Total Synthesis of the Polyketide Natural Product (–)-Pironetin and Studies Directed Toward the Total Synthesis of Iriomoteolide 1a.

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A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Chemistry.

Chapel Hill

2011

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ABSTRACT

Anne-Marie Roe Dechert Schmitt:

Total Synthesis of the Polyketide Natural Product (–)-Pironetin and Studies Directed Toward the Total Synthesis of Iriomoteolide 1a.
(Under the direction of Professor Michael T. Crimmins)

Polyketides are secondary metabolites with diverse structural scaffolds. The research summarized herein describes the biomimetic total synthesis of the polyketide (–)-pironetin utilizing iterative aldol additions of thiazolidinethiones to create five of the six total stereocenters of (–)-pironetin. This technology has also been applied to a convergent synthesis to the core of the polyketide iriomoteolide 1a.

For my family

Acknowledgments

I would like to take the opportunity to acknowledge those who have helped me in my journey through graduate school. First, I would like to thank my advisor, Professor Michael T. Crimmins, for his tremendous support over the past five years. I cannot accurately convey the immense gratitude I have for allowing me the opportunity to work for you. I have learned so much from you; thank you! I would like to thank all of the talented graduate students and postdocs that I have had the opportunity to work with. Yan Zhang, Luke Zuccerello, Anita Mattson, Mariam Shamszad, and Matt Haley were all especially kind and encouraging to me when I first started, and I learned so much from all of you. Thanks to Nicole and Troy Knight, you have my admiration and respect; and you guys are the best! Thanks to my undergraduate advisor, Professor Tim Dore, who worked with me one-on-one in the lab, and encouraged me to go to graduate school. My family has been unbelievably supportive of me my entire life, especially my mother. Mom, you have sacrificed so much of yourself so August and I can have better than what you had; I thank you every day. I also want to thank my father, who is always close to my heart. Thanks to my family, especially my aunts and uncles for their unwavering support. Thanks to my brother August, my "default" friend, who has always been an excellent role model. I always have your back, and I know you always have mine. Thanks to my in-laws, Ray Schmitt and Nancy Copley. Thank you for raising Dan to be the person that he is! Last, but not least, I would like to thank my husband, Dan Schmitt. You have been there for me every step of the way. You are everything to me, and I love you! Your unconditional love has helped me through the difficult times; thanks for being you.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF SCHEMES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Ac	acetyl
Bn	benzyl
CSA	10-camphorsulfonic acid
DCC	dicycohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyanon-1,4-benzoquinone
DIAD	diisopropylazadicarboxylate
DIBAL	diisobutylaluminum hydride
DIPEA	N,N-diisopropylethylamine
DMAP	4-N,N-dimethylamino pyridine
DMF	dimethylforamide
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
Et	ethyl
HMPA	hexamethyl phosphoramide
KCN	potassium cyanide
LiDBB	4,4'-di-*tert*-butyl-biphenyllithium
LDA	lithium diisopropylamine
Me	methyl
MeOH	methanol
Mes	mesityl
MOM	methoxymethyl
MS	molecular sieves
Ms	methanesulfonyl
NMO	N-methylmorpholine N-oxide
NMP	N-methylpyrolidinone

NOE	nu
Ph	phenyl
PMB	*para*-methoxybenzyl
PMP	4-methoxyphenyl
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
p-TsOH	*p*-toluenesulfonic acid
pyr	pyridine
TBAF	tetrabutyl ammonium fluoride
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TIPS	triisopropylsilyl
TMS	trimethylsilyl
THF	tetrahydrofuran
TPAP	tetrapropylammonium perruthenate
Ts	*p*-toluenesulfonyl

Chapter 1

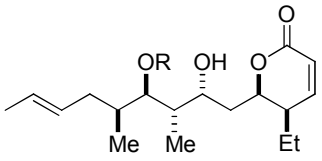
Total Synthesis of (–)-Pironetin

A. Introduction

1. Isolation and Biological Significance

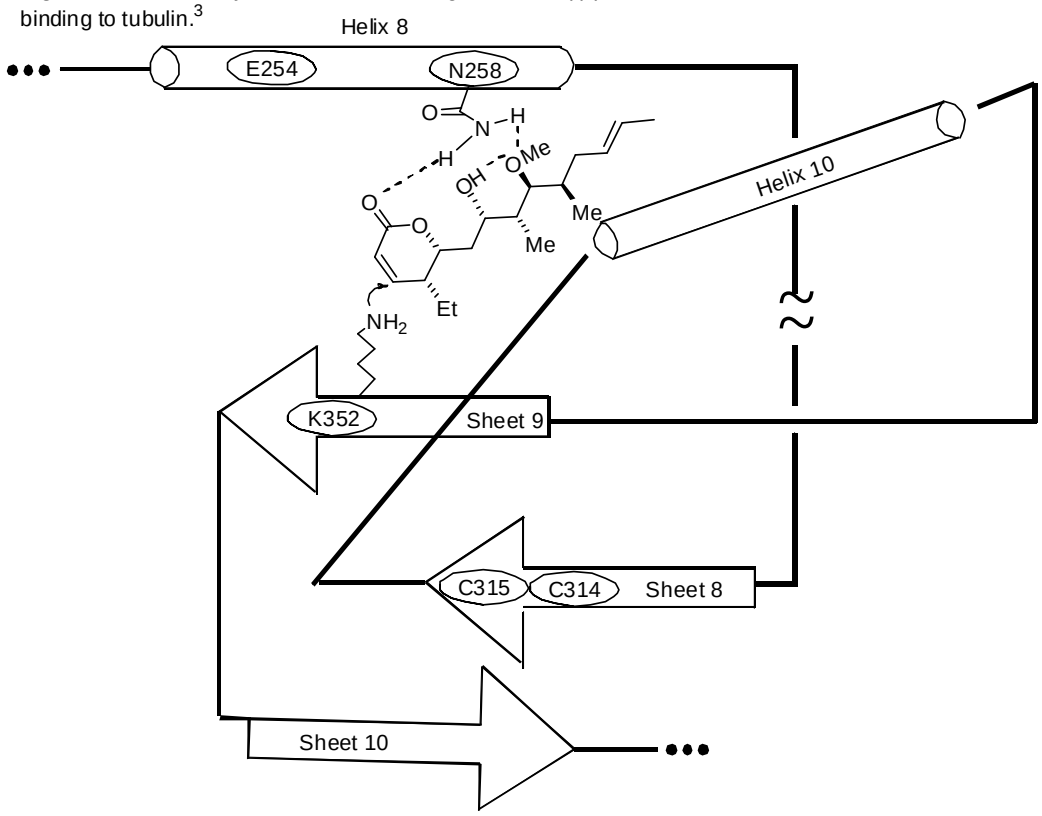
(–)-Pironetin (**1**, Figure 1.1) is a polyketide natural product that was independently isolated in 1994 by both the Yoshida and Kobayashi groups from the *Streptomyces* sp. NK10958a.[1] Structurally, (–)-pironetin consists of an α,β-unsaturated δ lactone possessing a linear alkyl chain containing four contiguous stereocenters and a *trans*-olefin. Initially determined to be a plant growth regulator[1b], (–)-pironetin was also identified as having both immunosuppressant activity and antiproliferative activity against several tumor cell lines, including murine tumor cell line P388 leukemia (20 ng/mL), HeLa (10 ng/mL), A2780 (10 ng/mL), and K-NRK (10 ng/mL).[2] Further examination of (–)-pironetin and its demethyl derivative (**2,** Figure 1.1), have shown that cell cycle progression is inhibited at the M-phase, which is where cells are most sensitive to radiation and DNA alkylating compounds.[2] Investigation of the mechanism of action has revealed that pironetin is a potent inhibitor of tubulin assembly, by way of a covalent binding interaction between the Lys352 of α–tubulin with the α,β–unsaturated δ lactone of (–)-pironetin, through Michael addition (Figure 1.2).[3]

Figure 1.1 (-)-pironetin



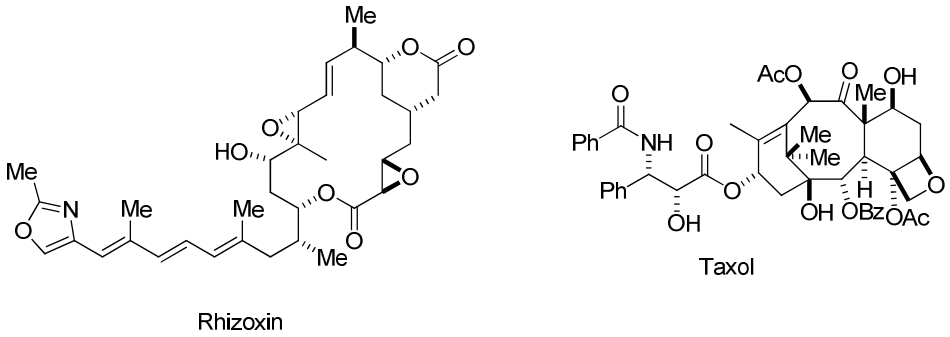
(-)-pironetin (**1**): R = Me
NK10958P (**2**): R=H

Figure 1.2: Secondary structure and binding model for (-)-pironetin binding to tubulin.[3]



Though (–)-pironetin shows moderate effects against the tumor cell lines mentioned above and toxicity *in vivo*, it is viewed as a potential lead compound for the development of cancer therapeutics due to its structural simplicity compared to other notable tubulin binding agents, such as Rhizoxin and Taxol (Figure 1.3).[4]

Figure 1.3: Other tubulin binding agents.



Polyketides represent an important class of natural products due to their wealth of pharmacological properties.[5] Because the synthesis of polyketides represents a worthy

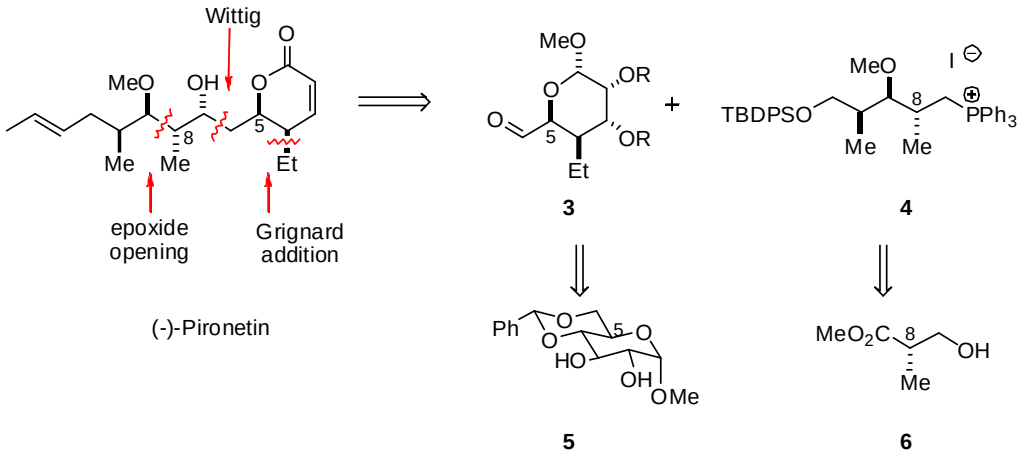
endeavor, several groups have developed methods to construct polyketide frameworks, and have applied these methods in the context of the total synthesis of (–)-pironetin.[6]

2. Previous Syntheses

2.1 Kawada's approach to (–)-pironetin

The first total synthesis of (–)-pironetin was reported by Kawada and co-workers in 1995.[6a] Kawada's convergent approach relied on a Wittig olefination of aldehyde **3** and phosphonium salt **4** to form the C6-C7 bond (Scheme 1.1). Aldehyde **3** would be derived from commercially available glucopyranoside **5**, which contains the correct configuration at C5, while phosphonium salt **4** takes advantage of the chiral pool by employing the (*S*)-Roche-ester **6**, which contains the correct configuration for C8.

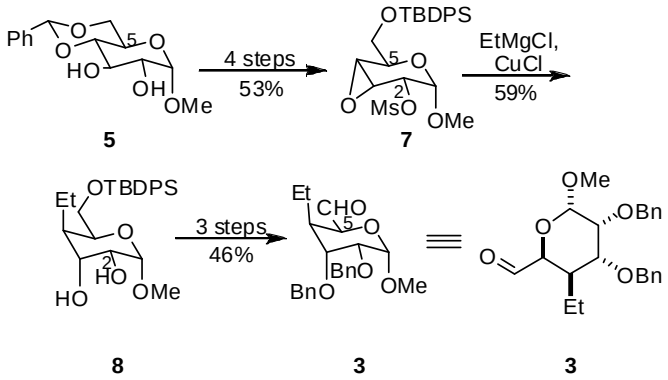
Scheme 1.1: Kawada's retrosynthetic analysis of (-)-pironetin



Beginning with commercially available glucopyranoside **5**, in a series of four steps involving formation of the dimesylate, opening of the acetal, protection, and epoxide formation, epoxide **7** was formed in 53% over four steps (Scheme 1.2). Opening of the epoxide with EtMgCl in the presence of CuCl delivered the expected axial alcohol **8**, with unexpected loss of the mesylate at C2. In three additional steps, the secondary alcohols

were protected as the benzyl ethers, the TBDPS ether was cleaved, and the resultant primary alcohol was oxidized to form aldehyde fragment **3**.

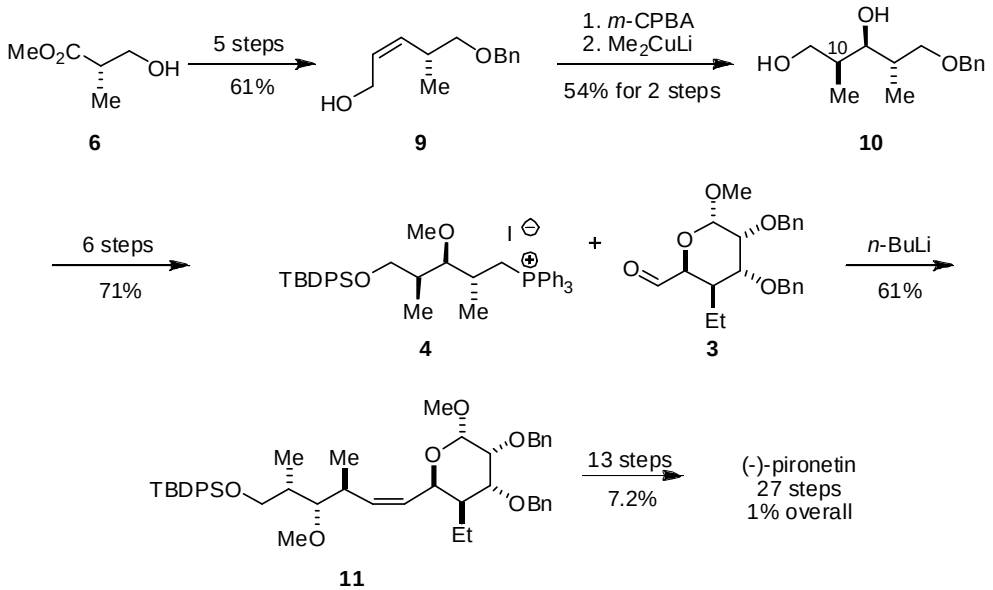
Scheme 1.2: Kawada's synthesis of aldehyde **3**.



5 **7** **8** **3** **3**

Phosphonium salt fragment **4** was prepared in eleven steps from (*S*)-Roche ester (**6**), beginning with a protection of the primary alcohol as the benzyl ether, and a four step manipulation of the methyl ester to form allylic alcohol **9** (Scheme 1.3). At this point, an epoxidation of allylic alcohol **9** with *m*-CPBA takes advantage of $A^{1,3}$-strain minimization to form the epoxide with the correct orientation at C9. Hydroxyl directed opening of the epoxide with Me_2CuLi generated primary alcohol **10**. In six steps, the primary alcohol was

Scheme 1.3: Kawada's approach to (-)-pironetin.



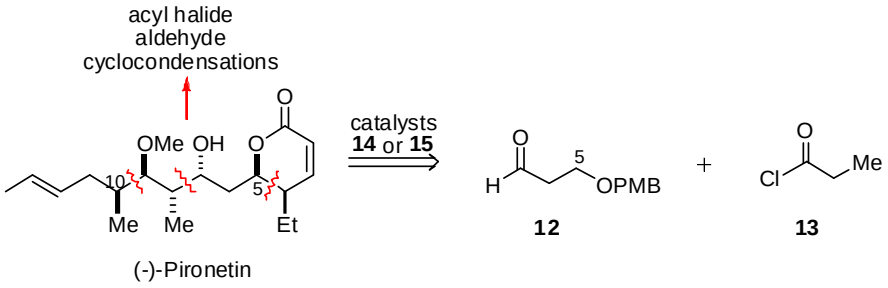
6 **9** **10** **4** **3** **11**

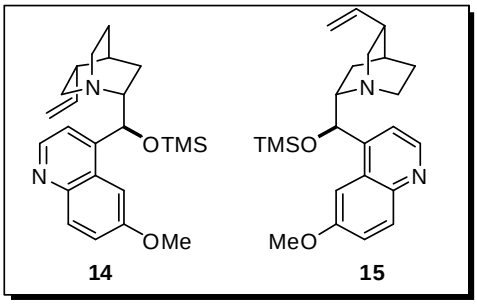
protected as the TBDPS ether, the secondary alcohol was methylated, and the benzyl ether was transformed into phosphonium salt **4**. A Wittig olefination between aldehyde **3** and phosphonium salt **4** formed the C6-C7 bond, to generate olefin **11**. However, to complete the synthesis, an additional 13 steps were necessary for both protecting group and functional group manipulations, generating the natural product in 27 linear steps and 1% overall yield. Kawada's approach represents the first total synthesis of (–)-pironetin, and confirmed the absolute stereochemistry of the natural product.

2.2 Nelson's approach to (–)-pironetin

Nelson's approach to (–)-pironetin showcases the acyl-halide aldehyde cyclocondensation (AAC) reactions developed in his laboratory.[6k] Beginning with easily prepared aldehyde **12** and propionyl chloride **13** (Scheme 1.4), Nelson utilizes the catalysts **14** and **15** to install all stereocenters of (–)-pironetin in an iterative fashion.

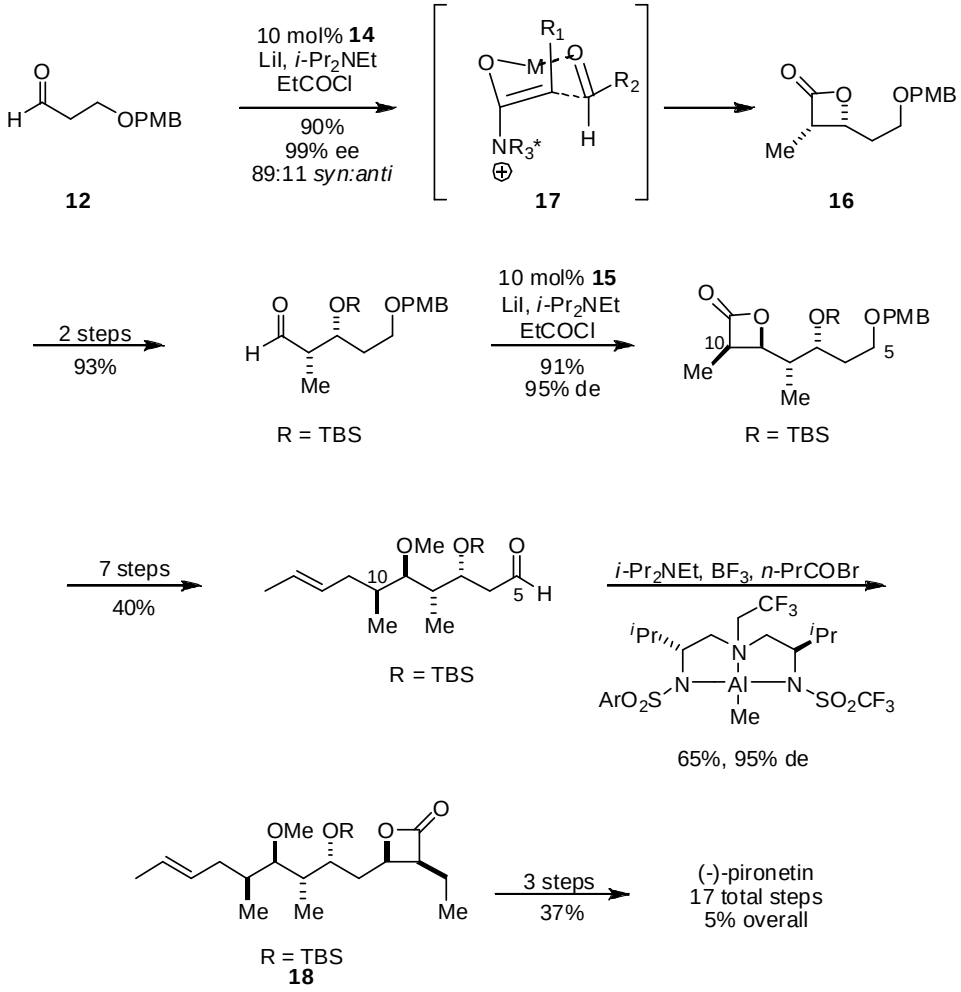
Scheme 1.4: Nelson's retrosynthetic analysis of (-)-pironetin.





To form β-lactone **16**, aldehyde **12**, prepared in two steps from 1,3 propane diol, underwent an AAC reaction with catalyst **14** and propionyl chloride to furnish **16** in 90% yield, 99% *ee*, and 89:11 *syn/anti* ratio (Scheme 1.5). The stereoselectivity of this reaction relies on formation of a metal template, closed transition state **17**.[7]

Scheme 1.5: Nelson's total synthesis of (-)-pironetin.



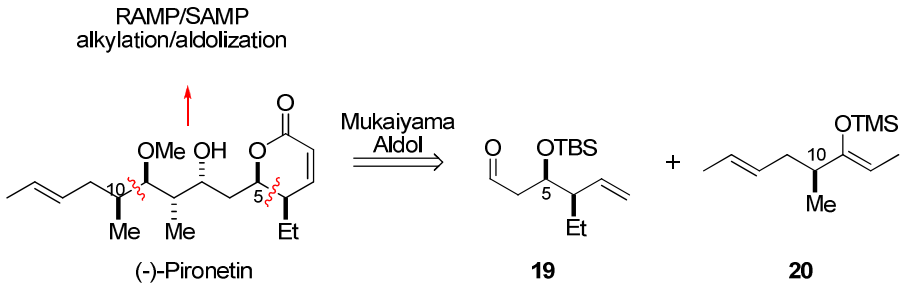
In two additional acyl-halide aldehyde cyclocondensation iterations, all six stereocenters of pironetin were formed in a modular fashion, in both high yield and high d.r. to arrive at β-lactone **18**. Opening of the β-lactone, cleavage of the silyl protecting group, and formation of the 2-pyranone unit was accomplished in three steps, generating pironetin in 17 total steps and 5% overall yield. This AAC approach to polypropionate units

represents a useful variant in aldol chemistry, generating polypropionate subunits in the absence of chiral auxiliaries, catalytically, and in an iterative fashion.

2.3 Enders' approach to (–)-pironetin

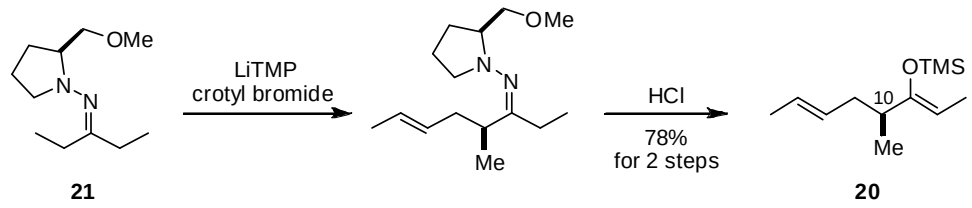
Enders approach to pironetin relied on the formation of three of the six stereocenters of (–)-pironetin utilizing RAMP/SAMP hydrazone alkylation and aldolization methodlogy.[6l] Hence, formation of pironetin would occur in a convergent manner from aldehyde **19** and silyl enol ether **20** through a Mukaiyama aldol addition (Scheme 1.6).

Scheme 1.6. Ender's retrosynthetic analysis of (-)-pironetin.



Construction of enol silane **20**, began with an alkylation of hydrazone **21**, followed by removal of the auxiliary under acidic conditions to reveal silyl enol ether **20** in 78% yield and 98% *ee* over 2 steps (Scheme 1.7).

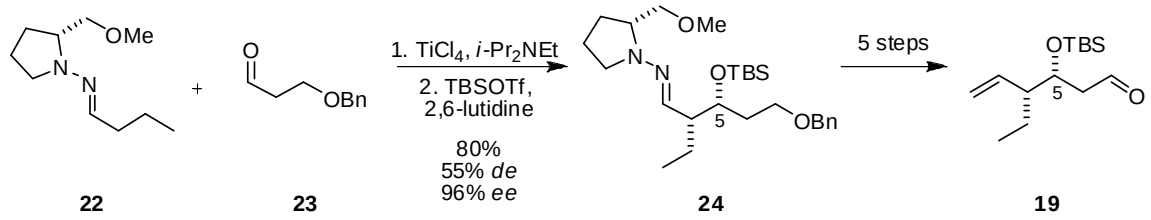
Scheme 1.7: Preparation of enol silane **20**.



To form the stereocenters at C4 and C5, an asymmetric hydrazone aldol employing butanal RAMP hydrazone **22**, and aldehyde **23** generated aldol adduct **24** in 80%, 55% *de*, and 96% *ee* after protection after protection as TBS ether (Scheme 1.8). In five additional

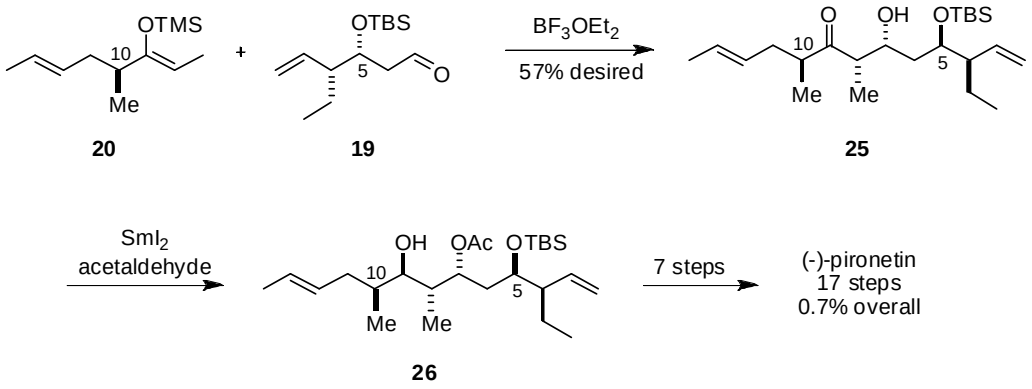
steps involving protecting group and functional group manipulations, aldehyde **19** was prepared.

Scheme 1.8: Preparation of aldehyde **19**.



Aldehyde fragment **19** and silyl enol ether fragment **20** were united through a Mukaiyama aldol, giving a mixture of diastereomers, favoring the desired aldol adduct **25** in 57% isolated yield (Scheme 1.9). A Tishchenko reduction of resultant ketone **25** generated secondary alcohol **26** which contains all 6 stereocenters of pironetin. In seven additional steps, pironetin was completed in 0.7% overall yield.

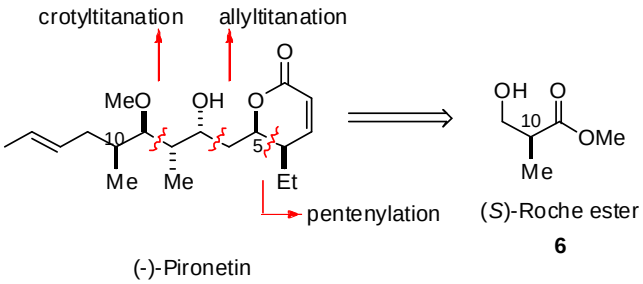
Scheme 1.9: Completion of (-)-pironetin.



2.4 Cossy's Approach

Cossy's approach to (–)-pironetin relied on allylation chemistry to form 5 of the 6 stereocenters of pironetin.[6m] It also, as other approaches have done, takes advantage of the chiral pool by utilizing the (*S*)-Roche ester (**6**), which contains the correct configuration at C10 (Scheme 1.10).

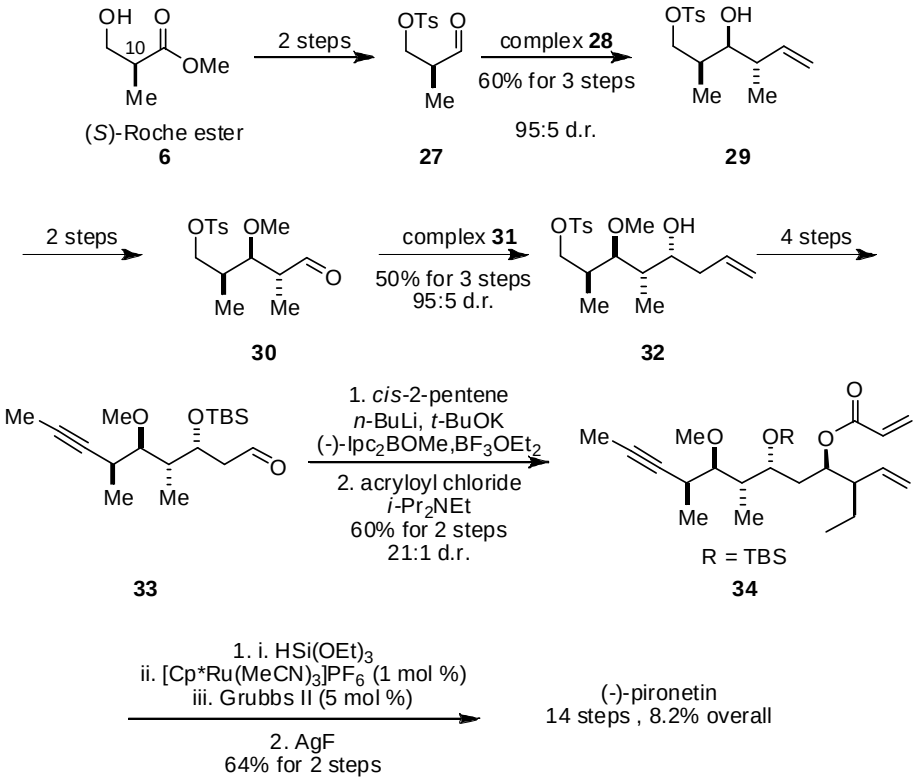
Scheme 1.10: Cossy's retrosythetic analysis of (-)-pironetin.

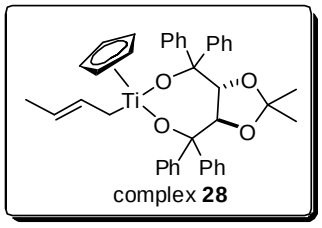


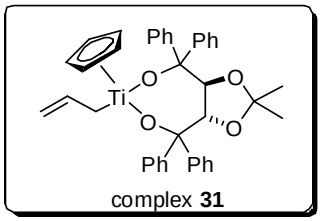
The synthesis began with a two step sequence to form aldehyde **27**, which was then subjected to a diastereoselective crotylation utilizing Ti-TADDOL-complex **28**, to generate secondary alcohol **29** in 95:5 d.r. and 60% yield over 3 steps (Scheme 1.11). Subsequent methylation and ozonolysis delivered aldehyde **30**, which underwent an asymmetric allylation employing Ti-TADDOL-complex **31** to provide secondary alcohol **32** in 95:5 d.r. and 50% yield over 3 steps. In four steps, the tosylate was transformed into an internal alkyne, and the olefin was selectively cleaved to form aldehyde **33**. A highly stereselective boron-mediated pentenylation, followed by acylation with acryloyl chloride yields dienyne **34**.

In a single pot operation, dienyne **34** was hydrosilylated under Trost's conditions, RCM of the resultant triene forms the δ-lactone, and treatment with AgF leads to protodesilylation to provide the *E*-olefin present in the natural product. Deprotection of the TBS group provides (–)-pironetin in 64% over 2 steps, and in fourteen linear steps.

Scheme 1.11: Cossy's total synthesis of (-)-pironetin.







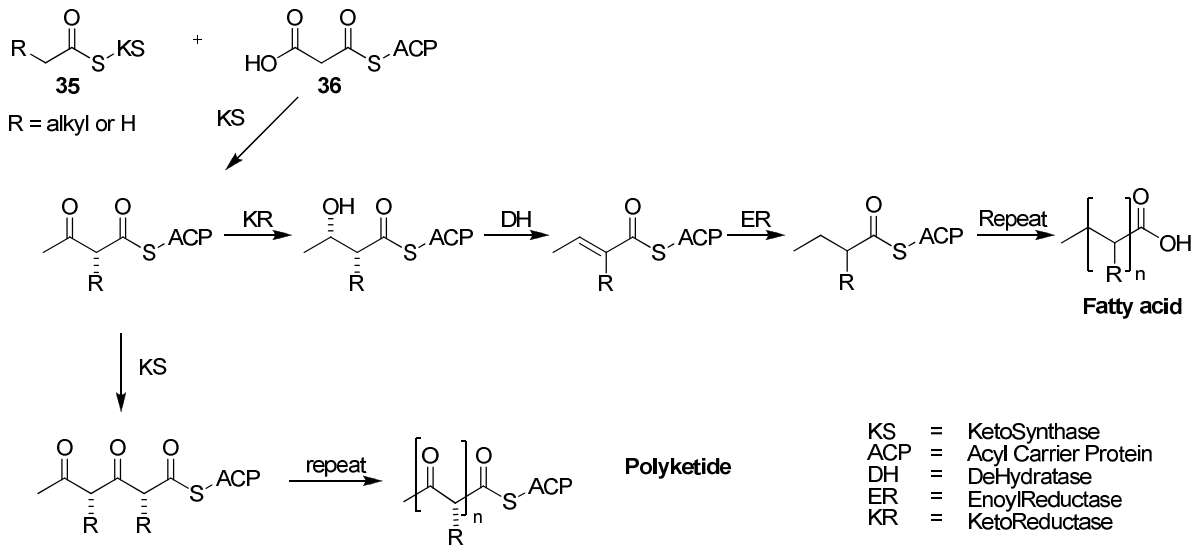
3. Use of the thiazolidinethione to access polyketide subunits

3.1 Biosynthesis of polyketides

Polyketides are structurally diverse secondary metabolites of plants, animals, fungus, or bacteria; and as such, possess a wealth of pharmacological activity, including anti-cancer, antibiotic, immunosupressent, and antifungal properties. Though polyketides are structurally diverse and have differing molecular complexity, the origin of these compounds is related through their biosynthesis.[5] In the biosynthesis of polyketides, a "starter unit" (**35**) where R = H or alkyl, but most commonly R is either CH_3 or C_2H_5, undergoes iterative chain

extensions with a -CHR-CO- "extender units" (**36**) (Scheme 1.12).[5] The starter unit is commonly derived from acetyl-CoA or propionyl-CoA, while the extender units are derivatives of malonic acid or a malonic acid thioester.[5] Extension of the starter unit occurs via a condensation reaction involving decarboxylation of the malonate extender units. Enzymes which are responsible for building the initial polyketide chain are known as polyketides synthases (PKS), and during the process of chain formation, the resultant carbonyl group may be transformed by the aid of enzymes, or retain its identity.[5] Some examples of enzymes that facilitate the production of polyketides include ketoreductases (KR) which reduce carbonyls to alcohols, dehydratases (DH) which eliminate alcohols to form olefins, and enoylreductases (ER) which reduces olefins to alkanes.[5]

Scheme 1.12: Biosynthesis of all polyketides.

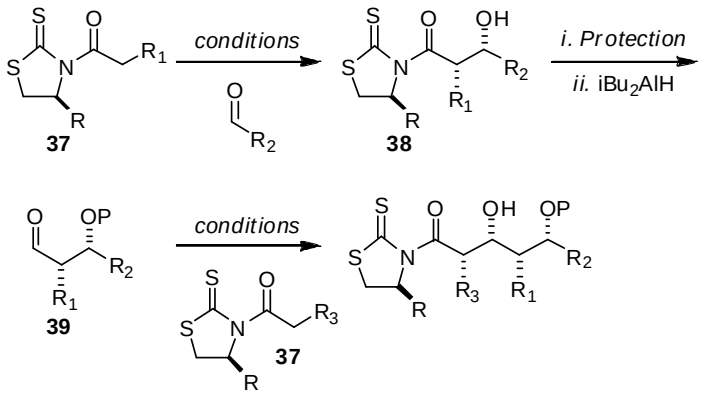


3.2 Thiazolidinethione technology in the context of total synthesis

It was conceived that the use of different variants of titanium tetrachloride mediated aldol additions of *N*-acylthiazolidinethiones and aldehydes or acetals would allow for (-)-pironetin to be synthesized in a "biomimetic" approach. In this approach, C-C bond formation would occur via a highly diastereoselective aldol reaction utilizing a

thiazolidinethione chiral auxiliary **37** to form aldol adduct **38**, which could be followed by protection of the resultant hydroxyl, and cleavage of the chiral auxiliary directly to aldehyde **39** that could be utilized in a second aldol iteration with thioimide **37** (Scheme 1.13). Use of the thiazolidinethione allows the entire process (C-C bond formation, protection, reduction to the aldehyde) to be accomplished in only three steps. Compared to the use of an oxazolidinone chiral auxiliary in an asymmetric aldol, the use of a thiazoldinethione chiral auxiliary represents a more direct approach as the aldol adduct of an oxazolidinone cannot be converted directly to an aldehyde. This strategy has previously been applied to the formal synthesis of deoxyerythronolide B.[8]

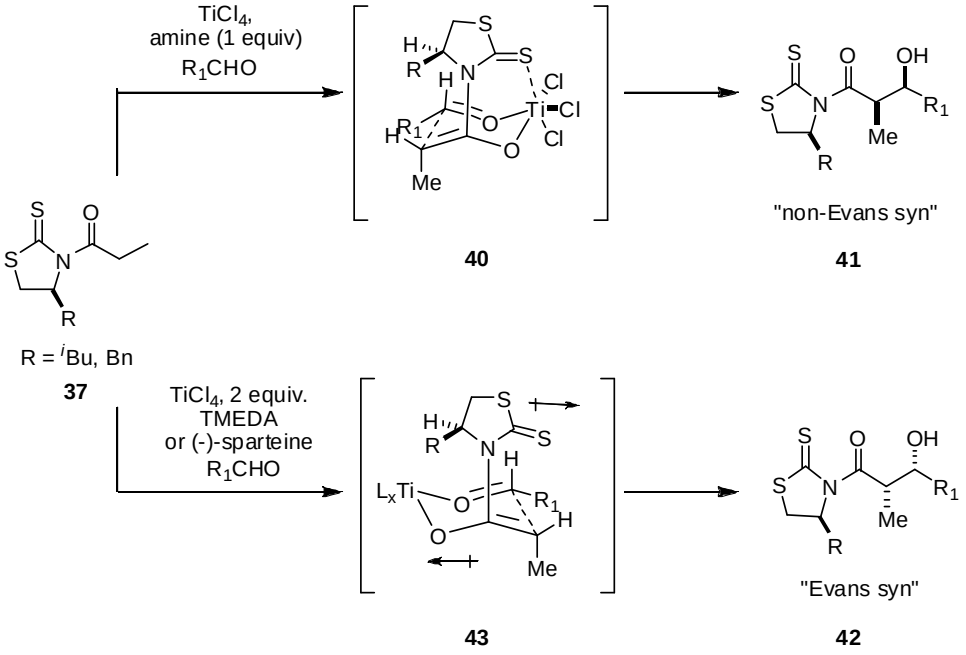
Scheme 1.13: Iterative aldol reactions of thiazolidinethiones.



Several years ago, the Crimmins group disclosed a method to access both Evans *syn* and non-Evans *syn* aldol adducts from the same antipode of acyl thiazolidinethiones **37**, simply by varying the nature and equivalents of the amine base that is employed.[9] To access non-Evans *syn* products, the *N*-acylthiazolidinethione (**37**) is treated with one equivalent of titanium tetrachloride, one equivalent of an amine base, and one equivalent of an aldehyde.[9] The reaction is believed to proceed through the formation of steric-minimized chelated chair-like transition state **40**, in which the nucleophilic thiocarbonyl chelates to the titanium metal center giving rise to non-Evans *syn* adduct **41**.[9] Alternatively, the use of two equivalents of (–)-sparteine or the use of NMP allows for Evans *syn* aldol adducts **42** to be

obtained in high diastereoselectivities.[9] This result is rationalized through a dipole and steric minimized transition state **43**, in which the extra equivalent of (–)-sparteine or NMP is thought to coordinate to the titanium metal center, preventing coordination of the thiocarbonyl.[9]

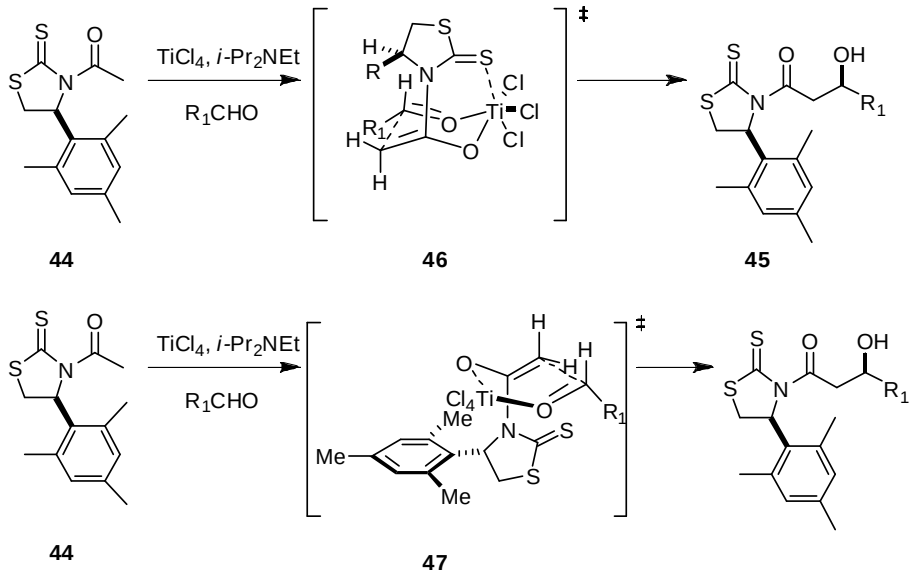
Figure 1.4: Access to Evans *syn* and non-Evans *syn* aldol adducts from thiazolidinethione **37**



Compared to the propionate aldol, the acetate aldol reaction has been more difficult to render highly diastereoselective with the same thiazolidinethione and oxazolidinone chiral auxiliaries, due to the lack of substitution on the α carbon. Mariam Shamszad, a former graduate student in the Crimmins lab, developed a highly diastereoselective acetate aldol addition utilizing a bulky mesityl substituted thiazolidinethione (Figure 1.5).[10] Treatment of thiazolidinethione **44** with one equivalent of $TiCl_4$, one equivalent of Hünig's base, and one equivalent of an aldehyde generates aldol adduct **45** in high diastereoeselctivity, which is believed to arise through the formation of a chelated six membered chair-like transition state **46**, in which the bulky mesityl group forces the R group of the aldehyde into a pseudo-equatorial position to avoid 1,3 diaxial interactions between the auxiliary and a methyl group

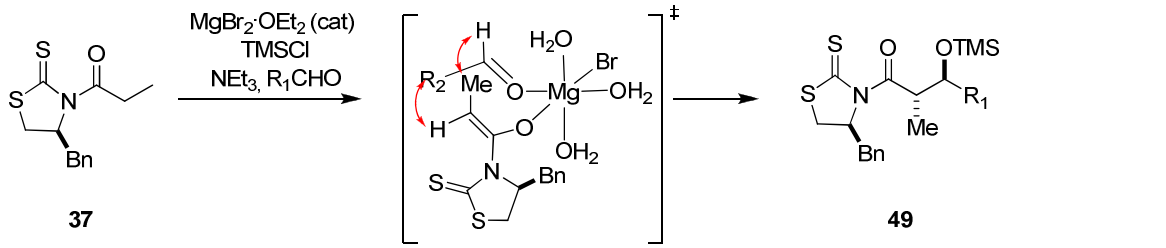
of the mesityl.[10] Another possible transition state (**47**) is also depicted in figure 1.5, in which the reaction proceeds through a dipole minimized nonchelated boat transition state.[10]

Figure 1.5: Possible transition states to account for the diastereoselection in the acetate aldol addition.



Direct access to the *anti* propionate aldol adduct utilizing alkyl substrates is not currently possible using the chlorotitanium enolates of *N*-acylthiazolidinethiones, and often requires expensive chiral auxiliaries or Lewis acids with other chiral auxiliary based approaches or exotic catalysts for non-auxiliary based approaches.[11] These approaches are not always convienent or widely applicable to a broad array of substrates. Evans and coworkers have developed an *anti* aldol reaction to access anti β-hydroxy aldol adducts utilizing magnesium enolates of oxazolidinones or thiazoldinethiones and various aromatic aldehydes (Figure 1.6).[12] Although aromatic aldehydes in combination with *N*-acylthiazolidinethiones give highly diastereoselective aldol adducts in high yields using this method, aliphatic aldehydes give significantly lower conversion. In this context, Mg facilitates formation of the *Z*-enolate of thioimide **37**, and the reaction is thought to proceed through a dipole minimized boat-like transition state **48** to form a magnesium aldolate, which is irreversibly trapped by trimethylsilyl chloride to form the product **49**, and regenerate the Mg catalyst.[12]

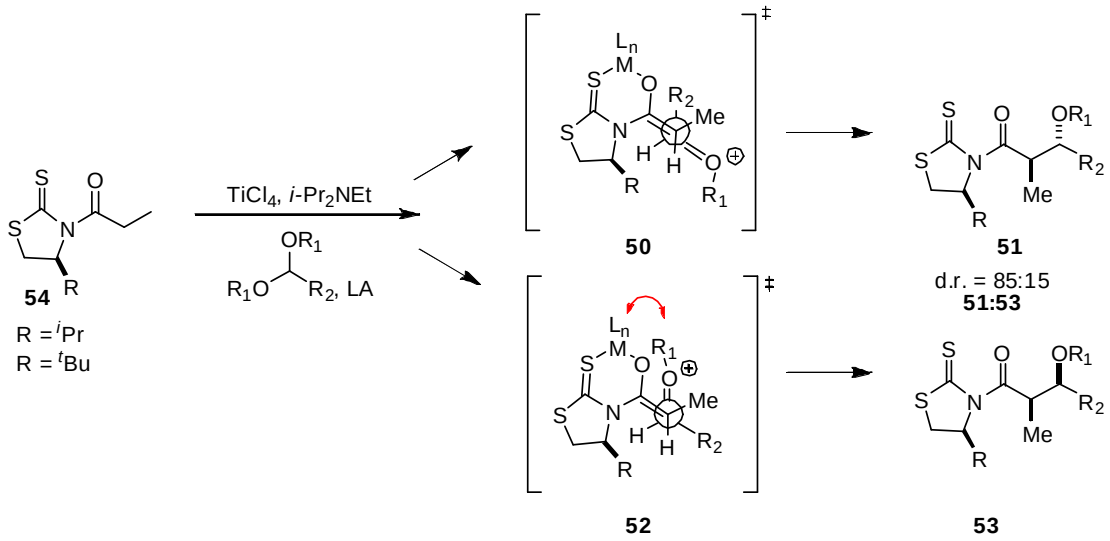
Figure 1.6: *Anti*-aldol reactions of *N*-acylthiazolidinethiones.



Recently, Hoye and coworkers reported an extension of the Evans magnesium halide catalyzed *anti* aldol reaction employing aliphatic aldehydes and oxazolidinones.[13] Because the primary byproducts in these reactions and related reactions with *N*-acyl thiazolidinethiones stem from the instability of the aldehyde, through silyl enol ether formation or self-aldol reactions of the aldehyde, it was reasoned that the use of a stoichiometric amount of the magnesium halide would result in an increase in the amount of enolate present in the reaction.[13] Furthermore, syringe pump addition of the aldehyde should result in a higher steady state enolate to aldehyde ratio, resulting in higher yields of the aldol adduct.[13] However, the yields reported in these instances remain subpar.

A viable alternative to generate the *anti* propionate subunit is through an *N*-acyl thiazolidinethione mediated acetal aldol, developed by Urpi, which allows access to *anti* β-alkoxy-α-methyl aldol adducts (Figure 1.7).[14] The diasteroselection associated with the acetal aldol, though modest, is thought to arise through a dipole and steric-minimized open transition state **50** in which the *in situ* generated oxocarbenium ion undergoes addition from the less hindered face of a chelated *Z* enolate, in an antiperiplanar arrangement (Figure 1.7) leading to aldol adduct **51**.[14a] The minor diastereomer arises through transition state **52**, giving rise to aldol adduct **53**.[14a]

Figure 1.7: Access to *anti* β-alkoxy-α-methyl aldol adducts.



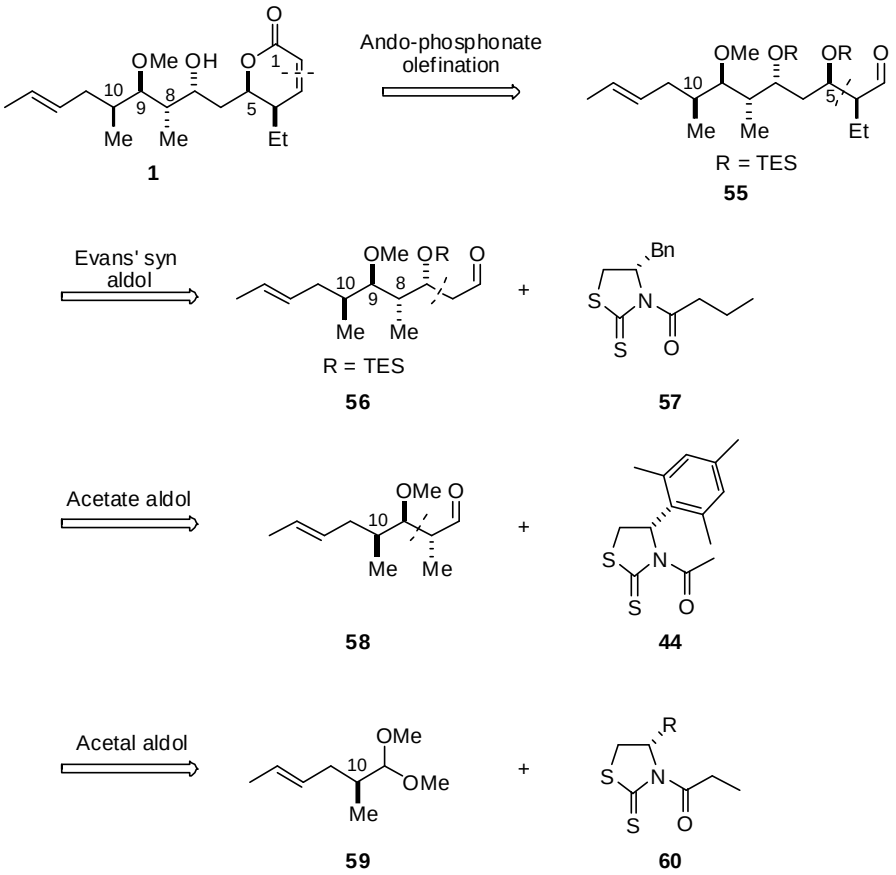
This acetal aldol addition of *N*-acylthiazolidinethiones is highly advantageous for two reasons: it gives rise to the *anti* subunit, and it circumvents an additional O-alkylation step. Alkylation of β–hydroxy carbonyls is difficult due to the tendency of these substrates to undergo retro-aldol cleavage under basic conditions. Furthermore, the use of more reactive alkylating agents (methyl triflate and methyl fluorosulfonate), which do not require basic conditions, also readily alkylate biological tissues, and therefore represents a serious safety concern. One key aspect that we wished to explore was the effect of other thiazolidinethiones on the diastereoselection of the acetal aldol addition. It was thought that employing bulkier R group on chiral auxiliary **54** (Figure 1.7) would lead to formation of *anti* β-alkoxy-α-methyl aldol adducts in higher diastereoselection, and this highly diastereoselective reaction could be applied to the total synthesis of (–)-pironetin.

B. Synthesis of (–)-pironetin

1. Retrosynthesis of (–)-pironetin

The retrosynthetic analysis of (–)-pironetin is shown in scheme 1.14. The synthesis of **1** relies on the formation of 5 out of 6 stereocenters through titanium tetrachloride mediated iterative aldol reactions utilizing the *N*-acylthiazolidinethione chiral auxiliary. It was envisioned that the *Z*-enoate of **1** would arise through a modified Horner-Emmons reaction with aldehyde **55**. Aldehyde **55** would be synthesized via and Evans *syn* aldol reaction with aldehyde **56** and thiazolidinethione **57**. Aldehyde **56** could be accessed via a highly diastereoselective acetate aldol reaction between mesityl substituted thiazolidinethione **44** and aldehyde **58**. Aldehyde **58**, in turn, would result from a highly diastereoselective acetal aldol addition between chiral dimethyl acetal **59** and propionate **60**.

Scheme 1.14: Retrosynthetic analysis of (-)-pironetin (**1**)

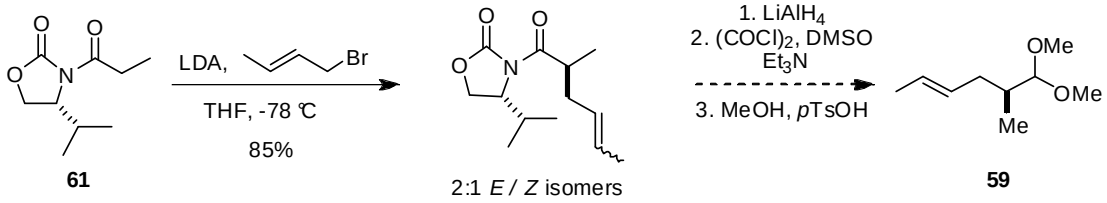


1 **55** **56** **57** **58** **44** **59** **60**

2. Preparation of Acetal 59

Initial efforts to prepare acetal **59** centered on the use of an asymmetric alkylation employing crotyl bromide, propionamide **61**, and LDA (Scheme 1.15) to form alkylated oxazolidinone **62**. The auxiliary would then be reductively cleaved, and the resultant alcohol

Scheme 1.15: Initial route to access dimethyl acetal **59**.

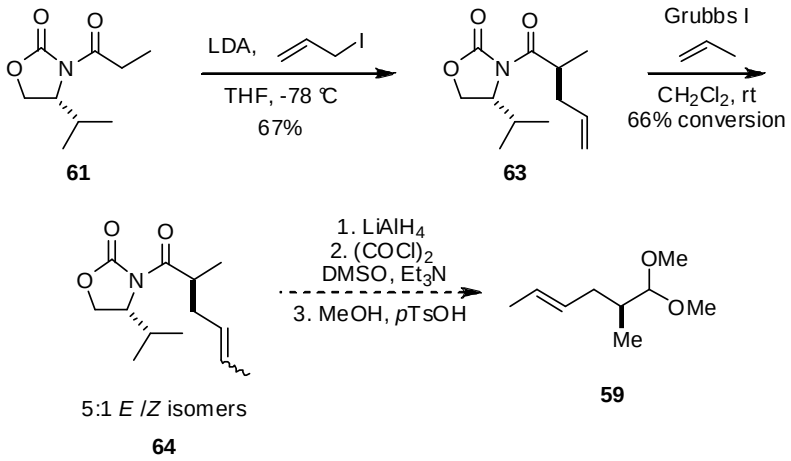


61 2:1 *E* / *Z* isomers **62** **59**

oxidized to deliver an aldehyde, which could be stirred with methanol and catalytic acid to deliver acetal **59**. It was found that under alkylation conditions which utilized 90% trans crotyl bromide, a 2:1 mixture of *E/Z* isomers resulted from the reaction conditions. This was attributed to isomerization of the crotyl bromide or product during the course of the reaction.

An alternative strategy to access **59** is outlined in scheme 1.16. Beginning with propionate **61**, an asymmetric alkylation employing allyl iodide delivered terminal olefin **63** in 67% yield and 20:1 d.r. A cross metathesis[15] between terminal olefin **63**, Grubbs' 1st generation catalyst, and propene gas was expected to deliver the crotylated product in higher *E* selectivity than what was obtained in the asymmetric alkylation. The cross metathesis generated olefin **64** in 66% conversion and as a 5:1 mixture of *E/Z* isomers. Due to the modest increase in *E* selectivity, this route was not seen a viable option to access acetal **59**.

Scheme 1.16: Alternative approach to access dimethyl acetal **59**.



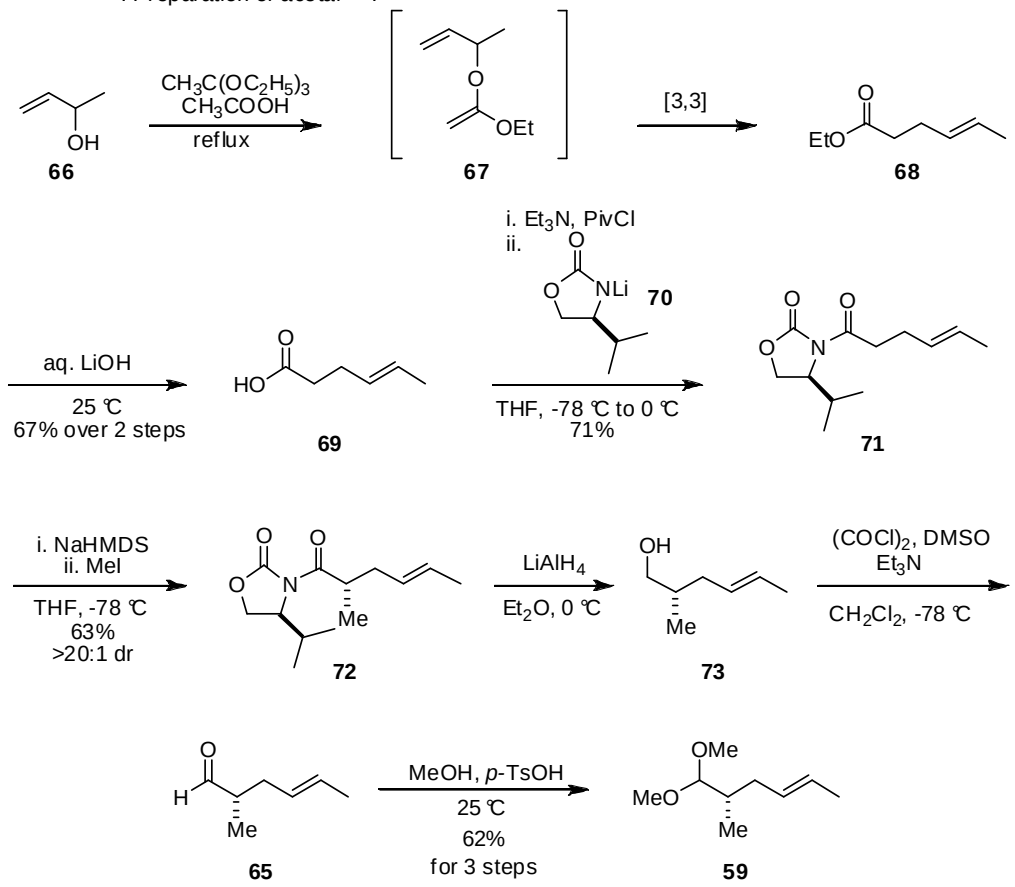
61 **63** **59**

5:1 *E* /*Z* isomers

64

An alternative strategy to synthesize aldehyde **65**, previously described by Evans, was instead employed in an effort to obtain acetal **59** (Scheme 1.17). Treatment of 3-buten-2-ol (**66**) with trimethyl orthoacetate and catalytic acid produced **67** *in situ* which underwent a Johnson-Claisen rearrangement to deliver isomerically pure ester **68**.[16] Ester **68** was saponified under basic conditions to form carboxylic acid **69**, which was transformed into the mixed anhydride upon treatment with **70** and triethylamine, and displaced by the lithiated oxazolidinone **71** to deliver acylated oxazolidinone **72**. An asymmetric alkylation employing LDA was used to install the stereocenter at C-10. Reductive cleavage of the oxazolindinone was affected utilizing $LiAlH_4$ to afford alcohol **73**, which was then oxidized under Swern conditions, and stirred in the presence of MeOH and *p*-TsOH to provide dimethyl acetal **59** in 62% yield for 3 steps.

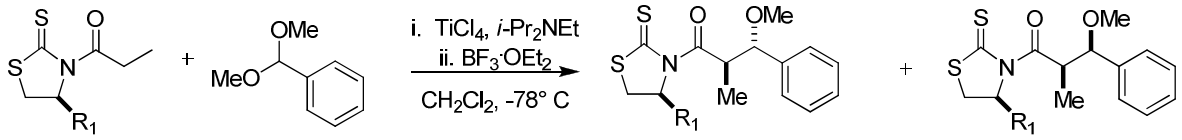
Scheme 1.17: Preparation of acetal **59**.



3. Attempts to improve the diastereoselectivity in the reaction of N-acyl thiazoldinethiones with dimethyl acetals

With dimethyl acetal **59** in hand, the key acetal aldol coupling was explored using a model system of benzaldehyde dimethyl acetal (**74**) and various thiazoldinethione chiral auxiliaries in attempts to improve the diastereoselection of the acetal aldol. Prior work by Urpi has shown that the use of benzaldehyde dimethyl acetal (**74**) in conjuction with valine derived thiazolidinethione chiral auxiliaries (**60**) can lead to *anti* aldol adducts (**75**) with moderate diastereoselection (Table 1.1, entry 1).[14a] Also formed in the reaction is the minor *syn* diastereomer **76**.

Table 1.1: Attempts to improve the diastereoselection in the acetal aldol addition with various thiazolidinethione chiral auxiliaries.



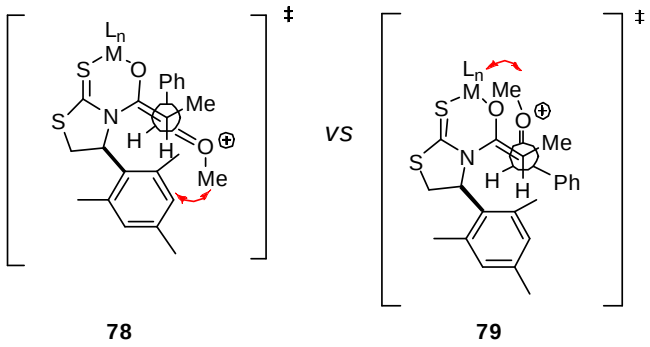
R_1 = *i*-Pr **60**
R_1 = Mes **77**
R_1 = Me **80**

74 **75** **76**

Entry	R^1 =	Yield	75:76
1	^{i}Pr	75%	87:13
2	Mes	64%	67:33
3	Me	64%	86:14

It was initially speculated that the use of a thiazolidinethione chiral auxiliary with a bulkier R group, such as the mesityl substituted thiazolidinethione **77**, would cause transition state **78** to be more favorable than transition state **79**, and lead to the formation of aldol adduct **75** in higher diastereselectivities than what Urpi had obtained with the use of valine derived thiazoldienthione **60** (Figure 1.8). However, the use of mesityl substiututed thiazoldinethione **77** caused a dramatic decrease in the diastereoselection under Urpi's conditions (Table 1.1, entry 2), which was likely due to an increased steric interaction between the *E*-oxocarbenium ion[14a] and the methyl groups of the mesityl (Figure 1.8). Since the use of a bulky chiral auxiliary had resulted in a decrease in diastereoselection, it was reasoned that the use of a smaller R group on the thiazolidinethione, such as a methyl, may provide enough steric bulk to provide the necessary facial selectivity for C-C bond formation, but not cause an unfavorable steric interaction with the *E*-oxocarbenium in transition state **78**, as the mesityl thiazoldinethione **77** had likely caused. A less sterically encumbered thiazolidinethione chiral auxiliary, **80**, derived from L-alaninol and prepared according to Le

Figure 1.8: Transition state considerations.



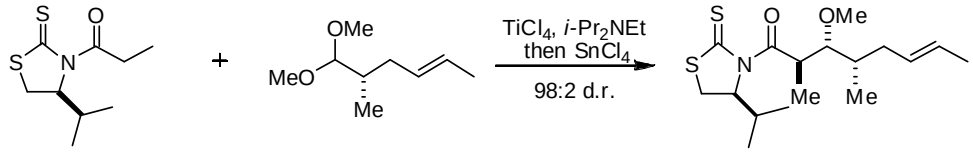
78 **79**

Corre's procedure[17] was then used in the asymmetric acetal aldol with benzaldehyde dimethyl acetal. This resulted in the formation of the products in an 86:14 ratio, which was not significantly different from what Urpi had reported (Table 1, entry 3).

4. Completion of (–)-pironetin

Instead of exploring the diastereoselectivity of the acetal aldol addition with chlorotitanium enolates of thiazolidinethiones further, the reaction conditions for the key acetal aldol reaction was probed employing dimethyl acetal **59** and valine derived thioimide **60** to form **81**. Initial attempts to utilize BF_3OEt_2 as a Lewis acid generated the product in low yields. Ultimately, $SnCl_4$, a stronger Lewis acid, was found to significantly affect the yield of the reaction (Table 1.2). The reaction was optimized by employing an excess of the

Table 1.2: Optimization of the key acetal aldol addition.



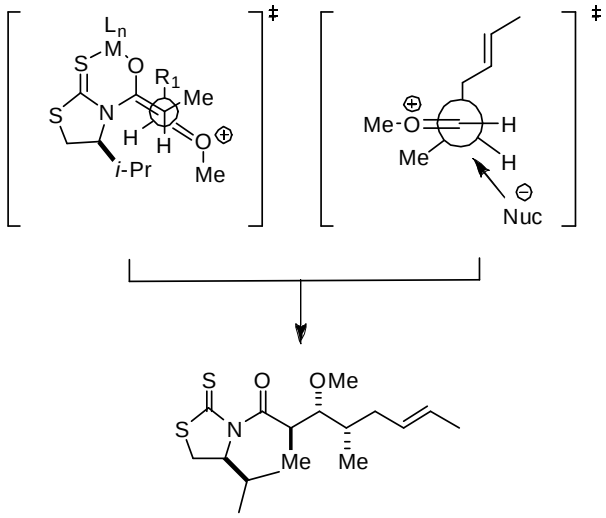
60 **59** **81**

Reaction Temperature	Yield
-78 ℃	16%
-50 ℃	33%
-20 ℃	64%

enolate (2 equivalents), using one equivalent of $SnCl_4$, and one equivalent of acetal **59** to generate aldol adduct **81** in 64% yield and 98:2 dr. The temperature of the reaction also had a pronounced effect, as the best yields were obtained when the reaction was warmed to -20 ℃ immediately following the addition of $SnCl_4$ and dimethyl acetal **59**. The high

diastereoselectivity observed in this case is explained by the presence of the α stereocenter of the acetal, which reinforces the favored transition state through Felkin control (Figure 1.9)

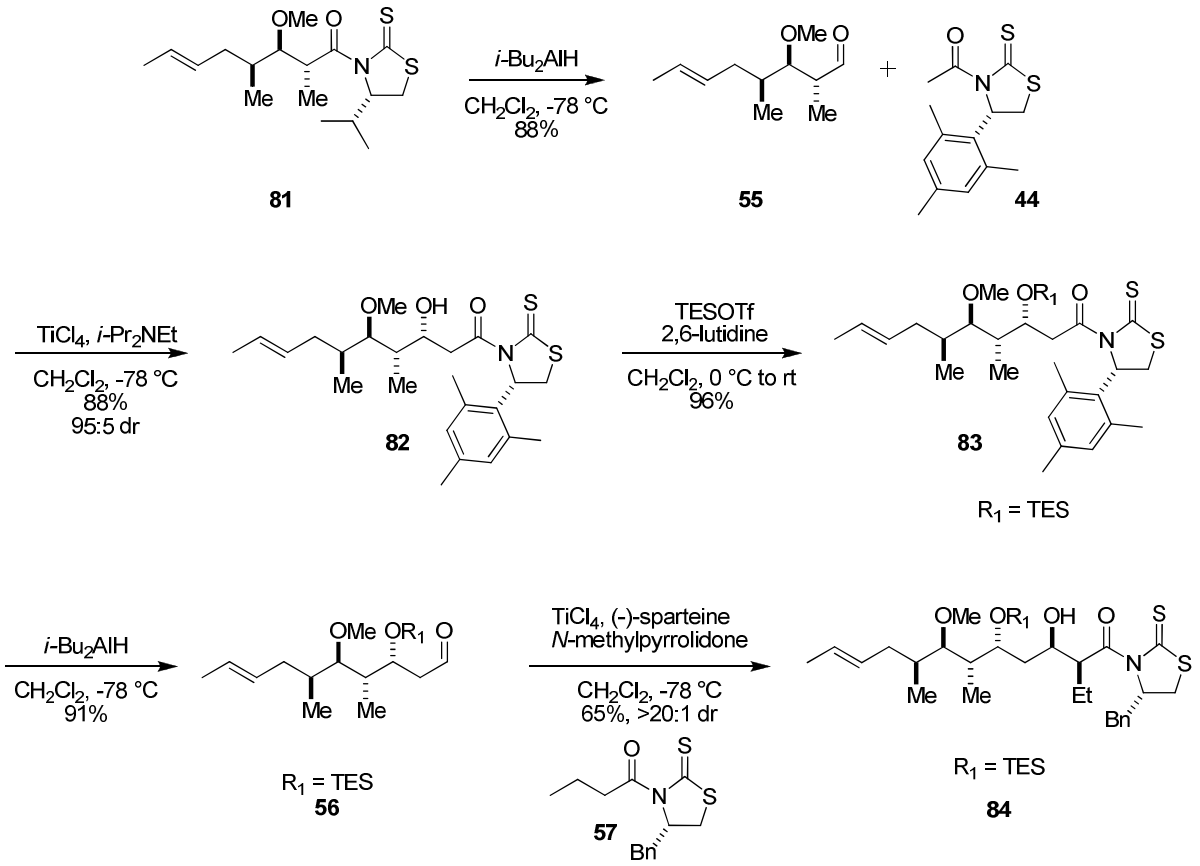
Figure 1.9: Explanantion of the high diastereselectivity observed in the acetal aldol addition of **59** with **75**.



81

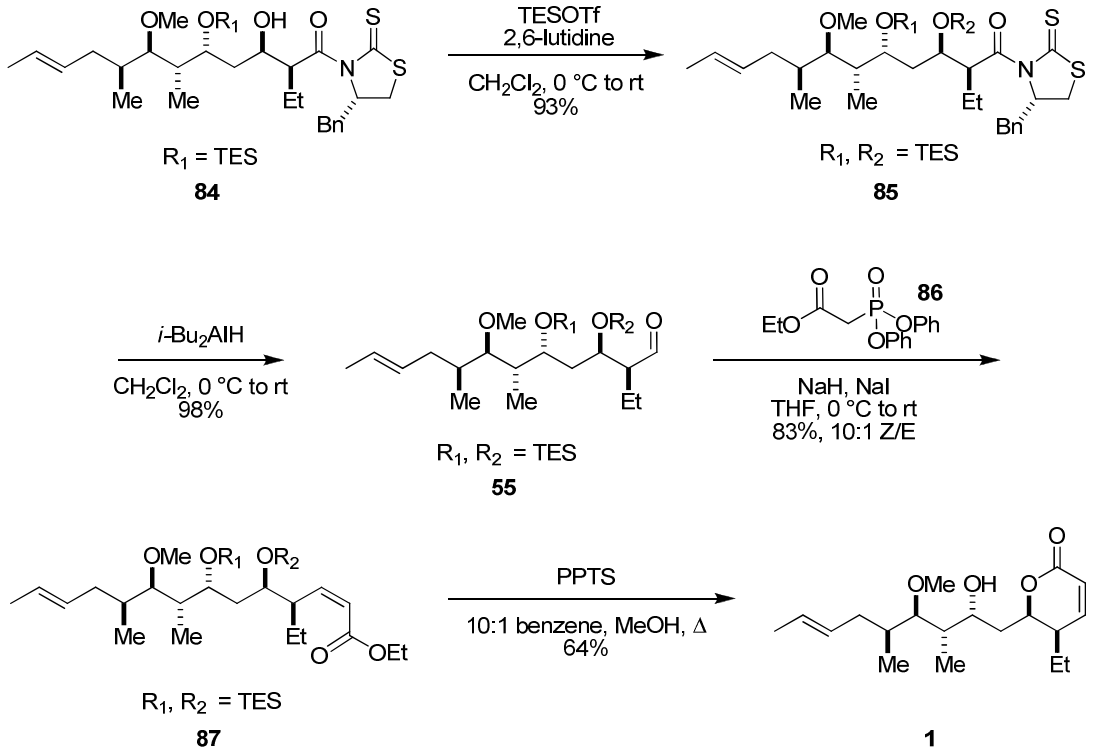
With aldol adduct **81** in hand, the auxiliary was reductively cleaved with *i*-Bu_2AlH to afford aldehyde **58**, which was immediately subjected to an acetate aldol reaction with thiazolidinethione **44** to afford alcohol **82** in 88% yield and 95:5 dr (Scheme 1.18). An excess of the enolate (1.5 equiv) was necessary to achieve complete conversion of the aldehyde to the aldol adduct. Protection of alcohol **82** as the triethylsilyl ether delivered thiazolidinethione **83**. Reductive removal of the auxiliary with *i*-Bu_2AlH[18] furnished aldehyde **56**, which was then subjected to an Evans *syn* aldol reaction[9] with thioimide **57**, affording aldol adduct **84** in >20:1 dr and 65% yield (Scheme 1.18).

Scheme 1.18: Preparation of aldol adduct **84**.



With all six stereocenters of (–)-pironetin installed, the synthesis proceeded with silylation of alcohol **84** to provide triethylsilyl ether **85**, which was then exposed to *i*-Bu_2AlH to effect reductive cleavage of the chiral auxiliary affording aldehyde **55** (Scheme 1.19). Thus, three iterative aldol reactions allowed the incorporation of 5 of the 6 stereocenters of pironetin, affording aldehyde **55** in 8 steps from known acetal **59**. To complete the synthesis, aldehyde **55** was treated with excess phosphonate **86**, to effect formation of *Z*-α,β unsaturated ester **87** as a 10:1 mixture of *Z/E* isomers.[19] Exposure of **87** to PPTS in 10:1 CH_2Cl_2/MeOH provided only the unprotected diol; however, upon heating ester **87** with PPTS in 10:1 benzene/MeOH to 60 °C both silyl ether p rotecting groups were cleaved and lactonization was induced to furnish (–)-pironetin (**1**) in 63% yield. Synthetic **1** was identical in all aspects to the natural product.

Scheme 1.19: Completion of (-)-pironetin.



C. Summary

In summary, the enantioselective total synthesis of (–)-pironetin was completed in 11 steps from previously prepared aldehyde **65** with an overall yield of 12.5%. Key steps include a highly diastereoselective acetal aldol addition, a highly diastereoselective acetate aldol addition, and a highly diastereoselective propionate Evans *syn*-aldol addition, all of which are controlled by thiazolidinethione chiral auxiliaries. The versatility of the chlorotitanium mediated asymmetric aldol reaction was demonstrated through an iterative sequence to rapidly construct pironetin in a highly stereoselective fashion.

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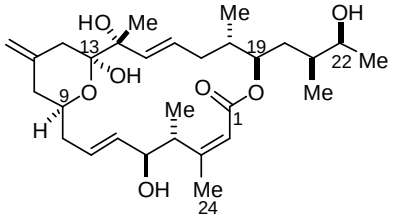
Chapter 2

Iriomoteolide 1a Background

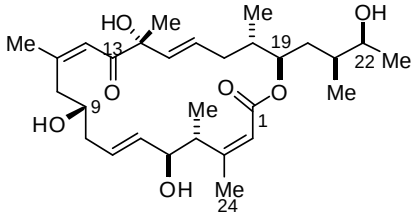
A. Isolation and biological activity

Marine dinoflagellates of the *Amphidinium* species are recognized as an important source of structurally diverse macrolides, termed amphidinolides, with noteworthy biological activity.[1] In the pursuit for new bioactive natural products, Tsuda and coworkers surveyed over 250 strains of the dinoflagellate sp. *Amphidinium* strain using a rapid identification technique known as one cell-PCR, which is based on identifiying a certain sequence of DNA that only macrolide producing *Amphidinium* strains possess.[2] From this analysis, and subsequent cytotoxic screening and metabolic analysis, *Amphidinium* strain HYA024 was identified as a producer of novel macrolides.[2] To date, four macrolides, iriomoteolide 1a (**2.1**), 1b (**2.2**), 1c (**2.3**), and 3a (**2.4**) have been isolated from strain HYA024, with three of the four displaying significant biological activity both *in vivo* and *in vitro* (Figure 2.1).[2-4]

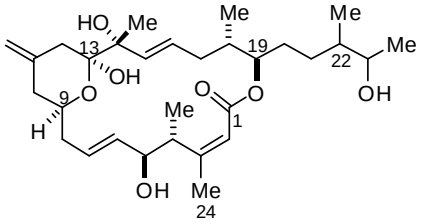
Figure 2.1: Macrolides isolated from *Amphidinium* strain HYA024.



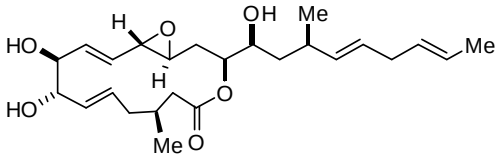
iriomoteolide 1a (**2.1**)



iriomoteolide 1b (**2.2**)



iriomoteolide 1c (**2.3**)



iriomoteolide 3a (**2.4**)

The structures and relative sterochemistry of the iriomoteolides were elucidated utilizing detailed 2D-NMR studies, while the absolute stereochemistry was assigned using a modified variant of Mosher's method.[2-4] Iriomoteolide 1a was originally identified to be a 20-membered macrolide, which contains three alcohols, one of which is tertiary. Other structural attributes include a hemiketal embedded in a tetrahydropyran ring, an exocyclic olefin, and three endogenous olefins.[2] Notably, iriomoteolide 1a was identified as the first isolated member from the amphidinolide family of natural products which possesses a *Z*-olefin.[2] Two other macrolides isolated, later identified as iriomoteolides 1b (**2.2**) and 1c (**2.3**), were also identified to contain a 20-membered macrocyclic ring system.[3] Based on NMR data, iriomoteolide 1b is thought to have only a monocyclic ring system, and instead of a C9-C13 tetrahydropyran ring system, which iriomoteolide 1a possesess, iriomoteolide 1b contains a ketone at C13 in conjugation with an *E* alkene at C11-C12, and a free hydroxyl group at C9.[3] Iriomoteolide 1c is thought to contain the same ring systems as iriomoteolide 1a, but has a 4-hydroxy-3-methyl pentyl sidechain at C19 containing two unidentified stereocenters, while iriomotelide 1a has a 3-hydroxy-2-methyl butyl side chain at C19.[3]

Iriomoteolide 3a (**2.4**) was also isolated from strain HYA024, and is a 15-membered macrolide containing an allyl epoxide.[4]

Notably, iriomoteolide 1a exhibits potent cytotoxicity against the human B lymphocyte DG-75 cells (IC_{50} = 0.002 μg/mL), which is 20 times as potent as the anticancer therapeutic drug doxorubicin (IC_{50} = 0.04 μg/mL), and is one of the most cytotoxic macrolides isolated from the *Amphidinium* species to date.[2] Iriomoteolide 1a has also been shown to possess potent cytotoxicity against Epstein-Barr virus (EBV) infected human B-lymphocyte Raji cells (IC_{50} = 0.003 μg/mL).[2] Tsuda et al. speculate that this toxicity may be due to the presence of the hemiketal embedded within a tetrahydropyran motif, as other highly cytotoxic marine natural products, an example being peloruside A, have also shown potent cytotoxicity and possess this architecture.[2,5] Remarkably, iriomoteolide 1c, which also possesses a hemiketal embedded within a tetrahydropyran ring, has exhibited comparable cytotoxicity (IC_{50} = 0.002 μg/mL against human B lymphocyte DG-75 cells, IC_{50} = 0.004 μg/mL against Epstein-Barr virus (EBV) infected human B-lymphocyte Raji cells) to iriomoteolide 1a, while iriomoteolide 1b is 450 times less potent (IC_{50} = 0.09 μg/mL) against human B lymphocyte DG-75 cells.[3] This data seems to support Tsuda's hypothesis that the hemiketal motif of iriomoteolides 1a and 1c may play a significant role in the biological mechanism of action. To date, there are no reports of biological studies or biosynthetic studies of the iriomoteolides.

B. Previous Syntheses of Iriomoteolide 1a

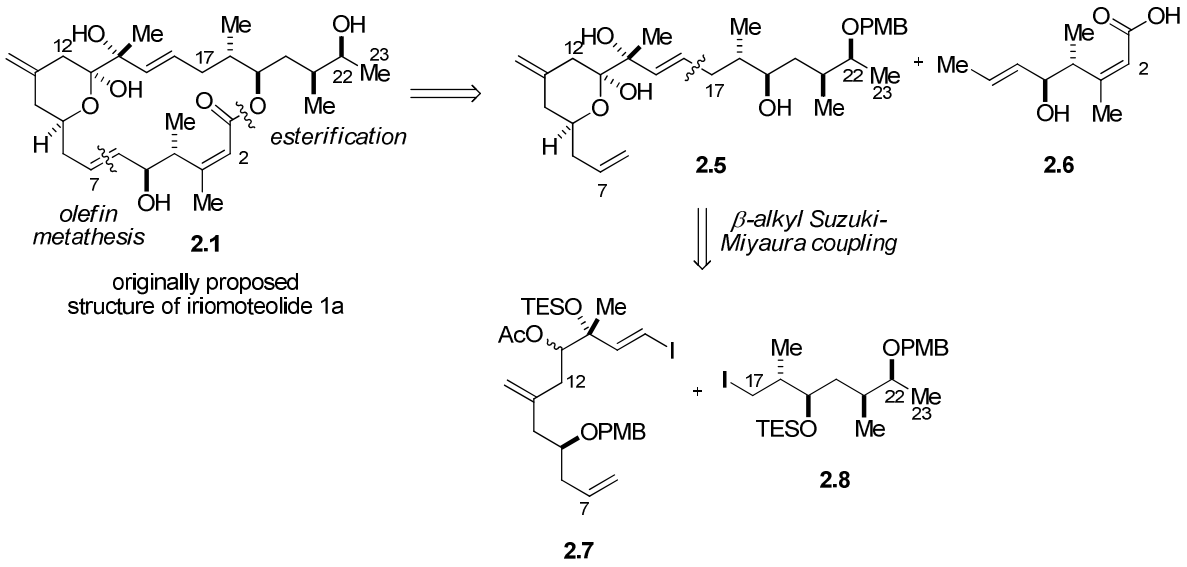
Because of the interesting biological profile of iriomoteolide 1a, several groups have undertaken the total synthesis of **2.1**. The groups of Loh,[6] Paterson,[7] Zhao,[8] Li,[9] and Dai[10] have reported approaches to complex fragments of iriomoteolide 1a, while Horne,[11] Ghosh,[12] and Yang[13] have completed the total synthesis of iriomoteolide 1a (**2.1**). During

the course of their synthetic studies, Horne, Ghosh, and Yang independently ascertained that the proposed structure of iriomoteolide 1a had been misassigned.[11-13] Their various approaches to the proposed structure and conclusions about the identity of the natural product are discussed in the proceeding sections.

1.1 Horne's Approach to Iriomoteolide 1a

Horne's retrosynthetic plan for iriomoteolide 1a is depicted in Scheme 2.1. Initially, it was believed that iriomoteolide 1a (**2.1**) would arise from an esterification of secondary alcohol **2.5** with acid **2.6**, followed by a late stage RCM to form **2.1**. Hemiketal **2.5** could be accessed from a β-alkyl Suzuki-Miyaura coupling of vinyl iodide **2.7** and alkyl iodide **2.8**.[11]

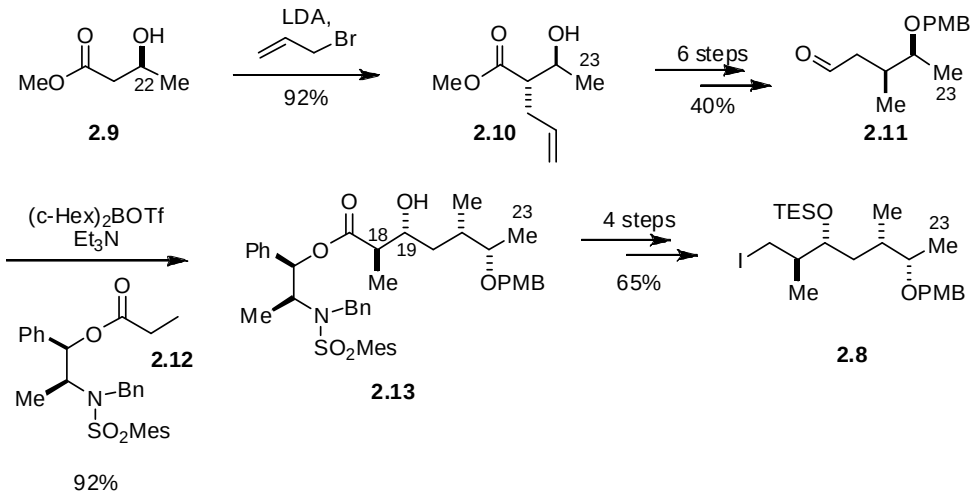
Scheme 2.1: Horne's retrosynthetic analysis of iriomoteolide 1a (**2.1**)



Preparation of alkyl iodide **2.8** began with a Frater-Seebach alkylation of enantiomerically enriched (3*S*)-methyl hydroxybutyrate (**2.9**), containing the correct orientation of the C22 hydroxyl, to provide allylated product **2.10** in 92% yield (Scheme 2.2).[14] In six steps, involving protection of the secondary alcohol at C22, reduction of the ester to an alkane, and cleavage of the terminal olefin using ozonoloysis, aldehyde **2.11** was formed which underwent a Masamune *anti* aldol with norphedrine based chiral auxiliary **2.12**

to generate aldol adduct **2.13** containing the stereocenters at C18 and C19 in 92% yield, and as a single diastereomer. In four additional steps, the resultant C19 hydroxyl was protected, the chiral auxiliary was cleaved under standard reduction conditions, and the resultant primary alcohol was transformed into alkyl iodide **2.8** in 65% yield over 4 steps and 12 steps overall.[14]

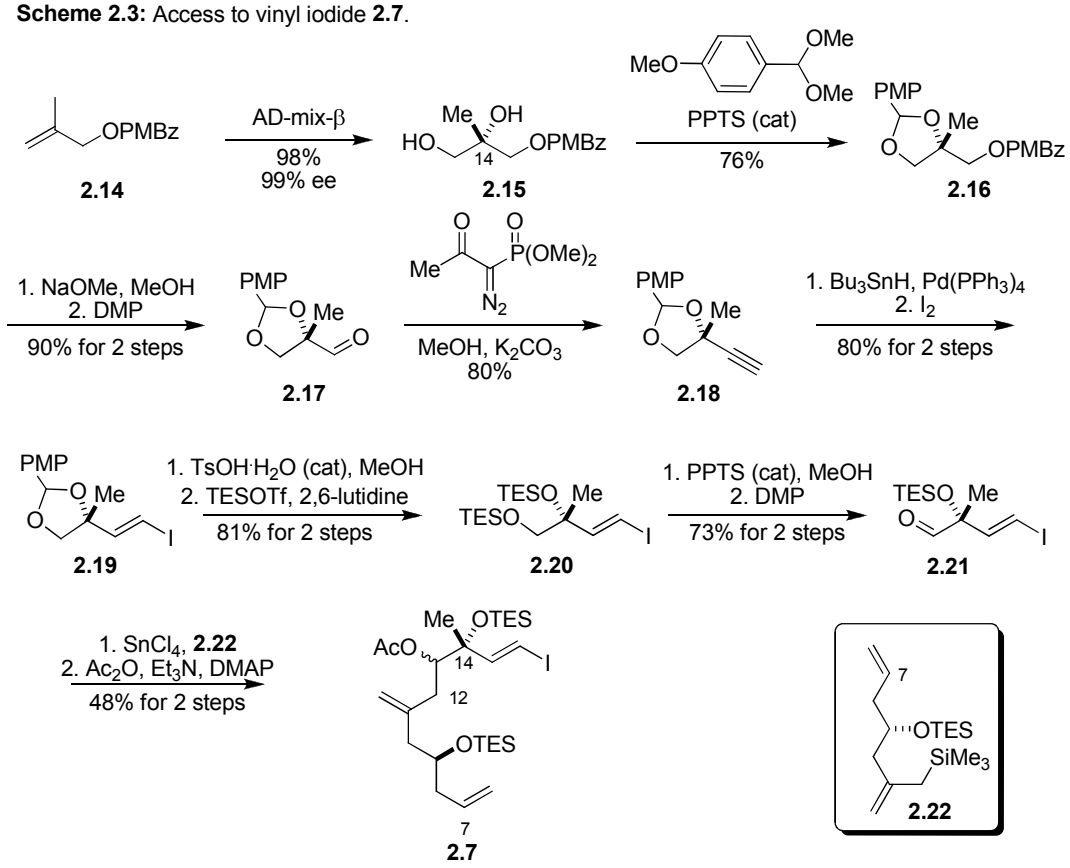
Scheme 2.2: Preparation of alkyl iodide **2.8**.



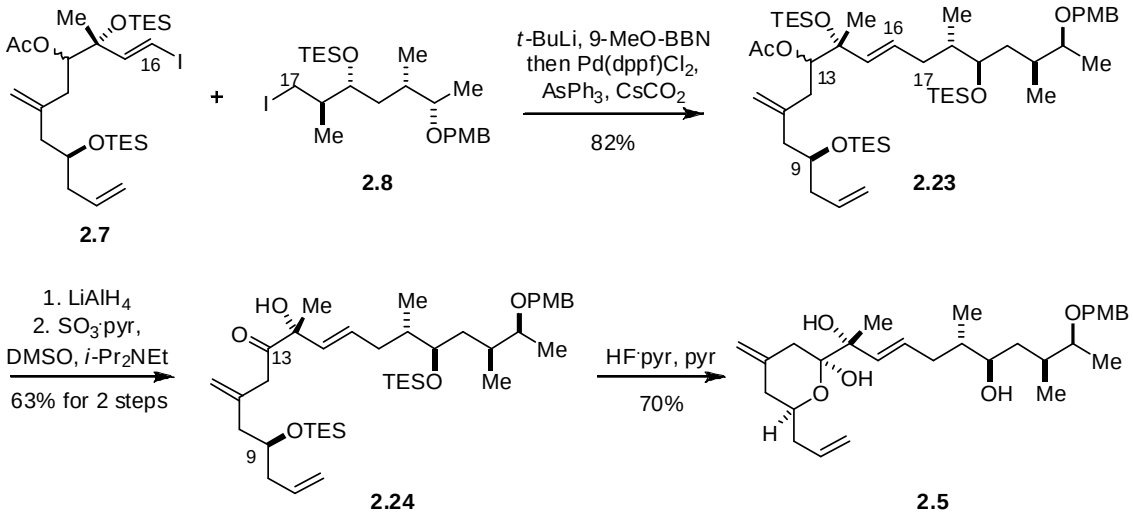
Construction of vinyl iodide **2.7** commenced with a Sharpess asymmetric dihydroxylation of olefin **2.14** to furnish tertiary alcohol **2.15**, which is the tertiary alcohol at C14 present in the natural product (Scheme 2.3).[15] Protection of the resultant diol as PMP acetal **2.16**, cleavage of the PMBz protecting group, followed by oxidation of the resultant primary alcohol provided aldehyde **2.17**.[14] In a three step sequence beginning with an Ohira-Bestmann reaction to produce alkyne **2.18**, followed by hydrohalogenation by sequential treatment with tributyl tin hydride in the presence of $Pd(PPh_3)_4$ and then iodination, *E*-vinyl iodide **2.19** was furnished. Deprotection of the PMP acetal under acidic conditions and protection of the resultant diol as the bis TES ether delivered **2.20**, which underwent a selective primary TES ether deprotection in the presence of catalytic PPTS and MeOH. Oxidation of the primary alcohol with Dess-Martin periodinane, produced aldehyde

2.21. Subseqent use of **2.21** in a Sakuri reaction with allyl silane **2.22**,[15] allowed for the C12-C13 carbon-carbon bond to be forged. Protection of the resultant secondary alcohol as the acetate provided vinyl iodide fragment **2.7**.

Scheme 2.3: Access to vinyl iodide **2.7**.



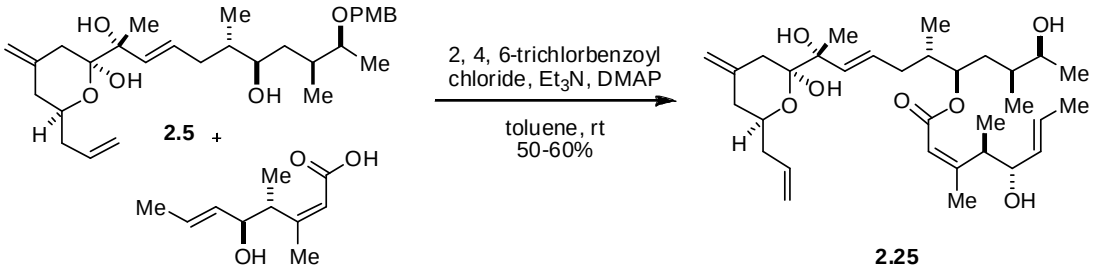
Scheme 2.4: Suzuki coupling of fragments **2.7** and **2.8**.



With the two necessary fragments in hand, exposure of alkyl iodide **2.8** and vinyl iodide **2.7** to Suzuki reaction conditions smoothly coupled the two fragments to form the C16-C17 bond in 82% yield (Scheme 2.4). The acetate of **2.23** was then cleaved using $LiAlH_4$ with concomitant loss of the tertiary TES ether, while the secondary TES ether remained intact.[14] Oxidation of the C13 hydroxyl delivered ketone **2.24**; subseqent exposure to mild ketalization conditions to prevent migration of the C11 olefin into conjugation, furnished hemiketal **2.5**.[14]

Attempts to complete the synthesis of the proposed structure hinged upon a successful Yamaguchi esterification of hemiketal **2.5** and acid **2.6**. However, due to the instability of the hemiketal unit, a 50-60% yield of ester **2.25** was obtained utilizing Yamaguchi esterifcation conditions, and subsequent chromatographic separation of **2.25** from side products of the reaction proved problematic (Scheme 2.5).[11]

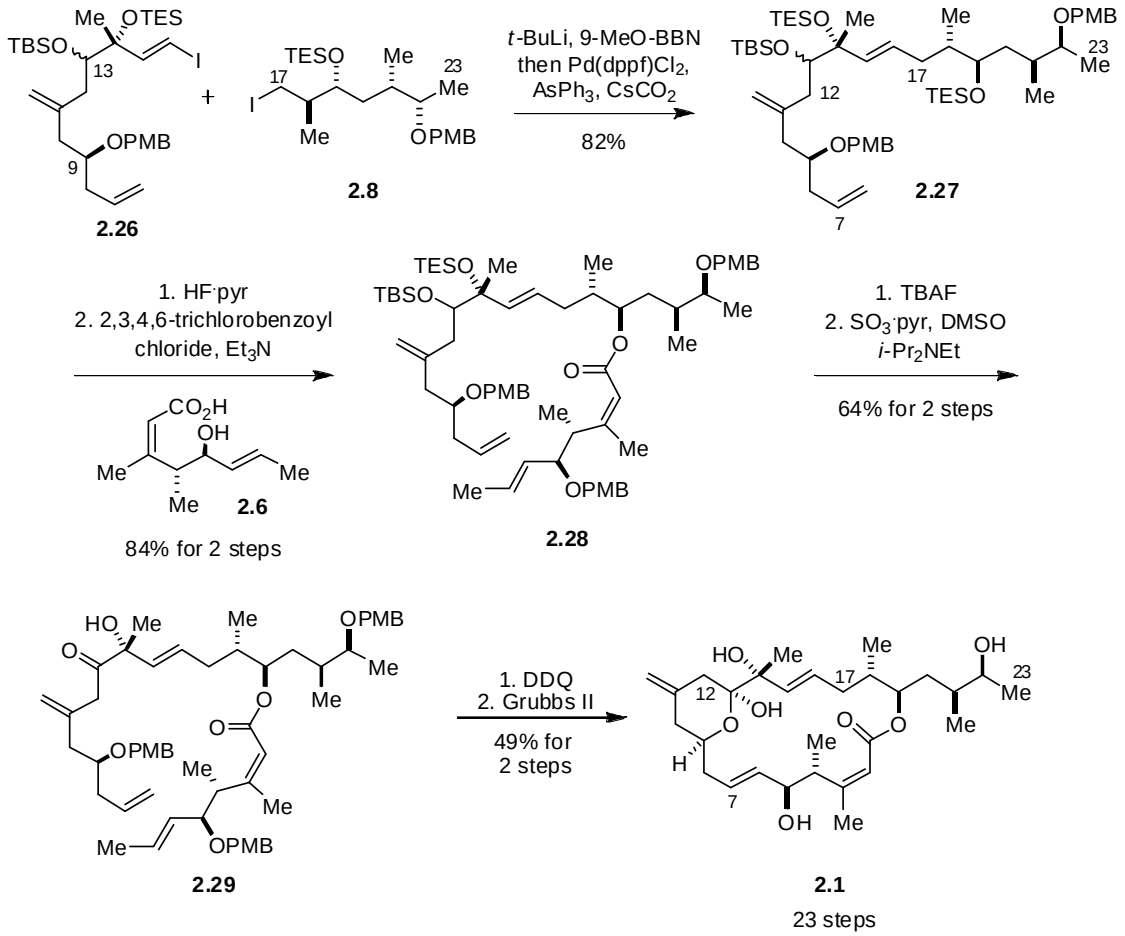
Scheme 2.5: Yamaguchi coupling of **2.5** and **2.6**.



Horne instead took an alternative approach to iriomoteolide 1a which would install the sensitive hemiketal functionality at the end of the synthesis. A few protecting group modifications were necessary in order to execute this strategy: the C9 TES ether was replaced as a PMB ether, while the C13 acetate was changed to a TBS ether to form new vinyl iodide **2.26** (Scheme 2.6).

To complete the synthesis, vinyl iodide fragment **2.26** was coupled under Suzuki conditions with alkyl iodide **2.8** to furnish the coupled product **2.27** (Scheme 2.6).[11] Selective deprotection of the TES ether of C19 followed by Yamaguchi esterification with acid **2.6** afforded **2.28** in higher yields (84% for 2 steps) compared to attempts with the hemiketal moiety already installed (Scheme 2.5). Deprotection of the silyl protecting groups and oxidation of the resultant diol delivered ketone **2.29** which was exposed to DDQ to effect global deprotection of the PMB groups with concomitant hemiketal formation. Formation of the macrocycle with Grubbs' 2nd generation catalyst gave the proposed structure of iriomoteolide 1a (**2.1**) in 49% yield over 2 steps and in 23 steps as the longest linear sequence.[11]

Scheme 2.6: Horne's completion of **2.1**.

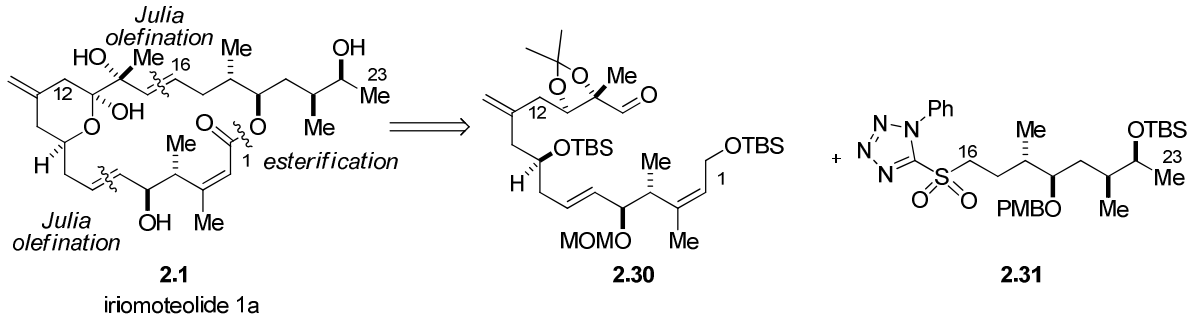


Comparison between synthetic iriomoteolide 1a and what was reported in the literature for the natural material revealed that the natural product was misassigned. Horne notes that the main discrepancies between the two spectra reside with the proton and carbon chemical shifts at C4, as synthetic iriomoteolide 1a C4 proton appears at 3.95 ppm and the carbon shift for C4 occurs at 41.0 ppm, compared to the natural compound which occurs at 2.46 ppm and 47.9 ppm for proton and carbon, respectively. Horne speculates that the discrepancies between the natural product and synthetic iriomoteolide 1a may reside in the C2-C3 olefin geometry, suggesting that the C2-C3 olefin is actually an *E* olefin and not a *Z* olefin, as it was initially assigned.

1.2 Ghosh's total synthesis of the proposed structure of iriomoteolide 1a

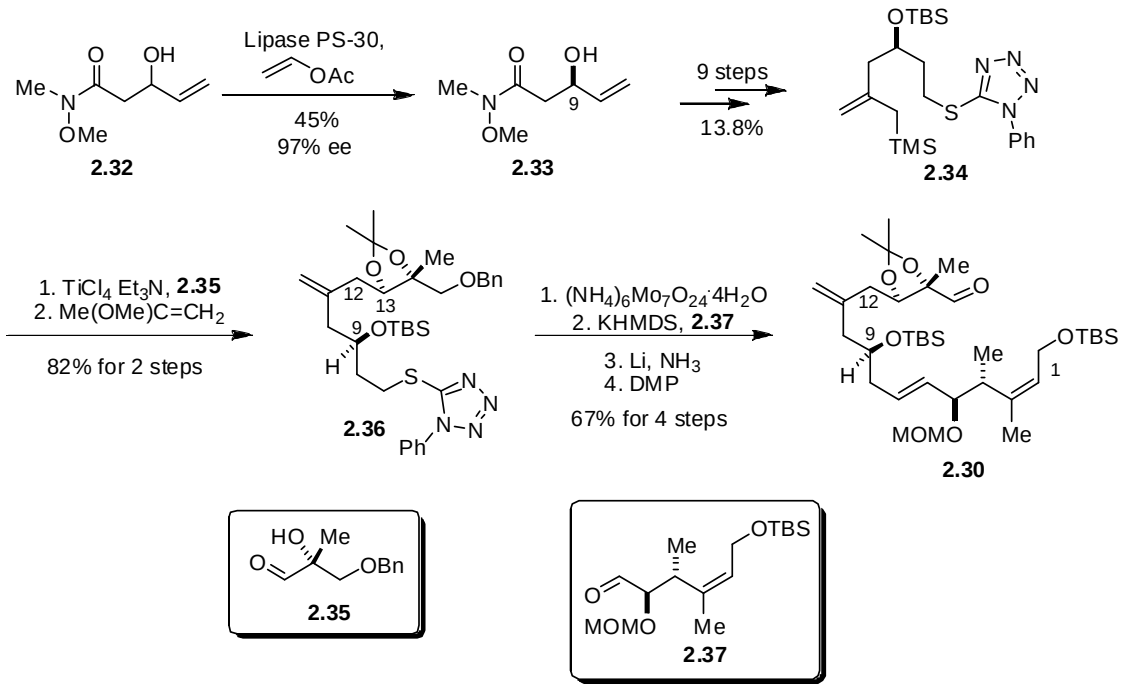
Ghosh concurrently published a synthesis of the proposed structure of iriomoteolide 1a in 2010. His approach, depicted in Scheme 2.7, relied on the convergency of two aldehyde **2.30** and sulfone **2.31** through a Julia- Kocienski olefination.[12]

Scheme **2.7:** Ghosh's retrosynthetic analysis of iriomoteolide 1a (**2.1**).



Construction of aldehyde **2.30** began with an enzymatic kinetic resolution of Weinreb amide **2.32** to deliver enantiomerically enriched β-hydroxy amide **2.33** in 45% yield and 97% *ee*, containing the C9 stereocenter (Scheme 2.8). In nine steps, **2.33** was converted to allyl silane **2.34** in 13.8% overall yield. Allyl silane **2.34** underwent a chelation controlled Sakurai addition with aldehyde **2.35**, prepared in four steps from 2- methylene-1,3-propanediol to deliver a diol as a 8:1 mixture of diastereomers at C13 which was then protected to provide acetonide **2.36**. Oxidation of the sulfide to the sulfone, and a Julia Kocienski olefination with aldehyde **2.37**, prepared in 15 steps from commercially available *tert*-butyl acetate, delivered the C1-C15 fragment of iriomoteolide 1a.[16]

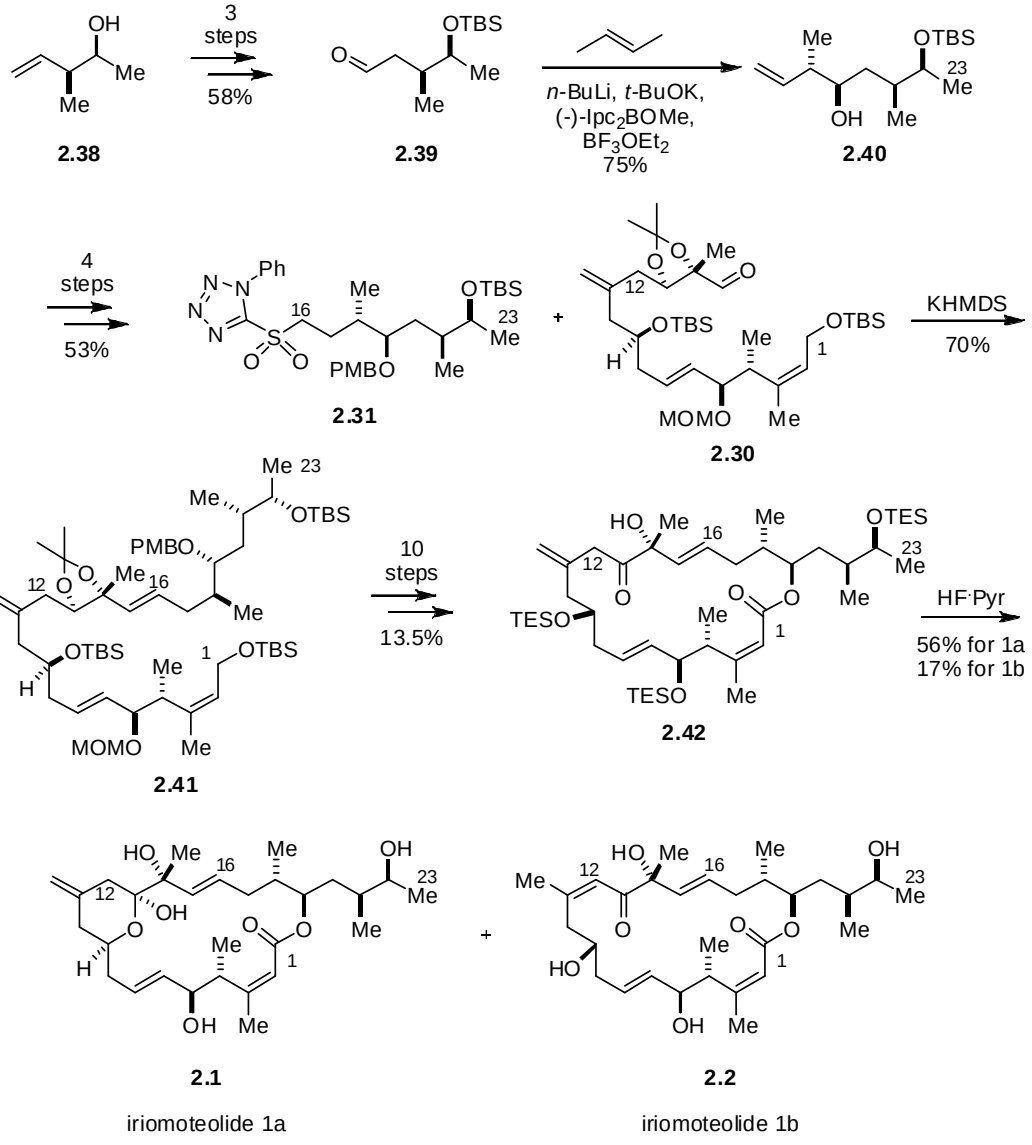
Scheme 2.8: Preparation of aldehyde fragment **2.30**.



Sulfone **2.31** was prepared from enantiomerically enriched alcohol **2.38**, prepared via a Brown crotylboration of acetaldehyde (Scheme 2.9). In three steps, alcohol **2.38** was elaborated into aldehyde **2.39** which underwent a second Brown crotylboration utilizing (–)-β-methoxydiisopinocamphenylborane and t*rans*-2-butene to deliver the *anti* alcohol **2.40** as a 10:1 mixture of diastereomers. Construction of sulfone **2.31** was completed after four additional manipulations, involving protection of the C19 hydroxyl group as the PMB ether, hydroboration of the olefin, and formation of the sulfone.[12]

To complete the synthesis, a Julia-Kocienski olefination was used to unite sulfone **2.31** and aldehyde **2.30** to provide olefin **2.41** in 70% yield. In ten steps, involving changes in oxidation state and protecting group modifications, the macrocycle is eventually closed utilizing a Yamaguchi macrolactonization to furnish **2.42**. Global deprotection of **2.42** followed by concomitant hemiketal formation was realized with HF·pyr to deliver the proposed structure of iriomoteolide 1a (**2.1**) in 56% yield and 17% of the proposed structure of iriomoteolide 1b (**2.2**) in 31 steps as the longest linear sequence.

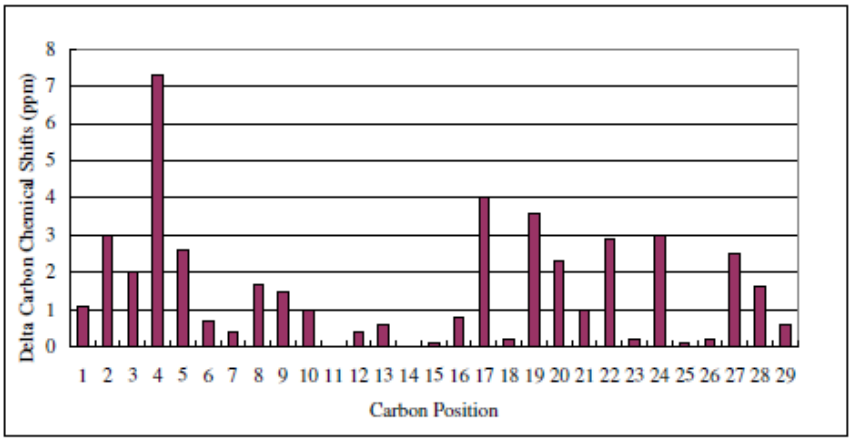
Scheme 2.9: Completion of the proposed structure of iriomoteolides 1a and 1b.



Ghosh also notes the discrepancies in the NMR data present between the proposed structure of iriomotoelide 1a and what was reported for the natural substance by publishing a histogram of differences in carbon shifts between the two spectra (Figure 2.2). Ghosh suggests, as Horne also suggested, that the enoate olefin geometry is *E* and not *Z* as indicated in the isolation paper, based on C24 chemical shift (1.96 and 20.8 ppm for synthetic **2.1** compared to 2.12 and 23.8 for natural **2.1**). In addition, Ghosh suggests that the discrepancy between the H1 and C13 shifts for C4 of the natural product versus

synthetic iriomoteolide 1a could indicate that the synthesized material is an epimer at the C4 position of the natural product.[12] The spectral data for synthetic iriomoteolide 1b also did not match the data reported for the natural material in the original isolation paper.

Figure 2.2: Ghosh's historgram of differences in C13 chemical shift for synthetic iriomoteolide 1a versus natural iriomoteolide 1a.[12]

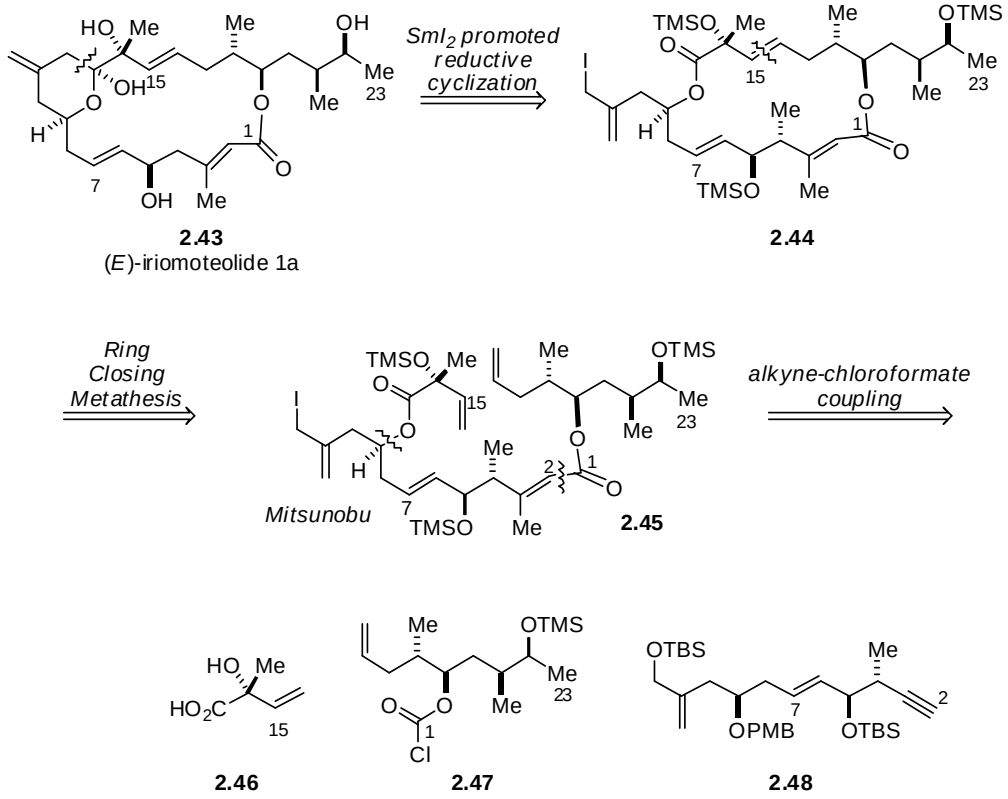


1.3 Yang's Approach to Iriomoteolide 1a

Yang and coworkers amended their strategy to the natural product to account for the discrepancy in enoate geometry, which they determined to be incorrectly assigned during the course of their synthetic studies, and hence targeted the proposed structure with the *E* enoate geometry (**2.43**, Scheme 2.10).[13] The primary reason they speculated that the enoate geometry was misassigned was with regards to the chemical shift at C24, which was thought to be too far downfield to be a *Z*-enoate (2.12 ppm and 23.8 ppm for proton and carbon, respectively), and was consistent with an *E*-enoate.[13,17] Additionally, Yang speculated that the ROESY correlation between C24-Me and C2-H was just a remnant of a COSY correlation which are also present in ROESY spectra, and should be disregarded (Figure 2.1).[13] Yang's retrosynthetic plan is highlighted in scheme 2.10. The hemiketal of (E)-iriomoteolide 1a (**2.43**) would be formed from an intramolecular reductive cyclization of iodide **2.44**.[13] The macrocyle would be installed through a ring closing metathesis across

the C15-C16 olefin from diene **2.45**. Diene **2.45** would be prepared via a Mitsunobu with carboxylic acid fragment **2.46** and a base mediated alkyne chloroformate coupling between chloroformate **2.47** and alkyne **2.48**.[13]

Scheme 2.10: Yang's approach to (*E*)-iriomoteolide 1a



2.43
(*E*)-iriomoteolide 1a

2.44

2.45

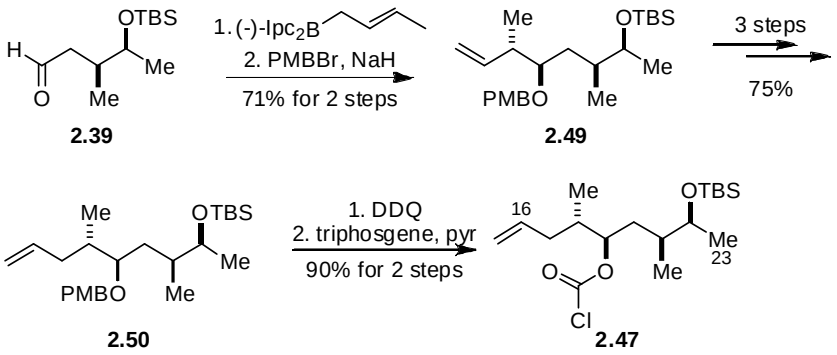
2.46

2.47

2.48

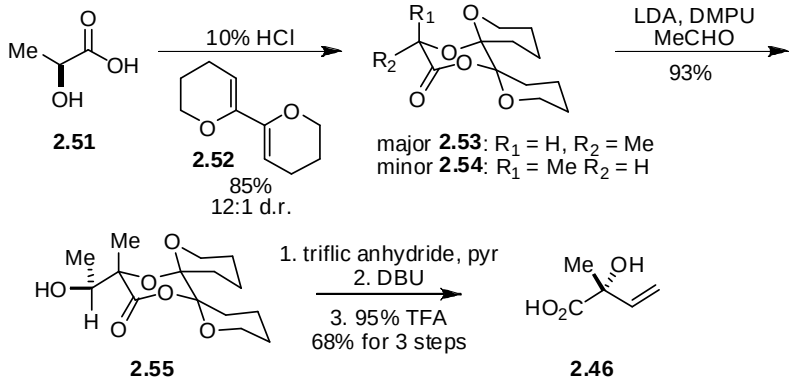
Chloroformate **2.47**, which embodies carbons C16-C23, was synthesized along a similar route as Ghosh's approach to the same fragment (Scheme 2.11).[13] Aldehyde **2.39** was prepared in four steps from acetaldehyde utilizing a Brown crotylation. Aldehyde **2.39** was then subjected to an iterative Brown crotylboration, and the resultant secondary hydroxyl group at C19 was protected to furnish PMB ether **2.49**. In three steps, PMB ether **2.49** was homologated to olefin **2.50**. Deprotection of the PMB ether followed by reaction of the secondary alcohol with triphosgene furnished chloroformate **2.47**.

Scheme 2.11: Yang's approach to the C16-C23 fragment of **2.1**.



Carboxylic acid **2.46** was synthesized according to Zhang's procedure (Scheme 2.12). Treatment of (*S*)-lactic acid (**2.51**) with acid and bis-dihydropyran **2.52** under Ley's conditions generated the "dispoke protected lactate" in a 12:1 d.r. with predominant diastereomer **2.53** having the methyl group occupying the equatorial position.[19] An aldol reaction of acetaldehyde and "dispoke" **2.53** yielded secondary alcohol **2.55** as the predominant diastereomer, which was tosylated, eliminated, and the auxiliary cleaved under acidic conditions to generate carboxylic acid **2.46**.[18]

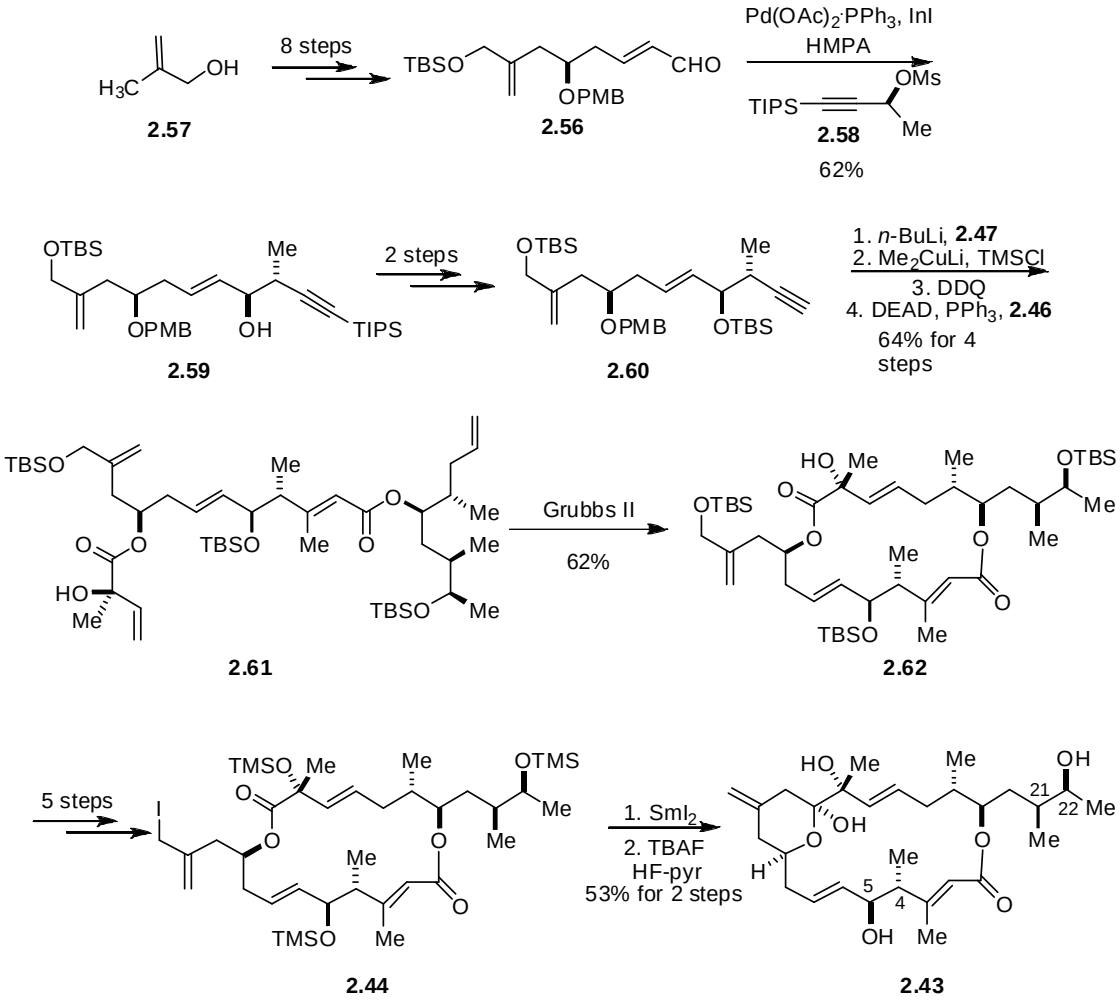
Scheme 2.12: Yang's approach to carboxylic acid **2.46**.



To synthesize alkyne **2.48**, Aldehyde **2.56**, which was formed in 8 steps for β-methallyl alcohol (**2.57**),[20] underwent an asymmetric propargyl addition with **2.58** via formation of the umpolung π allyl-In species, to provide secondary alcohol **2.59** in 62% yield

(Scheme 2.13). Deprotection of the TIPS alkyne and reprotection of the secondary alcohols as the silyl ethers delivered alkyne fragment **2.60**. Coupling of chloroformate **2.47** and acetylene **2.60** was accomplished under basic conditions to form an alkynoic ester, which was subjected to a cuprate addition employing TMSCl and the Gillman reagent to provide the desired *E*-enoate in 98% yield and a 1:10 *Z/E* ratio. At this point, oxidative cleavage of the PMB ether, followed by a Mitsunobu reaction with acid **2.46** formed trienyne **2.61**, which underwent smooth ring closing metathesis in the presence of Grubbs' 2nd generation catalyst to form **2.62**. Remarkably, **2.62** was obtained in 62% yield, with the *E* isomer being formed exclusively. In five steps, the primary TBS was transformed into iodide **2.44**, which was exposed to reductive cyclization conditions employing SmI_2 followed by global deprotection of the silyl ethers to give (*E*)-iriomoteolide 1a (**2.43**) in 53% yield over 2 steps and 22 steps as the longest linear sequence.[13]

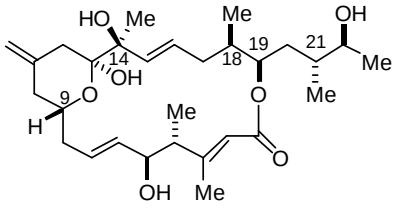
Scheme 2.13: Completion of (*E*)-iriomoteolide 1a (**2.43**).



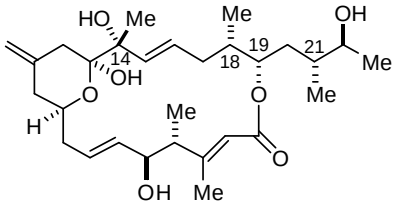
Comparison of the spectroscopic data for (*E*)-iriomoteolide 1a (**2.43**) to the natural product revealed that the synthesized structure is likely a diasteromer of the natural product, with one or more stereocenters being misassigned. Yang points out that the configurational analysis (analyzed by *J* couplings) for the C4-C5 and C21-C22 stereocenters in the original isolation paper is questionable, as the H23, H25, and H29 each belong to a conformationally unbiased methyl group, and is therefore not a reliable means of garnering coupling constants. This makes the assignment of all stereocenters in iriomoteolide 1a questionable, since their assignments were based on the correct assignment at C4-C5 and C21-C22.

Yang also synthesized two additional diastereomers (**2.63** and **2.64**, Figure 2.3) along the same synthetic sequence, in which stereocenters at C9, C14, C18, C19, and C21 differ from the proposed structure. These structures also did not match the data reported for the natural substance.

Figure 2.3: Other diastereomers of **2.43** prepared by Yang.



2.63



2.64

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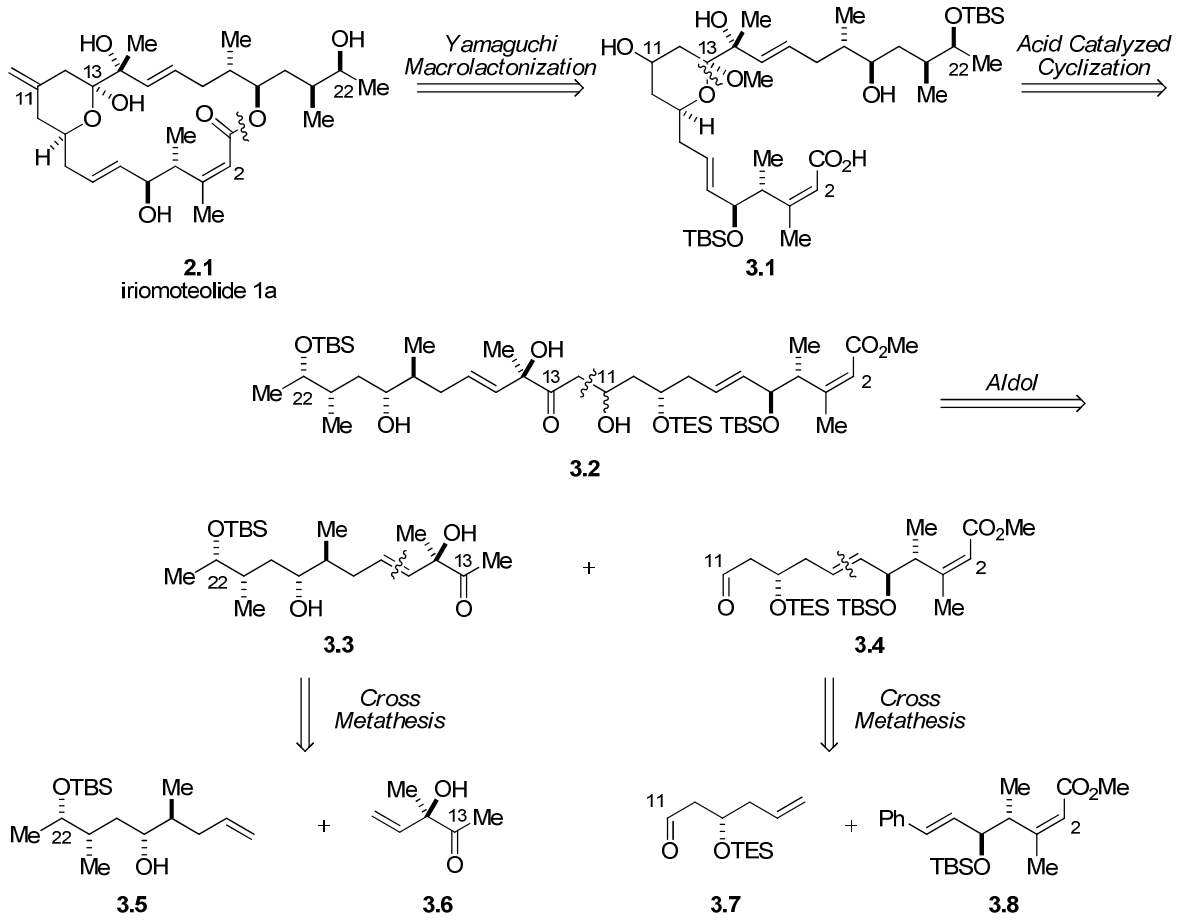
Chapter 3

Synthetic Studies Directed Toward the Total Synthesis of Iriomoteolide 1A

A. Retrosynthesis of iriomoteolide 1a

The major bond disconnections for iriomoteolide 1a are highlighted in scheme 3.1. It was envisioned that iriomoteolide 1a (**2.1**) would arise through a highly convergent approach in which the 20-membered macrolide would be installed via a late stage Yamaguchi macrolactonization of seco-acid **3.1**. Acid catalyzed deprotection of the triethylsilyl ether protecting group at C9 with concomitant cyclization of ketone **3.2** would afford mixed methyl ketal **3.1**. Ketone **3.2** was envisaged to result from a nonselective aldol reaction of ketone **3.3** and aldehyde **3.4**. It was thought that ketone **3.3** could be prepared via a cross metathesis of secondary alcohol **3.5** and tertiary alcohol **3.6**, and aldehyde **3.4** would also be prepared utilizing a cross metathesis of aldehyde **3.7** and ester **3.8**.

Scheme 3.1: Retrosynthetic analysis of iriomoteolide 1a (**2.1**).



2.1
iriomoteolide 1a

3.1

3.2

3.3

3.4

3.5

3.6

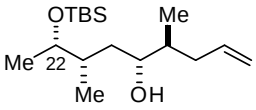
3.7

3.8

B. Preparation of the C16-C23 fragment of iriomoteolide 1a

Initial efforts toward the total synthesis of iriomoteolide 1a focused on the preparation of secondary alcohol **3.5** (Figure 3.1) utilizing the thiazolidinethione technology developed in the Crimmins laboratory to install all four stereocenters.[1-2] The stereocenters at C21 and C22 could be installed by performing an Evans *syn* aldol addition with (*R*)-benzyl thiazolidinethione **3.9** and acetaldehyde to deliver aldol adduct **3.10** in 87% yield and >20:1 d.r. (Scheme 3.2, **A**),[1,2] or alternatively a non-Evans *syn* aldol addition with (*S*)-benzyl thiazolidinethione **3.11** and acetaldehyde, which generated aldol adduct **3.12** in 80% yield and 20:1 d.r.[2] (Scheme 3.2, **B**). Due to a global shortage of (–)-

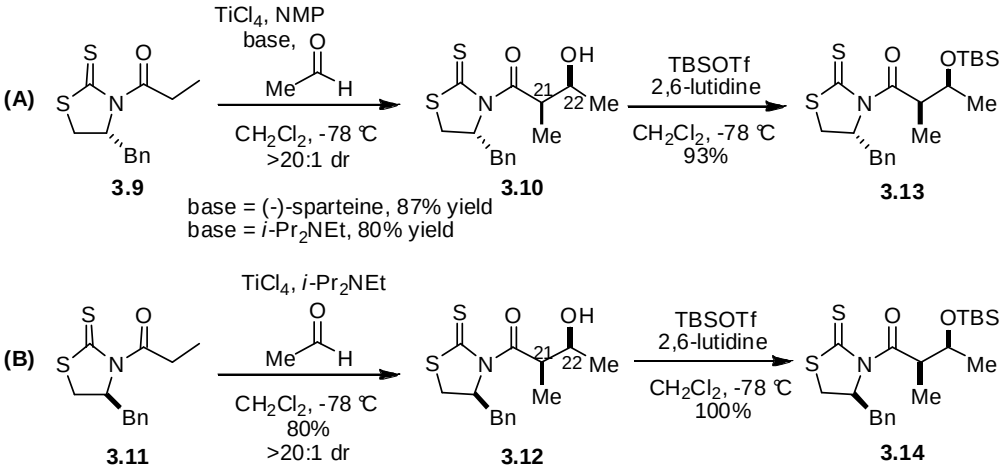
Figure 3.1: C16-C23 fragment of iriomoteolide 1a.



3.5

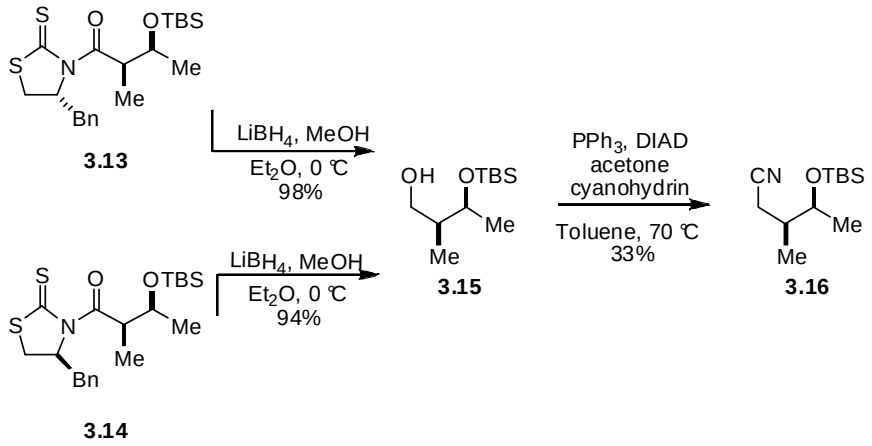
sparteine, the aldol addition which utilized Evans *syn* conditions to form aldol adduct **3.10** was explored utilizing a different base to effect enolization. In the absence of (–)-sparteine as a base, the aldol adduct could be formed utilizing *i*-Pr_2NEt as a base; however, an additional equivalent of NMP (2 equiv. total) was necessary to obtain consistently high levels of diastereoselectivity.[3] This generated the aldol adduct in slightly lower yields (80% yield) compared to the 87% yield obtained when (–)-sparteine was employed as a base, and is consistent with results obtained by former group member Jin She.[3]

Scheme 3.2: Generation of the C21 and C22 stereocenters.



At this juncture, protection of secondary alcohol **3.10** or **3.12** as the tert butyl dimethyl silyl (TBS) ether occurred in the presence of TBSOTf and 2,6-lutidine to afford TBS ethers **3.13** and **3.14** in high yield (Scheme 3.2). The auxiliaries were then reductively cleaved to deliver alcohol **3.15** (Scheme 3.3). Attempts to perform a one carbon homologation of **3.15** utilizing DIAD, PPh_3, and acetone cyanohydrin to produce nitrile **3.16** were investigated.

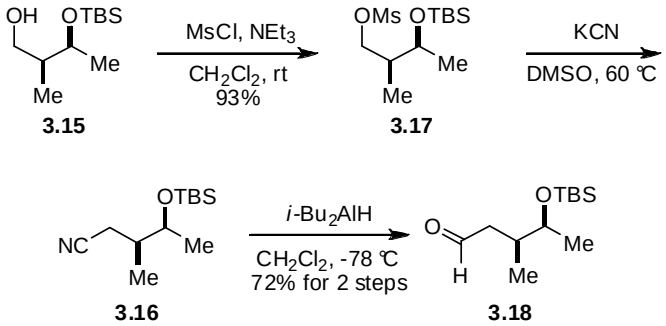
Scheme 3.3: An attempt to form nitrile **3.16** directly from alcohol **3.15**.



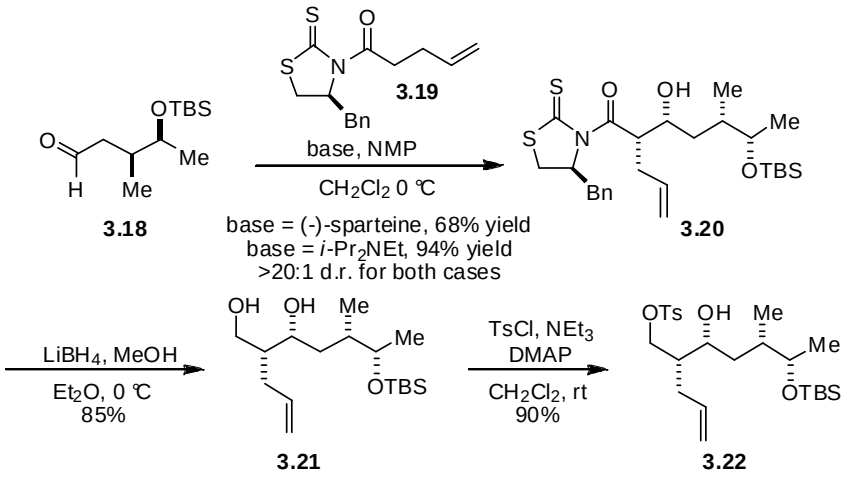
Employing 1.5 equiv. of DIAD, 1.5 equiv. PPh_3, and 10 equiv. of acetone cyanohydrin at 70 ℃ resulted in the formation of the product in low yields (33%). Furthermore, addition of an extra 1.5 equivalents of both PPh_3 and DIAD after 12 h, which improved the yield of nitrile formation in the synthesis of (+)-SCH 351448, did little to improve the yield of the reaction.[4] Additionally, resultant nitrile **3.16** was tainted with the excess DIAD used in the reaction, and difficult to purify via chromatography.

Therefore, a two step process was employed to form the desired nitrile (Scheme 3.4). Primary alcohol **3.15** was first transformed into mesylate **3.17** employing methanesulfonyl chloride and triethylamine in 93% yield. Exposure of mesylate **3.17** to KCN and heating to 55 ℃ for 2 days provided nitrile **3.16**, which upon immediate exposure to reducing conditions exploiting *i*-Bu_2AlH afforded aldehyde **3.18** in 72% yield over 2 steps.[5]

Scheme 3.4: Access to nitrile **3.16**.

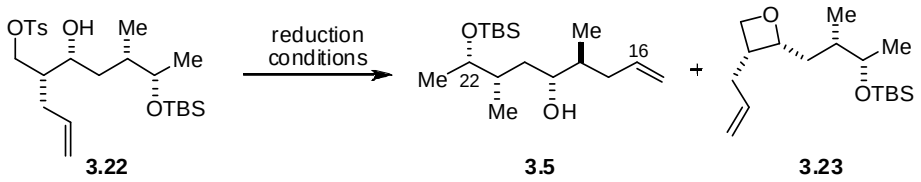


Scheme 3.5: Synthesis of tosylate **3.22**.



At this point, a second aldol iteration utilizing Evans *syn* aldol conditions with (S)-benzyl thiazolidinethione **3.19** was explored. Utilizing (–)-sparteine as a base allowed for the generation of aldol adduct **3.20** in moderate yield, and high diastereoselection (>20:1) (Scheme 3.5). Alternatively, Hünig's base was also effective, inducing both high diastereoselection and yield (Scheme 3.5). Reductive cleavage of the auxiliary with $LiBH_4$ revealed diol **3.21**, which was subjected to tosyl chloride, DMAP, and Et_3N to selectively form the primary tosylate **3.22**. It was thought that upon exposure of tosylate **3.22** to $LiEt_3BH$, a hydride would displace the tosylate to form olefin **3.5**.[6] However, upon exposure of **3.22** to $LiEt_3BH$ the desired product **3.5** along with oxetane **3.23** was formed in 1:3 ratio, favoring oxetane **3.23** (Table 3.1, entry 1).

Table 3.1: Attempts to form terminal olefin **3.5**

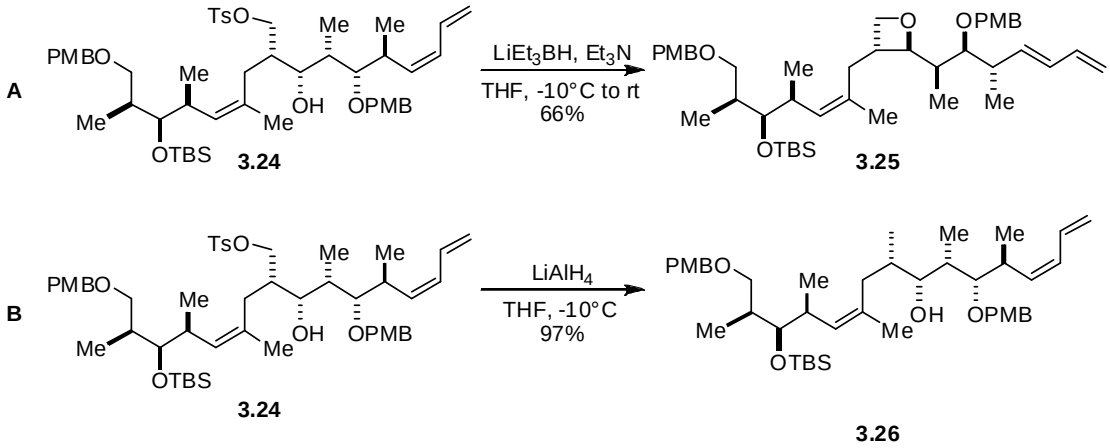


3.22 **3.5** **3.23**

Entry	Hydride source	Temperature	3.5:3.23	Yield
1	$LiEt_3BH$	-78 °C	1:3	n.d.
2	$LiAlH_4$	-78 °C to rt	1:1	42%

Paterson and coworkers also reported the formation of an oxetane utilizing $LiEt_3BH$ in a similar substrate toward the synthesis of (+)-discodermolide (Scheme 3.6, **A**), and found that treatment with LAH generated the desired alcohol in 97% yield (Scheme 3.6, **B**).[7] Subjecting tosylate **3.22** to Patterson's conditions utilizing LAH provided only a 1:1 mixture of the desired product **3.5** and oxetane **3.23** in 45% yield (Table 3.1, entry 2).

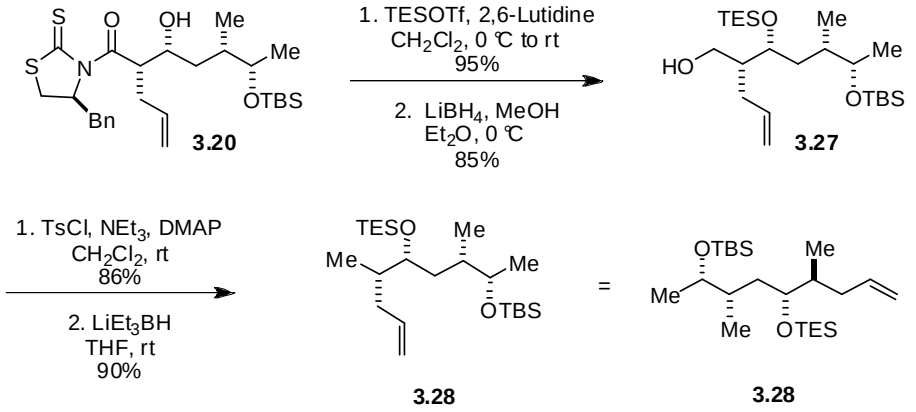
Scheme 3.6: Paterson's reversal in results in the detosylation of **3.24** with $LiEt_3BH$ and $LiAlH_4$.



Because of the propensity for the secondary alcohol at C19 to perform an intramolecular displacement of the C21 tosylate, the secondary alcohol was protected as the TES ether following aldol addition (Scheme 3.7) to deliver a TES ether. At this point, the auxiliary was reductively cleaved using $LiBH_4$ to afford primary alcohol **3.27**, which was

exposed to tosyl chloride, DMAP, and triethyl amine to furnish the tosylate. Displacement of the tosylate readily occurred at room temperature with $LiEt_3BH$ to generate terminal olefin **3.28** in 90% yield.

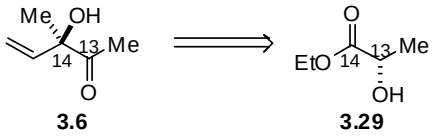
Scheme 3.7: Synthesis of the C16-C23 fragment of iriomoteolide 1a.



C. Synthesis of the C12-C15 fragment

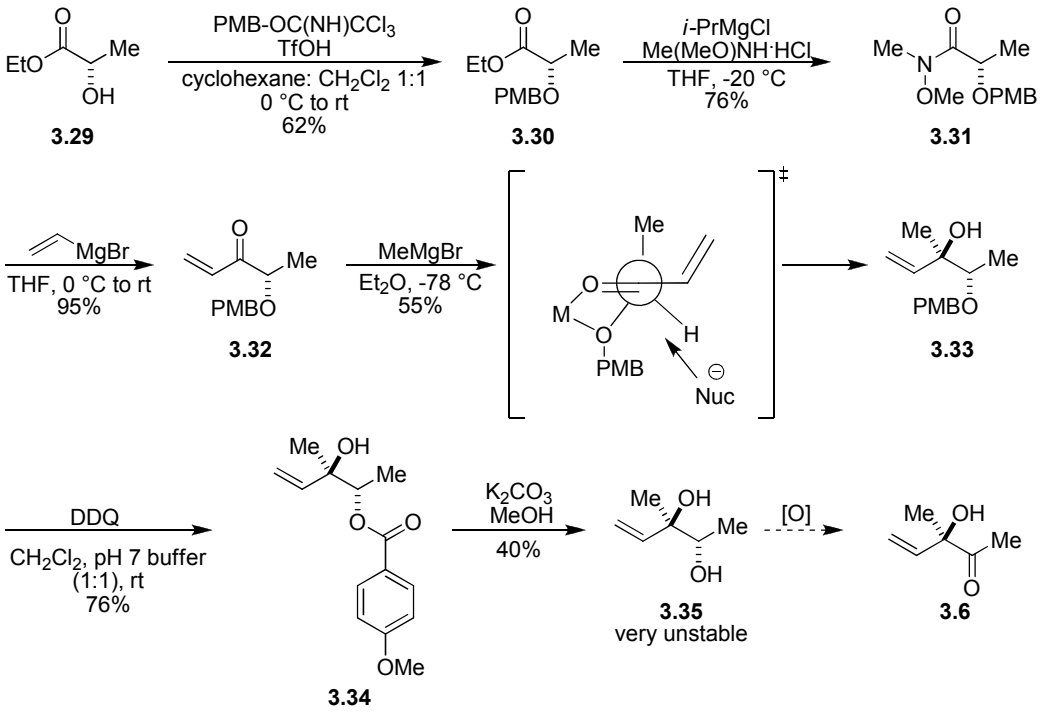
It was envisaged that the C12 - C15 fragment (**3.6**) could be accessed in short order from commercially available (*S*)-ethyl lactate (**3.29**) (Scheme 3.8). Following a literature procedure,[8] (*S*)-ethyl lactate (**3.29**) was exposed to PMB-acetimidate[9] and triflic acid to generate PMB ether **3.30** in 62% yield (Scheme 3.9). Transformation of the ester into the Weinreb amide was accomplished using *i*-PrMgCl and N,O-dimethylhydroxylamine hydrochloride to furnish amide **3.31** in 76% yield.[8] Vinyl Grignard addition then provided enone **3.32** in 95% yield. Resultant enone **3.32** was subjected to a chelation controlled addition using methyl magnesium bromide to deliver the desired tertiary alcohol **3.33** in reasonable yield and 20:1 d.r. Exposure of **3.33** to oxidative deprotection conditions utilizing DDQ resulted in the formation of ester **3.34** as the major product, when a twofold excess of DDQ was employed.

Scheme 3.8: Access to **3.6** from (*S*)-ethyl lactate.



While not an ideal cleavage of a protecting group by any means, it was believed that the resultant ester could be cleaved under basic or reducing conditions to reveal diol **3.35**. Treatment of the ester with K_2CO_3 and MeOH led to cleavage of the ester and formation of diol **3.35**, but unfortunatly, diol **3.35** proved to be quite difficult to work with, as it was complicated to isolate from the aqueous layer due to its hydrophilicity, and readily decomposed under other isolation methods.

Scheme 3.9: Initial attempts to prepare the C12-C15 fragment **3.6**.

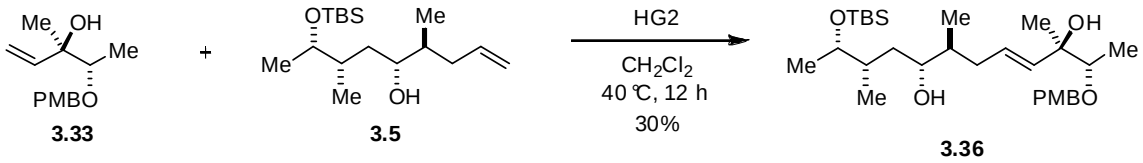


Because diol **3.35** proved difficult to isolate, we decided to explore the key cross metathesis between C16-23 fragment (olefin **3.5** or **3.28**) and the C12-C15 fragment before cleavage of the PMB ether, as it was reasoned that formation of a diol with more nonpolar substituents may be easier to isolate.

D. Cross metathesis attempts to form the C15-C16 bond

To this end, a cross metathesis was attempted with tertiary alcohol **3.33** and secondary alcohol **3.5** (Scheme 3.10). Utilizing Hoveyda-Grubbs 2nd generation catalyst,[10] 3 equiv. of **3.33** and 1 equiv. of **3.5**, the crossed product **3.36** was isolated in an unremarkable 30% yield. It was thought that better matching of the coupling partners based on olefin reactivity in the cross metathesis would result in higher yields.[11]

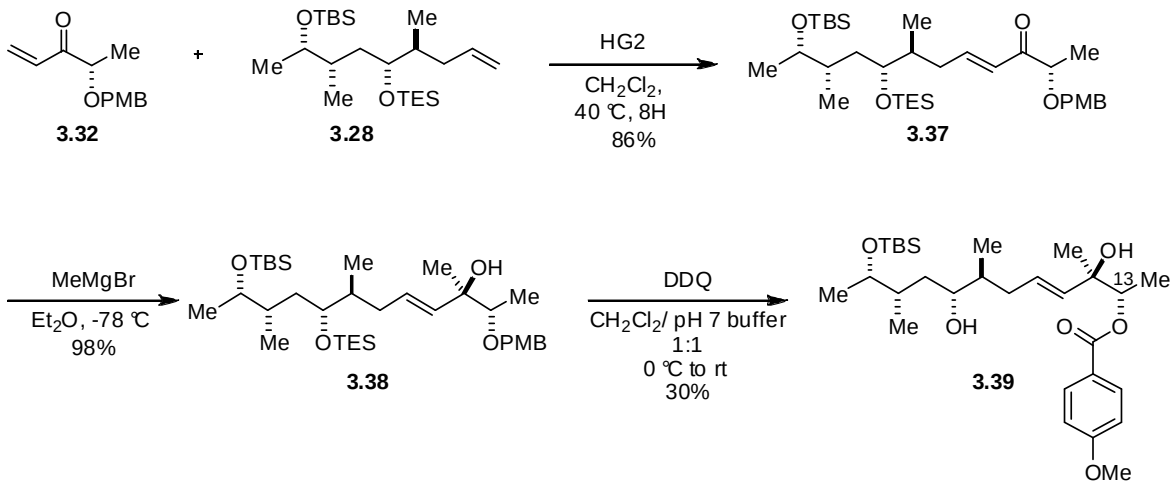
Scheme 3.10: Cross metathesis attempts between **3.33** and **3.5**.



3.33 **3.5** **3.36**

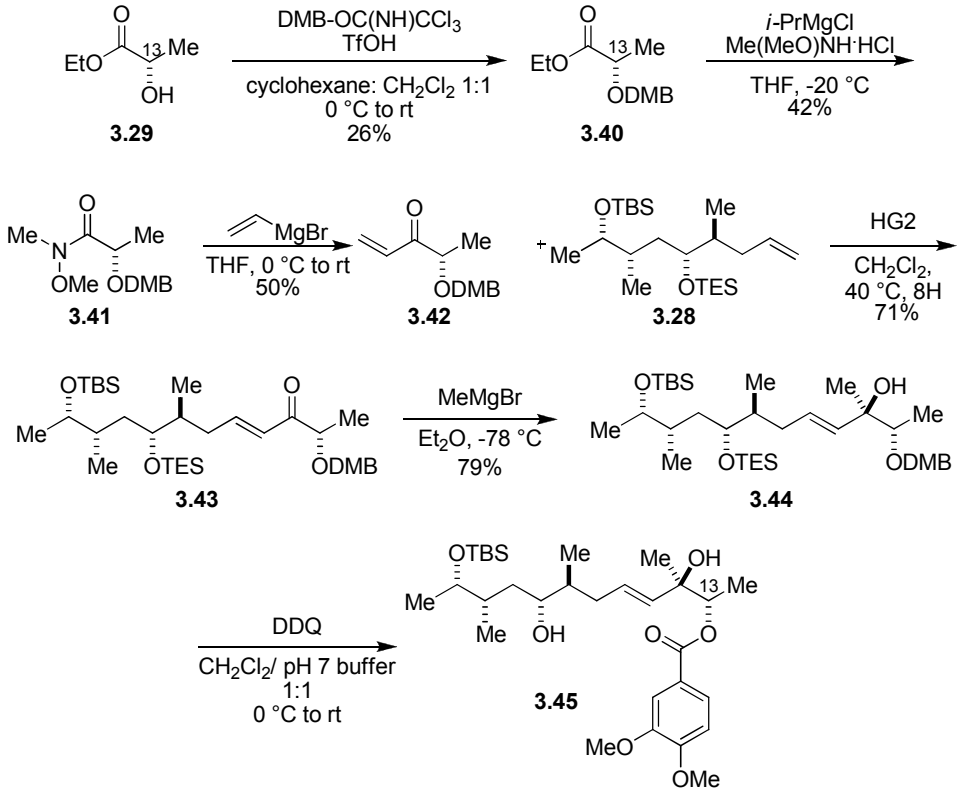
Therefore, a cross metathesis between enone **3.32** and terminal olefin **3.28** was investigated (Scheme 3.11). Utilizing Hoveyda-Grubbs' second generation catalyst, 2 equivalents of enone **3.32** and 1 equivalents of terminal olefin **3.28** allowed for enone **3.37** to be isolated in 86% yield. At this point, a chelation controlled addition with methyl Grignard afforded tertiary alcohol **3.38** in high diastereoselectivity (20:1). At this stage, it was thought that deprotection of the PMB ether with two equivalents of DDQ would form an ester, as it had in earlier work (Scheme 3.9). In this case, formation of the ester did occur; however, treatment with DDQ also resulted in concomitant loss of the TES protecting group to deliver secondary alcohol **3.39** in 30% yield.

Scheme 3.11: Cross metathesis of enone **3.32** with terminal olefin **3.28**.



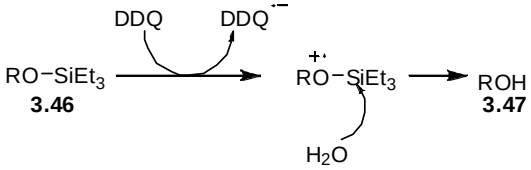
Due to this circumstance, different protecting groups were explored for the hydroxyl group at C13. It is known that DMB protecting groups cleave more readily in the presence of DDQ than a PMB, and thus be less likely to cleave a TES group due to prolonged exposure to DDQ.[12] To this end, the secondary alcohol of (*S*)-ethyl lactate (**3.29**) was protected to afford DMB ether **3.40**, transformed into Weinreb amide **3.41**, and vinyl Grignard addition was used to provide enone **3.42** along the previously developed synthetic route (Scheme 3.12).

Scheme 3.12: Attempts to prepare the C12-C23 fragment with a DMB protecting group at C13.



Cross metathesis of TES ether **3.28** with enone **3.42** generated the crossed product **3.43** in 71% yield as exclusively the *E* isomer. Chelation controlled methyl Grignard addition of **3.43** furnished tertiary alcohol **3.44** in 79% yield. However, upon exposure of **3.44** to DDQ, ester **3.45** was formed along with concomitant loss of the TES ether protecting group. Though there are examples of secondary TES ethers remaining intact in the presence of DDQ,[13] TES ethers **3.46** are also known to undergo oxidative cleavage in the presence of DDQ via a single electron transfer mechanism to form alcohols (**3.47**) (Scheme 3.13).[14]

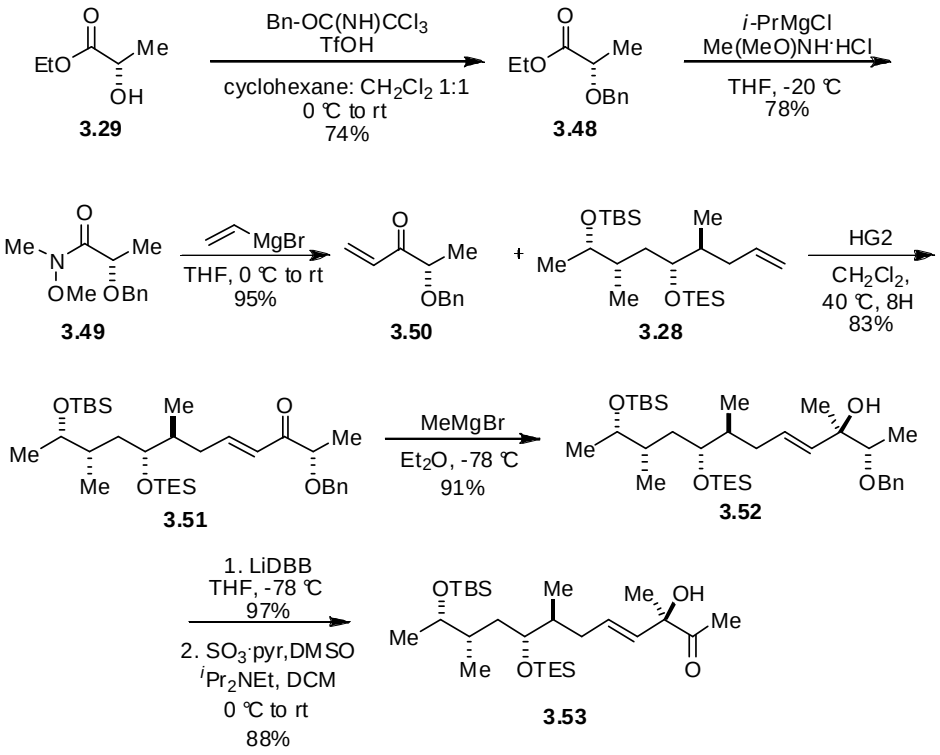
Scheme 3.13: Oxidative cleavage of silyl ethers with DDQ.[14]



Ultimately, the secondary alcohol of (*S*)-ethyl lactate (**3.29**) was protected as the benzyl ether to provide ester **3.48** (Scheme 3.14). Exposure to N,O-dimethylhydroxylamine

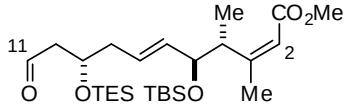
hydrochloride and *i*-PrMgCl delivered Weinreb amide **3.49**, which was subjected to a vinyl Grignard addition to furnish enone **3.50**. Cross metathesis with enone **3.50** and terminal olefin **3.28** generated enone **3.51**, which was exposed to methyl Grignard to deliver tertiary alcohol **3.52** in 20:1 d.r and 91% yield. Deprotection under reductive conditions employing LiDBB[15] proceeded smoothly to deliver a diol, which was oxidized under Parikh-Doering conditions[16] to form ketone fragment **3.53**.

Scheme 3.14: Completion of the C12-C23 fragment of iriomoteolide 1a.



E. Synthesis of the C1-C11 fragment

Figure 3.2: C1-C11 fragment of iriomoteolide 1a.

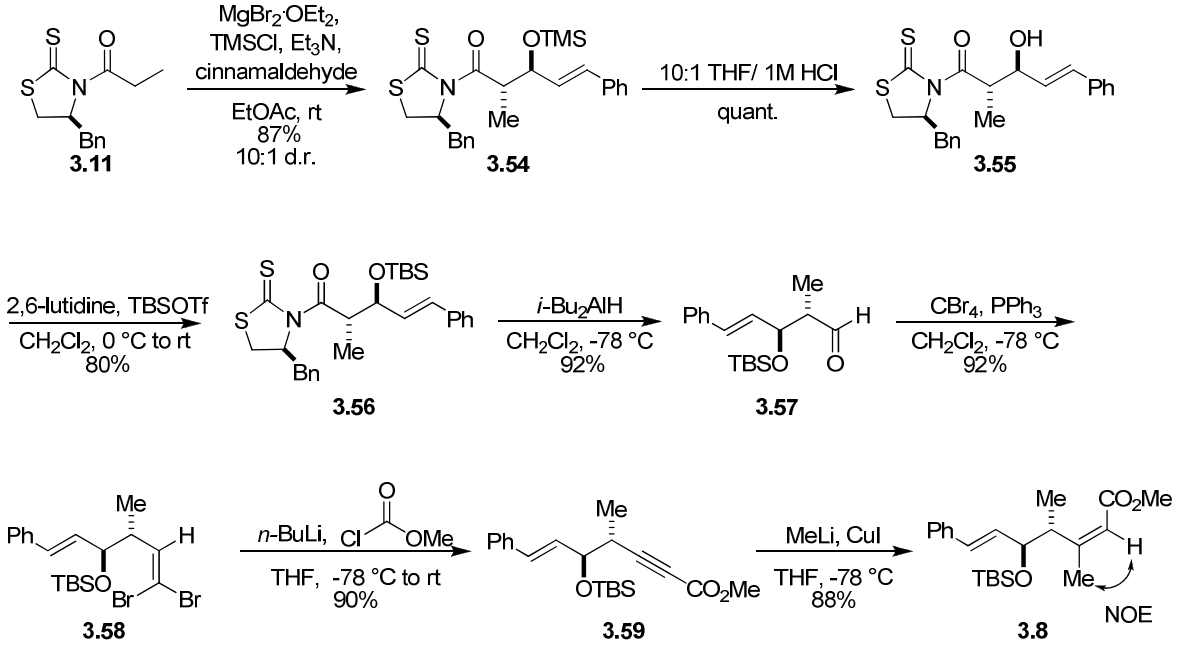


3.4

Synthesis of the C1-C11 fragment (Figure 3.2) commenced by performing an Evans *anti* aldol reaction between thioimide **3.11** and cinnamaldehyde to arrive at TMS protected aldol adduct **3.54** (Scheme 3.15).[17] Deprotection of the quite labile TMS group under acidic conditions, and replacement with a TBS group, generated TBS ether **3.56** in 87% yield over the two steps. Reductive cleavage of the chiral auxiliary was accomplished with *i*-Bu_2AlH to

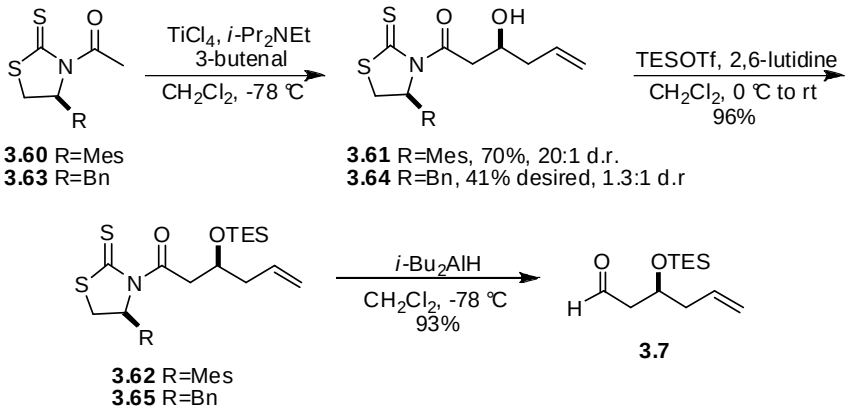
furnish aldehyde **3.57**, which was subjected to a two step Corey-Fuchs homologation[18] to arrive at ynoate **3.59**. A conjugate methyl addition to ynoate **3.59** utilizing the Gillman reagent[19] provided the *Z*-enoate **3.8**, as confirmed by observed NOESY interactions.

Scheme 3.15: An approach to the C1-C6 fragment of iriomoteolide 1a.



Preparation of the aldehyde fragment was straightforward, as it involved an acetate aldol addition between mesityl substituted thiazolidinethione **3.60**[20] and 3-butenal[21] generating aldol adduct **3.61** in 70% yield and 20:1 d.r (Scheme 3.16). Exposure of the resultant alcohol to silylation conditions provided TES ether **3.62**, and cleavage of the chiral auxiliary employing *i*-Bu_2AlH furnished aldehyde **3.7** to be used in the key cross metathesis. Alternatively, the same fragment could be accessed along the same synthetic sequence; however, instead of utilizing mesityl thiazoldinethione **3.60**, (*S*)-1-(4-benzyl-2-thioxothiazolidin-3-yl)ethanone (**3.63**) was employed in an aldol with 3-butenal to afford the desired aldol adduct in 40% yield.

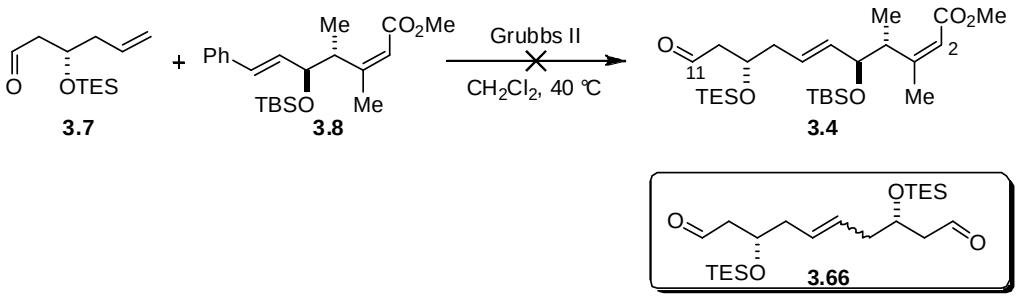
Scheme 3.16: Access to aldehyde **3.7**.



1.1 Cross metathesis attempts with aldehyde 3.7 and ester 3.8

A cross metathesis between **3.7** and **3.8** utilizing 10 mol% Grubbs' 2nd generation catalyst in refluxing CH_2Cl_2 was expected to deliver the C1-C11 fragment (**3.4**, Scheme 3.17). However, it was found that under these conditions, the only product obtained was homodimerized aldehyde **3.66** along with unreacted **3.8**. It was reasoned that the bulky TBS group was blocking the internal olefin, rendering it unreactive to cross metathesis conditions.

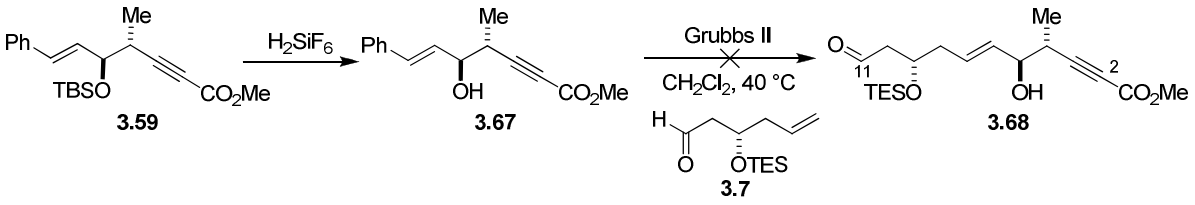
Scheme 3.17: Attempts to prepare the C1-C11 fragment utilzing cross metathesis.



An alternative approach utilizing ynoate **3.59** was also investigated (Scheme 3.18). Because the TBS ether was likely causing the internal olefin to be too hindered to undergo a cross metathesis, the TBS ether was cleaved under acidic conditions to reveal allylic alcohol **3.67**. However, a cross metathesis between allylic alcohol **3.67** and aldehyde **3.7** did not

provide any of the desired alkynoate **3.68**, but instead provided exclusive formation of the aldehyde dimer (**3.66**).

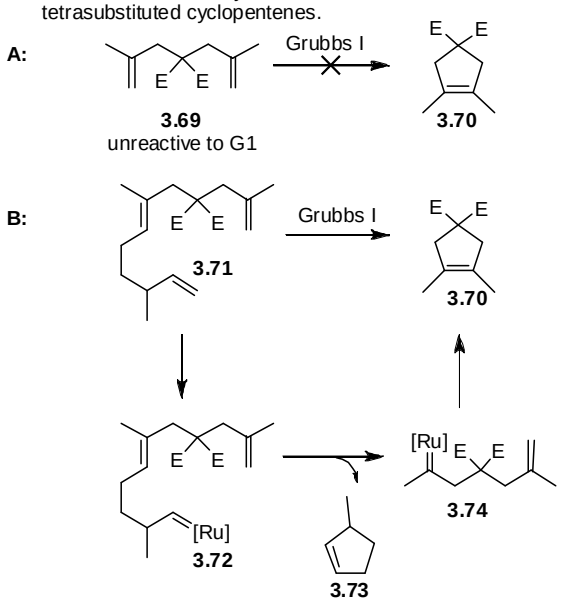
Scheme 3.18: Cross metathesis attempts to form the C6-C7 *E* olefin.



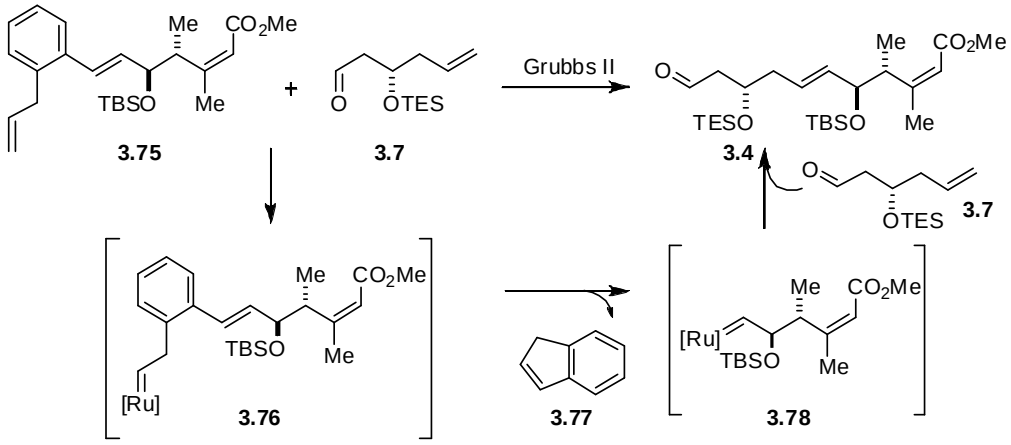
1.2. Relay cross metathesis strategy to access the C1-C11 fragment

At this stage, an unconventional cross metathesis strategy was examined. In the context of substrates containing two 1,1 disubstituted ethylene moieties (**3.69**), ring closing metathesis has proven to be a difficult task utilizing Grubbs' 1st generation catalyst, as the olefinic sites are quite sterically hindered (Scheme 3.19, A).[22a] Though 2nd and 3rd generation catalysts have been developed to overcome this challenge, forming tetrasubstituted olefins remains a daunting task.[23] One strategy to overcome this shortcoming came with the advent of relay RCM.[22] In this approach (Scheme 3.19, B), a temporary tether containing an unhindered terminal olefin (**3.71**) is introduced such that a kinetically favorable five membered ring is formed as a byproduct (**3.73**) while delivering the ruthenium catalyst onto the sterically encumbered internal position (**3.74**). Once the Ru is delivered onto the sterically hindered olefin, it can undergo a ring closing metathesis to generate the desired tetrasubstituted cyclopentene **3.70**.[22]

Scheme 3:19: Use of relay RCM to form tetrasubstituted cyclopentenes.



Scheme 3.20: Proposed relay ring-closing-cross metathesis strategy to form **3.4**.

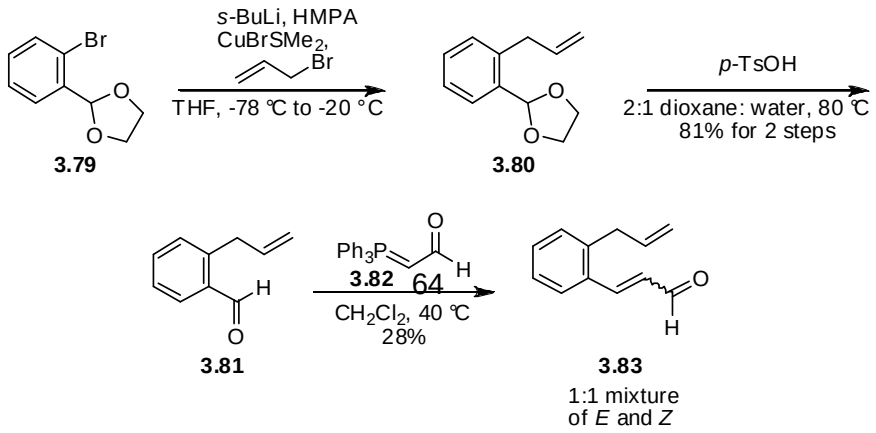


We believed that we could employ a relay strategy in the total synthesis of iriomoteolide 1a, specifically using this strategy to create the C6-C7 *E* olefin. In the proposed reaction, the Ru complex would first insert into the unhindered terminal olefin (**3.75**, Scheme 3.20), providing Ru-carbene **3.76**. Ru carbene **3.76** would undergo a kinetically favorable ring closing metathesis forming indene (**3.77**) as a byproduct, while delivering the Ru catalyst to the hindered internal olefin, to furnish **3.78**. Once the Ru carbene was on the sterically hindered position, **3.78** would undergo a cross metathesis with aldehyde **3.7** to generate the C1-C11 fragment (**3.4**).

1.2.1. Preparation of the Relay Partner 3.75

Preparation of the relay partner **3.75** commenced with an allylation of commercially available bromic

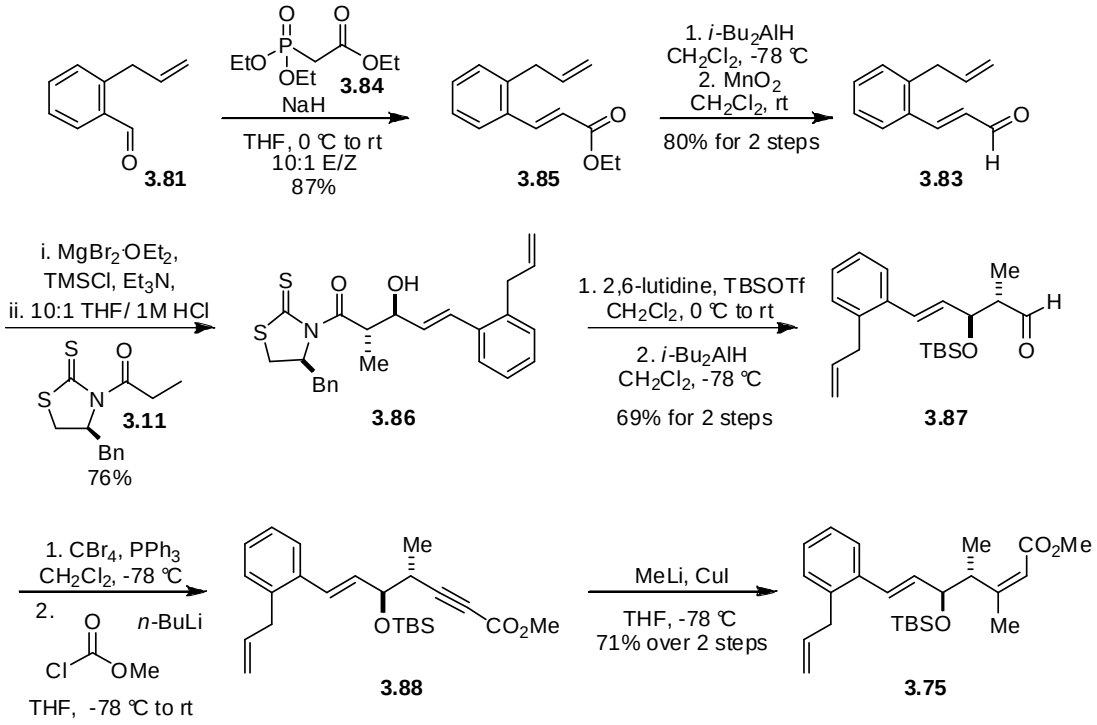
Scheme 3.21: Initial attempts to form enal **3.83**.



Deprotection of acetal **3.80** under acidic conditions afforded aldehyde **3.81**, which was exposed to ylide **3.82** to furnish enal **3.83**. Unfortunately, resultant enal **3.83** was isolated in a low 28% yield, as a 1:1 mixture of *E* and *Z* isomers.

A more straightforward, albeit lengthier, alternative approach proved to be a useful strategy to access enal **3.83** (Scheme 3.22). A Horner-Wadsworth Emmons olefination with phosphonate **3.84** and aldehyde **3.81** formed ester **3.85** in 87% yield as a 10:1 mixture of *E/Z* isomers. Reduction of ester **3.85** to the alcohol was accomplished utilizing *i*-Bu_2AlH, followed by allylic oxidation with MnO_2 delivered enal **3.83** in 80% yield for two steps. An Evans *anti* aldol with enal **3.83** and thioimide **3.11**, followed by an acidic workup, generated aldol adduct **3.86** in 76% yield. Protection of the secondary alcohol as the TBS ether and reductive removal of the chiral auxiliary afforded aldehyde **3.87**. In two steps, involving a Corey-Fuchs homologation and addition of the Gillman reagent, enoate **3.75** was formed in 71% yield.

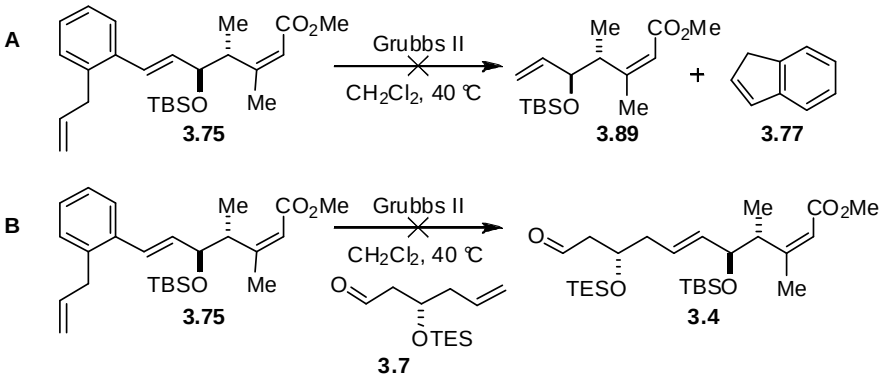
Scheme 3.22: Synthesis of the relay partner **3.75**.



1.2.2 Cross metathesis attempts with relay substrate 3.75

Exposure of the resultant relay substrate **3.75** to Grubbs' 2nd generation catalyst was expected to lead to the truncated terminal olefin **3.89** (Scheme 3.23, **A**). Unforturnatly, under cross metathesis conditions, a complex mixture was obtained, with no desired olefin **3.89** detected. Furthermore, exposure of the relay substrate to Grubbs' 2nd generation catalyst with aldehyde **3.7** did not lead to any of the desired C1-C11 fragment (**3.4**, **B**, Scheme 3.23).

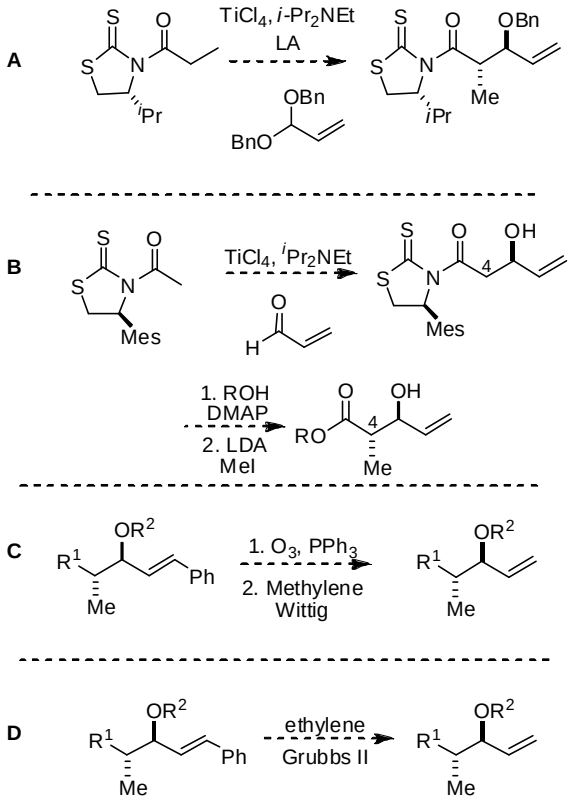
Scheme 3.23: Cross metathesis attempts with relay substrate **3.75**.



1.3 Other potential stratagies to access the C1-C11 fragment

Because the internal olefin was likely too hindered to undergo a relay ring closing-cross metathesis, we next explored replacing the cinnamyl group of the C1-C6 fragment with a terminal olefin. Though there appears to be a straightforward solution to access terminal olefin **3.89**, in simply replacing cinnamaldehyde with acrolein in the Evans *anti* aldol, acrolein has not been shown to be a suitable substrate for the Evans *anti* aldol.[17a] Several potential strategies were considered as a means to access a terminal olefin substrate. Use of Urpi's acetal aldol[25] in conjunction with acrolein dibenzyl acetal, would generate the desired stereochemistry and a terminal olefin; however, this sequence would add an additional deprotection step later in the synthesis of the natural product (Scheme 3.24, **A**).

Scheme 3.24: Potential strategies to access the C1-C6 fragment containing a terminal olefin with the correct configuration between C4-C5

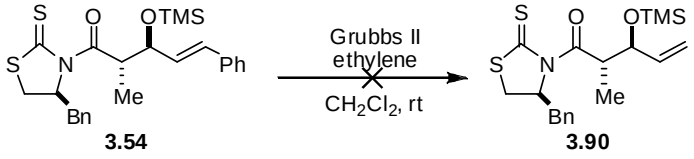


Alternatively, an acetate aldol with acrolein could provide β-hydroxy amide, which could subsequently be utilized in a Frater-Seebach alkylation[26] to form the C4 stereocenter (Scheme 3.24, **B**). This option would add at least three steps to the synthetic sequence. An ozonolysis/methylene Wittig sequence was also considered, but this could a problematic strategy if other olefins or aldehydes were present in the substrate undergoing ozonolysis/methylenation (Scheme 3.24, **C**). Another strategy which provided a "direct" approach to a terminal olefin from a cinnamyl substrate was a cross metathesis of one of the substrates along the developed synthetic route with ethylene (Scheme 3.24, **D**).

1.4 Attempts to form the C6 terminal olefin utilizing ethylene cross metathesis

From our earlier experience with attempted cross metatheses, it was known not to perform the cross metathesis with ethylene at a juncture when the TBS ether at C5 was installed, as the resultant internal olefin would be inaccessible to the olefin metathesis catalyst due to steric hindrance. Instead, a cross metathesis was attempted with TMS protected aldol adduct **3.54**, ethylene, and Grubbs 2nd generation catalyst (Scheme 3.25). It was reasoned that the smaller TMS group may allow for the catalyst to insert into the internal olefin of **3.54** and undergo a cross metathesis with ethylene, to generate terminal olefin **3.90**. However, this was not the case as terminal olefin **3.90** was not detected by NMR.

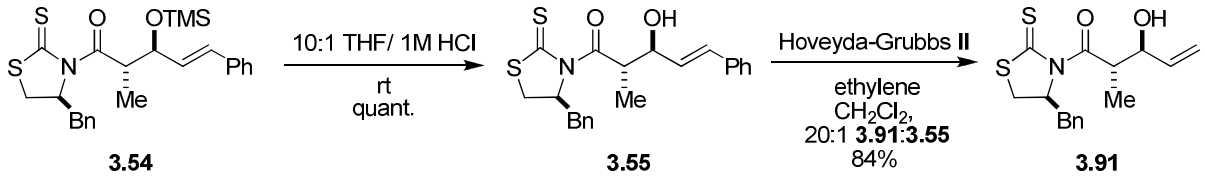
Scheme 3.25: An attempt to install a terminal olefin from cinnamyl substrate **3.54** with Grubbs 2nd generation catalyst and ethylene.



3.54 **3.90**

Instead, the TMS protecting group of **3.54** was removed under acidic conditions to reveal allylic alcohol **3.55** (Scheme 3.26). Upon exposure of **3.55** to Hoveyda-Grubbs 2nd generation catalyst, under an ethylene atmosphere at a concentration of 0.01 M in CH_2Cl_2, in a sealed tube, **3.91** was obtained in 84% yield as a 20:1 mixture of terminal olefin **3.91** to cinnamyl starting material **3.55**. Notably, the reaction temperature and volume of ethylene in the sealed tube had dramatic effects on the reaction. Heating the reaction above room temperature caused decomposition of the starting material. Critical for the success of the reaction was the volume of ethylene relative to the volume of solvent in the sealed tube, as a higher ratio of starting material to product was detected when the volume of methylene chloride exceeded 40% of the volume of the sealed tube.

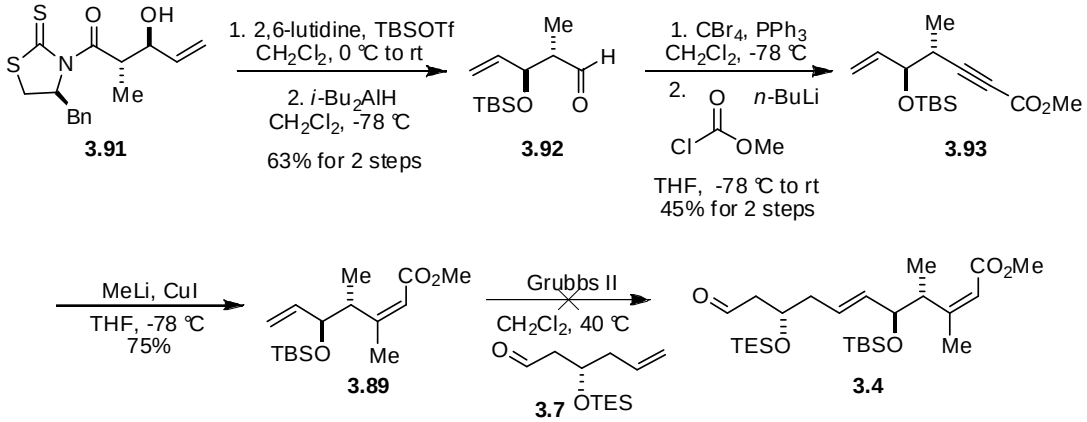
Scheme 3.26: Successful cross metathesis of free alcohol **3.55** and ethylene to generate terminal olefin **3.91**.



1.5 Cross metatheis attempts with terminal olefin 3.89 and aldehyde 3.7

With terminal olefin **3.91** in hand, the secondary alcohol was protected as the TBS ether, and the auxiliary was reductively cleaved with *i*-Bu_2AlH to deliver aldehyde **3.92** (Scheme 3.27). Corey-Fuchs homologation provided ynoate **3.93** was followed by treatment

Scheme 3.27: Generation of enoate **3.89** and cross metathesis attemps with aldehyde **3.7**



with the Gillman reagent to furnish *Z*-enoate **3.89**, as confirmed by NOESY analysis.

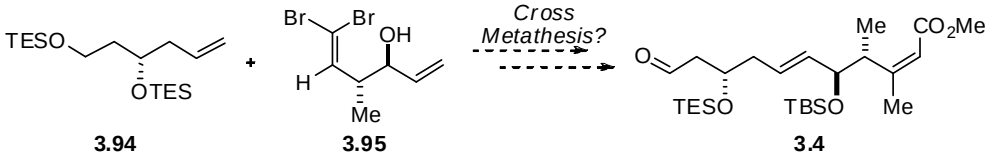
Subjecting terminal olefin **3.89** to a cross metathesis with aldehyde **3.7** did not generate the desired C1-C11 fragment **3.4**, but once again produced the dimer of aldehyde **3.7** as the sole product. It was speculated that syringe pump addition of aldehyde **3.7** may allow for the formation of fragment **3.4**, as a lower concentration of the aldehyde may limit aldehyde

dimerization and allow for the desired cross metathesis to occur. Unfortunately, **3.4** was not obtained when syringe pump addition was employed. Considering the precedent by Grubbs et. al.,[11] it seems logical that the Ru catalyst should be able to insert into olefin **3.89**, and undergo further cross metathesis. However, we and others[27] have found this transformation to be difficult, likely due to the steric effects imposed by the bulky silyl ether protecting groups.

1.6 Cross metathesis attempts with dibromide 3.95

Because the TBS group was posing a significant hurdle in our ultimate goal of synthesizing the C1-C11 fragment, it was believed that a cross metathesis of bis-silyl ether **3.94** and dibromide **3.95** and could potentially allow for the C6-C7 bond to be forged (Scheme 3.28). A selective deprotection of the primary silyl ether in the presence of a secondary silyl ether utilizing Swern conditions[28] could then furnish aldehyde **3.4**.

Scheme 3.28: An alternative approach to access the C1-C11 fragment.

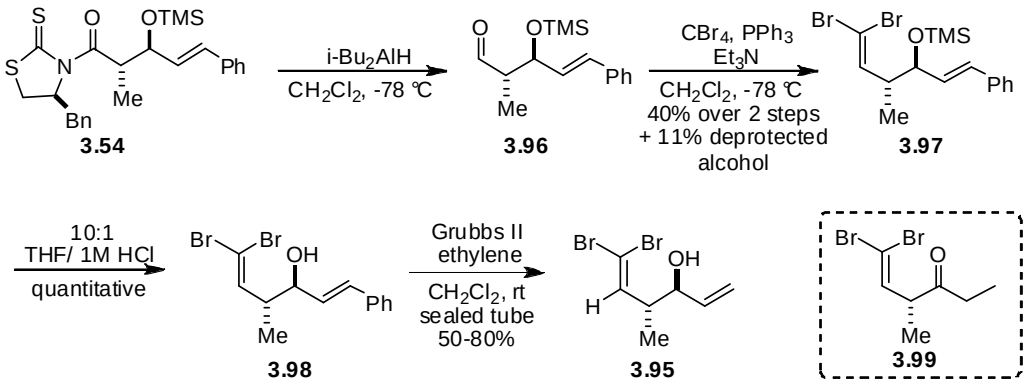


3.94 **3.95** **3.4**

To prepare dibromide **3.95**, aldol adduct **3.54** was reductively cleaved with *i*-Bu_2AlH to furnish aldehyde **3.96** (Scheme 3.29).[17b] Treatment of **3.96** with CBr_4 and PPh_3 resulted in deprotection of the TMS ether, and formation of an unidentified product. However, by employing 10 equiv. of triethylamine, TMS dibromide **3.97** was isolated in 40% yield over two steps + 11% of the deprotected alcohol substrate. Deprotection of the TMS group under acidic conditions provided allyl alcohol **3.98**, which was subjected to an ethylene cross metathesis with Grubbs 2nd generation catalyst to afford allylic alcohol **3.95**. The yield of this particular cross could be variable, as dibromoketone **3.99**, likely resulting

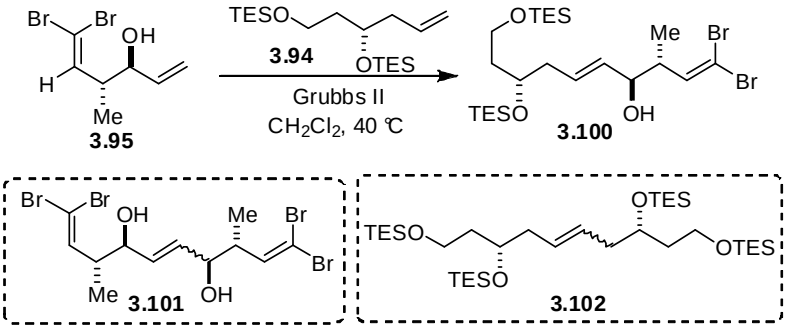
from olefin isomerization to the enol and tautomerization, was sometimes seen as a byproduct. Attempts to limit the formation of bromoketone **3.99** by using 1,4-benzoquinone as an additive[29] did not improve the overall yield of the reaction.

Scheme 3.29: Formation of dibromide **3.95**



Efforts to perform a cross metathesis of **3.95** with bis silylether **3.94** resulted in disappointing yields of **3.100** when 1 equiv. of bis silyl ether **3.94** and 1 equiv. of allylic alcohol **3.95** were employed (Table 3.2, entry 1). Dimerization of the dibromide **3.95** and bis silyl ether **3.94** were the primary byproducts of the reaction (**3.101** and **3.102**, respectively). The best results were obtained when 1.0 equivalent of allylic alcohol **3.95** and 3.4 equivalents of bis silyl ether **3.94** were used in the reaction generating allylic alcohol **3.100** in 60% yield (Table 3.2, entry 4).

Table 3.2: Attempts to perform a cross metathesis between **3.95** and **3.94**.

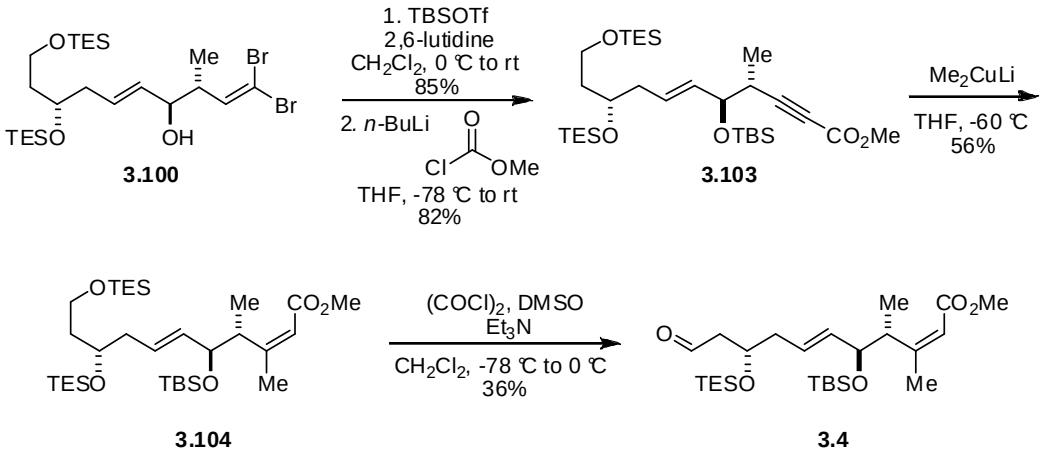


Entry	Equiv. 3.95	Equiv. 3.94	Yield
1	1.0	1.0	23%
2	1.0	1.3	39%
3	1.0	2.0	40%
4	1.0	3.4	60%

1.7 Attempts to complete the C1-C11 fragment

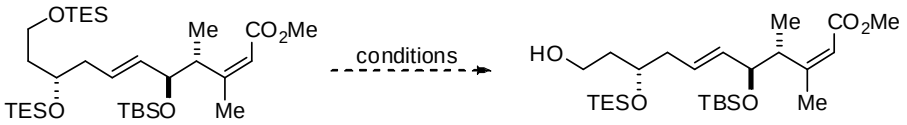
With **3.100** in hand, the secondary alcohol was protected as the TBS ether, and the dibromide transformed under basic conditions to afford ynoate **3.103** in 70% yield over 2 steps (Scheme 3.30). Following cuprate addition, bis TES ether **3.104** was exposed to Swern oxidation conditions[28] in hopes that a one-pot selective deprotection of the primary TES silyl ether would occur followed by oxidation to yield aldehyde **3.4**. However, low yields (38%) and significant decomposition were obtained under the reaction conditions. Attempts to improve the yield by distilling the oxalyl chloride prior to use did little to improve the outcome of the reaction.

Scheme 3.30: Attempts to access **3.4** utilizing a Swern monodeprotection/oxidation strategy.



A selective deprotection of the primary TES ether **3.104** was investigated (Table 3.3). Utilizing PPTS in 10:1 DCM/MeOH at -20 ℃ resulted in cleavage of both the primary and secondary TES groups (Table 3.3, entry 1). Use of a more hindered alcohol, *i*-PrOH, resulted in the formation of mixtures of products (Table 3.3, entry 2). Selective deprotection of the primary TES did occur with 1.3:0.1:0.3 THF/H_2O/AcOH; unfortunately, the highest yield obtained for this reaction was only 51% of **3.105** (Table 3.3, entry 3).

Table 3.3: Attempts to selectively deprotect the primary TES ether of **3.104** to afford **3.105**.



3.104 **3.105**

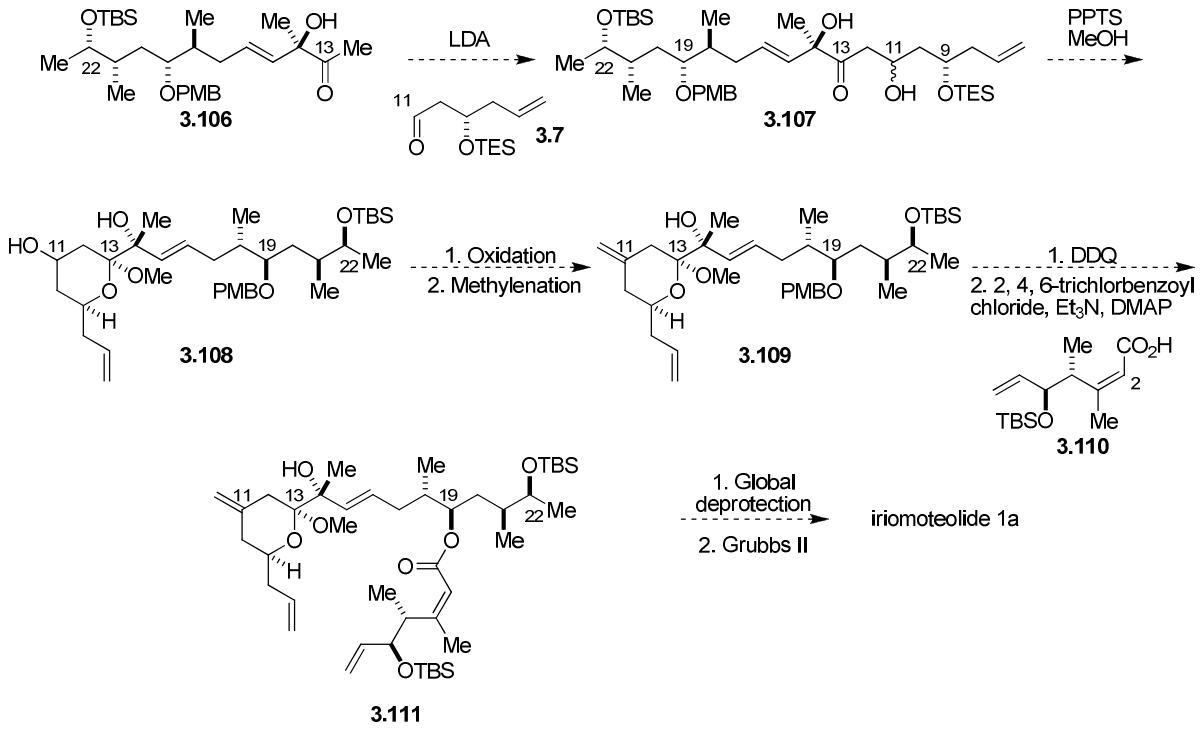
Entry	Conditions	Temperature (℃)	Result
1	10 mol % PPTS 10:1 CH_2Cl_2/MeOH	-20	cleavage of primary and secondary
2	10 mol % PPTS 10:1 CH_2Cl_2/ *i*-PrOH	-10	mixtures of products
3	1.0/0.1/0.3 THF/H_2O/AcOH	-10	51% monodeprotected product

F. Second Generation approach to iriomoteolide 1a

Because the cross metathesis between bis silyl ether **3.94** and dibromide **3.95** required in excess of 3.0 equivalents of bis silyl ether **3.94** to produce **3.100** in a reasonable yield, and because the selective deprotection of primary TES ether **3.104** was problematic, we decided to reassess our original strategy to access iriomoteolide 1a. Instead of performing a cross metathesis to form the C6-C7 *E* olefin, a ring closing metathesis would be used to install the macrocycle of iriomoteolide 1a while forging the C6-C7 *E* olefin. Horne also utilizes a ring closing metathesis in his synthesis or iriomoteolide 1a.[30] This strategy would require a few protecting group changes, as well as some changes in the order of steps (Scheme 3.31). It was envisioned that iriomoteolide 1a could arise from an unselective aldol reaction of aldehyde **3.7** and ketone **3.106** to produce **3.107**. Then acid catalyzed deprotection of the C9 TES ether of **3.107** followed by concomitant ketalization would deliver mixed methyl ketal **3.108**. Oxidation and methylenation of C11 alcohol would

install the exocyclic olefin of **3.109**. Deprotection of the C19 protecting group would form the free hydroxyl at C19, which could undergo a Yamaguchi esterification with acid **3.110** to provide ester **3.111**. Global deprotection and a ring closing metathesis would furnish iriomoteolide 1a.

Scheme 3.31: A modified strategy to access iriomoteolide 1a.



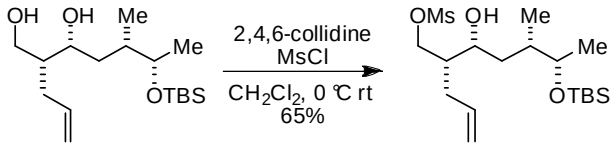
For this new synthetic strategy toward iriomoteolide 1a to be executed, a protecting group differentiation between the C19 and C9 hydroxyl group was necessary. It was believed that the C9 could remain protected as a TES ether, while the C19 could be changed from a TES ether to a PMB ether.

1.1 Protection of the C19 hydroxyl group as the PMB ether

Initial attempts to protect the C19 hydroxyl as the PMB ether centered on selective functionalization of the primary alcohol of **3.21** as the mesylate, followed by use of PMB acetimidate **3.113** to protect the secondary alcohol of **3.112**. Selective mesylation of the

primary alcohol was accomplished utilizing 2,4,6-collidine and methanesulfonyl chloride to generate the mesylate **3.112** in 65% yield (Scheme 3.32).[31]

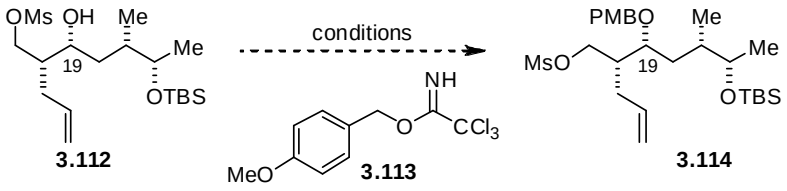
Scheme 3.32: Selective mesylation of primary alcohol **3.21**.



3.21 **3.112**

Attempts to protect the C19 hydroxyl of **3.112** utilizing PMB-acetimidate **3.113** resulted in decomposition under all conditions screened, and no detection of the product by NMR (Table 3.4).

Table 3.4: Attempts to protect the C10 hydroxyl as the PMB ether



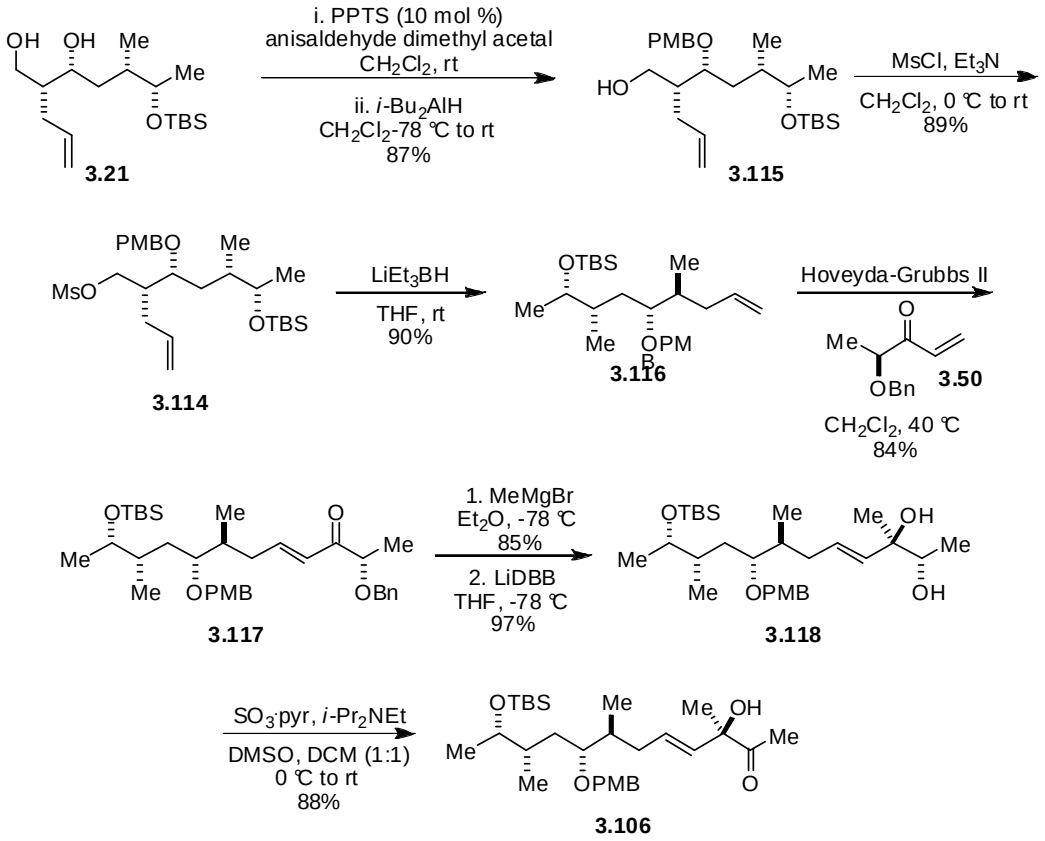
3.112 **3.113** **3.114**

Acid catalyst	Solvent	Temperature (℃)	Result
BF_3OEt_2	CH_2Cl_2	0	Decomposition
BF_3OEt_2	CH_2Cl_2	-78	Decomposition
p-TsOH	CH_2Cl_2	25	Deprotection of TBS group Decomposition of acetimidate
TfOH	CH_2Cl_2/C_6H_{12} (2:1)	0	Decomposition

Ultimately, the C19 hydroxyl was protected as the PMB ether following a two step sequence: initial formation of the PMP acetal of diol **3.21**, followed by *i*-Bu_2AlH assisted regioselective opening of the PMP acetal to form the PMB ether (Scheme 3.33).[32] Primary alcohol **3.115** was then transformed into mesylate **3.114** which was displaced utilizing $LiEt_3BH$ to provide terminal olefin **3.116**. Cross metathesis with enone **3.50** occurred as it

had in similar substrates providing **3.117** in high yield, which underwent a chelation controlled methyl Grignard addition and deprotection of the benzyl ether to afford diol **3.118**. Oxidation of diol **3.118** delivered ketone **3.106** in 88% yield.

Scheme 3.33: Formation of ketone **3.106**.

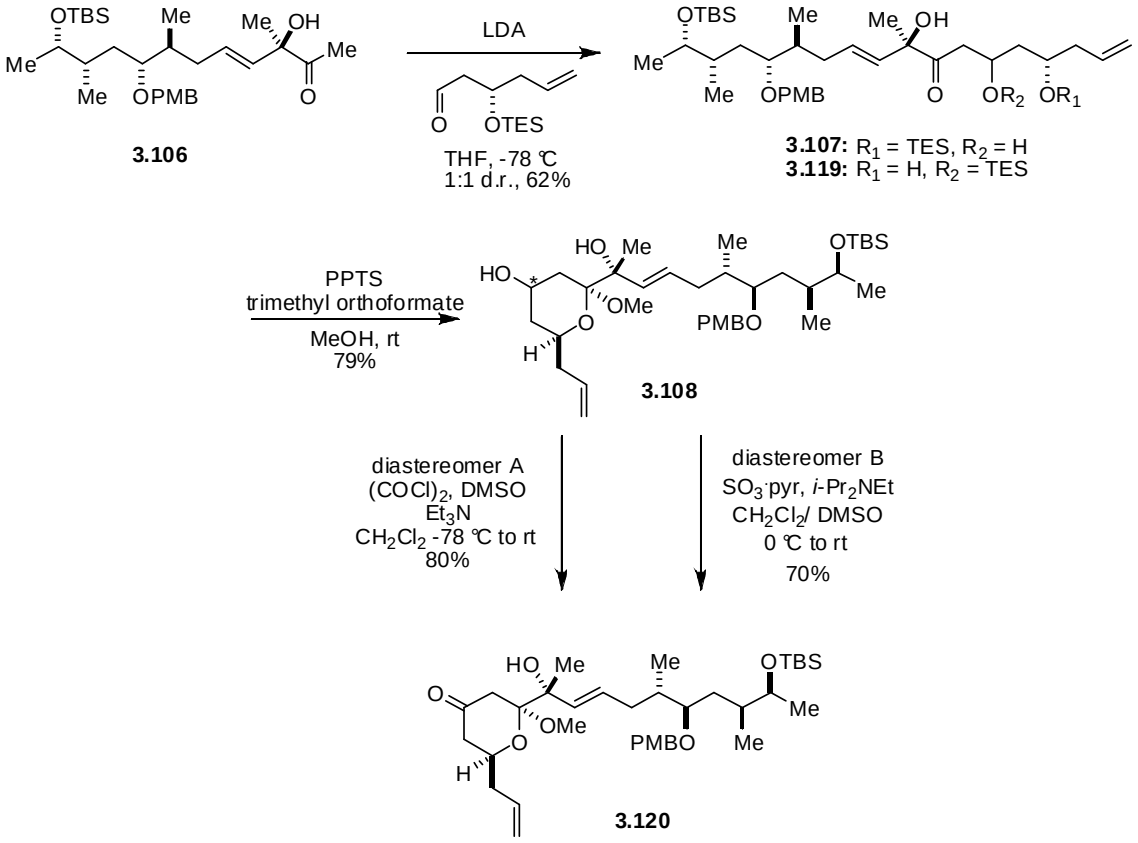


1.2 Efforts directed toward the installation of the exocyclic methylene at C11

With ketone **3.106** in hand, an nonselective aldol reaction employing LDA was utilized to forge the C11-C12 bond, generating the secondary alcohol products **3.107** in 60% yield as a 1:1 mixture of inseparable diastereomers, also containing some of the migrated TES ether substrate **3.119** (Scheme 3.34). Ketalization using 10 mol% PPTS in MeOH with 20 equiv. of trimethylorthoformate generated mixed methyl ketal diastereomers **3.108**, which

could be separated by column chromatography. Oxidation of the secondary alcohol of **3.108** to ketone **3.120** only occurred readily with one of the alcoholic substrates under Parikh-Doering conditions. Notably, the other alcoholic substrate, the stereochemistry of which was not identified, as the stereocenter was inconsequential, and was erased in the oxidation step, did not undergo oxidation utilizing Parikh-Doering oxidation conditions, but use of the Swern protocol provided ketone in 70% yield.

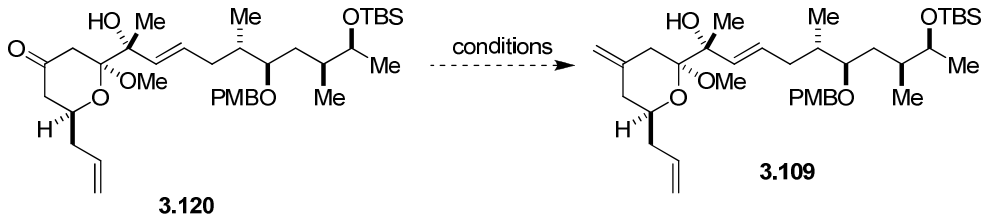
Scheme 3.34: Synthesis of ketone **3.120**.



With **3.120** in hand, a methylenation to install the exocyclic olefin was explored. Initial treatment of **3.120** with the Wittig reagent did not provide exocyclic olefin **3.109**, but resulted in elimination of the OMe group (Table 3.5, entry 1). This result was attributed to excess water being present in the phosphonium salt, generating hydroxide in the presence

of potassium *tert*-butoxide. Careful drying of the phosphonium salt prior to ylide formation, using an excess amount of the phosphonium salt relative to potassium *tert*-butoxide, or the use of a salt-free ylide were anticipated to lead to generation of desired exocyclic olefin **3.109**. However, this was not the case, as loss of the OMe group was experienced in every attempt which utilized a Wittig olefination. Other olefinations (Tebbe,[33] Tour,[34] and Takai-Nozaki[35]) were also explored, but these resulted in decomposition of the starting material (Table 3.5, entries 2-4).

Table 3.5: Attempts to install the exocyclic olefin of iriomoteolide 1a.



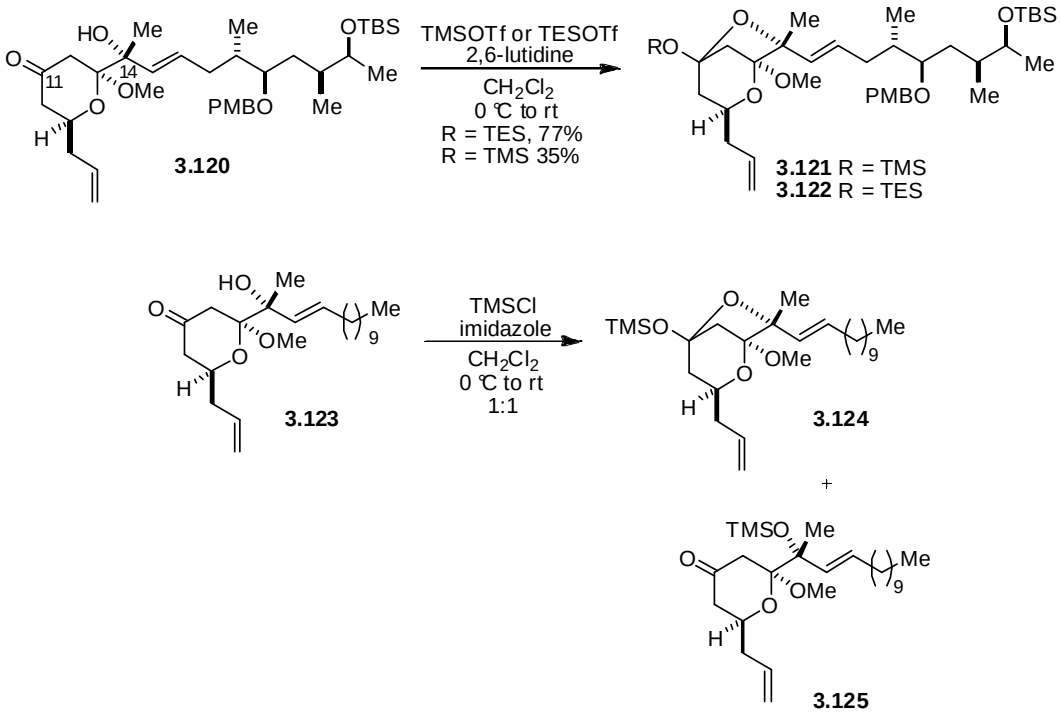
3.120 **3.109**

Entry	Reagent	Temperature	Result
1	Wittig	0 ℃	β-elimination
2	Tebbe	-40 ℃ to rt	Decomposition
3	Tour	Rt	Decomposition
4	Takai-Nozaki	0 ℃	Decomposition

It was believed that the unprotected tertiary alcohol at C14 could be the source of problems in the Wittig olefination, as it was likely that the ylide was deprotonating the tertiary alcohol, and then either an intermolecular or intramolecular elimination was leading to the loss of the OMe group. Due to these circumstances, it was thought that protection of the C14 tertiary alcohol may lead to increased reactivity of the C11 ketone. Attempts to protect tertiary alcohol of **3.120** as either the TES or TMS ether utilizing TMSOTf or TESOTf and Hünig's base led cleanly to the formation of mixed silyl ketal **3.121** (R = TMS) or **3.122** (R = TES) (Scheme 3.35). In similar systems, the use of a smaller silyl group that is less Lewis acidic

has been shown to favor protection of the alcohol over mixed silyl ketal formation.[36] Attempts to protect tertiary alcohol **3.123** of a model system with TMSCl led to a 1:1 mixture which appeared to be mixed silyl ketal **3.124** and TMS protected tertiary alcohol **3.125**.

Scheme 3.35: Attempts to protect the C14 tertiary alcohol as a silyl ether

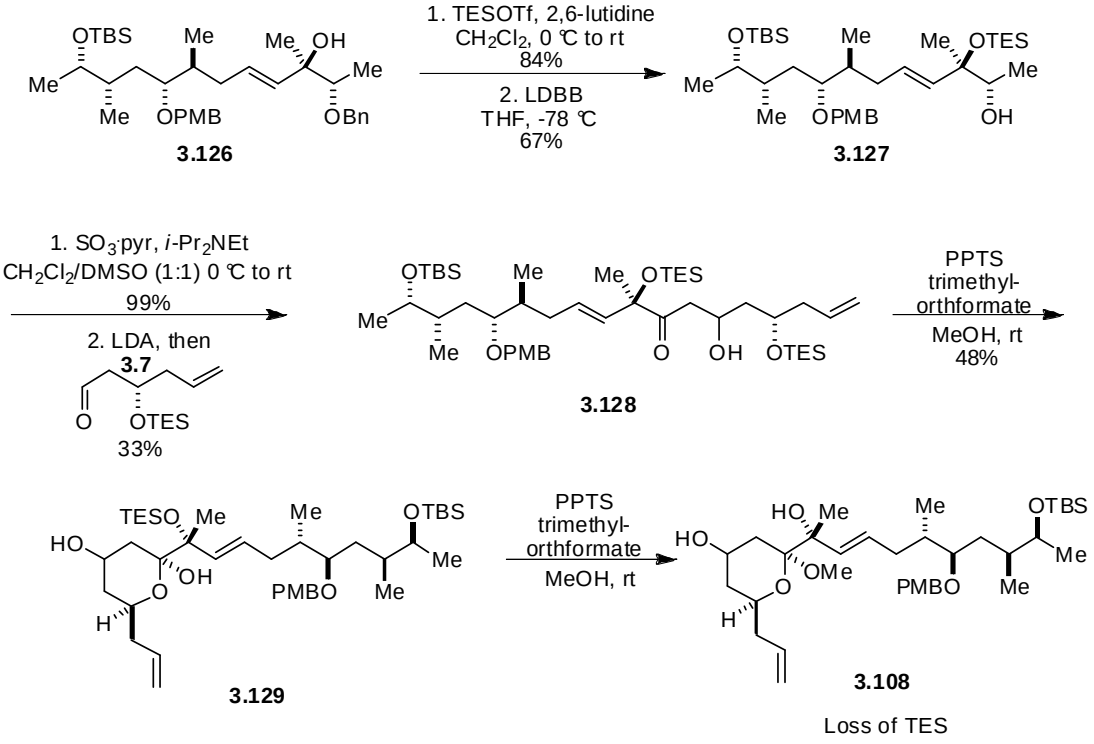


1.3 Attempts to protect the C14 tertiary alcohol as the triethylsilyl ether

Several strategies were attempted to protect the tertiary alcohol as the silyl ether at different intermediates. Protection of the tertiary alcohol of **3.126** was accomplished with TESOTf and 2,6-lutidine (Scheme 3.36), which was followed by cleavage of the benzyl ether protecting group to provide secondary alcohol **3.127**. Oxidation under Parikh-Doering conditions followed by an unselective aldol reaction with aldehyde **3.7** afforded aldol adduct **3.128** in low yields (33%). This lower, unoptimized yield in the aldol reaction was attributed to slower enolization of the protected ketone substrate, as the ketone starting material was recovered. Nonetheless, the resultant secondary alcohol **3.128** was exposed to ketalization conditions; instead of forming a mixed methyl ketal, hemiketal **3.129** was formed

predominantly, along with unidentified decomposition products. Reexposure of hemiketal **3.129** to the reaction conditions employing excess trimethyl orthoformate and PPTS led to eventual deprotection of the TES protecting group and formation of the mixed methyl ketal **3.108**.

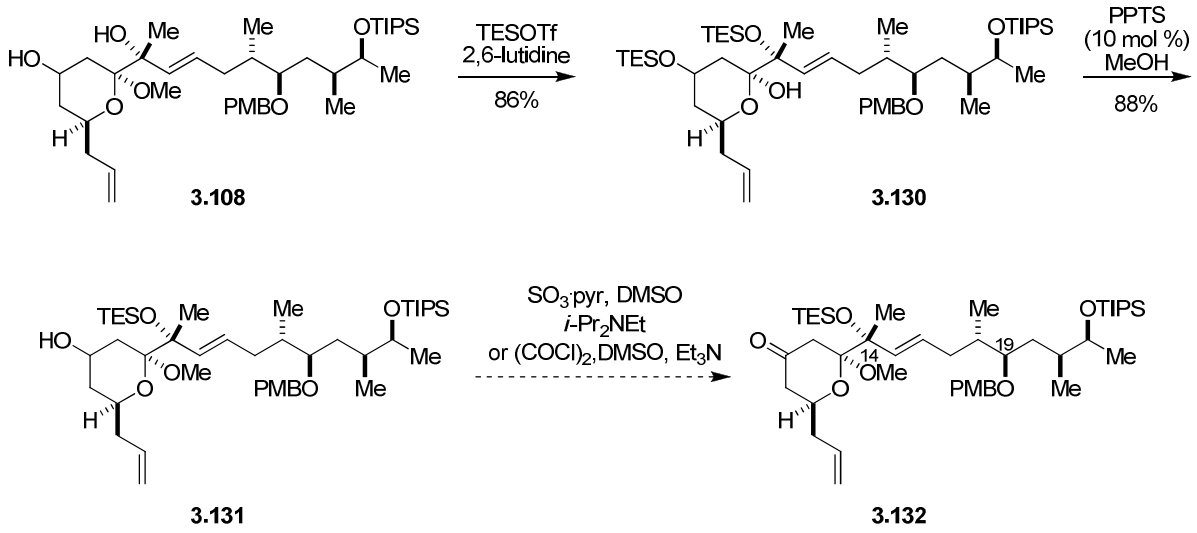
Scheme 3.36: Attempts to protect the C14 tertiary alcohol at intermediate **3.126**.



Due to the inability to protect the C14 tertiary alcohol and advance to the mixed methyl ketal, a protection of one of the diastereomers of the intermediate diol **3.108** as the bis silyl ether, followed by selective deprotection of the secondary TES ether was attempted (Scheme 3.37). Alcohol **3.108** was treated with TESOTf and 2,6-lutidine. It appeared that the product of this reaction was bis silyl ether **3.130** wherein the mixed methyl ketal was hydrolyzed to the hemiketal, which did not occur in prior attempts to protect ketone **3.120** (Scheme 3.35). Subjection of hemiketal **3.130** to monodeprotection conditions (catalytic PPTS/MeOH), resulted in the formation of a new product, which contained one triethylsilyl group and a mixed methyl ketal, tentatively assigned as **3.131**. However, when this product

was exposed to either Swern or Parikh-Doering oxidation conditions, which had previously been successful at oxidizing similar substrates, only starting material was recovered with some loss of the OMe group.

Scheme 3.37: Attempts to perform a selective deprotection of bis silyl ether **3.130**.

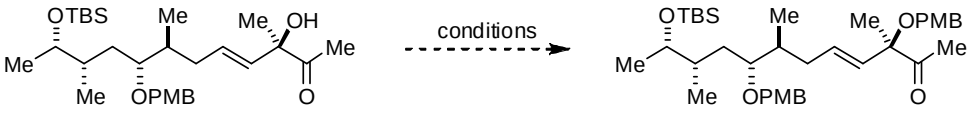


1.4 Attempts to protect the C14 tertiary alcohol as the PMB ether

Because the TES ether was being cleaved during ketalization conditions (Scheme 3.36), a more robust protecting group was explored. It was believed that a PMB protecting group or a TBS protecting group should be used to protect the tertiary alcohol of C14. A PMB ether was viewed as being the ideal protecting group in this case as it would be easier to cleave because oxidative conditions could be used, whereas a tertiary TBS group could potentially be difficult to cleave under mild conditions in the presence of sensitive functional groups in later steps. Additionally, the PMB ether at C14 could be deprotected during the same step as the deprotection of the C19 PMB ether, so an additional deprotection step would not be necessary. Furthermore, future Yamaguchi esterification should selectively occur at the less hindered secondary alcohol at C19.

Conditions to successfully protect the tertiary alcohol at C14 in the presence of a ketone were explored (Table 3.6). Unfortunately, at this juncture, none of the conditions explored (NaH and PMBCl, PMB-acetimidate and cat. TfOH) led to the formation of the desired product.

Table 3.6: Conditions surveyed to protect the C14 tertiary alcohol as the PMB ether.



3.106 **3.133**

Entry	Conditions	Result
1	NaH, PMBCl, DMF	Decomposition
2	PMB-acetimidate **3.113** Cat. TfOH	Decomposition

A model system was prepared in order to identify appropriate protection conditions at an earlier intermediate (Scheme 3.38). The model system was prepared from a cross metathesis of previously prepared enone **3.50** and 1-dodecene (**3.134**), followed by a chelation controlled addition with MeMgBr to arrive at tertiary alcohol **3.136**. Exposure of the tertiary alcohol to PMB protection conditions employing NaH, PMBCl and DMF did not result in the formation of the PMB ether **3.137** at room temperature or heating (Table 3.7, entries 1 and immediate removal of the ice bath upon addition of MeOTf led to decomposition (Table 3.7, entry 3). Maintaining the temperature at 0 ℃ for during the duration of the reaction seemed to generate a new product spot with starting material

Scheme 3.38: Preparation of a model system

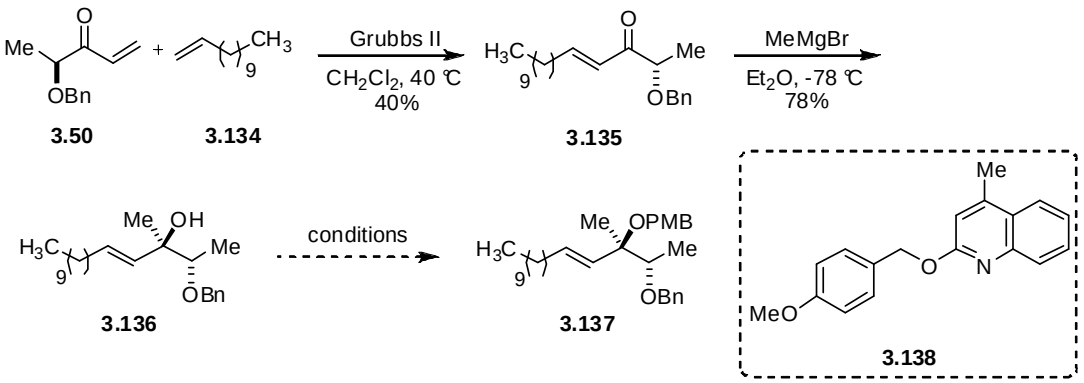


Table 3.7: Efforts directed toward the protection of tertiary alcohol **3.136** as the PMB ether (**3.137**)

Entry	Reagents	Solvent	Temperature	Result
1	NaH, PMBCl	DMF	25 °C	Starting material
2	NaH, PMBCl	DMF	50 °C	Starting material
3	**3.138**,[1] MeOTf, MgO	$PhCF_3$	0 °C, then rt	Decomposition
4	**3.138**[1] MeOTf, MgO	$PhCF_3$	0 °C	Decomposition upon workup
5	**3.138**[2] CSA	DCM	25 °C	44%[3]
6	**3.138**[4] MeOTf, MgO	$PhCF_3$	0 °C	60%[3]

[1] 2.0 equiv. Dudley reagent, 2.0 equiv. MeOTf, 2.0 equiv. MgO were used. [2] 2.0 equiv. Dudley regent were used. [3] Product was significantly tainted with a byproduct from the reaction. [4]5.0 equiv. Dudley, 5.0 equiv. MeOTf, and 10 equiv. of MgO were used.

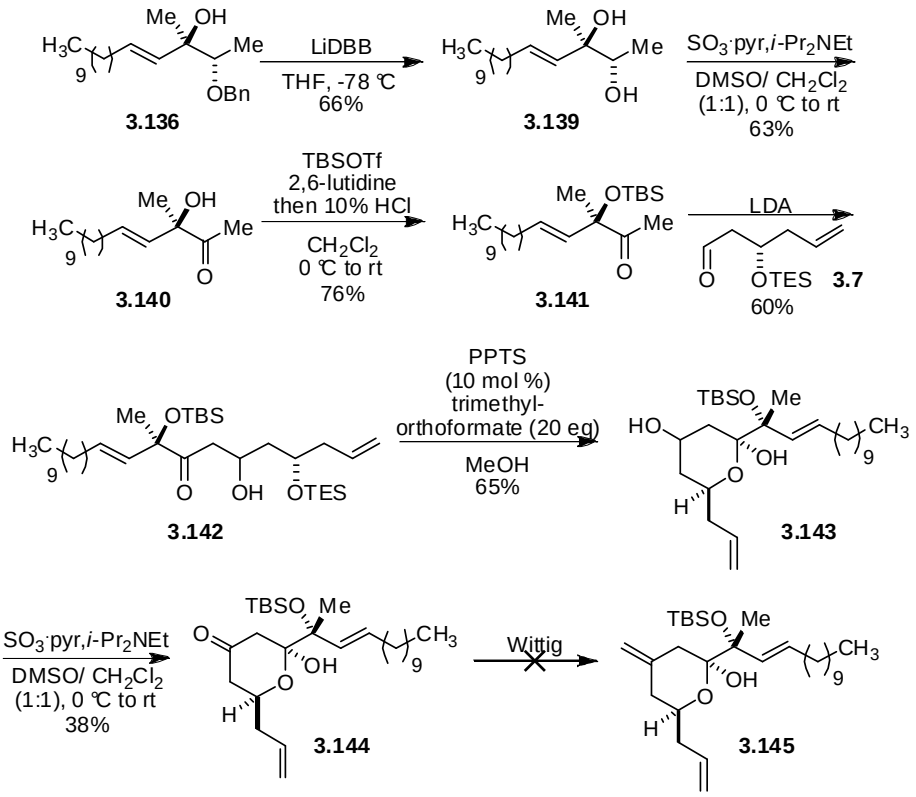
remaining; however, upon workup, the product and starting material both appeared to decompose (Table 3.7, entry 4). Different conditions and workups were also surveyed. Maintaining the temperature at 0 °C for the duratio n of the reaction, and employing 5 equiv. of the Dudley reagent, 5 equiv. of MeOTf, and 10 equiv. of MgO and skipping the workup generated the product in 60% yield, but this was significantly tainted with a byproduct from the reaction (Table 3.7, entry 6). Paquette's conditions, employing catalytic CSA in DCM

seemed to generate the product very slowly in low yields, but, once again, with a significant byproduct formation (Table 3.7, entry 5).[38]

1.5 Protection of the C14 tertiary alcohol as the TBS ether

Because of the difficulty associated with protecting the C14 tertiary alcohol of **3.136** as the PMB ether, the benzyl ether of **3.136** was reductively cleaved to afford diol **3.139** in 66% yield (Scheme 3.39). Oxidation of the diol furnished ketone **3.140** which was protected as the TBS ether **3.141**. Enolization of **3.141** for 3 h, followed by addition of aldehyde **3.7** delivered aldol adduct **3.142** as a 1:1 mixture of diastereomers. One of the diastereomers from the aldol addition was arbitrarily subjected to ketalization condtions (10 mol % PPTS, 20 equivalents of trimethyl orthoformate, and MeOH). As before, hemiketal **3.143** was formed predominantly. Exposure of hemiketal **3.143** to oxidation conditions provided a low yield of ketone **3.144**. Subsequently, upon treatment of ketone **3.144** to Wittig olefination conditions, no desired product was formed. This could be due to the instability of the lactol of **3.144**, as lactols are known to undergo olefinations when exposed to Wittig olefination conditions.[39]

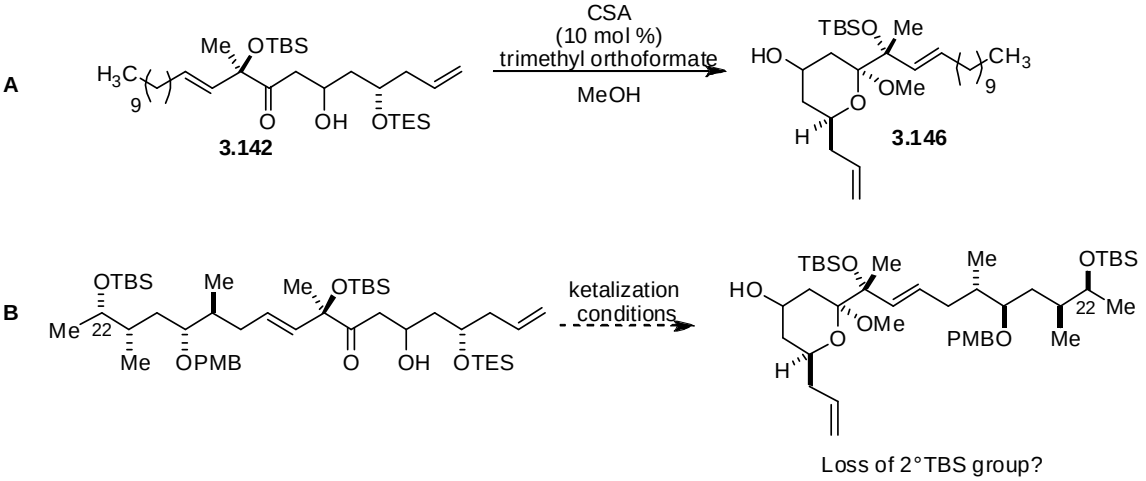
Scheme 3.39: Efforts toward the installation of an exocyclic methylene utilizing a model system.



There are several key points that deserve comment. Ketalization to form the mixed methyl ketal utilizing conditions (PPTS, MeOH, and trimethyl orthoformate) which were successful in other syntheses by the Crimmins group,[40] and others[41] failed to generate the desired mixed methyl ketal in good yields, and always gave the hemiketal as the major product. The only exception to this was when the tertiary alcohol at C14 was unprotected, and then the desired mixed methyl ketal product was obtained predominantly. In order to introduce the exocyclic olefin, it appeared as though the hemiketal should be protected as the mixed methyl ketal, given the results of the Wittig olefination of **3.144** (Scheme 3.39). Additionally, the mixed methyl ketal was a deemed a necessity for the future Yamaguchi esterification step, as Horne and coworkers had only limited success when trying to form an ester in the presence of the C13 unstable hemiketal, but saw an improvement in yield of the esterification step when the hemiketal was unmasked after the esterification had occured

(Scheme 2.5).[30] Therefore, it was believed that once a successful ketalization to form mixed methyl ketal was developed, the olefination to install the exocyclic methylene of iriomoteolide 1a should proceed smoothly, as should the subsequent Yamaguchi esterification.[30] A test reaction of model substrate **3.142** utilizing CSA/MeOH formed the desired mixed methyl ketal **3.146** (Scheme 3.40, **A**). However, because this reaction was successful, it would mean a change in protecting groups was necessary, as secondary TBS groups (which was protecting the C22 hydroxyl of the actual system) are cleaved in the presence of CSA/MeOH, and this could be problematic in later steps if deprotection of the C22 TBS ether were to occur (Scheme 3.40, **B**).

Scheme 3.40: Ketalization of **3.142** with CSA

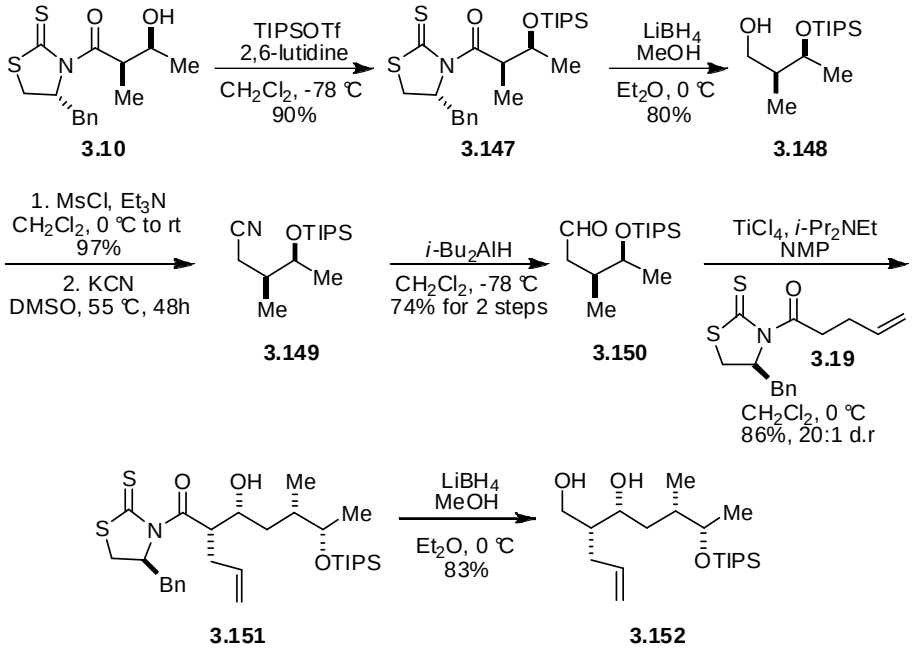


1.6 Successful installation of the C11 exocyclic olefin

To test this hypothesis, the TBS ether was replaced as the TIPS ether following aldol addition to provide **3.147** (Scheme 3.41). Cleavage of the auxiliary revealed primary alcohol **3.148** which was converted to the mesylate according to the previously established protocol. Treatment with KCN for 2 days at 55 ℃ generated the unstable nitrile **3.149**, which was immediately exposed to reducing conditions employing *i*-Bu_2AlH to arrive at aldehyde **3.150** in 74% for two steps. At this juncture, aldehyde **3.150** was utilized in an Evans *syn* aldol addition with thioimide **3.19** to provide aldol adduct **3.151** in 86% yield and 20:1 d.r.

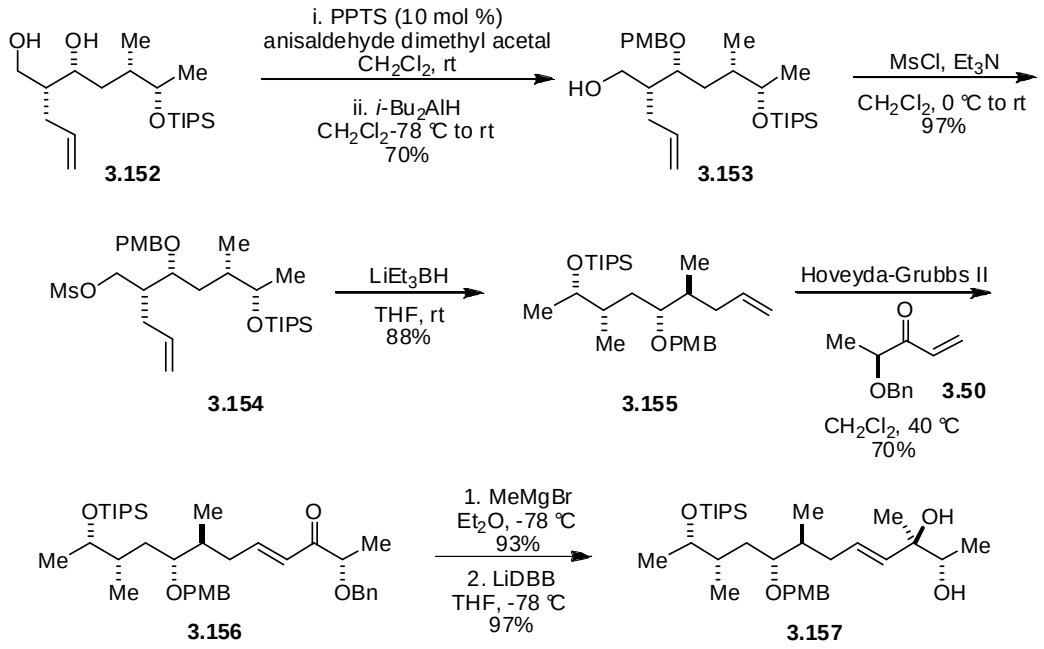
Reductive cleavage of the auxiliary was accomplished utilizing $LiBH_4$ and MeOH in Et_2O to form the diol **3.152** in 83% yield.

Scheme 3.41: Synthesis of diol **3.152**.



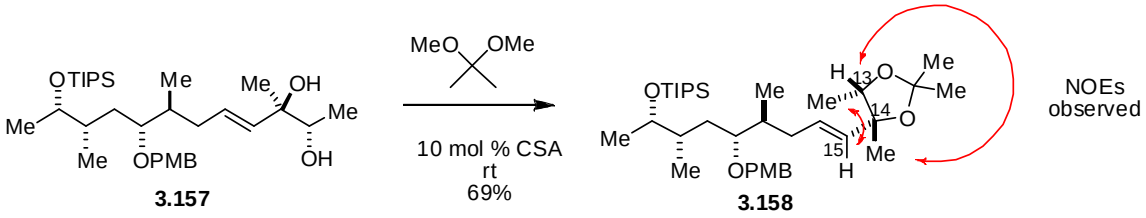
Exposure of diol **3.152** to catalytic PPTS and anisaldehyde dimethyl acetal formed the PMP acetal, which was regioselectively opened with *i*-Bu_2AlH to install the secondary PMB ether of **3.153** (Scheme 3.42). Mesylation of the resultant primary alcohol, followed by nucleophilic displacement of the mesylate generated terminal olefin **3.156** in 85% yield over two steps. Cross metathesis with Hoveyda-Grubbs second generation catalyst and enone **3.50** provided enone **3.156**, which was subjected to a chelation controlled addition with methyl Grignard to form a tertiary alcohol in 76% yield and as a 20:1 mixture of diastereomers. Reductive removal of the benzyl protecting group was accomplished with LDBB to furnish diol **3.157**.

Scheme 3.42: Preparation of diol **3.157**



The stereochemistry of the tertiary alcohol was proven by subjecting diol **3.157** to 1,1-dimethoxypropane and catalytic CSA to provide the acetonide **3.158** in 69% yield. NOESY correlations between C14 methyl group and the C13 hydrogen, and the C13 methyl group and the C15 hydrogen provided strong evidence to support the validity of the assigned structure of **3.158**.

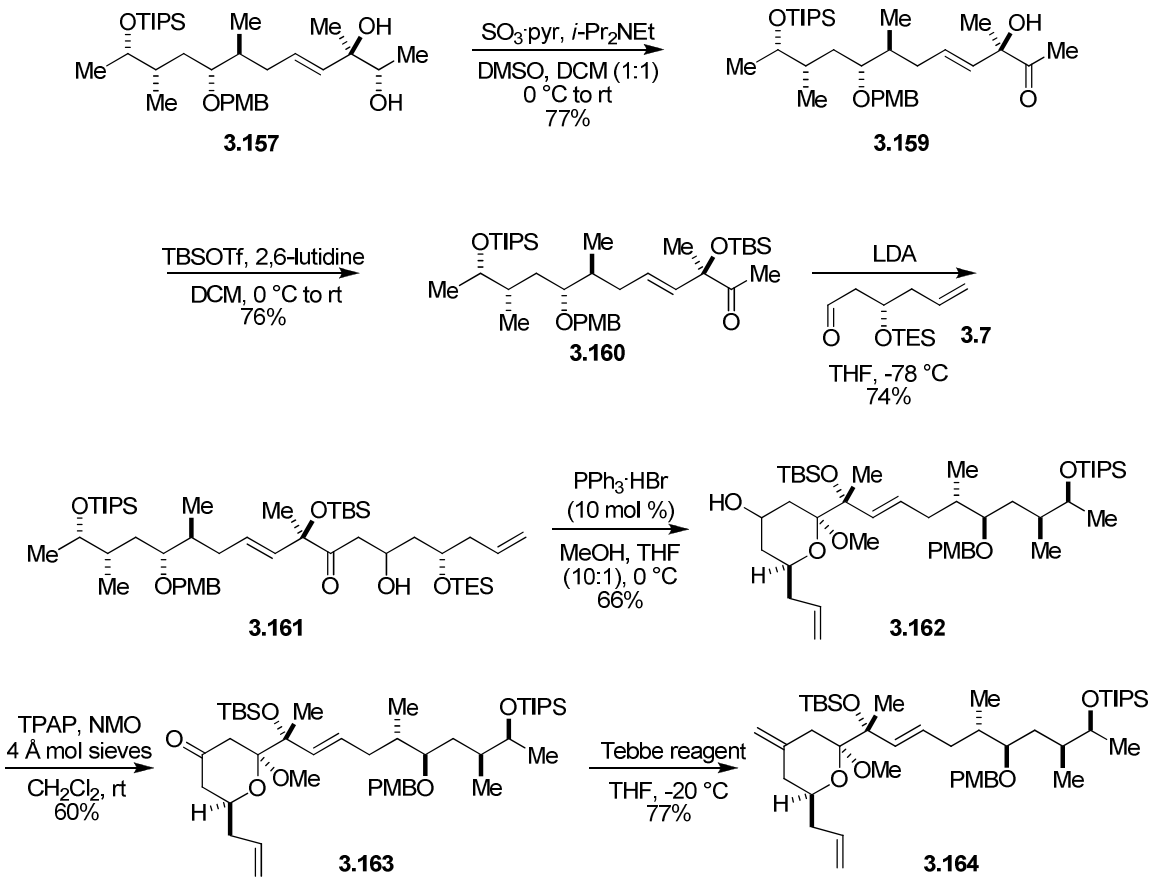
Scheme 3.43: Observed NOEs in acetonide **3.158**.



Diol **3.157** was next converted to ketone **3.159** by oxidation under Parikth-Doering conditions, followed by protection of the tertiary alcohol as the TBS ether to generate **3.160**. Exposure of **3.160** to LDA for three hours to effect enolization followed by addition of excess

aldehyde **3.7** (2 equiv) generated the product (1:1 d.r., inseparable) **3.161** in moderate yields (Scheme 3.44). Ketalization was successful employing 10 mol % triphenyl phosphonium hydrobromide salt[42] as which furnished a mixture of diasteromeric mixed methyl ketals **3.162** in 51% yield. The mixture of diastereomers was oxidized under Ley's conditions,[43] providing ketone **3.163**, which upon exposure to 10 equiv. of the Tebbe reagent at -20 ℃, underwent smooth olefination to install the exocyclic olefin of **3.164** in 77% yield. Protection of the C14 tertiary alcohol proved to be vital to the success for the C11 methylenation.

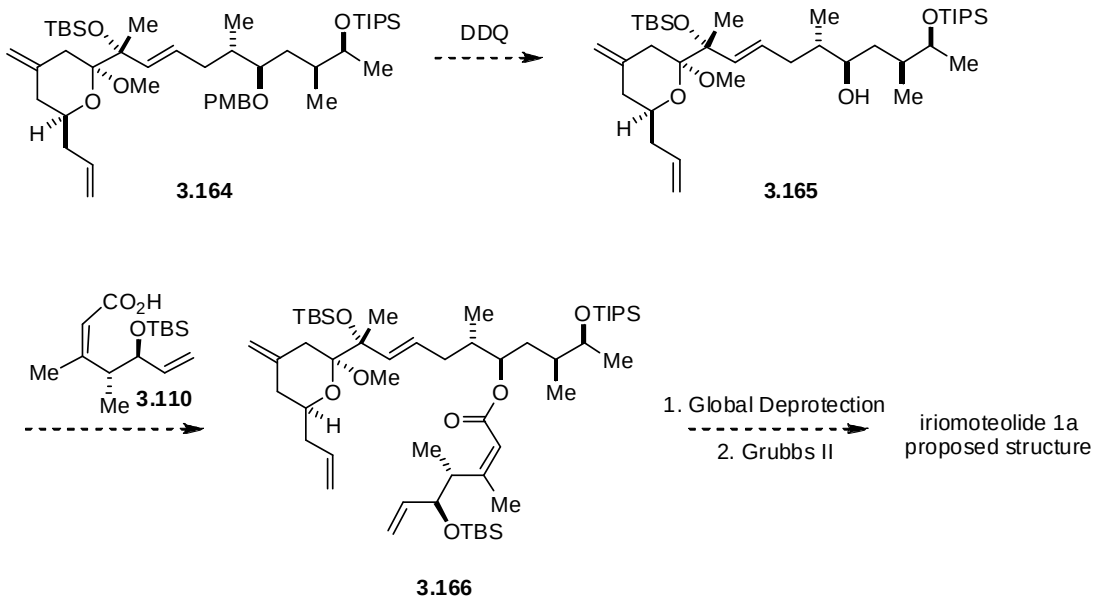
Scheme 3.44: Successful installation of the exocyclic methylene of iriomoteolide 1a.



1.7 Proposed completion of iriomoteolide 1a

To complete the synthesis, the PMB ether of **3.163** will be cleaved to reveal secondary alcohol **3.165** (Scheme 3.45). The secondary alcohol will be treated under Yamaguchi's conditions[44] with acid **3.110** to afford ester **3.166**. Global deprotection of the silyl ethers followed by a ring closing metathesis with Grubbs 2nd generation catalyst will provide the proposed structure of iriomoteolide 1a.

Scheme 3.45: Proposed completion of iriomoteolide 1a.



3.166

G. Summary

In conclusion, a concise and convergent synthesis to the core of iriomoteolide 1a has been developed. Key steps include four thiazolidinethione mediated aldol additions to generate 7 of the 9 stereocenters of iriomoteolide 1a, a chelation controlled addition with methyl magnesium bromide to form the tertiary alcohol at C14 in high diastereoselectivity, and a Tebbe olefination to install the exocyclic olefin at C11. Initially, our approach to iriomoteolide 1a relied on the formation of the C1-C11 fragment through cross metathesis. However, due to poor yields in the cross metathesis to create the C6-C7 *E* olefin, coupled

with difficulties in the selective deprotection of a primary triethylsilyl ether over a secondary triethylsilyl ether, an alternative strategy which will employ ring closing metathesis to form the C6-C7 *E*-olefin has been exploited to deliver advanced intermediate **3.164**, which can be transformed into the proposed structure in four additional steps. Once the proposed structure of iriomoteolide 1a is completed, diastereomers will be synthesized in an effort to elucidate the actual structure of the natural product.

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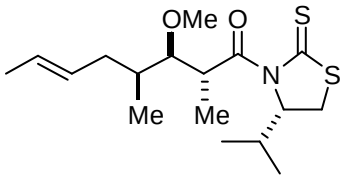
Chapter 4

Experimental Information and NMR Spectra for Chapter 1

Infrared (IR) spectra were obtained using a JACSO FT/IR 460-plus spectrometer. Proton and carbon nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded on the following instruments: Bruker Avance 400 (^{1}H at 400 MHz; ^{13}C at 100 MHz), Bruker AMX 300 (^{1}H at 300 MHz) and Bruker DRX 500 (^{1}H at 500 MHz; ^{13}C at 125 MHz). Multiplicities are reported as (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet, and (b) band. Optical rotations were determined using a JACSO P1010 polarimeter. Mass spectra were obtained using a Micromass Quattro II (triple quad) instrument with nanoelectrospray ionization. Thin layer chromatography (TLC) was conducted on silica gel 60 F_{254} TLC plates purchased from Dynamic Absorbants, Inc. Flash chromatography was carried out using silica gel (60 Å, 40 to 63 μm) purchased from Dynamic Absorbants, Inc. Dichloromethane (CH_2Cl_2) was dried by passing through a column of neutral alumina under nitrogen immediately prior to use. Alkylamines were distilled from calcium hydride immediately prior to use. Titanium tetrachloride was distilled prior to use and stored under argon. All other reagents and solvents were used as received from the manufacturer. All air and water sensitive reactions were performed under a positive flow of argon in flame dried flasks.

(*S*,*E*)-6,6-dimethoxy-5-methylhex-2-ene

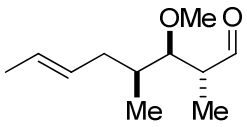
To a stirring solution of aldehyde **65** (130 mg, 1.16 mmol) in 5 mL MeOH was added *p*-TsOH (2 mg). After 8 h, the reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution and extracted into Et_2O (3 x 10 mL). The organic layer was sequentially washed with $NaHCO_3$ (1 x 10 mL), water (2 x 10 mL), and brine (2 x 10 mL). The organic layer was dried ($MgSO_4$) and concentrated at reduced pressure in an ice bath. The product was isolated by Kugelrohr distillation (55 mmHg, 100 ℃) to give 180 mg of acetal **59** (87%). 1H NMR (300 MHz, $CDCl_3$) δ 5.51-5.40 (band, 2H), 4.07 (d, *J* = 6.3, 1H), 3.37 (s, 6H), 2.23-2.18 (m, 1H), 1.85-1.77 (m, 1H), 1.69 (d, *J* = 4.8, 3H), 0.91 (d, *J* = 6.3, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.12, 126.52, 108.46, 54.08, 53.90, 36.01, 35.08, 17.93, 14.11; IR (thin film) ν 2962(w), 2922(w), 2112(w), 1782(m), 1644(s), 1462(m), 1382(w), 1260(w), 1204(w), 1093(w); $[\alpha]^{22}_D$ = -135 (*c* = 1.46, CH_2Cl_2).



(2*R*,3*R*,4*S*,*E*)-1-((*S*)-4-isopropyl-2-thioxothiazolidin-3-yl)-3-methoxy-2,4-dimethyloct-6-en-1-one

A solution of thione **60** (962 mg, 4.43 mmol) in 44 mL CH_2Cl_2 was cooled to 0 ℃. Neat $TiCl_4$ (0.53 mL, 4.86 mmol) was added dropwise, and the resulting slurry was stirred for 5 min. The reaction was then cooled to -78 ℃ and *i*-Pr_2NEt (0.85 mL, 4.86 mmol) in 1 mL of CH_2Cl_2 was added dropwise. The resulting dark red solution was warmed to -40 ℃ and stirred for 2 h. After 2 h, the reaction was cooled to -78 ℃ and freshly distilled, neat $SnCl_4$ (0.26 mL, 2.21 mmol) was added dropwise, followed by the addition of acetal **59** (350 mg, 2.21 mmol) in 1 mL CH_2Cl_2. After addition was complete, the reaction was allowed to stir at

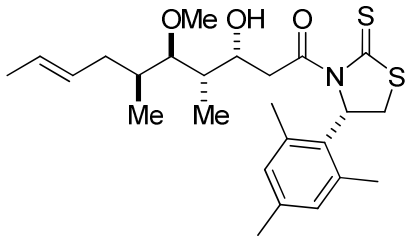
-78 ℃ for an additional 15 min, and then transferred into a -20 ℃ bath where it was allowed to stir for 2 h. The reaction was then quenched by the addition of a saturated aqueous NH_4Cl solution. The layers were separated and the aqueous layer was then extracted into CH_2Cl_2 (2 x 30 mL). The organic extracts were dried (Na_2SO_4) and evaporated to give a crude yellow oil which was purified by flash chromatography (10% CH_2Cl_2/hexanes to 60% CH_2Cl_2/hexanes) to afford 490 mg of the product **81** (64%), a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.51 (m, 2H), 5.30 (ddd, *J* = 6.8, 6.8, 0, 1H), 5.16 (m, 1H), 3.38 (s, 3H), 3.00 (dd, *J* = 11.2, 0, 1H), 2.36 (m, 1H), 2.31 (m, 1H), 2.21 (m, 1H), 2.04 (m, 1H), 1.69 (d, *J* = 5.6, 4H), 1.09 (d, *J* = 6.8, 3H), 1.05 (d, *J* = 6.8, 3H), 1.02 (d, *J* = 6.8, 3H), 0.89 (d, *J* = 6.8, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.61, 177.22, 129.94, 126.50, 86.09, 71.67, 60.83, 41.46, 37.90, 35.37, 30.54, 29.22, 19.00, 17.88, 17.32, 14.95, 12.93; IR (thin film) ν 2964(m), 2933(m), 1698(s), 1454(m), 1373(m), 1313(w), 1254(m), 1155(s), 1088(m), 1046(w), 1015(w); $[\alpha]^{22}_D$ = +51 (*c* = 0.36, CH_2Cl_2); MS (ESI) calculated for $C_{17}H_{29}NO_2Si_2$ $[M+Na]^+$: 366.2, found 366.2.



(2*R*,3*R*,4*S*,E)-3-methoxy-2,4-dimethyloct-6-enal

A solution of thiazolidinethione **81** (417 mg, 1.2 mmol) in CH_2Cl_2 (12 mL) was cooled to -78 ℃. A 1 M solution of *i*-Bu_2AlH in hexanes (2.40 mL, 2.40 mmol) was added slowly dropwise to the reaction mixture until the yellow color disappeared. The reaction was immediately quenched by the addition of saturated aqueous Na/K tartrate solution, and allowed to warm to room temperature and stir at room temperature for 1 h. The layers were then separated and the aqueous layer extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4), evaporated, and eluted through a plug of silica (8% EtOAc/hexanes to 50% EtOAc/hexanes)

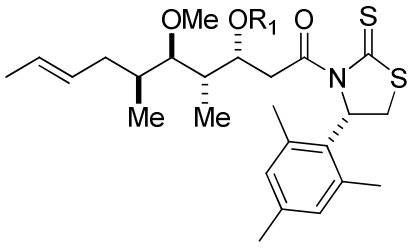
to give 194 mg of the product **55** (88%), a colorless oil which was used immediately. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (d, *J* = 2.4, 2H), 5.51 (band, 2H), 3.42 (s, 3H), 3.29 (dd, *J* = 4.0, 7.2, 1H), 2.67 (ddddd, *J* = 9.2, 9.2, 9.2, 6.8, 2.4, 1H), 2.19 (m, 1H), 1.98 (m, 1H), 1.79 (m, 1H), 1.70 (dd, , *J* = 6, 0.8, 3H), 1.07 (d, *J* = 6.8, 3H), 0.94 (d, *J* = 6.8, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.78, 129.29, 126.92, 85.82, 60.40, 49.23, 37.00, 36.10, 17.90, 13.76, 11.47; IR (thin film) ν 2965(s), 2933(s), 1724(m), 1456(m), 1378(w), 1258(w), 1156(w), 1093(m); $[\alpha]^{23}_{D}$ = -31 (*c* = 0.23, CH_2Cl_2); MS (ESI) calculated for $C_{11}H_{20}O_2$ $[M+Na]^+$: 207.2, found 207.2.



(3*R*,4*S*,5*R*,6*S*,*E*)-3-hydroxy-1-((*S*)-4-mesityl-2-thioxothiazolidin-3-yl)-5-methoxy-4,6-dimethyldec-8-en-1-one

A solution of thione **44** (154 mg, 0.56 mmol) in 6 mL CH_2Cl_2 was cooled to 0 ℃. $TiCl_4$ (60 μL, 0.56 mmol) was added dropwise and the reaction was allowed to stir 5 min. The reaction was then cooled to -78 ℃ and *i*Pr_2NEt (100 μL, 0.56 mmol) in 1 mL of CH_2Cl_2 was added dropwise. The reaction was allowed to warm to -40 ℃ and enolize for 2 h. After 2 h, the reaction was recooled to -78 ℃ and aldehyde **55** (68 mg, 0.37 mmol) was added as a solution in 1mL of CH_2Cl_2. After 4 h, the reaction was quenched with half saturated NH_4Cl solution and the layers were separated. The aqueous layer was further extracted with CH_2Cl_2 (3x), and the organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude material was purified via flash column chromatography (10% EtOAc/hexanes) to yield 150 mg of a yellow oil **16** (88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 2H), 6.44 (dd, *J* =

9.6, 9.6, 1H), 5.45 (b, 2H), 4.34 (brd, 1H), 3.72 (dd, *J* = 17.2, 9.2, 1H), 3.62 (dd, *J* = 11.2, 11.2, 1H), 3.43 (s, 3H), 3.37 (dd, *J* = 11.2, 9.2, 1H), 3.15 (m, 2H), 3.02 (dd, *J* = 7.2, 4.8, 1H), 2.42 (bds, 6H), 2.25 (s, 3H), 2.02 (m, 1H), 1.99 (m, 1H), 1.84 (m, 1H), 1.68 (m, 3H), 1.47 (m, 1H), 0.88 (d, *J* = 6.8, 3H), 0.83 (d, *J* = 6.8, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.50, 174.59, 137.79, 132.70, 129.74, 126.35, 87.90, 68.14, 67.50, 61.51, 45.07, 39.30, 37.43, 35.88, 32.50, 20.74, 20.22, 17.93, 13.58, 10.96; IR (thin film) ν 3477(s), 2964(s), 2927(s), 1708(s), 1611(w), 1455(m), 1372(m), 1330(w), 1260(m), 1181(m), 1128(w), 1088(w); $[\alpha]^{25}_{D}$ = +84.3 (*c* = 0.45, CH_2Cl_2); MS (ESI) calculated for $C_{25}H_{37}NO_3S_2$ $[M+Na]^+$: 486.2, found 486.2.

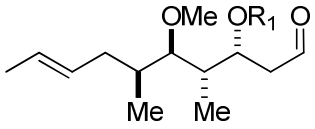


R_1 = TES

(3*R*,4*R*,5*R*,6*S*,*E*)-1-((*S*)-4-mesityl-2-thioxothiazolidin-3-yl)-5-methoxy-4,6-dimethyl-3-(triethylsilyloxy)dec-8-en-1-one

To a solution of alcohol **82** (321 mg, 0.69 mmol) in CH_2Cl_2 (6 mL) at 0 ℃ was added freshly distilled 2, 6-lutidine (160 μL, 1.39 mmol) followed by dropwise addition of neat TESOTf (242 μL, 1.07 mmol). After addition was complete, the ice bath was removed and the reaction was allowed to stir for an additional hour at room temperature. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3x), and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude yellow residue was purified by flash column chromatography (1% EtOAc/hexanes to 3% EtOAc/hexanes) to obtain 385 mg of a yellow

oil **83** (96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (s, 2H), 6.40 (dd, *J* = 10.2, 10.2, 1H), 5.42 (b, 2H), 4.55 (m, 1H), 3.71 (dd, *J* = 18, 5.2, 1H), 3.59 (dd, *J* = 10.8, 10.8, 1H), 3.39 (dd, *J* = 12, 0, 1H), 3.35 (s, 3H), 3.22 (dd, *J* = 18, 9.2, 1H), 3.00 (*J* = 8, 1H), 2.41 (brs, 6H), 2.22 (s, 3H), 2.06 (m, 1H), 1.93 (m, 1H), 1.67 (d, *J* = 5.6, 3H), 1.52 (m, 1H), 0.97 (b, 10H), 0.63 (b, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.64, 172.79, 137.69, 132.32, 130.47, 125.93, 84.26, 68.01, 67.83, 60.28, 45.90, 39.48, 38.27, 35.59, 32.33, 20.62, 20.12, 17.82, 12.50, 9.69, 6.93, 5.45; IR (thin film) ν 2958(s), 2876(s), 2731(w), 1713(s), 1611(w), 1456(m), 1403(w), 1371(m), 1329(w), 1302(w), 1260(m), 1177(m), 1124(w), 1091(w), 1062(w), 1017(m); $[\alpha]^{24}_{D}$ = +20 (*c* = 0.71, CH_2Cl_2); MS (ESI) calculated for $C_{31}H_{51}NO_3S_2Si$ $[M+H]^+$: 578.3, found 578.3.

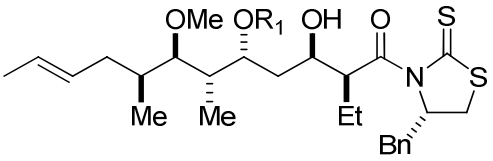


R_1 = TES

(3*R*,4*R*,5*R*,6*S*,*E*)-5-methoxy-4,6-dimethyl-3-(triethylsilyloxy)dec-8-enal

A solution of the thione **83** (155 mg, 270 mmol) in CH_2Cl_2 (3 mL) was cooled to -78 ℃. A 1 M solution of *i*-Bu_2AlH in hexanes (540 μL, 540 mmol) was added dropwise until the yellow color disappeared. The reaction was immediately quenched by the addition of a saturated aqueous sodium potassium tartrate solution and allowed to warm to room temperature with vigorous stirring. The reaction mixture was allowed to stir at room temperature for an additional hour or until the emulsion had dispersed. The layers were then separated and the aqueous layer was further extracted with CH_2Cl_2 (3x). The organic extracts were combined, dried (Na_2SO_4), and the solvent removed to afford a residue containing crystalline thiazolidinethione and the aldehyde. The crude product was purified via column chromatography (10% EtOAc/hexanes to 50% EtOAc/hexanes) to afford 83.5 mg of

aldehyde **56** (91%) which was used immediately in the next reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (dd, *J* = 2.4, 2.4, 1H), 5.49-5.37 (m, 2H), 4.65 (ddd, *J* = 6.4, 6.4, 2, 1H), 3.50 (s, 3H), 3.16 (dd, *J* = 1.6, 9.2, 1H), 2.67 (ddd, *J* = 2.4, 7.2, 16, 1H), 2.61 (ddd, *J* = 2.4, 6.4, 15.6, 1H), 2.18 (m, 1H), 2.06 (m, 1H), 1.70 (m, 1H), 1.69 (d, *J* = 5.6, 3H), 1.57 (m, 1H), 1.00 (t, *J* = 8, 9H), 0.84 (d, *J* = 7.2, 3H), 0.82 (d *J* = 6.8, 3H), 0.664 (q, *J* = 8, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.38, 130.27, 126.41, 84.37, 67.27, 60.64, 50.78, 42.28, 38.37, 35.67, 17.89, 12.90, 10.22, 6.91, 5.48; IR (thin film) ν 2959(s), 2912(s), 2877(s), 2718(w), 2359(m), 1728(s), 1456(m), 1415(w), 1381(w), 1240(w), 1134(w), 1090(m), 1016(w); $[\alpha]^{23}_{D}$ = -5 (*c* = 0.6, CH_2Cl_2); MS (ESI) calculated for $C_{19}H_{38}O_3Si$ $[M+Na]^+$: 365.2, found 365.2.

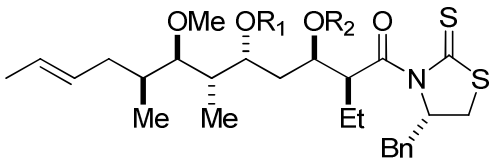


R_1 = TES

(2*S*,3*R*,5*R*,6*R*,7*R*,8*S*,*E*)-1-((*S*)-4-benzyl-2-thioxothiazolidin-3-yl)-2-ethyl-3-hydroxy-7-methoxy-6,8-dimethyl-5-(triethylsilyloxy)dodec-10-en-1-one

To a 0 ℃ solution of thione **57** (193 mg, 0.69 mmol) was added $TiCl_4$ (70 μL, 0.69 mmol). After 20 min of stirring at 0 ℃, (-)-sparteine (160 μL, 0.69 mmol) was added dropwise to the yellow slurry and the solution turned a deep black color. After 20 min more of stirring at 0 ℃, N-methyl-2-pyrrolidone (67 μL, 0.69 mmol) was added and the reaction was stirred at 0 ℃ for 20 min. After 20 min, the reaction was cooled to -78 ℃ and aldehyde **56** (70 mg, 0.20 mmol) was added in 500 μL CH_2Cl_2. The flask containing the aldehyde was rinsed with an additional 500 μL CH_2Cl_2 and added to the reaction flask. The reaction was allowed to warm slowly to -50 ℃, and stir overnight. The reacti on was then quenched with saturated

aqueous NH_4Cl solution. The layers were separated, and the aqueous layer was further extracted with CH_2Cl_2 (3x). The combined organic extracts were dried (Na_2SO_4) and evaporated to give a crude yellow residue which was purified by column chromatography (8% EtOAc/hexanes to 20% EtOAc/hexanes) to yield 83 mg alcohol **84** (65%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.29 (band, 5H), 5.47-5.35 (b, 3H), 4.93 (m, 1H), 4.17 (brd, 1H), 4.11 (m, 1H), 3.47 (s, 3H), 3.38 (dd, *J* = 5.6, 9.2, 1H), 3.30 (m, 1H), 3.15 (m, 3H), 2.88 (dd, *J* = 9.2, 0, 1H), 2.17 (m, 1H), 2.02-1.95 (b, 2H), 1.88 (m, 1H), 1.79 (b, 6H), 1.03 (b, 12H), 0.88 (d, *J* = 3.6, 3H), 0.85 (d, *J* = 4, 3H), 0.67 (q, *J* = 6.4, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.79, 172.26, 136.58, 130.25, 129.42, 128.88, 127.18, 126.51, 84.59, 71.58, 70.23, 69.38, 60.14, 50.37, 40.68, 39.69, 38.69, 36.83, 35.46, 31.81, 19.93, 18.00, 13.48, 7.02, 5.36; IR (thin film) ν 3439(br), 2959(s), 2359(w), 1693(m), 1455(m), 1340(w), 1263(m), 1190(w), 1163(m), 1135(w), 1034(w); $[\alpha]^{23}_D$ = +60.8 (*c* = 0.6 CH_2Cl_2); MS (ESI) calculated for $C_{33}H_{35}NO_4S_2Si$ $[M+Na]^+$: 644.3, found 644.3.

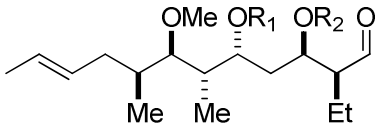


R_1, R_2 = TES

(2*S*,3*R*,5*R*,6*R*,7*R*,8*S*,*E*)-1-((*S*)-4-benzyl-2-thioxothiazolidin-3-yl)-2-ethyl-7-methoxy-6,8-dimethyl-3,5-bis(triethylsilyloxy)dodec-10-en-1-one

To a solution of alcohol **84** (26 mg, 0.042 mmol) in CH_2Cl_2 (1 mL) at 0 ℃ was added 2,6-lutidine (10 μL, 0.084 mmol) followed by addition of TESOTf (14 μL, 0.063 mmol). The reaction was allowed to slowly warm to room temperature and stir. After 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$ solution and the layers were separated. The aqueous layer was further extracted with CH_2Cl_2. The organic layers were combined,

dried (Na_2SO_4) and the solvent removed in vacuo to yield a crude yellow residue which was further purified by column chromatography (3% EtOAc/Hexanes) to obtain 28.6 mg of silyl ether **85** (93%), a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.28 (b, 5H), 5.52-5.39 (b, 2H), 5.27 (dddd, *J* = 8.5, 8.5, 3.2, 3.2, 1H), 4.78 (m, 1H), 4.13 (m, 1H), 4.03 (dd, *J* = 5.6, 11.2, 1H), 3.47 (s, 3H), 3.36-3.32 (m, 2H), 3.16 (dd, *J* = 9.6, 0, 1H), 3.11 (dd, *J* = 10.8, 12.8, 1H), 2.87 (dd, *J* = 11.2, 0, 1H), 2.18 (m, 1H), 2.04-1.88 (b, 3H), 1.84 (m, 1H), 1.78-1.57 (b, 6H), 1.05 (b, 21H), 0.85 (d, *J* = 7.2, 3H), 0.77 (d, *J* = 6.8, 3H), 0.69 (b, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.94, 175.88, 136.92, 130.72, 129.47, 128.86, 127.09, 126.10, 84.34, 71.18, 69.70, 69.45, 60.86, 51.45, 42.26, 40.55, 38.58, 36.66, 35.80, 31.98, 21.41, 17.91, 12.88, 11.91, 9.66, 7.12, 7.00, 6.03, 5.25; IR (thin film) ν 2957(s), 2912(s), 2876(s), 1696(m), 1604(w), 1495(w), 1456(m), 1414(w), 1379(w), 1340(m), 1318(w), 1292(w), 1263(w), 1190(m), 1164(s), 1134(w), 1084(w), 1040(m), 1010(m); $[\alpha]^{23}_D$ = +81.2 (*c* = 1.6, CH_2Cl_2); MS (ESI) calculated for $C_{39}H_{69}NO_4S_2Si_2$ $[M+Na]^+$: 758.5, found 758.5.

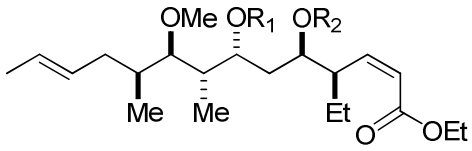


R_1, R_2 = TES

(2*S*,3*R*,5*R*,6*R*,7*R*,8*S*,*E*)-2-ethyl-7-methoxy-6,8-dimethyl-3,5-bis(triethylsilyloxy)dodec-10-enal

A solution of silyl ether **85** (60 mg, 0.082 mmol) in 2 mL CH_2Cl_2 was cooled to -78 ℃. A 1 M solution of *i*Bu_2AlH (0.16 mL, 0.16 mmol) in hexanes was added dropwise until the yellow color disappeared. The reaction was immediately quenched by the addition of aqueous saturated sodium potassium tartrate solution, and allowed to warm to room temperature with vigorous stirring. After dispersion of the emulsion, the layers were separated and the

aqueous layer was further extracted with CH_2Cl_2 (3x). The combined organic extracts were dried (Na_2SO_4) and concentrated under vacuo. The crude material, which contained the crystalline thione was purified via column chromatography (7% EtOAc/hexanes to 50% EtOAc/hexanes) to obtain 42 mg of the resultant aldehyde **55** (98%), a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 1H), 5.50-5.39 (b, 2H), 4.15 (ddd, *J* = 7.2, 7.2, 2.4, 1H), 4.02 (dd, *J* = 7.2, 7.2, 1H), 3.46 (s, 3H), 3.16 (dd, *J* = 9.6, 0, 1H), 2.20 (m, 2H), 2.05 (m, 1H), 1.87 -1.80 (b, 3H), 1.68 (b, 4H), 1.54 (m, 2H), 1.01 (b, 21H), 0.83 (d, *J* =6.8, 3H), 0.77 (d, *J* = 6.8, 3H), 0.65 (b, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.03, 130.57, 126.22, 84.26, 69.44, 69.10, 60.89, 57.78, 40.38, 40.10, 38.44, 35.71, 17.89, 16.18, 12.65, 12.59, 9.22, 7.00, 6.80, 5.85, 5.16; IR (thin film) ν 2958(s), 2877(s), 2360(m), 2341(m), 1726(m), 1458(s), 1415(s), 1379(w), 1239(w), 1138(w), 1082(s), 1016(m); $[\alpha]^{22}_D$ = -6 (*c* = 0.54, CH_2Cl_2); MS (ESI) calculated for $C_{29}H_{60}O_4Si_2$ $[M+H]^+$: 529.40, found 529.3.

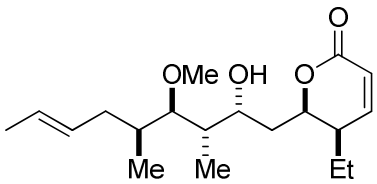


R_1, R_2 = TES

(2*Z*,4*R*,5*R*,7*R*,8*R*,9*R*,10*S*,12*E*)-ethyl-4-ethyl-9-methoxy-8,10-dimethyl-5,7-bis(triethylsilyloxy)tetradeca-2,12-dienoate

A solution of phosphonate **86** (261 mg, 0.814 mmol) in THF (10 mL) was cooled to 0 ℃. NaI (94 mg, 0.625 mmol) was added, and the solution was allowed to stir 5 min. NaH (33 mg, 0.814 mmol) as a 60% dispersion in mineral oil was then added to the reaction mixture, and allowed to stir an additional 15m. After 15m, the reaction flask was cooled to -78 ℃, and aldehyde **55** (42 mg, 0.079 mmol) was added as solution in THF (500 μL). The flask containing the aldehyde was washed with an additional 500 μL and transferred to the reaction flask. The reaction mixture was allowed to slowly warm to room temperature over

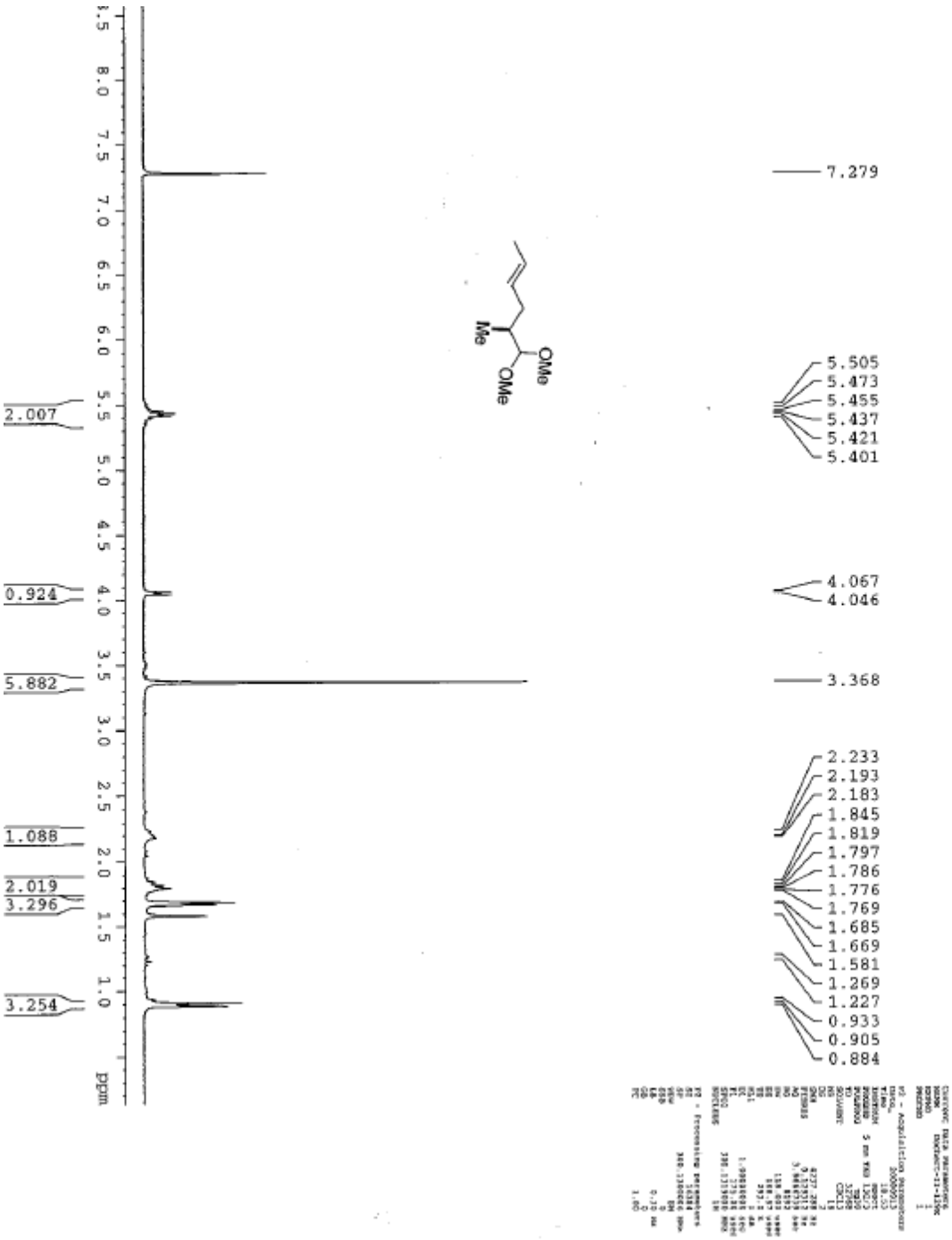
2h. After 2h, the reaction was quenched with saturated NH_4Cl solution, the layers separated, and the aqueous layer extracted with EtOAc (3x). The organic layer was then dried over Na_2SO_4, the solvent was evaporated and the crude material subjected to flash column chromatography (100% hexanes to 5% EtOAc/ Hexanes) to afford 40 mg of ester **21** (83%), a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (dd, *J* = 10.4, 10.4, 1H), 5.87 (d, *J* = 12, 1H), 5.48 (m, 2H), 4.23 (b, 3H), 3.72 (m, 1H), 3.47 (s, 3H), 3.43 (m, 1H), 3.18 (dd, *J* = 9.6, 0, 1H), 2.17 (m, 1H), 2.05 (m, 1H), 1.86 (m, 1H), 1.78-1.67 (b, 7H), 1.30 (b, 4H), 1.00 (b, 26H), 0.76 (d, *J* = 6.4), 0.66 (b, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.08, 152.08, 130.85, 126.03, 120.52, 84.44, 72.34, 69.35, 69.90, 59.70, 44.42, 41.20, 39.93, 38.61, 35.80, 21.58, 17.96, 14.29, 12.76, 11.73, 9.36, 7.11, 6.99, 6.93, 5.98, 5.90, 5.30, 5.18; IR (thin film) ν 2959(s), 2877(s), 2358(w), 1723(s), 1644(w), 1456(m), 1414(w), 1381(w), 1237(w), 1182(w), 1182(m), 1088(m), 1016(m); $[\alpha]^{22}_D$ = -55 (*c* = 0.21, CH_2Cl_2); MS (ESI) calculated for $C_{33}H_{66}O_5Si_2$ $[M+H]^+$: 599.5, found 599.5.



(-)-Pironetin

Ester **87** (38.7 mg, 0.065 mmol) was dissolved in 1 mL of a 10:1 mixture of C_6H_6 and MeOH. To this mixture was added PPTS (1 mg). The reaction was allowed to stir at room temperature for 3h, then it was heated to 60 ℃ and stirred for 3h. After 3h, the solvent was removed and the crude material was subjected to flash column chromatography (25% EtOAc/hexanes to 40% EtOAc/hexanes) to obtain 13.2 mg of pironetin **1** (63%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (dd, *J* = 6, 10, 1H), 6.05 (d, *J* = 10, 1H), 5.48-5.36 (m, 2H), 4.77 (m, 1H), 4.23 (brd, 1H), 3.49 (s, 3H), 3.48 (d, *J* = 2.5, 1H), 3.01 (dd, *J* = 4.0, 6.0, 1H), 2.30 (m, 1H), 2.13 (m, 1H), 1.89 (m, 2H), 1.80 (m, 1H), 1.74-1.64 (b, 6H), 1.55 (m, 1H), 1.03 (d, *J*

= 7, 3H), 1.00 (t, *J* = 8, 3H), 0.982 (d, *J* = 7, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.65, 150.60, 128.81, 126.90, 120.85, 91.14, 77.82, 67.47, 61.55, 39.15, 39.03, 37.30, 36.73, 36.20, 20.79, 17.93, 15.23, 12.19, 11.00; IR (thin film) ν 3479(s), 2965(s), 2934(s), 1715(s), 1457(m), 1381(m), 1315(w), 1256(m), 1138(w), 1094(m), 1027(m); $[\alpha]^{22}_{D}$ = -98 (*c* = 0.51, $CHCl_3$); MS (ESI) calculated for $C_{19}H_{32}O_4$ $[M+H]^+$: 325.23, found 325.23.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OMe
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5.401
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4.046
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2.233
2.193
2.183
1.845
1.819
1.797
1.786
1.776
1.769
1.685
1.669
1.581
1.269
1.227
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0.905
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2.019
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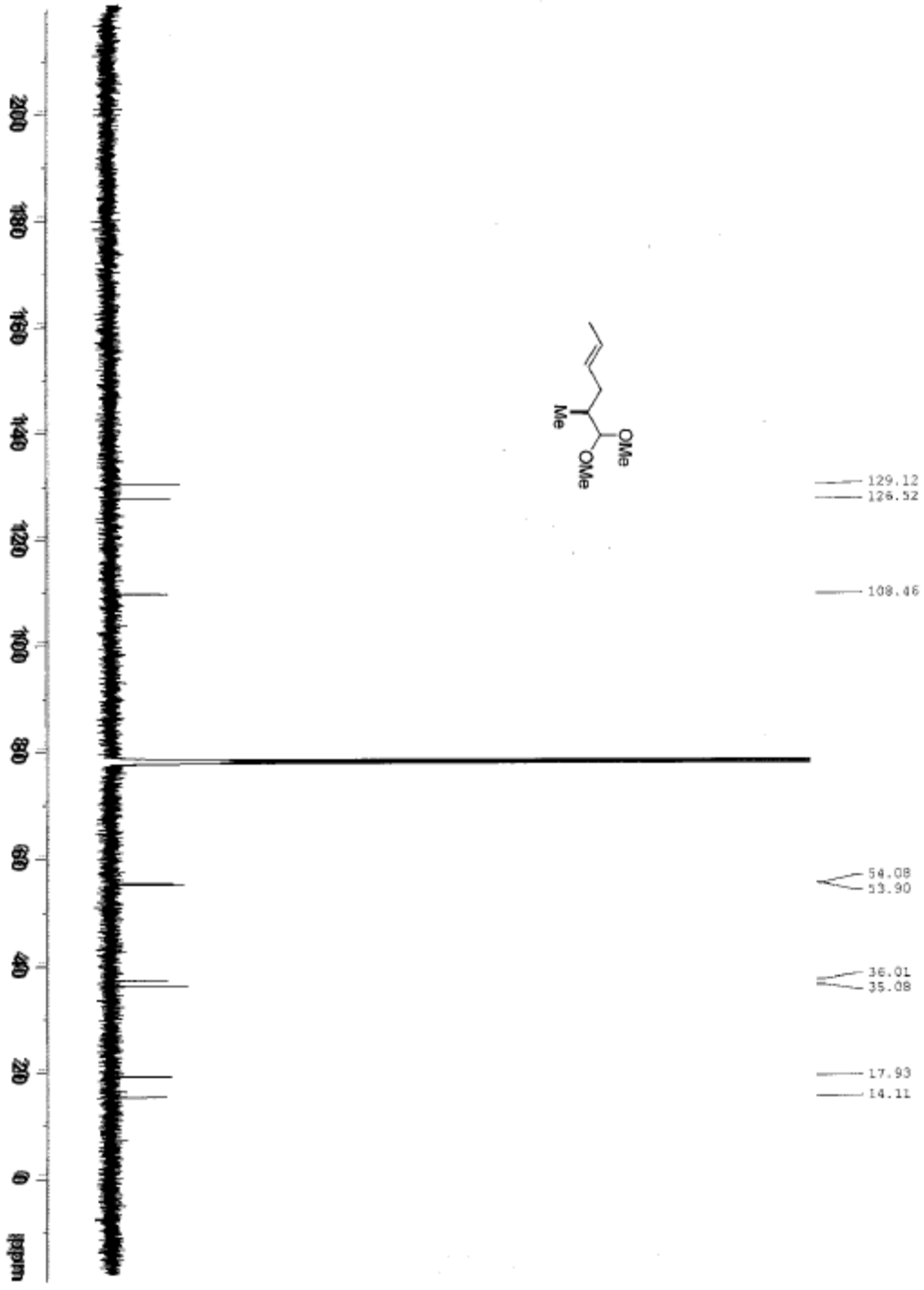
3.254
ppm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160
140
120
100
80
60
40
20
0
ppm
Me
OMe
OMe
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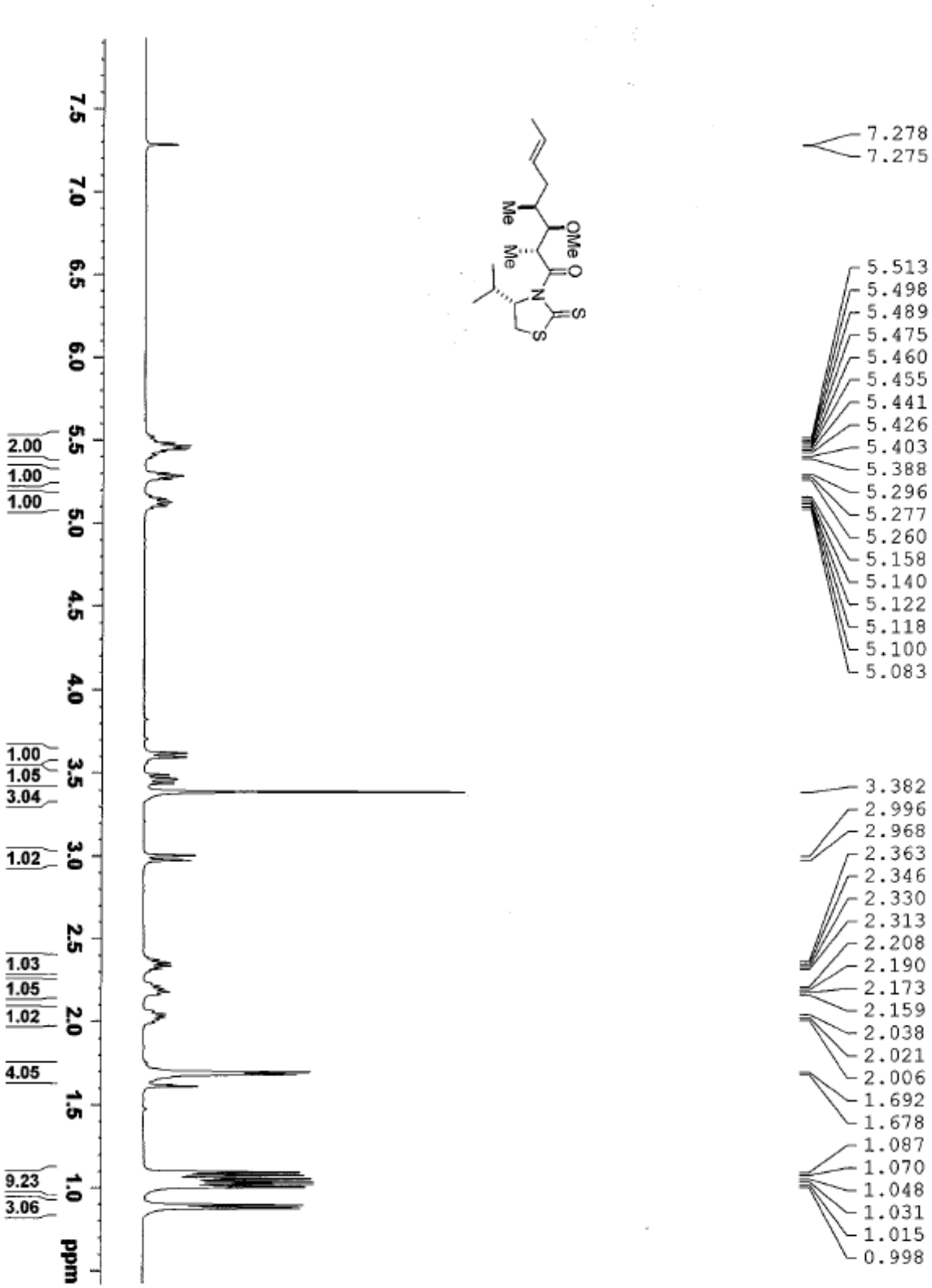
54.08
53.90
36.01
35.08
17.93
14.11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5.277
5.260
5.158
5.140
5.122
5.118
5.100
5.083
3.382
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2.173
2.159
2.038
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1.678
1.087
1.070
1.048
1.031
1.015
0.998
OMe
O
N
S
S
Me
Me
2.00
1.00
1.00
1.00
1.05
3.04
1.02
1.03
1.05
1.02
4.05
9.23
3.06
7.5
7.0
6.5
6.0
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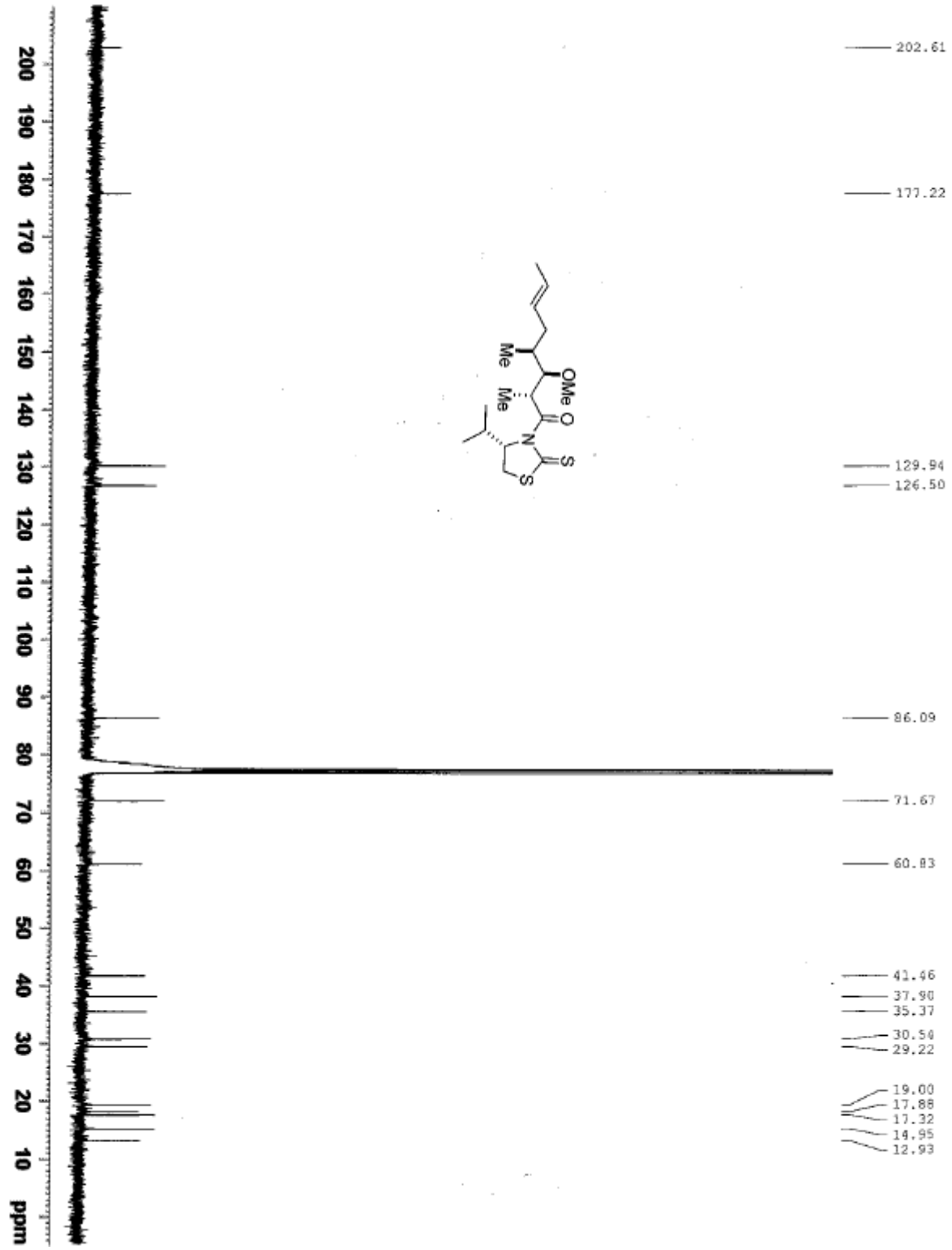
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm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86.09
71.67
60.83
41.46
37.90
35.37
30.54
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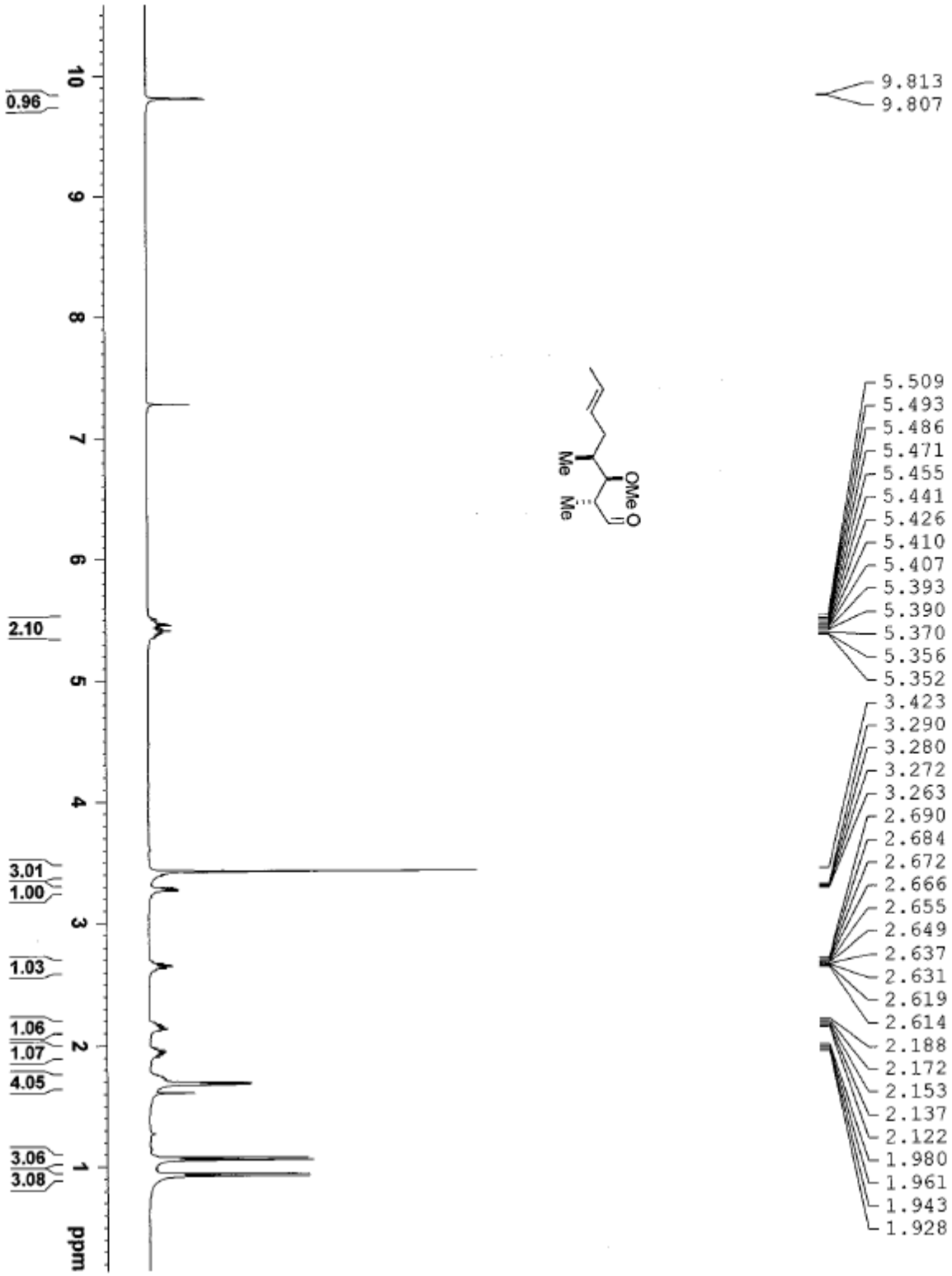
19.00
17.88
17.32
14.95
12.93
OMe
O
Me
Me
N
S
S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5.410
5.407
5.393
5.390
5.370
5.356
5.352
3.423
3.290
3.280
3.272
3.263
2.690
2.684
2.672
2.666
2.655
2.649
2.637
2.631
2.619
2.614
2.188
2.172
2.153
2.137
2.122
1.980
1.961
1.943
1.928
Me
Me
OMe
O
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2.10
3.01
1.00
1.03
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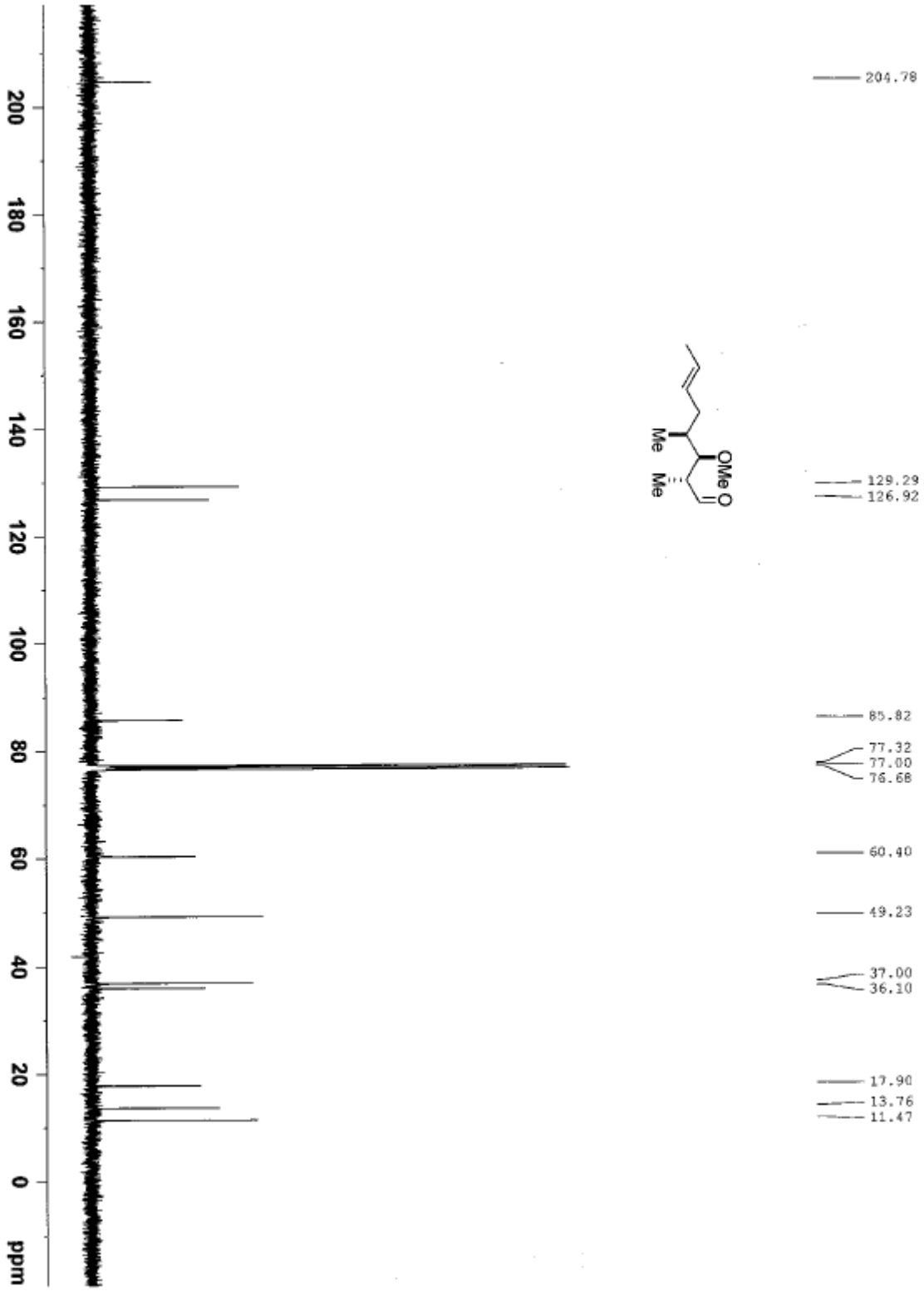
4.05
3.06
3.08
10
9
8
7
6
5
4
3
2
1
ppm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40
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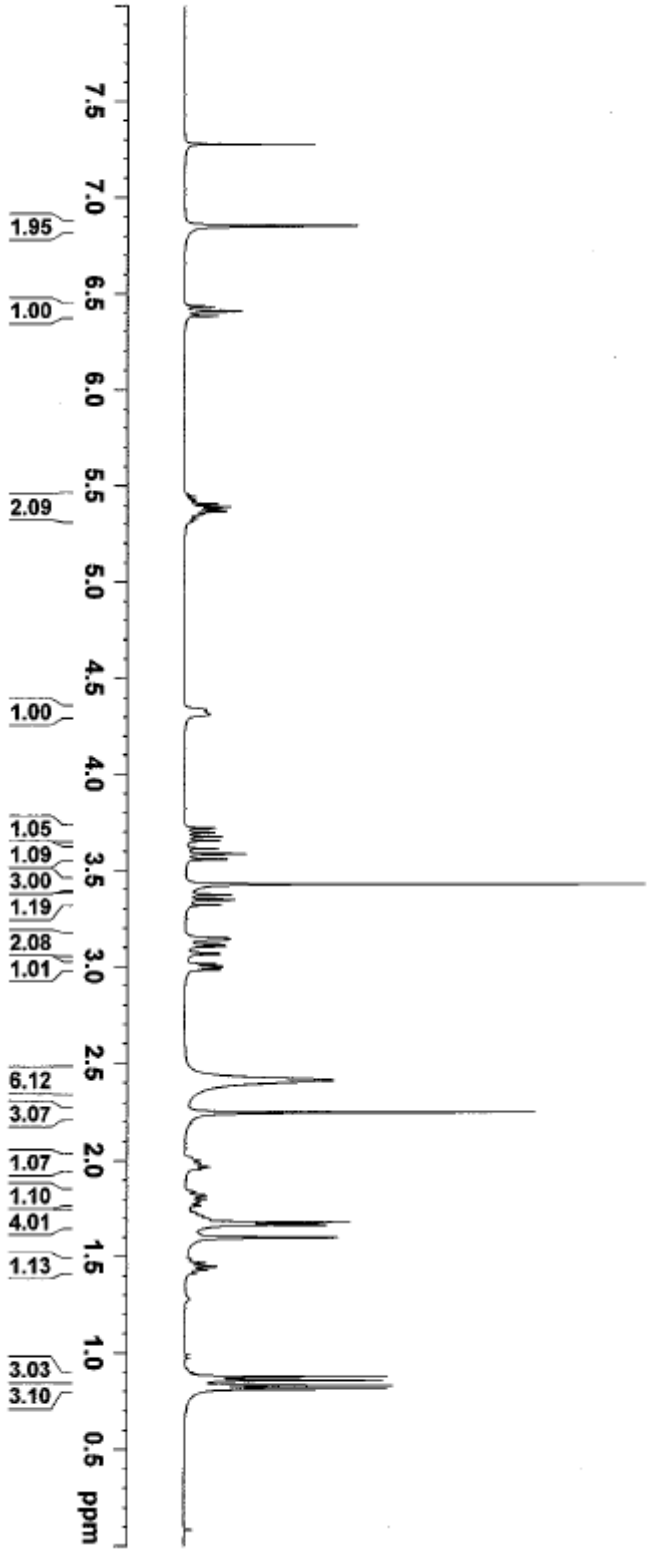
11.47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2.08
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1.10
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1.13
3.03
3.10
7.5
7.0
6.5
6.0
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4.5
4.0
3.5
3.0
2.5
2.0
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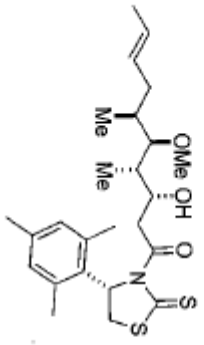
1.0
0.5
ppm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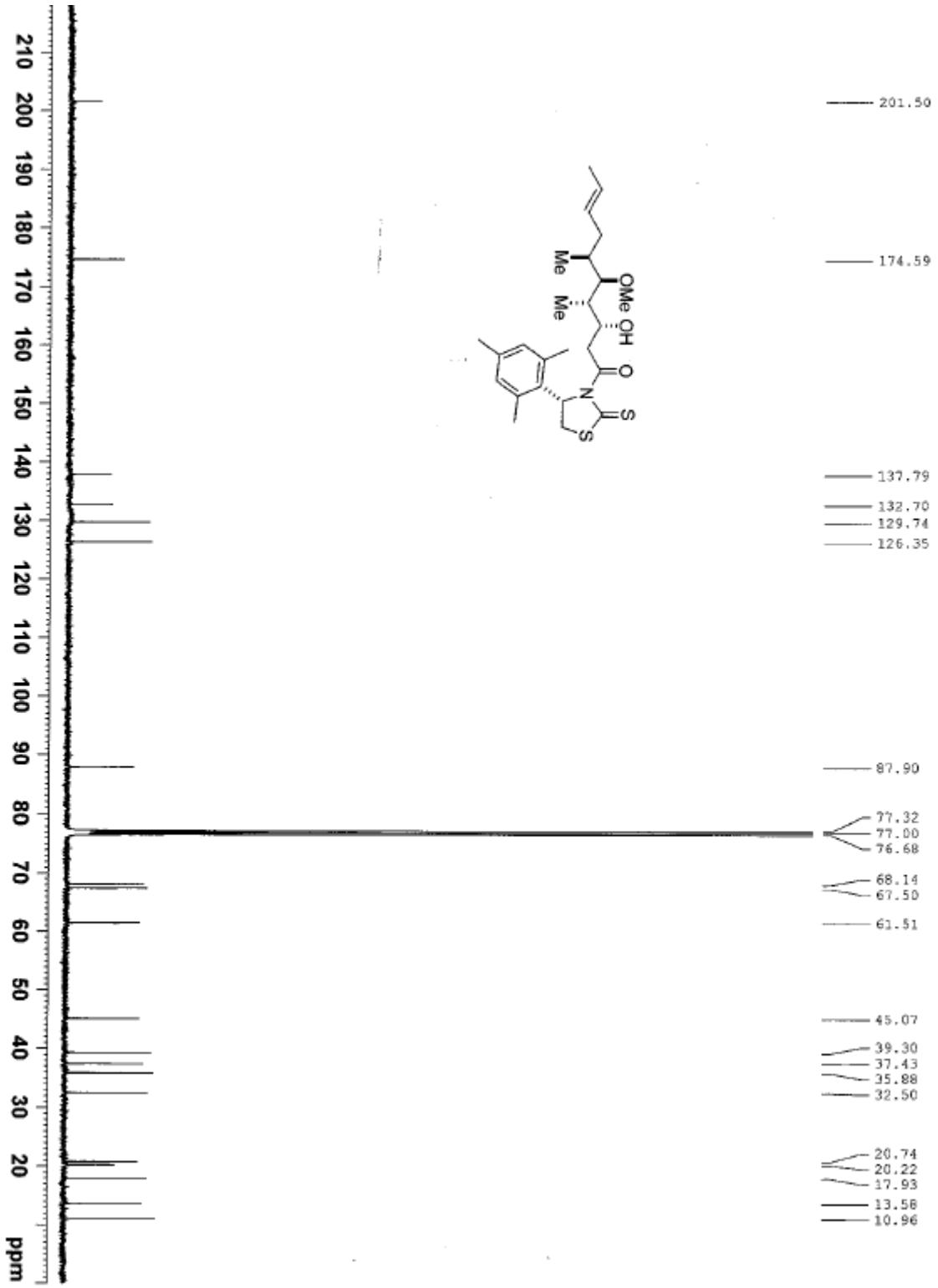
Me
OMe
OH
O
N
S
S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200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm
Me
Me
OMe
OH
O
N
S
S
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77.00
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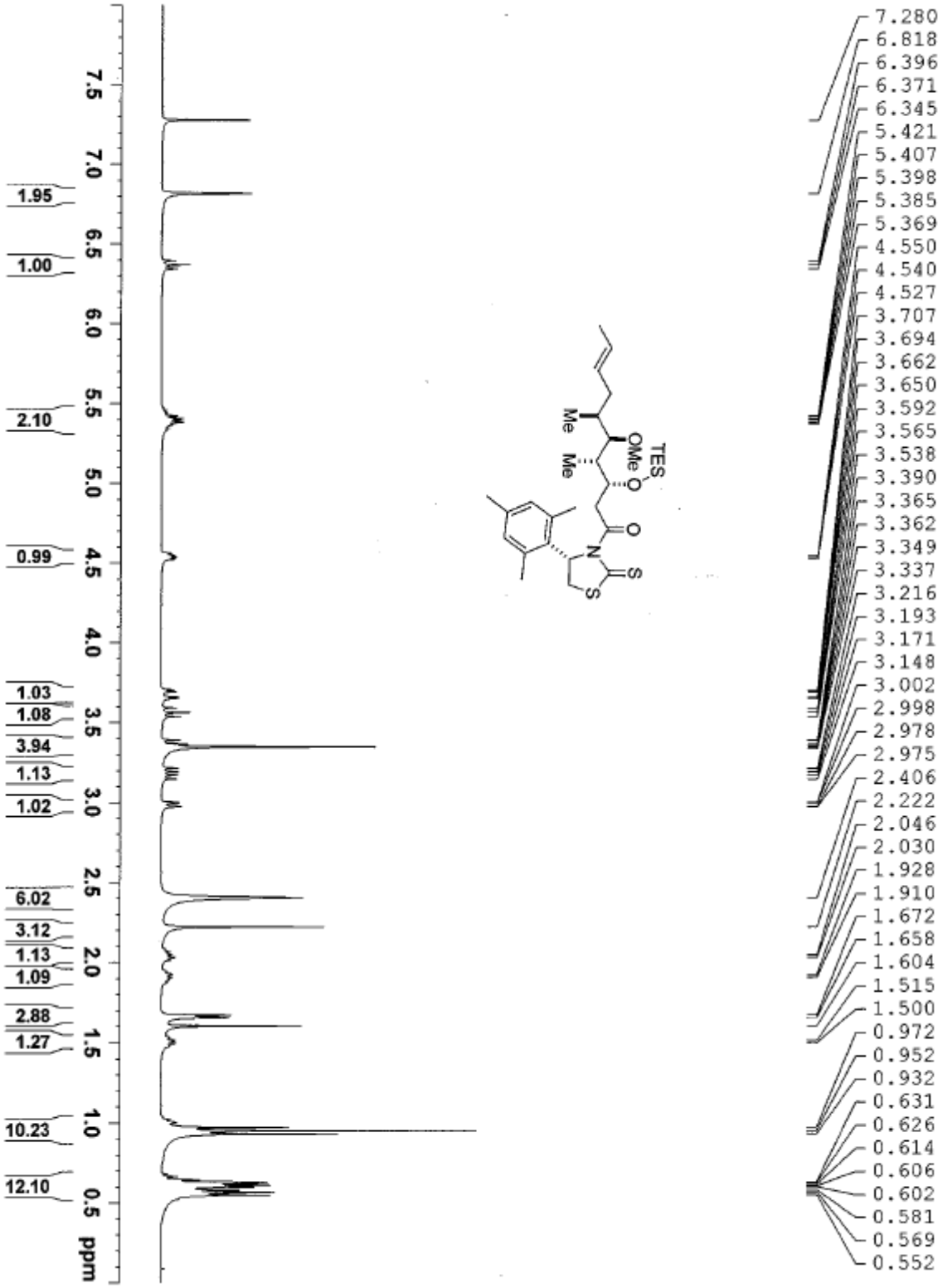
10.96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3.002
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1.604
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0.932
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0.614
0.606
0.602
0.581
0.569
0.552
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OMe
Me
Me
O
O
N
S
S
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1.00
2.10
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1.03
1.08
3.94
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1.02
6.02
3.12
1.13
1.09
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1.27
10.23
12.10
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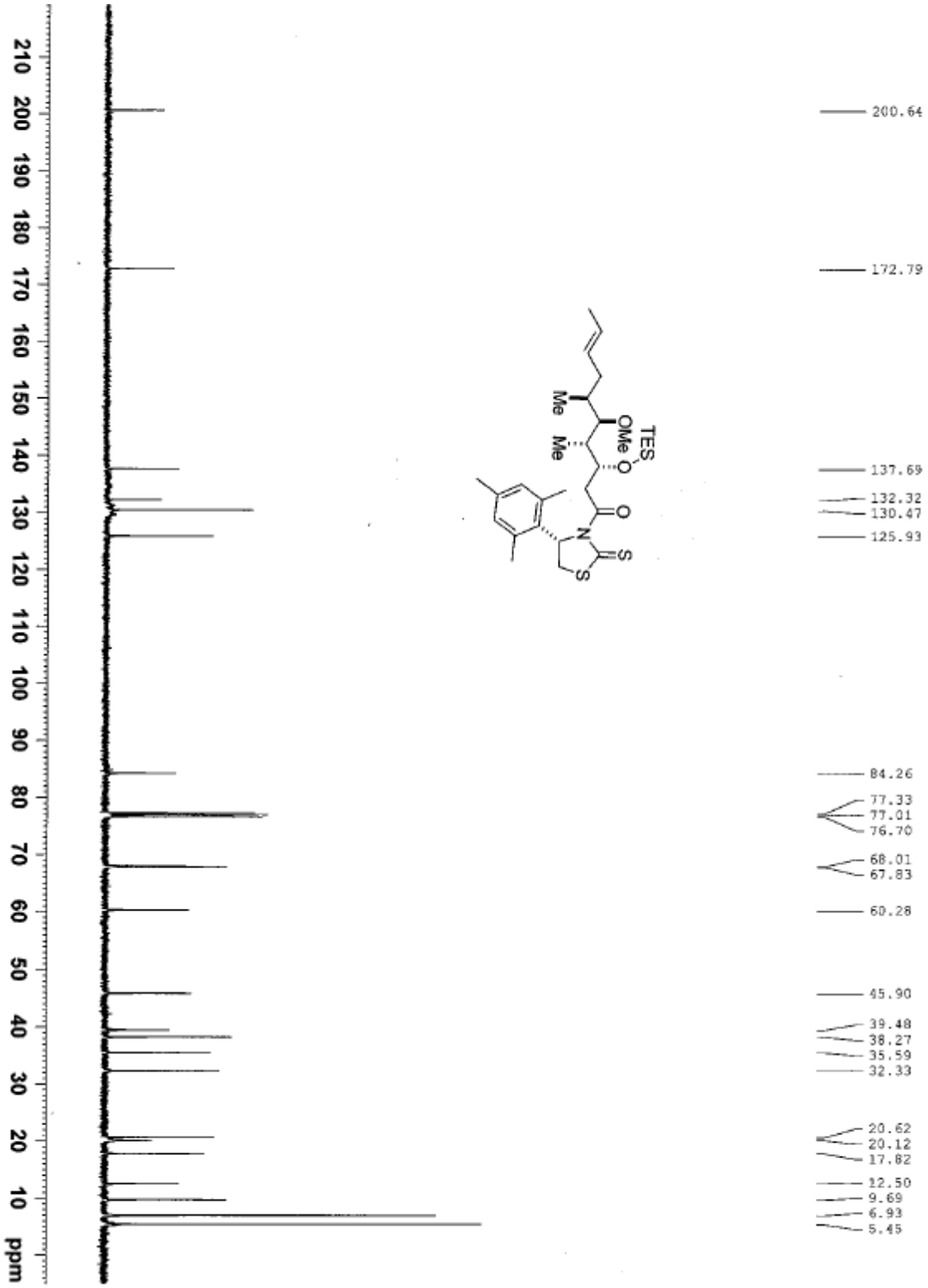
ppm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39.48
38.27
35.59
32.33
20.62
20.12
17.82
12.50
9.69
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OMe
Me
Me
O
O
N
S
S
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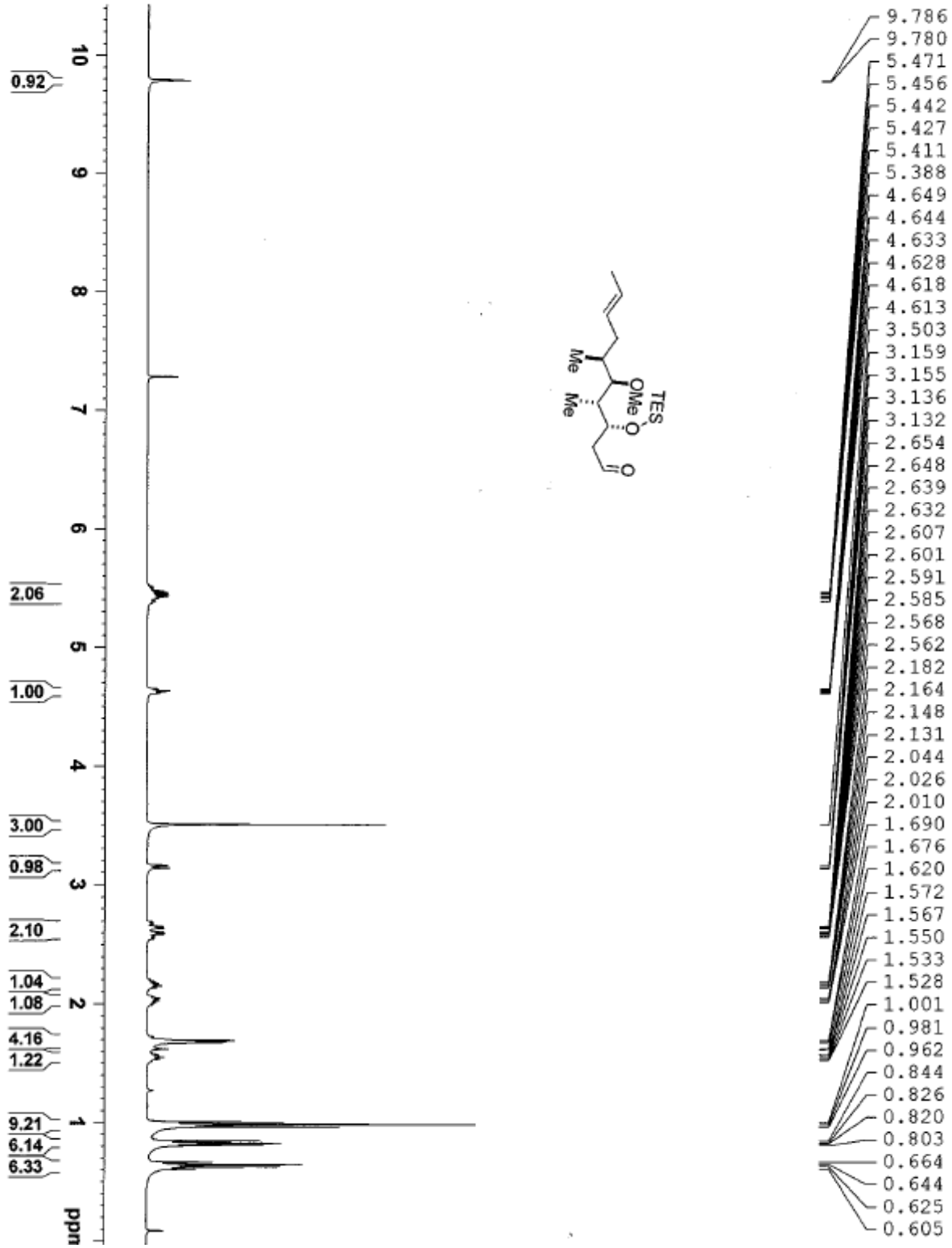
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1.08
4.16
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6.14
6.33
ppm
TES
OMe
Me
Me
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5.388
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4.633
4.628
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3.159
3.155
3.136
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1.567
1.550
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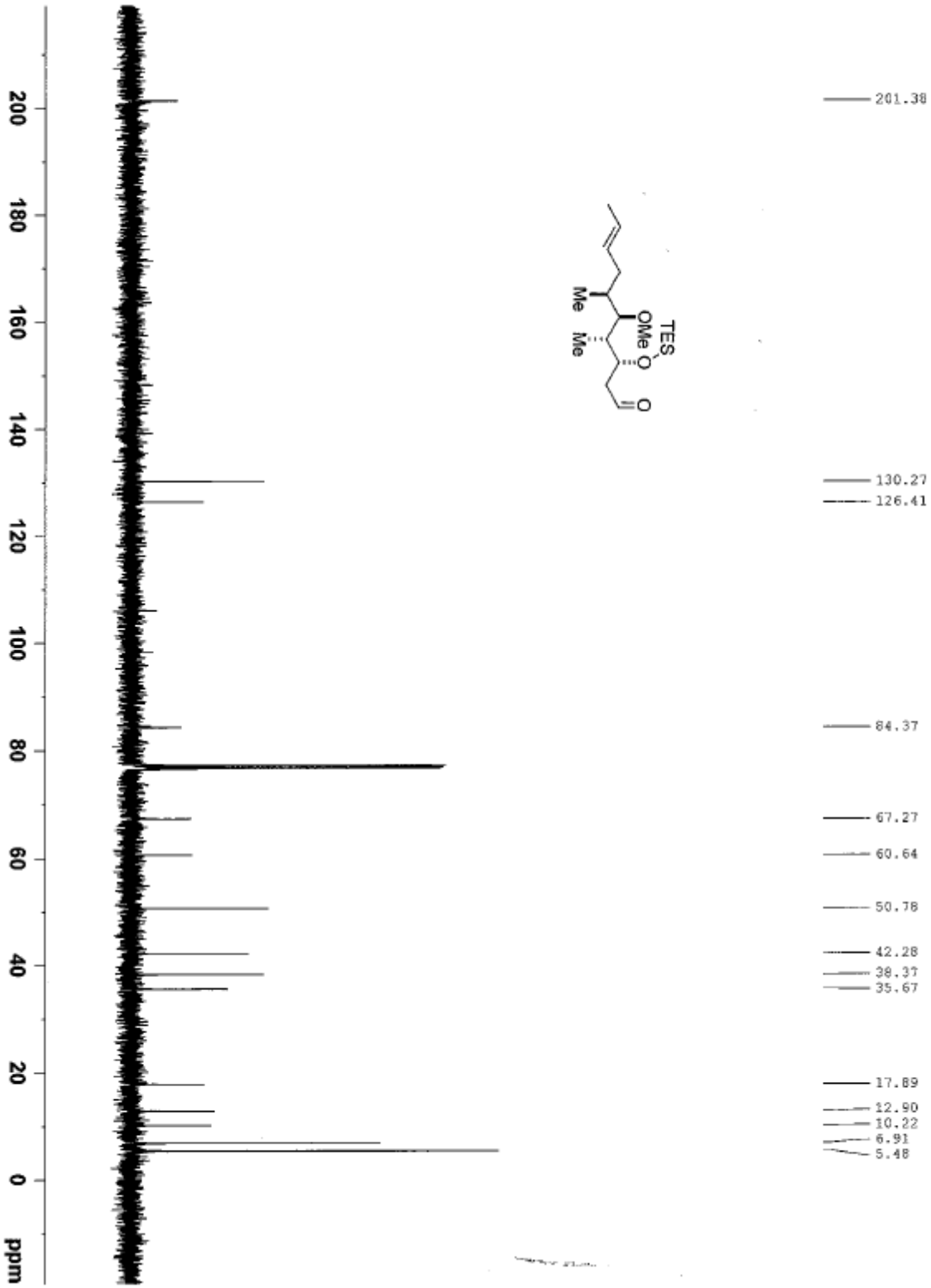
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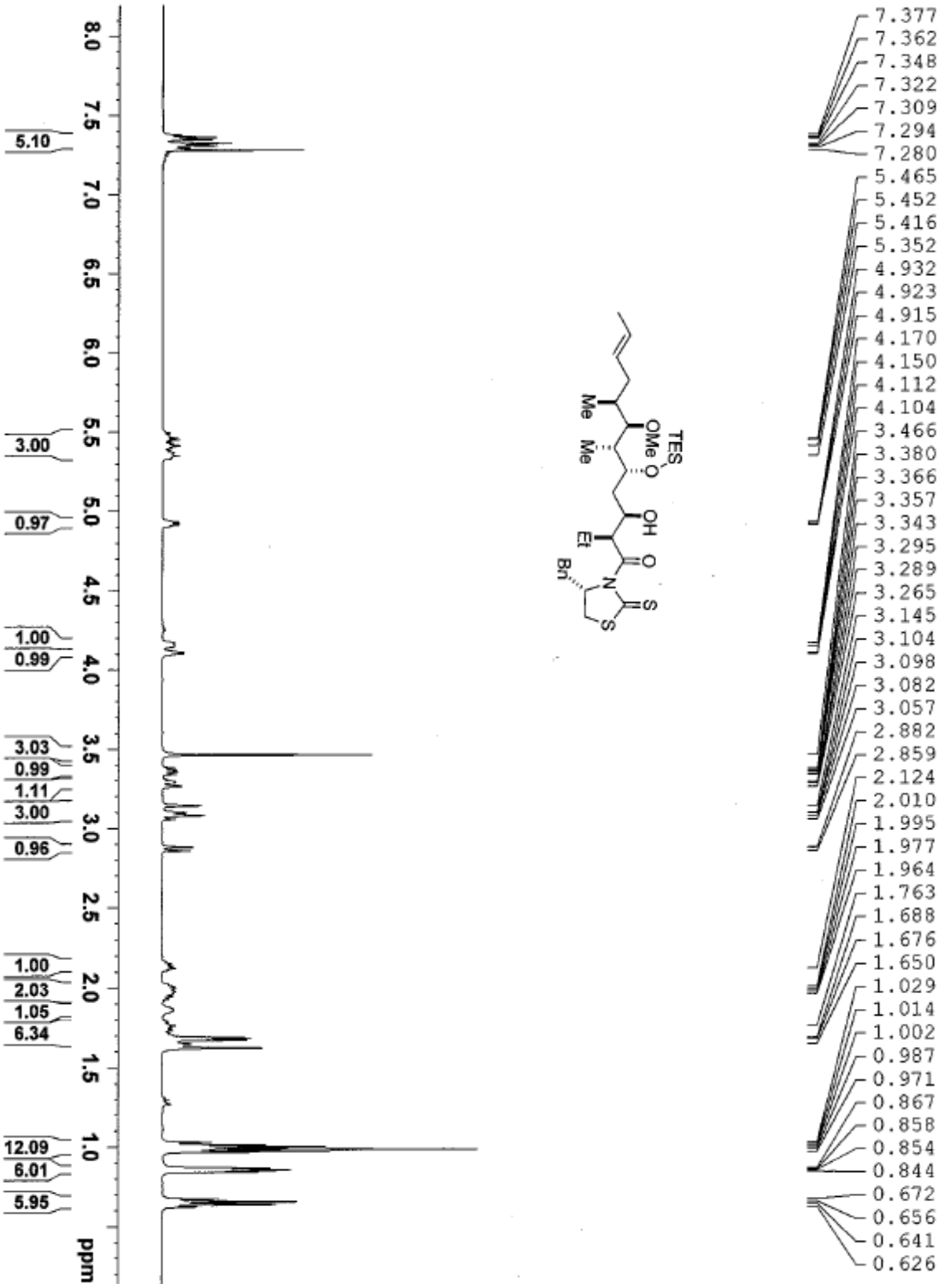
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1.0
ppm
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3.03
0.99
1.11
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0.96
1.00
2.03
1.05
6.34
12.09
6.01
5.95
TES
OMe
O
Me
Me
OH
O
Et
Bn
N
S
S
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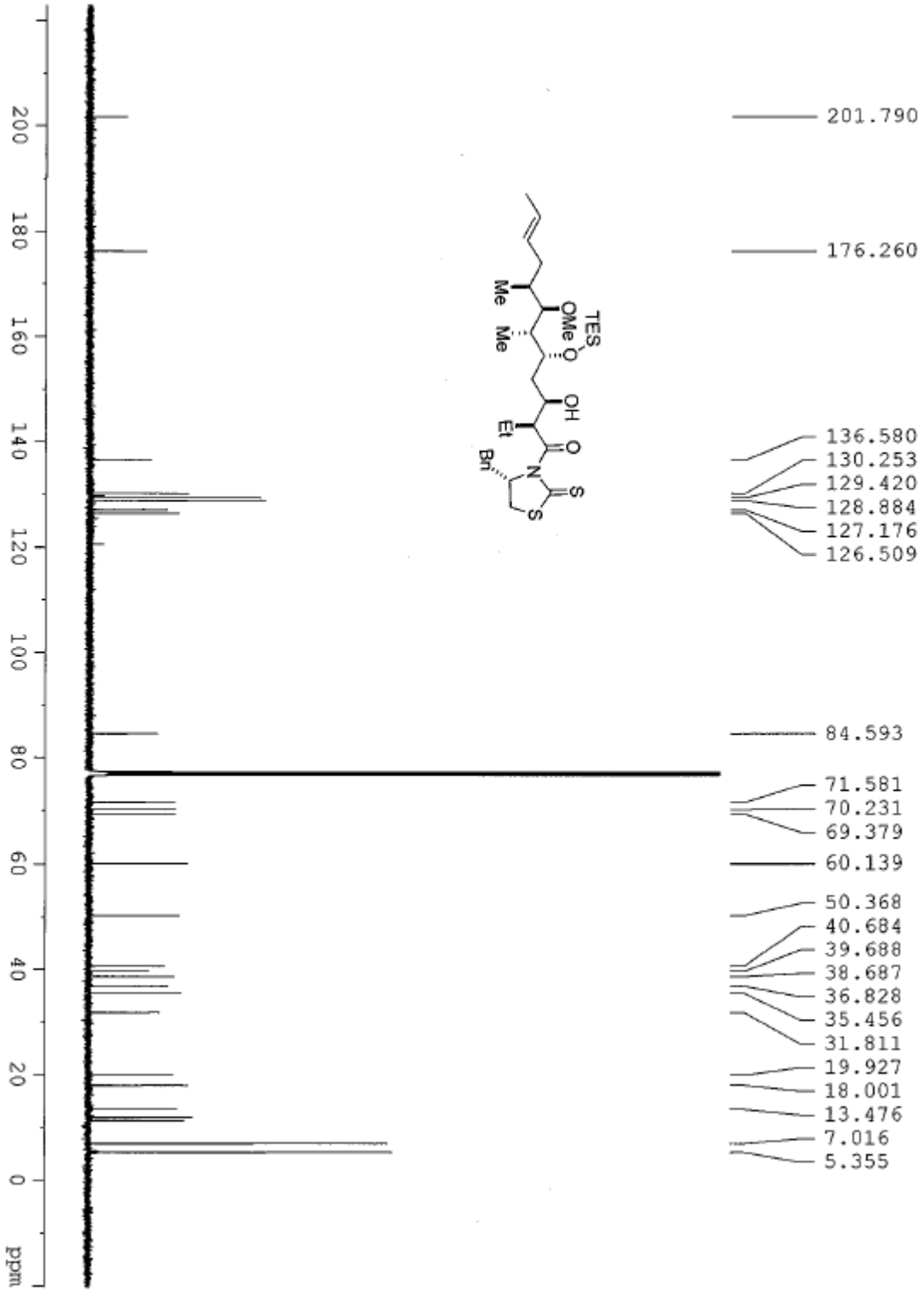
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50.368
40.684
39.688
38.687
36.828
35.456
31.811
19.927
18.001
13.476
7.016
5.355
200
180
160
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60
40
20
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ppm
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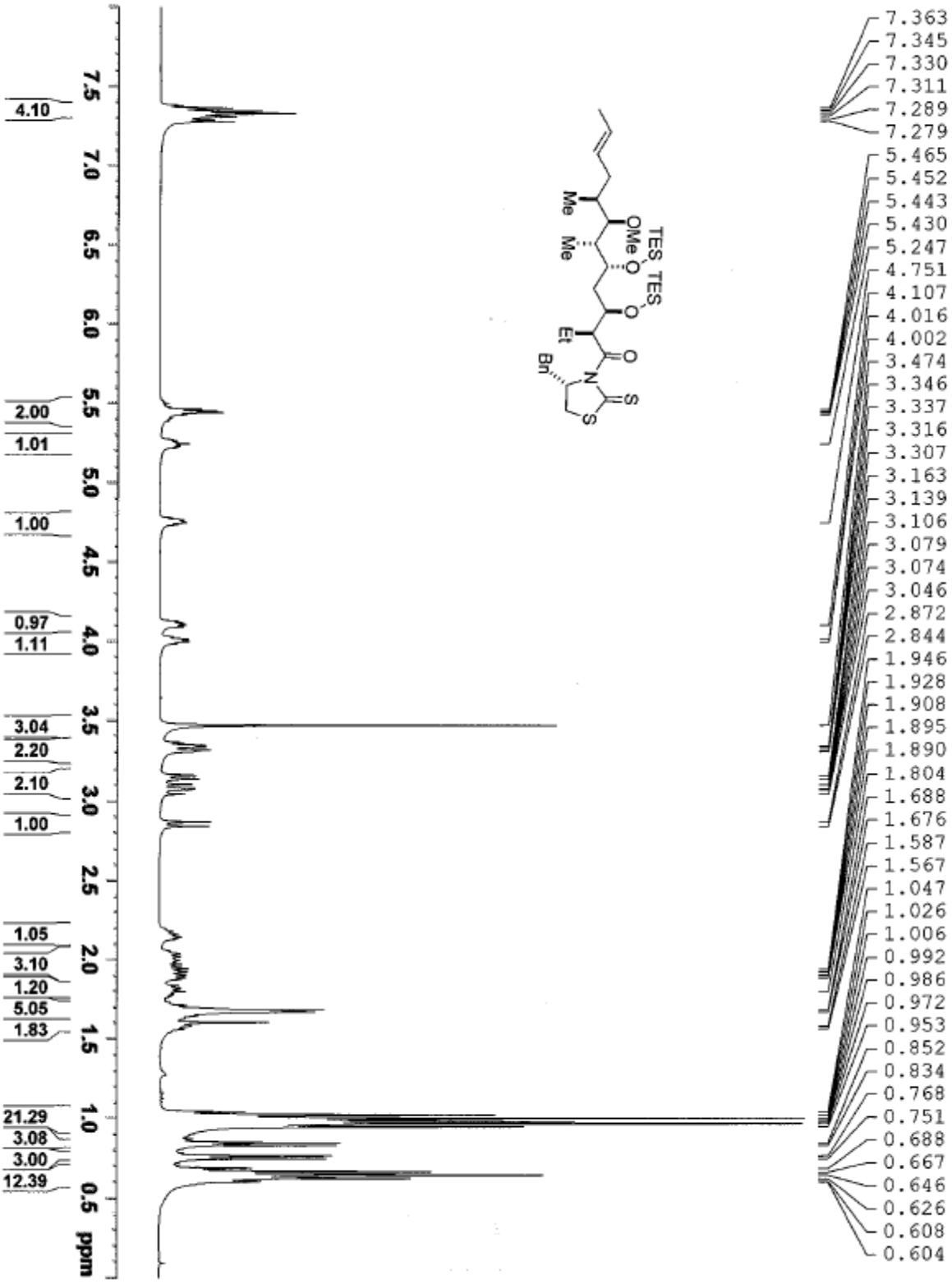
Me
Me
OH
Et
Br
O
N
S
S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4.016
4.002
3.474
3.346
3.337
3.316
3.307
3.163
3.139
3.106
3.079
3.074
3.046
2.872
2.844
1.946
1.928
1.908
1.895
1.890
1.804
1.688
1.676
1.587
1.567
1.047
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1.006
0.992
0.986
0.972
0.953
0.852
0.834
0.768
0.751
0.688
0.667
0.646
0.626
0.608
0.604
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2.00
1.01
1.00
0.97
1.11
3.04
2.20
2.10
1.00
1.05
3.10
1.20
5.05
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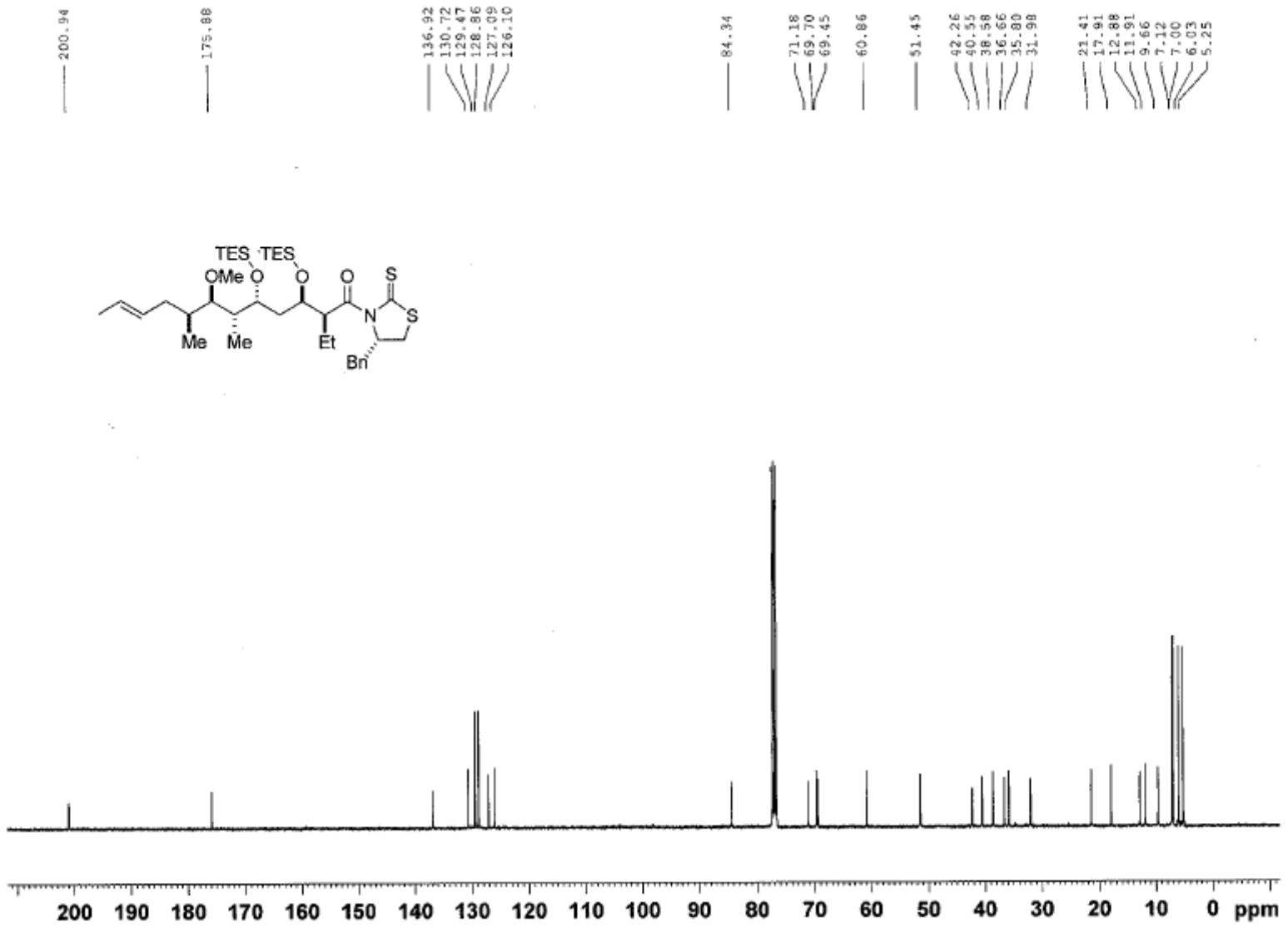
3.00
12.39
ppm
TES
TES
OMe
Me
Me
Et
Bn
O
N
S
S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11.91
9.66
7.12
7.00
6.03
5.25
TES
TES
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O
S
N
S
Me
Me
Et
Bn
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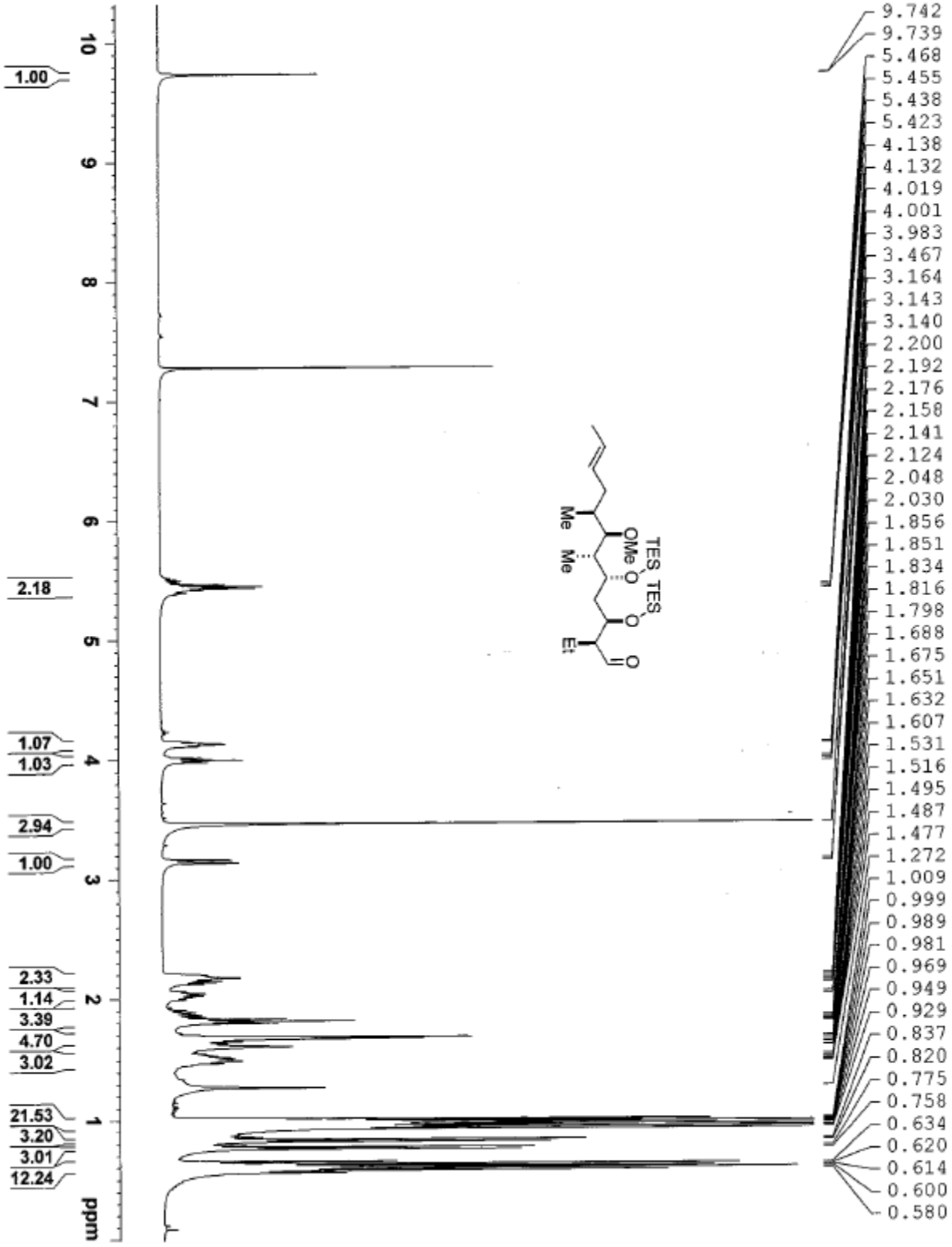
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1.798
1.688
1.675
1.651
1.632
1.607
1.531
1.516
1.495
1.487
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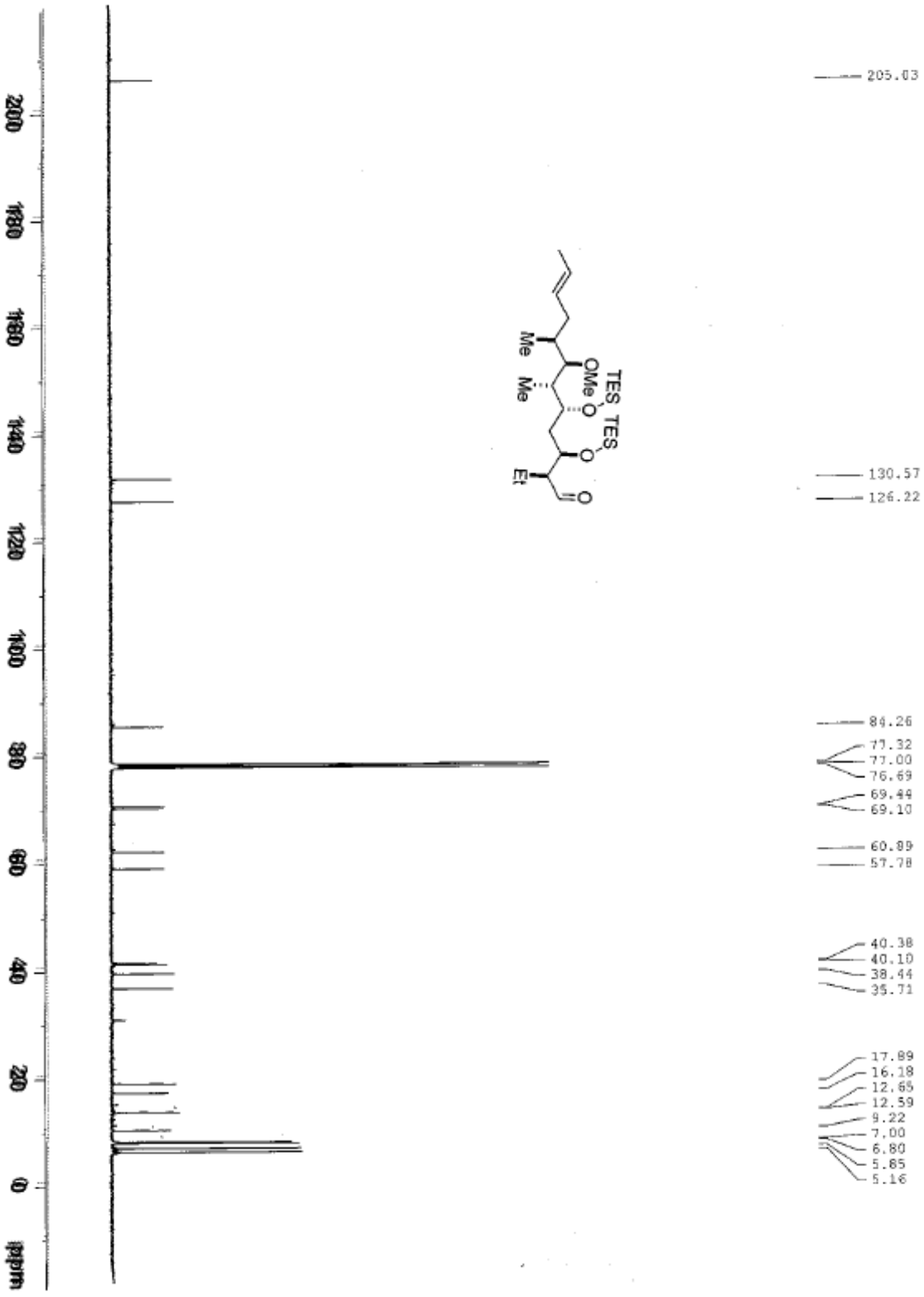
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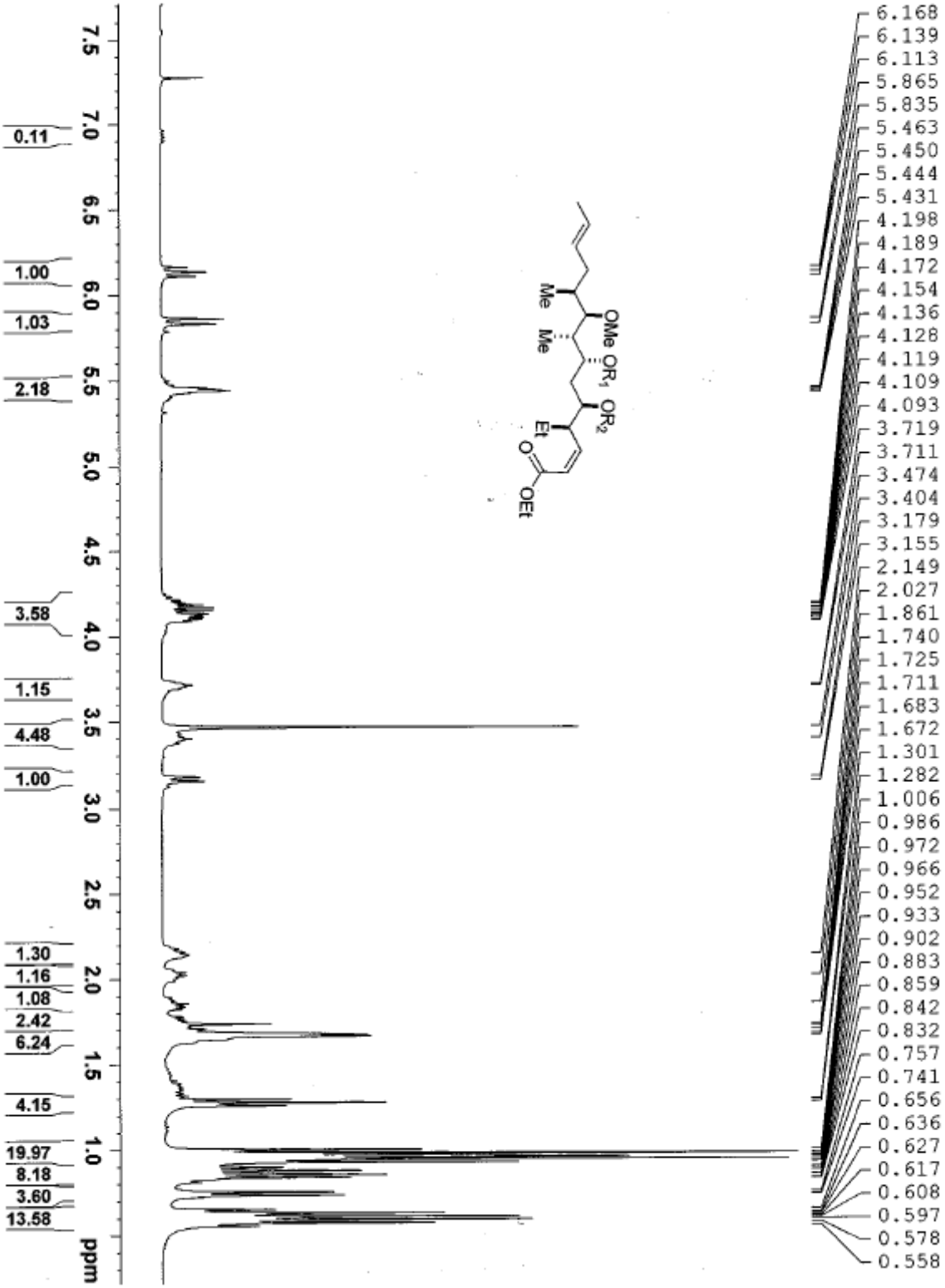
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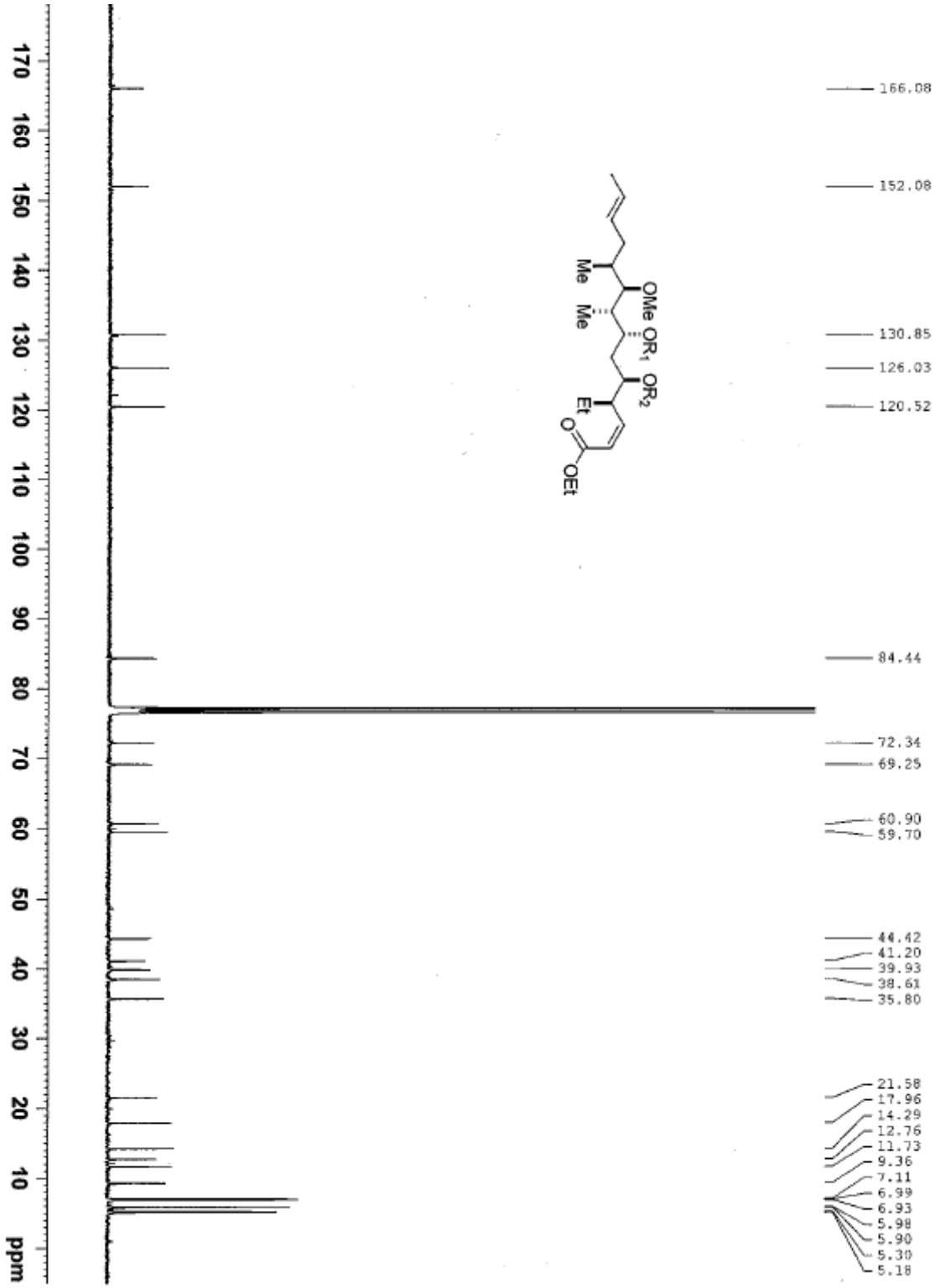
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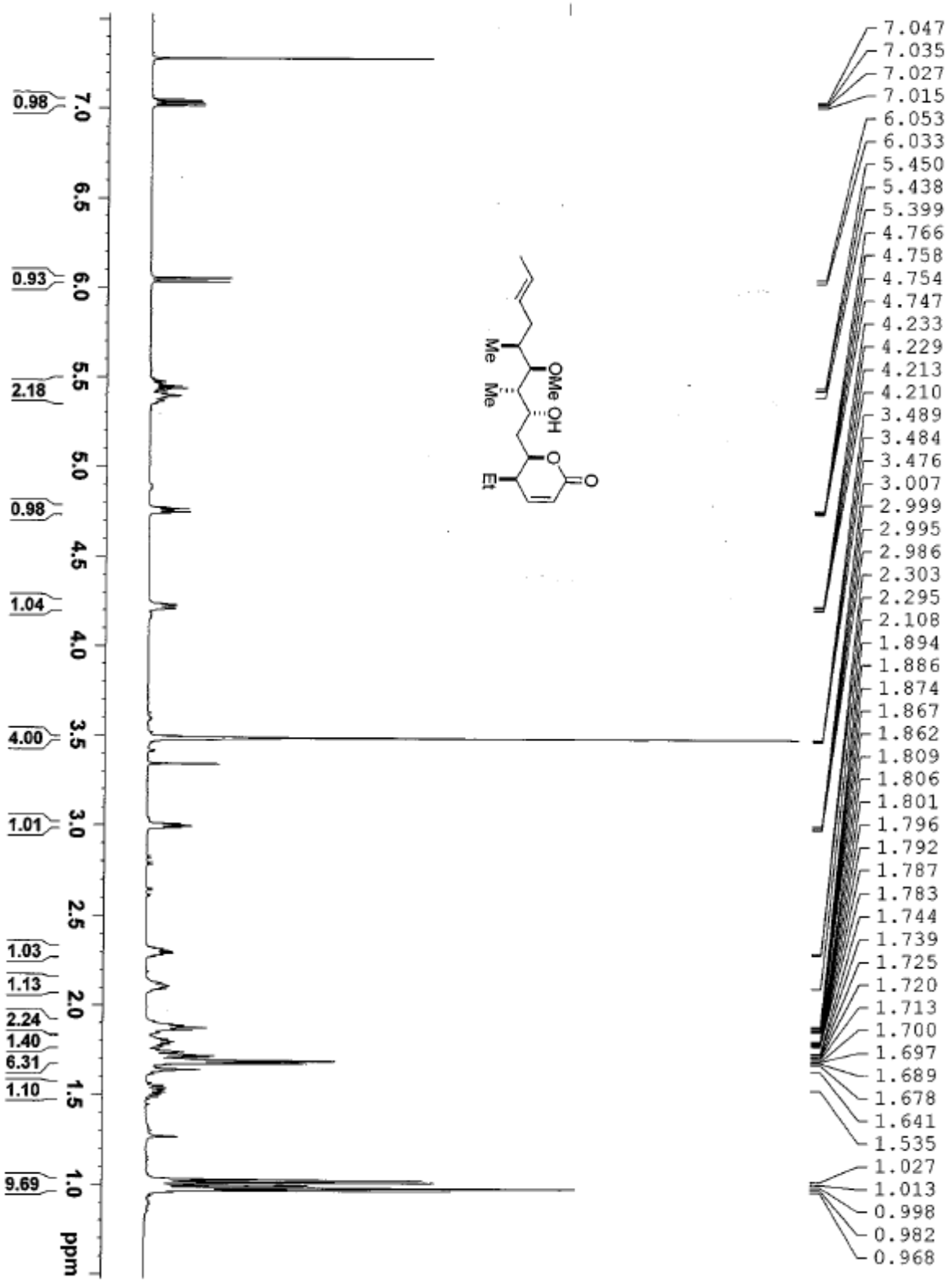
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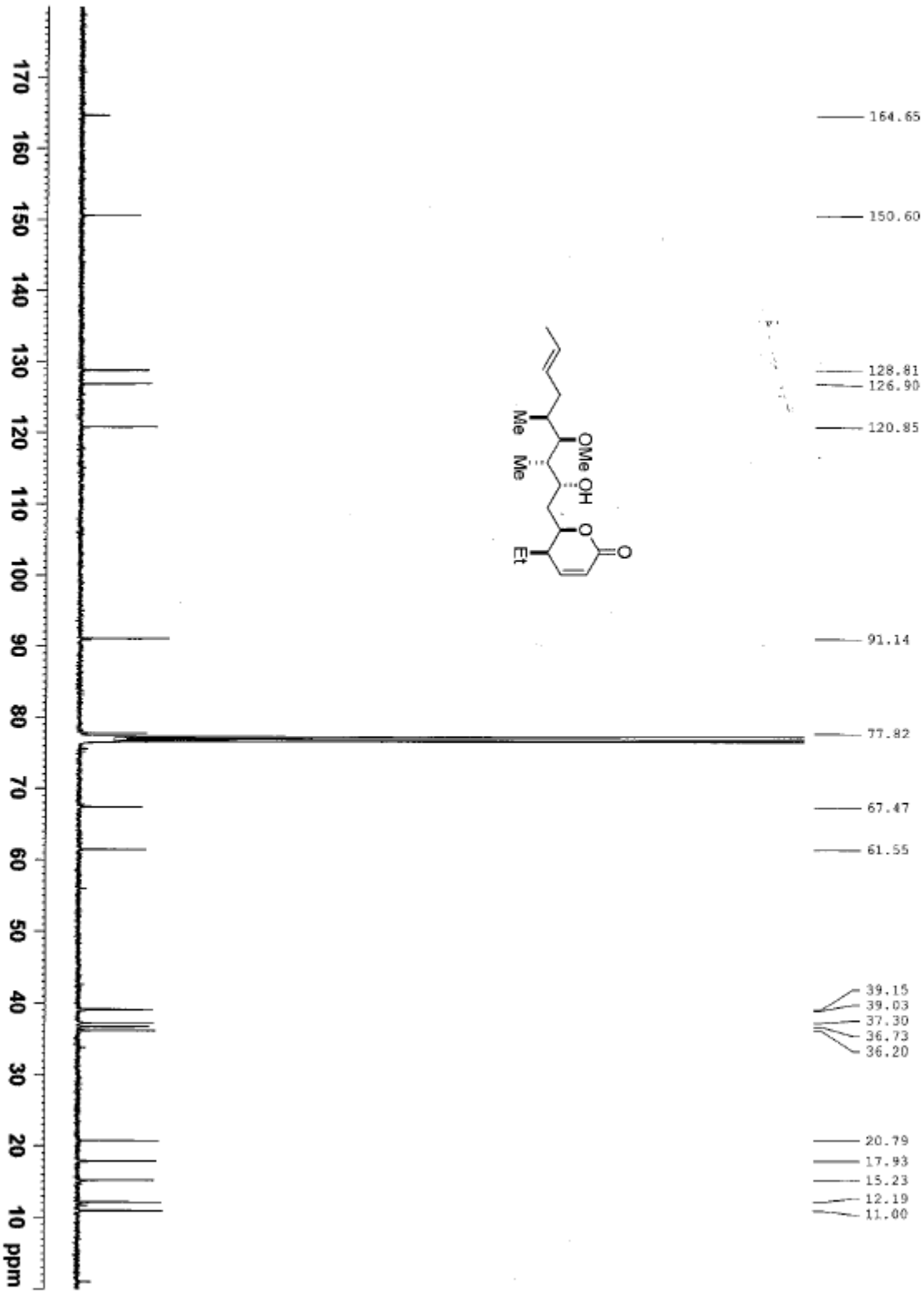
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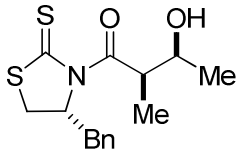
Chapter 5

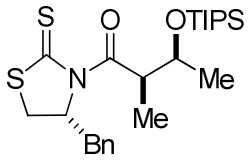
Experimental Information and NMR spectra for Chapter 3

Methods and Materials: Infared (IR) spectra were obtained using a Jasco 460 Plus Fourier transform infrared spectrometer and values reported in cm^{-1}. Proton and carbon nuclear magnetic resonance (1H and 13C NMR) spectra were recored on the Bruker 400 (^{1}H at 400 MHz; ^{13}C at 100 MHz), Bruker 500 (^{1}H at 500 MHz; ^{13}C at 125 MHz), and Bruker 600 (^{1}H at 600 MHz; ^{13}C at 150 MHz). Optical rotations were determined using a Jasco P1010 polarimeter. Thin layer chromatography (TLC) was conducted on silica gel F254 TLC plates purchased from Silacycle. Flash column chromatography was carried out using silica gel (32 μm) purchased from Scientific Absorbents, Inc. Diethyl either (Et_2O), tetrahydrofuran (THF), and dichloromethane (CH_2Cl_2) were dried by being passed throught a column of neutral alumina under nitrogen prior to use. Alkylamines were distilled from calcium hydride immediately prior to use. All other reagents and solvents were used as receieved from the manufacturer, unless otherwise specified. All air and water sensitive reactions were performed in flaskes flame dried under a positive flow of argon and conducted under an argon atmosphere.



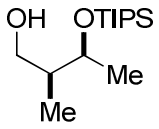
(2R,3S)-1-((R)-4-benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy-2-methylbutan-1-one

A solution of thione **3.9** (25 g, 94.3 mmol) in 940 mL CH_2Cl_2 was cooled to 0 ℃. Neat $TiCl_4$ (10.9 mL, 99.03 mmol) was added dropwise, and the resulting orange slurry was stirred for 5 min. *i*-Pr_2NEt was then added and the resultant black solution was stirred for 15 min. *N*-methyl-2-pyrrolidinone (18.1 mL, 188.6 mmol) was added dropwise at 0 ℃ and stirred. After 30 min, the reaction was cooled to -78 ℃, and a cetaldehyde (10.7 mL, 188.6 mmol) was added dropwise. Upon completion of the reaction by TLC analysis, the reaction was then quenched by addition of a saturated aqueous NH_4Cl solution. The layers were separated and the aqueous layer was then extracted into CH_2Cl_2 (2 x 200 mL). The organic extracts were dried (Na_2SO_4) and evaporated to give a crude yellow oil which was purified by flash chromatography (10% EtOAc/hexanes to 20% EtOAc/hexanes) to afford 23.28 g of the product **3.10** (80%), a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.39 (m, 5H), 5.37 (dddd, *J* = 3.6, 7.2, 1H), 4.43 (m, 1H), 4.16 (m, 1H), 3.42 (dd, *J* = 7.2, 11.6, 1H), 3.25 (dd, *J* = 3.6, 13.2, 1H), 3.07 (dd, *J* = 10.4, 13.2, 1H), 2.94 (d, *J* = 11.6, 1H), 2.755 (s, 1H), 1.30 (d, *J* = 6.8, 3H), 1.23 (d, *J* = 6.4, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.44, 178.55, 136.37, 129.46, 128.95, 127.30, 68.79, 68.45, 44.41, 36. 78, 32.14, 20.25, 10.48; IR (thin film) ν 3853, 3422, 3062, 3026, 2975, 2934, 2246, 1692, 1603, 1495, 1454, 1360, 1341, 1319, 1292, 1261, 1192, 1166, 1135, 1093, 1033, 1001; $[\alpha]^{22}_D$ = -107 (*c* = 18.5, CH_2Cl_2); MS (ESI) calculated for $C_{15}H_{19}NO_2S_2$ $[M+Na]^+$: 332.1, found 332.1.



(2R,3S)-1-((R)-4-benzyl-2-thioxothiazolidin-3-yl)-2-methyl-3-(triisopropylsilyloxy)butan-1-one

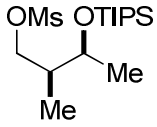
To a solution of secondary alcohol **3.10** (18.23 g, 60.0 mmol) at 0 ℃ was added 2,6-lutidine (14.0 mL, 120 mmol), followed by TIPSOTf (24.0 mL, 88.5 mmol). After addition, the cooling bath was removed, and the reaction was allowed to warm to room temperature. After 20 min, the reaction was quenched by the addition of a saturated $NaHCO_3$ solution. The layers were separated, and the aqueous layer was further extracted into CH_2Cl_2 (3 x 100 mL). The organic extracts were dried (Na_2SO_4) and evaporated to give a crude yellow oil which was purified by flash chromatography (100% hexanes to 5% EtOAc/Hexanes) to provide 24.1 g of the product **3.147** (94%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (m, 5H), 5.23 (m, 1H), 4.63 (m, 1H), 4.34 (m, 1H), 3.34 (m, 2H), 3.09 (dd, *J* = 11, 11, 1H), 2.91 (d, *J* = 11.5, 1H), 1.29 (m, 6H), 1.07 (s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.26, 176.63, 136.75, 129.52, 128.91, 127.17, 71.09, 69.57, 46.34, 36.51, 31.98, 21.35, 18.20, 18.13, 12.71, 12.02; IR (thin film) ν 2942, 2865, 1703, 1455, 1341, 1257, 1191, 1030; $[\alpha]^{22}_D$ = -57.8 (*c* = 8.15, CH_2Cl_2); MS (ESI) calculated for $C_{24}H_{39}NO_2S_2Si$ $[M+Na]^+$: 488.2, found 488.2.



(2S,3S)-2-methyl-3-(triisopropylsilyloxy)butan-1-ol

To a stirring solution of TIPS ether **3.147** (24.1 g, 52.3 mmol) in Et_2O (520 mL) at 0 ℃ was added MeOH (3.2 mL, 78.5 mmol). A solution of $LiBH_4$ (2M in THF, 39.27 mL, 78.5 mmol) was added slowly dropwise. The reaction was allowed to stir overnight, while warming to

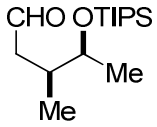
room temperature. The following day, the reaction was recooled to 0 ℃ and a saturated solution of $NaHCO_3$ was added slowly. Upon separation of the layers, the aqueous layer was further extracted with Et_2O (3 x 200 mL), and dried over $MgSO_4$. The organic extracts were concentrated to provide a crude oil containing solidified chiral auxiliary which was purified by flash chromatography (2% EtOAc/CH_2Cl_2) to provide 10.8 g of alcohol **3.148** (80%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.13 (m, 1H), 3.80 (m, 1H), 3.55 (m, 1H), 3.38 (s, 1H), 2.15 (m, 1H), 1.22 (d, *J* = 6, 3H), 1.09 (m, 22H), 0.79 (d, *J* =7, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 73.13, 65.44, 40.61, 18.08, 18.03, 17.63, 12.97, 12.33; IR (thin film) ν 3375, 2942, 2867, 1463, 1383, 1245, 1159, 1109, 1047; $[\alpha]^{22}_D$ = +3.1 (*c* = 19.7, CH_2Cl_2); MS (ESI) calculated for $C_{14}H_{32}O_2Si$ $[M+Na]^+$: 283.2, found 283.2.



(2S,3S)-2-methyl-3-(triisopropylsilyloxy)butyl methanesulfonate

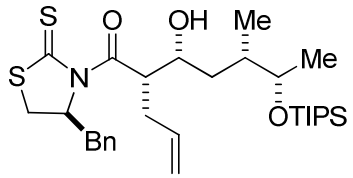
A solution of primary alchol **3.148** (10.8 g, 41.5 mmol) in CH_2Cl_2 (415 mL) was cooled to 0 ℃. Triethylamine (8.7 mL, 62.3 mmol) was added dro pwise, followed by the addition of freshly distilled methane sulfonyl chloride (3.85 mL, 49.8 mmol). The reaction was allowed to stir overnight while warming to room temperature. The following day, the reaction was quenched by the addition of a saturated $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted into CH_2Cl_2 (2 x 100 mL). The organic extracts were dried (Na_2SO_4), and evaporated to give a clear crude oil, which was purified by flash chromatography (10% EtOAc/hexanes to 20% EtOAc/hexanes) to give 13.4 g of the mesylate (96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (dd, *J* =6, 9.2, 1H), 4.17 (m, 2H), 3.02 (s, 3H), 2.07 (m, 1H), 1.19 (d, *J* = 6.4, 3H), 1.09 (m, 24H), 1.01 (d, *J* = 7.2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.20, 68.59, 40.47, 37.14, 20.06, 18.18, 18.13, 12.61, 11.41; IR (thin film) ν

3582, 2943, 2867, 1463, 1359, 1247, 1178, 1105, 1051, 1014; $[\alpha]^{22}_{D}$ = +0.44 (*c* = 37, CH_2Cl_2); MS (ESI) calculated for $C_{15}H_{34}O_4SSi$ $[M+Na]^+$: 361.2, found 361.2.



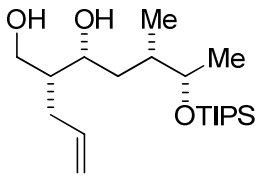
(3S,4S)-3-methyl-4-(triisopropylsilyloxy)pentanal

The mesylate (13.4 g, 39.6 mmol) above was dissolved in DMSO (400 mL). Potassium cyanide (5.15 g, 79.2 mmol) was added followed by TBAI (50 mg, 0.14 mmol). The reaction was heated to 60 ℃, and stirred at this temperature f or 2 days. The reaction was quenched by the addition of water (200 mL), and the aqueous phase was extracted with Et_2O (6 x 150 mL). The organic extracts were dried ($MgSO_4$) and evaporated at 0 ℃ to deliver 10.7 g of crude nitrile **3.149**. Crude nitrile **3.149** was immediately dissolved in CH_2Cl_2 (400 mL), and cooled to -78 ℃. Diisobutylaluminum hydride (1M solu tion in hexanes, 79.2 mL, 79.2 mmol, 2 equiv.) was added dropwise. The reaction was stirred at -78 ℃ for 3 h and quenched by the addition of a saturated sodium/potassium tartrate solution. The layers were then separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The organic extracts were dried (Na_2SO_4), and concentrated to provide a clear crude oil, which was purified by flash chromatography (5% EtOAc/hexanes) to deliver 8.00 g of aldehyde **3.150** (74% for 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (dd, *J* = 2, 2, 1H), 3.96 (m, 1H), 2.68 (ddd, *J* = 2, 5.2, 6.8, 1H), 2.32 (m, 1H), 2.20 (ddd, *J* = 2.4, 8.4, 10.8, 1H), 1.10 (m, 24H), 0.92 (d, *J* = 6.8, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 202.96, 71.25, 45.76, 35.46, 18.38, 18.14, 18.10, 16.05, 12.49; IR (thin film) ν 2943, 2867, 2714, 2360, 1727, 1566, 1462, 1382, 1396, 1245, 1201, 1157,1120, 1100, 1047; $[\alpha]^{22}_{D}$ = +8.4 (*c* = 53.4, CH_2Cl_2); MS (ESI) calculated for $C_{15}H_{32}O_2Si$ $[M+Na]^+$: 295.2, found 295.2.



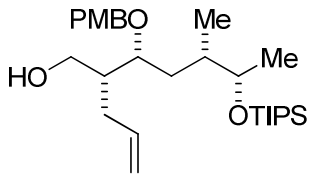
(2S,3R,5S,6S)-2-allyl-1-((S)-4-benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy-5-methyl-6-(triisopropylsilyloxy)heptan-1-one

A solution of thione **19** (5.4 g, 18.55 mmol) in 186 mL CH_2Cl_2 was cooled to 0 ℃. Neat $TiCl_4$ (2.14 mL, 19.05 mmol) was added dropwise, and the resulting slurry was stirred for 15 min. Hünig's base (3.55 mL, 20.4 mmol) was added dropwise, and the resulatant deep red solution was stirred for 15 m. *N*-methyl pyrrolidinone (3.60 mL, 37.1 mmol) was added at 0 ℃. After 30 min, aldehyde **3.150** was added dropwise in CH_2Cl_2 (10 mL). The reaction was stirred 1 h, and was quenched by the addition of a saturated $NaHCO_3$ solution. The layers were separated and the aqueous layer was then extracted into CH_2Cl_2 (2 x 30 mL). The organic extracts were dried (Na_2SO_4) and evaporated to give a crude yellow oil which was purified by flash chromatography (10% EtOAc/hexanes) to afford 9.01 g of secondary alcohol **3.151** (86%), a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 5H), 5.97 (dddd, *J* = 16.8, 10.0, 6.8, 6.8, 1H), 5.40 (dddd, *J* = 7.2, 7.2, 3.6, 3.6, 1H) 5.10 (m, 3H), 4.19 (m, 1H), 3.95 (m, 1H), 3.34 (dd, *J* = 7.2, 11.6, 1H), 3.24 (dd, *J* = 3.2, 13.2, 1H), 3.05 (m, 2H), 2.89 (d, *J* = 11.6, 1H), 2.73 (m, 1H), 2.62 (m, 1H), 2.00 (m, 1H), 1.73 (m, 1H), 1.46 (m, 1H), 1.16 (m, 24H), 0.92 (d, *J* = 7.2) ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.39, 175.80, 136.61, 135.97, 129.25, 128.91, 127.21, 116.77, 72.68, 70.85, 69.13, 48.08, 36.95, 36.75, 36.39, 31.52, 31.30, 18.22, 18.15, 17.82, 12.54; IR (thin film) ν 3464, 3065, 3027, 2942, 2890, 2865, 1692, 1640, 1603, 1495, 1455, 1364, 1341, 1319, 1293, 1260, 1190, 1160, 1134, 1037; $[\alpha]^{22}_D$ = +77 (*c* = 50.4, CH_2Cl_2); MS (ESI) calculated for $C_{30}H_{49}NO_3S_2Si$ $[M+Na]^+$: 586.3, found 586.3.



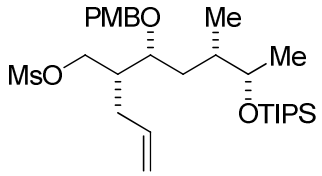
(2R,3R,5S,6S)-2-allyl-5-methyl-6-(triisopropylsilyloxy)heptane-1,3-diol

To a stirring solution of secondary alcohol **3.151** (8.50 g, 15.1 mmol) in Et_2O (151 mL) at 0 ℃ was added MeOH (0.91 mL, 22.62 mmol). A solution of $LiBH_4$ (2M in THF, 11.31 mL, 22.63 mmol) was added slowly dropwise. The reaction was allowed to stir overnight, while warming to room temperature. The following day, the reaction was recooled to 0 ℃ and a saturated solution of $NaHCO_3$ was added slowly. Upon separation of the layers, the aqueous layer was further extracted with Et_2O (3 x 75 mL), and dried over $MgSO_4$. The organic extracts were concentrated to provide a crude oil containing solidified chiral auxiliary which was purified by flash chromatography (2.5% EtOAc/CH_2Cl_2) to provide 4.5 g of alcohol **3.152** (83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (dddd, *J* = 17.2, 10, 10, 7.2, 1H), 5.13 (dd, *J* = 17.2, 8, 2H), 4.15 (m, 1H), 3.98 (m, 1H), 3.85 (m, 1H), 3.74 (m, 1H), 3.22 (d, *J* =3.2, 1H), 2.69 (m, 1H), 2.21 (ddd, *J* = 7.2, 0, 2H), 2.03 (m, 1H), 1.83 (m, 1H), 1.70 (s, 1H), 1.65 (m, 1H), 1.53 (m,1H), 1.16 (d, *J* = 6.4, 3H), 1.10 (m, 20H), 0.93 (d, *J* =7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.36, 116.20, 72.87, 72.39, 64.50, 43.95, 36.66, 35.20, 30.10, 18.17, 18.10, 17.99, 17.78, 12.50; IR (thin film) ν 3854, 3751, 3397, 3077, 2942, 2890, 2866, 1640, 1463, 1382, 1245, 1160, 1105, 1037; $[\alpha]^{22}_D$ = +9.43 (*c* = 20.1, CH_2Cl_2); MS (ESI) calculated for $C_{20}H_{42}O_3Si$ $[M+Na]^+$: 381.3, found 381.3.



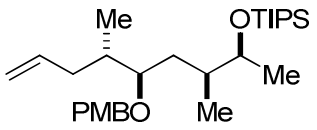
(2R,3R,5S,6S)-2-allyl-3-(4-methoxybenzyloxy)-5-methyl-6-(triisopropylsilyloxy)heptan-1-ol

A solution of diol **3.152** (2.14 g, 5.97 mmol) was dissolved in CH_2Cl_2 (60 mL). Benzaldehyde dimethylacetal (1.53 mL, 9 mmol) was added followed by pyridinium *p*-toluenesulfonate (0.150 g, 0.60 mmol). The reaction was stirred 2 h, quenched by the addition of triethylamine (0.5 mL), and concentrated. The resultant crude oil was purified through a plug of silica (10% EtOAc/hexanes) to deliver the crude PMP acetal, which was dissolved in CH_2Cl_2 (60 mL) and cooled to -78 ℃. A solution of diisobutylaluminum hydride (1M in hexanes, 12.0 mL, 12.0 mmol) was added dropwise, and allowed to slowly warm to room temperature. After stirring 8 h, the reaction was quenched by the addition of a saturated sodium/potassium tartrate solution. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The organic extracts were dried (Na_2SO_4) and evaporated to give a crude clear oil which was purified by flash chromatography (5% EtOAc/hexanes to 10% EtOAc/hexanes to 20% EtOAc/hexanes) to afford 1.90 g of the product **3.153** (70%), a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.8, 2H), 6.91 (d, *J* = 8.8, 2H), 5.88 (dddd, *J* = 17.2, 10, 7.2, 7.2, 1H), 5.10 (m, 2H), 4.55 (dd, *J* = 11.2, 11.2, 1H), 3.87 (m, 1H), 3.83 (s, 3H), 3.75 (m, 3H), 2.84 (dd, *J* = 5.6, 5.6, 1H), 2.11 (m, 3H), 1.87 (m, 1H), 1.67 (m, 1H), 1.47 (m, 1H), 1.11 (m, 25H), 0.93 (d, *J* = 6.8, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.27, 137.10, 130.34, 129.61, 116.15, 113.84, 80.58, 71.99, 70.69, 63.94, 55.20, 41.20, 38.08, 31.03, 30.71, 19.19, 18.29, 18.24, 16.10, 12.65; IR (thin film) ν 3434, 2942, 2866, 1613, 1513, 1463, 1381, 1302, 1248, 1172, 1038; $[\alpha]^{22}_D$ = -3.5 (*c* = 17.5, CH_2Cl_2); MS (ESI) calculated for $C_{28}H_{50}O_4Si$ $[M+Na]^+$: 501.3, found 501.3.



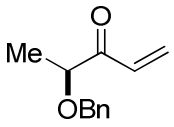
(2R,3R,5S,6S)-2-allyl-3-(4-methoxybenzyloxy)-5-methyl-6-(triisopropylsilyloxy)heptyl methanesulfonate

A solution of primary alchol **3.153** (973 mg, 2.03 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 ℃. Triethylamine (0.42 mL, 3.04 mmol) was added dr opwise, followed by the addition of freshly distilled methane sulfonyl chloride (0.19 mL, 2.43 mmol). The reaction was allowed to stir overnight while warming to room temperature. The following day, the reaction was quenched by the addition of a saturated $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted into CH_2Cl_2 (2 x 100 mL). The organic extracts were dried (Na_2SO_4), and evaporated to give a clear crude oil, which was purified by flash chromatography (10% EtOAc/hexanes to 20% EtOAc/hexanes) to give 1.10 g of the product **3.154** (97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 7.8, 2H), 6.91 (d, *J* = 8.4, 1H), 5.82 (m, 1H), 5.11 (dd, *J* =16.8, 1 H), 4.54 (d, *J* = 11.4, 1H), 4.43 (d, *J* = 11.4, 1H), 4.29 (dd, *J* = 9, 9, 1H), 4.21 (m, 1H), 3.89 (m, 1H), 3.83 (s, 3H), 3.71 (dd, *J* = 7.2, 7.2, 1H), 2.94 (s, 3H), 2.35 (s, 1H), 2.15 (m, 2H), 1.89 (m, 1H), 1.61 (m, 1H), 1.46 (m, 1H), 1.11 (m, 24H), 0.92 (d, 7.2, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.16, 136.16, 129.43, 117.00, 113.78, 76.06, 72.06, 70.95, 70.17, 55.27, 40.07, 37.58, 37.05, 31.04, 30.02, 19.00, 18.29, 18.26, 18.23, 15.74, 12.61; IR (thin film) ν 3411, 2942, 2866, 1641, 1613, 1586, 1513, 1463, 1359, 1302, 1248, 1177, 1036; $[\alpha]^{22}_D$ = -13.1 (*c* = 12.7, CH_2Cl_2); MS (ESI) calculated for $C_{29}H_{52}O_6SSi$ $[M+Na]^+$: 579.3, found 579.3.



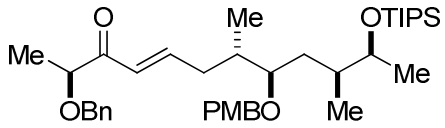
triisopropyl((2S,3S,5R,6S)-5-(4-methoxybenzyloxy)-3,6-dimethylnon-8-en-2-yloxy)silane

To a solution of mesylate **3.154** (3.21 g, 5.76 mmol) in THF (58 mL) was added a solution of lithium triethylborohydride in THF (1.1 M solution, 26.2 mL, 28.2 mmol) dropwise at room temperature. The reaction was stirred overnight. The following day, the reaction was cooled to 0 ℃ and H_2O was added slowoly dropwise. Following gas evolution, Et_2O (50 mL) was added. The layers were separated, and the aqueous layer was further extracted with Et_2O (3 x 50 mL). The organic extracts were dried ($MgSO_4$) and evaporated to give a crude clear oil which was purified by flash chromatography (5% EtOAc/hexanes) to afford 2.334 g of the product **3.155** (88%), a clear oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (d, *J* = 4.0, 2H), 6.90 (d, *J* = 5.2, 2H), 5.80 (m, 1H), 5.02 (dd, *J* = 18.6, 18.6, 2H), 4.49 (d, *J* = 10.8, 1H), 4.43 (d, *J* = 11.4, 1H), 3.87 (m, 1H), 3.83 (s, 1H), 3.38 (m, 1H), 2.23 (m, 1H), 1.92 (m, 2H), 1.79 (m, 1H), 1.67 (m, 1H), 1.27 (m, 1H), 1.09 (m, 23H), 0.94 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.00, 137.98, 131.27, 129.35, 115.53, 113.68, 81.79, 71.76, 70.67, 55.29, 38.15, 36.78, 35.39, 31.57, 19.50, 18.30, 18.26, 16.17, 14.78, 12.69; IR (thin film) ν 2942, 2866, 2360, 1640, 1614, 1513, 1463, 1381, 1301, 1248, 1171, 1040; $[\alpha]^{22}_D$ = 1.48 (*c* = 6.45, CH_2Cl_2); MS (ESI) calculated for $C_{28}H_{50}O_3Si$ $[M+Na]^+$: 485.3, found 485.3.



(*S*)-4-(benzyloxy)pent-1-en-3-one

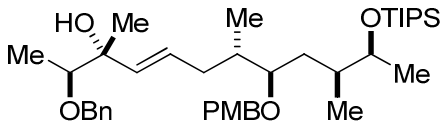
A solution of Weinreb amide **3.49** (1.0 g, 4.48 mmol) in THF (9 mL) was cooled to 0 ℃. A solution of freshly prepared vinyl magnesium bromide (1M solution in THF, 22.4 mL, 22.4 mmol) was added dropwise to the reaction mixture, and allowed to warm to room temperature. After TLC indicated consumption of starting material, the reaction was quenched by pouring into a 0 ℃ 10% HCl solution. After evolution of gas, the phases were separated and the aqueous phase was extracted with EtOAc (3 x 50). The organic extracts were dried (Na_2SO_4), concentrated, and purified via flash chromatography (10% EtOAc/Hexanes) to provide 810 mg of enone **3.50** (95%), a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 5H), 6.85 (dd, *J* =17.2, 10.4, 1H), 6.80 (dd, *J* =17.6, 10.4, 1H), 5.83 (dd, *J* =10.8, 1.6, 1H), 4.60 (d, *J* = 11.6, 1H), 4.47 (d, *J* =11.6, 1H), 4.14 (q, *J* =6.8, 1H), 1.40 (d, *J* =6.8, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.39, 137.50, 130.95, 129.89, 128.49, 127.93, 127.87, 79.85, 71.84, 17.75; IR (thin film) ν 2981, 1700, 1611, 1454, 1402, 1111; $[\alpha]^{22}_D$ = -4.13 (*c* = 7.9, CH_2Cl_2); MS (ESI) calculated for $C_{12}H_{14}O_2$ $[M+Na]^+$: 213.1, found 213.1.



(2S,7S,8R,10S,11S,E)-2-(benzyloxy)-8-(4-methoxybenzyloxy)-7,10-dimethyl-11-(triisopropylsilyloxy)dodec-4-en-3-one

To a degassed solution of enone **3.50** (1.36 g, 7.20 mmol) and terminal olefin **3.155** (2.22 g, 4.80 mmol) in CH_2Cl_2 (48 mL) was added Hoveyda-Grubbs 2nd generation catalyst (300 mg, 0.48 mmol). The reaction was heated to reflux, and stirred overnight. The following day, the reaction was concentrated to yield a crude black oil which was purified with flash

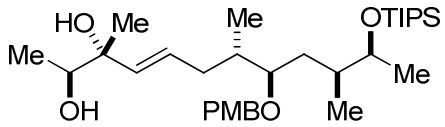
chromatography (100% hexanes to 5% EtOAc/hexanes to 10% EtOAc/hexanes) to provide 2.10 g of the product **3.156** (70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.39 (m, 9H), 7.09 (ddd, *J* = 7.8, 7.8, 12.6, 1H), 6.90 (d, *J* =7.8, 2H), 6.56 (d, *J* =15.6, 1H), 4.60 (d, *J* = 11.4, 1H), 4.45 (d, *J* =10.8, 3H), 4.10 (q, *J* =6.6, 1H), 3.87 (m, 1H), 3.83 (s, 3H), 3.38 (m, 1H), 2.43 (m, 1H), 2.15 (m, 1H), 1.97 (m, 1H), 1.81 (ddd, *J* = 13.8, 5.4, 5.4, 1H), 1.67 (m, 1H), 1.39 (d, *J* =6.6, 3H), 1.36 (m, 1H), 1.10 (m, 22H), 0.97 (d, *J* =6.6, 3H), 0.92 (d, *J* =6.6, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.17, 159.08, 148.97, 137.65, 130.96, 129.33, 128.48, 127.89, 127.87, 125.63, 113.73, 81.68, 79.96, 71.80, 71.79, 70.94, 55.29, 37.95, 35.28, 31.88, 19.35, 18.30, 18.25, 18.07, 16.05, 15.60, 12.67; IR (thin film) ν 2941, 2865, 1697, 1622, 1513, 1456, 1381, 1248, 1107; $[\alpha]^{22}_{D}$ = -12.8 (*c* = 3.5, CH_2Cl_2); MS (ESI) calculated for $C_{38}H_{60}NO_5Si$ $[M+Na]^+$: 647.4, found 647.4.



(2S,3R,7S,8R,10S,11S,E)-2-(benzyloxy)-8-(4-methoxybenzyloxy)-3,7,10-trimethyl-11-(triisopropylsilyloxy)dodec-4-en-3-ol

A solution of enone **3.156** (2.10 g, 3.36 mmol) in Et_2O (34 mL) was cooled to -78 ℃. A solution of MeMgBr (3 M in Et_2O, 5.6 mL, 16.8 mmol) was added slowly dropwise. The reaction was stirred for 3 h, and quenched by the addition of a saturated solution of NH_4Cl. The layers were separated and the aqueous layer was then extracted into Et_2O (2 x 30 mL). The organic extracts were dried (Na_2SO_4) and evaporated to give a clear crude oil which was purified by flash chromatography (10% EtOAc/hexanes) to afford 2.00 g of the tertiary alcohol (93%), a clear oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (m, 7H), 6.89 (d, *J* = 8.4, 2H), 4.71 (d, *J* = 10.8, 1H), 4.48 (m, 3H), 3.87 (m, 1H), 3.82 (s, 3H), 3.43 (m, 1H), 3.36 (m, 1H), 2.56 (s, 1H), 2.23 (m, 1H), 1.93 (m, 2H), 1.79 (m, 1H), 1.66 (m, 1H), 1.29 (s, 4H), 1.18 (d, *J*

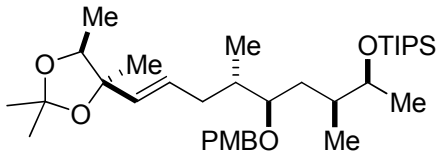
=6, 3H), 1.07 (m, 24H), 0.93 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.99, 138.56, 133.97, 131.27, 129.35, 128.63, 128.39, 127.66, 127.63, 113.68, 81.84, 81.52, 74.75, 71.81, 71.32, 70.65, 55.29, 38.19, 35.78, 35.28, 31.77, 24.63, 19.56, 18.31, 18.26, 16.08, 14.91, 14.12, 12.70; IR (thin film) ν 3433, 2940, 2866, 1612, 1513, 1462, 1379, 1247, 1071; $[\alpha]^{22}_D$ = +14.3 (*c* = 3.3, CH_2Cl_2); MS (ESI) calculated for $C_{39}H_{64}O_5Si$ $[M+Na]^+$: 663.3, found 663.3.



(2S,3R,7S,8R,10S,11S,E)-8-(4-methoxybenzyloxy)-3,7,10-trimethyl-11-(triisopropylsilyloxy)dodec-4-ene-2,3-diol

To a solution of ditertbutylbiphenyl (3.20 g, 12.0 mmol) in THF (17.1 mL) was added pieces of Li metal (83 mg, 12.0 mmol). The solution was sonicated for 2 h at room temperature to yield a dark green-blue solution which was used immediately. A solution of the tertiary alcohol (640 mg, 1.00 mmol) in THF (11 mL) was cooled to -78 ℃. A solution of freshly prepared LDBB in THF (0.7 M, 15.6 mL, 10.9 mmol) was added dropwise to the reaction. After consumption of the starting material by TLC, the reaction was quenched with a saturated solution of NH_4Cl. The layers were separated, and the aqueous layer was extracted into EtOAc (3 x 25 mL). The organic extracts were concentrated, and the crude solid was purified by flash chromatography (20% EtOAc/hexanes to 40% EtOAc/hexanes) to yield 532 mg of a clear oil (97%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8, 2H), 6.90 (d, *J* = 8, 2H), 5.75 (dddd, *J* = 15.5, 7.5, 7.5, 1H), 5.57(d, *J* = 15.5, 1H), 4.47 (d, *J* = 11, 1H), 4.44 (d, *J* = 11.5, 1H), 3.88 (m, 1H), 3.82 (s, 3H), 3.65 (m, 1H), 3.82 (m, 1H), 3.38 (m, 1H), 2.24 (m, 1H), 2.02 (s, 1H), 1.99 (m, 2H), 1.89 (m, 1H), 1.81 (m, 1H), 1.64 (m, 1H), 1.28 (m, 4H), 1.16 (d, *J* = 6.5, 3H), 1.09 (m, 24H), 0.94 (d, *J* = 7, 3H), 0.91 (d, *J* = 6.5, 3H) 5.30 (ddd, *J* = 6.8, 6.8, 0, 1H), 5.16 (m, 1H), 3.38 (s, 3H), 3.00 (dd, *J* = 11.2, 0, 1H), 2.36 (m, 1H), 2.31 (m,

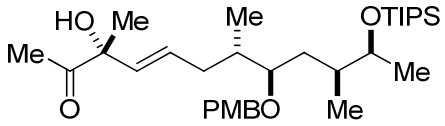
1H), 2.21 (m, 1H), 2.04 (m, 1H), 1.69 (d, *J* = 5.6, 4H), 1.09 (d, *J* = 6.8, 3H), 1.05 (d, *J* = 6.8, 3H), 1.02 (d, *J* = 6.8, 3H), 0.89 (d, *J* = 6.8, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.05, 132.90, 131.14, 130.12, 129.42, 113.68, 81.71, 75.14, 74.28, 71.89, 70.81, 55.27, 38.02, 35.60, 35.00, 31.85, 24.63, 19.41, 18.30, 18.25, 17.99, 16.02, 15.31, 12.69; IR (thin film) ν 3419, 2941, 2866, 1613, 1513, 1462, 1379, 1247, 1065; $[\alpha]^{22}_D$ = +2.2 (*c* = 3.5, CH_2Cl_2); MS (ESI) calculated for $C_{32}H_{58}O_5Si$ $[M+Na]^+$: 573.4, found 573.4.



triisopropyl((2S,3S,5R,6S,E)-5-(4-methoxybenzyloxy)-3,6-dimethyl-9-((4R,5S)-2,2,4,5-tetramethyl-1,3-dioxolan-4-yl)non-8-en-2-yloxy)silane

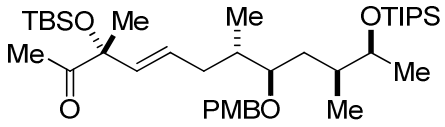
To a solution of the diol (50 mg, 0.09 mmol) in dimethoxypropane (5 mL) was added CSA (2 mg, 0.009 mmol). The reaction was stirred for 20 m, and quenched by the addition of a saturated sodium bicarbonate solution. Ethyl acetate (5 mL) was added and the resultant layers separated. The aqueous layer was further extracted into EtOAc (3 x 5 mL). The organic extracts were dried (Na_2SO_4), and concentrated to afford a crude oil. The oil was purified with flash chromatography (5% EtOAc/hexanes) to provide 37 mg of the product (69%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.51 (m, 2H), 7.29 (d, *J* = 8.4, 2H), 6.89 (dd, *J* = 6.6, 2.4, 2H), 5.68 (m, 1H), 5.48 (d, *J* = 15.6, 1H), 4.48 (d, *J* =11.4), 4.43 (d, *J* = 10.8, 1H), 4.01 (q, *J* =6, 1H), 3.89 (m, 1H), 3.83 (s, 3H), 3.38 (m, 1H), 2.24 (m, 1H), 1.95 (m, 1H), 1.81 (m, 1H), 1.68 (m, 1H), 1.52 (s, 3H), 1.43 (s, 3H), 1.35 (s, 3H), 1.31 (m, 1H), 1.19 (d, *J* = 6.6, 3H), 1.09 (m, 23H), 0.94 (d, *J* = 7.2, 3H), 0.92 (d, *J* = 7.2, 3H);^{13}C NMR (150 MHz, $CDCl_3$) δ 159.00, 132.35, 131.25, 129.42, 129.33, 113.68, 107.14, 82.33, 81.90, 79.81, 71.83, 70.71, 55.28, 38.22, 35.81, 35.18, 31.68, 28.33, 26.76, 24.00, 19.46, 18.31, 18.26, 16.11, 15.02,

14.98, 12.69; IR (thin film) ν 2940, 2866, 1613, 1587, 1513, 1462, 1376, 1301, 1248, 1213, 1187, 1097; $[\alpha]^{22}_D$ = 11.1 (*c* =16, CH_2Cl_2); MS (ESI) calculated for $C_{35}H_{62}O_5Si$ $[M+Na]^+$: 613.4, found 613.4.



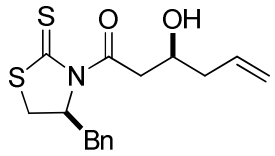
(3R,7S,8R,10S,11S,E)-3-hydroxy-8-(4-methoxybenzyloxy)-3,7,10-trimethyl-11-(triisopropylsilyloxy)dodec-4-en-2-one

A solution of the corresponding diol (800 mg, 1.45 mmol) in a 1:1 mixture of anhydrous DMSO/CH_2Cl_2 (5 mL DMSO/ 5 mL CH_2Cl_2) was cooled to 0 ℃. To this was added Hünig's base (2.02 mL, 11.6 mmol) followed by the sulfur trioxide pyridine complex (924 mg, 5.81 mmol) all in one portion. The reaction was allowed to warm to room temperature. Upon completion of the reaction by TLC analysis, the reaction was quenched by the addition of a saturated $NaHCO_3$ solution. The layers were separated and the aqueous phase was further extracted with CH_2Cl_2 (2 x 30 mL). The organic extracts were dried (Na_2SO_4), concentrated, and purified by flash chromatography (10% EtOAc/hexanes to 20% EtOAc/hexanes) to provide 550 mg of the product **3.159** (77%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 9, 2H), 6.89 (d, *J* = 9, 2H), 5.87 (m, 1H), 5.56 (d, *J* = 15.5, 1H), 4.44 (m, 2H), 4.04 (s, 1H), 3.88 (m, 1H), 3.82 (s, 3H), 3.36 (m, 1H), 2.22 (s, 4H), 1.96 (m, 2H), 1.79 (m, 1H), 1.75 (m, 1H), 1.32 (m, 1H), 1.09 (s, 26H), 0.91 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.82, 159.04, 132.08, 131.87, 131.15, 129.31, 113.70, 81.75, 78.75, 71.85, 70.78, 55.27, 38.08, 35.64, 34.86, 31.76, 24.61, 23.60, 19.40, 18.30, 18.24, 16.07, 15.16, 12.69; IR (thin film) ν 3474, 2941, 2866, 1713, 1613, 1586, 1513, 1462, 1356, 1301, 1247, 1172, 1098; $[\alpha]^{22}_D$ = -25.2 (*c* = 6.9, CH_2Cl_2); MS (ESI) calculated for $C_{32}H_{56}O_5Si$ $[M+Na]^+$: 571.4, found 571.4.



(3R,7S,8R,10S,11S,E)-3-(tert-butyldimethylsilyloxy)-8-(4-methoxybenzyloxy)-3,7,10-trimethyl-11-(triisopropylsilyloxy)dodec-4-en-2-one

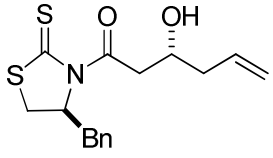
A solution of ketone **3.159** (190 mg, 0.35 mmol) in CH_2Cl_2 (4 mL) was cooled to 0 ℃. 2,6-lutidine (0.28 mL, 2.45 mmol) was added dropwise followed by TBSOTf (0.28 mL, 1.21 mmol). After TLC analysis indicated the absence of starting material, the reaction was quenched by the addition of a saturated $NaHCO_3$ solution. The layers were separated, and the aqueous phase was further extracted with CH_2Cl_2 (2 x 25 mL). The organic phase was stirred overnight with a 10% HCl solution (25 mL). The following day, the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 25 mL). The organic extracts were dried (Na_2SO_4), and concentrated to yield a crude oil. The oil was purified via flash chromatography (5% EtOAc/hexanes to 10% EtOAc/hexanes) to provide 175 mg of the product **3.160** (76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* =8.8, 2H), 6.90 (d, *J* = 10.4, 1H), 5.78 (ddd, *J* = 14.0, 6.4, 6.4, 1H), 5.47 (d, *J* =15.6, 1H), 4.48 (m, 2H), 3.88 (m, 1H), 3.83 (s, 3H), 3.36 (m, 1H), 2.24 (m, 4H), 1.94 (m, 2H), 1.80 (m, 1H), 1.65 (m, 1H), 1.45 (s, 3H), 1.32 (m, 1H), 1.09(m, 22H), 0.97(m, 16H), 0.14 (s, 3H), 0.12(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.75, 159.03, 133.62, 131.18, 130.90, 129.31, 113.70, 82.28, 81.93, 77.85, 70.81, 55.26, 38.18, 35.83, 35.00, 31.75, 25.92, 24.65, 24.19, 19.44, 18.20, 18.25, 16.08, 15.08, 12.69, -2.12, -2.43; IR (thin film) ν 2957, 2865, 2359, 1721, 1613, 1587, 1513, 1463, 1369, 1349, 1301, 1249, 1171, 1107, 1039, 1013; $[\alpha]^{22}_D$ = +32 (*c* = 2.35, CH_2Cl_2); MS (ESI) calculated for $C_{38}H_{70}O_5Si_2$ $[M+Na]^+$: 685.4, found 685.4.



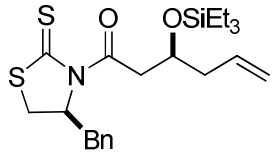
(S)-1-((S)-4-benzyl-2-thioxothiazolidin-3-yl)-3-hydroxyhex-5-en-1-one

A solution of thione **3.63** (3.58 g, 14.3 mmol) in 143 mL CH_2Cl_2 was cooled to 0 ℃. Neat $TiCl_4$ (1.57 mL, 14.3 mmol) was added dropwise, and the resulting slurry was stirred for 15 min. The reaction was then cooled to -78 ℃ and *i*-Pr_2NEt (2.49 mL, 14.3 mmol) was added dropwise. The resulting dark red solution was stirred for 2 h at -78 ℃. A solution of freshly prepared 3-butenal (1.00 g, 14.3 mmol) in CH_2Cl_2 (25 mL) was added dropwise. After 1 h of stirring at -78 ℃, the reaction was quenched by addition of a saturated solution of NH_4Cl, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL). The organic extracts were dried (Na_2SO_4), and concentrated to afford a crude yellow oil. The oil was purified by flash chromatography (10% EtOAc/hexanes) to deliver 1.45 g of the product **3.64** (41%), a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (m, 5H), 5.91 (m, 1H), 5.44 (m, 1H), 5.21 (m, 1H), 4.29 (m, 1H), 3.70 (dd, *J* = 2.5, 2.5, 1H), 3.45 (dd, *J* = 7.5, 11.5, 1H), 3.26 (m, 2H), 3.09 (dd, *J* = 10.5, 13, 2H), 2.93 (d, *J* =11.5), 2.74 (s, 1H), 2.41 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.41, 173.00, 136.40, 134.02, 129.45, 128.96, 127.31, 118.31, 68.34, 67.26, 45.27, 40.80, 36.82, 32.08; IR (thin film) ν 3432, 2923, 1692, 1495, 1435, 1342, 1293, 1263, 1192, 1164, 1137, 1044; $[\alpha]^{22}_D$ = +103.4 (*c* = 7.1, CH_2Cl_2); MS (ESI) calculated for $C_{16}H_{19}NO_2S_2$ $[M+Na]^+$: 344.1, found 344.1.

Other diastereomer:

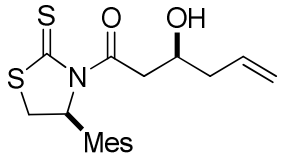


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (m, 5H), 5.90 (m, 1H), 5.45 (m, 1H), 5.20 (m, 2H), 4.18 (m, 1H), 3.67 (m, 3H), 3.26 (m, 1H), 2.23 (m, 2H), 2.95 (d, *J* = 11.5, 1H), 2.41 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.45, 173.57, 136.35, 134.02, 129.45, 128.97, 127.32, 118.22, 68.23, 67.90, 44.87, 40.95, 36.79, 32.05; IR (thin film) ν 3423, 1690, 1494, 1342, 1261, 1163, 1042; $[\alpha]^{22}_D$ = +27 (*c* = 11.1, CH_2Cl_2); MS (ESI) calculated for $C_{16}H_{19}NO_2S_2$ $[M+Na]^+$: 344.1, found 344.1.



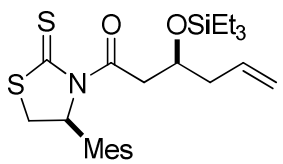
(S)-1-((S)-4-benzyl-2-thioxothiazolidin-3-yl)-3-(triethylsilyloxy)hex-5-en-1-one

A solution of secondary alcohol **3.64** (1.89 g, 5.88 mmol) in 58 mL CH_2Cl_2 was cooled to 0 ℃. 2.6-lutidine (1.36 mL, 11.76 mmol) was added dr opwise, followed by TESOTf (2.00 mL, 8.83 mmol). The reaction was warmed to room temperature and quenched by the addition of a saturated $NaHCO_3$ solution. The layers were separated and the aqueous layer was then extracted into CH_2Cl_2 (2 x 30 mL). The organic extracts were dried (Na_2SO_4) and evaporated to give a crude yellow oil which was purified by flash chromatography (3% EtOAc/hexanes) to afford 2.45 g of the product **3.65** (96%), a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (m, 5H), 5.89 (dddd, *J* = 17, 17, 7, 7, 1H), 5.31(m, 1H), 5.15 (dd, *J* = 10.5, 9, 2H), 4.46 (m, 1H), 3.54 (dd, *J* = 8.5, 17, 1H), 3.39 (dd, *J* =7, 11.5, 1H), 3.28 (dd, *J* = 13, 3.5, 2H), 3.08 (dd, *J* =11, 11, 1H), 2.92 (d, *J* = 11.5, 1H), 2.36 (dd, *J* = 6.5, 13, 2H), 0.99 (t, *J* = 8, 9H), 0.66 (q, *J* = 8, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.05, 172.21, 136.63, 134.23, 129.46, 128.94, 127.22, 117.91, 68.78, 45.73, 42.44, 36.53, 32.18, 6.91, 5.02; IR (thin film) ν 2953, 1698, 1455, 1341, 1263, 1190, 1164, 1136, 1092, 1044, 1006; $[\alpha]^{22}_D$ = +99 (*c* = 4, CH_2Cl_2); MS (ESI) calculated for $C_{22}H_{33}NO_2S_2Si$ $[M+Na]^+$: 458.2, found 458.2.



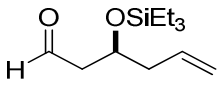
(S)-3-hydroxy-1-((S)-4-mesityl-2-thioxothiazolidin-3-yl)hex-5-en-1-one

A solution of thione **3.60** (150 mg, 0.54 mmol) in 3 mL CH_2Cl_2 was cooled to 0 ℃. Neat $TiCl_4$ (0.06 mL, 0.54 mmol) was added dropwise, and the resulting slurry was stirred for 5 min. The reaction was then cooled to -78 ℃ and *i*-Pr_2NEt (0.09 mL, 0.54 mmol) in 1 mL of CH_2Cl_2 was added dropwise. The resulting dark red solution was stirred at -78 ℃ for 1 h. Freshly prepared 3-butenal (0.625 g, 0.357 mmol) was added in 2 mL CH_2Cl_2. After addition was complete, the reaction was allowed to stir at -78 ℃ for 1 h, and then was quencedh by the addition of a saturated aqueous NH_4Cl solution. The layers were separated and the aqueous layer was then extracted into CH_2Cl_2 (2 x 10 mL). The organic extracts were dried (Na_2SO_4) and evaporated to give a crude yellow oil which was purified by flash chromatography (10% EtOAc/hexanes to 20% CH_2Cl_2/hexanes) to afford 85 mg of the product **3.61** (69%), a yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.88 (s, 2H), 6.42 (dd, *J* = 10.2, 10.2), 5.83 (dddd, *J* =0, 16.2, 16.2, 7.3, 1H), 5.13 (dd, *J* = 0, 13.2), 3.98 (m, 1H), 3.63 (m, 2H), 3.38 (dd, *J* =10.8, 10.8, 1H), 3.23 (dd, *J* = 0, 17.4, 1H), 2.87 (dd, *J* = 0, 4.2), 2.42 (s, 6H), 2.32 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.76, 174.71, 137.96, 133.95, 132.65, 118.14, 68.07, 67.78, 45.96, 40.84, 32.56, 20.83; IR (thin film) ν 3436, 2919, 2360, 1704, 1641, 1610, 1454, 1371, 1325, 1260, 1177, 1128; $[\alpha]^{22}_D$ = +87 (*c* = 5.5, CH_2Cl_2); MS (ESI) calculated for $C_{18}H_{23}NO_2S_2$ $[M+Na]^+$: 372.1, found 372.1.



(S)-1-((S)-4-mesityl-2-thioxothiazolidin-3-yl)-3-(triethylsilyloxy)hex-5-en-1-one

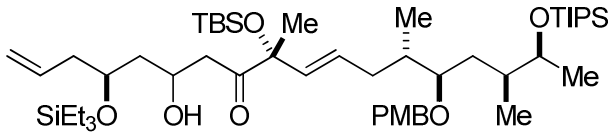
A solution of secondary alcohol **3.61** (86 mg, 0.25 mmol) in 6 mL CH_2Cl_2 was cooled to 0 ℃. 2,6-lutidine (0.06 mL, 0.50 mmol) was added dropwise, followed by TESOTf (0.08 mL, 0.37 mmol). The reaction was allowed to warm to room temperature. Upon consumption of the starting material as indicated by TLC analysis, the reaction was quenched by the addition of a saturated $NaHCO_3$ solution. The layers were separated, and the aqueous phase was further extracted with CH_2Cl_2 (2 x 5 mL). The organic extracts were dried (Na_2SO_4) and evaporated to give a crude yellow oil which was purified by flash chromatography (3% EtOAc/hexanes) to afford 110 mg of the product **3.62** (96%), a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.40 (dd, *J* = 10.2, 1H), 5.74 (m, 1H), 4.98 (d, *J* = 10.2, 1H), 4.84 (d, *J* = 16.8, 1H), 4.21 (m, 1H), 3.69 (dd, *J* = 4.8, 17.4, 1H), 3.38 (dd, *J* = 10.2, 1H), 3.12 (dd, *J* = 7.8, 17.4, 1H), 2.42 (s, 6H), 2.27 (s, 3H), 1.99 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.99, 173.14, 137.87, 134.44, 132.70, 117.26, 68.36, 67.94, 47.28, 41.21, 32.53, 20.78, 6.84, 4.84; IR (thin film) ν 2954, 2875, 1709, 1611, 1459, 1371, 1311, 1260, 1177, 1126, 1009; $[\alpha]^{22}_D$ = +71 (*c* = 7.5, CH_2Cl_2); MS (ESI) calculated for $C_{24}H_{37}NO_2S_2Si$ $[M+Na]^+$: 486.3, found 486.3.



(S)-3-(triethylsilyloxy)hex-5-enal

A solution of TES ether **3.61** (345 mg, 0.74 mmol) in CH_2Cl_2 (7 mL) was cooled to -78 ℃. A solution of *i*-Bu_2AlH (1 M in hexanes, 1.49 mL, 1.49 mmol) was added slowly dropwise. Upon disappearance of the yellow from the reaction, the reaction was quenched with a saturated sodium/potassium tartrate solution. Upon warming to room temperature and stirring for 1 h, the layers could be separated. The aqueous layer was further extracted with CH_2Cl_2 (5 mL x 2). The organic extracts were dried (Na_2SO_4) and evaporated to give a

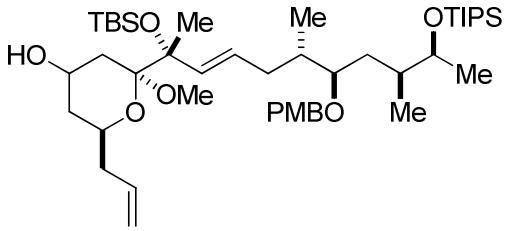
crude oil which was purified by flash chromatography (5% EtOAc/hexanes) to afford 160 mg of the product **3.7** (94%), a clear oil. Alternative strategy: A solution of TES ether **3.65** (600 mg, 1.38 mmol) in CH_2Cl_2 (14 mL) was cooled to -78 ℃. A solution of *i*-Bu_2AlH (1 M in hexanes, 2.76 mL, 2.76 mmol) was added slowly dropwise. Upon disappearance of the yellow from the reaction, the reaction was quenched with a saturated sodium/potassium tartrate solution. Upon warming to room temperature and stirring for 1 h, the layers could be separated. The aqueous layer was further extracted with CH_2Cl_2 (5 mL x 2). The organic extracts were dried (Na_2SO_4) and evaporated to give a crude oil which was purified by flash chromatography (5% EtOAc/hexanes) to afford 317 mg of the product **3.7** (100%), a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.51 (m, 2H), 9.82 (dd, *J* = 2.4, 1H), 5.85 (dddd, *J* = 16, 10.8, 7.2, 7.2 1H), 5.12 (m, 2H), 4.32 (dddd, *J* = 5.6, 5.6, 5.6, 5.6, 1H), 2.56 (m, 2H), 2.34 (m, 2H), 0.98 (t, *J* =8, 9H), 0.65 (q, *J* =7.6, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.96, 133.79, 118.14, 67.61, 50.43, 42.45, 6.79, 4.89; IR (thin film) ν 2956, 2912, 2877, 1726, 1642, 1459, 1415, 1239, 1102 $[\alpha]^{22}_D$ = +15.1 (*c* = 3, CH_2Cl_2); MS (ESI) calculated for $C_{12}H_{24}O_2Si$ $[M+H]^+$: 229.2, found 229.2.



(5S,10R,14S,15R,17S,18S,E)-5-allyl-10-(tert-butyldimethylsilyloxy)-3,3-diethyl-7-hydroxy-20,20-diisopropyl-15-(4-methoxybenzyloxy)-10,14,17,18,21-pentamethyl-4,19-dioxa-3,20-disiladocos-11-en-9-one

To a solution of *i*-Pr_2NH (0.10 mL, 0.72 mmol) in THF (2 mL) at 0 °C was added *n*-BuLi (0.45 mL of a 1.6M solution, 0.72 mmol) dropwise. After stirring 30 min, the reaction was cooled to -78 °C and a solution of ketone **3.160** (160 mg, 0.24 mmol) in THF (3 mL) was added dropwise. After stirring 3 h, a solution of aldehyde **3.107** (160 mg, 0.72 mmol) was added dropwise. The reaction was stirred for 3 h at -78 °C, and then quenched with a saturated

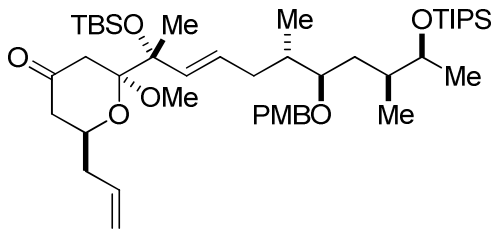
NH_4Cl solution, and warmed to room temperature. The layers were separated, and the aqueous phase was further extracted with EtOAc (3 x 5 mL). The organic extracts were dried (Na_2SO_4), concentrated, and purified via flash column chromatography (3% EtOAc/hexanes) to give 160 mg of the product **3.161** (74%). ^{1}H NMR (600 MHz, $CDCl_3$) (of the mixture) δ 7.28 (d, *J* = 10.2, 2H), 6.90 (d, *J* = 8.4, 2H), 5.4-5.9 (m, 4H), 5.04-5.15 (m, 2H), 4.41 (m, 2H), 4.27 (m, 1H), 4.03 (m, 2H), 3.83-3.93 (m, 5H), 3.35 (m, 2H), 2.89 (m, 1H), 2.72 (m, 1H), 2.21-2.31(m, 4H), 1.74-1.90 (m, 4H), 1.65 (m, 1H), 1.39-1.52 (m, 7H), 0.92-1.08 (m, 40H), 0.61-0.67 (m, 6H), 0.104 (m, 6H) ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 213.40, 159.01, 134.87, 134.78, 134.67, 133.92, 133.33, 131.38, 131.19, 129.32, 129.28, 117.31, 117.06, 113.70, 97.49, 92.64, 82.19, 81.96, 81.90, 79.86, 71.83, 70.79, 70.73, 69.23, 68.72, 68.11, 67.44, 64.16, 55.28, 43.91, 43.61, 43.08, 42.60, 42.44, 38.17, 35.80, 35.20, 35.11, 6.94, 6.91, 6.87, 5.07, 5.00, 4.95, -2.10, -2.25, -2.28; IR (thin film) ν 3519, 2955, 2874, 1720, 1641, 1613, 1513, 1461, 1380, 1301, 1248, 1097, 1040; $[\alpha]^{22}_D$ = +13 (*c* = 12.1, CH_2Cl_2); MS (ESI) calculated for $C_{50}H_{93}O_7Si_3$ $[M+Na]^+$: 913.5, found 913.5.



(2S,6S)-6-allyl-2-((5R,9S,10R,12S,13S,E)-15,15-diisopropyl-10-(4-methoxybenzyloxy)-2,2,3,3,5,9,12,13,16-nonamethyl-4,14-dioxa-3,15-disilaheptadec-6-en-5-yl)-2-methoxytetrahydro-2H-pyran-4-ol

To a solution of **3.161** (60 mg, 0.067 mmol) in a 10:1 mixture of MeOH:THF (3 mL : 0.3 mL) at 0 °C was added PPh_3·HBr (2.3 mg, 0.007 mmol) in 0.2 mL MeOH. The reaction was stirred for 4 h, and then quenched by the addition of a saturated $NaHCO_3$ solution. Et_2O (3

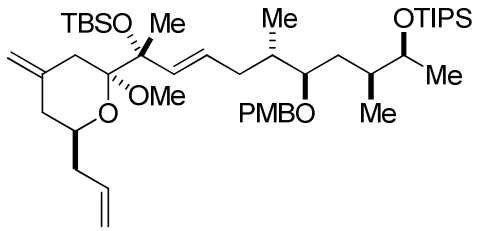
mL) was added, and the layers were separated. The aqueous layer was extracted (3 x 3 mL), dried over $MgSO_4$, and concentrated to reveal a crude oil which was purified via flash chromatography (10% EtOAc/hexanes to 25% EtOAc/hexanes) to afford 35 mg of **3.162** (66%), which was used directly in the next reaction.



(2S,6S)-6-allyl-2-((5R,9S,10R,12S,13S,E)-15,15-diisopropyl-10-(4-methoxybenzyloxy)-2,2,3,3,5,9,12,13,16-nonamethyl-4,14-dioxa-3,15-disilaheptadec-6-en-5-yl)-2-methoxydihydro-2H-pyran-4(3H)-one

To a solution of **3.162** (17 mg, 0.021 mmol) and 4 Å molecular sieves in CH_2Cl_2 (1 mL) was added NMO (3 mg, 0.025 mmol) and TPAP (0.07 mg, 0.002 mmol). The reaction was stirred overnight. The following day, the solvent was evaporated, and the crude product was purified via flash chromatography (10% EtOAc/hexanes) to afford 10 mg of **3.163** (60%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (d, *J* = 7.8, 2H), 6.90 (d, *J* = 8.4, 2H), 5.96 (m, 1H), 5.62 (brs, 2H), 5.19 (m, 1H), 4.48 (d, *J* =12, 1H), 4.43 (d, *J* = 10.2, 1H), 3.88 (m, 1H), 3.87 (m, 1H), 3.84 (s, 3H), 3.93 (s, 4H), 2.45 (m, 4H), 2.21 (m, 2H), 1.80 (m, 2H), 1.77 (m, 1H), 1.61 (m, 1H), 1.3-1.40 (m, 4H), 1.08 (m, 27H), 0.95 (m, 13 H), 0.13 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.20, 159.03, 134.87, 133.63, 131.19, 129.63, 129.31, 118.01, 113.71, 104.74, 82.02, 80.26, 71.85, 70.80, 70.27, 55.29, 52.31, 46.02, 40.28, 38.27, 35.91, 35.24, 31.76, 26.02, 19.48, 18.32, 18.27, 16.08, 15.29, 12.70, -1.82, -1.88; IR (thin film) ν 3414, 2957,

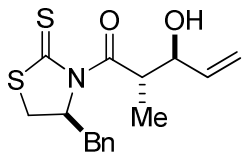
2865, 2359, 1725, 1613, 1513, 1463, 1380, 1301, 1248, 1097, 1039; $[\alpha]^{22}_{D}$ = -8.65 (*c* = 2, CH_2Cl_2); MS (ESI) calculated for $C_{45}H_{80}O_7Si_2$ $[M+Na]^+$: 811.5, found 811.5.



(5R,9S,10R,12S,13S,E)-5-((2S,6S)-6-allyl-2-methoxy-4-methylenetetrahydro-2H-pyran-2-yl)-15,15-diisopropyl-10-(4-methoxybenzyloxy)-2,2,3,3,5,9,12,13,16-nonamethyl-4,14-dioxa-3,15-disilaheptadec-6-ene

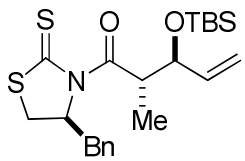
A solution of **3.163** (22 mg, 0.03 mmol) in 0.5 mL of THF was cooled to -20 ℃. A solution of the Tebbe reagent (0.5 M in toluene, 0.11 mL, 0.06 mmol) was added dropwise. After stirring 10 m at -20 ℃, the cooling bath was removed, and the reaction was warmed to room temperature. After TLC indicated consumption of the starting material (approximately 10 min), the reaction was quenched with 15% NaOH (1 mL) at -20 ℃. The reaction was diluted with Et_2O and filtered through a pad of celite. The organic extracts were dried ($MgSO_4$) and concentrated to afford a crude yellow product. The crude product was purified with flash chromatography (5% EtOAc/hexanes) to afford 17 mg of **3.164** (78%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (d, *J* =10.2, 2H), 6.90 (d, *J* = 7.6, 2H), 5.97 (m, 1H), 5.72 (d, *J* = 15.6, 1H), 5.65 (m, 1H), 5.14 (d, *J* = 17.4, 1H), 5.08 (d, *J* = 10.2), 4.80 (s, 1H), 4.75 (s, 1H), 4.49 (d, *J* = 11.4, 1H), 4.43 (d, *J* = 11.4, 1H), 3.87 (m, 1H), 3.83 (s, 3H), 3.64 (m, 1H), 3.41 (s, 3H), 3.37 (m, 1H), 2.37-2.44 (m, 2H), 2.19-2.29 (m, 3H), 1.88-1.96 (m, 3H), 1.76 (m, 1H), 1.66 (m, 1H), 1.28-1.38 (m, 4H), 0.92-1.1 (m, 40H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.00, 142.94, 135.78, 134.91, 131.26, 129.32, 128.54, 116.89, 113.69, 109.88, 102.32, 81.99, 80.72, 71.84, 71.48, 70.70, 55.28, 52.24, 40.55, 39.16,

38.35, 35.92, 35.35, 31.71, 26.08, 25.96, 22.31, 19.54, 18.48, 18.32, 18.27, 16.06, 15.16, 12.70, -1.80, -1.85; IR (thin film) ν 3403, 2957, 1613, 1513, 1463, 1380, 1248, 1097; $[\alpha]^{22}_{D}$ = -9.5 (*c* = 5, CH_2Cl_2); MS (ESI) calculated for $C_{46}H_{82}O_6Si_2$ $[M+Na]^+$: 809.6, found 809.6.



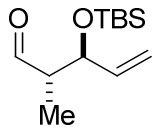
(2S,3S)-1-((S)-4-benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy-2-methylpent-4-en-1-one

Secondary alcohol **3.55** (1.30 g, 3.27 mmol) was dissolved in 327 mL CH_2Cl_2 and transferred to a sealed tube (1000 mL). Hoveyda-Grubbs 2nd generation catalyst (205 mg, 0.32 mmol) was then added, and a septum was attached. Ethylene gas was bubbled through the reaction for approximately 7 min, and the septum was replaced with a cap for the sealed tube. After 3h, the reaction was quenched utilizing the Galan cleanup procedure. The solvent was removed under reduced pressure to reveal a brown oil which was purified by flash column chromatography (20% EtOAc/hexanes to 30% EtOAc/hexanes) to afford 879 mg of the product **3.91** (84%), a yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (m, 5H), 5.92 (m, 1H), 5.37 (d, 17.4), 5.29 (m, 2H), 4.47 (m, 1H), 4.34 (dd, *J* = 6, 6, 1H), 3.44 (dd, *J* = 7.2, 11.4, 1H), 3.10 (dd, *J* = 12, 12, 1H), 2.94 (dd, *J* = 0, 11.4, 1H), 2.45 (d, *J* = 6.6, 1H), 1.32 (d, *J* = 6.6, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.61, 177.77, 138.47, 129.48, 128.94, 127.27, 116.97, 76.36, 68.89, 44.47, 36.68, 32.72, 14.69; IR (thin film) ν 3425, 1695, 1454, 1342, 1262, 1192, 1167, 1135, 1027; $[\alpha]^{22}_{D}$ = +361 (*c* = 3.5, CH_2Cl_2); MS (ESI) calculated for $C_{16}H_{19}NO_2S_2$ $[M+Na]^+$: 344.1, found 344.1.



(2S,3S)-1-((S)-4-benzyl-2-thioxothiazolidin-3-yl)-3-(tert-butyldimethylsilyloxy)-2-methylpent-4-en-1-one

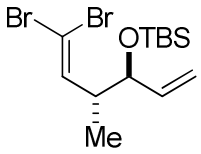
A solution of secondary alcohol **3.91** (1.05 g, 3.27 mmol) in 33 mL CH_2Cl_2 was cooled to 0 ℃. 2,6-lutidine (0.8 mL, 6.55 mmol) was added foll owed by TBSOTf (1.12 mL, 4.91 mmol). The reaction was warmed to room temperature and then quenched by the addition of a saturated $NaHCO_3$ solution. The layers were separated and the aqueous layer was then extracted into CH_2Cl_2 (2 x 15 mL). The organic extracts were dried (Na_2SO_4) and evaporated to give a crude yellow oil which was purified by flash chromatography (pure hexanes to 5% EtOAc/hexanes) to afford 1.15 g of the product (81%), a yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 (m, 5H), 5.74 (m, 1H), 5.25 (m, 3H), 4.37 (dd, *J* = 0, 5.4, 2H), 3.37 (m, 2H), 3.10 (dd, *J* = 12, 12, 1H), 2.92 (dd, *J* = 0, 11.4, 1H), 1.15 (d, *J* = 4.8, 1H), 0.86 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.17, 177.27, 139.11, 136.74, 129.49, 128.93, 127.17, 117.65, 78.49, 69.11, 45.62, 36.55, 32.33, 25.77, 17.97, 14.26, -3.90, -4.93; IR (thin film) ν 3027, 2954, 2884, 2856, 2360, 2341, 1697, 1603, 1495, 1455, 1361, 1341, 1293, 1260, 1192, 1167, 1133, 1057, 1027; $[\alpha]^{22}_D$ = +207 (*c* = 21.2, CH_2Cl_2); MS (ESI) calculated for $C_{22}H_{33}NO_2S_2Si$ $[M+H]^+$: 436.3, found 436.3.



(2S,3S)-3-(tert-butyldimethylsilyloxy)-2-methylpent-4-enal

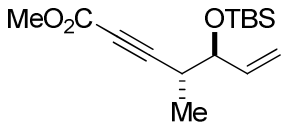
A solution of the TBS ether (770 mg, 1.61 mmol) in 16 mL CH_2Cl_2 was cooled to -78 ℃. *i*-Bu_2AlH (1M solution, 3.22 mL, 3.22 mmol) was added dropwise until the solution was colorless. The reaction was then quenched by the addition of a saturated Na/K tartrate solution, and warmed to room temperature. The layers were then separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The organic extracts were dried

(Na_2SO_4) and evaporated to give a crude oil which was purified by flash chromatography (5% EtOAc/hexanes) to afford 354 mg of aldehyde **3.92** (88%), a colorless oil, which was used directly in the next reaction. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (s, 1H), 5.88 (m, 1H), 5.27 (m, 2H), 4.32 (dd, *J* = 6.3, 6.3, 1H), 2.53 (m, 1H), 1.08 (d, *J* = 10, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).



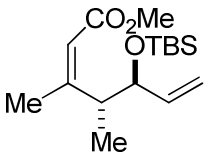
tert-butyl((3S,4R)-6,6-dibromo-4-methylhexa-1,5-dien-3-yloxy)dimethylsilane

A solution of aldehyde **3.92** (312mg, 1.37 mmol) in 14 mL THF was cooled to -78 ℃. PPh_3 (762 mg, 2.90 mmol) was added, followed by CBr_4 (481 mg, 1.45 mmol) in THF (2 mL). The reaction was warmed to -50 ℃ and stirred for 8 h. After TLC analysis indicated completion of the reaction, pentanes (20 mL) was added. The solvent was reduced until a precipitate was formed, and was filtered through a plug of silica. The crude oil was purified via flash column chromatography (pure hexanes) to reveal 355 mg of the product (68%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.32 (d, *J* = 9.5, 1H), 5.79 (ddd, *J* = 6, 10, 17, 1H), 5.21 (d, *J* =17.5, 1H), 5.15 (d, *J* =10, 1H), 4.03 (dd, *J* = 5.5, 1H), 2.61 (m, 1H), 1.02 (d, *J* =7, 3H), 0.93 (s, 9H), 0.08 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.71, 139.16, 115.67, 88.37, 76.10, 45.00, 25.82, 18.15, 15.05, -4.29, -4.90; IR (thin film) ν 2929, 2857, 1471, 1254, 1093, 1027; $[\alpha]^{22}_D$ = -18.5 (*c* = 1.75, CH_2Cl_2).



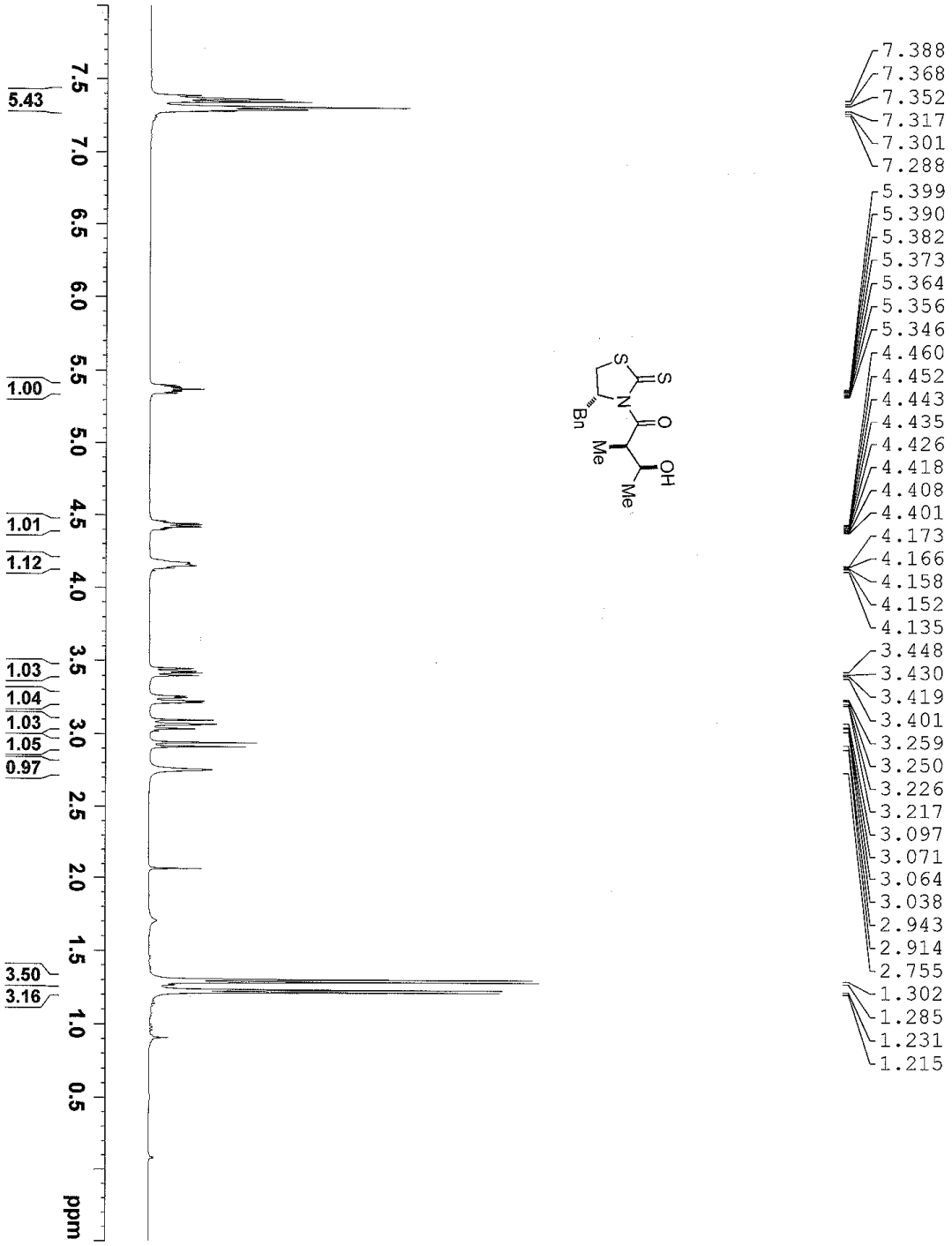
(4R,5S)-methyl 5-(tert-butyldimethylsilyloxy)-4-methylhept-6-en-2-ynoate

A solution of the dibromide (355 mg, 0.93 mmol) in 10 mL THF was cooled to -78 ℃. *n*-BuLi (1.3M solution, 2.86 mL, 3.72 mmol) was added dropwise and stirred for 30 min. Methyl orthoformate (0.4 mL, 5.12 mmol) was added dropwise. The reaction was warmed to room temperature. After TLC analysis indicated completion of the reaction, the reaction was quenched by the addition of a saturated aqueous NH_4Cl solution. The layers were separated and the aqueous layer was then extracted into EtOAc (2 x 15 mL). The organic extracts were dried (Na_2SO_4) and evaporated to give a crude oil which was purified by flash chromatography (pure hexanes to 3% EtOAc/hexanes) to afford 145 mg of the product **3.93** (55%), a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (ddd, *J* =6, 10, 16.5, 1H), 5.30 (d, *J* = 17, 1H), 5.22 (d, *J* =10.5, 1H), 4.20 (dd, *J* =5.5, 5.5, 1H), 3.78 (s, 3H), 2.73 (dq, *J* =6.5, 6.5, 6.5, 6.5, 1H), 1.18 (d, *J* = 7.5, 3H), 0.92 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.24, 137.64, 116.64, 91.10, 75.27, 74.16, 52.54, 33.40, 25.74, 18.16, 14.52, -4.52, -5.03; IR (thin film) ν 2955, 2857, 2237, 1719, 1472, 1434, 1361, 1255, 1137, 1089, 1033; $[\alpha]^{22}_D$ = -6.08 (*c* = 2.25, CH_2Cl_2); MS (ESI) calculated for $C_{15}H_{26}O_3Si$ $[M+Na]^+$: 305.1, found 305.1.



(4R,5S,*Z*)-methyl 5-(tert-butyldimethylsilyloxy)-3,4-dimethylhepta-2,6-dienoate

To a suspension of CuI (152 mg, 0.80 mmol) in THF (1.6 mL) at 0 ℃, was added MeLi (1.6 M solution in diethyl ether, 0.99 mL, 1.59 mmol). The reaction was stirred for 15 min at 0 ℃ and then cooled to -78 ℃. Ynoate **3.93** (45 mg, 0.16 mmol) was added in 1.6 mL of THF. The reaction was transferred to a -50 ℃ bath, and st irred for 4 hThe reaction was then quenched by the addition of a saturated aqueous NH_4Cl solution. The layers were separated and the aqueous layer was then extracted into EtOAc (3 x 4 mL). The organic extracts were dried (Na_2SO_4) and evaporated to give a crude oil which was purified by flash chromatography (5% EtOAc/hexanes) to afford 35 mg of the product **3.89** (75%), a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (m, 2H), 5.19 (m, 2H), 4.10 (m, 2H), 3.69 (s, 3H), 1.87 (d, *J* = 1.2, 3H), 1.03 (d, *J* =6.8, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.72, 162.16, 140.27, 117.30, 115.31, 50.72, 40.10, 25.77, 21.20, 18.10, 15.06, -3.90, -5.08; IR (thin film) ν 3397, 2956, 2857, 1722, 1641, 1434, 1378, 1254, 1224, 1157, 1078; $[\alpha]^{22}_D$ = -41.3 (*c* = 2.9, CH_2Cl_2); MS (ESI) calculated for $C_{16}H_{30}O_3Si$ $[M+Na]^+$: 321.2, found 321.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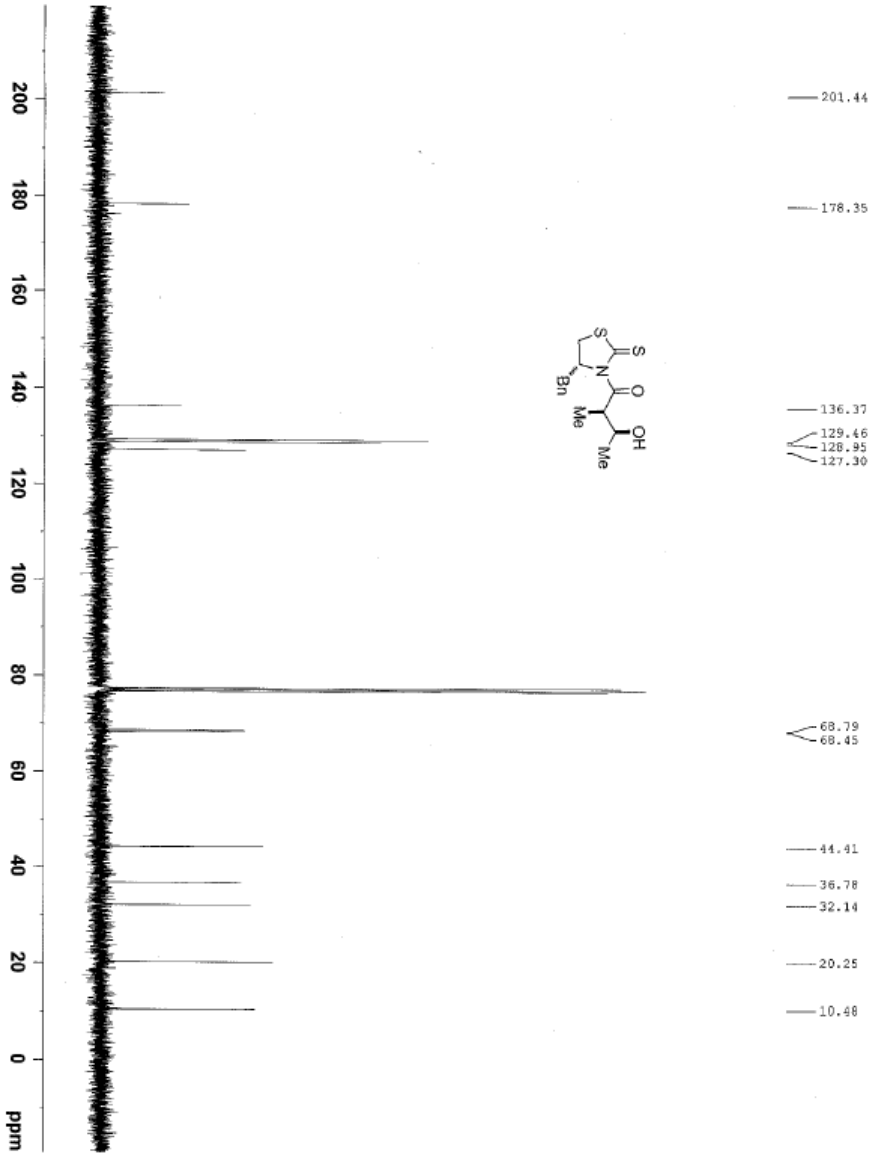
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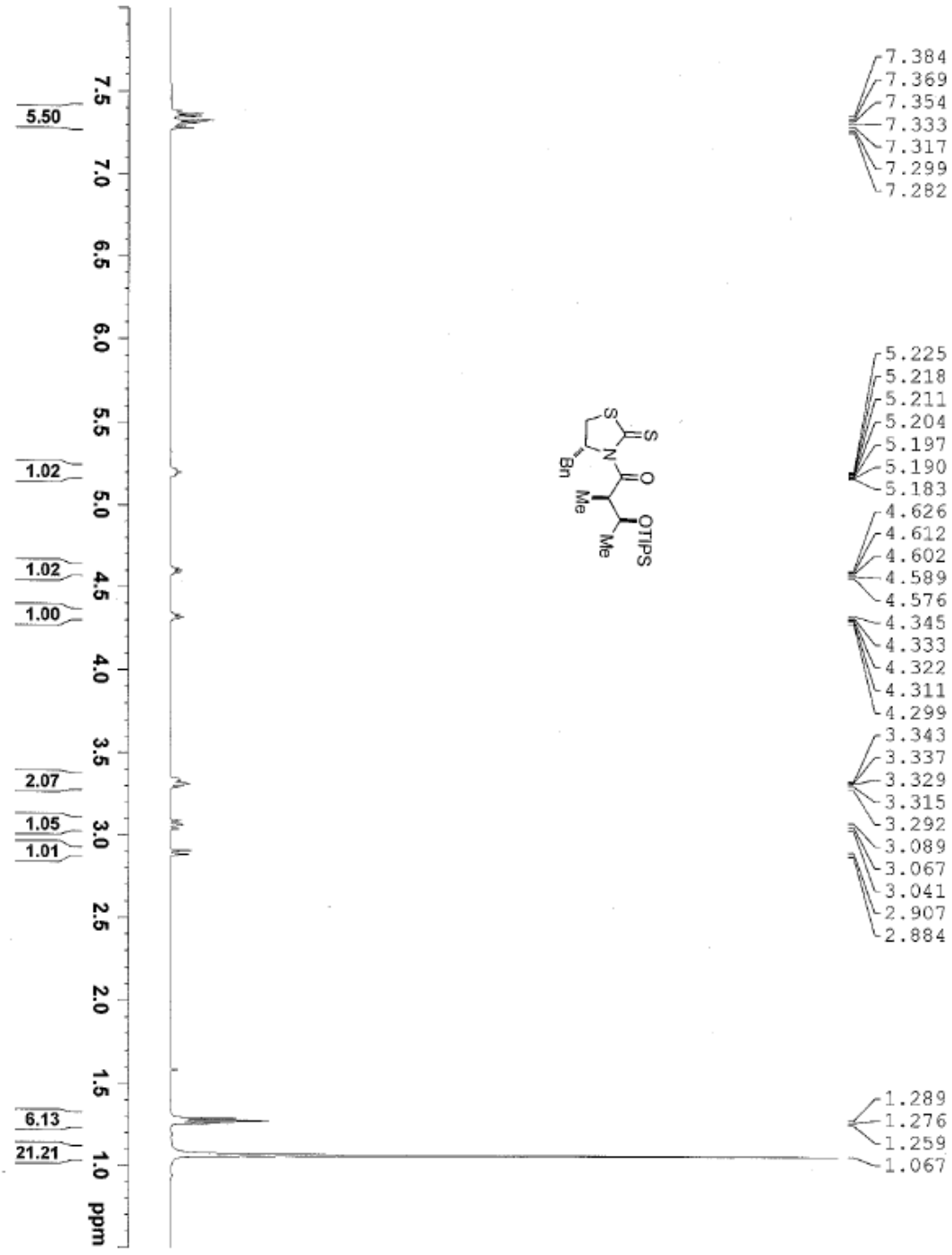
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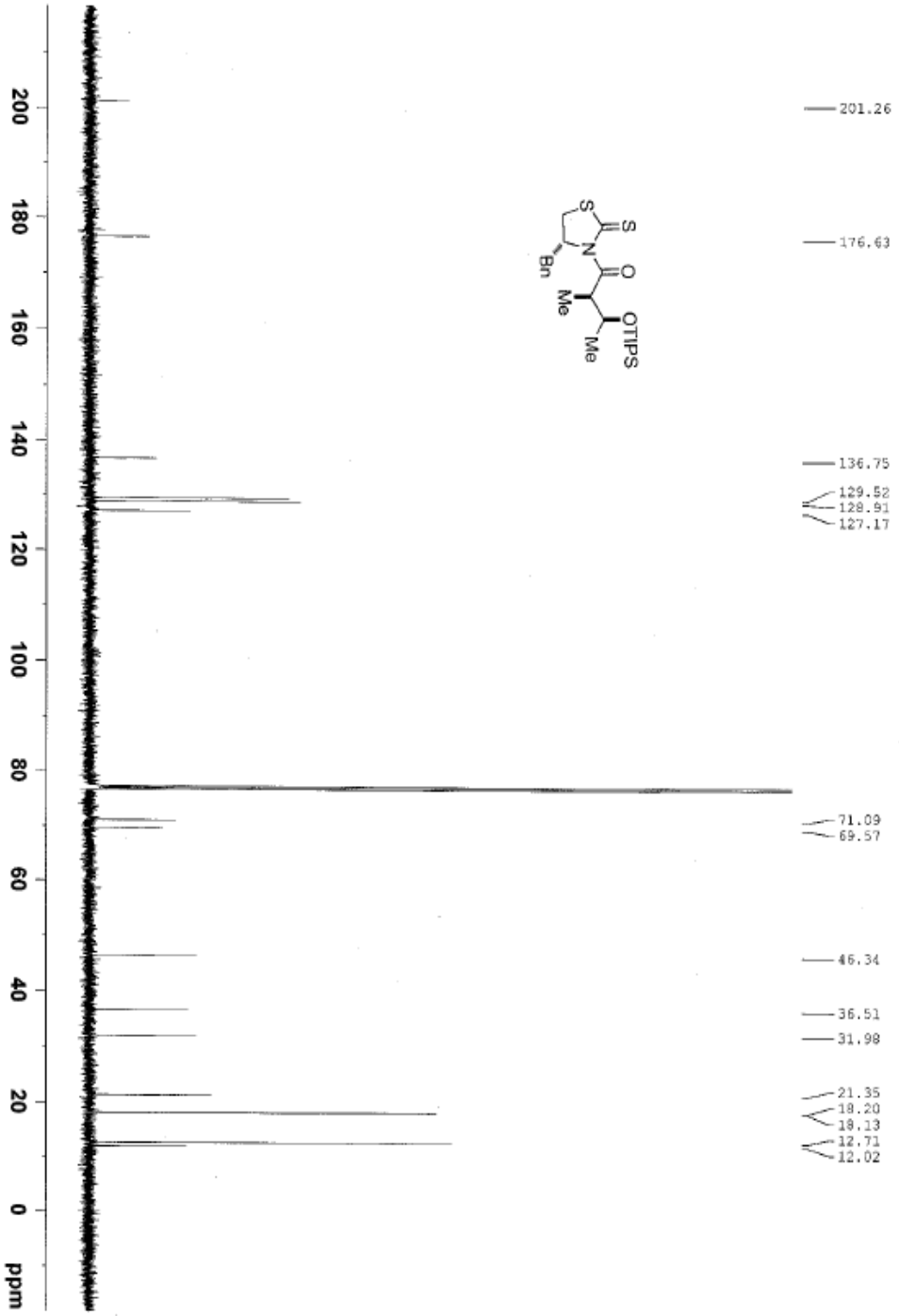
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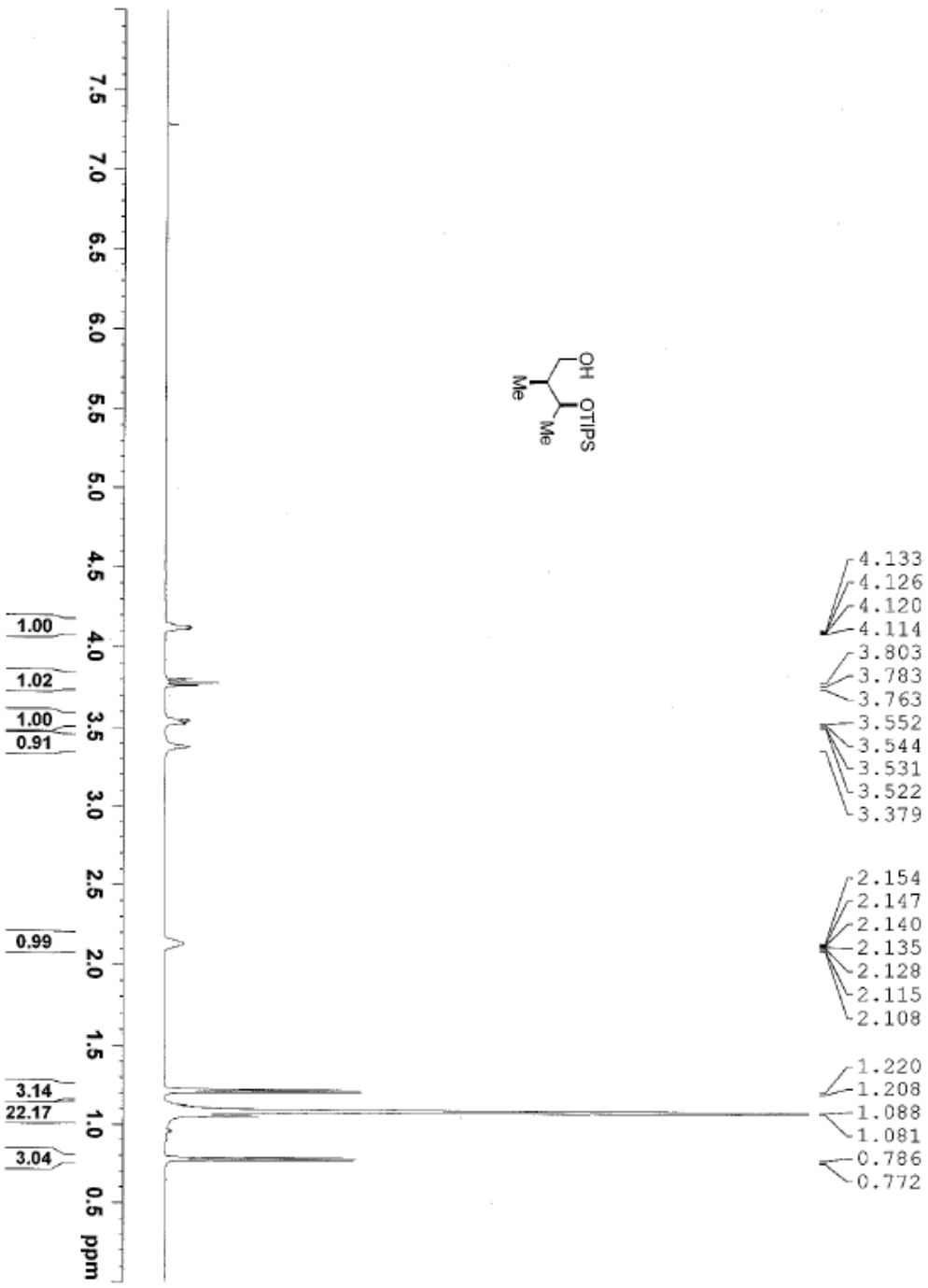
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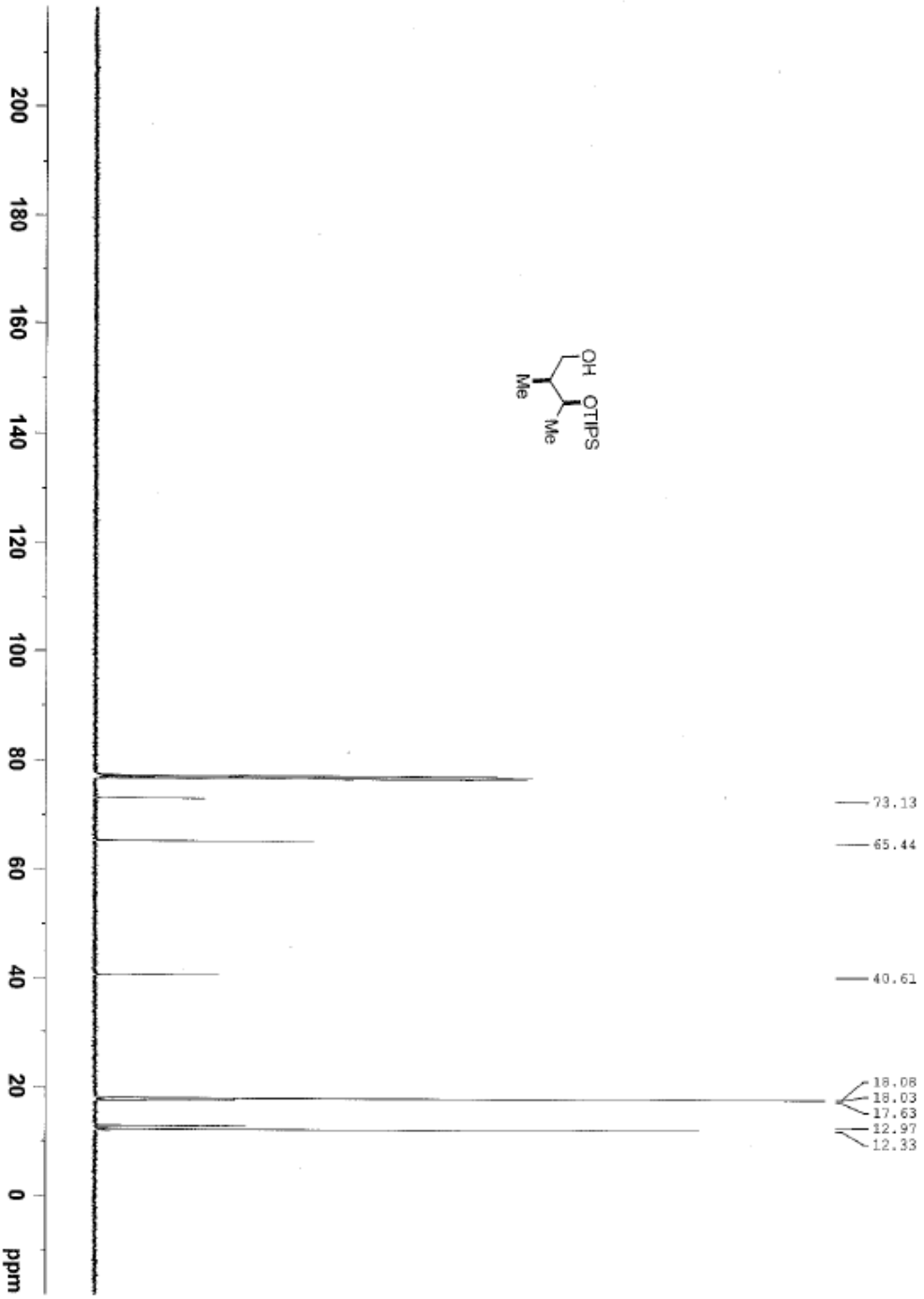
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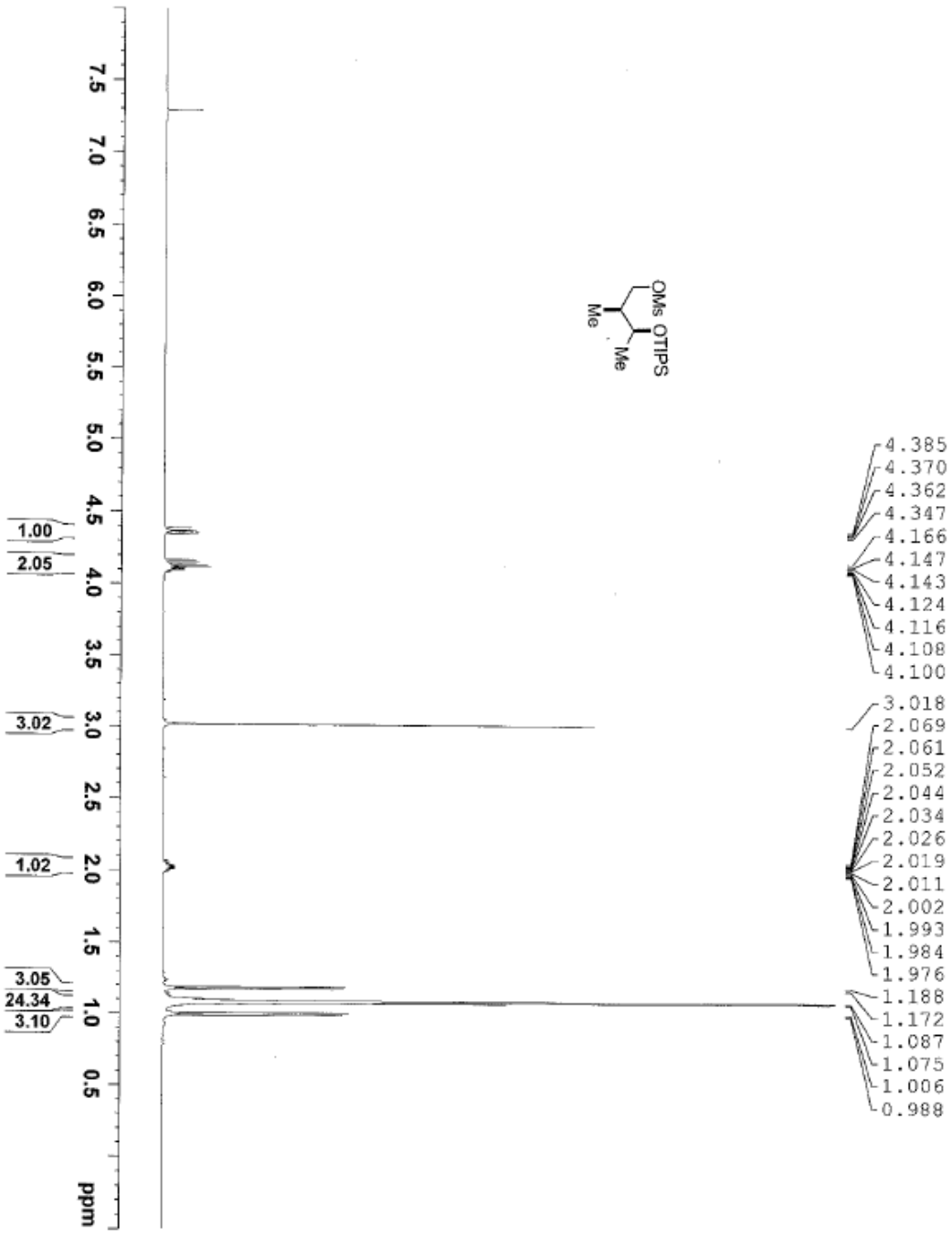
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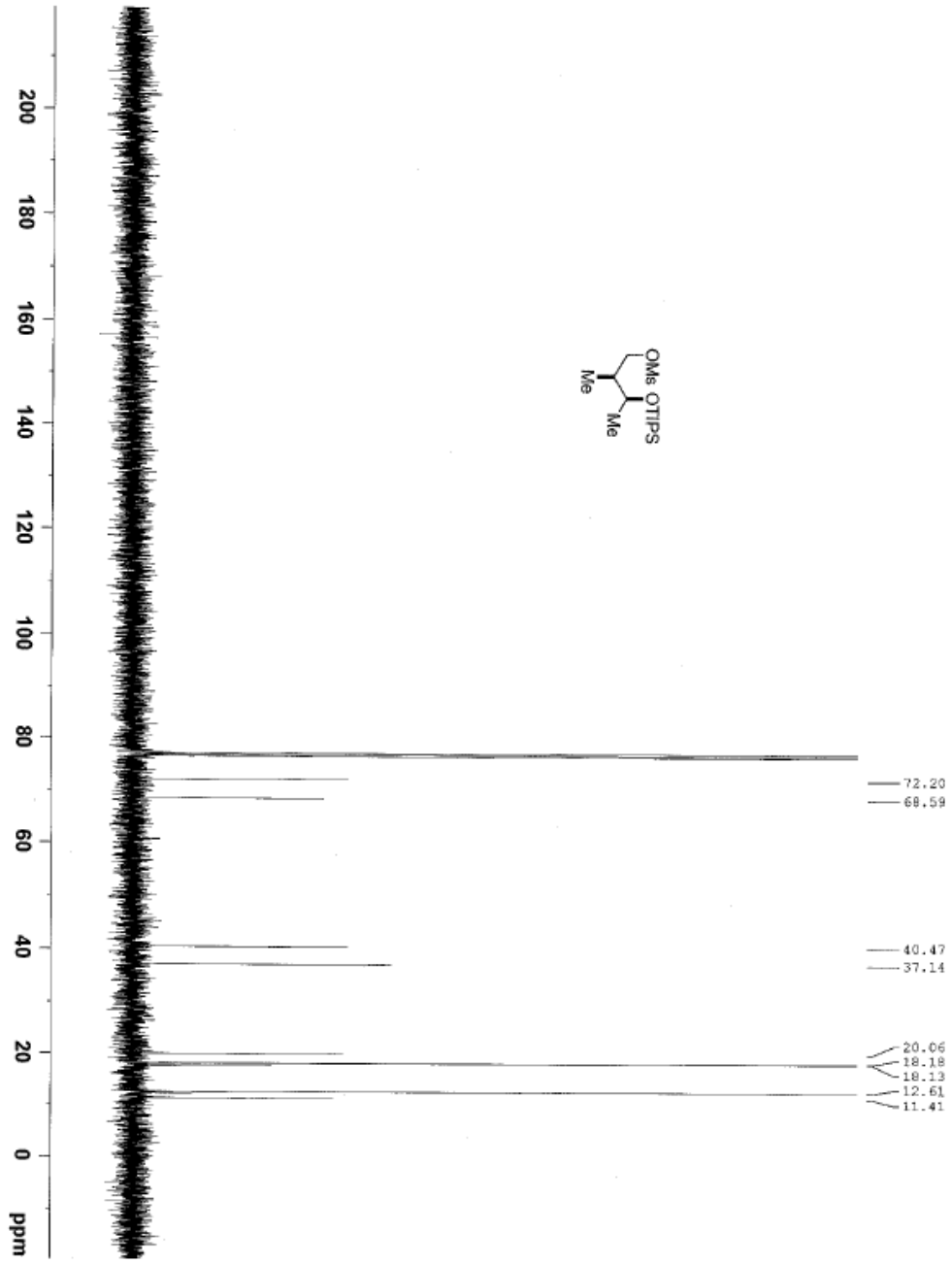
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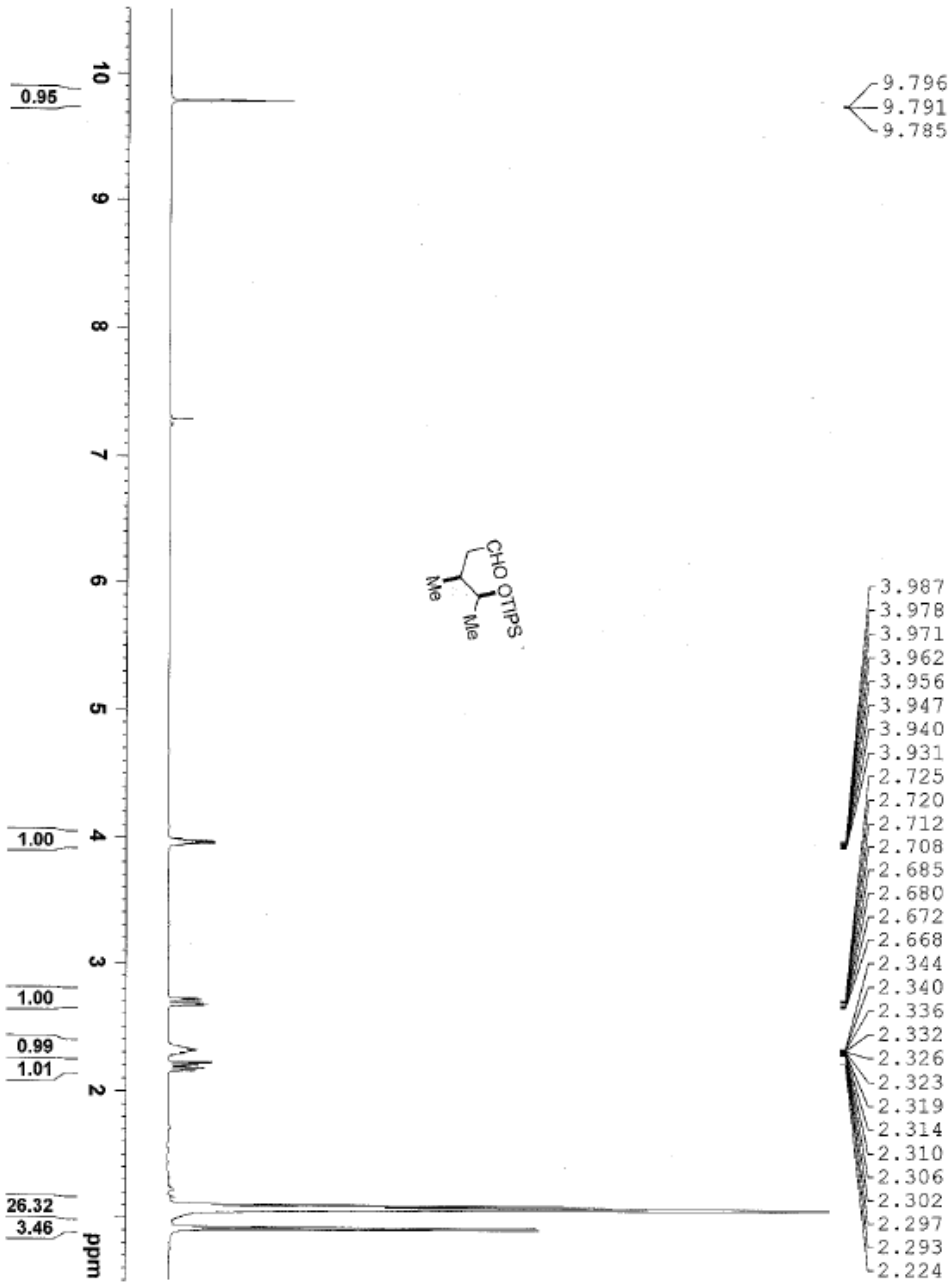
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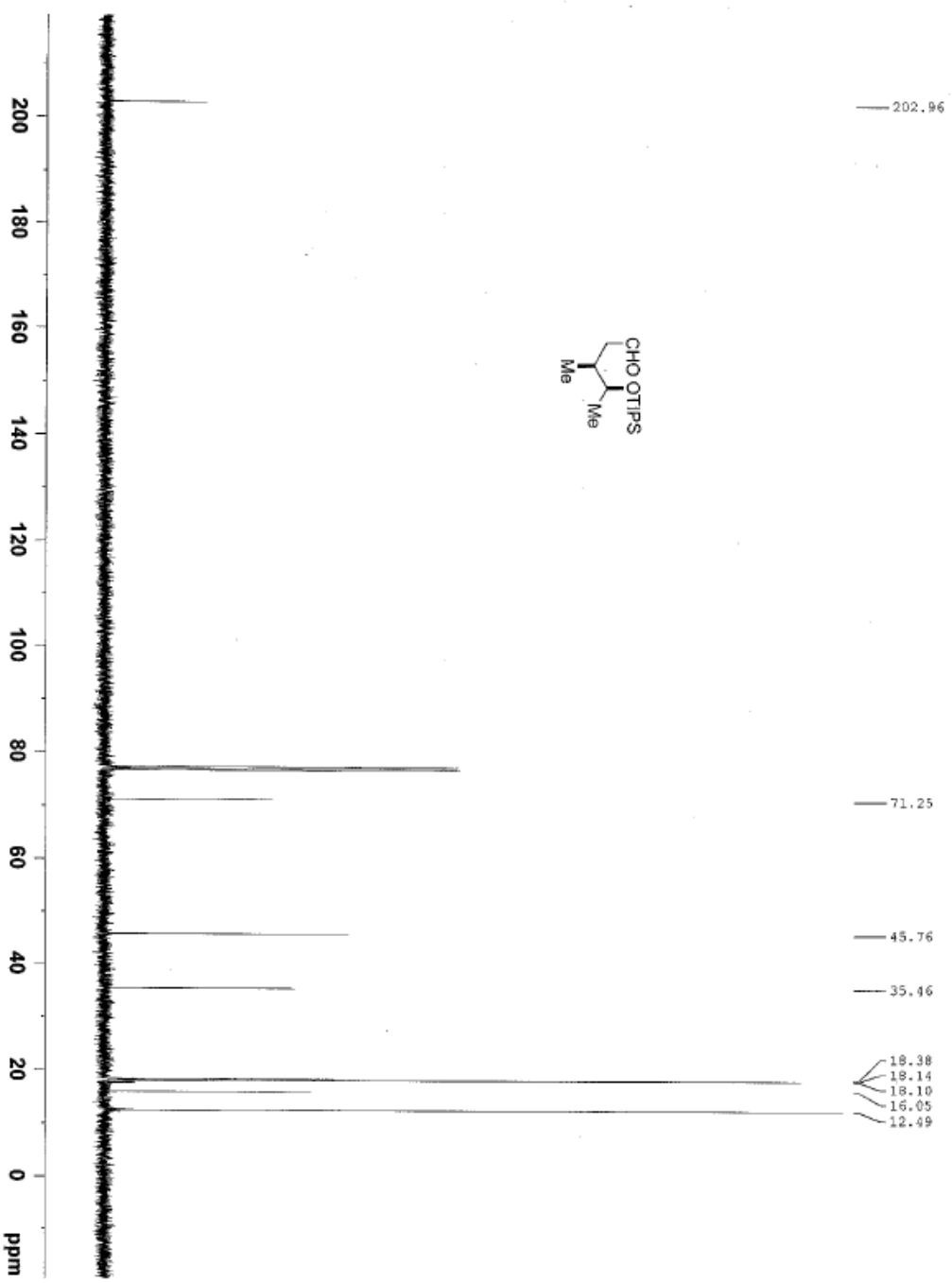
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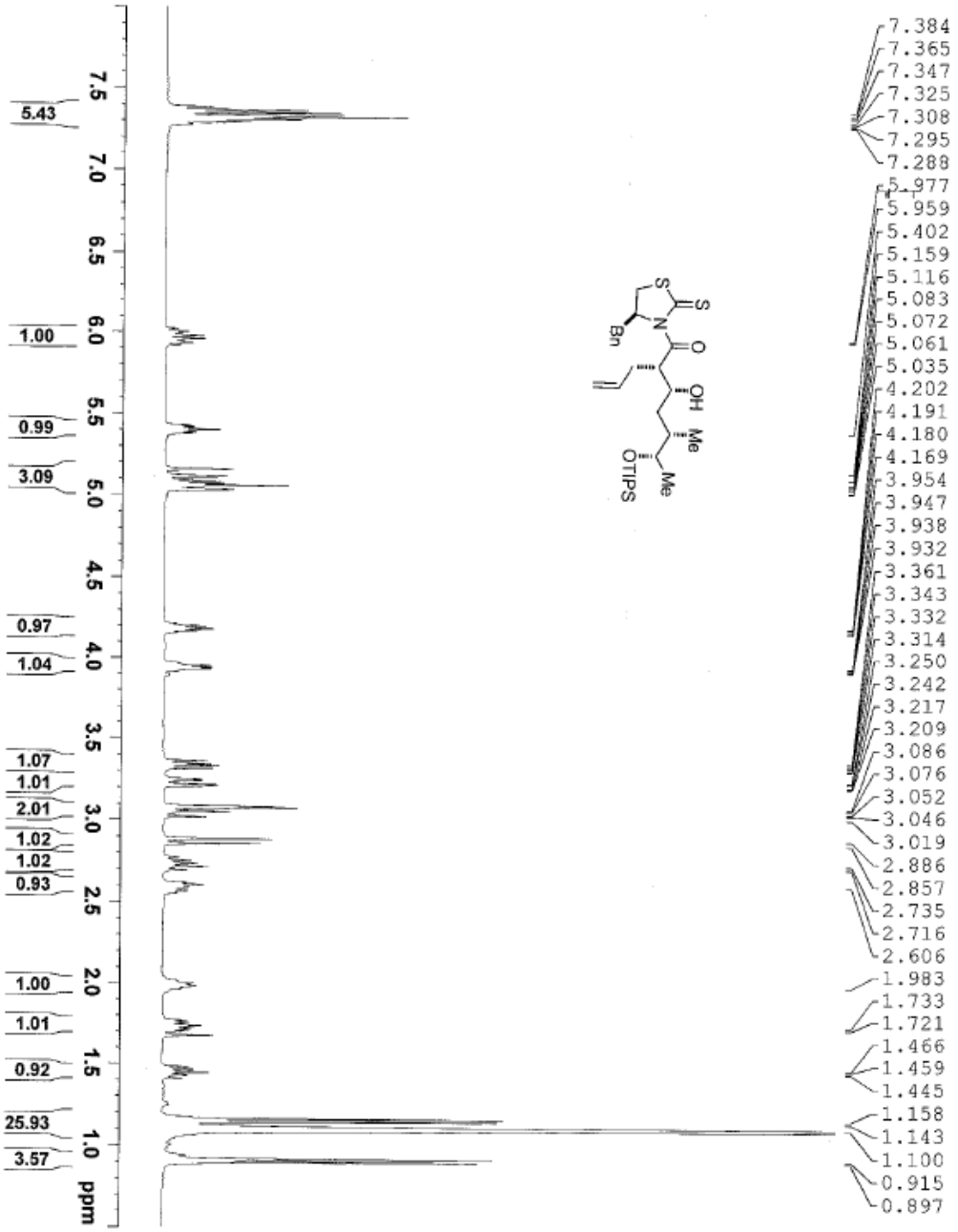
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3.954
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3.932
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3.242
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3.052
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3.019
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0.97
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1.07
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2.01
1.02
1.02
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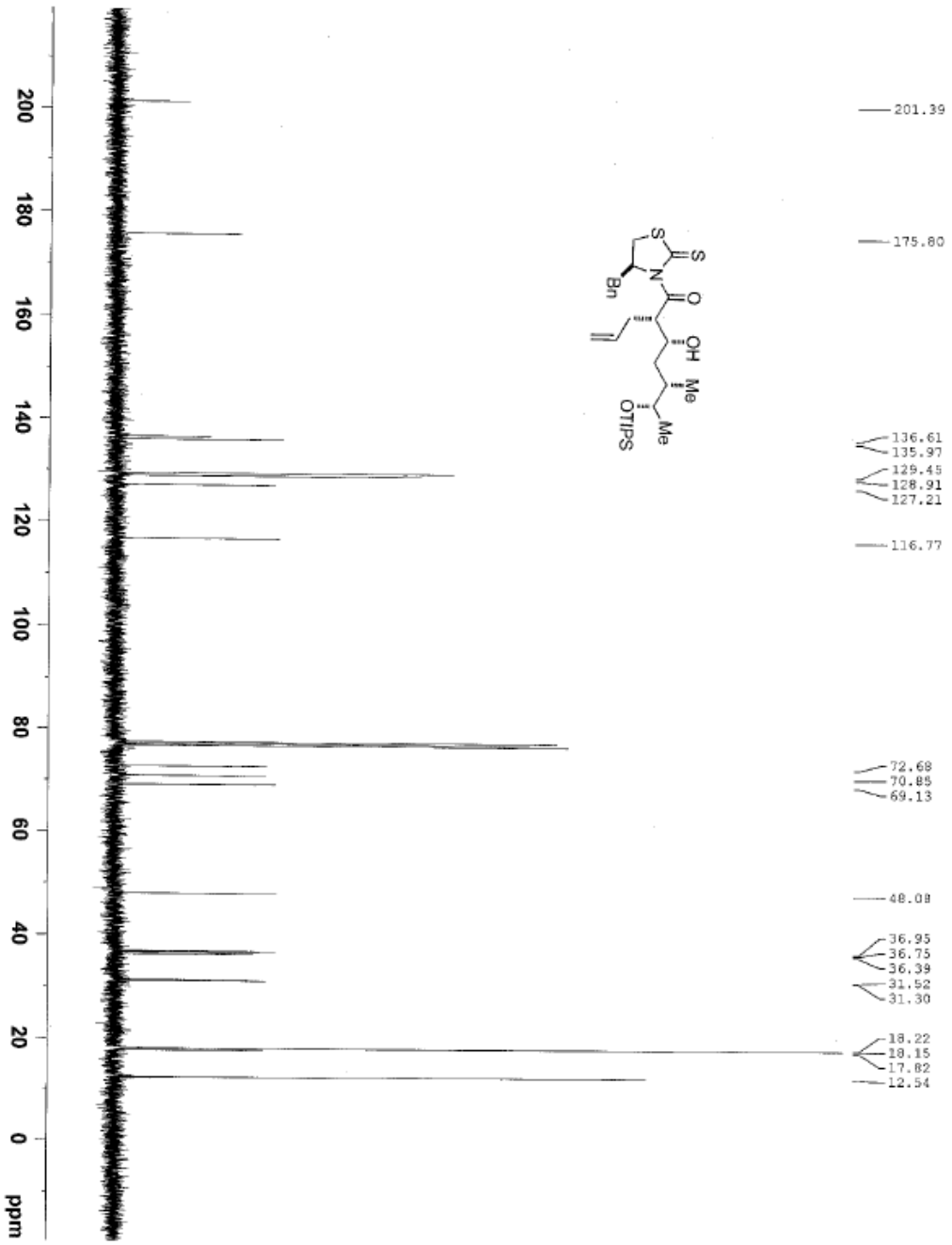
OH
Me
Me
OTIPS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31.52
31.30
18.22
18.15
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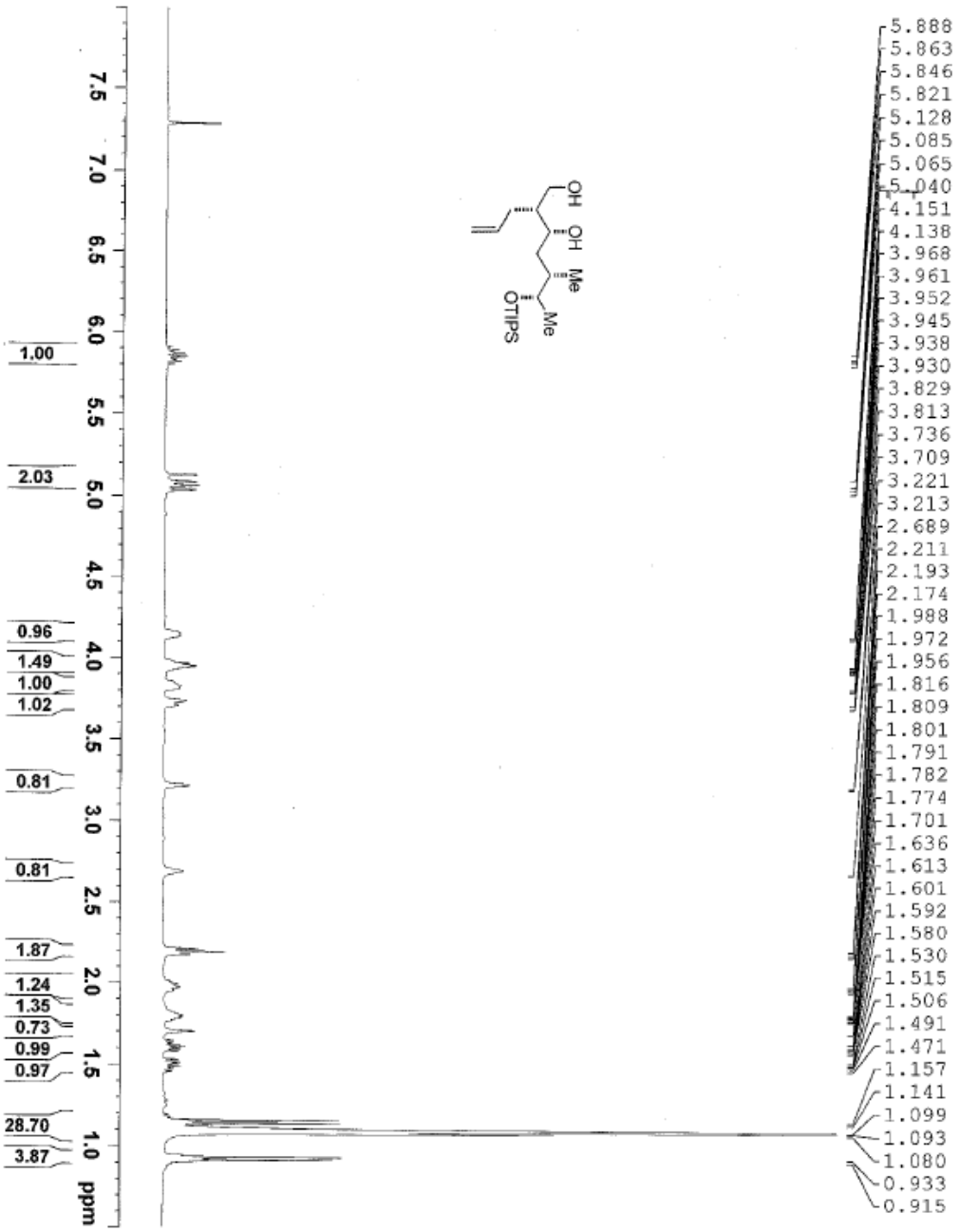
Me
OTIPS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Me
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3.952
3.945
3.938
3.930
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3.709
3.221
3.213
2.689
2.211
2.193
2.174
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1.972
1.956
1.816
1.809
1.801
1.791
1.782
1.774
1.701
1.636
1.613
1.601
1.592
1.580
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1.515
1.506
1.491
1.471
1.157
1.141
1.099
1.093
1.080
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0.915
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1.02
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0.81
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1.24
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0.97
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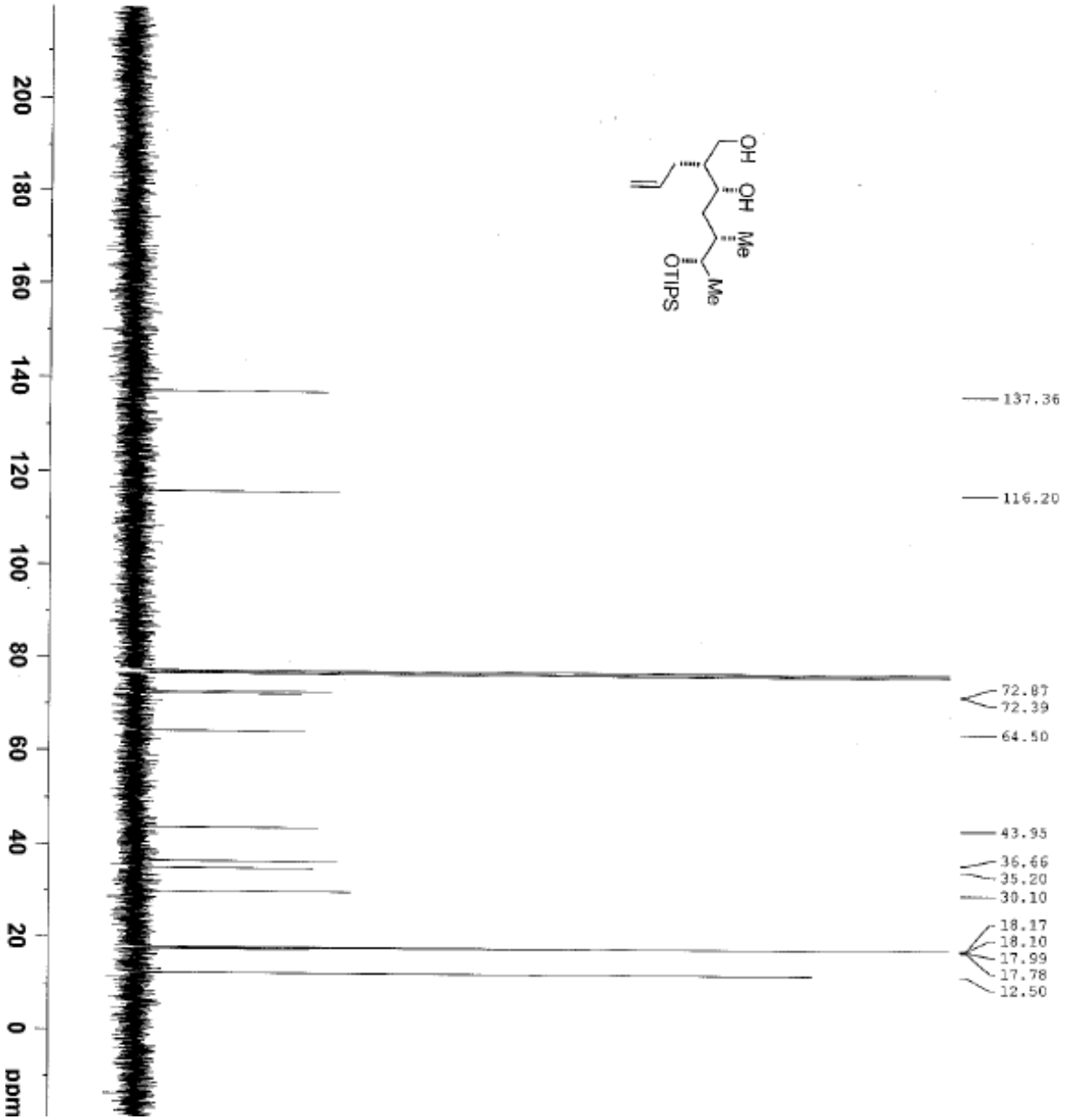
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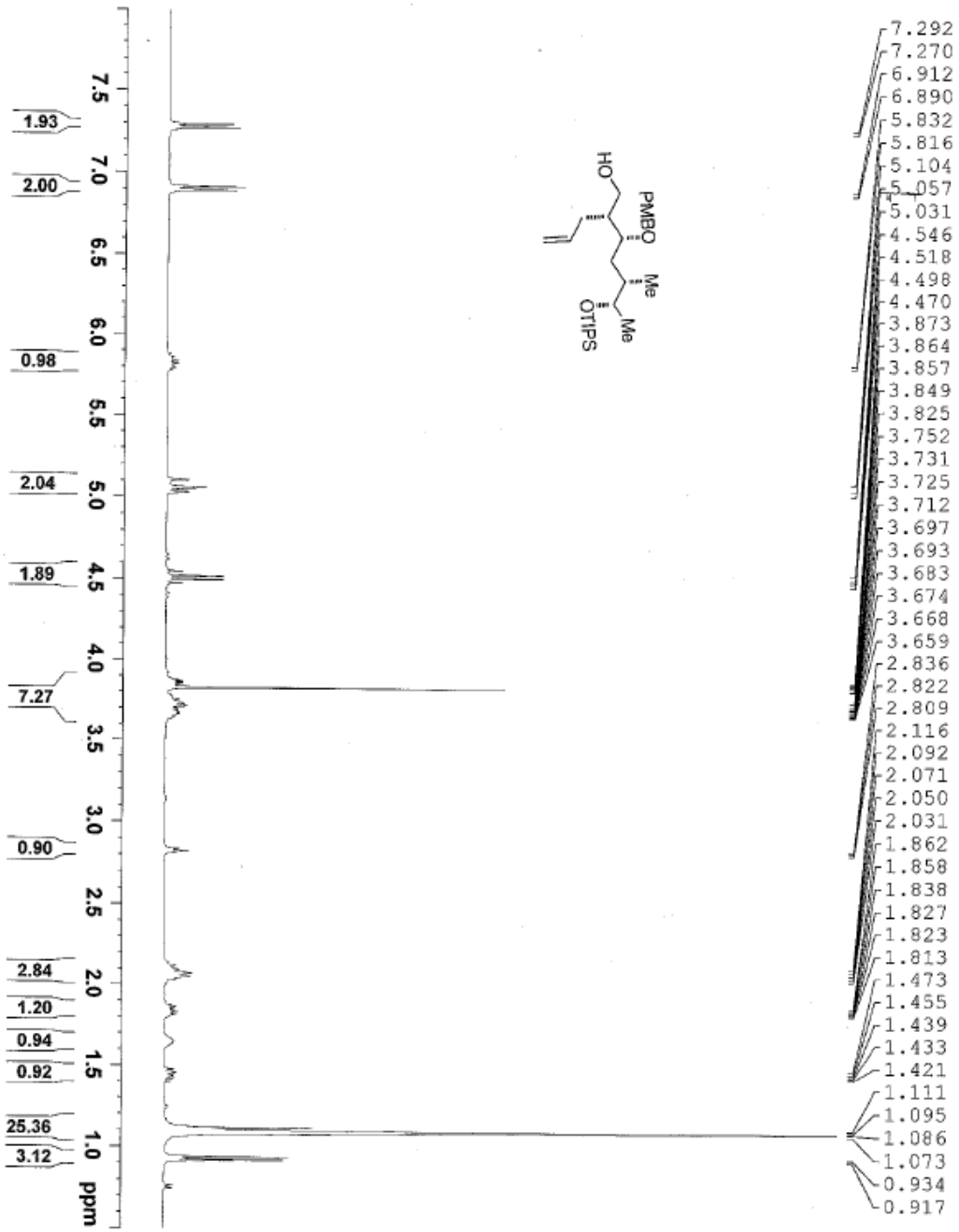
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2.822
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2.116
2.092
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2.050
2.031
1.862
1.858
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1.827
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1.439
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1.086
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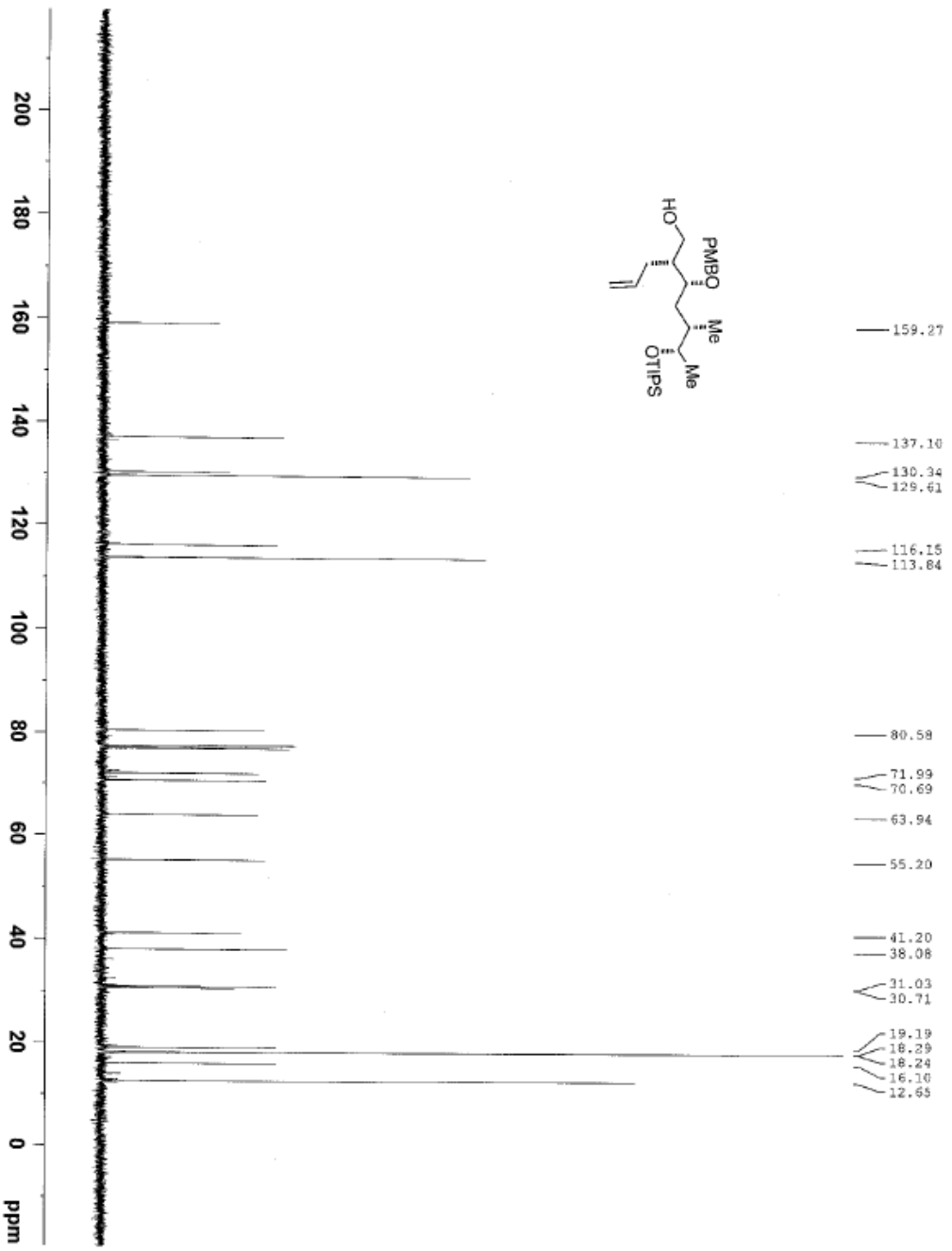
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70.69
63.94
55.20
41.20
38.08
31.03
30.71
19.19
18.29
18.24
16.10
12.65
200
180
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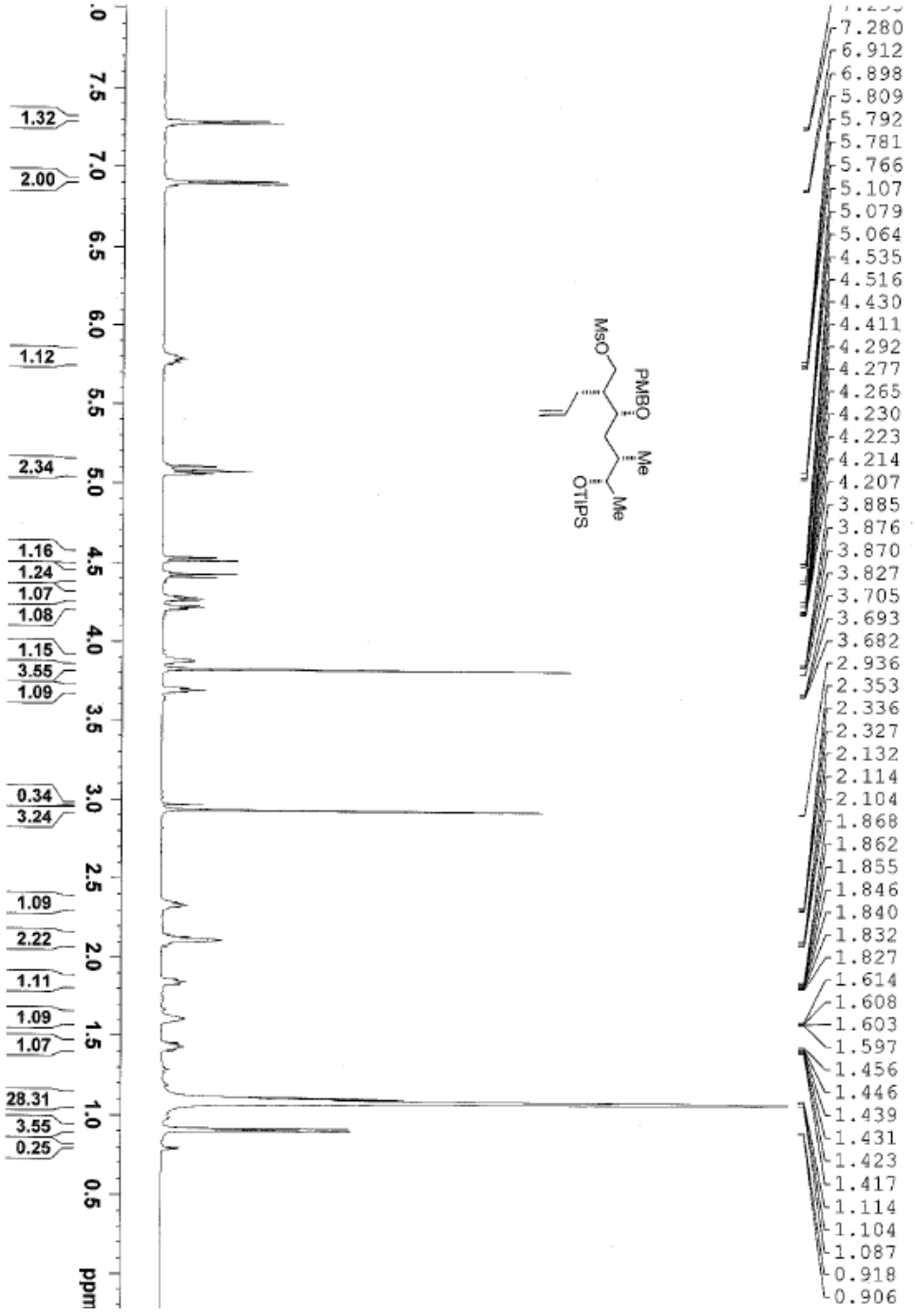
140
120
100
80
60
40
20
0
ppm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Me
Me
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1.07
1.08
1.15
3.55
1.09
0.34
3.24
1.09
2.22
1.11
1.09
1.07
28.31
3.55
0.25
7.280
6.912
6.898
5.809
5.792
5.781
5.766
5.107
5.079
5.064
4.535
4.516
4.430
4.411
4.292
4.277
4.265
4.230
4.223
4.214
4.207
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3.870
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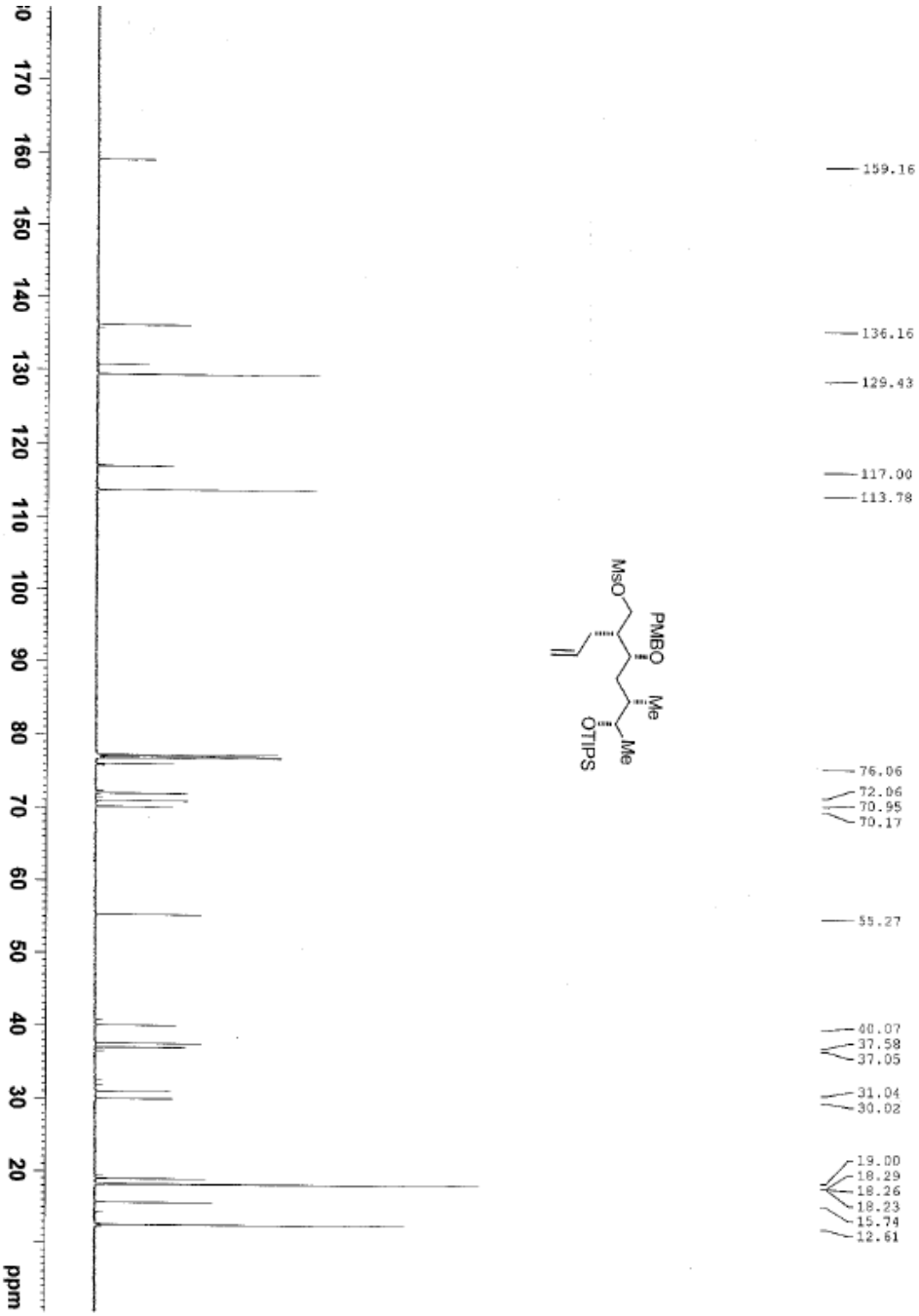
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Me
Me
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70.17
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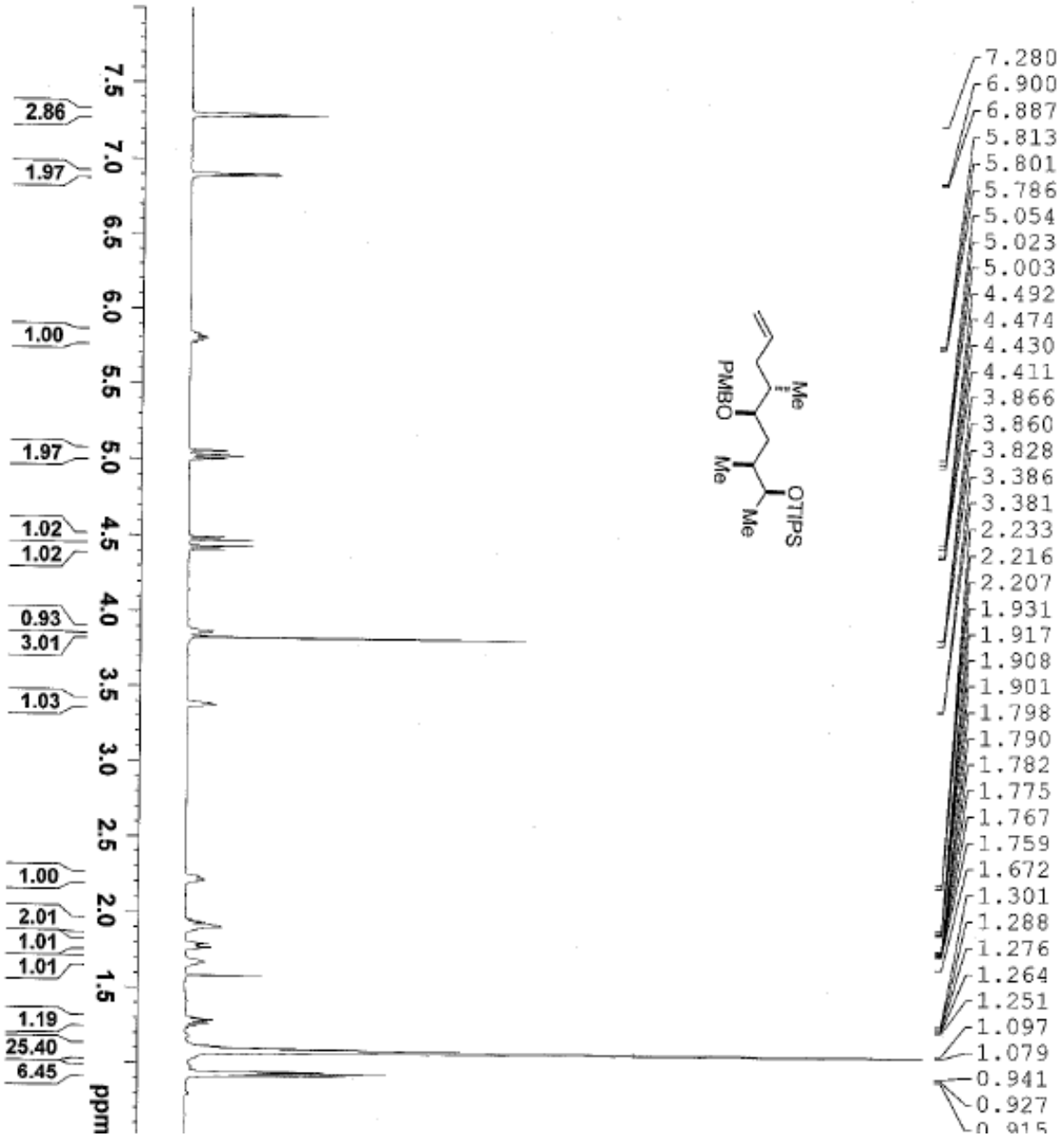
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2.207
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1.917
1.908
1.901
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1.790
1.782
1.775
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1.264
1.251
1.097
1.079
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0.927
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Me
Me
Me
OTIPS
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1.02
0.93
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1.03
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2.01
1.01
1.01
1.19
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1.5
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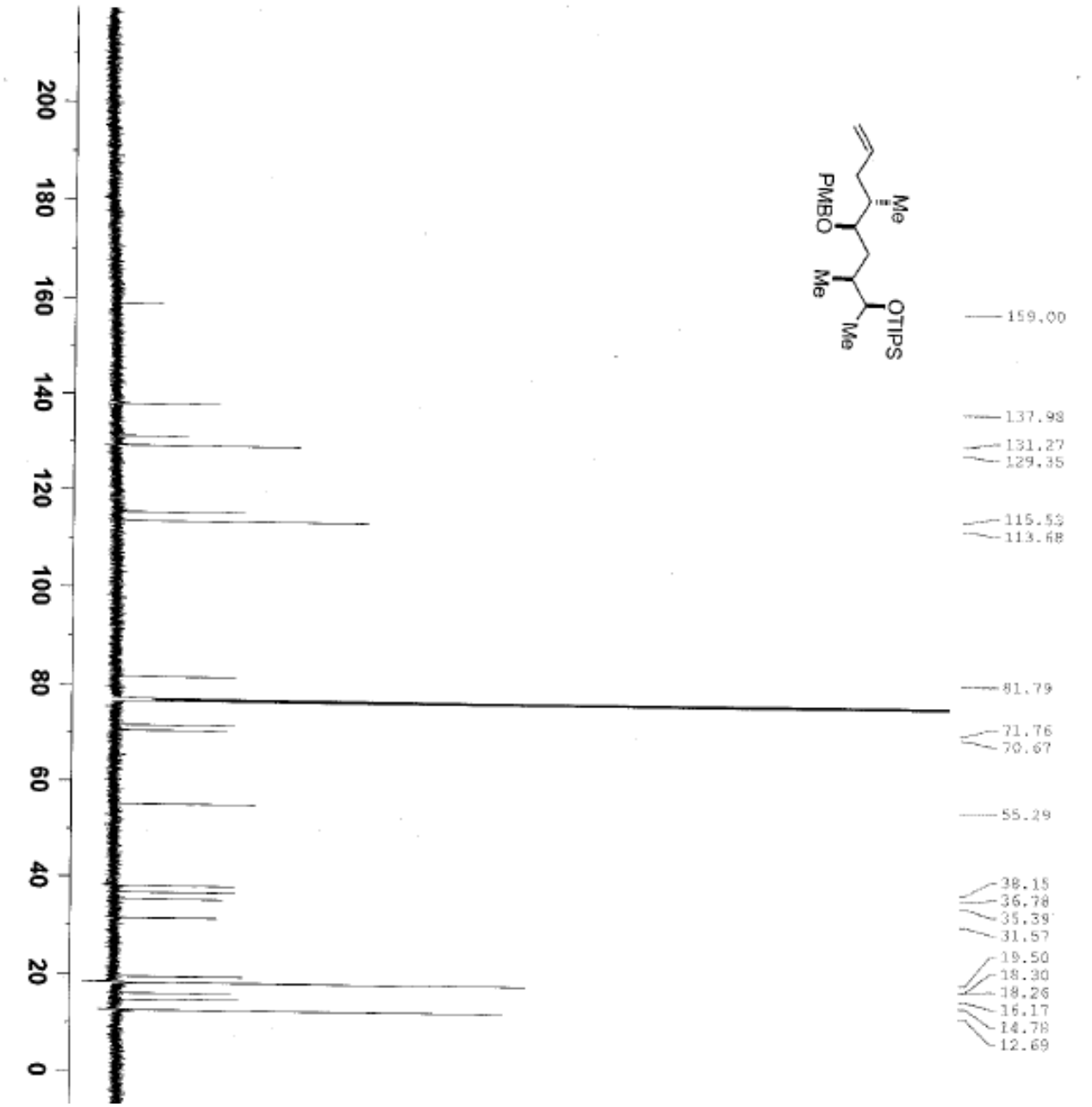
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Me
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55.29
38.15
36.78
35.39
31.57
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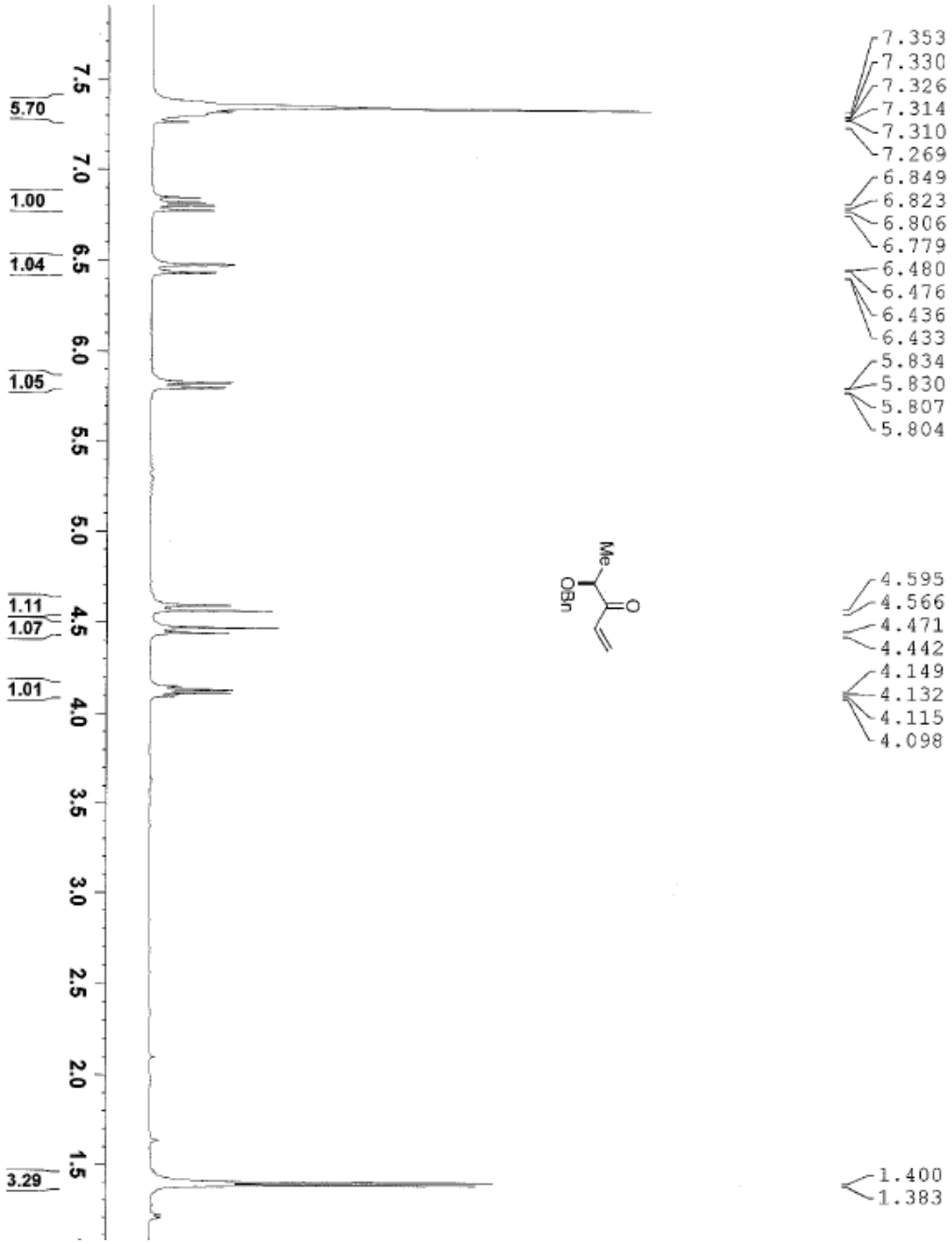
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6.433
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5.804
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4.115
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1.07
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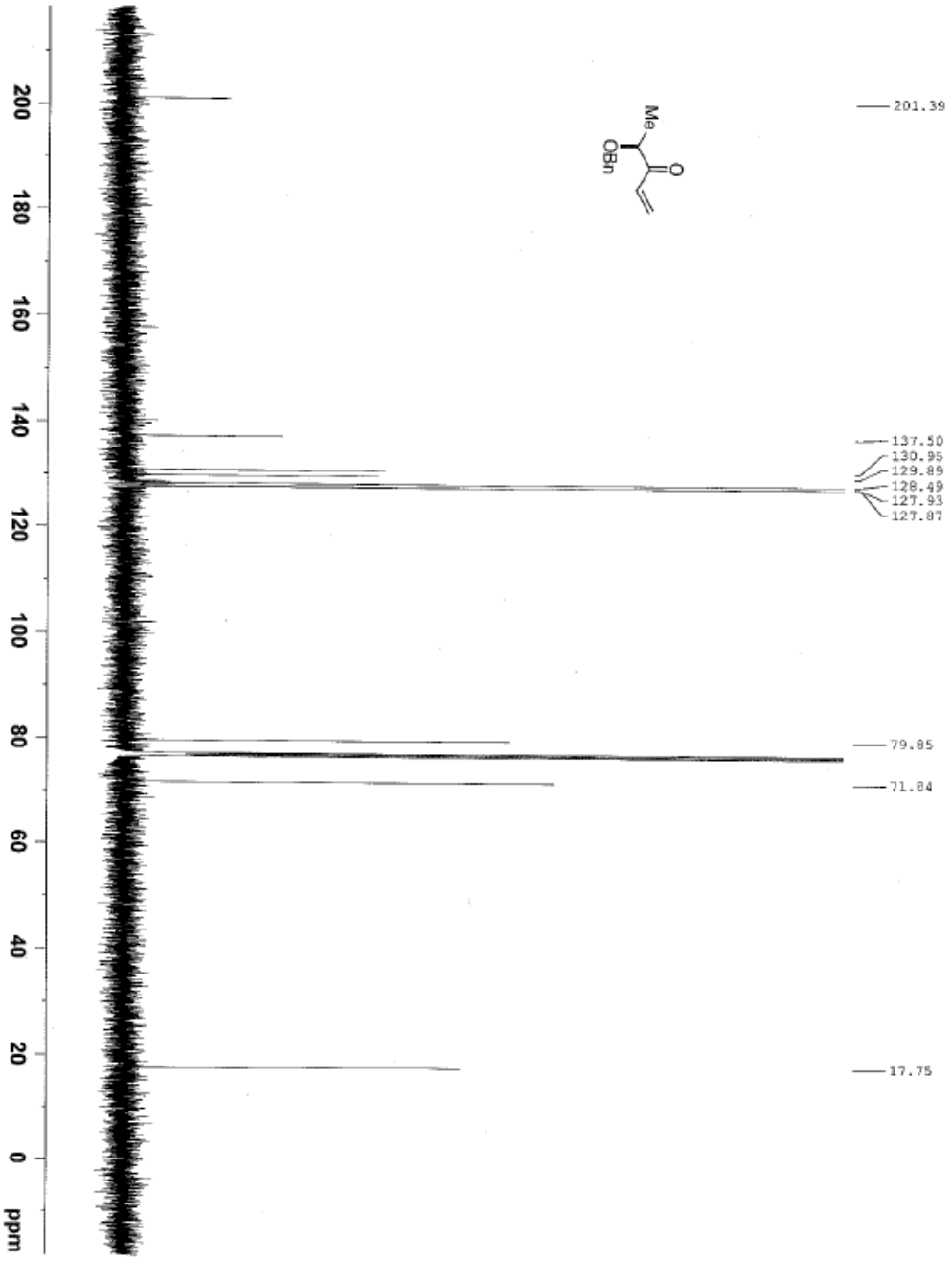
Me
OBn
O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120
100
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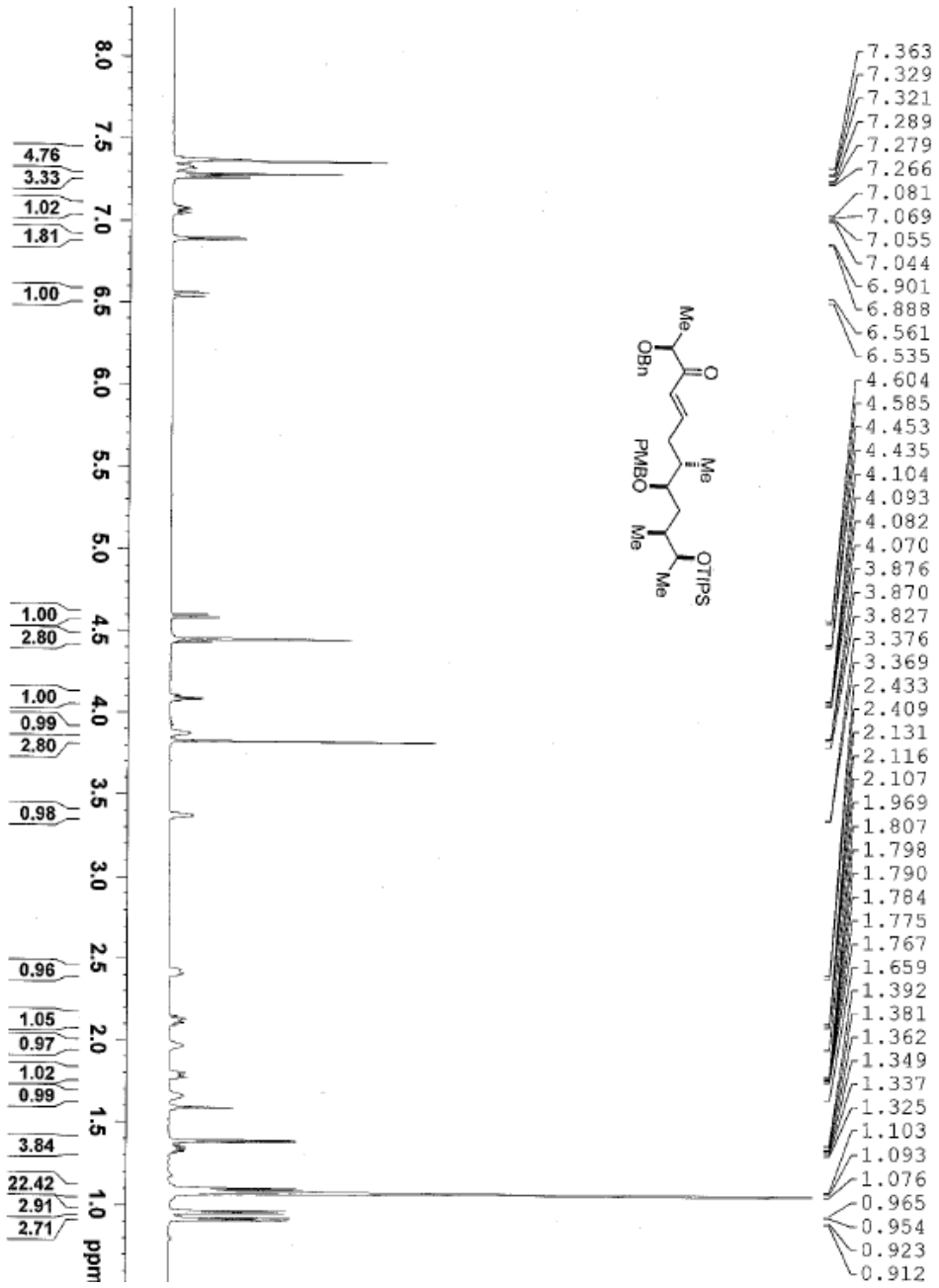
40
20
0
ppm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1.325
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O
Me
PMBO
Me
Me
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0.98
0.96
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1.02
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1.0
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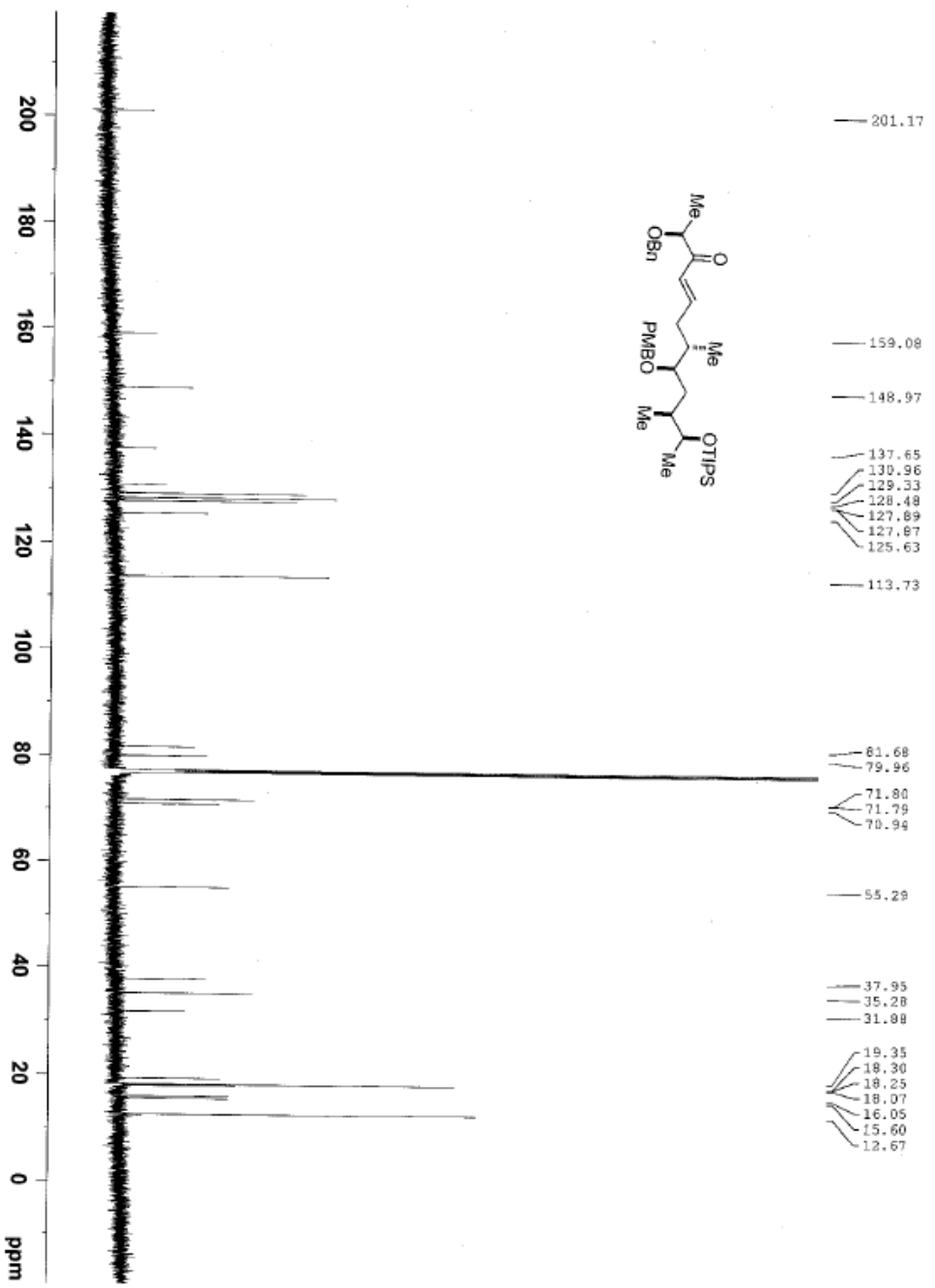
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Me
OBn
O
Me
PMBO
Me
Me
OTIPS
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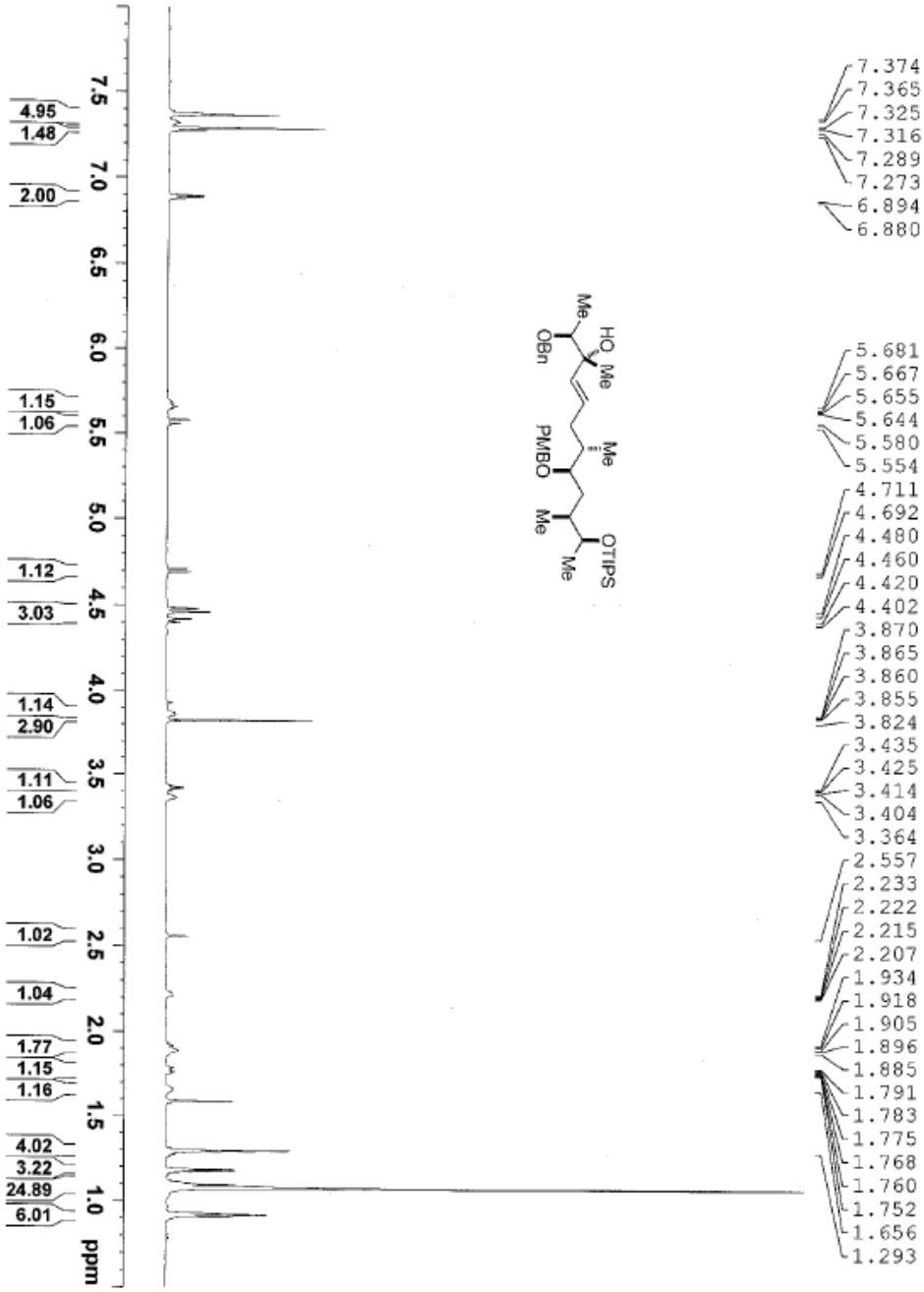
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1.02
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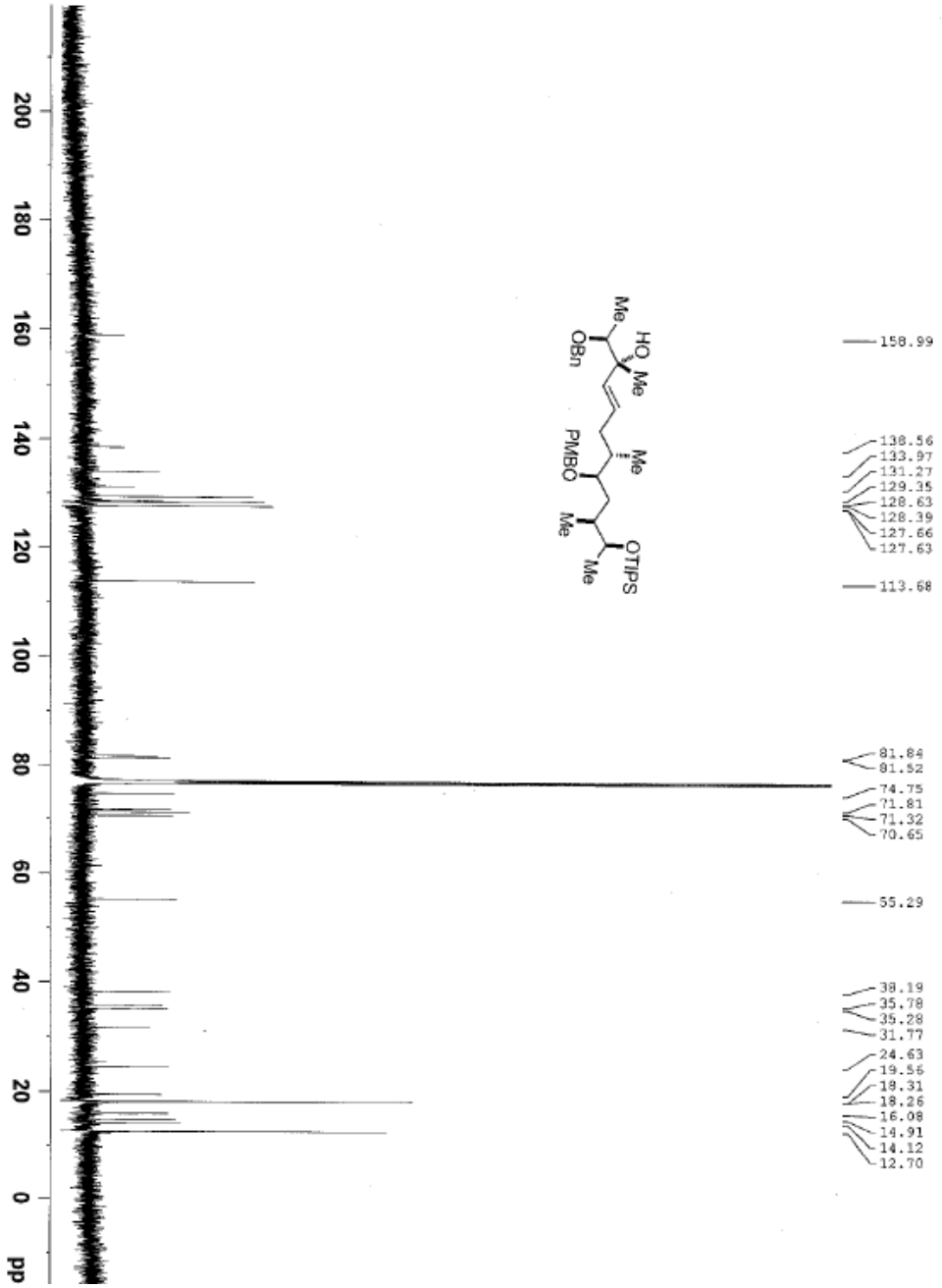
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55.29
38.19
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24.63
19.56
18.31
18.26
16.08
14.91
14.12
12.70
HO
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120
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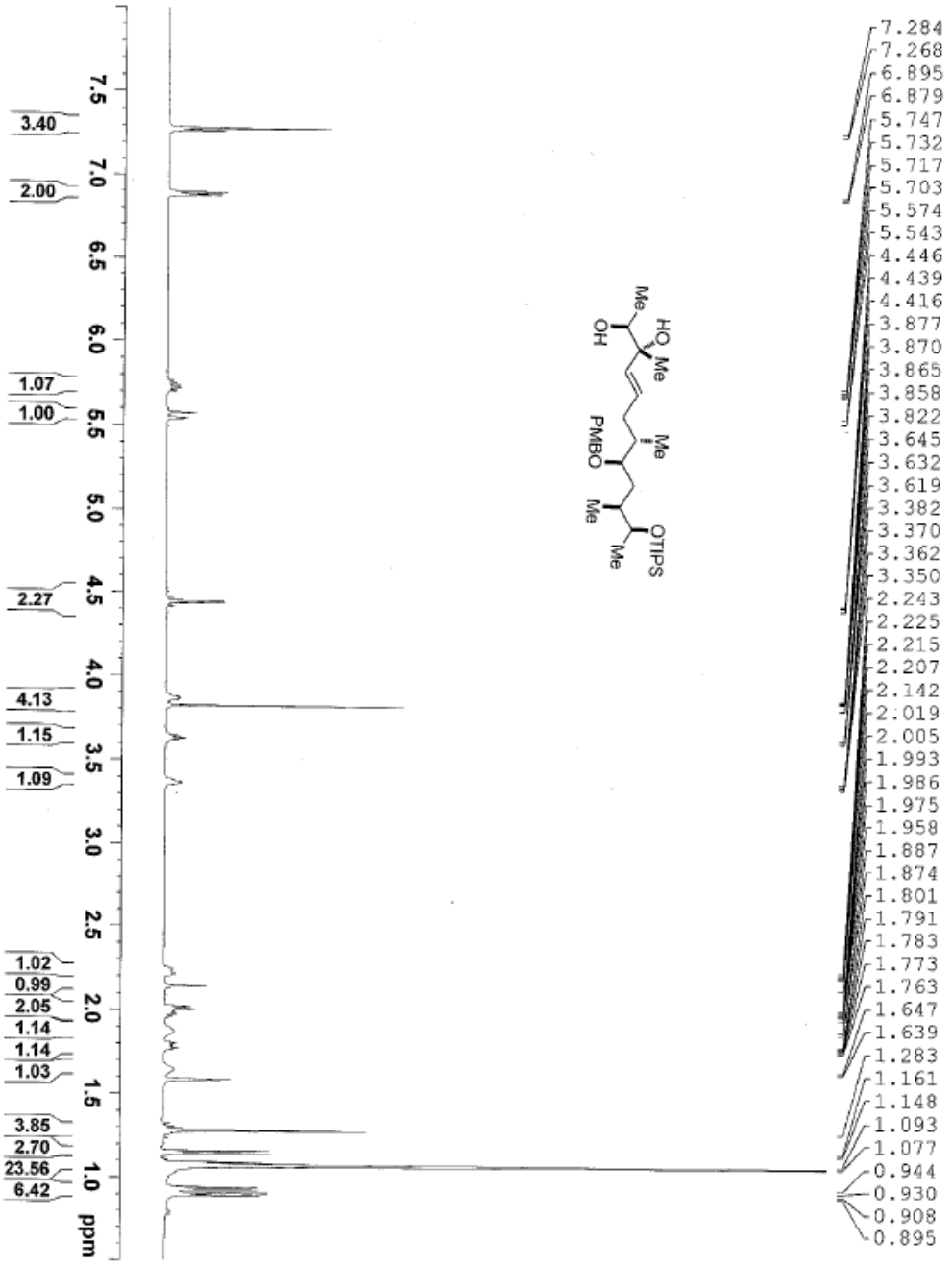
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OH
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PMBO
Me
Me
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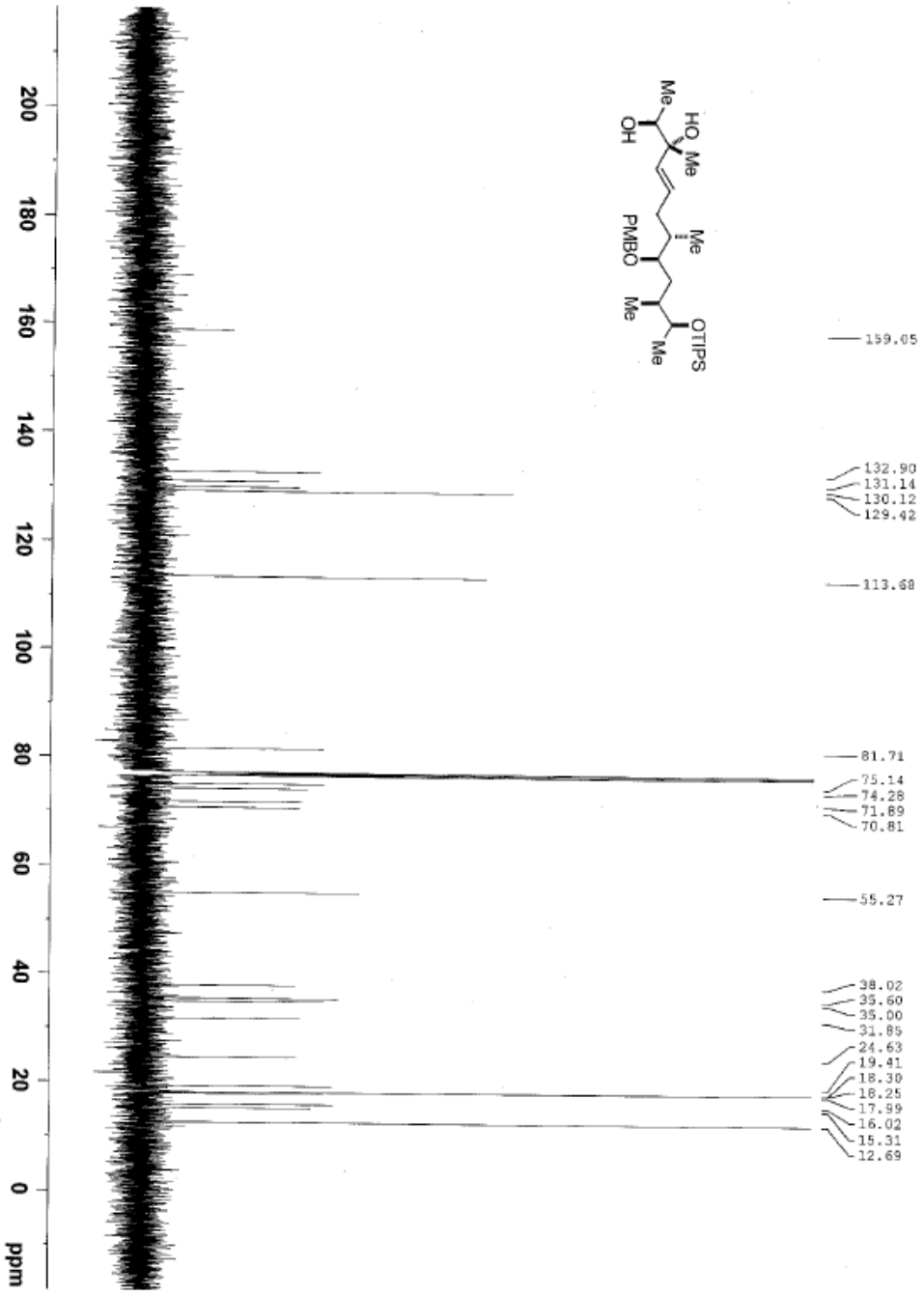
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PMBO
Me
Me
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35.00
31.85
24.63
19.41
18.30
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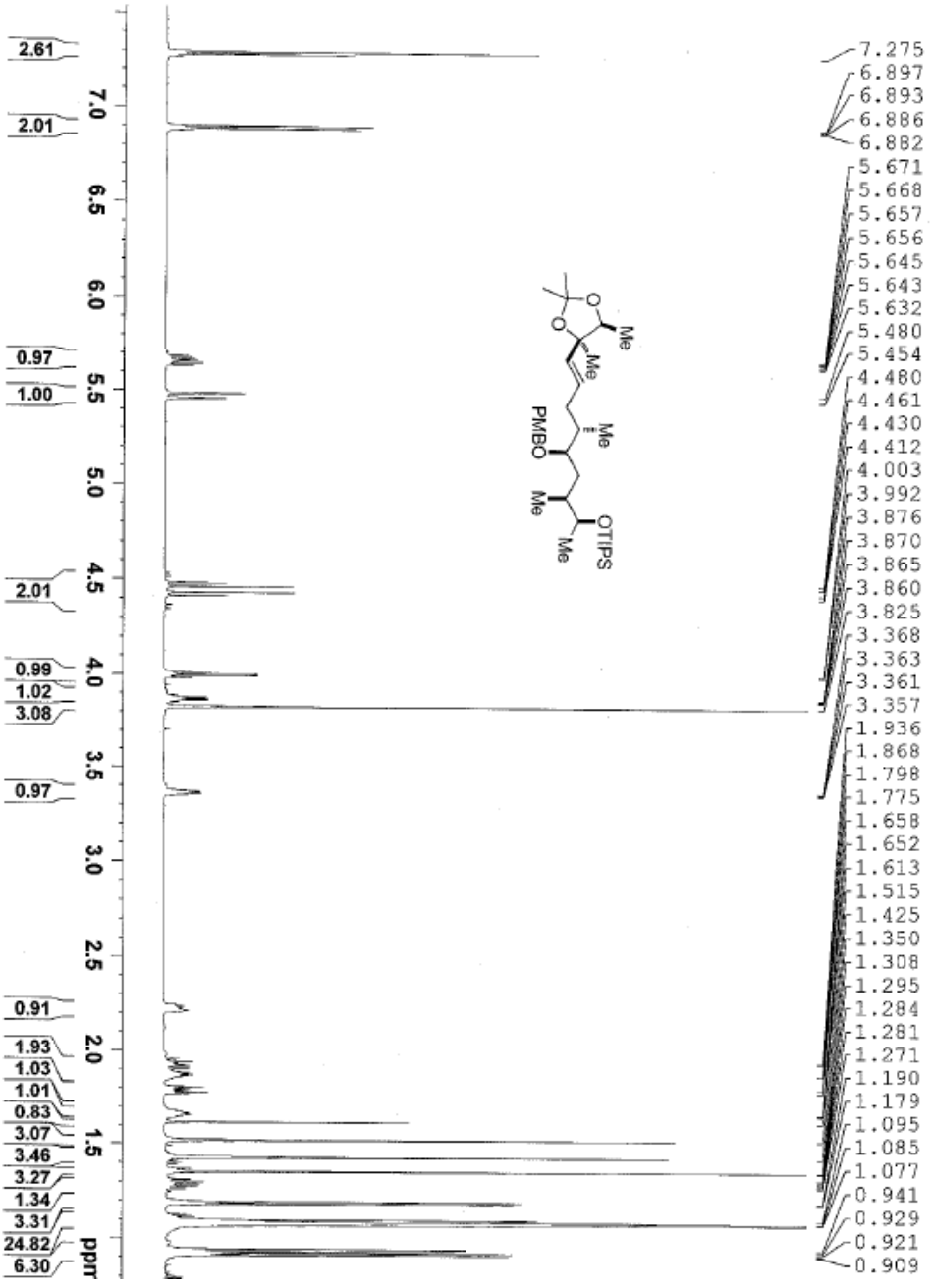
40
20
0
ppm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6.0
5.5
5.0
4.5
4.0
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3.0
2.5
2.0
1.5
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Me
Me
PMBO
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OTIPS
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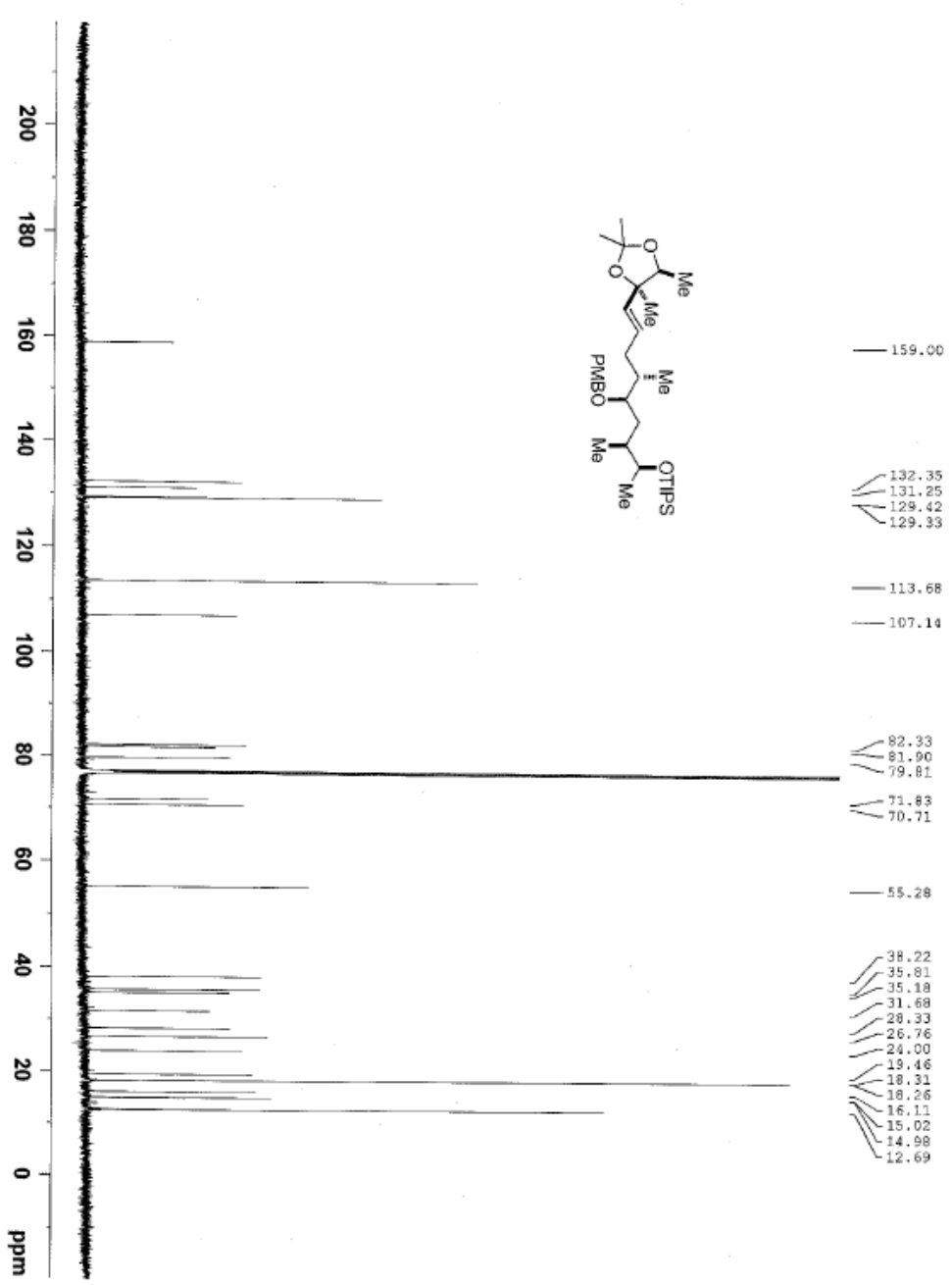
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Me
Me
PMBO
Me
OTIPS
Me
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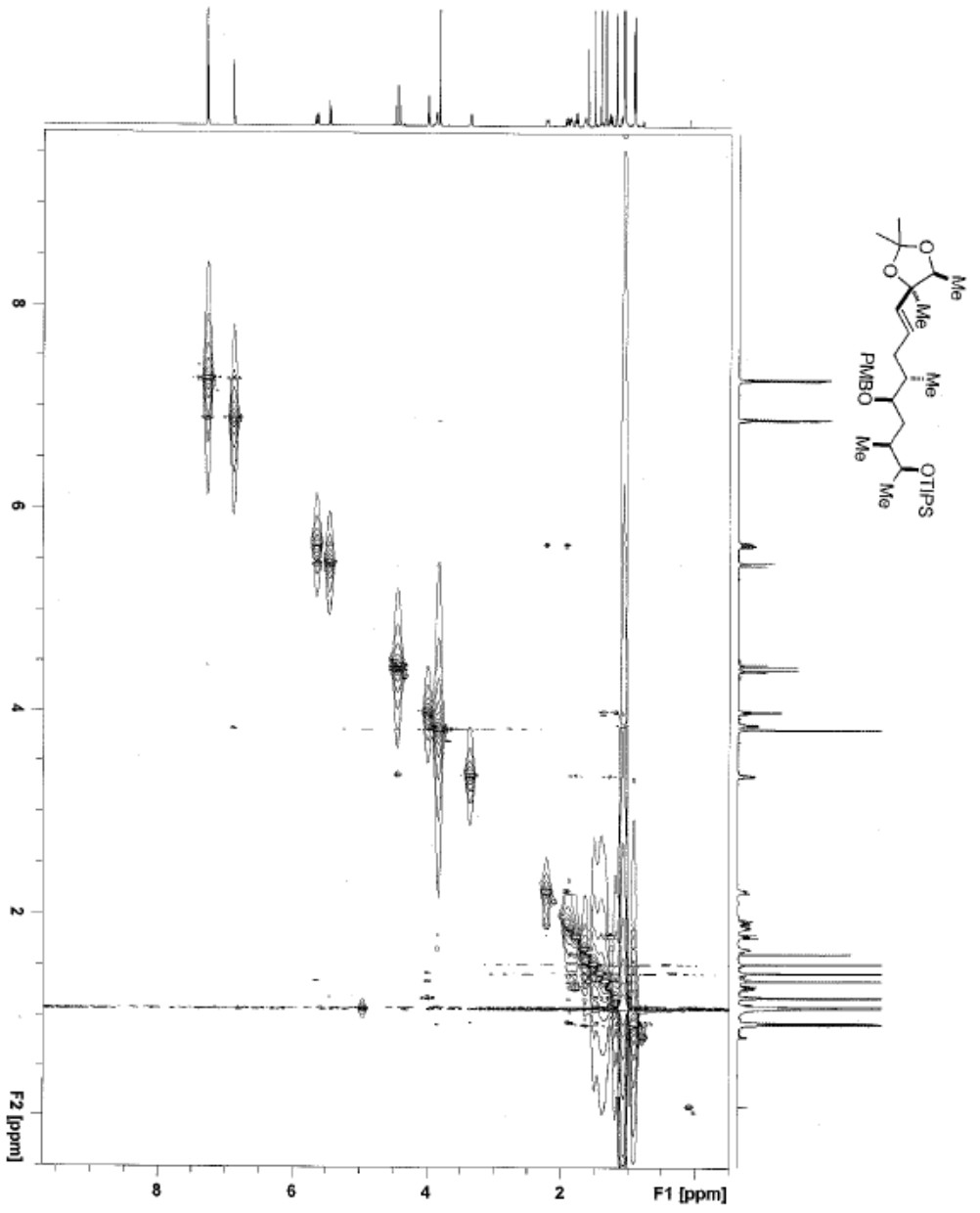
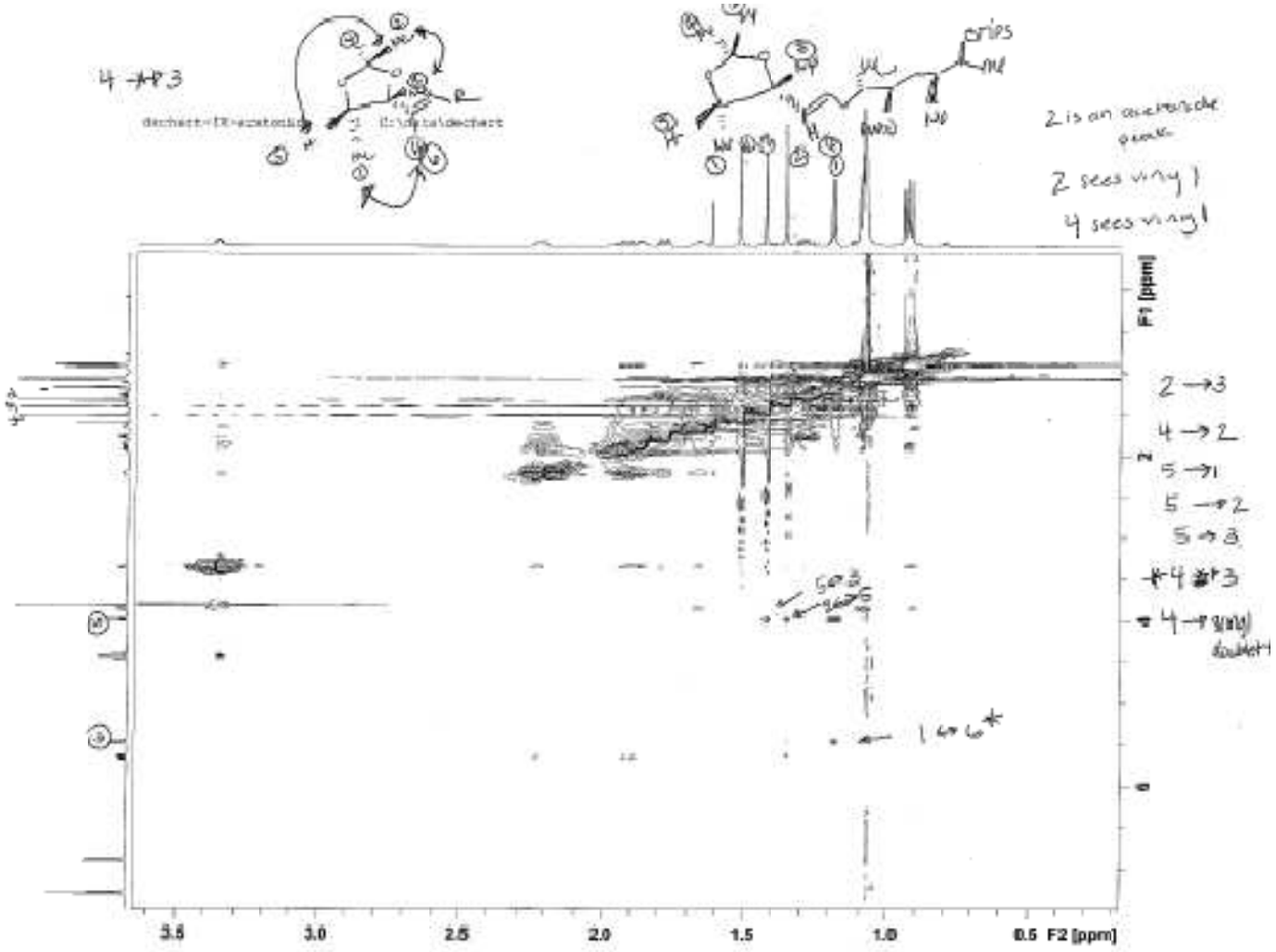
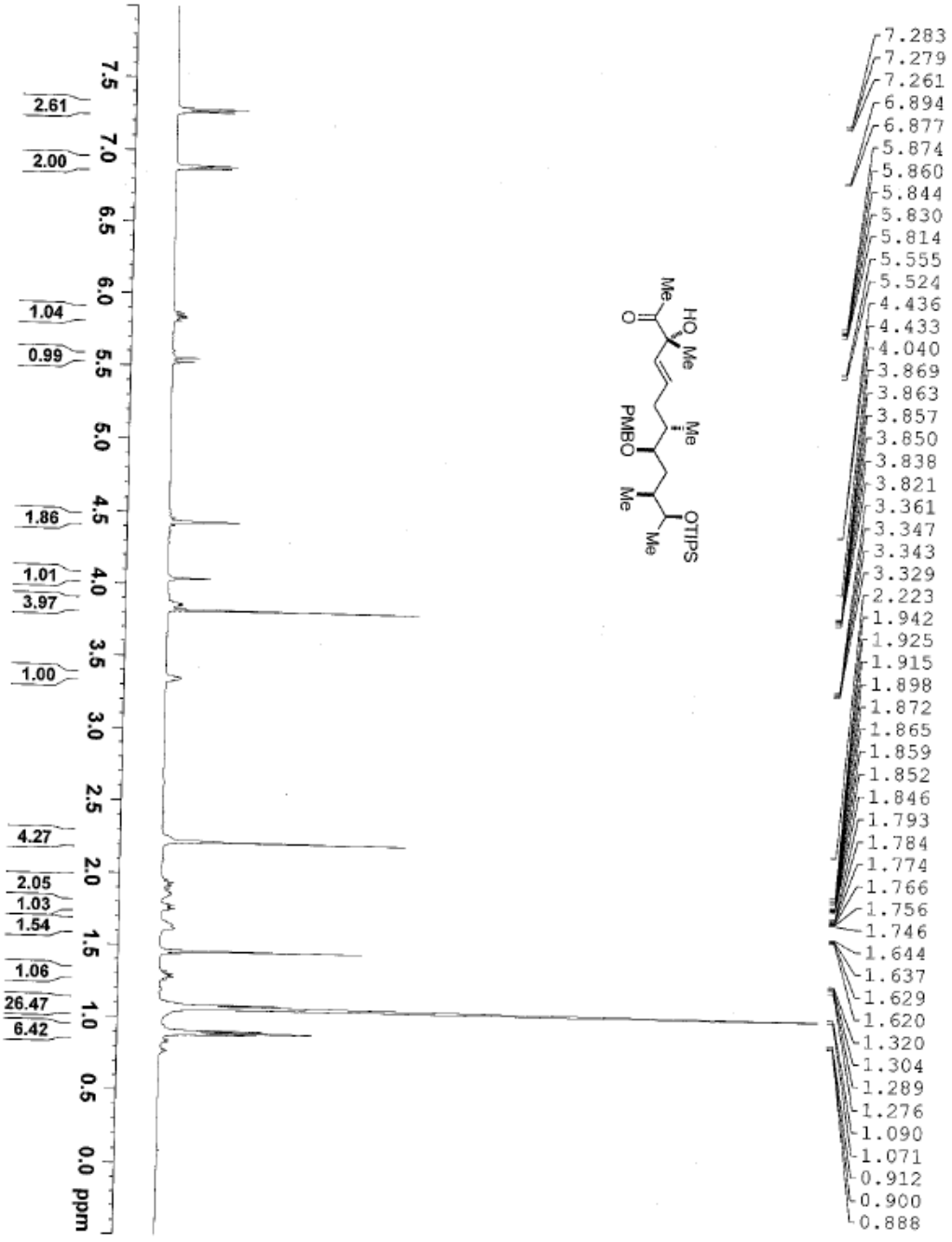
132.35
131.25
129.42
129.33
113.68
107.14
82.33
81.90
79.81
71.83
70.71
55.28
38.22
35.81
35.18
31.68
28.33
26.76
24.00
19.46
18.31
18.26
16.11
15.02
14.98
12.69
200
180
160
140
120
100
80
60
40
20
0
ppm


F2 [ppm]
F1 [ppm]
8
6
4
2
Me
Me
Me
PMBO
Me
OTIPS
Me


4 → #3
2 is an anomeric proton
2 sees vinyl
4 sees vinyl
2 → 3
4 → 2
5 → 1
5 → 2
5 → 3
#4 #3
F1 [ppm]
F2 [ppm]
3.5
3.0
2.5
2.0
1.5
1.0
0.5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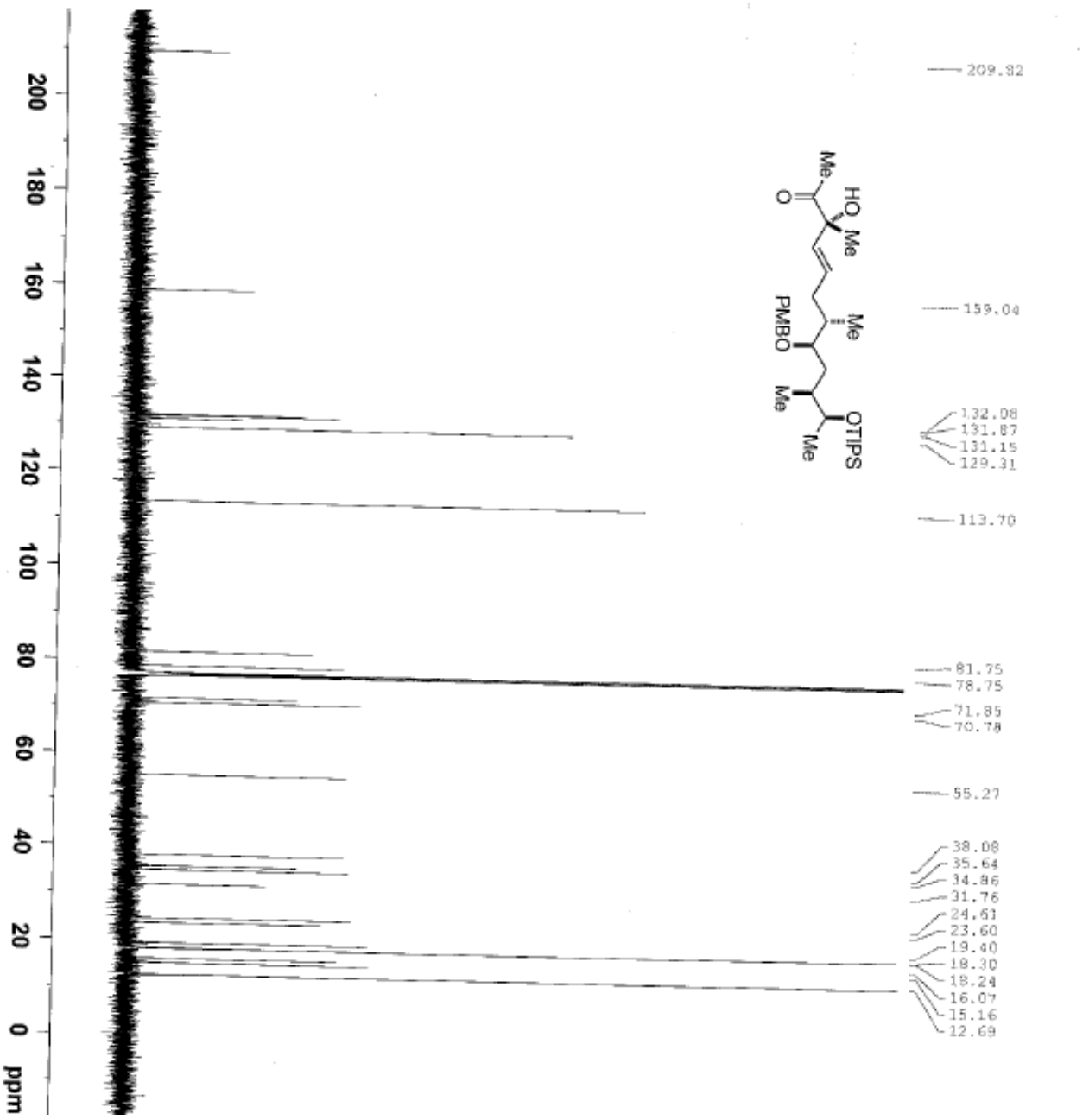
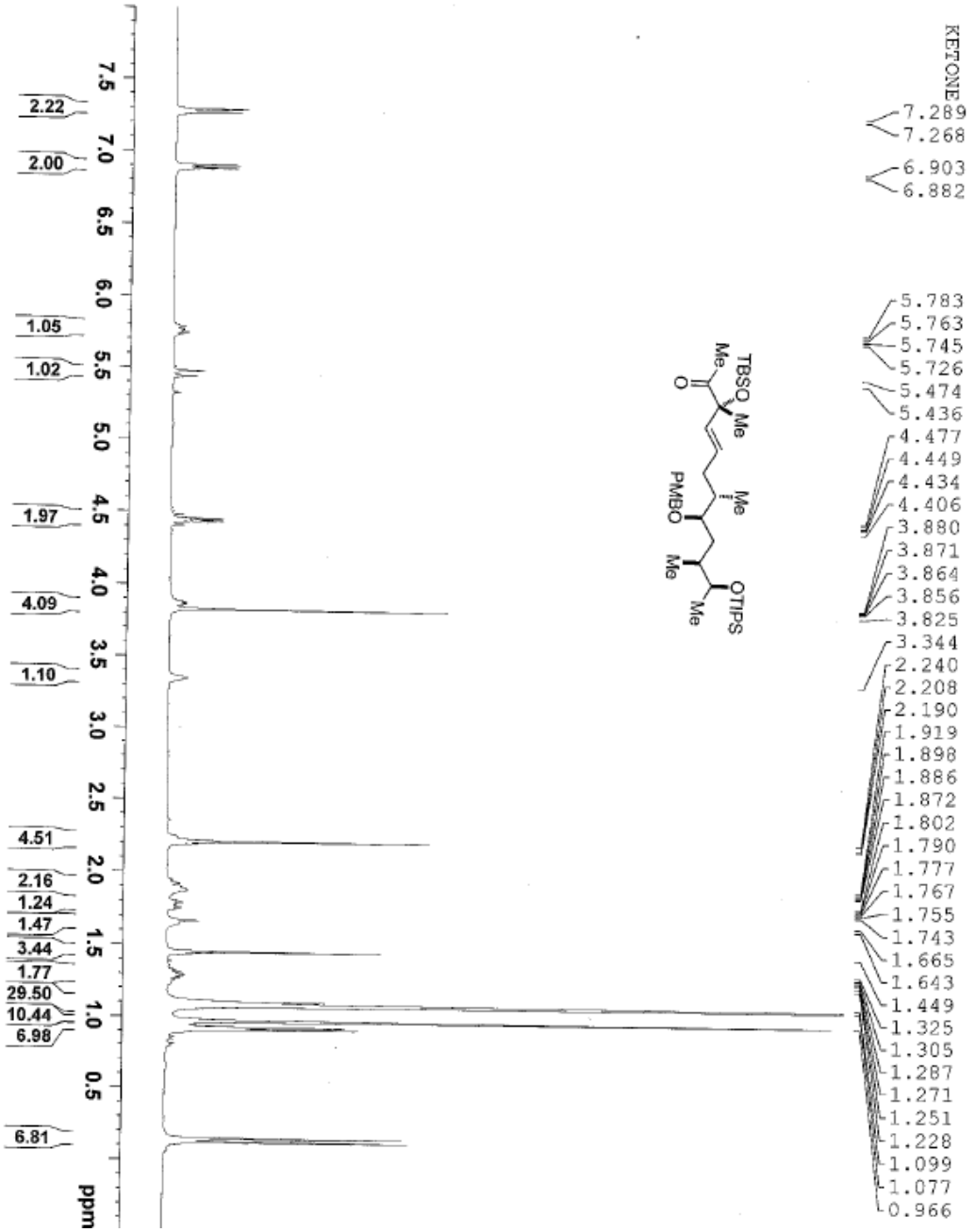
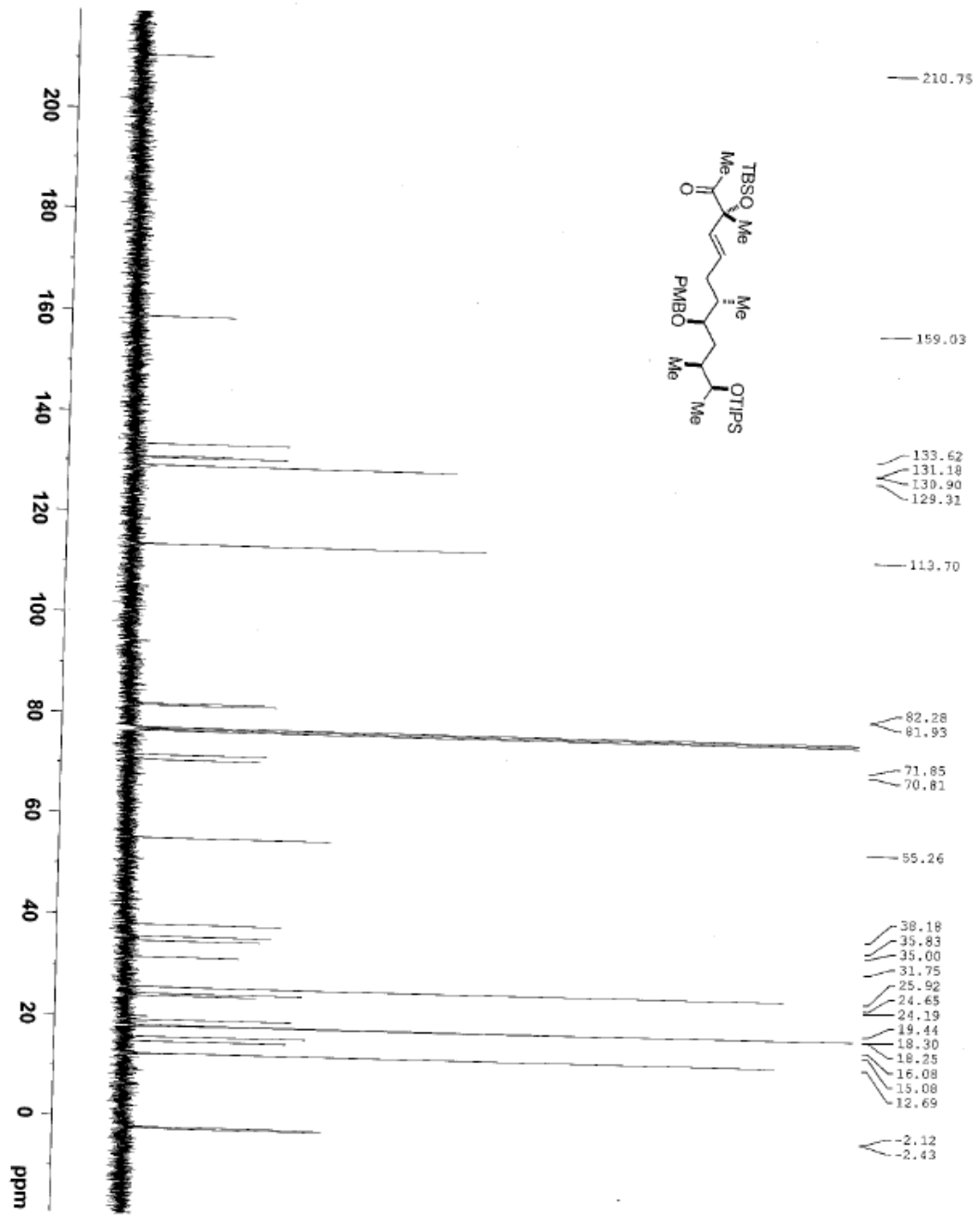
7.279
7.261
6.894
6.877
5.874
5.860
5.844
5.830
5.814
5.555
5.524
4.436
4.433
4.040
3.869
3.863
3.857
3.850
3.838
3.821
3.361
3.347
3.343
3.329
2.223
1.942
1.925
1.915
1.898
1.872
1.865
1.859
1.852
1.846
1.793
1.784
1.774
1.766
1.756
1.746
1.644
1.637
1.629
1.620
1.320
1.304
1.289
1.276
1.090
1.071
0.912
0.900
0.888
HO
Me
O
Me
PMBO
Me
Me
OTIPS
Me
2.61
2.00
1.04
0.99
1.86
1.01
3.97
1.00
4.27
2.05
1.03
1.54
1.06
26.47
6.42
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


209.82
159.04
132.08
131.87
131.15
129.31
113.70
81.75
78.75
71.85
70.78
55.27
38.08
35.64
34.86
31.76
24.61
23.60
19.40
18.30
18.24
16.07
15.16
12.69
HO
Me
O
Me
PMBO
Me
Me
OTIPS
200
180
160
140
120
100
80
60
40
20
0
ppm


KETONE
7.289
7.268
6.903
6.882
5.783
5.763
5.745
5.726
5.474
5.436
4.477
4.449
4.434
4.406
3.880
3.871
3.864
3.856
3.825
3.344
2.240
2.208
2.190
1.919
1.898
1.886
1.872
1.802
1.790
1.777
1.767
1.755
1.743
1.665
1.643
1.449
1.325
1.305
1.287
1.271
1.251
1.228
1.099
1.077
0.966
TBSO
Me
O
Me
PMBO
Me
Me
OTIPS
2.22
2.00
1.05
1.02
1.97
4.09
1.10
4.51
2.16
1.24
1.47
3.44
1.77
29.50
10.44
6.98
6.81
ppm


TBSO
Me
Me
O
Me
PMBO
Me
Me
OTIPS
210.75
159.03
133.62
131.18
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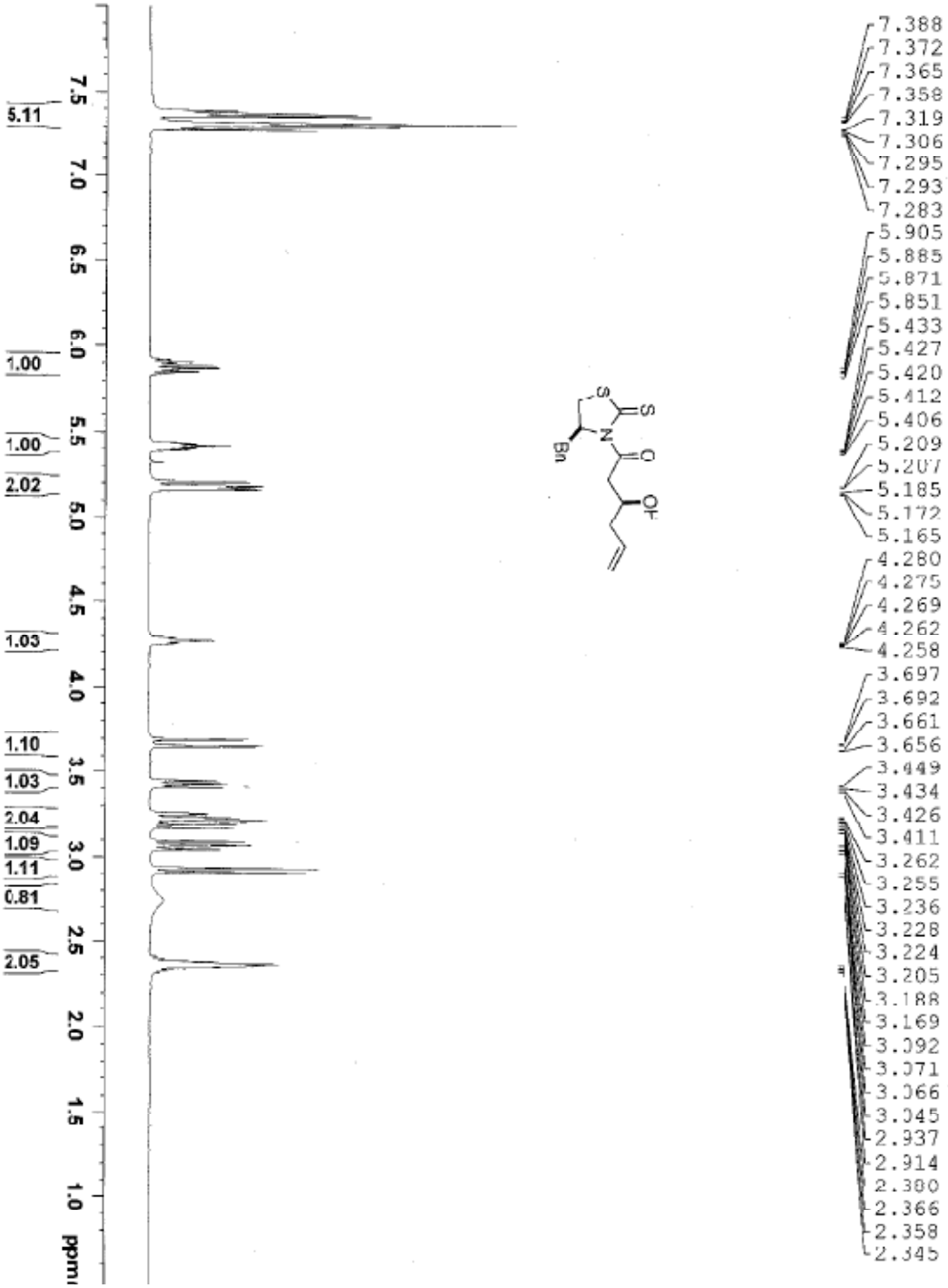
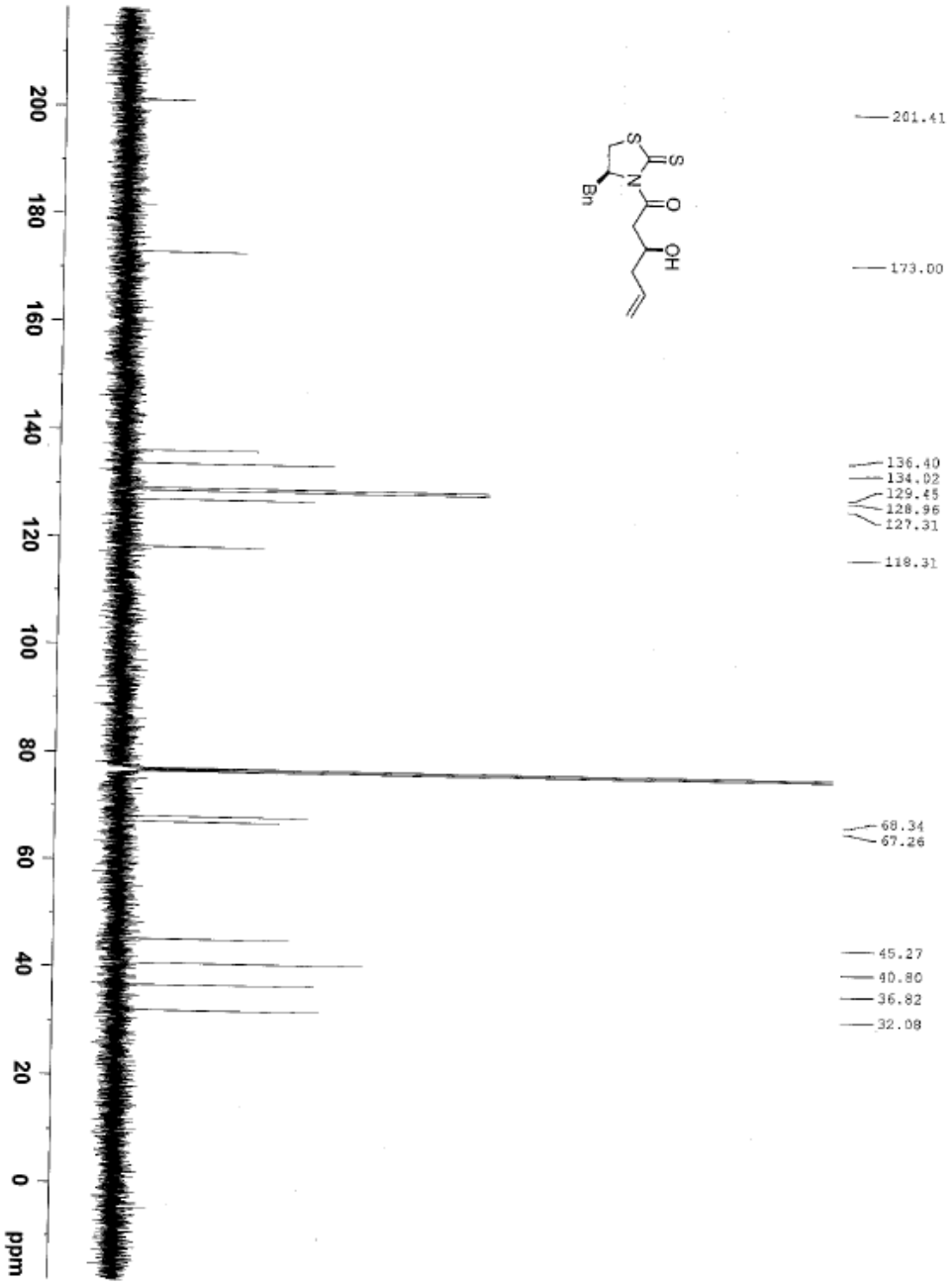
129.31
113.70
82.28
81.93
71.85
70.81
55.26
38.18
35.83
35.00
31.75
25.92
24.65
24.19
19.44
18.30
18.25
16.08
15.08
12.69
-2.12
-2.43
200
180
160
140
120
100
80
60
40
20
0
ppm


7.388
7.372
7.365
7.358
7.319
7.306
7.295
7.293
7.283
5.905
5.885
5.871
5.851
5.433
5.427
5.420
5.412
5.406
5.209
5.207
5.185
5.172
5.165
4.280
4.275
4.269
4.262
4.258
3.697
3.692
3.661
3.656
3.449
3.434
3.426
3.411
3.262
3.255
3.236
3.228
3.224
3.205
3.188
3.169
3.092
3.071
3.066
3.045
2.937
2.914
2.380
2.366
2.358
2.345
5.11
1.00
1.00
2.02
1.03
1.10
1.03
2.04
1.09
1.11
0.81
2.05
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
S
S
N
O
Bn
OH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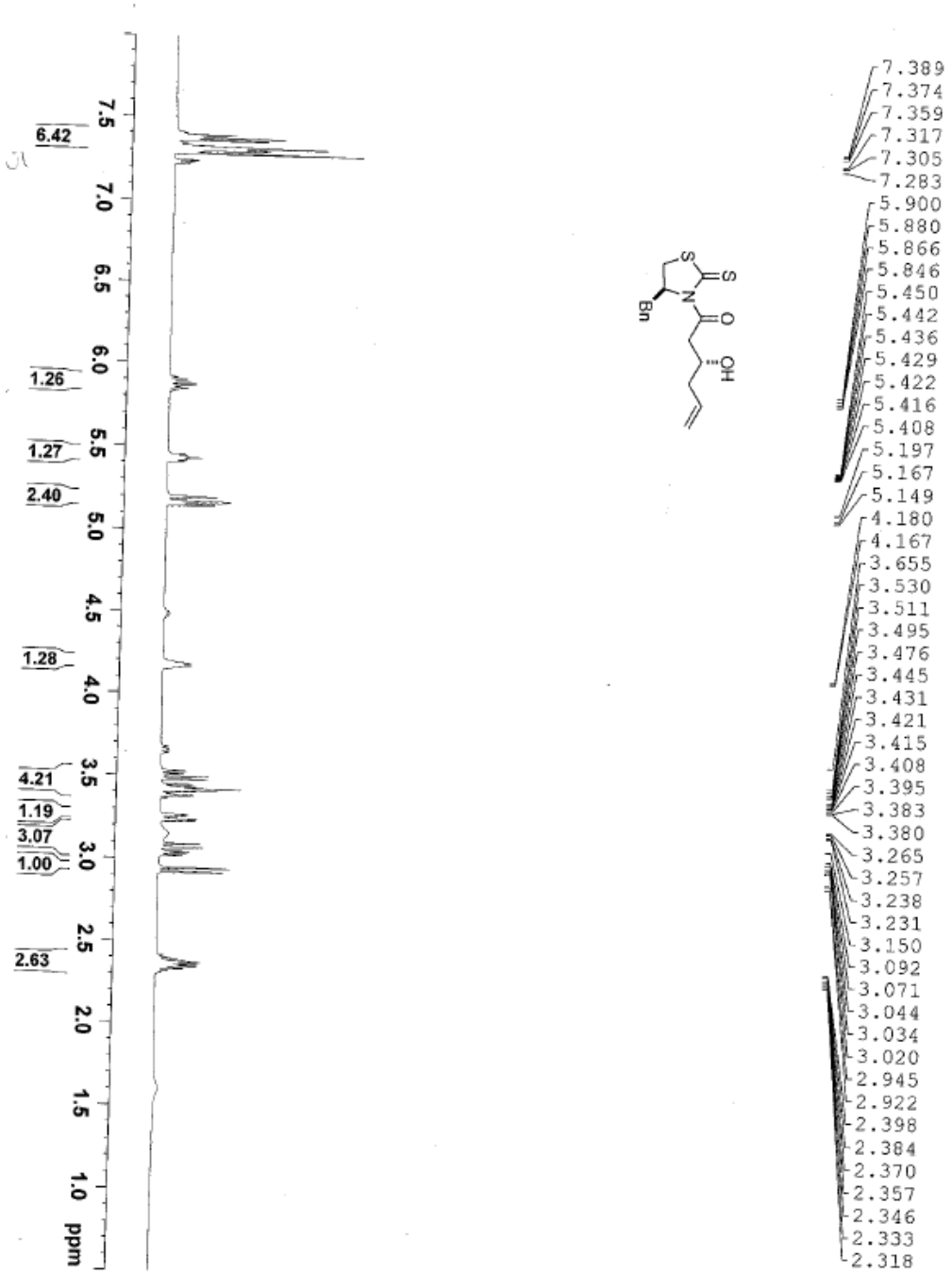
173.00
136.40
134.02
129.45
128.96
127.31
118.31
68.34
67.26
45.27
40.80
36.82
32.08
200
180
160
140
120
100
80
60
40
20
0
ppm
S
S
N
O
OH
Bn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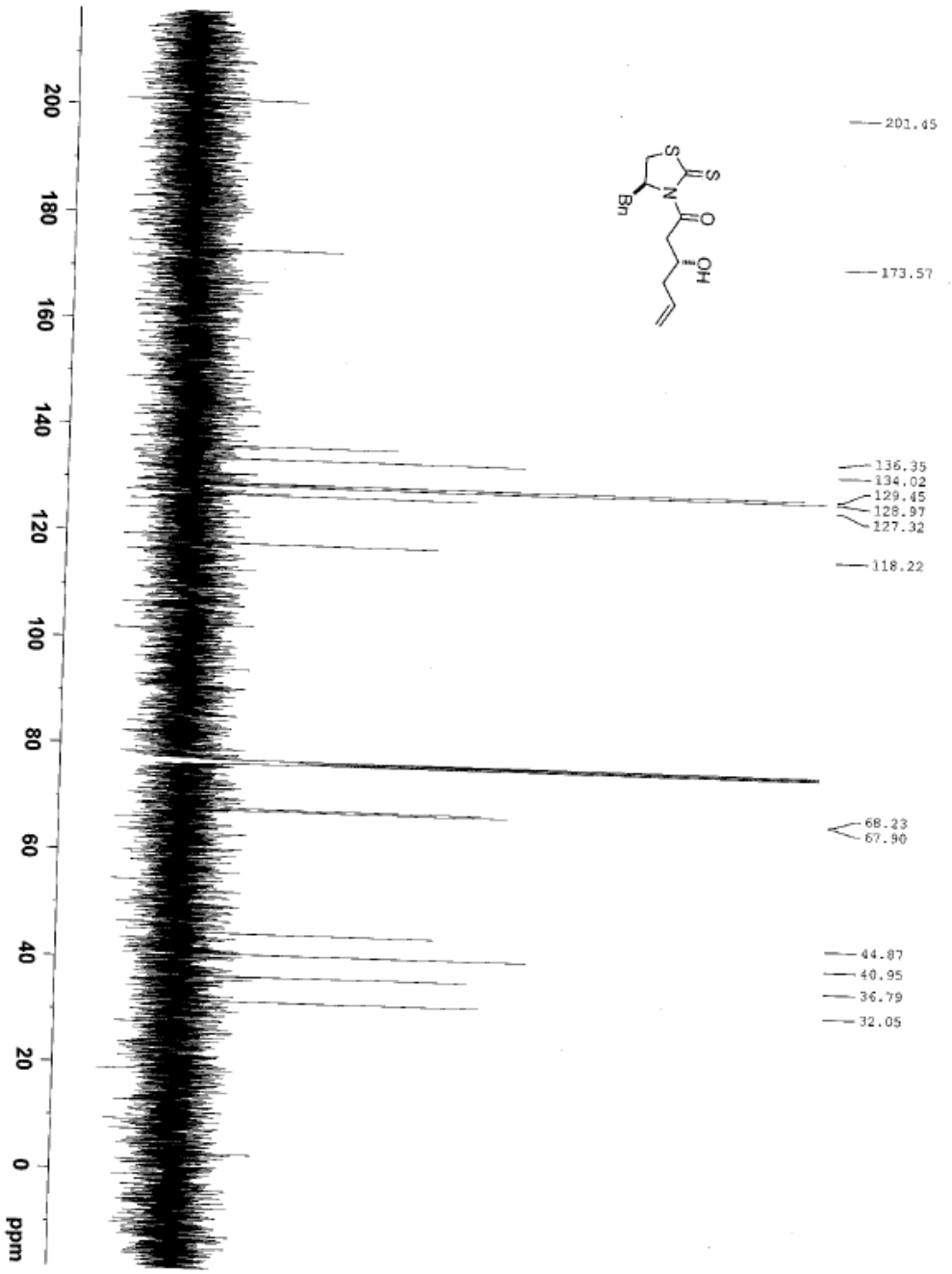
7.374
7.359
7.317
7.305
7.283
5.900
5.880
5.866
5.846
5.450
5.442
5.436
5.429
5.422
5.416
5.408
5.197
5.167
5.149
4.180
4.167
3.655
3.530
3.511
3.495
3.476
3.445
3.431
3.421
3.415
3.408
3.395
3.383
3.380
3.265
3.257
3.238
3.231
3.150
3.092
3.071
3.044
3.034
3.020
2.945
2.922
2.398
2.384
2.370
2.357
2.346
2.333
2.318
S
S
N
O
OH
Bn
6.42
1.26
1.27
2.40
1.28
4.21
1.19
3.07
1.00
2.63
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm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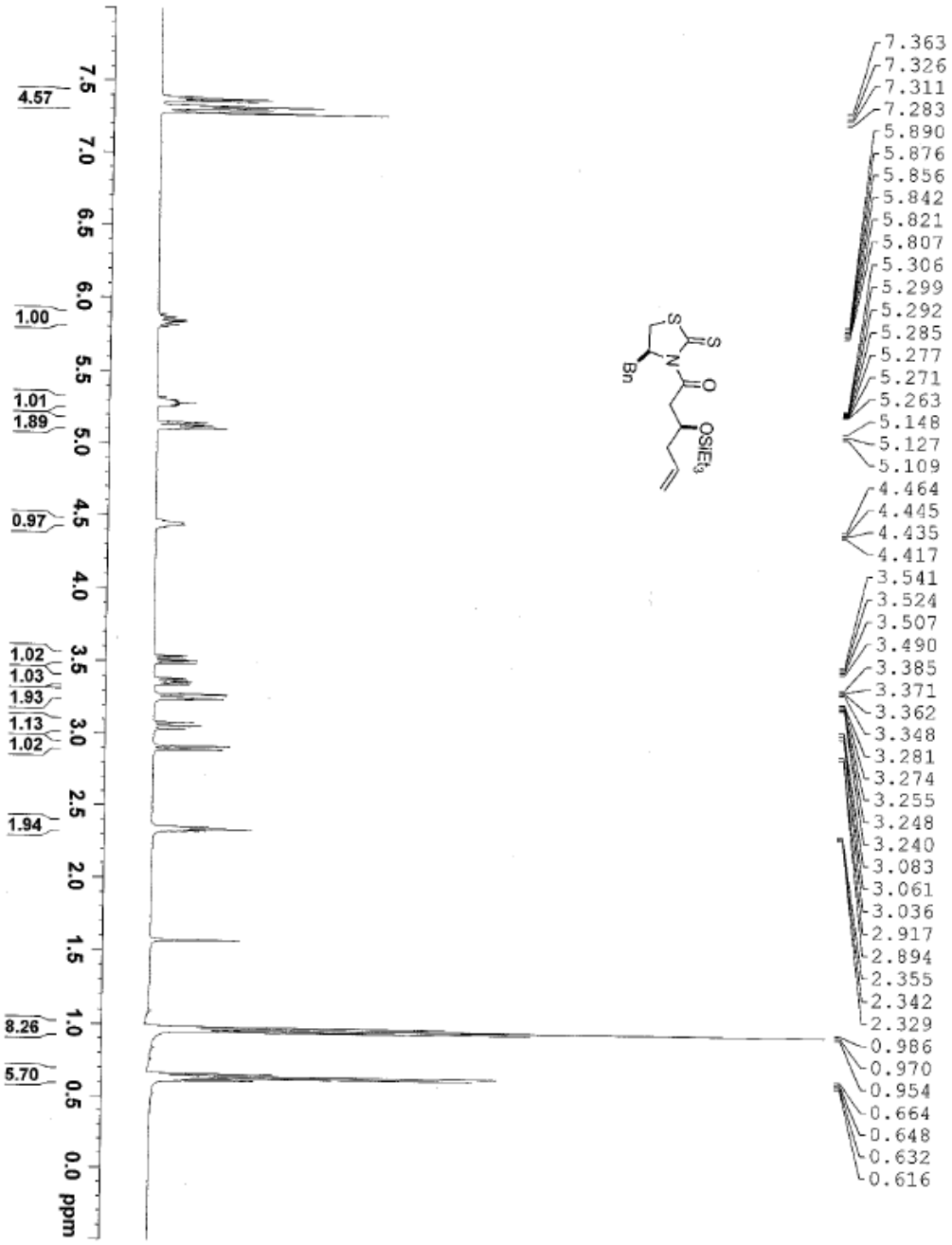
173.57
136.35
134.02
129.45
128.97
127.32
118.22
68.23
67.90
44.87
40.95
36.79
32.05
200
180
160
140
120
100
80
60
40
20
0
ppm
S
S
N
Bn
O
OH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1.00
1.01
1.89
0.97
1.02
1.03
1.93
1.13
1.02
1.94
8.26
5.70
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
Bn
OSiEt3
7.363
7.326
7.311
7.283
5.890
5.876
5.856
5.842
5.821
5.807
5.306
5.299
5.292
5.285
5.277
5.271
5.263
5.148
5.127
5.109
4.464
4.445
4.435
4.417
3.541
3.524
3.507
3.490
3.385
3.371
3.362
3.348
3.281
3.274
3.255
3.248
3.240
3.083
3.061
3.036
2.917
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2.342
2.329
0.986
0.970
0.954
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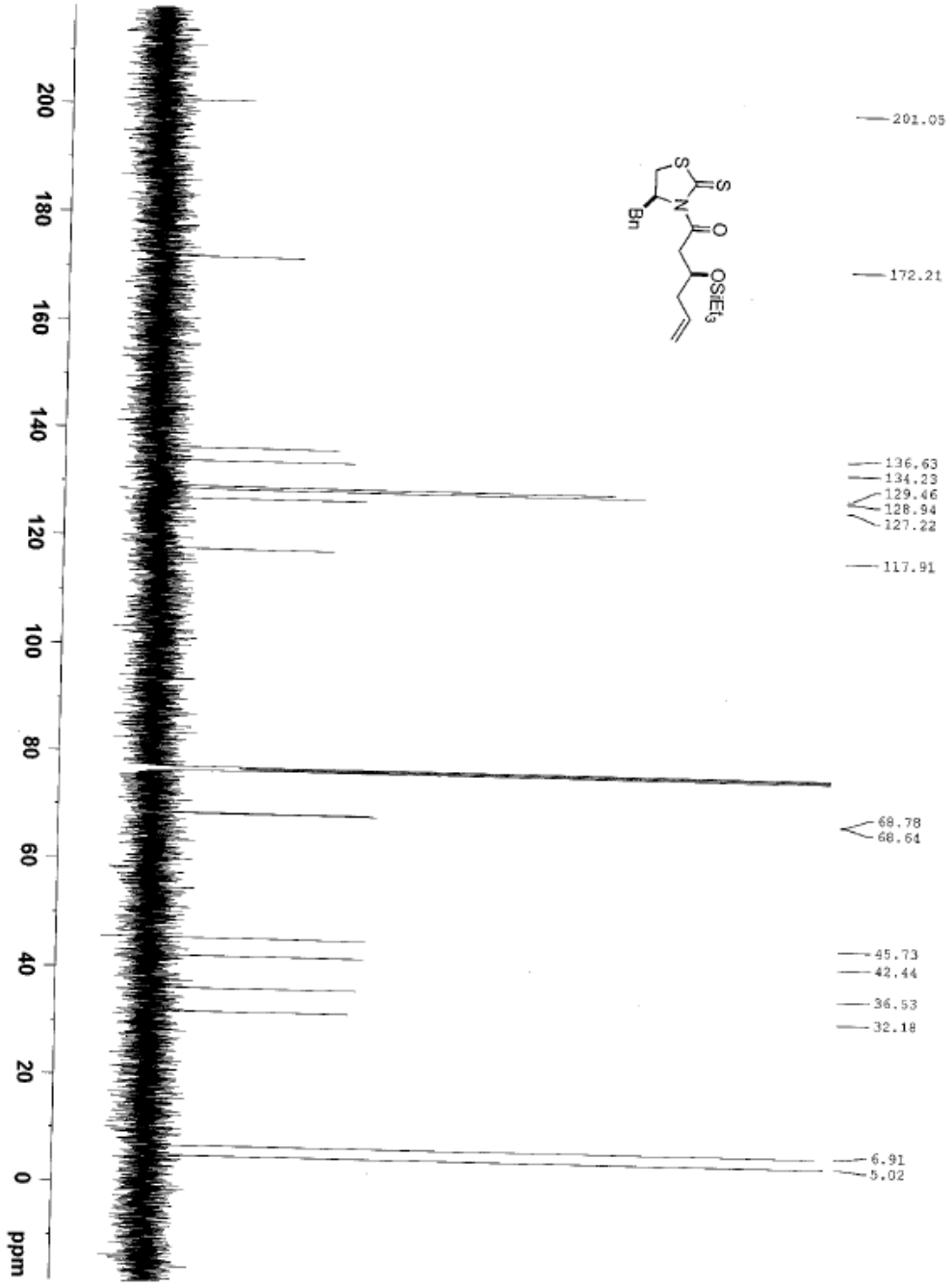
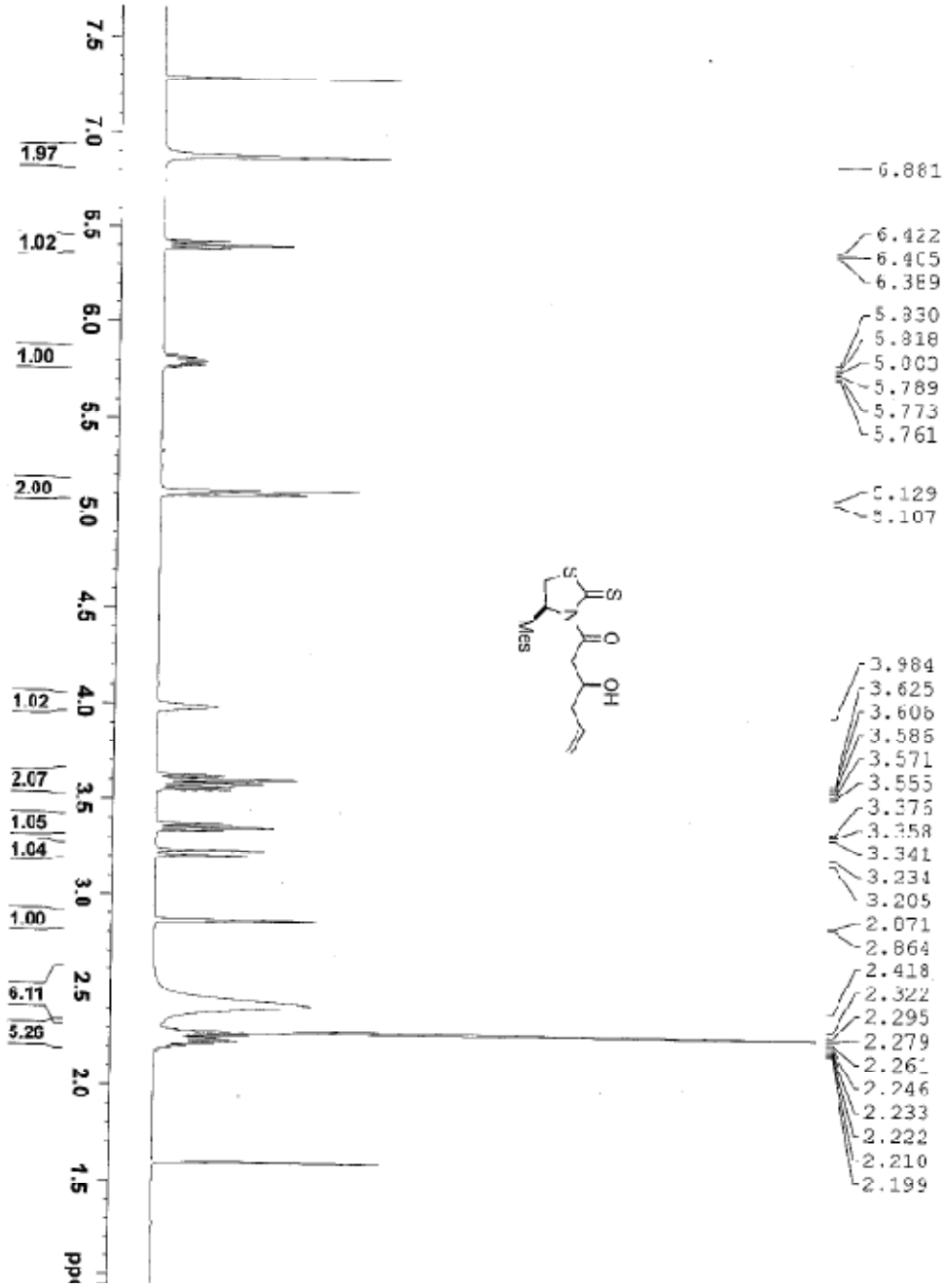
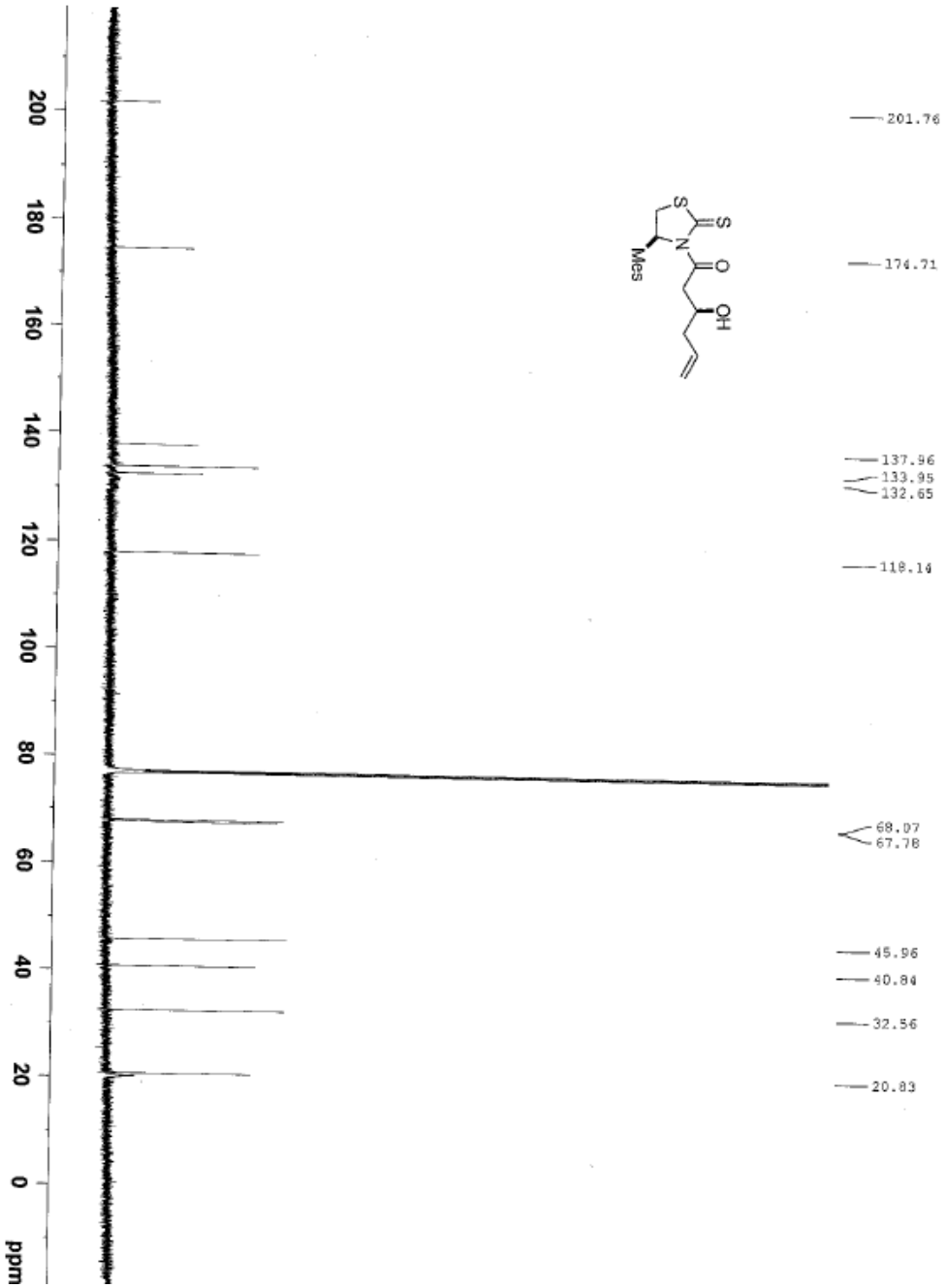
0.648
0.632
0.616


201.05
172.21
136.63
134.23
129.46
128.94
127.22
117.91
68.78
68.64
45.73
42.44
36.53
32.18
6.91
5.02
200
180
160
140
120
100
80
60
40
20
0
ppm
Bn
OSiEt3


7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.97
1.02
1.00
2.00
1.02
2.07
1.05
1.04
1.00
6.11
5.26
6.881
6.422
6.405
6.389
5.830
5.818
5.803
5.789
5.773
5.761
5.129
5.107
3.984
3.625
3.606
3.586
3.571
3.555
3.375
3.358
3.341
3.234
3.205
2.071
2.864
2.418
2.322
2.295
2.279
2.261
2.246
2.233
2.222
2.210
2.199
Mes
OH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174.71
137.96
133.95
132.65
118.14
68.07
67.78
45.96
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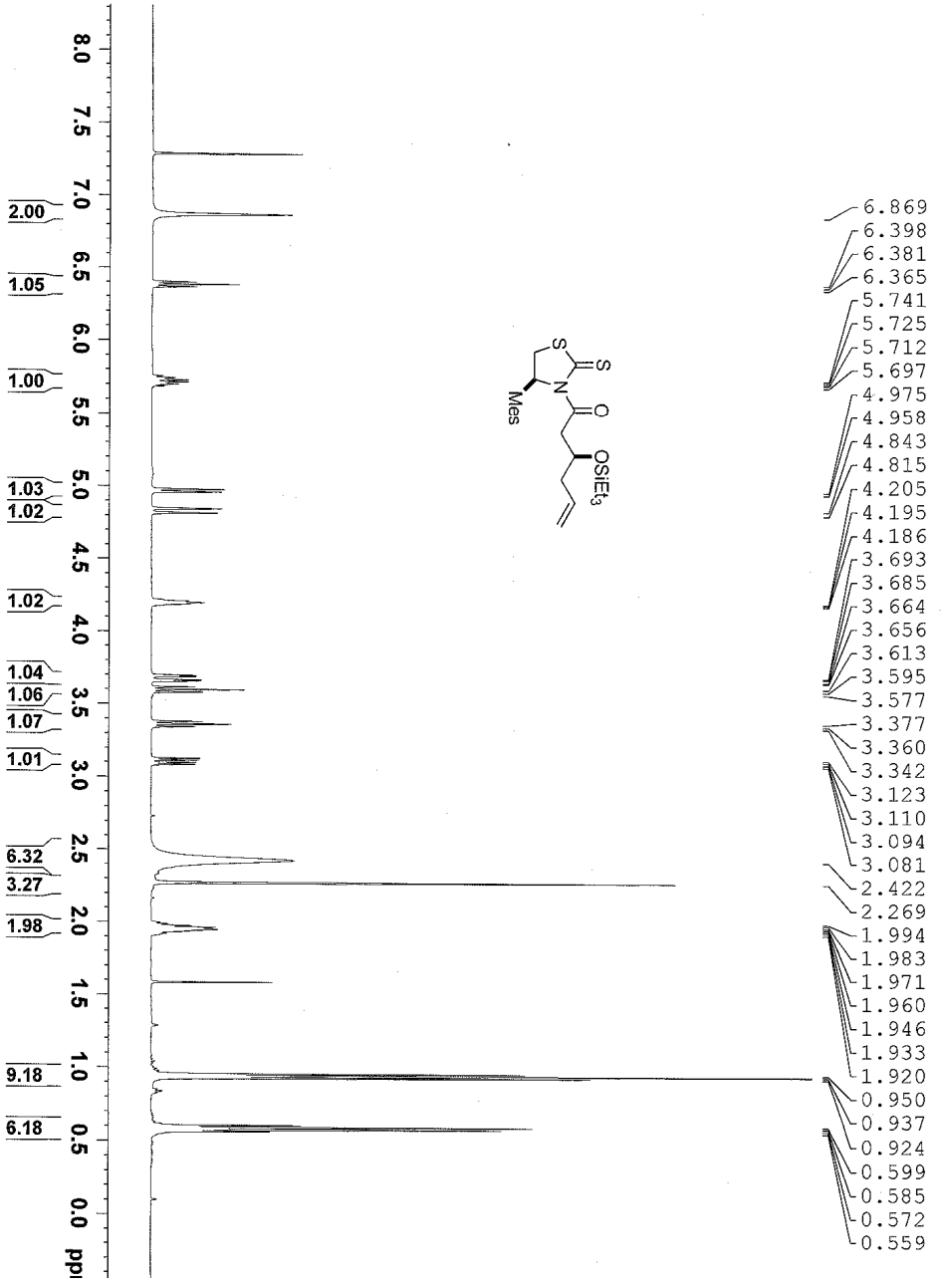
32.56
20.83
Mes
OH
200
180
160
140
120
100
80
60
40
20
0
ppm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6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
2.00
1.05
1.00
1.03
1.02
1.02
1.04
1.06
1.07
1.01
6.32
3.27
1.98
9.18
6.18
S
S
N
Mes
O
OSiEt3
6.869
6.398
6.381
6.365
5.741
5.725
5.712
5.697
4.975
4.958
4.843
4.815
4.205
4.195
4.186
3.693
3.685
3.664
3.656
3.613
3.595
3.577
3.377
3.360
3.342
3.123
3.110
3.094
3.081
2.422
2.269
1.994
1.983
1.971
1.960
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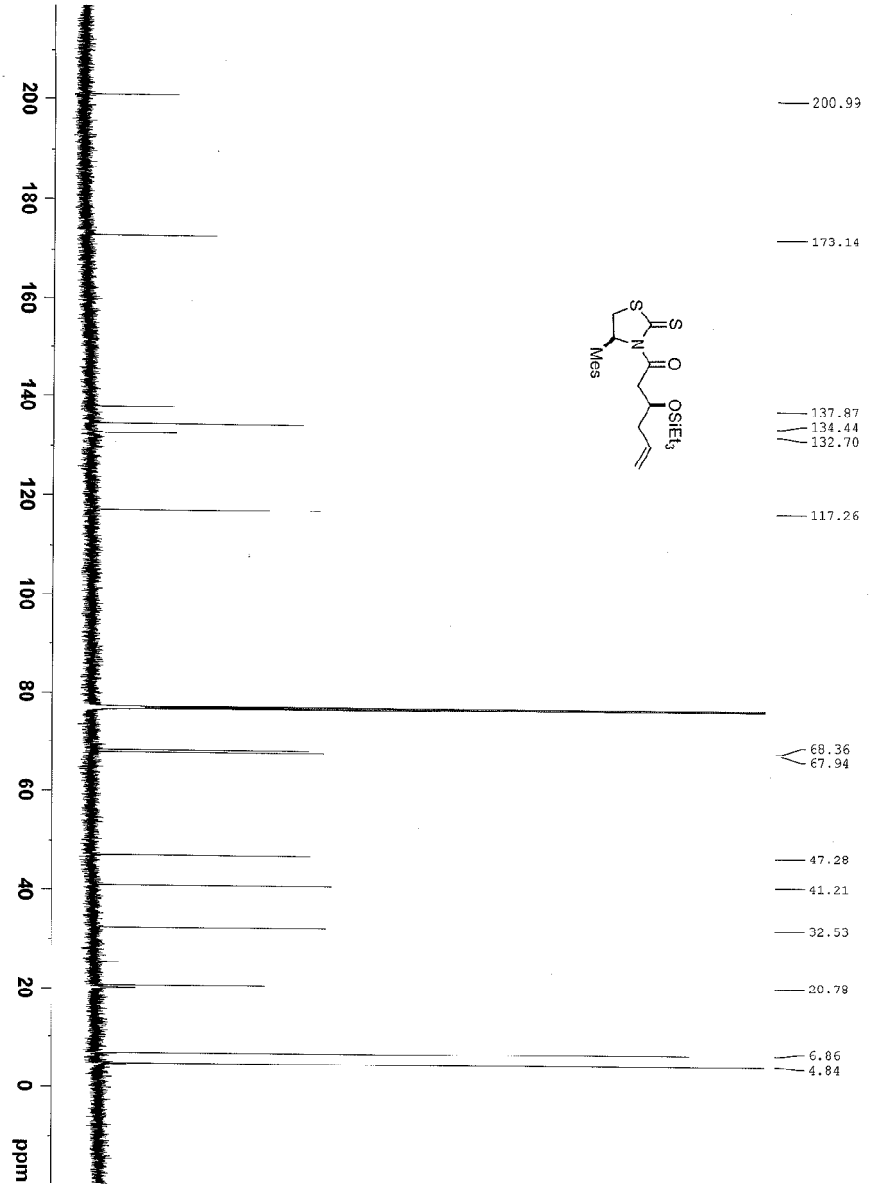
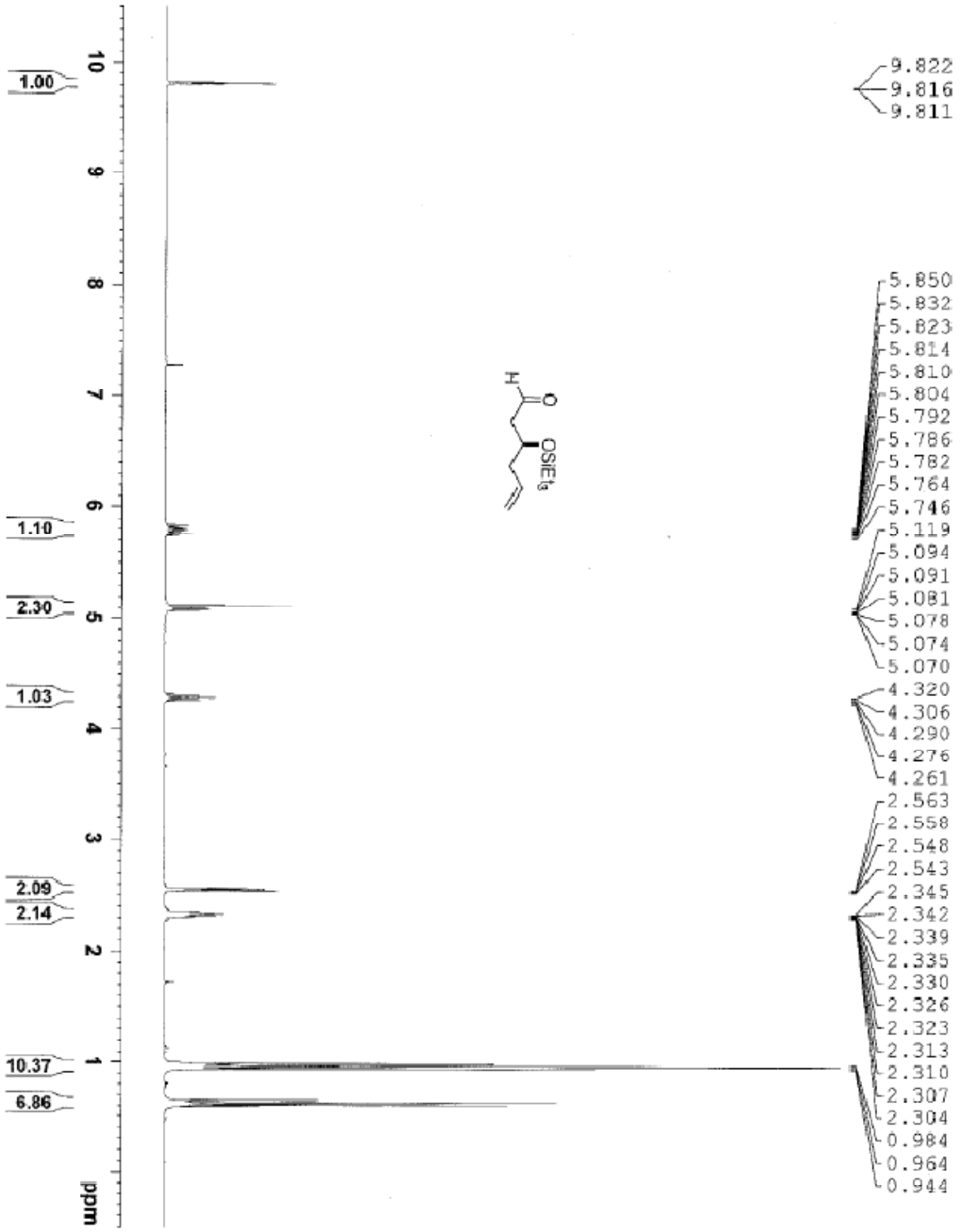
1.933
1.920
0.950
0.937
0.924
0.599
0.585
0.572
0.559


200.99
173.14
137.87
134.44
132.70
117.26
68.36
67.94
47.28
41.21
32.53
20.78
6.06
4.84
Mes
OSiEt3
200
180
160
140
120
100
80
60
40
20
0
ppm


1.00
1.10
2.30
1.03
2.09
2.14
10.37
6.86
ppm
OSiEt3
9.822
9.816
9.811
5.850
5.832
5.823
5.814
5.810
5.804
5.792
5.786
5.782
5.764
5.746
5.119
5.094
5.091
5.081
5.078
5.074
5.070
4.320
4.306
4.290
4.276
4.261
2.563
2.558
2.548
2.543
2.345
2.342
2.339
2.335
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2.326
2.323
2.313
2.310
2.307
2.304
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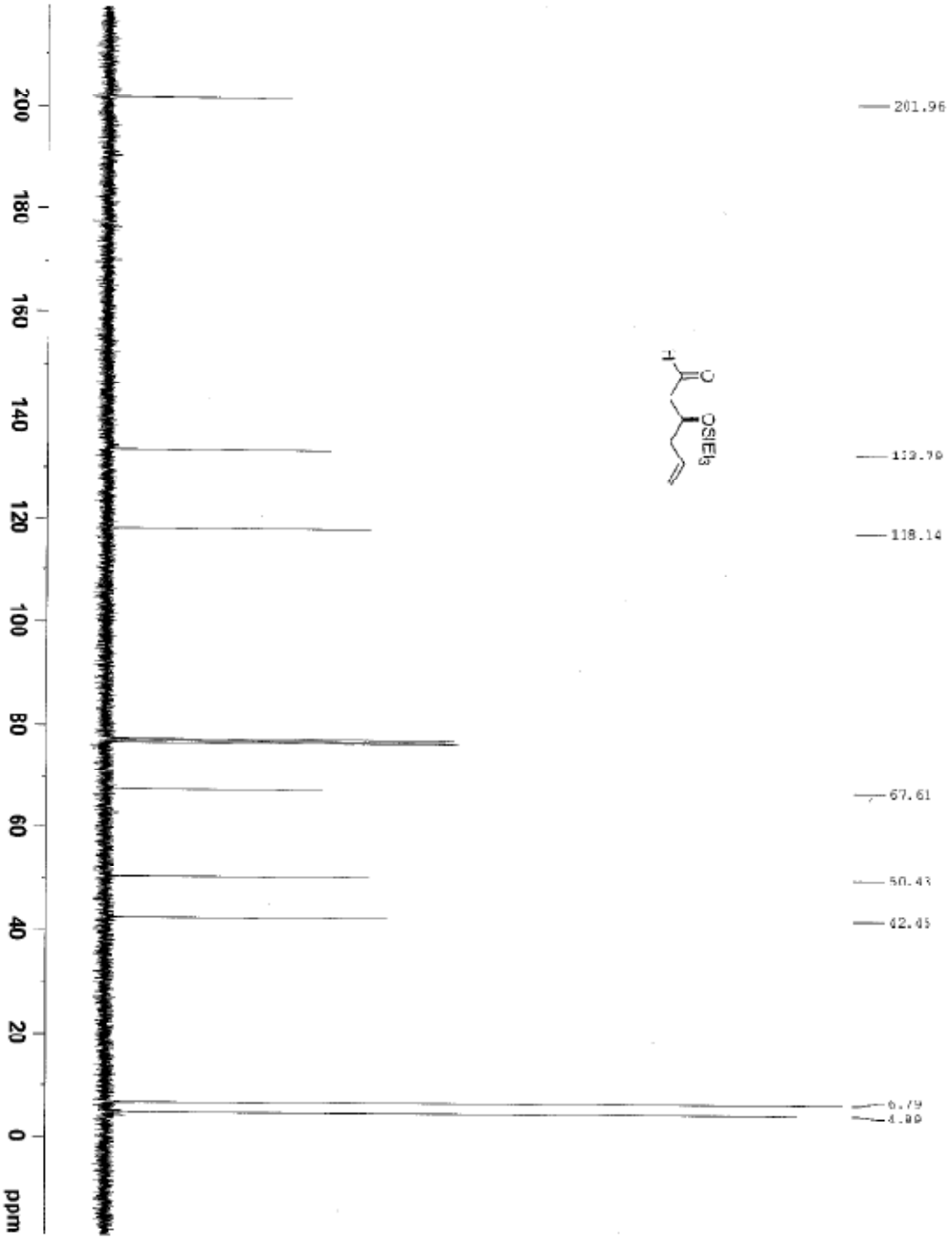
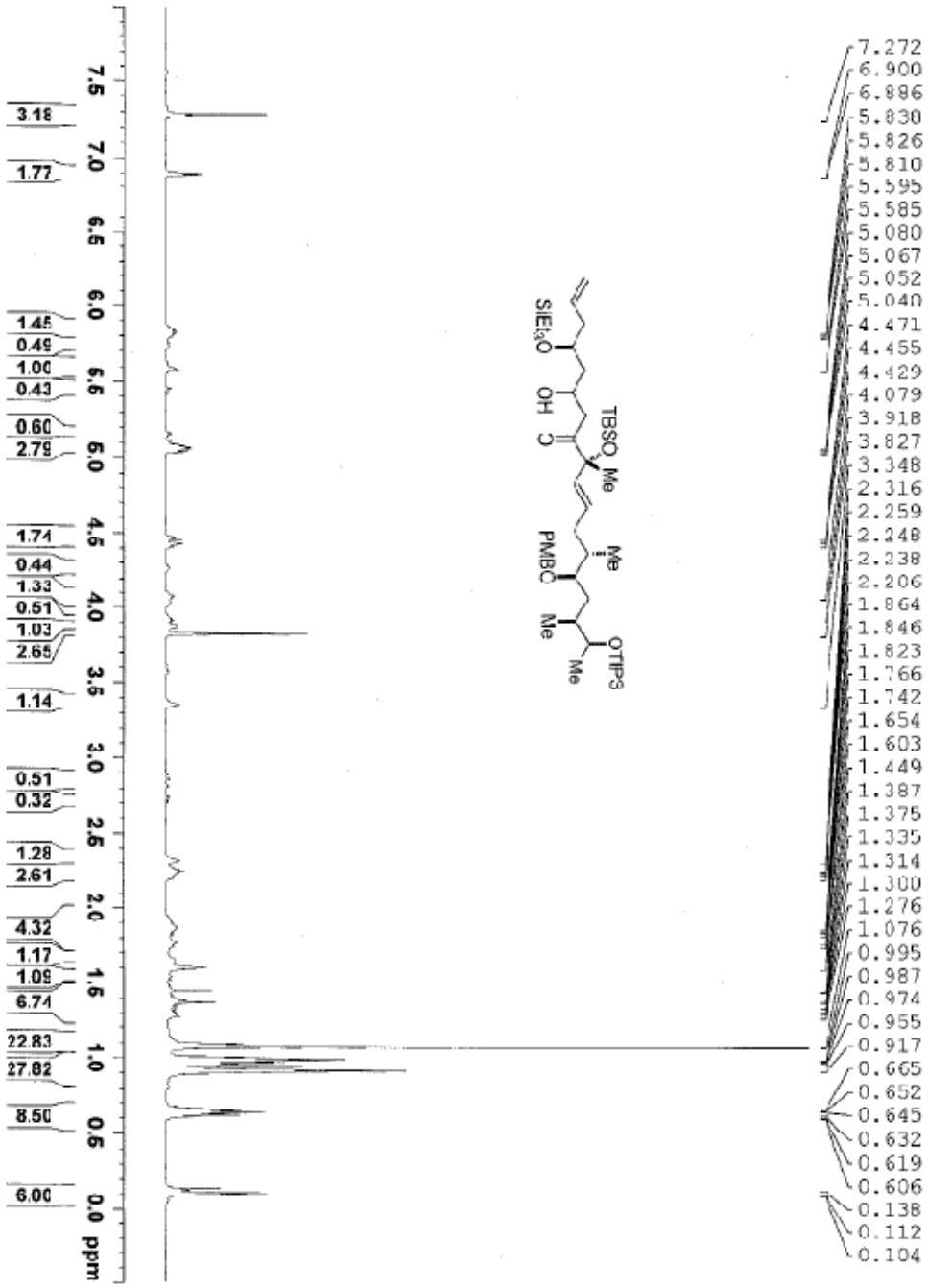
0.964
0.944


200
180
160
140
120
100
80
60
40
20
0
ppm
201.96
119.79
118.14
67.61
50.43
42.45
0.79
0.00
OSiEt3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6.886
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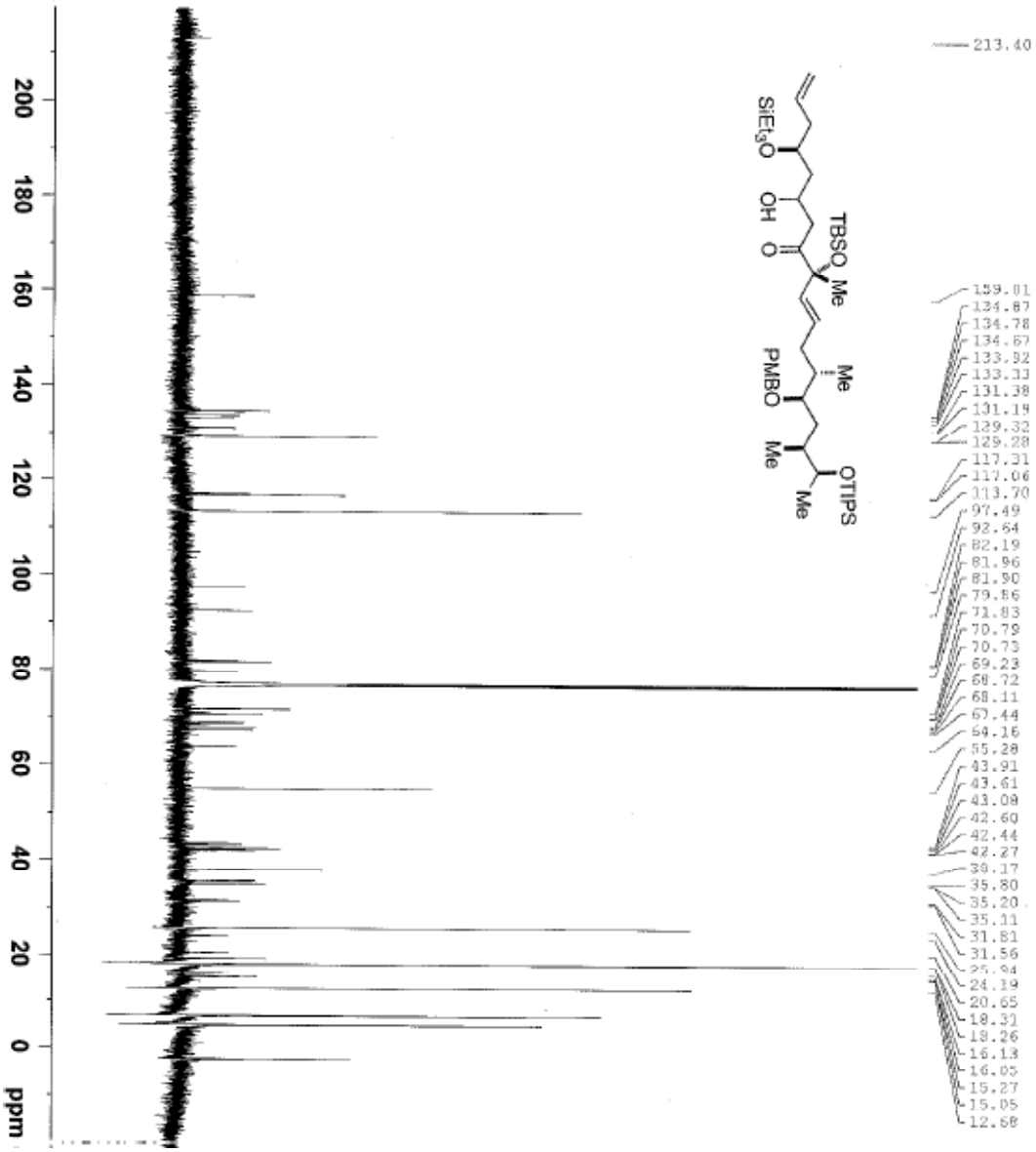
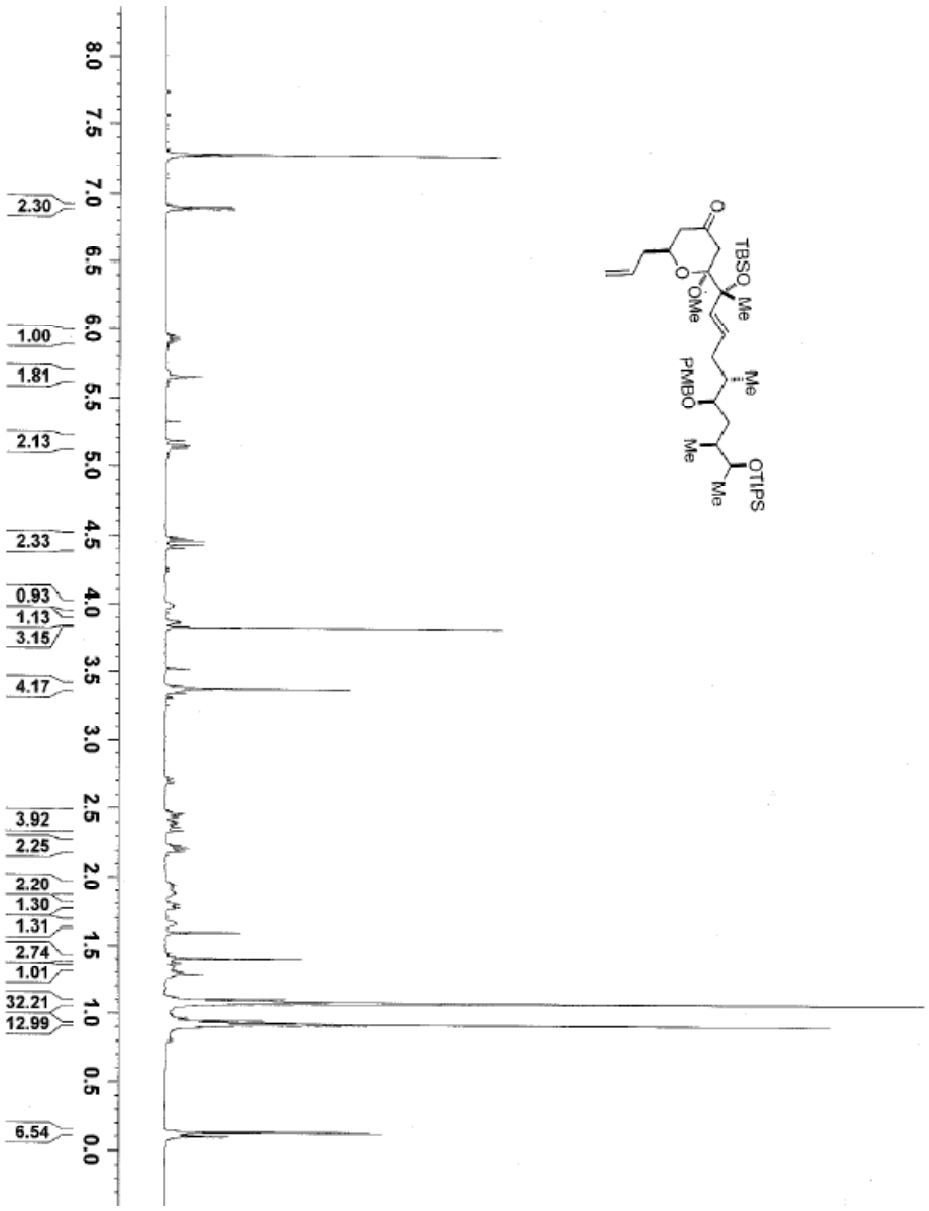
5.826
5.810
5.595
5.585
5.080
5.067
5.052
5.040
4.471
4.455
4.429
4.079
3.918
3.827
3.348
2.316
2.259
2.248
2.238
2.206
1.864
1.846
1.823
1.766
1.742
1.654
1.603
1.449
1.387
1.375
1.335
1.314
1.300
1.276
1.076
0.995
0.987
0.974
0.955
0.917
0.665
0.652
0.645
0.632
0.619
0.606
0.138
0.112
0.104
TBSO
Me
Me
PMBO
Me
OTIPS
Me
SiEt3O
OH
O
3.18
1.77
1.45
0.49
1.00
0.43
0.60
2.79
1.74
0.44
1.33
0.51
1.03
2.65
1.14
0.51
0.32
1.28
2.61
4.32
1.17
1.09
6.74
22.83
27.82
8.50
6.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


213.40
159.01
134.87
134.78
134.67
133.92
133.33
131.38
131.19
129.32
129.28
117.31
117.06
113.70
97.49
92.64
82.19
81.96
81.90
79.86
71.83
70.79
70.73
69.23
68.72
68.11
67.44
64.16
55.28
43.91
43.61
43.09
42.60
42.44
42.27
38.17
35.80
35.20
35.11
31.81
31.56
25.94
24.19
20.65
18.31
18.26
16.13
16.05
15.27
15.05
12.68
TBSO
Me
Me
PMBO
Me
OTIPS
Me
OH
O
O
SiEt3
200
180
160
140
120
100
80
60
40
20
0
ppm


8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2.30
1.00
1.81
2.13
2.33
0.93
1.13
3.15
4.17
3.92
2.25
2.20
1.30
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32.21
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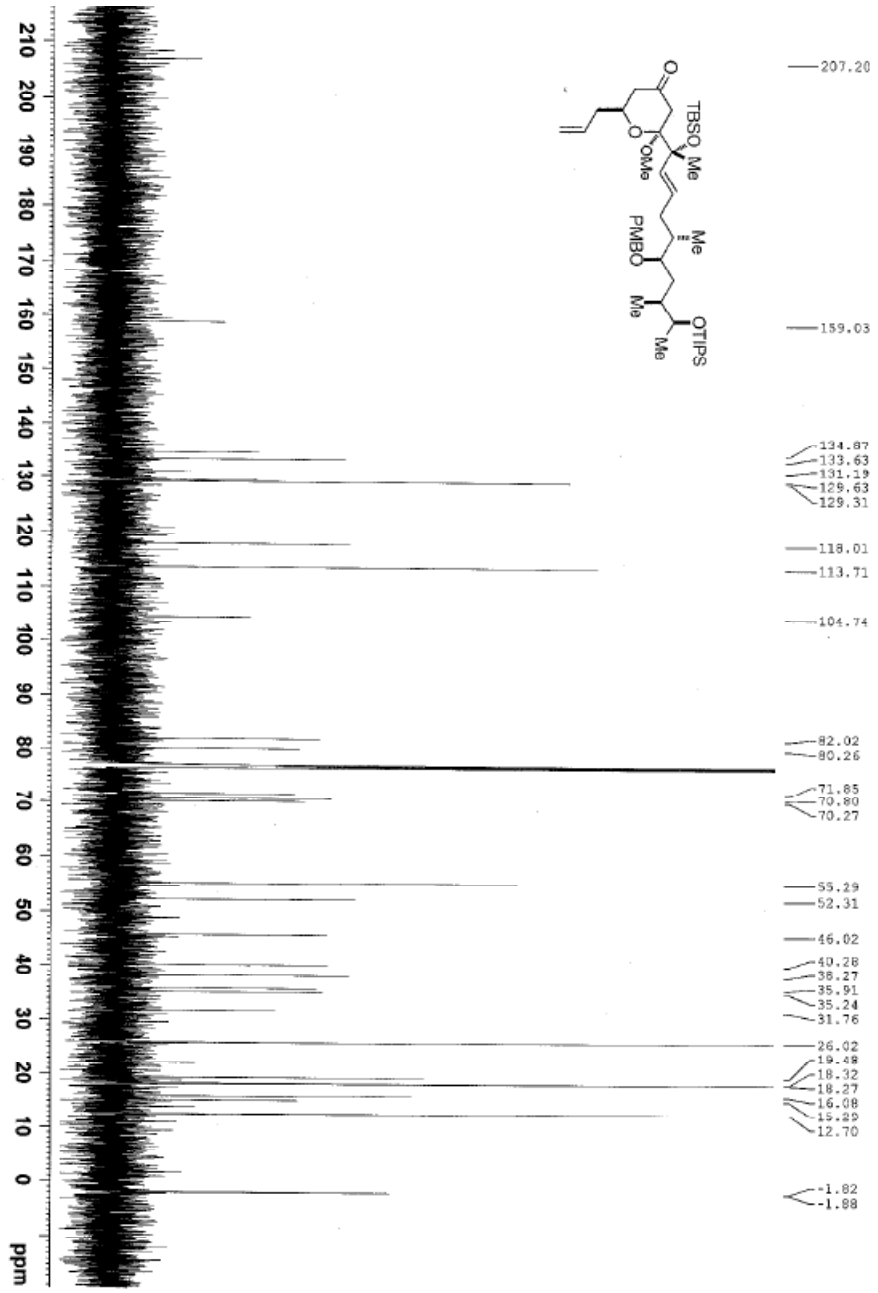
Me
OMe
PMBO
Me
Me
Me
OTIPS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O&Me
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Me
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134.87
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131.19
129.63
129.31
118.01
113.71
104.74
82.02
80.26
71.85
70.80
70.27
55.29
52.31
46.02
40.28
38.27
35.91
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26.02
19.48
18.32
18.27
16.08
15.29
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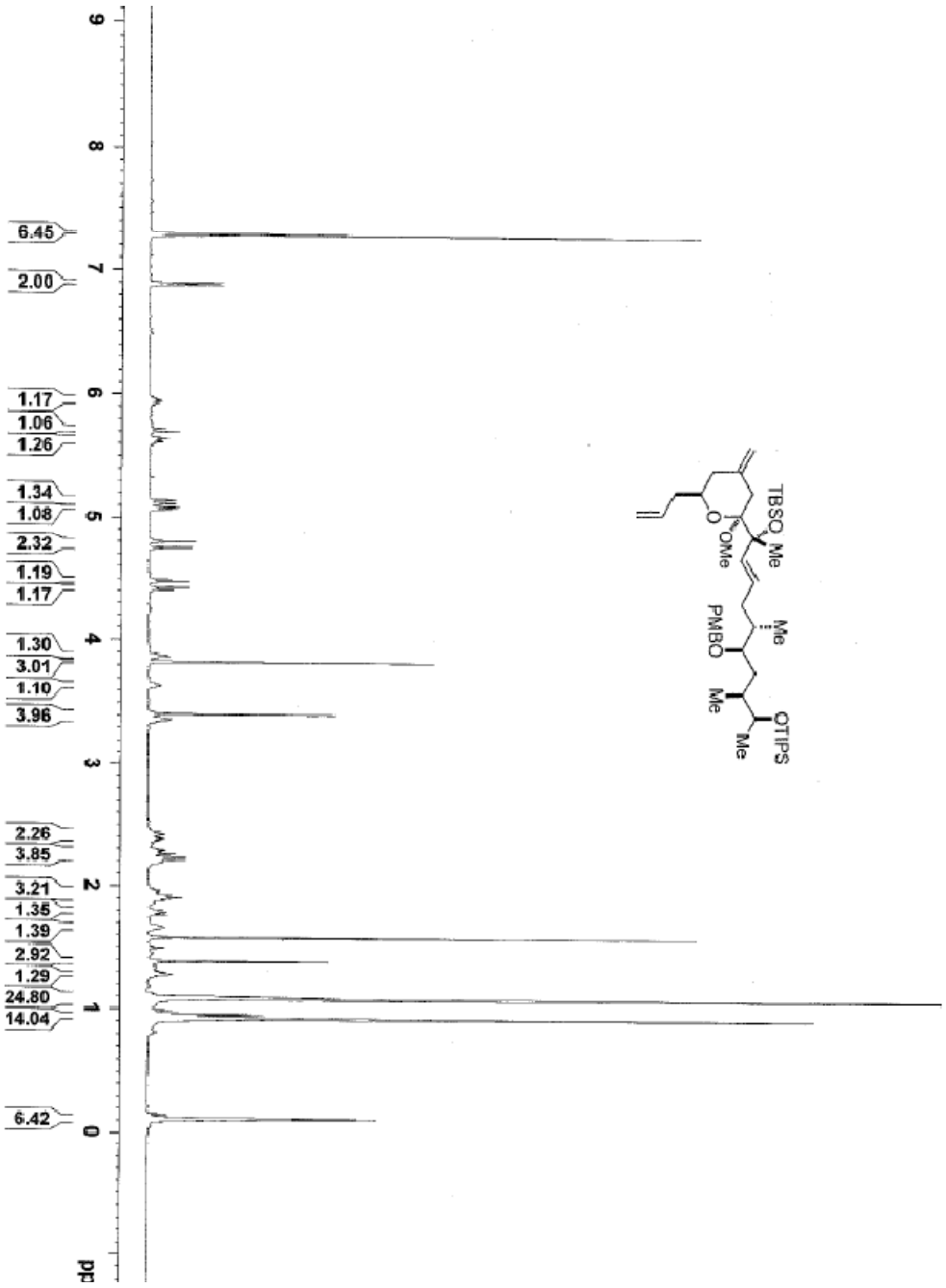
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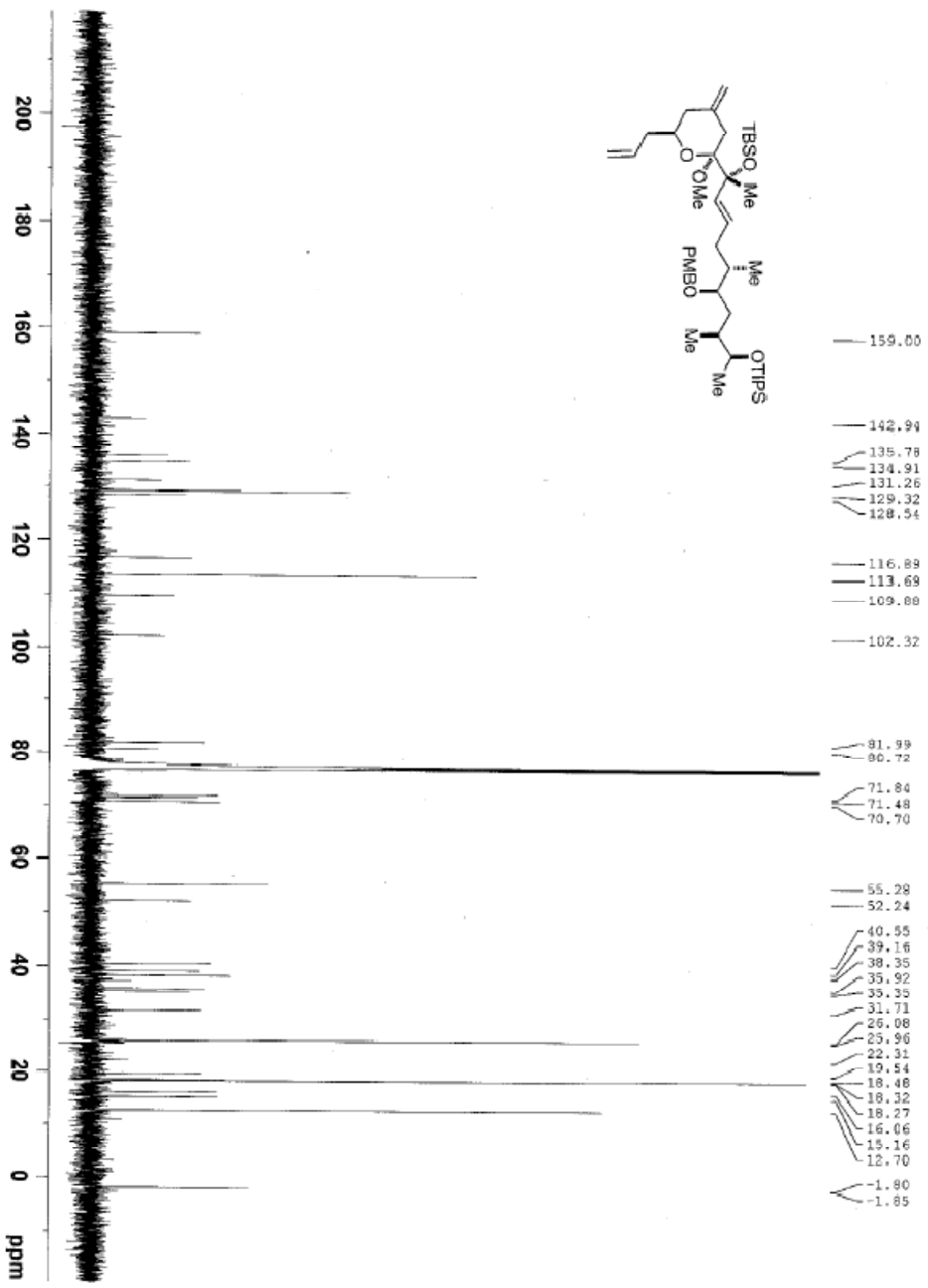
1.17
1.06
1.26
1.34
1.08
2.32
1.19
1.17
1.30
3.01
1.10
3.96
2.26
3.85
3.21
1.35
1.39
2.92
1.29
24.80
14.04
6.42
TBSO
Me
OMe
O
Me
PMBO
Me
OTIPS
Me
ppm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Me
OMe
Me
PMBO
Me
OTIPS
Me
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142.94
135.78
134.91
131.26
129.32
128.54
116.89
113.69
109.88
102.32
81.99
80.72
71.84
71.48
70.70
55.28
52.24
40.55
39.16
38.35
35.92
35.35
31.71
26.08
25.96
22.31
19.54
18.48
18.32
18.27
16.06
15.16
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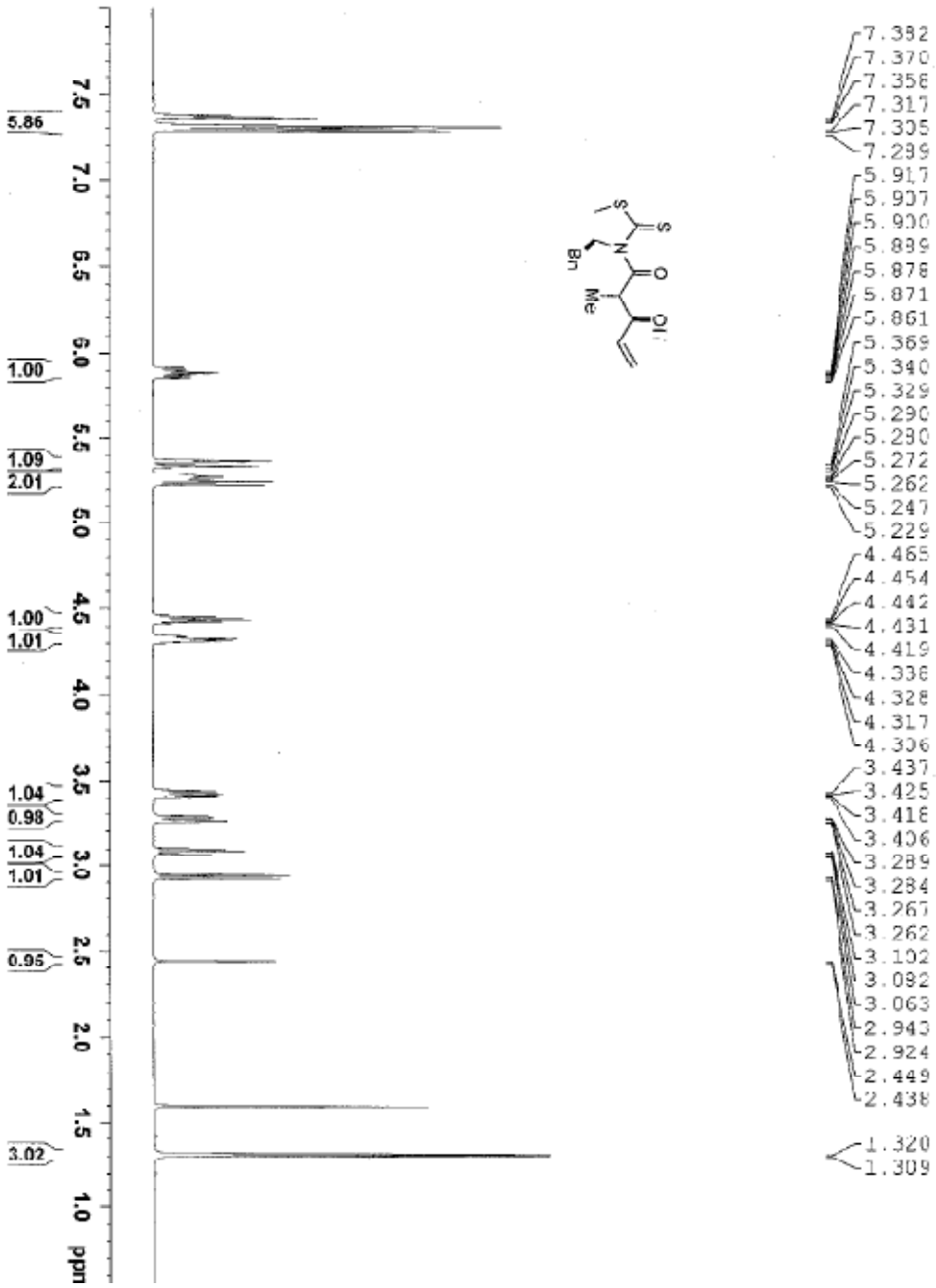
-1.80
-1.85
200
180
160
140
120
100
80
60
40
20
0
ppm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5.907
5.900
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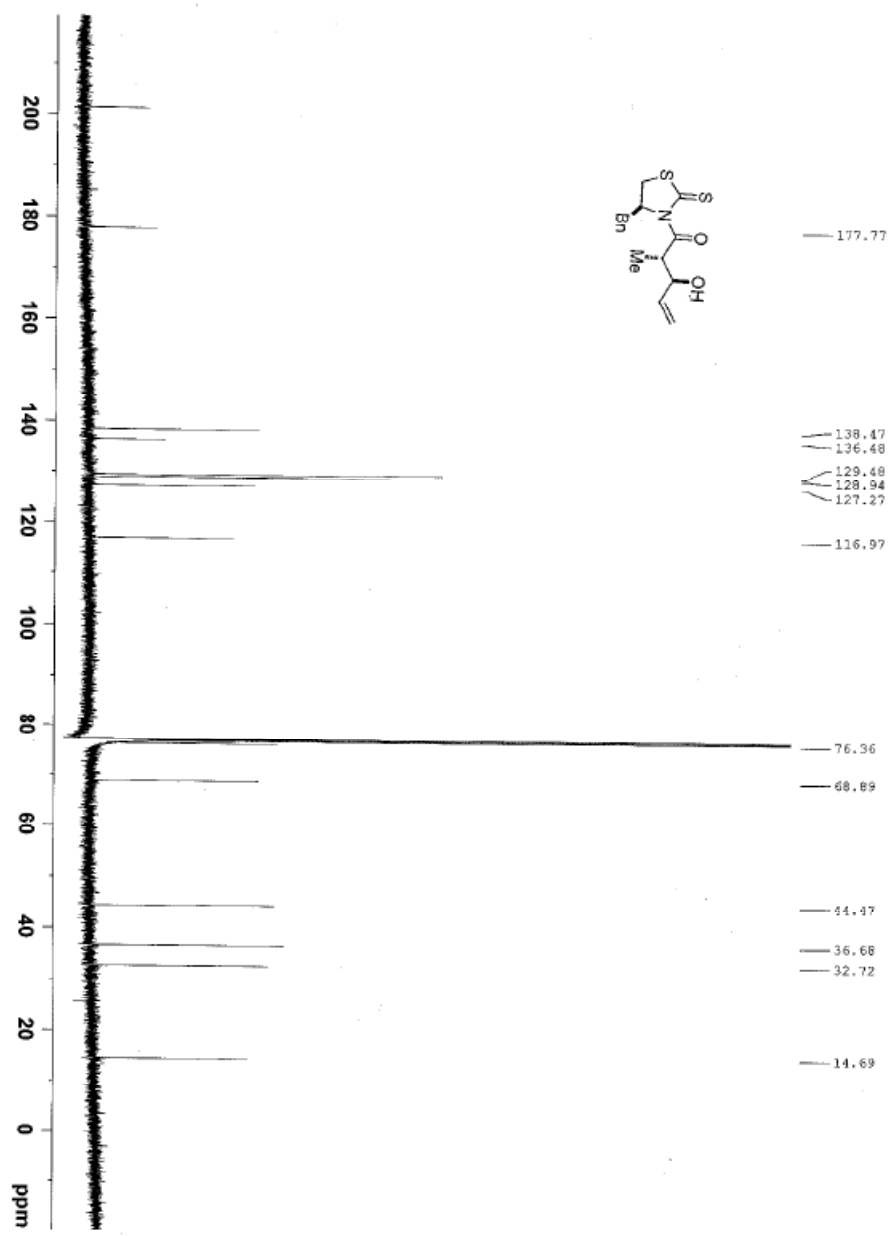
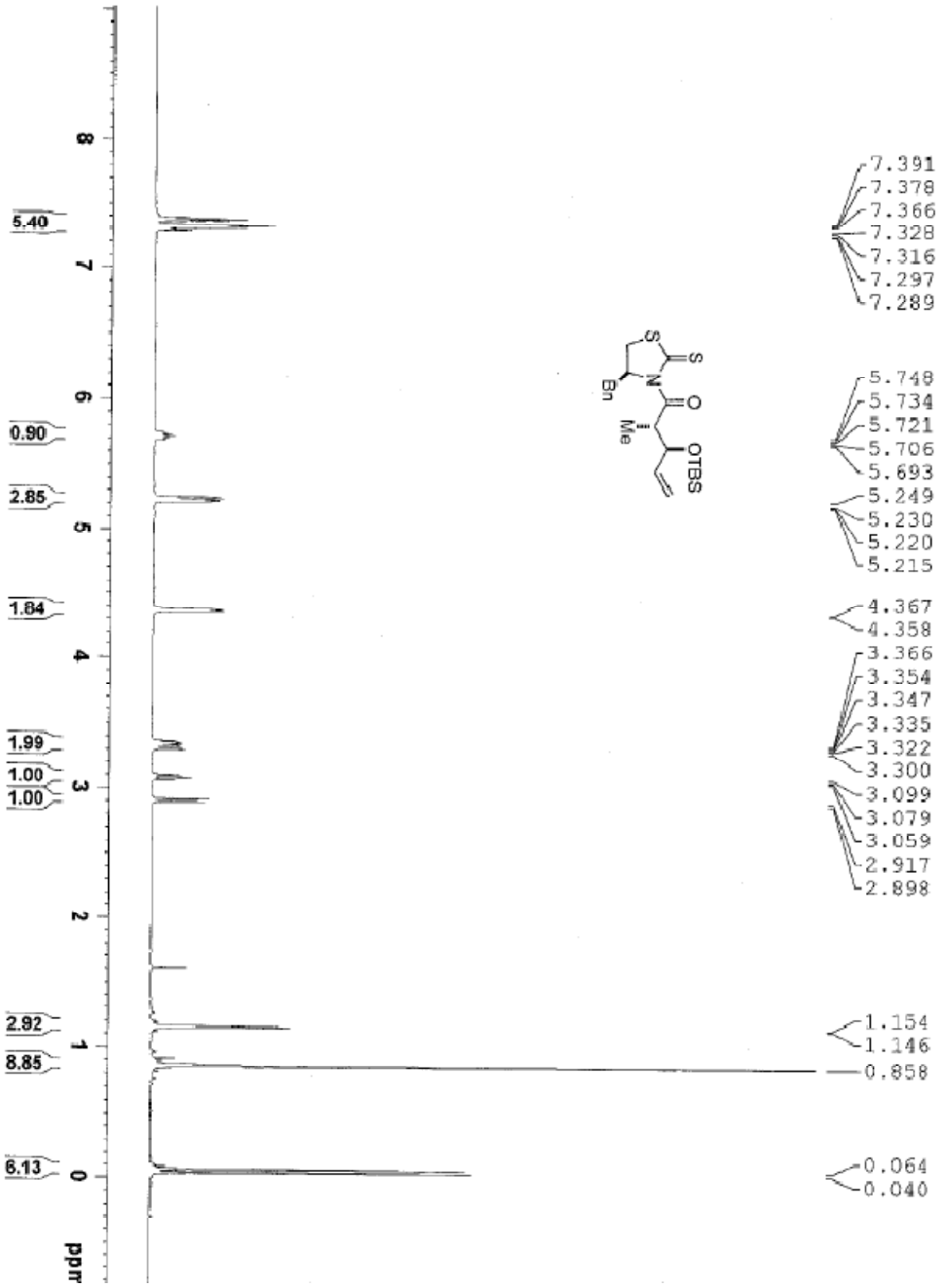
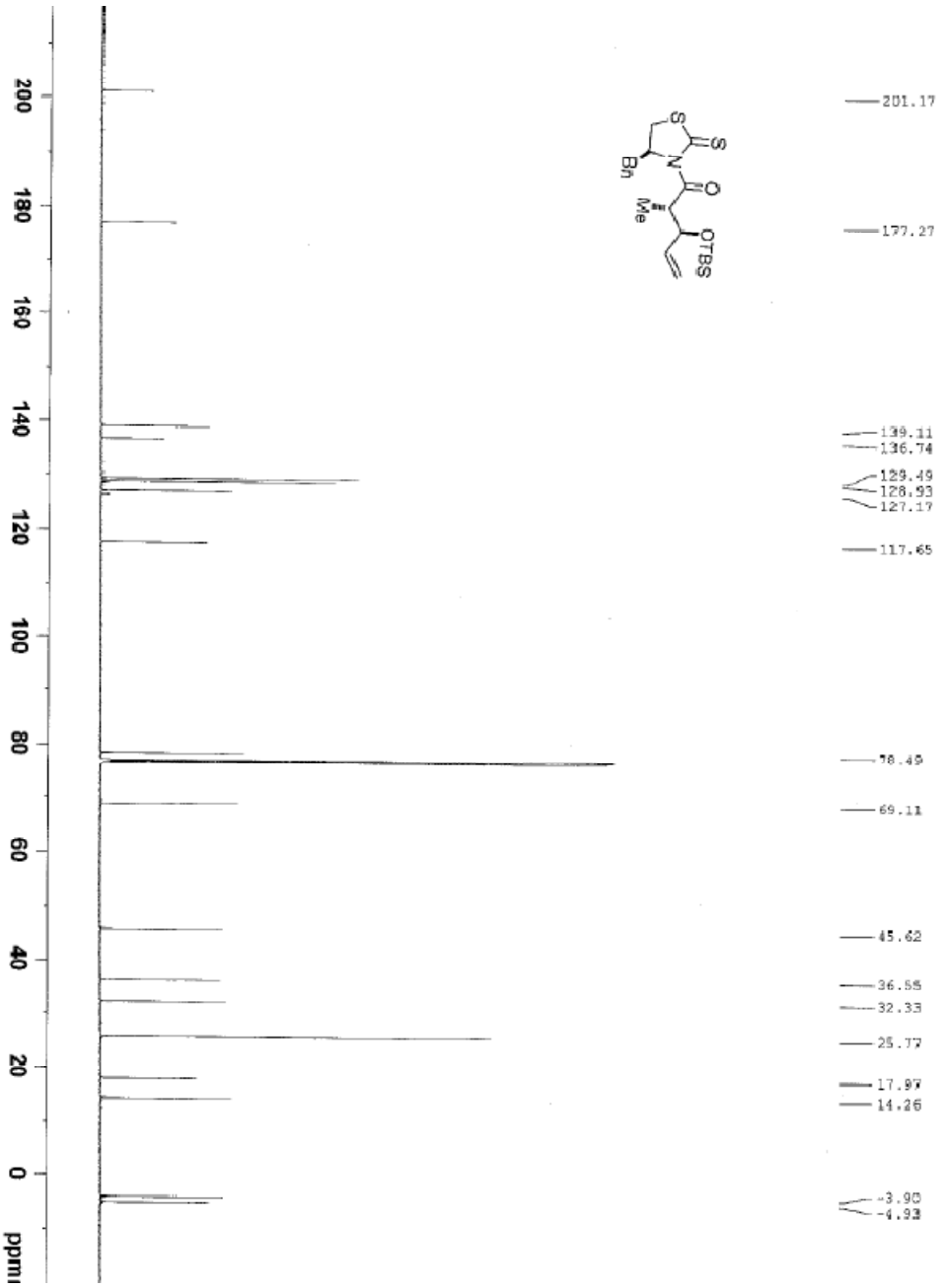
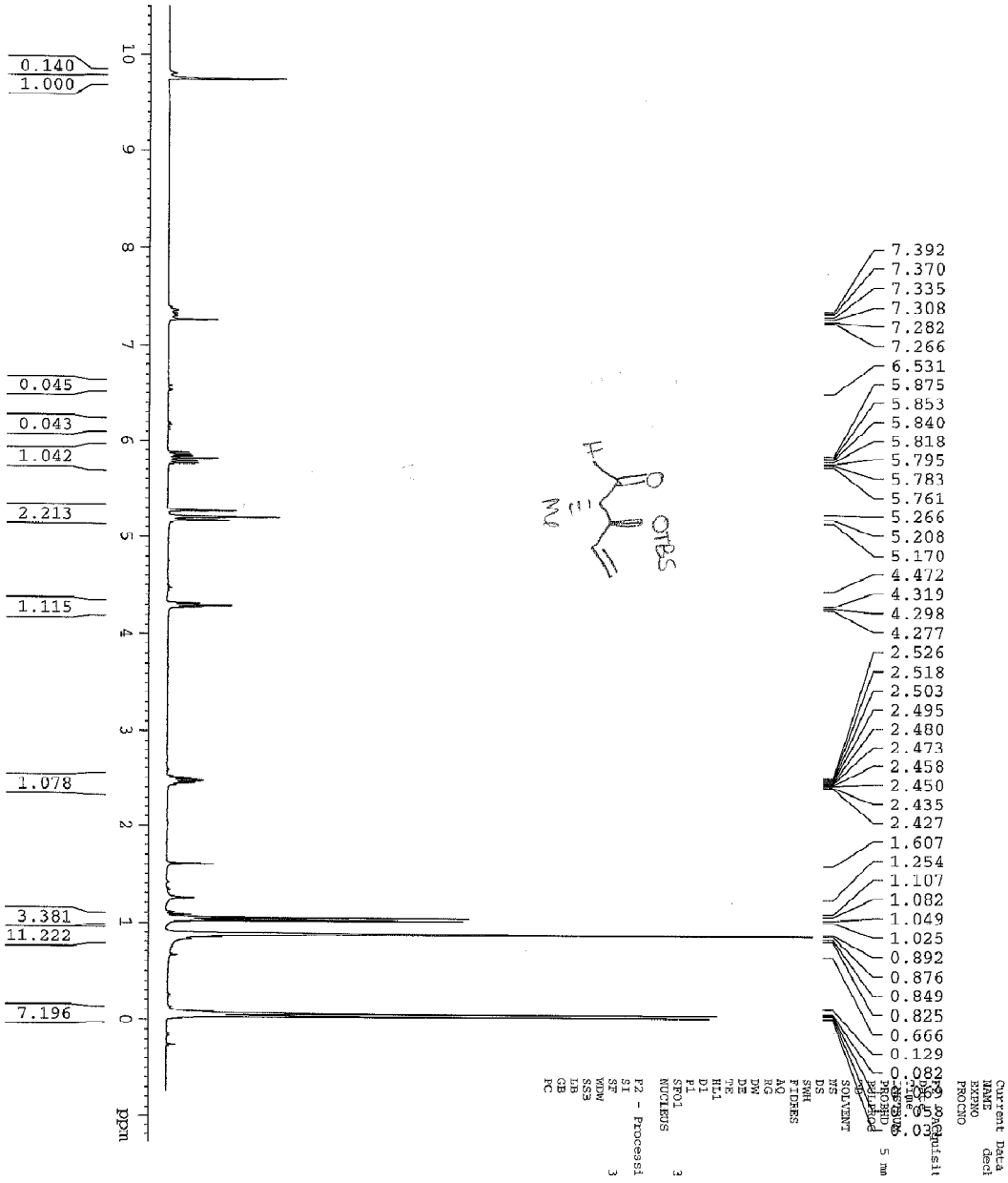
5.871
5.861
5.369
5.340
5.329
5.290
5.280
5.272
5.262
5.247
5.229
4.465
4.454
4.442
4.431
4.419
4.336
4.328
4.317
4.306
3.437
3.425
3.416
3.406
3.289
3.284
3.267
3.262
3.102
3.082
3.063
2.943
2.924
2.449
2.438
1.320
1.309
5.86
1.00
1.09
2.01
1.00
1.01
1.04
0.98
1.04
1.01
0.95
3.02
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
S
S
N
O
OH
Bn
Me


177.77
138.47
136.48
129.48
128.94
127.27
116.97
76.36
68.89
44.47
36.68
32.72
14.69
200
180
160
140
120
100
80
60
40
20
0
ppm
Bn
Me
OH


7.391
7.378
7.366
7.328
7.316
7.297
7.289
5.748
5.734
5.721
5.706
5.693
5.249
5.230
5.220
5.215
4.367
4.358
3.366
3.354
3.347
3.335
3.322
3.300
3.099
3.079
3.059
2.917
2.898
1.154
1.146
0.858
0.064
0.040
5.40
0.90
2.85
1.84
1.99
1.00
1.00
2.92
8.85
6.13
Bn
Me
OTBS
ppm


201.17
177.27
139.11
136.74
129.49
128.93
127.17
117.65
78.49
69.11
45.62
36.55
32.33
25.77
17.97
14.26
-3.90
-4.93
ppm
S
S
N
O
Bn
Me
OTBS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0.045
0.043
1.042
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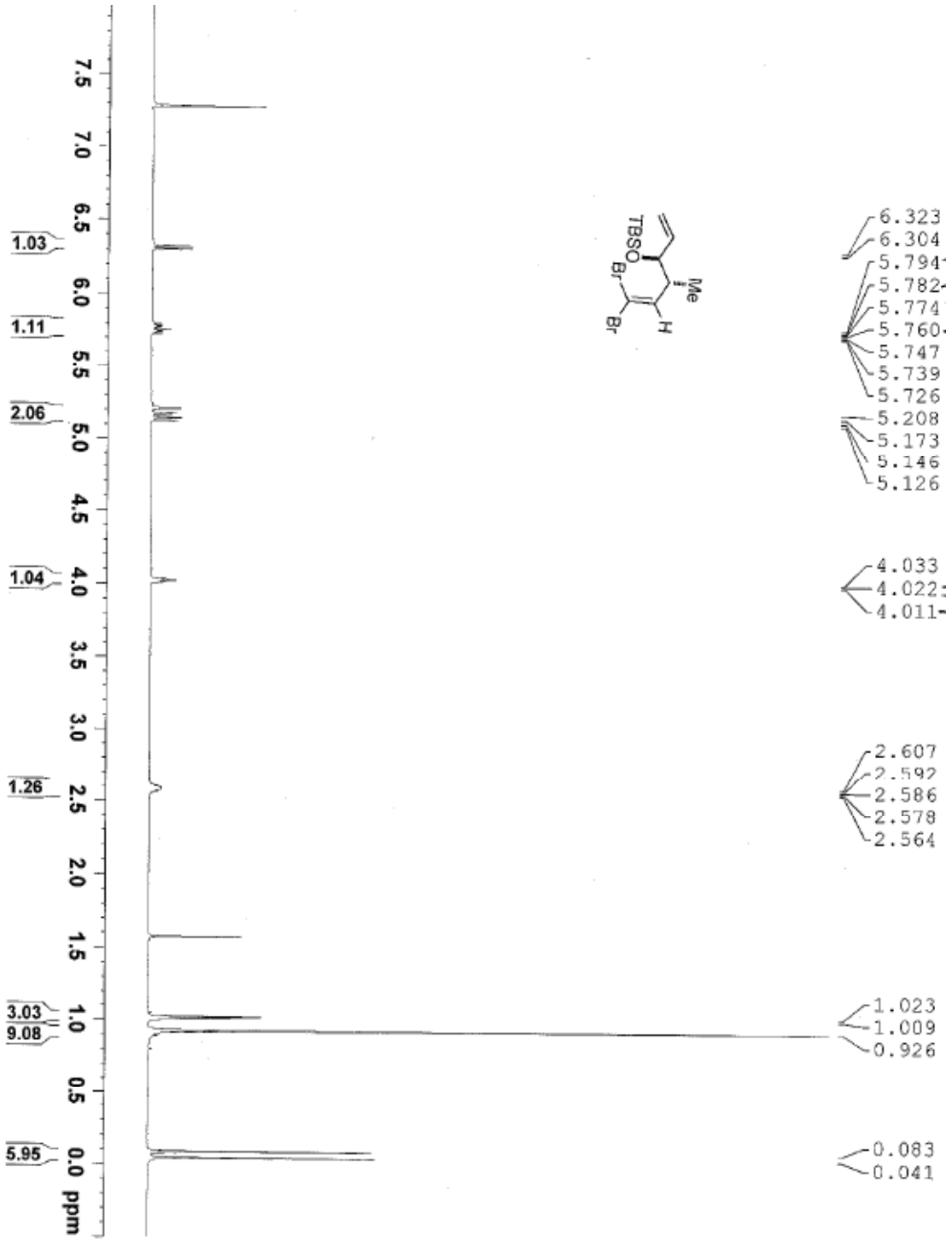
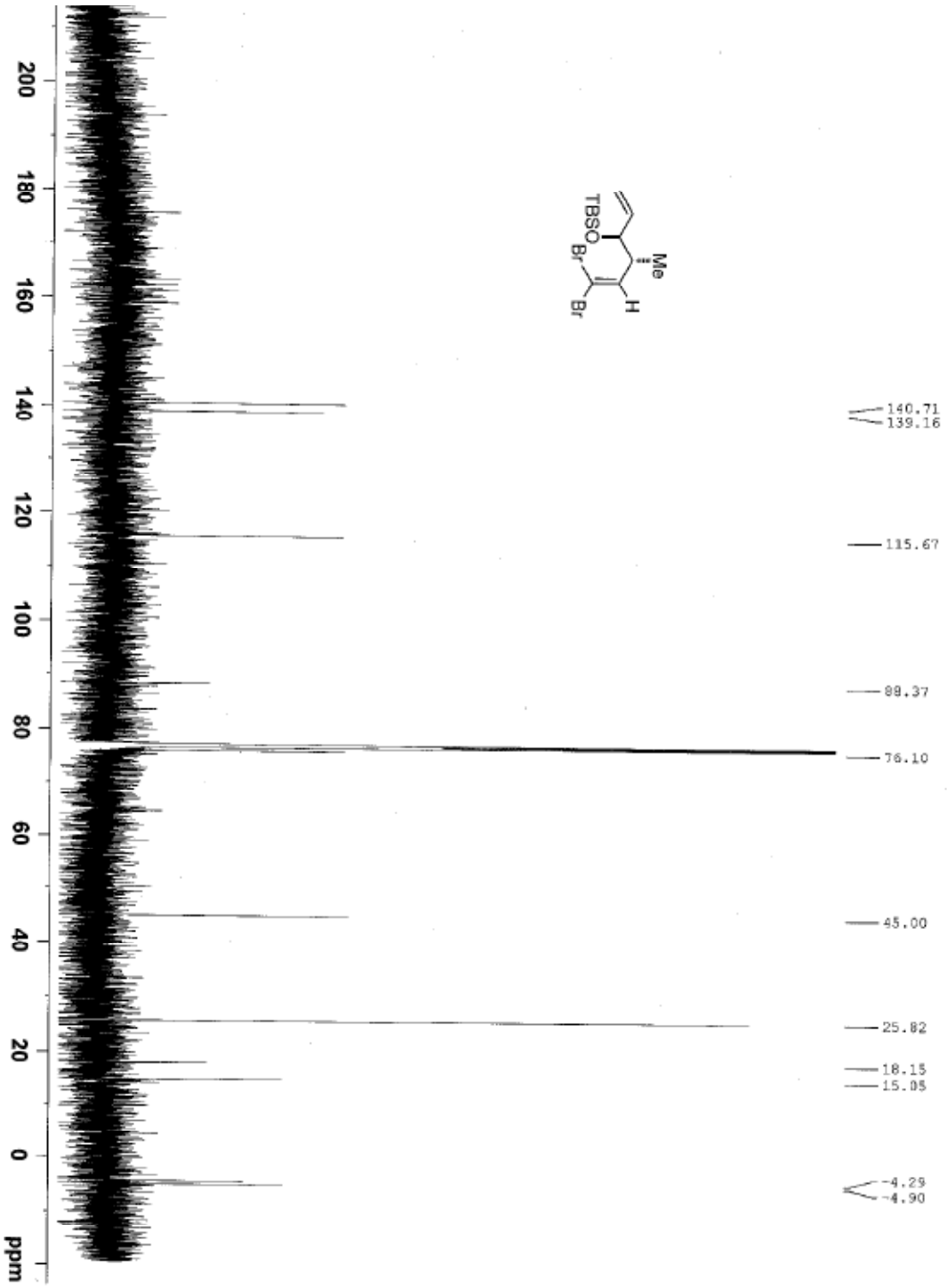
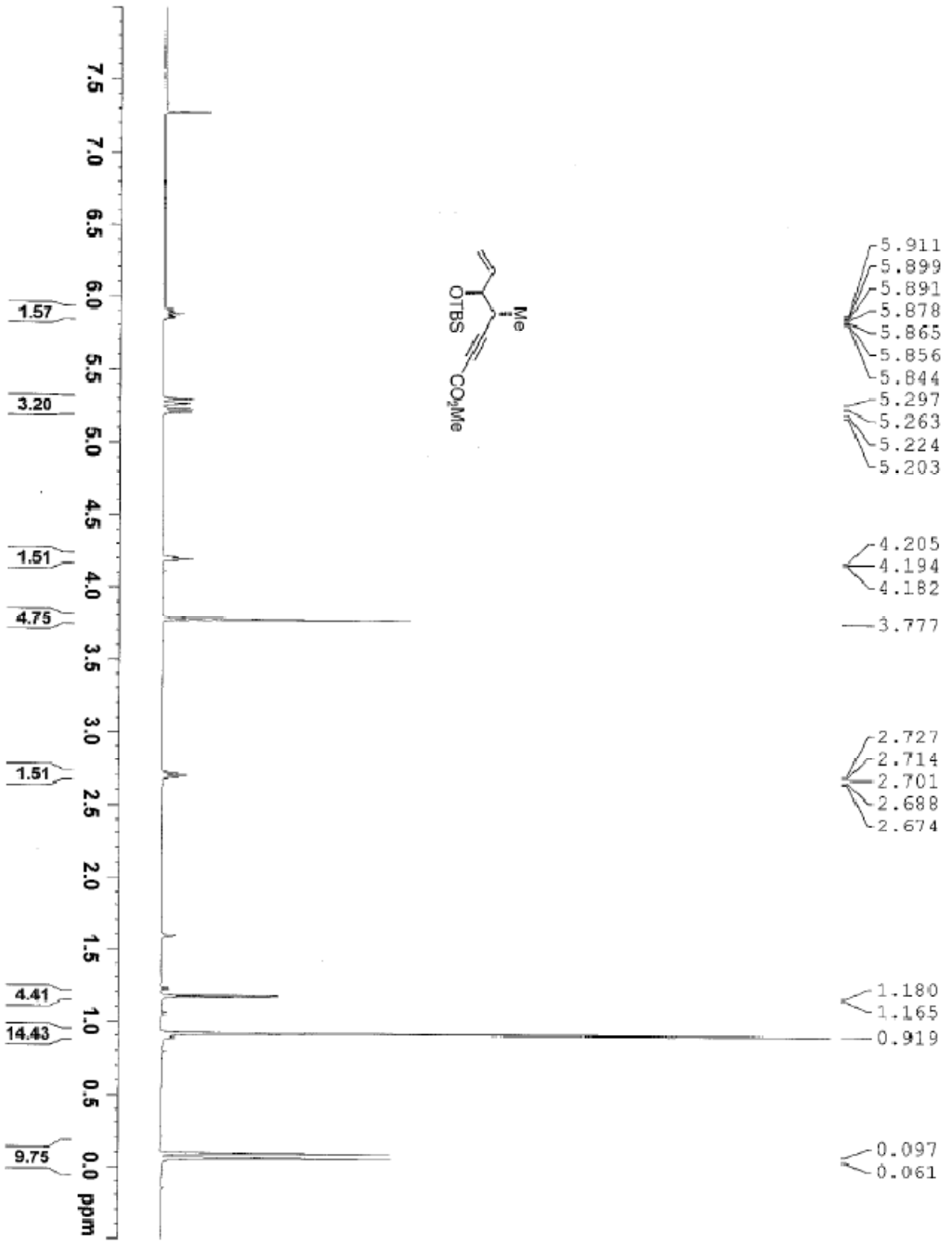
1.078
3.381
11.222
7.196
ppm
OTBS
7.392
7.370
7.335
7.308
7.282
7.266
6.531
5.875
5.853
5.840
5.818
5.795
5.783
5.761
5.266
5.208
5.170
4.472
4.319
4.298
4.277
2.526
2.518
2.503
2.495
2.480
2.473
2.458
2.450
2.435
2.427
1.607
1.254
1.107
1.082
1.049
1.025
0.892
0.876
0.849
0.825
0.666
0.129
0.082
0.000
Current Data
NAME
EXPNO
PROCNO
deci
SOLVENT
NUCLEUS
F2 - Processi
SF
WDW
SSB
LB
GB
PC


TBSO
Br
Br
Me
H
6.323
6.304
5.794
5.782
5.774
5.760
5.747
5.739
5.726
5.208
5.173
5.146
5.126
4.033
4.022
4.011
2.607
2.592
2.586
2.578
2.564
1.023
1.009
0.926
0.083
0.041
1.03
1.11
2.06
1.04
1.26
3.03
9.08
5.95
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


TBSO
Br
Br
Me
H
200
180
160
140
120
100
80
60
40
20
0
ppm
140.71
139.16
115.67
89.37
76.10
45.00
25.82
18.15
15.05
-4.29
-4.90


OTBS
Me
CO2Me
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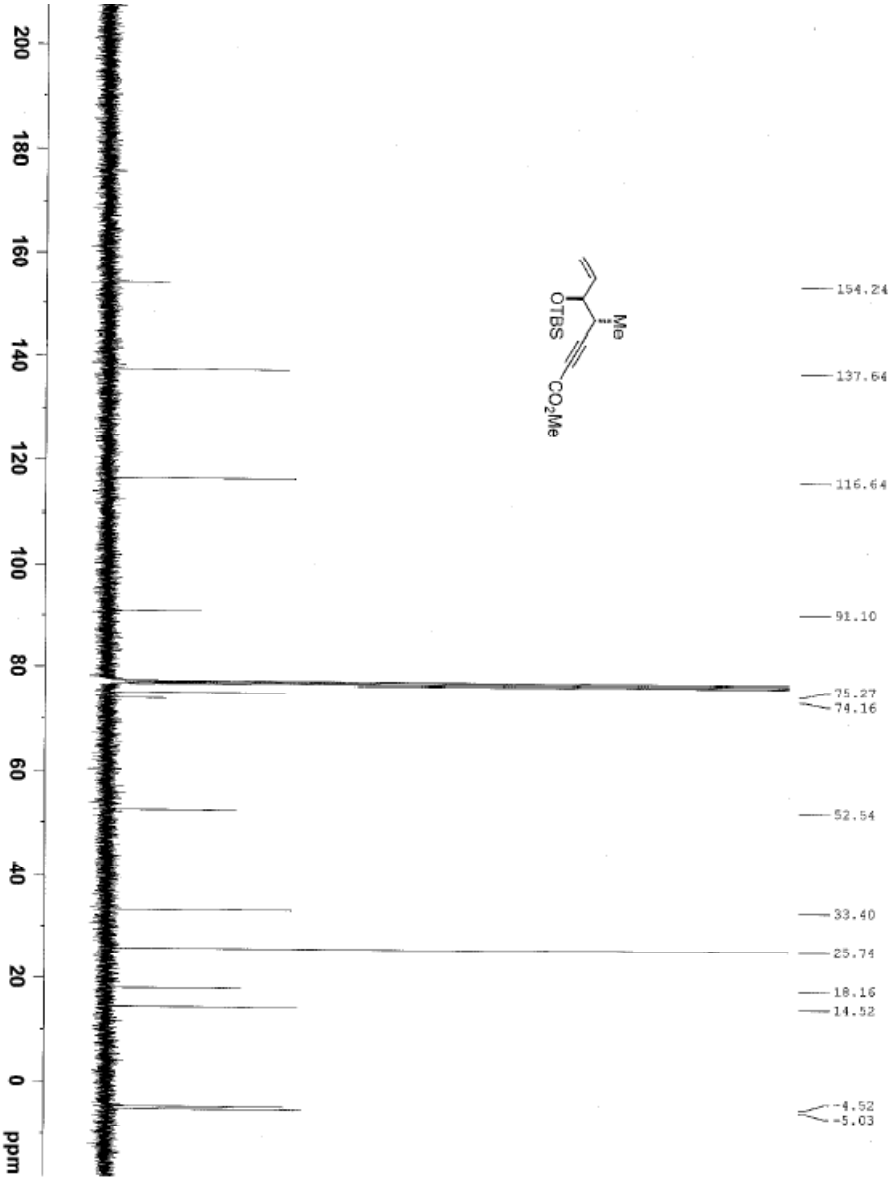
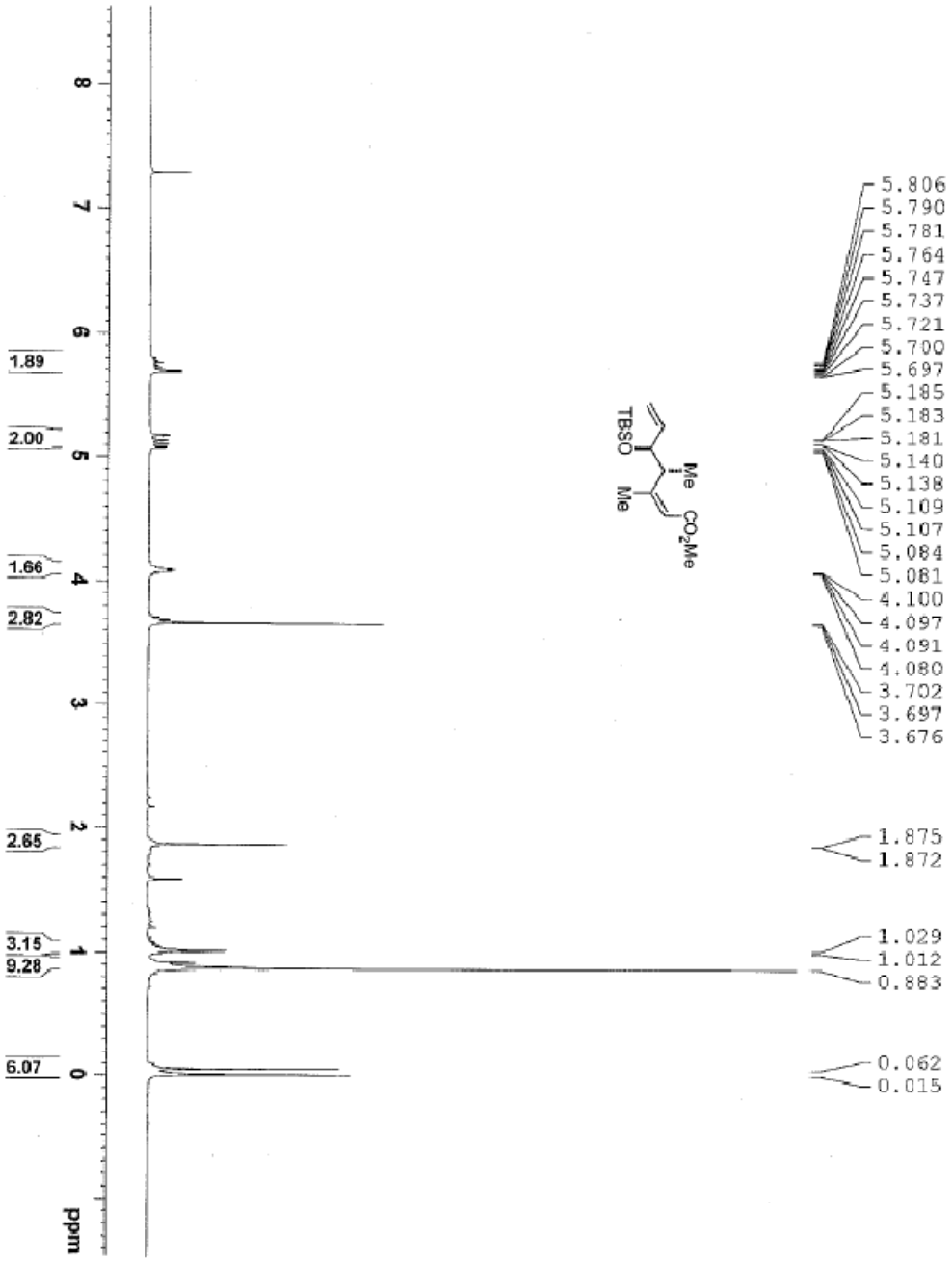
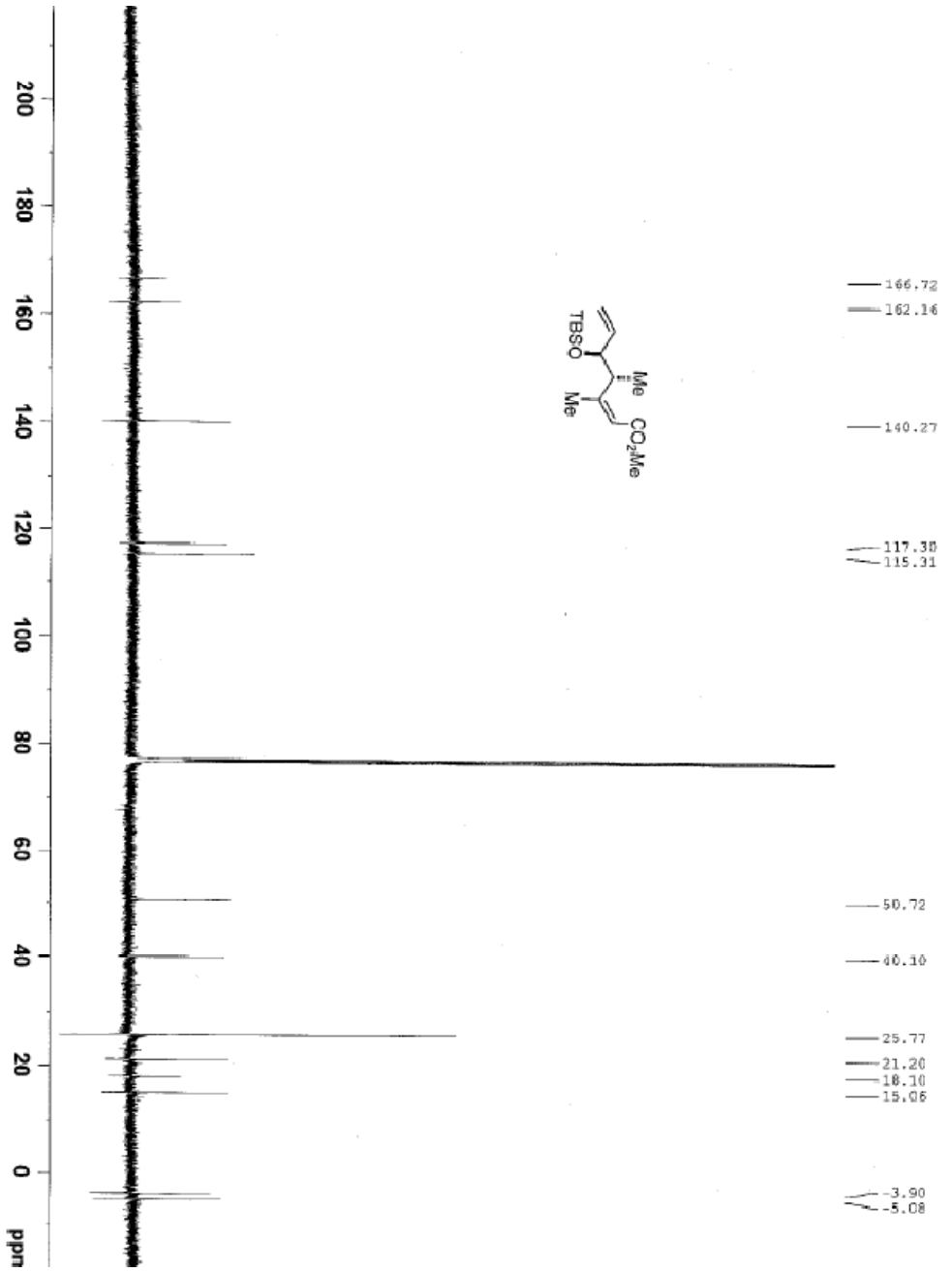
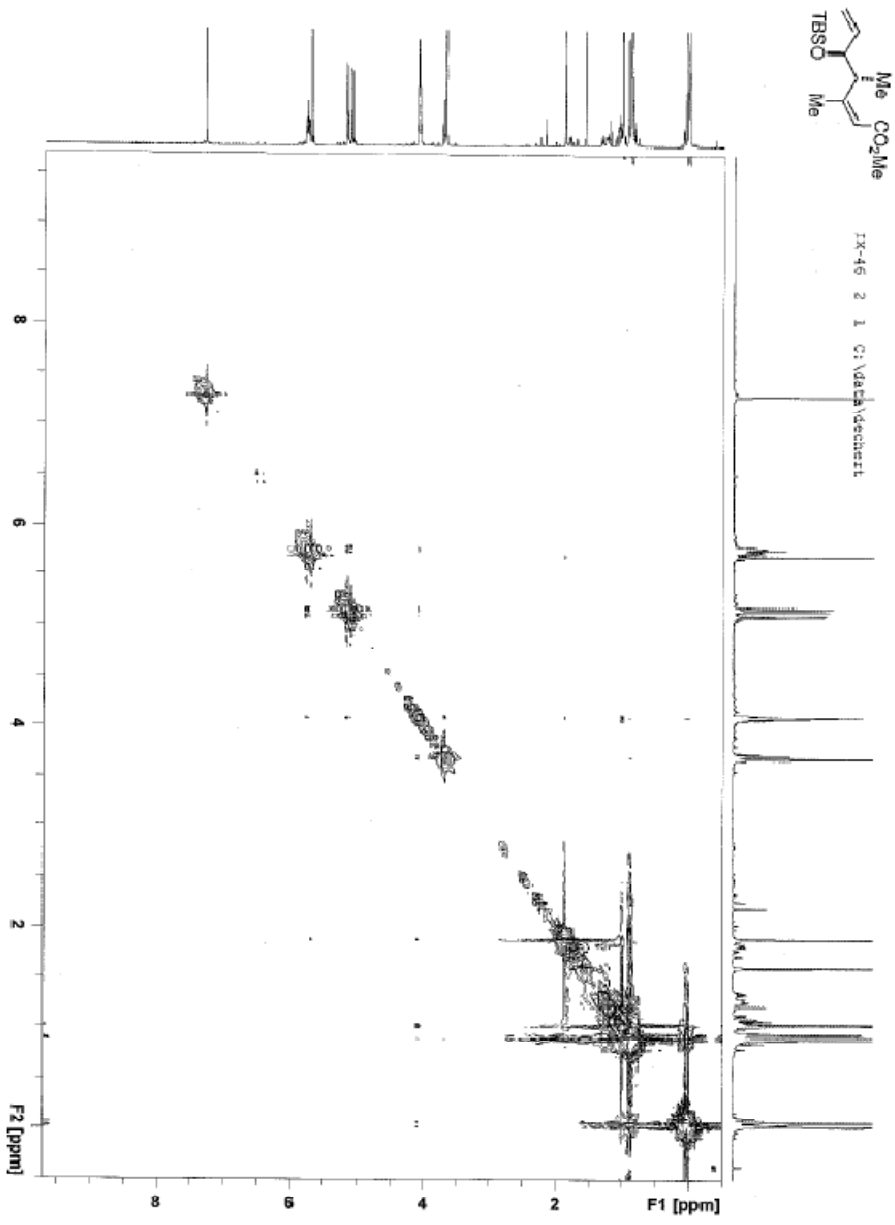
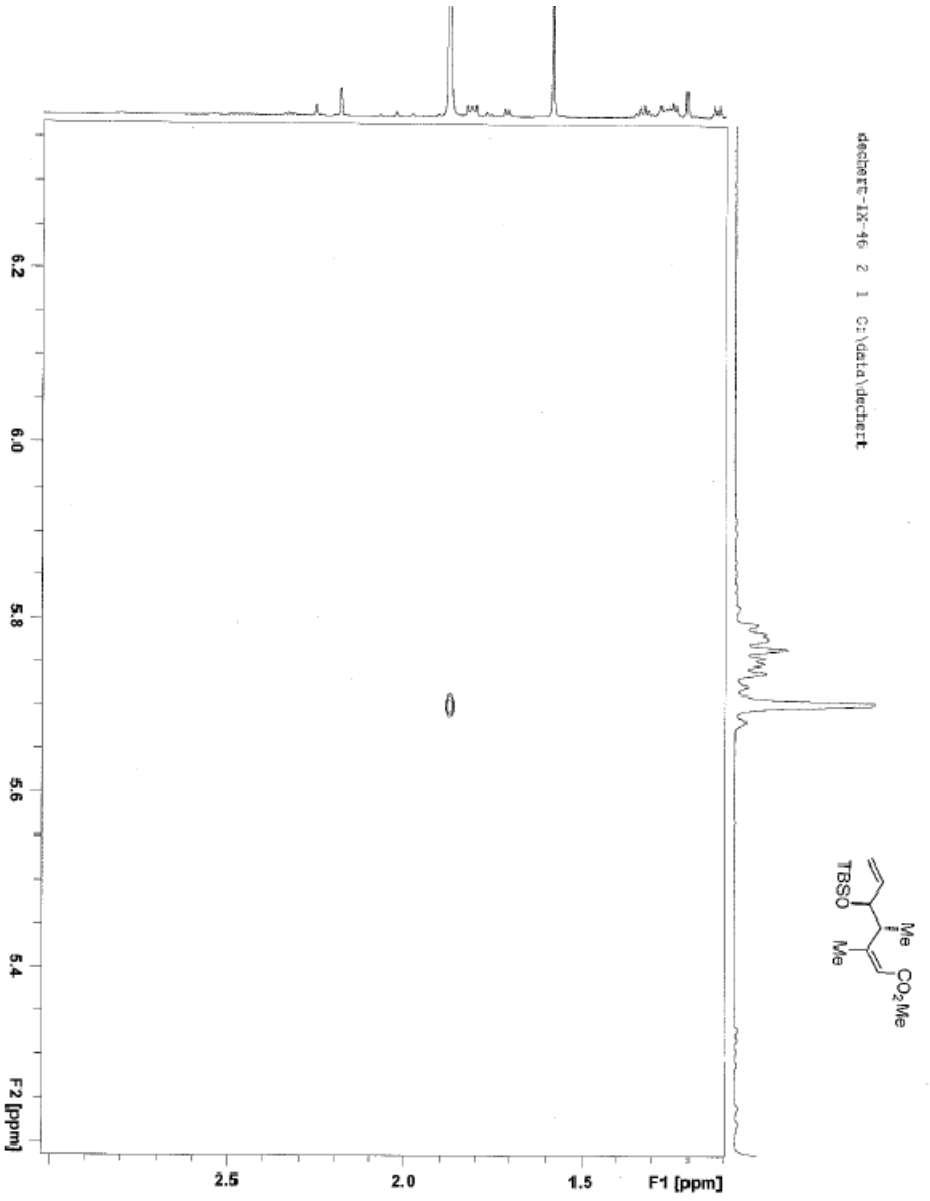
3.20
1.51
4.75
1.51
4.41
14.43
9.75
5.911
5.899
5.891
5.878
5.865
5.856
5.844
5.297
5.263
5.224
5.203
4.205
4.194
4.182
3.777
2.727
2.714
2.701
2.688
2.674
1.180
1.165
0.919
0.097
0.061
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


200
180
160
140
120
100
80
60
40
20
0
ppm
OTBS
Me
CO2Me
154.24
137.64
116.64
91.10
75.27
74.16
52.54
33.40
25.74
18.16
14.52
-4.52
-5.03


5.806
5.790
5.781
5.764
5.747
5.737
5.721
5.700
5.697
5.185
5.183
5.181
5.140
5.138
5.109
5.107
5.084
5.081
4.100
4.097
4.091
4.080
3.702
3.697
3.676
1.875
1.872
1.029
1.012
0.883
0.062
0.015
TBSO
Me
Me
CO2Me
1.89
2.00
1.66
2.82
2.65
3.15
9.28
6.07
ppm


200
180
160
140
120
100
80
60
40
20
0
ppm
TBSO
Me
Me
CO2Me
166.72
162.16
140.27
117.38
115.31
50.72
40.10
25.77
21.20
18.10
15.06
-3.90
-5.08


TBSO
Me
CO2Me
Me
TX-45 2 1 C:\data\decent
F2 [ppm]
F1 [ppm]
8
6
4
2


dechert-IX-46 2 1 C:\data\dechert
6.2
6.0
5.8
5.6
5.4
F2 [ppm]
2.5
2.0
1.5
F1 [ppm]
TBSO
Me
Me
CO2Me

References

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(2) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J.* Org. *Chem*. **2001**, *66*, 894.

(3) Crimmins, M. T.; She, J. *Synlett* **2004**, *8*, 1371.

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