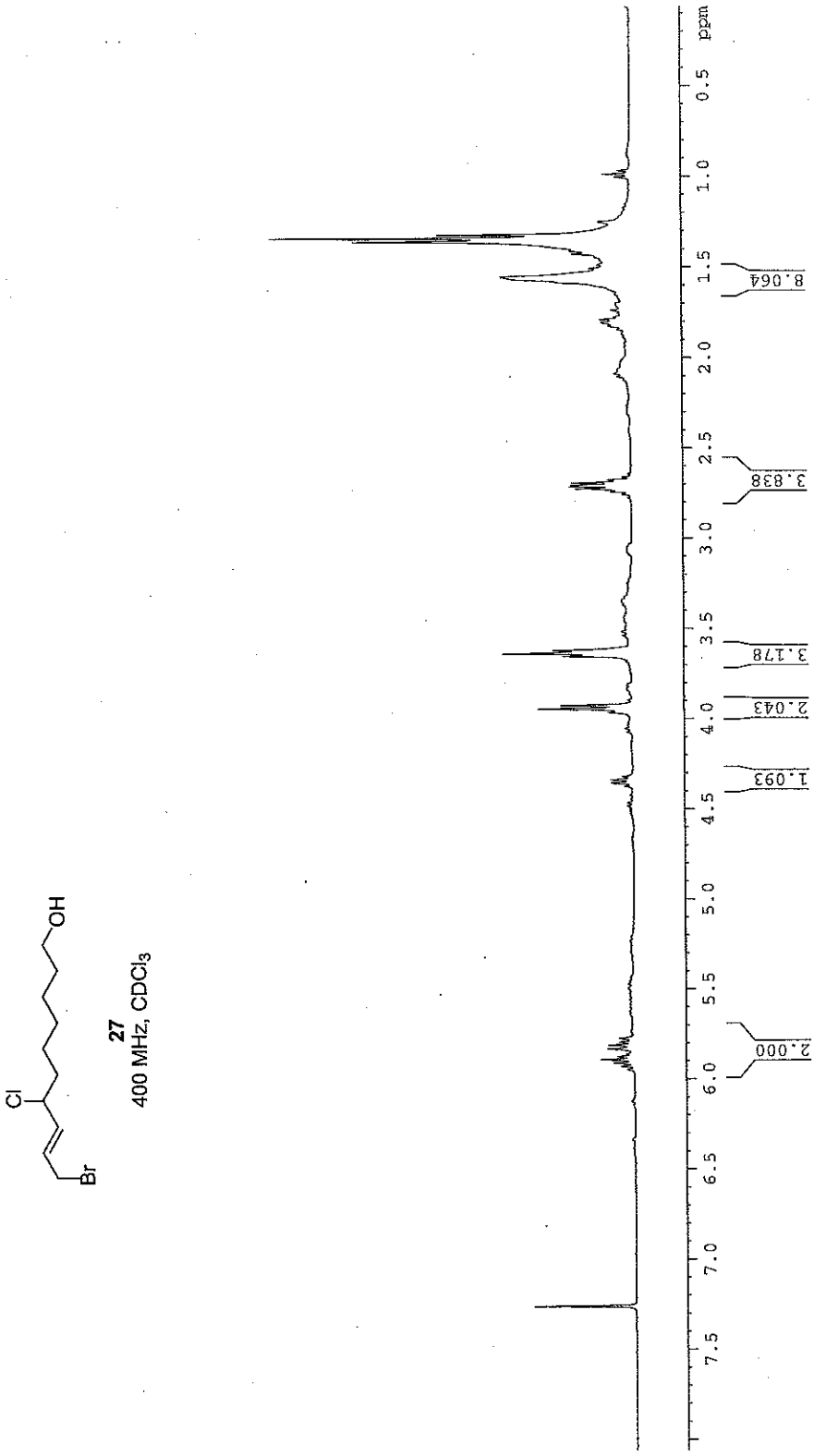

0.045
0.892
1.269
1.287
1.304
3.584
3.600
3.617
4.157
4.174
4.192
4.210
5.788
5.792
5.795
5.827
5.831
5.834
6.922
6.939
6.957
6.961
6.978
6.996
OTBS
EtO
O
Precursor to 22
400 MHz, CDCl3
ppm
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
6.196
9.391
3.121
2.055
3.422
2.012
2.125
2.036
1.030
1.000

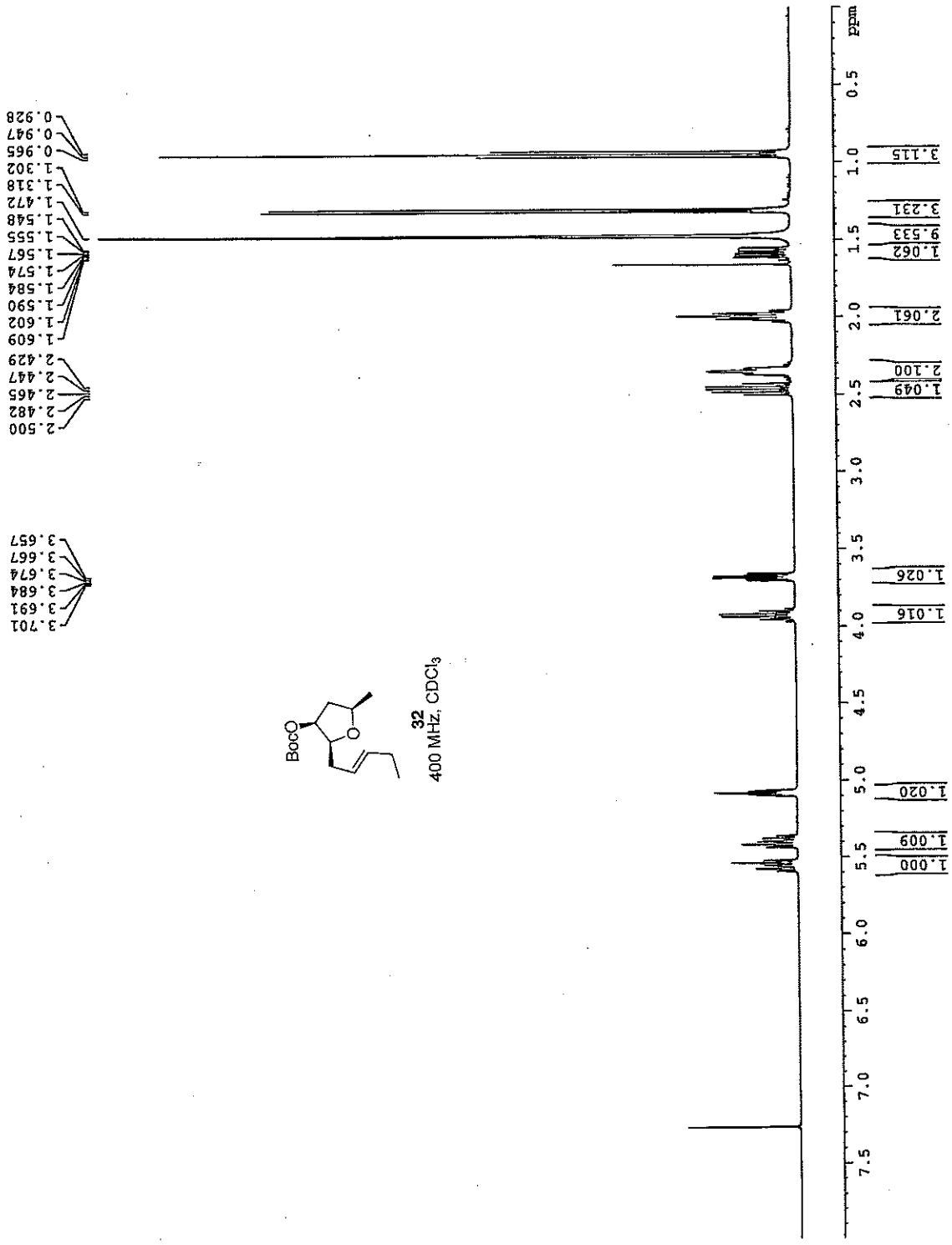

22
400 MHz, CDCl3
OH
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
16.713
6.866
2.235
2.125
1.041
1.142
1.021
1.117
1.000
2.119
2.103
2.086
2.068
3.652
3.636
3.620
6.346
6.320
6.303
6.295
6.278
6.252
6.075
6.049
6.037
6.011
5.729
5.712
5.693
5.673
5.656
5.098
5.057
4.961
4.936

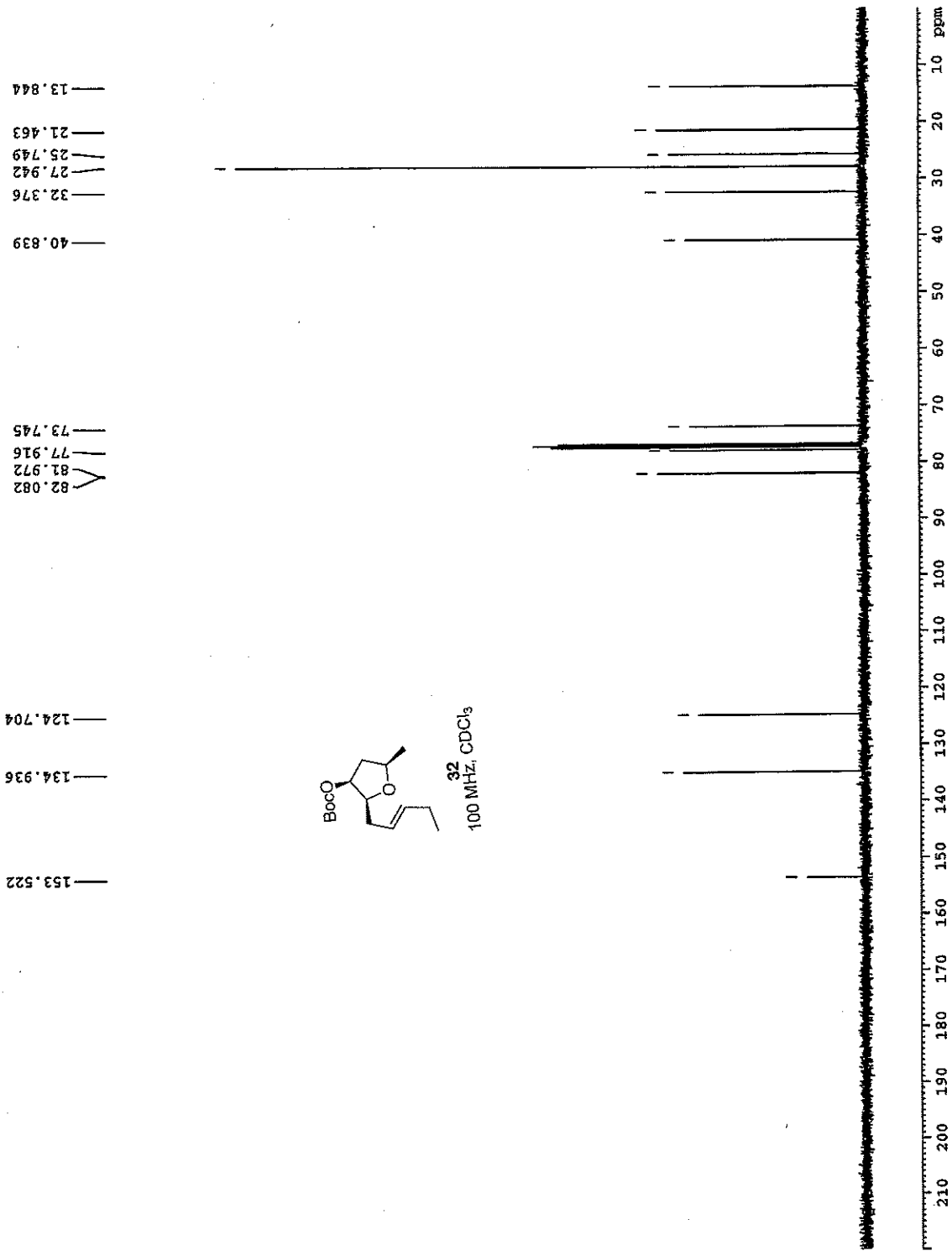

23
400 MHz, CDCl3
Br
O
5.808
5.795
5.769
5.757
3.966
3.947
3.635
3.626
3.616
3.606
3.594
3.586
3.576
9.367
1.104
1.160
1.878
1.130
1.066
0.890
ppm

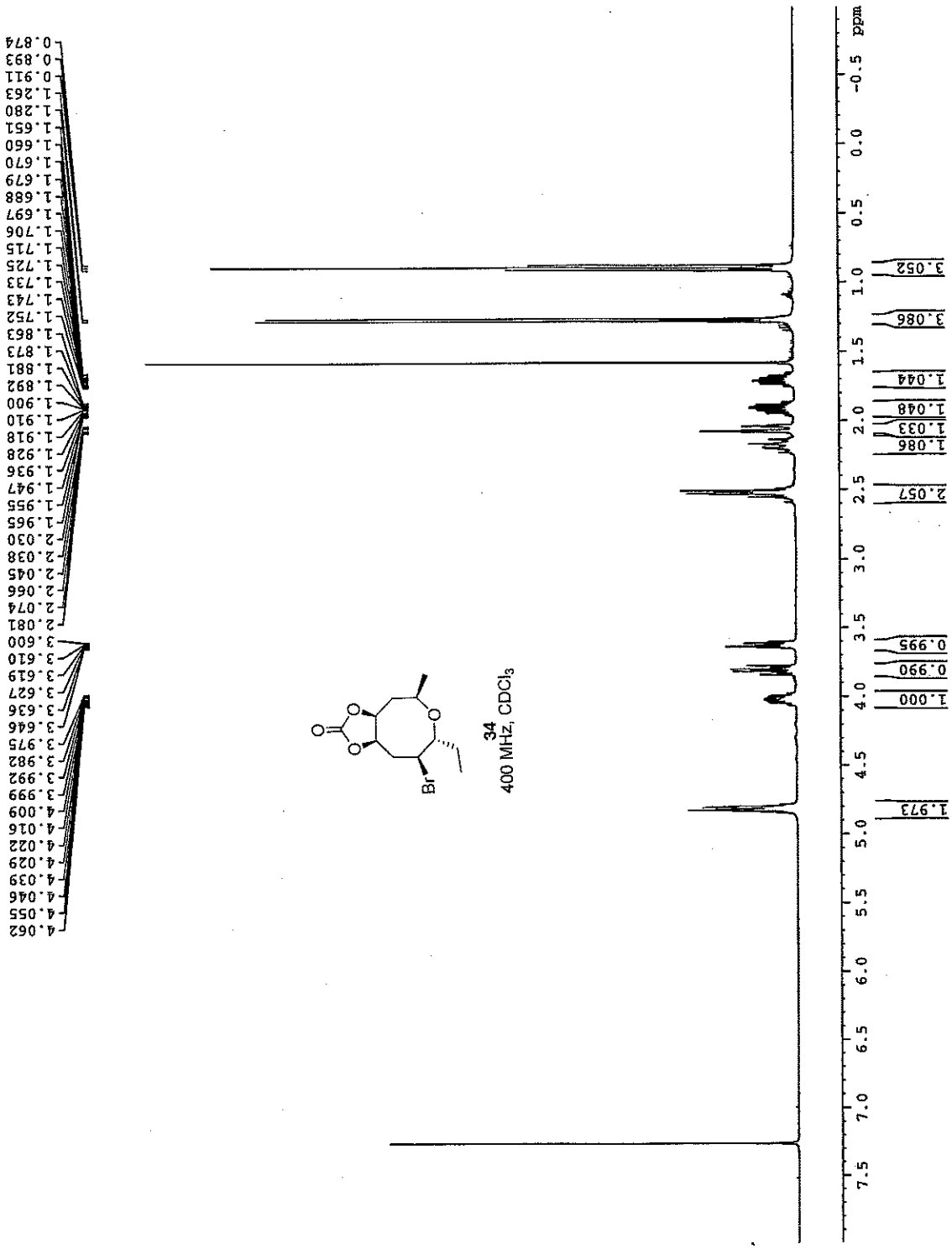

HO
OTBS
Precursor to 26
400 MHz, CDCl3
0.044
0.892
3.579
3.595
3.612
4.071
4.085
4.098
6.057
9.152
6.577
2.167
2.228
2.150
2.295
2.000
ppm

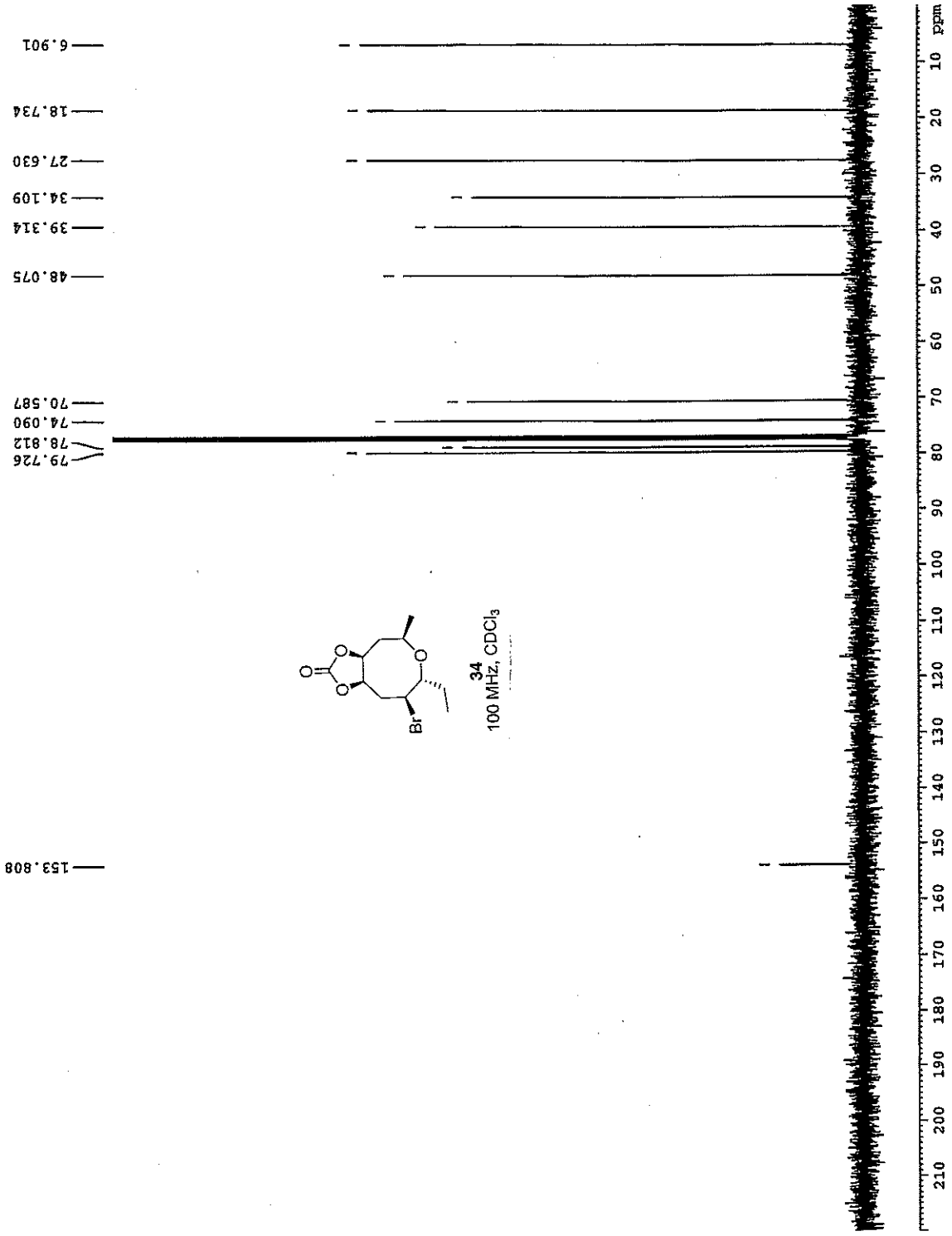

6.355
6.330
6.313
6.304
6.287
6.261
6.077
6.051
6.040
6.013
5.735
5.718
5.699
5.680
5.662
5.107
5.064
4.966
4.941
3.663
3.648
3.635
3.619
OH
26
400 MHz, CDCl3
1.000
1.009
0.994
1.060
1.001
2.150
2.155
2.830
6.234
0.5 ppm

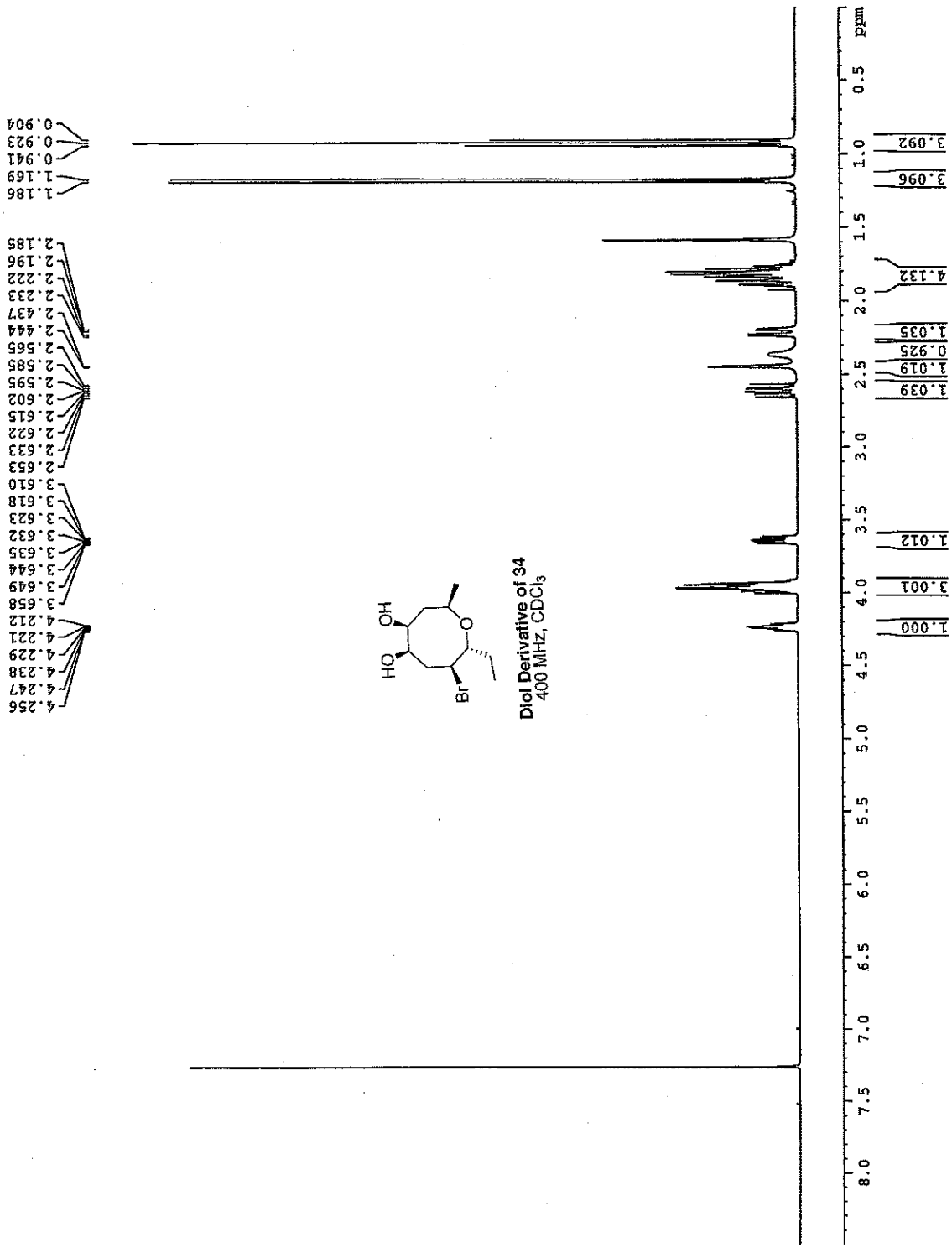

OH
Cl
Br
27
400 MHz, CDCl3
8.064
3.838
3.178
2.043
1.093
2.000
ppm

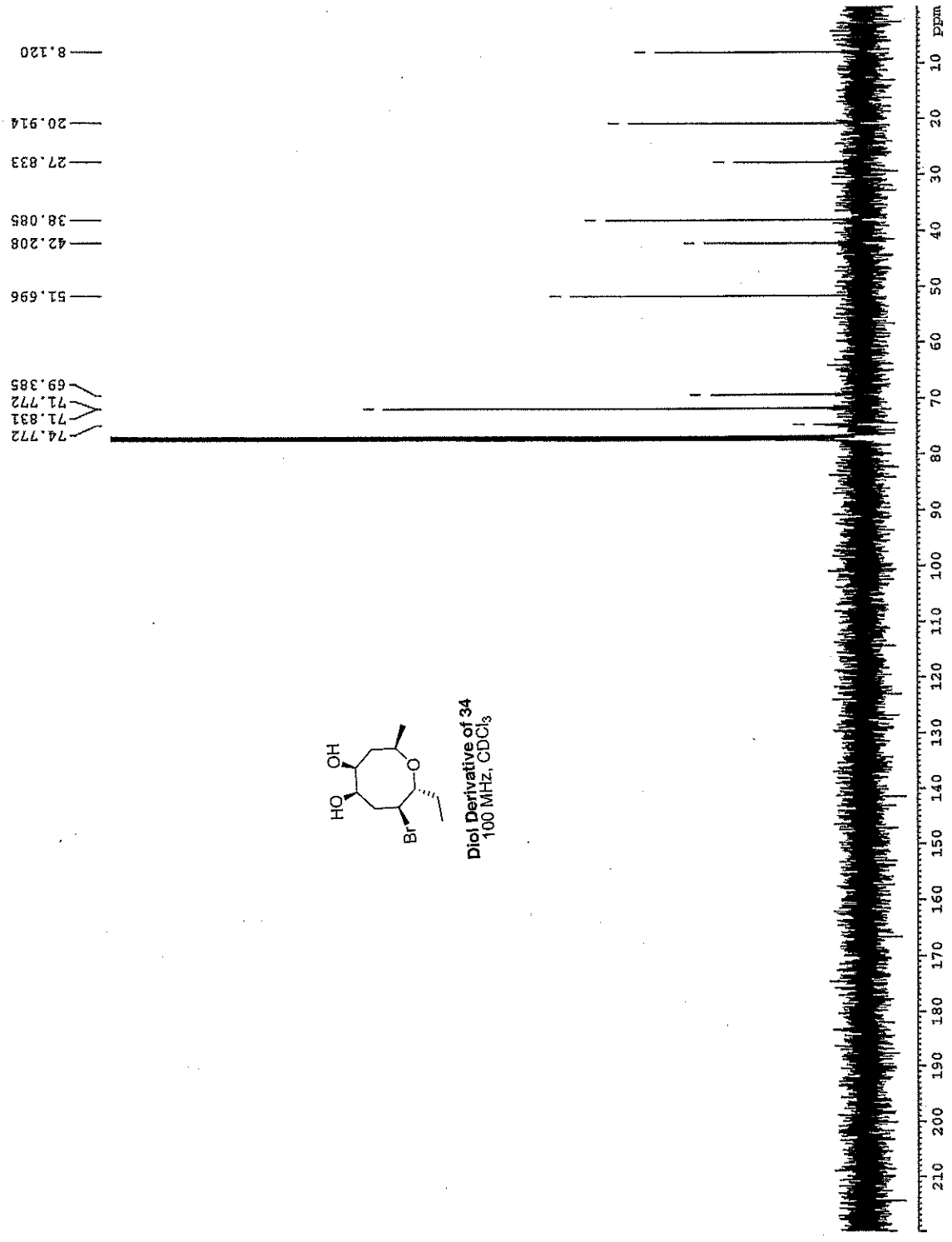

32
400 MHz, CDCl3
BocO
0.928
0.947
0.965
1.302
1.318
1.472
1.548
1.555
1.567
1.574
1.584
1.590
1.602
1.609
2.429
2.447
2.465
2.482
2.500
3.657
3.667
3.674
3.684
3.691
3.701
1.000
1.009
1.020
1.016
1.026
1.049
2.100
2.061
1.062
9.533
3.231
3.115
ppm

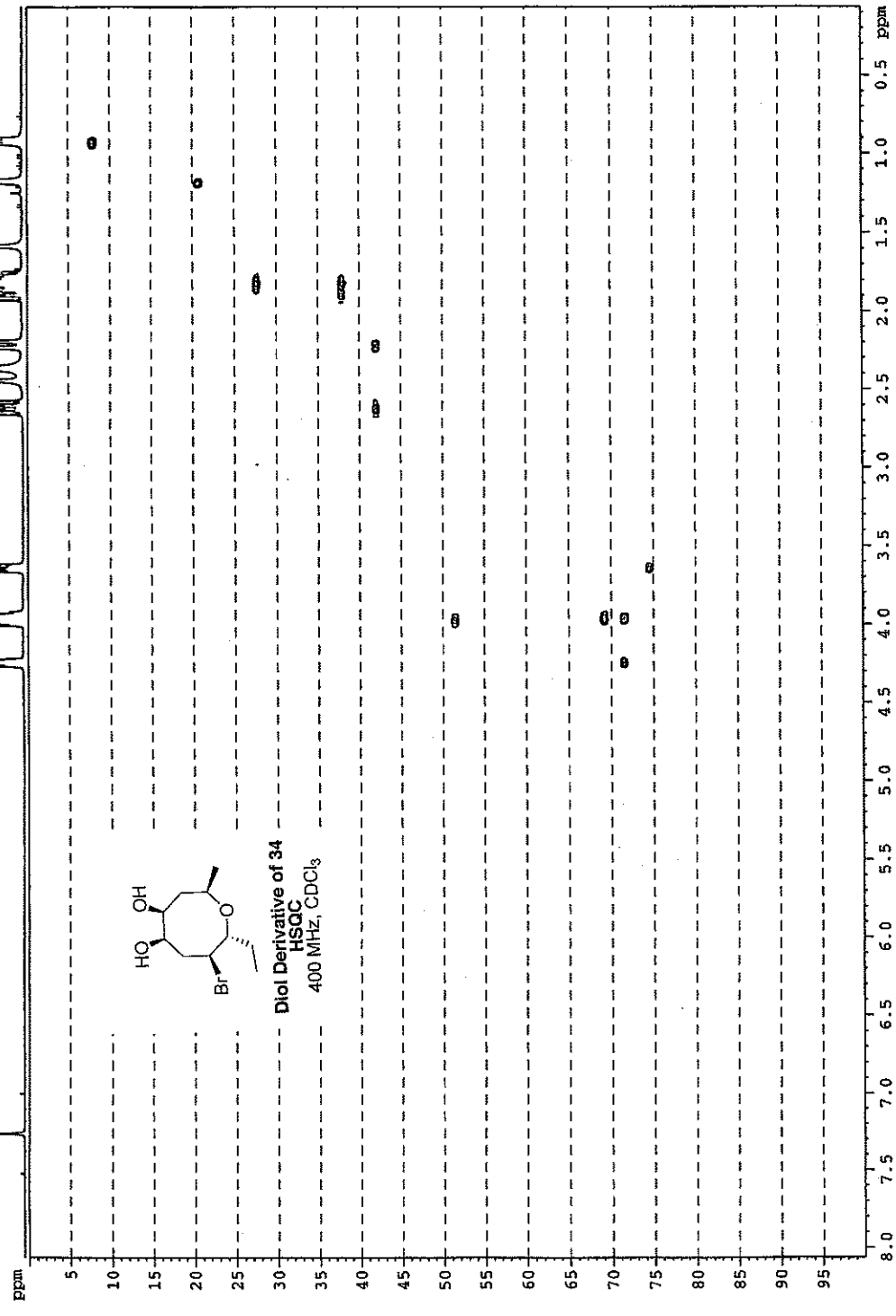

153.522
134.936
124.704
82.082
81.972
77.916
73.745
40.839
32.376
27.942
25.749
21.463
13.844
BocO
32
100 MHz, CDCl3
ppm

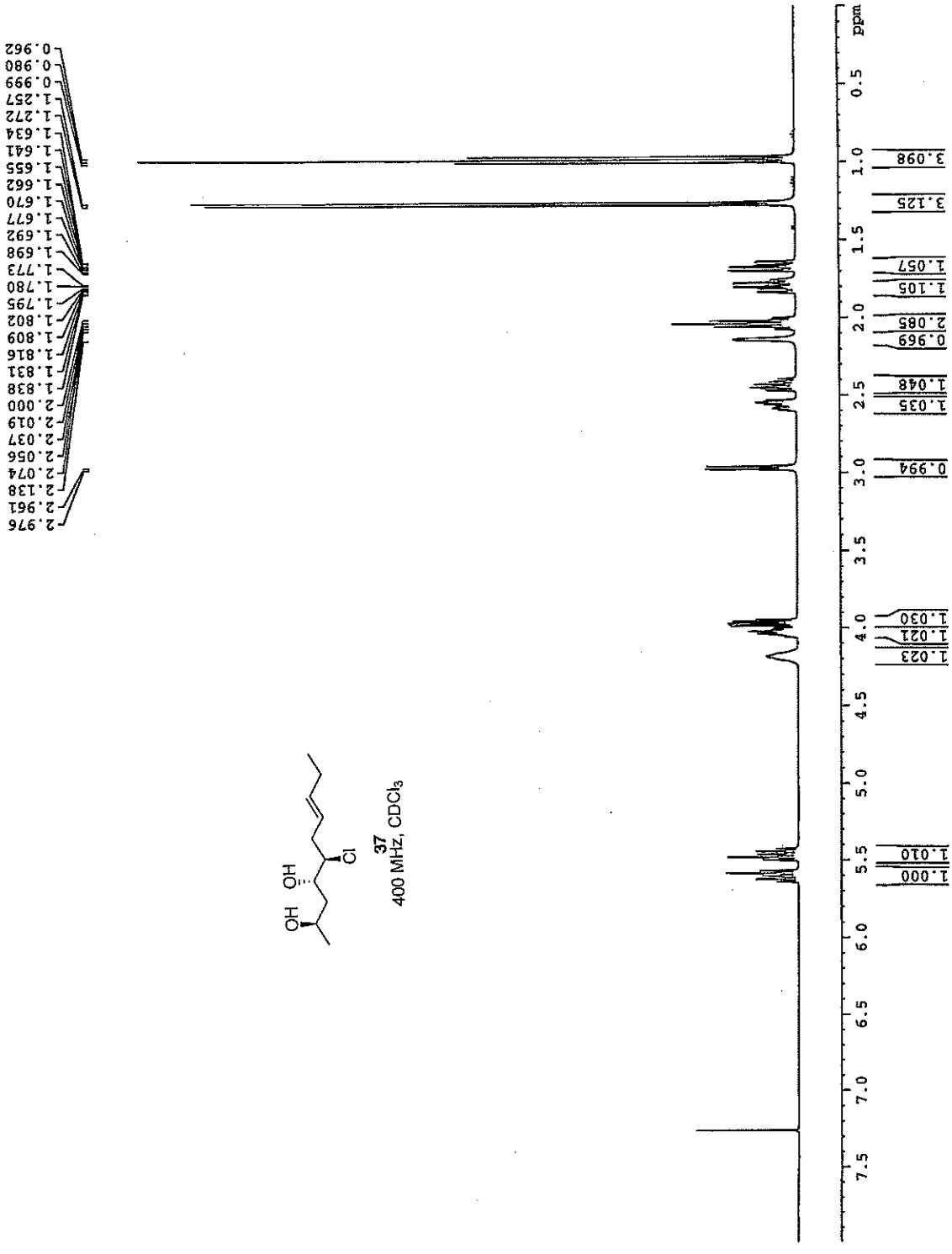

34
400 MHz, CDCl3
Br
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1.973
0.995
0.990
1.000
2.057
1.086
1.033
1.048
1.044
3.086
3.052
4.062
4.055
4.046
4.039
4.029
4.022
4.016
4.009
3.999
3.992
3.982
3.975
3.646
3.636
3.627
3.619
3.610
3.600
2.081
2.074
2.066
2.045
2.038
2.030
1.965
1.955
1.947
1.936
1.928
1.918
1.910
1.900
1.892
1.881
1.873
1.863
1.752
1.743
1.733
1.725
1.715
1.706
1.697
1.688
1.679
1.670
1.660
1.651
1.280
1.263
0.911
0.893
0.874

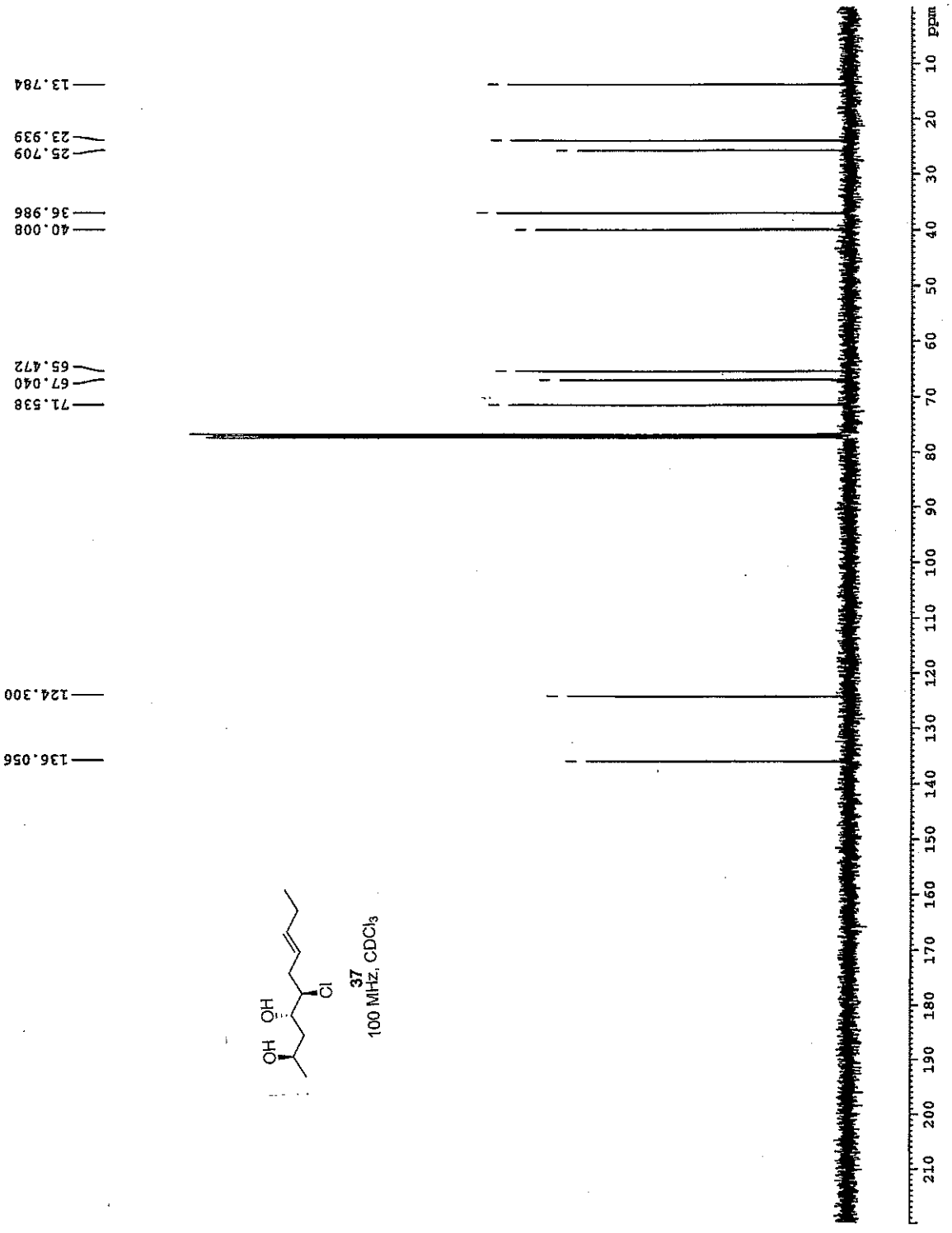

153.808
79.726
78.812
74.090
70.587
48.075
39.314
34.109
27.630
18.734
6.901
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
Br
O
O
O
O
34
100 MHz, CDCl3

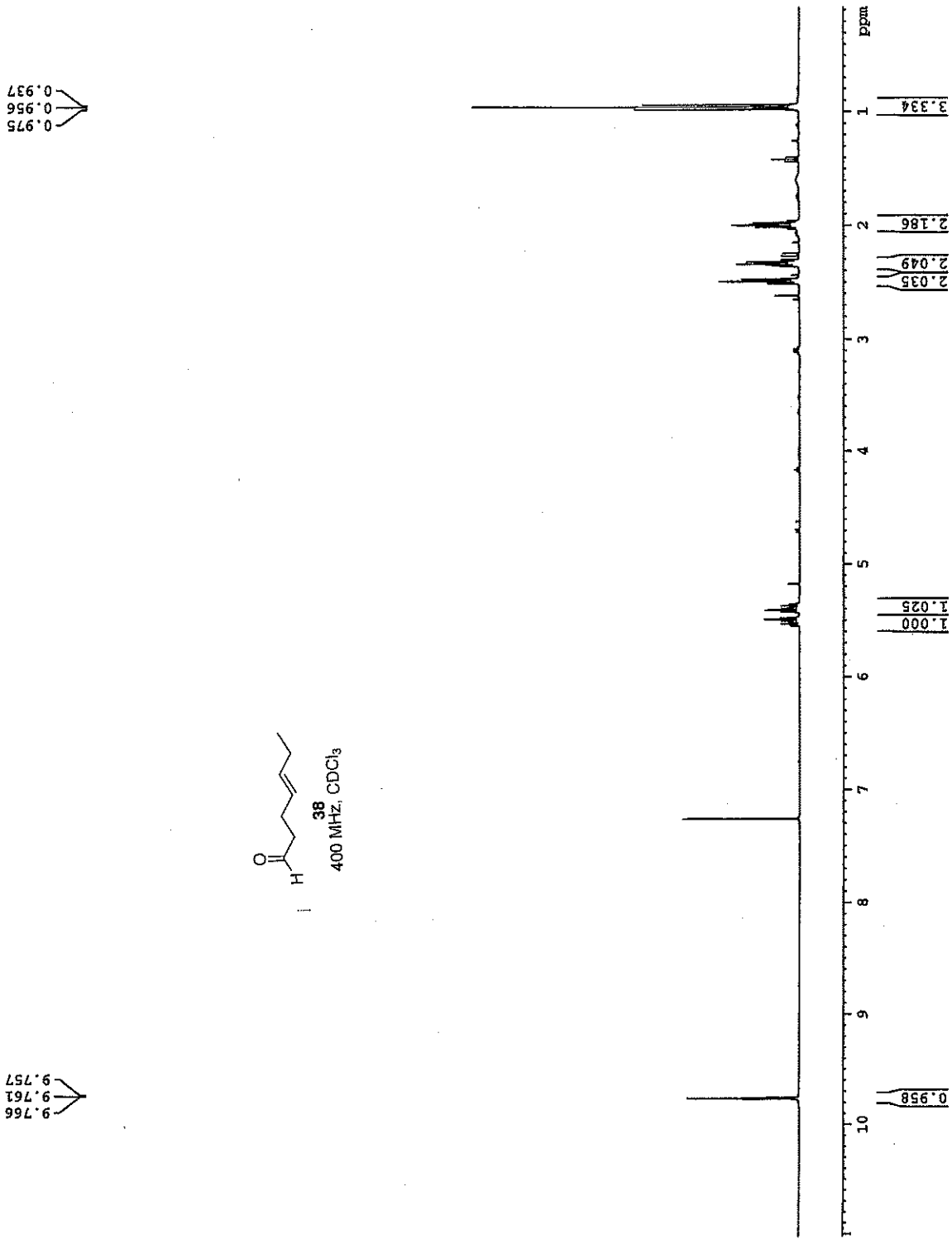

Diol Derivative of 34
400 MHz, $CDCl_3$
OH
HO
O
Br
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
1.000
3.001
1.012
1.039
1.019
0.925
1.035
4.132
3.096
3.092
0.904
0.923
0.941
1.169
1.186
2.185
2.196
2.222
2.233
2.437
2.444
2.565
2.585
2.595
2.602
2.615
2.622
2.633
2.653
3.610
3.618
3.623
3.632
3.635
3.644
3.649
3.658
4.212
4.221
4.229
4.238
4.247
4.256

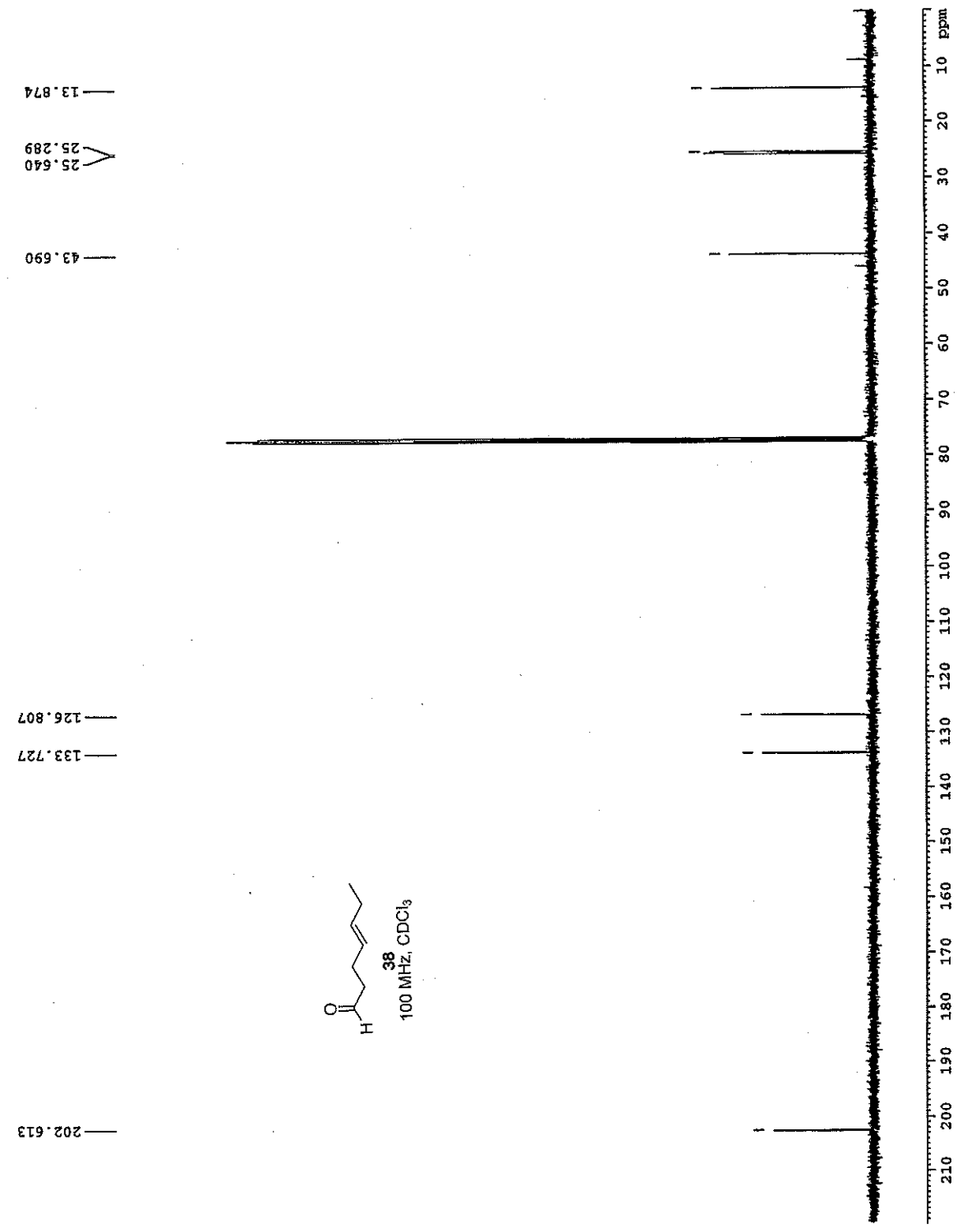

8.120
20.914
27.833
38.085
42.208
51.696
69.385
71.772
71.831
74.772
OH
HO
Br
O
Diol Derivative of 34
100 MHz, CDCl3
ppm

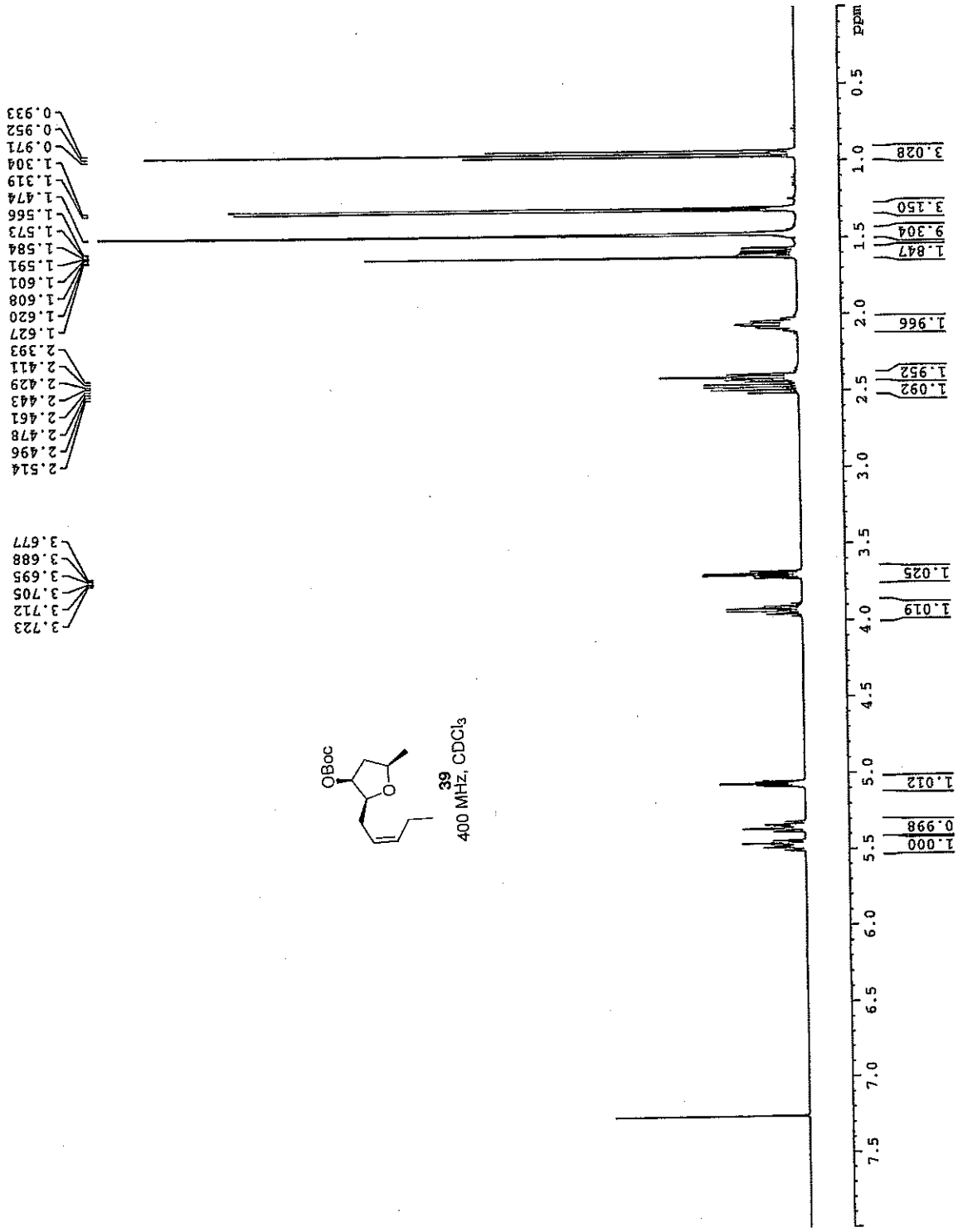

Diol Derivative of 34
HSQC
400 MHz, $CDCl_3$
OH
HO
O
Br
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

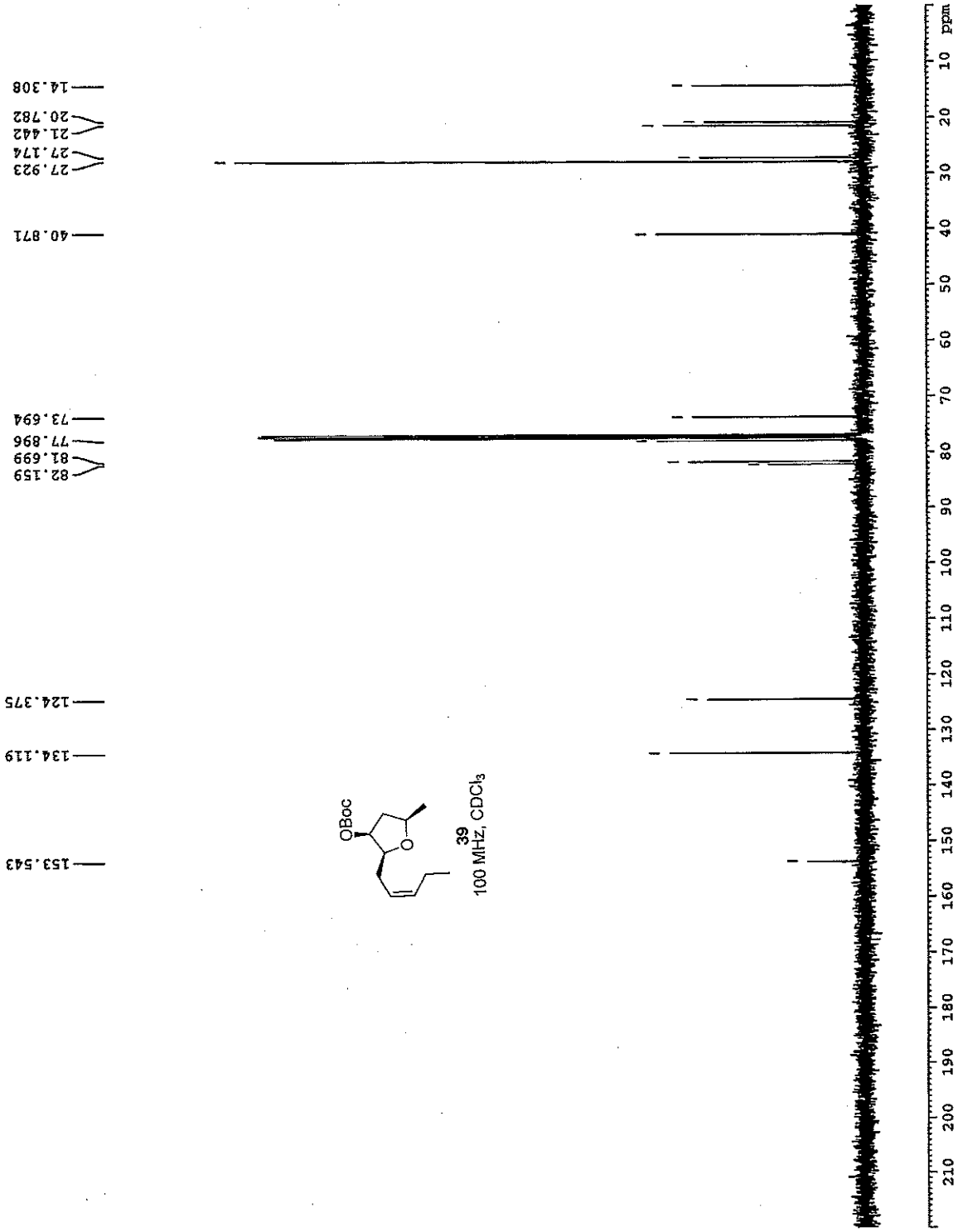

37
400 MHz, CDCl3
OH
OH
Cl
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
3.098
3.125
1.057
1.105
0.969
2.085
1.048
1.035
0.994
1.030
1.021
1.023
1.010
1.000
0.962
0.980
0.999
1.257
1.272
1.634
1.641
1.655
1.662
1.670
1.677
1.692
1.698
1.773
1.780
1.795
1.802
1.809
1.816
1.831
1.838
2.000
2.019
2.037
2.056
2.074
2.138
2.961
2.976

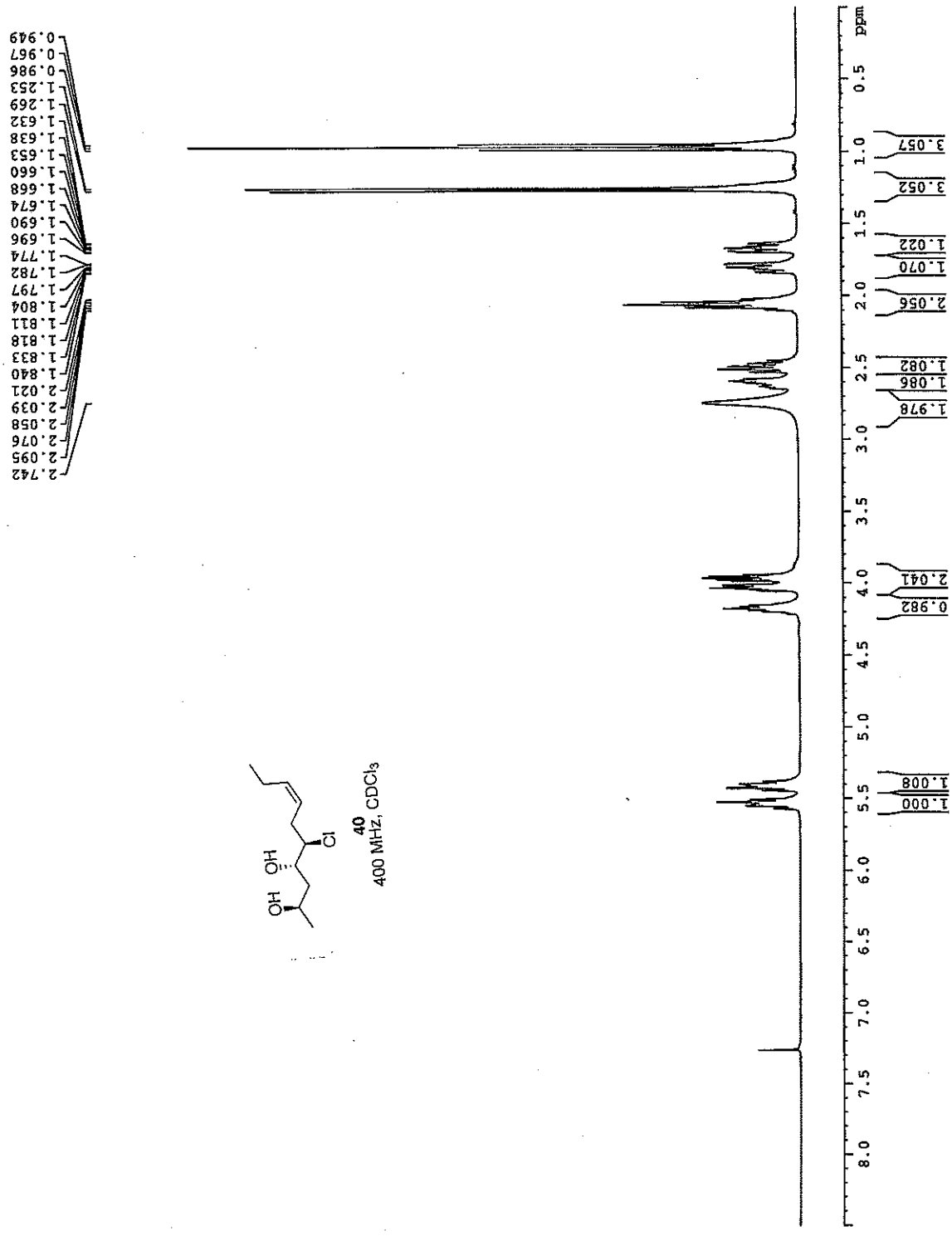

13.784
23.939
25.709
36.986
40.008
65.472
67.040
71.538
124.300
136.056
OH
OH
Cl
37
100 MHz, CDCl3
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
ppm

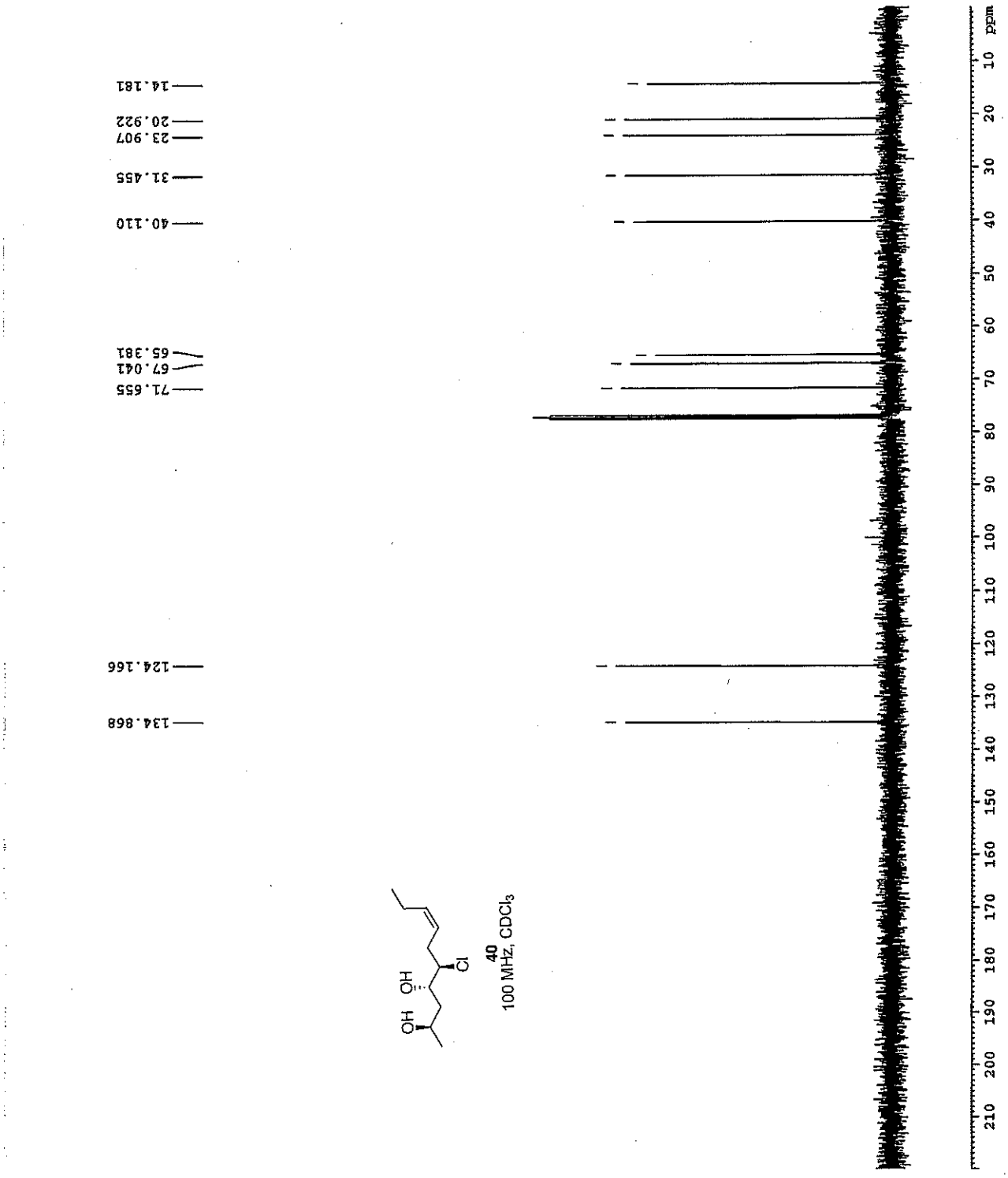

9.766
9.761
9.757
0.975
0.956
0.937
38
400 MHz, CDCl3
O
H
ppm
1
2
3
4
5
6
7
8
9
10
3.334
2.186
2.049
2.035
1.000
1.025
0.958

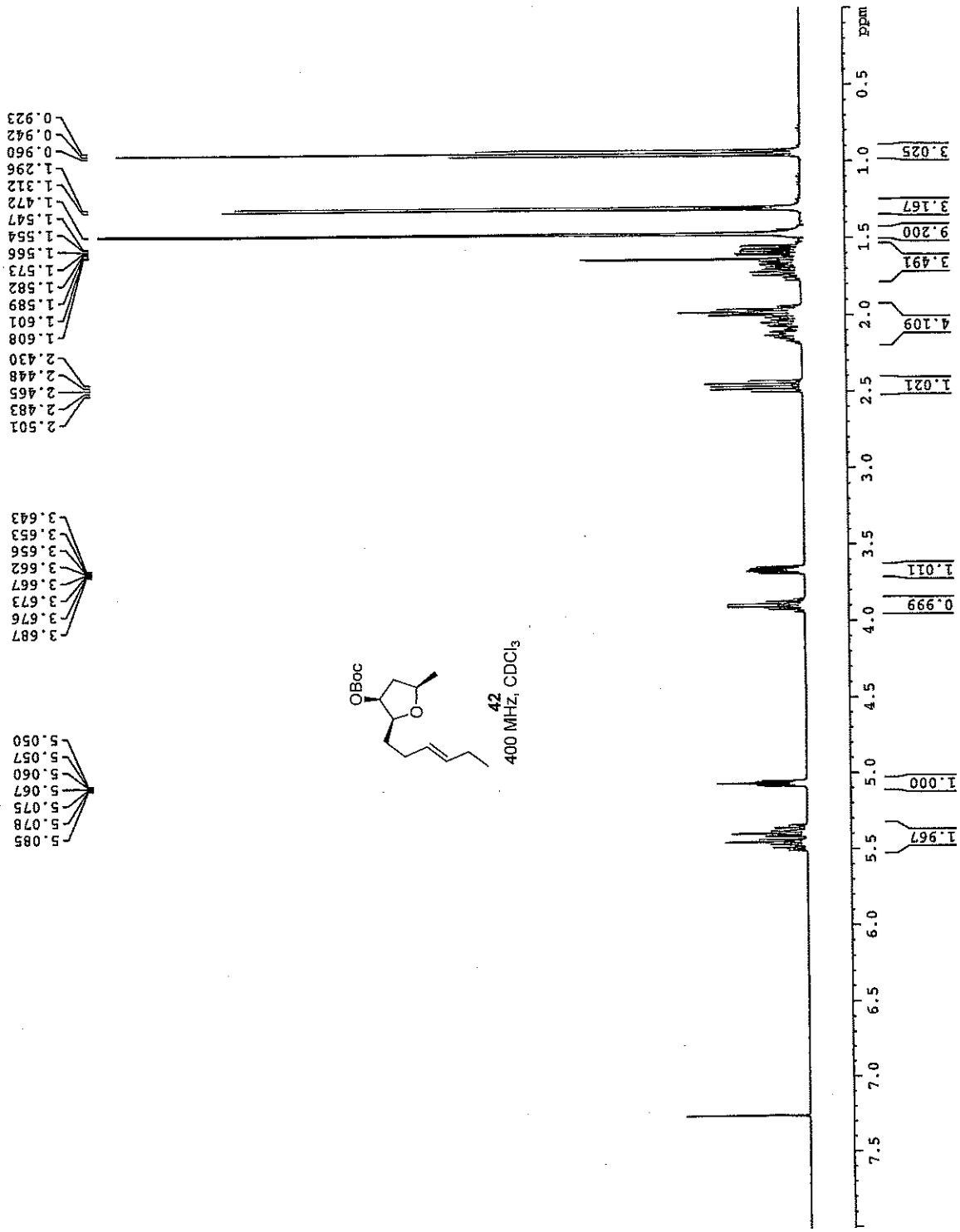

38
100 MHz, CDCl3
O
H
202.613
133.727
126.807
43.690
25.640
25.289
13.874
ppm

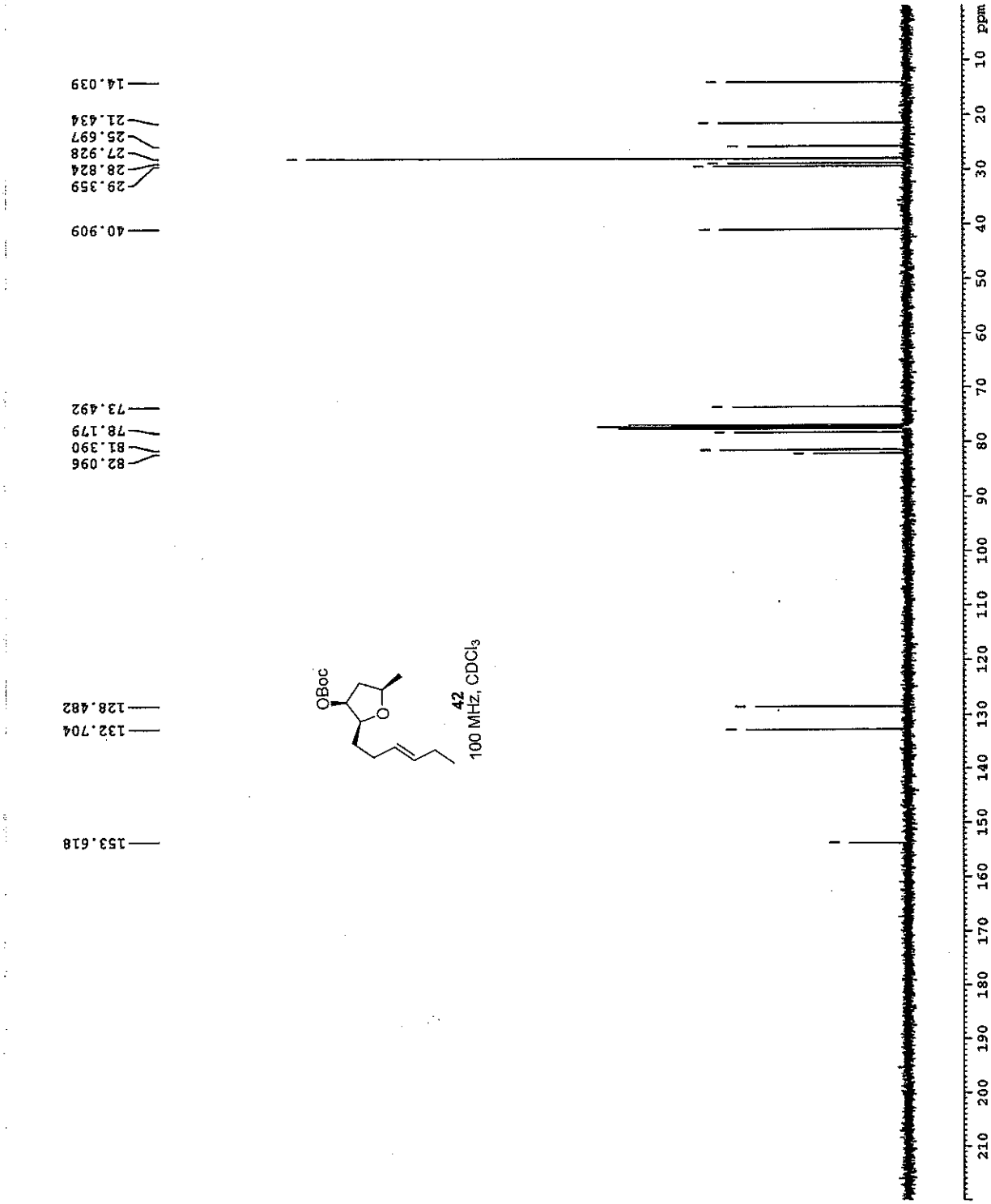

OBoc
39
400 MHz, $CDCl_3$
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
3.028
3.150
9.304
1.847
1.966
1.092
1.952
1.025
1.019
1.012
0.998
1.000
0.933
0.952
0.971
1.304
1.319
1.474
1.566
1.573
1.584
1.591
1.601
1.608
1.620
1.627
2.393
2.411
2.429
2.443
2.461
2.478
2.496
2.514
3.677
3.688
3.695
3.705
3.712
3.723

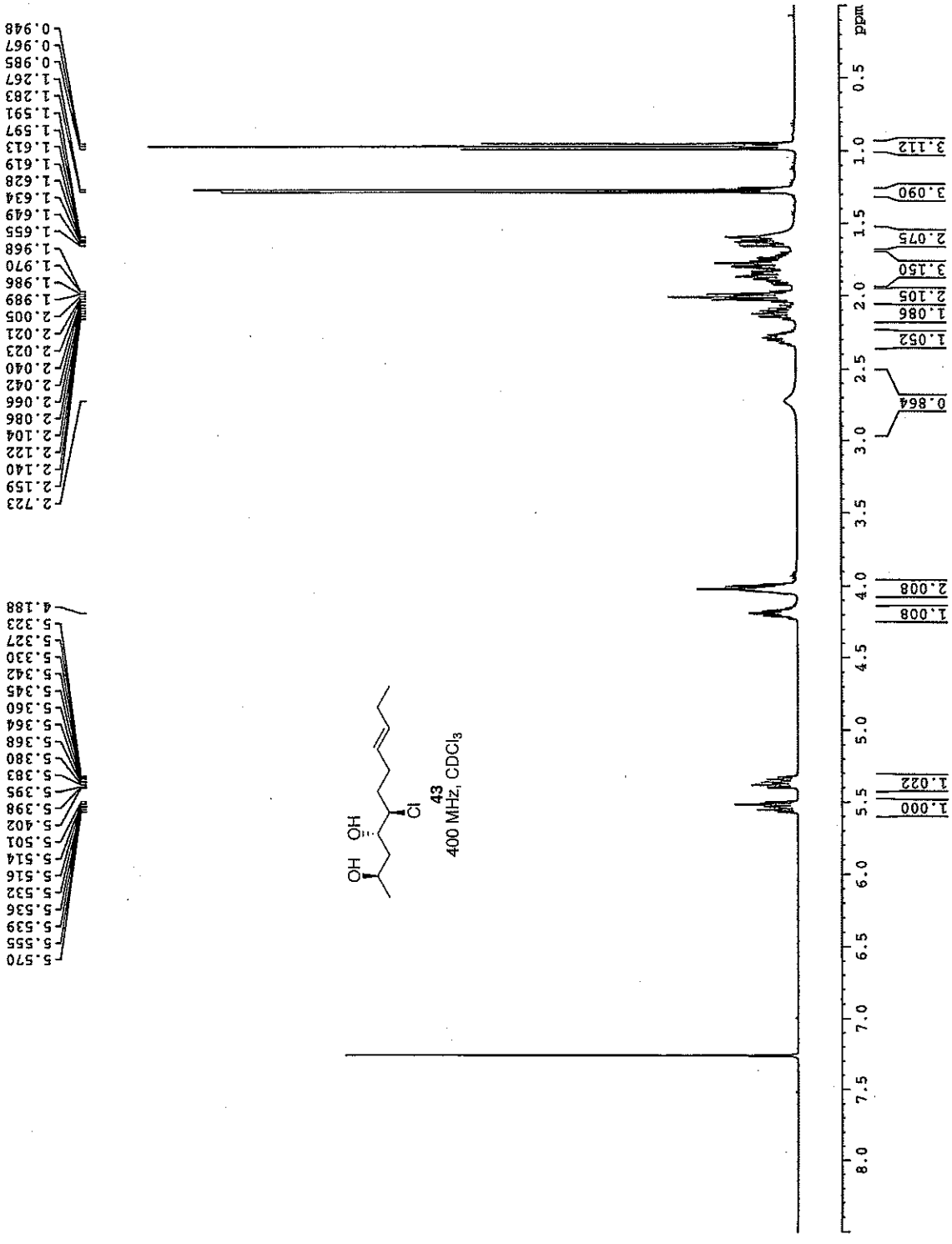

153.543
134.119
124.375
82.159
81.699
77.896
73.694
40.871
27.923
27.174
21.442
20.782
14.308
OBoc
39
100 MHz, CDCl3
ppm

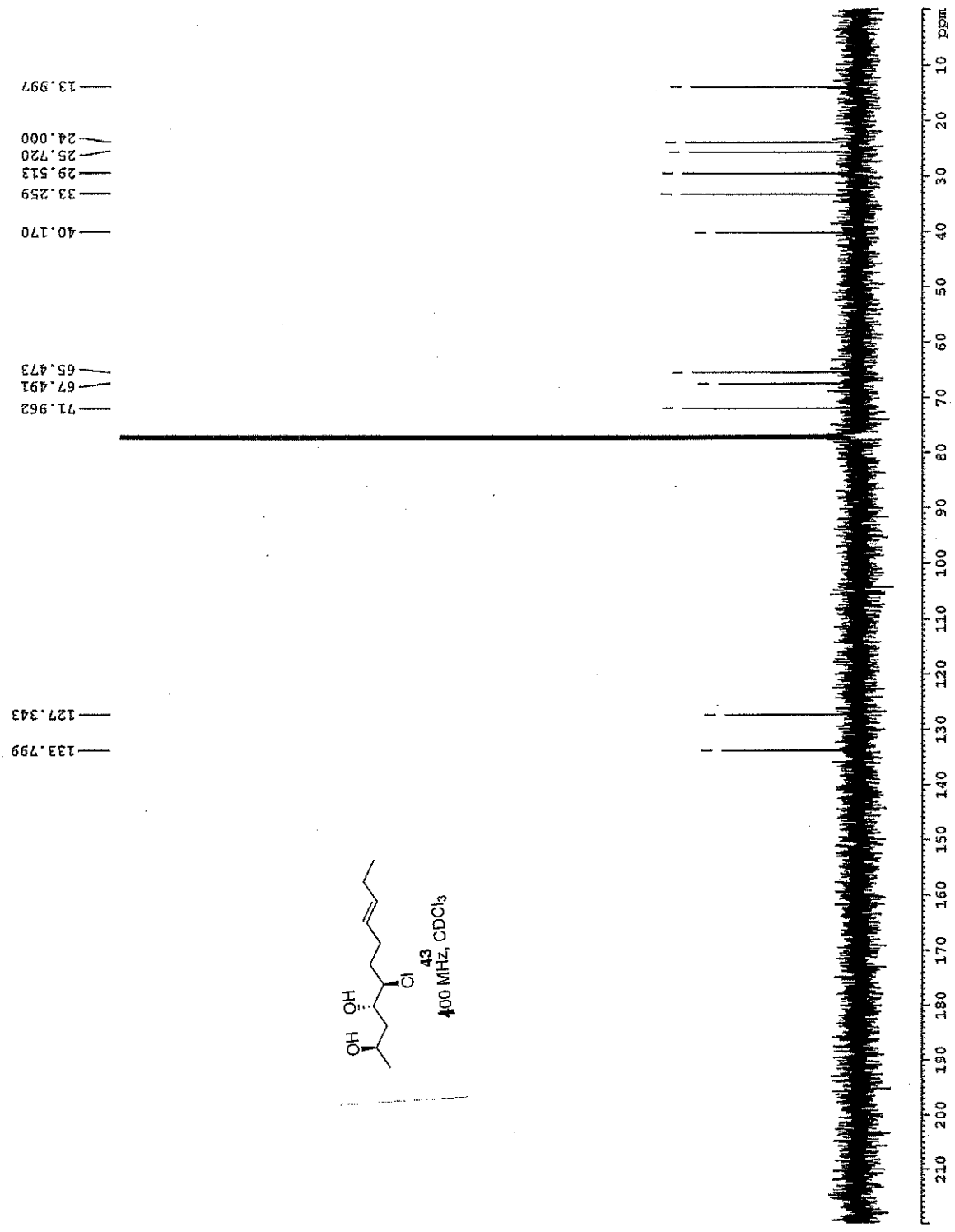

40
400 MHz, CDCl3
OH
OH
Cl
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
1.000
1.008
0.982
2.041
1.978
1.086
1.082
2.056
1.070
1.022
3.052
3.057
0.949
0.967
0.986
1.253
1.269
1.632
1.638
1.653
1.660
1.668
1.674
1.690
1.696
1.774
1.782
1.797
1.804
1.811
1.818
1.833
1.840
2.021
2.039
2.058
2.076
2.095
2.742

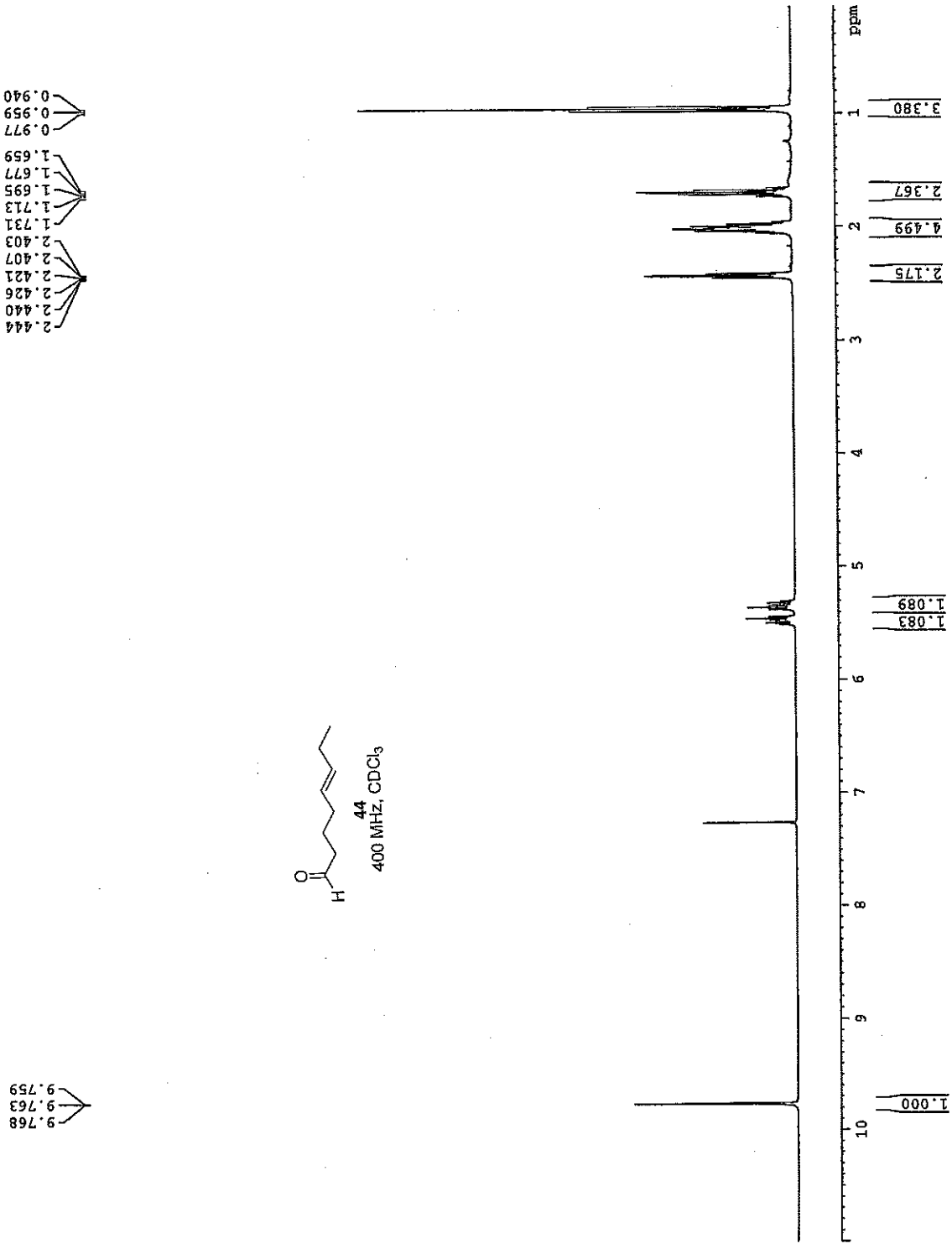

14.181
20.922
23.907
31.455
40.110
65.381
67.041
71.655
124.166
134.868
OH
OH
Cl
40
100 MHz, CDCl3
ppm

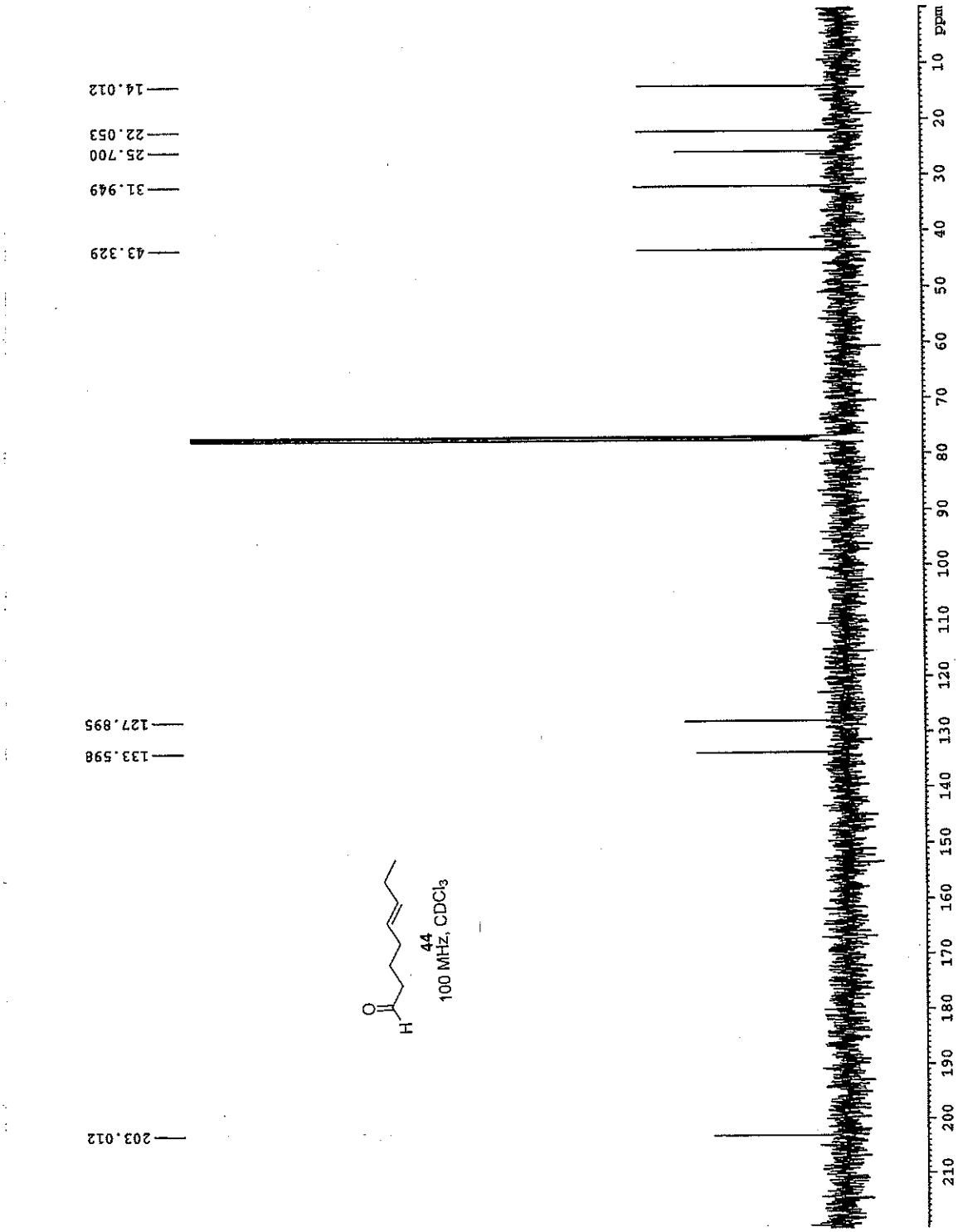

0.923
0.942
0.960
1.296
1.312
1.472
1.547
1.554
1.566
1.573
1.582
1.589
1.601
1.608
2.430
2.448
2.465
2.483
2.501
3.643
3.653
3.656
3.662
3.667
3.673
3.676
3.687
5.050
5.057
5.060
5.067
5.075
5.078
5.085
OBoc
O
42
400 MHz, CDCl3
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
3.025
3.167
9.200
3.491
4.109
1.021
1.011
0.999
1.000
1.967

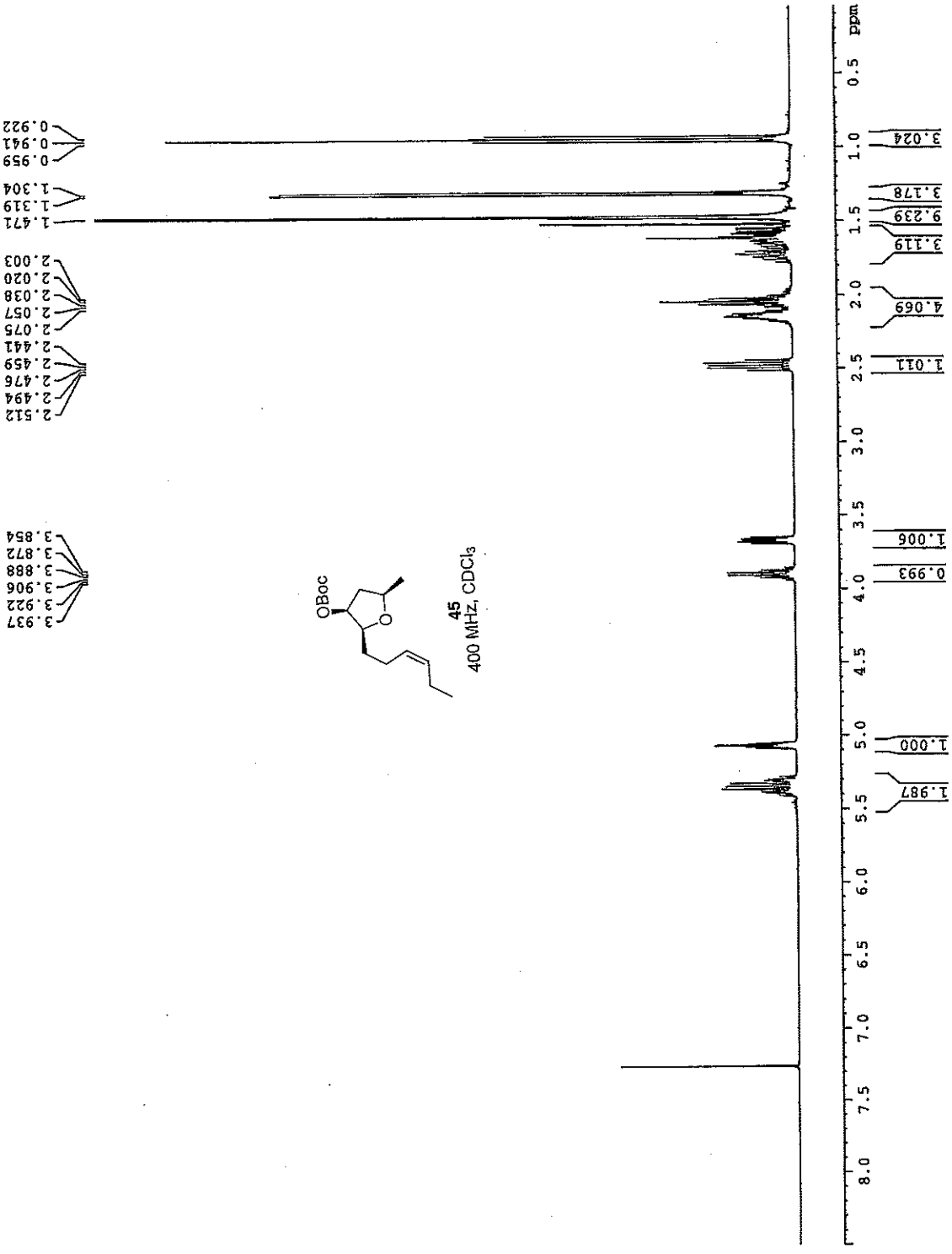

14.039
21.434
25.697
27.928
28.824
29.359
40.909
73.492
78.179
81.390
82.096
128.482
132.704
153.618
OBoc
O
42
100 MHz, CDCl3
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

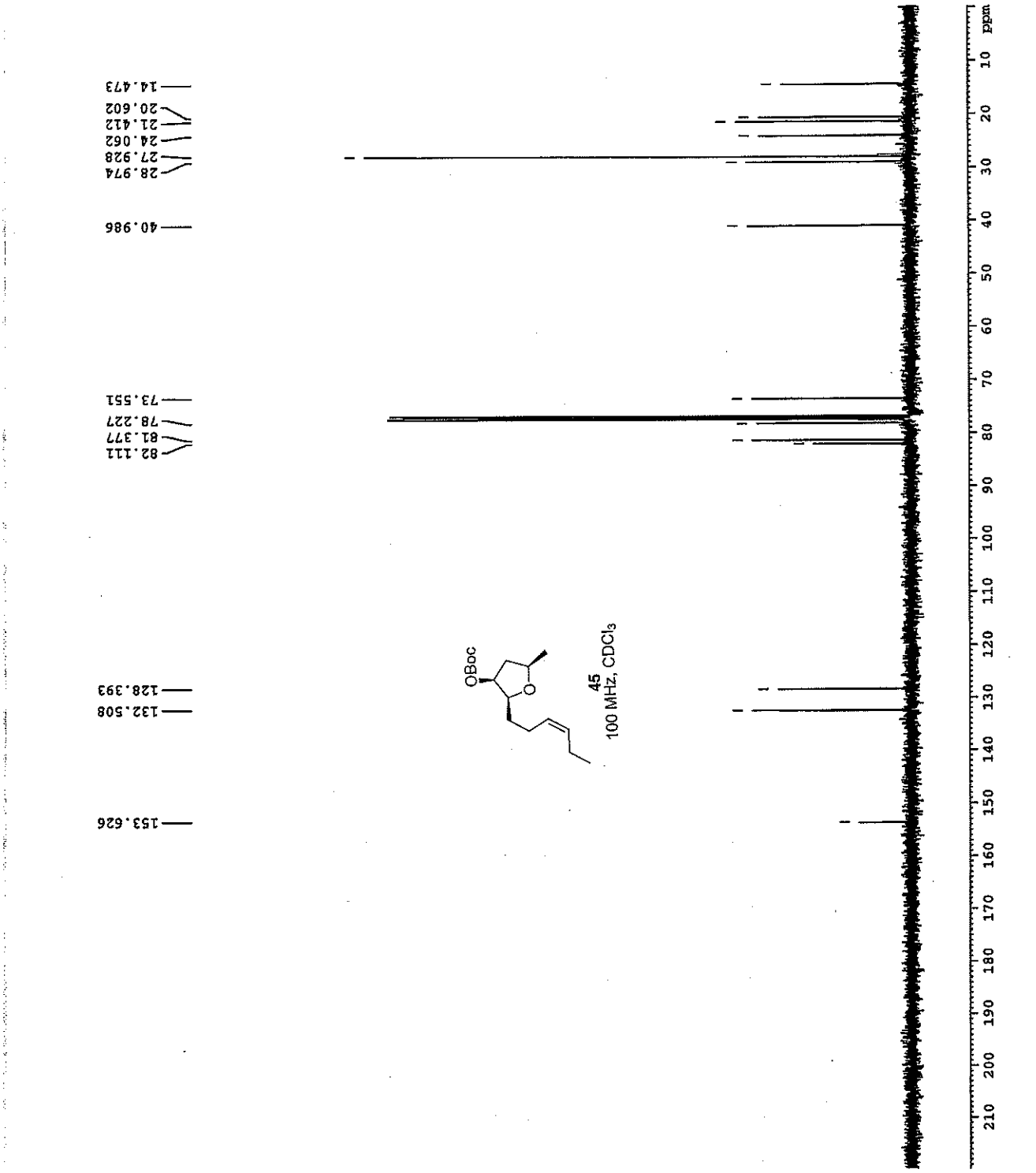

43
400 MHz, CDCl3
OH
OH
Cl
ppm
0.948
0.967
0.985
1.267
1.283
1.591
1.597
1.613
1.619
1.628
1.634
1.649
1.655
1.968
1.970
1.986
1.989
2.005
2.021
2.023
2.040
2.042
2.066
2.086
2.104
2.122
2.140
2.159
2.723
4.188
5.323
5.327
5.330
5.342
5.345
5.360
5.364
5.368
5.380
5.383
5.395
5.398
5.402
5.501
5.514
5.516
5.532
5.536
5.539
5.555
5.570
3.112
3.090
2.075
3.150
2.105
1.086
1.052
0.864
2.008
1.008
1.022
1.000

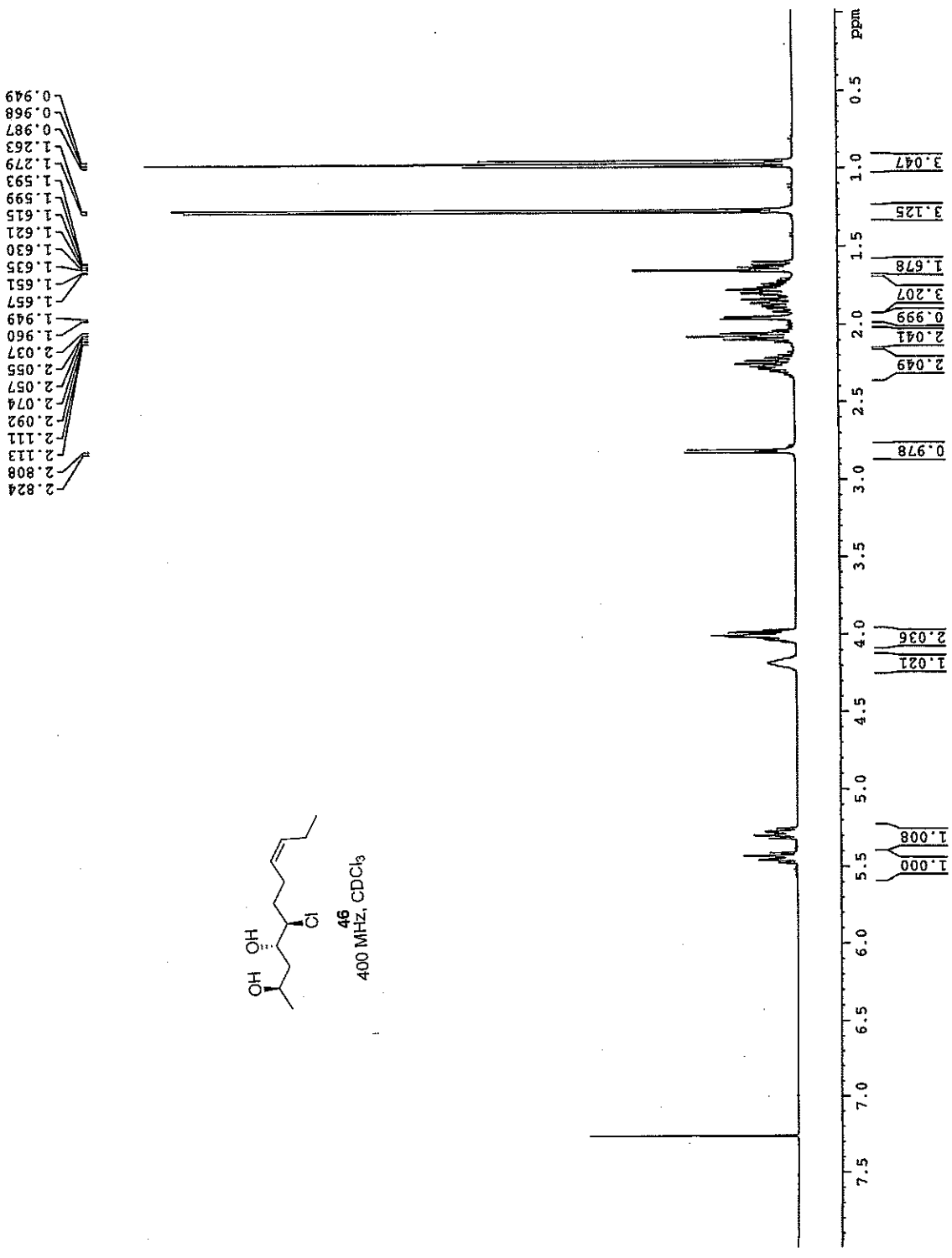

13.997
24.000
25.720
29.513
33.259
40.170
65.473
67.491
71.962
127.343
133.799
OH
OH
Cl
43
400 MHz, CDCl3
ppm

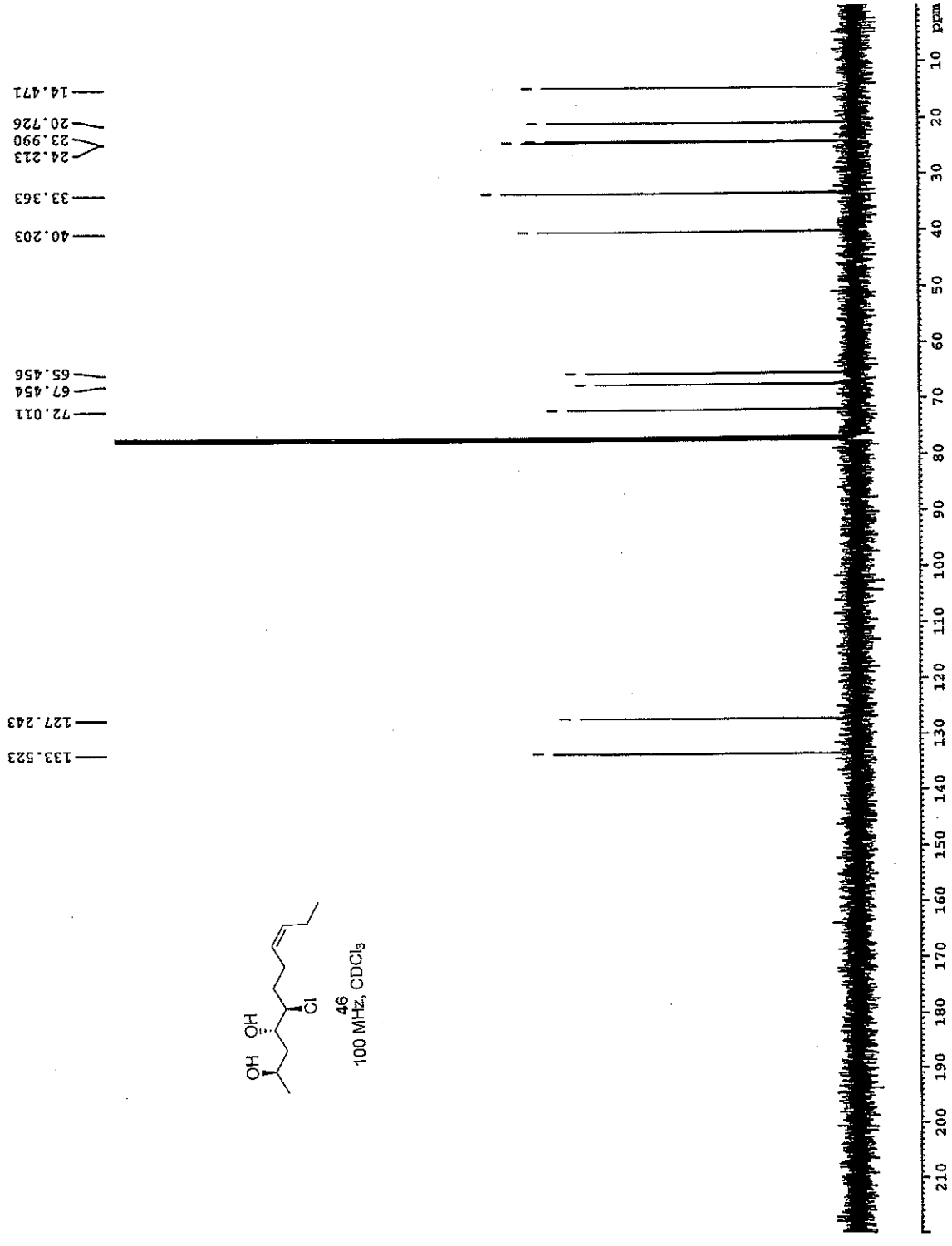

44
400 MHz, CDCl3
O
H
ppm
1.000
1.089
1.083
2.175
4.499
2.367
3.380
9.768
9.763
9.759
2.444
2.440
2.426
2.421
2.407
2.403
1.731
1.713
1.695
1.677
1.659
0.977
0.959
0.940


14.012
22.053
25.700
31.949
43.329
127.895
133.598
203.012
44
100 MHz, CDCl3
O
H
ppm

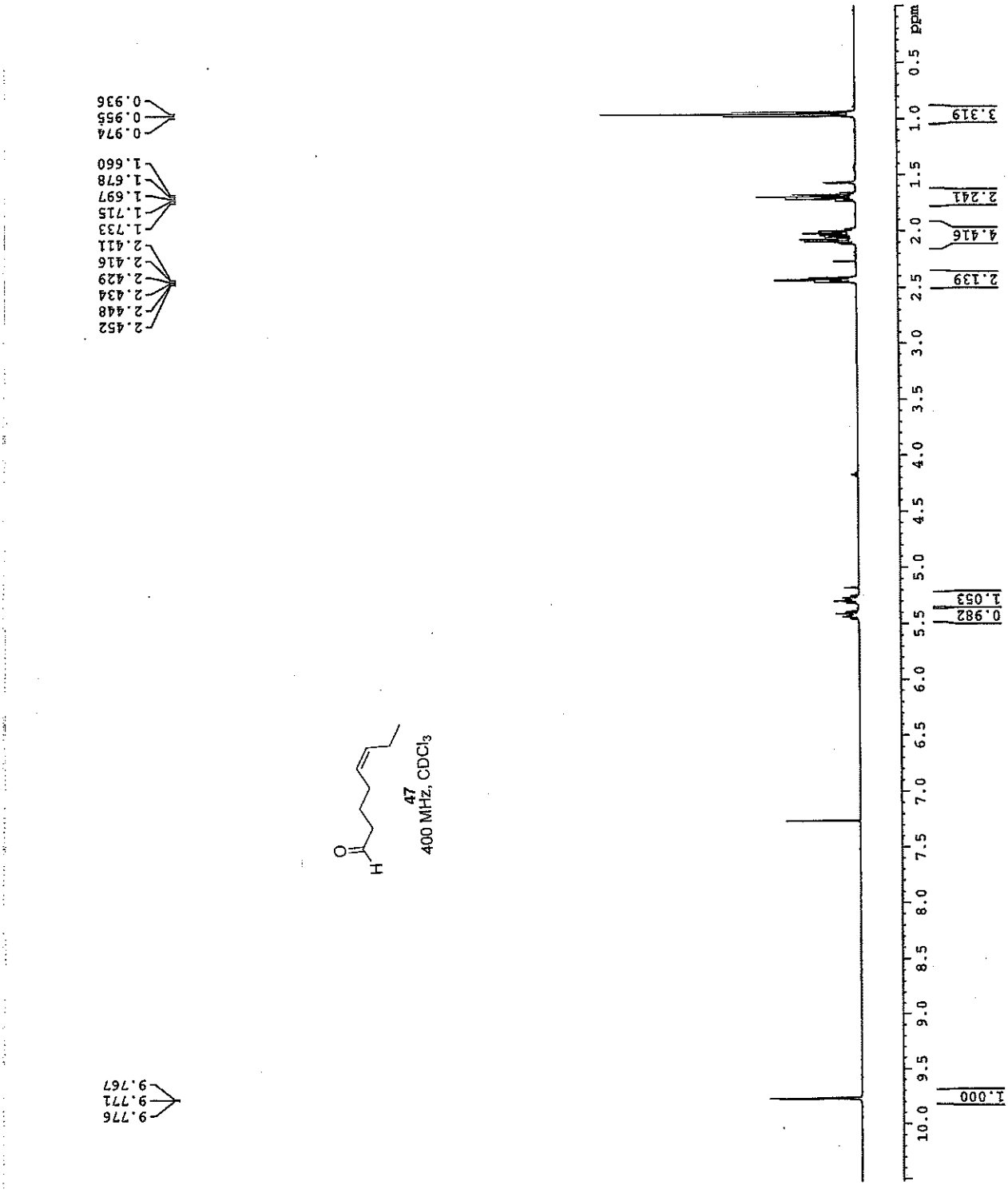

45
400 MHz, CDCl3
OBoc
0.922
0.941
0.959
1.304
1.319
1.471
2.003
2.020
2.038
2.057
2.075
2.441
2.459
2.476
2.494
2.512
3.854
3.872
3.888
3.906
3.922
3.937
3.024
3.178
9.239
3.119
4.069
1.011
1.006
0.993
1.000
1.987
ppm

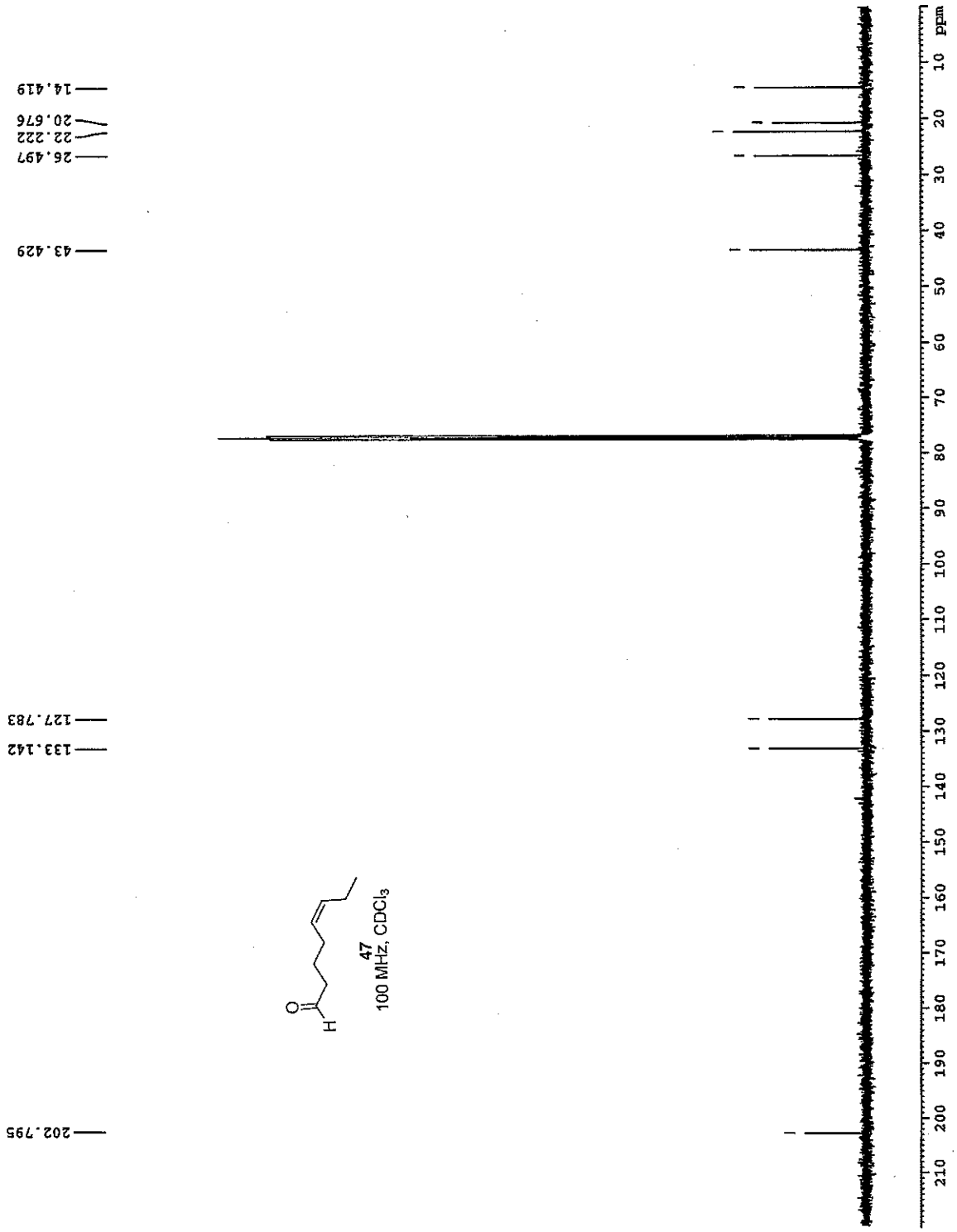

14.473
20.602
21.412
24.062
27.928
28.974
40.986
73.551
78.227
81.377
82.111
128.393
132.508
153.626
OBoc
45
100 MHz, CDCl3
ppm

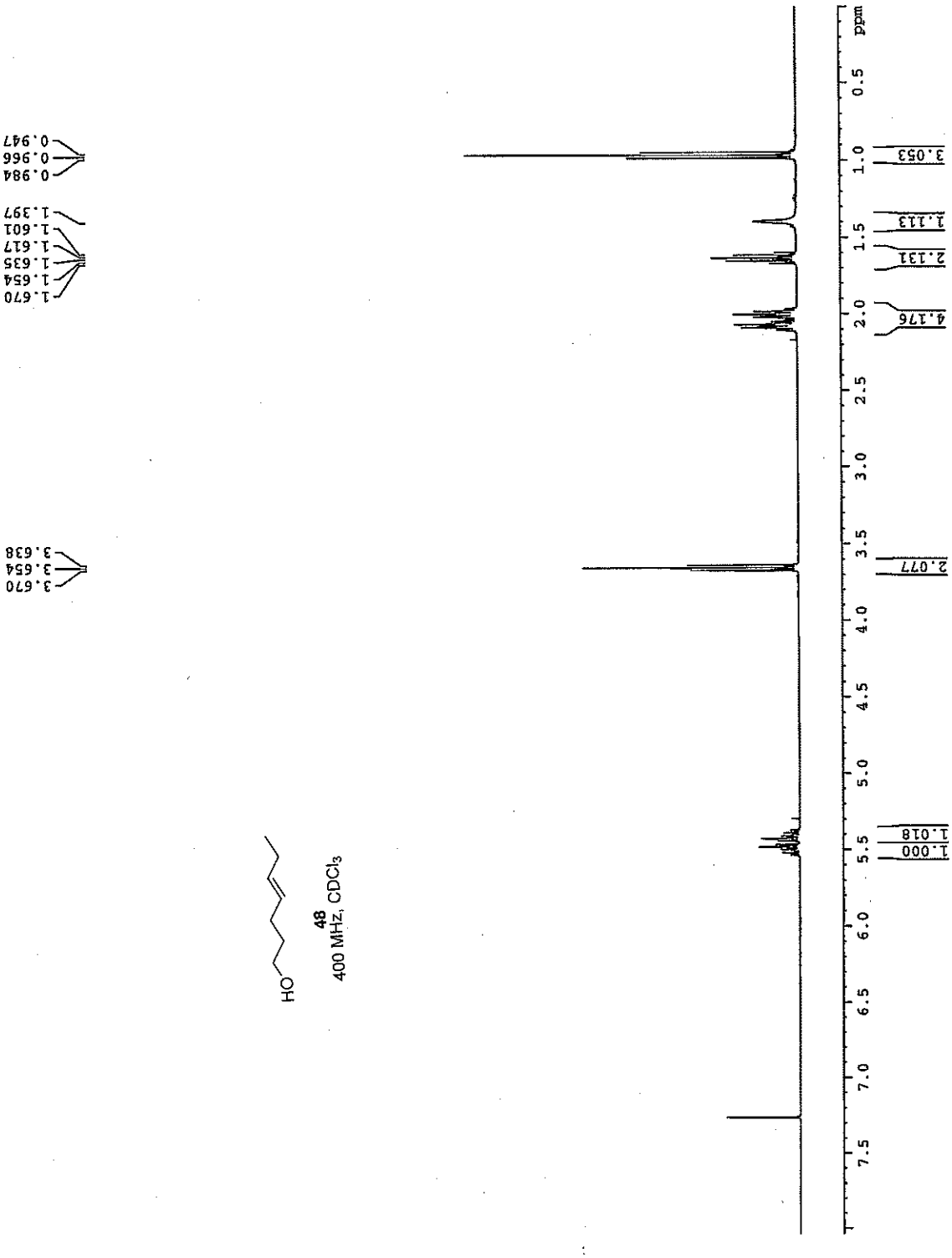

46
400 MHz, CDCl3
OH
OH
Cl
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
3.047
3.125
1.678
3.207
0.999
2.041
2.049
0.978
2.036
1.021
1.008
1.000
0.949
0.968
0.987
1.263
1.279
1.593
1.599
1.615
1.621
1.630
1.635
1.651
1.657
1.949
1.960
2.037
2.055
2.057
2.074
2.092
2.111
2.113
2.808
2.824

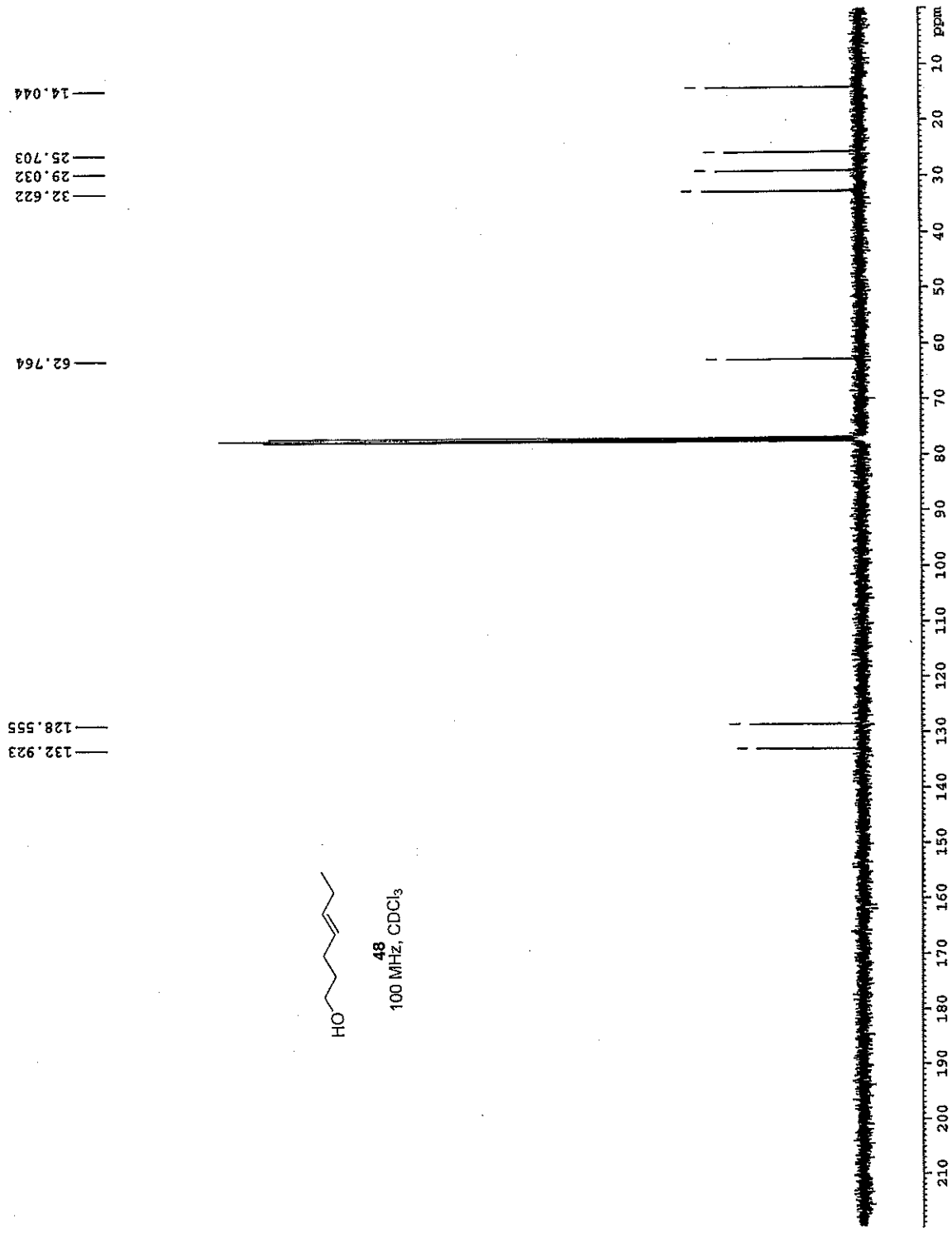


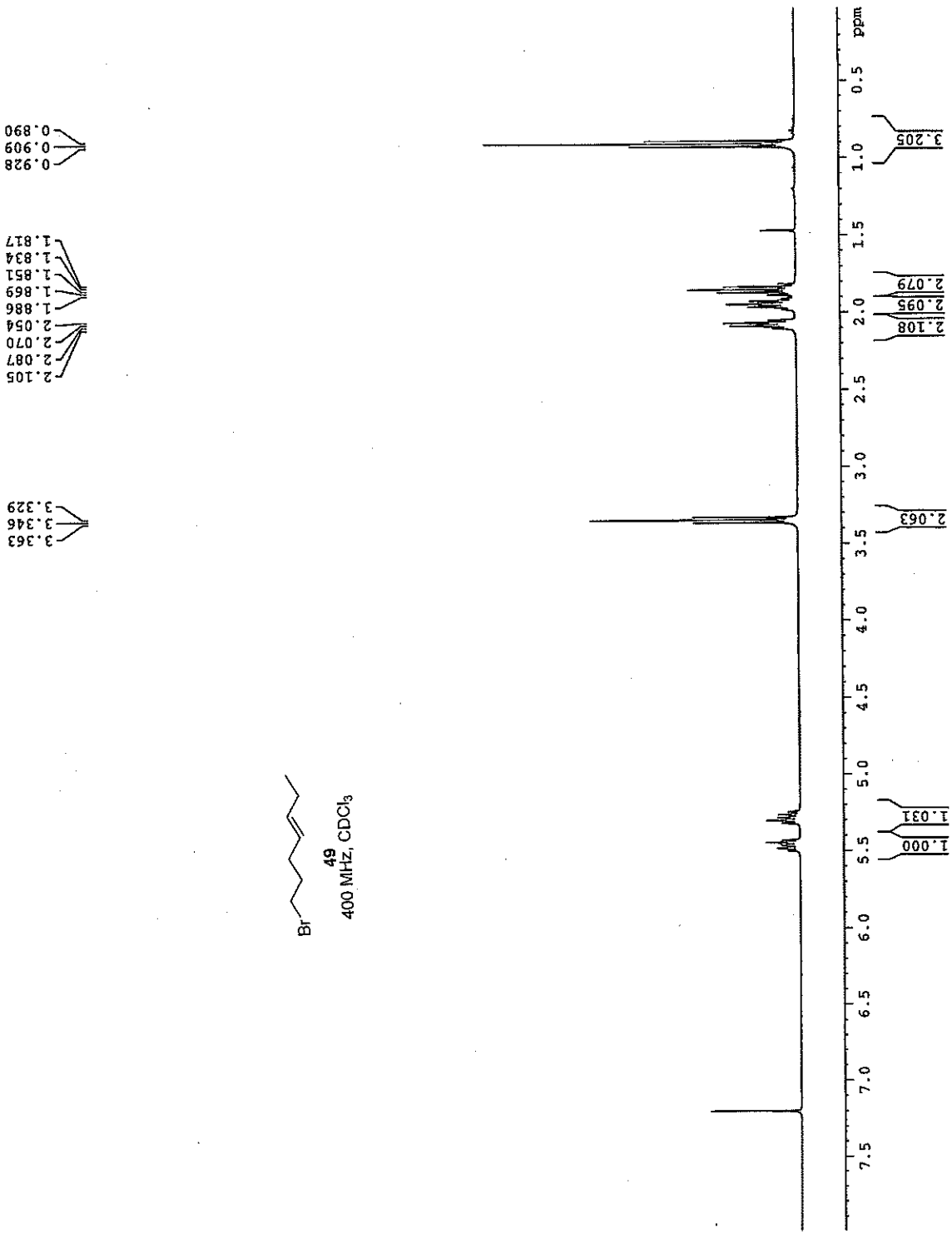
46
100 MHz, $CDCl_3$

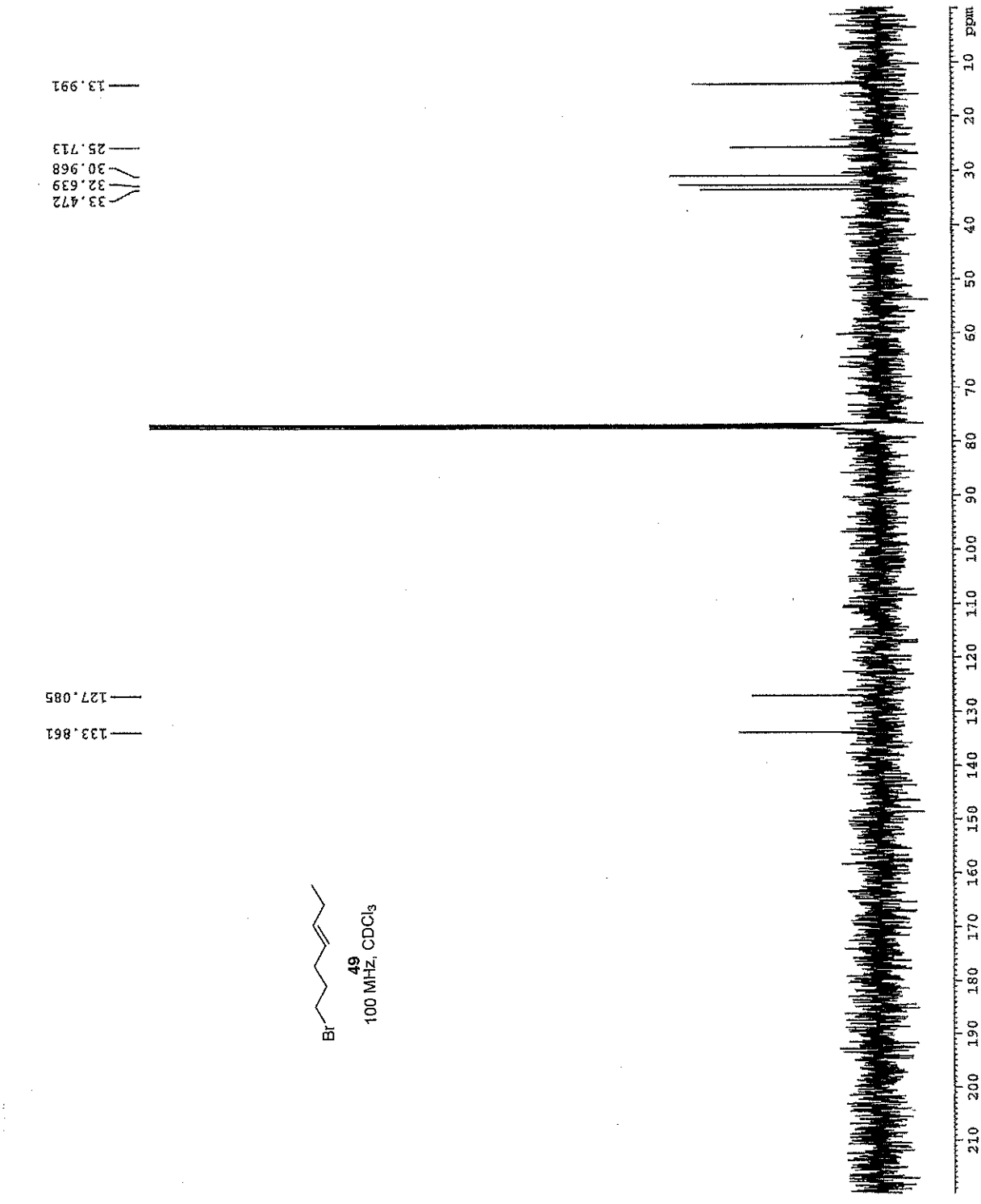

47
400 MHz, CDCl3
O
H
9.776
9.771
9.767
2.452
2.448
2.434
2.429
2.416
2.411
1.733
1.715
1.697
1.678
1.660
0.974
0.955
0.936
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.000
0.982
1.053
2.139
4.416
2.241
3.319

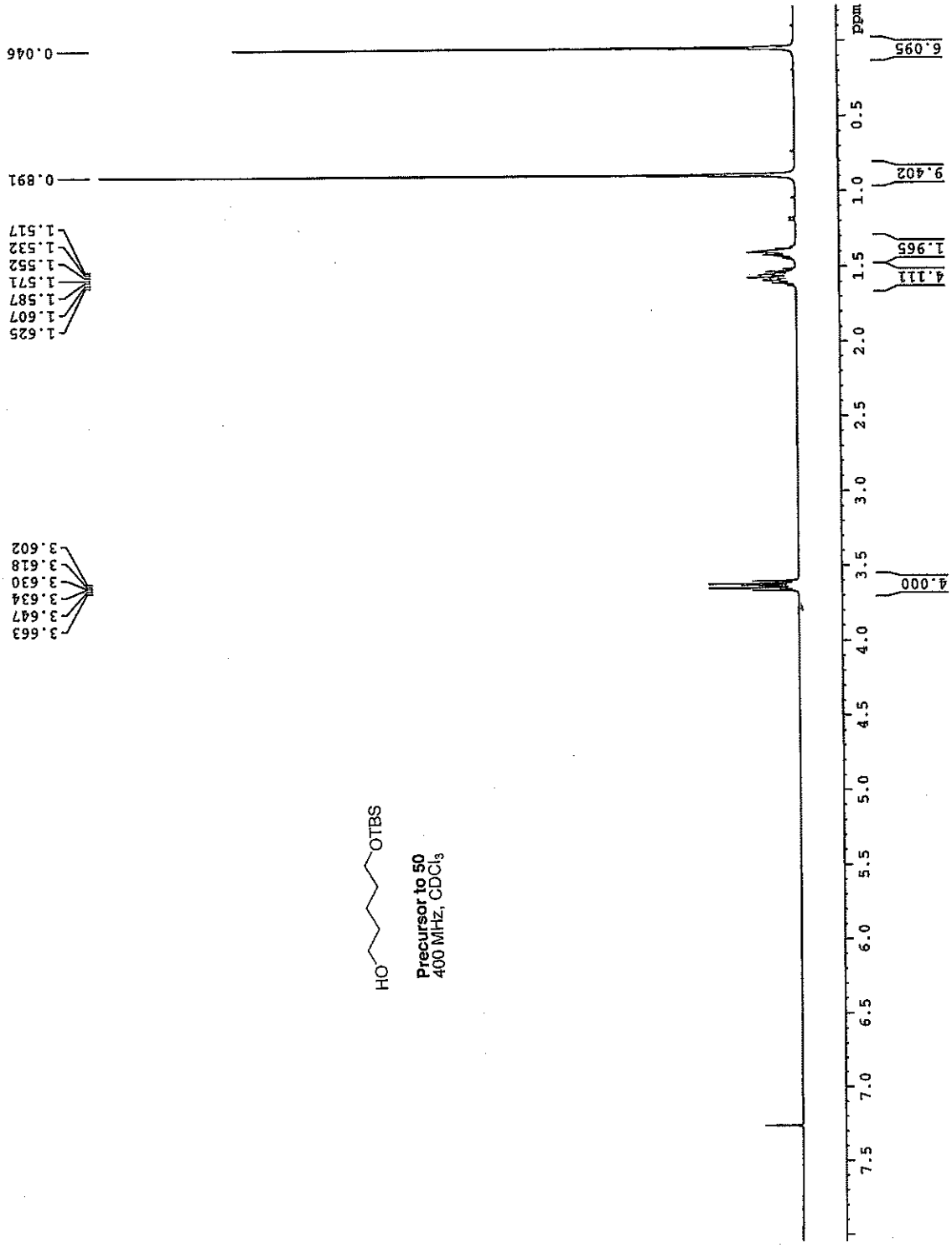

202.795
133.142
127.783
43.429
26.497
22.222
20.676
14.419
47
100 MHz, CDCl3
O
H
ppm

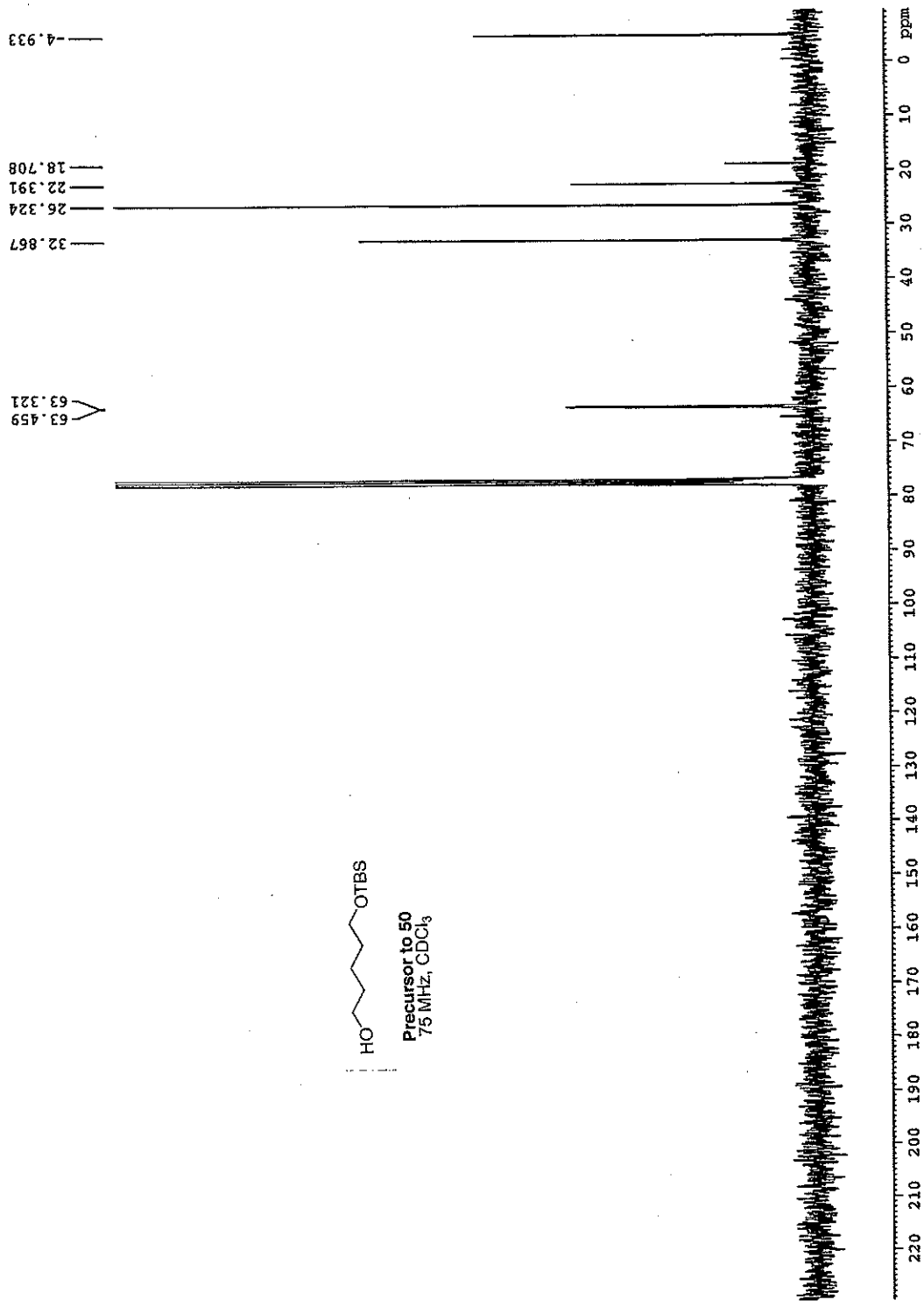

48
400 MHz, CDCl3
HO
0.947
0.966
0.984
1.397
1.601
1.617
1.635
1.654
1.670
3.638
3.654
3.670
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
3.053
1.113
2.131
4.176
2.077
1.018
1.000

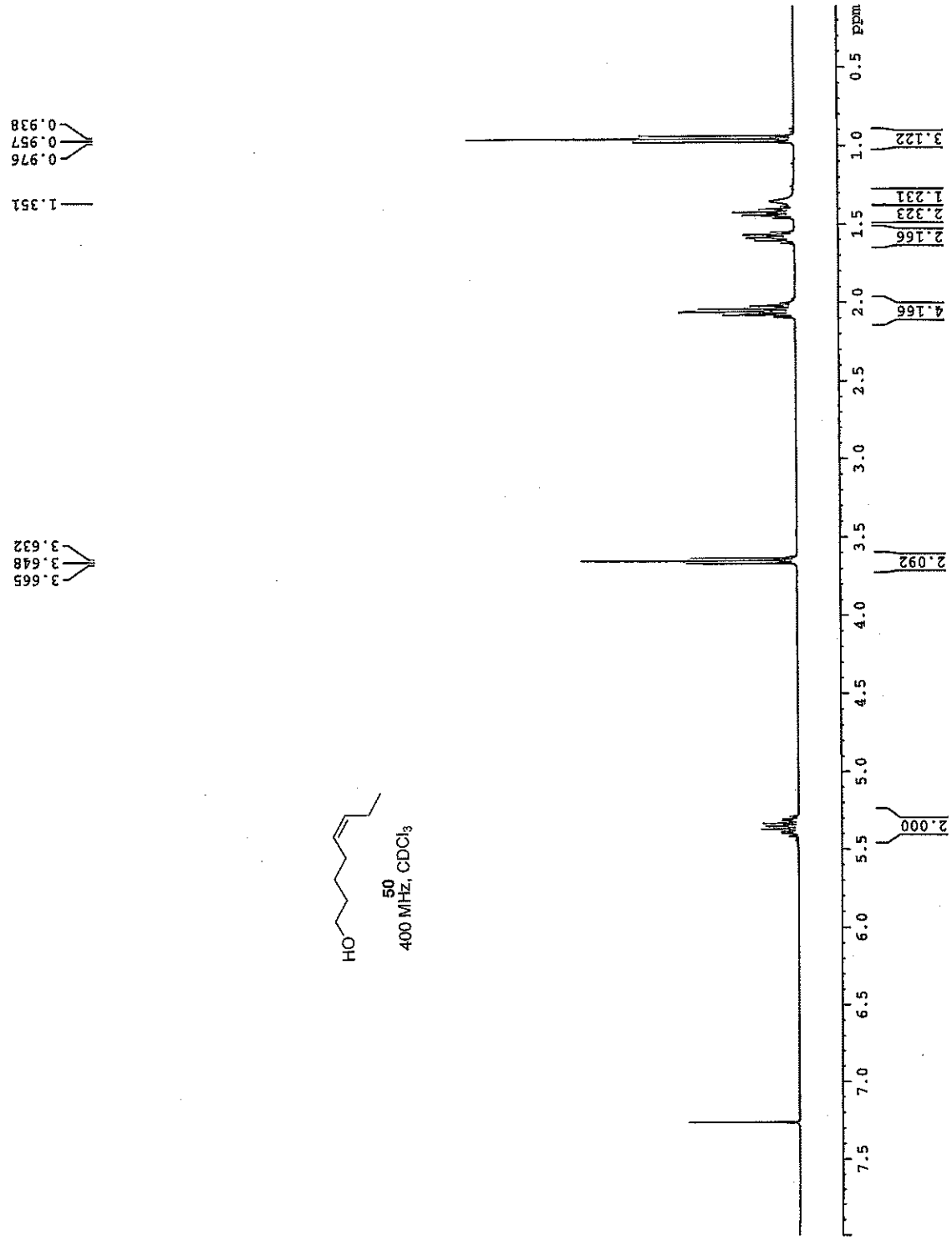

14.044
25.703
29.032
32.622
62.764
128.555
132.923
HO
48
100 MHz, CDCl3
ppm

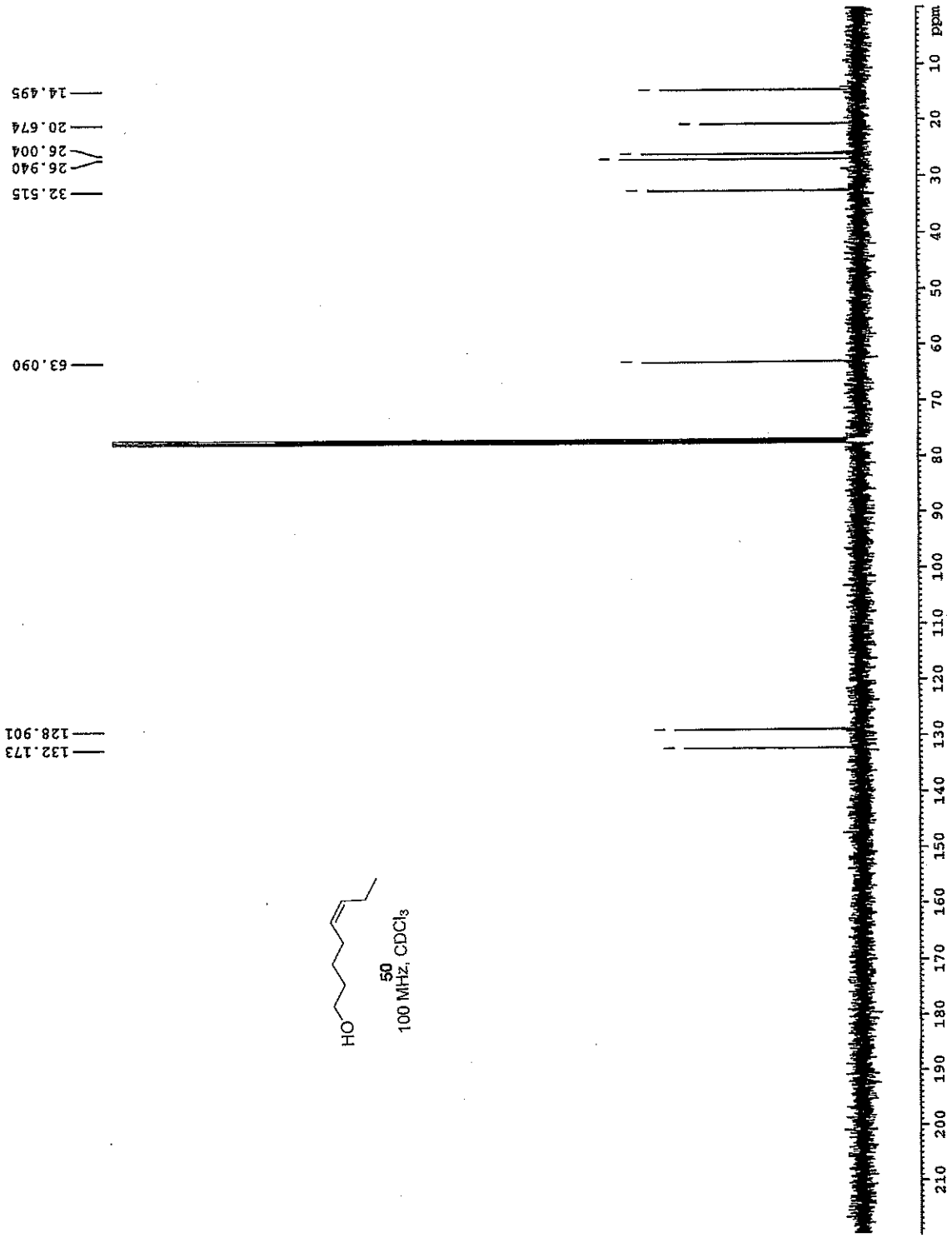

Br
49
400 MHz, CDCl3
0.928
0.909
0.890
1.817
1.834
1.851
1.869
1.886
2.054
2.070
2.087
2.105
3.329
3.346
3.363
3.205
2.079
2.095
2.108
2.063
1.031
1.000
ppm

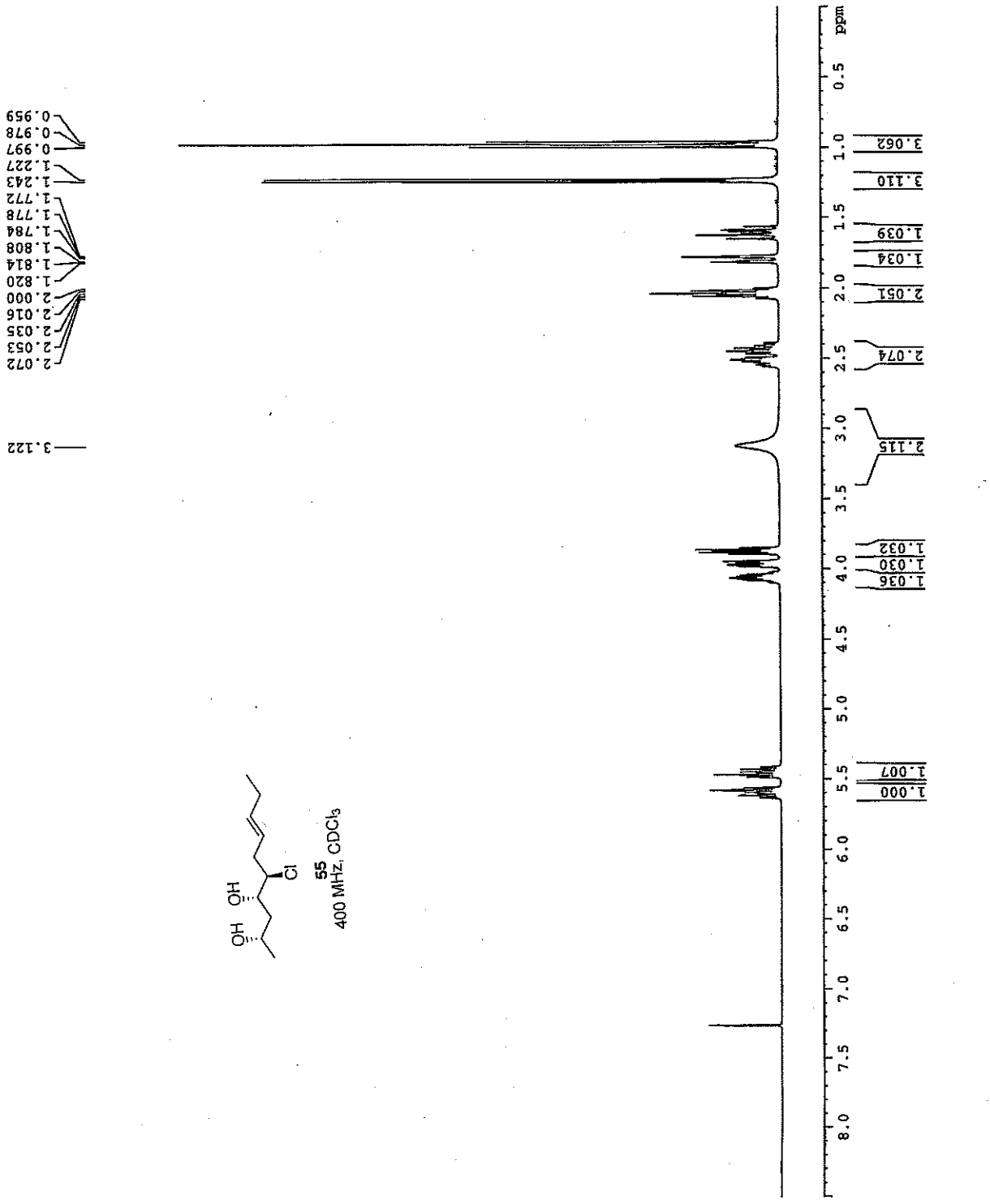

Br
49
100 MHz, CDCl3
133.861
127.085
33.472
32.639
30.968
25.713
13.991
ppm

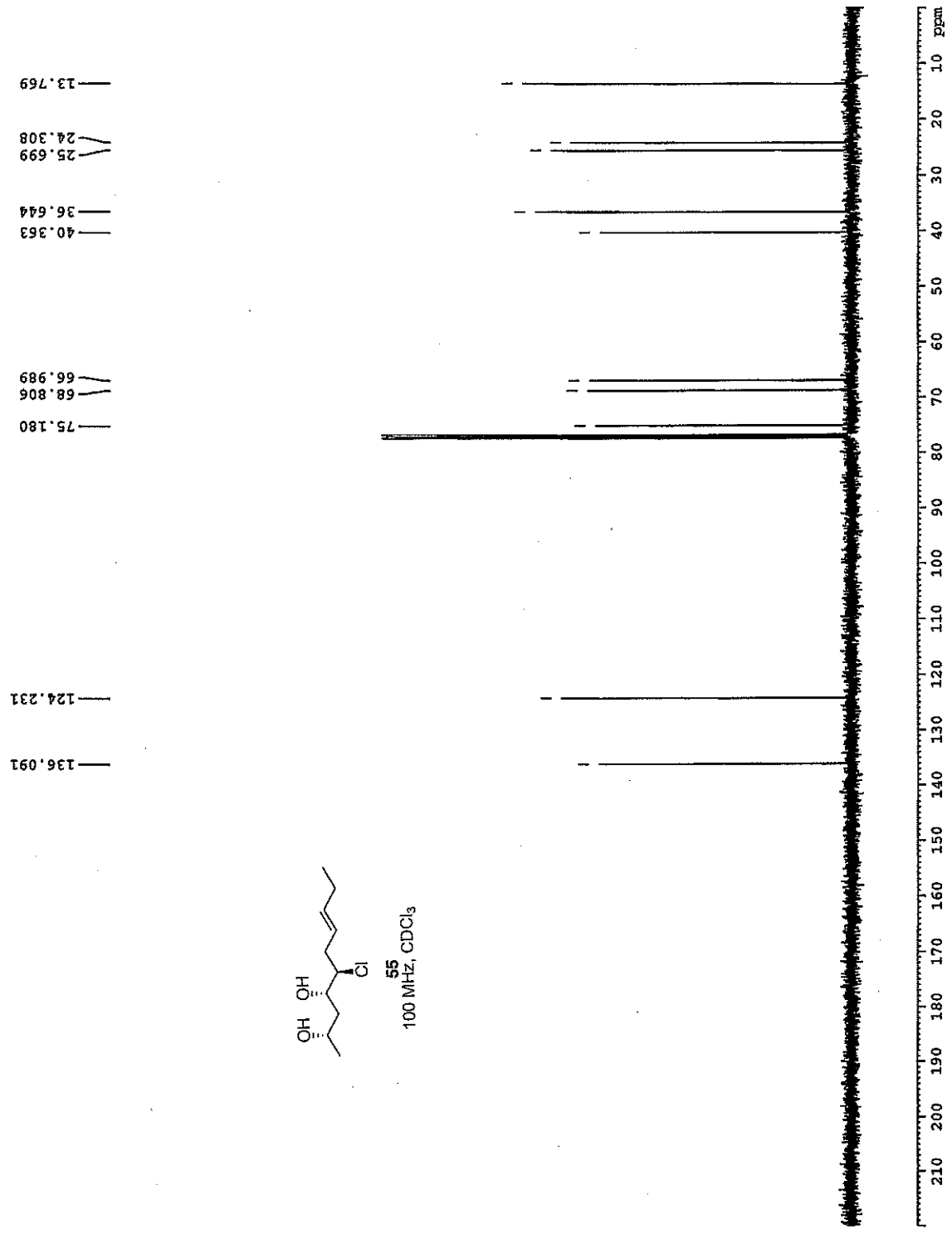

0.046
0.891
1.517
1.532
1.552
1.571
1.587
1.607
1.625
3.602
3.618
3.630
3.634
3.647
3.663
6.095
9.402
1.965
4.111
4.000
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
HO
OTBS
Precursor to 50
400 MHz, CDCl3

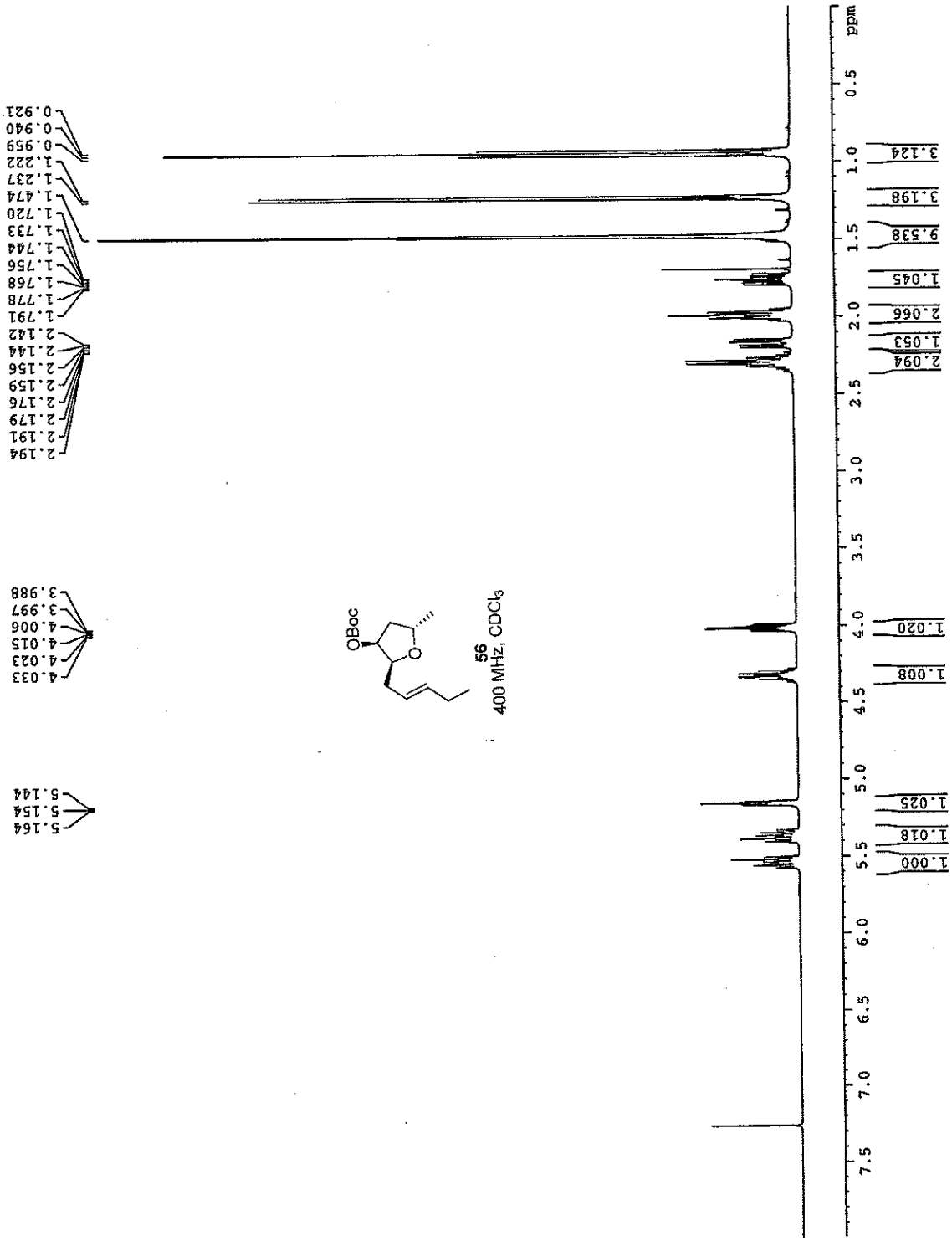

HO
OTBS
Precursor to 50
75 MHz, CDCl3
-4.933
18.708
22.391
26.324
32.867
63.459
63.321
ppm

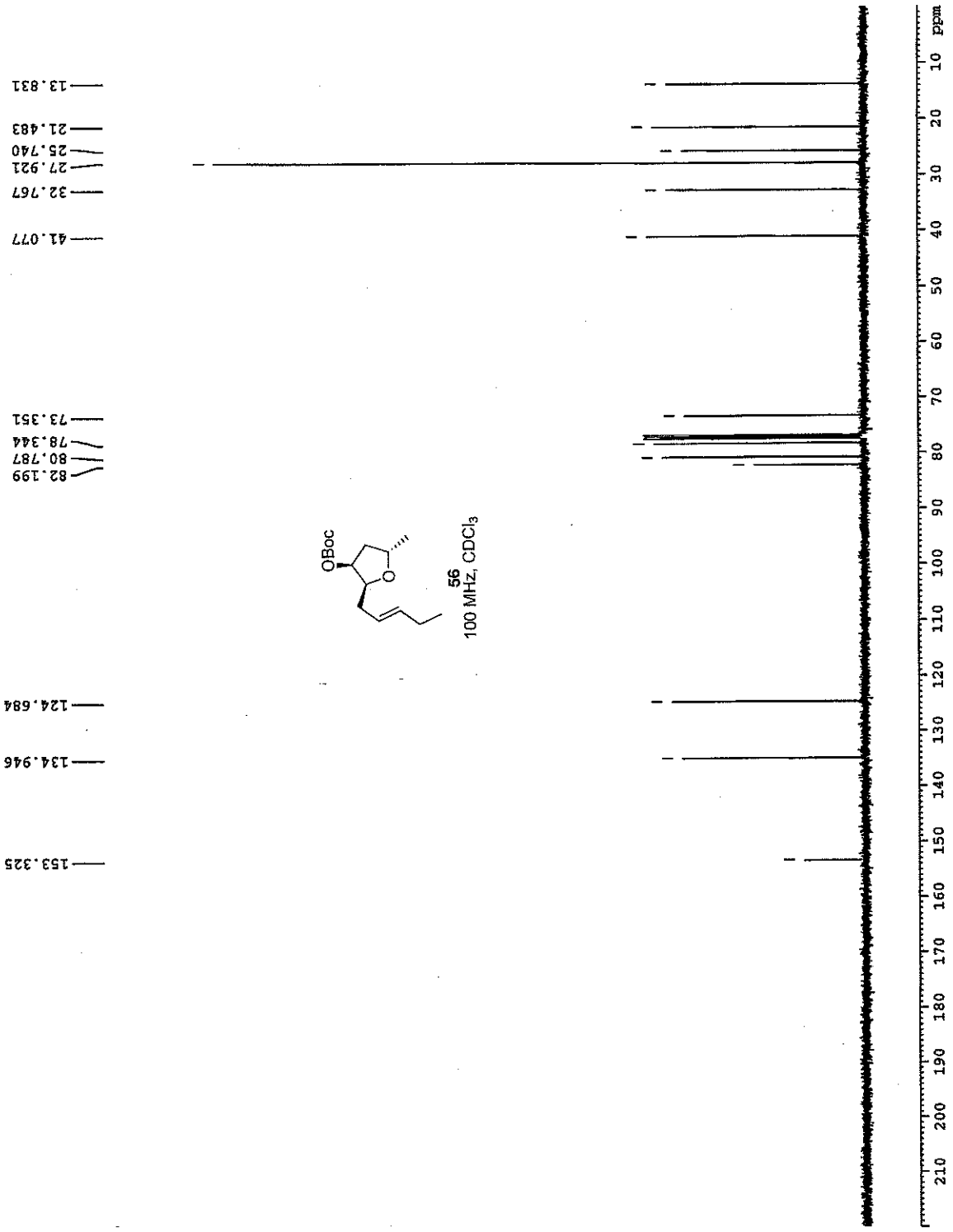

50
400 MHz, CDCl3
HO
0.938
0.957
0.976
1.351
3.632
3.648
3.665
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
3.122
1.231
2.323
2.166
4.166
2.092
2.000

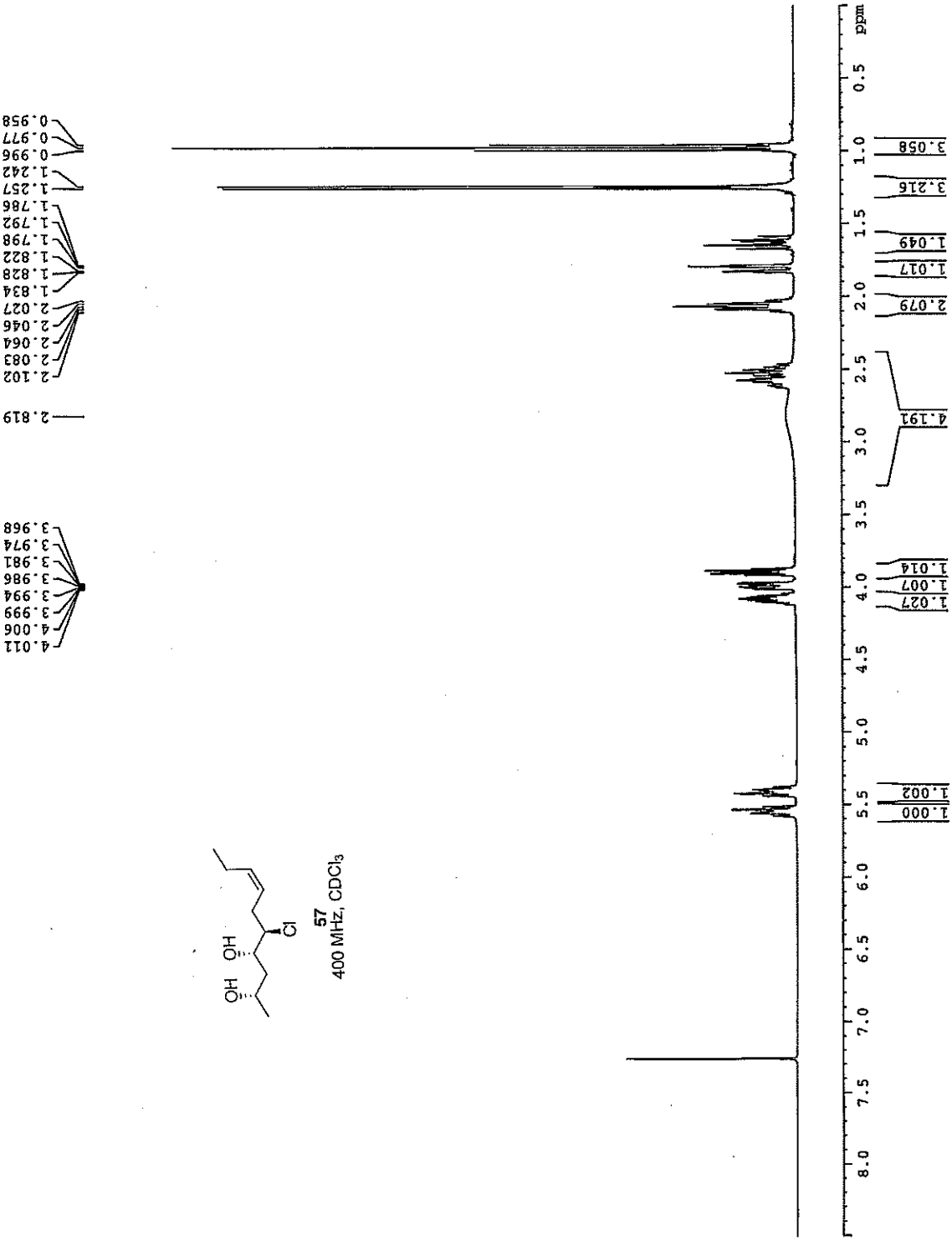

14.495
20.674
26.004
26.940
32.515
63.090
128.901
132.173
HO
50
100 MHz, CDCl3
ppm


55
400 MHz, CDCl3
OH
OH
Cl
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
1.000
1.007
1.036
1.030
1.032
2.115
2.074
2.051
1.034
1.039
3.110
3.062
3.122
2.072
2.053
2.035
2.016
2.000
1.820
1.814
1.808
1.784
1.778
1.772
1.243
1.227
0.997
0.978
0.959

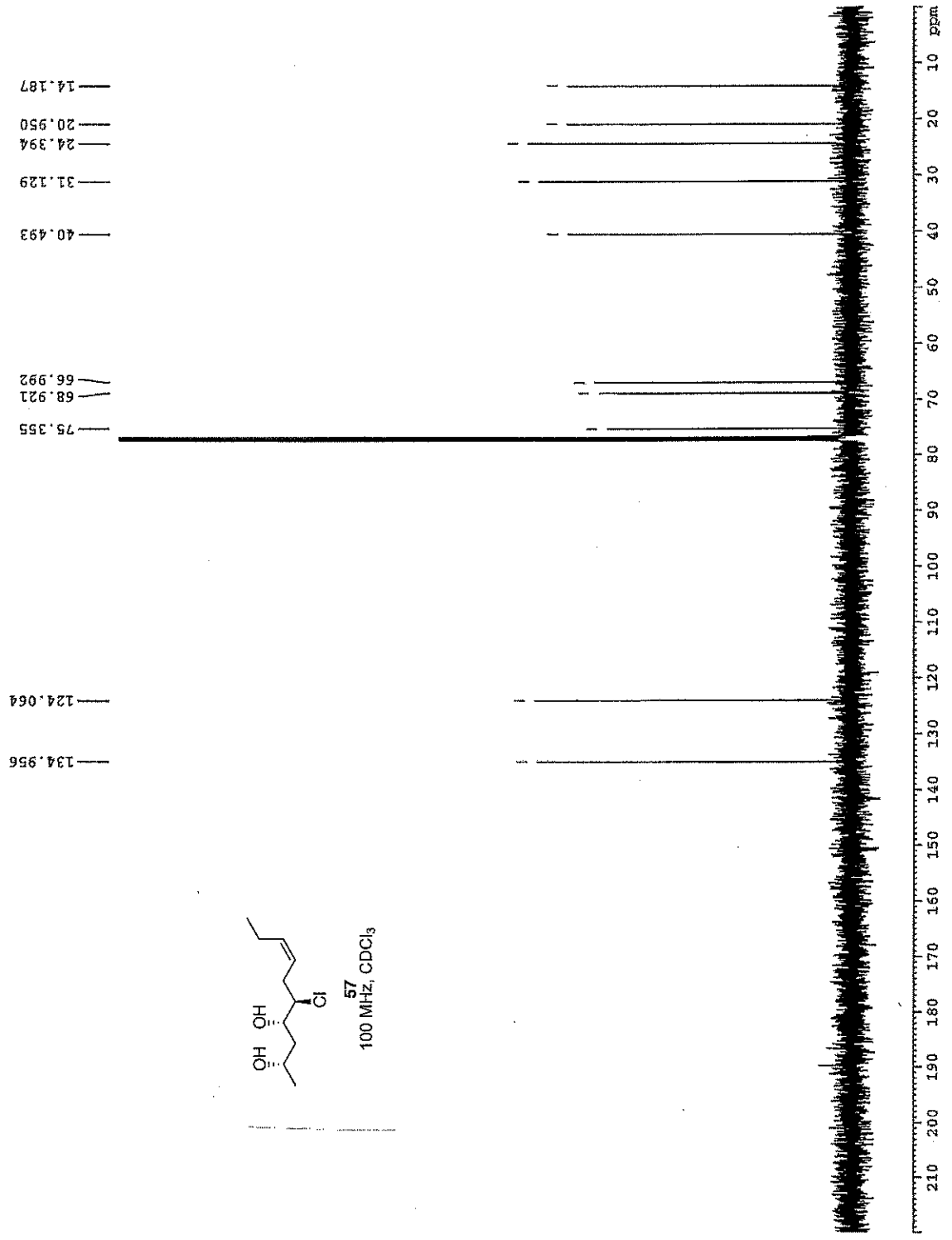

13.769
24.308
25.699
36.644
40.363
66.989
68.806
75.180
124.231
136.091
OH
OH
Cl
55
100 MHz, CDCl3
ppm

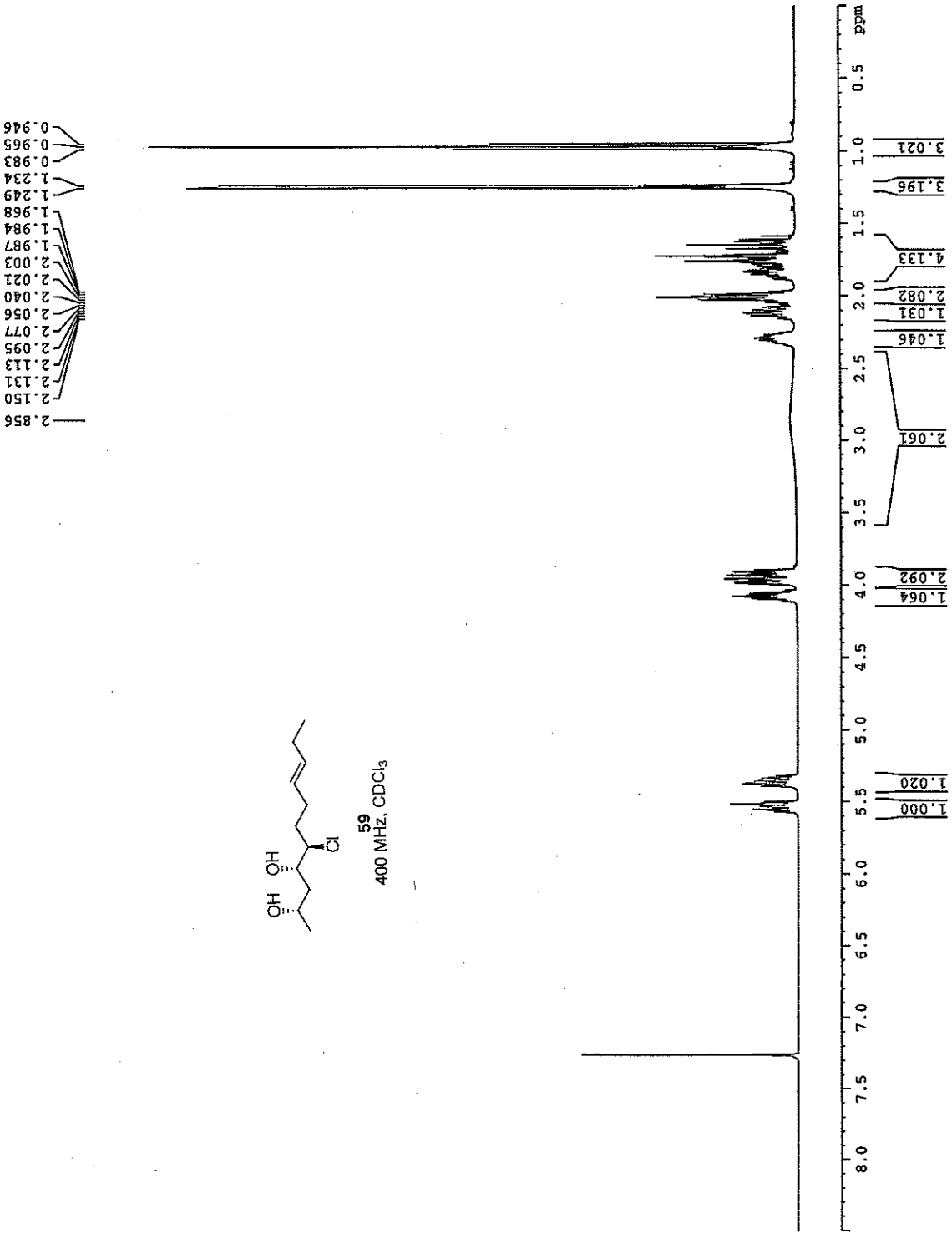

OBoc
56
400 MHz, CDCl3
ppm
0.921
0.940
0.959
1.222
1.237
1.474
1.720
1.733
1.744
1.756
1.768
1.778
1.791
2.142
2.144
2.156
2.159
2.176
2.179
2.191
2.194
3.124
3.198
9.538
1.045
2.066
1.053
2.094
3.988
3.997
4.006
4.015
4.023
4.033
1.020
1.008
5.144
5.154
5.164
1.025
1.018
1.000

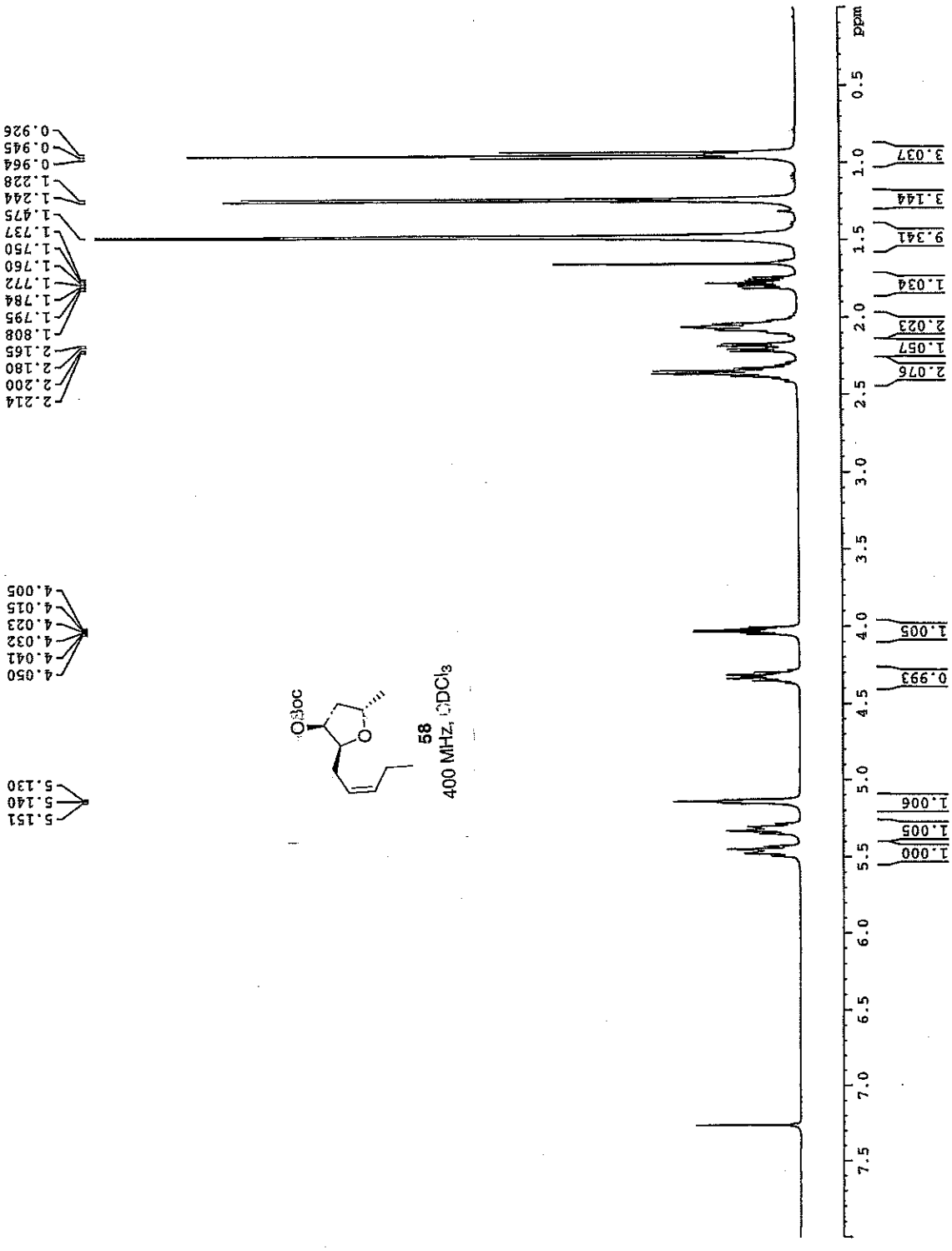

13.831
21.483
25.740
27.921
32.767
41.077
73.351
78.344
80.787
82.199
124.684
134.946
153.325
OBoc
O
56
100 MHz, CDCl3
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 ppm

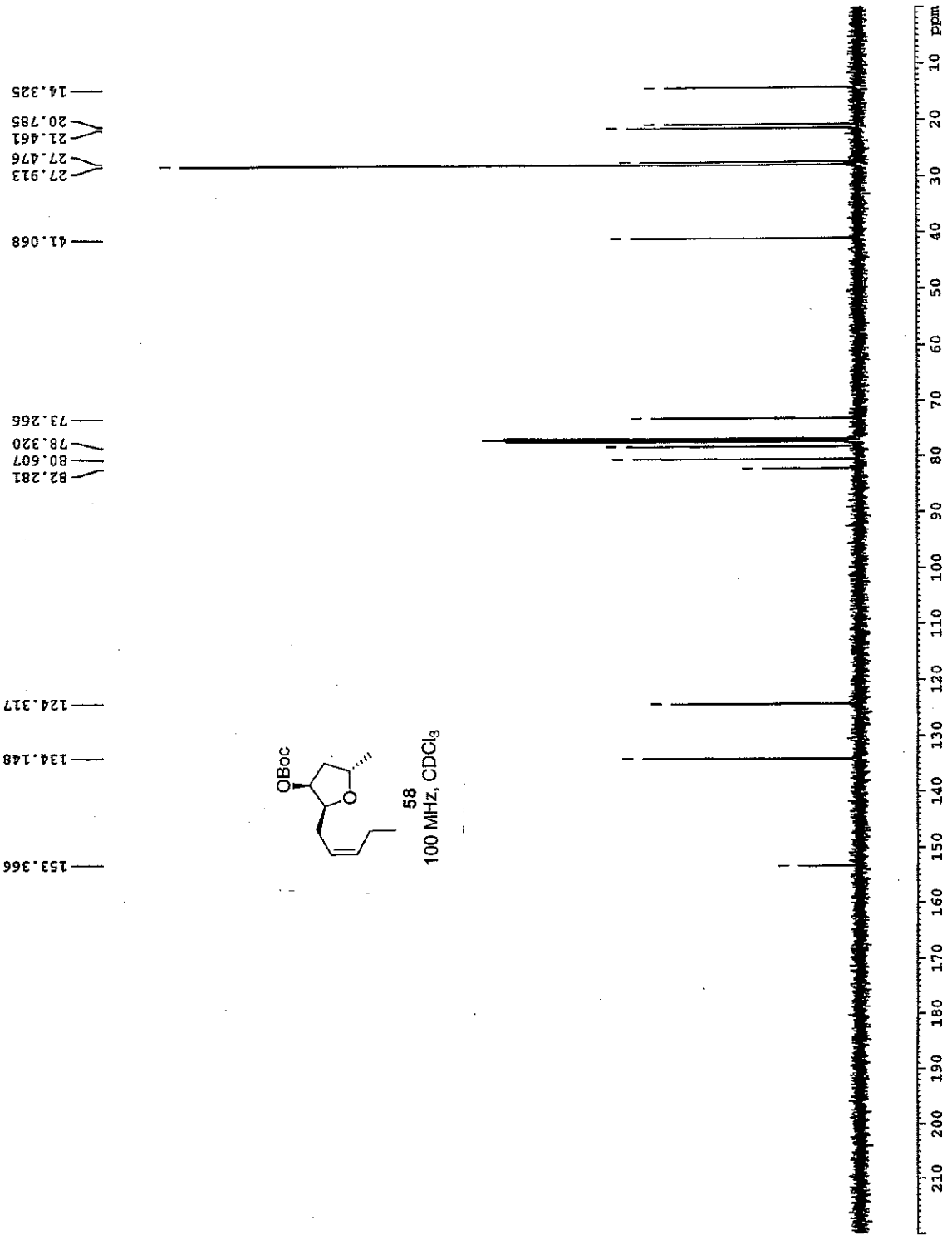


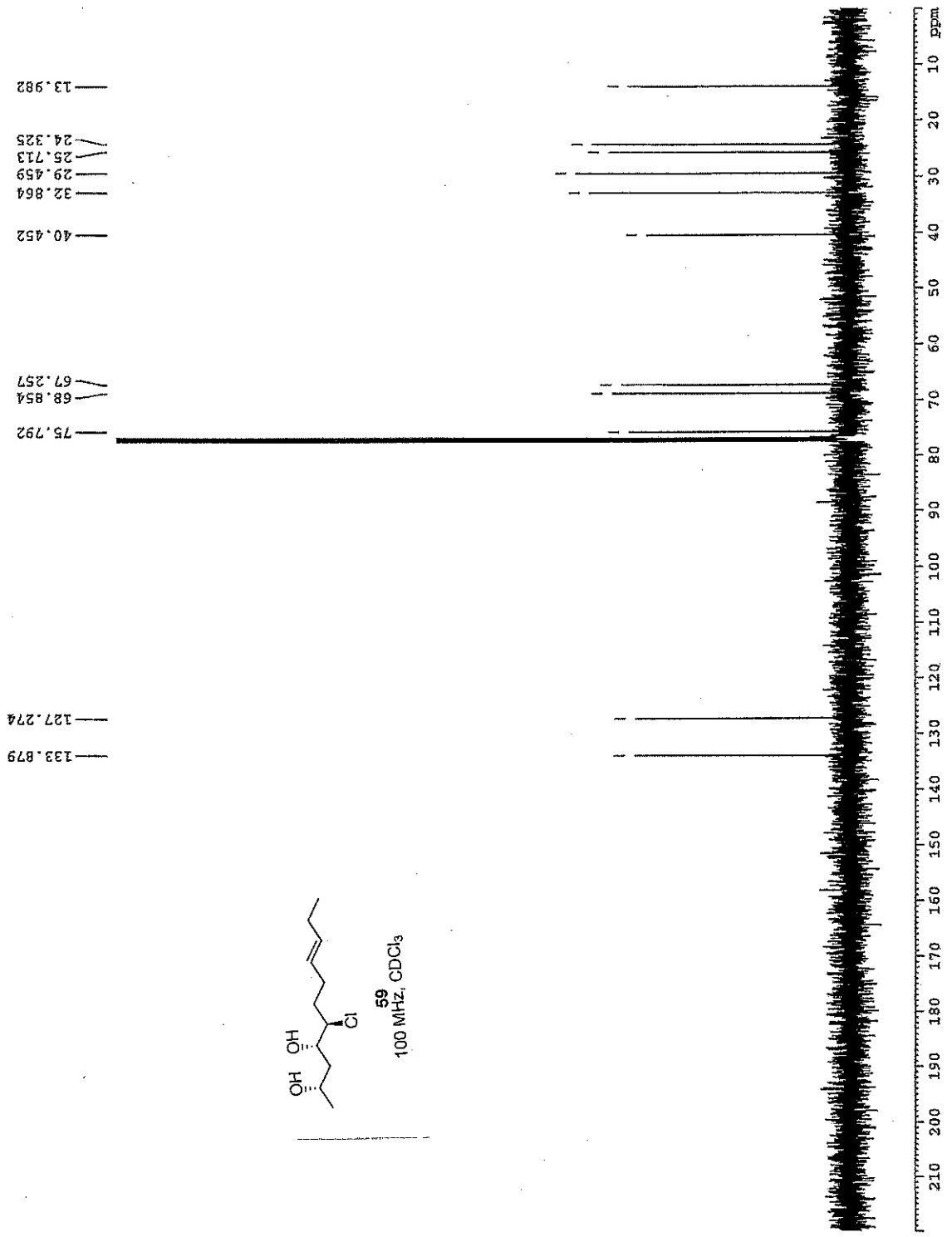
57
400 MHz, $CDCl_3$

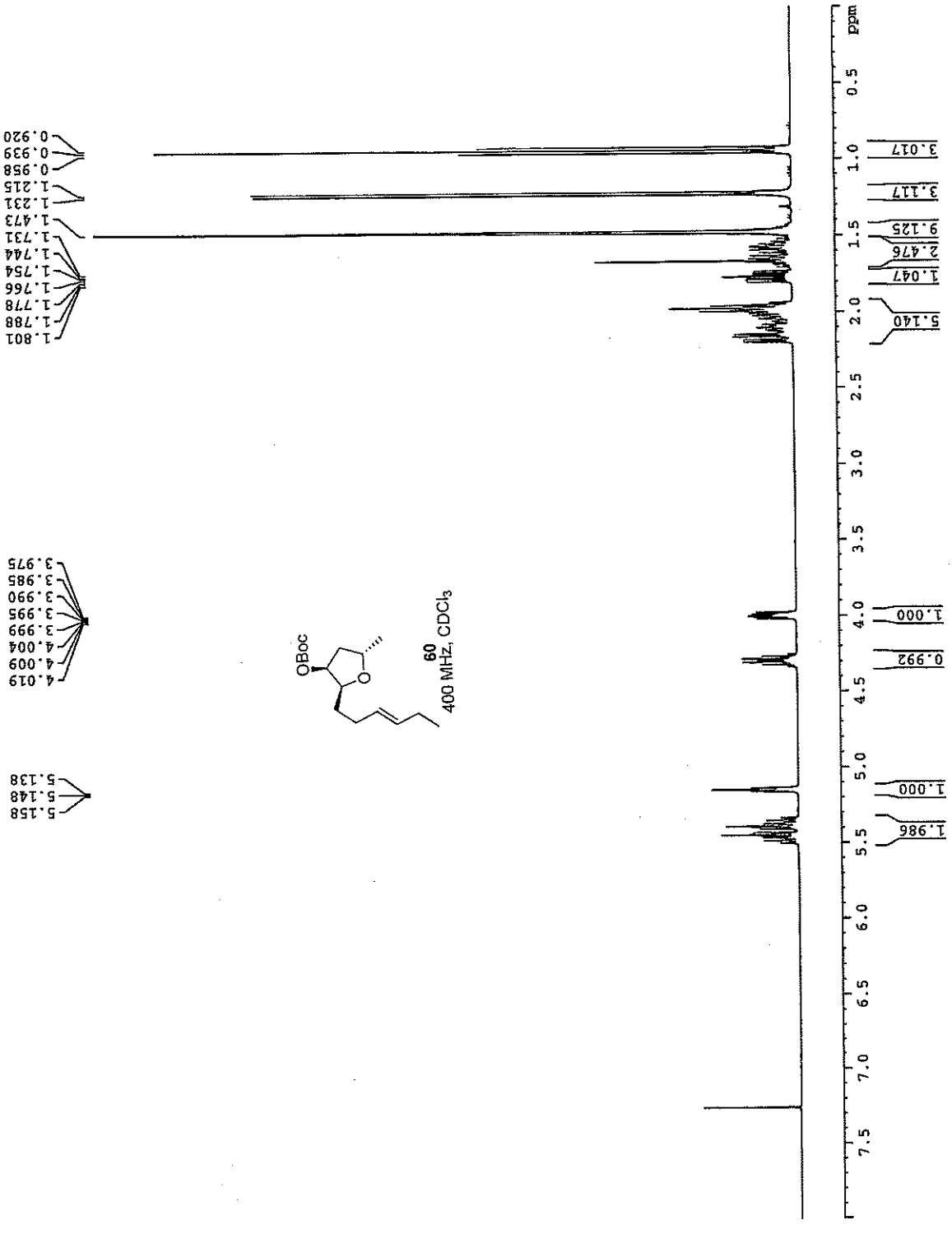

14.187
20.950
24.394
31.129
40.493
66.992
68.921
75.355
124.064
134.956
OH
OH
Cl
57
100 MHz, CDCl3
ppm

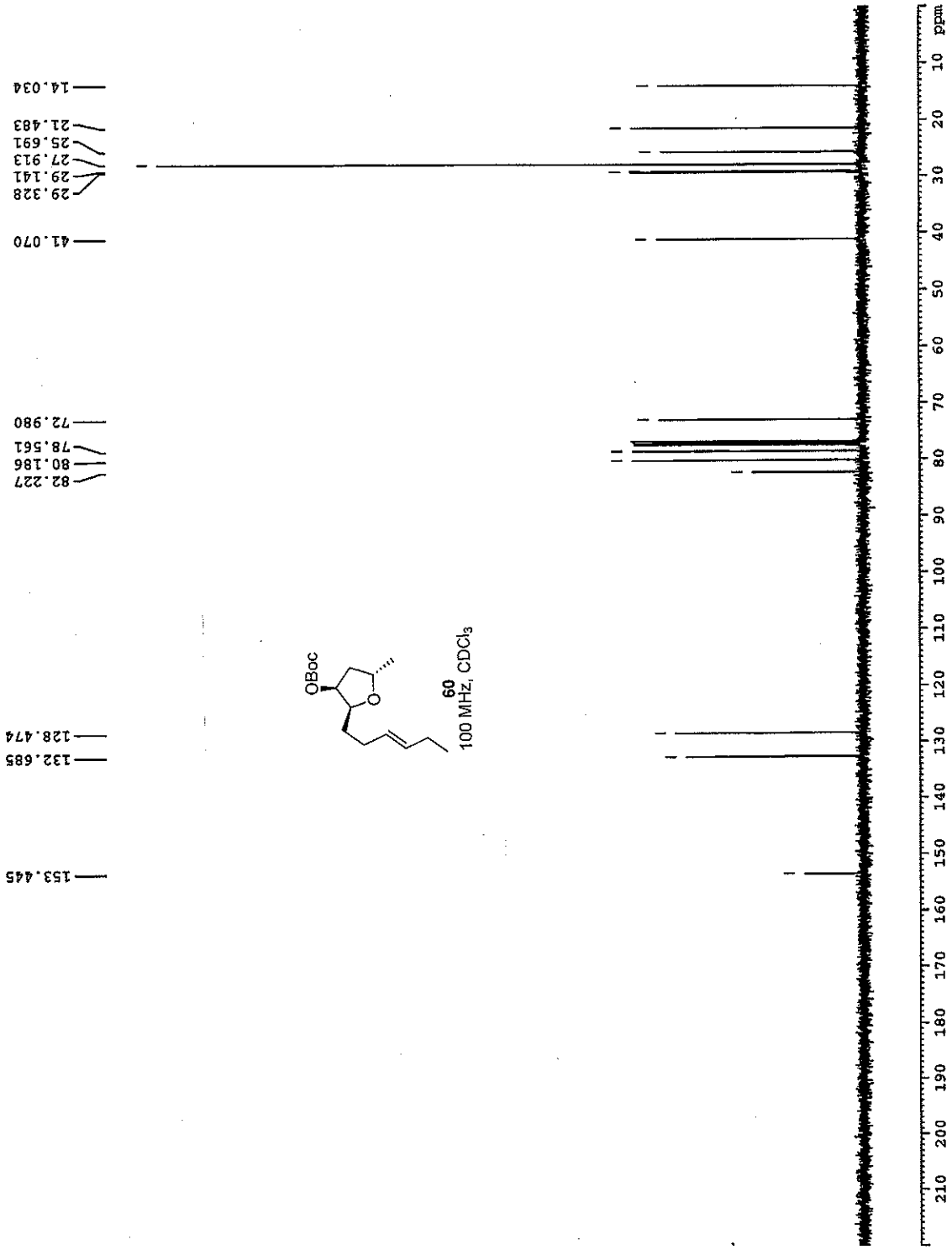

59
400 MHz, CDCl3
OH
OH
Cl
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
3.021
3.196
4.133
2.082
1.031
1.046
2.061
2.092
1.064
1.020
1.000
0.946
0.965
0.983
1.234
1.249
1.968
1.984
1.987
2.003
2.021
2.040
2.056
2.077
2.095
2.113
2.131
2.150
2.856

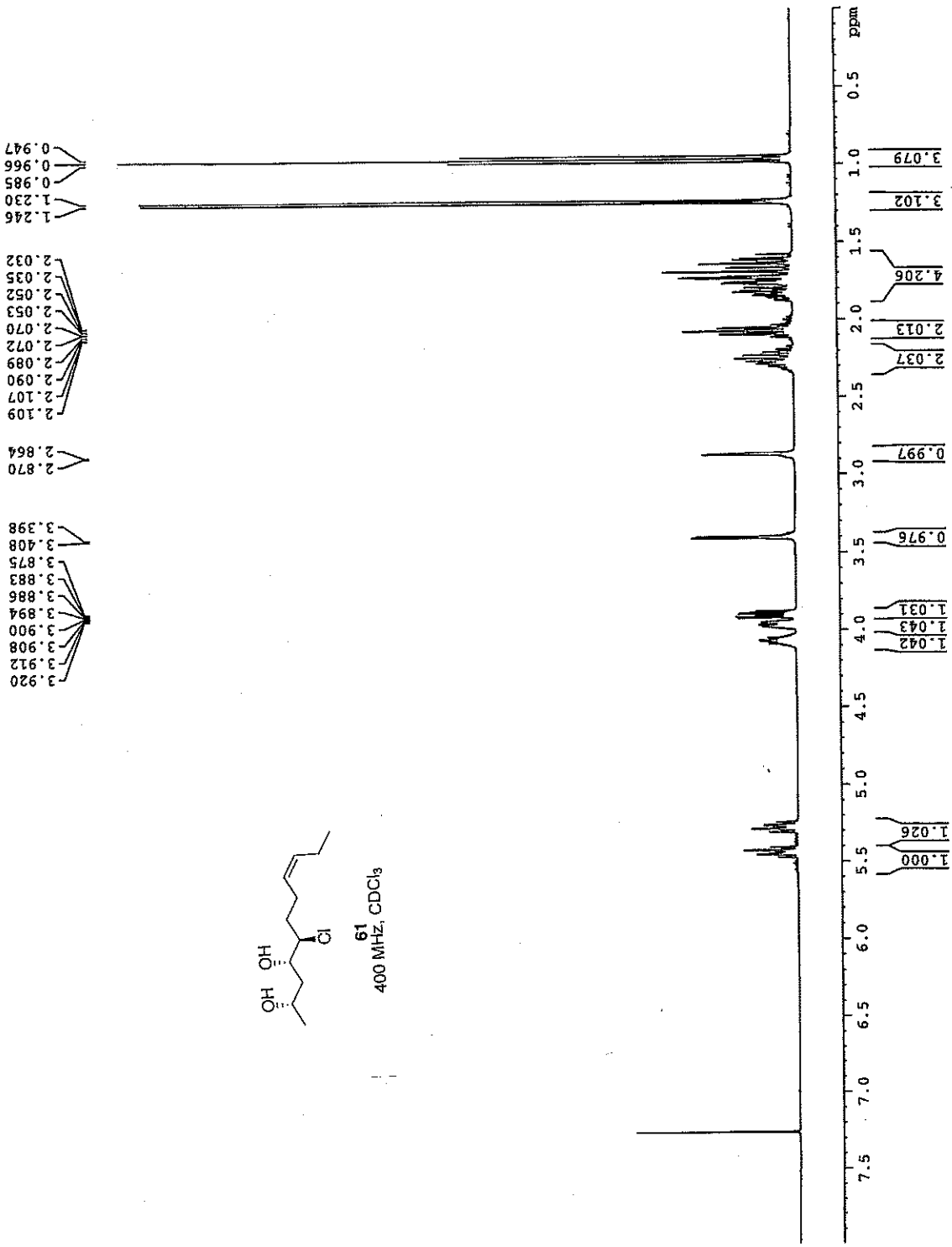

58
400 MHz, CDCl3
ppm
0.926
0.945
0.964
1.228
1.244
1.475
1.737
1.750
1.760
1.772
1.784
1.795
1.808
2.165
2.180
2.200
2.214
4.005
4.015
4.023
4.032
4.041
4.050
5.130
5.140
5.151
3.037
3.144
9.341
1.034
2.023
1.057
2.076
1.005
0.993
1.006
1.005
1.000

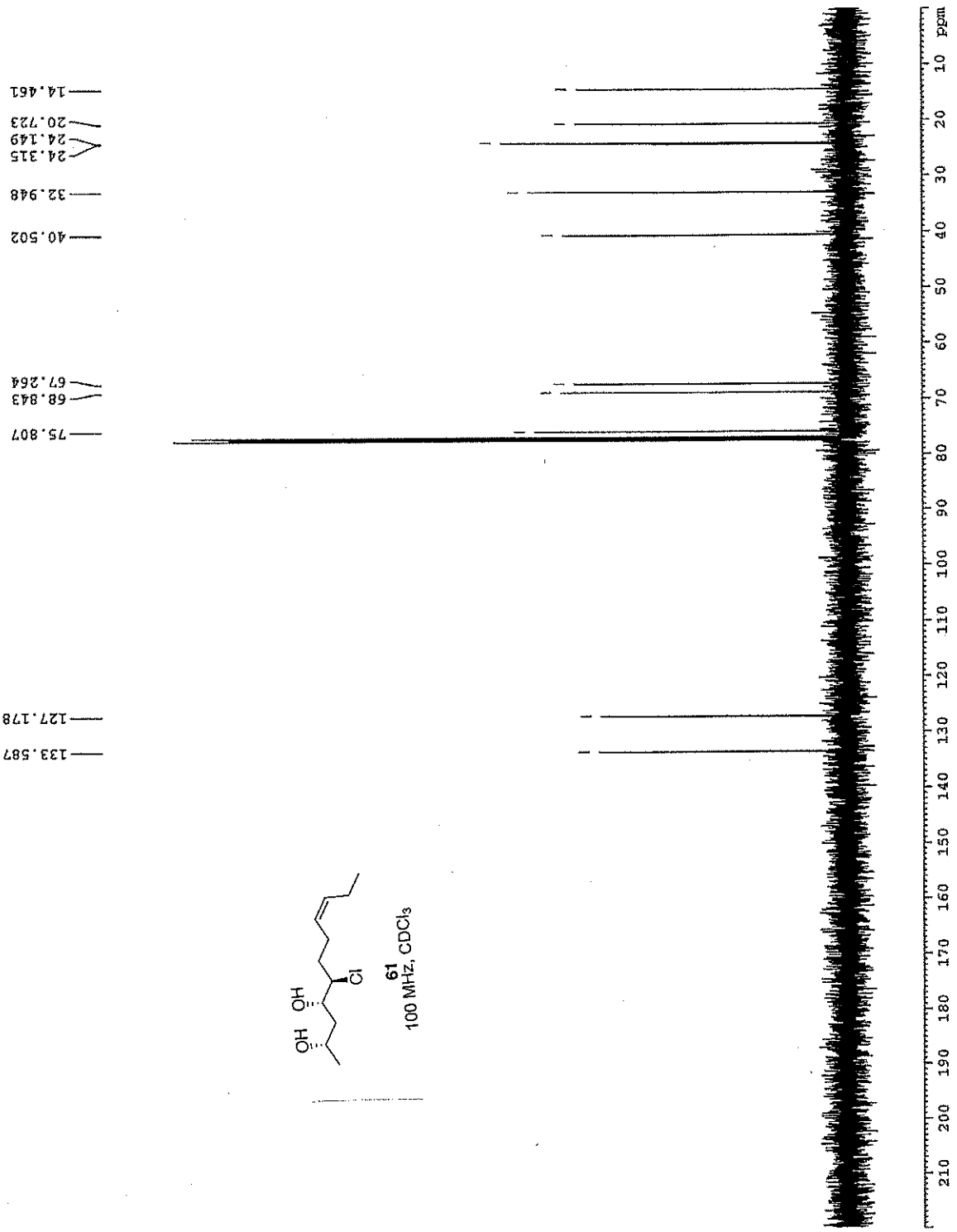

OBoc
58
100 MHz, $CDCl_3$
14.325
20.785
21.461
27.476
27.913
41.068
73.266
78.320
80.607
82.281
124.317
134.148
153.366
ppm

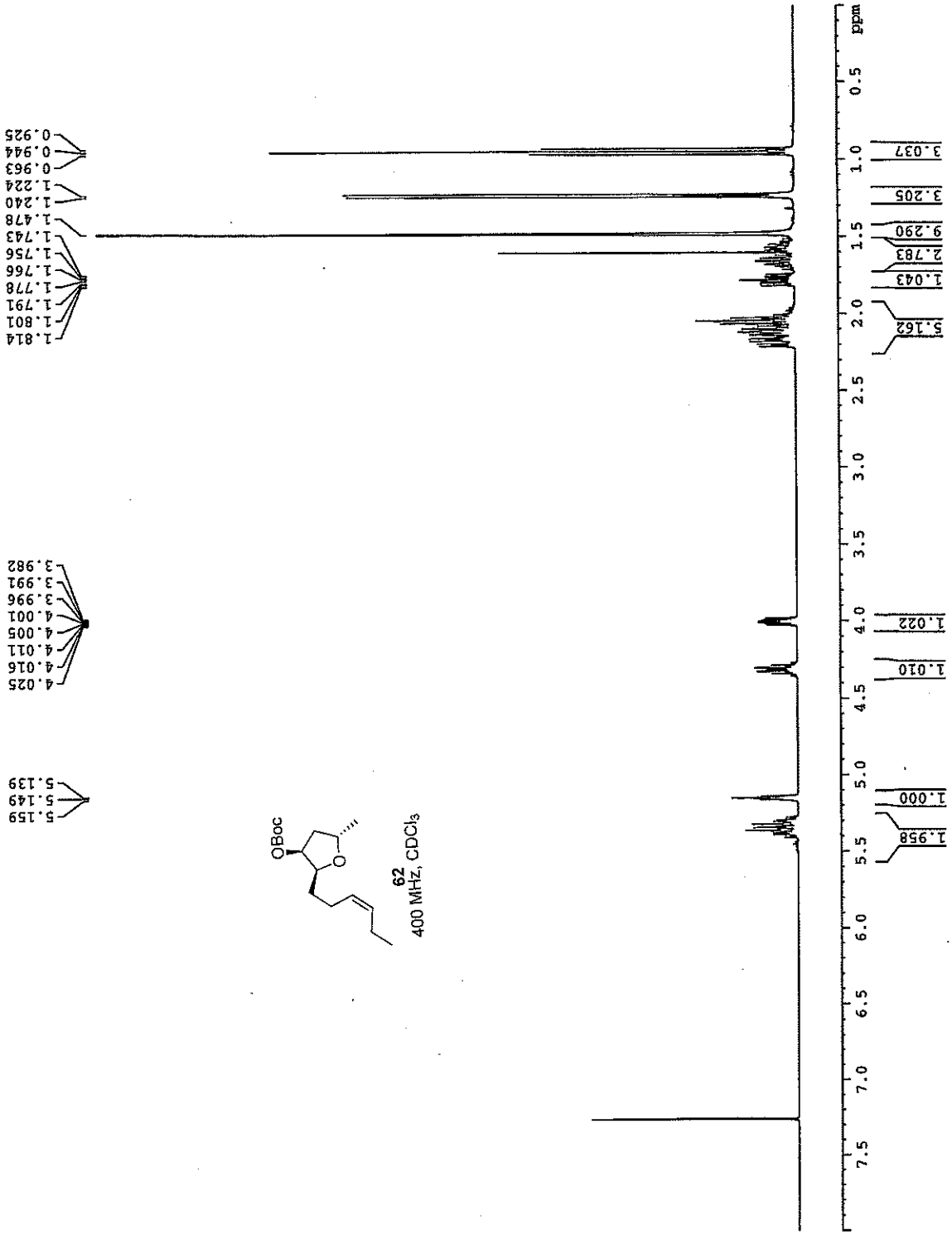

13.982
24.325
25.713
29.459
32.864
40.452
67.257
68.854
75.792
127.274
133.879
OH
OH
Cl
59
100 MHz, CDCl3
ppm

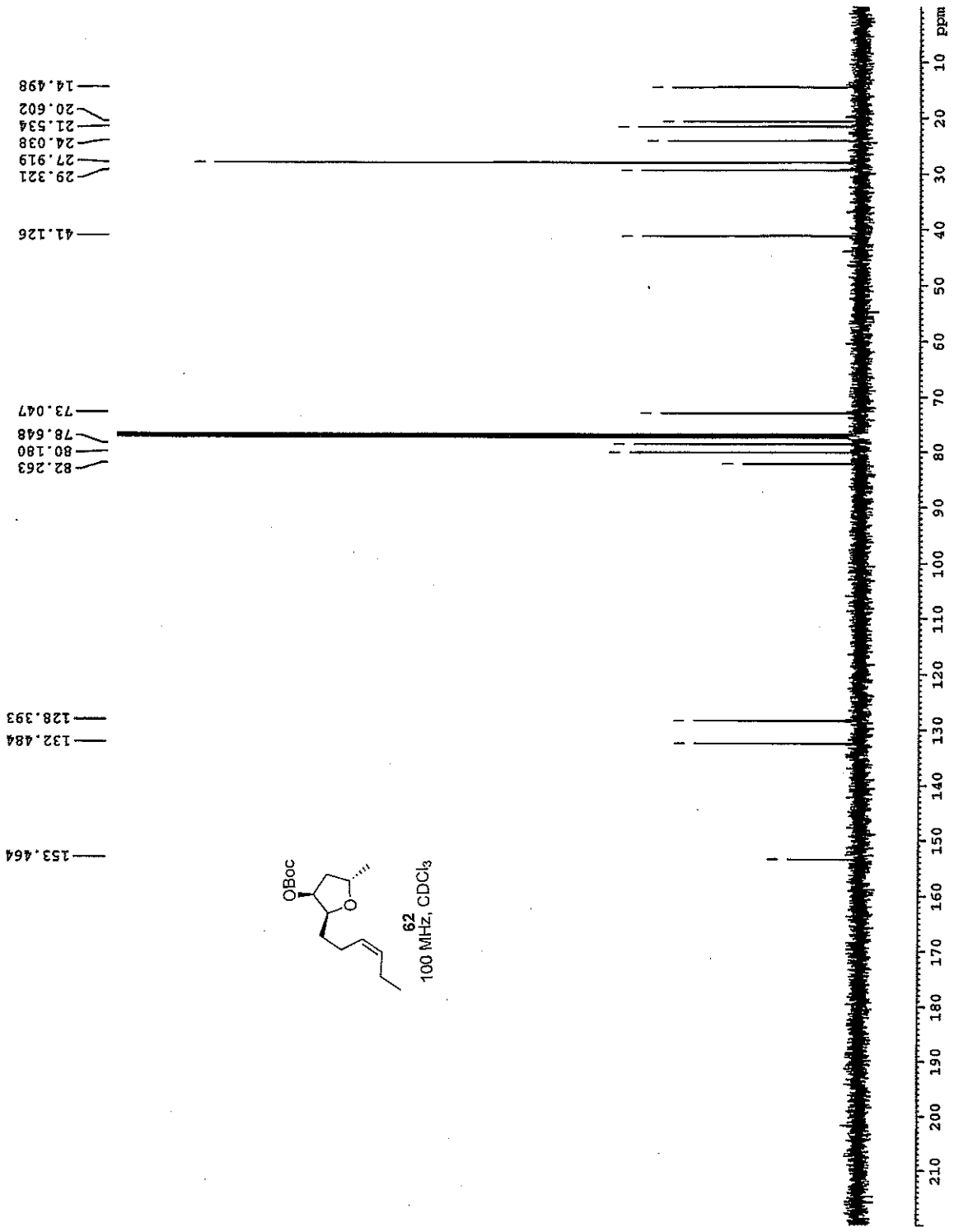

OBoc
60
400 MHz, CDCl3
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
3.017
3.117
9.125
2.476
1.047
5.140
1.000
0.992
1.000
1.986
0.920
0.939
0.958
1.215
1.231
1.473
1.731
1.744
1.754
1.766
1.778
1.788
1.801
3.975
3.985
3.990
3.995
3.999
4.004
4.009
4.019
5.138
5.148
5.158

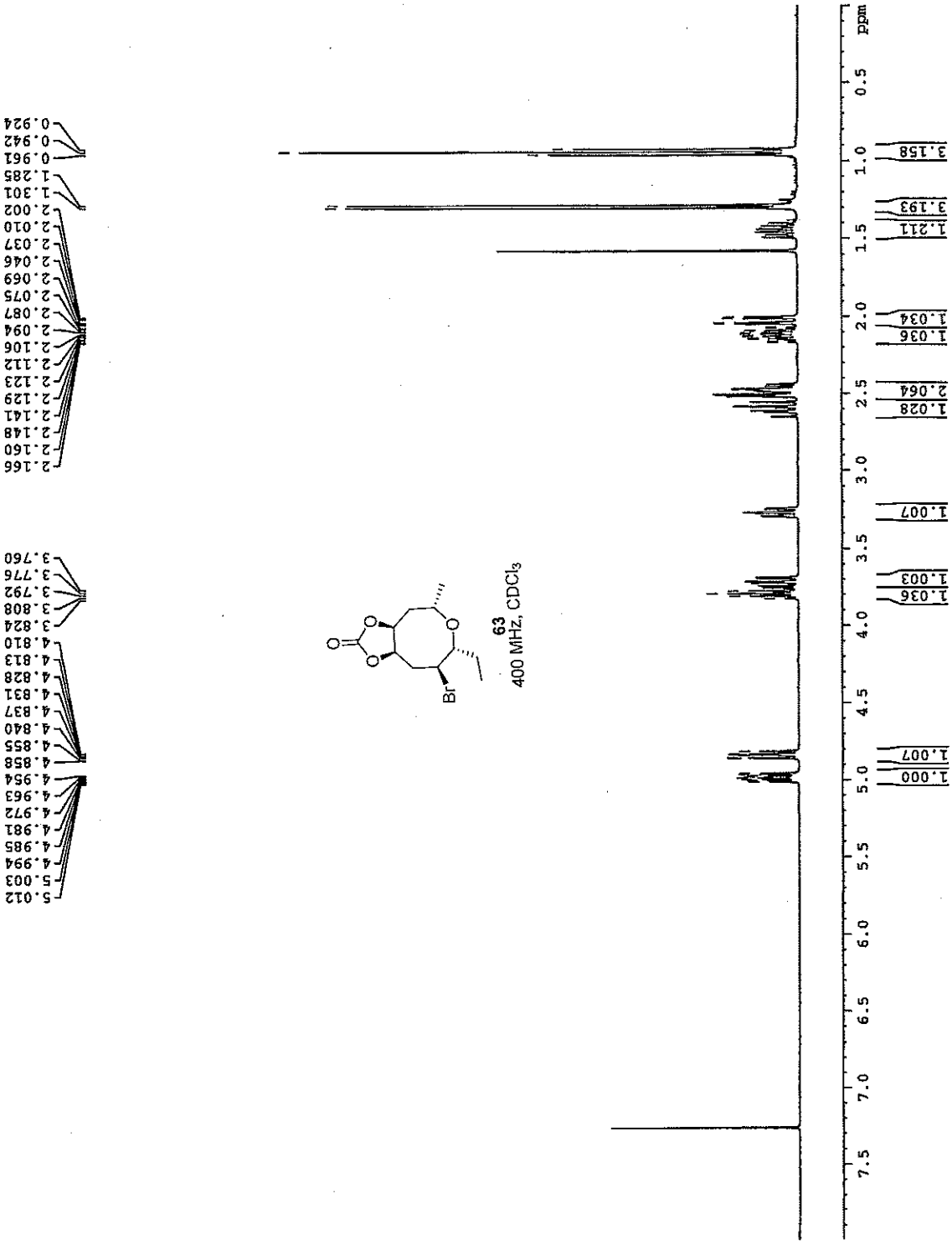

OBoc
60
100 MHz, CDCl3
14.034
21.483
25.691
27.913
29.141
29.328
41.070
72.980
78.561
80.186
82.227
128.474
132.685
153.445
ppm

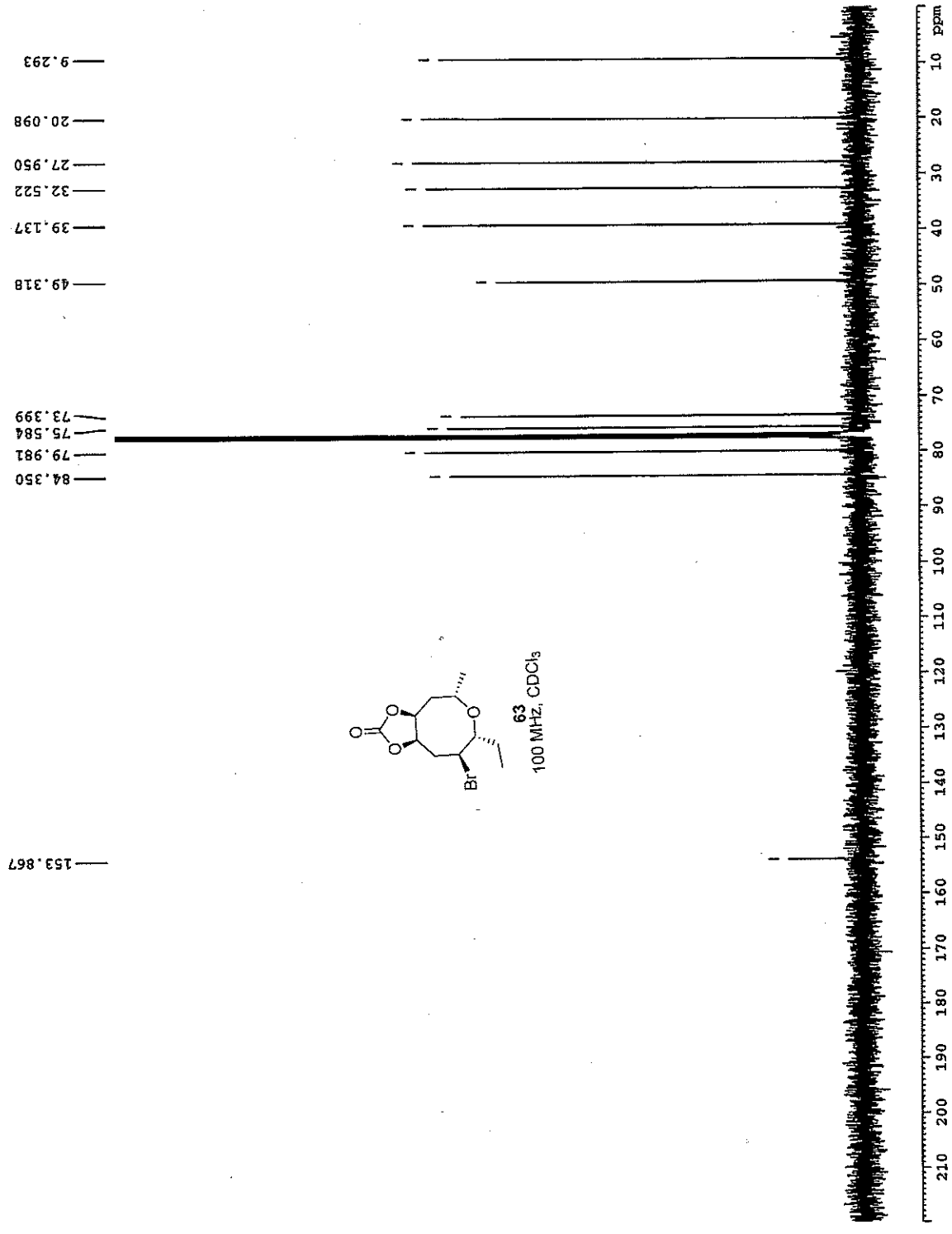

61
400 MHz, $CDCl_3$
OH
OH
Cl
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
3.079
3.102
4.206
2.013
2.037
0.997
0.976
1.031
1.043
1.042
1.026
1.000
0.947
0.966
0.985
1.230
1.246
2.032
2.035
2.052
2.053
2.070
2.072
2.089
2.090
2.107
2.109
2.864
2.870
3.398
3.408
3.875
3.883
3.886
3.894
3.900
3.908
3.912
3.920

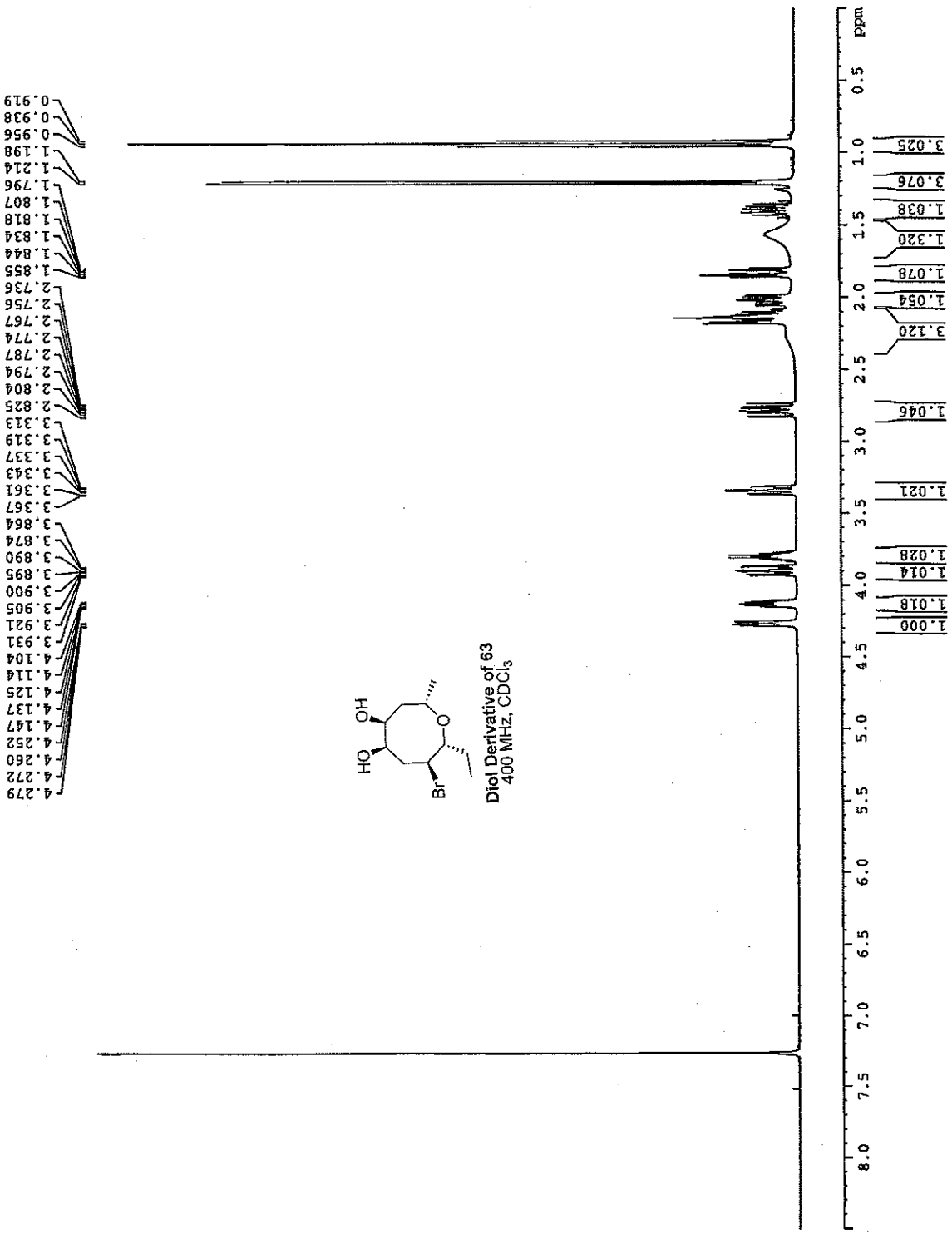

14.461
20.723
24.149
24.315
32.948
40.502
67.264
68.843
75.807
127.178
133.587
OH
OH
Cl
61
100 MHz, CDCl3
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

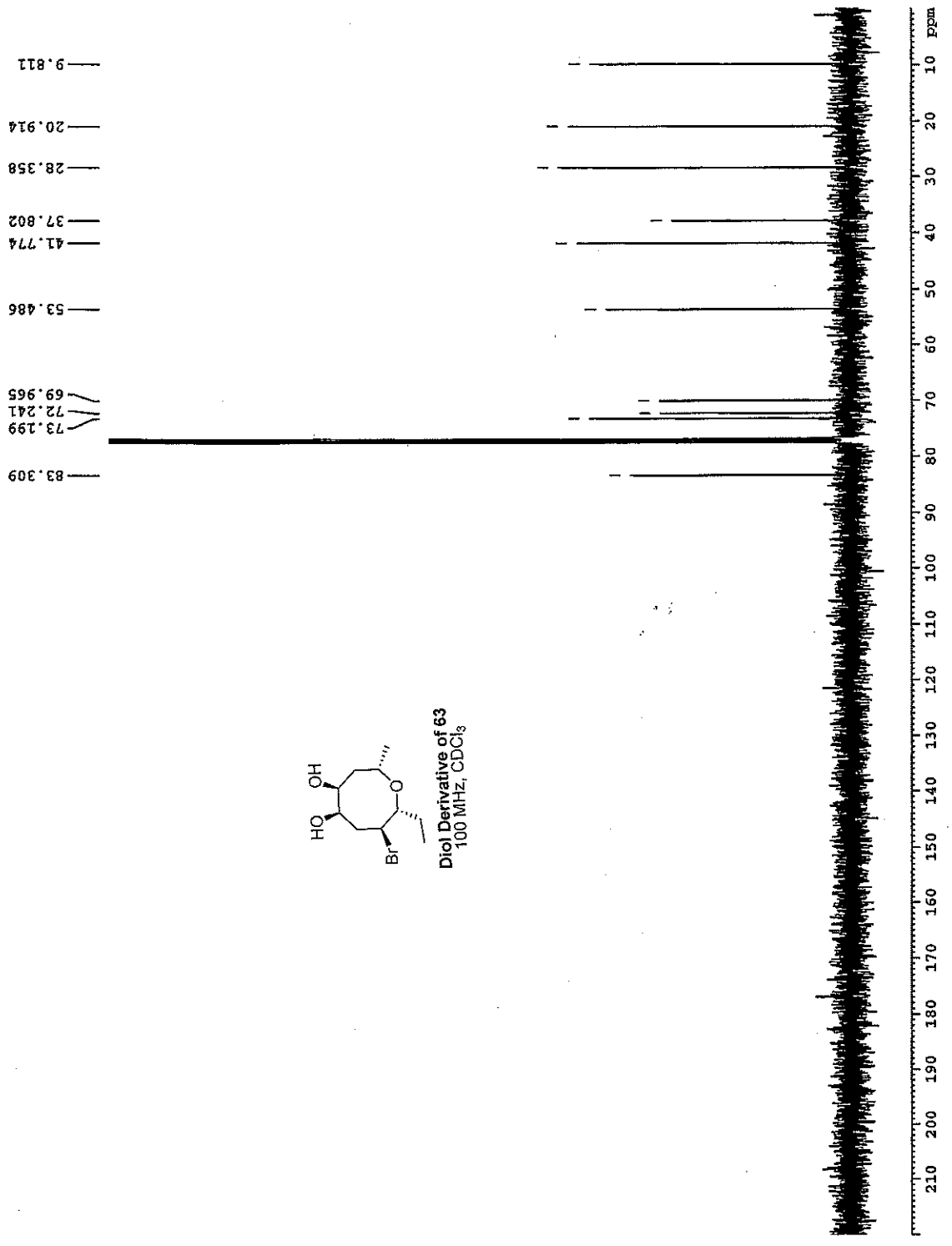

0.925
0.944
0.963
1.224
1.240
1.478
1.743
1.756
1.766
1.778
1.791
1.801
1.814
3.982
3.991
3.996
4.001
4.005
4.011
4.016
4.025
5.139
5.149
5.159
OBoc
O
62
400 MHz, CDCl3
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
3.037
3.205
9.290
2.783
1.043
5.162
1.022
1.010
1.000
1.958


14.498
20.602
21.534
24.038
27.919
29.321
41.126
73.047
78.648
80.180
82.263
128.393
132.484
153.464
OBoc
O
62
100 MHz, CDCl3
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

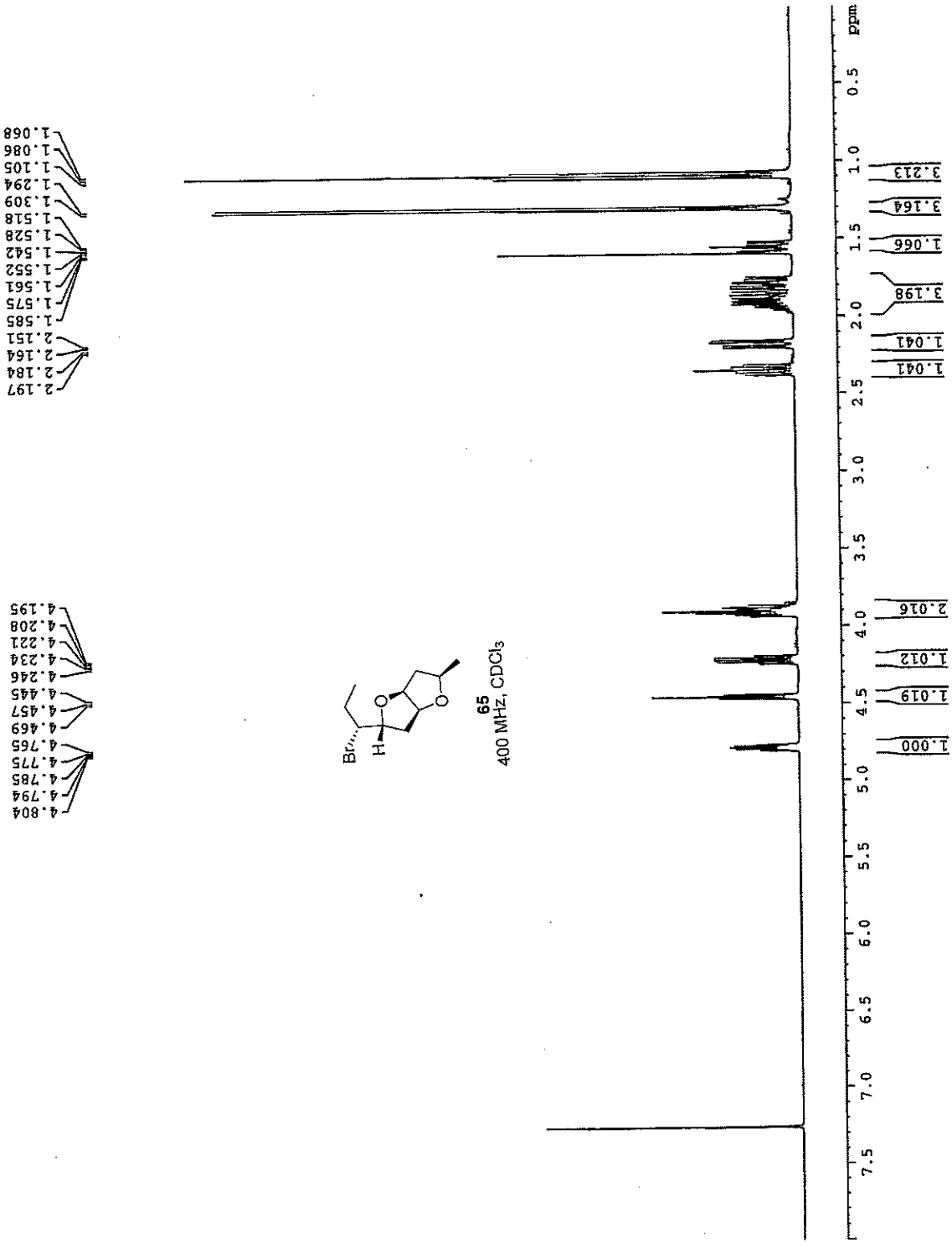

63
400 MHz, CDCl3
Br
ppm
0.924
0.942
0.961
1.285
1.301
2.002
2.010
2.037
2.046
2.069
2.075
2.087
2.094
2.106
2.112
2.123
2.129
2.141
2.148
2.160
2.166
3.760
3.776
3.792
3.808
3.824
4.810
4.813
4.828
4.831
4.837
4.840
4.855
4.858
4.954
4.963
4.972
4.981
4.985
4.994
5.003
5.012
3.158
3.193
1.211
1.034
1.036
1.028
2.064
1.007
1.003
1.036
1.007
1.000

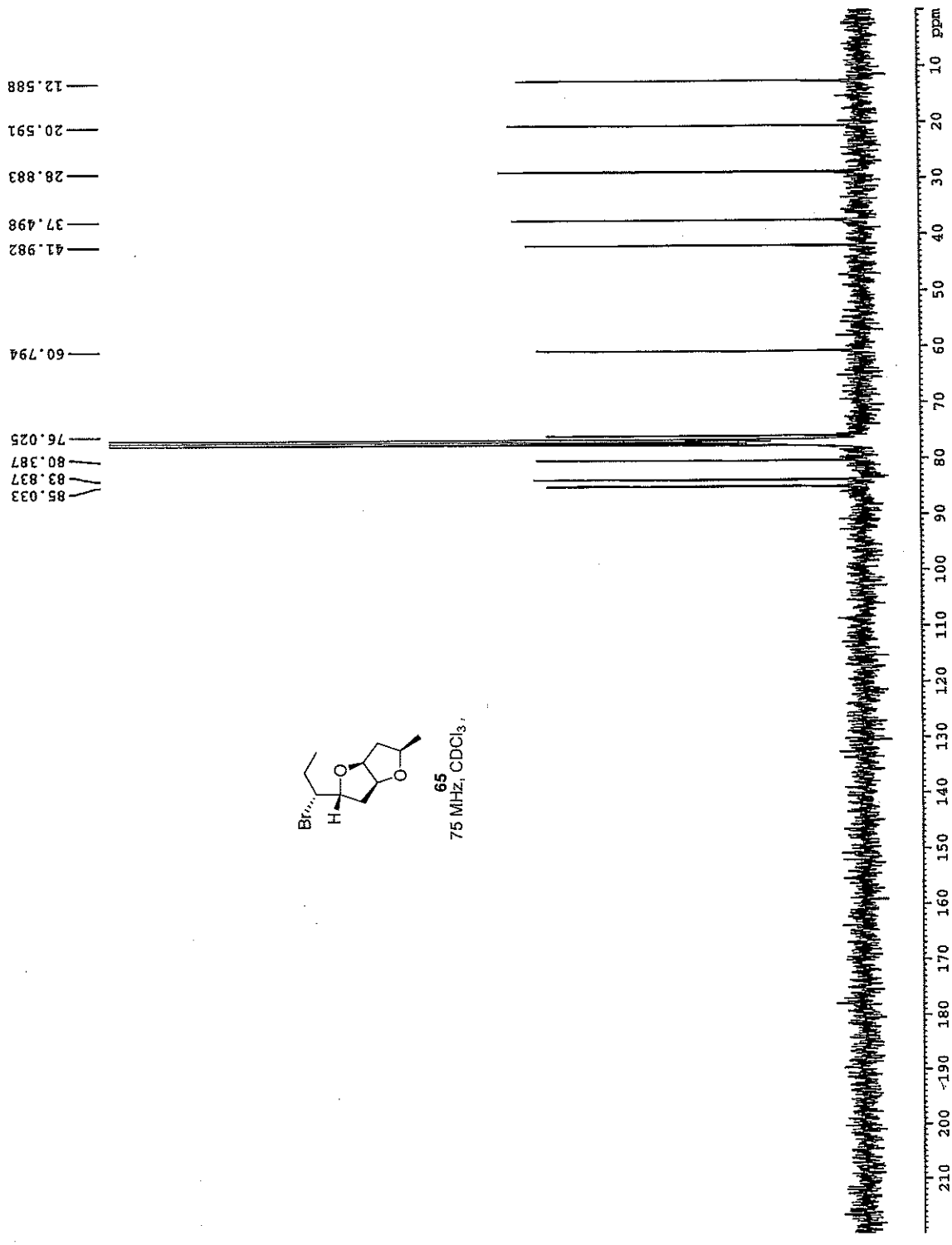

9.293
20.098
27.950
32.522
39.137
49.318
73.399
75.584
79.981
84.350
153.867
Br
63
100 MHz, CDCl3
ppm

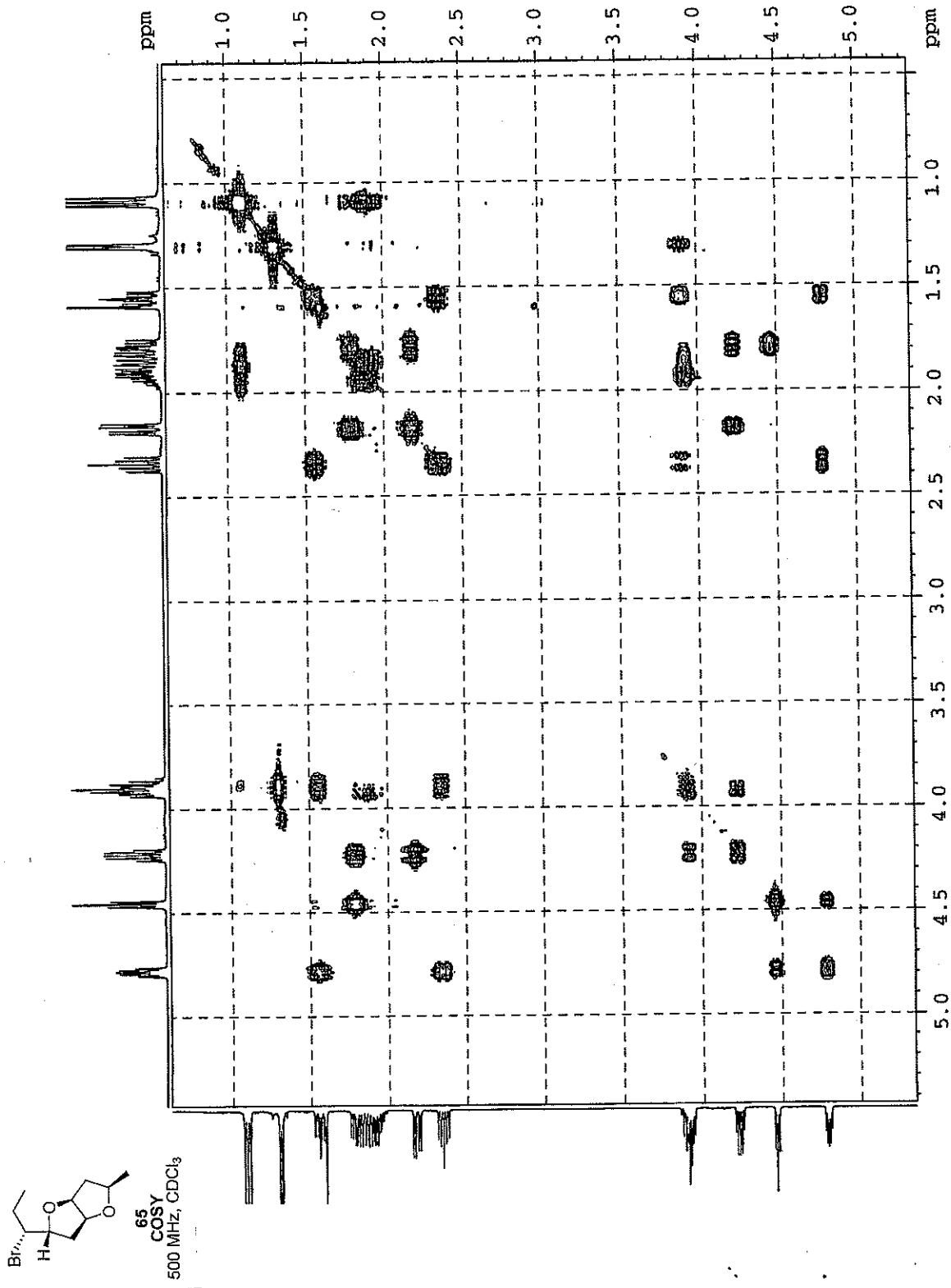

Diol Derivative of 63
400 MHz, CDCl3
OH
HO
O
Br
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
3.025
3.076
1.038
1.320
1.078
1.054
3.120
1.046
1.021
1.028
1.014
1.018
1.000
0.919
0.938
0.956
1.198
1.214
1.796
1.807
1.818
1.834
1.844
1.855
2.736
2.756
2.767
2.774
2.787
2.794
2.804
2.825
3.313
3.319
3.337
3.343
3.361
3.367
3.864
3.874
3.890
3.895
3.900
3.905
3.921
3.931
4.104
4.114
4.125
4.137
4.147
4.252
4.260
4.272
4.279



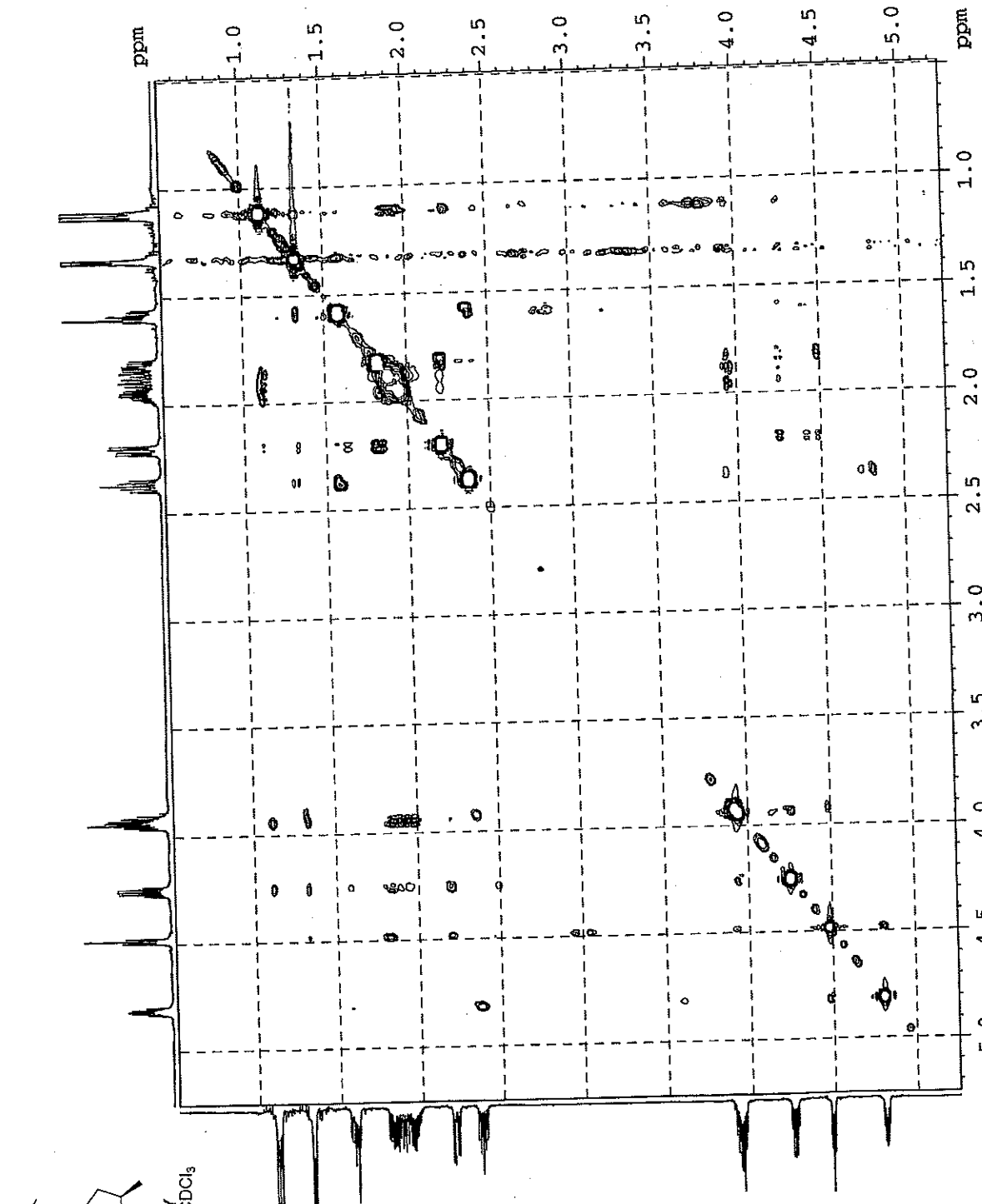
Diol Derivative of 63
100 MHz, $CDCl_3$


65
400 MHz, CDCl3
Br
H
O
O
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
3.213
3.164
1.066
3.198
1.041
1.041
2.016
1.012
1.019
1.000
1.068
1.086
1.105
1.294
1.309
1.518
1.528
1.542
1.552
1.561
1.575
1.585
2.151
2.164
2.184
2.197
4.195
4.208
4.221
4.234
4.246
4.445
4.457
4.469
4.765
4.775
4.785
4.794
4.804

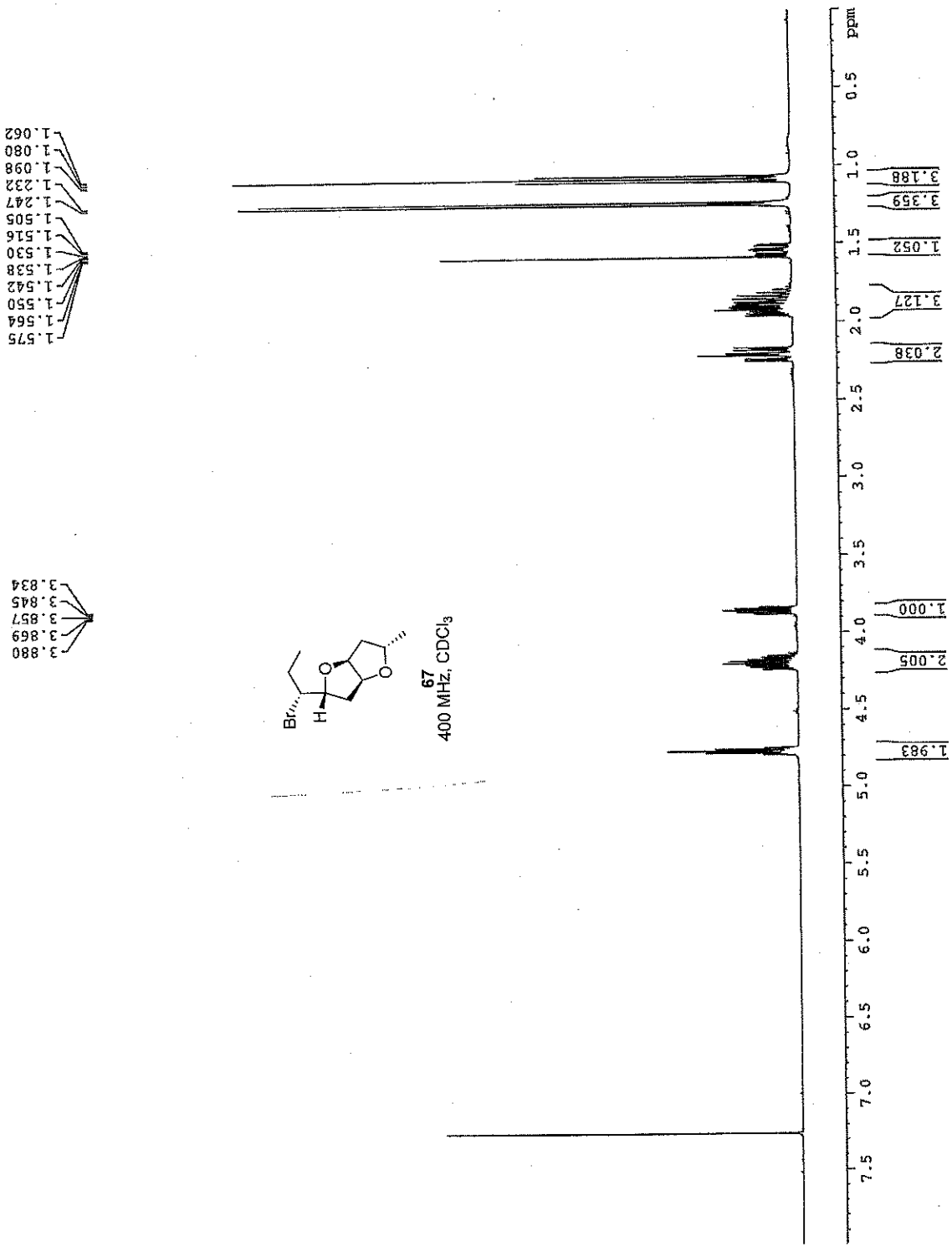

12.588
20.591
28.883
37.498
41.982
60.794
76.025
80.387
83.837
85.033
Br
H
O
O
65
75 MHz, CDCl3
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

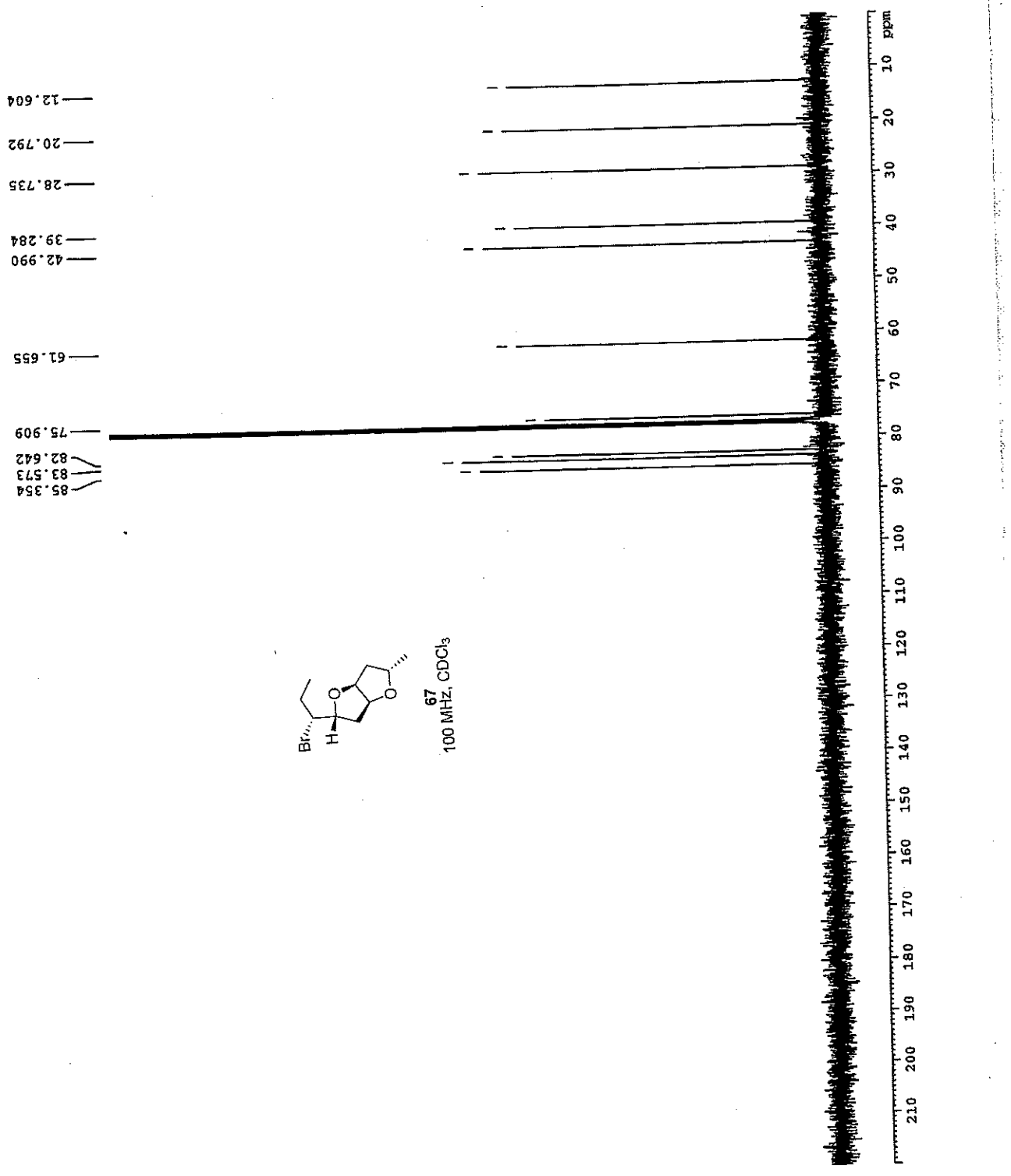


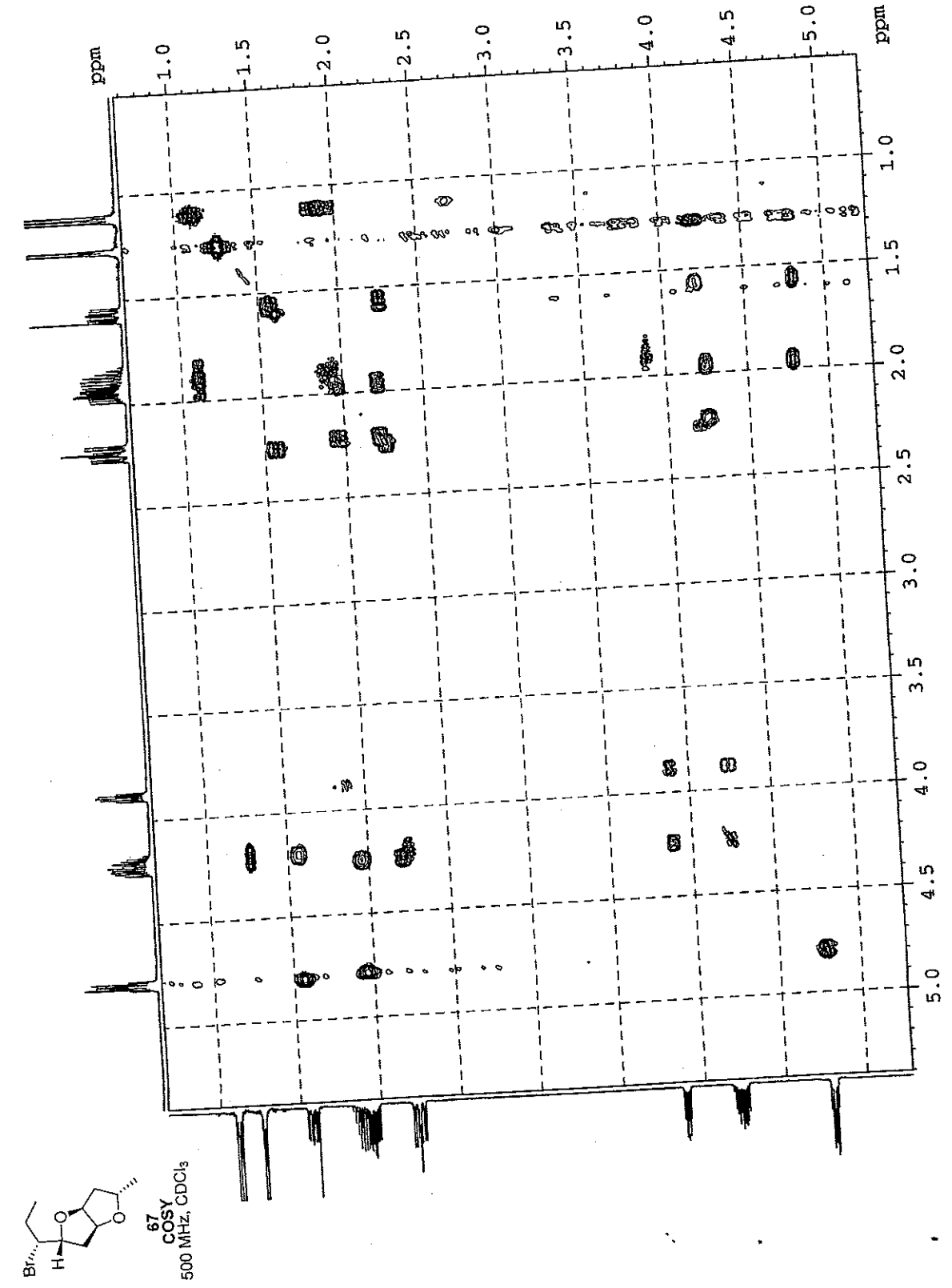
65
COSY
500 MHz, $CDCl_3$



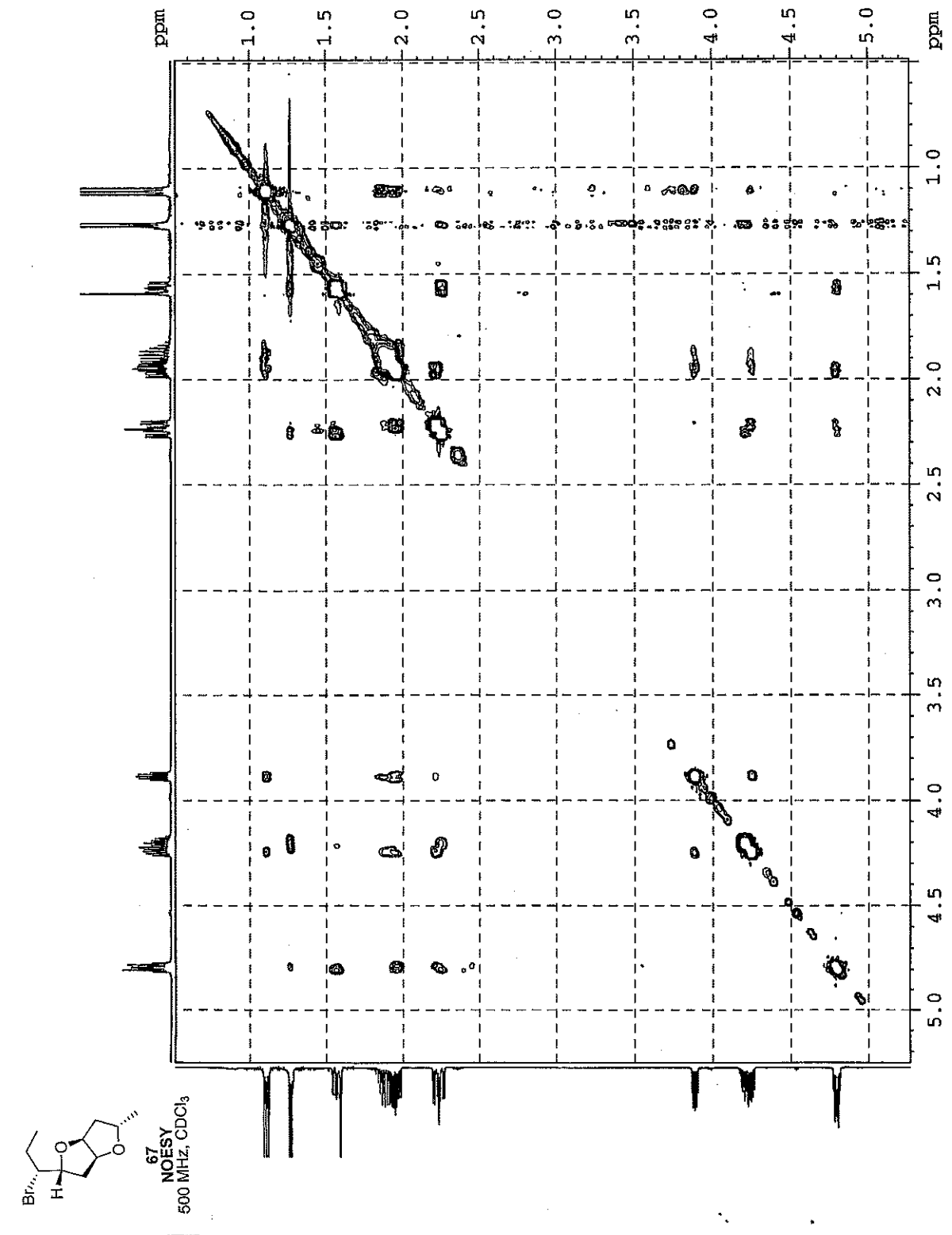
65
NOESY
500 MHz, $CDCl_3$

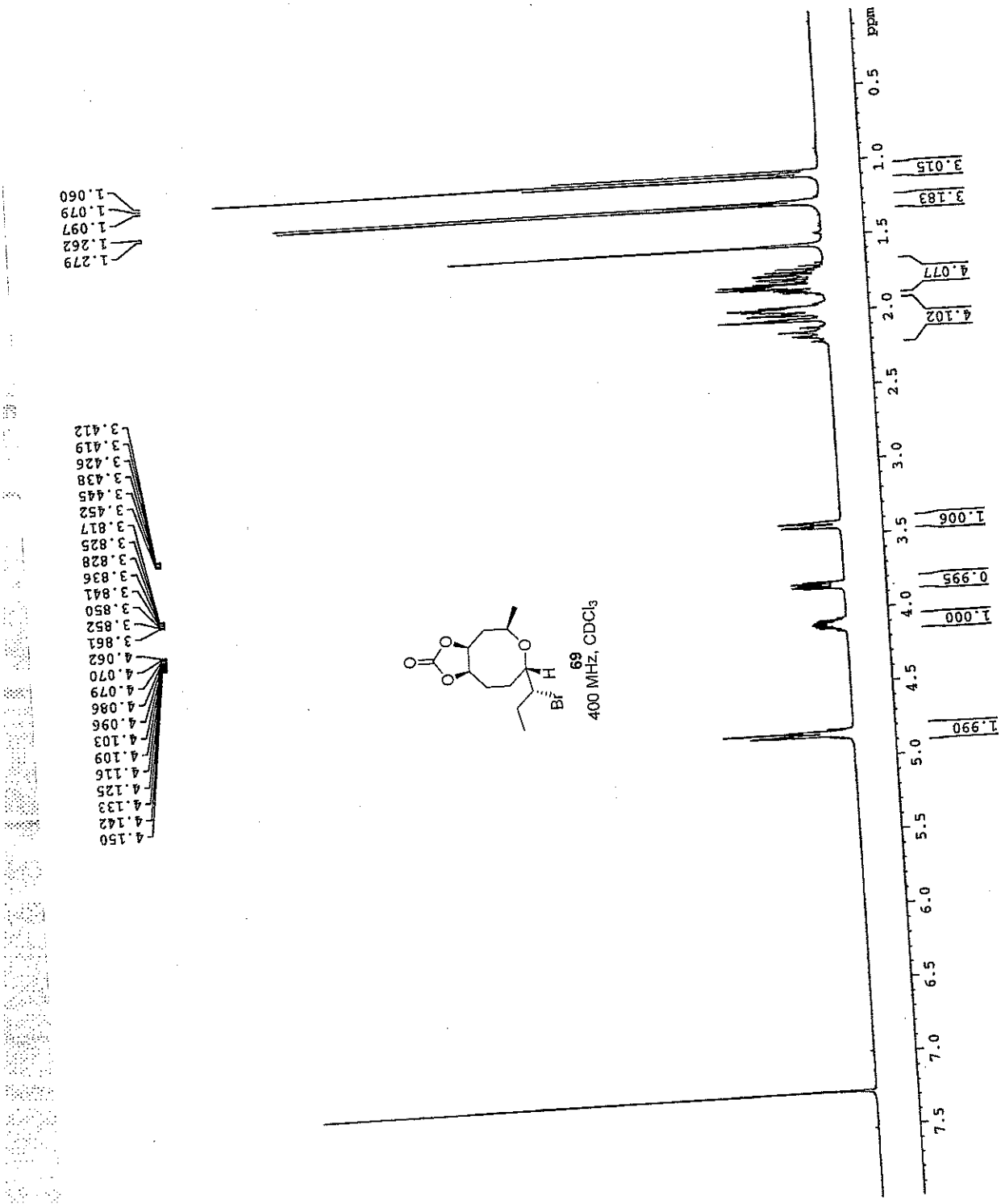

67
400 MHz, CDCl3
Br
H
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
3.188
3.359
1.052
3.127
2.038
1.000
2.005
1.983
1.062
1.080
1.098
1.232
1.247
1.505
1.516
1.530
1.538
1.542
1.550
1.564
1.575
3.834
3.845
3.857
3.869
3.880

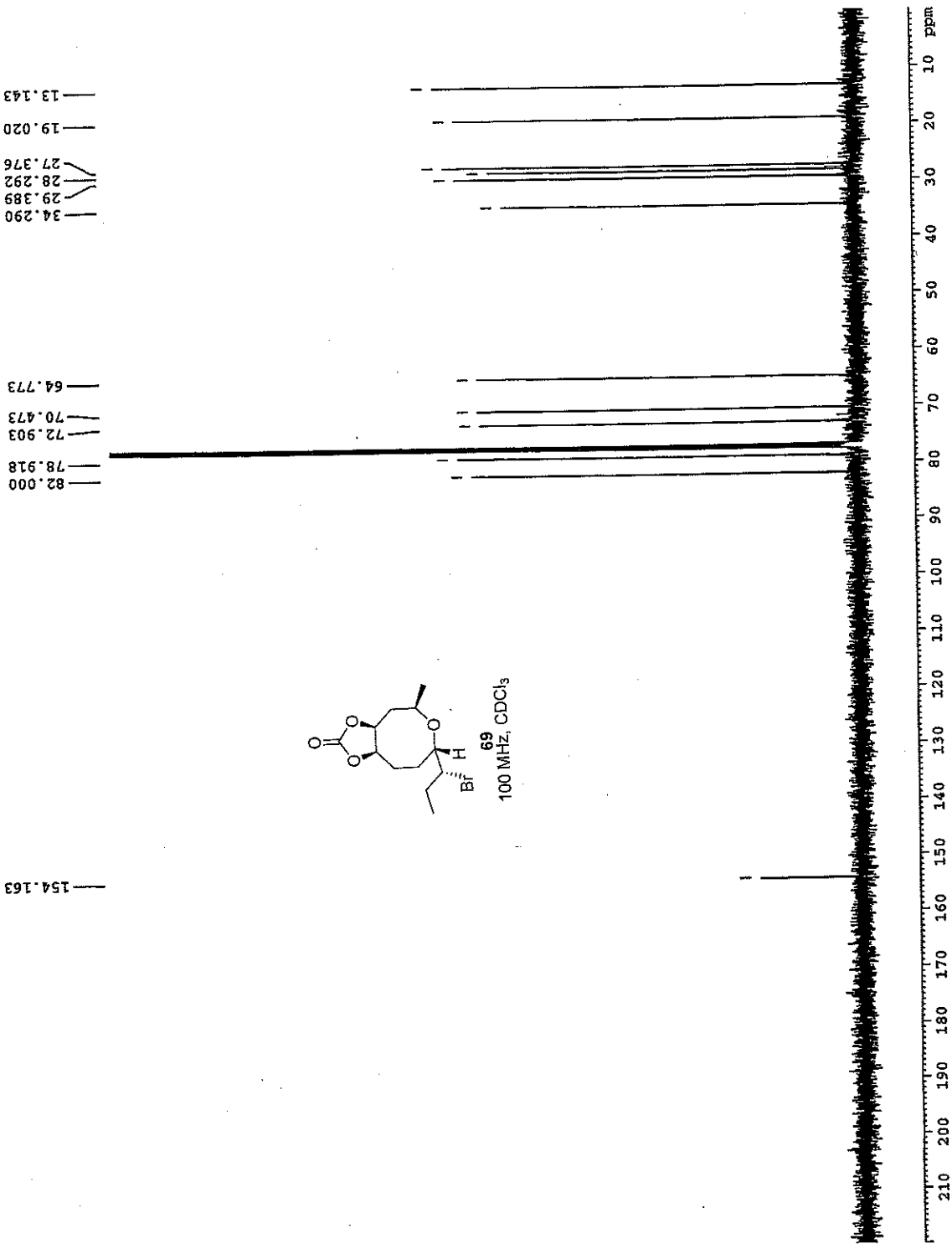

12.604
20.792
28.735
39.284
42.990
61.655
75.909
82.642
83.573
85.354
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
Br
H
O
O
67
100 MHz, CDCl3

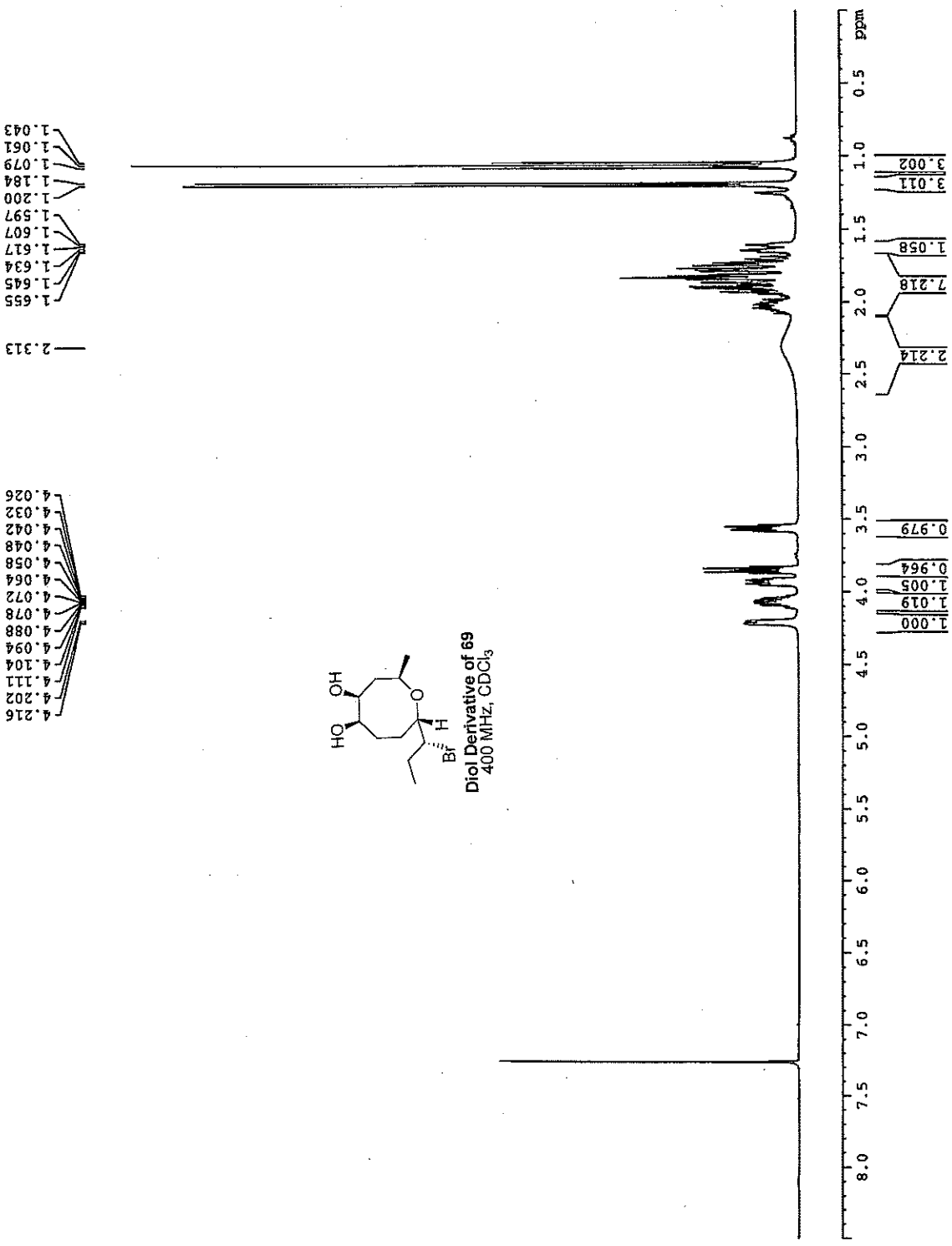


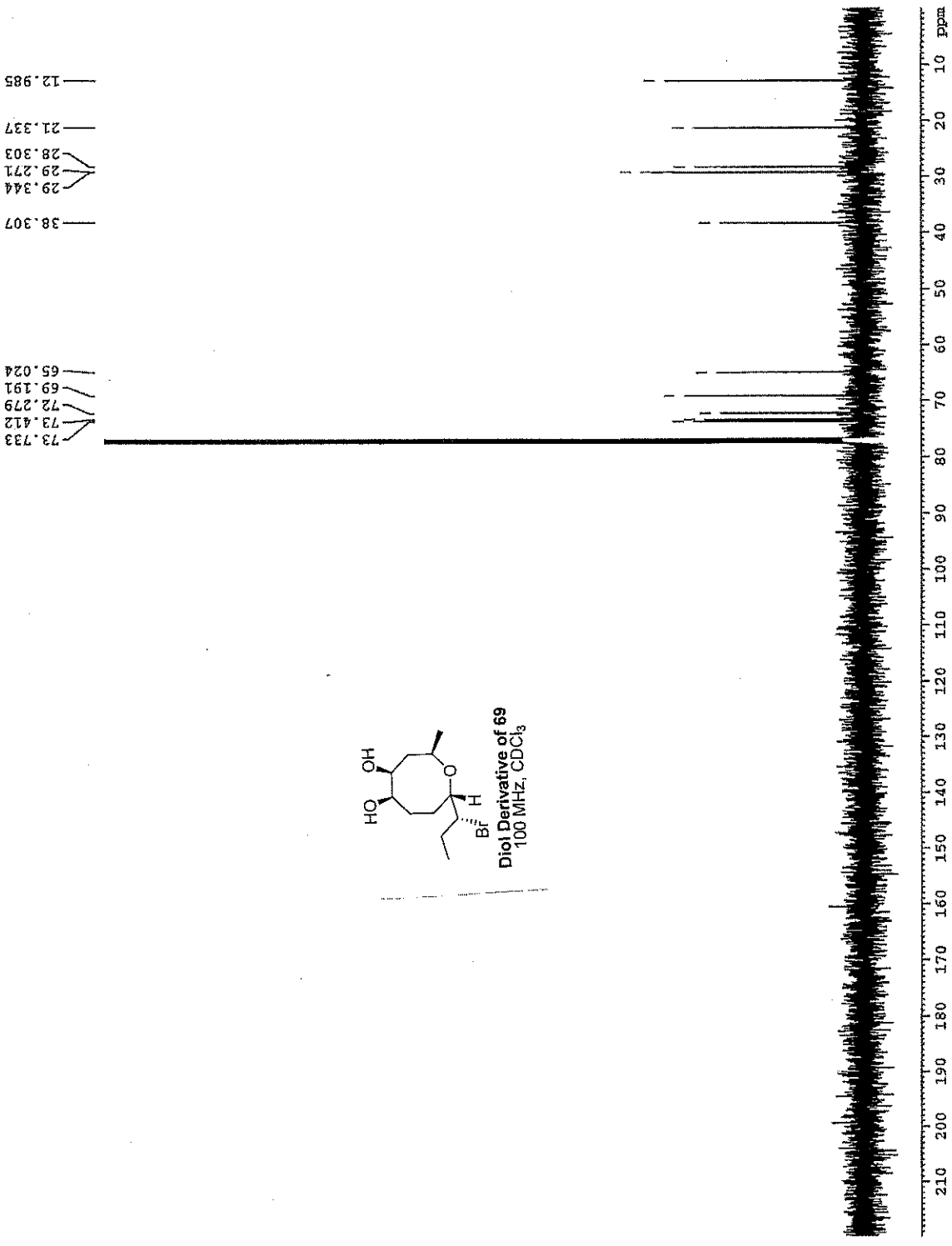
67
COSY
500 MHz, $CDCl_3$

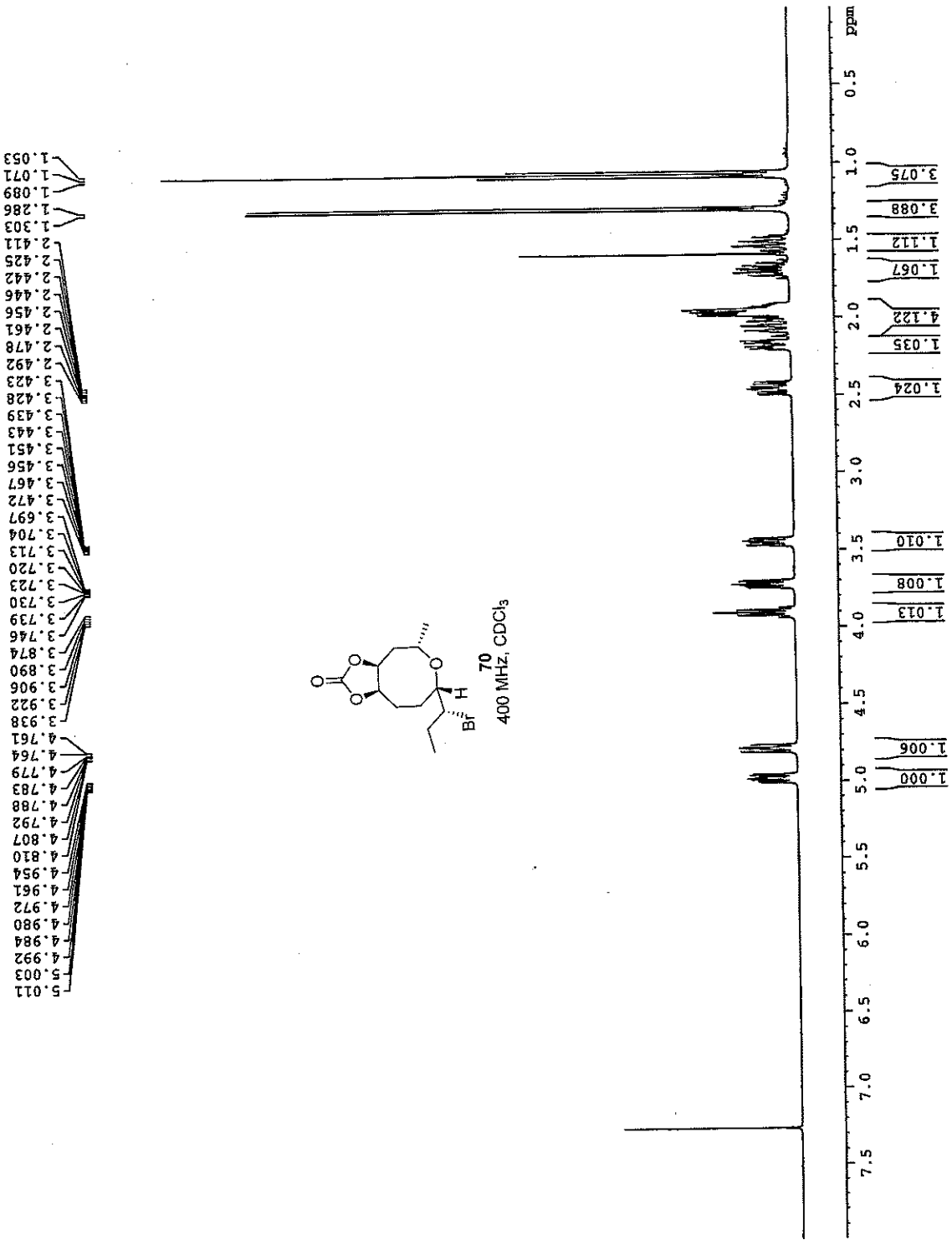

ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
ppm
Br
H
O
O
67
NOESY
500 MHz, CDCl3

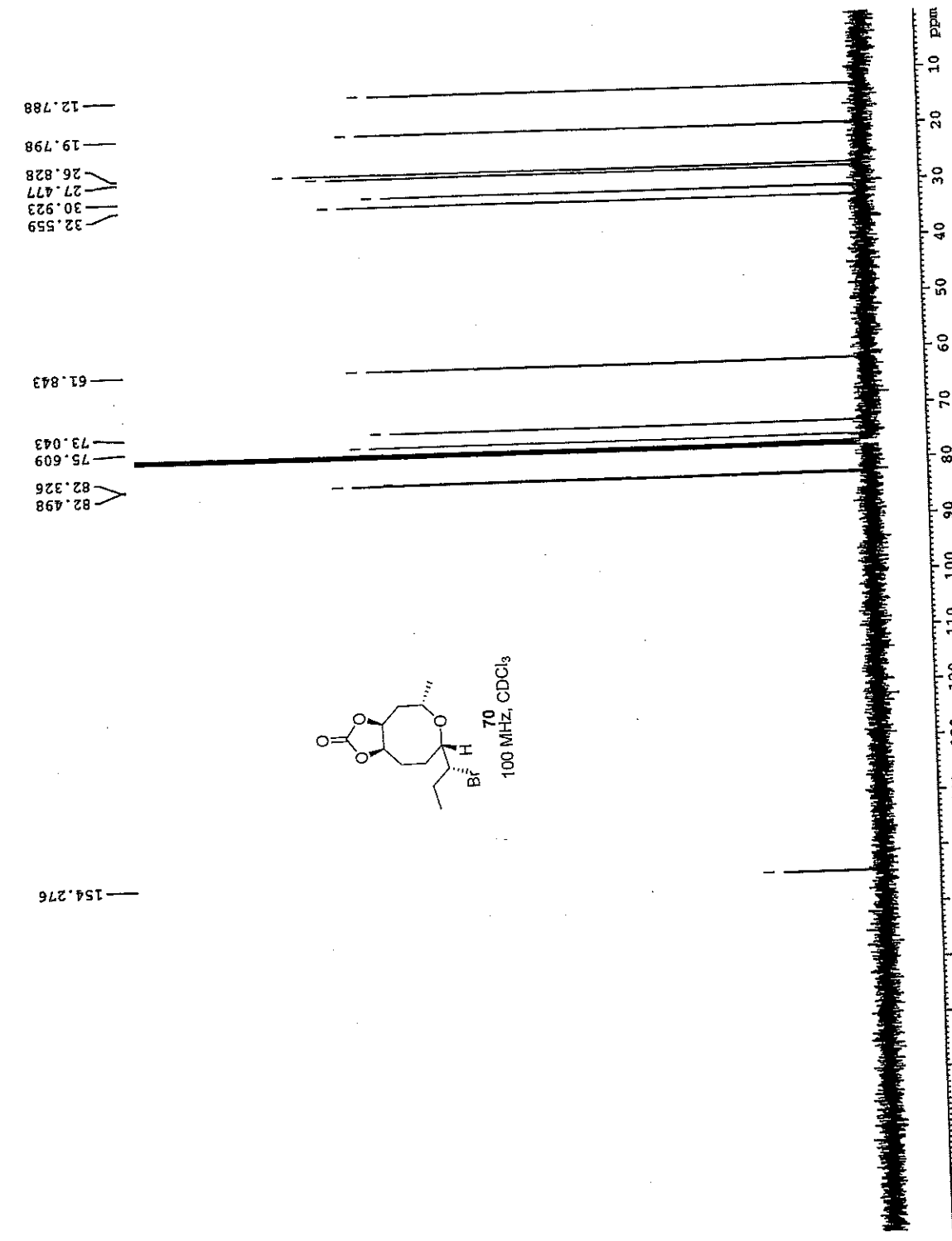

69
400 MHz, CDCl3
Br
H
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
3.015
3.183
4.077
4.102
1.006
0.995
1.000
1.990
1.060
1.079
1.097
1.262
1.279
3.412
3.419
3.426
3.438
3.445
3.452
3.817
3.825
3.828
3.836
3.841
3.850
3.852
3.861
4.062
4.070
4.079
4.086
4.096
4.103
4.109
4.116
4.125
4.133
4.142
4.150

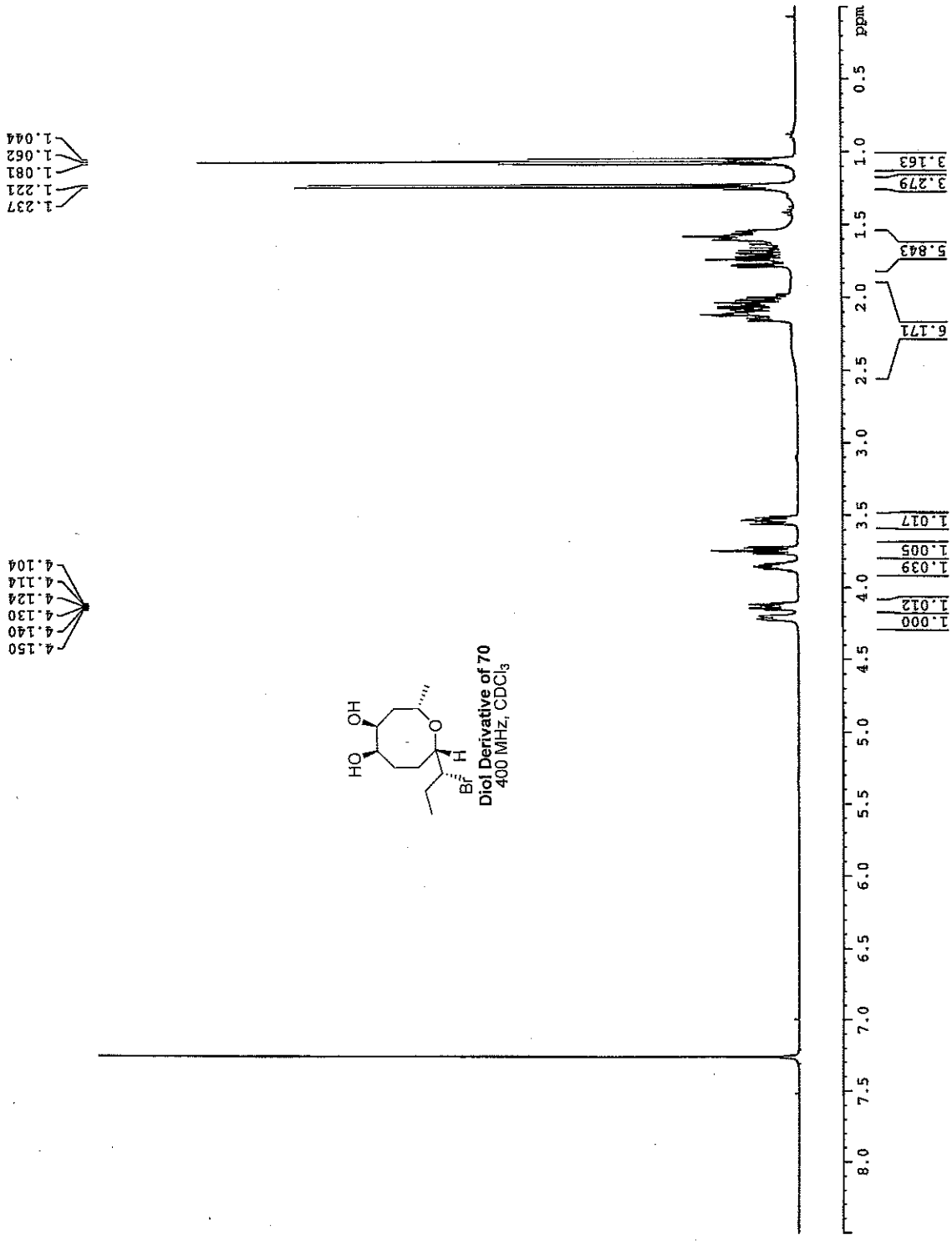

13.143
19.020
27.376
28.292
29.389
34.290
64.773
70.473
72.903
78.918
82.000
154.163
Br
H
69
100 MHz, CDCl3
ppm

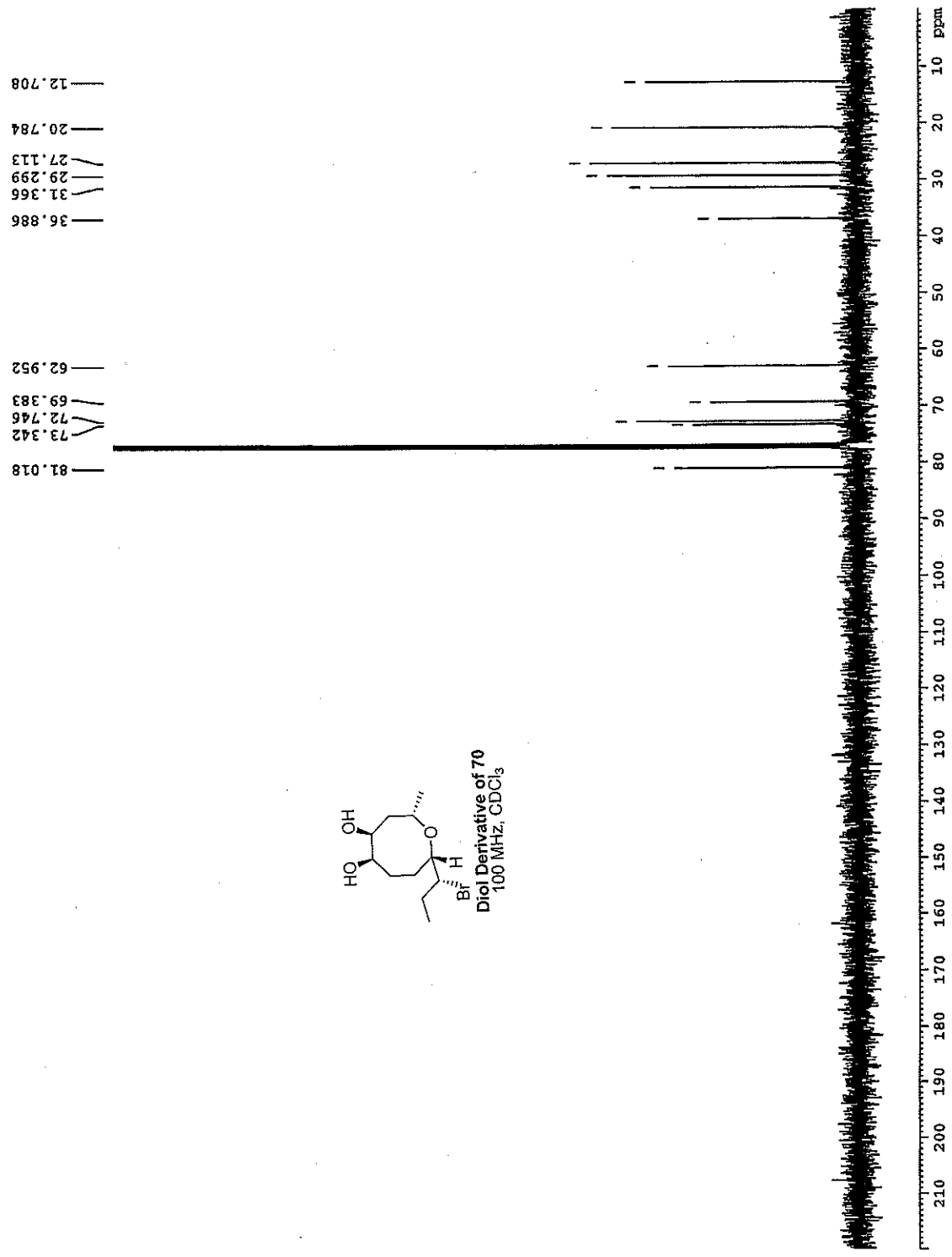

Diol Derivative of 69
400 MHz, CDCl3
OH
HO
O
H
Br
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
1.000
1.019
1.005
0.964
0.979
2.214
7.218
1.058
3.011
3.002
1.043
1.061
1.079
1.184
1.200
1.597
1.607
1.617
1.634
1.645
1.655
2.313
4.026
4.032
4.042
4.048
4.058
4.064
4.072
4.078
4.088
4.094
4.104
4.111
4.202
4.216

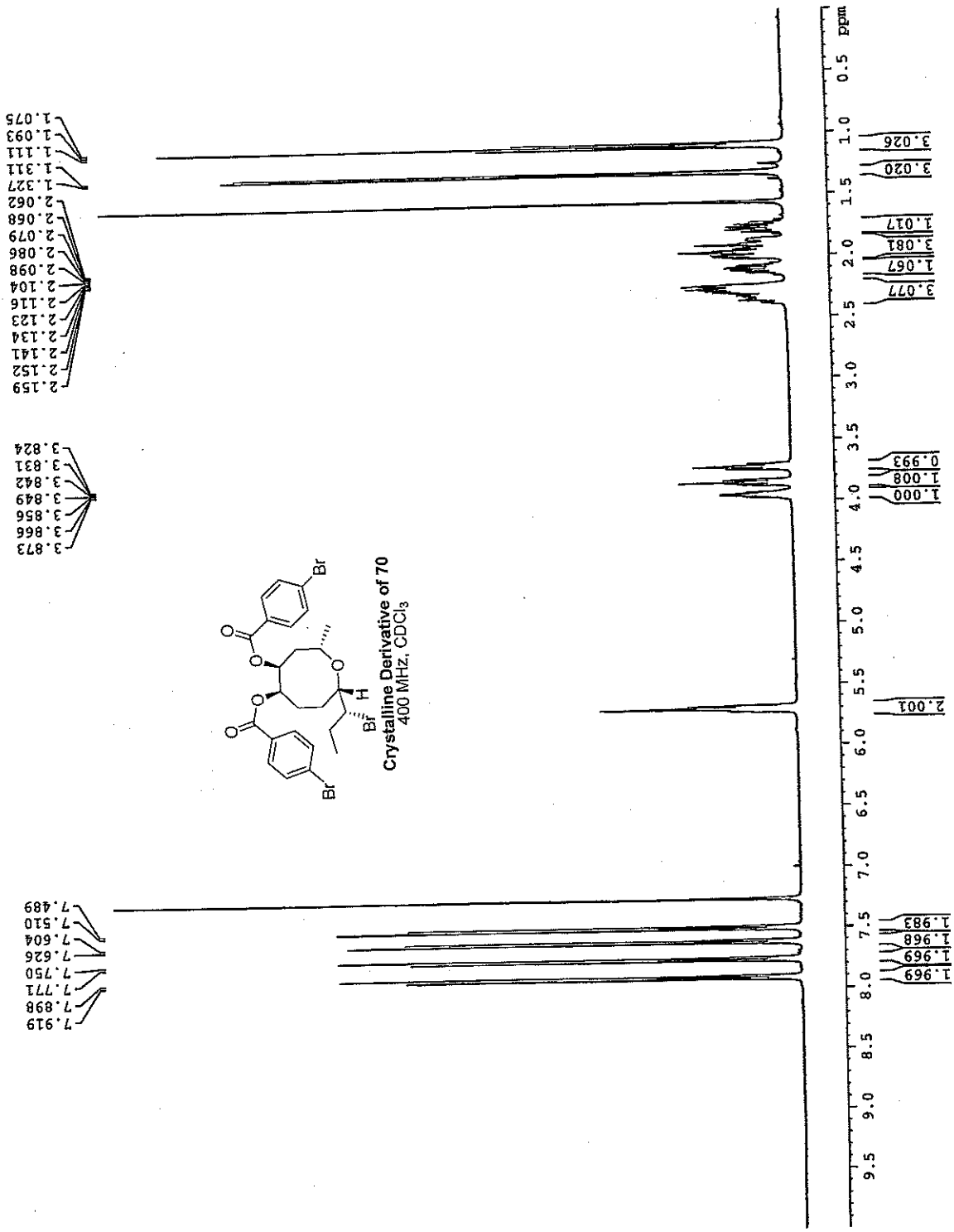

12.985
21.337
28.303
29.271
29.344
38.307
65.024
69.191
72.279
73.412
73.733
OH
HO
O
Br
H
Diol Derivative of 69
100 MHz, CDCl3
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
ppm

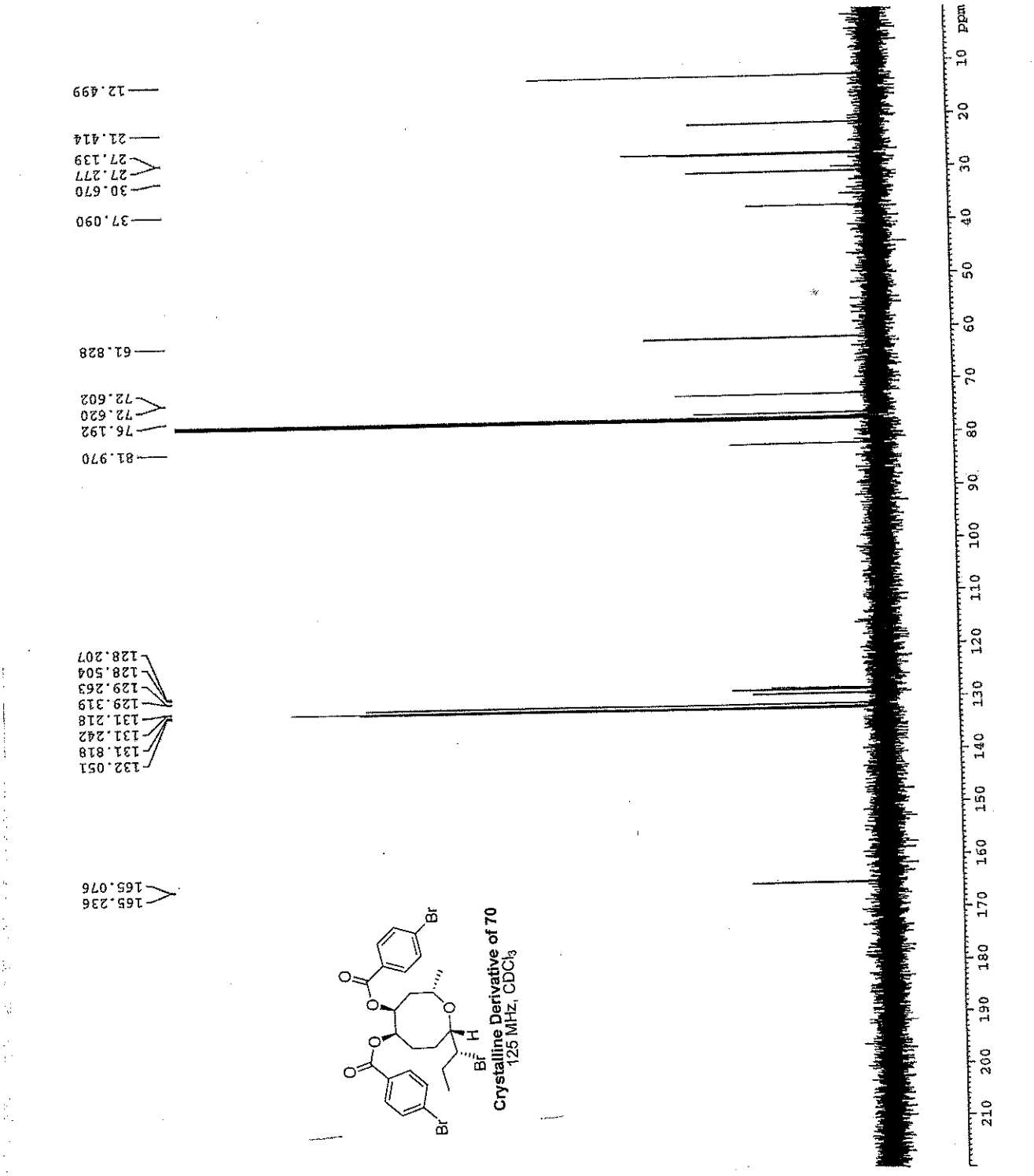

1.053
1.071
1.089
1.286
1.303
2.411
2.425
2.442
2.446
2.456
2.461
2.478
2.492
3.423
3.428
3.439
3.443
3.451
3.456
3.467
3.472
3.697
3.704
3.713
3.720
3.723
3.730
3.739
3.746
3.874
3.890
3.906
3.922
3.938
4.761
4.764
4.779
4.783
4.788
4.792
4.807
4.810
4.954
4.961
4.972
4.980
4.984
4.992
5.003
5.011
Br
H
70
400 MHz, CDCl3
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
3.075
3.088
1.112
1.067
4.122
1.035
1.024
1.010
1.008
1.013
1.006
1.000

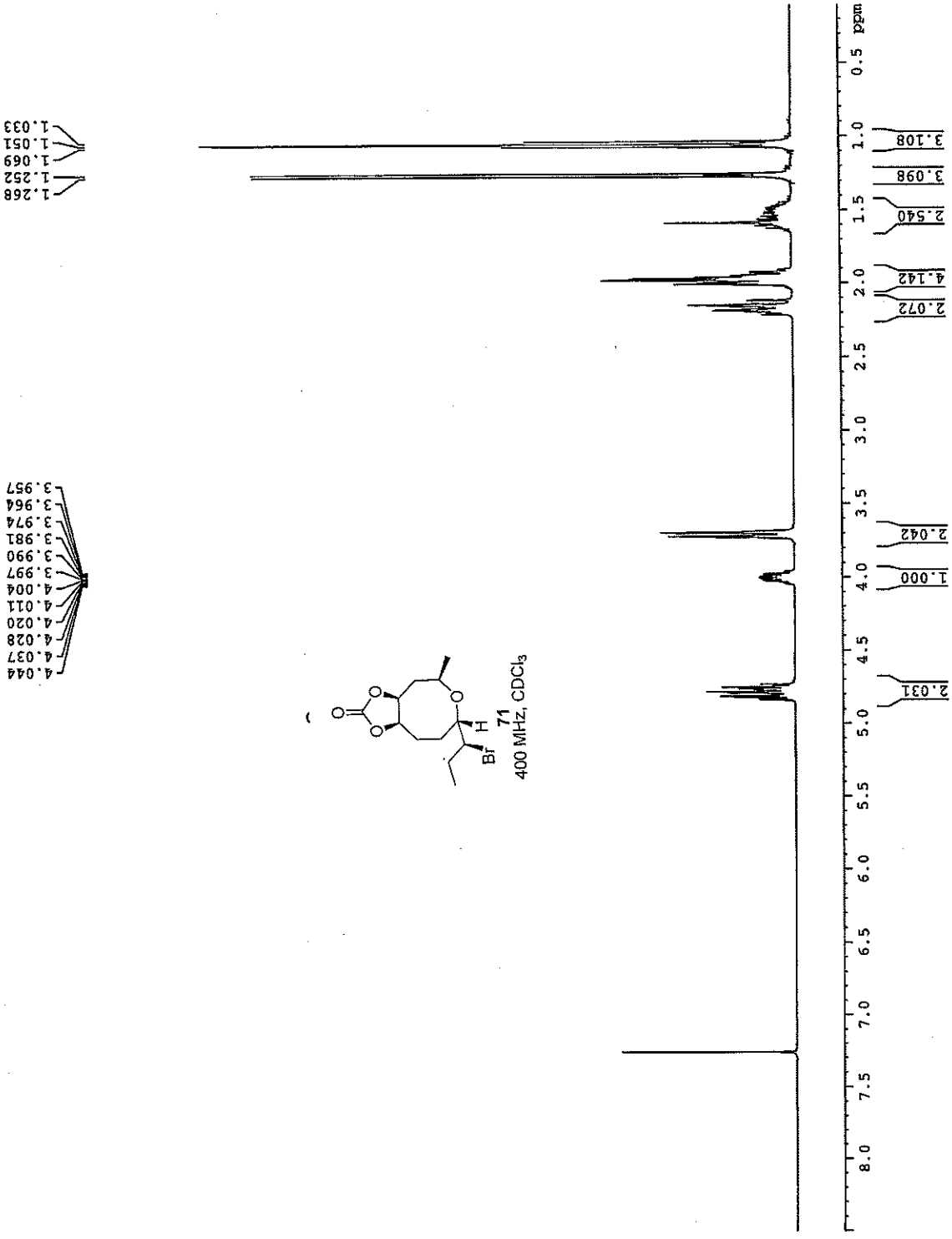

12.788
19.798
26.828
27.477
30.923
32.559
61.843
73.043
75.609
82.326
82.498
154.276
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
Br
H
O
O
O
O
70
100 MHz, CDCl3

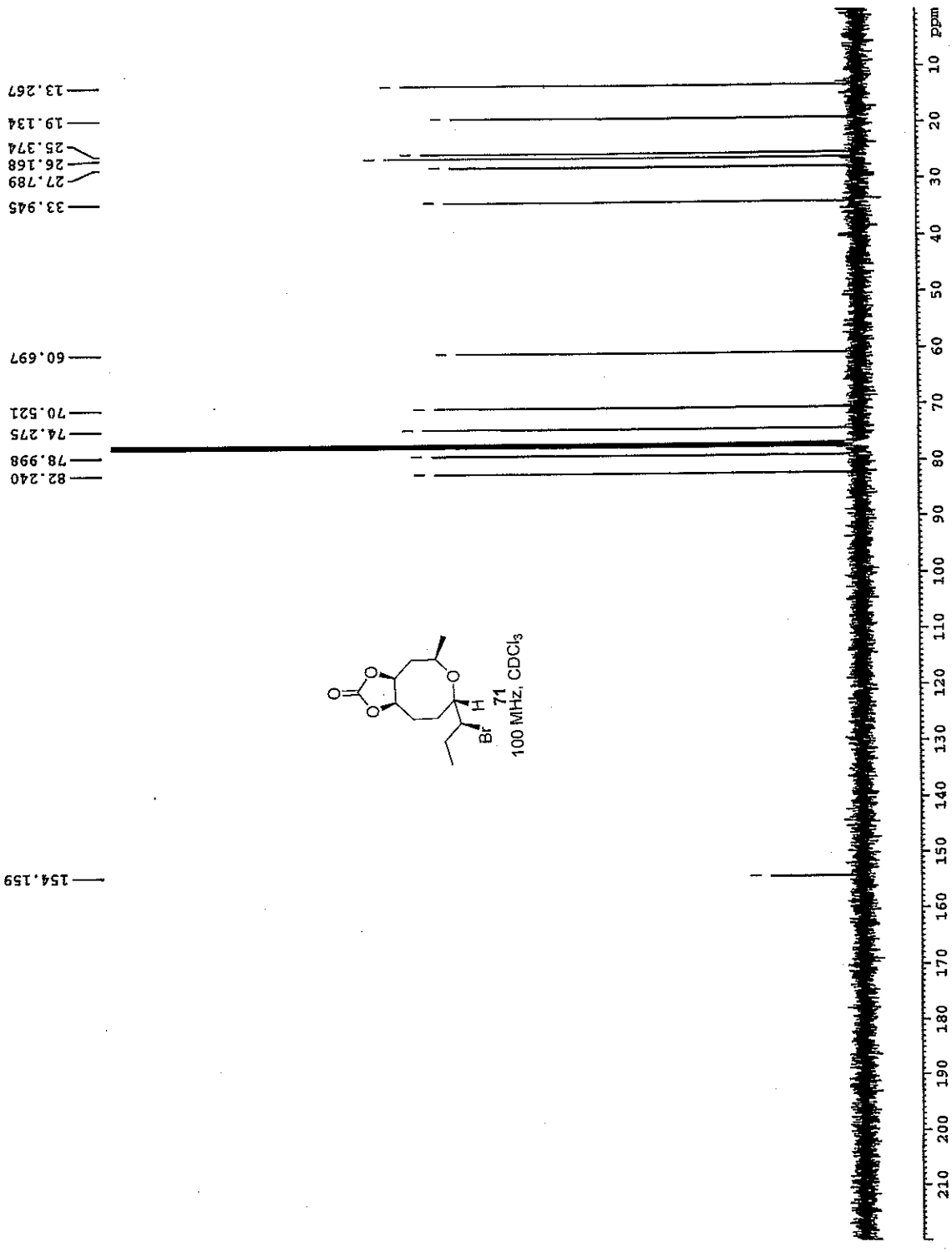

Diol Derivative of 70
400 MHz, CDCl3
HO
OH
O
Br
H
1.044
1.062
1.081
1.221
1.237
4.104
4.114
4.124
4.130
4.140
4.150
1.000
1.012
1.039
1.005
1.017
6.171
5.843
3.279
3.163
ppm

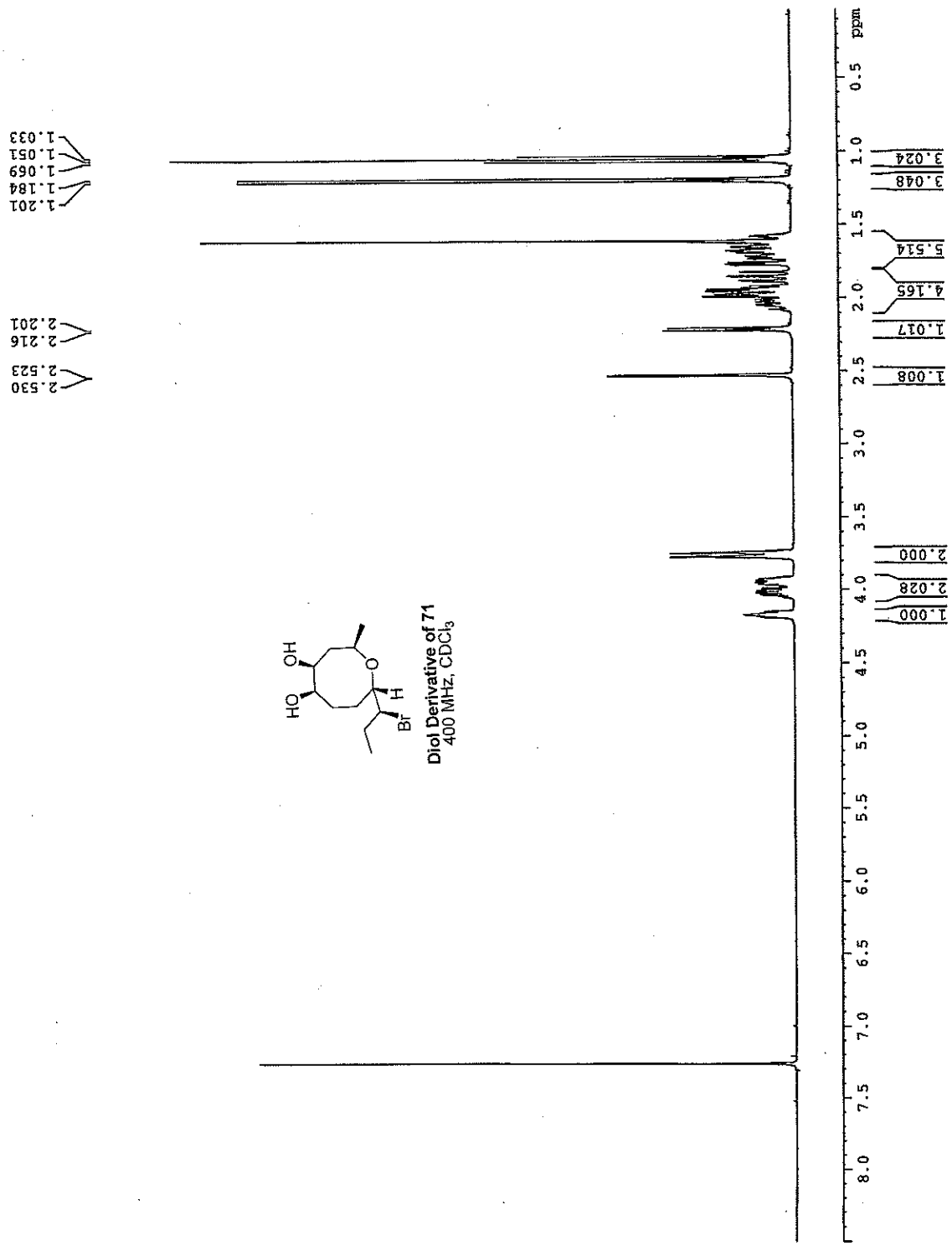

12.708
20.784
27.113
29.299
31.366
36.886
62.952
69.383
72.746
73.342
81.018
OH
HO
O
H
Br
Diol Derivative of 70
100 MHz, CDCl3
10 ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

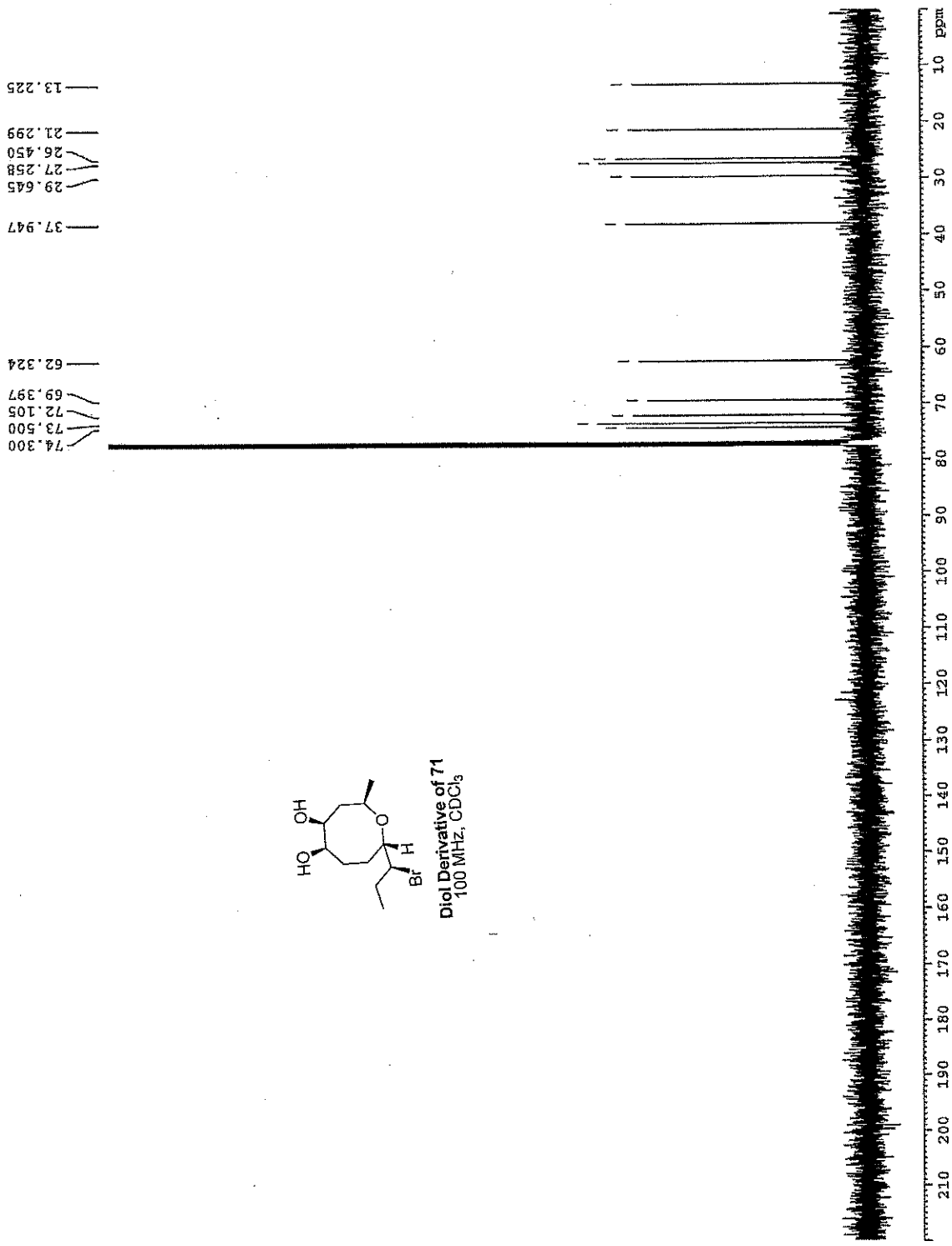

Crystalline Derivative of 70
400 MHz, CDCl3
Br
Br
H
Br
ppm


12.499
21.414
27.139
27.277
30.670
37.090
61.828
72.602
72.620
76.192
81.970
128.207
128.504
129.263
129.319
131.218
131.242
131.818
132.051
165.076
165.236
Br
Br
Br
H
O
O
O
O
Crystalline Derivative of 70
125 MHz, CDCl3
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

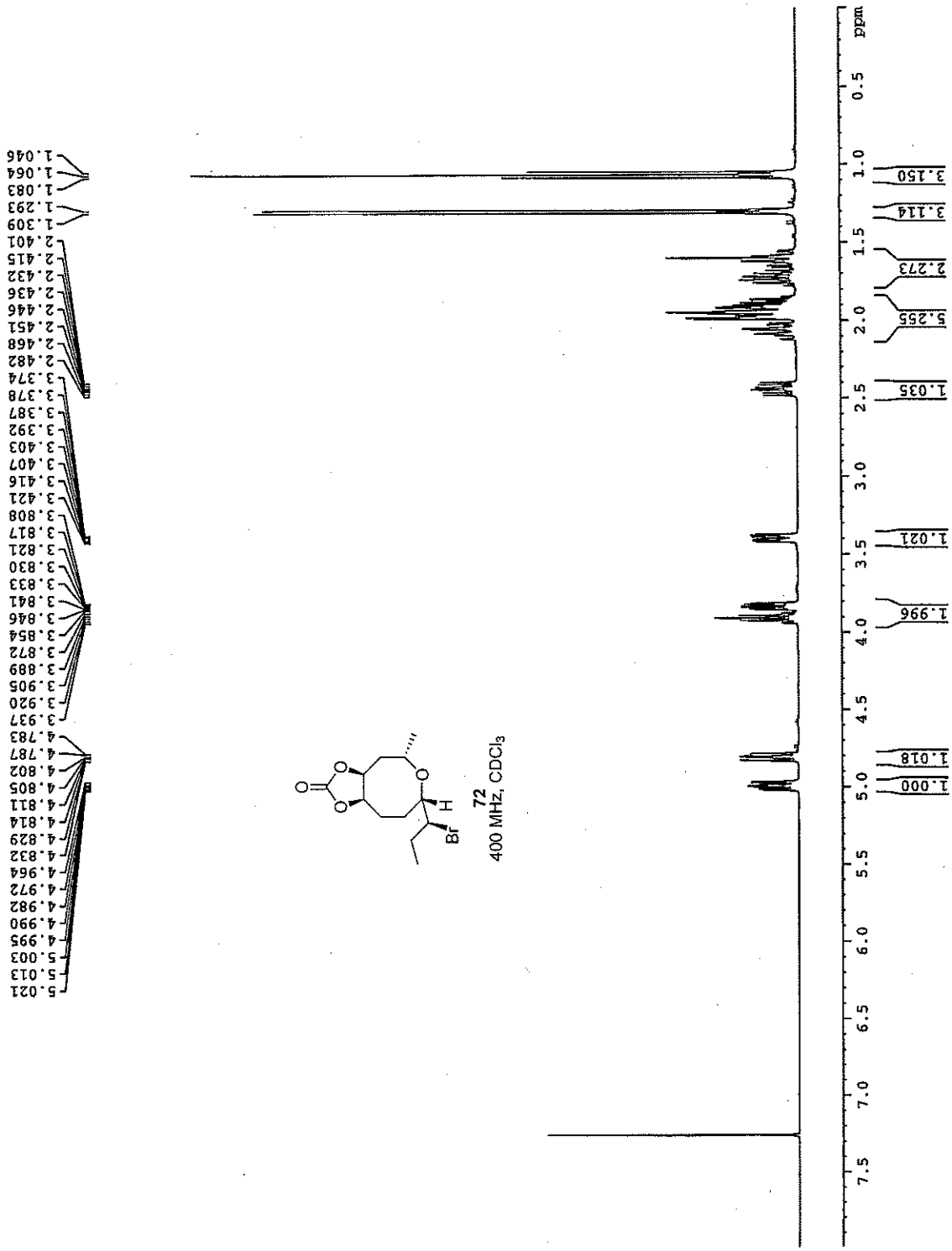

71
400 MHz, CDCl3
Br
H
O
O
O
O
1.033
1.051
1.069
1.252
1.268
3.957
3.964
3.974
3.981
3.990
3.997
4.004
4.011
4.020
4.028
4.037
4.044
3.108
3.098
2.540
4.142
2.072
2.042
1.000
2.031
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0

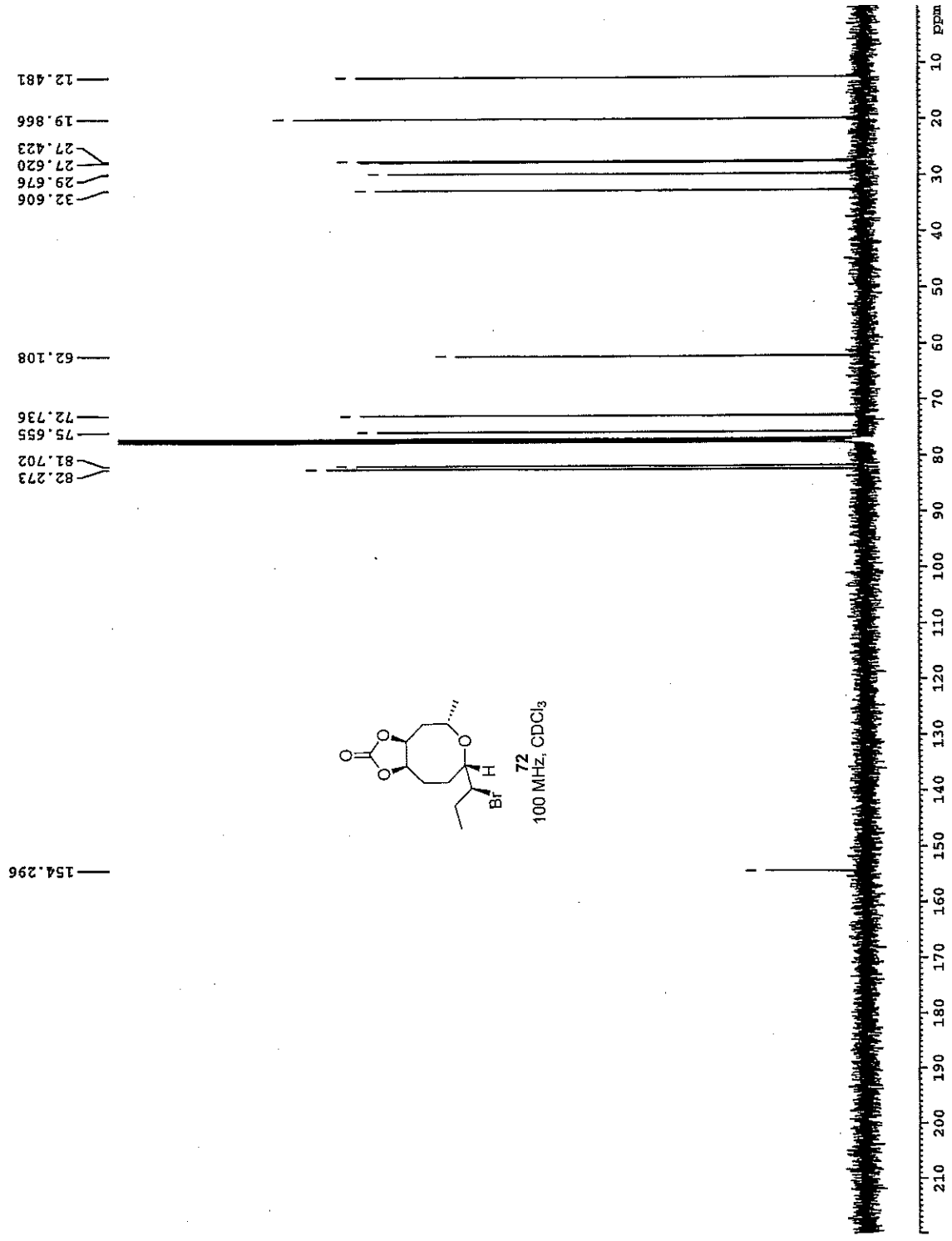

13.267
19.134
25.374
26.168
27.789
33.945
60.697
70.521
74.275
78.998
82.240
154.159
Br
H
71
100 MHz, CDCl3
ppm

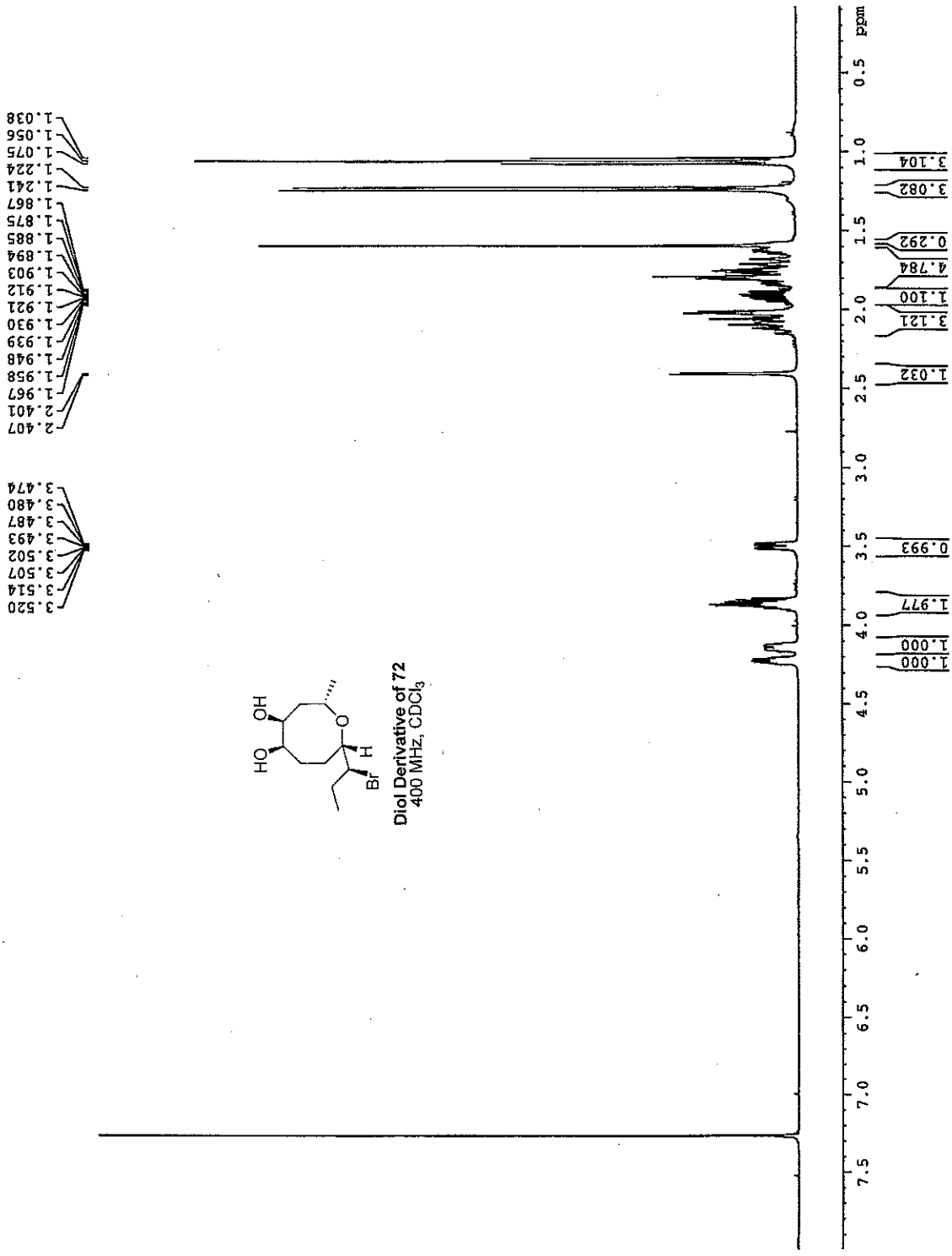

Diol Derivative of 71
400 MHz, CDCl3
OH
HO
O
H
Br
1.033
1.051
1.069
1.184
1.201
2.201
2.216
2.523
2.530
1.000
2.028
2.000
1.008
1.017
4.165
5.514
3.048
3.024
ppm

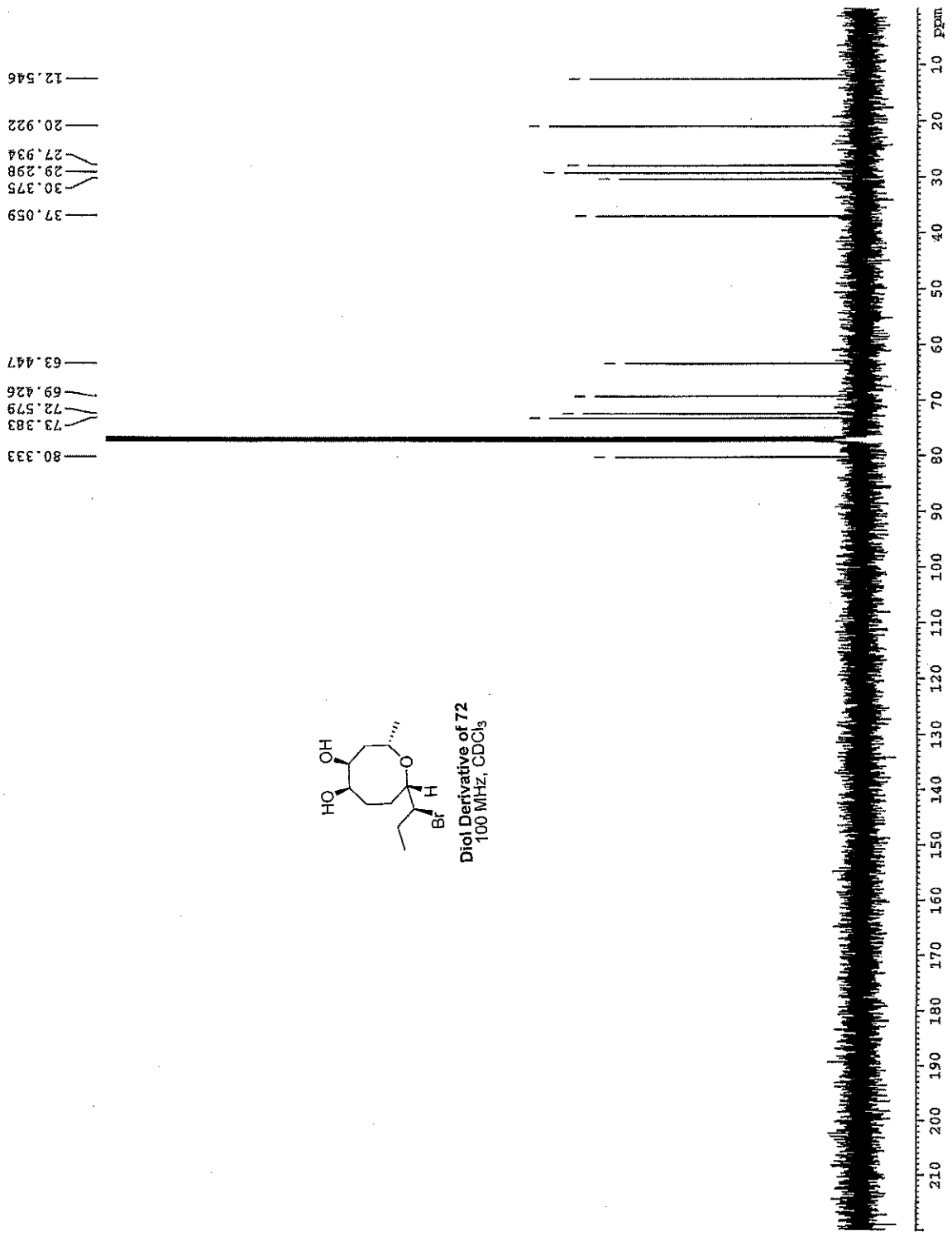


Diol Derivative of 71
100 MHz, $CDCl_3$

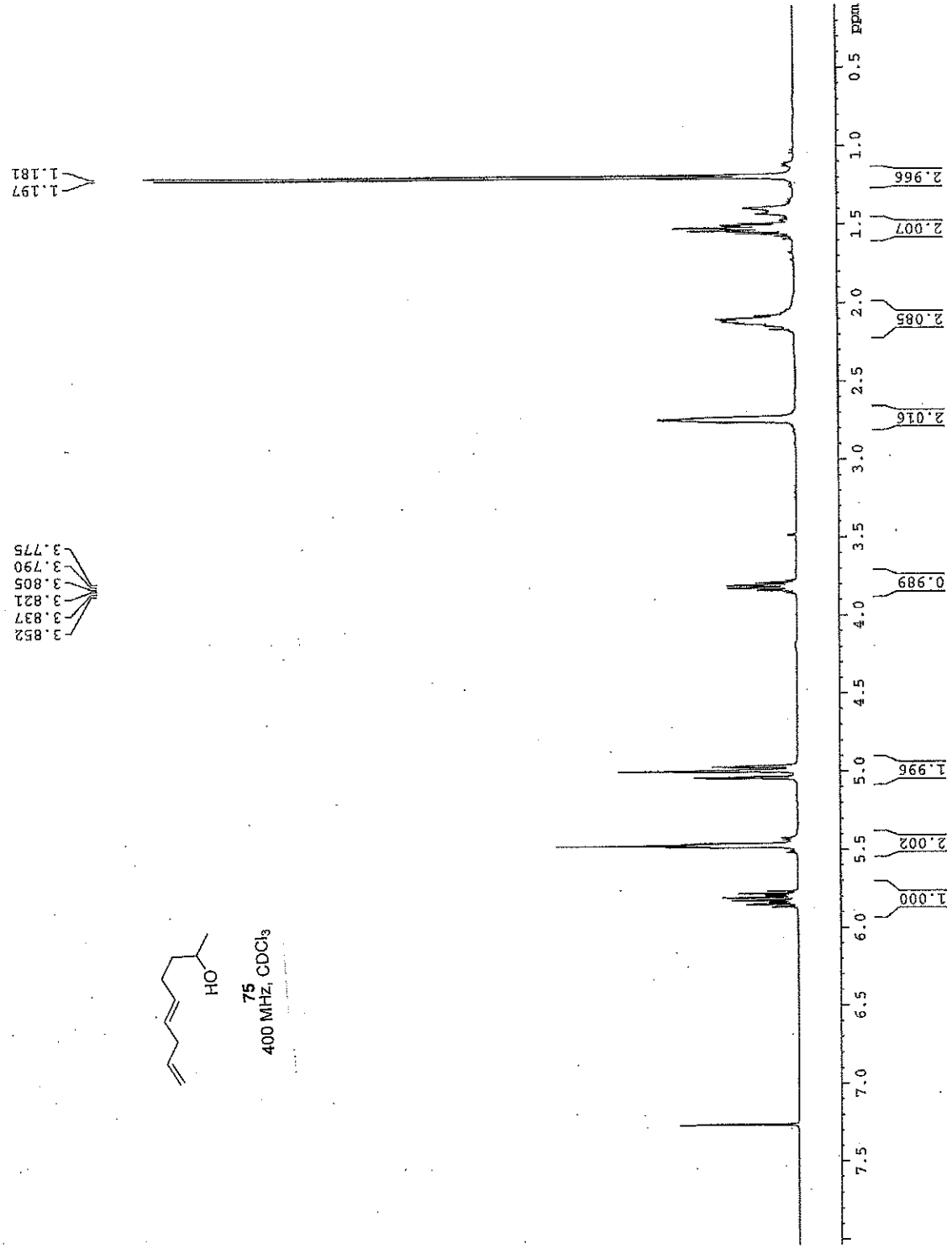

72
400 MHz, CDCl3
Br
H
O
O
O
O
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
3.150
3.114
2.273
5.255
1.035
1.021
1.996
1.018
1.000
1.046
1.064
1.083
1.293
1.309
2.401
2.415
2.432
2.436
2.446
2.451
2.468
2.482
3.374
3.378
3.387
3.392
3.403
3.407
3.416
3.421
3.808
3.817
3.821
3.830
3.833
3.841
3.846
3.854
3.872
3.889
3.905
3.920
3.937
4.783
4.787
4.802
4.805
4.811
4.814
4.829
4.832
4.964
4.972
4.982
4.990
4.995
5.003
5.013
5.021

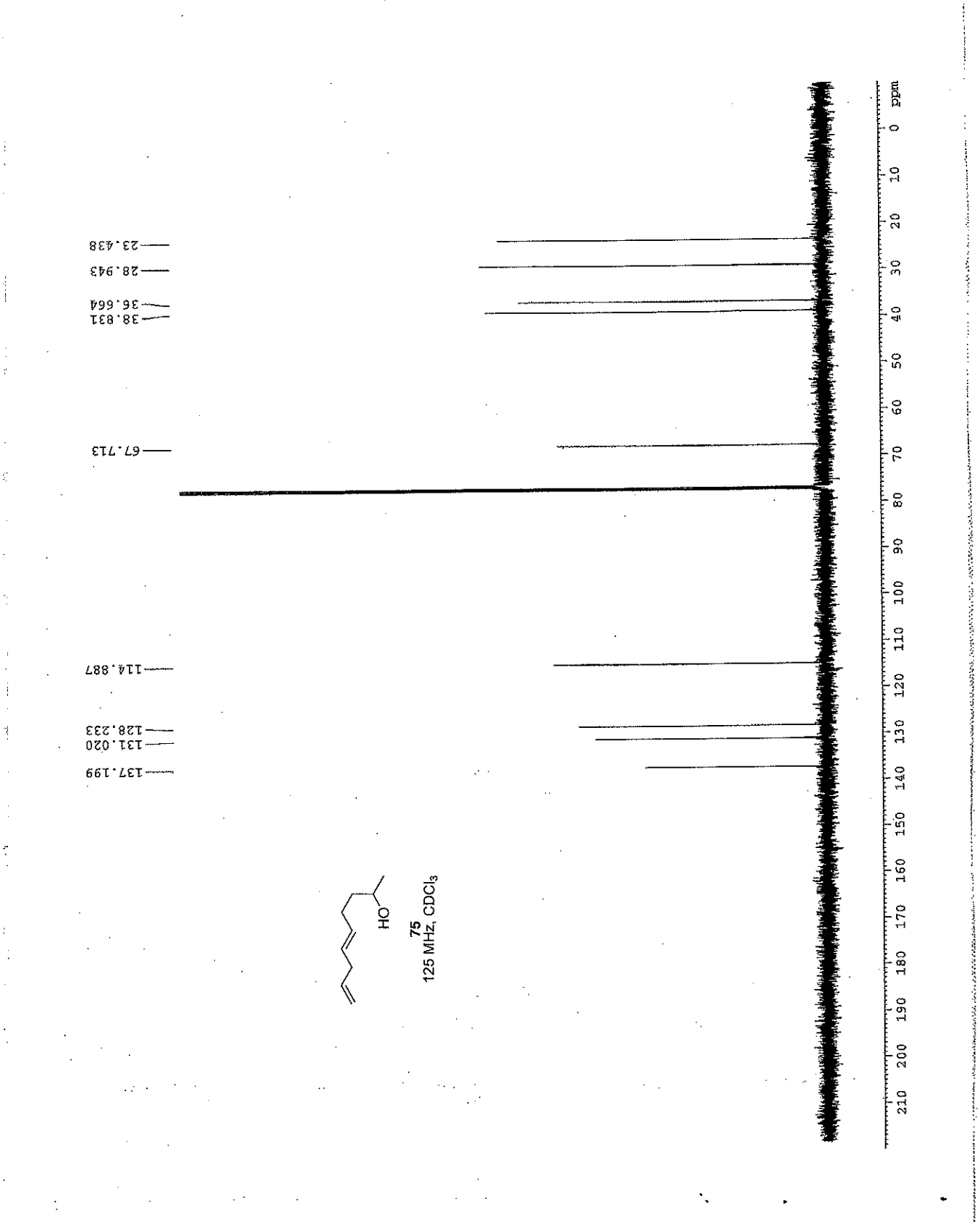

12.481
19.866
27.423
27.620
29.676
32.606
62.108
72.736
75.655
81.702
82.273
154.296
72
100 MHz, CDCl3
Br
H
O
O
O
O
10 ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

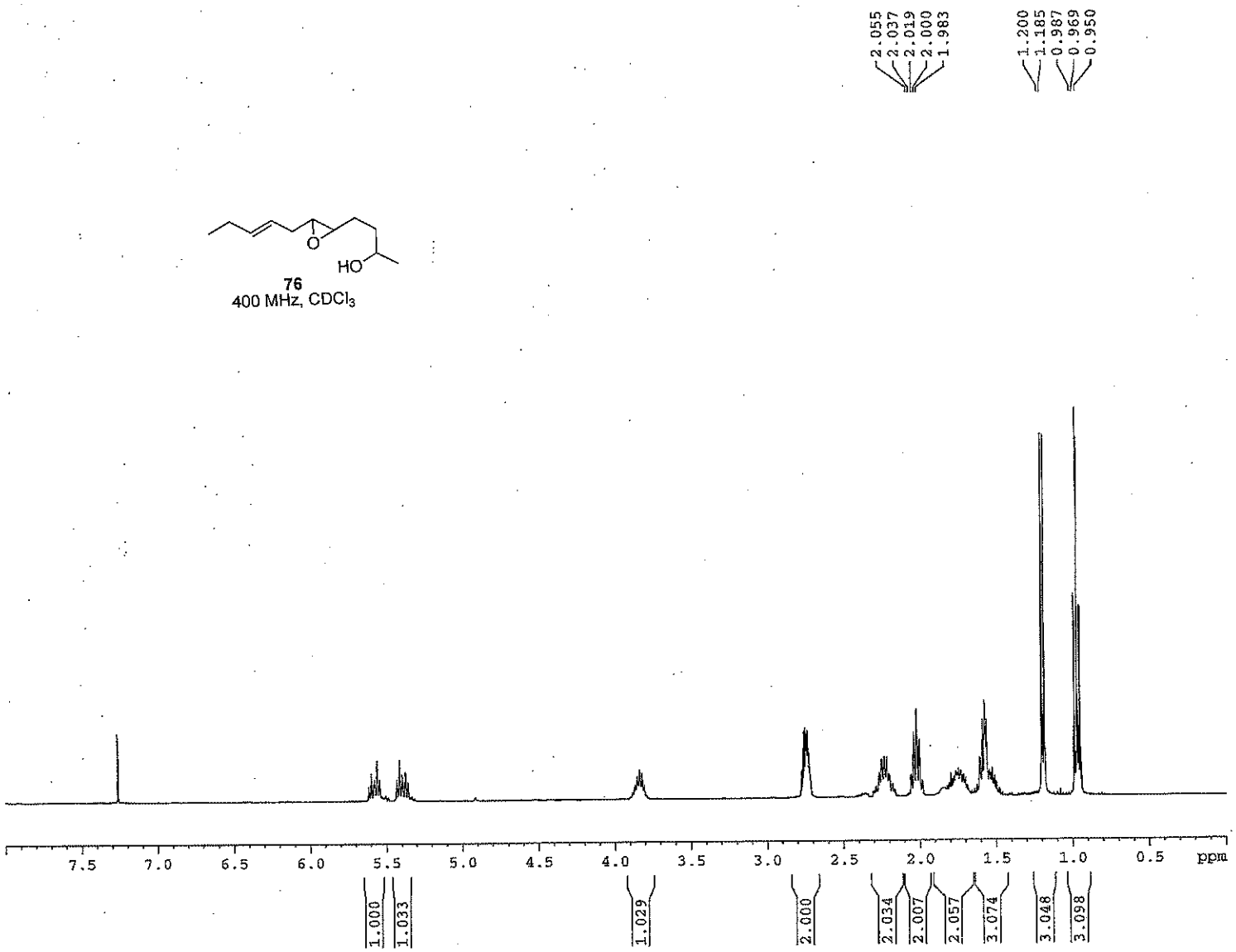

Diol Derivative of 72
400 MHz, $CDCl_3$
OH
HO
O
H
Br
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
3.104
3.082
0.292
4.784
1.100
3.121
1.032
0.993
1.977
1.000
1.000
1.038
1.056
1.075
1.224
1.241
1.867
1.875
1.885
1.894
1.903
1.912
1.921
1.930
1.939
1.948
1.958
1.967
2.401
2.407
3.474
3.480
3.487
3.493
3.502
3.507
3.514
3.520



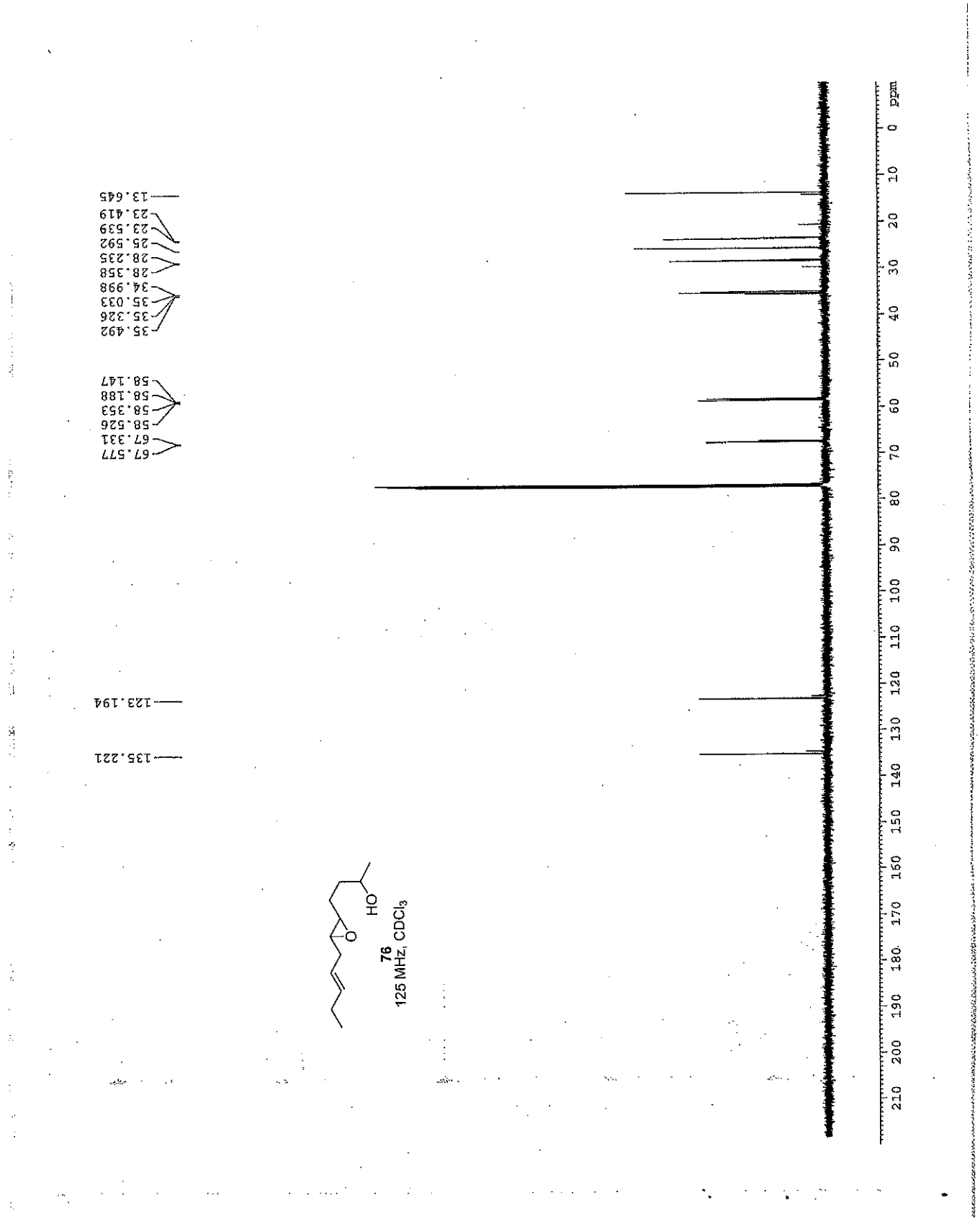
Diol Derivative of 72
100 MHz, $CDCl_3$

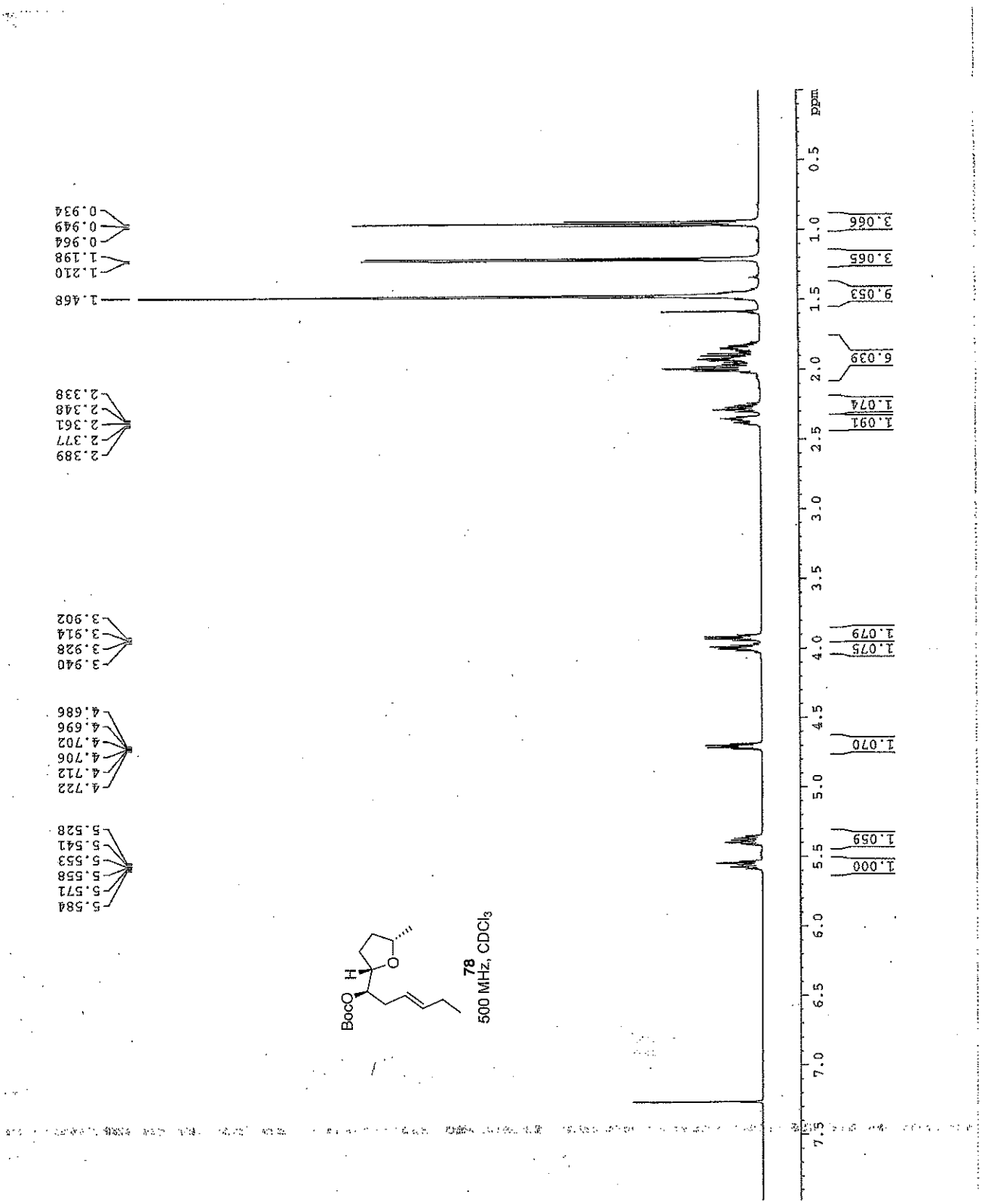

75
400 MHz, CDCl3
OH
1.197
1.181
3.852
3.837
3.821
3.805
3.790
3.775
1.000
2.002
1.996
0.989
2.016
2.085
2.007
2.966
ppm

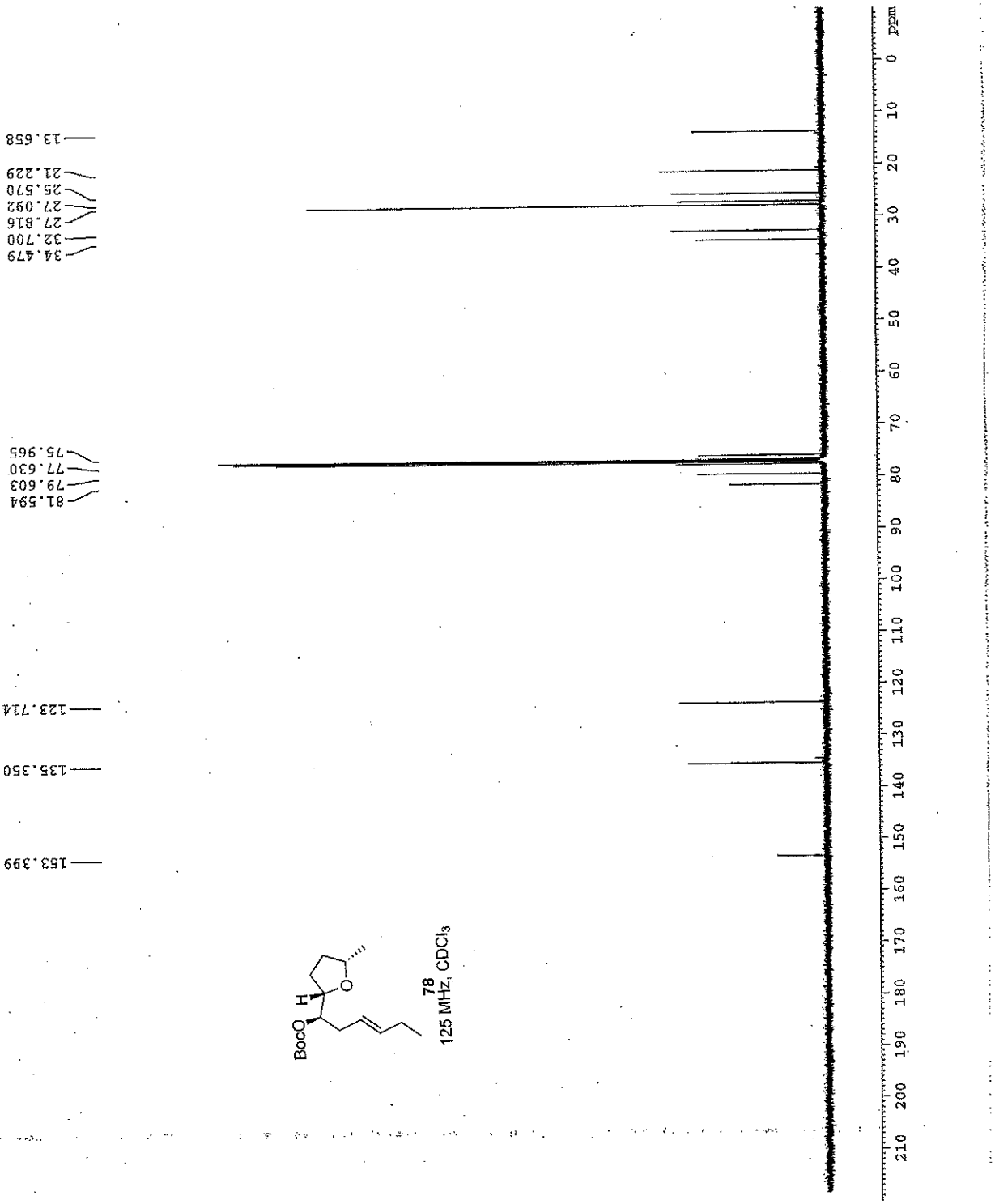

23.438
28.943
36.664
38.831
67.713
114.887
128.233
131.020
137.199
HO
75
125 MHz, CDCl3
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

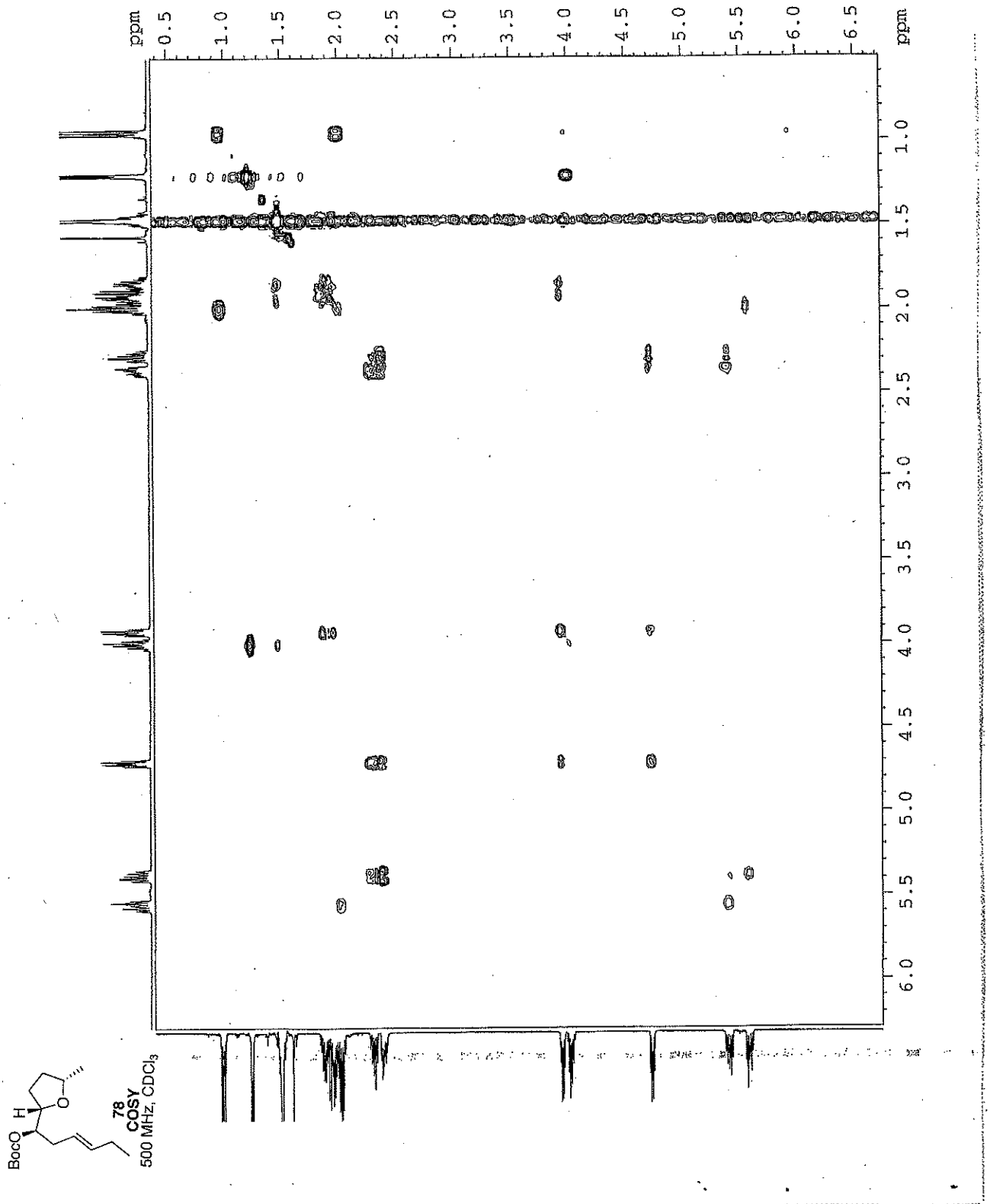


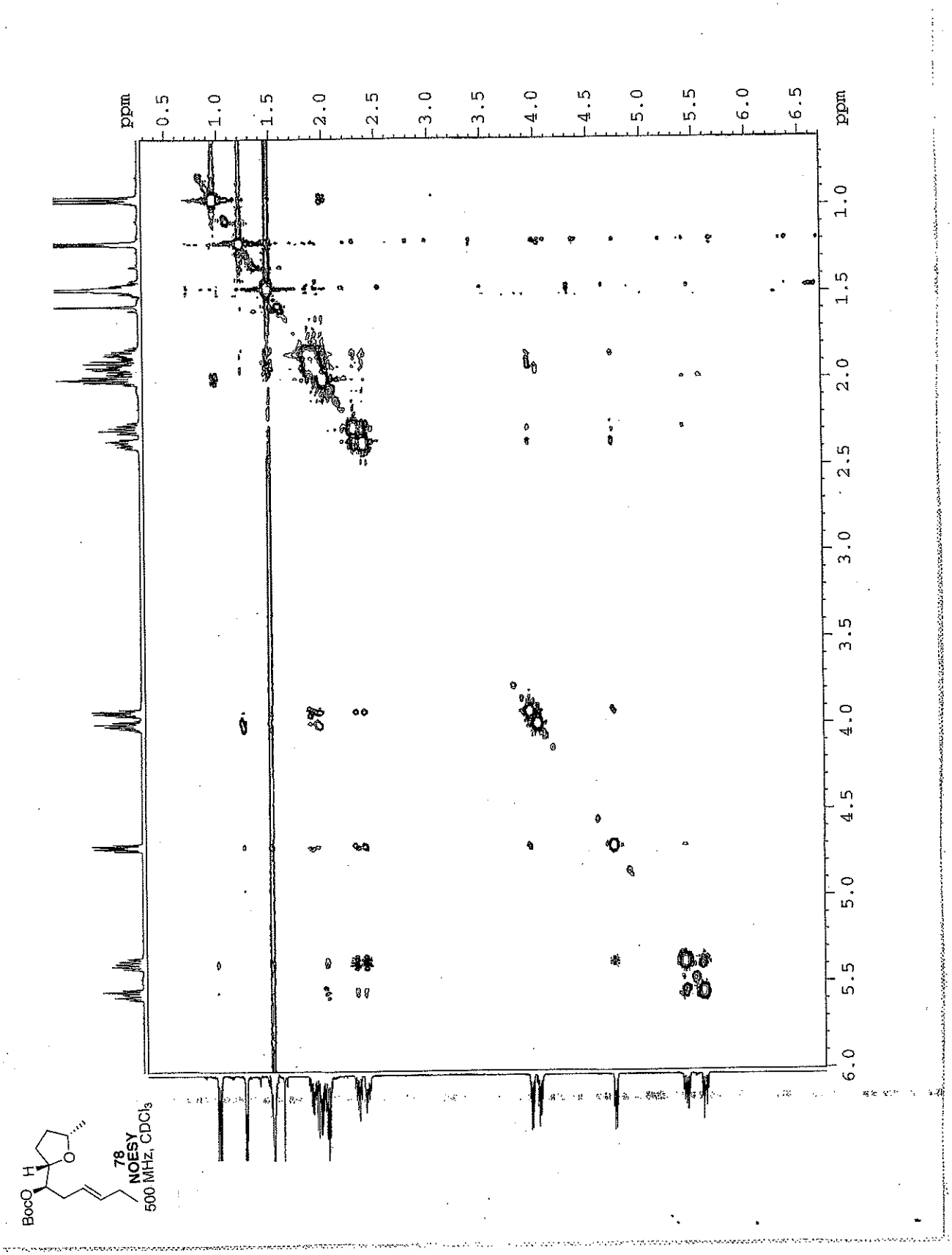
76
400 MHz, $CDCl_3$

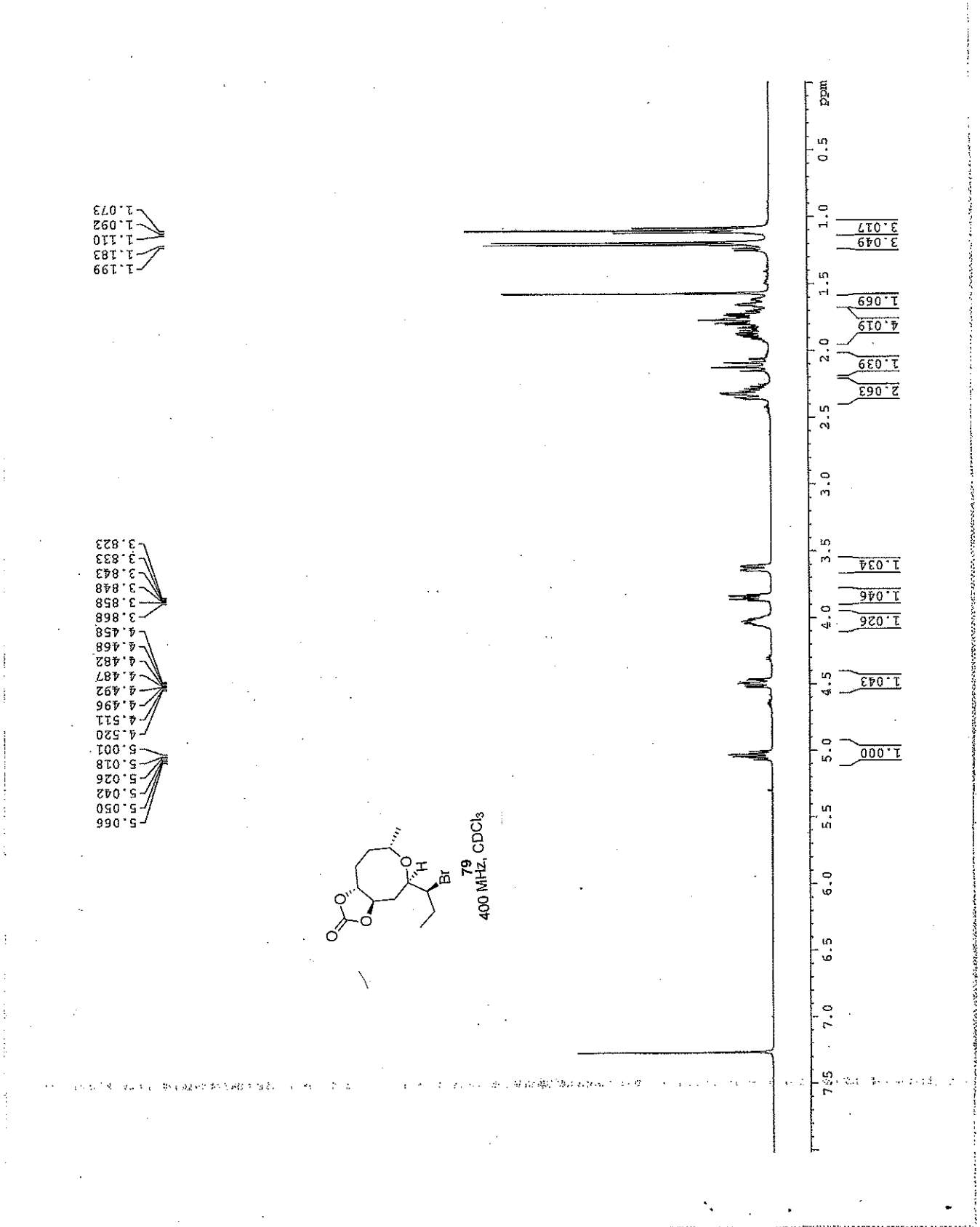

76
125 MHz, CDCl3
HO
O
13.645
23.419
23.539
25.592
28.235
28.358
34.998
35.033
35.326
35.492
58.147
58.188
58.353
58.526
67.331
67.577
123.194
135.221
ppm

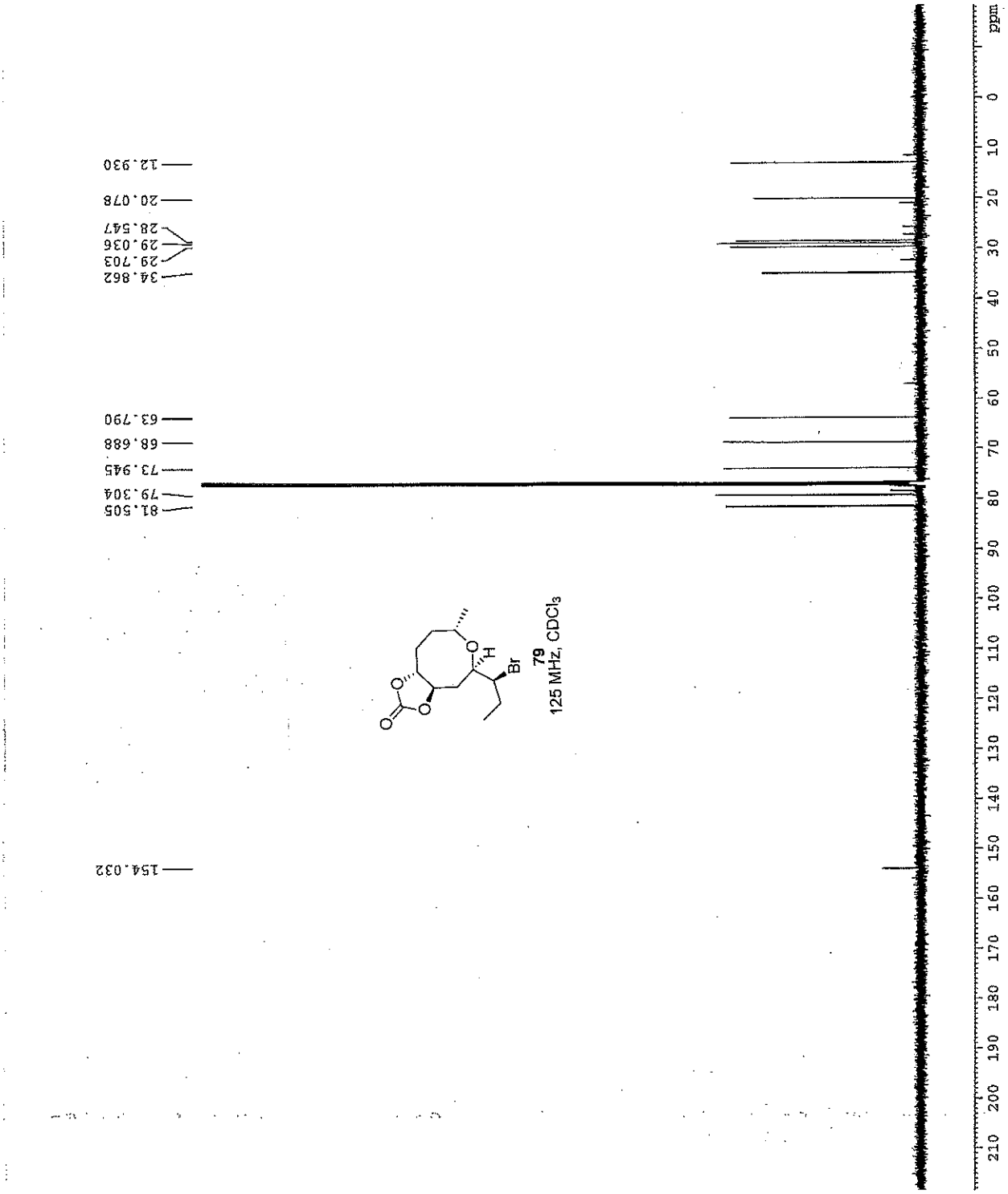

78
500 MHz, CDCl3
BocO
H
O
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
3.066
3.065
9.053
6.039
1.074
1.091
1.075
1.079
1.070
1.059
1.000
0.934
0.949
0.964
1.198
1.210
1.468
2.338
2.348
2.361
2.377
2.389
3.902
3.914
3.928
3.940
4.686
4.696
4.702
4.706
4.712
4.722
5.528
5.541
5.553
5.558
5.571
5.584

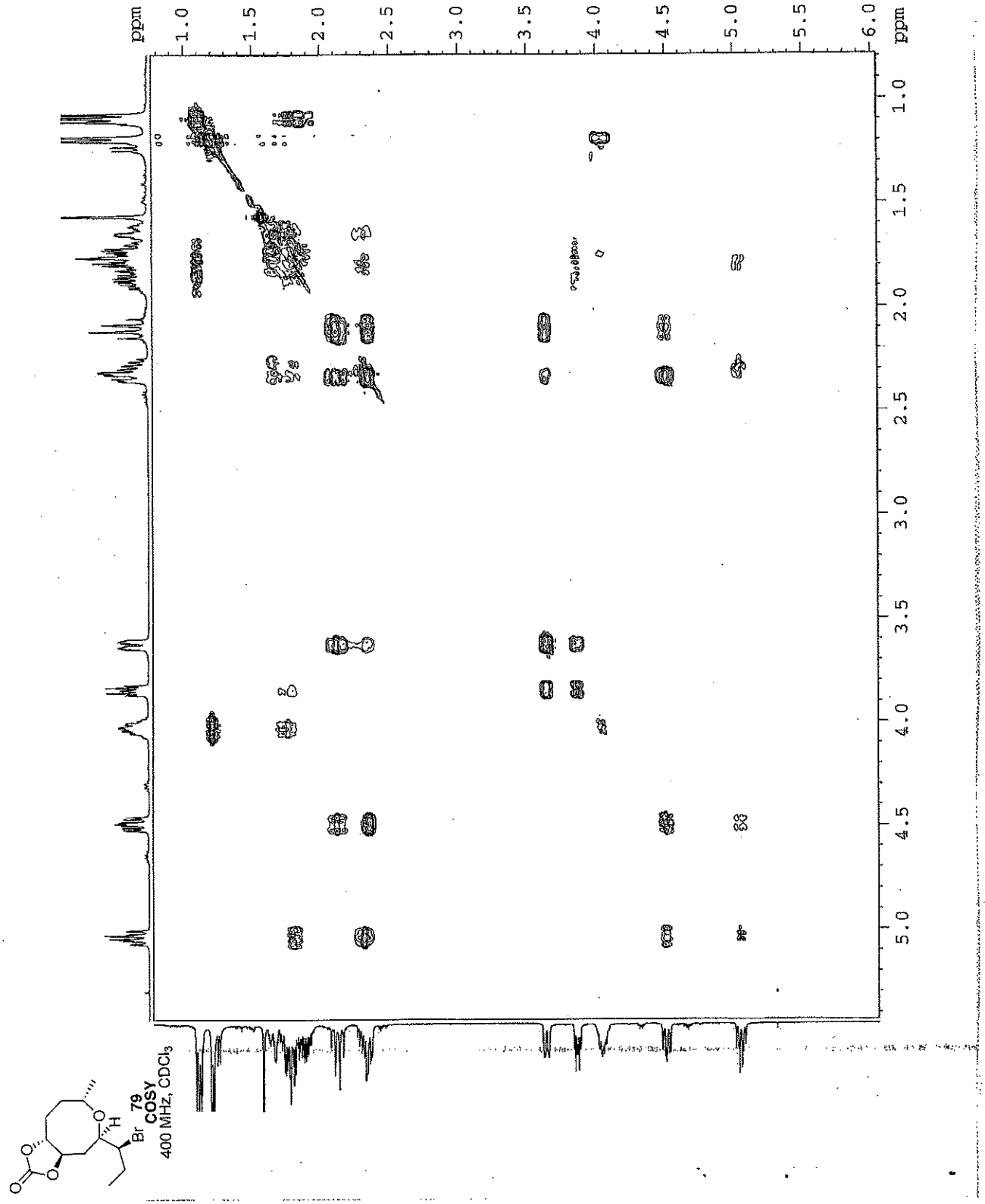

153.399
135.350
123.714
81.594
79.603
77.630
75.965
34.479
32.700
27.816
27.092
25.570
21.229
13.658
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
BocO
H
O
78
125 MHz, CDCl3

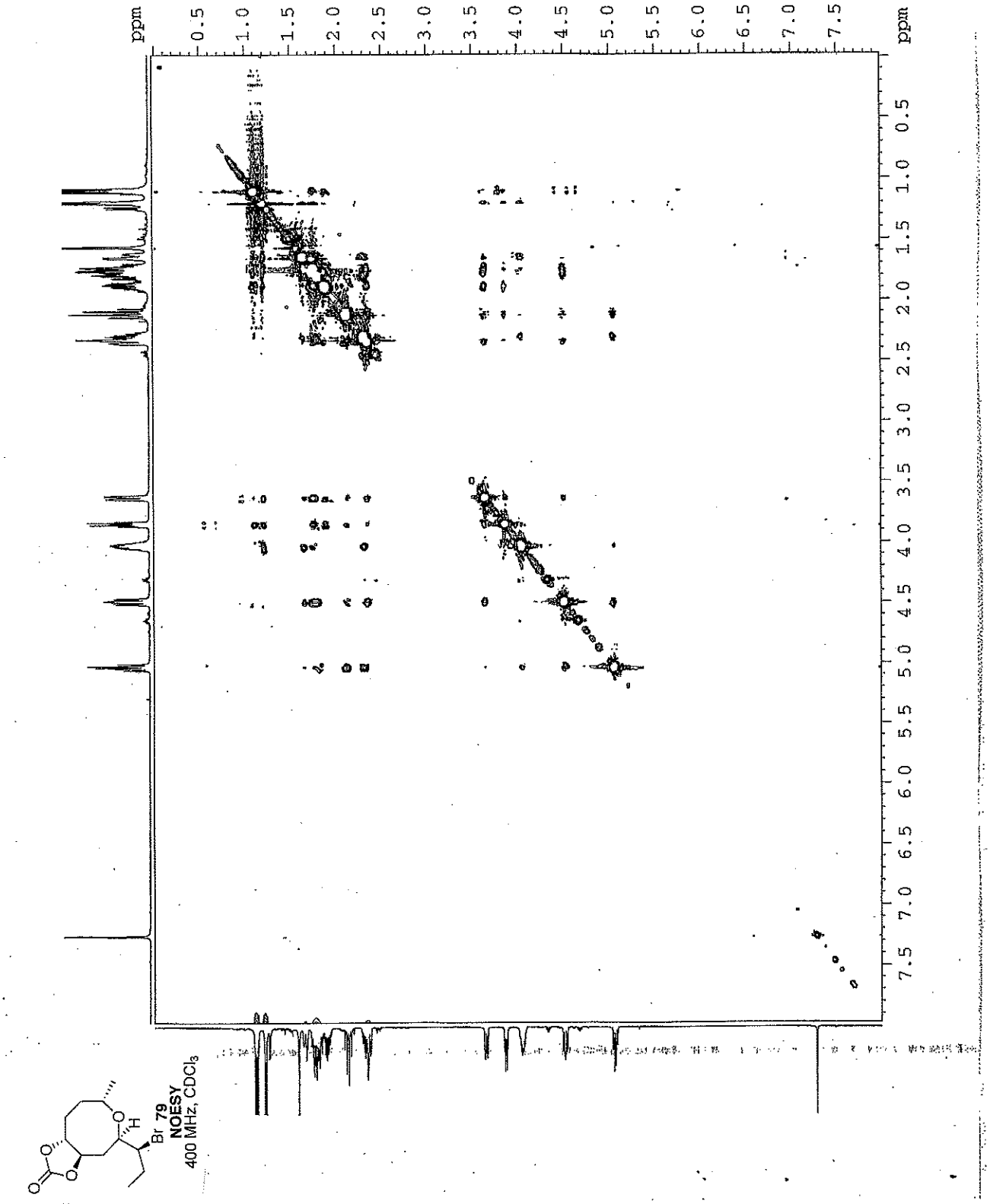

ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
BocO
H
O
78
COSY
500 MHz, CDCl3

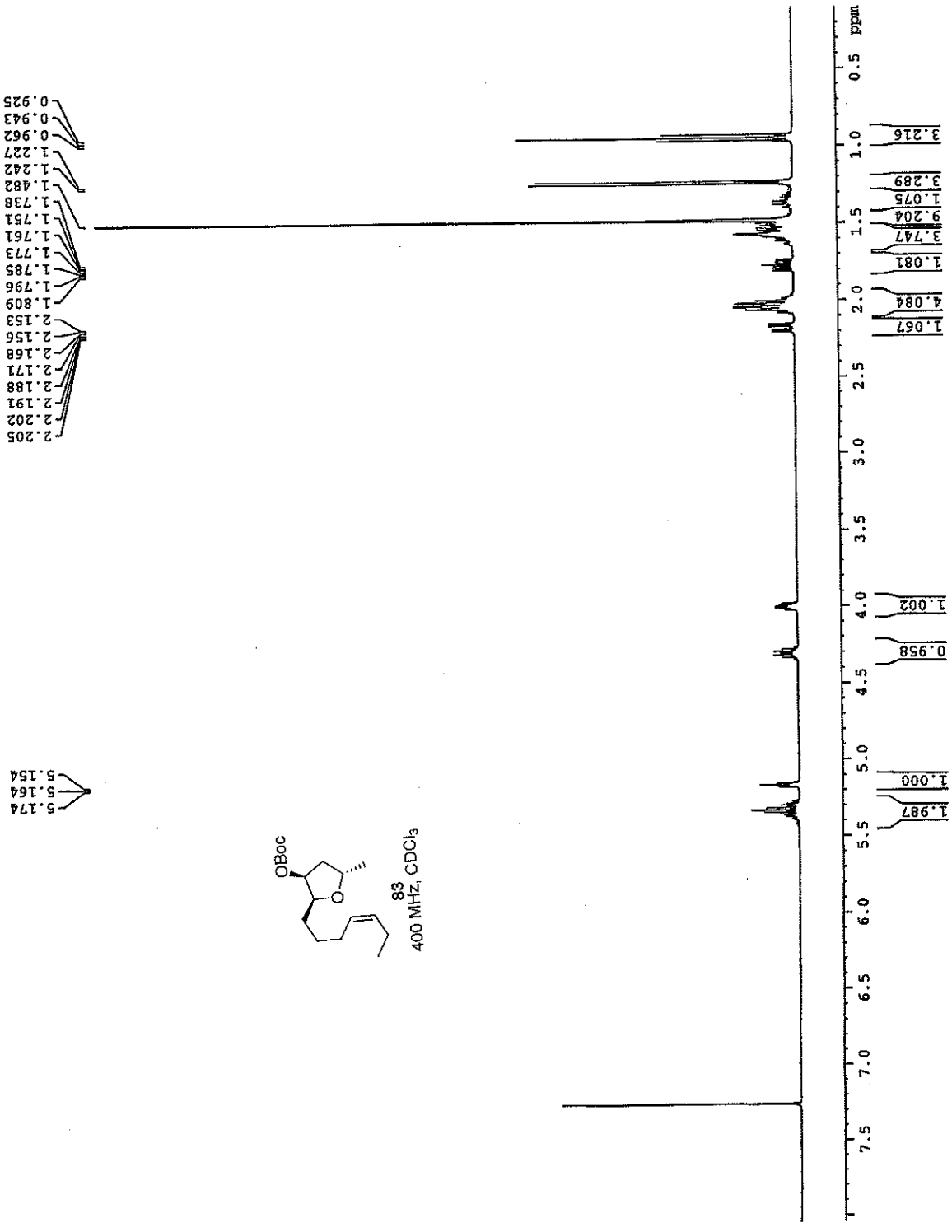

ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
ppm
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
BocO
H
O
78
NOESY
500 MHz, CDCl3

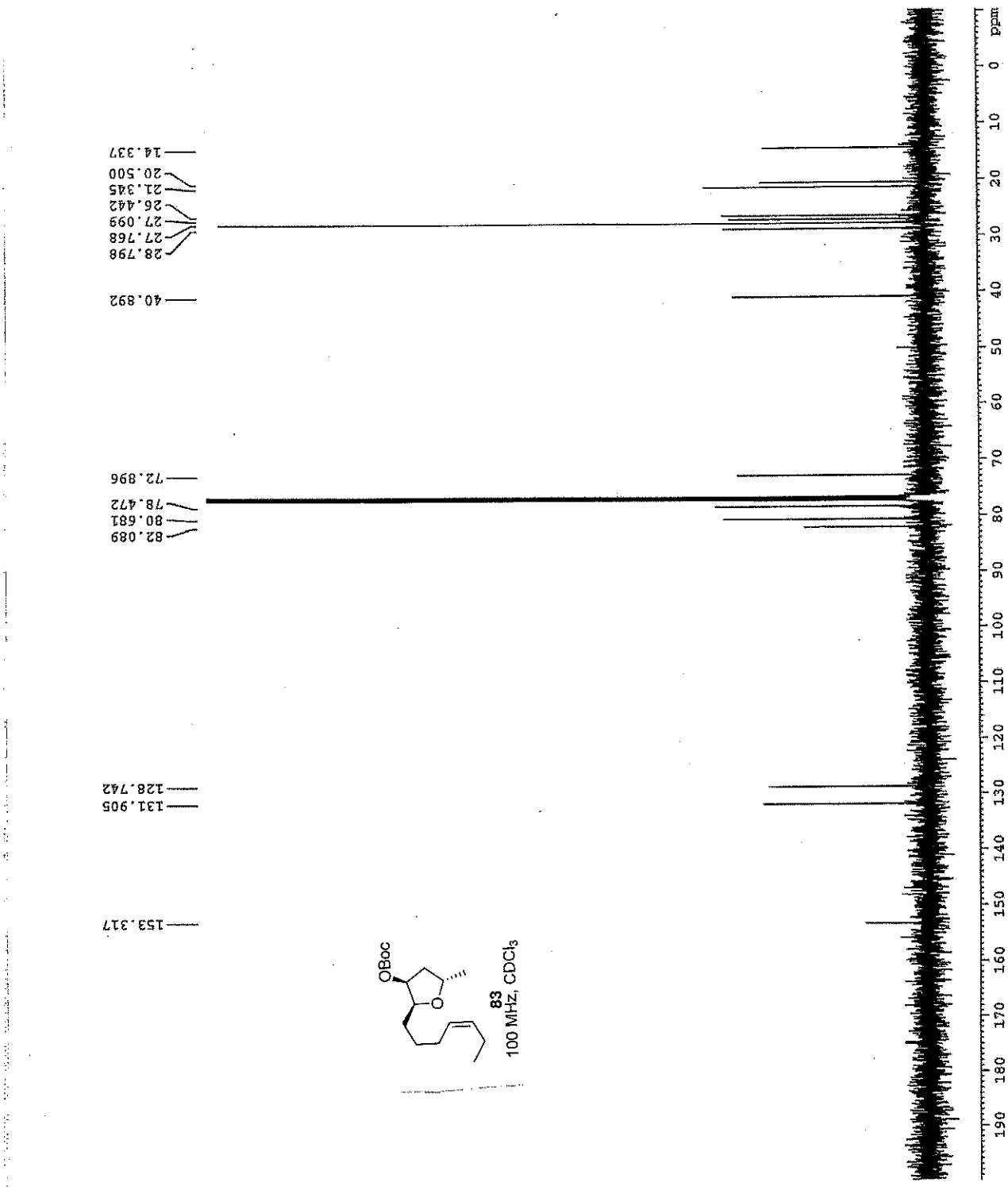

79
400 MHz, CDCl3
Br
H
O
O
O
O
1.199
1.183
1.110
1.092
1.073
3.868
3.858
3.848
3.843
3.833
3.823
4.458
4.468
4.482
4.487
4.492
4.496
4.511
4.520
5.001
5.018
5.026
5.042
5.050
5.066
1.000
1.043
1.026
1.046
1.034
2.063
1.039
4.019
1.069
3.049
3.017
ppm

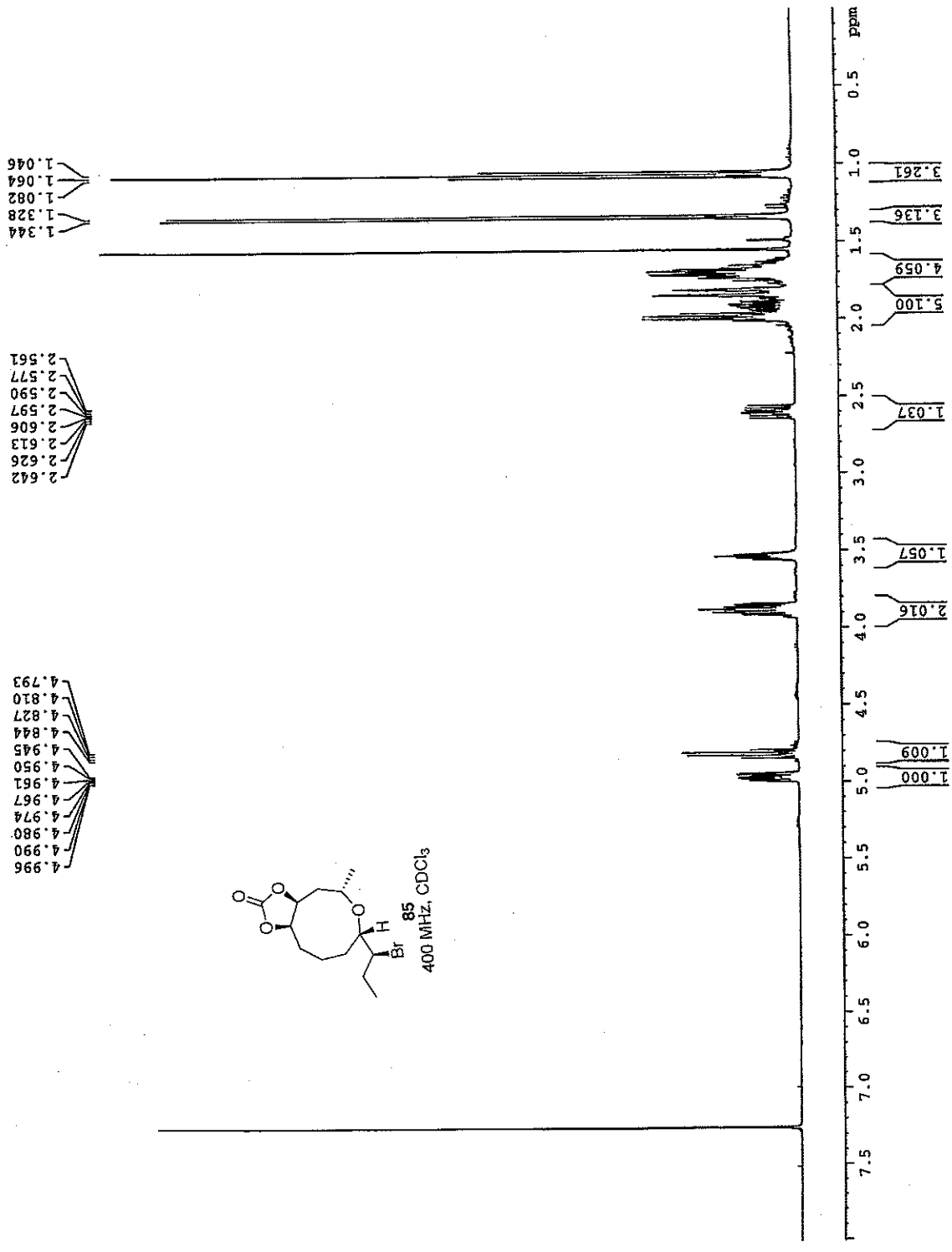

12.930
20.078
28.547
29.036
29.703
34.862
63.790
68.688
73.945
79.304
81.505
154.032
79
125 MHz, CDCl3
Br
H
O
O
O
O
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

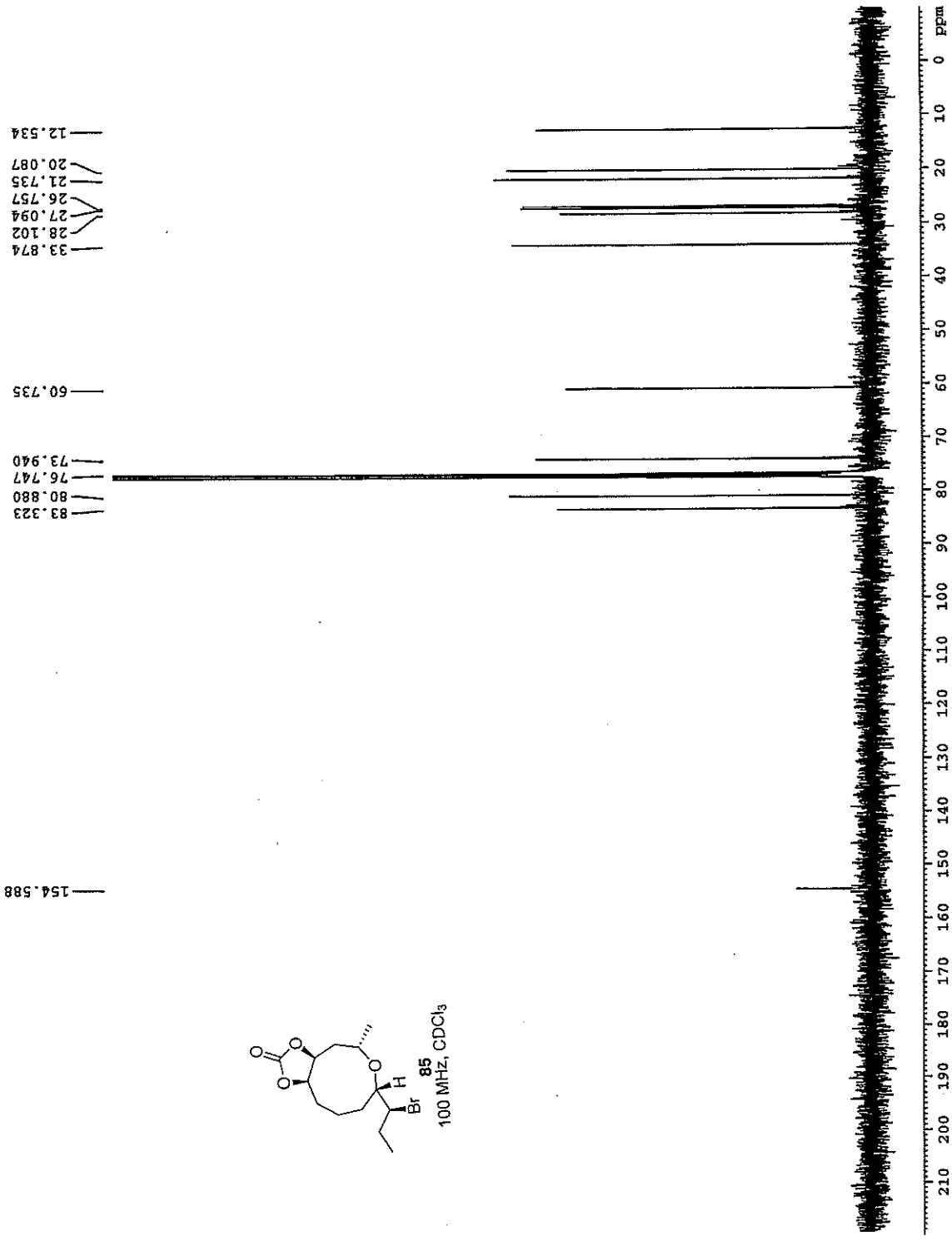

79
COSY
400 MHz, CDCl3
Br
H
O
O
O
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0

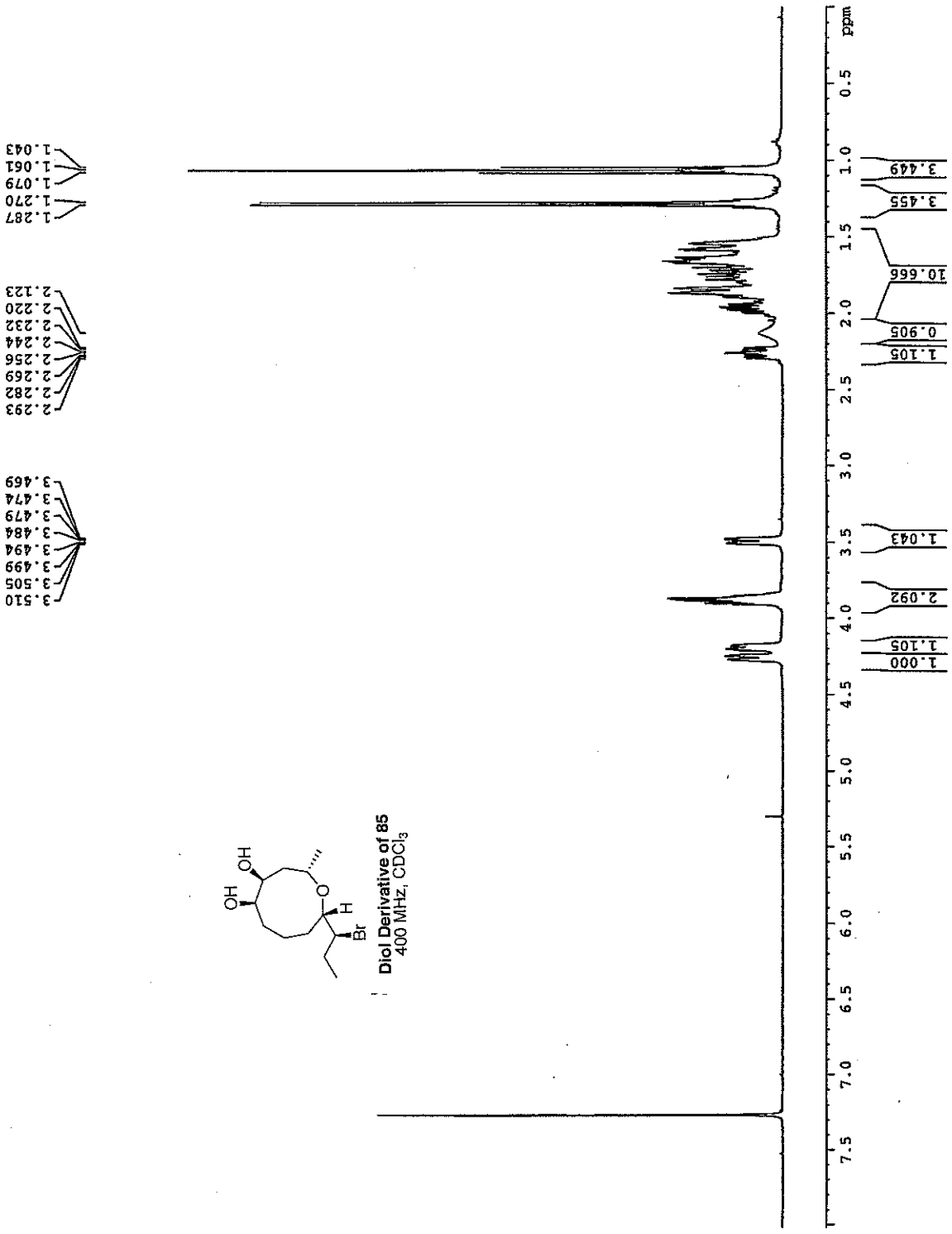

ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
Br
H
O
O
O
O
Br 79
NOESY
400 MHz, CDCl3

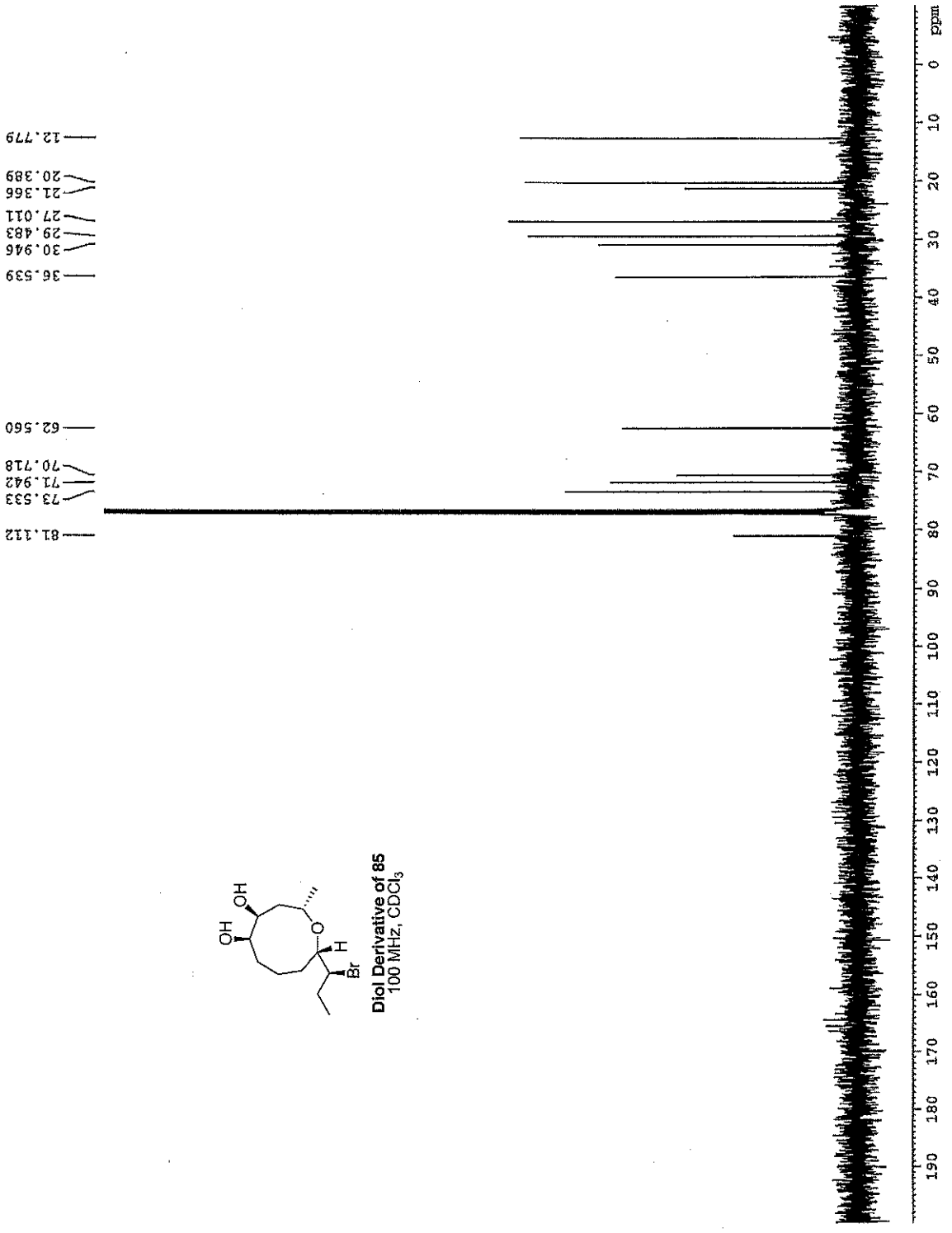

OBoc
83
400 MHz, CDCl3
5.174
5.164
5.154
2.205
2.202
2.191
2.188
2.171
2.168
2.156
2.153
1.809
1.796
1.785
1.773
1.761
1.751
1.738
1.482
1.242
1.227
0.962
0.943
0.925
3.216
3.289
1.075
9.204
3.747
1.081
4.084
1.067
1.002
0.958
1.000
1.987
ppm


153.317
131.905
128.742
82.089
80.681
78.472
72.896
40.892
28.798
27.768
27.099
26.442
21.345
20.500
14.337
OBoc
O
83
100 MHz, CDCl3
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190

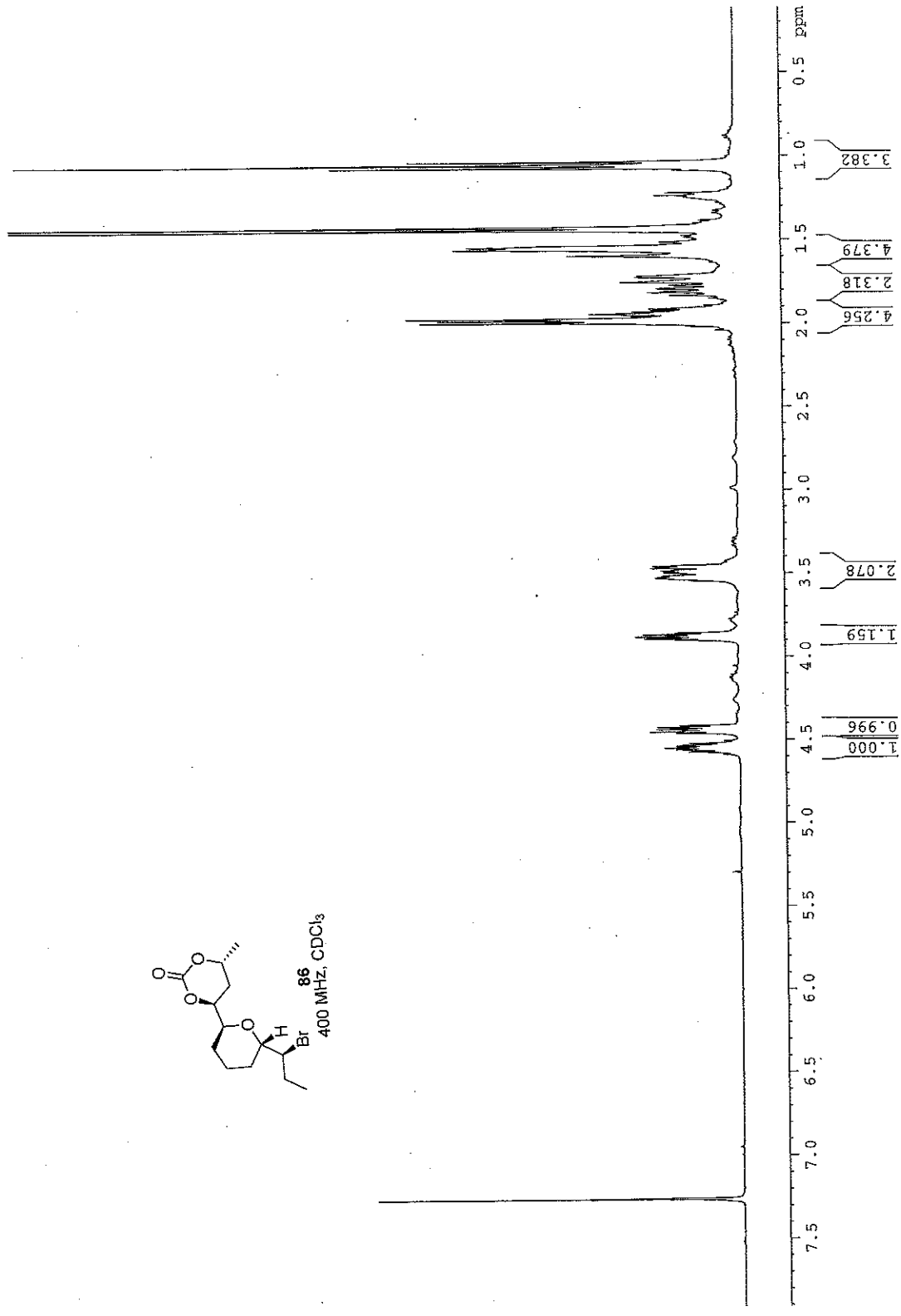

1.046
1.064
1.082
1.328
1.344
2.561
2.577
2.590
2.597
2.606
2.613
2.626
2.642
4.793
4.810
4.827
4.844
4.945
4.950
4.961
4.967
4.974
4.980
4.990
4.996
3.261
3.136
4.059
5.100
1.037
1.057
2.016
1.009
1.000
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
O
O
O
O
H
Br
85
400 MHz, CDCl3

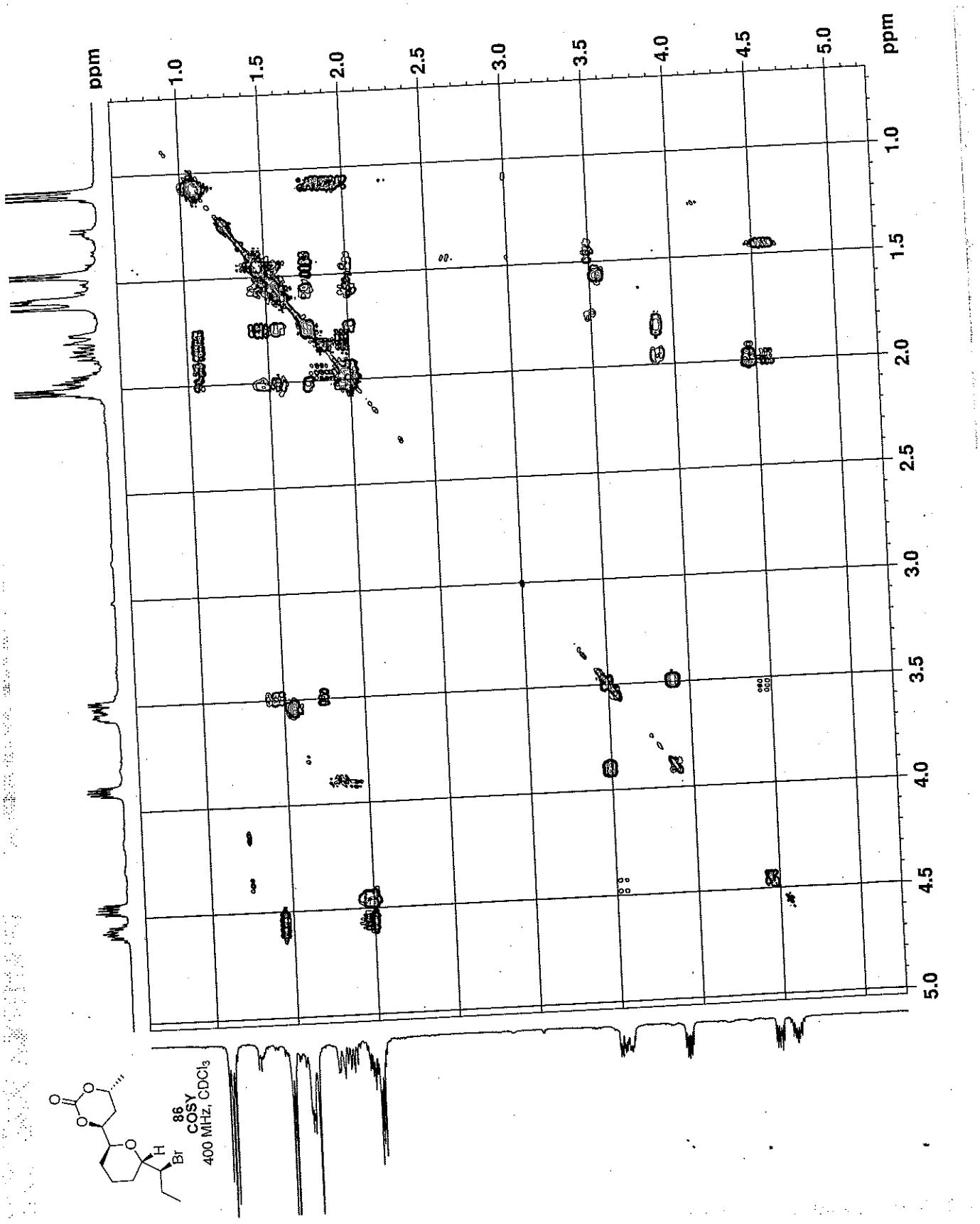

154.588
83.323
80.880
76.747
73.940
60.735
33.874
28.102
27.094
26.757
21.735
20.087
12.534
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
Br
H
85
100 MHz, CDCl3

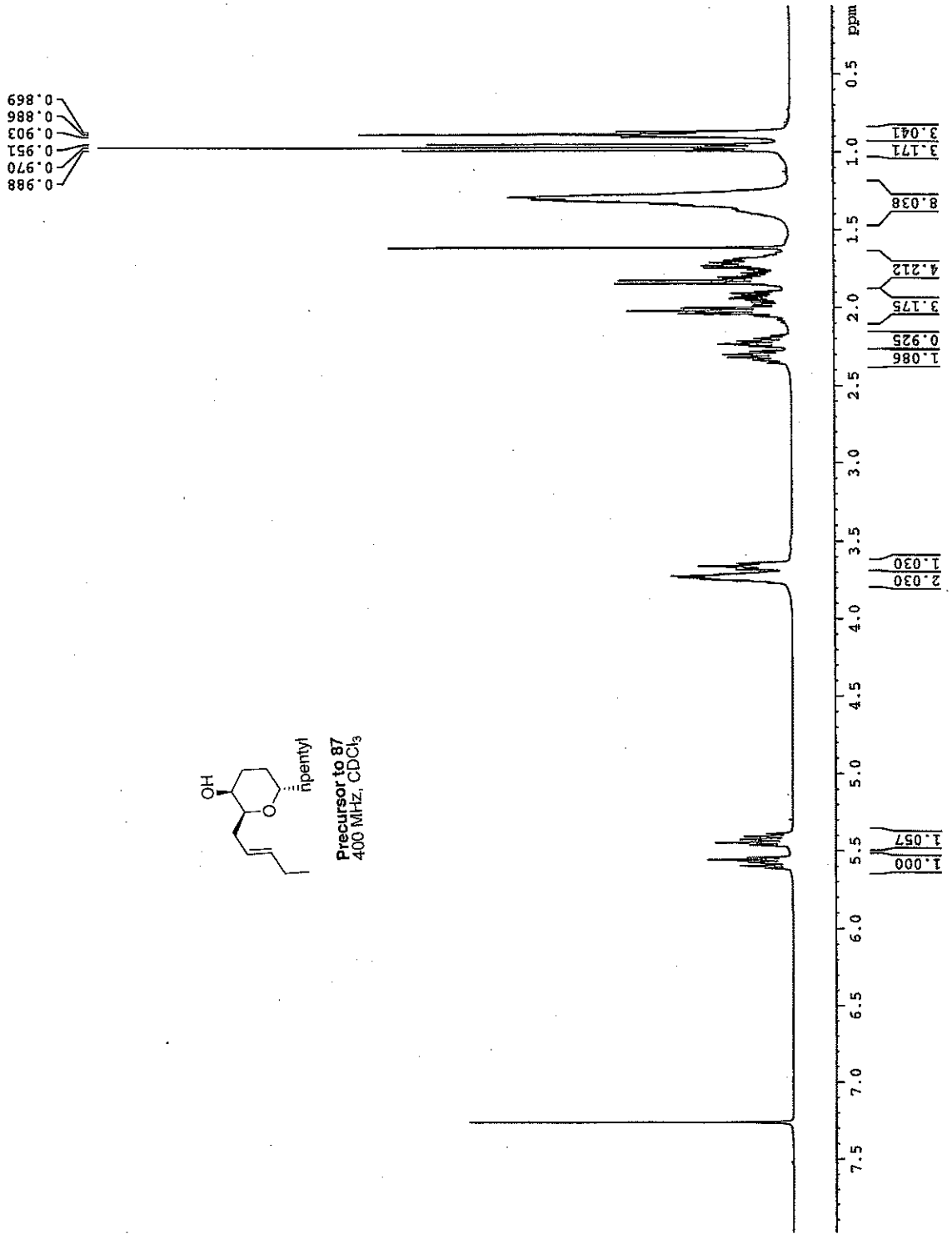

Diol Derivative of 85
400 MHz, CDCl3
OH
OH
O
H
Br
1.287
1.270
1.079
1.061
1.043
2.293
2.282
2.269
2.256
2.244
2.232
2.220
2.123
3.510
3.505
3.499
3.494
3.484
3.479
3.474
3.469
3.449
3.455
10.666
0.905
1.105
1.043
2.092
1.105
1.000
ppm

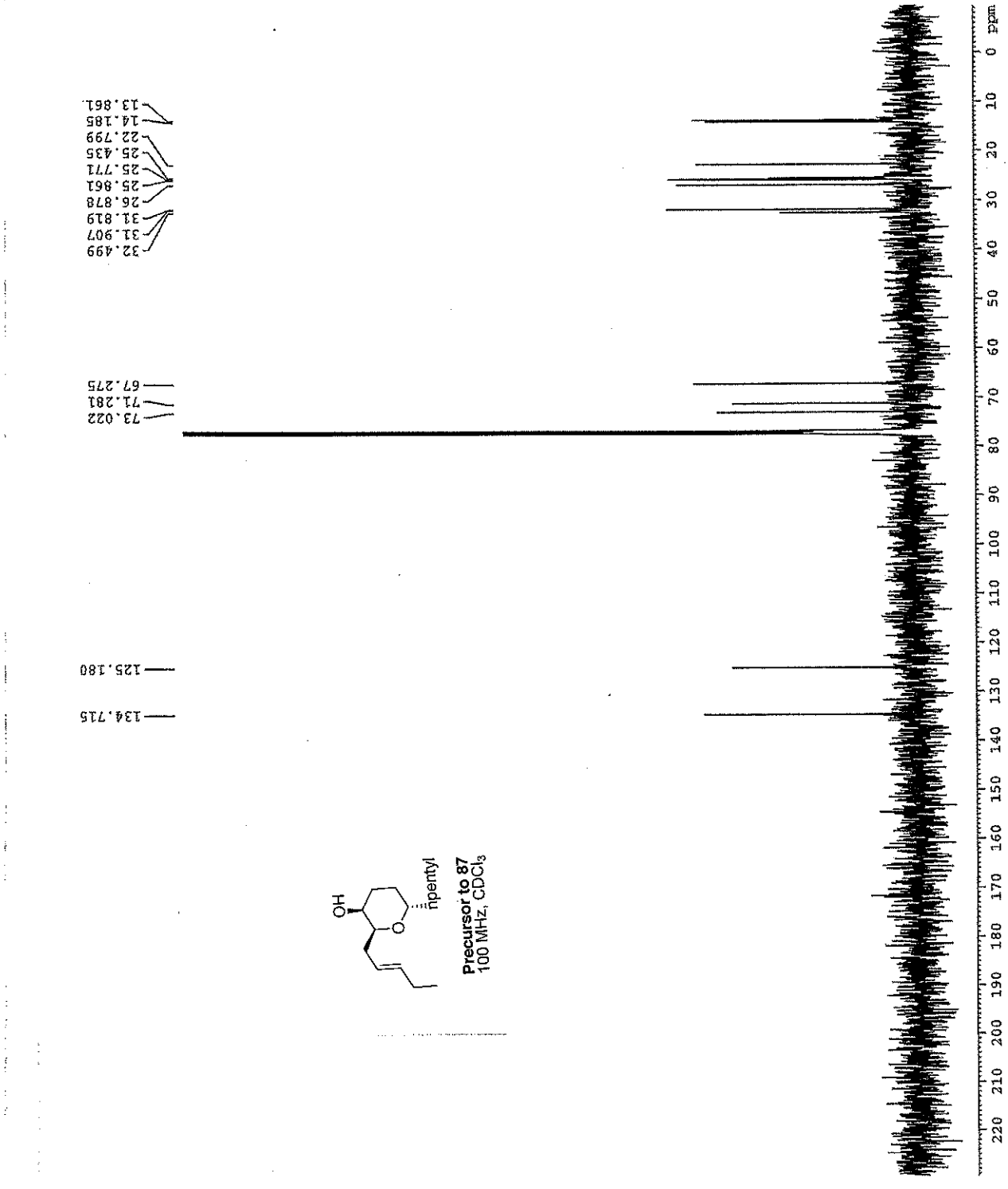


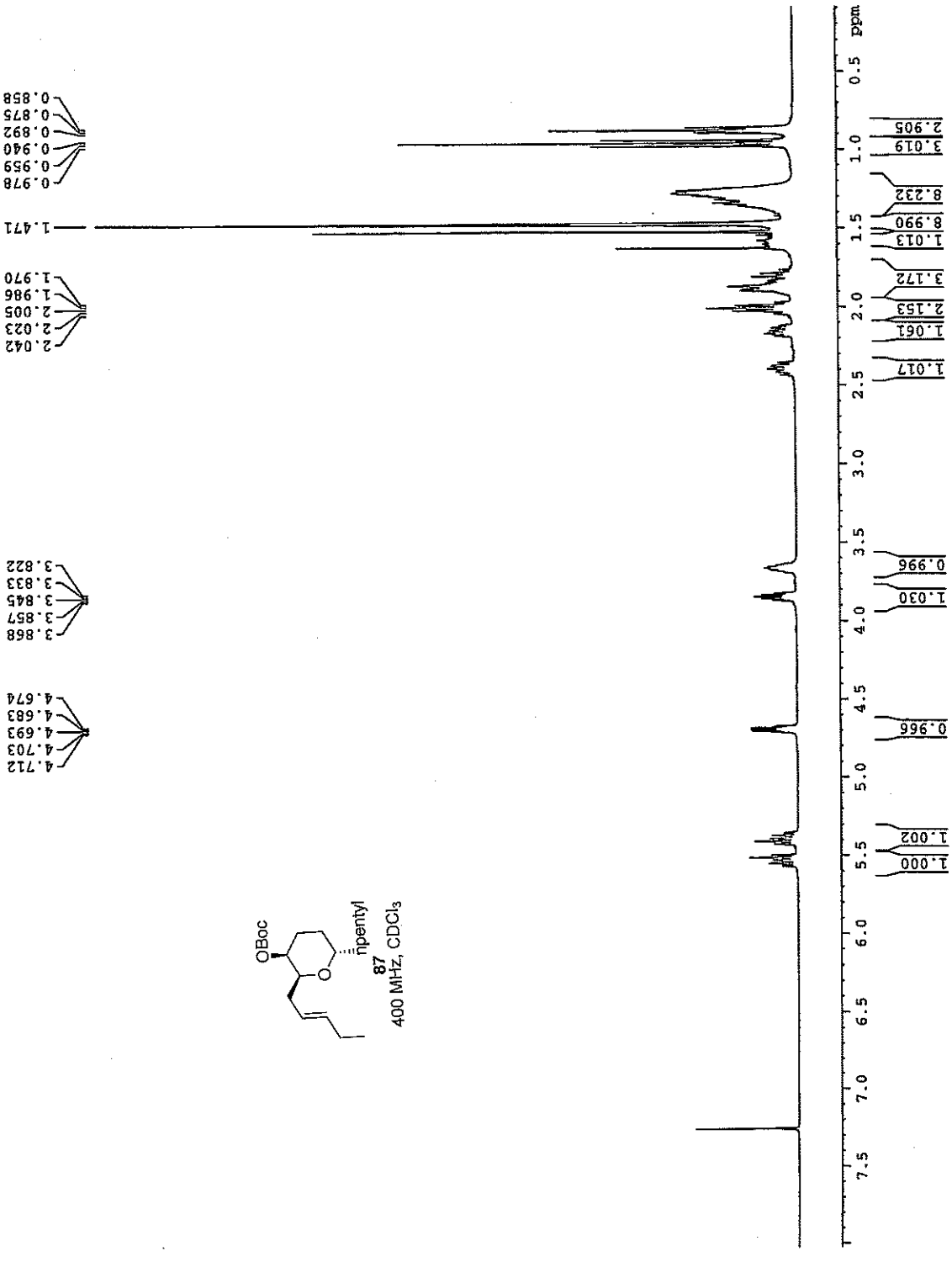
Diol Derivative of 85
100 MHz, $CDCl_3$

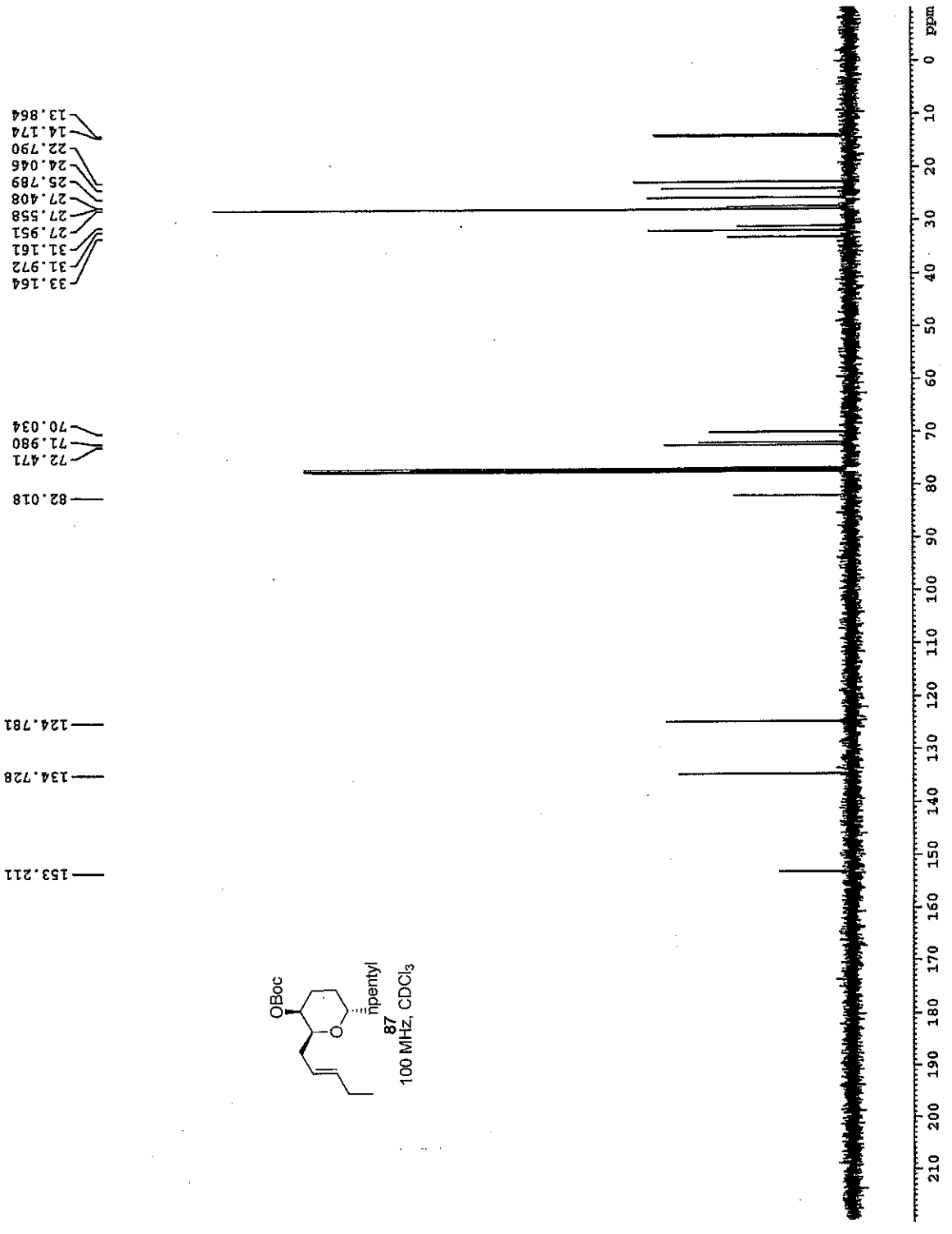

86
400 MHz, CDCl3
Br
H
O
O
O
O
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
3.382
4.379
2.318
4.256
2.078
1.159
0.996
1.000

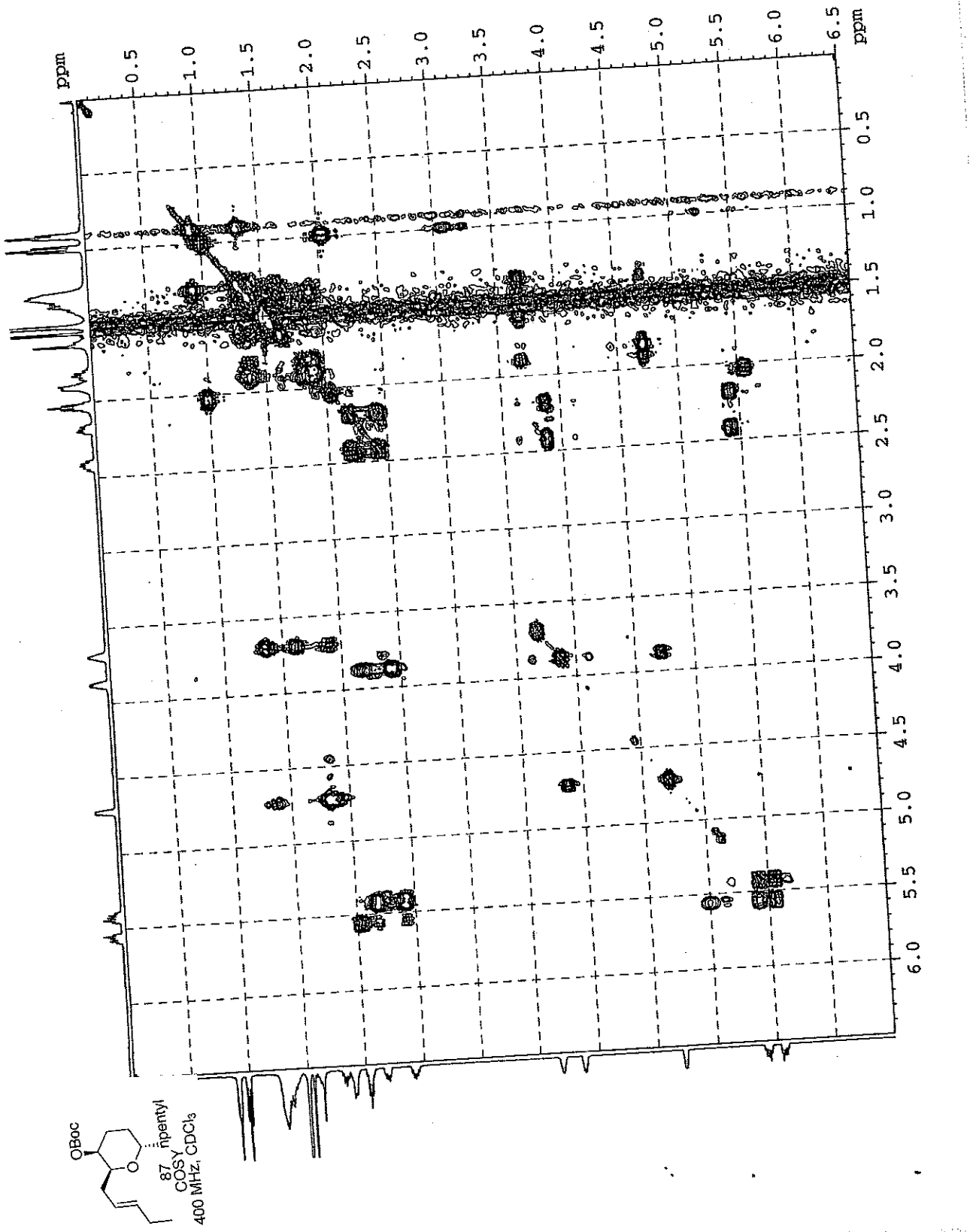

ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
86
COSY
400 MHz, CDCl3
H
Br

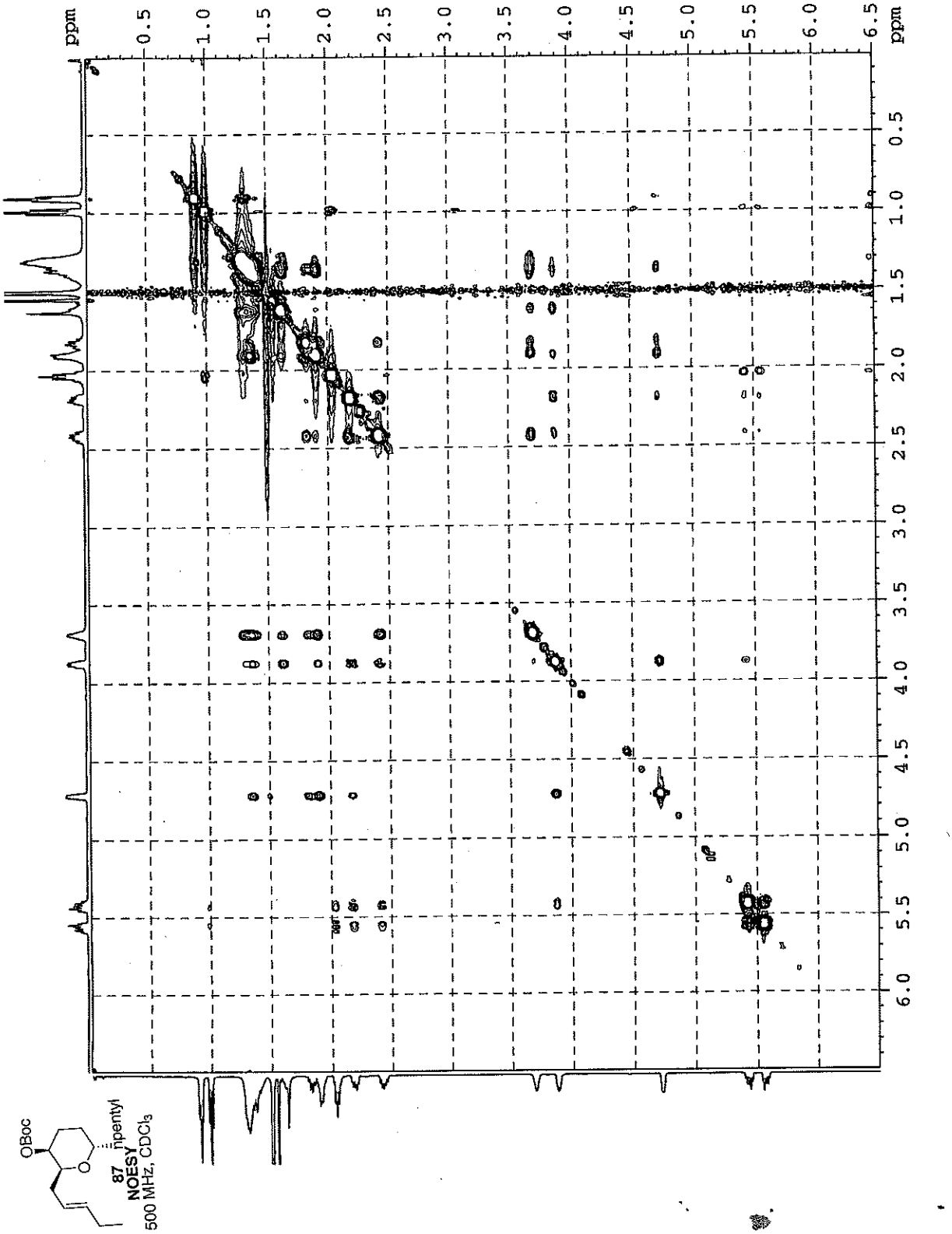

0.869
0.886
0.903
0.951
0.970
0.988
3.041
3.171
8.038
4.212
3.175
0.925
1.086
1.030
2.030
1.057
1.000
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
OH
O
npentyl
Precursor to 87
400 MHz, CDCl3

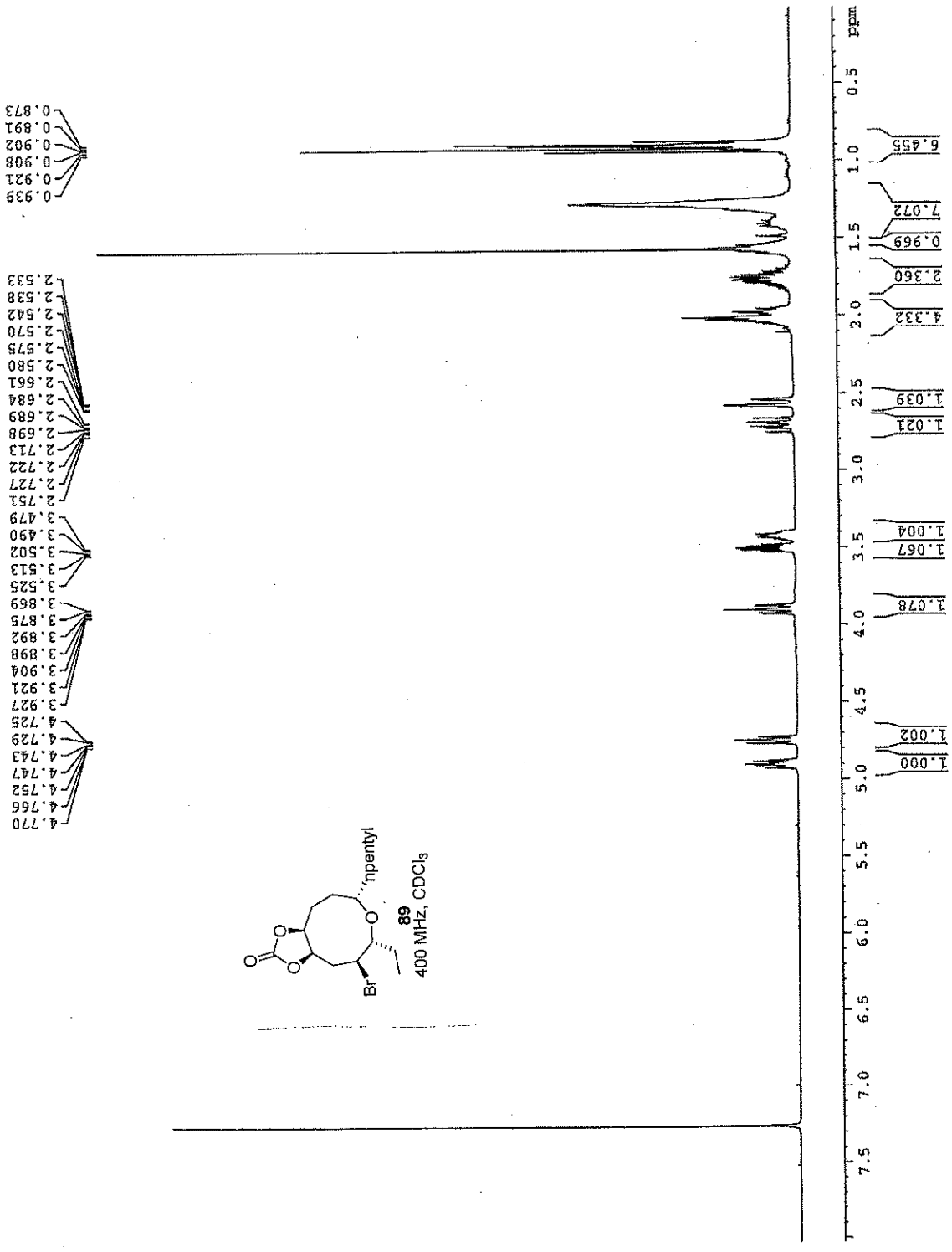

13.861
14.185
22.799
25.435
25.771
25.861
26.878
31.819
31.907
32.499
67.275
71.281
73.022
125.180
134.715
OH
npentyl
Precursor to 87
100 MHz, CDCl3
0 ppm

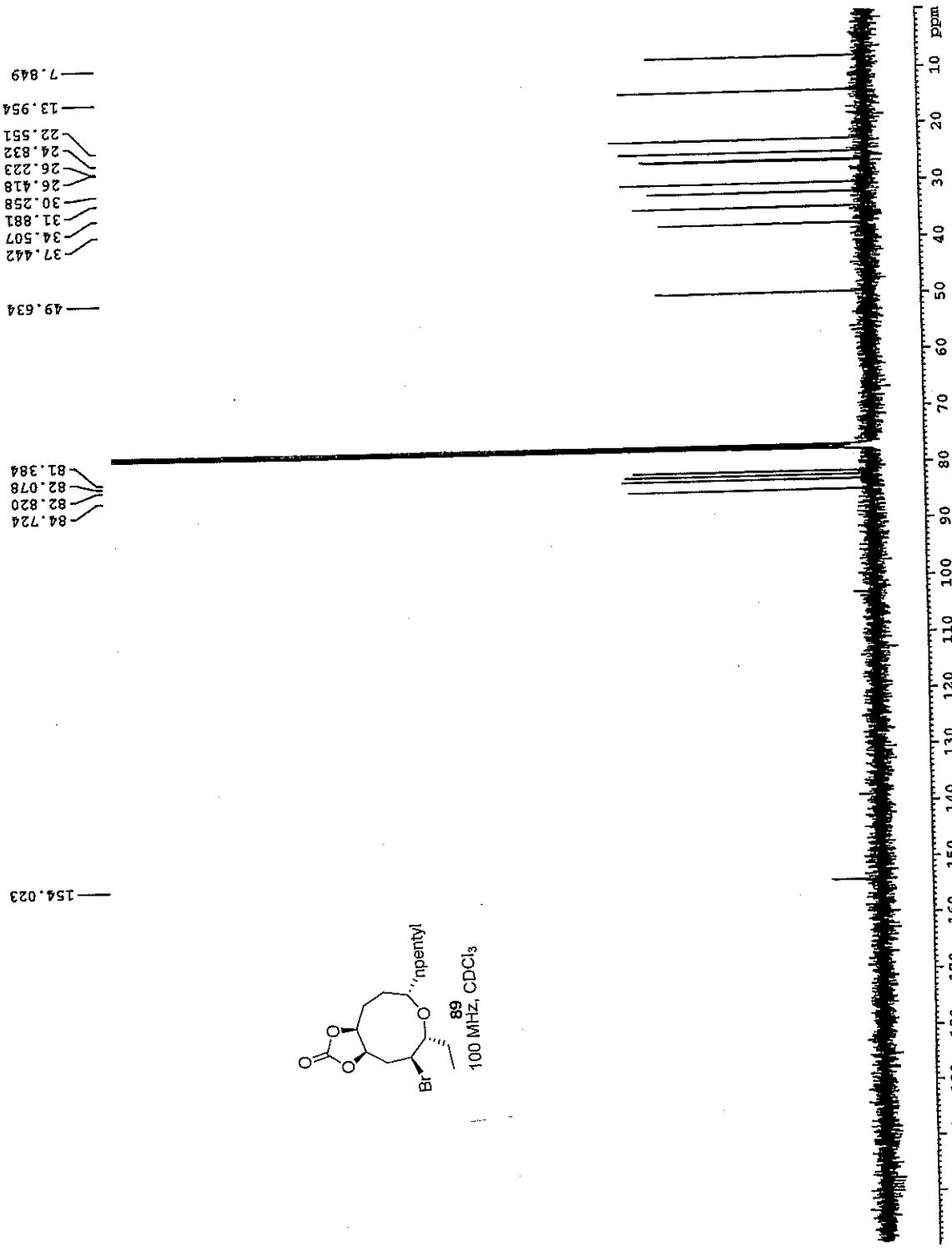

OBoc
npentyl
87
400 MHz, CDCl3
0.858
0.875
0.892
0.940
0.959
0.978
1.471
1.970
1.986
2.005
2.023
2.042
3.822
3.833
3.845
3.857
3.868
4.674
4.683
4.693
4.703
4.712
1.000
1.002
0.966
1.030
0.996
1.017
1.061
2.153
3.172
1.013
8.990
8.232
3.019
2.905
ppm

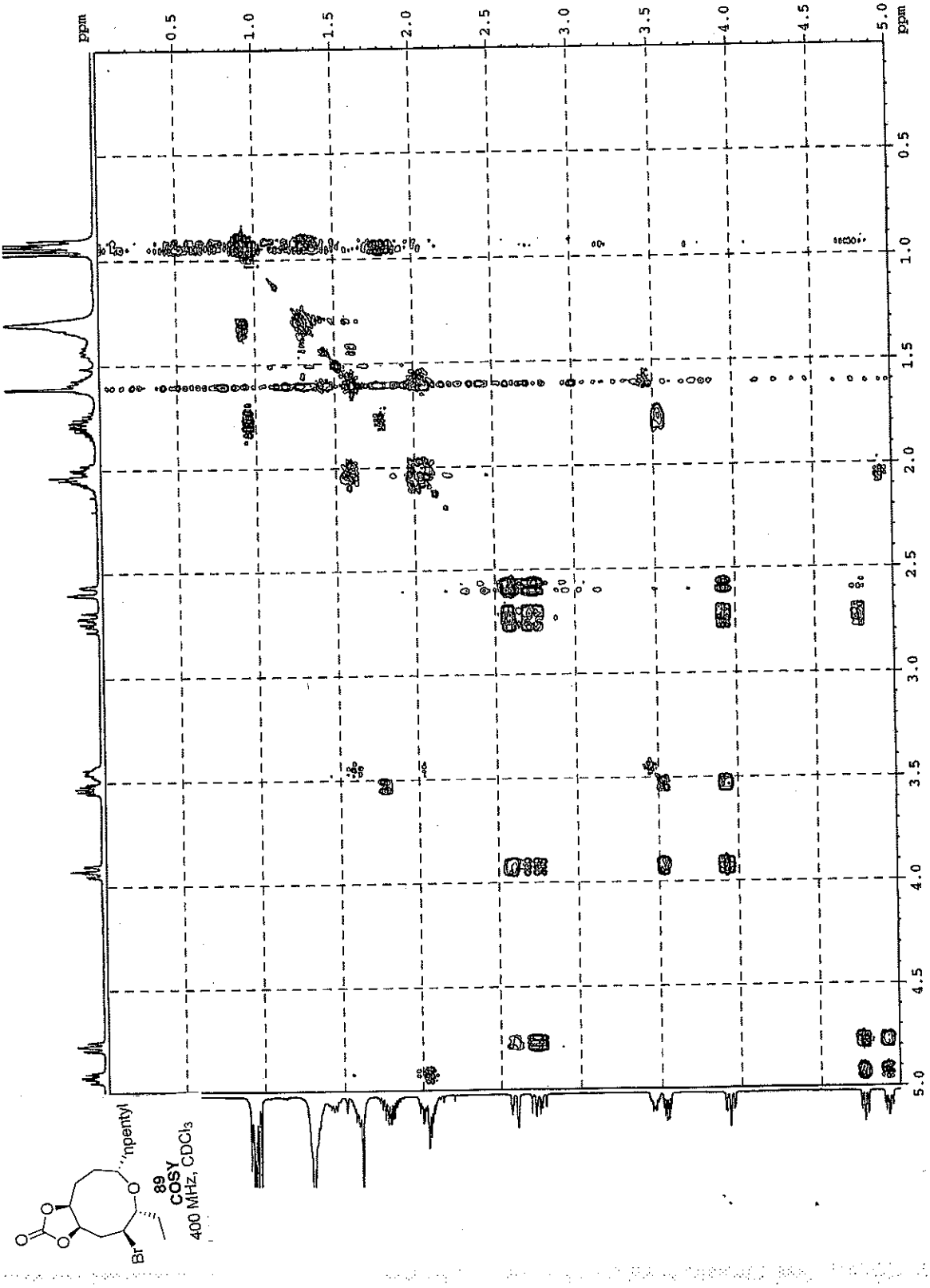

OBoc
npentyl
87
100 MHz, CDCl3
153.211
134.728
124.781
82.018
72.471
71.980
70.034
33.164
31.972
31.161
27.951
27.558
27.408
25.789
24.046
22.790
14.174
13.864
ppm

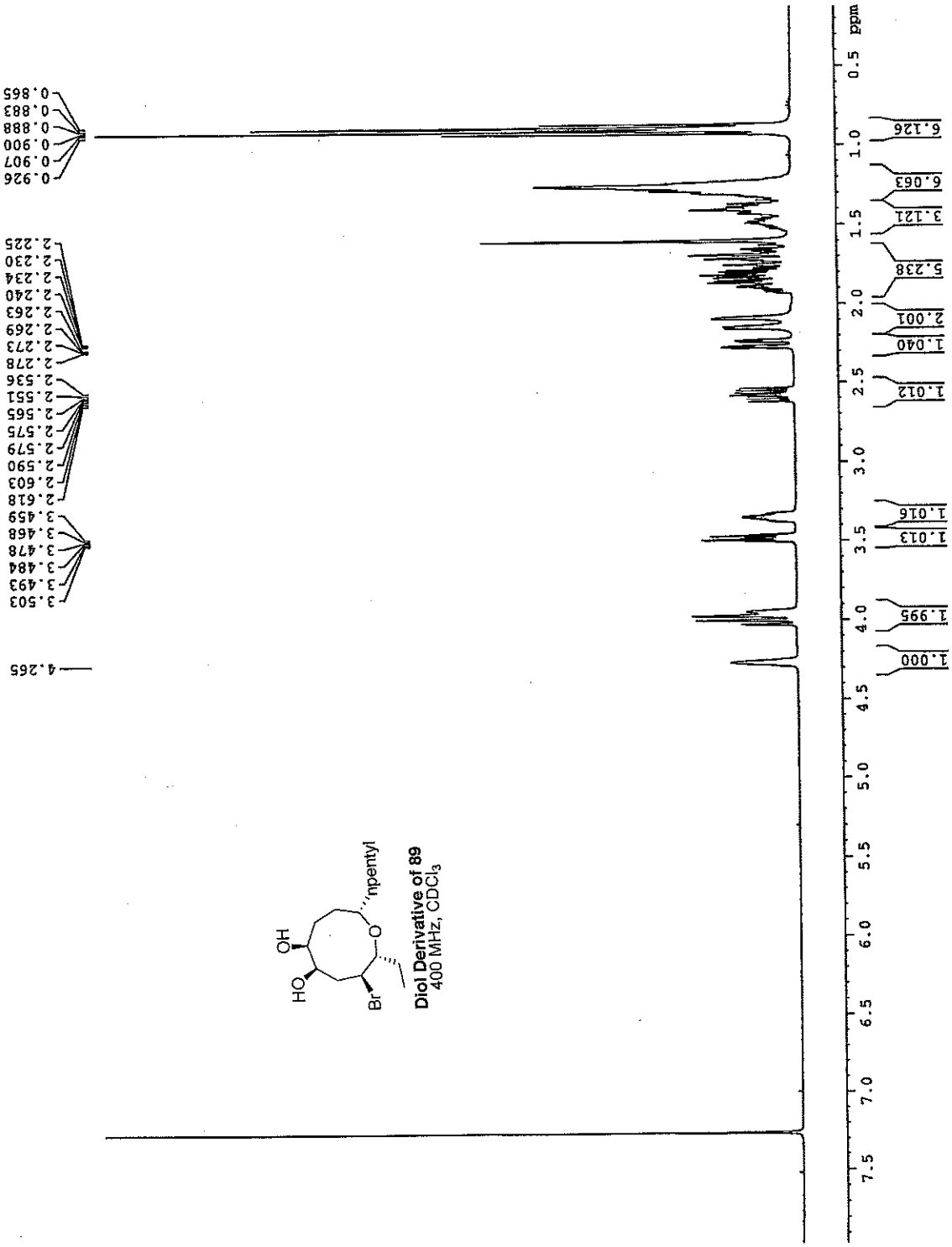

ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
OBoc
npentyl
87
COSY
400 MHz, CDCl3

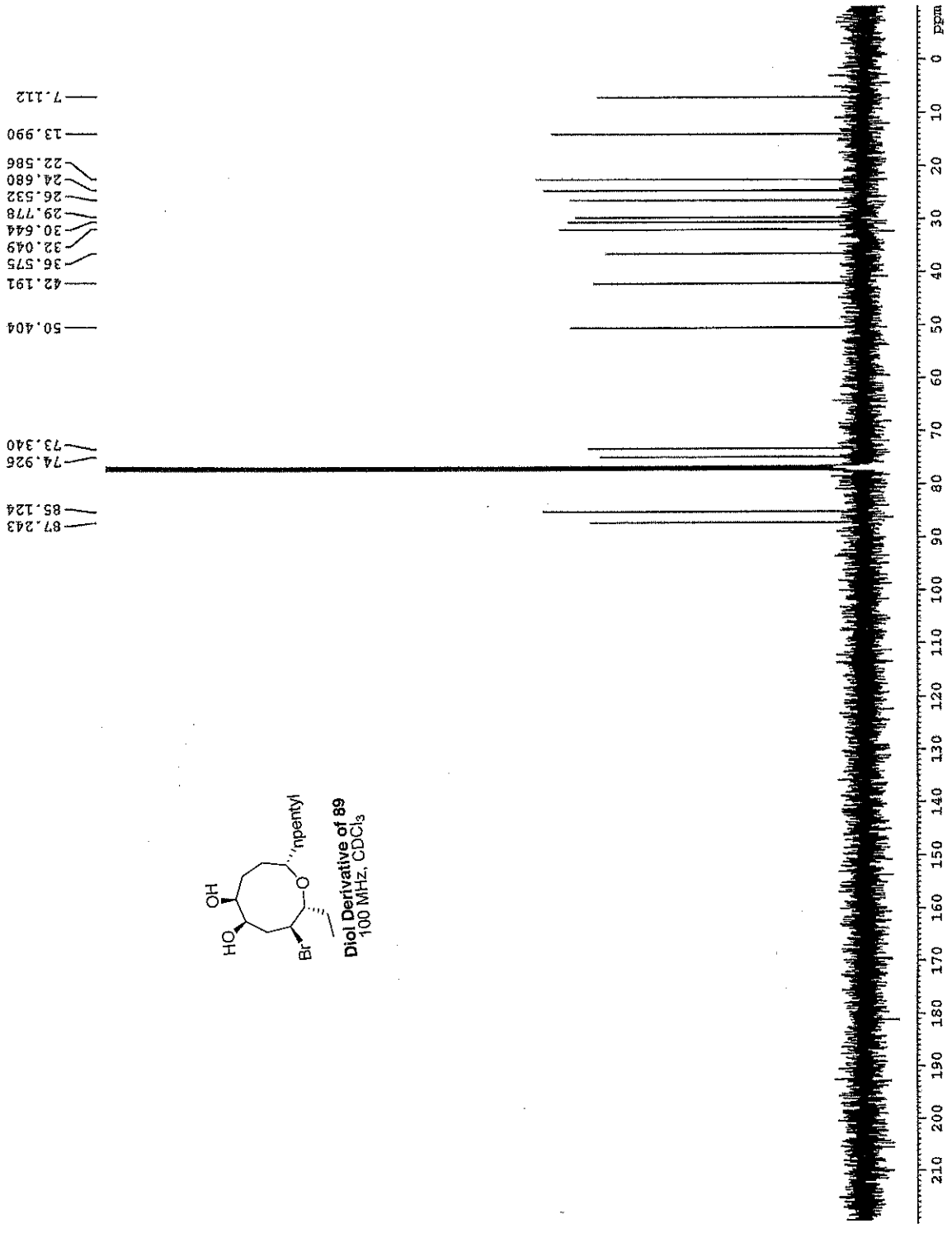

ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
OBoc
87 ipentyl
NOESY
500 MHz, CDCl3


89
400 MHz, CDCl3
npentyl
Br
ppm

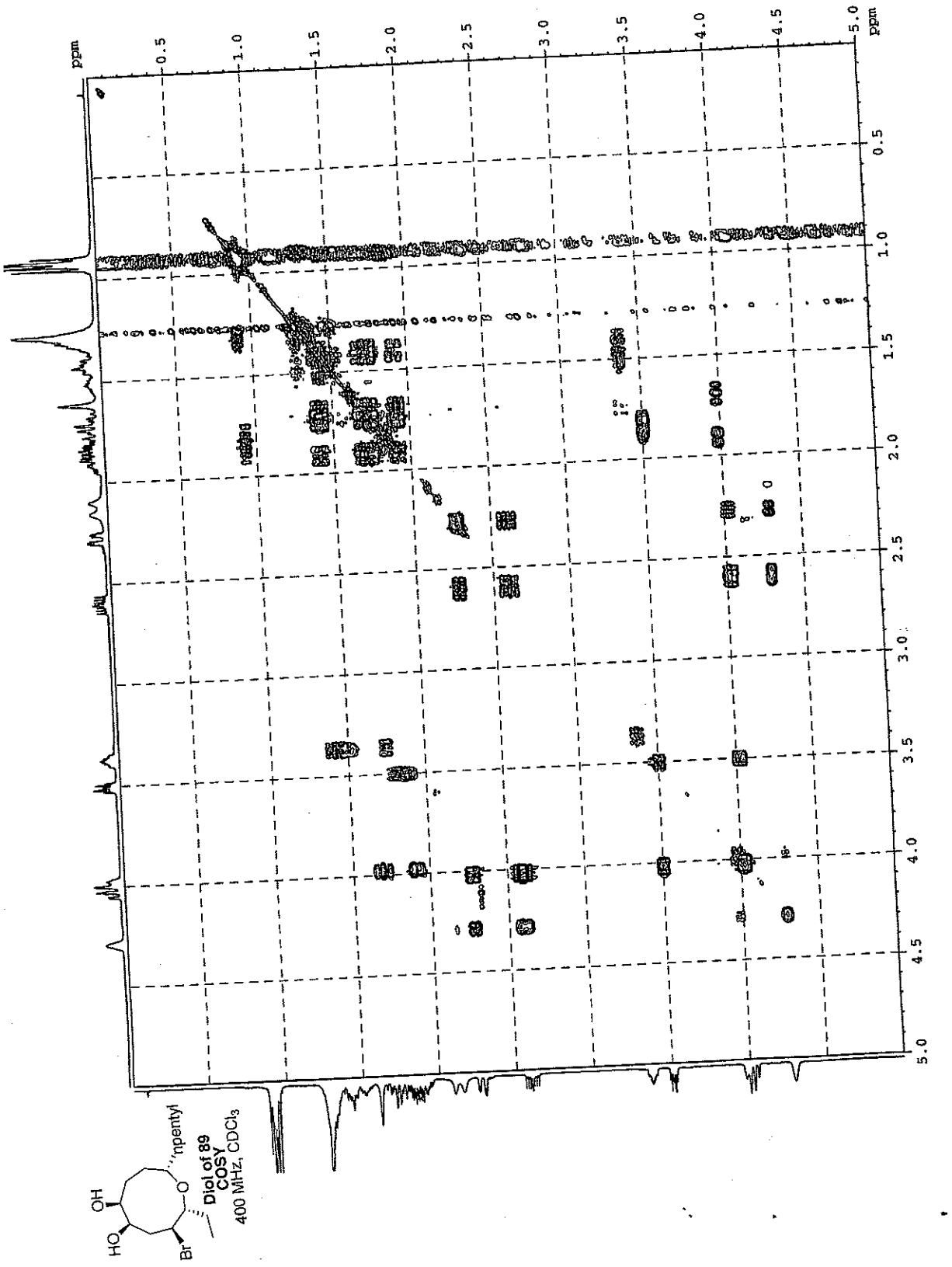

154.023
84.724
82.820
82.078
81.384
49.634
37.442
34.507
31.881
30.258
26.418
26.223
24.832
22.551
13.954
7.849
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
npentyl
O
O
O
O
Br
89
100 MHz, CDCl3

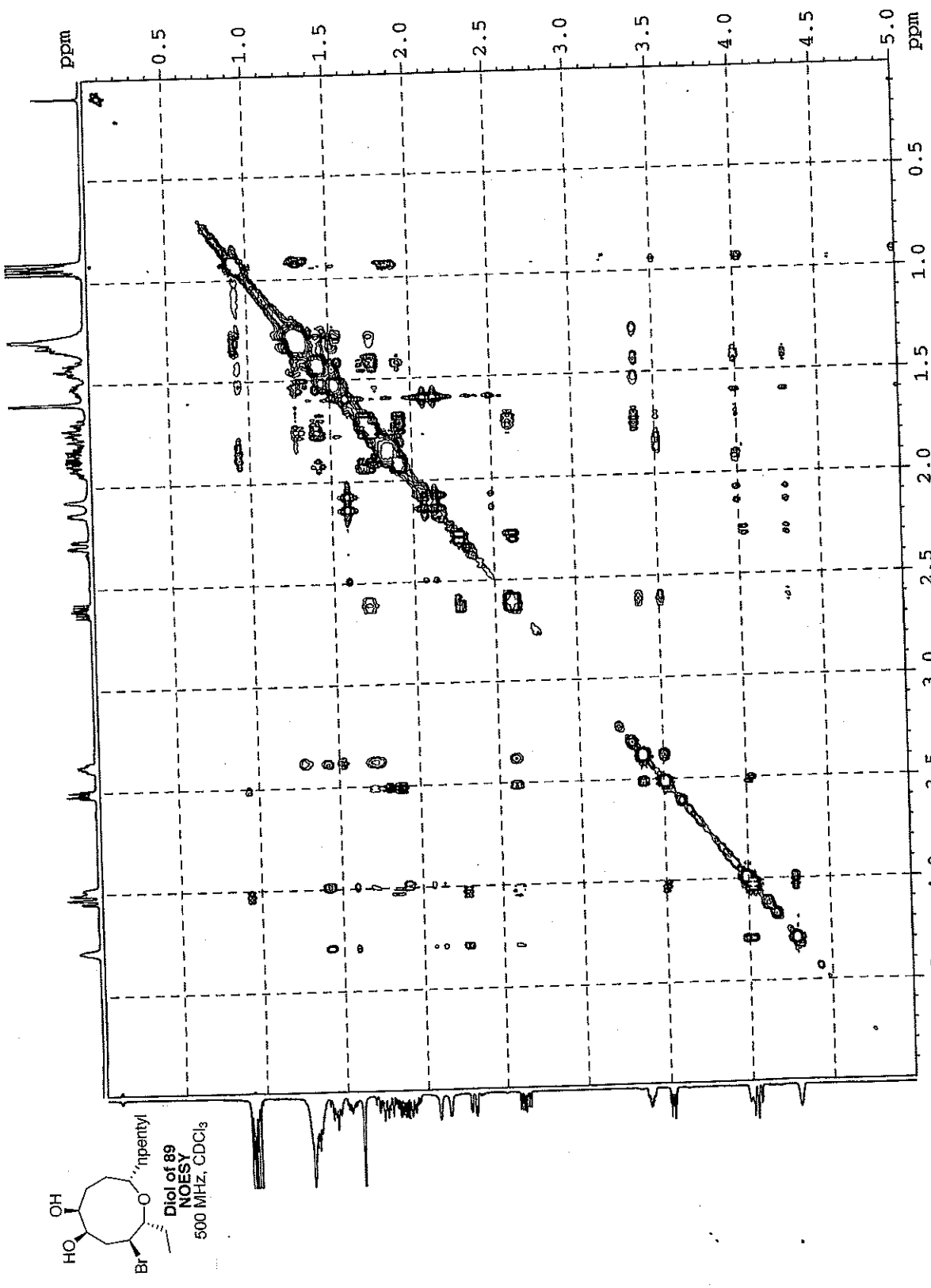

ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
npentyl
Br
89
COSY
400 MHz, CDCl3

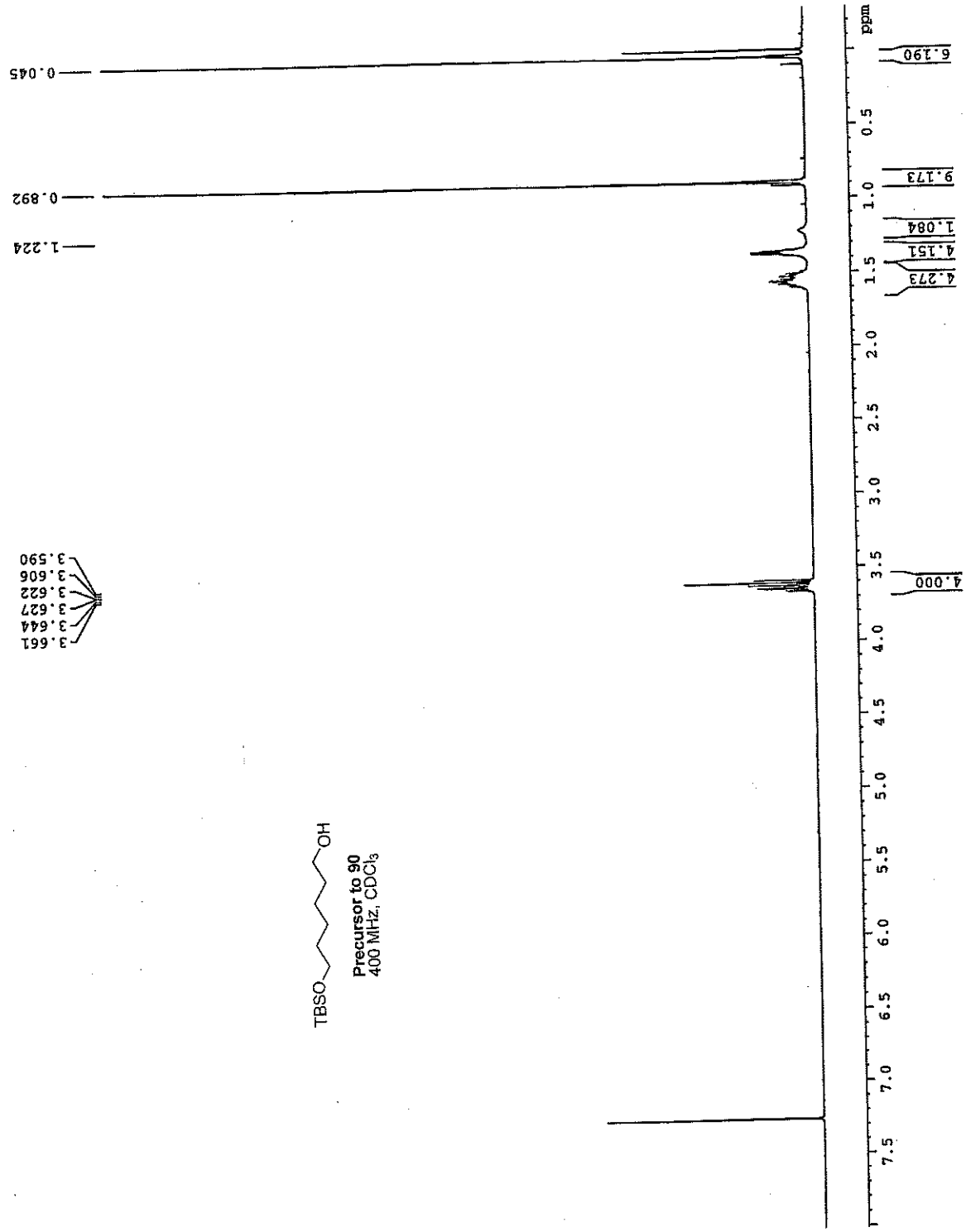

0.865
0.883
0.888
0.900
0.907
0.926
2.225
2.230
2.234
2.240
2.263
2.269
2.273
2.278
2.536
2.551
2.565
2.575
2.579
2.590
2.603
2.618
3.459
3.468
3.478
3.484
3.493
3.503
4.265
6.126
6.063
3.121
5.238
2.001
1.040
1.012
1.016
1.013
1.995
1.000
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
ppm
OH
HO
Br
O
npentyl
Diol Derivative of 89
400 MHz, CDCl3

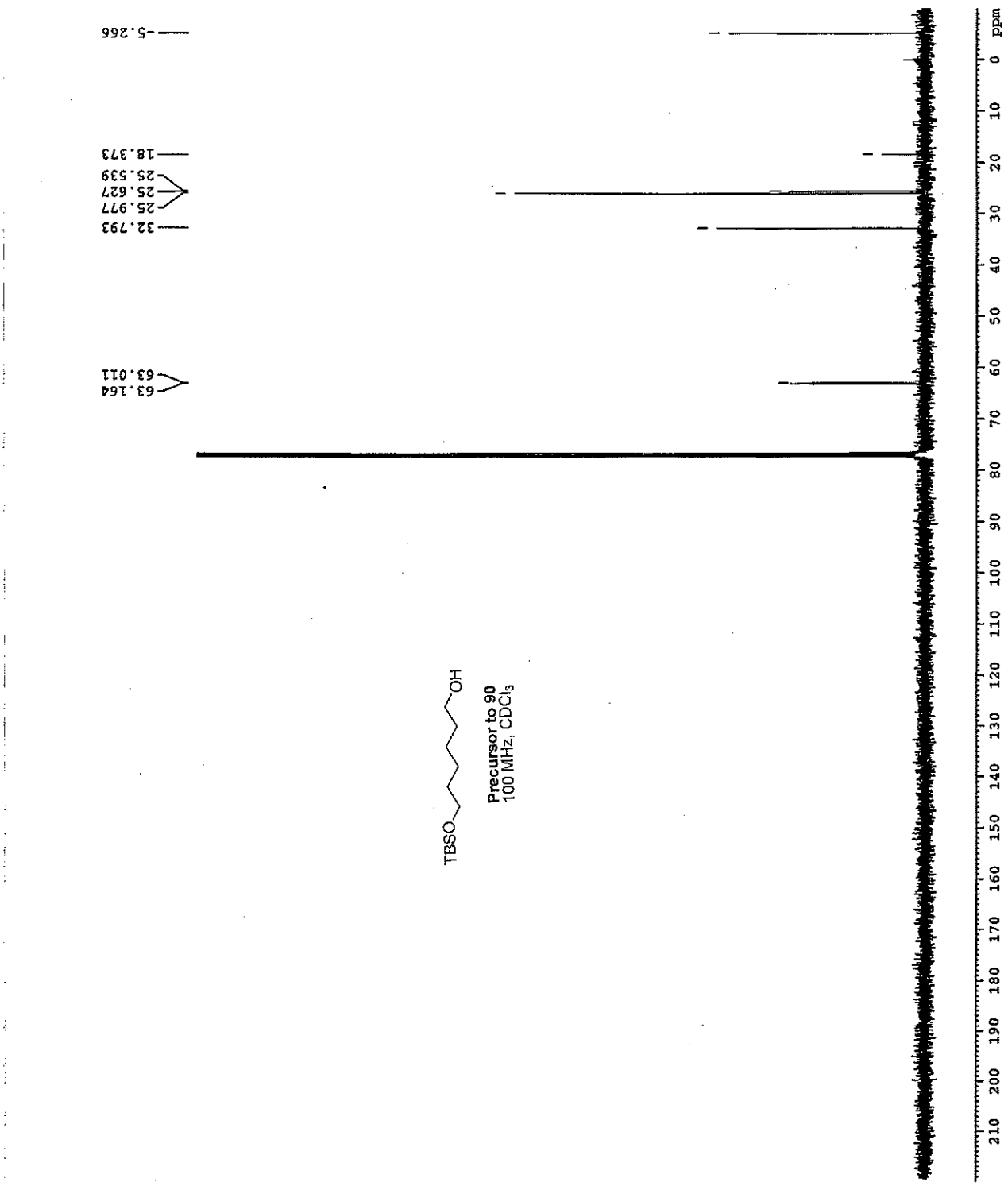


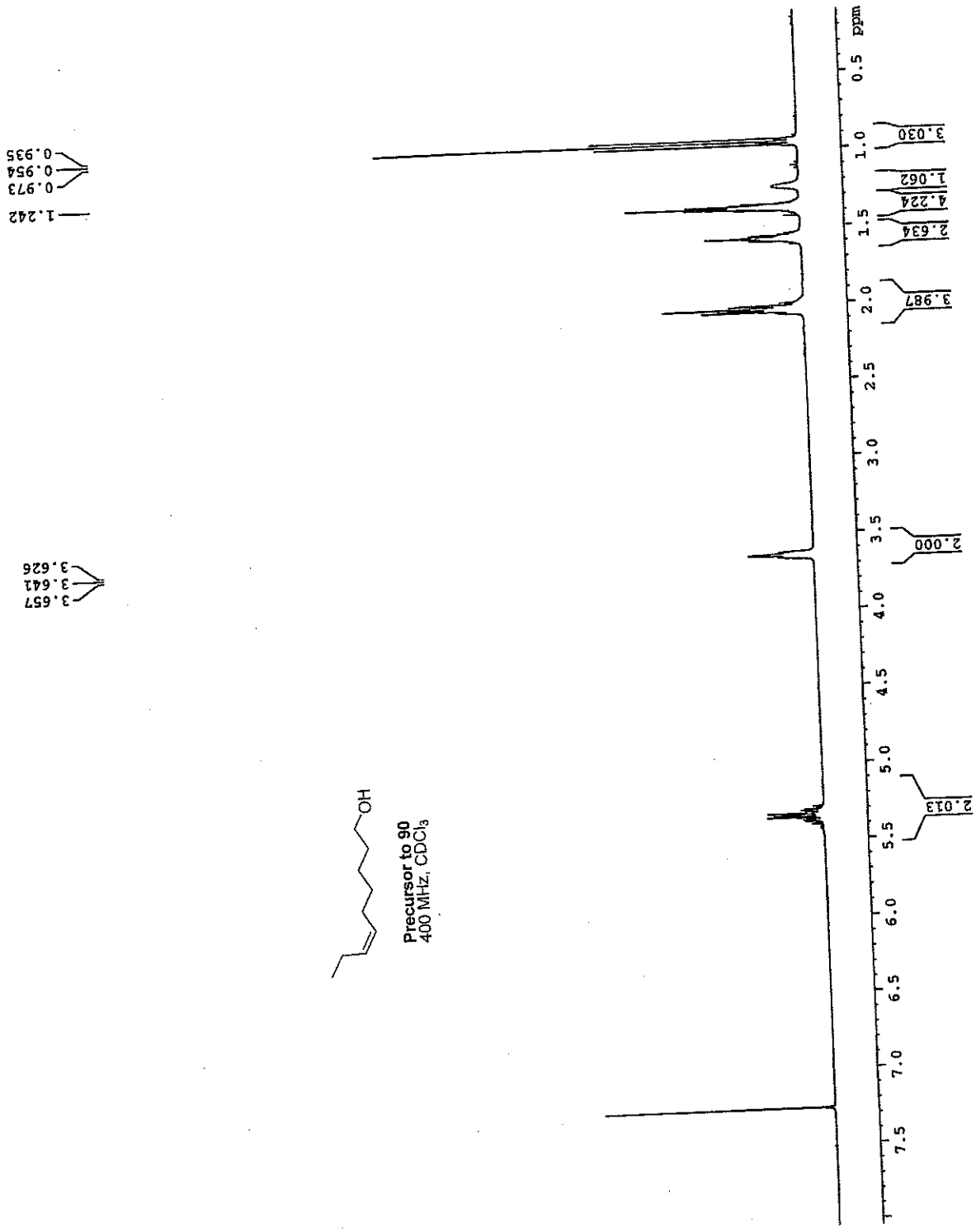
Diol Derivative of 89
100 MHz, $CDCl_3$

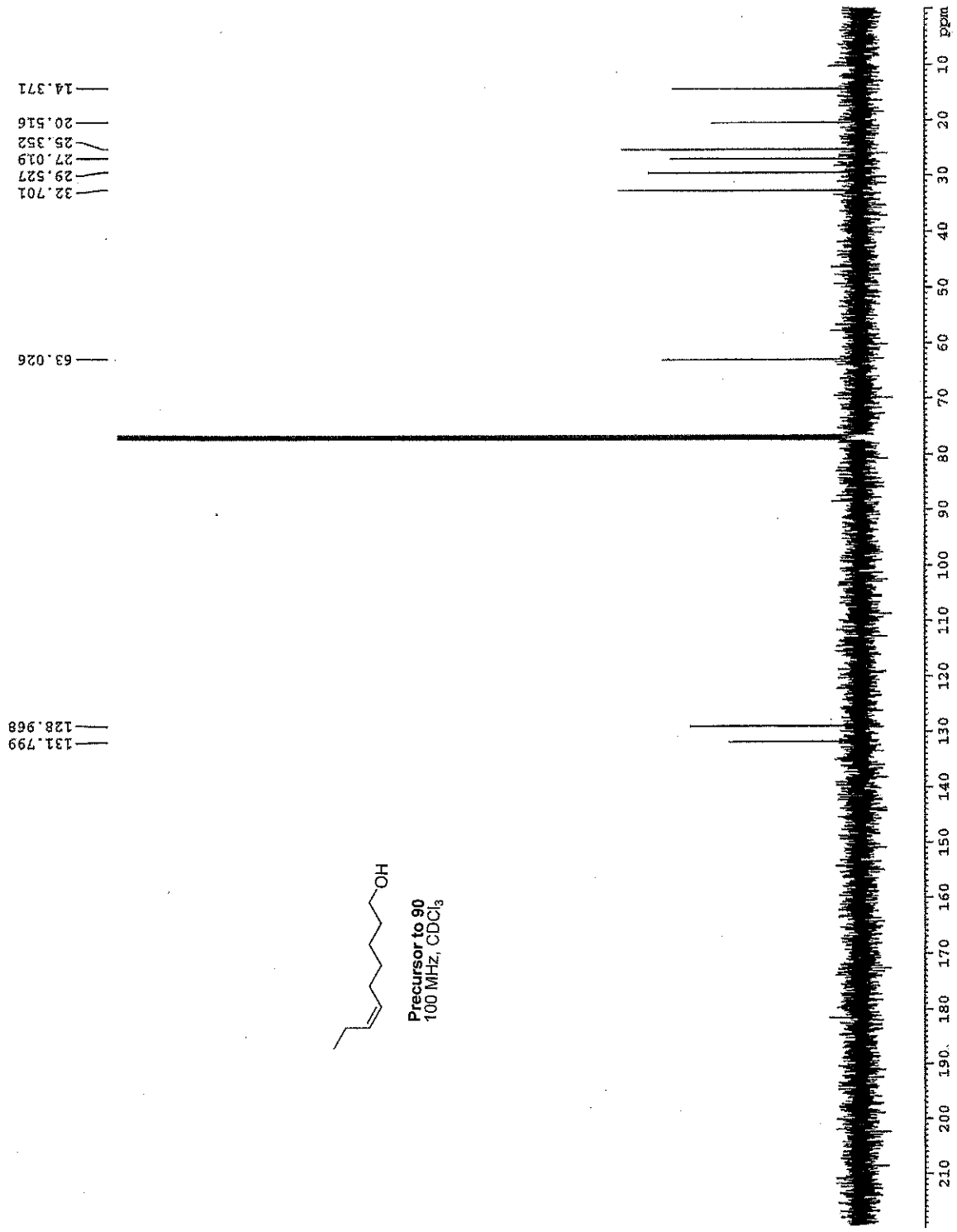

ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
OH
HO
Br
O
npentyl
Diol of 89
COSY
400 MHz, CDCl3

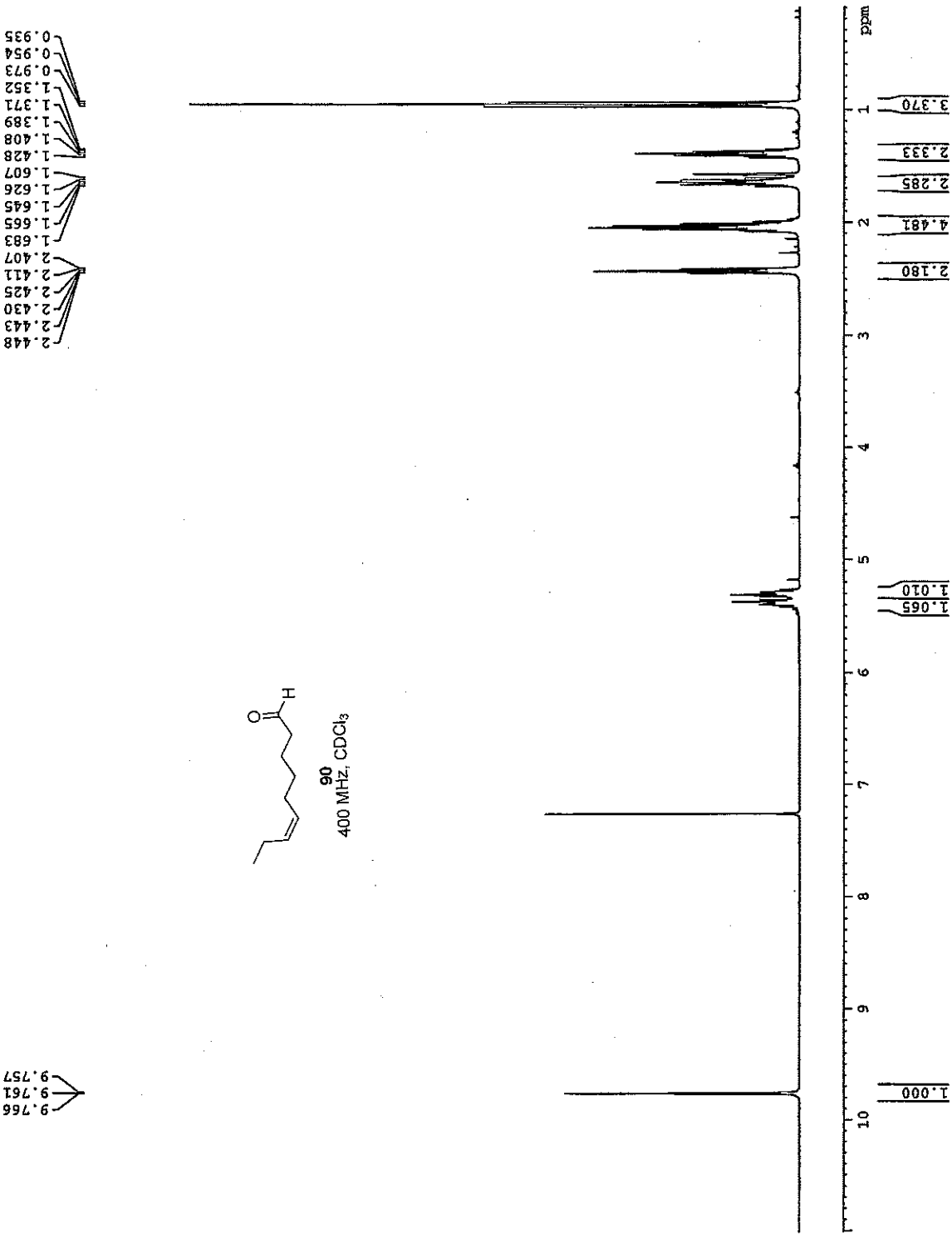

ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
OH
HO
Br
O
npentyl
Diol of 89
NOESY
500 MHz, CDCl3

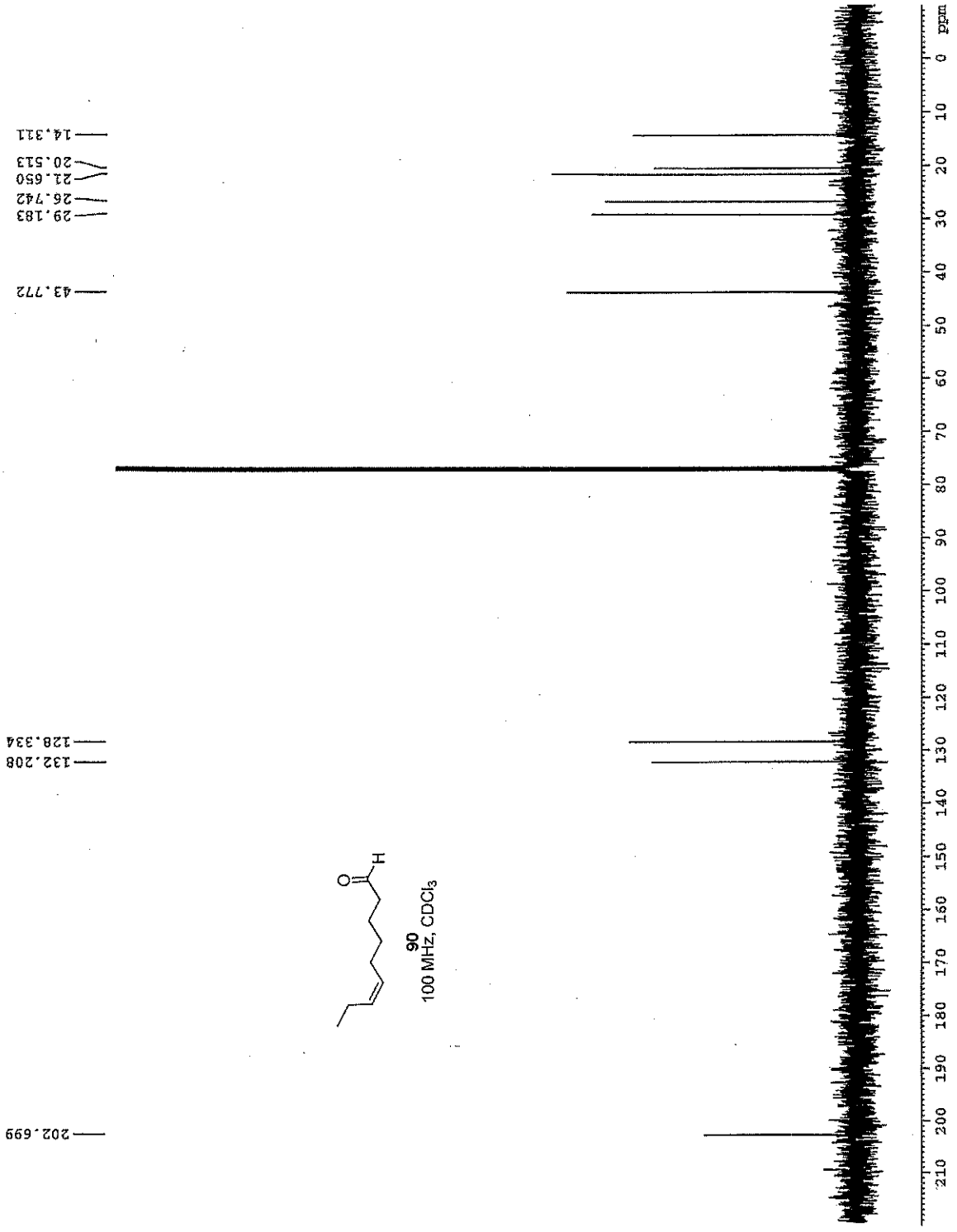

TBSO
OH
Precursor to 90
400 MHz, CDCl3
0.045
0.892
1.224
3.590
3.606
3.622
3.627
3.644
3.661
6.190
9.173
1.084
4.151
4.273
4.000
ppm

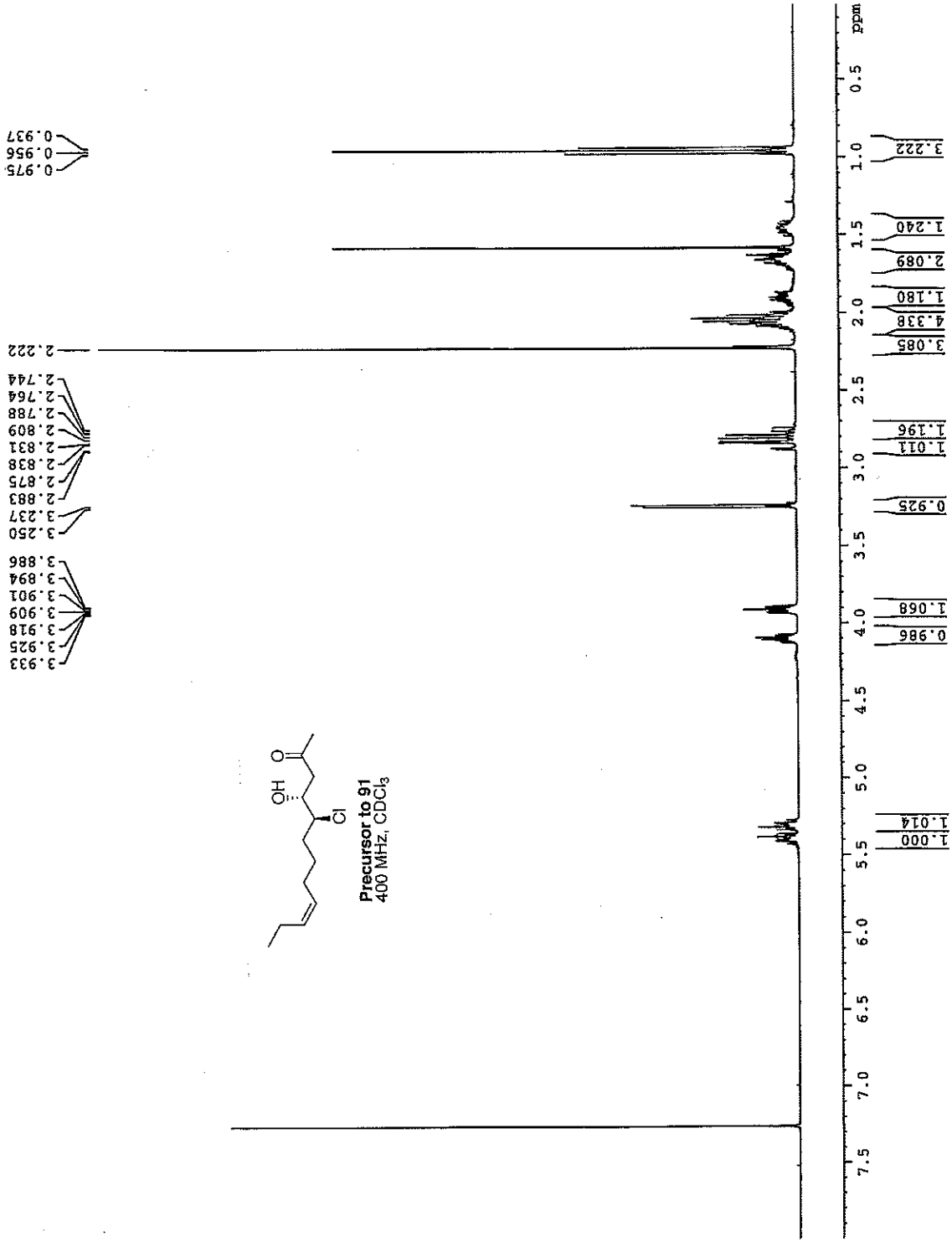

-5.266
18.373
25.539
25.627
25.977
32.793
63.011
63.164
TBSO
OH
Precursor to 90
100 MHz, CDCl3
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

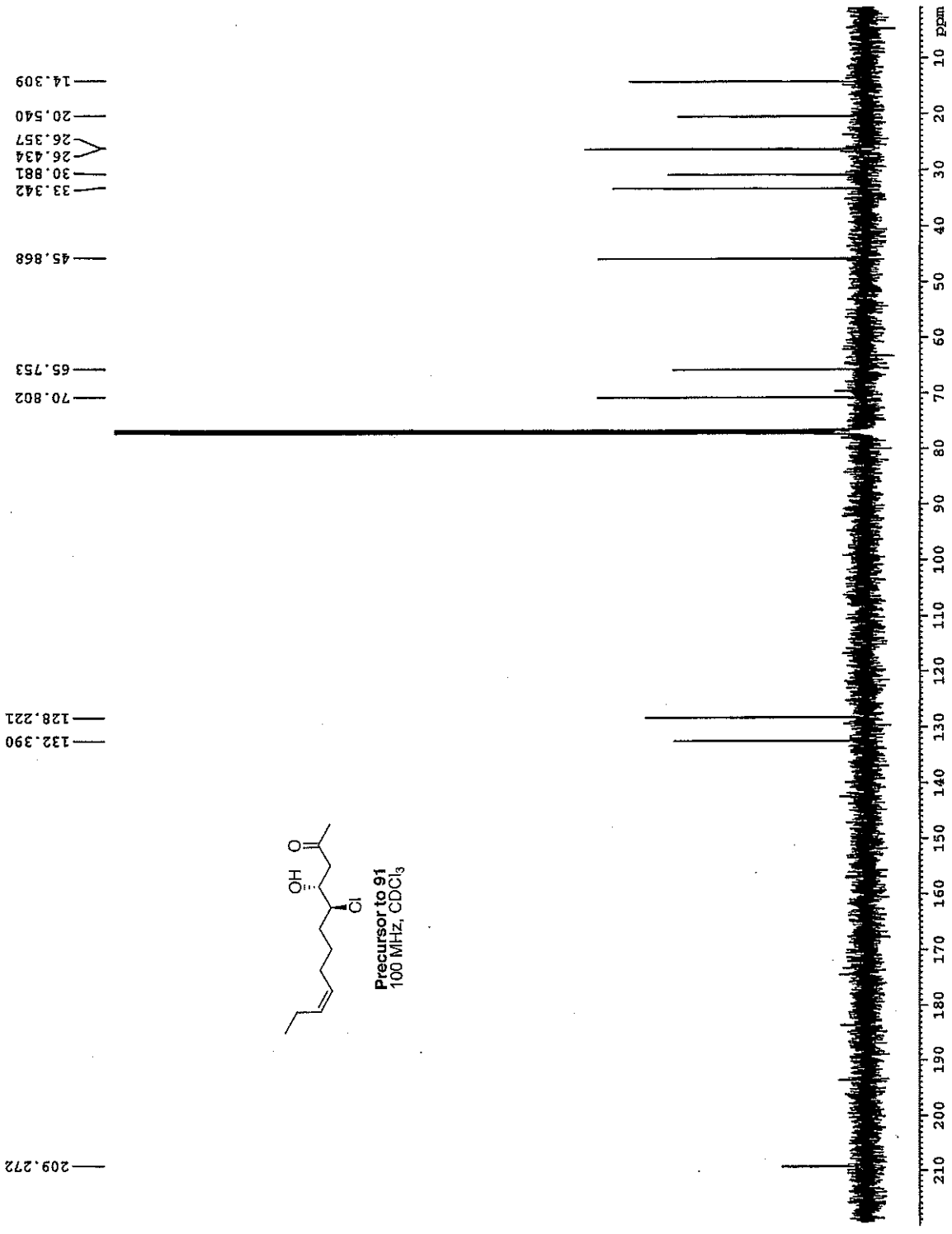

Precursor to 90
400 MHz, CDCl3
OH
3.657
3.641
3.626
1.242
0.973
0.954
0.935
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
3.030
1.062
4.224
2.634
3.987
2.000
2.013

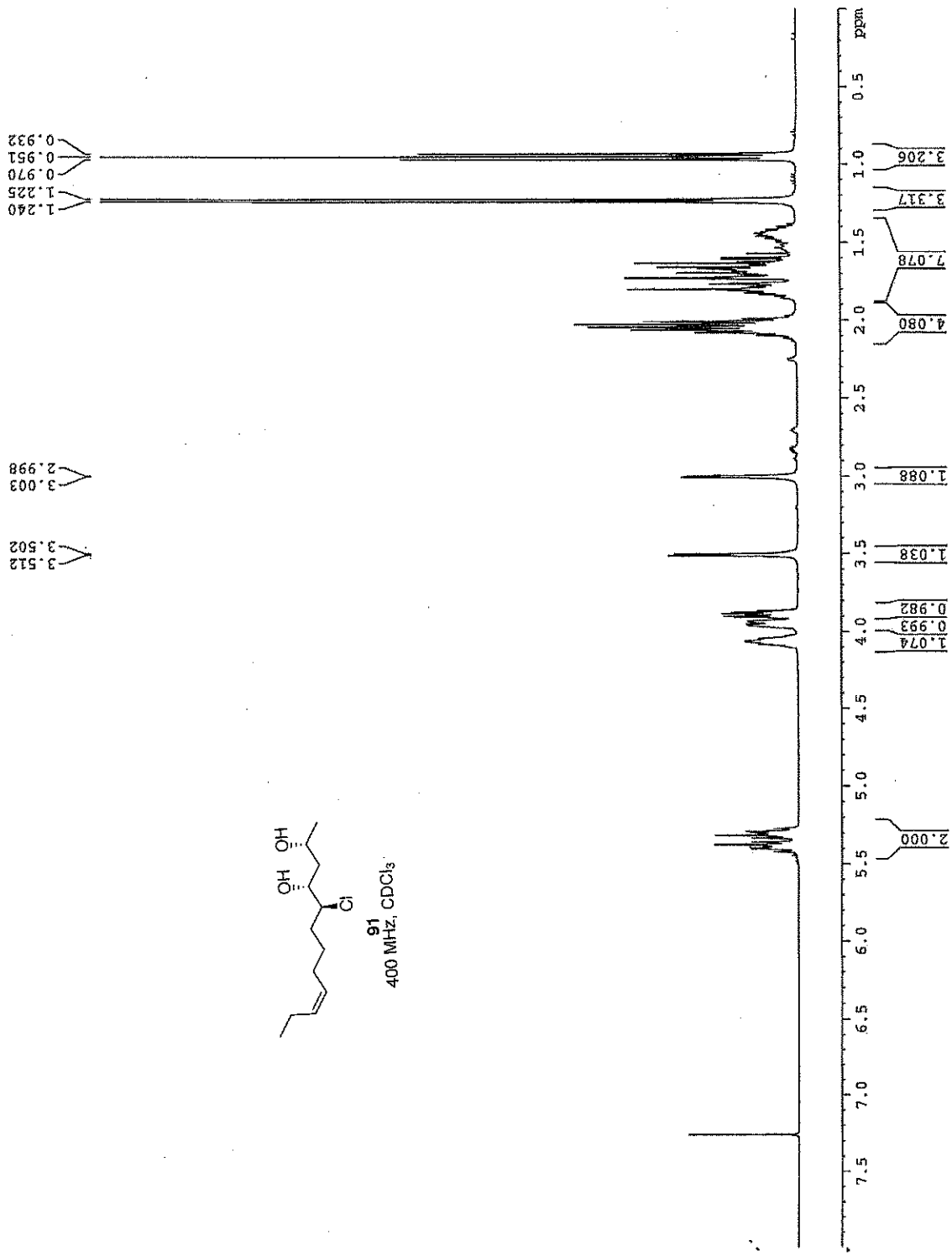

14.371
20.516
25.352
27.019
29.527
32.701
63.026
128.968
131.799
OH
Precursor to 90
100 MHz, CDCl3
ppm

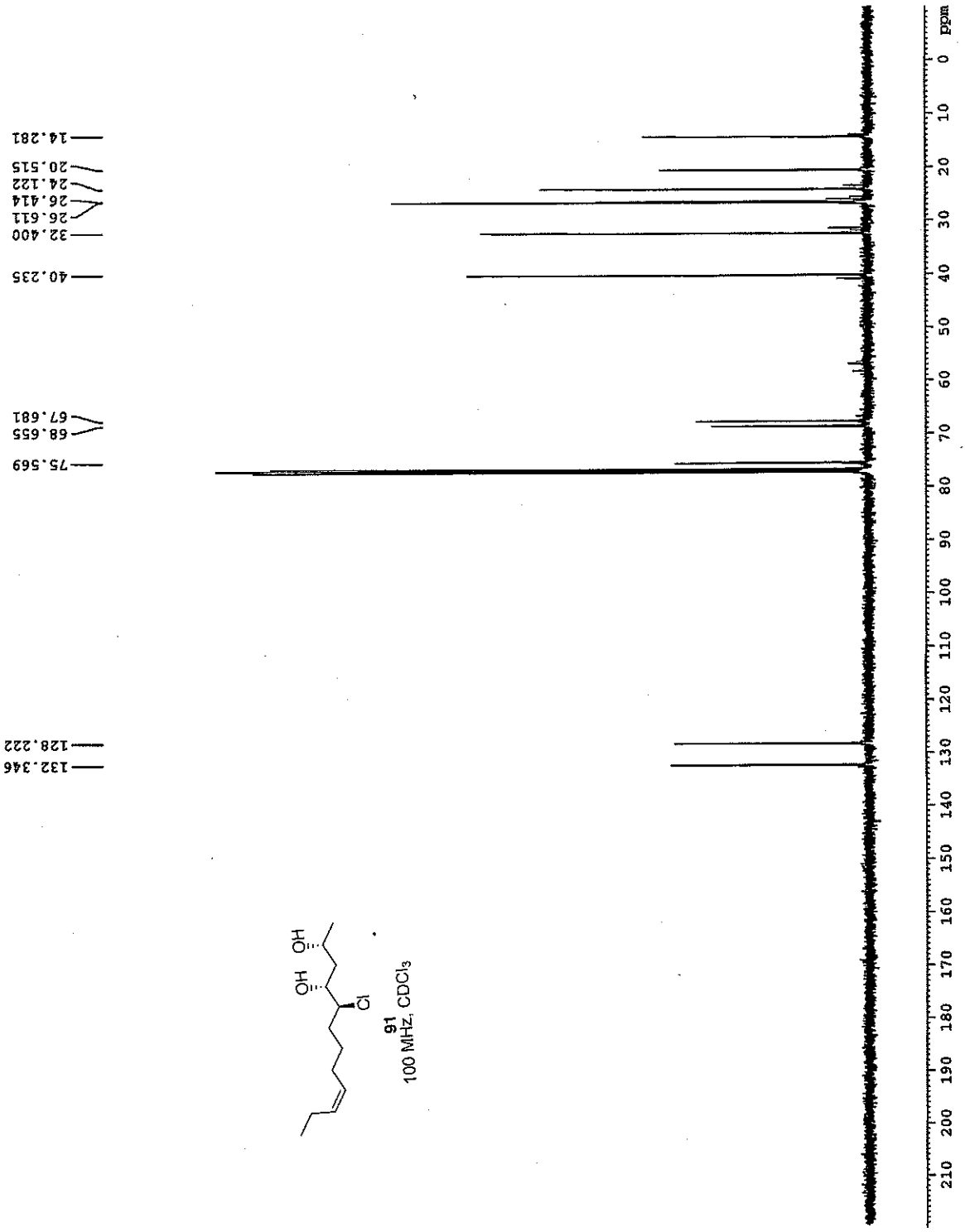

9.766
9.761
9.757
0.935
0.954
0.973
1.352
1.371
1.389
1.408
1.428
1.607
1.626
1.645
1.665
1.683
2.407
2.411
2.425
2.430
2.443
2.448
1.000
1.065
1.010
2.180
4.481
2.285
2.333
3.370
ppm
90
400 MHz, CDCl3

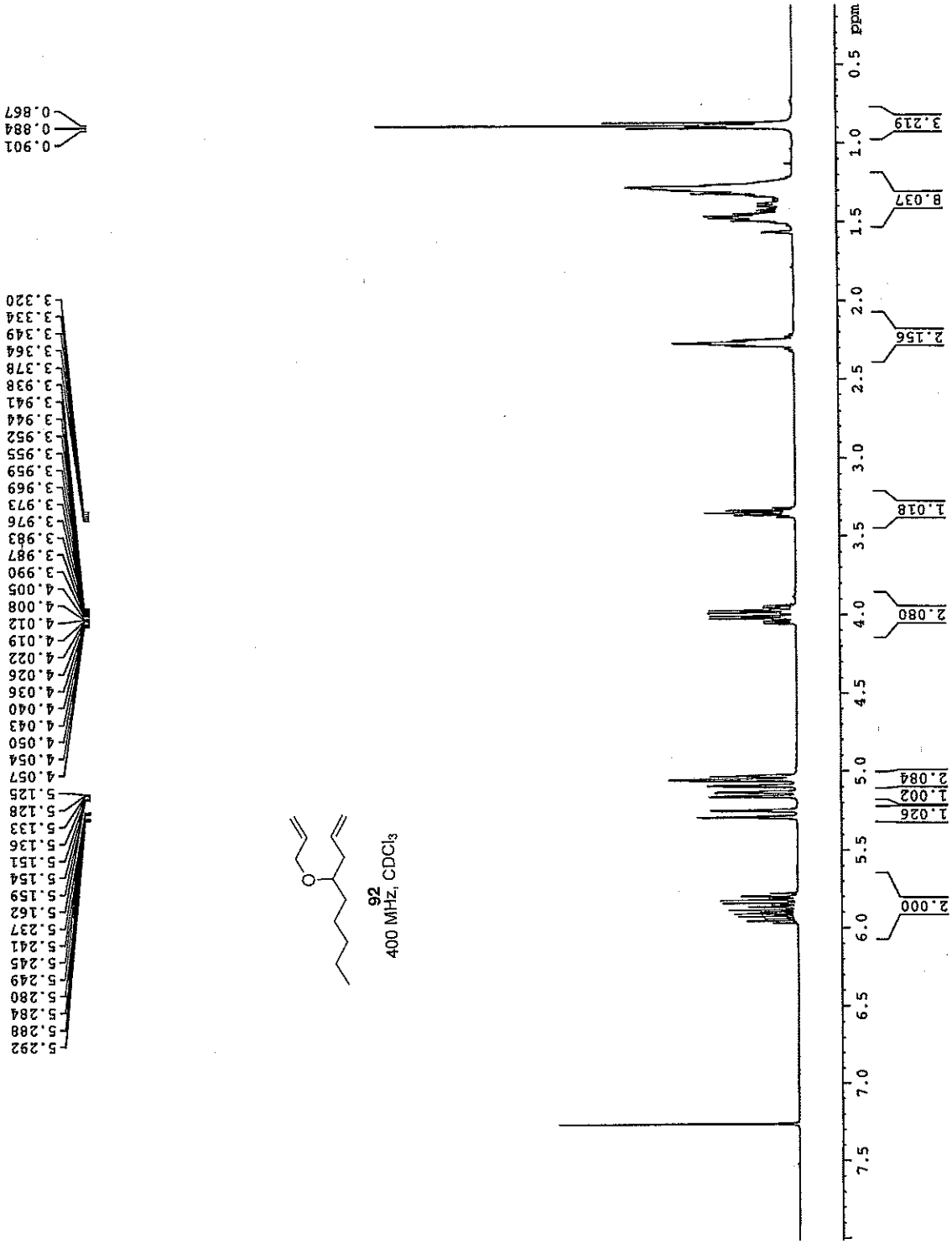

202.699
132.208
128.334
43.772
29.183
26.742
21.650
20.513
14.311
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
O
H
90
100 MHz, CDCl3


Precursor to 91
400 MHz, $CDCl_3$
OH
O
Cl
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
3.222
1.240
2.089
1.180
4.338
3.085
1.196
1.011
0.925
1.068
0.986
1.000
1.014
0.937
0.956
0.975
2.222
2.744
2.764
2.788
2.809
2.831
2.838
2.875
2.883
3.237
3.250
3.886
3.894
3.901
3.909
3.918
3.925
3.933


209.272
132.390
128.221
70.802
65.753
45.868
33.342
30.881
26.434
26.357
20.540
14.309
OH
O
Cl
Precursor to 91
100 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


OH
OH
Cl
91
400 MHz, CDCl3
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
2.000
0.982
0.993
1.074
1.038
1.088
4.080
7.078
3.317
3.206
1.240
1.225
0.970
0.951
0.932
2.998
3.003
3.502
3.512


14.281
20.515
24.122
26.414
26.611
32.400
40.235
67.681
68.655
75.569
128.222
132.346
OH
OH
Cl
91
100 MHz, CDCl3
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210


92
400 MHz, CDCl3
0.867
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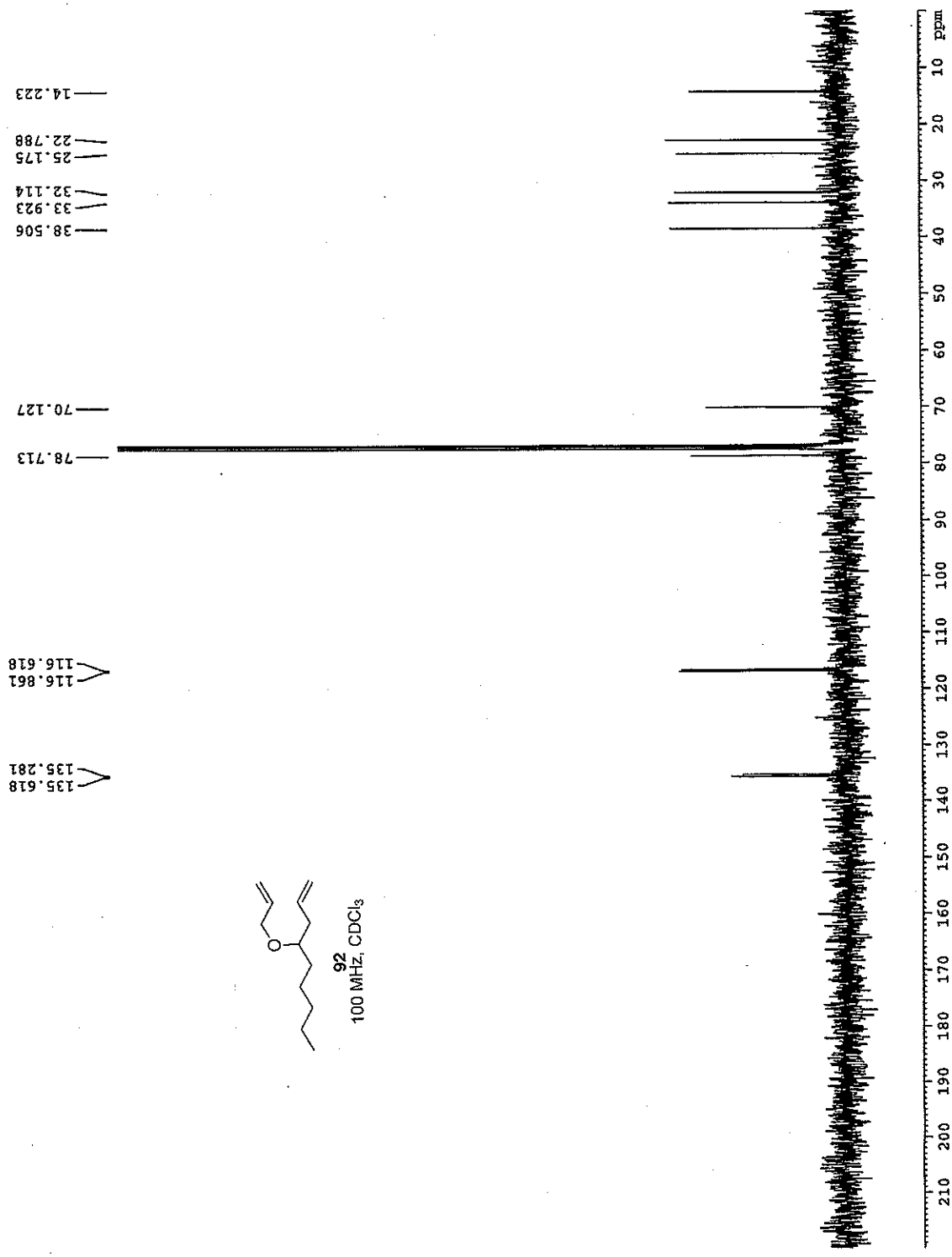
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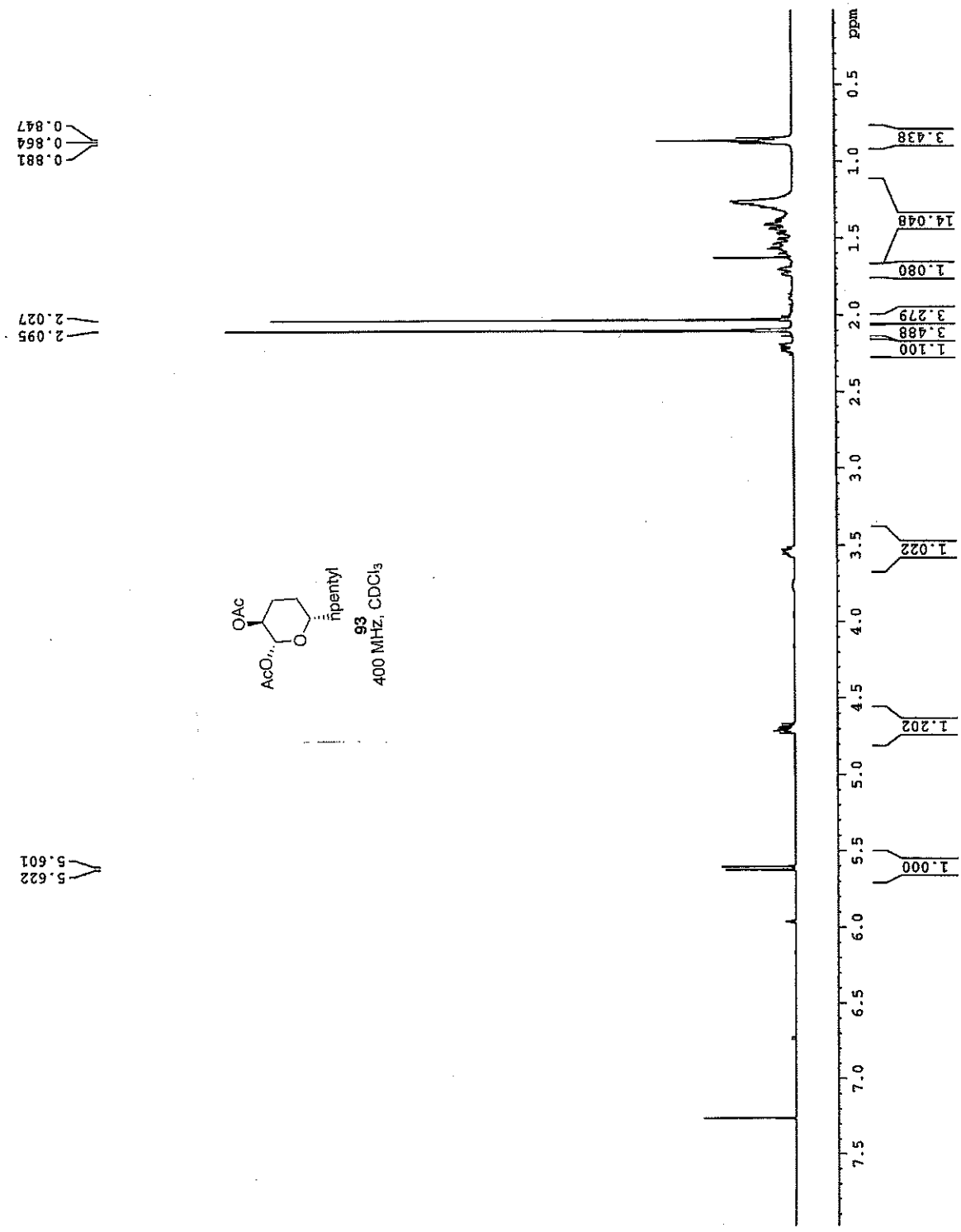
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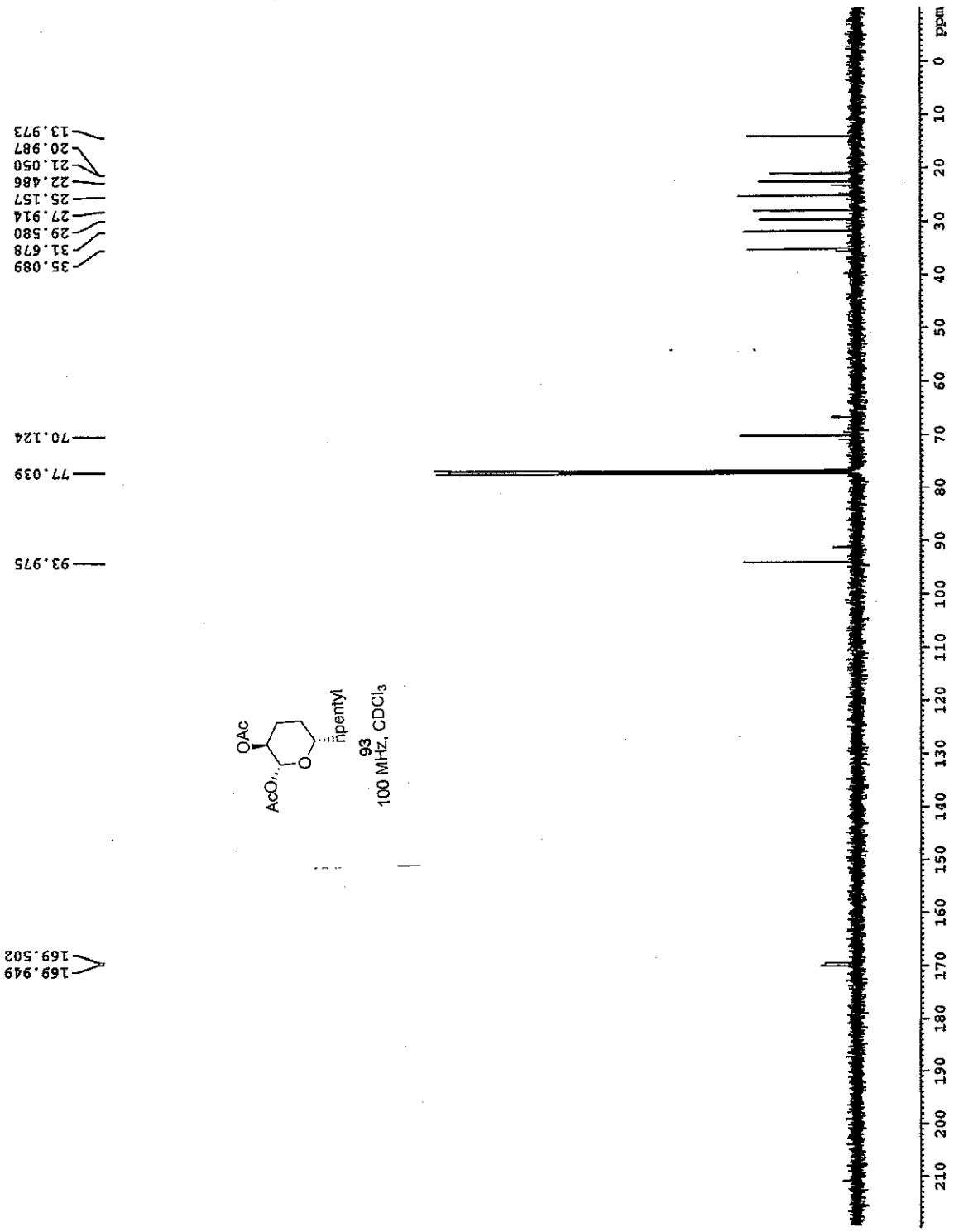
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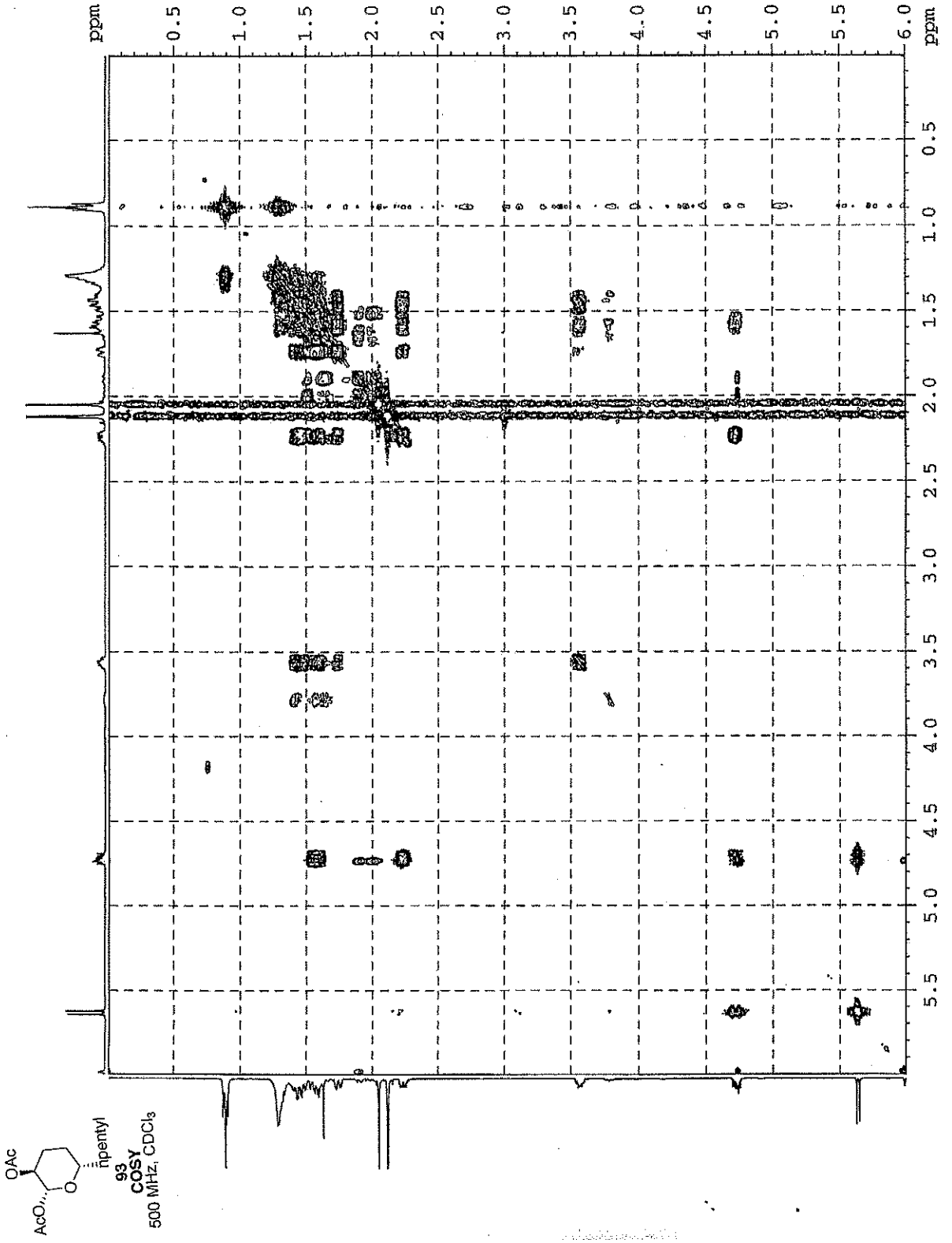
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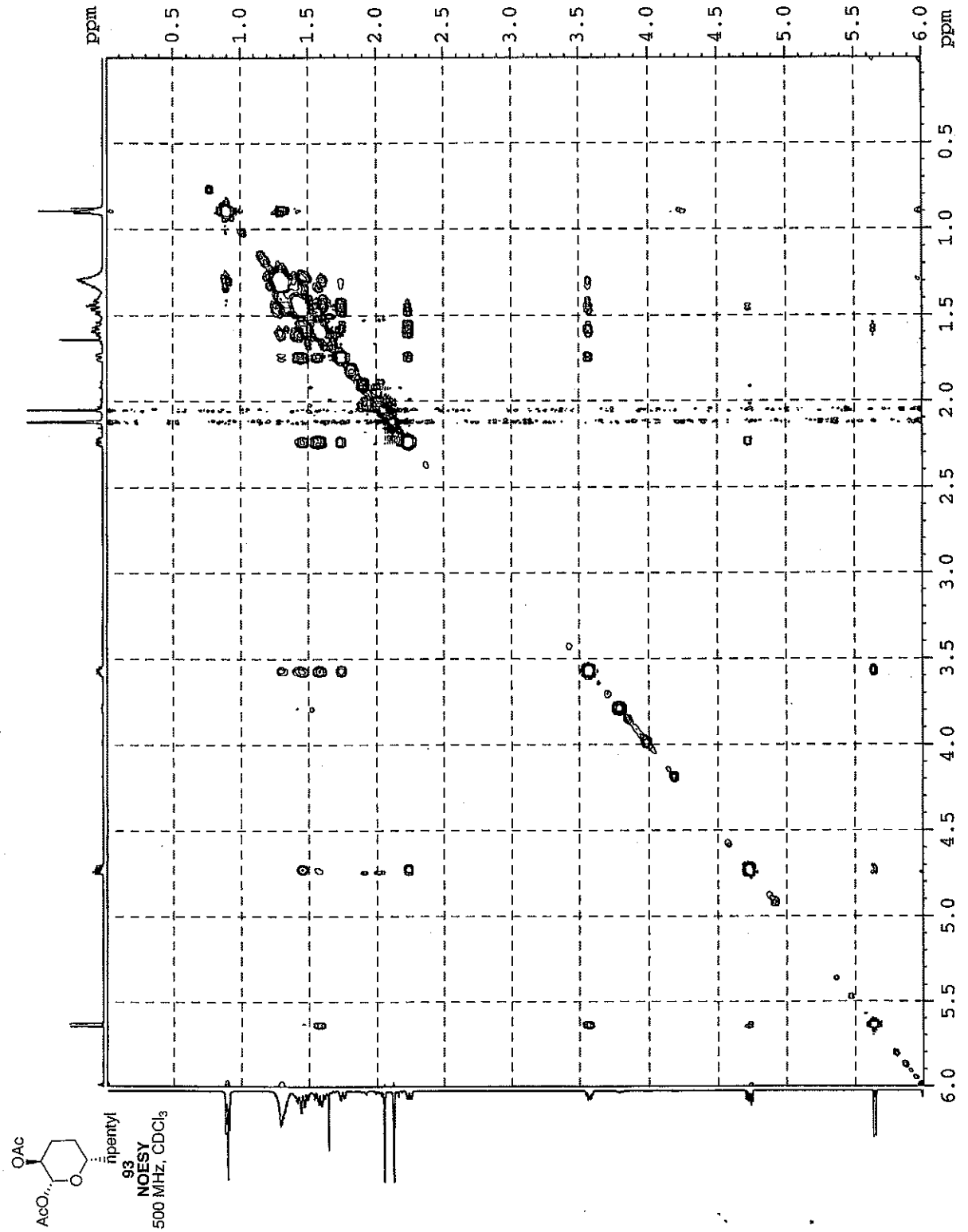
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CHAPTER 5

Formal Total Synthesis of Laurefucin and Evaluation of the Proposed Biosynthesis of Medium-Sized *Laurencia* Bromoethers

5.1 Introduction

Having developed a method to transform diverse tetrahydrofurans and tetrahydropyrans into 8- and 9-membered bromoethers in good yield and as single diastereomers,[1] we hoped to expand our model system explorations to the total synthesis of several natural products in the family. Laurefucin (**1**, Figure 1)[2] was initially chosen as an attractive testing substrate for its additional challenge of the bridging 5-membered ring, although we would not be pioneering its total synthesis, as Kim and coworkers have completed the target in 2008 through a route that encompassed 19 linear steps.[3] Using our ring expansion strategy, we hoped to significantly decrease the step count of the Kim precedent due to the efficiency of the key step coupled with the abundant literature resources on preparation of stereochemically dense tetrahydrofurans. Indeed, based on the findings of Chapter 4, the single step bromonium-induced ring expansion of the tetrahydrofuran precursor should be fully diastereoselective, rendering the overall approach as a rapid and concise way to generate a complex 8-membered bromoether.

This chapter will also discuss the biogenetic implications this ring expansion method has towards nature's potential syntheses of these medium-sized bromoethers. While this idea is not the first proposed biosynthesis of these natural products,[4] it is unique in its general conception of a ring expansion of a smaller ring system (a tetrahydrofuran) into a single medium sized ether. Additionally, this hypothesis lays the groundwork to incorporate the synthesis of additional natural isolates with varying stereochemistry and affords thoughts on natural products that could exist, but have yet to be discovered.

5.2 Formal Total Synthesis of Laurefucin

When comparing the products of our general ring expansion transformation from model compounds targeted to the natural isolate [i.e. laurefucin (**1**)], a few major challenges remained if success was to be achieved (Figure 1). Laurefucin (**1**) and model system **2** differ in that laurefucin has an additional tetrahydrofuran bridging the C6 and C9 positions, an additional enyne side chain attached to the C6 position, and altered stereochemistry of the oxygen atom attached to C9. With these differences in mind, we anticipated that the bridging tetrahydrofuran would need to be installed after the BDSB-induced ring expansion, since the C9 position must contain the essential trapping group for the key ring expansion step (see compound **3**). Similarly, the enyne side chain would need to be installed after this process as well, as bromonium electrophiles are known to react with enyne functional groups,[5] meaning that chemoselective engagement of the alkene could be difficult to achieve. In addition, because the C6 methyl of the model system would be difficult to functionalize in its current state, an alternative group would need to be installed for late stage manipulation. Finally, the alcohol stereochemistry at C9 would need to be inverted, either through the synthesis of a *trans*-cyclic carbonate along C9/C10 or via direct inversion of the *cis*-disposed carbonate post-cyclization. Globally, since 8-membered bromoethers of this class are prone to transannular rearrangements (something we observed in our model studies),[6] we chose to install as many functional groups prior to ring expansion as possible, including the inverted C9 stereochemistry.

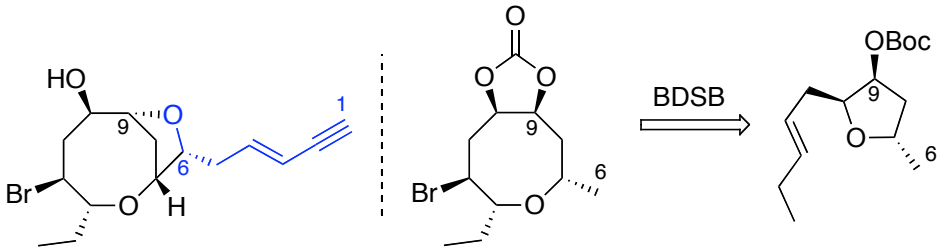
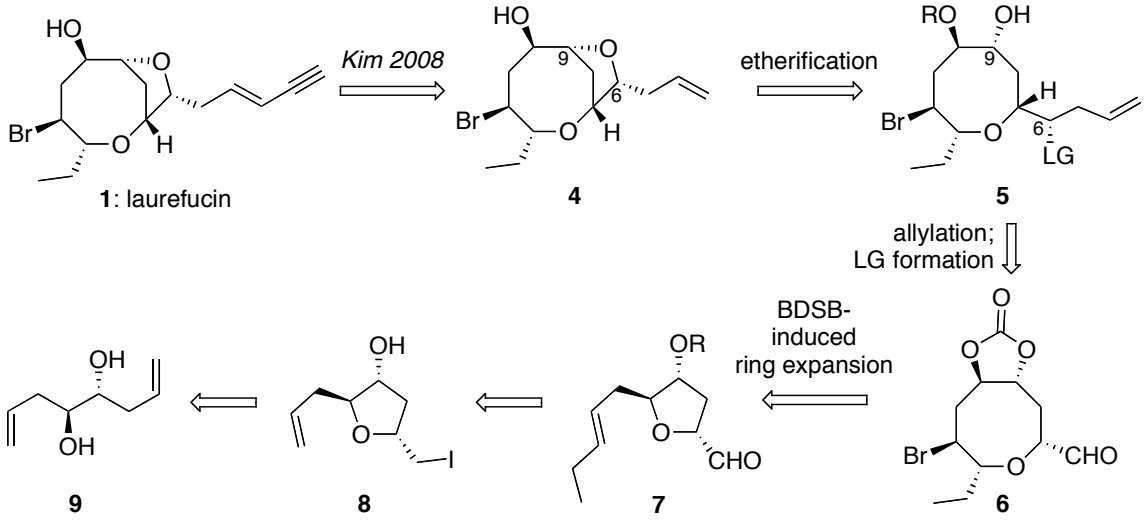


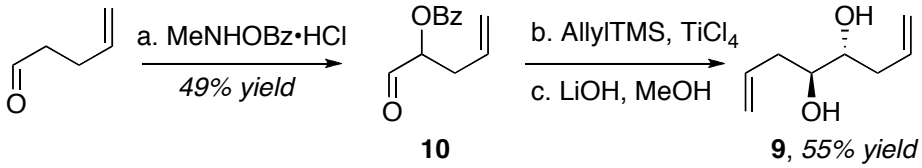
Figure 1: Comparison of Laurefucin to Model System

These general considerations led to the retrosynthesis of laurefucin shown in Scheme 1. The last steps would be the installation of the reactive enyne side chain; Kim and co-workers installed this moiety as the last two steps of their synthesis of laurefucin via an olefin cross metathesis and Colvins alkyne synthesis from compound **4**.[3] In turn, the bridged tetrahydrofuran of **4** was proposed to derive from a simple etherification of the corresponding leaving group at C6 and alkoxide at C9 of substrate **5**. We elected to utilize functionality attached to C6 as the leaving group (over the alternative at C9), as transannular rearrangements of the 8-membered ring ether are typical when leaving groups are present at C9 or C10.[6] Next, the 8-membered bromoether **5** was derived from common functional group manipulations to arrive at **6**, a molecule we anticipated could be derived from the bromonium-induced ring expansion of tetrahydrofuran **7**. This material, in turn, would be generated from elaboration of tetrahydrofuran **8**, itself accessible by an iodoetherification of linear *meso*-diol **9**.



Scheme 1: Retrosynthesis of Laurefucin

Putting these plans into action, the synthesis of meso-diol **9** was accomplished in three steps (Scheme 2). As shown, 4-pentenal was alpha-benzoylated in 49% yield using a procedure developed by Tomkinson and co-workers.[7] Then, aldehyde **10** was allylated and the benzoate protecting group was cleaved to afford the desired diol (**9**) in a 5:1 mixture of *trans:cis* isomers. Recrystallization in hot hexanes afforded pure *trans*-diol in 55% overall yield. It is worth noting that *meso*-diol **9** could also be synthesized in a single step from diallylation of glycol, though poor dr was observed for this process, rendering the route shown in Scheme 2 superior in terms of material throughput.[8]

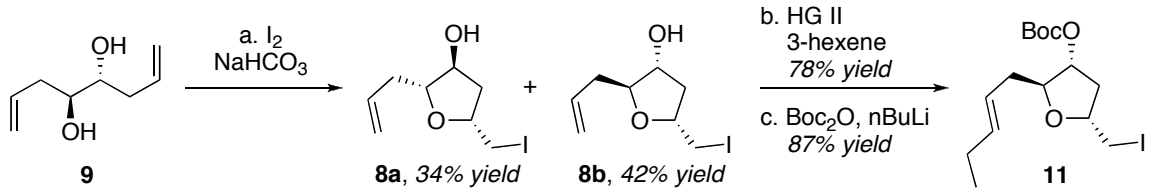


Reagents and Conditons: a. MeNHOBz•HCl (1.2 equiv), DMSO, 25°C, 5 h, 49%; b. $TiCl_4$ (1.2 equiv), allylTMS (1.2 equiv), CH_2Cl_2, -78 to -20°C, 3 h; LiOH (10 equiv), THF/MeOH/H_2O, 25°C, 2 h, 55%.

Scheme 2: Synthesis of *meso*-diol **9**

The transformation of diol **9** into the functionalized tetrahydrofuran was accomplished next. As indicated in Scheme 3, iodoetherification of **9** using I_2 and $NaHCO_3$ produced two separable diastereomers about the newly generated chiral center

in a 1.2:1 ratio, slightly favoring the desired diastereomer (**8b**). Numerous other haloetherification conditions were attempted with substrate **9**, though these standard conditions ultimately proved optimal. Of course, the generation of a mixture of diastereomers was not desired, yet the undesired diastereomer (**8a**) could potentially be deployed for the synthesis of a diastereomeric natural product. Fundamentally, the synthesized compound (**8b**) differs from the previously used model compound with the methyl now functionalized with a halogen, allowing for further derivatization. Pressing forward, cross metathesis with the Hoveyda-Grubbs second generation initiator and *tert*-butyl carbonate formation yielded tetrahydrofuran derivative **11**.

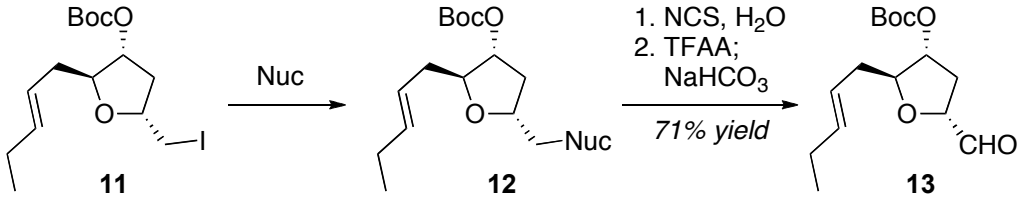


Reagents and Conditons: a. I_2 (2 equiv), $NaHCO_3$ (2 equiv), MeCN, 25°C, 3 h; b. *trans*-3-hexene (6 equiv), Hoveyda-Grubbs second generation (0.008 equiv), CH_2Cl_2, 25°C, 3 h, 78%; c. Boc_2O (4 equiv), Et_3N (1.5 equiv), DMAP (0.2 equiv), CH_2Cl_2, 25°C, 5 h, then KOH (5 equiv), DMSO, 25°C, 3 h, 87%.

Scheme 3: Synthesis of Tetrahydrofuran Core

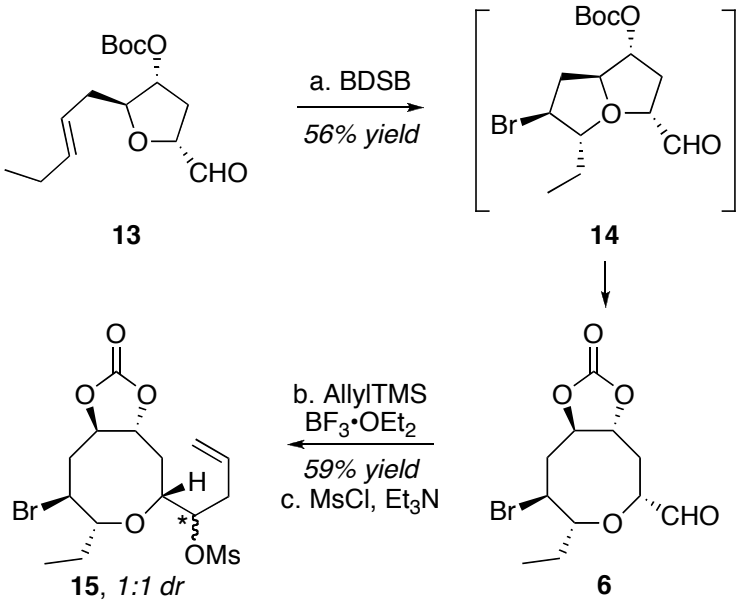
Our next goal, was the conversion of the primary iodine in **11** into an aldehyde. The simplest route to achieve this transformation, of course, would be to install an alcohol and then oxidize it directly. Unfortunately, all attempted oxygen-based nucleophiles (Table 1) failed to effect the desired transformation or did so in insufficient yield (Entries 1-6), typically leading to decomposition through rearrangement or cleavage of the *tert*-butyl carbonate. A thorough literature search unveiled an alternate three step method, which ultimately proved successful, one in which phenylsulfide displacement to **12a** (Entry 7) followed by oxidation and Pummerer rearrangement generated the desired aldehyde **13** in 60% overall yield.[9]

Table 1: Displacement of Iodide with Nucleophile



Entry	Nucleophile	Results
1	CsOAc, DMSO	27% -OAc
2	CsOH, DMSO	decomp
3	KOH, DMSO, 18C6	**11**
4	NaOAc, DMSO, 18C6	decomp
5	AgOAc, AcOH	decomp
6	$AgBF_4$, DMSO	**11**
7	NaSPh, DMF	85% **12a** Nuc = SPh

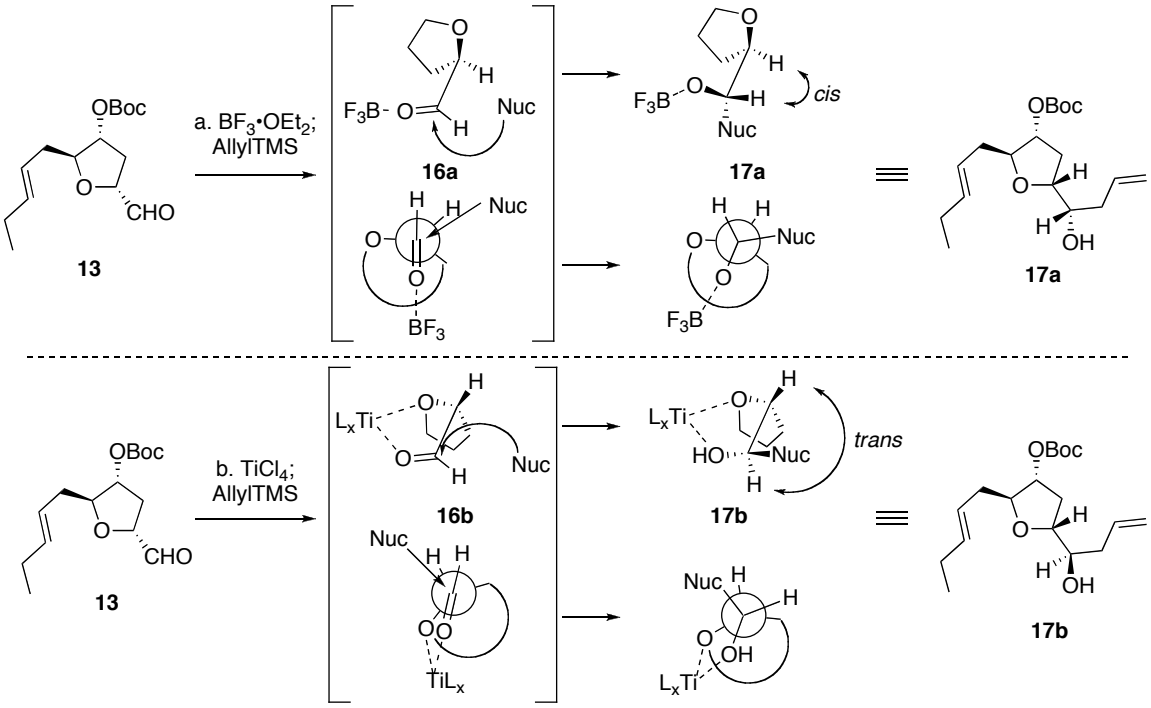
With the key tetrahydrofuran **13** in hand, the stage was set for our bromonium-induced ring expansion step. Pleasingly, treatment of aldehyde **13** with 1.2 equiv of BDSB at -25^{o}C generated the desired 8-membered bromoether core (**6**, Scheme 4) in a 54% yield. We found it was important to quench the reaction after only 2 min, as longer exposure to the reagents led to epimerization of the chiral center alpha to the aldehyde. Additionally, we were surprised this reaction proceeded without any additional bromination, as typically BDSB is competent in the alpha bromination of both aldehydes and ketones when these functionalities are present; clearly here the double bond proved to be more reactive. Subsequently, allylation and mesylation produced the desired product (**15**), but with a 1:1 dr about the new center. Even with use of alternate Lewis acids, no diastereoselectivity was observed. We hypothesize that this outcome reflects the additional flexibility of the 8-membered rings over alternative smaller, more rigid ring sizes. Given this lack of control, we decided to adjust the overall order of events in our strategy in hopes that greater (if not complete) diastereoselectivity could be achieved.



Reagents and Conditons: a. BDSB (1.2 equiv), $MeNO_2$, -25°C, 2 min, 56%; b. BF_3•OEt_2 (5 equiv), allylTMS (5 equiv), -78 to 25°C, 2 h, 59%; c. MsCl (2 equiv), Et_3N (4 equiv), CH_2Cl_2, 25°C, 1 h.

Scheme 4: Ring-expansion to 8-Membered Bromoether

Specifically, we believed that allylation at an earlier stage, with a tetrahydrofuran in place, had a greater potential to be diastereoselective. In this next attempted route, we decided to allylate aldehyde **13** prior to the BDSB-induced ring expansion step. Scheme 5 demonstrates how using the Felkin-Ahn stereoselectivity model, each diastereomer of the allylated product could be generated selectively (**17a** or **17b**) under the indicated conditions.[10] Using a Lewis acid with only one site of coordination (BF_3•OEt_2), **17a** was produced (this Lewis acid only assists in activation of the aldehyde within **13**, i.e. via **16a**). Alternatively, if a Lewis acid with multiple sites of chelation such as $TiCl_4$, was used, **17b** could be obtained as a single diastereomer via intermediate **16b**.



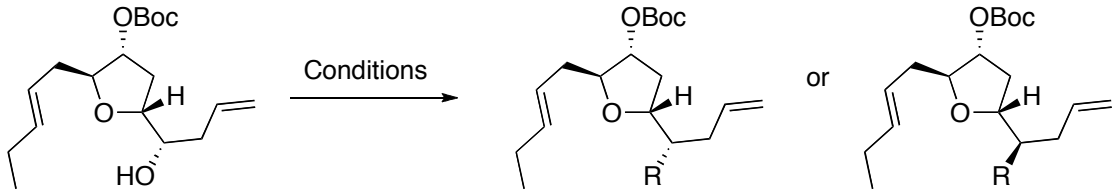
Reagents and Conditons: a. BF_3•OEt_2 (5 equiv), CH_2Cl_2, -78°C, 10 min; then allylTMS (5 equiv), -78 to -20°C, 3 h; b. $TiCl_4$ (5 equiv), CH_2Cl_2, -78°C, 10 min; then allylTMS (5 equiv), -78 to -20°C, 3 h.

Scheme 5: Felkin-Ahn Model for Allylation of Aldehyde **13**

While an alcohol was installed through this process, this position ultimately needed to contain a leaving group to furnish the bridged tetrahydrofuran of laurefucin. Initially, we believed that any leaving group would not survive the ring expansion step, so we opted to attempt to protect the C9 alcohol prior to treatment with BDSB. Indeed, prior studies revealed that BDSB (similar in structure to the active Swern oxidating reagent, chlorodimethylsulfonium chloride)[11] was capable of reacting with free alcohols, an undesired transformation we hoped to discourage. As indicated by Entries 1-3 of Table 2, efforts to install a silicon protecting group failed, leading to either decomposition or recovered starting material. The introduction of a benzoate could be accomplished using standard conditions (Entry 4), though now cleavage between the benzoate and carbonate could be problematic post-cyclization. Upon reflection, we then turned to direct installation of the leaving group prior to cyclization with the hope that it

would survive through the key step. Exploration of the conditions delineated in Entries 5-7 all led to decomposition, though the bromide and mesylate derivatives were both synthesized successfully (Entries 8 and 9).

Table 2: Attempts to Transform Alcohol **17a** into a Leaving Group

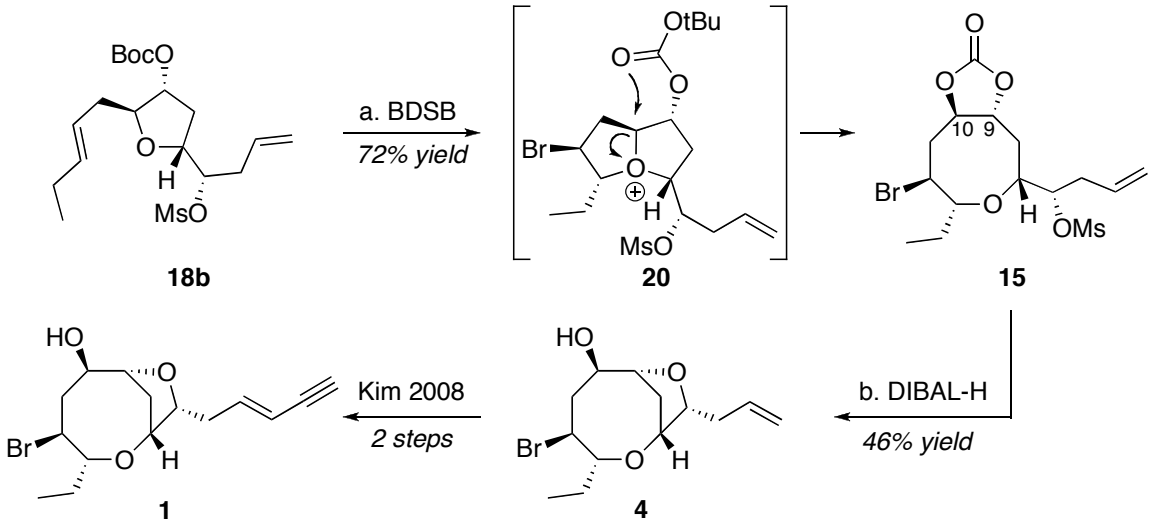


17a **18** **19**

Entry	Conditions	Results
1	TBDPSCl, NaH	decomp
2	TIPSCl, imid, DMAP	RSM
3	TIPSCl, I_2, Me-imid	decomp
4	BzCl, Et_3N, DMAP	73% **18a**, R = OBz
5	I_2, PPh_3, DMAP	RSM + decomp
6	MsCl, Et_3N; NaI	decomp
7	nBuLi, TsCl	decomp
8	PBr_3	quant. **19**, R = Br
9	MsCl, Et_3N	quant. **18b**, R = OMs

Next, bromide **19** and mesylate **18b** were tested using the standard ring expansion conditions, noting that these starting materials are much more complex than the previously studied model systems since they now include two alkenes and an allylic leaving group, both raising new chemoselectivity and functional group compatibility issues for the central bromonium-induced ring expansion step. It was found that bromide **19** rapidly decomposed with standard conditions, producing a variety of unidentified products. Yet, mesylate **18b** underwent the BDSB-promoted ring expansion cleanly to generate the 8-*endo* bromoether **15** in 72% yield as a single diastereomer (Scheme 6). BDSB was chemoselective for the more substituted, but also more hindered, alkene; no reactivity of the terminal olefin was observed. In addition, the allylic mesylate remained intact, a functionality key for the completion of the natural product. Mechanistically, we account for the stereoselectivity observed by noting that a 5-*endo* bromocyclization likely

generated oxonium **20**, which, upon opening at the central position by the pendent *tert*-butyl carbonate, yielded the desired product diastereoselectively.



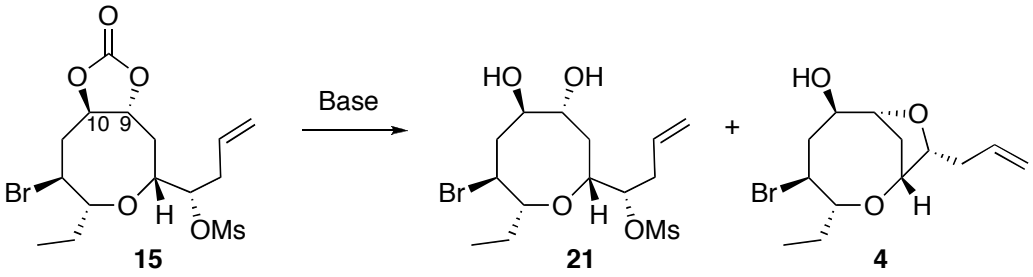
Reagents and Conditons: a. BDSB (1.5 equiv), $MeNO_2$, -25 to 25°C, 20 min, 72%; b. DIBAL-H (5 equiv), PhMe, -78 to 25°C, 6 h, 46%.

Scheme 6: End Game for Completion of Total Formal Synthesis of Laurefucin

With the 8-membered ring in place, the final steps were to cleave the carbonate and introduce the bridged tetrahydrofuran. We were hopeful that only the C9 oxygen would form the tetrahydrofuran, as the C10 oxygen, potentially poised to generate a 6-membered ether, is positioned *trans* to the leaving group. Many conditions were explored for this event as shown in Table 3; as indicated, the use of common carbonate cleavage conditions led mostly to decomposition or diol **21** (Entries 1-3). It was Entry 1, however, with the production of trace **4**, which first gave us the idea to combine the originally proposed two step sequence into a single step. This process was accomplished with the use of DIBAL-H in toluene in a 46% yield (Scheme 6 or Table 3, Entry 6). It was found that both carbonate cleavage and cyclization occurred simultaneously most likely due to a chelation effect at the aluminum center. Additionally, the unwanted tetrahydropyran alternative was not observed in any of the conditions used. With

compound **4** synthesized, we stopped our synthetic work here, though the formal total synthesis of laurefucin was thus completed by following Kim and co-workers' final two steps.[3] Our route to terminal alkene **4**, the formal synthetic precursor to laurefucin, proceeded in 11 linear steps in 1.8% yield. Therefore, the overall total synthesis of laurefucin was 13 linear steps, the shortest synthesis of any *Laurencia* isolate to date, and six steps shorter than the Kim precedent for this specific substrate.

Table 3: Attempts to Cleave Carbonate of **15**

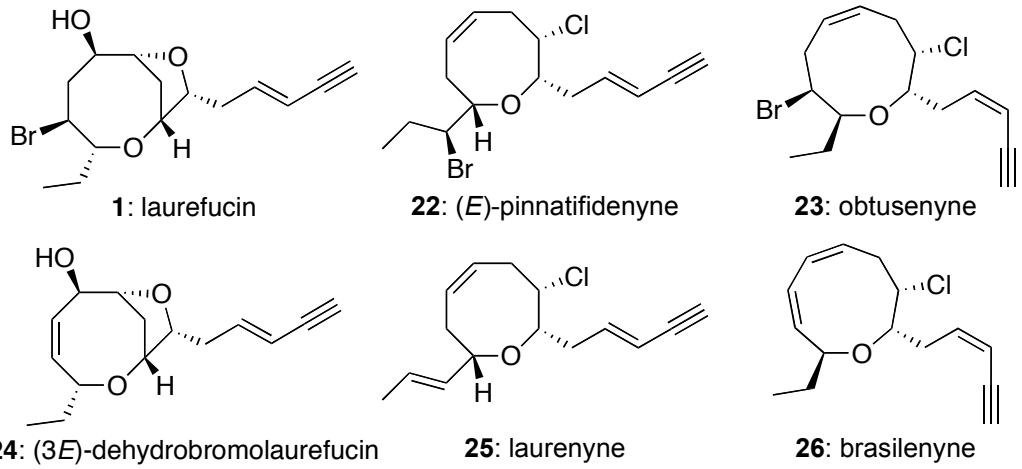


Entry	Base	Results
1	K_2CO_3, MeOH	30% **21**, trace **4**
2	K_2CO_3, DMSO	decomp
3	NaOMe, DMSO	decomp
4	PhMgBr	**15**
5	DIBAL-H, THF	decomp
6	DIBAL-H, PhMe	46% **4**

5.3 Chemoselective Synthesis of the Core of 3*E*-Dehydrobromolaurefucin

While we were able to install the 8-*endo* bromoether of laurefucin (**1**) diastereoselectively, it is worth noting that over a fourth of the medium-sized rings within this family lack this bromide, containing instead an alkene (i.e. **1** to **24**, **22** to **25**, or **23** to **26**, Figure 2).[12] With the synthesis of laurefucin completed, simple elimination of the bromide could, in principle, complete the total synthesis of (3*E*)-dehydrobromolaurefucin (**24**).[12a,b] Unfortunately, all attempts to effect this transformation were unsuccessful, typically leading instead to decomposition or transannular rearrangements. Yet, as noted

before, we have seen this problem of bromide elimination previously in the context of polyene cyclization, as described in Chapter 2. To solve this difficulty, just as performed earlier, we turned to installation of an alternative halogen, an iodide.



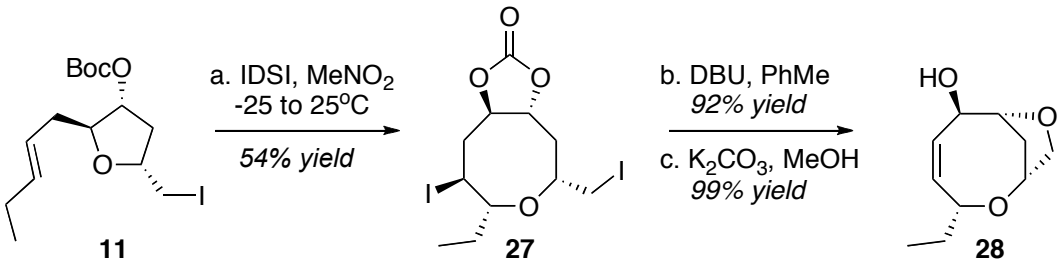
1: laurefucin **22**: (*E*)-pinnatifidenyne **23**: obtusenyne

24: (3*E*)-dehydrobromolaurefucin **25**: laurenyne **26**: brasilenyne

Figure 2: Natural Products Containing an Alkene

Using our iodinating reagent, IDSI, compound **11**, an intermediate in the previously described total synthesis of laurefucin, was smoothly expanded into 8-membered iodoether **27** in 54% yield (Scheme 7). Here, the addition of ICl across the alkene was the major by-product obtained from the event. From **27**, elimination of the secondary iodide with DBU provided the desired internal alkene without reacting at the primary iodide. This chemoselectivity observed for the more substituted iodide likely reflects its orientation within the 8-membered ether, one that could align it *anti*-periplanar to an axial hydrogen, allowing for a facile E2 elimination. By contrast, the primary iodide is proposed to be less accessible, with free rotation at its sp^3 center in combination with the need for removal of a more hindered hydrogen making it harder to eliminate, as observed. Next, treatment with K_2CO_3 in MeOH cleaved the carbonate backbone and *in situ* effected alcohol displacement of the primary iodide to afford the tetrahydrofuran in quantitative yield. This cyclization from the diol intermediate to the bridged

tetrahydrofuran is likely an easier process than compared to that explored previously (see Table 3), as compound **28** lacks the allyl group (found in compound **4**). That extra side chain of atoms is oriented on the concave face of the bicyclic structure (**4**), making the synthesis of laurefucin more challenging in terms of generating the bridged tetrahydrofuran.



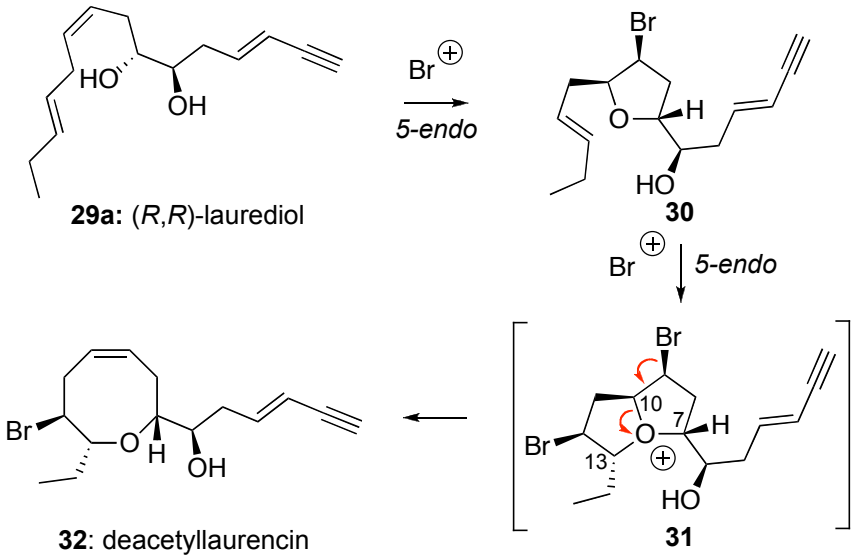
Reagents and Conditons: a. IDSI (1.2 equiv), $MeNO_2$, -25 to 25°C, 25 min, 54%; b. DBU (5 equiv), PhMe, 25°C, 24 h, 92%; c. K_2CO_3 (10 equiv), MeOH, 25°C, 12 h, 99%.

Scheme 7: IDSI-Promoted Ring-expansion of Tetrahydrofuran **11**

To conclude, these past two sections have demonstrated the generality of the bromonium-induced ring expansion method, one allowing for the use of additional functional groups including aldehydes, multiple alkenes, halides, and allylic leaving groups. Additionally, it has led to the rapid and concise formal total synthesis of laurefucin (**1**), the shortest synthesis of any 8-membered isolate in the family. The tetrahydrofuran template allows the use of robust, previously developed chemistry to assemble molecular complexity prior to ring expansion to the more reactive medium sized ethers. And, using our iodonium reagent (IDSI) in this process instead, we were also able to synthesize the core of 3*E*-dehydrobromolaurefucin followed by a chemoselective elimination of the installed iodide. The expediency of these syntheses is due to the ability to rapidly build complex tetrahydrofurans followed by a single diastereoselective XDSX-induced ring expansion step to generate the entire core of the *Laurencia* haloethers.

5.4 Biosynthetic Hypothesis

The generality of the developed bromonium-promoted ring expansion strategy has allowed access to seven diastereomeric cores as well as the completion of formal total syntheses of laurefucin (described above) and (*E*)- and (*Z*)-pinnatifidenyne.[13] Based on the breadth of this work accomplished to date, we believe the process may have biogenetic implications for the origin of these molecules in nature. The general idea is drawn in Scheme 8, one in which laurediol (**29a**), upon treatment with a bromonium electrophile, would undergo a 5-*endo* bromoetherification to tetrahydrofuran **30**. Other electrophiles that could incorporate an H or OH in such an event could also be reasonable biosynthetic pathways for some targets which lack the bromide. Critically, though, from **30** specifically, a second bromocyclization with the tetrahydrofuran oxygen as the nucleophile would generate oxonium intermediate **31**. Opening of this material at the central position (i.e. C10) via loss of bromonium would yield deacetyllaurencin (**32**).[14] Overall, this process reflects events similar to the BDSB-promoted ring expansion without the use of a carbonate trapping group. This proposed idea requires regioselective opening at the C10 position over the alternative C7 or C13 positions. Obviously here other pathways could be present, since opening at the C7 or C13 positions could produce new tetrahydrofuran derivatives. As circumstantial support, the second largest class of *Laurencia* natural isolates are tetrahydrofuran derivatives, the key intermediate proposed for this biosynthesis of the medium-sized bromoether members.



29a: (*R*,*R*)-laurediol

30

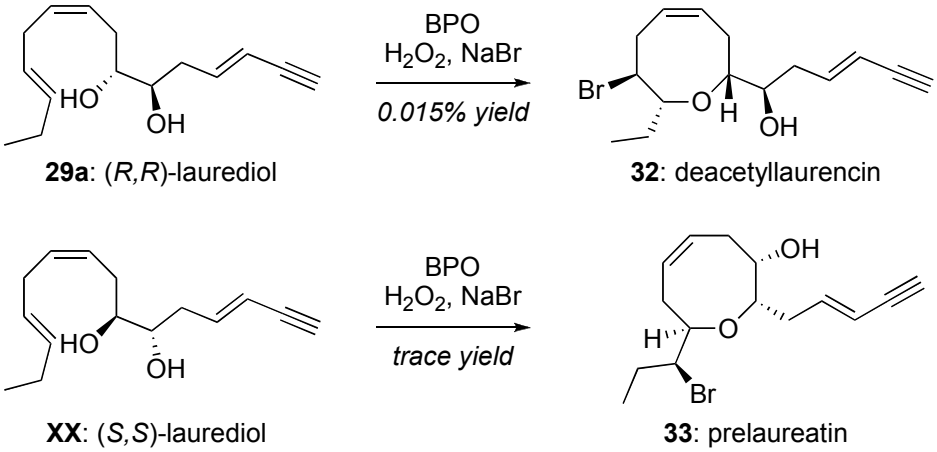
31

32: deacetyllaurencin

Scheme 8: Hypothesis on Generation of 8-Membered Bromoethers via Two 5-Membered Cyclizations

This biosynthetic hypothesis starting from linear precursors represents the first in which two smaller ring formations are prepared to account for the desired medium-sized bromoether. As noted earlier, Murai and coworkers were the first to support the original proposal of the biogenesis of these medium-sized rings via a direct 8-membered bromoetherification (Scheme 9).[4] As shown, their experimental results demonstrate that **29a** could be transformed into deacyllaurencin (**32**) using BPO (bromoperoxidase, the enzyme isolated from the same producing species as these natural products), hydrogen peroxide, and bromide anion. These conditions were used to recreate the enzymatic conditions of the *Laurencia* red algae in a laboratory setting. Similarly, its enantiomer (i.e. **29b**) produced 8-*exo* prelaureatin (**33**)[15] in trace yield under the same conditions. Yields here were very poor, with only small amounts of the desired 8-membered bromoether observed in both cases; this result, however, is not surprising as medium sized ether formation is both kinetically and thermodynamically disfavored. Yet, for over 20 years, this direct 8-membered bromoetherification from a linear precursor has been the

only accepted biosynthetic pathway for the generation of these natural isolates, probably because it was the only one with any modicum of support.



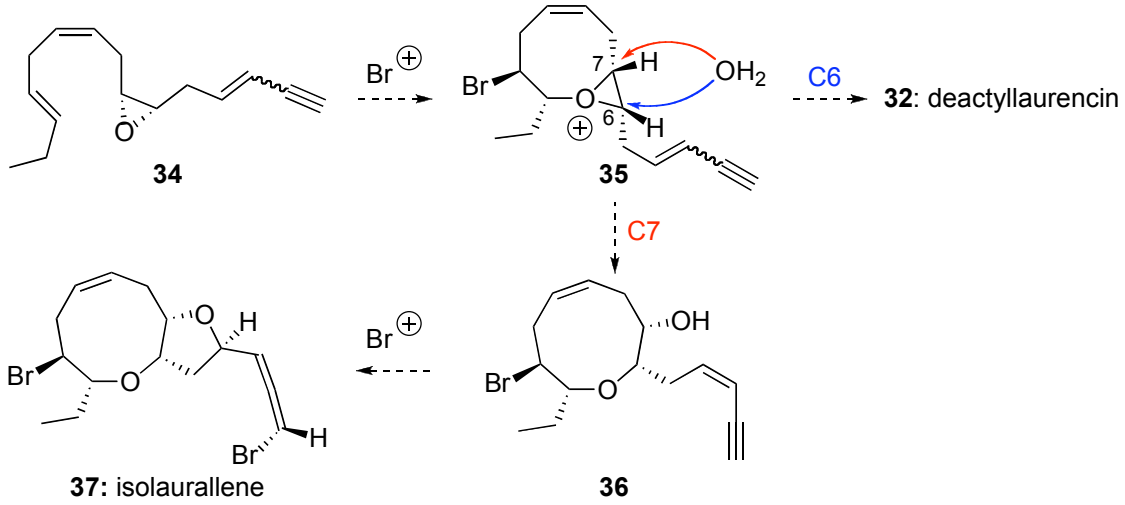
29a: (*R,R*)-laurediol **32**: deacetyllaurencin

XX: (*S,S*)-laurediol **33**: prelaureatin

Scheme 9: Murai and Co-workers' Results for Cyclization of Linear Laurediol

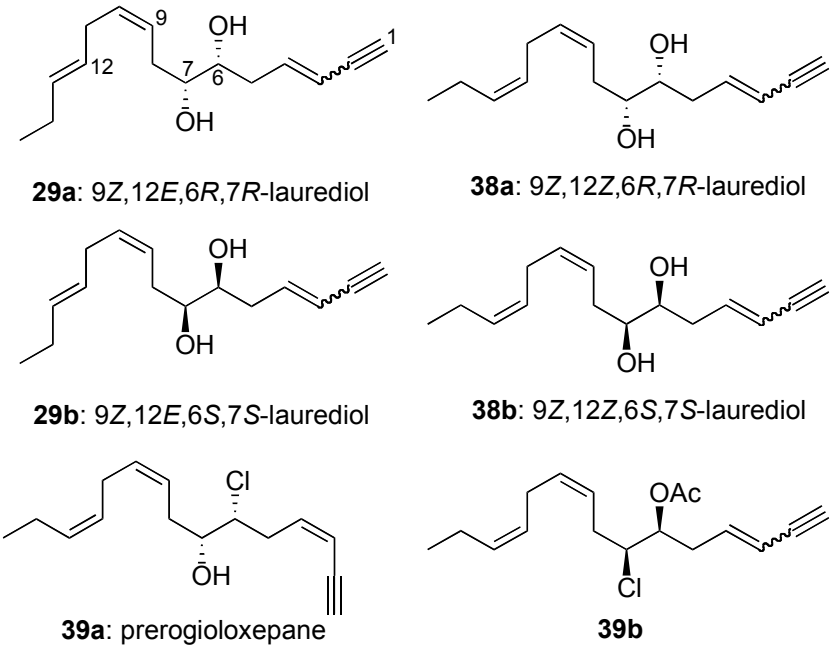
More recently, in 2012 (after the publication of our original work) Braddock and co-workers presented an alternate biosynthesis.[16] Instead of laurediol cyclizing to medium-sized ethers, the hypothesized precursor to these diols, epoxide **34**,[17] could undergo a bromonium-induced cyclization (Scheme 10). This route is then terminated by nucleophilic attack of either chloride or water, leading to a variety of substituted natural products. This proposal relies on the idea that nature synthesizes these products without any true specificity, since variety of ring sizes are generated without any regio- or diastereocontrol; if the compounds are defensive in origin, that proposal could be reasonable.[18] As a representative example, intermediate **35** could open at either the C6 or C7 positions to generate 8-*endo* bromoether **32** and/or 9-*endo* bromoether **37**.[19] Yet, intermediate **35** is just one of four possible intermediates that could arise from bromonium addition to epoxide **34**, with each additional alternative capable of generating multiple isolates as well as non-natural structures. Additionally, this proposal remains dependent on the generation of an 8-membered ring to promote formation of oxonium **35**,

from a precursor with no additional elements of control, creating in the process an oxonium containing a strained 3-membered ring.



Scheme 10: Braddock and Co-workers' Proposal for the Biosynthesis of *Laurencia* Medium Sized Bromoethers

While nature may not be selective in synthesizing each of these individually, we believe that pathways exist which could afford more control than the diversity-oriented synthesis proposal from the Braddock group. Looking at the known laurediol precursors, numerous stereochemically distinct derivatives have been isolated (Figure 3).[20] Each of these could be potential precursors for the synthesis of these medium-sized ethers, including both diol enantiomers (i.e. **29a** and **29b** or **38a** and **38b**), *cis*- or *trans*-C12/C13 alkene geometry, as well as chlorohydrin derivatives (**39a** or **39b**).[21] While the chlorohydrin variant of **39b** has not been isolated, it is probable that acetylated **39b** derives from such a structure.



29a: 9*Z*,12*E*,6*R*,7*R*-laurediol **38a**: 9*Z*,12*Z*,6*R*,7*R*-laurediol

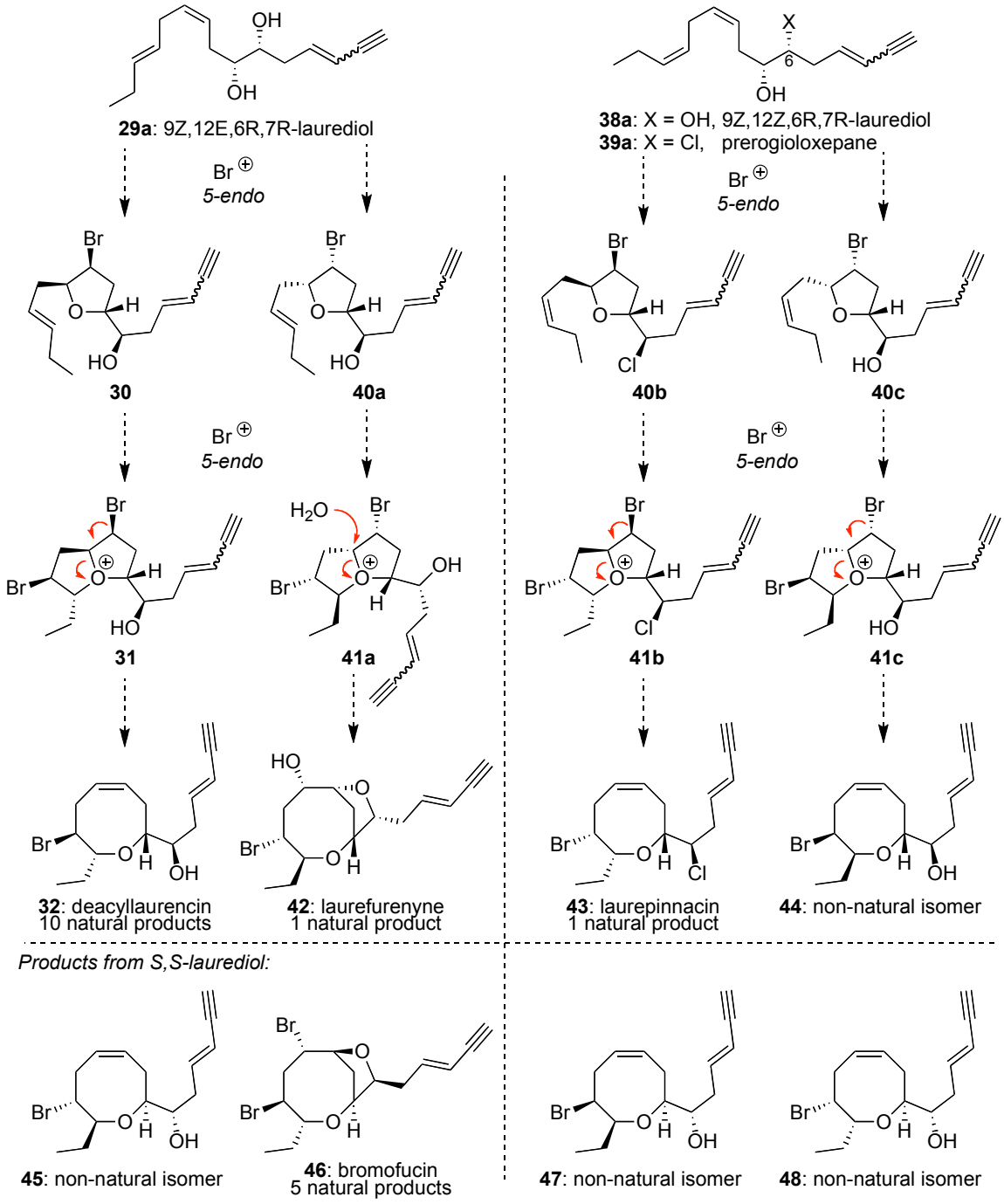
29b: 9*Z*,12*E*,6*S*,7*S*-laurediol **38b**: 9*Z*,12*Z*,6*S*,7*S*-laurediol

39a: prerogioloxepane **39b**

Figure 3. Isolated Laurediol Isomers and Derivatives

Putting each of these laurediol starting materials into our proposed biosynthesis scheme and focusing initially on only the 6*R*,7*R*-enantiomers, four distinct 8-*endo* bromoethers could be generated. As shown in Scheme 11, starting with **29a**, **38a**, or **39a**, a 5-*endo* bromoetherification would yield four possible diastereomers of the produced tetrahydrofuran ring system (**30** and **40a-c**). Each of these materials, in turn, could undergo a second 5-*endo* bromocyclization to generate oxoniums **31** and **41a-c**. Based on our previous work with model systems in Chapter 4, only a single diastereomer of the generated oxonium should be observed. These oxonium intermediates could then be opened in a variety of ways to produce a single diastereomer of the final bromoether products. A single product is drawn in each case, here, focused on 8-membered ring formation, though multiple products with the same stereochemical array may exist in each case (i.e. **32** has nine additional matching natural isolates).[22] Moreover, some pathways produce diastereomers that are non-natural, potentially isolates that have yet to be discovered (i.e. **44**). Following the same pathways, starting instead with 6*S*,7*S*-

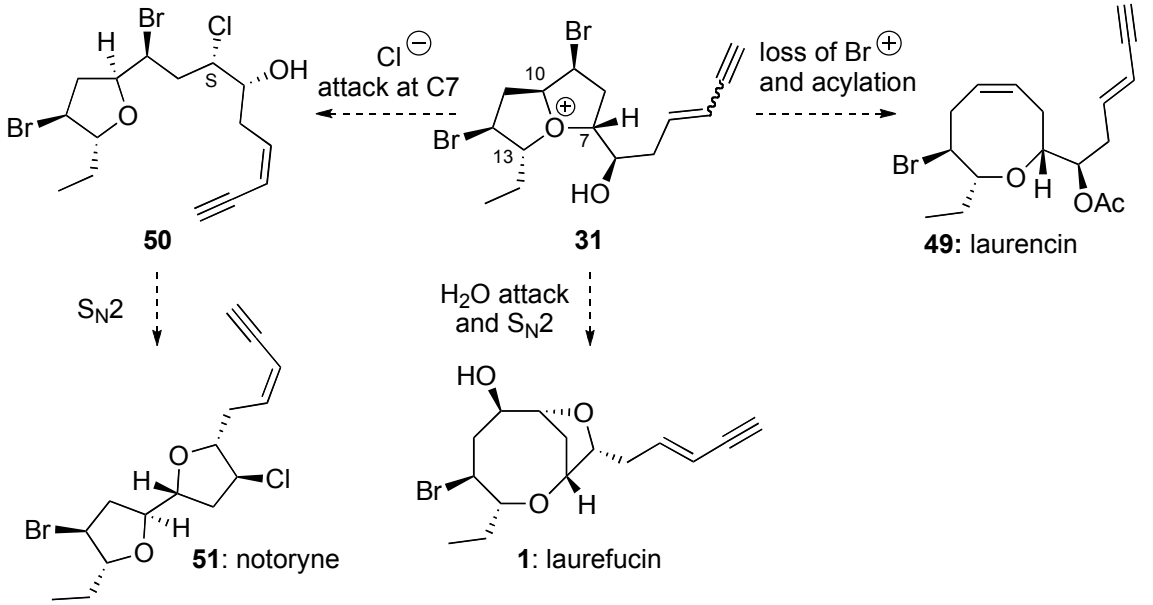
laurediol derivatives, the enantiomers of the above products would be observed (i.e. **45-48**).[23] Collectively, these comprise eight total diastereomers of the 8-*endo* bromoethers, which represent a majority of the natural isolates in the *Laurencia* family; four geometries are known (i.e. **32**, **42**, **43**, and **46**) and four are non-natural (**44**, **45**, **47**, and **48**). Interestingly, over half of the 8-*endo* bromoethers contain a chloride at the C6 position, an atom we believe is introduced in the starting material as shown in the synthesis of laurepinnacin (**43**).[22b] Instead of starting with laurediol, chlorohydrin **39a** could undergo the same desired transformation, now containing a chloride at C6 instead of an alcohol.



Scheme 11: Proposed Biosynthesis of 8-*endo* Bromoethers

Critically, the proposed key bicyclic oxonium is unique in its ability to be transformed into a variety of natural isolates, including intermediates of different sizes. Scheme 12 demonstrates how oxonium **31** could be opened at the C7, C10, and C13 positions, each leading to isolates found in the natural product collection. As shown,

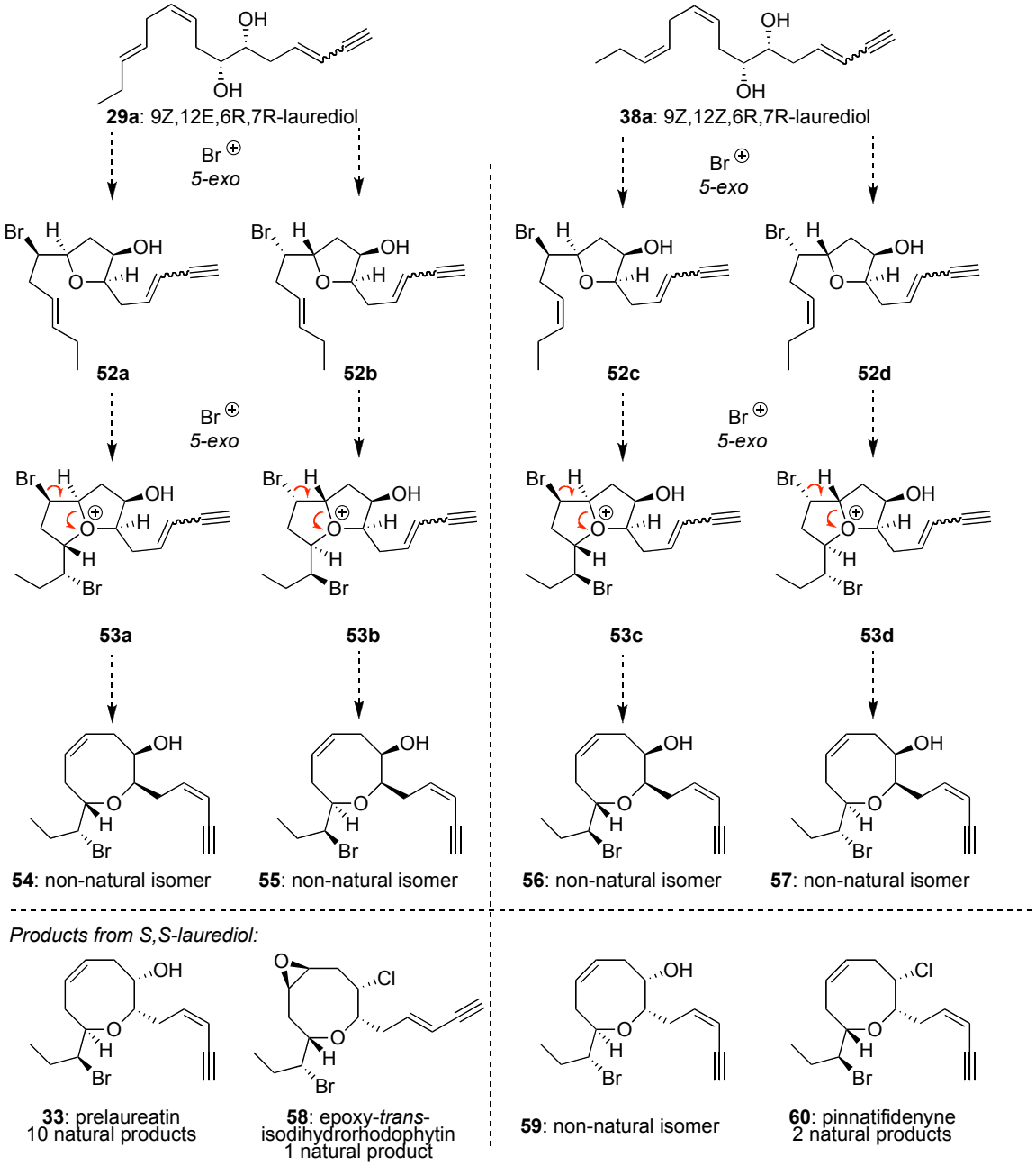
while opening at C7 and C13 would generate new tetrahydrofuran derivatives, attack at C10 would produce an 8-membered ring. Laurencin (**49**)[24] could be derived from loss of bromonium of C9 and acylation, while the same intermediate **31** could yield laurefucin (**1**) from H_2O attack at C10 and S_N2 of the alcohol onto the C9 bromide. Further support for this oxonium intermediate is in the generation of notoryne (**51**),[25] via opening of **31** at C7 with a chloride nucleophile followed by an S_N2 displacement of the bromide located outside of the tetrahydrofuran ring by the alcohol.



Scheme 12: Transformation of Key Bicyclic Oxonium Intermediate into Natural Product Isolates.

Looking next in detail at proposals for 8-*exo* bromoether formation, a slightly different pathway would need to occur. First, a 5-*exo* bromoetherification from the linear precursors would generate again four stereodistinct tetrahydrofuran intermediates (**52a-d**, Scheme 13). Next, a second 5-*exo* bromocyclization would produce oxoniums **53a-d**, which, upon opening, would lead to the desired 8-*exo* bromoether cores **54-57**. In this case, all of the stereoisomers derived from the 6*R*,7*R*-laurediols are not naturally

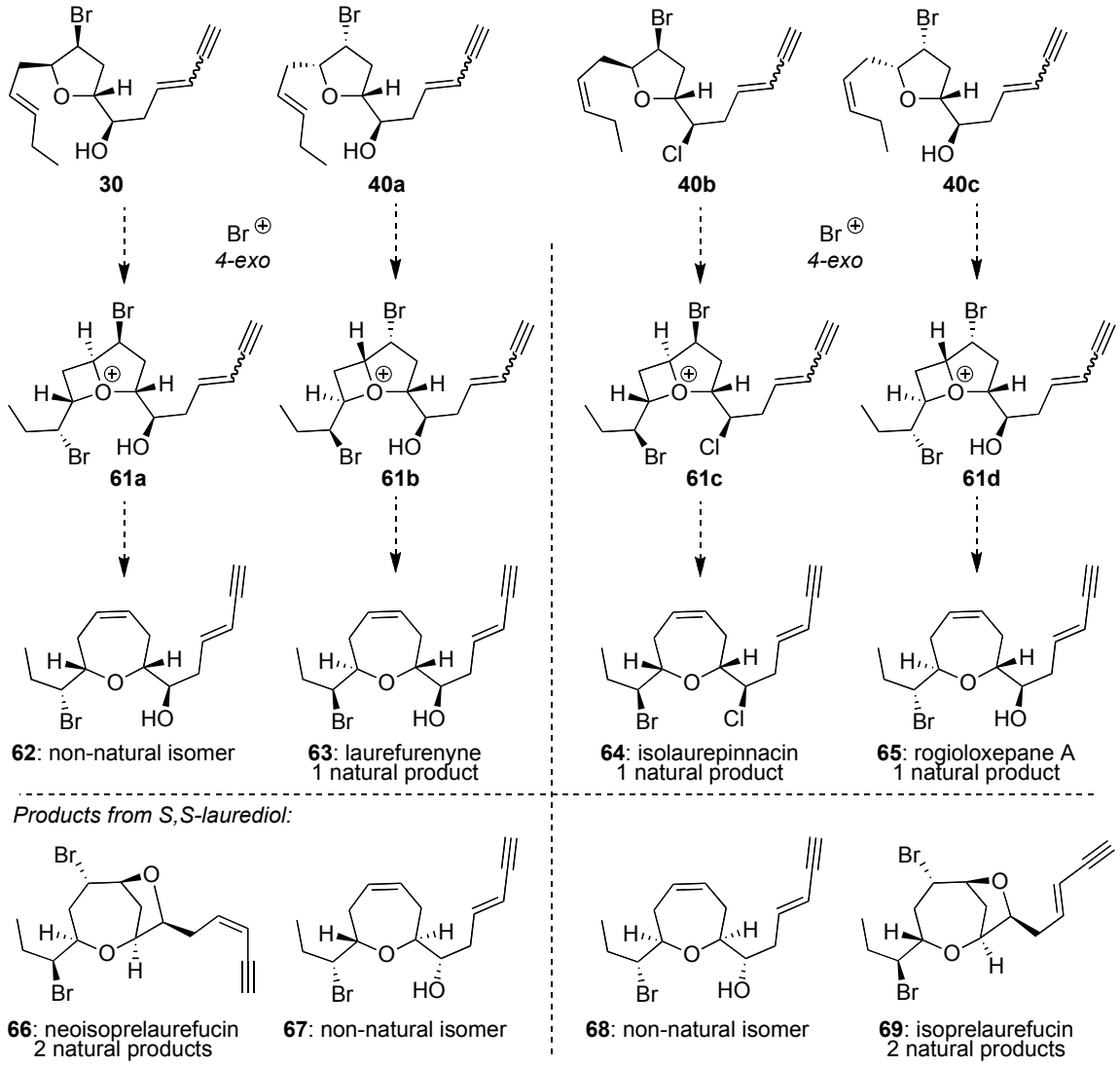
occurring (i.e. **54-57**), while those derived from the 6*S*,7*S*-laurediols (8-*exo* products **33** and **58-60**) correspond collectively to at least 13 natural isolates.[26]



Scheme 13: Proposed Biosynthesis of 8-*exo* Bromoethers

In addition to 8-membered bromoether cores, other medium-sized rings found in the same family include 7-*exo* and 9-*endo* bromoethers; there are no 7-*endo* or 9-*exo* isolates. Using this same general idea, 7-*exo* derivatives could arise from an initial 5-

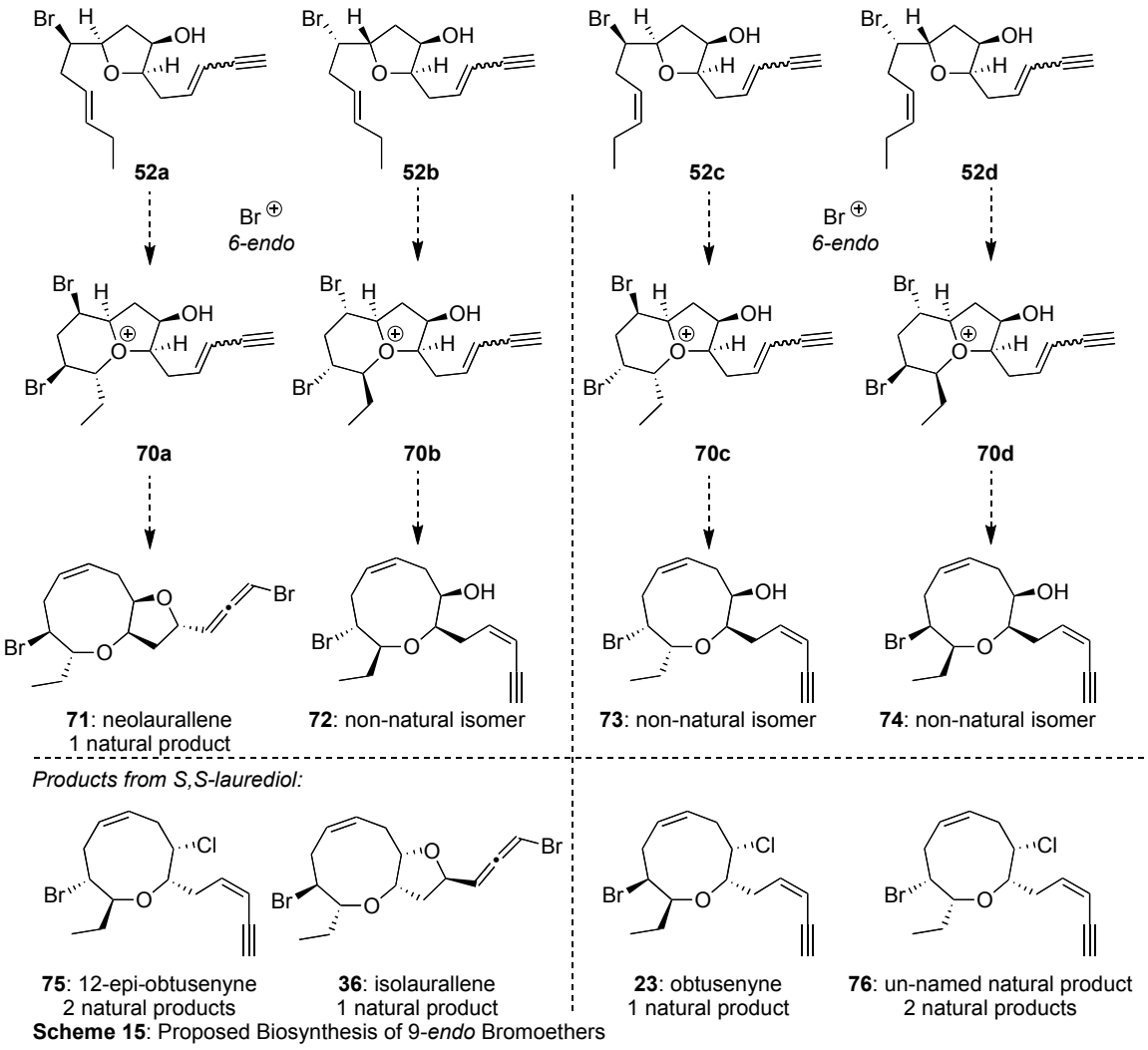
endo bromoetherification of linear laurediol to **30** and **40a-c**, followed by a 4-*exo* bromocyclization to overall generate **62 – 69** (Scheme 14). As drawn, this pathway would allow access to at least seven of the ten total isolated compounds with a 7-*exo* ring system.[27]



Scheme 14: Proposed Biosynthesis of 7-*exo* Bromoethers

The 9-*endo* alternatives could be produced via a 5-*exo* etherification followed by a 6-*endo* bromonium-induced cyclization to oxonium intermediates **70a-d**, which could then ring expand to the 9-*endo* bromoethers **71-76**, **23**, and **36** (Scheme 15).[28] In total,

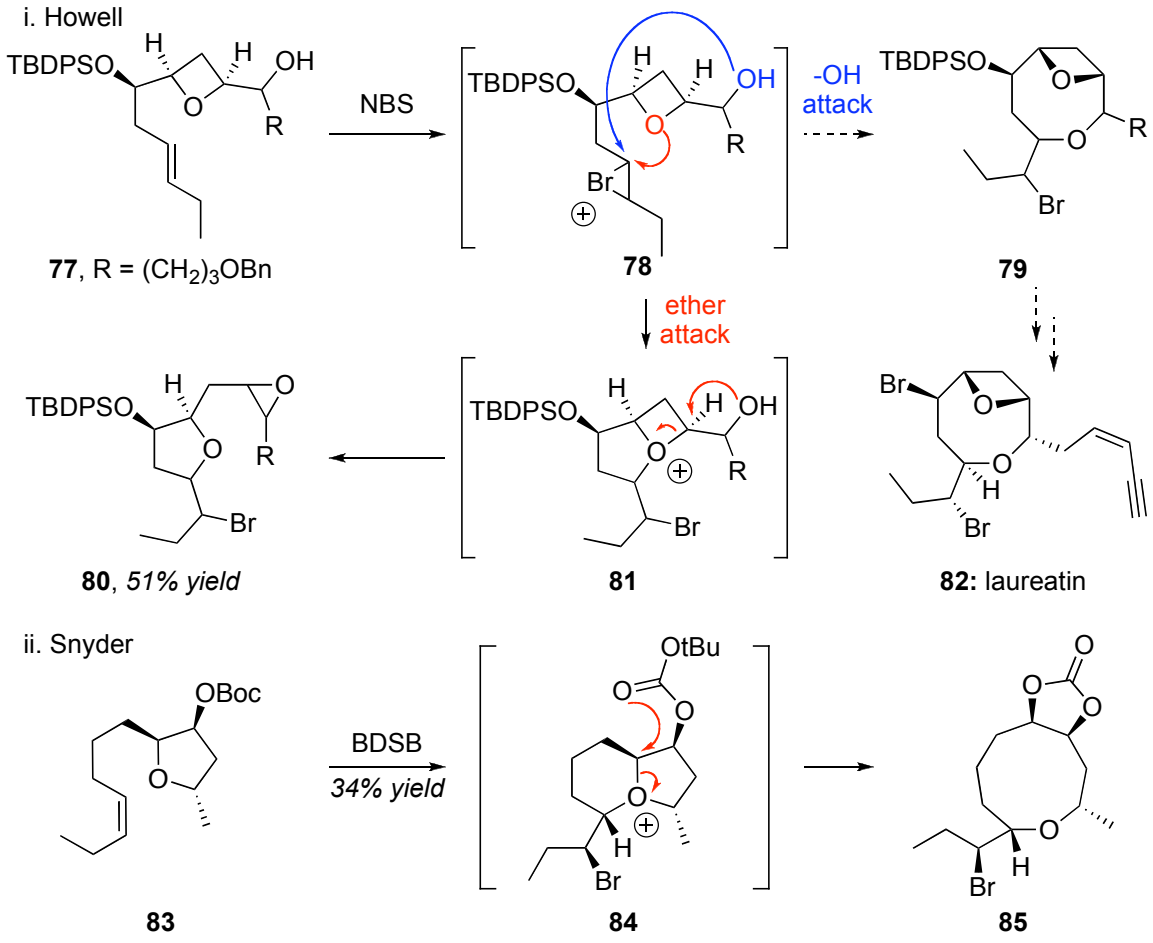
there are eight isolated 9-membered bromoethers; this proposed transformation accounts for the synthesis of seven of them along with three non-natural stereoisomers (**72-74**).



Scheme 15: Proposed Biosynthesis of 9-*endo* Bromoethers

These [2,3,0]- or [3,4,0]-oxonium intermediates, formed in these pathways leading to 7-*exo* or 9-*endo* systems, may not be as favored as the [3,3,0]-bicycle generated in the 8-membered rings synthesis, but they have been proposed by others, as intermediates previously to explain experimental results (Scheme 16).[29] A [2,3,0]-oxonium intermediate was first proposed by Howell and co-workers, when an unpredicted rearrangement occurred en route to their synthetic approach towards laureatin (**82**).[29b] Upon treatment of oxetane **77** with NBS, tetrahydrofuran **80** was

obtained in a 51% yield, presumably via the proposed oxonium intermediate **81**. The Howell group desired a direct 8-*exo* bromoetherification to occur with the free alcohol to generate **79**, again providing further support for the unlikelihood of such an unfavorable event. Additionally, as described in Chapter 4, in our own hands, a 6-*exo* bromocyclization of tetrahydrofuran **83** formed the [3,4,0]-oxonium species **84**, which then generated 9-*exo* bromoether **85**.[1]



Scheme 16: Examples of [2,3,0]- and [3,4,0]-oxonium Intermediates

This section has demonstrated how 7-*exo*, 8-*endo*, 8-*exo*, and 9-*endo* bromoethers can individually be generated from a linear laurediol precursor via a single biosynthesis hypothesis. The 7-*exo* isolates are derived from 5-*endo* and 4-*exo* bromocyclizations, while the 8-*endo* molecules would be synthesized via two 5-*endo* bromonium-induced

cyclizations. Additionally, the 8-*exo* and 9-*endo* products arise via a 5-*exo* bromoetherification followed by either a 5-*exo* or 6-*endo* bromocyclization. Based on further analysis of these medium-sized rings compared to the starting materials that they are derived from, it appears that the *R*-enantiomer of laurediol favors production of the 8-*endo* bromoethers while the 8-*exo* derivatives are derived mostly from the 6*S*,7*S*-laurediol linear precursors (Table 4). Interestingly, this idea is fully congruent with Murai and co-workers' results using enzymatic conditions as each enantiomer of laurediol only produced one 8-membered bromoether regioisomer (Scheme 9).[4] Because of this, we believe the *Laurencia* red algae are more selective in generating a variety of natural isolates, potentially choosing a single pathway for synthesis of a selected array of natural products, rather than Braddock's diversity-oriented hypothesis.[16]

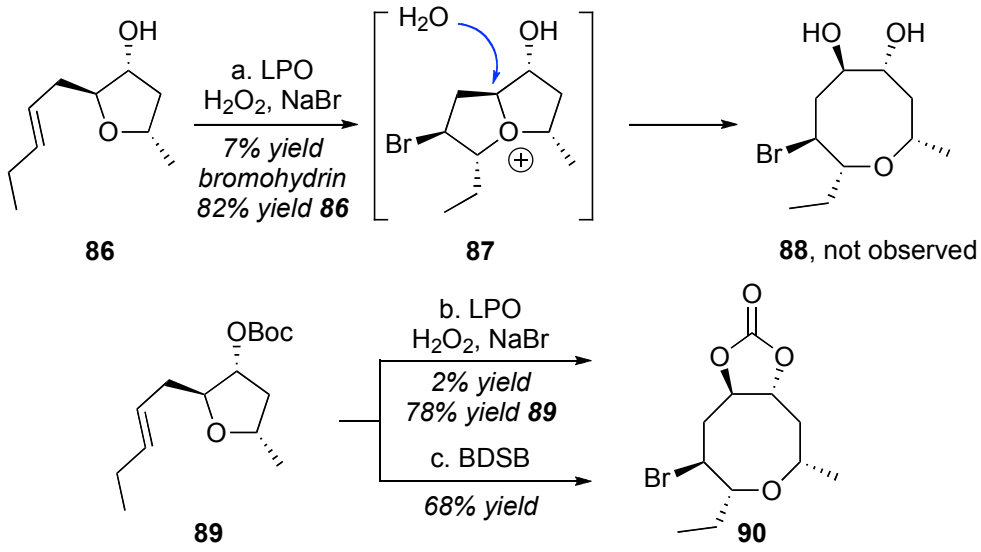
Table 4: Analysis of all Medium Sized Bromoethers

	Number of Natural Products Derived From:			
	R-enant		*S*-enant	
Product	**29a**	**38a**	**29b**	**38b**
7-*exo*	1	2	2	2
8-*endo*	**11**	**1**	5	0
8-*exo*	0	0	**10**	**2**
9-*endo*	1	0	3	3

5.5 Additional Evidence to Support Proposed Biogenetic Hypothesis

To provide additional support for above proposed biosynthesis, we decided to investigate two key experiments, namely: a) mimic enzymatic conditions and b) obtain proof of the existence of the proposed oxonium intermediates. The first follows the idea of Murai and co-workers using enzymes in a laboratory setting.[4] Specifically, since the Murai group has shown that LPO (lactoperoxidase) transformed linear laurediol into a 5-membered bromoether, we wished to examine the second half of our proposed

mechanism; that is, generation of the oxonium intermediate from the tetrahydrofuran followed by opening to the 8-membered bromoether. Additionally, the Murai team used both BPO and LPO in their enzymatic studies, showing both react similarly, though BPO is the active enzyme isolated in the *Laurencia* red algae. Since BPO is difficult to purify and LPO is commercially available, LPO was used for our studies in examining the ring expansion approach.

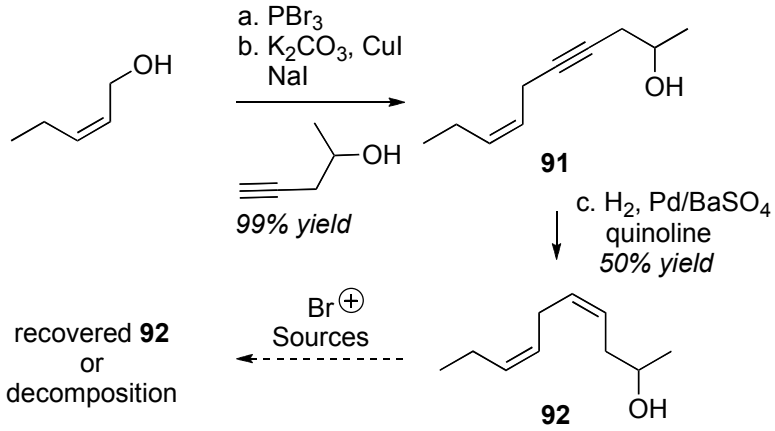


[a] Reagents and conditions: a. LPO (5 mg), H_2O_2, NaBr (1.0 equiv), phosphate buffer (50 mM, pH 5.5, 30 mL), 25 °C, 24 h, 0% yield **88**, 7% yield bromohydrin, 82% yield recovered **86**; b. LPO (5 mg), H_2O_2, NaBr (1.0 equiv), phosphate buffer (50 mM, pH 5.5, 30 mL), 25 °C, 24 h, 2% yield, 78% yield recovered **89**; c. BDSB (1.5 equiv), $MeNO_2$ (4.3 mL), -25 to 25 °C, 20 min, 68%.

Scheme 17: Mimicking Enzymatic Conditions from Tetrahydrofuran

Treatment of alcohol-containing tetrahydrofuran **86** (synthesized using the same sequence as in Chapter 4)[30] with LPO, hydrogen peroxide, and bromide anion did not generate any of the desired 8-membered bromoether (Scheme 17). Instead, most of the mass balance was unreacted **86** with an isolable amount of bromohydrin generation about the lone alkene in **86**. While characterization of these bromohydrins was challenging as multiple regioisomers and diastereomers were formed, treatment of the same starting

material (**86**) with NBS and water, a known procedure for bromohydrin generation,[31] produced the same ^{1}H NMR spectra. Since we previously learned that an intramolecular trap was necessary, tetrahydrofuran **89** was also tested, now producing 8-*endo* bromoether **90** in 2% yield along with mostly recovered **89**. To confirm this result, using our developed ring expansion method promoted by BDSB, **90** was generated in 68% yield as a single diastereomer. While nature here most likely does not use a *tert*-butyl carbonate as a trapping group, it does show that the enzyme generates a bromonium electrophile, either in the form of BrOH or Br_2, which is capable of performing the proposed transformation.[32] Thus, some assistance in ring opening is likely required.

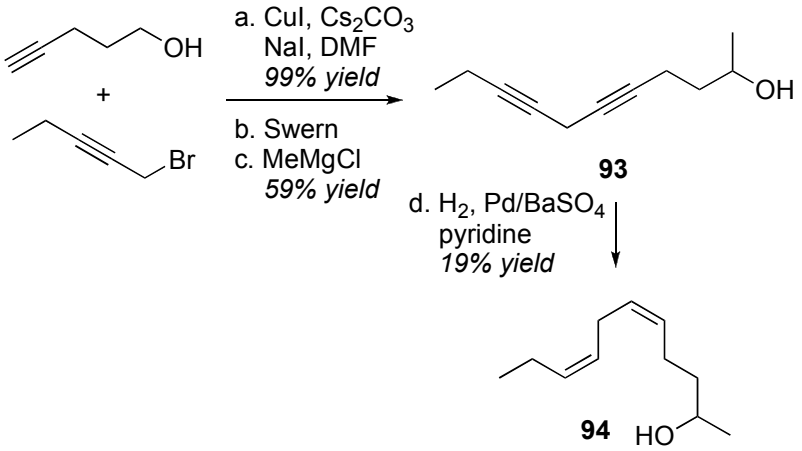


Reagents and Conditions: a. PBr_3 (1.2 equiv), Et_2O, 25°C, 1 h; b. 4-pentyn-2-ol (1 equiv), allylic bromide (2 equiv), K_2CO_3 (4 equiv), CuI (4 equiv), NaI (4 equiv), DMF, 25°C, 12 h, 99% yield; c. 5% Pd on $BaSO_4$, quinoline (0.2 equiv), EtOAc, H_2 balloon, 25°C, 5 h, 50% yield.

Scheme 18. Synthesis of Proposed 5-*endo* Linear Precursor

Next, we wondered how a linear source similar to laurediol without this directing group would behave in the presence of a bromonium electrophile(s) outside of enzymatic conditions. With an eye towards a linear precursor for 8-*endo* generation, produced via two 5-*endo* bromocyclizations, alcohol **92** was synthesized as it contains the same substitution pattern of the alcohol and alkenes as laurediol. As shown in Scheme 18, *cis*-

2-Penten-1-ol was first transformed into its bromide and then used as an electrophile to generate enyne **91**.[33] Reduction of the alkyne yielded skipped diene **92**, a compound that could not be transformed into the 5-*endo* bromoether despite the various conditions attempted.[34] This problem was encountered previously in Chapter 4, as 5-*endo* bromoetherifications are known to be slow and very substrate specific.

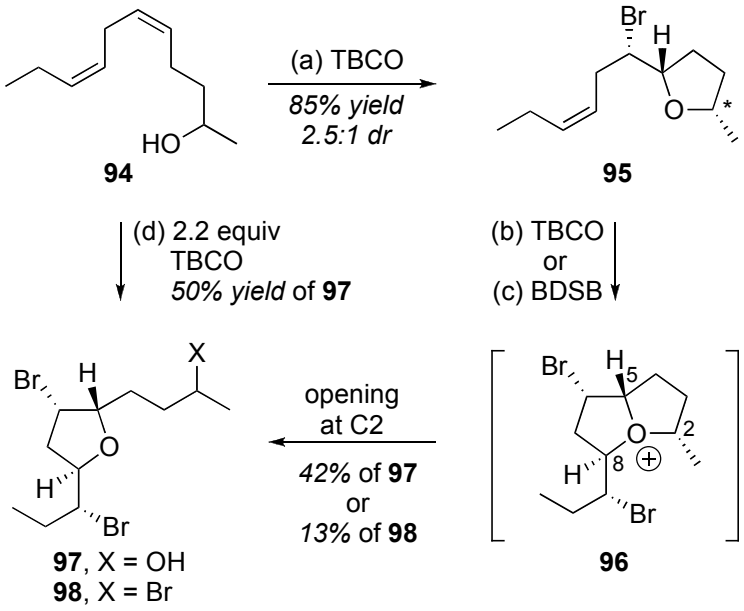


Reagents and Conditions: a. 4-bromo-2-pentyne (1.1 equiv), Cs_2CO_3 (2 equiv), NaI (2 equiv), CuI (1 equiv), DMF, 25°C, 2 h, 99% yield; b. $(COCl)_2$ (1.2 equiv), DMSO (2 equiv), Et_3N (4 equiv), CH_2Cl_2, -78 to 0°C, 3 h; d. MeMgCl (1.5 equiv), THF, -78 to -20°C, 2.5 h, 59% yield; d. 5% Pd on $BaSO_4$, pyridine, cyclohexene, H_2 balloon, 25°C, 3 h, 19% yield.

Scheme 19. Synthesis of Linear Skipped Diene Starting Material

With problems arising for this 5-*endo* cyclization, the 5-*exo* alternative was also attempted to be as thorough as possible. This linear starting material (**94**) would be poised for the generation of 8-*exo* bromoethers via two 5-*exo* cyclizations. Here, alkylation of 4-pentyn-1-ol followed by oxidation and Grignard addition produced diyne **93** in 58% overall yield (Scheme 19). Stereoselective reduction of both alkynes using poisoned palladium catalyst (i.e. Lindlar's catalyst) generated the desired skipped dieneol **94**,[16] the substrate used to test our hypothesis. Cyclization of linear precursor **94** using 1.1 equivalents of TBCO, an electrophilic bromonium source, produced the desired 5-*exo* bromoether **95** in 85% yield with 2.5:1 dr about the methyl stereocenter (Scheme 20).

BDSB was not used here since it is generally incompatible with free alcohols. Treatment of this new tetrahydrofuran **95** with another equivalent of TBCO in the presence of water produced dibromide **97** in 42% yield. We believe this product reflects a 5-*exo* bromocyclization to oxonium intermediate **96**, which, in the presence of water, opened at the least sterically hindered C2 position (over C5 or C8). It seems as though only a single diastereomer of the starting **95** (the major diastereomer) underwent this transformation, as the other diastereomer (minor) placed the methyl substituent in the concave face of the oxonium intermediate, possibly destabilizing the generated intermediate, which led to decomposition. Structural characterization of **97** was performed by 2D NMR spectroscopy, though additional structural conformation through derivatization to a crystalline solid and analysis by x-ray crystallography are in progress. Alternatively, treatment of 5-membered **95** with BDSB generated the same oxonium **96**, though now a bromide (from the $SbBrCl_5^-$ anion of BDSB) opened at C2 in a similar fashion to yield 13% of tetrahydrofuran **98**. It is likely here that a chloride is also opening the oxonium at C2 as numerous byproducts were detected using ^1H NMR analysis of the crude product mixture; their isolation and characterization proved too challenging to be practical.



[a] Reagents and conditions: (a) TBCO (1.1 equiv), CH_3CN (7.5 mL), -25 °C, 20 min, 85%, 2.5:1 dr; (b) TBCO (1.1 equiv), CH_3CN:H_2O (5:1, 11.2 mL), 25 °C, 15 min, 42% of **97**; (c) BDSB (1.2 equiv), $MeNO_2$ (13.8 mL), -25 to 25 °C, 20 min, 13% of **98**; (d) TBCO (1.1 equiv), CH_3CN (4.8 mL), - 25 °C, 15 min, then TBCO (1.1 equiv), H_2O (1.0 mL), 25 °C, 20 min, 50% of **97**.

Scheme 20. Experimental Results Supporting Hypothesized Biogenesis

Previously, only stepwise addition of a single equivalent of bromonium electrophile has been attempted; yet the overall transformation of linear alcohol **94** to tetrahydrofuran **95** underwent two 5-*exo* bromocyclizations, a new challenge we wished to probe directly. Surprisingly, treatment of skipped diene **94** with 2.2 equivalents of TBCO in the presence of water generated the desired alcohol **97** in 50% yield. This outcome suggests that this process could be completed in a single reaction pot, possibly something nature might also elect to deploy. With these systems, opening at C5 was not observed; once again, this reveals the need for enzymatic assistance or other participation to control opening to 8-membered rings.

5.6 Conclusion

The completed formal total synthesis of laurefucin has shown the effectiveness of our developed ring expansion strategy to transform easily prepared tetrahydrofuran derivatives into 8-membered bromoethers of the *Laurencia* family. This total synthesis is the shortest of the over 30 syntheses of any 8-membered ring in this family, demonstrating the efficiency of the single diastereoselective step. Due to the ability to synthesize complex tetrahydrofurans with great diastereocontrol, this transformation allows for the facile synthesis of stereochemically-rich medium-sized ethers. Additionally, the complexity of the derivatives used as starting materials in this chapter have shown the BDSB-promoted ring expansion step can encompass a variety of additional functional groups. This full article was highlighted in the January 2013 issue of Synfacts[35] and was also on the "Most Read Articles" list of JACS throughout November 2012.

Due to the ability to synthesize a variety of bromoether cores as well as three completed formal total syntheses, we believe this method may have implications in the biogenesis of these medium-sized bromoether isolates in nature. Instead of a direct, unfavorable 8-membered bromoetherification, two smaller ring formation events could generate the same products. We have been able to show that a tetrahydrofuran precursor was capable of transforming into an 8-membered ring under enzymatic conditions, albeit in trace yield. Additionally, the transformation of a linear precursor with two equivalents of bromonium electrophile was shown to intercept the proposed oxonium intermediate.

5.7 References

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5.8 Experimental Section

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry methylene chloride (CH_2Cl_2), benzene, toluene, diethyl ether (Et_2O) and tetrahydrofuran (THF) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns; nitromethane ($MeNO_2$) and acetonitrile (MeCN) were stored over 3 Å molecular sieves, pyridine was distilled from CaH_2 and stored over 3 Å molecular sieves; diisopropylamine (*i*-Pr_2NH) was distilled from KOH and stored over 3 Å molecular sieves; triethylamine (Et_3N) was distilled from KOH; acetone, dimethylsulfoxide (DMSO), *N,N*-dimethylformamide (DMF), ethanol (EtOH), and methanol (MeOH) were purchased in anhydrous form from Sigma-Aldrich and used as received. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Lactoperoxidase (LPO) from *Bovine Milk* was purchased from MP Biomedicals, LLC and stored at 2 °C in a phosphate buffer (pH 5.5, 50 mM). Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light and/or I_2 on silica as visualizing agents and an aqueous solution of phosphomolybdic acid and cerium sulfate or a solution of $KMnO_4$ in aqueous $NaHCO_3$ with heat as developing agents. Preparative thin-layer chromatography was carried out on 0.50 mm E. Merck silica gel plates (60F-254). SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. NMR spectra were recorded on Bruker DRX-300, DRX-

400, and 500 ASCEND instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. IR spectra were recorded on a Nicolet Avatar 370 DTGS series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded in the Columbia University Mass Spectral Core facility on a JOEL HX110 mass spectrometer using FAB (Fast Atom Bombardment) and EI (Electron Ionization) techniques.

Abbreviations. AcOH = acetic acid, BF_3•OEt_2 = boron trifluoride diethyl etherate, Boc_2O = di-*tert*-butyl dicarbonate, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIAD = diisopropyl azodicarboxylate, DIBAL-H = diisobutylaluminum hydride, 4-DMAP = 4-(dimethylamino)pyridine, MeMgCl = methyl magnesium chloride, MeNH(OBz)•HCl = *N*-(benzoyloxy)-methylamine hydrochloride, MsCl = methanesulfonyl chloride, NBS = *N*-bromosuccinimide, nBuLi = *n*-butyl lithium, NCS = *N*-chlorosuccinimide, TBCO = 2,4,4,6-tetrabromo-2,5-cyclohexadienone, TFAA = trifluoroacetic anhydride.

Formal Total Synthesis of Laurefucin:

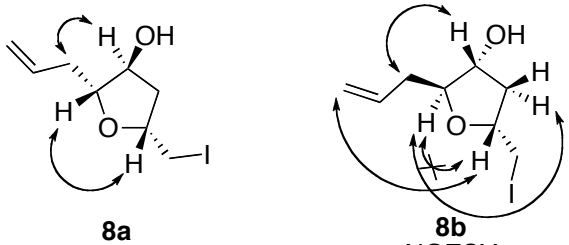
9. Prepared according to a procedure adapted from the work of Tomkinson and co-workers: a) Beshara, C. S.; Hall, A.; Jenkins, R. L.; Jones, T. C.; Parry, R. T.; Thomas, S. P.; Tomkinson, N. C. O. *Chem. Comm.* **2005**, 1478; b) Beshara, C. S.; Hall, A.; Jenkins, R. L.; Jones, K. L.; Jones, T. C.; Killeen, N. M.; Taylor, P. H.; Thomas, S. P.; Tomkinson, N. C. O. *Org. Lett.* **2005**, *7*, 5729. 4-Pentenal (2.69 g, 32.1 mmol, 1.0 equiv) was dissolved in DMSO (44 mL) at 25 °C, and then MeNH(OBz)•HCl (7.20 g,

38.5 mmol, 1.2 equiv) was added slowly. The resultant reaction solution was then stirred at 25 °C for 5 h. Upon completion (as monitored by ^{1}H NMR analysis of small reaction aliquots), the reaction mixture was quenched with water (50 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were then washed with water (3 × 20 mL), dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 19:1→1:1) to afford the desired alpha-benzoylated aldehyde **10** as a light yellow solid (3.18 g, 49% yield). Next, a portion of **10** (1.59 g, 7.80 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (94 mL) and cooled to –78 °C. A solution of $TiCl_4$ (1.0 M in CH_2Cl_2, 9.36 mL, 9.36 mmol, 1.2 equiv) was then added dropwise and the reaction was stirred for 15 min at –78 °C. Next, allyltrimethylsilane (1.49 mL, 9.36 mmol, 1.2 equiv) was added, and the reaction solution was allowed to warm slowly to –20 °C over the course of 3 h. Upon completion, the reaction mixture was quenched with saturated aqueous NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude residue was then dissolved in a mixture of THF (47 mL) and MeOH (16 mL) at 25 °C. A solution of LiOH (1.86 g, 77.7 mmol, 10 equiv) in water (16 mL) was added and the reaction solution was allowed to stir for 2 h at 25 °C. Upon completion, the reaction mixture was quenched with water (100 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 5:1→2:3) to afford **9** as a mixture of diastereoisomers (5:1 *trans*:*cis*). Recrystallization of this mixture from hot hexanes (20 mL) afforded the *trans*-isomer of **9** (0.614 g, 55% yield over 2 steps) as a white crystalline solid. **9**: R_f = 0.25

(silica gel, hexanes:EtOAc, 7:3); IR (film) ν_{max} 3313 (br), 3077, 2901, 1053, 989, 915, 869 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.85 (m, 2 H), 5.21–5.14 (m, 4 H), 3.67 (m, 2 H), 2.36 (m, 2 H), 2.24 (m, 2 H), 2.06 (br s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.6 (2 C), 118.4 (2 C), 72.6 (2 C), 36.4 (2 C); HRMS: No molecular ion peak was observed.

8. Prepared according to a procedure adapted from the work of Castillón and co-workers: Díaz, Y.; Bravo, F.; Castillón, S. *J. Org. Chem.* **1999**, *64*, 6508. To a solution of **9** (0.614 g, 4.32 mmol, 1.0 equiv) in MeCN (18 mL) at 25 °C was added solid $NaHCO_3$ (0.726 g, 8.64 mmol, 2.0 equiv), and the resultant slurry was stirred for 10 min at 25 °C. Solid I_2 (2.19 g, 8.64 mmol, 2.0 equiv) was then added, and the reaction contents were stirred for an additional 3 h at 25 °C. Upon completion, the reaction mixture was quenched with saturated aqueous Na_2SO_3 (10 mL) and the resultant biphasic mixture was stirred vigorously for 10 min at 25 °C. The layers were then diluted with water (100 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated, and the resultant crude residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 9:1→7:3) to afford separable diastereomers **8a** (0.389 g, 34% yield) and **8b** (0.468 g, 42% yield). **8a**: light yellow viscous oil; R_f = 0.38 (silica gel, hexanes:EtOAc, 7:3); IR (film) ν_{max} 3392 (br), 2929, 1431, 1102, 917, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.85 (m, 1 H), 5.18–5.09 (m, 2 H), 4.18 (quintet, *J* = 2.8 Hz, 1 H), 4.12 (m, 1 H), 3.91 (td, *J* = 6.4, 3.2 Hz, 1 H), 3.31 (dd, *J* = 10.4, 4.4 Hz, 1 H), 3.25 (dd, *J* = 10.4, 6.4 Hz, 1 H), 2.38 (m, 1 H), 2.29 (m, 1 H), 2.06 (ddd, *J* = 13.6, 6.4, 2.8 Hz, 1 H), 1.88 (ddd, *J* = 14.4, 8.8, 6.4 Hz, 1 H), 1.65 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.0, 117.8, 86.6, 77.3, 75.6, 41.2, 38.6, 10.1; HRMS (FAB) calcd for $C_8H_{14}IO_2$ $[M+H]^+$ 269.0039, found 269.0054. **8b**: light

yellow viscous oil; R_f = 0.56 (silica gel, hexanes:EtOAc, 7:3); IR (film) ν_{max} 3412 (br), 2927, 1429, 1062, 988, 918, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.83 (m, 1 H), 5.18–5.09 (m, 2 H), 4.23–4.15 (m, 2 H), 4.01 (dt, *J* = 6.8, 4.0 Hz, 1 H), 3.35 (m, 2 H), 2.43 (quintet, *J* = 6.8 Hz, 1 H), 2.36–2.21 (m, 2 H), 1.86 (ddd, *J* = 13.6, 5.6, 5.2 Hz, 1 H), 1.78 (d, *J* = 4.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.8, 117.8, 85.2, 77.4, 75.7, 40.1, 37.7, 11.2; HRMS (FAB) calcd for $C_8H_{14}IO_2$ $[M+H]^+$ 269.0039, found 269.0038.



11. Prepared according to a procedure adapted from the work of Snyder and co-workers: Snyder, S. A.; Treitler, D. S.; Brucks, A. P.; Sattler. W. *J. Am. Chem. Soc.* **2011**, *133*, 15898 and Campagne and co-workers: Moreau, X.; Bazán-Tejeda, B.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 7288. To a solution of **8b** (0.468 g, 1.80 mmol, 1.0 equiv) in CH_2Cl_2 (23 mL) at 25 °C was sequentially added *trans*-3-hexene (1.34 mL, 10.8 mmol, 6.0 equiv) and the 2nd generation Hoveyda-Grubbs (9 mg, 0.01 mmol, 0.008 equiv). The resultant reaction contents were stirred for 3 h at 25 °C. Upon completion (as monitored by ^1H NMR analysis of small reaction aliquots), the reaction was concentrated directly, and the resultant crude residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 9:1→7:3) to afford the desired cross-metathesized product (0.371 g, 78% yield) as a light yellow oil. Next, this newly synthesized material (0.371 g, 1.40 mmol, 1.0 equiv) and Boc_2O (1.22 g, 5.60 mmol, 4.0 equiv) were dissolved in CH_2Cl_2 (22 mL), and 4-DMAP (0.034 g, 0.28 mmol, 0.20 equiv) and Et_3N (0.293 mL,

2.10 mmol, 1.5 equiv) were added sequentially at 25 °C. The reaction solution was stirred at 25 °C for 5 h. Upon completion, the reaction contents were concentrated, taken up in DMSO (1.4 mL), and then powdered KOH (0.392 g, 7.00 mmol, 5.0 equiv) was added at 25 °C. This reaction mixture was then stirred vigorously for 3 h at 25 °C [this procedure was employed to remove the di-*tert*-butylcarbonate by-product] before being quenched with water (50 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were then washed with water (2 × 25 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant crude residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 99:1→9:1) to afford **11** (0.479 g, 87% yield over 2 steps, contaminated with ~5% of an unknown side-product) as a colorless viscous oil. **11**: R_f = 0.63 (silica gel, hexanes:EtOAc, 9:1); IR (film) ν_{max} 2974, 1738, 1369, 1278, 1163, 968 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.55 (m, 1 H), 5.36 (m, 1 H), 4.82 (dt, *J* = 6.4, 3.2 Hz, 1 H), 4.27 (m, 1 H), 4.15 (td, *J* = 6.0, 2.8 Hz, 1 H), 3.29 (dd, *J* = 9.6, 5.6 Hz, 1 H), 3.21 (dd, *J* = 9.6, 8.4 Hz, 1 H), 2.43 (quintet, 7.2 Hz, 1 H), 2.29–2.20 (m, 2 H), 2.05–1.95 (m, 3 H), 1.46 (s, 9 H), 0.94 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 135.6, 123.3, 83.7, 82.4, 79.8, 78.3, 37.0, 36.3, 27.7 (3 C), 25.5, 13.6, 9.7; HRMS (FAB) calcd for $C_{15}H_{26}IO_4$ $[M+H]^+$ 397.0876, found 397.0884.

13. Prepared according to a procedure adapted from the work of Fujioka and co-workers: Fujioka, H.; Maehata, R.; Wakamatsu, S.; Nakahara, K.; Hayashi, T.; Oki, T. *Org. Lett.* **2012**, *14*, 1054. Thiophenol (0.126 mL, 1.22 mmol, 2.0 equiv) was added dropwise to a suspension of NaH (60 % dispersion in mineral oil, 0.041 g, 1.2 mmol, 2.0 equiv) in DMF (3.0 mL) at 0 °C. The reaction flask was allowed to warm to 25 °C and maintained at that temperature for 1 h. Next, a solution of **11** (0.240 g, 0.610 mmol, 1.0

equiv) in DMF (3.0 mL) was added. After stirring for 4 h at 25 °C, the reaction contents were quenched with 1 M HCl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with water (2 × 10 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant crude residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 99:1→9:1) to afford the desired sulfide intermediate **12a** (0.195 g, 85% yield) as a colorless viscous oil. Moving forward, **12a** (0.195 g, 0.520 mmol, 1.0 equiv) was dissolved in a mixture of THF (4.4 mL) and water (1.3 mL), cooled to 0 °C, and NCS (0.076 g, 0.57 mmol, 1.1 equiv) was added in a single portion. The reaction contents were then allowed to warm slowly to 25 °C over 12 h with stirring. Upon completion, the reaction mixture was quenched with saturated aqueous Na_2SO_3 (5 mL) and stirred vigorously for 10 min. The contents were then diluted with water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to afford the desired sulfoxide intermediate, which was carried forward without any additional purification. Next, the newly prepared sulfoxide (0.520 mmol assumed) was dissolved in CH_2Cl_2 (4.5 mL) and cooled to 0 °C. TFAA (0.253 mL, 1.82 mmol, 3.5 equiv) and 2,6-lutidine (0.212 mL, 1.82 mmol, 3.5 equiv) were sequentially added dropwise. The reaction contents were stirred for 10 min at 0 °C, then water (5 mL) and excess solid $NaHCO_3$ were added at 0 °C. The resultant biphasic solution was stirred vigorously for 24 h at 25 °C, then poured into water (50 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resultant crude residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 9:1→7:3) to afford **13** (0.106 g, 71% yield over 2 steps, contaminated with ~5% of an unknown side product) as

a light yellow viscous oil. **13**: R_f = 0.61 (silica gel, hexanes:EtOAc, 7:3); IR (film) ν_{max} 2966, 2934, 1735, 1370, 1275, 1254, 1157, 1101 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.74 (d, *J* = 1.2 Hz, 1 H), 5.59 (m, 1 H), 5.40 (m, 1 H), 4.85 (dt, *J* = 6.2, 2.0 Hz, 1 H), 4.39 (ddd, *J* = 9.6, 2.8, 1.2 Hz, 1 H), 4.24 (td, *J* = 6.4, 1.6 Hz, 1 H), 2.45 (ddd, *J* = 14.8, 10.0, 6.0 Hz, 1 H), 2.28–2.21 (m, 3 H), 2.09–1.99 (m, 2 H), 1.46 (s, 9 H), 0.98 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.7, 152.7, 136.1, 123.1, 84.8, 82.8, 82.0, 78.9, 36.7, 34.1, 27.7 (3 C), 25.6, 13.6; HRMS (FAB) calcd for $C_{15}H_{25}O_5$ $[M+H]^+$ 285.1702, found 285.1693.

6. A solution of BDSB (0.066 g, 0.12 mmol, 1.2 equiv) in $MeNO_2$ (0.5 mL) was added quickly via syringe to a solution of **13** (0.028 g, 0.10 mmol, 1.0 equiv) in $MeNO_2$ (4.5 mL) at –25 °C. After stirring the reaction contents for 15 min at –25 °C, the flask was removed from the cooling bath and stirred at 25 °C for an additional 5 min. At this time, the reaction mixture was quenched by the addition of water (10 mL) and the reaction contents were extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. Purification of the resultant crude residue by flash column chromatography (silica gel, hexanes:EtOAc, 7:3→2:3) afforded **6** (0.017 g, 56% yield) as a light yellow viscous oil. **6**: R_f = 0.35 (silica gel, hexanes:EtOAc, 1:1); IR (film) ν_{max} 2936, 2882, 1802, 1737, 1207, 1057 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.70 (s, 1 H), 4.72 (t, *J* = 9.5 Hz, 1 H), 4.56 (ddd, *J* = 11.5, 9.0, 3.0 Hz, 1 H), 4.01 (ddd, *J* = 14.0, 10.0, 4.0 Hz, 1 H), 3.95 (dd, *J* = 12.0, 2.0 Hz, 1 H), 3.49 (ddd, *J* = 9.5, 6.0, 3.0 Hz, 1 H), 3.02 (dd, *J* = 15.0, 4.0 Hz, 1 H), 2.53 (dt, *J* = 13.5, 2.5 Hz, 1 H), 2.42 (m, 1 H), 2.11–2.00 (m, 2 H), 1.85 (septet, *J* = 7.0 Hz, 1 H), 1.00 (t, *J* =

7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.1, 152.7, 90.6, 84.9, 83.1, 82.2, 47.3, 43.3, 34.4, 27.5, 8.4; HRMS: No molecular ion peak was observed.

15. To a solution of **6** (0.012 g, 0.039 mmol, 1.0 equiv) in CH_2Cl_2 (0.52 mL) at –78 °C was added BF_3•OEt_2 (0.030 mL, 0.20 mmol, 5.0 equiv). After stirring for 10 min at –78 °C, allyltrimethylsilane (0.024 mL, 0.20 mmol, 5.0 equiv) was then added. The reaction contents were then allowed to warm to –20 °C over the course of 3 h with stirring. Upon completion, the reaction mixture was quenched with water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. The resultant crude residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 4:1→1:1) to afford the allylic alcohol intermediate (8 mg, 59% yield) as a colorless viscous oil. Moving forward, the allylic alcohol (8 mg, 0.023 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (0.1 mL) and cooled to 0 °C. MsCl (5.2 mL, 0.069 mmol, 3.0 equiv) and Et_3N (19 mL, 0.12 mmol, 6.0 equiv) were added sequentially, and the reaction mixture was then allowed to warm to 25 °C and was stirred at that temperature for 2 h. Upon completion, the reaction mixture was quenched with water (2 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 4:1→1:1) to afford **15** (8 mg, 59% yield, 1:1 d.r.) as a light yellow viscous oil.

17a. To a solution of **13** (0.050 g, 0.18 mmol, 1.0 equiv) in CH_2Cl_2 (2.4 mL) at –78 °C was added BF_3•OEt_2 (0.11 mL, 0.90 mmol, 5.0 equiv). After stirring for 10 min at –78 °C, allyltrimethylsilane (0.14 mL, 0.90 mmol, 5.0 equiv) was then added. The reaction contents were then allowed to warm to –20 °C over the course of 3 h with

stirring. Upon completion, the reaction mixture was quenched with water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated to provide the desired crude allyl alcohol **17a**. Only ^{1}H NMR was completed for characterization of **17a**.

17b. To a solution of **13** (0.050 g, 0.18 mmol, 1.0 equiv) in CH_2Cl_2 (1.8 mL) at –78 °C was added $TiCl_4$ (1.0 M in CH_2Cl_2, 0.18 mL, 0.18 mmol, 1.0 equiv). After stirring for 10 min at –78 °C, allyltrimethylsilane (0.034 mL, 0.21 mmol, 1.2 equiv) was then added. The reaction contents were then allowed to stir at –78 °C for 20 min. Upon completion, the reaction mixture was quenched with water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated to provide the desired crude allyl alcohol **17b**. Only ^{1}H NMR was completed for characterization of **17b**.

19. To a solution of the crude allylic alcohol **17a** (0.019 g, 0.058 mmol, 1.0 equiv) in Et_2O (0.35 mL) at –20 °C was added PBr_3 (2.7 μL, 0.029 mmol, 0.5 equiv). The reaction was allowed to stir at –20 °C for 30 min. Upon completion, the reaction mixture was quenched with water (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated to provide the desired crude allylic bromide **19**. Only ^{1}H NMR was completed for characterization of **19**.

18b. Allyl alcohol **17a** (0.18 mmol assumed, 1.0 equiv) was dissolved in CH_2Cl_2 (0.52 mL) and cooled to 0 °C. MsCl (0.041 mL, 0.53 mmol, 3.0 equiv) and Et_3N (0.147 mL, 1.06 mmol, 6.0 equiv) were added sequentially, and the reaction mixture was then allowed to warm to 25 °C and was stirred at that temperature for 2 h. Upon completion,

the reaction mixture was quenched with water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 9:1→7:3) to afford **18b** (0.058 g, 81% yield over 2 steps, contaminated with ~5% of an unknown side product) as a light yellow viscous oil. **18b**: R_f = 0.68 (silica gel, hexanes:EtOAc, 7:3); IR (film) ν_{max} 2966, 1738, 1356, 1277, 1255, 1170, 944, 915 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (m, 1 H), 5.56 (m, 1 H), 5.35 (m, 1 H), 5.20–5.14 (m, 2 H), 4.88–4.81 (m, 2 H), 4.14 (ddd, *J* = 10.4, 6.8, 4.0 Hz, 1 H), 4.06 (td, *J* = 6.8, 3.2 Hz, 1 H), 3.07 (s, 3 H), 2.53–2.35 (m, 3 H), 2.22–2.10 (m, 3 H), 2.01 (quintet, *J* = 7.6 Hz, 2 H), 1.48 (s, 9 H), 0.96 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 135.8, 132.0, 123.3, 119.1, 83.0, 82.6, 82.1, 79.2, 77.5, 38.5, 36.8, 35.6, 31.8, 27.7 (3 C), 25.6, 13.6; HRMS (FAB) calcd for $C_{19}H_{33}O_7S$ $[M+H]^+$ 405.1947, found 405.1961.

15. A solution of BDSB (0.037 g, 0.067 mmol, 1.5 equiv) in $MeNO_2$ (0.23 mL) was added quickly via syringe to a solution of **18b** (0.018 g, 0.045 mmol, 1.0 equiv) in $MeNO_2$ (2.0 mL) at –25 °C. After stirring the reaction contents for 5 min at –25 °C, the flask was removed from the cooling bath and stirred at 25 °C for an additional 10 min. At this time, the reaction mixture was quenched by the addition of 5% aqueous Na_2SO_3 (3 mL) and saturated aqueous $NaHCO_3$ (3 mL). After stirring the resultant mixture vigorously for 5 min at 25 °C, the reaction contents were extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. Purification of the resultant crude residue by flash column chromatography (silica gel, hexanes:EtOAc, 9:1→1:1) afforded **15** (0.014 g, 72% yield) as a colorless viscous oil.

15: R_f = 0.23 (silica gel, hexanes:EtOAc, 7:3); IR (film) ν_{max} 2972, 1801, 1351, 1207, 1173, 1056, 917 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.77 (m, 1 H), 5.25–5.19 (m, 2 H), 4.70–4.63 (m, 2 H), 4.53 (ddd, *J* = 11.5, 9.0, 3.0 Hz, 1 H), 4.02–3.92 (m, 2 H), 3.59 (dt, *J* = 10.0, 4.0 Hz, 1 H), 3.04 (s, 3 H), 2.98 (dd, *J* = 15.0, 3.5 Hz, 1 H), 2.53 (m, 1 H), 2.43–2.32 (m, 2 H), 2.27 (m, 1 H), 2.10–1.90 (m, 3 H), 0.97 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.8, 132.1, 119.8, 88.7, 83.3, 83.1, 82.3, 82.0, 46.4, 43.0, 38.8, 34.8, 33.9, 26.1, 6.5; HRMS (FAB) calcd for $C_{15}H_{24}BrO_7S$ $[M+H]^+$ 427.0426, found 427.0437.

4. A solution of **15** (6 mg, 0.014 mmol, 1.0 equiv) in toluene (0.14 mL) was cooled to –78 °C and DIBAL-H (1.0 M in toluene, 0.07 mL, 0.07 mmol, 5.0 equiv) was then added dropwise. The reaction contents were then allowed to warm to 25 °C over the course of 4 h with stirring, and then the maintained at that temperature for an additional 2 h. Upon completion, the reaction contents were quenched with 1 M aqueous sodium/potassium tartrate (1 mL) and the resulting biphasic solution was stirred vigorously for 2 h at 25 °C. The layers were then separated and the aqueous fraction was extracted with EtOAc (3 × 10 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. Purification of the resultant crude residue by flash column chromatography (silica gel, hexanes:EtOAc, 9:1→1:4) afforded **4** (2 mg, 46% yield) as a colorless viscous oil, which was spectroscopically identical to the same intermediate obtained in the original total synthesis by Kim et al: Kim, B.; Lee, M.; Kim, M. J.; Lee, H.; Kim, S.; Kim, D.; Koh, M.; Park, S. B.; Shin, K. J. *J. Am. Chem. Soc.* **2008**, *130*, 16807. **4**: R_f = 0.35 (silica gel, hexanes:EtOAc, 1:1); IR (film) ν_{max} 3404 (br), 2923, 1463, 1065, 969, 753 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.82 (m, 1 H), 5.14 (d, *J*

= 17.5 Hz, 1 H), 5.07 (d, *J* = 10.5 Hz, 1 H), 4.18 (dd, *J* = 8.0, 3.5 Hz, 1 H), 4.03 (br s, 1 H), 3.98 (br d, *J* = 8.5 Hz, 1 H), 3.87–3.82 (m, 2 H), 3.51 (t, *J* = 9.0 Hz, 1 H), 2.52 (d, *J* = 14.0 Hz, 1 H), 2.46–2.35 (m, 3 H), 2.30–2.19 (m, 2 H), 2.09 (m, 1 H), 1.89 (ddd, *J* = 14.0, 8.0, 2.0 Hz, 1 H), 1.48 (m, 1 H), 0.96 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.6, 117.2, 83.5, 83.2, 80.2, 77.8, 76.7, 53.0, 42.0, 34.2, 33.1, 28.2, 9.7; HRMS: No molecular ion peak was observed.

Table S1. Spectral comparison of intermediate **4**.

^{1}H NMR	
Kim et al	**Present Work**
5.82 (dddd, *J* = 17.2, 10.2, 7.0, 7.0 Hz, 1 H)	5.82 (m, 1 H)
5.14 (dd, *J* = 17.1, 1.3 Hz, 1 H)	5.14 (d, *J* = 17.5 Hz, 1 H)
5.07 (d, *J* = 10.2 Hz, 1 H)	5.07 (d, *J* = 10.5 Hz, 1 H)
4.18 (dd, *J* = 8.0, 3.8 Hz, 1 H)	4.18 (dd, *J* = 8.0, 3.5 Hz, 1 H)
4.03 (s, 1 H)	4.03 (br s, 1 H)
3.98–3.96 (m, 1 H)	3.98 (br d, *J* = 8.5 Hz, 1 H)
3.87–3.82 (m, 2 H)	3.87–3.82 (m, 2 H)
3.51 (ddd, *J* = 11.0, 11.0, 2.1 Hz, 1 H)	3.51 (t, *J* = 9.0 Hz, 1 H)
2.52 (d, *J* = 14.4 Hz, 1 H)	2.52 (d, *J* = 14.0 Hz, 1 H)
2.46–2.37 (m, 2 H)	2.46–2.35 (m, 3 H)
2.37 (dd, *J* = 9.8, 4.8 Hz, 1 H)	
2.30–2.25 (m, 1 H)	2.30–2.19 (m, 2 H)
2.10–2.07 (m, 1 H)	2.09 (m, 1 H)
1.89 (ddd, *J* = 14.3, 8.1, 2.3 Hz, 1 H)	1.89 (ddd, *J* = 14.0, 8.0, 2.0 Hz, 1 H)
1.51–1.45 (m, 1 H)	1.48 (m, 1 H)
0.96 (dd, *J* = 7.3, 7.3 Hz, 3 H)	0.96 (t, *J* = 7.5 Hz, 3 H)
^{13}C NMR	
134.8	134.6
117.4	117.2

83.7	83.5
83.5	83.2
80.5	80.2
77.9	77.8
76.9	76.7
53.2	53.0
42.2	42.0
34.4	34.2
33.3	33.1
28.4	28.2
9.9	9.7

Synthesis of the Core of 3E-Dehydrobromolaurefucin:

27. A solution of IDSI (0.048 g, 0.060 mmol, 1.2 equiv) in $MeNO_2$ (0.5 mL) was added quickly via syringe to a solution of **11** (0.020 g, 0.050 mmol, 1.0 equiv) in $MeNO_2$ (2.0 mL) at –25 °C. After stirring for 15 min at –25 °C, the flask was removed from the cooling bath and then stirred at 25 °C for an additional 10 min. At this time, the reaction mixture was quenched by the addition of 5% aqueous Na_2SO_3 (3 mL) and saturated aqueous $NaHCO_3$ (3 mL). After stirring the resultant mixture vigorously for 5 min at 25 °C, the reaction contents were extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. The resultant crude residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 9:1→3:2) to afford **27** (0.013 g, 54% yield) as a colorless viscous oil. **27**: R_f = 0.59 (silica gel, hexanes:EtOAc, 7:3); IR (film) ν_{max} 2964, 1801, 1354, 1208, 1050, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.67 (t, *J* = 9.0 Hz, 1 H), 4.51 (ddd, *J* = 11.5, 9.5, 3.5 Hz, 1 H), 4.07 (ddd, *J* = 14.5, 10.5, 4.0 Hz, 1 H), 3.62–3.55 (m, 2 H), 3.25 (dd, *J* = 10.5, 4.0

Hz, 1 H), 3.17 (dd, *J* = 10.0, 7.0 Hz, 1 H), 3.06 (dd, *J* = 15.0, 4.0 Hz, 1 H), 2.61 (ddd, *J* = 13.0, 3.5, 2.0 Hz, 1 H), 2.52 (ddd, *J* = 21.5, 12.0, 9.0 Hz, 1 H), 2.12–2.02 (m, 2 H), 1.95 (m, 1 H), 0.94 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 89.0, 83.7, 83.4, 80.0, 45.6, 38.9, 28.6, 26.0, 8.1, 7.5; HRMS (FAB) calcd for $C_{11}H_{17}I_2O_4$ $[M+H]^+$ 466.9216, found 466.9220.

28. DBU (0.014 mL, 0.095 mmol, 5.0 equiv) was added to a solution of **27** (9 mg, 0.019 mmol, 1.0 equiv) in toluene (0.19 mL) at 25 °C, and the resultant solution was stirred at 25 °C for 24 h. Upon completion, the reaction contents were purified directly by flash column chromatography (silica gel, hexanes:EtOAc, 9:1→3:2) to afford the desired olefin intermediate (6 mg, 92% yield) as a colorless viscous oil. Next, this newly synthesized material (6 mg, 0.018 mmol, 1.0 equiv) was dissolved in MeOH (0.18 mL) and solid K_2CO_3 (0.025 g, 0.18 mmol, 10. equiv) was added at 0 °C. The reaction contents were then allowed to warm to 25 °C and stirred for 12 h. Upon completion, the reaction mixture was quenched with water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. Purification of the resultant crude residue by flash column chromatography (silica gel, hexanes:EtOAc, 9:1→1:1) afforded **28** (4 mg, 99% yield) as a light yellow viscous oil. **28**: R_f = 0.29 (silica gel, hexanes:EtOAc, 1:1); IR (film) ν_{max} 3416 (br), 2935, 1120, 1041, 855, 687 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 5.48 (ddd, *J* = 12.0, 4.5, 2.0 Hz, 1 H), 5.16–5.10 (m, 2 H), 4.23 (dd, *J* = 7.0, 3.5 Hz, 1 H), 3.88 (d, *J* = 9.5 Hz, 1 H), 3.67 (t, *J* = 2.0 Hz, 1 H), 3.53 (dd, *J* = 9.5, 3.0 Hz, 1 H), 3.33 (m, 1 H), 2.30 (d, *J* = 13.5 Hz, 1 H), 2.02 (br s, 1 H), 1.41–1.34 (m, 2 H), 1.11 (ddd, *J* = 13.5, 7.0, 3.0 Hz, 1 H), 0.88 (t, *J* = 7.0

Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 133.6, 128.4, 86.1, 79.8, 78.8, 76.9, 73.8, 33.4, 28.9, 10.1; HRMS (FAB) calcd for $C_{10}H_{17}O_3$ $[M+H]^+$ 185.1178, found 185.1181.

Mimicking Enzymatic Conditions Results:

86. To solution of alcohol precursor synthesized in Chapter 4 (0.224 g, 1.43 mmol, 1.0 equiv) in toluene (14 mL) was added triphenylphosphine (0.563 g, 2.15 mmol, 1.5 equiv). The solution was cooled to 0 °C, and sequentially, AcOH (0.246 mL, 4.29 mmol, 3.0 equiv) then DIAD (0.338 mL, 1.72 mmol, 1.2 equiv) were added dropwise. The solution was then heated to 40 °C for 4 hours. Upon completion, the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with H_2O (5 mL), brine (5 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 1:0 to 20:3) to afford the desired inverted acetylated alcohol (0.244 g, 80% yield) as a colorless viscous oil. Next, K_2CO_3 (0.473 g, 3.42 mmol, 3.0 equiv) was added to a solution of the newly prepared tetrahydrofuran (0.244 g, 1.14 mmol, 1.0 equiv) in MeOH (11.0 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was quenched with water (5 mL) and saturated aqueous NH_4Cl (5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed brine (5 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the resultant oil by flash column chromatography (silica gel, hexanes:EtOAc, 1:0 to 2:3) afforded the desired alcohol (0.188 g, 97% yield) as a colorless viscous oil. **86**: R_f = 0.49 (silica gel, hexanes:EtOAc, 1:1); IR (film) ν_{max} 3412 (br), 2965, 2929, 1442, 1377, 1017, 966 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.58 (dt, *J*

= 15.2, 6.0 Hz, 1 H), 5.43 (dt, *J* = 15.2, 7.2 Hz, 1 H), 4.16 (sextet, *J* = 6.8 Hz, 1 H), 4.10 (q, *J* = 6.0 Hz, 1 H), 3.82 (q, *J* = 6.8 Hz, 1 H), 2.36 (dt, *J* = 13.2, 6.8 Hz, 1 H), 2.30 – 2.12 (m, 2 H), 2.02 (quintet, *J* = 6.8 Hz, 2 H), 1.79 (br s, 1 H), 1.56 (ddd, *J* = 12.8, 7.2, 6.0 Hz, 1 H), 1.30 (d, *J* = 6.4 Hz, 3 H), 0.97 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.3, 124.3, 84.4, 76.3, 73.3, 42.1, 36.4, 25.6, 22.2, 13.8; HRMS (FAB) calcd for $C_{10}H_{17}O_2$ $[M–H]^+$ 169.1229, found 169.1225.

Enzymatic Results with 86. Procedure adapted from the enzymatic work of Muria and coworkers: Fukuzawa, A.; Aye, M.; Nakamura, M.; Tamaura, M.; Murai, A. *Chemistry Lett.* **1990**, 1287. A solution of tetrahydrofuran **86** (0.0170 g, 0.100 mmol, 1.0 equiv) in DMSO (0.2 mL) was added to a separate solution of phosphate buffer (pH 5.5, 50 mM, 29.2 mL) containing NaBr (10.3 mg, 0.100 mmol, 1.0 equiv). To the mixture was added an aliquot of each solution of H_2O_2 (30% in water, 0.8 nM in final solution, 91 nL in 1.2 mL phosphate buffer) and LPO (5 mg in 1.2 mL phosphate buffer) divided into 12 portions over 2 h (0.1 mL aliquots each every 10 min). The reaction was stirred in the dark for 24 h at 25 °C. The reaction contents were extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with H_2O (20 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by preparative thin-layer chromatography (silica gel, hexanes:EtOAc 7:3) to afford the presumed bromohydrins of **86** (2 mg, 7% yield) along with recovered tetrahydrofuran **86** (0.0140 g, 82% yield RSM). An exhaustive characterization of the mix of regio- and diastereomeric bromohydrins was not completed, though the ^{1}H NMR was compared to that of the below reaction. R_f = 0.28 (silica gel, hexanes:EtOAc, 1:1); IR (film) ν_{max} 3397 (br), 2964, 2926, 1555, 1460, 1383, 1082 cm^{-1}; HRMS (FAB) calcd for $C_{10}H_{20}BrO_3$ $[M+H]^+$ 267.0596,

found 267.0594.

Bromohydrin Formation. To a solution of alcohol **86** (0.0100 g, 0.0588 mmol, 1.0 equiv) in THF (0.5 mL) and H_2O (0.1 mL) was added NBS (0.0126 g, 0.0706 mmol, 1.2 equiv) at 25 °C. The reaction was allowed to stir at 25 °C for 1 h. Upon completion, the reaction mixture was quenched by the addition of a combination of saturated aqueous $NaHCO_3$ and 5% aqueous Na_2SO_3 (1:1, 5 mL), and the resultant biphasic mixture was stirred vigorously for 20 min at 25 °C. The reaction contents were added to brine (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 4:1 to 1:4) to afford the bromohydrins (0.010 g, 52% yield calculated without succinimide impurity).

89. Alcohol **86** (0.056 g, 0.33 mmol, 1.0 equiv) was dissolved in THF (2.8 mL) and cooled to 0 °C. nBuLi (2.5 M in hexanes, 0.13 mL, 0.33 mmol, 1.0 equiv) was added dropwise and the resultant solution was stirred at 0 °C for 5 min. A solution of Boc_2O (0.065 g, 0.30 mmol, 0.9 equiv) in THF (0.5 mL) was then added dropwise, and the resultant colorless solution was removed from the ice bath and stirred at 25 °C for 1 h. Upon completion, the reaction mixture was quenched with water (5 mL) and NH_4Cl (5 mL), and extracted with Et_2O (3 × 5 mL). The combined organic layers were washed brine (5 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the resultant oil by flash column chromatography (silica gel, hexanes:EtOAc, 1:0 to 20:1) afforded the desired carbonate **89** (0.071 g, 80% yield) as a colorless viscous oil. **89**: R_f = 0.65 (silica gel, hexanes:EtOAc, 4:1); IR (film) ν_{max} 2971, 2933, 1737, 1254, 1109, 966 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.57 (td, *J* = 15.2, 6.4 Hz, 1 H), 5.41 (td, *J* = 15.2, 7.2 Hz, 1

H), 4.82 (quintet, *J* = 4.4 Hz, 1 H), 4.21 (sextet, *J* = 6.0 Hz, 1 H), 4.08 (td, *J* = 6.4, 3.2 Hz, 1 H), 2.44 (dt, *J* = 14.0, 7.2 Hz, 1 H), 2.24 (t, *J* = 6.8 Hz, 2 H), 2.02 (q, *J* = 7.2 Hz, 2 H), 1.67 (ddd, *J* = 13.6, 6.4, 4.4 Hz, 1 H), 1.48 (s, 9 H), 1.29 (d, *J* = 6.4 Hz, 3 H), 0.97 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 135.2, 124.0, 82.3, 82.2, 80.8, 73.7, 39.1, 36.2, 27.8 (3 C), 25.6, 21.7, 13.7; HRMS (FAB) calcd for $C_{15}H_{27}O_4$ $[M+H]^+$ 271.1909, found 127.1922.

Enzymatic Results with 89. Prepared according to the above enzymatic results procedure using tetrahydrofuran **89** (0.027 g, 0.10 mmol, 1.0 equiv). The resultant residue was purified by preparative thin-layer chromatography (silica gel, hexanes:EtOAc 7:3) to afford the desired 8-*endo* bromoether **90** (0.6 mg, 2% yield) as a colorless viscous oil along with recovered tetrahydrofuran **89** (0.021 g, 78% yield RSM). **90**: R_f = 0.53 (silica gel, hexanes:EtOAc, 7:3); IR (film) ν_{max} 2971, 2929, 1780, 1203, 1045, 776 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72 (t, *J* = 9.6 Hz, 1 H), 4.49 (ddd, *J* = 12.0, 9.2, 3.6 Hz, 1 H), 3.89 (ddd, *J* = 11.6, 10.0, 4.0 Hz, 1 H), 3.67 (sextet of d, *J* = 6.0, 4.0 Hz, 1 H), 3.38 (ddd, *J* = 9.6, 6.0, 3.2 Hz, 1 H), 2.94 (dd, *J* = 14.8, 4.0 Hz, 1 H), 2.38 (ddd, *J* = 21.6, 12.0, 9.6 Hz, 1 H), 2.22 (ddd, *J* = 13.6, 3.2, 2.0 Hz, 1 H), 2.05 – 1.88 (m, 2 H), 1.71 (sextet, *J* = 7.2 Hz, 1 H), 1.27 (d, *J* = 6.0 Hz, 3 H), 0.94 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 88.2, 84.0, 82.6, 77.8, 48.4, 43.4, 41.3, 27.3, 23.0, 8.2; HRMS (FAB) calcd for $C_{11}H_{18}BrO_4$ $[M+H]^+$ 293.0388, found 293.0388.

Control Experiments: The above enzymatic reaction was additionally performed exactly as above with these two variations:

1. Same conditions as above *without* addition of the LPO. This resulted in recovered tetrahydrofuran **89** (0.022 g, 82% yield RSM) and no observed 8-*endo*

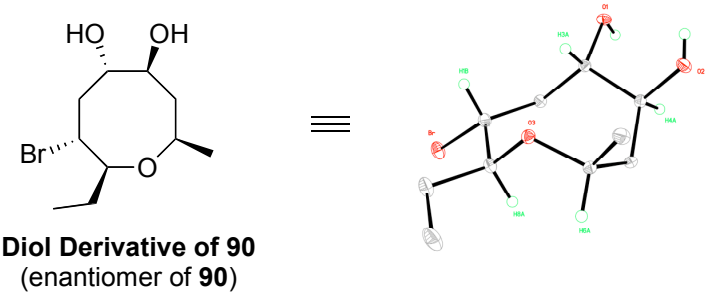
bromoether **90**.

2. Tetrahydrofuran **89** (0.022 g, 0.0822 mmol, 1.0 equiv) was dissolved in DMSO (0.16 mL). To this solution, the phosphate buffer (pH 5.5, 50 mM, 24.0 mL) and Br_2 (4.21 mL, 0.0822 mmol, 1.0 equiv) were added sequentially. The reaction was stirred in the dark for 24 h at 25 °C. The reaction contents were extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with H_2O (20 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by preparative thin-layer chromatography (silica gel, hexanes:EtOAc 7:3) to afford the desired 8-*endo* bromoether **90** (0.5 mg, 2% yield) along with recovered tetrahydrofuran **89** (0.017 g, 78% yield RSM).

Cyclization BDSB. A cold (–25 °C) solution of BDSB (0.0701 g, 0.128 mmol, 1.5 equiv) in $MeNO_2$ (0.3 mL) was added rapidly via syringe to a solution of the cyclization precursor **89** (0.0230 g, 0.0851 mmol, 1.0 equiv) in $MeNO_2$ (4.0 mL) at –25 °C. After stirring the resultant yellow solution for 15 min at –25 °C, the flask was removed from the cold bath and stirred for an additional 5 min. Upon completion, the reaction mixture was quenched by the addition of a combination of saturated aqueous $NaHCO_3$ and 5% aqueous Na_2SO_3 (1:1, 5 mL), and the resultant biphasic mixture was stirred vigorously for 20 min at 25 °C. The reaction contents were added to brine (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes:EtOAc) to afford the desired 8-*endo* bromoether **90** (0.017 g, 68% yield).

Diol Derivative of 90. To a solution of cyclic carbonate **90** (0.017 g, 0.058

mmol, 1.0 equiv) in MeOH (2.1 mL) and H_2O (0.23 mL) was added K_2CO_3 (0.080 g, 0.58 mmol, 10. equiv) at 0 °C. The reaction mixture was allowed to warm slowly to 25 °C and monitored by TLC. After 2 h, the reaction mixture was quenched with the addition of saturated aqueous NH_4Cl (5 mL) and water (5 mL), and the crude product was extracted into EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by flash column chromatography (silica gel, hexanes:EtOAc 4:1 to 1:4) afforded the desired diol derivative of **90** (0.011 g, 71% yield) as white crystalline solid. Recrystallization was performed by slow evaporation from a hexanes:CH_2Cl_2 mixture to afford single crystals suitable for X-ray diffraction. R_f = 0.38 (silica gel, hexanes:EtOAc, 1:1); IR (film) ν_{max} 3372 (br), 2969, 2935, 1452, 1120, 1030, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.98 – 3.88 (m, 2 H), 3.80 – 3.70 (m, 2 H), 3.34 (td, *J* = 9.6, 2.0 Hz, 1 H), 2.83 (br s, 1 H), 2.71 (br s, 1 H), 2.59 (m, 1 H), 2.34 (ddd, *J* = 16.0, 10.4, 6.0 Hz, 1 H), 2.12 – 2.11 (m, 2 H), 1.73 (m, 1 H), 1.36 (m, 1 H), 1.25 (d, *J* = 6.4 Hz, 3 H), 0.96 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 86.1, 76.6, 75.5, 75.4, 53.8, 42.7, 40.9, 27.8, 22.6, 10.1; HRMS (FAB) calcd for $C_{10}H_{20}BrO_3$ $[M+H]^+$ 267.0596, found 267.0591.



Diol Derivative of 90
(enantiomer of **90**)

Results using Bromonium Electrophile with Linear Precursors:

92. Prepared according to procedures adapted from the work of Taber and coworkers: Taber, D. F.; Reedy, P. G.; Arneson, K. O. *J. Org. Chem.* **2008**, *73*, 3467 and

Snyder and coworkers: Snyder, S. A.; Brucks, A. P.; Treitler, D. S.; Moga, I. *J. Am. Chem. Soc.* **2012**, *134*, 17714. A solution of *cis*-2-penten-1-ol (1.00 mL, 10.0 mmol, 1.0 equiv) in Et_2O (20 mL) was cooled to 0 °C and PBr_3 (1.13 mL, 12.0 mmol, 1.2 equiv) was added dropwise. The ice bath was removed and the solution was allowed to stir at 25 °C for 1 h. Upon completion, the reaction mixture was quenched with the addition of water (5 mL) and saturated aqueous $NaHCO_3$ (5 mL) and the crude product was extracted into Et_2O (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered, and carefully concentrated to afford the desired allylic bromide as a colorless oil, which was carried forward without any additional purification. To a solution of the freshly prepared allylic bromide (10.0 mmol assumed, 2.0 equiv) in DMF (6.0 mL) was added 4-pentyn-2-ol (0.472 mL, 5.0 mmol, 1.0 equiv), K_2CO_3 (2.76 g, 20.0 mmol, 4.0 equiv), CuI (1.90 g, 10.0 mmol, 2.0 equiv), and NaI (3.00 g, 20.0 equiv, 4.0 mmol) sequentially. The reaction was stirred for 12 h at 25 °C. Upon completion, the reaction mixture was quenched with the addition of water (10 mL), and the crude product was extracted into EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by flash column chromatography (silica gel, hexanes:EtOAc 9:1 to 7:3) afforded the desired product **91** (0.76 g, 99% yield, as a 4.7:1 desired:S_N2' alkylation) as a colorless viscous oil. Lastly, a portion of **91** (0.400 g, 2.65 mmol, 1.0 equiv) in EtOAc (13.3 mL) was added to a solution of 5% Pd on $BaSO_4$ (0.119 g) and quinoline (0.0626 mL, 0.530 mmol, 0.20 equiv) in EtOAc (13.3 mL). After the heterogeneous mixture was allowed to stirred for 5 h at 25 °C, the reaction mixture was filtered through a pad of Celite and rinsed with EtOAc (10 mL). The filtrate was washed with 1 M HCl (10 mL), dried ($MgSO_4$),

filtered, and concentrated. Purification by flash column chromatography (silica gel, hexanes:EtOAc 9:1 to 7:3) afforded the desired product **92** (0.225 g, 50% yield) as a colorless viscous oil (contaminated with ~10% of an inseparable, unidentified impurity). **92**: R_f= 0.42 (silica gel, hexanes:EtOAc, 7:3); IR (film) ν_{max} 3340 (br), 2924, 2963, 2874, 1457, 1375, 1077, 942, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.60 – 5.32 (m, 4 H), 3.81 (m, 1 H), 2.76 (t, *J* = 6.8 Hz, 2 H), 2.31 – 2.26 (m, 2 H), 2.04 – 1.93 (m, 2 H), 1.56 (br s, 1 H), 1.20 (d, *J* = 6.0 Hz, 3 H), 0.96 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.7, 131.3, 126.9, 125.6, 67.6, 37.0, 30.5, 25.5, 22.8, 13.8; HRMS: no molecular ion peak was observed.

93. Prepared according to a procedure adapted from the work of Pivnitsky and coworkers: Lapitskaya, M. A.; Vasiljeva, L. L.; Pivnitsky, K. K. *Synthesis* **1993**, 65. 1-Bromo-2-pentyne (1.12 mL, 11.0 mmol, 1.1 equiv), Cs_2CO_3 (6.52 g, 20.0 mmol, 2.0 equiv), NaI (3.00 g, 20.0 mmol, 2.0 equiv), and CuI (1.90 g, 10.0 mmol, 1.0 equiv) were added sequentially to a solution of 4-pentyn-1-ol (0.931 mL, 10.0 mmol, 1.0 equiv) in DMF (10. mL) at 25 °C. The reaction was allowed to stir at 25 °C for 2 h, then quenched by the addition of saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 9:1 to 1:1) to afford the desired internal alkyne (1.50 g, 99% yield) as an orange oil. Next, to a solution of oxalyl chloride (1.02 mL, 12.0 mmol, 1.2 equiv) in CH_2Cl_2 (90 mL) at –78 °C, DMSO (1.42 mL, 20.0 mmol, 2.0 equiv) was added dropwise over the course of 5 min, and the resultant colorless solution was stirred at –78 °C for 5 min. A solution of the freshly prepared alcohol (1.50 g, 10.0 mmol, 1.0 equiv) in CH_2Cl_2

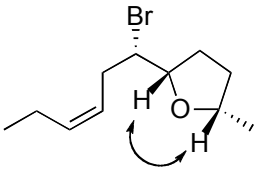
(10 mL) was then added slowly over the course of 10 min, and the resultant colorless solution was stirred for an additional 5 min at –78 °C. Finally, Et_3N (5.58 mL, 40.0 mmol, 4.0 equiv) was added slowly via syringe, and the reaction contents were allowed to warm slowly to 0 °C over the course of 3 h. Upon completion, the reaction contents were quenched by the addition of water (40 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were then washed with 1 M HCl (20 mL), dried ($MgSO_4$), filtered, and concentrated to afford the desired aldehyde as a light yellow oil, which was carried forward without any additional purification. The freshly prepared aldehyde (10.0 mmol assumed) was then dissolved in THF (50 mL), cooled to –78 °C, and MeMgCl (3.0 M in THF, 5.0 mL, 15.0 mmol, 1.5 equiv) was added dropwise. The reaction was allowed to warm slowly to –20 °C over the course of 2.5 h. Upon completion, the reaction contents were quenched by the slow addition of water (15 mL) and 1 M HCl (15 mL), then extracted with EtOAc (2 × 10 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 9:1 to 1:1) to afford the desired alcohol **93** (0.965 g, 59% yield over two steps) as a yellow oil. **93:** R_f = 0.42 (silica gel, hexanes:EtOAc, 7:3); IR (film) ν_{max} 3369 (br), 2972, 2935, 1320, 1127, 1078, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.93 (sextet, J = 6.0 Hz, 1 H), 3.10 (sextet, J = 2.4 Hz, 2 H), 2.31 – 2.26 (m, 2 H), 2.16 (qt, J = 7.6, 2.4 Hz, 2 H), 1.77 (br s, 1 H), 1.65 – 1.58 (m, 2 H), 1.20 (d, J = 6.4 Hz, 3 H), 1.11 (t, J = 8.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.9, 79.8, 75.3, 73.6, 67.2, 37.6, 23.3, 15.4, 13.8, 12.3, 9.7; HRMS (FAB) calcd for $C_{11}H_{15}O$ $[M–H]^+$ 163.1123, found 163.1123.

94. Prepared according to a procedure adapted from the work of Braddock and co-

workers: Bonney, K. J.; Braddock, D. C. *J. Org. Chem.* **2012**, *77*, 9574. To a solution of **93** (0.965 g, 5.88 mmol, 1.0 equiv) in MeOH (26.5 mL) and cyclohexene (5.9 mL) was added quinoline (1.04 mL, 8.82 mmol, 1.5 equiv) and 5% Pd on $BaSO_4$ (0.415 g) sequentially. The heterogenous mixture was stirred at 25 °C for 10 min, a balloon of H_2 was added, and the reaction was allowed to stir at 25 °C for 3 h. Upon completion, the reaction was filtered through a pad of Celite with EtOAc (30 mL) and then quenched by the addition of 1 M HCl (15 mL), then extracted with EtOAc (2 × 10 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 9:1 to 4:1) to afford the desired alcohol **94** (0.185 g, 19% yield) as a light yellow oil. **94:** R_f = 0.55 (silica gel, hexanes:EtOAc, 7:3); IR (film) ν_{max} 3341 (br), 3010, 2965, 2930, 1458, 1128, 1082, 719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.43 – 5.26 (m, 4 H), 3.82 (sextet, *J* = 6.4 Hz, 1 H), 2.80 (t, *J* = 6.4 Hz, 2 H), 2.23 – 2.12 (m, 2 H), 2.08 (quintet, *J* = 7.2 Hz, 2 H), 1.58 – 1.49 (m, 2 H), 1.42 (br s, 1 H), 1.20 (d, *J* = 6.0 Hz, 3 H), 0.97 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.0, 129.4, 128.7, 127.2, 67.8, 39.0, 25.5, 23.7, 23.5, 20.6, 14.3; HRMS (FAB) calcd for $C_{11}H_{20}O$ $[M]^+$ 168.1514, found 168.1524.

95. To a solution of alcohol **94** (0.076 g, 0.45 mmol, 1.0 equiv) in MeCN (7.5 mL) was added solid TBCO (0.204 g, 0.50 mmol, 1.1 equiv) at –25 °C. The reaction was stirred at –25 °C for 20 min. Upon completion, the reaction quenched by the addition of combination of saturated aqueous $NaHCO_3$ and 5% aqueous Na_2SO_3 (1:1, 5 mL), and the resultant biphasic mixture was stirred vigorously for 20 min at 25 °C. The reaction contents were added to brine (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and

concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes:EtOAc) to afford the 5-*exo* bromoether **95** (0.095 g, 77% yield, 2.5:1 dr) as a colorless viscous oil (contaminated with ~10% of an inseparable, unidentified impurity). **95:** R_f = 0.46 (silica gel, hexanes:EtOAc, 9:1); IR (film) ν_{max} 2966, 2872, 1458, 1090, 883, 748 cm^{-1}; *Major diastereomer:* ^1H NMR (400 MHz, C_6D_6) δ 5.57 – 5.36 (m, 2 H), 4.10 (m, 1 H), 3.93 (td, *J* = 7.2, 3.6 Hz, 1 H), 3.77 (td, *J* = 6.8, 3.2 Hz, 1 H), 2.71 (t, *J* = 6.8 Hz, 2 H), 1.99 (quintet, *J* = 7.2 Hz, 2 H), 1.78 – 1.60 (m, 3 H), 1.13 (m, 1 H), 1.08 (d, *J* = 6.0 Hz, 3 H), 0.88 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.4, 125.2, 80.5, 76.4, 59.5, 34.1, 33.0, 30.3, 21.1, 20.8, 14.0; HRMS (FAB) calcd for $C_{11}H_{18}BrO$ $[M–H]^+$ 245.0541, found 245.0532.



86
NOESY
(C_6D_6, 400 MHz)

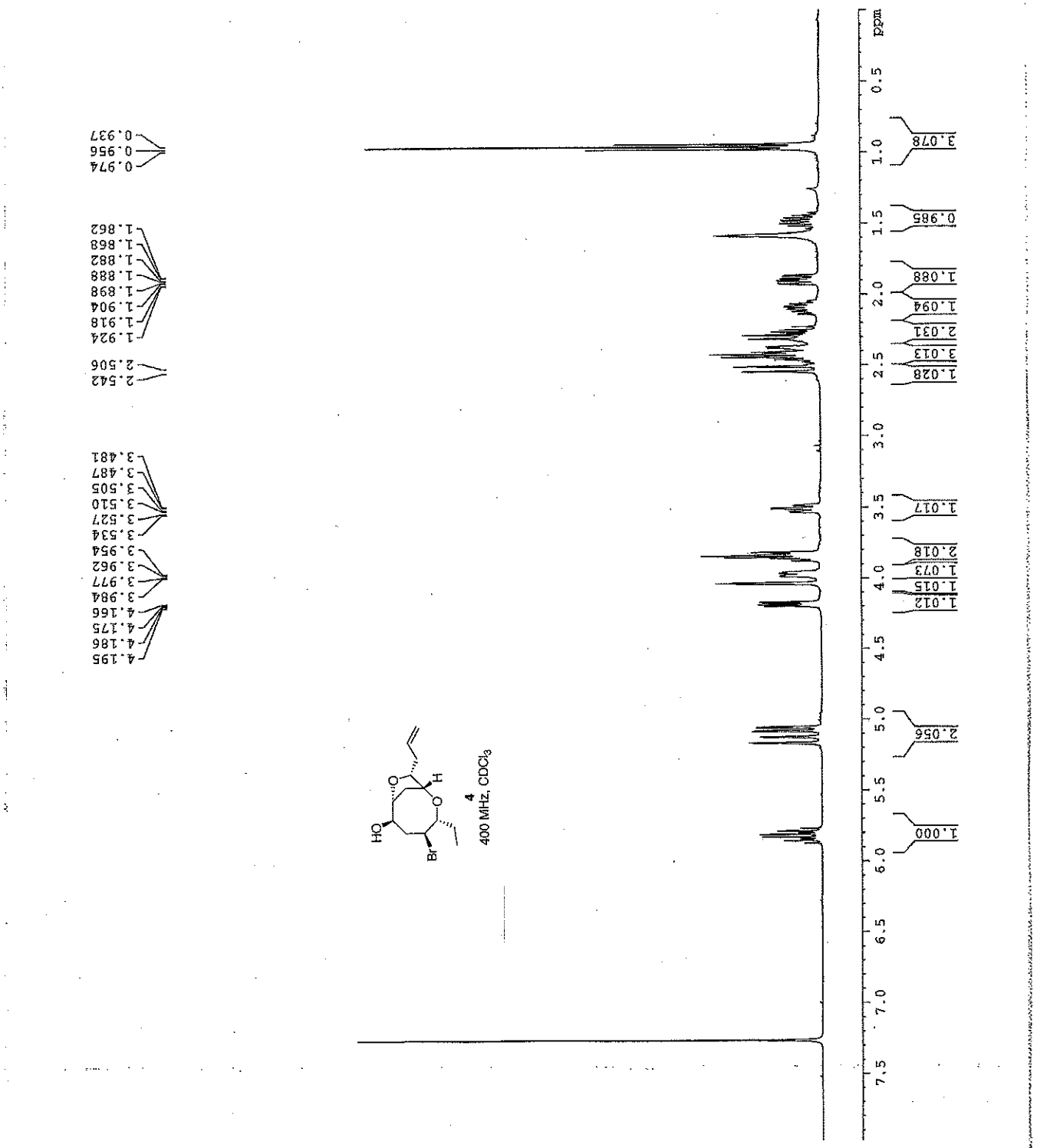
97. Solid TBCO (0.124 g, 0.303 mmol, 1.1 equiv) was added to a solution of substrate **95** (0.0680 g, 0.275 mmol, 1.0 equiv) in MeCN (9.3 mL) and water (1.9 mL) at 25 °C. The reaction was stirred at 25 °C for 15 min. Upon completion, the reaction quenched by the addition of combination of saturated aqueous $NaHCO_3$ and 5% aqueous Na_2SO_3 (1:1, 5 mL), and the resultant biphasic mixture was stirred vigorously for 20 min at 25 °C. The reaction contents were added to brine (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 9:1 to 7:3) to afford **97** (0.040 g, 38% yield)

as a colorless viscous oil (contaminated with ~10% of an inseparable, unidentified impurity). **97:** R_f = 0.35 (silica gel, hexanes:EtOAc, 7:3); IR (film) ν_{max} 3390 (br), 2966, 2930, 2875, 1456, 1107, 1062, 802 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 4.19 (m, 1 H), 3.95 (m, 1 H), 3.66 – 3.56 (m, 2 H), 3.42 (m, 1 H), 2.22 (ddd, *J* = 14.4, 9.6, 5.2 Hz, 1 H), 2.04 (dd, *J* = 14.0, 4.0 Hz, 1 H), 1.95 – 1.73 (m, 2 H), 1.72 – 1.53 (m, 2 H), 1.40 – 1.32 (m, 3 H), 1.01 (d, *J* = 6.4 Hz, 3 H), 0.88 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, C_6D_6) δ 83.6, 79.4, 67.3, 62.5, 56.3, 42.0, 36.0, 30.6, 29.5, 23.7, 12.8; HRMS (FAB) calcd for $C_{11}H_{21}BrO_2$ $[M+H]^+$ 342.9908, found 342.9895.

98. A solution of BDSB (0.181 g, 0.330 mmol, 1.2 equiv) in $MeNO_2$ (1.8 mL) was added rapidly via syringe to a solution of the cyclization precursor **95** (0.0680 g, 0.275 mmol, 1.0 equiv) in $MeNO_2$ (12 mL) at –25 °C. After stirring the resultant yellow solution for 10 min at –25 °C, the flask was removed from the cold bath and stirred for an additional 10 min. Upon completion, the reaction mixture was quenched by the addition of a combination of saturated aqueous $NaHCO_3$ and 5% aqueous Na_2SO_3 (1:1, 5 mL), and the resultant biphasic mixture was stirred vigorously for 20 min at 25 °C. The reaction contents were added to brine (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by preparative thin-layer chromatography (silica gel, hexanes:EtOAc 9:1) to afford **98** (0.013 mg, 10% yield) as a colorless viscous oil (contaminated with ~25% of an inseparable, unidentified impurity). **98**: R_f = 0.46 (silica gel, hexanes:EtOAc, 9:1); IR (film) ν_{max} 2968, 2929, 2877, 1441, 1203, 1108, 904, 802 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.58 (m, 1 H), 4.47 (ddd, *J* = 9.6, 6.4, 3.2 Hz, 1 H), 4.17 (m, 1 H), 3.98 – 3.91 (m, 2 H), 2.67 (ddd, *J* = 14.4, 9.6, 5.2

Hz, 1 H), 2.50 (dd, J = 14.0, 6.4 Hz, 1 H), 2.03 – 1.82 (m, 6 H), 1.73 (d, J = 6.4 Hz, 3 H), 1.10 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.6, 79.2, 61.8, 55.1, 51.2, 41.7, 37.6, 32.2, 28.9, 26.5, 12.7; HRMS (FAB) calcd for $C_{11}H_{18}Br_3O$ $[M–H]^+$ 402.8908, found 402.8902.

Double Bromonium Addition. To a solution of alcohol **94** (0.0505 g, 0.300 mmol, 1.0 equiv) in MeCN (4.8 mL) was added solid TBCO (0.135 g, 0.33 mmol, 1.1 equiv) at –25 °C. The reaction was stirred at –25 °C for 20 min. Water (1.0 mL) and another portion of TBCO (0.135 g, 0.33 mmol, 1.1 equiv) were added to the reaction mixture at 25 °C. The reaction was stirred at 25 °C for 30 min. Upon completion, the reaction quenched by the addition of combination of saturated aqueous $NaHCO_3$ and 5% aqueous Na_2SO_3 (1:1, 5 mL), and the resultant biphasic mixture was stirred vigorously for 20 min at 25 °C. The reaction contents were added to brine (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 9:1 to 7:3) to afford **97** (0.052 g, 50% yield).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3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
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1.088
1.094
2.031
3.013
1.028
1.017
2.018
1.073
1.015
1.012
2.056
1.000
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0.956
0.974
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1.868
1.882
1.888
1.898
1.904
1.918
1.924
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2.542
3.481
3.487
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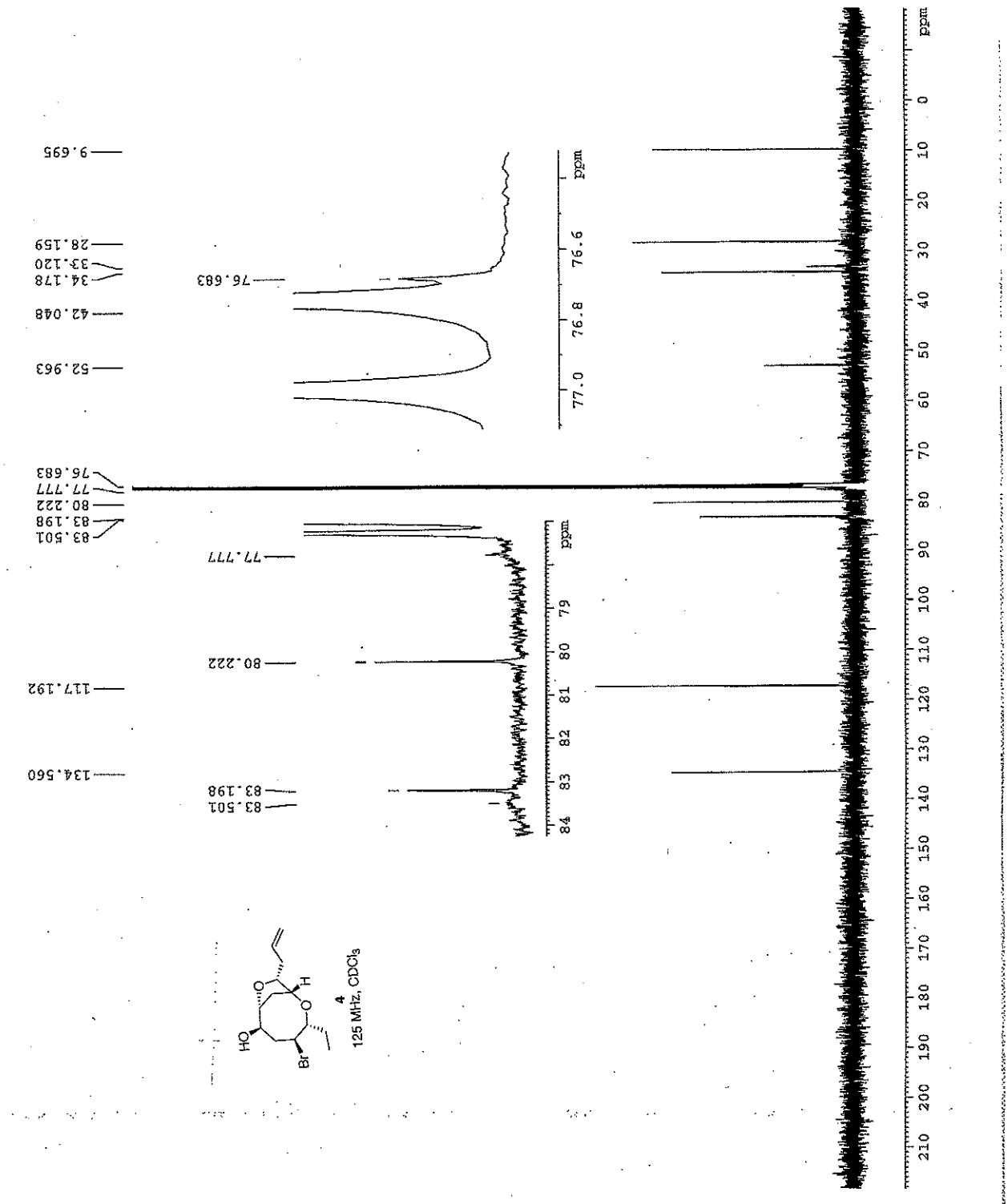
4.195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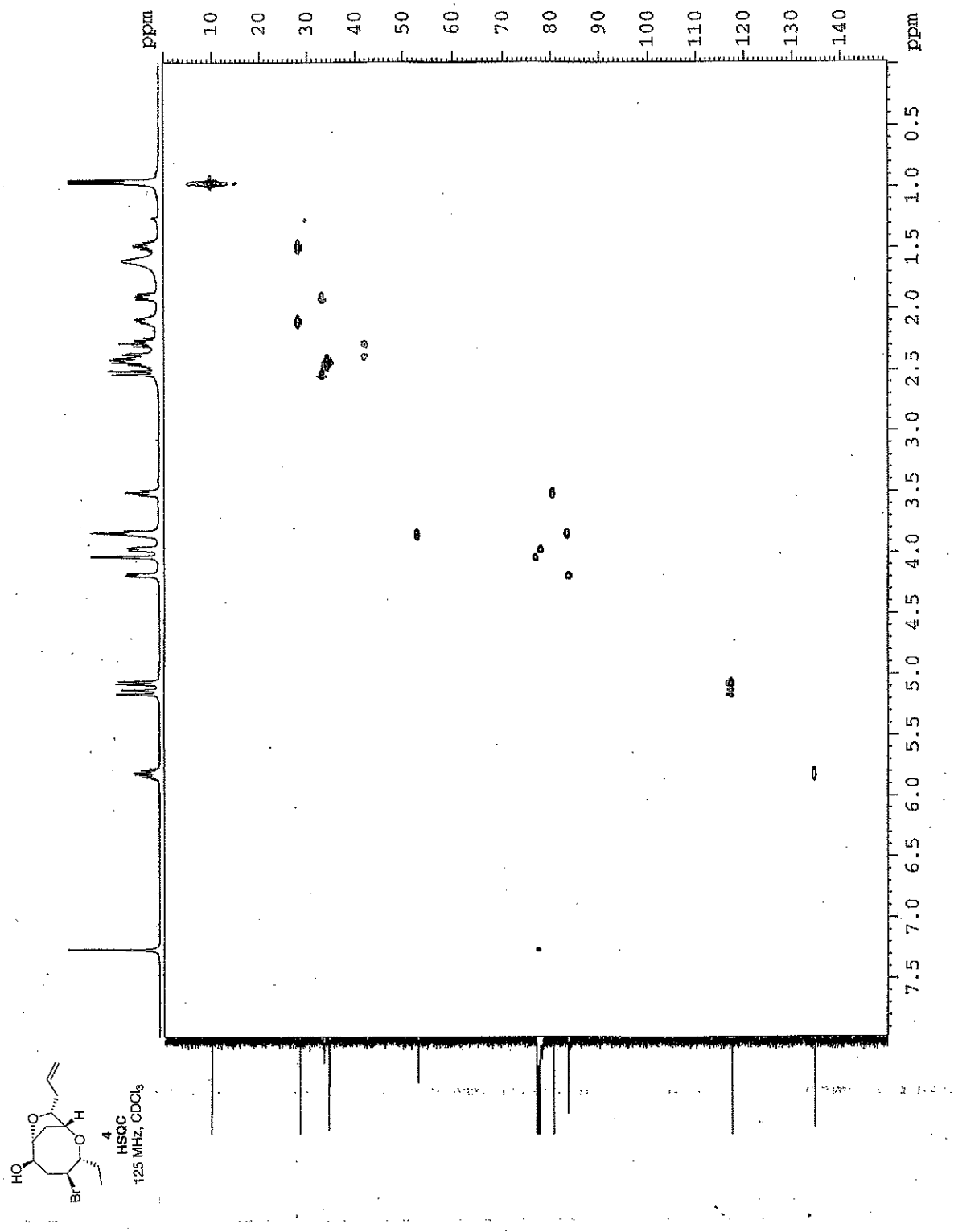
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O
H
Br
4
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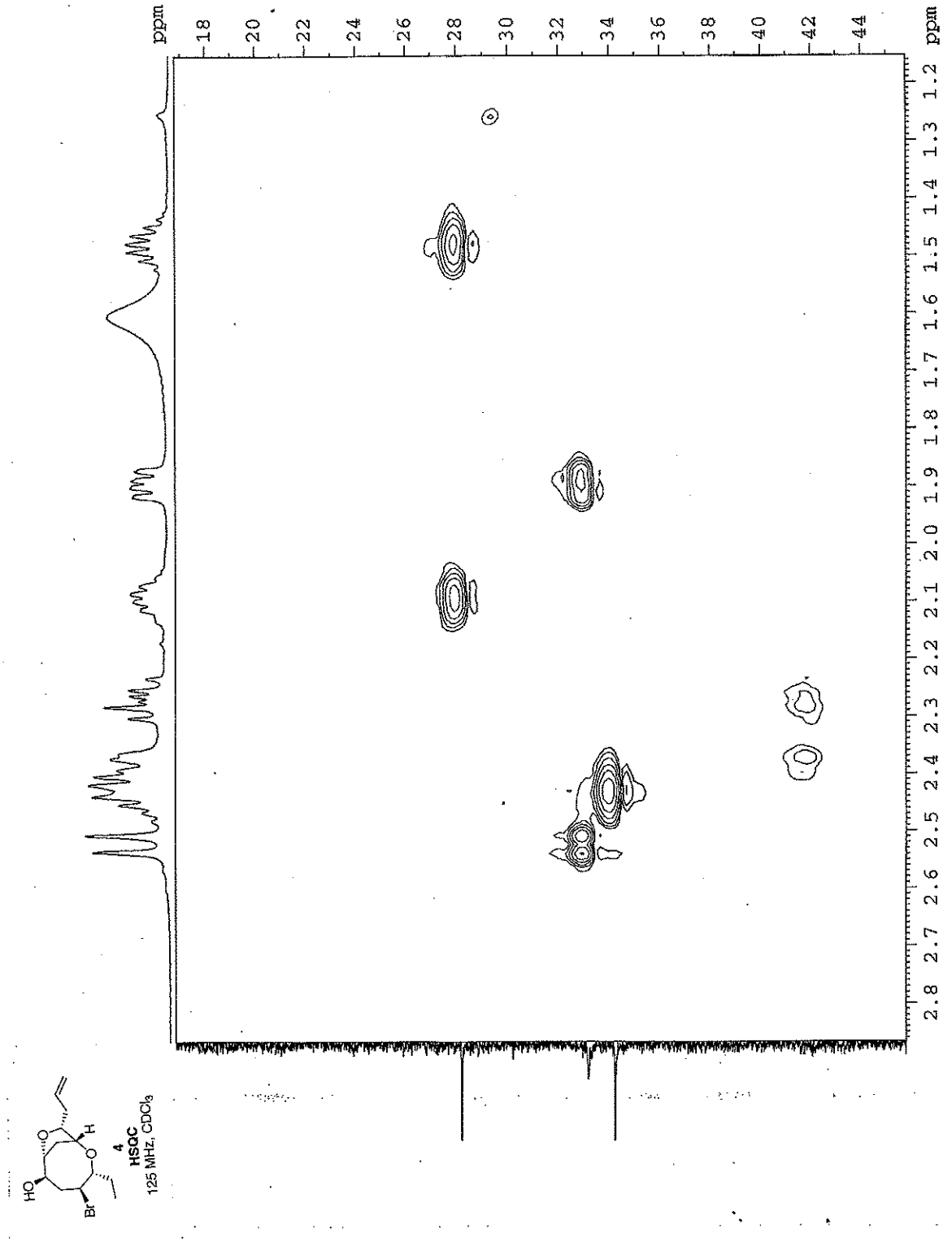
125 MHz, CDCl3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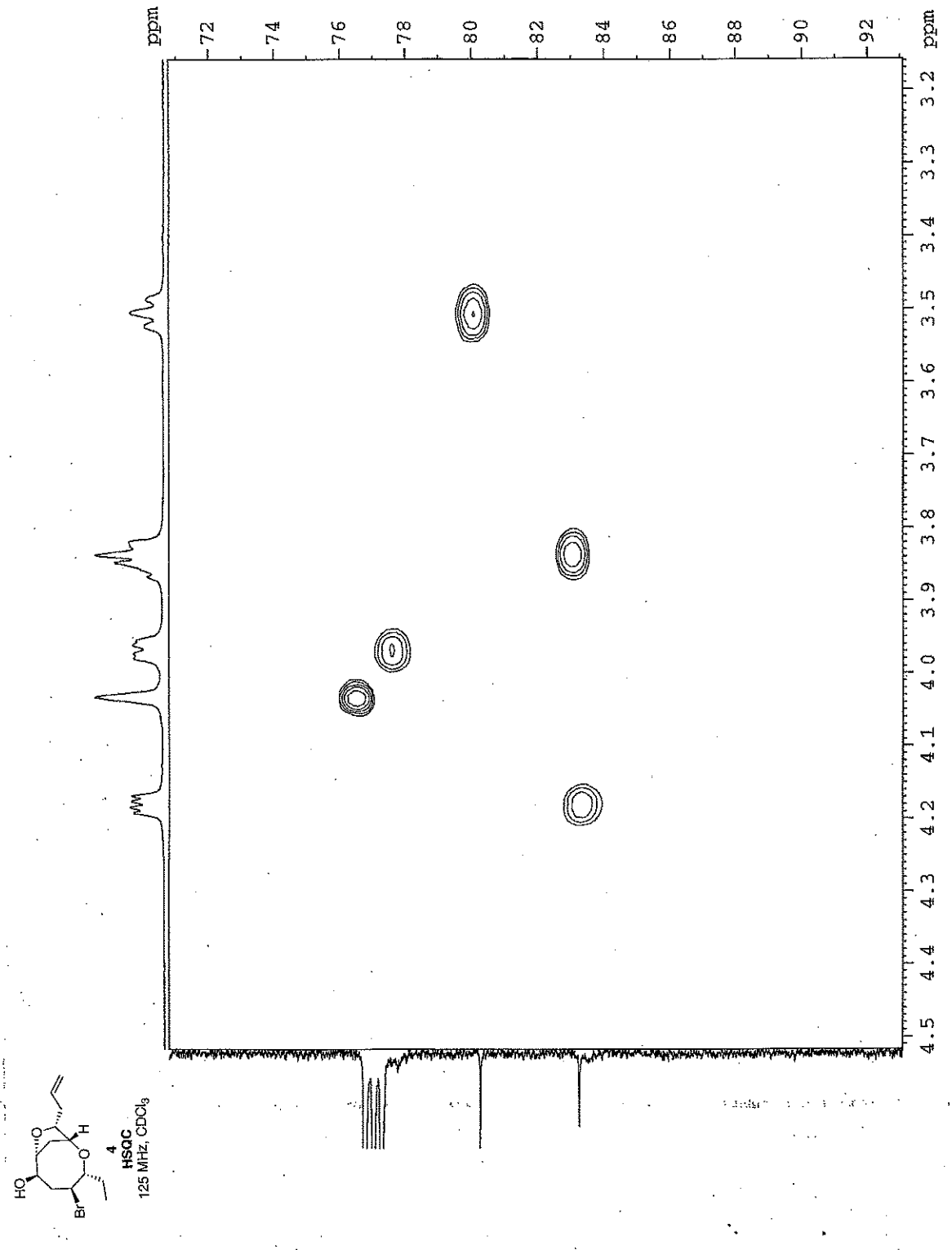
ppm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3.6
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Br
O
O
H
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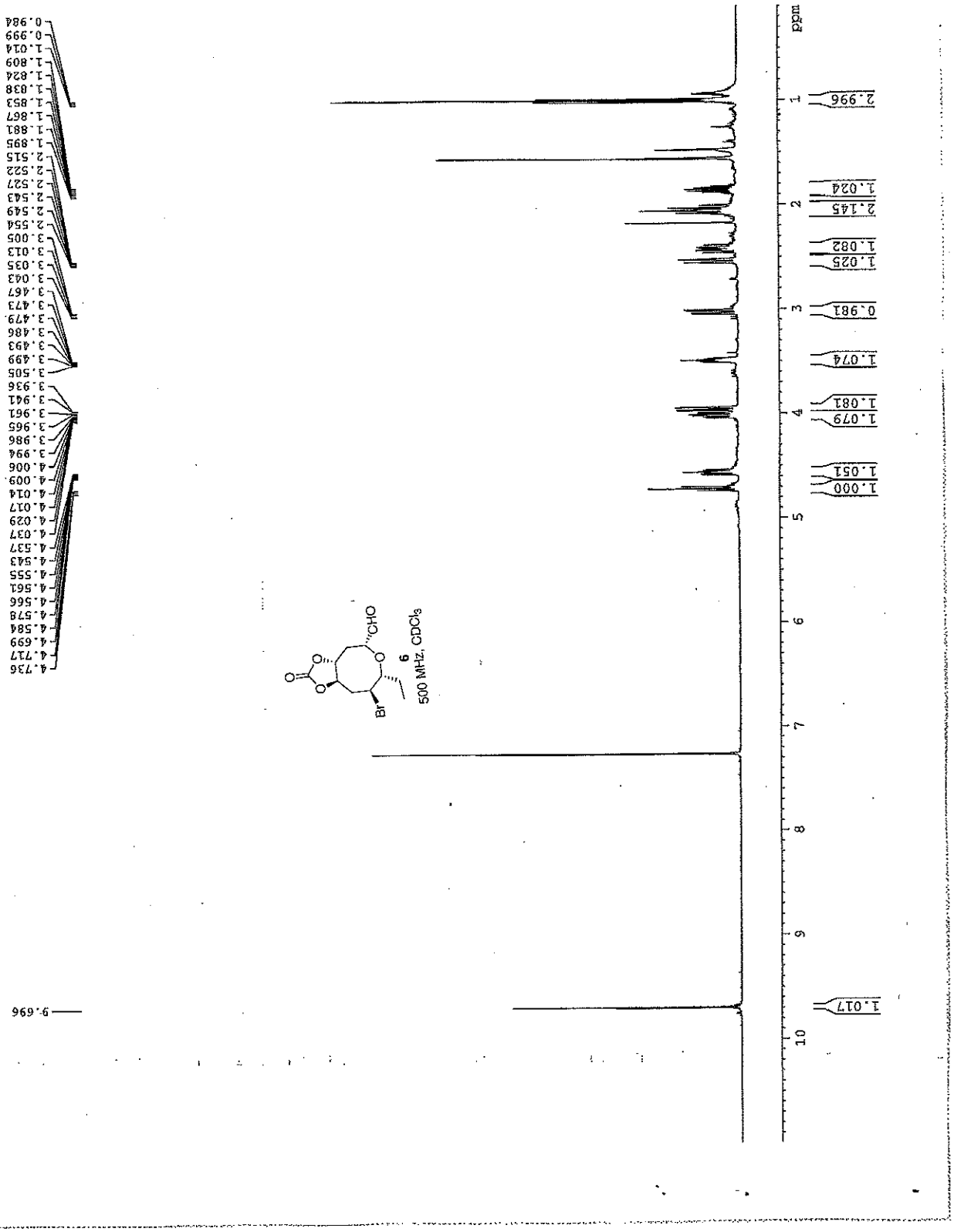
HSQC
125 MHz, CDCl3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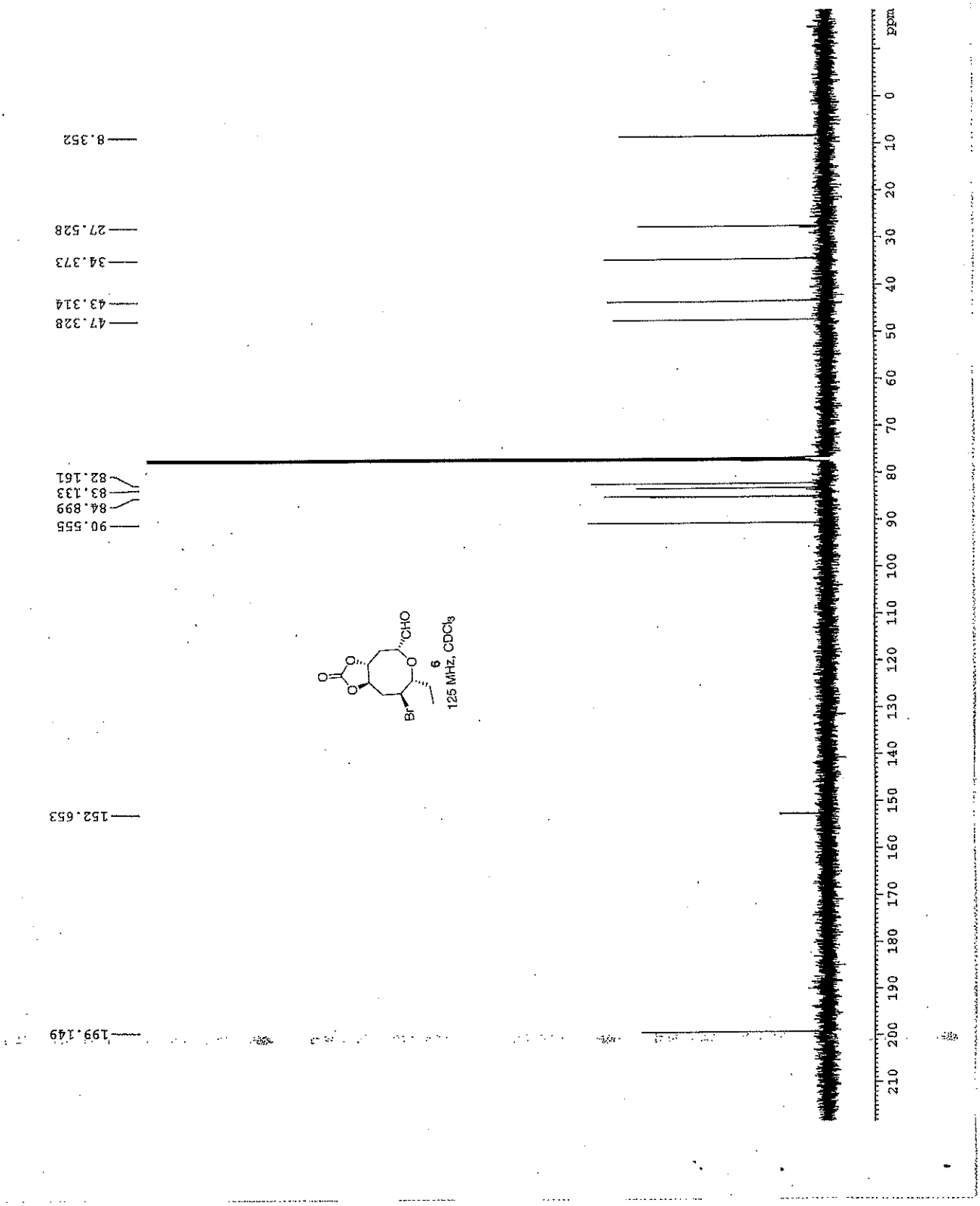
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Br
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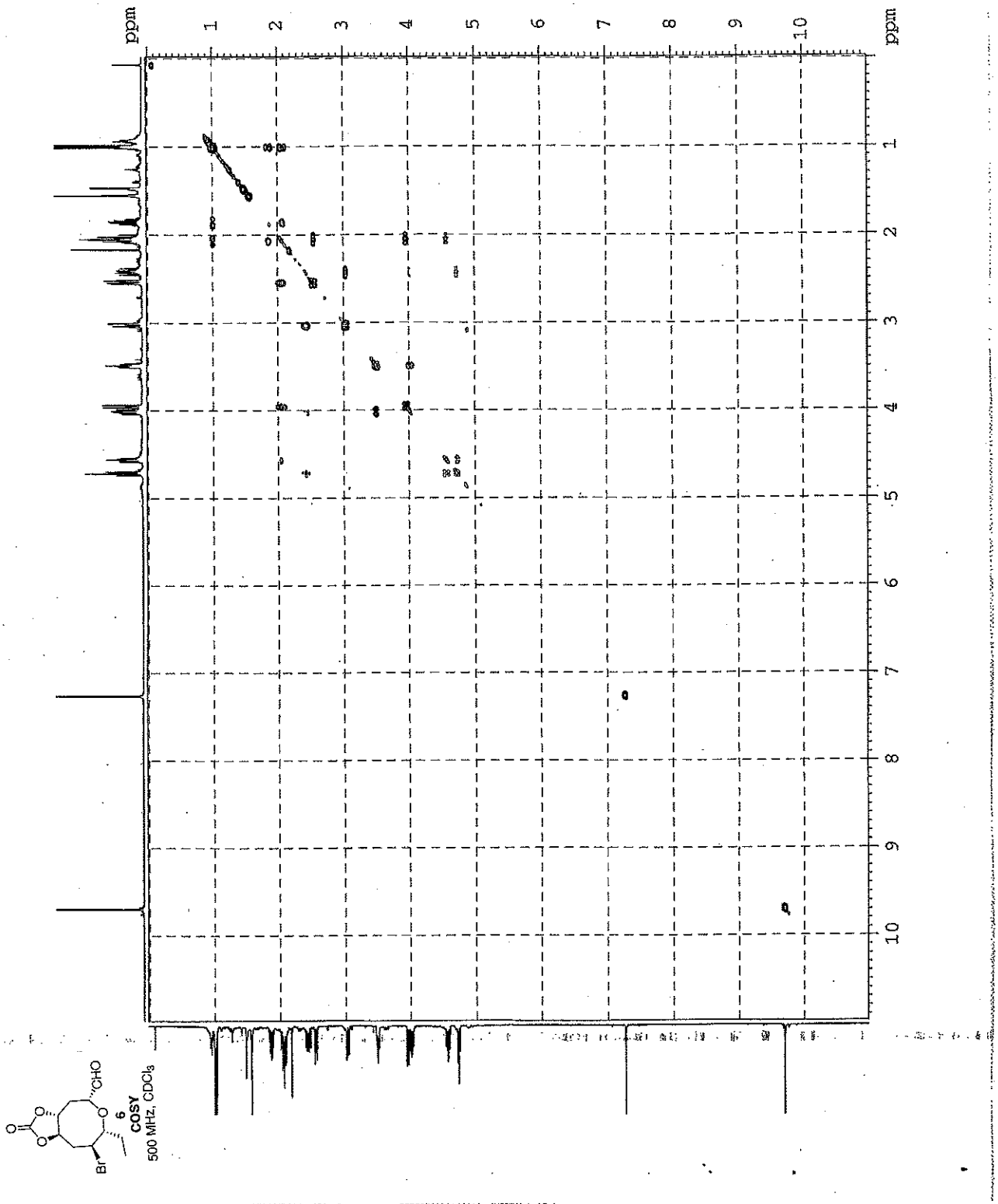
O
O
O
6
125 MHz, CDCl3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Br
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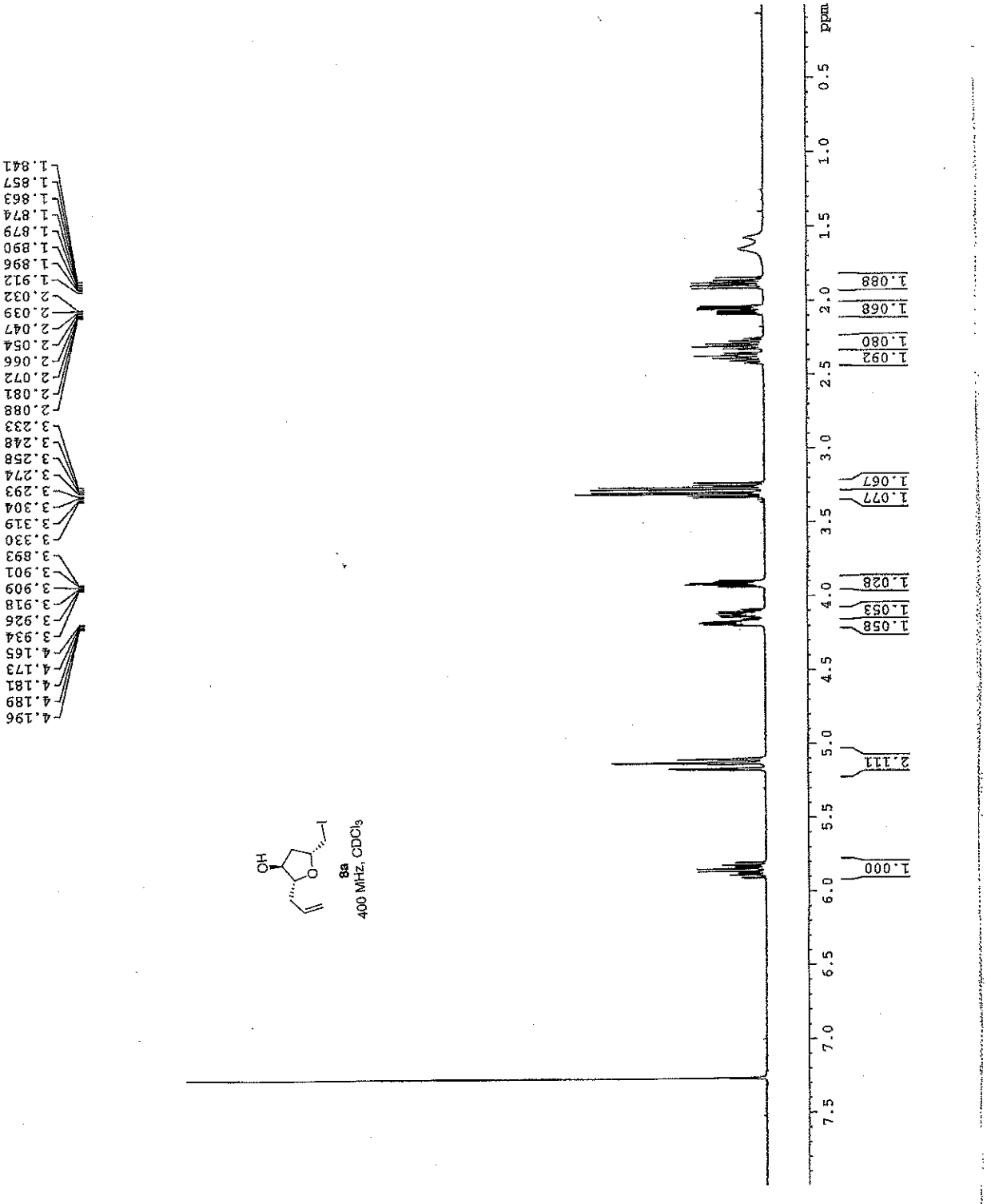
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2.0
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1.000
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1.053
1.028
1.077
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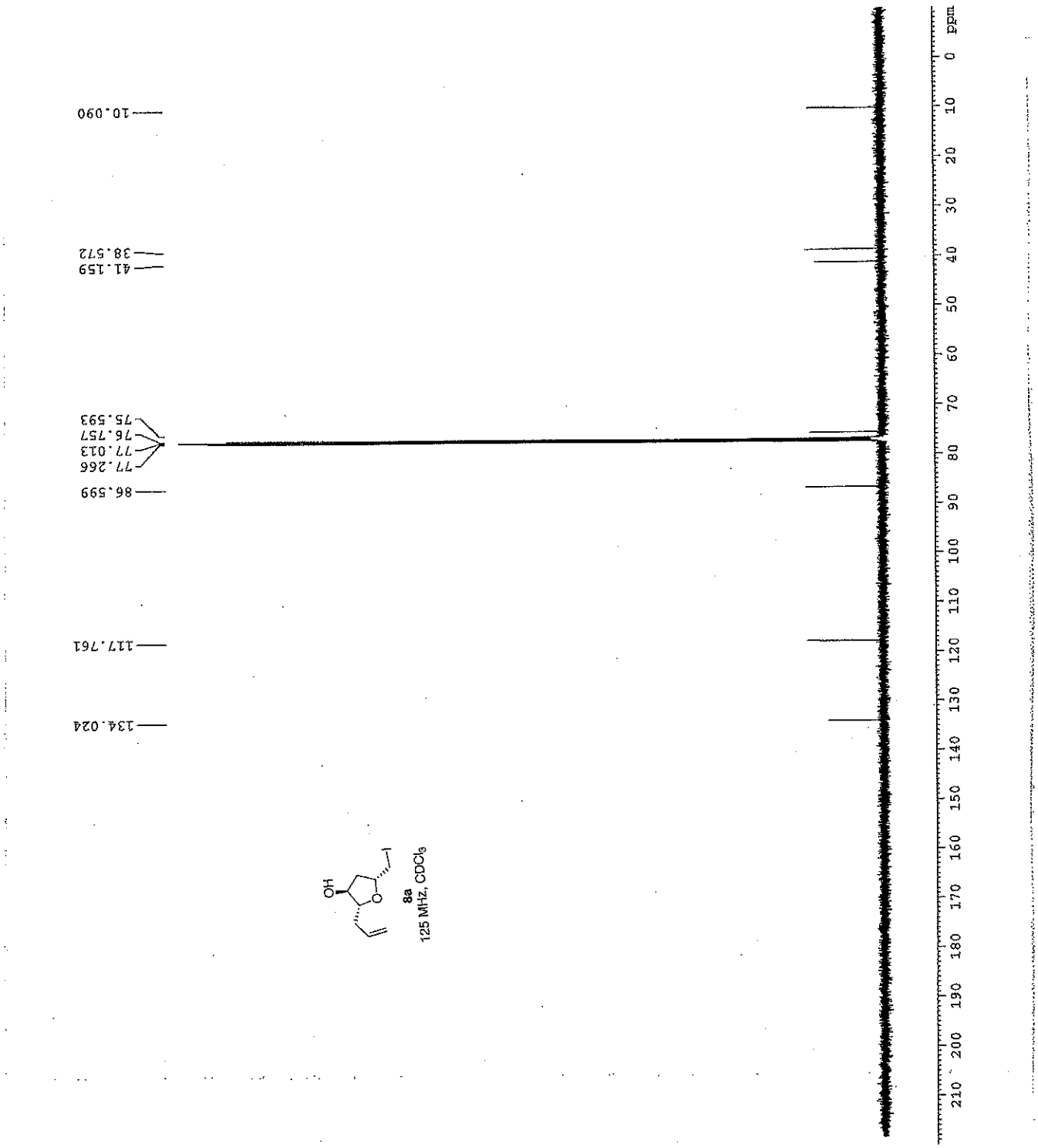
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125 MHz, CDCl3
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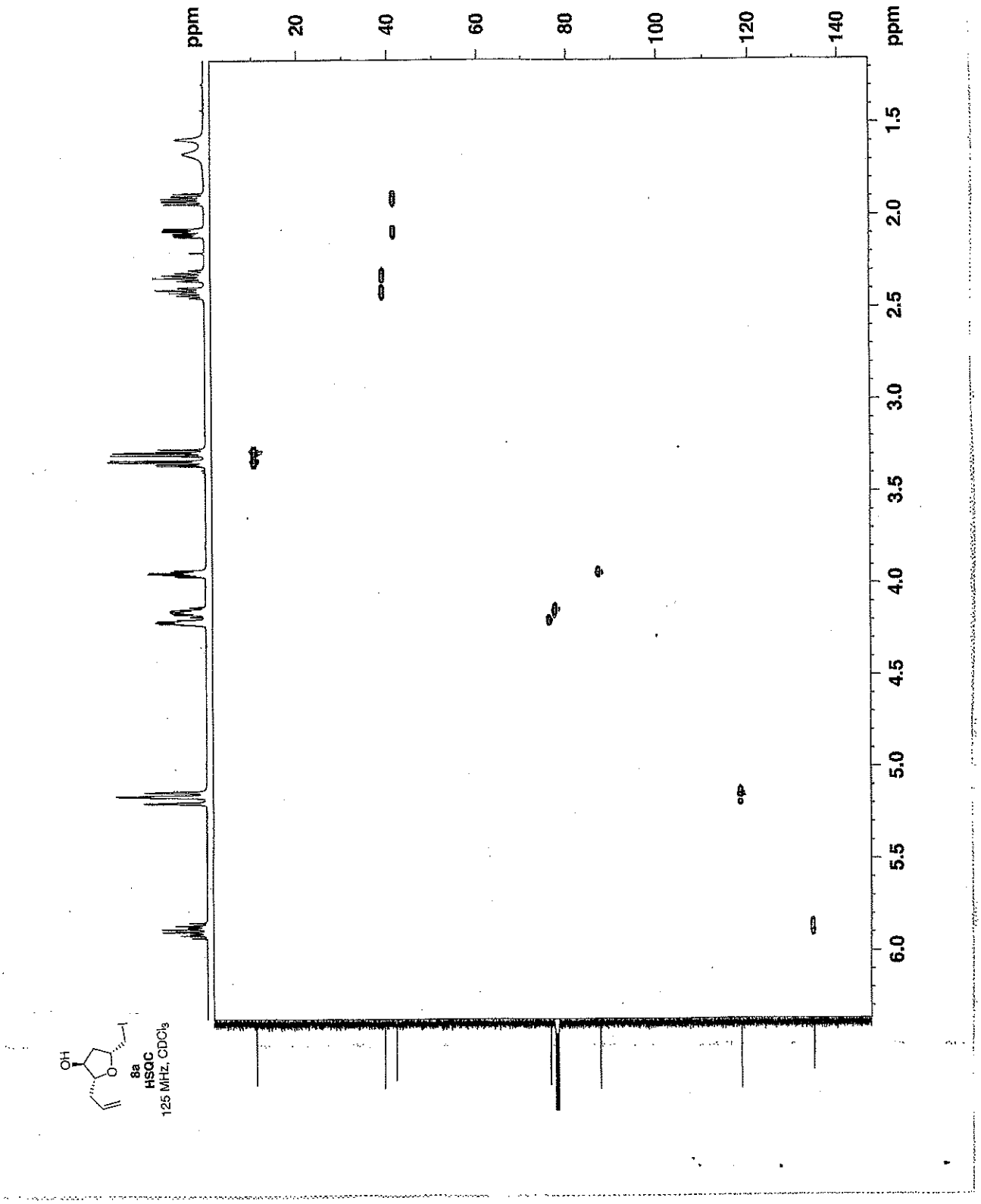
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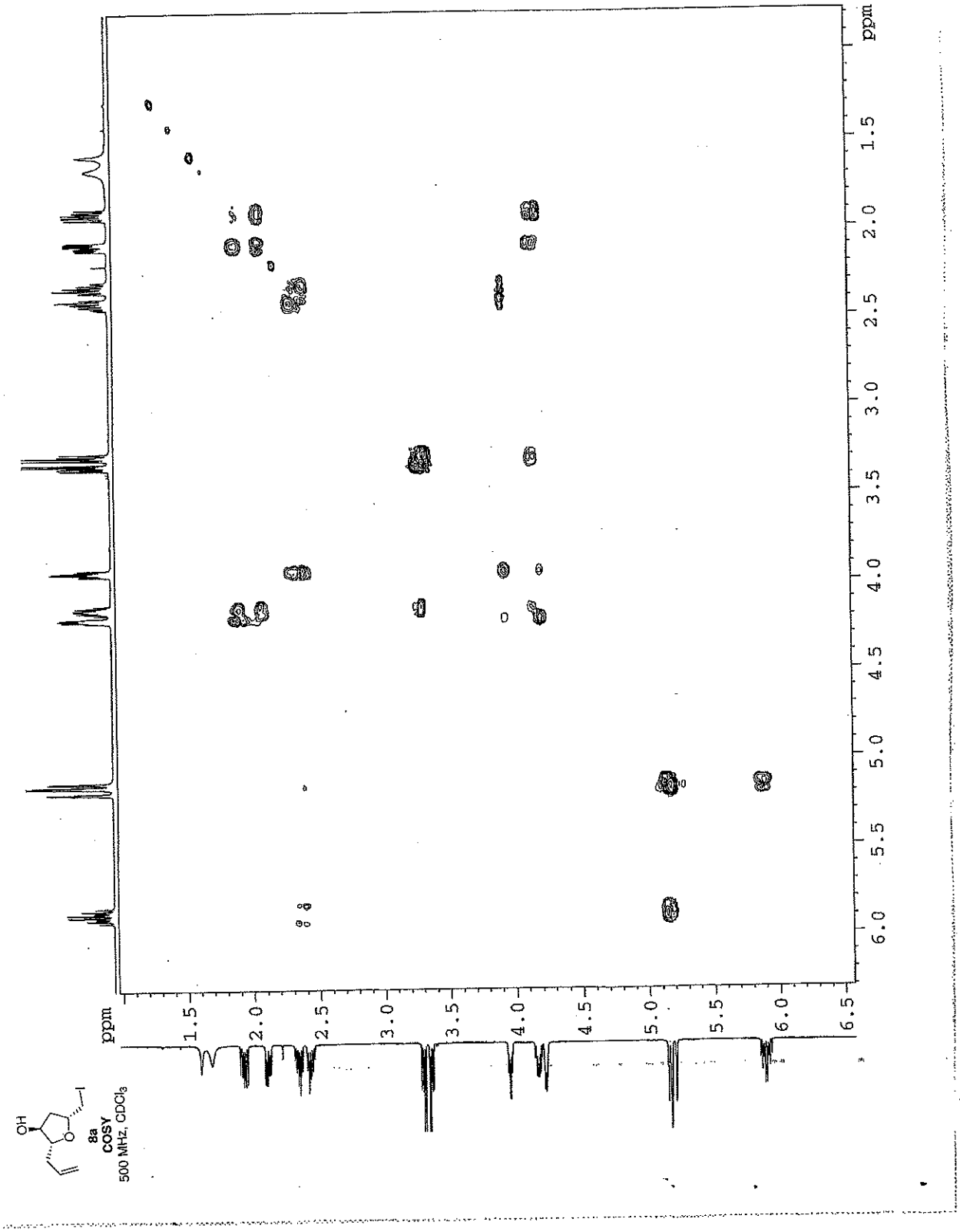
I
O
8a
HSQC
125 MHz, CDCl3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COSY
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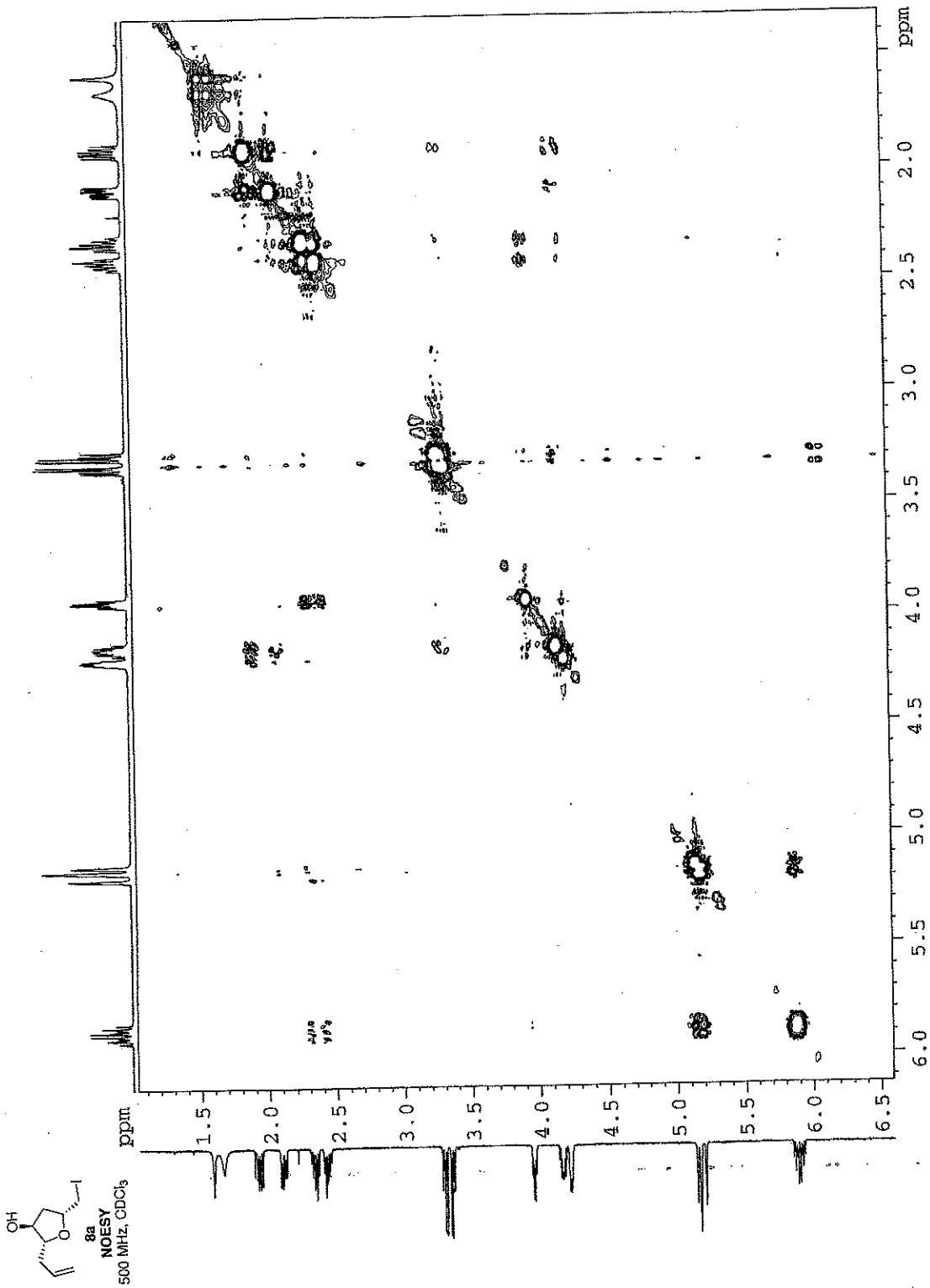
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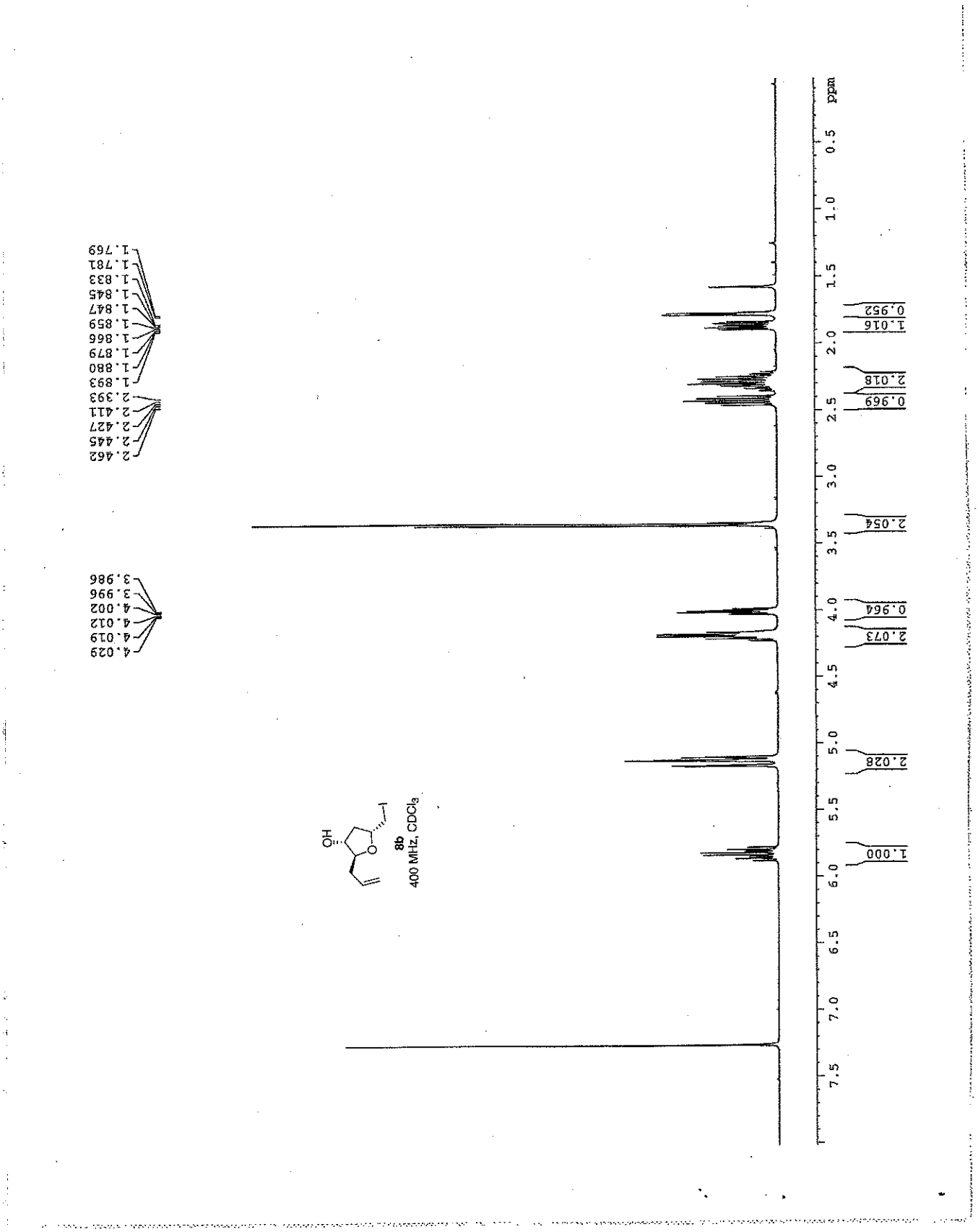
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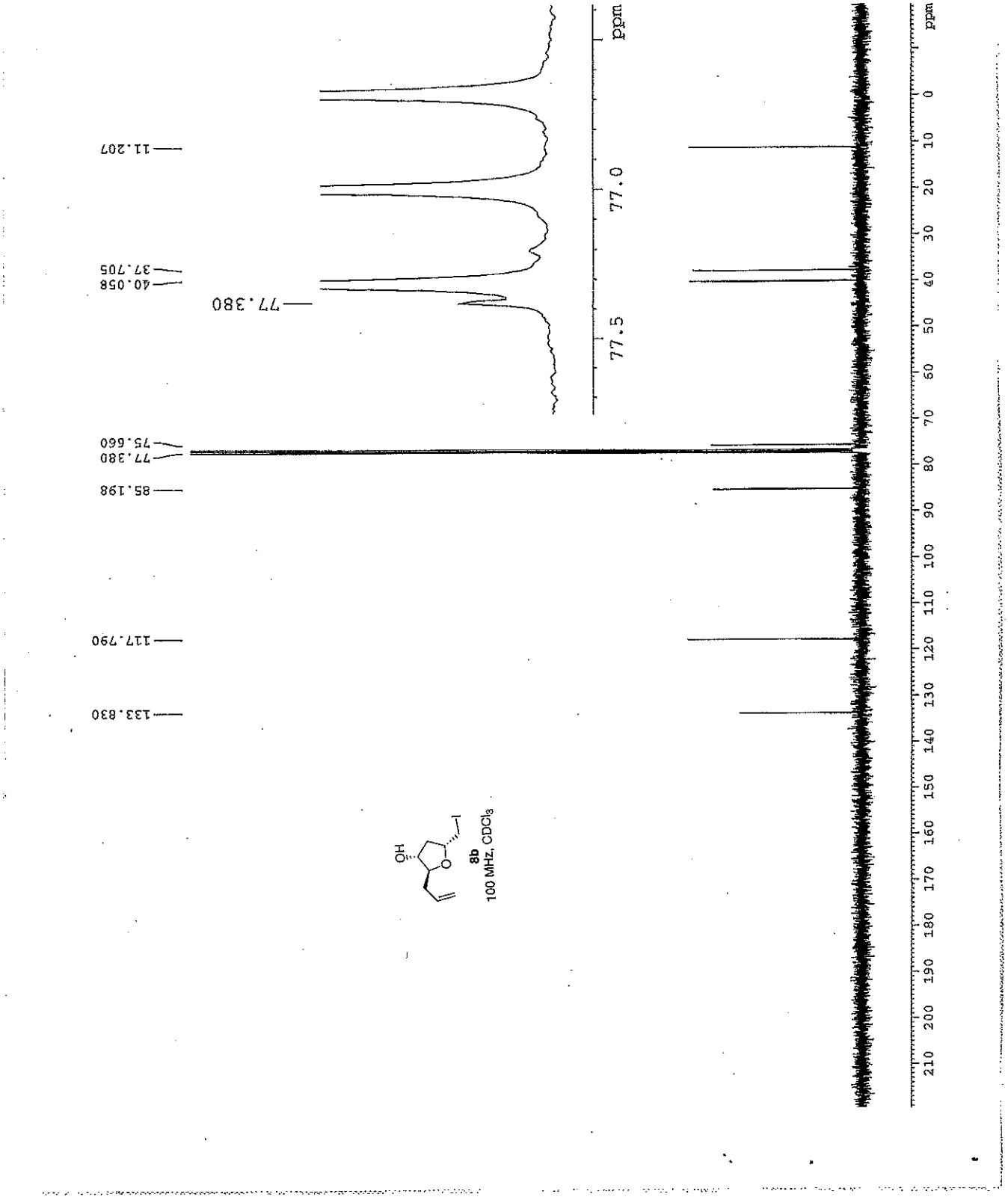
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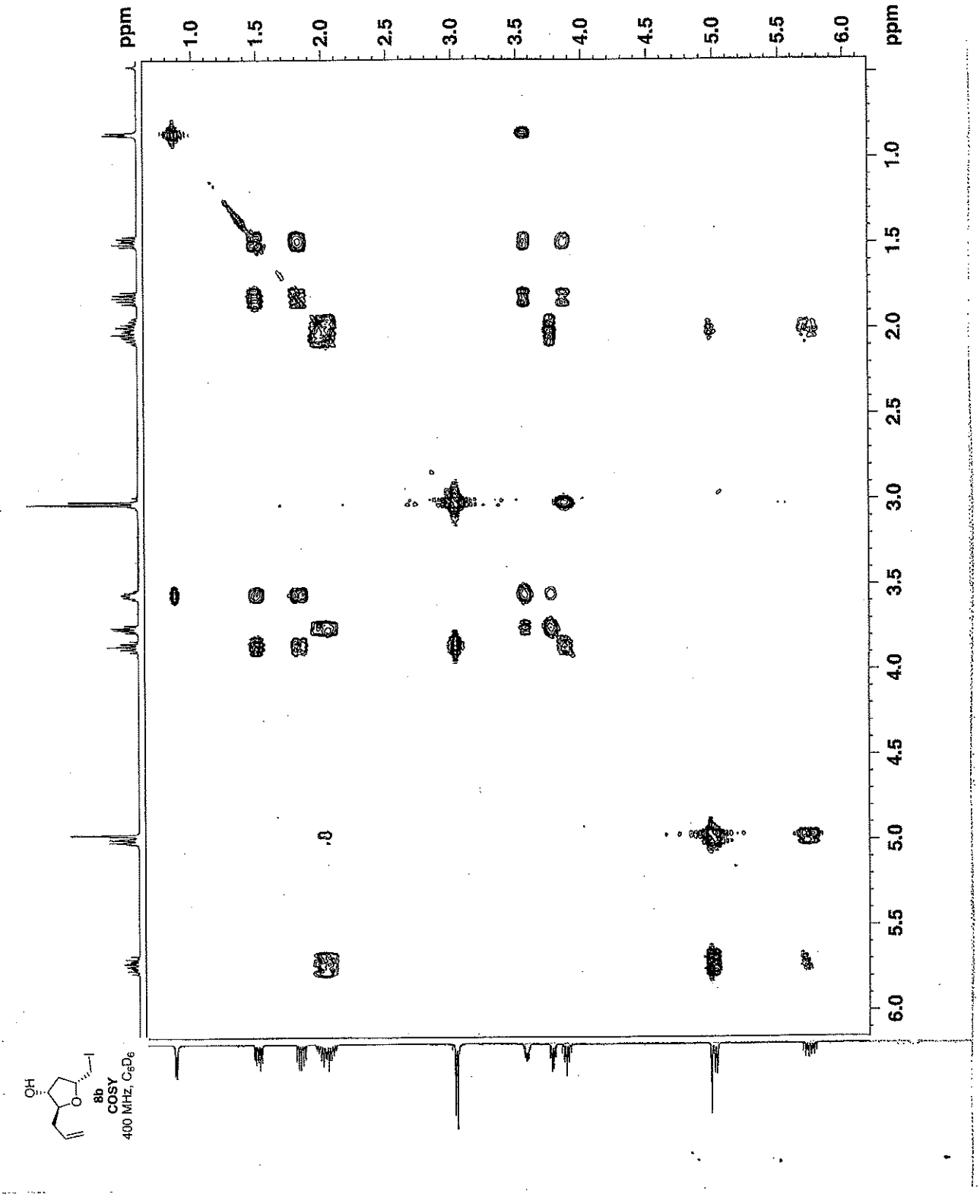
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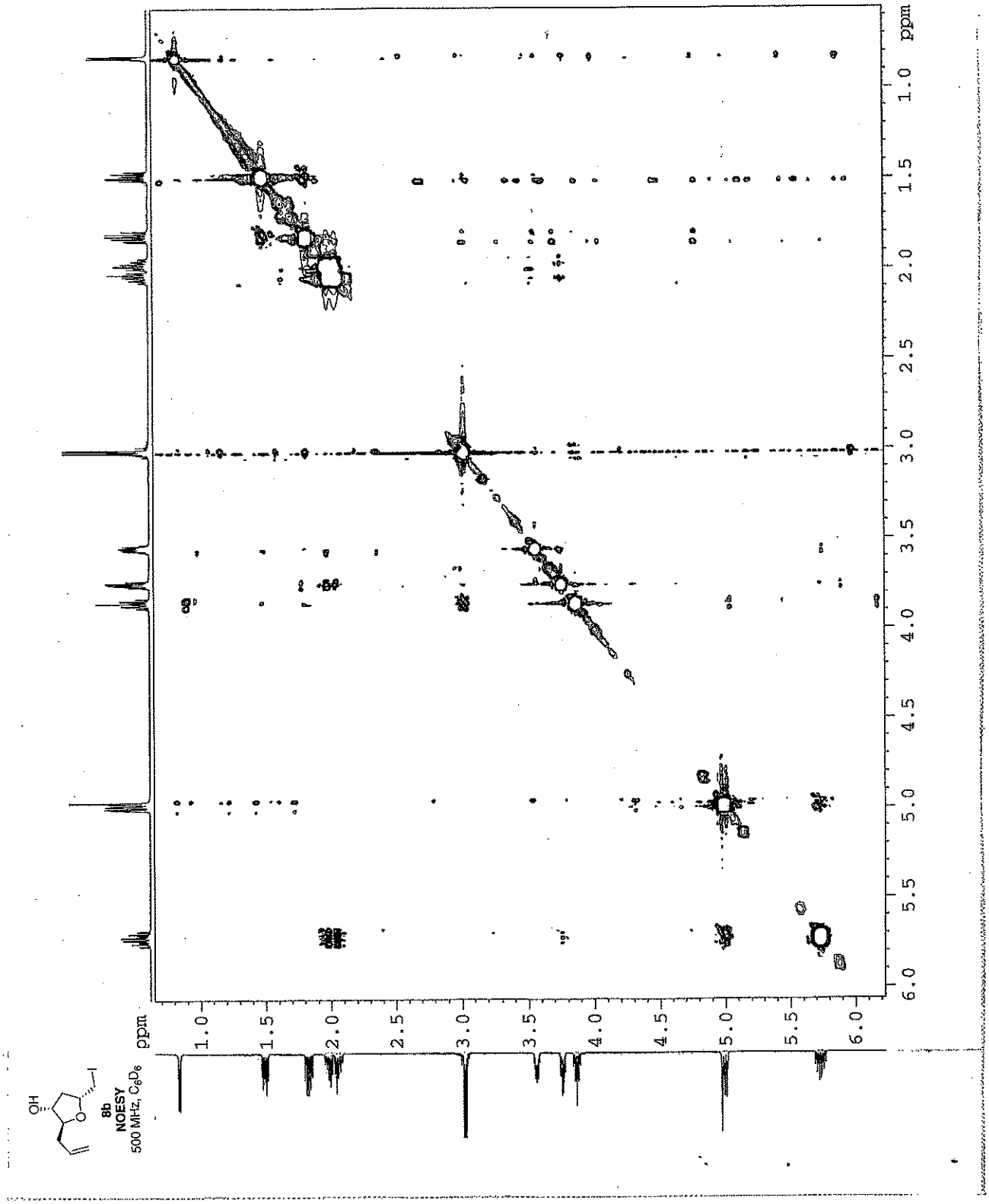
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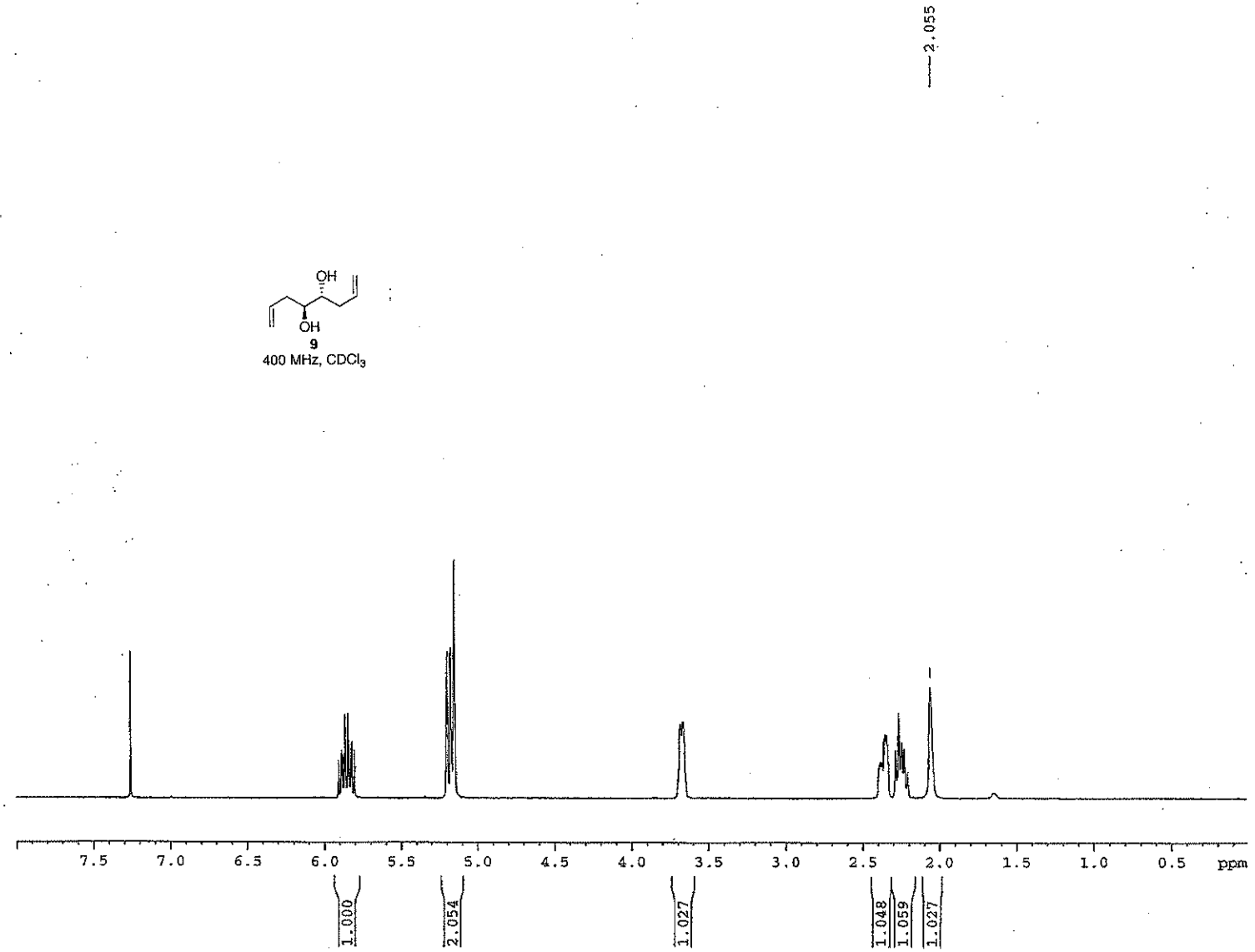
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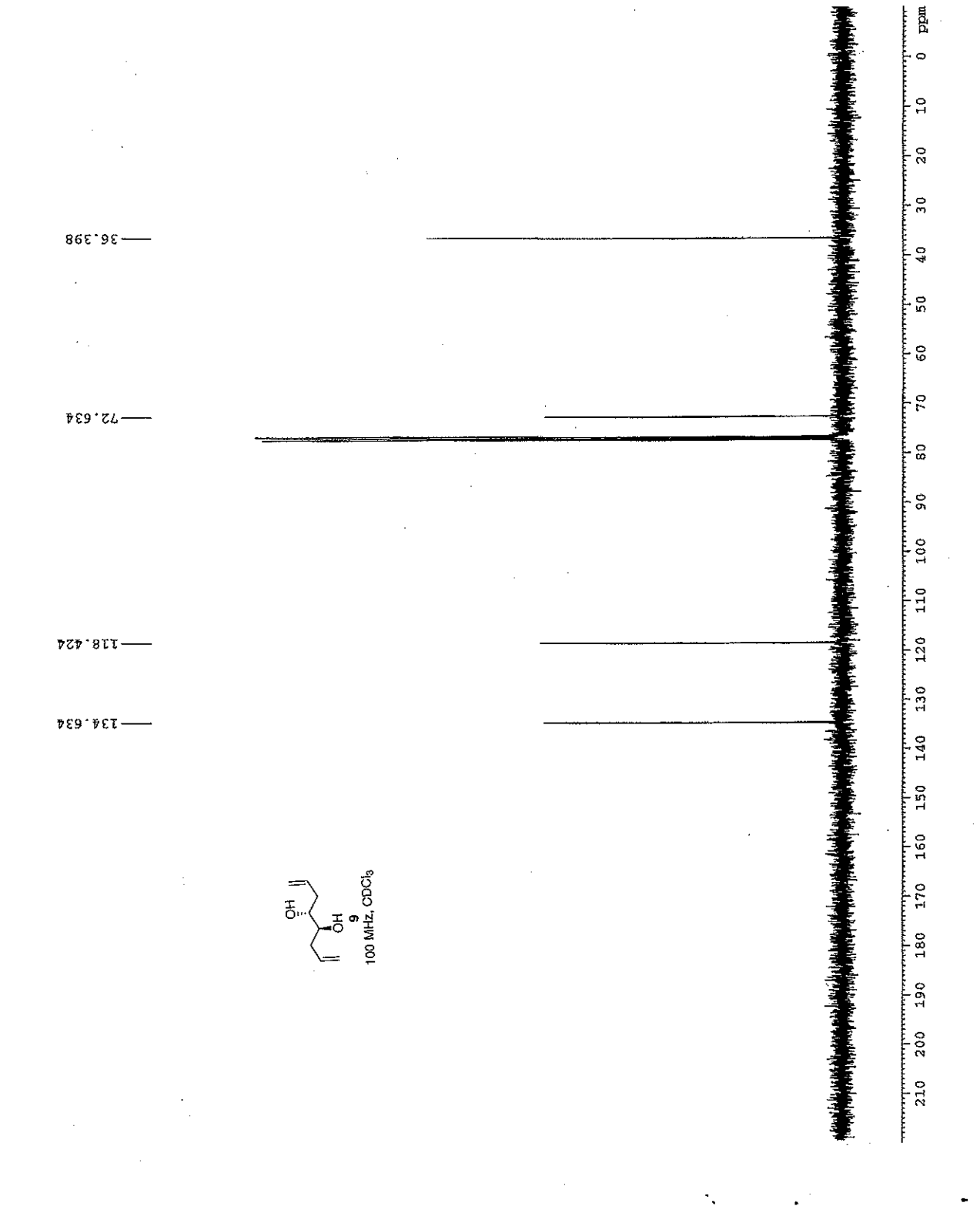
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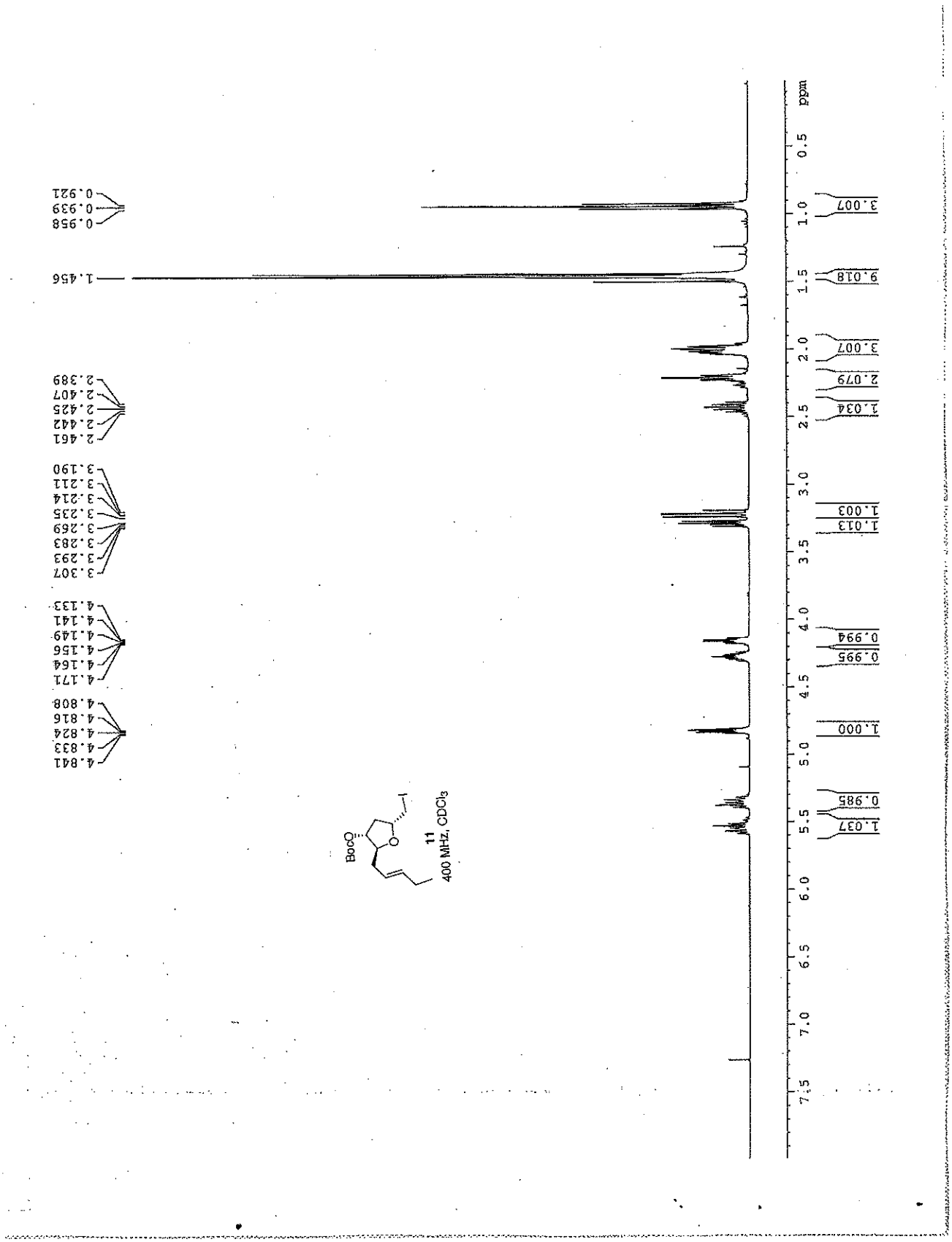
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3.235
3.269
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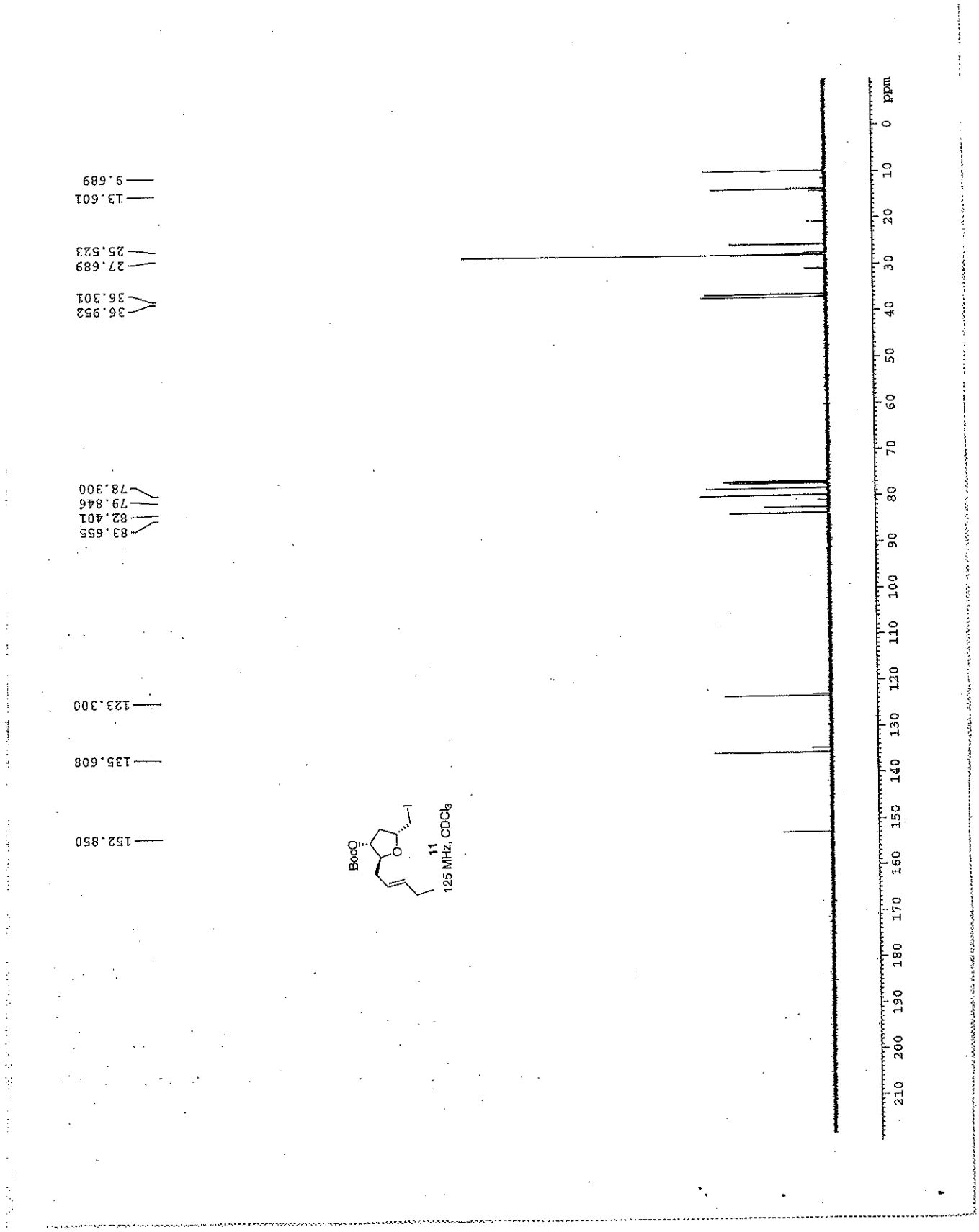
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BocO
O
I
11
125 MHz, CDCl3
ppm
0
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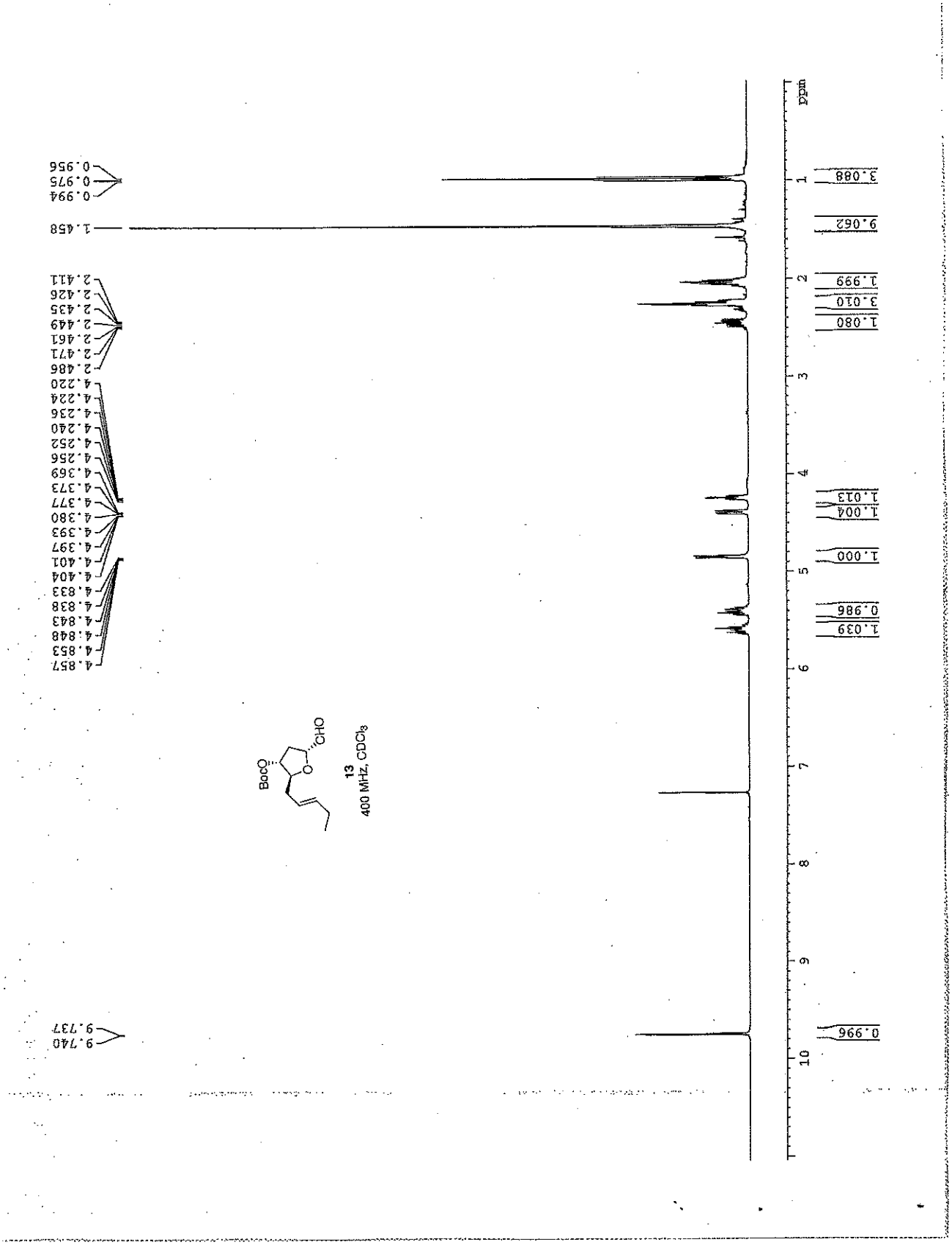
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4.224
4.220
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2.461
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2.435
2.426
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1.458
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0.975
0.956
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1.039
0.986
1.000
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1.013
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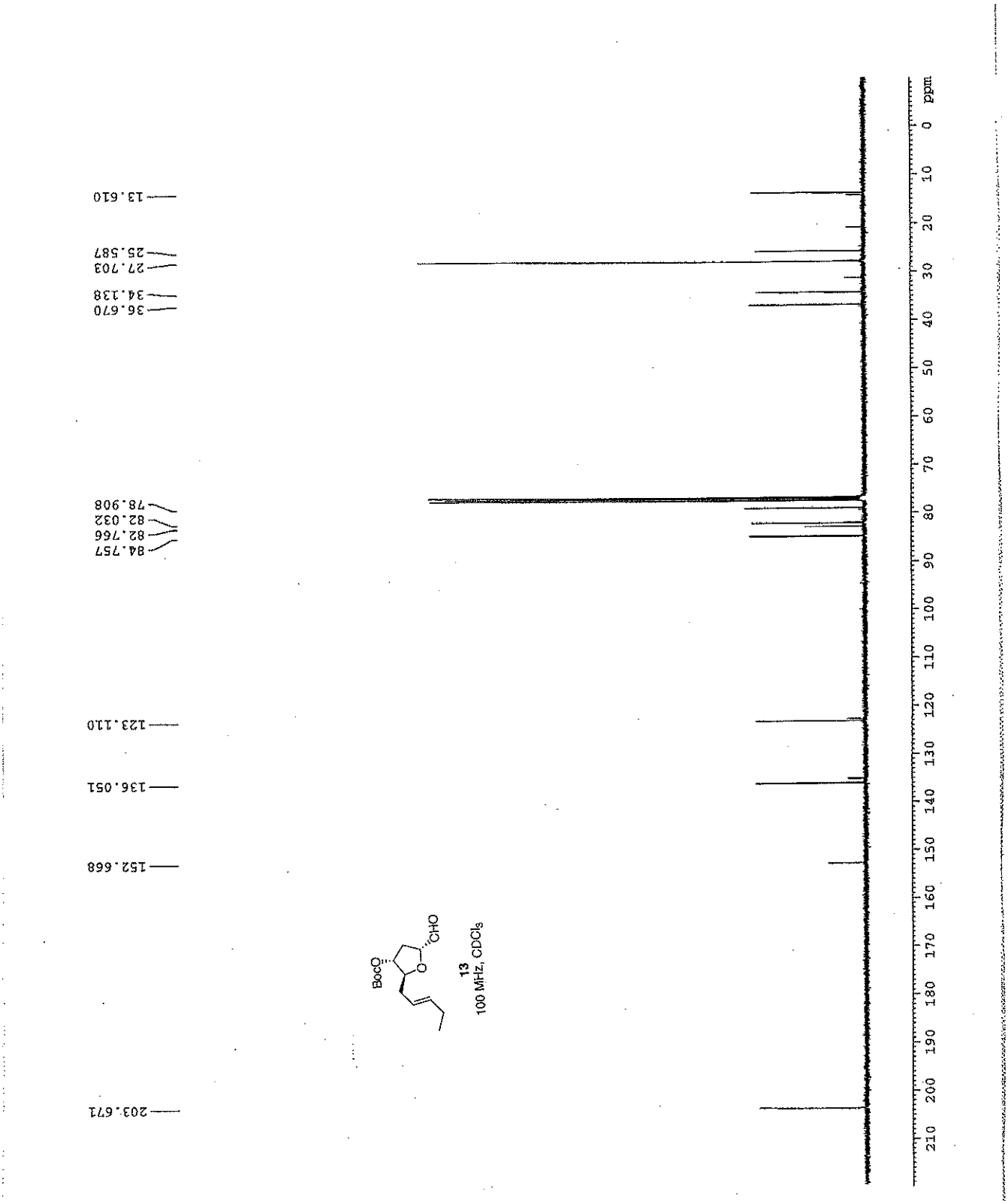
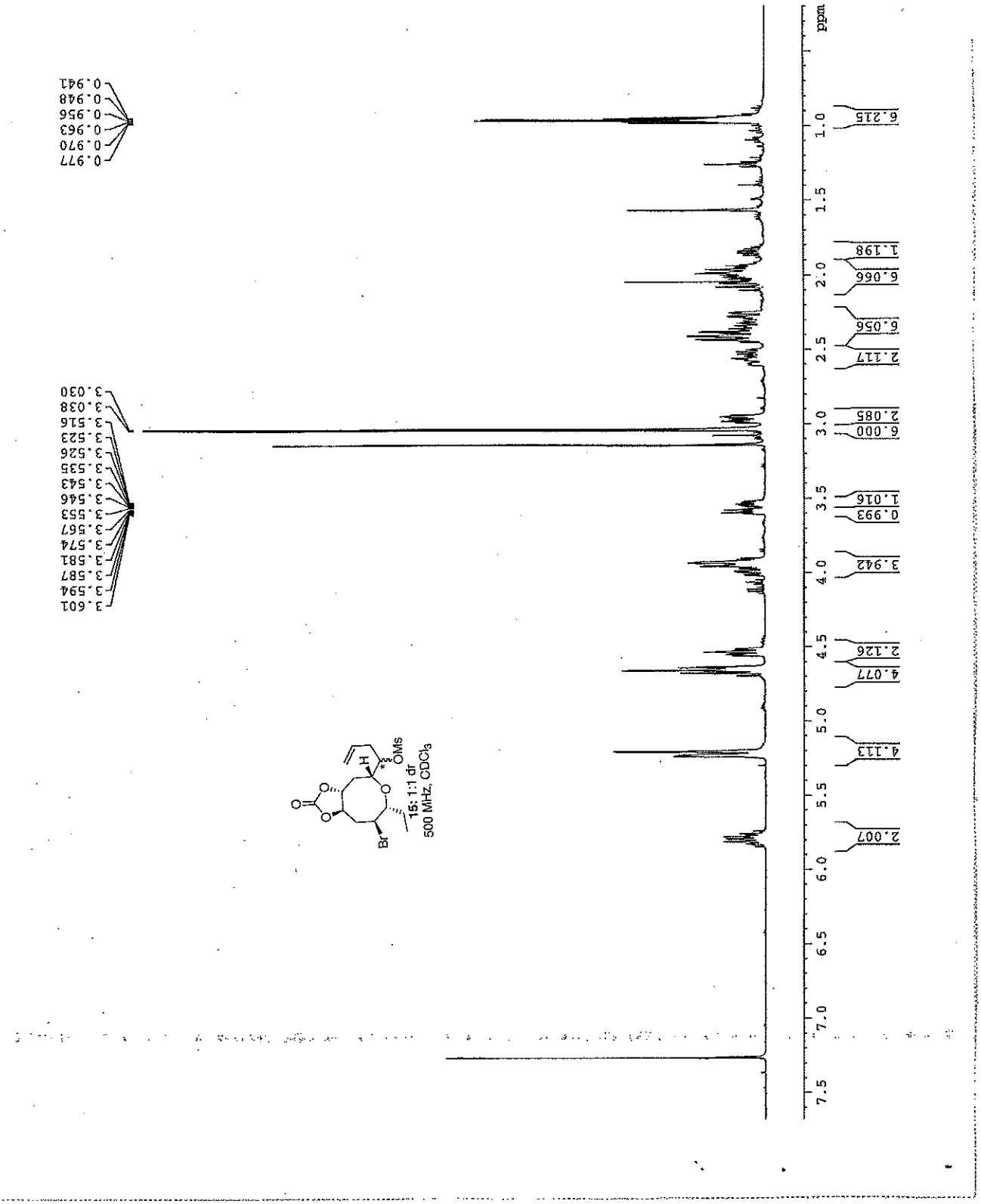
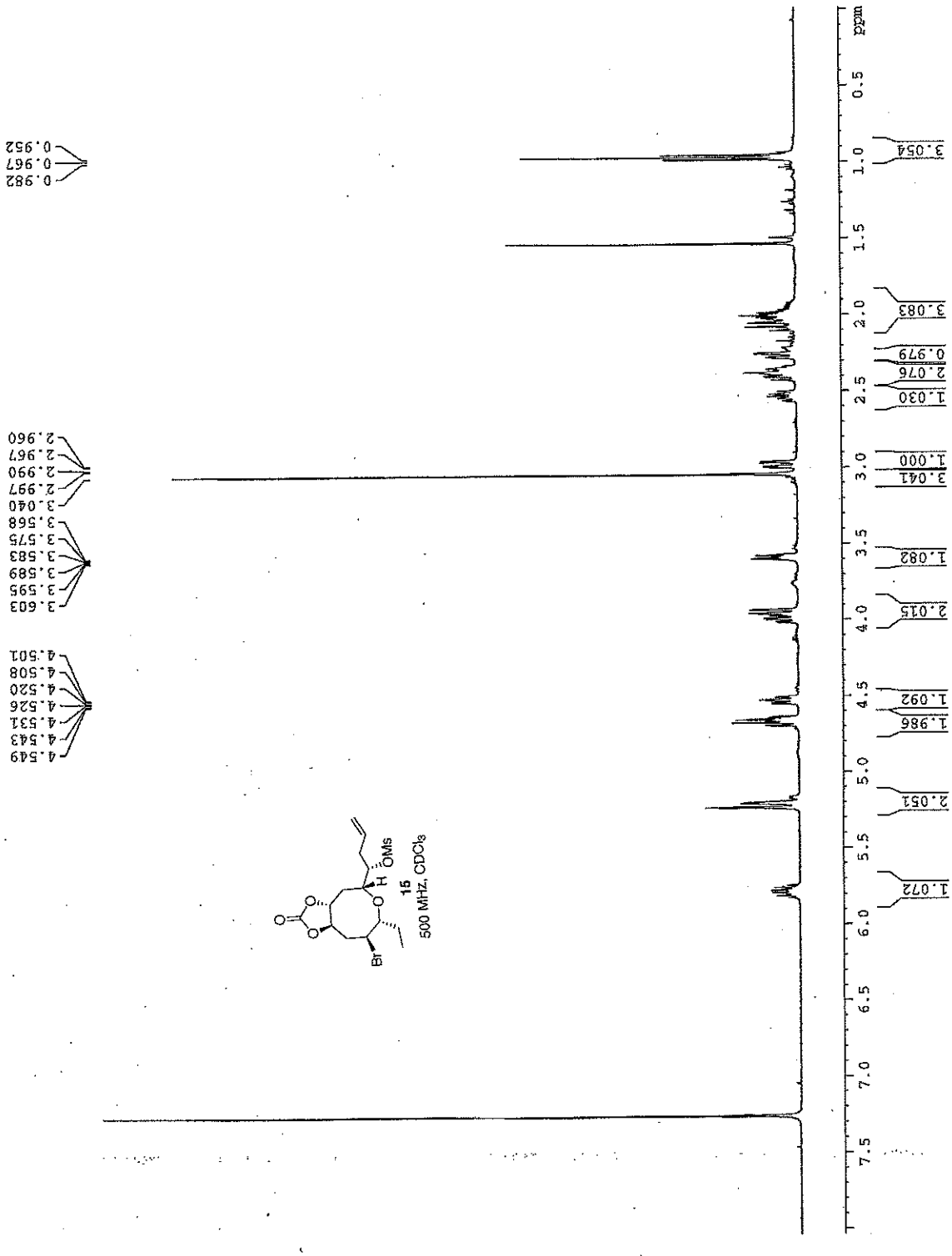
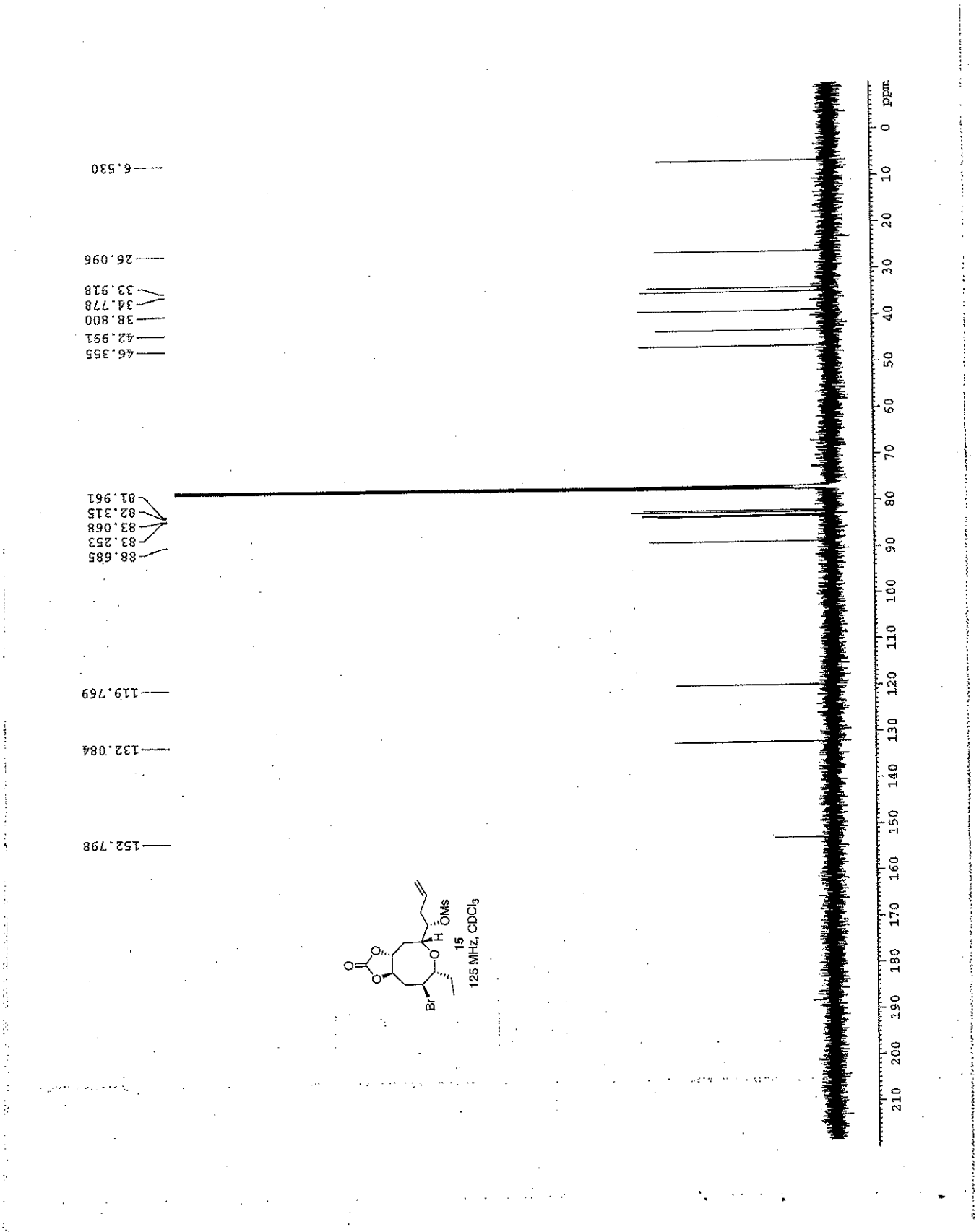
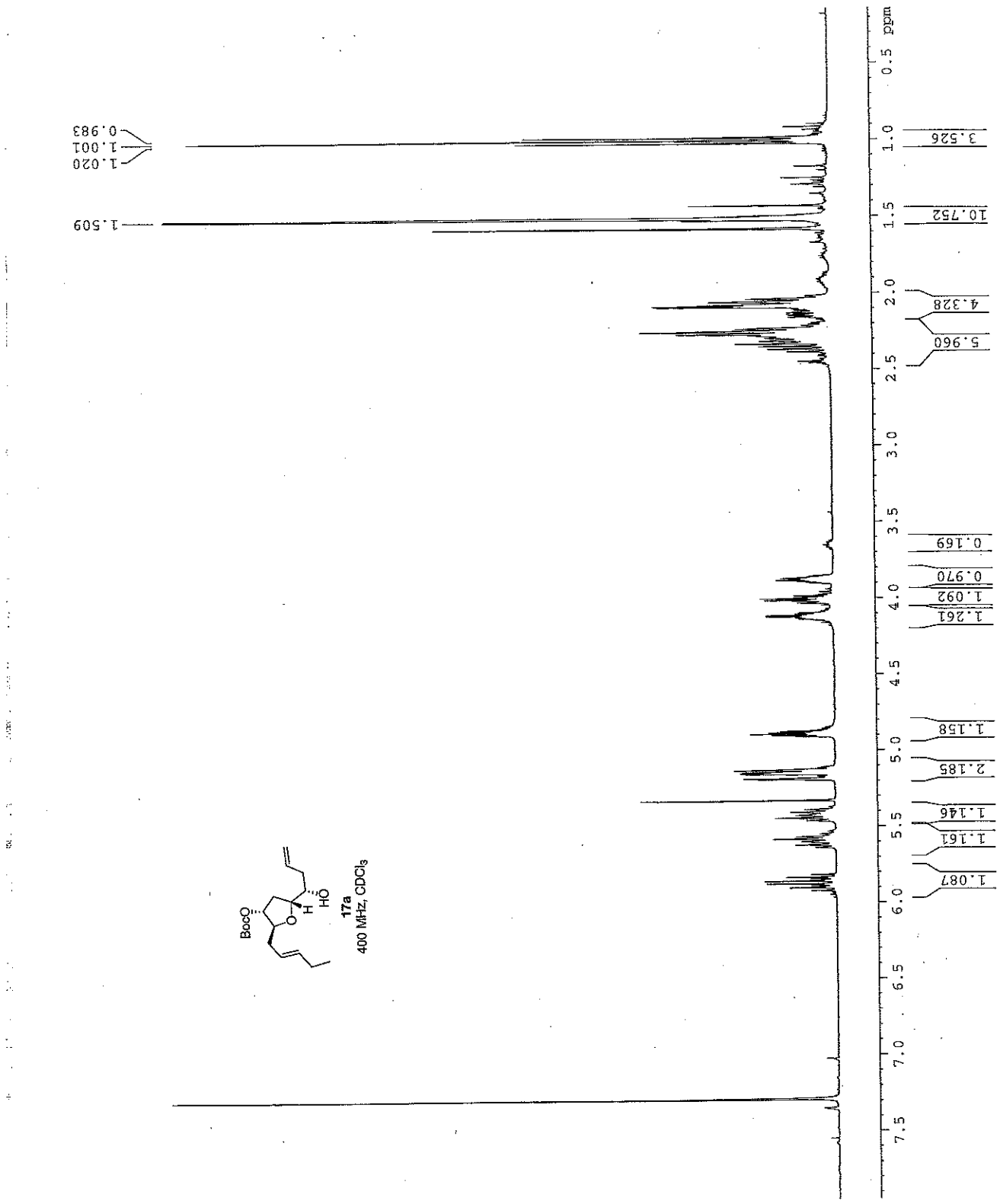
9.062
3.088

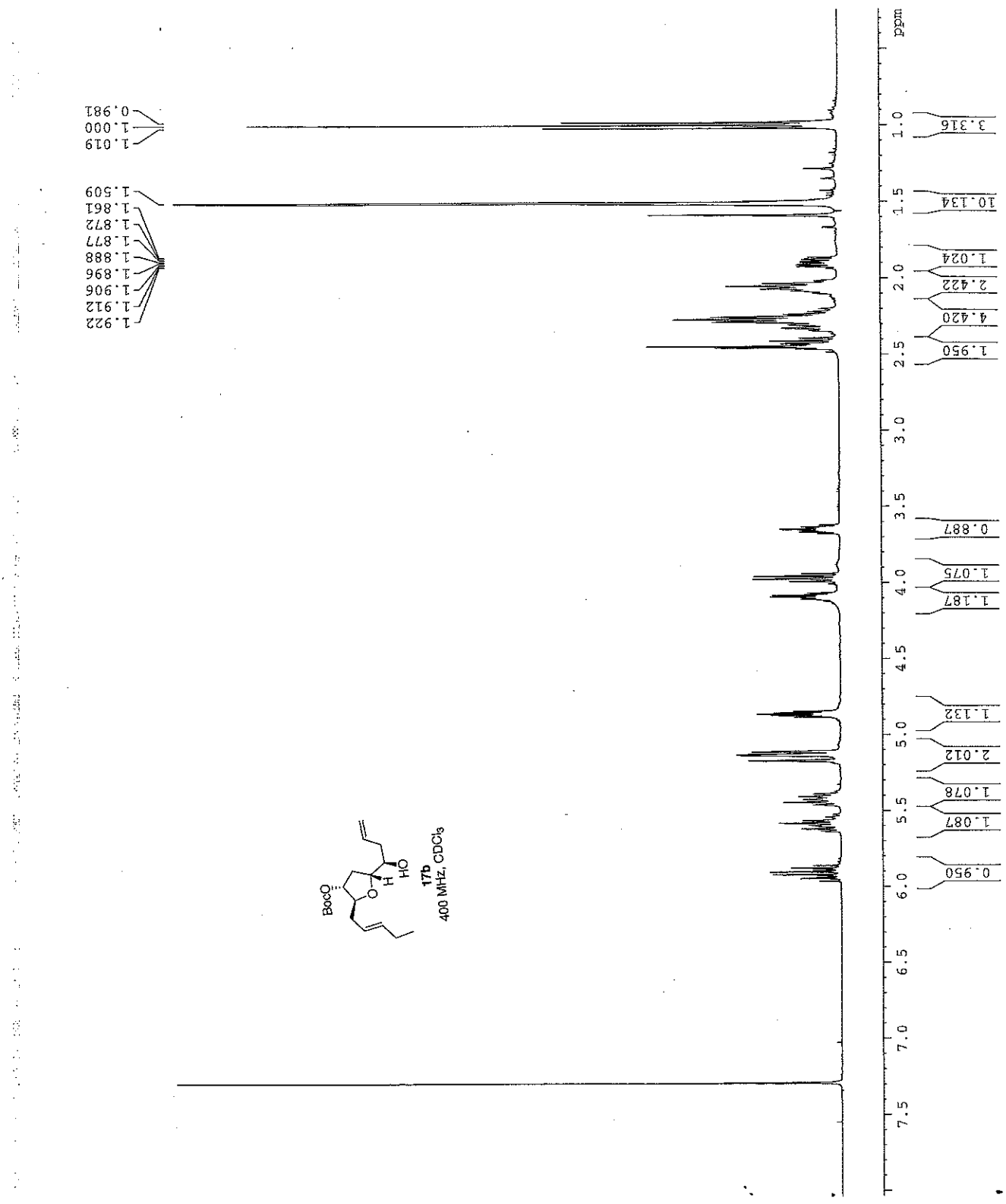

203.671
152.668
136.051
123.110
84.757
82.766
82.032
78.908
36.670
34.138
27.703
25.587
13.610
BocO
CHO
O
13
100 MHz, CDCl3
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 ppm

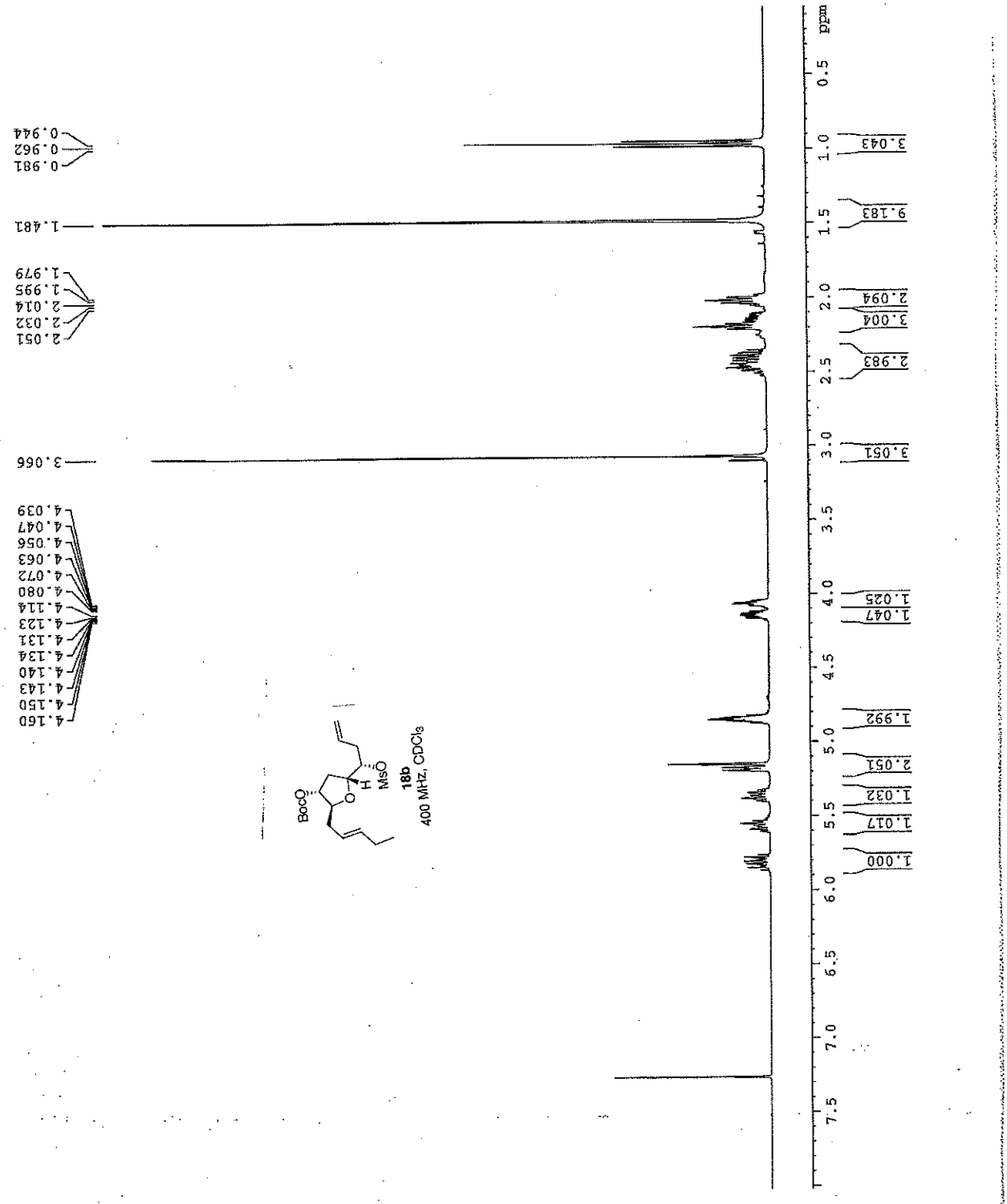

15: 1:1 dr
500 MHz, CDCl3
OMs
Br
H
ppm
0.941
0.948
0.956
0.963
0.970
0.977
3.030
3.038
3.516
3.523
3.526
3.535
3.543
3.546
3.553
3.567
3.574
3.581
3.587
3.594
3.601
6.215
1.198
6.066
6.056
2.117
6.000
2.085
1.016
0.993
3.942
4.077
2.126
4.113
2.007

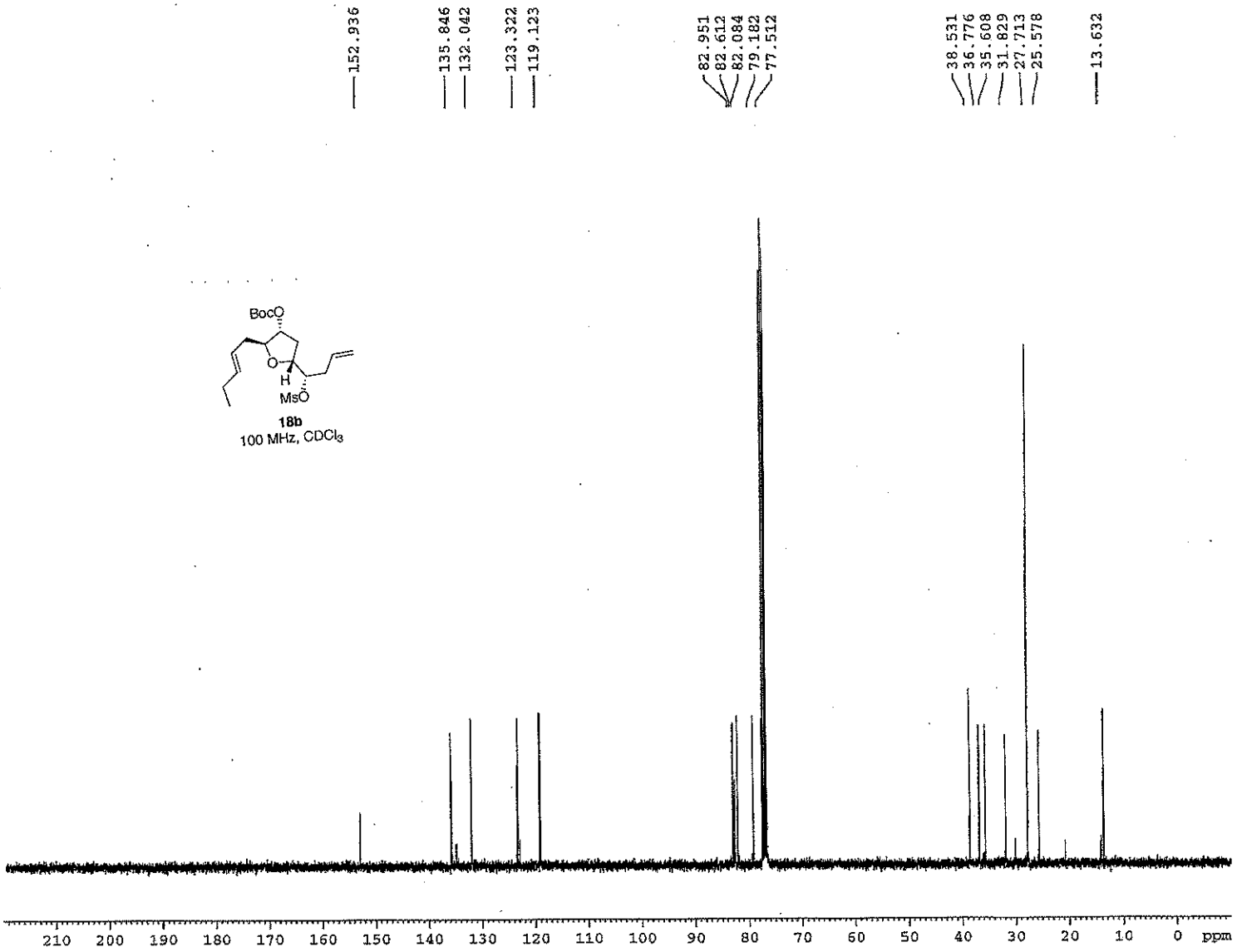

0.952
0.967
0.982
2.960
2.967
2.990
2.997
3.040
3.568
3.575
3.583
3.589
3.595
3.603
4.501
4.508
4.520
4.526
4.531
4.543
4.549
OMs
Br
15
500 MHz, CDCl3
3.054
1.072
2.051
1.986
1.092
2.015
1.082
3.041
1.000
1.030
2.076
0.979
3.083
ppm

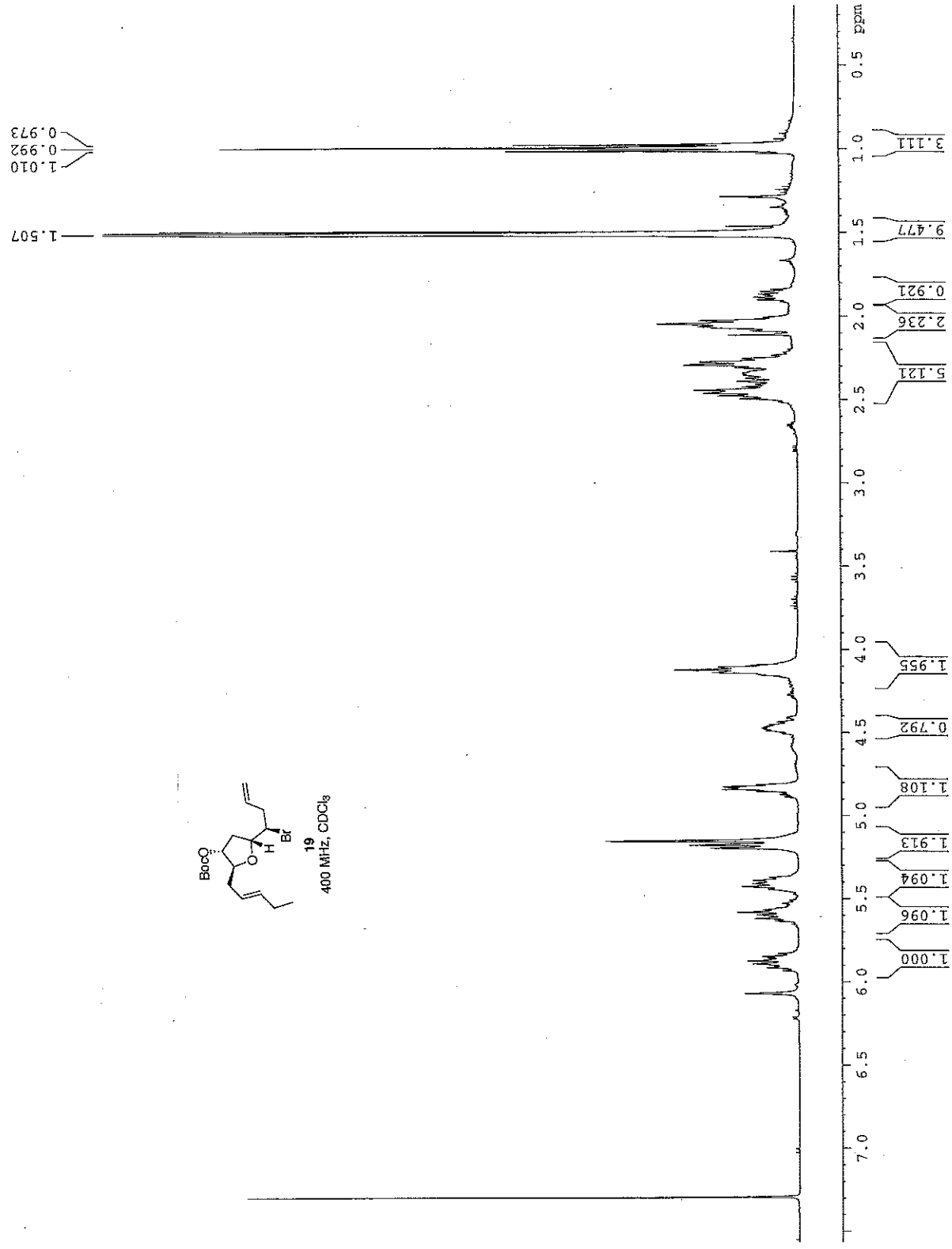

6.530
26.096
33.918
34.778
38.800
42.991
46.355
81.961
82.315
83.068
83.253
88.685
119.769
132.084
152.798
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
OMs
H
O
O
O
O
Br
15
125 MHz, CDCl3

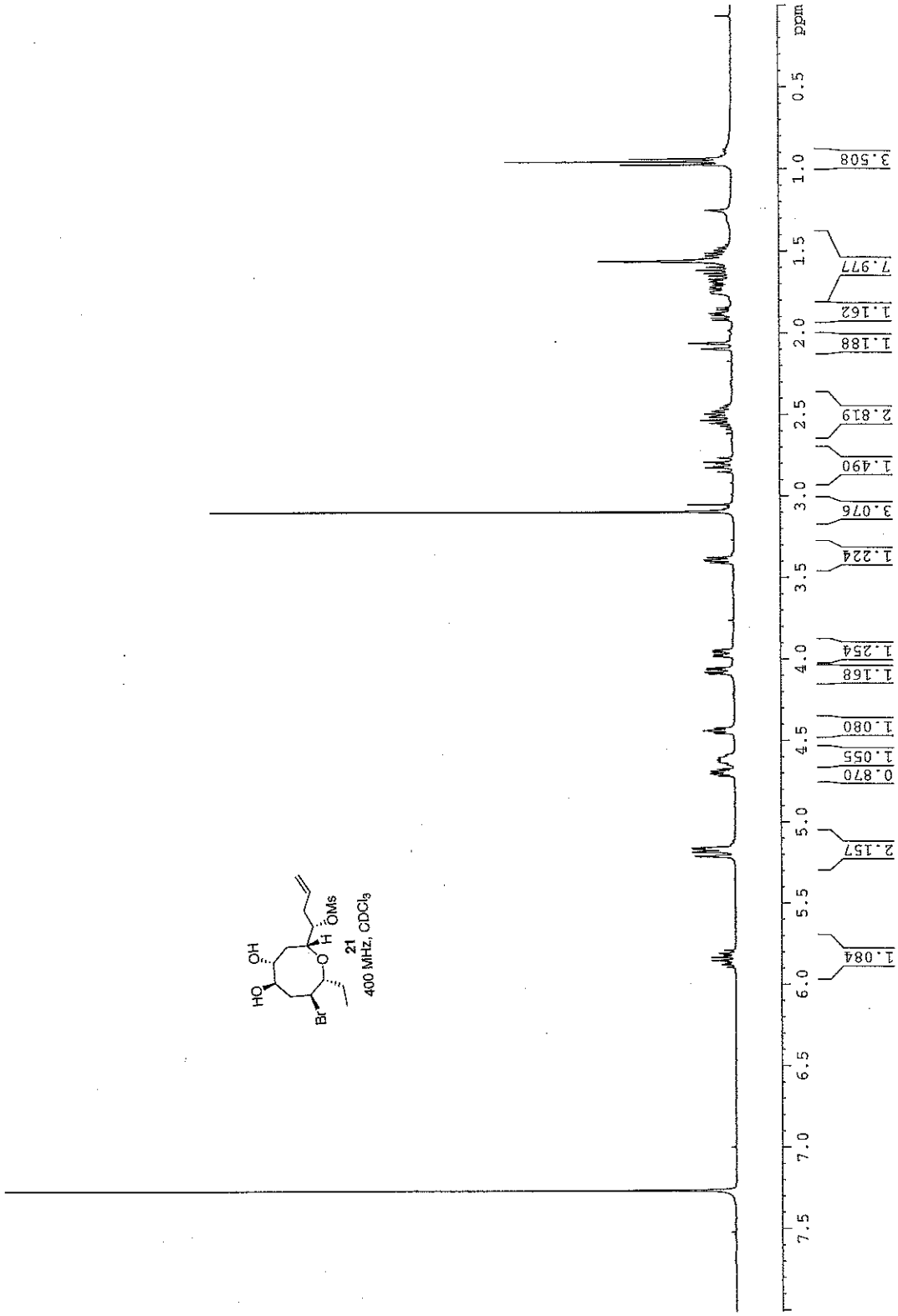

1.509
1.020
1.001
0.983
3.526
10.752
4.328
5.960
0.169
0.970
1.092
1.261
1.158
2.185
1.146
1.161
1.087
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5 ppm
BocO
H
HO
O
17a
400 MHz, CDCl3

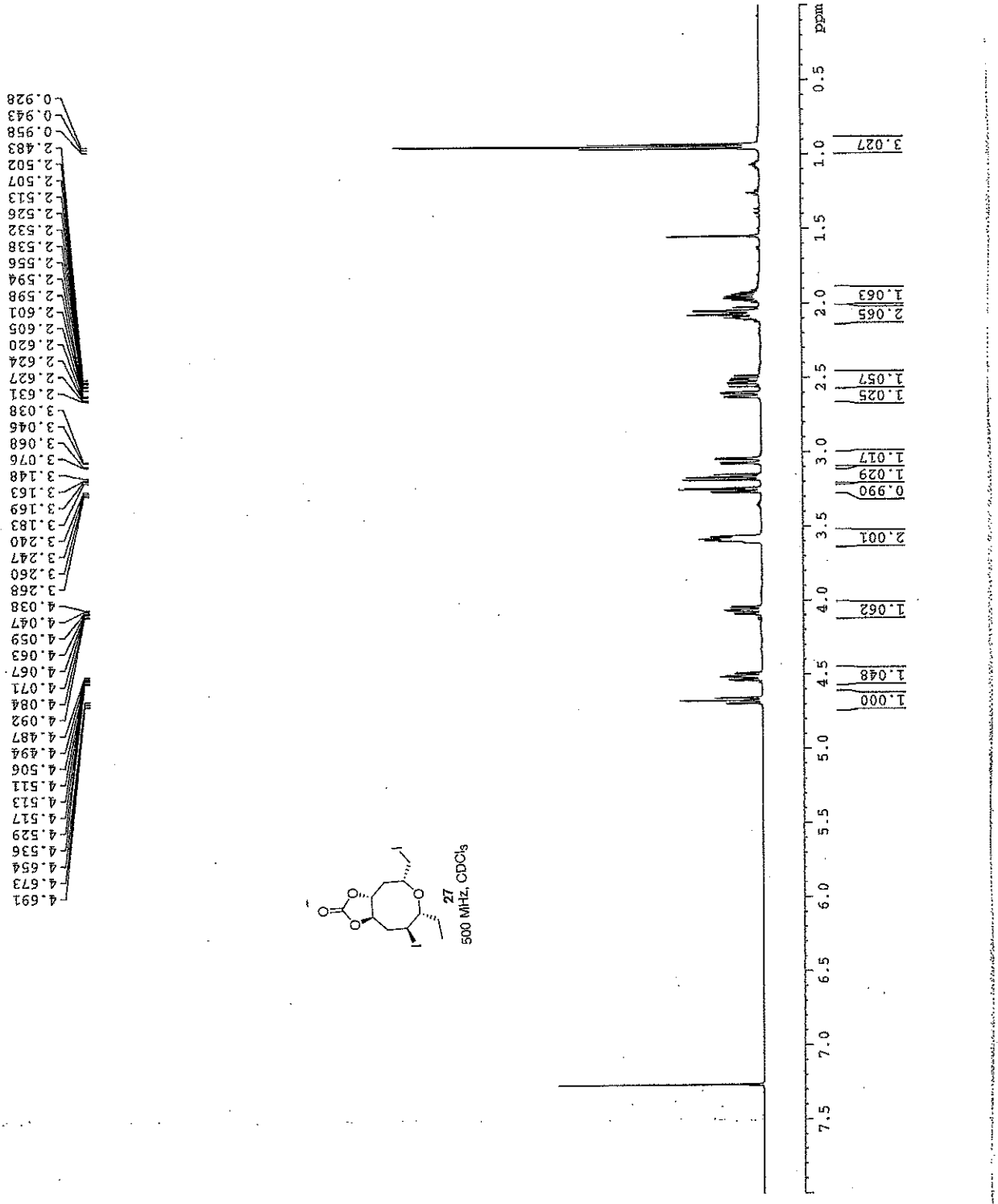

17b
400 MHz, CDCl3
BocO
OH
H
O
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.950
1.087
1.078
2.012
1.132
1.187
1.075
0.887
1.950
4.420
2.422
1.024
10.134
3.316
1.922
1.912
1.906
1.896
1.888
1.877
1.872
1.861
1.509
1.019
1.000
0.981

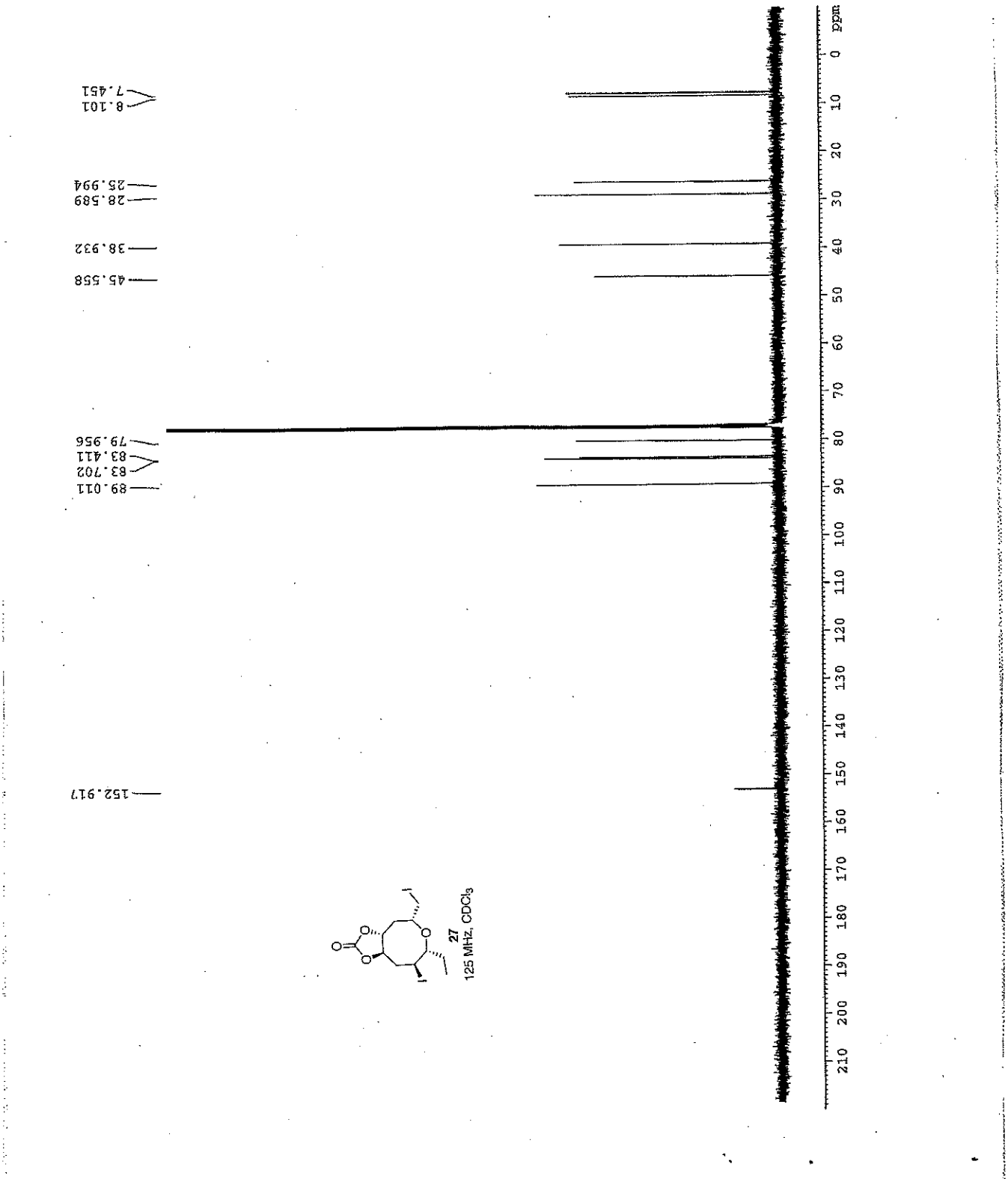

18b
400 MHz, CDCl3
BocO
MsO
H
O
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
3.043
9.183
2.094
3.004
2.983
3.051
1.025
1.047
1.992
2.051
1.032
1.017
1.000
0.944
0.962
0.981
1.481
1.979
1.995
2.014
2.032
2.051
3.066
4.039
4.047
4.056
4.063
4.072
4.080
4.114
4.123
4.131
4.134
4.140
4.143
4.150
4.160

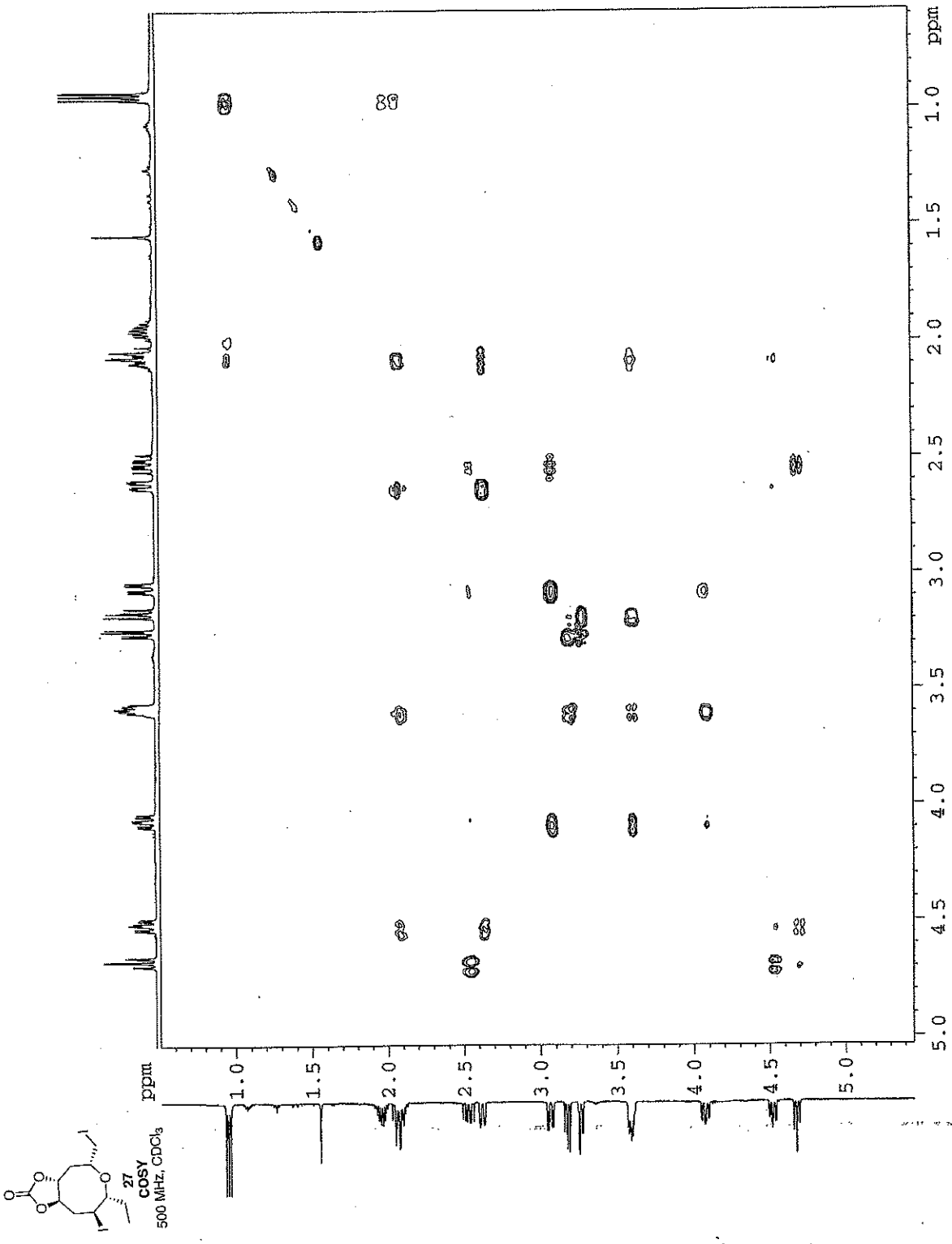

152.936
135.846
132.042
123.322
119.123
82.951
82.612
82.084
79.182
77.512
38.531
36.776
35.608
31.829
27.713
25.578
13.632
BocO
O
H
MsO
18b
100 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

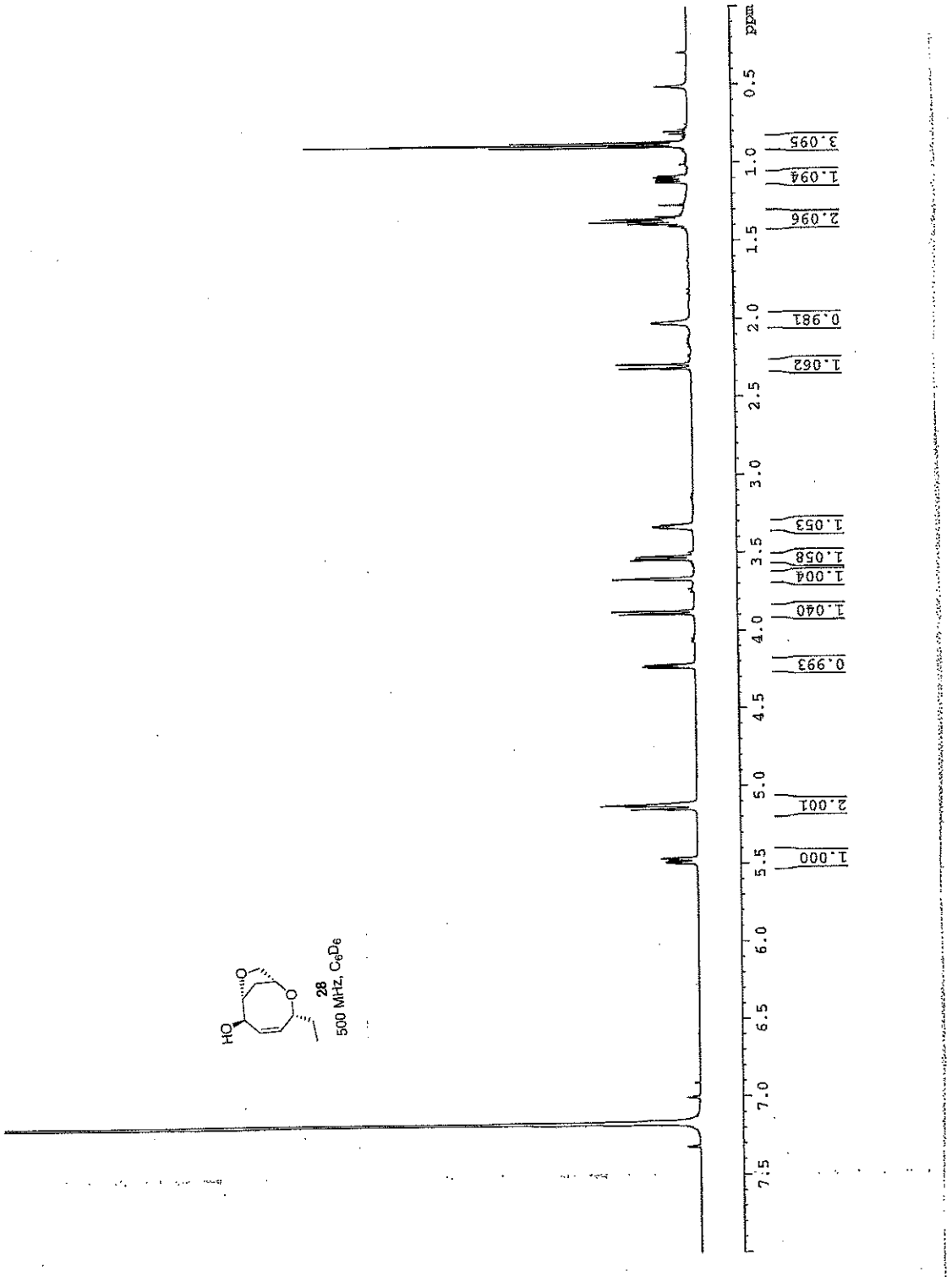

19
400 MHz, CDCl3
BocO
O
H
Br
1.507
1.010
0.992
0.973
ppm
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
1.000
1.096
1.094
1.913
1.108
0.792
1.955
5.121
2.236
0.921
9.477
3.111

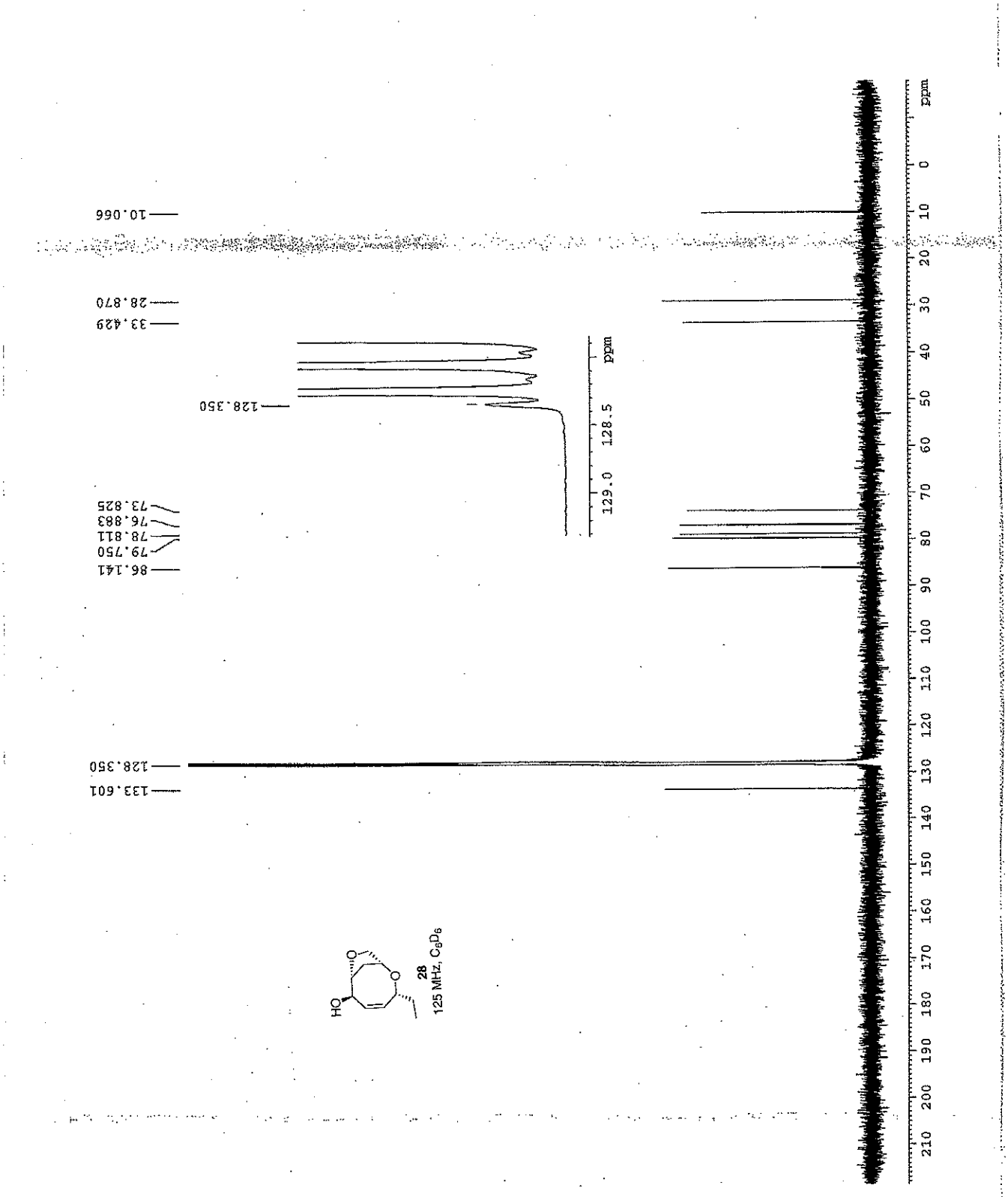

0.936
0.955
0.973
2.062
2.098
2.767
2.793
2.801
2.819
2.827
2.853
3.096
3.377
3.390
3.395
3.409
3.942
3.945
3.952
3.956
3.970
3.974
3.981
3.984
4.054
4.062
4.080
4.088
3.508
7.977
1.162
1.188
2.819
1.490
3.076
1.224
1.254
1.168
1.080
1.055
0.870
2.157
1.084
ppm
OH
HO
Br
H
OMs
21
400 MHz, CDCl3

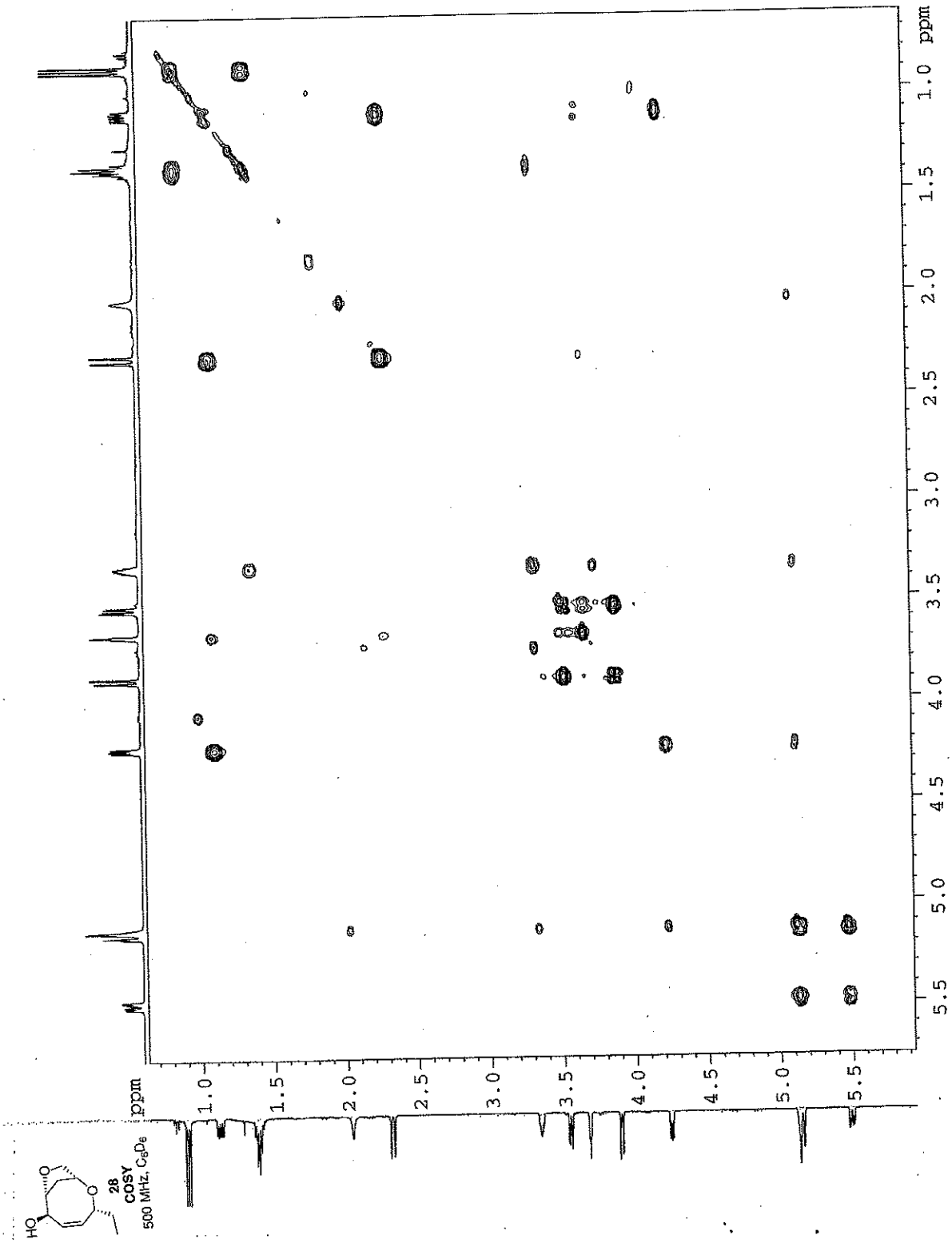

27
500 MHz, CDCl3
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
1.000
1.048
1.062
2.001
0.990
1.029
1.017
1.025
1.057
2.065
1.063
3.027
0.928
0.943
0.958
2.483
2.502
2.507
2.513
2.526
2.532
2.538
2.556
2.594
2.598
2.601
2.605
2.620
2.624
2.627
2.631
3.038
3.046
3.068
3.076
3.148
3.163
3.169
3.183
3.240
3.247
3.260
3.268
4.038
4.047
4.059
4.063
4.067
4.071
4.084
4.092
4.487
4.494
4.506
4.511
4.513
4.517
4.529
4.536
4.654
4.673
4.691

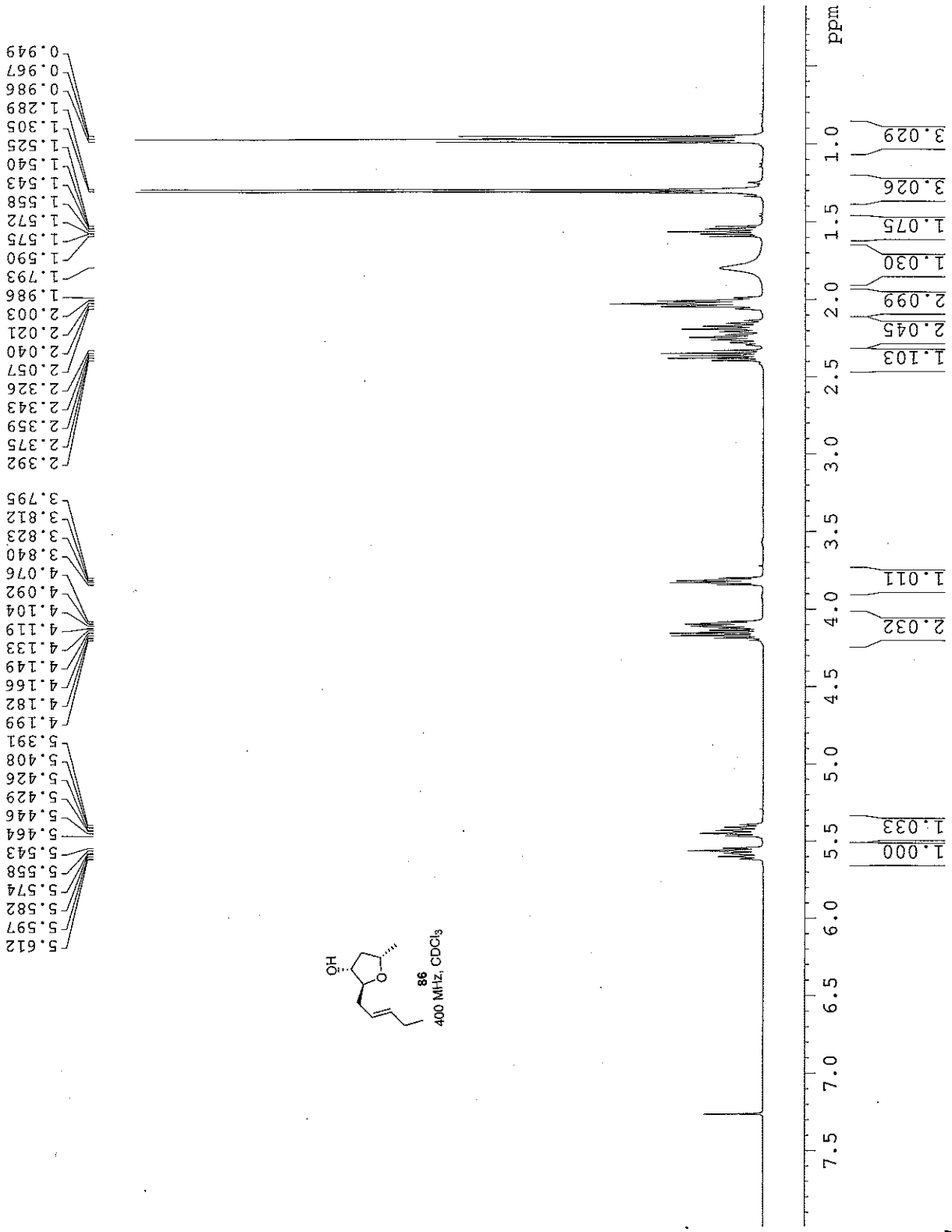

27
125 MHz, CDCl3
152.917
89.011
83.702
83.411
79.956
45.558
38.932
28.589
25.994
8.101
7.451
ppm

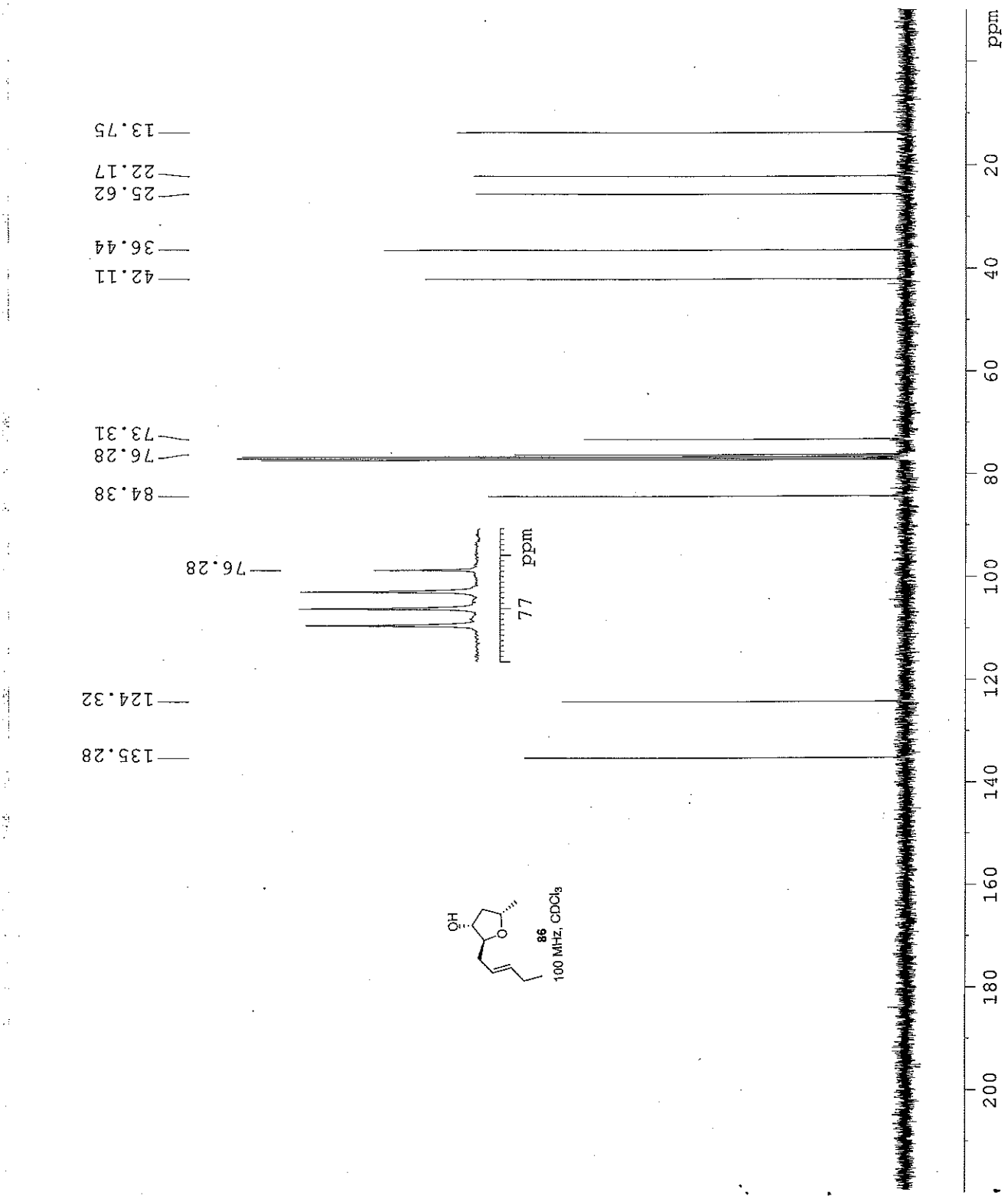

27
COSY
500 MHz, CDCl3
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0

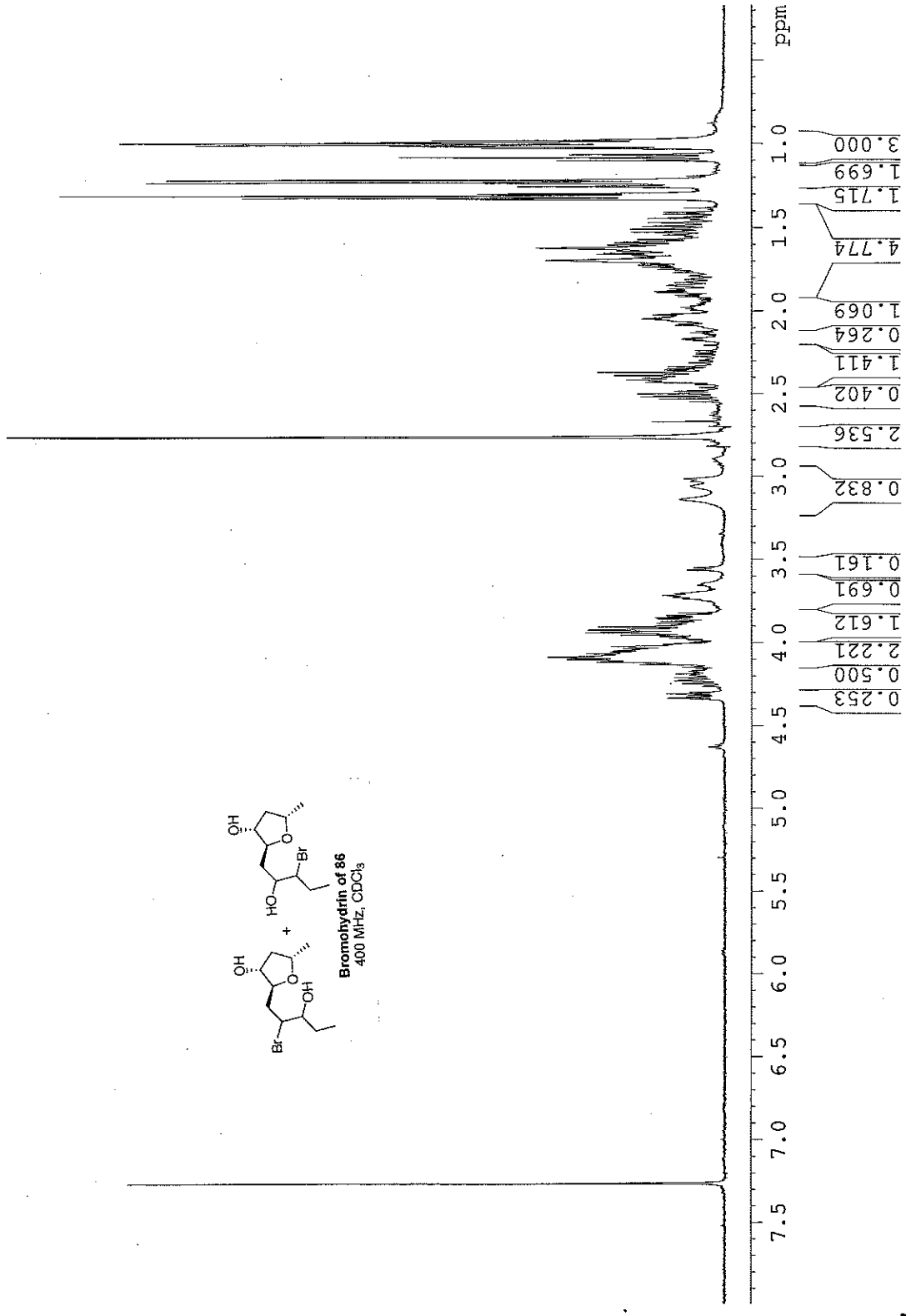

28
500 MHz, C_6D_6
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
3.095
1.094
2.096
0.981
1.062
1.053
1.058
1.004
1.040
0.993
2.001
1.000
0.864
0.879
0.893
1.080
1.085
1.094
1.099
1.107
1.112
1.120
1.126
2.023
2.285
2.312
3.518
3.524
3.537
3.543
3.661
3.666
3.670
3.872
3.891
4.215
4.222
4.229
4.236
5.460
5.464
5.469
5.473
5.483
5.488
5.493
5.497

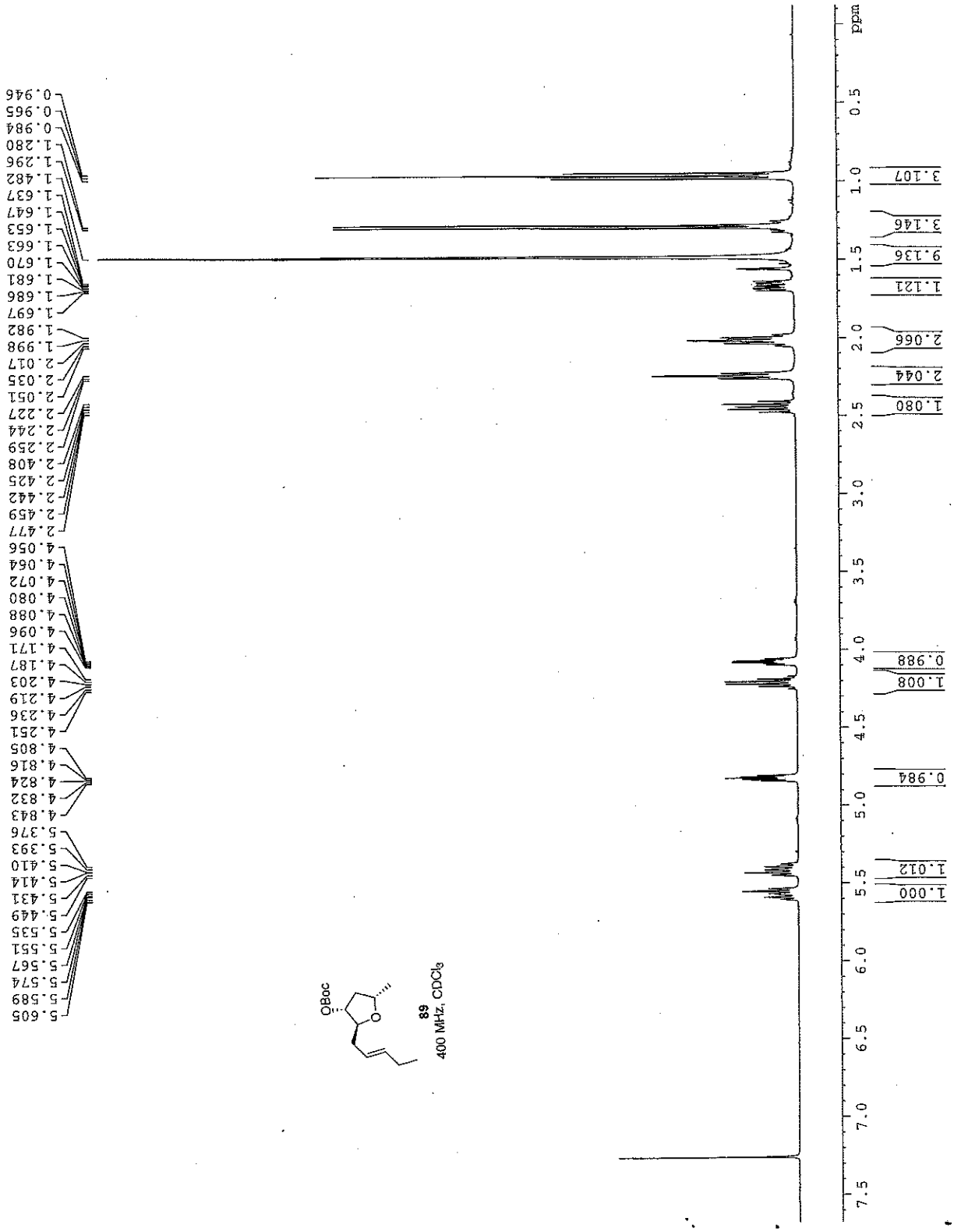

10.066
28.870
33.429
128.350
73.825
76.883
78.811
79.750
86.141
128.350
133.601
129.0
128.5
ppm
ppm
28
125 MHz, C6D6
HO

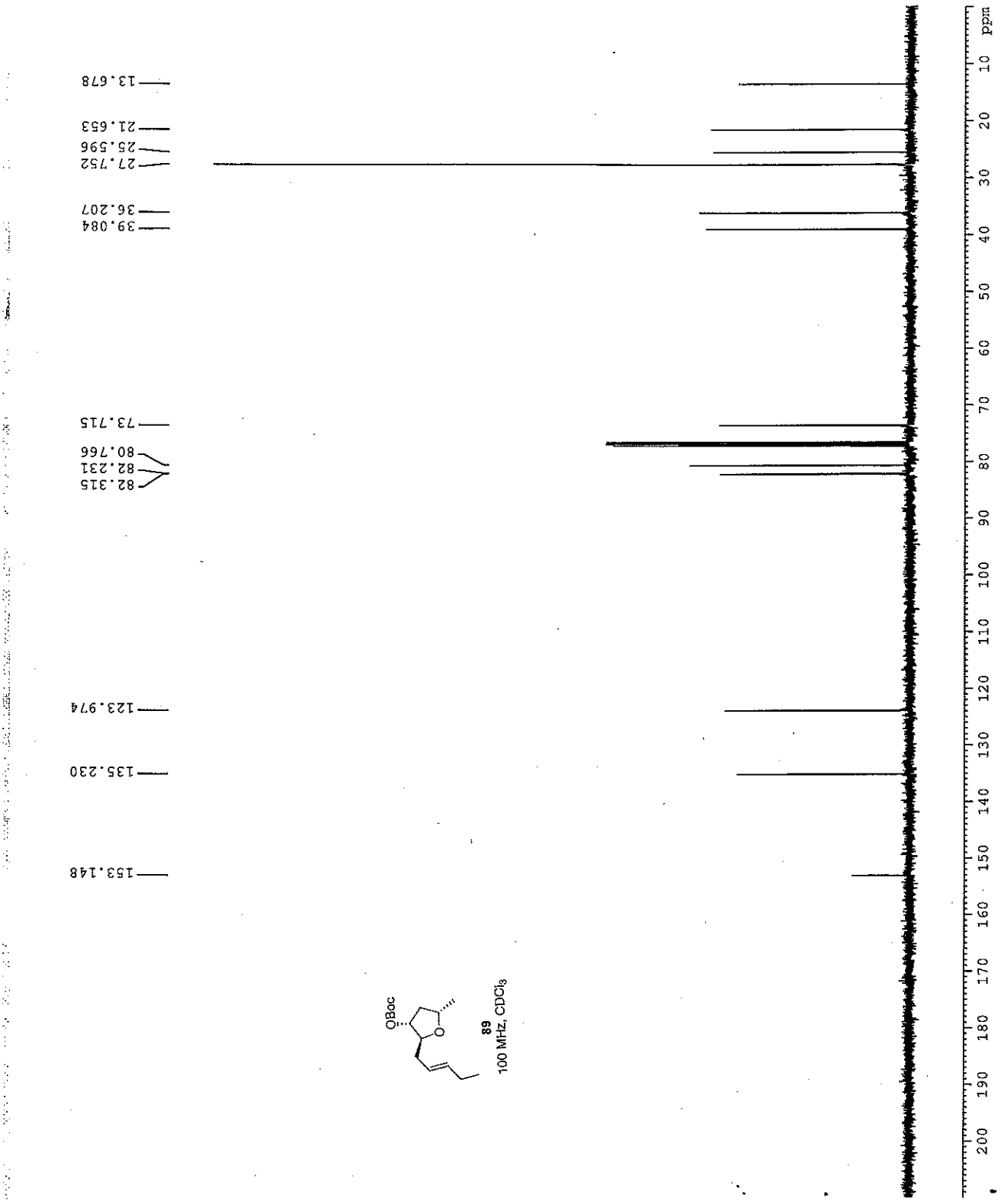

28
COSY
500 MHz, C_6D_6
HO
O
O
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5

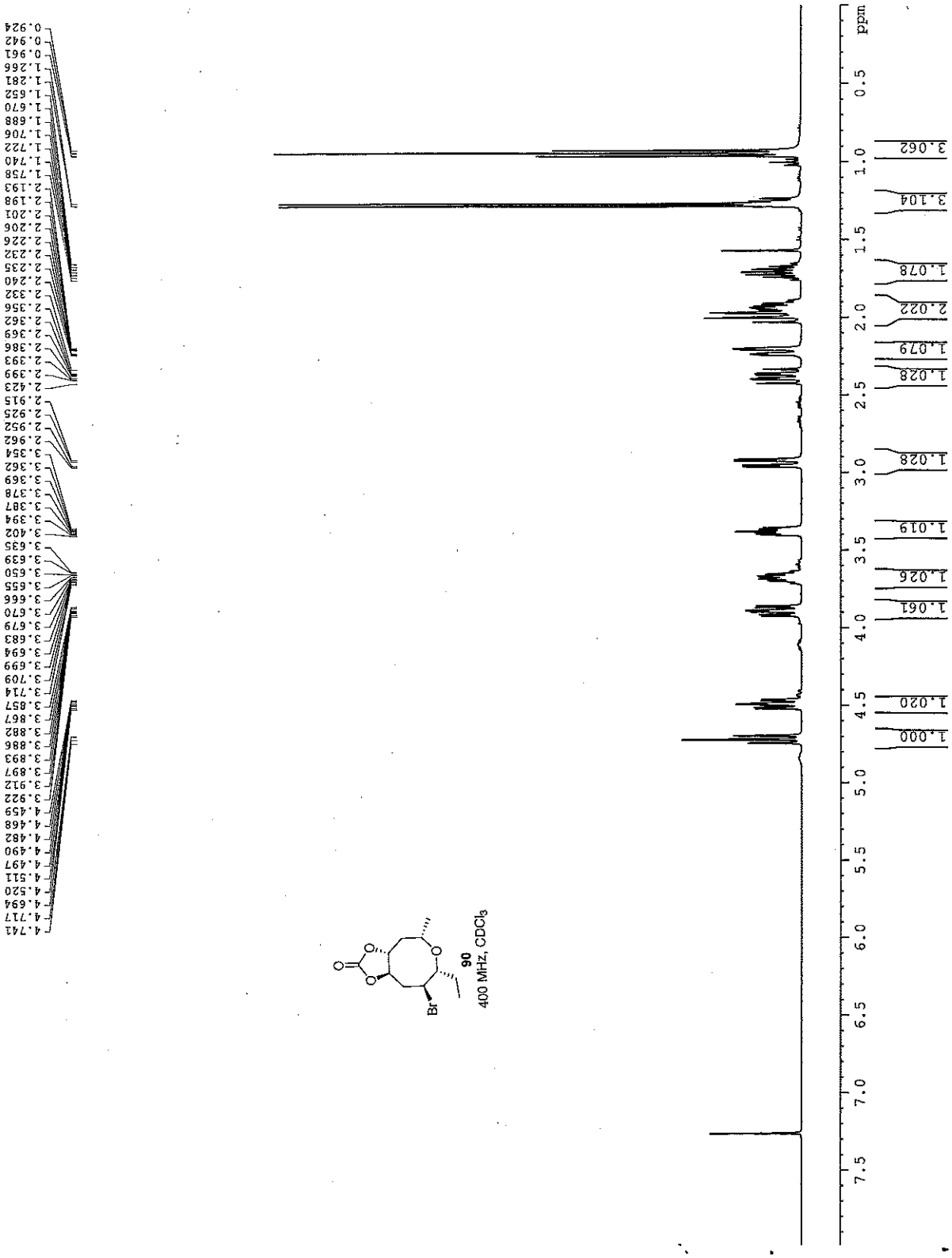

86
400 MHz, CDCl3
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
1.000
1.033
2.032
1.011
1.103
2.045
2.099
1.030
1.075
3.026
3.029
0.949
0.967
0.986
1.289
1.305
1.525
1.540
1.543
1.558
1.572
1.575
1.590
1.793
1.986
2.003
2.021
2.040
2.057
2.326
2.343
2.359
2.375
2.392
3.795
3.812
3.823
3.840
4.076
4.092
4.104
4.119
4.133
4.149
4.166
4.182
4.199
5.391
5.408
5.426
5.429
5.446
5.464
5.543
5.558
5.574
5.582
5.597
5.612

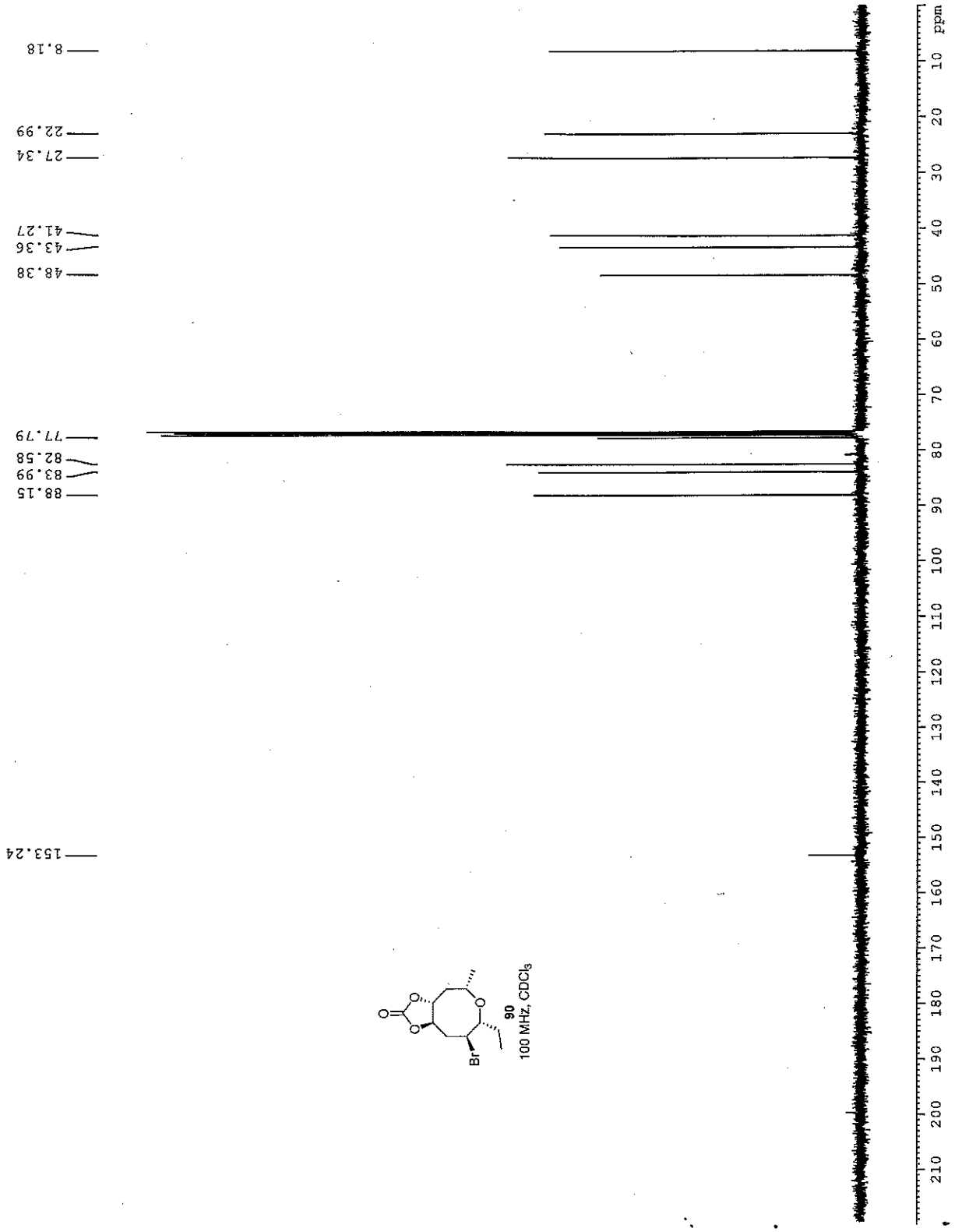

86
100 MHz, CDCl3
135.28
124.32
84.38
76.28
73.31
42.11
36.44
25.62
22.17
13.75
76.28
77
ppm
ppm
20
40
60
80
100
120
140
160
180
200

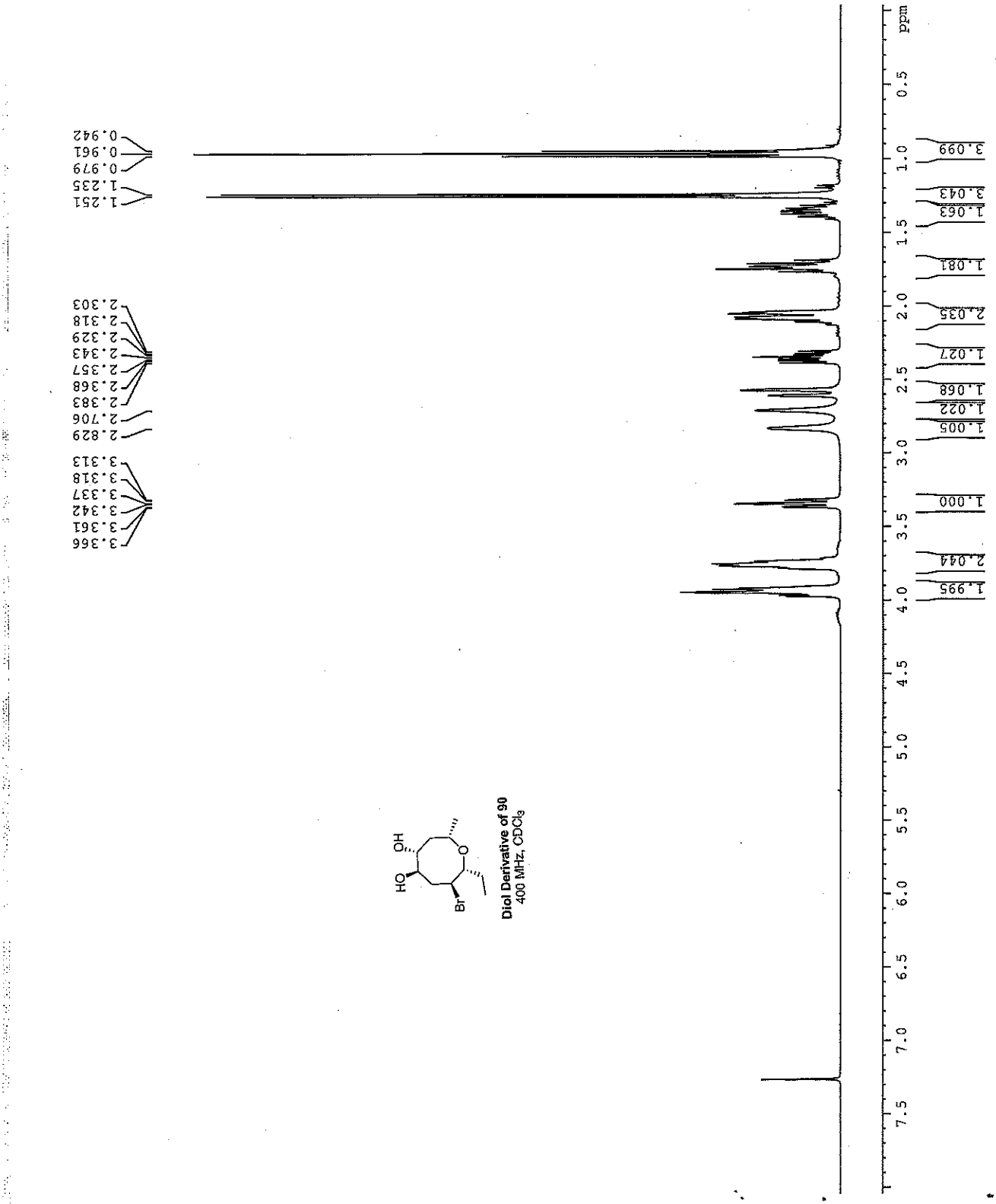

Bromohydrin of 86
400 MHz, $CDCl_3$
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.253
0.500
2.221
1.612
0.691
0.161
0.832
2.536
0.402
1.411
0.264
1.069
4.774
1.715
1.699
3.000

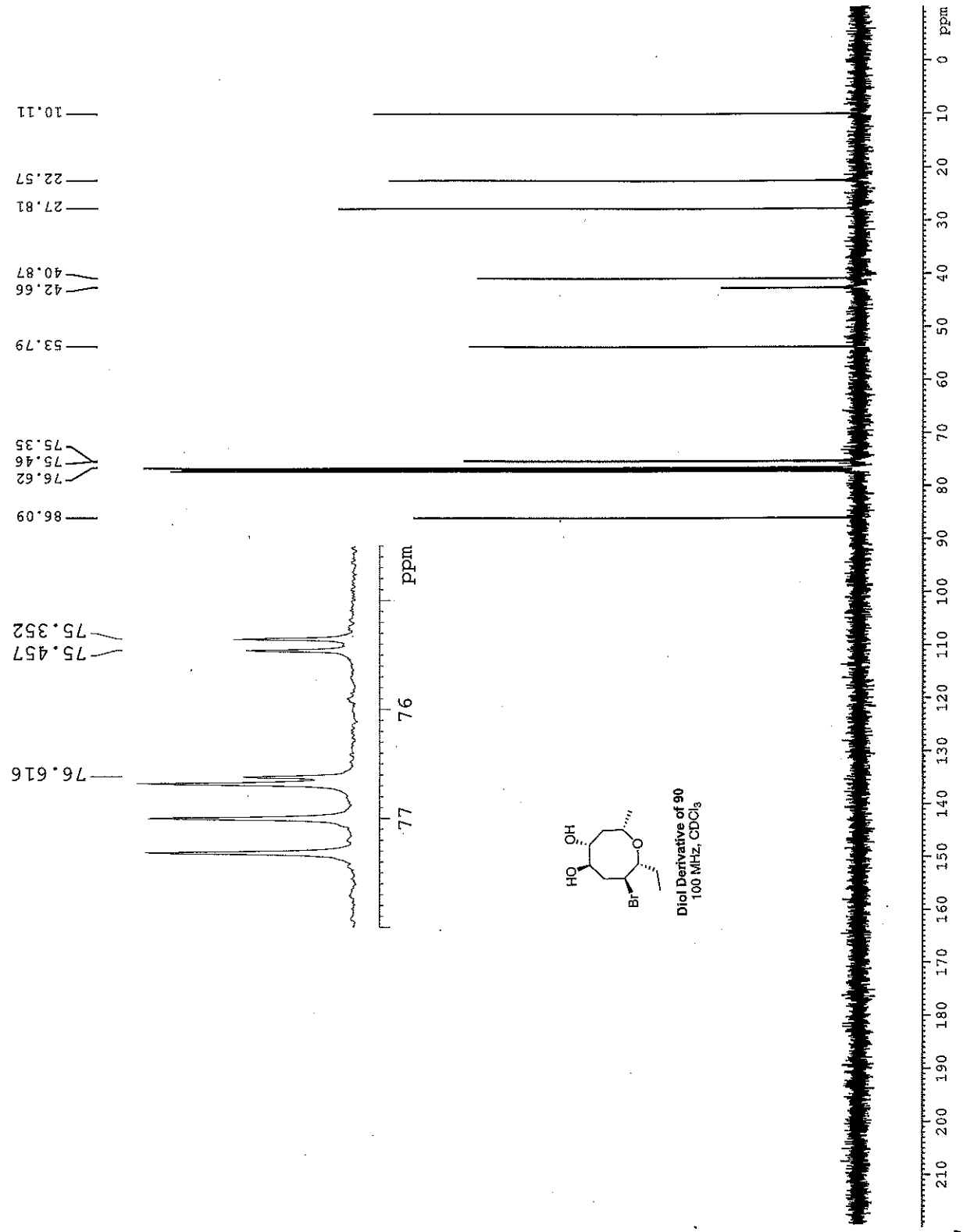

OBoc
89
400 MHz, CDCl3
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
3.107
3.146
9.136
1.121
2.066
2.044
1.080
0.988
1.008
0.984
1.012
1.000
0.946
0.965
0.984
1.280
1.296
1.482
1.637
1.647
1.653
1.663
1.670
1.681
1.686
1.697
1.982
1.998
2.017
2.035
2.051
2.227
2.244
2.259
2.408
2.425
2.442
2.459
2.477
4.056
4.064
4.072
4.080
4.088
4.096
4.171
4.187
4.203
4.219
4.236
4.251
4.805
4.816
4.824
4.832
4.843
5.376
5.393
5.410
5.414
5.431
5.449
5.535
5.551
5.567
5.574
5.589
5.605

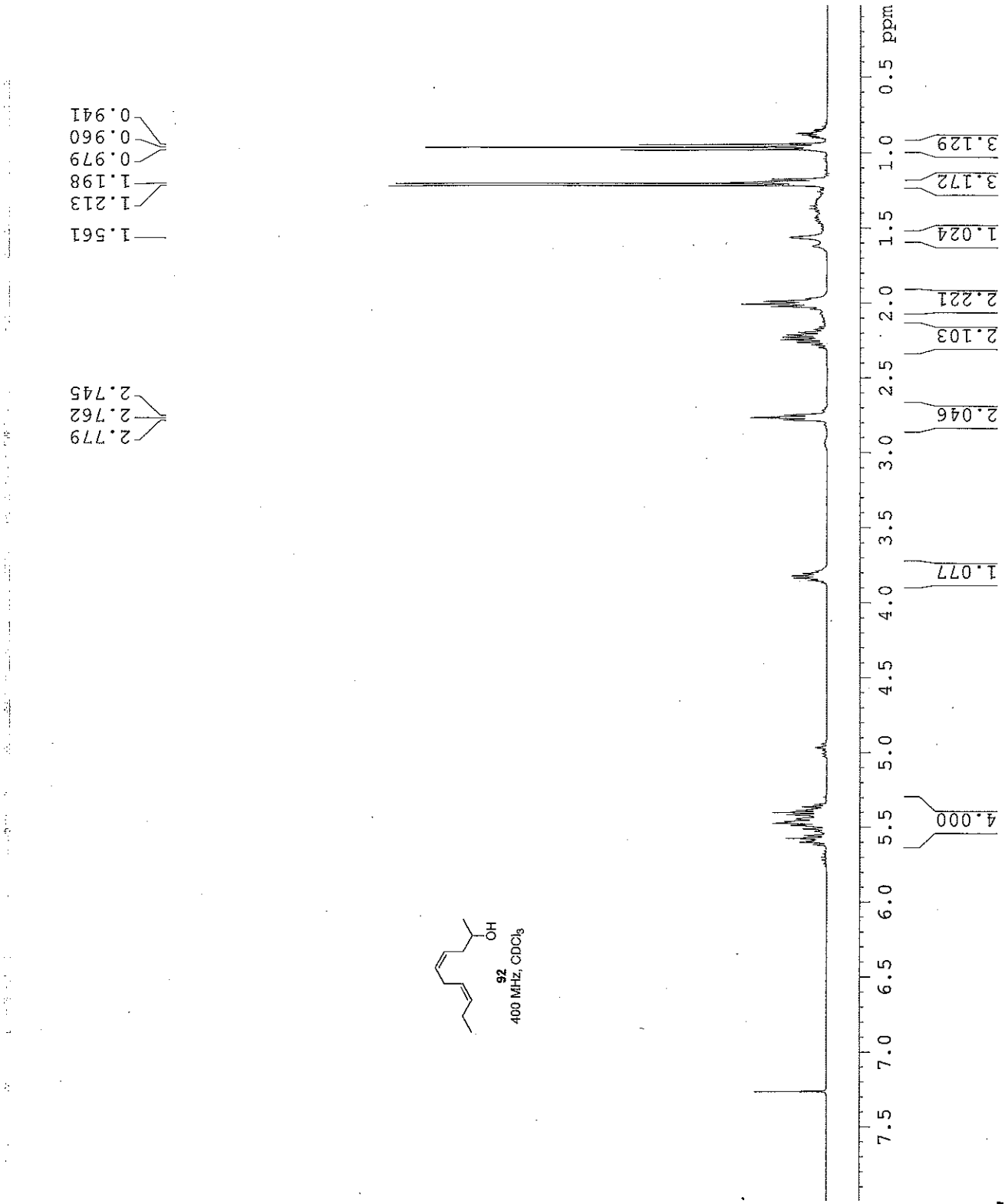

13.678
21.653
25.596
27.752
36.207
39.084
73.715
80.766
82.231
82.315
123.974
135.230
153.148
OBoc
89
100 MHz, CDCl3
ppm

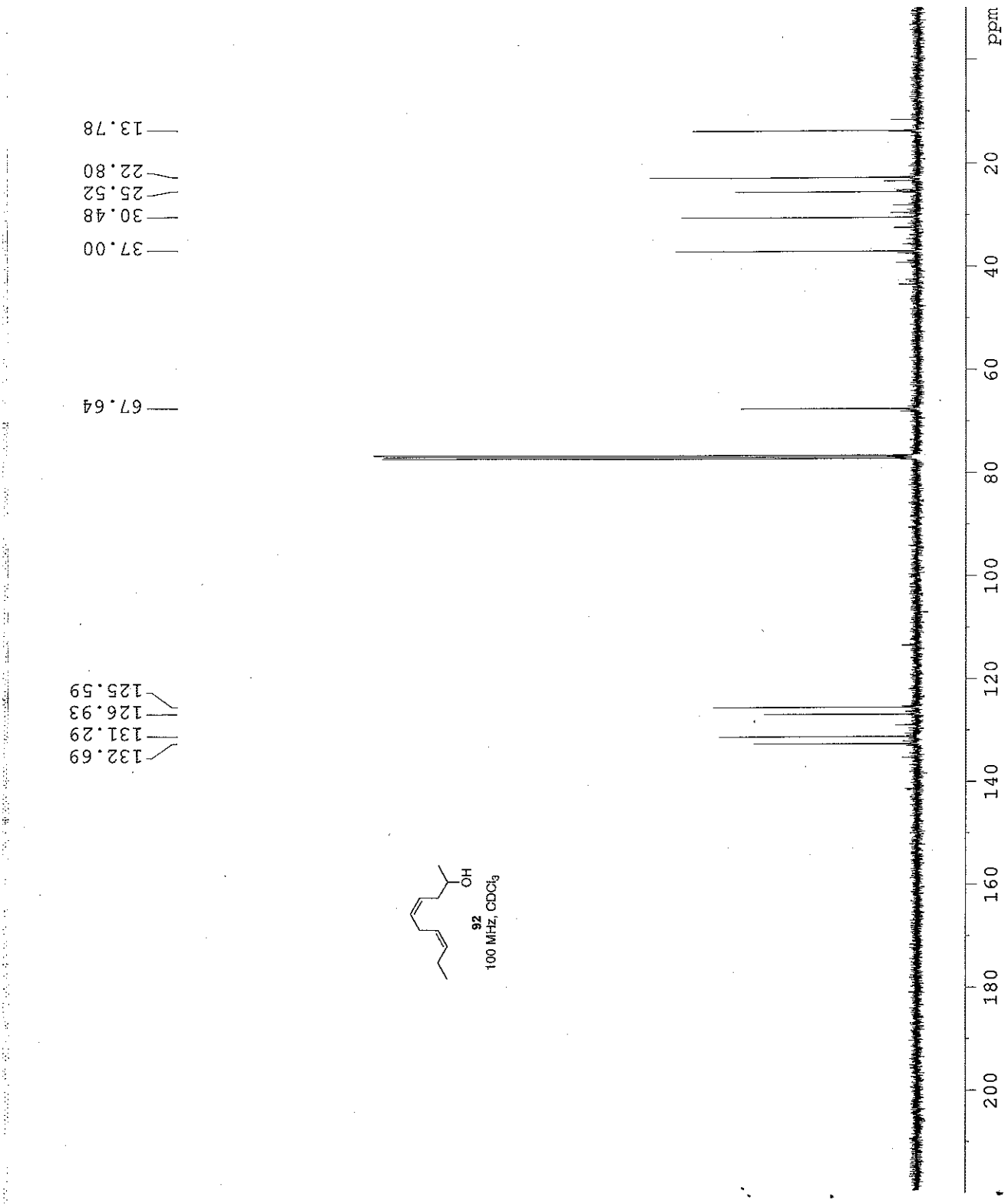

90
400 MHz, CDCl3
Br
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
3.062
3.104
1.078
2.022
1.079
1.028
1.028
1.019
1.026
1.061
1.020
1.000

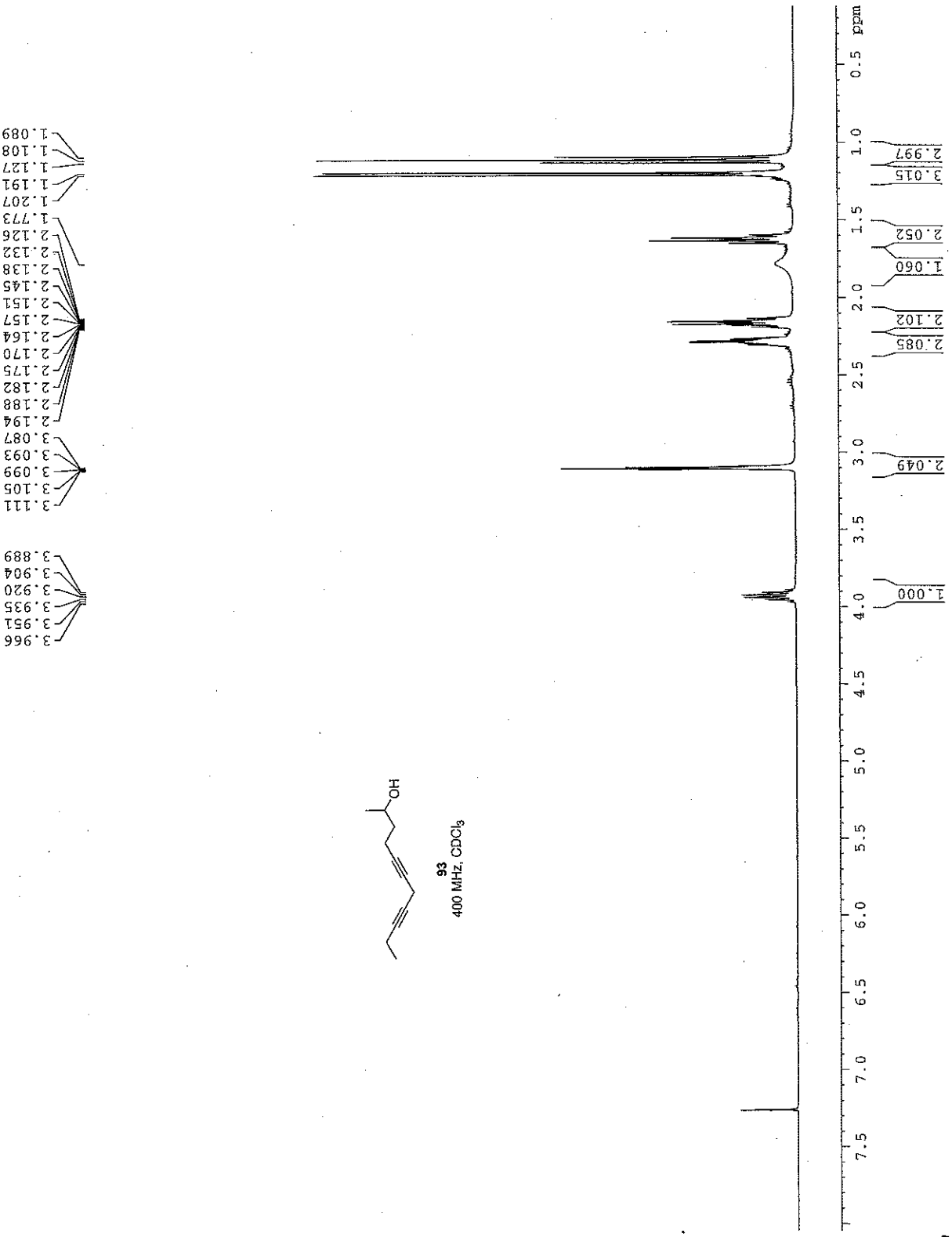

8.18
22.99
27.34
41.27
43.36
48.38
77.79
82.58
83.99
88.15
153.24
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
Br
90
100 MHz, CDCl3

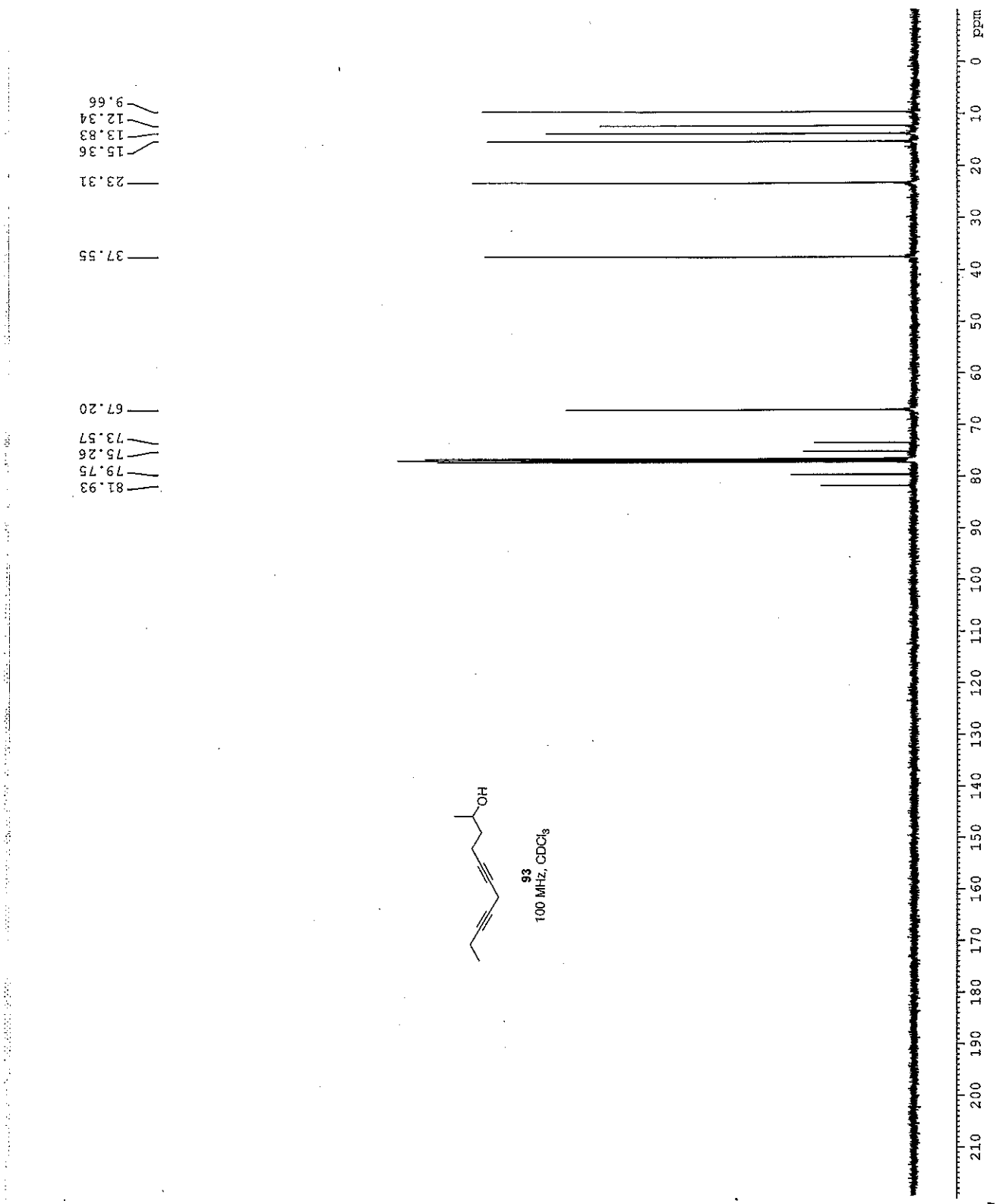

Diol Derivative of 90
400 MHz, CDCl3
OH
HO
O
Br
0.942
0.961
0.979
1.251
2.303
2.318
2.329
2.343
2.357
2.368
2.383
2.706
2.829
3.313
3.318
3.337
3.342
3.361
3.366
3.099
3.043
1.063
1.081
2.035
1.027
1.068
1.022
1.005
1.000
2.044
1.995
ppm

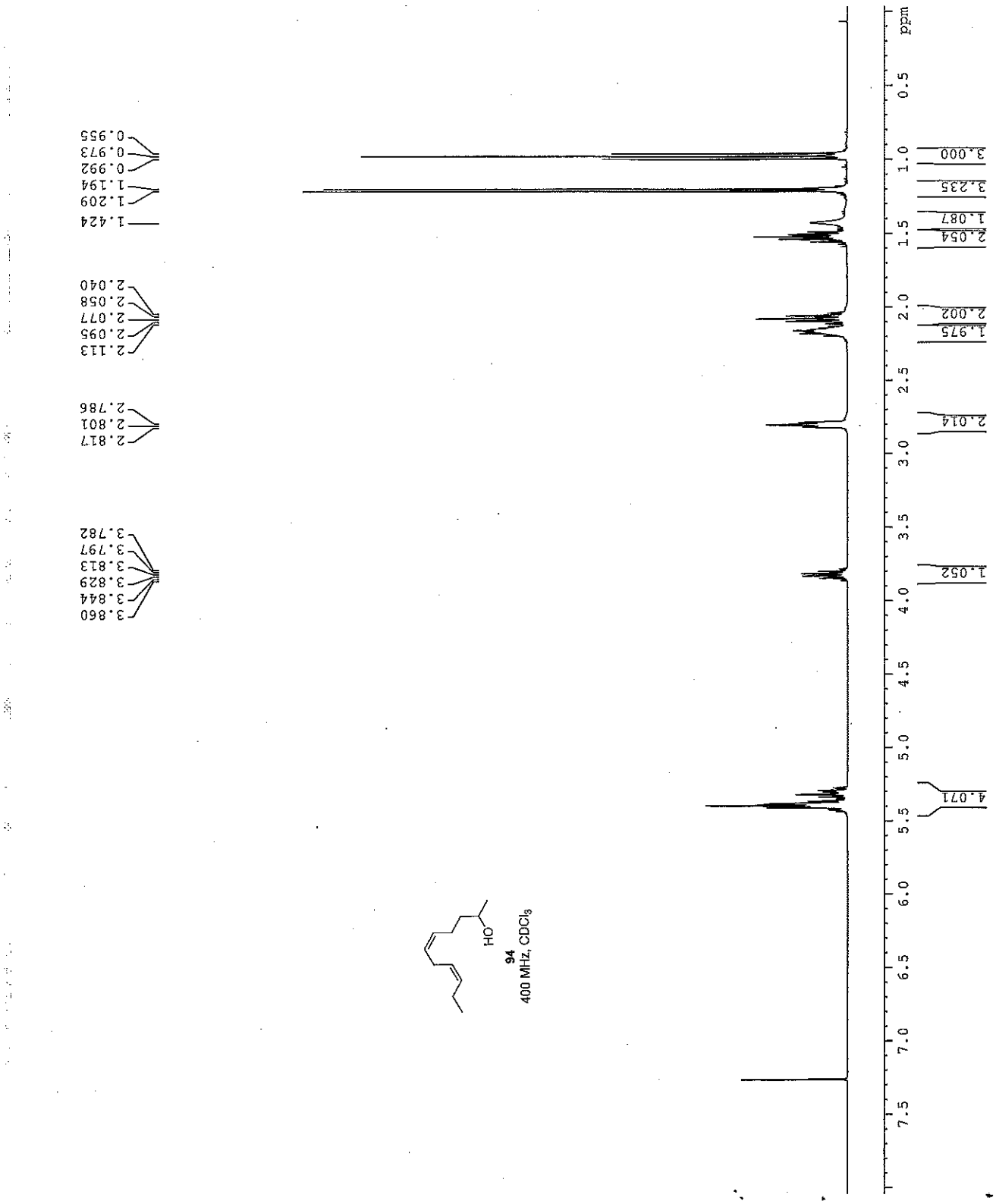

10.11
22.57
27.81
40.87
42.66
53.79
75.35
75.46
76.62
86.09
75.352
75.457
76.616
ppm
77
76
OH
HO
Br
O
Diol Derivative of 90
100 MHz, CDCl3
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

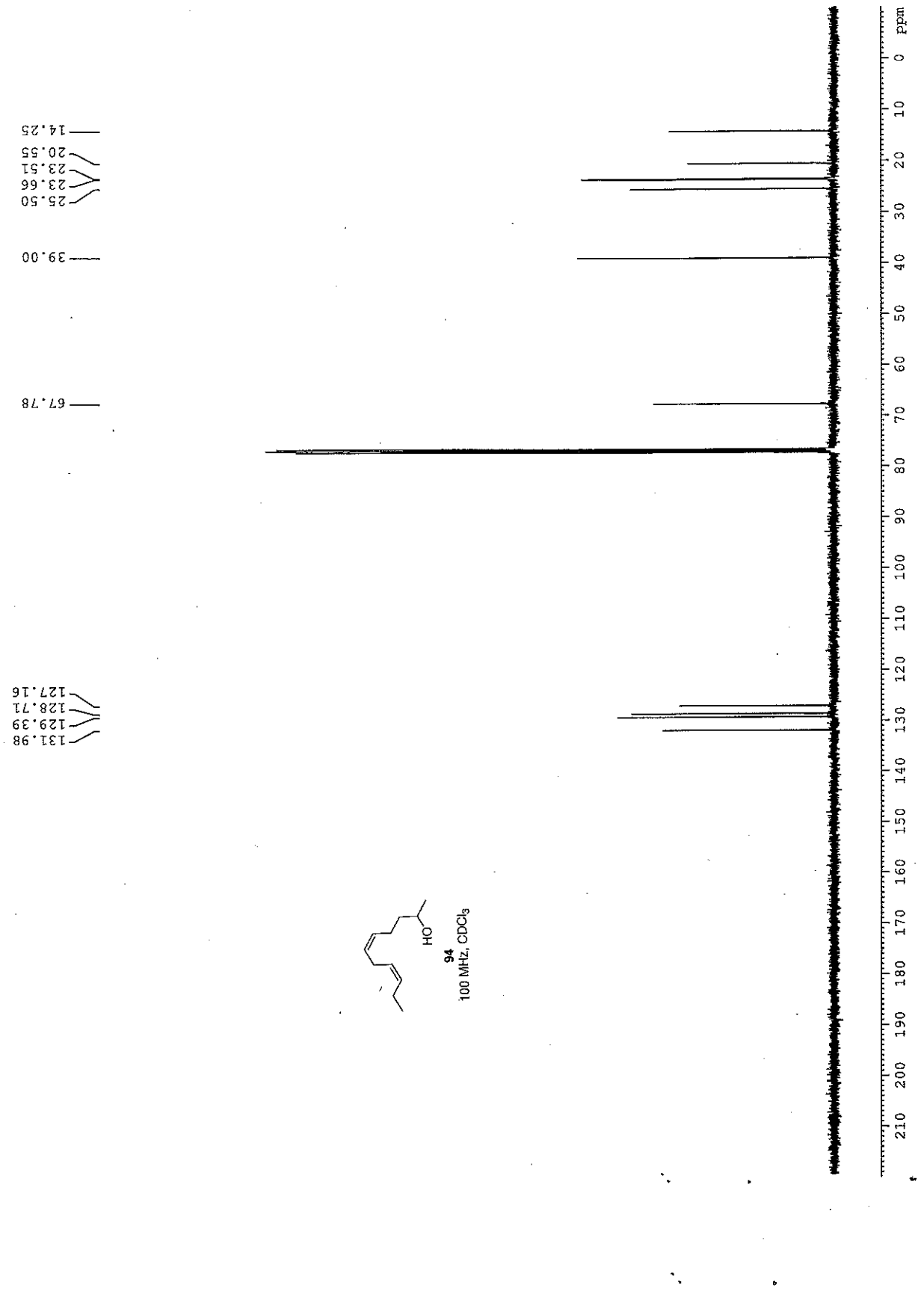

92
400 MHz, CDCl3
OH
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
3.129
3.172
1.024
2.221
2.103
2.046
1.077
4.000
0.941
0.960
0.979
1.198
1.213
1.561
2.745
2.762
2.779

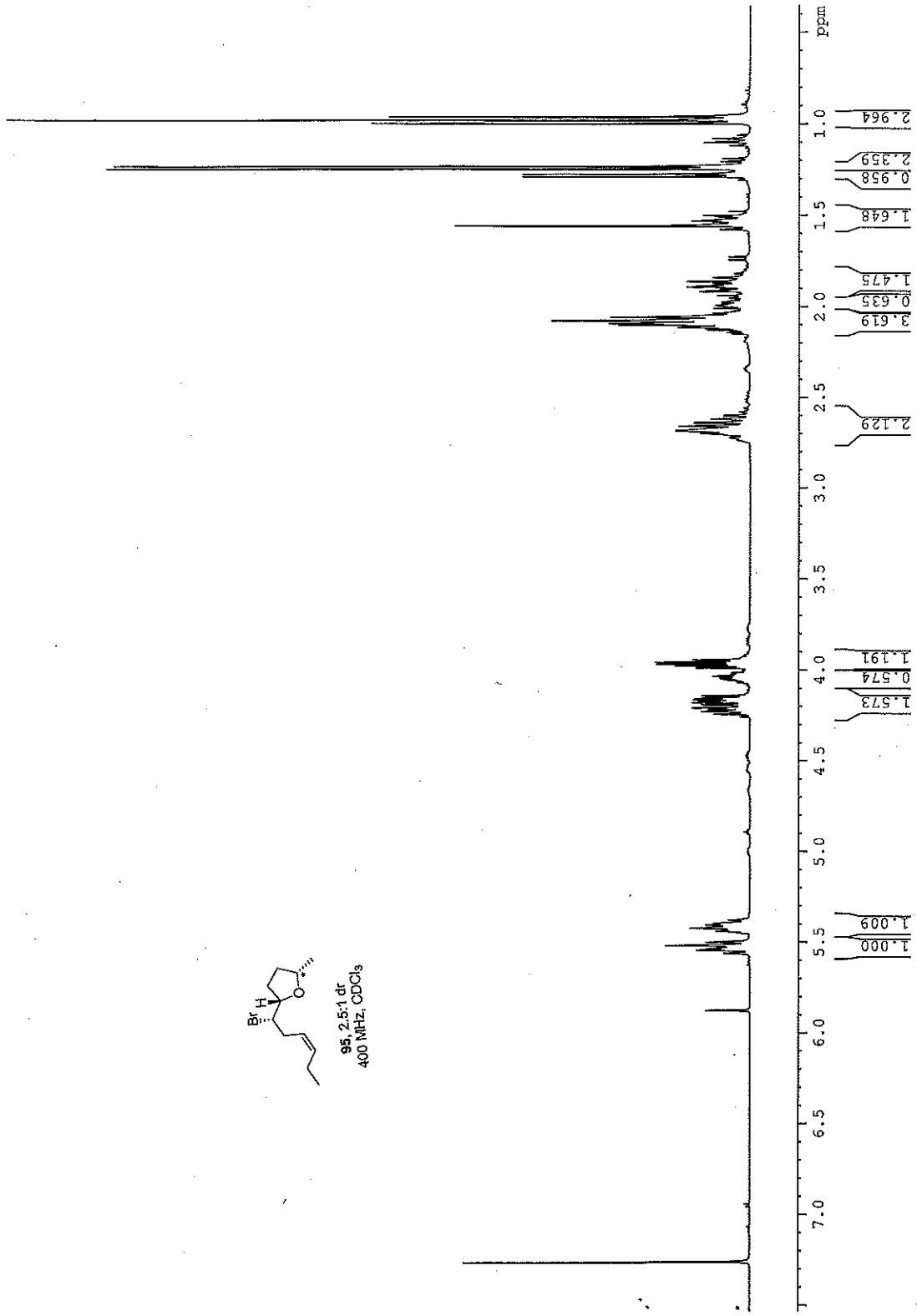

OH
92
100 MHz, $CDCl_3$
13.78
22.80
25.52
30.48
37.00
67.64
125.59
126.93
131.29
132.69
ppm
200
180
160
140
120
100
80
60
40
20

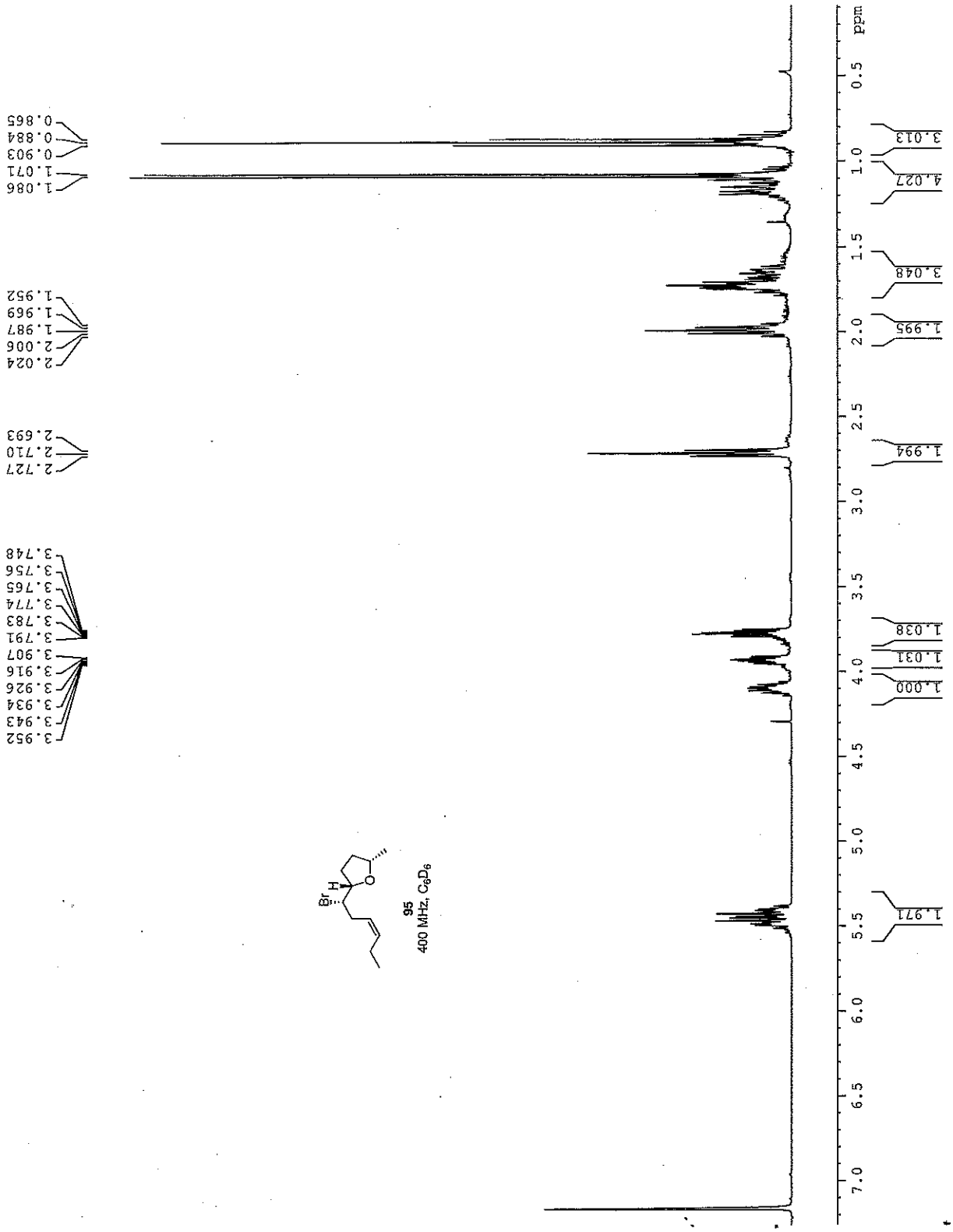

OH
93
400 MHz, CDCl3
1.089
1.108
1.127
1.191
1.207
1.773
2.126
2.132
2.138
2.145
2.151
2.157
2.164
2.170
2.175
2.182
2.188
2.194
3.087
3.093
3.099
3.105
3.111
3.889
3.904
3.920
3.935
3.951
3.966
1.000
2.049
3.015
2.997
2.052
1.060
2.102
2.085
ppm

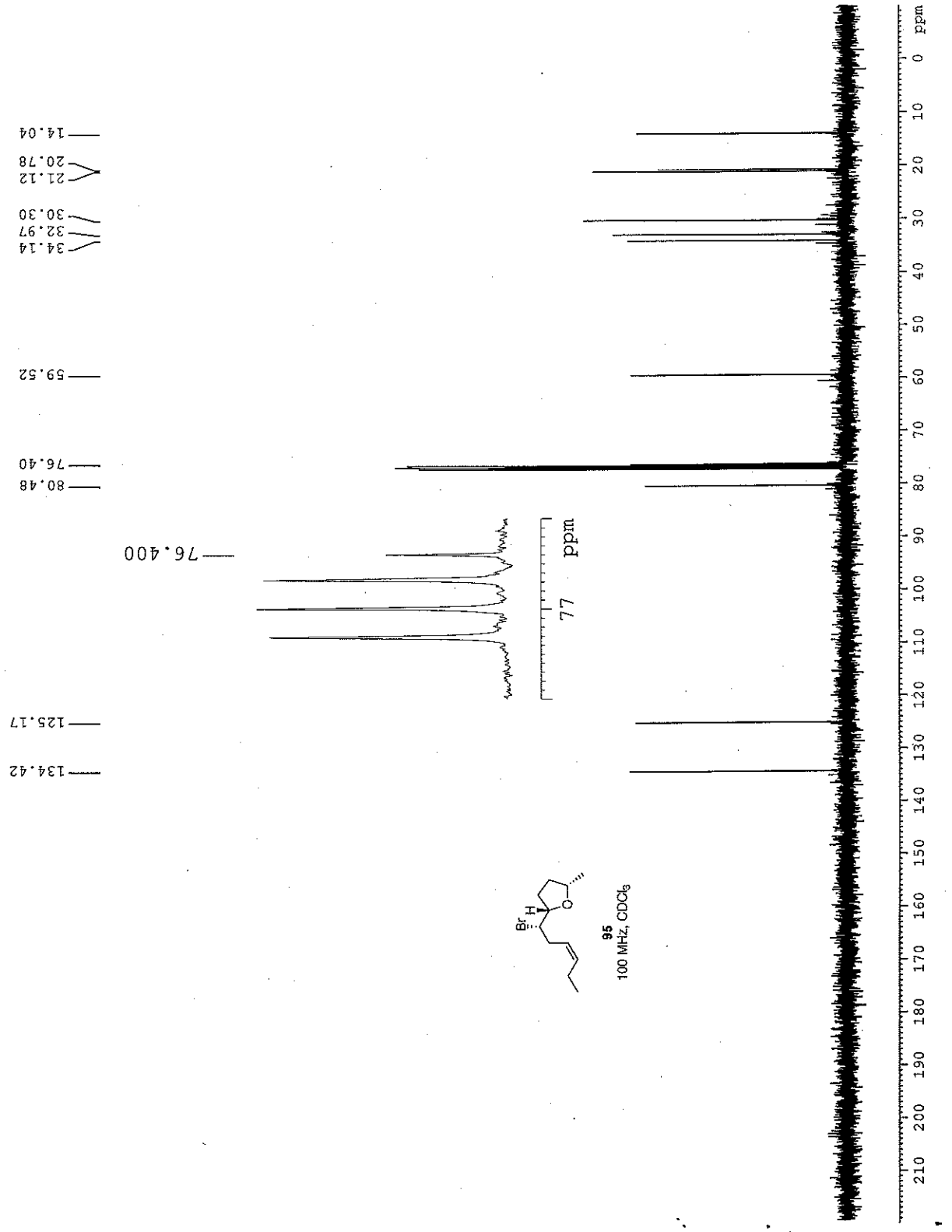

9.66
12.34
13.83
15.36
23.31
37.55
67.20
73.57
75.26
79.75
81.93
OH
93
100 MHz, CDCl3
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

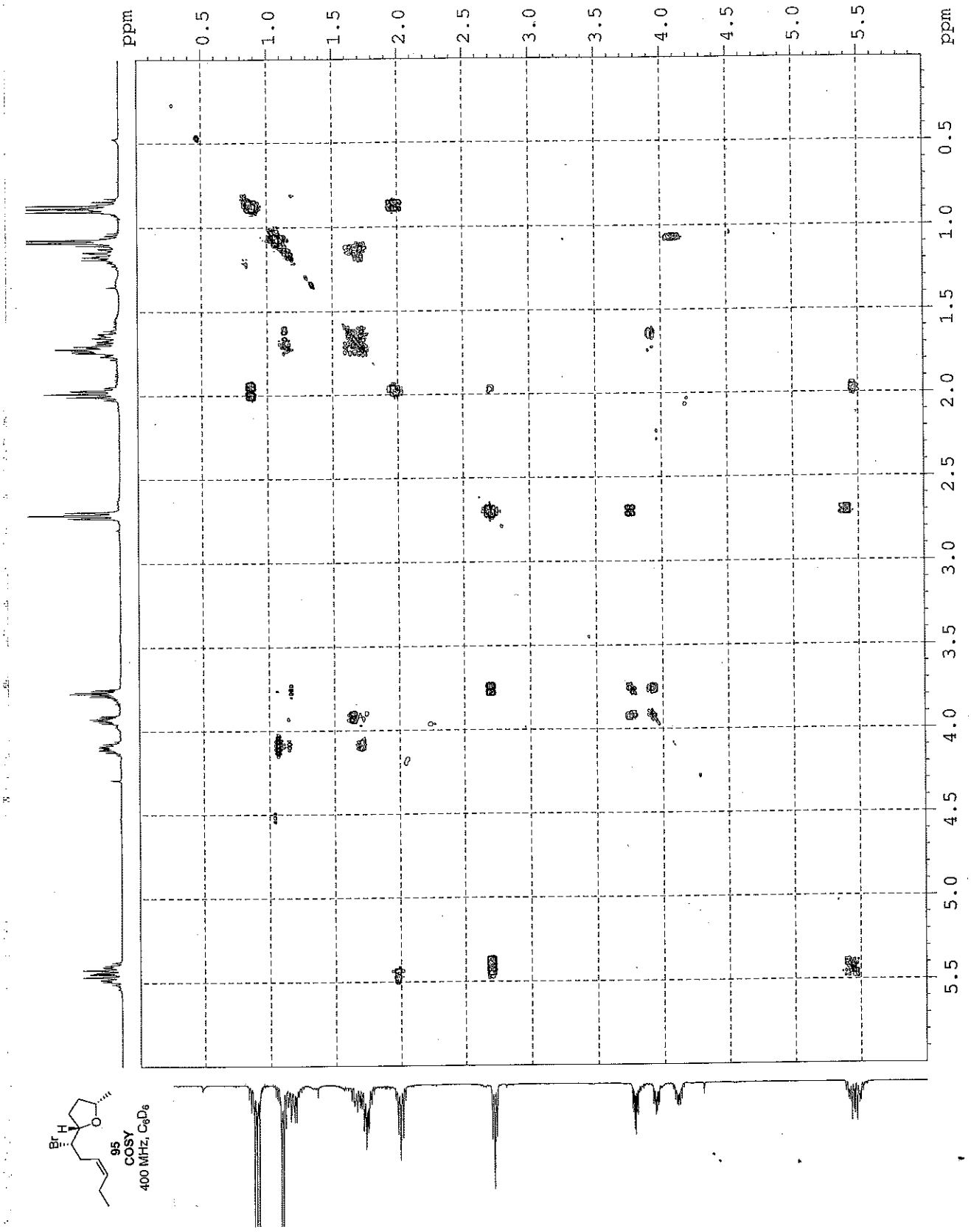

94
400 MHz, CDCl3
OH
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
5.0
5.5
6.0
6.5
7.0
7.5
3.000
3.235
1.087
2.054
2.002
1.975
2.014
1.052
4.071
0.955
0.973
0.992
1.194
1.209
1.424
2.040
2.058
2.077
2.095
2.113
2.786
2.801
2.817
3.782
3.797
3.813
3.829
3.844
3.860

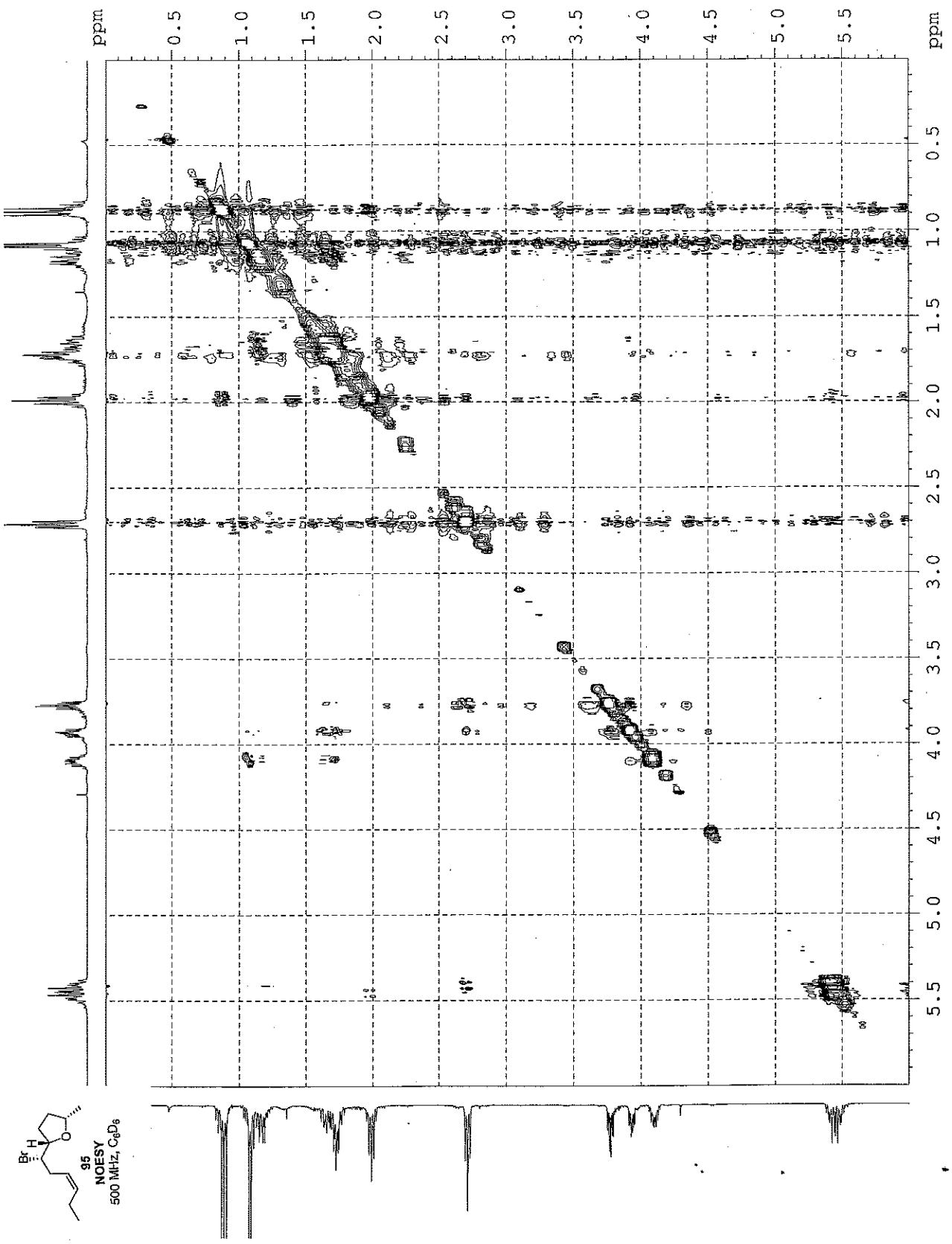

14.25
20.55
23.51
23.66
25.50
39.00
67.78
127.16
128.71
129.39
131.98
HO
94
100 MHz, CDCl3
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

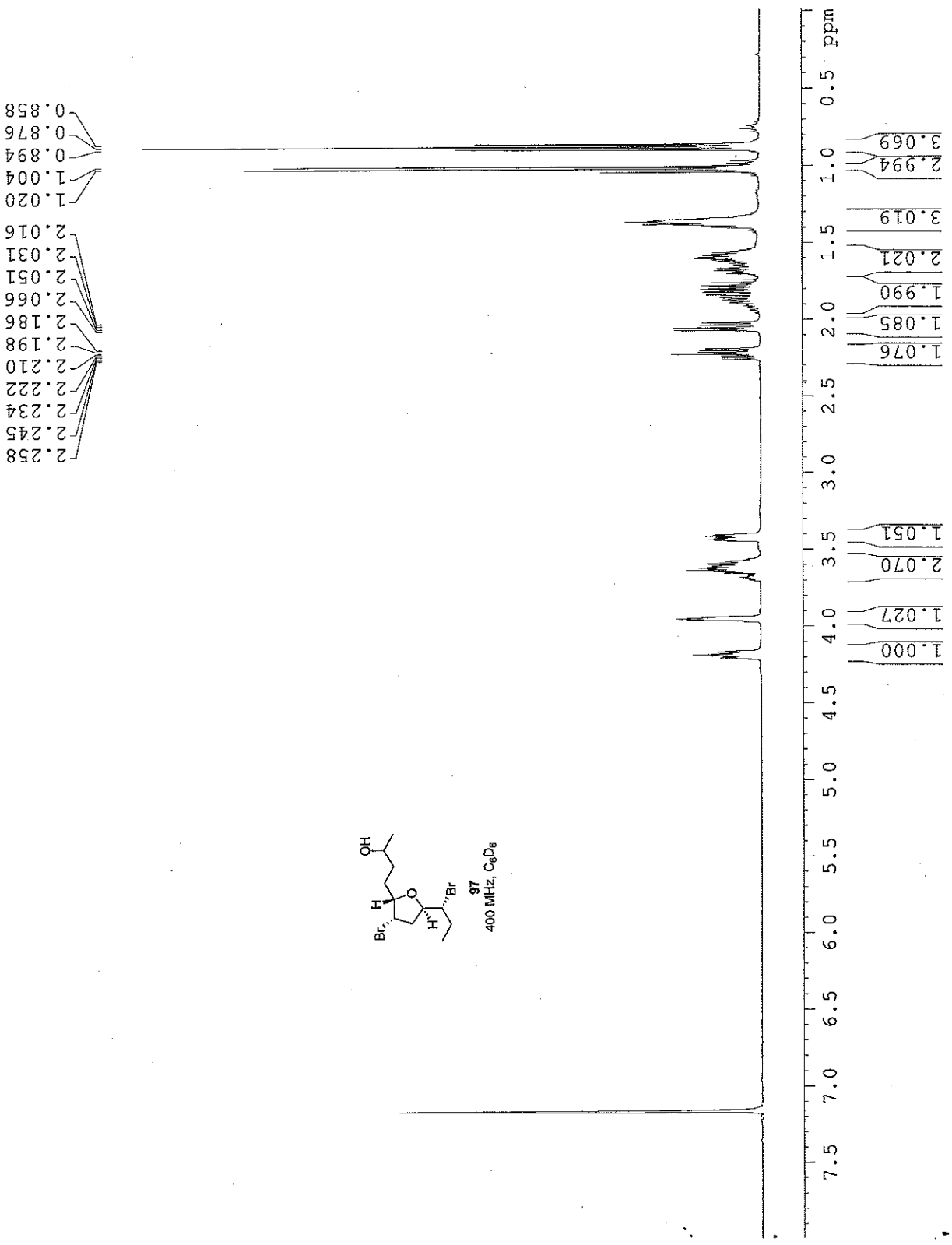

95, 2.5:1 dr
400 MHz, CDCl3
Br
H
O
ppm
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
1.000
1.009
1.573
0.574
1.191
2.129
3.619
0.635
1.475
1.648
0.958
2.359
2.964

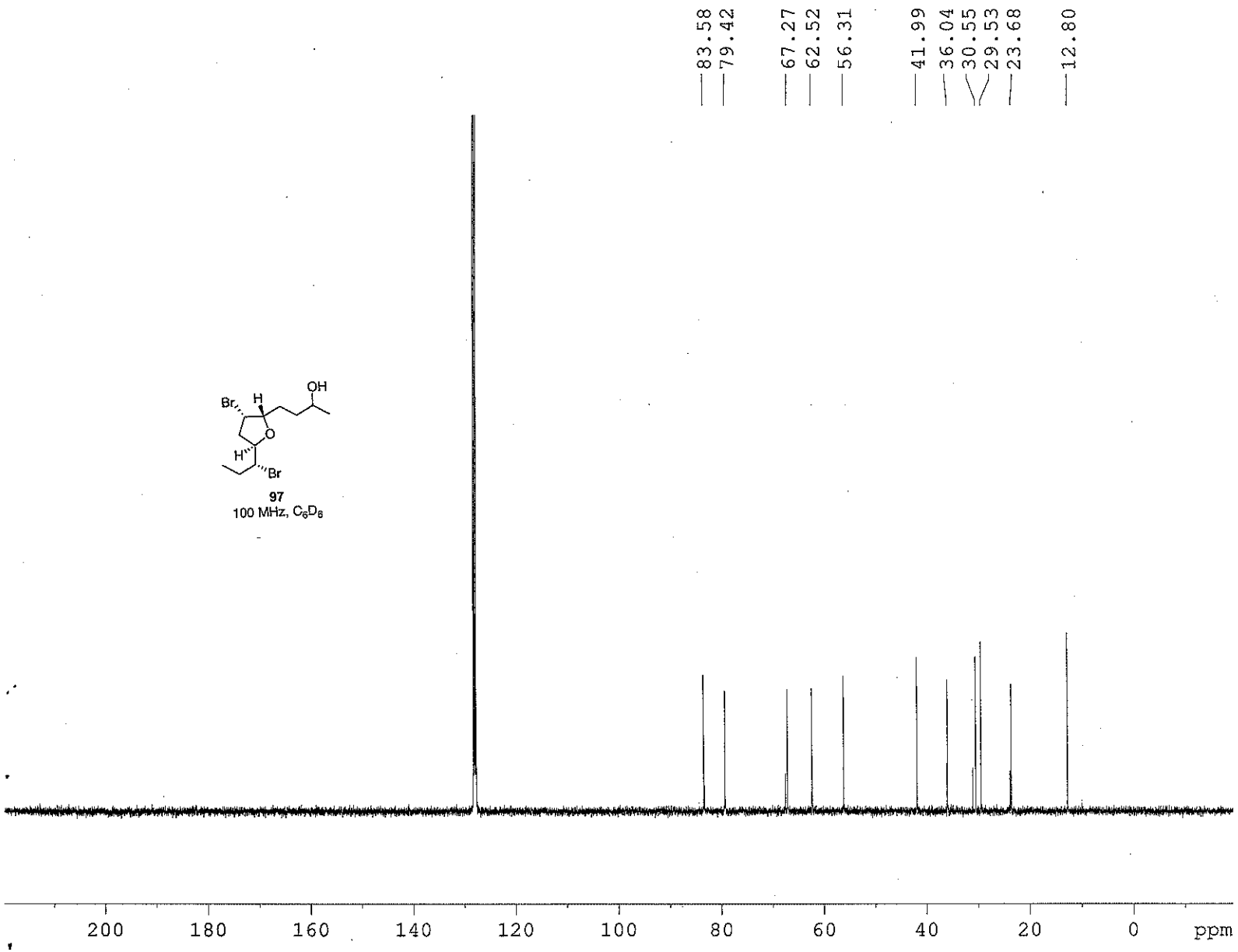

95
400 MHz, C_6D_6
Br
H
O
0.865
0.884
0.903
1.071
1.086
1.952
1.969
1.987
2.006
2.024
2.693
2.710
2.727
3.748
3.756
3.765
3.774
3.783
3.791
3.907
3.916
3.926
3.934
3.943
3.952
1.971
1.000
1.031
1.038
1.994
1.995
3.048
4.027
3.013
ppm
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

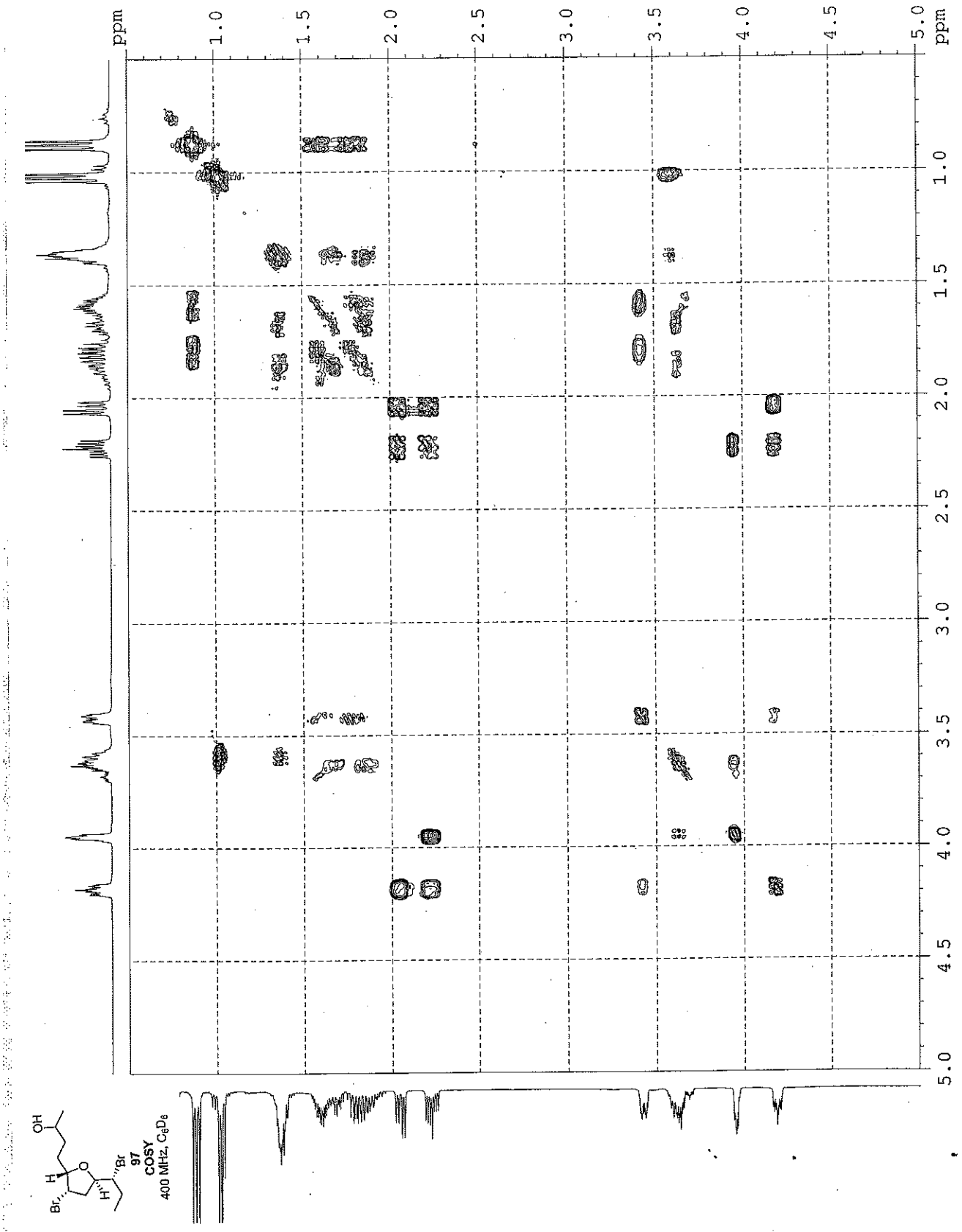

14.04
20.78
21.12
30.30
32.97
34.14
59.52
76.40
80.48
76.400
77 ppm
125.17
134.42
Br
H
O
95
100 MHz, CDCl3
ppm
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210

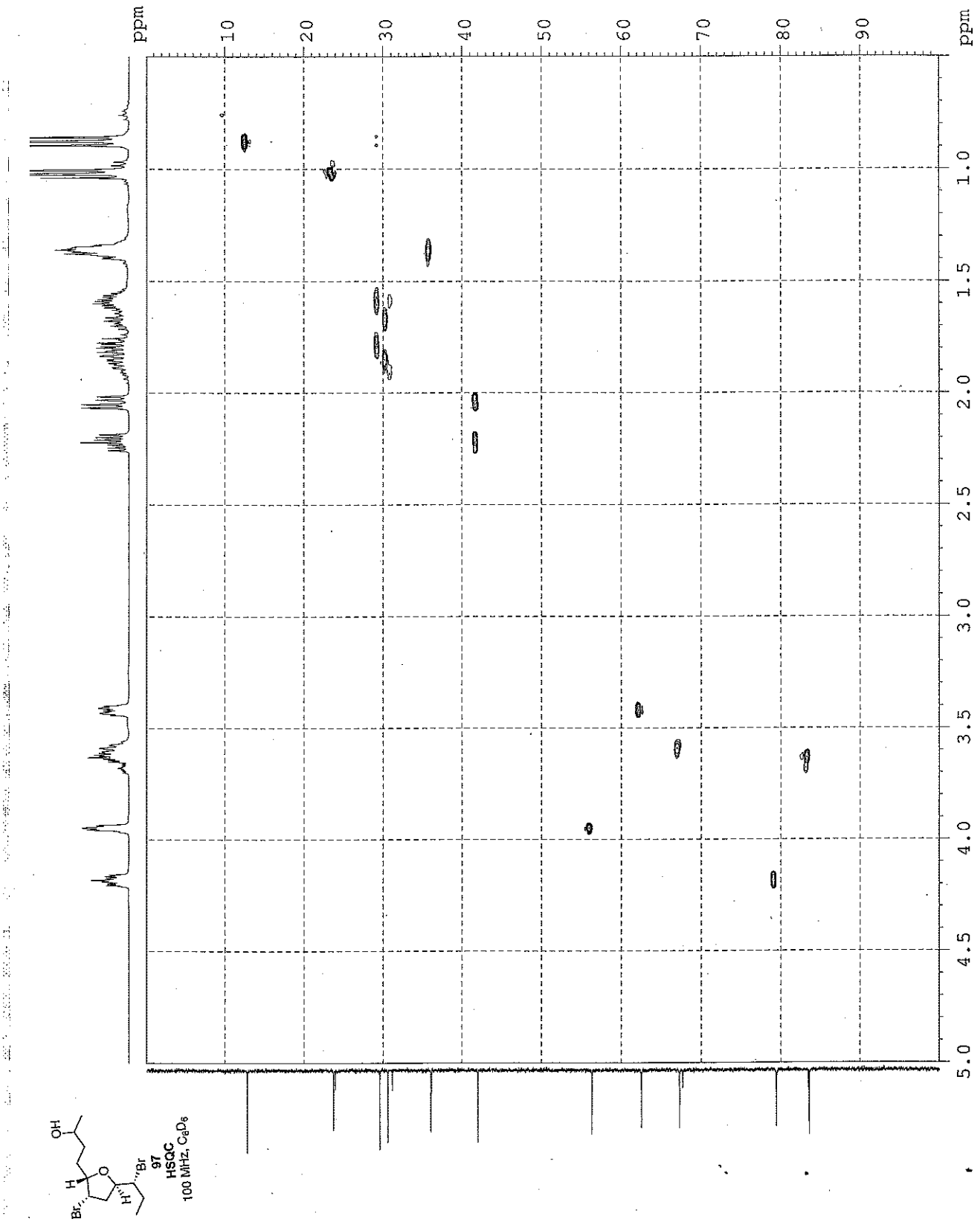

ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
Br
H
O
95
COSY
400 MHz, C6D6

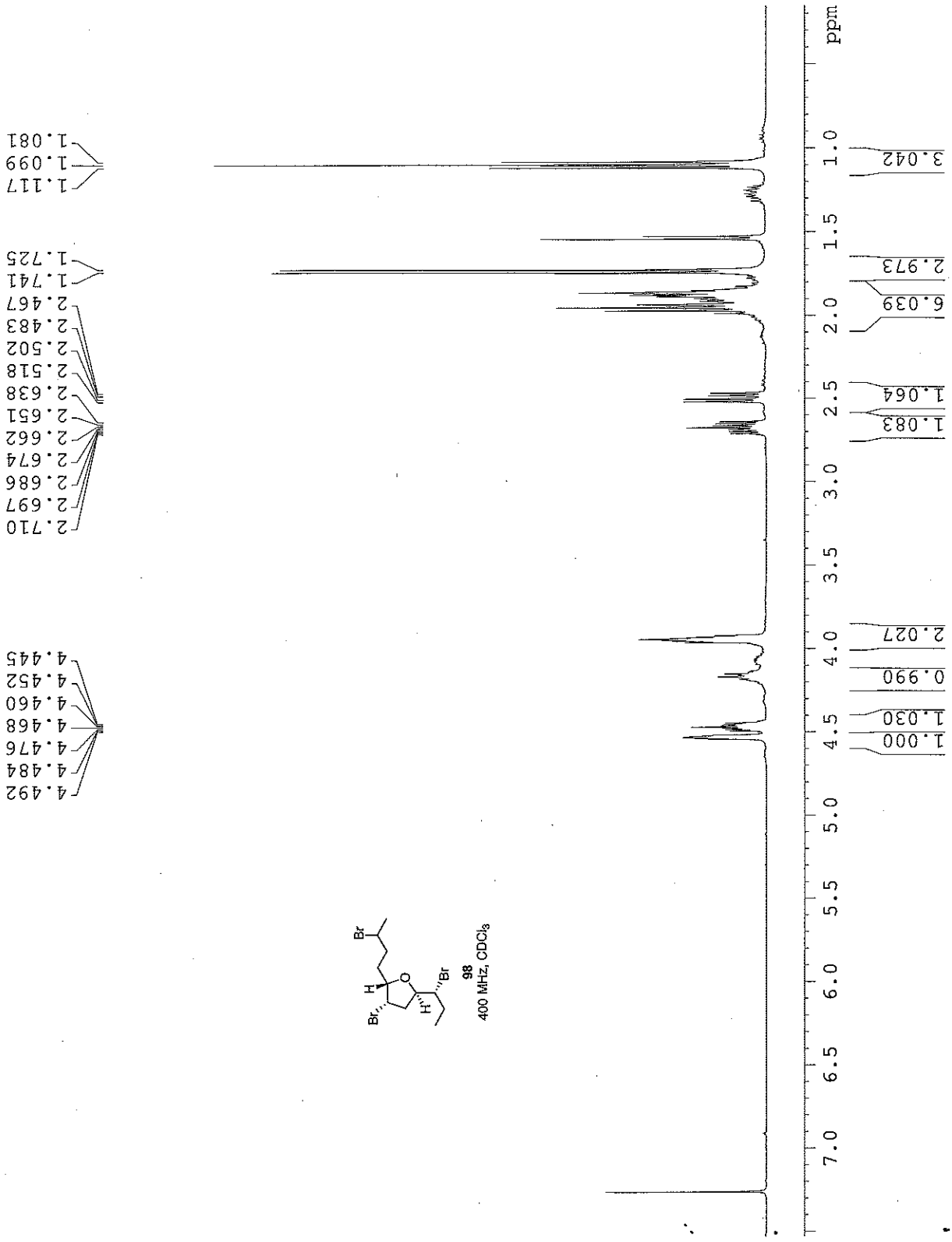

ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
Br
H
O
95
NOESY
500 MHz, C6D6

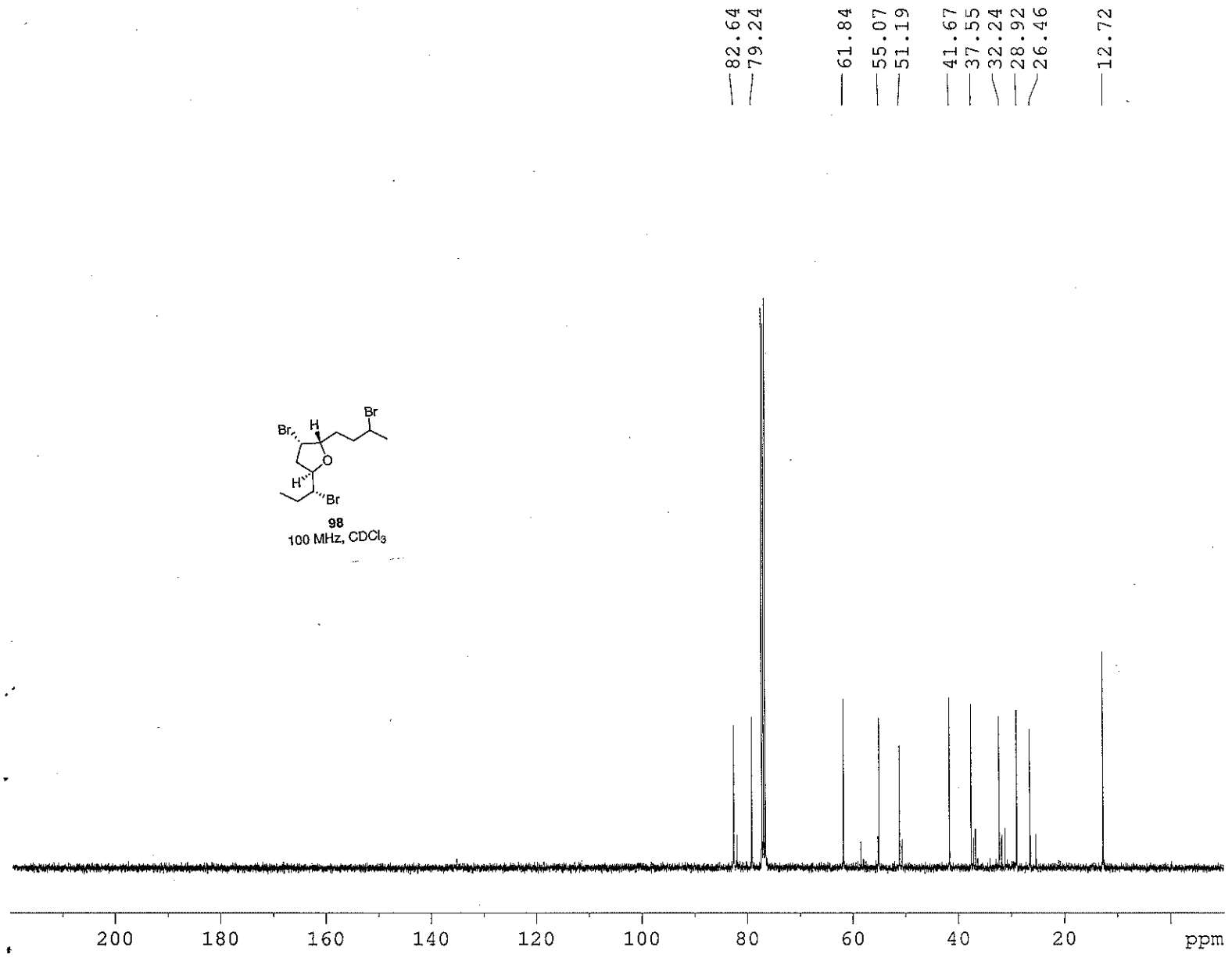

97
400 MHz, C6D6
ppm
0.858
0.876
0.894
1.004
1.020
2.016
2.031
2.051
2.066
2.186
2.198
2.210
2.222
2.234
2.245
2.258
3.069
2.994
3.019
2.021
1.990
1.085
1.076
1.051
2.070
1.027
1.000


83.58
79.42
67.27
62.52
56.31
41.99
36.04
30.55
29.53
23.68
12.80
Br
H
OH
O
H
Br
97
100 MHz, C6D6
200
180
160
140
120
100
80
60
40
20
0
ppm

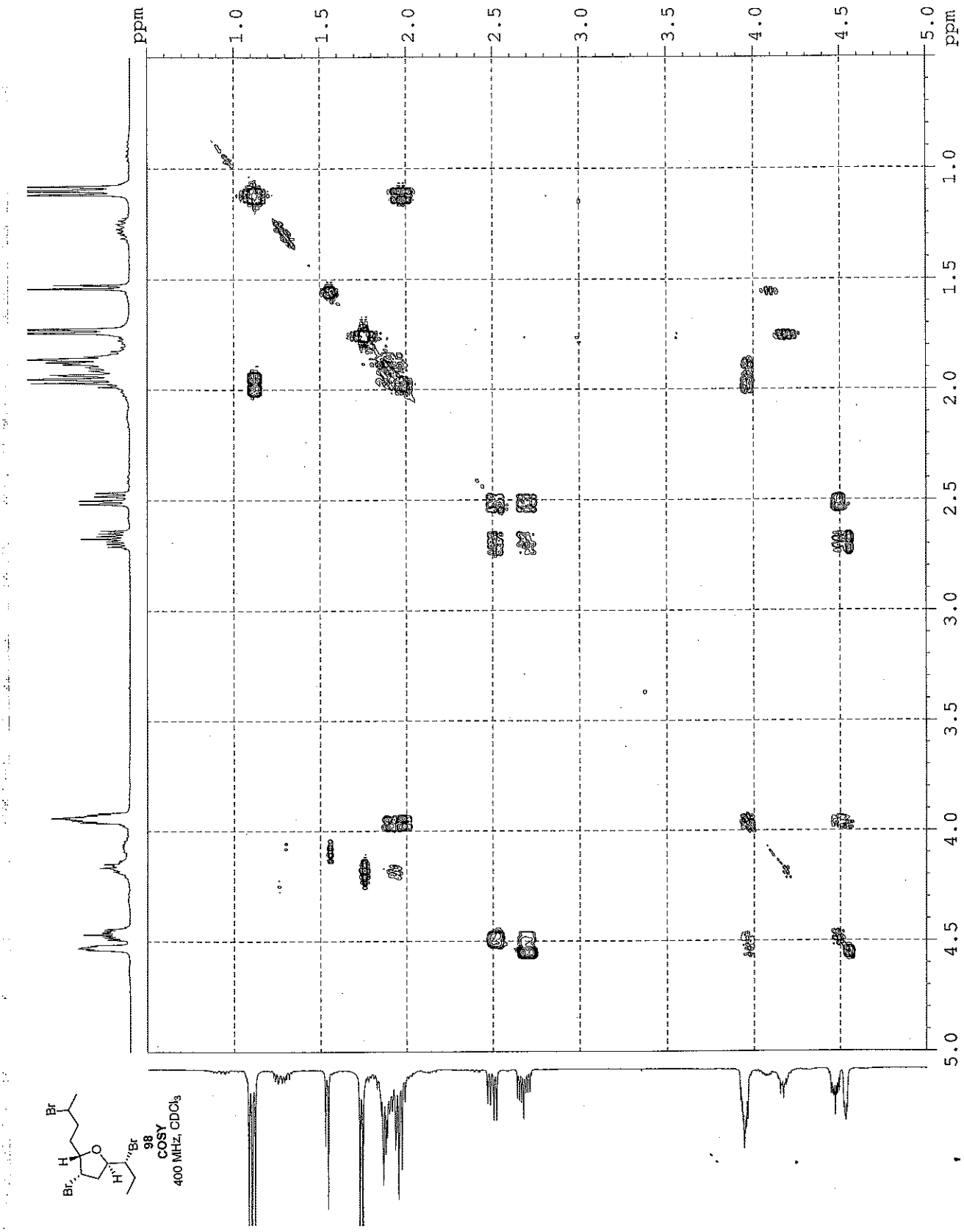

ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
OH
H
Br
O
H
Br
97
COSY
400 MHz, C6D6

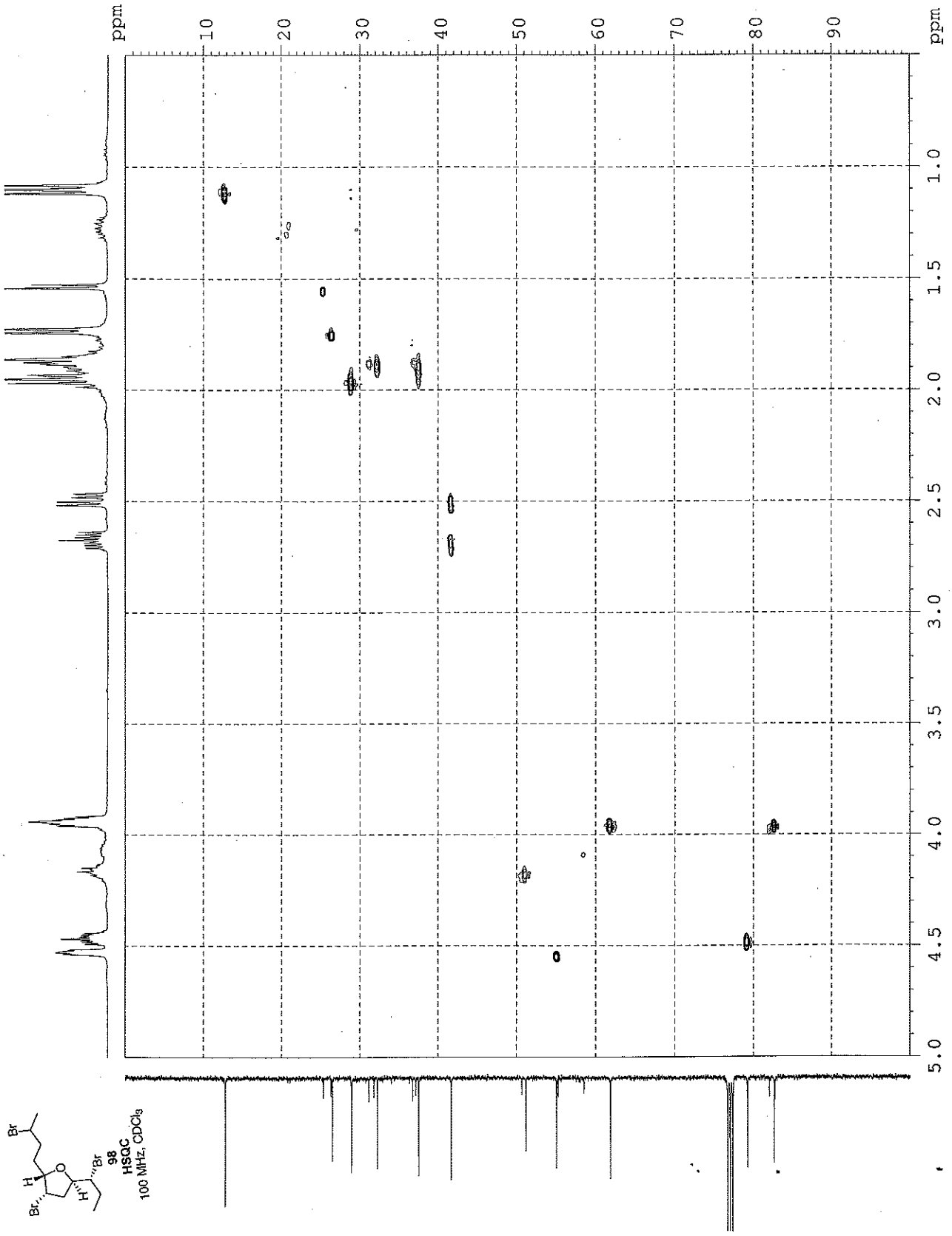

ppm
10
20
30
40
50
60
70
80
90
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
OH
H
Br
O
Br
H
97
HSQC
100 MHz, C6D6


98
400 MHz, $CDCl_3$
ppm
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
1.000
1.030
0.990
2.027
1.083
1.064
6.039
2.973
3.042
4.492
4.484
4.476
4.468
4.460
4.452
4.445
2.710
2.697
2.686
2.674
2.662
2.651
2.638
2.518
2.502
2.483
2.467
1.741
1.725
1.117
1.099
1.081



98
100 MHz, $CDCl_3$


ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
Br
H
O
Br
H
Br
98
COSY
400 MHz, CDCl3


ppm
10
20
30
40
50
60
70
80
90
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
Br
H
O
Br
H
Br
98
HSQC
100 MHz, CDCl3