FORMAL TOTAL SYNTHESIS OF PSEUDOPTEROXAZOLE. PROGRESS TOWARD TOTAL SYNTHESIS OF HAMIGERAN B.

A Dissertation

presented to

the Faculty of the Graduate School

at the University of Missouri-Columbia

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

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by

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JULY 2011

The undersigned, appointed by the dean of the Graduate School, have examined the dissertation entitled

FORMAL SYNTHESIS OF PSEUDOPTEROXAZOLE.
PROGRESS TOWARD TOTAL SYNTHESIS OF HAMIGERAN B

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a candidate for the degree of doctor of philosophy,

and hereby certify that, in their opinion, it is worthy of acceptance.

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Professor Paul R. Sharp

Professor Peter A. Tipton

Dedicated to my daughter Caroline, my wife Jing and my parents.

ACKNOWLEDGEMENTS

I would like to thank my supervisor, Professor Michael Harmata, for his inspiration and pedagogics. My research and dissertation could not be done without his encouragement and strong support. I also would like to thank all of my committee members: Professor Susan Lever, Professor Timothy Glass, Professor Paul Sharp and Professor Peter Tipton, for their advice and comments. Thanks Carissa and Eric for detailed proofreading of my first craft. Thanks Jing for scanning NMR, IR, etc.

I would like to acknowledge Dr. Wei Wycoff, for teaching and helping me on the NMR techniques and Dr. Charles Barnes for his X-ray crystallography support. Thanks Dr. Nathan for mass spectrum assistance. Thanks all of chemistry department staff, especially, Jerry Brightwell for his assistance and great patience.

Special thanks to all of the Harmata group members, past and present. When I was washing the filtration funnel, the memory of Amy teaching me how to press the acetone through the funnel is still so vivid and fresh; when I was using the high vacuum pump, I still recalled Gayatri training me how to make sure the sample is being dried completely by weighing the flask repeatedly. No matter how trivial the effort is for you to help others, your help is so memorable and grateful for people who need it. Thanks Carissa and Eric for their thorough proofreading of the first manuscript.

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LIST OF ABBREVIATIONS

Ac: acetyl

ACN: acetonitrile

Ar: aryl (substituted aromatic ring)

BINAP: 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

Boc: t-butoxycarbonyl

Bn: benzyl

dba: dibenzylideneacetone

DCM: dichloromethane

DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DIBAL: diisobutylaluminum hydride

DMAP: N,N-4-dimethylaminopyridine

DME: 1,2-dimethoxyethane

DMF: N,N-dimethylformamide

DMSO: dimethylsulfoxide

dppf: 1,1'-bis(diphenylphosphino)ferrocene

DBU: 1,8-diazabicyclo-[5.4.0]undec-7-ene

DIPEA: (Hünig's base) diisopropylethyl aimine

ee: enantiomeric excess

EWG: electron-withdrawing group

IBX: o-iodoxybenzoic acid

KHMDS: potassium bis(trimethylsilyl)amide

IR: infrared spectroscopy

LAH: lithium aluminum hydride

LDA: lithium diisopropylamide

LiHMDS: lithium bis(trimethylsilyl)amide

m-CPBA: meta chloroperbenzoic acid

MOM: methoxymethyl

Ms: mesyl (methanesulfonyl)

MS: molecular sieves

NBS: N-bromosuccinimide

NCS: N-chlorosuccinimide

NMO: N-methylmorpholine oxide

NMR: nuclear magnetic resonance

PCC: pyridinium chlorochromate

PDC: pyridinium dichromate

Ph: phenyl

Py: pyridine

PMHS: polymethylhydrosiloxane

p-TsOH: p-tolyl sulfonic acid

TEA: triethylamine

TBAF: tetra-n-butylammonium fluoride

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ABSTRACT

In the first chapter, a formal total synthesis of pseudopteroxazole is presented, highlightening an *E*-selective Horner-Emmons reaction, a Buchwald-Hartwig coupling, and a diastereoselective intramolecular Michael addition.

In the second chapter, the effort toward synthesizing anti-viral natural product hamigeran B is summarized. Several routes to the core structure were shown separately, including those unexpected discoveries when pursuing those routes. Tius-Nazarov cyclization was first applied in synthesizing natural product; an efficient palladium-catalyzed oxidative intramolecular carbocyclization was realized on an α-hydroxy enone for the first time; an interrupted Nazarov cyclization of a hydrolysis intermediate of dithiane was achieved.

CHAPTER ONE

FORMAL TOTAL SYNTHESIS OF PSEUDOPTEROXAZOLE

1.1 Introduction

It has been well recognized that the synthesis of natural products has played a significant role in the development of organic chemistry and chemistry as a whole in the past century. The richness of natural products available from terrestrial plants and water-born plants, and the metabolites of microorganisms provide practically unlimited structures for organic synthetic chemists to work on. By striving to synthesize natural products, numerous new reagents, new methodologies, new strategies, and even new concepts are developed, enriching the textbook of organic chemistry. Apart from the applications of total synthesis of natural products to the discovery of medicines, the pure beauty of designing the strategy, the exquisiteness of manipulating materials at the molecular level, and the beauty of structural transformations are more than enough to attract numerous people to devote years of the best time of their lives to this field. Becoming a true synthetic organic chemist is also demanding: one should be, at first, a skilled technician, good at hands-on bench work, always driven by challenges; he should be an artist with a heart for beauty; also, he should be a scientist who puts integrity above everything, practices logic, and discover the truth.

As the knowledge about organic synthesis exploded during the last century, new concepts, such as Corey's retrosynthetic analysis,[1] the Woodward-Hoffmann rules,[2] and Baldwin's rules were formulated[3]; challenging natural products, such as taxol, strychnine, vitamin B_{12}, and brevetoxin B were synthesized; bioactive small molecules were

discovered and developed into drugs that improved the quality of human health. With the introduction of modern combinatorial chemistry and high-throughput screening approaches to drug lead discovery, the importance of natural product guided approach for drug discovery has never be undermined.[4] What needs to be resolved at the synthesis stage is the efficiency of the syntheses.

In the first part of this chapter, the background of a natural product synthesis project will be introduced, including the source of the natural product, its natural relatives, and their bioactivities; the total syntheses of this natural product to date; and a proposed chemical relationship of this family of natural products to be scrutinized.

The second part of this chapter will introduce the synthetic plan and the detailed synthetic efforts leading to the formal total synthesis of pseudopteroxazole. The key reactions are: a completely *E*-selective Horner-Wordsworth-Emmons (HWE) reaction, a Buchwald-Hartwig coupling, and a stereoselective intramolecular Michael addition.

1.1.1 Marine Natural Products from *Pseudopterogorgia Elisabethae*

To natural product chemists, finding a good source for isolating novel natural products is obviously a very important factor for their productivity. To that end, the gorgonian coral (sea whip) *Pseudopterogorgia elisabethae* did not disappoint them.[5] In the genus of *Pseudopterogorgia* in the animal kingdom, *Pseudopterogorgia elisabethae* is typically found at a depth of 40 to 70 meters underwater. The animal samples used by the Rodriguez group to isolate pseudopteroxazole were collected in the eastern Caribbean sea.[6]

Figure 1

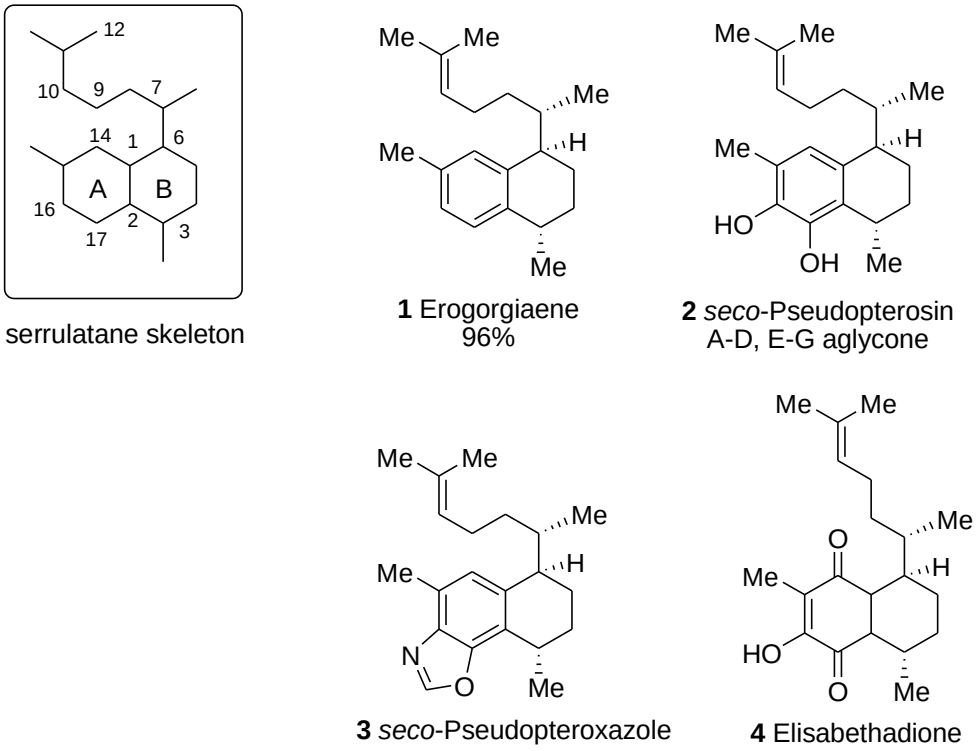
http://gorgonien.npage.de/pseudopterogorgia_elisabethae_neu_70837353.html

1.1.2 Selected Serrulatane Diterpenoids From *Pseudopterogorgia Elisabethae*

There are many novel carbon skeletons discovered from the natural products isolated from *Pseudopterogorgia elisabethae*. An excellent review by Heckrodt and Mulzer covered this topic more comprehensively.[5] In the following, five skeletons are shown, with the representatives for each skeleton and bioactivities of those natural products.

First, let us look at the serrulatane skeleton (Shown in Figure 2). Nine natural products possessing serrulatane carbon skeleton were discovered, four of which are shown in Figure 2. These differ in the substitution on the aromatic ring, or as for elisabethadione, the aromatic ring is oxidized. Two of the other natural products with the serrulatane skeleton are also of higher oxidation state, indicating the presence of an oxidizing environment producing these metabolites. Erogorgiaene showed 96% growth inhibition of *Mycobacterium tuberculosis, seco*-pseudoptersosin glycosides showed better anti-inflammatory and analgesic activity than existing drugs in animal models.[7]

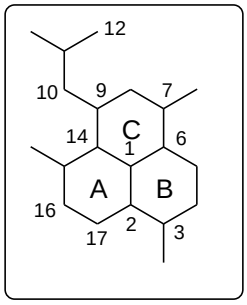
Figure 2



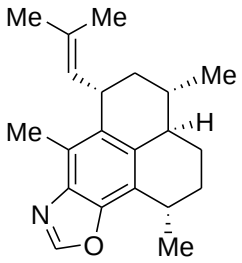
Nine natural products isolated from *Pseudopteroxazole elisabethae* share the amphilectane skeleton (Figure 3). Pseudopteroxazole falls into this class of natural

products. It has shown strong inhibition effects toward tuberculosis bacteria (TB). (97% inhibition at 12.5 μg/ml)[6] It is worth noting that some of them have different stereochemistry, such as pseudopterosin A-F aglycone, pseudopterosin K, L aglycone. The diversity of the stereochemistry is associated with the different collection sites of the *Pseudopterogorgia elisabethae* sample. The sample from which pseudopterosins G-J were isolated was collected near Bermuda Island; samples containing pseudopterosins M-O were collected from Florida Keys; pseudopterosins K and L were obtained from Bahamian samples.[8]

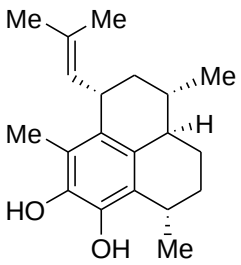
Figure 3



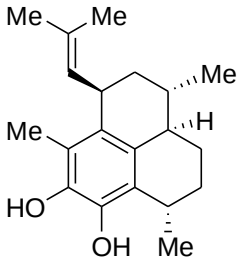
amphilectane skeleton



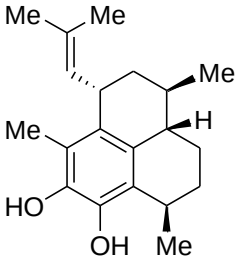
5 Pseudopteroxazole
97%



6 Pseudopterosin G-J,
M-O aglycone



7 Pseudopterosin
A-F aglycone

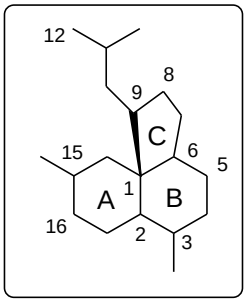


8 Pseudopterosin
K, L aglycone

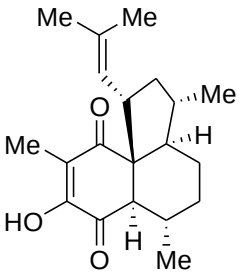
Elisabethin A and elisabethin D share a novel tricyclic core structure called elisabethin skeleton. (Figure 4) While the relative stereochemistry was unambiguously

determined by a single-crystal X-ray diffraction experiment, the absolute stereochemistry has not yet been determined. Though it was once thought to have been resolved by the total synthesis of elisabethin A,[9] it was later found that the total synthesis product was not actually the natural product, but rather the epimer of elisabethin A.[10] We expect the total synthesis of elisabethin A to come in the future since organic synthetic chemists are always ready to embark upon the formidable challenges.

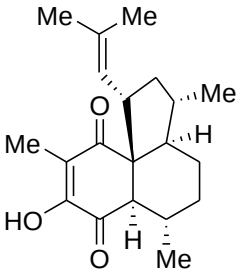
Figure 4



Elisabethin skeleton



9 Elisabethin A

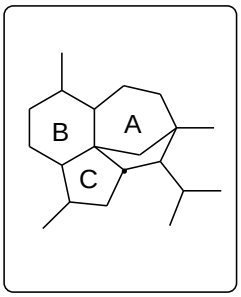


10 Elisabethin D

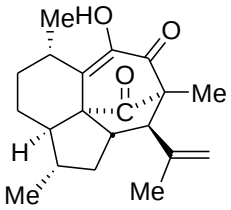
Another novel diterpene skeleton is the tetracyclic elisapterane skeleton (Figure 5). Through oxidation and cyclization, a variety of secondary metabolites containing elisapterane skeleton were also produced. Elisapterosin B exhibited anti-TB activity (79% inhibition). Elisapterosin A showed anticancer activity *in vitro*.[11]

The colombiane skeleton is represented in colombiasin A (Shown in figure 6).

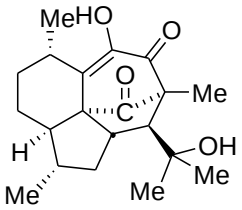
Figure 5



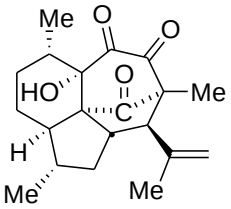
Elisapterane skeleton



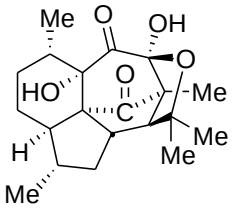
11 Elisapterosin B



12 Elisapterosin C

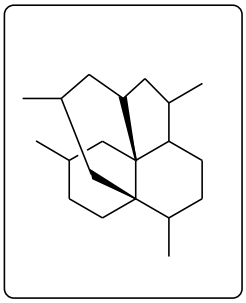


13 Elisapterosin D

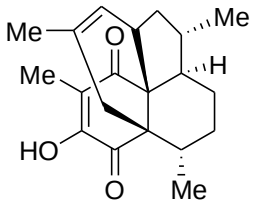


14 Elisapterosin A

Figure 6



Colombiane skeleton



15 Colombiasin A

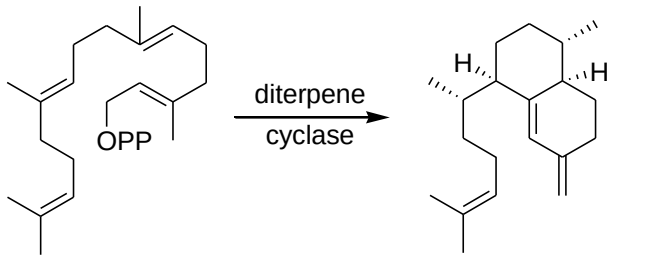
1.1.3 Biosynthesis of the Common Intermediate Elisabethatriene.

The biosynthesis of this class of natural products is believed to start with geranylgeranyl phosphate, and through a serrulatane intermediate, producing a diversity of carbon skeletons and stereochemical complexities. While the sea creature *Pseudopterogorgia elisabethae* has been using this kind of diversity-oriented synthesis to generate metabolites for quite a long time with its enzymes, humans are still trying hard

to mimic this feat in the hope to discover more bioactive molecules that could benefit people.[12]

As shown in Scheme 1, the biosynthesis of pseudopterosins was determined to start with geranylgeranyl pyrophosphate.[13] Elisabethatriene was found to be a product of a diterpene cyclase, based on radiolabelling experiments (Scheme 1).

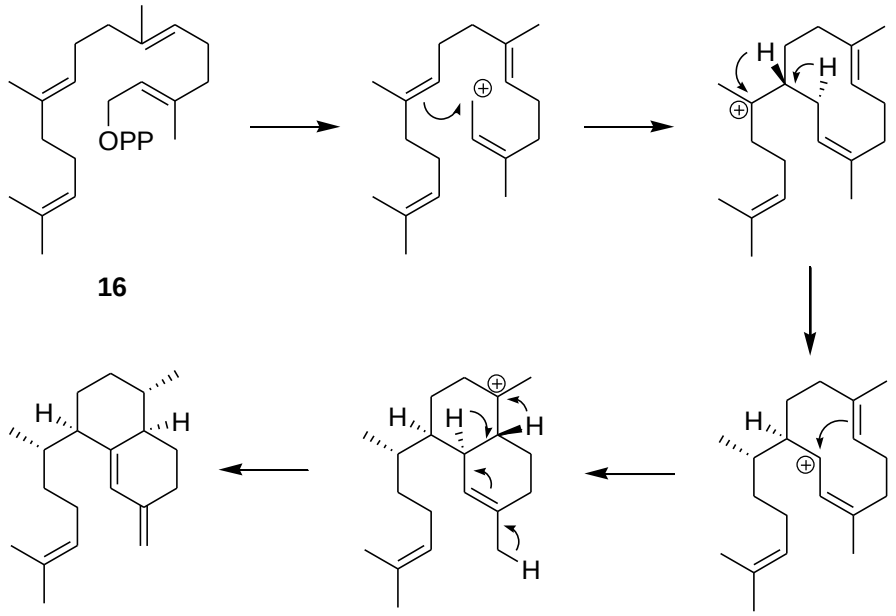
Scheme 1



16 **17** Elisabethatriene

The mechanism for the generation of elisabethatriene from geranylgeranyl pyrophosphate was proposed as shown in Scheme 2. Ionization of pyrophosphate yields an allylic cation, which could be trapped by an internal double bond. A series of hydride shifts generate another allylic cation at the same position, which can then react with another double bond to form a tertiary carbocation. The elimination of the terminal proton in addition to a couple of hydride shifts affords the elisabethatriene.

Scheme 2

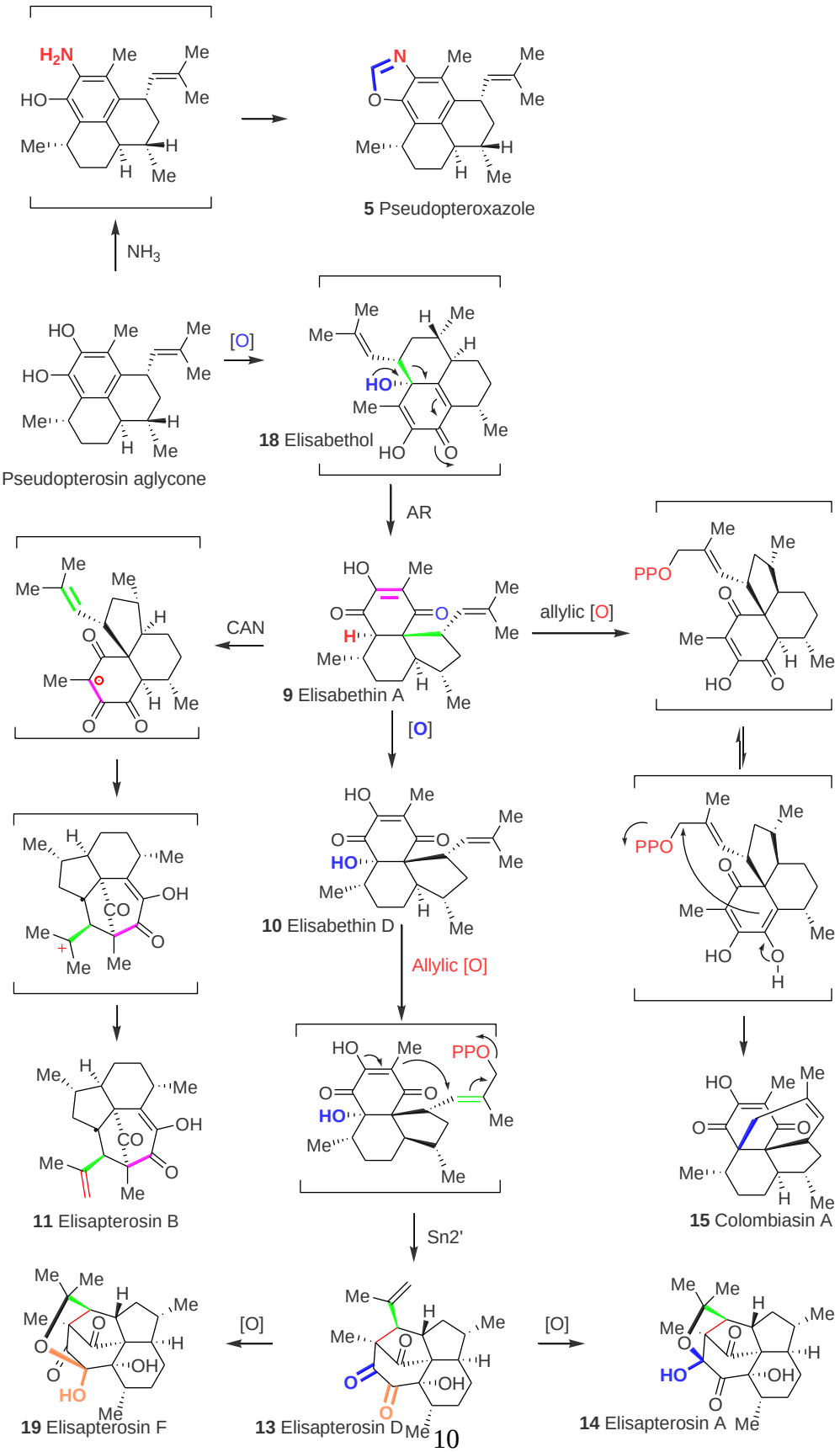


16

17 Elisabethatriene

1.1.4 Proposed Diversity Oriented Synthesis of Serrulatane Diterpenoids

Having discussed the biosynthesis of pseudopterosin diterpenoids, biomimetic syntheses of several of the natural products from this family were proposed as an alternative to what was proposed in Mulzer's review. As shown in scheme 3, pseudopteroxazole **5** could be produced via selective enamine formation and condensation with orthoformate. Oxidation of **6** could lead to elithabethol **18**, which could in turn generate elithabethin A **9**, after an acyloin rearrangement. Further oxidation leads to elithabethin D **10**, which, after allylic oxidation, phosphonation, and C15 allylation, yields elisapterosin D **13**. Hydration of **13** will lead to semiketal elisapterosin A **14** and F **19**. C2 allylation of **9** would generate colombiasin A **15**; CAN oxidation of **9** would lead to elisapterosin B **11**.

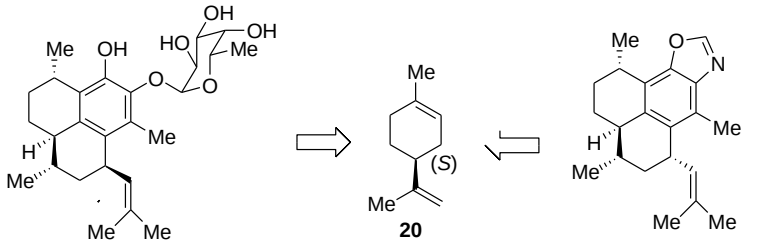

5 Pseudopteroxazole
NH3
[O]
6 Pseudopterosin aglycone
18 Elisabethol
AR
CAN
9 Elisabethin A
allylic [O]
[O]
10 Elisabethin D
Allylic [O]
11 Elisapterosin B
Sn2'
15 Colombiasin A
[O]
[O]
19 Elisapterosin F
13 Elisapterosin D
14 Elisapterosin A

Scheme 3

1.1.5 Total Synthesis of *Pseudopteroxazole* by the Corey Group

As early as 2001, Johnson and Corey published a total synthesis of the proposed structure of pseudopteroxazole.[14] In 2003, the Corey group reported the first total synthesis of pseudopteroxazole together with three diastereomers.[15] It took 19 steps to get the natural product in 7% overall yield from an abundant natural product, (*S*)-(-)-limonene **20** (Figure 7). This total synthesis showcased the use of inexpensive chiral natural products as chiral sources to set up the stereocenters in the synthesis of natural products. An earlier application of the enantiopure (*S*)-(-)-limonene in total synthesis came from the same laboratory in 1998, as evidenced by their paper of the total synthesis of pseudopterosins (Figure 7).[16]

Figure 7



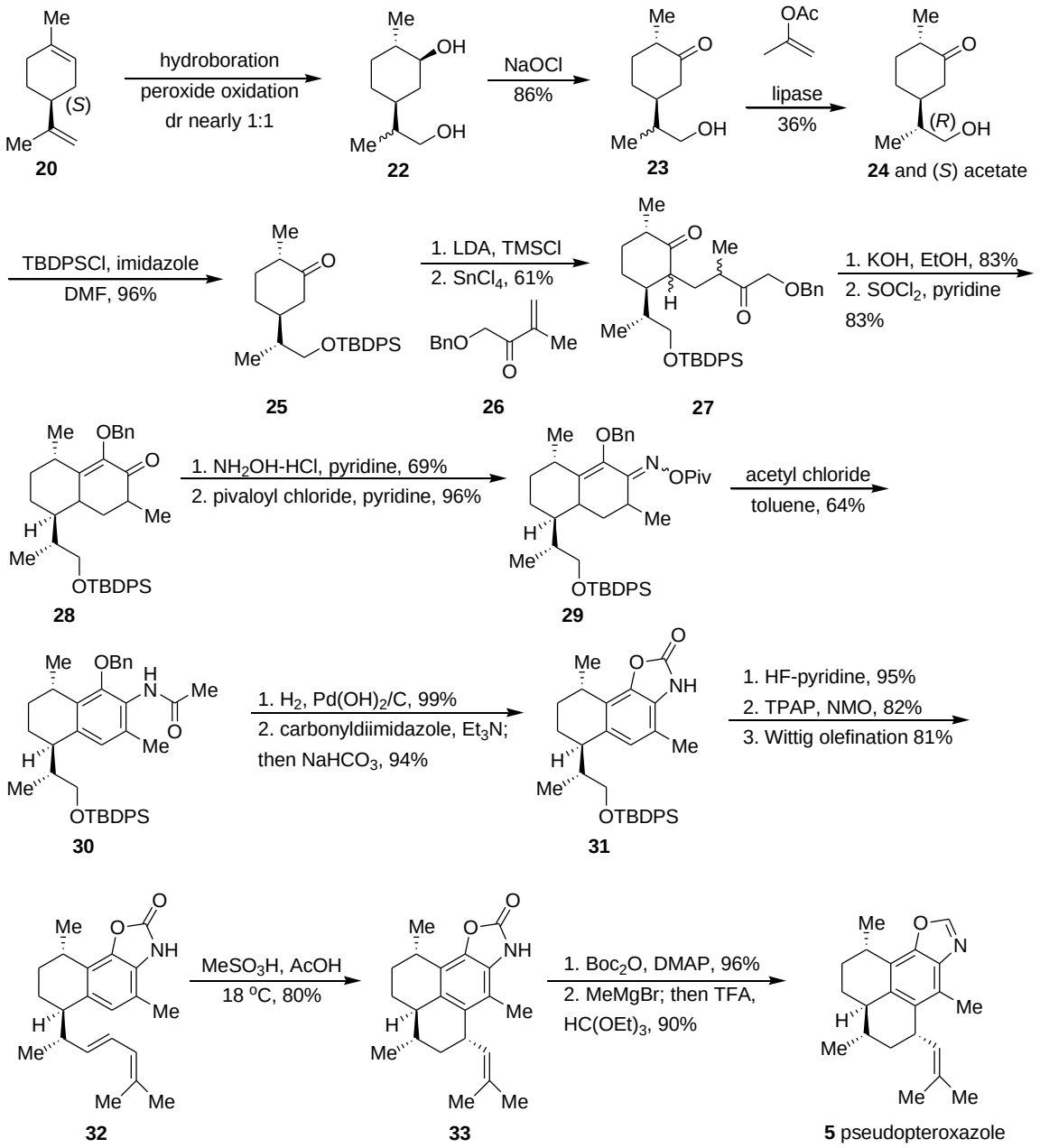
21 pseudopterosin E

20

5 pseudopteroxazole

As is illustrated in Scheme 4, starting from the readily available (*S*)-(-)-limonene **20**, TBDPS-protected (8*R*)-hydroxy ketone **25** (8R:8S = 99:1 from HPLC analysis of their corresponding derivatives) was obtained through hydroboration followed by oxidation, selective oxidation of secondary alcohol, diastereoselective acetylation catalyzed by Amano PS lipase, and protection with a *tert*-butyl-diphenylsilyl group. Next,

Scheme 4



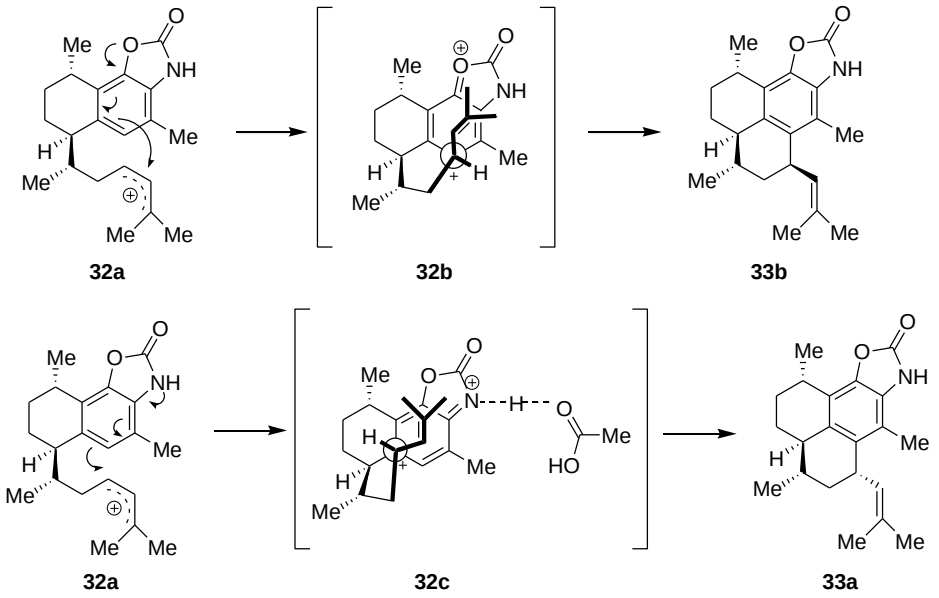
kinetic deprotonation with LDA followed by trapping with TMSCl led to an enol silyl ether, which underwent a Mukaiyama-type Michael addition with enone **26**, giving a 61% yield of **27** as a mixture of diastereomers (about 1:1 ratio). An intramolecular aldol

reaction followed by elimination of the tertiary hydroxyl group led to the net Robinson annulation product **28** in 69% yield. Oxime formation followed by acylation gave the oxime pivalate diastereomers **29**, which were aromatized under modified Wolff-Semmler conditions by heating with a stoichiometric amount of acetyl chloride in toluene in a sealed reaction vessel. Thus, the two diastereomers were converged to one aromatic compound **30**. Deprotection of the benzyl group freed the phenol, which was treated with carbonyldiimidazole to form the cyclic carbamate **31**. After hydrolysis of the carbamate, the TBDPS group was removed with a hydrofluoric acid-pyridine complex. Perruthenate-catalyzed oxidation led to the aldehyde, which reacted under Wittig-Vedejs *E*-selective olefination conditions to produce the diene **32**, setting up the stage for the key cationic cyclization to form **33**.

It is interesting to note that, in this catalytic cyclization, changing the solvent from acetic acid to dichloromethane completely reversed the diastereoselectivity. In order to explain this phenomenon, they proposed two transition states for the cationic cyclization (Scheme 5). First, the protonation of the conjugated diene **32** gave an allylic cation **32a**. Then, the road diverges. One path leads to a six-membered ring transition state **32b**, affording the undesired diastereomer **33b**; the other is through a five-membered ring transition state **32c**, leading to the other diastereomer **33a**. Presumably, when dichloromethane is used as the solvent, the oxygen is a better electron donor to the aromatic ring system than the nitrogen in the cyclic carbamate, activating the *para*-position of the aromatic ring (C14), forming the six-membered ring transition state. Rearomatization leads to the diastereomer **33b**. When acetic acid is used as the solvent, it is proposed to serve as a hydrogen bond acceptor, stabilizing the transition state in which

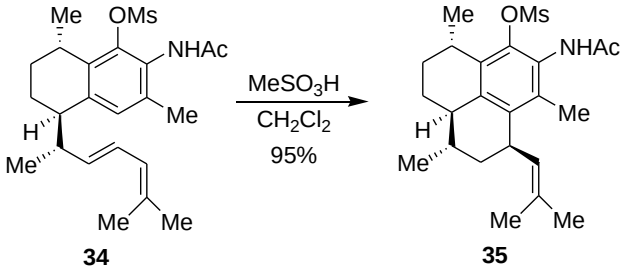
the nitrogen atom is a better electron donor (**32c**). The nitrogen atom activates the *para*-position relative to the nitrogen (C1), leading to the five-member ring transition state **32c**, which after rearomatization affords the other diastereomer **33a**.

Scheme 5



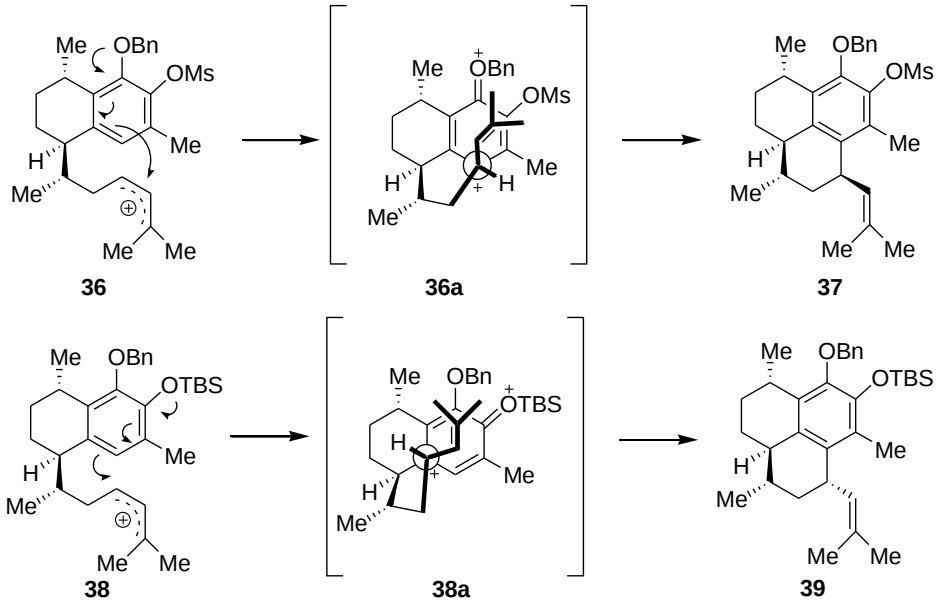
In other experiments with the corresponding mesylate (**34**) or triflate, the diastereomer **35**, generated from the oxygen-activated route was formed in a greater than 20:1 ratio, in either dichloromethane or acetic acid (Scheme 6). Keeping in mind that the methanesulfonyl group, being strongly electron withdrawing, should attenuate the electron donating ability of the oxygen atom, the acylated nitrogen atom failed in competing with the oxygen in activating the aromatic ring. Combined with the result of the cyclic carbamate **32**, it proves that the planarity of the cyclic carbamate enables the nitrogen's lone electron pair to be perpendicular with the aromatic ring, which is crucial for its ability to activate the aromatic ring.

Scheme 6



Having discussed this cationic cyclization, another set of examples should not be overlooked. In the paper about the total synthesis of pseudopterosins from the Corey group, the diastereoselectivity was switched, by switching the mesyl group to the TBS group (Scheme 7). Considering the different electronic properties of the two functional groups, the mesyl group being strongly electron withdrawing while TBS group being electron donating, the stereoselectivity can be rationalized based on different oxygen atoms serving as the predominant activating group. [17]

Scheme 7



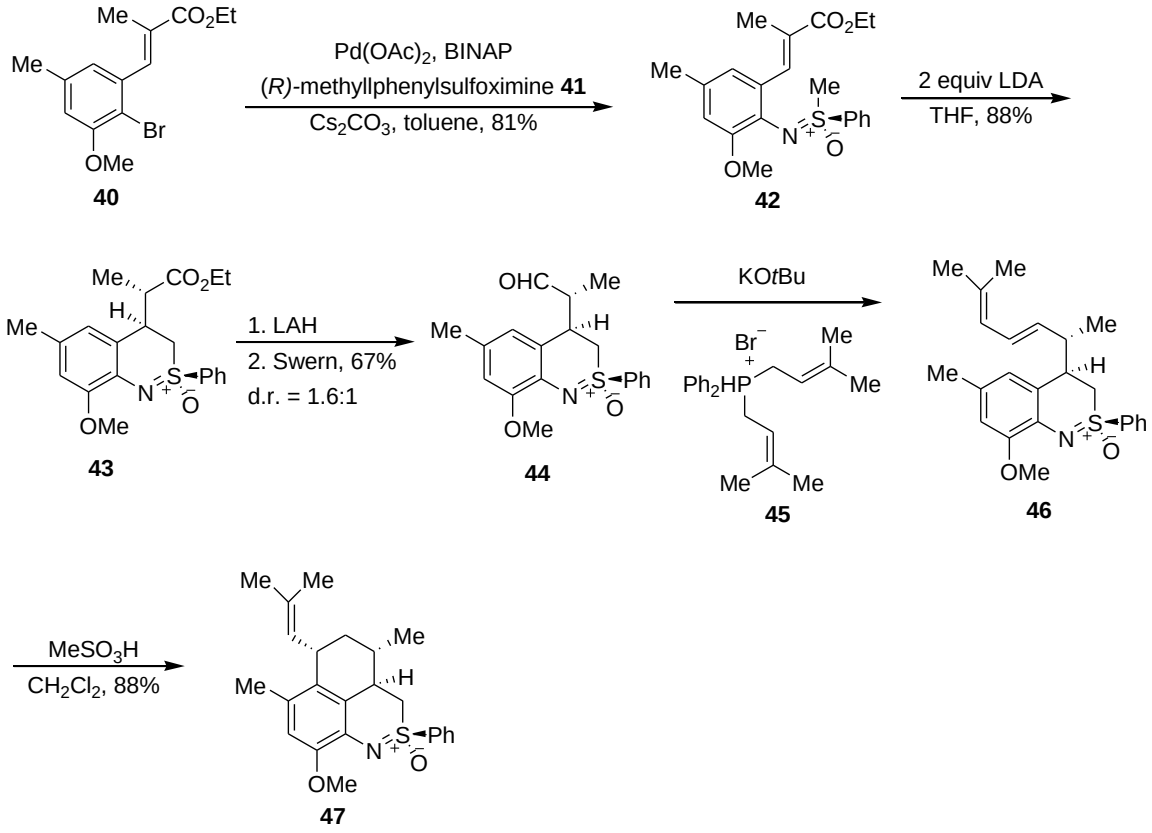
After this biomimetic cyclization, acylation of the free NH with Boc_2O, cleavage of the cyclic carbamate, and treatment with trifluoroacetic acid and triethyl orthoformate gave the desired natural product pseudopteroxazole **5**, confirming the absolute structure of this natural product at the same time.

1.1.6 Total Synthesis of Pseudopteroxazole by the Harmata Group

The second total synthesis of pseudopteroxazole came from our group in a couple of communications reported in 2004 and 2005.[18] In the first communication, Harmata and Hong applied the methodology they developed and published in 2003,[19] the intramolecular Michael addition of sulfoximine carbanions to α,β-unsaturated esters, to the synthesis of an intermediate for the total synthesis of pseudopteroxazole, which is essentially a benzothiazine analog of pseudopteroxazole. This endeavor proved the fidelity of the methodology in setting up the benzylic stereocenters diastereoselectively.

In this world of organometallic catalysis, organocatalysis, and enzymatic catalysis, auxiliary-controlled stereoselectivity is overlooked due to its intrinsic lack of step and atom economy. But when it comes to achieving as high stereoselectivity as nature does, (100% d.r. within detection limit) developing this unique chiral sulfoximine auxiliary-controlled intramolecular Michael addition is irresistible. What is more, the stability, the stereoregidity, the hydrophilicity, and being the bioisostere of the ester hydrolysis intermediate render the compounds containing this functional group more added values, with respect to the discovery of new medicines at least.[20]

Scheme 8

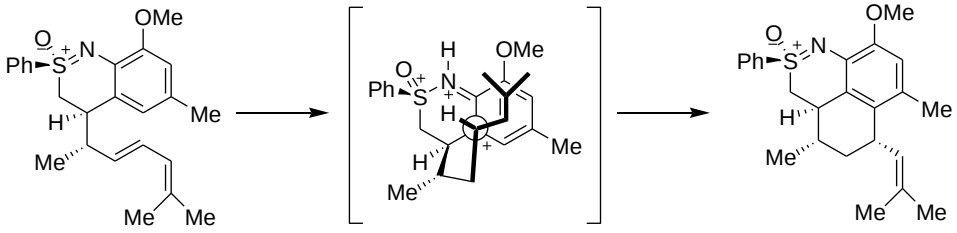


As shown in Scheme 8, the synthesis began with a known substituted *ortho*-bromocinnamate **40**, which can be made from commercially available anisole in five steps. (*R*)-*N*-methyl-*N*-phenylsulfoximine **41** was coupled to the *ortho*-bromocinnamate **40** via a Buchwald-Hartwig coupling reaction. Treatment with two equivalents of lithium diisopropylamide, followed by kinetic protonation, led to the Michael addition product **43** as 10:1 ratio of two diastereomers. Although there could be up to four diastereomeric products produced from this reaction, as there are two new stereogenic centers formed, there were only two diastereomers formed with diastereomeric ratio being ten to one, as determined by ^{1}H-NMR analysis. This application of the intramolecular Michael addition

of a sulfoximine stabilized carbanion to an unsaturated ester not only provided complete stereocontrol over the benzylic position, but also expanded the power of the reaction to the control of the stereogenic center next to the benzylic position. Although the reaction is highly stereoselective, it generated the products favoring the diastereomer with the wrong stereochemistry.

Nevertheless, Harmata and Hong pushed the mixture of products to the end of the total synthesis with great dedication and stamina. Lithium aluminum hydride reduction and Swern oxidation transformed the ethyl ester **43** to the aldehyde **44** in 67% yield. With prolonged reaction time in the presence of base, the mixture of two diastereomers underwent epimerization, giving another mixture of diastereomers favoring the one with the correct stereochemistry as the thermodynamically more stable aldehyde. To make the dienyl branch, a Wittig-Vedejs *E*-selective olefination was applied to this mixture of benzothiazines, generating a 52% yield of the diastereomer **46** with the required stereochemistry and a 33% yield of one with the wrong stereochemistry. These were separated by flash chromatography.

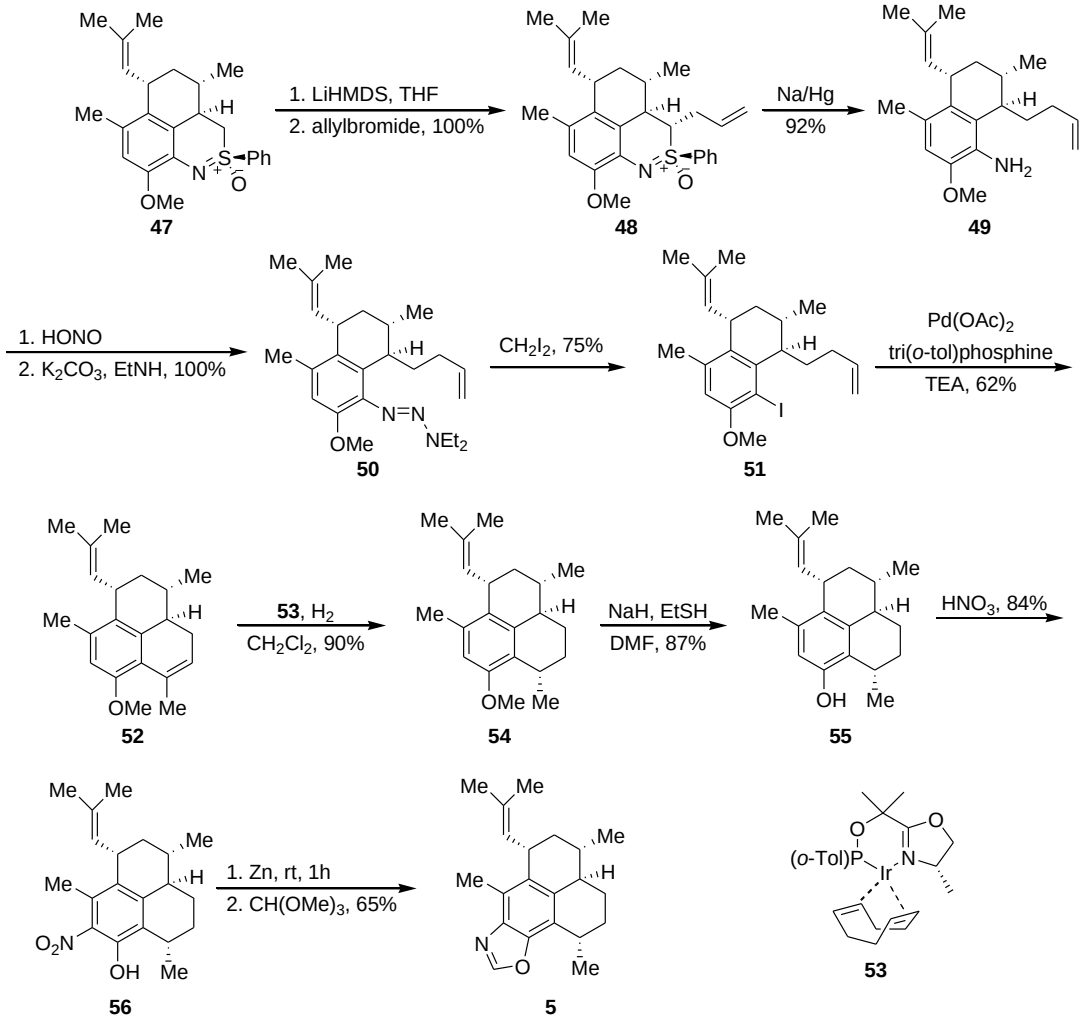
Scheme 9



46 **46a** **47**

The next step was a cationic cyclization, forming the six-membered ring with complete diastereoselectivity (Scheme 9). Assuming the nitrogen is a better electron donor, the cationic cyclization was rationalized by the steric hindrance between the S-phenyl group and the allylic cation through a five-membered ring transition state (**46a**). It was the first report on this type of cationic cyclization of benzothiazine. The diastereoselectivity was completely reversed if the oxygen is a better electron donor and the cationic cyclization processed through a six-membered ring transition state based on Corey's studies (Scheme 7, from **36** to **37**).[21]

Scheme 10



The second report from our group detailed the total synthesis of pseudopteroxazole in nine steps from the tricyclic benzothiazine **47** (Scheme 10). First, the benzothiazine **47** was deprotonated by LiHMDS diastereoselectively, presumably by the direction of the oxygen on the sulfur through lithium cation. Then the carbanion was trapped by allyl bromide, giving a quantitative yield of the allylated product **48** in diastereopure form. Next, sodium amalgam cleaved the sulfur-carbon bond, producing the aniline **49** in 92% yield. The aniline **49** was efficiently transformed to the corresponding iodide **51** through a 1-aryl-3,3-diethyltriazene intermediate **50**. The last ring was formed by an innovative intramolecular Heck coupling. The next step is another highlight of this total synthesis, the regioselective and diastereoselective homogeneous hydrogenation catalyzed by an iridium catalyst **53**. In this case, both the catalyst and the structure of the molecule worked together to enable the high regioselectivity and stereoselectivity of this hydrogenation in a near perfect fashion. Later, it was found that the rigidity of the tricycle is crucial for the selectivity.[22] After deprotection of the methoxy group by *in situ* generated NaSEt in refluxing DMF, nitration yielded the nitro phenol **56**, which was reduced and treated with methyl orthoformate to give the natural product pseudopteroxazole **5**.

1.2 Formal Total Synthesis of Pseudopteroxazole

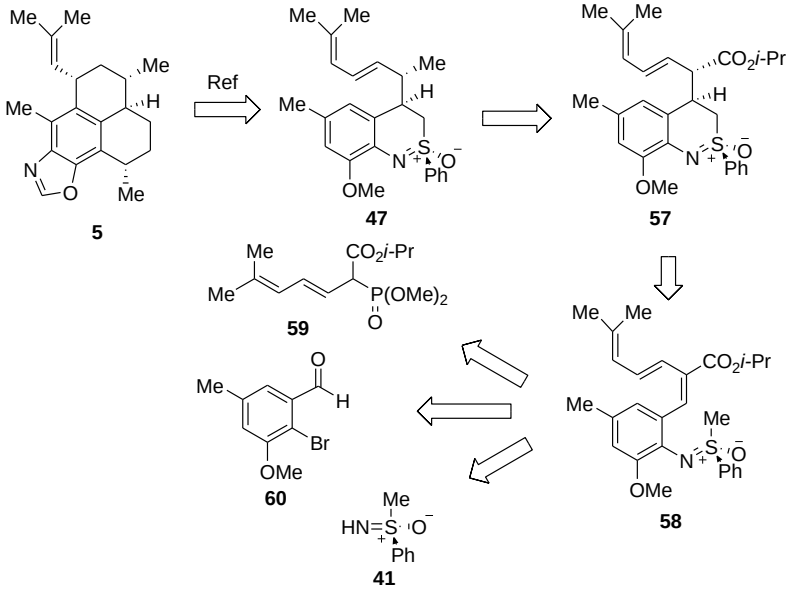
From the review of the first generation of total synthesis of pseudopteroxazole, the innate ability to control stereoselectivity by a sulfoximine as a chiral auxiliary was clearly demonstrated in the intramolecular Michael addition, which set up two of the four stereocenters contained in pseudopteroxazole. The preference for the wrong

diastereomer, however, diminished the usefulness of that synthetic route. Through strategic design, a new approach was proposed to ameliorate the drawback of the first total synthesis of pseudopteroxazole.

1.2.1 Synthetic Plan

Bearing in mind the major pitfall of the first generation of total synthesis being the highly diastereoselective intramolecular Michael addition favoring the diastereomer with the wrong stereochemistry, the methyl group on C-3 (pseudopteroxazole numbering) was changed to an ester group as a surrogate. Though reducing an ester to an alkane has been shown to be quite facile in a similar system,[22] a subtle change of the structure rendered this reduction process quite challenging, as will be discussed later. Another strategic change was made in the pursuit of better efficiency of the total synthesis. The diene branch was planned to be installed prior to the Buchwald-Hartwig coupling reaction. Though there are many "philosophic concepts" about the economy in total synthesis in the modern literature world,[23] in academic environment, the value of a good total synthesis can always be appreciated by its aesthetically pleasing transformations perceived by the mind through drawings on the paper, or more and more frequently, on a screen; and by its ease to perform, and hence the satisfying feelings arising from it, by the practitioners in the laboratory. To access the starting material **58** for the key reaction (intramolecular Michael addition), a two-step sequence (Horner-Wadsworth-Emmons reaction and Buchwald- Hartwig coupling) was designed to merge three relatively simple starting materials together convergently (Scheme 11).

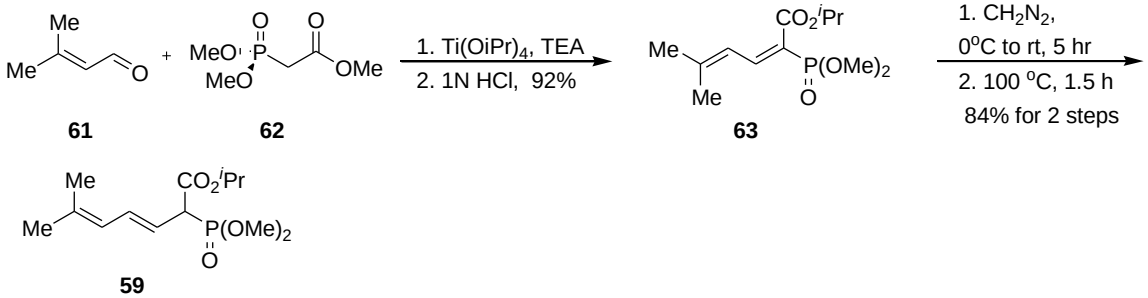
Scheme 11



1.2.2 Preparation of Coupling Partners

The (*R*)-(-)-*S*-methyl-*S*-phenylsulfoximine **41** was prepared according to the published procedure.[24] Another coupling partner, 2-bromo-3-methoxy-5-methylbenzaldehyde **60** was made following Koyama and Kamikawa's protocol.[25] The isopropyl dienonate **59** was synthesized through a modified Minami procedure in four to five steps, depending on which starting material used (Shown in Scheme 12).[26]

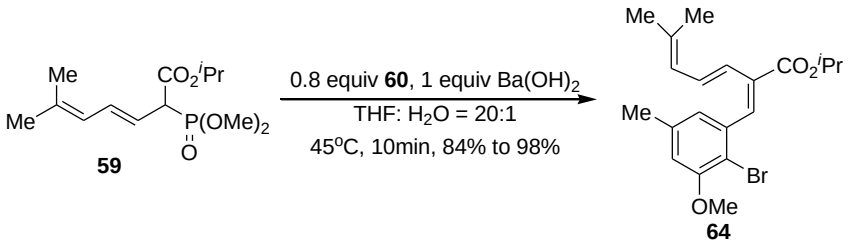
Scheme 12



3-Methyl-2-buten-1-al **61** could be purchased from Acros at a price of $180.6/25 mL, or it could be synthesized directly from 3-methyl-2-buten-1-ol ($55/kg) by pyridinium chlorochromate oxidation. We used 3-methyl-2-buten-1-ol as the initial starting material most of the time, for economic reasons. However, 3-methyl-2-buten-1-al **61** is very volatile, in spite of a relatively high boiling point (132-133^{o}C), and a significant amount of material was lost after distillation. Therefore, the aldehyde starting material **61** was used as a solution in dichloromethane in most cases. As for the Knoevenagel condensation between the allylic aldehyde **61** and the trimethyl phosphonate **62**, titanium isopropoxide was chosen as the Lewis acid instead of titanium chloride used by Minami and his coworkers.[26,27] The next step was a regioselective cyclopropane formation, followed by pyrolysis of the cyclopropane intermediate to the homologated isopropyl ester **59**.

After a cursory screening of conditions, 2-bromo-3-methoxy-5-methylbenzaldehyde **60** was coupled with the dienoate **59** under very mild conditions, barium hydroxide in THF and water at room temperature. This generated the coupled product **64** in 84% to 98% yield, with complete *E*-selectivity (Scheme 13).

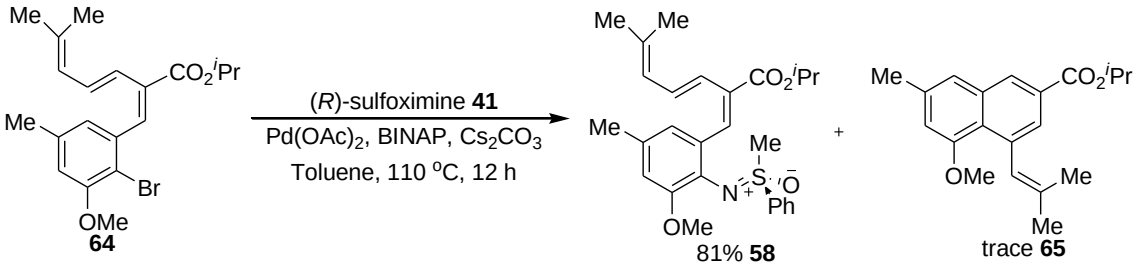
Scheme 13



1.2.3 Buchwald-Hartwig Coupling and the Intramolecular Michael Addition

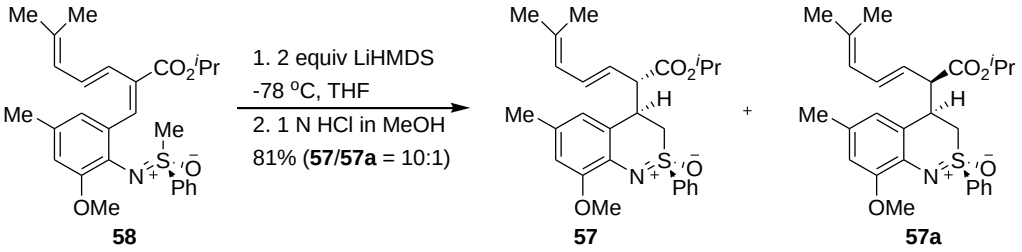
Aware of the possibility of an intramolecular Heck reaction,[28] we coupled the aryl bromide **64** with (*R*)-(-)-*S*-methyl-*S*-phenylsulfoximine **41** through a Buchwald-Hartwig reaction. Gratifyingly, the Buchwald-Hartwig coupling product **58** was produced with up to 81% yield. [29] Only trace amounts of the fluorescent Heck product **65** was formed, demonstrating the high selectivity of this catalyst system (Scheme 14).

Scheme 14

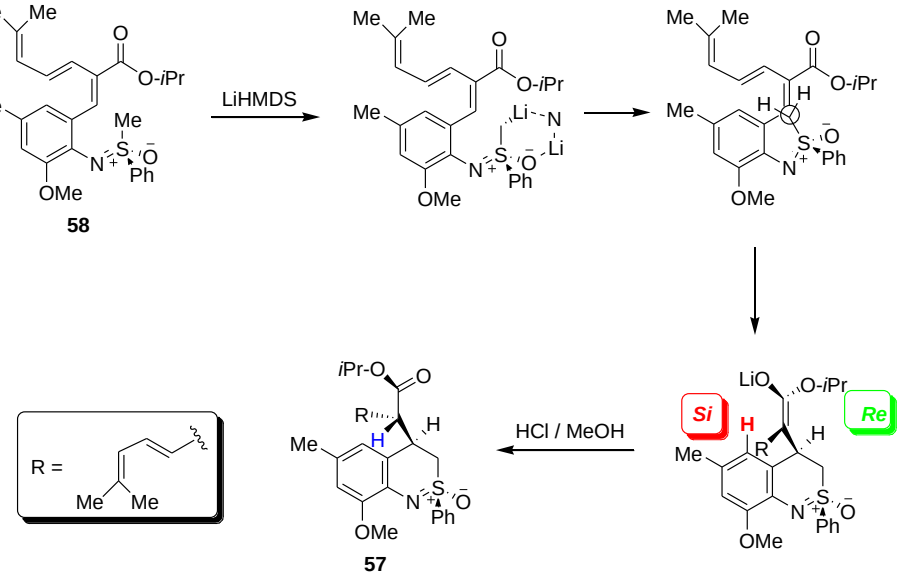


The highlight of this synthetic route would be the intramolecular Michael addition to generate chiral benzothiazine **57** with two contiguous chiral centers. At -78 ^{o}C, two equivalents of lithium hexamethyldisilamide in THF solution was added to a solution of starting material **58** in THF. After TLC analysis showed the complete consumption of starting material, the reaction mixture was quenched by slowly adding a pre-cooled HCl solution in MeOH. This reaction was clean and diastereoselective, favoring the product **57** with the right stereochemistry which was separated from **57a** with flash chromatography (Scheme 15).

Scheme 15



Scheme 16



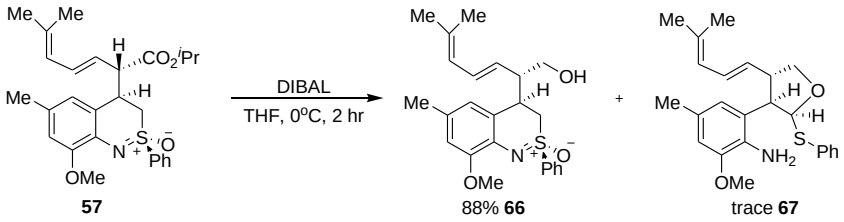
The stereocontrol over the benzylic position was consistent with all other related examples.[18a, 19] The stereoselectivity could be rationalized based on the steric interactions in the transition state, or it could be conceived as an oxygen-directed kinetic deprotonation of the α-carbon next to sulfur. Though the sigma bond connecting the α-carbon and sulfur could rotate freely, the chelation between the oxygen, lithium, and nitrogen could restrict the rotation about the sigma bond, forcing the Michael accepter approaching from the bottom face to react with the carbanion (Scheme 16). The

diastereoselectivity on the C-3 could be rationalized as the result of kinetic protonation from the *Re* face, since the *Si* face of the enolate was hindered by the aromatic system.

1.2.4 End Game of Formal Total Synthesis of Pseudopteroxazole

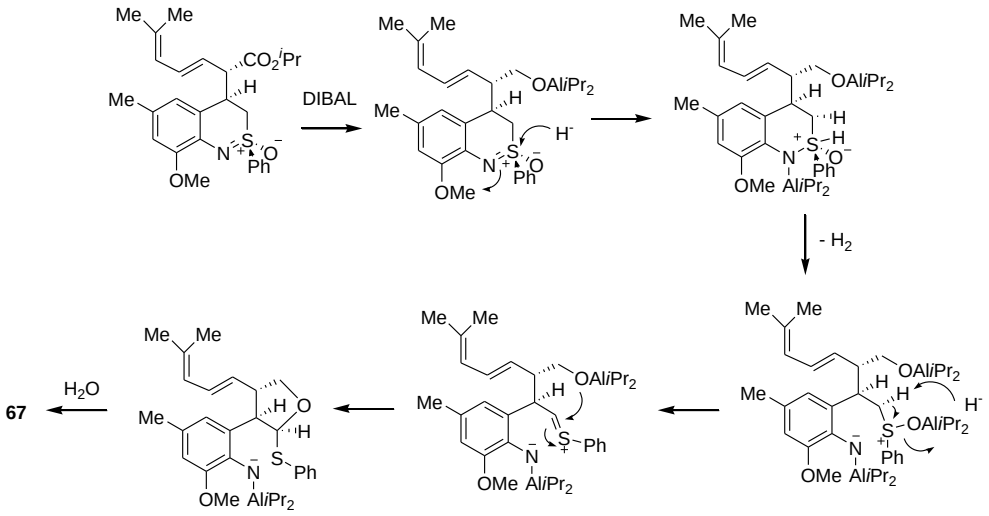
Now, what needed to be done was reduction of the isopropyl ester **57** to the **47**. There are a lot of tactics to furnish this transformation in organic chemists' arsenal.[30] However, this seemingly simple functional group transformation proved to be quite troublesome in this circumstance. First, after a cursory screening of reductants, DIBAL gave the best yield (88%) of the alcohol **66**, though in some cases, a variable amount of the aniline product **67** was isolated as byproduct (Scheme 17).

Scheme 17



A similar byproduct was identified by reducing an analogous benzothiazine with LAH. A proposed mechanism for the formation of the chiral tetrahydrofuran is shown in Scheme 18.[31] First, the isopropyl ester **57** was reduced to alkoxide by DIBAL; hydride reduction of the benzothiazine followed by elimination of hydrogen led to sulfoxide intermediate. The sulfoxide underwent a Pummerer rearrangement; elimination of the oxygen on the sulfur atom formed a sulfonium intermediate, which was trapped intramolecularly by the alkoxide to form the tetrahydrofuran product **67**.

Scheme 18



Having acquired the alcohol **66**, the last move now was to deoxygenate **66** to the **47**. The first strategy coming to mind for this transformation was converting the hydroxy group to a good leaving group, followed by hydride reduction. Thus, iodination of the alcohol **66** afforded the corresponding iodide **69** in rather low yield with a major byproduct **70** (Scheme 19).

Initially, the structure of this cyclopropane was established based on NMR study (Figure 8). The chemical shifts in the high field from δ1.7 to δ0.7 and the coupling pattern were typical for cyclopropanes. It is known that for cyclopropanes, the coupling constant between the two geminal hydrogens of the cyclopropanes is 5 Hz, while the coupling constants of the vicinal hydrogens are from 4 Hz to 5 Hz for trans-cyclopropanes and 8 Hz to 9 Hz for cis-cyclopropanes.[32] The chemical shifts and coupling constants for hydrogens on C10, C9, C16a, and C16b are: δ 1.64 (dddd, J = 4.5, 4.5, 8.5, 8.5 Hz, 1H), 1.04 (dddd, J = 4, 4, 9, 9 Hz, 1H), 0.85 (ddd, J = 5, 5.5, 8 Hz, 1H), 0.76 (ddd, J = 4.5, 5, 8 Hz, 1H) (Figure 9). The coupling constant between C10 and C9 is

about 5 Hz. This is in accordance with trans-cyclopropanes. This cyclopropane is stable at room temperature open to air for at least one year. And we were able to get the single crystal and thus the X-ray crystallography of **70**, which confirmed the trans-cyclopropane structure (Scheme 19).

Figure 8

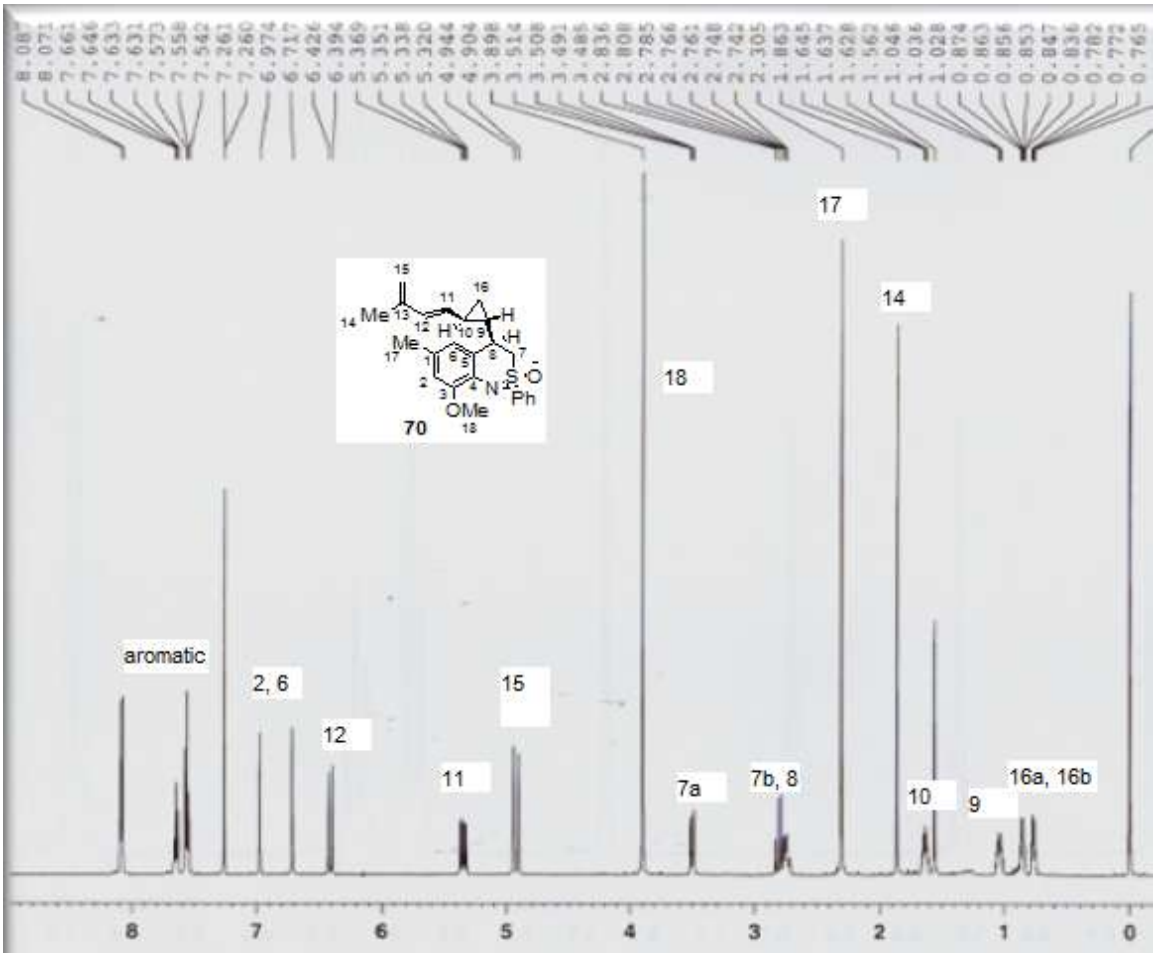
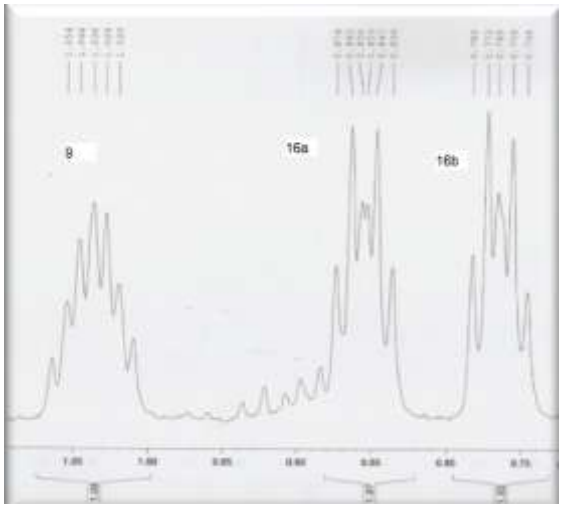
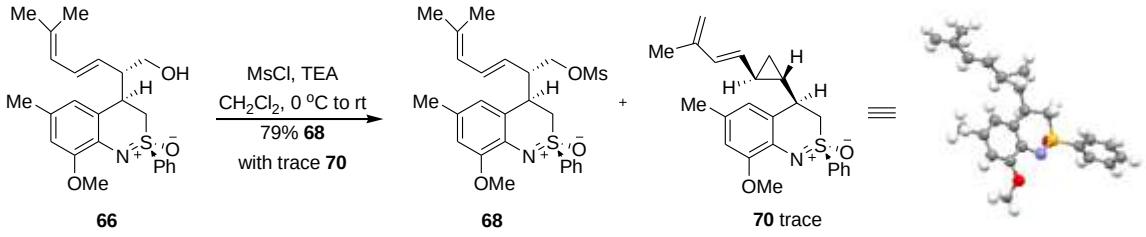


Figure 9



Scheme 19

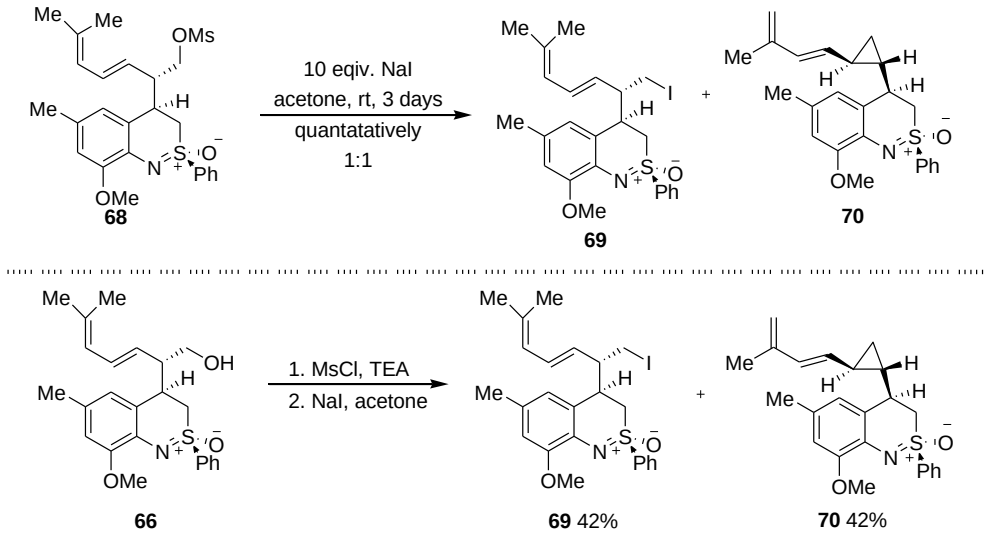


66 **68** **70** trace

Next mesylation was tried with success, giving the mesylate **68** in a 79% yield with trace amount of the same byproduct **70** as in the iodination (Scheme 20). Then, the mesylate **68** was treated with excess amount of NaI in acetone, in order to be transformed to the iodide **69**. However, it led to a mixture of the iodide **69** and again the same

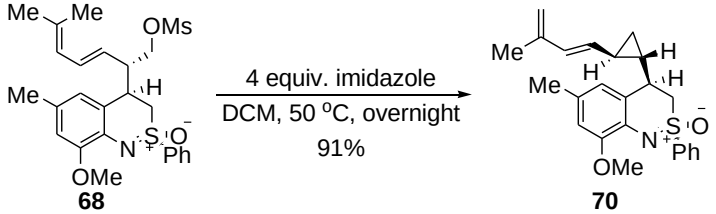
byproduct **70**. When the crude mesylate **68** was used directly for the iodination reaction, 42% of **69** and 42% of **70** were obtained (Scheme 20).

Scheme 20



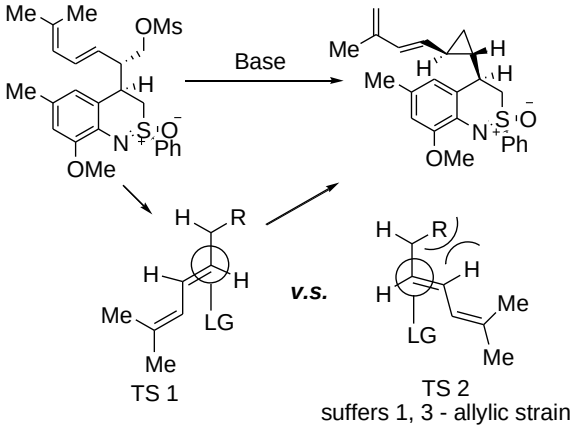
Though it was not the product we expected, the enantiopure cyclopropane compound **70** could be obtained in high yield, simply by treating the mesylate **68** with four equivalents of imidazole in refluxing acetone (Scheme 21).

Scheme 21



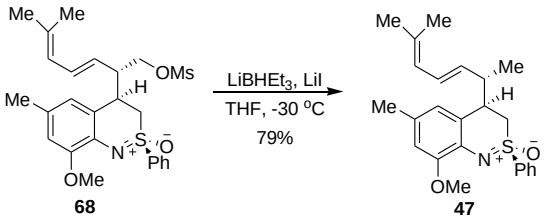
A working mechanism was proposed to rationalize the high stereoselectivity of this cationic cyclopropanation reaction. An ionization mechanism was unlikely due to the high energy of primary carbocation. An intramolecular SN_2 reaction of the mesylate **68** generated an allylic carbocation. Elimination by imidazole led to the final product **70**. The stereoselectivity was presumably the result of a strong 1,3-allylic strain between the benzothiazine group and the allylic hydrogen (Scheme 22).

Scheme 22



Finally, the mesylate **68** was reduced with a combination of lithium iodide and super hydride, giving up to a 79% yield of the deoxygenated product **47**. This reduction presumably involved the *in situ* formation of the corresponding iodide, followed by reduction by super hydride (Scheme 23).

Scheme 23

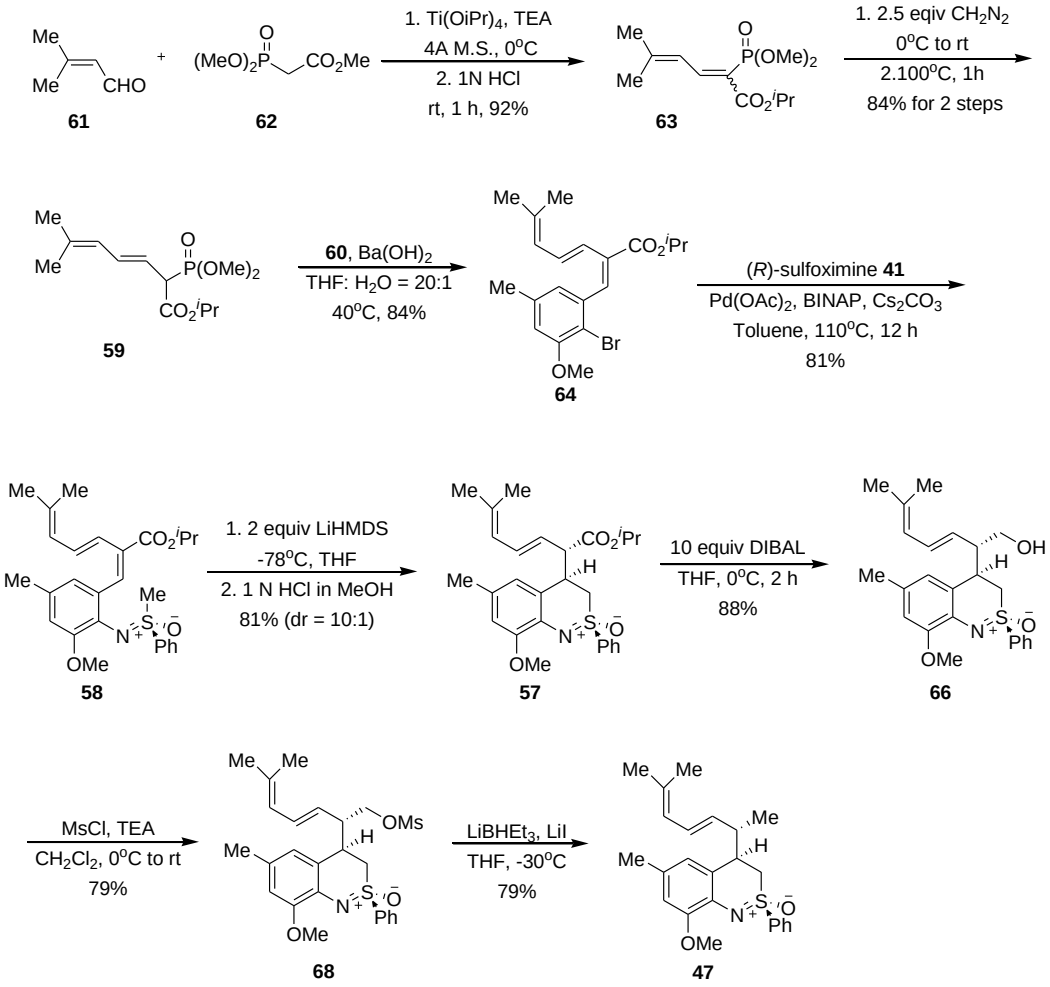


1.3 Concluding Remarks and Outlook

A convergent and diastereoselective formal total synthesis of pseudopteroxazole was achieved, once again demonstrated by the fidelity of the stereocontrol of chiral sulfoximine on the benzylic position (Scheme 24). This was the third report on synthesis of anti-TB natural product pseudopteroxazole. The newly developed synthetic route corrected the diastereoselectivity issue from the first total synthesis of pseudopteroxazole reported from our group. At the same time, it is more efficient and more step economic than our first synthesis. What is noteworthy in this sequence is the completely *E*-selective HWE reaction, the Buchwald-Hartwig coupling between a triene and sulfoximine, the highly diastereoselective intramolecular Michael addition, and the super hydride reduction of mesylate influenced by lithium iodide. During the synthesis progress, a diastereoselective formation of a tetrahydrofuran and a diastereoselective cyclopropane formation were also discovered, opening up opportunity to explore more new reactivity of chiral benzothiazine.

The drawback of this methodology is the same as all the others using chiral auxiliaries to control stereochemistry, poor atom economy and step economy. However, from another point of view, it provided the opportunity to make sulfoximine-substituted analogs of the natural products, which would certainly change their pharmacological properties. This should need to be tested.

Scheme 24


1. Ti(OiPr)4, TEA
4A M.S., 0°C
2. 1N HCl
rt, 1 h, 92%
1. 2.5 eqiv CH2N2
0°C to rt
2.100°C, 1h
84% for 2 steps
61
62
63
59
60, Ba(OH)2
THF: H2O = 20:1
40°C, 84%
64
(R)-sulfoximine 41
Pd(OAc)2, BINAP, Cs2CO3
Toluene, 110°C, 12 h
81%
58
1. 2 equiv LiHMDS
-78°C, THF
2. 1 N HCl in MeOH
81% (dr = 10:1)
57
10 equiv DIBAL
THF, 0°C, 2 h
88%
66
MsCl, TEA
CH2Cl2, 0°C to rt
79%
68
LiBHEt3, LiI
THF, -30°C
79%
47

1.4 References

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1.5 Experimental Section

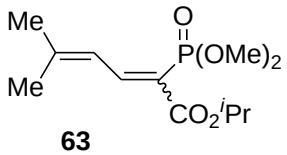
General Information:

All air and moisture sensitive reactions were carried out in flame-dried glassware under an argon or nitrogen atmosphere. Reactive liquid reagents (LHMDS, etc.) were measured and transferred by gastight syringes through rubber septa. Tetrahydrofuran (THF) was freshly distilled over sodium benzophenone kytyl. Toluene was distilled from CaH_2. The reaction mixture was concentrated by using a rotary evaporator attached to a water aspirator. Residue solvents were usually removed under reduced pressure using vacuum pump (approximately 1mm Hg).

Flash chromatographic separations were carried out on silica gel (230-400 mesh) with ACS reagent grade solvents. Analytical thin layer chromatography was performed on glass–backed silica gel plates with F254 indicator. Compounds were visualized under UV light or by developing in iodine, vanillin, phosphomolybdic acid solution or with potassium permanganate solution followed by heating in a hot plate to approximately 350^{o}C. Melting points were determined with a melting point apparatus.

^{1}H NMR spectra were recorded in Fourier transform mode at 250, 300 or 500 MHz, respectively, as $CDCl_3$ solutions with tetramethylsilane (δ = 0 ppm) as the internal standard. ^{13}C NMR spectra were recorded on the same instruments at 62.5, 75 or 125 MHz, respectively, with $CDCl_3$ (δ = 77 ppm) as the internal reference. ^{31}P NMR spectra were recorded on the same instruments at 101 MHz, respectively, with 85% H_3PO_4 (δ = 0 ppm) as the external standard. Chemical shifts (δ) were reported in parts per million (ppm). Multiplicities were reported as s (singlet), b (broad), d (doublet), t (triplet), q

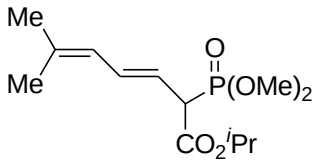
(quartet), m (multiplet), and dd (doublet of doublet), etc. In ^{1}H NMR spectra of diastereomeric mixtures, the signals for individual isomers were reported when possible. Infrared spectra were recorded on an FT-IR spectrometer. Optical rotations were recorded on a polarimeter with sodium D line at the temperatures as indicated in the experimental for specific compounds. High resolution mass spectra were obtained on a magnetic sector instrument with a resolution greater than 10,000.



63

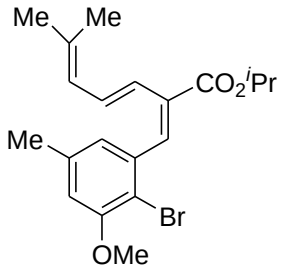
(E/Z)-isopropyl 2-(dimethoxyphosphoryl)-5-methylhexa-2,4-dienoate (63): A mixture of 3-methylbut-2-enal **61** (5 mL, 0.065 mol) and trimethyl phosphonoacetate **62** (5.26 mL, 0.033 mol) in THF (300 mL) with molecular sieves (4 Å) was placed in a 1 L round-bottom flask under an argon atmosphere. To this solution, Ti(O^{i}Pr)$_4$ (29 mL, 0.098 mol) was added. Then TEA (17 mL, 0.13 mol) was added over 30 min, and the mixture was stirred at 0^{o}C for 7 h. The reaction mixture was poured into 1 N HCl and vigorously stirred at rt for 1 h. It was extracted by ethyl acetate (3 x 300 mL) and the extract was washed with 300 mL saturated sodium bicarbonate solution and 300 mL brine. The organic layer was dried with anhydrous sodium sulfate and the solvent was evaporated, affording the product as a mixture of *E*/*Z* (2:1) isomers (5.82 g, 92%). (*Z*)-isomer: IR (neat): 2978, 2953, 2848, 1699, 1618, 1564, 1250, 1025, 829 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.20 (dd, 1 H, J = 12.5, 44.5 Hz), 7.22 (dd, 1 H, J = 1.0, 12.0 Hz), 5.12 (septet, 1 H, J = 6.5 Hz), 3.78 (s, 3 H), 3.75 (s, 3 H), 2.00 (s, 3H), 1.98 (s, 3H), 1.30 (d, 6 H, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.9 (d, J = 15.0 Hz), 155.2 (d, J = 2.5 Hz), 152.9

(d, J = 10.0 Hz), 122.4 (d, J = 5.0 Hz), 115.6 (d, J = 186.0 Hz), 68.7, 52.6 (d, J = 5.0 Hz), 27.6, 21.7 (d, J = 10.0 Hz), 19.0; HRMS calcd for $C_{12}H_{21}O_5PNa$ $[M+Na]^+$ 299.1019; Found: 299.1006; ^{31}P NMR ($CDCl_3$, 250 MHz) δ 23.4 (85% H_3PO_4 as external standard).



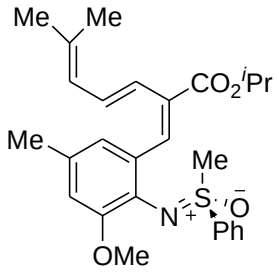
59

(*E*)-isopropyl 2-(dimethoxyphosphoryl)-6-methylhepta-3,5-dienoate (59): To a solution of **63** (4.86 g, 0.018 mol) in ether (20 mL) in a 50 mL round-bottom flask, a 0.5 M diazomethane solution in ether (0.088 mL, 0.045 mol) at 0 ^oC was added dropwise. The reaction was warmed to rt and stirred for 12 h. After the reaction was complete, the solvent was evaporated and the crude product was heated at 100 ^oC for 1 h. After flash chromatography with 50% ethyl acetate in hexanes, colorless oil (4.54 g, 84% for two steps) was obtained, the product **59** having only an (*E*) configuration. IR (neat): 2983, 2851, 1728, 1450, 1262, 1102, 1025, 829, 796 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.44 (ddd, 1H, J = 5.0, 11.0, 15.5 Hz), 5.85 (d, 1H, J = 11.0 Hz), 5.65 (ddd, 1H, J = 7.0, 9.5, 16.0 Hz), 5.07 (septet, 1H, J = 6.5 Hz), 3.81 (d, 3H, J = 11.0 Hz), 3.79 (d, 3H, J = 11.0 Hz), 3.75 (dd, 1H, J = 9.5, 24.0 Hz), 1.78 (s, 3H), 1.76 (s, 3H), 1.28 (d, 3H, J = 4.5 Hz), 1.26 (d, 3H, J = 4.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.0 (d, J = 5.0 Hz), 136.9 (d, J = 5.0 Hz), 131.9 (d, J = 12.5 Hz), 124.0 (d, J = 5.0 Hz), 118.5 (d, J = 12.5 Hz), 69.2, 53.7 (d, J = 7.5 Hz), 53.4 (d, J = 7.5 Hz), 50.6, 49.6 (d, J = 130.0 Hz), 25.8, 21.5 (d, J = 10.0 Hz), 18.2; HRMS calcd for $C_{13}H_{23}O_5PNa$ $[M+Na]^+$ 313.1175; Found: 313.1171.



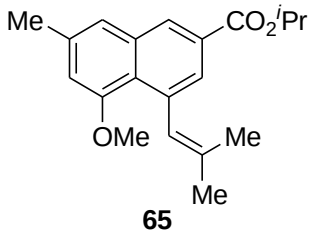
64

(2*E*, 3*E*)-Isopropyl 2-(2-bromo-3-methoxy-5-methylbenzylidene)-6-methylhepta-3,5-dienoate (64): To a solution of *o*-bromoaldehyde **60** (2.22 g, 10 mmol) and phosphonoacetate **59** (3.43 g, 12 mmol) in 120 mL THF and 6 mL of H_2O, $Ba(OH)_2$ (7.35 g, 43 mmol) was added in portions with vigorous stirring at 40 ^oC. After 10 min, the reaction was allowed to reach rt and was diluted with 200 mL CH_2Cl_2. It was washed with 1 x 100 mL saturated $NaHCO_3$ and 1 x 100 mL brine. It was dried with $MgSO_4$, filtered through Celite and concentrated in vacuo. After flash chromatography (1% TEA, 10% ethyl acetate in hexane), 3.2 g (84%) of the bromo ester **64** was obtained as a viscous oil. IR (neat): 2974, 2930, 1714, 1234, 1096 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.33(s, 1H), 7.16 (dd, 1H, J = 11.0, 15.6), 6.79 (s, 1H), 6.67 (s, 1H), 6.22 (d, 1H, J = 15.6 Hz), 5.82 (d, 1H, J = 11.0 Hz), 5.22 (septet, 1H, d = 6.0 Hz), 3.90 (s, 3H), 2.33 (s, 3H), 1.79 (s, 6H),1.38 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.0, 155.8, 138.3, 137.6, 137.4, 135.8, 132.2, 131.8, 126.2, 123.9, 122.2, 112.2, 110.1, 68.4, 56.2, 26.2, 21.8, 21.4, 18.6; HRMS calcd for $C_{20}H_{25}O_3BrNa$ $[M+Na]^+$ 415.0879; Found: 415.0875.



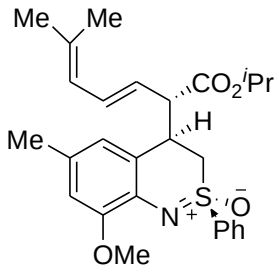
58

58: A 100 mL round bottom flask with condenser was charged with palladium acetate (15 mg, 0.065 mmol), *rac*-BINAP (60 mg, 0.1 mmol), in 35 mL toluene. The mixture was stirred for 15 min at room temperature. The bromo ester **64** 510 mg (0.5 mmol) and (*R*)-**41** 220 mg (0.77 mmol) in 5 mL toluene was added, followed by addition of Cs_2CO_3 (1.17 g, 2 mmol). It was refluxed at 110^{o}C for 12 h. Then it was diluted with 40 mL CH_2Cl_2, filtered through Celite, which was washed with 3 x 50 mL CH_2Cl_2, and concentrated in vacuo. After flash chromatography (25% ethyl acetate in hexanes), 491 mg (81%) of **58** was obtained as pale yellow semisolid. IR (film): 3064, 2974, 2925, 1703, 1560, 1454, 1336, 1270, 1233, 1094, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.00 (dd, 2H, J = 1.5, 10.0 Hz), 7.77 (s, 1H), 7.56-7.50 (m, 3H), 7.20 (dd, 1H, J = 11.0, 15.5 Hz), 6.80 (s, 1H), 6.60 (s, 1H), 6.40 (d, 1H, J = 15.5 Hz), 5.87 (d, 1H, J = 11.0 Hz), 5.21 (m, 1H, J = 6.0 Hz), 3.59 (s, 3H), 3.10 (s, 3H), 2.28 (s, 3H), 1.81 (s, 6H), 1.36 (s, 3H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.6, 152.2, 142.4, 137.2, 136.9, 132.3, 132.0, 131.6, 130.7, 130.2, 129.8, 128.9, 127.5, 126.6, 123.4, 113.1, 67.8, 55.6, 46.0, 26.2, 22.0, 21.2, 18.6; HRMS calcd for $C_{27}H_{33}NO_4SNa$ $[M+Na]^+$ 490.2022; Found: 490.2016; $[\alpha]^{25}_D$ = 77.975 (c 0.79, $CHCl_3$).



65

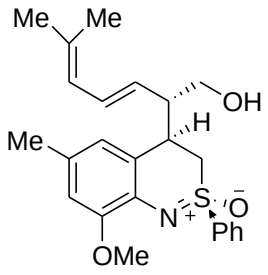
The Heck coupling product **65** is a byproduct that was formed in trace amount under the Buchwald coupling condition. It was isolated as a fluorescent colorless oil: IR (neat): 2978, 2917, 1708, 1573, 1454, 1372, 1274, 1221, 1136, 1103 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.28 (d, 1H, J = 1.5 Hz), 7.67 (s, 1H), 7.30 (s, 1H), 6.94 (s, 1H), 6.73 (d, 1H, J = 1.0 Hz),5.29 (septet, 1H, 6.0 Hz), 3.87 (s, 3H),1.96 (d, 3H, J = 1.0 Hz), 1.71 (d, 3H, J = 1.5 Hz), 1.40 (d, 6H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.4, 157.3, 136.1, 135.7, 135.3, 130.9, 128.5, 128.0, 127.7, 126.8, 124.9, 121.6, 110.4, 68.3, 55.9, 26.0, 22.0, 21.7, 19.1; HRMS calcd for $C_{20}H_{24}O_3Na$ $[M+Na]^+$ 335.1618; Found: 335.1618.



57

57: A 100 mL round-bottom flask was charged with bromo ester **58** (1.58 g, 3.38 mmol) in 40 mL THF. LiHMDS 6 mL (1 M in toluene, 6 mmol) was added dropwise to the solution at -78°C. After 10 min at -78 °C, the reaction was quenched with 1 N HCl in methanol at -78 °C. It was poured into water, extracted with 3 x 20 mL CH_2Cl_2, dried with $MgSO_4$, and concentrated in vacuo. After flash chromatography (30% ethyl acetate in hexane), 1.28 g (81%) of **57** was obtained as the major isomer. IR (film): 2970, 2921, 2868, 1720, 1462, 1245, 1102 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.10-8.12 (m, 2H), 7.62-7.66 (m, 1H), 7.54-7.57 (m, 2H), 6.68 (s, 1H), 6.64 (s, 1H), 6.26 (dd, 1H, J = 11.0, 15.0 Hz), 5.77 (d, 1H, J = 11.0 Hz), 5.49 (dd,

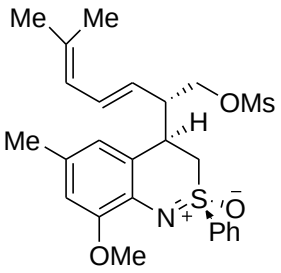
1H, J = 7.5, 15.0 Hz), 4.89 (septet, 1H, J = 6.0 Hz), 3.96 (t, 1H, J = 7.0 Hz), 3.88 (s, 3H), 3.60-3.64 (m, 1H), 3.52-3.56 (m, 2H), 2.3 (s, 3H), 1.75 (s, 3H), 1.69 (s, 3H), 1.15 (d, 3H, J = 6.5 Hz), 1.05 (d, 3H, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.3, 152.6, 139.4, 136.8, 133.8, 132.1, 131.1, 129.9, 129.5, 129.4, 124.9, 124.9, 124.3, 119.4, 111.9, 68.4, 56.2, 51.1, 49.2, 38.4, 26.2, 21.8, 21.6, 18.6; HRMS calcd for $C_{27}H_{33}NO_4SNa$ $[M+Na]^+$ 490.2022; Found: 490.2012; $[\alpha]^{25}_D$ = -60.48 (c 1.66, $CHCl_3$).



66

(2*S*,3*E*)-6-Methyl-2-[(2*R*,4*R*)-2-oxido-2-phenyl-3,4-dihydro-2l^4,1-benzothiazin-4-yl]hepta-3,5-dien-1-ol (66): To a solution of the ester **57 (**383mg, 0.819 mmol) in 8 mL THF, was slowly added 8.19 mL of DIBAL (1M in THF) at 0^{o}C. After 2 h, it was carefully quenched with ethyl acetate and water. After filtration, followed by washing with 20 mL ethyl acetate, it was concentrated. After flash chromatography (50% ethyl acetate in hexanes), 0.285 g (88%) of **66** was obtained as a semisolid. IR (film): 3448, 2962, 2917, 1577, 1462, 1250, 1102, 1017 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.10-8.12 (m, 2H), 7.63-7.66 (m, 1H), 7.54-7.57 (m, 2H), 6.69 (s, 1H), 6.69 (s, 1H), 6.40 (dd, 1H, J = 11.0, 15.5 Hz), 5.82 (d, 1H, J = 10.5 Hz), 5.51 (dd, 1H, J = 9.0, 15.5 Hz), 3.89 (s, 3H, CH_3), 3.69 (ddd, 1H, J = 4.0, 7.0, 11.0 Hz), 3.46-3.55 (m, 3H), 2.98-3.13 (m, 1H), 2.32 (s, 3H), 1.77 (s, 3H), 1.73 (s, 3H), 1.35 (dd, 1H, J = 4.5, 6.5 Hz); ^{13}C NMR ($CDCl_3$,

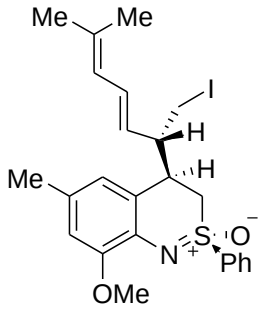
125 MHz) δ 152.8, 139.2, 136.1, 133.9, 132.2, 131.0, 130.2, 129.5, 128.4, 125.1, 124.7, 119.1, 111.6, 62.7, 56.2, 50.3, 45.0, 37.5, 26.2, 21.7, 18.6; HRMS calcd for $C_{24}H_{29}NO_3SNa$ $[M+Na]^+$ 434.1760; Found: 434.1751; $[\alpha]^{25}_D$ = -4.04 (c 3.02, $CHCl_3$).



68

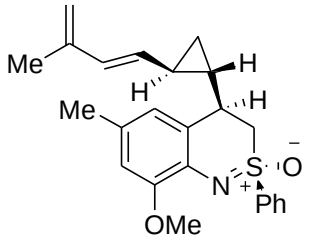
(2*R*,4*R*)-,4-[(1*S*,2*E*)-1-Methanesulfonyloxylmethyl-5-methyl-2,4-hexadienyl]-3,4-dihydro-8-methoxy-6-methyl-2-phenyl-2γ4-2,1-benzothiazine-2-oxide (**68**): To a solution of alcohol **66** (48 mg, 0.116 mmol) in 2 mL CH_2Cl_2 was added TEA (33 µl, 24 mg, 0.24 mmol) and mesyl chloride (14 µl, 21mg, 0.18 mmol) at 0°C. The reaction was allowed to reach rt and was stirred for 17 h. It was quenched with 1 mL saturated NH_4Cl, extracted with 2 mL CH_2Cl_2, washed with 2 mL brine, dried with Na_2SO_4, and concentrated in vacuo. After chromatography (50% ethyl acetate in hexanes), 45 mg (79%) of **68** was obtained as a white semisolid. IR (film): 3060, 2929, 2226, 1569, 1462, 11348, 1242, 1172, 1103, 964, 833, 731, 682 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.11 (d, 2H, J = 7.5 Hz), 7.66 (dd, 1H, J = 7.0, 8.0 Hz), 7.56 (dd, 2H, J = 8.0, 7.5 Hz), 6.70 (s, 1H), 6.67 (s, 1H), 6.37 (dd, 1H, J = 11.0, 15.5 Hz), 5.80 (d, 1H, J = 11.0 Hz), 5.47 (dd, 1H, J = 7.5, 15.0 Hz), 4.24 (dd, 1H, J = 4.5, 10.0 Hz), 4.05 (dd, 1H, J = 7.5, 10.0 Hz), 3.88 (s, 3H), 3.61 (dt, 1H, J = 11, 5 Hz), 3.51 (dd, 1H, J = 4.5, 13.0 Hz), 3.43 (m, 1H), 3.06 (dd, 1H, J = 11.5, 12.5 Hz), 2.90 (s, 3H), 2.33 (s, 3H), 1.77 (s, 3H), 1.72 (s, 3H); ^{13}C

NMR ($CDCl_3$, 125 MHz) δ 152.7, 138.5, 136.6, 133.8, 131.9, 130.9, 130.2, 129.3, 129.2, 126.0, 124.2, 123.5, 118.8, 111.6, 69.0, 56.0, 49.6, 41.9, 37.3, 37.2, 25.9, 21.4, 18.3; HRMS calcd for $C_{25}H_{31}NO_5S_2Na$ $[M+Na]^+$ 512.1536; Found: 512.1526; $[\alpha]^{25}_D$ = -13.82 (c 0.55, $CHCl_3$).



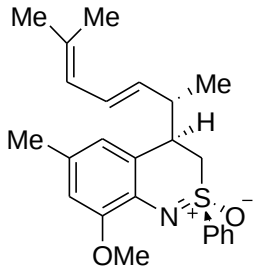
69

69: To a stirred solution of mesylate **68** 106 mg (0.22 mmol) in 2 ml CH_2Cl_2 was added 0.33 g NaI. It was stirred at rt for 3 days, diluted with 2 mI CH_2Cl_2, washed with 2 ml water, and 2 ml saturated $Na_2S_2O_3$, 2 ml brine, concentrated and column chromatographied using 30% ethyl acetate in hexane to get iodide **69** 60 mg (50%), and cyclopropane compound **70** 57 mg (50%). Iodide **69**: IR: 2909, 1573, 1462, 1332, 1246, 1160, 1107, 1017 cm^{-1}; ^1H NMR ($CDCl_3$, 500MHz, ppm) δ 8.14-8.16 (2H, m, ArH), 7.68-7.69 (1H, m, ArH), 7.58-7.62 (2H, m, ArH), 6.72 (1H, s), 6.65 (1H, s), 6.29 (1H, dd, J=11, 15 Hz), 5.84 (1H, d, J=11 Hz), 5.4 (1H, dd, J=9, 15 Hz), 3.91 (3H, s,CH_3), 3.48-3.54 (2H, m), 3.21-3.28 (2H, m), 3.11-3.17 (1H, m), 2.78 (1H, dd, J=9, 9 Hz), 2.36 (3H, s, CH_3), 1.80 (3H, s, CH_3), 1.74 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 500MHz, ppm) δ 153.0, 139.2, 136.4, 134.0, 132.1, 130.8, 130.6, 129.6, 129.4, 129.1, 124.5, 124.5, 119.4, 111.9, 56.3, 49.5, 44.8, 40.8, 26.2, 21.7, 18.6, 7.8; HRMS calcd for $C_{24}H_{28}INO_2SNa$ $[M+Na]^+$ 544.077764; Found: 544.075818; $[\alpha]^{25}_D$= -11.05(c 0.60, $CHCl_3$)



70

70: IR: 3066, 2936, 2852, 1630, 1463, 1326, 1275, 1231, 1202, 1159, cm^{-1}; ^{1}H NMR ($CDCl_3$, 500MHz, ppm) δ 8.07-8.08 (2H, m, ArH), 7.63-7.66 (1H, m, ArH), 7.54-7.57 (2H, m, ArH), 6.97 (1H, s), 6.72 (1H, s), 6.41 (1H, d, J=16 Hz), 5.34 (1H, dd, J=9, 15.5 Hz), 4.94 (2H, s), 4.90 (1H, s),3.90 (3H, s, CH_3), 3.50 (1H, dd, J=3, 11.5 Hz), 2.74-2.84 (2H, m), 2.30 (3H, s), 1.86 (3H, s, CH_3), 1.64 (1H, m), 1.04 (1H, m), 0.85 (1H, m), 0.76 (1H, m); ^{13}C NMR ($CDCl_3$, 500MHz, ppm) δ 133.7, 132.4, 131.5, 129.3, 129.2, 119.1, 114.5, 111.3, 56.0, 51.9, 39.0, 24.4, 24.2, 21.5, 18.7, 12.4; HRMS calcd for $C_{24}H_{27}NO_2SNa$ $[M+Na]^+$ 416.165471; Found: 416.164164; $[\alpha]^{25}_D$= -284.00(c 1.40, $CHCl_3$)



47

(2*R*,4*R*)-,4-[(1*S*,2*E*)-1,5-Dimethyl-2,4-hexadienyl]-3,4-dihydro-8-methoxy-6-methyl -2-phenyl-2γ4-2,1-Benzothiazine-2-oxide (47): To a solution of mesylate **68** (71 mg, 0.15 mmol) and LiI (201 mg, 1.5 mmol) in 7.5 mL dry THF at -30°C, was added 1.5 mL

of 1 M $LiBHEt_3$ in THF slowly. After it was kept at -30^oC for 26 h, it was diluted with 15 mL DCM and quenched with 10 mL 10% NaOH, and 5 mL 30% H_2O_2. After it was stirred for 30 min at rt, it was washed with 10 mL saturated $Na_2S_2O_3$ solution, followed by 30 mL brine. After drying with Na_2SO_4, it was concentrated under vacuum. Chromatography (20% ethyl acetate in hexanes) afforded 45 mg (79%) of **47** as a colorless oil. The NMR data matched the published.[33]

CHAPTER TWO

PORGRESS TOWARD TOTAL SYNTHESIS OF HAMIGERAN B

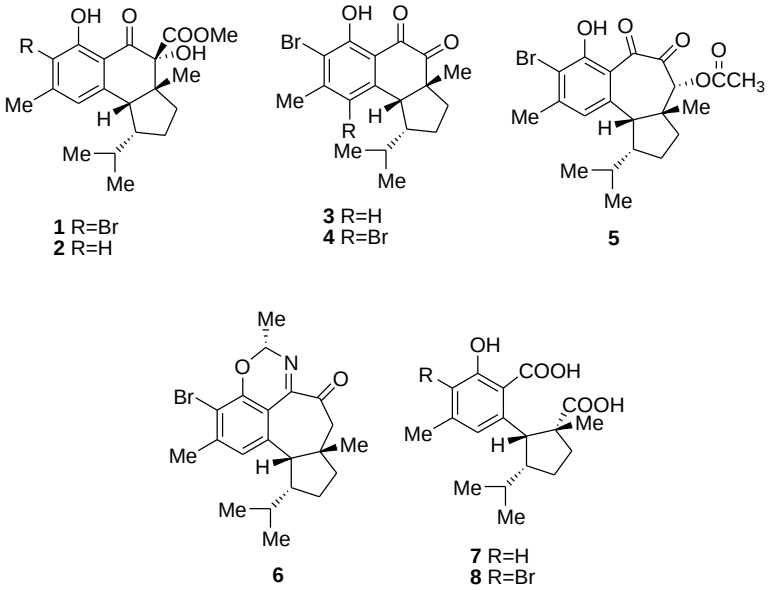
2.1 Introduction

Hamigerans are a family of natural products isolated from the poecilosclerid sponge *Hamigera tarangaensis* by Bergquist and Fremont from shallow water off the eastern coast of New Zealand.[1] Hamigeran B stands out in the family, due to its impressive inhibitory activities against herpes and polio viruses and *in vitro* activity against P-388 leukemia cell line.[1] The initial goal for this project was to apply a methodology that had been discovered and developed in our research group, the eight-electron cyclization reaction of cyclopentadienones to build the aromatic ring-fused [4.3.0] bicycle.[2] Since its appearance in the literature, hamigeran B has attracted a significant amount of synthetic effort among organic chemists, due to its interesting bioactivity, and novel, relatively complex structure within a fairly compact architecture.[3]

2.1.1 Hamigerans

Hamigeran A (**1**), debromohamigeran A (**2**), hamigeran B (**3**), 4-bromohamigeran B (**4**), hamigeran C (**5**), hamigeran D (**6**), hamigeran E (**7**), and debromohamigeran E (**8**) were isolated from poecilosclerid sponge *Hamigera tarangaensis*, which belongs to Anchinoidae family (Figure 1). Only phorboxazoles and the anchinopeptolides that have been isolated from Anchinoidae family members. Phorboxazoles attracted a lot of attention from organic chemists, leaving the anchinoperptolides almost uninvestigated.

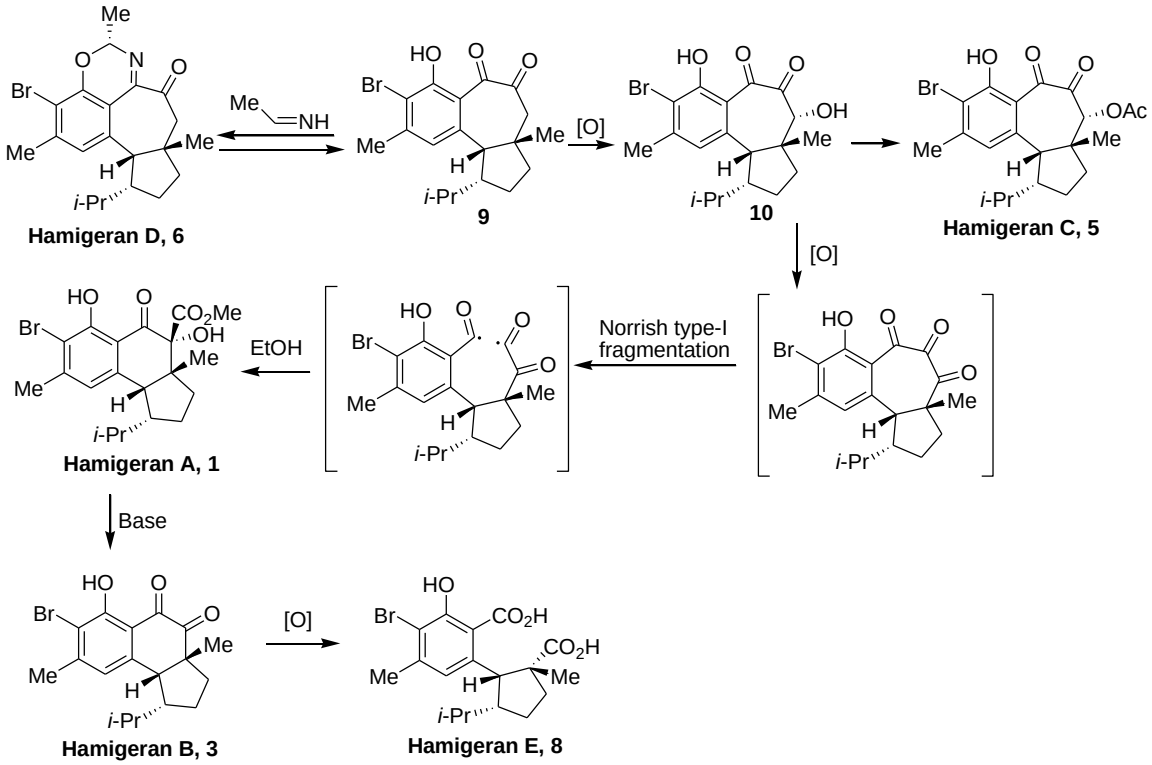
Figure 1



2.1.2 Proposed Chemical Relationship of Hamigerans

Though hamigerans are obviously structurally related, there is no reported biosynthesis of hamigerans. Based on their structural relationship, a biomimetic chemical relationship was proposed for the hamigeran family members (Scheme 1). Hamigeran D may be in equilibrium with the corresponding 1,2-diketone, which can be oxidized to an acyloin. Upon acylation, it will lead to hamigeran C; upon further oxidation to triketone, a Norrish type-1 fragmentation (which is possible since the sea sponge was collected in shallow sea water, where sunlight is abundant), followed by trapping with methanol, will give hamigeran A. After hydrolysis of the ester and decarboxylation, hamigeran B would be obtained. Further oxidative cleavage of hamigeran B would produce hamigeran E.

Scheme 1



2.1.3 Total Syntheses of Hamigeran B

A review by Clive, written in 2005, contains a collection of various total syntheses of hamigeran B.[3] Since this review, several formal total syntheses of this natural product by a variety of strategies have appeared.

2.1.3.1 Total Synthesis of Hamigeran B by Nicolaou, Gray and Tae

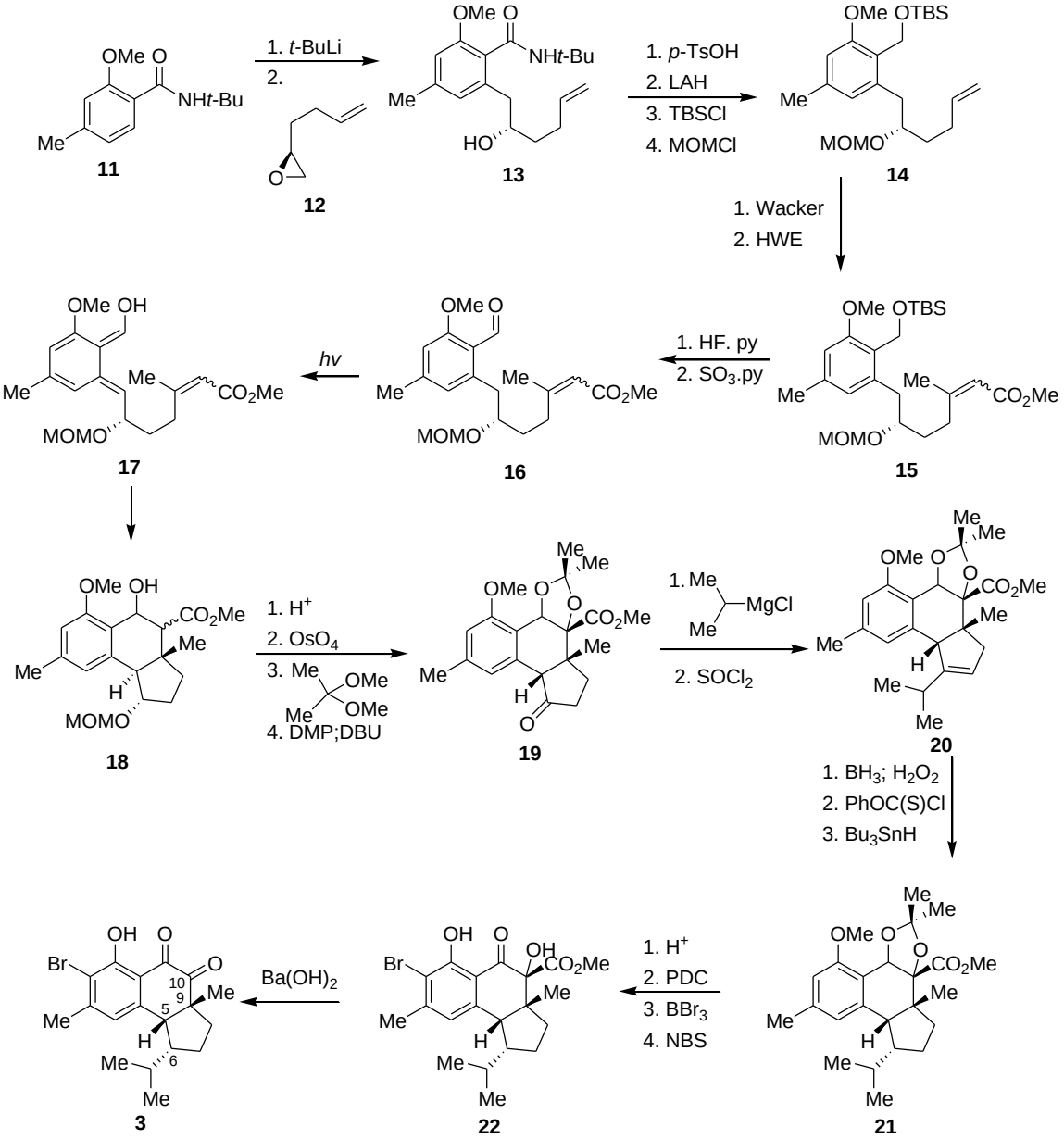
In 2001, two back-to-back communications in *Angewandte Chemie* reported Nicolaou, Gray and Tae's efforts in developing and applying the photoenolization of substituted benzaldehydes and subsequent Diels-Alder (PEDA) trapping of the hydroxyl-*o*-quinodimethanes.[4, 5] The full article published in 2003 provided the readers with more details (Scheme 2).[6]

Starting from benzamide **11**, enantiopure alcohol **13** was obtained by a sequence of directed lithiation and regioselective epoxide ring opening. Acid-catalyzed lactone formation, followed by LAH reduction yielded the diol, which was sequentially and selectively protected with TBS group and MOM group. Wacker oxidation of the terminal double bond of **14** led to a ketone, which further produced the α,β-unsaturated ester **15** (*E*/*Z* ratio was ca. 3.5:1) through a HWE reaction. The TBS group was selectively deprotected and the exposed benzylic alcohol was oxidized to the benzaldehyde **16**, which set the stage for the PEDA reaction. On irradiation, the substituted benzaldehyde **16** underwent photoenolization to give the quinone methide **17**. Intramolecular Diels-Alder cyclization then proceeded with high diastereocontrol to give ester **18** as a mixture of epimers.

The hydroxyl group on carbon 6 served as a handle to epimerize the stereocenter of carbon 5 once being oxidized. Next, it served as the electrophile to install the isopropyl group, leading to **20**. After failed attempts to hydrogenate the trisubstituted double bond in **20**, they found that hydroboration and oxidation led to the acetonide **21** as the major product.

Deprotection of the acetonide **21**, followed by oxidation and bromination, provided hamigeran A. Hydrolysis under aerobic conditions enabled a saponification, decarboxylation, and auto-oxidation cascade sequence to give (-)-hamigeran B. (Scheme 2)

Scheme 2

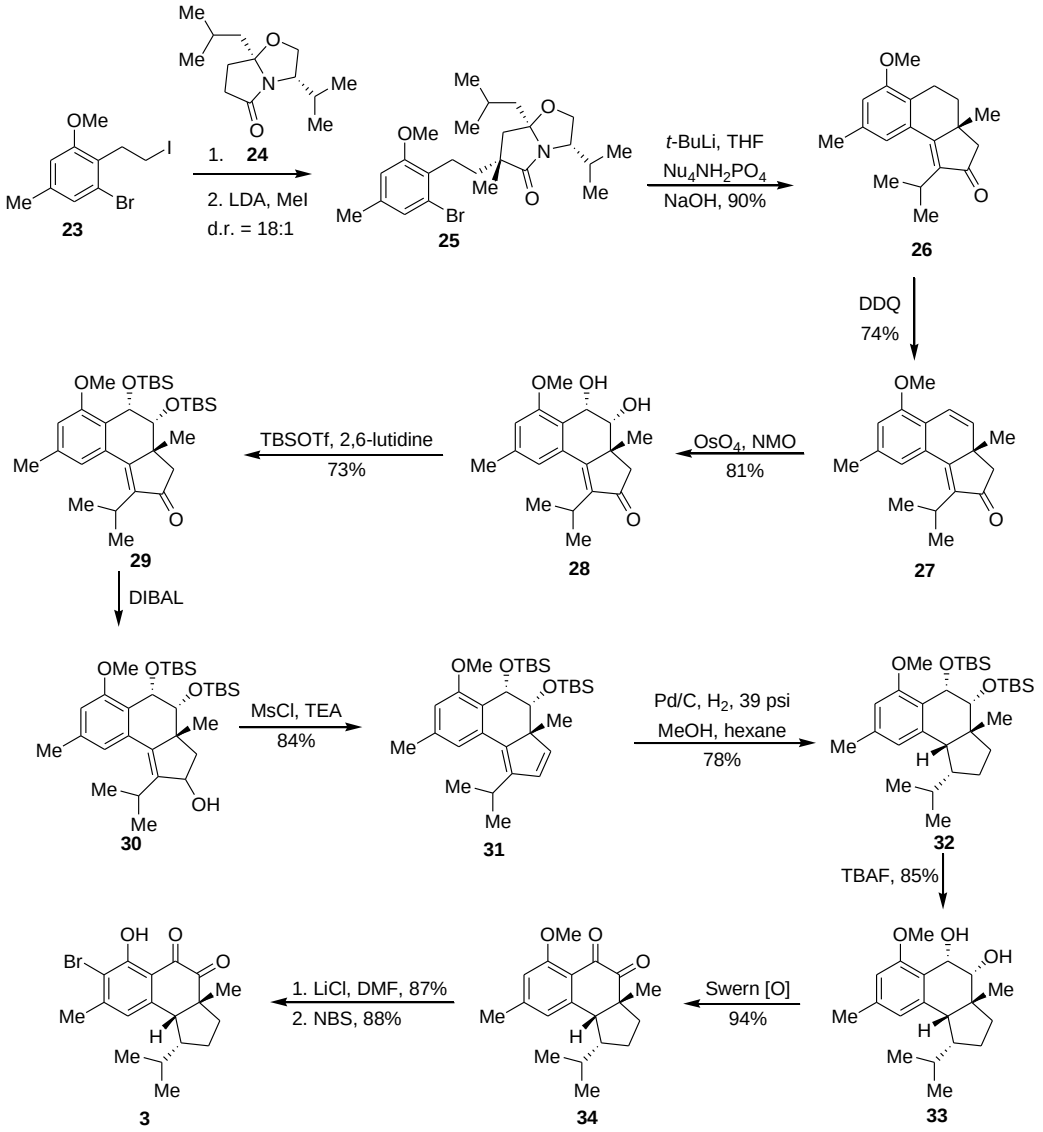


2.1.3.2 Total Synthesis of (-)-Hamigeran B by Clive and Wang

In 2003, Clive and Wang published their total synthesis of racemic hamigeran B and later, (-)-hamigeran B.[7, 8] Again, the stereochemistry of carbons 5 and 6 were controlled by the C9 stereogenic center. While Nicolaou's paper showed that

hydrogenation of the cylcopentene **20** produced a mixture of products with the one with an *exo*-isopropyl group as the major product under a variety of hydrogenation conditions,[6] Clive's synthetic route featured a hydrogenation of cyclopentadiene **31** to get the product with *endo*-isopropyl group.

Scheme 3



As shown in Scheme 3, the core carbon skeleton **26** was constructed very efficiently from the iodide **23** and Meyers' chiral lactam **24**. Then, dehydrogenation by DDQ, followed by dihydroxylation, and protection with TBSOTf produced cyclopentenone **29**. Moreover, it was reduced by DIBAL, and eliminated via the mesylate intermediate to give the cyclopentadiene **31**. A rather mild hydrogenation of **31** with Pd/C led to **32** with the right stereochemistry. It was proposed by the authors that the bulky TBS groups were essential for controlling the stereochemical outcome.

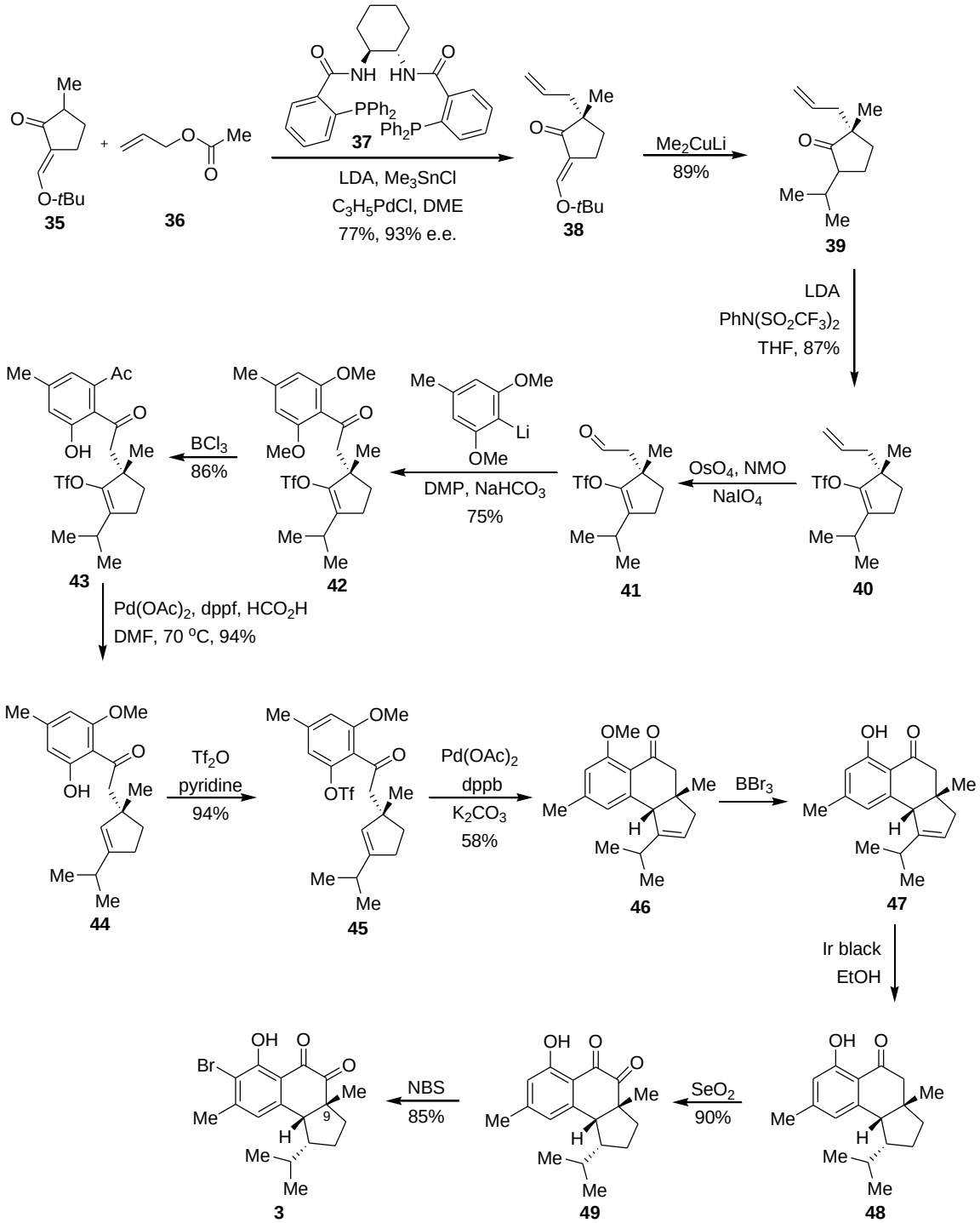
After removing the two TBS groups with TBAF, the diol **33** was oxidized to diketone **34**. Demethylation with LiCl in DMF, and mono-bromination gave hamigeran B (Scheme 3).

2.1.3.3 Total Synthesis of Hamigeran B by Trost, Pissot-Soldermann, Chen, and Schroeder

A year later, the Trost group published their total synthesis of (-)-hamigeran B, featuring their palladium-catalyzed asymmetric allylic alkylation reaction, which was used to install the quaternary stereogenic C9 center.[9] The full article on this work was published in 2005 and included more details of the total synthesis.[10] A noteworthy reaction in this sequence is the kinetic hydrogenation of the trisubstituted alkene **47** to **48** by iridium black under high pressure. Under similar conditions, Pd/C gave only the exo-isopropyl product, which was hypothesized to be the result of the undesired equilibration

of the semihydrogenation intermediates, leading to the thermodynamically more stable diastereomer (Scheme 4).

Scheme 4



A year later, the Trost group published their total synthesis of (-)-hamigeran B, featuring their palladium-catalyzed asymmetric allylic alkylation reaction, which was used to install the quaternary stereogenic C9 center.[9] The full article on this work was published in 2005 and included more details of the total synthesis.[10] A noteworthy reaction in this sequence is the kinetic hydrogenation of the trisubstituted alkene **47** to **48** by iridium black under high pressure. Under similar conditions, Pd/C gave only the exo-isopropyl product, which was hypothesized to be the result of the undesired equilibration of the semihydrogenation intermediates, leading to the thermodynamically more stable diastereomer (Scheme 4).

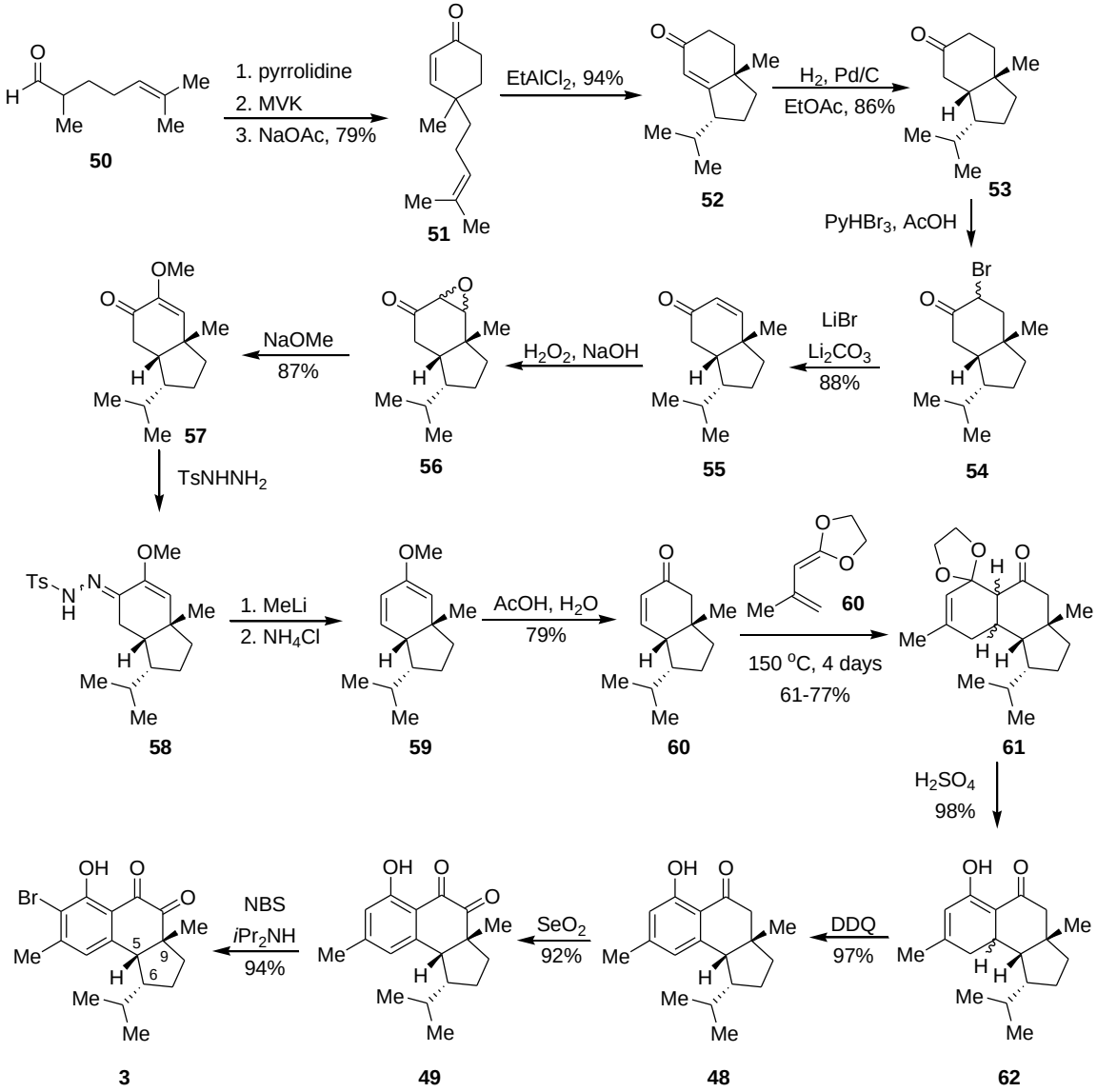
2.1.3.4 Total Synthesis of (±)-Hamigeran B by Piers and Lau

A different strategy, developed by Piers and Lau, for the synthesis of hamigeran B involved the installation of stereogenic centers, followed by the construction of the core structure. While most synthetic organic chemists prefer to use aromatic rings as one of the starting materials if the natural products contain them, Piers and Lau made the aromatic system instead of starting with it, in order to take advantage of the preset stereochemistry of the ketone **53**.

The enone **52** was prepared following the protocol developed by Snider, Corey and Engler. Hydrogenation with Pd/C yielded **53** with ease, setting up all of the three contiguous stereogenic centers. A Reusch enone migration protocol was later applied to convert enone **55** to epoxide **60**, which nicely set up the stage for a Diels-Alder reaction using an excess amount of the reactive diene **60**. Under rather harsh conditions (150 ^{o}C, 4 days), the DA product was formed in satisfying yields (61-77%). Hydrolysis and

aromatization led to a known ketone **48**, which upon bromination yielded racemic hamigeran B (Scheme 5).

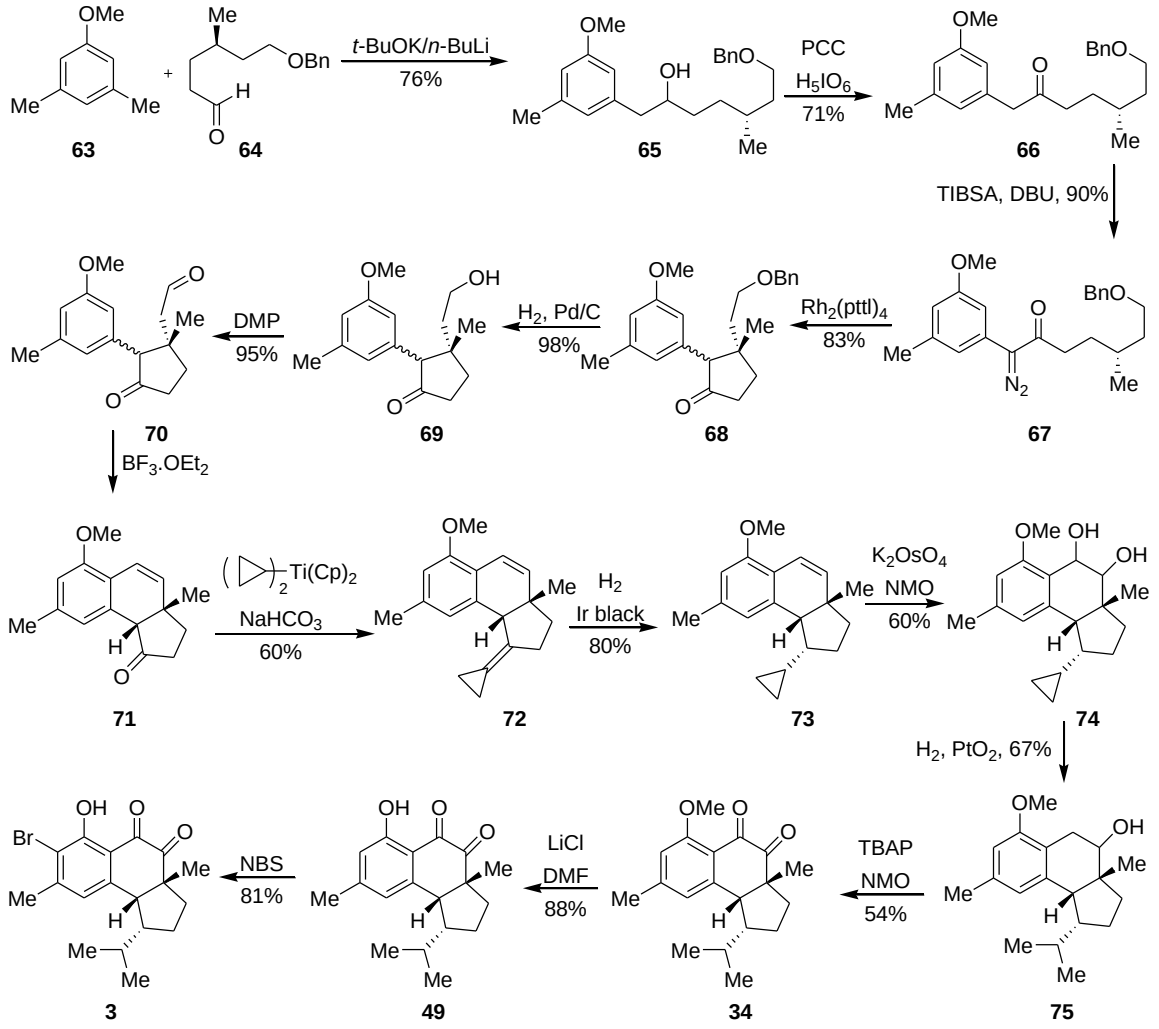
Scheme 5



2.1.3.5 Total Synthesis of (-)-Hamigeran B by Taber and Tian

In 2008, Taber and Tian reported their total synthesis of hamigeran B utilizing rhodium-mediated intramolecular C-H insertion, a methodology they developed.[11] They borrowed the stereochemistry of citronellal to get the enantiomerically pure citronellol

Scheme 6



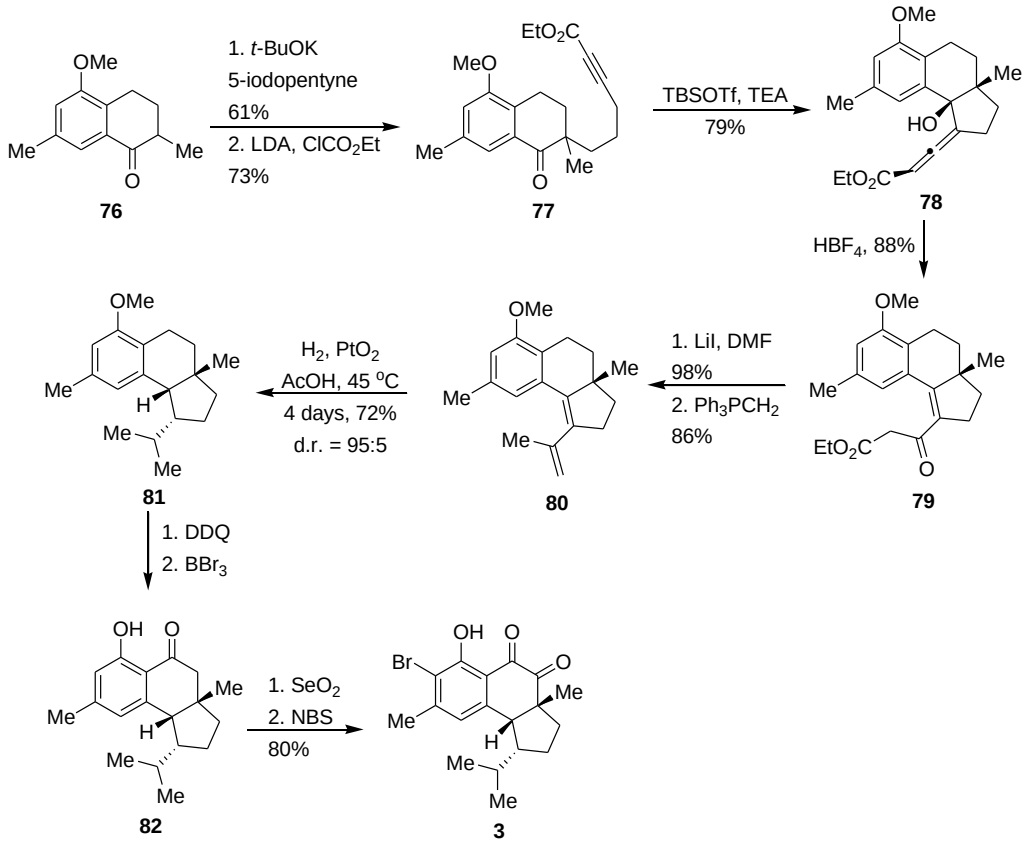
derivative **64** as the starting material. After extensive efforts aimed at optimizing the reaction conditions for the diazo transfer step and the Rh-mediated intramolecular C-H insertion step, three more operations led to ketone **71**. Olefination with the non-basic Petasis reagent, in the presence of $NaHCO_3$ to prevent isomerization of the product,

yielded an intermediate **72**. To their delight, the iridium-catalyzed hydrogenation with 1100 psi hydrogen gas in the Parr reactor selectively reduced the more strained double bond after 4-8 hours, leaving the benzylic alkene untouched. Upjohn dihydroxylation, hydrogenolytic cleavage of cyclopropane together with the benzylic alcohol, followed by TBAP/NMO oxidation led to a known diketone **34**. Following Clive's procedure, (-)-hamigeran B was obtained (Scheme 6).

2.1.3.6 Formal Total Synthesis of Hamigeran B by Miesch, Welsch, Rietsch, and Miesch

The Miesch group accomplished a formal total synthesis of racemic hamigeran B, using the methodology developed in their lab, the intramolecular akynylogous Mukiyama aldol-type reaction of cycloalkanones tethered to alkynyl esters (Scheme 7).[12]

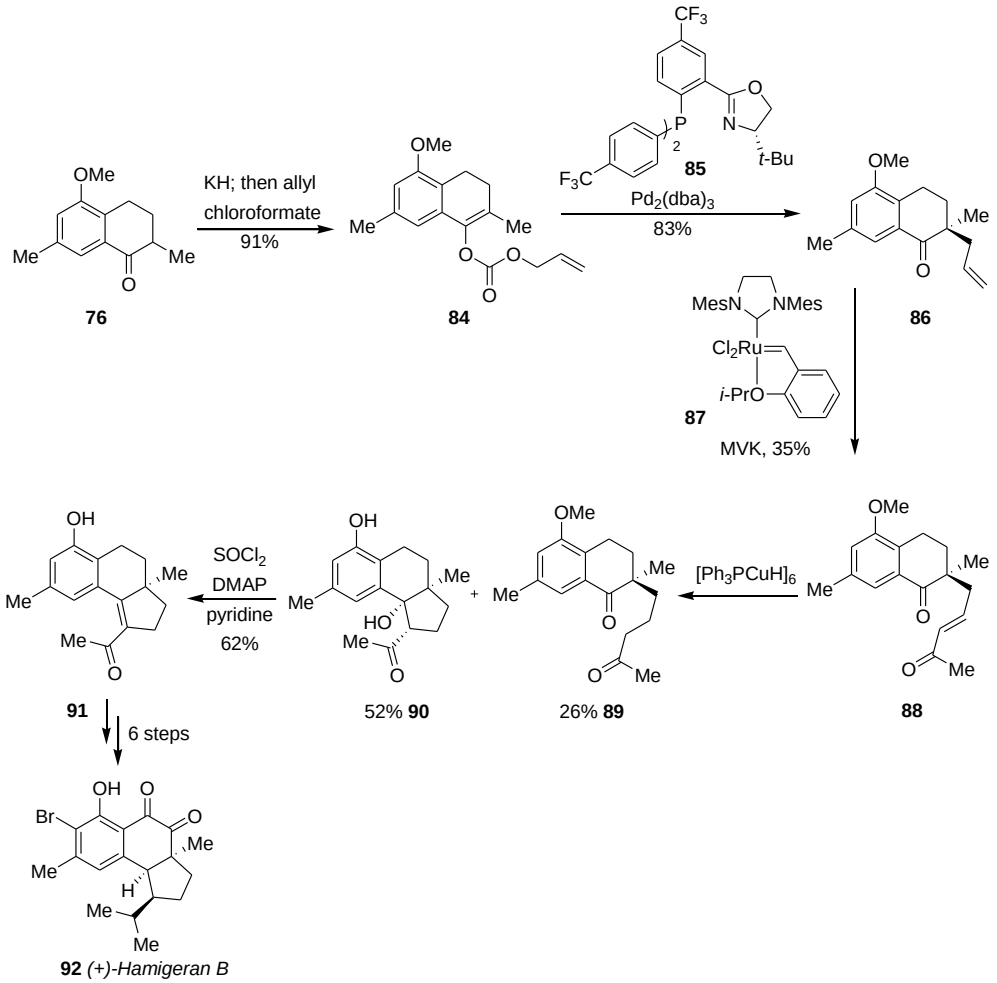
Scheme 7



2.1.3.7 Formal Total Synthesis of (+)-Hamigeran B by Mukherjee, McDougal, Virgil, and Stoltz

Starting from the same starting material Miesch used, the Stoltz group synthesized (+)-hamigeran B, using a palladium-catalyzed decarboxylative allylic alkylation reaction.[13]

Scheme 8



After the highly enantioselective (94% ee) decarboxylative allylic alkylation, catalyzed by $Pd_2(dba)_3$ using the trifluoromethylated derivative of (*S*)-*t*-BuPHOX (**85**) as

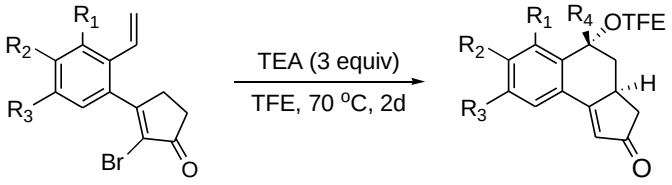
ligand, cross-metathesis and reductive cyclization yielded **90**, the core structure of hamigeran B. After dehydration of the β-hydroxyketone **90**, enone **91** was obtained, which was used to prepare (+)-hamigeran B (**92**) following Miesch's protocol.

2.2 Progress Toward Total Synthesis of Hamigeran B

2.2.1 The Eight-electron Cyclization Reaction

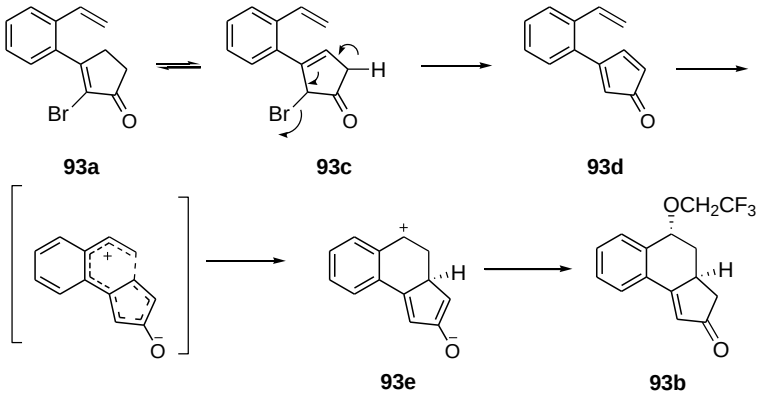
Harmata, Zheng, Schreiner and Navarro-Vázquez published a novel electrocyclization of 2-bromocyclopentenones to form aromatic ring fused [4.3.0] bicycles (Scheme 9).[2] The theoretical study supported a cyclopentadienone intermediate **93d**, which underwent an electrocyclization driven by deantiaromatization (Scheme 10).

Scheme 9



93a R_1, R_2, R_3 = H — 69% **93b**
94a R_1, R_3 = H; R_2 = OMe — 61% **94b**
95a R_1 = OMe; R_2 = H; R_3 = Me — 64% **95b**
96a R_1 = H; R_2, R_3 = -OCH_2O- — 61% **96b**

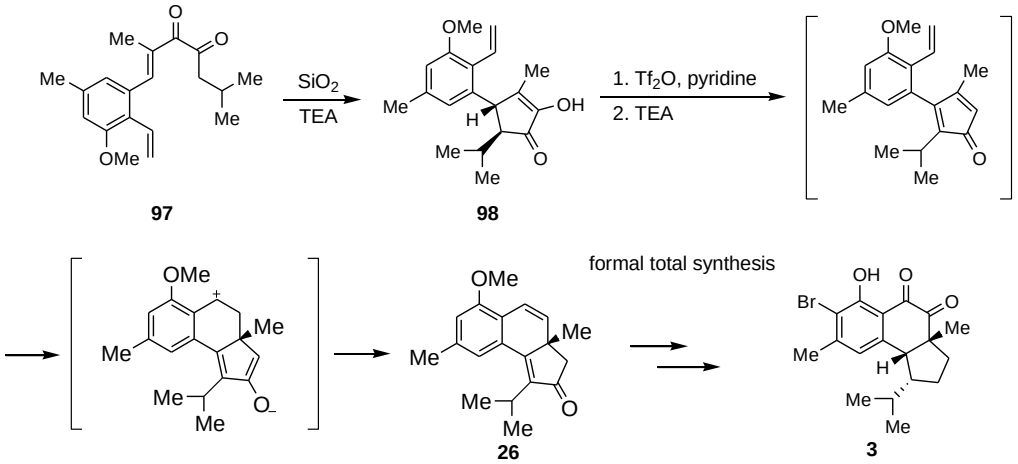
Scheme 10



2.2.2 Initial Synthetic Plan

Since the natural product hamigeran B has the aromatic ring fused [4.3.0] bicycle substructure, we thought this new methodology was perfect to synthesize hamigeran B. Since the Clive group had published their total synthesis of hamigeran B, using enone **26** as an intermediate, our initial efforts were focused on synthesizing **26** to realize a formal total synthesis.

Scheme 11



Retrosynthetic analysis revealed that **26** might be derived from a 2-hydroxycyclopentenone **98** via cyclopentadienone **99** as a reactive intermediate through

the electrocyclization reaction. Furthermore, **98** can be synthesized via a Tius-Nazarov cyclization reaction from the 1,2-diketone **97** (Scheme 11).[14, 15]

2.2.3 Preparation of 2-Hydroxycyclopentenone

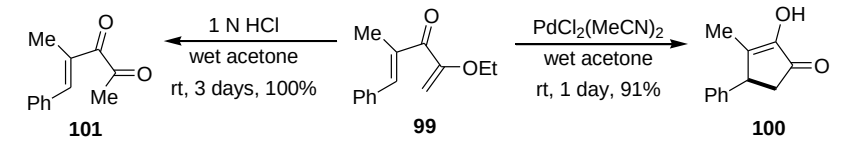
Based on the proposed synthetic route, making **98** would be the required for testing the electrocyclization reaction. Tius had pioneered the use of α-diketones and α-alkoxydienones as starting material for the Nazarov cyclization (Scheme 12). From their studies, α-ethoxydienone **99** readily underwent Nazarov cyclization in the presence of bis(acetonitrile)dichloropalladium(II) in wet acetone at room temperature. The possibility that the reaction was a Michael addition was considered unlikely, since the 5-*endo-trig* cyclization was not possible due to the poor orbital overlap. They also did a control experiment to rule out HCl serving as the catalyst. Formally, treatment of **99** with HCl led to the hydrolysis product **101** quantitatively. Moreover, they discovered a Nazarov cyclization of α-diketones such as **102** with the Lewis acid ytterbium(III) triflate, silica gel, or lithium tetramethylpiperidide (Scheme 11). We wanted to use this chemistry in the synthesis of **98**, since it is potentially the product of Nazarov cyclization of diketone **97**, α-siloxydienone or α-ethoxydienone (Scheme 12).

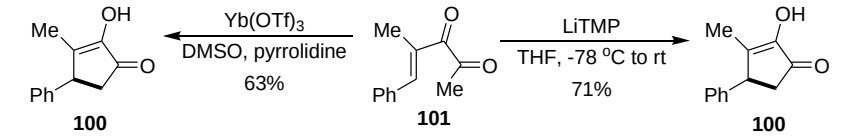
A variety of approaches to the synthesis of α-diketone **97** were considered, as shown in Scheme 13 and Scheme 14. In Scheme 13, the α-diketone **97** was envisioned to be assembled via an umplong approach from an electrophilic carbonyl component (acyl chloride, Weinreb's amide, N-acyl morpholine, etc.) and a nucleophilic carbonyl equivalent (dithiane, protected cyanohydrin, alkylvinyl ether, etc.). The vinyl group on

the aromatic ring can be installed via Pd-catalyzed coupling reaction. (Heck reaction, Suzuki coupling, Stille coupling, etc)

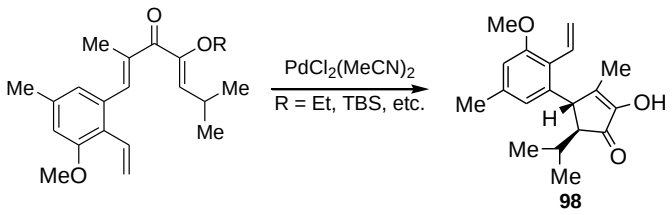
Scheme 12

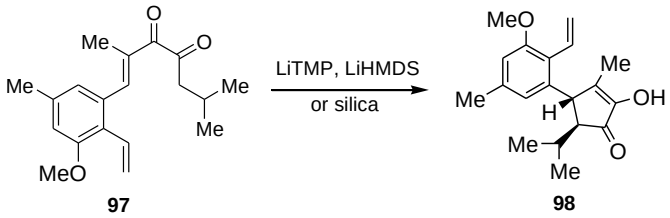
Tius' result:



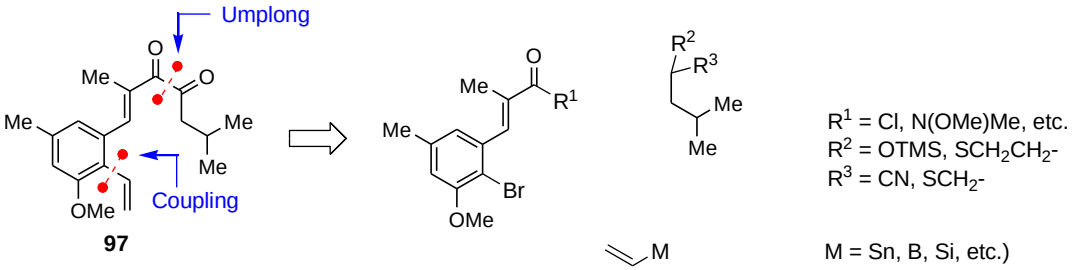


Proposed:



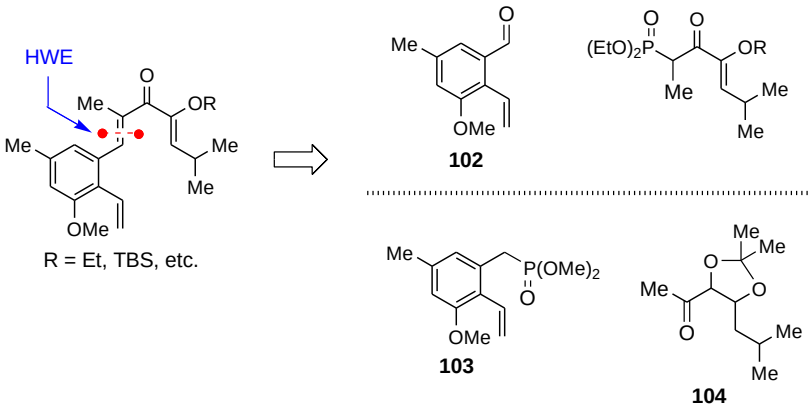


Scheme 13



In Scheme 14, α-siloxydienone or α-ethoxydienone was planned to be synthesized through HWE reaction, with either the aromatic part being the aldehyde coupling partner or being the phosphonate coupling partner.

Scheme 14

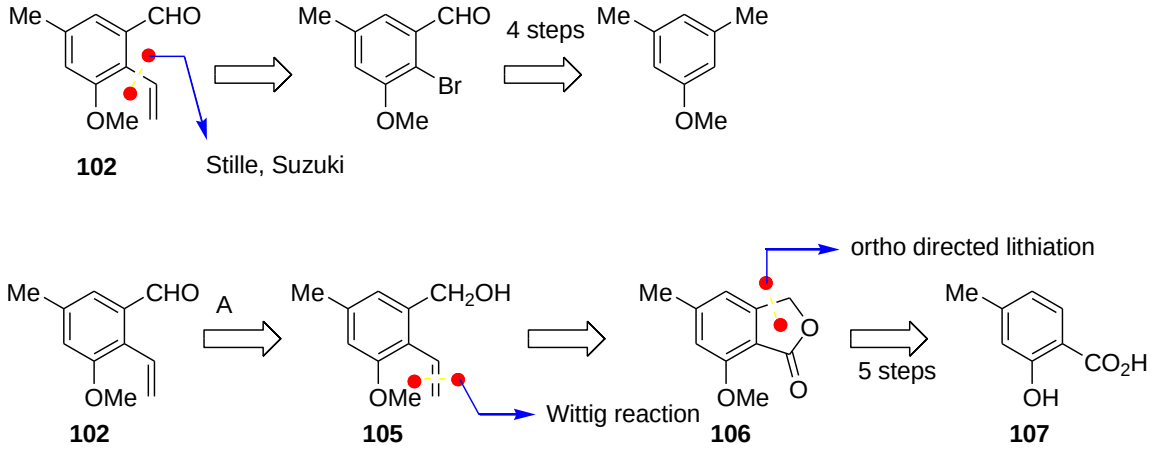


With many possible ways making the key intermediates **97** and its related derivatives, we identified the *ortho*-vinylbenzaldehyde being a versatile and important intermediate that can lead to many of the other possible starting materials. An efficient way of making large quantities of **102** would be crucial for the success of this project.

2.2.4 Preparation of Important Intermediate 102

Aldehyde **102** can be disassembled in at least two ways, as shown in Scheme 15. The vinyl group can be installed on the known *o*-bromobenzaldehyde via Stille coupling reaction with vinylstannanes or via Suzuki coupling reaction with vinylboronates. The alternative approach would be to form the vinyl group through Wittig reaction of a lactol intermediate generated from the known lactone **106**.

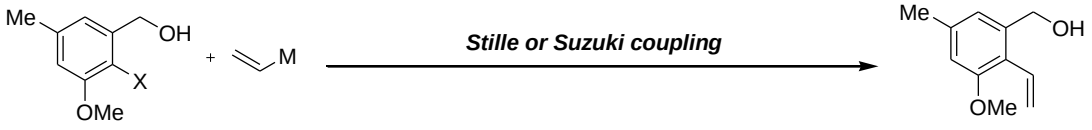
Scheme 15



2.2.4.1 Palladium-Catalyzed Coupling Reactions to 102

As shown in Table 1, (2-bromo-3-methoxy-5-methylphenyl)methanol reacted with tributylvinylstannane under standard Stille coupling condition to yield **105** in 23% yield, with 46% recovered starting material. (2-Iodo-3-methoxy-5-methylphenyl)methanol reacted with potassium vinyltrifluoroboronate under standard Suzuki coupling condition to generate **105** in 91% yield.

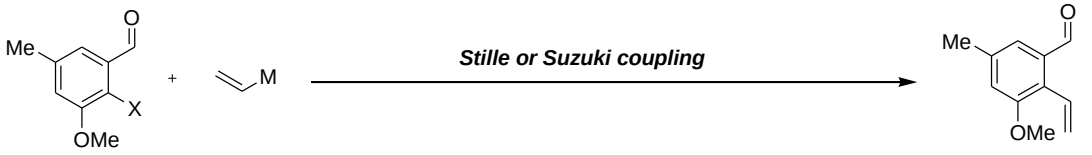
Table 1



M = $SnBu_3$, X = Br: 1.1 equiv,	1 mol% $Pd(Ph_3P)_2Cl_2$, 4 mol% Ph_3P, 1.5 equiv CsF, Toluene (0.12 M), 100°C, 18 h,	23% with 46% recovered SM
M = BF_3K, X = I: 1 equiv,	2 mol% $Pd(OAc)_2$, 6 mol% Ph_3P, 3 equiv Cs_2CO_3, THF/H_2O = 9:1(0.2 M), 90°C, 16.5 h,	91%

Starting with the known 2-bromo-3-methoxy-5-methylbenzaldehyde, Stille coupling yielded the vinylated product **102** in 82% yield; Suzuki reaction gave **102** in 51% yield. Using 2-iodo-3-methoxy-5-methyl-benzaldehyde as starting material, Stille reaction provided **102** in higher yield (74%, 78%) than Suzuki reaction (69%) (Table 2).

Table 2



102

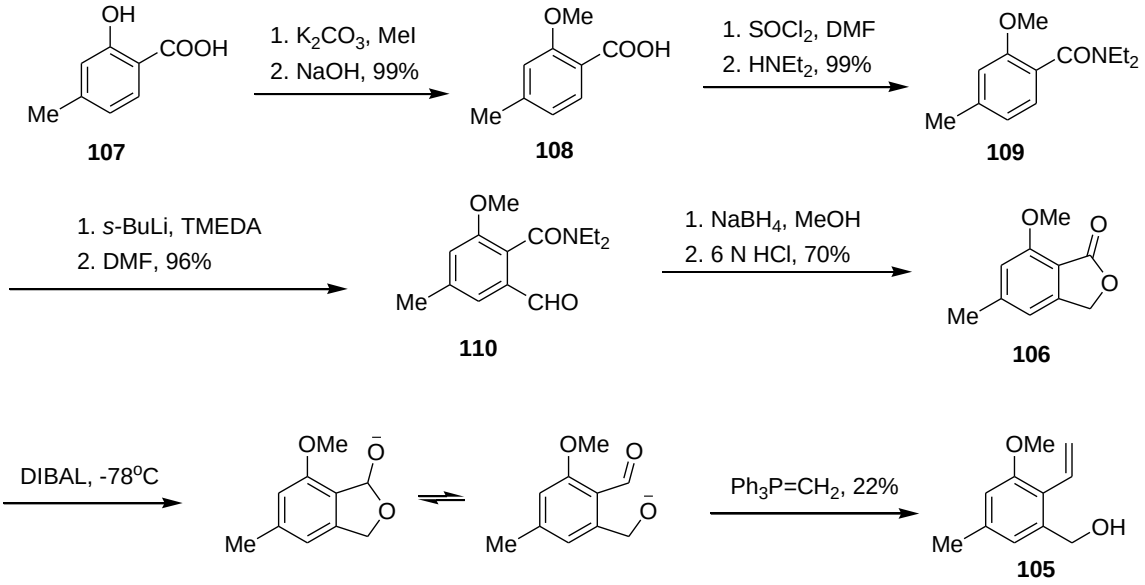
M = $SnBu_3$, X = Br: 1.1 equiv,	1 mol% $Pd(Ph_3P)_2Cl_2$, 4 mol% Ph_3P, 1.5 equiv CsF, Toluene, 100°C, 6 h,	82%
M = $SnBu_3$, X = I: 1.1 equiv,	1 mol% $Pd(Ph_3P)_2Cl_2$, 4 mol% Ph_3P, 1.5 equiv CsF, Toluene (0.25 M), 90°C, 16 h,	78%
1 equiv,	0.2 mol% $Pd(Ph_3P)_2Cl_2$, 0.8 mol% Ph_3P, 1.5 equiv CsF, Toluene (0.25 M), 90°C, 10 h,	74%
M = BF_3K, X = Br: 1.5 equiv,	2 mol% $Pd(OAc)_2$, 6 mol% Ph_3P, 3 equiv Cs_2CO_3, THF/H_2O = 9:1, microwave, 45°C, 30 min; 75°C, 60 min,	SM:P = 2:1
2 equiv,	2 mol% $Pd(OAc)_2$, 6 mol% Ph_3P, 3 equiv Cs_2CO_3 THF/H_2O = 9:1, seal tube, 85°C, 21 h,	51%
M = BF_3K, X = I: 1 equiv,	2 mol% $Pd(OAc)_2$, 6 mol% Ph_3P, 3 equiv Cs_2CO_3, THF/H_2O = 9:1(0.2 M), 90°C, 11 h,	69%

2.2.4.2 The Wittig Route to 102

The isobenzofuranone **106** was synthesized from 4-methylsalicylic acid **107** following Snider's protocol.[14] Double methylation of **107** and basic hydrolysis yielded acid **108** almost quantitatively. Amide **109** was obtained from acid **108** via the corresponding acyl chloride in almost quantitative yield. Directed lithiation by amide group generated an α-lithium benzamide that was trapped with *N*,*N*-dimethylformamide

to yield **120**. Reduction by sodium borohydride and acid-catalyzed lactonization led to **106** in 70% yield. Next, the isobenzofuranone **106** was reduced partially with diisobutyl aluminium hydride at -78 ^{o}C to the lactol. Treating the reaction mixture with Wittig reagent in the same pot generated the alcohol **105** in 22% yield (Scheme 16).

Scheme 16



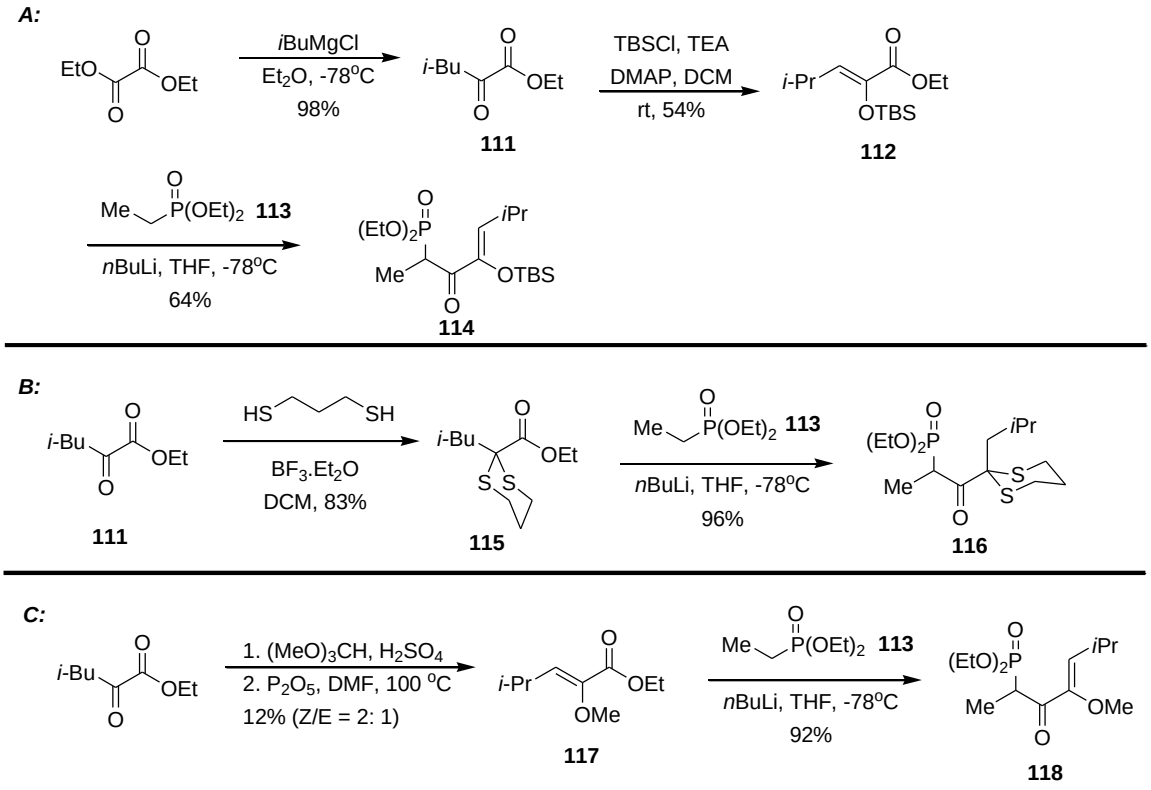
107 **108** **109** **110** **106** **105**

2.2.5 Preparation of Phosphonates for Olefination Reaction

As shown in Scheme 14, the HWE reaction requires the synthesis of phosphonate to react with the aldehyde **102**. Scheme 17 summarizes three routes to synthesize three different phosphonates from ethyl oxalate. In the first step, reacting the diethyl oxalate with isobutyl magnesium chloride at -78 ^{o}C generated the ketoester **111**. The second step of route A involved trapping the enol with a TBS group, giving only the *Z*-silyl enol ether **112**; the second step of route B consists of converting the carbonyl group to dithiane **115**, with BF_3 as Lewis acid catalyst; route C protected the carbonyl group as methyl vinyl

ether **117**. The last step was to install the phosphonate by an acylation reaction (Scheme 17).

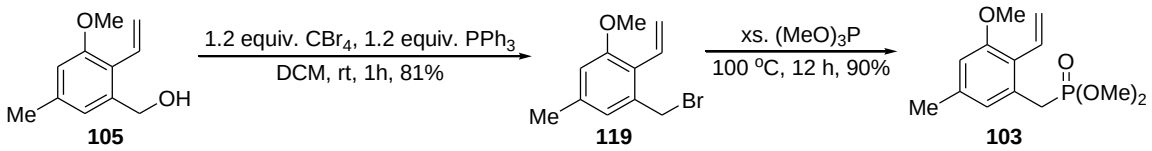
Scheme 17



2.2.6 Preparation of Methylphosphonate 103

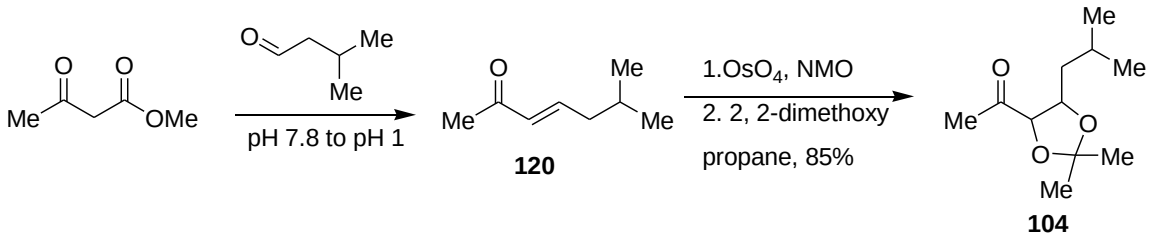
Bromination of alcohol **105** with tetrabromomethane and triphenylphosphine yielded benzyl bromide **119** in 81% yield. Methylphosphonate **103** was synthesized from **108** via a nucleophilic substitution with trimethyl phosphite (Scheme 18).

Scheme 18



The other coupling partner ketone **104** was prepared from (*E*)-5-methylhex-3-en-2-one **120** by dihydroxylation with osmium oxide and N-methyl morpholine N-oxide, and ketal formation with 2,2-dimethoxy propane in 85% yield. (*E*)-5-Methylhex-3-en-2-one **120** was made following Ragoussis' procedure for regioselective aldol condensation between methyl 3-oxobutanoate and isovaleraldehdye (Scheme 19) .[15]

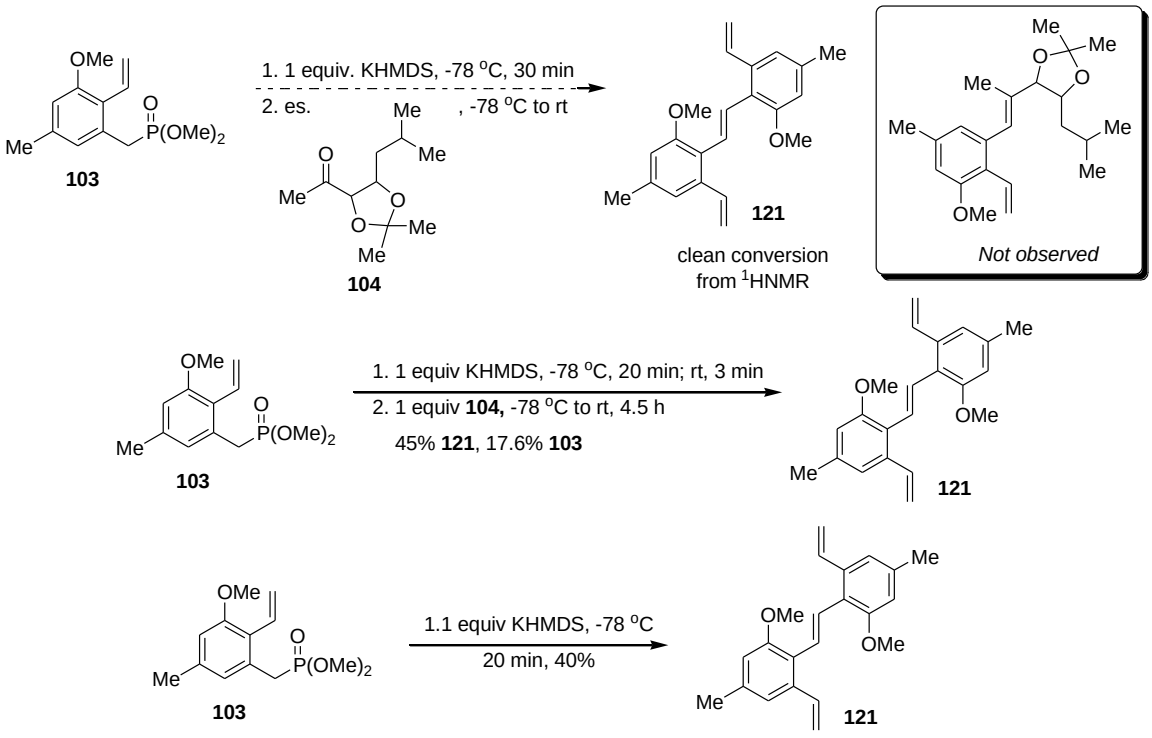
Scheme 19



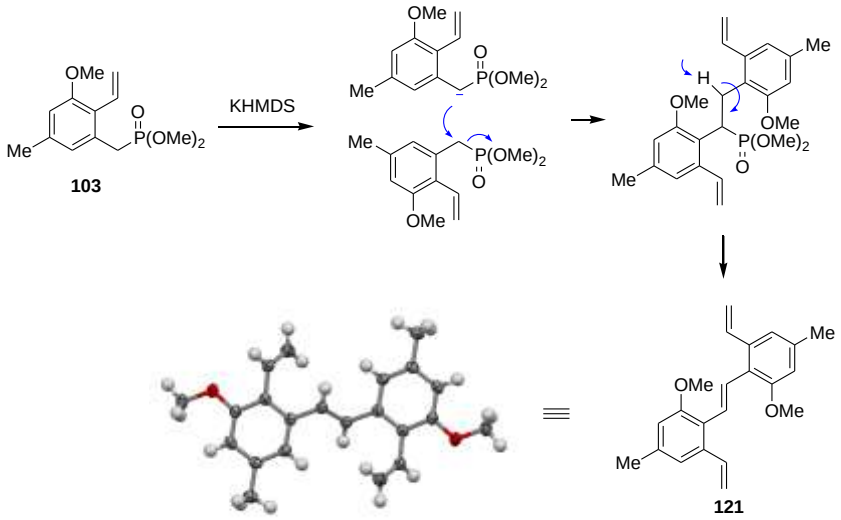
Next, the proposed olefination reaction was carried out. The solution of phosphonate **103** in THF was added with 1 equivalent of KHMDS (0.5 M in toluene) slowly. After 30 min at -78 ^{o}C, about two equivalents of the ketone **104** was added. The reaction mixture was allowed to rise to rt and quenched with water. However, the desired olefination product was not observed from the crude ^{1}H-NMR (Scheme 20). (*E*)-Stilbene **121** was formed cleanly from the analysis of crude ^{1}H-NMR. The structure of **121** was unambiguously confirmed by X-ray crystallography. It was repeated to get 45% of

stilbene with 17.6% of recovered phosphonate starting material. (*E*)-Stilbene **121** was formed exclusively when phosphonate **103** was treated with potassium hexamethyldisilazide at -78 ^{o}C for 20 minutes. Though the crude ^{1}H-NMR for this reaction was very clean, the isolated yield of stilbene **121** was 40% in this case. This is a rare example of stilbene formation from a phosphonate. If the reaction is general, it could provide an alternative for generation of stilbenes otherwise difficult to make. We proposed a possible mechanism for this transformation (Scheme 21). After the deprotonation of phosphonate **103** with KHMDS, the carbanion attacked another phosphonate fast enough to generate a new phosphonate. After elimination under basic conditions, the (*E*)-stilbene **121** was formed.

Scheme 20



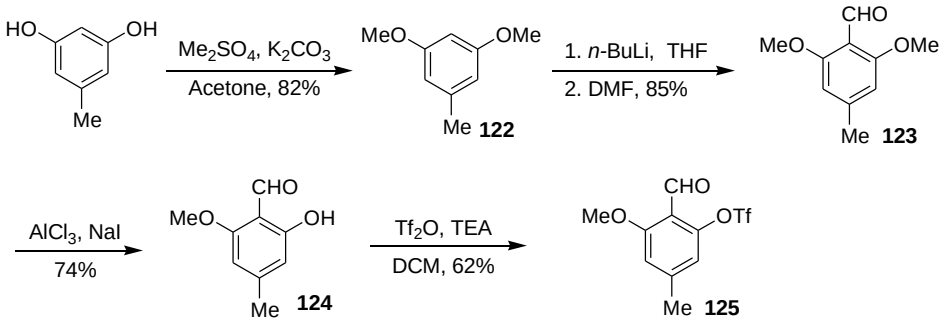
Scheme 21



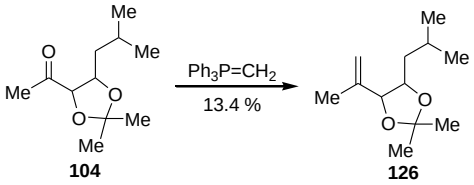
2.2.7 Heck Coupling Route to 97

Starting from orcinol, salicylic acid **124** was prepared according to Bräse's protocol.[18] The salicylic acid **124** was treated with triflic anhydride and triethylamine to yield the triflate **125** (Scheme 22). Ketone **104** was reacted with Wittig reagent to produce the disubstituted alkene **126** in low yield, a result caused by the volatility of this compound (Scheme 23).

Scheme 22

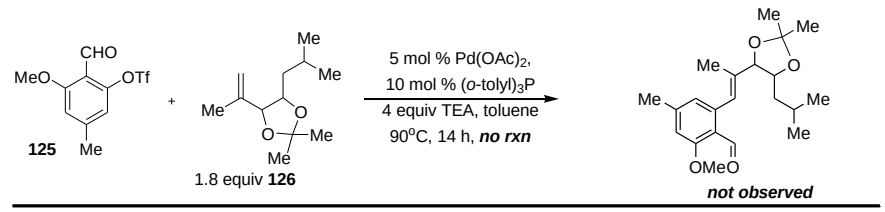


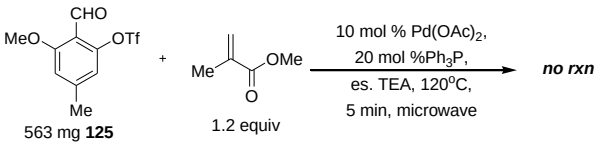
Scheme 23

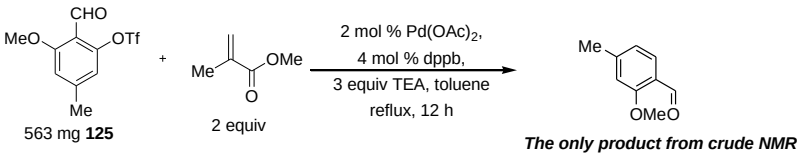


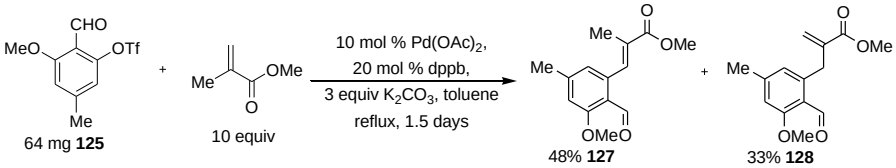
The Heck coupling reaction between triflate **125** and alkene **126** was tried but no coupling product was formed. Due to the low yield of alkene **126**, methyl methacrylate was used as the coupling partner for the Heck reaction. While, $Pd(OAc)_2$ with triphenyl-phosphine as ligand in triethylamine resulted in no converstion under microwave

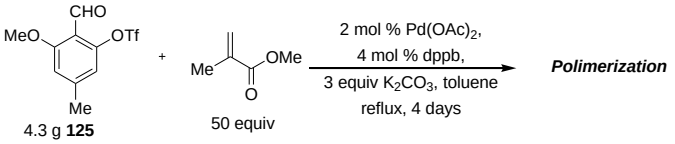
Scheme 24









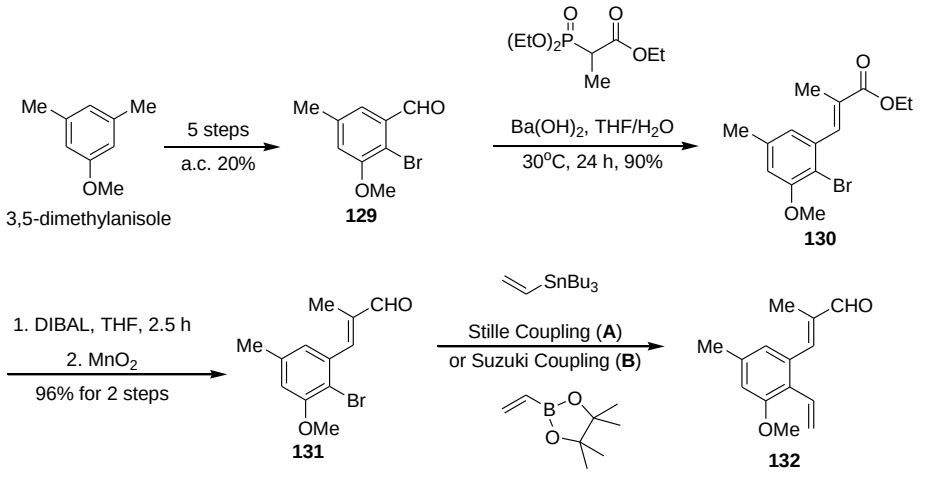


conditions, switching to dppb as ligand generated the detriflated benzaldehyde only from the analysis of crude proton NMR. The triflate **125** did react with methyl methacrylate to yield a mixture of two isomeric products in 48% and 33% yield (Scheme 24). However, this reaction failed when it was scaled up to 4.3 grams scale, due to the polymerization of methacrylate under the conditions.

2.2.8 Preparation of α-Hydroxyl Cyclopentenone

Finally, vinylation of *o*-bromo-α-methyl cinnamaldehyde was explored, generating excellent yields of the vinylated product. This working protocol was one of the earliest to be explored, since **129** was also the starting material used for the total synthesis of pseudopteroxazole. HWE reaction with triethyl 2-phosphonopropionate yielded the *o*-bromo-α-methylcinnamate **130** cleanly with complete (*E*)-selectivity. Reduction with DIBAL and allylic oxidation with manganese(IV) oxide led to the *o*-bromo-α-methylcinnamaldehyde **131** in very good yield. Very gratifyingly, both of the Suzuki and Stille coupling produced the vinylated α-methylcinnamaldehyde **132** in good yield (Scheme 25).

Scheme 25



Having the aldehyde **132** in hand, it was added to a solution of lithiated dithiane solution that was generated from 2-isobutyl-1,3-dithiane with *n*-butyl lithium at -20 ^{o}C. The crude mixture was hydrolyzed with mercury oxide and boron trifluoride-etherate to yield the hydroxyketone **134**, which was oxidized with IBX to generate α-diketone **97** in 83% yield (Scheme 26). α-Diketone **97** was treated with strong non-nucleophilic bases, lithium hexamethyldisilazide, lithium tetramethylpiperidide, and potassium hexamethyldisilazide (Table 3). Up to 71% yield of the desired product was obtained under optimized conditions. It also seemed that the acidification step during workup may contribute to the higher yield, since the ^{1}H-NMR of the crude product was consistently clean.

Scheme 26

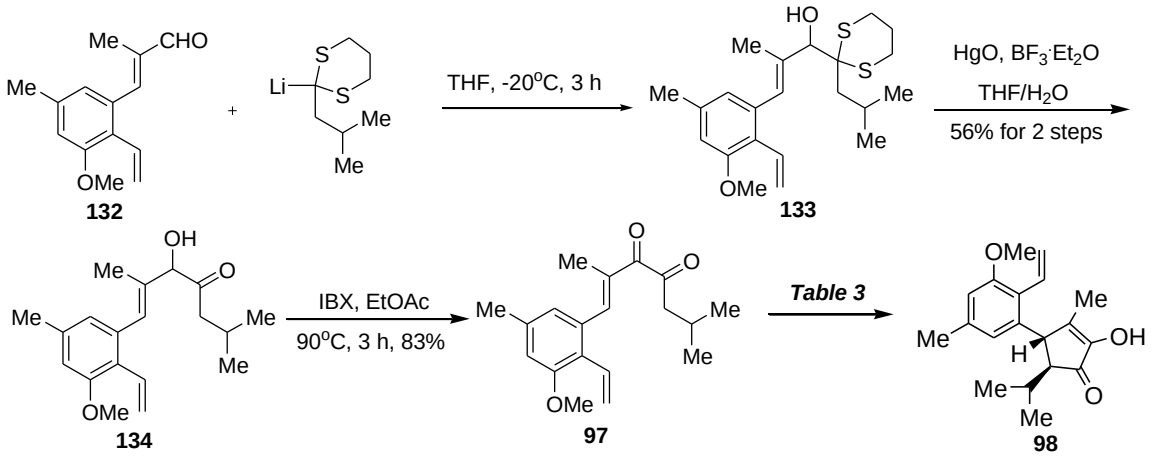


Table 3

97 **98**

Entry	
1	1.2 equiv LiTMP, THF, -78^{o}C to rt, 28 h, 59%
2	1.1 equiv LiHMDS, THF, -78^{o}C to rt, 21 h, 42%
3	1.2 equiv LiHMDS (0.24M in THF), THF, -78^{o}C to rt, 18 h, 44%
4	1.5 equiv LiHMDS (0.8M in THF), THF, -78^{o}C slowly to rt, 2 days, 71%
5	1.4 equiv LiHMDS (0.9M in THF), THF(0.1 M), -78^{o}C slowly to rt, 1 days, 64%

2.2.9 The Dead End and the Detour

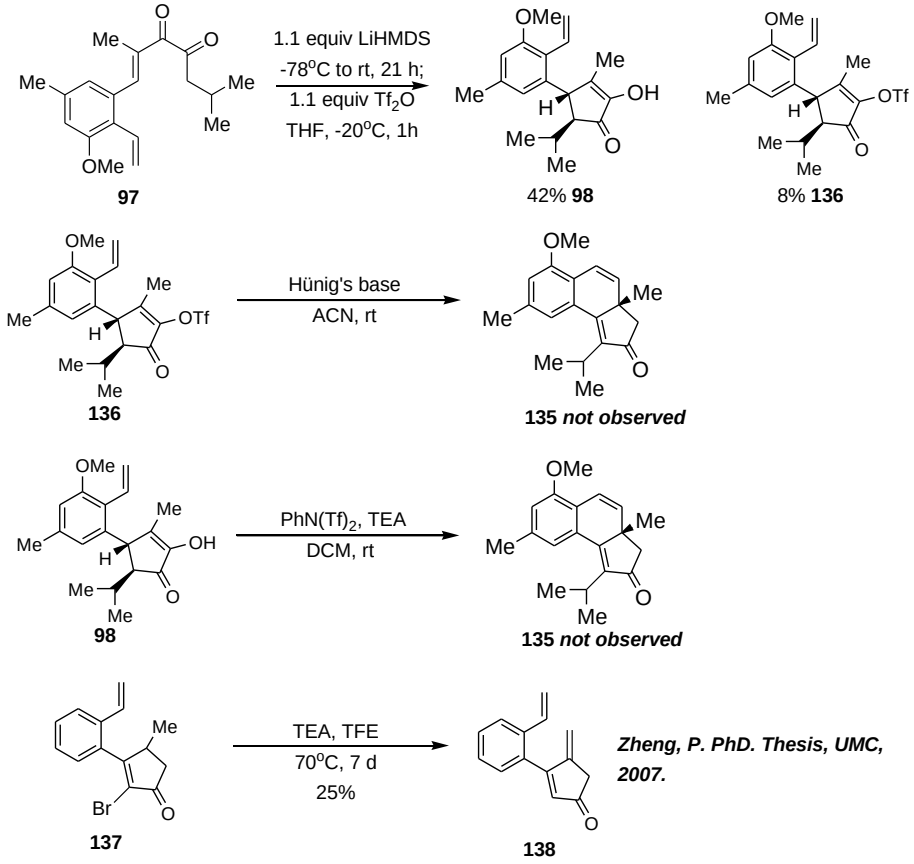
At this stage of synthesis, we were ready to try the key electrocyclization reaction on this α-hydroxycyclopentenone **98**.

2.2.9.1 The Key Reaction Did Not Go

Trapping the Tius-Nazarov cyclization product with triflic anhydride produced the triflate **136** in an 8% yield. Next, the triflate **136** was dissolved in acetonitrile and treated with Hünig's base, producing no desired product **135**. The crude ^{1}H-NMR showed only a mess. Treating α-hydroxycyclopentenone **98** with $PhN(Tf)_2$ and triethylamine in dichloromethane yielded a mess from the crude NMR too. The negative results were not

too surprising, since a β-substituted α-bromocyclopentenone (**137**) failed to undergo the electrocyclization too, yielding only the elimination product **138**.[16]

Scheme 27



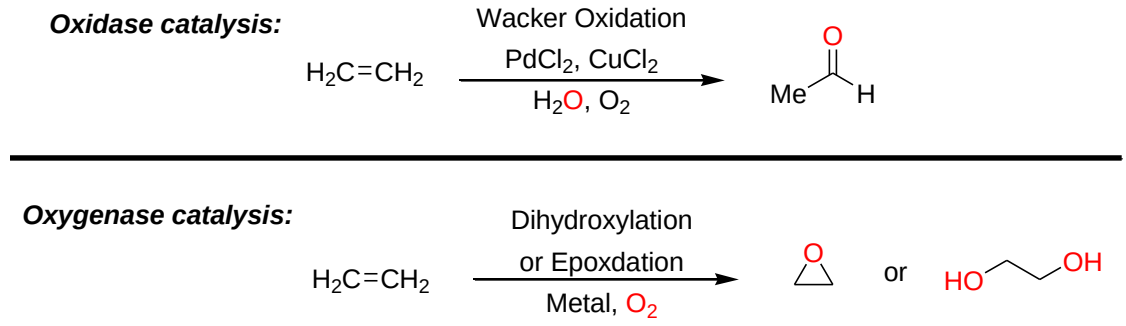
2.2.9.2 Wacker-type Oxidative Carbocyclization

Based on the above results, we decided to abandon the use of the electrocyclization method to construct the six-membered ring. Instead, we used this opportunity to invent new tactics, since there was no reported literature about this specific type of transformation. This also presents a common occurrence in the total synthesis, which requires discovery and development of new methodologies.

2.2.9.2.1 Wacker and Wacker-type Oxidations

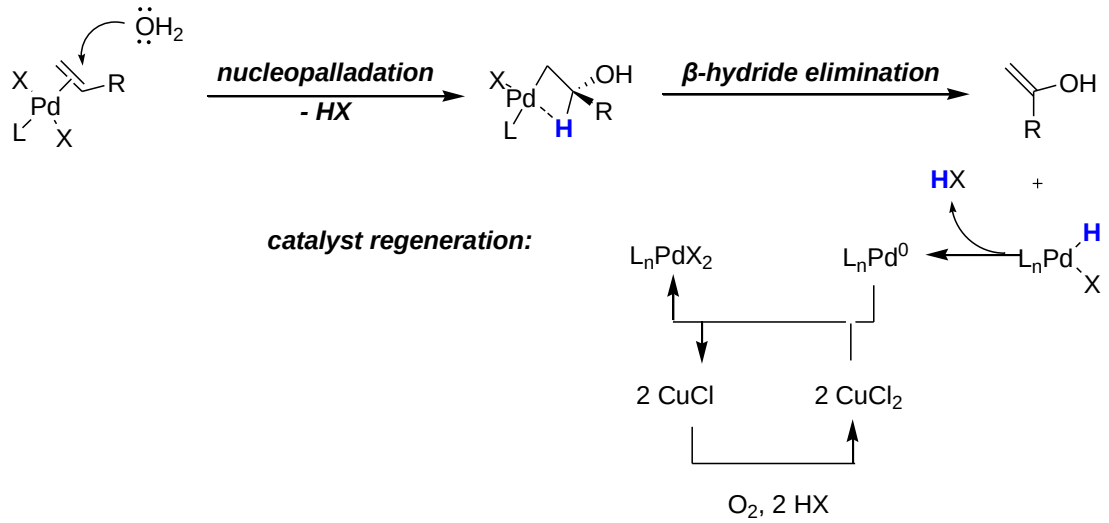
Using oxygen as an oxidant, nature evolved oxidase and oxygenase enzymes such as cytochrome P450 for oxidizing small organic molecules. In the world of organic synthesis, the Wacker oxidation uses oxygen as the ultimate oxidant too (Scheme 28). Though there was a review published after we overcame this obstacle, covering all kinds of "addition of metal enolate derivatives to unactivated carbon carbon multi-bonds",[20] we were specifically interested in a Wacker-type oxidative process for two reasons: the efficiency of Wacker oxidation has been proved for long time, though the mechanism is still under debate, and the process is relatively green and biomimetic, using molecular oxygen as oxidant rather than stoichiometric amount of metals or organic oxidants.

Scheme 28



The mechanism of Wacker oxidation generally is considered to include the activation of the alkene by the Lewis acidic palladium(II). A water molecule then attacks the activated alkene, followed by a facile β-hydride elimination. The palladium catalyst is regenerated by the copper salt, which is oxidized by oxygen ultimately (Scheme 29).

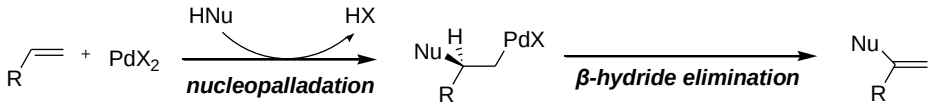
Scheme 29

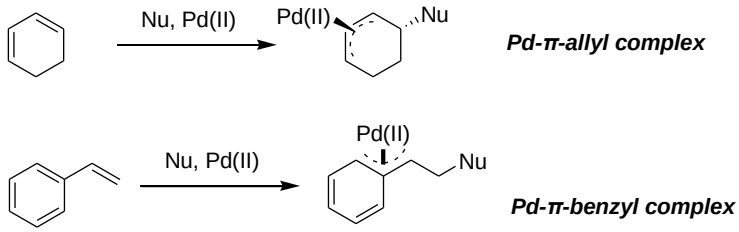


More recently, Wacker-type reactions using palladium(II) as a Lewis acid to activate alkenes and nucleophiles to form Pd-π-allyl complex or Pd-π-benzyl complex were developed (Scheme 30).[21]

Scheme 30

Wacker-type reactions:



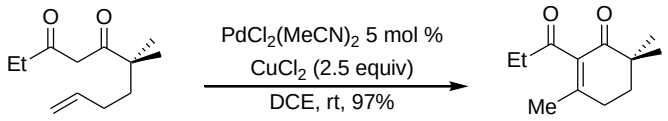


The work of Widenhoefer concerning nucleophilic addition of β-diketones to "unactivated" double bonds was found to be most similar to the Wacker-type oxidative

alkylation of an α-hydroxyenone with an adjacent vinyl group. It provided us a strong reason to try their conditions, based on the similar mechanisms of the two processes.[22, 23] Yang's work on β-ketoamides was also inspiring (Scheme 31).[24]

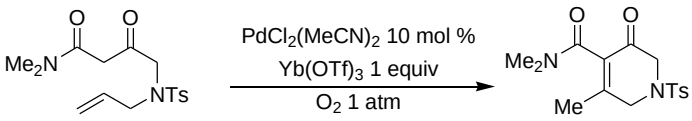
Scheme 31

Widenhoefer's intramolecular oxidative alkylation:



139 **140**

Yang's aerobic oxidative cyclization:

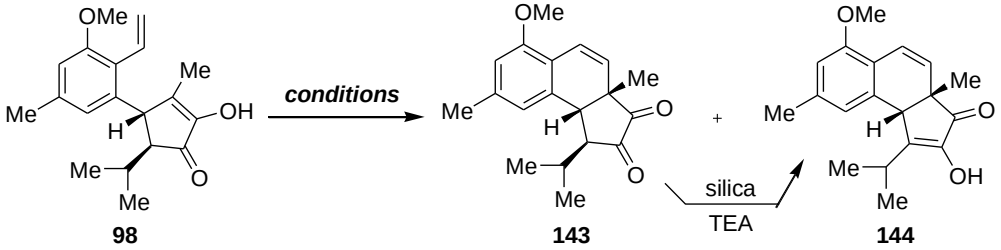


141 **142**

2.2.9.2.2 Pd(II) Catalyzed Oxidative 6-*endo*-*trig* Carbocyclization

We were really excited by the preliminary results on this reaction. With 0.3 equivalent of $PdCl_2(MeCN)_2$, the product to starting material ratio was 0.6 to 1 from the crude proton NMR (Table 4, entry 1). Using THF as solvent enabled the reaction to happen at room temperature (Table 4, entry 2). Further optimization indicated that oxygen gas is superior to air as the oxidant, and prolonged reaction time led quantitative yield of the enol ketone **144** after tautomerization with catalytic amount of silica and TEA (Table 4, entry 6).

Table 4



98 **143** **144**

Entry	*$PdCl_2(CH_3CN)_2$*	*CuI(mol %)*	*Oxidant*	*Solvent*	*Temp*	*Time*	*yield*
1	30 mol %			dioxane	40°C	30 min	SM/P = 1: 0.6
2	1 equiv			THF(0.01M)	rt	over night	66%[c]
3	(1 + 2) mol %[a]	1.5	O_2	THF(0.05M)	rt	48 h	87%[c]
4	10 mol %	15	air	THF(0.1M)	rt to 65°C	17 h	66%[c]
5	3.6 mol %	28[b]	O_2	DMF(0.05M)	rt	1 week	no rxn
6	4.3 mol %	5	O_2	THF(0.05M)	rt	1 week	100%[d]

[a] 2 mol % of catalyst was added one day after the addition of first 1 mol % of catalyst.

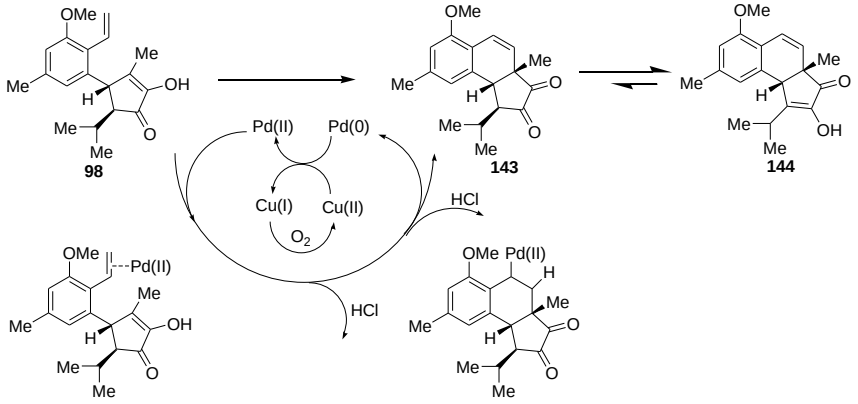
[b] CuCl was used instead of CuI.

[c] Products were mixture of two epimers.

[d] This is isolated two step yield, after epimerization to enone ketone.

We proposed a simplified mechanism for this reaction (Scheme 32). The Lewis acidic palladium(II) coordinates and activates the vinyl group. Then the adjacent nucleophilic enol attacks the electrophilic vinyl palladium complex. This is followed by β-hydride elimination, leading to the product **143**, which could be tautomerized to the more stable enol ketone **144**. The catalyst was regenerated with oxidation of Cu(II), which in turn was regenerated by oxygen.

Scheme 32

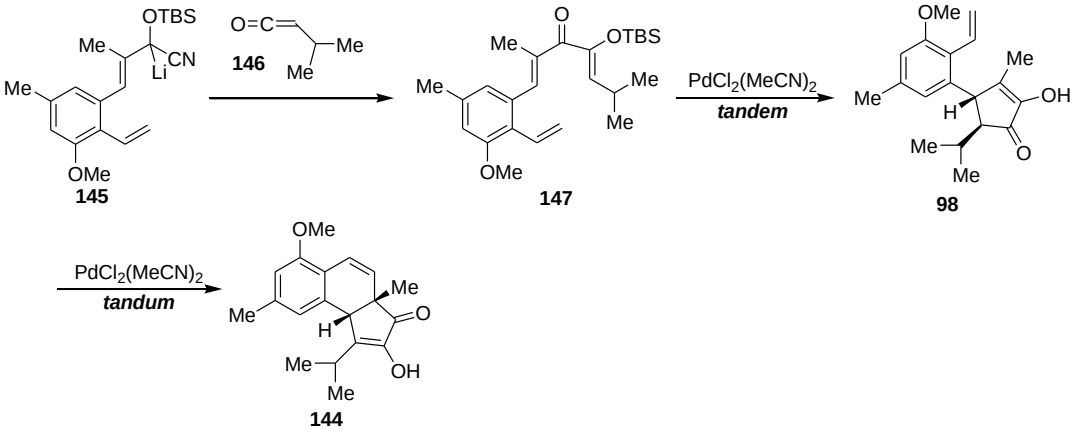


2.2.10 Attempts for Tandem Reactions

Having a working reaction for the carbocyclization available, we envisioned making this synthetic sequence more efficient and attractive by designing tandem reactions for the key cyclization steps. As shown in Scheme 33, treating the lithiated TBS cyanohydrin **145** with ketene **146** would generate the dienone **147**. Based on Tius' results on Nazarov cyclization and our result on Wacker-type oxidative carbocyclization, the benzene-fused [4.3.0] bicyclic compound **144** would be produced by the same catalyst: $PdCl_2(MeCN)_2$.

Scheme 33

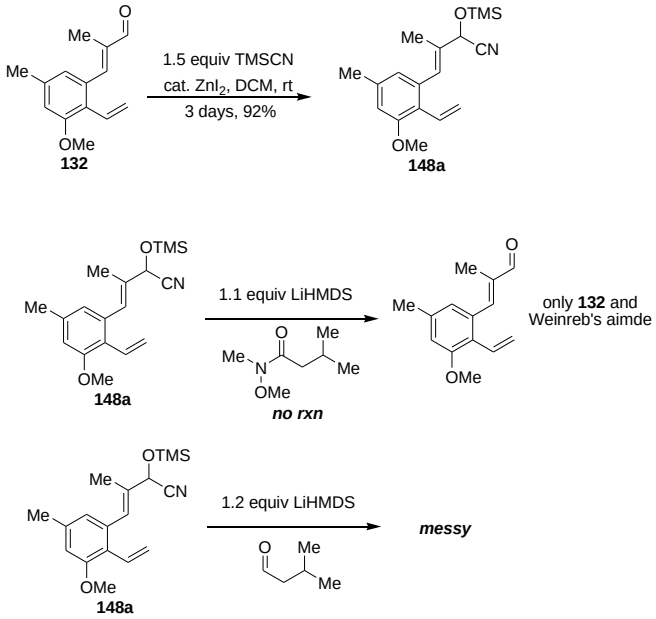
proposed tandem 1,2-addition and Nazarov cyclization:



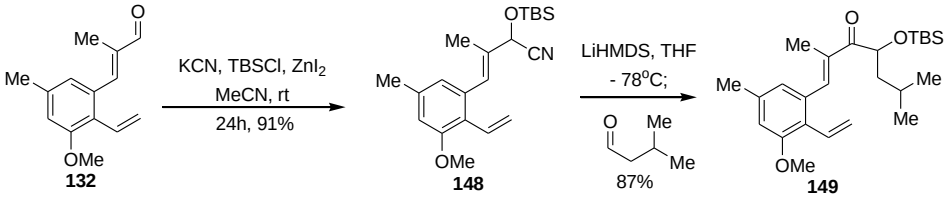
To try this idea out, the preparation of the TMS-protected cyanohydrin was attempted first, generating 92% of the crude **148a**. However, the product **148a** was too labile and decomposed back to the starting material on silica and alumina columns. After passing the crude material through a short pack of silica gel, **148a** was deprotonated with LiHMDS in THF at low temperature and trapped with isovaleraldehyde and the corresponding amide, leading to a complex mixture (Scheme 34).

Then, the TBS-protected cyanohydrin **148** was prepared directly from the vinylated cinnamaldehyde **132** with KCN, TBSCl and catalytic amount of ZnI_2 in 91% yield (Scheme 35). The dimerization of ketene **146** was too facile. And the attempted reactions for making it yielded only the dimer. Treating the deprotonated TBS-protected cyanohydrin **148** with isovaleraldehyde led to ketone **149** (Scheme 35). Oxidation of ketone **149** to dienone **150** would produce the same starting material for trying the palladium-catalyzed tandem reaction (Scheme 36). However, Saegusa oxidation and IBX oxidation did not yield the desired dienone.

Scheme 34

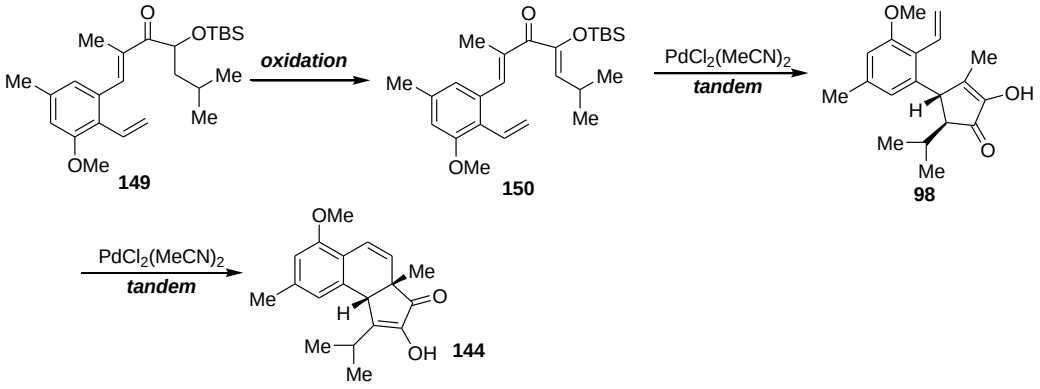


Scheme 35



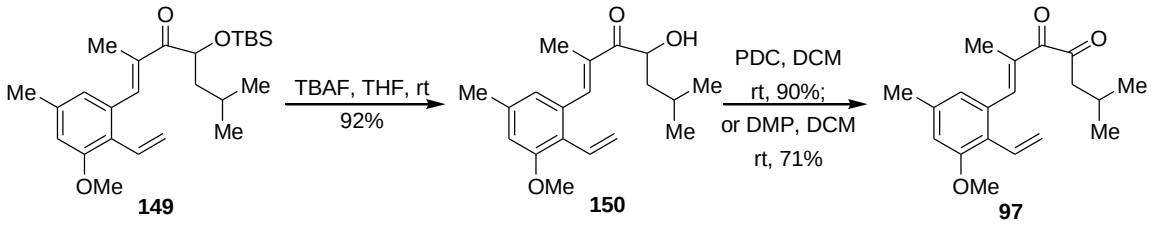
Scheme 36

proposed tandem Nazarov cyclization and Wacker-type oxidative cyclization:



Finally, the ketone **149** was deprotected with TBAF to generate the α-hydroxyketone **150**, which then was oxidized with pyridinium dichlorochromate or Dess-Martin periodinane to yield the α-diketone **97** in good yields (Scheme 37).[25]

Scheme 37



2.2.11 An Interrupted Nazarov Cyclization

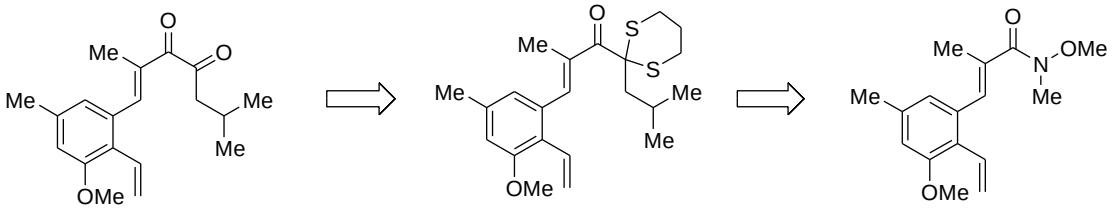
The Nazarov cyclization has been developed for decades. It has been applied in the total synthesis of natural products beautifully. Also known is the interrupted Nazarov cyclization, the trapping of the oxocarbenium intermediate with nucleophiles, such as aromatic rings, alkenes, or dienes.

During our study of making the α-diketone **97**, we discovered a rare stable hydrolysis intermediate of a dithiane, which upon treating with Lewis acids or Brønsted acids, underwent an interesting interrupted Nazarov cyclization.

It is well known that Weinreb's amide gives ketones when reacted with organolithium or Grignard's reagents. α-Diketone **97** could theoretically be synthesized from a Weinreb's amide **152** through a dithiane intermediate **151** (Scheme 38).

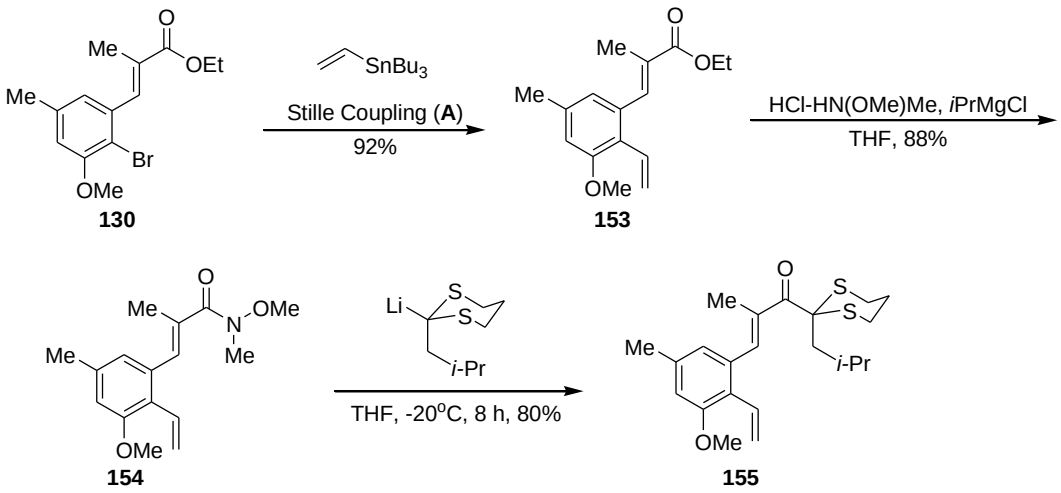
Scheme 38

the retrosynthesis of diketone from Weinreb's aimde:



Starting from the *o*-bromo-α-methacinnamate **130**, Stille coupling yielded the ethyl ester **153** in 92% yield. The ester was converted to Weinreb's amide **154** with *N*,*O*-dimethyl-*N*-hydroxyl amine hydrochloride and isopropyl magnesium chloride in 88% yield. The lithiated dithiane added to the amide to yield the dithiane **155** in 80% yield (Scheme 39).

Scheme 39



A: 1.5 equiv tributylvinyltin, 1 mol% $Pd(Ph_3P)_2Cl_2$, 4 mol% Ph_3P, 1.5 equiv CsF, toluene, (0.2 M) 110°C, 20 h, 92%

Many hydrolysis conditions known for converting dithianes to ketones were tried to hydrolyze the dithiane **155**. However, either no reaction happened or it gave a mess due to the decomposition of the α-diketone (Scheme 40, entry 1 to 4). From TLC, a significant new spot was detected only five minutes after adding NCS (Scheme 40, entry 5). It was estimated to be an intermediate of the hydrolysis of dithiane, based on the analysis of ^{1}H-NMR and ^{13}C-NMR. Changing the solvent to methanol and the base to 2,6-lutidine, the methyl sulfinate **156** was isolated in 86% yield (Scheme 40, entry 6). The structure of **156** was derived from ^{1}H-NMR, ^{13}C-NMR, DEPT135, COSY, high resolution mass spectrum and IR analysis. From HRMS, the observed mass 459.1636u (MNa^+) was consistent with a formula of $C_{23}H_{32}O_4S_2$. The IR showed a strong absorbent peak at 1642 cm^{-1}, indicating a conjugated carbonyl group. ^{13}C-NMR and DEPT135 showed one ketone's carbonyl group, six quaternary sp^2 hybridized carbons, five sp^2

hybridized CH, one sp^2 hydridized CH_2, five CH_3, three aliphatic CH_2, and one aliphatic CH (Figure 2 and 3). From ^{1}H-NMR, the diastereotopic hydrogens on the carbon next to sulfinate (p2 in Figure 4) were obviously observed based on the splitting pattern common to the diastereotopic hydrogens. Further, COSY showed the coupling between proton b and i1 (Figure 5); v1, v2, and v3 were from the vinyl group (Figure 6); p1, p2, and p3 from the propylene group (not shown here).

Figure 2. ^{13}C-NMR of **156**

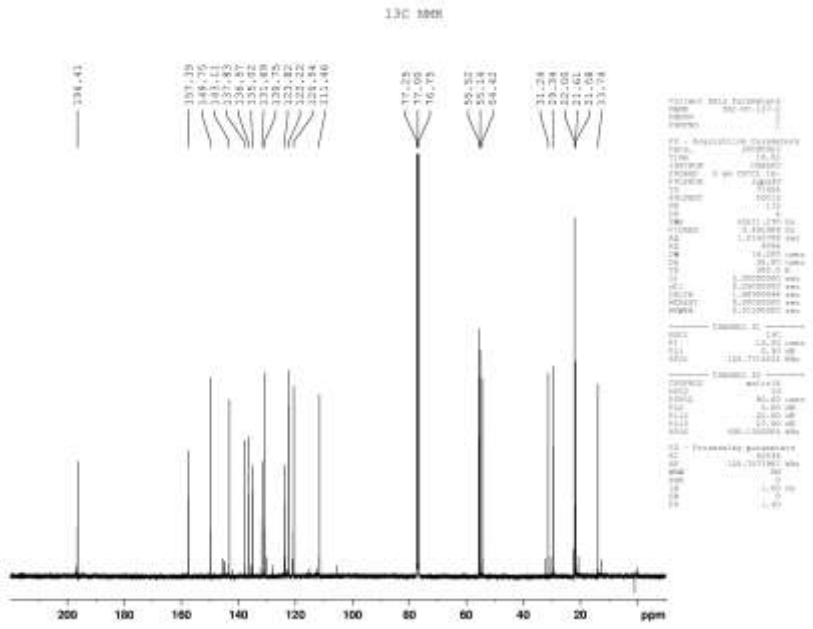


Figure 3. DEPT135 of **156**.

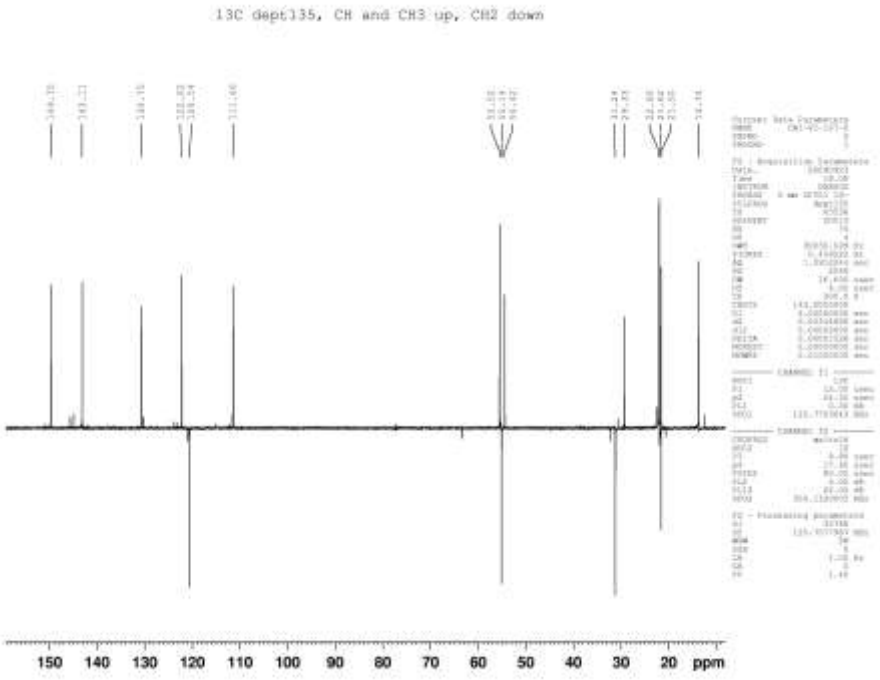


Figure 4. ^{1}H-NMR of **156**.

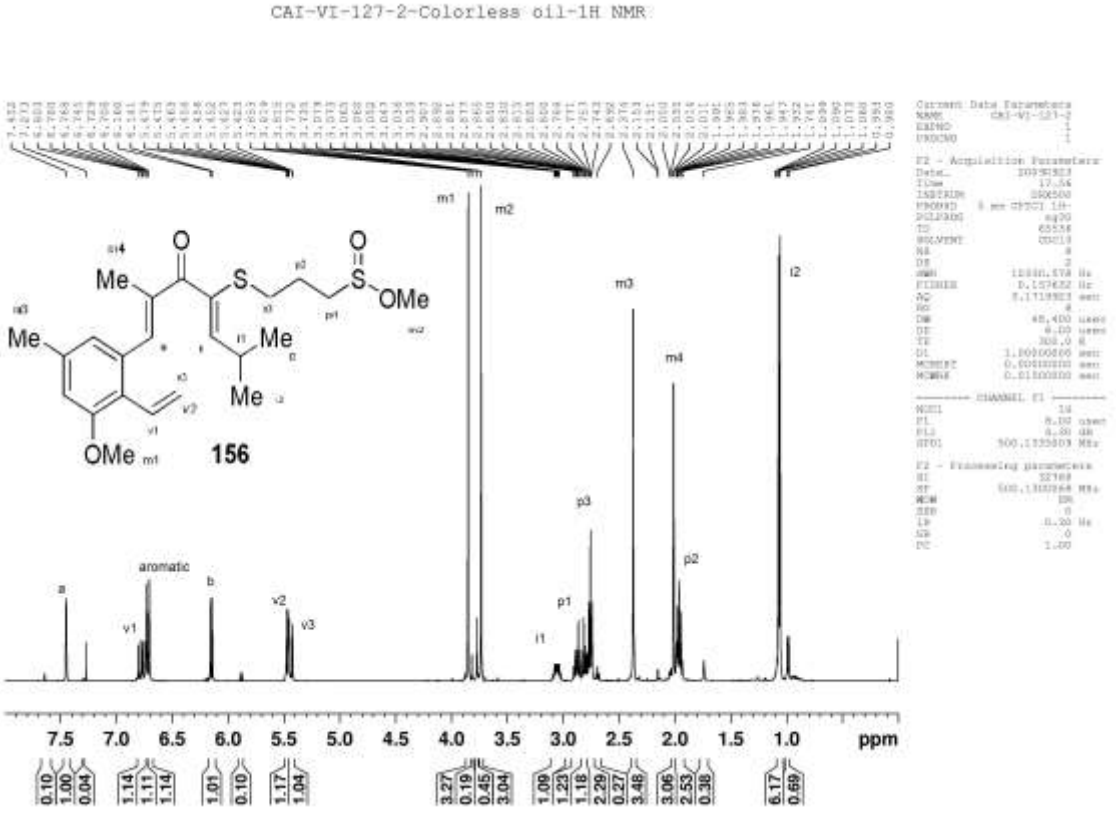


Figure 5. COSY showing b and i1.

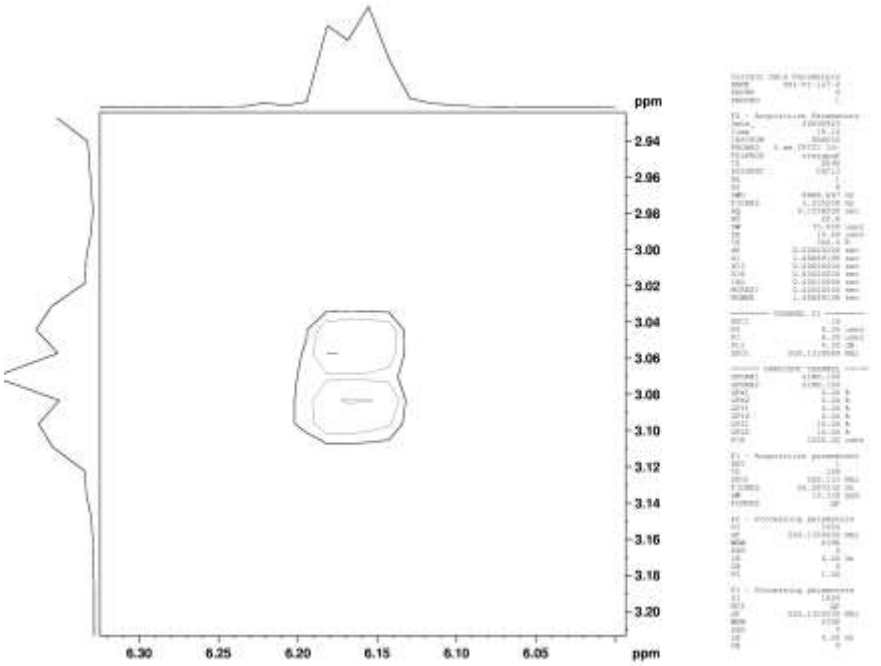
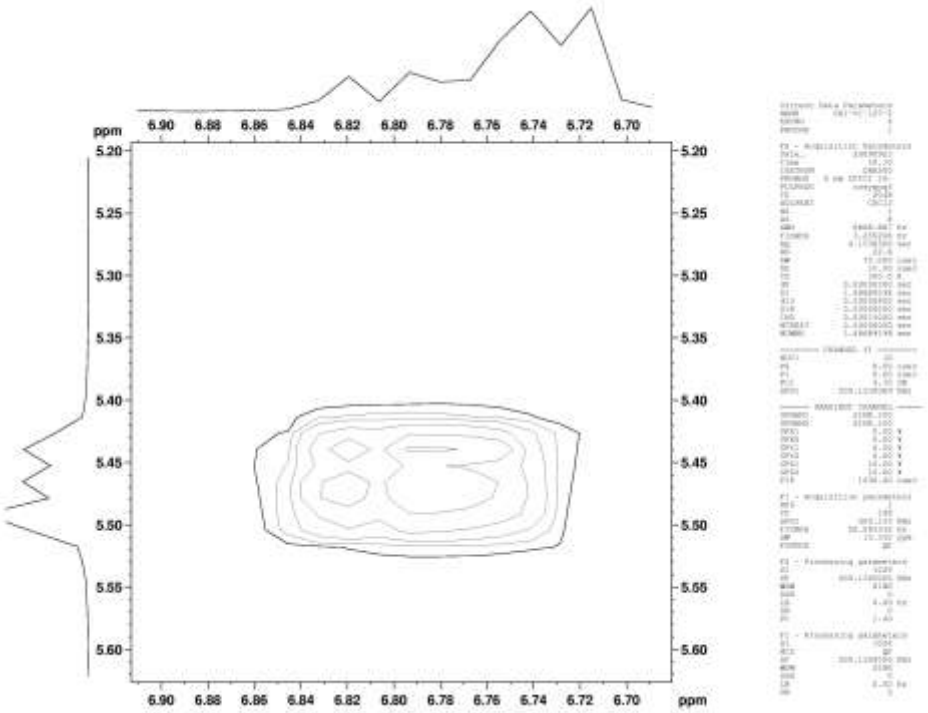
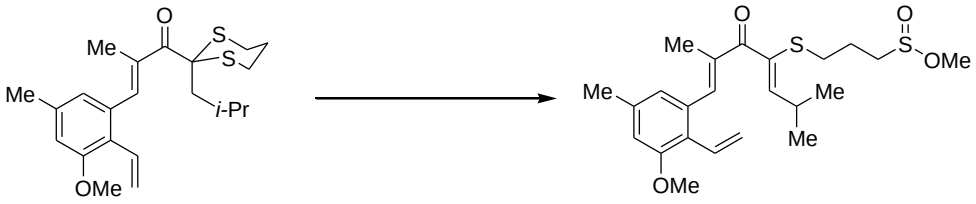


Figure 6. COSY showing the vinilic protons v1, v2, and v3.



Scheme 40



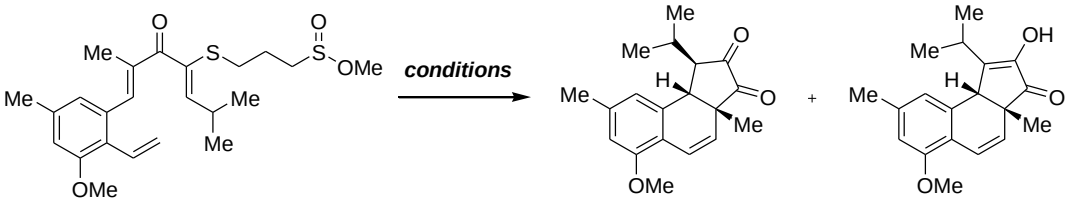
155 **156**

	Reagents	Solvents	Temperature	Product
1.	2.2 equiv HgO, 2.2 equiv $BF_3{\cdot}Et_2O$	THF/H_2O	rt	SM + mess
2.	5 equiv IBX, 0.1 equiv β-cyclodextrin	$Acetone/H_2O$	rt	SM
3.	$(CF_3CO_2)_2IPh$	ACN/H_2O (9:1)	rt	decomposition
4.	NBS	ACN/H_2O (9:1)	rt	SM
5.	NCS, Na_2CO_3, wet SiO_2	Acetone	rt	unknown
6.	NCS, 2,6-lutidine	MeOH	0^oC	**156** (86%)

It was a very rare example of hydrolysis intermediate of dithianes, once again supporting the oxidative hydrolysis mechanism for NCS-mediated deprotection of dithianes. Looking at the structure of the methyl sulfinate, it is likely that this α-heteroatom dienone could be a perfect starting material for an interrupted Nazarov cyclization. It would also be catalyzed by milder Lewis acids, since the oxygen of the sulfinate functional group could coordinate with the metal, forcing the dienone in the *cis*-configuration to facilitate the electrocyclization. And the adjacent vinyl group, being a nucleophile, could attach the thiocarbenium intermediate to generate the benzene fused [4.3.0] bicycle.

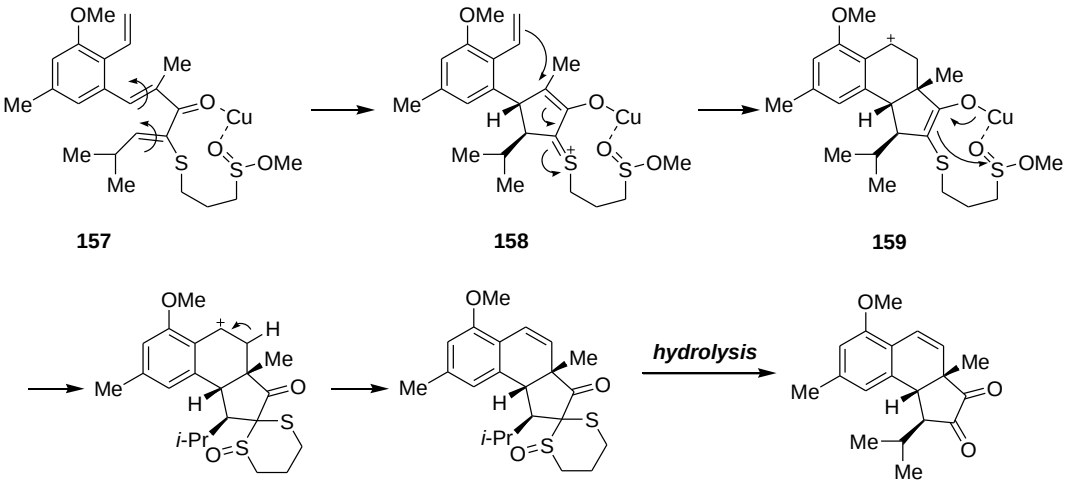
The initial results were quite promising, giving the desired product in up to 53% yield (Scheme 41 and Experimental Section). And we proposed a mechanism for this transformation as shown in Scheme 42.

Scheme 41



156 **143** **144**

Scheme 42

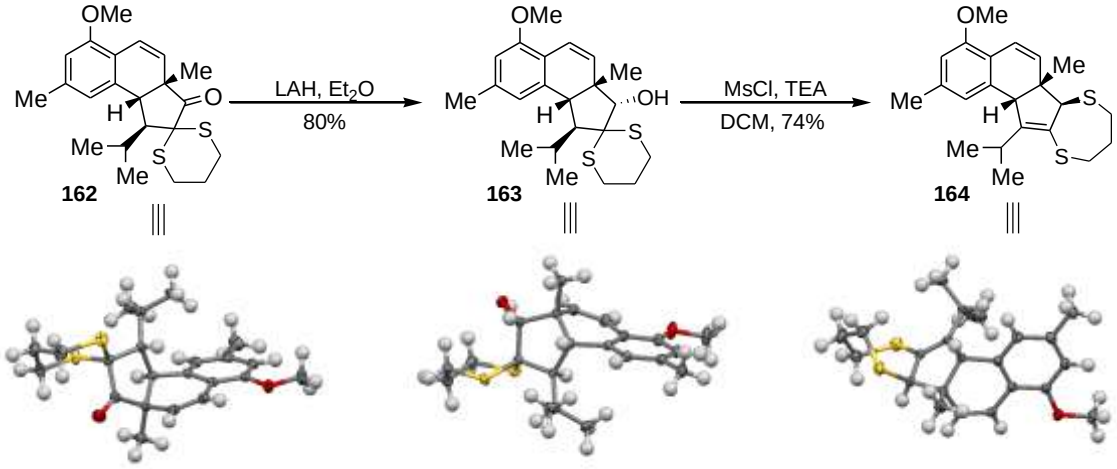


157 **158** **159** **160** **161** **143**

We then tried to optimize this interrupted Nazarov cyclization process. Numerous Lewis acids and Brønsted acids were screened. However, the yields were consistently low, being around 20% typically (See the Experimental Section for details). One of the byproducts isolated was determined to be the dithiane **162**, a reduced product of the sulfoxide intermediate **161**. This indicated there should be some auto-redox reaction happening. Being curious to see if this byproduct **162** could be transformed to a useful intermediate for the synthesis of natural product hamigeran B, a short sequence of

deoxygenation was executed on **162**. Reduction by LAH led to the secondary alcohol **163** with complete diastereoselectivity, with hydride coming from the convex face. Mesylation of the secondary alcohol **163**, however, led to an unexpected product **164** by that time (Scheme **43**). A literature research gave us another example of this type of reaction.[26] It is possible that the configuration of **164**, having the hydrogen, sulfur and mesyl group aligned antiparallel to each other, made the elimination of the mesyl group and the concomitant migration of sulfur a rather facile process.

Scheme 43



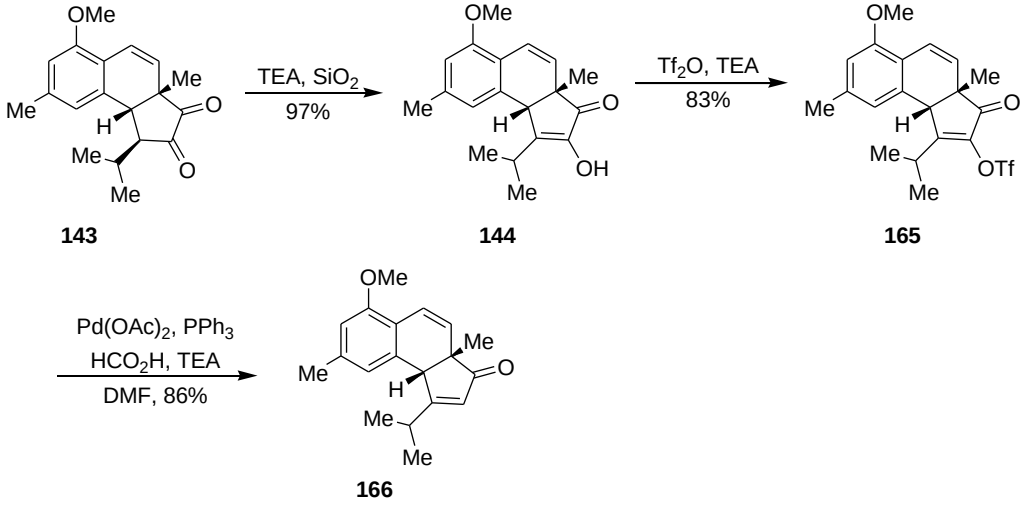
2.2.12 The Dead Ends

Starting from commercially available 3,3-dimethylaniline, the diketone **143** and its tautomer **144** with the core carbon structure of hamigeran B, were obtained in twelve to fourteen steps depending on which route was used. Now, it is the stage for the end game of the total synthesis, converting the diketone to the natural product through functional group manipulations. Obviously, the two carbonyl group needs to be reduced;

the benzylic double bond needs to be oxidized into a diketone. The stereochemistry of C6, the carbon bearing the isopropyl group, need to be inverted.

Taking advantage of the lability of the α-hydrogen of ketones, the stereochemistry of C6 was destroyed by epimerizing the diketone **143** to enone ketone **144** with silica and amine base. Treatment with triflic anhydride and triethylamine yielded the triflate **165** in 83% yield. Reduction with formic acid by palladium(0) catalysis led to the enone **166** in 86% yield (Scheme 44).

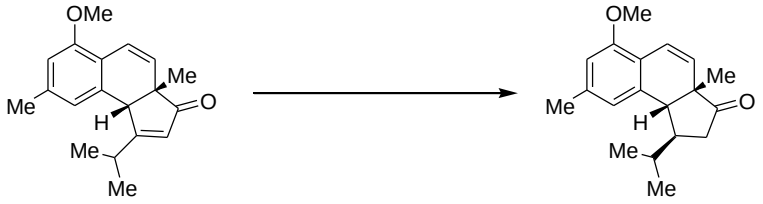
Scheme 44



143 **144** **165** **166**

With enone in hand **166**, it was very tempting to do a conjugate reduction to set the C6 stereochemistry by kinetic control with hydride attacking from the less sterically hindered convex face. However, Wilkinson's catalyst and copper hydride reduction yielded only the thermodynamic product with the *exo*-isopropyl group **167** (Table 5).

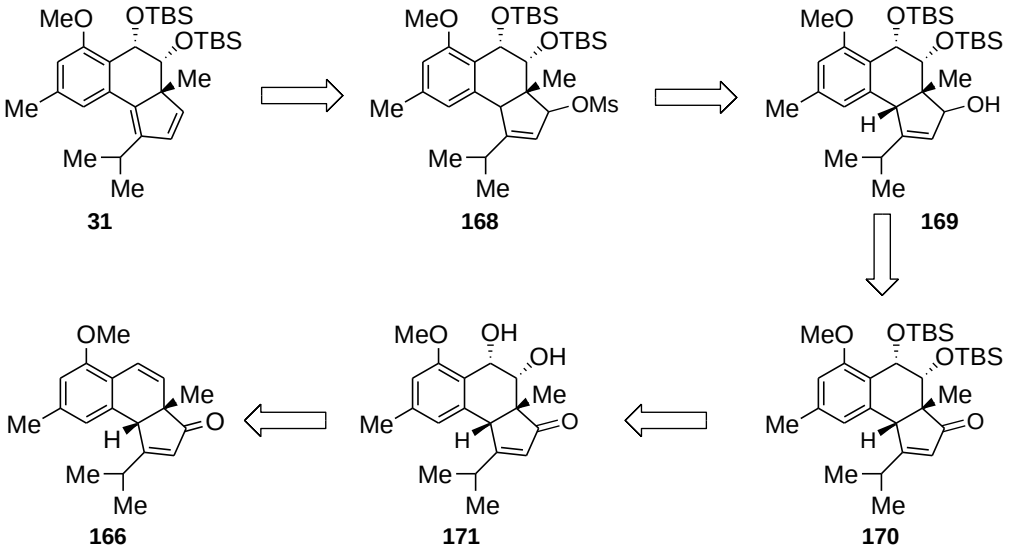
Table 5



Entry	
1	$(PPh_3)_3RhCl$, *i*-Pr_3SiH, PhMe, 80^oC, 33%
2	CuCl, *t*-BuONa, BINAP, PMHS, PhMe, rt, 11%
3	CuCl, NaOMe, (*R*)-DTBM-SEGPHOS, PMHS, PhMe, rt, 1 day, 24%

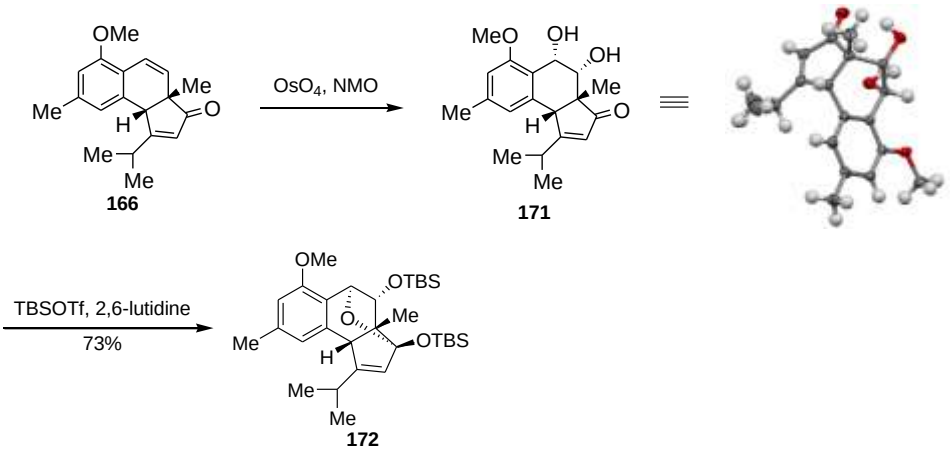
Given the difficulty of setting up the correct stereochemistry of C6 by conjugate reduction, we turned our attention to making Tius' TBS-protected cyclopentadiene **31** for a formal total synthesis purpose. To that end, the enone **166** needs to be oxidized to diol **171**, protected with TBS group to **170**, reduced to allylic alcohol **169**, mesylated and eliminated to the cyclopentadiene **31** (Scheme 45).

Scheme 45



The dihydroxylation with osmium(IV) oxide and NMO generated the diol **171** chemoselectively.[27] The protection of the diol **171** turned out to be rather tricky. Using TBSCl as silylation reagent under different conditions resulted in no conversion. Applying TBSOTf as the silylation reagent with 2,6-lutidine yielded TBS-protected hemiketal **172** as the only product, because of the proximity of the benzylic hydroxyl group and the carbonyl group (Scheme 46). The structure of **172** was identified from analysis of H-NMR, 13C-NMR, DEPT135, HMQC and COSY. Efforts to protect the diol **171** with other protecting groups, such as acetal, dimethylsilyl group did not produce satisfying result.

Scheme 46

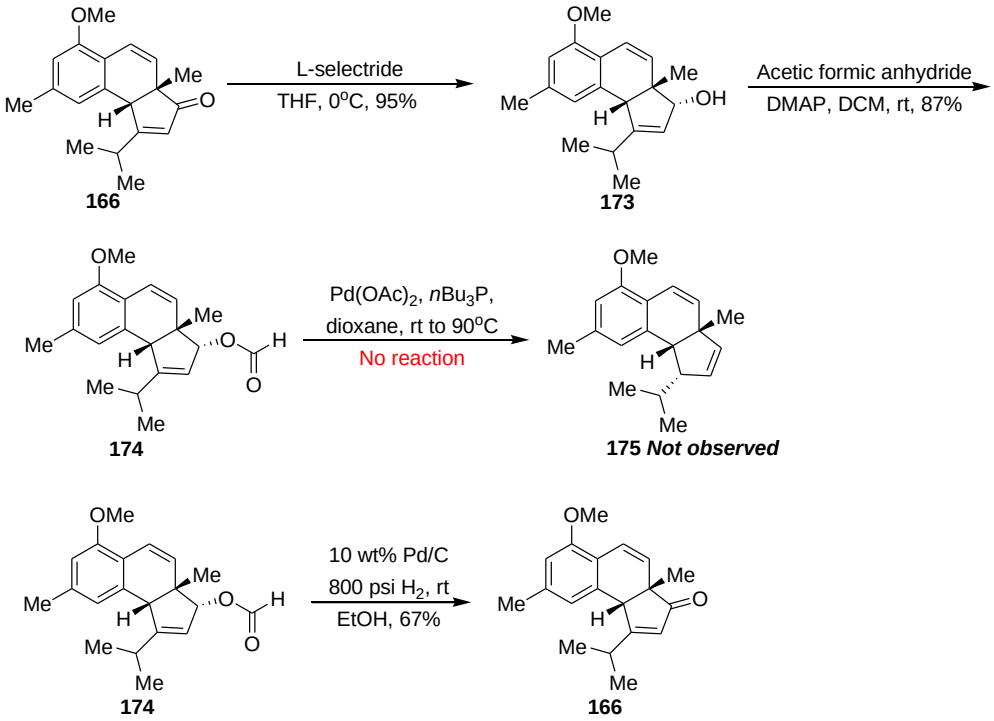


L-selectride reduces simple enones in a 1,4-manner, and reduces sterically hindered enones in a 1,2-manner. L-selectride reduced the enone **166** cleanly to generate the allylic alcohol **173**, the relative stereochemistry of which was determined through 2-D NMR analysis of the corresponding acetate (**176**) (Scheme 48). From the NOESY spectrum, the hydrogen on C15 (δ 5.64) showed correlation with hydrogens on C16 (δ

1.15), indicating the *cis*-relationship between them (Figure 2). Both of the two possible diastereomers of the allylic alcohol could be utilized for the setting up of C6 stereogenic center. Many allylic formats can be reduced by palladium(0) to alkene via S_N2-type fashion with inverstion of stereochemistry. The other allylic alcohol diastereomer could be reduced via OH-directed hydrogenation conditions for the construction of C6 stereochemistry.

For the formate formation, acetic formic anhydride was used to generate the formate **174** in 87% yield. However, the palladium(0) mediated reduction did not do anything to the starting material **174**. Interestingly, palladium on carbon led to the oxidized product **166** in 67% yield (Scheme 47).

Scheme 47



Scheme 48

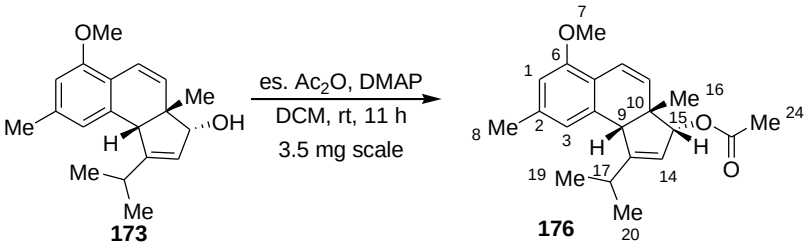
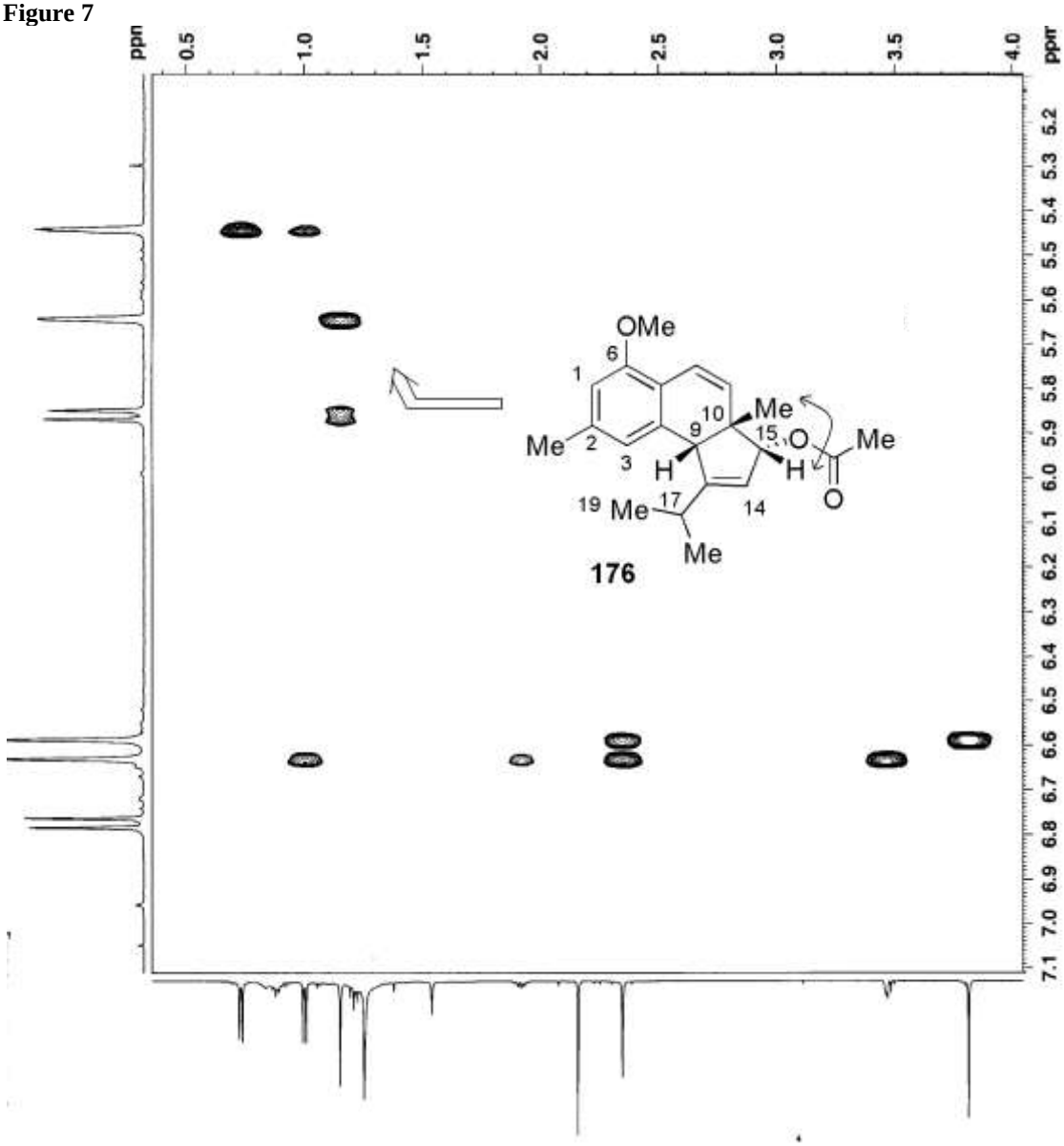


Figure 7



2.3 Concluding Remarks

In summary, the core structure of hamigeran B was constructed efficiently, using Tius-Nazarov cyclization and Wacker-type oxidative carbocyclization or an interrupted Nazarov cyclization. Instead of converting to the known intermediates for synthesis of hamigeran B through long sequence, we explored any efficient way of setting the stereochemistry of C6.

2.4 References

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25. PCC oxidation led to an unidentified product other than the desired diketone **97**.

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27. The relative stereochemistry of the diol was determined unambiguously through X-ray crystallography.

2.5 Experimental Section

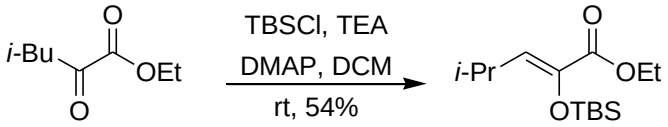
General Information:

All air and moisture sensitive reactions were carried out in flame-dried glassware under an argon or nitrogen atmosphere. Reactive liquid reagents (LHMDS, etc.) were measured and transferred by gastight syringes through rubber septa. Tetrahydrofuran (THF) was freshly distilled over sodium benzophenone kytyl. Toluene was distilled from CaH_2. The reaction mixture was concentrated by using a rotary evaporator attached to a water aspirator. Residue solvents were usually removed under reduced pressure using vacuum pump (approximately 1mm Hg).

Flash chromatographic separations were carried out on silica gel (230-400 mesh) with ACS reagent grade solvents. Analytical thin layer chromatography was performed on glass–backed silica gel plates with F254 indicator. Compounds were visualized under UV light or by developing in iodine, vanillin, phosphomolybdic acid solution or with potassium permanganate solution followed by heating in a hot plate to approximately 350^{o}C. Melting points were determined with a melting point apparatus.

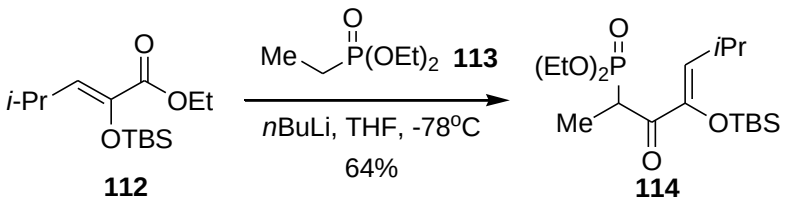
^{1}H NMR spectra were recorded in Fourier transform mode at 250, 300 or 500 MHz, respectively, as $CDCl_3$ solutions with tetramethylsilane (δ = 0 ppm) as the internal standard. ^{13}C NMR spectra were recorded on the same instruments at 62.5, 75 or 125 MHz, respectively, with $CDCl_3$ (δ = 77 ppm) as the internal reference. ^{31}P NMR spectra were recorded on the same instruments at 101 MHz, respectively, with 85% H_3PO_4 (δ = 0 ppm) as the external standard. Chemical shifts (δ) were reported in parts per million (ppm). Multiplicities were reported as s (singlet), b (broad), d (doublet), t (triplet), q (quartet), m (multiplet), and dd (doublet of doublet), etc. In ^{1}H NMR spectra of

diastereomeric mixtures, the signals for individual isomers were reported when possible. Infrared spectra were recorded on an FT-IR spectrometer. Optical rotations were recorded on a polarimeter with sodium D line at the temperatures as indicated in the experimental for specific compounds. High resolution mass spectra were obtained on a magnetic sector instrument with a resolution greater than 10,000.



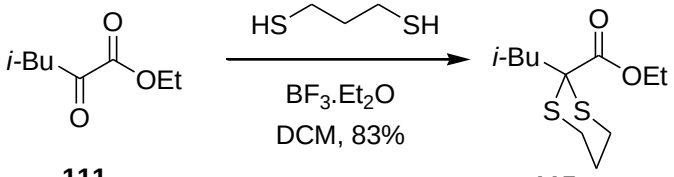
111 **112**

112: To a solution of **111** (1.38 g, 8.7 mmol) in DCM (17 mL, 0.5 M) was added TBSCl (1.57 g, 10.4 mmol), DMAP (0.1 g, 0.9 mmol), and TEA (1.76 g, 17.4 mmol) at rt sequentially. After 13 hours at rt, it was quenched with 10 mL water, washed with 10 mL brine, dried with Na_2SO_4, concentrated under reduced pressure at rt, and purified by FCC with 2-5% EA/Hex on silica gel to get **112** (1.28 g, 54%) as a colorless oil. IR (neat): 3428, 2962, 2929, 2856, 1720, 1642, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.84 (d, 1 H, J = 10 Hz), 4.19 (q, 2 H, J = 7.5 Hz), 2.87-2.80 (m, 1 H), 1.31 (t, 3 H, J = 7.5 Hz), 1.01 (d, 6 H, J = 7 Hz), 0.96 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.2, 138.9, 129.7, 60.8, 25.8, 25.1, 22.2, 18.6, 14.2, -4.4; HRMS calcd for $C_{14}H_{28}O_3SiNa$ $[M+Na]^+$ 295.1700; Found: 295.1697.



112 **114**

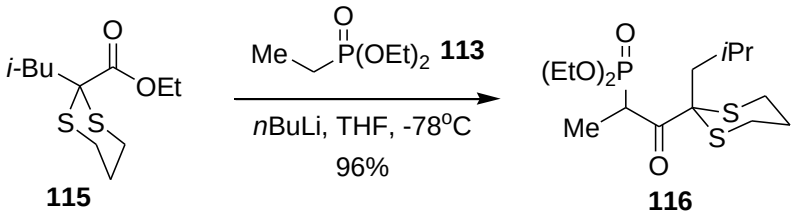
114: To a solution of **113** (446 mg, 2.69 mmol) in THF (8 mL, 0.34 M) was added *n*BuLi (1.4 mL, 1.9 M in THF, 2.69 mmol) at -78 ^{o}C slowly. After 1 hour, **112** (245 mg, 0.896 mmol) was added slowly. It was quenched after stirring at -78 ^{o}C for 10 hours with 10 mL sat. NH_4Cl, extracted with 3 x 10 mL EA, washed with 10 mL brine, dried with Na_2SO_4, concentrated under reduced pressure to get 495 mg crude yellow oil. Then it was purified by FCC with 50% EA/Hex to get **114** (151 mg, 43%) as colorless oil. IR (neat): 3469, 2958, 1675, 1622, 1250, 1025 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.80 (d, 1 H, J = 9 Hz), 4.16-4.07 (m, 4 H), 3.76 (dq, 1 H, J = 22.5, 7 Hz), 2.95 (m, 1 H), 1.41 (dd, 3 H, J = 7, 18 Hz), 1.31 (dt, 6 H, J = 7, 6.5 Hz), 1.05 (dd, 6 H, J = 6.5, 9.5 Hz), 0.95 (d, 9 H, J = 0.5 Hz), 0.18 (s, 3 H), 0.14 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 193.2 (d, J = 5 Hz), 146.9 (d, J = 2.5 Hz), 133.3, 62.6 (d, J = 7.5 Hz), 62.4 (d, J = 6 Hz), 40.2, 39.2, 25.9, 25.6, 22.1 (d, J = 2.5 Hz), 18.8, 16.4 (d, J = 3.8 Hz), 16.36 (d, J = 5 Hz), 12.5 (d, J = 6.2 Hz), -4.0, -4.2; HRMS calcd for $C_{18}H_{37}O_5PSiNa$ $[M+Na]^+$ 415.2040; Found: 415.2040.



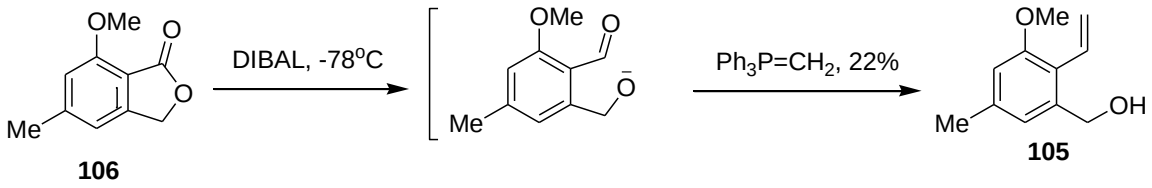
111 **115**

115: To a solution of **111** (309 mg, 1.95 mmol) and propane-1,3-dithiol (211 mg, 1.95 mmol) in DCM (10 mL, 0.2 M) was added trifluoroborane etherate (80 μL, 48%, 0.3 mmol) at 0 ^{o}C. It was stirred at rt for 5 hours. Then, it was quenched with sat. $NaHCO_3$, extracted with DCM, dried with $MgSO_4$, concentrated under reduced pressure, and purified by FCC with 5% EA/Hex to get **115** as a colorless oil (402 mg, 83%). IR (neat): 2958, 2925, 1716, 1209, 1119, 1025 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.24 (q, 2 H, J = 7 Hz), 3.26 (m, 2 H), 2.65 (m, 2 H), 2.16-2.11 (m, 1 H), 2.00 (d, 2 H, J = 1.5 Hz), 1.86

(m, 2 H), 1.33 (t, 3 H, J = 7.5 Hz), 0.94 (d, 6 H, J = 6 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.2, 61.7, 53.0, 16.9, 27.9, 25.1, 24.7, 23.6, 14.0; HRMS calcd for $C_{11}H_{20}O_2S_2Na$ $[M+Na]^+$ 271.0797; Found: 271.0791.

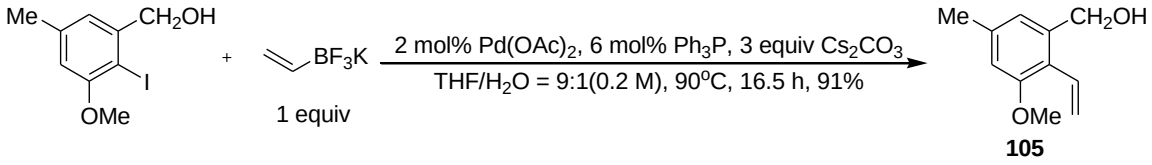


116: To a solution of **113** (287 mg, 1.73 mmol) in THF (2 mL, 0.86 M) was added *n*BuLi (0.95 mL, 1.9 M in THF, 1.8 mmol) at -78 °C slowly. After 1 hour, **115** (140 mg, 0.564 mmol) was added slowly. It was quenched after stirring at -78 °C for 2 hours with 2 mL sat. NH_4Cl, extracted with 3 x 2 mL EA, washed with 4 mL brine, dried with Na_2SO_4, concentrated under reduced pressure. Then it was purified by FCC with 50% EA/Hex to get **116** (200 mg, 96 %) as colorless oil. IR (neat): 2954, 1704, 1254, 1021 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.28-4.11 (m, 4 H), 3.95 (dq, 1 H, J = 25, 7 Hz), 3.36 (dt, 1 H, J = 3, 14 Hz), 2.79 (dt, 1 H, J = 2.5, 14 Hz), 2.61 (tt, 2 H, J = 3, 15.5 Hz), 2.16 (heptet, 1 H, J = 6 Hz), 2.06-2.01 (m, 1 H), 1.91 (dd, 3 H, J = 7, 18 Hz), 1.34 (dt, 6 H, J = 5, 7 Hz), 1.05 (d, 6 H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.6 (d, J = 3.75 Hz), 63.7 (d, J = 5 Hz), 62.9 (d, J = 7.5 Hz), 62.1 (d, J = 7.5 Hz), 44.8, 40.5, 39.5, 27.8 (d, J = 3.8 Hz), 25.3, 25.2, 25.1, 24.1, 16.4 (d, J = 6.2 Hz), 16.3 (d, J = 5 Hz), 16.0 (d, J = 6.2 Hz); HRMS calcd for $C_{15}H_{29}O_4PS_2Na$ $[M+Na]^+$ 391.1137; Found: 391.1127.



106 **105**

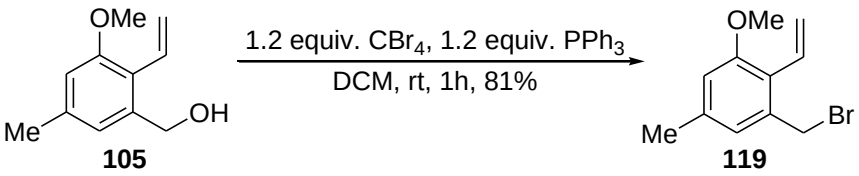
To a solution of lactone **106** (422 mg, 2.37 mmol) in DCM (10 mL, 0.2 M) was added DIBAL (4.74 mL, 1 M in Toluene, 4.74 mmol) at -78 ^{o}C. After 9 hours, it was quenched with ethyl acetate. Then it was poured to a solution of Wittig reagent (4.74 mmol) in THF at 0 ^{o}C. The reaction mixture was stirred at rt overnight, quenched with 50 mL water, and washed with sat. NH4Cl. Then it was purified by FCC with 25% EA/Hex after concentration under reduced pressure to get **105** (94 mg, 22%) as colorless wax with melting point of 58-60 ^{o}C. IR (neat): 3293, 3011, 2913, 1605, 1458, 1405, 1295, 1033, 907, 837 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.89 (s, 1 H), 6.81 (dd, 1 H, J = 12, 18 Hz), 6.68 (s, 1 H), 5.64 (dd, 1 H, J = 2, 18 Hz), 5.50 (dd, 1 H, J = 2, 11.5 Hz), 4.71 (s, 2 H), 3.83 (d, 3 H, J = 2 Hz), 2.35 (s, 3 H), 1.73 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157, 139, 138, 130, 123, 121, 119, 111, 63, 56, 22; HRMS calcd for $C_{11}H_{14}O_2Na$ $[M+Na]^+$ 379.1880; Found: 379.1881.



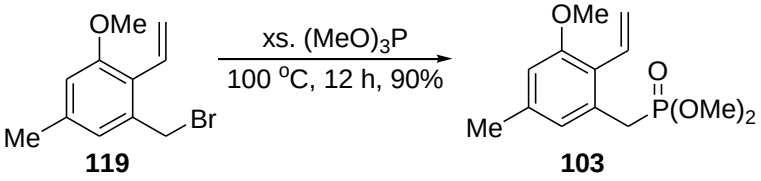
105

To a solution of (2-iodo-3-methoxy-5-methylphenyl)methanol (530 mg, 1.92 mmol) in THF/H_2O (9: 1) (10 mL, 0.2 M) was added $Pd(OAc)_2$ (8 mg, 0.038 mmol, 2 mol %), triphenylphosphine (26 mg, 0.115 mmol, 6 mol %), potassium vinyl fluoroborate (260 mg, 1.92 mmol), and Cs_2CO_3 (1.88 g, 5.76 mmol) at rt. After stirring at 90 ^{o}C for 16.5

hours, the top yellow organic layer was separated. The bottom aqueous layer with white solid was extracted with ethyl ether. Together, it was washed with brine, concentrated under reduced pressure, and purified by FCC with 25% EA/Hex to get **105** (310 mg, 91%).

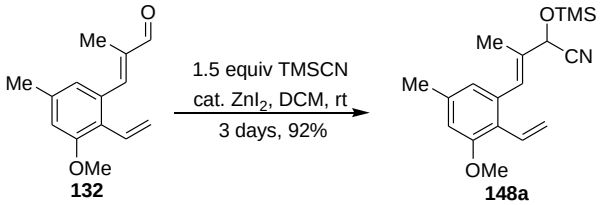


119: To a solution of **105** (92 mg, 0.516 mmol) in DCM (10 mL, 0.05 M) was added CBr4 (205 mg, 0.619 mmol) and triphenylphosphine (162 mg, 0.619 mmol) at rt. The colorless solution was stirred for 1 hour at rt and turned to coffee color solution. Then it was concentrated under reduced pressure, and purified directly by FCC with 25% EA/Hex to get **119** (100 mg, 81%) as white solid which melted at 73-74 ^{o}C. IR (neat): 2933, 2835, 1630, 1564, 1462, 1328, 1278, 927, 845 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.84 (s, 1 H), 6.81 (dd, 1 H, J = 12, 18 Hz), 6.66 (s, 1 H), 5.79 (dd, 1 H, J = 2, 18 Hz), 5.58 (dd, 1 H, J = 2, 12 Hz), 4.57 (s, 2 H), 3.82 (s, 3 H), 2.33 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158, 138, 136, 130, 124, 123.6, 120, 112, 56, 33, 21; HRMS calcd for $C_{11}H_{13}BrONa$ $[M+Na]^+$ 263.0042; Found: 263.0044.



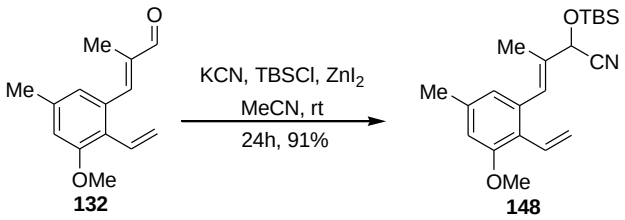
103: To a solution of **119** (56 mg, 0.23 mmol) was added trimethylphosphite (1 mL, 1.05 g, 8.47 mmol) and refluxed at 115 ^{o}C overnight. Then it was concentrated under reduced pressure and purified by FCC with EA to get **103** (57 mg, 90%) as colorless oil. IR

(neat): 3007, 2953, 2852, 1605, 1569, 1462, 1405, 1250, 1054 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.83 (s, 1 H), 6.72 (dd, 1 H, J = 12, 18 Hz), 6.61 (s, 1 H), 5.62 (dd, 1 H, J = 2.5, 18 Hz), 5.54 (dd, 1 H, J = 2, 11.5 Hz), 3.80 (s, 3 H), 3.68 (d, 3 H, J = 0.5 Hz), 3.65 (d, 3 H, J = 0.5 Hz), 3.29 (d, 2 H, J = 22 Hz), 2.33 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.5 (d, J = 3.8 Hz), 137.7 (d, J = 3.8 Hz), 131.1 (d, J = 1.25 Hz), 129.8 (d, J = 8.8 Hz), 124.6 (d, J = 7.5 Hz), 123.6 (d, J = 5 Hz), 119.9, 110.3 (d, J = 1.2 Hz), 55.4, 52.7 (d, J = 6.2 Hz), 30.4, 29.3, 21.5; HRMS calcd for $C_{13}H_{19}O_4PNa$ $[M+Na]^+$ 321.1226; Found: 321.1231.



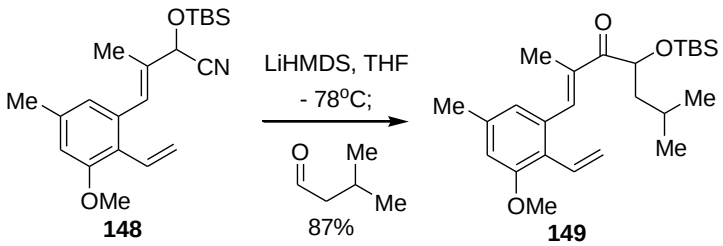
148a: To a solution of **132** (2.61 g, 12.1 mmol) in dichloromethane (24 ml, 0.5 M) was added TMSCN (1.20 g, 12.1 mmol) and ZnI_2 (1 mg, cat.). The reaction mixture was stirred at rt for 18 hours. Then another 0.6 g of TMSCN was added to the reaction mixture. After total reaction time of three days, the mixture was filtered through a well packed silic plug, and rinsed with DCM till the eluent became colorless. Then it was concentrated under reduced pressure to get yellow oil (3.49 g, 92% yield based on crude mass). Then it was purified on aluminum oxide (activated, basic, Brockmann I, standard grade, ~150 mesh, 58Å), it decomposed back to the starting material **132**. It was passed through another silic plug quickly for further reactions. IR (neat): 2958, 1603, 1459, 1255, 1159, 1023, 845 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.72 (dd, 1 H, J = 12, 18 Hz), 6.70 (s, 1H), 6.65 (s, 1 H), 6.62 (s, 1 H), 5.56 (dd, 1 H, J = 2, 18 Hz), 5.43 (dd, 1 H, J = 2,

11 Hz), 4.95 (s, 1 H), 3.83 (s, 3 H), 2.34 (s, 3 H), 1.85 (s, 3 H), 0.25 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.5, 137.6, 135.5, 132.2, 130.6, 129.5, 123.1, 122.6, 119.5, 118.6, 110.7, 67.0, 55.4, 21.5, 13.4, -0.3, -0.5.



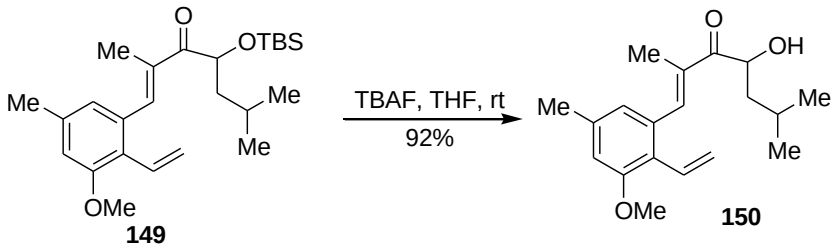
132 **148**

148: To a solution of **132** (1.84 g, 8.52 mmol) in acetonitrile (43 ml, 0.2 M) was added TBSCl (1.92 g, 12.8 mmol), NaCN (3.34 g, 68.2 mmol), and ZnI_2 (27 mg, 0.08 mmol). The yellow suspension was stirred at rt for 1 day, and quenched with 40 mL water, extracted with 3x40 mL EA, washed with 40 mL brine, dried with anhydrous MgSO4. Then, it was concentrated under reduced pressure. Flash chromatography purification with 0-5% EA/Hexane yielded the product **148** (2.77 g, 91%). The pink band was collected, with the following yellow band discarded. IR (neat): 2955, 2858, 1603, 1462, 1255, 1100, 840, 781 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.72 (dd, 1 H, J = 12, 18 Hz), 6.70 (s, 1 H), 6.66 (s, 1 H), 6.62 (s, 1 H), 5.55 (dd, 1 H, J = 2, 17.5 Hz), 5.42 (dd, 1 H, J = 2, 12 Hz), 4.95 (s, 1 H), 3.84 (s, 3 H), 2.35 (s, 3 H), 1.85 (d, 3 H, J = 1 Hz), 0.95 (s, 9 H), 0.23 (s, 3 H), 0.18 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.5, 137.6, 135.6, 132.3, 130.6, 129.3, 123.2, 122.6, 119.6, 118.7, 110.8, 67.3, 55.5, 25.5, 21.6, 18.2, 13.5, -5.2, -5.22.



148 **149**

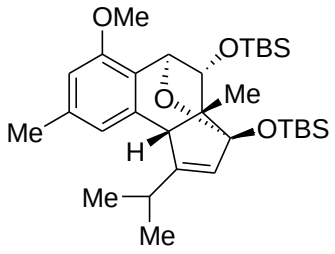
149: To a solution of **148** (1.2 g, 3.35 mmol) in THF (16.8 mL, 0.2 M) was added LiHMDS (4.47 mL, 0.9 M in THF, 4.02 mmol) slowly at -78 ^{o}C. The color turned red upon the addition of LiHMDS. After 10 min at -78 ^{o}C, isovaleraldehyde (0.346 g, 4.02 mmol) was added neat. The color of the solution turned yellow upon finishing adding isovaleradehyde at -78 ^{o}C. Immediately, it was quenched with saturated NH_4Cl and raised to rt. It was then extracted with ethyl ether, washed with brine, dried with $MgSO_4$, concentrated under reduced pressure, and purified by FCC (5-10% EA/Hex) to yield **149** (1.2 g, 89%). IR (neat): 2954, 2860, 1683, 1601, 1458, 1258, 1099, 1046, 833, 776 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.65 (s, 1 H), 6.81(dd, 1 H, J = 11.5, 17.5 Hz), 6.70 (d, 1 H, J = 3.5 Hz), 5.49 (dd, 1 H, J = 2, 11.5 Hz), 5.43 (dd, 1 H, J = 2, 18 Hz), 4.90 (dd, 1 H, J = 3.5, 10 Hz), 3.86 (s, 3 H), 2.37 (s, 3 H), 1.93 (s, 3 H), 1.89-1.84 (m, 1 H), 1.66 (m, 1 H), 1.48 (m, 1 H), 0.95 (d, 3 H, J = 2.5 Hz), 0.94 (d, 3 H, J = 3 Hz), 0.90 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 203.2, 157.4, 140.3, 137.8, 135.3, 131.0, 123.8, 122.4, 120.5, 111.3, 74.1, 55.6, 44.8, 25.8, 24.4, 23.6, 21.7, 21.4, 18.3, 13.7, -4.5, -5.2.



149 **150**

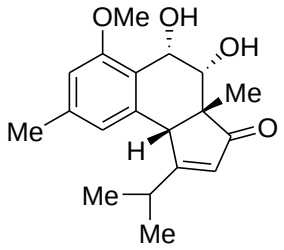
150: To a solution of **149** (150 mg, 0.36 mmol) in THF (1 mL, 0.36 M) was added TBAF (0.43 mL 1 M solution in THF, 0.43 mmol) at 0 ^{o}C. After 20 min, it was quenched with sat. NaHCO3, extracted with EA, washed with brine, dried with MgSO4, concentrated under reduced pressure, and purified by FCC with 5% EA/Hex to get **150** (100 mg, 92%).

IR (neat): 3471, 2954, 2920, 1661, 1601, 1563, 1464, 1049 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.48 (s, 1 H), 6.82 (dd, 1 H, J = 11.5, 18 Hz), 6.74 (s, 1 H), 6.72 (s, 1 H), 5.52 (dd, 1 H, J = 1.5, 11.5 Hz), 5.38 (dd, 1 H, J = 2, 17.5 Hz), 4.95 (ddd, 1 H, J = 2, 7, 9.5 Hz), 3.86 (s, 3 H), 3.56 (d, 1 H, J = 7 Hz), 2.38 (s, 3 H), 2.01 (s, 3 H), 1.61-1.56 (m, 1 H), 1.41-1.35 (m, 1 H), 1.02 (d, 3 H, J = 7 Hz), 0.95 (d, 3 H, J = 6.5 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 2.4.1, 157.4, 141.7, 138.0, 134.4, 133.8, 130.9, 124.3, 122.4, 121.0, 111.7, 70.9, 55.6, 45.4, 25.0, 23.7, 21.7, 21.3, 13.5.

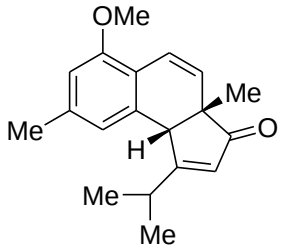


172: To a solution of diol (29 mg, 0.09 mmol) in dichloromethane (2 mL, 0.045 M), was added 2, 6-lutidine (52 μL, 0.45 mmol) and TBSOTf (63 μL, 0.27 mmol) consecutively at 0 ^{o}C. After TLC showed complete consumption of starting material, it was quenched with saturated ammonium chloride aqueous solution and extracted with dichloromethane. Then it was washed with brine, dried with $MgSO_4$, concentrated under reduced pressure, and purified by flash chromatography (1: 20 ethyl acetate in hexane) to get the silyl ether as a colorless oil (36 mg, 73%) ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.49 (s, 1 H), 6.41 (s, 1 H), 5.34 (s, 1 H), 5.33 (d, 1 H, J = 1.5 Hz), 3.82 (s, 1 H), 3.76 (s, 3 H), 3.30 (s, 1 H), 2.31 (heptet, 1 H, J = 6.5 Hz), 2.28 (s, 3 H), 1.16 (s, 3 H), 1.14 (d, 3 H, J = 7 Hz), 1.01 (d, 3 H, J = 6.5 Hz), 0.91 (s, 9H), 0.89 (s, 9H), 0.19 (s, 3H), 0.14 (s, 3 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.3, 154.4, 140.2, 138.4, 126.8, 124.2, 120.1,

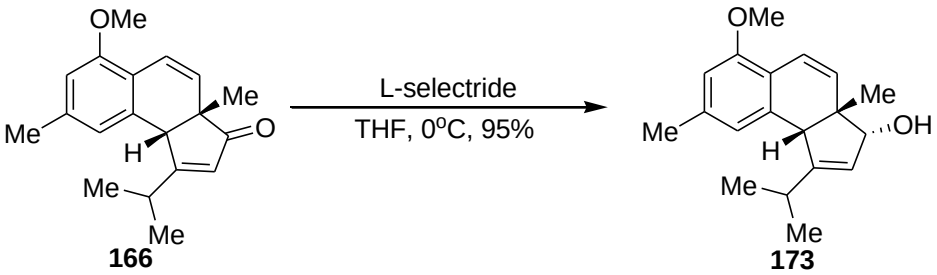
115.6, 109.5, 81.2, 77.9, 57.4, 56.2, 55.4, 26.3, 26.0, 25.9, 21.8, 20.8, 20.3, 18.6, 17.9, 15.5, -2.5, -3.4, -4.7, -4.8.



4,5-dihydroxy-6-methoxy-3a,8-dimethyl-1-(propan-2-yl)- 3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*a*]naphthalen-3-one (171): To a solution of enone (20 mg, 0.07 mmol) in 1 Ml acetone/water (4: 1), was added 2.5% OsO_4 in 2-methylpropanol (44 µL, 0.0035 mmol) and 60% NMO in water (35 µL, 0.33 mmol) at rt. After 24 hours, 1 mL water was added, followed by 1 mL saturated sodium thiolsulfate. The mixture was extracted with dichloromethane (3 x 3 mL), washed with 2 mL brine, and dried with Na_2SO_4. After purification by flash chromatography (25% to 50% ethyl acetate in hexane), 12 mg (54%) white solid was obtained: mp 155-156 ^oC; IR (neat): 3420, 2962, 2929, 1675, 1609, 1462, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.70 (s, 1 H), 6.63 (s, 1 H), 5.90 (s, 1 H), 5.17 (d, 1 H, J = 11.5 Hz), 5.166 (s, 1 H), 3.81 (s, 3 H), 3.76 (s, 1 H), 3.68 (dd, 1 H, J = 2.5, 13.5 Hz), 2.61 (heptet, 1 H, J = 7 Hz), 2.07 (d, 1 H, J = 2.5 Hz), 1.44 (s, 3 H), 1.28 (d, 3H, J = 7 Hz), 1.00 (d, 3 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 215.7, 188.2, 157.7, 139.7, 136.1, 124.8, 129.0, 121.7, 110.3, 79.2, 65.6, 56.9, 55.6, 45.2, 28.7, 24.9, 22.0, 21.9, 20.8; HRMS calcd for $C_{19}H_{24}O_4Na$ $[M+Na]^+$ 339.1567; Found: 339.1568.

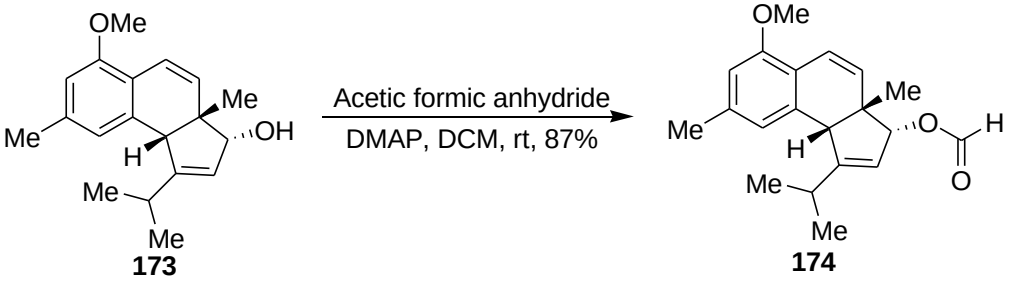


6-methoxy-3a,8-dimethyl-1-(propan-2-yl)-3a,9b-dihydro-3*H*-cyclopenta[*a*]naphthalen-3-one (166): To a solution of enol triflate (132 mg, 0.307 mmol) in 3 mL DMF (0.1 M), was added palladium (II) acetate (7mg, 0.03 mmol), triphenylphosphine (16 mg, 0.06 mmol), triethylamine (0.17 mL), and formic acid (56 μL, 1.5 mmol) at rt. The reaction was stirred at 70^{o}C for 12 hours, and quenched with 20 mL water and 20 mL diethyl ether at rt. Then the mixture was extracted with diethyl ether (3 x 20 mL), washed with 50 mL saturated ammonium chloride aqueous solution, 50 mL saturated sodium bicarbonate aqueous solution and 50 mL water. After drying with sodium sulfate and concentrated under reduced pressure, it was purified by flash chromatography (10% ethyl acetate in hexane) to get a white solid (75 mg, 86 %). mp 116 - 118^{o}C; IR (neat): 2966, 1704, 1687, 1605, 1458, 1381 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.73 (d, 1 H, J = 10 Hz), 6.72 (s, 1 H), 6.62 (s, 1 H), 5.99 (d, 1 H, J = 2 Hz), 5.50 (d, 1 H, J = 10 Hz), 3.82 (s, 3 H), 3.78 (d, 1 H, J = 1.5 Hz), 2.48 (heptet, 1 H, J = 7 Hz), 1.23 (d, 3 H, J = 7 Hz), 1.21 (s, 3 H), 0.83 (d, 3 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 210.7, 185.6, 155.4, 138.1, 132.0, 129.9, 124.4, 122.8, 119.0, 118.4, 110.7, 55.5, 53.7, 52.3, 28.7, 22.4, 21.9, 21.3, 20.4; HRMS calcd for $C_{19}H_{22}O_2Na$ $[M+Na]^+$ 305.1512; Found: 305.1508.



166 **173**

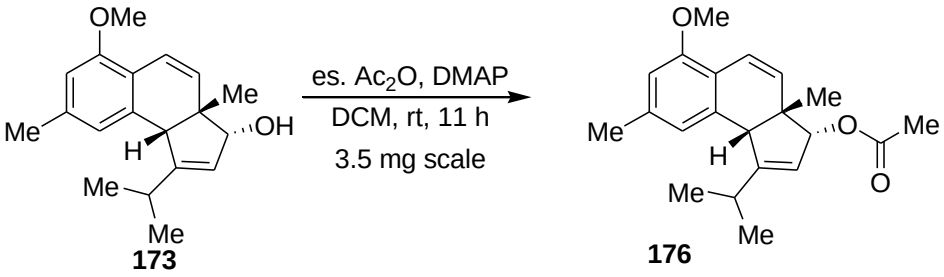
173: To a solution of **166** (42 mg, 0.149 mmol) in THF (1.5 mL, 0.1 M) was added L-selectride (0.179 mL, 1 M in THF, 0.179 mmol) at 0 ^{o}C slowly. It was quenched with 4 N NaOH and 30% H_2O_2 after 30 min at 0 ^{o}C. Then it was extracted with DCM, washed with brine, dried with $MgSO_4$, concentrated and purified by FCC with 25% EA/Hex to get the allylic alcohol **173** (40 mg, 95%). IR (neat): 3346, 2954, 2917, 2860, 1605, 1569, 1454, 1324, 1127, 1017, 821 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.81 (d, 1 H, J = 10.5 Hz), 6.62 (s, 1 H), 6.58 (s, 1 H), 5.85 (d, 1 H, J = 10.5 Hz), 5.43 (d, 1 H, J = 1.5 Hz), 4.65 (d, 1 H, J = 6.5 Hz), 3.81 (s, 3 H), 3.44 (s, 1 H), 2.35 (s, 3 H), 1.92 (heptet, 1 H, J = 7 Hz), 1.57 (s, 1 H), 1.00 (d, 3 H, J = 7 Hz), 0.73 (d, 3 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155, 152, 137, 133, 129, 124, 123, 119, 110, 86, 55.4, 55, 50, 27, 23, 22, 21.8, 21; HRMS calcd for $C_{19}H_{24}O_2Na$ $[M+Na]^+$ 307.1668; Found: 307.1683.



173 **174**

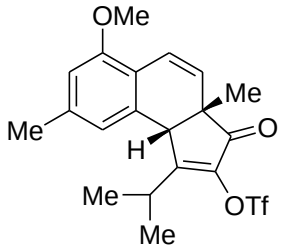
174: To a solution of **173** (18 mg, 0.063 mmol) in DCM (1 mL, 0.06 M) was added DMAP (15 mg, 0.123 mmol), formic acetic anhydride (11 mg, 0.125 mmol). It was concentrated under reduced pressure after 19 hours at rt, and purified by FCC with 10%

EA/Hex to get **174** (17.5 mg, 87%). IR (neat): 2959, 2922, 1725, 1463, 1174 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.24 (d, 1 H, J = 1 Hz), 6.78 (d, 1 H, J = 10 Hz), 6.63 (s, 1 H), 6.59 (s, 1 H), 5.85 (d, 1 H, J = 10 Hz), 5.76 (s, 1 H), 3.82 (s, 3 H), 3.48 (s, 1 H), 2.35 (s, 3 H), 5.45 (m, 1 H), 1.94 (heptet, 1 H, J = 6.5 Hz), 1.17 (s, 3 H), 1.01 (d, 3 H, J = 7 Hz), 0.74 (d, 3 H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.2, 154.9, 153.6, 137.4, 132.7, 128.8, 122.9, 120.8, 118.94, 118.9, 110.4, 86.6, 55.4, 54.7, 49.2, 27.2, 22.4, 22.2, 21.8, 21.1.

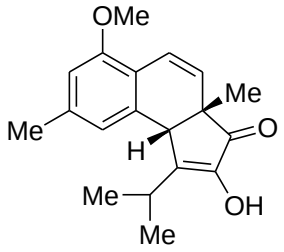


173 **176**

176: To a solution of **173** (3.5 mg, 0.012 mmol) in DCM was added Ac_2O (10.8 mg, 1.06 mmol) and DMAP (3 mg, 0.025 mmol) at rt. It was concentrated under reduced pressure after 11 hours at rt, and purified by FCC with 10% EA/Hex to get the acetate **176**. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.77 (d, 1 H, J = 10.5 Hz), 6.63 (s, 1 H), 6.59 (s, 1 H), 5.86 (d, 1 H, J = 10 Hz), 5.64 (s, 1 H), 5.44 (dd, 1 H, J = 1, 1.5 Hz), 3.82 (s, 3 H), 3.50-3.46 (m, 1 H), 2.35 (s, 3 H), 2.16 (s, 3 H), 1.92 (heptet, 1 H, J = 7 Hz), 1.15 (s, 3 H), 1.00 (d, 3 H, J = 7 Hz), 0.73 (d, 3 H, J = 7 Hz); DEPT135 ($CDCl_3$, 125 MHz) (CH, CH_3) δ 129.2, 123.0, 121.3, 118.8, 110.4, 86.8, 63.4, 55.5, 54.7, 27.2, 22.4, 22.2, 21.8, 21.3, 21.2.

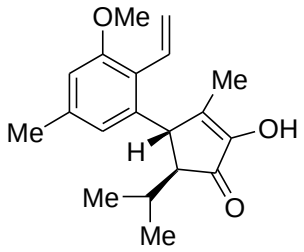


(3a,9b)-6-methoxy-3a,8-dimethyl-3-oxo-1-(propan-2-yl)-3a,9b-dihydro-3*H*-cyclopenta[*a*]naphthalen-2-yl trifluoromethanesulfonate (165): 2-hydroxy-6-methoxy-3a,8-dimethyl-1-(propan-2-yl)-3a,9b-dihydro-3*H*-cyclopenta[*a*]naphthalen-3-one (114 mg, 0.382 mmol) in 4 mL dichloromethane (0.1 M) was cooled to 0^{o}C by ice/water bath. To the solution was added triethylamine (106 μL, 0.764 mmol) at 0^{o}C. Then triflic anhydride (77 μL, 0.458 mmol) was added dropwisely at 0^{o}C, during which time the solution turned dark. The reaction mixture was allowed to warm up to rt by removing the cooling bath after stirring for 10 minutes at 0^{o}C. After 1.5 hours, the reaction mixture was concentrated under aspirator vacuum to get dark slow flow oil, which was directly purified by flash chromatography (10% ethyl acetate in hexane, between yellow band and red band) to get a colorless wax (136 mg, 83%): IR (neat): 2974, 2938, 1732, 1417, 1209, 1139, 992 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.82 (d, 1 H, J = 9.5 Hz), 6.71 (s, 1 H), 6.67 (s, 1 H), 3.78 (s, 3 H), 5.43 (d, 1 H, J = 9.5 Hz), 3.83 (s, 3 H), 3.76 (s, 3 H), 2.75 (heptet, 1 H, J = 7.0 Hz), 2.40 (s, 3 H), 1.24 (s, 3 H), 1.15 (d, 3 H, J = 7.0 Hz), 0.96 (d, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 119.9, 168.1, 156.6, 142.5, 138.9, 129.8, 128.2, 123.4, 119.9, 119.1, 118.5 (q, J = 319 Hz), 111.6, 55.5, 50.23, 50.15, 28.4, 21.9, 19.92, 19.89, 19.0; HRMS calcd for $C_{20}H_{21}F_3O_5SNa$ $[M+Na]^+$ 453.0954; Found: 453.0956.

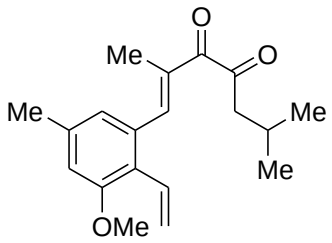


2-hydroxy-6-methoxy-3a,8-dimethyl-1-(propan-2-yl)-3a,9b-dihydro-3*H*-cyclopenta[*a*]naphthalen-3-one (144): 4-(2-ethenyl-3-methoxy-5-methylphenyl)-2-hydroxy-3-methyl-5-(propan-2-yl)cyclopent-2-en-1-one (134 mg, 0.440 mmol) in 10 mL THF was added bis(acetonitrile)palladium(II) chloride (1 mg, 0.004 mmol, 1 mol%), cuprous iodide (2 mg, 0.0105 mmol, 2 mol%) sequentially at rt. Then, nitrogen balloon was changed to oxygen balloon. After stirring for 10 minutes at rt, yellow solution turned red. After 36 hours at rt, the reaction mixture was filtered through a Celite plug, and rinsed with dichloromethane (2x10 mL). After removing the solvent under reduced pressure on rotvapor, 146 mg of red semisolid was obtained. H-NMR showed that it was a mixture of the diketone and its enol tautomer in three to one ratio. It was further purified by flash chromatography with 10% ethyl acetate in hexane to get a red solid powder (124 mg, 93%). The pure enol tautomer was obtained quantitatively by treating the red solution of mixture of the two isomers in THF with catalytic amount of TEA and silica gel, and stirring for 5 to 7 hours. The disappearance of the red color is a sign of completion of this tautomerization process. mp 195-198^{o}C; IR (neat): 3322, 2970, 2921, 1691, 1646, 1458, 1401, 1311, 1029 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.74 (d, 1 H, J = 10 Hz), 6.68 (s, 1 H), 6.62 (s, 1 H), 5.43 (d, 1 H, J = 10 Hz), 5.36 (s, 1 H), 3.81 (s, 3 H), 3.58 (s, 1 H), 2.54 (heptet, 1 H, J = 7 Hz), 2.39 (s, 3 H), 1.26 (d, 3 H, J = 7 Hz), 1.23 (s, 3 H), 0.90 (d, 3 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 204.9, 155.4, 148.9, 146.4,

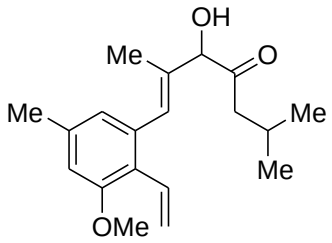
138.1, 132.6, 129.1, 123.4, 118.8, 118.6, 110.7, 55.5, 49.5, 48.8, 27.5, 21.9, 20.2, 20.0, 19.9; HRMS calcd for $C_{19}H_{22}O_3Na$ $[M+Na]^+$ 321.1461; Found: 321.1459.



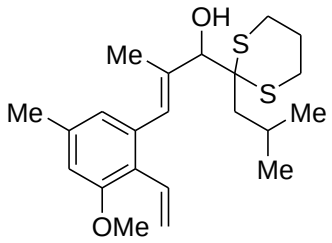
4-(2-ethenyl-3-methoxy-5-methylphenyl)-2-hydroxy-3-methyl-5-(propan-2-yl)cyclopent-2-en-1-one (98): (1*E*)-1-(2-ethenyl-3-methoxy-5-methylphenyl)-2,6-dimethylhept-1-ene-3,4-dione (224 mg, 0.746 mmol) in 10 mL THF was dropwise added LiHMDS (1 mL 0.9 M in THF, 0.9 mmol) at -78^{o}C.During the addition of LiHMDS, the yellow solution turned golden color gradually. The cooling bath was removed after 10 minutes. The reaction was quenched by adding 10 mL saturated aqueous ammonium chloride solution at 0 ^{o}C after stirring for 12 hours at rt. It was extracted with ethyl acetate (3x10 mL), washed with 20 mL brine, dried with Na_2SO_4, and concentrated under reduced pressure. After purification by flash chromatography (25% ethyl acetate in hexane), a colorless oil was obtained. (130 mg, 58%) IR (neat): 3326, 2954, 1699, 1650, 1462, 1401, 1115 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.78 (dd, 1 H, J = 12.5, 16.5 Hz), 6.57 (s, 1 H), 6.38 (s, 1 H), 5.61 (d, 1 H, J = 11 Hz), 5.46 (dd, 1 H, J = 2, 18 Hz), 4.12 (s, 1 H), 3.82 (s, 3 H), 2.32 (s, 1 H), 2.28 (s, 3 H), 2.22 - 2.15 (m, 1 H), 1.77 (s, 3 H), 0.89 (d, 3 H, J = 6 Hz), 0.88 (d, 3 H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 204.9, 157.1, 149.1, 146.5, 140.8, 138.5, 131.6, 125.0, 120.4, 119.2, 109.5, 60.1, 55.5, 43.0, 29.4, 21.6, 19.7, 18.5, 12.6; HRMS calcd for $C_{19}H_{24}O_3Na$ $[M+Na]^+$ 323.1618; Found: 323.1614.



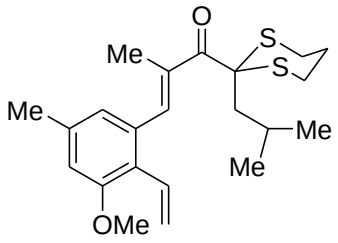
(1*E*)-1-(2-ethenyl-3-methoxy-5-methylphenyl)-2,6-dimethylhept-1-ene-3,4-dione (97): (1*E*)-1-(2-ethenyl-3-methoxy-5-methylphenyl)-3-hydroxy-2,6-dimethylhept-1-en-4-one (1.25 g, 4.13 mmol) in 25 mL anhydrous ethyl acetate was added IBX (5.78 g, 20.6 mmol) at rt at once. It was refluxed at 90^{o}C for 3 hours and cooled to rt, when the colorless solution turned yellow. Then, it was filtered thrugh a packed Celite plug, and rinsed with 100 mL ethyl acetate. After concentration under reduced pressure and purification by flash chromatography (5% ethyl acetate in hexane, collect the yellow band), a yellow oil was obtained. (1.03 g, 83%) IR (neat): 2962, 2929, 1708, 1654, 1458 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.54 (s, 1 H), 6.81 (dd, 1 H, J = 11.5, 18 Hz), 6.77 (s, 1 H), 6.72 (s, 1 H), 5.53 (dd, 1 H, J = 1.5, 11.5 Hz), 5.38 (dd, 1 H, J = 1.5, 17.5 Hz), 3.85 (s, 3 H), 2.67 (d, 2 H, J = 6.5 Hz), 2.37 (s, 3 H), 2.34 – 2.20 (m, 1 H), 2.01 (d, 3 H, J = 1 Hz), 0.99 (d, 6 H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 204.9, 197.1, 157.4, 147.7, 137.9, 134.0, 132.6, 130.5, 124.5, 122.3, 121.4, 112.0, 55.6, 48.2, 23.8, 22.6, 21.7, 12.3; HRMS calcd for $C_{19}H_{24}O_3Na$ $[M+Na]^+$ 323.1618; Found: 323.1628.



(1*E*)-1-(2-ethenyl-3-methoxy-5-methylphenyl)-3-hydroxy-2,6-dimethylhept-1-en-4-one (134): To a vigorously stirred suspension of HgO (5 g, 23 mmol) and $BF_3{\cdot}Et_2O$ (3.5 mL, 28 mmol) in 15% THF in water (120 mL) at rt, was added crude dithiane in 20 mL THF slowly. After stirring for 20 minutes at rt (only trace amount of red HgO left and a voluminous amount of white suspension formed), 100 mL diethyl ether and 50 mL brine was added. Then it was filtered though a well packed Celite, rinsed with 500 mL diethyl ether, separated and washed with saturated sodium bicarbonate (2x100 mL), brine (100 mL). after drying with sodium sulfate, and concentrated under reduced pressure, it was purified by flash chromatography (10% ethyl acetate in hexane) to get viscous oil (1.25 g, 56%): IR (neat): 3465, 2958, 2868, 1708, 1597, 1560, 1454, 1095 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.80 (dd, 1 H, J = 12, 18 Hz), 6.74 (s, 1 H), 6.69 (s, 1 H), 6.67 (s, 1 H), 5.68 (dd, 1 H, J = 2.5, 18 Hz), 5.48 (dd, 1 H, J = 2, 11.5 Hz), 4.69 (d, 1 H, J = 4.5 Hz), 4.05 (d, 1 H, J = 4.5 Hz), 3.87 (s, 3 H), 2.51 - 2.42 (m, 2 H), 2.37 (s, 3 H), 2.26 (heptet, 1 H, J = 7 Hz), 1.58 (d, 3 H, J = 1 Hz), 0.99 (d, 3 H, J = 6.5 Hz), 0.97 (d, 3 H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 210.3, 157.6, 137.6, 136.4, 134.6, 132.0, 131.0, 123.0, 122.6, 119.4, 110.6, 83.6, 55.4, 46.5, 24.5, 22.6, 22.5, 21.6, 12.3; HRMS calcd for $C_{19}H_{26}O_3Na$ $[M+Na]^+$ 325.1774; Found: 325.1770.

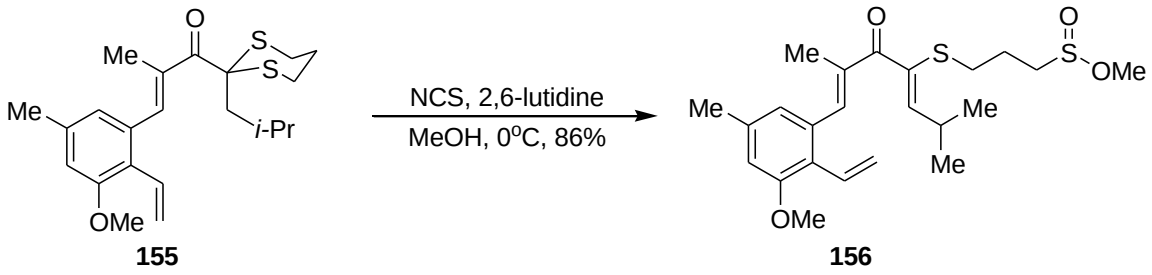


(E)-1-(2-isobutyl-1,3-dithian-2-yl)-3-(3-methoxy-5-methyl-2-vinylphenyl)-2-methylprop-2-en-1-ol (133): To a solution of dithiane (1.56 g, 8.9 mmol) in 20 mL THF, was added 2.4 M nBuLi at – 20^{o}C slowly. After it was stirred at – 20^{o}C for 3 hours, the aldehyde (1.6 g, 7.41 mmol) in 5 mL THF was added dropwisely, during which time the colorless solution turned dark. After 1 hour at – 20^{o}C, it was raised to rt and quenched with 20 mL saturated ammonium chloride solution. Then it was washed with 10 mL brine, dried with Na_2SO_4, and concentrated under reduced pressure to get viscous oil which went to the next step as crude: IR (neat): 3436, 2949, 1601, 1560, 1454, 1270, 907, 833, 731 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.80 (dd, 1 H, J = 11.5, 18 Hz), 6.68 (s, 1 H), 6.65 (s, 1 H), 6.63 (s, 1 H), 5.76 (dd, 1 H, J = 2, 17.5 Hz), 5.40 (dd, 1 H, J = 2.5, 12 Hz), 4.68 (s, 1 H), 3.84 (s, 3 H), 3.14 (d, 1 H, J = 1 Hz), 3.16 – 3.05 (m, 2 H), 2.68 – 2.62 (m, 2 H), 2.34 (s, 3 H), 2.16 – 2.09 (m, 2 H), 1.87 (s, 3 H), 1.94 – 1.83 (m, 2 H), 1.52 (dd, 1 H, J = 5, 15 Hz), 1.04 (d, 3 H, J = 6.5 Hz), 1.01 (d, 3 H, J = 6 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.7, 137.8, 137.2, 134.6, 131.2, 130.4, 123.0, 122.7, 119.0, 110.2, 75.4, 60.4, 55.4, 43.2, 26.6, 25.6, 25.5, 24.9, 24.2, 21.6, 17.5; HRMS calcd for $C_{22}H_{32}O_2S_2Na$ $[M+Na]^+$ 415.1736; Found: 415.1733.



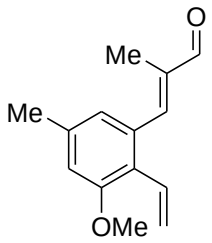
(E)-1-(2-isobutyl-1,3-dithian-2-yl)-3-(3-methoxy-5-methyl-2-vinylphenyl)-2-methylprop-2-en-1-one (155): To a solution of dithiane (2.68g, 15.2 mmol) in THF (30 mL, 0.5 M), was added *n*-buyl lithium (6 mL, 2.5 M in THF, 15 mmol) slowly over 10 minutes. After stirring for 3.5 hours at – 20 ^{o}C, weinreb's amide (4.19 g, 15.2 mmol) in 30 mL THF was added slowly, at which time the colorless solution turned to dark. After stirring at – 20 ^{o}C for 30 minutes (gradually turned to orange color), it was quenched with saturated ammonium chloride aqueous solution at – 20^{o}C. Then it was raised to rt and stirred for 10 minutes. 40 mL brine and 40 mL diethyl ether was added. It was then extracted with diethyl ether (3 x 50 mL), washed with brine (100 mL), and dried with Na_2SO_4. After removing the solvents under reduced pressure, it was purified by flash chromatography (5% to 10% ethyl acetate in hexane) to get pale yellow oil (5.31 g, 89%). IR (neat): 2958, 2921, 1658, 1597, 1560, 1458, 1201 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.98 (s, 1 H), 6.78 (dd, 1 H, J = 11.5, 17.5 Hz), 6.68 (s, 1 H), 6.64 (s, 1 H), 5.57 (dd, 1 H, J = 2, 17.5 Hz), 5.45 (dd, 1 H, J = 2, 12 Hz), 3.84 (s, 3 H), 3.14 (dd, 1 H, J = 2.5, 12 Hz), 3.12 (dd, 1 H, J = 2.5, 11.5 Hz), 2.74 (dd, 1 H, J = 3.5, 5 Hz), 2.71 (dd, 1 H, J = 3.5, 5 Hz), 2.36 (s, 3 H), 2.28 (d, 2 H, J = 6.5 Hz), 2.09 – 2.02 (m, 2 H), 1.99 (d, 3 H, J = 1 Hz), 1.93 – 1.84 (m, 1 H), 0.96 (d, 6 H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.9, 157.4, 138.9, 137.6, 135.7, 135.1, 130.7, 123.3, 122.1, 120.1, 110.9, 61.0, 55.4, 47.9,

28.0, 25.3, 24.6, 23.8, 21.6, 16.4; HRMS calcd for $C_{22}H_{30}O_2S_2Na$ $[M+Na]^+$ 413.1579; Found: 413.1578.



155 **156**

156: To a solution of **155** (5.31 g, 13.6 mmol) in methanol (35 mL, 0.4 M) was added 2,6-lutidine (9.38 g, 68 mmol) and NCS (3.6 g, 2.69 mmol) at 0 ^oC. After 7 min, the milky solution turned a yellow homogeneous solution. Then it was quenched with sat. $Na_2S_2O_3$, brine, and extracted with Et_2O 3 x 35 mL. After washing with 1N HCl, washing with brine, and drying with $MgSO_4$, it was concentrated under reduced pressure. FCC with 25% EA/Hex yielded **156** (5.1 g, 86%). IR (neat): 2962, 1642, 1454, 1234, 1127, 992 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.45 (s, 1 H), 6.78 (dd, 1 H, J = 11, 17.5 Hz), 6.73 (s, 1 H), 6.70 (s, 1 H), 6.15 (d, 1 H, J = 9.5 Hz), 5.45-5.40 (m, 2 H), 3.85 (s, 3 H), 3.74 (s, 3 H), 3.05 (m, 1 H), 2.91-2.79 (m, 2 H), 2.76 (t, 2 H, J = 7 Hz), 2.01 (d, 3 H, J = 1.5 Hz), 1.96 (t, 2 H, J = 7 Hz), 1.01 (d, 6 H, J = 5.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.5, 157.4, 149.8, 143.2, 137.9, 136.6, 135.1, 131.7, 130.8, 123.9, 122.3, 120.6, 111.5, 55.6, 55.2, 54.5, 31.3, 29.4, 22.0, 21.7, 21.6, 13.8; HRMS calcd for $C_{23}H_{32}O_4S_2Na$ $[M+Na]^+$ 459.1634; Found: 459.1636.



(2*E*)-3-(2-ethenyl-3-methoxy-5-methylphenyl)-2-methylprop-2-enal (132):

Stille coupling: CsF (1.8 g, 12 mmol) was added in one portion into a solution of bromoaldehyde (2.17 g, 8.05 mmol), vinyltributyltin (2.81 g, 8.86 mmol), bistriphenyl phosphine palladium (II) chloride (56 mg, 0.08 mmol) and triphenyl phosphine (73 mg, 0.32 mmol) in toluene (50 mL, 0.16 M). Then the mixture was stirred at 90^{o}C for 17 hours, during which time the yellow solution turned dark. It was cooled down to rt and filtered through a well packed Celite and rinsed with 100 mL ethyl acetate to get rid of the black solids. After concentrated under reduced pressure, it was purified by flashed chromatography (pure hexane, then 2% to 5% ethyl acetate in hexane) to get the yellow oil (1.63 g, 94%). IR (neat): 3003, 2958, 2831, 2709, 1683, 1622, 1597, 1458, 1201, 1017 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.63 (s, 1 H), 7.48 (s, 1 H), 6.83 (dd, 1 H, J = 11.5, 17.5 Hz), 6.79 (s, 1 H), 6.74 (s, 1 H), 5.52 (dd, 1 H, J = 2, 11.5 Hz), 5.41 (dd, 1 H, J = 2, 17.5 Hz), 3.86 (s, 3 H), 2.38 (s, 3 H), 1.95 (d, 3 H, J = 1.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 195.7, 157.4, 150.4, 138.5, 137.8, 134.1, 130.4, 124.2, 122.1, 121.1, 112.0, 55.6, 21.6, 10.8; HRMS calcd for $C_{14}H_{16}O_2Na$ $[M+Na]^+$ 239.1042; Found: 239.1045.

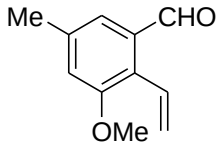
Suzuki coupling to make 132:

To a solution of bromoaldehyde (1.04 g, 3.87 mmol) in 20 mL propanol was added vinyl pinacol borate (0.90 g, 5.8 mmol) and purged with N_2 for 10 minutes at rt. The solution

was treated with palladium (II) acetate (8.7 mg, 0.039 mmol), triphenylphosphine (30 mg, 0.11 mmol), sodium carbonate (8 mL, 0.725 M, 5.8 mmol), and purged with N_2 for 10 minutes. Then the mixture was raised to 85^{o}C, and stirred under N_2 for 7 hours. TCL showed complete consumption of bromoaldehyde. Then, it was cooled to rt, diluted with ethyl acetate (20 mL), filtered through 2.5 g Florisil on top of a Celite plug (1 cm depth), and rinsed with ethyl acetate (2x30 mL). The two layers were separated. The aqueous layer was extracted with ethyl acetate (30 mL), washed with saturated aqueous sodium bicarbonate (50 mL), brine (50 mL), concentrated under reduced pressure, and purified by flash chromatography (10% ethyl acetate in hexane) to get a yellow oil (769 mg, 92%).

Oxidation by MnO_2 to make 132:

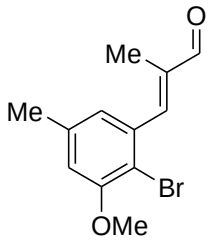
To a solution of the alcohol (470 mg, 2.15 mmol) in DCM (10 mL, 0.2 M) was added MnO_2 (1.87 g, 21.5 mmol) at rt in one portion. It was stirred at rt for 12 hour and filtered through Celite. After concentration under reduced pressure, it was purified by flash chromatography (5% ethyl acetate in hexane) to get the aldehyde (414 mg, 89%).



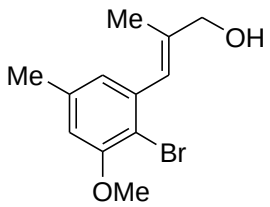
102

3-methoxy-5-methyl-2-vinylbenzaldehyde (102): It was synthesized from 2-iodo-3-methoxy-5-methylbenzaldehyde, or 2-bromo-3-methoxy-5-methylbenzaldehyde through Stille or Suzuki coupling similar to the above procedures in yields from 51% to 82% (Table 2) as a white wax. IR (neat): 3019, 2860, 1679, 1597, 1278, 1193, 1136, 1078, 996

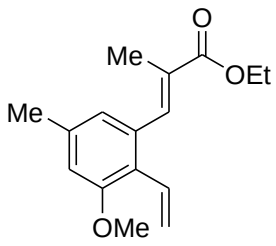
cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.2 (s, 1 H), 7.34 (s, 1 H), 7.00 (dd, 1 H, J = 11, 18 Hz), 6.90 (s, 1 H), 5.71 (dd, 1 H, J = 1.5, 11 Hz), 5.31 (dd, 1 H, J = 1.8, 18 Hz), 3.87 (s, 3 H), 2.40 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 193, 157, 139, 135, 129, 128, 124, 120, 116, 56, 22; HRMS calcd for $C_{11}H_{12}O_2Na$ $[M+Na]^+$ 199.0730; Found: 199.1727.



(2E)-3-(2-bromo-3-methoxy-5-methylphenyl)-2-methylprop-2-enal (131): To a solution of alcohol (470 mg, 2.15 mmol) in DCM (10 mL, 0.2 M) was added manganese oxide (1.87 g, 21.5 mmol) at rt. The mixture was stirred for 2 days at rt, filtered through Celite to get rid of solid, and purified by flash chromatography (10% ethyl acetate in hexane) to get colorless crystal (414 mg, 89%). mp 101 - 102^{o}C; IR (neat): 2917, 2848, 1679, 1569, 1311, 1197, 1017, 727 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.45 (s, 1 H), 7.26 (s, 1 H), 6.82 (s, 1 H), 6.74 (s, 1 H), 3.92 (s, 3 H), 2.37 (s, 3 H), 1.93 (d, 3 H, J = 1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 195.4, 155.5, 138.7, 137.2, 124.4, 123.4, 110.9, 110.0, 68.0, 56.1, 21.3, 15.0 HRMS calcd for $C_{12}H_{13}BrO_2Na$ $[M+Na]^+$ 290.9991; Found: 290.9989.



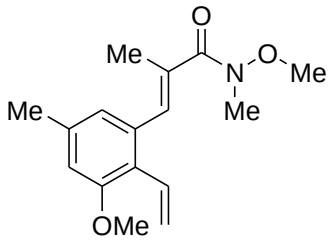
(2E)-3-(2-bromo-3-methoxy-5-methylphenyl)-2-methylprop-2-en-1-ol (131a): To a solution of the bromoester (5.64 g, 18 mol) in THF (200 mL, 0.09 M), was added DIBAL (54 mL, 1 M in toluene, 54 mmol) slowly at – 30 ^{o}C. After stirring for 2.5 hours at – 30 ^{o}C, it was raised to 0 ^{o}C and added 2.16 mL water slowly, 0.2 mL 4 N sodium hydroxide aqueous solution, 5.4 mL water sequentially at 0 ^{o}C. Then it was raised to rt and stirred for 15 minutes at rt, added 10 g anhydrous magnesium sulfate, stirred for 15 minutes, and filtered through Celite. After concentration under reduced pressure, it was purified by flash chromatography (25% ethyl acetate in hexane) to get the yellow oil (4.69 g, 96%). IR (neat): 3379, 2938, 2856, 1569, 1315, 1242, 1090, 1168, 911, 829, 731 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.69 (s, 1 H), 6.60 (s, 1 H), 6.50 (s, 1 H), 4.21 (d, 2 H, J = 4.5 Hz), 3.86 (s, 3 H), 2.49 (t, 1 H, J = 4.5 Hz), 2.30 (s, 3 H), 1.78 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.5, 138.7, 137.2, 124.4, 123.4, 110.9, 110.0, 68.0, 56.1, 21.3, 15.0; HRMS calcd for $C_{12}H_{15}BrO_2Na$ $[M+Na]^+$ 293.0148; Found: 293.0163.



Ethyl (2*E*)-3-(2-ethenyl-3-methoxy-5-methylphenyl)-2-methylprop-2-enoate (153):

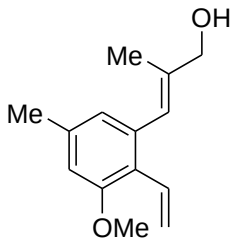
To a solution of bromo ester (5.06 g, 16.2 mmol), vinyltributyltin (7.71 g, 24.3 mmol), bistriphenyl phosphine palladium (II) chloride (171 mg, 0.16 mmol) and triphenyl phosphine (145 mg, 0.64 mmol) in toluene (80 mL, 0.2 M), was added CsF (3.70 g, 24.3 mmol). Then the mixture was stirred at 110 ^{o}C for 20 hours, during which time the

yellow solution turned to a grayish suspension. It was cooled down to rt and filtered through a short silica plug and rinsed with 200 mL diethyl ether. After concentrated under reduced pressure, it was purified by flashed chromatography (5% to 10% ethyl acetate in hexane) to get the yellow oil (3.86 g, 92%).IR (neat): 3085, 2979, 2958, 1704, 1597, 1560, 1454, 1242, 1115 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.73 (s, 1 H), 6.79 (dd, 1 H, J = 11.5, 17.5 Hz), 6.68 (s, 1 H), 6.67 (s, 1 H), 5.52 (dd, 1 H, J = 1.5, 18 Hz), 5.46 (dd, 1 H, J = 1.5, 11.5 Hz), 4.26 (q, 2 H, J = 7 Hz), 3.85 (s, 3 H), 2.35 (s, 3 H), 1.96 (s, 3 H), 1.34 (t, 3 H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.5, 157.5, 139.7, 137.6, 135.6, 130.5, 128.6, 123.5, 122.3, 120.1, 111.2, 60.7, 55.5, 21.6, 14.3, 14.0; HRMS calcd for $C_{16}H_{20}O_3Na$ $[M+Na]^+$ 283.1305; Found: 283.1305.



(2*E*)-3-(2-ethenyl-3-methoxy-5-methylphenyl)-*N*-methoxy-*N*,2-dimethylprop-2-enamide (154): To a well mixed suspension of ethyl ester (7.18 g, 27.6 mmol) and N-methoxymethanamine hydrochloride (5.40 g, 55.1 mmol) in THF (55 mL, 0.5 M) was added isopropyl magnesium chloride (55.2 mL, 2 M in diethyl ether) over 1 hour at –20 ^{o}C by the aid of slow addition pump, resulting a yellow solution with white solid floating at the bottom. The temperature was allowed to rise to – 5 ^{o}C slowly over 2 hours, and quenched with saturated ammonium chloride aqueous solution at – 5 ^{o}C, forming voluminous amount of white salt. After stirring at rt for 30 minutes, it was extracted with

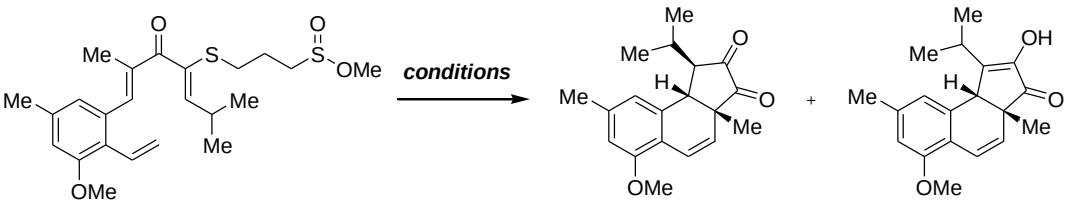
diethyl ether (3 x 100 mL), washed with brine (200 mL), dried with Na_2SO_4, and concentrated under reduced pressure. After purification by flash chromatography (50% ethyl acetate in hexane), the Weinreb's amide was obtained as a colorless viscous oil (6.75 g, 80%): IR (neat): 2962, 2938, 1650, 1560, 1454, 1368, 1291, 1201, 1103, 996, 911 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.86 (s, 1 H), 6.77 (dd, 1 H, J = 12, 18 Hz), 6.70 (s, 1 H), 6.67 (s, 1 H), 5.65 (dd, 1 H, J = 3.5, 18 Hz), 5.45 (dd, 1 H, J = 3.5, 12 Hz), 3.85 (s, 3 H), 3.71 (s, 3 H), 3.29 (s, 3 H), 2.35 (s, 3 H), 1.97 (d, 3 H, J = 2.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.5, 157.6, 137.5, 135.6, 132.2, 132.16, 130.6, 123.2, 122.5, 119.8, 110.8, 61.2, 55.5, 33.6, 21.6, 15.5; HRMS calcd for $C_{16}H_{21}NO_3Na$ $[M+Na]^+$ 298.1414; Found: 298.1413.



(2*E*)-3-(2-ethenyl-3-methoxy-5-methylphenyl)-2-methylprop-2-en-1-ol:

To a solution of the ester (540 mg, 2.07 mmol) in DCM (6 mL, 0.3 M), was added DIBAL (6.22 mL, 1 M in toluene, 6.22 mmol) slowly at 0 ^oC. After stirring for 1 hour at 0 ^oC, it was quenched with $MgSO_4 \cdot 7H_2O$ till no bubble was released. Then it was filtered through Celite, rinsed with 50 mL ethyl acetate, and concentrated under reduced pressure. After purification by flash chromatography (25% ethyl acetate in hexane), the alcohol was obtained (448 mg, 99%). IR (neat): 3354, 3015, 2913, 2852, 1605, 1564, 1454, 1303, 1156, 1095, 1005 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.75 (dd, 1 H, J = 12, 18 Hz), 6.63

(s, 2 H), 6.52 (s, 1 H), 5.68 (dd, 1 H, J = 2.5, 18 Hz), 5.39 (dd, 1 H, J = 2, 11.5 Hz), 4.18 (d, 2 H, J = 5.5 Hz), 3.83 (s, 3 H), 2.33 (s, 3 H), 1.73 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.6, 137.4, 137.3, 137.2, 131.0, 125.2, 123.0, 122.6, 118.9, 110.2, 68.5, 55.4, 21.6, 15.1; HRMS calcd for $C_{14}H_{18}O_2Na$ $[M+Na]^+$ 241.1199; Found: 241.1198.



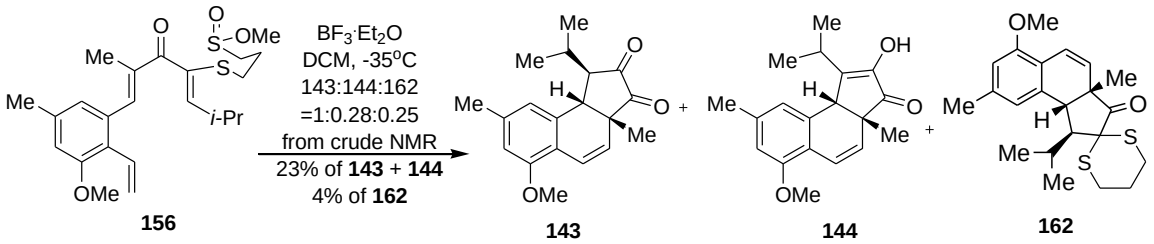
156 **143** **144**

Table 6

Catalyst,additive	Solvent(concentration)	Temperature, time,	yield(A to B ratio)
AcOH	MeOH	rt	SM
$Pd(ACN)_2Cl_2$	Acetone/H_2O	rt	decomposed
HCl	Acetone/H_2O	rt	decomposed
Cu(OTf)·benzene, $LiClO_4$	DCM	rt, 2h; reflux, 4.5 h	 (quick test)5:7
2 mol% Cu(OTf)·benzene 2 equiv. $LiClO_4$	DCE(0.05 M)	rt, 45 min; 42°C, 45 min; 55°C, 7 hours	SM gone; 3 new compounds; 53% (1: 3.8)
7 mol% Cu(OTf).benzene, 1 equiv. $LiClO_4$	DCE(0.1M)	rt, 1day; 35 °C, 14 h	trace amount of P; 35% (1:5)
12 mol% $Sc(OTf)_3$, 2 equiv. $LiClO_4$	DCE(0.025M)	rt, 15 min; 50 °C, 0.5 h	SM gone after 15 min 7%
10 mol% $Sc(OTf)_3$	DCE(0.1M)	rt, 1 h	no rxn
10 mol% $Sc(OTf)_3$, 1 equiv. $LiClO_4$	DCE(0.1M)	rt, 24h spot to spot to spot	24% (1:1.8) SM gone after 15 min

10 mol% $Cu(OTf)_2$, 1 equiv. $LiClO_4$, 20 mol% 2,6-lutidine	DCM(0.1M)	reflux	unknown
10 mol% $Cu(OTf)_2$, 2 equiv. $LiClO_4$	DCM(0.05 M)	rt, 1.5 days	10 %
2 mol% Cu(OTf)·benzene, 2 equiv. $LiClO_4$; Added $Cu(OTf)_2$	DCE(0.05 M)	Rt to 55°C, 19 hours; rt, 5 days	No rxn; 10 %
10 mol% $Cu(OTf)_2$	DCE(0.05 M)	40 °C, 20 hours	25 %
2 mol% $Cu(OTf)_2$	DCE(0.05 M)	Rt, 20 min; 40 °C, 6 hours	 28 %
2 mol% Cu(OTf)·benzene, 1 equiv. $LiClO_4$		Rt to 50 °C	19% for 2 steps
10 mol% $Pd(ACN)_2Cl_2$, 1 equiv. TEA	DCE	70 °C, 2 days	No rxn
10 mol% $AgSbF_6$	DCM	rt, 2 days	No rxn
10 mol% Dichloro(pentamethylcyclopentadienyl)iridium(III) dimer	DCM	Reflux, 7 hours	No rxn
1 equiv. $Ti(OiPr)_4$	DCM(0.2 M)	-78 °C to 45 °C	No rxn
4 equiv. BF3.Et2O	DCM(0.2 M)	-70 °C, 4 days	16 % (1: 0.3)
4 equiv. BF3.Et2O	DCM(0.2 M)	-50 °C, 11 hours	22 %
10 mol% $Hg(CO_2CF_3)_2$	DCM(0.2 M)	-20 °C, hours	%

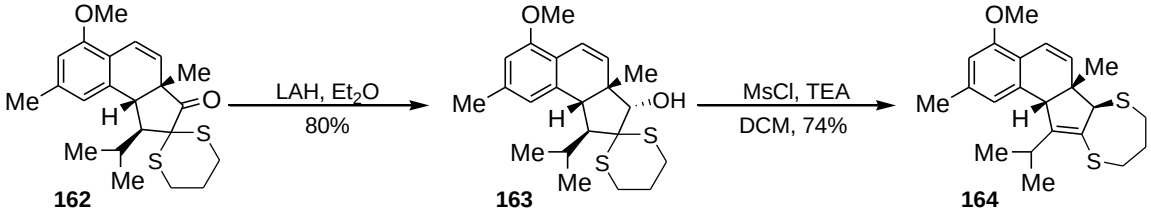
$Cu(ClO_4)_2 \cdot 6H_2O$	DCM	Reflux, 30 h	No rxn
$Cu(ClO_4)_2 \cdot 6H_2O$ Added 2 mol% Cu(OTf)·benzene and 2 equiv. $LiClO_4$	DCE(0.05M)	40 °C, 3 h; 48 °C, 23 h	No rxn 22 %



156 **143** **144** **162**

162: To a solution of **156** (3.6 g, 8.24 mmol) in DCM (55 mL, 0.15 M) at -35 °C was added trifluoroborane etherate (3.5 g, 24.7 mmol) dropwise. The solution turned red. After stirring at -35 °C for 5 min, it was raised to rt and stirred for 1 hour. Then, it was

cooled to 0 ^{o}C and quenched with 50 mL sat. $NaHCO_3$. The mixture was stirred for 30 min at rt. Then, it was washed with 2 x 50 mL brine, dried with $MgSO_4$, and concentrated under reduced pressure to get reddish oil. The crude H-NMR showed the ratio of **143**/**144**/**162** to be 1: 0.28: 0.25. After purification by FCC with 10% EA/Hex, 23% of **143** and **144** were isolated together with 4% of less polar **162**. IR (neat): 2958, 2933, 1720, 1605, 1278, 1086 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.87 (d, 1 H, J = 9.5 Hz), 6.75 (s, 1 H), 6.60 (s, 1 H), 5.44 (d, 1 H, J = 9.5 Hz), 4.02 (dt, 1 H, J = 2.5, 13.5 Hz), 3.82 (s, 3 H), 3.31 (d, 1 H, J = 12 Hz), 3.24 (dt, 1 H, J = 2.5 14 Hz), 2.56 (dt, 1 H, J = 14, 3 Hz), 2.48 (dt, 1 H, J = 13.5, 3.5 Hz), 2.34 (s, 3 H), 2.22-2.16 (m, 1 H), 2.15 (s, 1 H), 2.15-2.11 (m, 1 H), 1.88 (m, 1 H), 1.24 (d, 3 H, J = 7 Hz), 1.17 (s, 3 H), 0.81 (d, 3 H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 210.5, 155.3, 138.0, 134.7, 127.5, 123.6, 120.4, 117.6, 110.4, 55.4, 54.3, 52.6, 45.6, 27.1, 26.7, 25.5, 25.1, 23.2, 21.9, 21.8, 21.3; HRMS calcd for $C_{22}H_{28}O_2S_2Na$ $[M+Na]^+$ 411.1427; Found: 411.1419.



162 **163** **164**

163: To a solution of **162** (30 mg, 0.077 mmol) in Et2O was added LAH (10 mg, 0.26 mmol) at 0 ^{o}C. After 10 min, it was filtered through a silica plug, rinsed with Et2O, concentrated under reduced pressure to get the crude white solid product. It was purified by FCC with 25% EA/Hex to get analytically pure **163** (24 mg, 80%) as a white solid. Melting point is 143-146 ^{o}C. IR (neat): 3461, 2917, 1462, 1274 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.77 (d, 1 H, J = 10 Hz), 6.67 (s, 1 H), 6.56 (s, 1 H), 5.85 (dd, 1 H, J = 10, 1 Hz), 4.46 (d, 1 H, J = 12 Hz), 3.80 (s, 3 H), 3.44 (dt, 1 H, J = 3.5, 13 Hz), 3.08 (ddd, 1 H,

J = 2.5, 11.5, 14 Hz), 2.91 (d, 1 H, J = 12 Hz), 2.84 (dd, 1 H, J = 1.5, 12 Hz), 2.70 (dt, 1 H, J = 14, 4 Hz), 2.56 (dt, 1 H, J = 13.5, 3.5 Hz), 2.32 (s, 1 H), 2.19-2.11 (m, 1 H), 2.10-2.04 (m, 2 H), 1.91-1.82 (m, 1 H), 1.25 (d, 3 H, J = 7 Hz), 0.65 (d, 3 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.1, 137.3, 136.2, 127.9, 123.5, 119.2, 118.5, 110.2, 94.4, 62.6, 58.7, 55.4, 47.2, 46.9, 29.3, 27.7, 25.6, 24.2, 23.3, 23.0, 21.8, 20.4; HRMS calcd for $C_{22}H_{30}O_2S_2Na$ $[M+Na]^+$ 413.1579; Found: 413.1577.

164: To a solution of **163** (24 mg, 0.062 mmol) in DCM (1 mL, 0.06 M) was added TEA (12.4 mg, 0.123 mmol) and mesyl chloride (10 mg, 0.092 mmol) at 0 ^{o}C. Then it was stirred at rt for 1 hour and quenched with 2 mL sat. NH4Cl, extracted with 2x2 Ml DCM, washed with brine, dried with Na2SO4, concentrated to get a white solid crude product. It was purified by FCC to get pure **164** (17 mg, 74%) with a melting point of 168-170 ^{o}C; IR (neat): 2950, 1601, 1471, 1274, 1086 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.64 (d, 1 H, J = 10 Hz), 6.62 (s, 1 H), 6.57 (s, 1 H), 5.52 (d, 1 H, J = 9.5 Hz), 4.19 (s, 1 H), 3.79 (s, 3 H), 3.73 (s, 1 H), 3.30 (ddd, 1 H, J = 4.5, 11.5, 15.5 Hz), 3.09 (ddd, 1 H, J = 4.5, 11, 15 Hz), 2.76 (ddd, 1 H, J = 3.5, 5, 15 Hz), 2.64 (dt, 1 H, J = 15, 4 Hz), 2.49 (heptet, 1 H, J = 7.5 Hz), 2.34 (s, 3 H), 2.19-2.04 (m, 2 H), 1.53 (s, 3 H), 1.12 (s, 3 H), 0.91 (d, 3 H, J = 7 Hz), 0.81 (d, 3 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.7, 142.0, 137.2, 136.6, 133.7, 129.9, 124.4, 119.4, 118.4, 110.5, 61.5, 55.6, 55.5, 48.5, 34.5, 30.7, 28.9, 28.6, 21.8, 20.3, 18.9, 18.6; HRMS calcd for $C_{22}H_{28}OS_2Na$ $[M+Na]^+$ 395.1474; Found: 395.1472.

APPENDIX

Selected ^{1}H and ^{13}C NMR Spectra

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PROCNO 1
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FIDRES 0.157632 Hz
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RG 11.3
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DE 6.00 usec
TE 300.0 K
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MCWRK 0.01500000 sec
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LB 0.30 Hz
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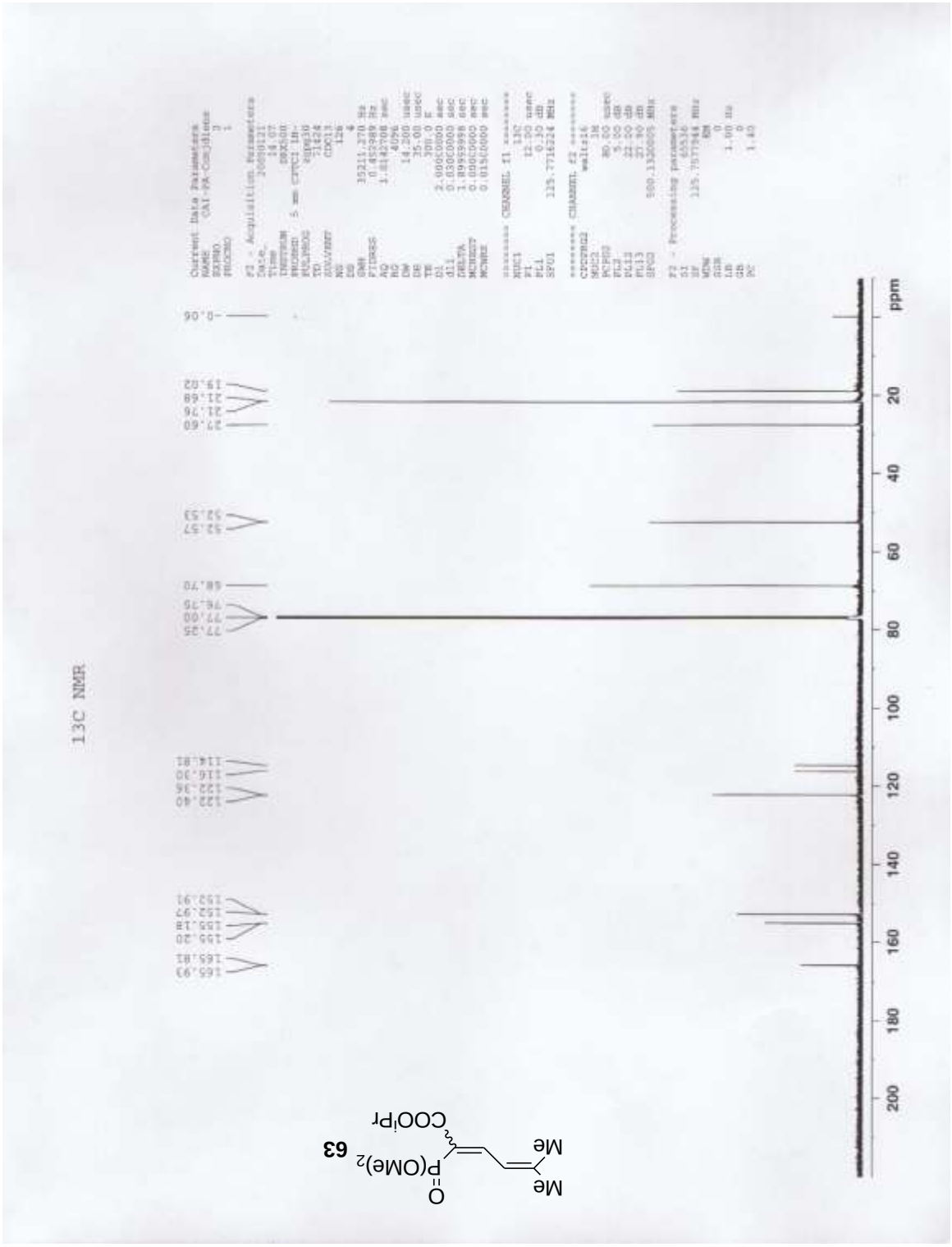
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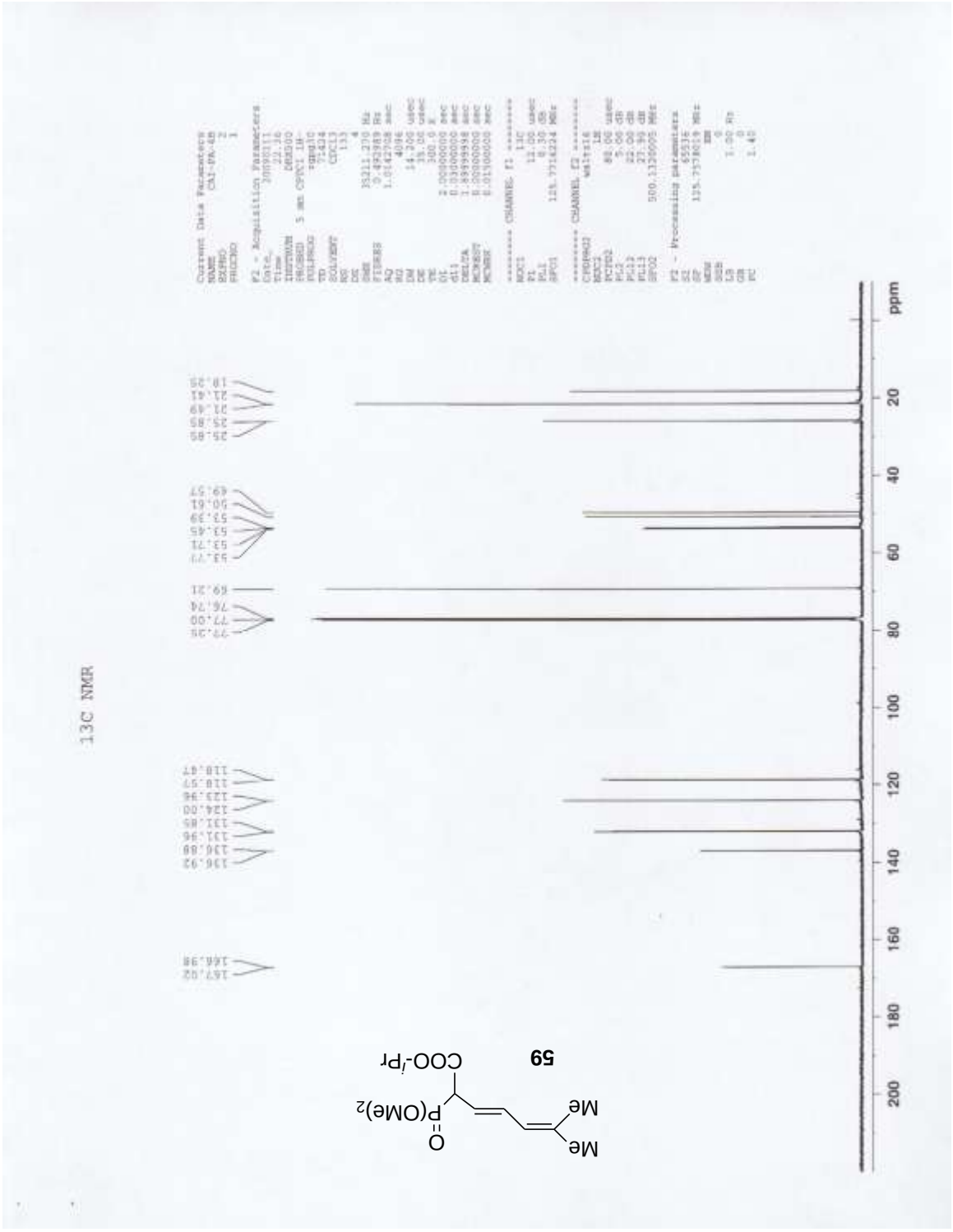
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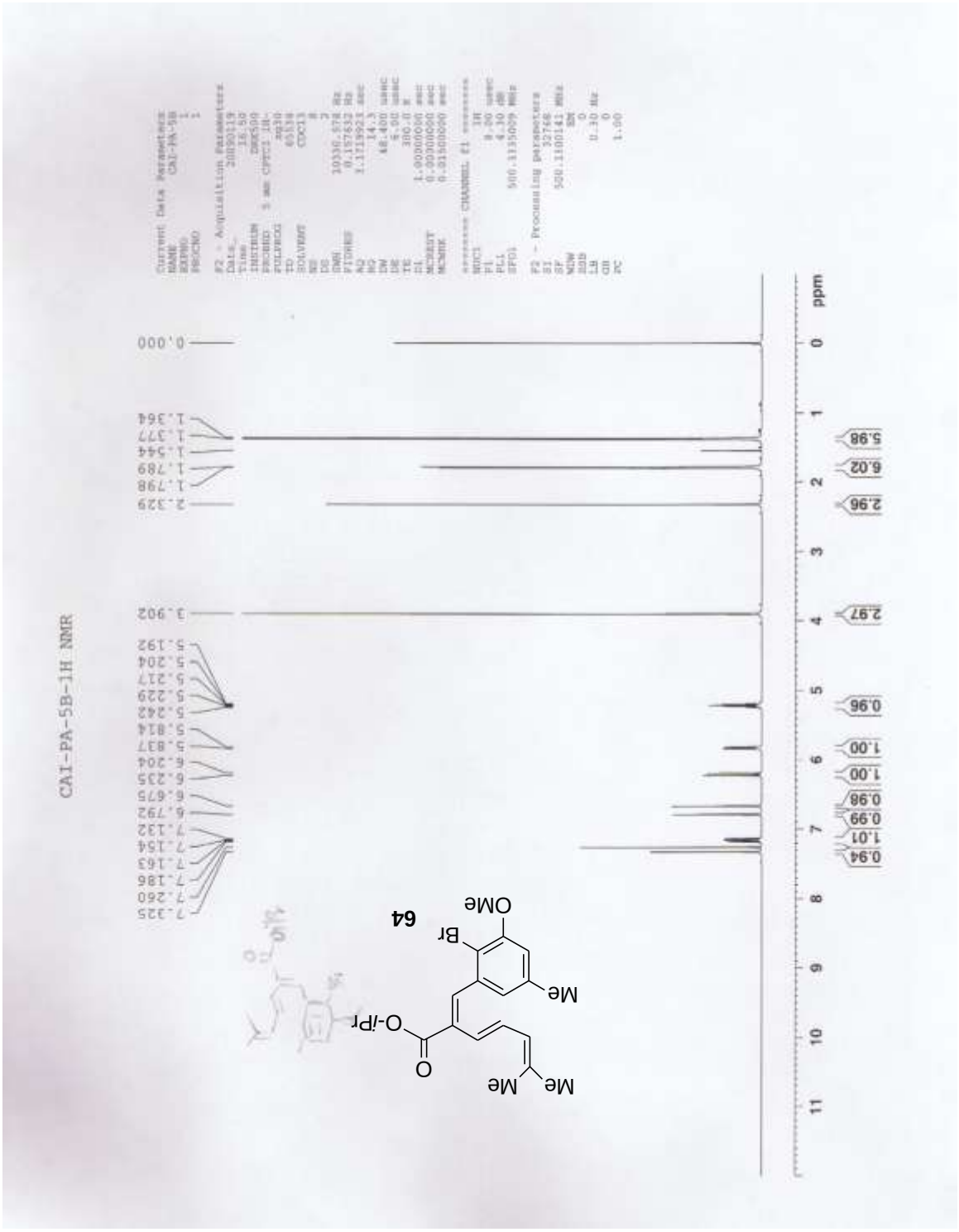
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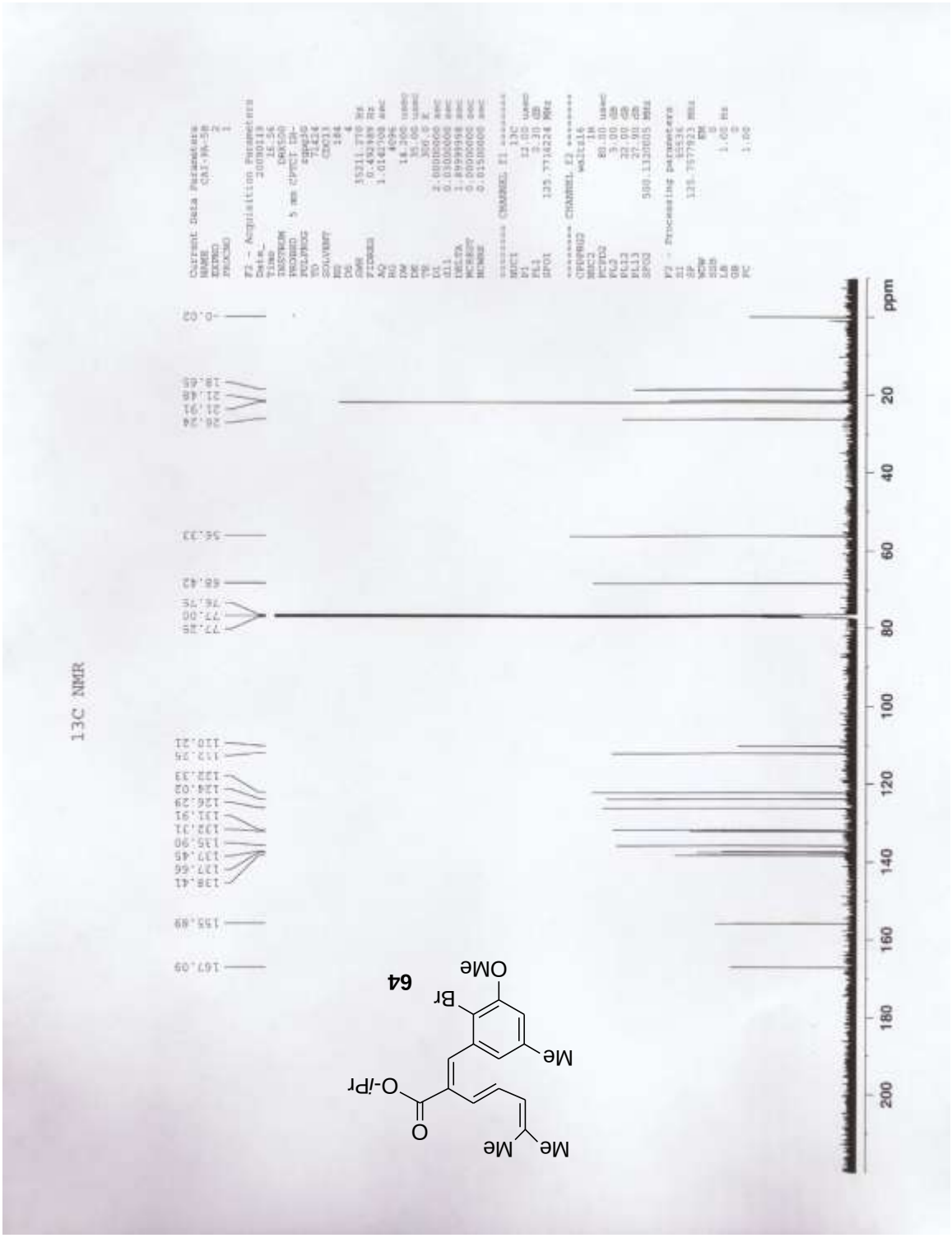
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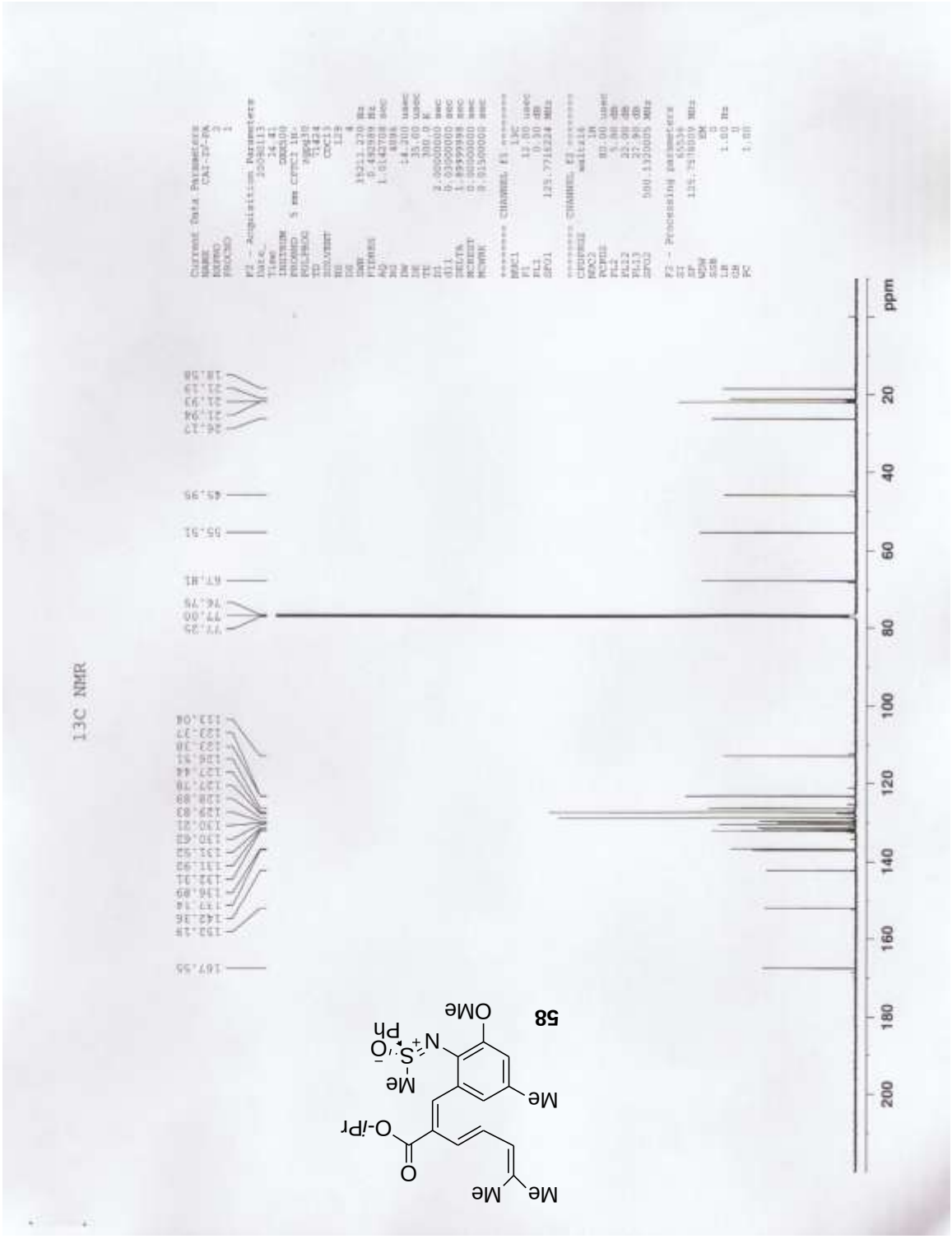
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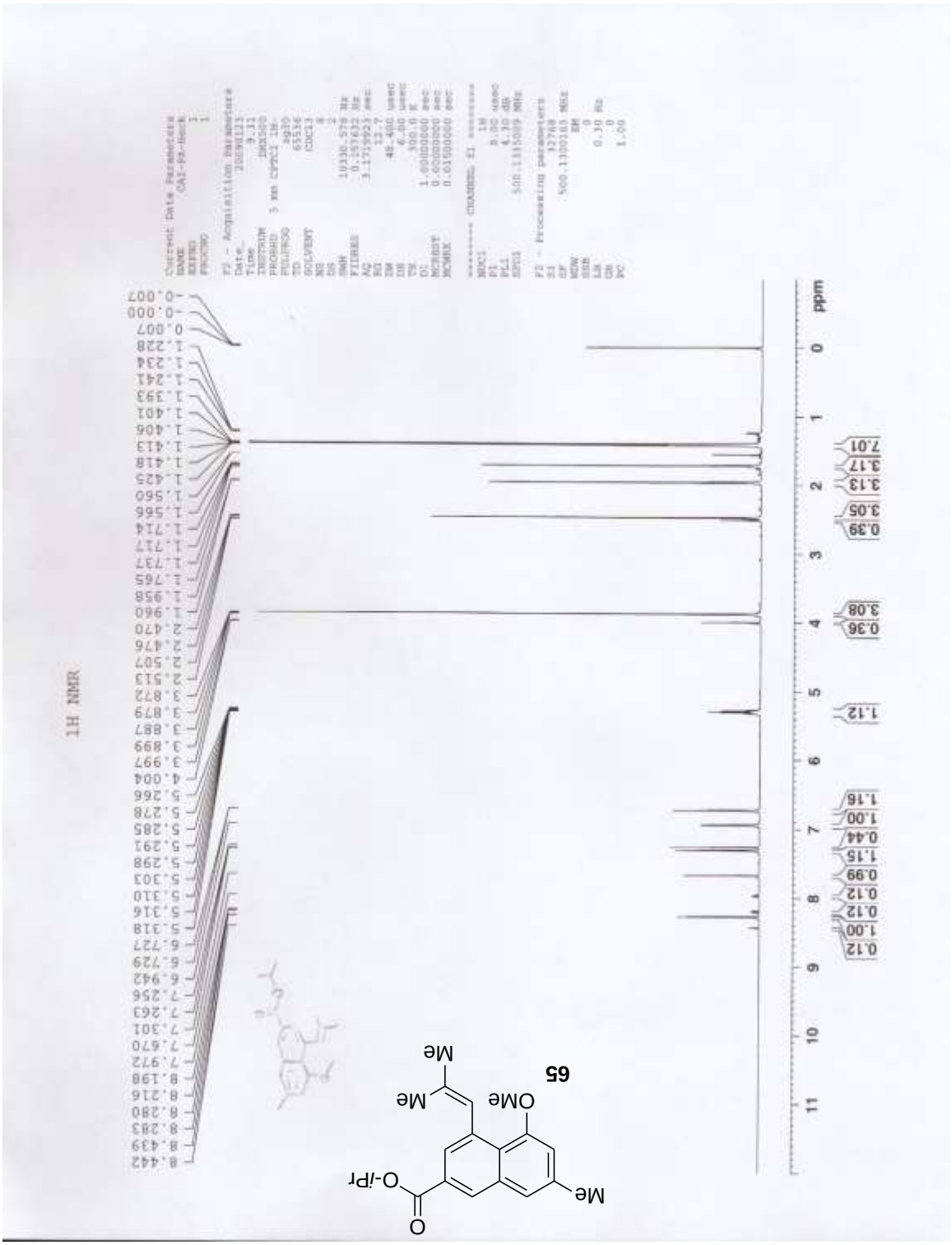
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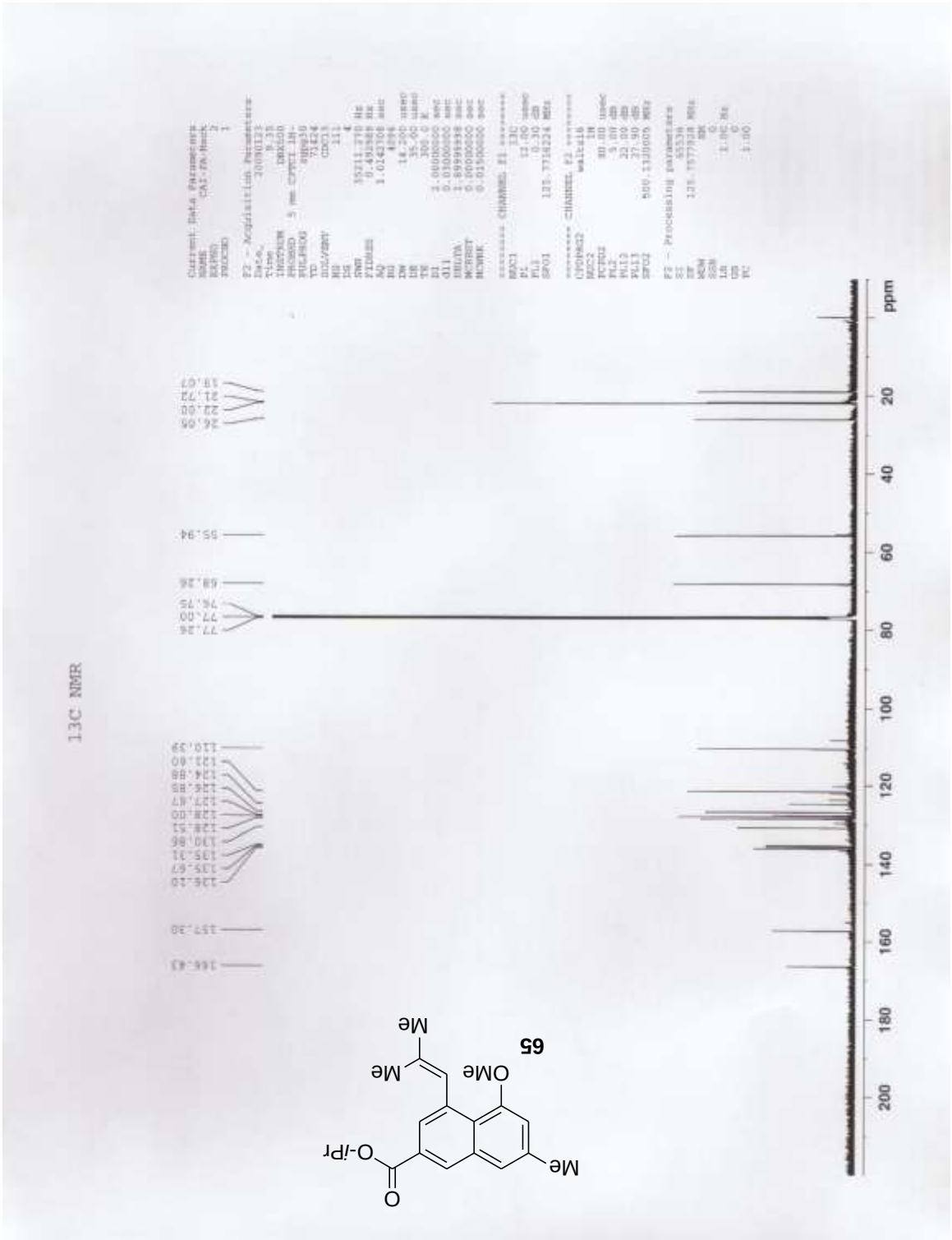
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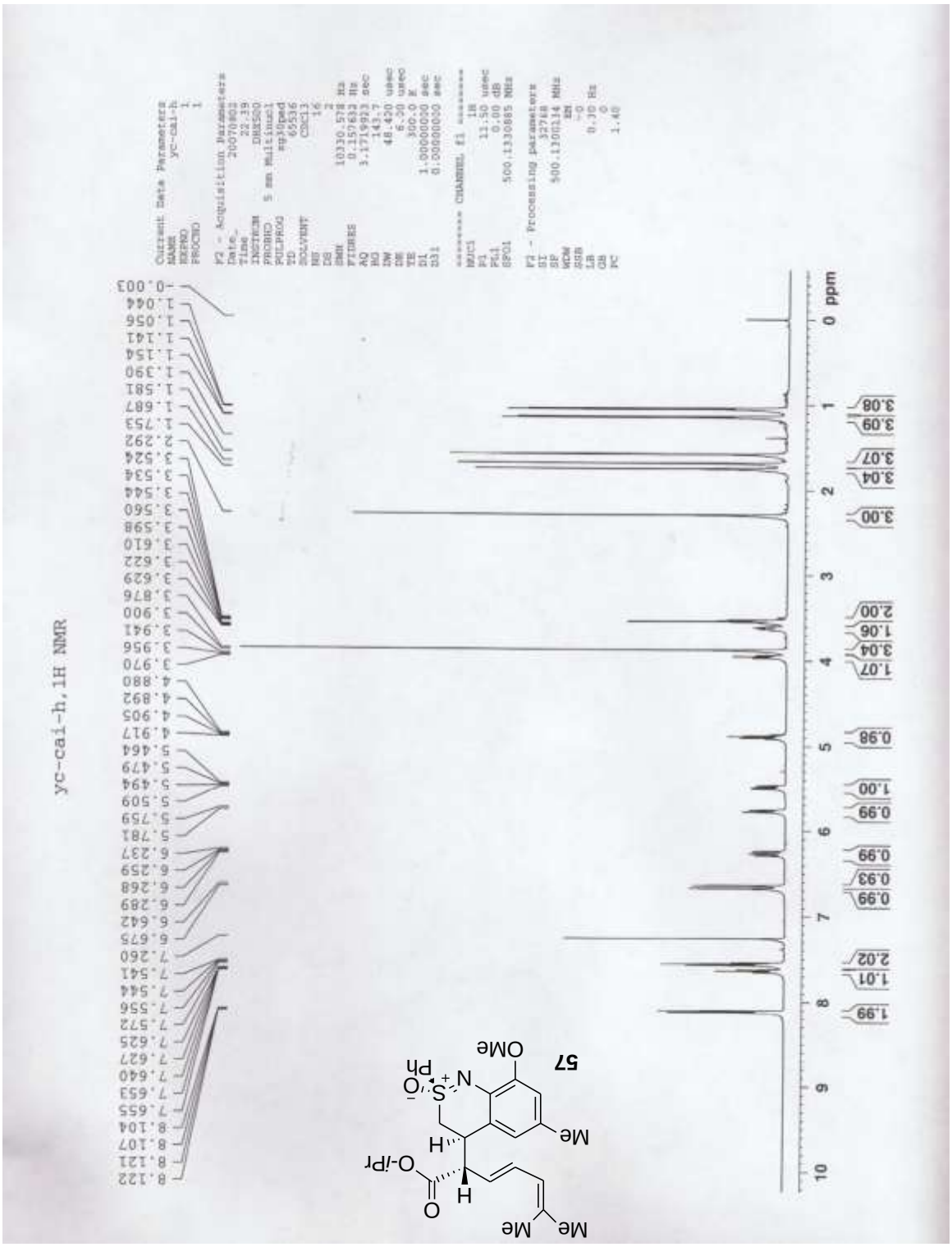
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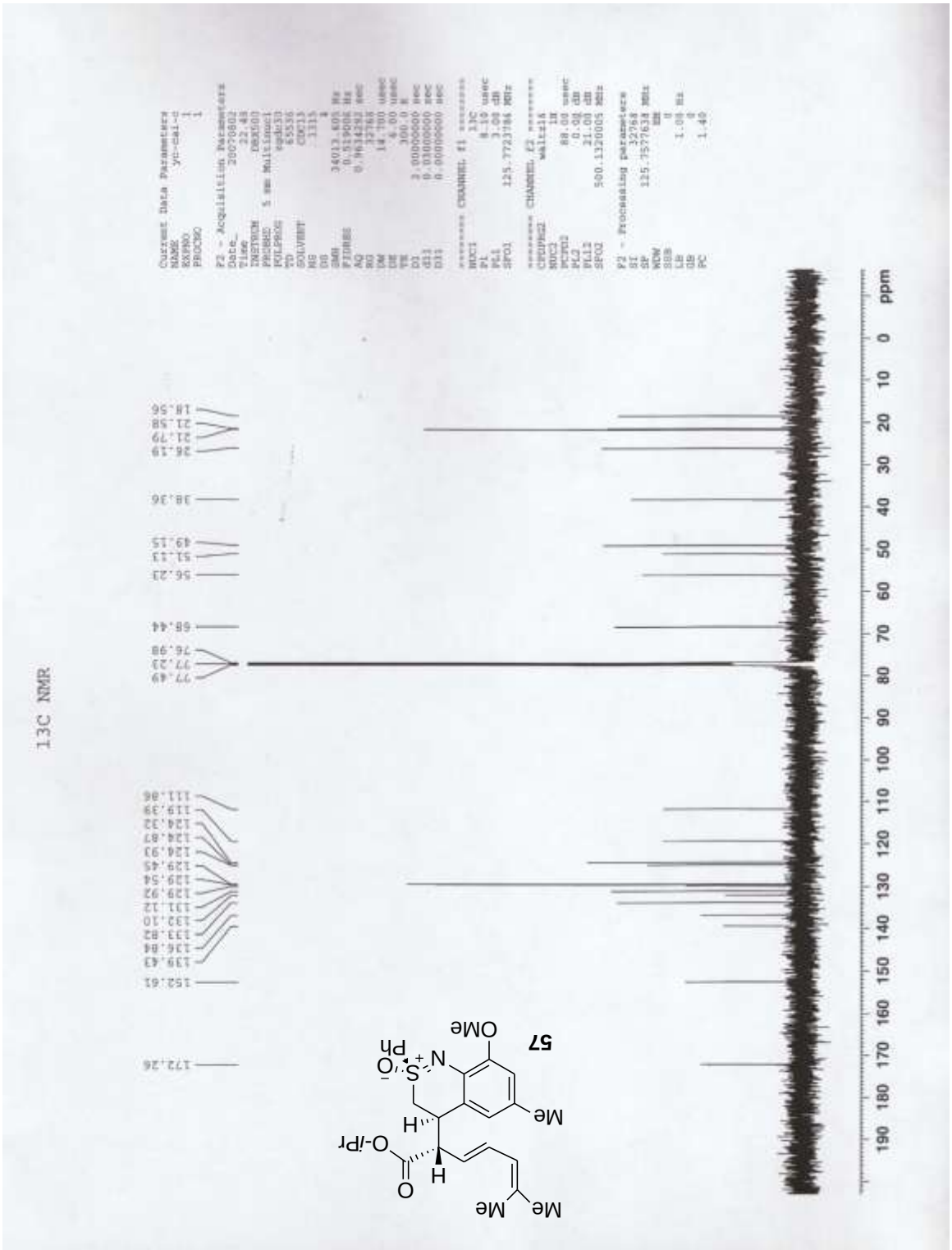
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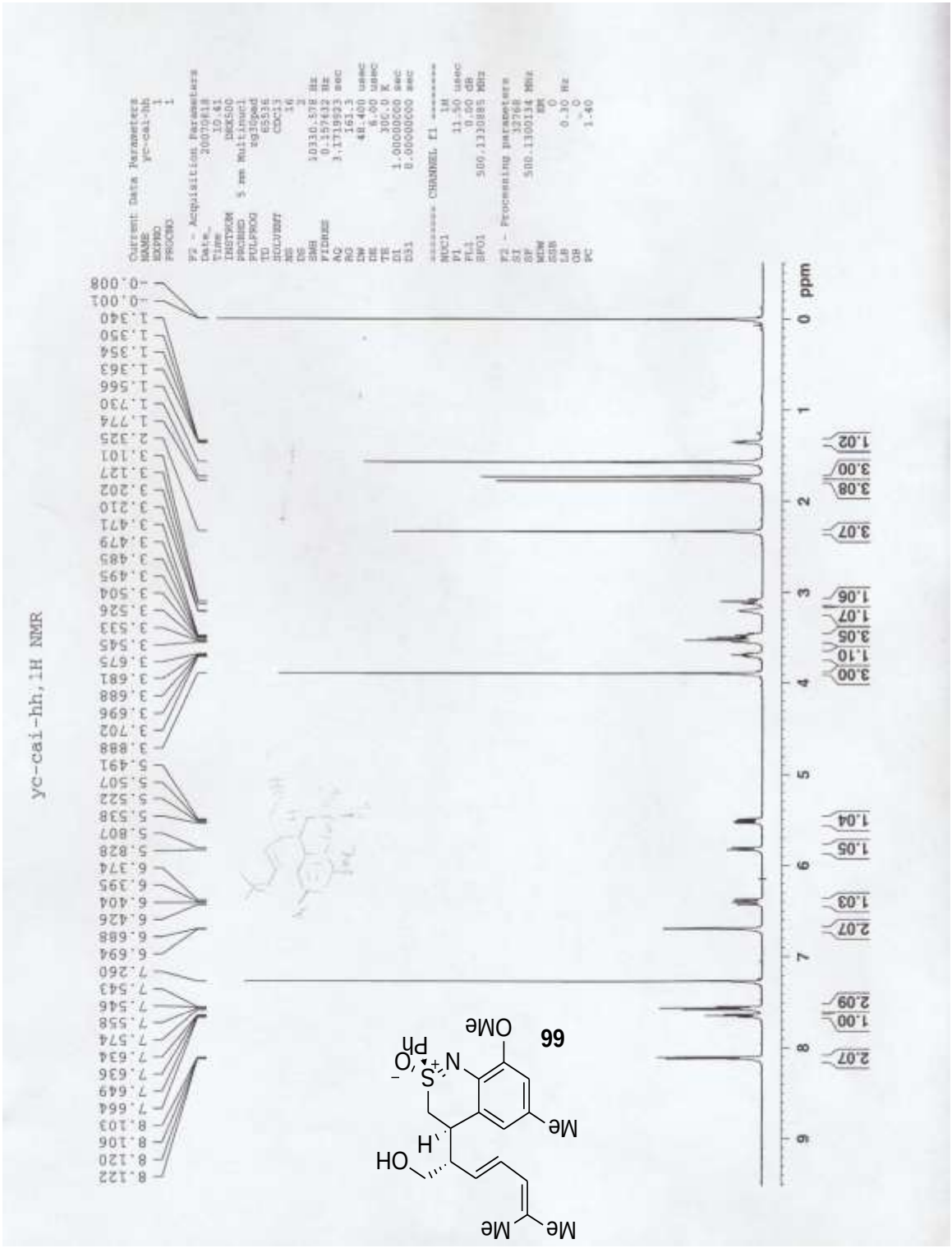
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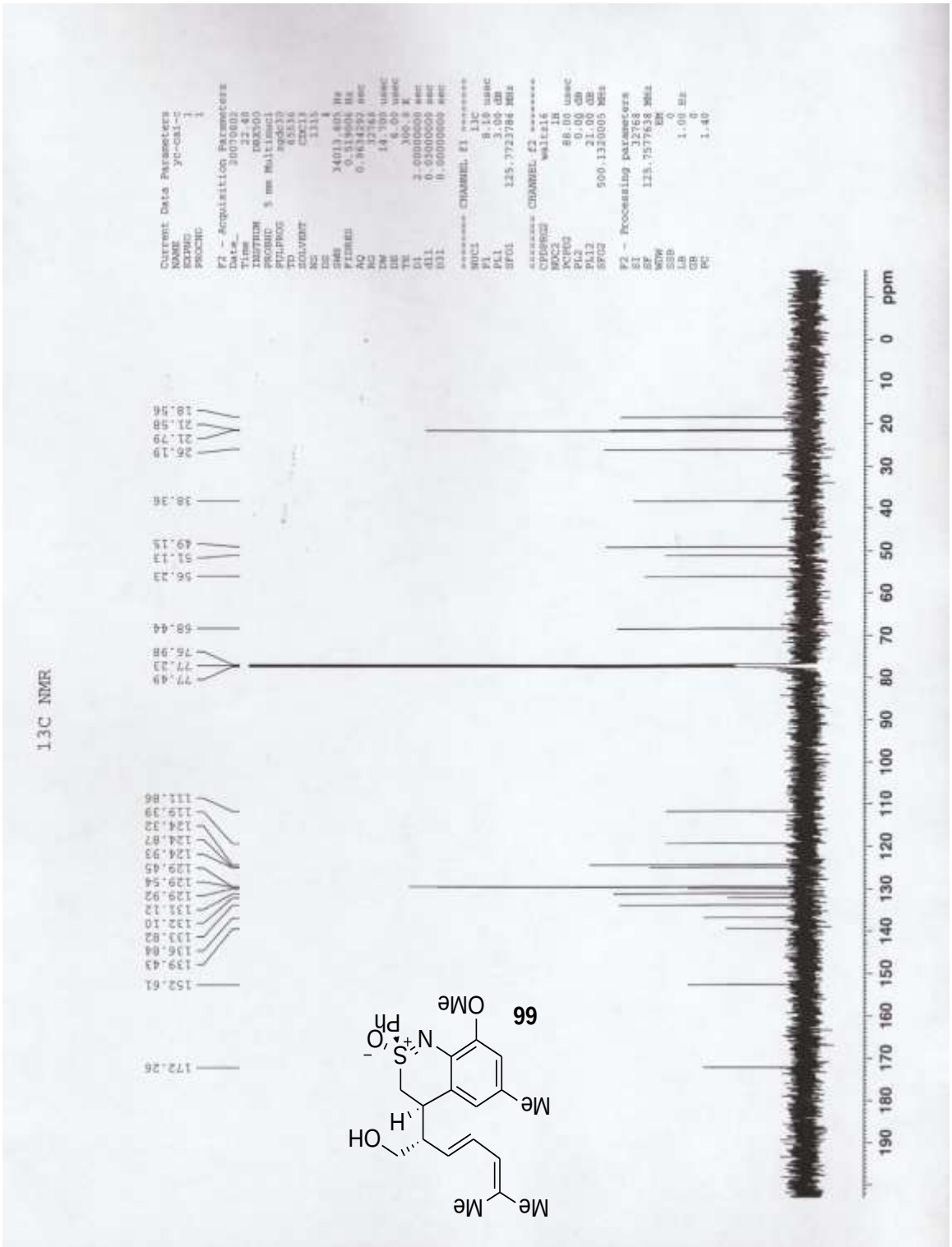
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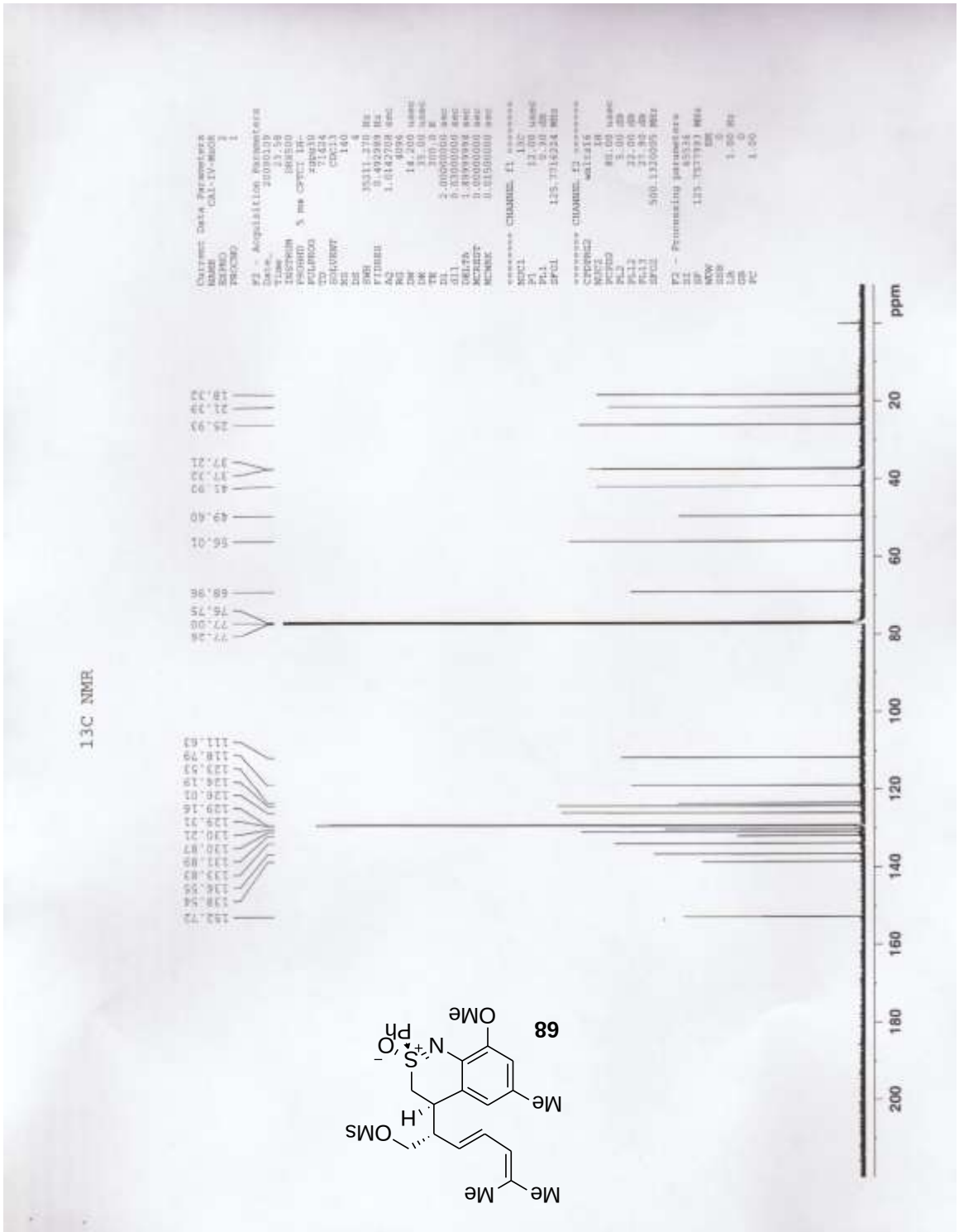
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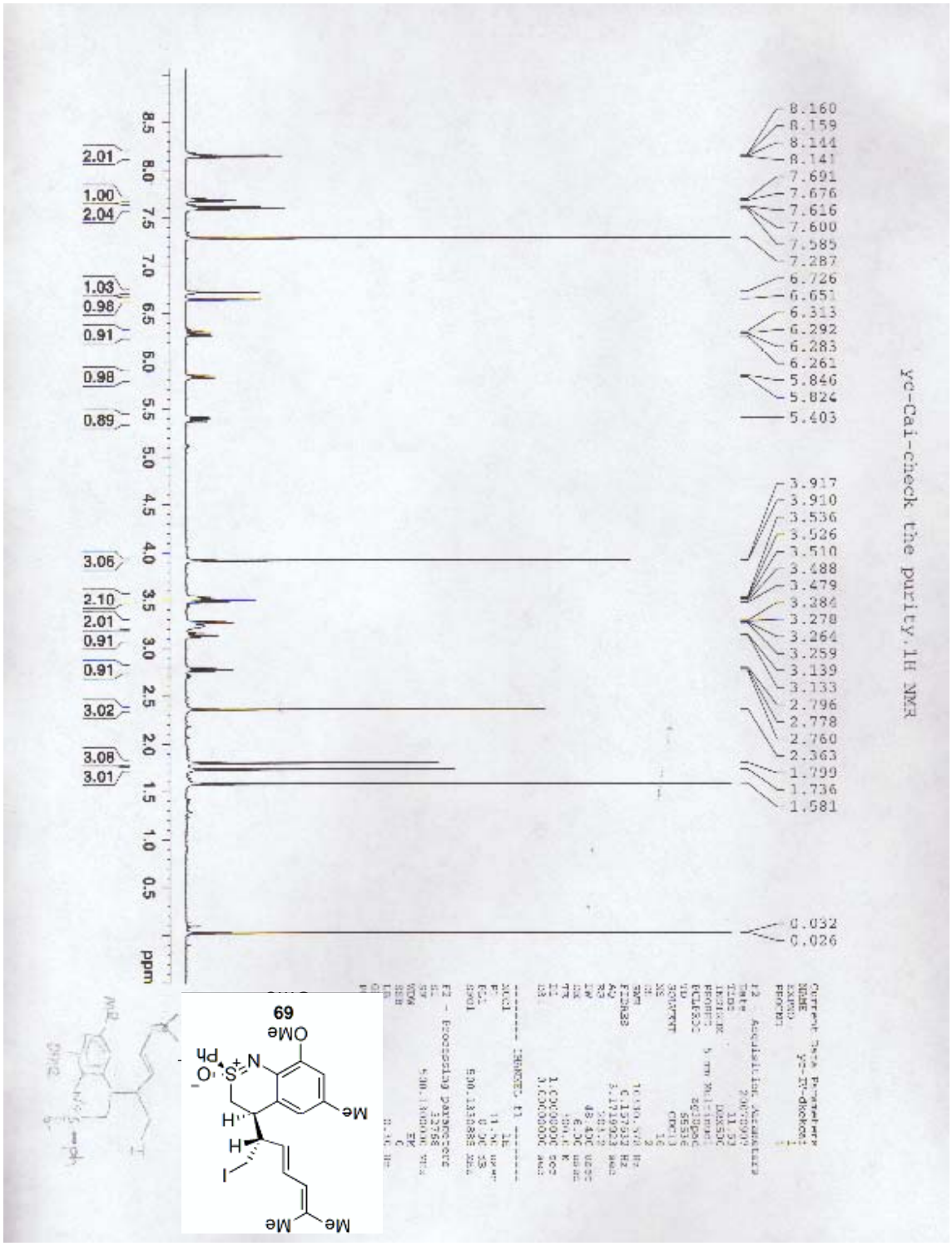
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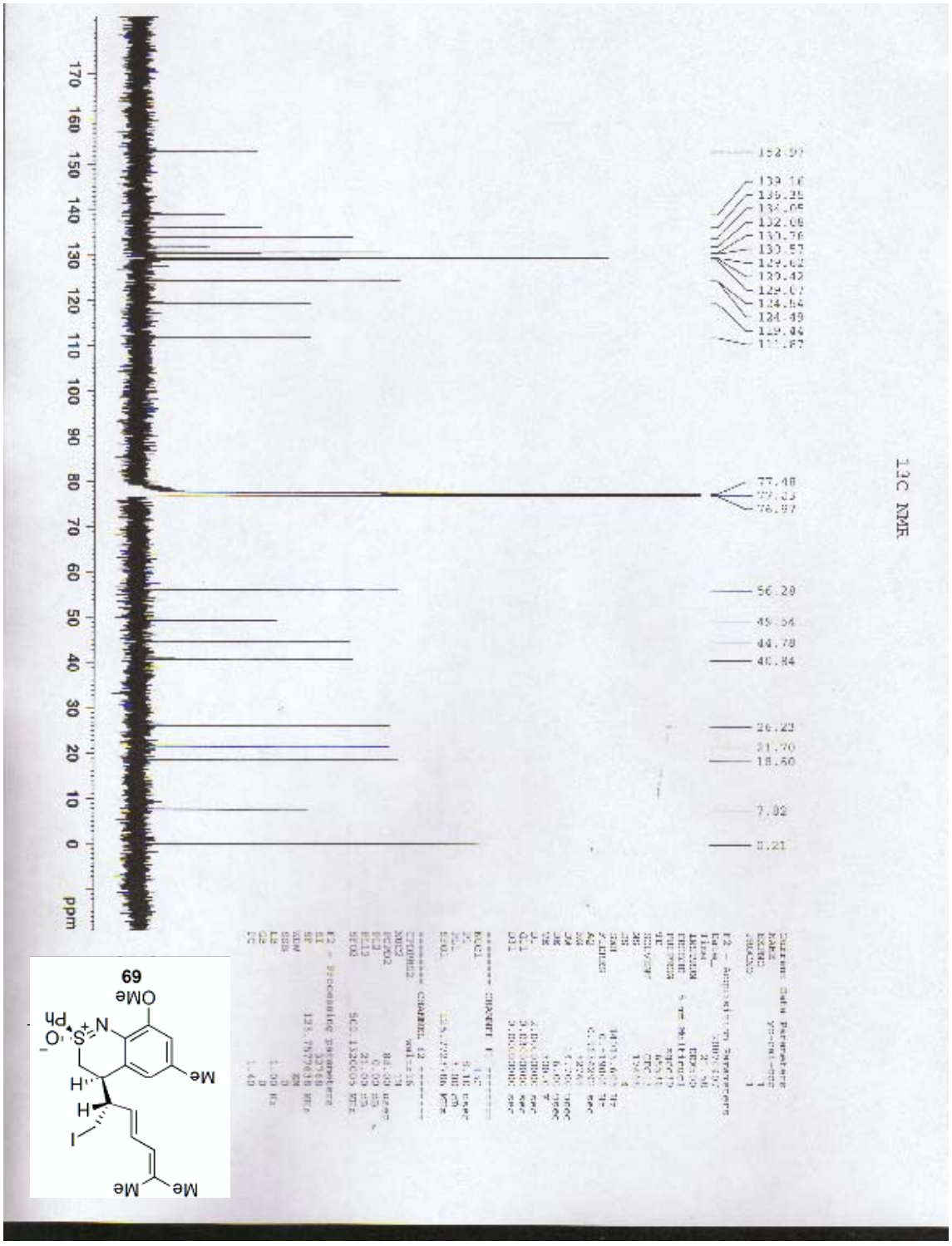
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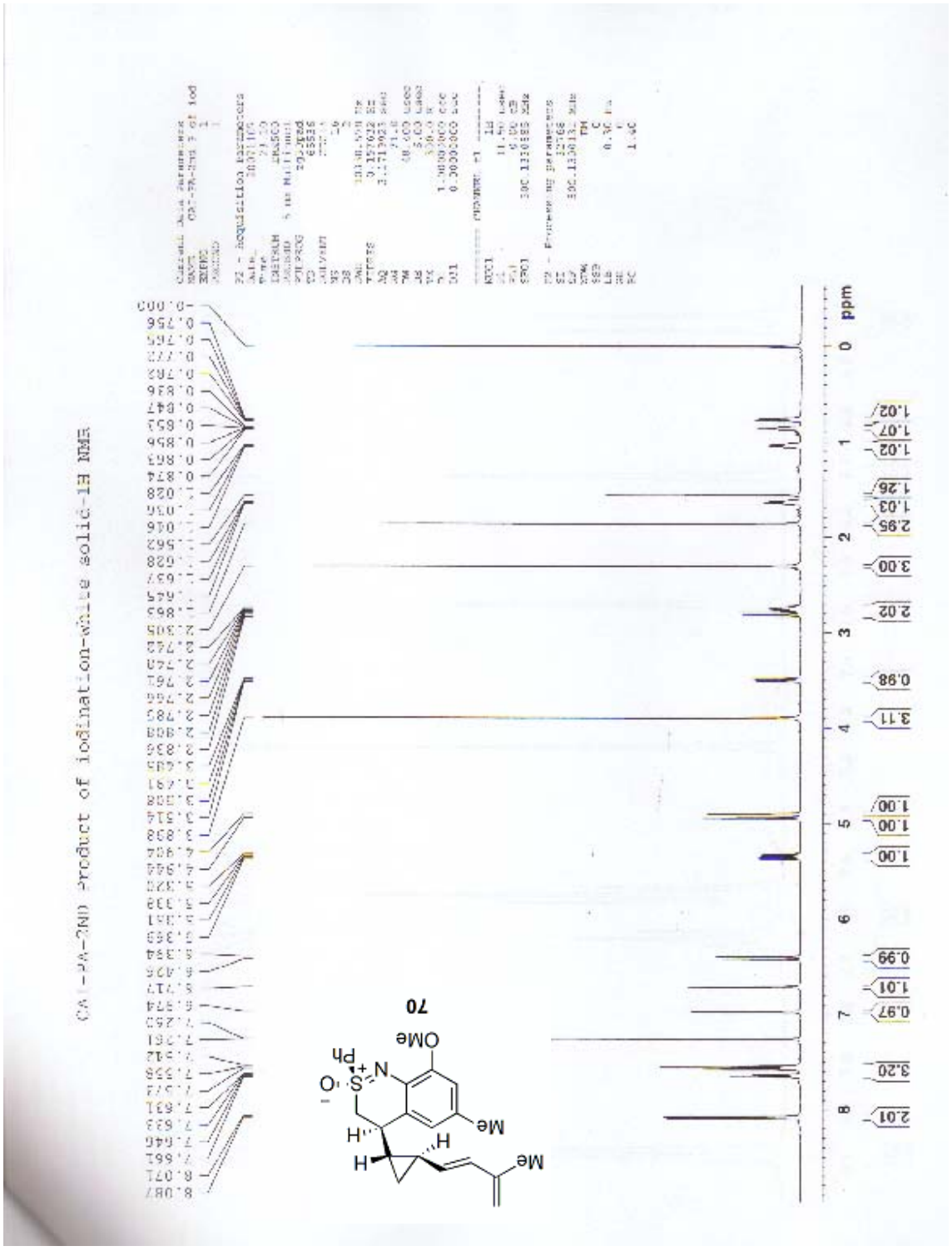
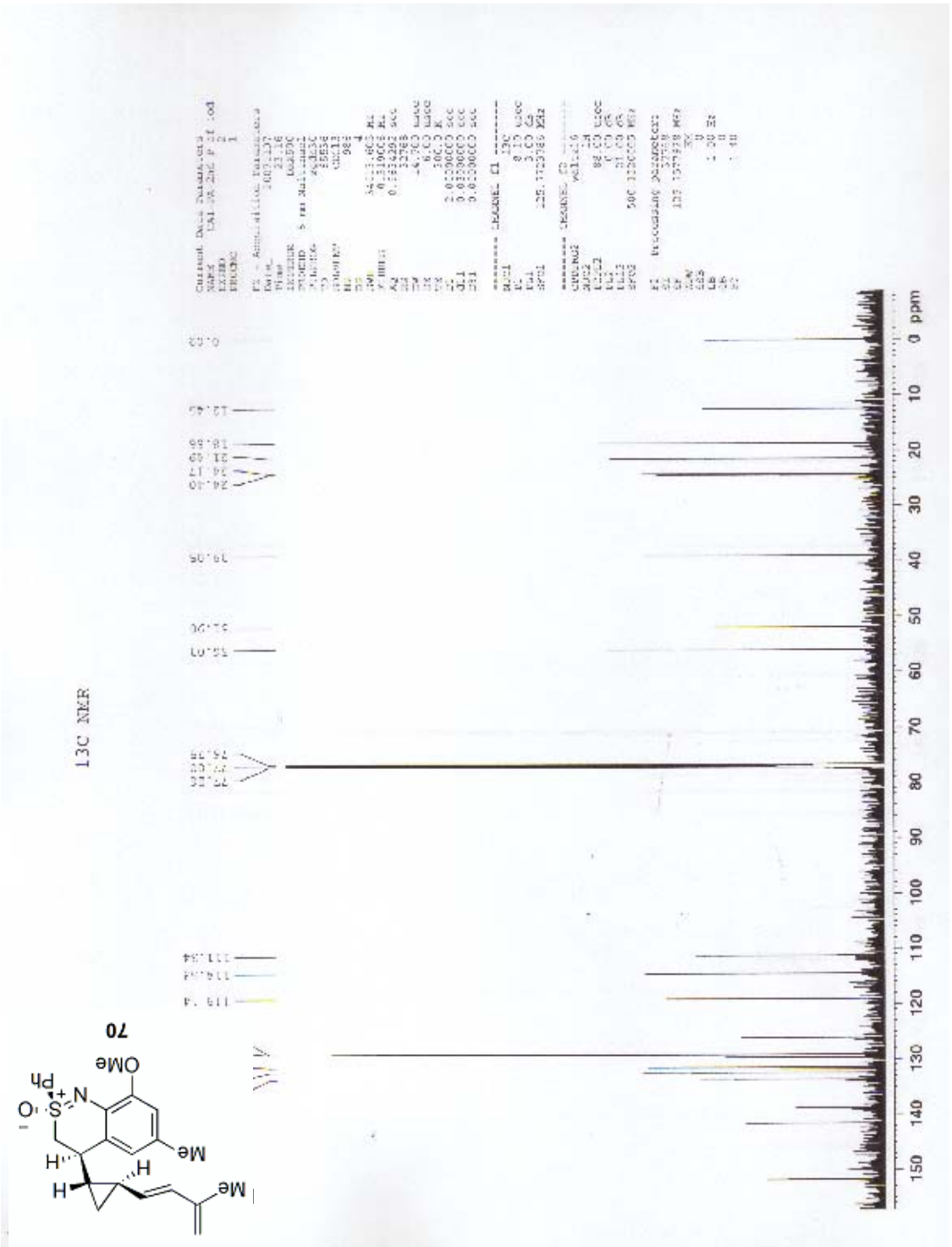
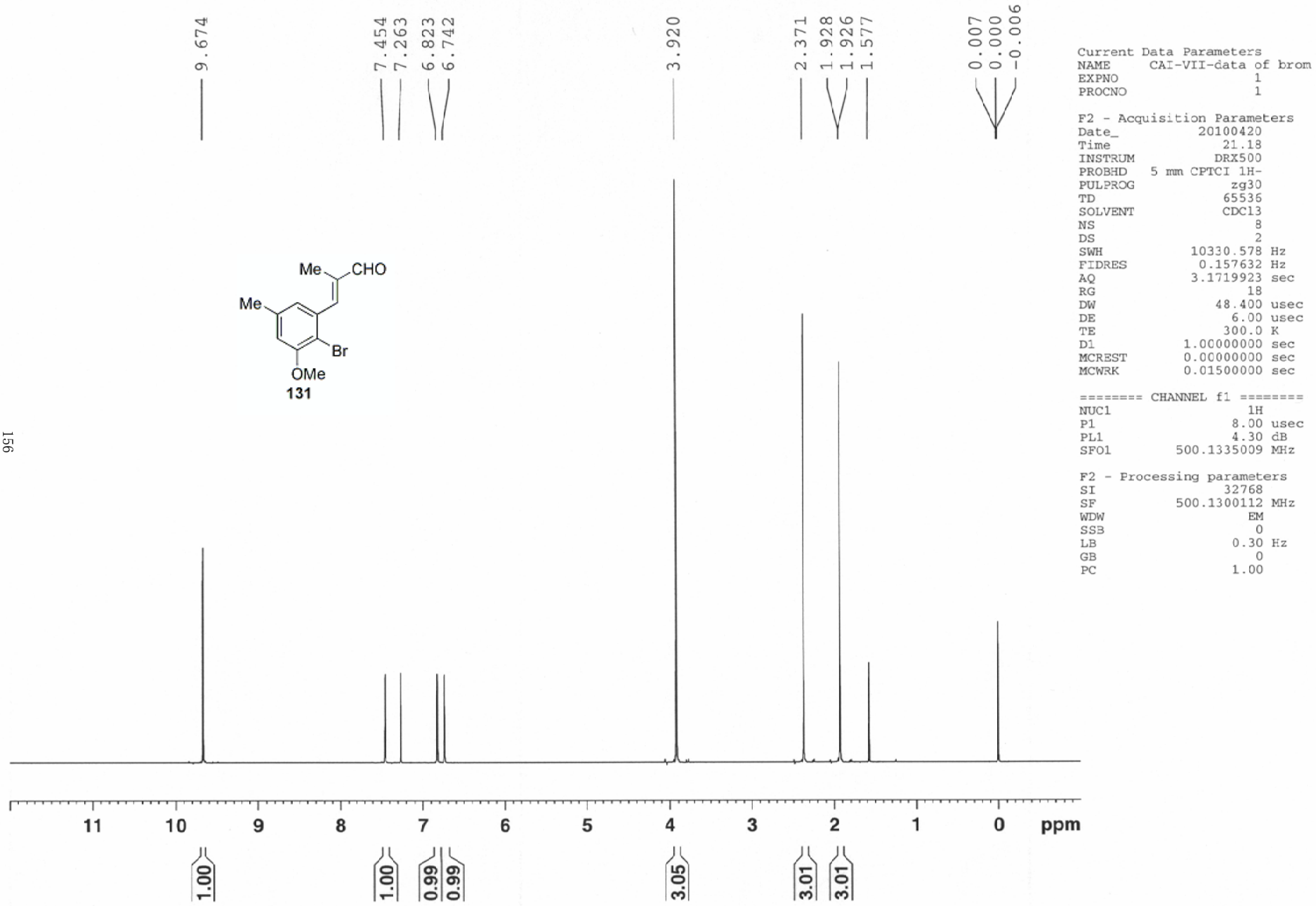
7.02
0.21


CA-JA-2ND product of iodination-white solid-1H NMR
70
OMe
Ph
N
S
O
Me
Me
H
H
H
ppm


13C NMR
70
OMe
Ph
O
S
N
Me
H
H
H
Me
0 ppm

CAI-bromoaldehyde-colorless crystal-1H NMR



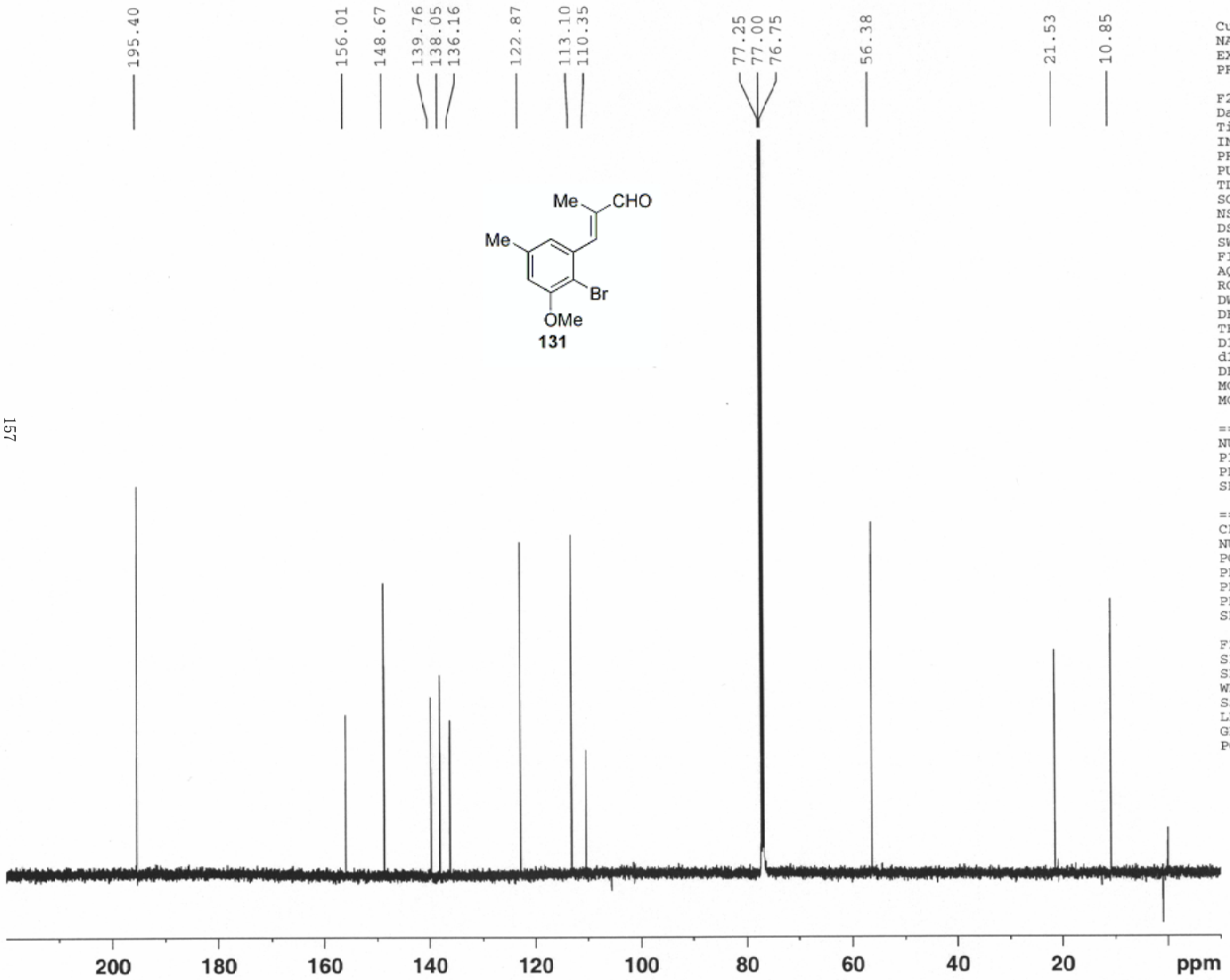

```
Current Data Parameters
NAME      CAI-VII-data of brom
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20100420
Time                 21.18
INSTRUM             DRX500
PROBHD   5 mm CPTCI 1H-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                        8
DS                        2
SWH              10330.578 Hz
FIDRES            0.157632 Hz
AQ               3.1719923 sec
RG                       18
DW                  48.400 usec
DE                   6.00 usec
TE                  300.0 K
D1              1.00000000 sec
MCREST          0.00000000 sec
MCWRK           0.01500000 sec

======== CHANNEL f1 ========
NUC1                     1H
P1                   8.00 usec
PL1                  4.30 dB
SFO1           500.1335009 MHz

F2 - Processing parameters
SI                    32768
SF             500.1300112 MHz
WDW                      EM
SSB                       0
LB                   0.30 Hz
GB                        0
PC                     1.00
```

13C NMR



157

```
Current Data Parameters
NAME      CAI-VII-data of brom
EXPNO                        2
PROCNO                       1

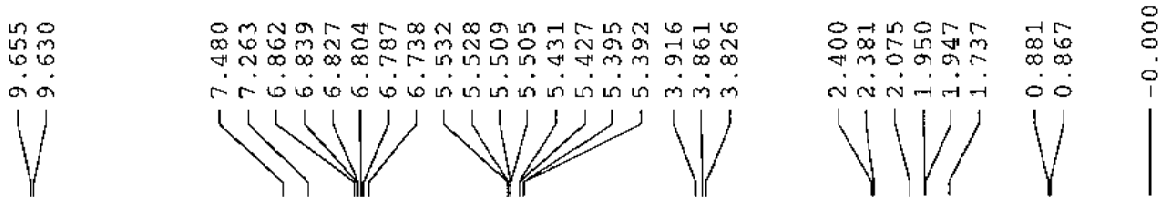
F2 - Acquisition Parameters
Date_              20100420
Time                 21.21
INSTRUM              DRX500
PROBHD   5 mm CPTCI 1H-
PULPROG              zgpg30
TD                    71424
SOLVENT               CDCl3
NS                      123
DS                        4
SWH              35211.270 Hz
FIDRES            0.492989 Hz
AQ               1.0142708 sec
RG                     4096
DW                  14.200 usec
DE                  35.00 usec
TE                  300.0 K
D1               2.00000000 sec
d11              0.03000000 sec
DELTA            1.89999998 sec
MCREST           0.00000000 sec
MCWRK            0.01500000 sec

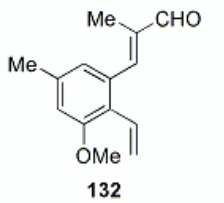
======== CHANNEL f1 ========
NUC1                    13C
P1                  12.00 usec
PL1                  0.30 dB
SFO1          125.7716224 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                    1H
PCPD2               80.00 usec
PL2                  5.00 dB
PL12                22.00 dB
PL13                27.90 dB
SFO2          500.1320005 MHz

F2 - Processing parameters
SI                     65536
SF            125.7577928 MHz
WDW                       EM
SSB                        0
LB                  1.00 Hz
GB                         0
PC                      1.00
```

CAI-IV-7-2-Yellow oil-1H NMR





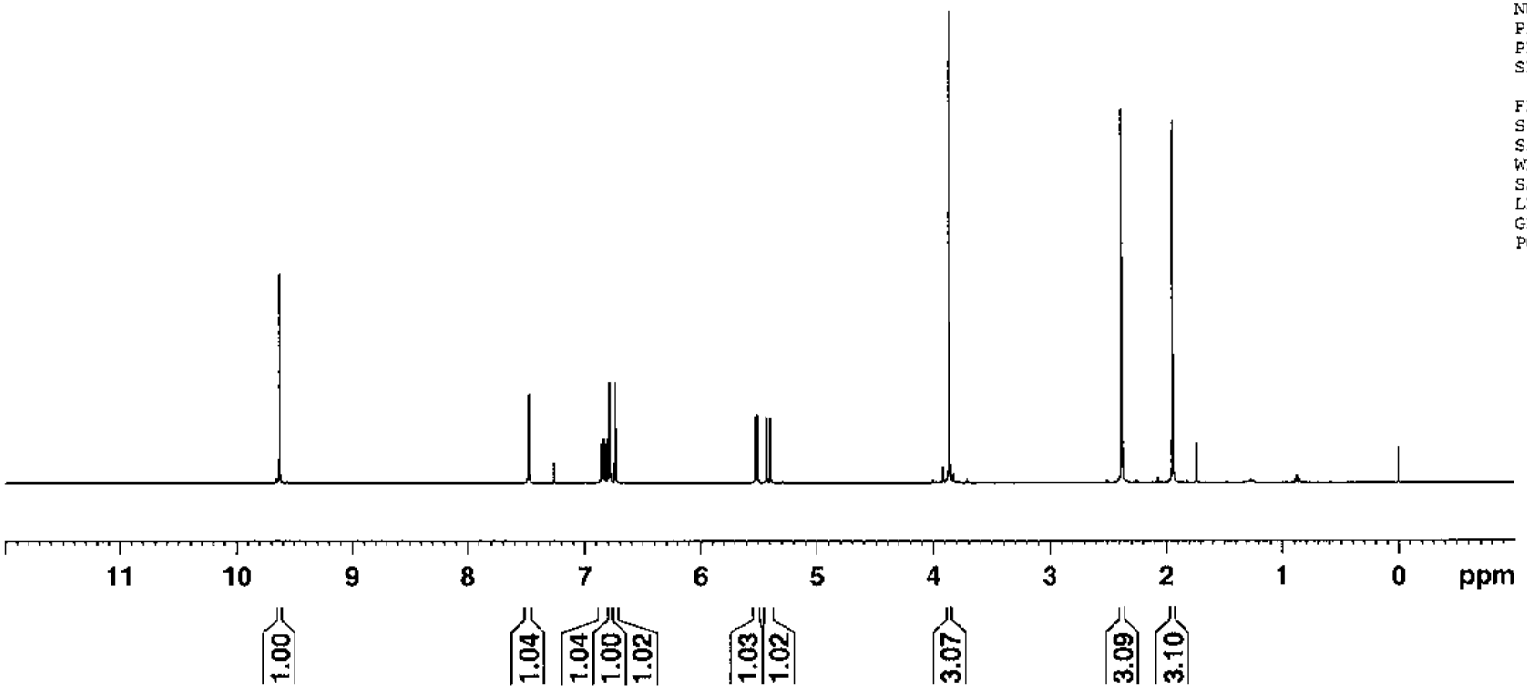
132

Current Data Parameters
NAME CAI-IV-7-2
EXPNO 1
PROCNO 1

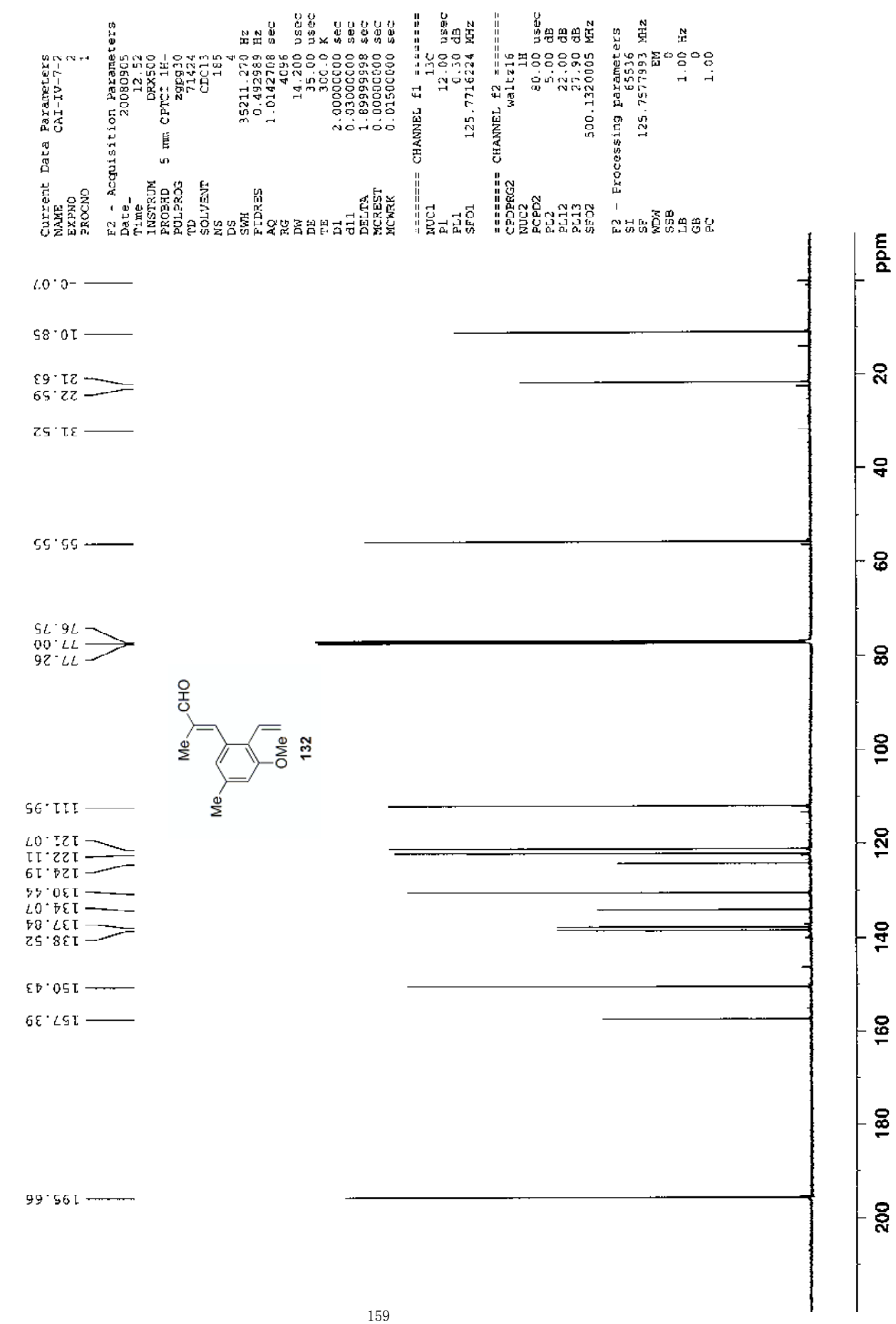
F2 - Acquisition Parameters
Date_ 20080905
Time 12.45
INSTRUM DRX500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 5
DW 48.400 usec
DB 6.00 usec
TE 300.0 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
PL1 4.30 dB
SFO1 500.1335009 MHz

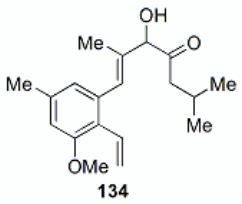
F2 - Processing parameters
SI 32768
SF 500.1300125 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



CAI-IV-7-Pale Yellow Oil-13C NMR



CAI-III-150-1-1H NMR



134

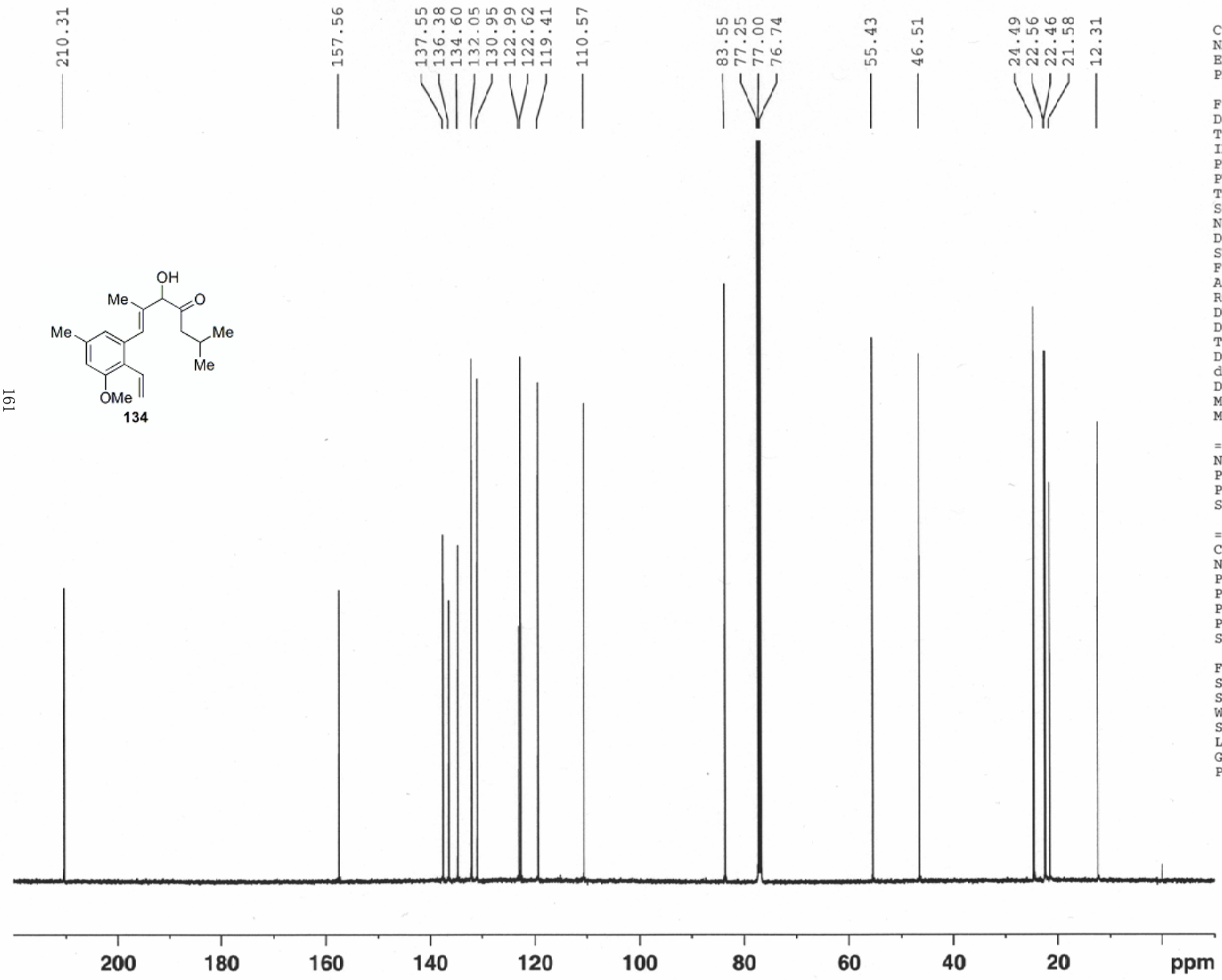

```
Current Data Parameters
NAME       CAI-III-150-1
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20080828
Time               17.33
INSTRUM           DRX500
PROBHD   5 mm CPTCI 1H-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                     8
DS                     2
SWH           10330.578 Hz
FIDRES         0.157632 Hz
AQ            3.1719923 sec
RG                     5
DW               48.400 usec
DE                6.00 usec
TE                300.0 K
D1           1.00000000 sec
MCREST       0.00000000 sec
MCWRK        0.01500000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 8.00 usec
PL1                4.30 dB
SFO1        500.1335009 MHz

F2 - Processing parameters
SI                 32768
SF          500.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

13C NMR




```
Current Data Parameters
NAME       CAI-III-150-1
EXPNO                  2
PROCNO                 1

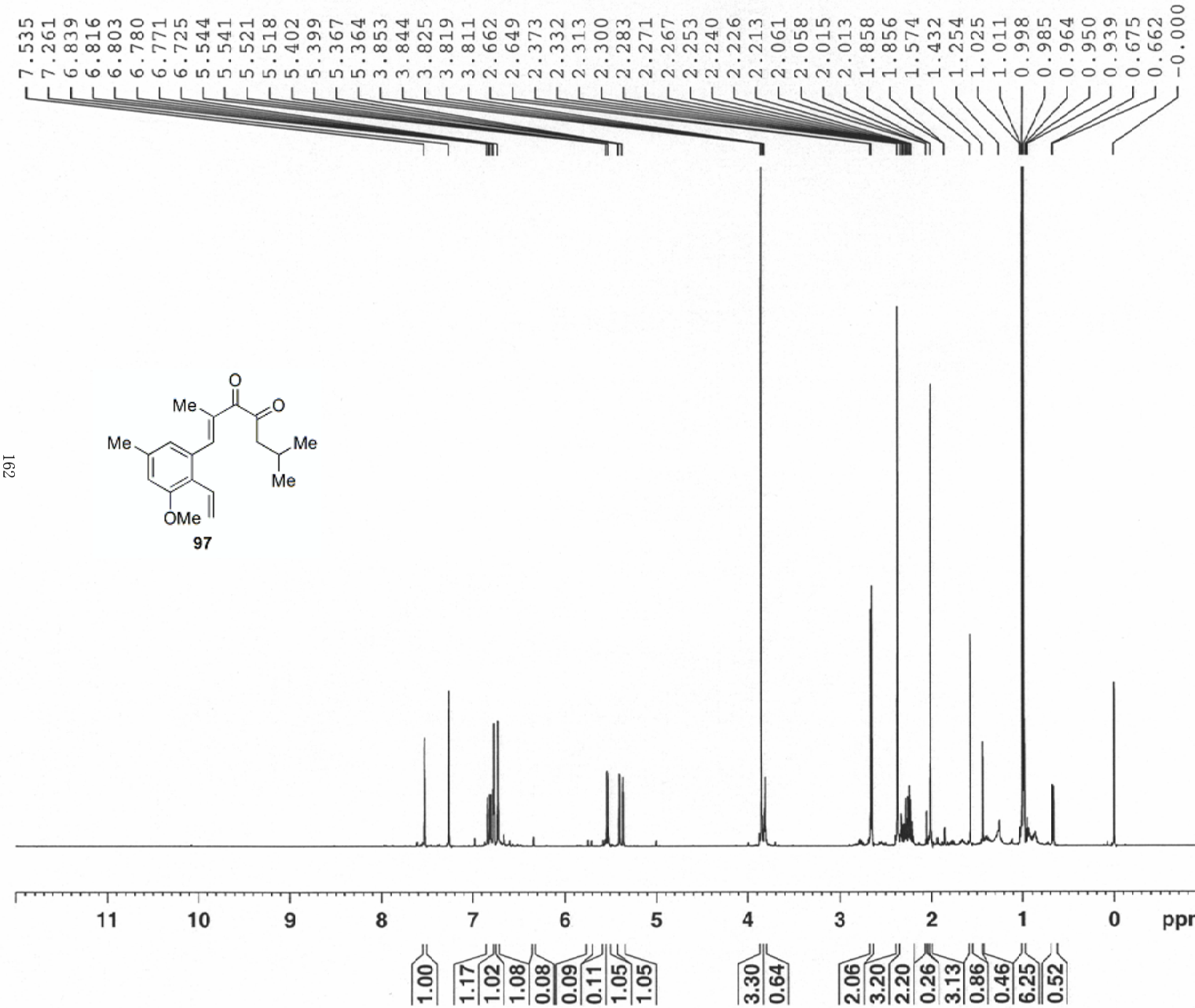
F2 - Acquisition Parameters
Date_           20080828
Time               17.43
INSTRUM           DRX500
PROBHD   5 mm CPTCI 1H-
PULPROG          zgpg30
TD                71424
SOLVENT           CDCl3
NS                  182
DS                    4
SWH           35211.270 Hz
FIDRES        0.492989 Hz
AQ            1.0142708 sec
RG                 4096
DW               14.200 usec
DE               35.00 usec
TE               300.0 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

======== CHANNEL f1 ========
NUC1                13C
P1               12.00 usec
PL1               0.30 dB
SFO1        125.7716224 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                1H
PCPD2            80.00 usec
PL2               5.00 dB
PL12             22.00 dB
PL13             27.90 dB
SFO2        500.1320005 MHz

F2 - Processing parameters
SI                 65536
SF          125.7577982 MHz
WDW                   EM
SSB                    0
LB                1.00 Hz
GB                     0
PC                1.00
```

CAI-V-98-Yellow oil-1H NMR



97

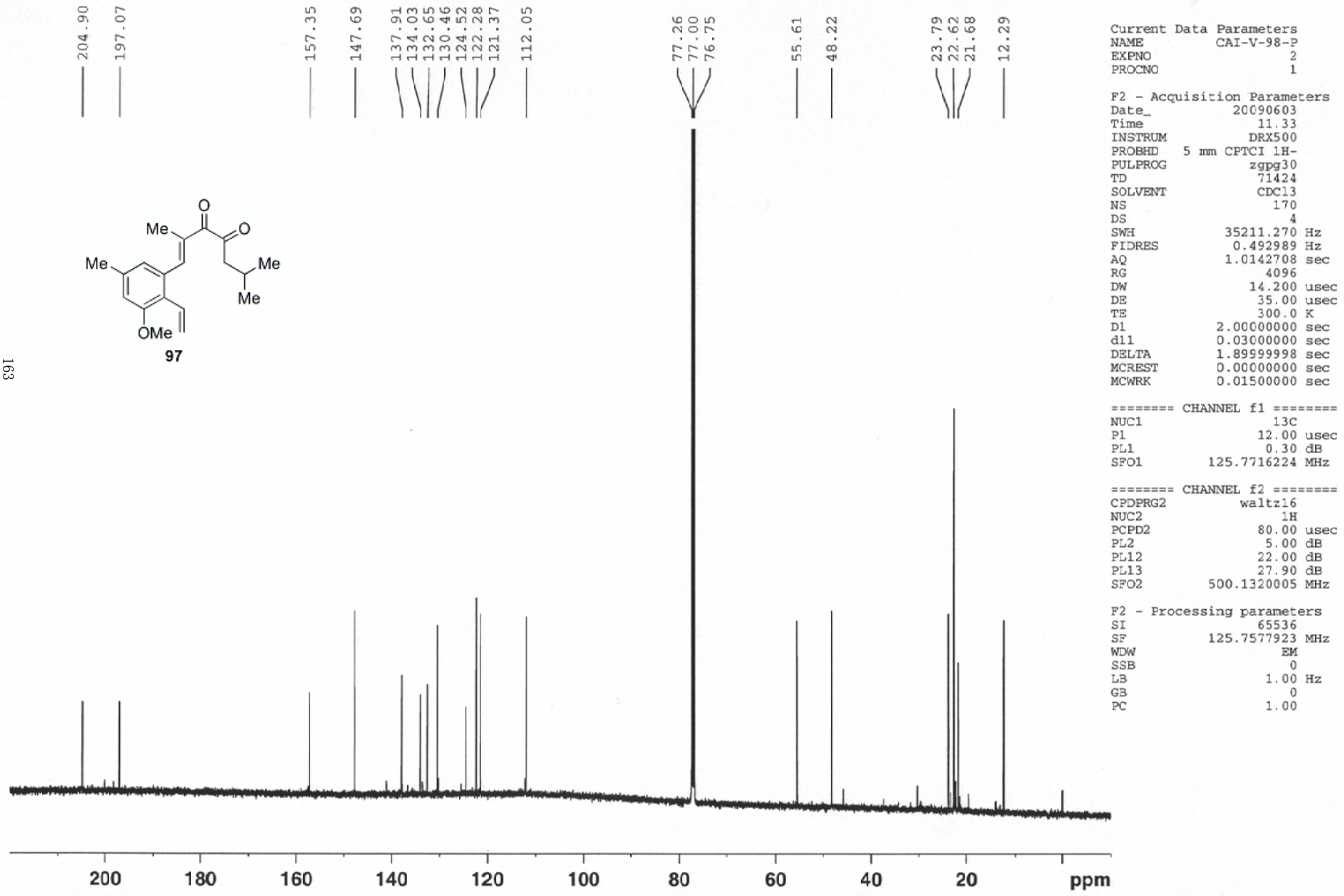
```
Current Data Parameters
NAME                 CAI-V-98-P
EXPNO                         1
PROCNO                        1

F2 - Acquisition Parameters
Date_                  20090603
Time                      11.27
INSTRUM                 DRX500
PROBHD    5 mm CPTCI 1H-
PULPROG                   zg30
TD                       65536
SOLVENT                  CDCl3
NS                           8
DS                           2
SWH                10330.578 Hz
FIDRES              0.157632 Hz
AQ                  3.1719923 sec
RG                          18
DW                     48.400 usec
DE                      6.00 usec
TE                      300.0 K
D1                 1.00000000 sec
MCREST             0.00000000 sec
MCWRK              0.01500000 sec

======== CHANNEL f1 ========
NUC1                        1H
P1                       8.00 usec
PL1                      4.30 dB
SFO1              500.1335009 MHz

F2 - Processing parameters
SI                       32768
SF                500.1300131 MHz
WDW                         EM
SSB                          0
LB                       0.30 Hz
GB                           0
PC                        1.00
```

13C NMR




```
Current Data Parameters
NAME                CAI-V-98-P
EXPNO                        2
PROCNO                       1

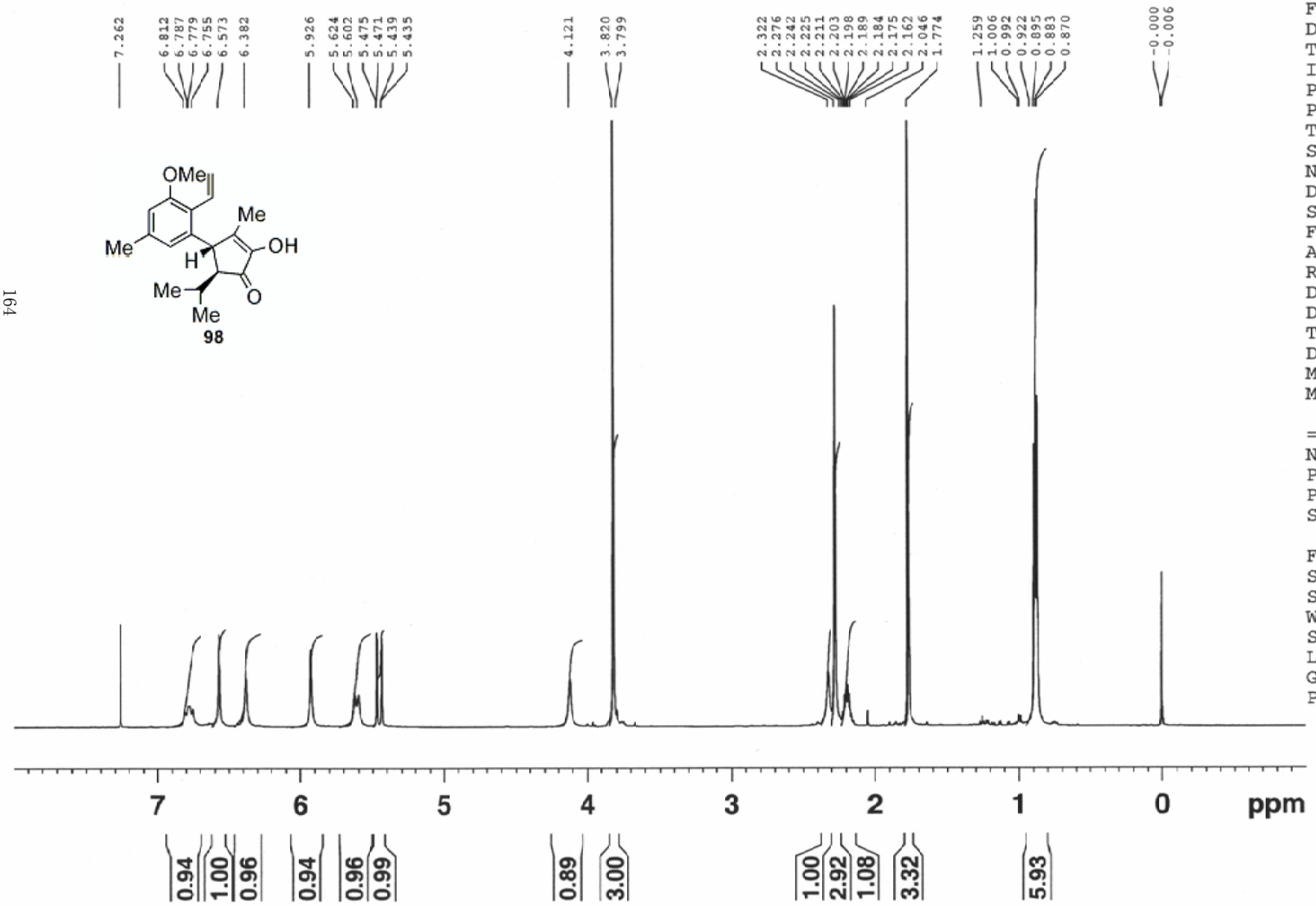
F2 - Acquisition Parameters
Date_                20090603
Time                    11.33
INSTRUM                DRX500
PROBHD    5 mm CPTCI 1H-
PULPROG                zgpg30
TD                      71424
SOLVENT                 CDCl3
NS                        170
DS                          4
SWH                35211.270 Hz
FIDRES             0.492989 Hz
AQ                 1.0142708 sec
RG                       4096
DW                     14.200 usec
DE                     35.00 usec
TE                     300.0 K
D1                 2.00000000 sec
d11                0.03000000 sec
DELTA              1.89999998 sec
MCREST             0.00000000 sec
MCWRK              0.01500000 sec

======== CHANNEL f1 ========
NUC1                      13C
P1                     12.00 usec
PL1                     0.30 dB
SFO1             125.7716224 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                  80.00 usec
PL2                     5.00 dB
PL12                   22.00 dB
PL13                   27.90 dB
SFO2             500.1320005 MHz

F2 - Processing parameters
SI                        65536
SF               125.7577923 MHz
WDW                          EM
SSB                           0
LB                     1.00 Hz
GB                            0
PC                     1.00
```

CAI-IV-22-4-Colorless oil-H NMR



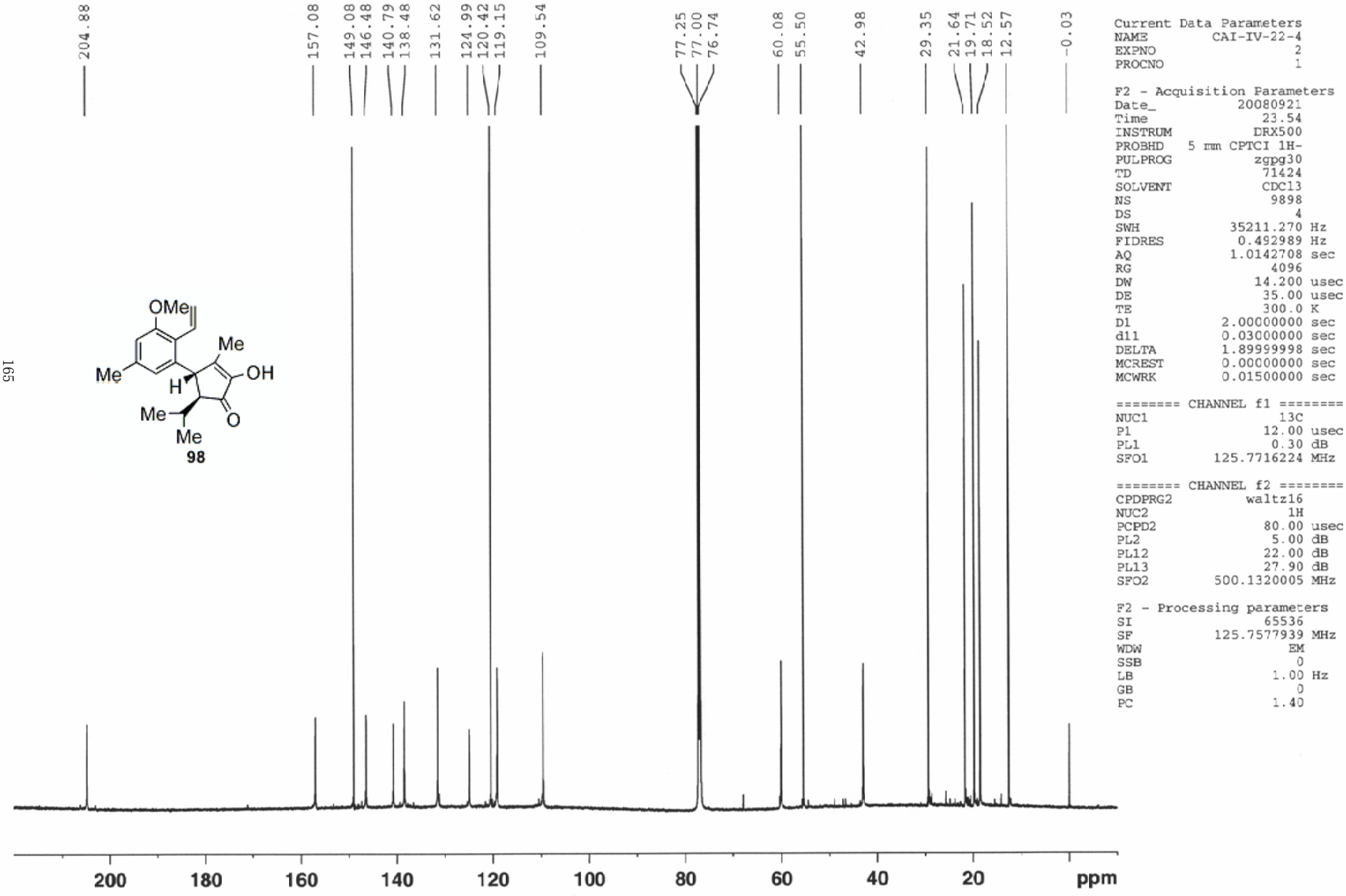

```
Current Data Parameters
NAME         CAI-IV-22-4
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20080921
Time               23.45
INSTRUM          DRX500
PROBHD   5 mm CPTCI 1H-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                     8
DS                     2
SWH          10330.578 Hz
FIDRES        0.157632 Hz
AQ            3.1719923 sec
RG                  14.3
DW                48.400 usec
DE                 6.00 usec
TE                300.0 K
D1           1.00000000 sec
MCREST       0.00000000 sec
MCWRK        0.01500000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  8.00 usec
PL1                 4.30 dB
SFO1         500.1335009 MHz

F2 - Processing parameters
SI                 32768
SF           500.1300131 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

13C NMR




```
Current Data Parameters
NAME          CAI-IV-22-4
EXPNO                   2
PROCNO                  1

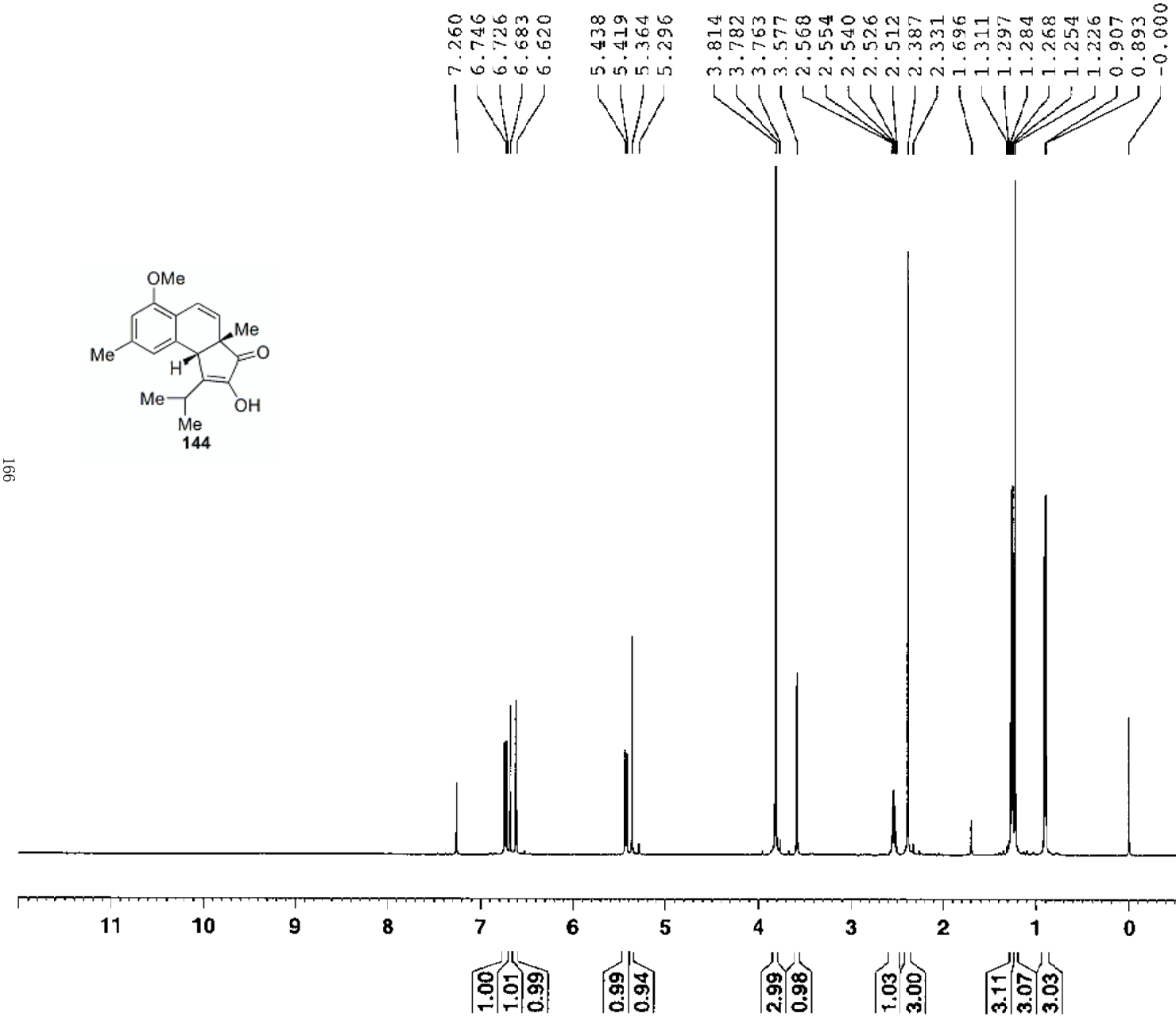
F2 - Acquisition Parameters
Date_            20080921
Time                23.54
INSTRUM            DRX500
PROBHD   5 mm CPTCI 1H-
PULPROG            zgpg30
TD                  71424
SOLVENT             CDCl3
NS                   9898
DS                      4
SWH           35211.270 Hz
FIDRES         0.492989 Hz
AQ            1.0142708 sec
RG                   4096
DW              14.200 usec
DE              35.00 usec
TE                300.0 K
D1           2.00000000 sec
d11          0.03000000 sec
DELTA        1.89999998 sec
MCREST       0.00000000 sec
MCWRK        0.01500000 sec

======== CHANNEL f1 ========
NUC1                13C
P1              12.00 usec
PL1              0.30 dB
SFO1       125.7716224 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                1H
PCPD2           80.00 usec
PL2              5.00 dB
PL12            22.00 dB
PL13            27.90 dB
SFO2       500.1320005 MHz

F2 - Processing parameters
SI                  65536
SF         125.7577939 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

CAI-IV-35-white solid-1H NMR



144

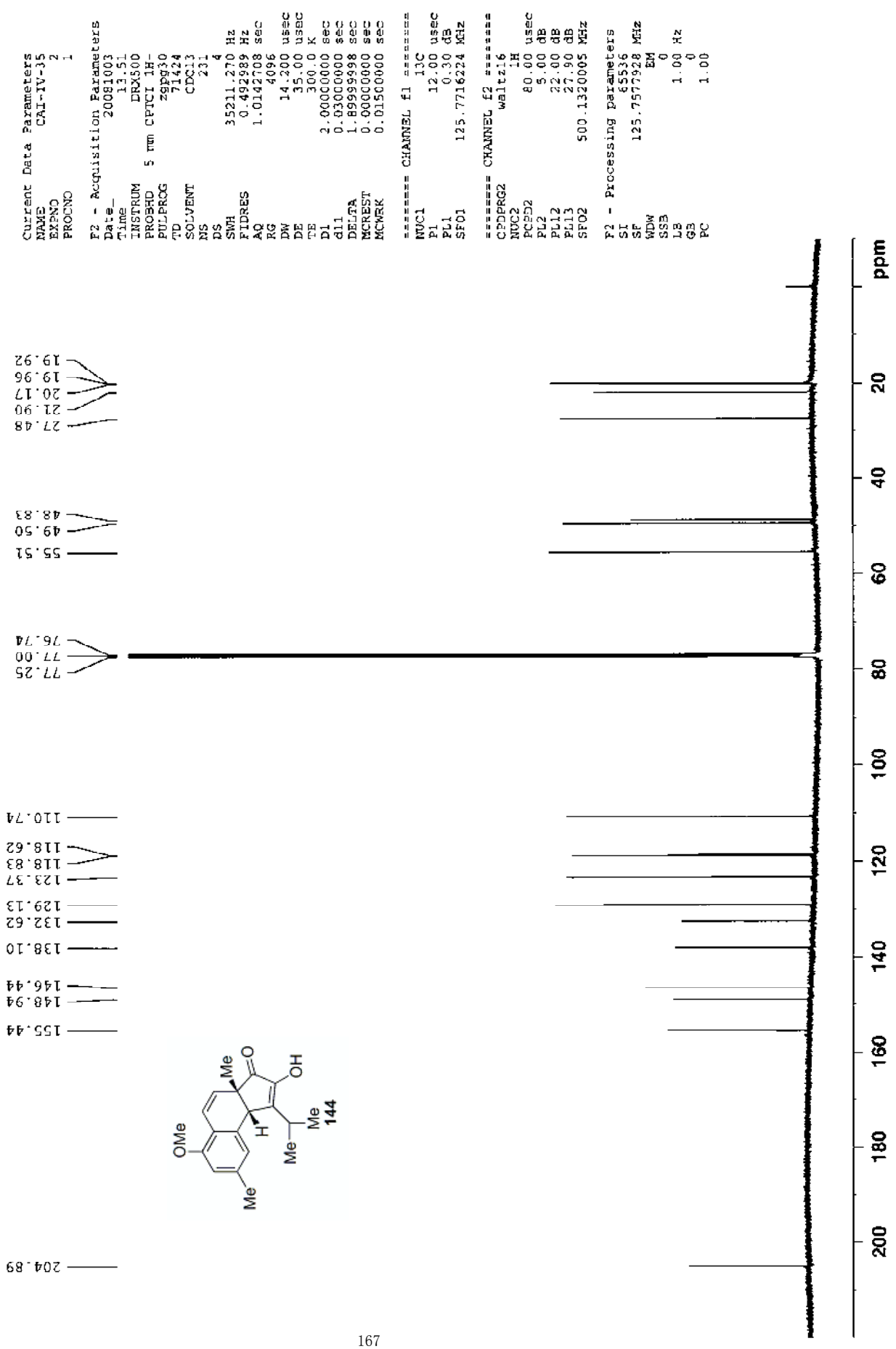
Current Data Parameters
NAME CAI-IV-35
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20081003
Time 13.44
INSTRUM DRX500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 16
DW 48.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

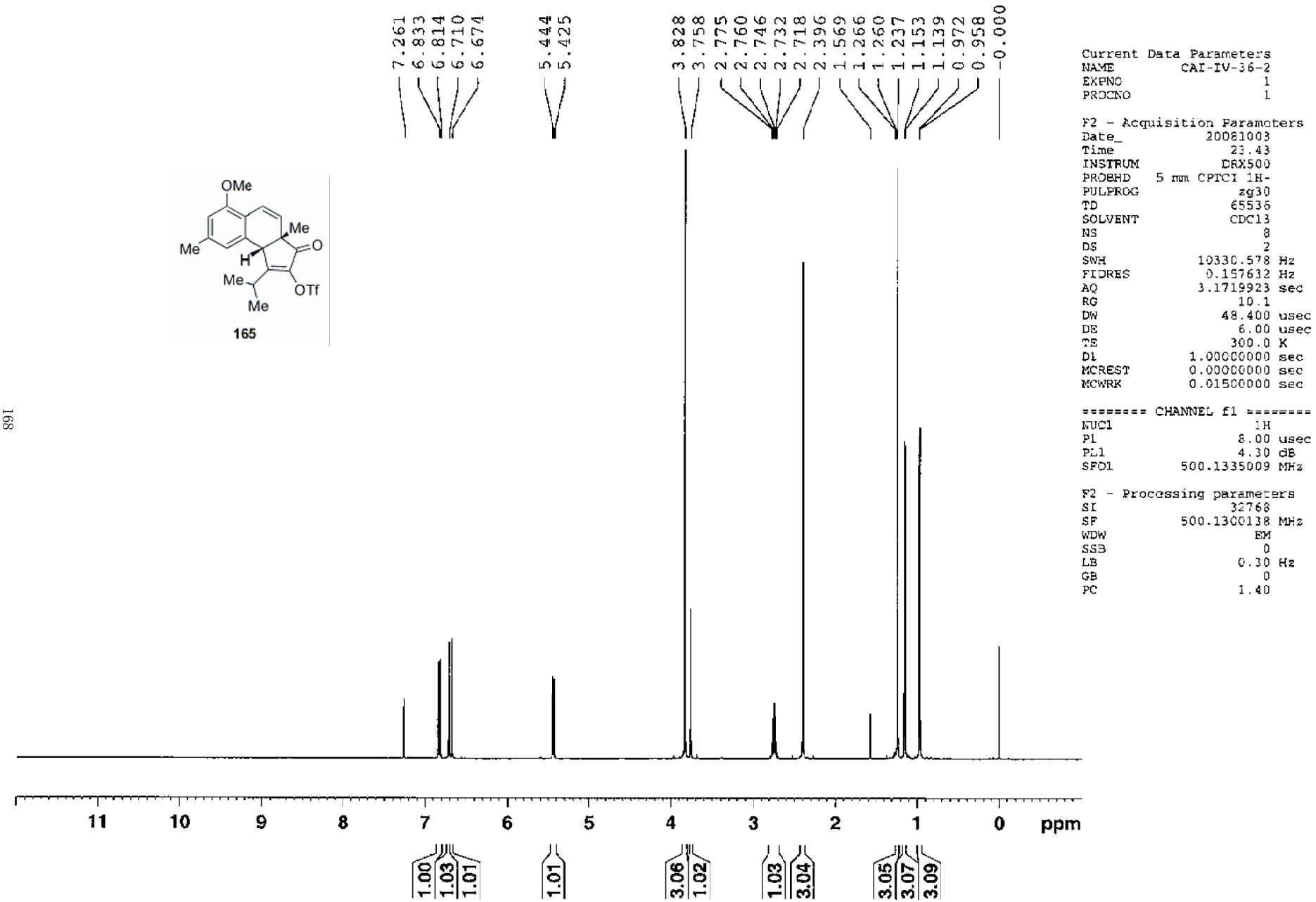
======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
PL1 4.30 dB
SFO1 500.1335009 MHz

F2 - Processing parameters
SI 32768
SF 500.1300144 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

13C NMR


Current Data Parameters
NAME CAI-IV-35
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20081003
Time 13.51
INSTRUM DRX500
PROBHD 5 mm CPTCI 1H-
PULPROG zgpg30
TD 71424
SOLVENT CDCl3
NS 231
DS 4
SWH 35211.270 Hz
FIDRES 0.492989 Hz
AQ 1.0142708 sec
RG 4096
DW 14.200 usec
DE 35.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 12.00 usec
PL1 0.30 dB
SFO1 125.7716224 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 5.00 dB
PL12 22.00 dB
PL13 27.90 dB
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 65536
SF 125.7577928 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
19.92
19.96
20.17
21.90
27.48
48.83
49.50
55.51
76.74
77.00
77.25
110.74
118.62
118.83
123.37
129.13
132.62
138.10
146.44
148.94
155.44
204.89
Me
O
OH
Me
H
Me
Me
OMe
144
ppm
200
180
160
140
120
100
80
60
40
20

CAI-IV-36-2-White solid-1H NMR



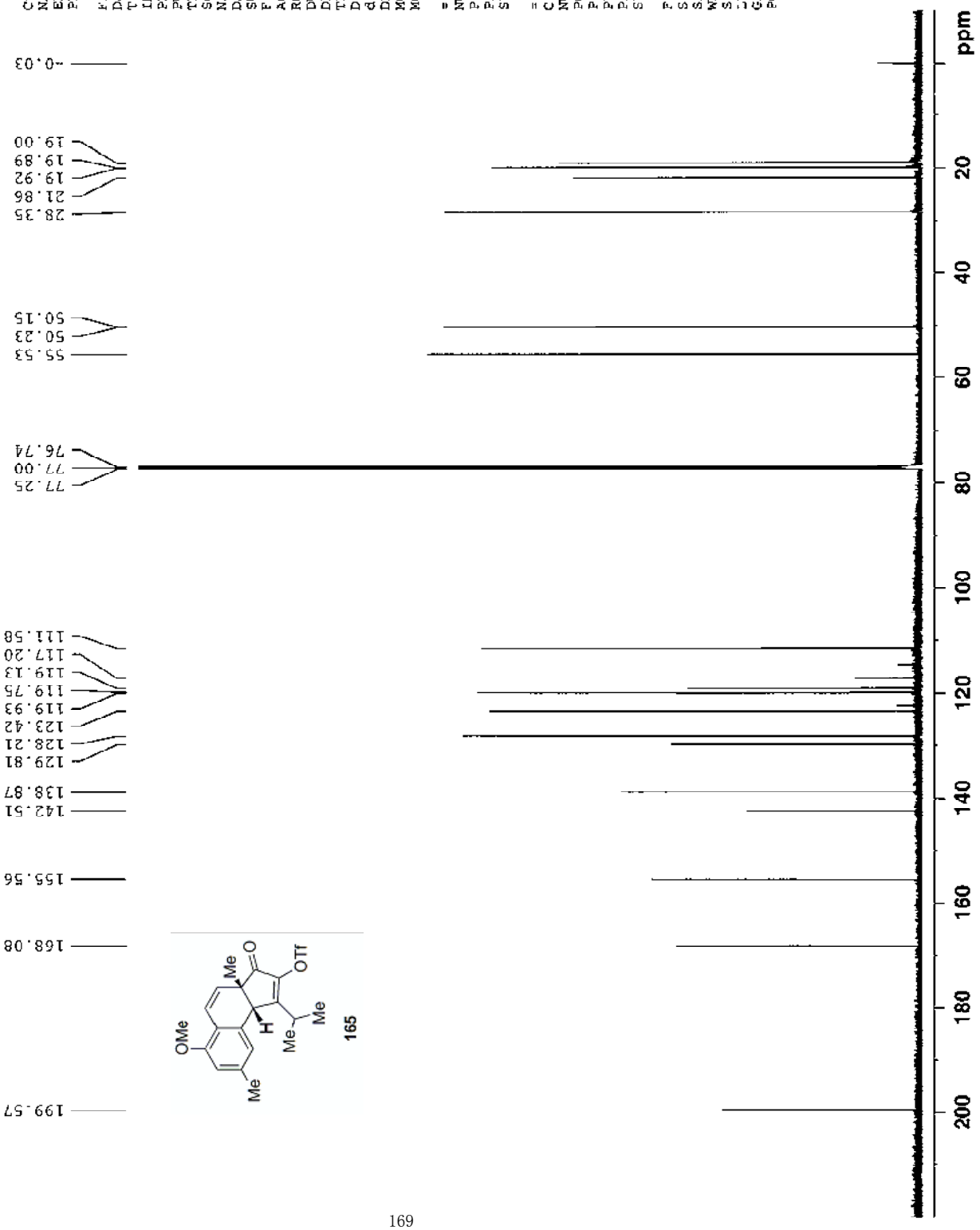
Current Data Parameters
NAME CAI-IV-36-2
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20081003
Time 23.43
INSTRUM DRX500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 10.1
DW 48.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

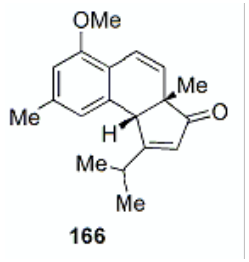
======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
PL1 4.30 dB
SFO1 500.1335009 MHz

F2 - Processing parameters
SI 32768
SF 500.1300138 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40

13C NMR


Current Data Parameters
NAME CAI-IV-36-2
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20081003
Time 23.49
INSTRUM DRX500
PROBHD 5 mm CPTCI 1H-
PULPROG zgpg30
TD 71424
SOLVENT CDCl3
NS 136
DS 4
SWH 35211.270 Hz
FIDRES 0.492989 Hz
AQ 1.0142708 sec
RG 4096
DW 14.200 usec
DE 35.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 12.00 usec
PL1 0.30 dB
SFO1 125.7716224 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 5.00 dB
PL12 22.00 dB
PL13 27.90 dB
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 65536
SF 125.7577923 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
199.57
168.08
155.56
142.51
138.87
129.81
128.21
123.42
119.93
119.75
119.13
117.20
111.58
77.25
77.00
76.74
55.53
50.33
50.15
28.35
21.86
19.92
19.89
19.00
-0.03
ppm
OMe
Me
O
OTf
H
Me
Me
Me
165

CAI-IV-38-2-White solid-1H NMR



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Current Data Parameters

NAME	CAI-IV-38-2
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20081005
Time	15.35
INSTRUM	DRX500
PROBHD	5 mm CPTCI 1H-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	8
DS	2
SWH	10330.578 Hz
FIDRES	0.157632 Hz
AQ	3.1719923 sec
RG	11.3
DW	48.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec
MCREST	0.00000000 sec
MCWRK	0.01500000 sec

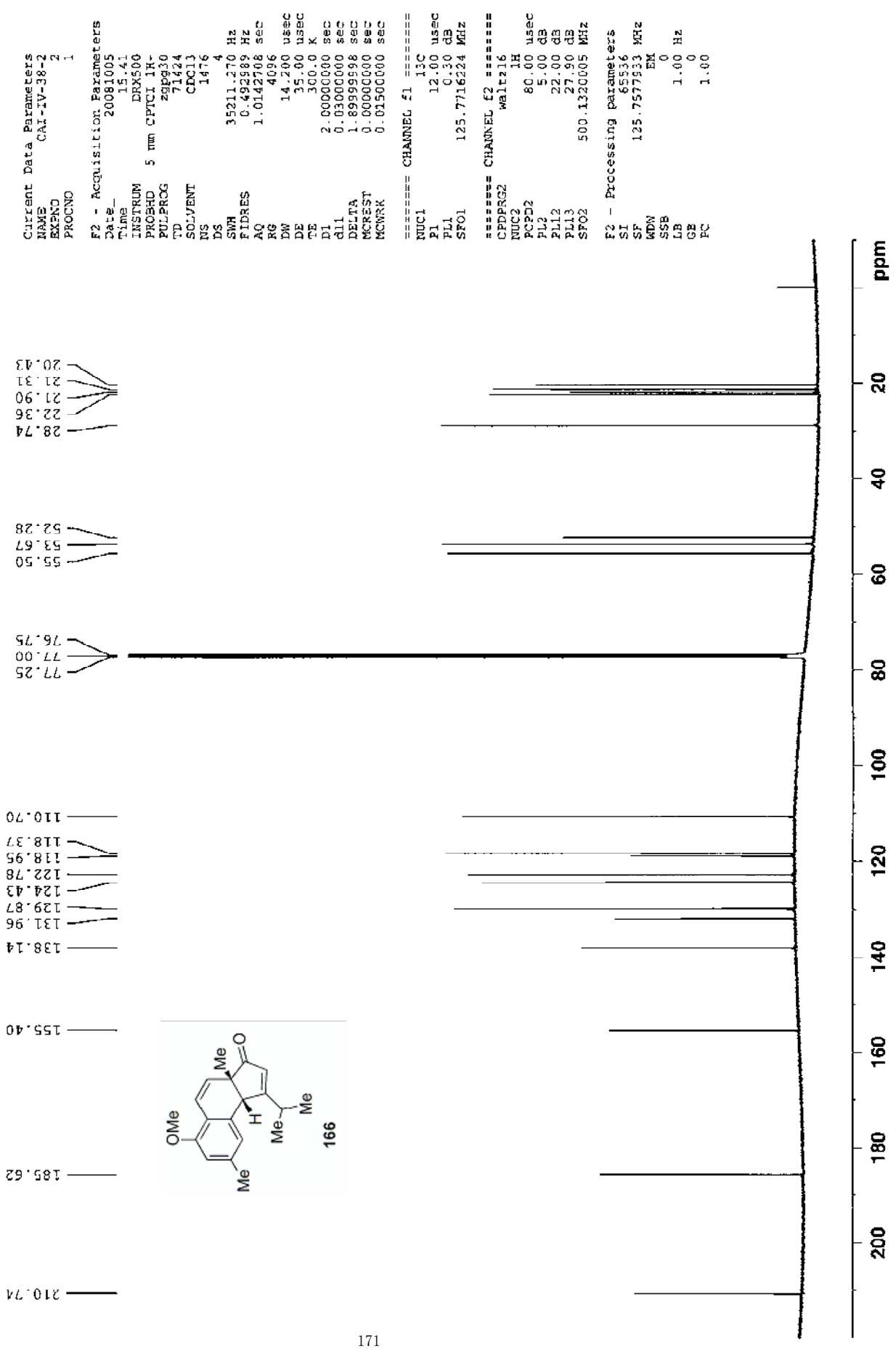
======== CHANNEL f1 ========

NUC1	1H
P1	8.00 usec
PL1	4.30 dB
SFO1	500.1335009 MHz

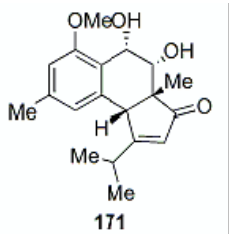
F2 - Processing parameters

SI	32768
SF	500.1300131 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

13C NMR


Current Data Parameters
NAME CAI-2V-38-2
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20081005
Time 15.41
INSTRUM DRX500
PROBHD 5 mm CPTCI 1H-
PULPROG zgpg30
TD 71424
SOLVENT CDCl3
NS 1476
DS 4
SWH 35211.270 Hz
FIDRES 0.492589 Hz
AQ 1.0142708 sec
RG 4096
DW 14.200 usec
DE 35.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 12.00 usec
PL1 0.30 dB
SFO1 125.7716224 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 5.00 dB
PL12 22.00 dB
PL13 27.90 dB
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 65536
SF 125.7577933 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
20.43
21.31
21.90
22.36
28.74
52.28
53.67
55.50
76.75
77.00
77.25
110.70
118.37
118.95
122.78
124.43
129.87
131.96
138.14
155.40
185.62
210.74
Me
O
OMe
H
Me
Me
Me
166
ppm
200
180
160
140
120
100
80
60
40
20

CAI-VII-89-DIOL-1H NMR



171

172

7.263 7.256 6.705 6.634 5.905 5.162 5.145 5.143 5.141 3.807 3.757 3.695 3.690 3.678 3.673 3.661 2.636 2.622 2.609 2.595 2.582 2.380 2.075 2.070 1.628 1.436 1.305 1.287 1.273 1.010 0.996 0.006 0.000

Current Data Parameters
NAME CAI-VII-89-3
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20100407
Time 11.09
INSTRUM DRX500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 18
DW 48.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

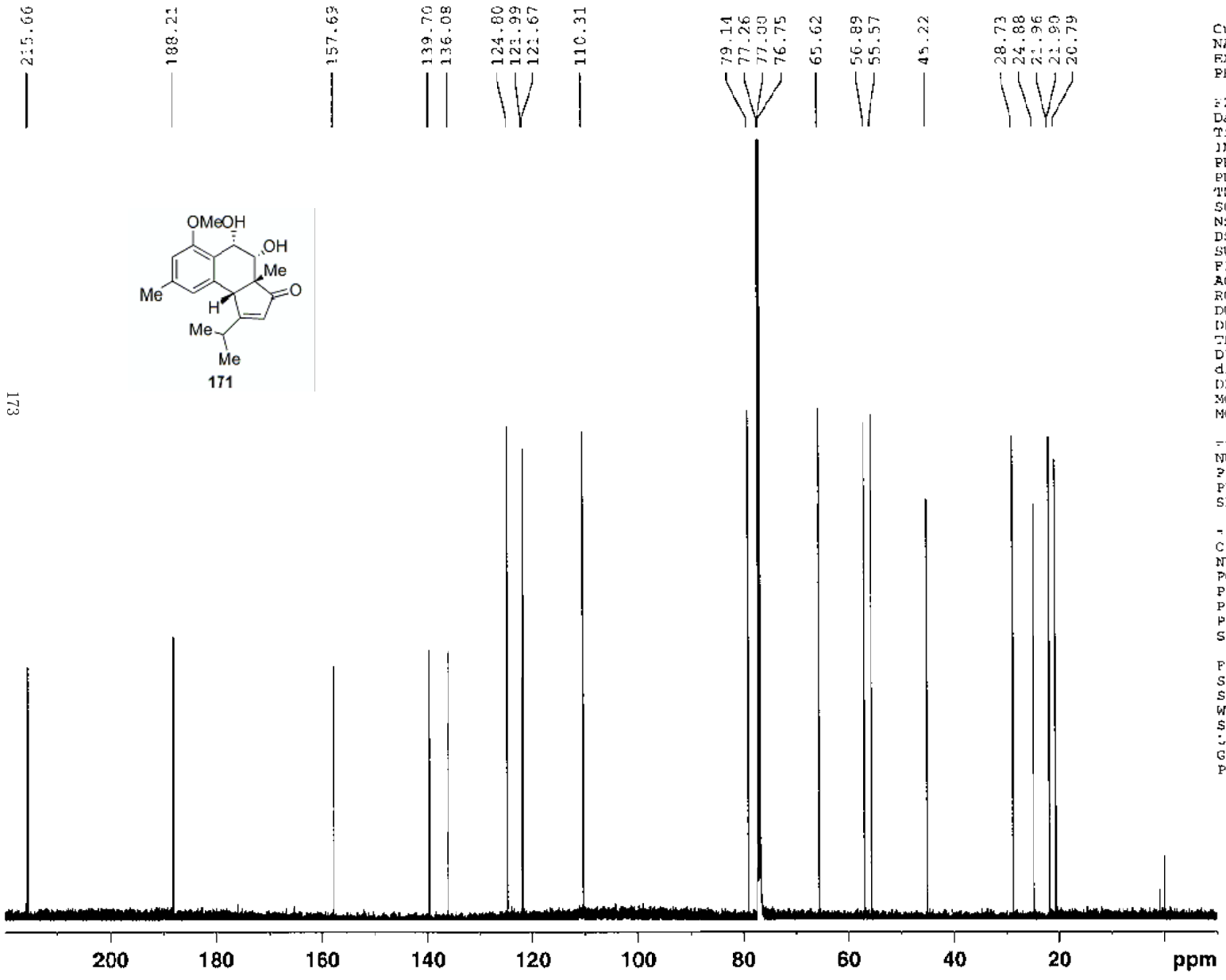
======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
PL1 4.30 dB
SFO1 500.1335009 MHz

F2 - Processing parameters
SI 32768
SF 500.1300116 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

11 10 9 8 7 6 5 4 3 2 1 0 ppm

1.03 1.01 1.00 2.06 3.10 1.04 1.05 1.03 3.04 1.00 3.06 3.10 3.08

13C NMR




```
Current Data Parameters
NAME          CAI-VII-89-3
EXPNO                    2
PROCNO                   1

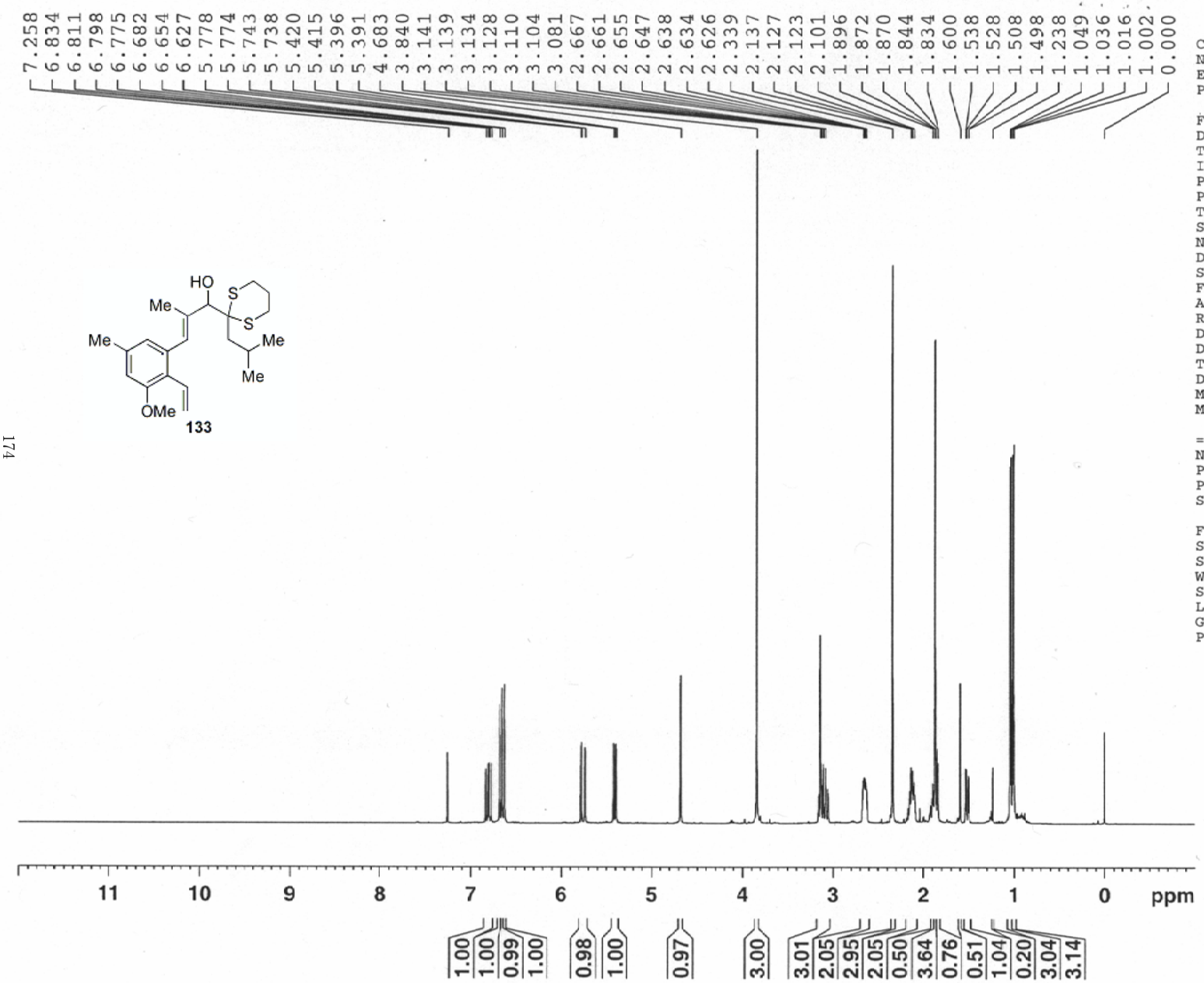
F2 - Acquisition Parameters
Date_              20100407
Time                 11.12
INSTRUM              DRX500
PROBHD   5 mm CPTCI 1H-
PULPROG              zgpg30
TD                    71424
SOLVENT               CDCl3
NS                      280
DS                        4
SWH                35211.270 Hz
FIDRES             0.492589 Hz
AQ                 1.0142708 sec
RG                     4096
DW                   14.200 usec
DE                   35.00 usec
TE                   300.0 K
D1                 2.00000000 sec
d11                0.03000000 sec
DELTA              1.89999998 sec
MCREST             0.00000000 sec
MCWRK              0.01500000 sec

======== CHANNEL f1 ========
NUC1                    13C
P1                    12.00 usec
PL1                    0.30 dB
SFO1          125.7716224 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                    1H
PCPD2                 80.00 usec
PL2                    5.00 dB
PL12                  22.00 dB
PL13                  27.90 dB
SFO2          500.1320005 MHz

F2 - Processing parameters
SI                     65536
SF            125.7577923 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.00
```

CAI-III-138-Colorless oil



Current Data Parameters

NAME	CAI-III-138-1
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20080821
Time	14.48
INSTRUM	DRX500
PROBHD	5 mm CPTCI 1H-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	8
DS	2
SWH	10330.578 Hz
FIDRES	0.157632 Hz
AQ	3.1719923 sec
RG	8
DW	48.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec
MCREST	0.00000000 sec
MCWRK	0.01500000 sec

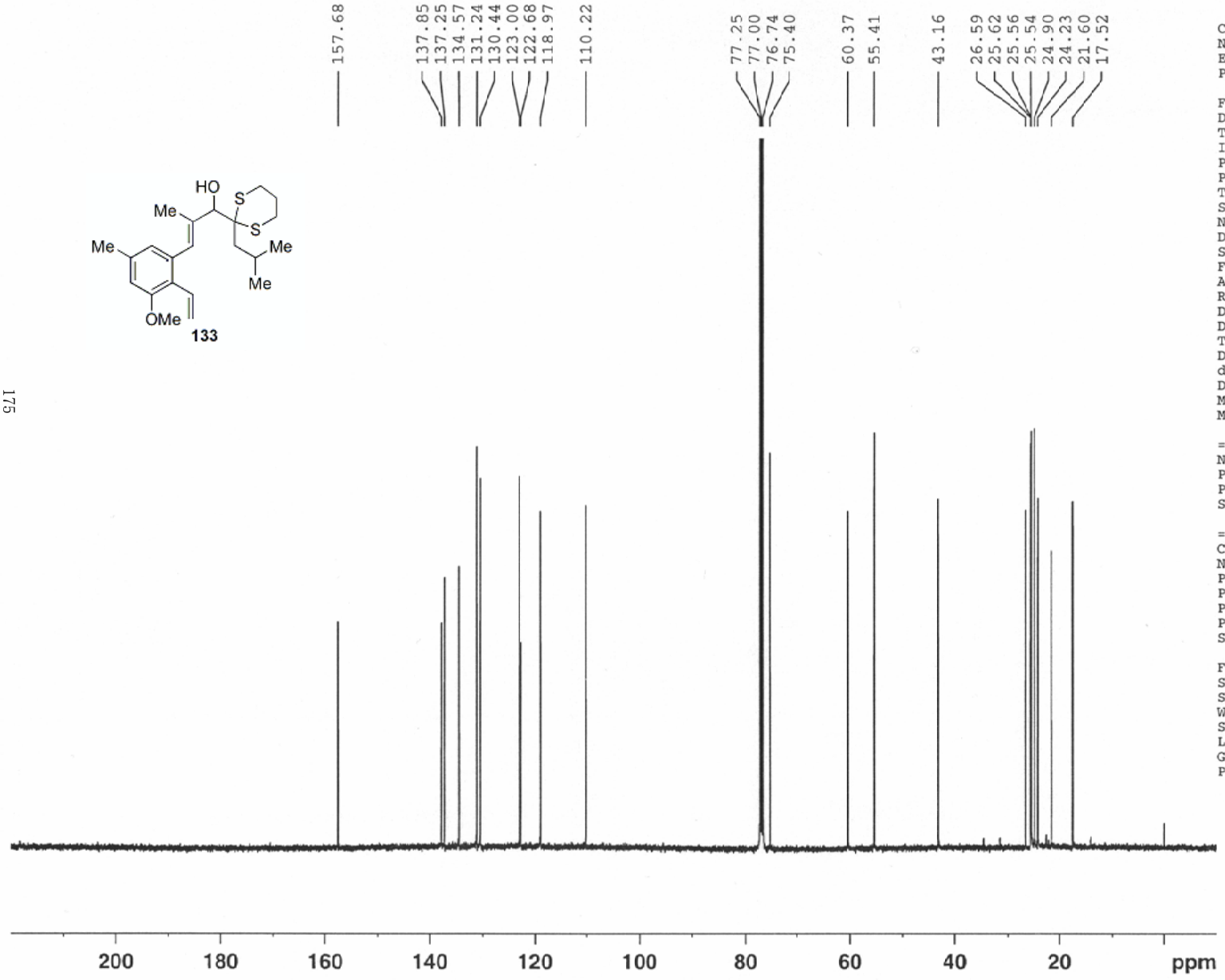
======== CHANNEL f1 ========

NUC1	1H
P1	8.00 usec
PL1	4.30 dB
SFO1	500.1335009 MHz

F2 - Processing parameters

SI	32768
SF	500.1300150 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

13C NMR




```
Current Data Parameters
NAME       CAI-III-138-1
EXPNO                  2
PROCNO                 1

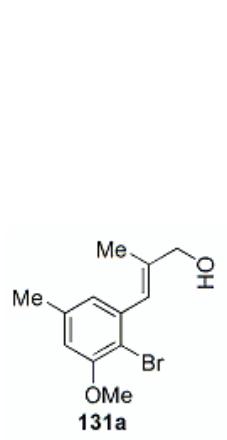
F2 - Acquisition Parameters
Date_           20080821
Time               14.54
INSTRUM           DRX500
PROBHD   5 mm CPTCI 1H-
PULPROG          zgpg30
TD                71424
SOLVENT           CDCl3
NS                  223
DS                    4
SWH           35211.270 Hz
FIDRES        0.492989 Hz
AQ            1.0142708 sec
RG                 4096
DW               14.200 usec
DE               35.00 usec
TE               300.0 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

======== CHANNEL f1 ========
NUC1               13C
P1               12.00 usec
PL1               0.30 dB
SFO1        125.7716224 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2               1H
PCPD2            80.00 usec
PL2               5.00 dB
PL12             22.00 dB
PL13             27.90 dB
SFO2        500.1320005 MHz

F2 - Processing parameters
SI                65536
SF          125.7577955 MHz
WDW                EM
SSB                 0
LB               1.00 Hz
GB                  0
PC               1.00
```

CAI-III-120-P-1H NMR



131a

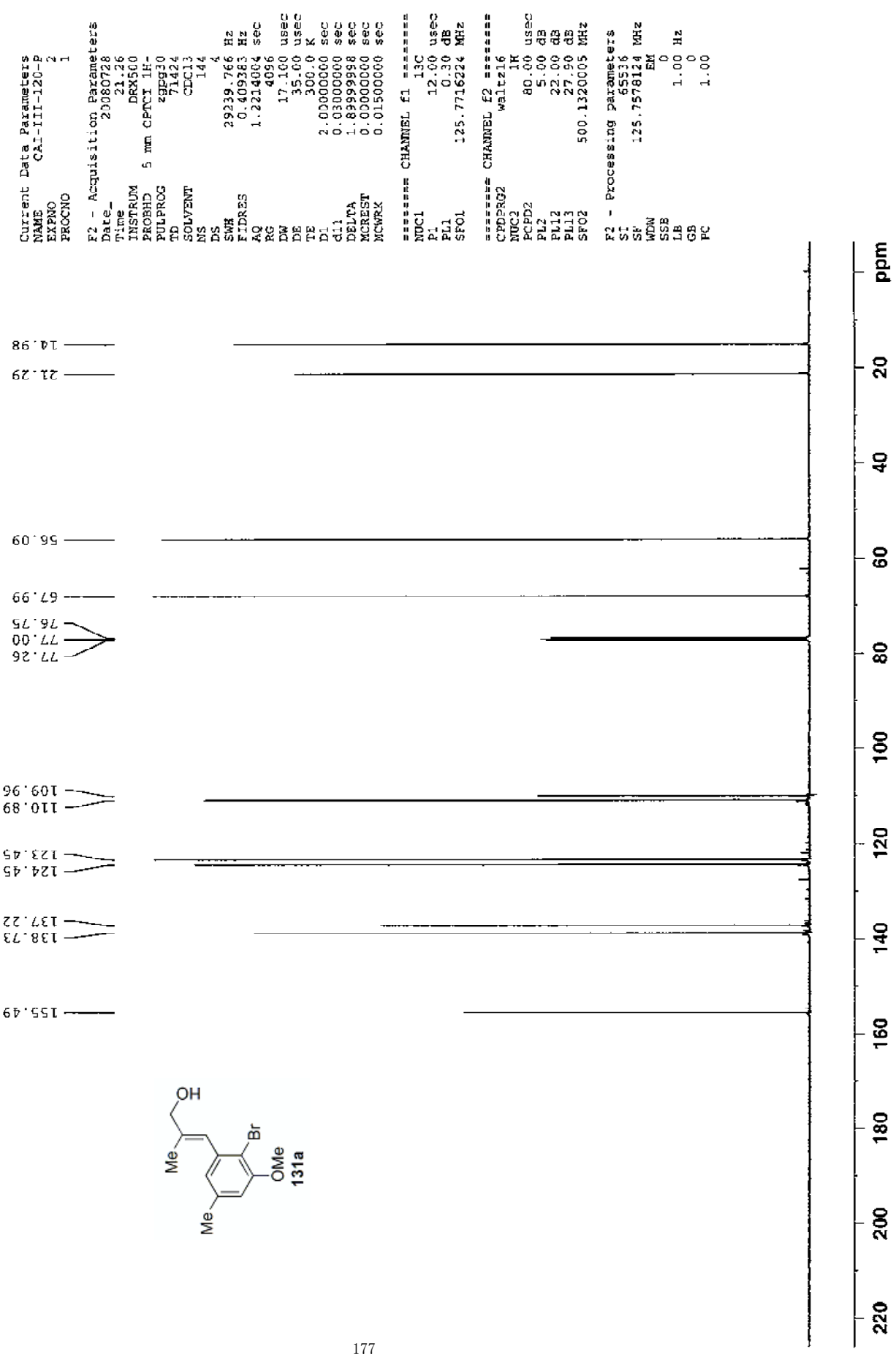

```
Current Data Parameters
NAME       CAI-III-120-P
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20080728
Time               21.20
INSTRUM          DRX500
PROBHD   5 mm CPTCI 1H-
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                    8
DS                    2
SWH           10330.578 Hz
FIDRES         0.157632 Hz
AQ             3.1719923 sec
RG                    5
DW               48.400 usec
DE                6.00 usec
TE                300.0 K
D1            1.00000000 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

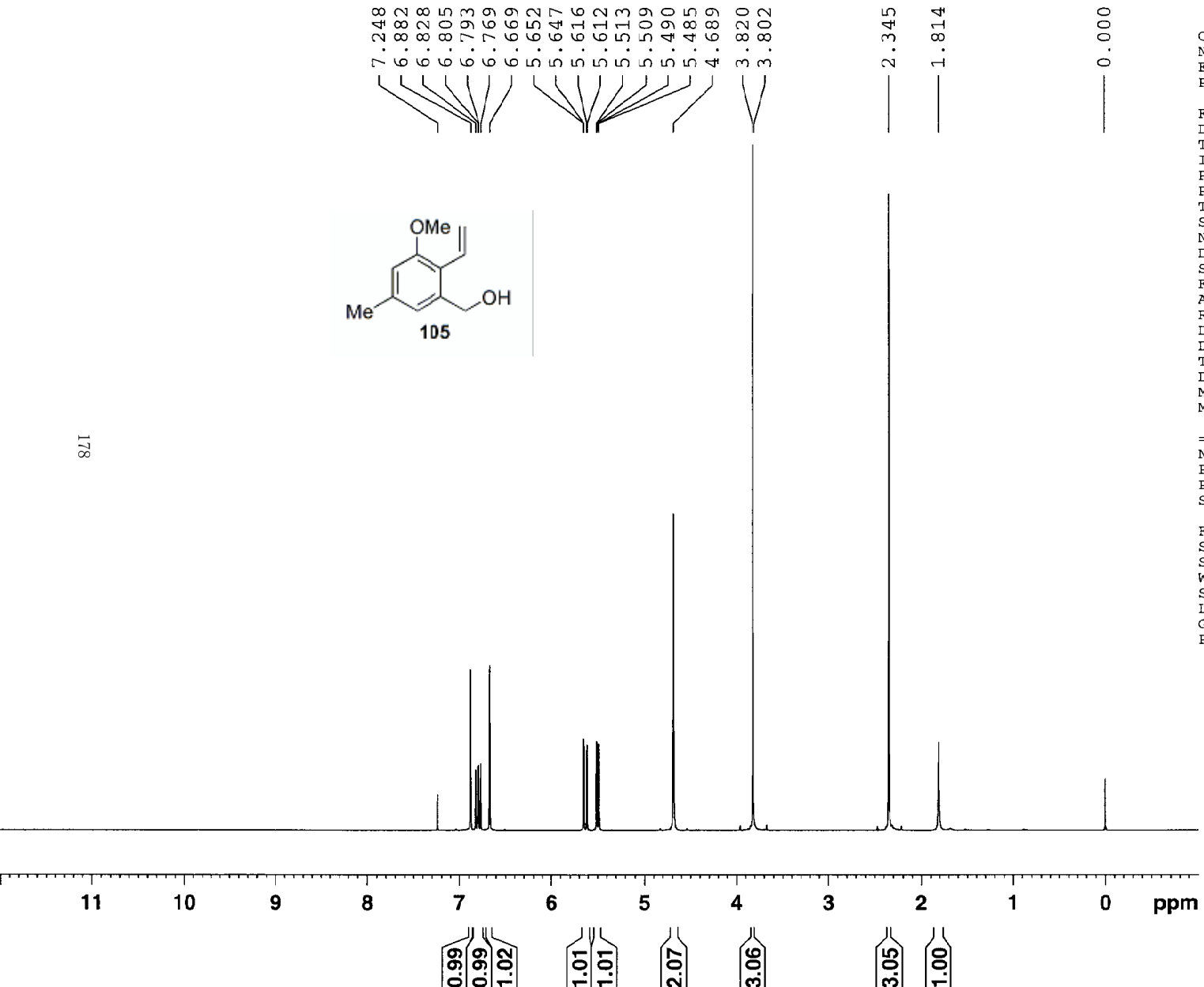
======== CHANNEL f1 ========
NUC1                  1H
P1                 8.00 usec
PL1                4.30 dB
SFO1         500.1335009 MHz

F2 - Processing parameters
SI                32768
SF          500.1300081 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.40
```

13C NMR


Current Data Parameters
NAME CAI-III-120-P
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080728
Time 21.26
INSTRUM DRX500
PROBHD 5 mm CPTCI 1H-
PULPROG zgpg30
TD 71424
SOLVENT CDCl3
NS 144
DS 4
SWH 29239.766 Hz
FIDRES 0.409363 Hz
AQ 1.2214064 sec
RG 4096
DW 17.100 usec
DE 35.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 12.00 usec
PL1 0.30 dB
SFO1 125.7716224 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 5.00 dB
PL12 22.00 dB
PL13 27.50 dB
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 65536
SF 125.7578124 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
14.98
21.29
56.09
67.99
76.75
77.00
77.26
109.96
110.89
123.45
124.45
137.22
138.73
155.49
OH
Me
Br
OMe
Me
131a
ppm
220
200
180
160
140
120
100
80
60
40
20

CAI-V-40-SM-1H NMR



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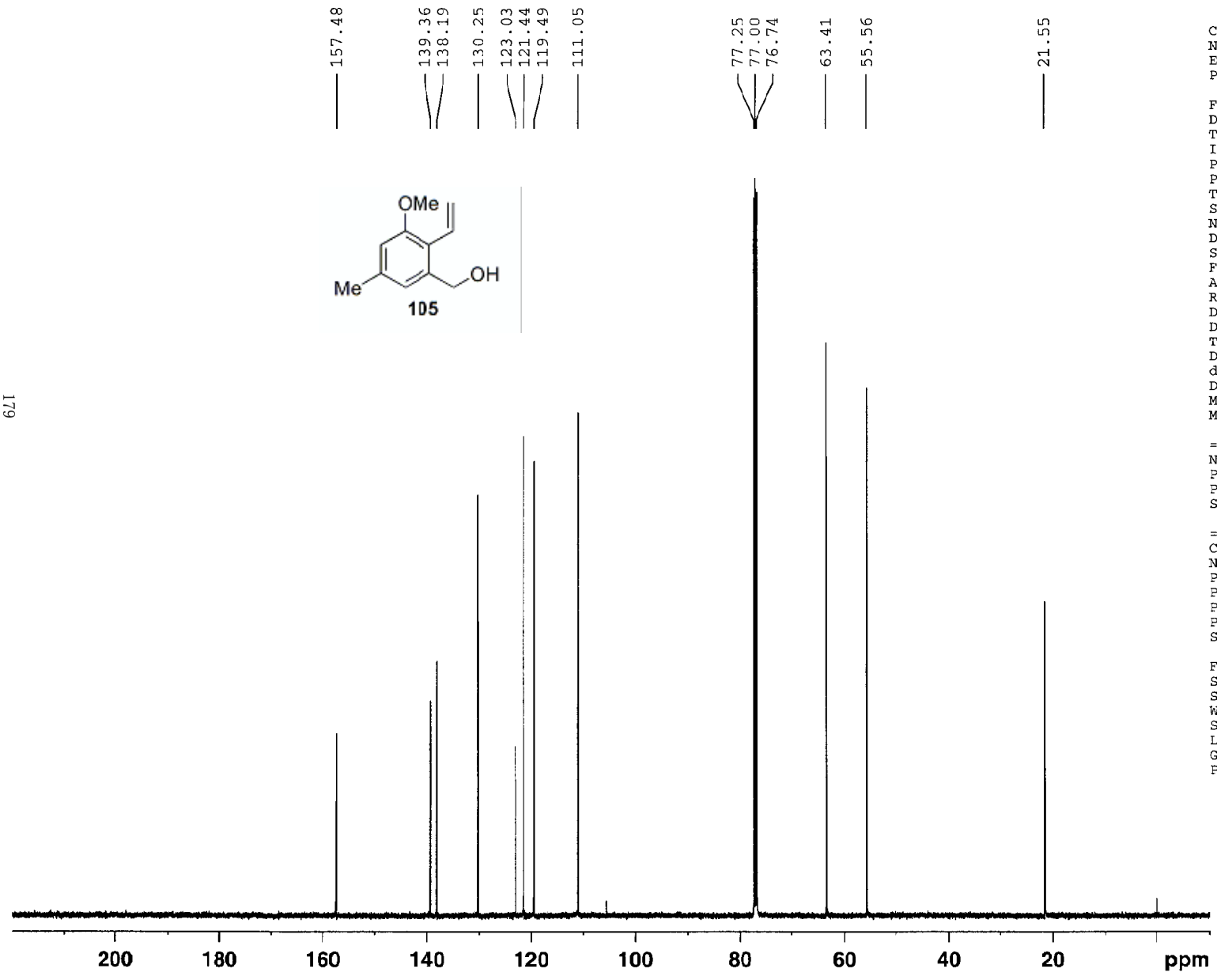
```
Current Data Parameters
NAME          CAI-V-40-SM
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameter
Date_           20090413
Time               11.01
INSTRUM          DRX500
PROBHD   5 mm CPTCI 1H-
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                    8
DS                    2
SWH          10330.578 Hz
FIDRES        0.157632 Hz
AQ           3.1719923 se
RG                    8
DW              48.400 us
DE               6.00 us
TE              300.0 K
D1          1.00000000 se
MCREST      0.00000000 se
MCWRK       0.01500000 se

======== CHANNEL f1 ======
NUC1                  1H
P1                 8.00 us
PL1                4.30 dB
SFO1        500.1335009 MH

F2 - Processing parameters
SI                32768
SF          500.1300198 MH
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```

13C NMR




```
Current Data Parameters
NAME          CAI-V-40-SM
EXPNO                   2
PROCNO                  1

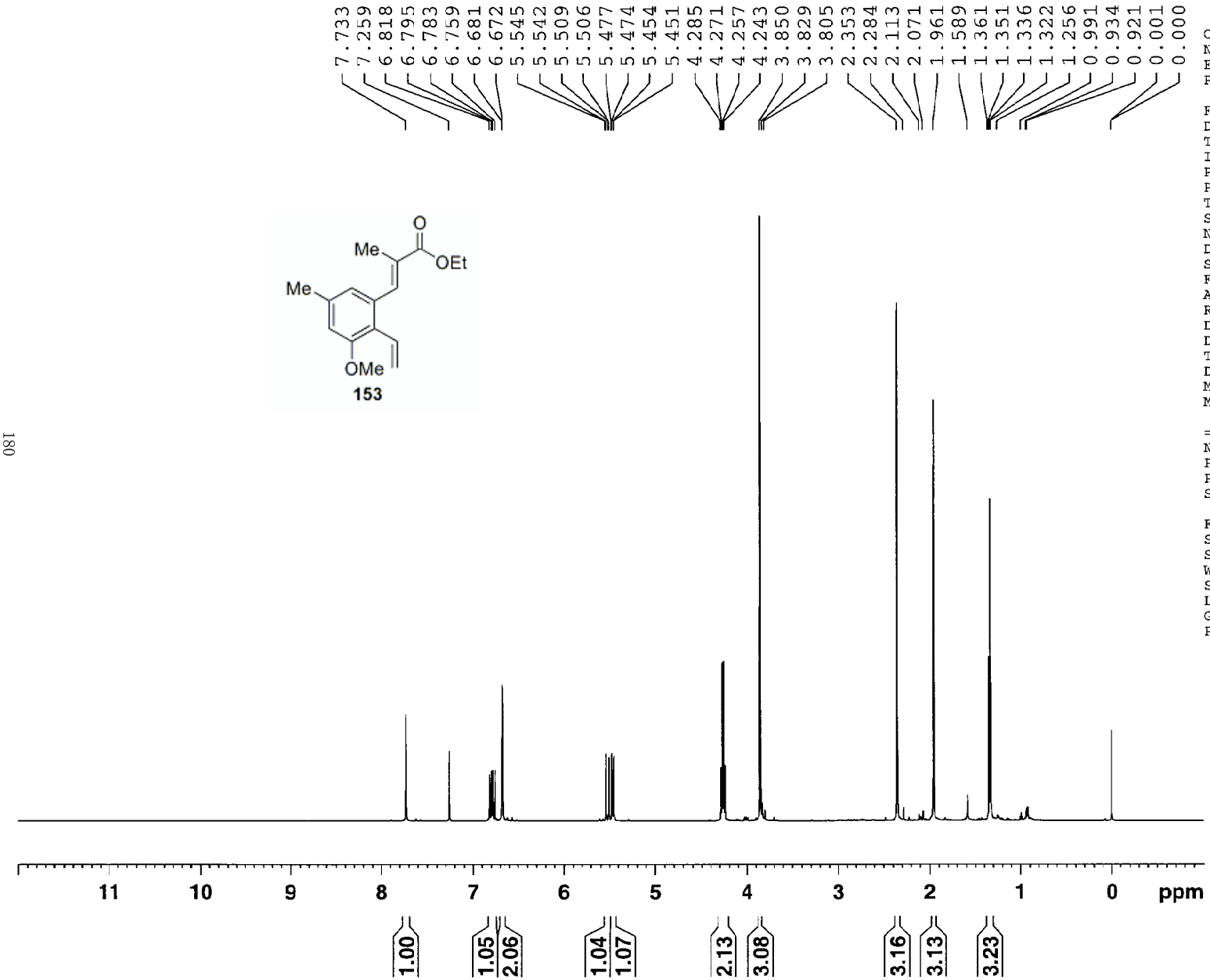
F2 - Acquisition Parameters
Date_            20090413
Time                11.05
INSTRUM           DRX500
PROBHD   5 mm CPTCI 1H-
PULPROG           zgpg30
TD                 71424
SOLVENT            CDCl3
NS                    75
DS                     4
SWH           35211.270 Hz
FIDRES         0.492989 Hz
AQ            1.0142708 sec
RG                  4096
DW                14.200 usec
DE                35.00 usec
TE                300.0 K
D1           2.00000000 sec
d11          0.03000000 sec
DELTA        1.89999998 sec
MCREST       0.00000000 sec
MCWRK        0.01500000 sec

======== CHANNEL f1 ========
NUC1                 13C
P1                 12.00 usec
PL1                 0.30 dB
SFO1        125.7716224 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2              80.00 usec
PL2                 5.00 dB
PL12               22.00 dB
PL13               27.90 dB
SFO2        500.1320005 MHz

F2 - Processing parameters
SI                 65536
SF          125.7577982 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.00
```

Left1-H NMR



Current Data Parameters

NAME	CAI-V-L1
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20090511
Time	13.19
INSTRUM	DRX500
PROBHD	5 mm CPTCI 1H-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	8
DS	2
SWH	10330.578 Hz
FIDRES	0.157632 Hz
AQ	3.1719923 sec
RG	9
DW	48.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec
MCREST	0.00000000 sec
MCWRK	0.01500000 sec

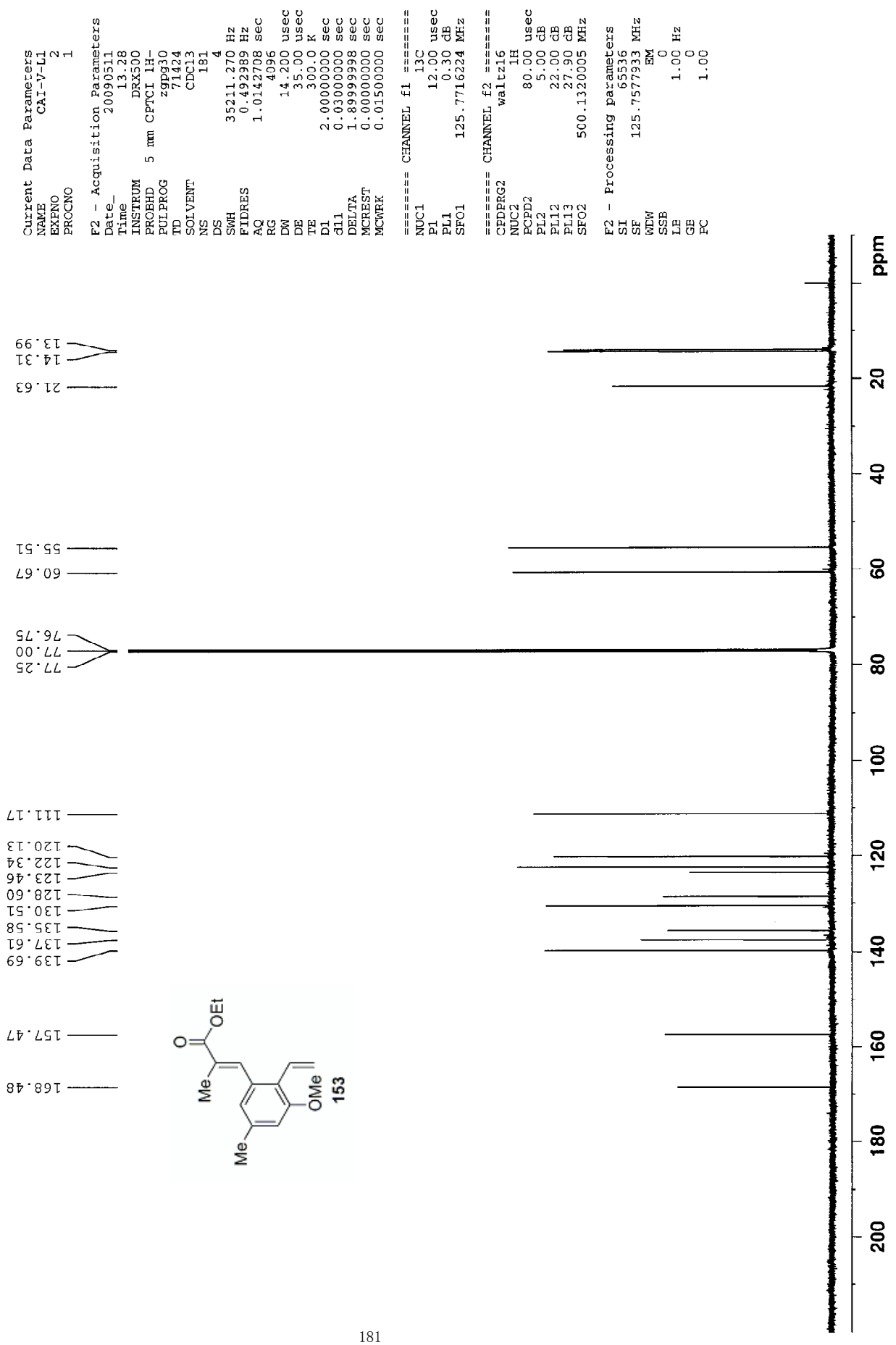
======== CHANNEL f1 ========

NUC1	1H
P1	8.00 usec
PL1	4.30 dB
SFO1	500.1335009 MHz

F2 - Processing parameters

SI	32768
SF	500.1300138 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

13C NMR


Current Data Parameters
NAME CAI-V-L1
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20090511
Time 13.28
INSTRUM DRX500
PROBHD 5 mm CPTCI 1H-
PULPROG zgpg30
TD 71424
SOLVENT CDC13
NS 181
DS 4
SWH 35211.270 Hz
FIDRES 0.492989 Hz
AQ 1.0142708 sec
RG 4096
DW 14.200 usec
DE 35.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 12.00 usec
PL1 0.30 dB
SFO1 125.7716224 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 5.00 dB
PL12 22.00 dB
PL13 27.90 dB
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 65536
SF 125.7577933 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
13.99
14.31
21.63
55.51
60.67
76.75
77.00
77.25
111.17
120.13
122.34
123.46
128.60
130.51
135.58
137.61
139.69
157.47
168.48
O
OEt
Me
Me
OMe
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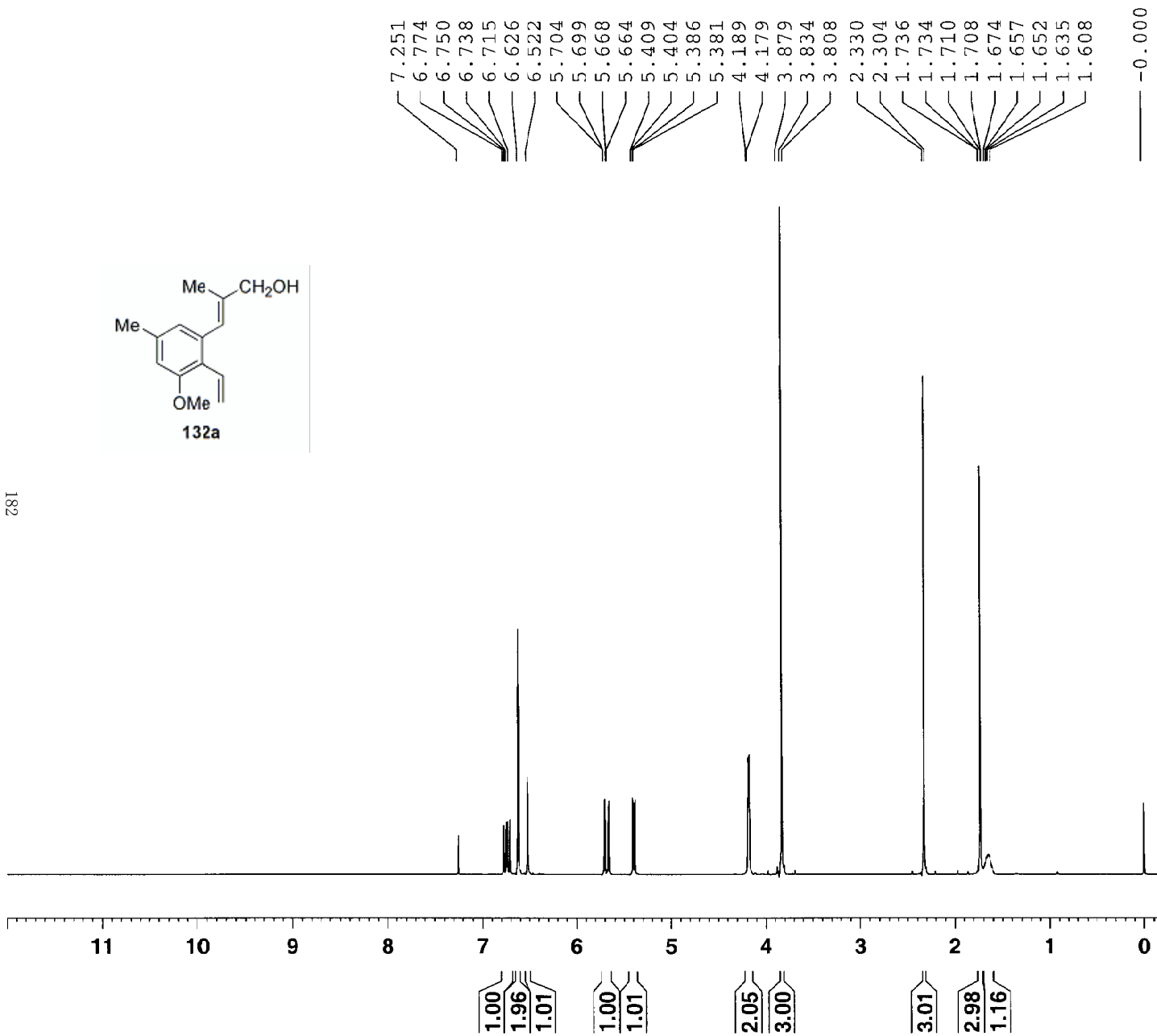
ppm
200
180
160
140
120
100
80
60
40
20

CAI-VIII-28-Yellow oil-1H NMR



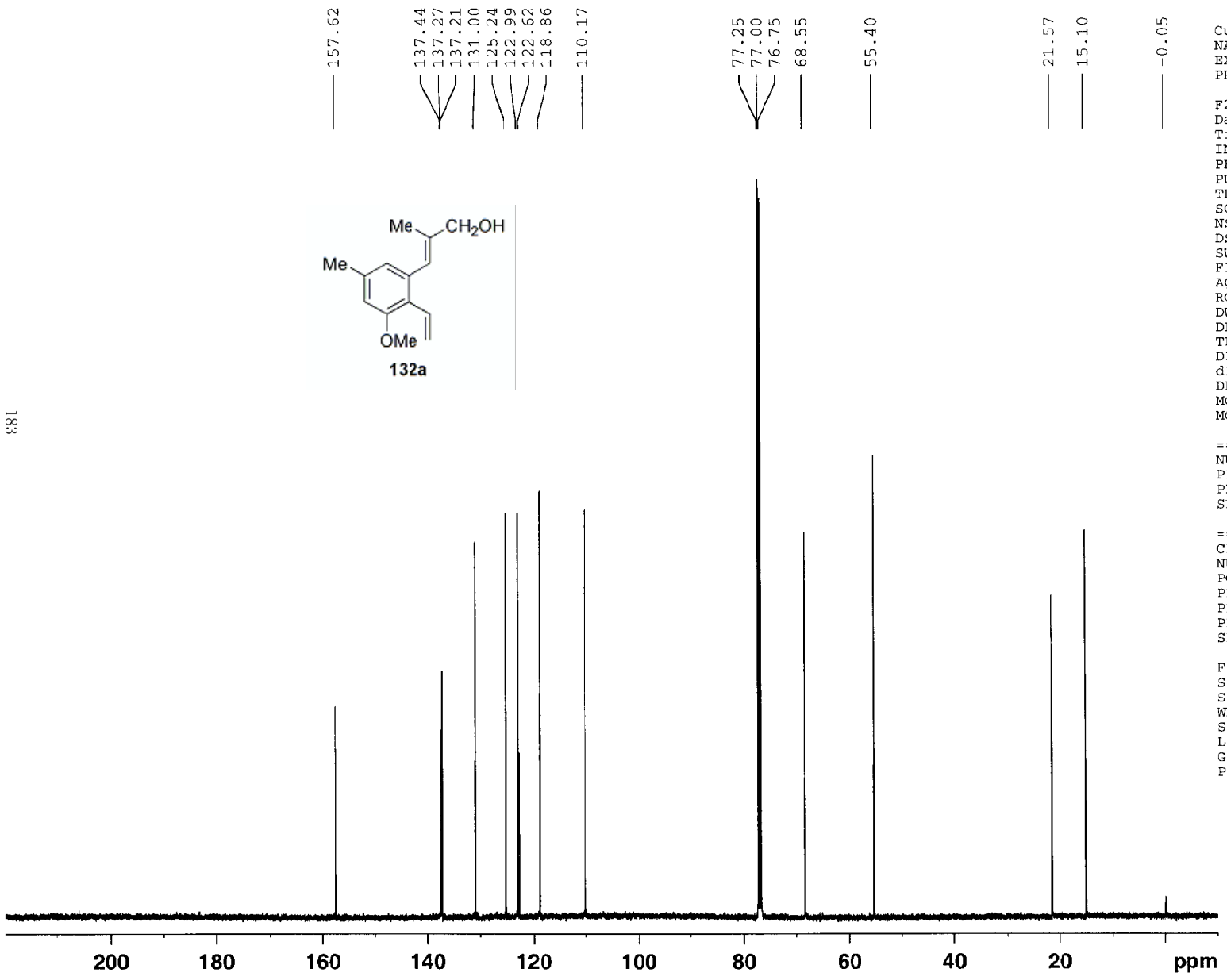

```
Current Data Parameters
NAME       CAI-VIII-28-2
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20100519
Time               18.42
INSTRUM          DRX500
PROBHD   5 mm CPTCI 1H-
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                    8
DS                    2
SWH           10330.578 Hz
FIDRES        0.157632 Hz
AQ            3.1719923 sec
RG                 10.1
DW                48.400 usec
DE                 6.00 usec
TE                300.0 K
D1           1.00000000 sec
MCREST       0.00000000 sec
MCWRK        0.01500000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 8.00 usec
PL1                4.30 dB
SFO1        500.1335009 MHz

F2 - Processing parameters
SI                 32768
SF          500.1300176 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.40
```

13C NMR



Current Data Parameters

NAME	CAI-VIII-28-2
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20100519
Time	18.45
INSTRUM	DRX500
PROBHD	5 mm CPTCI 1H-
PULPROG	zgpg30
TD	71424
SOLVENT	CDCl3
NS	81
DS	4
SWH	35211.270 Hz
FIDRES	0.492989 Hz
AQ	1.0142708 sec
RG	4096
DW	14.200 usec
DE	35.00 usec
TE	300.0 K
D1	2.00000000 sec
d11	0.03000000 sec
DELTA	1.89999998 sec
MCREST	0.00000000 sec
MCWRK	0.01500000 sec

======== CHANNEL f1 ========

NUC1	13C
P1	12.00 usec
PL1	0.30 dB
SFO1	125.7716224 MHz

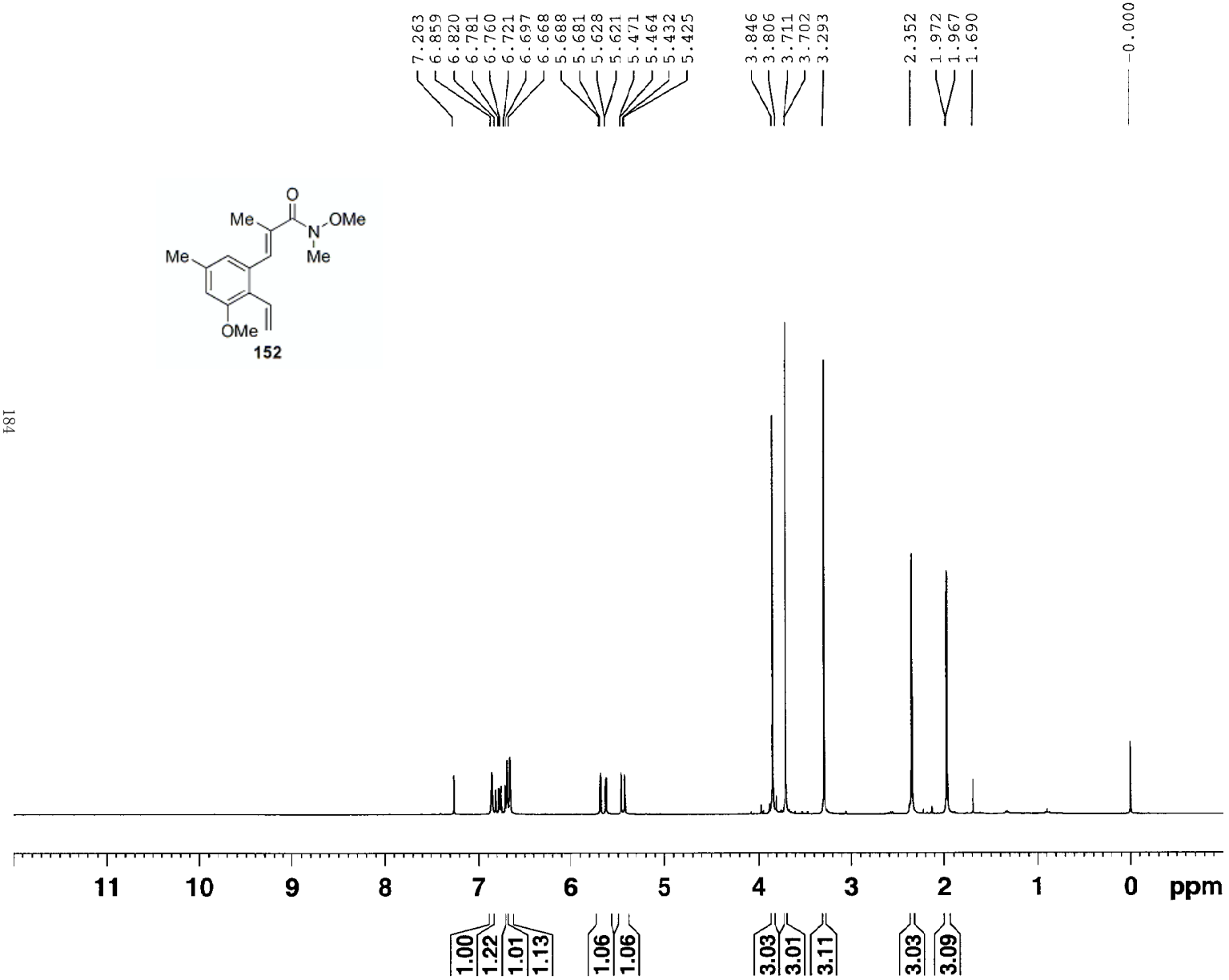
======== CHANNEL f2 ========

CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	5.00 dB
PL12	22.00 dB
PL13	27.90 dB
SFO2	500.1320005 MHz

F2 - Processing parameters

SI	65536
SF	125.7577971 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.00

CAI-VI-150-1-1H NMR



Current Data Parameters

NAME	CAI-VI-150-1a
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20091008
Time	21.40
INSTRUM	DRX300
PROBHD	5 mm Multinucl
PULPROG	zg30pad
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839 Hz
FIDRES	0.188380 Hz
AQ	2.6542580 sec
RG	256
DW	81.000 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec
D31	0.00000000 sec

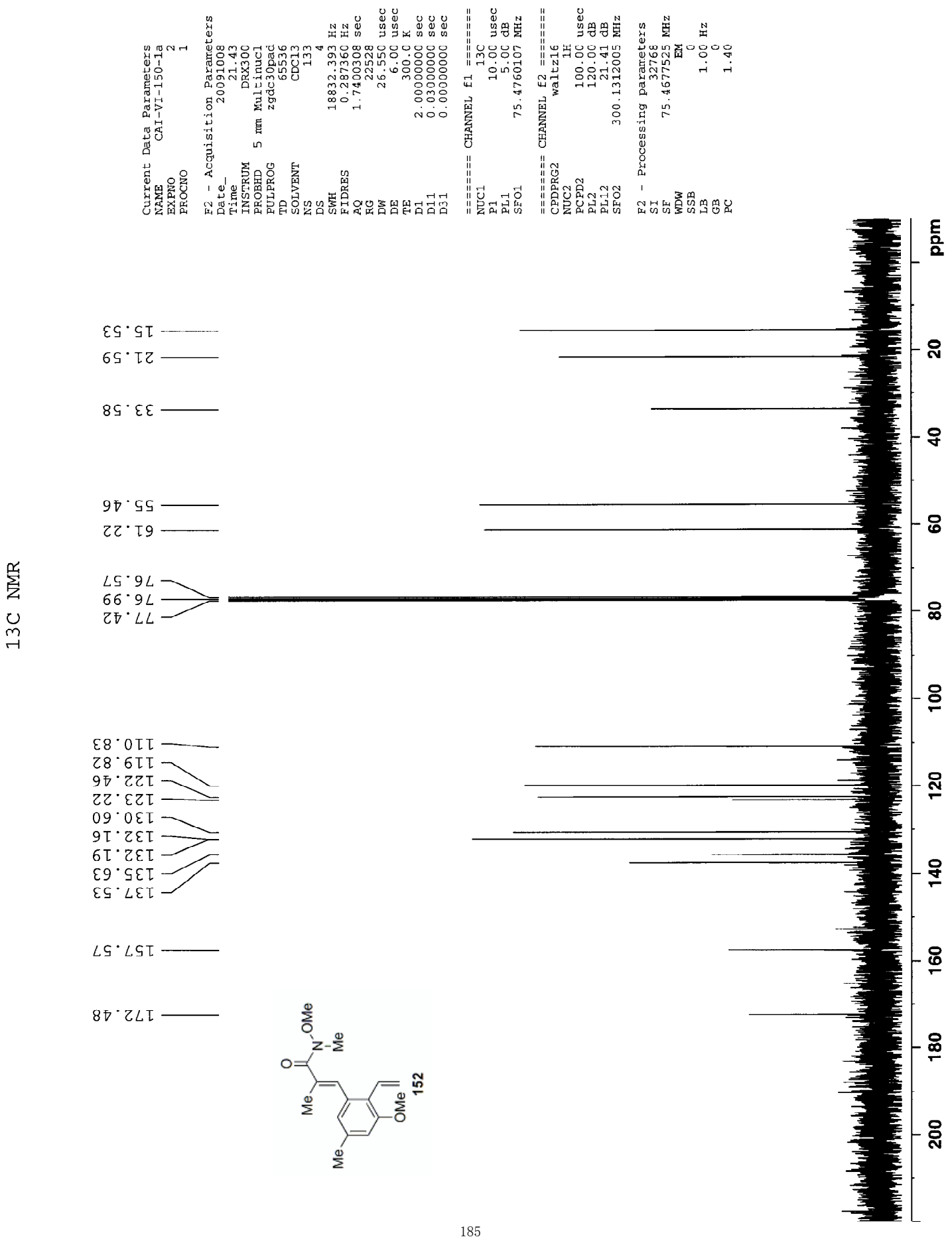
======== CHANNEL f1 ========

NUC1	1H
P1	7.05 usec
PL1	0.00 dB
SFO1	300.1318534 MHz

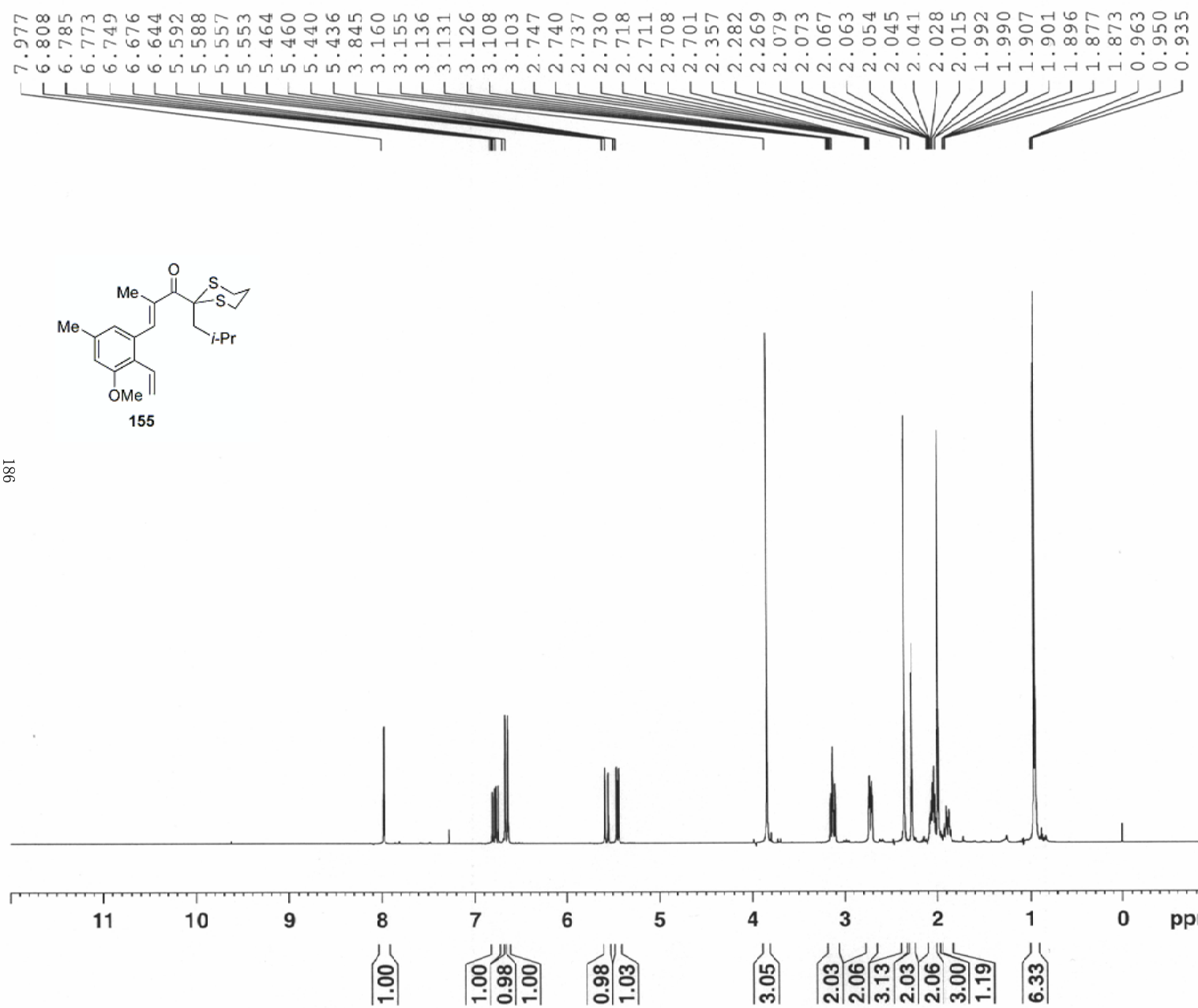
F2 - Processing parameters

SI	32768
SF	300.1300052 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.30

13C NMR


Current Data Parameters
NAME CAI-VI-150-1a
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20091008
Time_ 21.43
INSTRUM DRX300
PROBHD 5 mm Multinuc1
PULPROG zgdc30pad
TD 65536
SOLVENT CDC13
NS 133
DS 4
SWH 18832.393 Hz
FIDRES 0.287360 Hz
AQ 1.7400308 sec
RG 22528
DW 26.550 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
D31 0.00000000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 10.00 usec
PL1 5.00 dB
SFO1 75.4760107 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 120.00 dB
PL12 21.41 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
SI 32768
SF 75.4677525 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
172.48
157.57
137.53
135.63
132.19
132.16
130.60
123.22
122.46
119.82
110.83
77.42
76.99
76.57
61.22
55.46
33.58
21.59
15.53
ppm
Me
OMe
N
Me
O
Me
OMe
152

CAI-VII-94-3 1H NMR

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Current Data Parameters
NAME          CAI-VII-94-3
EXPNO                    1
PROCNO                   1

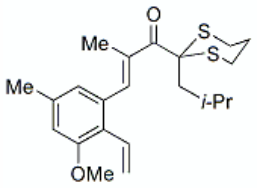
F2 - Acquisition Parameters
Date_             20100329
Time                 15.46
INSTRUM             DRX500
PROBHD    5 mm CPTCI 1H-
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                      8
DS                      2
SWH             10330.578 Hz
FIDRES              0.157632 Hz
AQ                3.1719923 sec
RG                      5
DW                 48.400 usec
DE                  6.00 usec
TE                300.0 K
D1              1.00000000 sec
MCREST          0.00000000 sec
MCWRK           0.01500000 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                  8.00 usec
PL1                 4.30 dB
SFO1          500.1335009 MHz

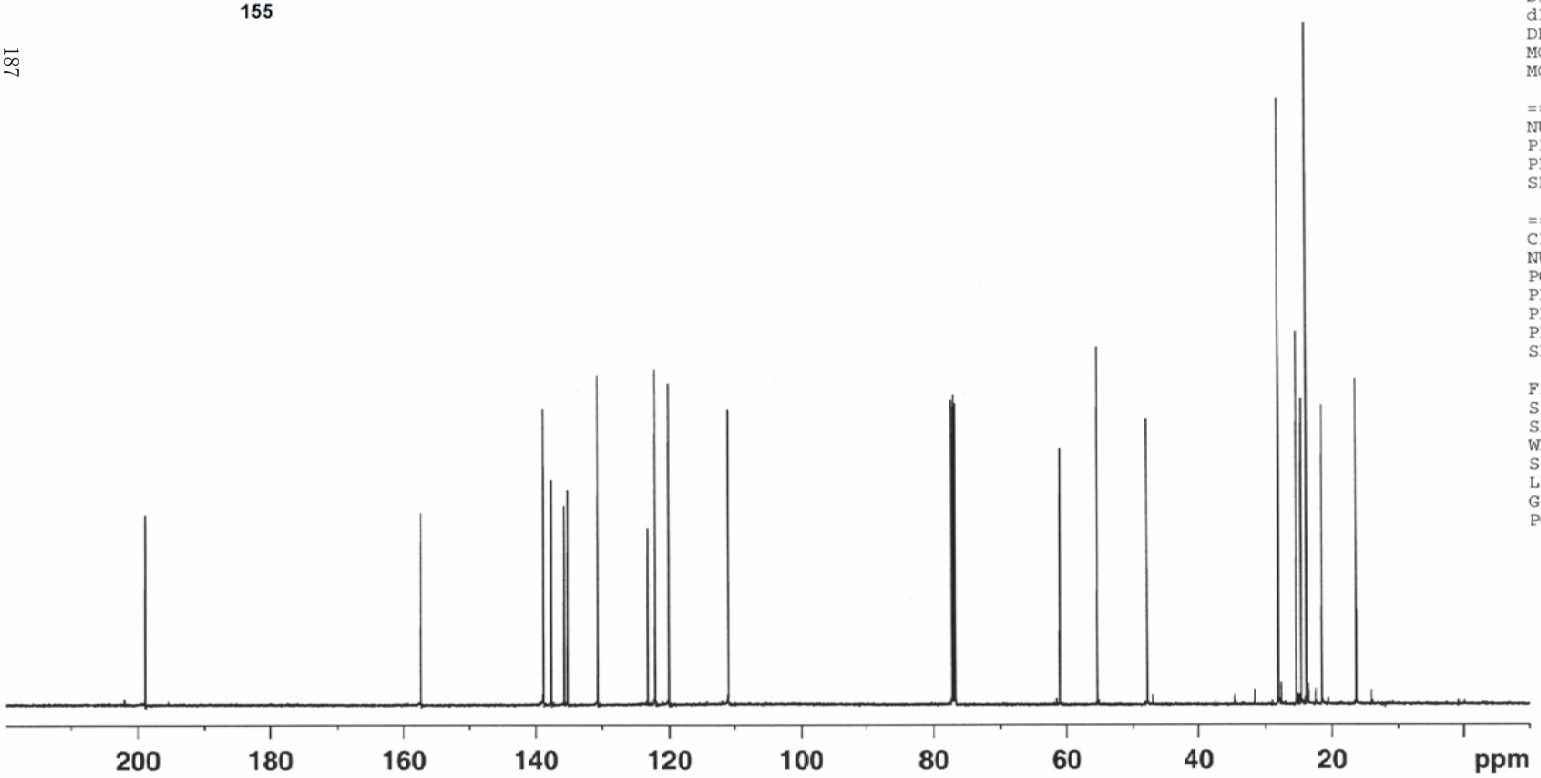
F2 - Processing parameters
SI                   32768
SF            500.1300043 MHz
WDW                     EM
SSB                      0
LB                  0.30 Hz
GB                       0
PC                    1.00
```

13C NMR

198.86
157.42
138.87
137.62
135.67
135.10
130.70
123.26
122.09
120.09
110.95
77.26
77.00
76.75
61.00
55.40
47.88
28.00
25.30
24.57
23.85
21.56
16.39



155




```
Current Data Parameters
NAME        CAI-VII-94-3
EXPNO                  2
PROCNO                 1

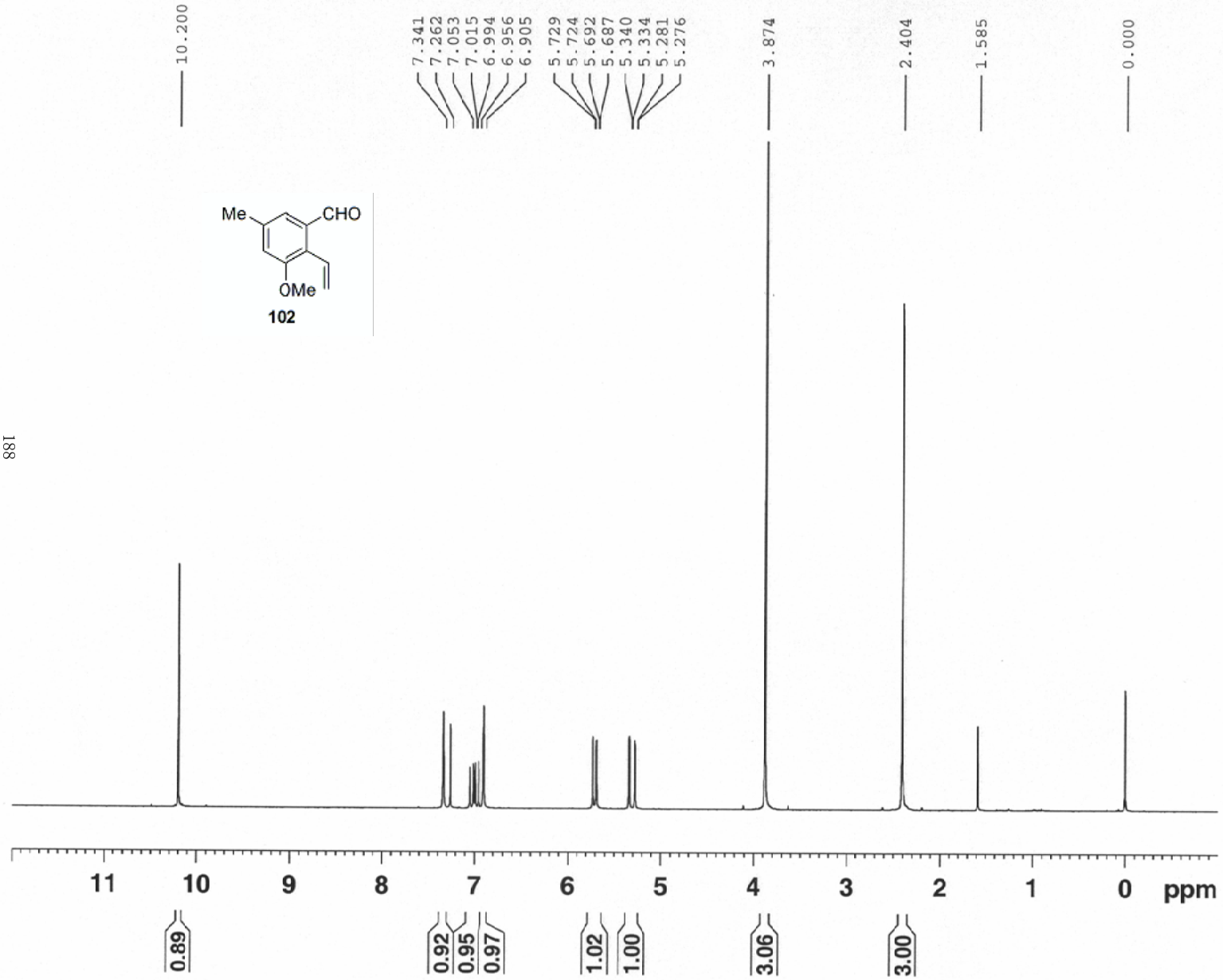
F2 - Acquisition Parameters
Date_           20100329
Time               15.50
INSTRUM           DRX500
PROBHD   5 mm CPTCI 1H-
PULPROG          zgpg30
TD                71424
SOLVENT           CDCl3
NS                   66
DS                    4
SWH           35211.270 Hz
FIDRES         0.492989 Hz
AQ            1.0142708 sec
RG                 4096
DW               14.200 usec
DE               35.00 usec
TE               300.0 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

======== CHANNEL f1 ========
NUC1                 13C
P1                12.00 usec
PL1                0.30 dB
SFO1        125.7716224 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2             80.00 usec
PL2                5.00 dB
PL12              22.00 dB
PL13              27.90 dB
SFO2        500.1320005 MHz

F2 - Processing parameters
SI                65536
SF          125.7578068 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.00
```

CAI-V-Recovered aldehyde-white wax-1H NMR



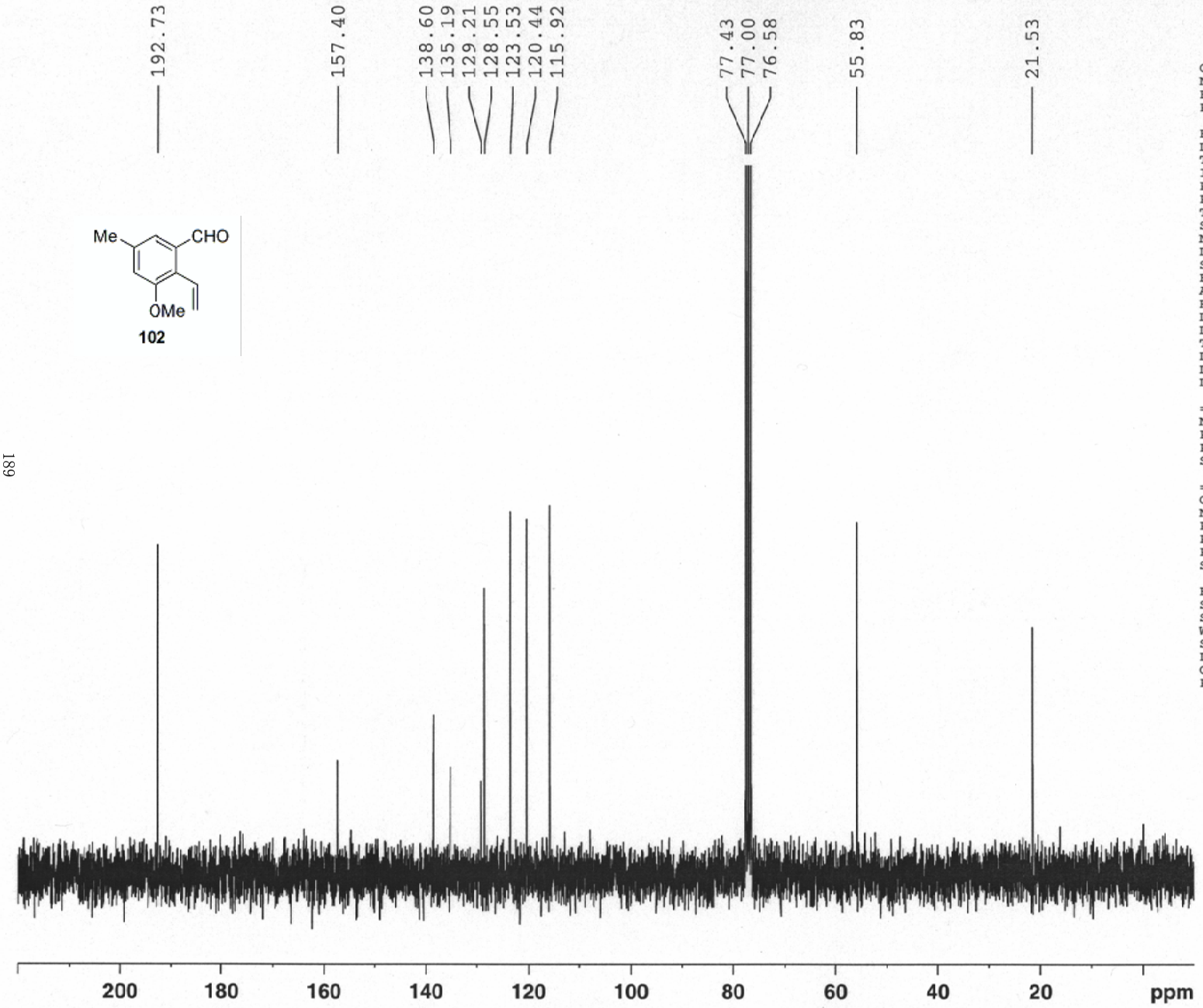

```
Current Data Parameters
NAME      CAI-V-Recover aldehyde
EXPNO                1
PROCNO               1

F2 - Acquisition Parameters
Date_          20090506
Time             22.02
INSTRUM          DRX300
PROBHD   5 mm Multinucl
PULPROG          zg30pad
TD               32768
SOLVENT          CDCl3
NS                  16
DS                   2
SWH           6172.839 Hz
FIDRES        0.188380 Hz
AQ            2.6542580 sec
RG               456.1
DW               81.000 usec
DE                6.00 usec
TE               300.0 K
D1          1.00000000 sec
D31         0.00000000 sec

======== CHANNEL f1 ========
NUC1                1H
P1                7.05 usec
PL1               0.00 dB
SFO1        300.1318534 MHz

F2 - Processing parameters
SI               32768
SF          300.1300056 MHz
WDW                 EM
SSB                  0
LB                0.30 Hz
GB                   0
PC                1.30
```

13C NMR




```
Current Data Parameters
NAME      CAI-V-Recover aldehyde
EXPNO                  2
PROCNO                 1

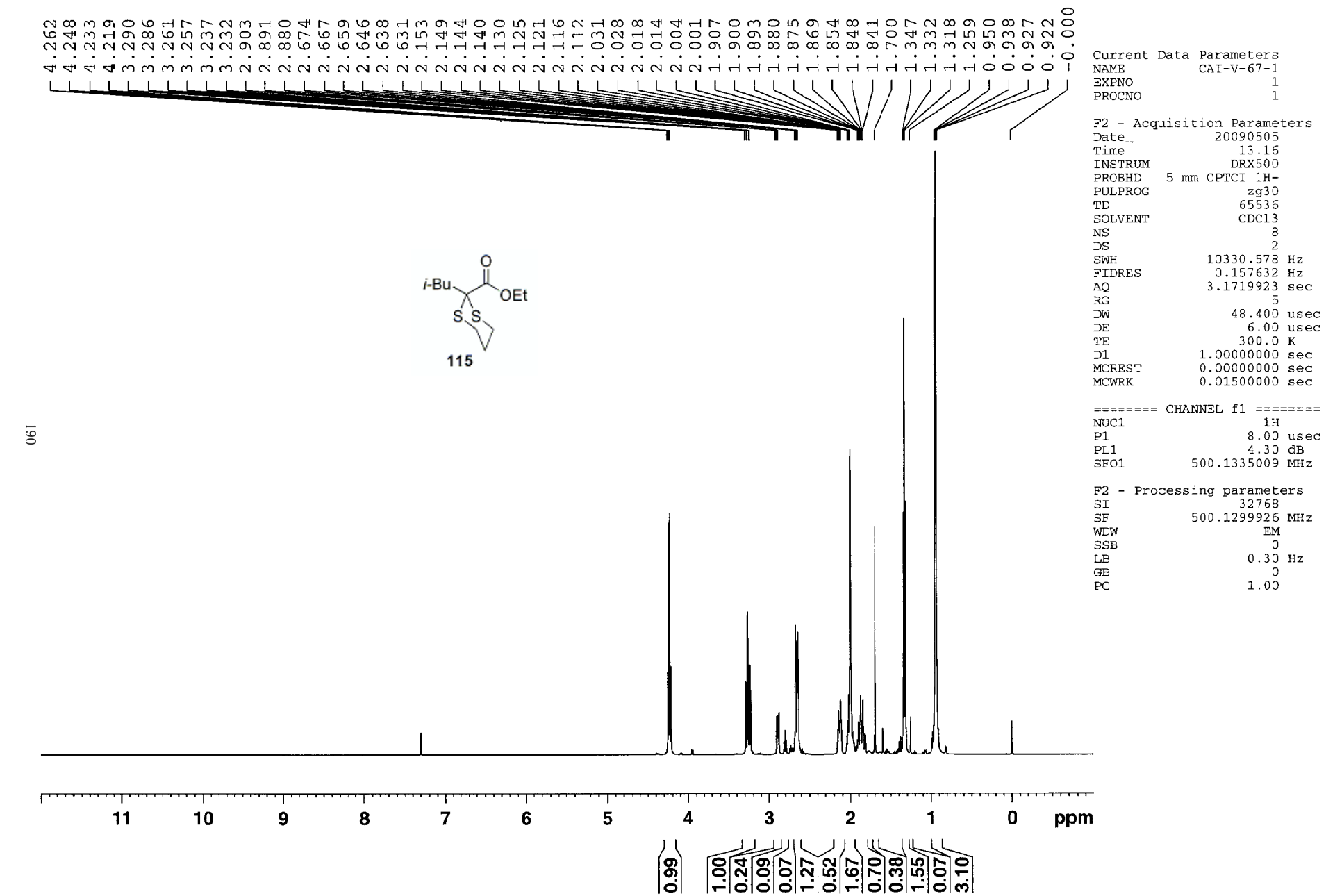
F2 - Acquisition Parameters
Date_           20090506
Time              22.08
INSTRUM          DRX300
PROBHD   5 mm Multinucl
PULPROG       zgdc30pad
TD               65536
SOLVENT           CDCl3
NS                  137
DS                    4
SWH           18832.393 Hz
FIDRES         0.287360 Hz
AQ             1.7400308 sec
RG                22528
DW               26.550 usec
DE                6.00 usec
TE               300.0 K
D1            2.00000000 sec
D11           0.03000000 sec
D31           0.00000000 sec

======== CHANNEL f1 ========
NUC1                13C
P1                10.00 usec
PL1                5.00 dB
SFO1          75.4760107 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                1H
PCPD2             100.00 usec
PL2               120.00 dB
PL12               21.41 dB
SFO2         300.1312005 MHz

F2 - Processing parameters
SI                 32768
SF           75.4677502 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.30
```

CAI-V-67-Colorless oil-1H NMR



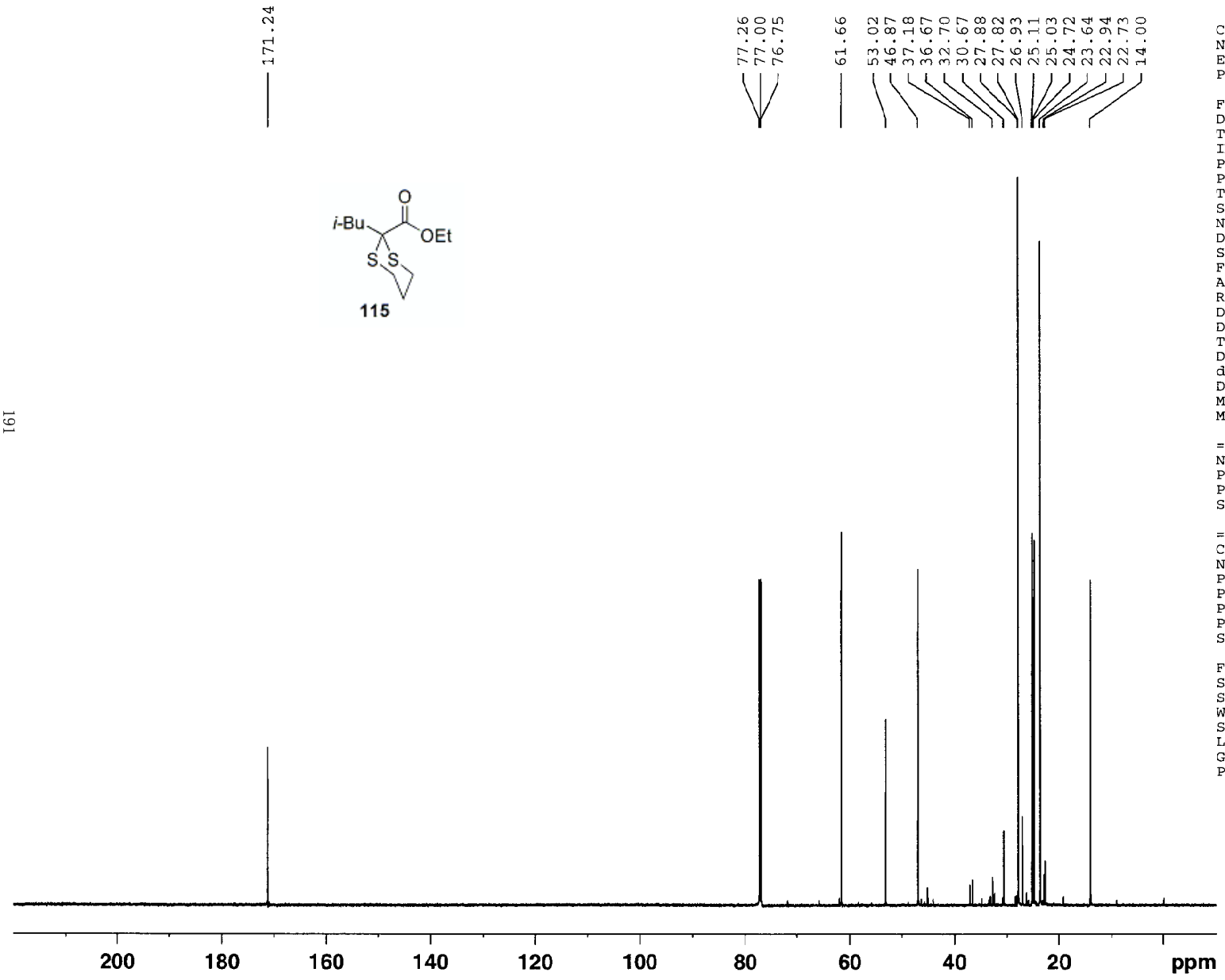
Current Data Parameters
NAME CAI-V-67-1
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20090505
Time 13.16
INSTRUM DRX500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 5
DW 48.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
PL1 4.30 dB
SFO1 500.1335009 MHz

F2 - Processing parameters
SI 32768
SF 500.1299926 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

13C NMR




```
Current Data Parameters
NAME          CAI-V-67-1
EXPNO                  2
PROCNO                 1

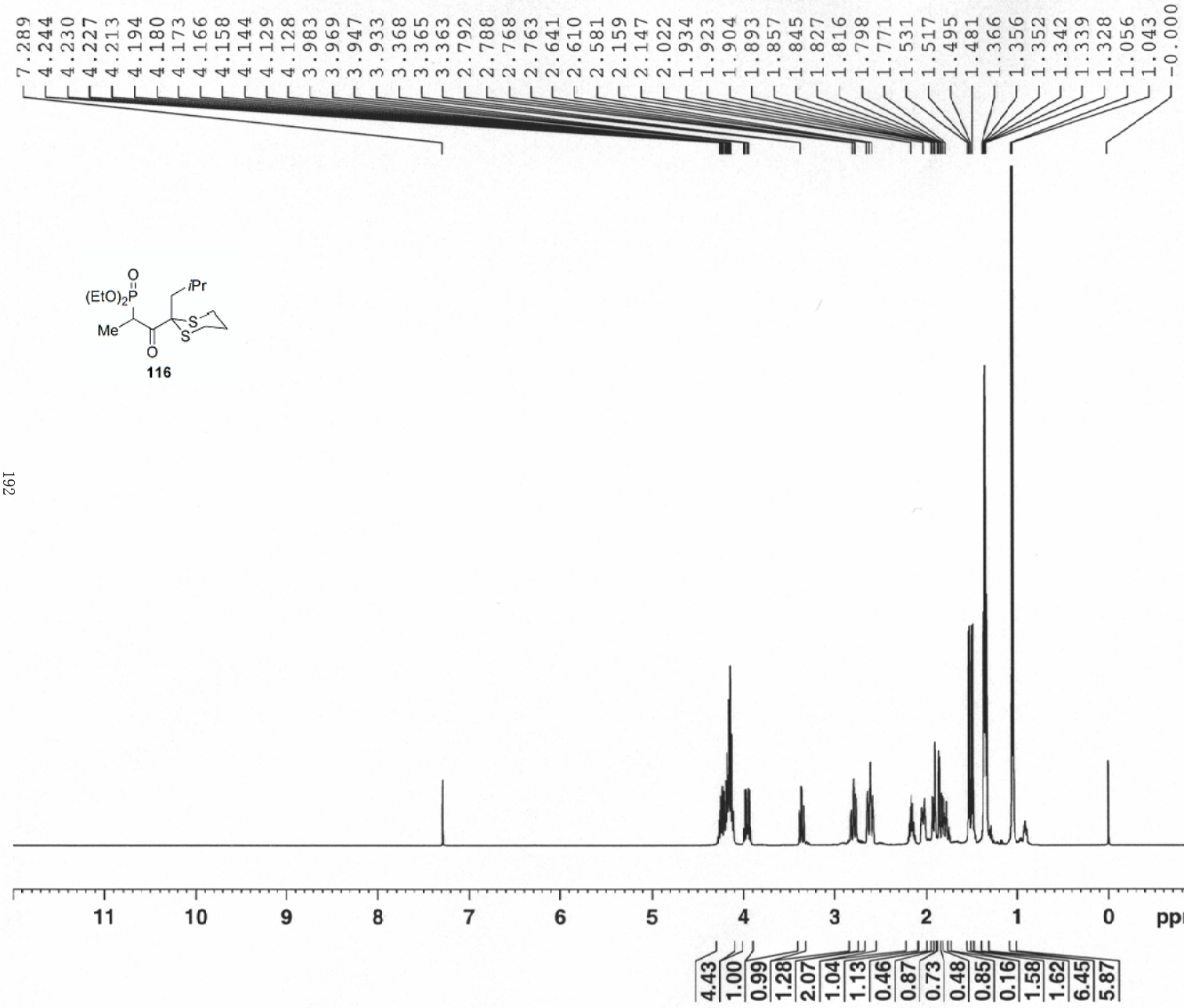
F2 - Acquisition Parameters
Date_           20090505
Time               13.20
INSTRUM           DRX500
PROBHD   5 mm CPTCI 1H-
PULPROG          zgpg30
TD                71424
SOLVENT           CDCl3
NS                   69
DS                    4
SWH           35211.270 Hz
FIDRES         0.492989 Hz
AQ             1.0142708 sec
RG                 4096
DW               14.200 usec
DE               35.00 usec
TE               300.0 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

======== CHANNEL f1 ========
NUC1                 13C
P1                12.00 usec
PL1                0.30 dB
SFO1        125.7716224 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2             80.00 usec
PL2                5.00 dB
PL12              22.00 dB
PL13              27.90 dB
SFO2        500.1320005 MHz

F2 - Processing parameters
SI                65536
SF          125.7578019 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.00
```

CAI-V-68-2-1H NMR



116

Current Data Parameters

NAME	CAI-V-68-2
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20090506
Time	14.48
INSTRUM	DRX500
PROBHD	5 mm CPTCI 1H-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	8
DS	2
SWH	10330.578 Hz
FIDRES	0.157632 Hz
AQ	3.1719923 sec
RG	9
DW	48.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec
MCREST	0.00000000 sec
MCWRK	0.01500000 sec

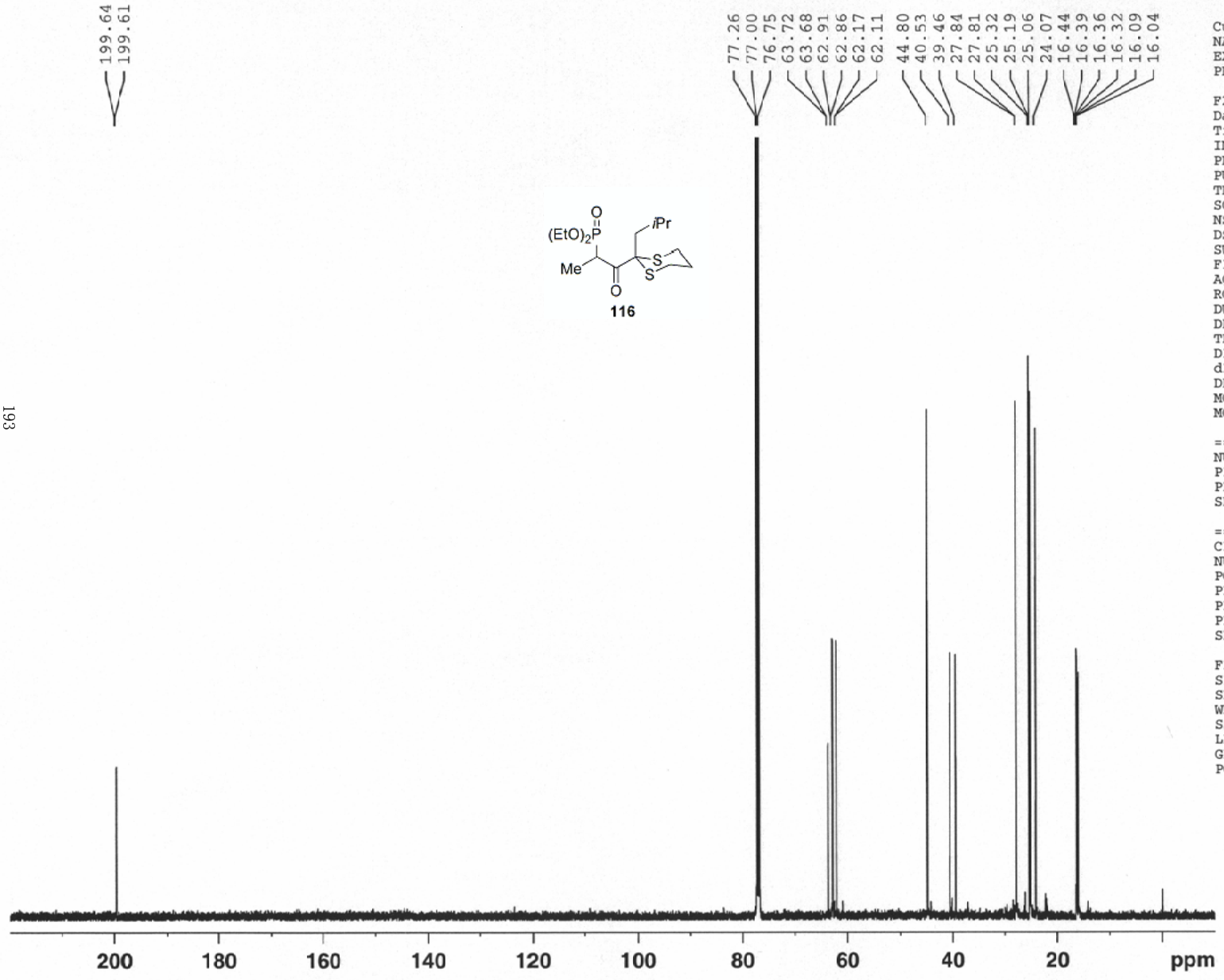
======== CHANNEL f1 ========

NUC1	1H
P1	8.00 usec
PL1	4.30 dB
SFO1	500.1335009 MHz

F2 - Processing parameters

SI	32768
SF	500.1299996 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

13C NMR




```
Current Data Parameters
NAME                  CAI-V-68-2
EXPNO                          2
PROCNO                         1

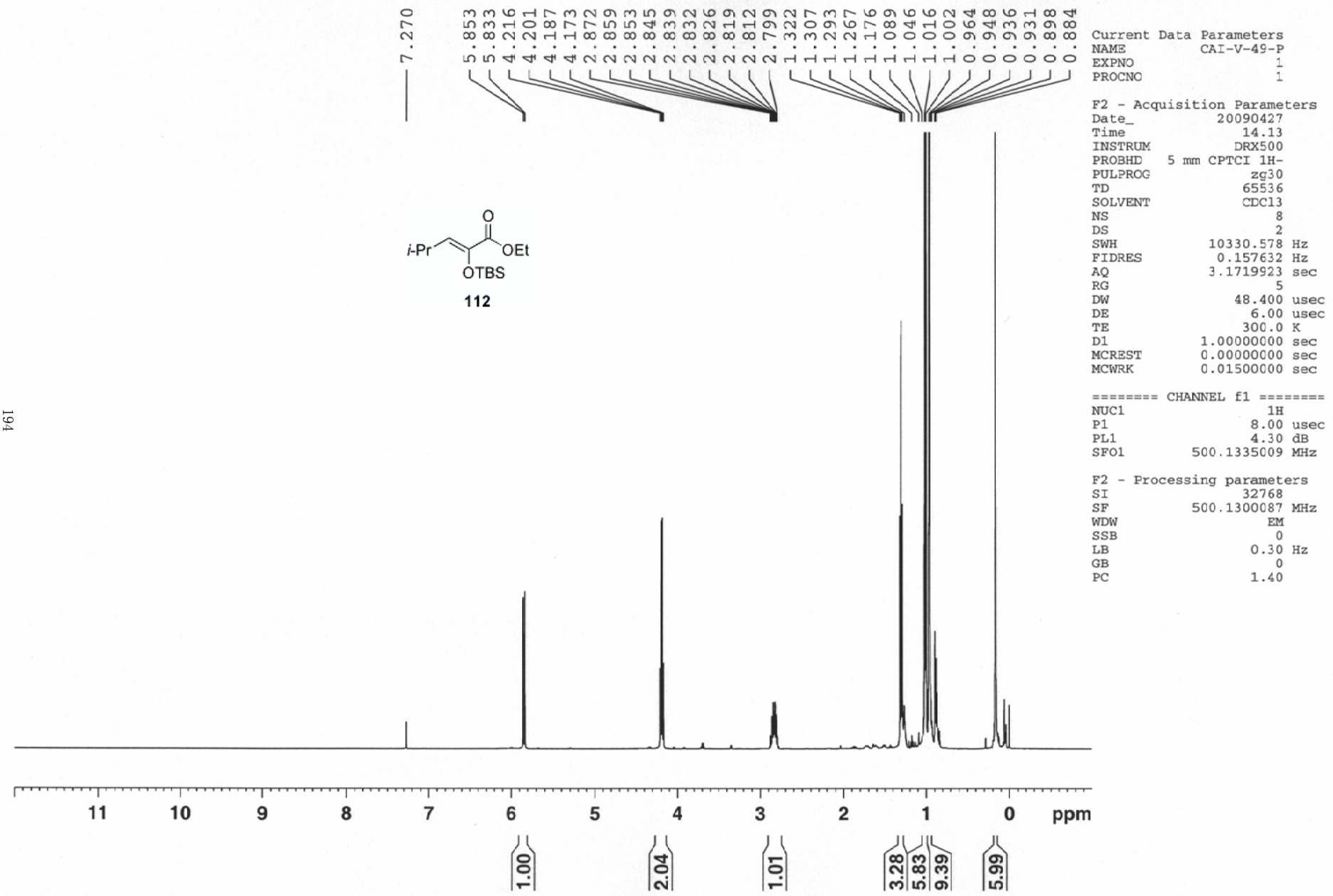
F2 - Acquisition Parameters
Date_                   20090506
Time                       14.52
INSTRUM                  DRX500
PROBHD    5 mm CPTCI 1H-
PULPROG                  zgpg30
TD                        71424
SOLVENT                   CDCl3
NS                          100
DS                            4
SWH                   35211.270 Hz
FIDRES                0.492989 Hz
AQ                    1.0142708 sec
RG                         4096
DW                       14.200 usec
DE                       35.00 usec
TE                       300.0 K
D1                    2.00000000 sec
d11                   0.03000000 sec
DELTA                 1.89999998 sec
MCREST                0.00000000 sec
MCWRK                 0.01500000 sec

======== CHANNEL f1 ========
NUC1                        13C
P1                       12.00 usec
PL1                       0.30 dB
SFO1                125.7716224 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                        1H
PCPD2                    80.00 usec
PL2                       5.00 dB
PL12                     22.00 dB
PL13                     27.90 dB
SFO2                500.1320005 MHz

F2 - Processing parameters
SI                          65536
SF                  125.7577960 MHz
WDW                            EM
SSB                             0
LB                        1.00 Hz
GB                              0
PC                         1.00
```

CAI-V-49-P-Colorless oil-1H NMR



Current Data Parameters

NAME	CAI-V-49-P
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20090427
Time	14.13
INSTRUM	DRX500
PROBHD	5 mm CPTCI 1H-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	8
DS	2
SWH	10330.578 Hz
FIDRES	0.157632 Hz
AQ	3.1719923 sec
RG	5
DW	48.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec
MCREST	0.00000000 sec
MCWRK	0.01500000 sec

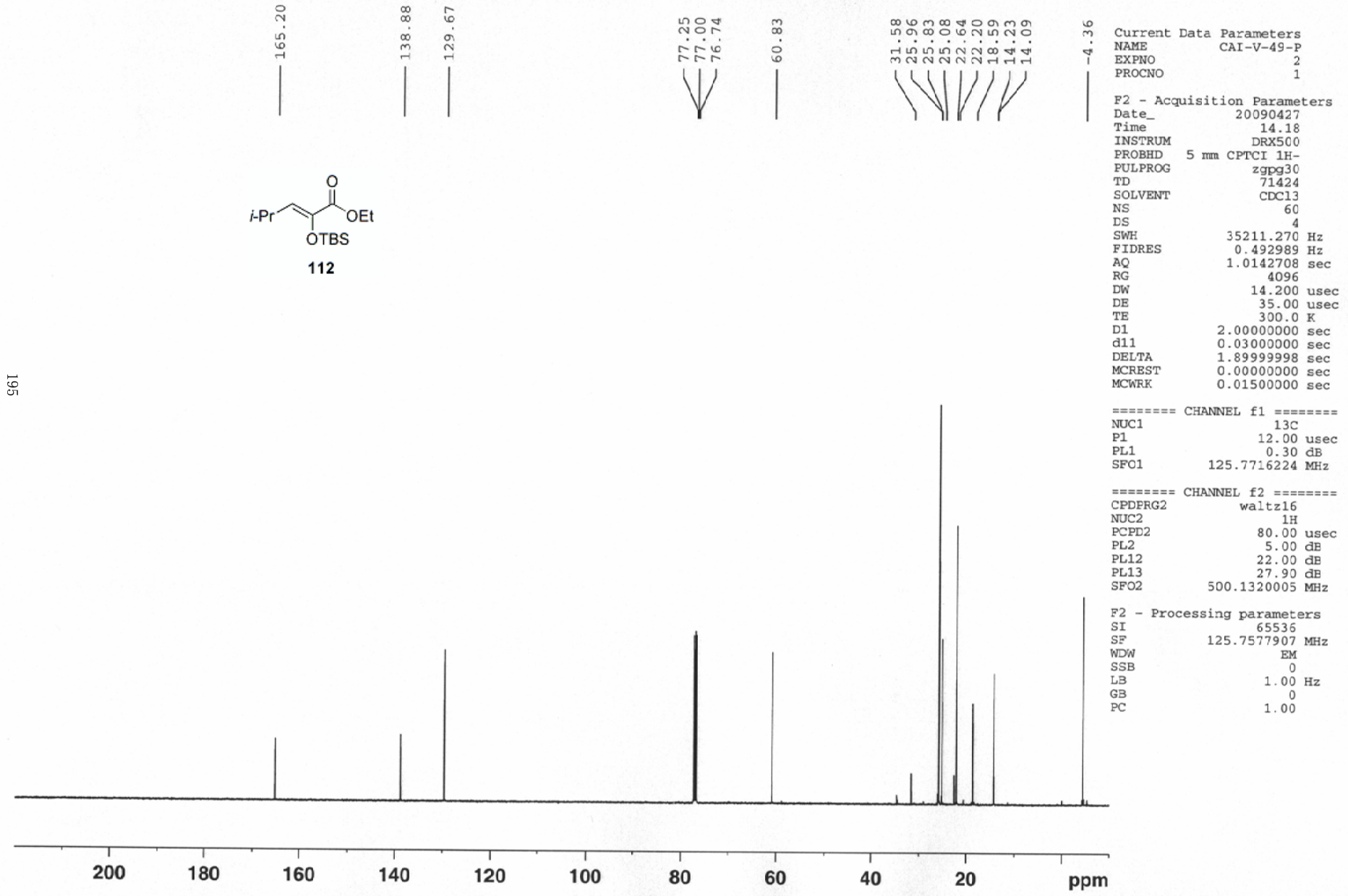
======== CHANNEL f1 ========

NUC1	1H
P1	8.00 usec
PL1	4.30 dB
SFO1	500.1335009 MHz

F2 - Processing parameters

SI	32768
SF	500.1300087 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

13C NMR



Current Data Parameters

NAME	CAI-V-49-P
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20090427
Time	14.18
INSTRUM	DRX500
PROBHD	5 mm CPTCI 1H-
PULPROG	zgpg30
TD	71424
SOLVENT	CDC13
NS	60
DS	4
SWH	35211.270 Hz
FIDRES	0.492989 Hz
AQ	1.0142708 sec
RG	4096
DW	14.200 usec
DE	35.00 usec
TE	300.0 K
D1	2.00000000 sec
d11	0.03000000 sec
DELTA	1.89999998 sec
MCREST	0.00000000 sec
MCWRK	0.01500000 sec

======== CHANNEL f1 ========

NUC1	13C
P1	12.00 usec
PL1	0.30 dB
SFO1	125.7716224 MHz

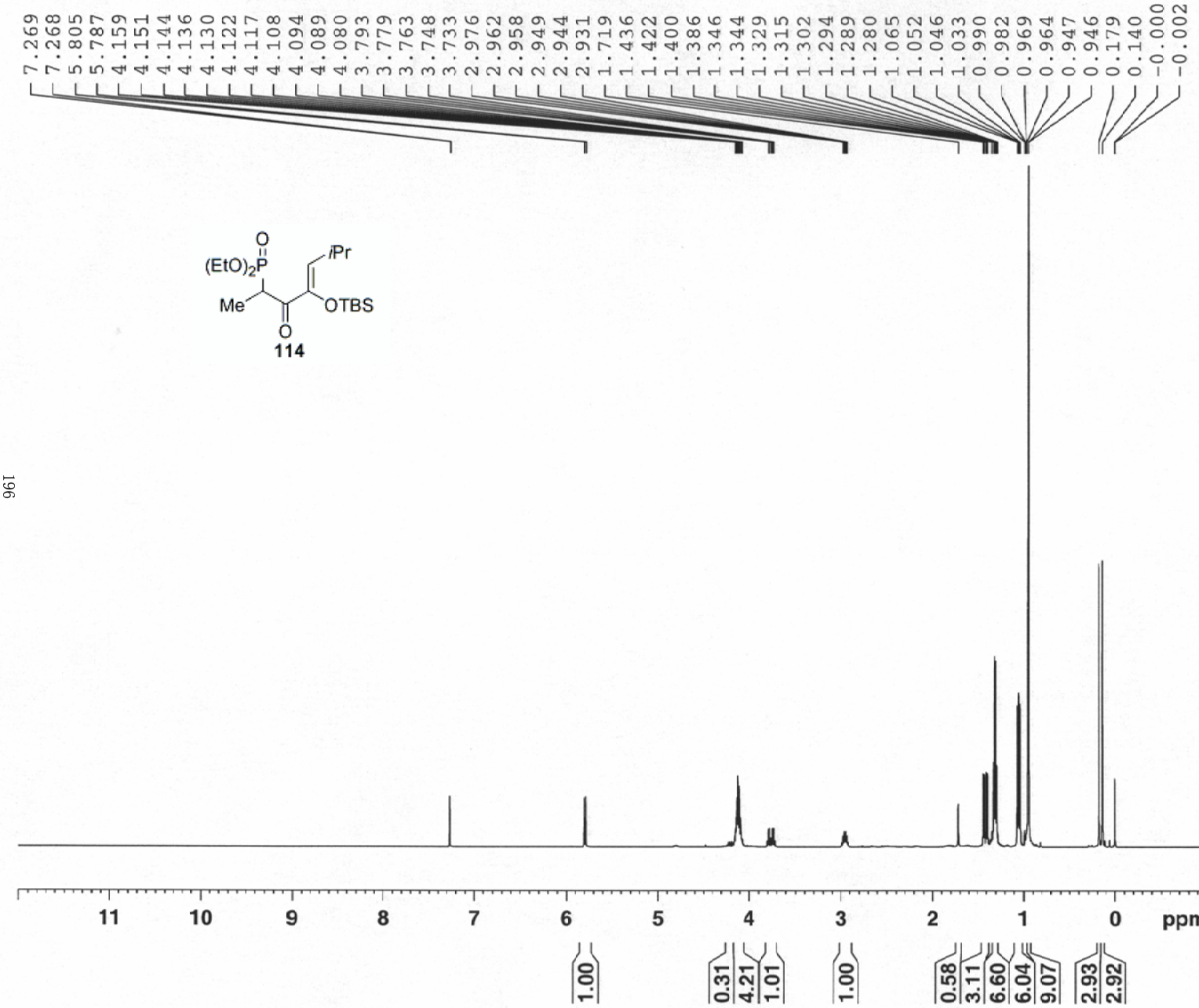
======== CHANNEL f2 ========

CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	5.00 dB
PL12	22.00 dB
PL13	27.90 dB
SFO2	500.1320005 MHz

F2 - Processing parameters

SI	65536
SF	125.7577907 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.00

CAI-V-53-P



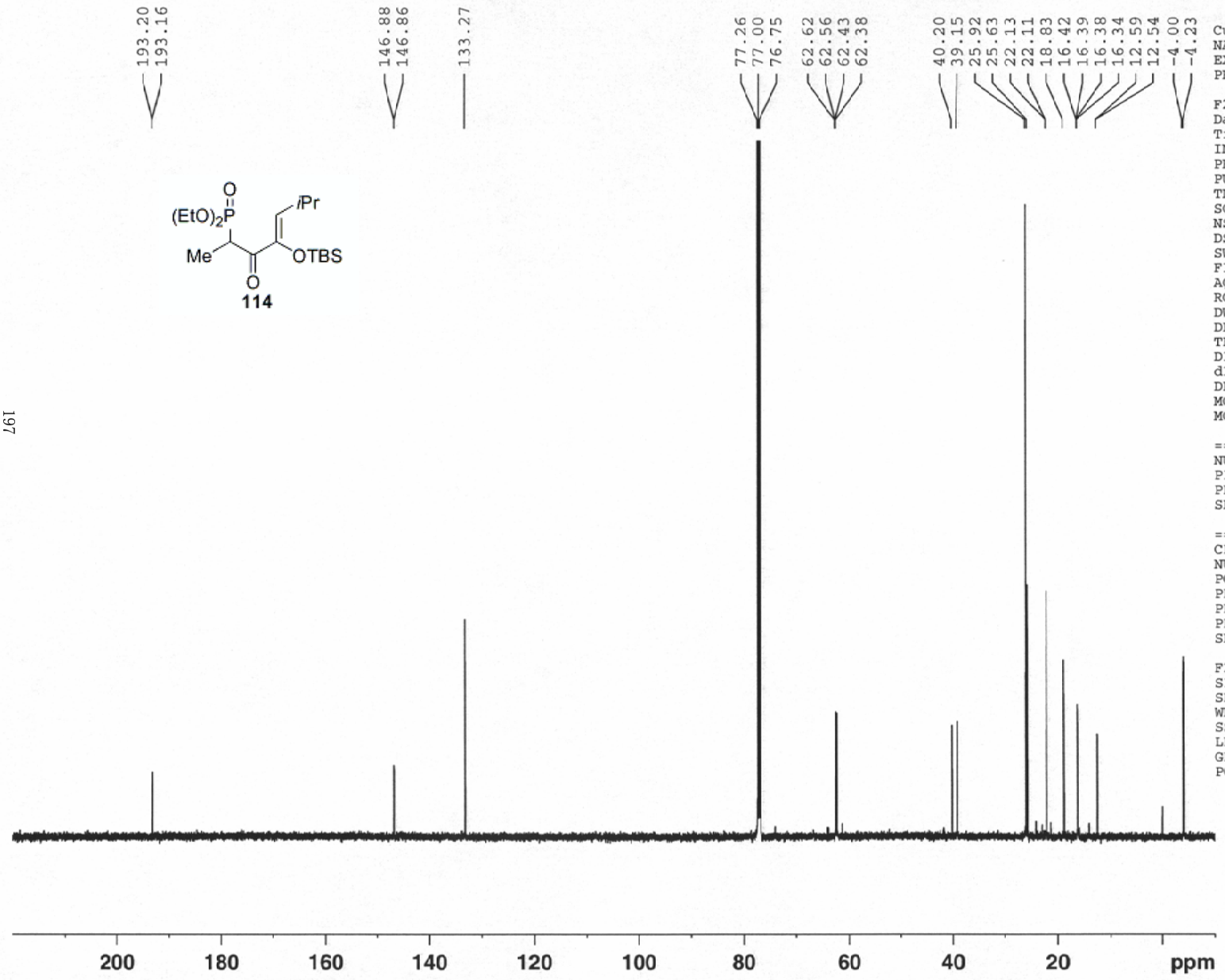
Current Data Parameters
NAME CAI-V-53-P
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20090423
Time 14.14
INSTRUM DRX500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 18
DW 48.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
PL1 4.30 dB
SFO1 500.1335009 MHz

F2 - Processing parameters
SI 32768
SF 500.1300094 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

13C NMR




```
Current Data Parameters
NAME                  CAI-V-53-p
EXPNO                          2
PROCNO                         1

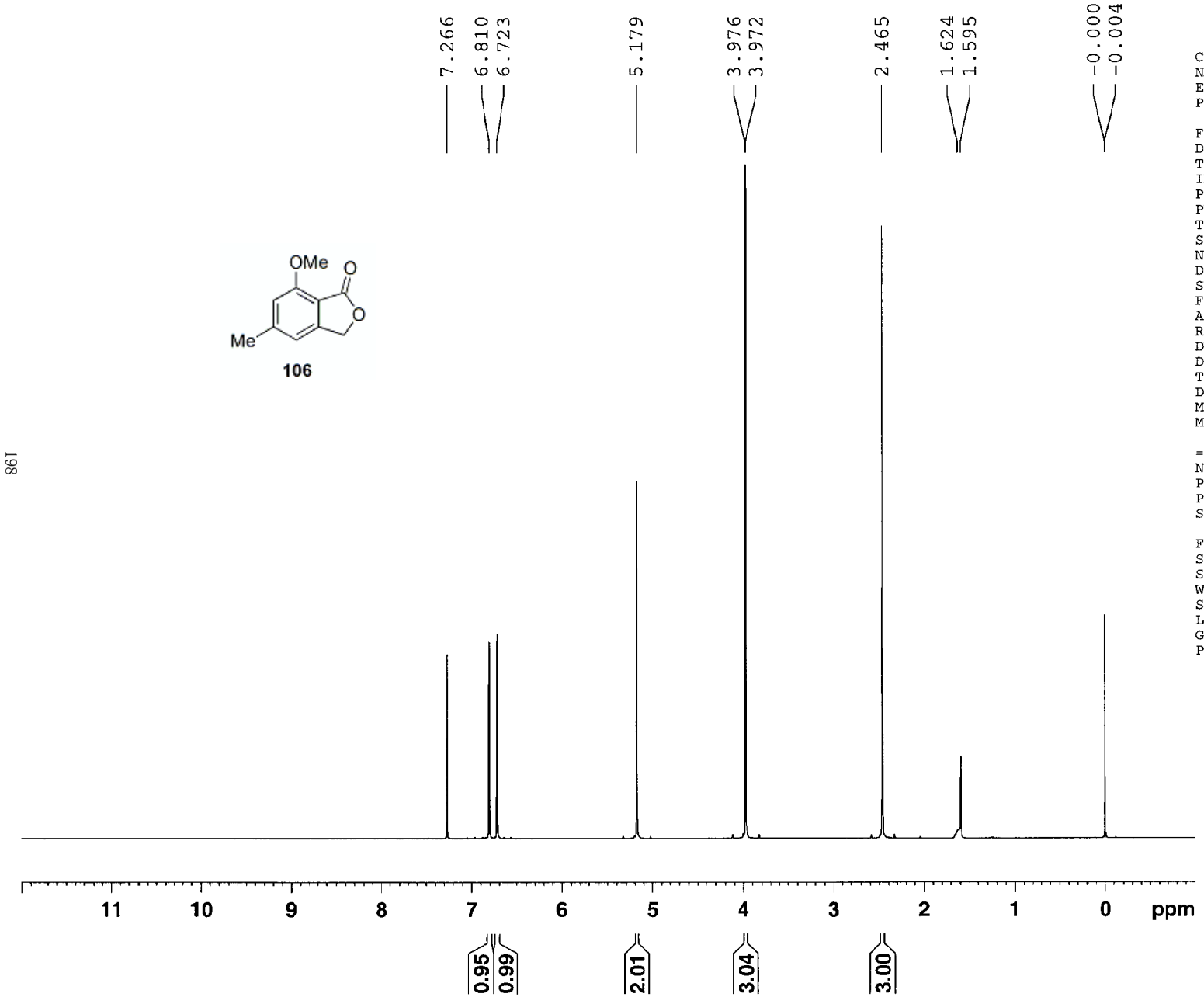
F2 - Acquisition Parameters
Date_                   20090423
Time                       14.22
INSTRUM                   DRX500
PROBHD    5 mm CPTCI 1H-
PULPROG                   zgpg30
TD                         71424
SOLVENT                    CDC13
NS                           161
DS                             4
SWH                  35211.270 Hz
FIDRES                0.492989 Hz
AQ                    1.0142708 sec
RG                          4096
DW                        14.200 usec
DE                        35.00 usec
TE                        300.0 K
D1                    2.00000000 sec
d11                   0.03000000 sec
DELTA                 1.89999998 sec
MCREST                0.00000000 sec
MCWRK                 0.01500000 sec

======== CHANNEL f1 ========
NUC1                         13C
P1                        12.00 usec
PL1                        0.30 dB
SFO1                125.7716224 MHz

======== CHANNEL f2 ========
CPDPRG2                  waltz16
NUC2                         1H
PCPD2                     80.00 usec
PL2                        5.00 dB
PL12                      22.00 dB
PL13                      27.90 dB
SFO2                500.1320005 MHz

F2 - Processing parameters
SI                         65536
SF                  125.7577923 MHz
WDW                           EM
SSB                            0
LB                         1.00 Hz
GB                             0
PC                          1.00
```

CAI-IV-199



198

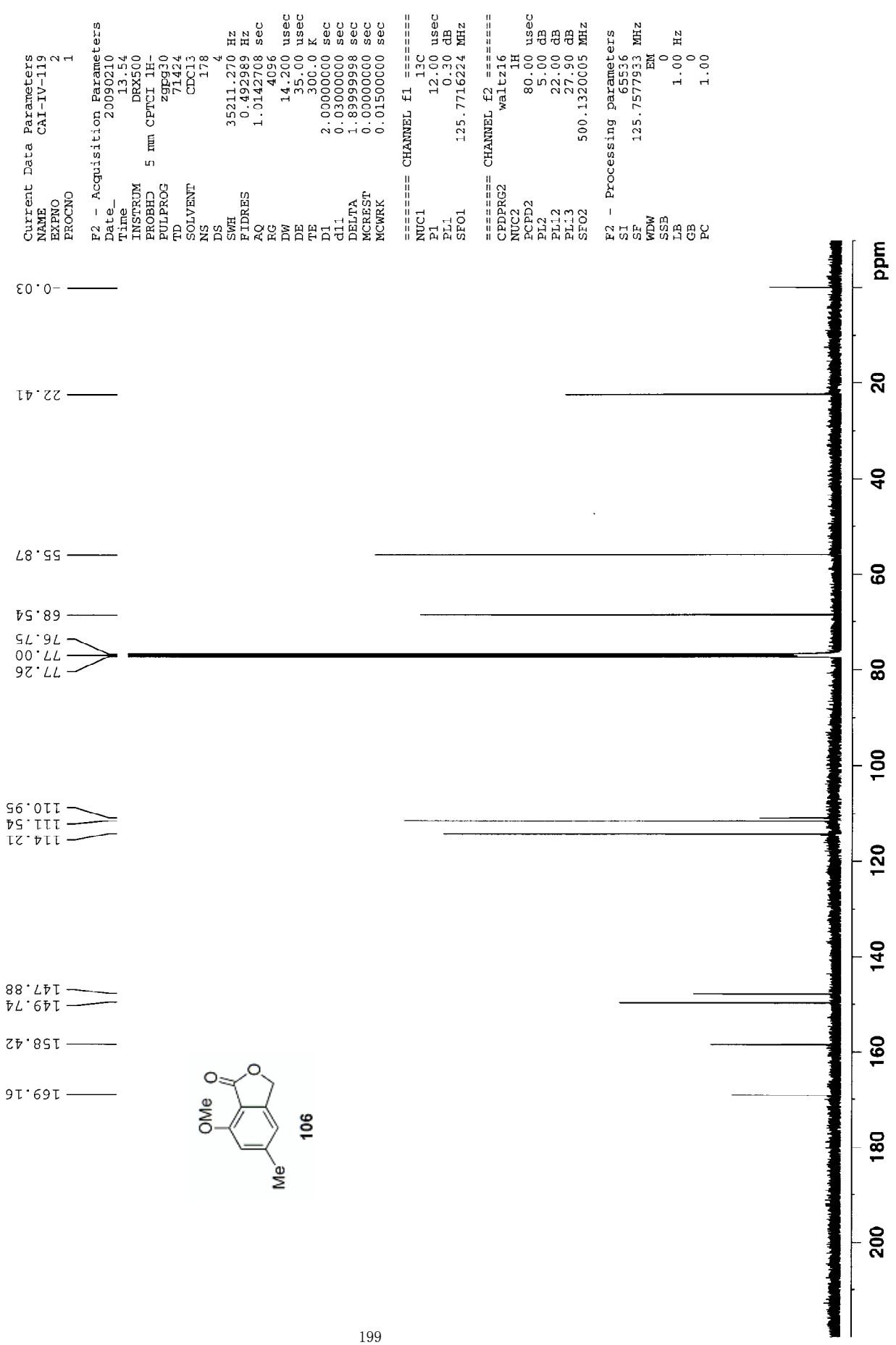
```
Current Data Parameters
NAME                 CAI-IV-119
EXPNO                         1
PROCNO                        1

F2 - Acquisition Parameters
Date_               20090210
Time                     13.46
INSTRUM                DRX500
PROBHD    5 mm CPTCI 1H-
PULPROG                  zg30
TD                      65536
SOLVENT                 CDCl3
NS                          8
DS                          2
SWH                 10330.578 Hz
FIDRES                0.157632 Hz
AQ                    3.1719923 sec
RG                         11.3
DW                       48.400 usec
DE                        6.00 usec
TE                       300.0 K
D1                  1.00000000 sec
MCREST              0.00000000 sec
MCWRK               0.01500000 sec

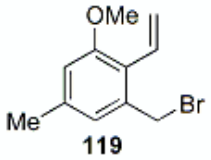
======== CHANNEL f1 ========
NUC1                         1H
P1                        8.00 usec
PL1                       4.30 dB
SFO1                500.1335009 MHz

F2 - Processing parameters
SI                       32768
SF                  500.1300112 MHz
WDW                         EM
SSB                          0
LB                        0.30 Hz
GB                           0
PC                        1.00
```

13C NMR


Current Data Parameters
NAME CAI-IV-119
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20090210
Time_ 13.54
INSTRUM DRX500
PROBHD 5 mm CPTCI 1H-
PULPROG zgpg30
TD 71424
SOLVENT CDCl3
NS 178
DS 4
SWH 35211.270 Hz
FIDRES 0.492989 Hz
AQ 1.0142708 sec
RG 4096
DW 14.200 usec
DE 35.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 12.00 usec
PL1 0.30 dB
SFO1 125.7716224 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 5.00 dB
PL12 22.00 dB
PL13 27.90 dB
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 65536
SF 125.7577933 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
-0.03
22.41
55.87
68.54
76.75
77.00
77.26
110.95
111.54
114.21
147.88
149.74
158.42
169.16
OMe
Me
106
ppm
200
180
160
140
120
100
80
60
40
20

CAI-IV-137-bromide-white solid-1H NMR



119

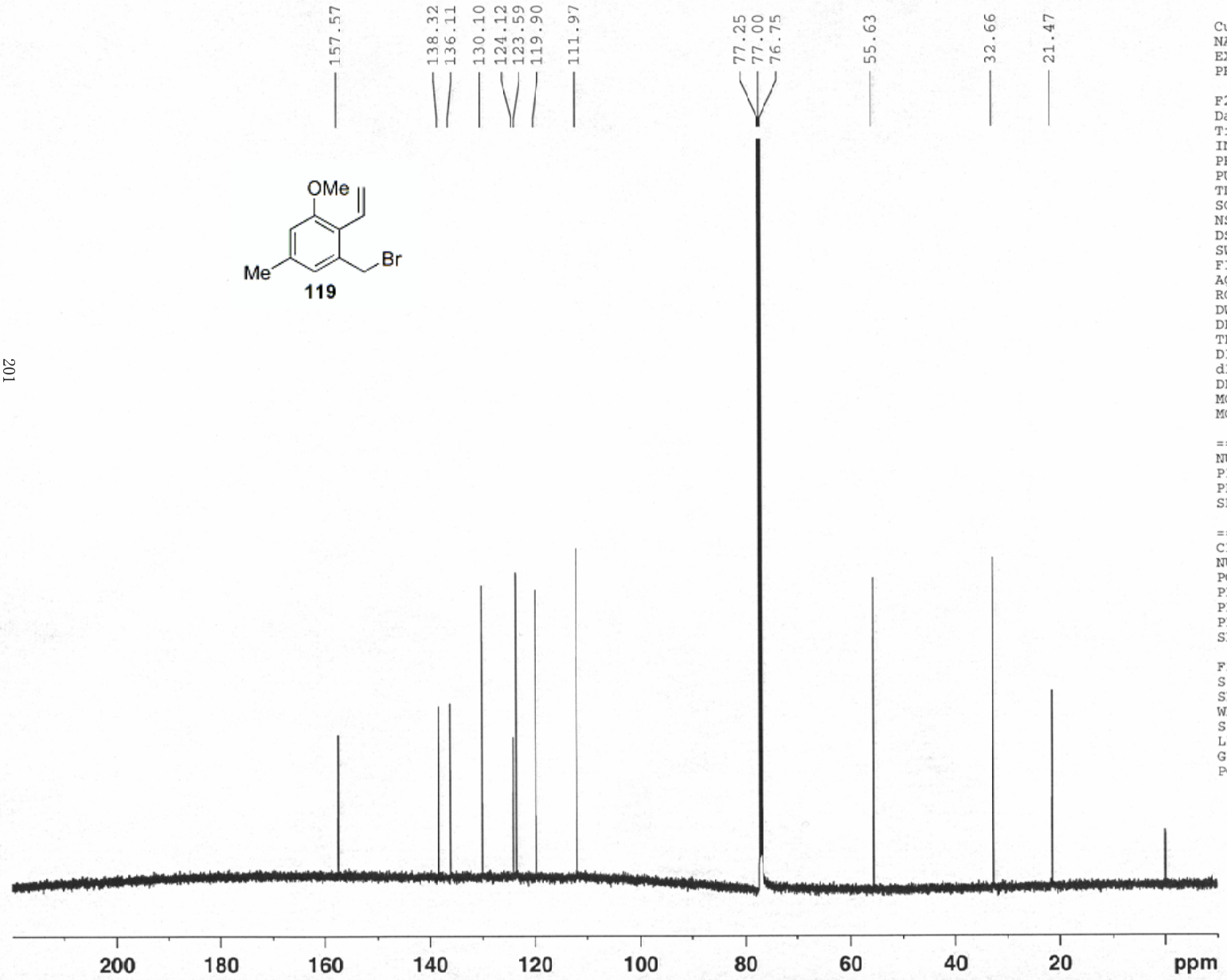

```
Current Data Parameters
NAME        CAI-IV-137-C
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20090221
Time               10.47
INSTRUM          DRX500
PROBHD   5 mm CPTCI 1H-
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                    8
DS                    2
SWH           10330.578 Hz
FIDRES         0.157632 Hz
AQ             3.1719923 sec
RG                 12.7
DW               48.400 usec
DE                6.00 usec
TE               300.0 K
D1            1.00000000 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 8.00 usec
PL1                4.30 dB
SFO1         500.1335009 MHz

F2 - Processing parameters
SI                32768
SF          500.1300166 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```

13C NMR




```
Current Data Parameters
NAME          CAI-IV-137-C
EXPNO                    2
PROCNO                   1

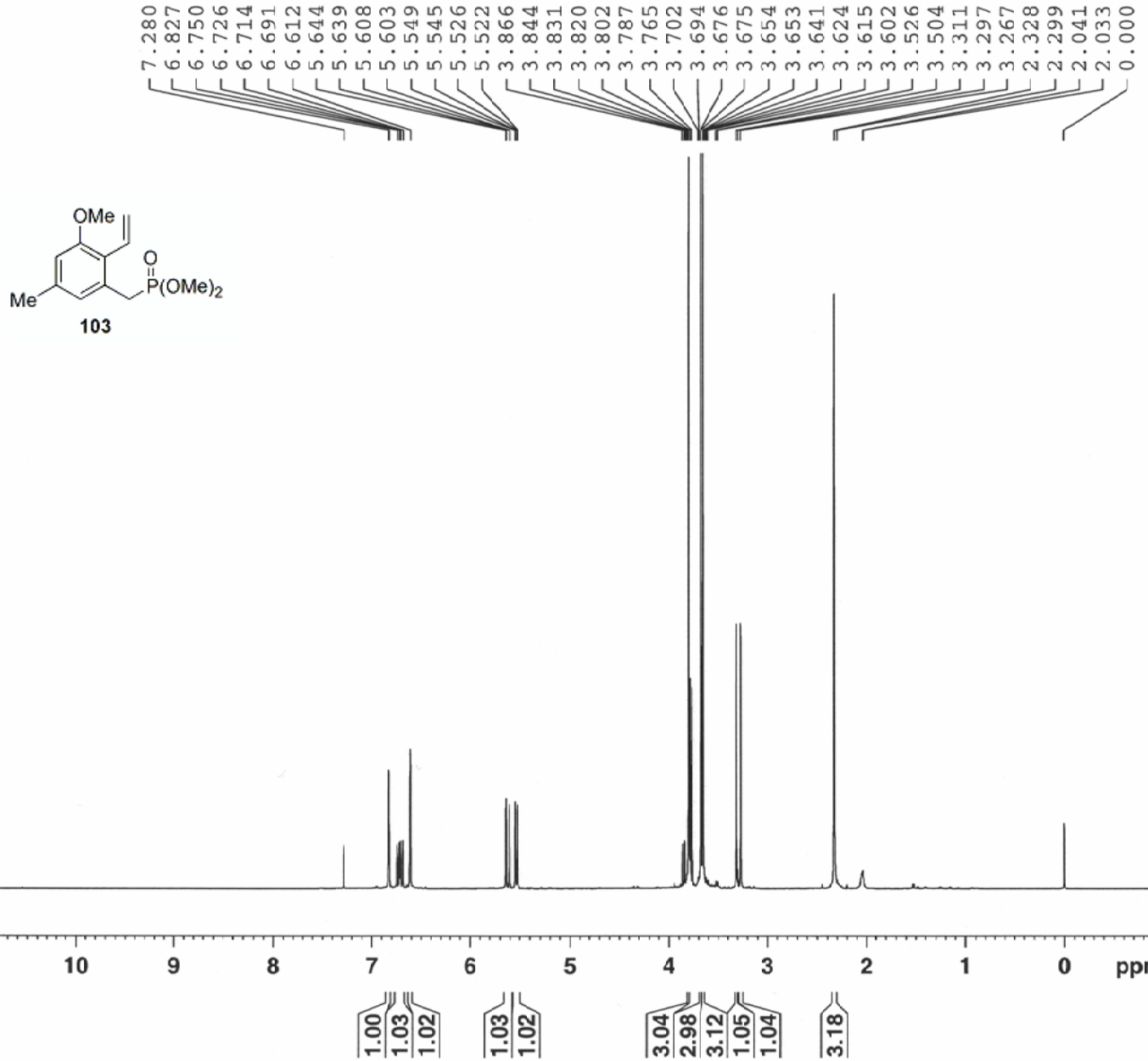
F2 - Acquisition Parameters
Date_             20090221
Time                 10.53
INSTRUM             DRX500
PROBHD   5 mm CPTCI 1H-
PULPROG             zgpg30
TD                   71424
SOLVENT              CDCl3
NS                     154
DS                       4
SWH              35211.270 Hz
FIDRES           0.492989 Hz
AQ               1.0142708 sec
RG                    4096
DW                14.200 usec
DE                35.00 usec
TE                300.0 K
D1             2.00000000 sec
d11            0.03000000 sec
DELTA          1.89999998 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec

======== CHANNEL f1 ========
NUC1                   13C
P1                 12.00 usec
PL1                 0.30 dB
SFO1         125.7716224 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                   1H
PCPD2              80.00 usec
PL2                 5.00 dB
PL12               22.00 dB
PL13               27.90 dB
SFO2         500.1320005 MHz

F2 - Processing parameters
SI                    65536
SF           125.7577933 MHz
WDW                      EM
SSB                       0
LB                 1.00 Hz
GB                        0
PC                     1.40
```

Phosphonate-colorless oil-1H NMR



103

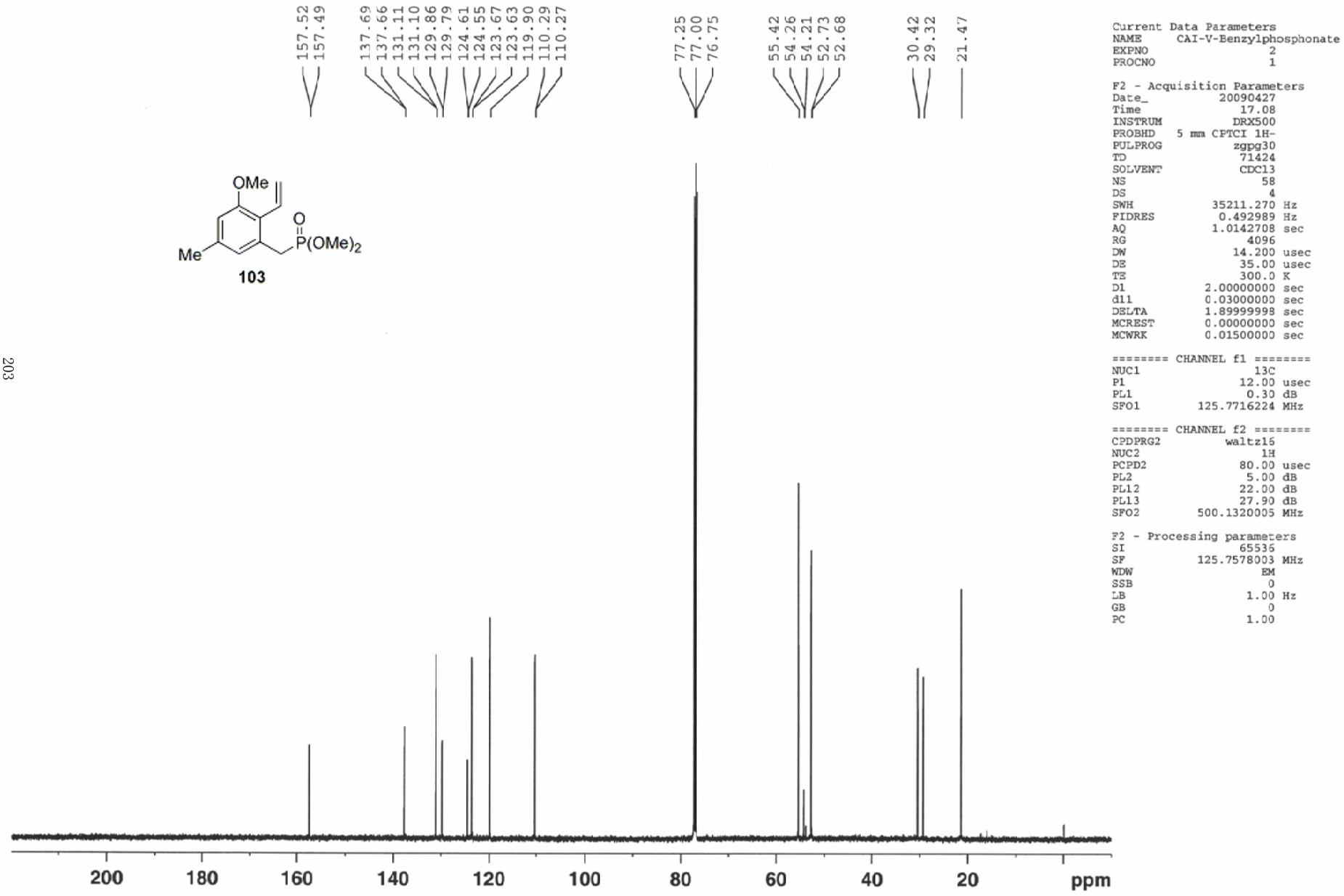
```
Current Data Parameters
NAME      CAI-V-Benzylphosphonate
EXPNO                           1
PROCNO                          1

F2 - Acquisition Parameters
Date_                    20090427
Time                        17.05
INSTRUM                   DRX500
PROBHD    5 mm CPTCI 1H-
PULPROG                     zg30
TD                         65536
SOLVENT                    CDCl3
NS                             8
DS                             2
SWH                    10330.578 Hz
FIDRES                  0.157632 Hz
AQ                      3.1719923 sec
RG                             8
DW                         48.400 usec
DE                          6.00 usec
TE                         300.0 K
D1                    1.00000000 sec
MCREST                0.00000000 sec
MCWRK                 0.01500000 sec

======== CHANNEL f1 ========
NUC1                           1H
P1                          8.00 usec
PL1                         4.30 dB
SFO1                500.1335009 MHz

F2 - Processing parameters
SI                         32768
SF                  500.1300037 MHz
WDW                           EM
SSB                            0
LB                          0.30 Hz
GB                             0
PC                          1.40
```

13C NMR




```
Current Data Parameters
NAME      CAI-V-Benzylphosphonate
EXPNO                           2
PROCNO                          1

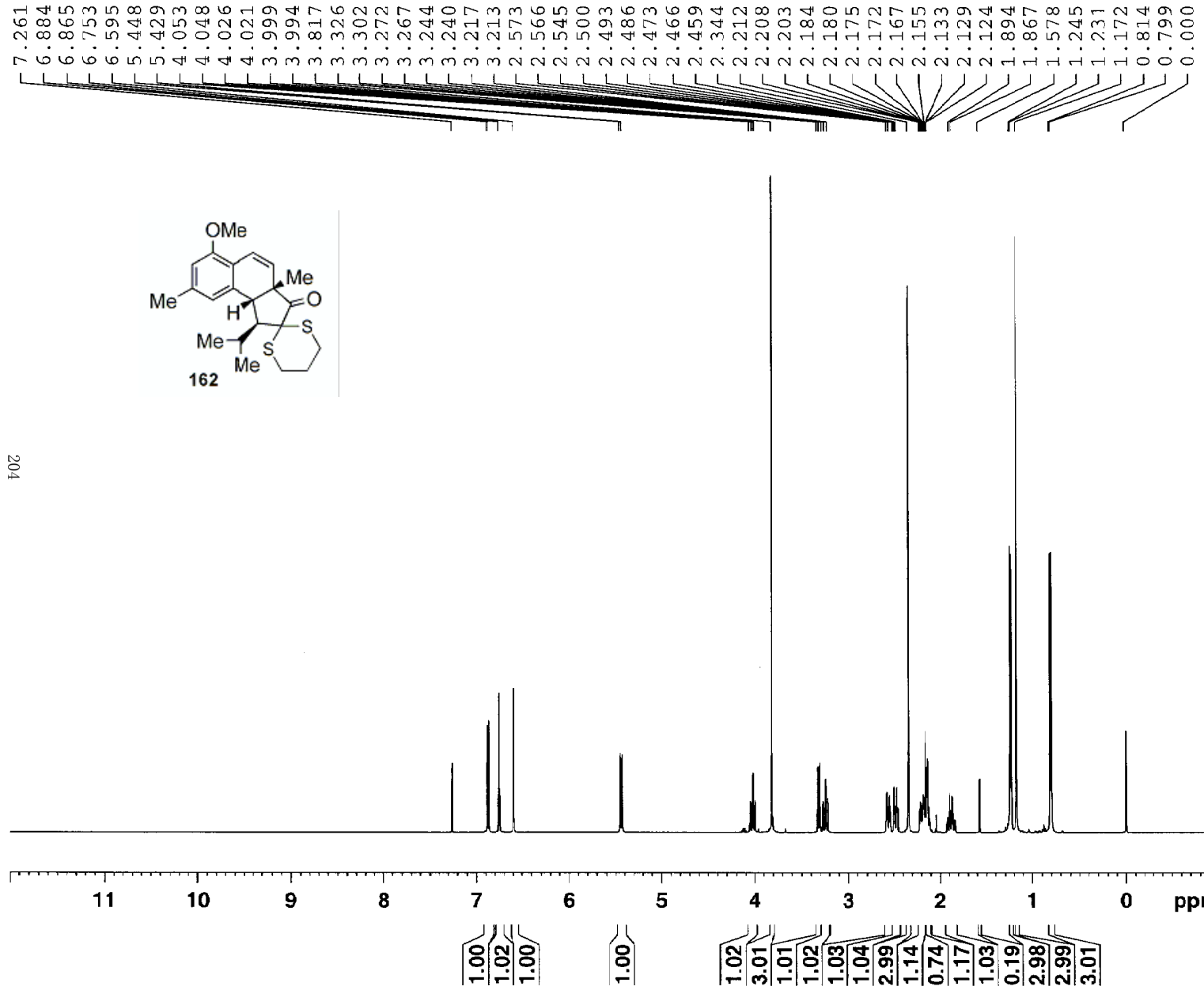
F2 - Acquisition Parameters
Date_                    20090427
Time                        17.08
INSTRUM                    DRX500
PROBHD   5 mm CPTCI 1H-
PULPROG                   zgpg30
TD                         71424
SOLVENT                    CDC13
NS                            58
DS                             4
SWH                    35211.270 Hz
FIDRES                  0.492989 Hz
AQ                     1.0142708 sec
RG                          4096
DW                        14.200 usec
DE                        35.00 usec
TE                        300.0 K
D1                    2.00000000 sec
d11                   0.03000000 sec
DELTA                 1.89999998 sec
MCREST                0.00000000 sec
MCWRK                 0.01500000 sec

======== CHANNEL f1 ========
NUC1                         13C
P1                        12.00 usec
PL1                        0.30 dB
SFO1                125.7716224 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                         1H
PCPD2                     80.00 usec
PL2                        5.00 dB
PL12                      22.00 dB
PL13                      27.90 dB
SFO2                500.1320005 MHz

F2 - Processing parameters
SI                          65536
SF                  125.7578003 MHz
WDW                            EM
SSB                             0
LB                         1.00 Hz
GB                              0
PC                         1.00
```

CAI-VII-148-1-Colorless crystal-1H NMR



Current Data Parameters

NAME	CAI-VII-148-1-a
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20100505
Time	16.44
INSTRUM	DRX500
PROBHD	5 mm CPTCI 1H-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	8
DS	2
SWH	10330.578 Hz
FIDRES	0.157632 Hz
AQ	3.1719923 sec
RG	10.1
DW	48.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec
MCREST	0.00000000 sec
MCWRK	0.01500000 sec

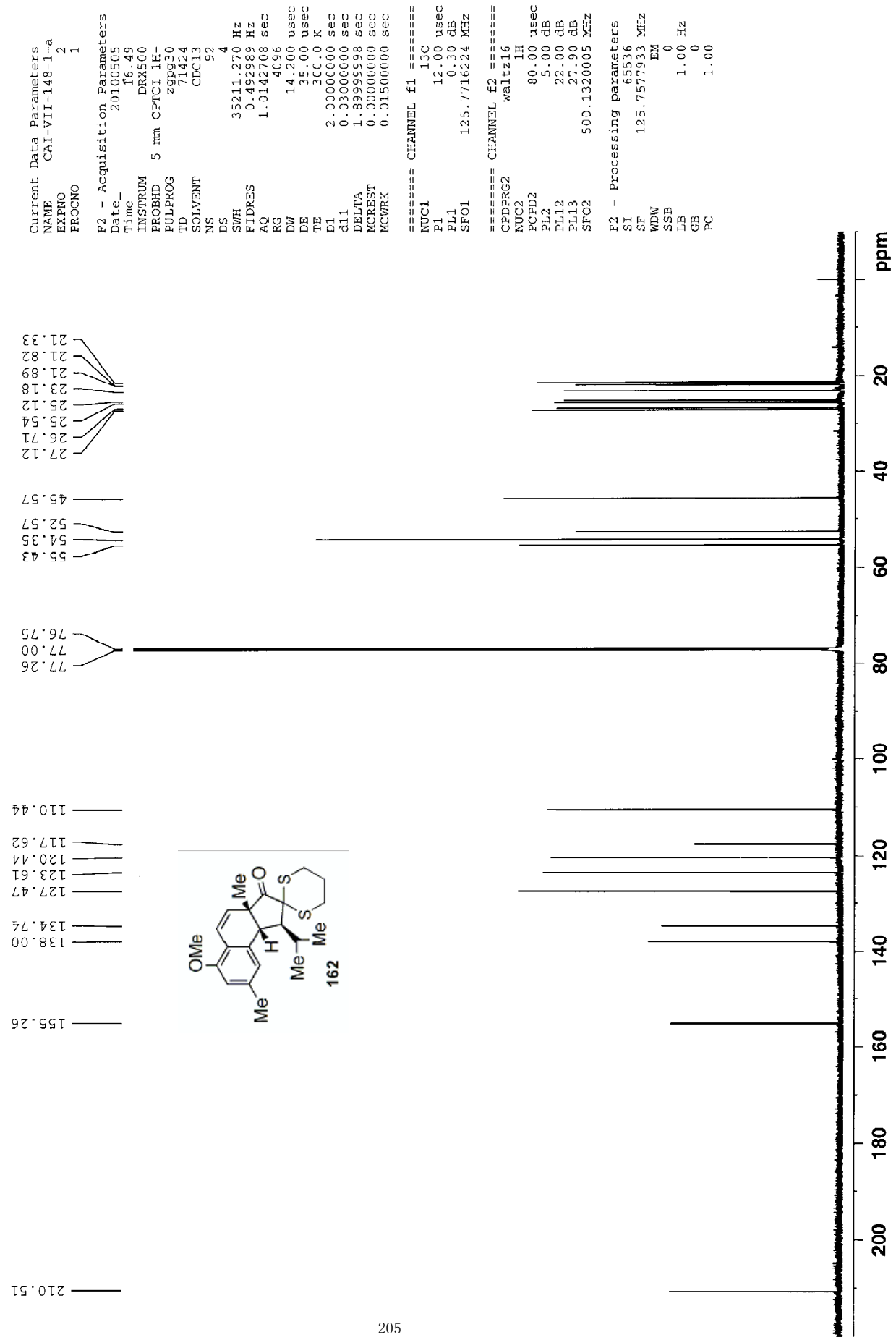
======== CHANNEL f1 ========

NUC1	1H
P1	8.00 usec
PL1	4.30 dB
SFO1	500.1335009 MHz

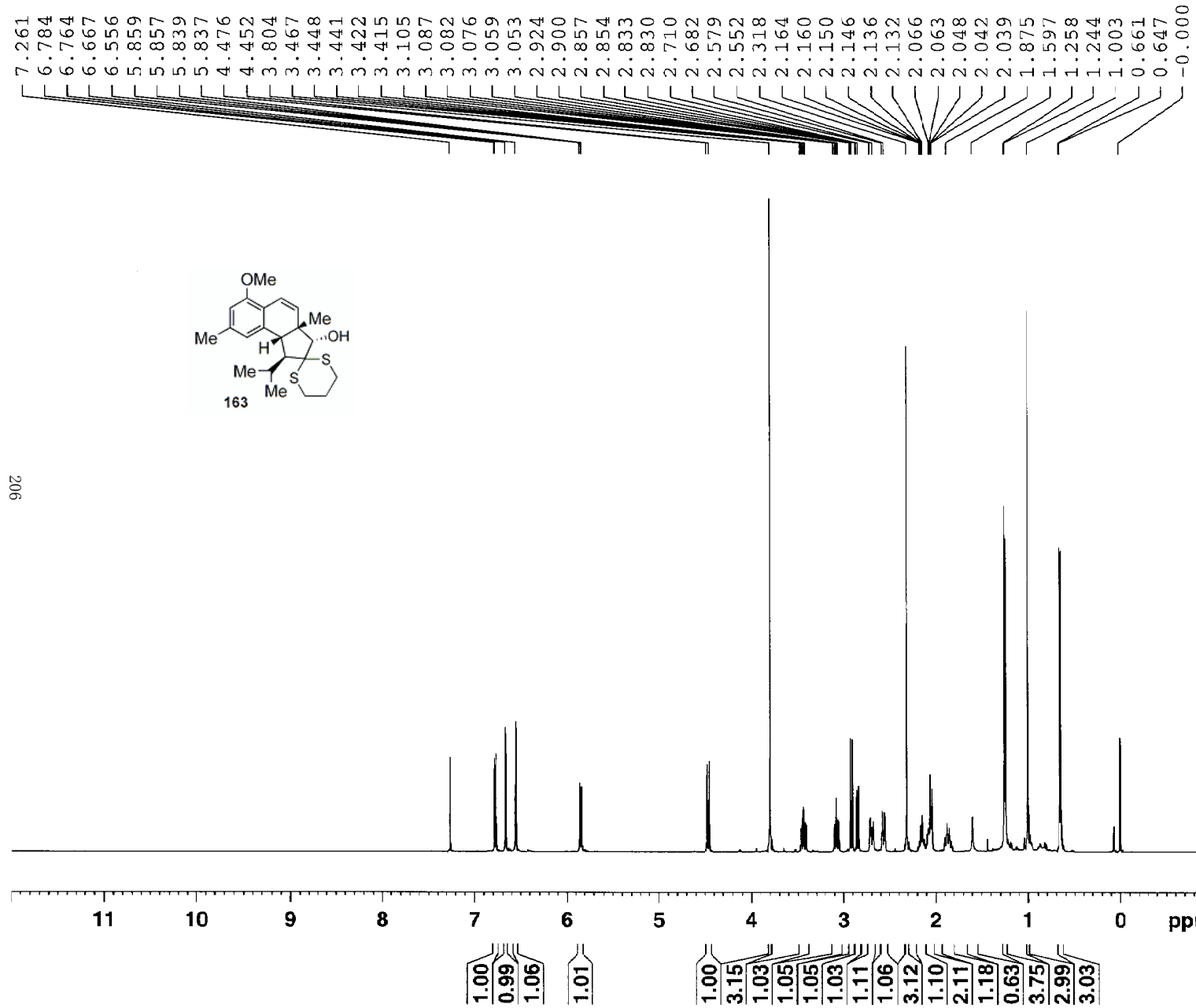
F2 - Processing parameters

SI	32768
SF	500.1300128 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

13C NMR


Current Data Parameters
NAME CAI-VII-148-1-a
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20100505
Time_ 16.49
INSTRUM DRX500
PROBHD 5 mm C/TCI 1H-
PULPROG zgpg30
TD 71424
SOLVENT CDCl3
NS 92
DS 4
SWH 35211.270 Hz
FIDRES 0.492989 Hz
AQ 1.0142708 sec
RG 4096
DW 14.200 usec
DE 35.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 12.00 usec
PL1 0.30 dB
SFO1 125.7716224 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 5.00 dB
PL12 22.00 dB
PL13 27.90 dB
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 65536
SF 125.7577933 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
210.51
155.26
138.00
134.74
127.47
123.61
120.44
117.62
110.44
77.26
77.00
76.75
55.43
54.35
52.57
45.57
27.12
26.71
25.54
25.12
23.18
21.89
21.82
21.33
ppm
OMe
Me
O
S
S
H
Me
Me
Me
162

CAI-VIII-27-White solid-1H NMR



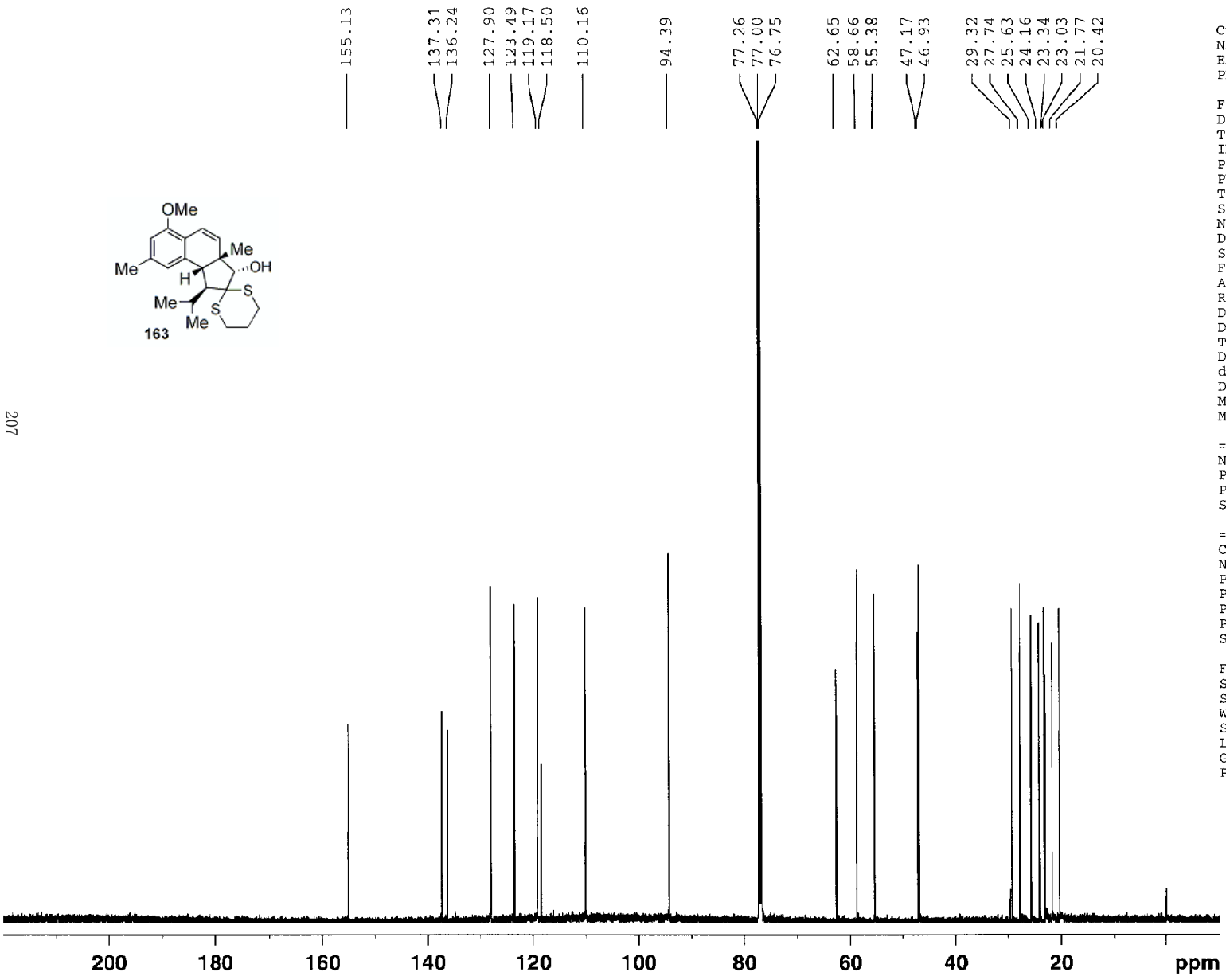

```
Current Data Parameters
NAME       CAI-VIII-27-a
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20100518
Time               11.23
INSTRUM           DRX500
PROBHD   5 mm CPTCI 1H-
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                    8
DS                    2
SWH           10330.578 Hz
FIDRES        0.157632 Hz
AQ            3.1719923 sec
RG                 10.1
DW               48.400 usec
DE                6.00 usec
TE               300.0 K
D1           1.00000000 sec
MCREST       0.00000000 sec
MCWRK        0.01500000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 8.00 usec
PL1                4.30 dB
SFO1        500.1335009 MHz

F2 - Processing parameters
SI                 32768
SF          500.1300128 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.40
```

13C NMR




```
Current Data Parameters
NAME       CAI-VIII-27-a
EXPNO                  2
PROCNO                 1

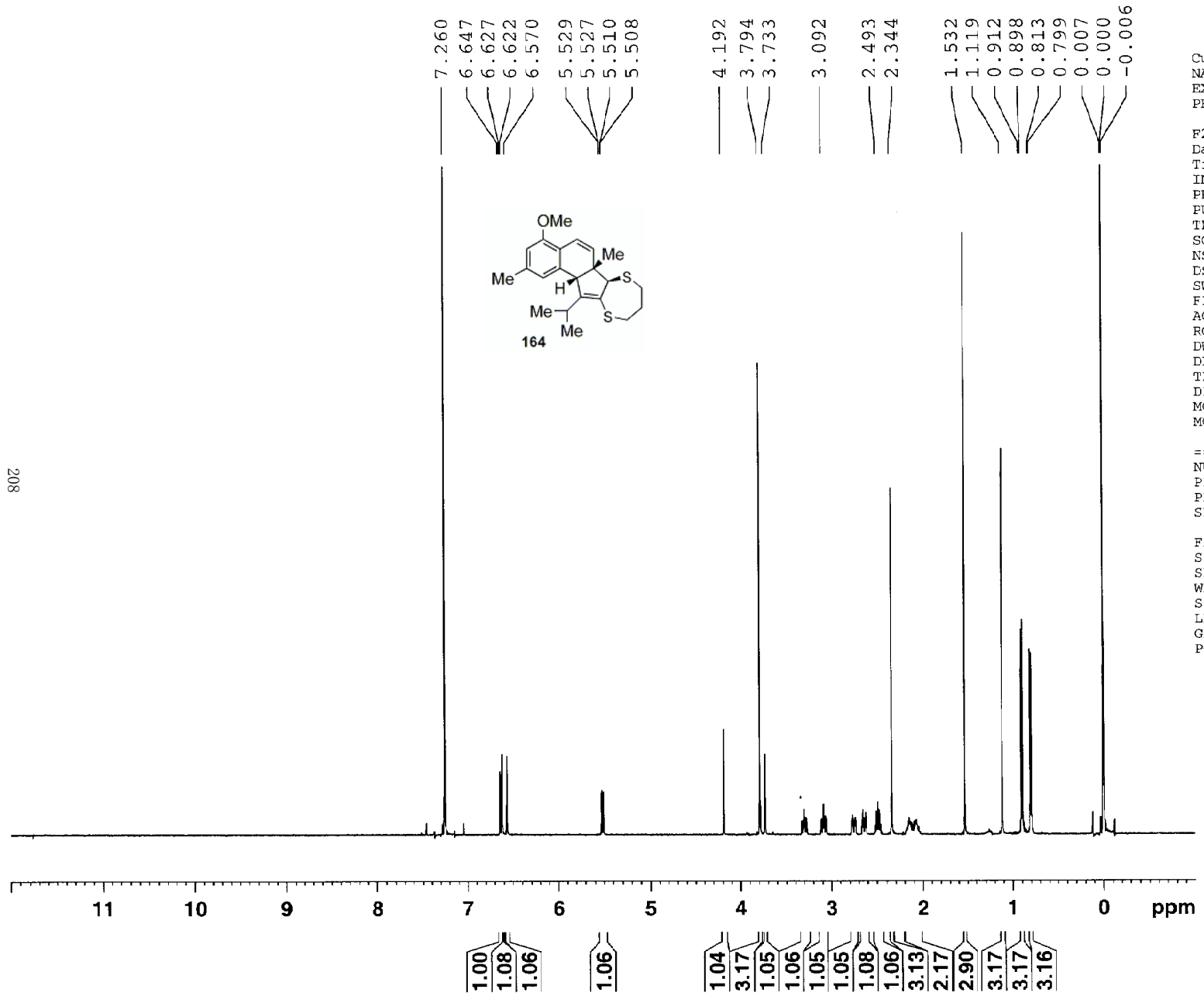
F2 - Acquisition Parameters
Date_           20100518
Time                11.19
INSTRUM            DRX500
PROBHD   5 mm CPTCI 1H-
PULPROG           zgpg30
TD                 71424
SOLVENT            CDCl3
NS                   117
DS                     4
SWH            35211.270 Hz
FIDRES             0.492989 Hz
AQ                 1.0142708 sec
RG                  4096
DW                 14.200 usec
DE                 35.00 usec
TE                 300.0 K
D1                 2.00000000 sec
d11                0.03000000 sec
DELTA              1.89999998 sec
MCREST             0.00000000 sec
MCWRK              0.01500000 sec

======== CHANNEL f1 ========
NUC1                   13C
P1                 12.00 usec
PL1                 0.30 dB
SFO1          125.7716224 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                   1H
PCPD2              80.00 usec
PL2                 5.00 dB
PL12               22.00 dB
PL13               27.90 dB
SFO2          500.1320005 MHz

F2 - Processing parameters
SI                 65536
SF            125.7577939 MHz
WDW                   EM
SSB                    0
LB                 1.00 Hz
GB                     0
PC                 1.00
```

CAI-VIII-30-1-white needles



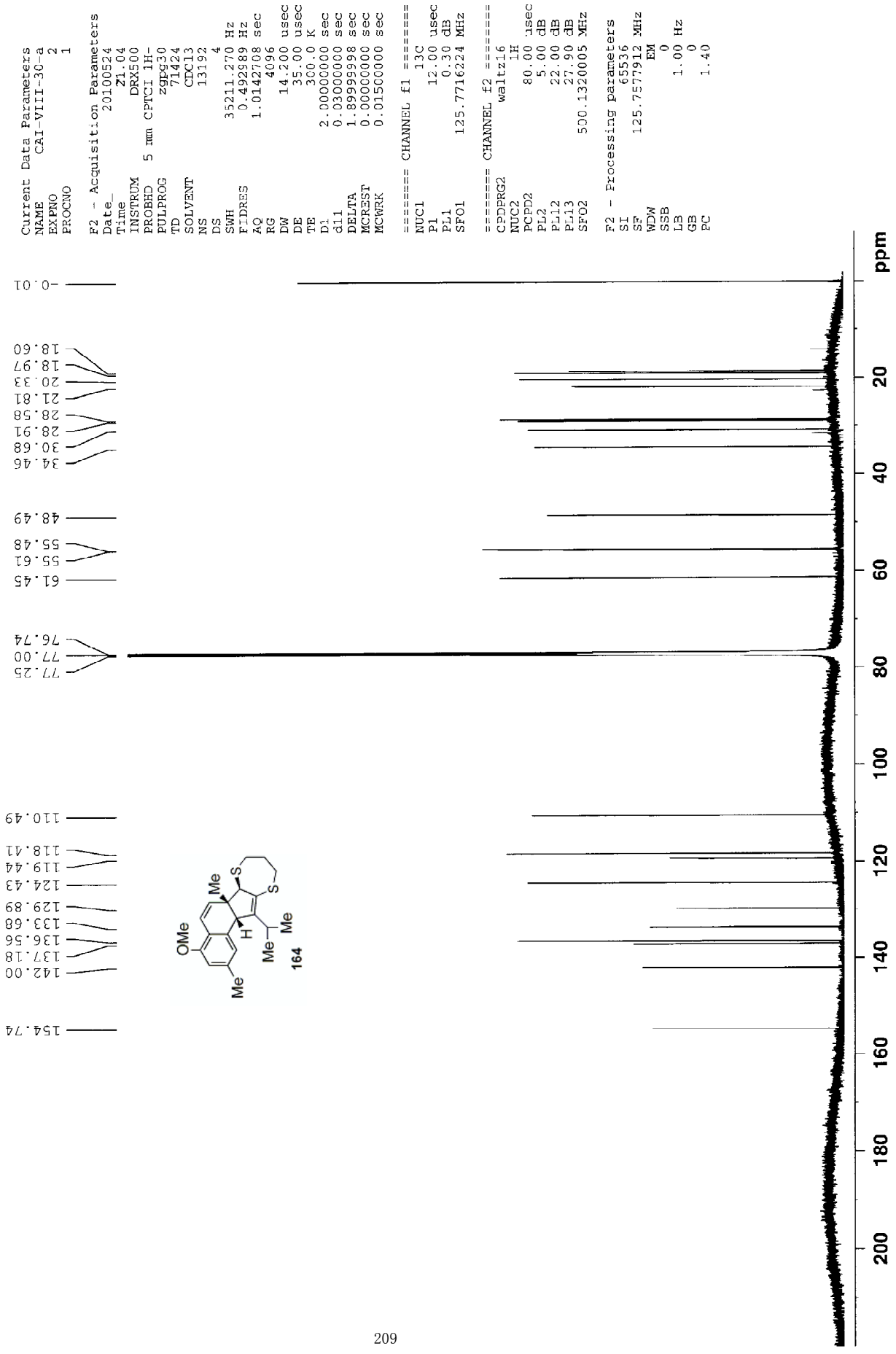

```
Current Data Parameters
NAME       CAI-VIII-30-a
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20100524
Time               20.58
INSTRUM           DRX500
PROBHD   5 mm CPTCI 1H-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                     8
DS                     2
SWH          10330.578 Hz
FIDRES        0.157632 Hz
AQ           3.1719923 sec
RG                  11.3
DW                48.400 usec
DE                 6.00 usec
TE                300.0 K
D1           1.00000000 sec
MCREST       0.00000000 sec
MCWRK        0.01500000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  8.00 usec
PL1                 4.30 dB
SFO1         500.1335009 MHz

F2 - Processing parameters
SI                 32768
SF          500.1300131 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

13C NMR


Current Data Parameters
NAME CAI-VIII-30-a
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20100524
Time 21.04
INSTRUM DRX500
PROBHD 5 mm CPTCI 1H-
PULPROG zgpg30
TD 71424
SOLVENT CDCl3
NS 13192
DS 4
SWH 35211.270 Hz
FIDRES 0.492989 Hz
AQ 1.0142708 sec
RG 4096
DW 14.200 usec
DE 35.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 12.00 usec
PL1 0.30 dB
SFO1 125.7716224 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 5.00 dB
PL12 22.00 dB
PL13 27.90 dB
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 65536
SF 125.7577912 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
-0.01
18.60
18.97
20.33
21.81
28.58
28.91
30.68
34.46
48.49
55.48
55.61
61.45
76.74
77.00
77.25
110.49
118.41
119.44
124.43
129.89
133.68
136.56
137.18
142.00
154.74
OMe
Me
Me
Me
Me
H
S
S
164
ppm
200
180
160
140
120
100
80
60
40
20

VITA

Zhengxin Cai was born at Huabei Oilfield, Hejian city, Hebei province in China in the winter of 1982. He went to Tianjin University in 2001, and got his B.S. degree from School of Pharmaceutical Science and Technology, Tianjin University in 2005.

He went to University of Missouri at Columbia in 2005. After a trip to New York City, he joined the Harmata group to study the art of total synthesis in 2006. In 2010, he decided to expand his passion in total synthesis to the field of molecular imaging. In 2011, after he got his Ph.D. degree, he moved to Pittsburgh to join Carolyn Anderson's group as a postdoctoral associate.