

Towards The Total Synthesis Of Tetrafibricin

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University of Pittsburgh, 2021

This work describes the continuation of the total synthesis of the marine natural product Tetrafibricin in the Curran Group. Retrosynthetic analysis of the framework of tetrafibricin lends to a convergent synthesis using 6 fragments: C1-C8, C9-C13, C14-C20, C21-C30, C31-C34 and C35-C40. Following the last attempt that yielded approximately 1 mg of fully protected tetrafibricin, this attempt features scale up and reaction selection improvements in order to provide enough of the fragments in order to realize the successful coupling strategy demonstrated in previous work. The synthesis was unsuccessful in that a material bottleneck occurred for the C21-C30 fragment, leading to the publication of the total synthesis by another academic group.

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1.0 Introduction

1.1 Tetrafibricin

Platelet aggregation is an important function in the wound healing process as a response to damaged blood vessels. When the receptors GPIIb/IIIa on the surface of the platelet are bound by an agonist, these receptors highly increase affinity toward fibrinogen. This allows fibrinogen to act as a crosslinker between platelet cells and adhere to the location of the damaged arterial endothelium. This aggregation is the beginning of the normal clotting process as a response to arterial damage. Normal agonists of the fibrinogen receptor include collagen, thrombin, and ADP.

1

Due to age or buildup of plaques, arteries become more constricted and easily damaged, thereby reducing the ability of blood to circulate to the heart. In the event of inflammation of a blood vessel, the occurrence of platelet aggregation at a constricted site can cause blockage, leading to heart attack or stroke. Inhibition to the mechanism of normal platelet aggregation in the event of a coronary blockage provides a potential target to reverse those blockages.

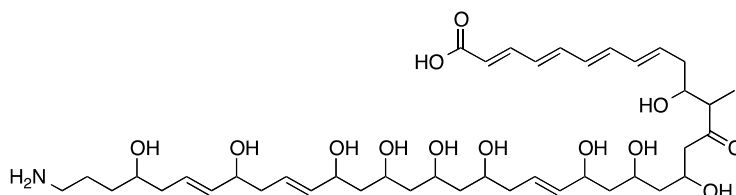
Recently, therapeutic fibrinogen antagonists have been reported,² in which many are peptidomimetic compounds of the site of fibrinogen that binds to its receptor, which competitively occupy the receptor site and disrupt platelet aggregation. Issues with these peptide mimics are a low half-life in vivo, and a lower affinity for the fibrinogen receptor binding site than fibrinogen itself.

Tetrafibricin is a fibrinogen receptor antagonist isolated from cultures of *Streptomyces neyagawaensis* NR0577.³ In biochemical assays, tetrafibricin is a strong competitive inhibitor (Ki

= 9.9 nm) to biotinylated fibrinogen binding to immobilized glycoprotein receptor GPIIb/IIIa, as well as an inhibitor to fibrinogen binding to its receptors ($IC_{50} = 46$ nM). ADP-, collagen-, and thrombin-induced human platelet aggregation was also inhibited at IC_{50} values of 5.6, 11.0, and 7.6 μ M respectively.² The ability of tetrafibricin to achieve strong in vitro inhibition of platelet aggregation makes it a good potential candidate for treatment of heart attack and stroke.⁴

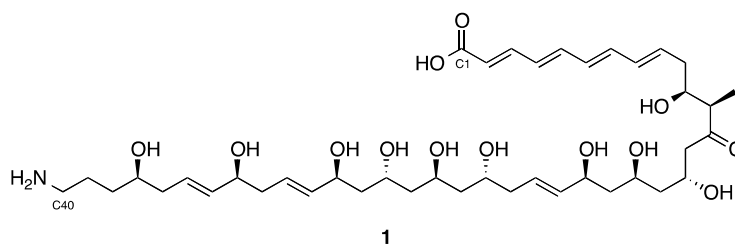
The structure of tetrafibricin was elucidated by the Kamiyama group in 1993, by carrying out various NMR, MS and other experiments.⁵ The molecular formula was determined as $C_{41}H_{67}NO_{13}$ from HRFAB-MS, and a combination of 1H NMR, ^{13}C NMR, 1H - 1H COSY, HSQC and HMBC experiments were used to deduce partial structures. Additional NMR experiments on a solution of *N*-acetyldihydrotetrafibricin methyl ester were carried out to establish the complete connectivity of those partial structures, such that a two-dimensional structure of tetrafibricin was proposed (Figure 1.1).

Figure 1.1 - Kamiyama's Proposed 2D Structure of Tetrafibricin



In 2003, the Kishi group reported the structural elucidation of the complete stereochemistry of tetrafibricin by comparison of its data with NMR databases of known compounds in achiral and chiral solvents (Figure 1.2).⁶ This approach came from a universal NMR database method that Kishi developed to assign the relative and absolute configuration of unknown compounds without modification or degradation.⁷

Figure 1.2 - Kishi's Elucidation of the Stereochemistry of Tetrafibricin 1



The interesting biological properties of **1** and its unique, complex structure containing a primary amine, a conjugated tetraenoic acid, and multiple 1,3- and 1,5-diol groups render tetrafibricin an excellent target for synthetic study. The development of a convergent and efficient synthesis of tetrafibricin will aid in confirming its structure, supplying material for biological study, as well as potentially facilitate structure-activity relationship studies designed to probe its biological properties.

The publications generated through the synthetic efforts put forth in the Curran group formed the basis for the strategy to prepare and couple the fragments of tetrafibricin⁸ To our knowledge at the time the work in this document was performed, there were four other research groups that had published their work towards the total synthesis of tetrafibricin. Cossy's group synthesized the C1-C13, C15-C25, and C27-C40 fragments of tetrafibricin by a sequence of chemoselective cross-metathesis reactions and enantioselective allyltitanations of aldehydes.⁹ Krische's group reported the synthesis and coupling of the C31-C40 and C21-C30 fragments through a series of asymmetric iridium catalyzed hydrogen transfer carbonyl allylation reactions and Grubb's olefin metathesis reactions.¹⁰

Roush's group reported the synthesis of the C1-C19 fragment of tetrafibricin via a highly diastereoselective double allylboration developed in their laboratory.¹¹ Later, they also reported improved double allylboration reagents to more efficiently allow access to (*E*)-1,5-*syn*-diols and demonstrated their application to the synthesis of the C23-C40 carbon framework of tetrafibricin.¹²

Friestad's group published an application of iterative Julia-Kocienski couplings of units with defined stereogenic centers to afford the repeating 1,5-polyol motif of C27-C40 fragment of tetrafibricin.¹³

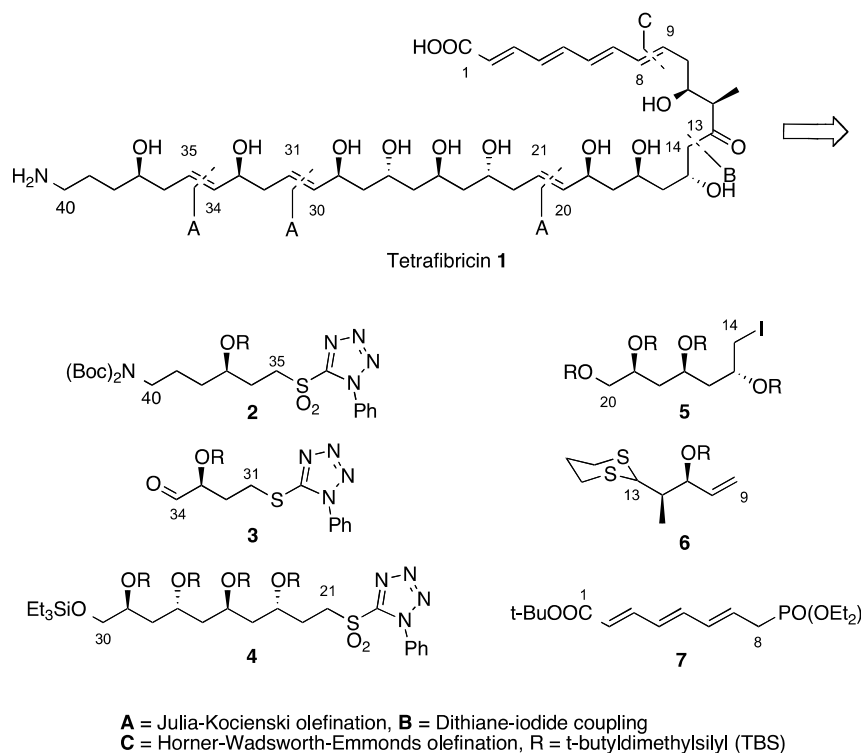
The Curran group's synthetic work on tetrafibricin was stopped in 2013 following a paper outlining the total synthesis of *N*-acetyl dihydrotetrafibricin methyl ester was published.¹⁴ They described the instability of tetrafibricin while attempting to isolate it in its pure form following global deprotection. They chose to proceed to instead complete the synthesis of a closely related derivative that Kishi had used in the spectroscopic determination tetrafibricin's structure, as this derivative was determined to be stable enough to be characterized spectroscopically and matched to previously obtained data.⁶ Characterization of the derivatized natural product confirmed Kishi's assignments.

In the period of time following the conclusion of this work, there have been further synthetic studies on construction of tetrafibricin's framework and stereochemical makeup. Krische's group in 2014 expanded the use of their iridium catalyzed asymmetric carbonyl allylation strategy and included ruthenium catalyzed *syn*-crotylation reactions to prepare the C9-C20 fragment.¹⁵ Friestad's group in 2017 presented and expanded version¹⁶ of their iterative Julia-Kocienski olefination strategy for the C15-C25 fragment¹⁷ and in 2018 released a pair of publications outlining the synthesis of the required subunits and their application to the syntheses of C15-C25 and C26-C40 fragments studies on conditions required to couple the fragments in an enantioselective manner.¹⁸

1.2 Retrosynthetic Analysis and Previous Work in the Curran Group

The retrosynthetic analysis of tetrafibricin **1** (Figure 1.3) can be envisioned such that a series of Julia-Kocienski olefination¹⁹ reactions would provide strategic disconnects to couple fragments **2**, **3**, **4**, **5** together to form bonds C20-C21, C30-31 and C34-C35 (disconnections A). An umpolung approach for forming the acyl C13-C14 (disconnection B) bond can be achieved with fragments **5** and **6**. The C8-C9 bond can be formed through a Horner-Wadsworth-Emmons (HWE) olefination to couple fragments **6** and **7** (disconnection C).

Figure 1.3 - Retrosynthetic Analysis of Tetrafibricin



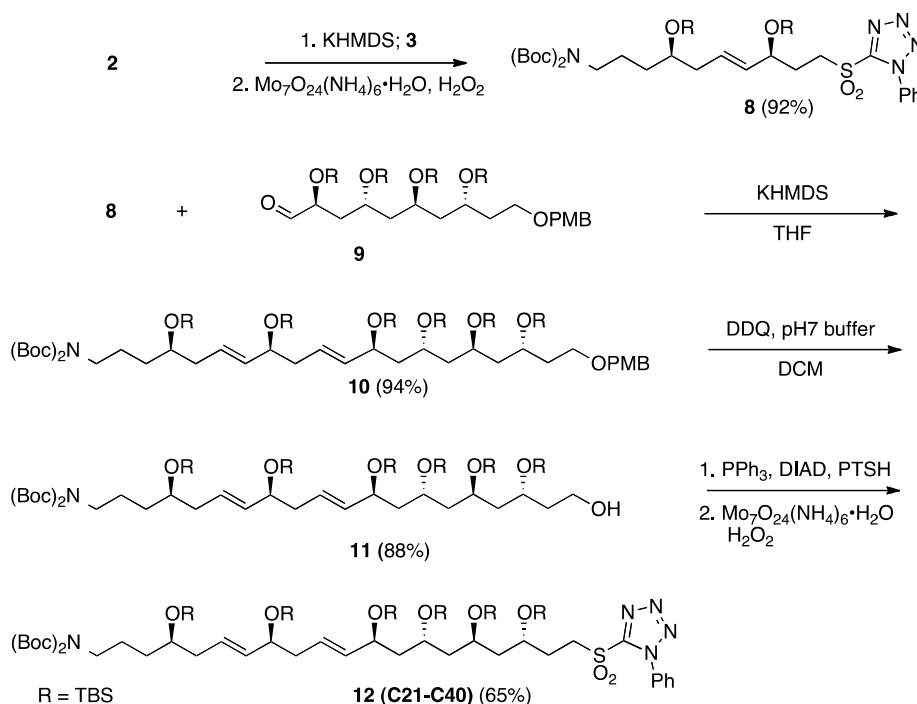
Dr. Venugopal Gudipati successfully synthesized all fragments **2-7**.⁸ The strategy was planned such that the full carbon framework of tetrafibricin would be coupled together in two large fragments with the key connection point being the C20-C21 bond. The C21-C40 fragment would be assembled from **2**, **3** and **4** (Figure 1.2) and the C1-C20 fragment would be assembled from **5**,

6, and **7**.

Fragments **2** and **3** were coupled first via a Julia-Kocienski olefination to give an alkene in a 9:1 *E/Z* isomeric mixture in 95% yield.²⁰ The conversion of sulfide to sulfone **8** with catalytic $\text{Mo}_7\text{O}_{24}(\text{NH}_4)_6 \cdot \text{H}_2\text{O}$ treated with H_2O_2 ²¹ occurred in 92% yield.

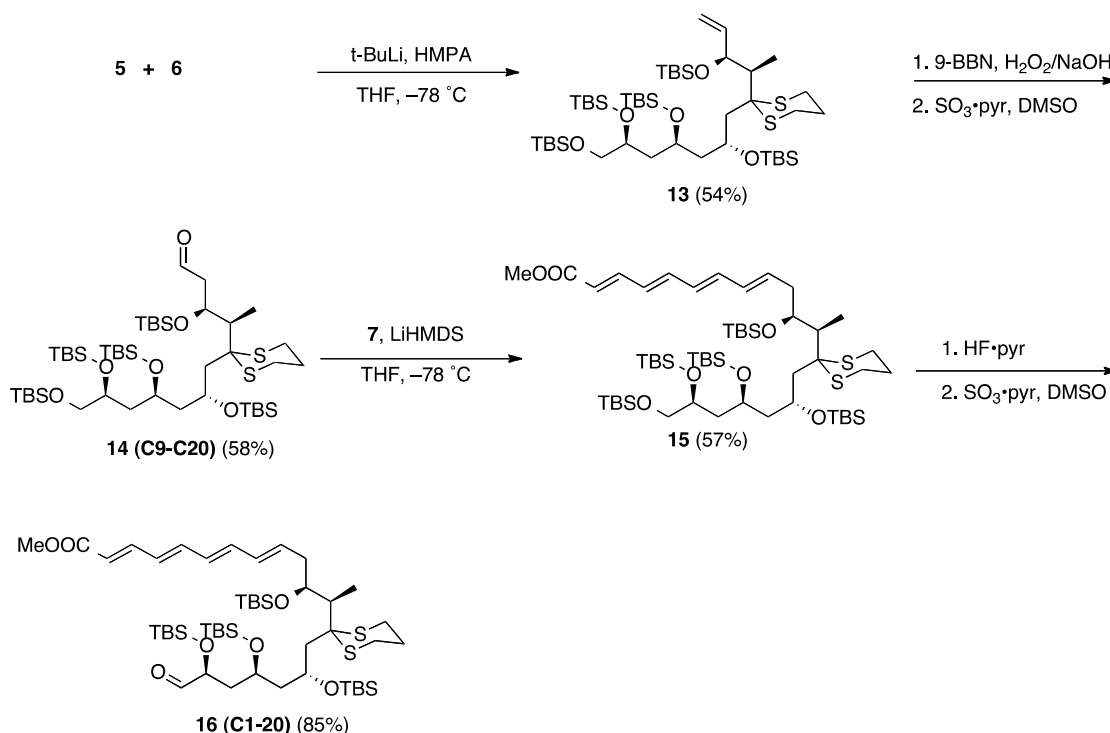
Another Julia-Kocienski olefination reaction between the sulfone **8** and aldehyde **9**, a precursor to **4**, provided the alkene **10** as a single (*E*)-isomer about the C30-C31 alkene in 94% yield. Removal of the PMB protecting group by using DDQ and pH 7 buffer in dichloromethane²² gave the primary alcohol **11** in 88% yield. Installation of the thiotetrazole via the Mitsunobu reaction,²³ employing commercially available 1-phenyl-1*H*-tetrazole-5-thiol (PTSH), followed by oxidation of the derived sulfide gave the sulfone **12**, the C21-C40 fragment, in 65% yield over two steps.

Figure 1.4 - Synthesis of the Large C21-C40 Fragment



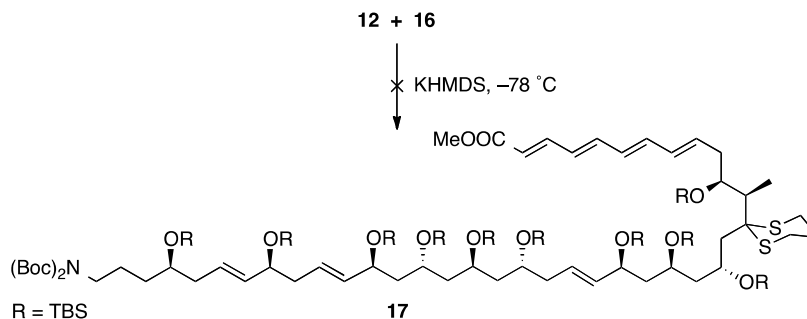
The synthesis of the C1-C20 fragment **12** was constructed by coupling the smaller fragments **5**, **6** and **7** (Figure 1.5). Deprotonation of dithiane **6** with t-BuLi followed by addition of iodide **5** provided the target alkylated dithiane **13** in 54% yield. Hydroboration and oxidation of alkene provided the primary alcohol, which was oxidized to aldehyde **14** with SO₃•pyr and DMSO²⁴ in 58% yield over two steps. A Horner-Wadsworth-Emmons olefination²⁰ was then carried out by deprotonation of phosphonate **7** with LiHMDS followed by the addition of **14** to afford **15** in 57% yield. The primary TBS-ether was cleaved with HF•pyr to give the primary alcohol in 45% yield. This was oxidized with SO₃•pyr and DMSO to give the C1-C20 fragment **16** in 85% yield.

Figure 1.5 - Synthesis of the Large C1-C20 Fragment



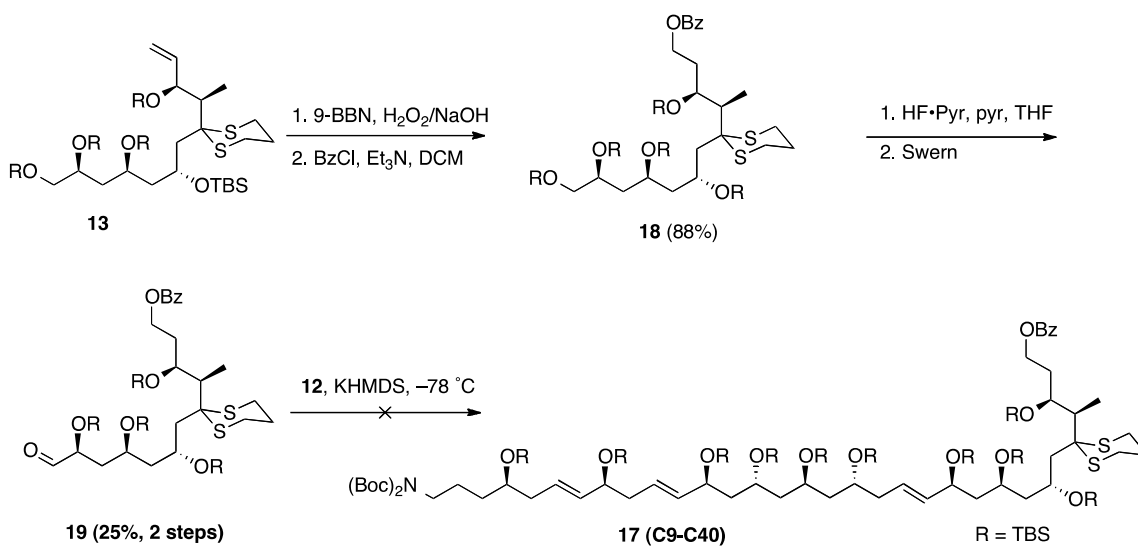
With the two large fragments in hand, coupling by a Julia-Kocienski olefination¹² was attempted (Figure 1.6). Sulfone **12** was deprotonated with KHMDS in THF at $-78\text{ }^{\circ}\text{C}$, followed by addition of aldehyde **16**. Unfortunately, the coupled product **17** was not isolated.

Figure 1.6 - Attempts at Coupling C1-C20 to C21-C40



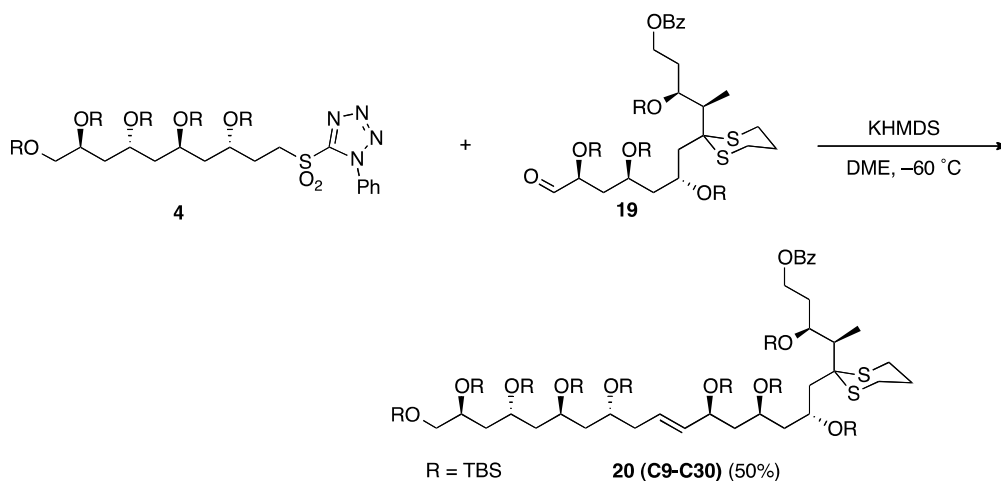
A revision of approach was carried out by Dr. Kai Zhang.²⁵ The six fragments were re-synthesized, and attempts were made to couple the fragments in a different order. The syntheses of the C21-C40 framework as sulfone **16** and preparation of C9-20 framework **13** were repeated (Figure 1.7). Alkene **13** was hydroborated/oxidized to give the primary alcohol in 68% yield, which was then protected as the benzoyl ester **18** in 88% yield. Selective desilylation of the primary alcohol using $\text{HF}\cdot\text{pyr}$ ²⁶ resulted in the primary alcohol in 42% yield, followed by Swern oxidation²⁷ to give aldehyde **19** in 60% yield. With the coupling partners prepared, Julia-Kocienski olefination was performed by deprotonating sulfone **12** with KHMDS in dry dimethoxyethane (DME). This did not yield the expected C9-C40 coupling product **17** after multiple attempts.

Figure 1.7 - Preparation of the C9-20 Fragment and Attempted Coupling of C21-C40



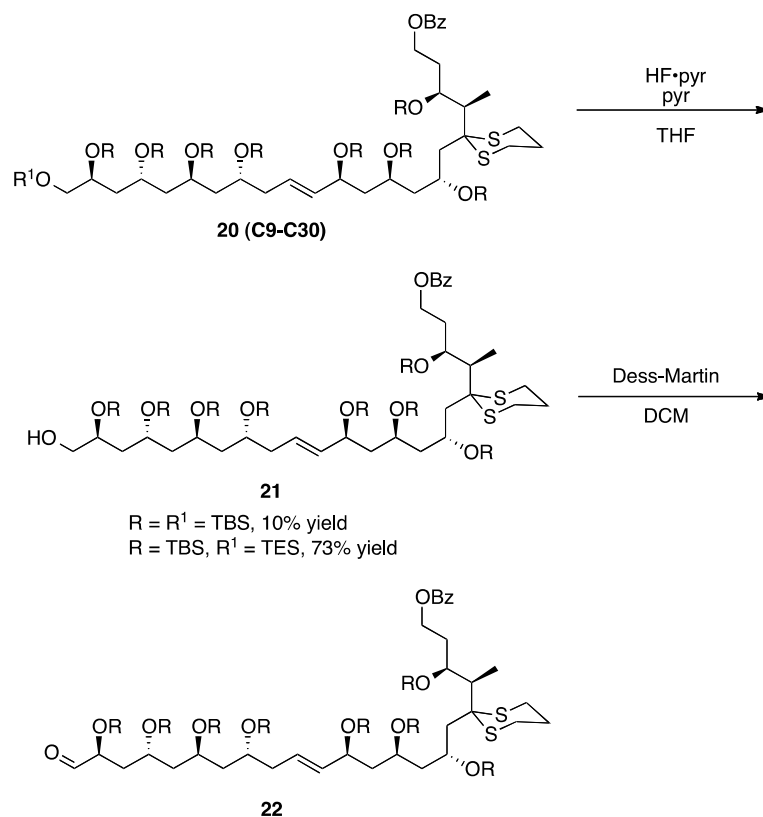
Given the two unsuccessful attempts at olefination at C20-C21, a strategy was devised to use the C21-C30 fragment **4** alone to couple with aldehyde **19**, while the C31-C40 framework from fragments **2** and **3** would be assembled separately, and then attached afterward (Figure 1.8). This plan succeeded, providing the connection at C20-C21 to give **20** in 50% yield as a single (*E*)-isomer.

Figure 1.8 - Successful Coupling of the C9-C30 Framework



Further modification of **20** was needed to allow coupling of the C31-C40 component. The primary TBS group needed to be removed in the presence of eight secondary TBS groups. Then, the resulting primary alcohol needed to be oxidized to make the aldehyde for the next Julia-Kocienski coupling (Figure 1.9). Silyl ether **20** was treated with HF•pyr in pyridine and THF to achieve a meager yield of **21**. To improve this step, the synthesis of **4** was revisited and it was determined that the substitution of a more labile triethylsilyl (TES) group on the primary alcohol to selectively cleaved in the presence of TBS groups. When the primary alcohol was protected with TES group, conversion to **21** was achieved in 73% yield compared to 10% yield using a TBS group.²⁵

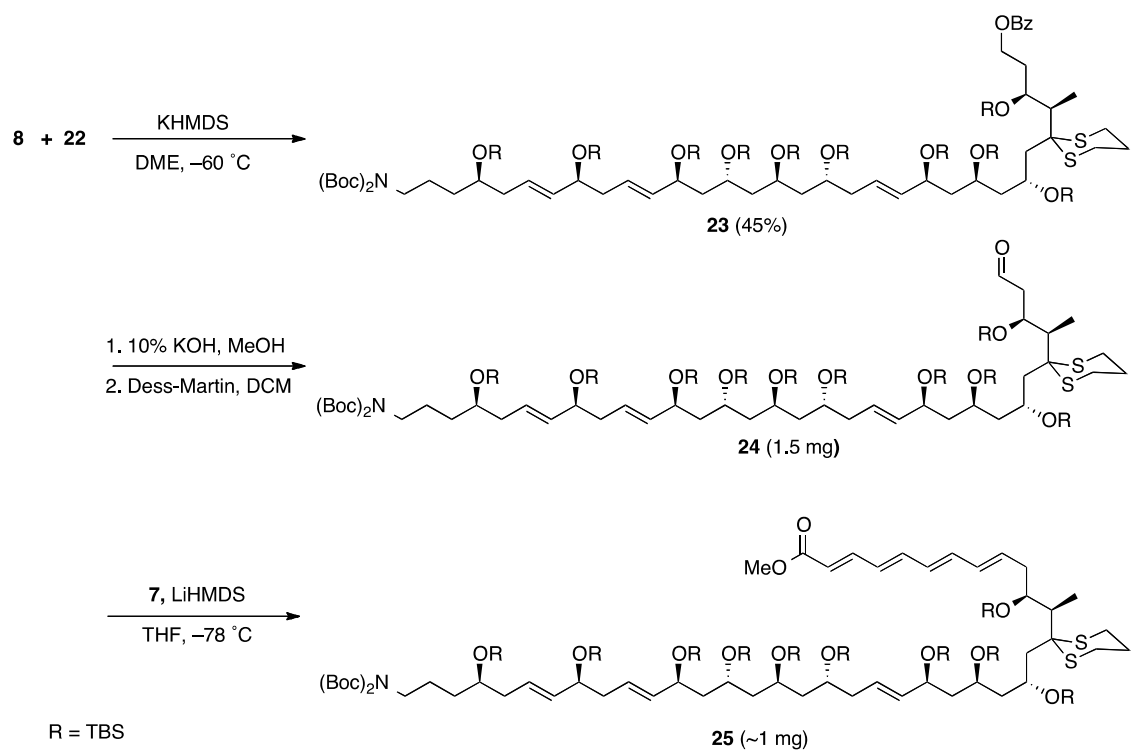
Figure 1.9 - Selectivity of the Primary Desilylation of TBS vs. TES Group



The C31-C40 fragment **8** was successfully coupled to **22** in 45% yield to give the C9-C40 fragment **23** (Figure 1.10). Saponification of the benzoyl ester with KOH and oxidation of the resulting alcohol with the Dess-Martin reagent²⁸ gave 1.5 mg of crude aldehyde **24**. The final Horner-Wadsworth-Emmons olefination for the final coupling of **7** to **24** yielded approximately 1 mg of fully protected tetrafibricin **25**. This was enough material for ¹H NMR characterization yet was not enough to carry through a global deprotection, as this would result in the loss of more than half of the molecular weight of the molecule.

A successful route to obtaining the carbon framework of tetrafibricin **1** was achieved. A goal of synthesizing 0.5 mmol of **1** has been set in order to undertake spectroscopic studies to compare to the natural product, as well as provide material for preliminary biological study.

Figure 1.10 - Final Fragment Coupling Reactions



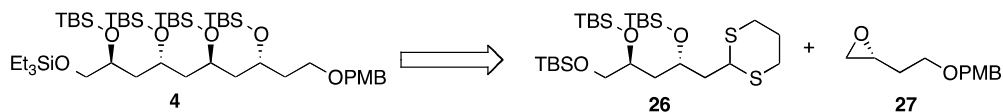
2.0 Synthesis of Tetrafibricin's Fragments

In order to successfully complete the total synthesis of tetrafibricin **1**, larger quantities of each of the fragments are needed. Deficiencies in the yields of key reactions and coupling strategies limited material throughput. Though the synthetic routes to each of the fragments are already in place, improvements need to be made in order to provide enough material to complete the synthesis.

2.1 Progress toward C21-C30 Fragment Synthesis

Synthesis of the C21-C30 fragment **4** of tetrafibricin was performed by Dr. Zhang up to compound **38** in Figure 2.4.²⁵ The key step in this reaction sequence is the coupling between dithiane **26** and epoxide **27**, and the selective deprotection of the primary alcohol in the final steps of the fragment synthesis (Figure 2.1).

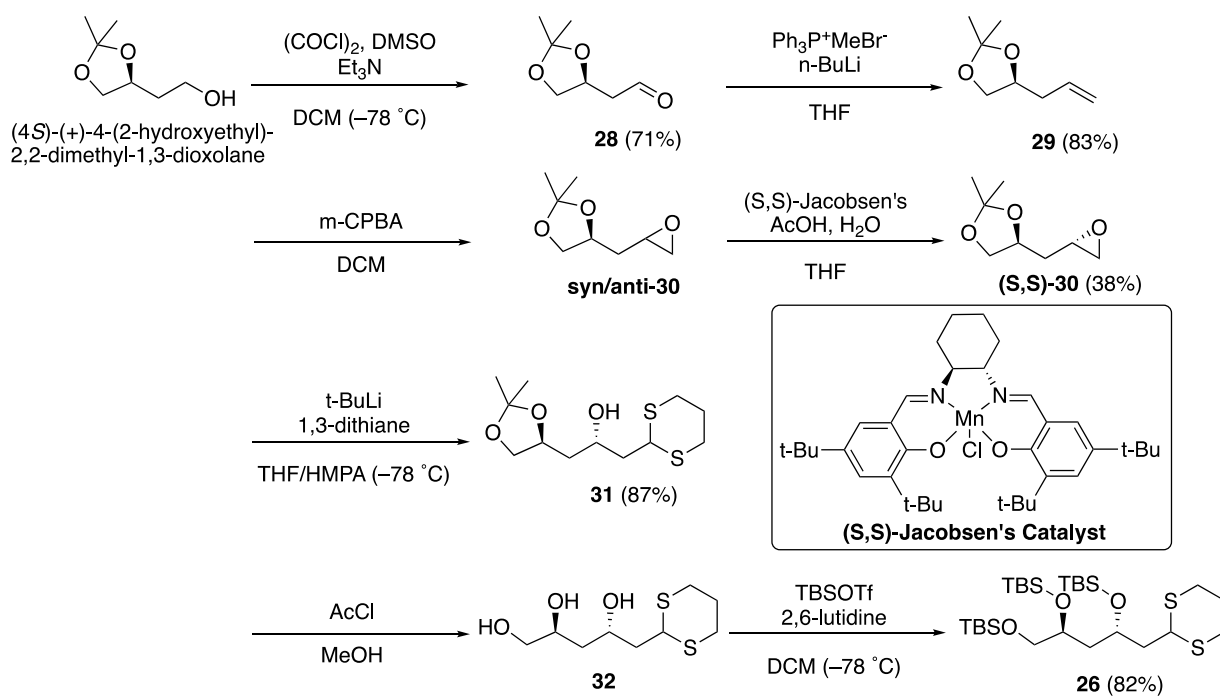
Figure 2.1 - Key Coupling Step Toward the C21-C30 Fragment



The “left hand side” **26** of the C21-C30 fragment was synthesized starting with commercially available (4*S*)-(+)-4-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolane (Figure 2.2). Swern oxidation²⁷ of the primary alcohol, followed by distillation under reduced pressure gave aldehyde **28** in 71% yield. Generation of the ylide of methyl triphenylphosphonium bromide with

n-butyllithium²⁹, followed by addition of **28** and purification by Kuhgelrohr distillation gave alkene **29** in 83% yield. The crude aldehyde was dissolved in DCM, and was treated with 3-chloroperoxybenzoic acid (*m*-CPBA) to afford oxirane **30** as a 58:42 mixture of *syn/anti* diastereomers. The crude epoxide was dissolved in AcOH and THF, and was treated with (*S,S*)-Jacobsen reagent³⁰ and water to affect a hydrolytic kinetic resolution. Enantiomerically pure (*S,S*)-**30** was obtained in 38% yield following Kuhgelrohr distillation under reduced pressure.

Figure 2.2 - Synthesis of the “Left Hand Side” of the C21-C30 Fragment

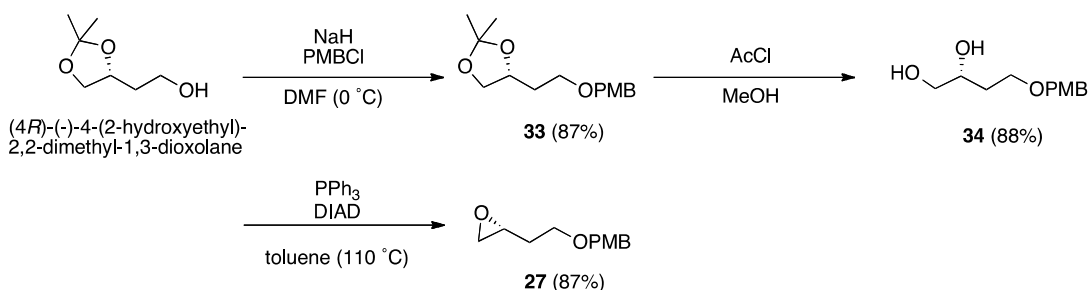


1,3-Dithiane was lithiated using *t*-BuLi at -78°C in THF and HMPA, followed by addition of epoxide (*S,S*)-**30**, which underwent nucleophilic ring opening to give dithiane **31** in 87% yield after purification by flash chromatography. Acetonide cleavage was effected by treatment of **31** with catalytic acetyl chloride in MeOH to give triol **32**. Without further purification, **32** was treated

with excess TBSOTf and 2,6-lutidine to afford tris-silyl ether **26** in 82% yield after flash chromatography.

The “right hand side” **27** of the C21-C30 fragment was synthesized following procedures outlined in the thesis of Dr. Zhang.²⁵ Starting from commercially available (4*R*)-(-)-4-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolane, deprotonation of the primary alcohol by NaH in DMF, followed by alkylation with *p*-methoxybenzyl (PMB) chloride gave PMB ether **33** in 87% yield. Acetonide cleavage with catalytic acetyl chloride in methanol gave diol **34** in 88% yield. Next, Mitsunobu conditions²³ were used to perform the final ring closing reaction. Diol **34** was dissolved in toluene with triphenylphosphine and diisopropylazodicarboxamide, and the mixture was heated to reflux temperature overnight to afford epoxide **27** in 87% yield.

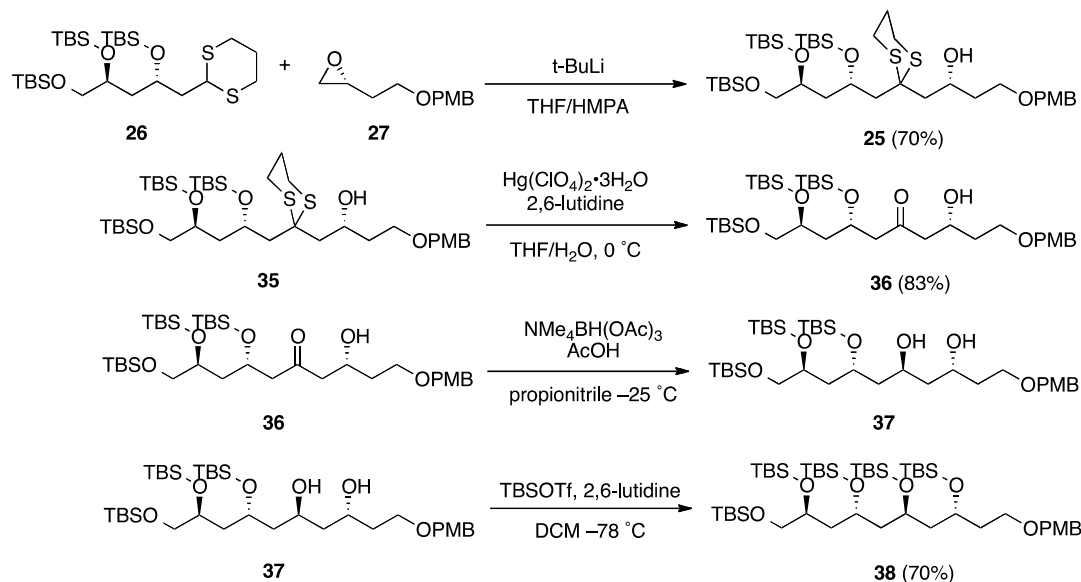
Figure 2.3 - Synthesis of the “Right Hand Side” of the C21-C30 Fragment



With compounds **26** and **27** in hand, coupling and further modification of the C21-C30 fragment was advanced (Scheme 2.4). Lithiation of **26** by *t*-BuLi at –78 °C in THF/HMPA followed by slow addition of epoxide **27** gave the coupling product **35** in 70% yield. Dithiane hydrolysis was achieved 83% yield after purification by flash chromatography by treating **35** with Hg(ClO₄)₂•3H₂O and 2,6-lutidine in 4:1 THF/H₂O at 0 °C to give ketone **36**.³¹ Directed 1,3-*anti* reduction was performed by addition of an acetic acid solution of tetramethylammonium

triacetoxyborohydride³² to solution of **36** in propionitrile at $-25\text{ }^{\circ}\text{C}$. Crude diol **37** was silylated with TBSOTf and 2,6-lutidine to give pentakis-silyl ether **38** in 70% yield after flash chromatography.

Figure 2.4 - Manipulation of C21-C30 Framework



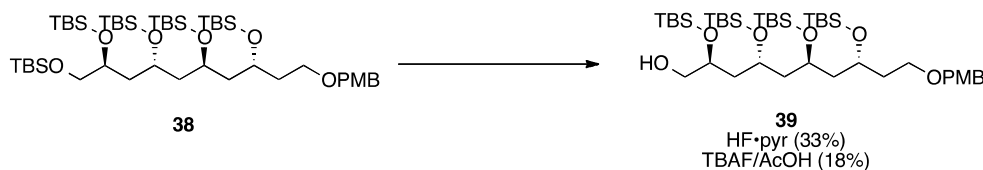
Attempts by Dr. Zhang to selectively cleave the primary TBS group from the primary alcohol of **38** by using $\text{HF} \cdot \text{pyr}$ in a pyridine/THF mixture resulted in a 33% yield of alcohol **39** (Figure 2.5). Low yield for this reaction became a limiting factor to procuring the necessary amount of material needed to successfully complete the synthesis. Thus, more selective conditions were sought after.

Further reactions were attempted to achieve selective desilylation of the primary alcohol of **38**.³³ Treating **38** with 20 mol% camphorsulfonic acid in dichloromethane did not show selective cleavage of the primary silyl group when monitoring by TLC. A reaction with 0.1 equiv of acetyl chloride in methanol at $-20\text{ }^{\circ}\text{C}$ resulted in multiple UV-active bands that observed by TLC. A

reaction using a 1:1 TBAF/AcOH reagent system as a source of buffered fluoride ion was performed. These conditions were the most successful alternative to HF•pyr, however this only resulted in 18% yield of **39**.

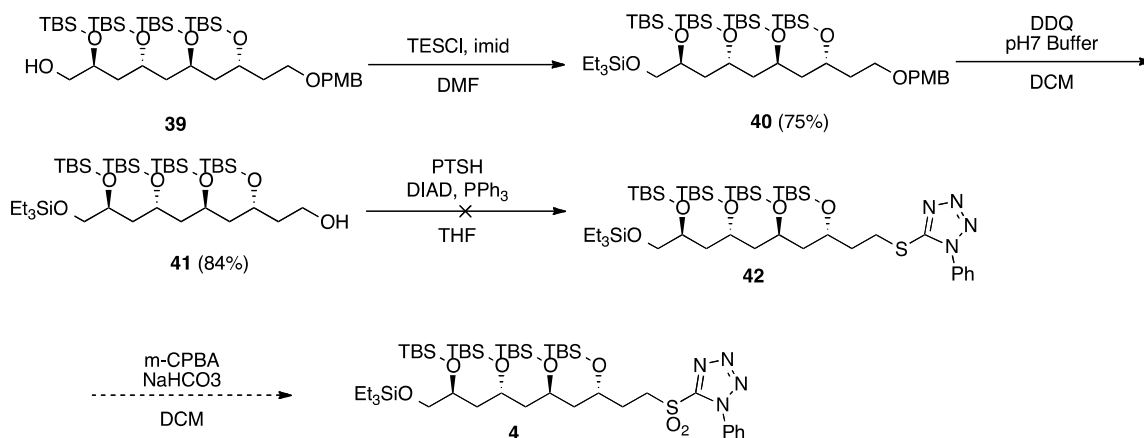
During subsequent attempts to repeat and improve upon this reaction, complex mixtures of **39** were observed. Separation of the impurities could not be achieved through automated flash chromatography. It has not been determined whether the impurities were present in the sources of **38**, or were the result of a lack of selectivity of the deprotection conditions.

Figure 2.5 - Selective Mono-Desilylation of 38



With the small amount of pure **39** obtained from desilylation, the completion of the synthesis of C21-C30 fragment **4** was attempted (Figure 2.6). Reprotection of the primary alcohol **39** using TESOTf resulted in an inseparable mixture of products. This reagent system is known to be incompatible with the PMB protective group due to the strong Lewis acidity of the silyl triflate present.³⁴ Treatment of alcohol **39** with TESCl, imidazole, and DMAP in DMF afforded the desired product **40** in 75% yield. Deprotection of the PMB ether of **40** was achieved in 84% yield in a biphasic DCM/aqueous pH 7 buffer solvent mixture by treatment with DDQ to give alcohol **41**. Synthesis of sulfide **42** was attempted through a Mitsunobu reaction between alcohol **41** and PTSH. The desired product was not detected in the crude mixture ¹H NMR spectroscopy, so the final steps were not attempted.

Figure 2.6 - Attempts Toward Synthesis of C21-C30 Fragment 4



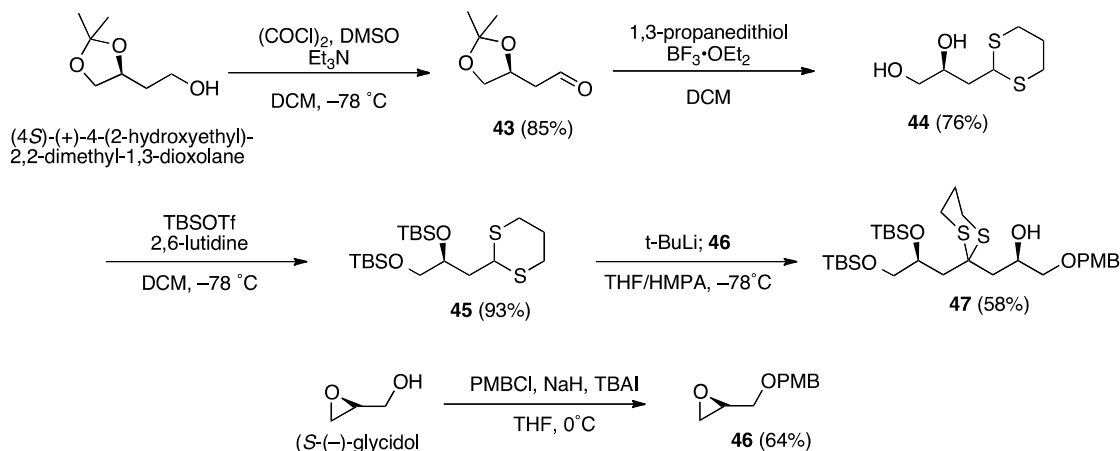
The difficulty in achieving selective removal of the primary silyl protecting group of **38** presents a barrier to producing enough of fragment **4** to ultimately complete the synthesis of tetrafibricin **1**. With compound **26** available, differentiation of the protecting groups installed on the primary and secondary alcohols can be done at an earlier stage. This can be achieved by deprotecting all three of the TBS ethers, selectively protecting the primary alcohol, and then protecting the remaining two secondary alcohols.

2.2 C14-C20 Fragment Synthesis

The synthesis of the C14-C20 fragment **5** was accomplished by using procedures in Dr. Zhang's thesis.²⁵ The assembly of the carbon framework of **5** began with commercially available (4*S*)-(+)-4-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolane (Figure 2.7). Oxidation under Swern

conditions, followed by distillation of the crude product under reduced pressure gave aldehyde **43** in 85% yield. Treatment of **43** with 1,3-propanedithiol and $\text{BF}_3 \cdot \text{OEt}_2$ for 1 h resulted in simultaneous acetonide cleavage and dithiane formation to give **44** in 76% yield after flash chromatography. Protection of the diol with TBSOTf and 2,6-lutidine resulted in dithiane **45** in 93% yield. Preparation of the coupling partner to **45** was achieved by deprotonation of (*S*)-(-)-glycidol with sodium hydride in THF, followed by addition of PMBCl and 10 mol % Bu_4NI to give **46** in 64% yield. Alkylation of **45** proceeded by treatment with *t*-BuLi and HMPA at -78°C , followed by slow addition of epoxide **46** to give **47** in 58% yield after flash chromatography.

Figure 2.7 - Synthesis of the Framework of C14-C20 Fragment



With the carbon framework of **5** in place, further work was necessary to set the final stereogenic center and manipulate protecting groups (Figure 2.8). Hydrolysis of dithiane **47** with $\text{Hg}(\text{ClO}_4)_2 \cdot 3\text{H}_2\text{O}$ in a 4:1 THF/ H_2O solution at 0°C gave ketone **48** in 87% yield following flash chromatography. Caution was taken to maintain the temperature of the mixture below 10°C during the portion-wise addition of the mercury salt to the reaction, especially at the multi-gram scale.

These conditions have demonstrated to be explosive in nature if the reaction is unable to dissipate heat efficiently.³¹ The reaction was carried out safely by using a sufficient volume of solvent to transfer heat, and closely monitoring the reaction temperature and operation of the magnetic stirring apparatus.

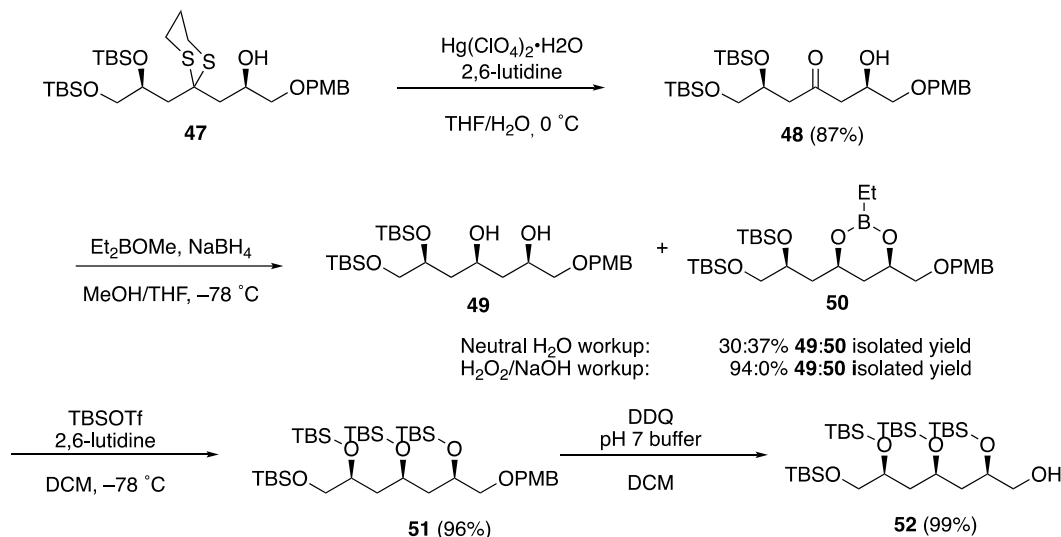
1,3-Syn-reduction of **48** was first attempted following a procedure described in the theses of Drs. Zhang and Gudipati^{8c, 25}. A solution of Et₂BOMe in THF³⁵ was added to a 4:1 THF/MeOH solution of **48** at -78 °C, followed by NaBH₄ after 30 min. After 3 h the reaction was quenched with H₂O, and subsequent extraction and flash chromatography gave *syn*-diol **49** in 88% yield. In contrast to these high yields, Dr. Mandel reported inconsistent yields up to 56% of **49** in more recent attempts.³⁶

When this procedure was repeated, purification of the crude product by flash chromatography gave not one product, but two. The second-eluting, minor product was determined to be the expected *syn*-diol **49** in 30% yield. This exhibited ¹H NMR and ¹³C NMR resonances identical to those previously reported. The first-eluting major product had NMR resonances similar to **49**, however, some of the chemical shifts were different. There were also new resonances corresponding to an ethyl group (δ 0.67, q, 2H, and δ 0.88, t, 3H). Based on this, the major product was proposed to be cyclic borinate ester **50**. A ¹¹B NMR spectrum was obtained, and a broad singlet at δ +31.0 was observed. This is consistent with ¹¹B NMR shifts to similar cyclic borinate esters.³⁷ Treatment of this major product with H₂O₂ and NaOH gave conversion to the desired *syn*-diol **49** further supporting **50** as the proposed structure.

Next, the reduction was repeated, and in lieu of quenching with water, the crude product was treated with aqueous H₂O₂ and NaOH for 1 h.³⁸ This resulted in isolation of *syn*-diol **49** in 94% yield after flash chromatography, with no trace of the previously observed borinate.

Silylation of **50** with TBSOTf and 2,6-lutidine resulted in **51** in 96% yield. Subsequent cleavage of PMB ether **51** with DDQ in DCM/aqueous pH 7 buffer resulted in primary alcohol **52** in 99% yield after flash chromatography.

Figure 2.8 - Protecting Group Manipulation of Fragment 5 Intermediates



Iodination of primary alcohol **52** (Figure 2.9) was initially achieved by using PPh_3 , I_2 , and imidazole³⁹ in DCM at $0\text{ }^\circ\text{C}$ in 36% yield (entry 1, Table 2.2.1), in contrast to 96% yield reported by Dr. Zhang.²⁵ Increasing the reaction time and gradually raising the temperature to $23\text{ }^\circ\text{C}$ (entry 2), or increasing the amount of the reagents used (entry 3) only afforded a minor increase in isolated yield with complex product mixtures. Fuwa and coworkers⁴⁰ reported that using benzene as a solvent achieved excellent conversion in a related system. Using this information, a series of ^1H NMR experiments were performed in order to determine the effects of the solvent used on the yield of the reaction.

A reaction performed in CD_2Cl_2 resulted in a complex mixture of products over 30 min (entry 4). A reaction in benzene- d_6 was monitored by ^1H NMR, and showed complete conversion

of **52** to the desired iodide **5** after 30 min (entry 5). A reaction was performed with toluene to explore an alternative solvent to benzene, however the yield of the reaction was only 25% (entry 6). These results showed that using benzene gave the best yield for this reaction. Under these optimized conditions, a scale-up synthesis of **5** was achieved in 99% yield after flash chromatography (entry 7) at a 15 g scale. Overall, the C14-C20 fragment **5** was synthesized in an overall yield of 26% over 10 steps.

Figure 2.9 - Conversion of 17 to the final C14-C20 Fragment (5)

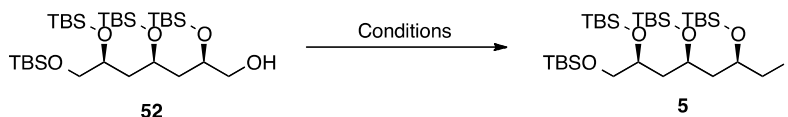


Table 2.1 - Optimization of Iodination Conditions

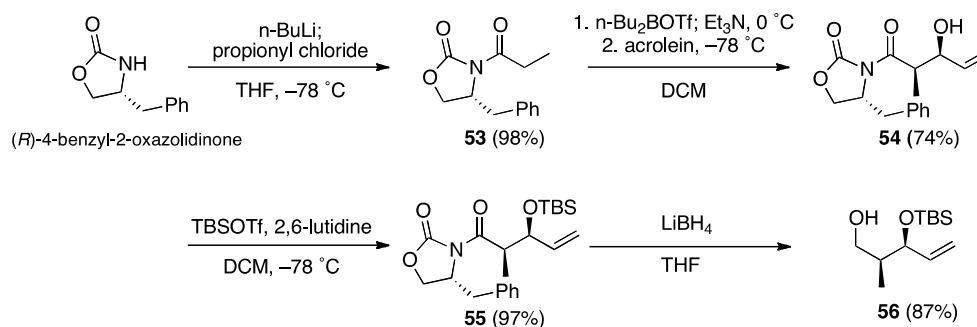
Entry	PPh ₃ (eq)	I ₂ (equiv)	imid. (equiv)	Solvent (conc)	Temp	Time	Yield 5
1	1.4	1.1	1.5	DCM (0.15 M)	°C	0.5 h	36% ^a (96%) ^c
2	1.4	1.1	1.5	DCM (0.15 M)	23 °C	7 h	41% ^a
3	2.5	2.0	3.0	DCM (0.15 M)	0 °C	3 h	51% ^a
4	1.8	1.9	2.0	CD ₂ Cl ₂ (0.08 M)	23 °C	0.5 h	Complex ^b
5	1.8	1.9	2.0	C ₆ D ₆ (0.08 M)	23 °C	0.5 h	100% ^b
6	1.8	1.9	2.0	PhMe (0.08 M)	23 °C	0.5 h	25% ^b
7	1.8	1.9	2.0	PhH (0.08 M)	23 °C	1 h	99% ^a

^a Isolated yield ^b Yield determined by NMR spectroscopy ^c Results reported by Dr. Zhang

2.3 C9-C13 Fragment Synthesis

The C9-C13 fragment **6** was synthesized by using procedures outlined by Dr. Zhang²⁵ (Figure 2.3.1). Chiral auxiliary (*R*)-4-benzyl-2-oxazolidinone was deprotonated with *n*-BuLi at $-78\text{ }^{\circ}\text{C}$, then the resulting anion was acylated with propionyl chloride resulting in **53** in 97% yield. An Evans aldol reaction⁴¹ was performed through enolization of **53** with dibutylboron trifluoromethanesulfonate and triethylamine at $0\text{ }^{\circ}\text{C}$. Cooling to $-78\text{ }^{\circ}\text{C}$ and addition of freshly distilled acrolein gave **54** in 15% yield. Protection of the alcohol of **54** with TBSOTf gave **55** in 97% yield after flash chromatography.

Figure 2.10 - Synthesis of the C9-C13 Chiral Framework

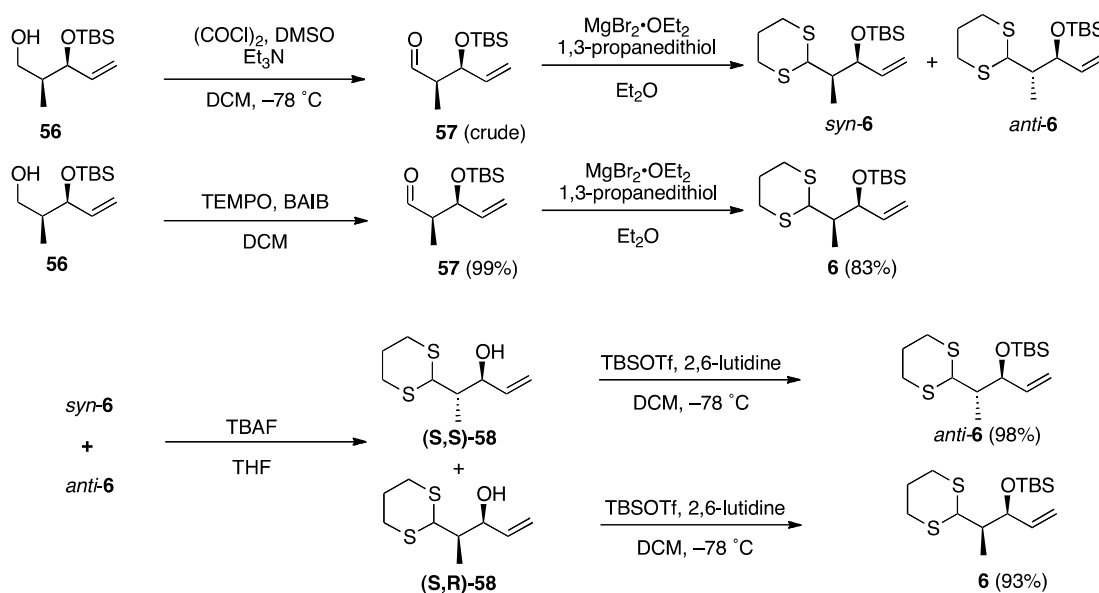


The remainder of the synthesis of fragment **6** was completed by Dr. Julien Monot. Reductive cleavage of the Evans auxiliary with LiBH₄ in THF³² gave alcohol **56** in 87% yield. Alcohol **56** was oxidized under Swern conditions to give crude aldehyde **57**, which was treated with MgBr₂•OEt₂ and 1,3-propane dithiol (Figure 2.3.2). After flash chromatography, it was determined by Dr. Monot that epimerization at methyl-bearing carbon had occurred during this sequence, giving *syn*-**6** mixed with *anti*-**6** in a ~7:3 ratio. This could have occurred due to reversible enolization by the triethylamine used in the Swern oxidation. The mixture of *syn*-**6** and *anti*-**6** was

treated with TBAF, and the diastereomers of the resulting alcohol were separated chromatographically to give (*S,R*)-**58** and (*S,S*)-**58**. The pure diastereomers were separately treated with TBSOTf and 2,6-lutidine by to give fragment **6** from (*S,R*)-**58** in 93% yield by Dr. Monot, and **25** from (*S,S*)-**23** in 98% yield by the author.

A 2,2,6,6-tetramethylpiperidinyloxy radical (TEMPO) oxidant / bis-acetoxiodobenzene (BAIB) co-oxidant system⁴² was evaluated to try to eliminate the epimerization. TEMPO/BAIB oxidation of alcohol **56** resulted in aldehyde **57** in 99% yield as a single diastereomer. Subsequent treatment of the crude aldehyde with $\text{MgBr}_2 \cdot \text{OEt}_2$ and 1,3-propane dithiol gave dithiane **6** in 83% yield without epimerization. Overall, C9-C14 fragment **6** was synthesized in 50% yield over six steps.

Figure 2.11 - Oxidation and Dithiane Formation

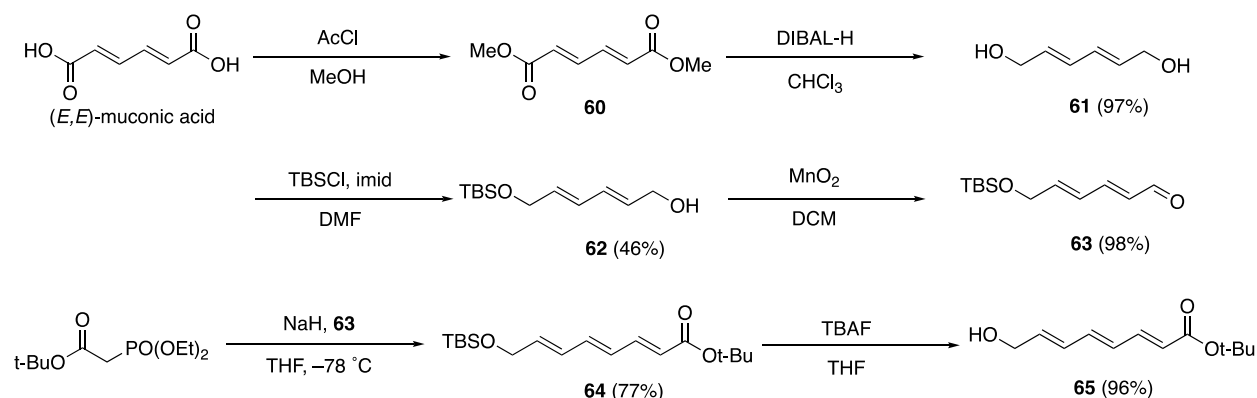


2.4 Synthesis of Fragment 7 (C1-C8)

The C1-C8 fragment **7** is the last fragment to be coupled to form the full carbon framework of tetrafibricin. The ethyl ester of **7** was synthesized by the Roush group as the C1-C8 synthon in their synthesis of the C1-C19 fragment of tetrafibricin¹¹. Due to the extended conjugation of **7**, care was taken to shield polyene intermediates from light during reactions and storage.

Synthesis of **7** began with diesterification of commercially available (*E,E*)-muconic acid to dimethyl ester **60**, which was achieved with acetyl chloride in methanol (Figure 2.12). Subsequent reduction of the crude material with DIBAL-H gave allylic diol **61** in 97% yield over two steps without purification. Monosilylated diol **62** was obtained from a statistical mixture in 46% yield, followed by allylic oxidation to aldehyde **63** with activated MnO₂ in 98% yield after flash chromatography. Horner-Wadsworth-Emmons olefination between **63** and *tert*-butyl diethylphosphonoacetate gave **64** as a single (*E*)-isomer in 77% yield. Desilylation with TBAF provided allylic alcohol **65** in 96% yield.

Figure 2.12 - Preparation of the C1-C8 Fragment Precursor **65**



Dr. Zhang's route²⁵ to the methyl ester analog of fragment **7** involved a traditional halogenation/Arbuzov reaction sequence.⁴³ The same reaction sequence to afford **7** from **65** proved

to be problematic. Treatment of allylic alcohol **65** with thionyl bromide gave bromide **66** in only 46% yield, likely due to the acid sensitivity of *tert*-butyl esters. Chromatographic purification and storage of **66** also proved problematic due to its relative instability to ambient laboratory conditions and light. Bromide **66** and triethylphosphite were heated to reflux in toluene in the dark to give phosphonate **7** in 56% yield. However, this reaction was not reproducible, which was attributed to thermal decomposition under these conditions.

Wiemer and coworkers⁴⁴ described a zinc iodide mediated Arbuzov-type reaction to convert allylic alcohols directly to their corresponding phosphonates at reflux in toluene. The reaction between zinc iodide, triethylphosphite and alcohol **65** at 55 °C gave a 31% yield of the target product **7** (Table 2.4.1, Entry 1). Elevating the temperature to 80 °C resulted in decomposition being observed after 1 h (Entry 2). A reaction in THF at 55 °C showed no conversion to **7** by TLC analysis. Running the reaction as a neat mixture at 55 °C showed an increase in yield to 54% (Entry 4), however running the reaction longer than 2.5 h showed no appreciable benefit.

Figure 2.13 - Conversion of Alcohol 65 to Phosphonate 7

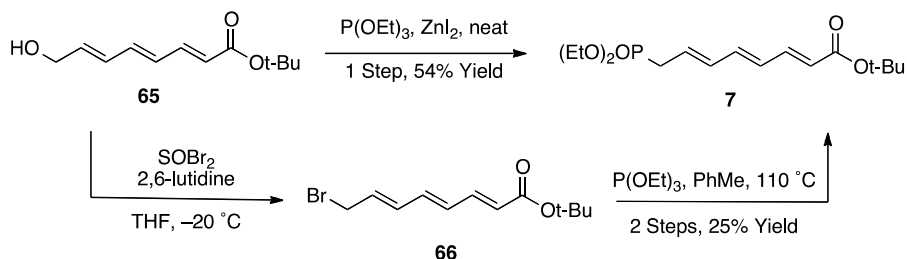


Table 2.2 - Optimization of ZnI₂ Mediated Arbuzov-Type Reaction

Entry	P(OEt) ₃ (eq)	ZnI ₂ (eq)	Solvent	Temp	Time	Yield
1	3.0	1.5	PhMe (0.1M)	5 °C	3 h	31 %
2	3.0	1.5	PhMe (0.1M)	0 °C	1 h	decomp
3	3.0	1.5	THF (0.1M)	5 °C	6 h	No conv
4	6.0	3.0	neat	5 °C	2.5 h	54 %

Replacement of the traditional halogenation/Arbuzov sequence with the optimized zinc mediated reaction conditions shortened the synthesis of **7** to seven steps from eight and led to increased conversion of allylic alcohol **65** to fragment **7** in 54% yield in one step rather than the previously achieved 25% yield over two steps. The C1-C8 fragment **7** was synthesized in an overall yield of 17% over seven synthetic steps.

2.5 C9-C13 and C14-20 Fragment Coupling and Modification

Once the synthesis of the individual fragments was complete, the carbon framework of tetrafibricin could be constructed through coupling the fragments. The first fragment coupling reaction was to join the C9-C13 fragment **6** and the C14-C20 fragment **5** through a Corey-Seebach reaction to give **13** (Scheme 2.14).³¹ Dithiane **6** was lithiated in the presence of HMPA with *t*-BuLi at -78 °C, followed by addition of iodide **5**. As reported by Dr. Zhang, the reaction between **5** and **6** in a 1:1 molar ratio in the presence of 1.1 equiv *t*-BuLi resulted in coupled product **13** in 54% yield (Table 3, entry 1). However, purification of the product by flash chromatography was difficult because the starting material and product co-eluted. Addition of 1.3 equiv of **5** to 1.0 equiv

of lithiated **6**, as suggested by a procedure performed by Hanessian and coworkers,⁴⁵ gave coupled product **13** in 75% yield (entry 2). Even with the large improvement in yield, chromatography was still difficult because both **5** and **6** still remained in the crude product mixture. Addition of 1.0 equiv of **5** to 1.1 equiv of lithiated **6** achieved nearly complete coupling to give **13** in 96% yield (entry 3).

Figure 2.14 - Coupling of C9-13 and C14-C20

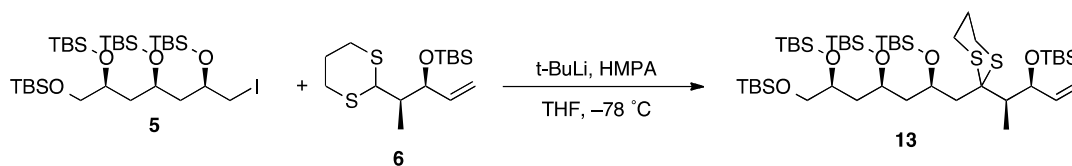


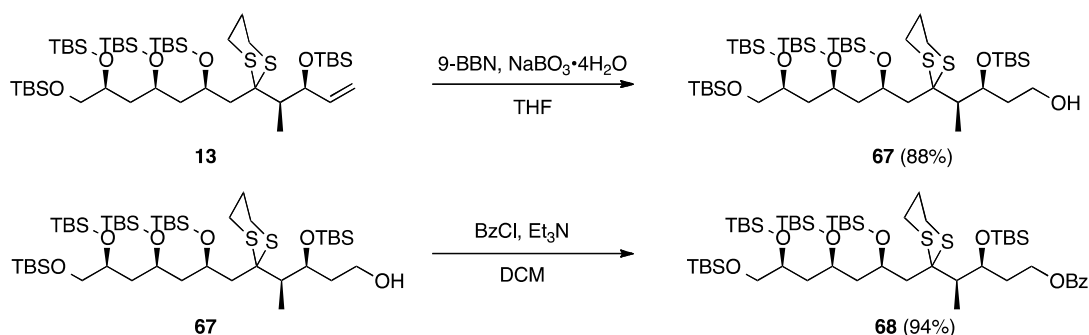
Table 2.3 - Conditions for the Coupling of Fragments 5 and 6

Entry	5 (equiv)	6 (equiv)	t-BuLi (equiv)	Time	Yield 13
1	1.0	1.0	1.1	2 h	54% ^a
2	1.3	1.0	1.2	2.5 h	75%
3	1.0	1.1	1.2	2 h	96 %

^a Results reported by Dr. Zhang

Following coupling, **13** was advanced to allow for further fragment coupling later in the synthesis (Figure 2.11). The terminal alkene of **13** was hydroborated with 9-BBN.⁴⁶ Oxidative workup with aqueous H₂O₂ and NaOH gave alcohol **67** in inconsistent yields. In many cases the product was contaminated with impurities that were difficult to separate by column chromatography. We considered that the dithiane of the substrate could react with the H₂O₂ used with the workup, so a milder oxidant was sought. Treatment of the *in situ* generated trialkylborane of **13** with NaBO₃•4H₂O gave **67** in 88% yield.⁴⁷ Protection of the primary alcohol as benzoate ester **68** was achieved with benzoyl chloride and triethylamine in 94% yield.

Figure 2.15 - Modification of Coupled Fragments 13



The next key step was to selectively deprotect the TBS group of the primary alcohol of **68** in the presence of the remaining four secondary silyl ethers (Figure 2.12). Dr. Zhang removed of the primary silyl group of **68** using HF•pyr/pyr in THF to afford **69** in 39% yield.

This reaction was repeated, and after 5 h, a 30% yield of **69** was isolated, 20% of the starting material **68** was recovered, and the remainder of the substrate was presumed to have been desilylated at more than one site to give **70** as a mixture of polyols. Improved conditions were sought after in order to increase selectivity of primary silyl ether removal to give **69** in higher yield, and also to make recovery of **70** more efficient in order to resilylate the deprotected alcohols to regenerate **68**. Recovered **68** would be subjected to the conditions again and recycled.³³

Acidic conditions were first attempted to remove of primary silyl group, because 1,4- and 1,5-silyl transfer readily occurs under basic conditions.³⁴ It had been reported that the treatment of **61** with “acidic chloroform,” prepared by treatment of chloroform with concentrated aqueous HCl successfully removed a primary silyl group in a similar 1,2-silyloxy system.³⁴ Tetrakis-silyl ether **61** was dissolved in acidic chloroform, and the reaction was monitored by TLC. Several UV-active bands were present in close proximity to the R_f of the desired product **69** when monitored by TLC, suggesting a lack of selectivity. After 4 h, an impure sample of primary alcohol **69** was isolated in

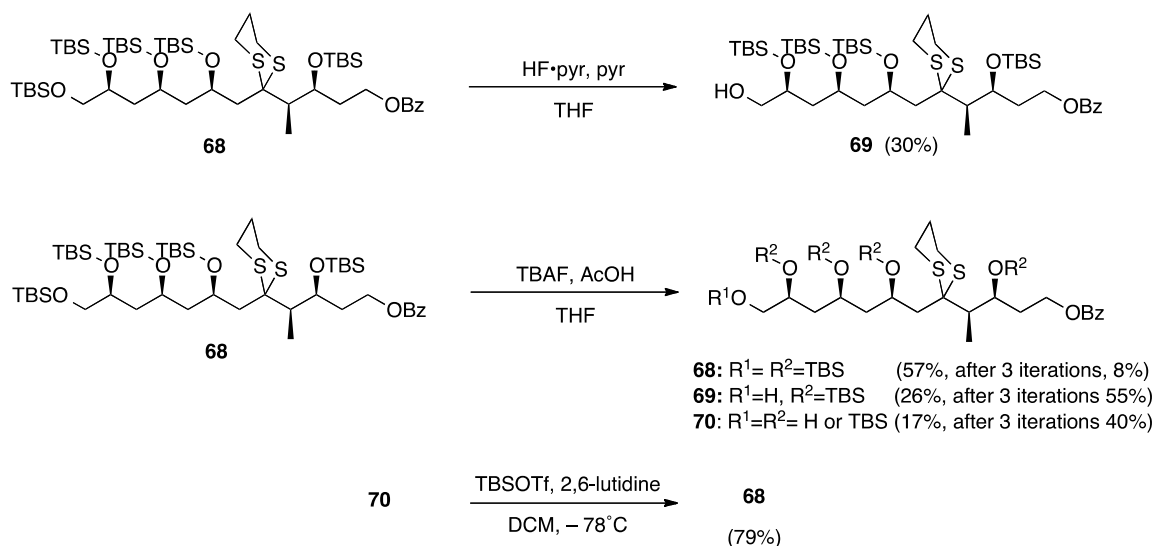
15% yield, along with 60% of **68**, with the remaining material isolated as a mixture of polyols (**70**). Treatment of **68** with AcOH in THF for 3 days resulted in the isolation of starting material in near quantitative yield.

Lewis acidic conditions were also unsuccessful. Treatment of **68** with 1 equiv of $\text{Cu}(\text{NO}_3)_2 \cdot \text{H}_2\text{O}$ resulted in non-selective desilylation as observed by TLC. Treatment of **68** with 5 equiv $\text{BF}_3 \cdot \text{OEt}_2$ also resulted in non-selective desilylation by TLC. Next, use of a basic fluoride source was attempted through the treatment of **68** with TBAF in THF. After two days there was no change to the reaction when monitored by TLC.

Next, buffered fluoride sources other than $\text{HF} \cdot \text{pyr}$ were used to affect selective desilylation. It was our hope that less reactive conditions would decrease the deprotection reaction rate of the secondary alcohols while maintaining reactivity with the primary silyl ether. Addition of NH_4F to a solution of **68** in MeOH showed no appreciable change to the mixture by TLC after two days. A solution of TBAF in THF buffered with AcOH was used to treat **68** to afford primary desilylation. After 6 h, the desired product **69** was isolated in 26% with recovered **68** in 57% yield, while over-reacted substrate **70** was recovered in approximately 17% yield. The polyol mixture **70** was treated with TBSOTf and 2,6-lutidine to afford **68** in 79% yield.

Though these conditions have a lower yield of **69** than using $\text{HF} \cdot \text{pyr}$, the total recovered mass balance is higher. Treatment of a sample of **68** in three iterations of deprotection and recovery resulted in an overall yield of 55% of **69**, recovery of **68** in 8% yield, and the remaining polyol mixture **70** isolated in approximately 40% yield.

Figure 2.16 - Selective Desilylation of the Primary Alcohol of 68



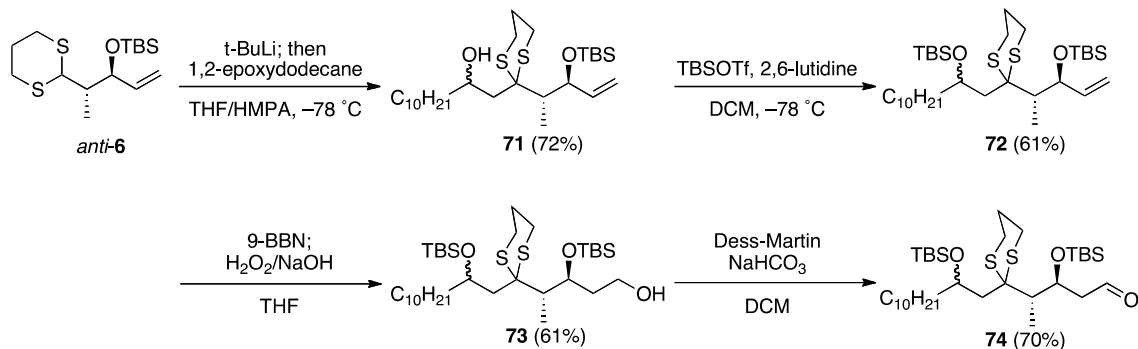
2.6 Model Coupling of C1-8 Fragment and Test Deprotection

After the final fragment **7** will be coupled to complete the full carbon framework of tetrafibricin, the deprotection strategy will be to first hydrolyze the dithiane at C13 to a ketone, followed by global deprotection of all of the silyl groups and the *tert*-butyl ester. In order to test the viability of dithiane hydrolysis in the presence of the tetraene moiety introduced by coupling fragment **7**, a model system was constructed and subjected to conditions to afford this transformation.

Lithiation of *anti*-**6** with *t*-BuLi in the presence of HMPA at -78°C , followed by alkylation with 1,2-epoxydodecane gave **71** in 72% yield after flash chromatography (Figure 2.13). The resulting diastereomeric mixture of alcohols was silylated with TBSOTf at -78°C to give **72** in 75% yield. The alkene of **72** was hydroborated with 9-BBN, then treated with H_2O_2 and NaOH to afford primary alcohol **73** in 61% yield.

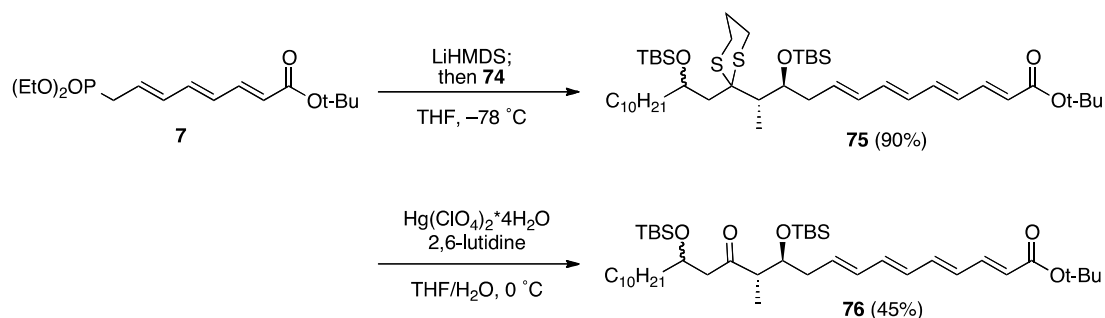
Oxidation of **73** with TEMPO and BAIB⁴² afforded an impure sample of aldehyde **74** in 27% yield. However, the by-products were difficult to separate from the product. In contrast, oxidation with Dess-Martin periodinane afforded aldehyde **75** in 70% yield in good purity after flash chromatography.

Figure 2.17 - Synthesis of the Model System Precursor 74



Next, **74** and **7** were coupled through a Horner-Wadsworth-Emmons olefination reaction (Figure 2.14).²⁰ Treatment of **7** with LiHMDS at $-78\text{ }^{\circ}\text{C}$, followed by addition of aldehyde **74** to give tetraene **75** in 90% yield as a single (*E*)-isomer, evident from the coupling constants of the new alkene resonances (6.37 ppm, dd, $J = 14.6\text{ Hz}, 11.7\text{ Hz}$; 6.13 ppm, dd, $J = 15.0, 10.7\text{ Hz}$). Dithiane **75** was then treated with $\text{Hg}(\text{ClO}_4)_2 \cdot 3\text{H}_2\text{O}$ and 2,6-lutidine in a 4:1 mixture of THF/ H_2O at $0\text{ }^{\circ}\text{C}$ for 1 h to afford ketone **76** in 45% yield after flash chromatography. Analysis of the ^1H NMR spectra of **76** shows the dithiane resonances are not present as compared to **75**, and the eight alkene resonances remain present (refer to the spectra in the experimental section). Resonances observed in the ^{13}C NMR show the presence of a ketone for each of the diastereomers (212.3 and 211.9 ppm). This experiment shows the tetraene is stable to the conditions required for final dithiane deprotection.

Figure 2.18 - Coupling and Deprotection of the Model System



2.7 Attempts to Complete the Synthesis of the C21-C30 Fragment

The resynthesis of the C21-C30 fragment for the purpose of completing this work was started by Dr. Zhang, however the resulting material was below the required amount to complete the synthesis at or above the target quantity. The first priority at this stage in the synthesis was to perform the final steps toward synthesis of the C21-C30 fragment **4** in preparation for the Julia-Kocienski coupling reaction to the C9-C20 framework. A decision was made to proceed using the available late stage intermediates available. The most readily available source of an intermediate leading to **4** was the fully TBS protected framework **38** synthesized by Dr. Zhang. Differentiation of the protecting group on the primary alcohol to a more labile silyl group (in this case, a TES group) was the primary objective in order to facilitate later stage deprotection for coupling when material is more limited (Figure 2.15). Using the conditions that were determined to be most successful for the selective desilylation of the primary alcohol leading to C9-C20 fragment **69**,

Figure 2.19 - Selective Deprotection of 38

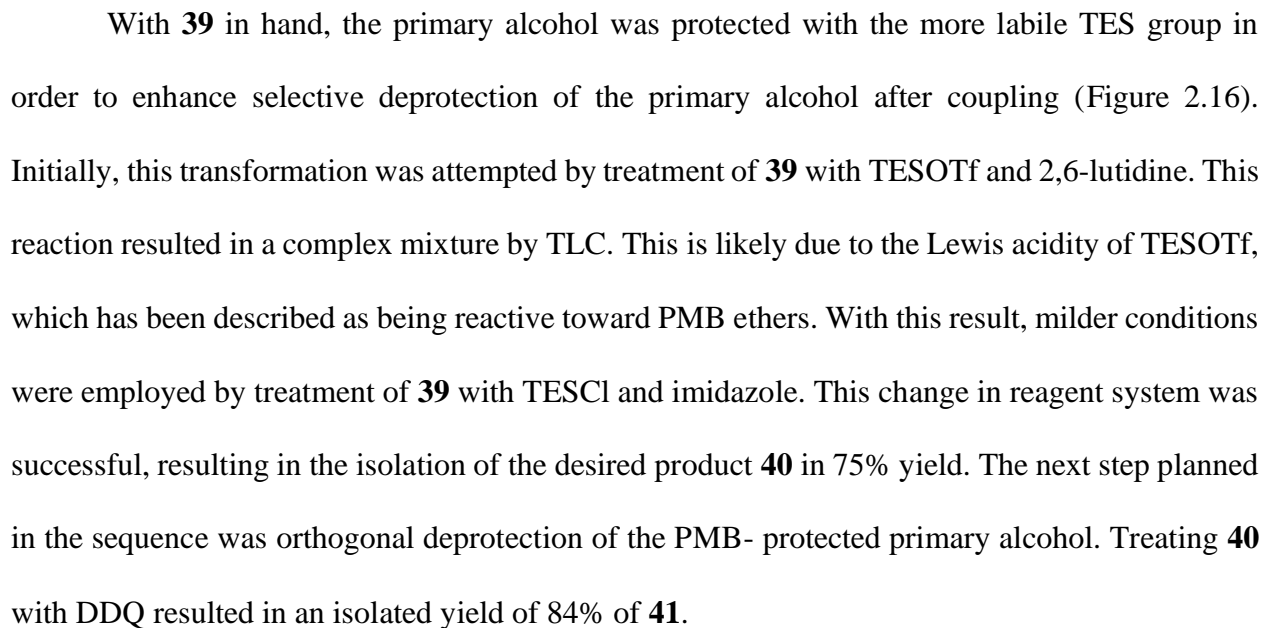
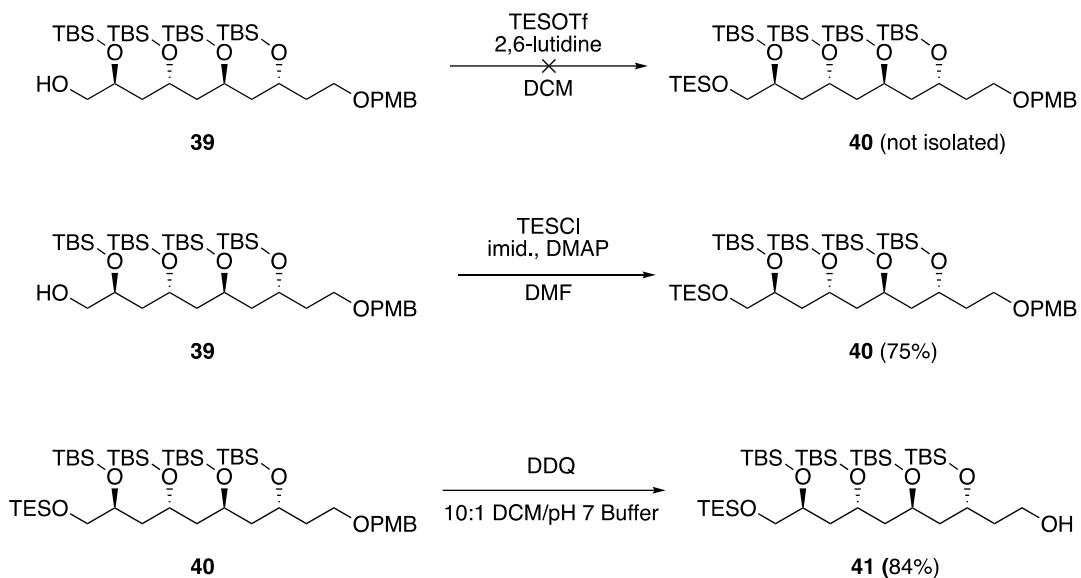
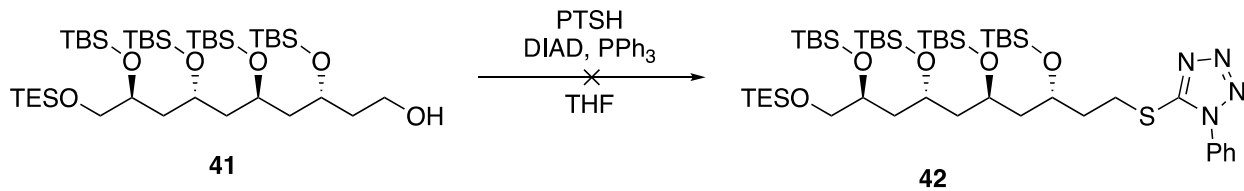


Figure 2.20 - Modification of 39



With **41** (approx. 125 mg) in hand, the final modifications to prepare the coupling partner for the Julia-Kocienski olefination reaction were underway. Primary alcohol **41** was subjected to Mitsunobu conditions using PTSH as a nucleophile in order to arrive at sulfide **42** (Scheme 2.7.3). After two attempts with limited material, analysis of the crude ^1H NMR determined that the reaction mixture did not contain the desired product. At this point, it was evident that greater quantities of the C21-C30 fragment were to be necessary in order to move the synthesis forward.

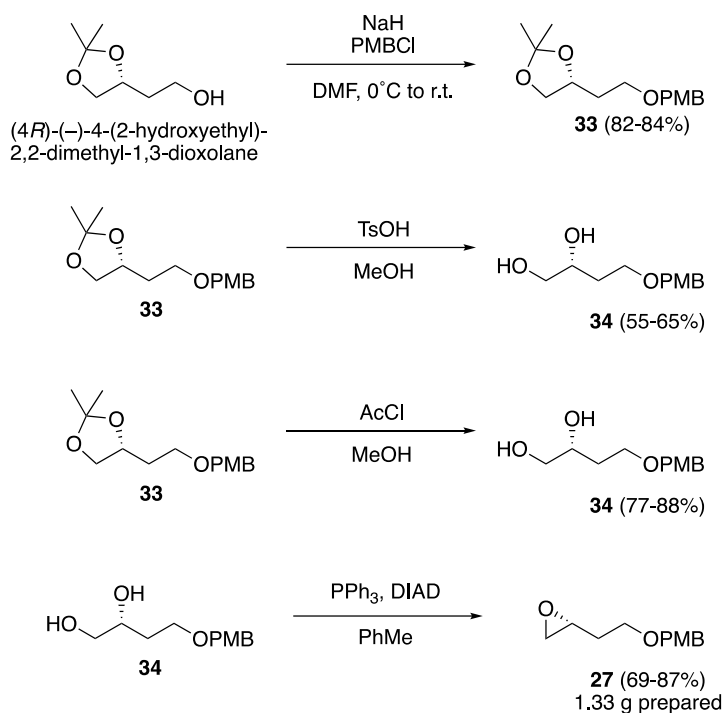
Figure 2.21 - Preparation of the Julia-Kocienski Coupling Partner 42



2.8 Attempts to Produce Additional Quantities of Fragment C21-C30

The synthetic pathway outlined by Dr. Zhang²⁵ was decided to be the best course of action to most rapidly access the material needed to continue the coupling of the final fragments that were already in hand. Dithiane **27** was available in multi-gram quantities to move forward with the resynthesis, such that furthering the material towards the full C21-C30 required epoxide **27** (Scheme 2.1.4). The first step was to protect commercially available (4*R*)-(-)-4-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolane by synthesis of its *p*-methoxybenzyl ether **84** by treatment with PMBCl (Figure 2.18). The reaction was performed twice on a 5 g scale, to result in 15.45 g of **33** to continue with the required transformations. The following step was deprotection of the acetonide of **33** under acidic conditions. Initially, 10 mol% *p*-toluenesulfonic acid monohydrate was used, however this led to less than ideal yield with lowered material throughput. Conditions using 20 mol% acetyl chloride to generate hydrogen chloride *in situ* resulted in improved yields of **34**. The resulting diol **34** underwent ring closing epoxidation under Mitsunobu conditions²³ to give a total of 1.33 g of **27** in the desired stereochemical configuration.

Figure 2.22 - Initial Transformations for the C21-C30 Fragment Resynthesis



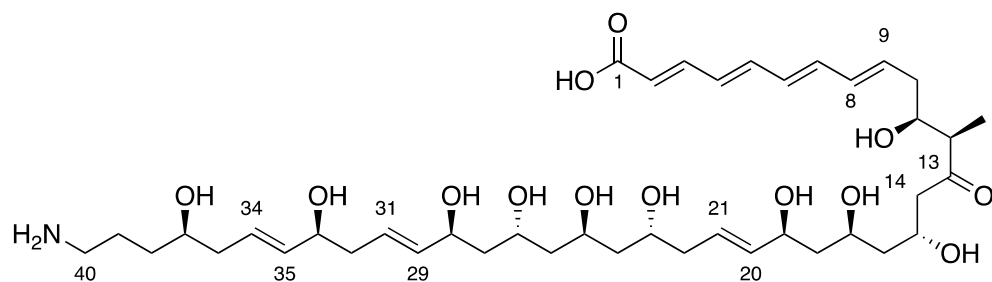
2.9 Publication of the Total Synthesis of *N*-Acetyl Dihydro-Tetrafibricin Methyl Ester

In the midst of efforts to scale up the material required to carry out the rest of the synthesis, the Roush group published their attempts at the synthesis of tetrafibricin.¹⁴ The work performed in this document overlapped with previously published work to come out of the Curran group, and the strategy did not provide a benefit over the synthesis reported by Roush. As the result of this, work towards the total synthesis of tetrafibricin ceased.

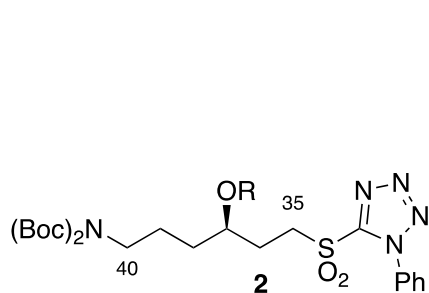
2.10 Summary

Most of the fragments **2–7** have been synthesized in quantities to achieve the synthesis of a target amount of 0.5 mmol of tetrafibricin **1** following the successful fragment coupling strategy demonstrated by Dr. Zhang.¹⁸ Fragment **2** (C35-C40) is available in a 3.9 mmol quantity, and fragment **3** (C31-C34) in a 15.0 mmol quantity. Compound **69** (C9-C20), derived from fragments **5** (C14-C20) and **6** (C9-C13), is available in a 1.3 mmol quantity, with advanced precursors totaling over 10 mmol in quantity. Fragment **7** (C1-C8) is available as the more stable allylic alcohol **65** in a 1.1 mmol quantity (Figure 2.23).

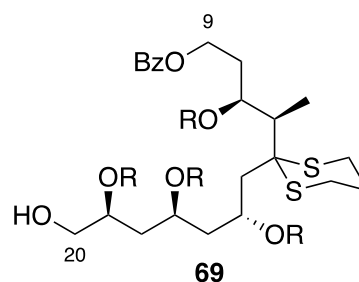
Figure 2.23 - Summary of the Fragments of Tetrafibricin



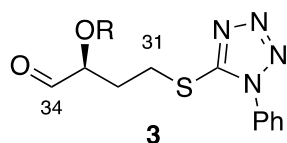
Tetrafibricin 1



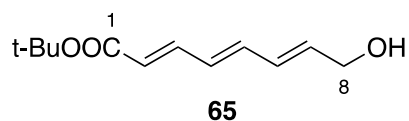
C35-C40 Fragment - 3.9 mmol available



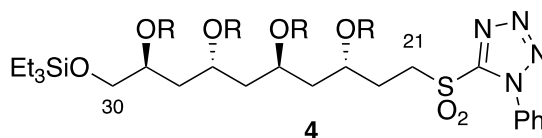
C9-C20 Fragment - 1.3 mmol available
> 10 mmol available as alkene **13**



C31-C34 Fragment - 15.0 mmol available



C1-C8 Fragment - 1.1 mmol available
1 step precursor to **7**



R = *t*-butyl dimethylsilyl

C21-C30 Fragment - **Limited**

The challenges within this synthesis were the result of difficulties stemming from selective protecting group manipulation. Finding conditions to differentiate of which silyl groups cleaved was difficult and time consuming, and the presence of a large number of silyl groups led to

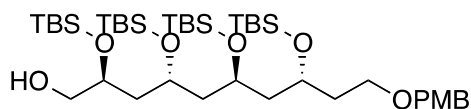
difficulties separating out impurities through physical or chromatographic means to avoid carrying them through to late stage intermediates.

Improvements to the planned synthetic route within this work included reduction the number of steps required to synthesize the C1-C8 fragment by introducing an zinc mediated Arbuzov reaction to arrive at the final phosphonate **7**. Conversion to the final C14-C20 fragment was optimized to increase the yield to 99% on a multi-gram scale. The dithiane-iodide coupling reaction between the C9-C13 and C14-C20 fragments was improved to a yield of 98% through altering the stoichiometry of the coupling partners. A more mild deprotection strategy was deployed on the C9-C20 and C21-C30 fragments in order to selectively cleave a primary silyl-protected alcohol in the presence of multiple secondary silyl-protected alcohols. This work also determined that the tetraenoate moiety of tetrafricin **1** can tolerate the deprotection conditions required to hydrolyze a 1,3-dithiane to a ketone using mercury perchlorate trihydrate.

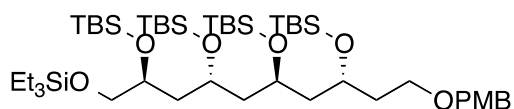
The work presented in this chapter did not result in publication. The content overlapped with previously published work, nor provided an appreciable benefit over the synthesis published by the Roush group. However, the studies and improvements made to the synthesis were highly beneficial for material throughput to fulfill increased material demands to perform the final fragment coupling strategy.

3.0 Experimental

Commercially available chemicals were used as received (Sigma-Aldrich). Solvents were dried by passing through an activated alumina column under and atmosphere of argon, unless otherwise noted. When noted, dry THF was prepared by distillation from sodium benzophenone ketyl under a dry argon atmosphere. Water-sensitive reactions were carried out under an inert atmosphere of dry argon. TLC analysis was performed by illumination with a UV lamp (254 nm) or by staining with a PMA solution in ethanol and heating. All flash chromatography was performed on a CombiFlash instrument (Teledyne Isco), using pre-packed silica gel cartridges. ^1H NMR spectra were recorded at 293K on a Bruker Avance 300 and 400 instruments using deuterated chloroform (CDCl_3) as solvent, unless otherwise indicated. ^{13}C NMR spectra were measured on Bruker Avance instruments at 75 and 100 MHz, unless otherwise indicated. The chemical shifts in spectra were measured in parts per million (ppm) on the delta (δ) scale. ^1H NMR spectra were calibrated relative to the tetramethylsilane (δ 0.00 ppm). ^{13}C NMR spectra were calibrated relative to CDCl_3 (δ 77.16 ppm).⁴³

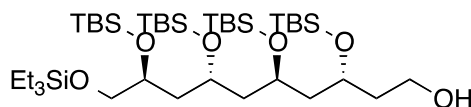


(2*S*,4*R*,6*S*,8*R*)-2,4,6,8-Tetrakis(*tert*-butyldimethylsilyloxy)-10-(4-methoxybenzyloxy)decan-1-ol (39**):** AcOH (0.31 mL, 5.5 mmol) and TBAF (1M in THF, 5.5 mL, 5.5 mmol) was added to a solution of **38** (1.02 g, 1.1 mmol) in THF (22 mL). After 7 h, the reaction was quenched with saturated NaHCO₃, and extracted with Et₂O. The combined organic layers were dried over MgSO₄, and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO₂, 10% ethyl acetate in hexanes) to give **39** (159 mg, 18%), recovered **38** (479 mg, 46%), and a mixture of desilylated products (179 mg). ¹H NMR (400 MHz, CDCl₃) δ 7.24 (d, 2H), 6.86 (d, *J* = 8.2 Hz, 2H), 4.44 (s, 2H), 3.90-3.75 (m, 7H), 3.60 (dd, *J* = 10.7, 4.6 Hz, 1H), 3.52-3.39 (m, 3H), 1.88 (t, *J* = 6.1 Hz, 1H), 1.81 (quint, *J* = 6.2 Hz, 1H), 1.74-1.52 (m, 6H), 0.92-0.82 (m, 36H), 0.11-0.01 (m, 24H).



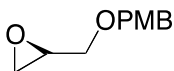
(5*R*,7*S*,9*R*,11*S*)-7,9,11-Tris(*tert*-butyldimethylsilyloxy)-14,14-diethyl-5-(2-(4-methoxybenzyloxy)ethyl)-2,2,3,3-tetramethyl-4,13-dioxo-3,14-disila-hexadecane (40**):** Triethylsilyl chloride (0.11 mL, 0.65 mmol) was added to a solution of **39** (193 mg, 0.24 mmol), imidazole (64 mg, 0.93 mmol), and DMAP (~2 mg) in DMF (2.5 mL). After 3 h, the reaction was quenched with saturated NaHCO₃ (3 mL) and extracted with Et₂O. The organic layers were combined, dried over MgSO₄, and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO₂, 5% ethyl acetate in hexanes) to give **40** (166 mg, 75%)

as a clear oil. ^1H NMR (400 MHz, CDCl_3) δ 7.24 (d, 2H), 6.86 (d, $J = 8.3$ Hz, 2H), 4.41 (s, 2H), 3.93-3.74 (m, 7H), 3.54-3.43 (m, 3H), 3.37 (dd, $J = 10.0, 5.4$ Hz, 1H), 1.86-1.40 (m, 8H), 0.95 (t, $J = 8.0$ Hz, 9H), 0.90-0.82 (m, 36H), 0.58 (q, $J = 7.9$ Hz, 6H), 0.08-0.01 (m, 24H).



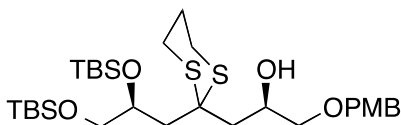
(3R,5S,7R,9S)-3,5,7,9-Tetrakis(*tert*-butyldimethylsilyloxy)-10-(triethylsilyloxy)decan-1-ol

(41): 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (16 mg, 0.070 mmol) was added to a solution of PMB ether **40** (50 mg, 0.054 mmol) in dichloromethane (1.8 mL) and pH 7 buffer (0.18 mL). After 2.5 h, the reaction was quenched with saturated NaHCO_3 (2 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over MgSO_4 , concentrated, and purified via flash chromatography to yield alcohol **41** (35 mg, 85%) as a clear oil. ^1H NMR (400 MHz, CDCl_3) δ 3.97 (t, $J = 5.4$ Hz, 1H), 3.93-3.66 (m, 5H), 3.50 (dd, $J = 9.9, 5.6$ Hz, 1H), 3.40 ($J = 9.9, 5.4$ Hz, 1H), 2.39 (t, $J = 5.2$ Hz, 1H), 1.94-1.59 (m, 6H), 1.52-1.41 (m, 1H), 0.95 (t, $J = 8.0$ Hz, 9H), 0.92-0.82 (m, 36H), 0.59 (q, $J = 7.8$ Hz, 6H), 0.11-0.03 (m, 24H).



(S)-2-(4-Methoxybenzyloxymethyl)oxirane (46): A solution of (*S*)-(-)-glycidol (5.0 g, 67.5 mmol) in dry THF (10 mL) was slowly added to a suspension of NaH (60%, 4.05 g, 101.2 mmol) in THF (40 mL) at 0 °C. After 1 h, *p*-methoxybenzyl chloride (13.8 mL, 101.2 mmol) and *n*-

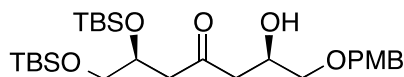
tetrabutylammonium iodide (3.7 g, 10.1 mmol) were added. The reaction was warmed to room temperature overnight, then poured in H₂O (50 mL). The organic layer was separated, and the aqueous layer was extracted with Et₂O. The combined organic layers were washed with H₂O (50 mL) then brine (50 mL), dried over MgSO₄, then concentrated. The crude product mixture was purified by flash chromatography to give **46** (8.4 g, 64%) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.28 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.52 (q, *J* = 11.6 Hz, 2H), 3.81 (s, 3H), 3.73 (dd, *J* = 11.4, 3.1 Hz, 1H), 3.42 (dd, *J* = 11.4, 5.8 Hz, 1H), 3.17 (sext, *J* = 3.1 Hz, 1H), 2.80 (t, *J* = 4.6 Hz, 1H), 2.61 (dd, *J* = 5.0, 2.7 Hz, 1H).



(*R*)-1-(2-((*S*)-2,3-Bis(*tert*-butyldimethylsilyloxy)propyl)-1,3-dithian-2-yl)-3-(4-

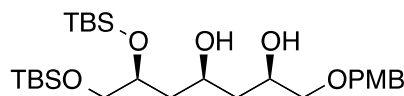
methoxybenzyloxy)propan-2-ol (47**):** *tert*-Butyllithium (1.7 M in pentane, 31 mL, 50 mmol) was added to a solution of dithiane **45** (20.2 g, 47.9 mmol) in freshly distilled THF (80 mL) and HMPA (20 mL) at −78 °C. After 10 min, a solution of epoxide **46** (22.2 g, 114 mmol) in THF (130 mL) was added over 1 h. The reaction was warmed to 0 °C after 15 min, and allowed to stir at that temperature for 1.5 h. The reaction mixture was poured into saturated aqueous NH₄Cl solution (100 mL) and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over MgSO₄, concentrated, and purified by flash column chromatography (25% ethyl acetate in hexanes) to provide **47** (14.6 g, 58%) as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.49 (s, 2H), 4.33-4.25 (m, 1H), 4.10-4.03 (m, 1H), 3.81 (s, 3H), 3.59 (dd, *J* = 9.7, 4.7 Hz, 1H), 3.45-3.35 (m, 3H), 3.14 (d, *J* = 2.7 Hz, 1H), 2.96-2.78

(m, 3H), 2.78-2.68 (m, 1H), 2.60 (dd, $J = 15.1, 2.8$ Hz, 1 H), 2.25 (dd, $J = 15.4, 8.3$ Hz, 1H), 1.98-1.85 (m, 3H), 0.90 (s, 9H), 0.86 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.08-0.05 (m, 6H).



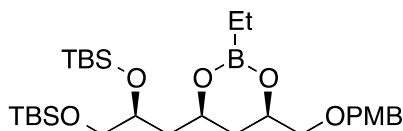
(2*R*,6*S*)-1-(4-Methoxybenzyloxy)-6,7-bis(*tert*-butyldimethylsilyloxy)-2-hydroxyheptan-4-one

(48): (**CAUTION:** Mercury (II) perchlorate trihydrate poses a risk of explosion if the reaction is not able to dissipate heat efficiently!²⁵ Monitor reaction temperature closely while *slowly* adding the mercury salt to the reaction!) Hg(ClO₄)₂•3H₂O (7.06 g, 16.9 mmol) was added in portions to a solution of **47** (4.16 g, 6.7 mmol) and 2,6-lutidine (3.9 mL, 33.7 mmol) in 4:1 THF/H₂O (100 mL) at 0 °C. After 1.5 h, the reaction was filtered through a pad of celite, and rinsed with ethyl acetate. The mixture was diluted with ethyl acetate (200 mL), and washed with saturated aqueous NH₄Cl. The combined organic layers were extracted with ethyl acetate, and the combined organic layers were dried over MgSO₄, concentrated, and purified by flash chromatography (25% ethyl acetate in hexanes) to give ketone **48** (3.10 g, 87%) as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 7.25 (d, $J = 8.6$ Hz, 2H), 6.88 (d, $J = 8.5$ Hz, 2H), 4.45 (s, 2H), 4.28-4.20 (m, 1H), 4.20-4.14 (m, 1H), 3.81 (s, 3H), 3.56 (dd, $J = 9.9, 4.9$ Hz, 1H), 3.47-3.34 (m, 3H), 3.01 (d, $J = 3.6$ Hz), 2.75-2.60 (m, 3H), 2.55 (dd, $J = 15.7, 7.3$ Hz, 1 H), 0.87 (s, 9H), 0.84 (s, 9H), 0.06 (s, 3H), 0.05-0.02 (m, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 209.8, 159.4, 130.2, 129.5, 114.0, 73.2, 73.1, 69.7, 67.1, 66.9, 55.4, 48.6, 47.5, 26.0, 25.9, 18.5, 18.1, -4.4, -4.8, -5.2, -5.3.



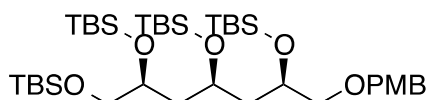
(2*R*,4*S*,6*S*)-1-(4-Methoxybenzyloxy)-6,7-bis(*tert*-butyldimethylsilyloxy)heptane-2,4-diol

(49): Diethylmethoxyborane (1.0 M in THF, 32.9 mL, 32.9 mmol) was added to a solution of ketone **48** (15.8 g, 29.9 mmol) in THF (240 mL) and MeOH (60 mL) at -78°C . After 30 minutes, sodium borohydride (1.36 g, 35.9 mmol) was added in portions. The reaction was warmed to 0°C after 3 h, to which was added 3 N NaOH (46 mL), and 30% H_2O_2 (19 mL). After 1 h, the reaction was quenched with H_2O (500 mL) and diluted with diethyl ether (500 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with H_2O (500 mL) then brine (500 mL), dried over MgSO_4 , and concentrated. The crude product was purified by flash chromatography (25% ethyl acetate in hexanes) to give *syn,syn*-diol **50** (14.94 g, 94%) as a clear oil. ^1H NMR (400 MHz, CDCl_3) δ 7.26 (d, $J = 8.6$ Hz, 2H) 6.87 (d, $J = 8.6$ Hz, 2H), 4.49 (s, 2H), 4.12-4.00 (m, 2H), 3.94 (s, 1H), 3.93-3.85 (m, 1H), 3.81 (s, 3H), 3.65 (d, $J = 1.5$ Hz, 1H), 3.59 (dd, $J = 10.1, 4.3$ Hz, 1H), 3.47 (dd, $J = 10.1, 6.6$ Hz, 1H), 3.44-3.37 (m, 2H), 1.75 (ddd, $J = 14.3, 5.1, 3.1$ Hz, 1H), 1.69-1.56 (m, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.09 (s, 6H), 0.06 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 159.3, 130.3, 129.4, 113.8, 74.1, 73.0, 72.1, 70.8, 69.7, 67.6, 55.2, 42.5, 40.2, 26.0, 25.9, 18.3, 18.0, -4.2 , -4.8 , -5.4 , -5.4 .



(4*R*,6*S*)-2-Ethyl-4-(4-methoxybenzyloxymethyl)-6-((2*R*)-2,3-bis(*tert*-

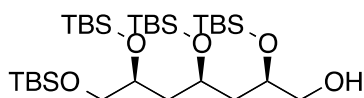
butyldimethylsilyloxy)propyl)-1,3,2-dioxaborinane (50): This compound was isolated from the purification of **50**, as a clear oil. ^1H NMR (400 MHz, CDCl_3) δ 7.27 (d, $J = 8.6$ Hz, 2H), 6.87 (d, $J = 8.6$ Hz, 2H), 4.52 (s, 2H), 4.17-4.04 (m, 2H), 3.91 (quint, $J = 5.6$ Hz, 1H), 3.81 (s, 3H), 3.61 (dd, $J = 10.3, 5.6$ Hz, 1H), 3.54-3.48 (m, 2H), 3.39 (dd, $J = 9.9$ Hz, 5.4 Hz), 1.96 (dt, $J = 13.8, 2.7$ Hz, 1H), 1.69 (t, $J = 6.2$ Hz, 2H), 1.37 (dt, $J = 13.7, 11.5$ Hz, 1H), 0.90-0.84 (m, 21H), 0.67 (q, $J = 7.8$ Hz, 2H), 0.08-0.02 (m, 12H); ^{13}C NMR (75 MHz, CDCl_3) δ 159.3, 130.3, 129.2, 113.8, 73.5, 73.1, 70.5, 70.3, 68.1, 67.7, 55.1, 42.6, 36.2, 26.0, 26.0, 18.4, 18.1, 7.9, 7.2, -4.2, -4.8, -5.3, -5.3; ^{11}B NMR (96 MHz, CDCl_3) δ +31.0 (br s); LRMS (TOF ES) m/z : Calcd for $\text{C}_{29}\text{H}_{56}\text{BO}_6\text{Si}_2$ $[\text{M}+\text{H}]^+$ 567; Found 567.



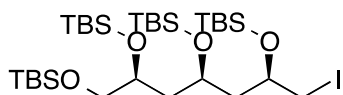
1-(((2*R*,4*S*,6*S*)-2,4,6,7-Tetrakis(*tert*-butyldimethylsilyloxy)heptyloxy)methyl)-4-

methoxybenzene (51): *tert*-Butyldimethylsilyl trifluoromethanesulfonate (8.7 mL, 37.8 mmol) was added to a solution of diol **50** (9.09 g, 17.2 mmol) and 2,6-lutidine (6.0 mL, 51.6 mmol) in dichloromethane (85 mL) at 0 °C. The reaction was warmed to room temperature overnight, then poured into H_2O (85 mL). The organic layer was separated and washed with H_2O . The organic layer was dried over MgSO_4 , concentrated, and purified via flash chromatography (10% ethyl

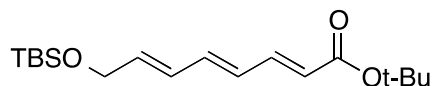
acetate in hexanes to yield **51** (12.6 g, 96%) as a clear oil. ^1H NMR (400 MHz, CDCl_3) δ 7.24 (d, $J=8.6$ Hz, 2H), 6.85 (d, $J=8.3$ Hz, 2H), 4.44 (q, $J=10.9$ Hz, 2H), 3.98-3.91 (m, 1H), 3.87-3.75 (m, 5H), 3.51 (dd, $J=9.9, 4.5$ Hz, 1H), 3.47-3.36 (m, 2H), 3.30 (dd, $J=9.7, 6.3$ Hz, 1H), 1.77-1.64 (m, 2H), 1.63-1.52 (m, 2H), 0.90-0.84 (m, 36H), 0.06-0.01 (m, 24H); ^{13}C NMR (75 MHz, CDCl_3) δ 159.2, 130.8, 129.3, 113.8, 74.7, 73.0, 70.8, 69.3, 67.9, 66.9, 55.3, 43.0, 42.8, 26.2, 26.1, 26.1, 18.5, 18.3, 18.3, 18.1, -3.9, -4.0, -4.2, -4.3, -4.5, -4.5, -5.1, -5.2.



(2R,4S,6S)-2,4,6,7-Tetrakis(*tert*-butyldimethylsilyloxy)heptan-1-ol (52): 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (2.61 g, 11.5 mmol) was added to a solution of PMB ether 51 (6.69 g, 8.8 mmol) in dichloromethane (166 mL) and pH 7 buffer (9 mL). After 1 h, the reaction was diluted with dichloromethane (100 mL) and quenched with saturated NaHCO_3 (100 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over MgSO_4 , concentrated, and purified via flash chromatography to yield alcohol 52 (5.50 g, 98%) as a clear oil. ^1H NMR (400 MHz, CDCl_3) δ 3.99-3.89 (m, 2H), 3.69 (sext, $J=4.7$ Hz, 1H), 3.62-3.54 (m, 1H), 3.53-3.37 (m, 3H), 2.71 (dd, $J=7.9, 5.4$ Hz, 1H), 1.82-1.74 (m, 2H), 1.73-1.58 (m, 2H), 0.90-0.86 (m, 36H), 0.10-0.03 (m, 24H); ^{13}C NMR (75 MHz, CDCl_3) 70.8, 70.0, 67.9, 67.2, 66.6, 42.4, 41.8, 26.1, 26.0, 26.0, 18.5, 18.2, 18.1, -3.8, -4.2, -4.3, -4.5, -4.6, -5.2, -5.2.

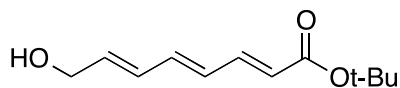


(2*S*,4*R*,6*R*)-1,2,4,6-Tetrakis(*tert*-butyldimethylsilyloxy)-7-iodoheptane (5): Imidazole (214 mg, 3.14 mmol), triphenylphosphine (740 mg, 2.82 mmol), and iodine (756 mg, 2.98 mmol) were added in that order to a solution of alcohol **52** (1.00 g, 1.57 mmol) in benzene (20 mL). After 1 h, the reaction was quenched with saturated Na₂S₂O₃ (20 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether. The combined organic extracts were dried over MgSO₄ and concentrated. The crude product was purified by flash chromatography (5% dichloromethane in hexanes) to yield iodide **5** (1.16g, 99%) as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 3.81 (ddd, *J* = 10.4, 7.4, 5.4 Hz, 1H), 3.85-3.70 (m, 2H), 3.68-3.61 (m, 1H), 3.51-3.43 (m, 2H), 3.34 (dd, *J* = 10.2, 4.1 Hz, 1H), 3.20 (dd, *J* = 10.2, 4.8 Hz, 1H), 1.83-1.56 (m, 4H), 0.91-0.87 (m, 36H), 0.11 (s, 3H), 0.09-0.03 (m, 21H); ¹³C NMR (75 MHz, CDCl₃) δ 70.8, 68.4, 67.7, 66.9, 45.3, 42.3, 26.2, 26.1, 26.1, 26.0, 18.5, 18.3, 18.2, 18.1, 15.4, -3.9, -4.1, -4.2, -4.3, -5.1, -5.2.

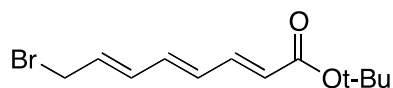


(2*E*,4*E*,6*E*)-*tert*-Butyl-8-(*tert*-butyldimethylsilyloxy)octa-2,4,6-trienoate (64): *tert*-Butyldiethylphosphonoacetate (0.20 mL, 0.87 mmol) was slowly added to a suspension of NaH (35 mg, 0.87 mmol) in THF (8 mL) at 0 °C. After 20 min, the reaction was cooled to -78 °C. The reaction mixture was added via cannula to a solution of aldehyde **63** (178 mg, 0.79 mmol) in THF (8 mL) at -78 °C. The reaction was allowed to warm to room temperature and after 2 h was

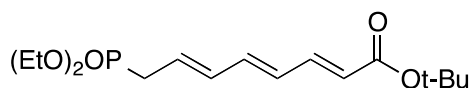
quenched with saturated aqueous NaHCO₃ solution (8 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous NaCl solution, dried over MgSO₄ and concentrated. The crude product was purified by flash column chromatography (SiO₂, 5% ethyl acetate in hexanes) to yield ester **64** (197 mg, 77%) as a clear oil. ¹H NMR (300 MHz, CDCl₃) δ 7.20 (dd, *J* = 15.2, 11.2 Hz, 1H), 6.54 (dd, *J* = 14.8, 10.8 Hz, 1H), 6.37-6.23 (m, 2H), 5.96 (dt, *J* = 15.2, 5.2 Hz, 1 H), 5.80 (d, *J* = 15.2, 1H), 4.27 (d, *J* = 4.4 Hz, 2H), 1.49 (s, 9H), 0.92 (s, 9H), 0.08 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 166.6, 143.5, 139.6, 138.6, 137.3, 133.5, 129.5, 128.8, 124.9, 122.9, 80.2, 63.3, 29.8, 28.3, 26.0, 18.5, -5.2; HRMS (TOF ES) *m/z*: Calcd for C₁₈H₃₃O₃Si [M+H]⁺ 325.2193; Found 325.2155; IR (neat) cm⁻¹ 2955, 2931, 2888, 2857, 1708, 1620, 839.



(2E,4E,6E)-tert-Butyl 8-hydroxyocta-2,4,6-trienoate (65): A solution of tetrabutylammonium fluoride (1.0M in THF 1.31 mL) was added directly to silyl ether **64** (404 mg, 1.24 mmol). After 30 min, the mixture was diluted with ethyl acetate (85 mL) and washed with water. The organic layer was dried over MgSO₄ and concentrated. The crude mixture was purified by flash chromatography (SiO₂, 5-50% ethyl acetate in hexanes) to yield alcohol **65** (250 mg, 96%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.20 (dd, *J* = 15.2, 12.0 Hz, 1H), 6.54 (dd, *J* = 15.2, 10.8 Hz, 1H), 6.33 (m, 2H), 6.02 (dt, *J* = 15.2, 5.2 Hz, 1H), 5.82 (d, *J* = 15.6 Hz, 1H), 4.26 (t, *J* = 4.8 Hz, 2H), 1.49 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 166.6, 143.5, 139.5, 137.1, 129.8, 129.6, 80.4, 62.6, 28.1; R (neat) cm⁻¹ 3411, 2978, 2931, 1701, 1618, 1134, 1004, 849.

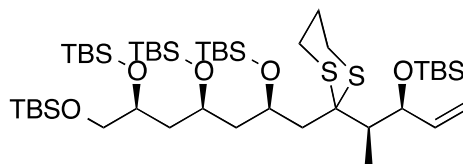


(2E,4E,6E)-tert-Butyl 8-bromoocta-2,4,6-trienoate (66): 2,6-lutidine (0.33 mL, 2.85 mmol), then thionyl bromide (0.18 mL, 2.38 mmol) was added to a solution of alcohol **65** (200 mg, 0.95 mmol) in THF (3.5 mL) at -20 °C and stirred for 1.5 h. The reaction was allowed to slowly warm to room temperature over 1.5 h, then was quenched with saturated NaHCO₃ solution (8 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over MgSO₄ and concentrated. The crude product was purified by flash chromatography (SiO₂, 10% ethyl acetate in hexanes) to give bromide **66** (119 mg, 46%) as a pale yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 7.18 (dd, *J* = 15.3, 11.1 Hz, 1H), 6.50 (dd, *J* = 14.7, 10.8 Hz, 1H), 6.39-6.28 (m, 2H), 6.03 (dt, *J* = 15.0, 7.8 Hz, 1H), 5.84 (d, *J* = 15.3 Hz, 1 H), 4.04 (d, *J* = 7.8 Hz, 2H), 1.49s (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 166.2, 142.6, 137.9, 134.0, 132.4, 132.0, 80.5, 32.5, 28.2; IR (neat) cm⁻¹ 3053, 3008, 2979, 2931, 1694, 1617, 1365, 1238, 1134, 1000, 846.



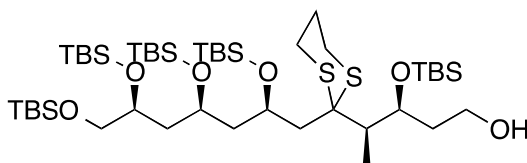
(2E,4E,6E)-tert-Butyl 8-(diethoxyphosphoryl)octa-2,4,6-trienoate (7): *Procedure A:* Bromide **66** (118 mg, 0.43 mmol) was added to a sealed flask and dissolved in toluene (1.6 mL). Triethyl phosphite (1.6 mL) was added, the flask was sealed, and the reaction was heated to 110 °C for 9 h. The reaction was cooled to room temperature, concentrated under reduced pressure, and the

crude product was purified by flash chromatography (SiO₂, 50% ethyl acetate in hexanes) to give phosphonate **7** (75 mg, 56%) as a white, waxy solid. *Procedure B*: Triethylphosphite (0.49 mL, 2.85 mmol), zinc iodide (455mg, 1.43 mmol), and allylic alcohol **65** (100mg, 0.48 mmol) were added to a sealed flask in that order, and heated at 55 °C for 2.5 h. The mixture was cooled to room temperature and added to 2 M NaOH (200 mL), then extracted with diethyl ether. The combined organic layers were dried over MgSO₄ and concentrated. Then crude product mixture was purified by flash column chromatography (25 to 100% ethyl acetate in hexanes) to give phosphonate **7** (86 mg, 54%) as white waxy solid. ¹H NMR (400 MHz, CDCl₃) δ 7.17 (dd, *J* = 15.2, 11.2 Hz, 1H), 6.51 (dd, *J* = 14.8, 10.8 Hz, 1H), 6.30-6.22 (m, 2H), 5.88-5.79 (m, 2H), 4.11 (dq, *J* = 7.2, 2.0 Hz, 4H), 2.69 (dd, *J* = 23.2, 8.0 Hz, 2H), 1.49 (s, 9H), 1.32 (t, *J* = 6.8 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 166.4, 143.2, 139.0 (*J*_{C-P} = 5 Hz), 134.4 (*J*_{C-P} = 15 Hz), 129.8 (*J*_{C-P} = 5 Hz), 80.3, 62.1 (*J*_{C-P} = 7 Hz), 31.2 (*J*_{C-P} = 139 Hz), 28.2, 16.5 (*J*_{C-P} = 6 Hz). HRMS (TOF ES) *m/z*: Calcd for C₁₆H₂₈O₅P [M+H]⁺ 331.1669; Found 331.1696; IR (neat) cm⁻¹ 2979, 2931, 1702, 1618, 1243, 1132, 1025, 964, 846. The spectroscopic data is in agreement with the previously reported ethyl ester of this compound.¹⁰



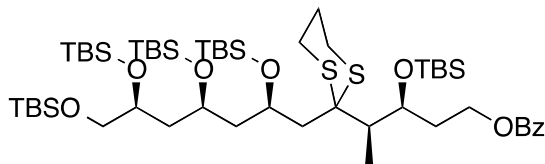
2-((2R,4S,6S)-2,4,6,7-Tetrakis(*tert*-butyldimethylsilyloxy)heptyl)-2-((2R,3S)-3-(*tert*-butyldimethylsilyloxy)pent-4-en-2-yl)-1,3-dithiane (13**):** *tert*-Butyllithium (1.7 M in pentane, 0.20 mL, 0.3 mmol) was added to a solution of dithiane **6** (1.00 g, 3.14 mmol) and HMPA (2.1 mL) in freshly distilled THF (15 mL) at -78 °C until a yellow color persisted, after which the

remainder (2.0 mL, 3.4 mmol) was added. After 1 h, a solution of iodide **5** (2.10 g, 2.81 mmol) in THF (4 mL) was added dropwise. After 2 h, the reaction was quenched with saturated NH₄Cl (15 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with H₂O, then brine, dried over MgSO₄, concentrated, and purified by flash chromatography (10% dichloromethane in hexanes) to yield **13** (2.53 g, 96%) as a white waxy solid. ¹H NMR (400 MHz, CDCl₃) δ 5.94 (ddd, *J* = 17.3, 10.1, 7.4 Hz, 1H), 5.12 (d, *J* = 17.1 Hz, 1H), 5.01 (d, *J* = 10.6 Hz, 1H), 4.93 (d, *J* = 7.7 Hz, 1H), 4.21 (quin, *J* = 5.2 Hz, 1H), 3.88-3.84 (m, 1H), 3.78-3.75 (m, 1H), 3.61 (dd, *J* = 10.1, 3.6 Hz, 1H), 3.43 (dd, *J* = 10.0, 7.2 Hz, 1H), 2.88-2.76 (m, 2H), 2.59-2.48 (m, 2H), 2.27 (q, *J* = 7.0 Hz, 1H), 1.98-1.87 (m, 3H), 1.85-1.58 (m, 5H), 1.09 (d, *J* = 7.0 Hz, 3H), 0.91-0.85 (m, 45H), 0.20 (s, 3H), 0.13 (s, 3H), 0.10-0.02 (m, 24H); ¹³C NMR (100 MHz, CDCl₃) δ 143.5, 113.7, 71.2, 67.8, 67.5, 67.0, 58.2, 49.5, 44.4, 44.0, 42.8, 26.4, 26.2, 26.2, 26.1, 26.0, 24.6, 18.5, 18.4, 18.3, 18.2, 9.0, -2.8, -2.9, -3.8, -3.9, -4.1.



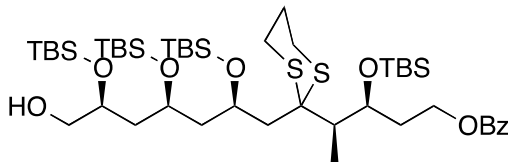
(3*S*,4*R*)-4-(2-(((2*R*,4*S*,6*S*)-2,4,6,7-Tetrakis(*tert*-butyldimethylsilyloxy)heptyl)-1,3-dithian-2-yl)-3-(*tert*-butyldimethylsilyloxy)pentan-1-ol (67**):** 9-BBN (0.5 M in THF, 42.7 mL, 21.3 mmol) was added directly to alkene **13** (5.0 g, 5.3 mmol). After 12 h the reaction was cooled to 0 °C, then H₂O (45 mL) and NaBO₃•4H₂O (9.84 g, 64.0 mmol) was added. After 5 h, the reaction was diluted with H₂O (45 mL) and diethyl ether (90 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether. The combined organic extracts were dried over MgSO₄,

concentrated, and purified by flash chromatography (15% ethyl acetate in hexanes) to give alcohol **67** (4.35 g, 85%) as a clear oil. ^1H NMR (400 MHz, CDCl_3) δ 4.46 (dd, $J = 9.1, 3.2$ Hz, 1H), 4.22-4.13 (m, 1H), 3.92-3.82 (m, 1H), 3.82-3.67 (m, 3H), 3.61 (dd, $J = 10.1, 3.3$ Hz, 1H), 3.42 (dd, $J = 10.0, 7.3$ Hz, 1H), 2.88 (ddd, $J = 13.7, 11.5, 2.3$ Hz, 1H), 2.78 (ddd, $J = 13.4, 10.8, 2.5$ Hz, 1H), 2.67-2.54 (m, 2H), 2.45-2.37 (m, 1H), 2.02-1.60 (m, 12H), 1.05 (d, $J = 6.9$ Hz, 3H), 0.96-0.79 (m, 45H), 0.18 (s, 3H), 0.13-0.02 (m, 27H); ^{13}C NMR (100 MHz, CDCl_3) δ 71.2, 69.3, 68.1, 67.8, 67.5, 67.1, 60.0, 58.1, 49.5, 44.5, 42.6, 42.1, 41.4, 40.7, 27.3, 26.3, 26.2, 26.1, 26.0, 25.8, 25.8, 24.8, 24.6, 18.5, 18.4, 18.4, 18.2, 18.2, 10.2, -2.9, -2.9, -3.8, -3.9, -4.2, -5.1, -5.2.



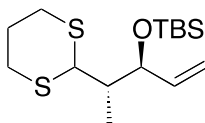
(3S,4R)-4-(2-((2R,4S,6S)-2,4,6,7-Tetrakis(*tert*-Butyldimethylsilyloxy)heptyl)-1,3-dithian-2-yl)-3-(*tert*-butyldimethylsilyloxy)pentyl benzoate (68**):** Benzoyl chloride (0.13 mL, 1.04 mmol) was added to a solution of alcohol **67** (0.90 g, 0.94 mmol), triethylamine (0.20 mL, 1.41 mmol), and DMAP (12 mg, 0.094 mmol) in dichloromethane (10 mL). After 4h, the reaction was quenched with saturated NaHCO_3 (10 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over MgSO_4 , concentrated, and purified by flash chromatography (10% ethyl acetate in hexanes) to yield benzoyl ester **68** (0.94 g, 94%) as a clear oil. ^1H NMR (400 MHz, CDCl_3) δ 8.05 (d, $J = 7.3$ Hz, 2H), 7.56 (t, $J = 7.4$ Hz, 1H), 7.44 (t, $J = 7.6$ Hz, 2H), 4.64 (dd, $J = 9.0, 3.4$ Hz, 1H), 4.45-4.27 (m, 2H), 4.22-4.14 (m, 1H), 3.93-3.83 (m, 1H), 3.82-3.71 (m, 1H), 3.62 (dd, $J = 10.0, 3.4$ Hz, 1H), 3.41 (dd, $J = 10.0, 7.4$ Hz, 1H), 2.85-2.70 (m, 2H), 2.54-2.39 (m, 3H), 2.12-1.57 (m, 10H), 1.09

(d, $J = 7.2$ Hz, 3H), 0.92-0.82 (m, 45H), 0.19-0.01 (m, 30H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.7, 133.1, 130.3, 129.7, 128.5, 71.3, 68.9, 67.8, 67.5, 67.1, 62.1, 57.9, 49.7, 44.6, 42.7, 41.2, 37.2, 26.3, 26.2, 26.2, 24.5, 18.5, 18.4, 18.4, 18.2, 18.2, 9.9, -3.0, -3.0, -3.7, -3.8, -3.9, -3.9, -4.2, -4.4, -5.1, -5.2.

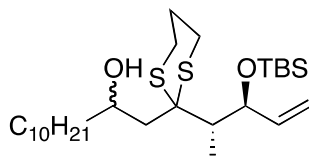


(3S,4R)-4-(2-((2R,4S,6S)-2,4,6-Tris(*tert*-Butyldimethylsilyloxy)-7-hydroxyheptyl)-1,3-dithian-2-yl)-3-(*tert*-butyldimethylsilyloxy)pentyl benzoate (69**):** AcOH (0.24 mL, 4.6 mmol) and TBAF (1M in THF, 4.6 mL, 4.6 mmol) were added to a solution of **68** (487 mg, 0.46 mmol) in THF (4.6 mL) at 0 °C. The reaction was warmed to room temperature, and was quenched after 6 h with 8 mL saturated NaHCO_3 (8 mL), and diluted with diethyl ether (8 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over MgSO_4 , concentrated, and purified by flash chromatography (10% ethyl acetate in hexanes) to give primary alcohol **69** (114 mg, 26%) as well as recovered **68** (280 mg, 57%), and a mixture of desilylated products **70** (73 mg). Recovered **68** was resubjected to these conditions to provide additional **69**. ^1H NMR (400 MHz, CDCl_3) δ 8.05 (d, $J = 7.4$ Hz, 2H), 7.57 (t, 7.3 Hz, 1H), 7.44 (t, $J = 7.7$ Hz, 2H), 4.57 (dd, $J = 9.3, 3.1$ Hz, 1H), 4.43-4.28 (m, 2H), 4.18-4.04 (m, 2H), 3.96-3.86 (m, 2H), 3.62-3.53 (m, 1H), 3.52-3.43 (m, 1H), 2.92-2.70 (m, 1H), 2.54-2.40 (m, 1H), 2.15-1.65 (m, 10H), 1.08 (d, $J = 6.9$ Hz, 3H), 0.92-0.85 (m, 36H), 0.20-0.01 (m, 24H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.7, 133.1, 130.3, 129.7, 128.5, 70.4, 68.8, 67.7, 67.0, 66.6, 62.0, 57.6, 49.3, 45.3, 41.4, 41.1, 37.1, 26.4, 26.3, 26.2, 26.0, 25.7, 24.2, 18.4, 18.2, 18.2,

18.1, 10.1, -2.8, -2.9, -3.9, -4.0, -4.1, -4.3, -4.5, -4.6.

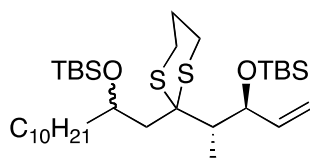


(3S, 4S)-3-tert-Butyldimethylsilyloxy-4-(1,3-dithian-2-yl)-1-pentene (anti-6): *tert*-Butyldimethylsilyl trifluoromethanesulfonate (2.9 mL, 12.7 mmol) was added to a solution of (*S,S*)-**58** (2.35 g, 11.5 mmol) and 2,6-lutidine (1.6 mL, 13.8 mmol) in dichloromethane (115 mL) at -78 °C. After 15 min, the reaction was warmed to 0 °C. After 2 h, the reaction was allowed to warm to room temperature overnight. The reaction was quenched with H₂O (50 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over MgSO₄, concentrated, and purified via flash chromatography (10% ethyl acetate in hexanes) to give *anti*-**6** (3.60 g, 98%) as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 5.68 (ddd, *J* = 17.3, 10.2, 7.5 Hz, 1H), 5.20-5.11 (m, 2H), 4.47 (d, *J* = 4.3 Hz, 1H), 4.13 (t, *J* = 8.0 Hz, 1H), 3.01-2.76 (m, 4H), 2.15-2.06 (m, 1H), 1.94-1.79 (m, 2H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.91 (s, 9H), 0.10 (s, 3H), 0.04 (s, 3H).



2-((2S,3S)-3-(tert-Butyldimethylsilyloxy)pent-4-en-2-yl)-2-(2-hydroxydodecyl)-1,3-dithiane (71): *tert*-Butyllithium (1.7 M in pentane, 7.0 mL, 11.9 mmol) was added slowly to a solution of dithiane *anti*-**6** (3.44 g, 10.8 mmol) and HMPA (4.3 mL) dissolved in freshly distilled THF (17

mL) at $-78\text{ }^{\circ}\text{C}$. After 10 min, a solution of 1,2-epoxydodecane (2.6 mL, 11.9 mmol) in THF (5 mL) was added to the reaction. After 15 min, the reaction was warmed to $0\text{ }^{\circ}\text{C}$. After 1 h, the reaction was quenched with saturated NH_4Cl (20 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over MgSO_4 , concentrated, and purified by flash chromatography (SiO_2 , 5% ethyl acetate in hexanes) to give **71** (3.95 g, 72%) as a 55:45 mixture of two diastereomers. ^1H NMR (400 MHz, CDCl_3) **Major diastereomer:** δ 5.94 (ddd, $J=17.1, 10.5, 6.5\text{ Hz}$, 1H), 5.19-5.10 (m, 2H), 4.68-4.61 (m, 1H), 4.12-4.03 (m, 1H), 3.45 (d, $J=1.6\text{ Hz}$, 1H), 1.18 (d, $J=7.0\text{ Hz}$, 3H); **Minor diastereomer:** δ 6.09 (ddd, $J=16.4, 11.0, 6.0\text{ Hz}$, 1H), 5.30-5.19 (m, 2H), 4.93-4.87 (m, 1H), 4.03-3.96 (m, 1H), 3.65 (d, $J=1.2\text{ Hz}$, 1H), 1.00 (d, $J=7.1\text{ Hz}$, 3H); **Shared peaks:** δ 2.98-2.74 (m, 8H), 2.54-2.37 (m, 2H), 2.32-2.21 (m, 1H), 2.11-1.88 (m, 8H), 1.34-1.23 (m, 36H), 0.92-0.85 (m, 24H), 0.11 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 139.0, 138.4, 116.5, 115.9, 73.3, 73.3, 68.5, 68.4, 55.9, 55.7, 46.7, 46.1, 42.9, 42.8, 38.1, 32.0, 29.8, 29.8, 29.7, 29.5, 26.5, 26.4, 26.1, 26.0, 26.0, 25.9, 25.7, 25.7, 25.0, 24.7, 22.8, 18.3, 18.2, 18.2, 14.3, 9.5, 9.4, -4.1 , -4.2 , -4.5 , -4.6 .



2-((2*S*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)pent-4-en-2-yl)-2-(2-*tert*-

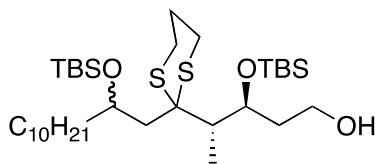
butyldimethylsilyloxy)dodecyl-1,3-dithiane

(72):

tert-Butyldimethylsilyl

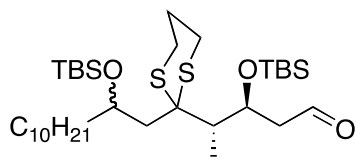
trifluoromethanesulfonate (1.52 mL, 8.64 mmol) was added to a solution of alcohol **71** (3.95 g, 7.85 mmol) and 2,6-lutidine (1.10 mL, 9.43 mmol) in dichloromethane (78 mL) at $-78\text{ }^{\circ}\text{C}$. After

15 min, the reaction was warmed to 0 °C. After 2 h, the reaction was allowed to warm to room temperature overnight. The reaction was quenched with H₂O (40 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over MgSO₄, concentrated, and purified via flash chromatography (10% ethyl acetate in hexanes) to give **72** (3.62 g, 75%) as a 53:47 mixture of two diastereomers. ¹H NMR (400 MHz, CDCl₃) **Major diastereomer**: δ 5.14-5.09 (m, 2H), 4.07-4.03 (m, 2H), 2.78-2.65 (m, 4H), 1.06 (d, *J* = 7.3 Hz, 3H); **Minor diastereomer**: δ 5.27-5.29 (m, 2H), 4.91-4.84 (m, 2H), 2.92-2.78 (m, 4H), 1.02 (d, *J* = 7.0 Hz, 3H); **Shared peaks**: δ 6.08-5.95 (m, 2H), 2.55-2.42 (m, 2H), 2.14-2.03 (m, 2H), 2.02-1.58 (m, 10H), 1.51-1.36 (m, 2H), 1.35-1.20 (m, 38H), 0.92-0.85 (m, 42H), 0.12-0.01 (m, 24H).



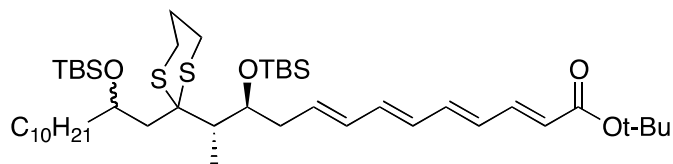
(3*S*,4*S*)-3-(*tert*-Butyldimethylsilyloxy)-4-(2-(2-(*tert*-butyldimethylsilyloxy)dodecyl-1,3-dithian-2-yl)pentan-1-ol (73**):** A solution of 9-BBN (0.5 M in THF, 25.3 mL, 12.64 mmol) was added to a solution of alkene **72** (2.60 g, 4.21 mmol) in THF (42 mL). After 15 h, the reaction was cooled to 0 °C. H₂O₂ (30% in H₂O, 21 mL), then 3N NaOH (26 mL) were added to the reaction and allowed to warm to room temperature. After 7 h, the reaction was diluted with ethyl acetate (210 mL) and H₂O (105 mL). The organic layer was separate, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO₂, 10% ethyl acetate in hexanes) to give alcohol **73** (1.64g, 61%) as a 1:1 mixture of two diastereomers. ¹H

NMR (400 MHz, CDCl₃) δ 4.53 (t, J = 9.8 Hz, 2H), 4.07-3.98 (m, 2H), 3.83-3.66 (m, 4H), 3.02-2.79 (m, 4H), 2.78-2.67 (m, 3H), 2.66-2.50 (m, 2H), 2.44-2.38 (m, 2H), 2.37-2.21 (m, 4H), 2.20-2.05 (m, 4H), 2.04-1.93 (m, 4H), 1.93-1.83 (m, 4H), 1.45-1.34 (m, 6H), 1.33-1.19 (m, 36H), 1.15 (d, J = 7.0 Hz, 3H), 1.07 (d, J = 7.0 Hz, 3H), 0.92-0.85 (m, 42H), 0.16-0.12 (m, 12H), 0.10-0.07 (m, 12H); ¹³C NMR (100 MHz, CDCl₃) δ 76.8, 71.7, 71.3, 70.4, 70.0, 61.4, 61.2, 55.8, 55.8, 45.9, 45.4, 44.1, 43.9, 42.0, 39.3, 39.0, 36.2, 35.5, 32.0, 30.0, 29.9, 29.8, 29.8, 29.7, 29.4, 27.3, 27.0, 26.6, 26.5, 26.2, 26.2, 26.0, 26.0, 25.8, 25.4, 25.3, 24.8, 24.6, 24.2, 2.8, 18.3, 18.1, 18.1, 14.3, 8.7, 7.7, -3.5, -3.8, -3.9, -4.5.

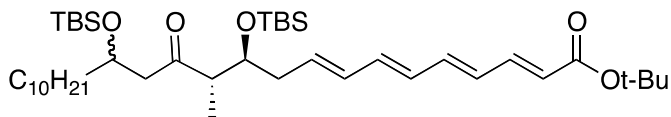


(3*S*,4*S*)-3-(*tert*-Butyldimethylsilyloxy)-4-(2-(2-(*tert*-butyldimethylsilyloxy)dodecyl)-1,3-dithian-2-yl)pentanal (74): NaHCO₃ (100 mg, 1.19 mmol) and Dess-Martin periodinane (100 mg, 0.23 mmol) was added to a solution of alcohol **73** (136 mg, 0.214 mmol) in dichloromethane (4.5 mL). After 8 h, the reaction was quenched with saturated NaHCO₃ (10 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over MgSO₄, then concentrated. The crude product was purified by flash chromatography (SiO₂, 10% ethyl acetate in hexanes) to give aldehyde **74** (98 mg, 70%) as a mixture of two diastereomers. ¹H NMR (400 MHz, CDCl₃) δ 9.83-9.76 (m, 2H), 5.02 (d, J = 9.2 Hz, 2H), 4.07-3.93 (m, 2H), 3.16-3.07 (m, 1H), 3.03-2.79 (m, 5H), 2.78-2.65 (m, 3H), 2.65-2.47 (m, 3H), 2.40-2.15 (m, 4H), 2.15-1.93 (m, 4H), 1.92-1.78 (m, 2H), 1.77-1.62 (m, 2H), 1.47-1.19 (m, 36H), 1.15 (d, J = 7.0 Hz, 3H), 1.06 (d, J = 7.1 Hz, 3H), 0.93-0.77 (m, 42H), 0.16-0.03 (m,

24H); ^{13}C NMR (100 MHz, CDCl_3) δ 202.3, 202.1, 70.22, 69.9, 68.3, 68.2, 55.8, 55.5, 49.0, 48.2, 46.0, 45.3, 44.0, 43.6, 39.3, 39.0, 32.0, 30.0, 30.0, 29.8, 29.7, 29.7, 29.4, 26.9, 26.4, 26.3, 26.3, 26.2, 26.2, 25.9, 25.8, 25.3, 25.1, 24.5, 24.2, 22.8, 18.2, 18.2, 18.0, 18.0, 14.2, 9.0, 8.0, -3.8, -3.8, -3.9, -4.0, -4.4, -4.5.



(2E,4E,6E,8E,11S,12S)-tert-Butyl-11-tert-butyldimethylsilyloxy-12-(2-(2-(tert-butyldimethylsilyloxy)dodecyl)-1,3-dithian-2-yl)trideca-2,4,6,8-tetraenoate (75): A solution of LiHMDS (1.0M in toluene, 0.16 mL, 0.16 mmol) was added to a solution of phosphonate **7** (56 mg, 0.17 mmol) in THF (0.85 mL) at -78°C . After 15 min, a solution of aldehyde **74** (68 mg, 0.11 mmol) in THF (0.70 mL) was slowly added. After 30 min, the reaction was warmed to 0°C . After 1 h, the reaction was quenched with saturated NH_4Cl (2 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over MgSO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2 , 10% ethyl acetate in hexanes) to give **75** (78 mg, 90%) as a mixture of two diastereomers. ^1H NMR (400 MHz, CDCl_3) δ 7.22 (dd, $J = 15.2, 11.4$ Hz, 2H), 6.51 (dd, $J = 14.5, 11.0$ Hz, 2H), 6.40-6.07 (m, 8H), 5.92-5.82 (m, 2H), 5.78 (d, $J = 15.2$ Hz, 2H), 4.34 (dd, 9.2, 3.1 Hz, 2H), 4.03 (dd, $J = 15.0, 4.6$ Hz, 2H), 3.01-2.57 (m, 10H), 2.35-2.13 (m, 6H), 2.12-1.83 (m, 6H), 1.78-1.57 (m, 2H), 1.49 (s, 18H), 1.35-1.22 (m, 36H), 1.14 (d, $J = 7.1$ Hz, 3H), 1.06 (d, $J = 7.1$ Hz, 3H), 0.92-0.84 (m, 42H), 0.11-0.02 (m, 24H); HRMS (TOF ES) m/z : Calcd for $\text{C}_{45}\text{H}_{85}\text{O}_4\text{S}_2\text{Si}_2$ $[\text{M}+\text{H}]^+$ 809.5422; Found 809.5486.

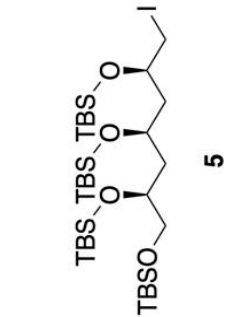


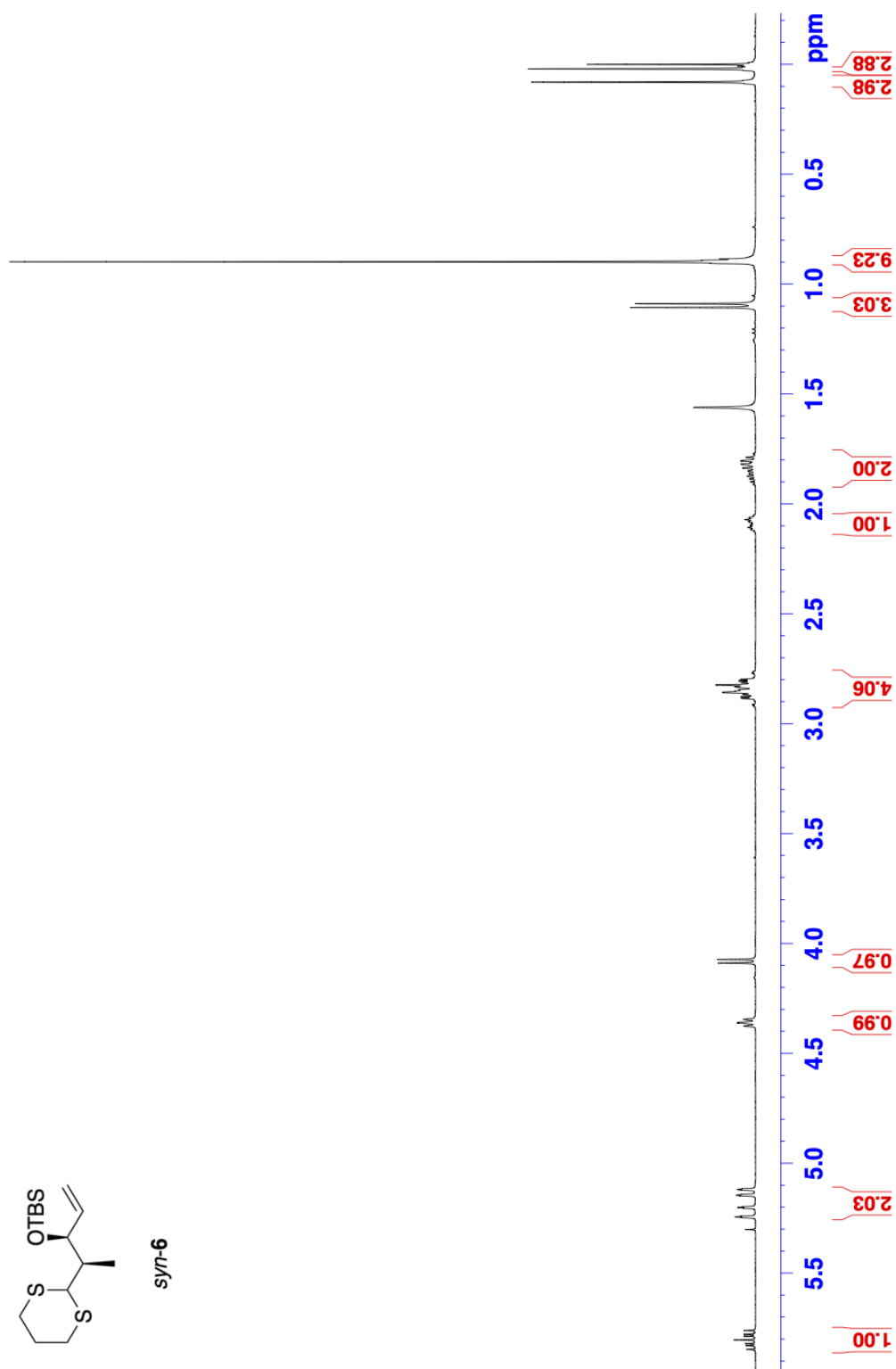
(2E,4E,6E,8E,11S,12S)-tert-Butyl-11,15-bis(tert-butyldimethylsilyloxy)-12-methyl-13-

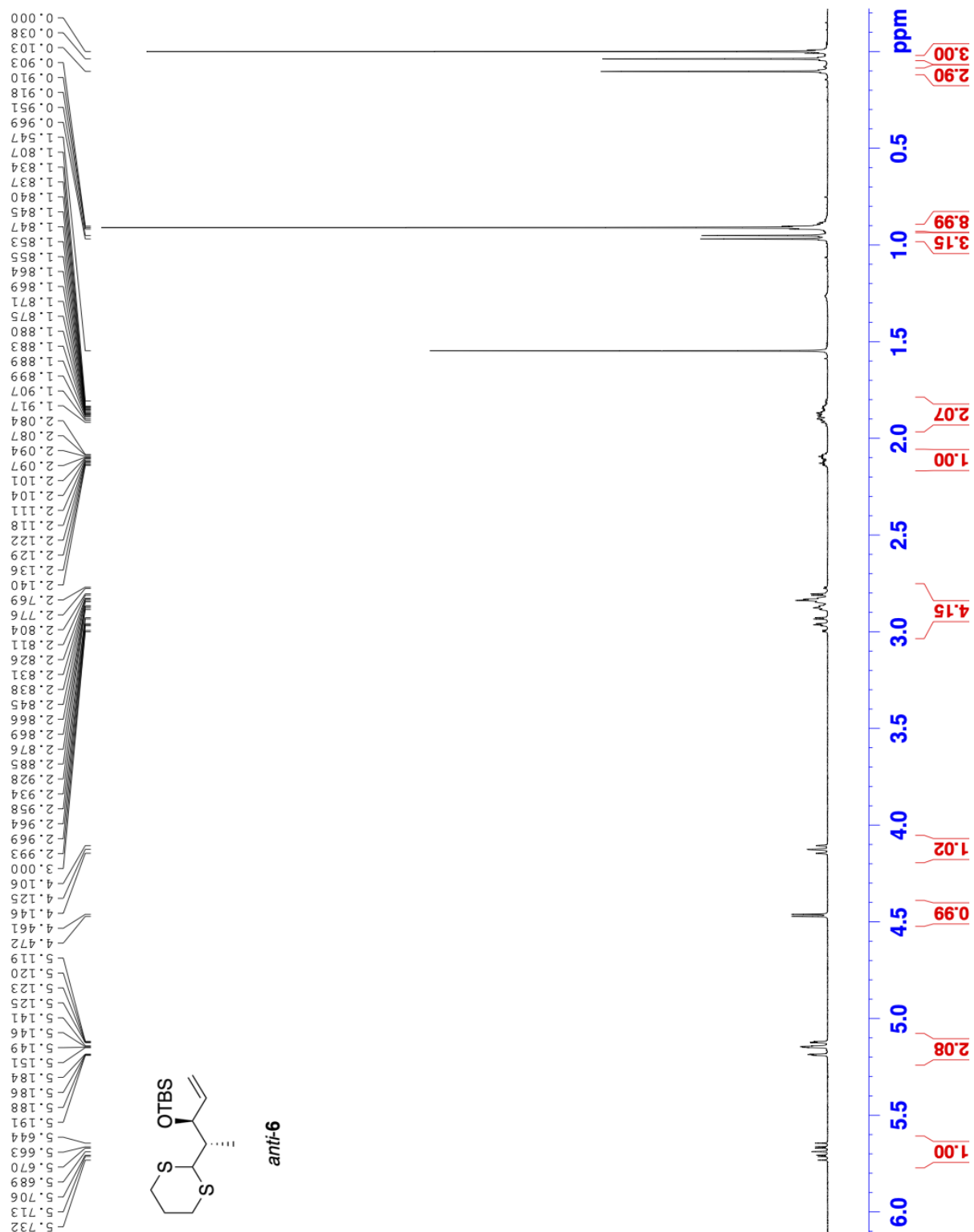
oxopentacos-2,4,6,8-tetraenoate (76): Hg(ClO₄)₂•H₂O (59 mg, 0.14 mmol) was added to a solution of dithiane **75** (22 mg, 0.028 mmol) and 2,6-lutidine (44 μL, 0.38 mmol) in THF (0.48 mL) and H₂O (0.12 mL) at 0 °C. After 45 min, the reaction mixture was filtered through a pad of celite and rinsed through with ethyl acetate. The filtrate was diluted with ethyl acetate to a volume of 30 mL, and poured into saturated NH₄Cl (30 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO₂, 10% ethyl acetate in hexanes) to give ketone **76** (9.4 mg, 46%) as a mixture of two diastereomers. ¹H NMR (600 MHz, CDCl₃) δ 7.22 (dd, *J* = 15.2, 11.4 Hz, 2H), 6.54 (dd, *J* = 14.8, 11.1 Hz, 2H), 6.36, (dd, *J* = 14.4, 12.1 Hz, 2H), 6.28 (d, *J* = 14.7, 11.4 Hz, 2H), 6.20 (t, *J* = 12.9 Hz, 2H), 6.13 (dd, *J* = 15.1, 10.7 Hz, 2H), 5.88-5.81 (m, 2H), 5.79 (d, *J* = 15.4 Hz, 2H), 4.19-4.09 (m, 2H), 4.02-3.94 (m, 2H), 2.74-2.60 (m, 5H), 2.56 (dd, *J* = 16.5, 5.3 Hz, 1H), 2.44 (dd, *J* = 16.7, 4.6 Hz, 1H), 2.33-2.20 (m, 4H), 1.49 (s, 18H), 1.30-1.21 (s, 18H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.90-0.82 (m, 42H), 0.09-0.02 (m, 24H); ¹³C NMR (150 MHz, CDCl₃) δ 212.3, 211.9, 166.7, 166.3, 143.6, 140.3, 136.9, 133.1, 133.0, 131.1, 130.5, 129.8, 129.8, 122.6, 80.3, 73.3, 73.2, 68.6, 68.1, 52.1, 52.1, 51.6, 51.0, 38.0, 37.6, 37.5, 32.1, 29.9, 29.8, 29.7, 29.5, 28.4, 28.3, 26.0, 25.3, 25.2, 22.8, 18.2, 14.3, 12.1, 11.9, 0.1, -4.3, -4.3, -4.4, -4.5, -4.7, -4.7.

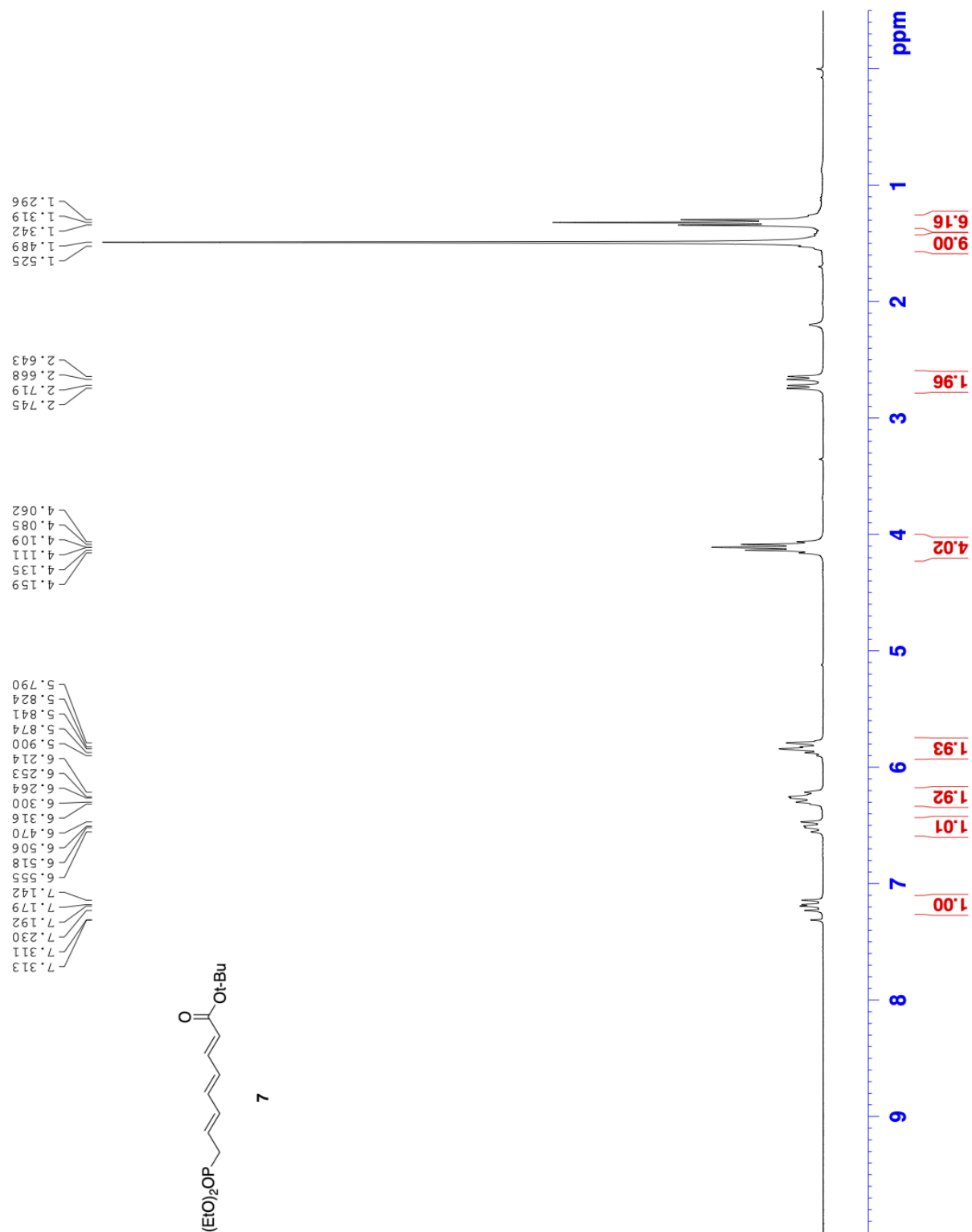
Appendix A NMR Spectra of Selected Compounds

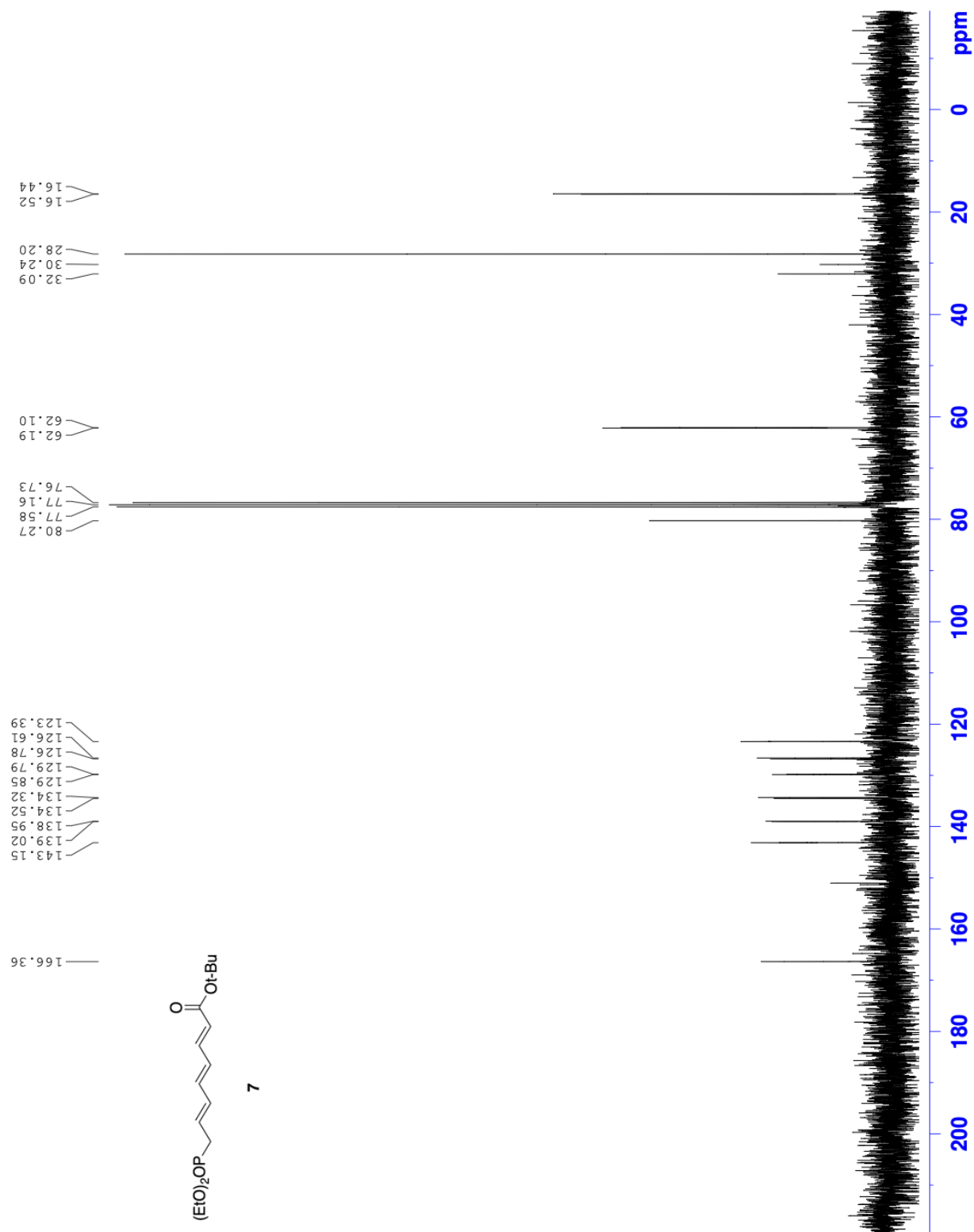
NMR spectra of compounds **5, 6, 7, 13, 39, 40, 41, 46, 47, 48, 49, 50, 51, 52, 64, 65, 66, 67, 68, 69, 71, 72, 73, 74, 75**, and **76** are listed below.

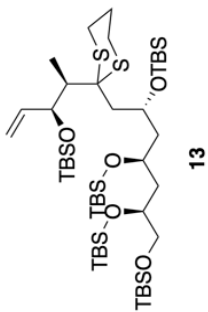




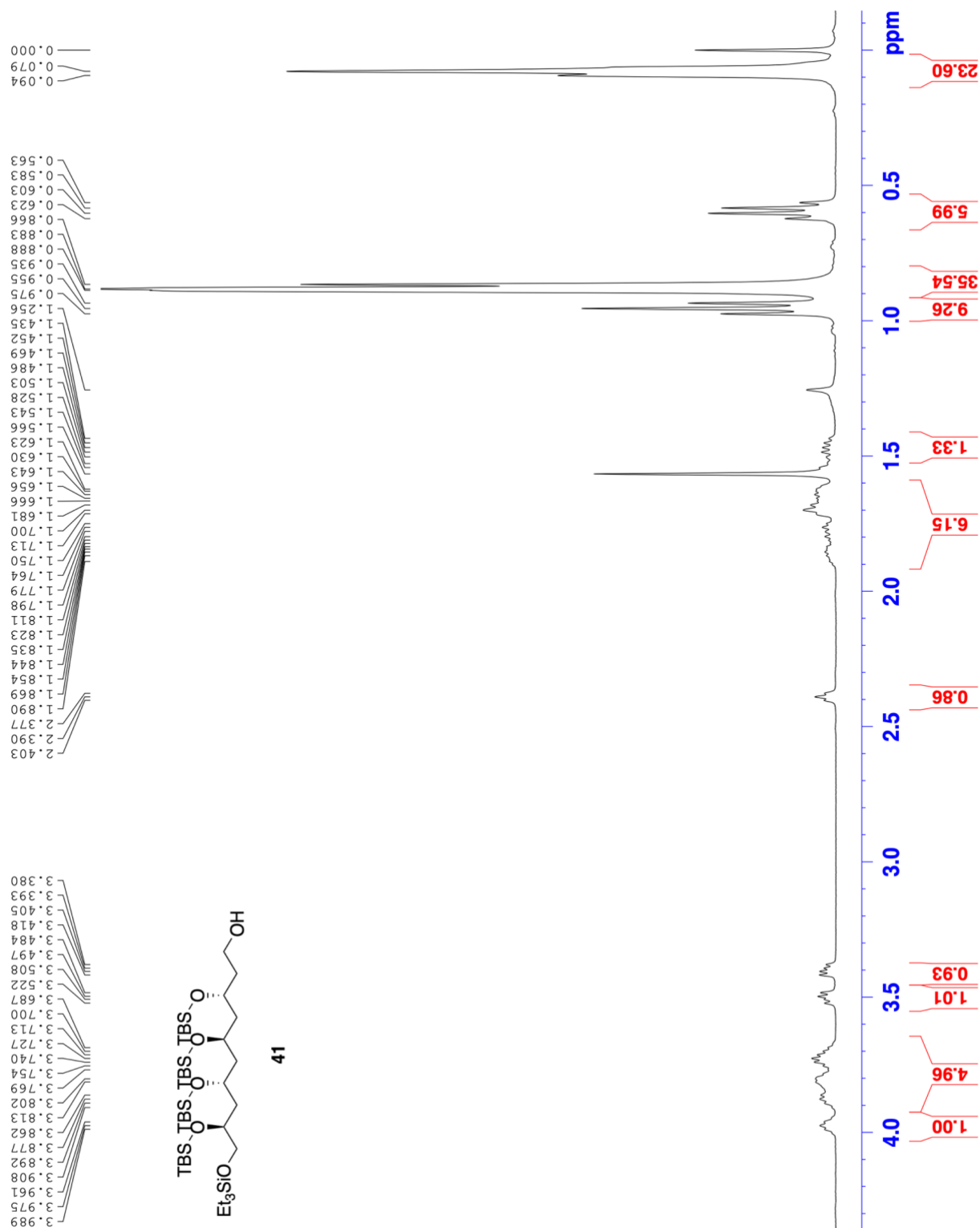


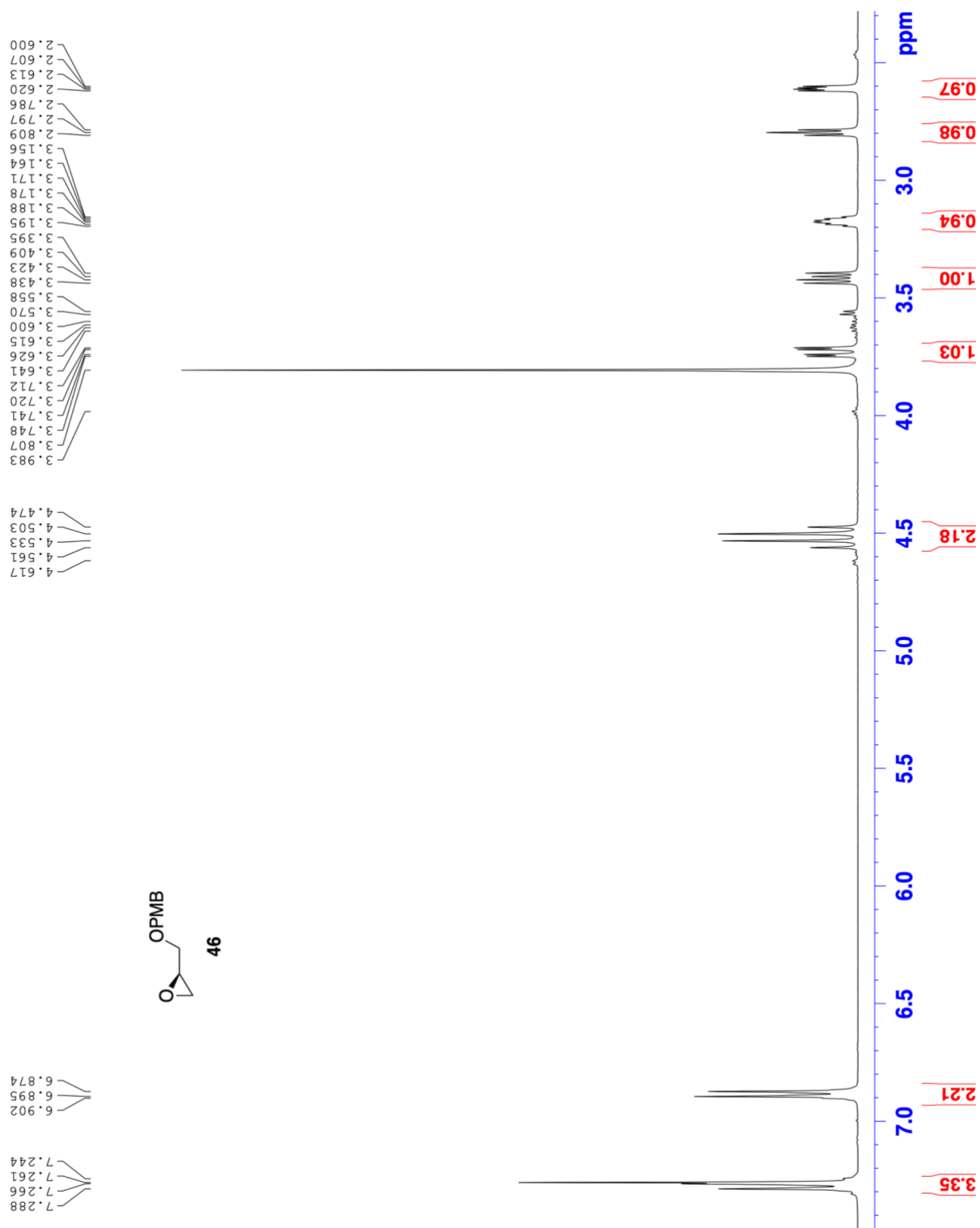


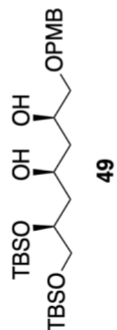


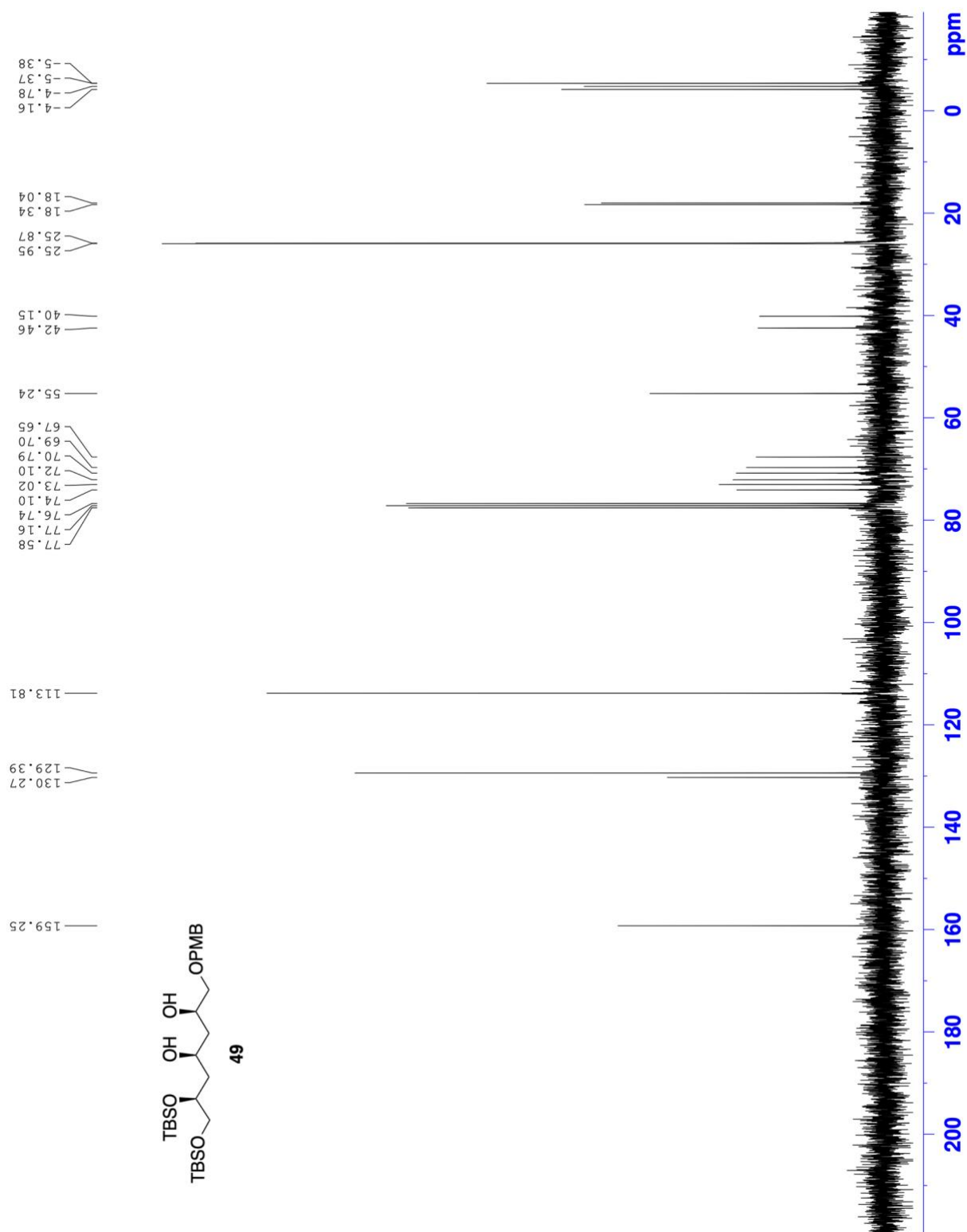


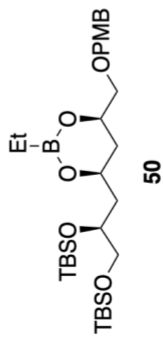




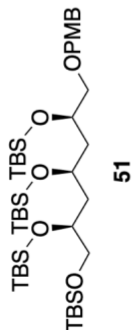


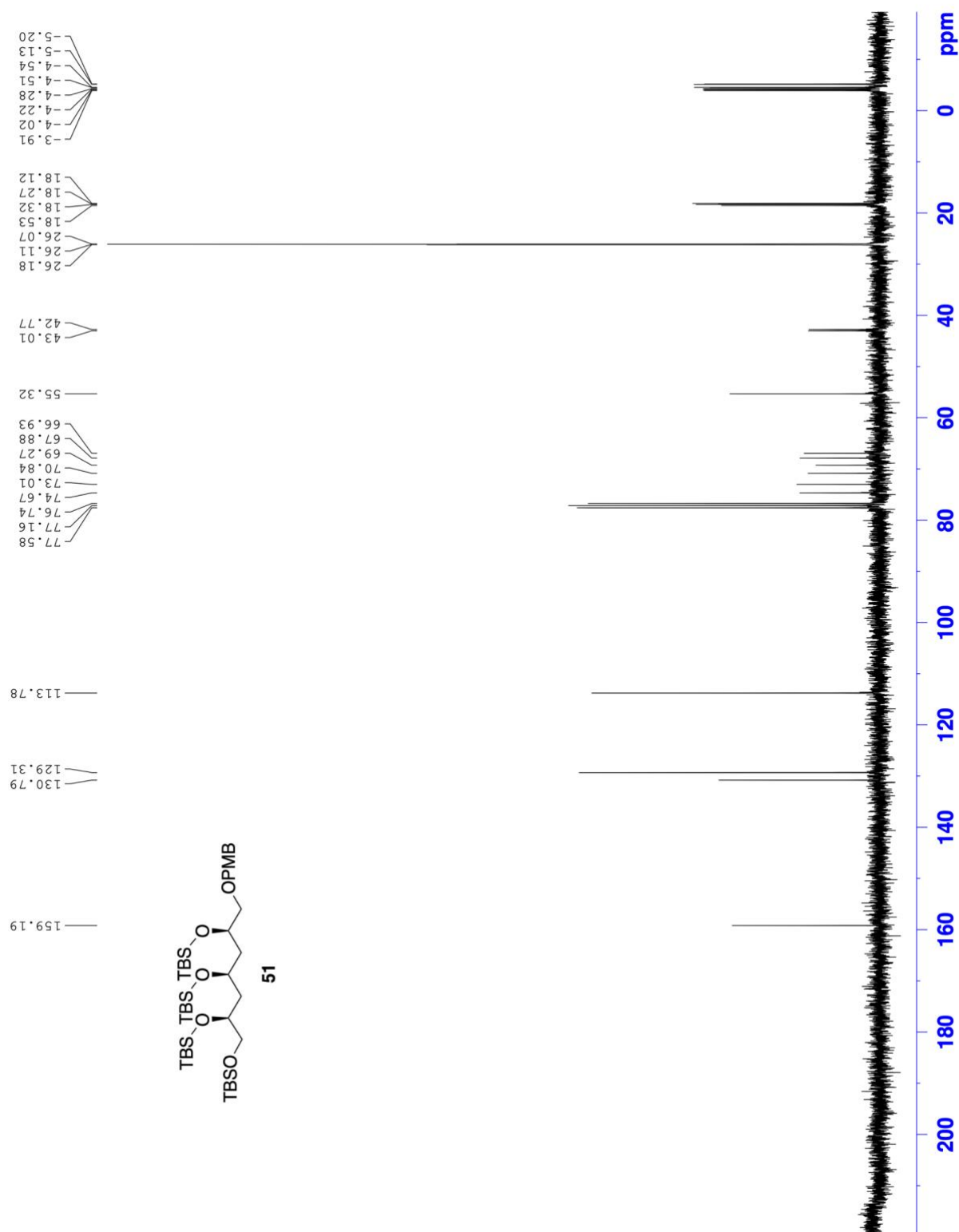


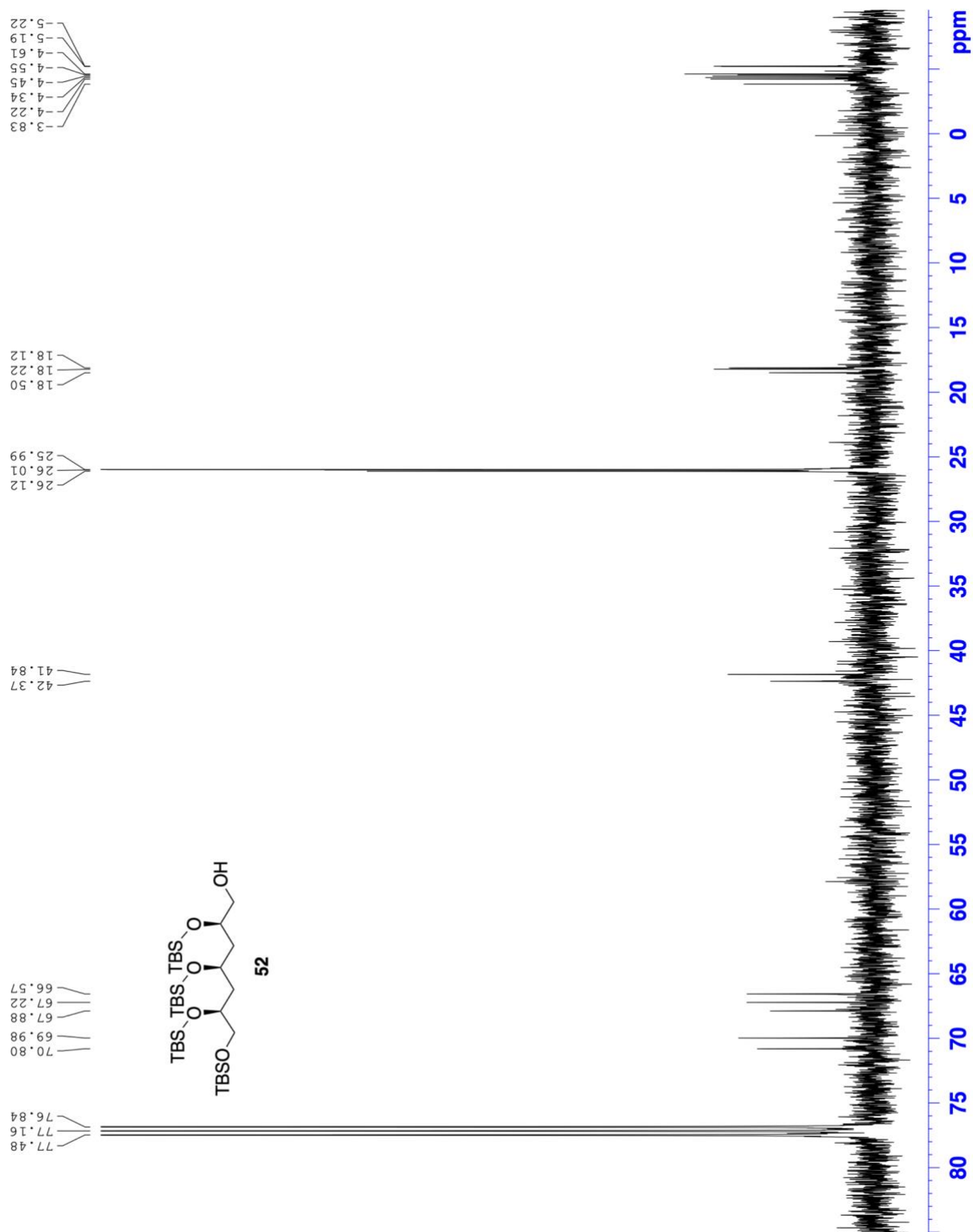


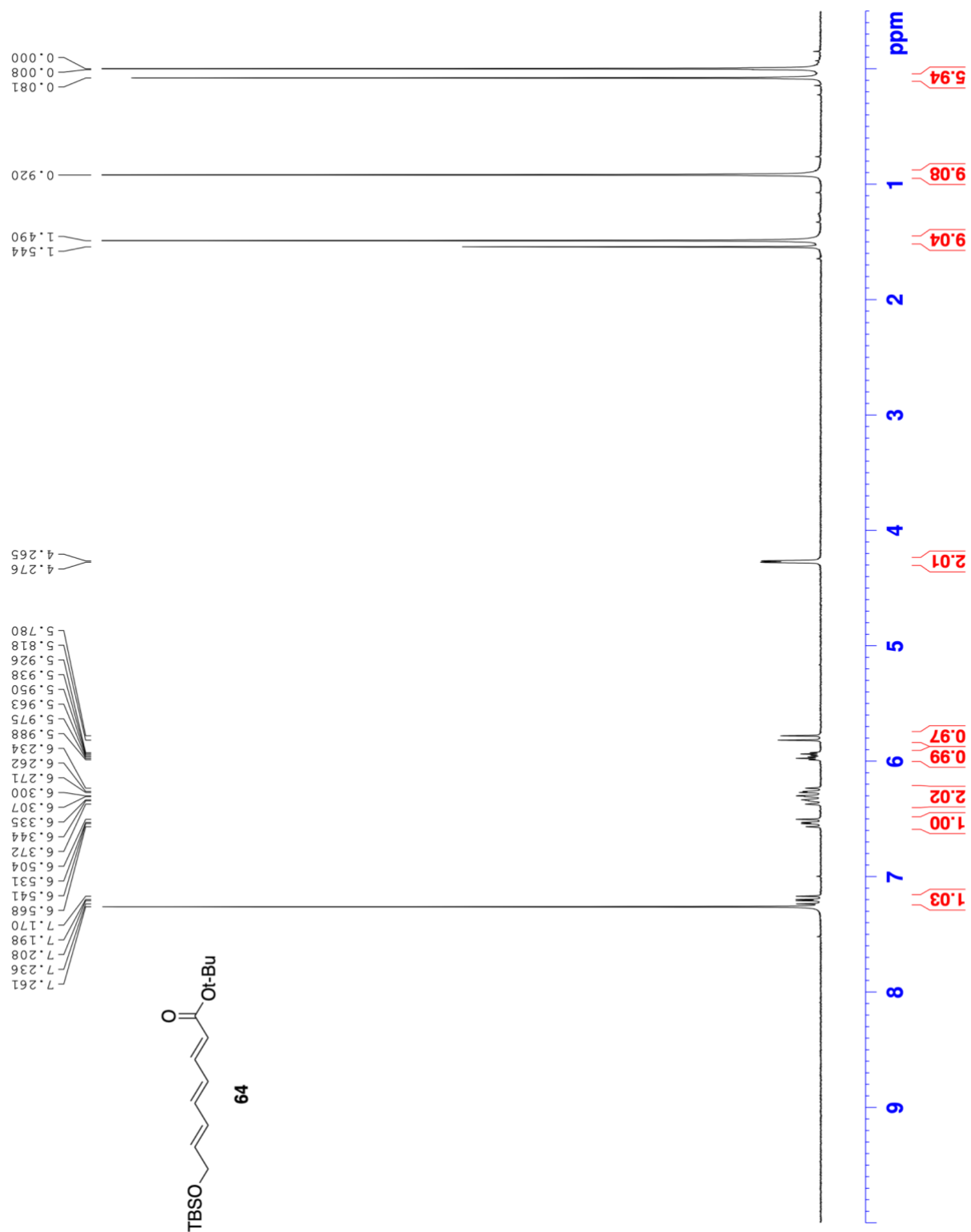


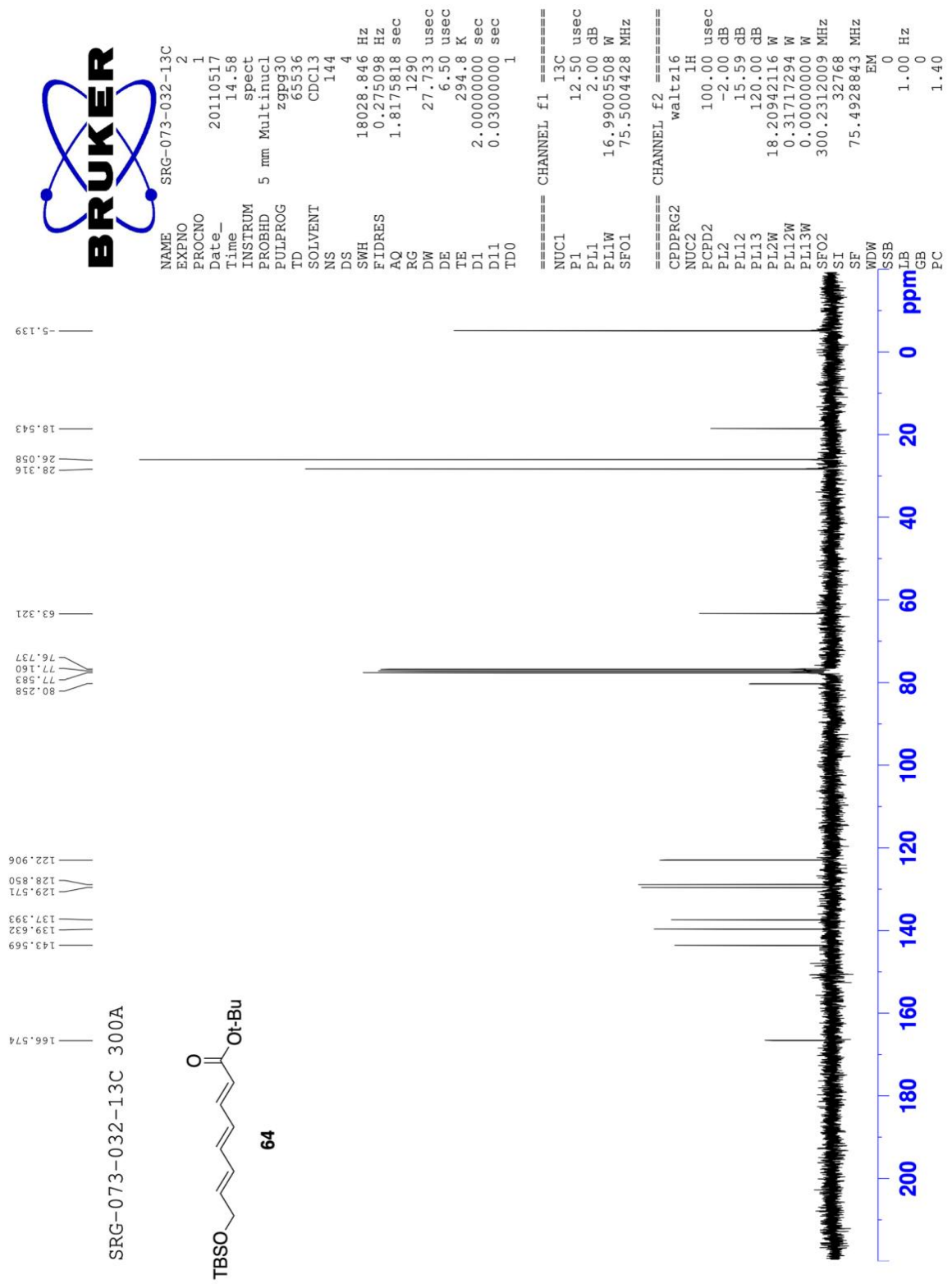


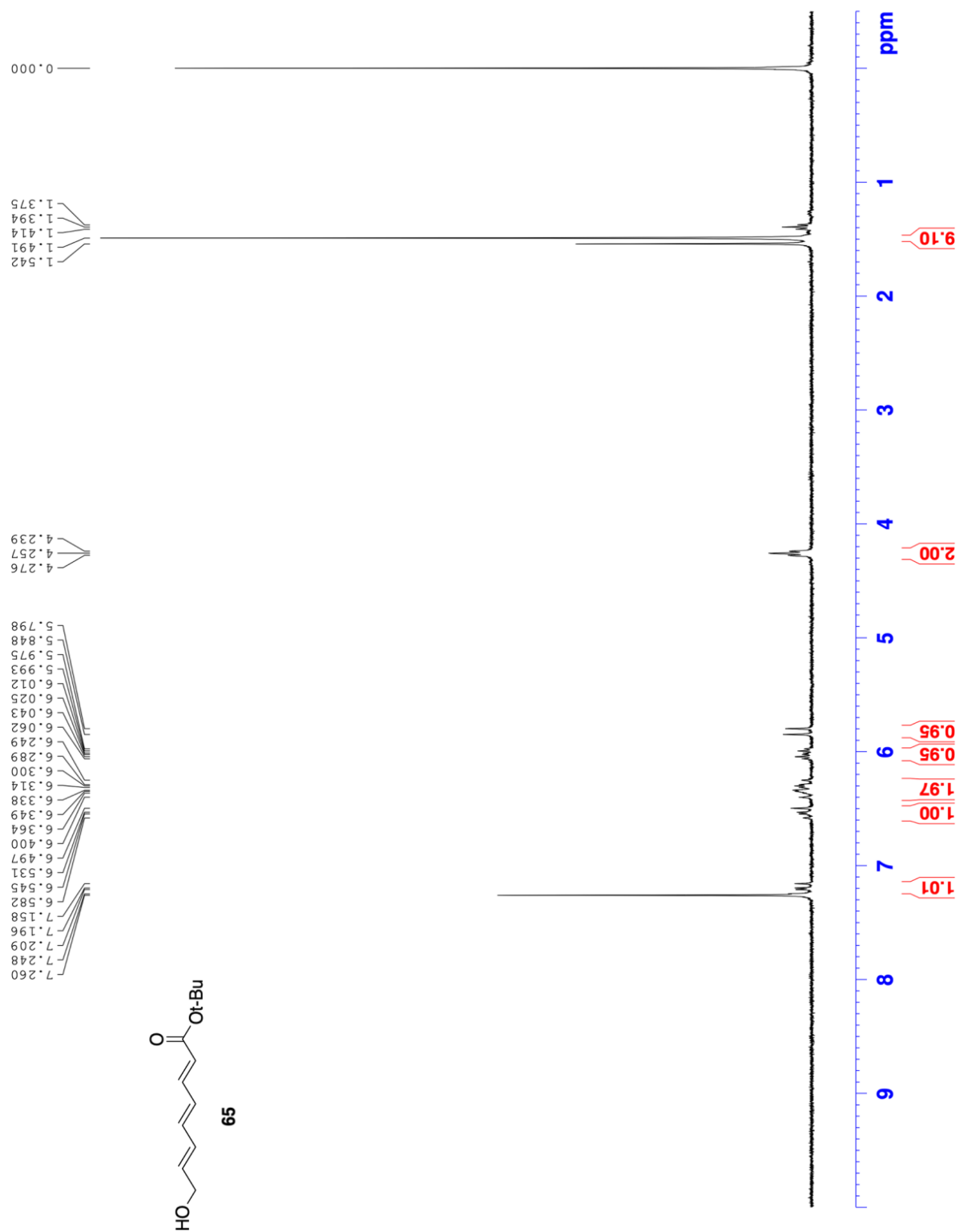










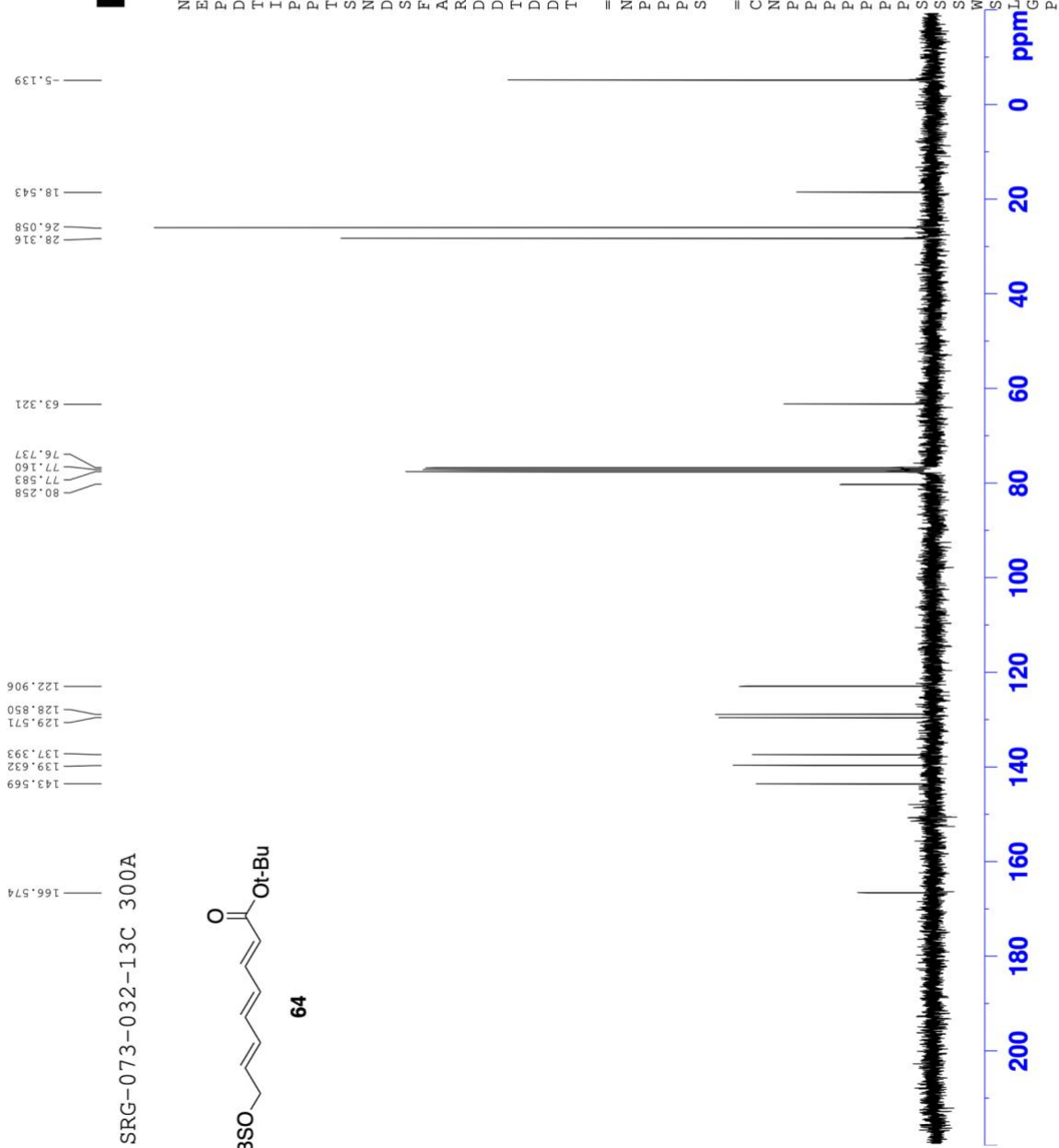


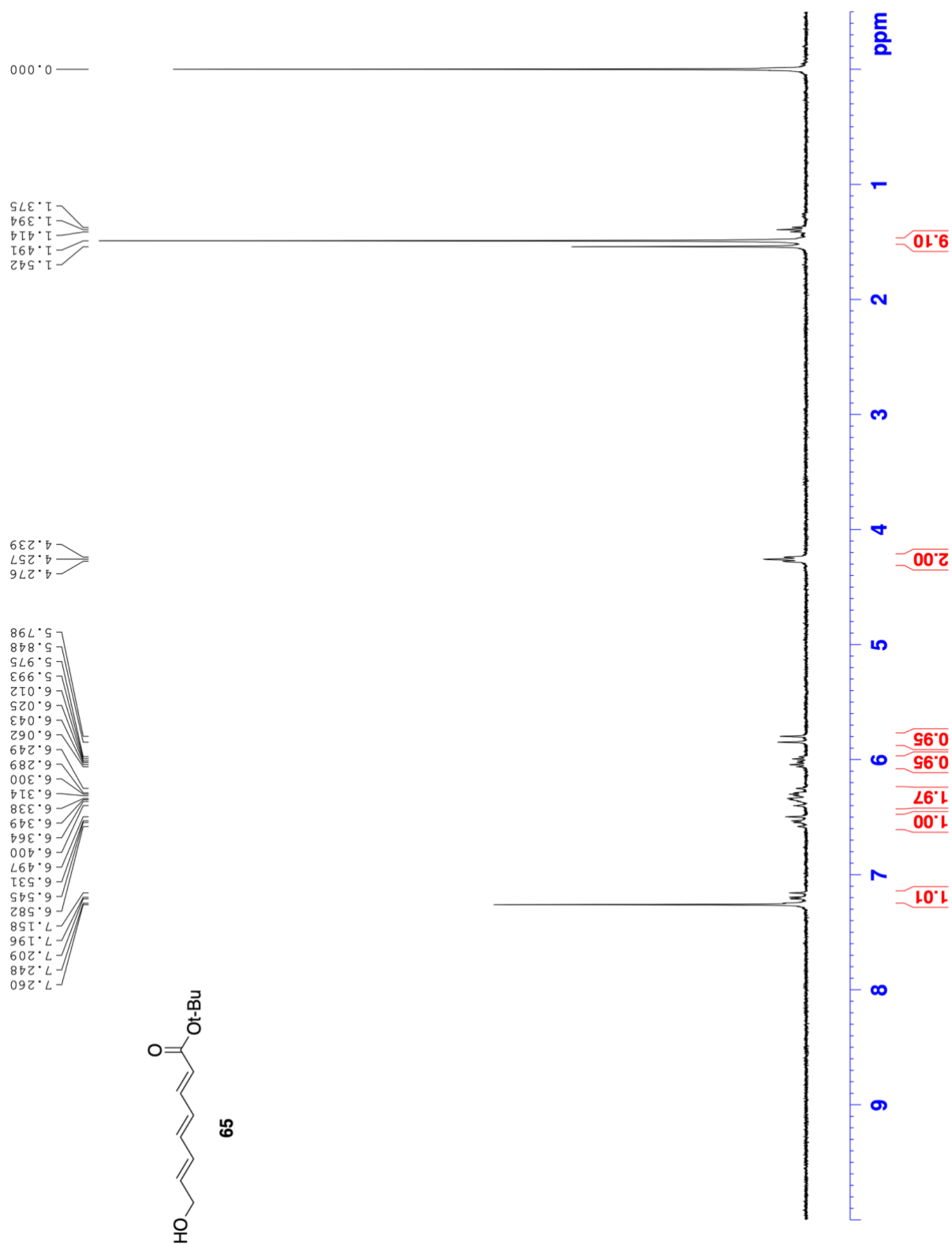


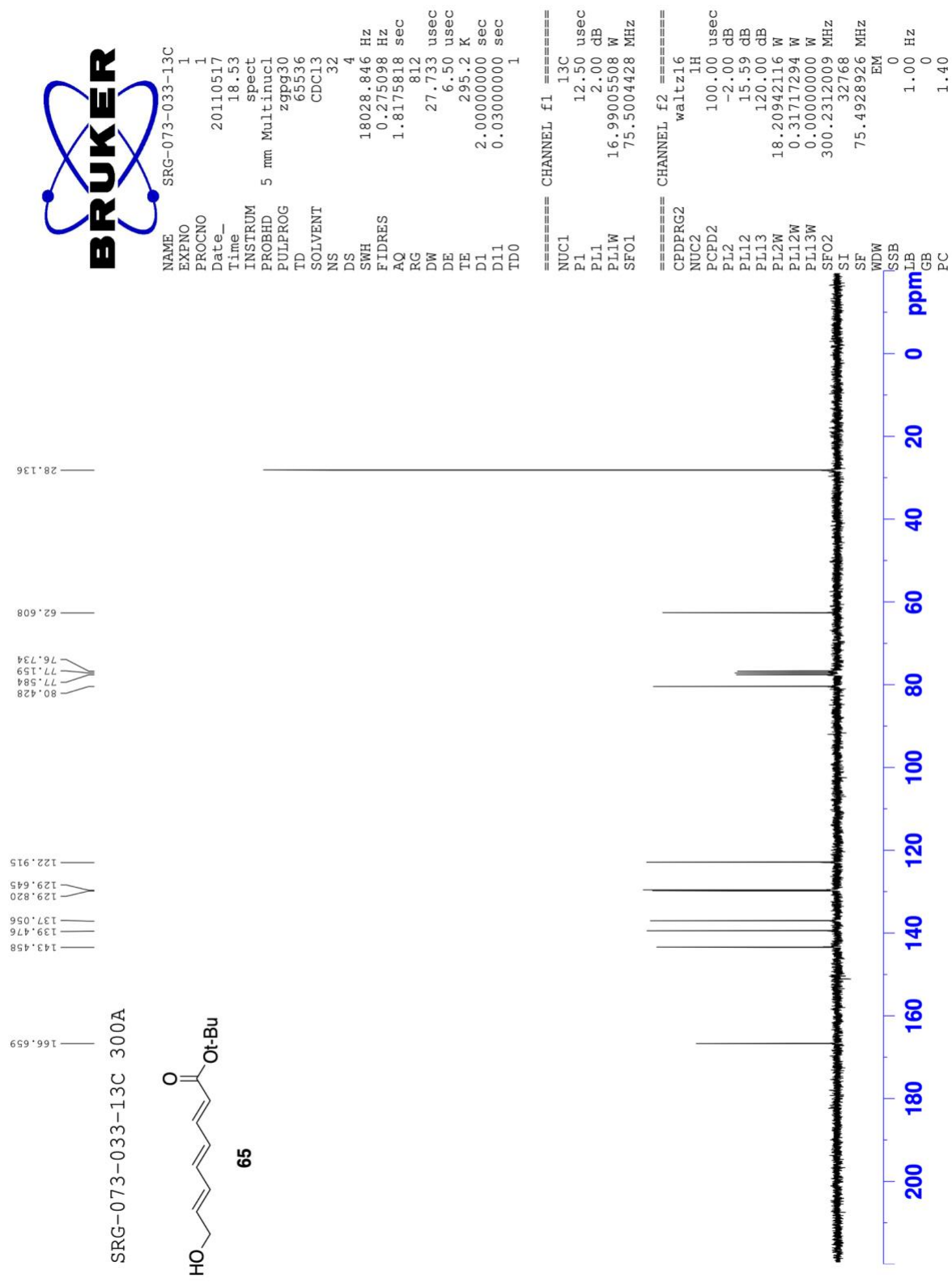
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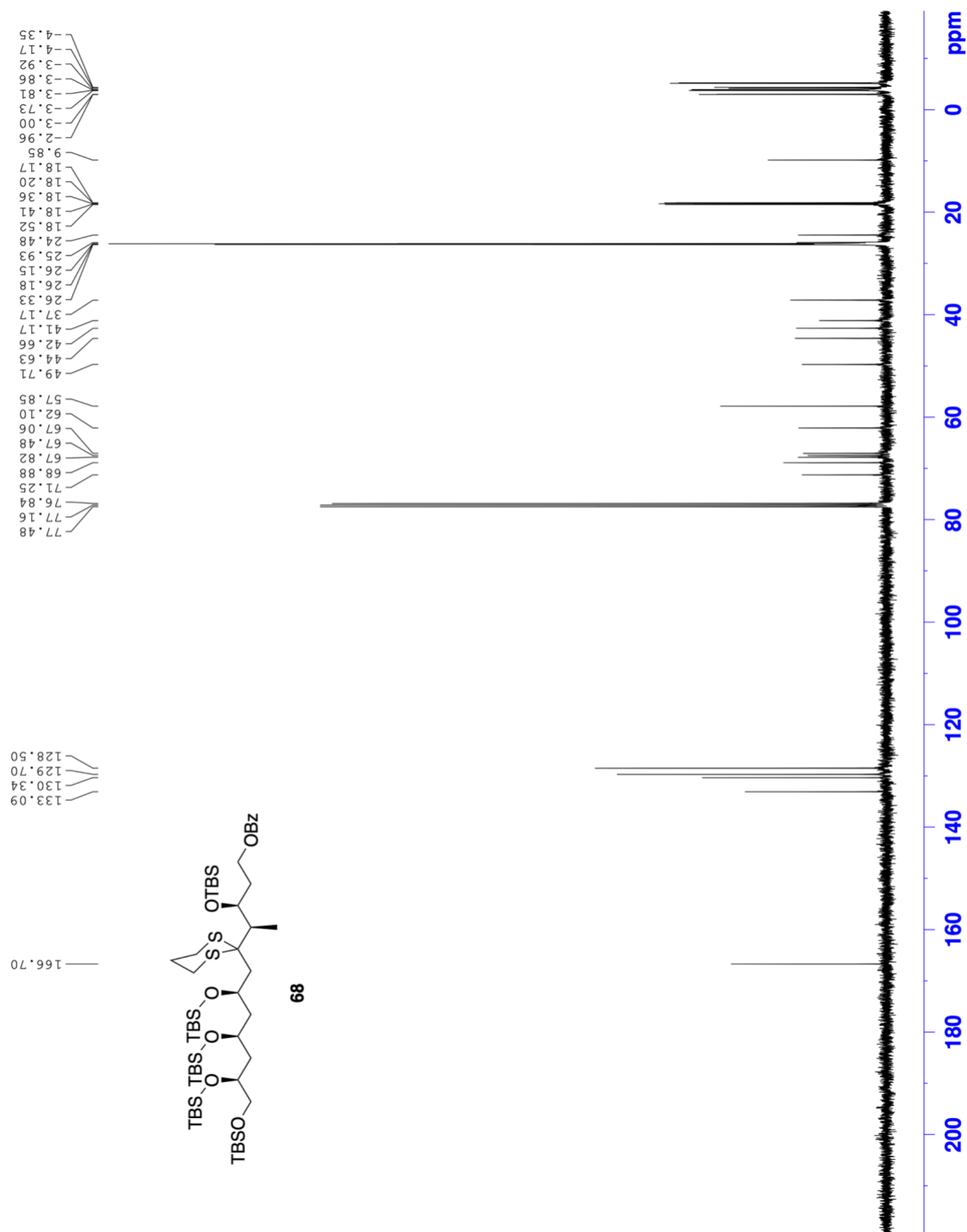
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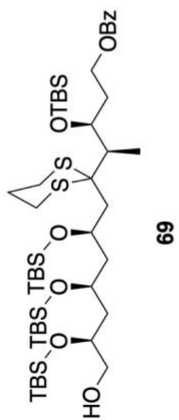


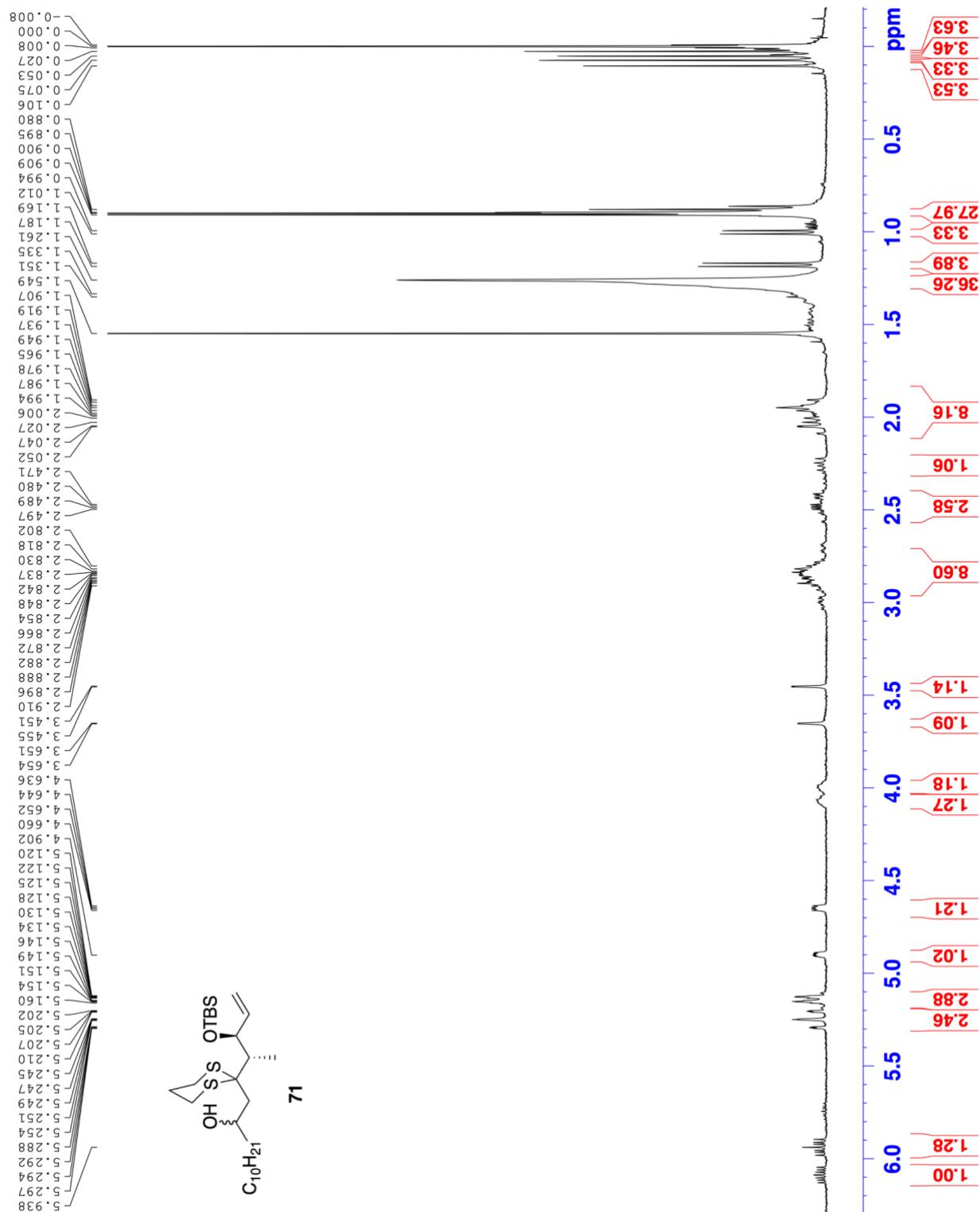


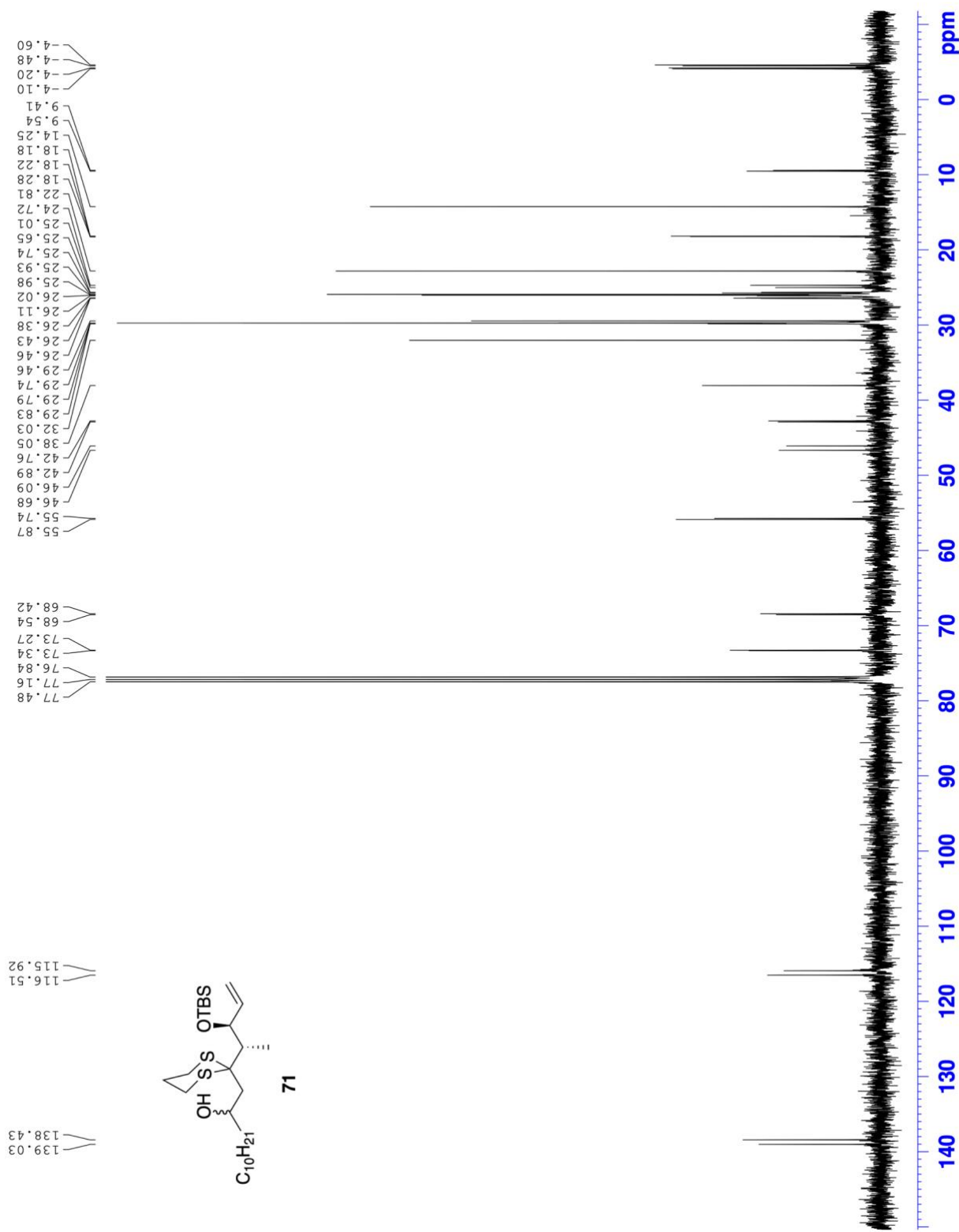


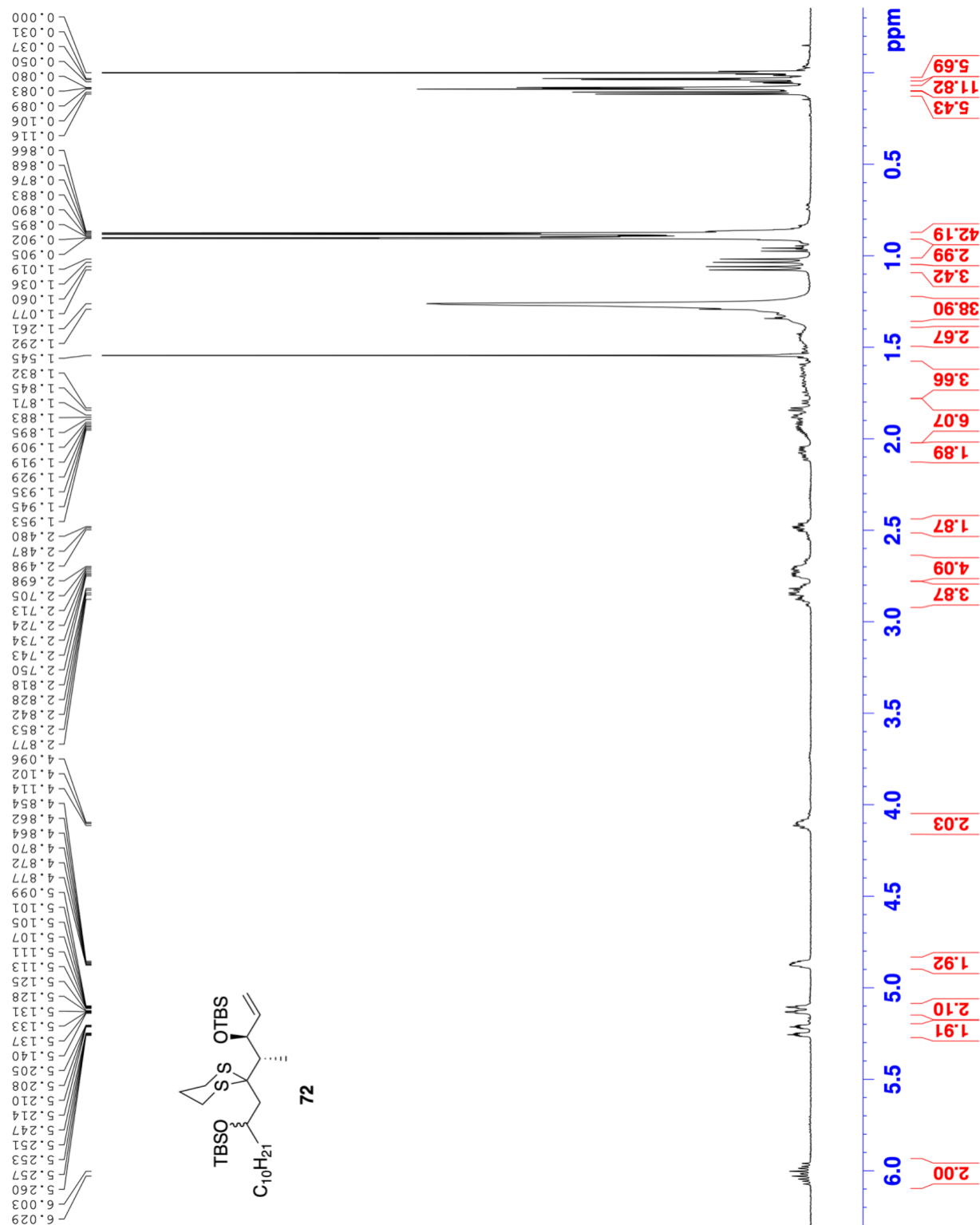


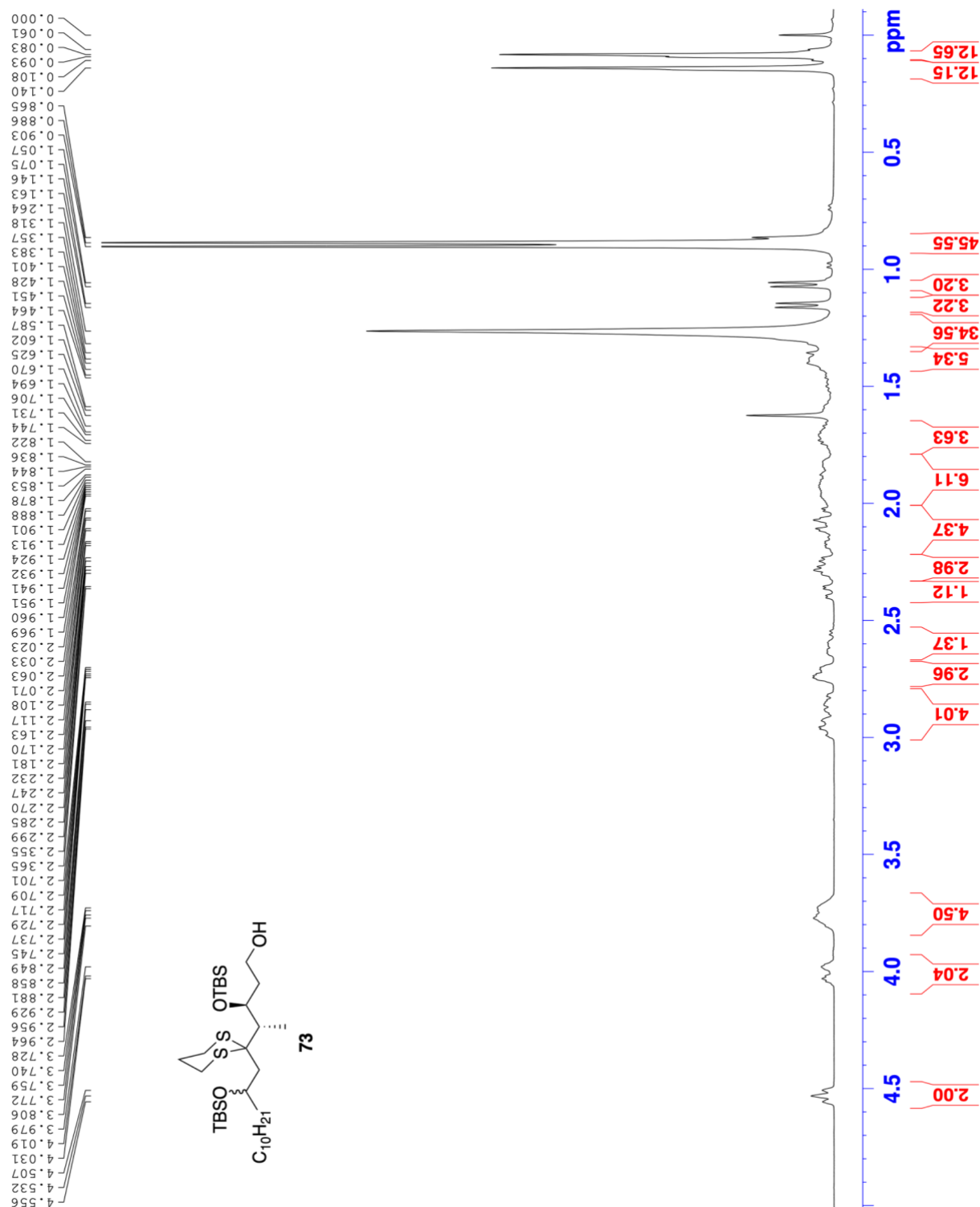




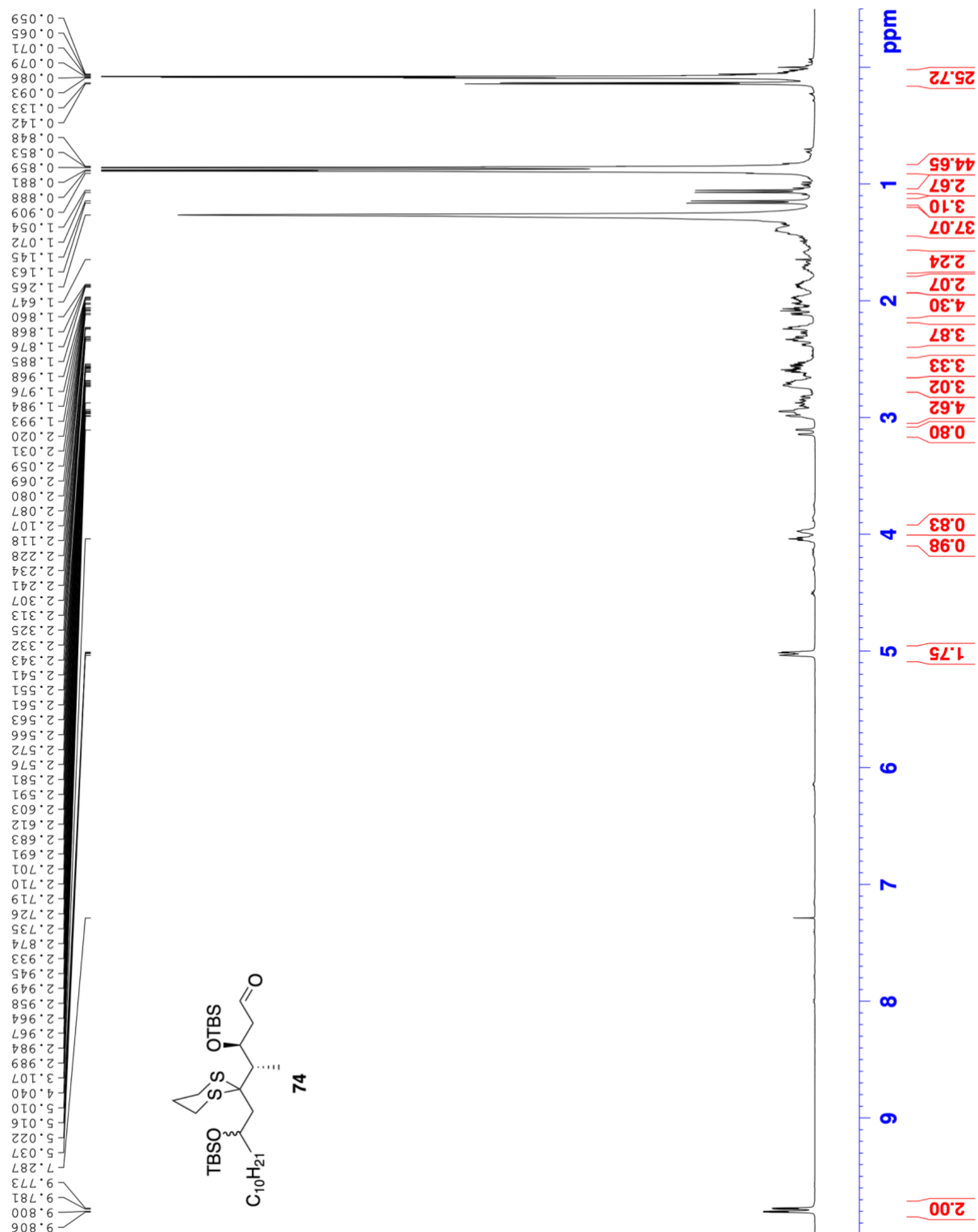


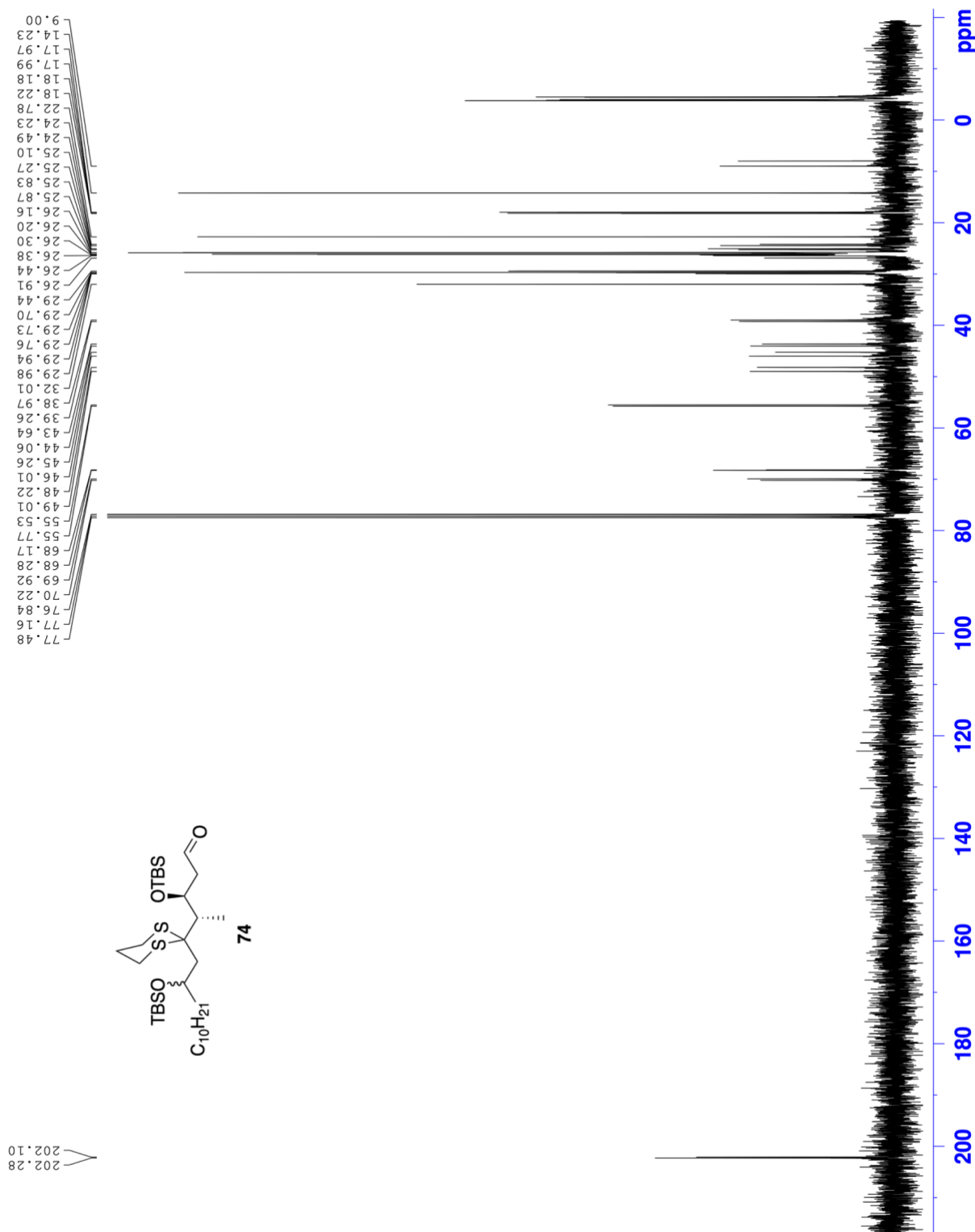


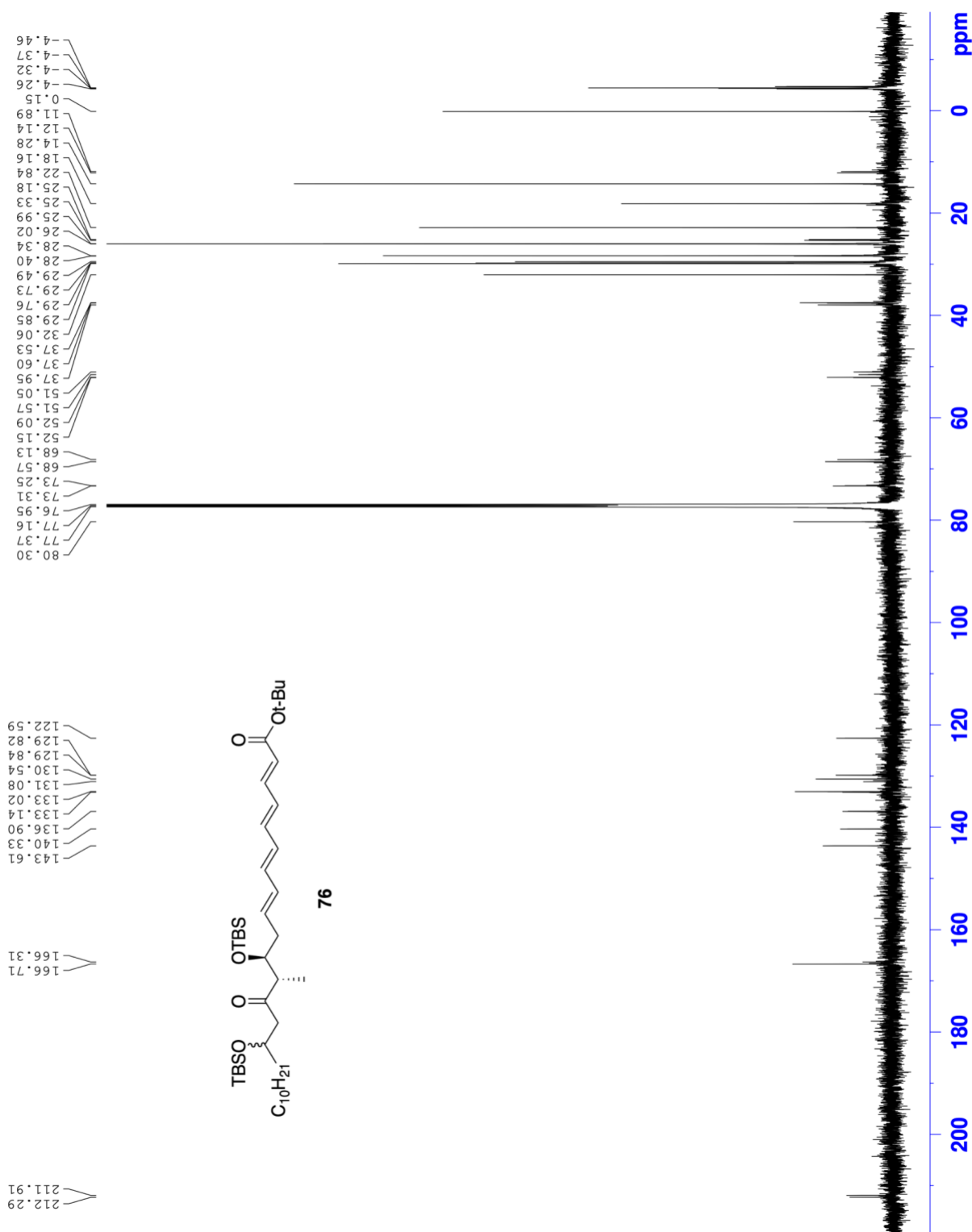












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