Title

Total Synthesis of Amphilectolide, Sandresolide B, Archazolid B and towards Archazolid A and Caribenol A

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Ingrid T. Chen

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Professor Dirk Trauner, Co-Chair
Professor Dean Toste, Co-Chair
Professor Matthew Francis
Professor Leonard Bjeldanes

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Abstract

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Doctor of Philosophy in Chemistry

University of California, Berkeley

Professor Dirk Trauner, Co-Chair
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The total synthesis and synthetic efforts toward norditerpene natural products isolated from *Pseudopterogorgia elisabethae* and macrocyclic polyketides from *Archangium gephyra* is described. A highly convergent synthesis of archazolid B, uniting three linear subunits, is accomplished using various modern transition-metal catalyzed reactions. A relay ring-closing metathesis is featured for closure of the 24-membered macrocyclic ring. Construction of the carbon skeleton of archazolid A is also described, featuring two robust, scaleable building blocks and their unification. New strategies for the construction and elaboration of a 1,4 skipped diene moiety are established in this synthesis.

The total synthesis of norditerpenes amphilectolide and sandresolide B are also described. A palladium mediated carbonylative coupling is featured en route to the preparation of a key furan building block that can be used to access several norditerpene natural products produced from *Pseudoterogorgia elisabethae*. This key building block was then elaborated to amphilectolide utilizing a lanthanide catalyzed ring closure and furan oxidation with singlet oxygen. The ring-closure product may also be used to access caribenol B.

The furan building block was also used to construct sandresolide B, where a Myers alkylation overcame steric constraints in this system. An intramolecular Friedel Crafts acylation is used to close a 7-membered ring. These strategies also provide insight to a next generation route toward caribenol A, and the progress toward the initial strategy via Stork Danheiser ring closure is described.

For Sol
My greatest friend and companion

Table of Contents

Chapter 1. Total Synthesis of (−)-Archazolid B

Chapter 2. Construction of Carbon Skeleton of Archazolid A

Chapter 3. Total Synthesis of Amphilectolide and Sandresolide B and Progress towards Caribenol A

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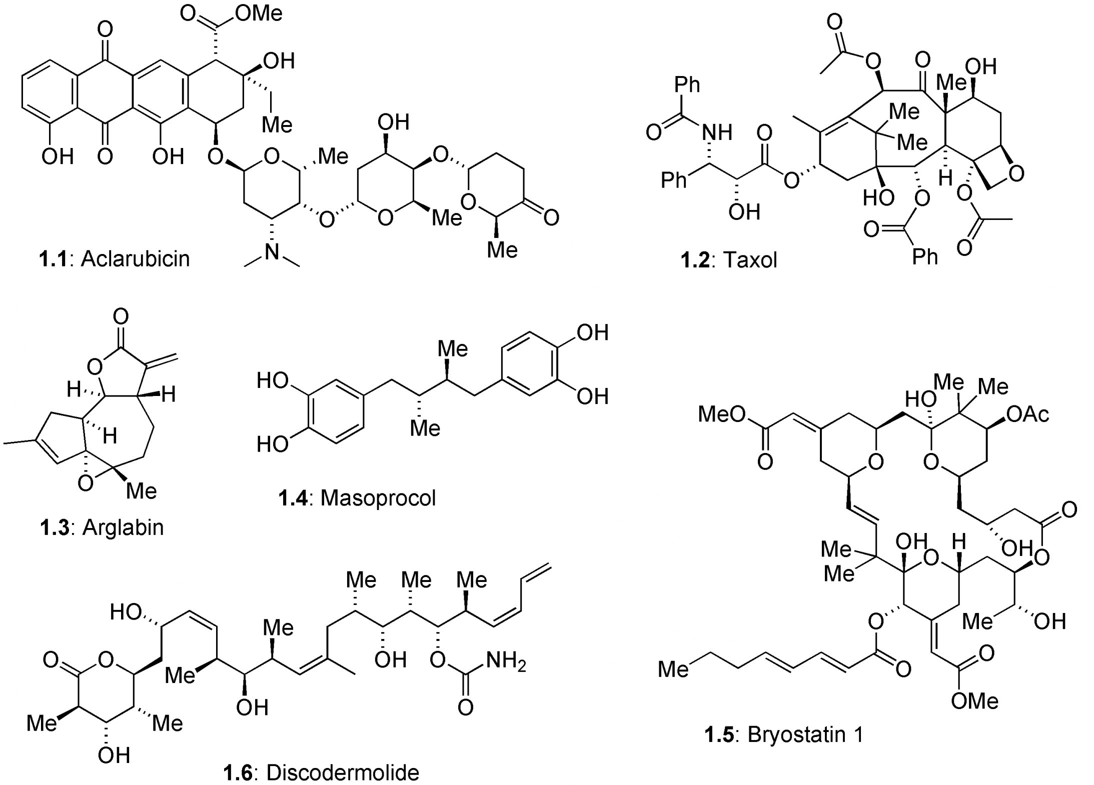
Chapter 1. Total Synthesis of (−)-Archazolid B

Section 1.1. The role of natural products as anticancer agents

The structure and activity of natural products has been a constant source of inspiration and application in drug discovery and development. Many approaches for drug discovery have been explored, and natural products remain unique in that they exploit the inherent activity of molecules that nature and evolution have engineered for its parent organism to their application as therapeutic agents in the human body. Between 1981 and 2006, 27% of the 1010 new chemical entities marketed as drugs were natural products or derivatives thereof.[1] Notably, their application as anticancer agents was particularly high; out of 54 drugs, there exists one totally synthetic drug for every two drugs from natural products and their derivatives.[1] A few representative natural products for chemotherapy include aclarubicin (**1.1**), taxol (**1.2**), arglabin (**1.3**) and masoprocol (**1.4**) (Figure 1.1). These compounds are structurally diverse and treat many different types of cancer. Aclarubicin (**1.1**) and masoprocol (**1.4**) are type II polyketides for the treatment of leukemia and skin cancer, respectively, while taxol (**1.2**) and arglabin (**1.3**) are terpenoids useful for a variety of tumors. Cytotoxic type I polyketides bryostatin 1 (**1.5**) and discodermolide (**1.6**) are currently undergoing clinical trials.[2,3]

Figure 1.1. Representative natural products for the treatment of cancer



1.1: Aclarubicin

1.2: Taxol

1.3: Arglabin

1.4: Masoprocol

1.5: Bryostatin 1

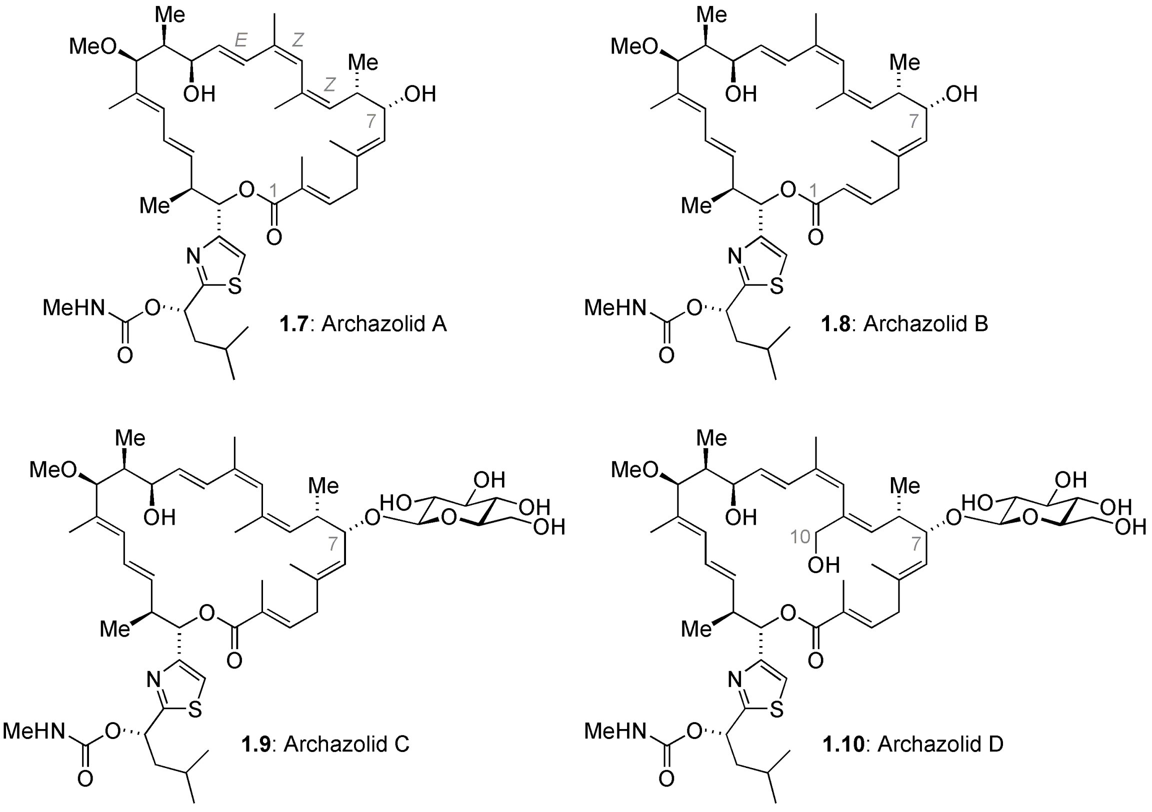
1.6: Discodermolide

The vast structural differences between these compounds imply that they operate via different modes of action and, furthermore, that new natural products featuring unique selectivity profiles and promising anticancer activity are attractive candidates for further investigation.

Section 1.2. Background and significance of archazolids A-D

The archazolids (**1.7**-**1.10**) are a family of unsaturated polyketide natural products that are potent inhibitors of vacuolar-type ATPases (V-ATPases) with IC_{50} values of 0.6 nM for **1.7** and **1.8**, 2.1 μM for **1.9** and 330 nM for **1.10** (Figure 1.2).[4-6] Their specificity against mammalian V-ATPases, together with a reversible mode of binding, render these antimitotic agents as valuable lead compounds for the treatment of renal acidosis, osteoporosis, and cancer in drug and pro-drug approaches.[7] Our interest in the archazolids is derived from their exceptional bioactivity and as well as their unique structural features, which include a 24-membered macrolactone ring and rare *E, Z, Z cis*-triene moiety. Additionally, the isolated quantities of these compounds (240 mg of **1.7**, 54 mg of **1.8**, 35 mg of **1.9** and 4 mg of **1.10**)[5-6] has hampered full biological evaluation, increasing their attractiveness as synthetic targets.

Figure 1.2. Structures of archazolids A-D



1.7: Archazolid A

1.8: Archazolid B

1.9: Archazolid C

1.10: Archazolid D

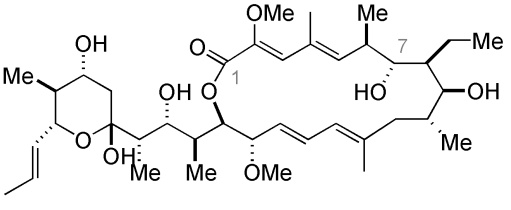
Archazolids A (**1.7**) and B (**1.8**) were first isolated in 1993 by Höfle *et al.* from the myxobacterium *Archangium gephyra* cultivated from a soil sample collected in the Karawank mountains of Austria.[8] In 2006, the relative and absolute configurations of **1.7** and **1.8** were established by Menche and coworkers through a combination of degradation studies as well as extensive NMR analysis of ^1H-^{13}C coupling constants.[4] The results of these studies were confirmed in 2007 through a total synthesis of archazolid A by the same group.[9] The following year, archazolids C (**1.9**) and D (**1.10**), which are β-glucoside derivatives of **1.7** with the latter featuring a hydroxyl group at C(10), were isolated from the myxobacterium *Cystobacter violaceus*.[7] Since **1.9** and **1.10** exhibit less activity compared to **1.7** and **1.8**, the free hydroxyl at C(7) is most likely an important component of the pharmacophore.[7]

V-ATPase inhibitors are valuable targets for cancer research because these proton pumps are overexpressed in cancer cells. Two families of potent naturally-occurring V-ATPase inhibitors have been the subject of extensive study over the past 20 years: plecomacrolide antibiotics and benzolactone derivatives (Figure 1.3). Concanamycin F (**1.11**) and bafilomycin A_1 (**1.12**) are representative members of the former family and are perhaps the most well-studied V-ATPase inhibitors. They were isolated from *Streptomyces griseus* and *Streptomyces diastatochromogenes* respectively,[10] and possess low nanomolar inhibition against V-ATPases as well as micromolar inhibition against ion transporting P-ATPases. While they are attractive structures for total synthesis and valuable tools for studying cellular processes involving V-ATPases inhibitors, they are far too toxic to possess therapeutic potential.

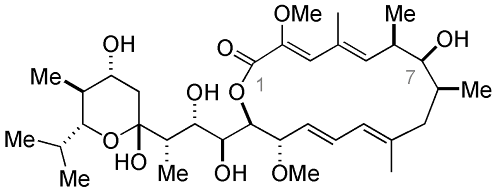
Several years ago, competition studies had established that the archazolids at least partly share a common binding site with concanamycin (**1.11**) in the V_0 subunit c of V-ATPase.[5] Recently, a fluorescent tagged derivative of archazolid A (**1.7**) was used to establish that only one amino acid of eleven involved in the bafilomycin (**1.12**) binding site is shared with the fluorescent archazolid derivative.[11] It is curious to speculate as to which portions of the archazolids are important in the active site. Structurally, it contains a slightly larger macrolactone than **1.11** and **1.12** and a similar structural pattern is shared between C(1) and C(7), which also bears a free hydroxyl group that has been noted to be significant for the archazolid pharmacophore. These structural similarities suggest that the active part of the molecule may be within its southeastern portion and raises an interesting question as to which structural aspects of the archazolids offer specificity against mammalian V-ATPases, a property that is lacking for the other plecomacrolides under investigation.

Another class of potent V-ATPase inhibitors are benzolactone enamides, which possess a completely different mechanism of action from the aforementioned compounds as shown by competition experiments with radiolabeled concanamycin derivatives.[10] Currently, two compounds possessing promising biological profiles are apicularen A (**1.13**) and saliclihalamide A (**1.14**), which were isolated from the myxobacterium *Chondromyces* and the *Haliclona* sponge, respectively.[10] These natural products are under active investigation in both structure-activity relationship (SAR) studies and in total synthesis endeavors, illustrating their utility for studying V-ATPases and their potential as therapeutic candidates. The archazolids have rapidly drawn attention in this field and since our initial interest in 2006, they have been recognized as a new player in V-ATPase inhibition.[10] This chapter describes the total synthesis of archazolid B, our first target in this family.

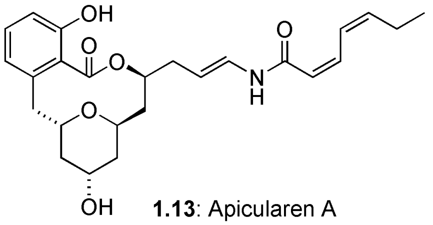
Figure 1.3. Representative naturally occurring V-ATPase inhibitors



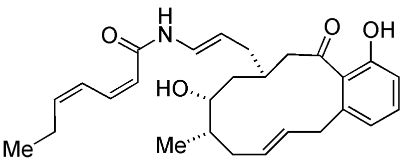
1.11: Concanamycin F



1.12: Bafilomycin A$_1$



1.13: Apicularen A



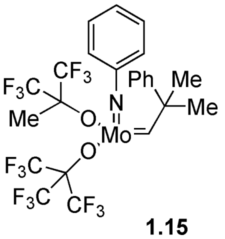
1.14: Salicylihalamide A

Section 1.3. Significance of ring-closure using olefin metathesis

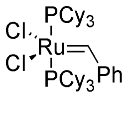
Since the serendipitous advent of olefin metathesis in the 1960's,[12] numerous developments have led to its application in the total synthesis of natural products. Initially, over a decade was spent elucidating the mechanism, after which catalysts were developed and optimized.[13] However, it was not until Greg Fu's arrival as a post-doc at Cal-Tech that olefin metathesis was applied to synthesis. Fu concentrated on ring-closing metathesis (RCM) to form 5, 6 and 7-membered rings using molybdenum alkylidenes **1.15** and later demonstrated that ruthenium-based catalysts promoted similar reactions with the advantage of having greater functional group tolerance (Figure 1.4).[14]

Since molybdenum is an "earlier" transition metal, the electrophilicity of the high oxidation-state metal center pronounces its sensitivity to air and certain polar functional groups.[15] As a result, Grubbs' generation I and II ruthenium complexes (**1.16** and **1.17**, respectively), which are air-stable and thus much more practical to handle, have gained unrivaled popularity in the synthetic community. To further illustrate the appeal of air-stable catalysts to synthetic chemists, ruthenium-based catalyst **1.18**, which is effective for RCM of trisubstituted olefins,[13,14] was introduced concomitantly and independently by the Hoveyda[16] and Blechert[17] groups in 2000 (Figure 1.4).

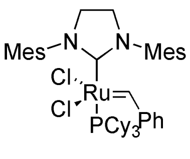
Figure 1.4. Structures of common olefin metathesis catalysts



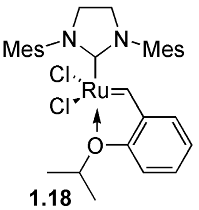
1.15



1.16



1.17

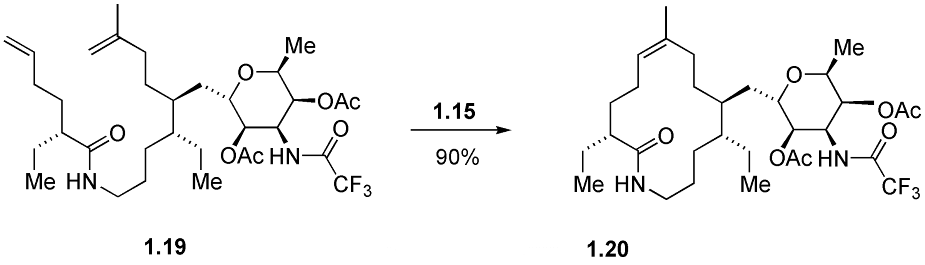


1.18

An added advantage to **1.18** is that is it recoverable on silica, although all aforementioned catalysts, which are shown in figure 1.4, are commercially available. Catalysts **1.16**-**1.18** are typical for olefin metathesis and exhibit subtle differences on reactivity. Schrock catalyst **1.15** is useful for sterically crowded systems[13] while **1.17** demonstrates increased activity as compared to **1.16** since the carbene ligand improves the rate of coordination to the olefin as compared to the rate of recoordination of the phosphine.[18] Additionally, **1.17**, which survives in toluene at 100 °C for one hour, exhibits significantly enhanced thermal stability compared to **1.16**, which decomposes up to 75% under those conditions.[18] Hoveyda catalyst **1.18** is yet more active than **1.17** because phosphine ligand dissociation, which is the rate limiting step for commencement of the catalytic cycle, is no longer required. Derivatives of ruthenium catalysts **1.16**, **1.17** and **1.18** have been developed although they are less frequently used in synthesis.[19, 20]

Olefin metathesis in synthesis rapidly took off in the late 1990's, as this method proved to be a new and reliable synthetic strategy to access olefins and small rings in natural products. An interest in forming larger rings developed,[21] posing new challenges to circumvent side reactions since ring-strain can then become a significant contributor to ring-opening metathesis (ROM) and ring-opening metathesis polymerization (ROMP).[18] Hoveyda's synthesis of Sch 38516 in 1996, which accessed a 14-membered ring **1.20** through RCM of **1.19**, was one of the first demonstrations of macrocyclic RCM (Scheme 1.1).[22]

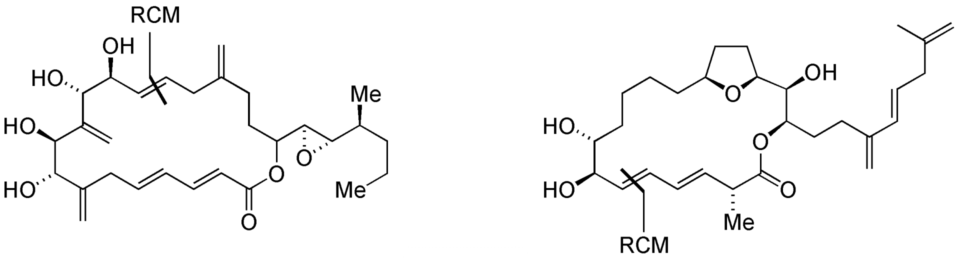
Scheme 1.1. RCM in the total synthesis of Sch 38516 [22]



In this case, as with many early metathesis reactions, Schrock's tetracoordinated alkylidene molybdenum catalyst **1.15** was used (Figure 1.4). Since then, numerous natural products have been furnished using macrocyclic RCM, allowing for the development of a greater understanding of reaction conditions that encourage successful macrocyclization. One challenging factor that should be noted is the *E* to *Z* selectivity of the product. At the time of this work, the result was typically unpredictable and could be influenced by the selection of catalyst or identity of remote substituents. At this point, chiral ligands on metathesis catalysts have achieved enantioselectivity in applicable substrates,[23] but no known resolution to control of olefin geometry has been reported.

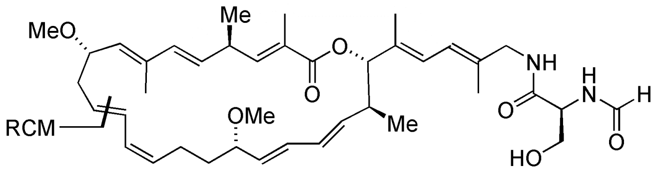
More recently, the application of RCM to close unsaturated and large rings was exemplified by the synthesis of amphidinolides A[24] and E[25] (**1.21** *according to an incorrect original structural assignment and **1.22**, respectively, Figure 1.5). Even more impressive is the application of RCM to complete highly unsaturated iejimalide B (**1.23**),[26] where possible competing reactions with other unsaturated sites are of obvious concern. Inspired by this work, we sought to further demonstrate the use of RCM to close highly unsaturated macrocycles through its application to a total synthesis of archazolid B (**1.8**).

Figure 1.5. Demonstration of RCM in highly unsaturated macrolides



1.21: Amphidinolide A*

1.22: Amphidinolide E

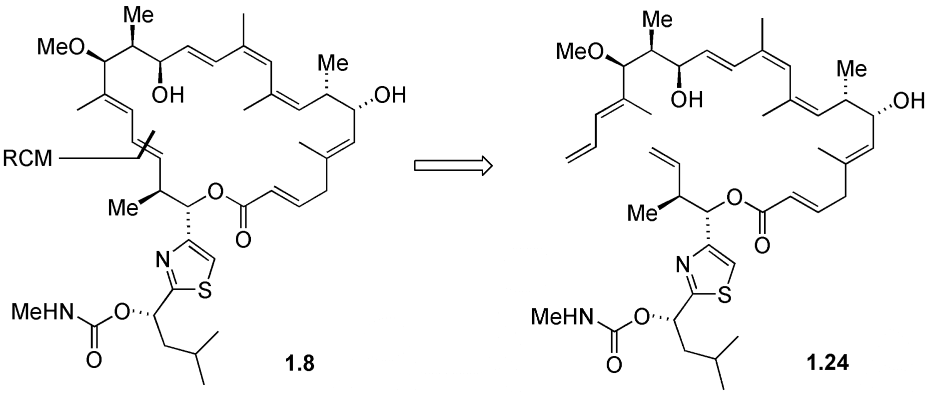


1.23: Iejimlalide B

Section 1.4. Retrosynthetic analysis

In order to close the ring of archazolid B (**1.8**) using RCM, we chose the retrosynthetic disconnection at the disubstituted *E*-olefin (Figure 1.6), tracing it back to the linear precursor **1.24**. The presence of no less than eight double bonds in this substrate presents obvious risks although fortunately, many of the olefins can be differentiated by their substitution.

Figure 1.6. Ring closure via a RCM strategy

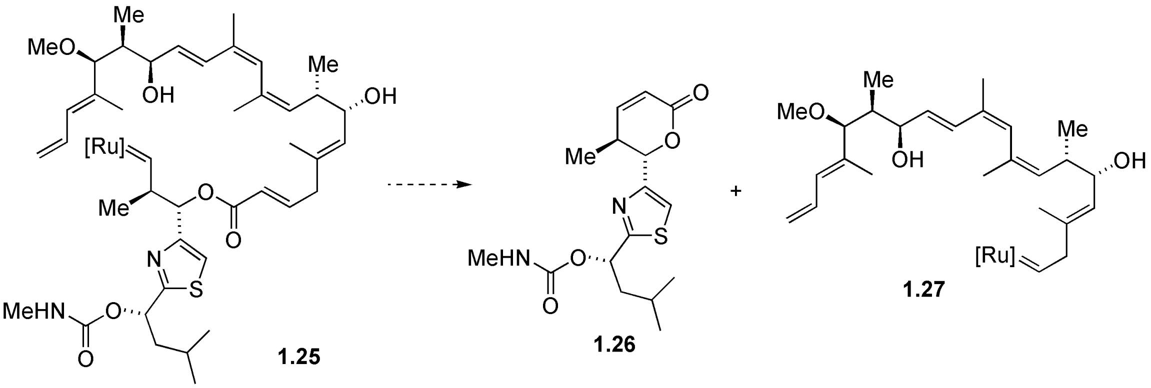


1.8

1.24

We expected metathesis to initiate at one of the terminal olefins but had doubts that it would be selective toward the more electon rich diene. If metathesis initiated at the other terminal olefin, we were concerned that the resulting ruthenium alkylidene **1.25** would further react, leading to an undesirable excision of γ-lactone **1.26** (Scheme 1.2).

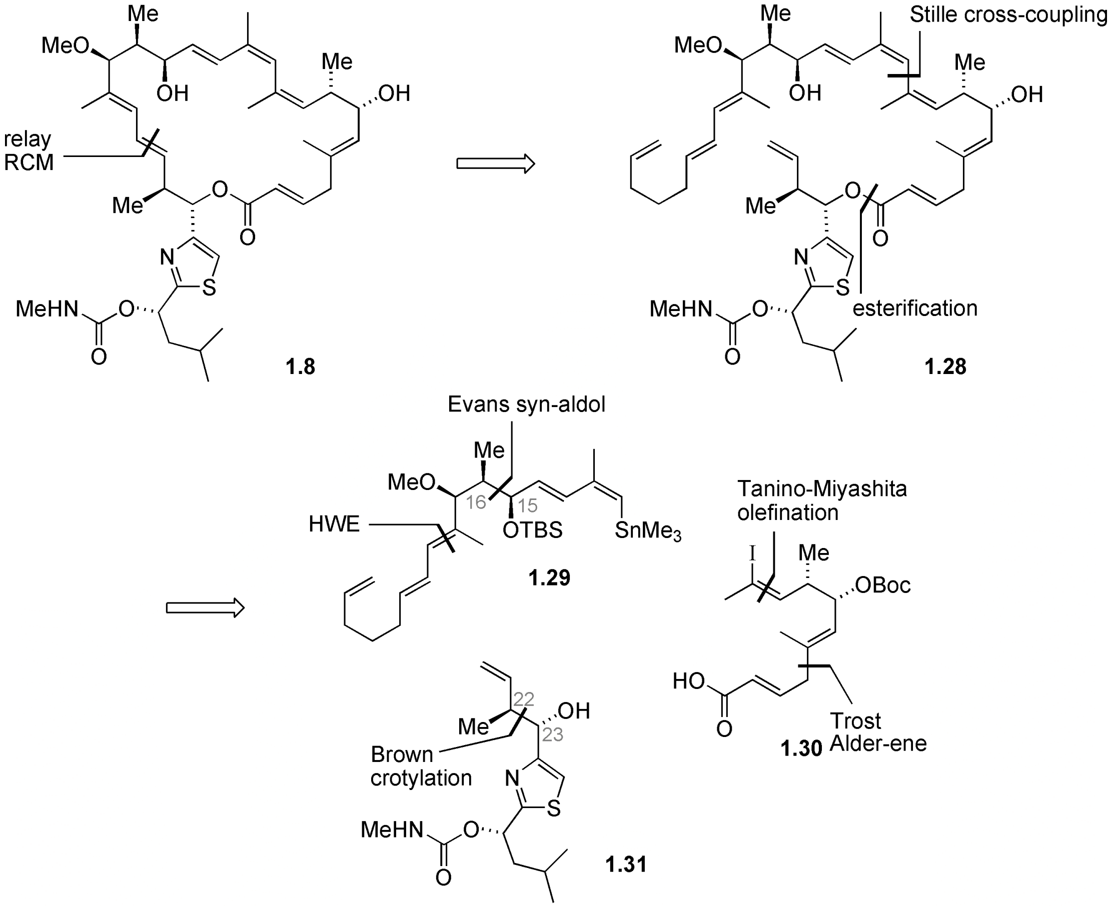
Scheme 1.2. A potential undesirable side reaction from RCM



Therefore, we turned to a relay strategy, where the tether of **1.28** would promote the desired initiation at the least sterically hindered terminal alkene, liberate cyclopentene, and react with the remaining terminal double bond (Scheme 1.3).[27] This strategy was not precedent for the construction of naturally occurring macrocycles and could demonstrate new horizons for RCM, particularly when the selectivity of initiation site can affect the outcome of the reaction.

Further retrosynthetic considerations included the introduction of the *E, Z, Z*-triene using a Stille cross coupling at a late stage due to its propensity to (cyclo)isomerize. Esterification of the lactone is an obvious disconnection, revealing three linear precursors: stannane **1.29**, iodide **1.30,** and thiazole **1.31** corresponding to the northwestern, northeastern and southern regions of archazolid B (**1.8**), respectively. An Evans *syn* aldol could install the requisite C(15)-C(16) stereochemistry for **1.29**, and the tether can be introduced via a Horner-Wadsworth-Emmons (HWE) olefination. For **1.30**, the vinyl iodide moiety could arise from an olefination using the methodology of Tanino and Miyashita[28] and a Trost Alder-ene reaction, which is a method we have effectively utilized in our prior work, can produce the skipped diene.[29] Finally, preparation of **1.31** will employ a Brown crotylation to produce the *anti* stereochemical relationship between C(22) and C(23).[30]

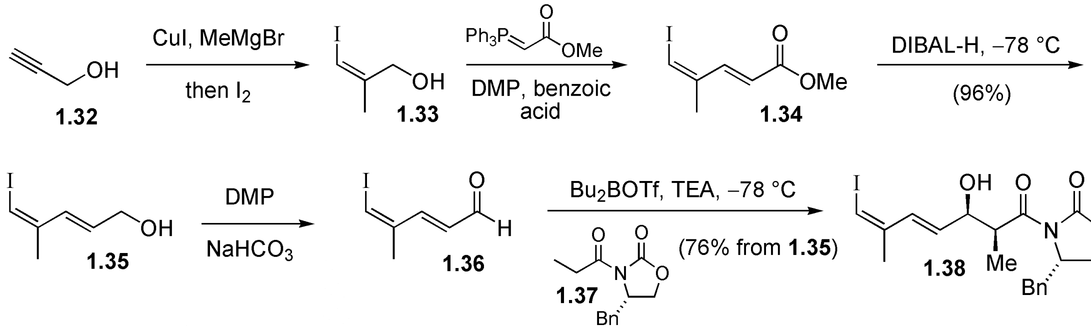
Scheme 1.3. Retrosynthetic strategy for archazolid B



Section 1.5. Synthesis of the northwestern fragment

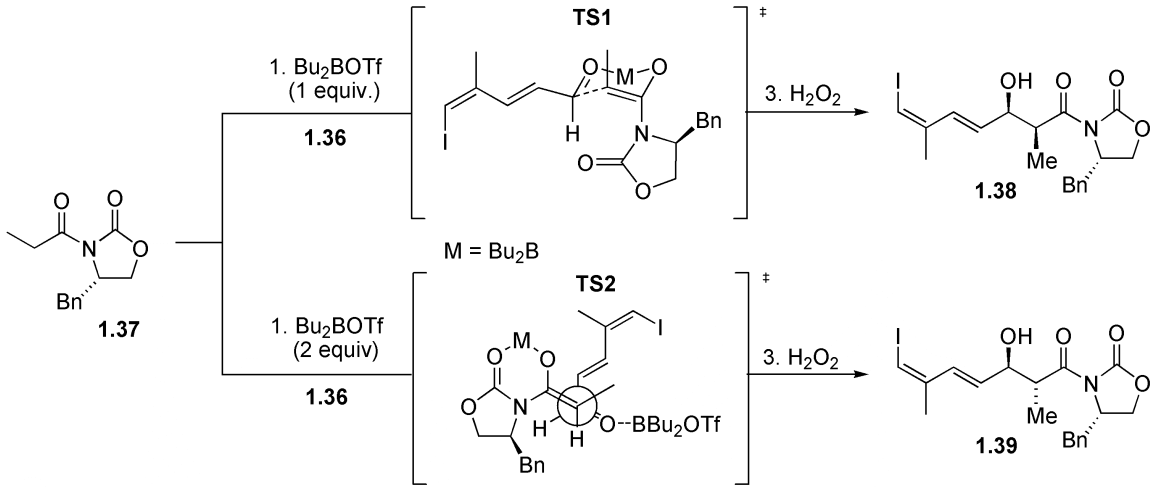
The synthesis of stannane **1.29** commenced with preparation of known (*Z*)-olefin **1.33** through a copper catalyzed carbo-metallation of propargyl alcohol **1.32** followed by an iodine quench to obtain (*Z*)-olefin **1.33** (Scheme 1.4). *In situ* oxidation and Wittig olefination then afforded the (*E*)-olefin of **1.34**[31] which, following oxidation state adjustment to aldehyde **1.36**, underwent an efficient Evans *syn* aldol reaction[32] with the (*Z*)-boron enolate of benzyl oxazolidinone **1.37** to furnish **1.38** as a single diastereomer.

Scheme 1.4. Preparation of Evans *syn* aldol product **1.38**



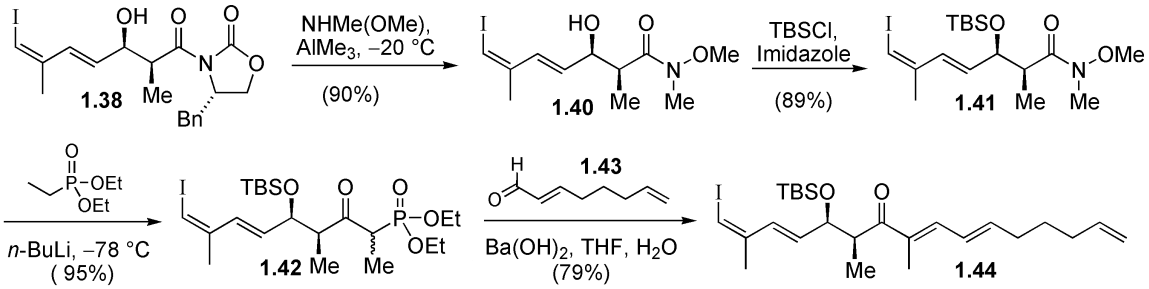
The reliability of the Zimmerman-Traxler model[33] for Evans' *syn* aldol transition states was verified during optimization of this reaction. Specifically, 1.10 equivalents of di-*n*-butylboron triflate (Bu_2BOTf) afforded **1.38** as a single diastereomer via a closed transition state (**TS1**), which is favored because the dipoles of the enolate and the carbonyl of the oxazolidinone are opposed and the benzyl moiety is pointed away from the cyclic transition state (Scheme 1.5). Greater amounts of Bu_2BOTf presumably led to an open transition state (**TS2**) to produce the *anti*-diastereomer **1.39**, which was separable from **1.38** by column chromatography.

Scheme 1.5. Effect of equivalents of Lewis acid on transition state of the Evans aldol reaction



Following the Evans *syn* aldol reaction, transamidation of **1.38** was achieved using *N,O*-dimethylhydroxylamine hydrochloride and trimethylaluminum to afford Weinreb amide **1.40** (Scheme 1.6). The secondary alcohol function within **1.40** was then protected as the *tert*-butyldimethylsilyl (TBS) ether to afford **1.41**, which was subsequently converted into an inconsequential mixture of β-keto phosphonates **1.42** through a phosphonate Claisen reaction.[34] Dienone **1.44** was produced from a barium hydroxide promoted Horner-Wadsworth-Emmons (HWE) reaction[35] with known enal **1.43**.[36]

Scheme 1.6. Preparation of dienone **1.44**



Under all other attempted conditions, both starting material **1.42** and product **1.44** suffered from unwanted elimination of TBS alkoxide to form **1.46**, as well as the unstable ene-one **1.45** (Scheme 1.7, Table 1.1).

Scheme 1.7. Observed base sensitivity of HWE reactant and product

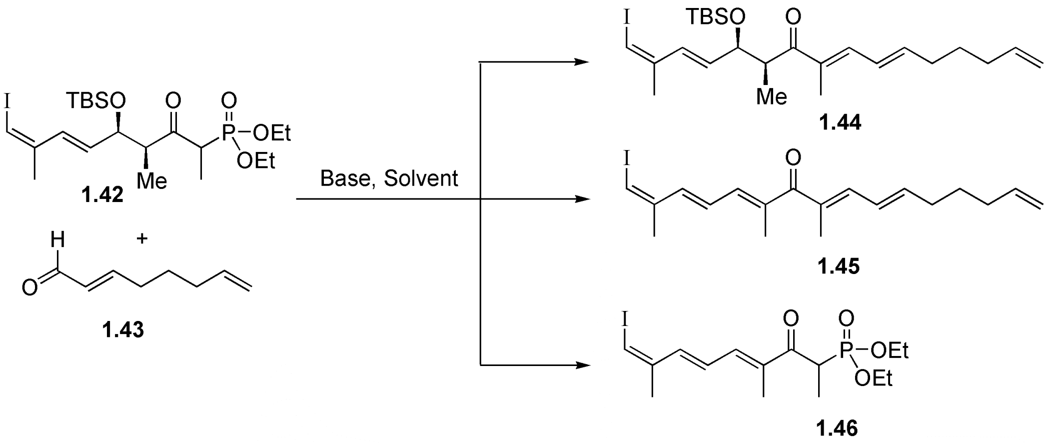
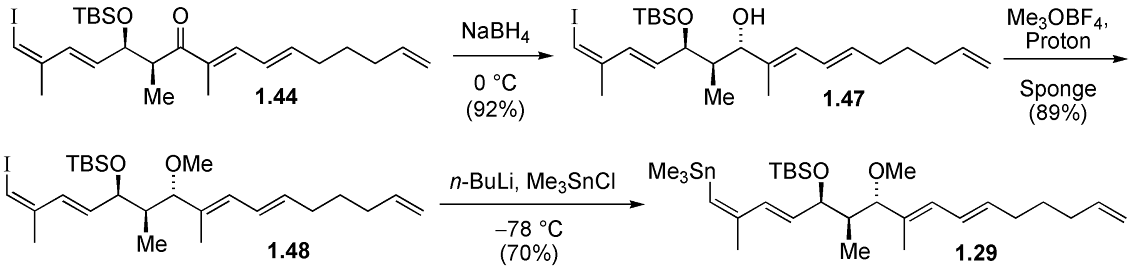


Table 1.1. Conditions explored for HWE reaction

Conditions	Major Product(s)
One-pot from X, −78 °C to rt	1.45, 1.46
LiCl, DBU, MeCN, rt	1.46
LiCl, DIEA, MeCN, rt	No Reaction
NaH, THF, 40 °C	Mixture of 1.44, 1.45, 1.46
Ba(OH)$_2$, THF/H$_2$O, rt	Exclusively 1.44 (79% yield)

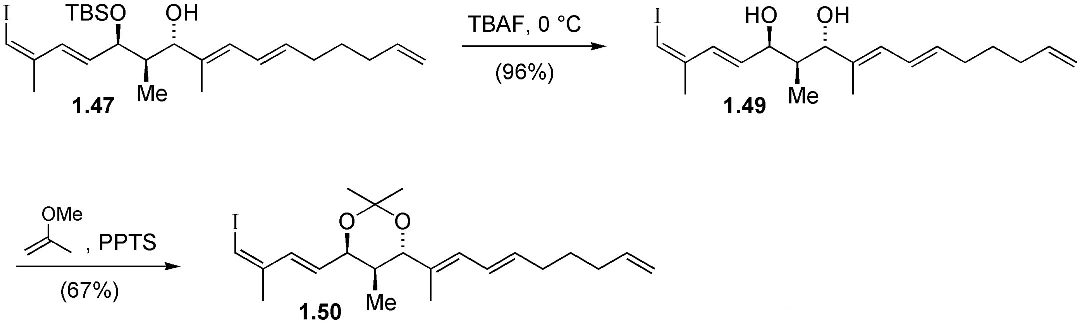
To our delight, a highly diastereoselective reduction of **1.44** was then achieved using sodium borohydride (NaBH$_4$) to produce **1.47** (Scheme 1.8). The resulting configuration was rationalized as the expected Felkin-Anh addition product where the carbon bearing the TBS-ether is designated as the larger substituent.

Scheme 1.8. Completion of stannane building block **1.29**



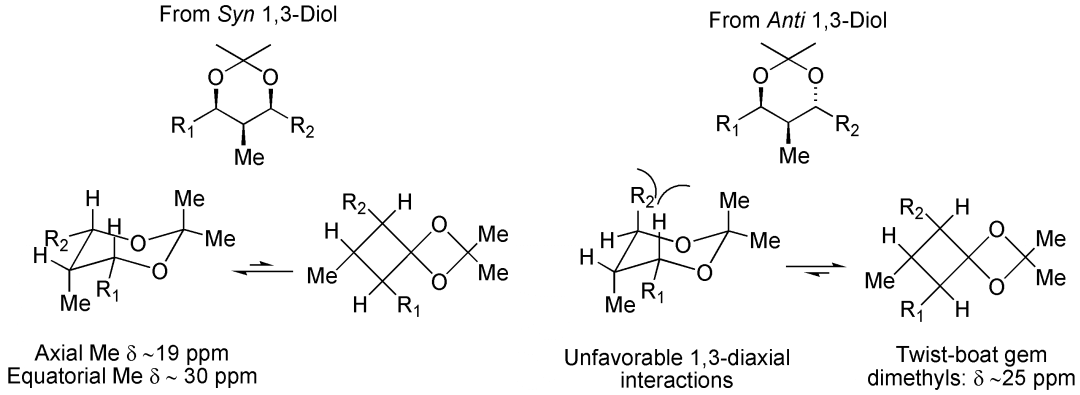
The relative stereochemistry of **1.47** was confirmed by analysis of the corresponding acetonide **1.50**, which was formed through tetrabutylammonium flouride (TBAF) deprotection of **1.47** to afford diol **1.49**, followed by reaction with 2-methoxypropene and catalytic pyridinium *p*-toluene-sulfonate (PPTS) (Scheme 1.9).

Scheme 1.9. Preparation of acetonide **1.50**



The relative acetonide stereochemistry of **1.50** was then determined through analysis of ^{13}C NMR shifts. Rychnovsky and coworkers have demonstrated that acetonides from 1,3-*syn* diols favor a chair conformation (the axial and equatorial methyl groups have chemical shifts of 19 and 30 ppm, respectively), whereas 1,3-diaxial interactions of the 1,3-*anti* acetonide favor a twist-boat conformation (chemical shifts of the gem-dimethyl carbons are ~ 25 ppm) (Scheme 1.10).[37] The ^{13}C NMR spectrum of acetonide **1.50** contains gem dimethyl peaks at δ = 25.3, 24.2 ppm, confirming the desired *anti* relationship corresponding to C(15) and C(17) of the natural product **1.8**.

Scheme 1.10. Conformational preferences of acetonides to dictated by relative stereochemistry of parent 1,3-diols

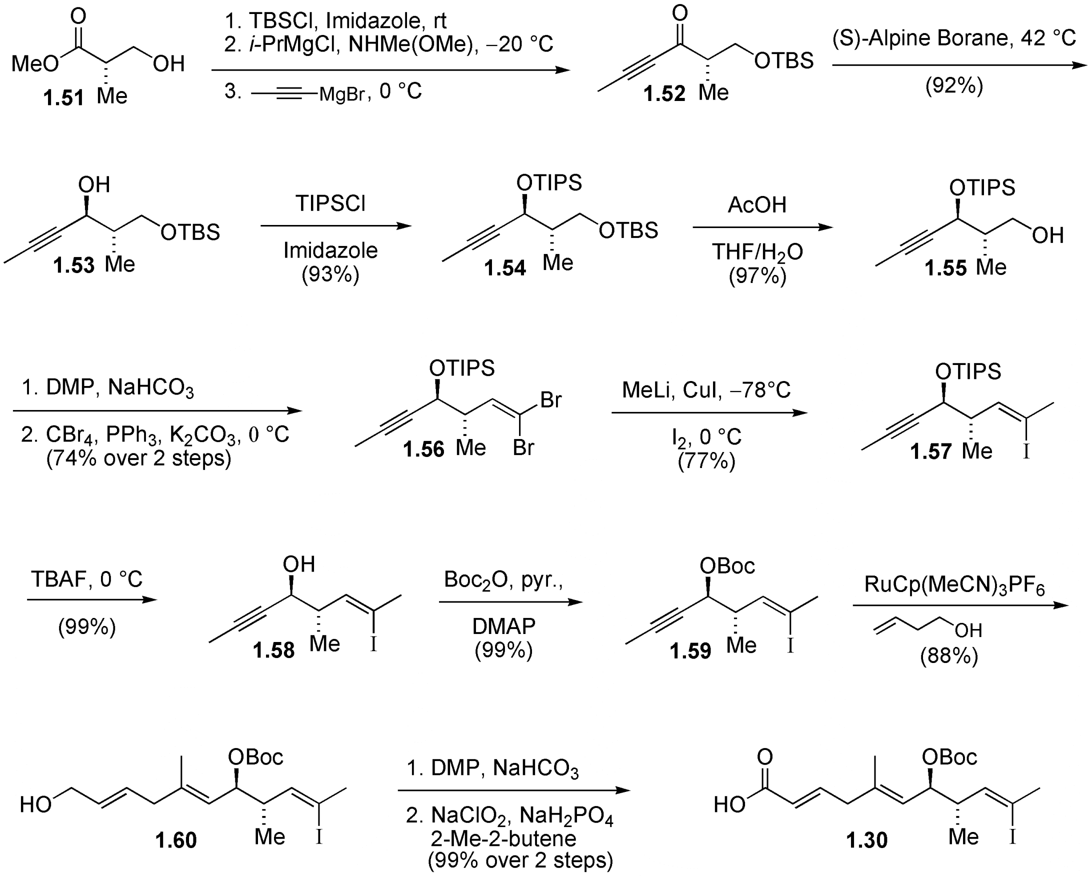


The hydroxy functionality of **1.47** was then methylated with trimethyloxonium tetrafluoroborate to produce **1.48** in 36% overall yield (9 steps) from known iododienoate **1.34**. Stannane **1.29** was prepared through lithium-halogen exchange of the vinyl iodide within substrate **1.48** followed by trapping with trimethyltin chloride. This reaction was highly sensitive and the best yields were obtained when a fresh bottle of *n*-BuLi was used.

Section 1.6. Synthesis of the northeastern fragment

Preparation of vinyl iodide **1.30** commences with a three-step conversion of (*S*)-Roche ester **1.51** into the known ynone **1.52**,[38] which was then diastereoselectively reduced using Midland's reduction conditions.[39] This reaction proceeds through reagent-induced diastereoselectivity using chiral (*S*)-alpine borane to produce **1.53**, and the resulting secondary alcohol was then protected as the triisopropylsilyl (TIPS) ether **1.54** and selectively desilylated to give primary alcohol **1.55** (Scheme 1.11). Oxidation with Dess-Martin periodinane (DMP), followed by Corey-Fuchs olefination afforded dibromoalkene **1.56**, to which (*Z*)-vinyl iodide **1.57** was installed using methodology of Tanino and Miyashita.[38] This utilizes the addition of an *in situ* generated Gilman reagent (Me_2CuLi) to dibromoalkene **1.56** followed by an iodine quench to afford **1.57** as the only observed regioisomer. By comparison, a Stork-Zhao olefination proceeded with inferior yield and stereoselectivity. The secondary silyl protecting group was then exchanged for a *tert*-butoxycarbonate (Boc) protecting group to give **1.59** in preparation for a Ru-catalyzed Trost Alder-ene reaction with 3-butenol. The presence of a coordinating carbonate protecting group enhanced regioselectivity during the formation of triene **1.60**. Additionally, the protecting group swap from TIPS to Boc also proved to be necessary, since installation of the vinyl iodide could not be achieved with a Boc-protected derivative of **1.56**. A DMP-mediated oxidation of **1.60**, followed by Pinnick oxidation[40] afforded the desired building block **1.30**.

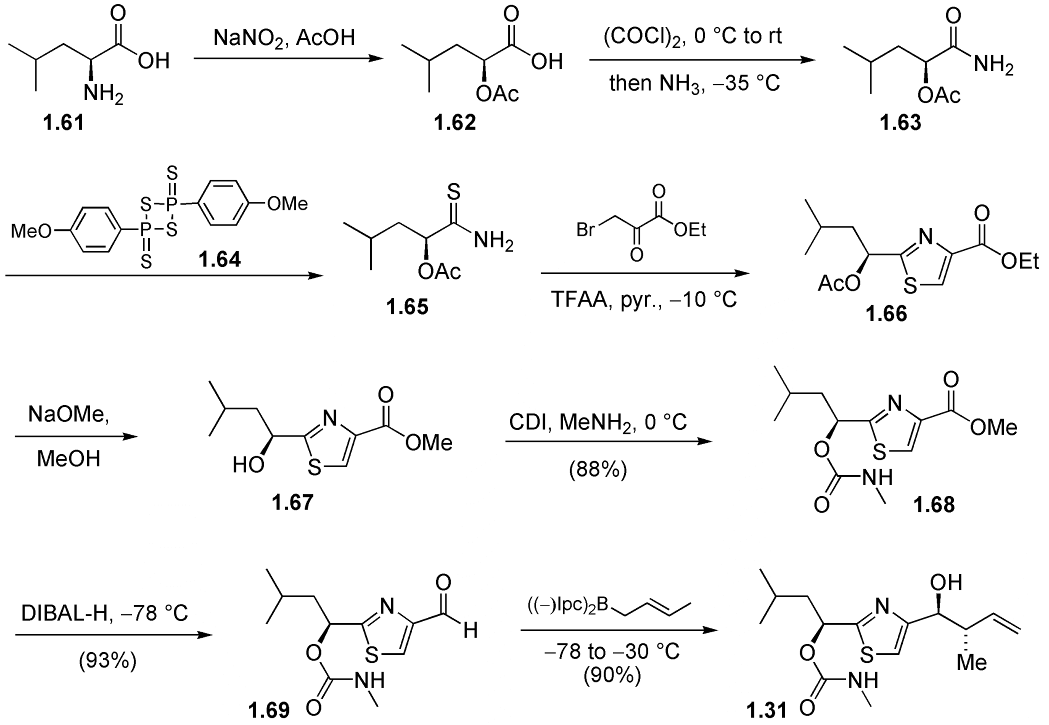
Scheme 1.11. Construction of vinyl iodide **1.30**



Section 1.7. Synthesis of the southern building block

Preparation of thiazole **1.31** entailed the elaboration of known hydoxyalkyl thiazolecarboxylate **1.67**, which is available from leucine (**1.61**) in 6 steps (Scheme 1.12).[41] Specifically, diazotination of **1.61** provided acetate **1.62** via double-inversion, which was converted to the corresponding acid chloride. An *in situ* quench with ammonia produced amide **1.63**, which was treated with Lawesson's reagent (**1.64**) to provide thioamide **1.65**. A Hantzsch reaction provided the thiazole **1.66** via condensation, and the acetate was subsequently removed using sodium methoxide with concomitant transesterification, furnishing secondary alcohol **1.67**. Carbamoylation of **1.67** provided **1.68**, which was subjected to a chemoselective reduction to produce **1.69** followed by Brown crotylation[30] to afford the building block **1.31**.

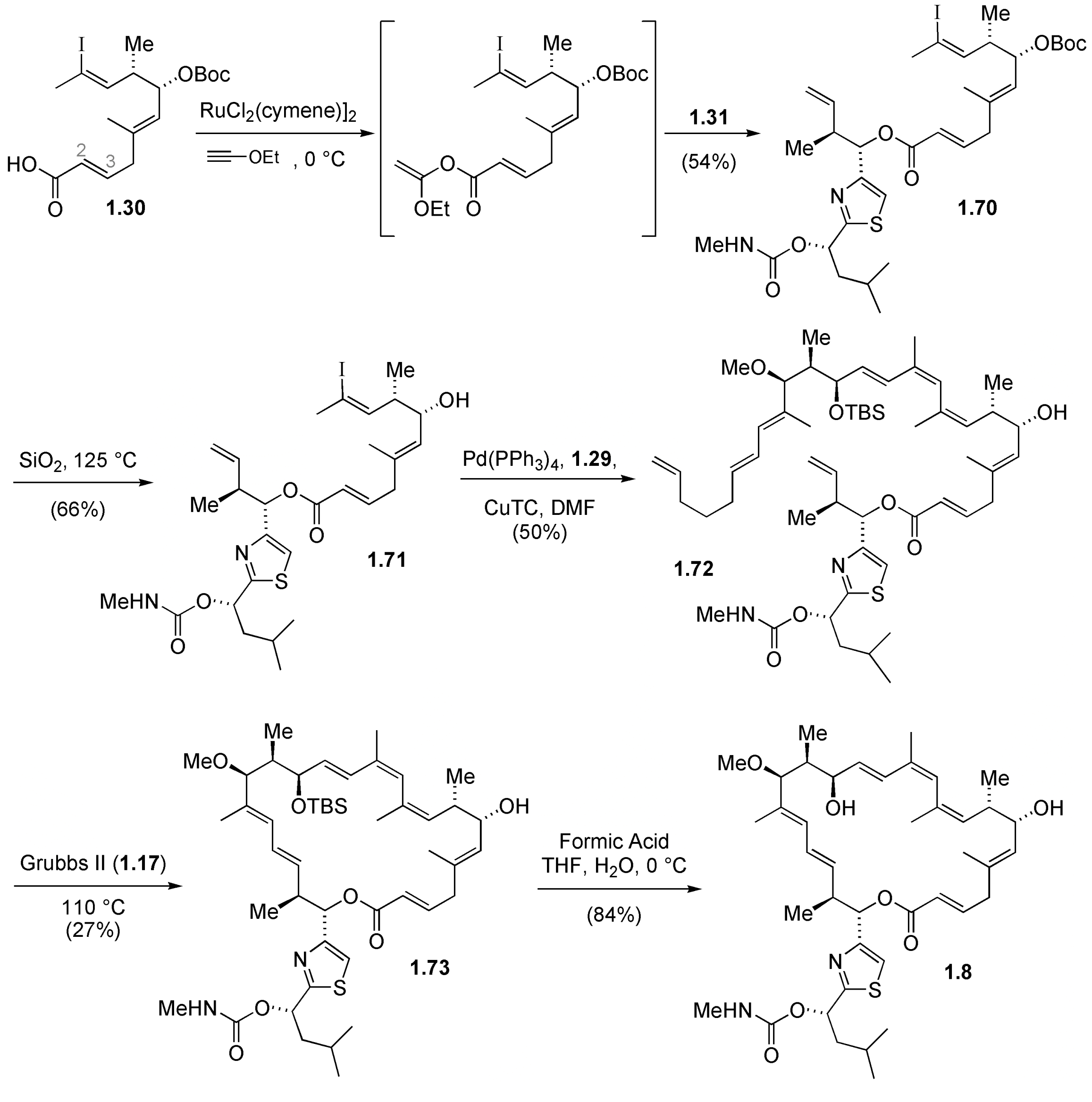
Scheme 1.12. Preparation of thiazole **1.31** from leucine (**1.61**)



Section 1.8. Endgame

Unison of the three building blocks commenced with activation of the acid of **1.30** followed by transesterification with the secondary alcohol of **1.31** to furnish **1.70** (Scheme 1.13). Initial attempts to perform the esterification under basic conditions led to migration of the C(2)-C(3) double bond out of conjugation with the ester. This problem was eventually averted by employing Ru-catalyzed activation of the acid, a method developed by Kita and coworkers.[42] Boc-deprotection using silica gel under thermal conditions then afforded **1.71**, which was coupled with stannane **1.29** under modified Liebeskind conditions to form **1.72**.[43] Comparatively, cross coupling with Boc-protected **1.70** proceeded with only 19% yield, and little to no reaction was observed with a TBS-deprotected derivative of **1.29** under any attempted conditions, suggesting that the free hydroxyl may have resulted in coordination with palladium, halting the catalytic cycle. The cross coupling also required both palladium and copper(I) in the form of copper thiophenecarboxylate (CuTC), as the reaction did not proceed with palladium alone, and addition of copper before palladium led to protodestannylation of **1.29** to form the terminal alkene.

Scheme 1.13. Completion of archazolid B (**1.8**)



Metathesis precursor **1.72** was then subjected to Grubbs' second generation catalyst **1.17** to provide the desired macrocycle **1.73** in 27% yield and finally, **1.73** was deprotected using aqueous formic acid to provide archazolid B as an off-white solid with spectra in good agreement with published data.[44] It is also interesting to note that macrocycle **1.73** was unreactive to HF·pyridine and aqueous hydrofluoric acid, and decomposed upon treatment with TBAF.

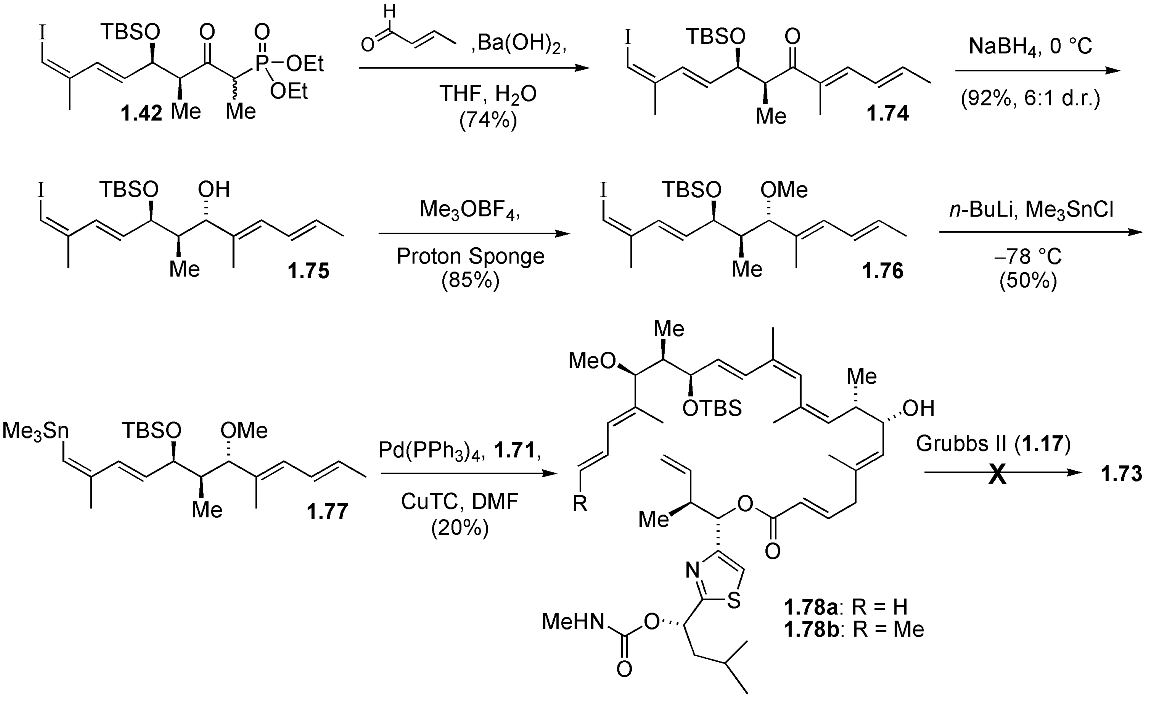
We were delighted that our bold strategy to close the ring via the relay RCM approach was effective. Numerous attempts were made to improve the yield, thus, it was found that similar yields were achieved using the Hoveyda-Grubbs' catalyst **1.18**, while no reaction was observed with Grubbs' first generation catalyst **1.16**. It has been shown that when using **1.16** for RCM, the presence of sulfur can inhibit the catalytic cycle but that the reaction may proceed using more active catalyst **1.17**.[18] It is therefore plausible that the sulfur atom of the thiazole formed a stable chelated intermediate with **1.16** that halted the catalytic cycle.

Importantly, this reaction was conducted under 'infinite dilution' conditions, which is a common practice for macrocyclization[45] and can also help to minimize commonly problematic RCM side-reactions such as ring-opening metathesis (ROM), ring-opening metathesis polymerization (ROMP), and acyclic diene metathesis polymerization (ADMET).[46] A high 20% catalyst loading was also employed in each case as these catalysts decompose at high temperatures. With concentration and a high catalyst loading kept as constant variables, a number of solvents, catalysts, and temperatures were also investigated but the yield could not be improved beyond 27%.

One concern was that the catalyst was still active when the reaction was complete and may have caused the desired product to undergo undesirable side reactions during concentration prior to chromatography. Thus, two methods to deactivate the catalyst were employed. Firstly, simple isocyanide $CN(CH_2)CO_2K$, as reported by Diver,[47] was prepared. This ligand is reported to quench the catalyst through insertion of the alkylidene into the mesityl group, hampering the catalyst from further activity. However, decomposition of our substrate was observed following its use. Dimethylsulfoxide (DMSO) may also be used for the same purpose[48] but did not improve the yield for this reaction.

Finally, we were also interested in verifying the necessity of the relay strategy by attempting RCM on the non-tethered substrate **1.78a** (Scheme 1.14). The requisite HWE reaction with **1.42** proved to be challenging due to the propensity of acrolein to effect polymerization and only 4% of the desired dienone could be isolated. We then changed our target to **1.78b**, in which all reactions proceeded similarly to that of the tethered substrate. As expected, RCM of **1.78b** did not lead to formation of the desired macrocycle. Although this does not prove that metathesis precursor **1.78a** would also be ineffective for ring closure, these studies indicated that our synthetic strategy renders **1.78a** less accessible than our tethered substrate **1.72** and furthermore, that its relay tether promotes the desired ring closure that cannot be effected by synthetically accessible **1.78b**.

Scheme 1.14. Demonstration of the necessity of the relay strategy



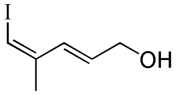
Section 1.9. Conclusion

The first total synthesis of (−)-archazolid B has been achieved in less than 40 total steps; the longest linear sequence starting from (*S*)-Roche ester (**1.51**) requires only 19 steps. The utility of transition metal catalysis has been demonstrated in several key steps. Additionally, relay ring closing metathesis (RRCM) has been implemented on an unprecedented level of functional complexity. The synthesized material has since incited an extensive collaboration with the research group of Professor Angelika Vollmar at Ludwig Maximilians Universität (Munich, Germany) to determine how these V-ATPase inhibitors selectively induce apoptosis in cancer cells.

Section 1.10. Experimental procedures

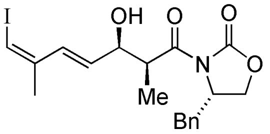
General Experimental Details: All reactions were carried out under an inert N_2 atmosphere in oven-dried glassware. Flash column chromatography was carried out with EcoChrom ICN SiliTech 32-63 D 60 Å silica gel. Reactions and chromatography fractions were monitored with Merck silica gel 60 F_{254} plates and visualized with potassium permanganate, ceric ammonium molybdate, and anisaldehyde. Tetrahydrofuran (THF), toluene ($PhCH_3$), diethyl ether (Et_2O), and methylene chloride (CH_2Cl_2) were dried by passage through activated alumina columns. *N*-Butyllithium (*n*BuLi) was titrated with diphenylacetic acid prior to use. All other reagents and solvents were used without further purification from commercial sources. Organic extracts were dried over $MgSO_4$ unless otherwise noted.

Instrumentation: FT-IR spectra were obtained on NaCl plates with an ATI Mattson Gemini spectrometer. Proton and carbon NMR spectra (^{1}H NMR and ^{13}C NMR) were recorded in deuterated chloroform ($CDCl_3$) on a Bruker DRX-500 spectrometer and calibrated to residual solvent peaks. Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet. Melting points were deteremined with an electrothermal apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 Polarimeter. High resolution mass spectra (HRMS) were obtained using the Micro-Mass Facility at the College of Chemistry, University of California Berkeley using electron impact (EI) at 70 eV or fast atom bombardment (FAB).



Alcohol 1.35. To a solution of **1.34** (16.8 g, 66.7 mmol) in CH_2Cl_2 (500 mL) at –78 °C was added diisobutylaluminum hydride (DIBAL-H) (1.5 M in $PhCH_3$, 161 mL, 241 mmol) via cannula. The reaction mixture was stirred at –78 °C for 15 min then diluted with CH_2Cl_2 (500 mL), and a 1 : 1 solution of saturated aqueous Rochelle's salt solution and H_2O (1200 mL total) was added. The biphasic mixture was vigorously stirred at rt for 2 h. The layers were separated, and the aqueous solution was extracted with Et_2O (1 x 200 mL). The organic materials were dried, filtered, and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography (25% EtOAc/Hexanes) to give 14.3 g (96%) of **1.35** as a yellow oil.

R_f 0.28, 25 % EtOAc/Hexanes. ^{1}H NMR (500 MHz): δ 6.61 (d, 1 H, J = 15.5 Hz), 6.32 (s, 1 H), 6.02 (dt, 1 H, J = 16.0, 5.5 Hz), 4.26 (dd, 1 H, J = 5.5, 1.0 Hz), 2.15 (s, 1 H), 1.95 (s, 3 H). ^{13}C NMR (125 MHz): δ 141.3, 133.4, 132.1, 79.8, 63.1, 21.2. IR: 3331, 3120, 2914, 2852, 1675, 1439, 1295, 1156, 1096, 1025, 1005, 966 cm^{-1}. HRMS (FAB+) calcd for C_6H_9IO (M^+) 223.9698, found 223.9697. Anal. Calcd for C_6H_9IO: C, 32.17; H, 4.05. Found: C, 32.34; H, 4.01.

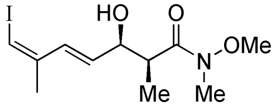


Evans syn aldol product 1.38. To a solution of **1.35** (14.4 g, 64.1 mmol) in CH_2Cl_2 (500 mL) was added $NaHCO_3$ (18.8 g, 224 mmol). The reaction mixture was cooled to 0 °C, and the apparatus was wrapped in aluminum foil. Dess-Martin periodinane (DMP) (27.57 g, 65 mmol) was added to the reaction mixture in one solid portion. After 20 min, a 1:1:1 solution of saturated $NaHCO_3$, saturated $Na_2S_2O_3$, and H_2O (600 mL total) was added to the reaction mixture. The resulting biphasic mixture was stirred vigorously for 30 min. The layers were separated, and the aqueous solution was extracted with Et_2O (1 x 200 mL). The organic materials were dried, filtered, and concentrated *in vacuo*. The crude material was filtered through a pad of silica to give 14.2 g (>99%) of an unstable aldehyde **26** as white solid, (note that product was generally taken on in crude form and that isomerization and polymerization were observed on exposure to light).

R_f 0.50, 25 % EtOAc/Hexanes. ^{1}H NMR (400MHz): δ 9.73 (d, 1 H, *J* = 7.6 Hz), 7.48 (d, 1 H, *J* = 15.6 Hz), 6.78 (s, 1 H), 6.29 (dd, 1 H, *J* = 15.6, 7.6 Hz), 2.03 (s, 3 H). ^{13}C NMR (100 MHz): δ 193.9, 152.1, 141.1, 132.1, 90.8, 21.0. IR: 3055.5, 2980, 2820, 2720, 1681, 1608, 1441, 1304, 1265, 1165, 1122, 970, 742, 705 cm^{-1}. HRMS (FAB+) calcd for C_6H_7IO (M^+) 221.9542, found 221.9537.

To a solution of **1.37** (5.92 g, 25.4 mmol) in CH_2Cl_2 (60 mL) at 0 °C was added freshly distilled dibutyl boron triflate (Bu_2BOTf) (6.73 mL, 26.9 mmol) dropwise, followed by Et_3N (4.70 mL, 34.0 mmol). The light orange solution was stirred at 0 °C for 40 min, then cooled to –78 °C and covered flask in foil to protect it from light. A solution of the crude aldehyde **1.36** (6.21 g, 29.0 mmol) in CH_2Cl_2 (15 mL) was added dropwise over 15 min. The reaction was stirred at –78 °C for 10 min, then a 1:3 solution of pH 7 phosphate buffer (20 mL) and MeOH (60 mL) was added. The mixture was warmed to 0 °C, stirred for 10 min. Then a 1:2 solution of 30 % H_2O_2 (25 mL) and MeOH (50 mL) was added. After 30 min, the mixture was warmed to rt and stirred for an additional 90 min. The solution was diluted with EtOAc (200 mL), washed with a saturated $NaHCO_3$ solution (2 x 200 mL), then brine (100 mL). The combined organic layers were dried, filtered, and concentrated *in vacuo*. The crude product was recrystallized from ether and hexanes (1:20). The condensed mother liquor was purified by flash column chromatography (25% EtOAc/Hexanes) to afford 8.12 g (70%) of **1.38** as a white crystalline solid, as a single diastereomer. (76% on 1.0 g scale)

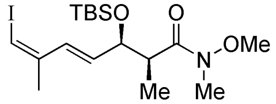
mp 92-93 °C. R_f 0.49, 5 % EtOAc/CH_2Cl_2. ^{1}H NMR (500 MHz): δ 7.32 (m, 1 H), 7.26 (m, 1 H), 7.19 (d, 1 H, *J* = 7.5 Hz), 6.65 (d, 1 H, *J* = 15.5 Hz), 6.14 (s, 1 H), 5.89 (dd, 1 H, *J* = 15.5, 6.0 Hz), 4.71 (m, 1 H), 4.60 (s, 1 H), 4.18 (m, 2 H), 3.93 (m, 1 H), 3.22 (dd, 1 H, *J* = 13.5, 3.0 Hz), 3.13 (s, 1 H), 2.79 (dd, 1 H, *J* = 12.5, 9.5 Hz), 2.07 (s, 3 H), 1.24 (d, 3 H, *J* = 7.0 Hz). ^{13}C NMR (125 MHz): δ 176.0, 153.2, 141.3, 135.1, 134.0, 132.6, 129.5, 128.9, 127.4, 80.3, 72.6, 66.3, 55.1, 42.9, 37.7, 21.2, 11.7. IR: 3691, 3054, 2987, 2685, 2305, 1782, 1551, 1422, 1263, 1157, 896, 750 cm^{-1}. $[\alpha]^{25}_D$ +38.0° (*c* = 1.00, $CHCl_3$). HRMS (FAB+) calcd for $C_{19}H_{22}INO_4Li$ [$(M + Li)^+$] 462.0754, found 462.0745. Anal. Calcd for $C_{19}H_{22}INO_4$: C, 50.12; H, 4.87; N, 3.08. Found: C, 50.28; H, 4.77; N, 3.00.



Weinreb amide 1.40. To a solution of N,O-dimethylhydroxylamine hydrochloride (6.87 g, 70.4 mmol) in THF (30 mL) at 0 °C was added a solution of trimethyl aluminum (Me_3Al) (2.0 M in toluene, 35.2 mL, 70.4 mmol) dropwise. Methane gas evolved. The reaction mixture was warmed to rt for 15 min, then cooled to –20 °C. A solution of **1.38** (8.02 g, 17.6 mmol) in THF (30 mL) was added. A white precipitate formed in the flask. The mixture was warmed to 0 °C and stirred for 1 h. A solution of

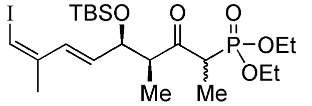
0.5 N HCl (100 mL) in CH_2Cl_2 (100 mL) at 0 ºC was added via cannula. Vigorous gas evolution was observed. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The combined organic layers were washed sequentially with a saturated $NaHCO_3$ solution (2 x 100 mL) and brine (50 mL). The combined organic materials were dried, filtered, and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography (50% EtOAc/Hexanes) to give 4.80 g (80%) of **1.40** as a light yellow solid. (91% on 300 mg scale).

mp 70-71 °C. R_f 0.42, 55 % EtOAc/Hexanes. ^1H NMR (500 MHz): δ 6.67 (d, 1 H, *J* = 15.5 Hz), 6.14 (s, 1 H), 5.88 (dd, 1 H, *J* = 15.5, 5.5 Hz), 4.56 (s, 1 H), 3.94 (s, 1 H), 3.66 (s, 3 H), 3.20 (s, 3 H), 3.00 (br s, 1 H), 1.95 (s, 3 H), 1.18 (d, 3 H, *J* = 7.0 Hz). ^{13}C NMR (125 MHz): δ 177.4, 141.3, 134.1, 132.4, 79.7, 72.2, 61.6, 39.6, 31.9, 21.1, 10.8. IR: 3451, 3054, 2984, 2940, 2305, 1658, 1641, 1631, 1422, 1390, 1265, 1179, 1158, 995, 969, 896, 822, 738 cm^{-1}. $[\alpha]^{25}_D$ –1.4° (*c* = 1.00, $CHCl_3$). HRMS (FAB+) calcd for $C_{11}H_{19}INO_3$ $[(M + H)^+]$ 340.0410, found 340.0420. Anal. Calcd for $C_{11}H_{18}INO_3$: C, 38.95; H, 5.35; N, 4.13. Found: C, 39.06; H, 5.40; N, 4.01.



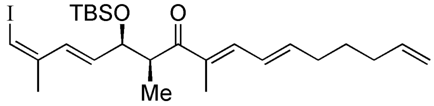
TBS Weinreb amide 1.41. To a solution of **1.40** (4.70 g, 13.9 mmol) in CH_2Cl_2 (70 mL) was added imidazole (2.08 g, 30.5 mmol) followed by *tert*-butyldimethylsilyl chloride (TBSCl) (4.18 g, 27.7 mmol). The reaction mixture was stirred at rt for 16h. It was then diluted with Et_2O (50 mL). The organic materials were washed with a saturated $NaHCO_3$ solution (2 x 40 mL) and brine (30 mL). The organic materials were then dried, filtered, and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography (12 % EtOAc/Hexanes) to give 5.58 g (89%) of **1.41** as a yellow oil.

R_f 0.48, 25 % EtOAc/Hexanes. ^1H NMR (500 MHz): δ 6.55 (d, 1 H, *J* = 16.0 Hz), 6.08 (s, 1 H), 5.91 (dd, 1 H, *J* = 15.5, 6.0 Hz), 4.36 (t, 1 H, *J* = 7.0 Hz), 3.77 (s, 3 H), 3.13 (s, 3 H), 3.04 (br s, 1 H), 1.90 (s, 3 H), 1.19 (d, 3 H, *J* = 7.0 Hz), 0.92 (s, 9 H), 0.20 (s, 3 H), 0.15 (s, 3 H). ^{13}C NMR (125 MHz): δ 175.5, 141.4, 136.3, 131.4, 79.0, 74.6, 61.5, 43.1, 32.1, 25.9, 21.2, 18.1, 14.4, –4.0, –4.9. IR: 3054, 2958, 2932, 2896, 2857, 2306, 1653, 1472, 1463, 1421, 1387, 1264, 1158, 1129, 1066, 1019, 995, 895, 838, 740 cm^{-1}. $[\alpha]^{25}_D$ –1.2° (*c* = 1.00, $CHCl_3$). HRMS (FAB+) calcd for $C_{17}H_{32}INO_3Si$ (M^+) 453.1196, found 453.1193. Anal. Calcd for $C_{17}H_{32}INO_3Si$: C, 45.03; H, 7.11; N, 3.09. Found: C, 44.73; H, 7.22; N, 3.08.



β-keto phosphonate 1.42. To a solution of diethylethylphosphonate (1.56 mL, 9.70) mmol) in THF (20 mL) at –78 °C was added *n*BuLi (2.50 M in hexanes, 3.57 mL, 8.92 mmol) dropwise. The reaction was stirred for 15 min and then a solution of **1.41** (1.76 g, 3.88 mmol) in THF (20 mL) was added dropwise. The dark yellow solution was stirred at –78 °C for 15 min, and then a saturated NH_4Cl solution (20 mL) was added. The mixture was warmed to rt and diluted with H_2O (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic materials were dried, filtered, and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography (25 % to 50% EtOAc/Hexanes) to afford 2.05 g (95%) of **1.42** as a yellow oil and mixture of diastereomers of stereocenter alpha to phosphonate ester.

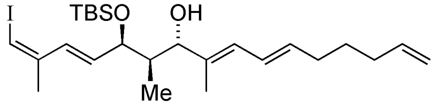
R_f 0.42, 65 % EtOAc/Hexanes. ^{1}H NMR (500 MHz) of major diastereomer: δ 6.47 (d, 1 H, *J* = 15.5 Hz), 6.12 (s, 1 H), 5.73 (dd, 1H, *J* = 15.5, 7.0 Hz), 4.25 (t, 1 H, *J* = 6.0 Hz), 4.10 (m, 4 H), 3.58 (m, 1 H), 3.38 (m, 1 H), 1.91 (s, 3 H), 1.28 (m, 10 H), 1.04 (d, 2 H, *J* = 7.0 Hz), 0.88 (s, 9 H), 0.02 (d, 6 H, *J* = 16.5 Hz). ^{13}C NMR (125 MHz), major diastereomer: δ 208.1, 141.1, 133.7, 132.5, 79.8, 76.1, 62.3, 62.3, 53.6, 48.8, 47.8, 25.8, 25.7, 21.1, 18.1, 16.4, 13.1, 11.4, –3.92, –4.23. IR: 3054, 2986, 2958, 2686, 2356, 1305, 1710, 1422, 1266, 1158, 1053, 1025, 1025, 972, 896, 838, 703 cm^{-1}. $[\alpha]^{25}_D$ +42.1° (*c* = 1.00, $CHCl_3$) for 3:1 mixture of diastereomers. HRMS (FAB+) calcd for $C_{21}H_{40}IO_5PSiLi$ [(M + Li)$^+$] 565.1587, found 565.1576. Anal. Calcd for $C_{21}H_{40}IO_5PSi$: C, 45.16; H, 7.22. Found: C, 45.57; H, 7.47.



Dienone 1.44. Barium hydroxide ($Ba(OH)_2$) (6.59 g, 11.8 mmol) was dried *in vacuo* at 120 °C for 5 hours then cooled to rt and added to a solution of **1.42** (2.81 g, 5.03 mmol) in THF (35 mL). The light yellow suspension was stirred for 30 min. Then a solution of **1.43**[36] in wet THF (40:1 THF/ H_2O, 41 mL) was added. The bright orange solution was stirred for 12 h. A saturated $NaHCO_3$ solution (50 mL) was added, followed by Et_2O (100 mL). The organic materials were washed sequentially with a saturated $NaHCO_3$ solution (2 x 100 mL) and brine (50 mL). The organic materials were dried, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (2.5 % EtOAc/Hexanes) to afford 4.95 g (79 %) of **1.44** as yellow oil. Product should be used promptly upon purification due to its instability.

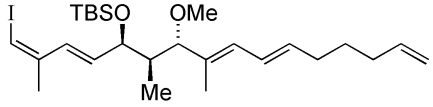
R_f 0.47, 10 % EtOAc/Hexanes. ^{1}H NMR (500 MHz): δ 6.99 (d, 1 H, *J* = 10.5 Hz), 6.51 (d, 1 H, *J* = 16.0 Hz), 6.41 (t, 1 H, *J* = 14.0 Hz), 6.12 (m, 1 H), 6.06 (s, 1 H), 5.80 (dd, 2 H, *J* = 15.5, 6.0 Hz), 5.02 (d, 1 H, *J* = 17.0 Hz), 4.97 (d, 1 H, *J* = 10.5 Hz), 4.35 (t, 1 H, *J* = 6.5 Hz), 3.40 (t, 1 H, *J* = 7.0 Hz), 2.22 (d, 1 H, *J* = 7.5 Hz), 2.08 (d, 1 H, *J* = 7.0 Hz), 1.84 (d, 6 H, *J* = 2.0 Hz), 1.55 (m, 2 H), 1.16 (d, 3 H, *J* = 6.5 Hz), 0.93 (s, 9 H), 0.07 (s, 3 H), 0.03 (s, 3 H). ^{13}C NMR (125 MHz): δ 204.2, 143.5, 141.4, 139.0, 138.2, 136.1, 134.5, 131.3, 126.9, 114.9, 79.0, 75.2, 46.7, 33.1, 32.7, 28.0, 25.9, 21.1, 18.1, 15.2, 11.7,

–4.0, –4.9. IR: 3054, 2986, 2957, 2931, 2857, 2685, 2360, 2306, 1654, 1631, 1472, 1422, 1362, 1265, 1158, 1127, 1026, 971, 896, 838, 739 cm^{-1}. $[\alpha]^{25}_{D}$ –28.3° (*c* = 1.00, $CHCl_3$).



Alcohol 1.47. To a solution of **1.44** (4.95 g, 9.36 mmol) in methanol (120 mL) at 0 °C was added sodium borohydride ($NaBH_4$) (2.12 g, 56.2 mmol). There was vigorous evolution of gas. The reaction was stirred at 0 °C for 20 min. Then a saturated NH_4Cl solution (50 mL) was added. The mixture was extracted with 2 x Et_2O (100 mL). The combined organic layers were washed with brine (75 mL). The organic layers was then dried, filtered, and concentrated *in vacuo*. The crude oil was purified by flash column chromatography (10 % EtOAc/Hexanes) to give 4.55 g (92 %) of **1.47** as a yellow oil with > 95 : 5 diastereoselectivity.

R_f 0.35, 10 % EtOAc/Hexanes. ^{1}H NMR (500 MHz): δ 6.58 (d, 1 H, *J* = 15.5 Hz), 6.24 (m, 1 H), 6.13 (s, 1 H), 5.93 (m, 2 H), 5.79 (m, 1 H), 5.65 (m, 1 H), 4.99 (d, 1 H, *J* = 17.5 Hz), 4.94 (d, 1 H, *J* = 10.0 Hz), 4.55 (s, 1 H), 3.89 (d, 1 H, *J* = 9.5 Hz), 3.56 (s, 1 H), 2.11 (m, 2 H), 2.05 (m, 2 H), 1.97 (s, 1 H), 1.90 (m, 1 H), 1.71 (s, 3 H), 1.48 (dt, 2 H, *J* = 15.0, 7.5 Hz), 0.95 (s, 9 H), 0.67 (d, 3H, *J* = 7.0 Hz), 0.12 (s, 3 H), 0.08 (s, 3 H). ^{13}C NMR (125 MHz): δ 141.3, 138.6, 135.8, 134.5, 134.3, 132.4, 127.7, 126.3, 114.5, 80.4, 79.3, 75.8, 41.6, 33.2, 32.3, 28.6, 25.9, 25.9, 21.3, 18.1, 12.2, 11.2, –4.1, –5.2. IR: 3459, 3053, 2955, 2930, 2857, 2360, 1767, 1640, 1471, 1462, 1441, 1362, 1297, 1265, 1157, 1074, 1039, 1005, 970, 914, 894, 838, 811, 778, 740, 705 cm^{-1}. $[\alpha]^{25}_{D}$ +0.41° (*c* = 1.00, $CHCl_3$).



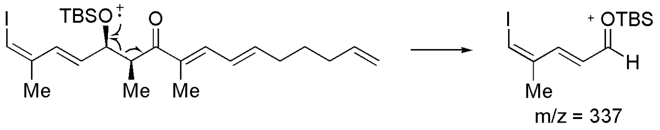
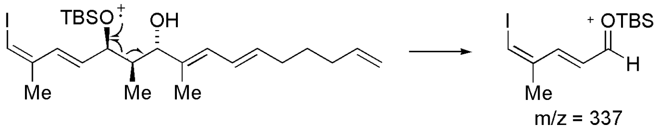
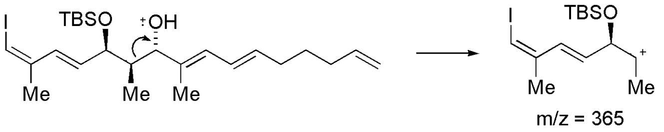
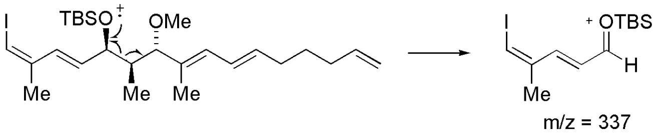
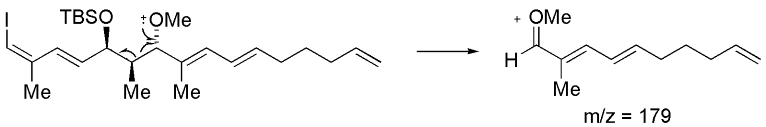
Methoxy ether 1.48. To a solution of **1.47** (4.70 g, 8.85 mmol) in CH_2Cl_2 (180 mL) was added proton sponge (7.59 g, 35.4 mmol) and trimethyloxonium tetrafluoroborate (Me_3OBF_4) (3.93 g, 26.6 mmol). The tan solution was stirred for 2 h and then ice cold H_2O (150 mL) was added. The combined organic layers were washed with a saturated $NaHCO_3$ solution (2 x 150 mL) and brine (100 mL). The aqueous layer was extracted 1 x Et_2O (100 mL). The combined organic layers were dried, filtered, and concentrated *in vacuo*. The crude oil was purified by flash column chromatography (2.5 % to 12 % EtOAc/Hexanes) to give 4.28 g (89 %) of **1.48** as a yellow oil.

R_f 0.55, 10 % EtOAc / Hexanes. ^{1}H NMR (500 MHz): δ 6.57 (d, 1 H, *J* = 16.0 Hz), 6.27 (m, 1 H), 6.06 (s, 1 H), 5.90 (m, 2 H), 5.81 (m, 1 H), 5.71 (dt, 1 H, *J* = 15.0, 7.5 Hz), 5.02 (d, 1 H, *J* = 17.5 Hz), 4.96 (d, 1 H, *J* = 10.5 Hz), 4.80 (d, 1 H, *J* = 5.5 Hz), 3.77 (d, 1 H, *J* = 10.0 Hz), 3.16 (s, 3 H), 2.14 (m, 2 H), 2.08 (m, 2 H), 1.94 (s, 3 H), 1.66 (m, 1 H), 1.62

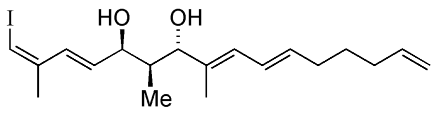
(s, 3 H), 1.52 (dt, 2 H, *J* = 15.0, 7.5 Hz), 0.98 (s, 9 H), 0.63 (d, 3 H, *J* = 7.0 Hz), 0.09 (s, 3 H), 0.05 (s, 3 H). ^{13}C NMR (125 MHz): δ 141.5, 138.5, 138.3, 134.5, 133.2, 131.8, 130.5, 129.9, 126.2, 114.7, 88.1, 78.1, 70.7, 55.6, 41.8, 33.3, 32.4, 28.7, 26.1, 21.3, 18.2, 10.6, 9.0, –3.6, –5.3. IR: 2928, 2856, 1461, 1440, 1383, 1251, 1131, 1085, 1093, 969, 912, 876, 838, 808, 775, 743 cm^{-1}. $[\alpha]^{25}_{D}$ –0.11° (*c* = 0.93, CHCl$_3$). Anal. Calcd for $C_{26}H_{45}IO_2Si$: C, 57.34; H, 8.33. Found: C, 57.36; H, 8.34.

Mass spectrometry of **1.44**, **1.47**, and **1.48** resulted in consistently predominant cleavage at m/z = 337 using both electrospray ionization (EI) and fast atom bombardment (FAB) methods. This resulted from cleavage of the single carbon-carbon bond at the TBS substituent; presumably, ionization is favored from the non-bonding orbital of oxygen in the TBS ether, and α-cleavage follows (Table 1.2). For this reason, high resolution mass spectra for these compounds were not reported.

Table 1.2. Analysis of Mass Spectrometry Fragmentation

Compound	Major Fragments Observed
1.44	
1.47	 
1.48	 

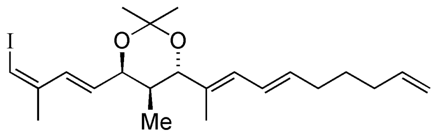
*Schemes commence with species ionized from oxygen nonbonding electrons



Diol 1.49. To a solution of **1.47** (120 mg, 0.226 mmol) in THF (3.5 mL) at 0 °C was added tetrabutylammonium fluoride (TBAF) (1.0 M in THF, 0.25 mL 0.25 mmol).

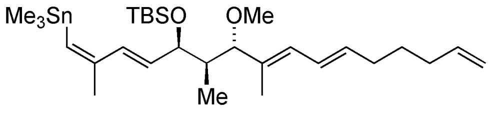
After 20 min, a saturated $NaHCO_3$ solution (2 mL) was added. The mixture was diluted with Et_2O (5 mL). The layers were separated. The combined organic layers were washed with brine (5 mL) then dried, filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography (65% Et_2O/Hexanes) to give 90.0 mg (96 %) of **1.49** as a yellow oil.

R_f 0.19, 25 % EtOAc/Hexanes. ^{1}H NMR (500 MHz): δ 6.63 (d, 1 H, *J* = 16.0 Hz), 6.25 (m, 1 H), 6.14 (s, 1 H), 5.98 (m, 2 H), 5.80 (m, 1 H), 5.70 (m, 1 H), 5.01 (d, 1 H, *J* = 17.0 Hz), 4.95 (d, 1 H, *J* = 10.5 Hz), 4.48 (s, 1 H), 4.01 (d, 1 H, *J* = 8.0 Hz), 3.25 (br s, 1 H), 2.45 (br s, 1 H), 2.07 (m, 2 H), 2.04 (m, 3 H), 2.00 (s, 3 H), 1.74 (s, 3 H), 1.50 (dt, 2 H, *J* = 15.0, 7.5 Hz), 0.80 (d, 3 H, *J* = 7.0 Hz). ^{13}C NMR (500 MHz): δ 141.3, 138.6, 135.4, 135.3, 134.7, 132.3, 127.5, 126.0, 114.6, 81.1, 79.4, 74.4, 40.1, 33.2, 32.3, 28.5, 21.3, 12.3, 11.8. IR: 3346, 3061, 2975, 2925, 2855, 1640, 1439, 1376, 1297, 1265, 1218, 1157, 1085, 1009, 966, 912, 756, 703, 686 cm^{-1}. $[\alpha]^{25}_{D}$ +0.59° (*c* = 1.0, $CHCl_3$). HRMS (FAB+) calcd for $C_{19}H_{29}IO_2$ [(M + Li^+)] 423.1372, found 423.1371.



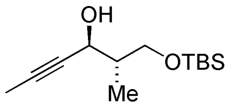
Acetonide 1.50. To a solution of **1.49** (28 mg, 0.067 mmol) in CH_2Cl_2 (0.8 mL) was added 2-methoxypropene (0.013 mL, 0.13 mmol) and pyridinium para-toluenesulfonate (PPTS) (< 0.5 mg). After 20 min, a saturated $NaHCO_3$ solution (2 mL) and CH_2Cl_2 (5 mL) were added. The layers were separated, and then the organic layer was washed 1 x brine (5 mL). The combined organic layers were dried, filtered, and concentrated *in vacuo*. The crude material was purified by flash column hromatography (10 % EtOAc/Hexanes) to give 21 mg (67%) of **1.50** as a yellow oil.

R_f 0.62, 25 % EtOAc/Hexanes. ^{1}H NMR (500 MHz): δ 6.59 (d, 1 H, *J* = 16.0 Hz), 6.25 (m, 1 H), 6.14 (s, 1 H), 6.02 (d, 1 H, *J* = 11.0 Hz), 5.87 (dd, 1 H, *J* = 15.5, 7.0 Hz), 5.71 (m, 1 H), 5.70 (m, 1 H), 5.01 (d, 1 H, *J* = 17.0 Hz), 4.95 (d, 1 H, *J* = 10.0 Hz), 4.58 (t, 1 H, *J* = 6.0 Hz), 3.76 (d, 1 H, *J* = 8.0 Hz), 2.12 (m, 2 H), 2.07 (m, 3 H), 1.97 (s, 3 H), 1.49 (m, 2H), 1.25 (s, 6 H), 0.82 (d, 3 H, *J* = 7.0). ^{13}C NMR (500 MHz): δ 141.4, 138.6, 135.1, 133.2, 132.5, 132.2, 127.4, 126.2, 114.6, 100.8, 80.5, 79.5, 71.0, 38.1, 33.2, 32.3, 28.5, 25.3, 24.2, 21.1, 12.6, 12.5. IR: 2984, 2926, 2854, 1640, 1455, 1439, 1378, 1338, 1313, 1221, 1173, 1159, 1122, 1088, 1070, 1014, 992, 967, 936, 910, 753, 675 cm^{-1}. $[\alpha]^{25}_{D}$ –0.77° (*c* = 1.0, $CHCl_3$). Anal. Calcd for $C_{22}H_{33}IO_2$: C, 57.90; H, 7.29. Found: C, 57.89; H, 7.58.



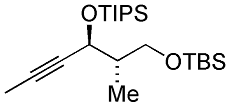
Stannane 1.29. To a solution of **1.48** (1.09 g, 2.00 mmol) in THF (13 mL) at –78 °C was added *n*BuLi (2.44 M in hexanes, 902 μL, 2.20 mmol) dropwise. After 20 min, a

solution of trimethyltin chloride (Me_3SnCl) (1.0 M in THF, 3.00 mL, 3.00 mmol) was added over 2 min. After 1.5 h at –78 ºC, the reaction was poured onto H_2O (20 mL) and Et_2O (10 mL). The layers were separated. The combined organic layers were dried, filtered, and concentrated *in vacuo* to give ~1.1 g of **1.29**. This material was taken on without further purification and not fully characterized due to extreme sensitivity.



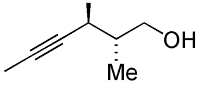
Propargylic alcohol 1.53. To neat **1.52** (16.2 g, 67.4 mmol) was added a solution of (*S*)-Alpine Borane (0.5 M in THF, 270 mL, 135 mmol). The solution was concentrated to make the reaction mixture approximately 1 M in THF. The reaction was stirred at 40 ºC for 42 h. The reaction was cooled to rt and propionaldehyde (10 mL) was added. After 30 min, the reaction was cooled to 0 ºC, diluted with Et_2O (135 mL) and a 3:2 mixture of 3 M NaOH and 30% aqueous H_2O_2 (70 mL) was added slowly. After stirring at rt for 18 h, the reaction mixture was poured onto a saturated K_2CO_3 solution (100 mL). The layers were separated, and the aqueous layer was extracted 1 x Et_2O (100 mL). The combined organic layers were dried, filtered, and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography twice (7-9% EtOAc/Hex) to give 14.5 g (89%) of **1.53** as a colorless oil.

R_f 0.42, 20% EtOAc/Hexanes. ^{1}H NMR (500 MHz): δ 4.35 (m, 1 H), 3.89 (dd, 1 H, *J* = 10, 4 Hz), 3.56 (dd, 1 H, *J* = 10, 6.5 Hz), 3.46 (br d, 1 H, *J* = 5 Hz), 1.88 (m, 1 H), 1.86 (s, 3 H), 0.99 (d, 3 H, *J* = 7 Hz), 0.90 (s, 9 H), 0.76 (s, 6 H). ^{13}C (125 MHz): δ 81.3, 79.2, 67.1, 66.9, 40.8, 25.7, 18.1, 13.0, 3.5, –5.6, –5.7. IR: 3417, 2956, 2929, 2858.



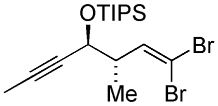
TIPS-TBS propargylic alcohol 1.54. To a solution of **1.53** (9.70 g, 40.0 mmol) in CH_2Cl_2 was added imidazole (3.27 g, 48.0 mmol), triisopropylsilyl chloride (9.42 mL, 44.0 mmol), and DMAP (49 mg, 0.40 mmol). After stirring at rt for 18 h, filtered through celite with CH_2Cl_2. The solution was concentrated *in vacuo*. The crude oil was purified by flash column chromatography (1% EtOAc/Hex) to give 14.8 g (93%) of **1.54** as a colorless oil.

R_f 0.48, 100% Hexanes. ^{1}H NMR (500 MHz): δ 4.64 (m, 1 H), 3.52 (m, 2 H), 1.94 (m, 1 H), 1.81 (m, 3 H), 1.11 (m, 21 H), 0.93 (d, 3 H, *J* = 7 Hz), 0.89 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H). ^{13}C (125 MHz): δ 80.8, 78.9, 65.0, 64.5, 43.2, 25.8, 18.2, 18.0, 12.3, 11.2, 3.4, –5.5, –5.6. IR: 2944, 2893, 2866, 1464, 1255 1084 cm^{-1}. $[\alpha]^{25}_D$ +3.1° (*c* = 0.97, $CHCl_3$). HRMS (EI+) calcd for $C_{21}H_{43}O_2Si_2$ [$(M - Me)^+$] 383.2802, found 383.2807.



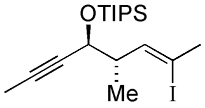
TIPS protected propargylic alcohol 1.55. A solution of **1.54** (11.3 g, 28.3 mmol) in 2:1:1 acetic acid/THF/H_2O (160 mL total) was stirred at rt 16 h. The reaction mixture was then poured onto H_2O (200 mL) and Et_2O (150 mL). The layers were separated. The combined organic layers were washed 2 x H_2O (200 mL) and 1 x saturated $NaHCO_3$ solution (200 mL) then dried, filtered, and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography (10% EtOAc/Hexanes) to give 7.77 g (97%) of **1.55** as a colorless oil.

R_f 0.31, 10% EtOAc/Hexanes. ^1H NMR (500 MHz): δ 4.49 (m, 1 H), 3.77 (dd, 1 H, J = 11, 4 Hz), 3.62 (dd, 1 H, J = 11, 7 Hz), 2.48 (br s, 1 H), 1.92 (m, 1 H), 1.82 (s, 3 H), 1.15 (m, 3 H), 1.10, (m, 18 H), 1.01 (d, 3 H, J = 7 Hz). ^{13}C (125 MHz): δ 81.7, 79.6, 67.4, 65.9, 42.4, 18.0, 13.0, 12.3, 3.4. IR: 3385, 2943, 2866, 1462 cm^{-1}. $[\alpha]^{25}_D$ –34.0° (c = 0.77, $CHCl_3$). HRMS (EI+) calcd for $C_{13}H_{25}O_2Si$ $[(M - C_3H_7)^+]$ 241.1624, found 241.1625.



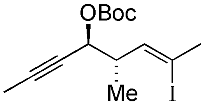
Vinyl dibromide 1.56. To a solution of **1.55** (10.2 g, 36.0 mmol) in CH_2Cl_2 (144 mL) was added $NaHCO_3$ (15.1 g, 180 mmol) followed by Dess-Martin periodinane (16.0 g, 37.8 mmol). After 20 min, a 1:1:1 solution of saturated $NaHCO_3$, saturated $Na_2S_2O_3$, and H_2O (150 mL total) was added. The resulting biphasic mixture was stirred vigorously for 30 min. The layers were separated, and the aqueous layer was extracted 1 x CH_2Cl_2 (75 mL). The combined organic layers were dried, filtered, and concentrated *in vacuo*. Meanwhile, to a solution of triphenyl phosphine (PPh_3) (49.1 g, 187 mmol) and potassium carbonate (K_2CO_3) (6.47 g, 46.8 mmol) in CH_2Cl_2 (187 mL) at 0 ºC was added tetrabromomethane (CBr_4) (31.0 g, 93.6 mmol) in CH_2Cl_2 (94 mL) via cannula over 30 min. After 40 min, the aldehyde in CH_2Cl_2 (36 mL) was added over 5-10 min. After 1 h, the reaction mixture was poured onto a saturated $NaHCO_3$ solution (200 mL). The layers were separated, and the aqueous layer was extracted 1 x CH_2Cl_2 (100 mL). The combined organic layers were dried, filtered, and concentrated *in vacuo*. A 1:1 solution of Et_2O and hexanes was added. The suspension was filtered and washed with Et_2O. The solution was concentrated and this was repeated three times. The resulting oil was purified by flash column chromatography (100 % Hexanes) to give 11.8 g (75%) of **1.56** as a colorless oil.

R_f 0.53, 100% Hexanes. ^1H NMR (500 MHz): δ 6.34 (d, 1 H, J = 9.5 Hz), 4.38 (m, 1 H), 2.71 (m, 1 H), 1.83 (s, 3 H), 1.51-1.07 (m, 24 H). ^{13}C (125 MHz): δ 140.4, 88.7, 81.5, 78.7, 65.1, 45.7, 18.0, 13.7, 12.2, 3.5. IR: 3423, 2943, 2866, 1463, 1095, 1066 cm^{-1}. $[\alpha]^{25}_D$ +38.5° (c = 1.11, $CHCl_3$). HRMS (EI+) calcd for $C_{14}H_{23}OSiBr_2$ $[(M - C_3H_7)^+]$ 396.9844, found 396.9845.



(*Z*)-Vinyl iodide 1.57. To a suspension of CuI (14.3 g, 75.0 mmol) in Et_2O (214 mL) at 0 ºC was added methyl lithium (MeLi) (1.60 M in Et_2O, 93.8 mL, 150 mmol) over 30 min via syringe pump. After 5 min, cooled to –78 ºC. A solution of **1.56** (11.0 g, 25.0 mmol) in Et_2O (100 mL) was added via syringe pump with the needle wrapped in dry ice over 1 h. After 30 min, I_2 (38.0 g, 150 mmol) in Et_2O (150 mL) was added via cannula over 20 min. The reaction mixture had difficulty stirring after addition of the I_2 solution. After 10 min, the reaction was warmed to 0 ºC upon which stirring resumed. The reaction was poured onto a saturated NH_4Cl solution (400 mL). The layers were separated, and the aqueous layer was extracted 1 x Et_2O (200 mL). The combined organic layers were dried, filtered, and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography (100% hexanes) to give 8.91 g (72%) of **1.57**. (77% on 2.7 g scale). The product was often contaminated with dimethyl adduct and/or vinyl bromide as noted by Tanino and Miyashita. Analytically pure material could be obtained by flash column chromatography with 6% by weight $AgNO_3$ on SiO_2 and eluted with 100% hexanes.

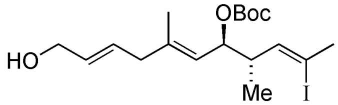
R_f 0.46, 100% Hexanes. ^{1}H NMR (500 MHz): δ 5.32 (dd, 1 H, *J* = 9, 1.5 Hz), 4.39 (m, 1 H), 2.61 (m, 1 H), 2.50 (s, 3 H), 1.83 (s, 3 H), 1.17-1.04 (m, 24 H). ^{13}C (125 MHz): δ 137.3, 100.5, 80.9, 79.2, 65.5, 48.7, 33.8, 18.0, 13.7, 12.3, 3.5. IR: 2943, 2891, 2866, 1462, 1085, 1065 cm^{-1}. $[\alpha]^{25}_D$ +80.0° (*c* = 1.03, $CHCl_3$). HRMS (EI+) calcd for $C_{15}H_{26}OSiI$ $[(M - C_3H_7)^+]$ 377.0798, found 377.0787.



Boc Ester 1.59. To a solution of **1.58** (7.50 g, 17.8 mmol) in THF (49 mL) at 0 ºC was added tetrabutylammonium fluoride (1.0 M in THF, 22.3 mL, 22.3 mmol) over 5 min. After 20 min at 0 ºC, the reaction was warmed to rt. Then after 15 min, the mixture was poured onto a saturated $NaHCO_3$ solution (75 mL). The layers were separated, and the aqueous layer was extracted 1 x Et_2O (50 mL). The combined organic layers were dried, filtered, and concentrated *in vacuo*. The resulting oil was dissolved in CH_2Cl_2 (59 mL) and pyridine (4.33 mL, 53.5 mmol), di-*tert*-butyl dicarbonate (Boc_2O) (8.55 g, 39.2 mmol), and DMAP (218 mg, 1.78 mmol) were added sequentially. After 1.5 h, the reaction mixture was poured onto 0.5 M citric acid solution (75 mL). The layers were separated, and the aqueous layer was extracted 1 x CH_2Cl_2 (50 mL). The combined organic layers were dried, filtered, and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography (3% EtOAc/Hexanes) to give 6.45 g (99%) of **1.59** as a colorless oil.

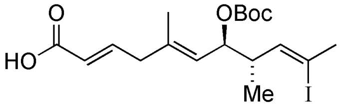
R_f 0.42, 5% EtOAc/Hexanes. ^{1}H NMR (500 MHz): δ 5.35 (dd, 1 H, *J* = 9, 1.5 Hz), 5.11 (m, 1 H), 2.78 (m, 1 H), 2.50 (s, 3 H), 1.86 (s, 3 H), 1.49 (s, 9 H), 1.11 (d, 3 H, *J* = 6.5

Hz). ^{13}C (125 MHz): δ 152.7, 135.6, 101.9, 83.3, 82.4, 74.8, 69.5, 46.0, 33.8, 27.7, 14.8, 3.7. IR: 2978, 1743, 1275, 1254 cm^{-1}. $[\alpha]^{25}_{D}$ +49.2° (c = 0.65, $CHCl_3$). HRMS (FAB+) calcd for $C_{14}H_{22}O_3I$ [$(M + H)^+$] 365.0614, found 365.0610.



Skipped diene 1.60. To a solution of **1.59** (1.00 g, 2.75 mmol) in acetone (5.5 mL) was added 3-buten-1-ol (709 μL, 8.24 mmol) followed by $RuCp(MeCN)_3PF_6$ (60 mg, 0.14 mmol). After 25 min, the reaction mixture was concentrated *in vacuo*. The resulting was purified by flash column chromatography (25% EtOAc/Hexanes) to give 1.05 g (88%) of **1.60** as a light yellow oil.

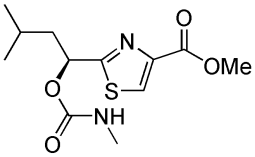
R_f 0.33, 25% EtOAc/Hexanes. ^1H NMR (500 MHz): δ 5.66 (m, 2 H), 5.33 (d, 1 H, J = 8 Hz), 5.29 (m, 1 H), 5.18 (m, 1 H), 4.09 (m, 2 H), 2.74 (m, 2 H), 2.61 (m, 1 H), 2.49 (s, 3 H), 1.72 (s, 3 H), 1.46 (s, 9 H), 0.97 (d, 3 H, J = 7 Hz). ^{13}C (125 MHz): δ 153.2, 139.7, 136.4, 131.1, 129.8, 122.6, 101.5, 81.7, 76.4, 63.5, 46.3, 42.1, 33.7, 27.8, 17.1, 15.6. IR: 3385, 2977, 2931, 2872, 1736, 1276, 1254, 1159 cm^{-1}. $[\alpha]^{25}_{D}$ +44.4° (c = 0.50, $CHCl_3$). HRMS (FAB+) calcd for $C_{18}H_{29}O_4ILi$ [$(M + Li)^+$] 443.1271, found 443.1272.



Acid 1.30. To a solution of **1.60** (2.32 g, 5.32 mmol) in CH_2Cl_2 (27 mL) was added $NaHCO_3$ (2.23 g, 26.6 mmol) followed by Dess-Martin periodinane (2.37 g, 5.58 mmol). After 20 min, a 1:1:1 solution of saturated $NaHCO_3$, saturated $Na_2S_2O_3$, and H_2O (30 mL total) was added. The resulting biphasic mixture was stirred vigorously for 30 min. The layers were separated, and the aqueous layer was extracted 1 x CH_2Cl_2 (25 mL). The combined organic layers were dried, filtered, and concentrated *in vacuo*. The resulting oil was dissolved in *t*BuOH (20.2 mL) and 2-methyl-2-butene (1.06 mL). To the solution was added a solution of $NaClO_2$ (80% purity, 5.41 g, 47.9 mmol) and NaH_2PO_4 in H_2O (21.3 mL). After 45 min, the yellow, biphasic reaction mixture was poured onto H_2O (30 mL) and Et_2O (60 mL). The mixture was acidified using a 1 M HCl solution (>5 mL). The layers were separated. The combined organic layers were dried, filtered, and concentrated *in vacuo*. This gave 2.38 g (99%) of **1.30** as a light yellow oil and was taken on without further purification.

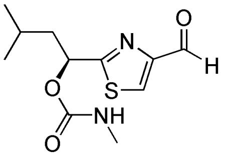
R_f 0.48, 40% EtOAc/Hexanes. ^1H NMR (500 MHz): δ 7.03 (dt, 1 H, J = 15.5, 7 Hz), 5.85 (d, 1 H, J = 15.5 Hz), 5.34 (d, 1 H, J = 9 Hz), 5.28 (m, 1 H), 5.24 (m, 1 H), 2.92 (d, 2 H, J = 7 Hz), 2.63 (m, 1 H), 2.49 (s, 3 H), 1.75 (s, 3 H), 1.48 (s, 9 H), 0.95 (d, 3 H, J = 7 Hz). ^{13}C (125 MHz): δ 171.2, 153.1, 148.7, 137.2, 136.0, 124.5, 122.1, 101.8, 81.9, 76.1, 46.1, 42.0, 33.7, 27.8, 17.3, 15.6. IR: 2977, 1736, 1698, 1276, 1254, 1157 cm^{-1}. $[\alpha]^{25}_{D}$ +46.5°

(*c* = 1.26, $CHCl_3$). HRMS (FAB+) calcd for $C_{18}H_{27}O_5ILi$ [$(M + Li)^+$] 457.1063, found 457.1069.



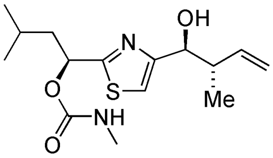
Thiazole methyl ester 1.68. To a solution of **1.67** (17.2 g, 75.0 mmol) in CH_2Cl_2 (150 mL) was added carbonyldiimidazole (CDI) (24.3 g, 150 mmol) in portions over 1.5 h. The reaction was cooled to 0 ºC and a solution of methylamine ($MeNH_2$) (2.0 M in THF, 46.9 mL, 93.8 mmol) was added. The reaction was warmed to rt and after 10 min a saturated $NaHCO_3$ solution (200 mL) was added. The layers were separated, and the aqueous layer was extracted 1 x CH_2Cl_2 (100 mL). The combined organic layers were dried, filtered, and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography (40-45% EtOAc/Hexanes) to give 16.9 g (79%) of **1.68** as a white solid. (88% on 2.3 g scale)

mp 77-79 ºC. R_f 0.45, 50% EtOAc/Hexanes. ^1H NMR (500 MHz): δ 8.11 (s, 1 H) 6.08 (m, 1 H), 4.89 (br s, 1 H) 3.92 (s, 3 H), 2.80 (d, 3 H, *J* = 4.5 Hz) 1.87 (m, 2 H), 1.74 (m, 1 H), 0.95 (d, 3 H, *J* = 6.5 Hz), 0.92 (d, 3 H, *J* = 6.5 Hz). ^{13}C (125 MHz): δ 172.7, 161.8, 155.8, 146.7, 127.5, 72.1, 52.4, 44.2, 27.6, 24.6, 23.1, 21.7. IR: 3358, 2957, 1724, 1533, 1244 cm^{-1}. $[\alpha]^{25}_D$ –36.7° (*c* = 1.01, $CHCl_3$). HRMS (EI+) calcd for $C_{12}H_{19}N_2O_4S$ [$(M + H)^+$] 287.1066, found 287.1076.



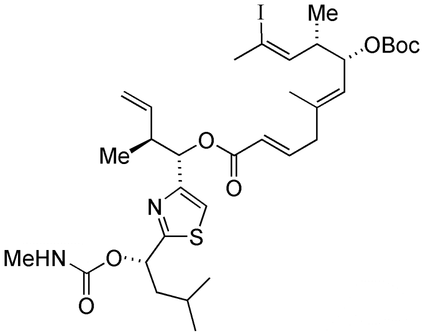
Thiazole Aldehyde 1.69. To a solution of **1.68** (9.70 g, 33.9 mmol) in THF (68 mL) at –78 ºC was added a solution of DIBAL-H (1.0 M in $PhCH_3$, 81.3 mL, 81.3 mmol) via cannula over 45 min. After 1.5 h, a ½ saturated Rochelle's salt solution (150 mL) was added. The reaction mixture was stirred vigorously for 2 h at rt. The layers were separated, and the aqueous layer was extracted 1 x Et_2O (100 mL). The combined organic layers were dried, filtered, and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography (40% EtOAc/Hexanes) to give 6.92 g (80%) of **1.69** as a white solid. (85% on 860 mg scale).

mp 57-59 ºC. R_f 0.47, 40% EtOAc/Hexanes. ^1H NMR (500 MHz): δ 10.0 (s, 1 H), 8.13 (s, 1 H), 6.07 (m, 1 H), 4.87 (br s, 1 H), 2.82 (d, 3 H, *J* = 5 Hz), 1.93 (m, 1 H), 1.86 (m, 1 H), 1.74 (m, 1 H), 0.99 (m, 6 H). ^{13}C (125 MHz): δ 184.7, 173.0, 155.8, 154.7, 127.4, 71.9, 44.1, 27.6, 24.5, 23.0, 21.8. IR: 3355, 2958, 1701, 1539, 1253, 1132 cm^{-1}. $[\alpha]^{25}_D$ –32.1° (*c* = 0.93, $CHCl_3$). HRMS (EI+) calcd for $C_{11}H_{17}N_2O_3S$ [$(M + H)^+$] 257.0960, found 257.0967.



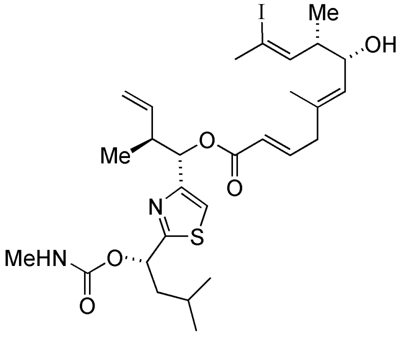
Crotylation Product 1.31. To a solution of trans-2-butene (condensed) in THF (26 mL) at –78 ºC was added a solution of KO*t*Bu (3.37 g, 30.0 mmol) in THF (30 mL) via cannula over 15 min. A solution of *n*BuLi (2.50 M in hexanes, 12.0 mL, 30.0 mmol) was then added dropwise to give a bright yellow solution. After warming to –45 ºC and stirring for 45 min, the mixture was cooled to –78 º C. A solution of (–)-MeOB(Ipc)$_2$ (10.3 g, 32.5 mmol) in THF (33 mL) was added over 5 min. The reaction mixture became clear upon this addition. After 1 h at –78 ºC, a solution of **1.69** (6.41 g, 25.0 mmol) in THF (25 mL) was added dropwise. The reaction was warmed to –30 ºC over 3 h. A 3:2 mixture of 3 M NaOH/30% aqueous H_2O_2 (50 mL total) was added slowly. The reaction mixture was stirred at rt 18 h. The layers were separated, and the aqueous layer was extracted 1 x Et_2O (150 mL). The combined organic layers were dried, filtered, and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography (40% EtOAc/Hexanes) to give 7.01 g (90%) of **1.31** as a clear, viscous oil.

R_f 0.36, 40% EtOAc/Hexanes. ^{1}H NMR (500 MHz): δ 7.07 (s, 1 H), 6.01 (m, 1 H), 5.76 (m, 1 H), 5.11 (s, 1 H), 5.09 (s, 1 H), 4.86 (br s, 1 H), 4.60 (d, 1 H, *J* = 6 Hz), 2.79 (d, 3 H, *J* = 5 Hz), 2.73 (m, 1 H), 2.63 (br s, 1 H), 1.88 (m, 1 H), 1.81 (m, 1 H), 1.68 (m, 1 H), 0.98 (d, 3 H, *J* = 6.5 Hz), 0.94 (m, 6 H). ^{13}C (125 MHz): δ 170.8, 158.0, 156.0, 139.5, 116.5, 114.2, 74.0, 72.0, 44.3, 44.1, 27.6, 24.5, 22.9, 22.0, 16.0. IR: 3346, 2959, 2871, 1709, 1527, 1258, 1131 cm^{-1}. $[\alpha]^{25}_D$ –79.6° (*c* = 2.00, $CHCl_3$). HRMS (EI+) calcd for $C_{15}H_{25}N_2O_3S$ [(M+H)+] 313.1586, found 313.1583.



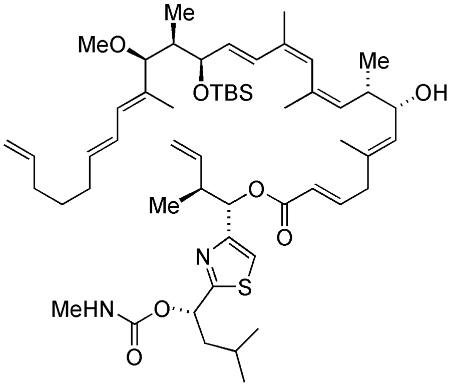
Boc-ester 1.70. To a solution a solution of **1.30** (2.00 g, 4.44 mmol) in $PhCH_3$ (22 mL) at 0 ºC was added $[RuCl_2(cymene)]_2$ (136 mg, 0.222 mmol) followed by ethoxyacetylene (50% w/w in hexanes, 2.60 mL, 13.3 mmol) dropwise. After 10 min, the reaction was warmed to rt. Then after 20 min, the mixture was filtered through a plug of SiO_2 (30% EtOAc/Hex). After concentration, the resulting oil was added via syringe pump in CH_2Cl_2 (6.3 mL) to a solution of **1.31** (1.80 g, 5.77 mmol) and dry *p*-toluenesulfonic acid (TsOH) (153 mg, 0.888 mmol) in CH_2Cl_2 (11.5 mL) over 3 h. After stirring at rt for 16 h, the mixture was concentrated *in vacuo*. The resulting oil was purified by flash column chromatography (25% EtOAc/Hexanes) to give 1.80 g (54%) of **1.70** as a yellow oil. All excess **1.31** could be recovered and reused.

R_f 0.48, 30 % EtOAc/Hexanes. ^{1}H NMR (500 MHz): 7.07 (s, 1 H), 6.92 (dt, 1 H, *J* = 15.5, 7 Hz), 6.03 (m, 1 H), 5.86 (m, 2 H), 5.73 (m, 1 H), 5.31 (d, 1 H, *J* = 8 Hz), 5.18 (m, 2 H), 4.99 (m, 2 H), 4.81 (br s, 1 H), 2.99 (m, 1 H), 2.87 (m, 2 H), 2.80 (d, 3 H, *J* = 5 Hz), 2.60 (m, 1 H), 2.46 (s, 3 H), 1.85 (m, 2 H), 1.83 (s, 3 H), 1.82 (m, 1 H), 1.47 (s, 9 H), 0.96 (m, 12 H). ^{13}C NMR (500 MHz): δ 171.2, 164.4, 155.9, 154.1, 153.1, 146.5, 139.0, 137.5, 136.0, 124.2, 122.6, 116.1, 115.7, 101.8, 81.8, 76.1, 75.0, 72.1, 46.1, 44.3, 42.0, 41.6, 33.7, 27.8, 27.6, 24.5, 23.0, 22.1, 17.2, 16.3, 15.5. IR: 3388, 2967, 2933, 1737, 1728, 1716, 1272, 1255, 1158 cm^{-1}. $[\alpha]^{25}_{D}$ –11.2° (*c* = 1.51, CHCl$_3$). HRMS (FAB+) calcd for $C_{33}H_{50}IO_7N_2S$ [(M + H)$^+$] 745.2384, found 745.2382.



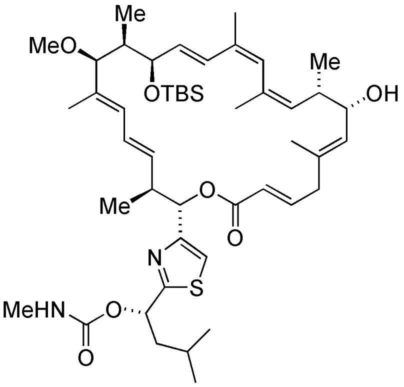
Vinyl iodide 1.71. To a solution of **1.70** (900 mg, 1.21 mmol) in Et$_2$O (25 mL) was added SiO$_2$ (14.5 g, 12 g/mmol of substrate). The slurry was concentrated *in vacuo*. The dry SiO$_2$ was heated under vacuum at 125 °C for 5 min. The SiO$_2$ was washed and filtered with Et$_2$O (~100 mL). The solution was concentrated *in vacuo*. The resulting oil was purified by flash column chromatography (40% EtOAc/Hexanes) to give 335 mg (43%) of **1.71** as a colorless oil. (66% on 60 mg scale)

R_f 0.37, 40 % EtOAc/Hexanes. ^{1}H NMR (500 MHz): 7.08 (s, 1 H), 6.91 (dt, 1 H, *J* = 15.5, 7 Hz), 6.05 (m, 1 H), 5.88 (m, 2 H), 5.75 (m, 1 H), 5.33 (d, 1 H, *J* = 9 Hz), 5.25 (d, 1 H, *J* = 9 Hz), 5.00 (m, 2 H), 4.78 (br s, 1 H), 4.26 (dd, 1 H, *J* = 9, 6.5 Hz), 3.01 (m, 1 H), 2.89 (d, 2 H, *J* = 7 Hz), 2.82 (d, 3 H, *J* = 5 Hz), 2.51 (s, 3 H), 2.48 (m, 1 H), 1.85 (m, 2 H), 1.72 (m, 1 H), 1.69 (s, 3 H), 0.95 (m, 12 H). ^{13}C NMR (500 MHz): δ 171.3, 165.5, 155.9, 154.1, 146.8, 139.1, 137.0, 135.9, 128.2, 122.6, 116.2, 115.7, 102.0, 75.0, 72.2, 71.4, 47.9, 44.4, 42.2, 41.6, 33.8, 27.6, 24.5, 23.0, 22.1, 17.0, 16.3, 15.5. IR: 3364, 2960, 2930, 2871, 1716, 1707, 1264 cm^{-1}. $[\alpha]^{25}_{D}$ –40.6° (*c* = 0.68, CHCl$_3$). HRMS (FAB+) calcd for $C_{28}H_{42}IO_5N_2S$ [(M + H)$^+$] 645.1859, found 645.1856.



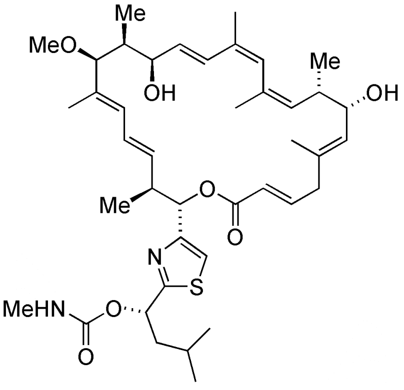
Linear RCM precursor 1.72. To a solution of **1.71** (300 mg, 0.465 mmol) and stannane **1.29** (338 mg, 0.582 mmol) in DMF (4.7 mL) was added tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) (54 mg, 0.047 mmol) and copper thiophenecarboxylate (CuTC) (133 mg, 0.698 mmol) simultaneously. After 30 min, a saturated $NaHCO_3$ solution (15 mL) and Et_2O (15 mL) added. The layers were separated, and the aqueous layer was extracted 1 x Et_2O (10 mL). The combined organic layers were dried, filtered, and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography (25% EtOAc/Hexanes) to give 130 mg (30%) of **1.72** as a yellow oil and 203 mg of **1.71** was recovered (92% based on recovered starting material). No conditions attempted saw complete consumption of **1.71** although a 50% yield could be afforded using 2.5 equivalents of stannane and 3.5 equivalents of CuTC.

R_f 0.69, 40 % EtOAc/Hexanes. ^{1}H NMR (500 MHz): 7.07 (s, 1 H), 6.91 (dt, 1 H, J = 15.5, 7 Hz), 6.41 (d, 1 H, J = 16 Hz), 6.27 (dd, 1 H, J = 15, 11 Hz), 5.90-5.66 (m, 8 H), 5.18 (d, 1 H, J = 9 Hz), 5.12 (d, 1 H, J = 10 Hz), 4.98 (m, 4 H), 4.78 (br d, 1 H, J = 4.5 Hz), 4.69 (d, 1 H, J = 6.5 Hz), 4.01 (t, 1 H, J = 8.5 Hz), 3.35 (d, 1 H, J = 10 Hz), 3.12 (s, 3 H), 3.00 (m, 1 H), 2.87 (m, 2 H), 2.80 (d, 3 H, J = 4.5 Hz), 2.36 (m, 1 H), 2.13 (m, 2 H), 2.07 (m, 2 H), 1.85 (m, 2 H), 1.84 (s, 6 H), 1.72 (m, 2 H), 1.69 (s, 3 H), 1.61 (m, 1 H), 1.60 (s, 3 H), 1.52 (m, 2 H), 0.99 (m, 9 H), 0.91 (s, 9 H), 0.83 (d, 3 H, J = 7 Hz), 0.63 (d, 3 H, J = 7 Hz), 0.03 (s, 3 H), –0.02 (s, 3 H). ^{13}C NMR (500 MHz): δ 171.2, 165.5, 155.9, 154.2, 147.0, 146.8, 139.0, 138.6, 135.8, 135.7, 135.6, 134.4, 134.3, 133.5, 133.4, 130.6, 129.8, 128.3, 128.0, 127.3, 126.0, 122.4, 122.1, 88.2, 75.0, 72.1, 72.0, 71.9, 71.4, 55.5, 44.4, 42.3, 41.7, 40.3, 33.3, 32.3, 28.5, 27.6, 25.9, 24.9, 24.5, 23.0, 22.1, 20.4, 18.2, 17.1, 16.3, 16.2, 10.5, 9.0, –4.0, –5.1. IR: 3363, 2957, 2928, 1723, 1711, 1255 cm^{-1}. $[\alpha]^{25}_D$ –31.2° (c = 0.92, $CHCl_3$). HRMS (FAB+) calcd for $C_{54}H_{87}O_7N_2SSi$ [$(M + H)^+$] 935.6003, found 935.6010.



TBS-Archazolid B 1.73. To a solution of **72** (57 mg, 0.061 mmol) in PhCH$_3$ (120 mL) at 110 ºC was added Grubbs' second generation catalyst (**1.17**) (2.6 mg, 3.0 x 10^{-3} mmol). Over the next 2 h, additional catalyst added each 30 min (3 x 5 mol%). The reaction was cooled to rt and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography (30% EtOAc/Hexanes) to give 14 mg (27%) of **1.73** as a yellow foam.

R$_f$ 0.69, 40 % EtOAc/Hexanes. ^{1}H NMR (500 MHz): 7.05 (s, 1 H), 6.82 (dt, 1 H, J = 15.5, 7.5 Hz), 6.37 (d, 1 H, J = 16 Hz), 6.06 (m, 2 H), 5.99 (d, 1 H, J = 5.5 Hz), 5.83 (m, 2 H), 5.72 (dd, 1 H, J = 16, 6.5 Hz), 5.63 (s, 1 H), 5.55 (m, 1 H), 5.23 (d, 1 H, J = 10 Hz), 5.09 (d, 1 H, J = 9.5 Hz), 4.76 (m, 1 H), 4.62 (br s, 1 H), 3.90 (t, 1 H, J = 9.5 Hz), 3.25 (d, 1 H, J = 9.5 Hz), 3.12 (m, 1 H), 3.09 (s, 3 H), 2.85 (m, 6 H), 2.20 (m, 1 H), 1.91 (m, 2 H), 1.88 (s, 3 H), 1.78 (s, 3 H), 1.73 (m, 2 H), 1.72 (s, 3 H), 1.62 (s, 3 H), 1.56 (m, 2 H), 1.08 (d, 3 H, J = 6.5 Hz), 0.97 (m, 6 H), 0.92 (s, 9 H), 0.84 (d, 3 H, J = 7 Hz), 0.64 (d, 3 H, J = 7 Hz), 0.03 (s, 3 H), –0.01 (s, 3 H). ^{13}C NMR (500 MHz): δ 171.2, 165.2, 155.9, 154.7, 147.0, 146.9, 136.0, 135.8, 134.8, 133.3, 132.7, 130.4, 128.9, 128.4, 128.1, 127.0, 126.2, 122.5, 115.6, 86.8, 76.0, 75.7, 72.6, 72.1, 55.7, 44.4, 44.4, 43.3, 40.7, 40.0, 29.7, 27.6, 25.9, 24.6, 24.6, 23.0, 22.0, 21.0, 18.2, 16.9, 16.8, 14.2, 10.5, –4.1, –5.4. IR: 3356, 2957, 2927, 2855, 1723, 1712, 1253 cm^{-1}. $[\alpha]^{25}_{D}$ –91.7º (c = 0.62, CHCl$_3$). HRMS (FAB+) calcd for $C_{47}H_{75}O_7N_2SSi$ [(M + H)$^+$] 839.5064, found 839.5057.



Archazolid B (1.8). To a solution of **1.73** (22 mg, 0.026 mmol) in THF (600 μL) at 0 ºC was added H_2O (100 μL) and formic acid (300 μL). After 26 h at 0 ºC, the reaction mixture was poured onto H_2O (5 mL) and Et_2O (10 mL). A saturated $NaHCO_3$ solution (5 mL) was added. The layers were separated, and the aqueous layer was extracted 1 x Et_2O (10 mL). The combined organic layers were dried, filtered, and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography to give 16 mg (84%) of archazolid B (**1.8**) as a white solid.

R_f 0.33, 40% EtOAc/Hex. $[\alpha]^{25}_{D}$ –61.9º (*c* = 0.52, MeOH).

^{1}H NMR isolation	^{1}H NMR current	^{13}C NMR isolation	^{13}C NMR current
7.31 (s, 1 H)	7.29 (s, 1 H)	174.2	174.4
6.94 (ddd, 1 H, J = 15.5, 8.4, 6.4 Hz)	6.92 (ddd, 1 H, J = 15, 8.5, 6.5 Hz)	166.7	166.8
6.60 (d, 1 H, J = 15.8 Hz)	6.59 (d, 1 H, J = 16 Hz)	158.3	158.4
6.28 (ddd, 1 H, J = 15.3, 10.7, 1.0 Hz)	6.26 (dd, 1 H, J = 15, 10.5 Hz)	155.7	155.9
6.03 (dd, 1 H, J = 8.9, 4.8 Hz)	6.01 (dd, 1 H, J = 9, 4.5 Hz)	149.0	149.2
5.92 (d, 1 H, J = 15.7 Hz)	5.92-5.88 (m, 3 H)	136.2	136.4
5.90 (d, 1 H, J = 4.4 Hz)		135.6	135.7
5.90 (d, 1 H, J = 10.2 Hz)		135.5	135.6
5.79 (d, 1 H, J = 0.6 Hz)	5.78-5.70 (m, 3 H)	134.6	134.7
5.77 (dd, 1 H, J = 16.2, 5.6 Hz)		133.5	133.6
5.75 (dd, 1 H, J = 15.3,		133.4	133.5
5.28 (d, 1 H, J = 9.7 Hz)	5.27 (d, 1 H, J = 9.5 Hz)	132.9	133.1
5.18 (dd, 1 H, J = 9.2, 1.0 Hz)	5.17 (d, 1 H, J = 9.5 Hz)	130.7	130.9
4.38 (dd, 1 H, J = 5.6, 3.2 Hz)	4.37 (br s, 1 H)	130.7	130.9
4.03 (dd, 1 H, J = 9.2, 9.2 Hz)	4.02 (t, 1 H, J = 9.5 Hz)	130.0	130.2
3.47 (d, 1 H, J = 9.2 Hz)	3.45 (d, 1 H, J = 9 Hz)	129.4	129.5
3.19 (s, 3 H)	3.18 (s, 3 H)	127.3	127.4
3.09 (ddq, 1 H, J = 6.6, 4.6, 6.8 Hz)	3.07 (m, 1 H)	123.3	123.5
2.96 (dd, 1 H, J = 14.7, 8.6 Hz)	2.97-2.88 (m, 2 H)	117.5	117.5
2.91 (dd, 1 H, J = 14.7, 6.6 Hz)		90.0	90.1
2.75 (s, 3 H)	2.73 (s, 3 H)	77.2	77.4

2.30 (ddq, 1 H, J = 9.5, 9.5, 7.0 Hz)	2.29 (m, 1 H)	74.8	74.9
1.93 (d, 3 H, J = 1.1 Hz)	1.92 (s, 3 H)	73.8	73.9
1.92 (m, 2 H)	1.92 (m, 1 H), 1.81 (m, 1 H)	73.4	73.5
1.79 (m, 1 H)	1.78 (m, 1 H)	56.4	56.5
1.79 (br s, 3 H)	1.78 (s, 3 H)	46.0	46.1
1.78 (m, 1 H)	1.78 (m, 1 H)	44.0	44.2
1.74 (d, 3 H, J = 1.0 Hz)	1.72 (s, 3 H)	44.0	44.1
1.67 (d, 3 H, J = 1.0 Hz)	1.65 (s, 3 H)	41.5	41.6
1.11 (d, 3 H, J = 6.8 Hz)	1.10 (d, 3 H, J = 7 Hz)	41.3	41.4
1.02 (d, 3 H, J = 6.1 Hz)	1.01 (d, 3 H, J = 6 Hz)	27.5	27.7
1.01 (d, 3 H, J = 6.6 Hz)	1.00 (d, 3 H, J = 6.5 Hz)	25.8	26.0
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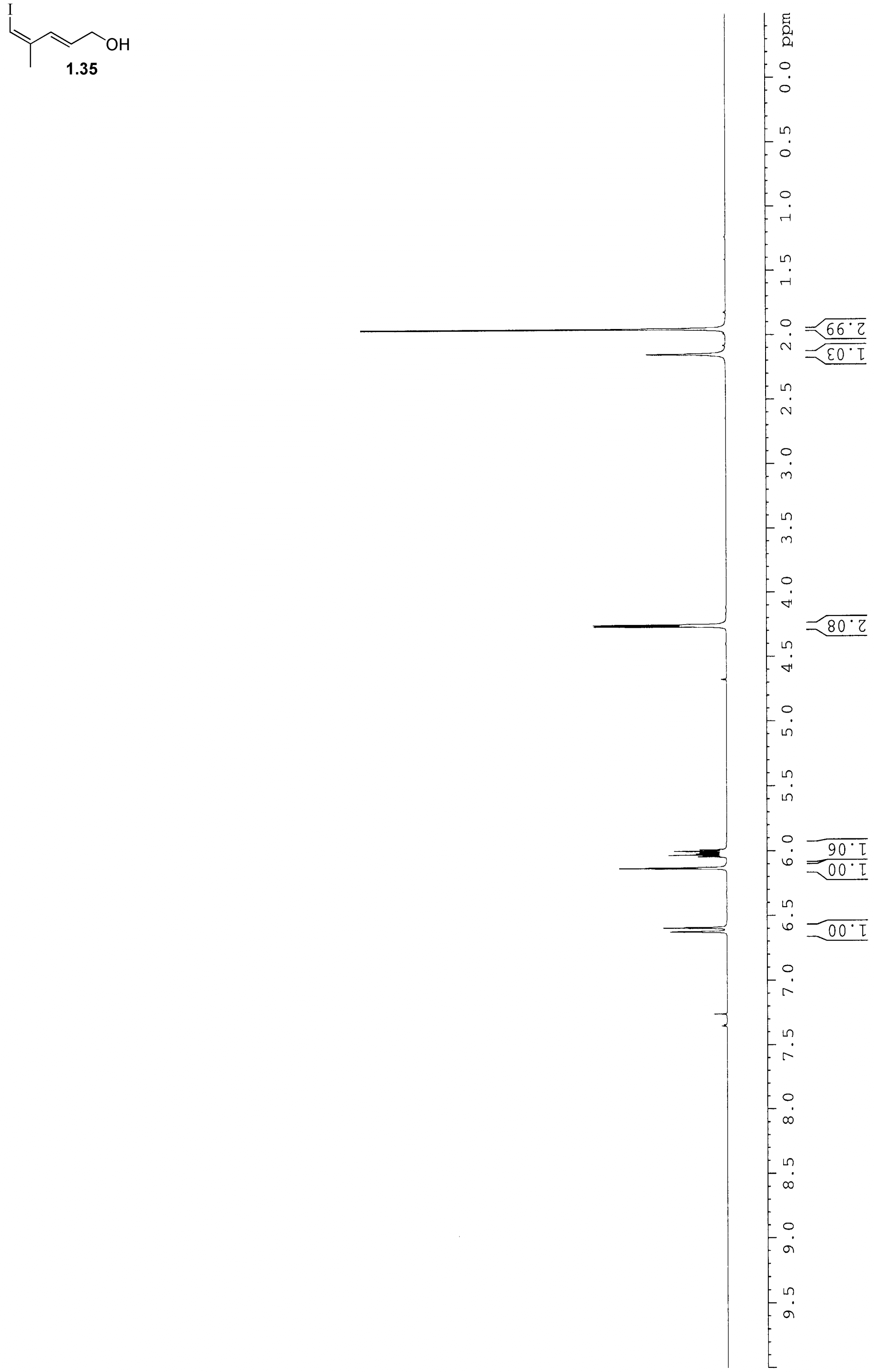
		19.9	20.1
		17.7	17.9
		17.1	17.2
		16.9	17.1
		12.6	12.7

1.11. Appendix

Characterization data for 1.35, 1.36, 1.38, 1.40, 1.41, 1.42, 1.44, 1.47, 1.48, 1.49, 1.50, 1.53, 1.54, 1.55, 1.56, 1.57, 1.59, 1.60, 1.30, 1.68, 1.69, 1.31, 1.70, 1.71, 1.72, 1.73, 1.8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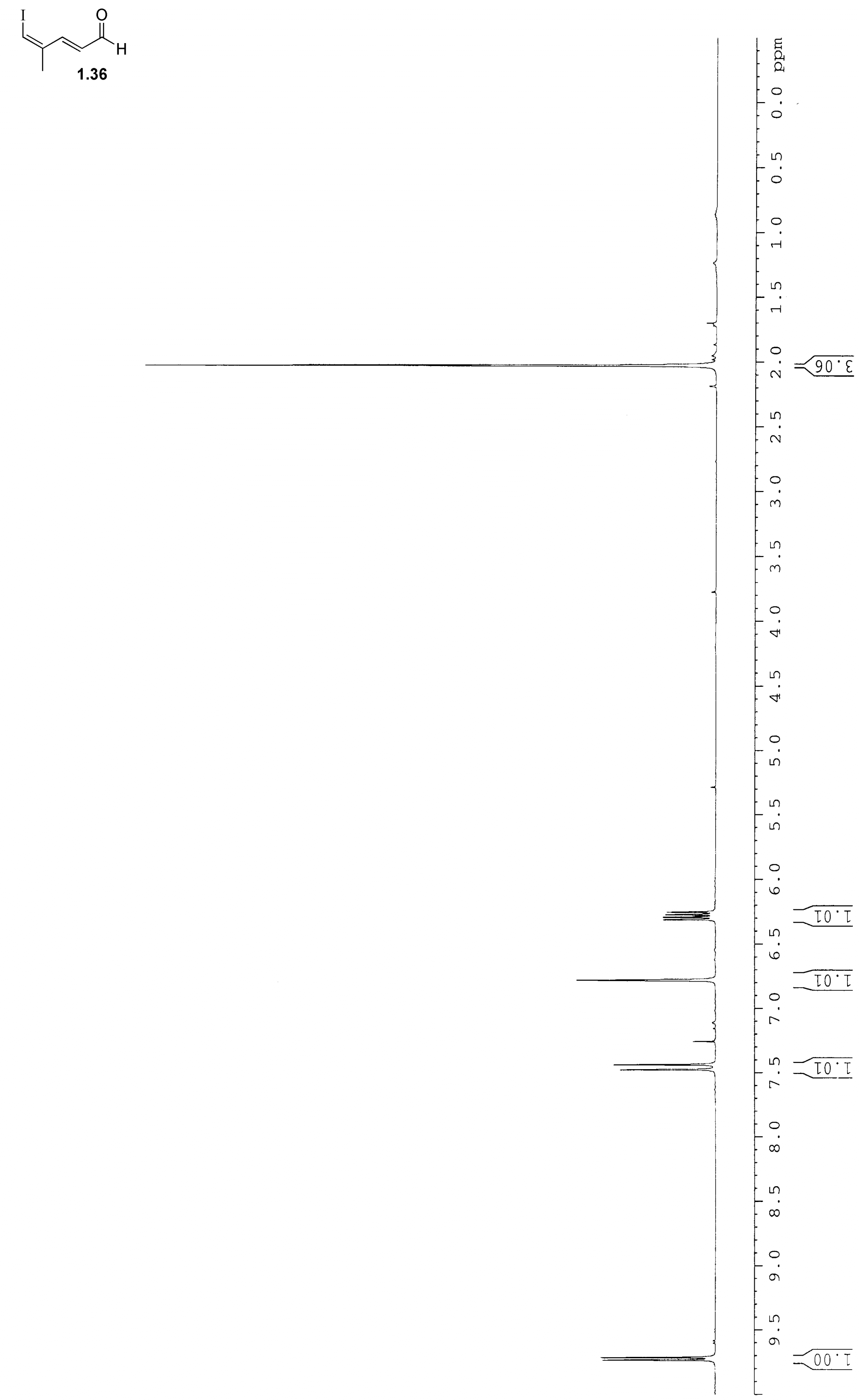
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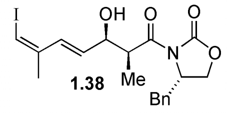
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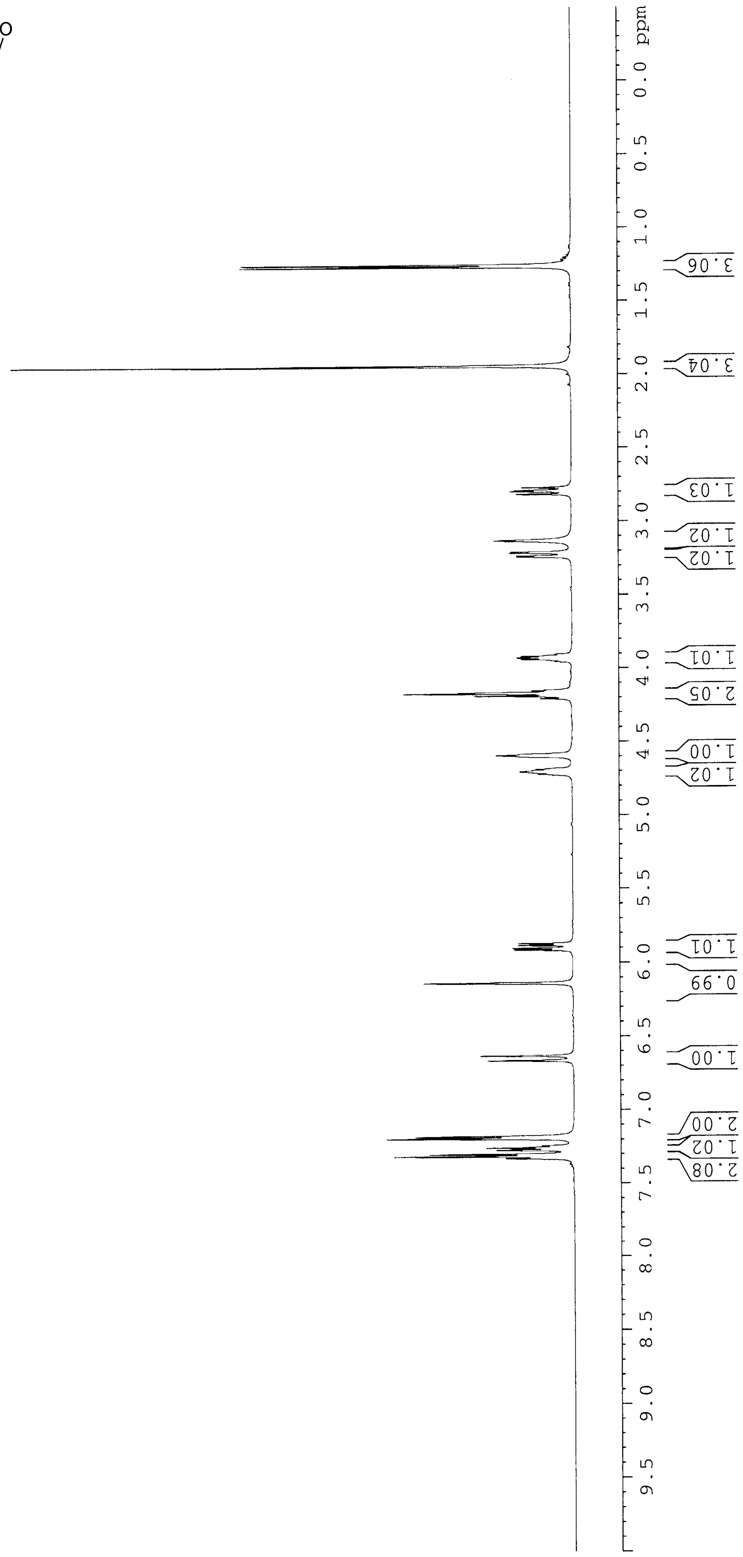
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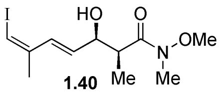
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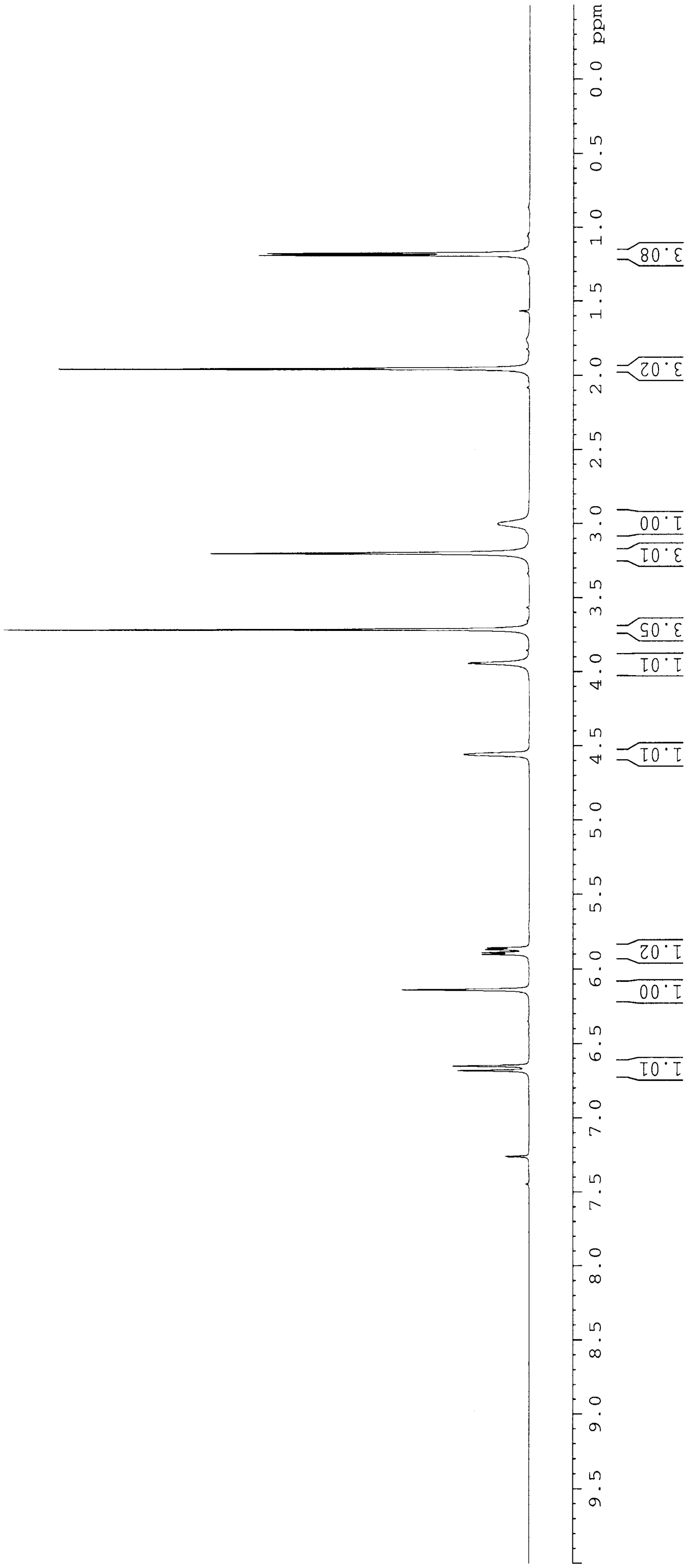
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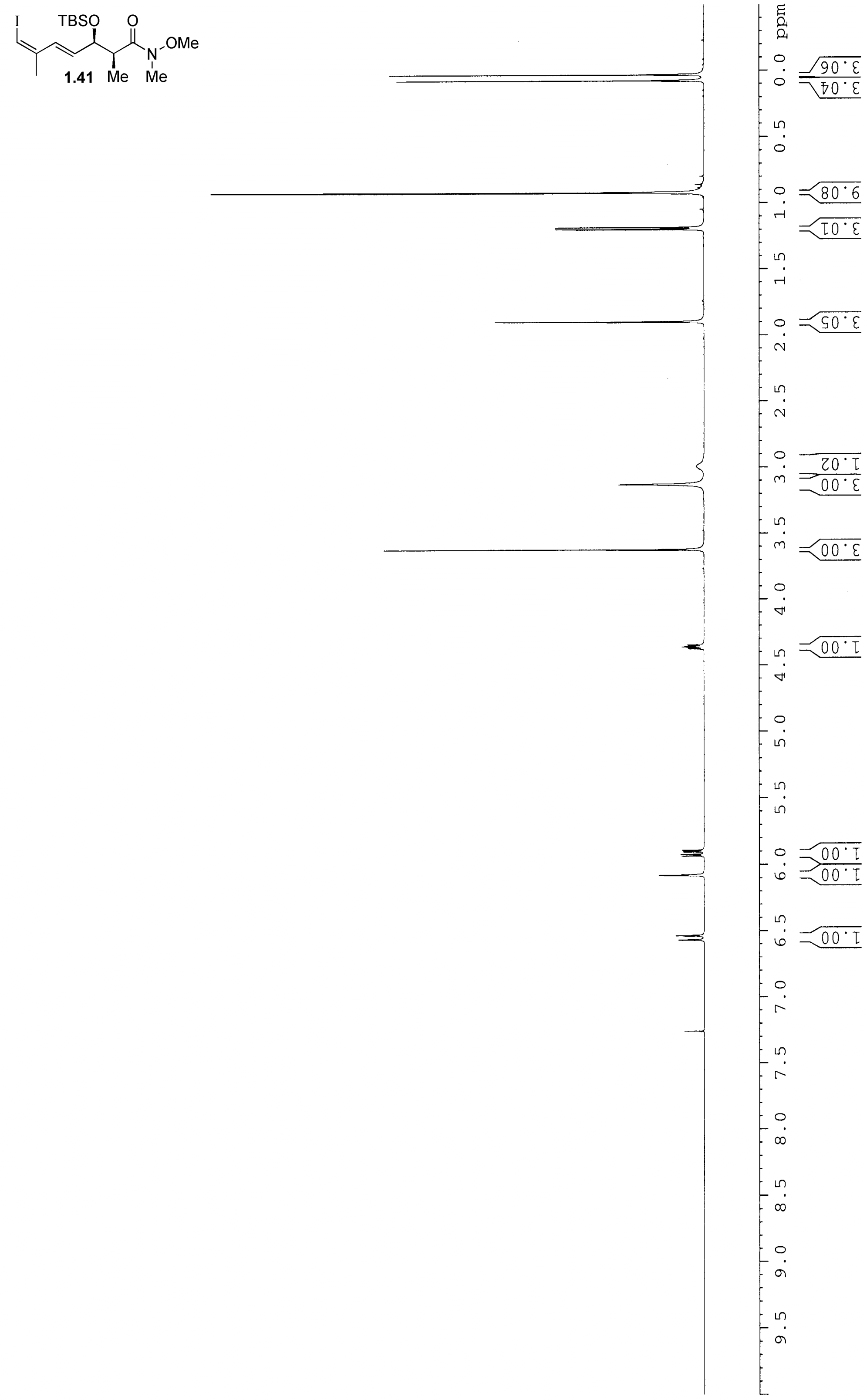

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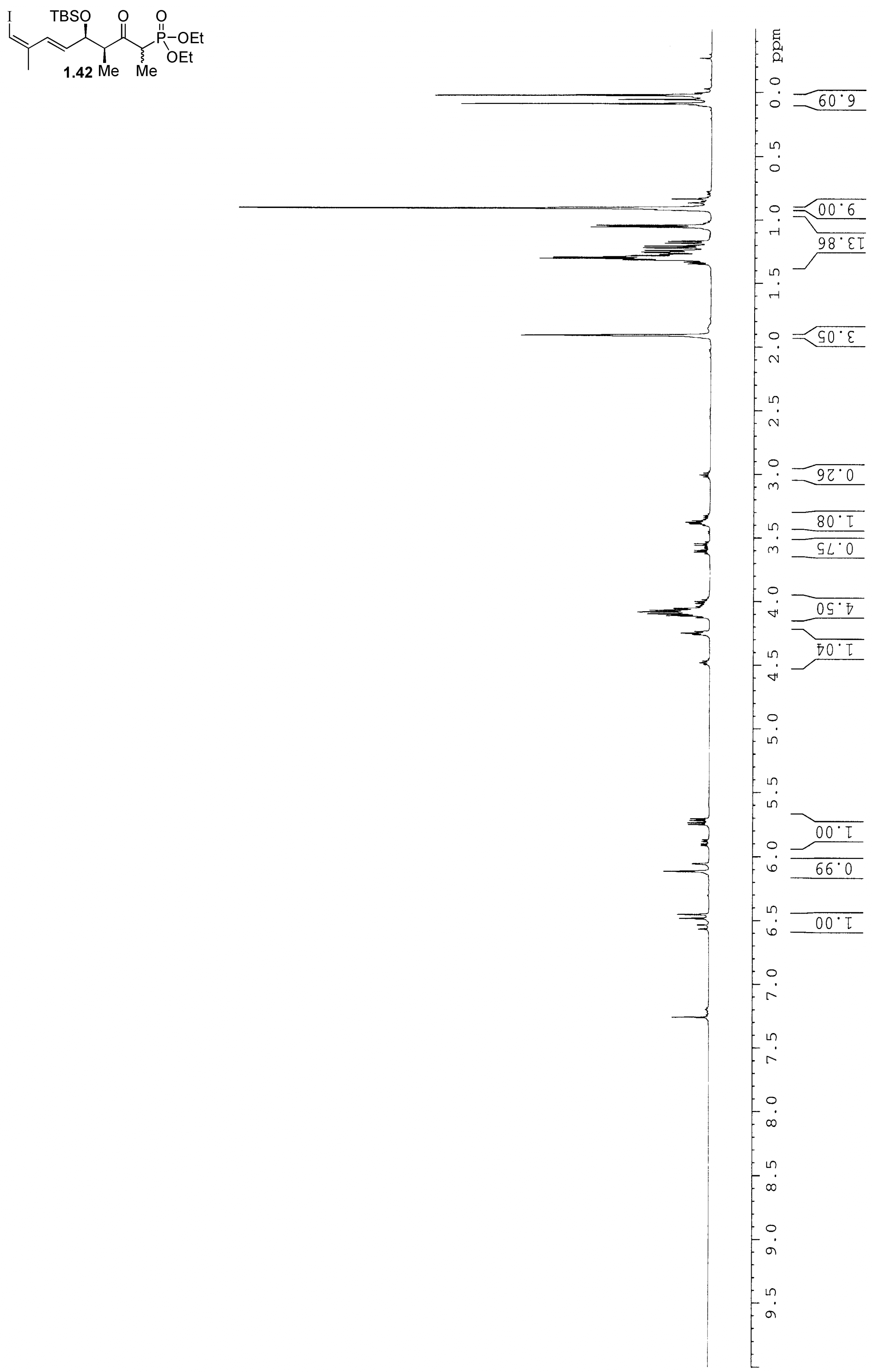

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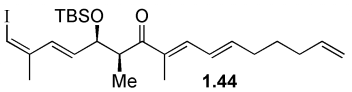
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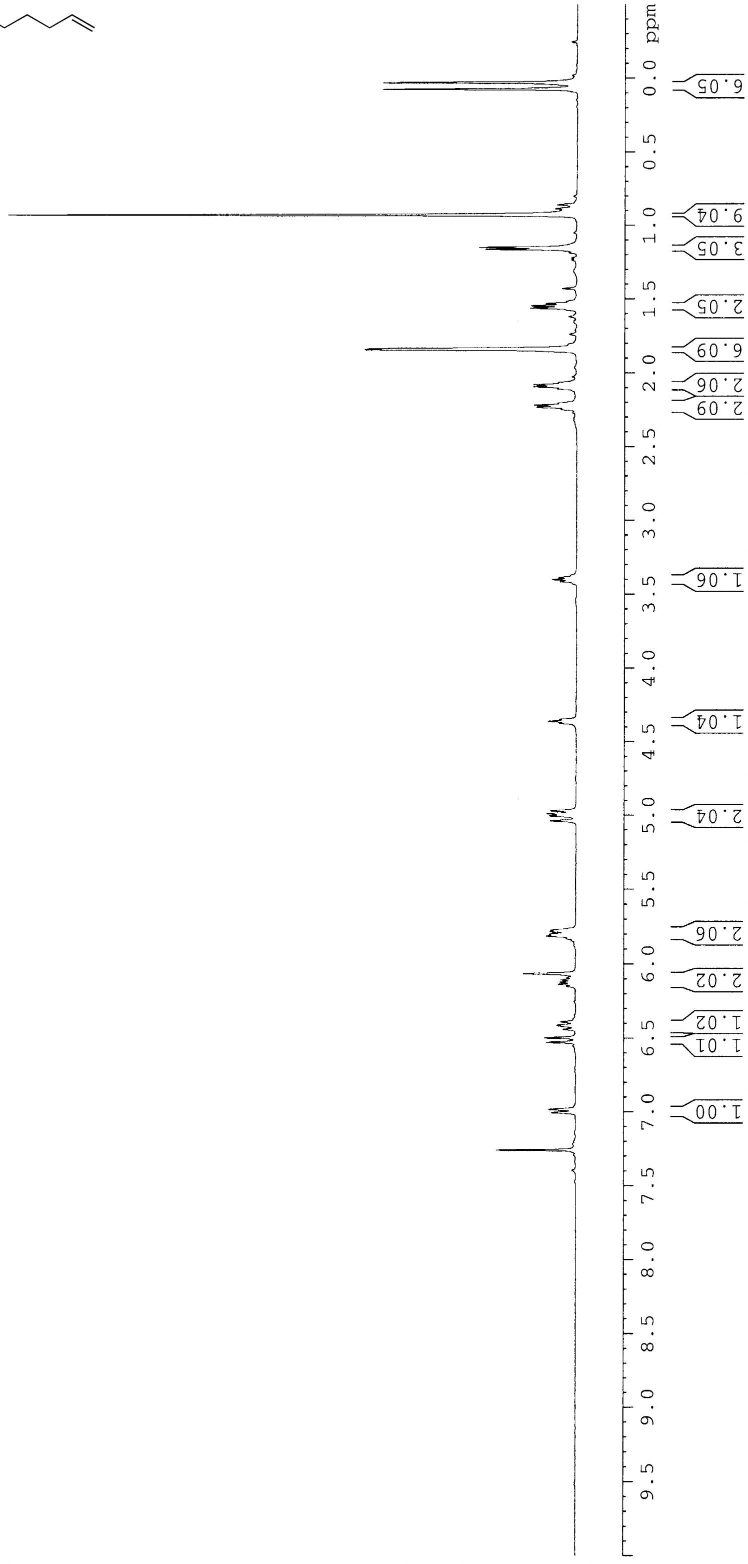
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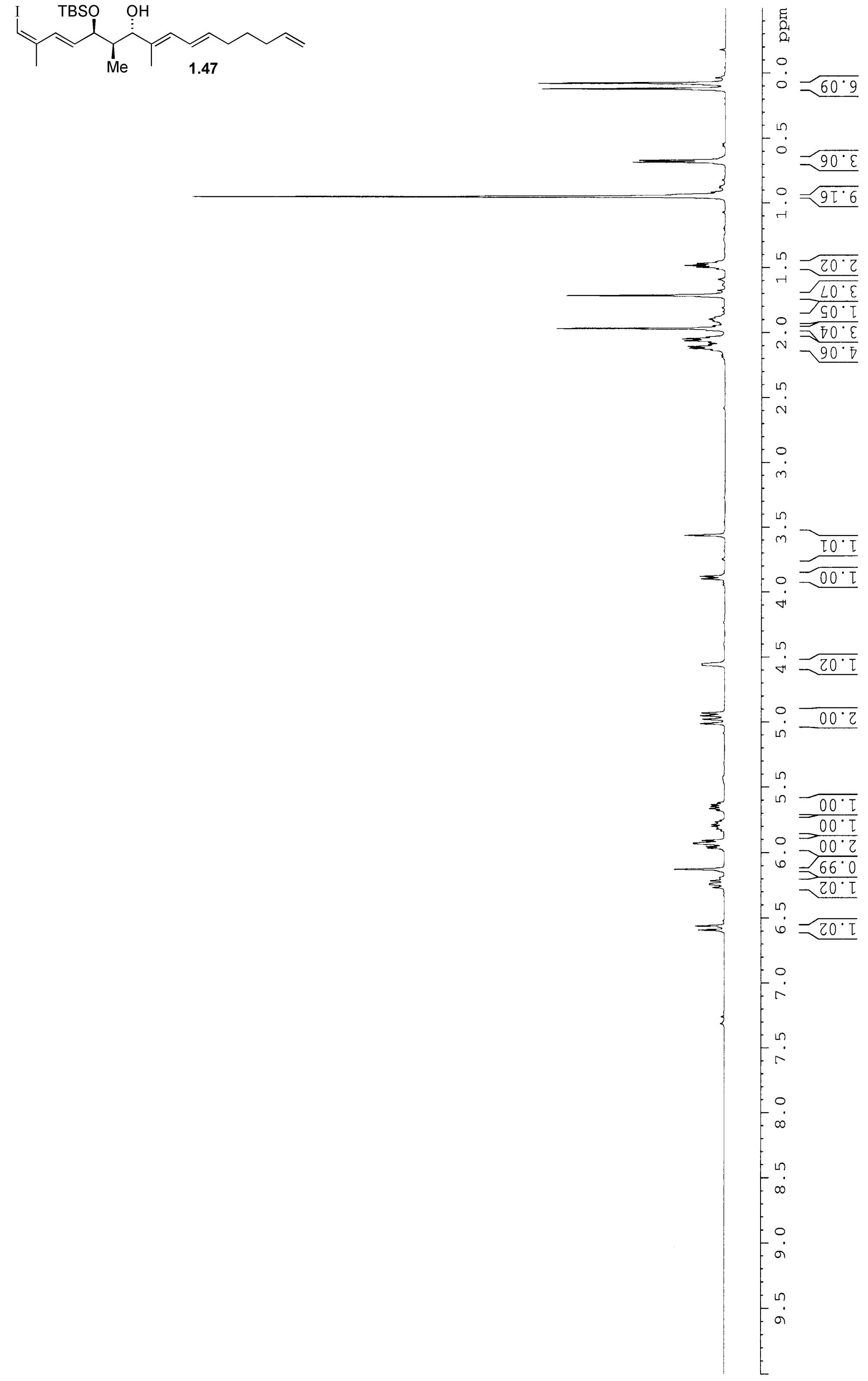
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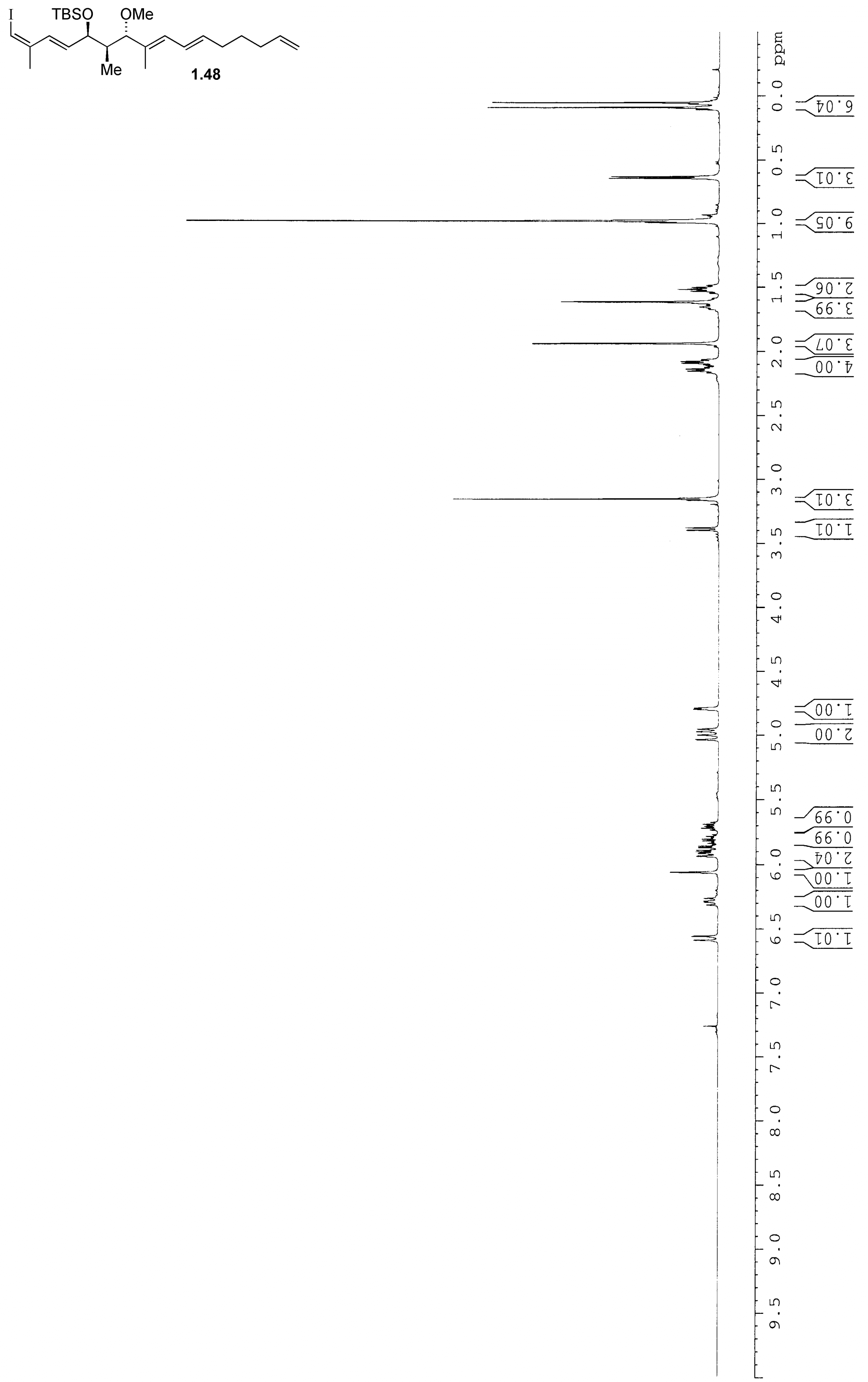
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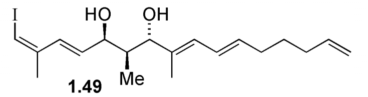

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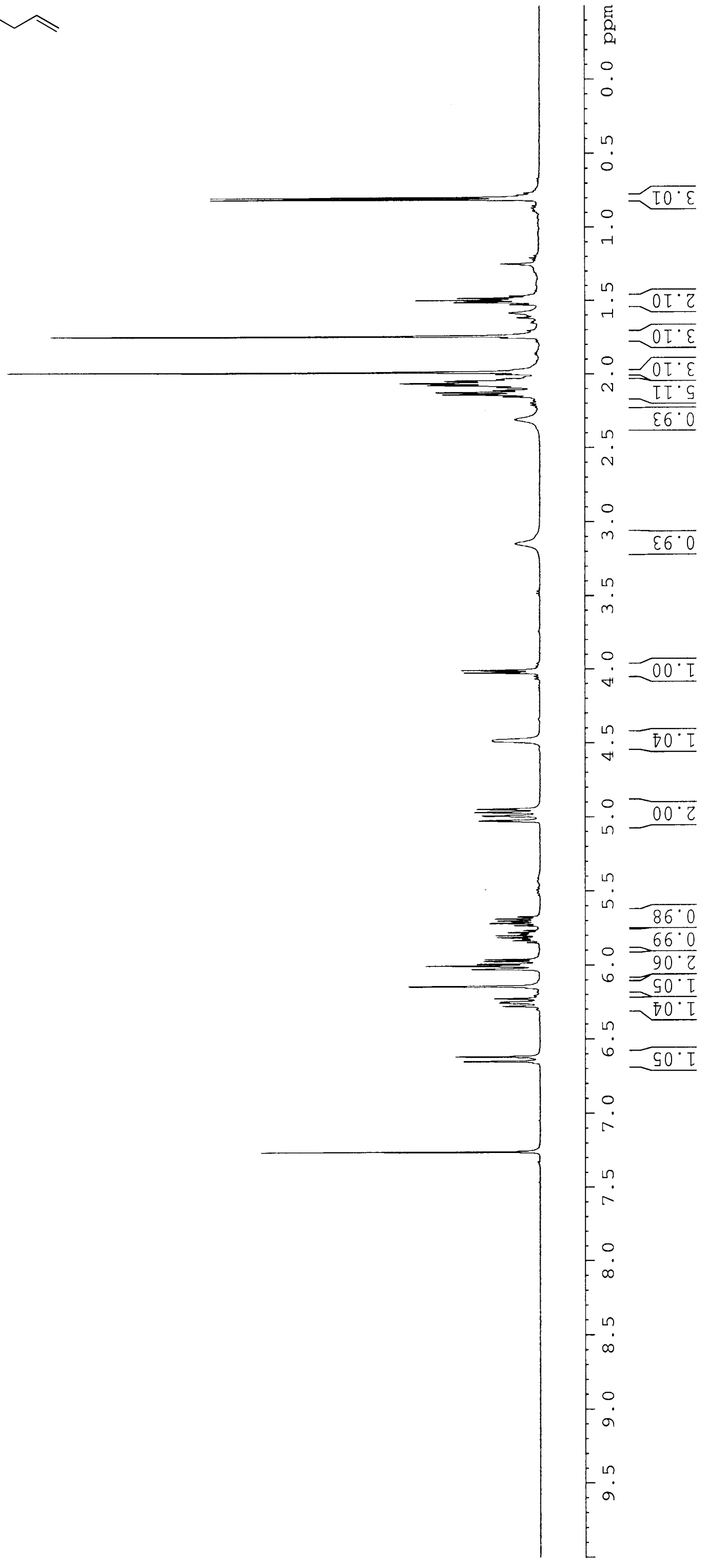

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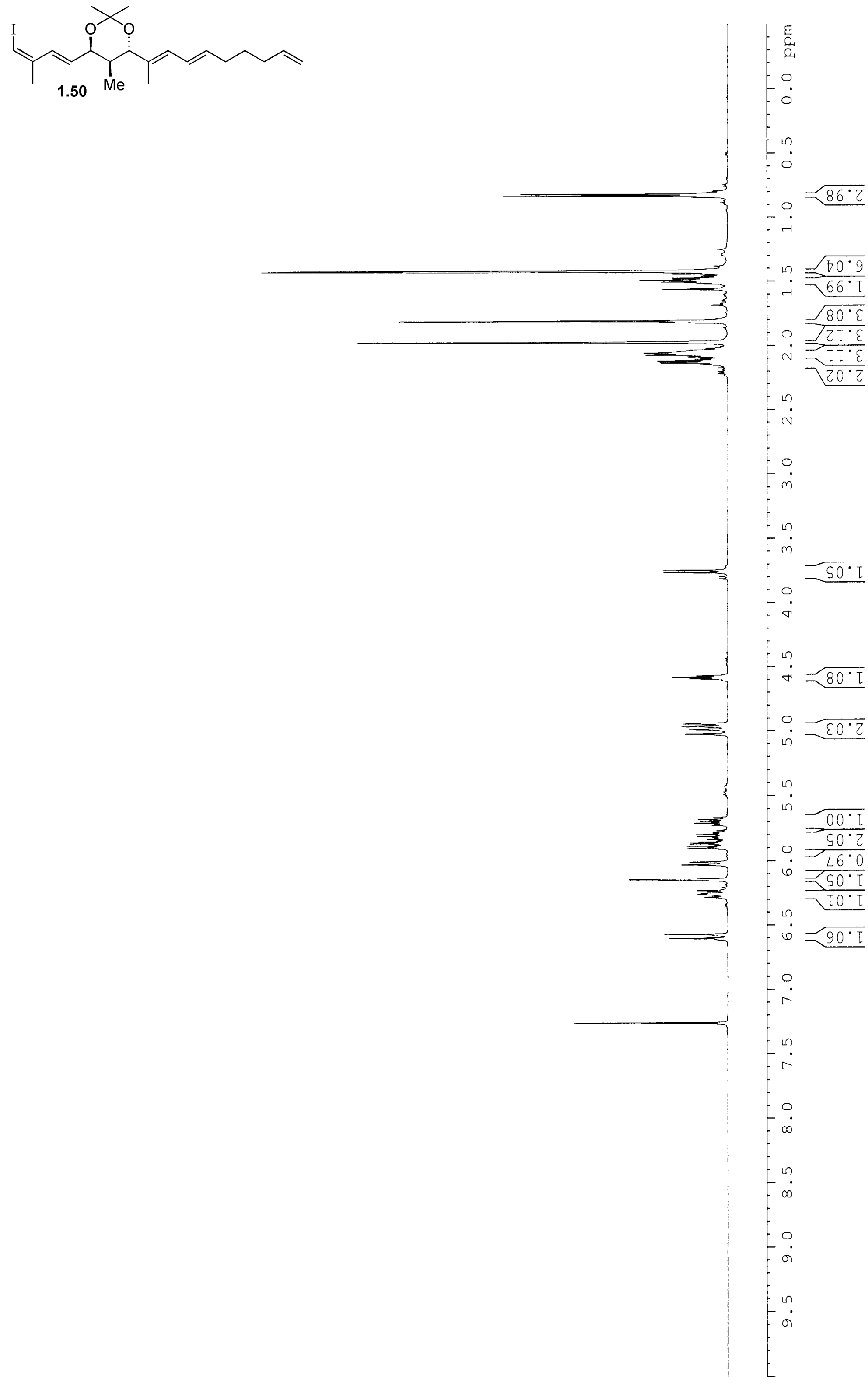

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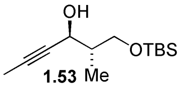
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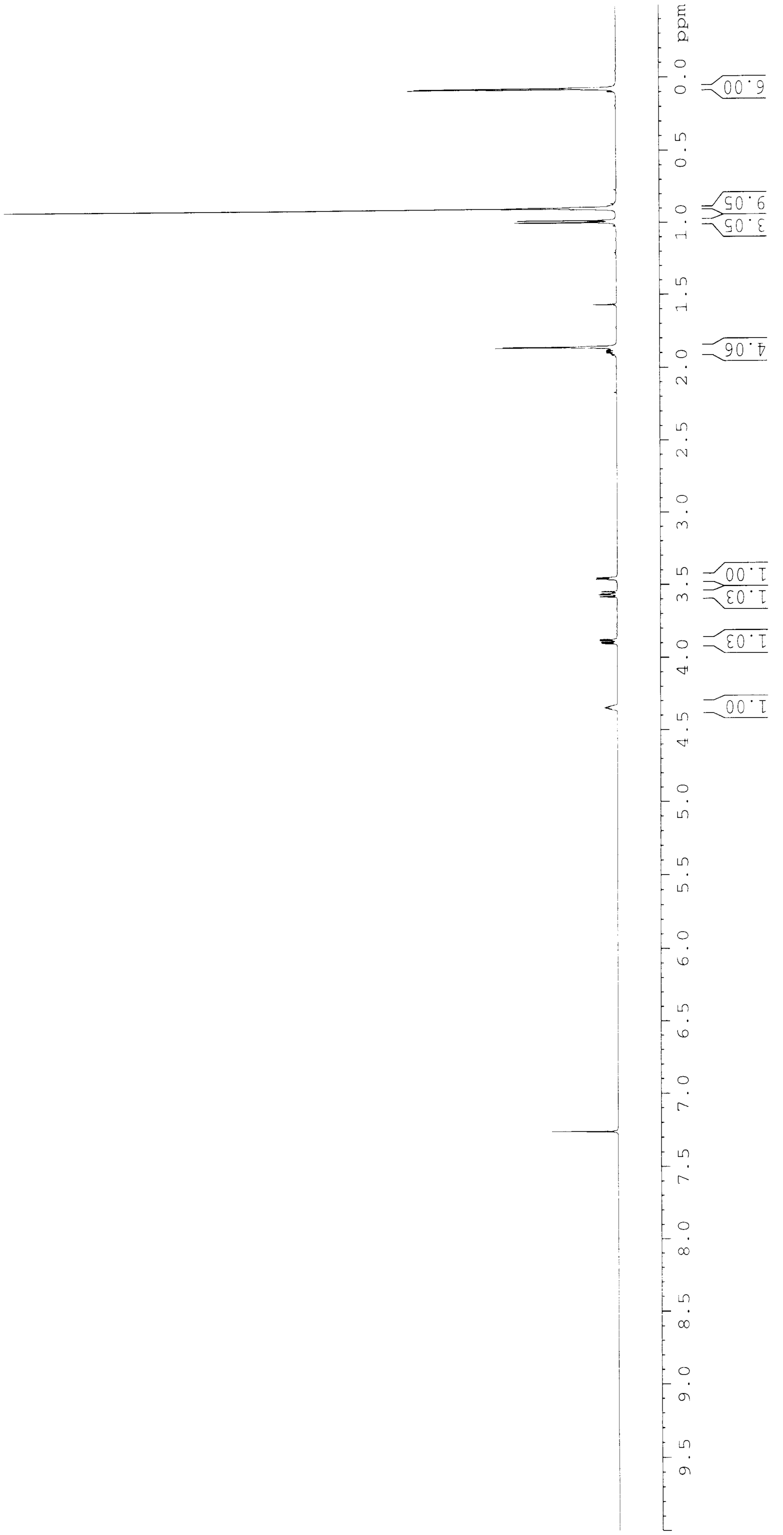
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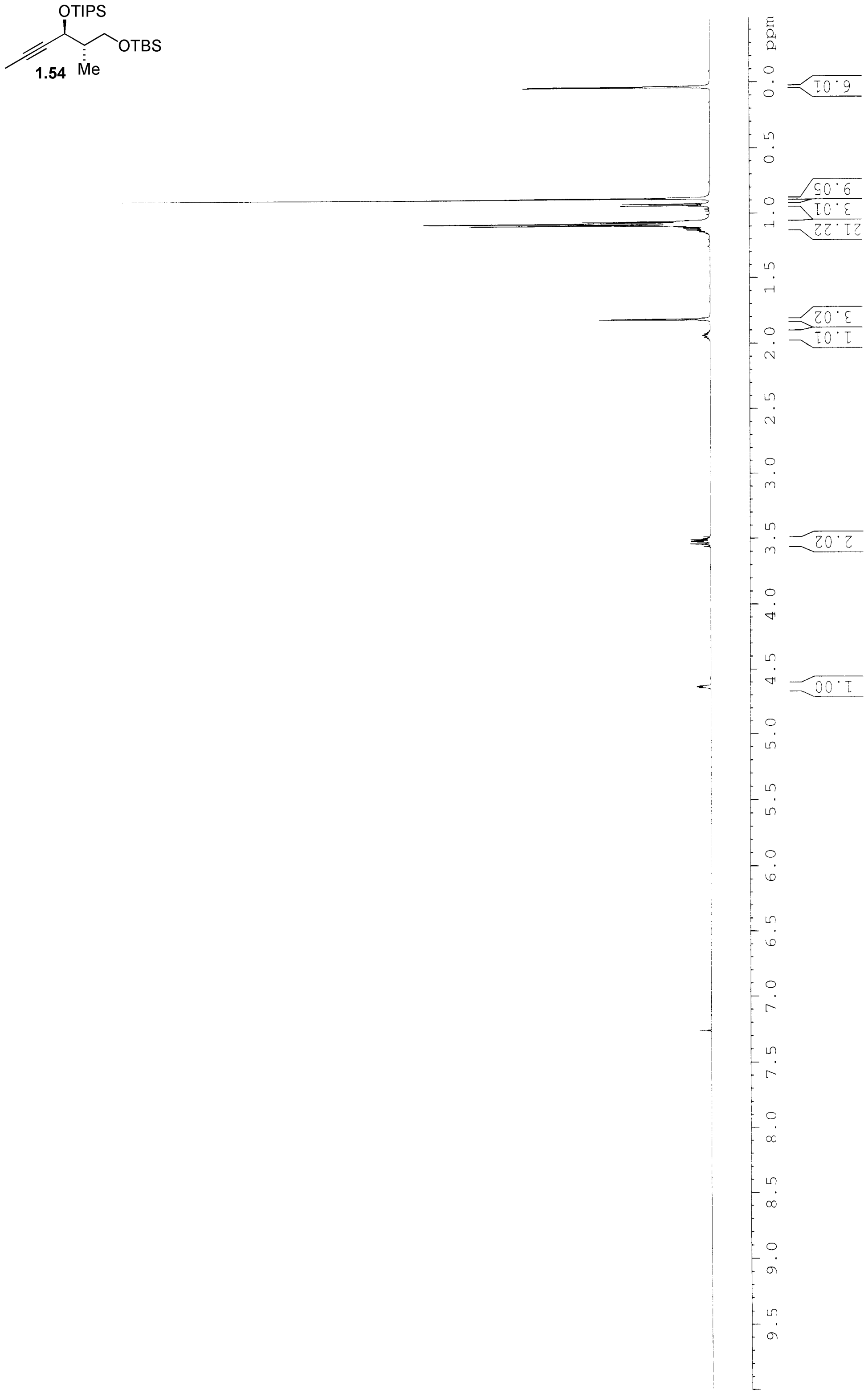
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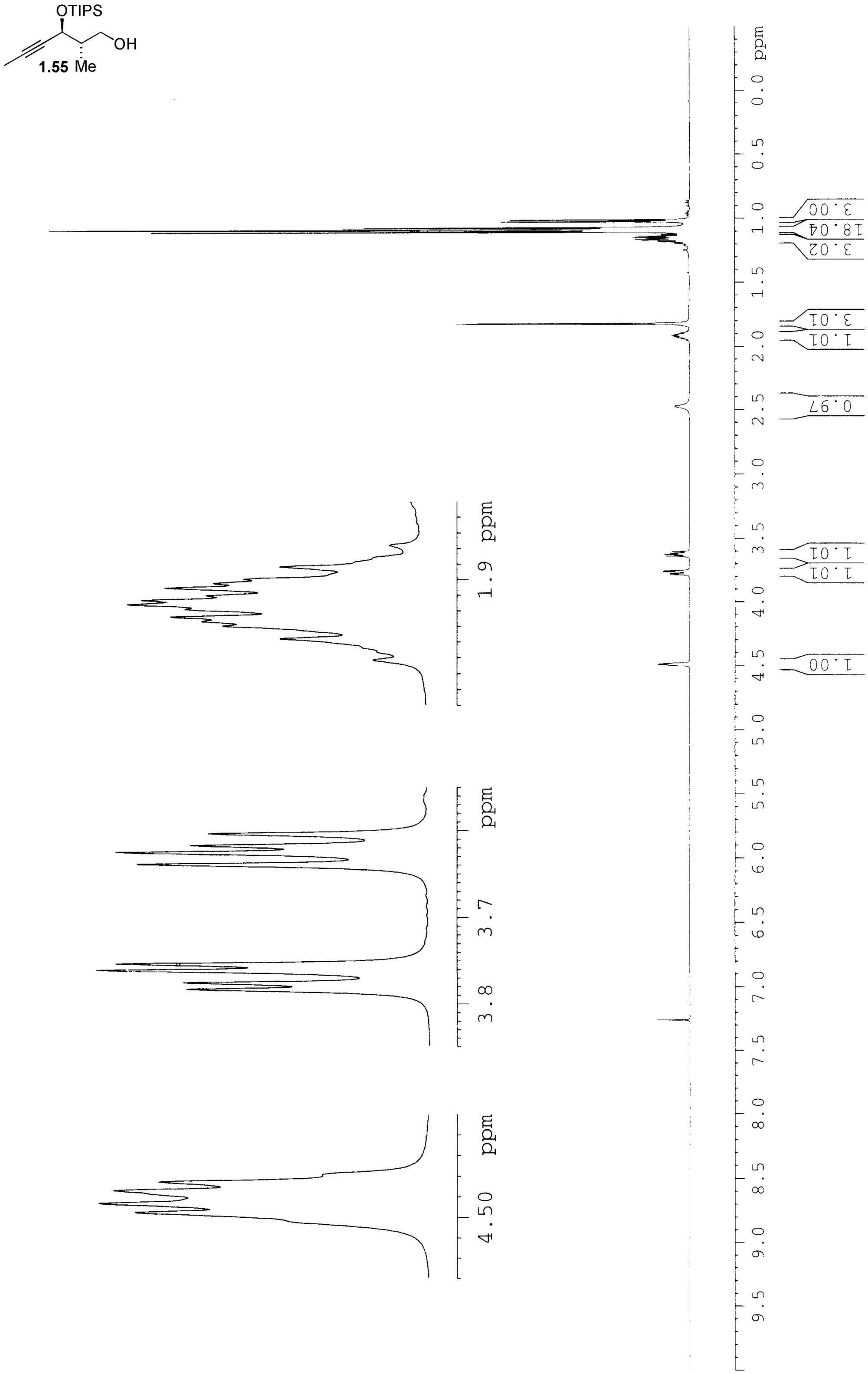
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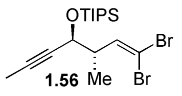
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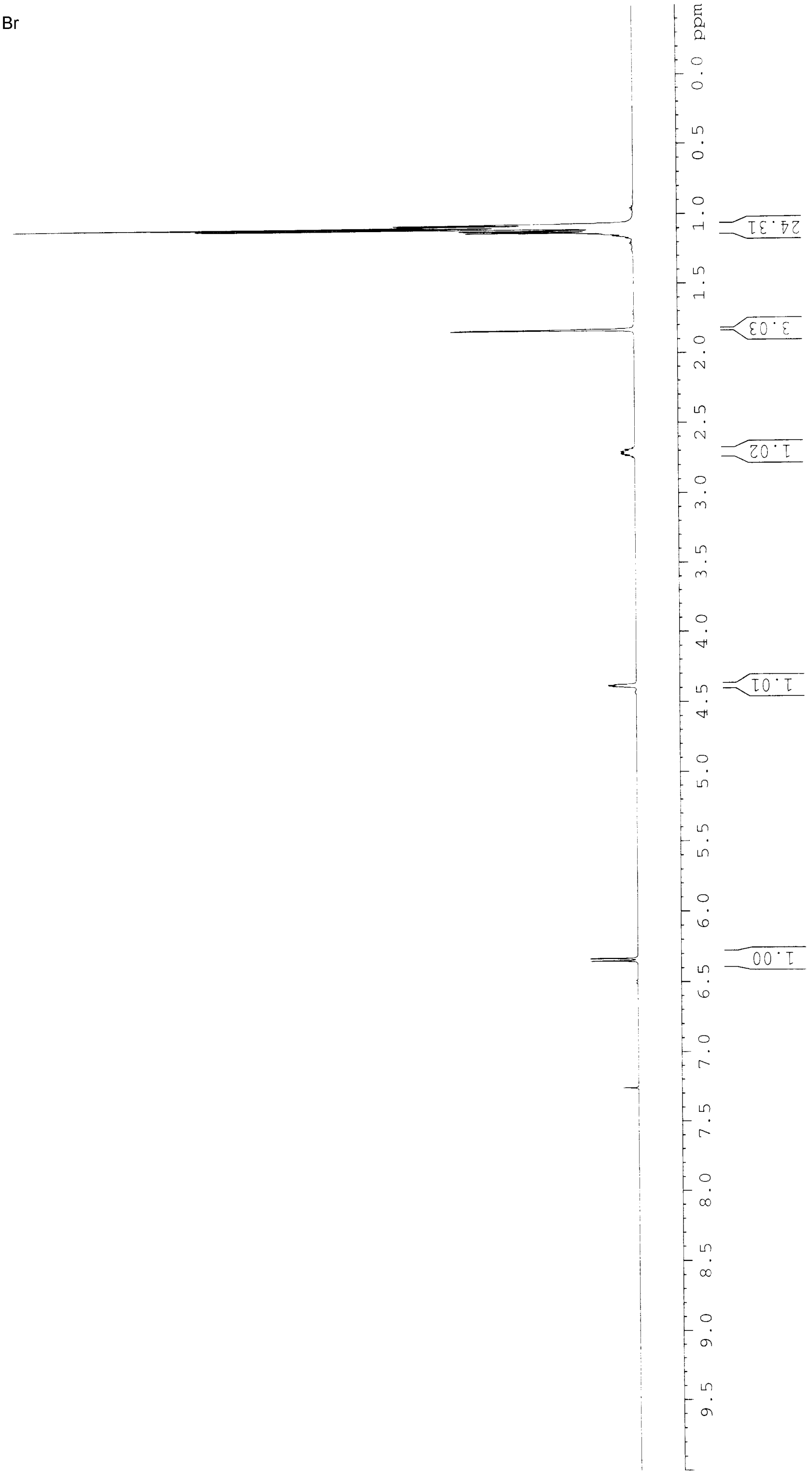
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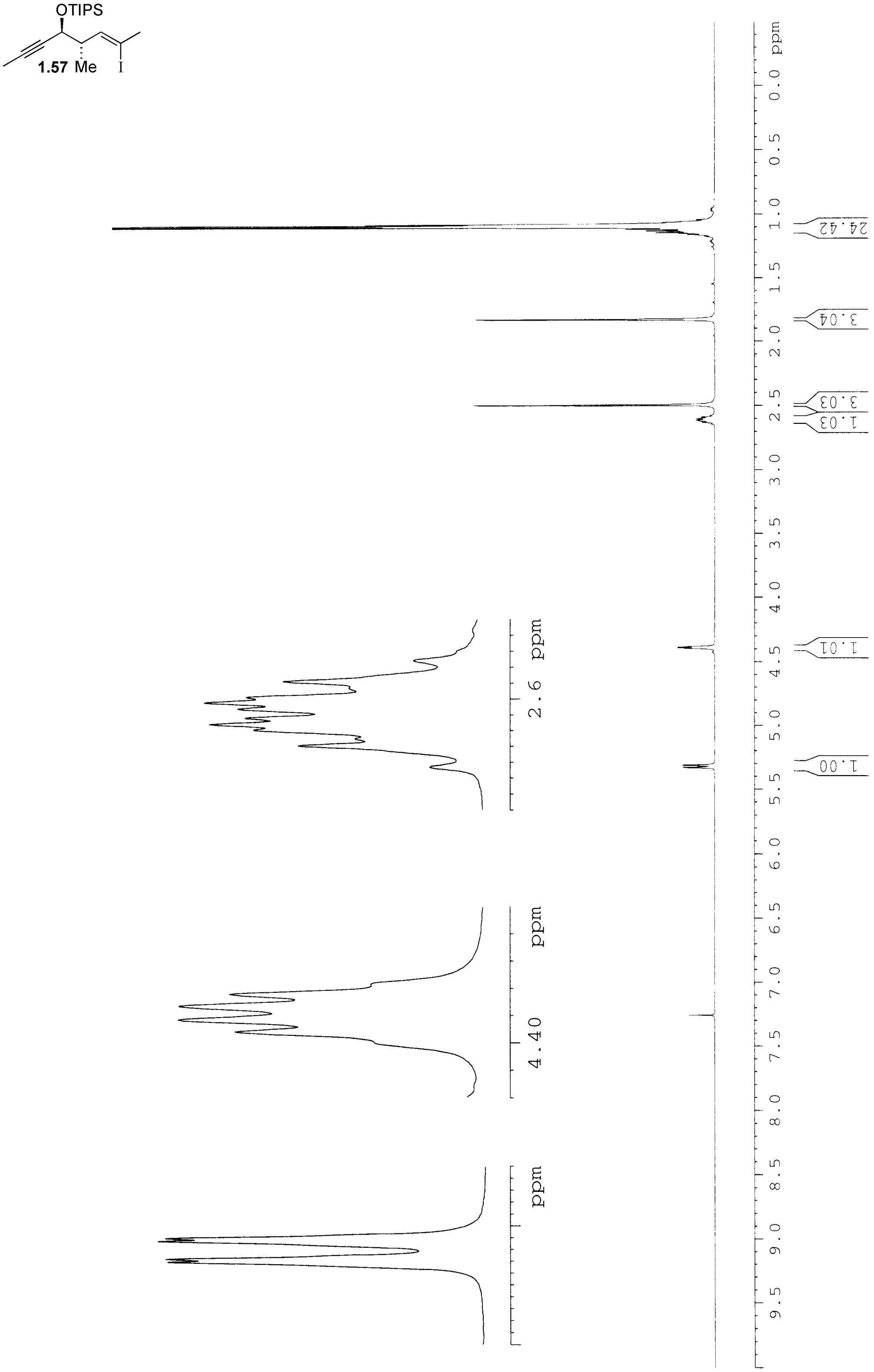
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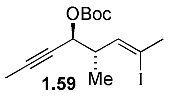
ppm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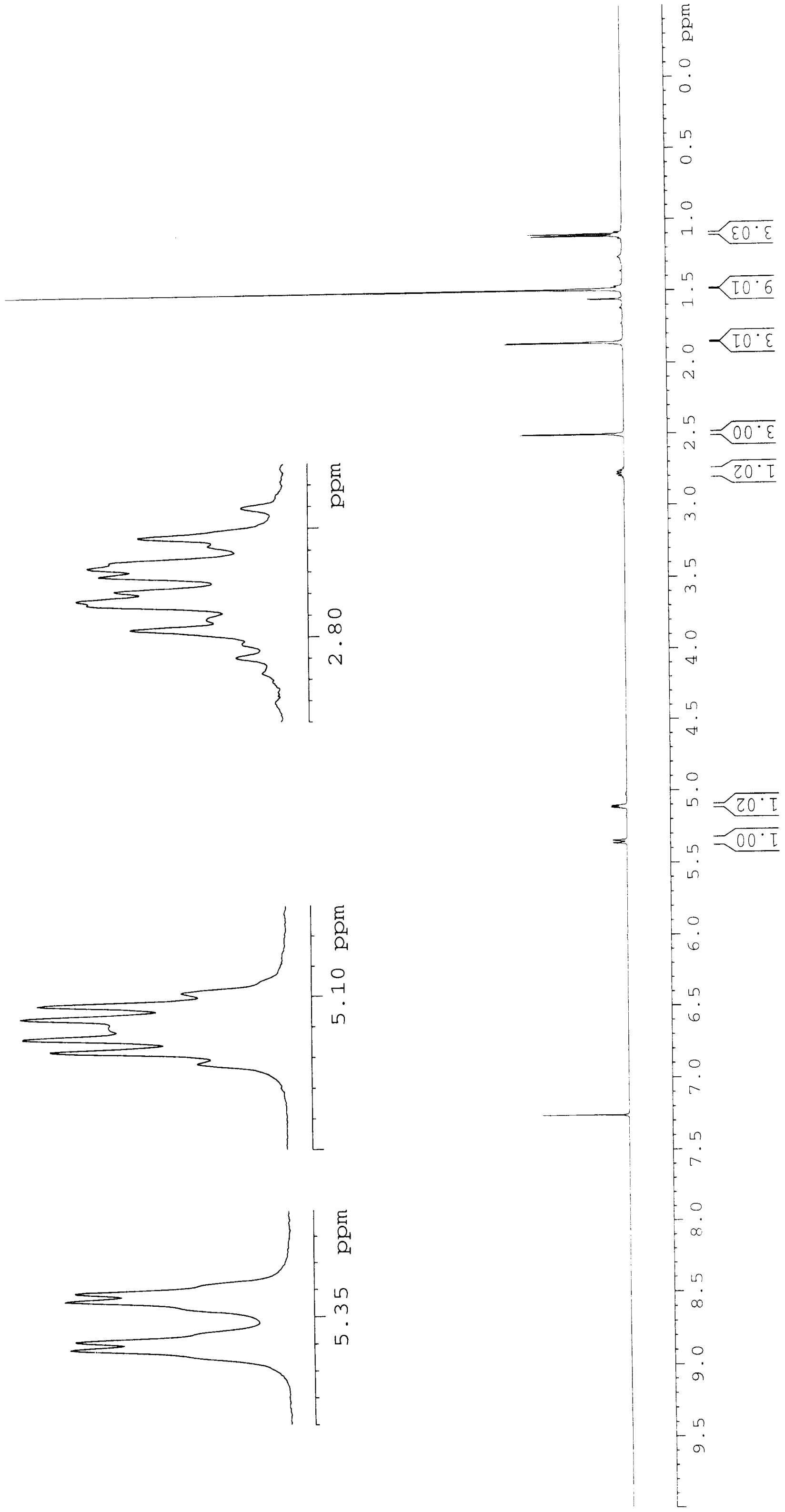
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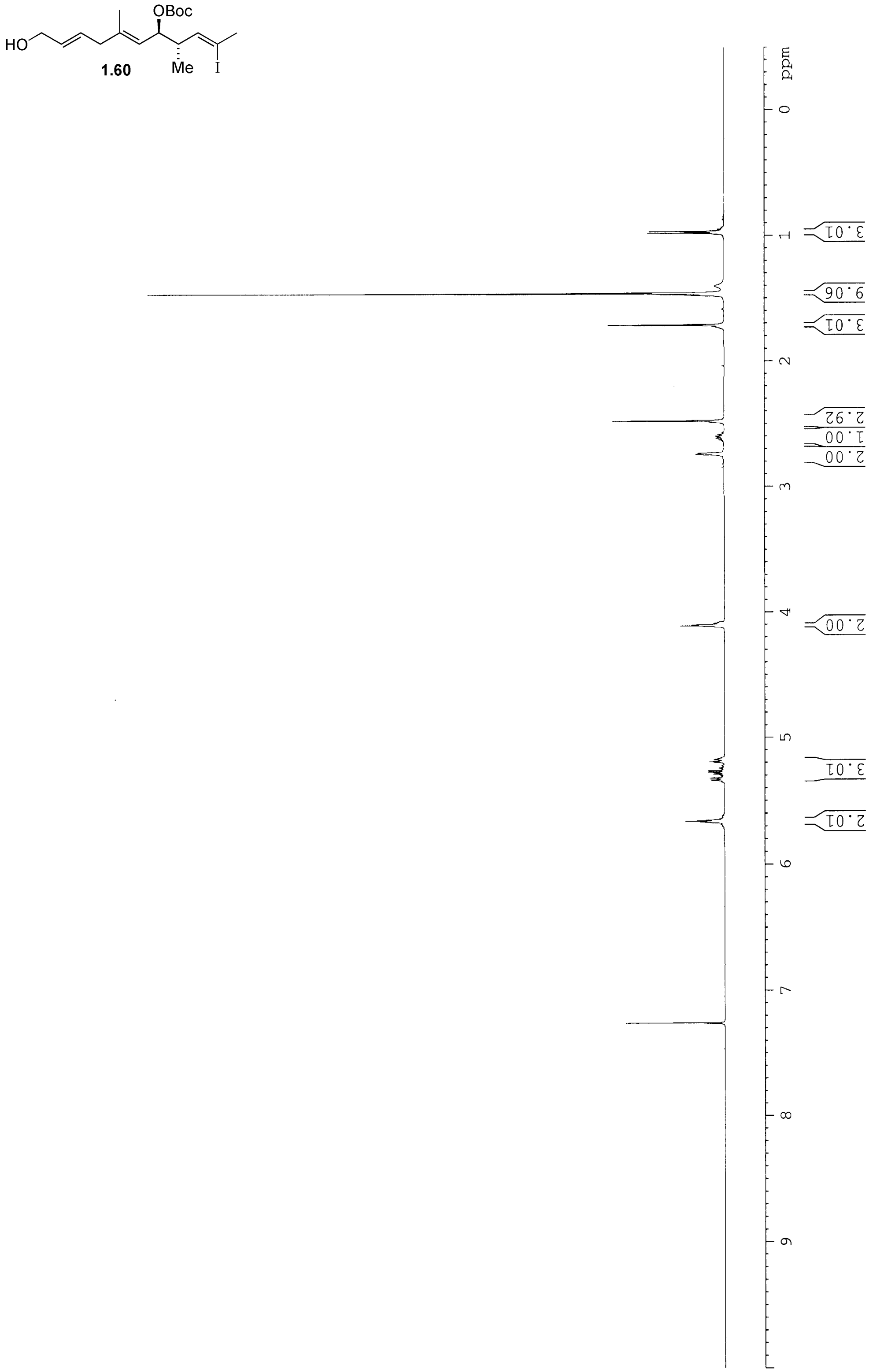

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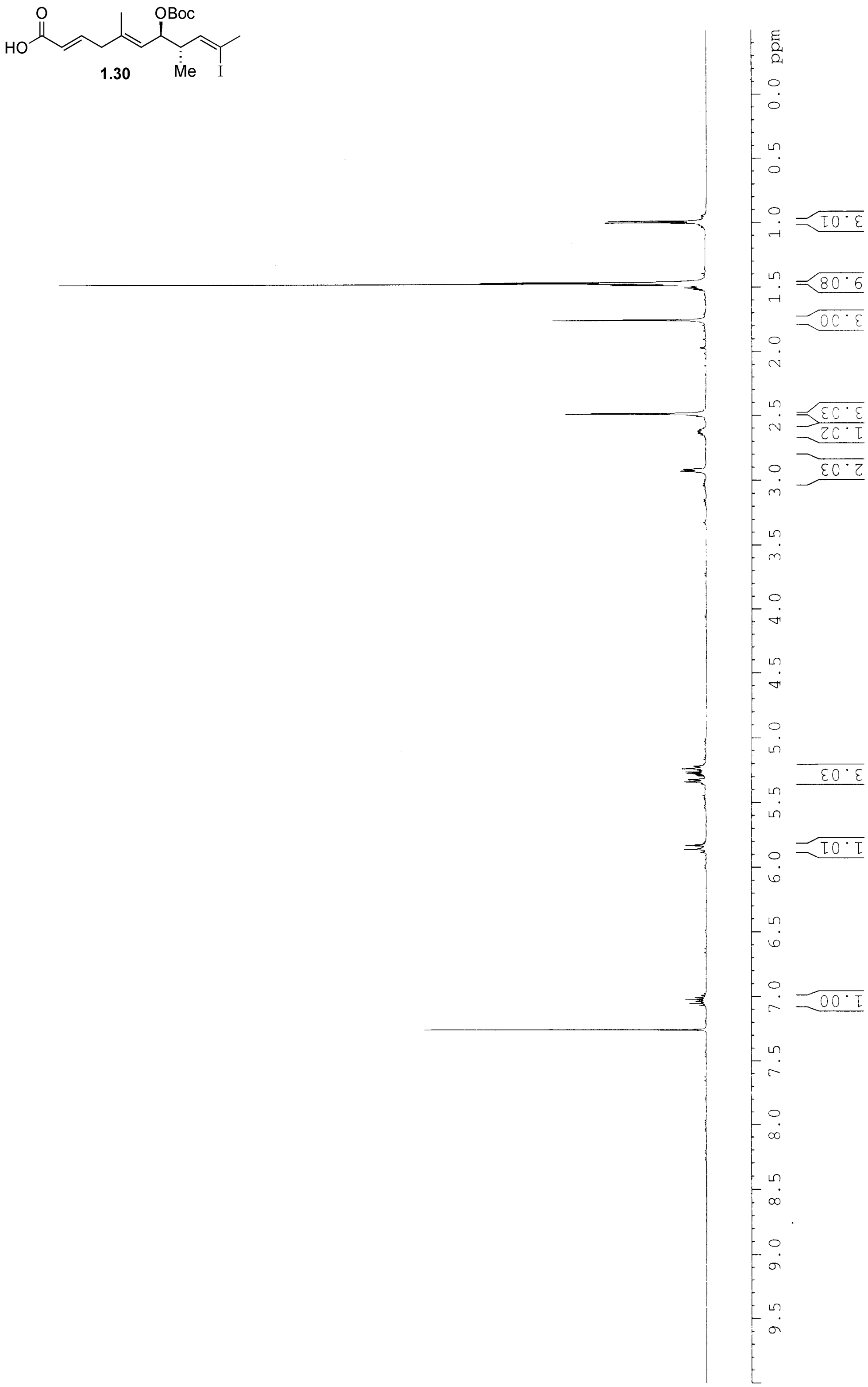

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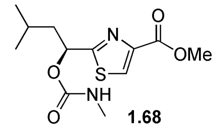
1.30



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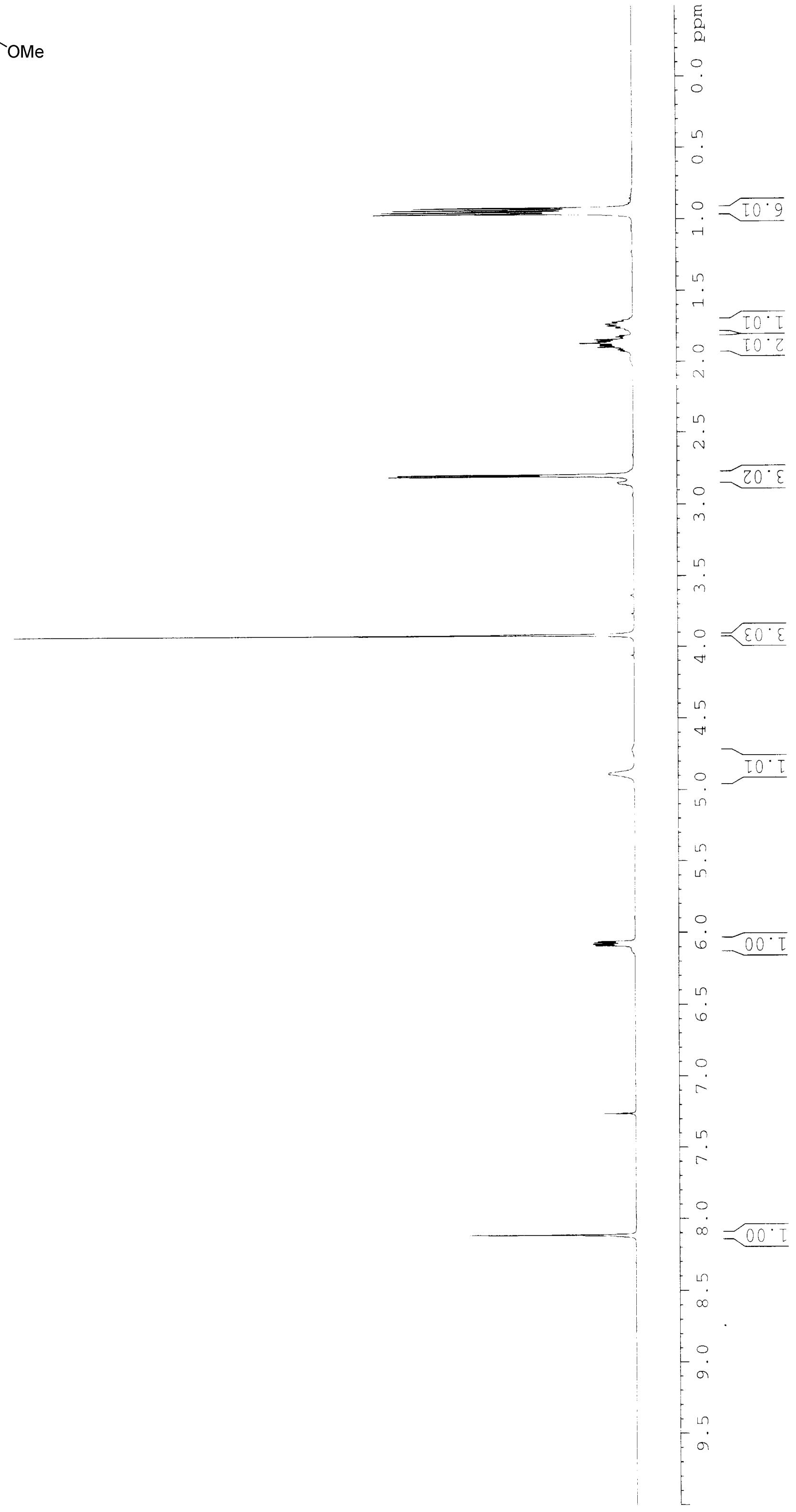

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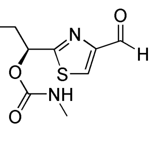

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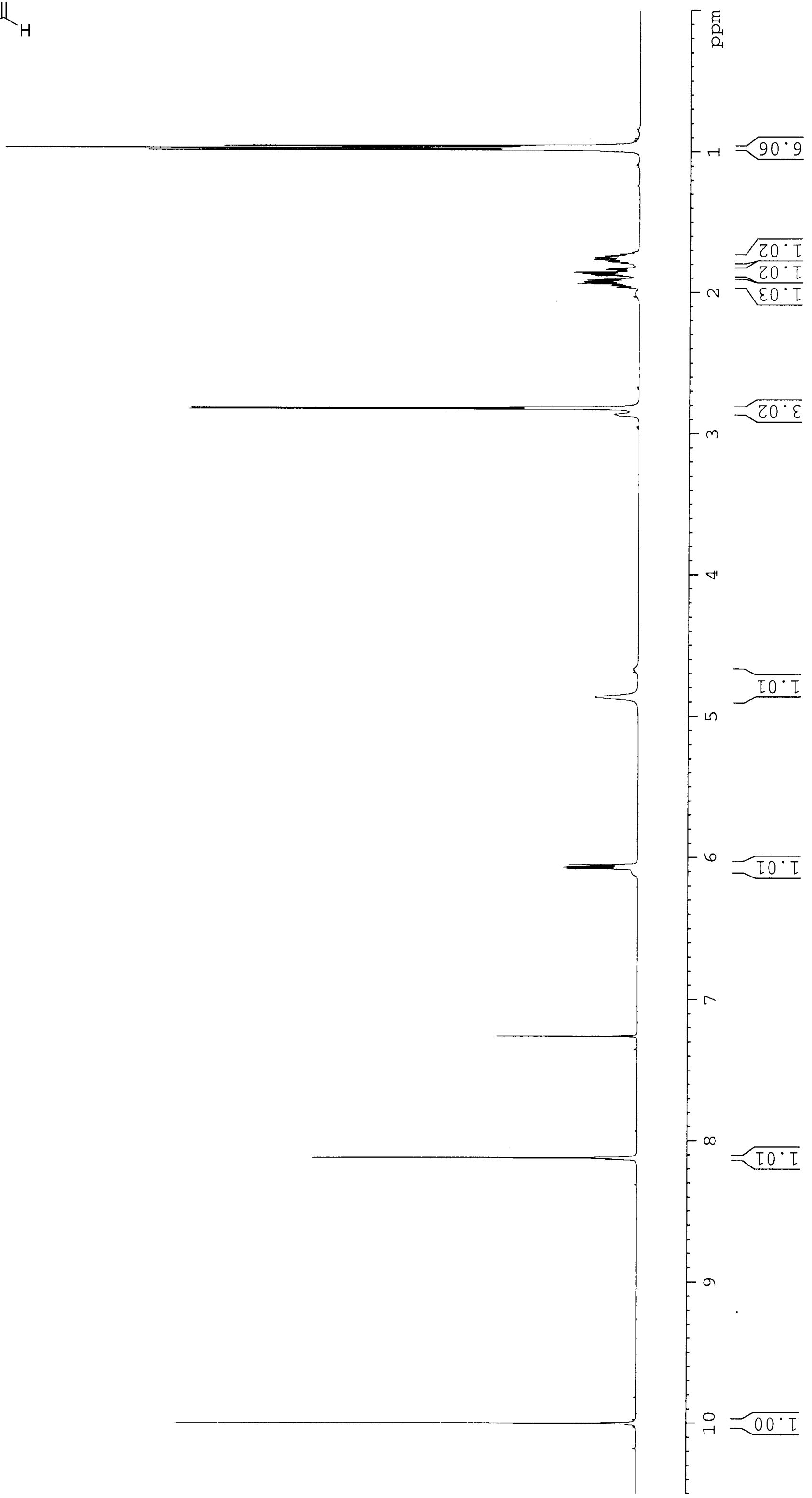

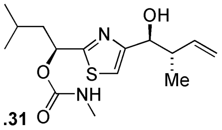
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O
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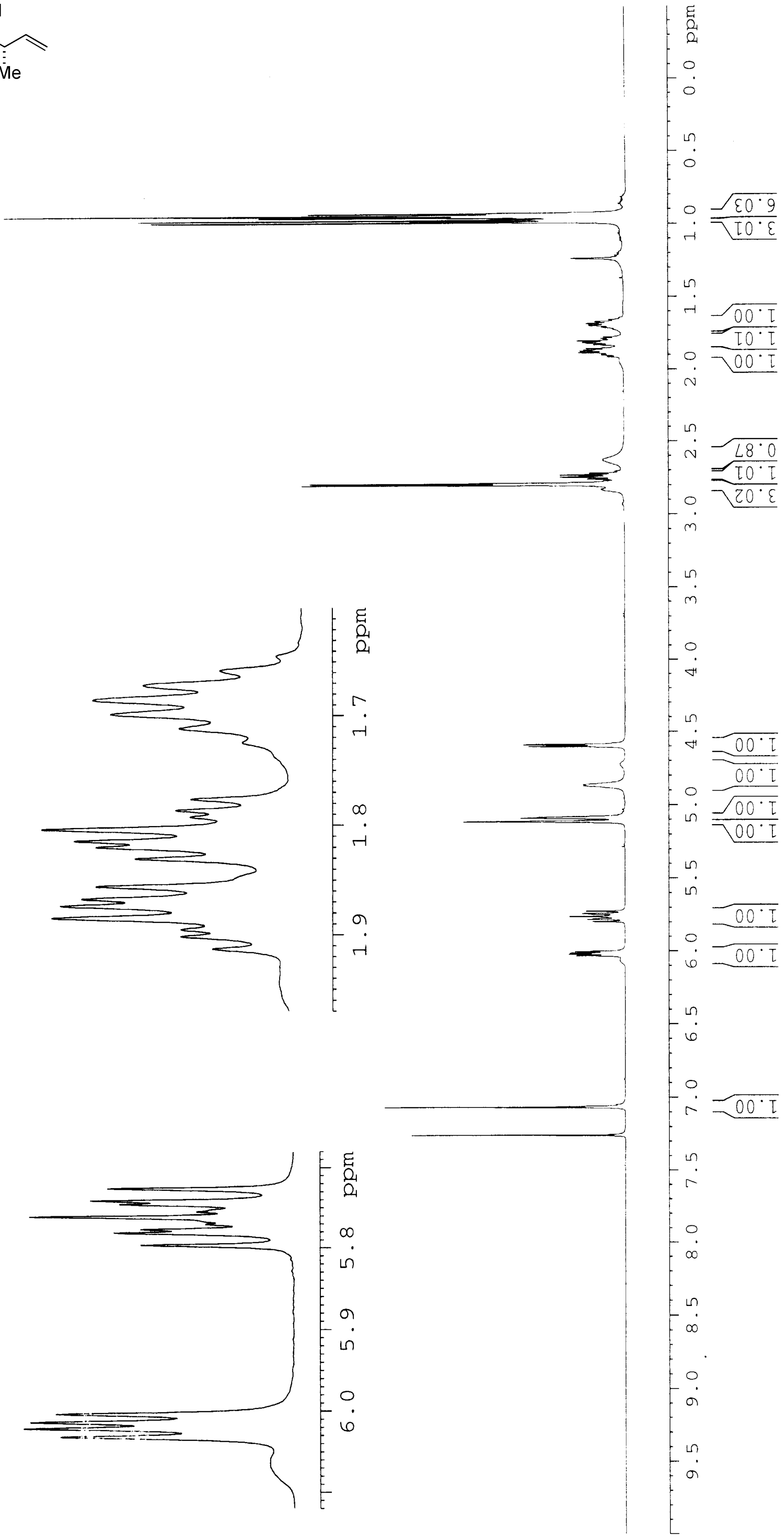
1.31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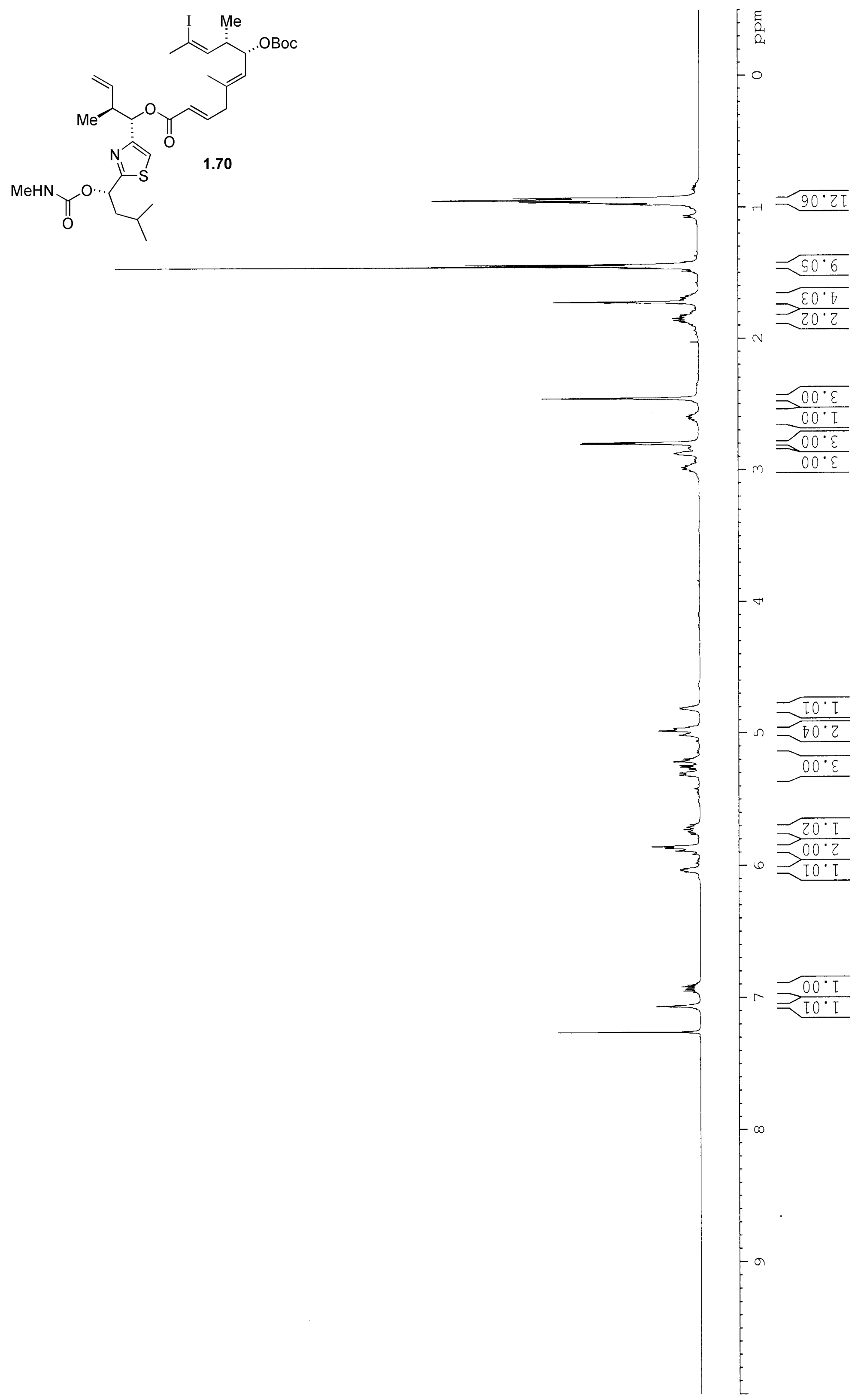

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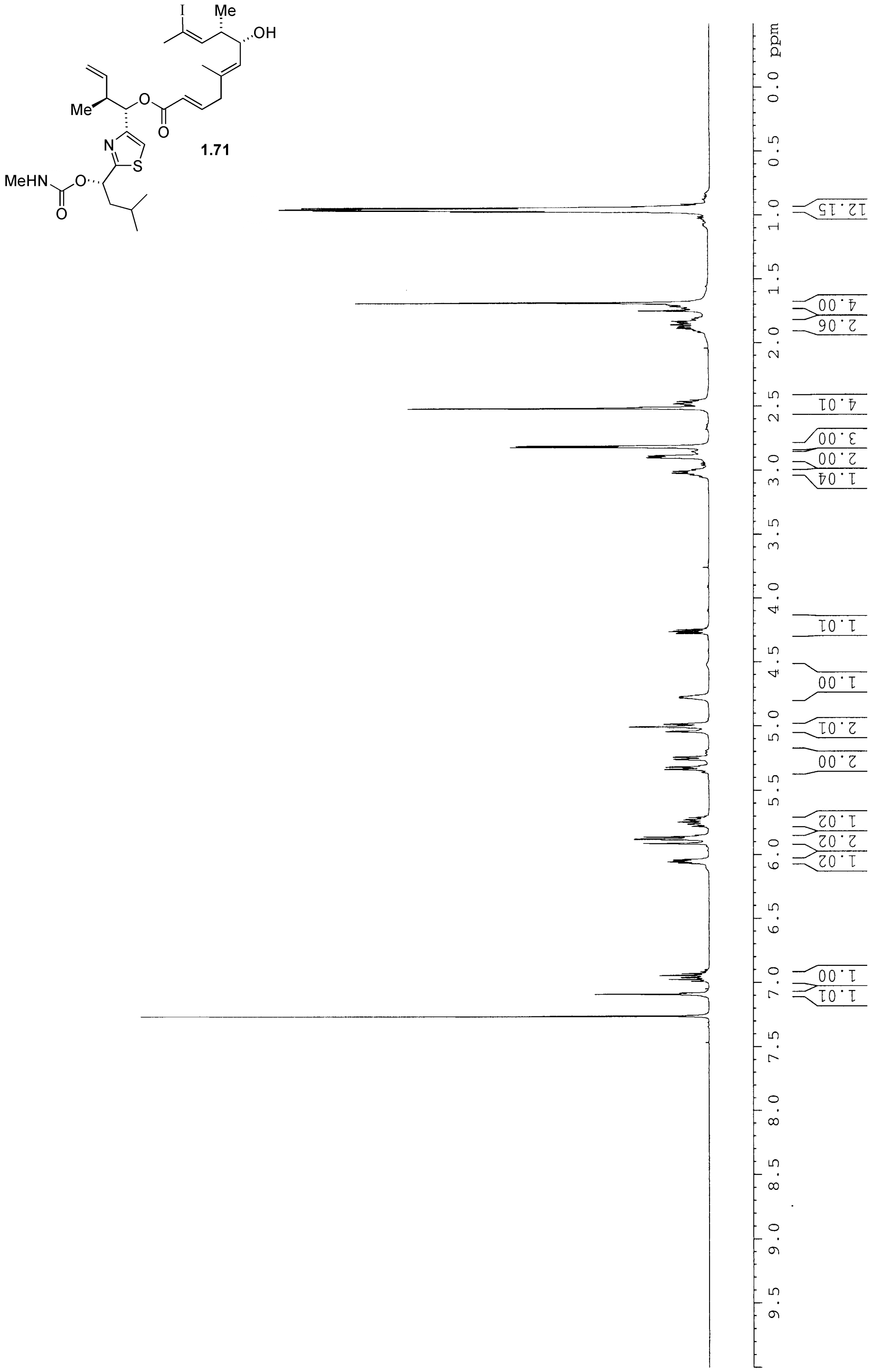
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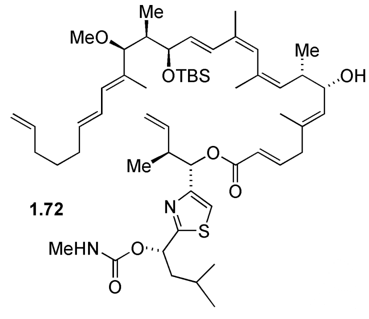
1.71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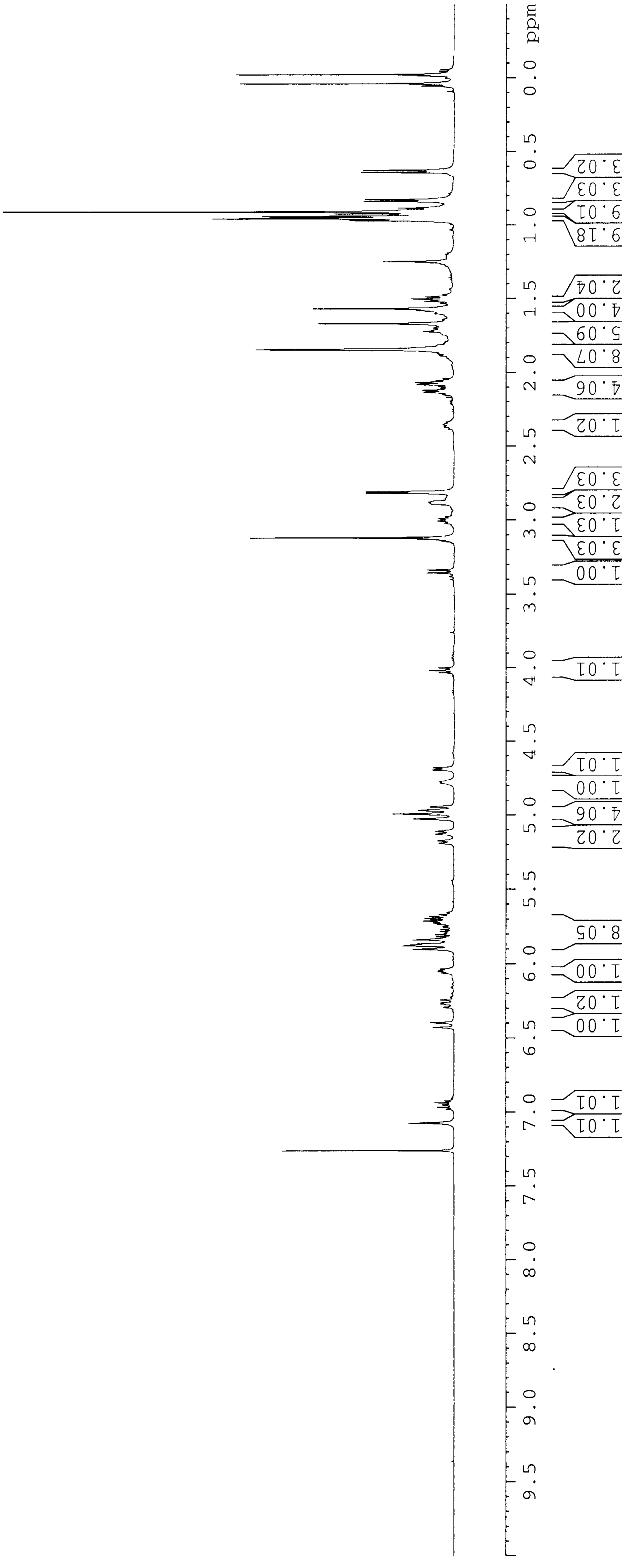
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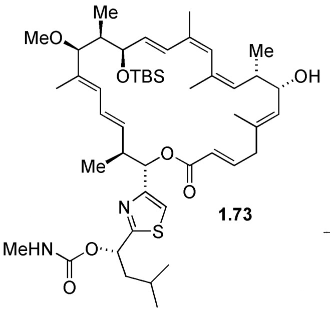
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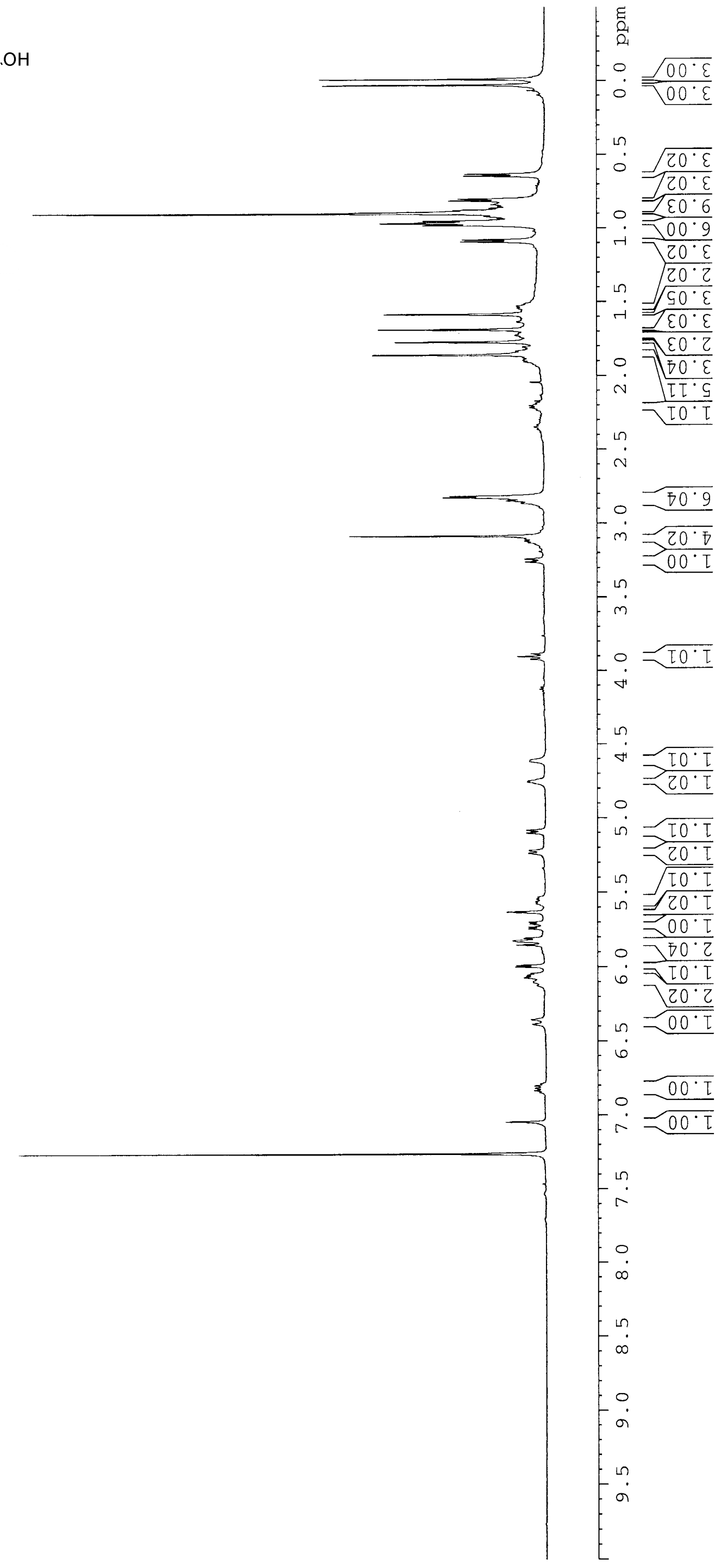
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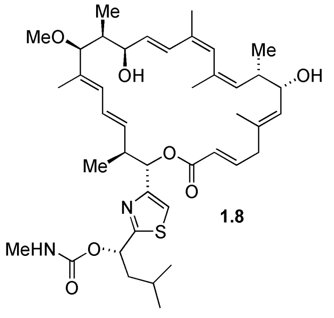
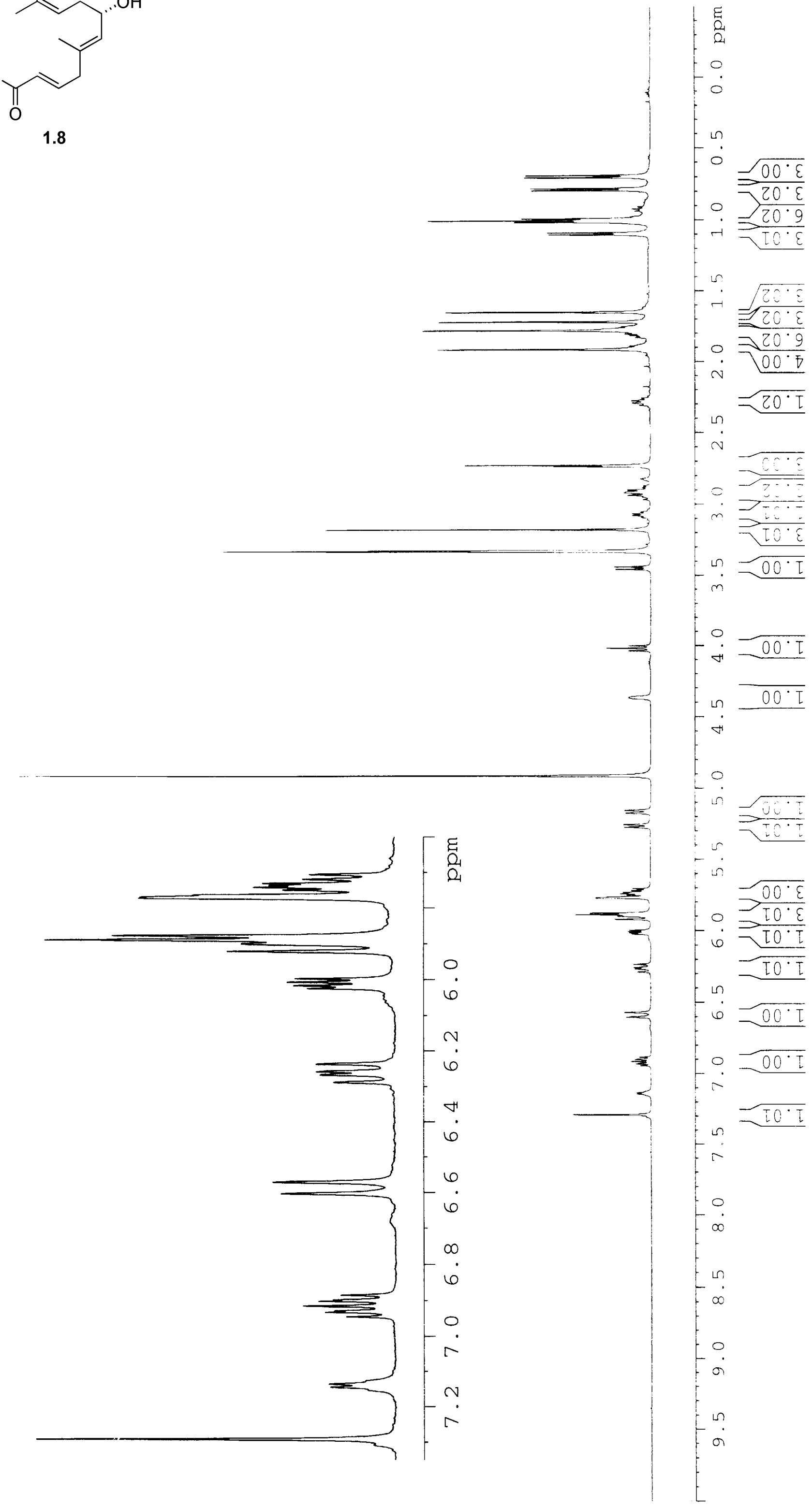


1.8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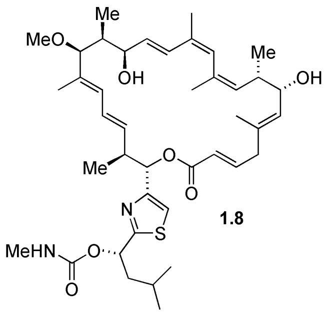
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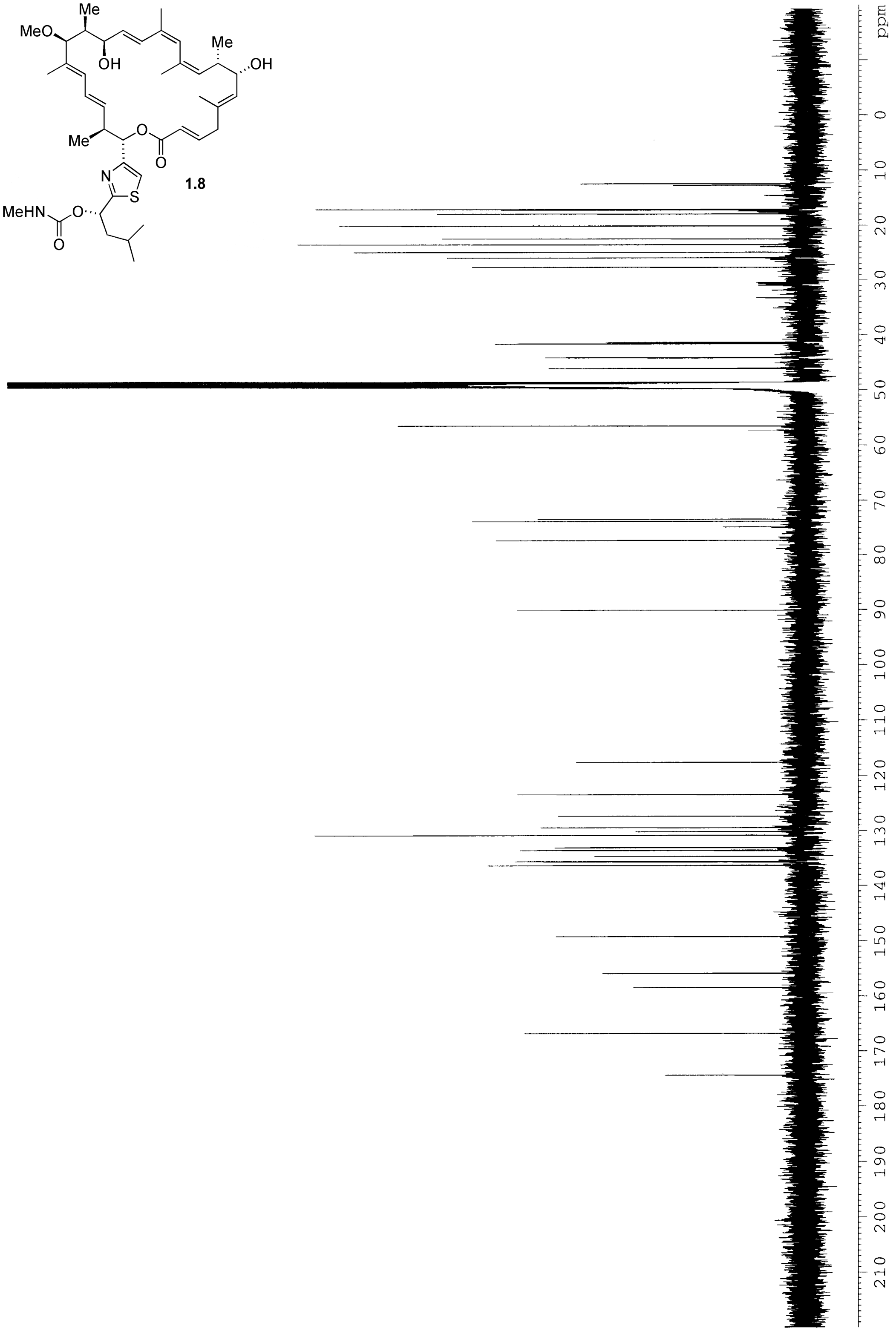
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210

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Chapter 2. Construction of Carbon Skeleton of Archazolid A

Section 2.1. The desire for improved synthetic access to the archazolids

As discussed in section 1.1, natural products and their derivatives have proven to be valuable anticancer agents, and the quest for new scaffolds offers potential to both enhance our understanding of mechanisms that cause cancer and to improve chemotherapy. In collaboration with Professor Angelika Vollmar and Romina Wiedmann at Ludwig Maximilians Universität (Munich, Germany), our synthetic material from the total synthesis of archazolid B (**1.8**) was used to establish that this compound inhibits the growth of highly invasive cancer cells as well as their migration, which causes metastasis.[1] While we have demonstrated new horizons for ring-closing metathesis by way of a relay strategy in our previous synthesis, it has not created a practical and economical method to generate large quantities of this material for further study.

Currently, the interest in the molecular mechanisms of the archazolid molecules and their biological targets is also being explored by the Sieber (Technical University in Munich) and Werz groups (University of Jena, Germany), whose goals are to identify and validate the targets of myxobacterial compounds in cancer cell proteomes. Additionally, the Werz group is also using myxobaceterial compounds to investigate mechanisms related to key pathways linking inflammation to cancer. On a drug discovery front, innovative biotechnological and biosynthetic approaches for the production of simplified analogues are also underway. To this end, the Wenzel group (Saarland University, Germany) has already identified the biosynthetic gene cluster responsible for archazolid biosynthesis. This may allow for mutasynthesis, where late biosynthetic intermediates or their analogues, accessed through synthesis, may be fed into the biosynthetic gene cluster to obtain natural products and their corresponding analogues. Finally, detailed computer-assisted design of simplified analogues ("archazologs") is being carried out by the Schneider group (ETH, Zurich).

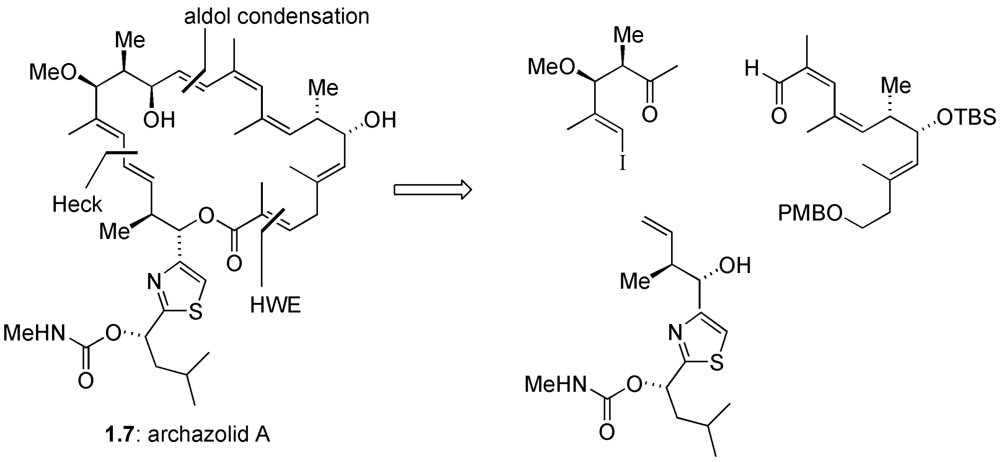
At present, all of these studies are limited by the supply of the archazolid natural products and their biosynthetic intermediates. Improved synthetic methods toward these compounds would potentially overcome this obstacle and this chapter describes progress toward a second generation total synthesis of the archazolids. We have chosen archazolid A, our next target in the family, to explore more robust fragment coupling strategies which we hope will provide valuable insight on the carbon-carbon bond formation of various fragments and provide simpler, easier to access analogues.

Section 2.2. The need for a scaleable strategy

At the onset of this second generation synthesis, a total synthesis of archazolid A (**1.7**) had been reported by Menche and coworkers, featuring a Horner-Wadsworth-Emmons (HWE) macrocyclization (Scheme 2.1).[2] Their strategy features the unity of 3 three fragments by way of a key Heck coupling to stitch the diene in the northeastern fragment and an aldol condensation to construct the triene, whose *Z-Z* motif was introduced by iterative Still-Gennari olefinations. This synthesis makes use of the same thiazole building block **1.31** that we used for archazolid B (**1.8**) but otherwise utilizes different carbon-carbon bond forming methods to produce the macrocycle. While this is an insightful demonstration of a convergent and flexible total synthesis, like our synthesis, it proceeds in 4% overall yield and thus it does not overcome the scaleability issues which we too faced in our first generation synthesis.

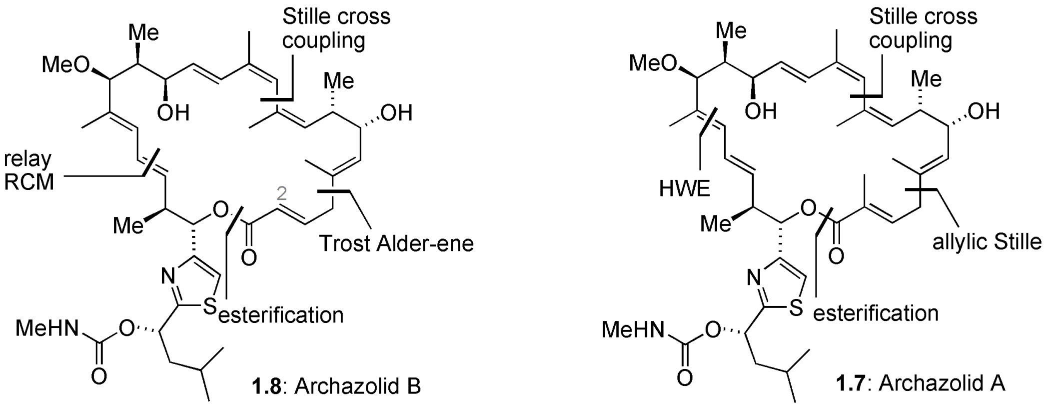
It is interesting to note that in 2009, Menche and coworkers published a full paper on this work, which included optimization of a few key reactions in this synthesis, the preparation of archazolid B (**1.8**), and an alternate ring-closing strategy with a Heck cross coupling.[3] The emphasis on increased robustness and the exploration of alternate fragment-coupling strategies parallels the goals described here, which we too pursued between 2007 and 2009.

Scheme 2.1. A total synthesis of archazolid A by Menche[2]



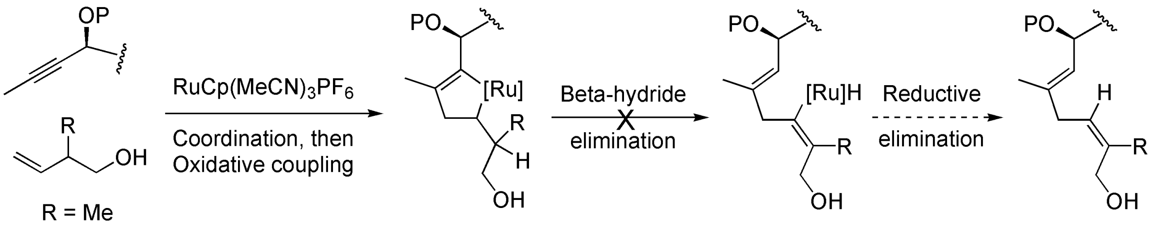
Our goal for a scaleable second-generation synthesis was geared towards archazolid A (**1.7**), which possesses nearly the same activity as archazolid B (**1.8**) but provides us with a new albeit small structural difference; a methyl group at C(2), to explore and investigate (Figure 2.1). Our previous strategy to access archazolid B allowed for possible gram-scale quantities of all three key fragments, however a low yielding endgame sequence precluded obtaining large-scale amounts of the natural product in this manner.[4] The relay RCM strategy in particular, while bold and demonstrative, was not a practical method to apply to this second-generation synthesis; rather, a HWE olefination to link northwest and southwest fragments should be more robust. Esterification and Stille cross-coupling are both conventional methods to unite large fragments for type I polyketide synthesis so we proposed to retain those major disconnections. As macrocyclization has been demonstrated through both of these methods, we expected that either reaction could be employed as the key macrocyclization step and lead to higher yields than our previous synthesis.

Figure 2.1. Retrosynthetic comparison of first and second generation strategies



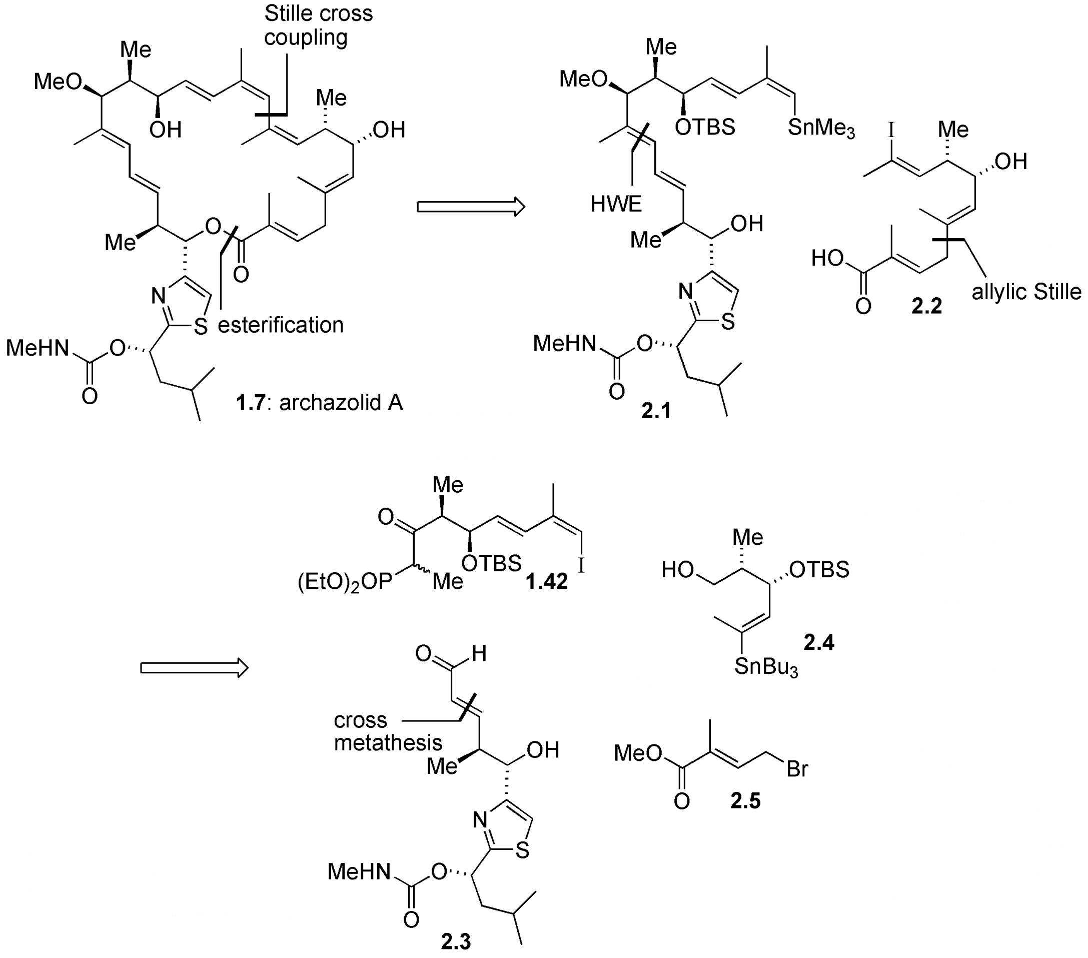
With these major disconnections in mind, the structural difference between archazolids A and B and hence strategic modifications also needed to be addressed. The 1,4-skipped diene was introduced by way of a Trost Alder-ene reaction for archazolid B (**1.8**). No known reactions of this kind have been reported to prepare the corresponding more substituted olefin required for archazolid A. We confirmed our suspicions when all attempts made in our laboratory did not produce the desired product; we hypothesize that the steric bulk introduced by the methyl group may prevent the requisite β-hydride elimination from proceeding (Figure 2.2, for archazolid B, R = H and for archazolid A, R = Me). Thus, the revised strategy to introduce the skipped diene for archazolid A focused on the use of an allylic Stille reaction.[5]

Figure 2.2. Mechanism for Trost Alder-ene reaction



Taken together, the retrosynthetic plan for archazolid A (**1.7**) features the unity of advanced intermediates **2.1** and **2.2** to form the macrocycle through a combination of Stille cross-coupling and esterification (Scheme 2.2). These two halves of the molecule can be further traced back to four subunits: the western fragment **2.1** deriving from a HWE disconnection between β-keto-phosphonate **1.42** (which was established in our previous synthesis), and cross metathesis elaborated thiazole **2.3**, while the eastern fragment **2.2** derives from allylic Stille cross coupling of tributyl stannane **2.4** and known allylic bromide **2.5**.[6] First we describe the construction of western fragment **2.1**, then the preparation and optimization of eastern fragment **2.2** and finally, our progress in the assembly of these two halves.

Scheme 2.2. Retrosynthetic plan for archazolid A

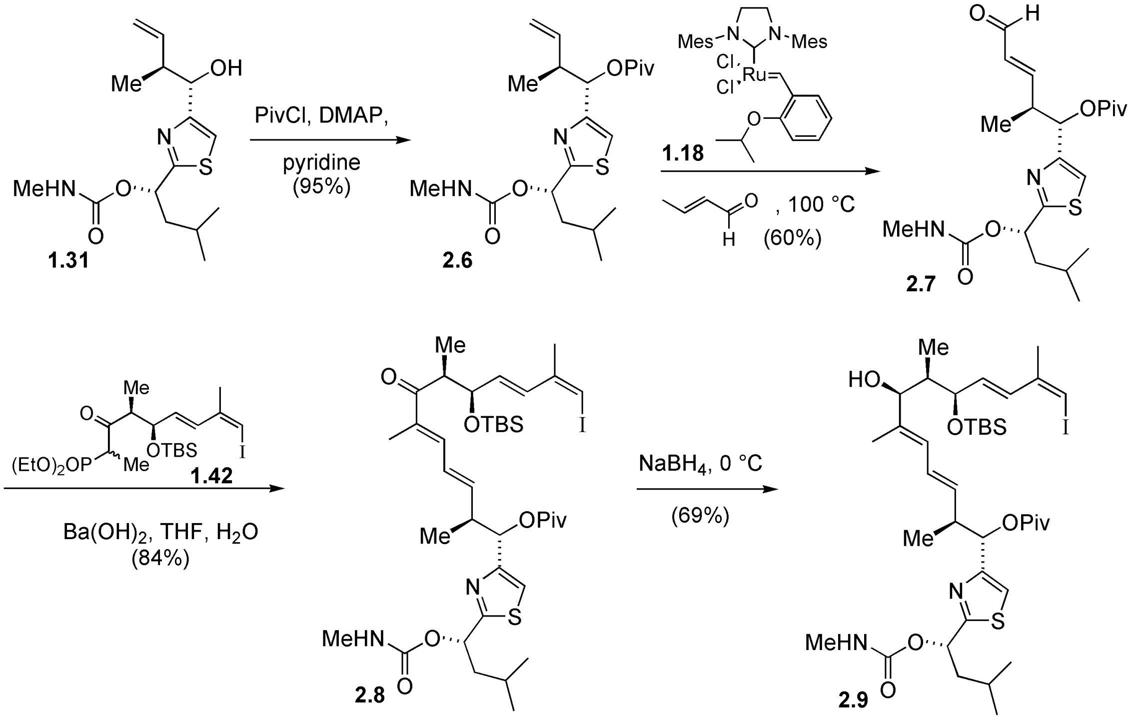


Section 2.3. Preparation of the western fragment

2.3.1. Initial route uniting known thiazole 1.31 with β-keto-phosphonate 1.42

We commenced our efforts to construct the western fragment with thiazole **1.31**, as prepared in our previous synthesis. The first step was to elaborate the terminal alkene to aldehyde **2.7** by way of cross metathesis with crotonaldehyde (Scheme 2.3).

Scheme 2.3. First generation establishment of western fragment



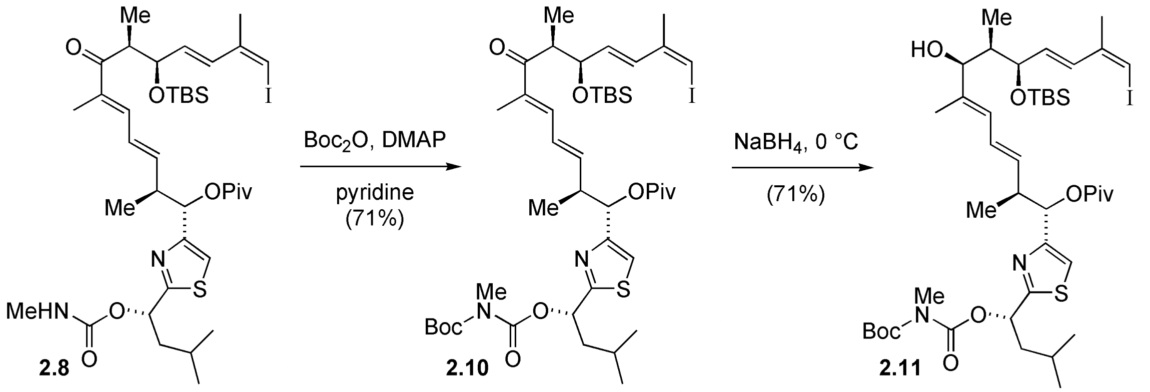
Initial attempts for cross metathesis in the presence of the free alcohol of **1.31** could not effect this reaction; most likely, coordination of the lone pairs on oxygen with the active ruthenium alkylidene species hampered its further reactivity. Fortunately, the presence of a bulky protecting group such as a Piv ester or TBS ether on the alcohol allowed this reaction to proceeded smoothly using an excess of crotonaldehyde and Hoveyda Grubbs 2nd generation catalyst (**1.18**). A Horner Wadsworth Emmons (HWE) reaction with phosphonate **1.42**, prepared from the previous synthesis, proceeded very smoothly and subsequent reduction with sodium borohydride produced alcohol **2.9** as a single diastereomer. However, methylation of this alcohol proved to be challenging due to the presence of the carbamate. While precedence has shown that O-methylation can be effected in the presence of a carbamate,[7] our substrate **2.9** showed that N-methylation on the carbamate was found to proceed more easily than O-methylation (Table 2.1).

Table 2.1. Methylation Attempts for **2.9**

Reagents	Solvent	Temp (°C)	Results
Me_3OBF_4, Proton sponge	DCM	rt	N methylation
Me_3OBF_4, Proton sponge	Toluene	60	N and O-methylation
MeI, Ag_2O	MeCN	60	Partial decomposition and recovery of SM
MeI, Ag_2O	DMF	rt	N-methylation

For this reason, a *tert*-butyl carbamate (Boc) protecting group was introduced onto the nitrogen atom of **2.9**. Initial attempts involved protection of thiazole **2.6**; while cross metathesis proceeded smoothly, the HWE yield was only 23%. Gratifyingly, introduction of the Boc protecting group on **2.8** following HWE of **2.7** and **1.42** was much more scaleable and subsequent reduction of ketone **2.10** also proceeded smoothly (Scheme 2.4).

Scheme 2.4. Preparation of Boc-protected **2.11** for methylation

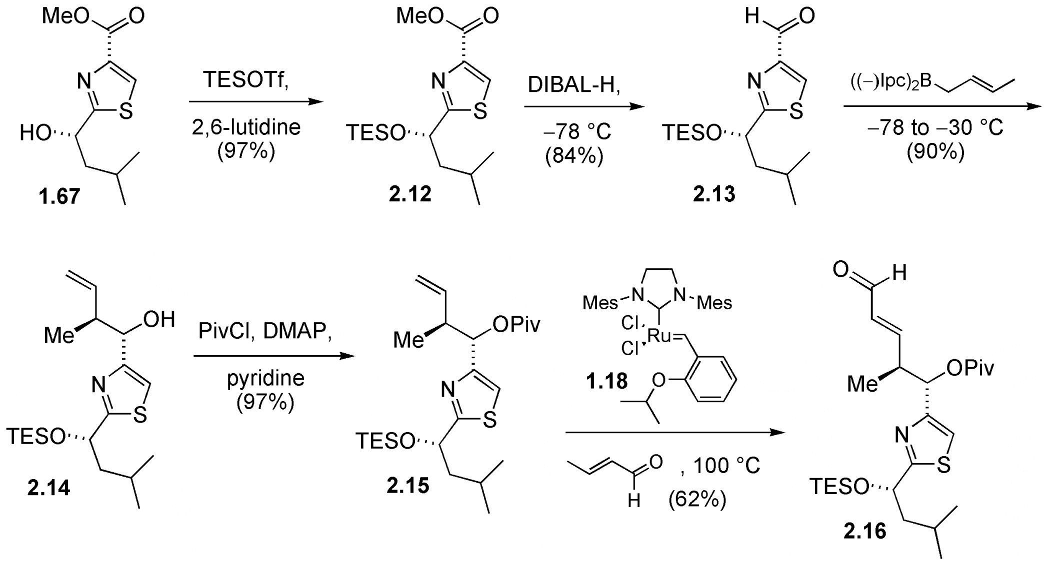


Methylation of this substrate **2.11** faced multiple challenges. Initial attempts with methyl iodide or dimethyl sulfate, using sodium hydride (NaH) as a base, resulted in no reaction and then decomposition upon heating of the reaction. Further study at a later point in the project determined that poor quality NaH was the likely culprit for these results. At the time however, this led us to suspect that steric hindrance around the hydroxyl group was inhibiting reactivity and thus we turned to highly electrophilic methyl sources (magic methyl or methyl triflate). These conditions led to significant amounts of side-products, however, the desired product could be obtained through a few minutes of reaction with methyl triflate and hindered base 2,6-di-*tert*-butylpyridine in 15% yield (83% based on recovered starting material). Removal of the Boc group was attempted on this material using trifluoroacetic acid; this led to decomposition and we decided to revise the route so as to minimize protecting-group operations, which were leading to complication in the synthesis.

2.3.2. Revised route that introduces carbamate functionality after methylation

Since the presence of the carbamate was problematic for methylation of **2.9** and the introduction of a Boc protecting group of **2.11** added more steps and posed further challenges, we decided to install the carbamate following the methylation step. This strategy made use of the protection of thiazole substrate **1.67** as the corresponding triethylsilyl (TES) ether (Scheme 2.5). These reactions proceeded very similarly to substrates discussed previously to afford aldehyde **2.16**.

Scheme 2.5. Preparation of revised thiazole building block

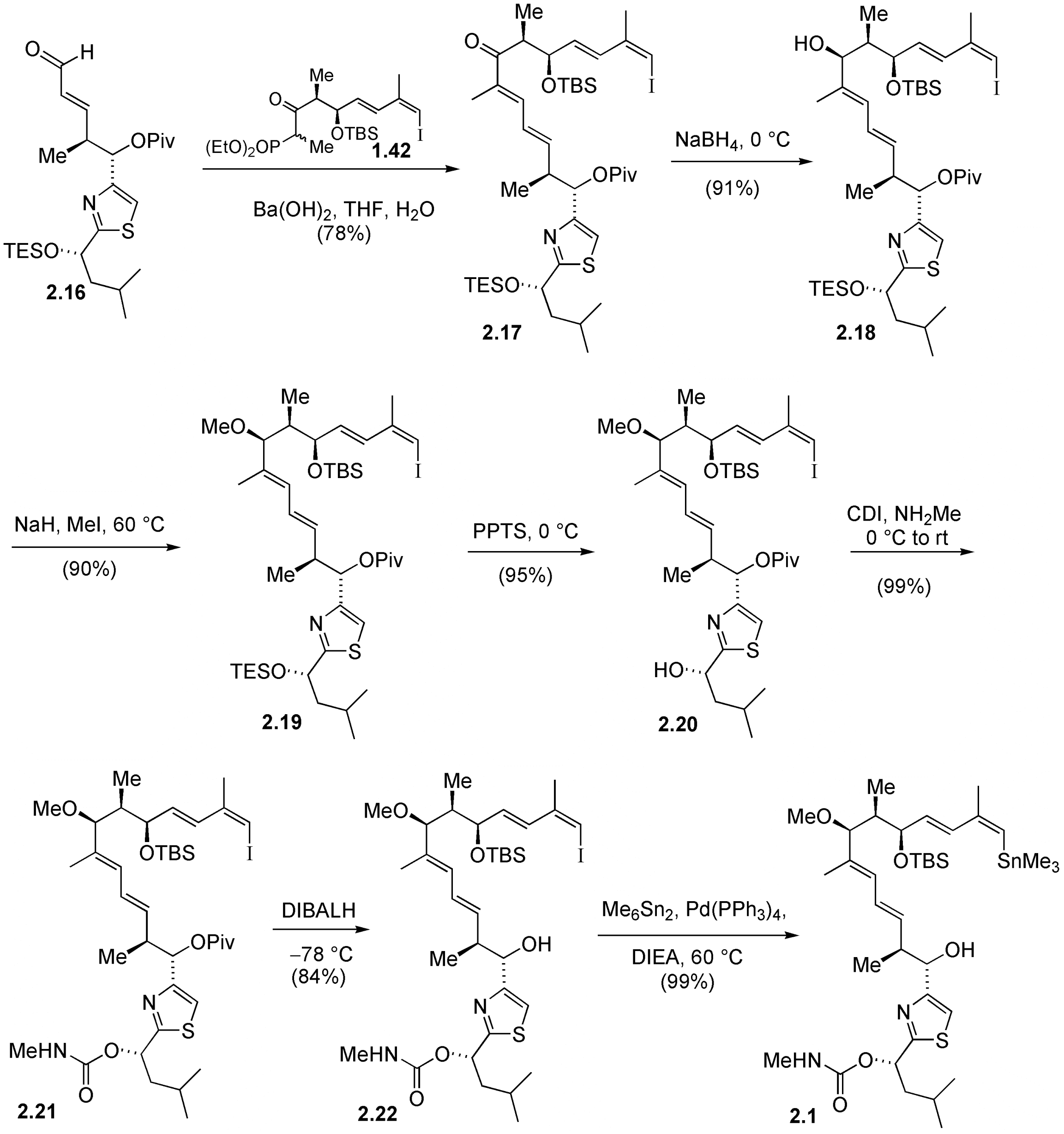


Gratifyingly, aldehyde **2.16** underwent HWE olefination and reduction of the resulting ketone **2.17** cleanly, leading to a highly scaleable synthesis of the methylation precursor **2.18** (Scheme 2.6). It was at this juncture that it was determined our source of sodium hydride had become compromised and new sodium hydride provided optimal yields of the methylated product (Table 2.2). Additionally, it was established that the side-product seen when methyl triflate was used as the methyl source was the result of N-methylation from the thiazole ring (in addition to hydroxymethylation), underscoring the need to properly tune the reactivity of the methyl source employed.

Table 2.2. Methylation Conditions Screened for **2.18**

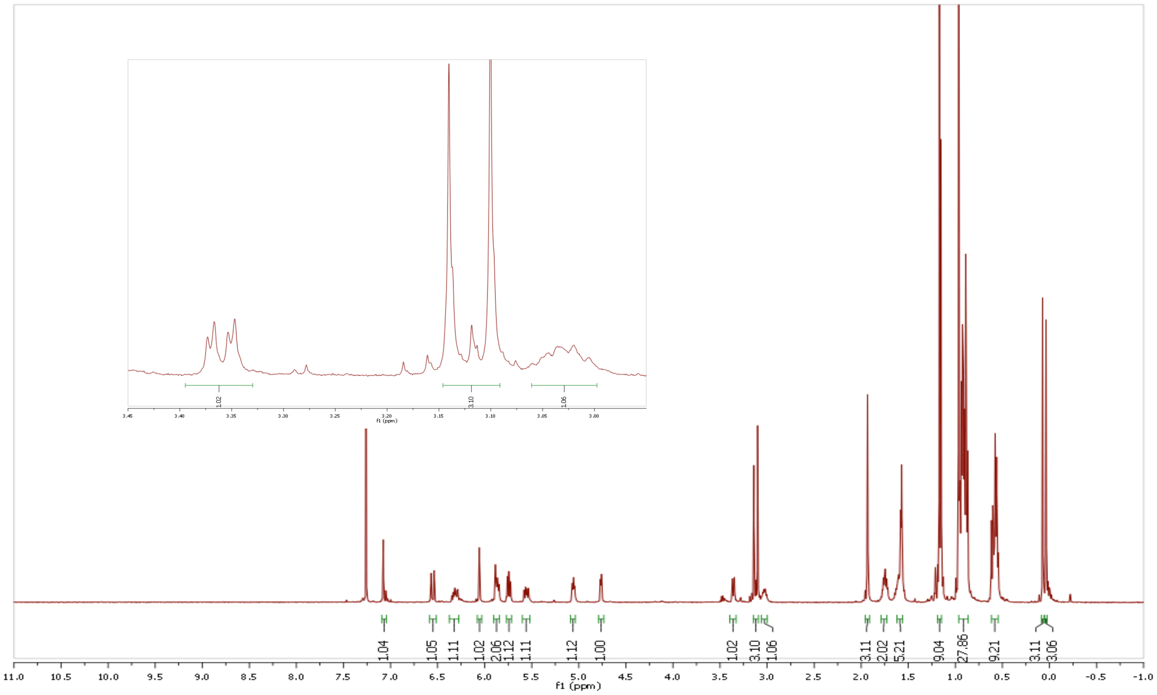
Methylation reagent	Base	Temp (°C)	Results
Me_3OBF_4	Proton sponge	rt	No reaction
MeI	KHMDS, 18-crown-6	rt	Decomposition
MeOTf	2,6-di-t-butylpyridine	rt	O-methylation and N-methylation of thiazole
MeI	NaH	60	91% yield
Me_2SO_4	NaH	50	33% yield

Scheme 2.6. Completion of western fragment **2.1**

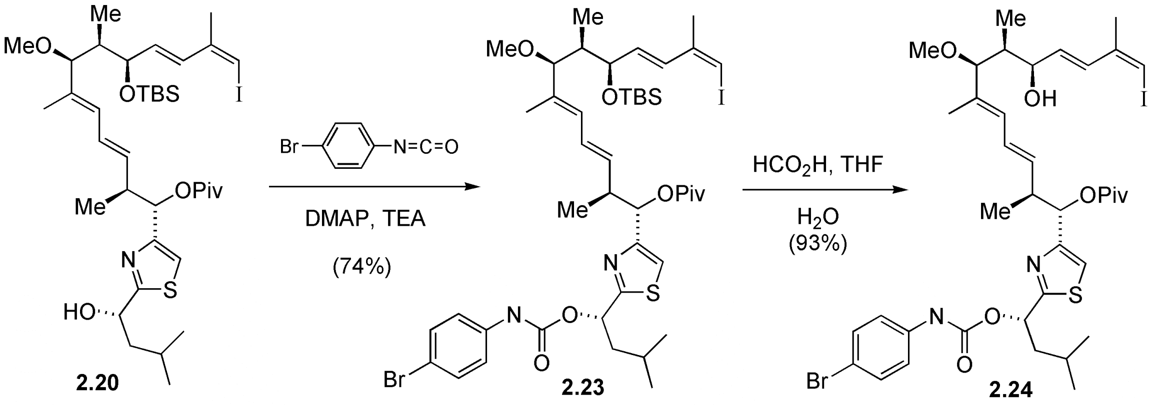


Concern over the characterization of **2.19** however, arose from the methoxy signal observed in the proton NMR spectrum at δ 3.12 ppm. An usual pattern appearing as an asymmetric doublet with a shoulder was integrated as 3H (see supplementary information and Figure 2.3). A COESY spectrum showed no coupling of this methyl peak with other peaks and all other characterization strongly suggested that the material was a single product. In attempt to gain unequivocal structural confirmation, we synthesized bromocarbamate derivative **2.24** in 3 steps with the hope of obtaining a crystal structure (Scheme 2.7).

Figure 2.3. Unusual splitting pattern observed for methoxy ether signal for **2.19** (600 MHz ^{1}H NMR)

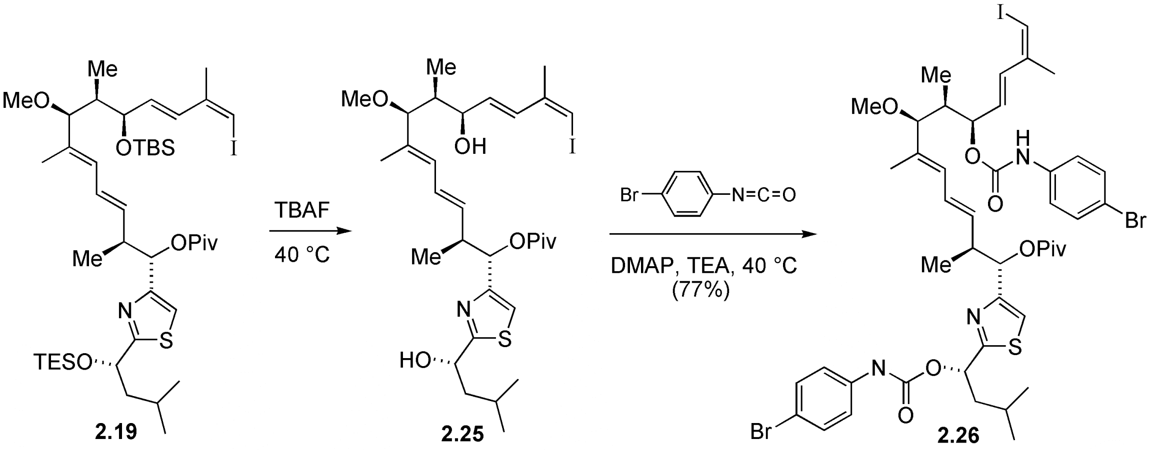


Scheme 2.7. Preparation of bromocarbamate **2.24**



Unfortunately none of our recrystallization attempts of the foamy solid **2.24** were effective; we infer that the carbon chain has too many degrees of flexibility to crystallize. By heating the deprotection to 40 °C and adding excess tetrabutylammonium fluoride, both the TBS and TES groups could be removed (Scheme 2.8). The bis bromocarbamate substrate **2.26** was prepared from this diol **2.25**, but was unfortunately too unstable for obtaining quality crystals.

Scheme 2.8. Preparation of bis-bromocarbamate **2.26**



Unable to fully rule out the presence of an additional substance in substrate **2.19**, we determined to continue on with the material in hand, reasoning the if indeed it contained more than one compound, they would become separable at a later point in the sequence. We therefore completed the synthesis of the western fragment **2.1** with carbamoylation to afford **2.21**, a deprotection of the Piv ester to provide **2.22**, and a palladium catalyzed iodine-tin exchange to complete **2.1**, all of which proceeded in high yield (Scheme 2.6). Initial attempts to deprotect the Piv ester of **2.21** in the presence of sodium methoxide gave significantly lower yields and no reaction was observed using potassium *tert*-butoxide, leading to the use of di-*iso*-butylaluminum hydride (DIBAL-H) in a reductive deprotection strategy.

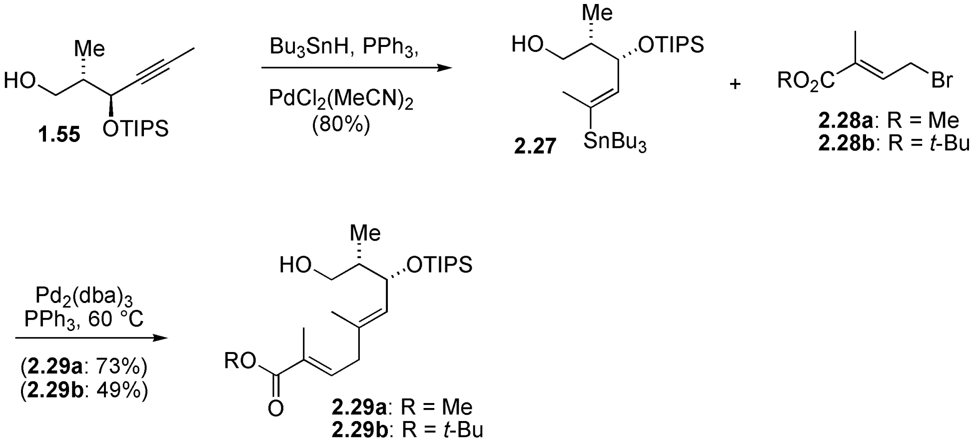
The unusual pattern with the methyl peaks in the proton NMR persisted through this sequence of reactions. Temperature experiments of **2.21** in *d*-toluene and *d*-DMSO were conducted in the 500 MHz NMR. While peak broadening was observed, they did not coalesce at 120 °C and the samples were not heated above this temperature. Additionally, all NMR data aside from the pattern observed for the methoxy group suggested the presence of a single compound and curiously, after removal of the Piv protecting group, the methoxy peak for **2.22** appeared more as a shouldered singlet. Further, HPLC analysis of methoxy ether **2.19** only showed one peak. It is possible that two major confirmations of this carbon chain exist and could explain the cause of this spectral conundrum. Nevertheless, if two compounds are indeed present, we believed that separation could be achieved at a later stage, for example, during the final steps of the synthesis, when large structural changes would occur so that if two compounds were present, they could be separated. For these reasons, we commenced our investigation of uniting stannane **2.1** as prepared via this method with vinyl iodide **2.2**, whose preparation is described in the following section.

Section 2.4. Preparation of the eastern fragment

2.4.1. Initial strategy elaborating TIPS ynol to methyl and *tert*-butyl esters

We started exploring the allylic Stille strategy toward intermediate **2.2** with ynol **1.55**, which had been prepared in our archazolid B synthesis. As discussed previously, this sequence will construct the segment of archazolid A that contains the structural difference from archazolid B. In addition to installing the requisite carbon-carbon bond, this transformation could also, in one step, provide an ester for later conversion to the corresponding acid, minimizing oxidation state adjustments. Of concern was the potential sensitivity of the skipped diene to alkene migration to the thermodynamically more stable conjugated diene. Not knowing *a priori* whether the skipped diene would be more sensitive to acidic or basic conditions, we prepared two derivatives of this substrate: one methyl ester **2.29a** from known allylic bromide **2.28a** as well as its *tert*-butyl variant **2.29a** (Scheme 2.9), hoping that with careful tuning of reaction conditions, saponification of one of the esters could be achieved.

Scheme 2.9. Preparation of TIPS protected esters **2.29a** and **2.29b**



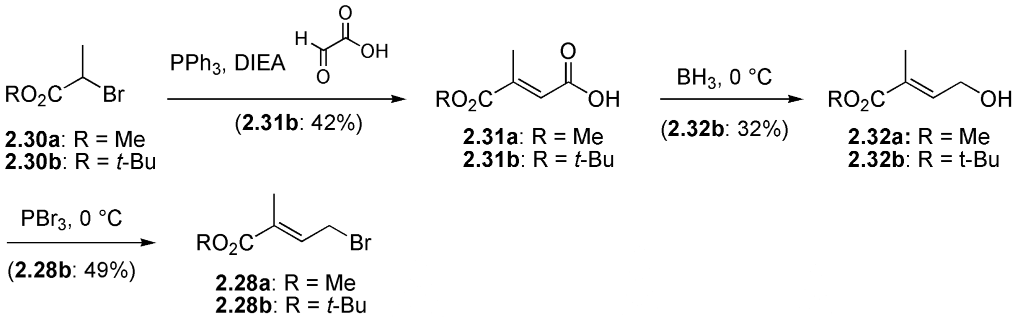
Starting from alkyne **1.55** established in the previous synthesis, a regioselective hydrostannylation was found to be optimal. The reaction conditions explored are shown (Table 2.3). Unsatisfactory yields using traditional conditions led to the use of bis(acetonitrile)dichloropalladium(II) ($PdCl_2(MeCN)_2$) and triphenylphosphine; conditions which previously have not been reported for affecting hydrostannylation. It was also found that a slow, dropwise addition of tributyltin hydride (Bu_3SnH) was crucial for obtaining high yields and that the presence of 1% triethylamine in the flash column chromatography eluent was necessary for minimizing protodestannylation. Interestingly, none of the undesired regioisomer was observed, most likely due to greater steric size of the internal position clashing with the bulky tributylstannyl functionality.

Table 2.3. Reaction conditions explored for hydrostannylation of alkyne **1.55**

Catalyst	Ligand	Solvent	Temp. (°C)	Result
$Pd(PPh_3)_4$	--	THF	0-40	2% yield
$Pd(OAc)_2$	PCy_3	Hexanes	rt	Complex mixture
$PdCl_2(PPh_3)_2$	--	THF	0-rt	Complex mixture, no desired product observed
$Pd_2(dba)_3$	PPh_3	THF	60	35% yield
$Pd(dppf)Cl_2$	--	THF	rt	38% yield
$PdCl_2(MeCN)_2$	PPh_3	THF	rt	80% yield

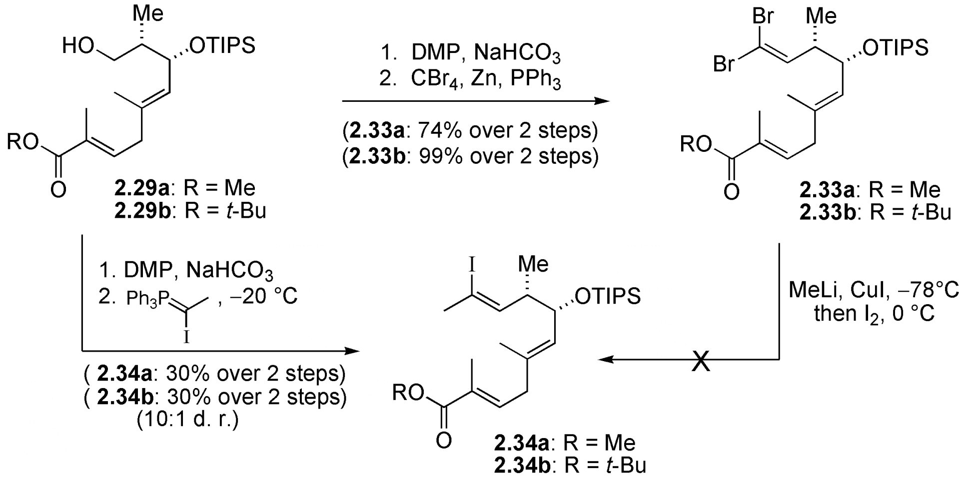
The allylic Stille reaction was originally investigated with methyl ester **2.29a**, which was prepared in 5 known steps from methyl 2-bromopropionate **2.30a** (Scheme 2.10).[6] Specifically, Wittig reaction with glyoxylic acid monohydrate provided **2.31a** and selective reduction of the carboxylic acid provided allylic alcohol **2.32a**. Upon conversion to allylic bromide **2.28a** using phosphorous tribromide, the allylic Stille reaction proceeded smoothly under both known sets of conditions: a satisfactory 51% yield of **2.29a** was observed using $PdCl_2(MeCN)_2$ in chloroform and the yield improved to 73% with tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) with triphenylphosphine (Scheme 2.9). This reaction proceeded in a slightly lower 49% yield for the corresponding *t*-butyl ester **2.29b**, which was prepared in an analogous manner to the methyl ester allylic bromide **2.28a** from *tert*-butyl 2-bromo propionate (Scheme 2.10).

Scheme 2.10. Preparation of tiglic acid ester derivatives **2.28a** and **2.28b**



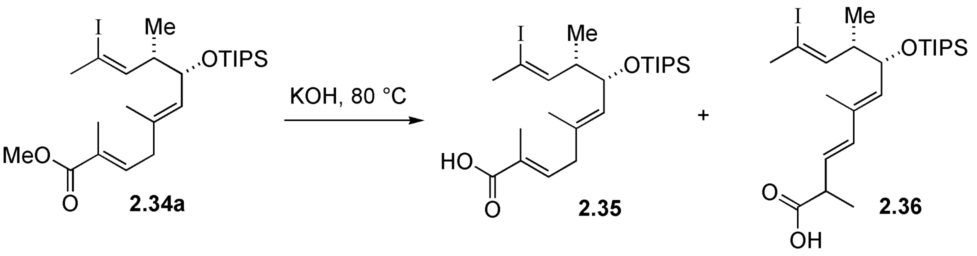
Vinyl dibromides **2.33a** and **2.33b** were optimally prepared using zinc, tetrabromomethane and triphenylphosphine (Scheme 2.11). By comparison, if potassium carbonate was used instead of zinc, the product **2.33a** was formed in 37% yield accompanied by 50% elimination of TBS-alkoxide. This set the stage for installation of the vinyl iodide by employing Tanino-Miyashita conditions reported for archazolid B.[8] However, no reaction was observed for either dibromoalkene **2.33a** or **2.33b**, indicating that most likely, the presence of an ester functionality hampers this reaction. An alternate route consisting of oxidation of alcohol **2.29a** or **2.29b** to the corresponding aldehyde followed by Stork-Zhao olefination installed the vinyl iodide of **2.34a** or **2.34b** successfully in 30% yield and 10:1 regioselectivity.

Scheme 2.11. Installation of vinyl iodide of **2.34a** and **2.34b**



Saponification of the methyl ester of **2.34a** was met with initial challenges: preliminary experiments on this substrate produced the requisite acid **2.35** at best in 50% yield with the other 50% resulting in olefin migration, curiously to the less substituted olefin **2.36** (Scheme 2.12). This illustrates that conjugation provides greater thermodynamic stability than substitution in this case. This reaction required at least two equivalents of potassium hydroxide and needed to be heated to 80 °C overnight, suggesting that the carbonyl of the ester was difficult to access due to the methyl group α to the ester. Reaction with lithium hydrogen peroxide, generated in situ, was also attempted since peroxides are better nucelophiles than hydroxides.[9] However, no reaction was observed using these reagents at room temperature.

Scheme 2.12. Saponification of methyl ester **2.34a**



Attempts to saponify the corresponding *tert*-butyl substrate **2.34b** proved to be less successful. The use of trifluoroacetic acid resulted in saponification with concomitant loss of triisopropylsilanol (TIPSOH), whereas reaction with toluenesulfonic acid monohydrate demonstrated that only the elimination of the TIPS silanol proceeded with short reaction times whereas longer reaction times resulted in subsequent saponification. It was therefore apparent that in an acid catalyzed pathway, the undesirable elimination of TIPS silanol proceeded more favorably than saponification and the methyl ester **2.34a** was therefore a better choice of substrate than the corresponding *tert*-butyl ester **2.34b**.

Initial cross coupling attempts were conducted on free acid **2.35** since Stille couplings in the presence of free acids are known.[10] Preliminary experiments on small scale were conducted under the modified Liebeskind conditions used for archazolid B. Typically, only traces of the desired product were obtained. Because the yield was consistently under 10%, we considered it possible that the bulky TIPS protecting group near the vinyl iodide was causing steric hindrance that prevented this reaction from proceeding smoothly. All conditions found to deprotect TIPS ethers make use of fluoride sources, and our attempts to deprotect this silyl ether accordingly were ineffective (Table 2.4). Due to difficulties in removing this TIPS group, we decided to remake the substrate using a more labile *tert*-butyldimethylsilyl (TBS) protecting group.

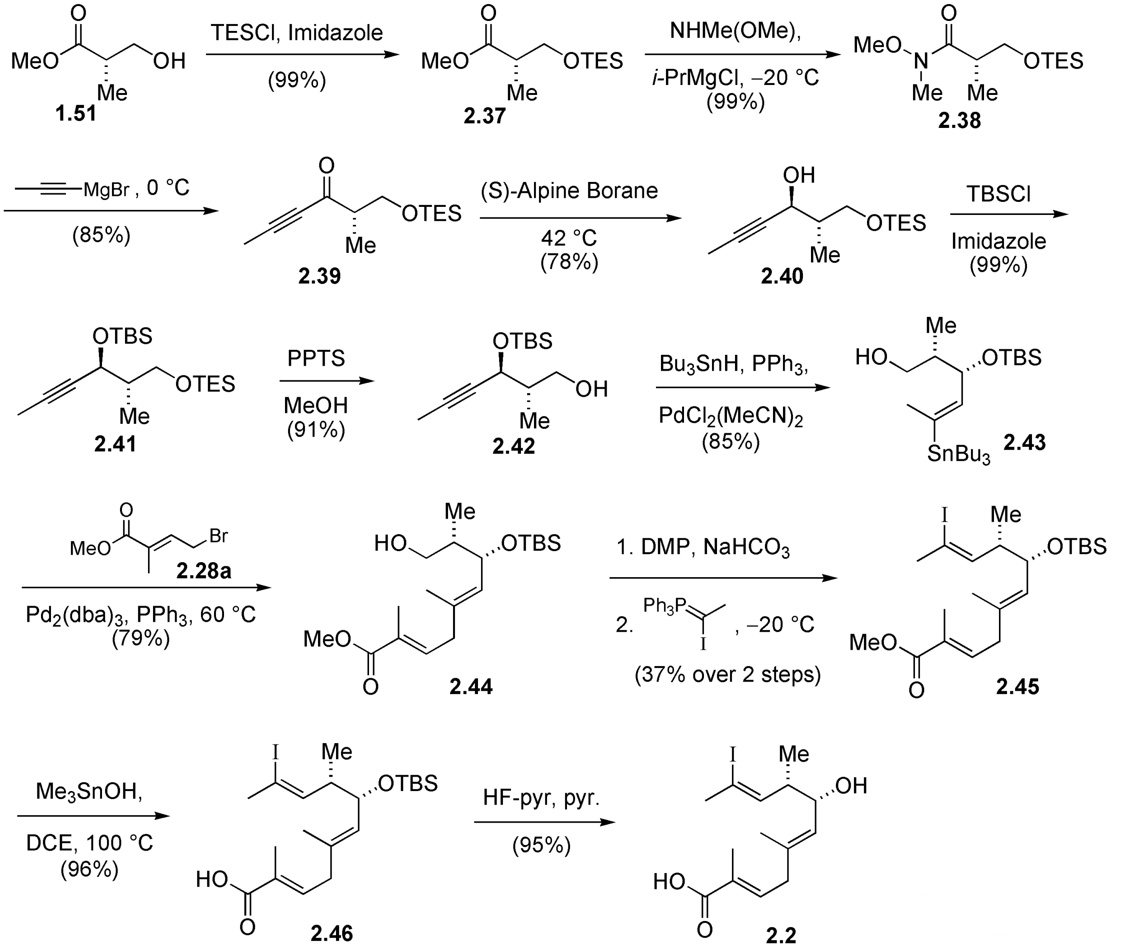
Table 2.4. Attempted Conditions for TIPS Deprotection of **2.35**

Conditions	Results
HF in MeCN	Immediate decomposition
TBAF in THF	Only elimination of TIPS alkoxide observed
TASF in THF, DMF	No reaction
HF-pyr., pyridine, THF	Only decomposition observed.

2.4.2 Revised route containing TBS protecting group

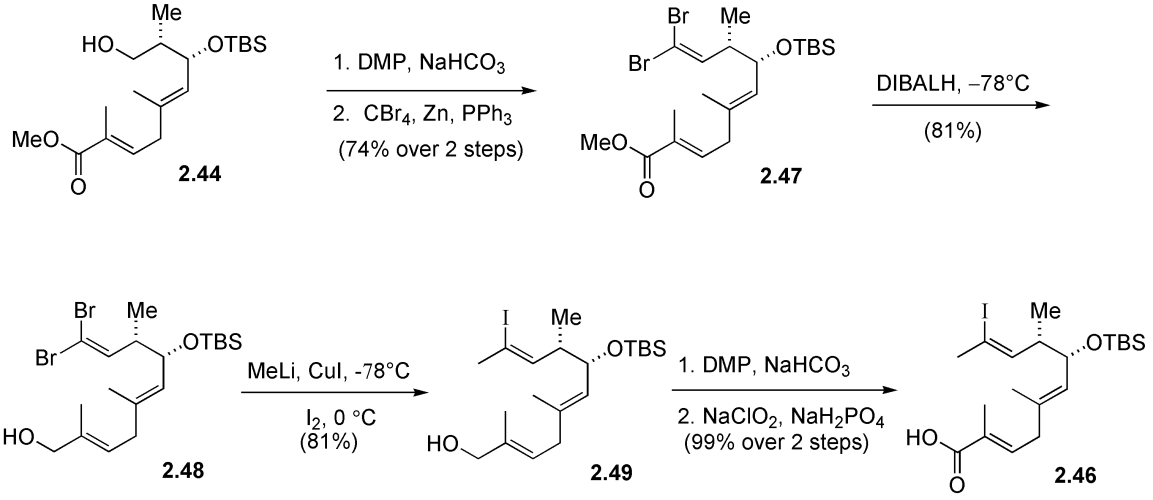
Vinyl iodide **2.46** was prepared accordingly to methods described both in chapter 1 and earlier in this section (Scheme 2.13). Fortunately, the presence of a TBS protecting group rather than a TIPS protecting group did not affect the reactivity of this substrate. The resynthesis of this fragment with a new protecting group offered us an opportunity to optimize several of the steps in the sequence. The saponification of methyl ester **2.45** was optimized using trimethyltin hydroxide (Me_3SnOH), a method developed by Nicolaou and coworkers.[11] Other conditions attempted included heating with barium hydroxide or silver oxide, both of which resulted in no reaction. Trimethyltin hydoxide was mild enough to prevent the troublesome isomerization that stronger bases cause, yet this reaction required 100 equivalents at 100 °C overnight. Compared to the 1-10 equivalents and temperature of 60-80 °C reported by Nicolaou, these strongly forcing conditions also played a significant role in the difficulty of this transformation.

Scheme 2.13. Completion of **2.2** using a TBS protecting group strategy



While we had now solved the issue of low yield in the saponification of **2.45**, the Stork-Zhao olefination to access **2.45** still presented difficulties. At best, it could only be achieved in 37% yield and of even greater concern was an ability for it to be reproduced on large scale. After consistently providing yields under 10% on a multigram scale, we sought a more reliable pathway to obtain this *Z*-vinyl iodide. We decided to reinvestigate the method developed by Tanino and Miyashita to install this functionality, which had performed reliably in our synthesis of archazolid B.[8] As previously discussed, we believed the presence of an ester was preventing the success of this reaction, and indeed, reduction of the ester of **2.47** to alcohol **2.48** allowed for effective installation of the vinyl iodide **2.49** in a satisfying 81% yield (Scheme 2.14). Oxidation using Dess-Martin periodinane followed by Pinnick conditions provided the requisite acid in 54% over 6 steps. While this sequence required more steps than a Stork-Zhao olefination, it was more reliable and thus became our chosen method to obtain large quantities of vinyl iodide **2.46**.

Scheme 2.14. A scaleable alternate method to access vinyl iodide **2.46**



With compound **2.46** now in hand, only removal of the TBS protecting group remained to complete the synthesis of this fragment **2.2**. A screen was conducted (Table 2.5), and while most attempts led to either decomposition or else no reaction, HF-pyridine buffered in pyridine led to clean removal of the TBS group.

Table 2.5. Investigation of TBS Deprotection of **2.46**

Conditions	Temp (°C)	Result	Ref.
1% Otera's catalyst	rt	No reaction	12
1% Otera's catalyst	70	Decomposition	
CsF, 9:1 MeCN/H_2O	90	No reaction	13
H_2O_2, NaOH, MeOH	rt	No reaction	14
LiCl, H_2O, DMF	90	Decomposition	15
$BF_3{\cdot}OEt_2$, MeCN	0 to rt	No reaction	16
KF, 18-crown-6, MeCN	rt	No reaction	17
TMSOTf, DCM	0	Decomposition	18
H_2SiF_6, MeCN	rt	Traces of product and decomposition	19
H_2SiF_6, TEA, MeCN	rt	Traces of product and decomposition	
TBAF, $BF_3{\cdot}OEt_2$	rt	Decomposition	
HF-pyridine, pyridine, DCM	rt	95%	

Section 2.5. Efforts to unite eastern and western fragments

With both building blocks **2.1** and **2.2** in hand, we were prepared to attempt to unite them. This could be achieved through either esterification followed by macrocylic ring closure through Stille coupling, or cross coupling followed by macrolactonization. First we describe our efforts towards the former, then the latter.

Section 2.5.1. Investigation of esterification approach

A number of esterification conditions were attempted through activation of the acid of **2.46** (Scheme 2.15, Table 2.6). All of the conditions employed gave different results; Yamaguchi esterification[20] led to isomerization, indicated by the absence of the enoate peak and appearance of two new olefins in the proton NMR. The use of *m*-nitrobenzoic anhydride and 4-(dimethyl)aminopyridine (Shiina conditions)[21] led to decomposition while more traditional methods such as the Corey-Nicolaou method[22] or activation with *iso*-propyl chloroformate saw no reaction following formation of the activated ester. The presence of the acid sensitive stannane of **2.1** provided further challenges, as reaction with N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide (EDC) led to successful coupling, but with concomitant protodestannylation and Keck conditions[23] did not lead to the desired product. We also attempted esterification under the Kita conditions employed for archazolid B.[24] Presumably, the steric difference introduced by the presence of the methyl group of archazolid A prevented coupling from taking place under these conditions. In addition, the catalytic acid used in this method was enough to lead to protodestannylation of **2.1**. Although these experiments did not yield our desired product, they suggest that after cross coupling, EDC might be a viable way to close this ring after the stannane functionality is no longer present in the molecule.

Scheme 2.15. Esterification strategy to unite building blocks **2.1** and **2.46**

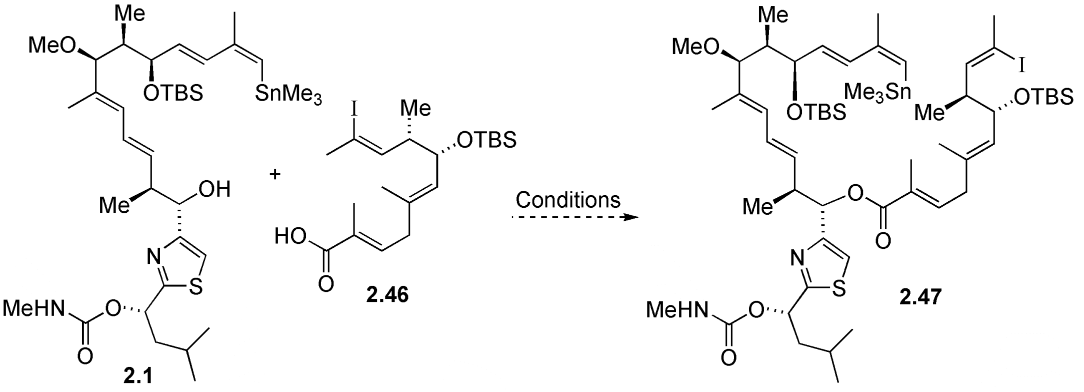


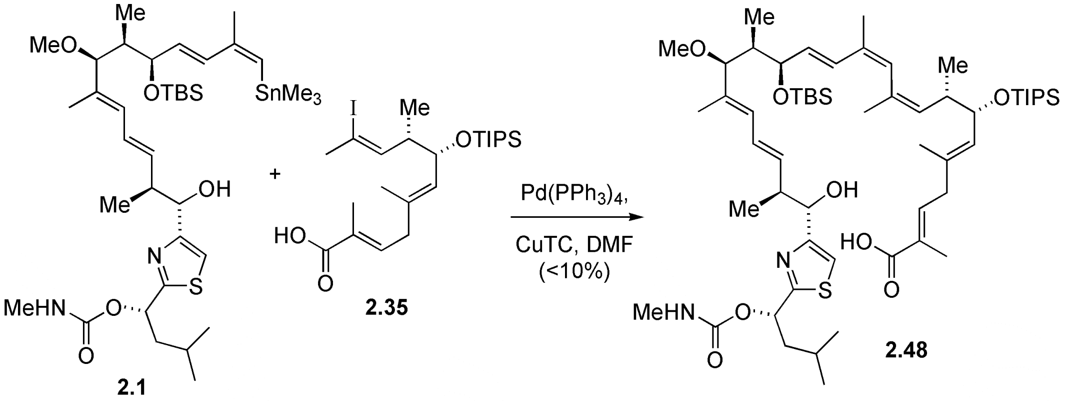
Table 2.6. Attempts to Esterify **2.1** and **2.46**

Reagents	Temp (°C)	Results
2,4,6-trichlorobenzoyl chloride, DMAP, TEA	rt	79% isomerization of enoate olefin
m-nitrobenzoic anhydride, DMAP	rt	Decomposition
2,2-dipyridyl disulfide, PPh_3	rt to 115	Active ester, stannane decomposition
iPr chloroformate	0 to 50	Active ester did not react further
EDC, DMAP	rt to 40	Coupling and protodestannylation
DCC, DMAP	0-120	2 products that were not identified
Ethoxyacetylene, $(RuCl_2(cym)_2)_2$, cat TsOH	rt	No coupling, protodestannylation

Section 2.5.2. Investigation of Stille cross coupling approach

With this insight in hand, we turned our attention to the second strategy: Stille cross coupling. As noted earlier, our first result for this reaction was low yielding and we suspected the steric bulk of the TIPS protecting group was the cause for this (Scheme 2.16).

Scheme 2.16. First attempt for Stille cross coupling



For this reason, the intial conditions screened were conducted with the deprotected substrate **2.2**, the synthesis of which was described in section 2.4 (Scheme 2.17, Table 2.7). The conditions employed included the modified Liebeskind conditions used for uniting analogous fragments in archazolid B as well as other catalyst and ligand combinations known to effect cross coupling in the presence of a free acid. Additionally, conditions developed by Corey and Stolz were also used since they have previously been effective in our laboratories for a challenging hindered cross coupling.[25]

Scheme 2.17. Initial screen for Stille cross coupling of **2.1** and **2.2**

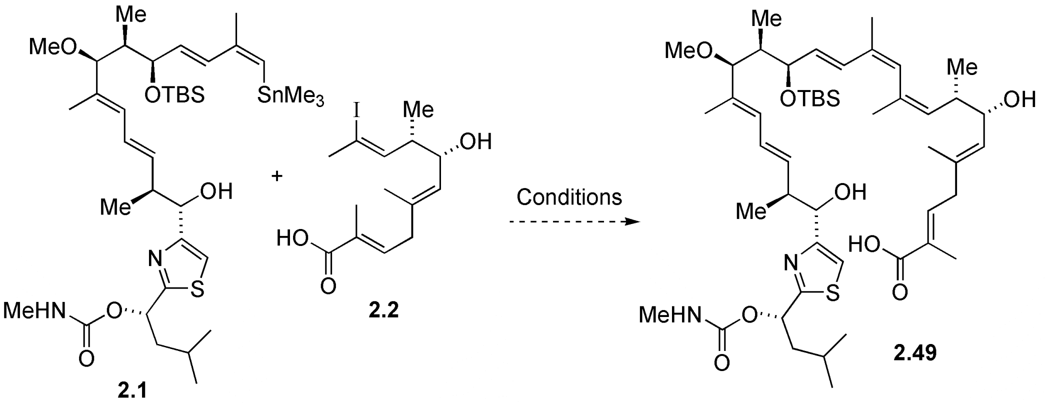


Table 2.7. Initial screen for Stille cross coupling of **2.1** and **2.2**

Conditions	Temp (°C)	Results
$Pd(PPh_3)_4$, CuTC, DMF	0	Stannane dimerization, iodide recovered
$Pd(PPh_3)_4$, CuTC, DMF	rt	Stannane dimerization, iodide recovered
$PdCl_2(PhCN)_2$, CuI, $AsPh_3$, NMP	rt to 80	Stannane decomposition
$ClBnPd(PPh_3)_2$, P(o-tol)$_3$, DMF	60 to 100	No reaction
$Pd(MeCN)_2Cl_2$, DMF	rt	Stannane decomposition
$Pd(PPh_3)_4$, CuCl, LiCl, DMSO	60	Not desired product

These results unfortunately showed that the previous hypothesis was incorrect; the steric bulk of the silyl group on the eastern fragment **2.35** was not the cause of low yielding cross coupling. The analogous cross coupling was achieved for archazolid B where the only notable difference in terms of functionality was the presence of a carboxylic acid. We therefore sought to mask this functionality of **2.46** in our subsequent attempts at coupling these fragments (Scheme 2.18, Table 2.8).

Scheme 2.18. Additional vinyl iodide substrates investigated for cross coupling

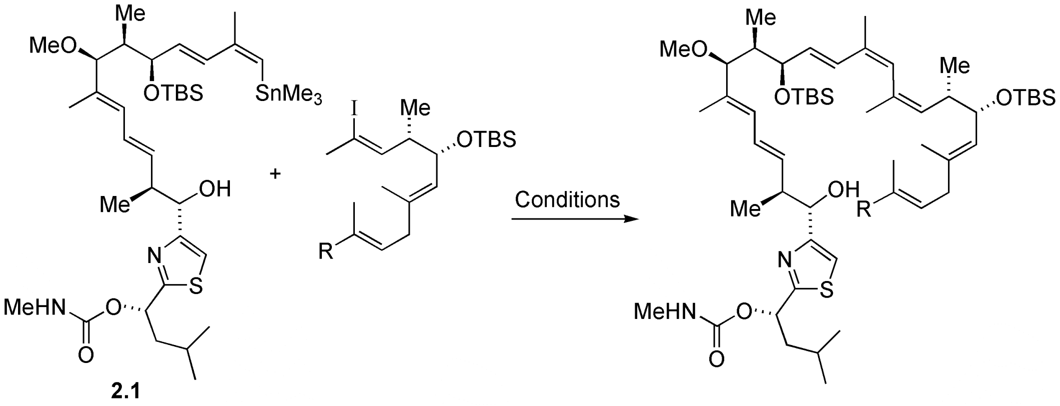
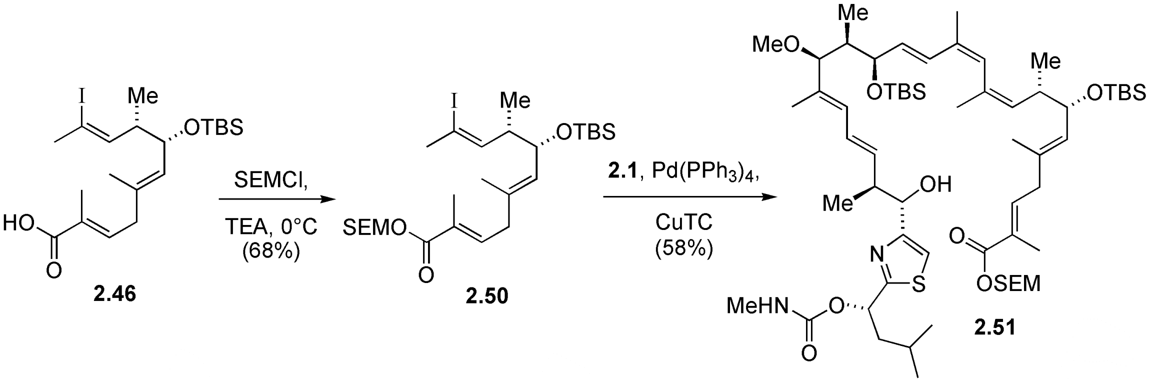


Table 2.8. Cross coupling investigation with various vinyl iodide substrates

R	Conditions	Temp (°C)	Results
CO_2Me	$ClBnPd(PPh_3)_2$, P(o-tol)$_3$, DMF	60 to 100	No reaction
CO_2Me	$Pd(PPh_3)_4$, CuTC, DMF	rt	38% yield
CO_2SEM	$Pd(PPh_3)_4$, CuTC, DMF	rt	58% yield, 15% protodestannylation, 25% dimerization
CO_2SEM	$Pd(PPh_3)_4$, CuTC, DMF	0	Protodestannylation
OH	$Pd(PPh_3)_4$, CuTC, DMF	rt	19% yield, 70% dimerization
OTES	$Pd(PPh_3)_4$, CuTC, DMF	rt	Protodestannylation, dimerization
CO_2TIPS	$Pd(PPh_3)_4$, CuTC, DMF	rt	<10% yield

The first attempt that led to successful cross coupling was achieved with methyl ester **2.46**. Attempts to saponify the ester of the coupled product with trimethyltin hydroxide led to decomposition however, so we pursued further cross coupling attempts in the presence of esters that might be saponified under more mild conditions. The trimethylsilyl ethoxymethyl (SEM) ester **2.50** provided a satisfactory 58% yield of **2.51**; the remainder of the stannane could be accounted for through dimerization and protodestannylation whereas the unreacted iodide **2.50** could be recovered (Scheme 2.19). The identity of the functional group replacing the carboxylic acid and its influence on the reaction led us to explore additional functionality at this position. A free alcohol provided the coupled product in 19%, whereas a triethylsilyl protecting group in that position led to complete protodestannylation and dimerization. A triisopropylsilyl (TIPS) protecting group was also introduced on the acid, since they are known to be less labile than other silyl group protected acids. Unfortunately the coupling yield in this case was also under 10%. To date, it is unclear as to why what might appear to be benign changes to a remote functionality play such a drastic role in the success of the Stille cross coupling.

Scheme 2.19. Preparation of SEM ester **2.50** and its cross coupling with **2.1**



With our optimal substrate **2.51** bearing a SEM ester, we carried on to investigate its deprotection. Typically, this protecting group is removed with magnesium bromide etherate or using hydrofluoric acid. When neither of these conditions worked for **2.51**, we explored a collection of fluoride-based reagents (Table 2.9), most of which either led to no reaction or decomposition. While reaction with buffered HF-pyridine initially looked promising, the presence of the methylene singlet of the SEM group was still observed by proton NMR. Mass spectral data further confirmed that the TMS of the SEM ester had undergone protodesilylation concomitant with deprotection of the TBS ether.

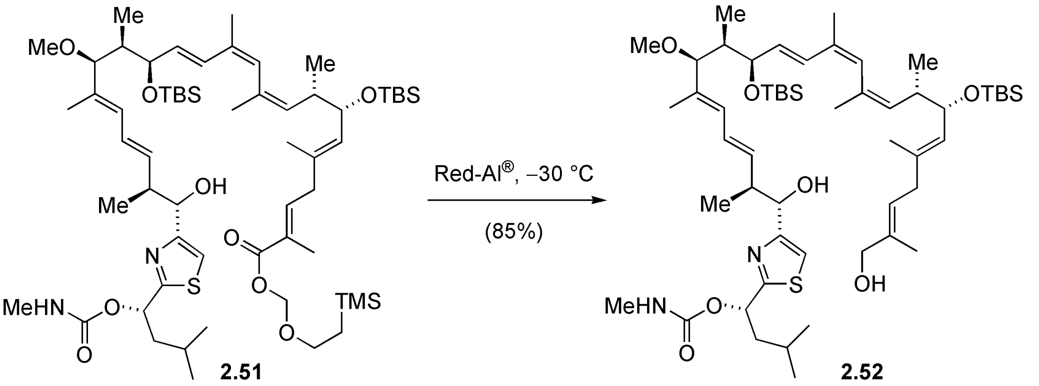
Table 2.9. Deprotection conditions attempted for SEM ester **2.51**

Conditions	Temp (°C)	Results
$MgBr_2(OEt)_2$	–20 to rt	No reaction, then decomposition
HF, MeCN	0	Decomposition
H_2SiF_6, MeCN	0	Decomposition
HF-pyridine, pyr., THF	0 to rt	TMS and TBS removed

NH_4F, MeOH	60	No reaction
KF, 18-crown-6, MeCN	rt	No reaction
TASF	rt to 40	No reaction
TBAF, AcOH, THF	rt	No reaction
TBAF, THF	−20 to 40	No reaction
CsF	100	Decomposition

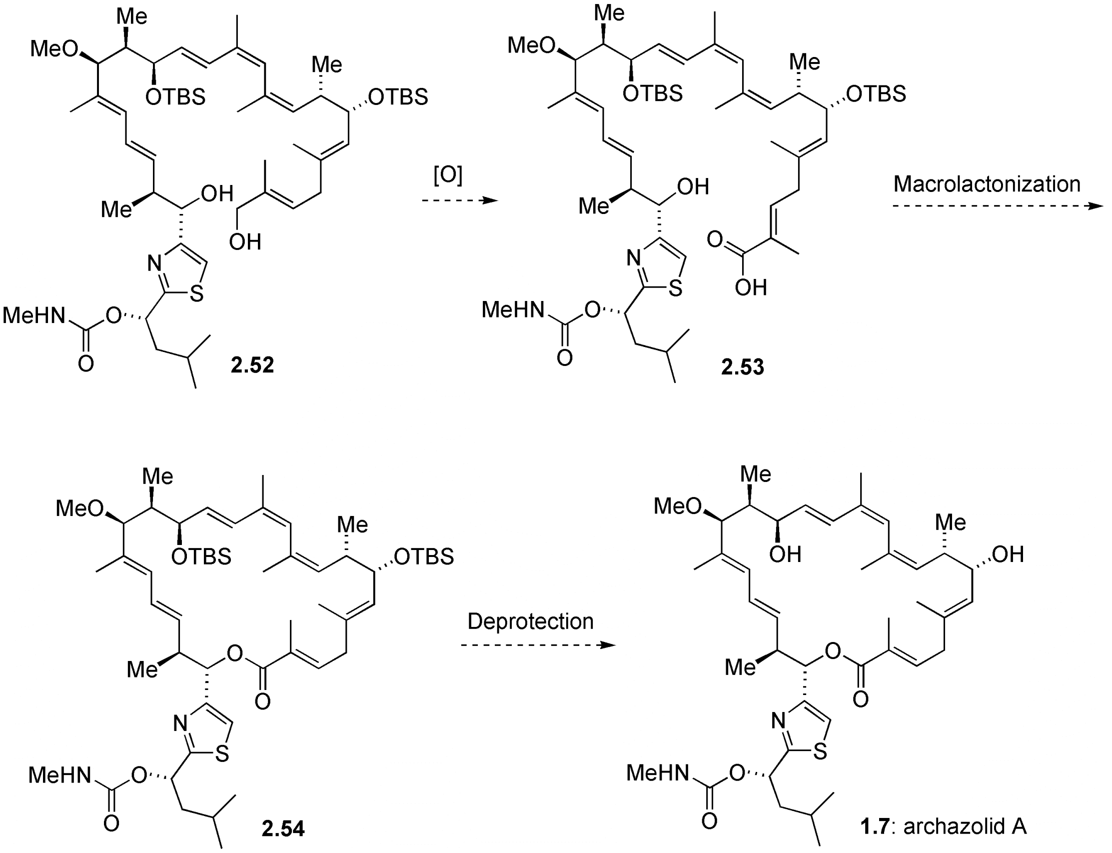
Due to these challenges, our next consideration was to remove the SEM ester of **2.51** through reduction to the corresponding alcohol **2.52**. This was achieved with Redal® in a satisfactory 85% yield (Scheme 2.20).

Scheme 2.20. Reductive deprotection of the SEM ester



In order to obtain macrolactonization precursor **2.53**, a selective oxidation of the primary allylic alcohol in the presence of the secondary alcohol (α to the thiazole) had to be effected. Our first choice of oxidant was manganese oxide, a typical reagent for allylic oxidations. Unfortunately no reaction was observed and reaction with buffered Dess-Martin periodinane led to clean conversion of an undesired substrate whose identity was not established. Finally, a Swern oxidation was attempted, but the desired product was not observed and the starting material had converted to an unidentified side-product. Due to material limitations, further reaction conditions were not investigated. A Ley oxidation using tetrapropylammonium perruthenate (TPAP) and 4-methylmorpholine N-oxide (NMO) could be attempted in future work although in the Menche synthesis,[2] those conditions on a substrate with the triene in tact led to undesired isomerization. If selective oxidation cannot be achieved, other esters for cross coupling could also be investigated. Preliminary attempts to install a relatively labile TMSE (trimethylsilyl ethyl) ester via a Mitsunobu reaction were unsuccessful due to a lack of reactivity of the hindered acid, but other conditions may exist to overcome this obstacle. Once oxidation to the acid **2.53** can be achieved, two alternative approaches to complete the molecule may be explored. In the first, a macrolactonization and silyl deprotection would complete this synthesis (Scheme 2.21). In the second, silyl deprotection will provide the open chain seco substrate, which is the postulated biosynthetic precursor to the natural product. In collaboration with the Wenzel group, this material could be fed into the biosynthetic machinery responsible for bacterial synthesis of the archazolids to investigate a biotechnological alternative to traditional macrolactonization.

Scheme 2.21. Future work to complete a total synthesis of archazolid A



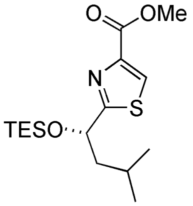
Section 2.6. Conclusion

Scaleable access to both fragments of archazolid A have been achieved and they have been united through a highly optimized Stille cross coupling. In this process, thirty-one new synthetic steps have been executed including an efficient allylic Stille cross coupling, which is an underused method in natural product total synthesis. At present, only three steps are required to complete this natural product and valuable insight has already been gained toward macrocyclization by way of esterification studies of the two building blocks. Oxidation and deprotection of the latest substrate can also be valuable for mutasynthetic feeding experiments with our collaborators. These findings, combined with our first generation synthesis, have created a vast reservoir of knowledge on the construction of individual carbon-carbon bonds in these attractive molecules and their chemical environments, sensitivity, and behavior. This will certainly provide valuable insight for the synthesis of simplified analogs that are currently being designed by our collaborators.

Section 2.7. Experimental procedures

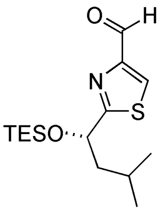
General Experimental Details: All reactions were carried out under an inert N_2 atmosphere in oven-dried glassware. Flash column chromatography was carried out with EcoChrom ICN SiliTech 32-63 D 60 Å or Merck 40-60μM 60 Å silica gel. Reactions and chromatography fractions were monitored with Merck silica gel 60 F_{254} plates and visualized with potassium permanganate, ceric ammonium molybdate, and anisaldehyde. Tetrahydrofuran (THF), toluene ($PhCH_3$), diethyl ether (Et_2O), and methylene chloride (CH_2Cl_2) were dried by passage through activated alumina columns. Et_2O and THF were also distilled from sodium benzophenone ketyl. *n*-Butyllithium (*n*BuLi) was titrated with diphenylacetic acid prior to use. All other reagents and solvents were used without further purification from commercial sources. Organic extracts were dried unless otherwise noted.

Instrumentation: FT-IR spectra were obtained on NaCl plates with an ATI Mattson Gemini spectrometer or as a neat sample on a Perkin-Elmer BXII-FTIR spectrometer. Proton and carbon NMR spectra (^1H NMR and ^{13}C NMR) were recorded in deuterated chloroform ($CDCl_3$) on a Bruker DRX-500 spectrometer or Varian Mercury 600 MHz spectrometer and calibrated to residual solvent peaks. Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet. Melting points were deteremined with an electrothermal apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 Polarimeter. High resolution mass spectra (HRMS) were obtained using the Micro-Mass Facility at the College of Chemistry, University of California Berkeley using electron impact (EI) at 70 eV or fast atom bombardment (FAB) or at Ludwig-Maximilians Universität using EI or electrospray ionization (ESI).



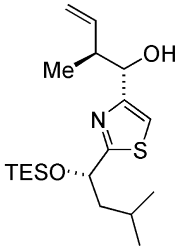
TES thiazole 2.12. To a solution of 9.51g of **1.67** (40.7 mmol) in 100 mL DCM and then was added 5.80 mL (49.4 mmol) 2,6-lutidine followed by 9.80 mL (43.26 mmol) triethylsilyl trifluoromethanesulfonate (TESOTf). After 40 minutes, the solution was quenched with saturated NH_4Cl. The organic layer was washed with saturated NH_4Cl, dried, filtered, and concentrated. The crude oil was purified by flash colum chromatography (10% EtOAc/Hexanes) to give 13.67 g (94% over 2 steps) **2.12** as a pale yellow oil.

Rf: 0.55, 25% EtOAc/Hexanes. ^1H NMR (500 MHz): δ 8.05 (s, 1H), 5.06 (t, 1H, $J = 4.5$ Hz), 3.84 (s, 3H), 1.73 (m, 2H), 1.53 (m, 1H), 0.85 (m, 15H), 0.52 (m, 6H). ^{13}C NMR (125 MHz): δ 178.94, 161.84, 146.01, 127.33, 71.42, 52.18, 48.80, 23.93, 23.37, 21.94, 6.58, 4.61. IR: 3123, 3055, 2959, 2878, 2307, 1734, 1487, 1435, 1325, 1217, 1184, 1096, 1004, 896, 853. $[\alpha]^{25}_D$ –0.491 (c = 1.0, $CHCl_3$). HRMS (FABS) calcd for $C_{16}H_{30}NO_3SSi$ ($M + H^+$) 344.171569, found 344.171100.



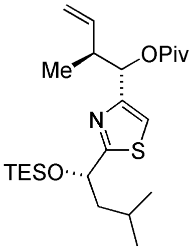
Thiazole aldehyde 2.13. To a solution of 5.39 g **2.12** (15.7 mmol) in 35 mL THF at –78 ºC was added 15.7 mL of 1.0 M DIBAL-H in toluene. After 1 hour, an additional 0.5 mL of neat DIBAL-H was added dropwise. The solution was stirred for another hour at –78 ºC, then quenched with 200 mL of a half-saturated Rochelle's salt solution. The solution was then diluted with 150 mL Et_2O and stirred vigorously for 12 hours. The layers were separated, and the organic layers was washed with with $NaHCO_3$ (saturated), then brine. The organic layer was then dried, filtered, and evaporated. The crude oil was purified by flash column chromatography (5 to 10 to 25% EtOAc/hexanes) to obtain 4.14g of **2.13** (84%) as a clear, colorless oil and 0.49 g of the corresponding alcohol.

Rf: 0.63, 25% EtOAc/Hexanes. ^{1}H NMR (500 MHz): δ 9.80 (s, 1H), 8.11 (s, 1H), 5.12 (m, 1H), 1.78 (m, 2H), 1.64 (m, 1H), 0.96 (m, 15H), 0.60 (m, 6H). ^{13}C NMR δ (125 MHz): δ 184.47, 179.45, 154.45, 128.13, 71.30, 48.67, 23.90, 23.15, 22.11, 6.59, 4.61. IR: 3115, 2959, 2878, 2839, 2362, 1701, 1487, 1466, 1266, 1136, 1092, 1004, 895, 744. $[\alpha]^{25}_D$ –0.443 (*c* = 1.0, $CHCl_3$). HRMS (FABS) calcd for $C_{15}H_{28}NO_2SSi$ (M + H^+) 314.161005, found 314.161670.



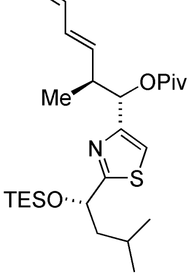
Crotylation product 2.14. Trans-2-butene (5 mL) was condensed at –78 ºC, and then 7 mL THF, 0.773 g (6.89 mmol) potassium *tert*-butoxide in 7 mL THF, and 2.8 mL (6.89 mmol) of 2.5M *n*-butyl lithium were added sequentially. The reaction mixture turned yellow and was warmed to –45 ºC for 45 minutes, then re-cooled to –78 ºC. At this point, 2.83 g (8.96 mmol) of (–)-MeB(Ipc)$_2$ in 7mL THF was added. The reaction mixture was stirred at –78 ºC for one hour, at which point the solution became colorless. A solution of 1.8g (5.74 mmol) **2.13** in 7 mL THF was then added and gradually warmed to –50 ºC over 1 hour. The reaction mixture was then quenched with 6.6 mL of 3.0M NaOH and 4.4 mL 30% H_2O_2 (added slowly, as vigorous gas evolution was observed). The solution was then warmed to room temperature and stirred for 16 h. The layers were then separated and extracted with Et_2O. The organic layer was dried, filtered, and evaporated. The crude oil was then purified by flash column chromatography (12% EtOAc/hexanes) to obtain 1.767 g (78%) of **2.14** as a pale yellow oil which was a single diastereomer.

Rf: 0.26, 10% EtOAc/Hexanes. ^{1}H NMR (500 MHz): δ 7.04 (s, 1H), 5.78 (ddd, 1H, *J* = 28, 8, 2 Hz), 5.14 (dd, 2H, *J* = 11.5, 6 Hz), 5.05 (t, 1H, *J* = 5 Hz), 4.57 (t, 1H, *J* = 6 Hz), 2.75 (dd, 1H, *J* = 14, 7 Hz), 2.44 (d, 1H, *J* = 5.0 Hz), 1.74 (m, 2H), 1.62 (m, 1H), 0.98 (d, 3H, *J* = 4.5 Hz), 0.93 (m, 15H), 0.61 (m, 6H). ^{13}C NMR (125 MHz): δ 177.45, 157.06, 139.66, 116.43, 113.97, 74.12, 71.48, 48.95, 44.21, 24.04, 23.26, 22.30, 15.97, 6.70, 4.70. IR: 3407, 2959, 2878, 2362, 1647, 1522, 1466, 1417, 1240, 1195, 1092, 1005, 744. $[\alpha]^{25}_{D}$ –0.708 (*c* = 1.0, CHCl$_3$). HRMS (FABS) calcd for $C_{19}H_{36}NO_2SSi$ ($[M + H]^+$) 370.223605, found 370.224320.



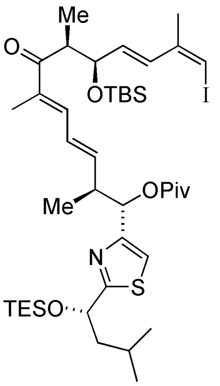
Piv thiazole 2.15. To a solution of 1.76 g (4.44 mmol) **2.14** in 40 mL DCM was added 2.2 mL (27.5 mmol) pyridine, 1.64 mL (13.3 mmol) trimethylacetyl chloride, and 109 mg (0.89 mmol) DMAP. Stirred at room temperature for 23 hours, then added 1.1 mL pyridine, 0.8mL trimethylacetyl chloride, and 55 mg DMAP. After 27 hours, another 1.1 mL pyridine and 0.8mL trimethylacetyl chloride was added and stirred for an additional 12 hours. The clear, colorless solution which contained a white precipitate was then quenched with NaHCO$_3$ (saturated) and was washed with NaHCO$_3$ twice, then with NaCl (saturated). The organic layer was dried, filtered, and evaporated. The crude oil was then purified by flash column chromatography (2 to 4% EtOAc/hexanes) to obtain 1.94 g (97%) **2.15** as a pale yellow oil.

Rf: 0.36, 10% EtOAc/Hexanes. ^{1}H NMR (500 MHz): δ 7.01 (s, 1H), 5.86 (d, 1H, *J* = 6.5 Hz), 5.75 (m, 1H), 5.04 (t, 1H, *J* = 8 Hz), 4.99 (d, 1H, *J* = 6.5 Hz), 4.97 (s, 1H), 2.96 (m, 1H), 1.75 (m, 2H), 1.57 (m, 1H), 1.20 (s, 9H), 0.82 (m, 18H), 0.55 (m, 6H). ^{13}C NMR (125 MHz): δ 177.42, 173.84, 153.41, 138.98, 115.51, 115.31, 74.85, 71.47, 49.15, 41.84, 40.08, 26.41, 24.11, 23.21, 22.15, 16.47, 6.65, 4.67. IR: 3055, 2961, 2877, 2362, 1808, 1727, 1458, 1420, 1369, 1265, 1158, 1087, 1005, 896, 730. $[\alpha]^{25}_{D}$ –0.904 (*c* = 1.0, CHCl$_3$). HRMS (FABS) calcd for $C_{24}H_{44}NO_3SSi$ ($M + H^+$) 454.281120, found 454.280760.



Aldehyde 2.16. To a solution of 0.500 g (1.1 mmol) **2.15** in 7.5 mL $PhCH_3$ was added 0.91 mL (11 mmol) of freshly distilled crotonaldehyde and 69 mg (0.11 mmol) Hoveyda-Grubbs second generation catalyst (**1.18**). The reaction mixture was heated to 100 ºC for 16 hours, then another 69 mg (0.11 mmol) catalyst was added. After 7 hours at 100 ºC, another 30 mg catalyst was added and the reaction mixture was heated to 110 ºC for 45 minutes. The dark brown solution was then cooled and filtered through celite, which was washed with EtOAc. The solvent was evaporated purified by flash column chromatography (10 to 15% EtOAc/hexanes) to obtain 330 mg (62%) of **2.16** as a brown oil. The product could be decolorized to a clear, colorless oil using active charcoal (50 mg / 1 mg **1.18**) although this process did not affect the purity of the product as assessed by ^{1}H NMR.

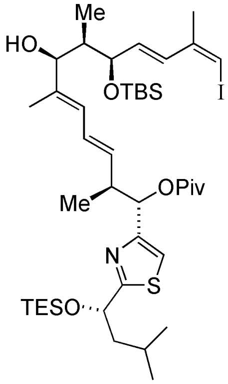
Rf 0.61 (25% EtOAc/Hexanes). ^{1}H NMR (500 MHz): δ 9.47 (d, 1H), 7.07 (s, 1H), 6.79 (dd, 1H, J = 16, 8 Hz), 6.09 (dd, 1H, J = 15, 7.5 Hz), 5.91 (d, 1H, J = 8 Hz), 3.34 (m, 1H), 1.73 (m, 2H), 1.58 (m, 1H), 1.18 (m, 9H), 1.08 (d, 3H, J = 6.5 Hz), 0.89 (m, 15H), 0.57 (m, 6H). ^{13}C NMR (125 MHz): δ 193.72, 178.27, 177.24, 158.21, 152.55, 133.38, 116.02, 73.96, 71.46, 49.11, 40.83, 38.93, 27.13, 24.14, 23.19, 22.23, 15.77, 6.70, 4.71. IR: 2959, 2362, 1734, 1697, 1279, 1146, 1085, 1005, 740. $[\alpha]^{25}_{D}$ –0.575 (c = 1.0, $CHCl_3$). HRMS (FABS) calcd for $C_{25}H_{44}NO_4SSi$ (M + H^+) 482.276035, found 482.275640.



Dienone 2.17. A solution of 1.05 g (1.88 mmol) phosphonate ester **1.42** and 276 mg $Ba(OH)_2 \cdot 8H_2O$ (which had been heated in vacuo at 120 ºC for 5 hours) in 4 mL THF was stirred for an hour. To the orange solution was then added 0.60 g (1.25 mmol) **2.16** in 2 mL THF and 0.05 mL H_2O. The solution turned bright orange after 30 minutes and gradually became brown. After 18 hours, the solution was quenched with $NaHCO_3$ (saturated) and diluted with Et_2O. The layers were separated and the aqueous layer was extracted with EtOAc three times. The organic layers were combined and dried, filtered, and evaporated. The crude oil was purified by flash column chromatography (10% EtOAc/Hexanes) to afford 0.862 g **2.17** (78%) as a yellow oil.

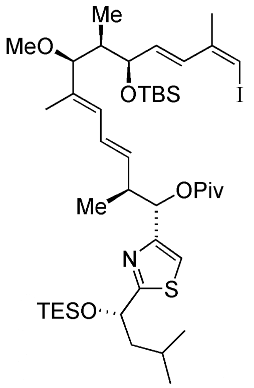
Note: We believe that compounds **2.17**-**2.21** exist as 2 conformers due to the bulky Piv protecting group because many of the carbon peaks are doubled with another peak within a few Hz for the next few compounds. The sister peaks are written in brackets below and are no longer present after the Piv group is removed.

Rf: 0.53, 15% EtOAc/Hexanes. ^{1}H NMR (500 MHz): δ 7.03 (d, 1H, *J* = 7 Hz), 6.93 (d, 1H, *J* = 10.5 Hz), 6.52 (dd, 1H, *J* = 15.5, 5.5 Hz), 6.41 (m, 1H), 6.07 (s, 1H), 6.01 (m, 1H), 5.84 (d, 1H, *J* = 6.5 Hz), 5.79 (dd, 1H, *J* = 15, 6.0 Hz), 5.04 (m, 1H), 4.35 (m, 1H), 3.38 (m, 1H), 3.15 (m, 1H), 1.84 (d, 3H, *J* = 7.5 Hz), 1.80 (s, 3H), 1.74 (m, 2H), 1.57 (m, 1H), 1.19 (s, 9H), 1.16 (t, 3H, *J* = 7.5 Hz), 1.01 (d, 3H, *J* = 6.5 Hz), 0.95 (m, 24H), 0.55 (m, 6H), 0.06 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (125 MHz): δ 204.28 (204.20), 177.86, 177.28, 152.91 (152.89), 143.49 (143.42), 141.36 (141.28), 138.49 (138.27), 135.99 (135.94), 135.22, 131.36 (131.33), 127.60 (127.56), 115.85 (115.80), 79.10 (79.04), 75.17 (75.05), 74.51 (74.43), 71.48, 49.14, 46.81 (46.70), 41.76 (41.61), 38.86, 27.07, 25.92 (25.74), 24.14, 23.25, 22.23, 21.15 (21.13), 18.11, 16.79 (16.74), 15.22 (15.15), 11.71 (11.68), 6.67, 4.71 (4.67), -3.98, -4.89. IR: 3054, 2959, 2412, 2305, 1728, 1654, 1459, 1265, 1156, 1085, 1027, 974, 896, 837, 744. $[\alpha]^{25}_D$ –0.502 (*c* = 1.0, CHCl$_3$). HRMS (FABS) calcd for $C_{42}H_{73}INO_5SSi_2$ (M + H$^+$) 886.379281, found 886.381410.



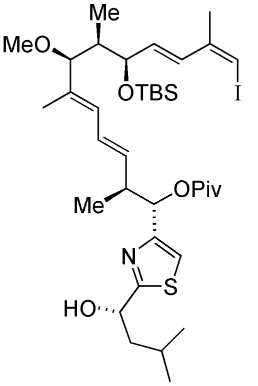
Alcohol 2.18. A solution of 235 mg (0.265 mmol) **2.17** in 5 mL MeOH was cooled to 0 ºC, and then 100 mg (2.65 mmol) of NaBH$_4$ was added. Gas evolution was observed. The clear, colorless solution containing a white precipitate was warmed to room temperature over the course of 4 hours and stirred for at room temperature for an additional 12 h. The solution was quenched with NaHCO$_3$ (saturated) and diluted with with Et$_2$O. The layers were separated and the organic layer was washed with NaHCO$_3$ (saturated), NH$_4$Cl (saturated), and then a saturated brine solution. The organic layer was dried, filtered, and evaporated (the crude material was clean and it should also be noted that this compound degrades on silica gel). Obtained 215 mg (91%) of **2.18** as a sticky white foamy oil (89% yield on 0.80 g scale).

Rf: 0.39, 15% EtOAc/Hexanes. ^{1}H NMR (500 MHz): δ 7.04 (d, 1H, *J* = 14 Hz), 6.58 (d, 1H, *J* = 15.5 Hz), 6.20 (m, 1H), 6.15 (s, 1H), 5.96 (dd, 1H, *J* = 16, 6.5 Hz), 5.89 (d, 1H, *J* = 10.5 Hz), 5.76 (dd, 1H, *J* = 11.5, 6.5 Hz), 5.55 (m, 1H), 5.05 (t, 1H, *J* = 7 Hz), 4.53 (m, 1H), 3.89 (d, 1H, *J* = 9.5 Hz), 3.68 (d, 1H, *J* = 30.5 Hz), 3.01 (m, 1H), 1.98 (s, 3H), 1.84 (m, 1H), 1.74 (m, 2H), 1.68 (d, 3H, *J* = 8.5 Hz), 1.57 (m, 1H), 1.21 (m, 9H), 0.94 (m, 27H), 0.54 (m, 9H), 0.07 (d, 6H). ^{13}C NMR (125 MHz): δ 177.44 (Piv carbonyl and thiazole carbon), 153.39 (153.26), 141.26, 136.69 (136.64), 134.86 (134.66), 134.05, 132.54, 127.50 (127.33), 127.17, 115.73, 80.39, 79.43, 76.15, 74.94 (74.69), 71.50, 49.14, 41.55, 41.38 (41.31), 38.83 (38.79), 27.07 (27.05), 25.85, 24.14, 23.27, 22.22, 21.26, 18.02, 17.16 (16.90), 12.33 (12.15), 11.20 (11.04), 6.68, 4.71 (4.67), -4.14, -5.17. IR: 3718, 2956, 2930, 2877, 2350, 2340, 1734, 1653, 1472, 1458, 1367, 1282, 1255, 1154, 1087, 1019, 1005, 973, 836, 775, 736, 668. $[\alpha]^{25}_{D}$ –0.318 (*c* = 1.0, CHCl$_3$). HRMS (FABS) calcd for $C_{42}H_{74}INO_5SSi_2$ (M^+) 887.387106, found 887.387680.



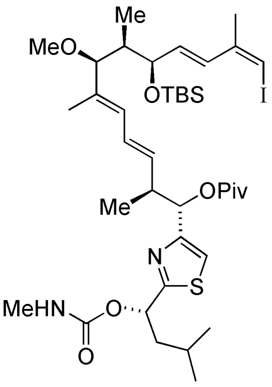
Methyl ether 2.19. To a solution of 639 mg (0.719 mmol) **2.18** in 7.0 mL THF was added 165 mg (4.31 mmol) NaH (60% dispersion in mineral oil), newly opened bottle from Sigma Aldrich. Gas evolution was observed, and the reaction mixture was stirred for 5 minutes, then 0.450 mL (7.19 mmol) MeI was added. The Schlenck tube was flushed with N_2, then heated to 60 ºC. After 1 h 45 min, the reaction mixture was quenched with NaHCO$_3$ (saturated), then diluted with Et$_2$O. The layers were separated and the organic layer was washed with NaHCO$_3$, then NaCl (saturated). The organic layer was dried, filtered, and evaporated. The crude oil was purified by chromatography (50% DCM/hexanes to 15% EtOAc/hexanes) to obtain 581 mg (90%) **2.19** as an off-white foamy oil (dissolves to form a yellow solution in CHCl$_3$).

Rf: 0.53 (15% EtOAc/hexanes), ^{1}H NMR (500MHz): δ 7.08 (s, 1H), 6.57 (d, 1H, *J* = 15.5 Hz), 6.30 (m, 1H), 6.06 (s, 1H), 5.88 (m, 2H), 5.76 (dd, 1H, *J* = 7.5, 2 Hz), 5.55 (m, 1H), 5.06 (m, 1H), 4.77 (d, 1H, *J* = 6.0 Hz), 3.37 (d, 1H, *J* = 10.0 Hz), 3.12 (d, 3H, *J* = 11.0 Hz), 3.02 (m, 1H), 1.94 (s, 3H), 1.76 (m, 2H), 1.57 (m, 5H), 1.17 (m, 9H), 0.91 (m, 27H), 0.59 (m, 9H), 0.08 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (125 MHz): δ 177.59, 177.34, 153.18, 141.58, 138.29, 134.96, 134.18, 132.31, 130.49, 127.10, 116.28 (116.15), 88.07 (88.03), 78.04, 74.63 (74.57), 71.52, 70.50, 55.56, 55.41, 49.14, 41.65, 41.57, 38.79, 27.04, 26.05, 24.16, 23.27, 22.23, 21.23, 18.17, 16.95 (16.91), 10.48, 8.86, 6.71 (6.67), 4.71 (4.66), -3.61, -5.30. IR: 3459, 2956, 2877, 2360, 1733, 1647, 1458, 1368, 1458, 1368, 1256, 1153, 1084, 1005, 974, 840, 775, 740, 678. $[\alpha]^{25}_{D}$ –0.383 (*c* = 1.0, CHCl$_3$). HRMS (FABS) calcd for $C_{43}H_{76}INO_5SSi_2$ (M^+) 901.402756 (M^+), found 901.403600.



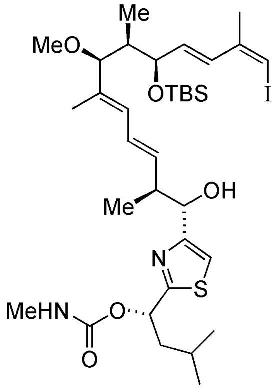
Alcohol 2.20. A solution of 384 mg (0.426 mmol) **2.19** in 5 mL MeOH and 5 mL DCM was cooled to 5 ºC. After 10 minutes, 161 mg (0.639 mmol) PPTS was added. The solution was kept at 5 ºC for 18 h, then quenched with $NaHCO_3$ (saturated) and diluted with Et_2O. The layers were separated and the organic layer was washed with $NaHCO_3$ (saturated), then brine. The organic layer was dried, filtered, and evaporated, then purified by flash column chromatography (20% EtOAc/hexanes) to afford 318 mg (95%) **2.20** as white foam. Note: this reaction was later found to work equally well with 1.5 equiv. TBAF at 0 ºC in THF in 5 minutes.

Rf: 0.57, 25% EtOAc/Hexanes. ^{1}H NMR (500 MHz): δ 7.10 (s, 1H), 6.56 (d, 1H, *J* = 16 Hz), 6.30 (m, 1H), 6.06 (s, 1H), 5.89 (m, 2H), 5.76 (dd, 1H, *J* = 17.5, 7.5 Hz), 5.56 (m, 1H), 5.04 (br s, 1H), 4.76 (d, 1H, *J* = 5.5 Hz), 3.36 (d, 1H, *J* = 10 Hz), 3.14 (m, 3H), 2.92 (m, 1H), 2.69 (s, 1H), 1.93 (s, 3H), 1.88 (m, 1H), 1.72 (m, 2H), 1.60 (m, 1H), 1.57 (s, 3H), 1.18 (d, 9H, *J* = 5.5 Hz), 0.96 (m, 18H), 0.61 (m, 3H), 0.07 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (125 MHz): δ 177.40 (177.37), 175.57, 153.84, 141.54, 138.22, 134.76 (134.73), 134.46 (134.33), 130.51, 129.61 (129.53), 127.19 (127.14), 116.14 (116.02), 88.07 (88.04), 78.09, 74.63 (74.58), 70.47, 70.19, 55.55, 47.30, 41.70, 41.61, 38.81, 27.12 (27.07), 26.06 (25.96), 24.54, 23.26, 21.83, 21.23, 18.16, 16.95 (16.91), 10.51, 8.86, -3.61, -5.30. IR: 3422, 2959, 2930, 2857, 2819, 1729, 1471, 1386, 1313, 1281, 1254, 1153, 1085, 1038, 1004, 973, 838, 775, 755. $[\alpha]^{25}_D$ –0.508 (*c* = 1.0, $CHCl_3$). HRMS (FABS) calcd for $C_{37}H_{62}INO_5SSi$ (M^+) 787.316277, found 787.31490.



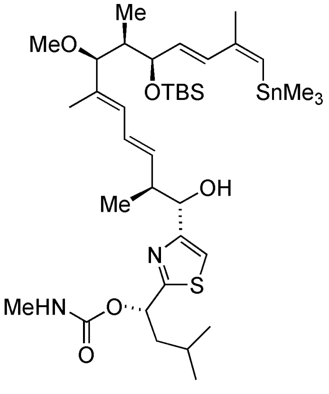
Carbamate 2.21. To a solution of 300 mg (0.381 mmol) **2.20** in 1.5 mL DCM was added 154 mg (0.95 mmol) 1,1 carbonyldiimidazole in portions over 1.5 hours. The solution was cooled to 0 ºC, then 0.06 mL of a 33% by weight solution of methylamine in EtOH was added. After 10 minutes, the clear pale yellow solution was allowed to warm to room temperature. After 10 minutes, another 0.8 mL of methylamine in EtOH was added. The solution was stirred for an additional 20 minutes at room temperature, then quenched with $NaHCO_3$ (saturated). The layers were separated and the organic layer was washed with $NaHCO_3$ (saturated), then brine. The organic layer was dried, filtered, and evaporated. The clear, colorless crude oil was purified by flash column chromatography (25% EtOAc/hexanes) to afford 320 mg **2.21** (99%) as a white foam.

Rf: 0.34, 25% EtOAc/Hexanes. ^{1}H NMR (500 MHz): δ 7.05 (s, 1H), 6.57 (d, 1H, *J* = 15.5 Hz), 6.25 (m, 1H), 6.06 (m, 2H), 5.85 (m, 2H), 5.81 (dd, 1H, *J* = 9.5, 7.5 Hz), 5.55 (dd, 1H, *J* = 15, 8.5 Hz), 4.77 (br s, 2H), 3.37 (d, 1H, *J* = 10 Hz), 3.14 (m, 3H), 2.95 (m, 1H), 2.83 (s, 3H), 1.96 (s, 3H), 1.88 (m, 1H), 1.60 (s, 3H), 1.16 (d, 12H, *J* = 16.1 Hz), 0.95 (m, 18H), 0.59 (dd, 3H, *J* = 18.7, 7.0 Hz), 0.06 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (125 MHz): δ 177.31, 170.77, 155.92, 154.33, 141.55 (141.53), 138.26, 134.62 (134.42), 134.28, 130.48, 129.62 (129.52), 127.16 (127.11), 115.73 (115.63), 88.03 (88.00), 78.07, 74.83, 71.94, 70.48, 55.54, 55.41, 44.27, 41.80, 41.62, 38.82, 27.57, 27.10, 26.06, 24.55, 22.92, 22.10, 21.22, 18.16, 16.92 (16.88), 10.48, 8.85, -3.62, -5.29. IR: 3802, 3676, 3650, 3370, 2958, 2932, 2361, 2340, 1793, 1734, 1718, 1654, 1559, 1541, 1508, 1458, 1251, 1154, 1133, 1086, 1042, 972, 936, 837, 774, 758. $[\alpha]^{25}_D$ –0.540 (*c* = 1.0, $CHCl_3$). HRMS (FABS) calcd for $C_{39}H_{65}IN_2O_6SSi$ (M^+) 844.337741, found 844.335820.



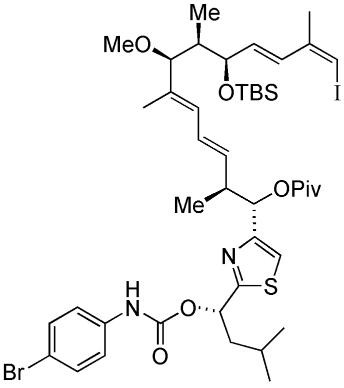
Free alcohol 2.22. A solution of 198 mg (0.234 mmol) **2.21** in 5 mL $PhCH_3$ was cooled to –78 ºC. A solution of 0.133 mL neat DIBAL-H (0.749 mmol) in 1 mL $PhCH_3$ was added via syringe. The clear, colorless solution was stirred for 20 minutes at –78 ºC, then quenched with a ½ saturated Rochelle's salt solution. The emulsion was diluted with EtOAc and the layers were stirred vigorously for 1 hour, after which the layers separated. The aqueous layer was extracted with EtOAc, then the combined organic layers were dried, filtered, and evaporated. The crude colorless oil was purified by flash column chromatography (30 to 40% EtOAc/hexanes) to isolate 150 mg **2.22** (84%) as a white foam.

Rf: 0.52, 40% EtOAc/hexanes. ^{1}H NMR (500 MHz): δ 7.10 (s, 1H), 6.57 (d, 1H, *J* = 16 Hz), 6.35 (m, 1H), 6.06 (br s, 2H), 5.88 (m, 2H), 5.62 (m, 1H), 4.81 (br s, 1H), 4.77 (d, 1H, *J* = 5.5 Hz), 4.62 (m, 1H), 3.36 (d, 1H, *J* = 9.5 Hz), 3.15 (m, 3H), 2.82 (d, 3H, *J* = 4.5 Hz), 2.53 (br s, 1H), 1.94 (s, 3H), 1.88 (m, 1H), 1.83 (m, 1H), 1.72 (m, 1H), 1.58 (m, 4H), 1.21 (s, 1H), 0.96 (m, 18H), 0.61 (t, 3H, *J* = 7 Hz), 0.07 (s, 3H), 0.04 (s, 3H). ^{13}C NMR: δ 170.90, 158.05, 155.96, 141.54, 138.23, 134.94, 134.54, 130.49, 129.65, 127.43, 114.40, 88.05, 78.11, 74.40, 71.95, 70.49, 55.61, 44.34, 43.65, 41.64, 27.58, 26.06, 24.54, 22.98, 22.05, 21.33, 18.16, 16.64, 10.60, 8.92, -3.59, -5.30. IR: 3461, 2957, 2928, 2858, 2821, 1715, 1527, 1465, 1372, 1256, 1128, 1086, 1041, 1005, 974, 932, 876, 837, 773, 757, 700, 646. $[\alpha]^{25}_D$ –0.608 (*c* = 1.0, CHCl$_3$). HRMS (FABS) calcd for $C_{34}H_{57}IN_2O_5SSi$ ([M + Li]$^+$) 760.2802, found 767.296230.



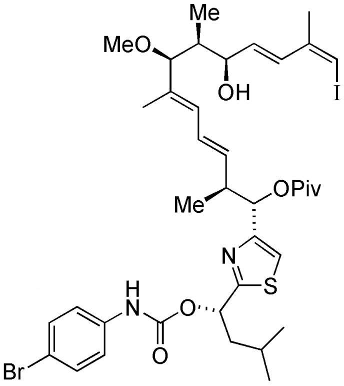
Western building block 2.1. To a solution of 32 mg (0.0394 mmol) **2.22** in 1.5 mL PhH was added 0.040 mL hexamethylditin (Me_6Sn_2) (0.197 mmol), 2.0 μL DIEA (0.12 mmol), and 2.3 mg Pd(PPh$_3$)$_4$ (2.0 μmol). The reaction mixture was flushed with N$_2$ and heated to 60 ºC for 17 hours, then the resulting black suspension was cooled to room temperature. The volatiles were evaporated, and the crude material was purified by flash column chromatography (40% EtOAc/hexanes and 1% TEA) to isolate 37 mg **2.1** (99%) as an off-white foam (88% on 75 mg scale).

Rf: 0.44, 40% EtOAc/hexanes. δ 7.09 (s, 1H), 6.35 (dd, 1H, *J* = 15, 7 Hz), 6.20 (d, 1H, *J* = 15.5 Hz), 6.05 (dd, 1H, *J* = 8.5, 5 Hz), 5.93 (d, 1H, *J* = 10.5 Hz), 5.84 (s, 1H), 5.74 (dd, 1H, *J* = 9, 6.5 Hz), 5.63 (m, 1H), 4.75 (br s, 1H), 4.73 (d, 1H, *J* = 6.5 Hz), 4.61 (dd, 1H, *J* = 12, 7 Hz), 3.38 (d, 1H, *J* = 10 Hz), 3.14 (d, 3H, *J* = 4.5 Hz), 2.83 (d, 3H, *J* = 5.0 Hz), 2.44 (br s, 1H), 1.98 (s, 3H), 1.91 (m, 2H), 1.88 (m, 1H), 1.83 (m, 1H), 1.59 (s, 3H), 1.21 (m, 1H), 0.97 (m, 9H), 0.92 (s, 9H), 0.64 (t, 3H, *J* = 6.5 Hz), 0.17 (s with satellites, 9H), 0.061 (s, 3H), -0.005 (s, 3H).



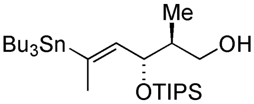
TBS Bromocarbamate 2.23. To a solution of 50 mg (0.063 mmol) of **2.20** in 3 mL DCM was added 0.025 mL (0.184 mmol) TEA, 36 mg (0.184 mmol) 4-bromophenyl isocyanate, and 7.8 mg (0.063 mmol) DMAP. The reaction mixture was stirred for 1.5 hours, during which time it changed from a clear, yellow solution to an orange solution with white precipitate. The reaction mixture was then quenched with $NaHCO_3$ (saturated), diluted with Et_2O, and the layers were separated. The organic layer was washed twice with $NaHCO_3$ (saturated), once with NaCl (saturated), and then dried, filtered, and evaporated. Flash column chromatography (10% EtOAc/hexanes) afforded 48 mg of **2.23** (76%) as a white foam.

Rf: 0.30, 10% EtOAc/hexanes. ^{1}H NMR (600 MHz): δ 7.42 (d, 2H, *J* = 12 Hz), 7.30 (br s, 2H), 7.09 (s, 1H), 6.72 (br s, 1H), 6.57 (d, 1H, *J* = 15.7 Hz), 6.26 (dd, 1H, *J* = 14.8, 10.2 Hz), 6.11 (m, 1H), 6.06 (s, 1H), 5.82 (m, 3H), 5.56 (m, 1H), 4.77 (m, 1H), 3.36 (dd, 1H, *J* = 10, 4 Hz), 3.13 (m, 3H), 3.01 (m, 1H), 1.96 (m, 1H), 1.93 (s, 3H), 1.73 (m, 1H), 1.55 (m, 4H), 1.18 (m, 9H), 0.96 (m, 18H), 0.60 (d, 3H, *J* = 21.7 Hz), 0.07 (s, 3H), 0.04 (s, 3H). ^{13}C NMR: δ 177.33, 169.44, 169.40, 154.83, 154.59, 152.02, 141.62, 138.31, 136.60, 134.57, 132.03, 130.55, 129.52, 127.19, 120.17, 116.03, 88.06, 75.84, 72.87, 72.41, 70.58, 55.60, 44.42, 44.11, 41.87, 41.69, 38.88, 29.69, 27.13, 26.09, 24.65, 23.81, 22.85, 22.19, 21.25, 18.21, 16.95, 10.55, 8.89, -3.59, -5.24. IR: 3328, 2929, 2361, 1981, 1732, 1596, 1532, 1398, 1250, 1214, 1152, 972, 837, 776, 669 cm^{-1}.



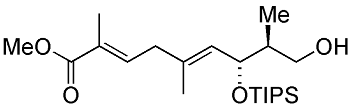
Bromocarbamate 2.24. To a solution of 112 mg (0.114 mmol) **2.23** in 3 mL THF was added 1.5 mL formic acid and 0.5 mL H_2O. The solution was stirred vigorously for 23 hours, then worked up with $NaHCO_3$ (saturated), dried, filtered, and evaporated. Flash column chromatography of the crude oil (10 to 15 to 20 to 25% EtOAc/hexanes) afforded 93 mg **2.24** (94%) as a white glassy solid that, after rotary evaporation with $CHCl_3$, became a white foam.

Rf: 0.46, 25% EtOAc/hexanes. ^{1}H NMR (600 MHz): δ 7.43 (d, 2H, J = 12 Hz), 7.29 (br s, 2H), 7.08 (d, 1H, J = 6 Hz), 6.73 (br s, 1H), 6.67 (d, 1H, J = 15.7 Hz), 6.24 (t, 1H, J = 14.8 Hz), 6.11 (m, 2H), 5.95 (m, 1H), 5.88 (d, 1H J = 10.9 Hz), 5.81 (m, 1H), 5.56 (m, 1H), 4.35 (br s, 1H), 3.75 (br s, 1H), 3.38 (d, 1H, J = 9.5 Hz), 3.17 (d, 3H, J = 16 Hz), 3.01 (m, 1H), 1.99 (s, 3H), 1.97 (m, 1H), 1.73 (m, 1H), 1.55 (m, 4H), 0.98 (m, 18H), 0.73 (m, 3H). IR: 3330, 2961, 1732, 1596, 1534, 1491, 1398, 1306, 1216, 1155, 1075, 1008, 970 cm^{-1}.



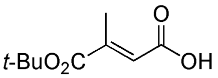
TIPS stannane 2.27. To a solution of 0.500 g (1.78 mmol) **1.55** in 20 mL $PhCH_3$ was added 12 mg (0.044 mmol) PPh_3, 23 mg (0.088 mmol) bis(acetonitrile)dichloropalladium(II), and 0.6 mL (2.19 mmol) tributyltin hydride (Bu_3SnH). Stirred at room temperature for 28 h, then added 0.6 mL Bu_3SnH. After 21 h, another 12 mg PPh_3 and 23 mg bis(acetonitrile)dichloropalladium (II) was added, then 0.3 mL Bu_3SnH dropwise. After 24 h, 12 mg PPh_3 and 23 mg bis(acetonitrile)dichloropalladium (II) were added, followed by 1 mL Bu_3SnH dropwise (over 2 hours, syringe pump). After 2 hours, the solvent was evaporated. The black crude oil was purified by flash column chromatography (1% Et_3N/10% EtOAc/hexanes) to give 0.812 g of **2.27** (80%) as a yellow oil.

Rf: 0.35, 10% EtOAc/Hexanes. ^{1}H NMR (500 MHz): δ 5.66 (d, 1H, J = 8 Hz), 4.68 (t, 1H, J = 6 Hz), 3.78 (m, 1H), 3.62 (m, 1H), 2.89 (t, 1H, J = 6 Hz), 1.84 (s with satellites, 3H), 1.73 (m, 1H), 1.49 (m, 6H), 1.31 (m, 6H), 1.07 (m, 21H), 0.95 (d, 3H, J = 7.5 Hz), 0.90 (m, 15H). ^{13}C NMR (125 MHz): δ 143.12, 139.33, 73.78, 66.35, 41.96, 29.21, 27.35, 19.98, 18.07, 17.64, 13.64, 12.53, 8.97 (with satellites). IR: 3447, 3053, 2958, 2869, 2362, 1653, 1464, 1377, 1265, 1082, 1023, 943, 883, 801, 743, 683. $[\alpha]^{25}_{D}$ –0.260 (c = 1.0, $CHCl_3$).



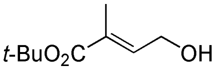
TIPS 1,4-diene 2.29a. To a solution of 26 mg (0.248 mmol) $Pd_2(dba)_3$ and 13 mg (0.05 mmol) PPh_3 in 1.5 mL THF was added 160 mg (0.827 mmol) **2.28a**, then 0.500 g (0.869 mmol) **2.27**. The Schlenck tube was flushed with N_2 and heated to 60 ºC for 25 hours (became clear yellow solution after 30 minutes). The solution was then cooled to 30 ºC and stirred for 48 hours. The solvent was then evaporated and the crude oil was purified by flash column chromatography (30% Et_2O/DCM) to isolate 242 mg **2.29a** (73%) as light yellow oil. (71% on 623 mg scale).

Rf: 0.49, 25% EtOAc/Hexanes. ^{1}H NMR (500 MHz): δ 6.75 (t, 1H, J = 9 Hz), 5.30 (d, 1H, J = 9 Hz), 4.50 (dd, 1H, J = 9, 6 Hz), 3.75 (s, 3H), 3.70 (m, 1H), 3.57 (m, 1H), 2.87 (d, 2H, J = 15.5 Hz), 2.76 (t, 1H, J = 5.5 Hz), 1.85 (s, 3H), 1.76 (m, 1H), 1.59 (s, 3H), 1.05 (s, 21H), 0.91 (d, 3H, J = 7 Hz). ^{13}C NMR (125 MHz): δ 168.33, 138.94, 133.12, 129.28, 128.79, 74.52, 66.25, 51.70, 42.23, 38.32, 18.04, 17.95, 17.39, 13.36, 12.47. IR: 3480, 2964, 2944, 2869, 2785, 2742, 2362, 2342, 1718, 1653, 1602, 1559, 1541, 1498, 1458, 1437, 1391, 1352, 1306, 1289, 1259, 1204, 1171, 1126, 1077, 1059, 1033, 996, 943, 883, 845, 795, 748, 679. $[\alpha]^{25}_{D}$ –0.219 (c = 1.0, $CHCl_3$). HRMS (FABS) calcd for $C_{22}H_{42}O_4Si$ (M^+) 348.29, found



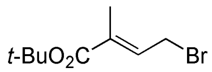
***t*-Butyl ester 2.31b**. To a solution of 10 g (47.8 mmol) of 2-bromopropionic *t*-butyl ester (TCI) (**2.30b**) in 115 mL MeCN was added 11.95 g (45.6 mmol) PPh_3. The reaction mixture was heated to 65 ºC for 7 h, then cooled to rt. After 3 hours, the reaction mixture was cooled to 0 ºC, then 7.95 mL (45.6 mmol) DIEA followed by 4.19 g (45.6 mmol) glyoxylic acid monohydrate was added. The solution was then allowed to warm to room temperature overnight. After 12 hours, another 0.480 g (4.60 mmol) of glyoxylic acid monohydrate was added. After 4.5 hours at room temperature, half of the solvent was evaporated, and the resulting solution was then diluted with EtOAc. This mixture was washed with $NaHCO_3$ (saturated), then the aqueous layer was washed with EtOAc. The layers were separated and the aqueous layer was then slowly acidified with 20 mL of concentrated HCl and extracted with Et_2O. The Et_2O extracts were combined and dried, filtered, and evaporated to obtain 3.55 g of **2.31b** (42%) as a yellow oil.

Rf: 0.5, 50% EtOAc/Hexanes. ^{1}H NMR (500 MHz): δ 6.70 (s, 1H), 2.26 (s, 3H), 1.54 (s, 9H).



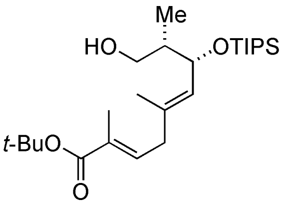
***t*-Butyl allylic alcohol 2.32b**. To solution of 3.55 g (19.06 mmol) **2.31b** in 150 mL THF, cooled to –10 ºC, was added 24 mL (24 mmol, 1.0 M) BH_3 THF. The solution was allowed to warm to room temperature overnight, after which it was quenched with 10 mL of 50% glacial AcOH in H_2O. The solution was then neutralized with a slow addition of 125 mL of $NaHCO_3$ (saturated). The solution was then extracted with Et_2O, and the combined organic layers were dried, filtered, and evaporated to obtain 1.04 g of **2.32b** (32%) as a clear, colorless oil.

Rf: 0.62, 50% EtOAc/Hexanes. ^{1}H NMR (500 MHz): δ 6.73 (t, 1H, J = 6 Hz), 4.35 (d, 2H, J= 5.5 Hz), 3.68 (br s, 1H), 1.80 (s, 3H), 1.52 (s, 9H).



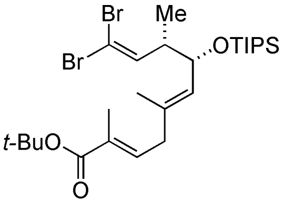
***t*-Butyl allylic bromide 2.28b**. To a solution of 600 mg (3.48 mmol) **2.32b** in 10 mL Et_2O at –3 ºC was added 0.010 mL (0.087 mmol) pyridine, followed by 0.11 mL (1.15 mmol) PBr_3. After 1 hour, the reaction mixture was slowly quenched with $NaHCO_3$ (saturated). The solution was then diluted with Et_2O and washed with $NaHCO_3$ (saturated), then NaCl (saturated). The organic layer was dried, filtered, and evaporated. The crude oil was then purified by flash column chromatography (10% EtOAc/hexanes) to give 403 mg **2.28b** (49%) as a yellow oil. This compound is known through another route.[26]

Rf: 0.64, 25% EtOAc/Hexanes. ^{1}H NMR (500 MHz): δ 6.82 (t, 1H, *J* = 8.5 Hz), 4.03 (d, 2H, *J* = 8.5 Hz), 1.87 (s, 3H), 1.49 (s, 9H).



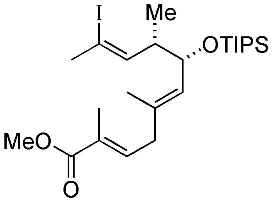
***t*-Butyl skipped diene 2.29b**. To a solution of 320 mg (0.556 mmol) stannane **2.27** in 1 mL THF was added 124 mg (0.529 mmol) bromide **2.28b**, 17 mg (0.016 mmol) $Pd_2(dba)_3$, and 9 mg (0.032 mmol) PPh_3. The Schlenck tube was flushed with N_2, then heated to 50 ºC for 17 h (some black solid crashed out). The solvent was then evaporated, and the crude oil was purified by flash column chromatography (12 to 20% EtOAc/hexanes) to isolate 123 mg **2.29b** (48%) as a yellow oil.

Rf: 0.30, 15% EtOAc/Hexanes. ^{1}H NMR (500 MHz): δ 6.63 (t, 1H, *J* = 8 Hz), 5.29 (d, 1H, *J* = 9 Hz), 4.49 (dd, 1H, *J* = 8, 7 Hz), 3.72 (m, 1H), 3.60 (m, 1H), 2.85 (m, 3H), 1.81 (s, 3H), 1.73 (m, 1H), 1.64 (s, 3H), 1.48 (s, 9H), 1.05 (s, 21H), 0.97 (d, 3H, *J* = 6.5 Hz). ^{13}C NMR (125 MHz): δ 167.20, 137.47, 133.39, 130.52, 129.13, 80.05, 74.82, 66.40, 42.19, 38.38, 28.06, 18.07, 17.96, 17.41, 13.46, 12.49, 12.35.



***t*-Butyl dibromide 2.33b**. To a solution of 150 mg (0.34 mmol) **2.29b** in 5 mL DCM was added 86 mg (1.02 mmol) $NaHCO_3$ and 151 mg (0.357 mmol) Dess-Martin Periodinane. After a hour and 15 minutes of stirring at room temperature, the reaction mixture was quenched with 10 mL of a 1:1:1 mixture of H_2O, $NaHCO_3$ (saturated), and $Na_2S_2O_3$ (saturated). The mixture was stirred vigorously and the layers were then separated, dried, filtered, and evaporated to afford 149 mg of the corresponding aldehyde (quantitative yield). Rf: 0.45, 15% EtOAc/Hexanes. To a solution of 108 mg (0.246 mmol) of the crude aldehyde in 5 mL DCM was added 285 mg (0.86 mmol) CBr_4, 56 mg (0.86 mmol) Zn, and 226 mg (0.86 mmol) PPh_3. The reaction mixture was stirred for 45 minutes at room temperature, then diluted with Et_2O and quenched with $NaHCO_3$ (saturated), washed with NaCl (saturated), dried, filtered, and evaporated. The crude oil was purified by flash column chromatography (10% EtOAc/hexanes) to afford 152 mg of **2.33b** (quantitative yield). Traces of bromoform were present.

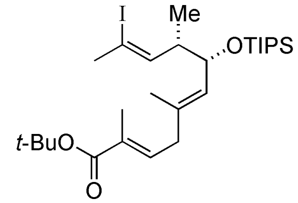
Rf: 0.66, 15% EtOAc/Hexanes. ^{1}H NMR (500 MHz): δ 6.63 (t, 1H, J = 7 Hz), 6.25 (d, 1H, J = 9.5 Hz), 5.19 (d, 1H, J = 9 Hz), 4.44 (dd, 1H, J = 9, 7 Hz), 2.84 (d, 2H, J = 8 Hz), 2.60 (m, 1H), 1.81 (s, 3H), 1.63 (s, 3H), 1.49 (s, 9H), 1.04 (s, 24H).



TIPS vinyl iodide 2.34a. To a solution of 134 mg (0.339 mmol) **2.29a** in 5 mL DCM was added 142 mg (1.70 mmol) $NaHCO_3$ and 158 mg (0.373 mmol) Dess-Martin Periodinane. After 2 h of stirring at room temperature, the reaction mixture was quenched with 10 mL of a 1:1:1 mixture of H_2O, $NaHCO_3$ (saturated), and $Na_2S_2O_3$ (saturated). The mixture was stirred vigorously and the layers were then separated, dried, filtered, and evaporated to afford the crude aldehyde.

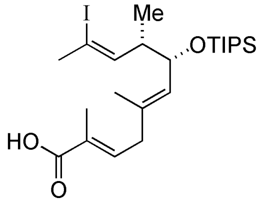
To a solution of 850 mg (2.03 mmol) of ethyl triphenylphosphonium iodide was added 0.81 mL (2.03 mmol) of 2.5M BuLi in hexanes. The resulting orange solution was cannulated into a solution of 3 mL of THF and 447 mg (1.76 mmol) of I_2 at −78 ºC. After 5 minutes of vigorous stirring, the solution was warmed to −20 ºC, and then 1.70 mL (1.70 mmol) of 2.0M sodium bis(trimethylsilyl)amide (NaHMDS) in THF was added. The solution turned orange and became easier to stir. At this point, a solution of the crude aldehyde in 3.0 mL THF was added. After 10 minutes, the solution was warmed to room temperature, and after 20 minutes, was quenched with $NaHCO_3$ (saturated), washed with NaCl (saturated) twice, dried, filtered, and evaporated. The crude oil was purified by flash column chromatography (1.5% EtOAc/hexanes) to afford 33 mg of **2.34a** (25%) as a 10:1 mixture of *Z*:*E* vinyl iodides.

Rf: 0.52, 10% EtOAc/Hexanes. ^{1}H NMR (500 MHz): δ 6.76 (t, 1H, J = 7 Hz), 5.19 (t, 2H, J = 7.5 Hz), 4.44 (dd, 1H, J = 8.5, 1.8 Hz), 3.74 (s, 3H), 2.85 (d, 2H, J = 7 Hz), 2.50 (m, 1H), 2.46 (s, 3H), 1.85 (s, 3H), 1.60 (s, 3H), 1.03 (s, 24H). ^{13}C NMR (125 MHz): δ 168.46, 139.46, 137.82, 132.39, 128.84, 128.61, 100.13, 71.54, 51.70, 48.90, 38.41, 33.70, 18.10, 17.98, 17.33, 14.53, 12.39, 12.36.



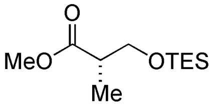
***t*-Butyl vinyl iodide 2.34b**. To a solution of 200 mg (0.48 mmol) of ethyl triphenylphosphonium iodide was added 0.19 mL (0.48 mmol) of 2.5M BuLi in hexanes. The resulting orange solution was cannulated into a solution of 3 mL of THF and 106 mg (0.42 mmol) of I_2 at −78 ºC. After 5 minutes of vigorous stirring, the solution was warmed to −20 ºC, and then 0.2 mL (0.40 mmol) of 2.0M NaHMDS in THF was added. The solution turned orange and became easier to stir. At this point, a solution of 35 mg (0.080 mmol) of the aldehyde of **2.29b** (prepared analogously to the procedure for **2.34a**) in 3.0 mL THF was added. Within 10 minutes, complete consumption of the starting material was observed by TLC and the solution was quenched with $NaHCO_3$ (saturated), washed with NaCl (saturated) twice, dried, filtered, and evaporated. The crude oil was purified by flash column chromatography (6% EtOAc/hexanes) to afford 15 mg of **2.34b** (30%) as a 10:1 mixture of *Z*:*E* vinyl iodides. The material was difficult to completely separate from triphenylphosphine oxide.

Rf: 0.52, 10% EtOAc/Hexanes. ^{1}H NMR (500 MHz): δ 6.65 (t, 1H, *J* = 6 Hz), 5.21 (t, 2H, *J* = 8.5 Hz), 4.45 (m, 1H), 2.83 (d, 2H, *J* = 7.5 Hz), 2.53 (m, 1H), 2.50 (s, 3H), 1.81 (s, 3H), 1.60 (s, 3H), 1.49 (s, 9H), 1.05 (s, 24H).



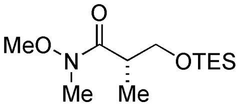
TIPS acid 2.35. To a solution of 67 mg (0.125 mmol) **2.34a** in 4.5 mL THF and 1.5 mL H_2O was added 15 mg NaOH. The Schlenck tube was sealed and heated to 80 ºC for 23 hours. The reaction mixture was then quenched with $NaHCO_3$ (saturated), extracted with Et_2O, washed with NaCl (saturated), dried, filtered, and evaporated. The crude oil was purified by flash column chromatography (20% EtOAc/hexanes) to afford 29 mg of **2.35** (45%, 50% borsm).

Rf: 0.56, 25% EtOAc/Hexanes. ^{1}H NMR (500 MHz): δ 6.92 (t, 1H, *J* = 7.5 Hz), 5.21 (d, 2H, *J* = 9 Hz), 4.44 (dd, 1H, *J* = 8.5, 4.5 Hz), 2.89 (d, 2H, *J* = 7.5 Hz), 2.55 (m, 1H), 2.46 (s, 3H), 1.86 (s, 3H), 1.61 (s, 3H), 1.04 (s, 21H), 1.00 (d, 3H, *J* = 6.5 Hz). ^{13}C NMR (125 MHz): δ 172.29, 141.94, 137.77, 132.07, 129.08, 127.97, 100.20, 71.48, 48.87, 38.61, 33.71, 18.10, 18.05, 17.97, 17.33, 14.50, 12.51, 12.38, 12.02.



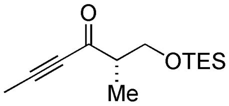
TES Roche ester 2.37. To a solution of 19.3 g (163 mmol) (*S*)-Roche ester **1.51** in 150 mL DCM was added 16.2 g (245 mmol) imidazole, followed by 36 mL (212 mmol) TESCl. An exotherm was observed so the flask was then placed in a water bath. After 20 minutes, the reaction mixture was quenched with $NaHCO_3$ (saturated). The layers were separated, and the organic layer was dried, filtered, and evaporated to obtain 37.90 g of **2.37** (99.8%).

Rf: 0.50, 10% EtOAc/Hexanes. ^{1}H NMR (500 MHz): δ 3.81 (dd, 1H, *J* = 13, 7 Hz), 3.72 (s, 3H), 3.65 (dd, 1H, *J* = 19, 6 Hz), 2.66 (m, 1H), 1.18 (d, 3H, *J* = 15 Hz), 0.97 (m, 9H), 0.56 (m, 6H). HRMS (EI) calcd for $C_{10}H_{21}O_3Si$ ($M - CH_3^+$) 217.1260, found 217.1242.



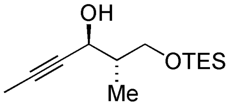
TES Weinreb amide 2.38. A solution of 21.12 g (90.0 mmol) **2.37** in 180 mL THF was added 9.31 g (95.45 mmol) N,O-dimethylhydroxylamine hydrochloride, then cooled to −20 ºC, and then 100 mL (200 mmol) of *i*-PrMgCl (2.0 M in THF) was cannulated into this solution to result in a clear, colorless suspension. The addition took place over 45 minutes and then became a brown solution that had warmed to 0 ºC. The reaction mixture was then quenched with NH_4Cl (saturated) and warmed to room temperature. Gas evolution was observed. The layers were then separated, and the aqueous layer was extracted with DCM. The combined organic layers were then dried, filtered, and evaporated to obtain 23.63 g of **2.38** (quantitative yield).

Rf: 0.41, 25% EtOAc/Hexanes. ^{1}H NMR (500 MHz): δ 3.84 (dd, 1H, *J* = 9.5, 7 Hz), 3.73 (s, 3H), 3.48 (dd, 1H, *J* = 19, 5 Hz), 3.19 (br s, 3H), 2.70 (m, 1H), 1.08 (d, 3H, *J* = 6.5 Hz), 0.95 (m, 9H), 0.60 (m, 6H). HRMS (ESI) calcd for $C_{12}H_{27}O_3NSiNa$ ($M + Na^+$) 284.1658, found 284.1654.



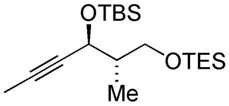
TES ynone 2.39. To a solution of 10.89 g (41.6 mmol) **2.38** in 80 mL THF that was cooled to 0 ºC was cannulated 100 mL propynyl-magnesium bromide (0.5 M in THF, 50 mmol) over 20 min. The reaction mixture was slowly warmed to room temperature over 3 hours, then quenched with H_2O. The layers were separated, and the organic layer was dried, filtered, and the volatile solvents were evaporated. The crude oil was purified by flash column chromatography (10% EtOAc/hexanes) to obtain 8.10 g of **2.39** (81%).

Rf: 0.36, 10% EtOAc/Hexanes. ^{1}H NMR (500 MHz): δ 3.89 (dd, 1H, *J* = 16.5, 6 Hz), 3.73 (dd, 1H, *J* = 10, 6 Hz), 2.74 (m, 1H), 2.03 (s, 3H), 1.16 (d, 3H, *J* = 7 Hz), 0.93 (m, 9H), 0.60 (m, 6H). HRMS (EI) calcd for $C_{12}H_{21}O_2Si$ (M – 3H$^+$) 225.1310, found 225.1311.



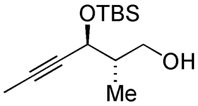
Alcohol 2.40. A neat solution of 8.81 g (36.6 mmol) **2.39** was added via cannula to 146 mL (73 mmol) of 0.5M *S*-Alpine Borane, and the resulting solution was concentrated to ~75 mL. The yellow solution was then heated to 40 ºC for 42 hours, at which point complete consumption of the starting material was observed. Propionaldehyde (5.5 mL) was then added, and after 30 minutes, the solution was cooled to 0 ºC. A mixture of 24 mL of 3.0M NaOH and 17 mL 30% H_2O_2 (in H_2O) was then added very slowly. The solution was allowed to stir for another 18 hours at room temperature, and then 50 mL of K_2CO_3 (saturated) was added. The layers were separated and the aqueous layer was extracted with Et_2O. The organic layers were combined, dried, filtered, and evaporated, then purified by flash column chromatography (7 to 9% EtOAc/hexanes) to obtain 6.91 g of **2.40** (78%) as a pale yellow oil.

Rf: 0.24, 10% EtOAc/Hexanes. ^{1}H NMR (500 MHz): δ 4.35 (m, 1H), 3.91 (dd, 1H, *J* = 16.5, 5 Hz), 3.62 (d, 1H, *J* = 4.5 Hz), 3.57 (dd, 1H, *J* = 10, 6 Hz), 1.86 (m, 4H), 0.96 (m, 12H), 0.62 (m, 6H). ^{13}C NMR (75 MHz): δ 81.23, 79.28, 67.15, 66.68, 40.90, 12.98, 6.59, 4.18, 3.48.



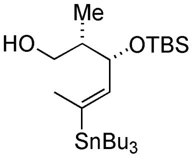
TBS TES diol 2.41. To a solution of 6.65 g (27.4 mmol) **2.40** in 50 mL DCM was added 2.24 g (32.88 mmol) imidazole followed by 4.54 g (30.14 mmol) TBSCl. A white precipitate was immediately formed. The solution was stirred for 18 hours, then filtered through celite, evaporated, and purified by flash column chromatography (2% EtOAc/hexanes)to obtain 9.68 g **2.41** (99%) as a clear, colorless oil.

Rf: 0.71, 10% EtOAc/Hexanes. ^{1}H NMR (500 MHz): δ 4.34 (m, 1H), 3.61 (dd, 1H, *J* = 10, 4 Hz), 3.50 (dd, 1H, *J* = 9.5, 4 Hz), 1.82 (m, 4H), 0.97 (m, 21H), 0.57 (m, 6H), 0.13 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (75 MHz): δ 80.84, 79.10, 64.72, 64.58, 43.16, 25.85, 18.25, 12.01, 6.75, 4.44, 3.47, -4.55, -5.17. IR: 2955, 2878, 1463, 1251, 1065, 1004, 814, 774, 740, 668 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{41}O_2Si_2$ (M + H$^+$) 357.2645, found 357.2643.



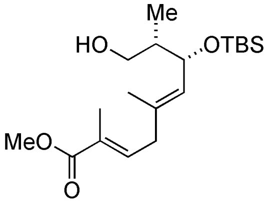
Mono protected diol 2.42. To a solution of 5 g (14 mmol) **2.41** in 100 mL EtOH was added 704 mg (2.8 mmol) PPTS. The resulting solution was stirred at room temperature for 1.5 hours, then quenched and washed with $NaHCO_3$ (saturated), then washed with NaCl (saturated). The combined aqueous layers were extracted with Et_2O, and the combined organic layers were then dried, filtered, and evaporated. Flash column chromatography (10% EtOAc/hexanes) afforded 2.34 g of **2.42** (69%, 77% borsm) as a clear, colorless oil. (Running the reaction until all starting material was consumed often resulted in removal of the TBS group).

Rf: 0.28, 10% EtOAc/Hexanes. ^{1}H NMR (400 MHz): δ 4.33 (m, 1H), 3.88 (d, 1H, *J* = 23 Hz), 3.65 (m, 1H), 2.61 (br s, 1H), 1.90 (m, 4H), 1.02 (d, 3H), 0.91 (m, 9H), 0.17 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (75 MHz): δ 81.73, 79.59, 67.87, 65.93, 42.05, 25.77, 18.11, 13.42, 3.47, -4.45, -5.28.



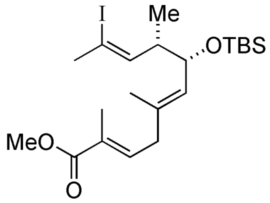
TBS stannane 2.43. To a solution of 1.50 g (6.19 mmol) of **2.42** in 50 mL $PhCH_3$ was added 80 mg (0.31 mmol) $(MeCN)_2Pd(PPh_3)_2$, 163 mg (0.62 mmol) PPh_3, and then 1.75 mL (6.50 mmol) of Bu_3SnH dropwise over the course of 2 hours. After addition was complete, another 80 mg (0.31 mmol) $(MeCN)_2Pd(PPh_3)_2$, 163 mg (0.62 mmol) PPh_3, and 1.75 mL (6.50 mmol) of Bu_3SnH was added and the reaction mixture was stirred for another 90 minutes. The volatiles were then evaporated and the resulting black crude oil was purified by flash column chromatography (0 to 10% EtOAc/hexanes, 1% TEA) to afford 2.80 g of **2.43** (85%) as a clear, colorless oil.

Rf: 0.37, 10% EtOAc/Hexanes. ^{1}H NMR (300 MHz): δ 5.58 (dd, 1H, *J* = 2, 8 Hz), 4.47 (t, 1H, *J* = 7 Hz), 3.72 (m, 1H), 3.62 (m, 1H), 3.01 (dd, 1H, *J* = 5, 6 Hz), 1.85 (s with satellites, 3H), 1.71 (m, 1H), 1.47 (m, 6H), 1.32 (m, 6H), 0.89 (m, 24H), 0.08 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (75 MHz): δ 143.32, 139.50, 74.21, 66.79, 41.30, 29.18, 27.37, 25.83, 19.91, 18.04, 13.69, 13.66, 9.12 (with satellites), -4.10, -5.01. IR: 3392, 2956, 2872, 1463, 1250, 1044, 834, 774, 670 cm^{-1}.



TBS 1,4 skipped diene 2.44. To a solution of 95 mg (0.092 mmol) $Pd_2(dba)_3$, 48 mg (0.184 mmol) PPh_3, and 1.44 g (3.07 mmol) **2.43** in 5 mL THF was added 0.740 g (3.84 mmol) **2.28a** in 4 mL THF. The sealed tube was then flushed with argon and heated to 60 ºC for 46 hours. The solvent was then evaporated and the crude oil was purified by flash column chromatography (15 to 20% EtOAc/hexanes) to obtain 0.760 g of **2.44** (79%) as a light yellow oil.

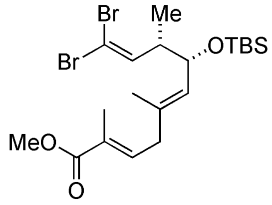
Rf: 0.46, 25% EtOAc/Hexanes. ^{1}H NMR (300 MHz): δ 6.74 (ddd, 1H, *J* = 9, 7.5, 1.5 Hz), 5.24 (d, 1H, *J* = 9 Hz), 4.28 (dd, 1H, *J* = 9, 7 Hz), 3.74 (s, 3H), 3.68 (m, 1H), 3.61 (m, 1H), 2.87 (d with shoulder, 3H, *J* = 7.7 Hz), 1.85 (s, 3H), 1.68 (m, 1H), 1.64 (s, 3H), 0.86 (m, 12H), 0.05 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (75 MHz): δ 168.42, 138.97, 133.40, 129.42, 128.99, 75.29, 66.63, 51.77, 41.59, 38.43, 25.80, 17.99, 17.29, 13.76, 12.41, -4.04, -5.01. IR: 3440, 2929, 1716, 1436, 1254, 1030, 814, 774, 668 cm^{-1}.



TBS vinyl iodide 2.45. To a solution of 400 mg (1.12 mmol) **2.44** in 10 mL DCM was added 470 mg (5.6 mmol) $NaHCO_3$ and 523 mg (1.23 mmol) Dess-Martin Periodinane. After 30 min of stirring at room temperature, the reaction mixture was quenched with a 1:1:1 mixture of H_2O, $NaHCO_3$ (saturated), and $Na_2S_2O_3$ (saturated). The mixture was stirred vigorously and the layers were then separated, dried, filtered, and evaporated to afford the crude aldehyde, of which 50 mg was carried on to the following procedure:

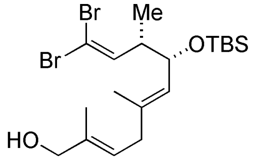
To a solution of 246 mg (0.588 mmol) of ethyl triphenylphosphonium iodide was added 0.24 mL (0.6 mmol) of 2.5M BuLi in hexanes. The resulting orange solution was cannulated into a solution of 3 mL of THF and 129 mg (0.509 mmol) of I_2 at −78 ºC. After 5 minutes of vigorous stirring, the solution was warmed to −20 ºC, and then 0.50 mL (0.50 mmol) of 1.0M NaHMDS in THF was added. The solution turned orange and became easier to stir. At this point, a solution of 50 mg (0.139 mmol) of the crude aldehyde in 3.0 mL THF was added. After 10 minutes, the solution was warmed to room temperature, and after 20 minutes, was quenched with $NaHCO_3$ (saturated), washed with NaCl (saturated) twice, dried, filtered, and evaporated. The crude oil was purified by flash column chromatography (1% EtOAc/hexanes) to afford 15.4 mg of **2.45** (37%) as an inseparable 10:1 mixture of *Z*:*E* vinyl iodides.

Rf: 0.52, 10% EtOAc/Hexanes. ^{1}H NMR (600 MHz) of major isomer: δ 6.76 (t, 1H, *J* = 7.7 Hz), 5.24 (d, 2H, *J* = 8.9 Hz), 5.14 (d, 1H, *J* = 8.8 Hz), 4.26 (dd, 1H, *J* = 8.8, 5 Hz), 3.74 (s, 3H), 2.85 (d, 2H, *J* = 7.6 Hz), 2.47 (s, 3H), 2.41 (m, 1H), 1.85 (s, 3H), 1.68 (s, 3H), 0.86 (s, 9H), 0.02 (s, 3H), -0.02 (s, 3H). ^{13}C NMR (150 MHz): δ 168.51, 139.51, 137.79, 132.64, 128.92, 100.33, 72.04, 65.84, 51.72, 48.51, 38.51, 33.71, 25.80, 18.12, 17.17, 15.35, 12.40, -4.37, -4.86. IR: 2928, 2856, 1716, 1435, 1360, 1254, 1120, 1067, 1028, 835 cm^{-1}.



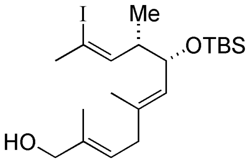
TBS vinyl dibromide 2.47. To a solution of 1.27 g (3.56 mmol) alcohol **2.44** in 30 mL of DCM was added 1.50 g (17.8 mmol) $NaHCO_3$ and 1.66 g (3.92 mmol) Dess-Martin Periodinane. After 5 min of stirring at room temperature, the reaction mixture was quenched with a 1:1:1 mixture of H_2O, $NaHCO_3$ (saturated), and $Na_2S_2O_3$ (saturated). The mixture was stirred vigorously and the layers were then separated, dried, filtered, and evaporated to afford the crude aldehyde, which was immediately dissolved in 30 mL DCM. At this point, 2.36 g (7.12 mmol) CBr_4, 0.466 g (7.12 mmol) Zinc dust and 1.87 g (7.12 mmol) PPh_3. The solution was stirred for 30 minutes, then quenched with $NaHCO_3$ (saturated). The layers were separated and the organics were dried, filtered, and evaporated. The crude oil was purified by flash column chromatography (7% EtOAc/hexanes) to afford 1.34 g of **2.47** (74%) as a clear, colorless oil.

Rf: 0.56, 10% EtOAc/Hexanes. ^{1}H NMR (600 MHz): δ 6.75 (t, 1H, *J* = 7.7 Hz), 6.27 (d, 1H, *J* = 9.5 Hz), 5.13 (d, 1H, *J* = 8.8 Hz), 4.22 (dd, 1H, *J* = 8.8, 6.6 Hz), 3.74 (s, 3H), 2.86 (d, 2H, *J* = 7.7 Hz), 2.51 (m, 1H), 1.86 (s, 3H), 1.65 (s, 3H), 0.95 (d, 3H, *J* = 6 Hz), 0.91 (s, 9H), 0.02 (s, 3H), -0.02 (s, 3H). ^{13}C NMR (150 MHz): δ 168.44, 141.15, 139.11, 133.50, 128.94, 128.48, 88.19, 71.79, 51.74, 45.47, 38.43, 25.74, 18.05, 17.17, 15.04, 12.39, -4.28, -4.95. IR: 2929, 2856, 1716, 1435, 1256, 1199, 1067, 835 cm^{-1}.



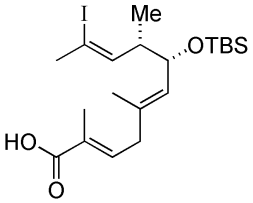
Allylic alcohol 2.48. A solution of 1.24 g (2.43 mmol) **2.47** in 50 mL DCM was cooled to −78 ºC, and then a solution of 1.9 mL (10.94 mmol) of neat DIBALH in 7 mL of $PhCH_3$ was added via cannula. After 5 minutes, the reaction mixture was slowly quenched with Rochelle's salt (saturated), then diluted with DCM and H_2O and stirred vigorously until no emulsion was observed. The layers were separated, the aqueous layer was then extracted with Et_2O and the organic layers were combined, dried, filtered, and evaporated to afford 1.13 g of **2.48** (97%).

Rf: 0.61, 25% EtOAc/Hexanes. ^{1}H NMR (600 MHz): δ 6.28 (d, 1H, *J* = 9.5 Hz), 5.44 (t, 1H, *J* = 7.4 Hz), 5.11 (d, 1H, *J* = 8.9 Hz), 4.23 (dd, 1H, *J* = 8.9, 5.4 Hz), 4.04 (s, 2H), 2.73 (d, 2H, *J* = 7.4 Hz), 2.48 (m, 1H), 1.69 (s, 3H), 1.62 (s, 3H), 1.53 (s, 1H), 0.97 (d, 3H, *J* = 6.9 Hz), 0.86 (s, 9H), 0.07 (s, 3H), -0.02 (s, 3H). ^{13}C NMR (150 MHz): δ 141.41, 136.59, 135.20, 127.13, 123.15, 87.96, 71.88, 68.86, 45.58, 37.54, 25.78, 25.63, 18.09, 17.03, 15.05, 13.66, -4.21, -4.94.



Vinyl iodide 2.49. To a suspension of 1.31 g (6.90 mmol) CuI in 12.5 mL Et_2O (freshly distilled) at 0 ºC was added 8.6 mL (13.81 mmol) of 1.6M MeLi over 30 minutes (syringe pump). The solution turned yellow and then became a clear suspension with a gritty brown solid throughout the course of this addition. The reaction mixture was then cooled to –78 ºC and a solution of 1.11 g (2.30 mmol) **2.48** in 9.0 mL Et_2O was added over an hour (syringe pump). The reaction mixture became a brown solid that was difficult to stir. After 30 minutes, the mixture was quenched with a solution of 3.5 g (13.81 mmol) I_2 in 11 mL Et_2O and was warmed to 0 ºC over 20 minutes. The reaction mixture was quenched with NH_4Cl (saturated), washed with $Na_2S_2O_3$ (saturated), then washed with NaCl (saturated). The organic layer was dried, filtered, and evaporated. The clear, colorless crude oil was purified by flash column chromatography (15% EtOAc/hexanes) to afford 0.867 g of **2.49** (81%).

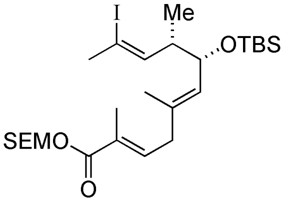
Rf: 0.31, 15% EtOAc/Hexanes. ^{1}H NMR (600 MHz): δ 5.42 (m, 1H), 5.25 (d, 1H, *J* = 8.9 Hz), 5.12 (d, 1H, *J* = 8.9 Hz), 4.25 (dd, 1H, *J* = 8.9, 5 Hz), 4.02 (s, 2H), 2.87 (d, 2H, *J* = 7.3 Hz), 2.47 (s, 3H), 2.41 (m, 1H), 1.68 (s, 3H), 1.60 (s, 3H), 0.92 (d, 3H, *J* = 6.9 Hz), 0.83 (s, 9H), 0.06 (s, 3H), -0.03 (s, 3H). IR: 3314, 2956, 1672, 1471, 1380, 1250, 1064, 814, 774.



Acid 2.46. To a solution of 0.800 g (1.72 mmol) alcohol **2.49** in 30 mL of DCM was added 0.722 g (8.6 mmol) $NaHCO_3$ and 0.802 g (1.89 mmol) Dess-Martin Periodinane. After 10 min of stirring at room temperature, the reaction mixture was quenched with a 1:1:1 mixture of H_2O, $NaHCO_3$ (saturated), and $Na_2S_2O_3$ (saturated). The mixture was stirred vigorously and the layers were then separated, dried, filtered, and evaporated to afford the crude aldehydes, which was immediately dissolved in 54 mL of a 1:1 mixture of H_2O/*t*BuOH. At this point, 2.8 mL of 2-methyl-2-butene (excess), 2.06 g (17.2 mmol)of monobasic sodium phosphate (NaH_2PO_4), and 1.40 g sodium chlorite ($NaClO_2$, 15.48 mmol) was added. The resulting biphasic mixture was stirred for 4 hours, and then Et_2O was added to the reaction mixture and it was concurrently quenched with $NaHCO_3$ (saturated). The layers were separated and the organics were dried, filtered, and evaporated. The crude oil was purified by HPLC to fully remove trace impurities from vinyl iodide step to afford 707 mg of **2.46** (86%) as a clear, colorless oil.

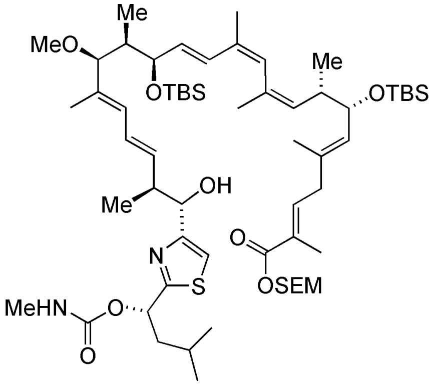
This compound could also be prepared from methyl ester **2.45** using 15 equiv of Me_3SnOH at 100 ºC in DCE in a sealed tube for 48 hours. Note: ^{1}H NMR Spectrum shown was the same sample as that characterized below but residual solvents were fully removed on the rotovap and the sample was taken on a 400 MHz machine.

Rf: 0.27, 15% EtOAc/Hexanes. ^{1}H NMR (600 MHz): δ 6.90 (t, 1H *J* = 9.4 Hz), 5.24 (d, 1H, *J* = 11.2 Hz), 5.15 (d, 1H, *J* = 13.3 Hz), 4.25 (dd, 1H, *J* = 13, 5 Hz), 3.74 (s, 3H), 2.87 (d, 2H, *J* = 11.5 Hz), 2.47 (s, 3H), 2.42 (m, 1H), 1.85 (s, 3H), 1.63 (s with shoulder [OH], 4H), 0.95 (d, 3H, *J* = 10.3 Hz), 0.86 (s, 9H), 0.02 (s, 3H), -0.04 (s, 3H). ^{13}C NMR (100 MHz): δ 173.32, 142.09, 137.72, 132.31, 129.15, 128.23, 100.43, 71.98, 48.48, 38.71, 33.72, 25.79, 18.12, 17.16, 15.32, 12.02, -4.19, -4.87.



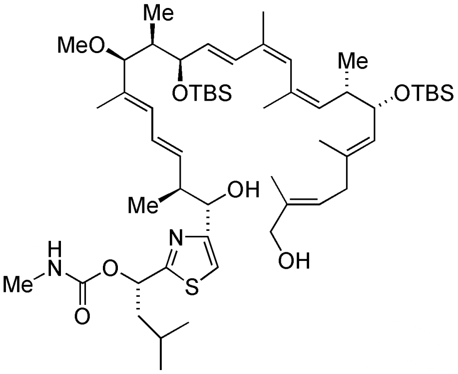
SEM ester 2.50. To a solution of 22 mg (0.0459 mmol) **2.49** in 1 mL DCM at 0 ºC was added 8.00 μL (0.0597 mmol) TEA followed by 10 μL (0.055 mmol) SEMCl. After 3 minutes, the reaction mixture was quenched with $NaHCO_3$ (saturated). The layers were separated and the organic layer was washed with NaCl (saturated), then dried, filtered, and evaporated to afford 19 mg of **2.50** (68%) as a clear, colorless oil.

Rf: 0.77, 25% EtOAc/Hexanes. ^{1}H NMR (600 MHz): δ 6.82 (t, 1H *J* = 7.7 Hz), 5.36 (s, 2H), 5.25 (d, 1H, *J* = 8.9 Hz), 5.16 (d, 1H, *J* = 8.8 Hz), 4.26 (dd, 1H, *J* = 8.8, 5 Hz), 3.73 (t, 2H, *J* = 14 Hz), 2.89 (d, 2H, *J* = 7.7 Hz), 2.47 (s, 3H), 2.43 (m, 1H), 1.87 (s, 3H), 1.62 (s, 3H), 1.55 (s, 2H), 0.94 (d, 3H, *J* = 7 Hz), 0.87 (s, 9H), 0.02 (m, 15H).



SEM Stille product 2.51. To a solution of 10 mg (0.0112 mmol) stannane **2.1** and 6.8 mg (0.0112 mmol) iodide **2.50** in 1.0 mL DMF was added 1.3 mg (1.1 μmol) $Pd(PPh_3)_4$. After 5 minutes of stirring at room temperature, added 3.2 mg (0.0168 mmol) CuTC. After 30 minutes, another 3.2 mg (0.0168 mmol) of CuTC was added. The reaction mixture was then quenched with H_2O, added NaCl (saturated), then extracted with Et_2O. The organic extracts were dried, filtered, and evaporated. Flash column chromatography (20 to 25 to 30 to 60% EtOAc/hexanes) afforded 7 mg of **2.51** (58%).

Rf: 0.52, 40% EtOAc/hexanes. ^{1}H NMR (600 MHz): δ 7.07 (s, 1H), 6.80 (t, 1H *J* = 7.6 Hz)), 6.43 (d, 1H, *J* = 16 Hz), 6.35 (m, 1H), 6.05 (m, 1H), 5.92 (d, 1H, *J* = 11 Hz), 5.84 (s, 1H), 5.68 (m, 3H), 5.36 (s, 2H), 5.15 (d, 1H, *J* = 9.2 Hz), 5.05 (d, 1H, *J* = 9.5 Hz), 4.74 (br s, 1H), 4.68 (dd, 1H, *J* = 18, 6 Hz), 4.60 (m, 1H), 4.09 (m, 1H), 3.72 (m, 2H), 3.34 (t, 1H, *J* = 12 Hz), 3.13 (m, 3H), 2.82 (m, 5H), 2.36 (m, 2H), 1.91 (m, 1H), 1.87 (m, 6H), 1.83 (d, 6H), 1.72 (m, 2H), 1.60 (m, 6H), 1.18 (m, 3H), 0.91 (m, 27H), 0.58 (m, 3H), 0.00 (m, 21H). HRMS (ESI) calcd for $C_{60}H_{106}N_2O_9SSi_3Na$ ([M + Na]$^+$) 1137.6825, found 1137.6768.

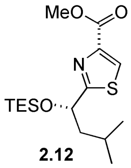


Reduced SEM ester 2.52. To a solution of 6 mg (5.37 μmol) **2.51** in 1 mL $PhCH_3$ cooled to –25 ºC was added 8 μL (0.027 mmol) Redal® (3.5 M in $PhCH_3$). The solution was stirred for 1 hour, then quenched with $NaHCO_3$ (saturated) and diluted with Et_2O. The layers were separated, and the organic layer was then dried, filtered, and evaporated. Flash column chromatography (40% EtOAc/hexanes) afforded 4.4 mg **2.52** (85%) as well as 2 mg of the product of 1,4 reduction, which was copolar with the starting material.

Rf: 0.52, 40% EtOAc/hexanes. ^{1}H NMR (600 MHz): δ 7.11 (s, 1H), 6.44 (d, 1H *J* = 16 Hz)), 6.35 (t, 1H, *J* = 11 Hz), 6.05 (m, 1H), 5.92 (m, 1H), 5.85 (s, 1H), 5.68 (m, 2H), 5.42 (m, 1H), 5.10 (d, 1H, *J* = 8.5 Hz), 5.06 (d, 1H, *J* = 9.7 Hz), 4.76 (br s, 1H), 4.68 (m, 1H), 4.60 (s, 1H), 4.13 (dd, 1H, *J* = 14, 7 Hz), 4.02 (s, 2H), 3.34 (d, 1H, *J* = 16 Hz), 3.11 (m, 3H), 2.82 (s, 3H), 2.72 (d, 2H, *J* = 7.6 Hz), 2.45 (m, 1H), 2.36 (m, 1H), 1.84 (m, 21H), 1.20 (m, 3H), 0.85 (m, 27H), 0.62 (m, 3H), 0.03 (m, 12H). HRMS (ESI) calcd for $C_{54}H_{94}N_2O_7SSi_2Cl$ ([M + Cl]$^-$) 1005.6009, found 1005.6050.

2.8. Appendix

Characterization data for 2.12, 2.13, 2.14, 2.15, 2.16, 2.17, 2.18, 2.19, 2.20, 2.21, 2.22, 2.1, 2.23, 2.24, 2.27, 2.29a, 2.29b, 2.33b, 2.34a, 2.35, 2.37, 2.38, 2.39, 2.40, 2.41, 2.42, 2.43, 2.44, 2.45, 2.47, 2.48, 2.49, 2.46, 2.50, 2.51, 2.52



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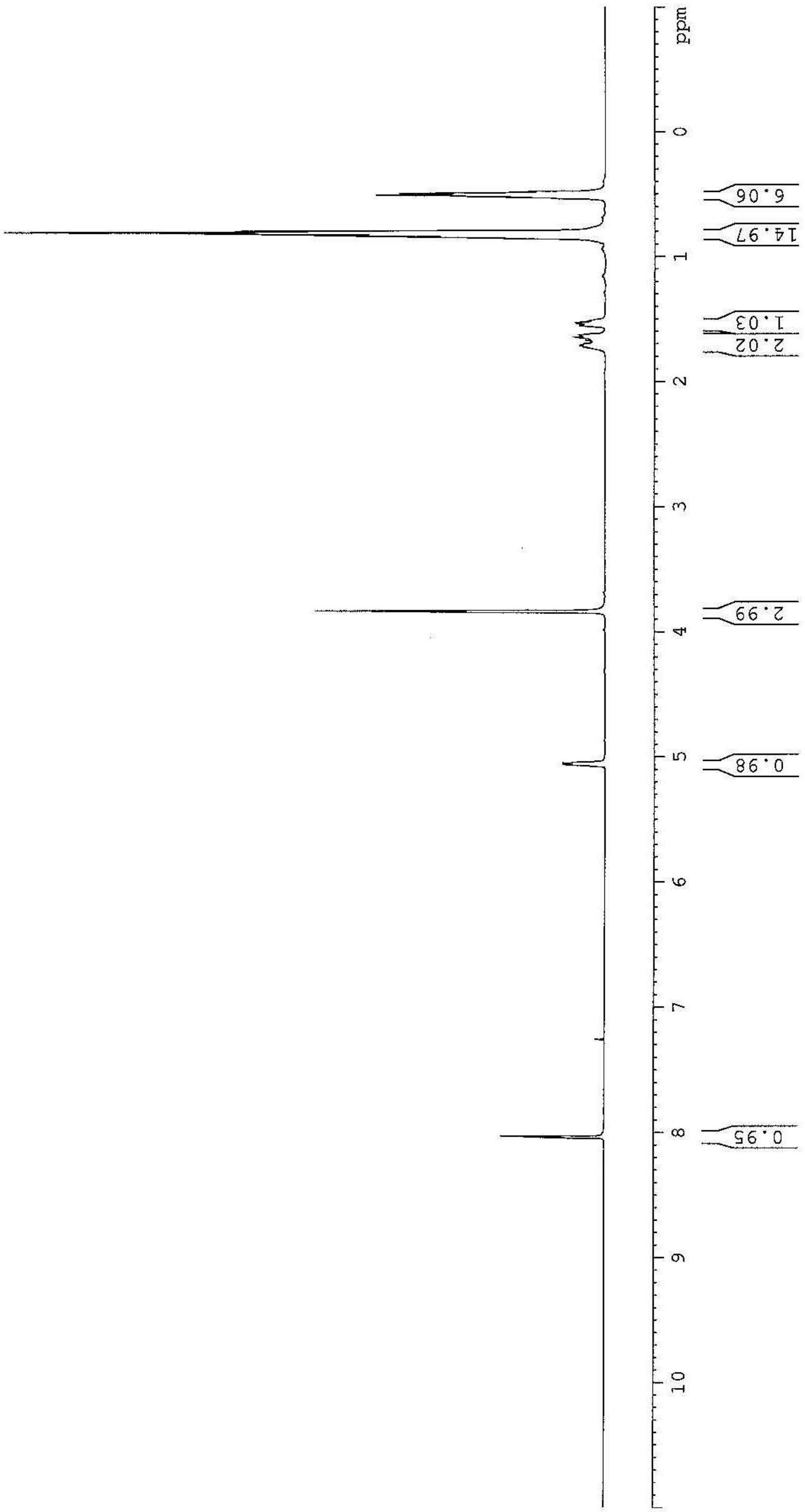

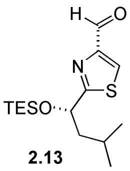

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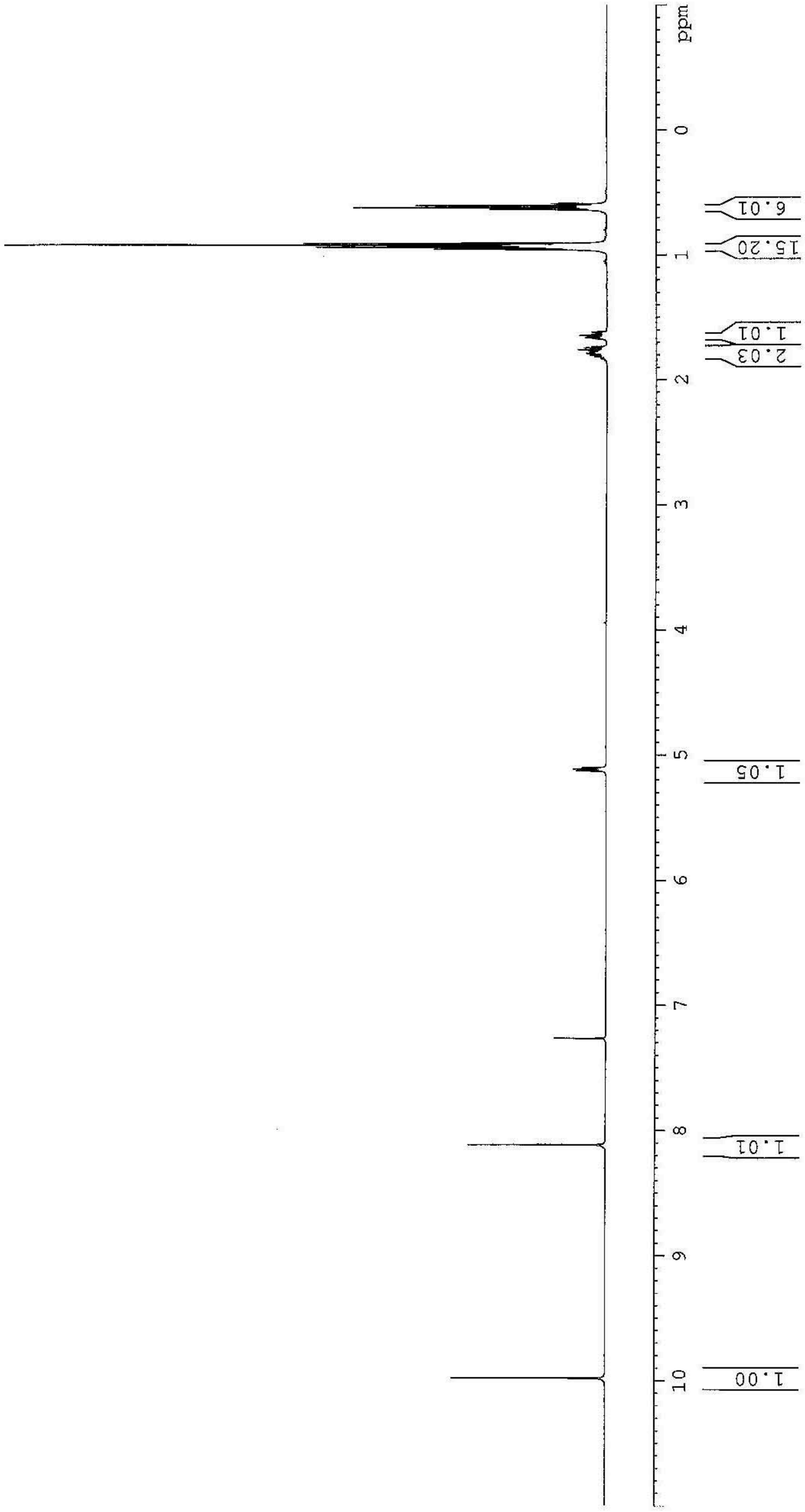

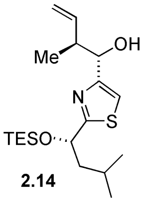

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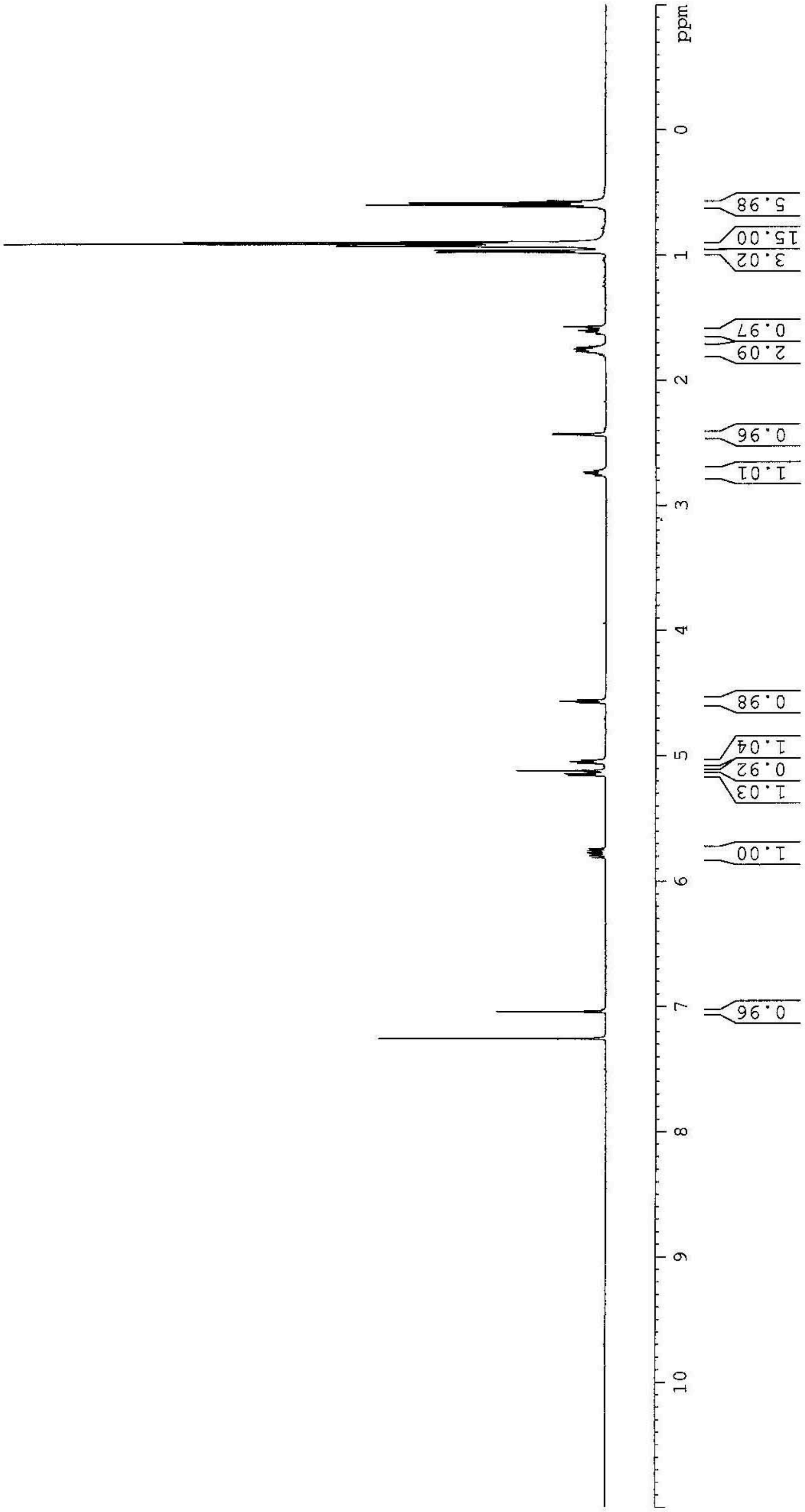

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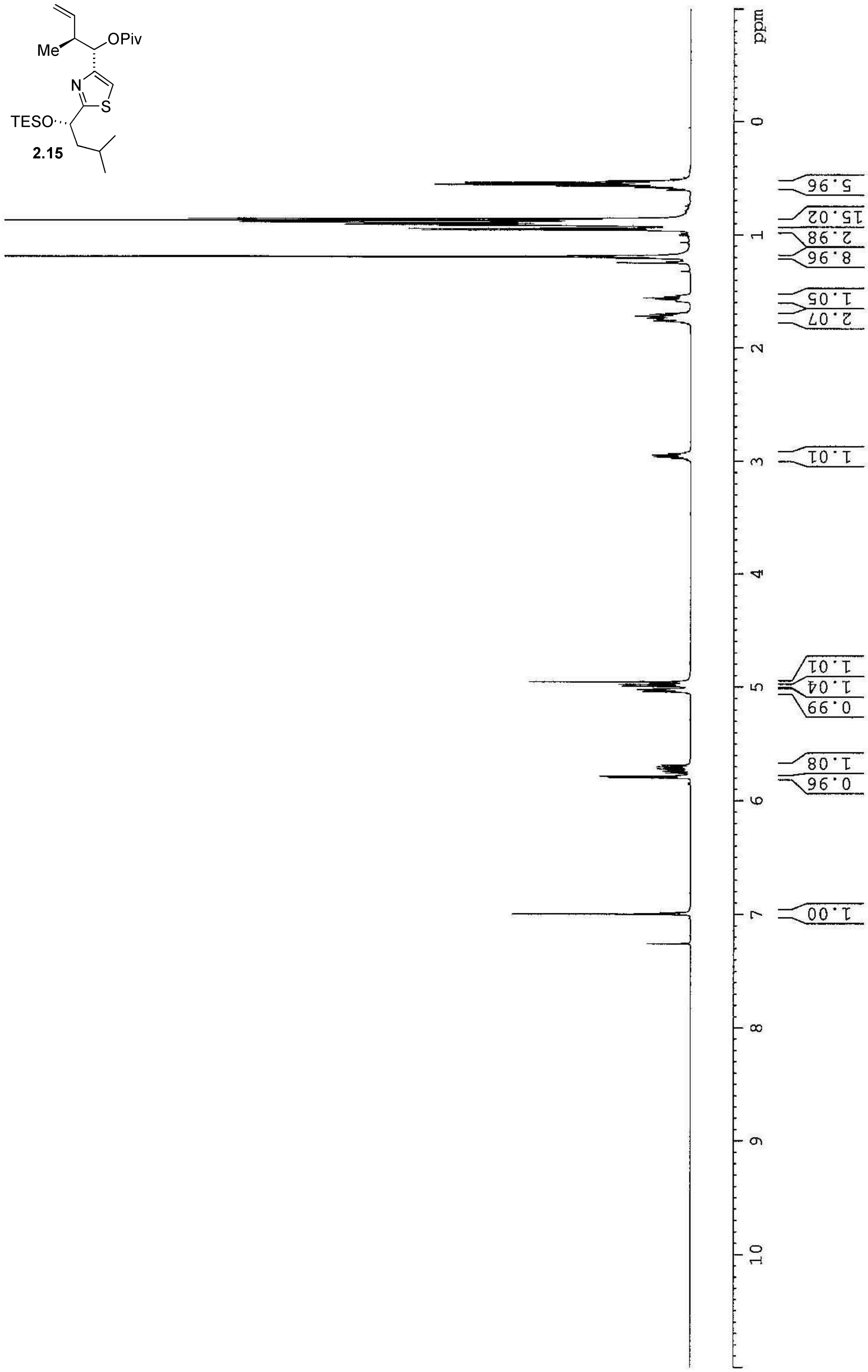

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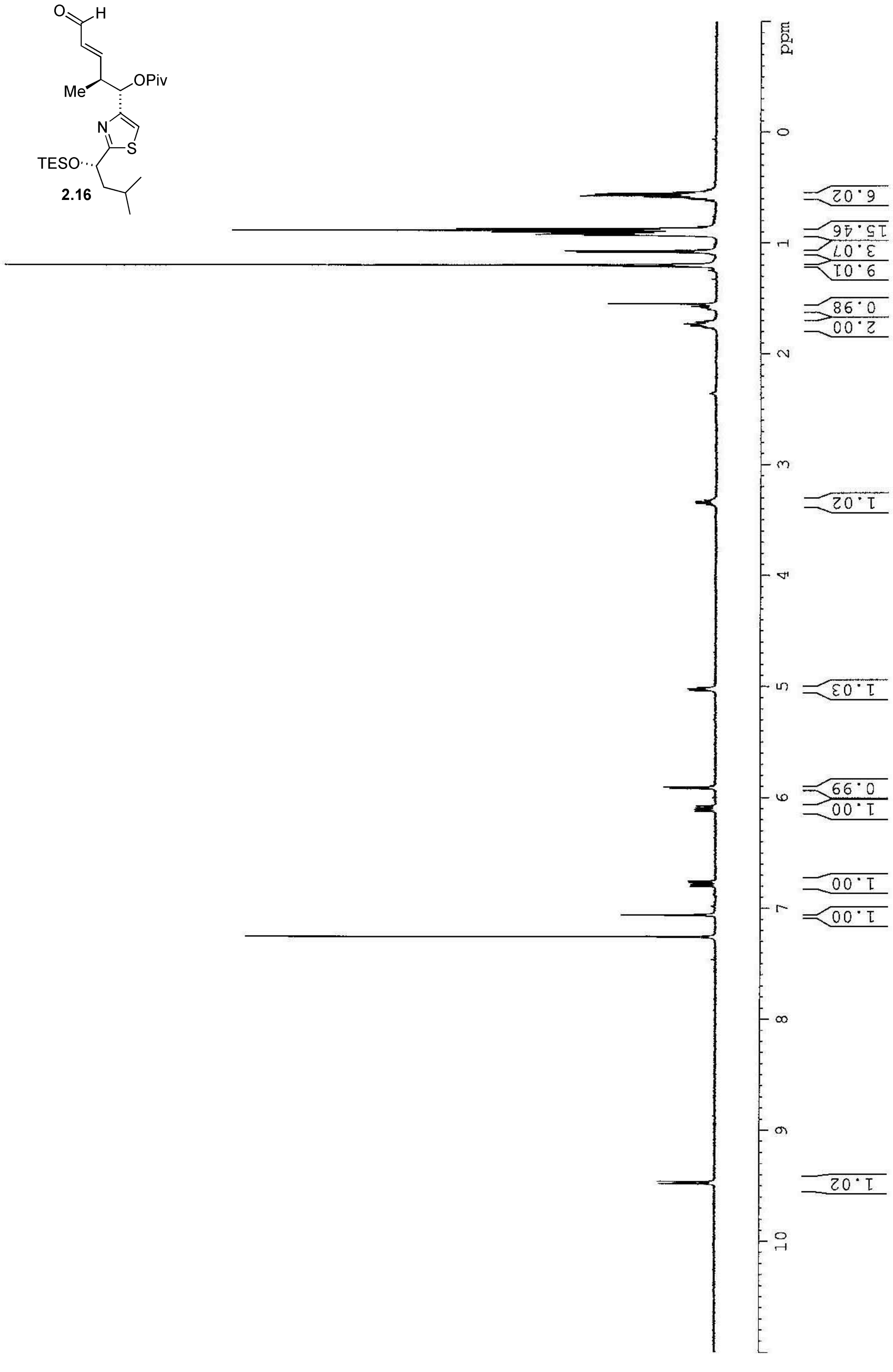
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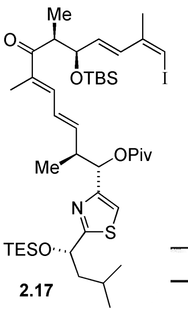
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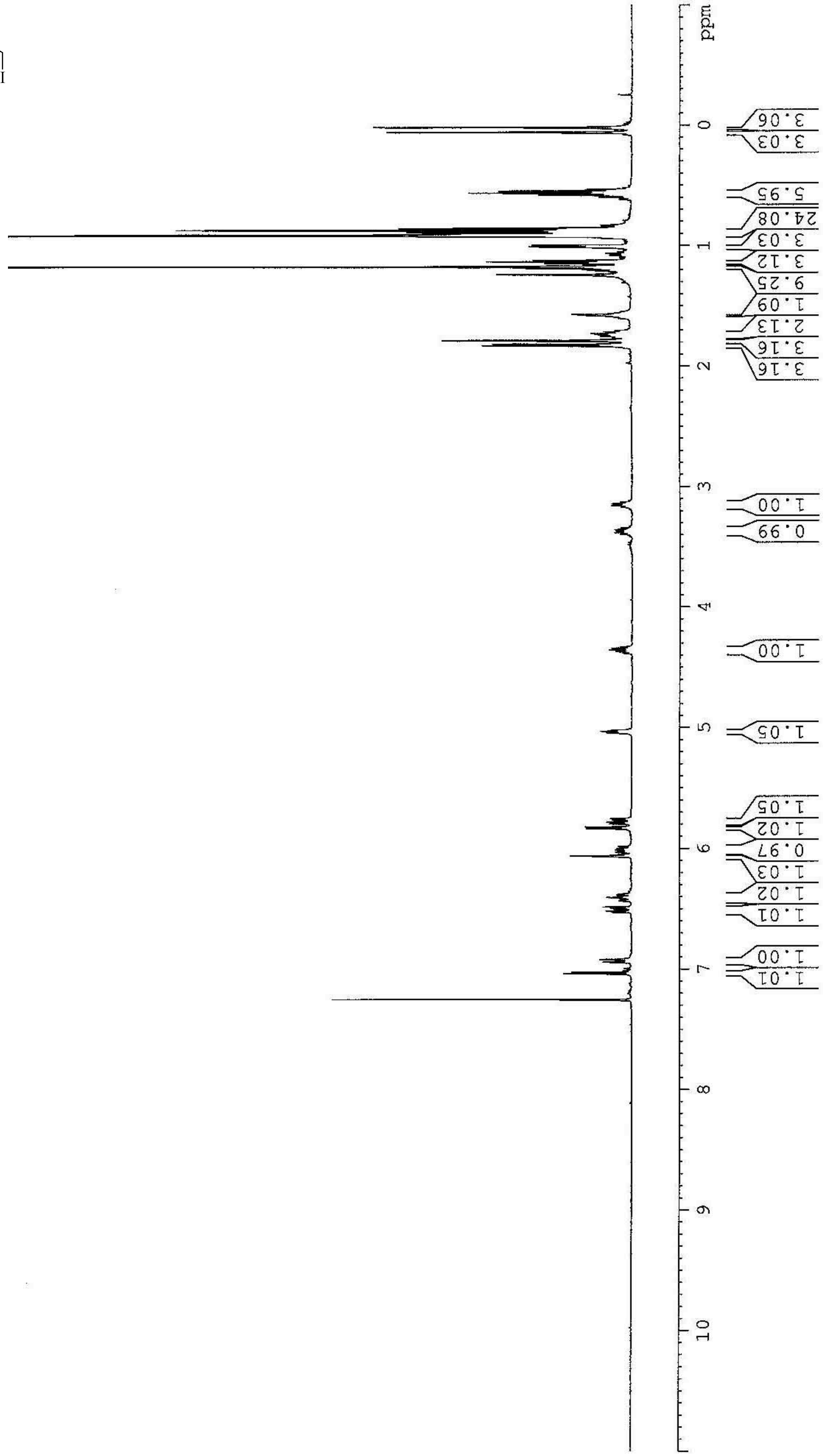
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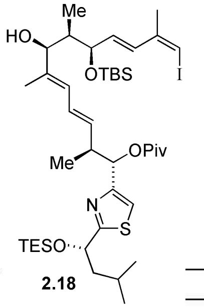
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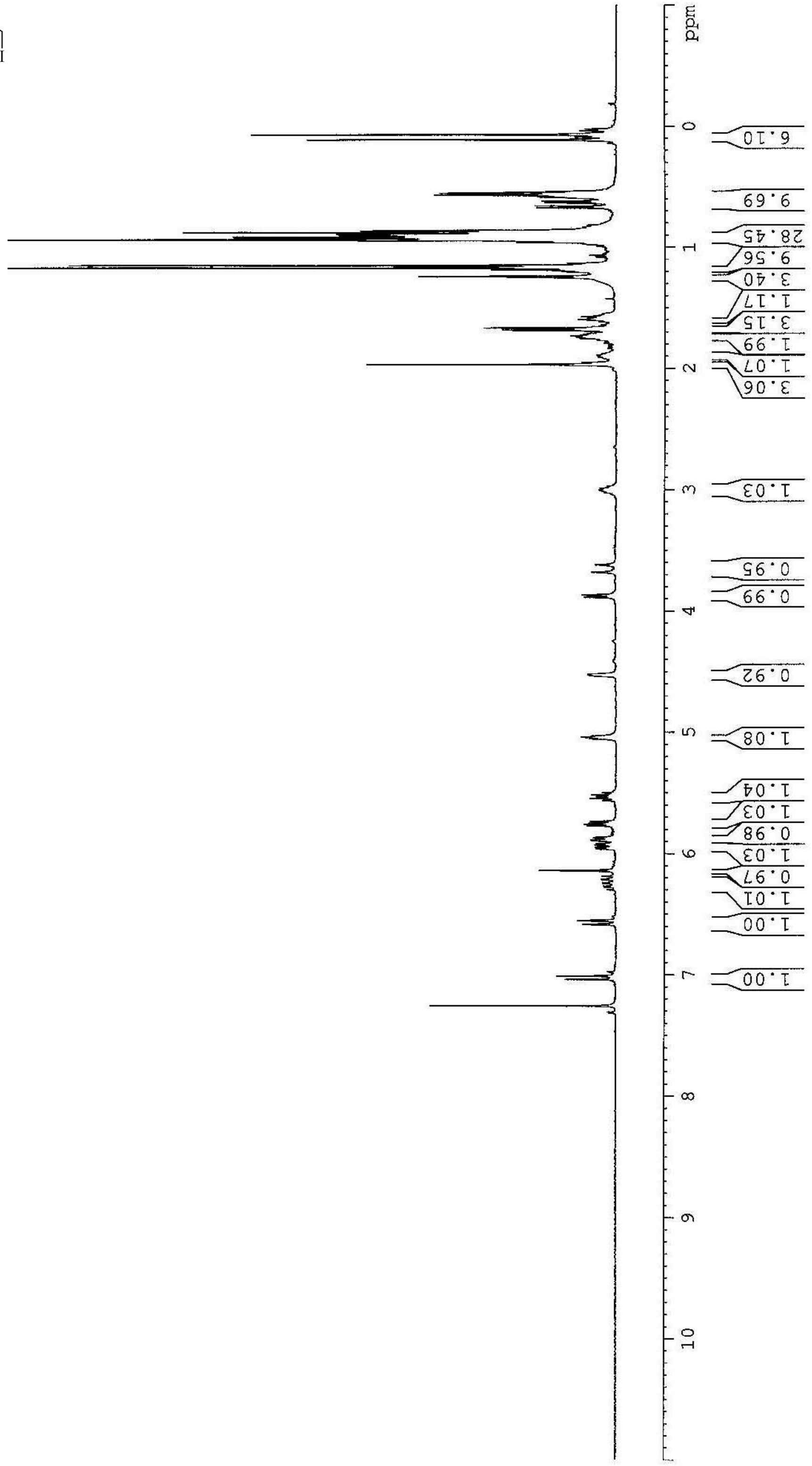
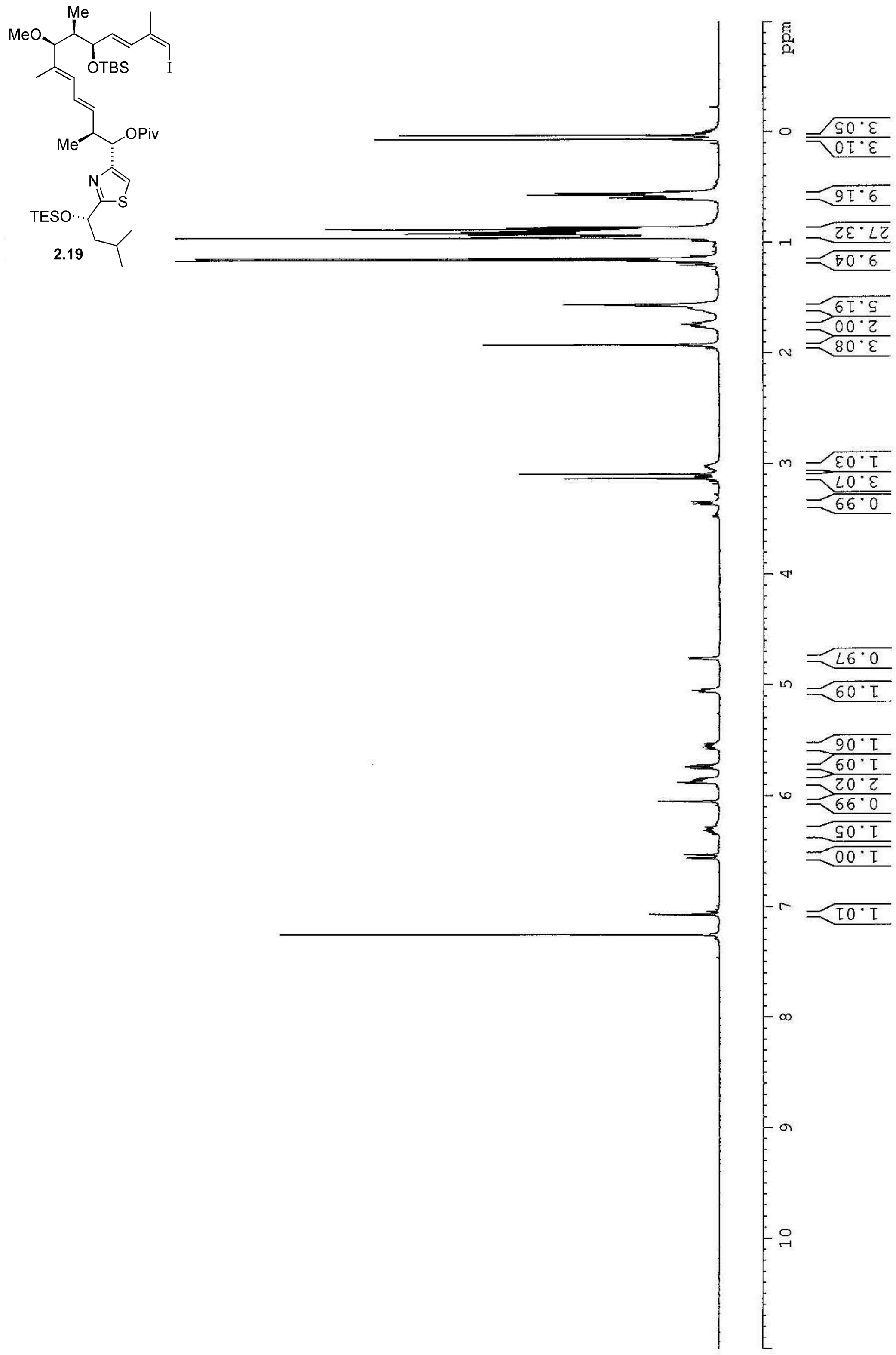
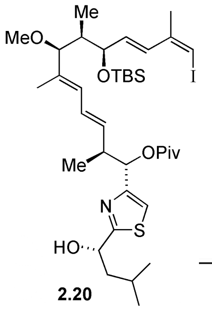
TESO

2.18

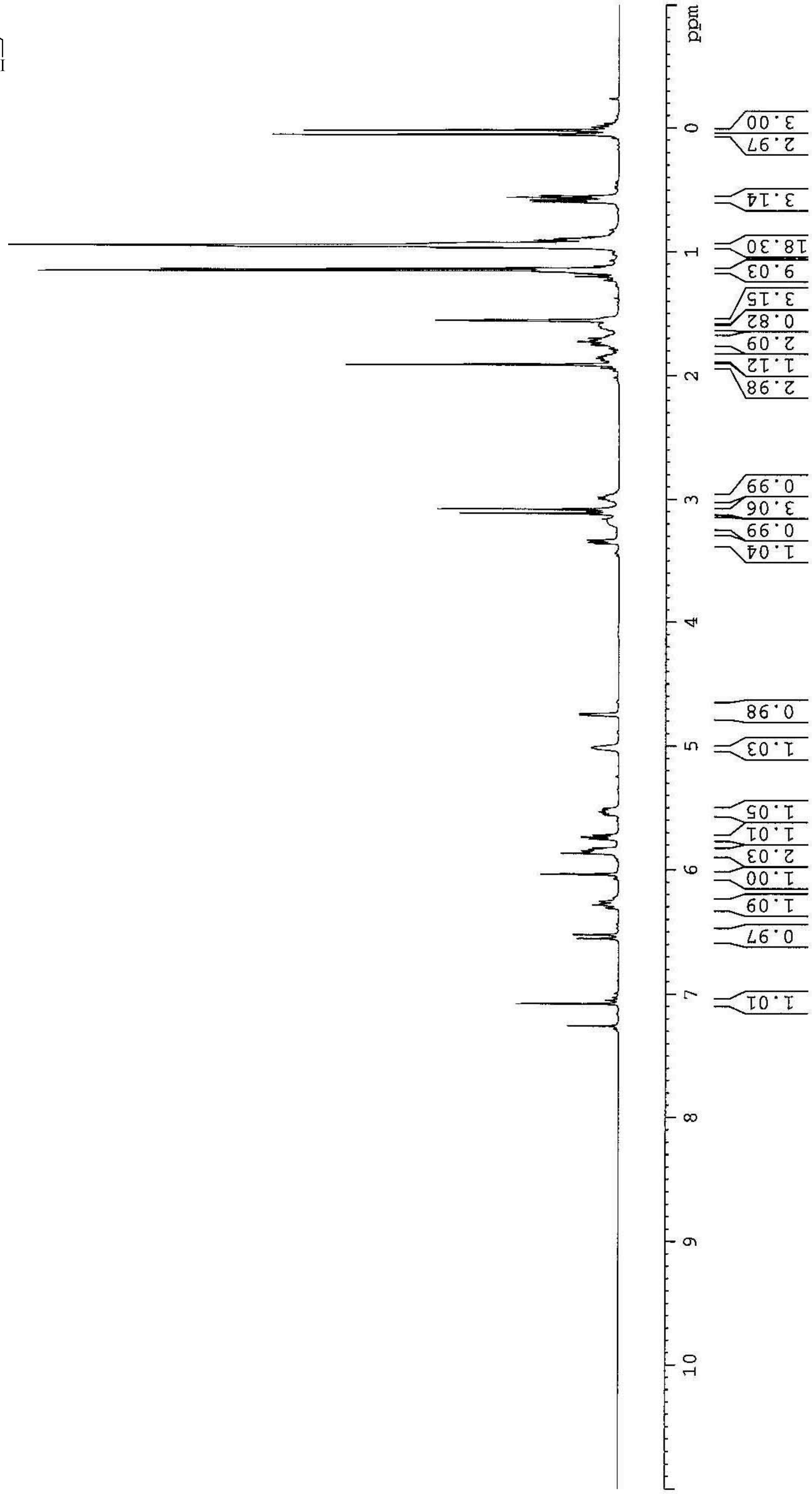

ppm
0
1
2
3
4
5
6
7
8
9
10
6.10
9.69
28.45
9.56
3.40
1.17
3.15
1.99
1.07
3.06
1.03
0.95
0.99
0.92
1.08
1.04
1.03
0.98
1.03
0.97
1.01
1.00
1.00

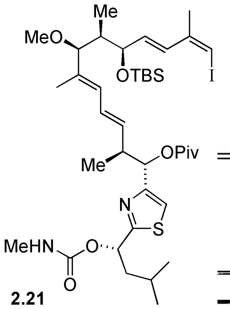

MeO
Me
OTBS
I
Me
OPiv
N
S
TESO
ppm
0
1
2
3
4
5
6
7
8
9
10
3.05
3.10
9.16
27.32
9.04
5.19
2.00
3.08
1.03
3.07
0.99
0.97
1.09
1.06
1.09
2.02
0.99
1.05
1.00
1.01

2.19

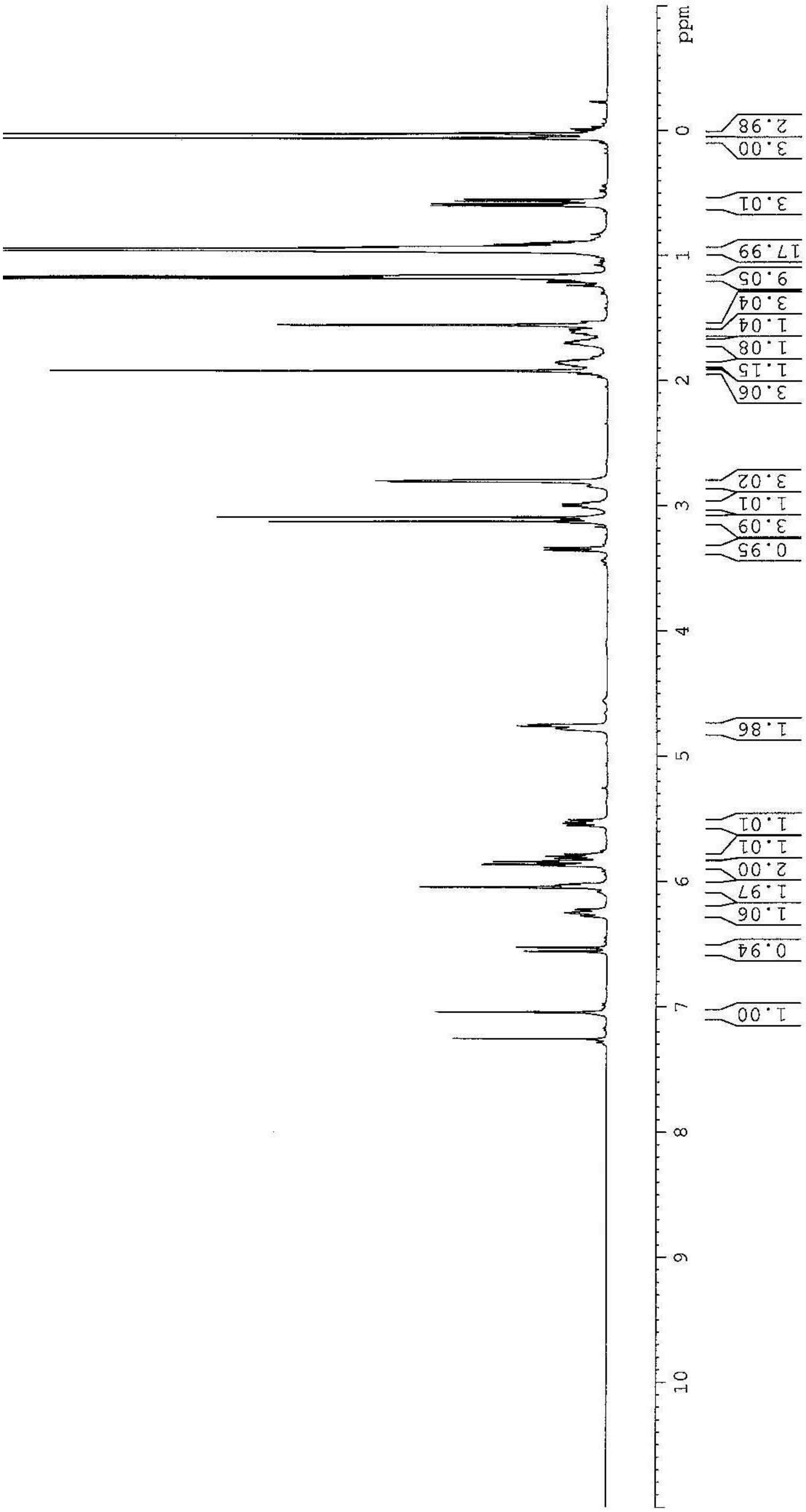

MeO
Me
OTBS
I
Me
OPiv
N
S
HO

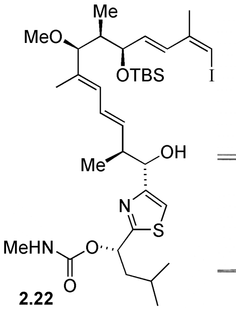
2.20


ppm
0
1
2
3
4
5
6
7
8
9
10
3.00
2.97
3.14
18.30
9.03
3.15
0.82
2.09
1.12
2.98
0.99
3.06
0.99
1.04
0.98
1.03
1.05
1.01
2.03
1.00
1.09
0.97
1.01

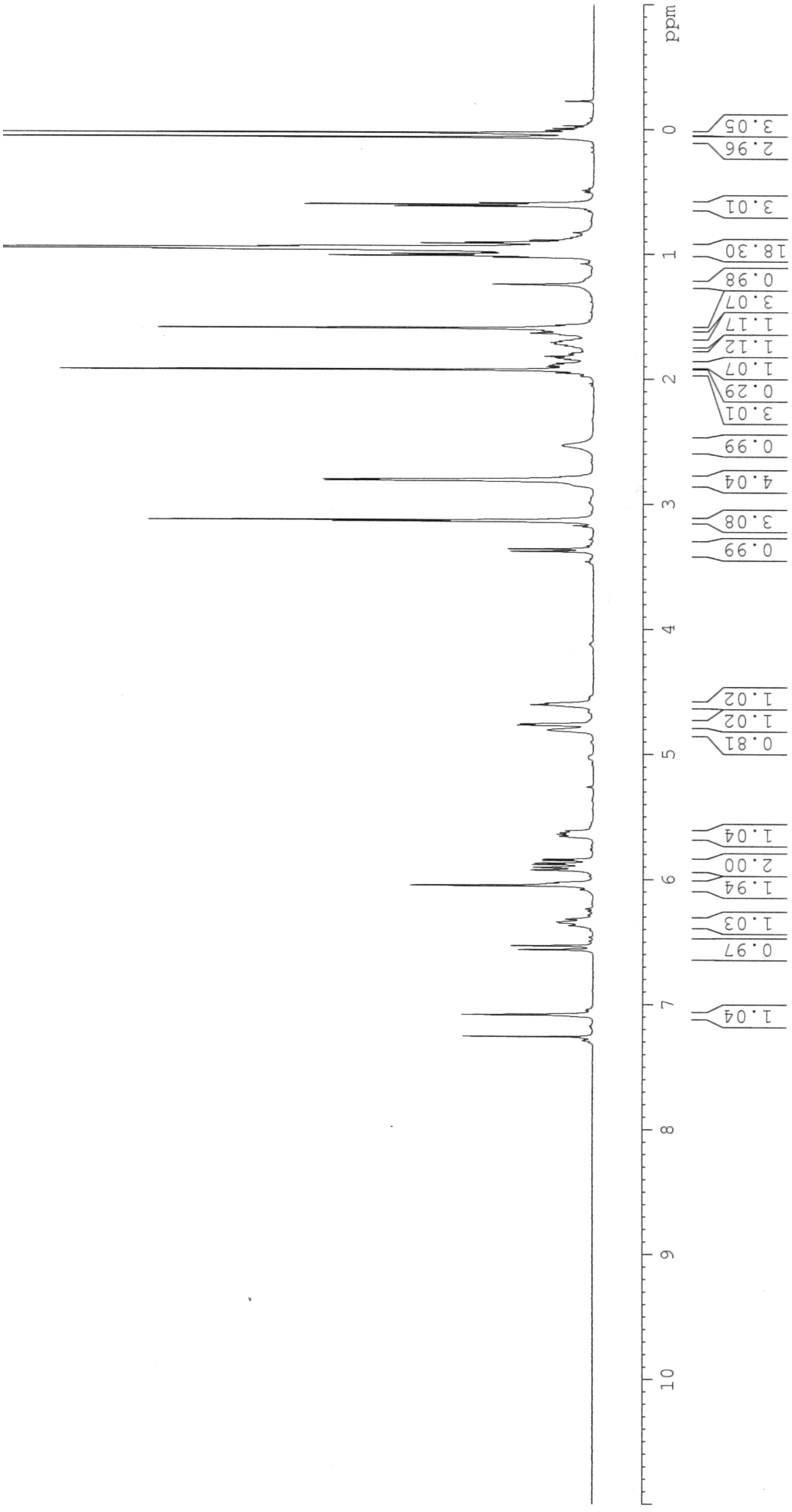

Me
MeO
OTBS
I
Me
OPiv
N
S
MeHN
O
O

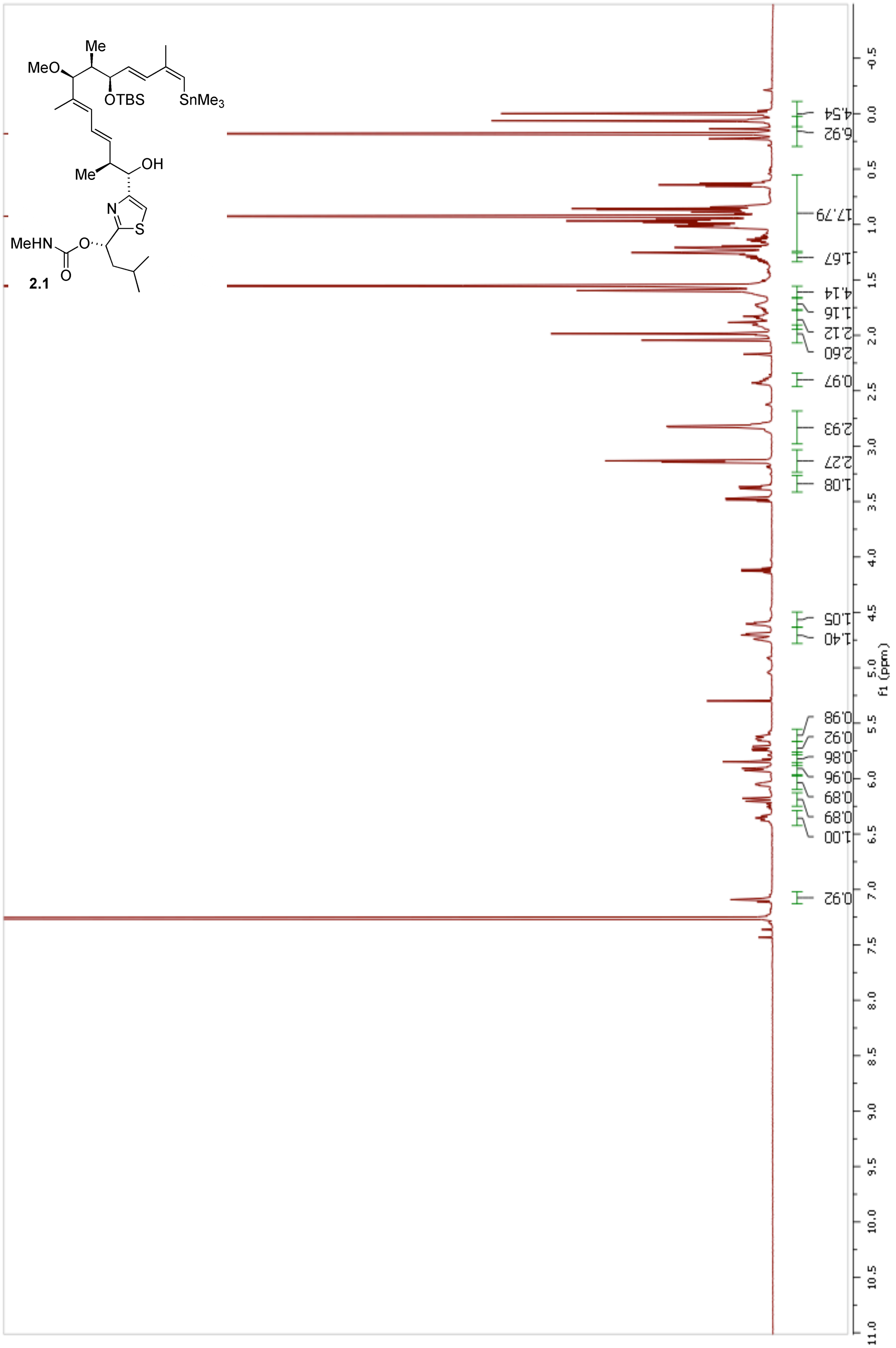
2.21


ppm
0
1
2
3
4
5
6
7
8
9
10
2.98
3.00
3.01
17.99
9.05
3.04
1.04
1.08
1.15
3.06
3.02
1.01
3.09
0.95
1.86
1.01
1.01
2.00
1.97
1.06
0.94
1.00

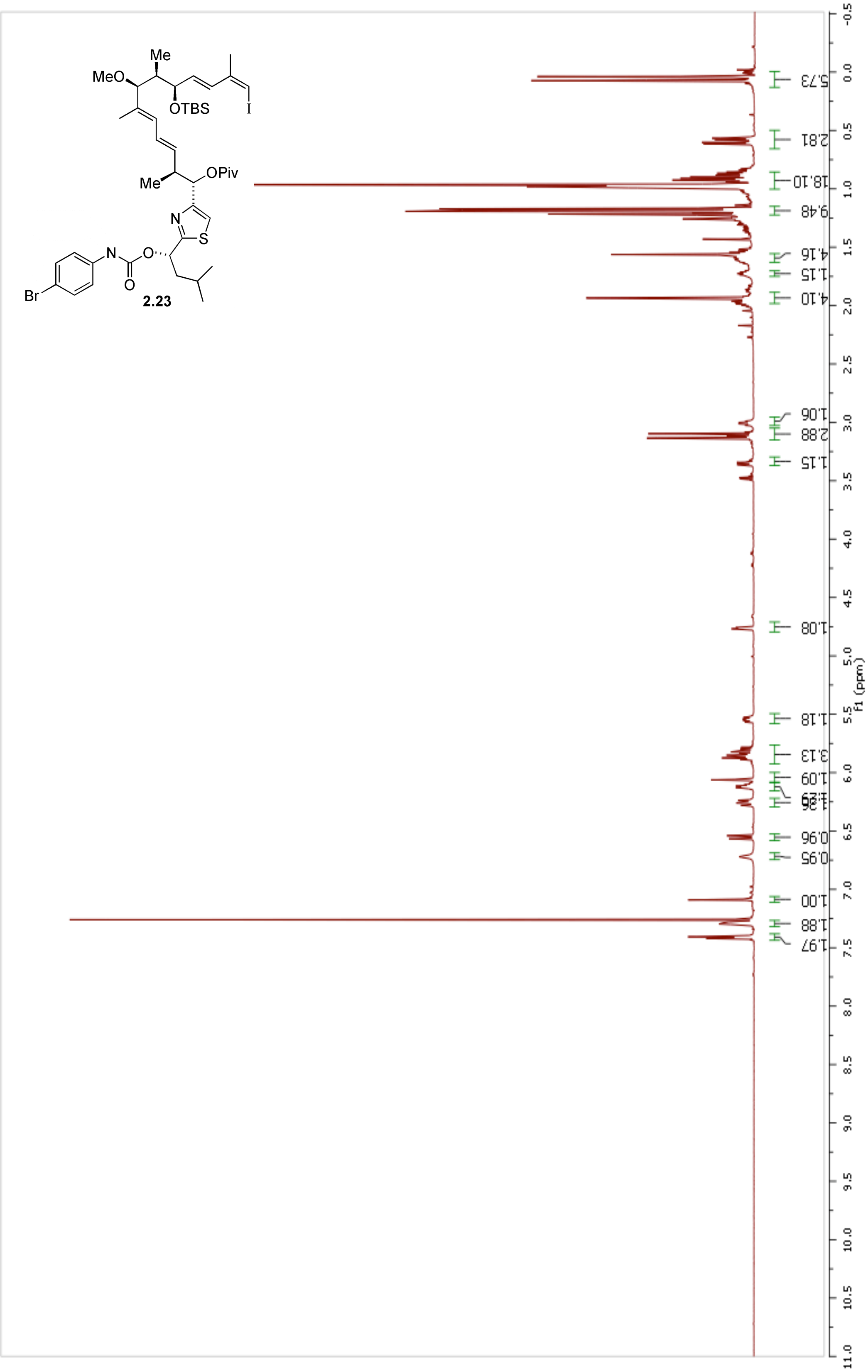

Me
MeO
OTBS
I
Me
OH
N
S
MeHN
O
O

2.22

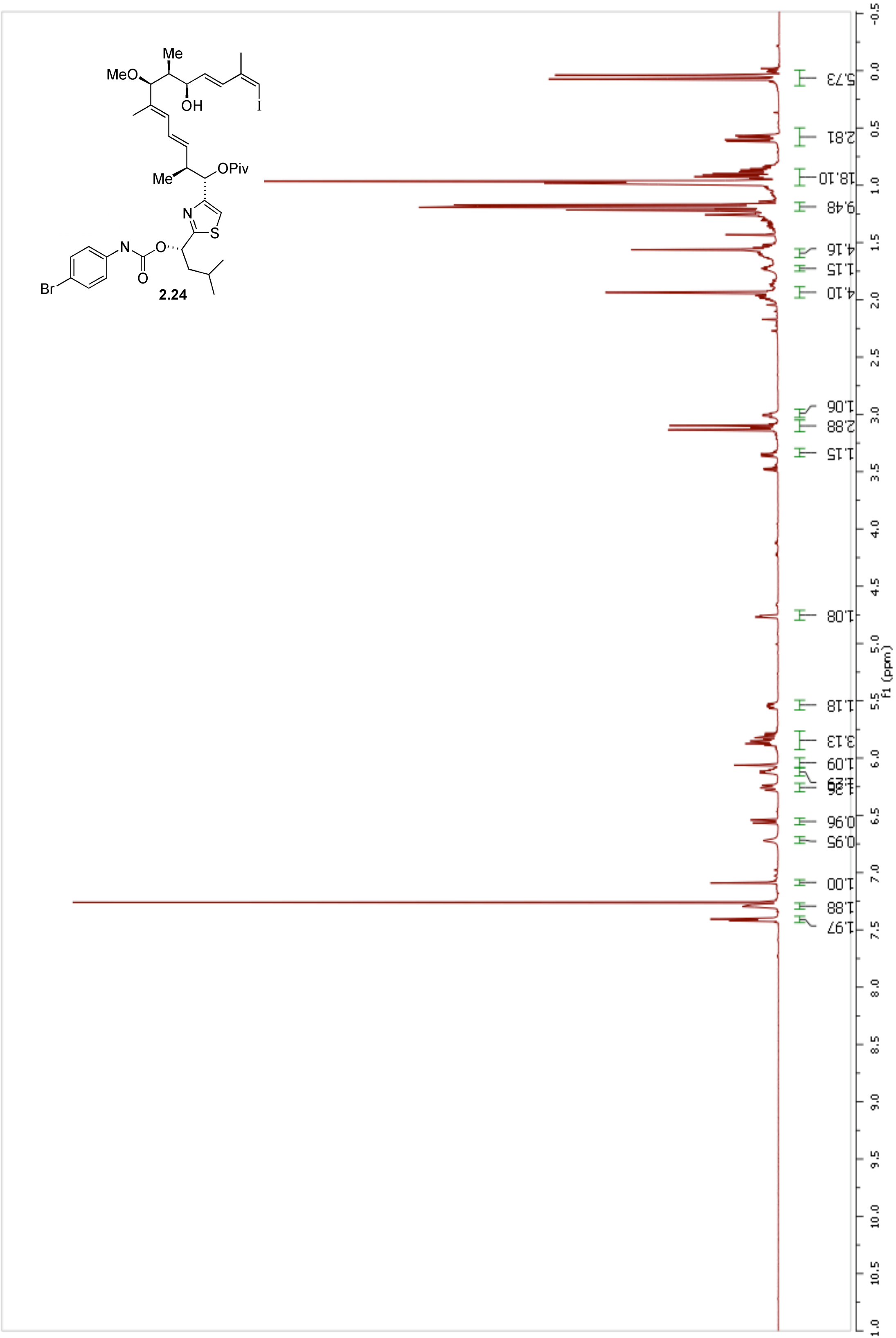

ppm
0
1
2
3
4
5
6
7
8
9
10
3.05
2.96
3.01
18.30
0.98
3.07
1.17
1.12
1.07
0.29
3.01
0.99
4.04
3.08
0.99
1.02
1.02
0.81
1.04
2.00
1.94
1.03
0.97
1.04

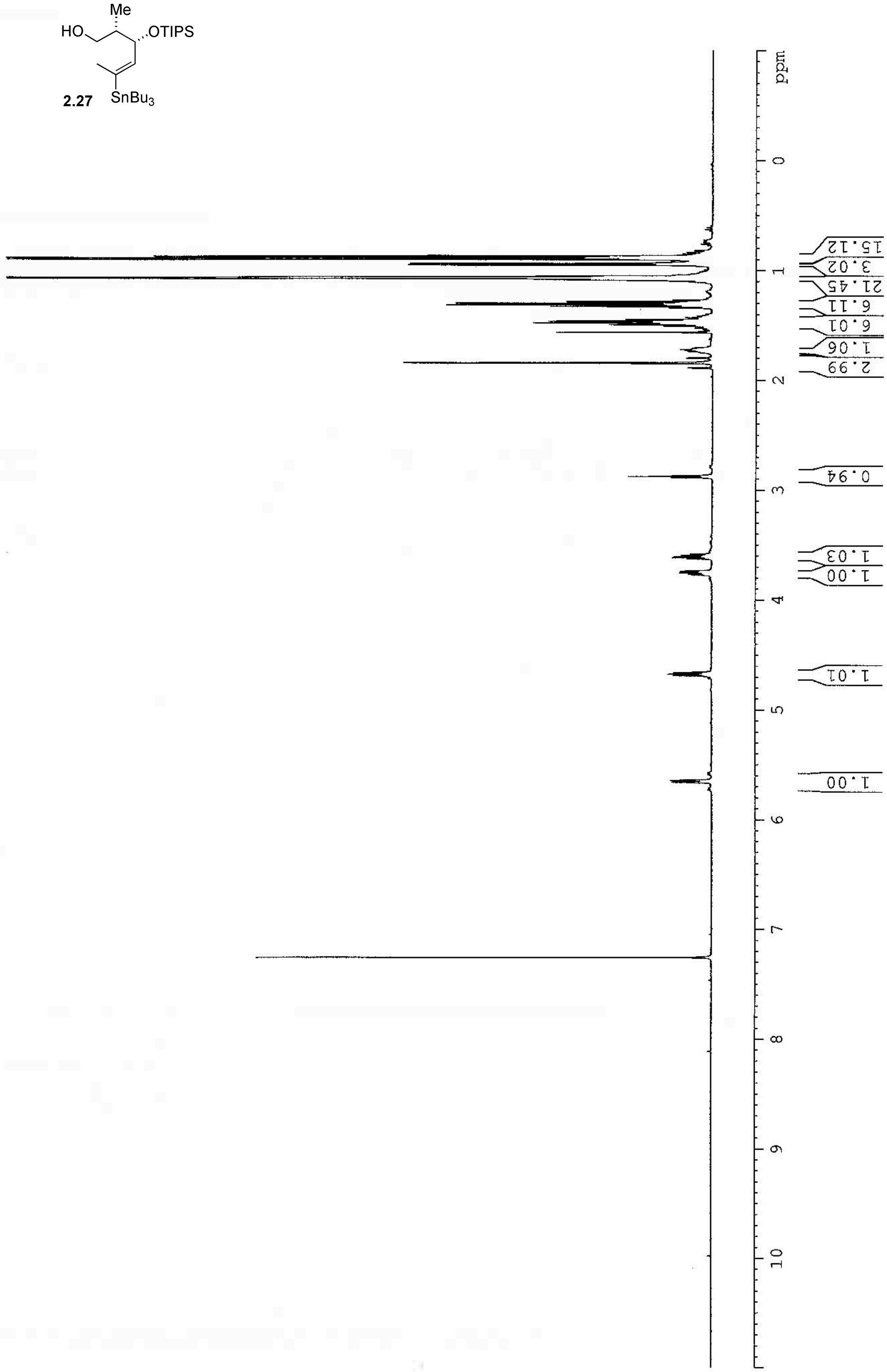

MeO
Me
OTBS
SnMe3
OH
Me
N
S
MeHN
O
O
4.54
6.92
17.79
1.67
4.14
1.16
2.12
2.60
0.97
2.93
2.27
1.08
1.05
1.40
0.98
0.92
0.86
0.96
0.89
0.89
1.00
0.92
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
f1 (ppm)
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10.5
11.0

2.1

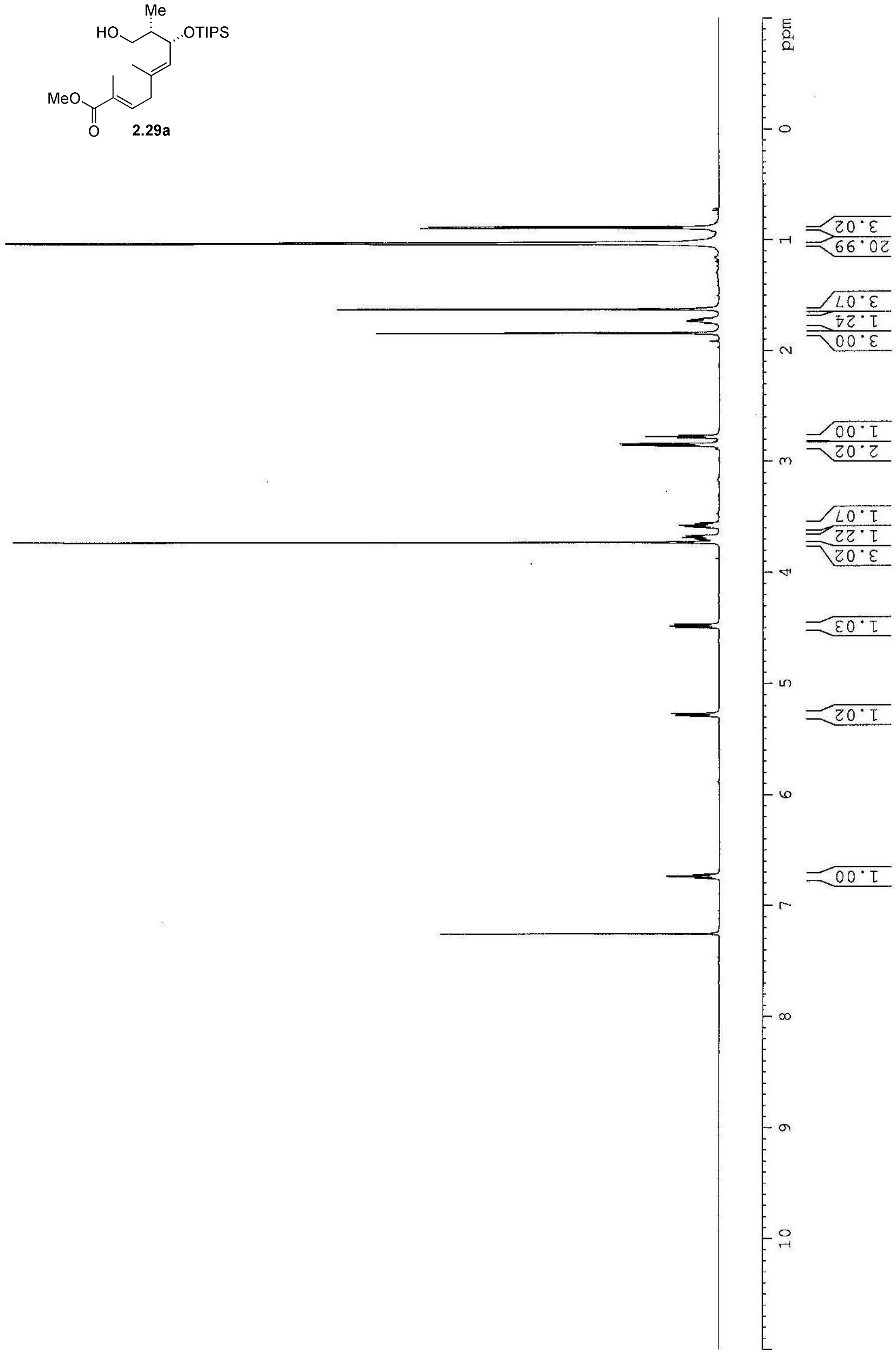


MeO
Me
OTBS
I
Me
OPiv
N
S
O
N
O
Br
2.23
5.73
2.81
18.10
9.48
4.16
1.15
4.10
1.06
2.88
1.15
1.08
1.18
3.13
1.09
1.29
1.36
0.96
0.95
1.00
1.88
1.97
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10.5
11.0
f1 (ppm)


MeO
Me
OH
I
OPiv
Me
N
S
N
O
O
Br
2.24
5.73
2.81
18.10
9.48
4.16
1.15
4.10
1.06
2.88
1.15
1.08
1.18
3.13
1.09
1.29
1.36
0.96
0.95
1.00
1.88
1.97
f1 (ppm)
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10.5
11.0

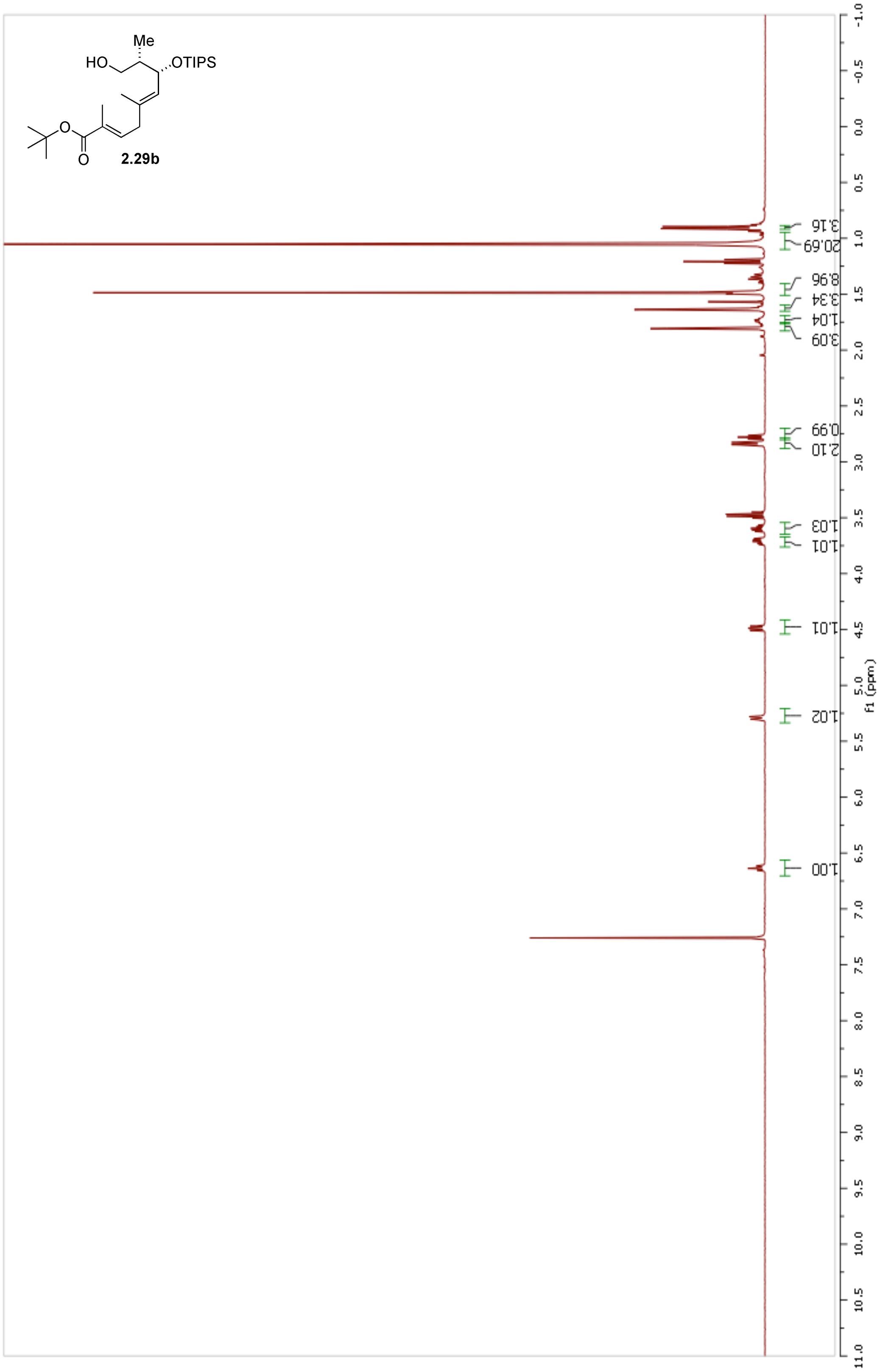

2.27

Me
HO
OTIPS
SnBu$_3$
ppm
0
1
2
3
4
5
6
7
8
9
10
15.12
3.02
21.45
6.11
6.01
1.06
2.99
0.94
1.03
1.00
1.01
1.00

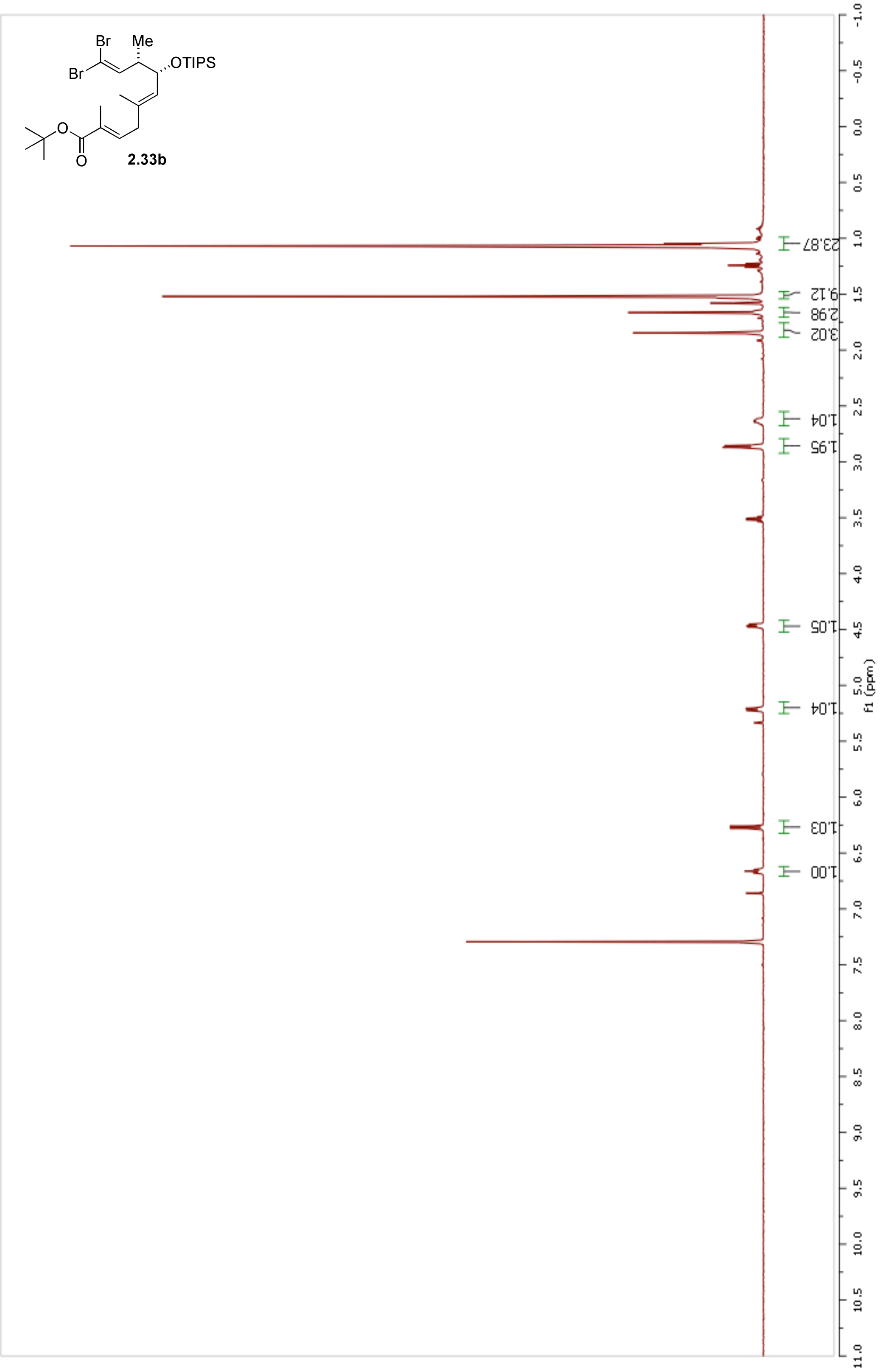


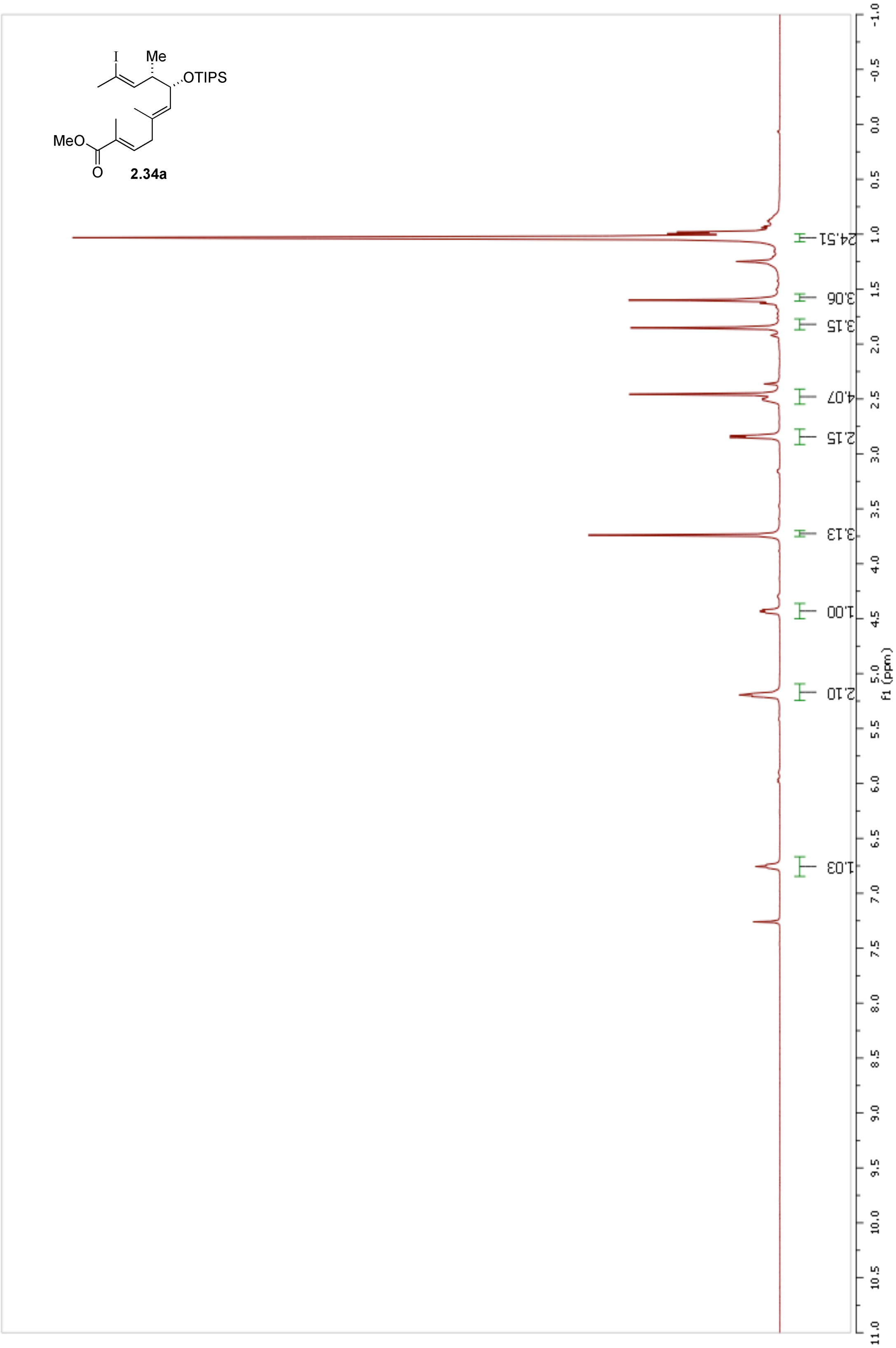
2.29a

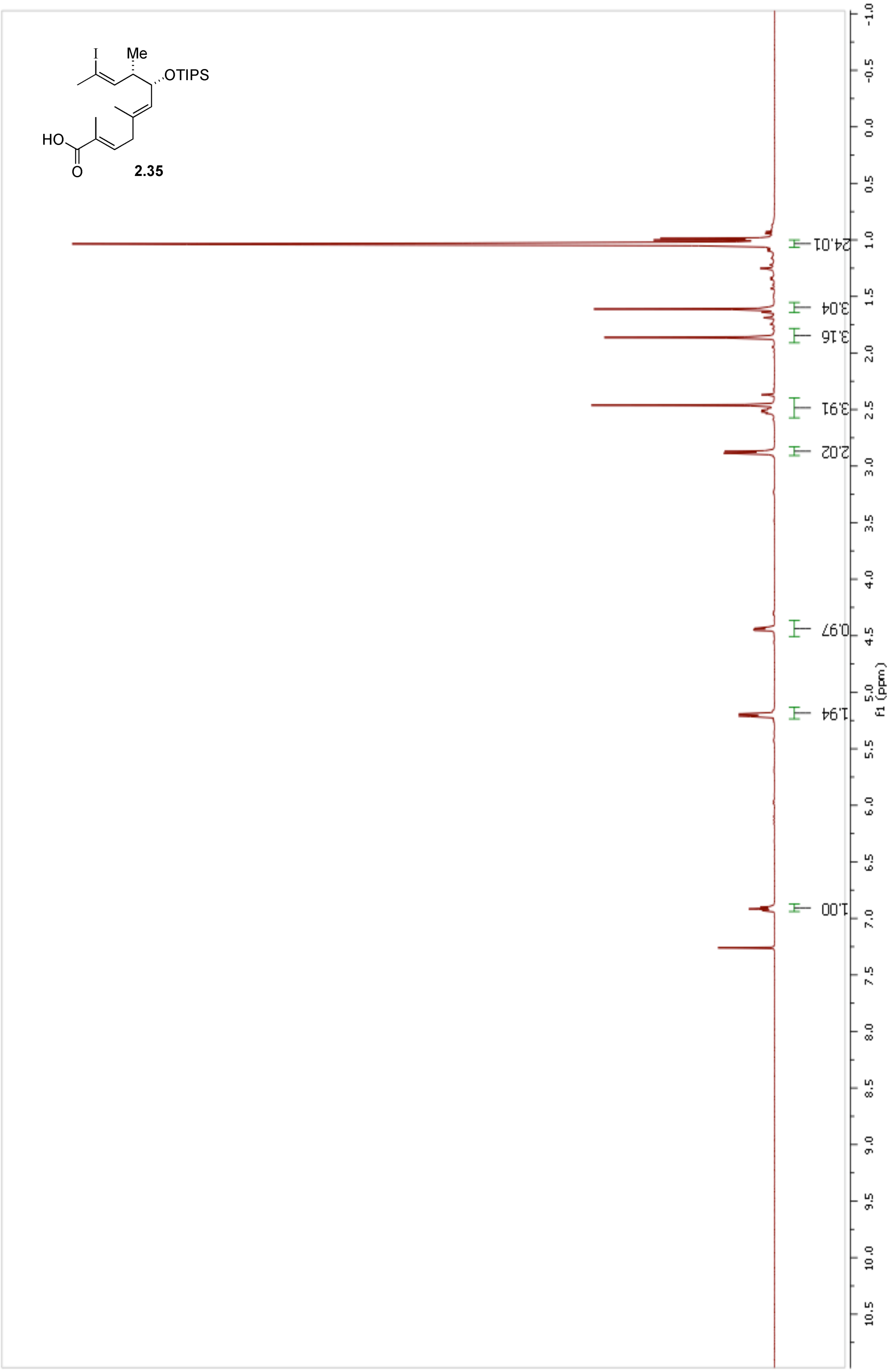
Me
HO
OTIPS
MeO
O
ppm
0
1
2
3
4
5
6
7
8
9
10
3.02
20.99
3.07
1.24
3.00
1.00
2.02
1.07
1.22
3.02
1.03
1.02
1.00


Me
HO
OTIPS
O
O
3.16
20.69
8.96
3.34
1.04
3.09
0.99
2.10
1.03
1.01
1.01
1.02
1.00
-1.0
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10.5
11.0
f1 (ppm)

2.29b

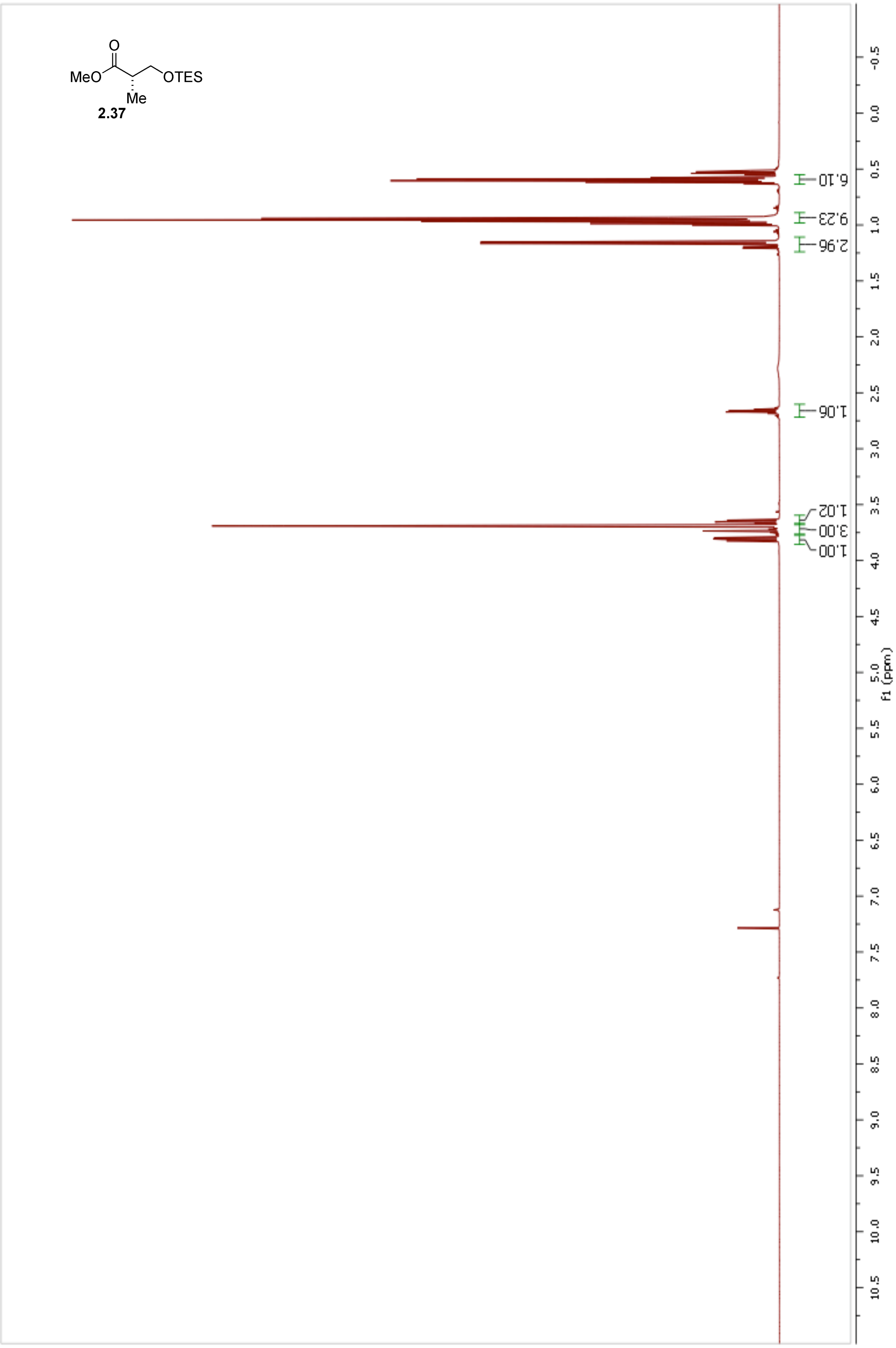

Br
Br
Me
OTIPS
O
O
2.33b
23.87
9.12
2.98
3.02
1.04
1.95
1.05
1.04
1.03
1.00
-1.0
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10.5
11.0
f1 (ppm)


I
Me
OTIPS
MeO
O
2.34a
24.51
3.06
3.15
4.07
2.15
3.13
1.00
2.10
1.03
-1.0
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10.5
11.0
f1 (ppm)

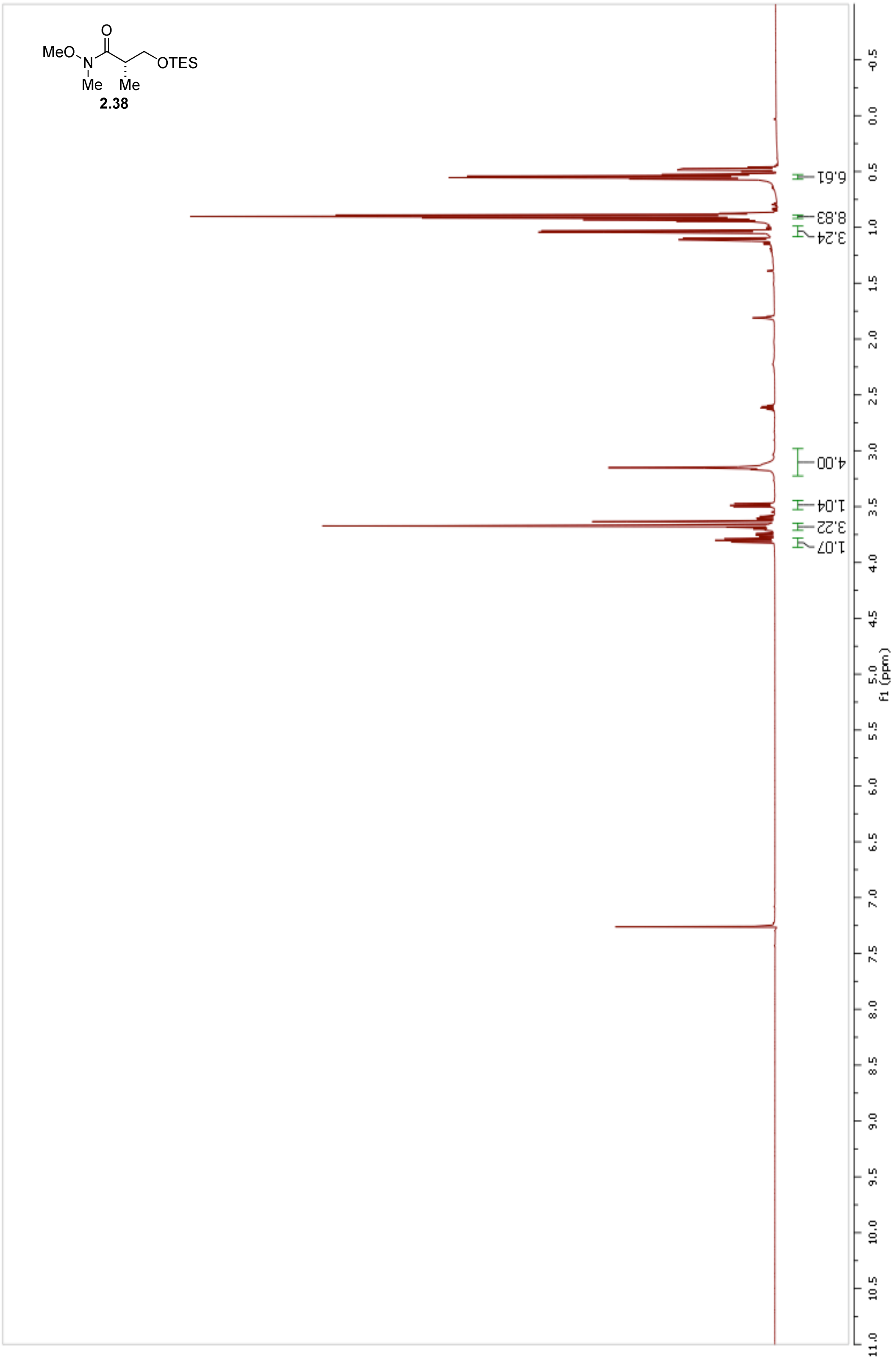


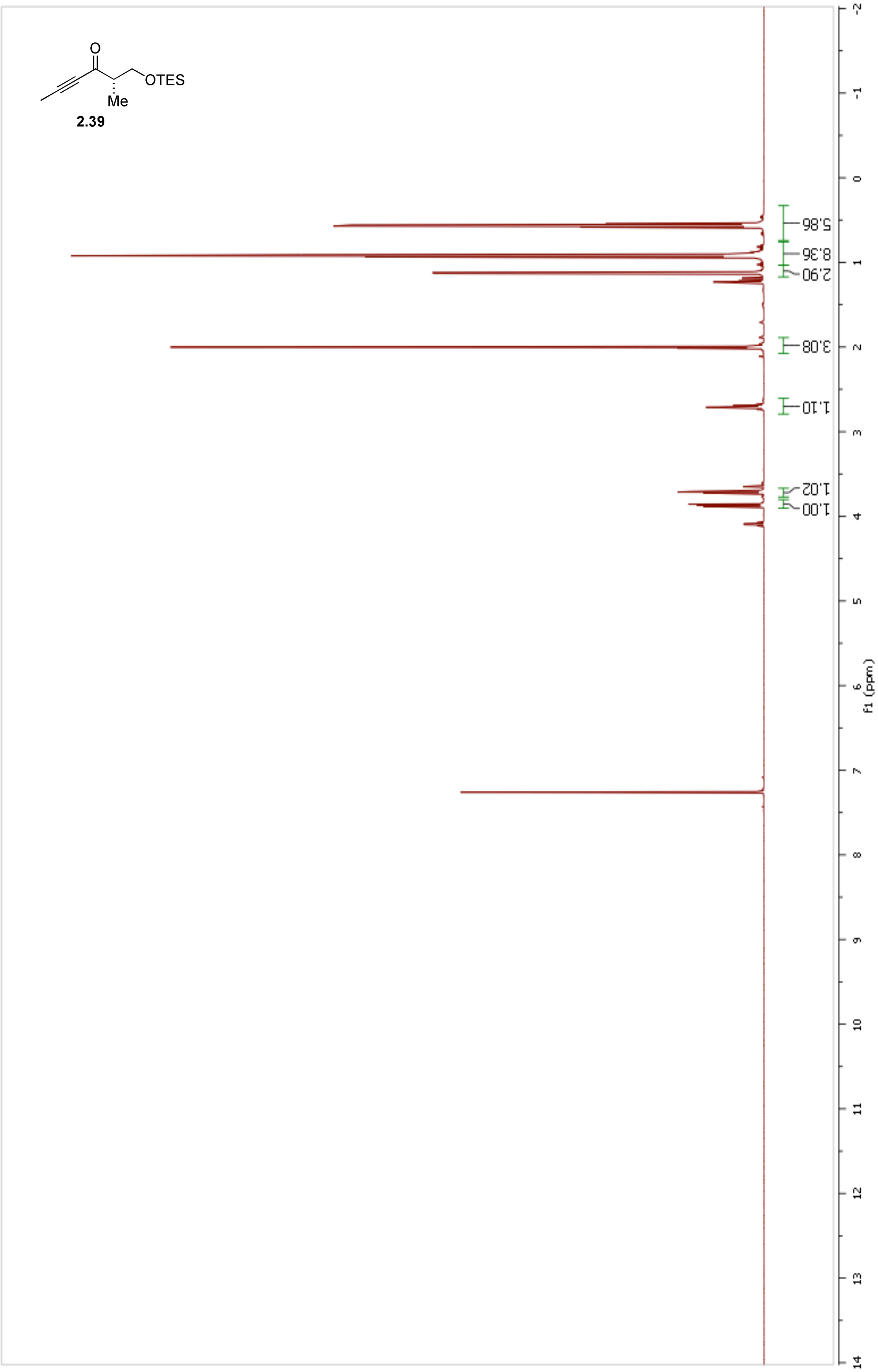
2.35

I
Me
OTIPS
HO
O
24.01
3.04
3.16
3.91
2.02
0.97
1.94
1.00
-1.0
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10.5
f1 (ppm)

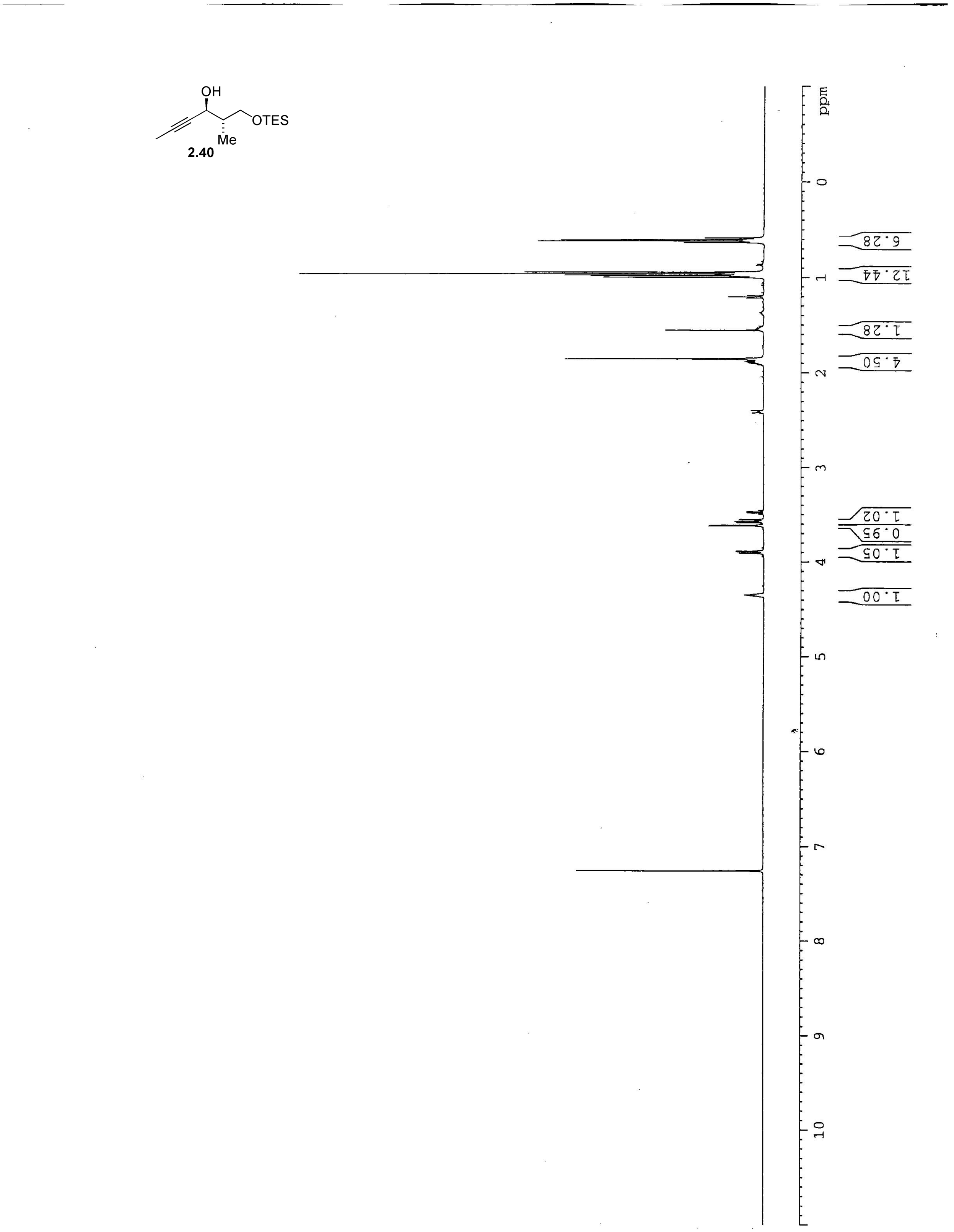

2.37

MeO
O
OTES
Me
6.10
9.23
2.96
1.06
1.02
3.00
1.00
f1 (ppm)
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10.5

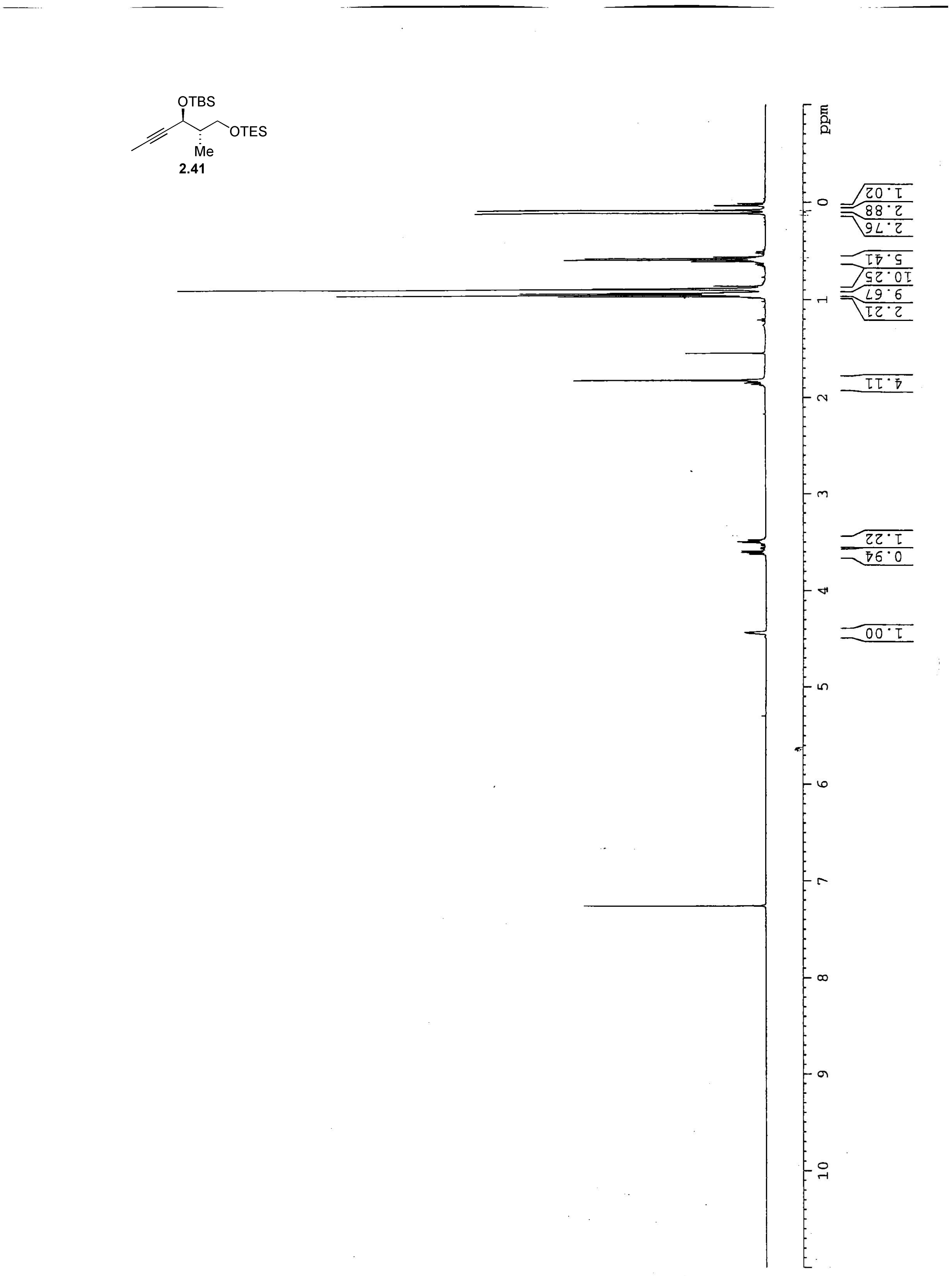

MeO
N
Me
O
Me
OTES
2.38
6.61
8.83
3.24
4.00
1.04
3.22
1.07
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10.5
11.0
f1 (ppm)


O
OTES
Me
5.86
8.36
2.90
3.08
1.10
1.02
1.00
-2
-1
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
f1 (ppm)

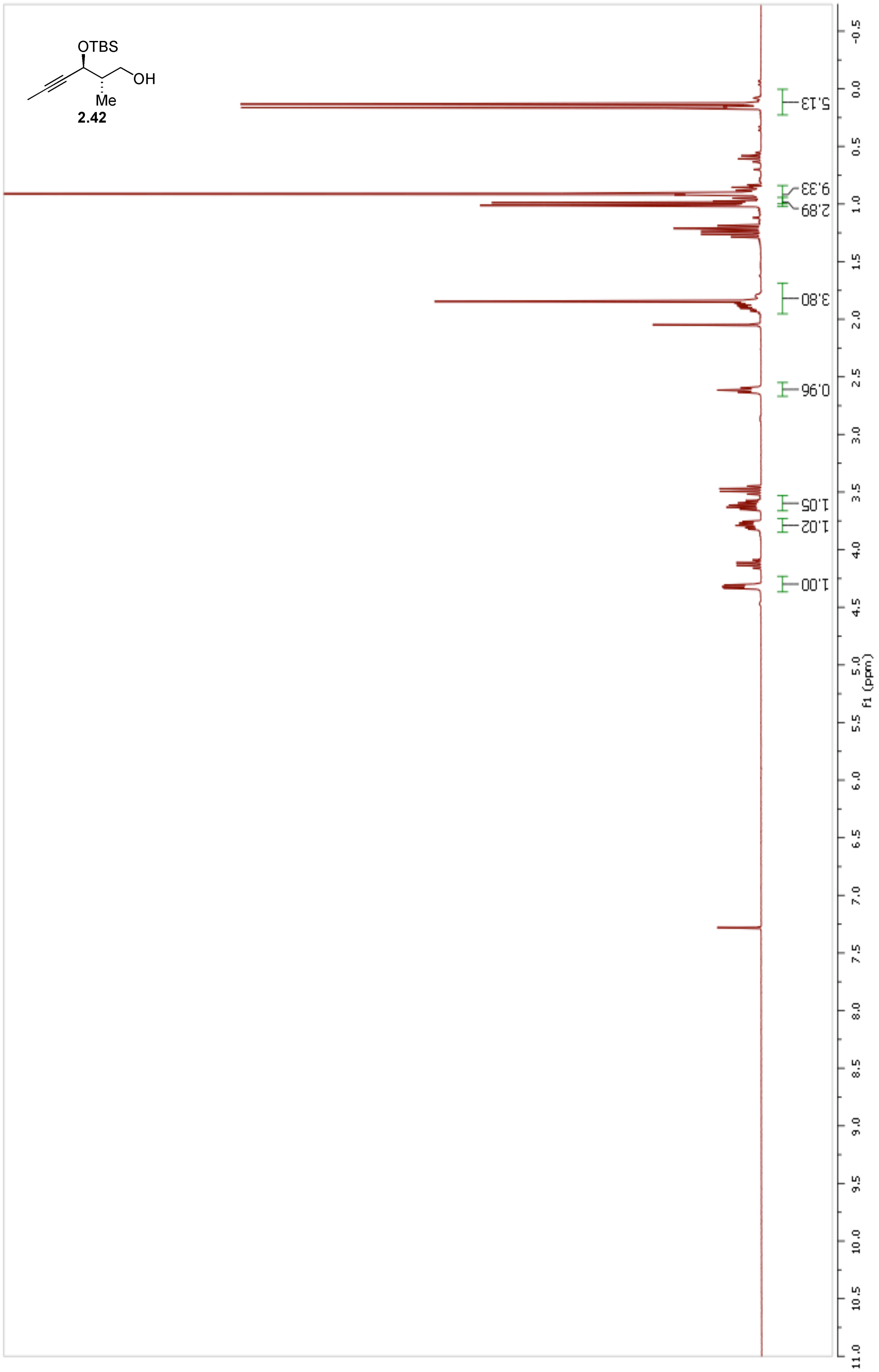
2.39

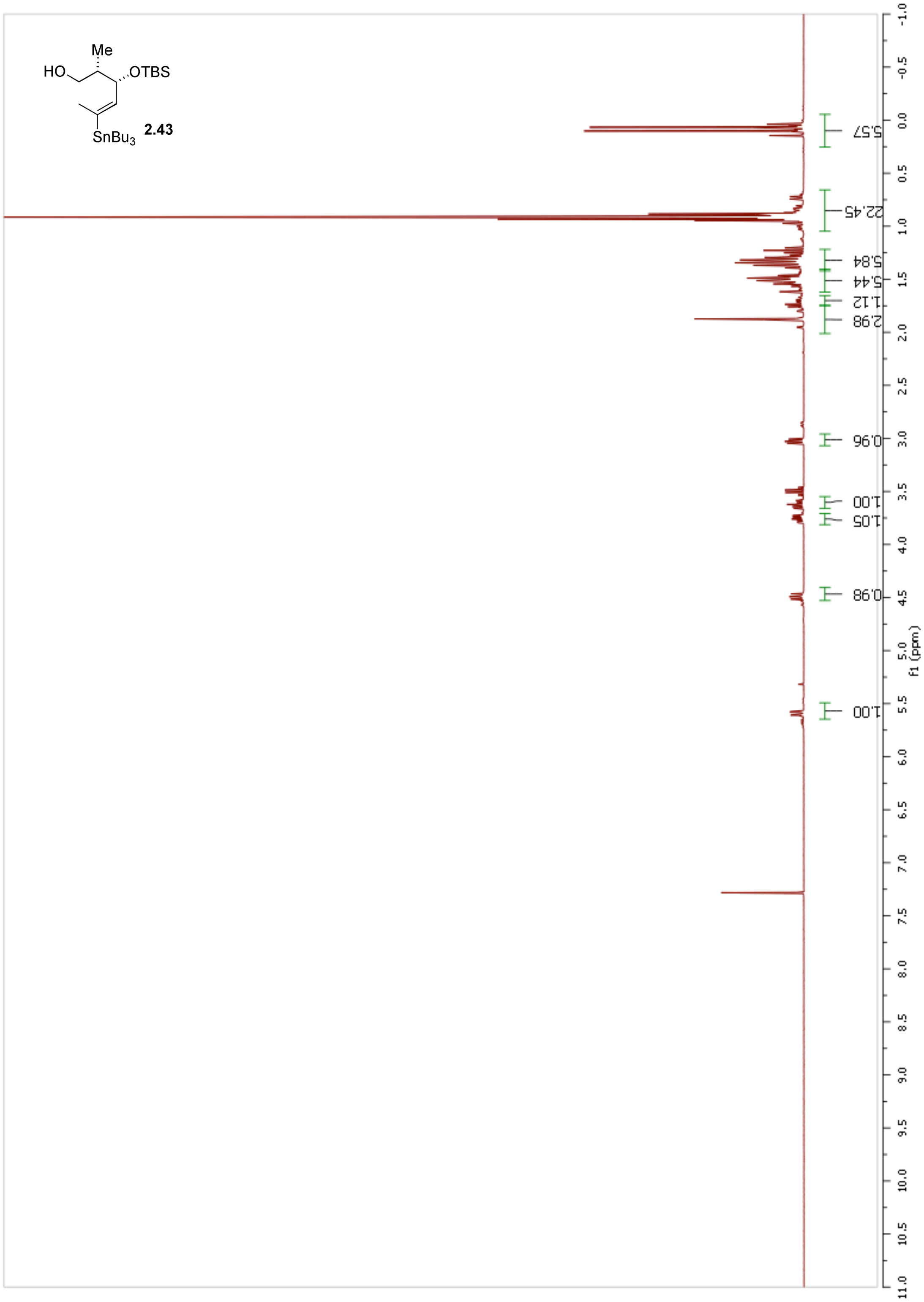


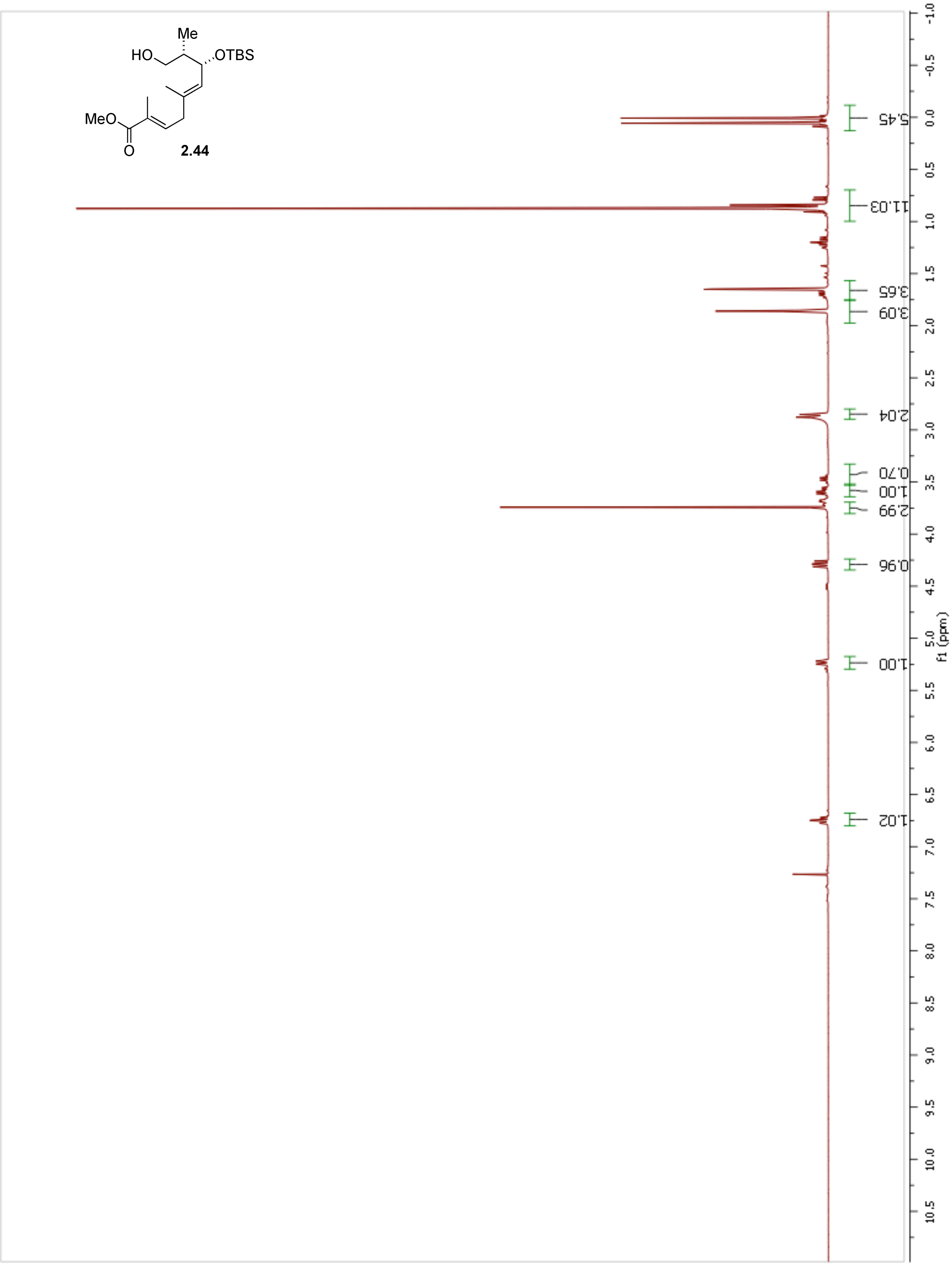
2.40



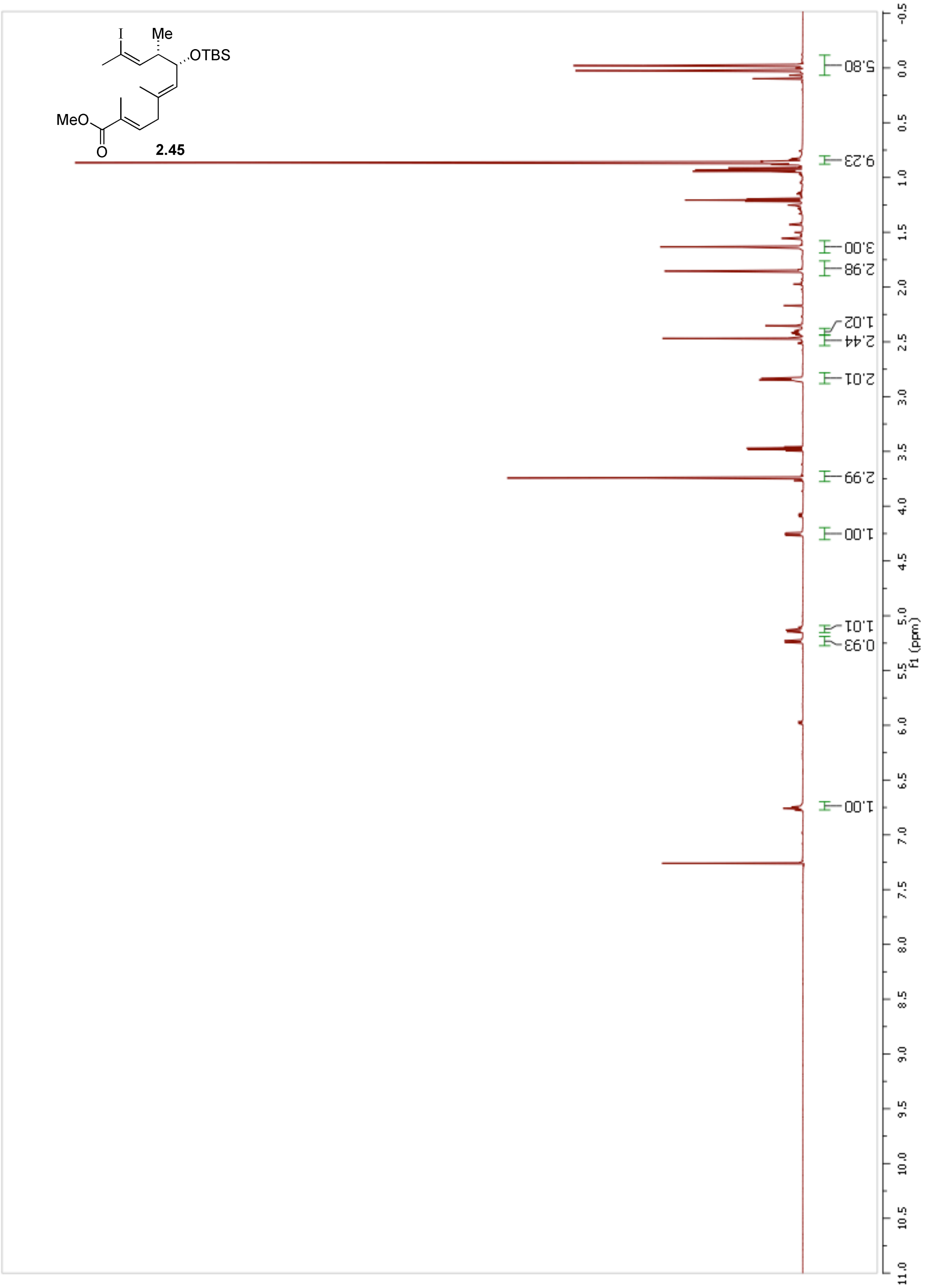
2.41


OTBS
OH
Me
2.42
5.13
9.33
2.89
3.80
0.96
1.05
1.02
1.00
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10.5
11.0
f1 (ppm)

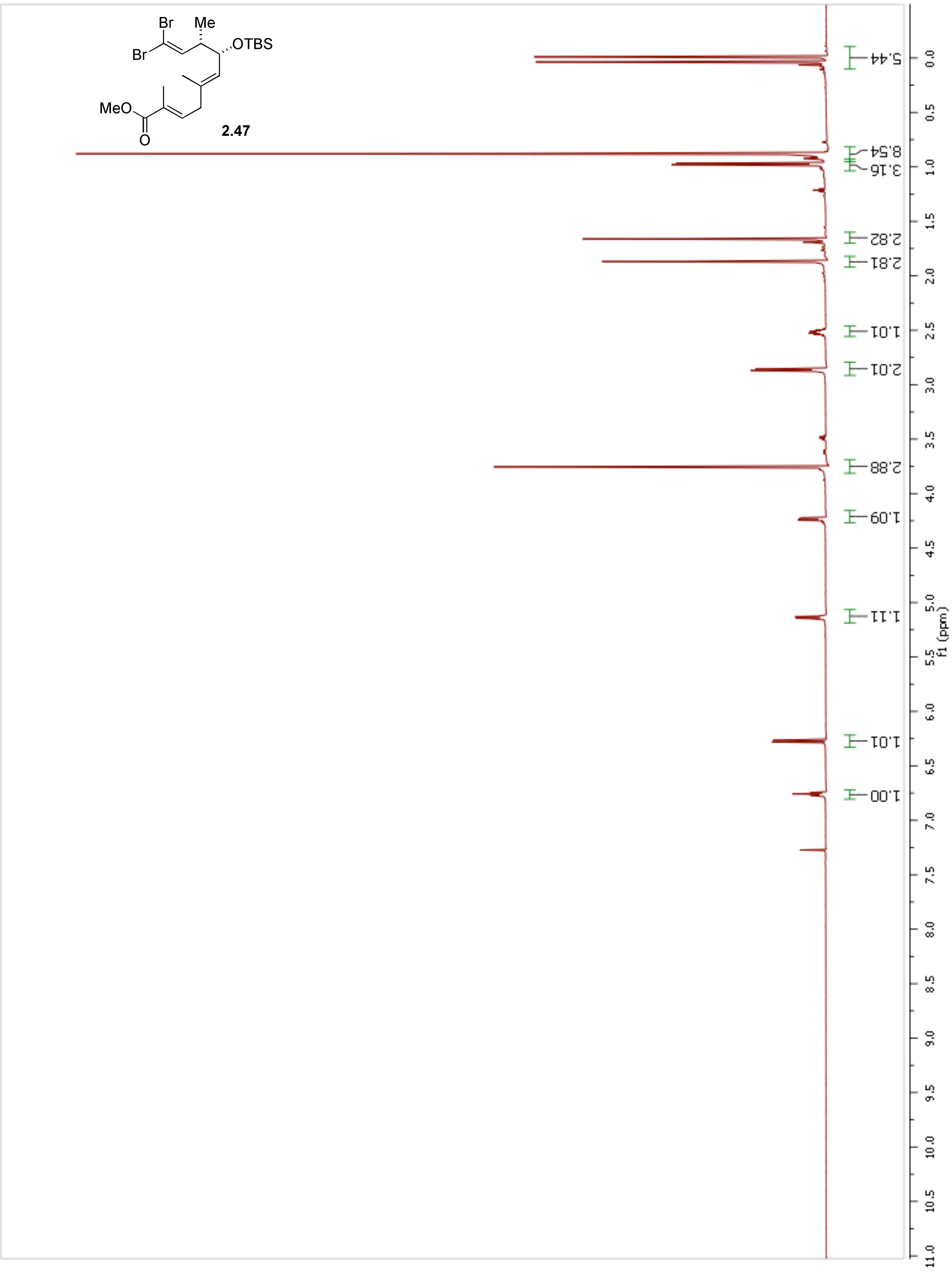

Me
HO
OTBS
SnBu3
2.43
5.57
22.45
5.84
5.44
1.12
2.98
0.96
1.00
1.05
0.98
1.00
-1.0
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10.5
11.0
f1 (ppm)


Me
HO
OTBS
MeO
O
5.45
11.03
3.65
3.09
2.04
0.70
1.00
2.99
0.96
1.00
1.02
-1.0
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10.5
f1 (ppm)

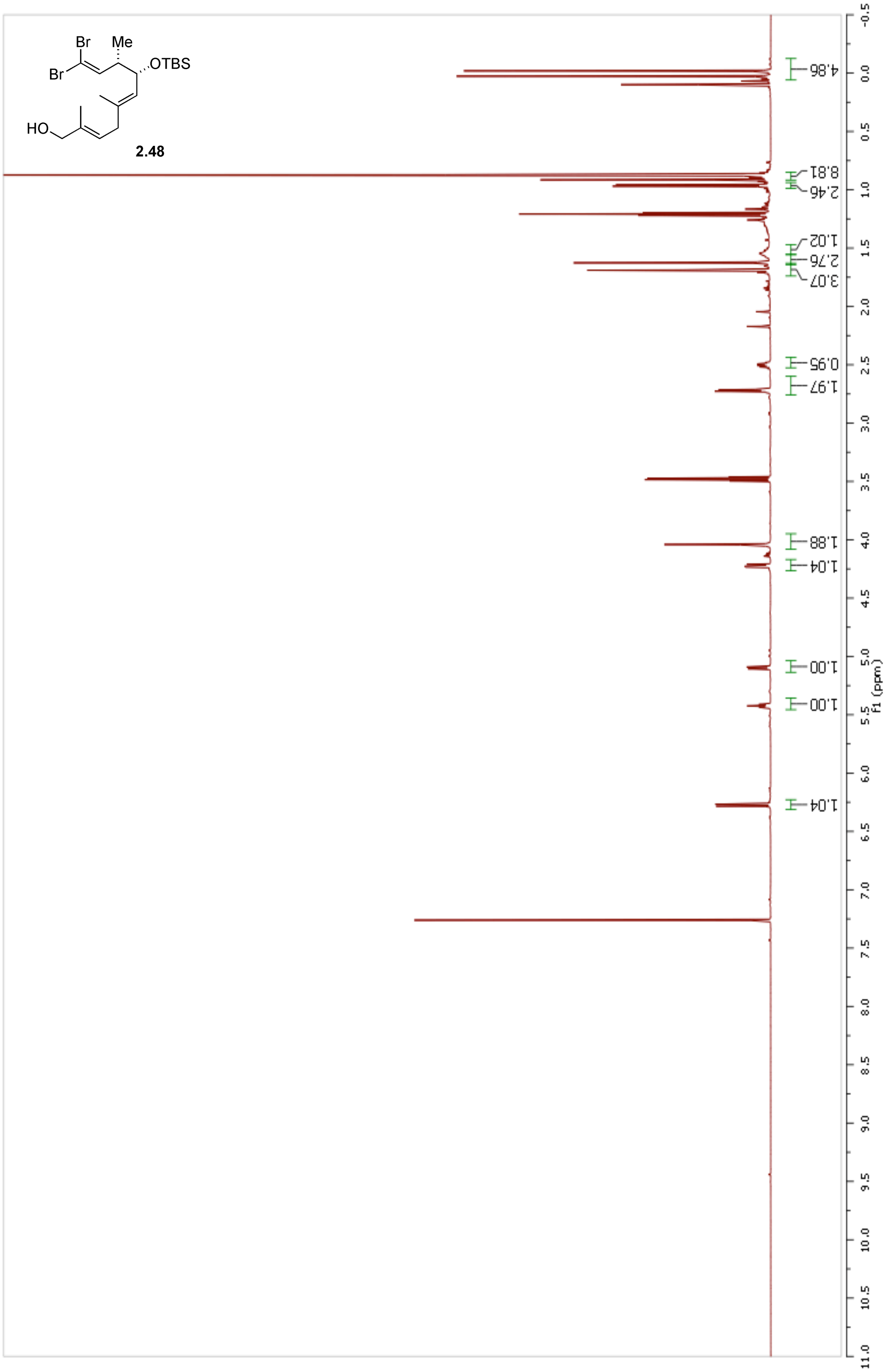
2.44


I
Me
OTBS
MeO
O
5.80
9.23
3.00
2.98
1.02
2.44
2.01
2.99
1.00
1.01
0.93
1.00
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10.5
11.0
f1 (ppm)

2.45

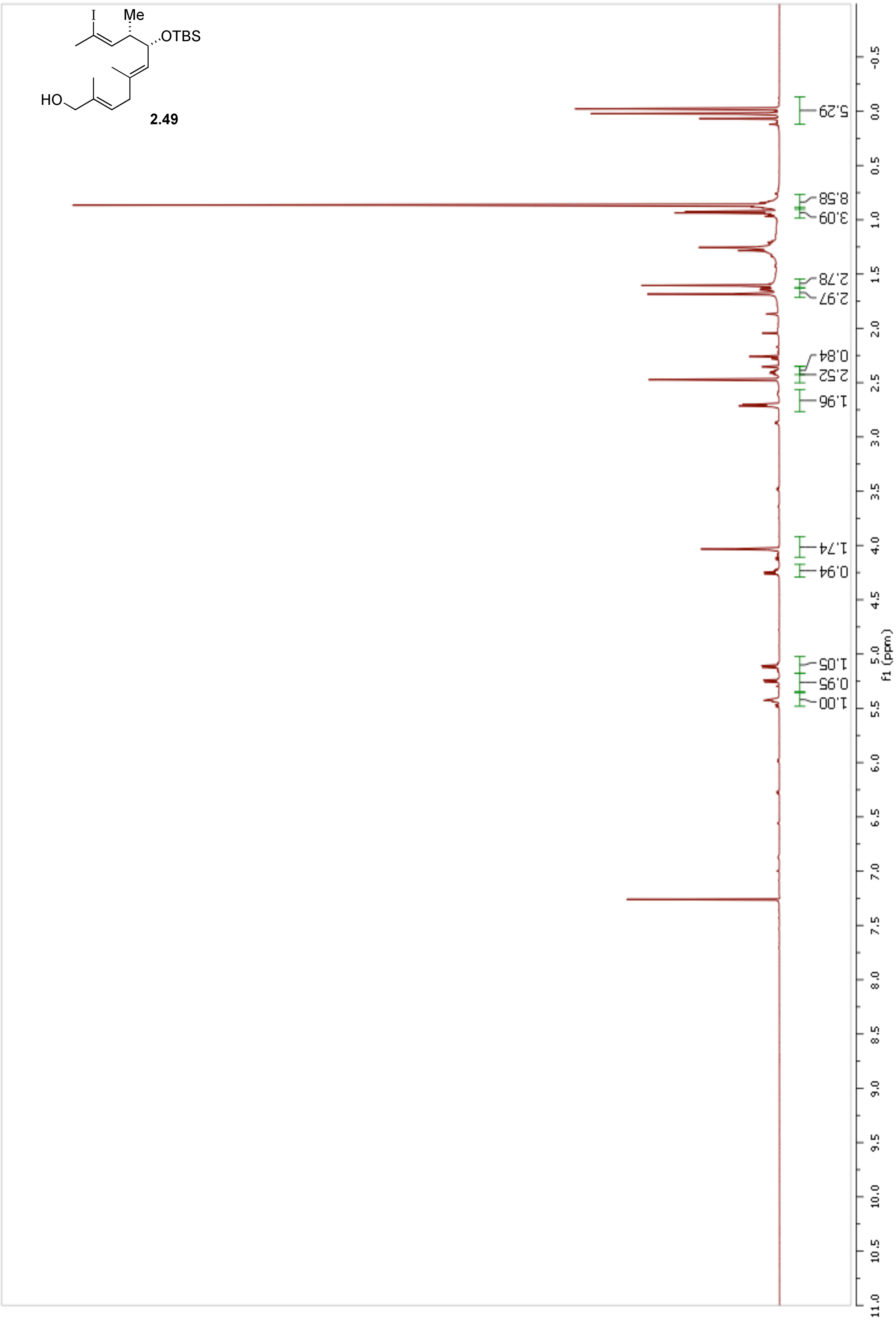

Br
Br
Me
OTBS
MeO
O
5.44
8.54
3.16
2.82
2.81
1.01
2.01
2.88
1.09
1.11
1.01
1.00
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10.5
11.0
f1 (ppm)

2.47

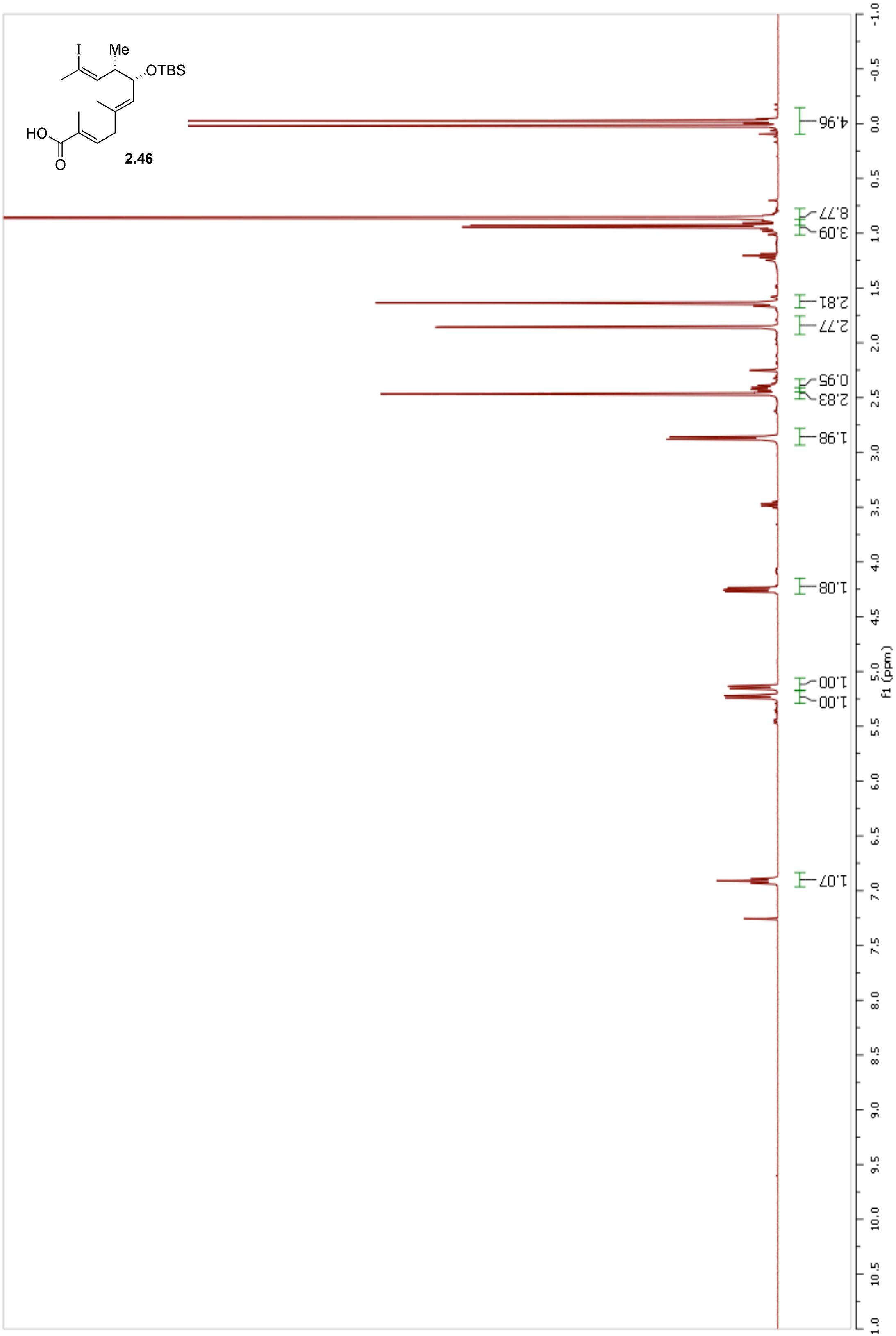


2.48

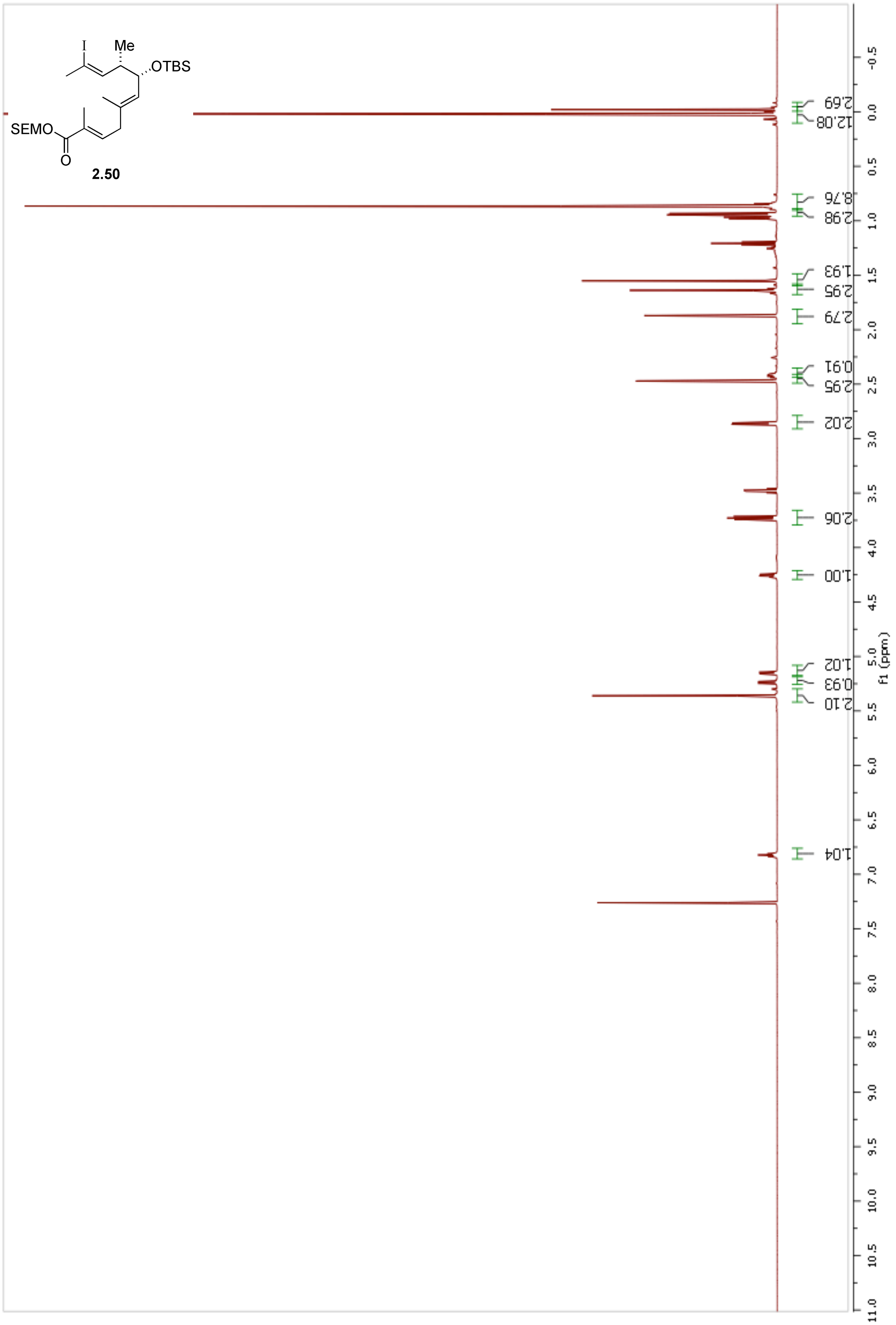
Br
Br
Me
OTBS
HO
4.86
8.81
2.46
1.02
2.76
3.07
0.95
1.97
1.88
1.04
1.00
1.00
1.04
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10.5
11.0
f1 (ppm)



I
Me
OTBS
HO
2.49
5.29
8.58
3.09
2.78
2.97
0.84
2.52
1.96
1.74
0.94
1.05
0.95
1.00
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10.5
11.0
f1 (ppm)


I
Me
OTBS
HO
O
4.96
8.77
3.09
2.81
2.77
0.95
2.83
1.98
1.08
1.00
1.00
1.07
-1.0
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10.5
11.0
f1 (ppm)

2.46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OTBS
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12.08
8.76
2.98
1.93
2.95
2.79
0.91
2.95
2.02
2.06
1.00
1.02
0.93
2.10
1.04
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
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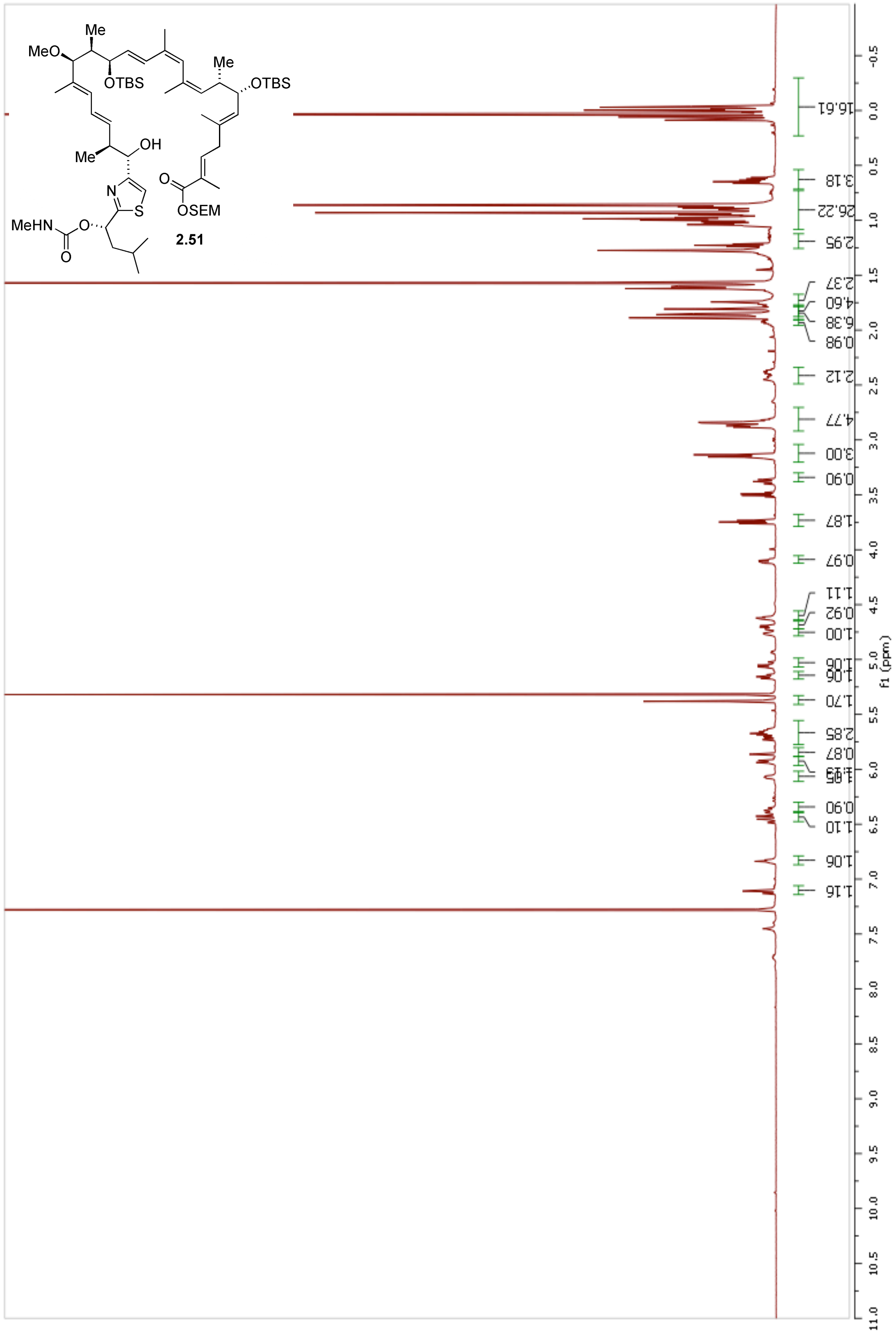
10.0
10.5
11.0
f1 (ppm)

2.50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O
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3.18
26.22
2.95
2.37
4.60
6.38
0.98
2.12
4.77
3.00
0.90
1.87
0.97
1.11
0.92
1.00
1.06
1.06
1.70
2.85
0.87
1.13
1.05
0.90
1.10
1.06
1.16
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0.5
1.0
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6.0
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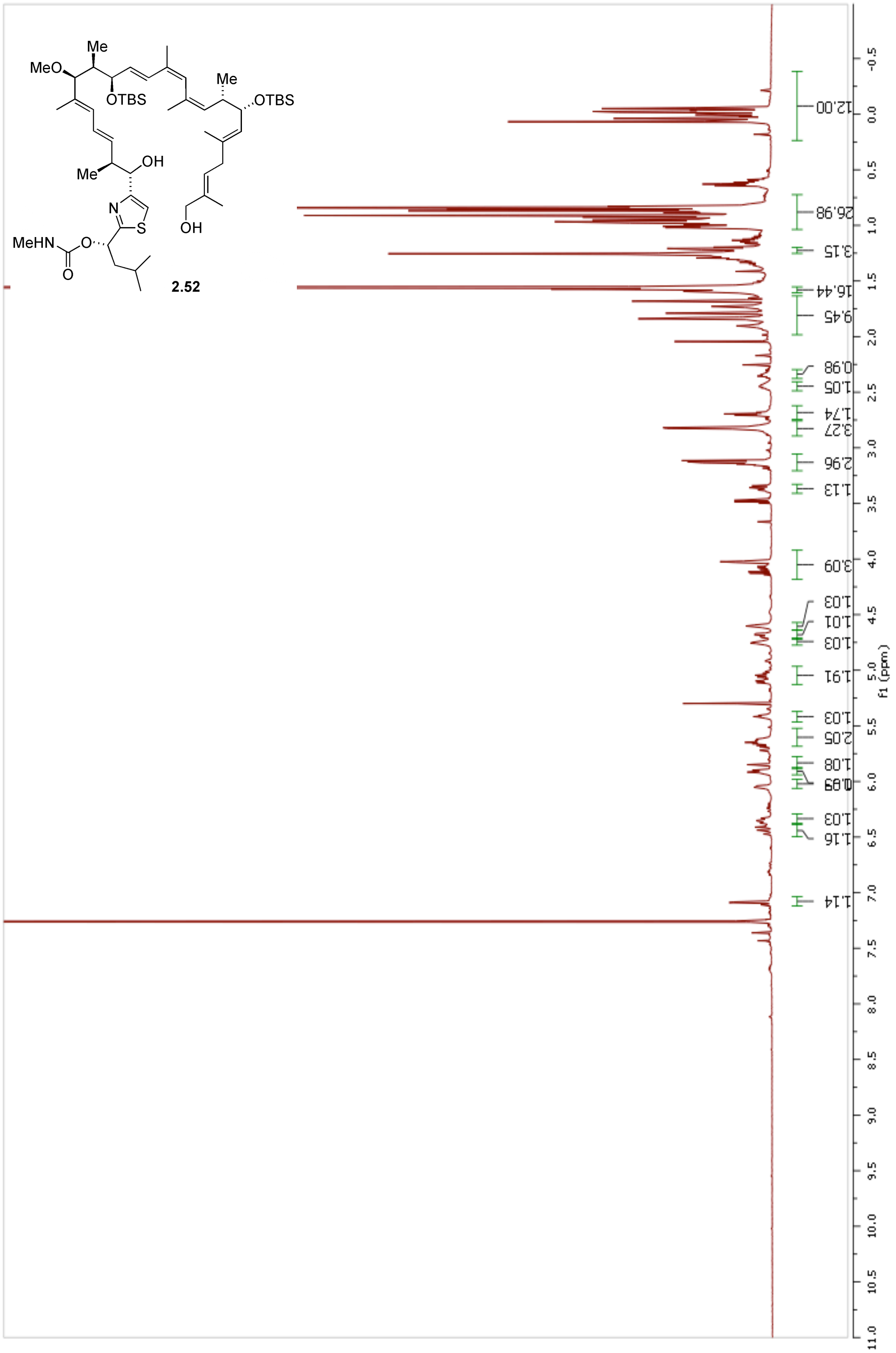
11.0
f1 (ppm)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OTBS
Me
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Me
OH
N
S
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O
O
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3.15
16.44
9.45
0.98
1.05
1.74
3.27
2.96
1.13
3.09
1.03
1.01
1.03
1.91
1.03
2.05
1.08
0.89
1.03
1.16
1.14
-0.5
0.0
0.5
1.0
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10.5
11.0
f1 (ppm)

2.9. References

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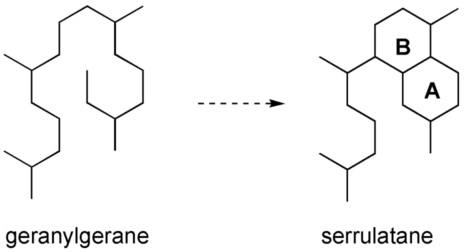
Chapter 3. Total Synthesis of Amphilectolide and Sandresolide B and Progress towards Caribenol A

Section 3.1. Natural products isolated from *Pseudopterogorgia elisabethae*

Natural products isolated from the Caribbean octacoral *Pseudopterogorgia elisabethae* have attracted the interest of the synthetic community for years.[1] In the 1980s, the Fenical group first isolated natural products from this family and from the late 1990s to the present day, the Rodríguez group from Puerto Rico has isolated and structurally elucidated numerous novel marine metabolites from these sea whips. Geographically, collection sites of this species are mostly in deeper reef communities in the tropical western Atlantic, for example, in the Florida Keys or in the Bahamas. The majority of samples collected by the Rodríguez group are from deep waters near San Andrés island, off the coast of Colombia.

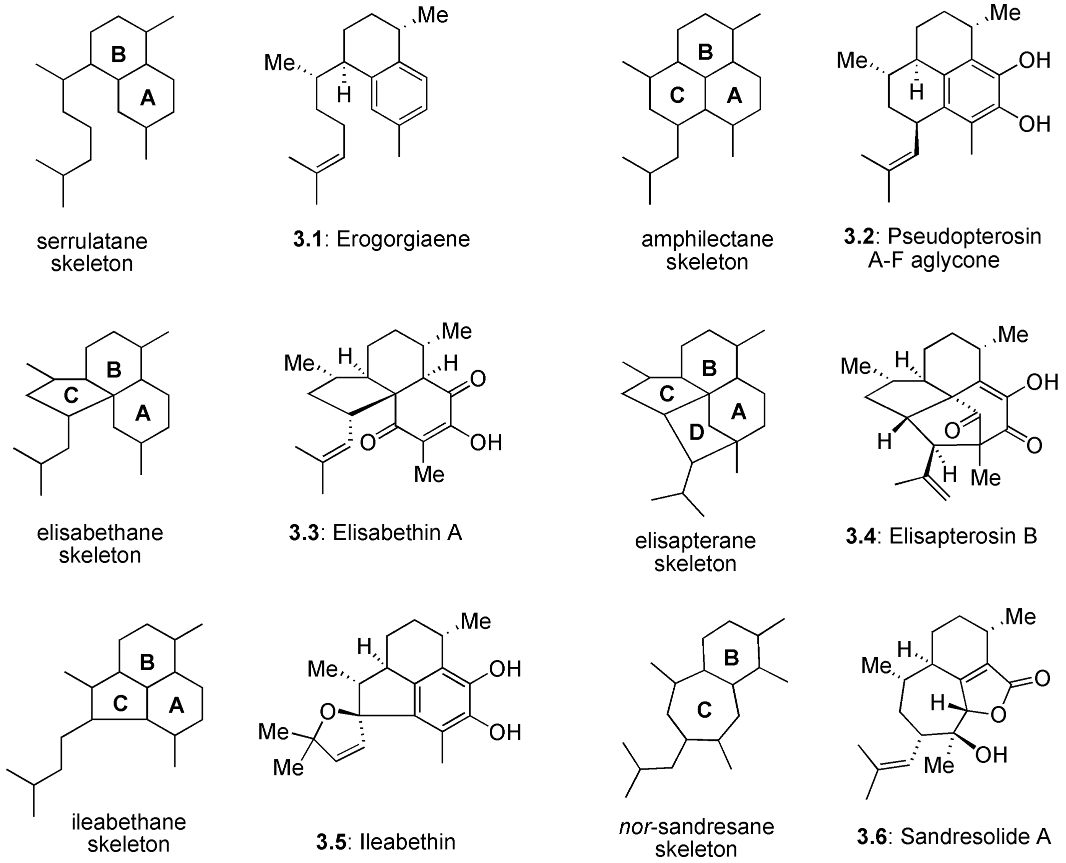
The structural diversity and broad spectrum of biological activity of compounds from this chemically prolific species have captured the attention of natural product chemists. Furthermore, all of the compounds isolated from this family share certain structural patterns. Biosynthetic postulations indeed link all compounds in this class to a serrulatane core from geranyl geranyl phosphate (Figure 3.1).[1] However, the function and origin of the biosynthetic machinery in the organism remain mysterious.

Figure 3.1. Derivation of geranylgerane to the serrulatane skeleton



Over forty natural products from *Pseudopterogorgia elisabethae* have been isolated, and at least seventeen carbon skeletons that originate from the serrulatane skeleton have been identified. Representative structures and their corresponding skeletons are illustrated in figure 3.2.

Figure 3.2. Selected skeletons and natural products from *Pseudopterogorgia elisabethae*



serrulatane skeleton

3.1: Erogorgiaene

amphilectane skeleton

3.2: Pseudopterosin A-F aglycone

elisabethane skeleton

3.3: Elisabethin A

elisapterane skeleton

3.4: Elisapterosin B

ileabethane skeleton

3.5: Ileabethin

nor-sandresane skeleton

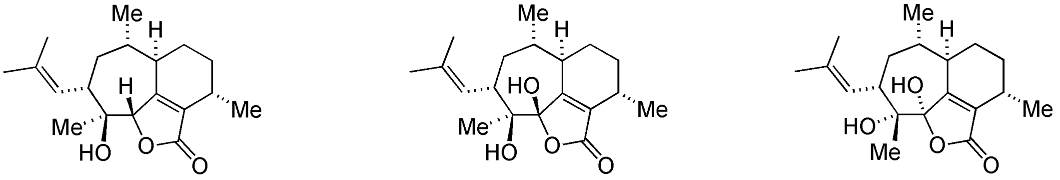
3.6: Sandresolide A

Erogorgiaene (**3.1**), isolated in 2001,[2] bears the simple serrulatane skeleton with a representative **A** and **B** ring as shown. An additional carbon-carbon bond can form the amphilectane skeleton as represented by Pseudopterosin A-F aglycone (**3.2**). Several members bearing this skeleton exist and many of them are highly conjugated. An elisabethane skeleton bearing a 5-membered **C** ring and elisapterane skeleton with another carbon-carbon bond to form a **D** ring are core structures of over a dozen molecules of varying complexity. Elisabethin A (**3.3**) and elisapterosin B (**3.4**) are relatively simple representatives of this class, which has been an area of particular interest in total synthesis perhaps because many compounds bearing these tricyclic and tetracyclic cores are structurally complex and therefore challenging targets.[3-6] The last two examples shown are unusual deviations from the rest of the family. Ileabethin (**3.5**) contains an **A**-**C** ring juncture at a different point than the elisabethanes and elisapteranes and also features an unusual spiro dihydrofuran as opposed to the standard prenyl appendage. Finally, sandresolide A (**3.6**) is a representative *nor* compound where the **A** ring has been truncated. The **C** ring has also been expanded; one biosynthetic postulation suggests that a ring-expansion from amphilectane with a concomitant alkyl shift may provide this framework.[1]

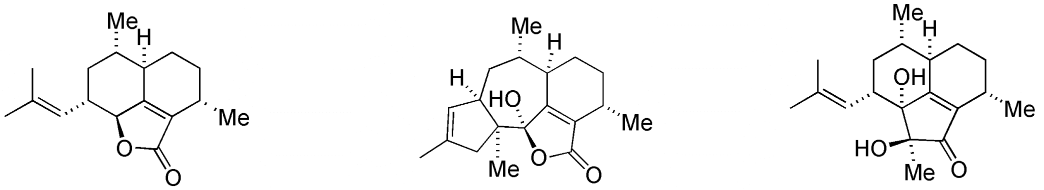
Section 3.2. Recognition of a common retrosynthetic precursor for *nor*-diterpenes

From a synthetic perspective, *Pseudopterogorgia elisabethae*, which produces numerous natural products diverging from a common intermediate, provides an ideal platform for synthetic exploration. From the outset, our interest was focused on members of this family that contain butenolide or hydroxybutenolide motifs due to our prior experience with furan substrates and oxidized variants thereof (Figure 3.3).[7-12] The butenolide typically originates from truncation of the **A** ring, therefore all of our targets **3.6** – **3.11** are degraded *nor* variants of serrulatane-originating diterpenes. Curiously, **3.9** – **3.11** were all obtained during a deep-sea expedition near San Andrés island, Colombia by Rodríguez and coworkers in 1996.

Figure 3.3. Selected *nor*-diterpene targets



3.6: Sandresolide A **3.7**: Sandresolide B **3.8**: Sandresolide C



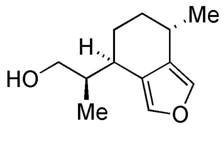
3.9: Amphilectolide **3.10**: Caribenol A **3.11**: Caribenol B

As noted above, sandresolides A-C (**3.6**-**3.8**) possess a *nor*-sandresane skeleton that could arise from rearrangement and carbon loss of the amphilectane skeleton. Sandresolides A (**3.6**) and B (**3.7**) were first reported in 1999,[13] while sandresolide C (**3.8**), a diastereomer of sandresolide B (**3.7**) with respect to the hydroxyl and acetal stereochemistry, was disclosed in 2009.[14] Initial biological screening of sandresolide C (**3.8**) has shown 15% inhibition of *Mycobacterium tuberculosis* growth at 6.25 μg/mL concentration, as well as an IC_{50} of 18 μg/mL against the *Plasmodium falciparum* W2 (chloroquine-resistant) strain; an evaluation of **3.6** and **3.7** has not been reported. Typically, compounds from *Pseudopterogorgia elisabethae* are screened for activity against inflammation, tuberculosis, cancer and antiplasmodial activity[1] since most of their promise as pharmacological agents are in these areas. It is therefore likely that material limitations have hampered full biological evaluation of sandresolides A and B (**3.6** and **3.7**), enhancing their value as synthetic targets.

Amphilectolide (**3.9**) has a *trisnor*-amphilectane skeleton resulting from truncation of the **A** ring. Its structural elucidation was reported in 2000 [15] along with its biological activity against *Mycobacterium tuberculosis* $H_{37}R_V$ (41% at 6.25 μL/mL). Finally, caribenols A (**3.10**) and B (**3.11**) both represent new carbon skeletons from this family that were reported in 2007.[16] Biologically, they both possess inhibitory activity against *Mycobacterium tuberculosis* (61% for **3.10** and 94% for **3.11**). Additionally, caribenol A (**3.10**) shows antiplasmodial activity against chloroquine-resistant *Plasmodium falciparum*. Structurally, it was these two molecules that first attracted our interest in the family. Caribenol A (**3.10**), with its 7-membered **C**-ring, bears a strong structural resemblance to sandresolide C (**3.8**) with its isobutene moiety masked as a fused cyclopentene adduct. On the other hand, caribenol B (**3.11**) may very well be derived from the amphilectane skeleton with fewer carbon losses than amphilectolide (**3.9**) to form a truncated 5-membered **A**-ring that is highly functionalized.

Structurally, all of these targets share a common motif within the **B**-ring and part of the **C**-ring. Additionally, the **B**-ring is typically fused to an oxidized furan variant (or for caribenol B (**3.11**), a substrate that can be derived from a furan). For this reason, we envisioned that the construction of fused furan **3.12** could provide access to our selected members of this family (Figure 3.4). We describe herein the synthesis of the key building block **3.12** followed by its elaboration toward caribenol A and the completion of amphilectolide (**3.9**) and sandresolide B (**3.7**).

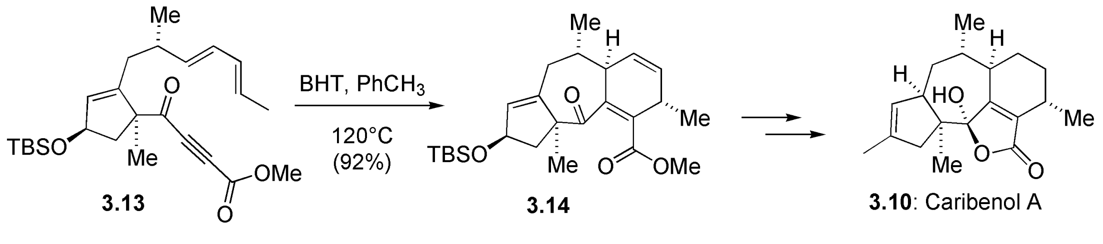
Figure 3.4. A fused furan **3.12** that could potentially access **3.6**-**3.11**



3.12

Several other total synthesis groups have been inspired by these attractive structures; to date, one total synthesis of these targets has been reported. In late 2010, the Yang group reported an impressive first total synthesis of caribenol A featuring an intramolecular Diels-Alder cycloaddition (Scheme 3.1).[17] This is an elegant and efficient method to stereoselectively construct multiple rings, and presents a very different strategy from our approach.

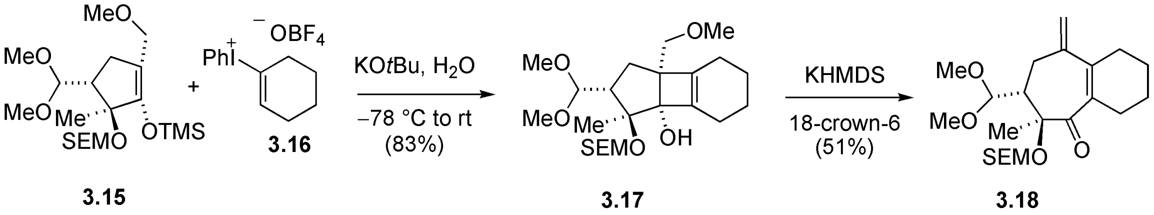
Scheme 3.1. Key step in the Yang synthesis of caribenol A (**3.10**)[17]



In 2010, Carreira and coworkers reported a method to access medium-sized fused rings through cyclohexyne ring insertion followed by ring expansion.[18] Sandresolide A (**3.6**) is reported to be potentially accessible through this strategy and a model study that constructs the **B** and **C** rings is presented (Scheme 3.2). Cyclohexyne, generated in situ from **3.16**, first undergoes a formal base-catalyzed [2+2] addition to form cyclobutene intermediate **3.17**. Further treatment with strong base allows for ring opening with concomitant elimination of methoxide anion to provide the desired sandresolide skeleton.

In both this case and in Yang's total synthesis of caribenol A, the fusion of the rings is the key step and the (hydroxy)butenolide is formed through lactonization as opposed to our strategy, which masks this functionality as a furan installed early on. Our approach is also unique in that it allows for divergence of one key intermediate to several targets in this family.

Scheme 3.2. A model system toward sandresolide A by Carreira[18]

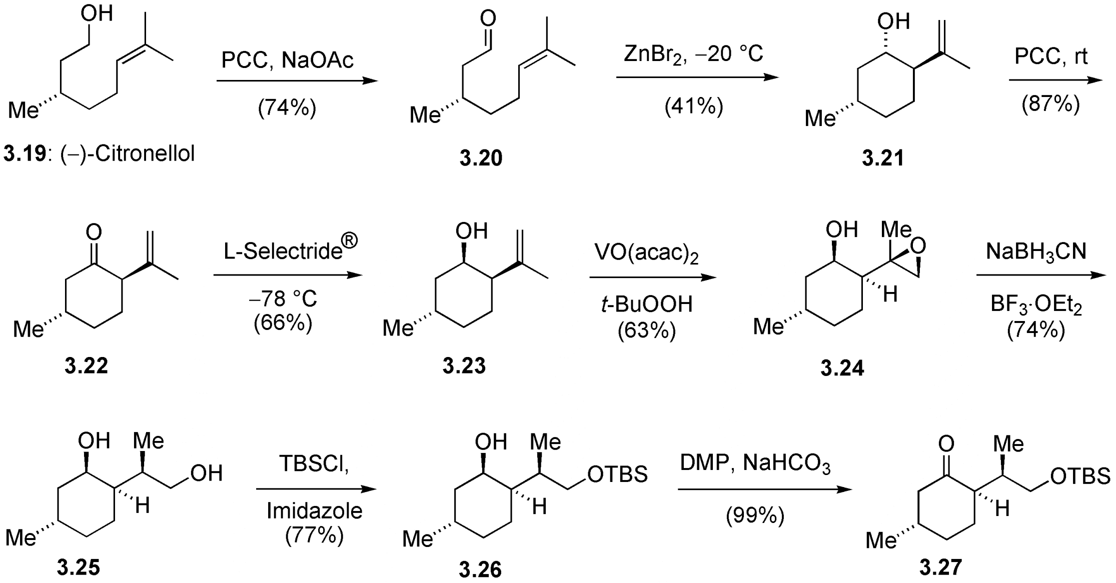


Section 3.3. Preparation of the key furan core

In order to prepare our key building block, we envisioned elaborating known ketone **3.27**, which is available in 8 steps from β-citronellol (**3.19**), to furan **3.12** (Scheme 3.3).[19] Two potential methods were initially considered; the first features a Corey Chaykovsky epoxidation followed by mercury(II) induced rearrangement,[20] and the second makes use of a carbonylative coupling with palladium catalyzed introduction of carbon monoxide.[21] Investigations into both strategies are described.

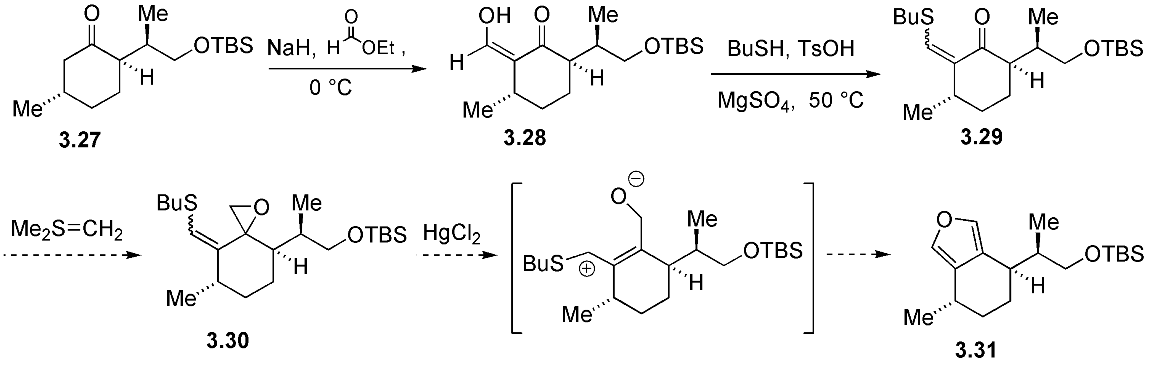
In order to prepare known core **3.27**, conversion of β-citronellol (**3.19**) to (–)-isopulegone (**3.22**) can be effected either using a 1-pot procedure reported by Corey using 2.5 equivalents of pyridinium chlorochromate (PCC),[22] or by following the 3-step sequence shown below. Both methods were effective and some insight was gained into the one-pot procedure, where the requisite ring closure takes place using this oxidant due to its mildly acidic properties. Specifically, the addition of celite as a solid support to this reaction (1 g / mmol **3.19**) facilitated the workup procedure, in which the product was otherwise embedded in sticky tar-like chromium byproducts. Flash column chromatography was also found to be optimal for the purification of isopulegone (**3.22**), as heating the product above 100 °C for distillation led to complete conversion to the corresponding enone pulegone, which is copolar with isopulegone (**3.22**). Although the one-pot procedure was reliable after these findings, we found the three-step sequence easier to work with due to the smaller quantities of PCC required for each of the two oxidation steps. This sequence entails a rapid PCC oxidation buffered with sodium acetate to provide (–)-citronellal (**3.20**), with which ring closure to (+)-isopulegol (**3.21**) may be effected using catalytic zinc bromide as an acid. A subsequent oxidation provides (–)-isopulegone (**3.22**), to which a bulky hydride source such as L-Selectride® could deliver the hydride via equatorial attack to provide **3.23** as a single diastereomer. Curiously, a slow dropwise addition of the reducing agent was essential, otherwise an undesired byproduct that was not the opposite diastereomer of the desired alcohol **3.23** resulted. This alcohol allowed for a directed epoxidation to provide **3.24** as a white crystalline solid, which was reductively opened to the corresponding primary alcohol **3.25**. A selective TBS monoprotection provided **3.26**, which could either undergo oxidation via either buffered Dess-Martin periodinane or Swern conditions to provide our requisite ketone **3.27**.

Scheme 3.3. Elaboration of β-citronellol to produce **3.27**



Our first strategy to convert ketone **3.27** into the desired furan was to use a method devised by Garst and Spencer.[20] This typically proceeds through formylation of the ketone in the less substituted alpha position followed by addition elimination of butane thiol to produce the corresponding thio enol ether. A Corey-Chaykovsky reaction provides an additional carbon, and finally, treatment with mercury(II) salts, which are thiophilic, should allow for an allylic transposition concomitant with epoxide opening to form the charged intermediate shown (Scheme 3.4). Closure of this ring followed by mercury induced elimination of the thioether should provide building block **3.31**.

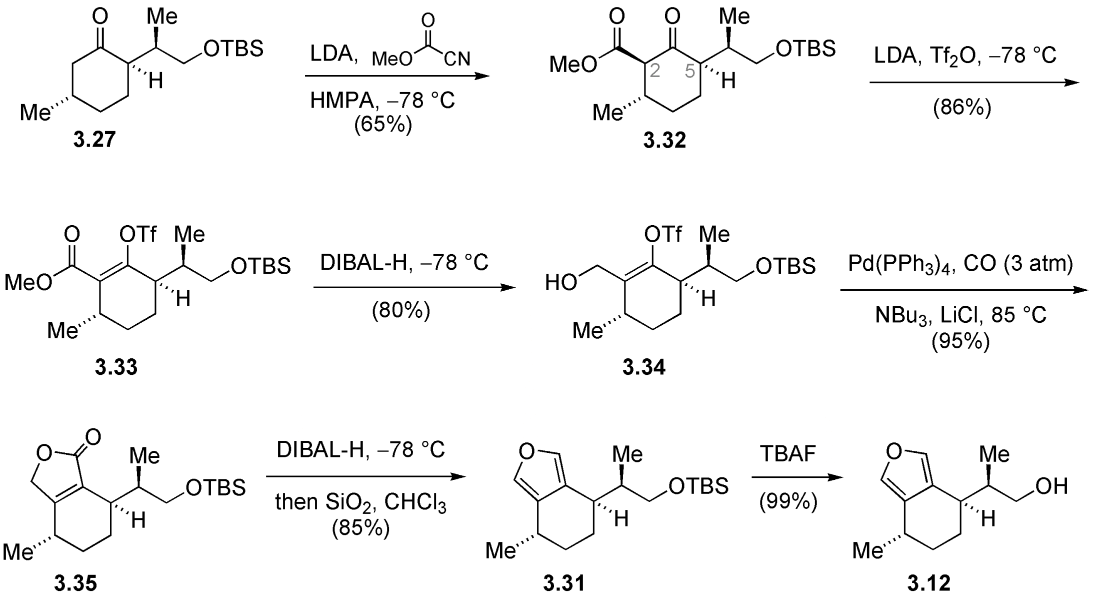
Scheme 3.4. Initial route toward furan **3.31**



Our progress in this route was met with limited success, but provided the first clues that many sites of reactivity in this system are sterically hindered. Formylation of **3.27** was effective using 15 equivalents of sodium hydride and a 1:1 mixture of dimethoxyethane and ethyl formate as a solvent, which are similar conditions to those reported by Danishefsky and coworkers in a sterically hindered substrate.[23] The product **3.28** was unstable to chromatography, so a yield was not confidently established. Conversion to thioether **3.29** was typically conducted by heating the system in butanethiol with catalytic toluenesulfonic acid and magnesium sulfate as a dehydrating agent; the product obtained was unstable on silica gel as well as in chloroform, although its presence was confirmed by ESI mass spectrometry. Once complete consumption of starting material was observed by thin layer chromatography, the volatiles were evaporated and the Corey-Chaykovsky reaction was attempted. The reactive sulfur ylide species were generated *in situ*; those produced using trimethylsulfonium salts are less stable and more reactive than those generated with trimethylsulfoxonium iodide. The reaction was attempted using both types of sulfur ylides but this route was ultimately abandoned because the desired epoxide **3.30** was never isolated and the instability and difficulty of characterization of intermediates added many variables to the system.

Instead, we pursued a method used by Molander and coworkers using a carbonylative coupling strategy which was able to deliver furan **3.12** (Scheme 3.5).[21] Homologation of ketone **3.27** with Manders' reagent after kinetic deprotonation with LDA proceeded in 65% yield to provide **3.32**, the relative stereochemistry of which was established by an NOE correlation between protons attached to C(2) and C(5). This was expected, as all of the substituents are in the equatorial positions of the ring. Triflation of **3.32** to **3.33** also required low temperature and a strong base, and reduction of the resulting ester provided carbonylative coupling precursor **3.34**, preparing us for exploration of this key step.

Scheme 3.5. Preparation of furan **3.12** using a carbonylative coupling strategy



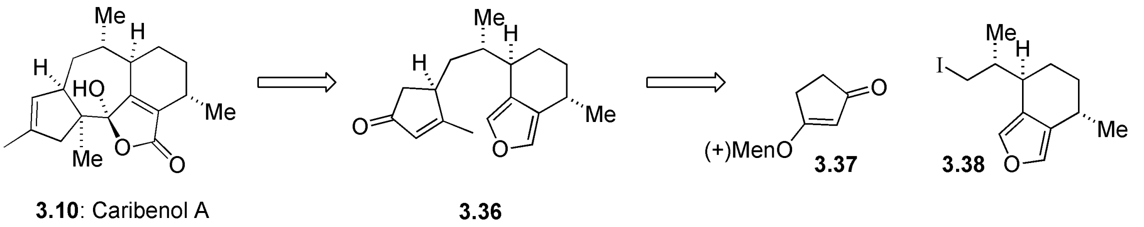
Initial experiments were guided by known butenolide-producing couplings on similar but simpler substrates. Typically, bubbling carbon monoxide (CO) through the solution for 20 minutes and running the reaction under a CO atmosphere in the presence of tetrakis(triphenylphosphine)palladium(0), lithium chloride and tributylamine were sufficient for the conversion to take place. In our case, no reaction was observed. An alternative set of conditions that entailed the use palladium(II) acetate and 1,3-bis(diphenylphospino)propane (dppp) ligand with the inclusion of triethylamine led to decomposition at 100 °C.[24] Finally, it was found that running the reaction under high pressure CO was the key. Specifically, 3-5 bar of carbon monoxide was applied to a degassed solution of the substrate **3.34**, tetrakis(triphenylphosphine)palladium(0), tributylamine, and lithium chloride in acetonitrile. Heating the reaction mixture at reflux for 48 hours provided a nearly quantitative conversion to our desired butenolide **3.35**. The product and starting material could not be separated from each other in any solvent system investigated and could only be distinguished through staining of the thin layer chromatography plate with *p*-anisaldehyde. The starting material **3.34** produces a dark blue color upon staining, whereas the butenolide **3.35** appears as a faint green spot. This carbonylation reaction was therefore required to go to completion in order to cleanly isolate the butenolide **3.35**.

Reduction of butenolide **3.35** to the corresponding furan **3.31** revealed that toluene was the most reliable solvent for this DIBAL-H reduction. Results varied when the reduction was conducted in DCM, resulting in yields from 10% to 77% while no reaction would occur if THF was used as the solvent. Deprotection of **3.31** to reveal the free alcohol **3.12** proceeded smoothly using tetrabutylammonium fluoride, producing our building block for all of the subsequent substrates.

Section 3.4. Progress towards caribenol A

The first elaboration of **3.12** was applied toward a total synthesis of caribenol A (**3.10**). Retrosynthetically, we envisioned installing the hydroxybutenolide through singlet oxygen oxidation of the corresponding furan, which in turn could be derived from intramolecular furanyl nucelophilic addition to the Michael system of **3.36** (Scheme 3.6). The key carbon-carbon bond extension of our building block features a diastereoselective alkylation of **3.38** with known menthol cyclopentenone **3.37**,[25] which we then expected to undergo a Stork-Danheiser enone transposition to complete **3.36**.[26]

Scheme 3.6. Retrosynthetic analysis of caribenol A



In the forward sense, iodide **3.38**, which is light sensitive, was prepared through mesylation of **3.12** followed by a Finkelstein reaction of **3.39** with sodium iodide (Scheme 3.7). Our first indication that the displacement of the iodide within **3.38** would be met with steric challenges occurred during investigation of the key alkylation reaction, which we performed with the zinc enolate of **3.37**. Zinc enolates tend to be more effective than the corresponding lithium enolates for these systems since they are less prone to react with one another.[27] Unfortunately, no reaction was observed when only one equivalent of the zinc enolate of **3.37** was used, and eventually, the best result provided a low 21% yield that required 15 equivalents of the zinc enolate of **3.37** (Scheme 3.7). Alkylation could only be effected with the iodide **3.38**; no reaction was observed using the corresponding mesylate **3.39**. Moving on from this difficult alkylation, the next challenge was the methyl addition into the ketone of **3.40** (Table 3.1).

Scheme 3.7. Progress towards caribenol A

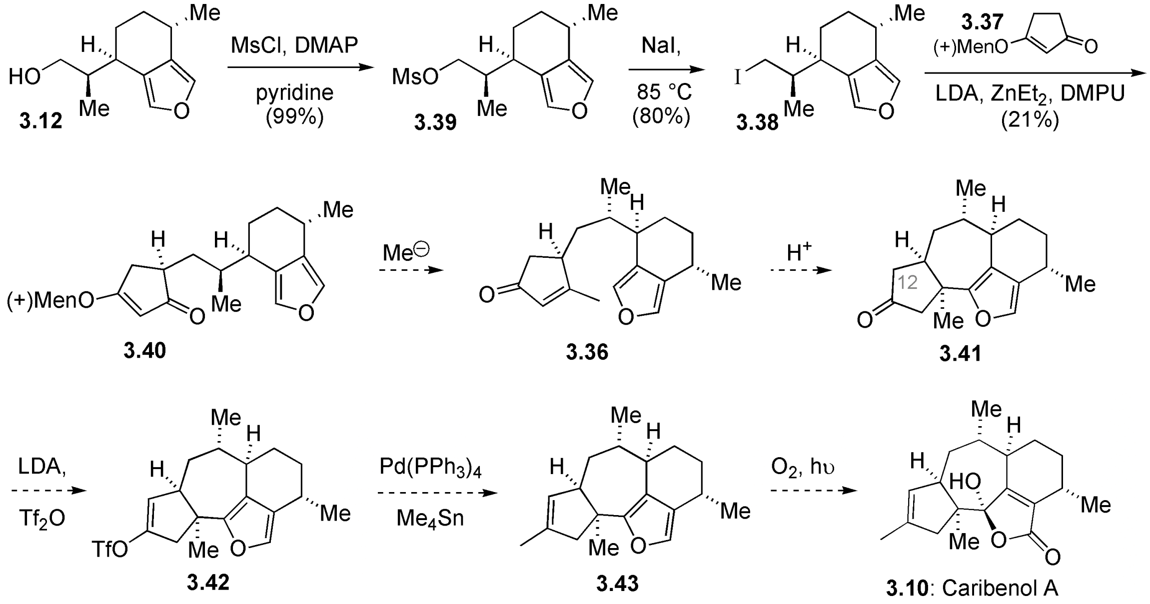


Table 3.1. Methylation attempts on ketone **3.40**

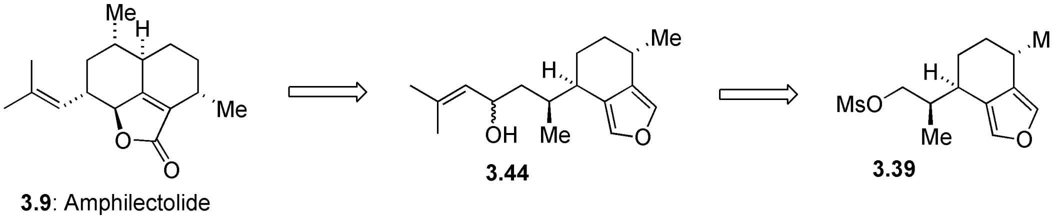
Conditions	Temp. (°C)	Result
10 eq. MeMgBr	0 to 50	No reaction
15 eq MeLi, Et_2O then $BF_3{\cdot}OEt_2$	50 to 70	No reaction
12-crown-4, MeLi	50	No reaction
$CeCl_3$, LiCl, MeMgBr	rt	Promising but inconclusive

Initially, efforts employing a standard Grignard addition to **3.40** resulted in no reaction and thus methyl lithium, the most common alternative methyl anion, was employed. Again, no reaction was observed, and therefore boron trifluoride diethyletherate was then added in the hope that a Lewis acid could activate the electrophilic carbonyl to prompt methyl addition.[28] Unfortunately, still no reaction was observed. Our next strategy was to use 12-crown-4 ether, which is selective for cationic lithium (Li^+) salts. We hoped that this would enhance the nucleophilicity of the naked methyl anion enough to drive the reaction forward, yet still, no reaction was observed. Our last attempt used cerium trichloride in the presence of lithium chloride to activate the Michael system, which are carefully optimized conditions previously found in our laboratory for challenging methyl additions.[29] We obtained a complex mixture in which trace quantities of one of the products was promising. One attempt using formic acid in cyclohexane was made to close the ring on this alleged product.[30] When degradation resulted, we turned our attention to other natural products that could be produced by this series as both reactivity challenges and a lack of atom economy in the alkylation reaction of **3.37** and **3.38** rendered this an ineffective strategy to complete this molecule.

Section 3.5. Total synthesis of amphilectolide

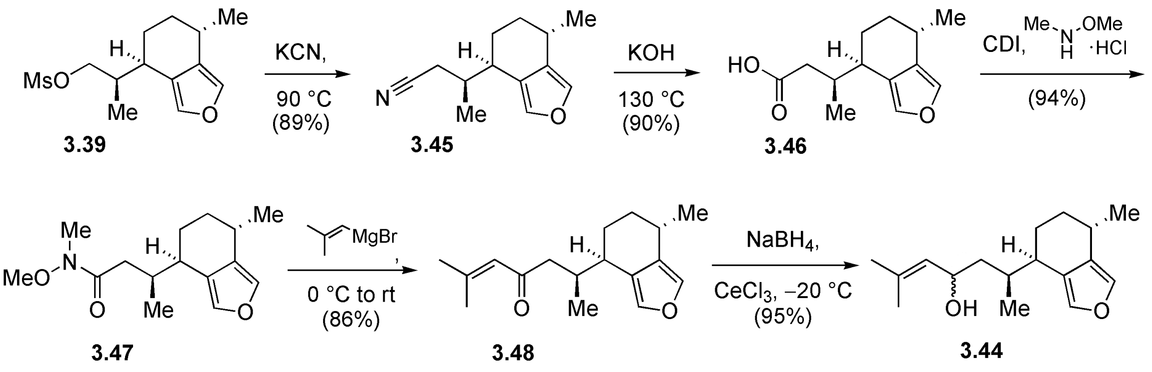
Amphilectolide (**3.9**) is the structurally simplest molecule in this series featuring a 6-membered ring which we envisioned closing through an intramolecular SN_1 displacement of the allylic alcohol with the nucleophilic furan moiety of **3.44**. We expected **3.44** to be derived through carbon chain extension of mesylate **3.39** (Scheme 3.8).

Scheme 3.8. Retrosynthetic analysis of amphilectolide



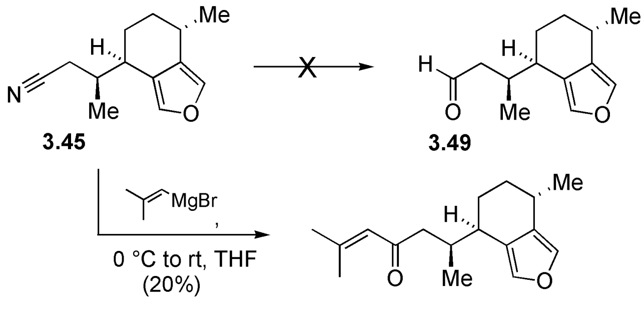
The elaboration of mesylate **3.39** to allylic alcohol **3.44** proceeded optimally in five steps. Specifically, homologation of **3.39** to nitrile **3.45** was followed by saponification to **3.46**, and the resulting carboxylic acid was converted to the Weinreb amide **3.47**. A Grignard addition of commercially available 2-methyl-2-propenylmagnesium bromide to **3.47** provided unstable enone **3.48**, which was immediately reduced under Luche conditions to afford ring closure precursor **3.44** (Scheme 3.9).

Scheme 3.9. Preparation of ring-closure precursor **3.44**



Initially, we had planned to arrive at **3.44** through a straight-forward Grignard addition to aldehyde **3.49**, which we expected to obtain from reduction of the nitrile **3.45** (Scheme 3.10). In retrospect, we believe that this aldehyde is unstable due to its electrophilicity and the nucleophilicity and of the proximal furan ring. A variety of workup conditions were explored for reduction of the nitrile using DIBAL-H and Redal®, none of which provided stable products. When a direct addition of the Grignard reagent to the nitrile of **3.45** was employed, enone **3.48** was obtained in a low 20% yield.

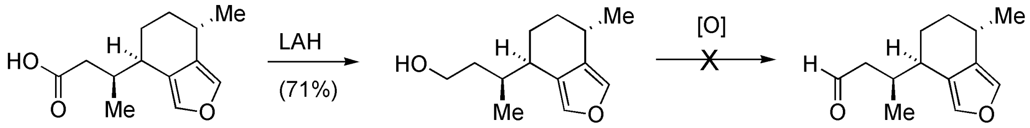
Scheme 3.10. Initial attempts to arrive at alcohol **3.44** via aldehyde **3.49**



3.45 **3.49** **3.48**

We received further confirmation of our suspicion of the instability of aldehyde **3.49** when we attempted to access it through oxidation of alcohol **3.50**, obtained through facile reduction of acid **3.46** (Scheme 3.11). Three standard oxidations were employed; both buffered Dess-Martin Periodinane and Swern conditions led to complex mixtures whereas a Ley oxidation led to clean conversion to a byproduct. These experiments led us to proceed via the five-step sequence described in Scheme 3.9; most likely, another similar system had to go through the same route due to similar incompatibilities between a furan and aldehyde that could potentially form a 6-membered ring.[31]

Scheme 3.11. Attempt to access aldehyde **3.49** via oxidation



3.46 **3.50** **3.49**

Having gained access to the allylic alcohol **3.44**, ring-closure was found to be optimal using lanthanum(III) triflate (Scheme 3.12). A variety of conditions using lanthanide(III) salts or protic acids were investigated (Table 3.2).[32] Unfortunately, the diastereoselectivity of ring closure to **3.51** was poor; we had originally hoped that the thermodynamically favored product that placed the prenyl group in the pseudoequatorial position would predominate. A few variables were investigated, but the selectivity was not significantly improved and furthermore, the two diastereomers of **3.51** could not be separated by high pressure liquid chromatography or flash column chromatography.

Scheme 3.12. Completion of amphilectolide

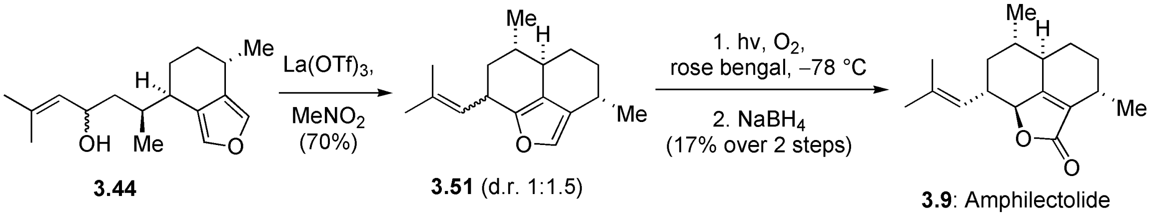


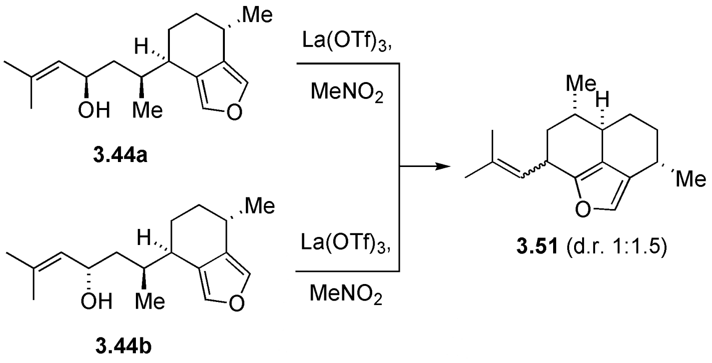
Table 3.2. Conditions Investigated for Ring Closure of **3.44**

Catalyst	Solvent	Temp. (°C)	Yield	d.r.*
$Sc(OTf)_3$	$MeNO_2$	rt	62%	1 : 1.5
$Sc(OTf)_3$	$MeNO_2$	−25 to 0	50%	1 : 1.2
$La(OTf)_3$	$MeNO_2$	rt	70%	1 : 1.5
$La(OTf)_3$	$MeNO_2$	50	60%	1 : 1.5
$La(OTf)_3$	MeCN	rt to 50	<30%	1 : 1.5
TsOH	THF/H_2O (3:1)	65	30%	1 : 1.3

* In all cases, the major product of the reaction was observed at δ 5.23 for the prenyl olefin, the minor corresponding signal was at δ 5.31

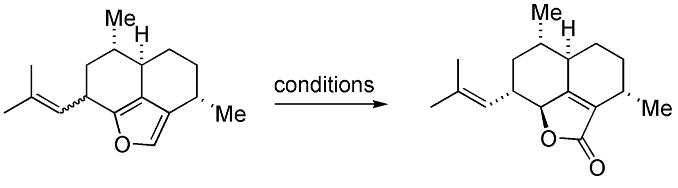
As shown, varying the solvent, temperature or reagents did not improve the diastereoselectivity of ring closure to form **3.51**. The reaction with lanthanum triflate was also verified to proceed via an SN_1 mechanism as the two diastereomers of the starting material were chromatographically separated (Scheme 3.13). When either was subjected to ring closure at room temperature, the same 1:1.5 ratio of diastereomers of **3.51** resulted.

Scheme 3.13. Verification that ring-closure proceeds via an SN_1 mechanism



All oxidation reactions to complete amphilectolide (**3.9**) were conducted on a 1 : 1.5 mixture of diastereomers of furan **3.51**. The oxidation conditions screened make use of known conversions of furans to butenolides both from literature and our laboratory (Table 3.3).[12, 33-35]

Table 3.3. Conditions explored for oxidation of furan **3.51**

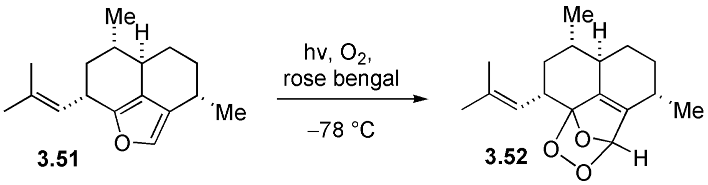


3.51 (d.r. 1:1.5) **3.9**: Amphilectolide

Reaction Conditions	Additional workup details	Results
m-CPBA, trace HCl, THF	--	Product unstable on column
m-CPBA, trace HCl, DCM	--	Decomposition
Magnesium bis (monoperoxyphthalate) hexahydrate, AcOH, DCM	--	Decomposition
Rose Bengal, hv, O_2, -78 °C	Dimethylsulfide	Unstable product
Rose Bengal, hv, O_2, -78 °C, DIEA then $NaBH_4$	--	17% or 25% yield (see text)
Rose Bengal, hv, O_2, -78 °C, DIEA then $NaBH_4$	Camphor sulfonic acid	Unstable product
Rose Bengal, hv, O_2, -78 °C	Camphor sulfonic acid, then $NaBH_4$	Complex mixture, no desired product observed

As shown, the desired product was never observed through the use of peracids. Rather, the best results were obtained using a singlet oxygen addition with rose bengal as a sensitizer, followed by immediate reduction of the acetal with sodium borohydride. Optimization of this reaction proved to be challenging since the products of singlet oxygen addition were unstable, so it was difficult to assess the cause of undesired side reactions and thus how to optimize the reaction conditions. A number of workup conditions were explored including reductive workup with dimethylsulfide, or the addition of mild acid or base to encourage collapse of the endoperoxide **3.52** (Scheme 3.14). When camphorsulfonic acid was added to the stirring crude mixture either before or after reduction with sodium borohydride, no desired product was seen. Rather, a base-mediated endoperoxide collapse was affected using diisopropylethylamine, and the yield of the natural product was not affected by the amount of base added (1-20 equivalents).

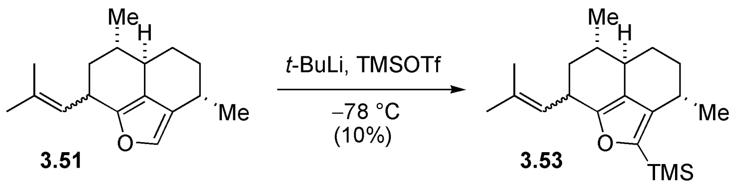
Scheme 3.14. Singlet oxygen oxidation proceeds through an endoperoxide intermediate



More insight into this challenging reaction was later gained in the analogous oxidation for sandresolide B, where the analysis of more stable products revealed that breakdown of the endoperoxide did not proceed smoothly due to steric congestion of the bridgehead hydrogen required for attack via elimination. Further investigation with this potential insight may guide the optimization of this reaction.

Finally, we also attempted to introduce a silyl functionality on the furan substrate in attempt to optimize this oxidation reaction (Scheme 3.15). Unfortunately, of the various silyl species, equivalents of base, and reaction temperatures investigated, the silylated product was only observed using an excess of *tert*-butyl lithium and trimethylsilyl triflate and never led to more than 10% isolation of the desired product **3.53** mixed with 90% starting material (shown by ^{1}H NMR analysis of both crude and chromatographed reaction products).

Scheme 3.15. Attempted introduction of silyl functionality to furan **3.51**

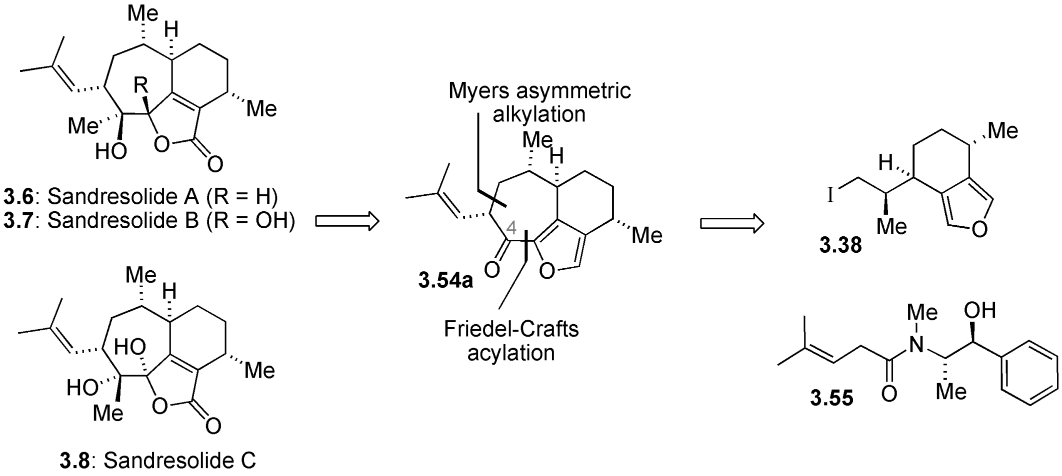


These results indicate that from allylic alcohol **3.44**, amphilectolide (**3.9**) could be prepared in 11% yield over 3 steps. Material losses resulted from both the poor selectivity of the ring closure and production of unstable byproducts in the singlet oxygen oxidation. Depending on whether the ring closure product **3.51** predominantly comprised of the desired diastereomer or the undesired one, the last 2 steps proceeded in either 17% or 25% yield.

Section 3.6. Total synthesis of sandresolide B

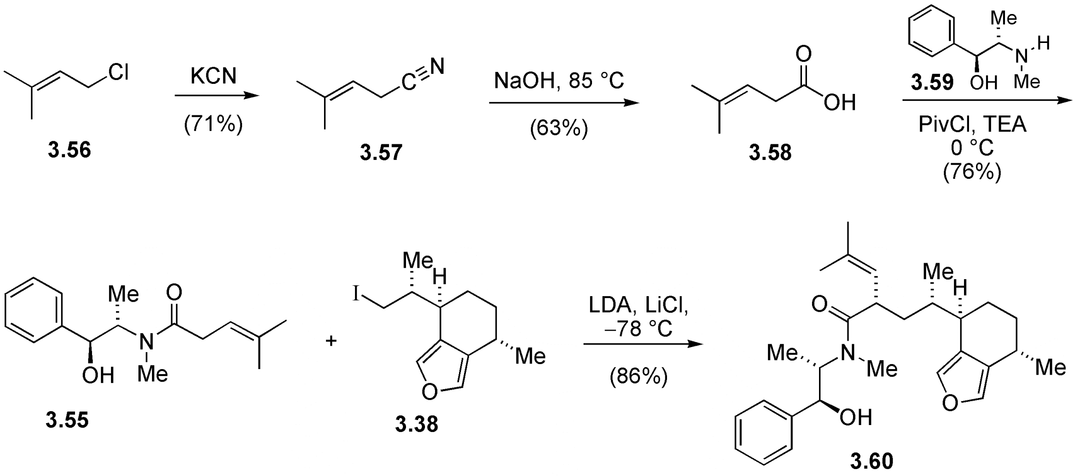
Our final targets in this family of compounds are the sandresolides, their most prominent features being a 7-membered ring and a hydroxybutenolide (**3.7**, **3.8**) or butenolide (**3.6**) which we also planned for introduction via singlet oxygen addition to a furan. Our strategy to produce this set of molecules both builds off of prior knowledge established throughout the course of the above work and also exploits the caveat of the poor diastereoselectivity of ring closure in the total synthesis of amphilectolide. Specifically, sandresolide A (**3.6**) can be derived from acetal reduction of sandresolide B (**3.7**), and since sandresolides B (**3.7**) and C (**3.8**) are diastereomers of one another, both can arise from an unselective methyl addition to **3.54a** at C(4) followed by singlet oxygen oxidation (Scheme 3.16). The 7-membered ring of **3.54a** could arise from an intramolecular Friedel-Crafts acylation, and with prior knowledge that iodide **3.38** is a sterically hindered electrophile, our route to the sandresolides features a Myers asymmetric alkylation, which is known to be effective for sterically encumbered systems.[36]

Scheme 3.16. Retrosynthetic analysis for sandresolides A-C



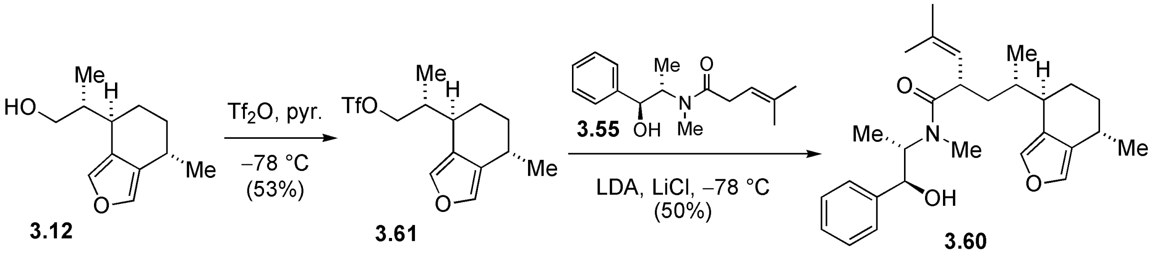
In anticipation of the Myers alkylation, this synthesis commences with the preparation of pseudoephedrine derivative **3.55**, prepared via acid **3.58** from prenyl chloride in 3 known steps (Scheme 3.17).[37] Activation of acid **3.58** as the Piv-anhydride allowed for coupling with (+)-pseudoephedrine (**3.59**) to provide **3.55**, which upon double deprotonation with lithium diisopropylamide, forms a highly nucleophilic enolate. The presence of an excess of lithium chloride accelerates the reaction and suppresses O-alkylation,[38] allowing for production of substrate **3.60** in 86% yield at best. However, on large scale, the yield was typically around 66%.

Scheme 3.17. Preparation of **3.60** via Myers alkylation



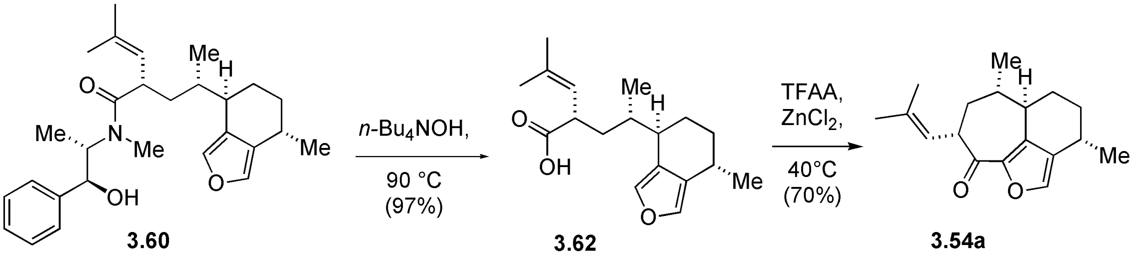
The conditions investigated to achieve optimal alkylation yields include using iodide **3.38** or the corresponding trifluoromethansulfonate derivative **3.61** as electrophiles (Scheme 3.18). Although reaction **3.61** produced the desired product, the yield was lower since no reactivity was observed below –50 °C and above that temperature, the triflate began converting to a compound that was not identified (but was not the product of beta-triflate elimination). It was also observed that the active dianion is highly water sensitive, so the reaction is best conducted above 20 mg scale, and the presence of the dianion can be indicated by a bright orange color. The product **3.60** exists as a 3:1 mixture of rotamers about the amine, which is typical for products from this class of reactions.

Scheme 3.18. Myers alkylation with triflate **3.61**



A nearly quantitative removal of the psuedoephedrine auxiliary via saponification to acid **3.62** was achieved using tetrabutylammonium hydroxide[39] although a lower 63% yield was also obtained using sodium hydroxide (Scheme 3.19). Both of these conditions required high temperatures and long reaction times. On the other hand, acid catalyzed saponification using catalytic sulfuric acid led to immediate decomposition.

Scheme 3.19. Synthesis of tricyclic substrate **3.54a**



With key carboxylic acid **3.62** in hand, the intramolecular Friedel-Crafts reaction was investigated using various Lewis and Brønsted acids and activation methods (Table 3.4). Curiously, one major competing reaction led to repeated formation of an unstable product whose structure was not established. Its presence was apparent by an immediate blue color on staining the thin layer chromatography plate with anisaldehyde that disappeared on heating or prolonged standing. The only combination that was found to provide our desired product **3.54a** entailed activation with trifluoroacetic anhydride followed by heating with zinc chloride.

Table 3.4. Investigation of Intramolecular Friedel-Crafts reaction with **3.62**

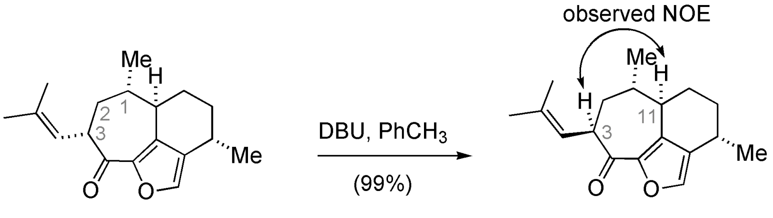
Activating Agent	Lewis acid (eq)	Temp. (°C)	Time (hr)	Results
TFAA	--	–20 to 40	4	Decomposition and reisolation of SM
TFAA	$SnCl_4$ (excess)	–20 to 0	1	Undesired unstable

				product
$(COCl)_2$	$SnCl_4$ (2.5 equiv)	−20 to −15	2.5	Undesired unstable product
TFAA (added pyridine)	--	0 to rt	4	Decomposition
TFAA	$ZnCl_2$ (2.5 equiv)	0 to 40	1	71% yield
TFAA	BF_3-OEt_2	0 to rt	1	Undesired unstable product
$(COCl)_2$	$ZnCl_2$ (1.0 equiv)	0 to rt	1	Undesired unstable product
TFAA	$ZnCl_2$ (0.2 equiv)	0 to 40	4.5	23% yield, 23% epimerization

Of importance was the use of stoichiometric quantities of zinc chloride for this reaction as well as short reaction times; after an hour, epimerization of the stereocenter in the α-position to the carbonyl to produce **3.54b** was observed. The initial appearance of the diastereomer **3.54b** confused us about which diastereomer was the correct one. This is because when catalytic zinc chloride was used, a 1:1 mixture of the epimers was observed and we were unsure about whether epimerization occurs due to the presence of excess zinc chloride or as a result of longer reaction time. A few avenues of inquiry were pursued in order to elucidate the correct diastereomer. It was noted that the two separable diastereomers had different physical properties. One was a white solid and the other was a yellow oil. Recrystallization was attempted on the white solid, although at best, needles that were too thin for crystallography were obtained. It was also observed that treatment of the white solid with diazabicycloundecene produced the yellow oil, which was therefore the thermodynamic product.

At the same time, NOESY measurements were taken; initially we expected that the correct diastereomer, **3.54a** should have a correlation between the protons at C(3) and C(1) (Scheme 3.20). Unfortunately, while a correlation was observed between C(3) (δ3.47 ppm) and another proton at δ1.86 ppm, this shift corresponds to C(2) or C(1), which share an overlapping signal. Thus, this correlation could not provide conclusive evidence for the stereochemistry of **3.54a** since a C(2) to C(3) correlation could very well exist as a result of their proximity. Surprisingly, the opposite diastereomer **3.54b** held the key correlation to establish the structure: protons at C(3) and C(11) showed correlations (at δ3.44 ppm and δ2.45 ppm respectively), therefore the yellow oil was **3.54b**.

Scheme 3.20. Conversion of **3.54a** to **3.54b** and NOE correlation for characterization

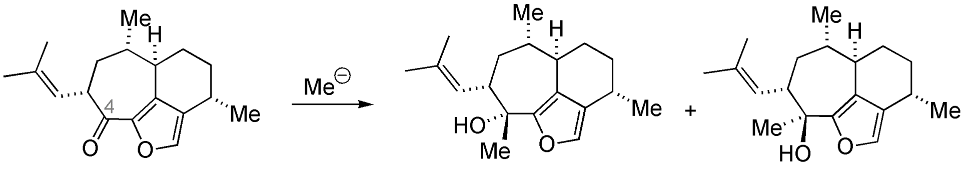


3.54a (white solid) **3.54b** (yellow oil)

While these measurements were underway, a conformational search using Macromodel was conducted (10,000 step Monte Carlo search, solvent-free OPLS algorithm). This further confirmed the above findings, as the undesired diastereomer was found to be the thermodynamic product by 6.7 kcal/mol. Thus, this reaction is best conducted with stoichiometric zinc chloride with short reaction times to give the kinetic product **3.54a**.

Completion of sandresolide B required methylation followed by oxidation to form the hydroxybutenolide of **3.7**. Methylation proceeded smoothly, although the resulting benzylic tertiary alcohol was extremely unstable. Initial experiments showed that addition using methyl magnesium bromide proceeded on either side of the carbonyl to presumably provide **3.63** and **3.64**, whereas methyl lithium gave exclusive formation of one diastereomer **3.63** or **3.64** (Scheme 3.21). We were not concerned about which diastereomer was formed because one in theory could lead to sandresolide B and the other to sandresolide C.

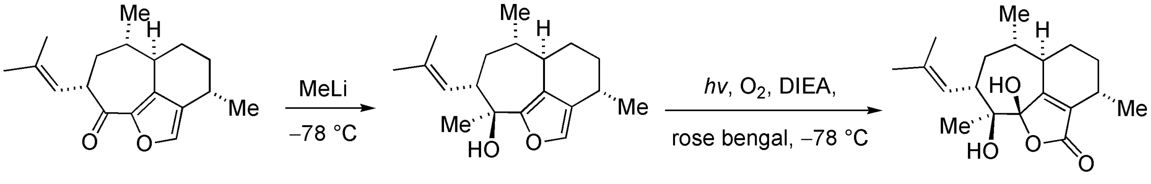
Scheme 3.21. Diastereoselectivity of methyl addition



3.54a **3.63** **3.64**

The first total synthesis of sandresolide B was completed using addition of methyl lithium followed by immediate oxidation (Scheme 3.22).

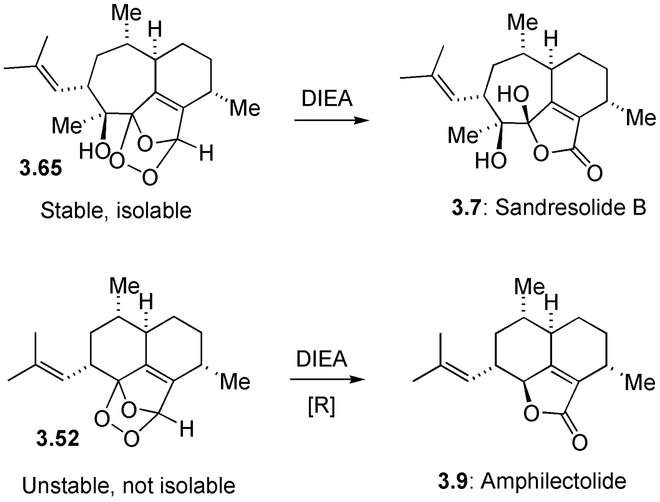
Scheme 3.22. Completion of sandresolide B



3.54a **3.64** **3.7**: Sandresolide B

Interestingly, the byproducts formed in this case were much more stable than those found in the corresponding reaction with amphilectolide, shedding light on this reaction in both projects (Scheme 3.23). Analysis suggested that the endoperoxide was isolable and stable; indeed, treatment of a sample of **3.65** with diisopropylamine in chloroform for 2 weeks provided its partial conversion to sandresolide B. This result was initially surprising, since collapse of the endo peroxide is usually rapid, but the proton required for elimination is in a congested bridgehead position, which may explain this observed phenomenon. This also shed further light as to why in the first few experiments, the reproducibility of this reaction was in question; most likely, the rate of collapse of the endoperoxide varies with scale and other variables, including time spent on the rotary evaporator and its exact temperature.

Scheme 3.23. Endoperoxide comparison between sandresolide B and amphilectolide precursors



3.65 Stable, isolable

3.7: Sandresolide B

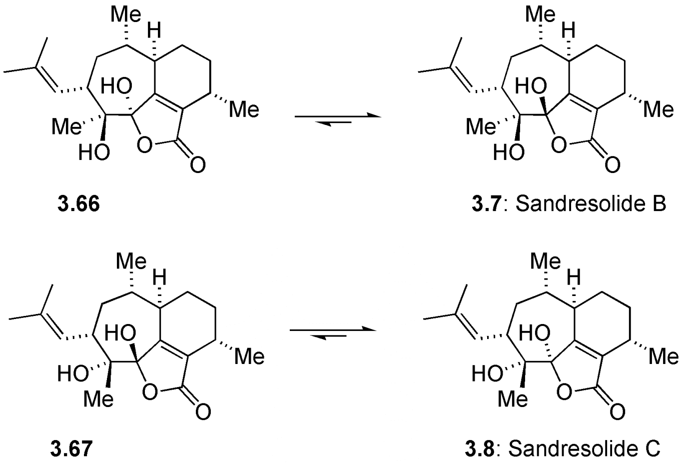
3.52 Unstable, not isolable

3.9: Amphilectolide

The proton NMR data of sandresolide B (**3.7**) was in accordance to literature except for the axial proton at C(10), which is reported to have the same shift as the equatorial proton in the isolation paper.[13] We believe that this is a mistake because the axial and equatorial protons are consistently found with different shifts of approximately δ1.3 ppm and δ2.0 ppm respectively for all compounds in this project. Additionally, spectra reported for sandresolide C[14] and amphilectolide[15] also indicate that the equatorial and axial protons at this position are different. HSQC analysis also shows a correlation between the carbon at δ28.2 ppm and protons at δ1.27 ppm and δ2.00 ppm, whereas the reported HMBC correlates the carbon at δ28.2 ppm with two protons at δ2.00 ppm. Due to the match between coupling constants and carbon shifts with these preliminary spectra, we are reasonably confident that we have completed sandresolide B (**3.7**) although correspondence with the isolationist, Abimael D. Rodríguez, should further confirm this. Irina Albrecht aided in the characterization of this natural product during further studies into the singlet oxygen oxidation, where an improved ^{1}H NMR spectrum of sandresolide B (**3.7**) and the first ^{13}C NMR were acquired (shown in the experimental section). She also provided HSQC data, which was particularly helpful for supporting the peak misassignment discussed above.

Finally, since 1:1 diastereoselectivity of methyl addition to the Friedel-Crafts product **3.54a** using methyl Grignard, singlet oxygen oxidation of this mixture was attempted in the hopes that both sandresolides B (**3.7**) and C (**3.8**) would be isolated. Preliminary results did not reveal the formation of sandresolide C, although the isolated endoperoxide could be used for future studies. Additionally, many of the byproducts that were isolated are similar to the reported natural product spectra, and one possibility is that they result from addition of singlet oxygen to the opposite face of that required to provide natural products, providing diastereomers **3.66** and **3.67** (Scheme 3.24). We assume that these hydroxybutenolide natural products are thermodynamic products with respect to acetal stereochemistry since they exist in aqueous marine environments, so it should be possible to equilibrate incorrect diastereomers such as **3.66** and **3.67**.

Scheme 3.24. Postulated equilibration of undesired diastereomers to sandresolides B and C

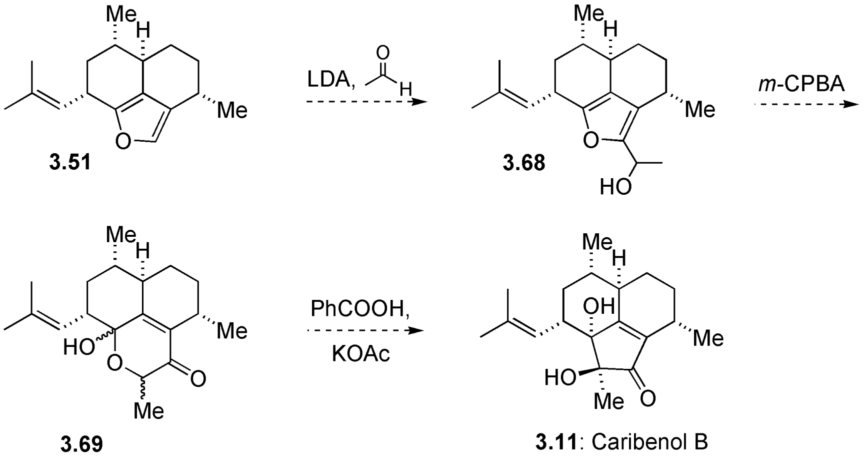


Section 3.7. Conclusion

We have developed a scaleable route to key furan core **3.12** which can be used to access a number of norditerpenes isolated from *Pseudopterogorgia elisabethae*. Through preliminary experiments toward caribenol A (**3.10**) and the completion of amphilectolide (**3.9**) and sandresolide B (**3.7**), an understanding of the reactivity in various sites of this system has been deduced. Further studies in our laboratory may provide a better understanding of the singlet oxidation reaction and also shed further retrospective insight on the challenges that were confronted for this reaction in the amphilectolide synthesis.

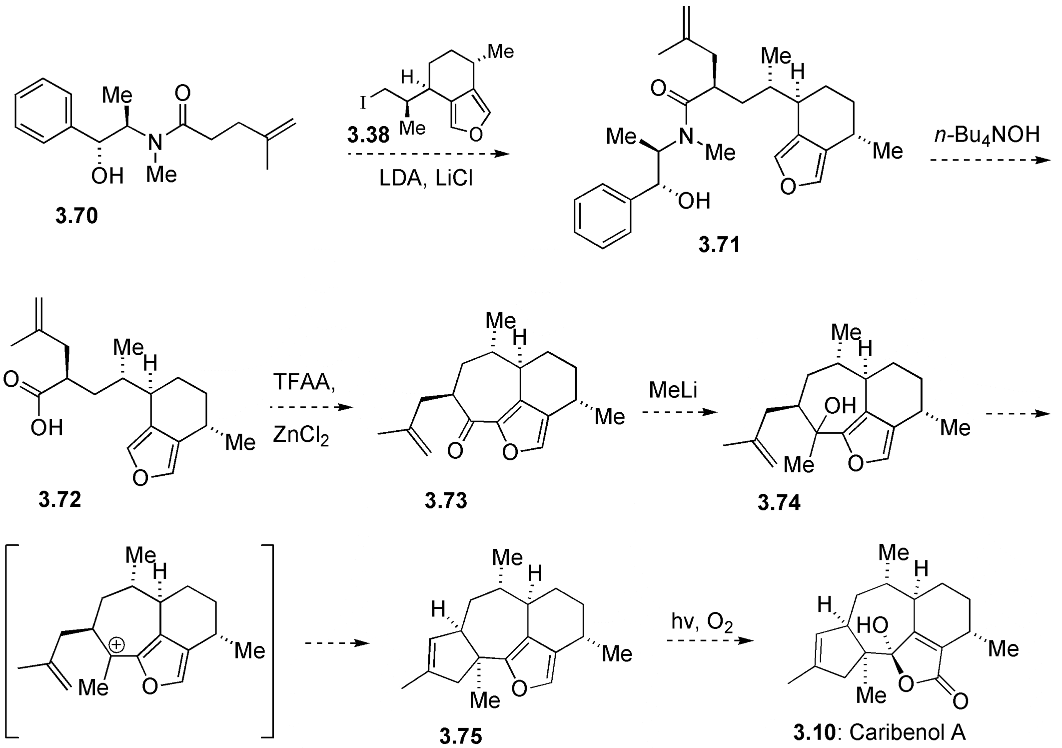
Two possible future directions arise through these studies. In the first, intermediate **3.51** from the amphilectolide synthesis may be elaborated to caribenol B (**3.11**) (Scheme 3.25). Specifically, alkylation of the furan with acetaldehyde can provide **3.68**, to which an Achmatowicz reaction[39] can convert the furan to the dihydropyran of **3.69**. A ring contraction can allow for collapse of the dihydropyran into caribenol B (**3.7**); the conditions suggested follow one study[40] where the hydroxides consistently resulted in the requisite *trans* relationship.

Scheme 3.25. Potential for elaboration of **3.51** to caribenol B



Another avenue that would be interesting to pursue is the application of the Myers alkylation found to be effective in the sandresolide B (**3.7**) synthesis to provide the requisite carbon-carbon bond toward caribenol A (**3.10**). To reiterate, the limitation to the first generation strategy resulted in difficulties arising from alkylation of the key iodide **3.38**. A new strategy that makes use of the Myers alkylation could unite **3.70** with iodide **3.38** which, upon saponification, would produce acid **3.72** (Scheme 3.26). A Friedel-Crafts acylation as before could close the ring to form **3.73**. It is interesting to note that in this case, the substituent in the α position to the carbonyl possesses the opposite stereochemistry as that of sandresolide B (**3.7**). One could infer that epimerization would be less of a problem for this substrate since the α substituent should be in the thermodynamically favorable position. Methyl addition to the carbonyl of **3.73** would provide **3.74**, and a mild acid should allow for the formation of the cationic intermediate shown, which is both tertiary and benzylic. Next, the olefin should trap the cation to result in another tertiary cation and the stereochemistry should be dictated by C(3); *cis*-fused 5-membered rings are typically much less strained than those that are *trans*-fused. The selectivity of elimination in the β position of the last cation is difficult to predict but one could also imagine this to be an allylation, where a concerted mechanism including olefin formation takes place in one step from **3.74** to **3.75**. Regardless, we expect that this is a viable route to explore the chemistry toward caribenol A (**3.10**) and make use of the insight gained thus far.

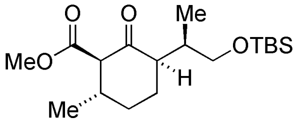
Scheme 3.26. A proposed second generation route to caribenol A



Section 3.8. Experimental procedures

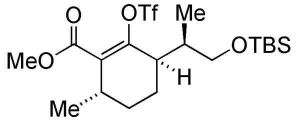
General Experimental Details: All reactions were carried out under an inert N_2 atmosphere in oven-dried glassware. Flash column chromatography was carried out with Merck 40-60μM 60 Å silica gel. Reactions and chromatography fractions were monitored with Merck silica gel 60 F_{254} plates and visualized with potassium permanganate, ceric ammonium molybdate, and anisaldehyde. Tetrahydrofuran (THF), and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl. *n*-Butyllithium (*n*BuLi) was titrated with diphenylacetic acid prior to use. All other reagents and solvents were used without further purification from commercial sources. Organic extracts were dried unless otherwise noted.

Instrumentation: FT-IR spectra were obtained as neat samples on a Perkin-Elmer BXII-FTIR spectrometer. Proton and carbon NMR spectra (^1H NMR and ^{13}C NMR) were recorded in deuterated chloroform ($CDCl_3$) on a Varian Mercury 400MHz or 600 MHz spectrometer and calibrated to residual solvent peaks. Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet. Optical rotations were measured on a Perkin-Elmer 241 Polarimeter. High resolution mass spectra (HRMS) were obtained at Ludwig-Maximilians Universität using electron impact (EI) or electrospray ionization (ESI).



Methyl Ester 3.32. To a solution of 1.48 mL (10.5 mmol) diisopropylamine (DIA) in 80 mL THF cooled to 0 °C was added 6.80 mL (10.5 mmol) of *n*-BuLi (1.55M in hexanes) dropwise. The solution was allowed to stir for 2 hours, at which point it was cooled to −78 °C. A solution of 1.0 g (3.51 mmol) **3.27** [19,22] in 20 mL THF was then added dropwise and the reaction mixture was stirred for another hour before addition of 1.8 mL (10.53 mmol) hexamethylphosphoramide (HMPA) followed by 0.840 mL (10.5 mmol) methyl cyanoformate (Mander's reagent). The solution became a pale yellow color and after 10 minutes at −78 °C, was quenched with H_2O. The layers were separated and the organic layer was washed with NaCl (saturated). The organic layer was then dried, filtered, and evaporated and then purified by flash column chromatography (8 to 12% Et_2O/hexanes) to afford 780 mg of **3.32** (65%) as a pale yellow oil.

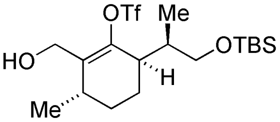
Rf: 0.41, 10% EtOAc/Hexanes. ^{1}H NMR (600 MHz): δ 3.73 (s, 3H), 3.48 (dd, 1H, *J* = 10, 5.5 Hz), 3.36 (dd, 1H, *J* = 10, 8 Hz), 3.04 (d, 1H, *J* = 12 Hz), 2.51 (m, 1H), 2.15 (br m, 2H), 1.99 (m, 1H), 1.94 (m, 1H), 1.44 (dd, 2H, *J* = 12, 10 Hz), 1.01 (d, 3H, *J* = 12 Hz), 0.86 (s, 9H), 0.79 (d, 3H, *J* = 7 Hz), 0.01 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (150 MHz): δ 206.90, 170.38, 65.61, 65.54, 51.85, 49.80, 37.40, 33.17, 32.88, 26.29, 25.90, 25.62, 21.07, 18.26, 12.60, -5.40, -5.50. IR: 1748, 1472, 1359, 1251, 1090 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{34}O_4SiNa$ ($[M + Na]^+$) 365.2124, found 365.2117. $[\alpha]^{25}_D$ +8.4 (*c* = 1.0, $CHCl_3$).



Triflate 3.33. To a solution of 0.45 mL (3.24 mmol) DIA in 50 mL THF at 0 °C was added 1.30 mL (3.24 mmol) *n*BuLi (2.5 M in hexanes). The yellow solution was stirred for 20 minutes, then cooled to −78 °C and a solution of 0.701 g (2.16 mmol) **3.32** in 10 mL THF was added dropwise. After an hour, 0.55 mL (3.24 mmol) trifluoromethansulfonate anhydride (Tf_2O) was added dropwise. The solution became a darker yellow color and after 15 minutes, complete consumption of starting material was observed by TLC. The reaction mixture was then quenched with aqueous $NaHCO_3$ (saturated). The layers were separated and the organic layer was dried, filtered, and evaporated then purified by flash column chromatography (5 to 10% EtOAc/hexanes, 1% TEA) to afford 833 mg of **3.33** (86%) as a pale yellow oil, 92% borsm.

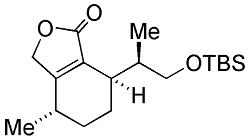
Rf: 0.59, 10% EtOAc/Hexanes. ^{1}H NMR (400 MHz): δ 3.81 (s, 3H), 3.53 (dd, 1H, *J* = 10, 6 Hz), 3.41 (t, 1H, *J* = 9.3 Hz), 2.86 (m, 1H), 2.76 (m, 1H), 2.20 (m, 1H), 1.80 (m, 2H), 1.50 (m, 1H), 1.30 (m, 1H), 1.11 (d, 3H, *J* = 6.9 Hz), 0.86 (m, 9H), 0.76 (d, 3H, *J* = 7 Hz), 0.03 (s, 6H). ^{13}C NMR (150 MHz): δ 165.32, 151.96, 130.99, 118.5 (with 3 satellites), 65.02, 51.93, 37.77, 35.32, 31.99, 28.46, 25.75, 20.15, 19.95, 11.28, -5.57, -

5.74. IR: 2933, 2859, 1733, 1472, 1422, 1246, 1140, 1068 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{33}O_6F_3SiNa$ ([M + Na]$^+$) 497.1617, found 497.1611. $[\alpha]^{25}_D$ –5.3 (*c* = 0.87, $CHCl_3$).



Triflate alcohol 3.34. A solution of 0.910 g (1.92 mmol) **3.33** in 50 mL DCM was cooled to to –78 °C, and then 4.5 mL of DIBAL-H (5.38 mmol, 1.2 M in $PhCH_3$) was added dropwise. After 1 hour of stirring, another 0.50 mL of DIBAL-H (0.42 mmol) was added. After 3 minutes, the reaction mixture was warmed to room temperature for 10 minutes, at which point it was quenched with a 1:1 mixture of H_2O/Rochelles Salt (saturated) and diluted with DCM. The layers were stirred vigorously until no emulsion was present. The layers were then separated, the organic layer was dried, filtered, and evaporated. Flash column chromatography (10 to 15 to 20% EtOAc/hexanes and 1% TEA) afforded 639 mg of **3.34** (80%) as a clear, colorless oil.

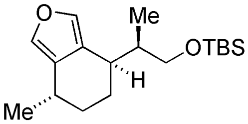
Rf: 0.55, 25% EtOAc/Hexanes. ^{1}H NMR (600 MHz): δ 4.37 (d, 1H, *J* = 7.5 Hz), 4.26 (dd, 1H, *J* = 12.7, 1.6 Hz), 3.51 (dd, 1H, *J* = 10, 7 Hz), 3.43 (dd, 1H, 8.8, 1.2 Hz), 2.86 (m, 1H), 2.56 (m, 1H), 2.18 (m, 1H), 1.83 (m, 1H), 1.77 (m, 1H), 1.60 (br s, 1H (OH)), 1.46 (m, 1H), 1.30 (m, 1H), 1.20 (d, 3H, *J* = 7 Hz), 0.88 (s, 9H), 0.76 (d, 3H, *J* = 7 Hz), 0.02 (d, 6H, *J* = 1.5 Hz). ^{13}C NMR (100 MHz): δ 1147.21, 136.18, 119.94 (with satellites), 65.19, 58.23, 38.26, 35.01, 32.17, 29.75, 25.76, 20.98, 19.41, 18.15, 11.03, -5.53, -5.68. IR: 3342, 2931, 1673, 1473, 1415, 1248, 1140, 1090, 972, 883, 819, 775, 667 cm $^{-1}$. HRMS (ESI) calcd for $C_{18}H_{33}O_5ClF_3SiS$ ([M + Cl]$^-$) 481.1459, found 481.1458. $[\alpha]^{25}_D$ –12 (*c* = 0.33, $CHCl_3$).



Butenolide 3.35. To a solution of 2.80 g (6.27 mmol) **3.34** in 100 mL MeCN was added 869 mg (0.750 mmol) $Pd(PPh_3)_4$, 292 mg (6.90 mmol) LiCl (dried under high vacuum), and 2.99 mL (12.5 mmol) NBu_3. The solution was degassed with N_2 for 20 minutes, then transferred to a Paar bomb. The apparatus was filled with CO (3 bar) and flushed three times, then filled with 2.5 bar CO and heated to 85 °C. The solution became orange after 5 minutes. After 48 hours, the solution was cooled to room temperature and the apparatus was flushed with N_2 before it was opened. The solvent was evaporated, and then flash column chromatography (10% EtOAc/hexanes) afforded 1.98 g (97%) of **3.35** as a light yellow oil.

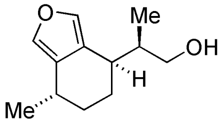
Rf: 0.55, 25% EtOAc/Hexanes. ^{1}H NMR (600 MHz): δ 4.71 (m, 2H), 3.50 (m, 2H), 2.82 (m, 1H), 2.74 (m, 1H), 2.50 (m, 1H), 1.97 (m, 1H), 1.78 (m, 1H), 1.42 (m, 1H), 1.29 (m, 1H), 1.14 (d, 3H, *J* = 7 Hz), 0.88 (s, 9H), 0.66 (d, 3H, *J* = 7 Hz), 0.05 (d, 6H *J* = 5 Hz).

^{13}C NMR (100 MHz): δ 173.54, 166.09, 127.58, 69.85, 65.83, 33.99, 33.28, 30.71, 30.29, 25.90, 21.21, 18.59, 18.23, 11.35, -5.35, -5.5. IR: 2929, 1750, 1661, 1462, 1254, 1086, 1020 cm $^{-1}$. HRMS (ESI) calcd for $C_{18}H_{33}O_3Si$ ($[M + H]^+$) 325.2199, found 325.2194. $[\alpha]^{25}_D$ +43 (*c* = 0.33, $CHCl_3$).



Furan 3.31. A solution of 0.970 g (3.07 mmol) **3.35** in 30 mL $PhCH_3$ was cooled to to −78 °C, and then 4.0 mL of a freshly prepared DIBAL-H solution in $PhCH_3$ (1.0M, 4.0 mmol) was added dropwise. After 15 minutes, another 0.5 mL (0.50 mmol) of DIBAL-H was added, and this was repeated another 5 minutes later. After 5 minutes, the reaction mixture was quenched with a 1:1 mixture of H_2O/Rochelles Salt (saturated) and diluted with DCM. The layers were stirred vigorously until no emulsion was present. The layers were then separated, the organic layer was dried, filtered, and evaporated. To the crude mixture was added 6.14 g silica gel and ~50 mL $CHCl_3$, then stirred for 16 hours (to promote aromatization). This mixture was then filtered, washed with Et_2O, and evaporated, then purified on a silica pad (5% EtOAc/hexanes) to afford 784 mg of **3.31** (85%) as a clear, colorless oil.

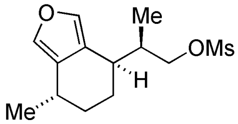
Rf: 0.61, 10% EtOAc/Hexanes. ^1H NMR (600 MHz): δ 7.18 (s, 1H), 7.14 (s, 1H), 3.55 (m, 2H), 2.90 (m, 1H), 2.58 (m, 1H), 2.07 (m, 1H), 1.88 (m, 1H), 1.71 (m, 1H), 1.28 (m, 1H), 1.21 (d, 3H, *J* = 7 Hz and m, 1H), 0.90 (s, 9H), 0.79 (d, 3H, *J* = 7 Hz), 0.06 (d, 6H, *J* = 2 Hz). ^{13}C NMR (100 MHz): δ 137.26, 137.11, 128.78, 135.04, 66.17, 39.12, 33.42, 32.70, 27.86, 25.93, 23.34, 21.13, 18.30, 11.87, -5.32, -5.38. IR: 2956, 2856, 1462, 1415, 1361, 1250, 1208, 1141, 1089 cm $^{-1}$. HRMS (EI) calcd for $C_{18}H_{32}O_2Si$ ($[M]^+$) 308.2172, found 308.2172. $[\alpha]^{25}_D$ +56 (*c* = 0.33, $CHCl_3$).



Deprotected furan 3.12. A solution of 762 mg (2.47 mmol) **3.31** in 25 mL THF was cooled to 0 °C, and then 3.1 mL (3.1 mmol) of a tetrabutylammonium fluoride (TBAF) solution (1.0M in THF) was added dropwise. The tan solution was then warmed to room temperature and after 1 hour, another 0.5 mL (0.5 mmol) of TBAF was added. After 30 minutes, the reaction mixture was quenched with $NaHCO_3$ (saturated), diluted with Et_2O, and the layers were separated. The organic layer was washed with NaCl (saturated), dried, filtered, and evaporated. Flash column chromatography (25% EtOAc/hexanes) afforded 475 mg (99%) of **3.12** as a clear, colorless oil.

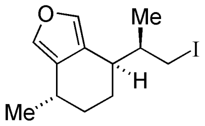
Rf: 0.35, 25% EtOAc/Hexanes. ^1H NMR (400 MHz): δ 7.19 (s, 1H), 7.17 (s, 1H), 3.63 (m, 2H), 2.89 (m, 1H), 2.59 (m, 1H), 2.11 (m, 1H), 1.90 (m, 1H), 1.76 (m, 1H), 1.51 (br s, 1H), 1.34 (m, 2H), 1.22 (d, 3H, *J* = 9 Hz), 0.90 (s, 9H), 0.88 (d, 3H, *J* = 9 Hz). ^{13}C

NMR (75 MHz): δ 137.34, 137.15, 128.75, 124.62, 66.27, 39.35, 33.76, 32.63, 27.83, 23.67, 21.11, 12.12. IR: 3333, 2956, 1538, 1453, 1374, 1232, 1129, 1024, 890 cm $^{-1}$. HRMS (EI) calcd for $C_{12}H_{18}O_2$ ($[M]^+$) 194.1307, found 194.1303. $[\alpha]^{25}_D$ +76 (*c* = 0.40, $CHCl_3$).



Mesylate 3.39. To a solution of 100 mg (0.51 mmol) **3.12** in 10 mL DCM was added 0.080 mL (1.0 mmol) pyridine, 0.060 mL (0.77 mmol) mesyl chloride, and 12 mg (0.10 mmol) DMAP. The flask was flushed with N_2 and covered and stirred for room temperature for 18 hours, after which another 0.060 mL (0.77 mmol) mesyl chloride, and 12 mg (0.10 mmol) DMAP was added. After another 16 hours, yet another 0.060 mL (0.77 mmol) mesyl chloride, and 6 mg (0.05 mmol) DMAP was added and the reaction mixture was stirred for another 9 hours at room temperature, at which point it was quenched with $NaHCO_3$ (saturated), extracted with $CHCl_3$, dried, filtered, and evaporated. Flash column chromatography (25% EtOAc/hexanes) afforded 139 mg (99%) of **3.39** as a slightly tan oil.

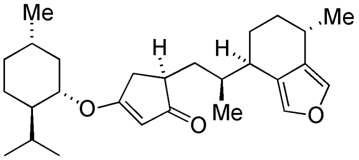
Rf: 0.66, 40% EtOAc/hexanes. ^{1}H NMR (400 MHz): δ 7.19 (d, 1H, *J* = 1.6 Hz), 7.17 (d, 1H, *J* = 1.6 Hz), 4.23 (dd, 1H, *J* = 9.7, 2.4 Hz), 4.15 (dd, 1H, *J* = 9.7, 6.9 Hz), 3.02 (s, 3H), 2.89 (m, 1H), 2.57 (m, 1H), 2.35 (m, 1H), 1.92 (m, 1H), 1.77 (m, 1H), 1.33 (ddd, 1H, *J* = 24, 13, 2 Hz), 1.21 (m, 4H), 0.94 (d, 3H, *J* = 7 Hz). ^{13}C NMR (75 MHz): δ 137.61, 137.18, 128.57, 123.46, 72.42, 37.34, 36.50, 33.68, 32.35, 27.70, 23.79, 21.05, 12.14. IR: 2959, 2361, 1540, 1455, 1353, 1129, 1042 cm $^{-1}$. HRMS (ESI) calcd for $C_{13}H_{20}O_4SiCl$($[M + Cl]^-$) 307.0771, found 307.0775. $[\alpha]^{25}_D$ +49 (*c* = 0.47, $CHCl_3$).



Iodide 3.38. To a solution of 50 mg (0.18 mmol) **3.37** in 8 mL acetone (anhydrous) in a pressure tube was added 138 mg (0.920 mmol) of NaI. The mixture was excluded from light and heated to 85 °C, and after 1 hour, another 138 mg (0.920 mmol) of NaI was added. After 30 minutes, yet another 138 mg (0.920 mmol) of NaI was added. After another 4 hours at 85 °C, the reaction was quenched with H_2O and diluted with Et_2O. The layers were separated and the organic layer was washed with NaCl (saturated), dried, filtered, and evaporated. Flash column chromatography (2% EtOAc/hexanes) afforded 45 mg (80%) of **3.38** as a light sensitive oil.

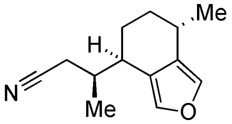
Rf: 0.38, hexanes. ^{1}H NMR (400 MHz): δ 7.18 (d, 1H, *J* = 1.6 Hz), 7.16 (d, 1H, *J* = 1.6 Hz), 3.25 (dd, 2H, *J* = 7.0, 1.2 Hz), 2.96 (m, 1H), 2.56 (m, 1H), 2.12 (m, 1H), 1.89 (m, 1H), 1.73 (m, 1H), 1.25 (m, 5H), 0.99 (d, 3H, *J* = 6.9 Hz). ^{13}C NMR (75 MHz):

δ 137.46, 137.31, 128.56, 124.04, 39.63, 36.68, 32.25, 27.72, 23.14, 21.10, 15.98, 13.42. IR: 2854, 1455, 1376, 1194, 1045 cm $^{-1}$. HRMS (EI) calcd for $C_{12}H_{17}IO$ ($[M]^+$) 304.0324, found 304.0322. $[\alpha]^{25}_{D}$ +31 (*c* = 0.37, $CHCl_3$).



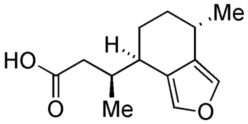
Menthol alkylation product 3.40. A solution of 0.15 mL (1.1 mmol) DIA in 12 mL of THF was cooled to 0 °C, and then 0.79 mL (1.1 mmol) of a 1.4 M solution of *n*-BuLi was added dropwise. After 20 minutes, the reaction mixture was cooled to −78 °C, and then a solution of 260 mg (1.1 mmol) of menthol substrate **3.37** in 5 mL of THF was added dropwise. After 20 minutes, 1.1 mL (1.1 mmol) of a 1.0 M solution of $ZnEt_2$ in hexanes was added dropwise and the solution was stirred for another 30 minutes, at which point a solution of 28 mg (0.092 mmol) of iodide **3.38** in 7 mL THF was added dropwise. Upon completion of iodide addition, 1.33 mL (11.0 mmol) of DMPU was added and the reaction mixture was gradually warmed to room temperature overnight. After 19 hours, the dark orange solution was quenched with H_2O, the layers were separated, and the organic layer was dried, filtered, and evaporated. The crude material was purified using flash column chromatography (15% EtOAc/hexanes) followed by preparatory TLC (25% EtOAc/hexanes) to afford 8 mg (21%) of **3.40** as a yellow oil.

Rf: 0.51, 25% EtOAc/Hexanes. ^{1}H NMR (600 MHz): δ 7.19 (dt, 1H, *J* = 3.7, 1.6 Hz), 7.14 (dt, 1H, *J* = 8.5, 1.7 Hz), 5.27 (s, 1H), 3.96 (m, 1H), 2.78 (m, 1H), 2.56 (m, 2H), 2.37 (m, 1H), 2.12 (m, 2H), 2.04 (m, 2H), 1.91 (m, 1H), 1.81 (m, 1H), 1.74 (m, 2H), 1.54 (m, 1H), 1.45 (m, 2H), 1.33 (m, 3H), 1.22 (d, 3H, *J* = 6.7 Hz), 1.17 (m, 1H), 1.04 (m, 2H), 0.94 (m, 6H), 0.87 (m, 3H), 0.78 (d, 3H, *J* = 7.0 Hz). ^{13}C NMR (150 MHz): δ 208.41, 188.02, 137.31, 137.07, 128.85, 125.01, 103.18, 82.29, 47.37, 43.32, 39.39, 36.54, 36.22, 36.02, 34.89, 34.08, 32.82, 31.33, 27.92, 26.29, 23.53, 22.98, 21.92, 21.00, 20.55, 16.62, 15.78. HRMS (ESI) calcd for $C_{27}H_{41}O_3$ ($[M + H]^+$) 413.3056, found 413.3047.



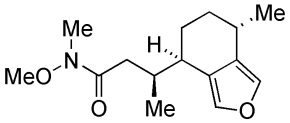
Nitrile 3.45. To a solution of 130 mg (0.477 mmol) of **3.39** in 12 mL DMF (anhydrous) in a pressure tube was added 68 mg (1.1 mmol) of KCN. The mixture was heated to 70 °C for 2.5 hours, then to 95 °C for 4 hours. The reaction mixture was then cooled to 70 °C for 16 hours, quenched with $NaHCO_3$ (saturated), and diluted with Et_2O. The layers were separated and the organic layer was dried, filtered, and evaporated. Flash column chromatography (15% EtOAc/hexanes) afforded 86 mg (89%) of **3.45** as a white solid.

Rf: 0.61, 25% EtOAc/hexanes. ^{1}H NMR (600 MHz): δ 7.20 (d, 1H, *J* = 1.6 Hz), 7.17 (d, 1H, *J* = 1.5 Hz), 2.86 (m, 1H), 2.58 (m, 1H), 2.34 (m, 2H), 2.31 (m, 1H), 1.91 (m, 1H), 1.78 (m, 1H), 1.35 (ddd, 1H, *J* = 24, 11, 2 Hz), 1.21 (m, 1H and d, 3H, *J* = 6.7 Hz), 1.05 (d, 3H, *J* = 6.8 Hz). ^{13}C NMR (150 MHz): δ 137.67, 137.30, 128.42, 123.11, 119.22, 36.49, 34.31, 32.09, 27.61, 23.91, 22.15, 21.02, 15.50. IR: 3104, 2942, 2243, 1541, 1457, 1328, 1266, 1122, 1035 cm $^{-1}$. HRMS (EI) calcd for $C_{13}H_{17}NO$ ($[M]^+$) 203.1310, found 203.1303. $[\alpha]^{25}_D$ +41 (*c* = 0.33, $CHCl_3$).



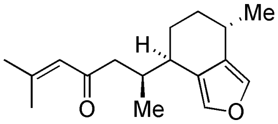
Carboxylic acid 3.46. To a solution of 45 mg (0.22 mmol) **3.45** in 4.0 mL ethylene glycol and 1.0 mL H_2O in a sealed tube was added 0.99 g (17.6 mmol) potassium hydroxide (KOH). The reaction mixture was heated to 130 °C for 2 hours and after 2 hours, the light yellow solution was cooled to room temperature, then diluted with H_2O and extracted with EtOAc. The organic layer was extracted once more with H_2O and the combined aqueous layers were then acidified with 2M HCl until the pH was adjusted to 4. The resulting aqueous solution was then extracted once with EtOAc and the resulting organic layer was dried, filtered, and evaporated. Filtration through a silica pad (70% EtOAc/hexanes) afforded 44 mg (90%) of **3.46** as a pale yellow solid.

Rf: 0.10 ,25% EtOAc/hexanes. ^{1}H NMR (600 MHz): δ 7.20 (t, 1H, *J* = 1.6 Hz), 7.18 (t, 1H, *J* = 1.6 Hz), 2.76 (m, 1H), 2.57 (m, 1H), 2.44 (m, 2H), 2.33 (m, 1H), 1.90 (m, 1H), 1.78 (m, 1H), 1.36 (ddd, 1H, *J* = 25, 14, 2 Hz), 1.21 (m, 1H and d, 3H, *J* = 6.7 Hz), 0.94 (d, 3H, *J* = 6.9 Hz). ^{13}C NMR (150 MHz): δ 179.33, 137.45, 137.37, 128.60, 124.05, 39.04, 37.02, 33.52, 32.53, 27.79, 23.85, 21.01, 15.27. IR: 2928, 1708, 1538, 1455, 1413, 1291, 1129, 1044 cm $^{-1}$. HRMS (EI) calcd for $C_{13}H_{18}O_3$ ($[M]^+$) 222.1256, found 222.1245. $[\alpha]^{25}_D$ +67 (*c* = 0.33, $CHCl_3$).



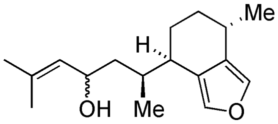
Weinreb Amide 3.47. A solution of 70 mg (0.32 mmol) **3.46** in 15 mL DCM (anhydrous) was cooled to 0 °C, and then 112 mg (0.69 mmol) of 1,1 carbonyldiimidazole (CDI) portionwise over 70 minutes, warming to room temperature after a few minutes. The yellow solution was then cooled to 0 °C, and then 61 mg (0.63 mmol) of N,O-Dimethylhydroxylamine hydrochloride was added. The solution was warmed to room temperature and after 40 minutes, another 30 mg (0.31 mmol) of N,O-Dimethylhydroxylamine hydrochloride was added. The reaction mixture was stirred for another 16 hours at room temperature, and then another 10 mg of N,O-Dimethylhydroxylamine hydrochloride was added and after 1.5 hours, the mixture was quenched with NH_4Cl (saturated) and diluted with DCM. The layers were separated and the organic layer was washed with $NaHCO_3$ (saturated), then NaCl (saturated), dried, filtered, and evaporated. Flash column chromatography (30% EtOAc/hexanes) afforded 79 mg (94%) of **3.47** as a clear, colorless oil.

Rf: 0.59, 40% EtOAc/hexanes. ^{1}H NMR (600 MHz): δ 7.21 (t, 1H, *J* = 1.6 Hz), 7.17 (t, 1H, *J* = 1.6 Hz), 3.68 (s, 3H), 3.19 (s, 3H), 2.72 (m, 1H), 2.58 (m, 1H), 2.56 (m, 1H), 2.44 (m, 2H), 1.90 (m, 1H), 1.78 (m, 1H), 1.37 (ddd, 1H, *J* = 25, 13, 2 Hz), 1.21 (m, 1H and d, 3H, *J* = 6.7 Hz), 0.90 (d, 3H, *J* = 6.8 Hz). ^{13}C NMR (150 MHz): δ 174.07, 137.53, 137.22, 128.63, 124.43, 61.19, 37.36, 36.43, 33.04, 32.69, 27.85, 24.07, 21.05, 15.41. IR: 2929, 1666, 1455, 1378, 1177, 1128, 1042 cm $^{-1}$. HRMS (EI) calcd for $C_{15}H_{23}NO_3$ ($[M]^+$) 265.1678, found 265.1674. $[\alpha]^{25}_D$ +10 (*c* = 0.60, $CHCl_3$).



Enone 3.48. A solution of 200 mg **3.47** (0.750 mmol) in 50 mL THF was cooled to 0 °C and then 4.0 mL (3.0 mmol) of a 0.5 M 2-methyl-1-propenylmagnesiumbromide solution in THF was added dropwise. The reaction mixture was warmed to room temperature for 10 minutes, then quenched with a saturated aqueous solution of $NaHCO_3$. The layers were separated and the organic layer was washed with NaCl (saturated), dried, filtered, and evaporated. Flash column chromatography (5% EtOAc/hexanes) afforded 169 mg (86%) of **3.48** as a clear, colorless oil that was unstable in $CHCl_3$ and $CDCl_3$.

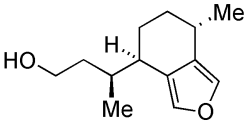
Rf: 0.59, 10% EtOAc/hexanes. ^{1}H NMR (600 MHz, C_6D_6): δ 7.10 (t, 1H, *J* = 1.6 Hz), 7.09 (t, 1H, *J* = 1.1 Hz), 5.83 (quintet, 1H, *J* = 1.3 Hz), 2.63 (m, 1H), 2.57 (m, 1H), 2.40 (m, 1H), 2.27 (dd, 1H, *J* = 15.6, 5.5 Hz), 2.18 (dd, 1H, *J* = 15.8, 6.0 Hz), 2.14 (d, 3H, *J* = 1.1 Hz), 1.64 (m, 1H), 1.54 (m, 1H), 1.49 (d, 3H, *J* = 1.3 Hz), 1.18 (ddd, 1H, *J* = 24.6, 12.9, 2.4 Hz), 1.05 (m, 1H and d, 3H, *J* = 6.7 Hz), 0.90 (d, 3H, *J* = 6.8 Hz). ^{13}C NMR (100 MHz, C_6D_6): δ 198.65, 153.43, 137.56, 137.24, 128.39, 124.29, 124.05, 48.73, 37.21, 27.83, 26.82, 24.28, 20.74, 20.17, 15.47. IR: 2928, 2367, 1686, 1633, 1447, 1377, 1266, 1129, 1043 cm $^{-1}$. HRMS (EI) calcd for $C_{17}H_{23}O_2$ ($[M - H]^-$) 259.1698, found 259.1704.



Allylic alcohol 3.44. A solution of 167 mg (0.640 mmol) **3.48** in 35.0 mL DCM (anhydrous) was cooled to −40 °C and then 8.0 mL (3.2 mmol) of a freshly prepared 0.4 M $CeCl_3$ solution in MeOH was added dropwise. The reaction mixture was stirred for 10 minutes before 121 mg (3.20 mmol) of $NaBH_4$ was added, and then the mixture was allowed to gradually warm to −25 °C over 50 minutes at which point it was quenched slowly with a saturated aqueous solution of $NaHCO_3$. The layers were separated and the organic layer was dried, filtered, and evaporated. Flash column chromatography (10%

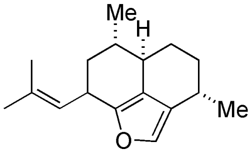
EtOAc/hexanes) afforded 159 mg (95%) of **3.44** as a clear, colorless oil that was a mixture of diastereomers.

Rf: 0.21, 10% EtOAc/hexanes. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.16 (t, 1 H, *J* = 1.6 Hz), 7.14 (dd, 1 H, *J* = 3.4, 1.7 Hz), 5.19 (m, 0.6H), 5.18 (m, 0.4H), 4.47 (m, 1H), 2.76 (m, 0.4H), 2.67 (m, 0.6H), 2.56 (m, 1H), 2.07 (m, 0.6H), 1.88 (m, 1.4H), 1.73 (2 sets of dd, 6H, *J* = 11, 1.3 Hz), 1.62 (br m, 1.4H), 1.59 (m, 0.6H), 1.33 (m, 2H), 1.25 (t, 1H *J* = 3.4 Hz), 1.20 (d, 3H, *J* = 6.7 Hz), 1.15 (m, 1H), 0.85 (2 sets of d, 3H, *J* = 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.56, 134.77, 67.14, 66.74, 42.37, 42.33, 37.68, 37.38, 32.94, 32.88, 32.57, 27.94, 25.81, 25.75, 23.82, 23.74, 21.02, 18.24, 18.16, 15.69, 15.04. IR: 3358, 2959, 2361, 1672, 1538, 1449, 1376, 1265, 1129, 1044 cm $^{-1}$. HRMS (EI) calcd for $C_{17}H_{26}O_2$ ($[M]^+$) 262.1933, found 262.1926.



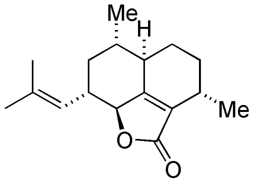
Alcohol 3.50. A solution of 12 mg (0.054 mmol) **3.46** in 4 mL THF was cooled to 0 °C, and then 6.0 mg (0.16 mmol) of LAH was added. The reaction mixture was then warmed to room temperature for 45 minutes, then quenched with H_2O and a 10% aqueous solution of NaOH. The layers were separated and the aqueous layer was dried, filtered, and evaporated. The crude material was purified using flash column chromatography (25% EtOAc/hexanes) to afford 8 mg (71%) of **3.50** as a clear, colorless oil.

Rf: 0.19, 25% EtOAc/Hexanes. ^{1}H NMR (600 MHz): δ 7.18 (t, 1H, *J* = 1.5 Hz), 7.15 (t, 1H, *J* = 1.6 Hz), 3.75 (m, 2H), 2.68 (m, 1H), 2.57 (m, 1H), 2.04 (m, 1H), 1.90 (m, 1H), 1.76 (m, 1H), 1.69 (m, 1H), 1.55 (m, 2H), 1.32 (m, 1H), 1.20 (d, 3H, *J* = 6.0 Hz), 1.18 (m, 1H), 0.86 (d, 3H, *J* = 6.9 Hz). ^{13}C NMR (150 MHz): δ 137.28, 137.23, 128.77, 124.80, 61.47, 37.51, 37.42, 32.81, 27.91, 23.74, 21.03, 15.10.



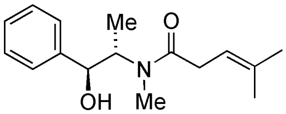
Furan 3.51. To a solution of 22 mg **3.44** (0.084 mmol) in 6 mL $MeNO_2$ was added 1.5 mL of a freshly prepared solution of 1 mg / mL $La(OTf)_3$ in $MeNO_2$ over 5 minutes. The pink reaction mixture was stirred for 15 minutes until it was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc. The layers were separated and the organic layer was washed with $NaHCO_3$ (saturated) until no pink color remained. It was then washed with NaCl (saturated), dried, filtered, and evaporated. Flash column chromatography (0.1 to 2 to 5% EtOAc/hexanes) afforded 14 mg (70%) of **3.51** as a clear, colorless oil that was a 0.4:0.6 mixture of diastereomers at the position of ring closure.

Rf: 0.48, hexanes. ^{1}H NMR (400 MHz, C_6D_6): δ 7.08 (dd, 0.4H, J = 2.6, 0.8 Hz), 7.07 (dd, 0.6 H, J = 2.5, 1.1 Hz), 5.31 (d of quintets, 0.4H, J = 13.8, 1.4 Hz), 5.23 (d of quintets, 0.6H, J = 13.7, 1.4 Hz), 3.73 (m, 1H), 2.57 (m, 1H), 1.96 (br m, 0.6H), 1.83 (m, 2.4H), 1.70 (m, 6H), 1.47 (m, 0.6H), 1.34 (m, 1H), 1.30 (m, 1.4H), 1.16 (doublet with shoulder, 3H, J = 10.2 Hz), 1.10 (br m, 2H), 0.91 (d with shoulder, 3H, J = 9.5 Hz). ^{13}C NMR (100 MHz, C_6D_6): δ 150.30, 136.52, 136.42, 132.44, 120.98, 109.90, 40.86, 40.28, 39.99, 39.82, 36.10, 35.42, 33.74, 33.63, 33.22, 32.19, 28.33, 28.26, 27.37, 25.56, 25.43, 21.72, 18.16, 18.03, 17.77, 17.66. IR: 2955, 2361, 1650, 1550, 1452, 1375, 1309, 1256, 1130, 1088 cm $^{-1}$. HRMS (EI) calcd for $C_{17}H_{24}O$ ($[M]^+$) 244.1827, found 244.1839.



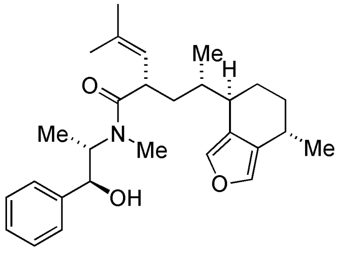
Amphilectolide (**3.9**). To a solution of 30 mg (0.12 mmol) **3.51** in 6 mL DCM was added 6 mg (0.006 mmol) Rose Bengal, 3 mL MeOH, and 0.10 mL (0.60 mmol) DIEA. The solution was cooled to – 78 °C and irradiated with a UV lamp (Replux Belgium RL 160W, 225-235 Volts). O_2 was bubbled through for 15 minutes, then the reaction mixture was quickly evaporated at 30 °C, taken up in 6 mL EtOH; 23 mg (0.60 mmol) of $NaBH_4$ was then added. After 10 minutes, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$, diluted with Et_2O, washed with NaCl (saturated), dried, filtered, and evaporated. Flash column chromatography (6% Et_2O/hexanes followed by 5% EtOAc/hexanes) afforded 3.3 mg (17% or 25%, depending on which diastereomer of the starting material was predominant) of amphilectolide (**3.9**) as a white solid.

^{1}H NMR isolation	^{1}HNMR current	^{13}C NMR isolation	^{13}C NMR current
5.07, br dd (1.2, 9.0)	5.07, dt (1.4, 9.0)	172.9	172.93
4.35, d (10.5)	4.35, d (9.0)	165.0	165.05
2.42, m	2.42, m	134.5	134.53
2.23, m	2.24, m	128.1	128.11
2.16, m	2.17, m	125.2	125.15
2.01, m	2.05, m	83.6	83.64
1.86, m	1.91, m	44.1	44.11
1.72, br s	1.72, d (1.44)	41.0	40.95
1.62, br d (0.9)	1.63 d (1.38)	39.5	39.51
1.56, m	1.56, m	38.4	38.36
1.23, d (7.2)	1.23, d (8.0)	31.2	31.19
1.20, m	1.20, m	27.3	27.32
1.13, m	1.13, m	27.2	27.17
1.11, m	1.11, m	25.8	25.85
1.06, m	1.06, m	19.1	19.12
1.04, d (7.2)	1.04, d (6.5)	18.3	18.33
		17.8	17.83



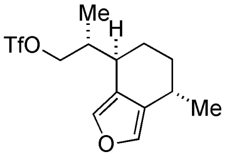
Pseudoephedrine substrate 3.55. A solution of 1.16 g (10.2 mmol) **3.58** [37] and 2.5 mL (18 mmol) triethylamine (TEA) in 20 mL MeCN was cooled to 0 °C, and then 1.9 mL (15 mmol) of pivaloyl chloride was added. To the resulting white slurry was added 5 mL THF to enhance solubility. The reaction mixture turned yellow, and after 20 minutes, a solution of 1.70 g (10.2 mmol) of (+) pseudoephedrine (**3.55**) and 1.4 mL (10.2 mmol) of TEA in 15 mL THF was added. The reaction mixture was warmed to room temperature and stirred for another 75 minutes, at which point it was quenched with water. The volatiles were removed by rotary evaporation, and then a solution of NaOH (0.5N) was added. This solution was extracted with a mixture of 10% methanol in DCM twice, and the resulting organic layer was washed with a 1N NaOH solution. The organic layer was then dried, filtered, and evaporated and the crude oil purified by flash column chromatography (60% EtOAc/hexanes) to provide 2.04 g (76%) **3.55** as a white solid that was a 1:2 mixture of rotamers.

Rf: 0.31, 60% EtOAc/Hexanes. ^{1}H NMR (300 MHz) of major rotamer: δ 7.32 (m, 5H), 5.21 (t, 1H, J = 7.1 Hz), 4.60 (t, 1H, J = 7.7 Hz), 4.48 (br s, 1H), 4.39 (m, 1H), 3.03 (d, 2H, J = 6.7 Hz), 2.79 (s, 3H), 1.74 (s, 3H), 1.63 (s, 3H), 1.13 (d, 3H, J = 7.0 Hz). ^{13}C NMR (75 MHz) of major rotamer: δ 174.35, 142.48, 134.92, 128.30, 127.56, 126.38, 116.58, 75.42, 58.62, 34.56, 33.17, 25.69, 18.06, 14.39. IR: 3373, 2916, 2363, 1633, 1453, 1403, 1262, 1115 cm^{-1}. HRMS (EI) calcd for $C_{16}H_{24}NO_2$ ($[M + H]^+$) 262.1807, found 262.1802. $[\alpha]^{25}_D$ +116 (c = 0.38, $CHCl_3$).



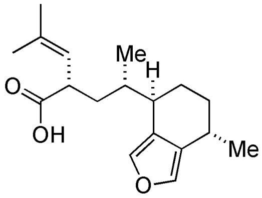
Myers alkylation product 3.60. A suspension of 0.940 mL (6.68 mmol) DIA and 992 mg (23.4 mmol) LiCl in 16mL THF was cooled to −78 °C, and then 2.68 mL (6.68 mmol) of n-BuLi (2.5 M in hexanes) was added dropwise. After 5 minutes, the reaction mixture was warmed to 0 °C for 5 minutes, and then recooled to −78 °C. A solution of 873 mg (3.34 mmol) of chiral auxiliary **3.55** in 20 mL THF was then added dropwise. The reaction mixture turned bright yellow. After an hour of stirring at room temperature, the reaction mixture was warmed to 0 °C for 15 minutes and became an orange solution during this process. The reaction mixture was then warmed to room temperature for 4 minutes, recooled to 0 °C, and a solution of 507 mg (1.67 mmol) of iodide **3.38** was added dropwise. The reaction mixture was warmed to room temperature and became a bright yellow solution. The flask was covered with foil to protect it from light. After 19 hours at room temperature, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ and diluted with Et_2O. The layers were separated, and the organic layer was washed with NaCl (saturated). The organic layer was then dried, filtered, and evaporated and the crude oil purified by flash column chromatography (1 to 15 to 40 to 60% EtOAc/hexanes) to provide 483 mg (66%) **3.60** as a dark yellow oil that was a 2:1 mixture of rotamers. Excess chiral auxiliary **3.55** was also recovered (430 mg).

Rf: 0.39, 40% EtOAc/Hexanes. ^{1}H NMR (600 MHz) of major rotamer: δ 7.35 (m, 5H), 7.18 (s, 1H), 7.12 (s, 1H), 5.10 (d, 1H, J = 9.7 Hz), 4.64 (m, 1H), 4.38 (br s, 1H), 3.78 (m, 1H), 3.41 (m, 1H), 2.81 (s, 3H), 2.67 (m, 1H), 2.58 (m, 1H), 1.90 (m, 2H), 1.74 (m, 2H), 1.66 (d, 1H, J = 4.5 Hz), 1.37 (m, 2H), 1.20 (m, 9H), 0.88 (m, 3H), 0.81 (d, 3H, J = 6.9 Hz). ^{13}C NMR (150 MHz) of major rotamer: δ 176.89, 142.52, 137.22, 137.16, 133.34, 128.84, 128.70, 128.25, 127.47, 126.77, 126.23, 124.80, 123.66, 76.50, 57.87, 40.93, 37.38, 37.33, 33.85, 32.89, 27.99, 27.94, 25.70, 23.77, 21.00, 18.15, 15.63, 14.40. IR: 3376, 2929, 2871, 2361, 1628, 1452, 1405, 1264, 1127, 1044 cm^{-1}. HRMS (EI) calcd for $C_{28}H_{39}NO_3$ ($[M]^+$) 437.2930, found 437.2931. $[\alpha]^{25}_D$ +117 (c = 0.40, $CHCl_3$).



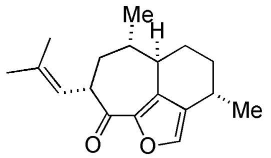
Triflate 3.61. To a solution of 20 mg (0.10 mmol) **3.12** and 0.010 mL (0.124 mmol) pyridine in 3 mL DCM cooled to −78 °C was added 0.020 mL (0.124 mmol) Tf_2O, upon which a white precipitate was observed. The solution then became clear and colorless and was stirred for 3.5 hours, and then it was warmed to −20 °C and 11 mL of THF was added. After 10 minutes, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$. The layers were separated and the organic layer was dried, filtered, and evaporated. The crude oil was purified by flash column chromatography (10 to 25% EtOAc/hexanes) to provide 17 mg (53%, 72% borsm) of triflate **3.61** as a clear, colorless oil.

Rf: 0.68, 25% EtOAc/Hexanes. ^{1}H NMR (600 MHz): δ 7.22 (t, 1H, J = 1.6 Hz), 7.18 (t, 1H, J = 1.6 Hz), 3.56 (dd, 1H, J = 9.8, 7.2 Hz) , 3.53 (dd, 1H, J = 9.8, 7.2 Hz), 2.92 (m, 1H), 2.61 (m, 1H), 2.43 (m, 1H), 1.93 (m, 1H), 1.78 (m, 1H), 1.42 (m, 1H), 1.22 (d, 3H, J = 6.7 Hz), 1.00 (d, 3H, J = 7.0 Hz).



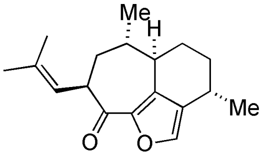
Acid 3.62. To a solution of 483 mg (1.10 mmol) **3.60** was added 11.0 mL (11.0 mmol) of a 1.0M solution of tetrabutylammonium hydroxide (Bu_4NOH) in methanol, 10 mL H_2O, and 3.0 mL *t*-BuOH. The solution was stirred at 100 °C; firstly the MeOH was evaporated under a stream of N_2, then the solution was stirred for another 3 hours, then 90 °C for 20 hours. The reaction mixture was then partitioned between a 0.5N solution of NaOH and ethyl acetate. The layers were separated, and the aqueous layer was extracted with EtOAc twice. The combined organic layers were then dried, filtered, and evaporated. The crude material was purified using flash column chromatography (40% EtOAc/hexanes and 1% AcOH) and the fractions containing product were washed with $NaHCO_3$ (saturated), then dried, filtered, and evaporated to afford 311 mg (97%) of **3.62** as a pale yellow oil.

Rf: 0.46, 60% EtOAc/Hexanes. ^{1}H NMR (600 MHz): δ 7.16 (t, 1H, *J* = 1.6 Hz), 7.09 (t, 1H, *J* = 1.5 Hz), 5.13 (d, 1H *J* = 9.5 Hz), 3.38 (m, 1H), 2.67 (m, 1H), 2.55 (m, 2H), 1.87 (m, 3H), 1.74 (d with shoulder, 4H *J* = 1.3 Hz), 1.69 (d, 3H *J* = 1.4 Hz), 1.43 (m, 1H), 1.31 (m, 1H), 1.20 (d, 3H, *J* = 6.7 Hz), 1.17 (m, 1H), 0.86 (d, 3H, *J* = 6.7 Hz). ^{13}C NMR (150 MHz): δ 181.04, 137.22, 137.18, 135.51, 128.79, 124.71, 122.24, 42.85, 37.22, 36.70, 33.98, 32.85, 27.93, 25.77, 23.54, 20.99, 18.21, 15.52. IR: 2959, 2926, 1710, 1448, 1377, 1292, 1130, 1044 cm^{-1}. HRMS (EI) calcd for $C_{18}H_{26}O_3$ ($[M]^+$) 290.1882, found 290.1883. $[\alpha]^{25}_D$ +78 (*c* = 0.63, $CHCl_3$).

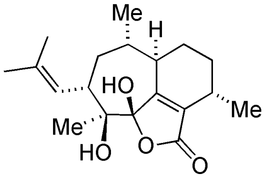


Friedel-Crafts product 3.54a. A solution of 20 mg (0.069 mmol) **3.62** in 20 mL DCM was cooled to 0 °C, and then 24 μL (0.17 mmol) of trifluoroacetic anhydride (TFAA) was added. The reaction mixture was warmed to room temperature, and after 10 minutes, 0.17 mL of a 1.0 M solution of $ZnCl_2$ in THF was added dropwise. The pale yellow reaction mixture was stirred at room temperature for 30 minutes, then warmed to 40 °C for one hour. The reaction mixture was then quenched with a 1.0 N aqueous solution of HCl, the layers were separated, and the organic layer was subsequently washed with a saturated aqueous solution of $NaHCO_3$, then NaCl (saturated). The organic layers were then dried, filtered, and evaporated. The crude material was purified using flash column chromatography (10% EtOAc/hexanes) to afford 14 mg (71%) of **3.54a** as a crystalline white solid.

Rf: 0.58, 25% EtOAc/Hexanes. ^{1}H NMR (600 MHz): δ 7.38 (d, 1H, *J* = 1.6 Hz), 5.28 (dm, 1H *J* = 8.7 Hz), 3.47 (m, 1H), 2.65 (m, 1H), 2.35 (m, 1H), 2.13 (m, 1H), 2.03 (m, 1H), 1.86 (m, 3H), 1.78 (s, 3H), 1.65 (s, 3H), 1.24 (m with d, 5H *J* = 6.6 Hz), 1.13 (d, 3H, *J* = 6.1 Hz). ^{13}C NMR (150 MHz): δ 190.36, 147.51, 142.16, 134.31, 133.74, 129.52, 123.73, 50.20, 43.61, 41.37, 38.66, 32.90, 28.68, 27.25, 25.78, 21.59, 21.23, 18.12. IR: 2955, 2923, 1650, 1525, 1442, 1400, 1284 cm^{-1}. HRMS (EI) calcd for $C_{18}H_{24}O_2$ ($[M]^+$) 272.1776, found 272.1773. $[\alpha]^{25}_D$ +14 (*c* = 0.30, $CHCl_3$).



Epimerized Friedel-Crafts Product 3.54b. To a solution of 17 mg (0.062 mmol) **3.54a** in 2 mL $PhCH_3$ was added 0.028 mL DBU (0.19 mmol) and the solution was stirred at room temperature for 48 hours, then concentrated and purified by flash column chromatography (10% EtOAc/hexanes) to obtain 17 mg (quantitative) of **3.54b** as a yellow oil. ^{1}H NMR (600 MHz): δ 7.38 (d, 1H, *J* = 1.5 Hz), 5.43 (d, 1H *J* = 9.1 Hz), 3.45 (m, 1H), 2.62 (m, 1H), 2.46 (m, 1H), 2.22 (m, 1H), 1.94 (m, 2H), 1.79 (m, 1H), 1.77 (s, 3H), 1.62 (s, 3H), 1.61 (m, 1H), 1.30 (m, 1H), 1.24 (m with d, 4H *J* = 6.7 Hz), 1.12 (d, 3H, *J* = 6.7 Hz). ^{13}C NMR (150 MHz): δ 190.26, 147.79, 141.60, 135.49, 133.39, 130.02, 122.44, 46.13, 39.97, 39.61, 35.81, 32.61, 29.46, 27.68, 25.99, 20.76, 20.59, 18.11.



Sandresolide B (**3.7**). A solution of 13 mg (0.048 mmol) of a 1:1 mixture of **3.54a** and **3.54b** in 3 mL Et_2O was cooled to −78 °C, and then 0.12 mL (0.19 mmol) of a 1.6M solution of methyl lithium was added. After 10 minutes, the reaction mixtures was quenchend with a saturated aqueous solution of $NaHCO_3$ and diluted with Et_2O. The layers were separated, and the organic layer was dried, filtered, and evaporated. The resulting crude material was immediately dissolved in 3 mL DCM and 1.5 mL MeOH was added 2.5 mg (0.0024 mmol) Rose Bengal and 0.040 mL (0.24 mmol) DIEA. The solution was cooled to −78 °C and irradiated with a UV lamp (Replux Belgium RL 160W, 225-235 Volts). O_2 was bubbled through the solution for 10 minutes, then the reaction mixture was evaporated. The resulting crude mixture was purified by flash column chromatography (10 to 20 to 25% EtOAc/hexanes) and then once again with 30% Et_2O/hexanes to obtain < 1mg of sandresolide B (**3.7**) as a white solid. ^{1}H spectrum shown and ^{13}C spectrum were provided by Irina Albrecht from further investigation of singlet oxygen oxidation.

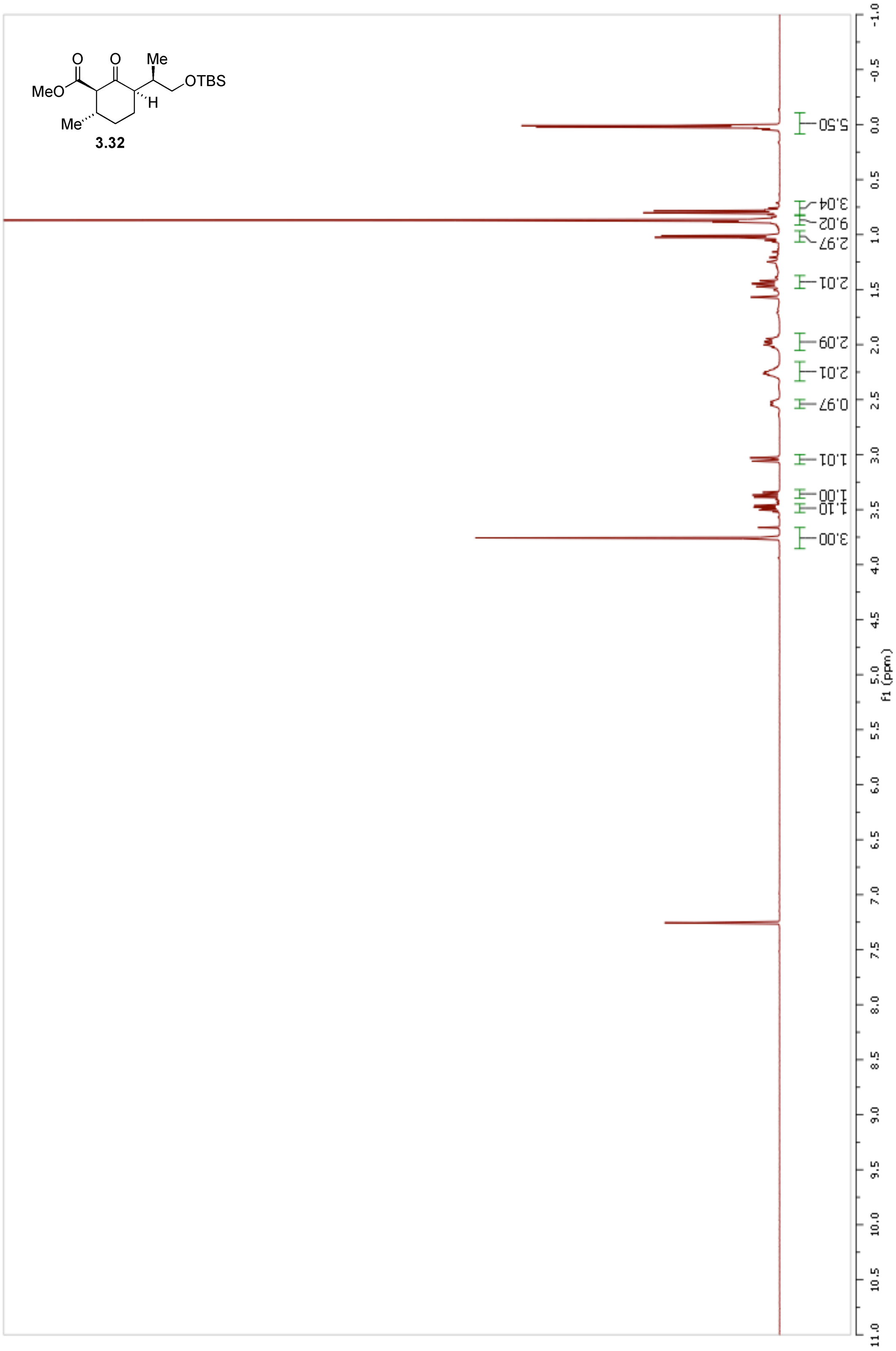
^{1}H NMR isolation	^{1}H NMR current	^{13}C NMR isolation	^{13}C NMR current
5.05 br d, (10.0 Hz)	5.05 br d (9.9 Hz)	170.8	170.7
3.02 ddd (10.0, 8.5, 3.9 Hz)	3.01 ddd (9.9, 8.2, 3.6 Hz)	162.0	161.9
2.53, m	2.55, m	134.8	134.7
2.18, m	2.19, m	132.4	132.4
2.08, m	2.08, m	124.3	124.3
2.00, m	2.00, m	108.2	108.2

2.00, m*	1.27, m	77.2	77.3
1.92, m	1.92, m	46.0	46.1
1.77, d, 1.2 Hz	1.77, d, (1.9 Hz)	43.9	43.9
1.72, d, 1.1 Hz	1.71, d, (1.4 Hz)	43.8	43.8
1.57, m	1.57 (m)	33.3	33.2
1.24, m	1.24 (m)	31.7	31.7
1.24, d, (6.5 Hz)	1.24 (d, 7.0 Hz)	28.2	28.2
1.18, m	1.18 (m)	27.5	27.5
1.12, s	1.11 (s)	26.2	26.3
0.94, d, (6.8 Hz)	0.95, d, (6.9 Hz)	21.0	21.0
		19.1	19.1
		18.4	18.5
		16.9	16.9

* Purported error in isolation paper (see discussion above). Correspondence with the author needs to be made for confirmation.

3.9. Appendix

Characterization data for 3.32, 3.33, 3.34, 3.35, 3.31, 3.12, 3.39, 3.38, 3.40, 3.45, 3.46, 3.47, 3.48, 3.44, 3.50, 3.51, 3.9, 3.55, 3.60, 3.61, 3.62, 3.54a, 3.7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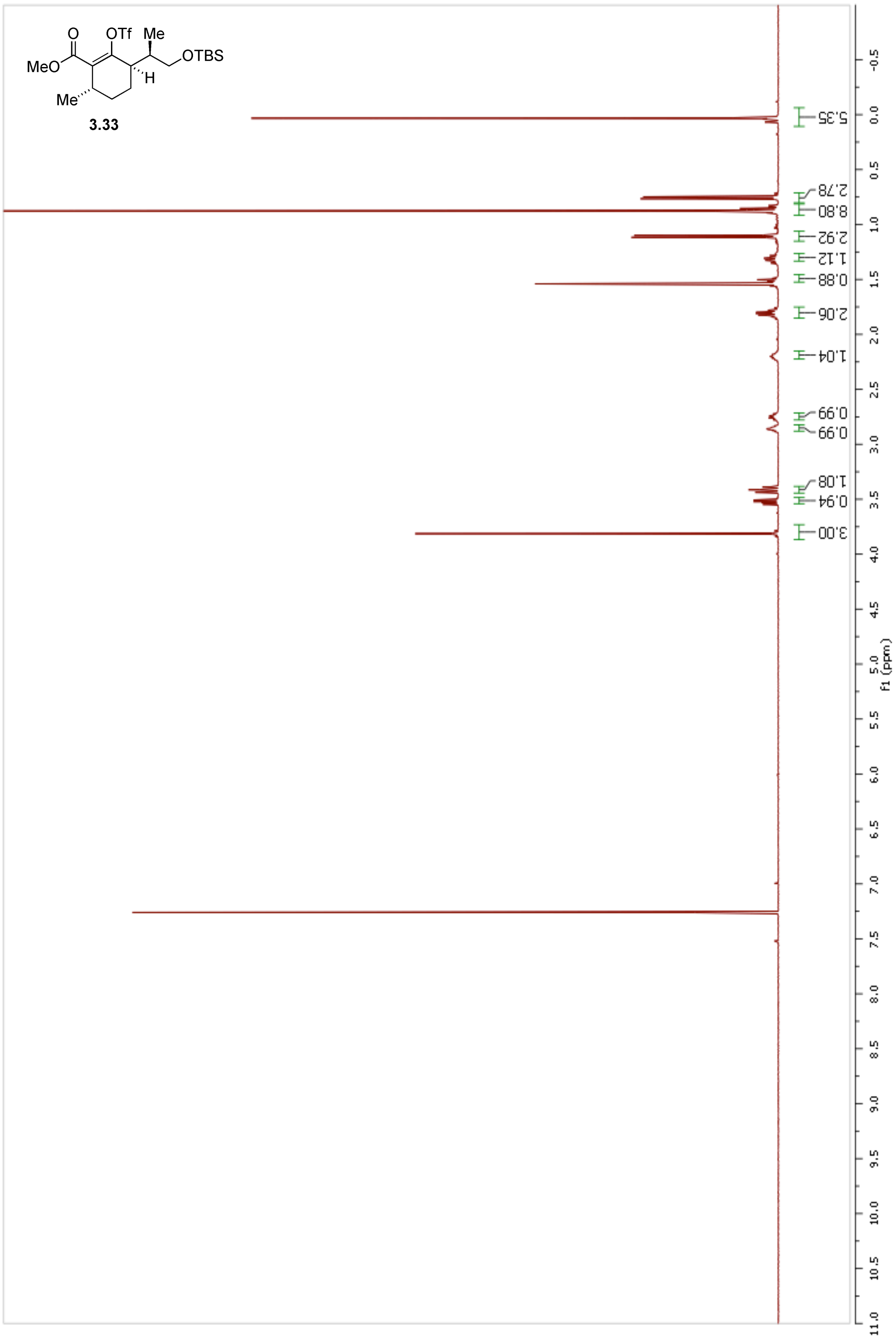
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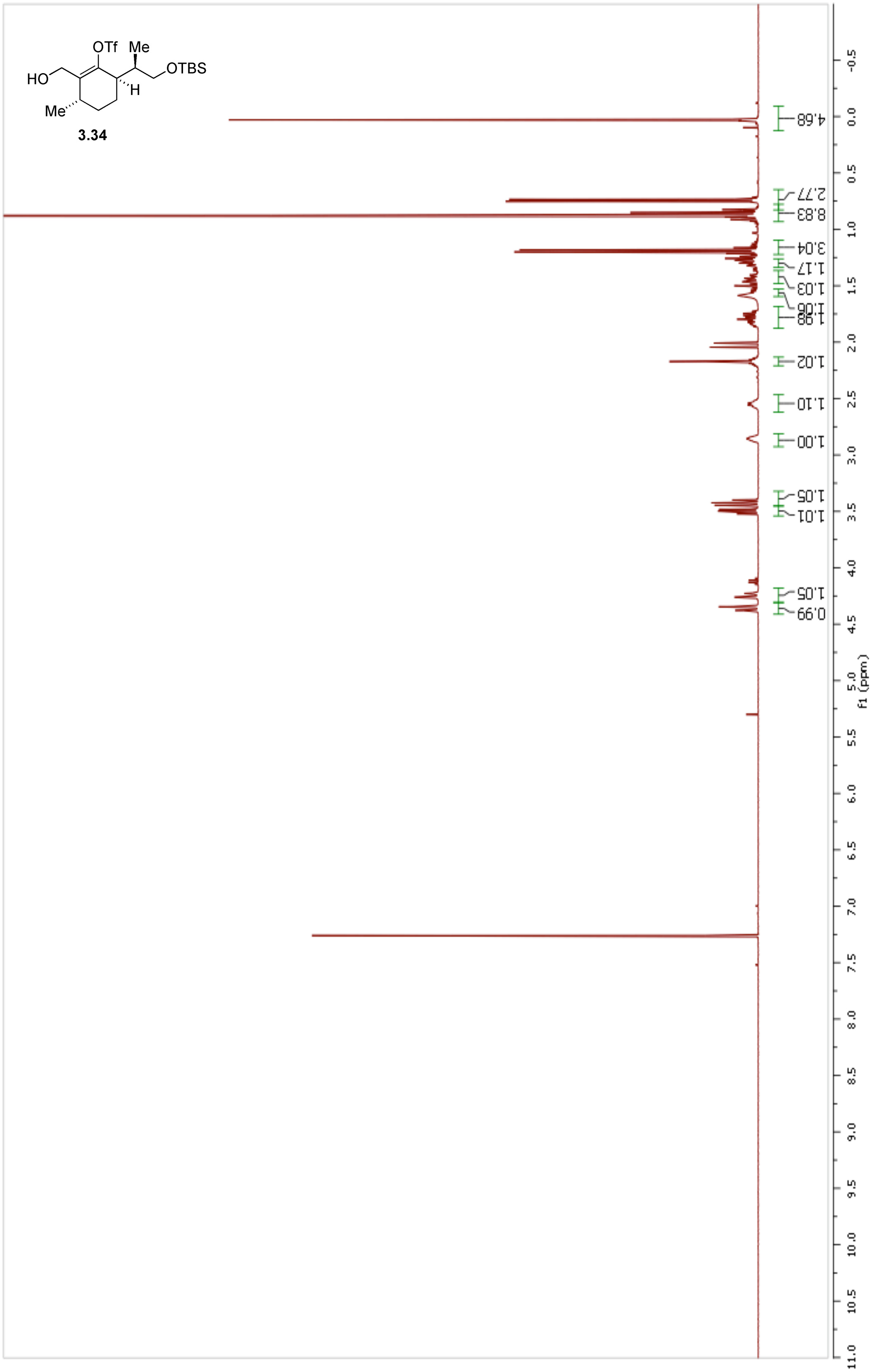
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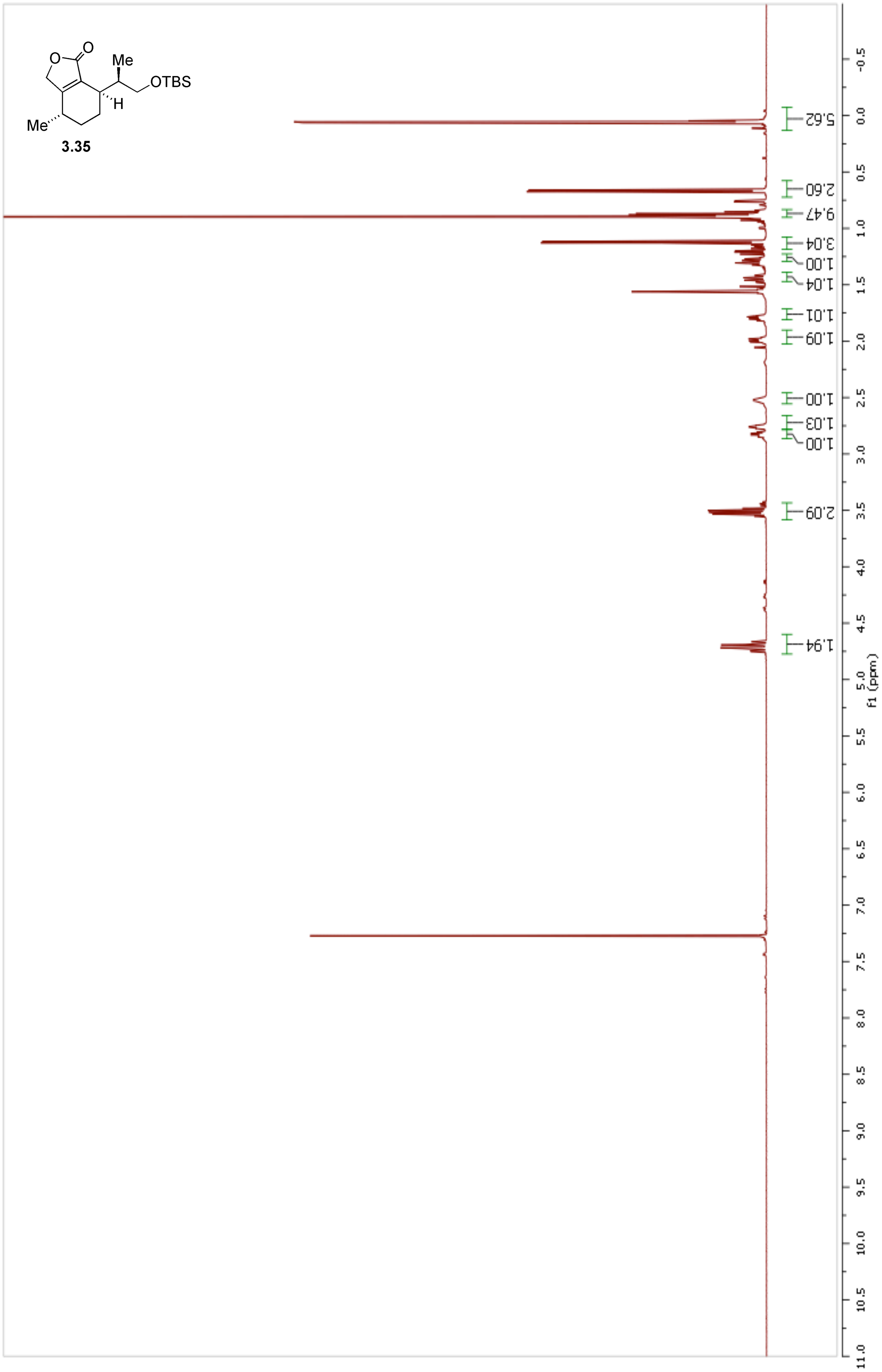

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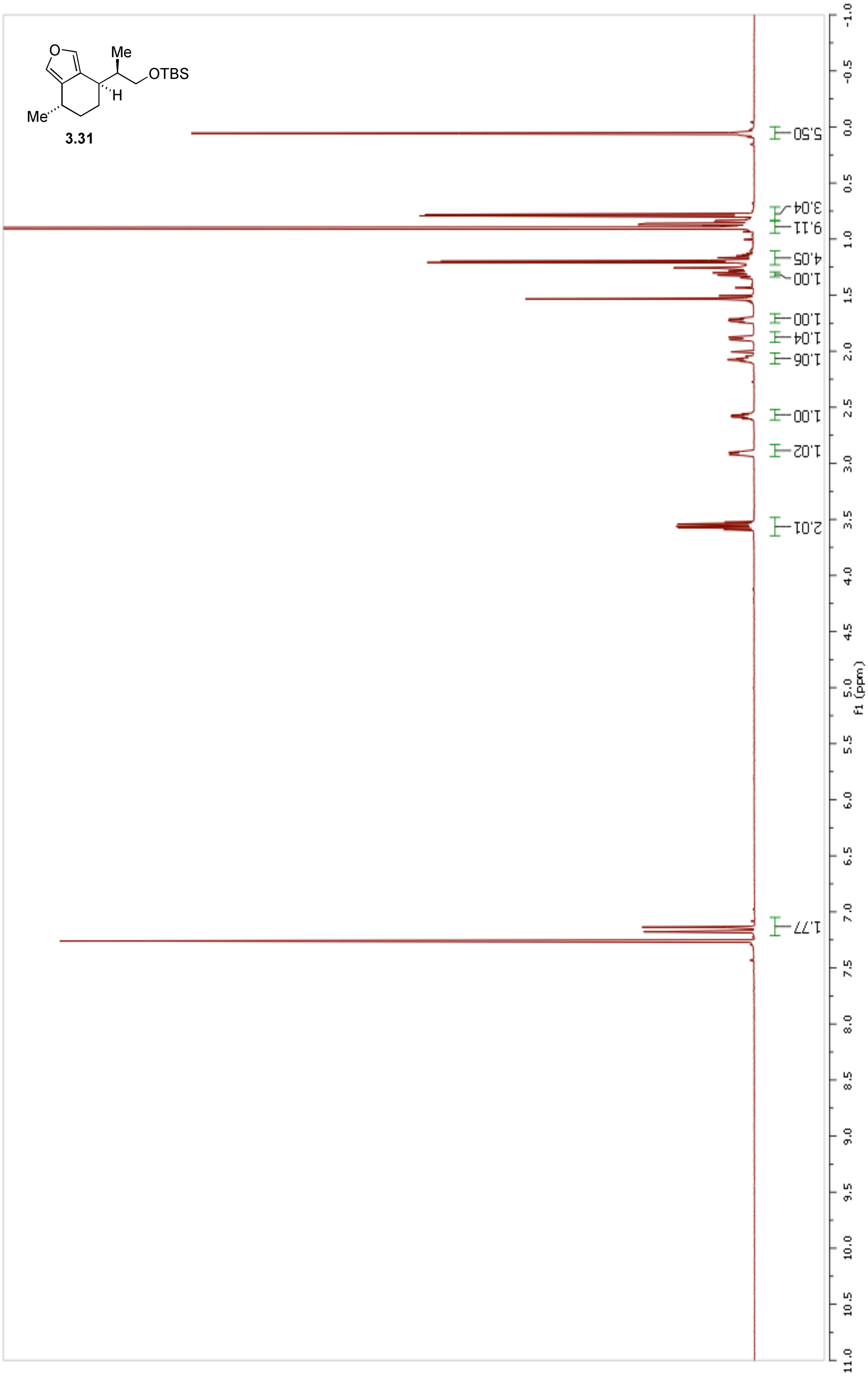

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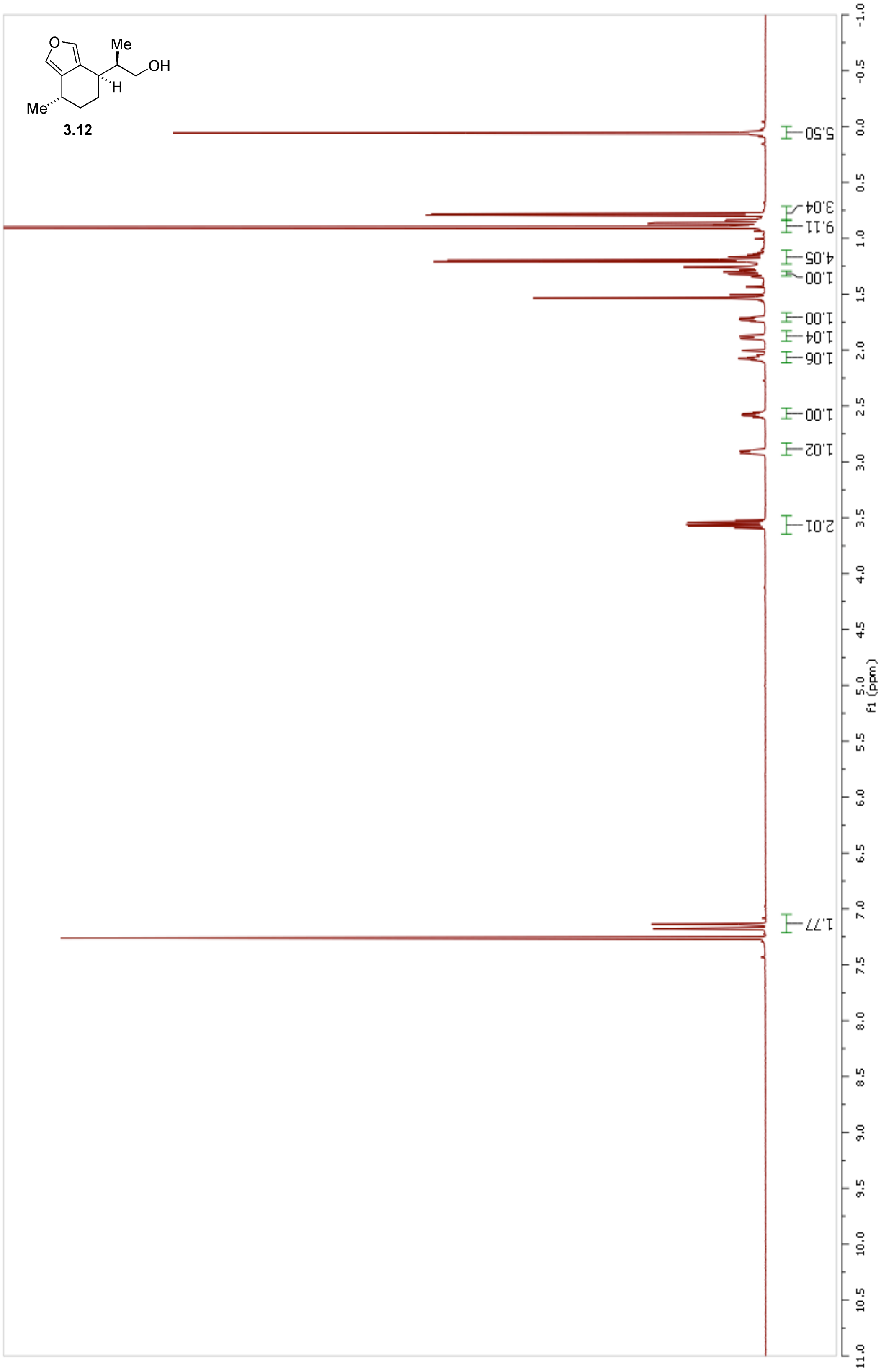
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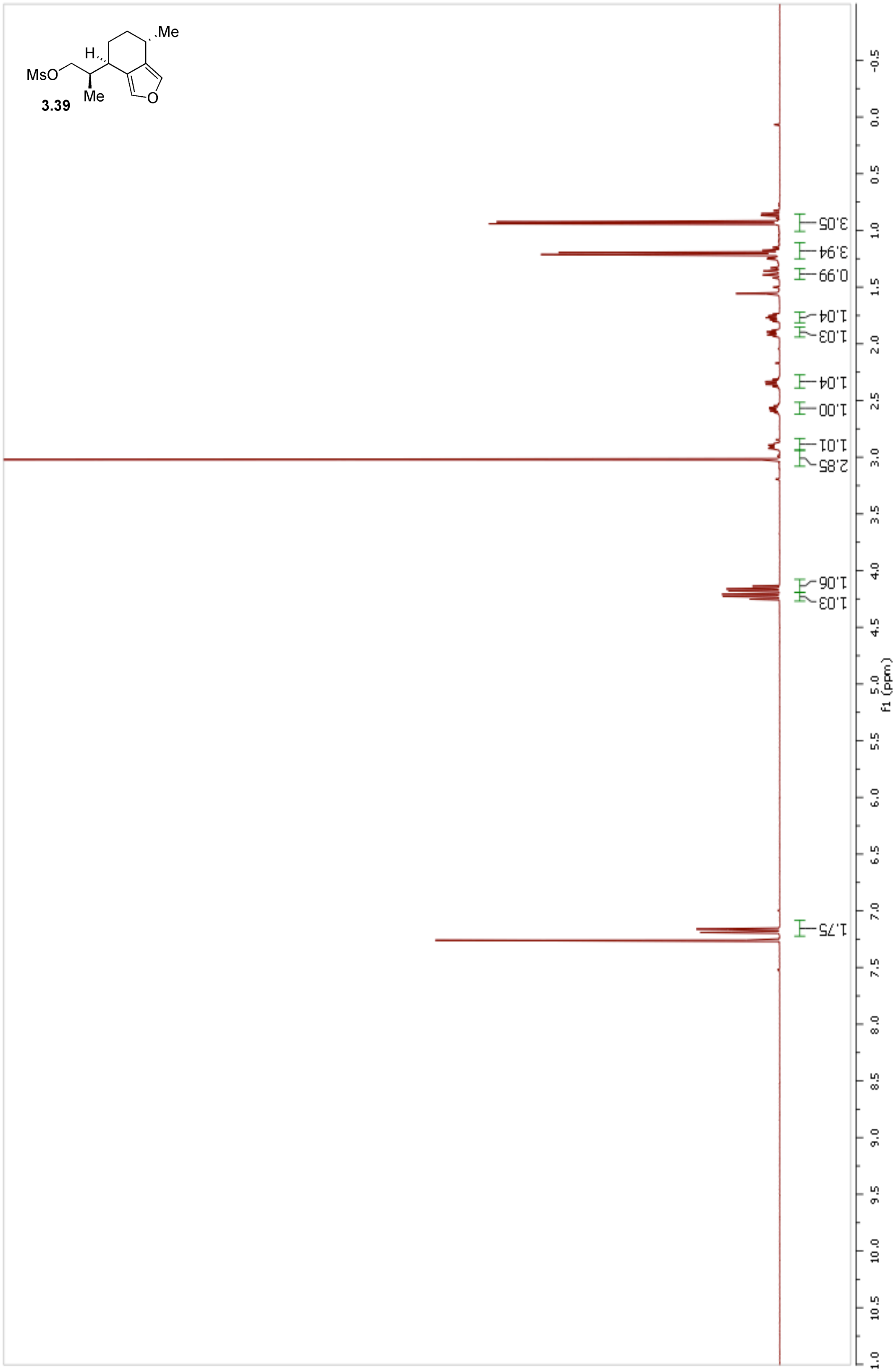
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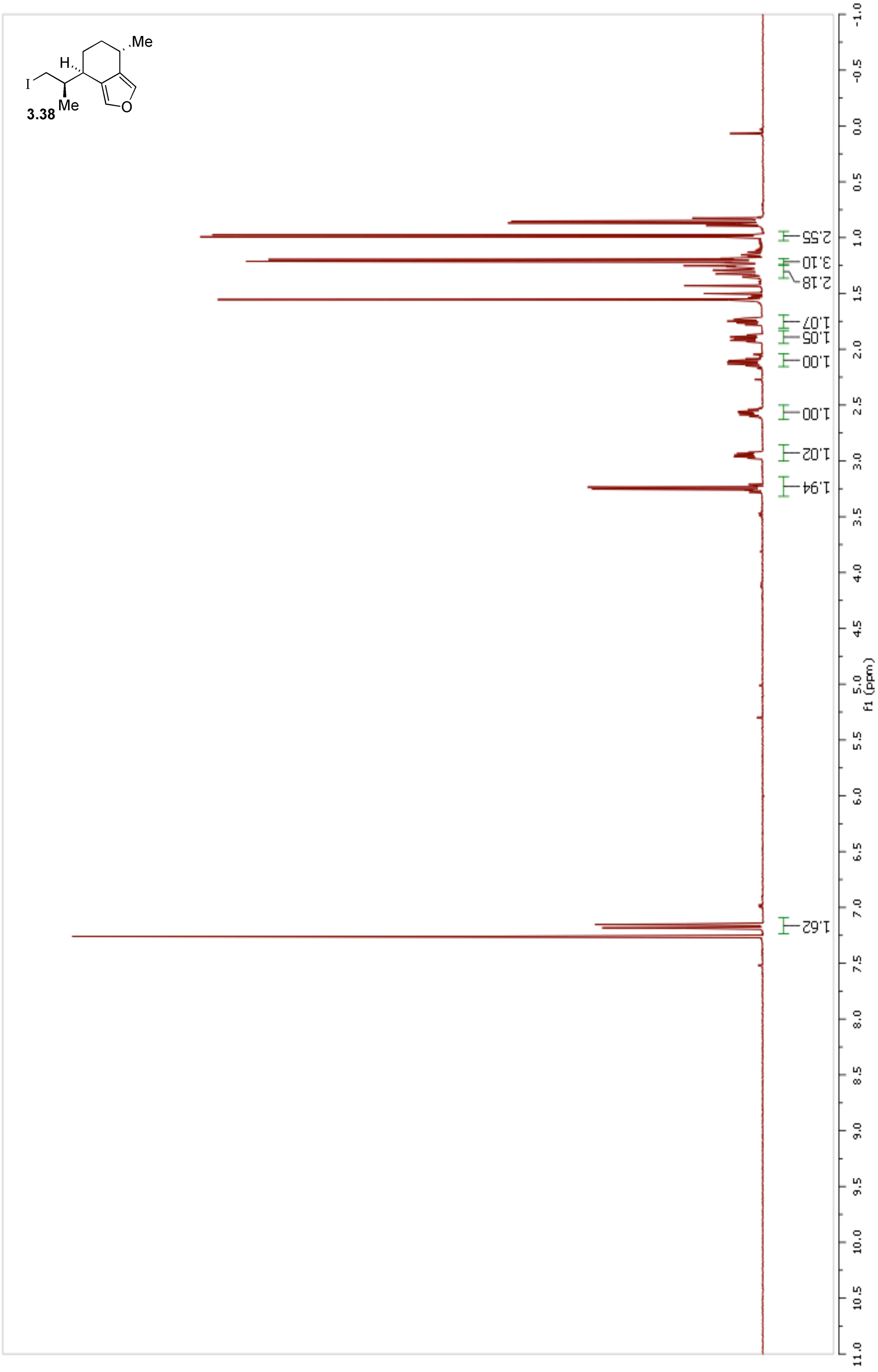
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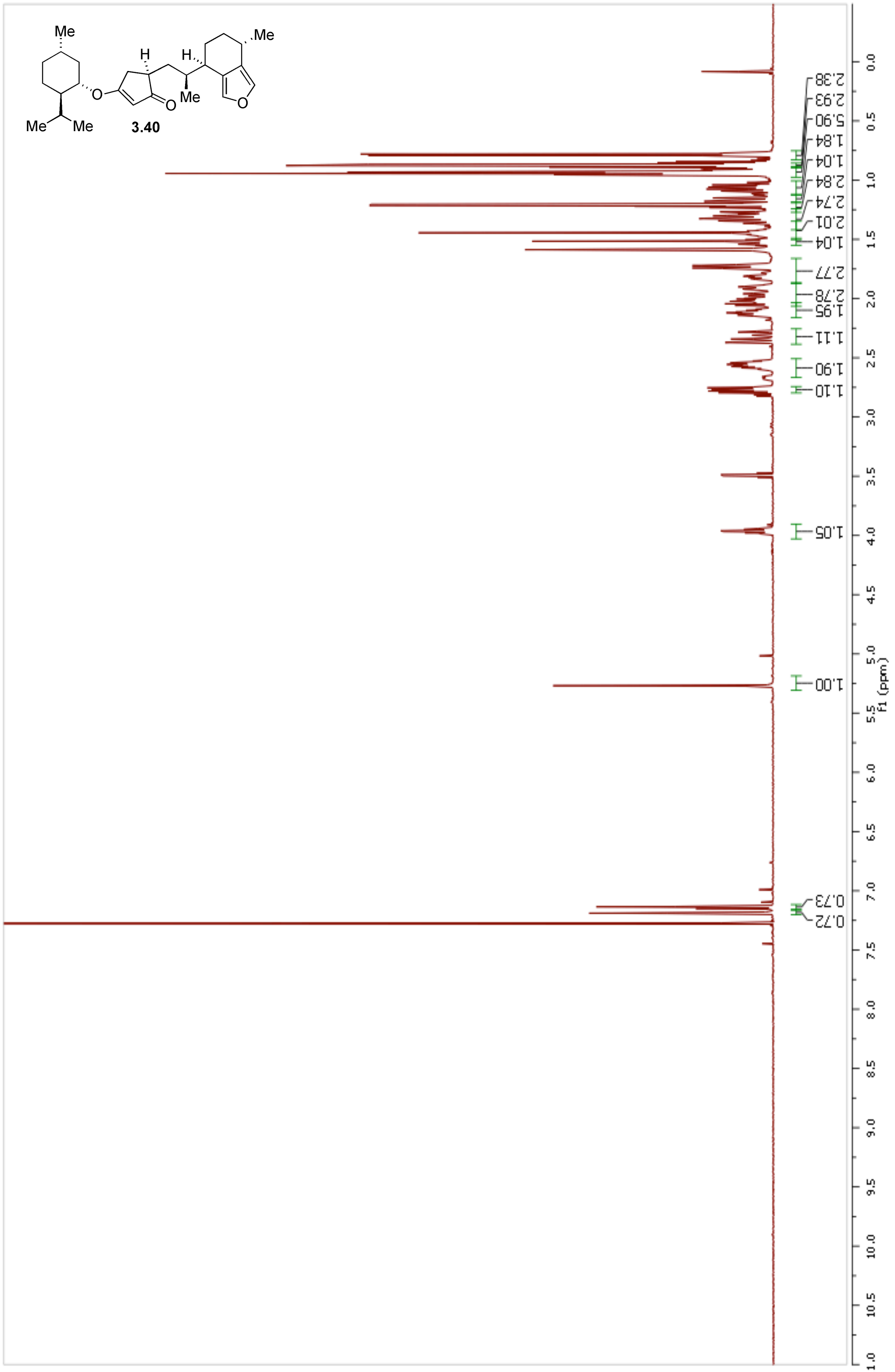
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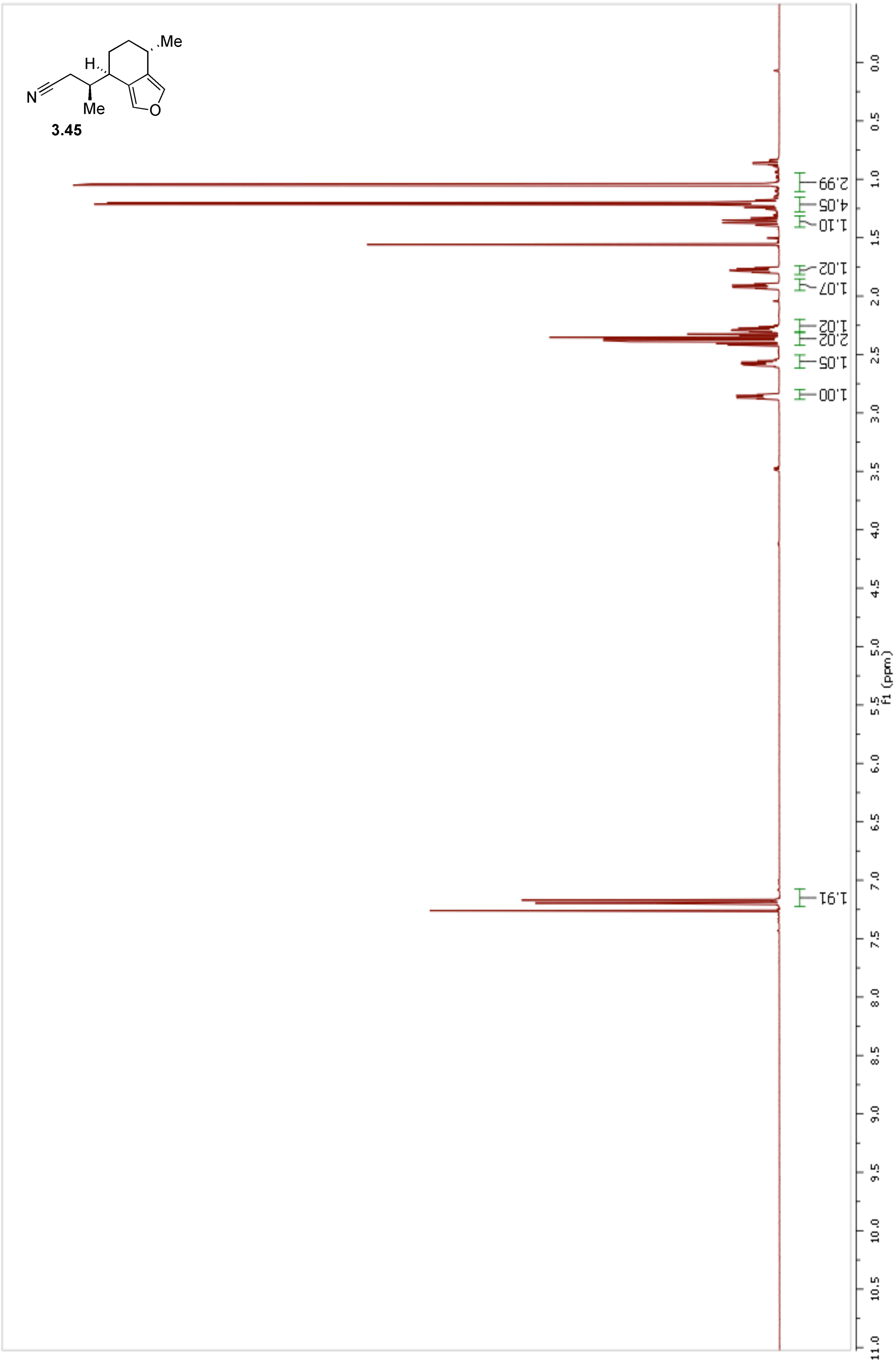
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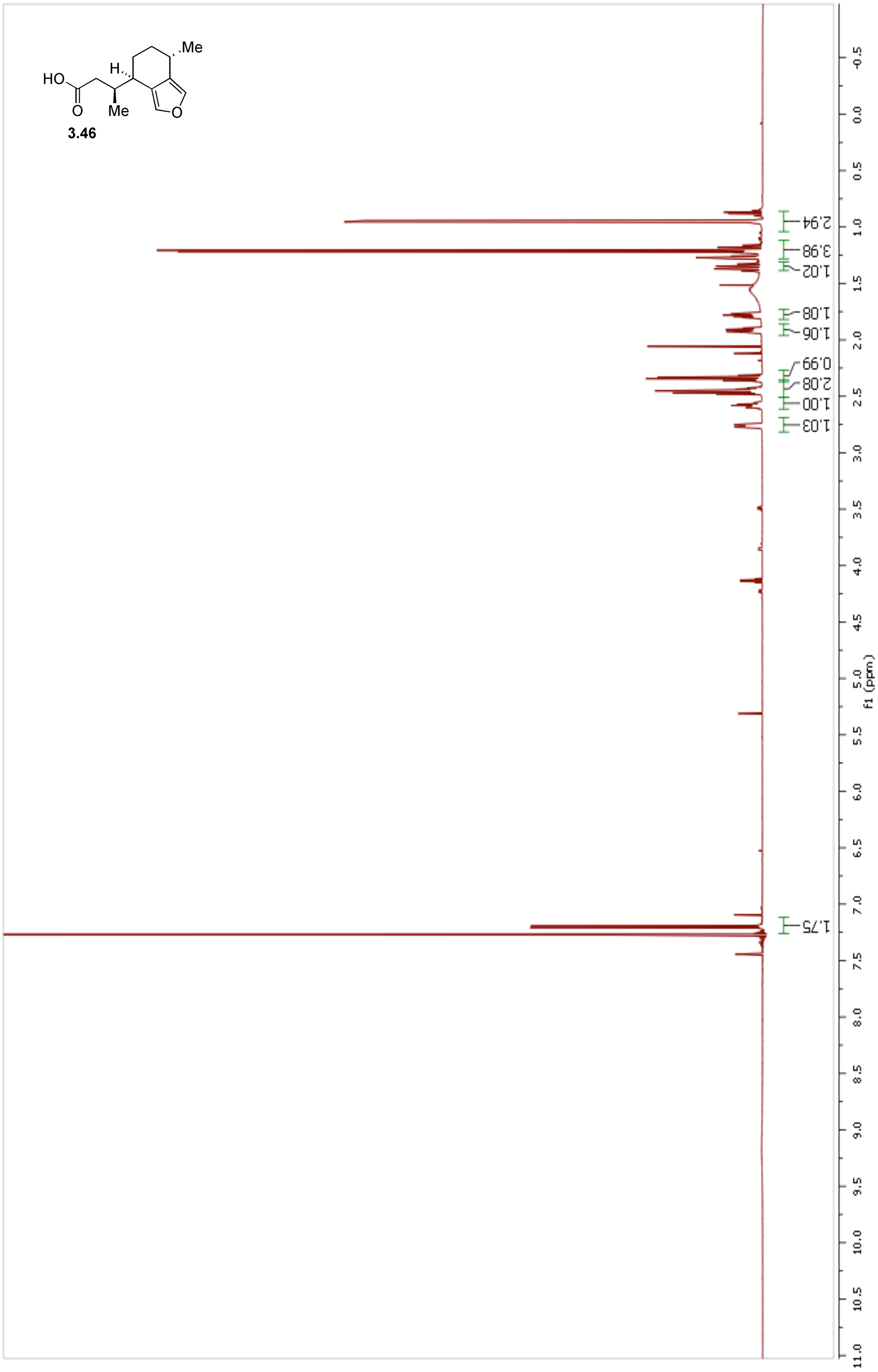

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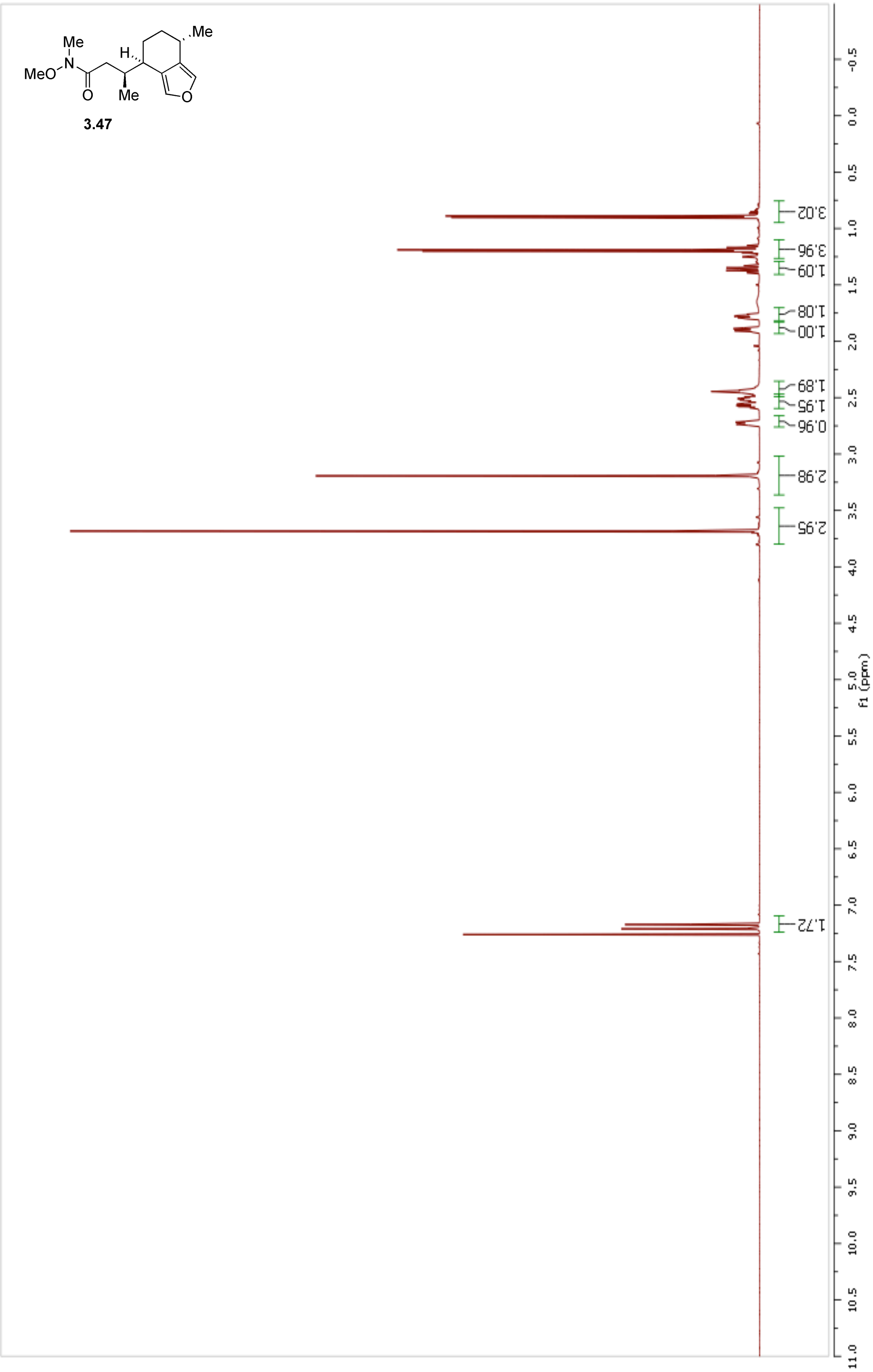
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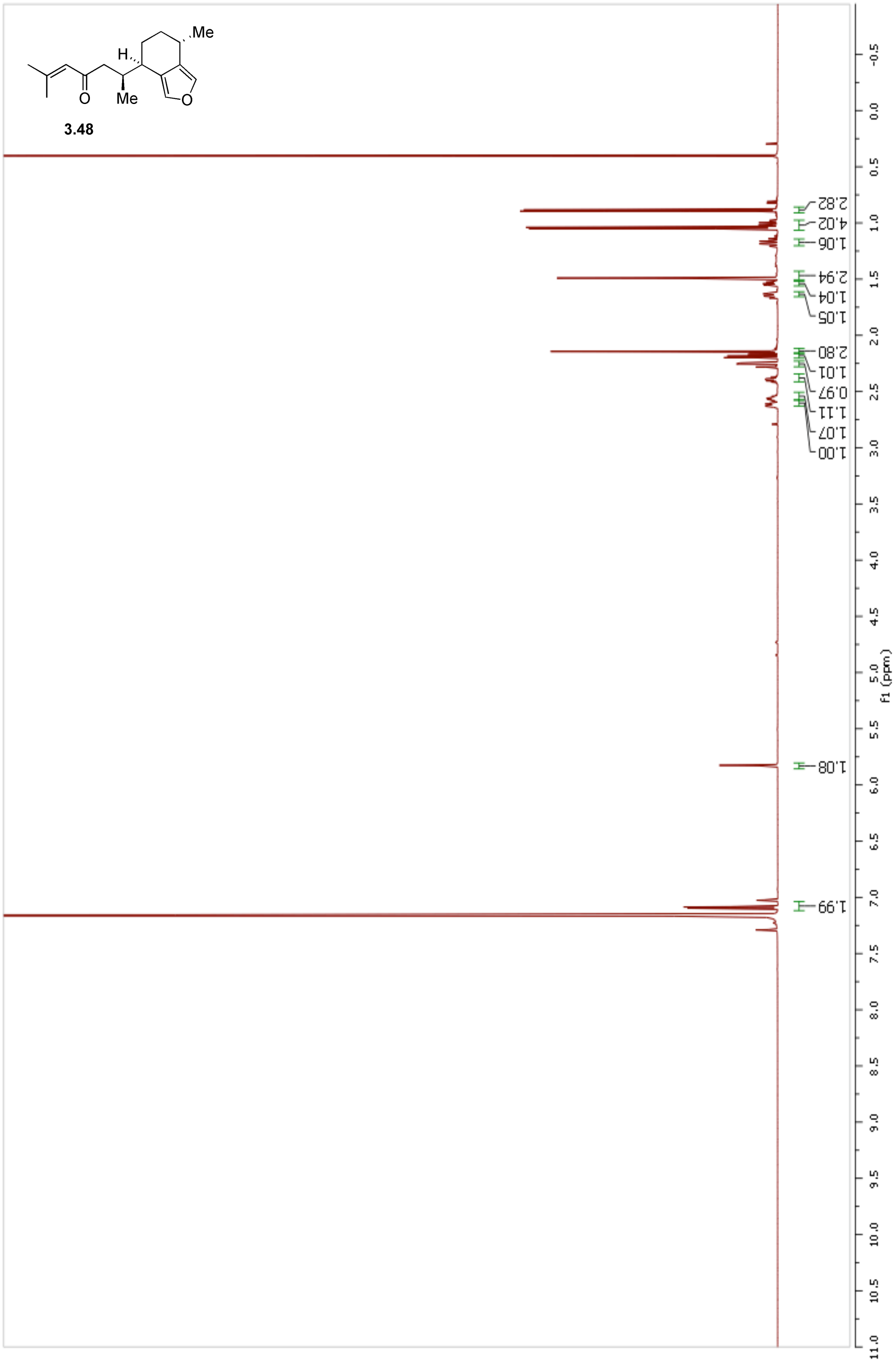

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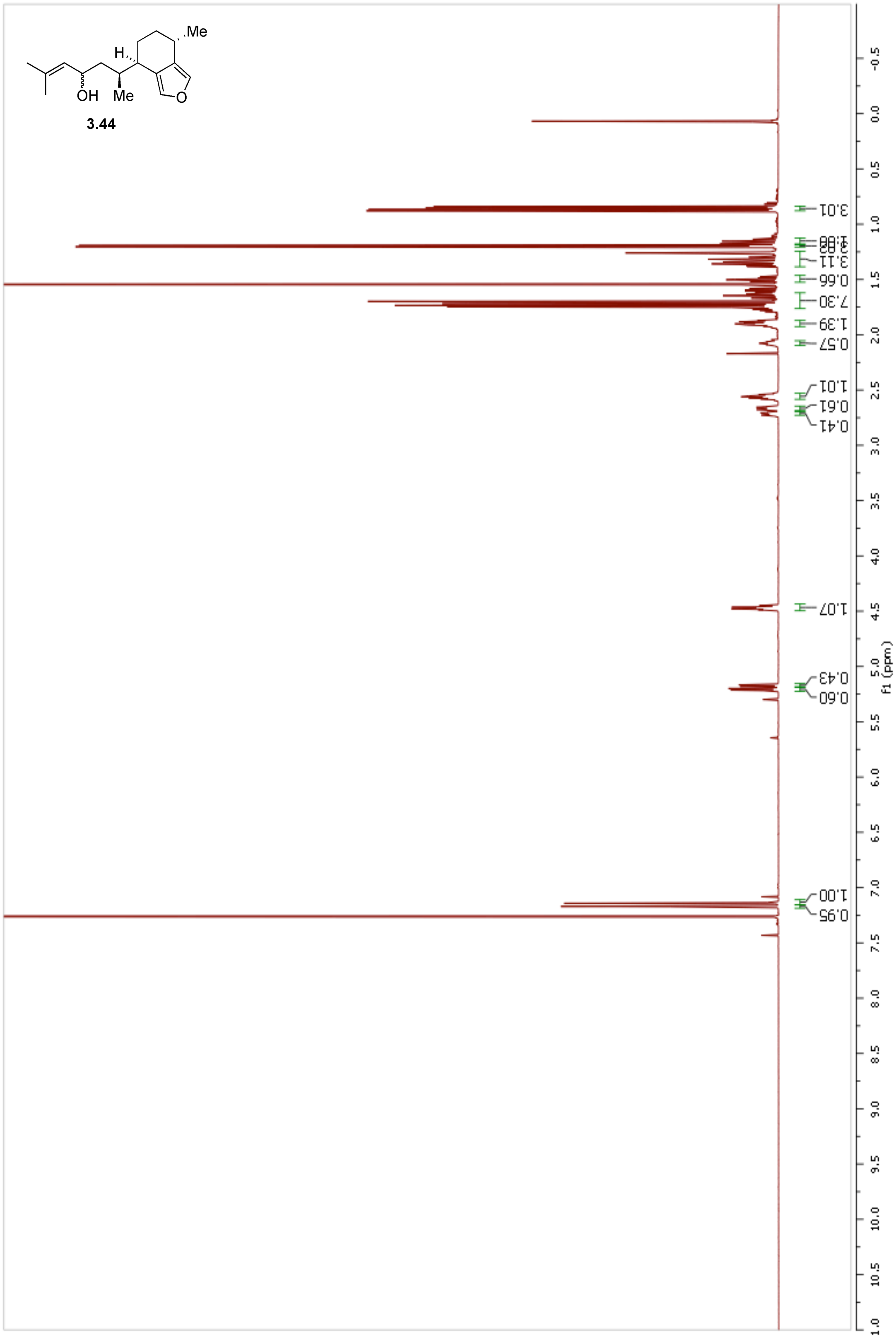
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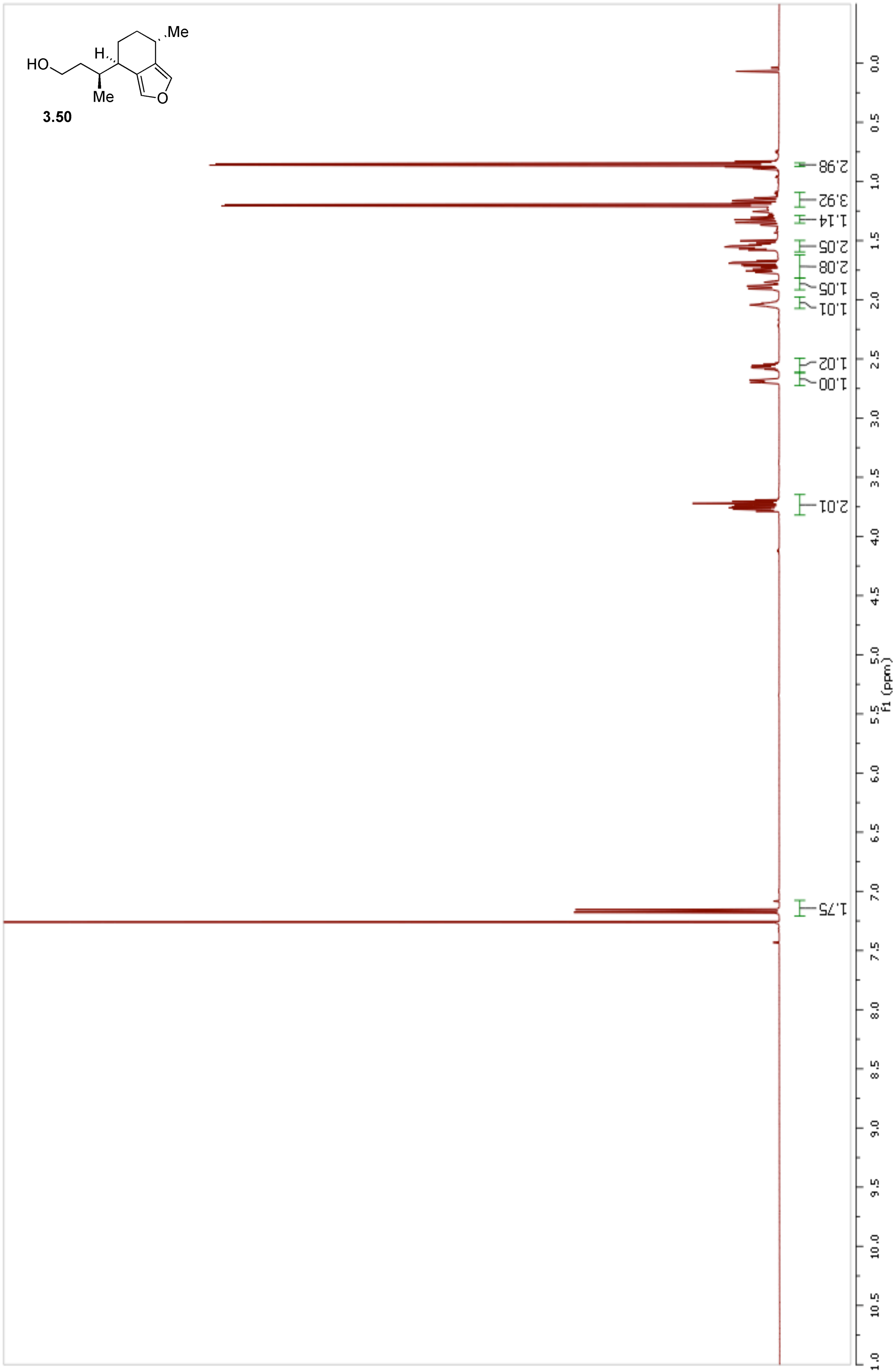
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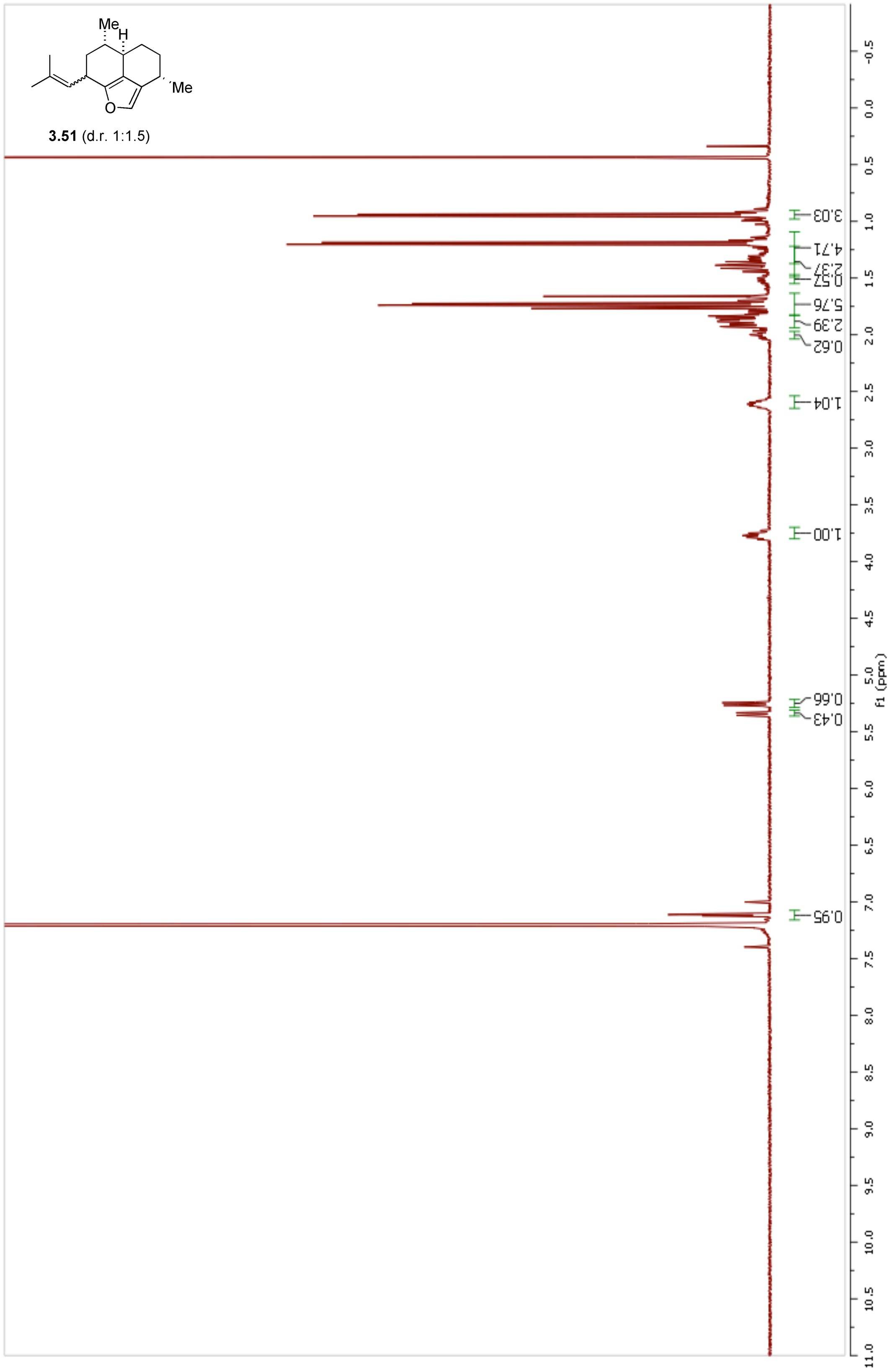
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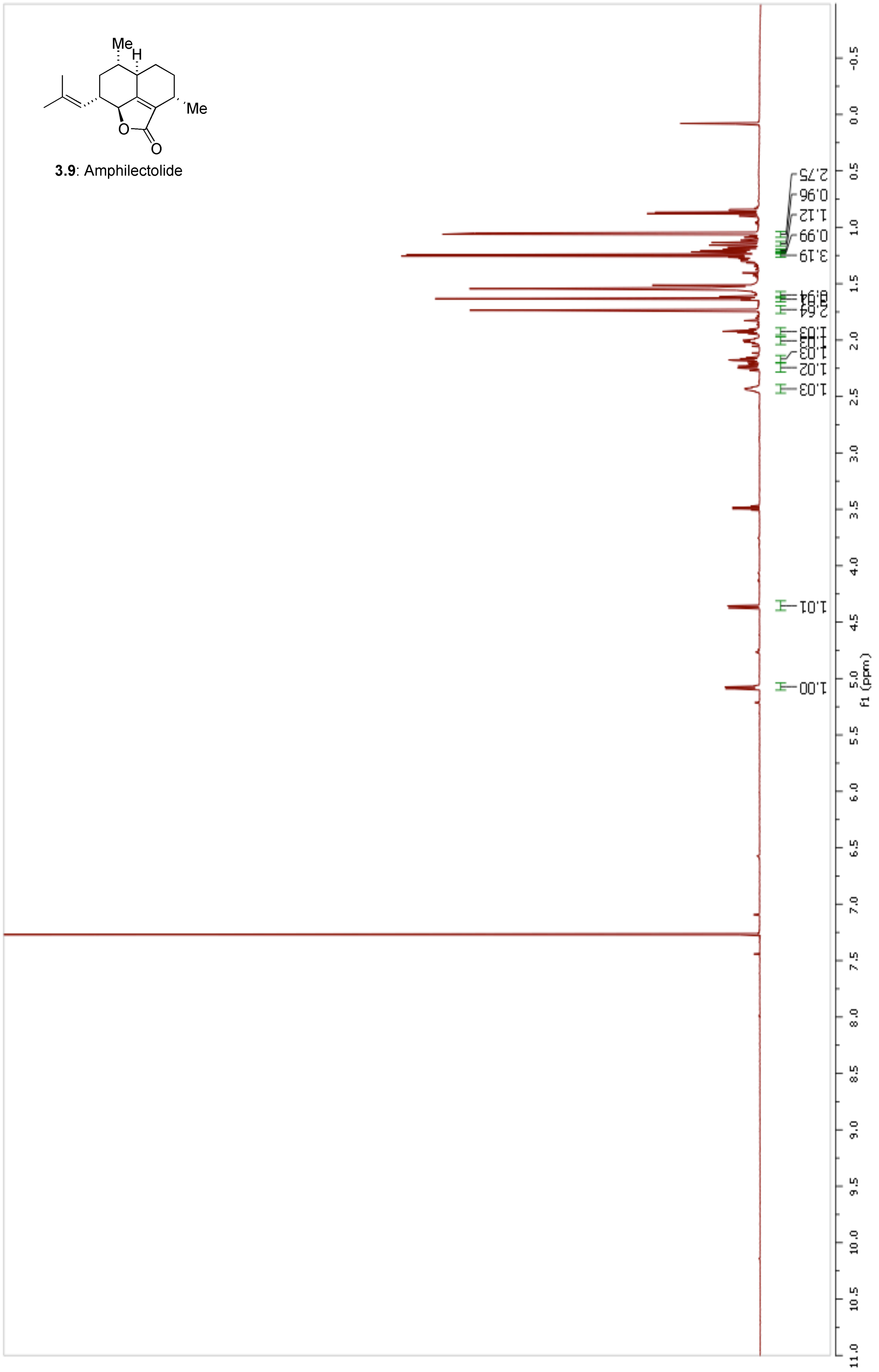
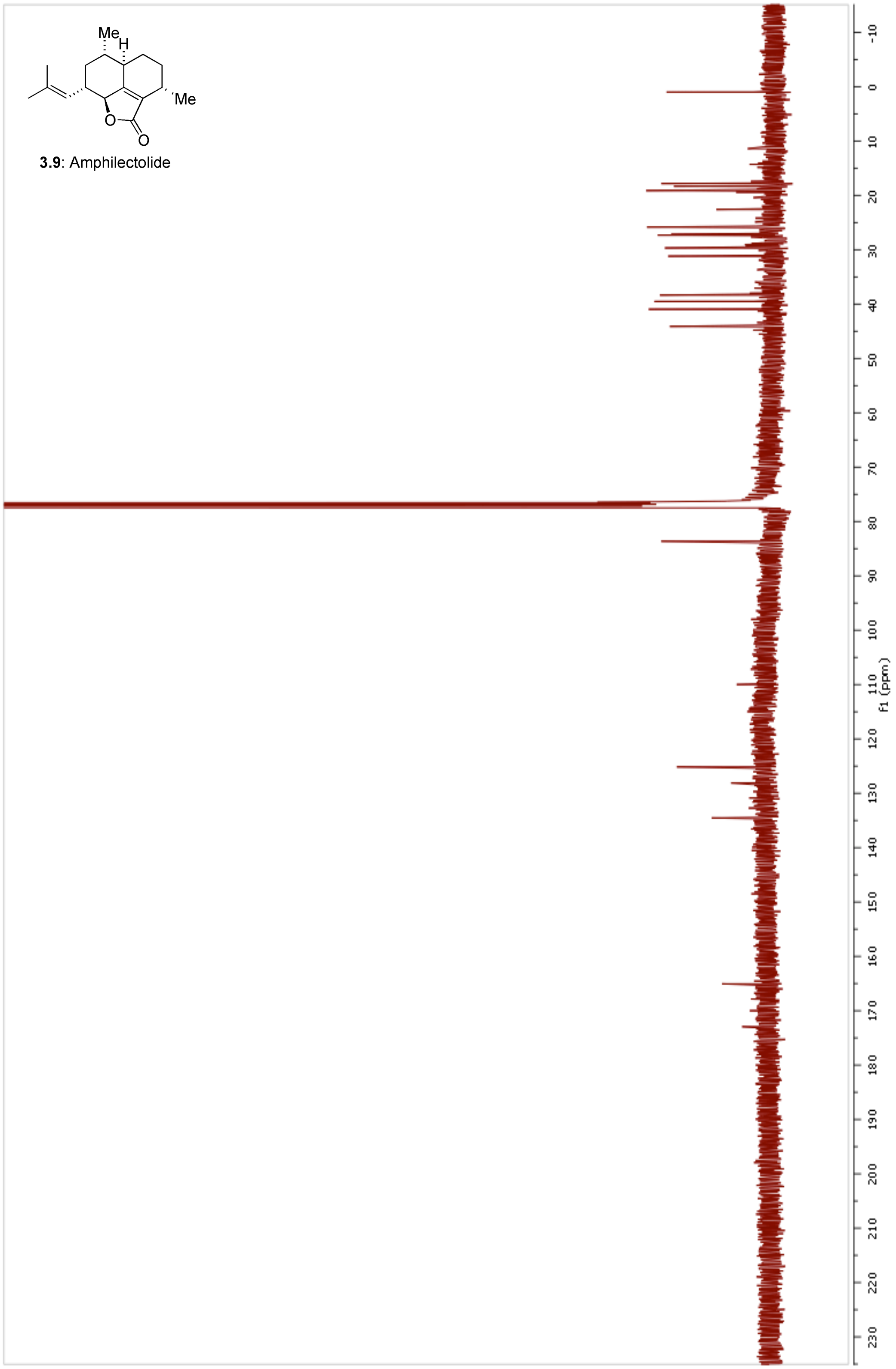
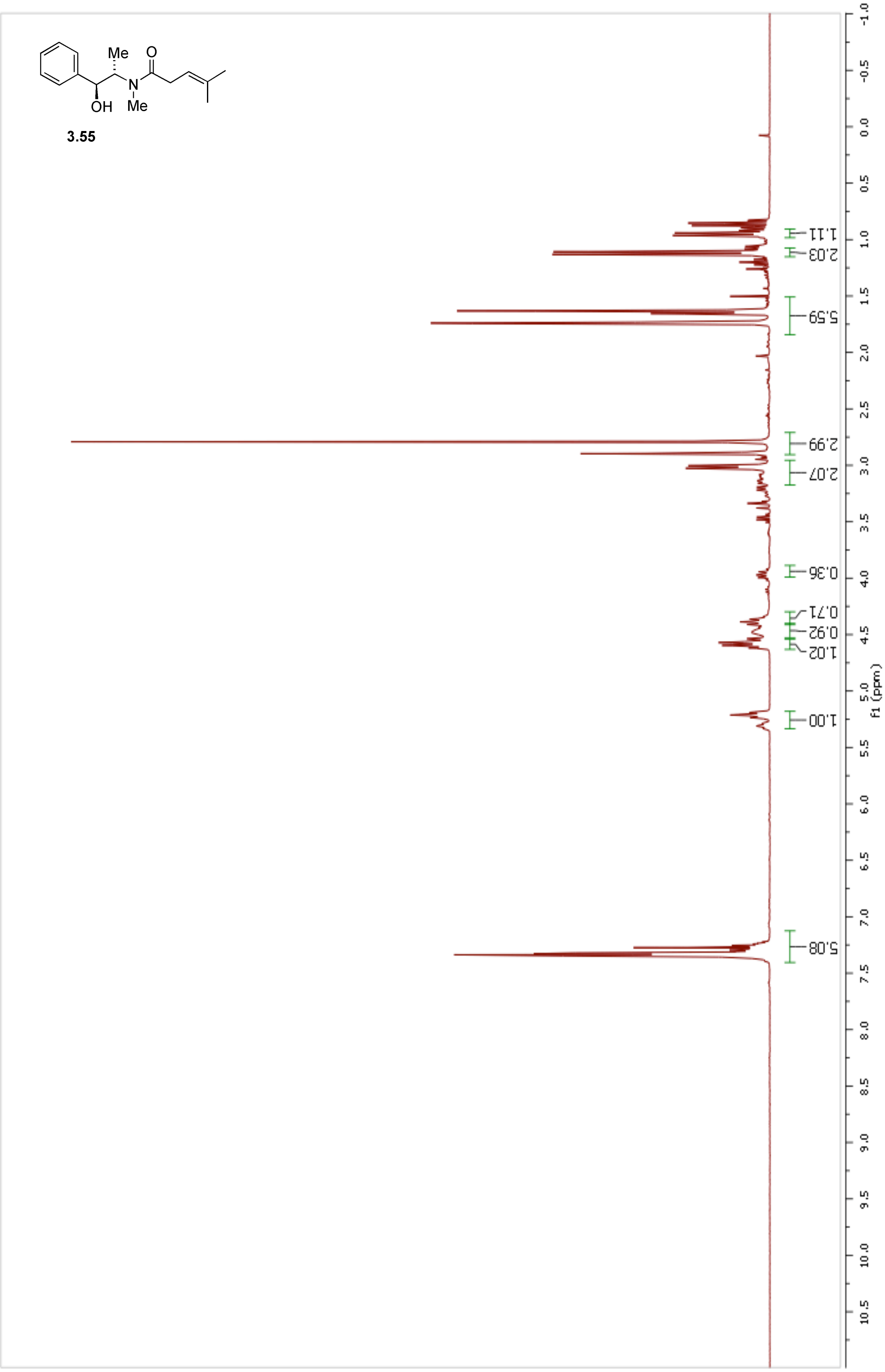


3.9: Amphilectolide

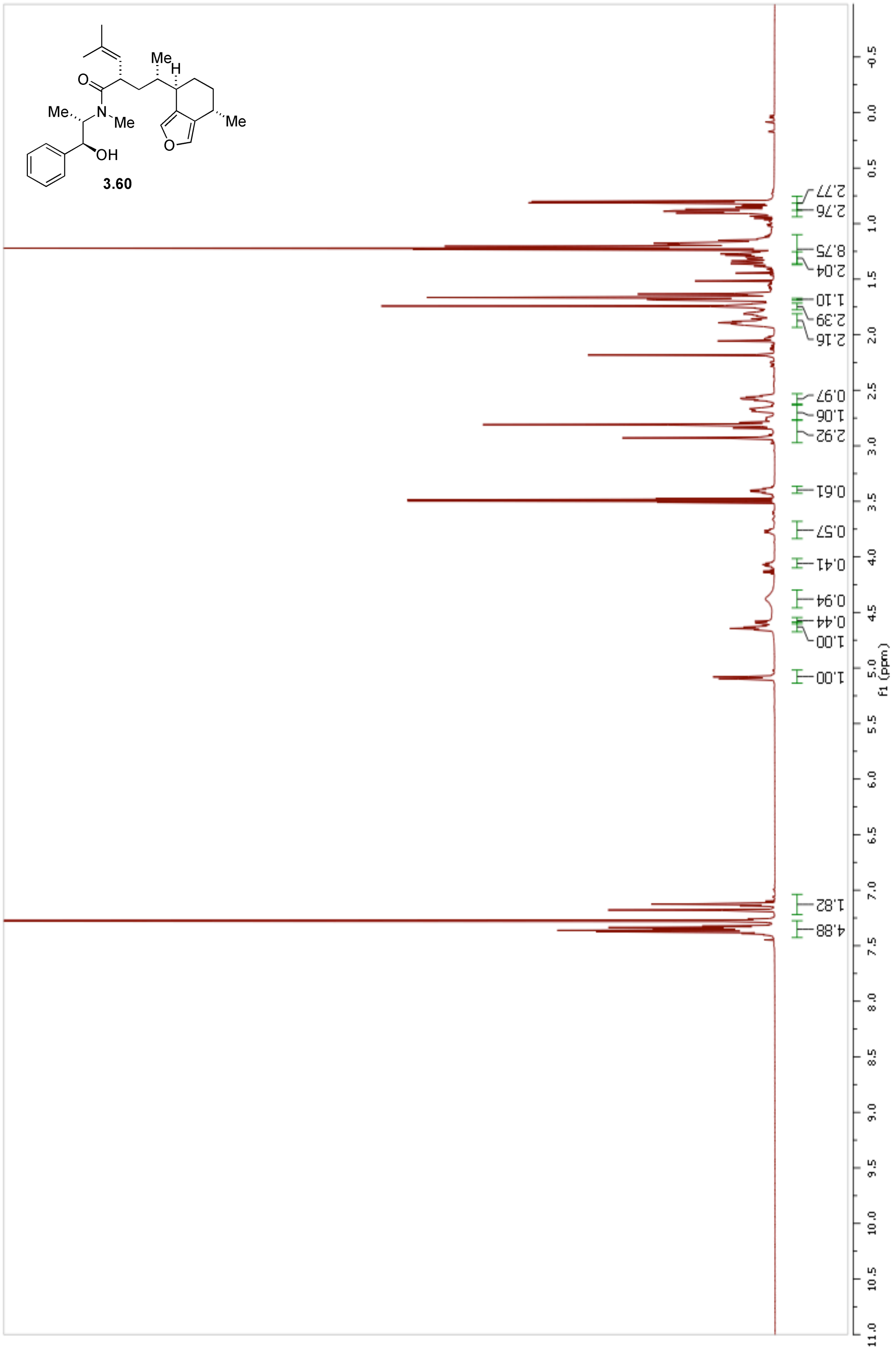


3.9: Amphilectolide

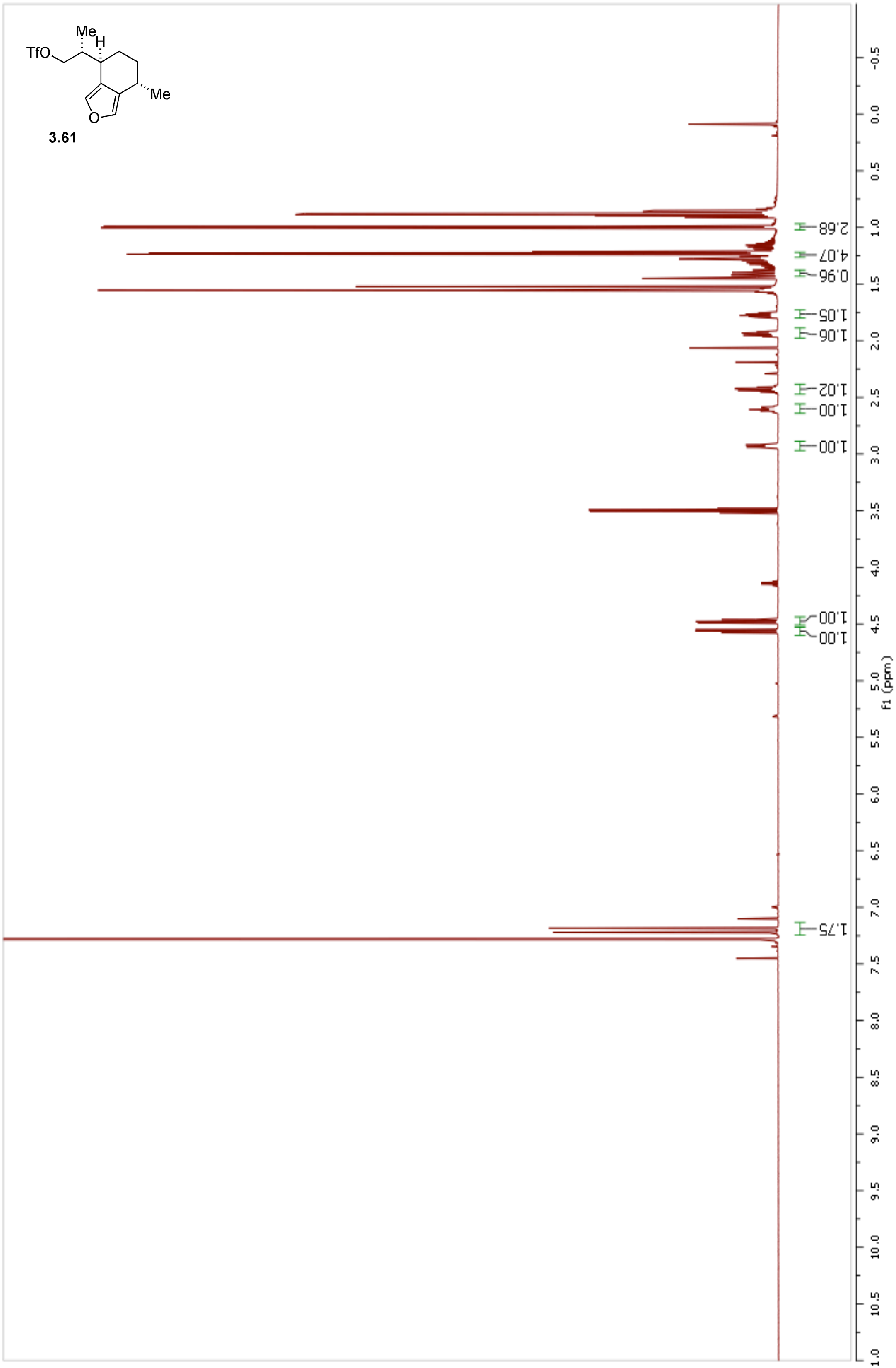


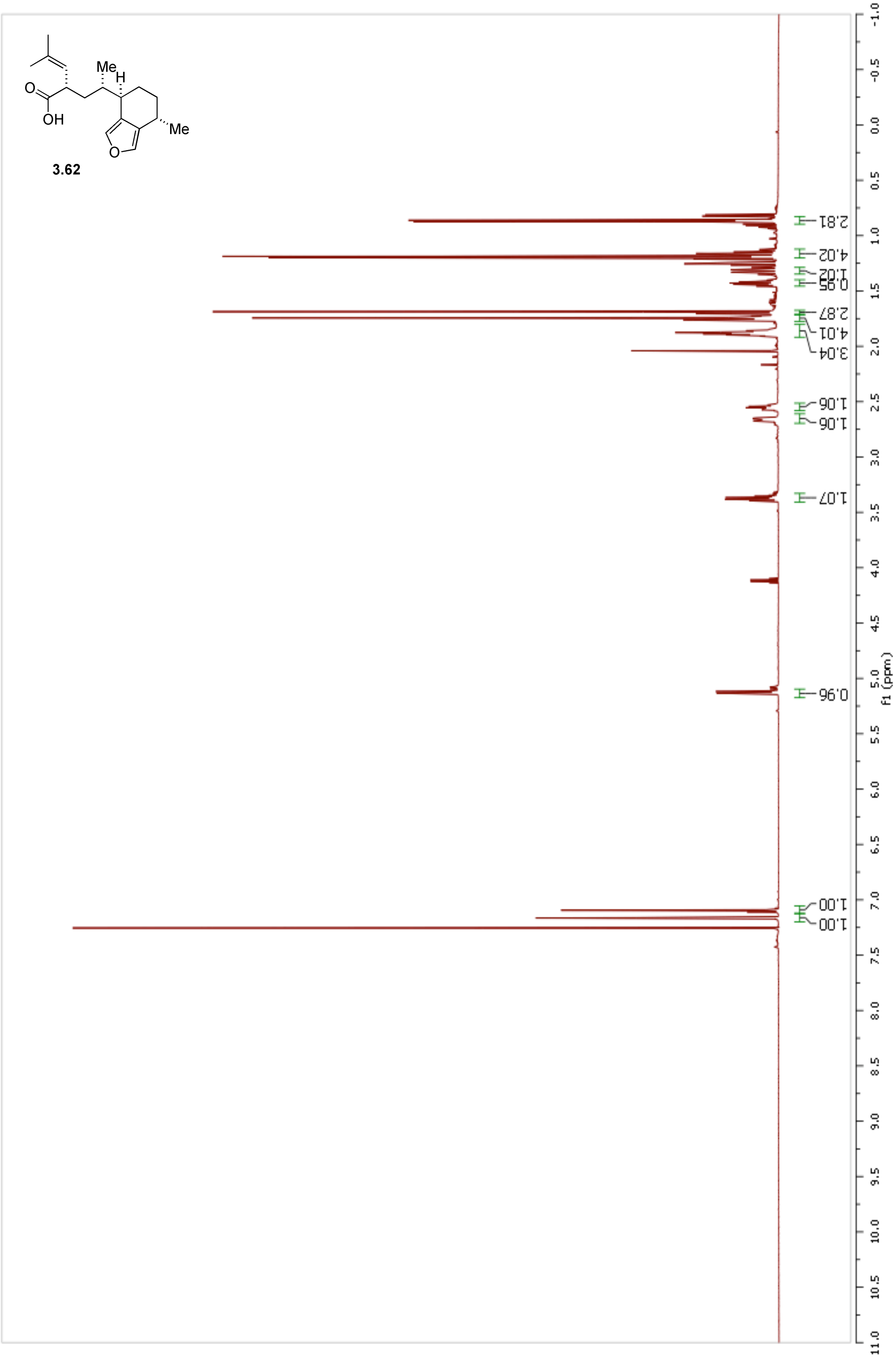
3.55

Me
O
N
OH
Me
1.11
2.03
5.59
2.99
2.07
0.36
0.71
0.92
1.02
1.00
5.08
-1.0
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10.5
f1 (ppm)

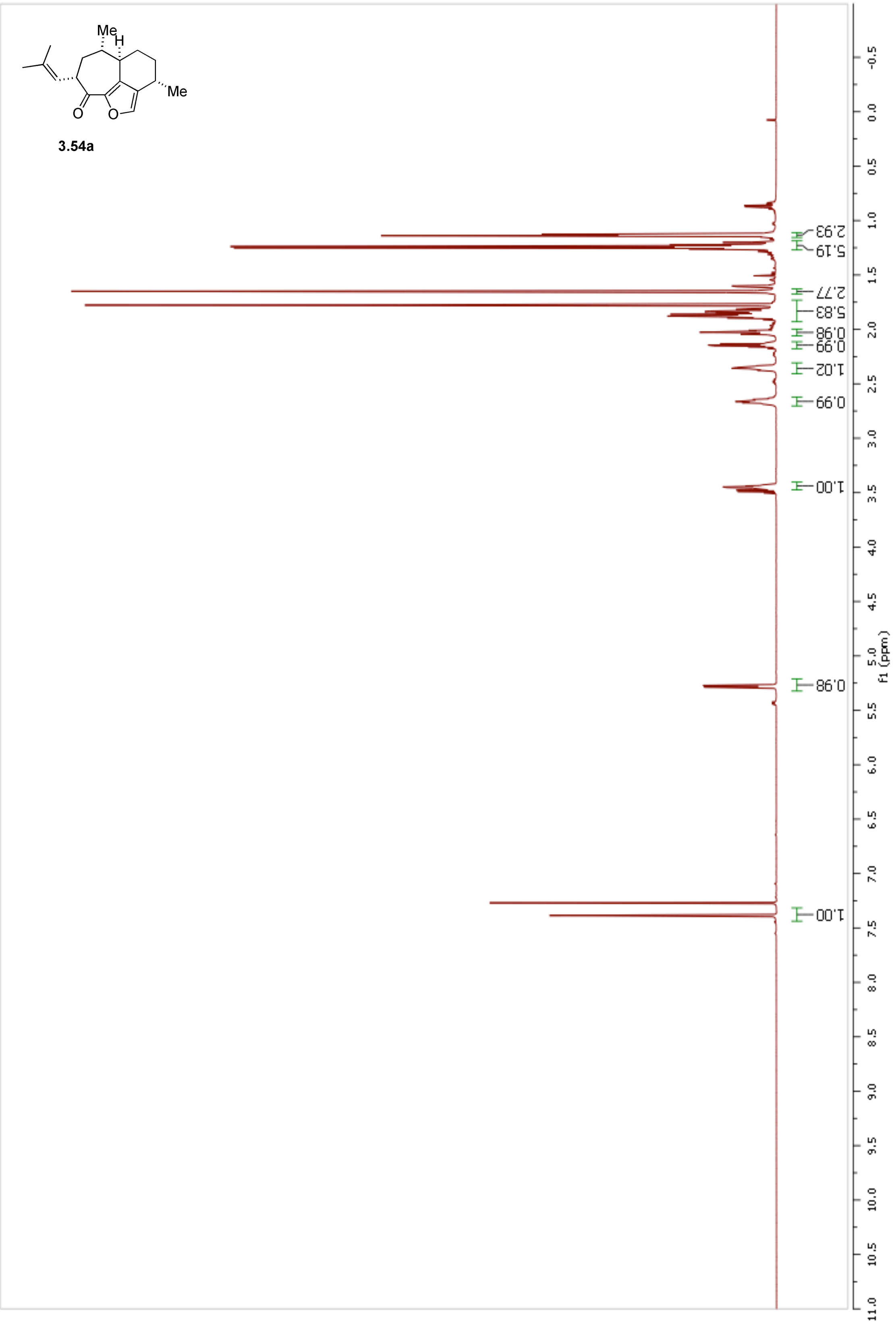

Me
H
O
Me
N
Me
Me
O
OH
2.77
2.76
8.75
2.04
1.10
2.39
2.16
0.97
1.06
2.92
0.61
0.57
0.41
0.94
0.44
1.00
1.00
1.82
4.88
f1 (ppm)

3.60


TfO
Me
H
Me
O
3.61
2.68
4.07
0.96
1.05
1.06
1.02
1.00
1.00
1.00
1.00
1.75
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10.5
11.0
f1 (ppm)


3.62

O
OH
Me
H
Me
O
2.81
4.02
1.02
0.95
2.87
4.01
3.04
1.06
1.06
1.07
0.96
1.00
1.00
-1.0
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
f1 (ppm)
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10.5
11.0


Me
H
Me
O
O
3.54a
2.93
5.19
2.77
5.83
0.98
0.99
1.02
0.99
1.00
0.98
1.00
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
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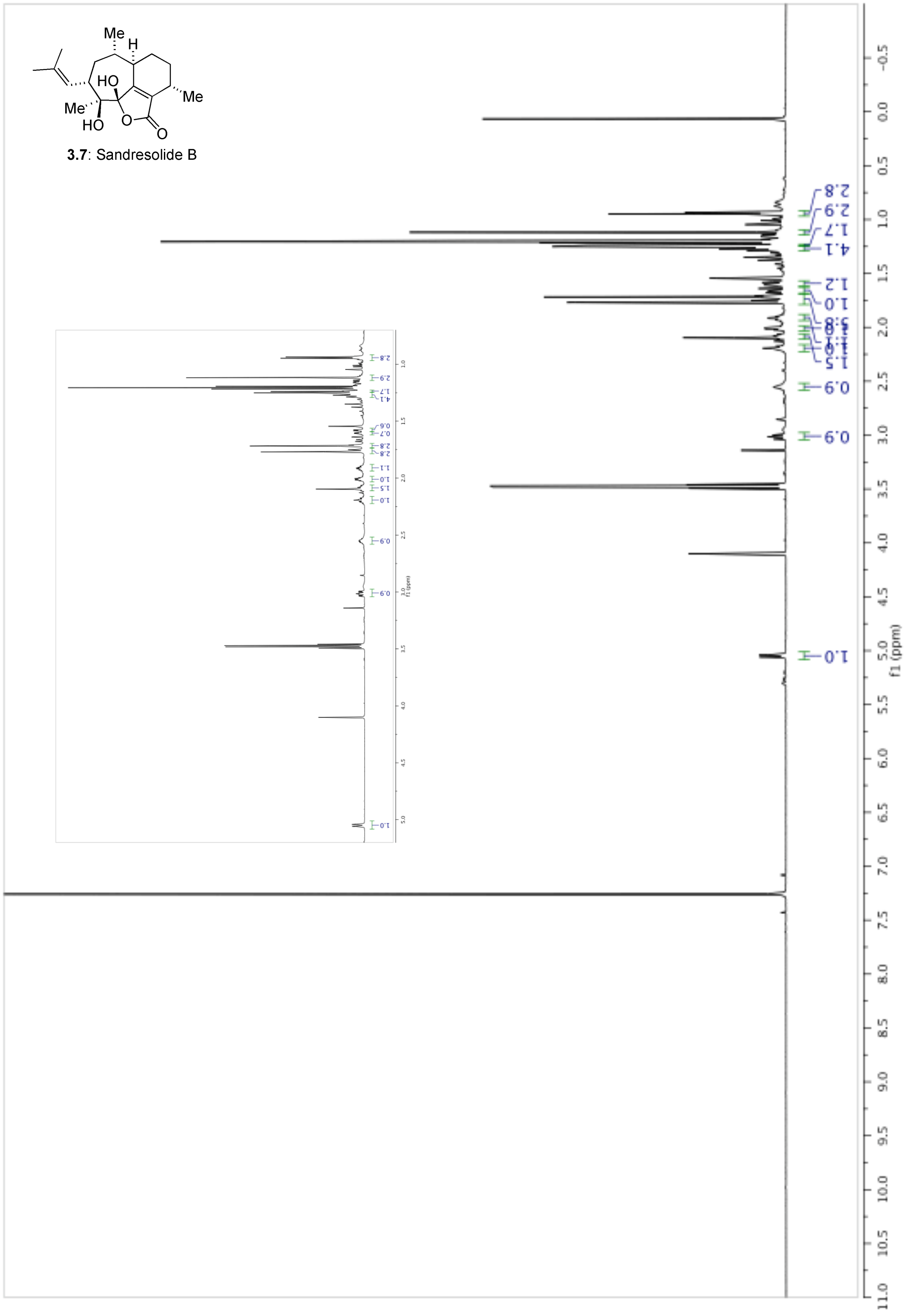
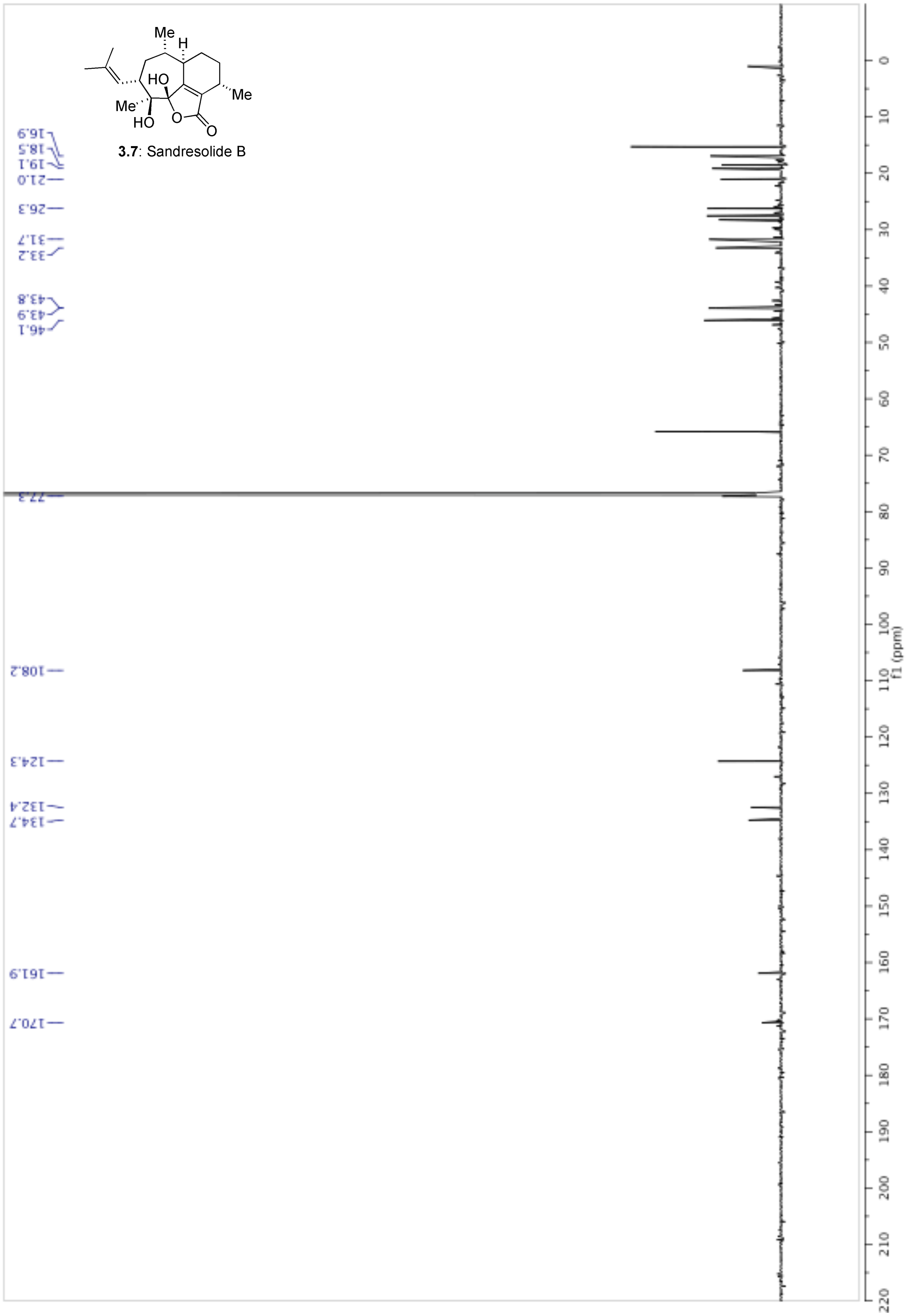
10.0
10.5
11.0
f1 (ppm)



3.7: Sandresolide B



3.7: Sandresolide B

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