Title
Efforts Towards the Synthesis of Ceylonamide A via a Stereocontrolled Polyene Cyclization

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Efforts Towards the Synthesis of Ceylonamide A via a Stereocontrolled Polyene Cyclization

THESIS

submitted in partial satisfaction of the requirements for the degree of

MASTER OF SCIENCE

in Chemistry

by

Glynis Longworth Coyne

Thesis Committee:
Professor Christopher D. Vanderwal, Chair
Professor Scott D. Rychnovsky
Professor Sergey V. Pronin

2019

DEDICATION

To my family and my friends, for their endless support

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LIST OF ACRONYMS AND ABBREVIATIONS

μ	micro
°C	degrees Celsius
Ac	acetyl
AIBN	azobisisobutyronitrile
Å	Ångstrom
aq.	aqueous
9-BBN	9-borabicyclo[3.3.1]nonane
9-BBN·OMe	9-methoxy-9-borabicyclo[3.3.1]nonane
Bn	benzyl
n-Bu	*n*-butyl
t-Bu	*tert*-butyl
cat.	catalytic
calcd	calculated
Cp	cyclopentadienyl
DCE	dichloroethane
DCM	dichloromethane
decomp.	decomposition
DIBAL-H	Diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
DTBP	2,6-di-*tert*-butylpyridine
dr	diastereomeric ratio
ent.	enantiomer(s)
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
g	gram(s)
h	hour(s)
HMPA	hexamethylphosphoramide
HRMS	high-resolution mass spectrometry
Hz	Hertz
imid.	imidazole
J	coupling constant
K	Kelvin (absolute temperature)
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
M	molar; molecular ion
m/z	mass-to-charge ratio
Me	methyl
mg	milligram(s)
MHz	megahertz

min	minute(s)
mmol	millimole(s)
mol	mole(s)
mol. sieves	molecular sieves
Ms	methanesulfonyl (mesyl)
N	normal
NMR	nuclear magnetic resonance
Ph	phenyl
PhMe	toluene
ppm	parts per million
i-Pr	isopropyl
pyr	Pyridine
quant.	quantitative
rsm	recovered starting material
rt	room temperature
sat.	saturated
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethysilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin-layer chromatography
TOF	time-of-flight
Ts	*p*-toluenesulfonyl (tosyl)
UV	ultraviolet

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I have to begin by thanking Professor Christopher Vanderwal for allowing me to join his group and for being a truly wonderful advisor. His patience and support throughout the ups and downs of my academic career have been crucial factors in my accomplishments as a student. Furthermore, his guidance has been instrumental to my development as a scientist, teaching me the knowledge and skills I needed to effectively solve research problems while still giving me the freedom to grow as an independent researcher. Thank you, Chris, for all your encouragement, understanding, and support. Working in your group has been genuinely enjoyable in spite of the challenges I have faced; of all the paths I could have taken, I am profoundly grateful to have found myself on this one.

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upon for a sympathetic ear, as well as the finest quality memes, historical trivia, and information about rotation students. I am so happy we got to be desk buddies once more before I left.

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Over the course of my time in the Vanderwal lab, I had the privilege of knowing our excellent and highly motivated undergraduate students – Kimberly Buck, Susanna Liang, Sierra Nguyen, Bilal Saudi, and Michael Lehman. I had a lot of fun getting to know them all, and I know they will all go on to do great things.

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I am incredibly privileged and grateful to have made truly wonderful friends throughout my life who continued to support me through my graduate school experience. Sierra, Amanda, Bronte, Hayley, Dolores, and Britteny, you all have been so supportive since day one (literally, because we all met at orientation) – I wouldn't have survived without friends like you and I will mis you all terribly. To Carly and Brenna and the rest of the D&D crew, our game nights were often some of the best and most hilarious parts of my week. To my UNC friends, in particular the ladies of Bamboo Wilds – Maddie, Elle, and Eileen – you guys mean so much to me and were always there for me despite being thousands of miles and multiple timezones away. To my Kent girls, I love you all. Lydia – thanks for being my oldest friend and my closest confidante. To all of my friends who have supported me, even if I couldn't list you by name, thank you for everything. Even the smallest gestures of friendship meant a great deal to me.

Finally, I have to thank my family. I consider myself fortunate to have a large extended family who have been beyond supportive and encouraging throughout my journey. I want to thank my brother Aidan Coyne, for understanding all my most niche jokes and for commiserating with

me when I needed it the most. And last but certainly not least, I would like to thank my parents, Monica Longworth and Michael Coyne. I love you so much, thank you for everything you have given me and for always supporting me through thick and thin. I can’t even express how grateful I am for you.

ABSTRACT OF THE THESIS

Efforts Towards the Synthesis of Ceylonamide A via a Stereocontrolled Polyene Cyclization

By

Glynis Longworth Coyne

Master of Science in Chemistry

University of California, Irvine, 2019

Professor Christopher D. Vanderwal, Chair

This thesis describes efforts made towards the synthesis of ceylonamide A via a stereocontrolled cationic polyene cyclization. Chapter 1 provides background on the ceylonamide family of natural products and reviews the use of cationic polyene cyclizations as a general synthetic approach. This chapter reviews a particular cyclization methodology recently reported by the Vanderwal group which allows for a new mode of access to specific polycyclic structural motifs. A novel application of this technology is proposed towards the synthesis of the bioactive diterpene ceylonamide A.

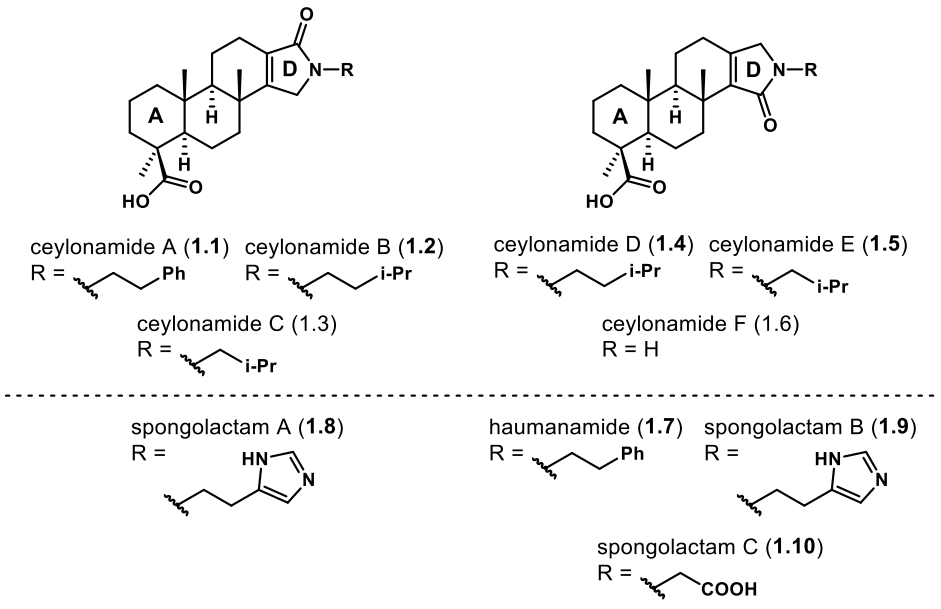
Chapter 2 discusses the efforts made towards the synthesis of ceylonamide A. The preparation of a key intermediate and attempts to carry out the desired cyclization are described. In addition, control studies to investigate the confounding factors of this cyclization are detailed, along with the synthesis of the substrates utilized in each experiment.

CHAPTER 1: Background on the Ceylonamide Natural Products and Cationic Polyene Cyclizations

1.1 Introduction

The ceylonamides are a class of nitrogenous tetracyclic spongian diterpenes whose isolation was first reported by Tsukamoto and coworkers in 2016 from the Indonesian marine sponge *Spongia ceylonensis* (Figure 1.1).[1] These tetracyclic compounds are composed of three cis-fused 6-membered rings, with oxygenation of the axial (C19) methyl carbon on the A-ring, and a characteristic α,β-unsaturated γ-lactam D-ring, with oxygenation at either C15 or C16 (Figure 1.1). They are part of the general class of spongianes,[2] and structurally similar molecules in this family have been previously reported, including haumanamide, reported by Scheuer and coworkers in 1992 (**1.7**),[3] and the spongolactams A–C, reported by Ojika and coworkers in 2007 (**1.8**–**1.10**).[4]

Figure 1.1: Ceylonamides A–F and related terpenes



From a bioactivity standpoint, Tsukamoto and coworkers found that ceylonamides A and B (**1.1** and **1.2**, respectively) exhibited inhibitory activity towards receptor activator of nuclear

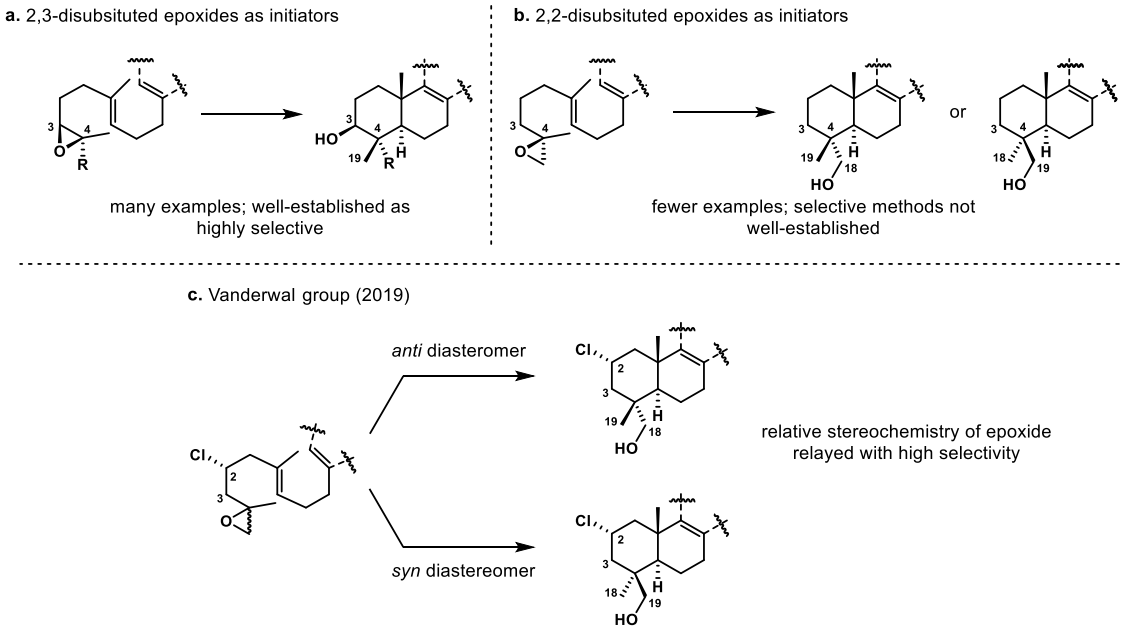
factor-κB ligand (RANKL); stimuli from this ligand activate downstream signaling pathways which result in the up-regulation of osteoclastogenesis.[5] Thus, these molecules represent possible candidates for the suppression of bone breakdown by osteoclasts, particularly ceylonamide A (IC_{50} = 13 μM; ceylonamide B, IC_{50} = 18 μM). A variety of bone density-related disorders, such as osteoporosis, bone metathesis, and some bone cancers have been linked to malfunctions in osteoclast regulation, especially with respect to RANKL activity.[5-7] In addition, RANKL inhibition has been shown to have anti-tumor effects;[8] as a result, RANKL-inhibiting drugs have become of major clinical interest.[6]

1.2 Cationic polyene cyclizations

Cationic polyene cyclizations have been well-established as powerful and effective methods of accessing complex polycyclic structures, both in nature and in the laboratory, due to their utility as a method of rapidly constructing multiple rings in a stereocontrolled fashion.[9] In nature, these complex transformations are carried out by enzymes with high efficiency, which initiate cationic cyclization with excellent stereocontrol and high yield.[9,10] Synthetically, researchers have been able to mimic these results in both radical and cationic manifolds.[9]

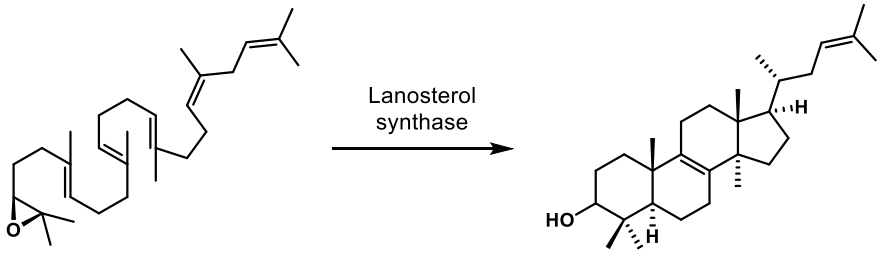
One of the most powerful and widely-used methods is the epoxide-initiated cationic polyene cyclization (Figure 1).[11] However, despite the depth of research in the literature, there has been little exploration into methods of directly accessing C18 and C19 oxygenation (Figure 1.2b, below). Our group recently disclosed an approach to epoxide-initiated polycyclizations which allows for direct access to these structural motifs in a stereocontrolled fashion (Figure 1.2c).[12] We envisioned applying this cyclization technology to a convergent synthesis of ceylonamide A.

Figure 1.2: Epoxide-initiated polyene cyclizations



1.2.1 Epoxide-initiated cationic polyene cyclizations

Scheme 1.1: Biosynthetic polyene cyclization by lanosterol synthase

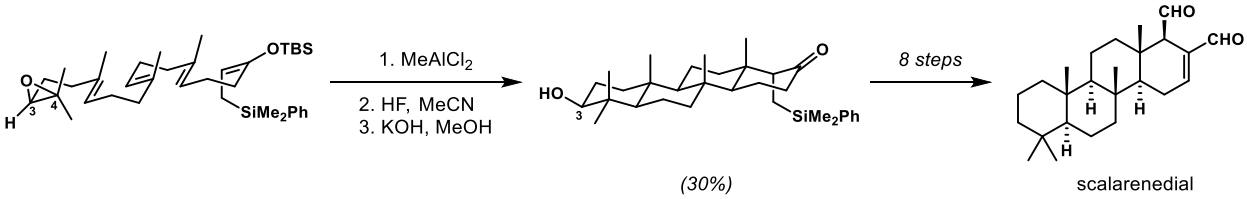


2,3-oxidosqualene (**1.11**) lanosterol (**1.12**)

Lanosterol synthase is an oxidosqualene cyclase enzyme that performs an enzymatic epoxide-initiated cationic polyene cyclization to form lanosterol, a key intermediate in the cholesterol biosynthetic pathway in humans (Scheme 1.1).[13] The mechanism of this biosynthetic transformation begins with a pre-organization of the substrate (**1.11**) into the desired chair-boat-chair reactive conformation; protonation of the epoxide then leads to the formation of the A-ring, and a subsequent stepwise cascade of ring-forming reactions via alkene attack on the intermediate carbocations assembles the polycyclic core.[13, 14] Subsequent hydride and methyl shifts form the final lanosterol product (**1.12**). While the advantage of active site pre-organization is, of course,

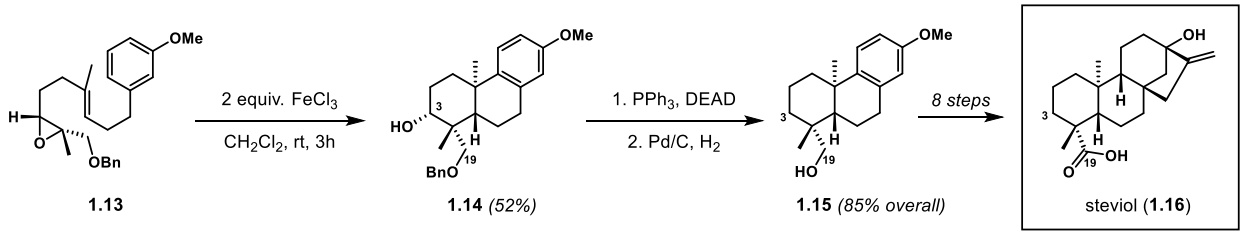
one factor that cannot readily be replicated in the laboratory, these epoxide-initiated transformations have nevertheless been successfully utilized for a variety of total syntheses.[10,11,15,16]

Scheme 1.2: Corey (1997): example of stereoselectivity in internal-epoxide-initiated cyclizations



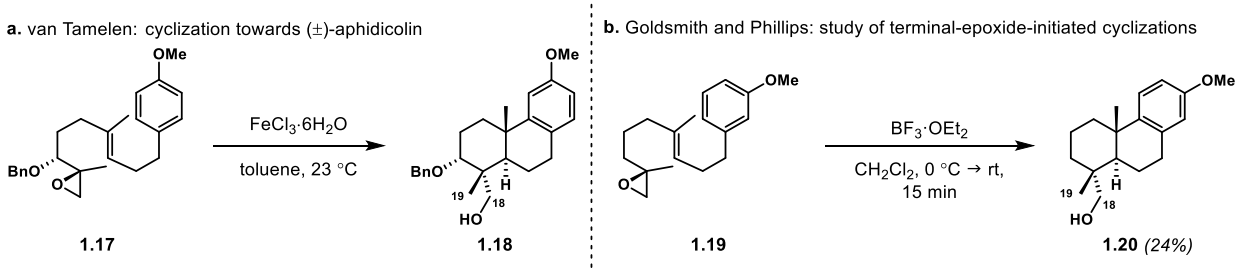
Much like the biosynthetic pathway, the vast majority of epoxide-initiated polyene cyclizations utilize a 2,3-disubstituted epoxide motif, wherein the oxirane is on C3 and C4 (Scheme 1.2). Stereocontrol is imposed by the configuration of the epoxide, as the most favorable reactive conformation will place the epoxide in a pseudo-equatorial orientation, resulting in preferential formation of the corresponding product stereochemistry.[10,17] Furthermore, internal-epoxide-initiated cyclizations result in oxygenation at the C3 position. While this is ideal for the construction of natural products with that oxygenation pattern, such as the sterols, this complicates the issue of how to install oxygenation at the C18 or C19 position – the desired oxygenation pattern for the ceylonamides, among others (e.g. steviol, **1.16**; neotripterifordin, **1.24**; see below). The most common strategy used for accessing C19 oxygenation when assembling a polycyclic core via epoxide-initiated polyene cyclization is to pre-install oxygenation at the desired position, and excise the undesired C3-carbinol formed by the epoxide ring opening.[17,18]

Scheme 1.3: Baran's synthesis of (±)-steviol via epoxide-initiated polyene cyclization

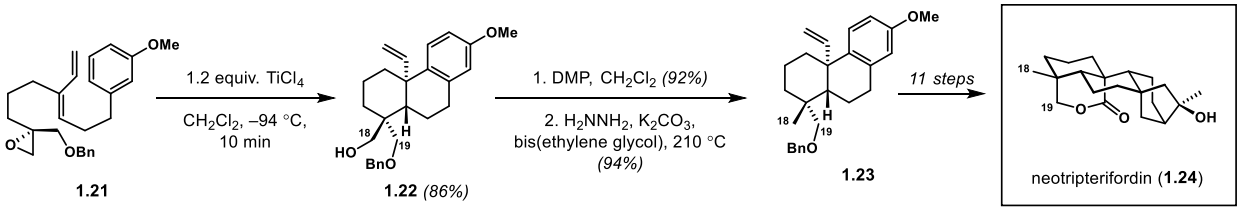


Baran and coworkers utilized this strategy in their 2013 synthesis of (±)-steviol (**1.16**).[17] Their key ring forming step was carried out using a substrate (**1.13**) which had the desired C19 oxygenation pre-installed and protected as the benzyl ether (Scheme 1.3). They were able to accomplish a terminal-epoxide-initiated bicyclization to access tricycle **1.14** selectively. The authors justify their strategy by making the point that, absent any other element to impose stereocontrol, cyclizations utilizing terminal epoxides result in preferential C18 oxidation – that is, oxygenation on the equatorial methyl group, as demonstrated in van Tamelen and coworkers' 1983 synthesis of (±)-aphidicolin (Figure 1.3a), and in Goldsmith and Phillips's 1969 study of terminal-epoxide-initiated bicyclizations (Figure 1.3b).[18-21] The preference of the epoxide for a pseudo-equatorial orientation resulted in the desired placement of the benzyl ether into the pseudo-axial position for cyclization, affording the desired C19 oxygenation in tricycle **1.15**; however, this route subsequently required two steps to remove the undesired C3 oxygenation.

Figure 1.3: Examples of terminal-epoxide-initiated polyene cyclizations



Scheme 1.4: Corey's synthesis of neotripterifordin via terminal-epoxide-initiated polyene cyclization

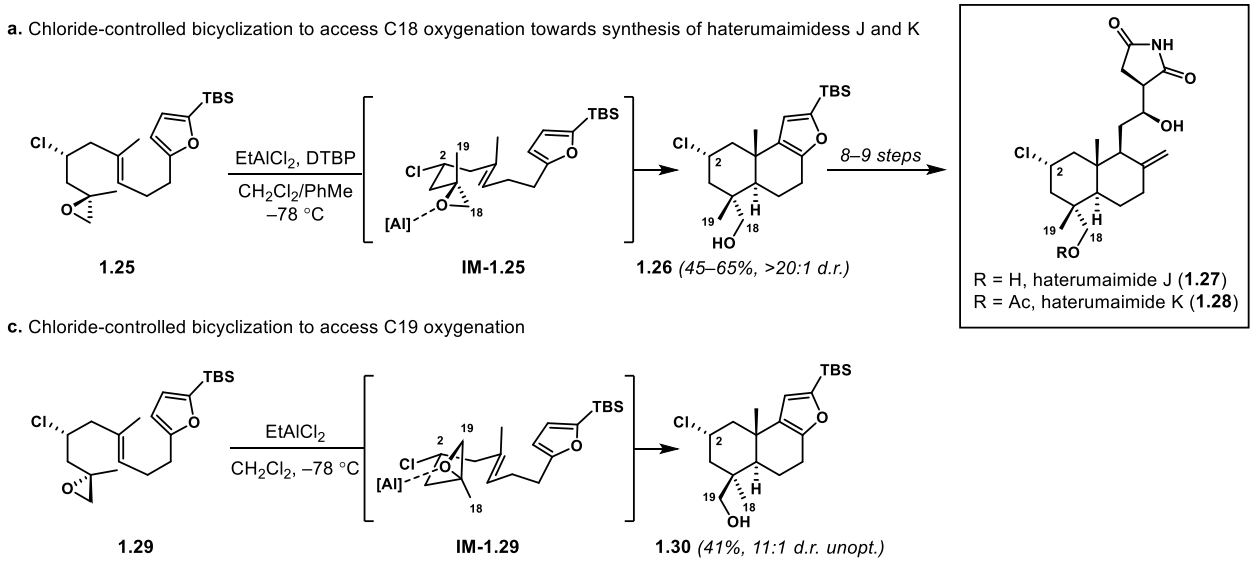


Similarly, in their 1997 synthesis of neotripterifordin (**1.24**), Corey and coworkers also elected to pre-install the C19 oxygenation on their cyclization substrate (**1.21**); however, in contrast to Baran's strategy towards (±)-steviol, they elected to utilize a terminal epoxide as their

initiating group (Scheme 1.4), and were able to accomplish this cyclization to afford tricycle **1.22** an 89% yield, much higher than the typical yields for similar polyene cyclizations.[11,18] The authors attribute the efficiency of this cyclization to bidentate coordination of the $TiCl_4$ by the proximal epoxy and ethereal oxygens, which they believed minimized side reactivity.[18] As with most terminal-epoxide-initiated cyclizations (Figure 1.3, above), this reaction resulted in epoxide ring opening to give the equatorial (C18) hydroxymethyl group, hence why it was necessary to pre-install the C19 oxygen as the benzylic ether. This undesired C18 oxygenation required two steps to excise to afford **1.23**, which was then elaborated to the natural product (**1.24**).

1.2.2 Chlorine-atom-controlled, terminal-epoxide-initiated polyene cyclizations

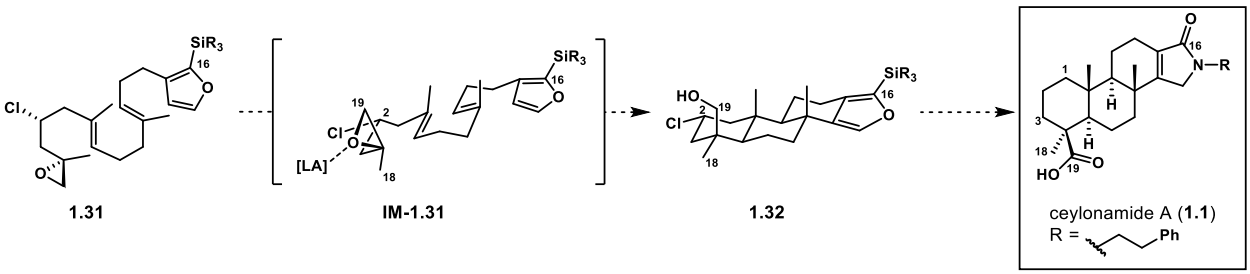
Figure 1.4: Vanderwal (2019): stereoselective terminal-epoxide-initiated bicyclizations via a proximal chloride auxiliary



Recently, our group reported a total synthesis of the lissoclimide natural products haterumaimides J and K, in which one of the key steps was a highly diastereoselective terminal-epoxide-initiated polyene cyclization, wherein a proximal chloride served as a key element of stereocontrol (Figure 1.4).[12] These results were obtained by coworker Sharon Michalak, who carried out a number of cyclization studies on these systems.[22] When substrate **1.25** was subjected

to cyclization conditions, bicycle **1.26** was obtained with >20:1 dr favoring carbinol formation at C18 (Figure 1.4a). In contrast, the des-chlorinated analogue of **1.25** (not shown) was found to afford a 5:1 dr favoring C18 oxygenation.[22] We hypothesized that the C2 chloride preferred to sit pseudo-equatorial position in the reactive conformation (**IM-1.25**), thus dictating the orientation of the epoxide during the cyclization. In addition, Sharon Michalak prepared the *anti* diastereomer of the cyclization substrate (**1.29**), and subjected it to similar cyclization conditions (Figure 1.4b). This afforded bicycle **1.30** in an 11:1 dr favoring the C19 carbinol. In light of this, we believed that this cyclization chemistry could be applied to the synthesis of ceylonamide A to furnish the desired C19 oxygenation without the necessity of pre-installing it (Scheme 1.5, below).

Scheme 1.5: Proposed cyclization strategy towards the synthesis of ceylonamide A



1.3 Furans as terminating groups in cationic polyene cyclizations

In Scheme 1.5 (above), proposed substrate **1.31** contains a 2,3-disubstituted furan as the terminating group for the cyclization. Given that the D ring of the ceylonamides is a pyrrolidine, the ideal strategy would presumably be to use a pyrrolidinone, rather than a furan. However, there have been no reports in the literature of the use of nitrogenous heterocycles as terminating groups for cationic polyene cyclizations. On the other hand, furan-terminated cationic cyclizations have been established as useful terminating groups for these reactions, and can be converted to the desired pyrrolidine.[23-25] Notably, Tanis and coworkers published a series of studies on the use of furans as terminating groups.[24-27] Unfortunately, in all of the reported cases, cyclization took place with nucleophilic addition from the 2 or 3 position of the furan. Furthermore, there are no literature

reports of cationic polyene cyclizations onto the 4 position of a furan; indeed, one report by Tanis suggests that cyclization onto a 3-substituted furan occurs preferentially to the 2-position over the 4-position (Scheme 1.6, below).[24] Nevertheless, we propose that installation of a silyl group at the 2 position of the furan (C16), as shown in cyclization substrate **1.31** (Scheme 1.5), would prevent bond formation at the 2 position, because of the steric bulk of the silyl group and because addition at the 4 position would allow the ring to re-aromatize by deprotonation.

We also elected to utilize a terminating furan because tetracycle **1.36** (Figure 1.5) is a known natural product that could presumably be accessed from cyclization product **1.32** in a few steps and thus could be used to confirm that we achieved our desired stereochemistry from the key cyclization step.[1]

Scheme 1.6: Tanis (1983): cyclizations of 3-substituted furans

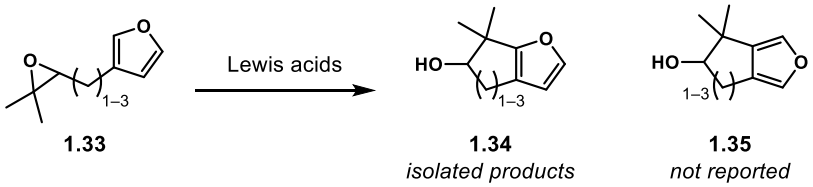
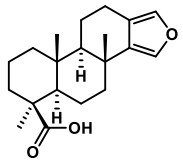


Figure 1.5: Furanyl diterpene **1.36**



spongia-13(16),14-dien-19-oic acid (**1.36**)

1.4. Conclusion

Polyene cyclizations are well-established as useful and powerful methods for rapidly assembling polycyclic natural product cores. In particular, the recently-reported chlorine-atom-controlled cyclization methodology by my coworkers in the Vanderwal group represents a useful extension of the field, specifically for the installation of C18 and C19 oxygenation. We felt that a

potential application of this technology would be the construction of the tetracyclic core of ceylonamide A, wherein the desired C19 oxygenation could be directly accessed from the initiating epoxide, without the necessity of pre-installing an oxygen functionality prior to cyclization.

1.5 References

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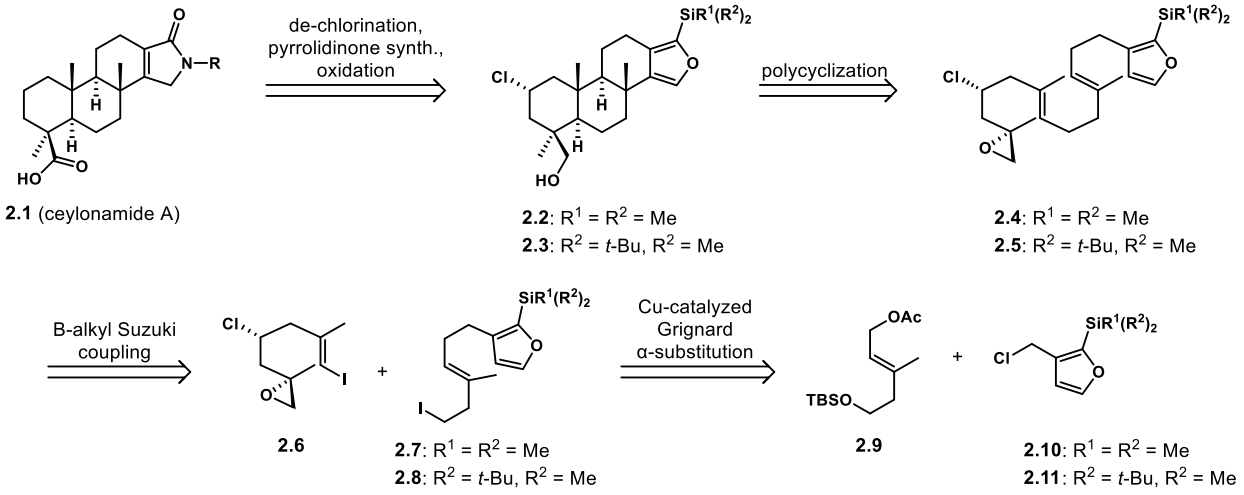
CHAPTER 2: Efforts Towards the Synthesis of Ceylonamide A via a Stereocontrolled Cationic Polyene Cyclization

2.1 Introduction

As established in Chapter 1, we hoped to utilize the chloride-controlled epoxide-initiated polyene cyclization technology as our key step, in order to achieve the formation of a tetracycle such as compound **2.2** (Scheme 2.1). We believed that this could be elaborated to the natural product ceylonamide A (**2.1**) by a few functional group manipulations. We imagined that cyclization substrate **2.4** could be accessed via B-alkyl Suzuki between known vinyl iodide **2.6** and alkyl iodide **2.8**. Alkyl iodide **2.8** could, in turn, be accessed from a copper-catalyzed allylic substitution between allylic acetate **2.9** and chloromethyl furan **2.10**.[1-3] This synthetic route was chosen because it involves the assembly of a few key fragments, each representing one terpene fragment, and whose structures are either known or whose synthesis could be achieved by well-precedented transformations.

Scheme 2.1: Retrosynthetic analysis of ceylonamide A

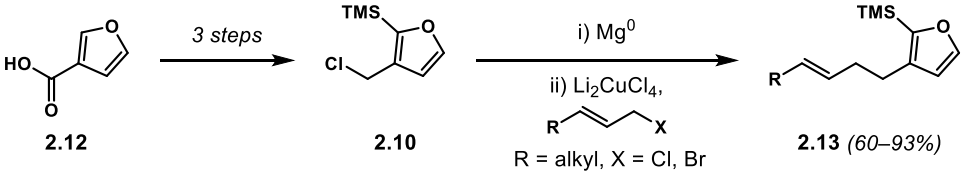


2.2 Synthesis of Tricyclization Substrate

2.2.1 Allylic substitution

Our plan to carry out the allylic substitution of acetate **2.9** with the Grignard reagent derived from chloromethyl furan **2.10** was inspired by the work of Tanis and coworkers, who have disclosed in multiple reports the preparation of chloromethyl furan **2.10**, from which was prepared the corresponding Grignard reagent for the copper-catalyzed substitution of allylic electrophiles (Scheme 2.2).[1, 4]

Scheme 2.2. Tanis (1984): precedent for allylic substitution with 3-furylmethylmagnesium chloride as nucleophile

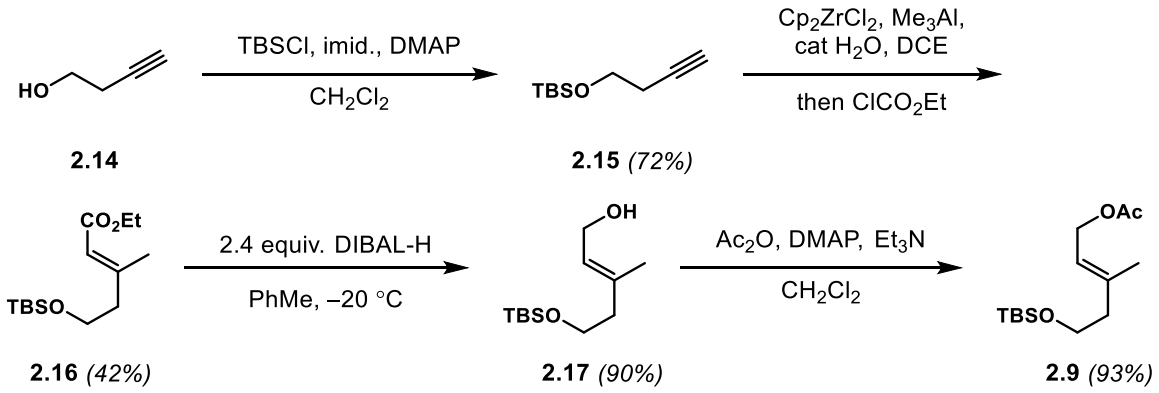


2.12 **2.10** **2.13** *(60–93%)*

To that end, we elected to synthesize known trimethylsilylated chloromethyl furan **2.10**. Rather than the allylic halides utilized by Tanis and coworkers in their study, we elected to utilize allylic acetate **2.9** as the electrophilic partner. While the regioselectivity of substitution with allylic acetates can be easily tuned to favor the desired α-substitution, allylic halides can often have a preference for undesired γ-substitution, which has been attributed to the higher reactivity of the allylic halides relative to the analogous acetate.[2]

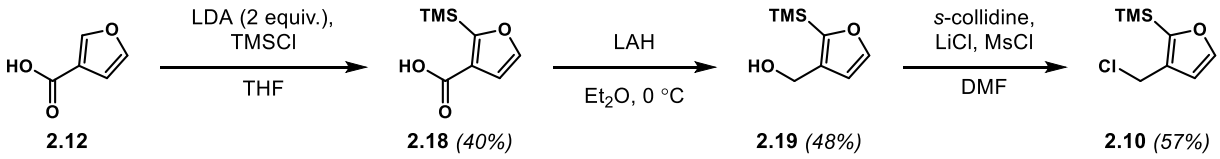
Our synthetic efforts commenced with the preparation of the allylic acetate (Scheme 2.3). While we initially considered a Horner–Wadsworth–Emmons olefination route, this was set aside in favor of a highly *E*-selective zirconocene-catalyzed carboalumination. At lower temperatures, and in the absence of any potential coordinating groups, these carboaluminations have shown complete selectivity for the *E* product, and generally predictable regiochemistry.[5-8]

Scheme 2.3: Synthesis of allylic acetate **2.9**



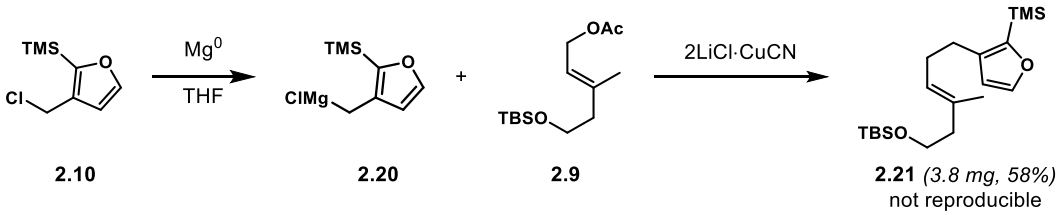
Known silyl ether **2.15** (Scheme 2.3), prepared from commercially available but-3-yn-1-ol (**2.14**), was then subjected to zirconocene-catalyzed carboalumination followed by addition to ethyl chloroformate to form α,β-unsaturated ester **2.16**. This ester was then readily reduced to allylic alcohol **2.17** by treatment with excess DIBAL-H. Acetylation with acetic anhydride and catalytic DMAP also proceeded cleanly and in high yield to afford **2.9**. With this electrophile in hand, we then began our investigations into the preparation of the Grignard precursor.

Scheme 2.4: Synthesis of silylated chloromethylfuran **2.10**



We first elected to synthesize silylated chloromethyl furan **2.10**, where the 2-position is substituted with a trimethylsilyl group. Following the route reported by Tanis (Scheme 2.4),[1,4] commercially-available 3-furoic acid **2.12** was ortho-functionalized to afford silylated furoic acid **2.18**. Subsequent LAH reduction afforded alcohol **2.19**, and allylic chlorination gave chloromethyl furan **2.10**. Having synthesized the required fragments, we then began our attempts to effect the copper-catalyzed allylic substitution reaction (Scheme 2.5).

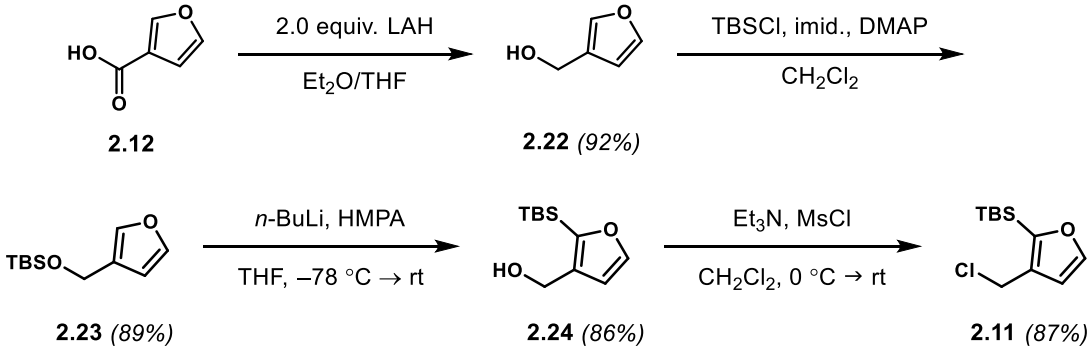
Scheme 2.5: First attempt at allylic substitution of **2.9** with **2.10**



2.10 **2.20** **2.9** **2.21** *(3.8 mg, 58%)* not reproducible

Unfortunately, attempts to carry out this reaction using **2.10**, while initially promising, were ultimately unproductive. While the desired product (**2.21**) was isolated successfully a single time, serving as a proof of concept, this result was not replicable. Furthermore, efforts to synthesize greater amounts of material to investigate and troubleshoot the reaction were hindered by the volatility of furanyl alcohol **2.19** and chloromethyl furan **2.10**, making them difficult to handle and resulting in lower-than-expected yields overall from this route. Furthermore, coworker Sharon Michalak experienced difficulties with protodesilylation when using a trimethylsilyl-substituted furan, which she resolved by instead utilizing a (*t*-butyl)dimethylsilyl-substituted furan.[9] In light of this, we elected to prepare the analogous chloromethyl furan **2.11**, which we presumed would have a lower volatility, making it easier to handle, and less of a potential source of difficulty later in the synthesis. Fortuitously, we found that the synthesis of furanylmethanol **2.24** (Scheme 2.6, below) has been reported in the literature, and so we commenced on a synthetic route to prepare **2.11** as the Grignard precursor.[10]

Scheme 2.6: Synthesis of silylated chloromethylfuran **2.11**

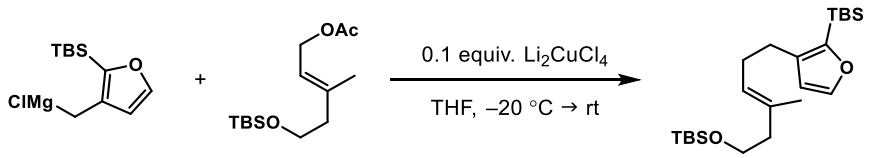


2.12 **2.22** *(92%)*

2.23 *(89%)* **2.24** *(86%)* **2.11** *(87%)*

Lithium aluminum hydride reduction of 3-furoic acid (**2.12**, Scheme 2.6) afforded 3-furanylmethanol **2.22**, which was silylated with (*t*-butyl)dimethylsilyl chloride to give silyl ether **2.23**. This silyl ether was treated with *n*-BuLi in HMPA/THF at cryogenic temperature to induce a retro-Brook 1,4-shift to afford silylated furyl alcohol **2.24**. With this furan, it was found that the allylic chlorination could be carried out simply by treating **2.24** with Et_3N and mesyl chloride to give chloromethyl furan **2.11** in high yield. With this Grignard precursor available via a scalable route, we were able to optimize the protocols for both the Grignard reagent preparation and the copper-catalyzed substitution reaction. Accordingly, furylmethylmagnesium chloride **2.25** could be prepared from chloride **2.11** with high conversion (Scheme 2.7, below), which was then used to carry out the allylic substitution reaction with catalytic Li_2CuCl_4 to afford **2.26** in reproducibly good yields.

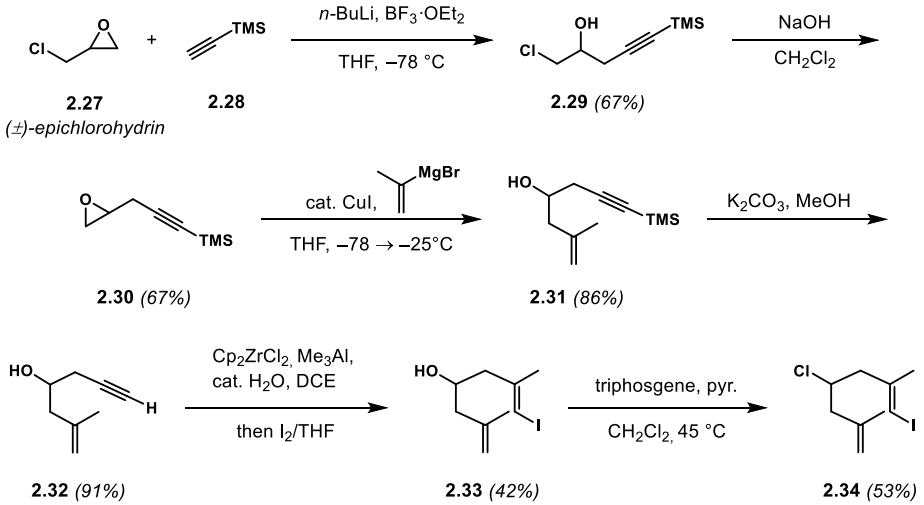
Scheme 2.7: Allylic substitution of **2.9** with furylmethyl Grignard **2.25**



2.25 *2.0 equiv.* **2.9** **2.26** *(90%)*

*2.2.2. Preparation of epoxide-containing fragment **2.6***

Scheme 2.8: Towards synthesis of epoxide **2.6**



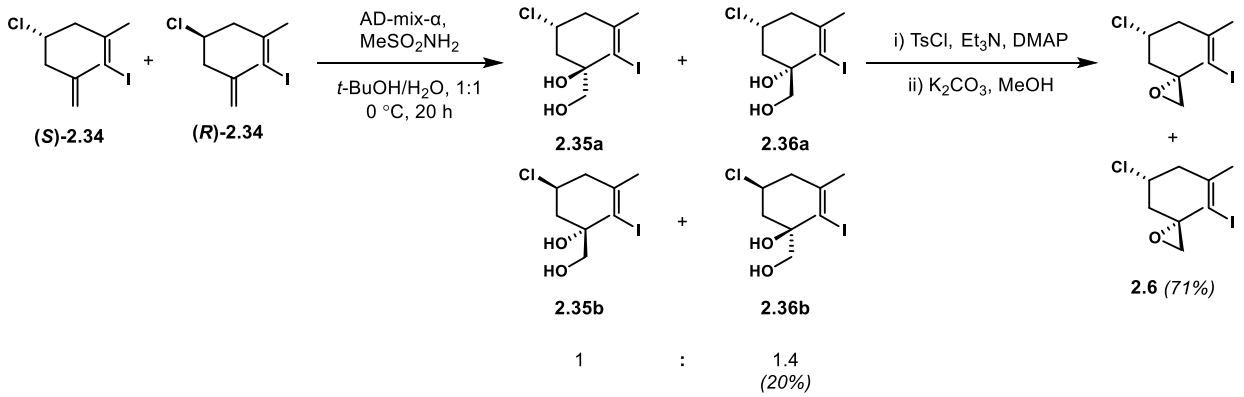
2.27 *(±)-epichlorohydrin* **2.28** **2.29** *(67%)*

2.30 *(67%)* **2.31** *(86%)*

2.32 *(91%)* **2.33** *(42%)* **2.34** *(53%)*

With the furanyl fragment (**2.26**) in hand, we commenced preparation of the epoxide coupling fragment **2.6**. The synthesis of this known molecule was first developed by Sharon Michalak. [11] As shown in Scheme 2.8, lithiated trimethylsilyl acetylene was added to commercial (±)-epichlorohydrin (**2.27**) to afford chlorohydrin **2.29**, which underwent epoxide formation under basic conditions to give oxirane **2.30**. Addition of isopropenyl cuprate to the less substituted position of the epoxide afforded alcohol **2.31**. Desilylation of this alkyne with potassium carbonate in methanol gave terminal alkyne **2.32**. This alkyne was then subjected to carboalumination followed by iodination to afford vinyl iodide **2.33**. Chlorination was carried out by treatment of **2.33** with triphosgene and pyridine, conditions developed by the Kartika group which minimized undesired elimination pathways, to give chloride **2.34**.[12]

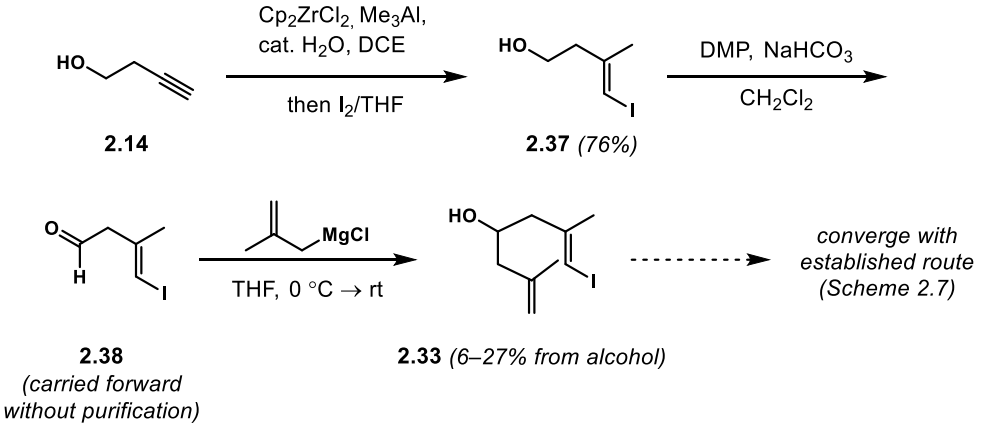
Scheme 2.9: Sharpless dihydroxylation and completion of synthesis of **2.6**



Sharpless dihydroxylation with $(DHQ)_2PHAL$ ligand selectively oxidized the terminal alkene of **2.**34 to afford diols (±)-**2.35** (undesired diastereomer) and (±)-**2.36** (desired diastereomer) as a 1:1.4 mixture of diastereomers.[13] This dr is notably lower than the 6:1 syn:anti dr previously reported by our group; however, that dihydroxylation had been carried out on enantiopure material.[11] In our case, the outcome was complicated by the fact that this asymmetric dihydroxylation was carried out on racemic material. Based on the empirical mnemonic reported by Sharpless and coworkers, the dihydroxylation of **(±)-2.34** with $(DHQ)_2PHAL$ ligand should

afford diols **2.35b** and **2.36a** as the major products in equal amounts, and **2.35a** and **2.36b** as the minor products in equal amounts; therefore, the expected outcome would be a 1:1 mixture of diols **2.35** and **2.36**.[13,14] However, the phthalazine ligands used in the Sharpless asymmetric dihydroxylation are chiral molecules, and it is reasonable to presume that $(DHQ)_2PHAL$ might not exhibit the same facial selectivity with **(*R*)-2.34** as with **(*S*)-2.34** due to the proximal chloride stereocenter, which could influence the approach of the sterically bulky ligand. Indeed, Lannou and coworkers investigated the dihydroxylation of substrates similar to ours – terminal alkenes with stereocenter in the homoallylic position – and found that these ligands did not exhibit the same diastereofacial selectivity of between the two enantiomers of a given substrate.[15] As we did not investigate the enantiomeric ratios of diols **2.35** and **2.36** obtained from the dihydroxylation of **2.34**, it is not known which enantiomer of **2.34** represents the matched case versus the mis-matched case for the facial selectivity of the DHQ and DHQD ligands. Our decision to utilize $(DHQ)_2PHAL$ was informed by empirical results obtained by coworker Sharon Michalak from her preliminary investigations into the dihydroxylation of **2.34**. These diastereomers are separable by silica gel column chromatography, allowing desired diol **2.36** to be isolated; therefore, we considered this outcome acceptable for an initial synthetic attempt. Diol **2.36** was carried through epoxidation conditions to afford the desired coupling fragment **2.6**.

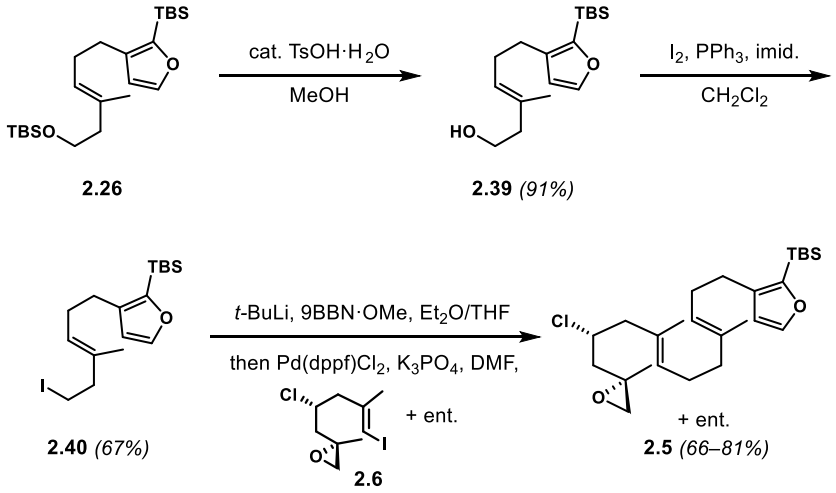
Scheme 2.10: Efforts toward a simplified synthetic route to **(±)-2.6**



This route is fairly lengthy, and as we were not yet interested in preparing enantiopure material, its major advantage of starting from chiral pool material was rendered inconsequential. We undertook some preliminary investigation into an alternative and much shorter route to advance racemic material more quickly. We considered a disconnection at the site of the secondary chloride. The planned route was to carry out nucleophilic addition to known aldehyde **2.38** to form alcohol **2.33** (Scheme 2.10).[16-19] From here, this would simply converge with the established route (Scheme 2.8, above). Thus aldehyde **2.38** was prepared via carboalumination of commercially available but-3-yn-1-ol (**2.14**) followed by iododealumination to afford homoallylic alcohol **2.37**, which was then oxidized with Dess–Martin periodinane to afford the desired aldehyde (**2.38**). We found that this species was unstable to purification attempts and prone to decomposition in air and in solution at room temperature; thus, **2.38** was carried forward without purification. Nucleophilic addition of methallylmagnesium chloride to **2.38** afforded the desired alcohol **2.33**, but in low, inconsistent yields. Attempts to carry out this route on gram scale were complicated by the decomposition of the aldehyde, which was exacerbated on larger scale. This rendered the route inefficient for its intended purpose of rapidly advancing significant amounts of material; therefore, these attempts were abandoned. We nevertheless consider this disconnection worth pursuing if any further use is made of epoxide substrate **2.6**. One potential route might be the application of the Krische group's iridium-catalyzed asymmetric methallylation of alcohols.[20]

2.2.3 Assembly of tricyclization substrate

Scheme 2.11: Assembly of cyclization substrate **2.5**



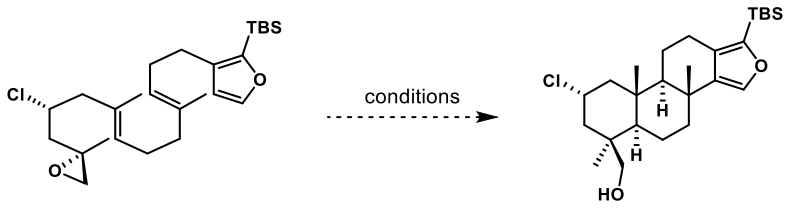
With epoxide fragment **2.6** in hand, our attention turned to the assembly of the cyclization substrate (Scheme 2.11). The alkyl iodide coupling partner was prepared by deprotection of silyl ether **2.26** with catalytic acid to afford alcohol **2.39**, which underwent an Appel reaction to afford **2.40**. This alkyl iodide was coupled with epoxide **2.6** via a B-alkyl Suzuki reaction to afford cyclization substrate **2.5**.

2.3 Cyclization studies

2.3 Initial tricyclization attempts

With this substrate in hand, we attempted to screen conditions in order to effect the desired tricyclization reaction. A logical starting point was the conditions previously reported by our group for chloride-controlled terminal-epoxide polycyclizations; however, as table 2.1 (below) shows, a wide range of conditions were screened in the hopes of effecting this transformation.

Table 2.1: Attempts to cyclize substrate **2.5**

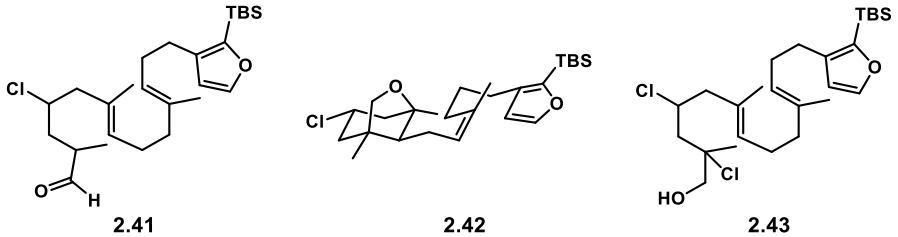


2.5 **2.3**

Lewis acid	Solvent	Temp (°C)	Time	Full conversion?	Isolated products
excess $BF_3 \cdot OEt_2$	CH_2Cl_2	–78	30 min	No	**2.41***
1.7 equiv. $EtAlCl_2$, cat DTBP	CH_2Cl_2	–78 → –70	30 min	Yes	**2.41***
3.0 equiv. Et_2AlCl	CH_2Cl_2	–78	1 h	No	**2.41***
2.0 equiv. $MeAlCl_2$	CH_2Cl_2	–78	1 h	No	**2.5**
1.2 equiv. $TiCl_4$	CH_2Cl_2	–94	30 min	No	**2.5**
excess $TiCl_4$	CH_2Cl_2	–78	30 min	Yes	**2.42, 2.43**
excess Ti(O*i*-Pr)Cl_3	CH_2Cl_2	–78	45 min	Yes	*
3.0 equiv. Ti(O*i*-Pr)$_2Cl_2$	CH_2Cl_2	–78 → –10	5 h	Yes	**2.41, 2.42***
3.0 eq $FeCl_3 \cdot H_2O$	CH_2Cl_2	rt	30 min	Yes	**2.41***
3.0 eq $FeCl_3$	CH_2Cl_2	0 → rt	30 min	Yes	decomp.
2.0 eq $AlCl_3$	CH_2Cl_2	–78	1 h	Yes	*
1.5 eq $Sc(OTf)_3$	CH_2Cl_2	–78 → rt	14 h	Yes	**2.42***
excess $SnCl_4$	CH_2Cl_2	–78	30 min	No	*

* = also observed product of unknown structure, tentatively considered product of a monocyclization pathway

Figure 2.1: Products isolated from attempted cyclization reactions of **2.5**



2.41 **2.42** **2.43**

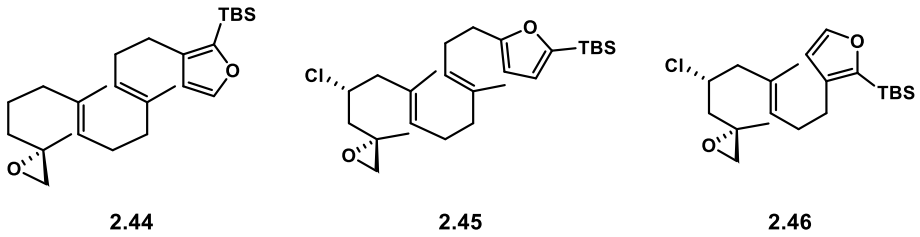
While it is difficult to establish any trends from this data, a few commonalities can be observed. Complete conversion was favored mostly by temperatures of –78 °C or slightly higher.

Furthermore, a few common products were consistently isolated from these reactions. One of the most common was aldehyde **2.41**, likely formed as a result of a Meinwald rearrangement of the terminal epoxide.[21] Another major product isolated, a putative monocyclization product whose structure has not been successfully identified, is perhaps the result of Prins-type cyclization of this aldehyde (**2.41**) from further reactivity with trace protons or excess Lewis acid.[22] A further isolated product was oxabicycle **2.42**, presumed to form as a result of the pseudo-axial Lewis acid-coordinated oxygen of the epoxide being poised to trap the positive charge formed at the C10 carbon during the cyclization. Another product isolated is **2.43**, which is presumed to be the result of chloride addition resulting in epoxide ring opening. In addition to the isolable products discussed above, most cyclization attempts resulted in the formation of additional, minor products, which were observed by TLC but could never be isolated. The material either decomposed or was too small in amount to be observed.

2.3.2 Cyclization control studies

As we were unable to observe any of the desired cyclization product, our focus turned to the possibility that the substrate itself was incapable of cyclization. To investigate this, we carried out control studies with a variety of substrates to uncover the confounding factors. We identified three possible issues to examine. First, my coworker Sharon Michalak found in her own cyclization studies that the chlorinated cyclization substrates tended to have a decreased rate of reaction compared to their des-chlorinated analogues; therefore, we would examine the des-chlorinated analogue of our tricyclization substrate **2.5**.[9] Additionally, when comparing this failed chlorine-atom-controlled cyclization with those which have proven succesful,[11] the key differences are the identity of the terminating group and the attempted formation of a third ring. To investigate these factors, we prepared substrates **2.44**, **2.45**, and **2.46**, respectively.

Figure 2.2: Substrates for cyclization control studies

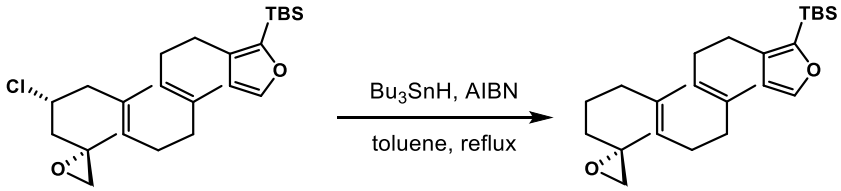


2.44 **2.45** **2.46**

*2.3.3. Des-chlorinated tricyclization substrate **2.44***

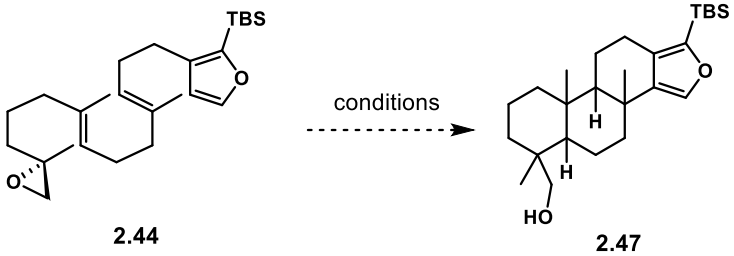
In the interest of efficiency, we elected to prepare des-chlorinated analogue **2.44** by de-chlorination of substrate **2.5** (Scheme 2.12). This was accomplished by treating **2.5** with excess tributyltin hydride and AIBN, cleanly affording des-chloride substrate **2.44**. This was then subjected to similar cyclization conditions as the previous substrate (Table 2.2).

Scheme 2.12: De-chlorination of cyclization substrate **2.5**



2.5 **2.44** *(quant.)*

Table 2.2. Cyclization of des-chlorinated analogue of tricyclization substrate.

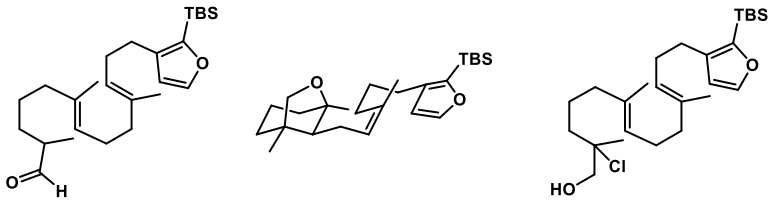


2.44 **2.47**

Conditions	Solvent	Temp (°C)	Time	Isolated products
4.0 eq Ti(O*i*-Pr)Cl_3	CH_2Cl_2	–78 → –60	1 h	**2.48, 2.49***
3.0 eq $EtAlCl_2$	CH_2Cl_2	–78 → –60	1 h	**2.50**
3.0 $BF_3{\cdot}OEt_2$	CH_2Cl_2	–78 → –60	1 h	**2.48, 2.49, rsm**
3.0 $TiCl_4$,	PhMe/CH_2Cl_2	–78 → –60	1 h	**2.49***
3.0 eq $EtAlCl_2$	PhMe/CH_2Cl_2	–78 → –60	1 h	**2.50**
3.0 $BF_3{\cdot}OEt_2$	PhMe/CH_2Cl_2	–78 → –60	1 h	**2.48, 2.49**

* = also observed non-polar isolated product, structure unassigned

Figure 2.3: Products isolated from attempted cyclization reactions of **2.44**



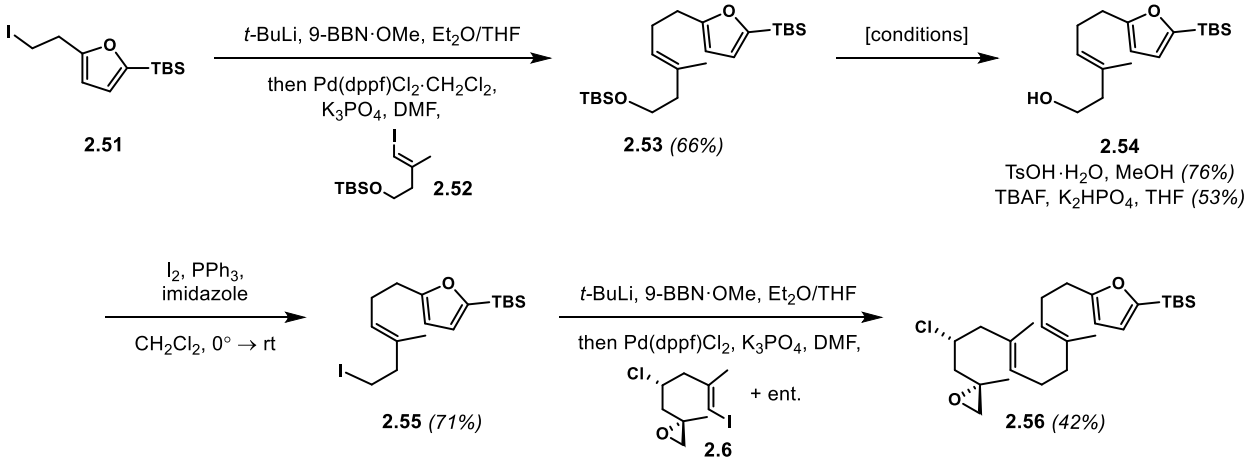
2.48 **2.49** **2.50**

Unfortunately, none of the desired tetracycle **2.47** was ever observed as a product of these cyclizations (Table 2.2). Three major products were isolated and were identified as aldehyde **2.48**, oxabicycle **2.49**, and dichloride **2.50** both presumably formed through similar reactivity as in the case of substrate **2.5**. In addition, a major non-polar product, thought to be the product of monocyclization, was also isolated. The results of this attempted cyclization indicated that the presence of the chloride is not the only confounding factor in this cyclization.

2.3.4. Alteration of terminating furan

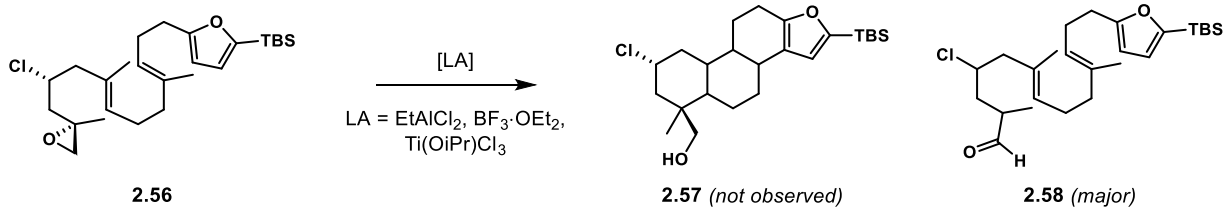
In order to investigate the effect of the terminating furan, we attempted a tricyclization wherein the terminating group was the 2,5-substituted furan motif found in the cyclization substrates that previously led to successful outcomes.[11] Synthesis of substrate **2.45** (Scheme 2.13, below) was accomplished by coupling known vinyl iodide **2.51** with known alkyl iodide **2.52** via a B-alkyl Suzuki to afford silyl ether **2.53**. Treatment with catalytic acid, unlike 2,3-disubstituted furan **2.26**, resulted in partial protodesilylation at C16 in addition to formation of the desired product, alcohol **2.54**. Treatment with TBAF prevented protodesilylation, but resulted in a lower yield. Iodination of **2.54** afforded alkyl iodide **2.55**, which was then subjected to B-alkyl Suzuki conditions with **2.6** to give cyclization substrate **2.56**.

Scheme 2.13: Synthesis of tricyclization substrate **2.56**



This substrate was subjected to cyclization conditions; however, once again, formation of the desired tetracycle was not observed. In this case, a much smaller screen of conditions was performed. The fact that the previously optimized conditions for analogous bicyclization – $EtAlCl_2$ in dichloromethane – were not successful served as a strong indication that this cyclization was not going to be fruitful. We presume the presence of the additional double bond insulates the epoxide from the electron-rich furan, such that this known terminating group was not able to induce this cyclization. In this case, the major isolated product was the aldehyde, indicating that the cyclization is once again not able to outcompete undesired reactivity pathways.

Scheme 2.14: Attempted tricyclization of substrate **2.56**

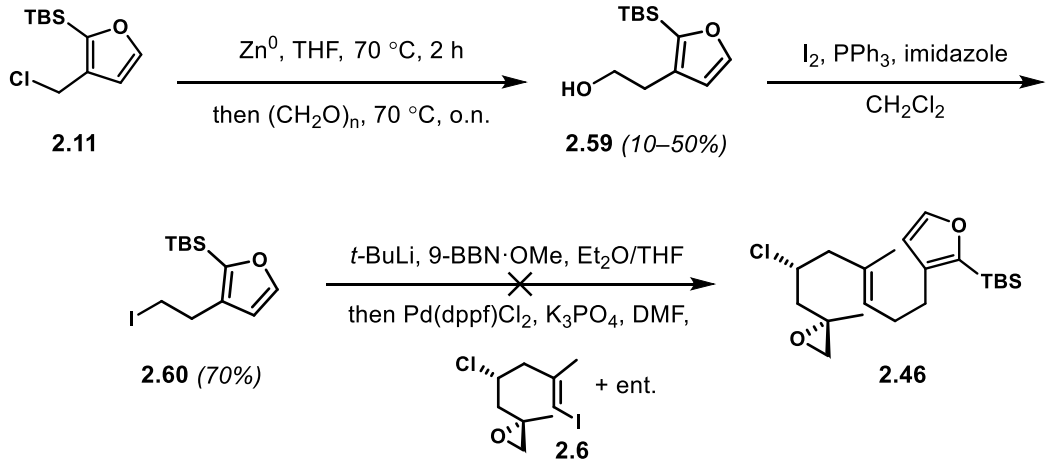


2.3.5. Bicyclization control study

Finally, to investigate the suitability of the 2,3-substituted furan moiety as a terminating group for the cyclization, we decided to test a bicyclization analogue of our initial cyclization substrate, again utilizing the 2,3-disubstituted furan terminating group. Since it is known that this

exact reaction works with the 2,5-disubstitued furan, this would be a crucial result to confirm whether the terminating group was a confounding factor. As discussed in chapter 1, cyclization onto the 4-position of the furan is poorly precedented, so it follows that it may be one of the key issues.

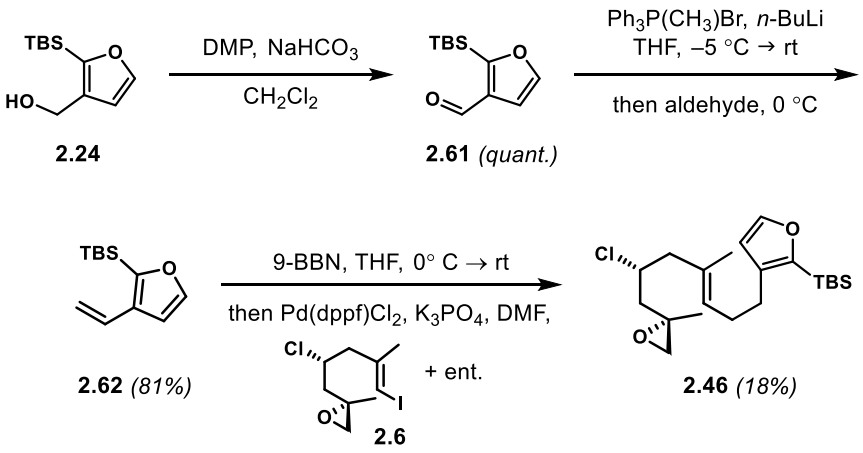
Scheme 2.15: Attempted synthesis of bicyclization substrate **2.46**



Initially, we planned to prepare bicyclization substrate **2.46** via a B-alkyl Suzuki reaction between alkyl iodide **2.60** and vinyl iodide **2.6** (Scheme 2.15). Chloromethyl furan **2.11** was homologated by formation of the organozinc followed by addition to formaldehyde to give alcohol **2.59**. This alcohol was then subjected an Appel reaction to afford alkyl iodide **2.60**. The B-alkyl Suzuki coupling of **2.60** and **2.6** was then attempted; however, we were surprised to find that we did not observe formation of the expected product. Suspecting that the issue lay with the initial in situ formation of the alkyl borane via lithiation, we carried out a few NMR experiments wherein lithiation of the alkyl iodide was carried out in ethereal solvent and then quenched with deuterated methanol. Instead of the expected deuteration at the former site of the iodine atom, we instead observed a shift in the silyl peaks, and a minor peak indicating the presence of a proton at the 2-position, presumably as a result of quenching by an adventitious proton source. Although no products were isolated from these experiments, we presumed that these results might indicate an

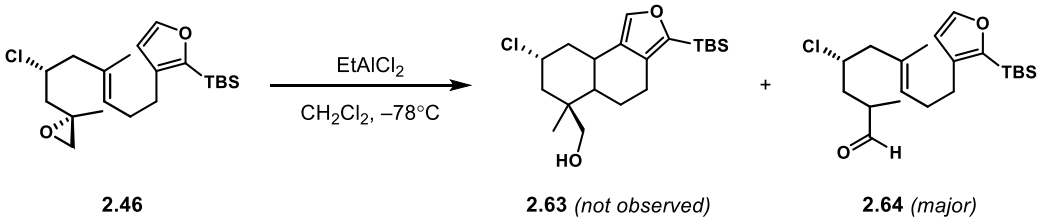
undesired 1,4-silyl migration. As such, we elected to pursue a different approach to the formation of this substrate.

Scheme 2.16: Synthesis of bicyclization substrate **2.46**



Rather than relying on in situ formation of the alkyl borane via lithiation of an alkyl iodide, we planned instead to carry out an in-situ hydroboration of an alkene (Scheme 2.16). Starting from furanyl alcohol **2.24**, oxidation with Dess-Martin periodinane cleanly afforded aldehyde **2.61**, which was then subjected to a Wittig olefination to afford vinyl furan **2.62**. Having confirmed via a hydroboration-oxidation experiment that **2.62** would form the desired alkyl borane on treatment with 9-BBN, vinyl furan **2.62** was subjected to a B-alkyl Suzuki reaction to couple with **2.6**, affording bicyclization substrate **2.46**.

Scheme 2.17: Attempted cyclization of **2.46**



On subjecting **2.46** to Lewis-acidic cyclization conditions (Scheme 2.17), formation of the desired cyclization product was not observed. Since this substrate was otherwise identical to one of the substrates known to be competent for cyclization, the 2,3-furan moiety is clearly not a

sufficiently active terminating group for this system.[11] As discussed above, cyclizations to the 4 position of furans is, to our knowledge, unknown in the literature. We have concluded that the furanyl moiety required to synthesize the ceylonamides via this tricyclization method is simply not suitable as a terminating group.

2.4. Conclusion

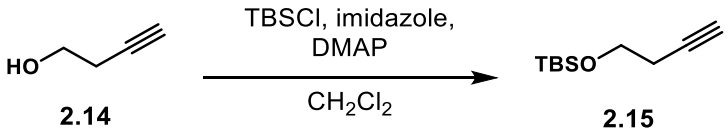
Synthesis of the desired tricyclization substrate (**2.5**) towards the synthesis of ceylonamide A was achieved in a relatively straightforward manner; however, attempts to carry out the key cyclization step were not fruitful. The desired product was not observed under a range of conditions which are well-precedented in the body of literature on cationic epoxide-initiated polycyclizations. To better understand this result, we carried out a number of control studies, the results of which point to two main confounding factors: the difficulty of accomplishing a tricyclization relative to a bicyclization, and the unsuitability of the furanyl terminating group needed for this synthesis. While there are a number of other control studies that would be worth considering, such as analogues utilizing the syn-diastereomer of the chloroepoxide fragment, or adjustments to the silyl group on the furan, the results obtained from the control studies are sufficiently damning for the feasibility of this synthetic route. As a result, serious reworking would need to be undertaken in order to carry out this synthesis, especially if the synthetic route were to rely on the chloride-controlled cyclization method.

The chloride-controlled polyene cyclization technology can be imagined to be applicable to the wide range of C18 and C19-oxygenated terpene and terpenoid natural products; however, the results of this project demonstrate that the key groups must be carefully considered, as this chemistry is not applicable in all cases. Further investigations are required in order to expand the generality and applicability of this exciting method of epoxide-initiated polyene cyclization.

2.5. Experimental Procedures

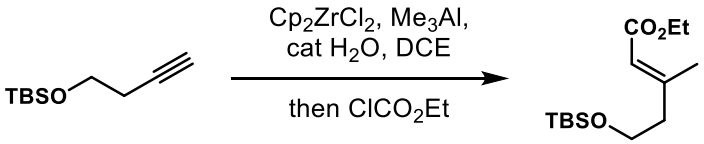
Unless otherwise noted, all reactions were performed under an atmosphere of argon using flame-dried or oven-dried glassware and Teflon® coated stir bars. Anhydrous solvents were prepared by passage through columns of activated alumina. All amine bases were distilled from calcium hydride prior to use except for *s*-collidine and 2,6-di-*tert*-butylpyridine, which was used as received. HMPA was distilled from CaH_2 and stored over molecular sieves. DCE specified as "dry" and TMSCl were distilled over CaH_2 prior to use. Anhydrous solvents were prepared by passage through a column of activated alumina and a column packed with Q5 reactant, a supported copper catalyst for scavenging oxygen, under a positive pressure of argon. All other reagents were used as received or prepared according to literature procedures, unless otherwise noted. Unless otherwise specified, reaction progress was monitored by thin-layer chromatography (TLC) performed on Merck silica gel 60 F_{254} glass-backed TLC plates visualized with UV (254 nm) and potassium permanganate (KMnO4)/heat or *p*-anisaldehyde/heat as developing agents. Column chromatography was performed using EMD Millipore 60 Å (0.040–0.063 mm) mesh silica gel (SiO2), and eluent systems are reported as %v/v.

^{1}H NMR spectra were recorded at 298 K on Bruker GN500 (499 MHz), Bruker CRYO500 (500 MHz), and Bruker AVANCE600 (600 MHz) spectrometers. ^{13}C NMR spectra were recorded at 298 K on Bruker CRYO500 (125 MHz) and Bruker AVANCE600 (151 MHz) spectrometers. Chemical shifts are reported in ppm, referenced from $CDCl_3$ residual peaks at 7.26 ppm (^{1}H NMR) and 77.16 ppm (^{13}C). Coupling constants (*J*) are reported in Hz. Peak multiplicities are reported as ap (apparent), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). High resolution mass spectra (HRMS) were recorded on a Waters LCT Premier spectrometer using ESI-TOF. Low resolution mass spectra (LRMS) were recorded on a Waters LCT Premier spectrometer using ESI-TOF.



2.14 2.15

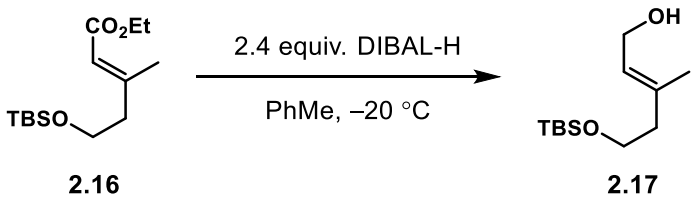
(but-3-yn-1-yloxy)(*tert*-butyl)dimethylsilane 2.15. Imidazole (4.95 g, 72.7 mmol), TBSCl (4.73 g, 31.4 mmol), and DMAP (404 mg, 3.30 mmol) were dissolved in anhydrous DCM (330 mL) and cooled to 0 °C with stirring. 3-butyn-1-ol **2.14** (2.5 mL, 33.0 mmol) was added slowly, and the reaction was allowed to stir overnight, coming to rt. The reaction was quenched by the addition of 250 mL sat. aq. NH_4Cl and 150 mL brine. The layers were separated, and the aqueous layer was extracted with DCM (4 × 50 mL). The combined organic extracts were dried over $MgSO_4$. Solvent was removed carefully under vacuum due to the high volatility of the product. The crude residue was purified on a short plug of silica (2% EtOAc:hexanes) to afford **2.15** as a clear oil (4.18 g, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 (t, J = 7.1 Hz, 1H), 2.40 (td, J = 7.1, 2.7 Hz, 2H), 1.96 (t, J = 2.6 Hz, 1H), 0.90 (s, 9H), 0.08 (s, 6H). Spectral data matched those previously reported.[23]



2.15 2.16

Ethyl (*E*)-5-((*tert*-butyldimethylsilyl)oxy)-3-methylpent-2-enoate (2.16). Cp_2ZrCl_2 (3.89 g, 13.3 mmol) was added to a 250 mL round-bottomed flask. The vessel was evacuated and backfilled with argon, and to it was added 13 mL DCE plus 20 mL dry DCE. The mixture was cooled in a salt-ice bath to –5 °C, and $AlMe_3$ (10.2 mL, 106 mmol) was added slowly. The reaction mixture was stirred for 5 min in the ice bath (kept between –5 °C and 0 °C) and then 10 min at rt. The reaction vessel was then returned to the ice bath, approx. 20 μL of DI water was added, and the reaction mixture was then stirred at rt for another 15 min. Then the flask was cooled to –20 °C, and a solution of alkyne **2.15** (9.80 g, 53.1 mmol) in 4 mL DCE was added slowly, followed by 6

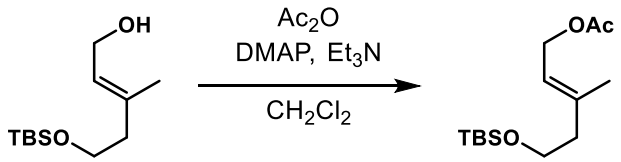
mL DCE. The reaction mixture was then slowly warmed to rt over 3 h, and allowed to stir overnight at rt. The flask was then cooled to –25 °C and ethyl chloroformate (7.62 mL, 79.7 mmol) was added slowly. The reaction mixture was allowed to warm to room temperature over 2.5 h and then stirred at rt for a further 1 h. The flask was cooled again to –20 °C and the reaction was quenched by the slow addition of sat. aq. citric acid, with vigorous stirring, until the bubbling was no longer vigorous, and warmed to rt. Then the reaction mixture was diluted with sat. aq. citric acid and sat. aq. potassium sodium tartrate until two clear layers formed. This mixture was then diluted with Et_2O and the layers were separated. The aqueous layer was extracted 3 times with Et_2O. The combined organic layers were washed successively with water and brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was subjected to column chromatography (2% EtOAc:hexanes) to afford **2.16** (6.04, 42%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68 (d, *J* = 1.1 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.74 (t, *J* = 6.7 Hz, 2H), 2.34 (t, *J* = 6.7 Hz, 2H), 2.18 (d, *J* = 1.2 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.88 (s, 9H), 0.04 (m, 6H). The spectral data matched those previously reported.[24]



2.16 **2.17**

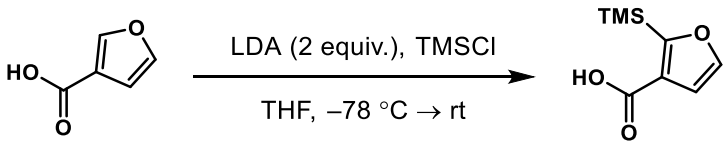
***(E)*-5-((*tert*-butyldimethylsilyl)oxy)-3-methylpent-2-en-1-ol (2.17).** Ester **2.16** (1.17 g, 4.31 mmol) was dissolved in anhydrous toluene and cooled to –20 °C. A 1.0 M solution of DIBAL-H in hexanes (10.3 mL, 10.3 mmol) was added slowly. The reaction mixture was stirred for 30 min at rt, then cooled to –20 °C and diluted with additional toluene. The reaction was quenched by the slow addition of 0.04 mL water, followed by 0.04 mL of 15% w/w aqueous NaOH, and then 1 mL of water. The mixture was stirred for 30 min, warming to rt. Solid $MgSO_4$ was added, and the

mixture was stirred for an additional 15 min at rt, then filtered over celite. Solvent was removed under vacuum to afford **2.17**, which was carried forward without purification (890 mg, 90%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 5.44 (tdd, *J* = 6.9, 2.4, 1.2 Hz, 1H), 4.15 (t, *J* = 6.2 Hz, 2H), 3.70 (t, *J* = 7.0 Hz, 2H), 2.24 (t, *J* = 7.0 Hz, 2H), 1.70 (s, 3H), 1.55 (s, 1H), 1.11 (t, *J* = 5.5 Hz, 1H), 0.89 (s, 9H), 0.05 (s, 6H). The spectral data matched those previously reported.[25]



2.17 **2.9**

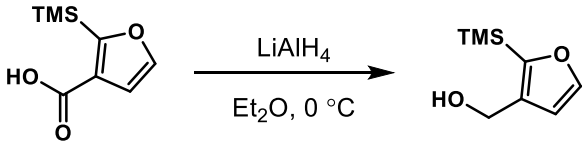
***(E)*-5-((*tert*-butyldimethylsilyl)oxy)-3-methylpent-2-en-1-yl acetate (2.9).** Allylic alcohol **2.17** (889 mg, 3.86 mmol) and DMAP (9.4 mg, 0.077 mmol) were dissolved in anhydrous DCM (8 mL). The flask was cooled to 0 °C, and Et_3N (0.81 mL, 5.79 mmol) and Ac_2O (0.44 mL, 4.63 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min. The reaction was quenched by the addition of water (10 mL). The layers were separated and the aqueous layer was extracted 3 times with DCM. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was purified by column chromatography (5% EtOAc:hexanes) to afford **2.9** (928 mg, 93%). 1H NMR (500 MHz, CDCl3) δ 5.37 (ddd, J = 8.4, 5.9, 1.3 Hz, 1H), 4.58 (d, J = 7.2 Hz, 2H), 3.70 (t, J = 6.8 Hz, 2H), 2.25 (t, J = 6.8 Hz, 2H), 2.05 (s, 3H), 1.72 (s, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C (150 MHz, $CDCl_3$) δ 171.24, 139.63, 120.25, 61.94, 61.38, 42.89, 26.05, 21.18, 18.45, 16.96, 5.19.



2.12 **2.18**

2-(trimethylsilyl)furan-3-carboxylic acid (2.18). *i*-Pr_2NH (7.50 mL, 53.5 mmol) was dissolved

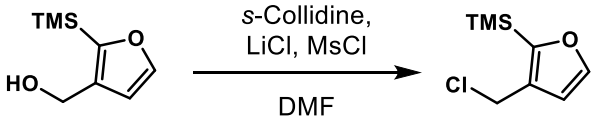
in anhydrous THF (27 mL) and cooled to –10 °C. A 2.5 M solution of *n*-BuLi in hexanes (21.4 mL, 53.5 mmol) was added slowly, and the solution stirred at –10 °C for 30 min. The flask was then cooled to –78 °C, and a solution of 3-furoic acid **2.12** (3.00 g, 26.8 mmol) in 16 mL anhydrous THF was added slowly. The reaction mixture was stirred at –78 °C for 30 min, then distilled TMSCl (11.9 mL, 93.7 mmol) was added. The flask was then allowed to come to rt, with stirring, over 1 h. The reaction was quenched by the addition of 15 mL of water and 24 mL of 2 N HCl. This mixture was stirred for 20 min at rt, then diluted with 25 mL water. The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 25 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was purified by column chromatography to afford **2.18** as an off-white solid (1.97 g, 40%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 1.7 Hz, 1H), 6.79 (d, *J* = 1.7 Hz, 1H), 0.37 (s, 9H). The spectral data matched those previously reported.[26]



2.18 **2.19**

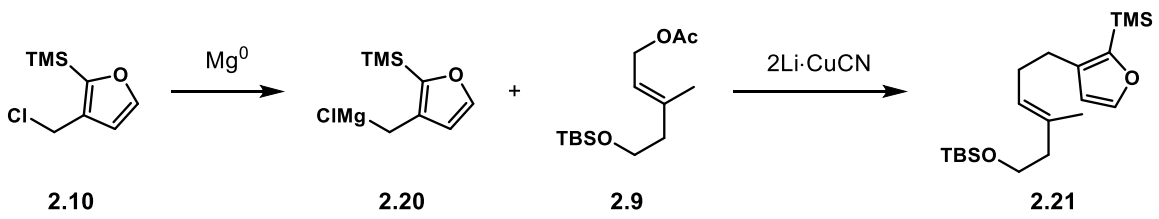
(2-(trimethylsilyl)furan-3-yl)methanol (2.19). To a stirring suspension of LAH (134 mg, 3.53 mmol) in anhydrous Et_2O (4.1 mL) in a fame-dried flask equipped with magnetic stirring and cooled to 0 °C was added furancarboxylic acid **2.18** (500 mg, 2.71 mmol) as a 1.25 M solution in anhydrous Et_2O, under argon. The reaction was then stirred for 1.5 h at rt, then cooled to 0 °C and diluted with Et_2O. Water (0.13 mL) was added slowly, followed by 15% w/w aqueous NaOH (0.13 mL) and water (0.4 mL). The mixture was stirred vigorously for 30 min at rt. Solid $MgSO_4$ was added, and the mixture was stirred for an additional 15 min at rt, and then filtered over celite, washing with Et_2O. The product solution was concentrated under vacuum to afford **2.19**, which

was carried forward without purification (378 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 1.5 Hz, 1H), 6.45 (d, *J* = 1.6 Hz, 1H), 4.59 (s, 2H), 1.51 (br, 1H), 0.31 (s, 9H). The spectral data matched those previously reported.[26]



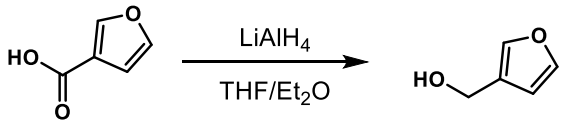
2.19 **2.10**

(3-(chloromethyl)furan-2-yl)trimethylsilane (2.10). LiCl (126 mg, 2.97 mmol) was placed into a round-bottom flask, which was evacuated and backfilled with argon, and the LiCl was then flame dried under vacuum. Anhydrous DMF (3.15 mL) and furan methanol **2.19** (253 mg, 1.48 mmol) were added to the flask at rt, followed by *s*-collidine (0.39 mL, 2.97 mmol). The solution was cooled to 0 °C and MsCl (0.17 mL, 2.22 mmol) was added slowly. The reaction was stirred for 30 min at 0 °C, then allowed to come to rt and stirred for 4.5 h. The reaction was quenched by the addition of 10 mL water and 10 mL Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with 3 x 8 mL sat. aq. $CuSO_4$, 8 mL water, and 8 mL brine. The combined aqueous washes were then extracted with 10 mL Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was purified by column chromatography with pH 7 silica (100% hexanes) to afford **2.10** as a red oil (160 mg, 57%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 1.7 Hz, 1H), 6.44 (d, *J* = 1.7 Hz, 1H), 0.34 (s, 9H); The spectral data matched those previously reported.[1]



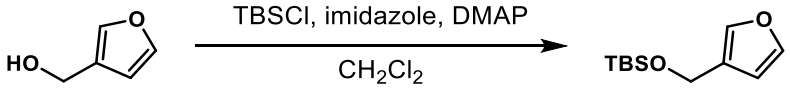
2.10 **2.20** **2.9** **2.21**

***(E)-tert*-butyldimethyl((3-methyl-6-(2-(trimethylsilyl)furan-3-yl)hex-3-en-1-yl)oxy)silane (2.21).** Grignard **2.20** was prepared as follows: metallic magnesium was crushed with a mortar and pestle, then 400 mg were transferred to a vial, which was then evacuated and backfilled. The Mg was activated by flame drying under vacuum, and then by addition of 1,2-dibromoethane and a drop of a concentrated solution of I_2 in anhydrous THF. To the activated magnesium in THF, cooled to 0 °C, was added chloride **2.10** (86 mg, 0.45 mmol) as a solution in THF, dropwise, to a total volume of 0.9 mL. The mixture was stirred 1 h at rt, then allowed to settle over 45 min. The supernatant solution titrated to 0.06 M (titration indicator: salicylaldehyde phenylhydrazone). To a solution of acetate **2.9** (5 mg, 0.014 mmol) in THF (0.10 mL) was added a drop of 1.0 M 2Li·CuCN (~0.01 mL, ~0.01 mmol). The solution was cooled to –30 °C, and Grignard reagent **2.20** (0.4 mL, 0.024 mmol) was added quickly. The reaction mixture was stirred for 2 h, with the cooling bath kept below –15 °C. The reaction was quenched by the addition of sat. aq. NH_4Cl. The reaction mixture was extracted with Et_2O, and the organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude residue was purified by column chromatography (100% hexanes → 5% Et_2O:hexanes) to afford **2.21** (3.8 mg, 58%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.28 (s, 9H), 0.89 (s, 9H), 1.60 (s, 3H), 2.18–2.24 (m, 4H), 2.48–2.52 (m, 2H), 3.66 (t, 2H, *J* = 7.0 Hz), 5.19–5.22 (m, 1H), 6.28 (d, 1H, *J* = 1.6 Hz), 7.52 (d, 1H, *J* = 1.6 Hz); ^{13}C (150 MHz, $CDCl_3$) δ –5.11, –0.80, 16.60, 18.50, 25.97, 26.11, 29.96, 43.19, 62.56, 111.40, 125.80, 132.93, 135.49, 146.02, 154.40.



2.12 **2.22**

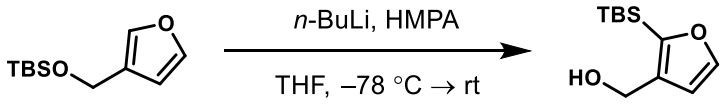
Furan-3-ylmethanol (2.22). A solution of furancarboxylic acid **2.12** (10 g, 89 mmol) in 25 mL THF was added slowly to a stirring suspension of LAH (6.8 g, 178 mmol) in Et_2O (44 mL) at 0 °C. The reaction was then stirred for 15 min at °C then for 2.5 h at rt. The reaction mixture was then diluted with 10 mL Et_2O and cooled to 0 °C. DI water (6.8 mL) was added slowly, with occasional venting of the flask, followed by 15% w/w aqueous NaOH (6.8 mL), slowly, and finally water (21 mL). The mixture was warmed to rt and stirred vigorously for 30 min. The flask was then cooled to 0 °C and solid $MgSO_4$ was added in portions. The flask was sonicated briefly (~1 min) and then stirred vigorously at rt until the slurry was homogenous and stirring freely. The mixture was then filtered over celite, washing with Et_2O. Solvent was removed under vacuum to afford **2.22**, which was carried forward without purification (8.1 g, 92%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 2H), 6.46 – 6.43 (m, 1H), 4.57 (s, 2H), 1.61 (br, 1H). The spectral data matched those previously reported.[27]



2.22 **2.23**

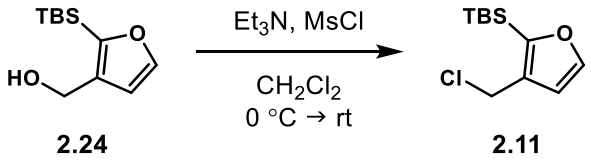
***Tert*-butyl(furan-3-ylmethoxy)dimethylsilane (2.23).** Imidazole (12.4 g, 182 mmol), TBSCl (11.9 g, 78.7 mmol), and DMAP (1.01 g, 8.29 mmol) were dissolved in anhydrous DCM at 0 °C. Then furan-3-ylmethanol **2.22** (8.13 g, 82.9 mmol) in 3 mL anhydrous CH_2Cl_2 was added slowly. The reaction mixture was stirred at 0 °C for 15 min, then allowed to come to rt and stirred for 16 h. An additional 1.01 g DMAP was added and the reaction mixture was stirred for a further 2.5 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (150 mL) and brine (50 mL) and

stirred vigorously until two clear layers were observed. The layers were separated and the aqueous layer was diluted with water and extracted with DCM (4 × 100 mL). The combined organic extracts were washed with 150 mL of water and 200 mL of brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was purified by a short plug of silica (100% hexanes → 5% EtOAc:hexanes) to afford **2.23** (15.7 g, 89%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.38 – 7.34 (m, 2H), 6.37 (s, 1H), 4.60 (s, 2H), 0.92 (s, 9H), 0.09 (s, 6H). The spectral data matched those previously reported.[10]



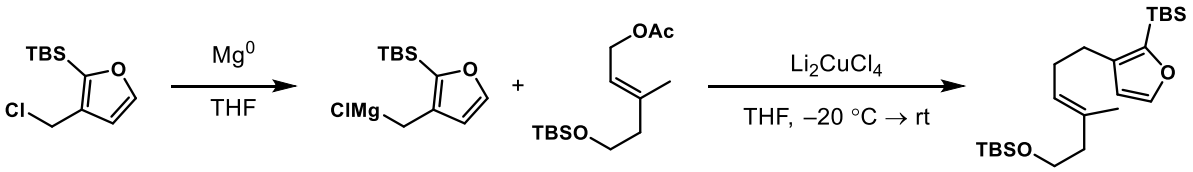
2.23 **2.24**

(2-(*tert*-butyldimethylsilyl)furan-3-yl)methanol (2.24). Silyl ether **2.23** (14.2 g, 67.1 mmol) was dissolved in anhydrous THF (200 mL) and the solution was cooled to –78 °C. Distilled HMPA (12.9 mL, 73.8 mmol) was added, followed by a 1.6 M solution of *n*-BuLi in hexanes (46.1 mL, 73.8 mmol), and the reaction mixture was allowed to stir overnight, coming to rt. The reaction was quenched by the addition of 100 mL of sat. aq. NH_4Cl to the vigorously-stirring reaction mixture. After a white precipitate was observed, the mixture was diluted with water until it just turned clear. The layers were separated, and the aqueous layer was extracted with Et_2O (4 × 80 mL). The combined organic extracts were washed with 200 mL sat. aq. $CuSO_4$, followed by water, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude residue was purified by column chromatography (5% → 15% EtOAc/hexanes, stepwise gradient) to yield **2.24** as an off-white solid (12.3 g, 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, J = 1.2 Hz, 1H), 6.48 (d, J = 1.3 Hz, 1H), 4.59 (d, J = 5.3 Hz, 2H), 1.34 (t, J = 5.5 Hz, 1H), 0.91 (s, 9H), 0.29 (s, 6H). The spectral data matched those previously reported.[10]



2.24 **2.11**

***tert*-butyl(3-(chloromethyl)furan-2-yl)dimethylsilane (2.11).** Alcohol **2.24** (1.03 g, 4.85 mmol) was dissolved in anhydrous DCM (12 mL) at 0 °C. Et_3N (1.35 mL, 9.69 mmol) was added, followed by MsCl (0.64 mL, 8.24 mmol), and the reaction mixture stirred overnight at rt. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ and the mixture was diluted with Et_2O. The layers were separated, and the aqueous layer was extracted 3 times with Et_2O. The combined organic extracts were washed successively with sat. aq. $Na_2S_2O_3$, water, and brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was passed through a plug of silica (100% hexanes) to afford **2.11** as a clear oil. 1H NMR (600 MHz, CDCl3) δ 7.59 (d, J = 1.7 Hz, 1H), 6.46 (d, J = 1.7 Hz, 1H), 4.54 (s, 2H), 0.92 (s, 9H), 0.32 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.27, 147.05, 132.97, 111.10, 38.29, 26.35, 17.38, -5.81. HRMS (ESI) *m / z* calcd for $C_{11}H_{19}ClOSi$ [M^+] 230.0894, found 230.0893.

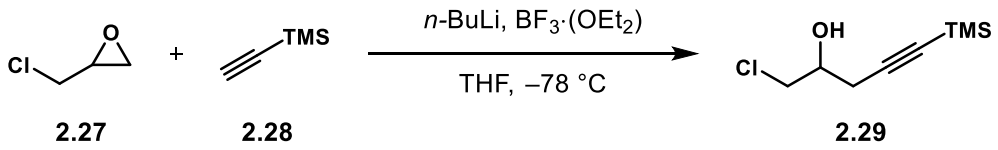


2.11 **2.25** **2.9** **2.26**

(*E*)-*tert*-butyl((6-(2-(*tert*-butyldimethylsilyl)furan-3-yl)-3-methylhex-3-en-1-yl)oxy)dimethylsilane (2.26). Grignard reagent **2.25** was prepared as follows: Magnesium was ground with a mortar and pestle and 1.1 g was placed in a round-bottom flask, which was then evacuated and backfilled with argon three times. Anhydrous THF (4 mL) was added to the flask. The magnesium was activated by the addition of a crystal of iodine and 0.1 mL dibromoethane, followed by sonication and heating. The flask was allowed to cool, and dibromoethane was added

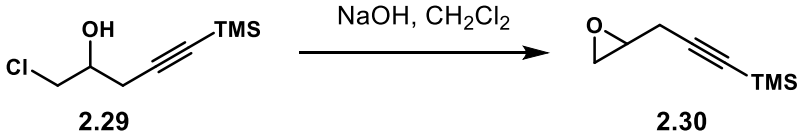
dropwise, with periodic sonication followed by heating and cooling, until production of gas was observed immediately on addition. The flask was cooled to 0 °C and diluted with a further 1.8 mL anhydrous THF. Chloromethylfuran **2.25** was added in a solution of anhydrous THF (5 mL), slowly, followed by additional drops of dibromoethane. The reaction mixture was allowed to warm to rt over 1 h with stirring, and then stirred for a further 2 h at rt. The supernatant solution titrated to 0.06 M (titration indicator: salicylaldehyde phenylhydrazone). Li_2CuCl_4 was prepared as reported in the literature.

Allylic acetate **2.9** (763 mg, 2.8 mmol) and Li_2CuCl_4 (0.28 mL, 0.28 mmol, 1.0 M in THF) were dissolved in anhydrous THF (6.4 mL). The reaction vessel was cooled to –40 °C, and the solution of furylmethylmagnesium chloride **2.25** (9.0 mL, 5.6 mmol) was added over 2.5 min. The reaction mixture was stirred for 15 h, coming to rt. The reaction mixture was cooled to 0 °C and quenched by the portion-wise addition of sat. aq. NH_4Cl (20 mL) and Et_2O (12 mL) over 30 min with vigorous stirring. Water (5 mL) was added to give two clear layers. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed successively with 20 mL of water and brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude residue was purified by column chromatography (100% hexanes → 2% EtOAc/hexanes) to afford **2.26** (1.03 g, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 1.5 Hz, 1H), 6.30 (d, *J* = 1.5 Hz, 1H), 5.21 (dd, *J* = 7.1, 6.1 Hz, 1H), 3.66 (t, *J* = 7.0 Hz, 2H), 2.50 (dd, *J* = 9.1, 6.8 Hz, 2H), 2.27 – 2.10 (m, 4H), 1.61 (s, 3H), 0.91 – 0.88 (m, 18H), 0.26 (s, 6H), 0.05 (s, *J* = 2.8 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.89, 146.13, 136.42, 132.75, 125.80, 111.06, 62.43, 43.07, 29.79, 26.49, 26.03, 26.00, 18.39, 17.64, 16.48, –5.22, –5.49. HRMS (ESI) *m / z* calcd for $C_{23}H_{44}O_2Si_2Na$ $[M+Na]^+$ 431.2778, found 431.2771.



2.27 **2.28** **2.29**

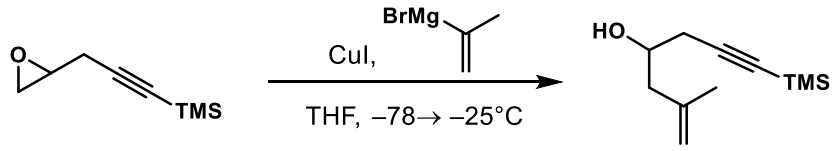
1-chloro-5-(trimethylsilyl)pent-4-yn-2-ol (28). Trimethylsilyl acetylene **2.28** (9.23 mL, 64.9 mmol) was dissolved in anhydrous THF (12 mL) and cooled to –78 °C. To this stirring mixture was added a 2.5 M solution of *n*-BuLi in hexanes (26.0 mL, 64.9 mmol) slowly, followed by $BF_3{\cdot}OEt_2$ (8.0 mL, 64.9 mmol), and the reaction mixture was allowed to stir for 10 min. Epichlorohydrin **2.27** (3.38 mL, 43.2 mmol) was added as a 3 M solution in anhydrous THF, and the reaction mixture was stirred for 1 h at –78 °C. The reaction vessel was placed in an ice-water bath and allowed to come to 0 °C, where it stirred for 30 min. The reaction was quenched by the addition of sat. aq. NH_4Cl. The layers were separated and the aqueous layer was extracted 3 times with Et_2O. The combined organic extracts were washed with brine, dried over MgSO4, filtered, and concentrated under vacuum. The crude product was carried forward without further purification (5.56 g, 67%). The spectral data matched those previously reported.[28]



2.29 **2.30**

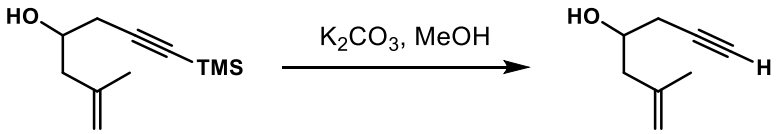
Trimethyl(3-(oxiran-2-yl)prop-1-yn-1-yl)silane (2.30). Chlorohydrin **2.29** (5.56 g, 29.2 mmol) was dissolved in anhydrous DCM (58 mL) and cooled to 0 °C. Powdered NaOH (4.08 g, 102 mmol) was added in portions, and the reaction mixture was stirred for 18 h at rt. The reaction was quenched by the addition of sat. aq. NH_4Cl (75 mL) with vigorous stirring, followed by water (25 mL). The layers were separated, and the aqueous layer was extracted with 1:1 Et_2O:hexanes (3 × 35 mL). The combined organic extracts were washed successively with 50 mL water and 50 mL brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was purified

via Kugelrohr distillation to afford **2.30** (3.00 g, 67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.13 – 3.08 (m, 1H), 2.82 – 2.77 (m, 1H), 2.67 (ddd, *J* = 9.6, 7.2, 4.4 Hz, 2H), 2.49 (dd, *J* = 17.5, 5.2 Hz, 1H), 0.16 (s, 9H). The spectral data matched those previously reported.[28]



2.30 **2.31**

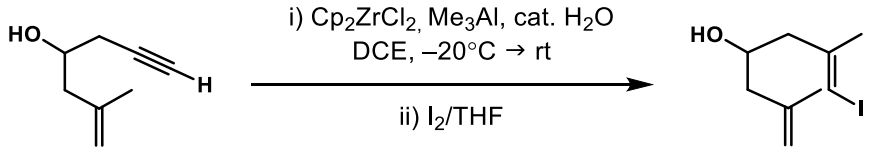
2-methyl-7-(trimethylsilyl)hept-1-en-6-yn-4-ol (2.31). CuI (259 mg, 1.36 mmol) and oxirane **2.30** (3.00 g, 19.4 mmol) were dissolved in anhydrous THF (35 mL) and cooled to –78 °C. Isopropenylmagnesium bromide (81.7 mL, 40.8 mmol, 0.5 M in THF) was added dropwise via addition funnel under positive pressure of argon. The reaction mixture was then stirred for 1 h at –78 °C, then allowed to come to –30 °C and stirred for 3 hours. Reaction progress was measured by ^{1}H NMR analysis of aliquots. When complete conversion was observed, the reaction mixture was diluted with 10 mL of Et_2O, 20 mL sat. aq. NH_4Cl, then another 10 mL of Et_2O, and was allowed to come to rt with stirring. Water was added until all solids were just dissolved. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with 50 mL brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was immediately carried forward without purification (3.27 g, 86%).



2.31 **2.32**

2-methylhept-1-en-6-yn-4-ol (2.32). Alcohol **2.31** (3.27 g, 16.7 mmol) was dissolved in methanol and cooled to 0 °C. K_2CO_3 (6.92 g, 50.1 mmol) was added. The solution was stirred for 30 min at 0 °C, and then at rt for 2 h. Then the reaction mixture was concentrated under vacuum to about

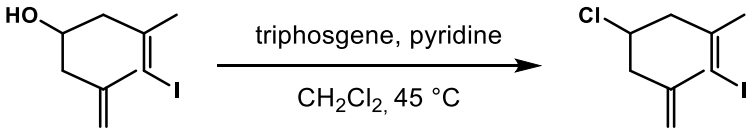
half its volume then diluted with Et_2O. The reaction was quenched by the addition of sat. aq. NH_4Cl, and the mixture was diluted with water. The aqueous layer was extracted 3 times with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The crude product **2.32** was carried forward without further purification (1.88 g, 91%). The spectral data matched those previously reported.[11]



2.32 **2.33**

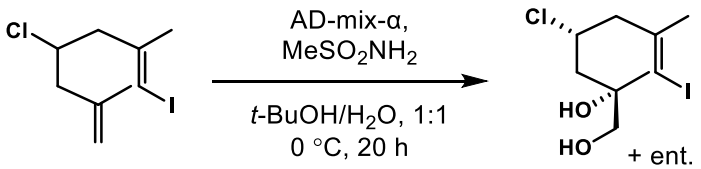
***(E)*-1-iodo-2,6-dimethylhepta-1,6-dien-4-ol (2.33)**. Cp_2ZrCl_2 (4.07 g, 13.9 mmol) was placed into a round-bottom flask, which was evacuated and backfilled with argon. DCE (40 mL) was added, and the resulting mixture was cooled to 0 °C. $AlMe_3$ (10.0 mL, 104 mmol) was added slowly under positive pressure of argon. The reaction mixture was then warmed to rt and stirred for 15 min. The reaction mixture was cooled to 0 °C and three drops of water were added. The reaction mixture was stirred 5 min at 0 °C and then 10 min at rt. The reaction mixture was again cooled to –20 °C, and alkyne **2.31** (4.32 g, 34.6 mmol) was added, followed by an additional 18 mL DCE for rinsing. The reaction mixture was stirred at rt for 19h, and then cooled to –78 °C. I_2 (26.5 g, 104.4 mmol) was added slowly as a solution in THF. The reaction mixture was allowed to come to –40 °C and then to rt, where it was stirred for 2 h. The flask was cooled, and the reaction was quenched by the careful addition of water, followed by 1N HCl. The reaction mixture was extracted with hexanes, and the organic extracts washed successively with sat. aq. $Na_2S_2O_3$, sat. aq. citric acid, and water. The organic extracts were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was purified by column chromatography to afford **2.33** (3.91 g, 40%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 6.02 (s, *J* = 1.0 Hz, 1H), 4.89 (s, 1H), 4.80 (s, *J* = 0.8 Hz,

1H), 3.92 – 3.85 (m, 1H), 2.39 – 2.35 (m, 2H), 2.20 – 2.09 (m, 2H), 1.89 (d, *J* = 0.9 Hz, 3H), 1.76 (s, 3H), 1.71 (br s, 1H). The spectral data matched those previously reported.[11]



2.33 **2.34**

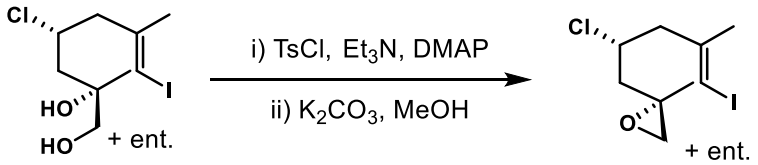
***(E)*-4-chloro-1-iodo-2,6-dimethylhepta-1,6-diene (2.34).** In a heavy-wall glass pressure flask, triphosgene (3.09 g, 10.4 mmol) was dissolved in 10 mL anhydrous DCM under positive pressure of argon. The vessel was cooled to 0 °C. Alcohol **2.33** (2.77 g, 10.4 mmol) was added as a solution in 10 mL anhydrous DCM and 1.68 mL pyridine, slowly, under positive pressure of argon. An additional 6 mL anhydrous DCM was used for rinsing. An additional 1.68 mL of pyridine was added slowly. The headspace was purged with argon, and then the vessel was sealed with a threaded PTFE cap, allowed to come to rt, then heated at 45 °C for 7 h. The reaction mixture was cooled to 0 °C, and the reaction was quenched by the slow addition of water, followed by 1 N HCl. The mixture was then diluted with 1:1 Et_2O:hexanes and stirred for 1 h. The layers were separated and the aqueous was layer extracted with 1:1 Et_2O:hexanes. The combined organic extracts were washed with water and brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude residue was purified by column chromatography to afford **2.34** (1.55 g, 53%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.90 (s, 1H), 4.83 (s, 1H), 3.97 – 3.88 (m, 1H), 2.48 – 2.31 (m, 3H), 2.24 (dd, *J* = 13.8, 8.6 Hz, 1H), 2.07 (t, *J* = 2.6 Hz, 1H), 2.00 (d, *J* = 3.8 Hz, 1H), 1.78 (s, 3H). The spectral data matched those previously reported.[11]



2.34 **2.36**

Diol 2.36. $K_3Fe(CN)_6$ (3.79 g, 11.5 mmol), $(DHQ)_2PHAL$ (171 mg, 0.22 mmol), K_2CO_3 (1.88 g, 13.6 mmol), and $MeSO_2NH_2$ (571 mg, 6.00 mmol) were dissolved in 40 mL of a 1:1 mixture pf *t*-BuOH:water. The slurry was cooled to 0 °C, and $K_2OsO_2 \cdot (H_2O)_6$ (40.5 mg, 0.11 mmol) was added. Alkene **2.34** (1.55 g, 5.46 mmol) was added as a solution in 15 mL of the solvent mixture. The reaction mixture was then stirred overnight at 0 °C. The reaction was quenched by the addition of saturated aqueous $NaSO_3$. The mixture was diluted with EtOAc and stirred for 20 min at 0 °C, then 10 min at rt. The layers were separated and the aqueous layer was extracted 3 times with EtOAc. The combined organic extracts were dried with MgSO4, filtered, and concentrated under vacuum. The crude residue was subjected to column chromatography (25% → 45% EtOAc/hexanes, stepwise gradient). The fractions containing the pure product as a mixture of diastereomers were collected, and the accumulated material was divided between two samples, each of which was re-subjected to the same column conditions, to afford **2.36** as a single diastereomer and as a white solid (351 mg, 20%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.07 (s, *J* = 1.0 Hz, 1H), 4.27 (tdd, *J* = 8.9, 6.1, 3.1 Hz, 1H), 3.49 (dd, *J* = 34.3, 11.0 Hz, 2H), 2.65 (qd, *J* = 14.3, 7.1 Hz, 2H), 2.37 (br, 2H), 2.02 (dd, *J* = 15.3, 3.2 Hz, 1H), 1.92 – 1.88 (m, 1H), 1.87 (s, *J* = 0.9 Hz, 3H), 1.26 (s, 3H). The spectral data matched those previously reported.[11]

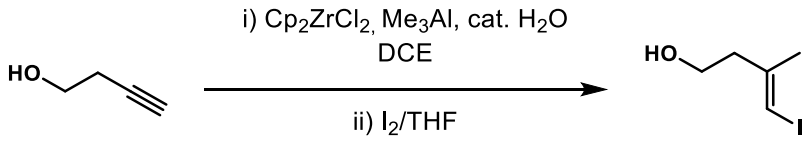
Diol 2.35 was also observed as a product of the reaction. The spectral data matched those previously reported.[11]



2.36 **2.6**

Epoxide 2.6. Diol **2.36** (367 mg, 1.15 mmol) was dissolved in anhydrous DCM (7.7 mL) and cooled to 0 °C. DMAP (105 mg, 0.86 mmol), TsCl (285 mg, 1.5 mmol), and Et_3N (0.32 mL, 2.3

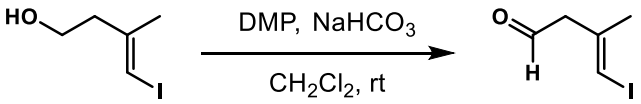
mmol) were added. The reaction mixture was stirred for 20 min at 0 °C then at rt overnight. The reaction mixture was diluted with 8 mL DCM and the reaction was quenched by the addition of 5 mL sat. aq. $NaHCO_3$. The mixture was poured into a separatory funnel with an additional 20 mL sat. aq. $NaHCO_3$ and shaken. The layers were separated, and the aqueous layer was extracted with DCM (4 × 5 mL). The combined organic extracts were washed successively with sat. aq. NH_4Cl, sat. aq. $NaHCO_3$, and brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was taken up in anhydrous MeOH, cooled to 0 °C, and K_2CO_3 (636 mg, 4.6 mmol) was added portion-wise. The reaction mixture was stirred for 2 h, then the volatiles were removed under vacuum until the volume was reduced by approximately two-thirds. The solution was then diluted with 50 mL of a 1:4 Et_2O:hexanes solvent mixture, followed by sat. aq. NH_4Cl and water, until all solids dissolved. The layers were separated, and the aqueous layer was extracted 3 times with the solvent mixture. The combined organic extracts were washed successively with water and brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was purified by column chromatography (2% → 10% EtOAc/hexanes) to afford **2.6** (247 mg, 71%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.09 (app s, *J* = 2.1, 1.0 Hz, 1H), 4.15 (dddd, *J* = 10.0, 8.3, 5.7, 4.1 Hz, 1H), 2.74 – 2.62 (m, 4H), 2.11 (ddd, *J* = 14.4, 4.1, 1.1 Hz, 1H), 1.89 (d, *J* = 1.0 Hz, 3H), 1.70 (dd, *J* = 14.4, 10.2 Hz, 1H), 1.38 (s, 3H). The spectral data matched those previously reported.[11]



2.14 **2.37**

(*E*)-4-iodo-3-methylbut-3-en-1-ol (2.37). Cp_2ZrCl_2 (512 mg, 1.75 mmol) was placed into a round-bottom flask, which was then evacuated and backfilled with argon. Freshly-distilled DCE (8.3 mL) was added. The mixture was stirred until the Cp_2ZrCl_2 was mostly dissolved, and then

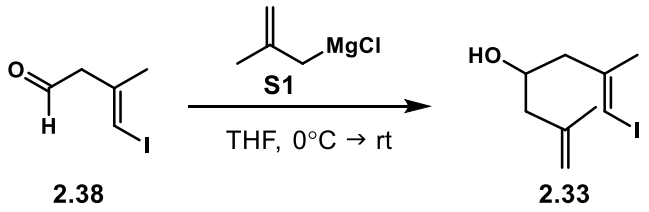
cooled to 0 °C. $AlMe_3$ (1.24 mL, 12.9 mmol) was added slowly to the reaction vessel, then a further 0.20 mL (2.1 mmol) was added slowly to a solution of 1-butyn-1-ol **2.14** (0.38 mL, 5.0 mmol) in anhydrous DCM (2.5 mL) pre-cooled to 0 °C. The reaction mixture was stirred at 0 °C for 5 min then at rt for 15 min. The reaction vessel was cooled again to 0 °C, and water (2 μL) was added. The reaction mixture was stirred at 0 °C for 5 min and then at rt for 15 min. The reaction mixture was then cooled to –40 °C, and the solution of **2.14** with $AlMe_3$ was added slowly. The reaction mixture was stirred overnight, slowly warming to rt. The reaction mixture was then diluted with 7 mL anhydrous THF and cooled to –40 °C. I_2 (3.54 g, 15.0 mmol) was added as solution in anhydrous THF (17 mL) over 1 h via syringe pump addition. The reaction mixture was then stirred for 2 h at rt. The reaction mixture was cooled to 0 °C, diluted with 5 mL Et_2O, and quenched by the slow addition of sat. aq. potassium sodium tartrate, with vigorous stirring, until no more evolution of gas was observed. The mixture was then warmed to rt and diluted with water and Et_2O until two clear layers were observed. The layers were separated, and the aqueous layer was extracted 3 times with Et_2O. The combined organic extracts were washed successively with sat. aq. $Na_2S_2O_3$, water, and brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was purified via column chromatography (45% Et_2O/hexanes) to afford **2.37** (802 mg, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 (app s, 1H), 3.72 (br t, J = 6.0 Hz, 2H), 2.48 (t, J = 6.3 Hz, 2H), 1.87 (d, J = 0.9 Hz, 3H), 1.44 (br s, 1H). The spectral data matched those previously reported.[19]



2.37 **2.38**

(*E*)-4-iodo-3-methylbut-3-enal (2.38). Alcohol **2.37** (100 mg, 0.472 mmol) was taken up in anhydrous DCM (2.9 mL) in a reaction vessel open to air and cooled to 0 °C. $NaHCO_3$ (198 mg,

2.36 mmol) was added, followed by DMP (640 mg, 1.51 mmol), and the reaction mixture was stirred for 1.25 hours. The mixture was diluted with pentane and quenched by the addition of a 2:1:1 mixture of sat. aq. $Na_2S_2O_3$:sat. aq. $NaHCO_3$:water. The mixture was stirred until 2 clear layers were observed. The layers were separated, and the aqueous layer was extracted with pentane. The combined organic extracts were washed 2 times with water and 1 time with brine, dried over Na_2SO_4, filtered and concentrated under vacuum to afford aldehyde **2.38**, which was carried forward immediately without purification. The spectral data matched those previously reported.[19]

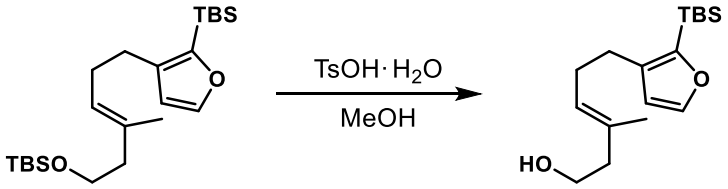


2.38 **2.33**

(*E*)-1-iodo-2,6-dimethylhepta-1,6-dien-4-ol (2.33). Grignard reagent **S1** (methallylmagnesium chloride) was prepared as follows: 125 mg of magnesium, freshly ground with a mortar and pestle, was placed into a flask, which was evacuated and backfilled with argon three times. The magnesium was flame dried and allowed to cool. Then anhydrous THF was added to the vessel, followed by 0.05 mL dibromoethane. The mixture was sonicated, heated briefly, and allowed to cool. The vessel was then cooled to 0 °C and methallyl chloride (0.17 mL, 1.71 mmol) was added slowly, followed by a drop of dibromoethane. The mixture was then stirred for 1 h, coming to rt, and then allowed to stand for 45 min until all precipitate had settled. The supernatant solution titrated to 0.8 M (titration indicator: salicylaldehyde phenylhydrazone).

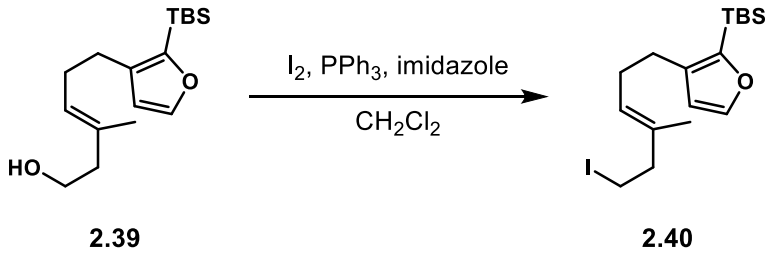
The crude product **2.38** (90 mg, estimated 0.43 mmol) was dissolved in anhydrous THF and cooled to 0 °C. Grignard reagent **S1** (0.54 mL, 0.43 mmol) was added slowly. The reaction mixture was stirred at rt for 1 h. The reaction was quenched by the slow addition of sat. aq. NH_4Cl at 0 °C, and

the mixture was diluted with Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed successively with water and brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was purified by column chromatography (2% →10% EtOAc/hexanes, stepwise gradient) to afford **2.33** (28 mg, 25%). The spectral data matched those previously observed for **2.33** (see above) as well as those previously reported.[11]



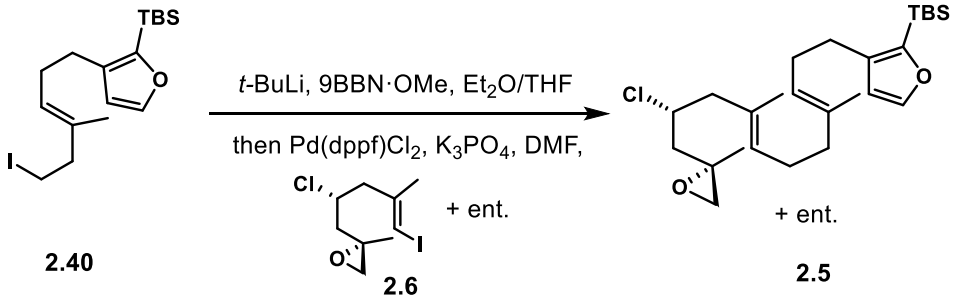
2.26 **2.39**

(*E*)-6-(2-(*tert*-butyldimethylsilyl)furan-3-yl)-3-methylhex-3-en-1-ol (2.39). Silyl ether **2.26** (444 mg, 1.1 mmol) was dissolved in MeOH (11 mL) in a flask open to air. $TsOH·H_2O$ (21 mg, 0.11 mmol) was added and the reaction mixture was stirred for 1.5 h. The reaction was quenched by the addition of 11 mL sat. aq. $NaHCO_3$, and the mixture was diluted with Et_2O. Water was added until the mixture just turned to two clear layers. The layers were separated, and the aqueous layer was extracted four times with Et_2O. The combined organic extracts were washed with brine, dried over MgSO4, filtered, and concentrated under vacuum. The crude residue was purified via column chromatography (1% → 10% EtOAc/hexanes, stepwise gradient) to afford **2.39** as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (s, 1H), 6.28 (s, 1H), 5.28 (t, *J* = 7.0 Hz, 1H), 3.65 (app s, 2H), 2.54 (t, *J* = 7.7 Hz, 2H), 2.33 – 2.20 (m, *J* = 12.4, 6.8 Hz, 5H), 1.63 (s, 3H), 1.27 (br s, 1H), 0.91 (s, 9H), 0.27 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.17, 146.36, 146.35, 136.19, 132.00, 127.49, 111.03, 60.18, 42.83, 29.71, 26.59, 26.00, 17.75, 15.89, –5.38. HRMS (ESI) *m / z* calcd for $C_{17}H_{30}O_2SiNa$ $[M+Na]^+$ 317.1913, found 317.1927.



2.39 2.40

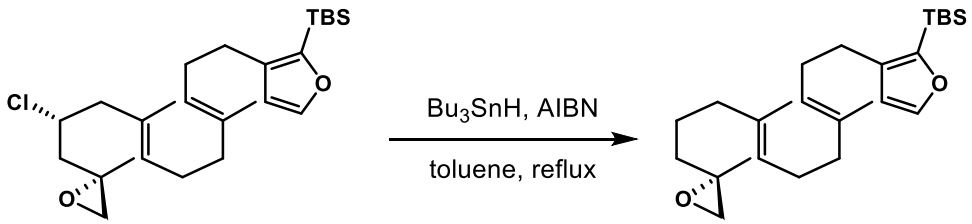
(*E*)-*tert*-butyl(3-(6-iodo-4-methylhex-3-en-1-yl)furan-2-yl)dimethylsilane (2.40). Alcohol **2.39** (200 mg, 0.68 mmol) was dissolved in anhydrous DCM (2.3 mL) and cooled to 0 °C. PPh_3 (212 mg, 0.81 mmol) and imidazole (95 mg, 1.4 mmol), were added to this solution, followed by I_2 (206 mg, 0.81 mmol). The reaction mixture was stirred for 15 min at 0 °C then for 3 h at rt. The reaction was quenched by the addition of sat. aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$. The mixture was diluted with DCM and water and the layers were separated. The aqueous layer was extracted three times with DCM. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was dry-loaded onto silica and purified via column chromatography (100% hexanes) to afford **2.40** (183 mg, 67%). 1H NMR (500 MHz, CDCl3) δ 7.55 (d, J = 1.4 Hz, 1H), 6.30 (d, J = 1.5 Hz, 1H), 5.26 (t, J = 7.1 Hz, 1H), 3.22 (t, J = 7.7 Hz, 2H), 2.57 – 2.50 (m, 4H), 2.23 (dd, J = 15.3, 7.5 Hz, 2H), 1.60 (s, 3H), 0.91 (s, 9H), 0.26 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.01, 146.20, 136.17, 134.12, 126.89, 111.00, 43.85, 29.67, 26.50, 25.82, 17.65, 15.38, 4.90, –5.47. HRMS (ESI) *m / z* calcd for $C_{17}H_{29}IOSiH$ $[M+H]^+$ 405.1111, found 405.1112.



2.40 2.6 2.5

Substrate 2.5. Alkyl iodide **2.40** (87 mg, 0.22 mmol) was dissolved in anhydrous Et_2O (1.0 mL)

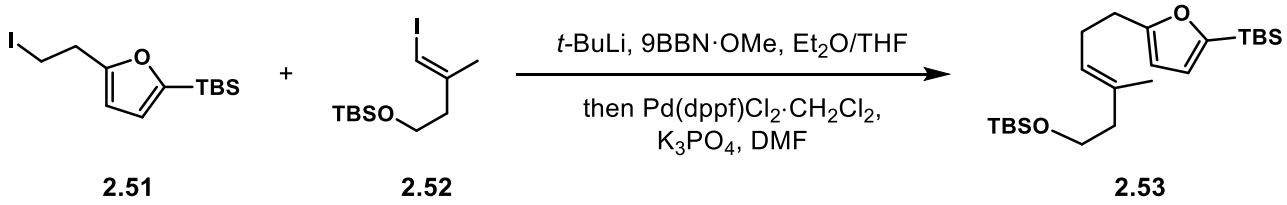
and cooled to –78 °C. *t*-BuLi (0.55 mL, 0.83 mmol, 1.5 M in pentane) was added to the solution quickly, followed by 9-BBN·OMe (0.75 mL, 0.75 mmol, 1.0 M in hexanes), dropwise. The reaction mixture was then diluted with anhydrous THF (0.3 mL) and stirred for 1 h at –78 °C then warmed slowly to rt and stirred for 2.5 h. The reaction vessel was then cooled to 0 °C, and K_3PO_4 (0.14 mL, 0.41 mmol, 3 M in water) was added, followed by vinyl iodide **2.6** (50 mg, 17 mmol) as a solution in anhydrous DMF (0.31 mL) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (20 mg, 25 μmol). The resultant dark green mixture was stirred overnight at rt. The reaction was quenched by the addition of water and brine, and the mixture was diluted with Et_2O. The layers were separated and the aqueous layer was extracted four times with Et_2O. The combined organic extracts were washed successively with water and brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude residue was purified via column chromatography (100 % hexanes → 10% EtOAc/hexanes, stepwise gradient) to afford **2.5** (60 mg, 81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 1.6 Hz, 1H), 6.30 (d, *J* = 1.6 Hz, 1H), 5.25 – 5.15 (m, 2H), 4.17 – 4.07 (m, 1H), 2.76 – 2.67 (m, 2H), 2.53 – 1.97 (m, 12H), 1.67 – 1.51 (m, 7H), 1.37 (s, 3H), 0.91 (s, 9H), 0.26 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.99, 146.23, 136.55, 135.32, 130.64, 128.99, 124.26, 111.17, 58.09, 55.62, 55.47, 49.61, 45.47, 39.50, 29.78, 26.65, 26.61, 26.19, 20.45, 17.75, 16.14, 16.03, –5.37.



2.5 **2.44**

Substrate 2.44. Substrate **2.5** (60 mg, 0.13 mmol) was dissolved in anhydrous, degassed toluene (1.3 mL) at rt. Bu_3SnH (0.3 mL, 1.1 mmol) and AIBN (66 mg, 0.40 mmol) were added. The

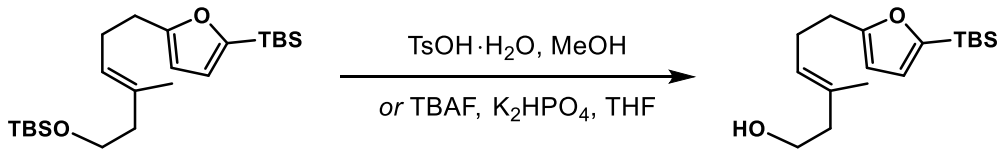
reaction vessel was sealed tightly and heated to 90 °C for 1.5 h, then cooled to rt. Additional Bu_3SnH (0.15 mL) and AIBN (33 mg) were added, and the vessel was sealed and heated to 100 °C for 5 h. The reaction mixture was cooled again to rt and the volatiles removed under vacuum. The crude residue was purified via column chromatography (100% hexanes → 10% EtOAc/hexanes) to afford **2.44** in quantitative yield (54 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 1.3 Hz, 1H), 6.30 (d, *J* = 1.5 Hz, 1H), 5.18 (t, *J* = 7.1 Hz, 1H), 5.10 (t, *J* = 6.9 Hz, 1H), 2.58 (dd, *J* = 16.9, 4.9 Hz, 2H), 2.50 (dd, *J* = 9.1, 6.6 Hz, 2H), 2.29 – 2.18 (m, 2H), 2.11 – 1.95 (m, 6H), 1.59 (d, *J* = 4.2 Hz, 6H), 1.52 – 1.43 (m, 2H), 1.31 (s, 3H), 0.91 (s, 9H), 0.26 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.88, 146.12, 136.47, 135.56, 134.62, 124.65, 123.88, 111.08, 57.05, 54.01, 39.74, 39.57, 36.31, 29.70, 26.59, 26.50, 26.11, 23.57, 21.00, 17.64, 16.08, 15.86, –5.48.



2.51 **2.52** **2.53**

(*E*)-*tert*-butyl((6-(5-(*tert*-butyldimethylsilyl)furan-2-yl)-3-methylhex-3-en-1-yl)oxy)dimethylsilane (2.53). To a solution of *t*-BuLi (0.54 mL, 0.92 mmol, 1.7 M in pentane) in anhydrous Et_2O (1.0 mL) at –78 °C was added alkyl iodide **2.51** (100 mg, 0.30 mmol, in 0.5 mL anhydrous Et_2O), quickly, followed by 9-BBN·OMe (1.0 mL, 1.0 mmol, 1 M in THF), dropwise. The reaction mixture was diluted with 0.43 mL anhydrous THF and allowed to warm to rt, with stirring, over 1.25 h, then stirred at rt for 2 h. The reaction vessel was then cooled to 0 °C, and K_3PO_4 (0.19 mL, 0.58 mmol, 3 M in water) was added, dropwise, followed by vinyl iodide **2.52** (75 mg, 0.23 mmol, in 1.2 mL anhydrous DMF), followed by $Pd(dppf)Cl_2·CH_2Cl_2$ (28 mg, 35 μmol). The reaction mixture was stirred overnight, warming to rt. The reaction vessel was then cooled to 0 °C and quenched by the addition of 5 mL brine and 5 mL, and the mixture was diluted

with 10 mL Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed successively with 11 mL of water and brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was subjected to column chromatography (100% hexanes → 50% EtOAc/hexanes). The product-containing fractions were collected and concentrated under vacuum, and the resulting residue was purified via column chromatography (5% DCM/hexanes → 10% DCM/hexanes → 2% EtOAc/10% DCM/88% hexanes) to afford **2.53** (62 mg, 66%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.52 (d, *J* = 3.0 Hz, 1H), 5.96 (d, *J* = 3.0 Hz, 1H), 5.19 (t, *J* = 7.1 Hz, 1H), 3.67 – 3.61 (m, 2H), 2.67 (t, *J* = 7.6 Hz, 2H), 2.33 (q, *J* = 7.4 Hz, 2H), 2.19 (t, *J* = 7.1 Hz, 2H), 1.59 (s, 3H), 0.90 (m, 18H), 0.20 (s, 6H), 0.04 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.58, 156.83, 133.20, 125.40, 121.73, 105.00, 62.69, 43.18, 28.50, 26.77, 26.51, 26.11, 18.50, 16.94, 16.56, –5.11, –6.08.



2.53 **2.54**

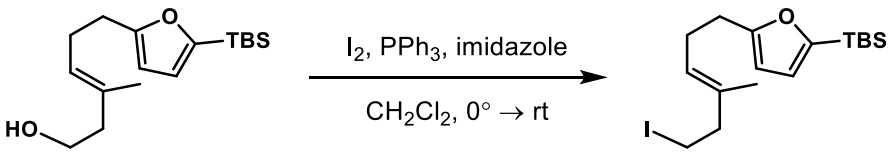
(*E*)-6-(5-(*tert*-butyldimethylsilyl)furan-2-yl)-3-methylhex-3-en-1-ol (2.54).

Procedure 1: Silyl ether **2.53** (52 mg, 0.13 mmol) was dissolved in MeOH in a reaction vessel open to air. $TsOH·H_2O$ (2.5 mg, 13 μmol) was added, and the reaction was stirred for 1.5 h at rt. The reaction mixture was diluted with Et_2O and quenched by the addition of water and sat. aq. $NaHCO_3$. The layers were separated and the aqueous layer was extracted two times with Et_2O and two times with EtOAc. The combined organic extracts were washed successively with water and brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was purified via column chromatography (10% → 15% EtOAc/hexanes) to afford **2.54** (29 mg, 76%). ^{1}H NMR

(500 MHz, $CDCl_3$) δ 6.53 (d, *J* = 3.1 Hz, 1H), 5.96 (d, *J* = 3.0 Hz, 1H), 5.25 (t, *J* = 7.1 Hz, 1H), 3.61 (q, *J* = 6.0 Hz, 2H), 2.71 (t, *J* = 7.3 Hz, 2H), 2.39 (q, *J* = 7.2 Hz, 2H), 2.22 (t, *J* = 6.1 Hz, 2H), 1.58 (s, 3H), 0.91 (s, 9H), 0.20 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.21, 157.17, 132.37, 127.04, 121.74, 105.28, 60.01, 42.77, 28.41, 26.79, 26.50, 16.92, 15.76, –6.09.

Note: the double-desilylated product (not shown) was also observed in the crude product mixture.

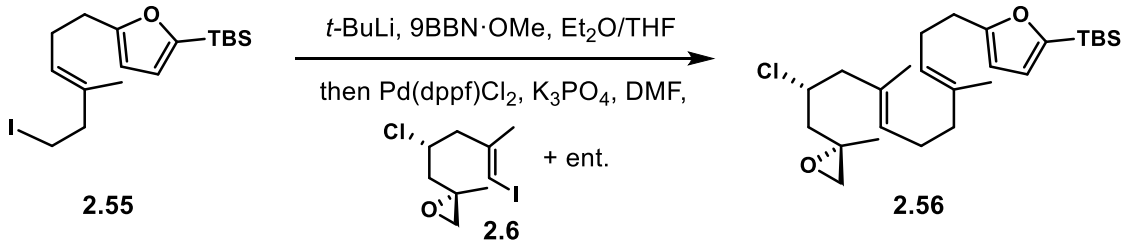
Procedure 2: Silyl ether **2.53** (65 mg, 0.16 mmol) was dissolved in anhydrous THF (0.5 mL) and cooled to 0 °C. A drop of sat. aq. K_2HPO_4 was added, followed by TBAF (0.29 mL, 0.29 mmol, 1 M in THF), dropwise. The reaction mixture was allowed to come to rt over 1 h, then stirred for a further 4 h at rt. The reaction was quenched by the addition of sat. aq. NH_4Cl. The layers were separated and the aqueous layer was extracted three times with 20% EtOAc/hexanes. The combined organic extracts were washed successively with water and brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was purified by column chromatography (30% EtOAc/hexanes) to afford **2.54** (25 mg, 53%). The spectral data matched those obtained for the product of procedure 1, above.



2.54 **2.55**

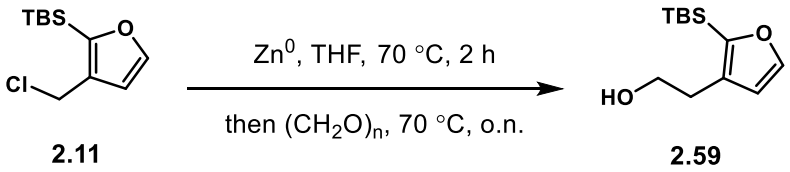
(*E*)-*tert*-butyl(5-(6-iodo-4-methylhex-3-en-1-yl)furan-2-yl)dimethylsilane (2.55). Alcohol **2.54** (29 mg, 0.10 mmol) was dissolved in anhydrous DCM (0.5 mL) and cooled to 0 °C. PPh_3 (34 mg, 0.13 mmol) and imidazole (20 mg, 0.30 mmol) were added to this solution, followed by I_2 (30 mg, 0.12 mmol). The reaction mixture was stirred for 30 min at 0 °C then overnight at rt. The reaction was quenched by the addition of sat. aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$. The mixture was diluted with DCM and water and the layers were separated. The aqueous layer was extracted three times

with DCM. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was purified via column chromatography (100% hexanes) to afford **2.55** (29 mg, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.52 (d, *J* = 3.1 Hz, 1H), 5.96 (d, *J* = 3.1 Hz, 1H), 5.25 (t, *J* = 7.1 Hz, 1H), 3.61 (t, *J* = 6.1 Hz, 2H), 2.71 (t, *J* = 7.3 Hz, 2H), 2.39 (q, *J* = 7.2 Hz, 2H), 2.22 (t, *J* = 6.1 Hz, 2H), 1.58 (s, 4H), 0.91 (s, 9H), 0.20 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.27, 156.97, 134.60, 126.48, 126.48, 121.75, 105.19, 43.93, 28.28, 26.77, 26.51, 16.94, 15.45, 5.01, –6.08.



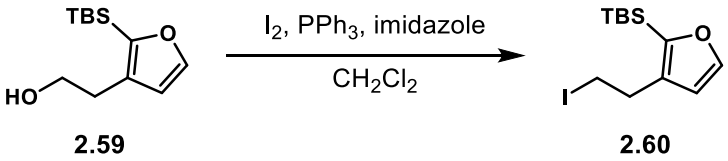
Substrate 2.56. Alkyl iodide **2.55** (28 mg, 69 μmol) was dissolved in anhydrous Et_2O (0.3 mL) and cooled to –78 °C. To this solution was added *t*-BuLi (0.13 mL, 0.21 mmol, 1.7 M in pentane), quickly, followed by 9-BBN·OMe (0.75 mL, 0.75 mmol, 1.0 M in hexanes), dropwise. The reaction mixture was diluted with anhydrous THF (0.2 mL) and stirred for 1 h, slowly warming from –78 °C, then for 3 h at rt. The reaction vessel was then cooled to 0 °C, and K_3PO_4 (0.05 mL, 0.13 mmol, 3 M in water) was added, followed by vinyl iodide **2.6** (17 mg, 53 μmol) as a solution in anhydrous DMF (0.34 mL), then $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (7 mg, 8 μmol). The reaction mixture was stirred overnight at rt. The reaction was quenched by the addition of water and brine, and the mixture was diluted with Et_2O. The layers were separated and the aqueous layer was extracted three times with Et_2O. The combined organic extracts were washed successively with water and brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was purified via column chromatography (2% → 20% Et_2O/hexanes, stepwise gradient) to afford **2.56** (10 mg, 42%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.52 (d, *J* = 3.1 Hz, 1H), 5.96 (d, *J* = 3.1 Hz, 1H), 5.18 (dt,

J = 7.1, 5.9 Hz, 2H), 4.12 (dtd, *J* = 10.7, 7.2, 3.4 Hz, 1H), 2.77 – 2.62 (m, 4H), 2.50 – 2.30 (m, 4H), 2.20 (ddd, *J* = 14.4, 3.4, 1.2 Hz, 1H), 2.04 (dt, *J* = 45.9, 7.6 Hz, 4H), 1.67 – 1.48 (m, 9H), 1.37 (s, 3H), 0.91 (s, 9H), 0.20 (s, 6H).



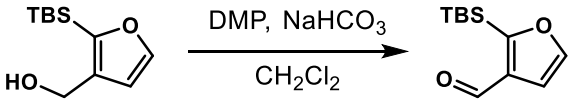
2.11 **2.59**

2-(2-(*tert*-butyldimethylsilyl)furan-3-yl)ethan-1-ol (2.59). Zinc dust (28 mg, 0.43 mmol) was added to a vial which was then evacuated and backfilled with argon. Anhydrous THF (0.86 mL) was added, and the zinc was activated by the addition of dibromoethane and distilled TMSCl. Chloromethyl furan **2.11** (50 mg, 0.22 mmol) was added as a solution in anhydrous THF (0.44 mL). The vial was sealed tightly and the reaction mixture was heated to 70 °C for 2 h, with stirring. The reaction vessel was allowed to cool to rt, then paraformaldehyde (20 mg, 1.3 mmol) was added. The reaction mixture was heated to 70 °C for 6 h. The reaction vessel was then allowed to cool to rt, and then further cooled to 0 °C, where the reaction was quenched by the addition of sat. aq. NH_4Cl. The mixture was diluted with EtOAc, the layers were separated, and the aqueous layer was extracted three times with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was purified via column chromatography (10% EtOAc/hexanes) to afford **2.59** (25 mg, 50%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 1.5 Hz, 1H), 6.33 (d, *J* = 1.6 Hz, 1H), 3.79 (t, *J* = 6.6 Hz, 2H), 2.77 (t, *J* = 6.6 Hz, 2H), 0.90 (d, *J* = 6.2 Hz, 9H), 0.28 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.70, 146.80, 132.35, 111.07, 63.33, 29.39, 26.58, 17.71, –5.29.



2.59 **2.60**

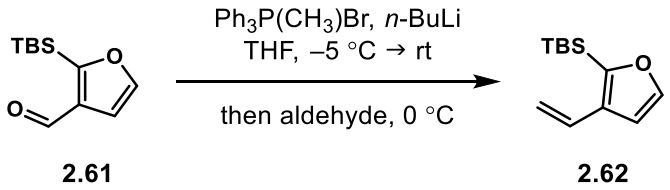
***tert*-butyl(3-(2-iodoethyl)furan-2-yl)dimethylsilane (2.60).** Alcohol **2.59** (46 mg, 0.20 mmol) was dissolved in anhydrous DCM (1 mL) and cooled to 0 °C. To this solution was added PPh_3 (66 mg, 0.25 mmol) and imidazole (27 mg, 0.40 mmol), followed by I_2 (63 mg, 0.25 mmol). The reaction mixture was stirred for 15 min at 0 °C then 3 h at rt. The reaction was quenched by the addition of sat. aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$. The mixture was diluted with DCM and water and the layers were separated. The aqueous layer was extracted three times with DCM. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was purified via column chromatography (100% hexanes) to afford **2.60** (47 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 0.7 Hz, 1H), 6.30 (d, *J* = 1.1 Hz, 1H), 3.25 (t, *J* = 7.9 Hz, 2H), 3.07 (t, *J* = 8.0 Hz, 2H), 0.91 (s, 9H), 0.28 (s, 6H).



2.24 **2.61**

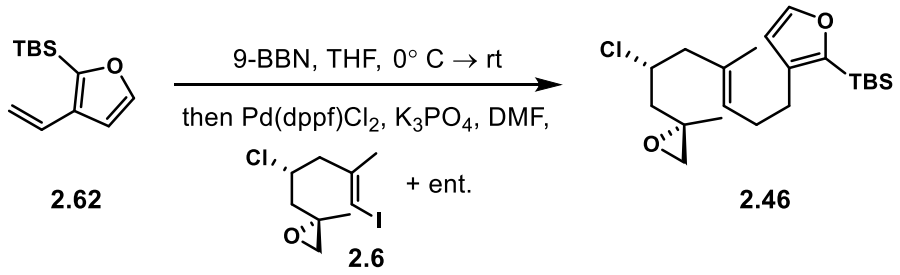
2-(*tert*-butyldimethylsilyl)furan-3-carbaldehyde (2.61). Alcohol **2.24** (250 mg, 1.18 mmol) was dissolved in DCM (6 mL) in a flask open to air and cooled to 0 °C. Solid $NaHCO_3$ (346 mg, 4.12 mmol) was added, followed by DMP (999 mg, 2.35 mmol) and an additional 4 mL DCM. The reaction mixture was stirred for 1 h at rt. The reaction was quenched by the addition of sat. aq. $Na_2S_2O_3$ (10 mL), and the mixture was diluted with 10 mL water. The layers were separated and the aqueous layer was extracted with DCM (3 × 5 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum to afford **2.61** (245 mg, quant). The crude product was carried forward without further purification. 1H NMR (500

MHz, CDCl3) δ 10.07 (s, 1H), 7.63 (dd, J = 1.7, 0.7 Hz, 1H), 6.81 (d, J = 1.7 Hz, 1H), 0.94 (s, 9H), 0.39 (s, 6H).



2.61 **2.62**

***tert*-butyldimethyl(3-vinylfuran-2-yl)silane (2.62).** Methyltriphenylphosphonium bromide (539 mg, 1.51 mmol) was placed in a round-bottom flask, which was then evacuated and backfilled with argon. Anhydrous THF (6 mL) was added, and the vessel was cooled to 0 °C. *n*-BuLi (0.56 mL, 1.4 mmol, 2.5 M in hexanes) was added dropwise. The reaction mixture was stirred at 0 °C for 15 min and then at rt for 1.5 h. The reaction vessel was cooled to 0 °C and aldehyde **2.61** (245 mg, 1.16 mmol) was added slowly as a solution in anhydrous THF (2.3 mL). The reaction mixture was stirred for 1 h at 0 °C. The reaction was quenched by the addition of pH 7 phosphate buffer (10 mL), and the mixture was diluted with 1:4 Et_2O:pentane (10 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with the solvent mixture (3 × 9 mL). The combined organic extracts were washed successively with 20 mL of water and brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was purified via column chromatography (100% hexanes → 5% Et_2O/hexanes) to afford **2.62** as a clear oil (196 mg, 81%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.55 (s, 1H), 6.73 (dd, *J* = 17.4, 10.8 Hz, 1H), 6.59 (s, 1H), 5.46 (d, *J* = 17.4 Hz, 1H), 5.13 (d, *J* = 10.8 Hz, 1H), 0.91 (s, 9H), 0.30 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.37, 146.77, 135.48, 128.44, 113.51, 107.14, 26.52, 17.80, –5.47.



Substrate 2.46. 9-BBN (1.1 mL, 0.55 mmol, 0.5 M in THF) and anhydrous THF (0.2 mL) were added to a vial and cooled to 0 °C. Vinyl furan **2.62** (33 mg, 0.16 mmol) was added as a solution in 0.8 mL anhydrous THF. The reaction mixture was stirred for 1 h at 0 °C, then for 5 h at rt. K_3PO_4 (0.10 mL, 0.31 mmol, 3 M in water) was added, followed by vinyl iodide **2.6** (40 mg, 0.12 mmol) as a solution in 0.6 mL anhydrous DMF, then $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (15 mg, 18 μmol). The reaction mixture was stirred overnight at rt, then quenched by the addition of brine (2 mL) and water (1 mL) with vigorous stirring. The mixture was diluted with Et_2O (1 mL), the layers were separated and the aqueous layer was extracted with Et_2O (3 × 1 mL). The combined organic extracts were washed successively with water and brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was purified by column chromatography (6% EtOAc/hexanes) to afford **2.46** (11 mg, 18%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 1.6 Hz, 1H), 6.29 (d, *J* = 1.6 Hz, 1H), 5.28 (t, *J* = 7.1 Hz, 1H), 4.13 (dtd, *J* = 10.8, 7.1, 3.5 Hz, 1H), 2.77 – 2.64 (m, 2H), 2.57 – 2.38 (m, 4H), 2.31 – 2.14 (m, 3H), 1.59 (d, *J* = 47.2 Hz, 9H), 1.37 (s, 3H), 0.90 (s, 9H), 0.26 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.12, 146.32, 136.21, 131.26, 128.52, 111.08, 58.01, 55.60, 55.44, 49.58, 45.51, 29.72, 26.60, 25.90, 20.45, 17.76, 16.06, –5.38.

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C and [1,4] C → O Silyl Migrations of Silyl Ethers and Esters Attached to Furan and Thiophene Rings. *J. Org. Chem.* **1997,** *62,* 8741-8749.

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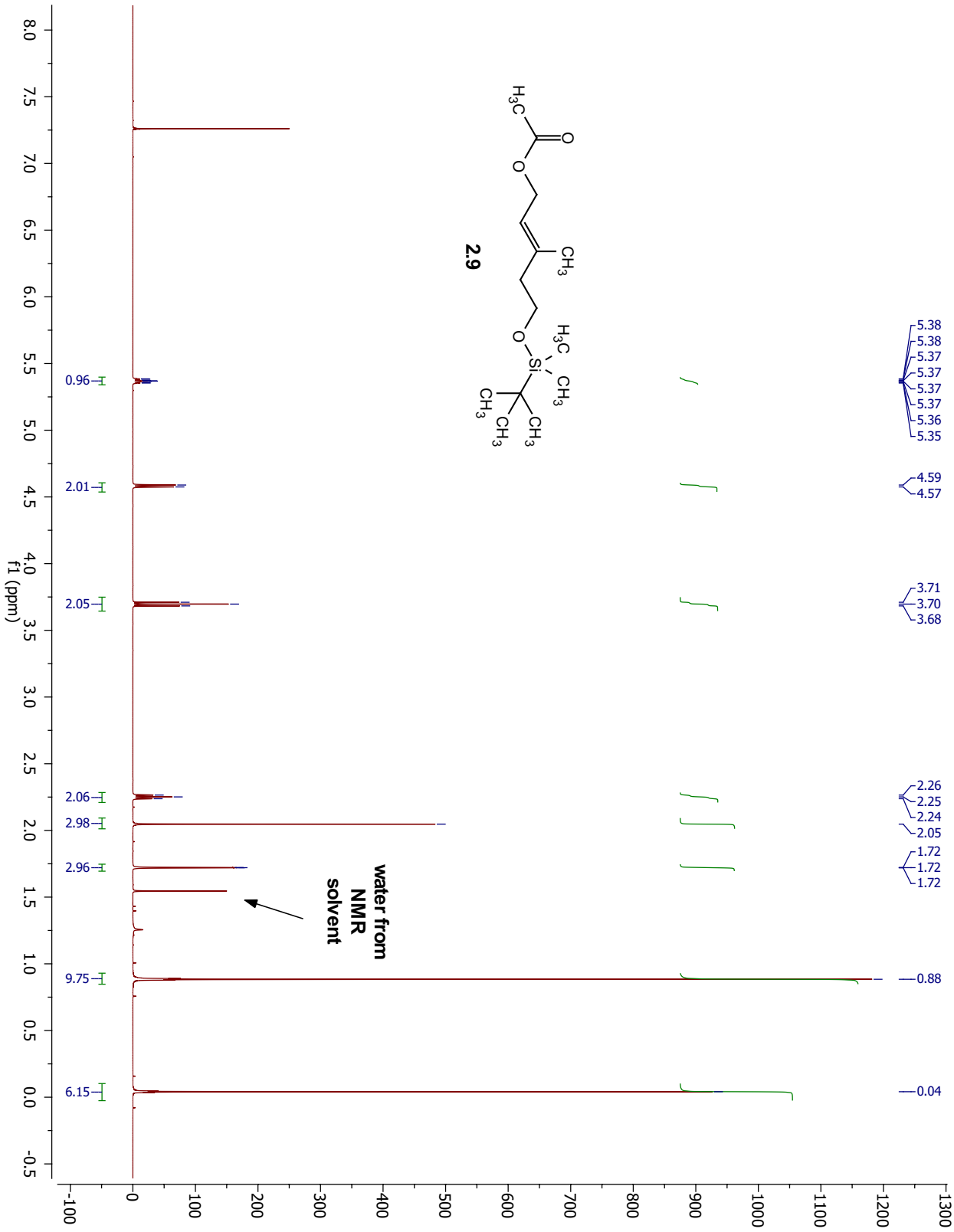
APPENDIX: NMR Data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5.37
5.37
5.37
5.37
5.36
5.35
4.59
4.57
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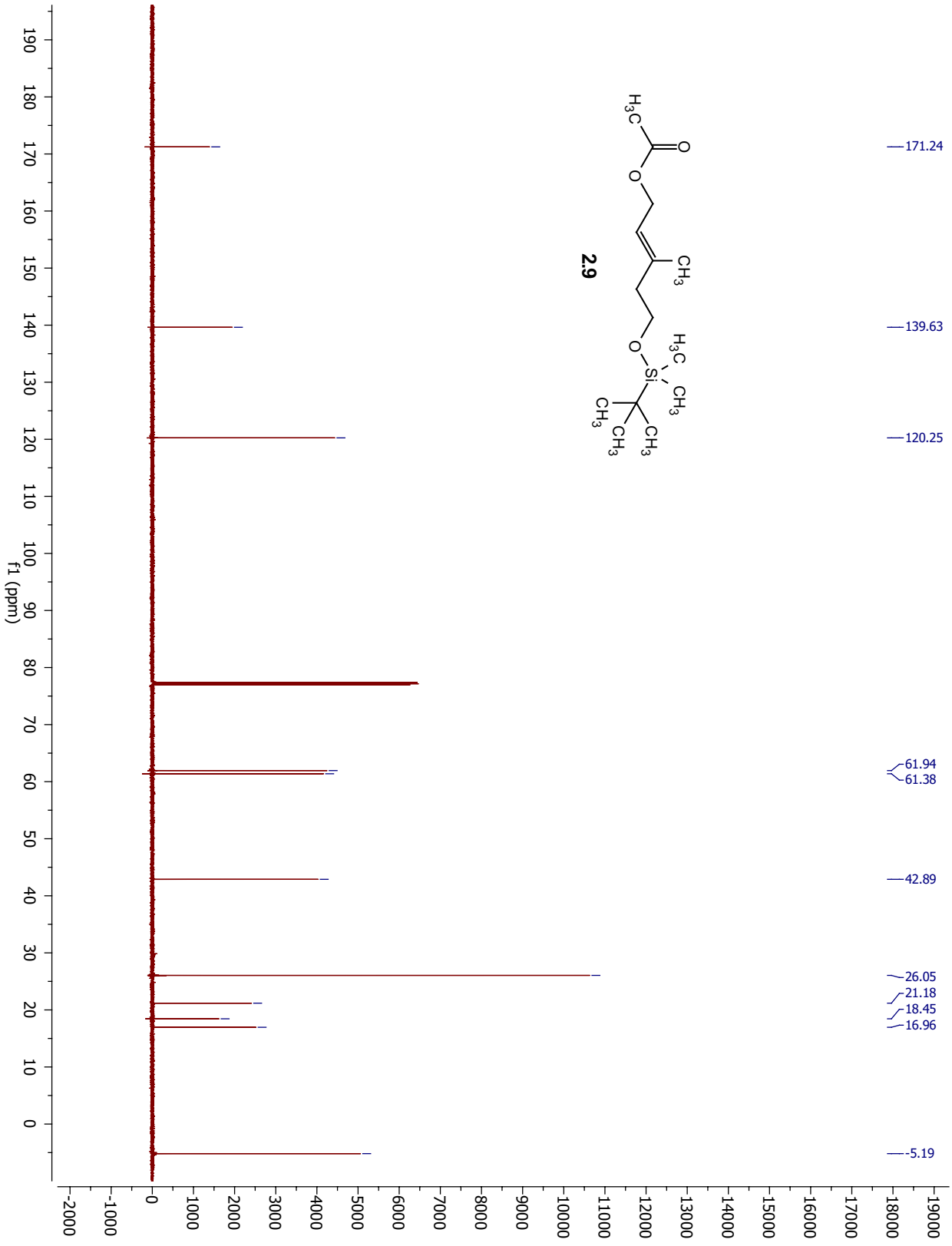
0.04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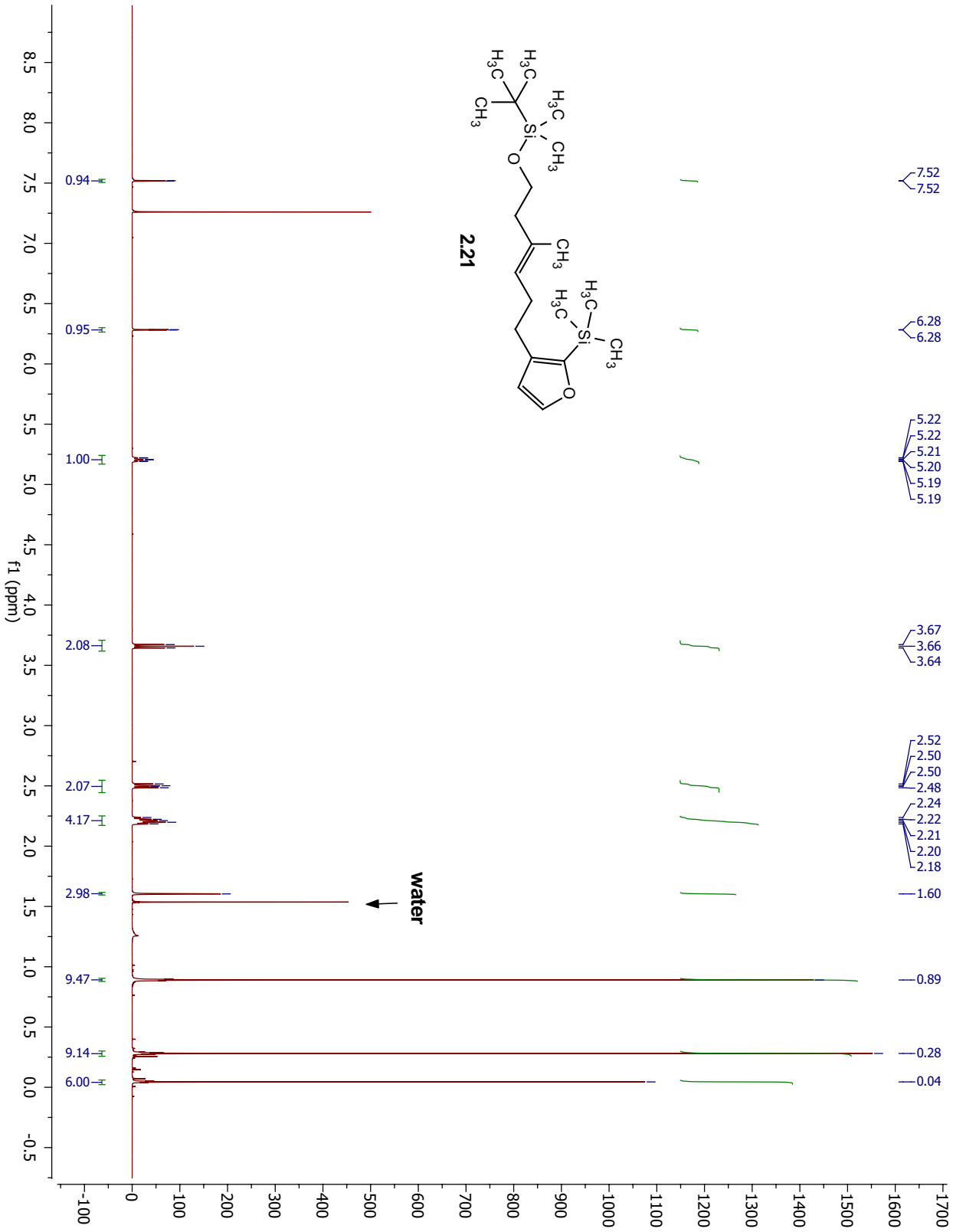
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7.52
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6.28
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5.22
5.21
5.20
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3.66
3.64
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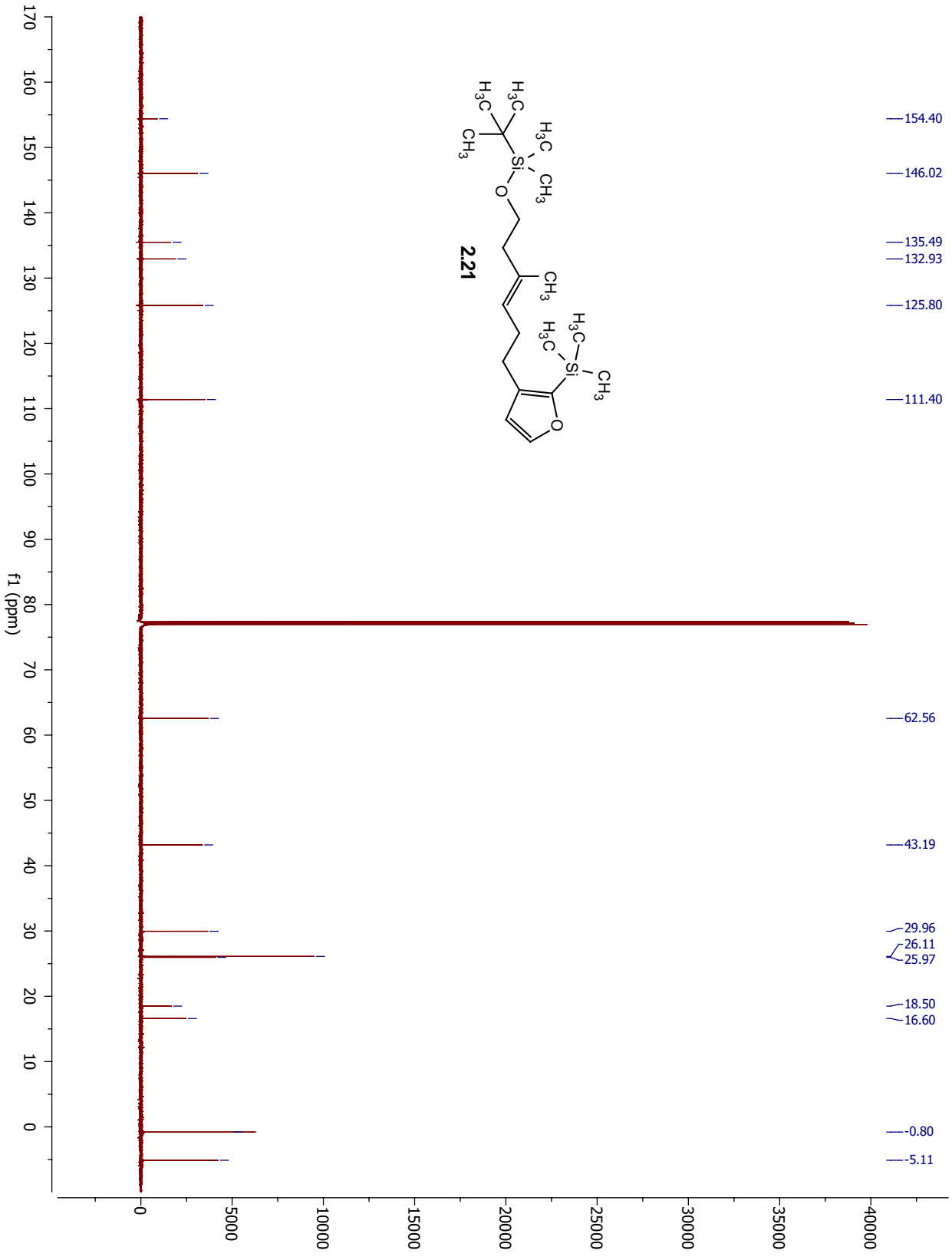
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16.60
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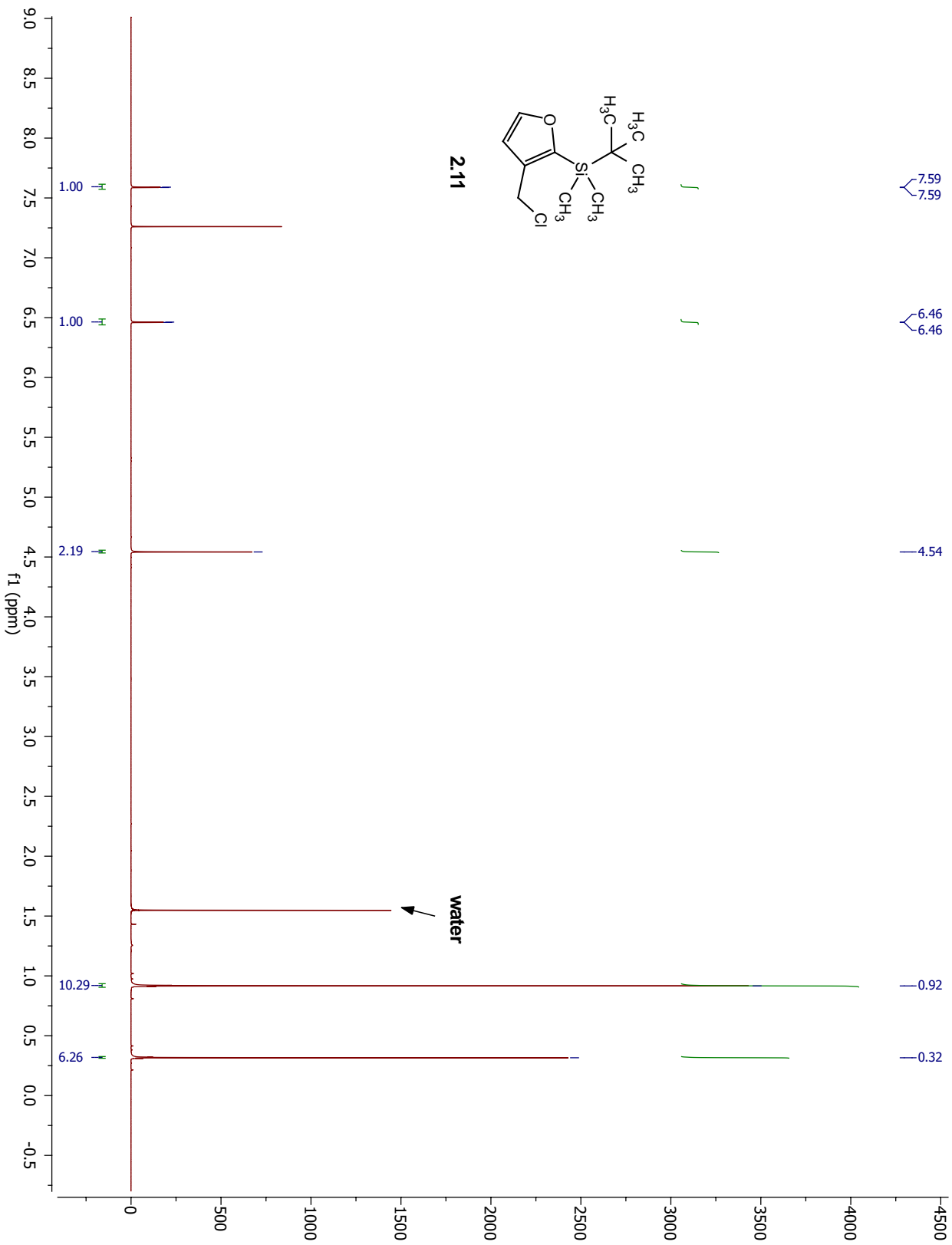
f1 (ppm)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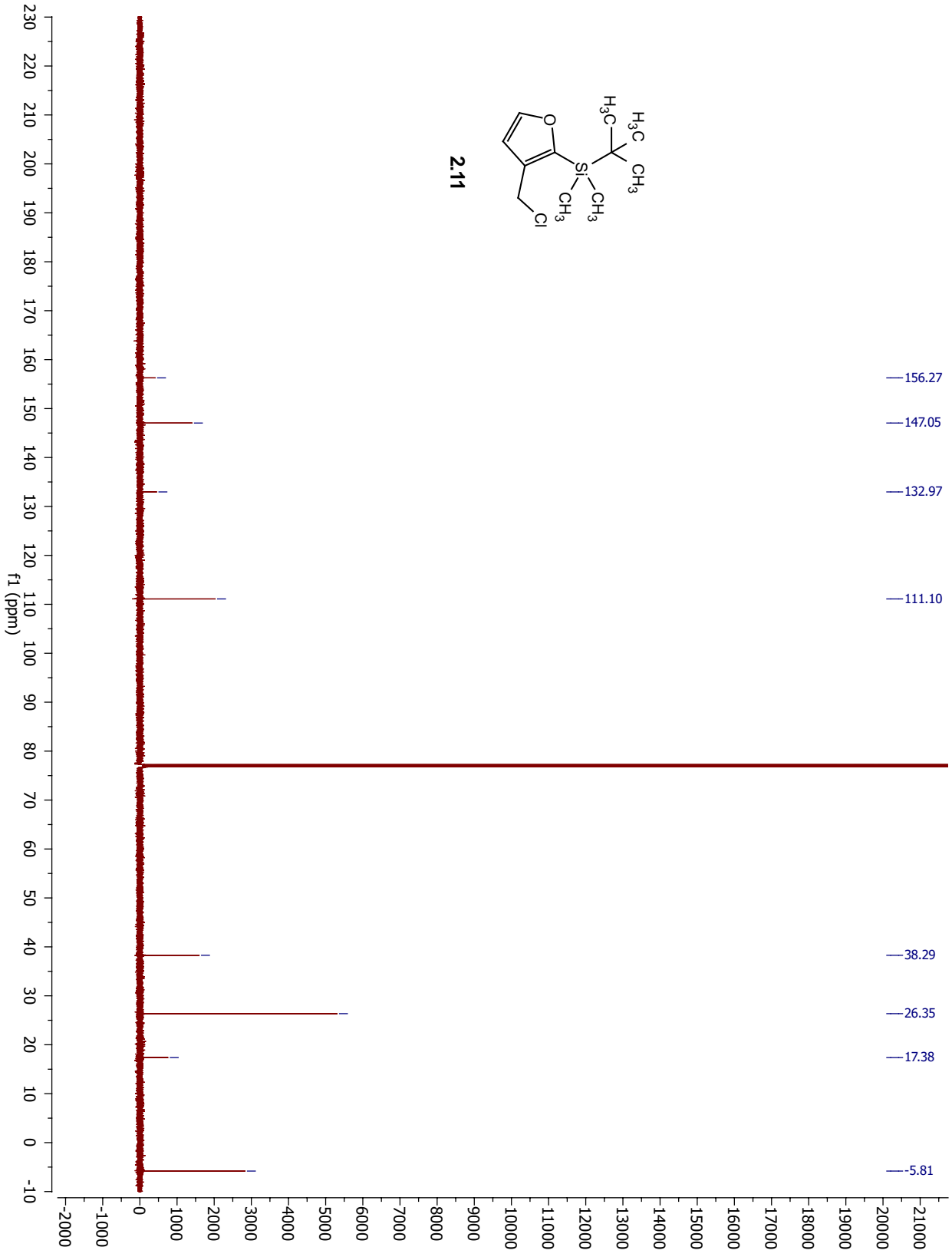
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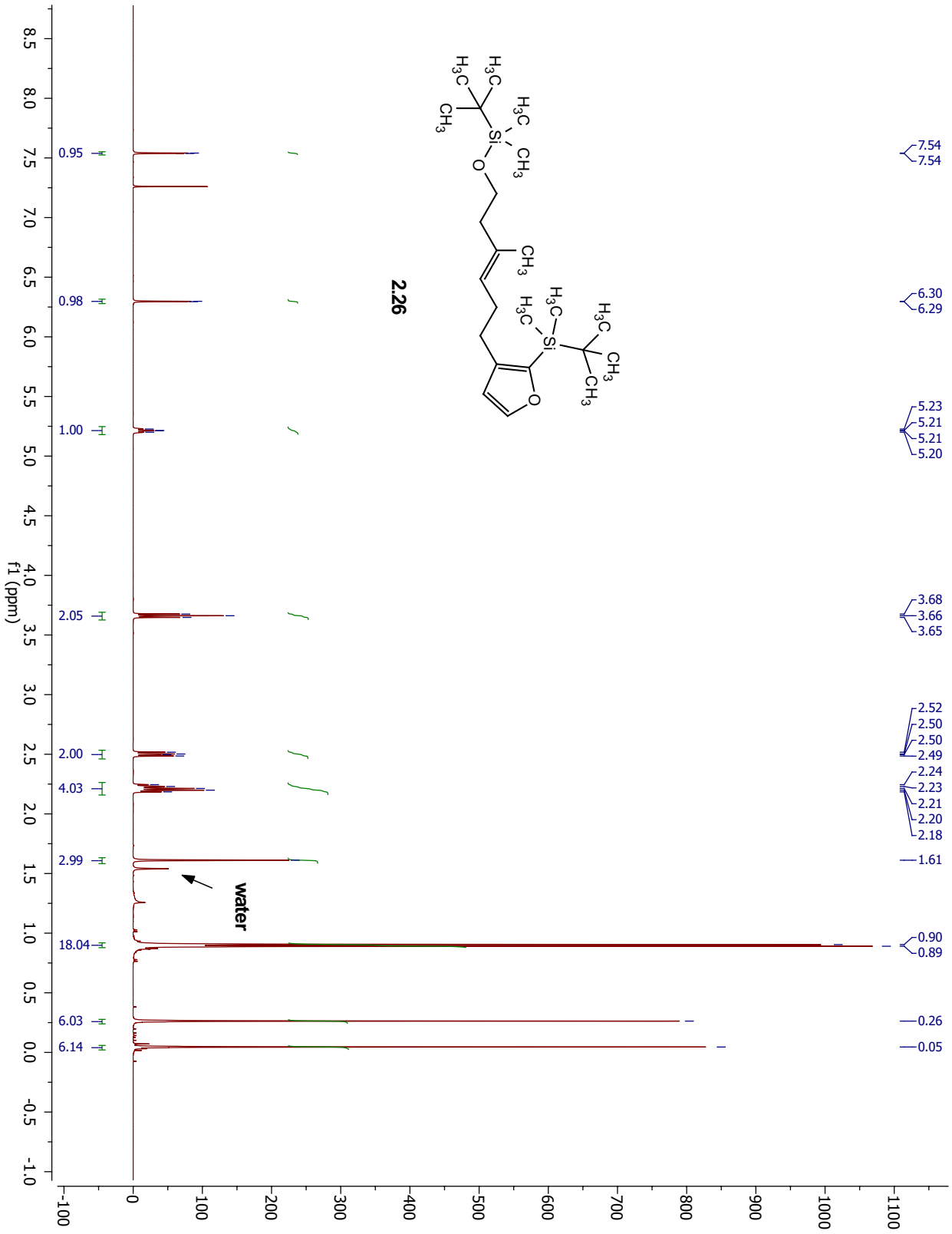
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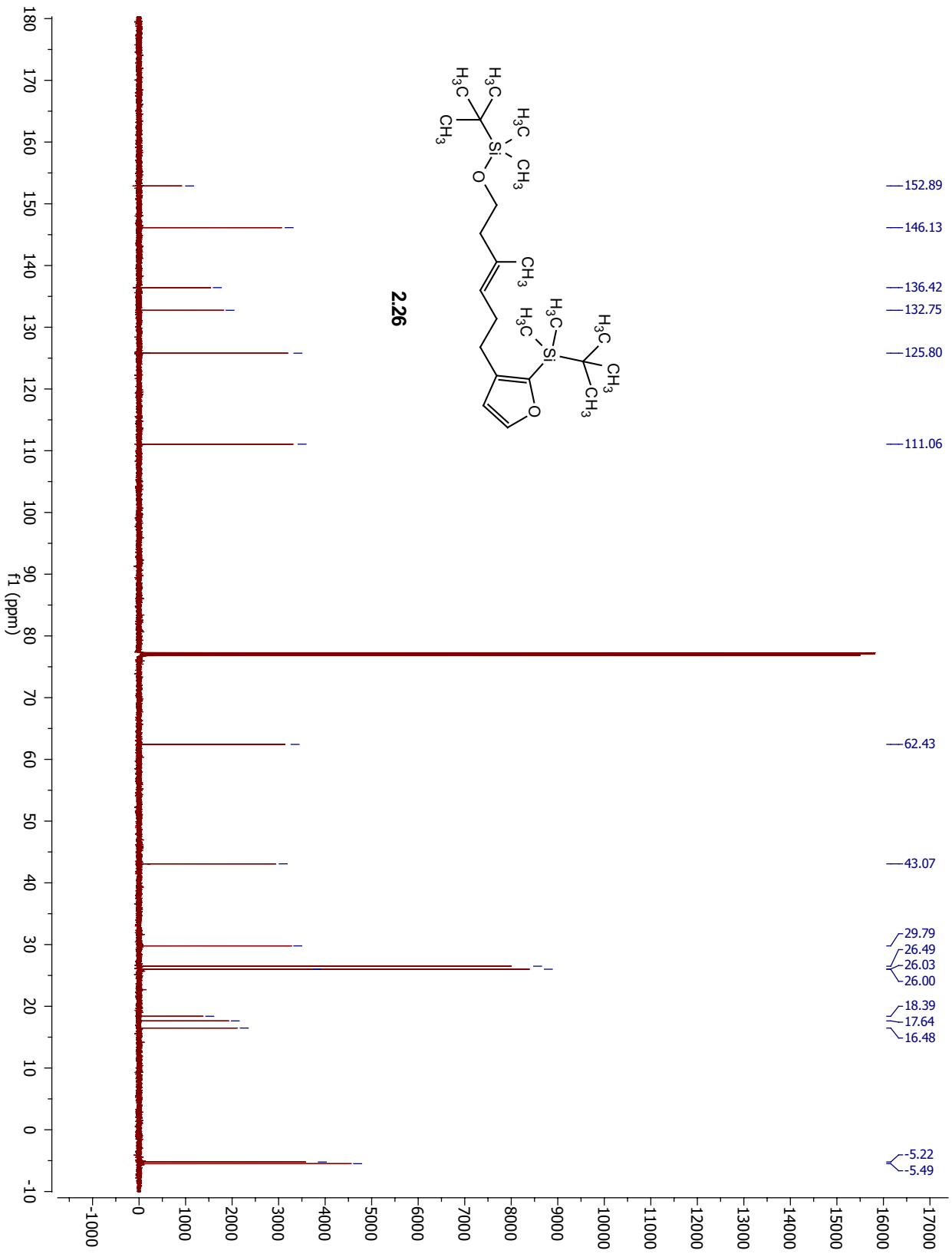
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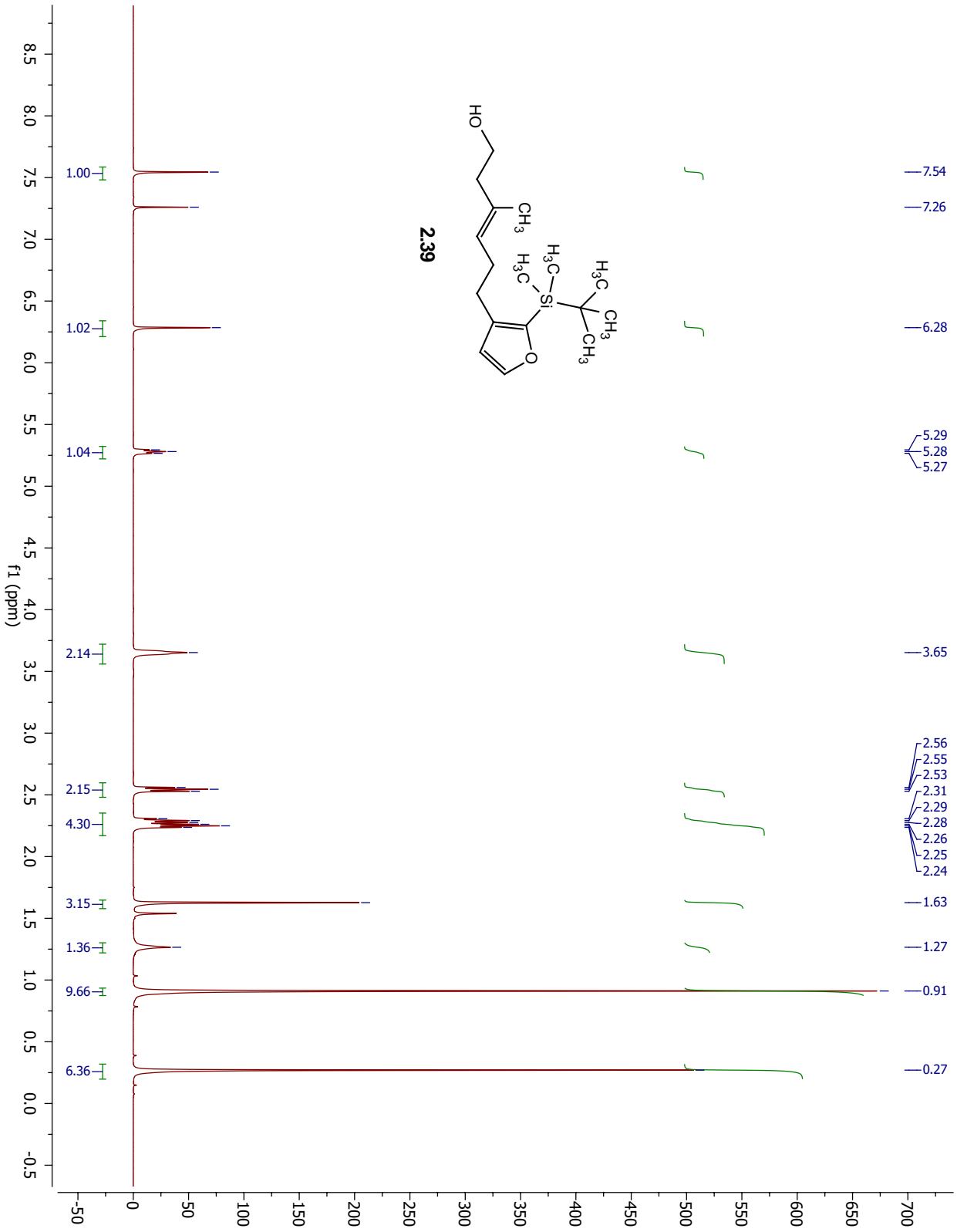
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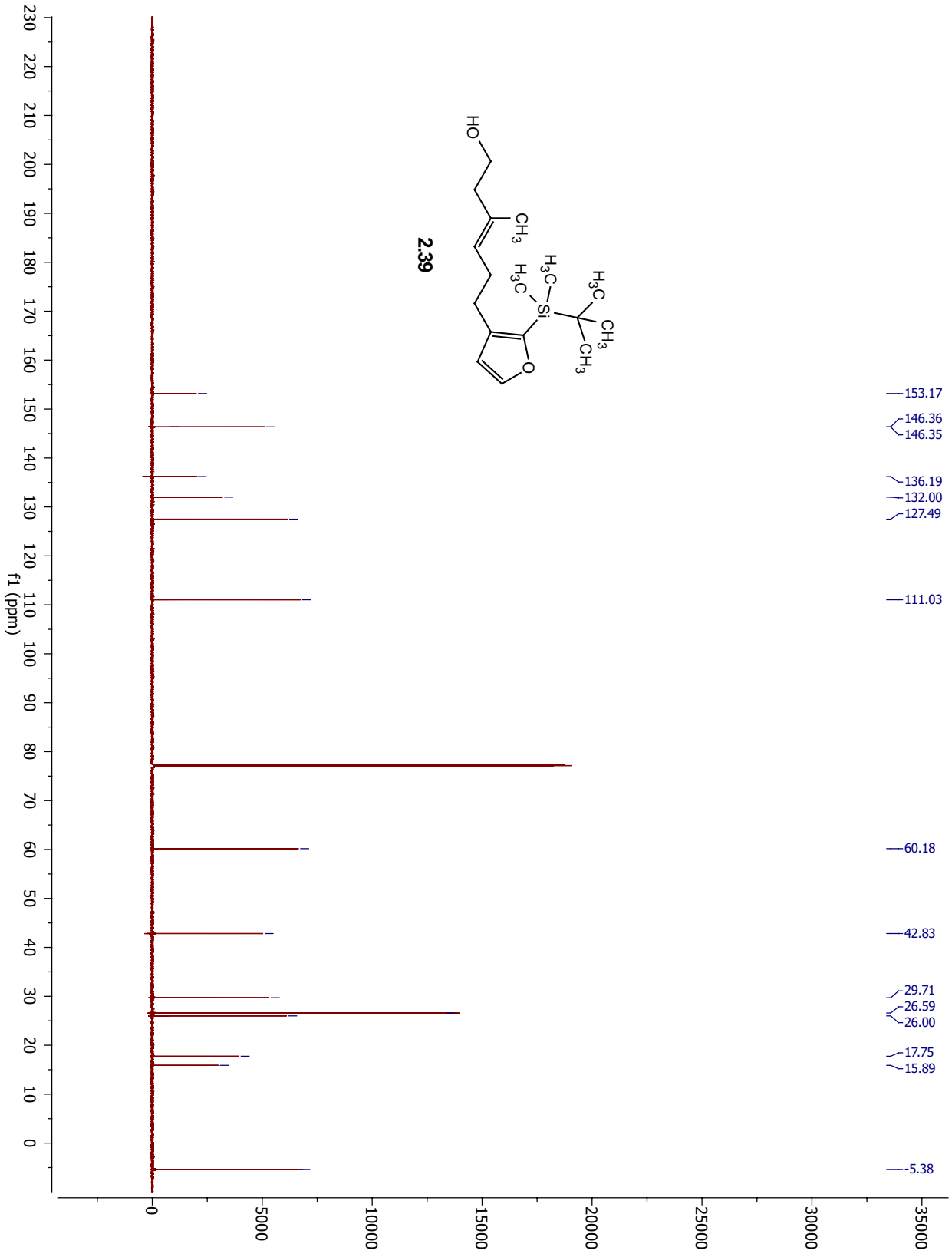
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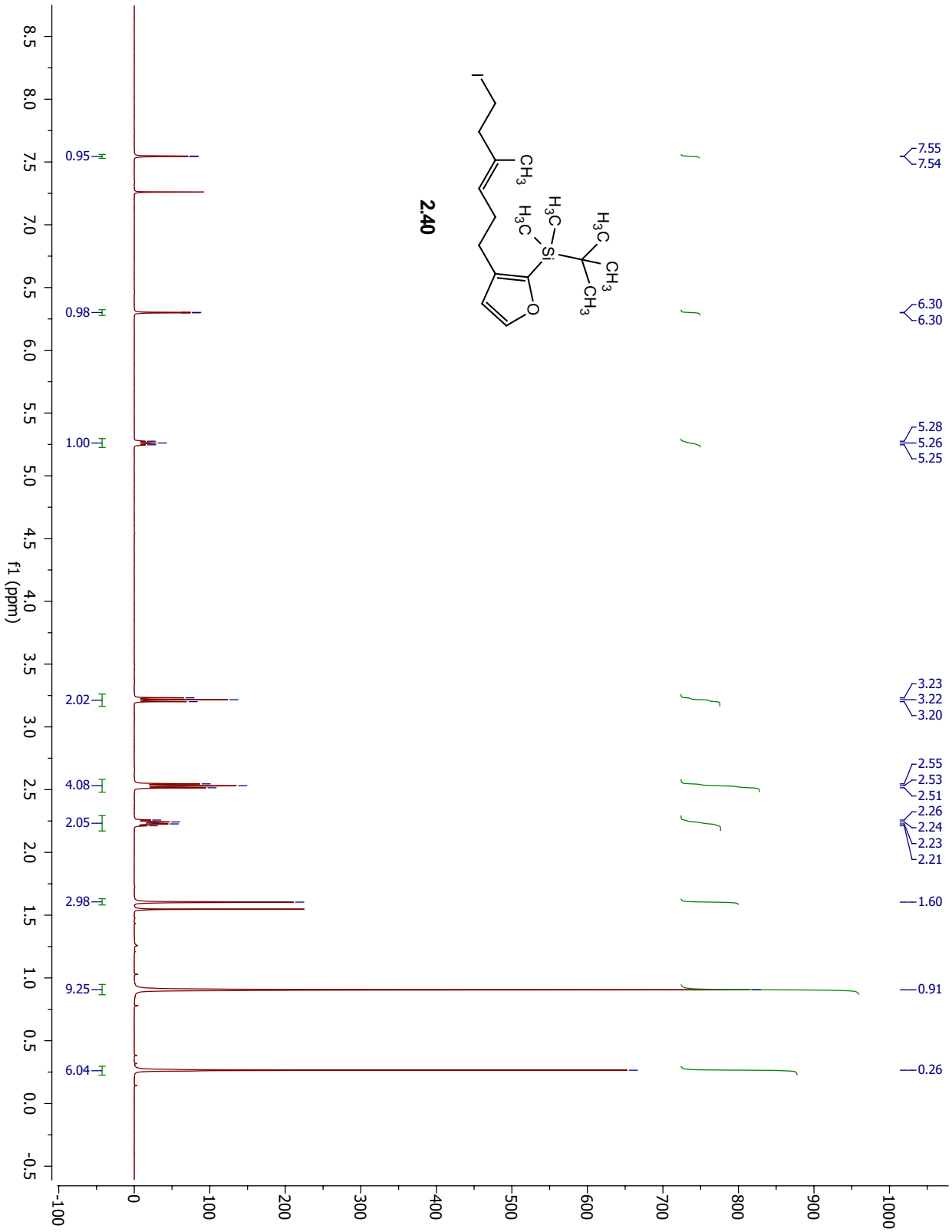
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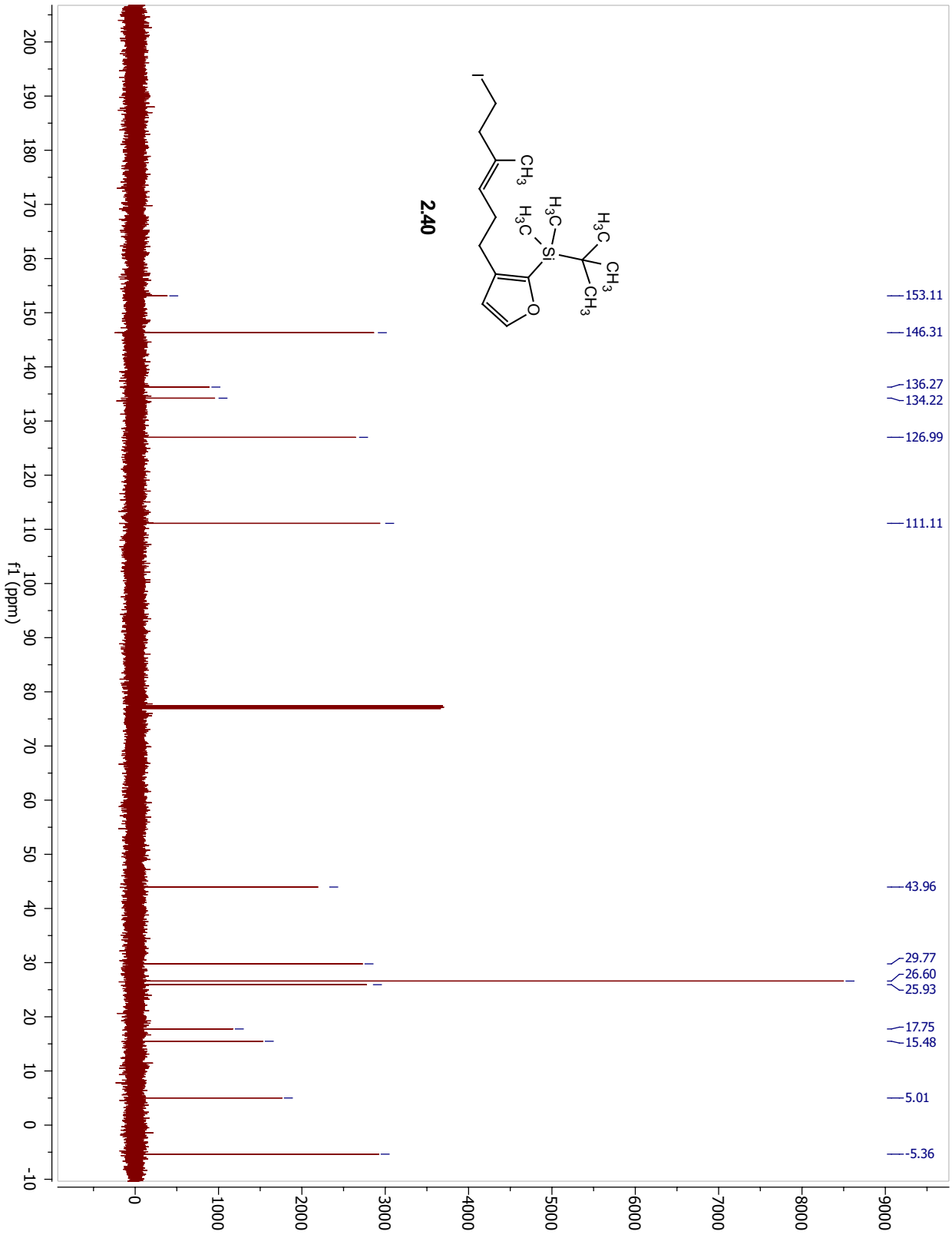
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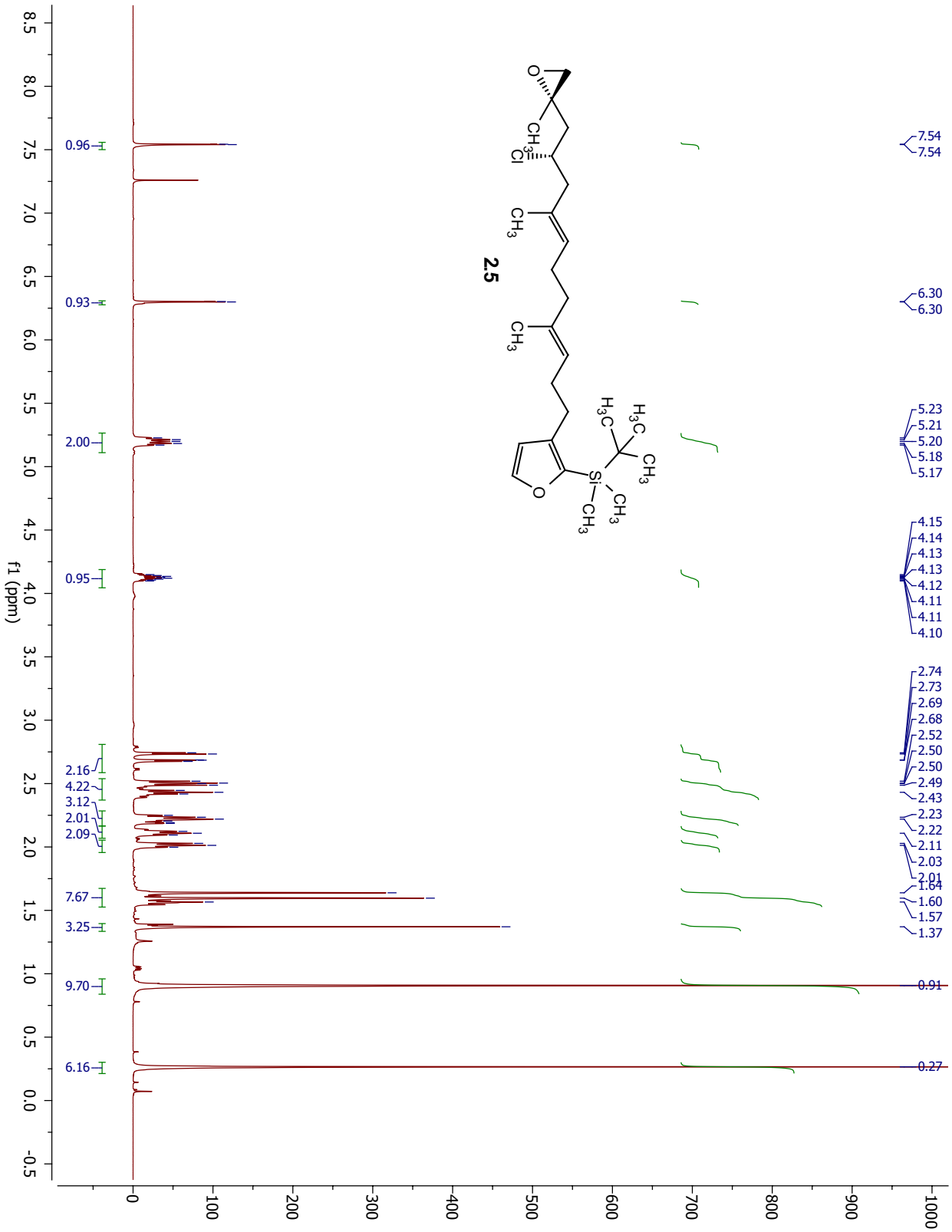
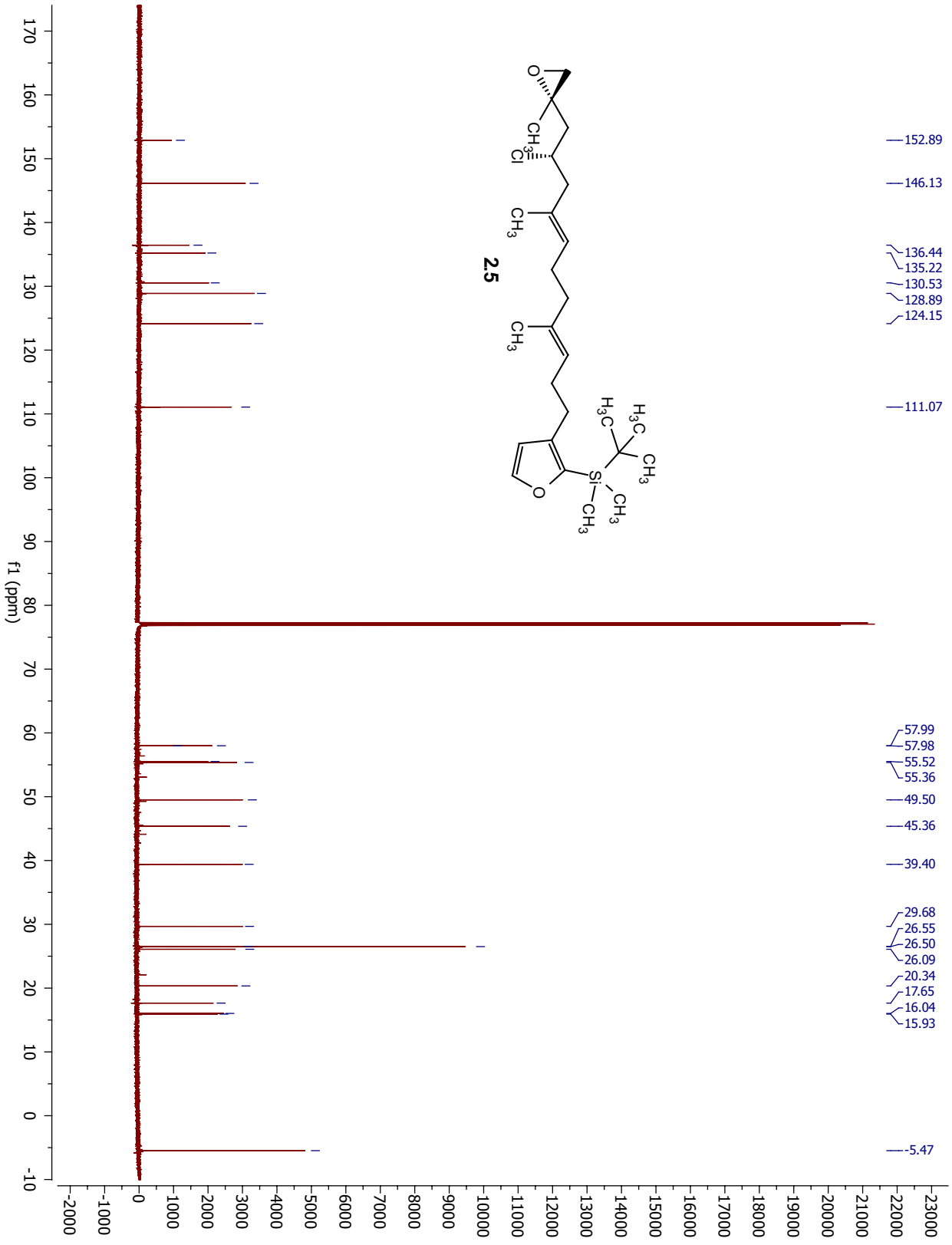
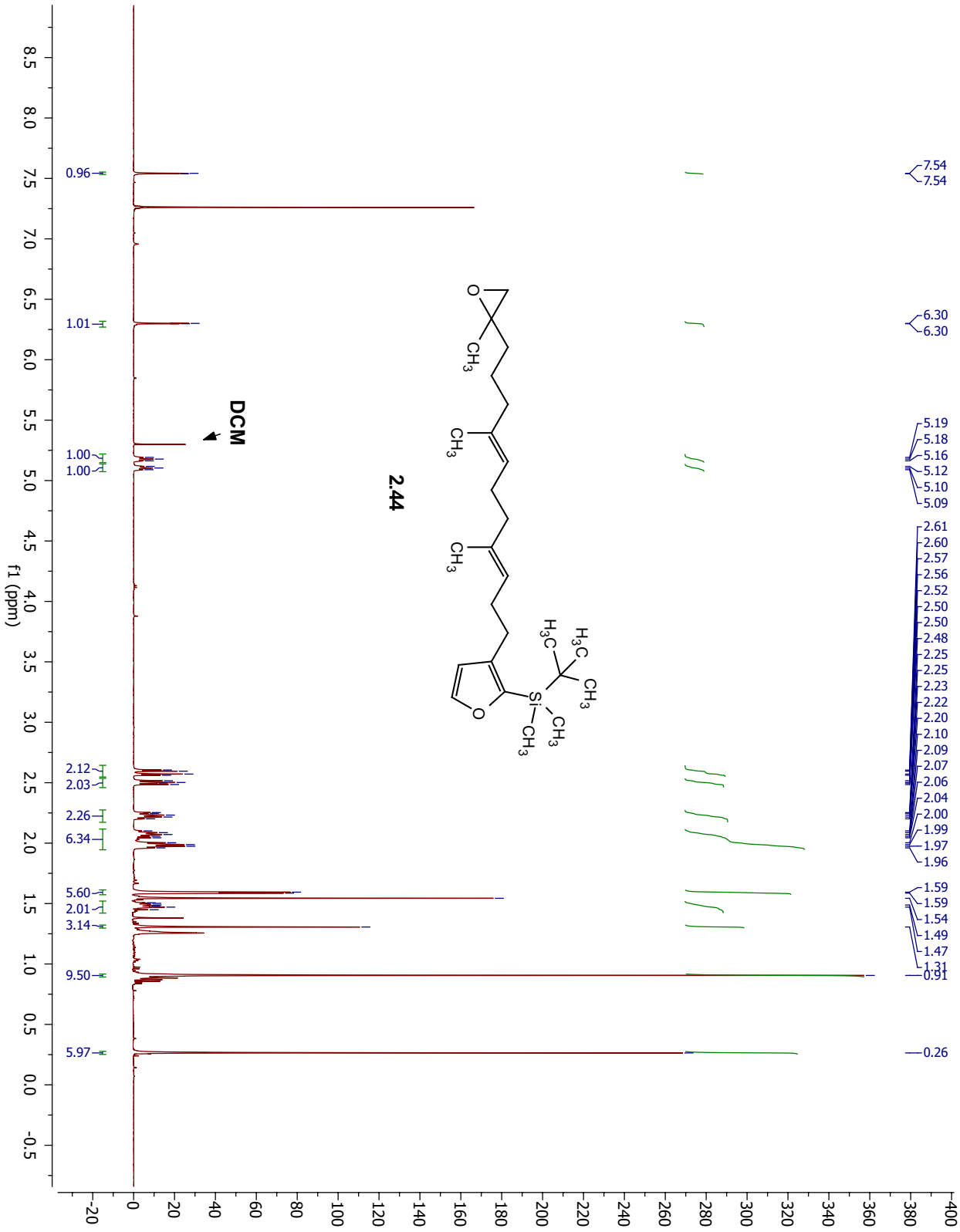
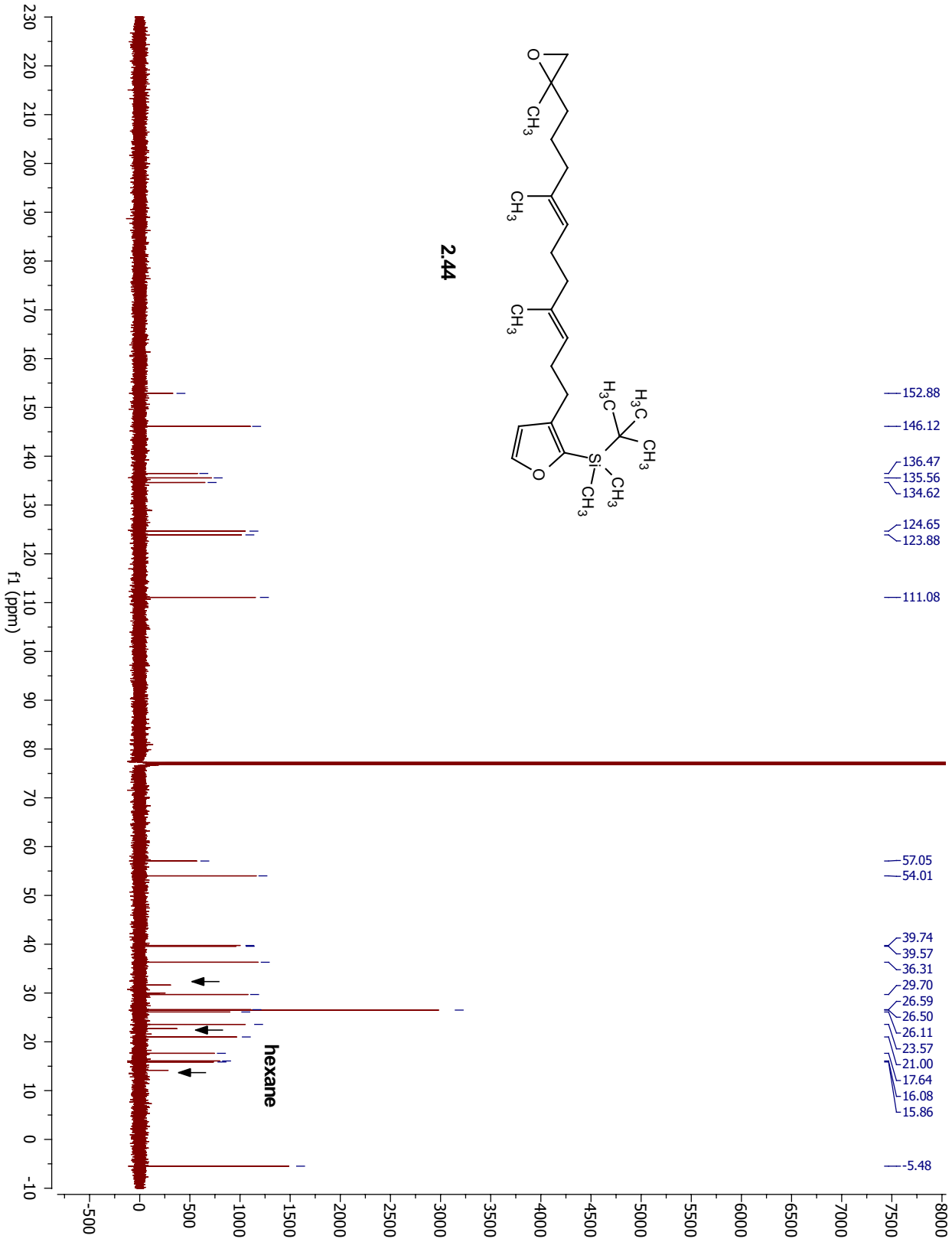
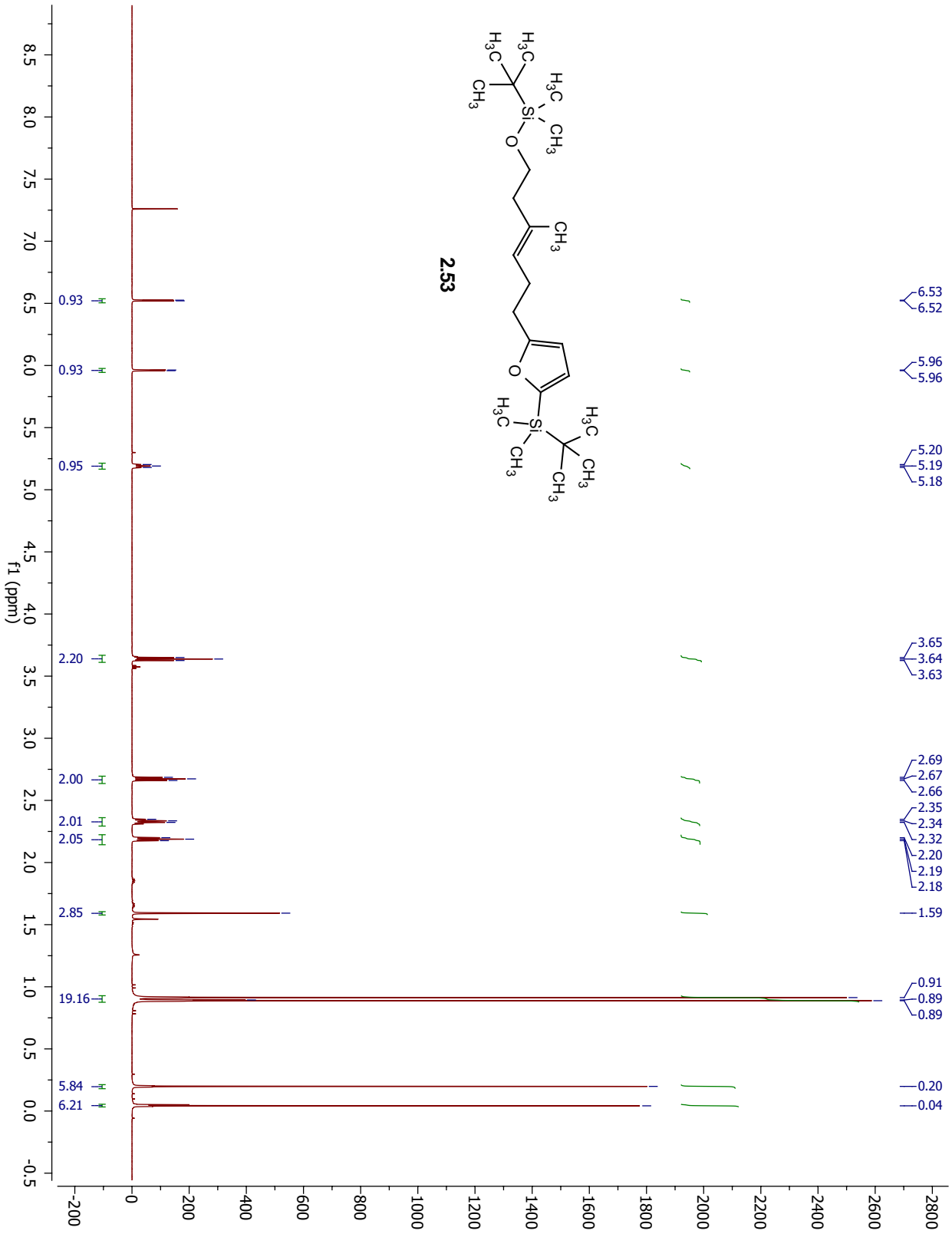
-5.36
f1 (ppm)

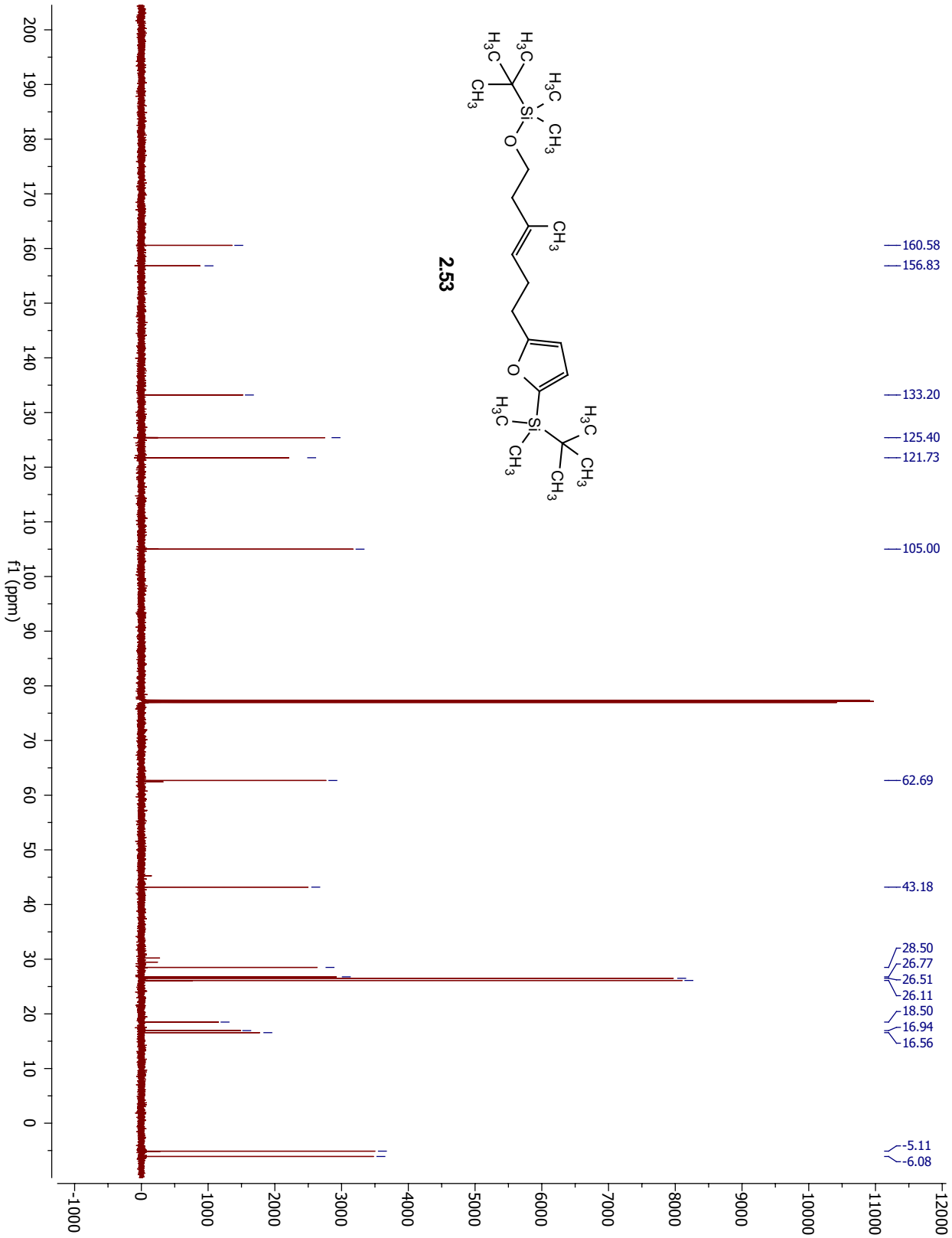

2.5
f1 (ppm)
0.96
0.93
2.00
0.95
2.16
4.22
3.12
2.01
2.09
7.67
3.25
9.70
6.16
7.54
7.54
6.30
6.30
5.23
5.21
5.20
5.18
5.17
4.15
4.14
4.13
4.13
4.12
4.11
4.11
4.10
2.74
2.73
2.69
2.68
2.52
2.50
2.50
2.49
2.43
2.23
2.22
2.11
2.03
2.01
1.64
1.60
1.57
1.37
0.91
0.27

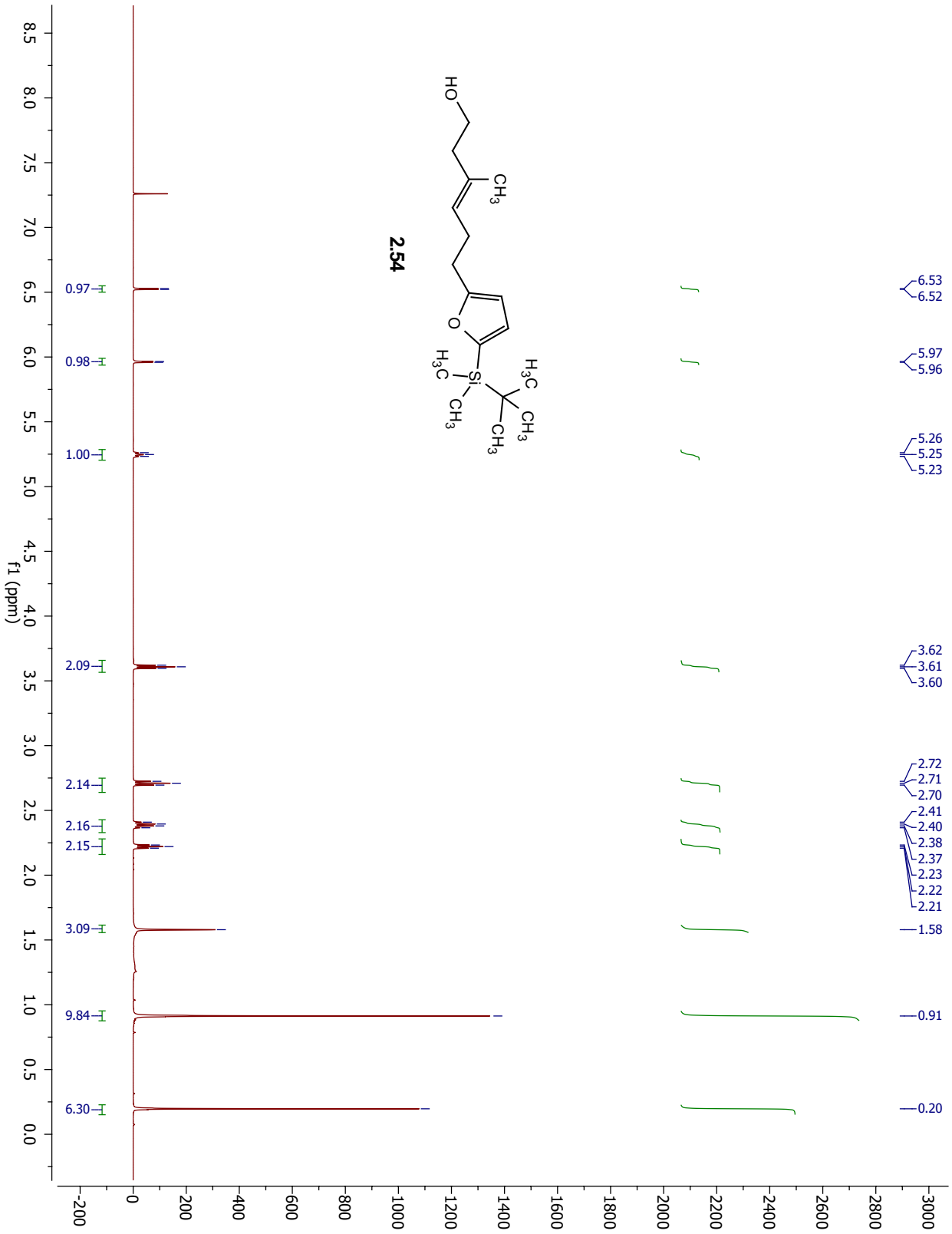

2.5
152.89
146.13
136.44
135.22
130.53
128.89
124.15
111.07
57.99
57.98
55.52
55.36
49.50
45.36
39.40
29.68
26.55
26.50
26.09
20.34
17.65
16.04
15.93
-5.47
f1 (ppm)

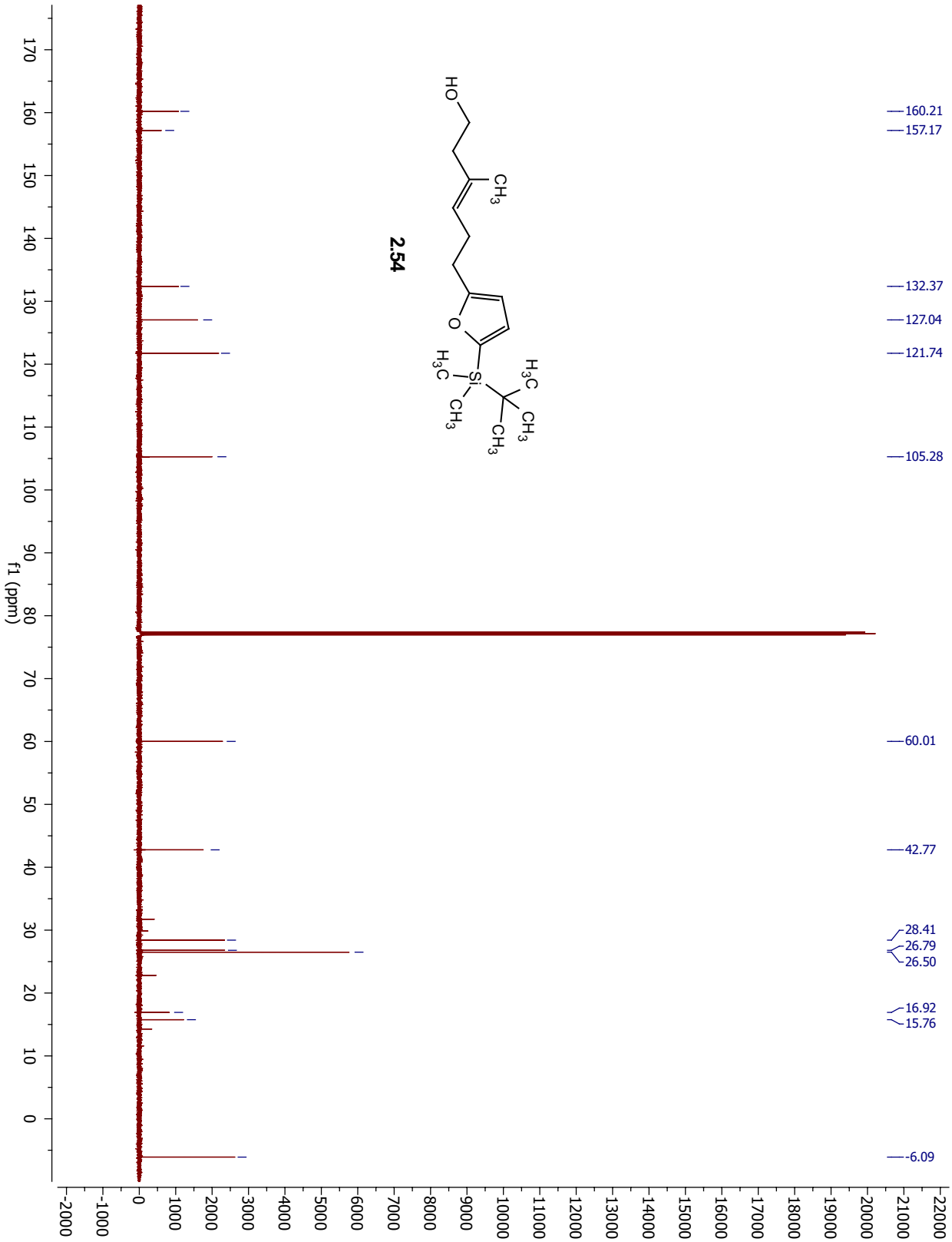

DCM
2.44
f1 (ppm)
0.96
1.01
1.00
1.00
2.12
2.03
2.26
6.34
5.60
2.01
3.14
9.50
5.97
7.54
7.54
6.30
6.30
5.19
5.18
5.16
5.12
5.10
5.09
2.61
2.60
2.57
2.56
2.52
2.50
2.50
2.48
2.25
2.25
2.23
2.22
2.20
2.10
2.09
2.07
2.06
2.04
2.00
1.99
1.97
1.96
1.59
1.59
1.54
1.49
1.47
1.31
0.91
0.26

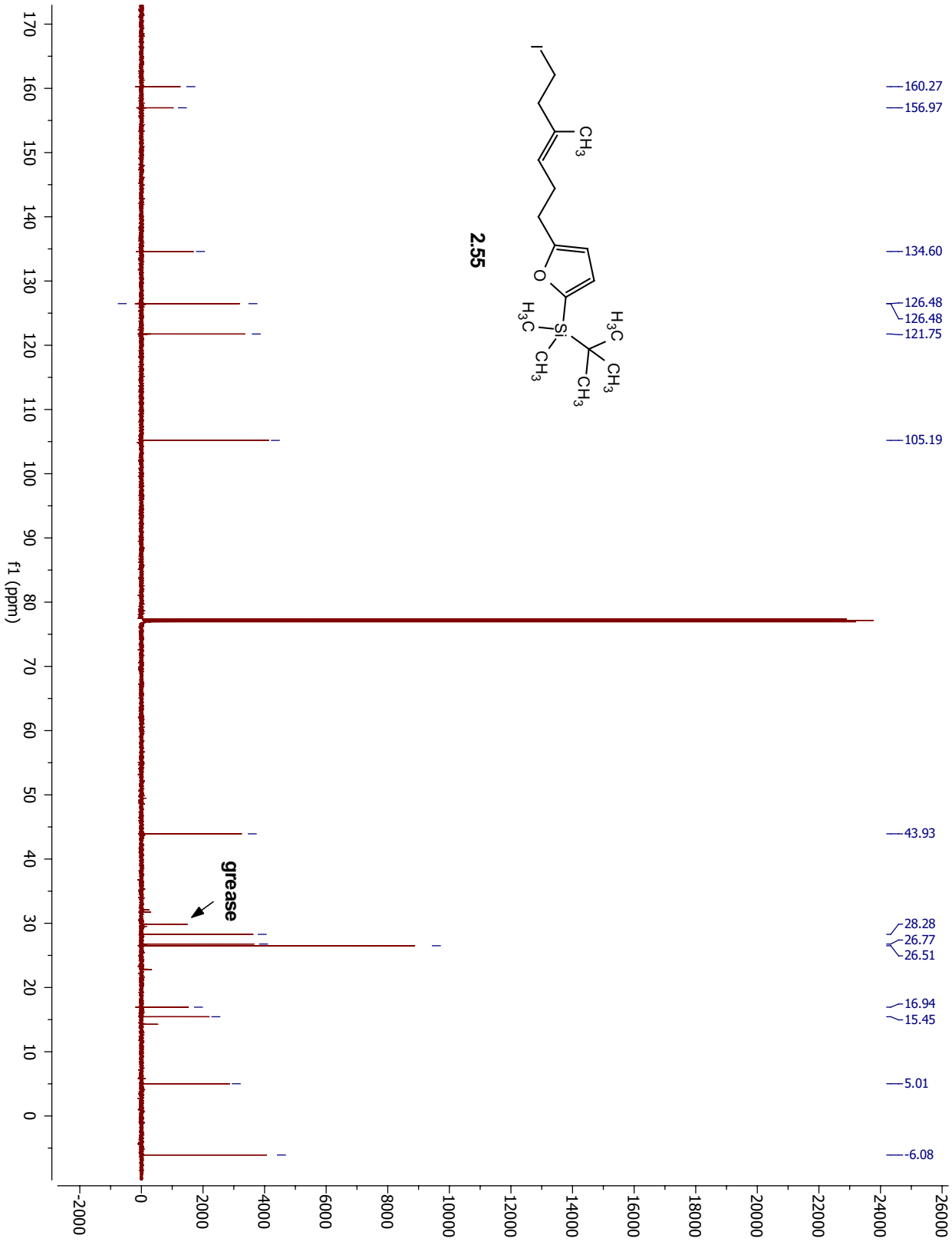

2.44
hexane
f1 (ppm)
152.88
146.12
136.47
135.56
134.62
124.65
123.88
111.08
57.05
54.01
39.74
39.57
36.31
29.70
26.59
26.50
26.11
23.57
21.00
17.64
16.08
15.86
-5.48

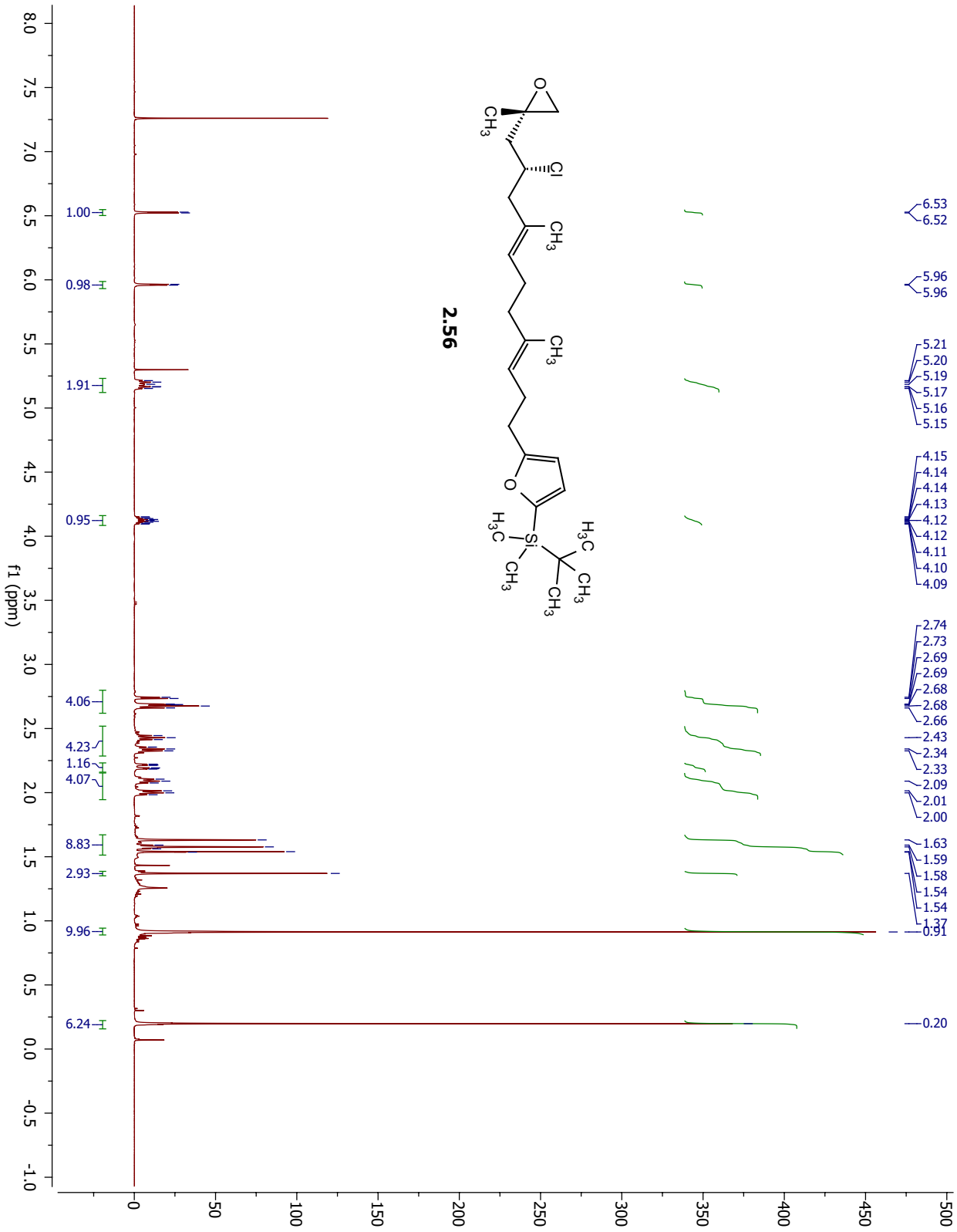

2.53
f1 (ppm)
0.93
0.93
0.95
2.20
2.00
2.01
2.05
2.85
19.16
5.84
6.21
6.53
6.52
5.96
5.96
5.20
5.19
5.18
3.65
3.64
3.63
2.69
2.67
2.66
2.35
2.34
2.32
2.20
2.19
2.18
1.59
0.91
0.89
0.89
0.20
0.04

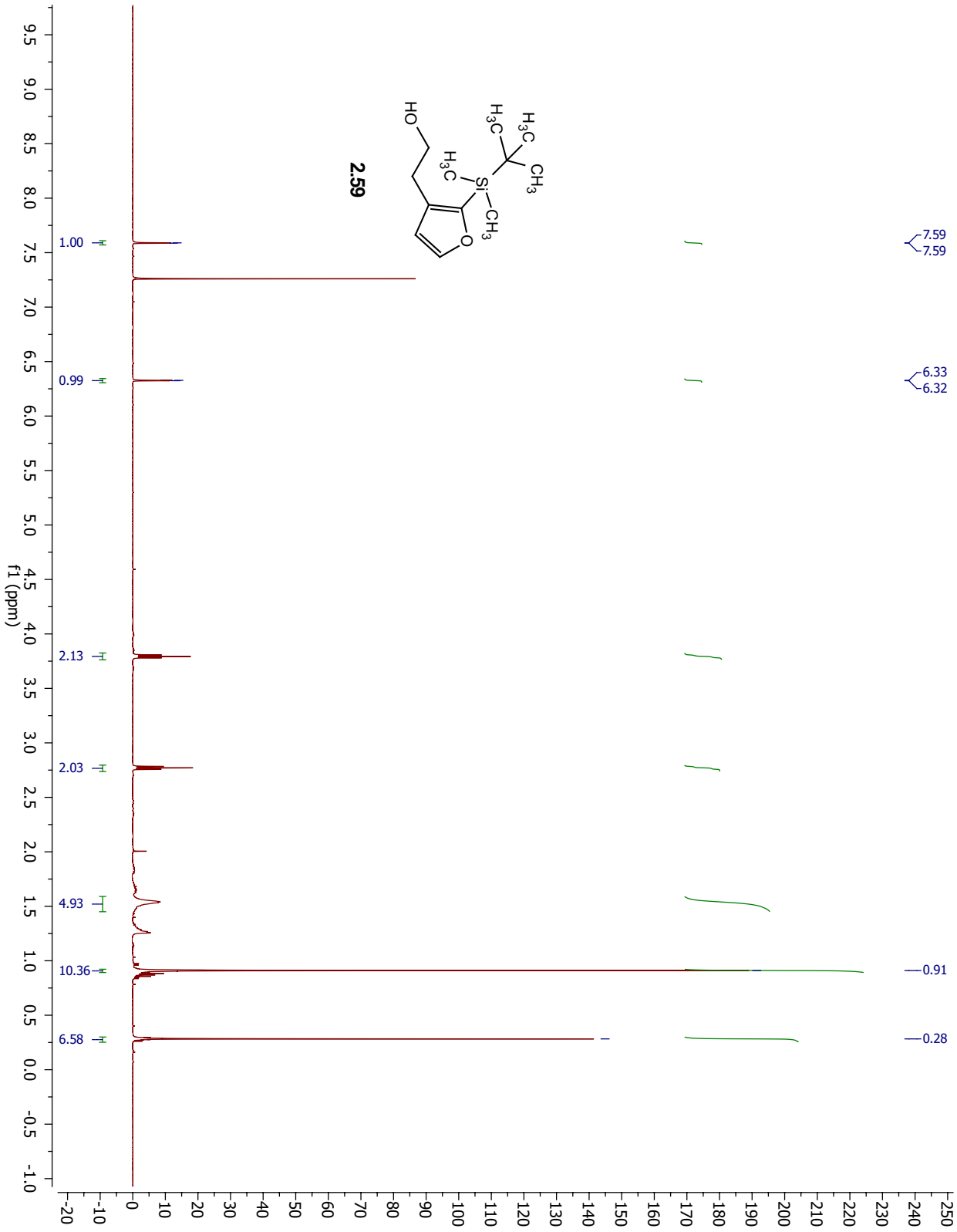

2.53
160.58
156.83
133.20
125.40
121.73
105.00
62.69
43.18
28.50
26.77
26.51
26.11
18.50
16.94
16.56
-5.11
-6.08
f1 (ppm)

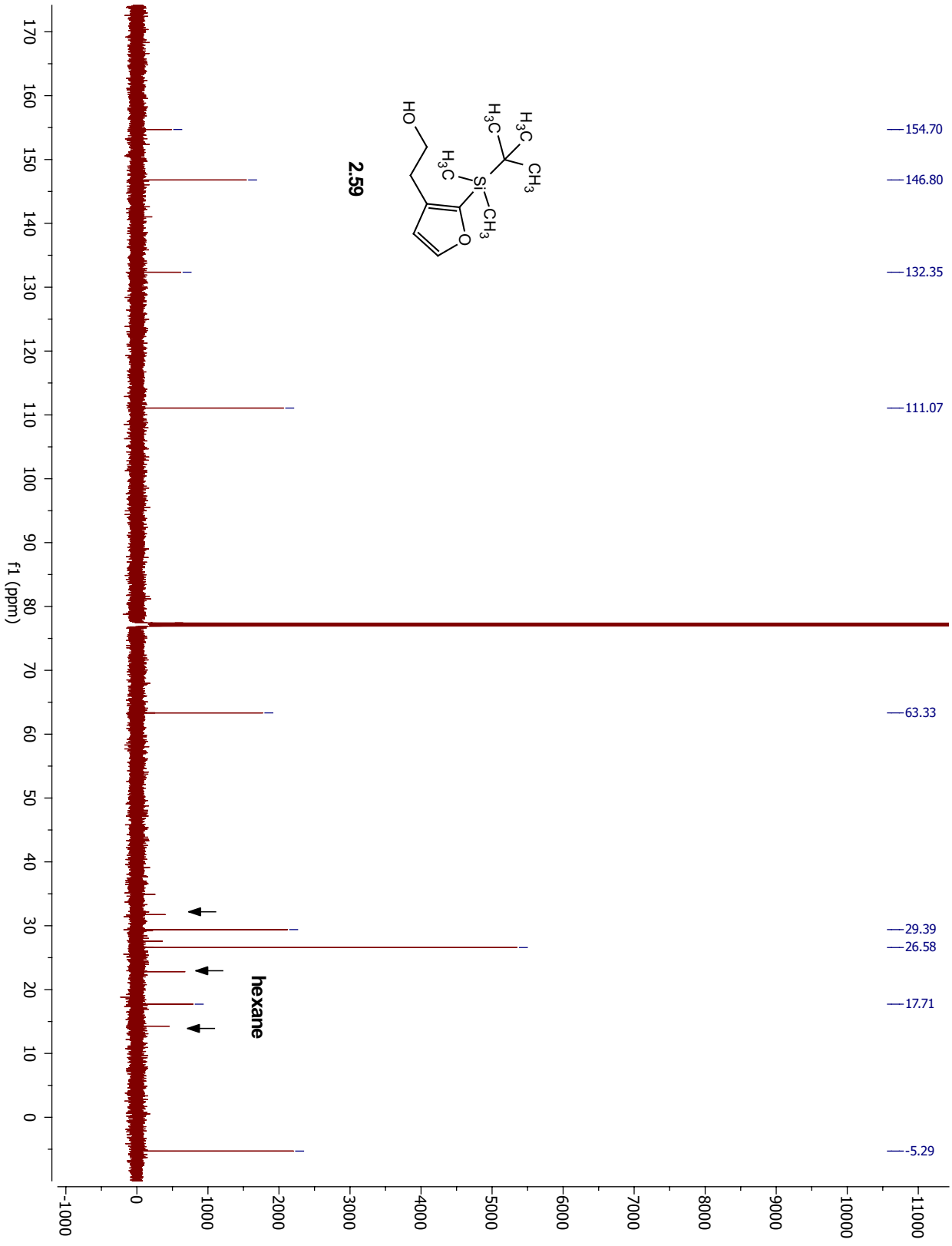

2.54
HO
CH3
O
Si
H3C
CH3
H3C
CH3
CH3
f1 (ppm)
0.97
0.98
1.00
2.09
2.14
2.16
2.15
3.09
9.84
6.30
6.53
6.52
5.97
5.96
5.26
5.25
5.23
3.62
3.61
3.60
2.72
2.71
2.70
2.41
2.40
2.38
2.37
2.23
2.22
2.21
1.58
0.91
0.20

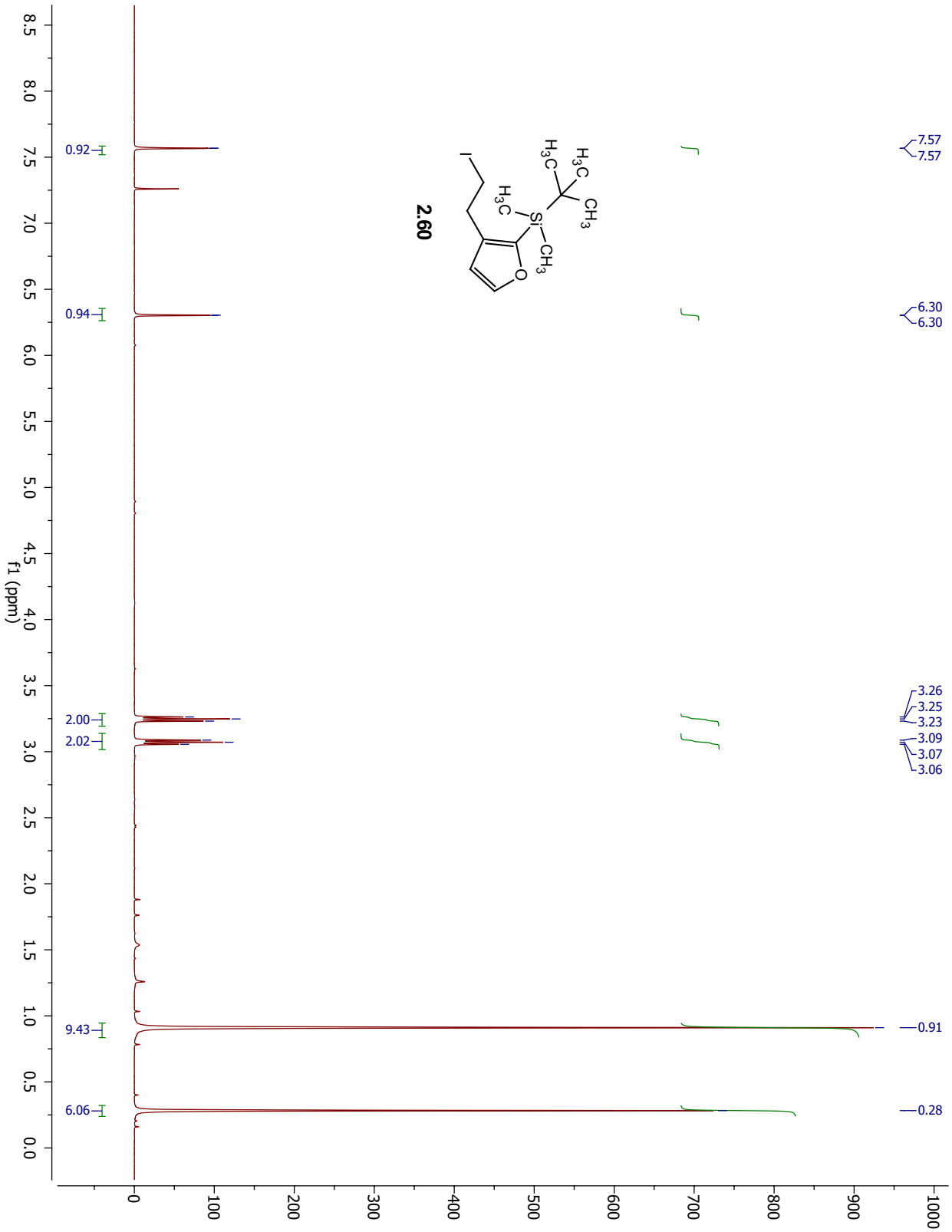

HO
CH3
O
H3C
Si
CH3
H3C
CH3
CH3
2.54
160.21
157.17
132.37
127.04
121.74
105.28
60.01
42.77
28.41
26.79
26.50
16.92
15.76
-6.09
f1 (ppm)

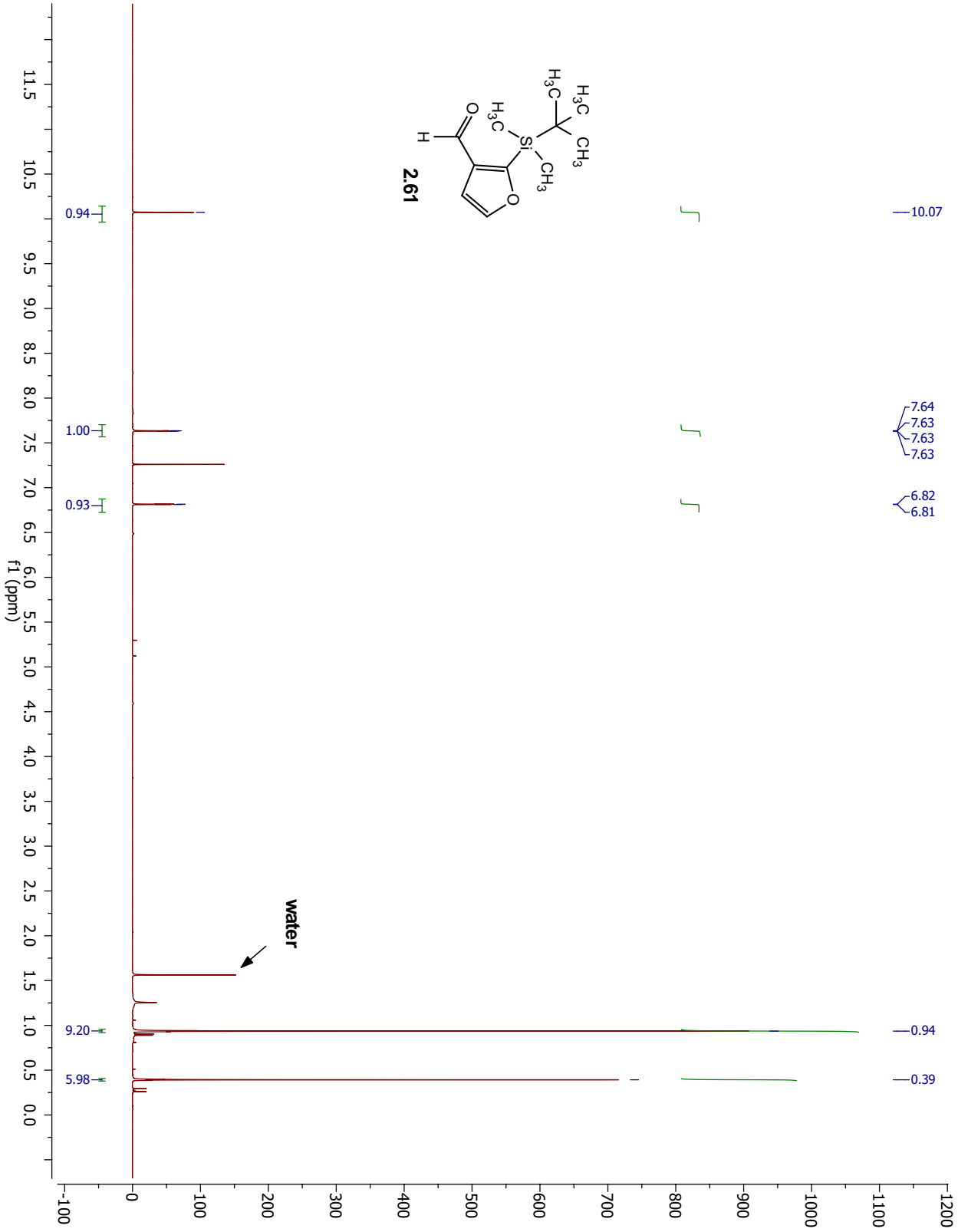

2.55
grease
160.27
156.97
134.60
126.48
126.48
121.75
105.19
43.93
28.28
26.77
26.51
16.94
15.45
5.01
-6.08
f1 (ppm)

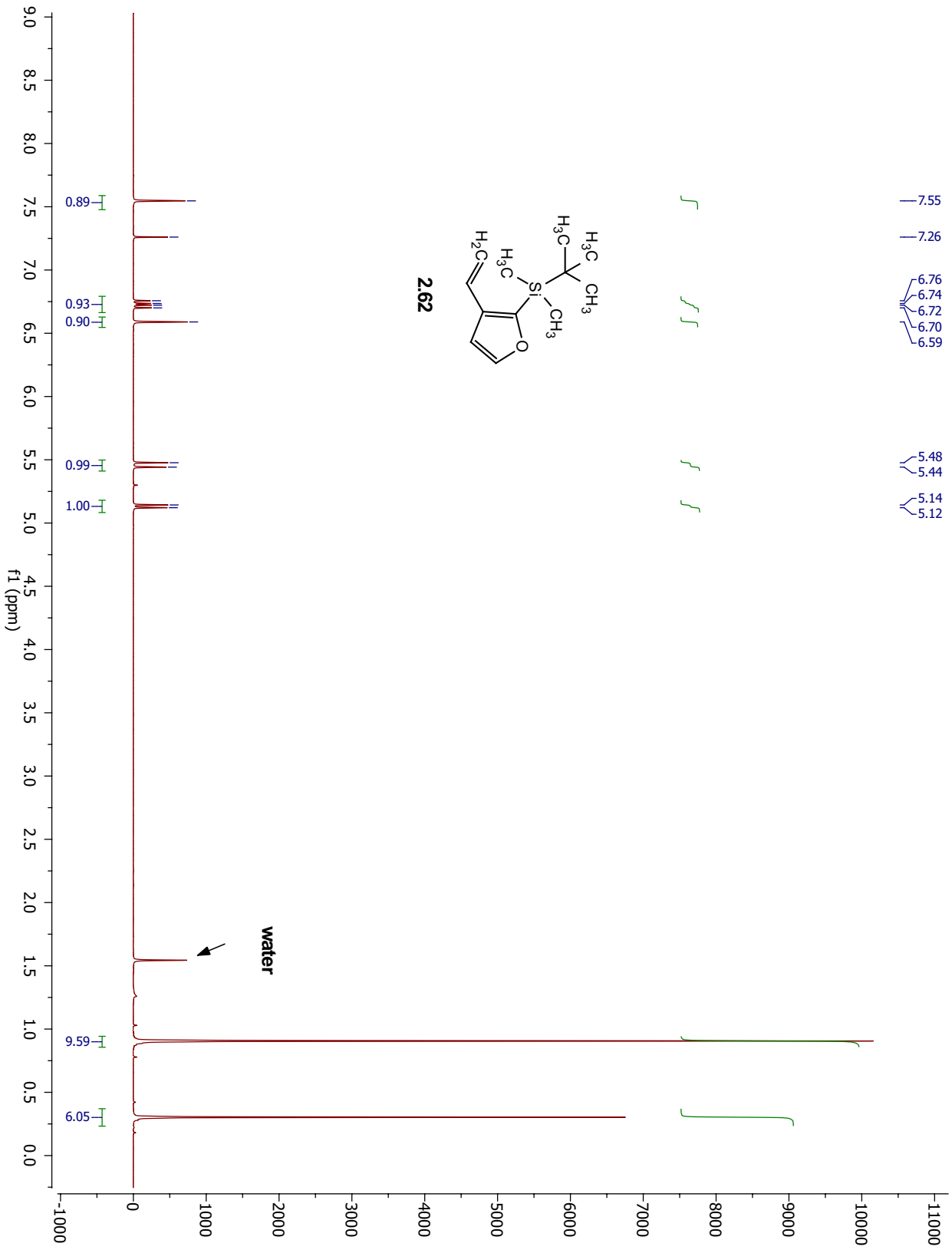

2.56
f1 (ppm)
1.00
0.98
1.91
0.95
4.06
4.23
1.16
4.07
8.83
2.93
9.96
6.24
6.53
6.52
5.96
5.96
5.21
5.20
5.19
5.17
5.16
5.15
4.15
4.14
4.14
4.13
4.12
4.12
4.11
4.10
4.09
2.74
2.73
2.69
2.69
2.68
2.68
2.66
2.43
2.34
2.33
2.09
2.01
2.00
1.63
1.59
1.58
1.54
1.54
1.37
0.91
0.20

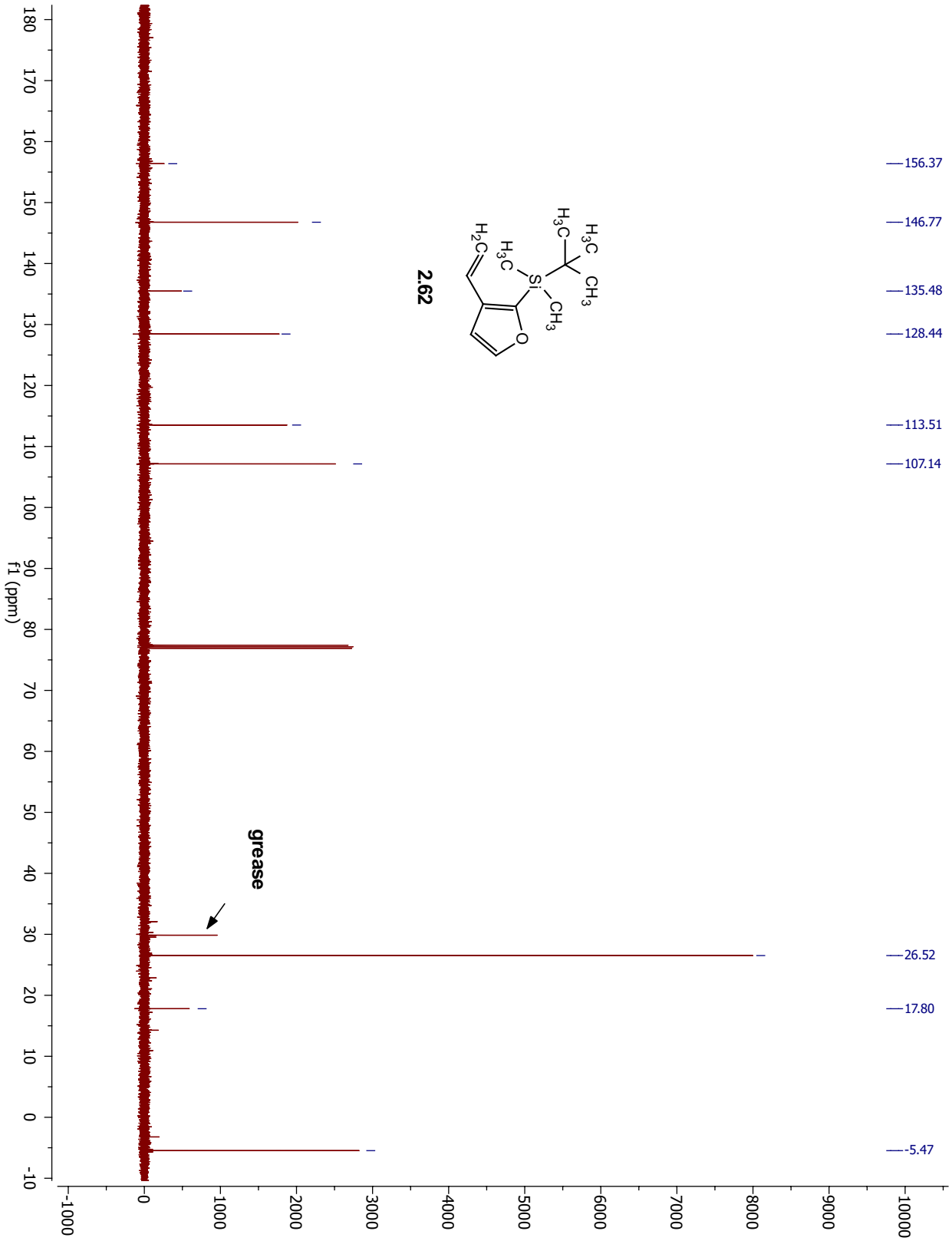

2.59
HO
H3C
H3C
CH3
H3C
Si
CH3
O
1.00
0.99
2.13
2.03
4.93
10.36
6.58
7.59
7.59
6.33
6.32
0.91
0.28
f1 (ppm)

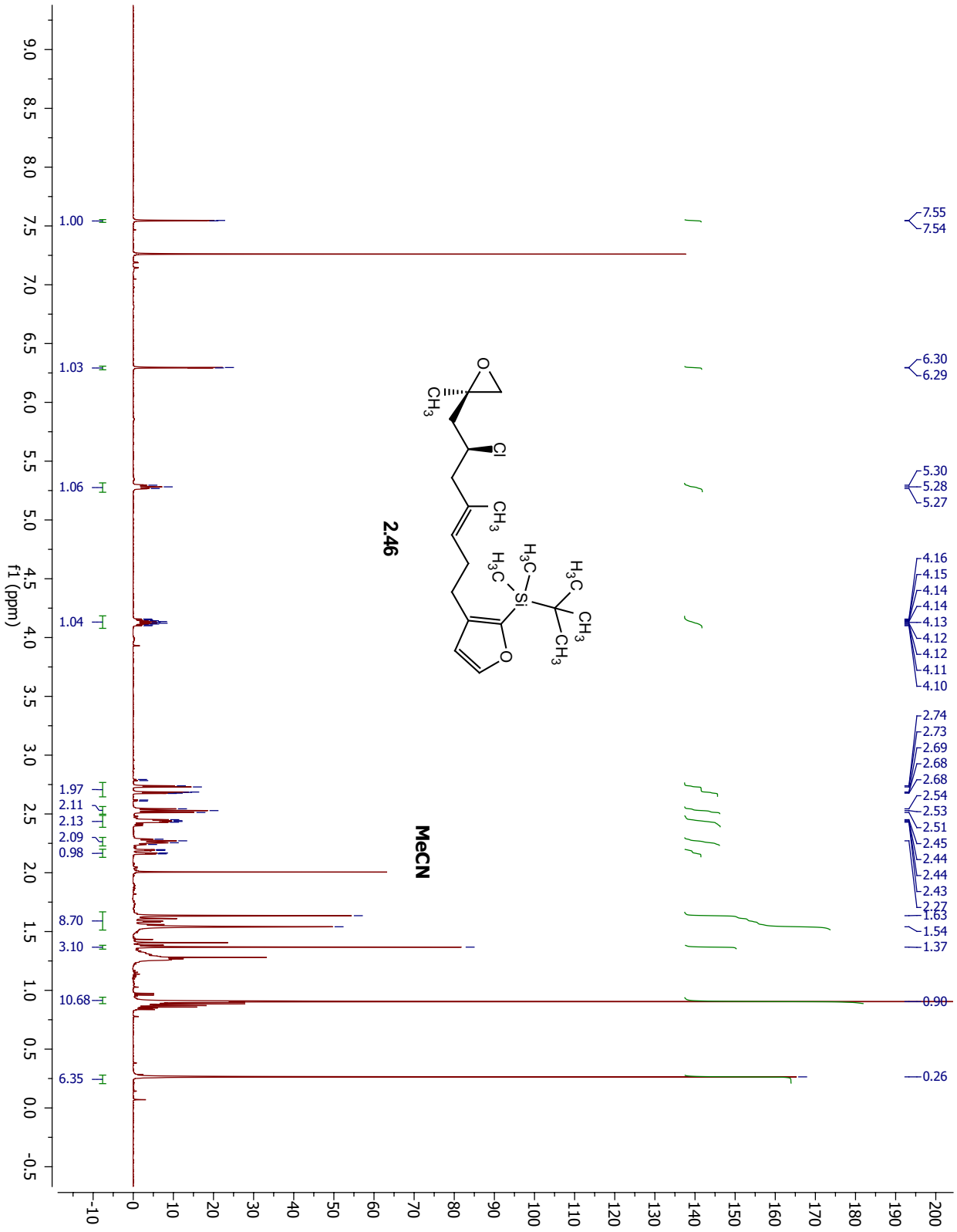

2.59
HO
H3C
H3C
CH3
H3C
Si
CH3
O
154.70
146.80
132.35
111.07
63.33
29.39
26.58
17.71
-5.29
hexane
f1 (ppm)

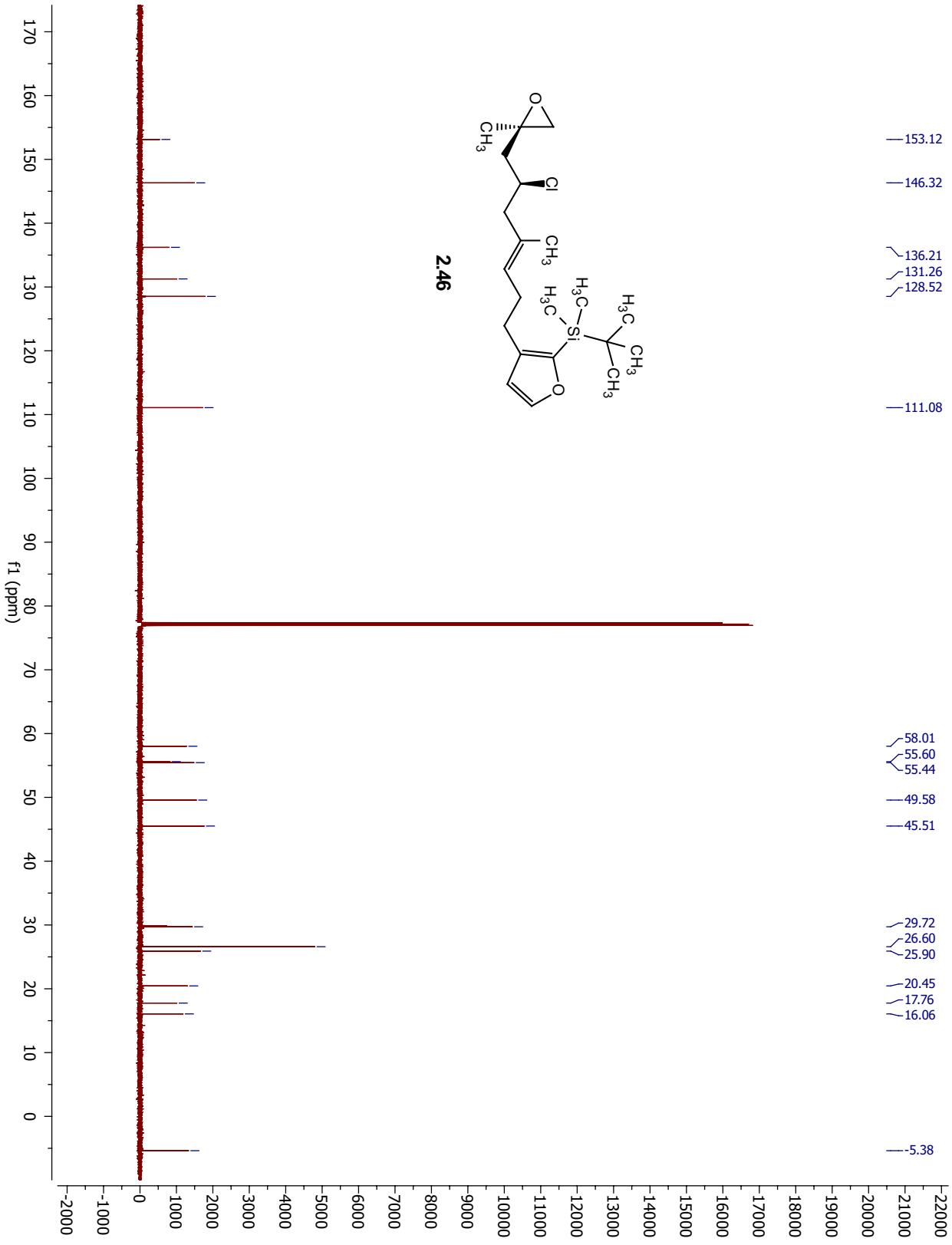

2.60
f1 (ppm)
0.92
0.94
2.00
2.02
9.43
6.06
7.57
7.57
6.30
6.30
3.26
3.25
3.23
3.09
3.07
3.06
0.91
0.28


2.61
water
0.94
1.00
0.93
9.20
5.98
10.07
7.64
7.63
7.63
7.63
6.82
6.81
0.94
0.39
f1 (ppm)


2.62
water
0.89
0.93
0.90
0.99
1.00
9.59
6.05
7.55
7.26
6.76
6.74
6.72
6.70
6.59
5.48
5.44
5.14
5.12
f1 (ppm)


156.37
146.77
135.48
128.44
113.51
107.14
26.52
17.80
-5.47
grease
2.62
f1 (ppm)


2.46
MeCN
f1 (ppm)
1.00
1.03
1.06
1.04
1.97
2.11
2.13
2.09
0.98
8.70
3.10
10.68
6.35
7.55
7.54
6.30
6.29
5.30
5.28
5.27
4.16
4.15
4.14
4.14
4.13
4.12
4.12
4.11
4.10
2.74
2.73
2.69
2.68
2.68
2.54
2.53
2.51
2.45
2.44
2.44
2.43
2.27
1.63
1.54
1.37
0.90
0.26


153.12
146.32
136.21
131.26
128.52
111.08
58.01
55.60
55.44
49.58
45.51
29.72
26.60
25.90
20.45
17.76
16.06
-5.38
f1 (ppm)
2.46