Title
Part I. A Concise Total Synthesis of Garsubellin A Part II. Synthetic Studies towards Acutumine Alkaloids

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Part I. A Concise Total Synthesis of Garsubellin A
Part II. Synthetic Studies towards Acutumine Alkaloids

By

Xingyu Shen

A dissertation submitted in partial satisfaction of the

requirements for the degree of

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Committee in Charge:
Prof. Thomas J. Maimone, Chair
Prof. Richmond Sarpong
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Abstract

Part I. A Concise Total Synthesis of Garsubellin A
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Doctor of Philosophy in Chemistry

University of California, Berkeley

Professor Thomas J. Maimone, Chair

In this two-part dissertation, several different strategies are developed to attempt concise synthesis of complex natural products. In the first part, a concise total synthesis of garsubellin A, is reported. Starting from commercially available 2-methyl cyclopentenone, this synthesis of garsubellin A was enabled by a series of powerful C-C bond forming reactions, including a tandem *oxy*-Cope/methylation reaction, a diketene annulation, a ring expansion reaction and a novel regioselective prenyl coupling reaction. Meanwhile, a novel palladium catalyzed Wacker-type oxidation was developed to construct the characteristic tetrahydrofuran ring of garsubellin A. As we hoped this synthetic strategy could serve as a modular synthetic solution of diverse PPAP meroterpenes, an enhanced substrate scope of the diketene reaction was reported.

In the second part of this dissertation, our synthetic studies of acutumine is described. In this chapter, a background introduction is first given, including the isolation and structure determination of acutumine alkaloids, biosynthetic studies, bioactivates of acutumine family, and the prior synthetic studies of (–)-acutumine. Meanwhile, several different strategies for achieving a concise total synthesis of (–)-acutumine were developed and discussed in this dissertation. A novel [3+2] cyclization protocol was developed, which, in three steps, converts commercially available starting materials to a [3.3.0] aza-bicyclic intermediate. From this advanced bicyclic intermediate, a series of efforts to transfer this advanced bicyclic intermediate to (–)-acutumine was explored and reported.

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Acknowledgement

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To **Danny Huang**: You told me you know little chemistry during the campus visiting weekend, and it's very fake of you! From within, I know you are a very talented researcher (maybe one of the most talented). I am sure this talent will help you overcome any challenge and bring you fame for finishing your synthesis with a truly

classic route!

To **Paulo**: To you I own too much. You helped me too many things and paying you gas and foods surely won't cover it. You are a kind person, a good friend and a diligent researcher. Good luck with the rest of your PhD journey!

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To **Mom** and **Dad**: I appreciate all your helps and advice along my way grown-up. I hope you both are proud of what I have achieved. I love you.

List of Abbreviations

12-crown-4	1,4,7,10-tetraoxacyclododecane
15-crown-5	1,4,7,10,13-Pentaoxacyclopentadecane
18-crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane
[O]	oxidation
Ac	Acetyl
acac	acetylacetonate
ad	adamantane
AIBN	azobisisobutyronitrile
aq.	aqueous
BDE	bond dissociation energy
BDP	1,2-bis(diphenylphosphino)benzene
BDSB	Bromodiethylsulfonium bromopentachloroantimonate(V)
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
BOX	bisoxazoline
BPAP	bicyclic polyprenylated acylphloroglucinol
Bz	benzoyl
CBS	Corey-Bakshi-Shibata
ChAT	choline acetyltransferase
CoA	coenzyme A
CPhos	2-Dicyclohexylphosphino-2′,6′-bis(N,N-dimethylamino)biphenyl
DAH	dechloroacutumine halogenase
d.r.	diastereomeric ratio
dba	dibenzylideneacetone
DBSB	
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N*'-dicyclohexylcarbodiimide
DCM	dichloromethane
DFT	density functional theory
$(DHQD)_2PHAL$	Hydroquinidine 1,4-phthalazinediyl diether
DIBAL-H	diisobutylaluminium hydride
DIPEA	*N,N*-dissopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dppf	1,1′-Ferrocenediyl-bis(diphenylphosphine)
dppp	1,3-Bis(diphenylphosphino)propane

E2	elimination bimolecular
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
EI	electron ionization
ESI	electrospray ionization
Et	ethyl
HAT	hydrogen atom transfer
HBV	hepatitis B virus
HG-II	Hoveyda-Grubbs catalyst, 2nd generation
HIV	human immunodeficiency virus
HMDS	hexamethyldisilane
HMPA	hexamethylphosphoric triamide
HRMS	high resolution mass spectrometry
Hz	Hertz
hv	photoirradiation
IBX	2-iodoxybenzoic acid
IMCA	intramolecular cyclopropanation
Imid	imidazole
i-Pr	*iso*-propyl
IPr	1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene
IR	infrared
J	coupling constant
KHMDS	potassium hexamethyldisilane
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilane
LTMP	lithium 2,2,6,6-tetramethylpiperidide
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MMPP	Magnesium bis(monoperoxyphthalate)
MOM	methoxymethyl
MoOPH	oxodiperoxymolybdenum(pyridine)-(hexamethylphosphoric triamide
MPAP	monocyclic polyprenylated acylphloroglucinol
Ms	mesyl
MS	molecular sieves
NaHMDS	sodium hexamethyldisilane
NBS	*N*-bromosuccinimide
n-Bu	butyl
NCS	*N*-chlorosuccinimide
Nf	nonaflyl
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect

p-ABSA	4-Acetamidobenzenesulfonyl azide
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PIDA	(diacetoxyiodo)benzene
PIFA	[bis(trifluoroacetoxy)iodo]benzene
Piv	pivaloyl
PMHS	polymethylhydrosiloxane
PPAP	polycyclic polyprenylated acylphloroglucinol
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
pyr	pyridine
RCM	ring-closure metathesis
RuPhos	2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
TBACl	tetrabutylammonium chloride
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBA(OAc)	tetrabutylammonium acetate
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butylhydroperoxide
TBME	*tert*-butyl methyl ether
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
TCCA	trichloroisocyanuric acid
T-cells	thymus cells
TEA	triethylamine
$TEACl_3$	tetraethylammonium trichloride
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMEDA	tetramethylethylenediamine
TMG	1,1,3,3-Tetramethylguanidine
TMS	trimethylsilyl
Tol	toluene
TPAP	Tetrapropylammonium perruthenate
Ts	tosyl
SET	single electron transfer
S_N2	substitution nucleophilic bimolecular
UV	ultraviolet
Δ	heat

μW	microwave

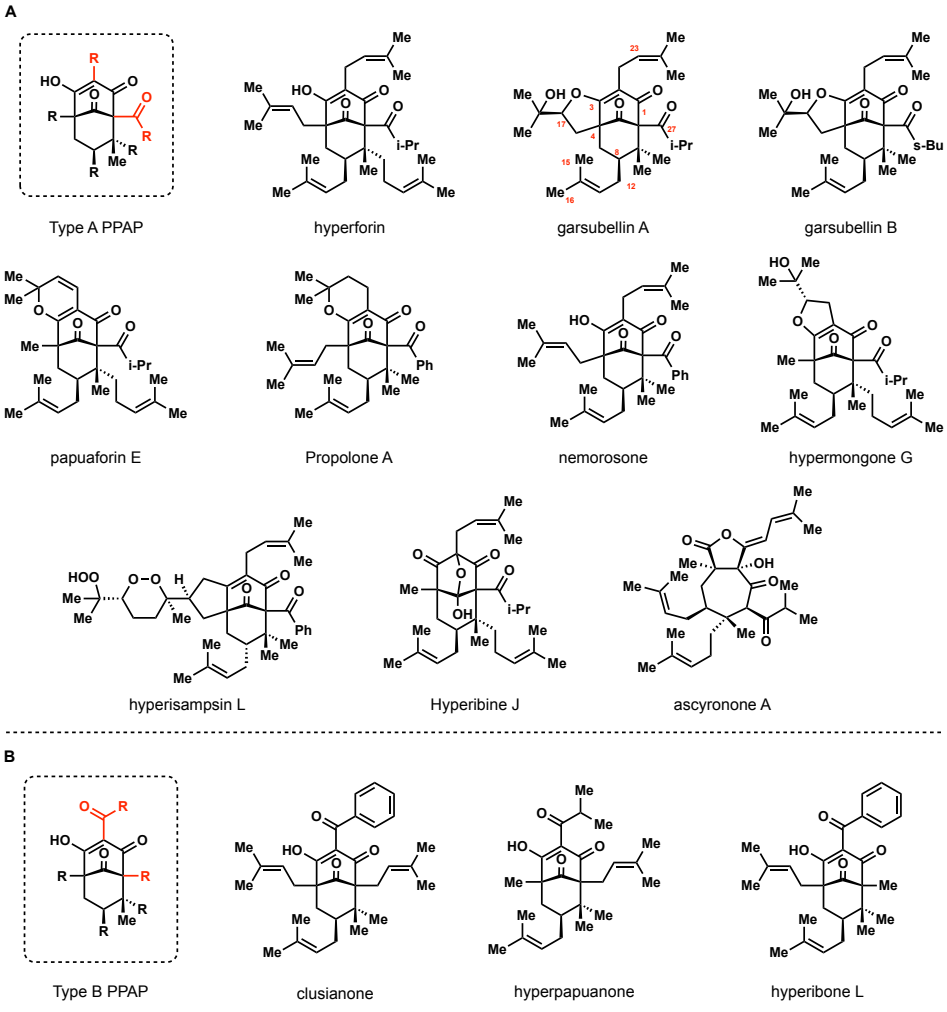
Chapter 1

A Concise Total Synthesis of Garsubellin A

1.1 Background and Introduction

1.1.1 Classification and biosynthesis of PPAP natural products

The structurally complex polycyclic polyprenylated acylphloroglucinol (PPAP) natural product family, a group of over 400 structures,[1] has exhibited many impressive biological properties, including antidepressant,[2] antiproliferative,[3] antibacterial,[4] anti-HIV[5] and antiviral activities.[6] For instance, the first isolated PPAP natural product, hyperforin, was found to be the major active species of the medical, herbal antidepressant St. John's Wort.[2] Given their impressive biological properties and enticing molecular structures, it is not surprising that PPAP meroterpenes have received significant synthetic attention from a large number of research groups.[7,8]



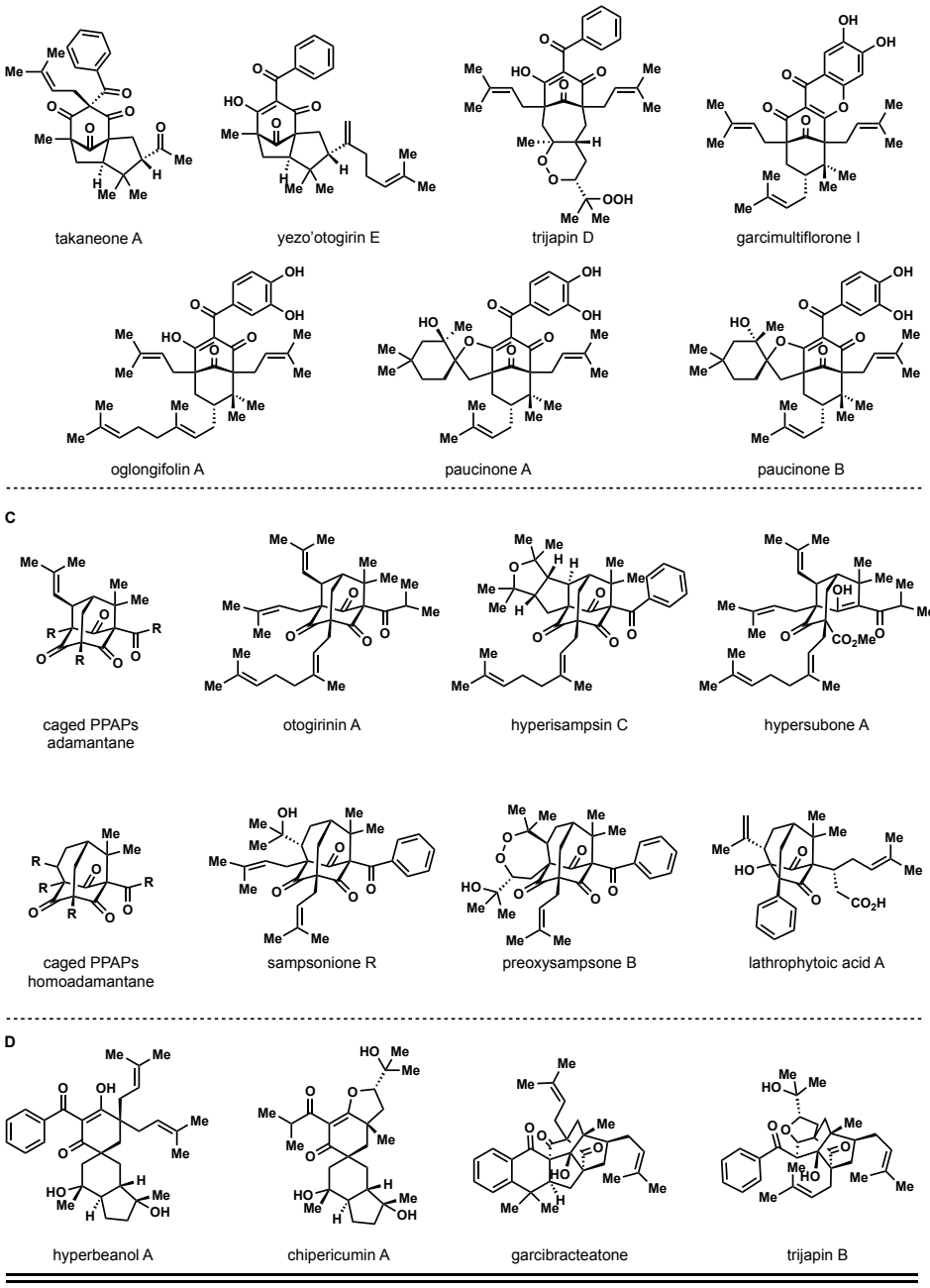
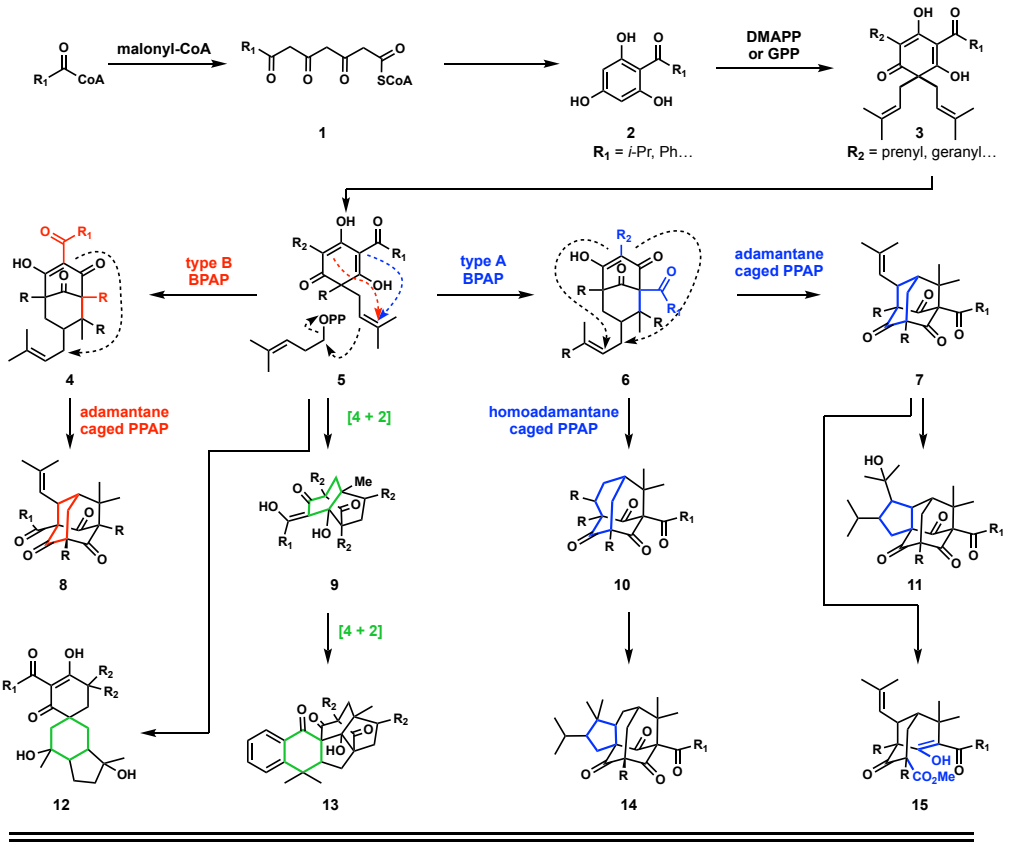


Figure 1. 1 Selected PPAP meroterpenes and their classifications. A) type A PPAP (BPAP) natural products, b) type B PPAP (BPAP) natural products, c) caged PPAP natural products, d) MPAP-type natural products

Given their large chemical diversity, PPAP natural products have been classified into different subtypes based on the substitution patterns and stereochemistries of the various sidechains decorating the parent polycycle as well as further cyclization mode status.[1] More than one-half of PPAP natural products feature a bridged bicyclic core (typically a bicyclo[3.3.1]nonane ring system) and are further classified as bicyclic prenylated acylphloroglucinol (BPAP) (Figure 1, A and B) natural products. BPAP-type

natural products can be further cyclized to yield a group of PPAP natural products containing a characteristic caged-adamantane or other cores (Figure 1, C). BPAP and caged PPAP meroterpenes are further classified as either type A or type B PPAPs. Type A PPAP meroterpenes have an acyl group at C-1 along with a contiguous C-8 quaternary center, while type B PPAP meroterpenes are C-3 acylated. An older designation of PPAPs, namely type C, which were proposed to possess C-1 acyl groups and a C-6 quaternary center, have all been reassigned as type A structures.[9] In addition to the canonical type A and type B PPAP natural products, several structurally distinct PPAP natural products, likely derived from a monocyclic polyprenylated acylphloroglucinol (MPAP) (Figure 1, D, E), have also been isolated.



Scheme 1. 1 Proposed biosynthesis of PPAP natural products

To understand the origin of the structural diversity, the biosynthesis of PPAPs has been extensively studied. To date, both labeling experiments and enzymologic studies indicated that the acylphloroglucinol core **2** comes from condensations of three equivalents of malonyl-CoA and one equivalent of acyl-CoA (Scheme 1.1).[1a,10,11] Using prenyl or geranyl pyrophosphate, the acylphloroglucinol core **2** can be converted to the MPAP core (**3**) by a series of enzyme-catalyzed prenylation/geranylation reactions, respectively.[12] From this dearomatized monocyclic acylphloroglucinol core (**3**), it is proposed that a secondary alkylation/cationic cyclization occurs to forge the bicyclic core (**4**/**6**) along with an additional hydrocarbon chain.[13] Based on the different

regioselectivities of the cyclization processes, these MPAP natural products were then converted to type A or type B BPAP natural products. BPAP natural products arised from further cyclizations to deliver more topologically complex caged PPAP natural products (**4→8, 6→14**, **7→11/15**) .[1b,14] MPAP natural products could also undergo a direct [4+2] cycloaddition or *ipso*-cyclization to give unclassified PPAP natural products with unique topological features (**5→12/13**).

1.1.2 Isolation and bioactivities of garsubellin A (16)

Garsubellin A was isolated in 1997 by Fukuyama and coworkers from the wood of *Garcinia subellipitica,* most commonly known as the Fukugi tree[15a]. Garsubellin A was reported to increase choline acetyltransferase (ChAT) by 154% in P10 rat septal neurons at a 10 µM concentration.[15] ChAT is known to be a key enzyme in the synthesis of acetylcholine. It has been reported that low concentrations of acetylcholine are associated with neurodegenerative diseases.[16] For this reason, small molecule enhancers of ChAT have received considerable interest. Additionally, garsubellin A has also demonstrated inhibition of ß-glucuronidase and histamine release with a half maximal inhibitory concentration (IC_{50}) of 15.6 µM.[17,18] This property is of interest as it can be associated with anti-inflammatory activity. It is noteworthy that similar biological properties were rarely displayed by other acylphloroglucinols isolated from *Garcinia subellipitica*.[18]

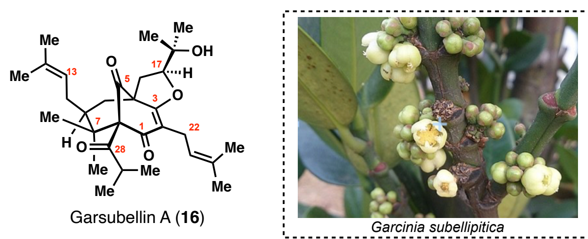


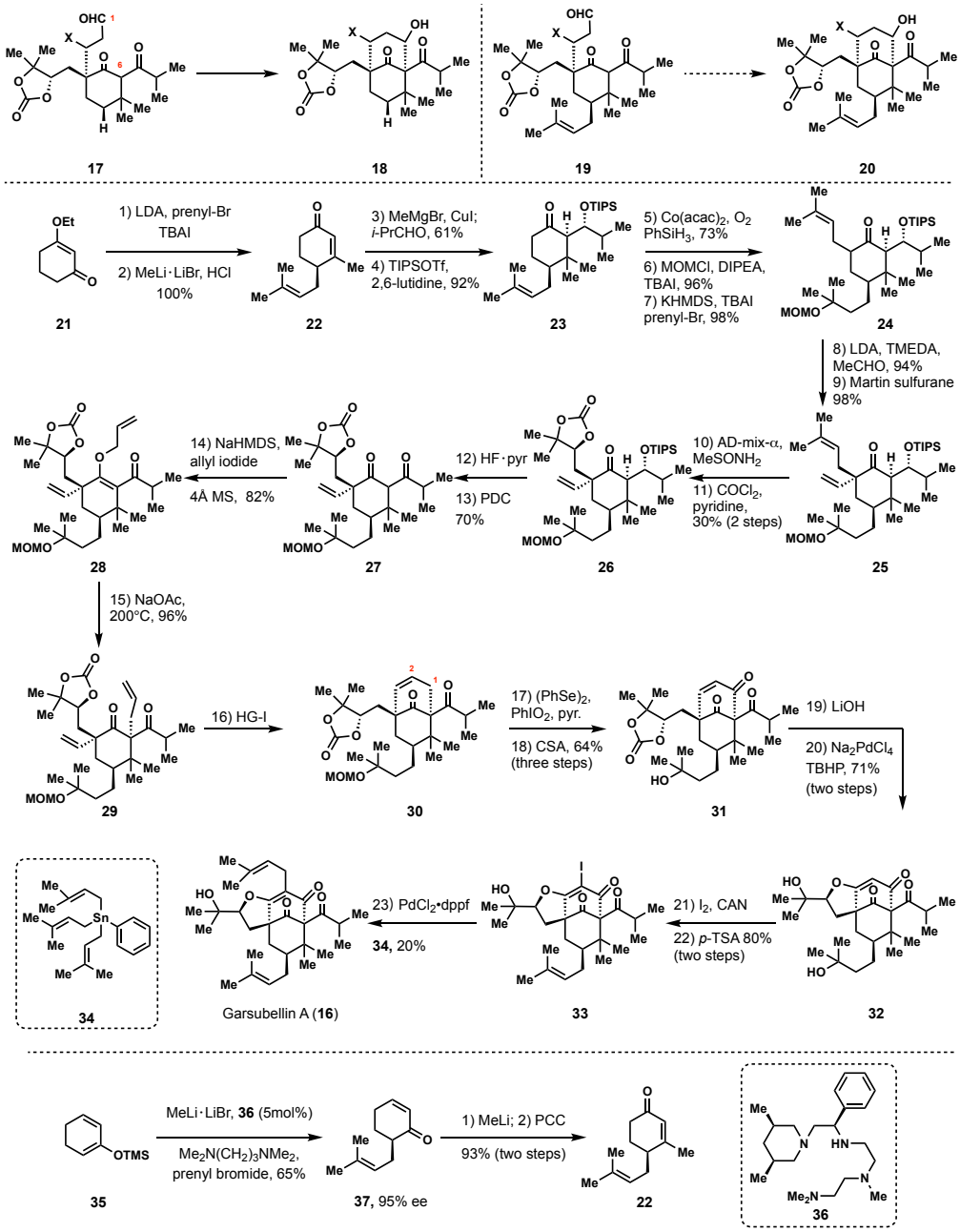
Figure 1. 2 Garsubellin A, isolated from *Garcinia subellpitica*

The structure of garsubellin A (**16**) features a typical BPAPs' bicyclo [3.3.1] nonane ring system. This heavily functionalized bridged bicycle has three stereogenic centers, one *gem*-dimethyl group, two prenyl groups, an isobutyryl functional group at the bridgehead position (C-6), and two all-carbon quaternary stereocenters, including a pair of congested, contiguous quaternary centers (one non-stereogenic). Additionally, garsubellin A also possesses a unique tetrahydrofuran ring with a stereogenic center at C-17.

1.1.3 Previous total syntheses of garsubellin A (16)

Owning to these structural and biological properties, it is not surprising that garsubellin A (**16**) has garnered considerable interest from the synthetic community.[19] Yet, to this date, only three total syntheses of this complex PPAP have been reported.[20-22]

1.1.3.1 Shibasaki's total synthesis of garsubellin A (16)



Scheme 1. 2 Shibasaki's total synthesis of garsubellin A

In 2005, Shibasaki and coworkers reported the first total synthesis of garsubellin A (**16**).[20] They realized that the formation of the sterically congested quaternary center at C–6 in the type A PPAPs would present a formidable challenge for chemical synthesis. To construct this motif, they envisioned an intramolecular aldol strategy. To assess the feasibility of this strategy, a model study was executed to yield the desired cyclization

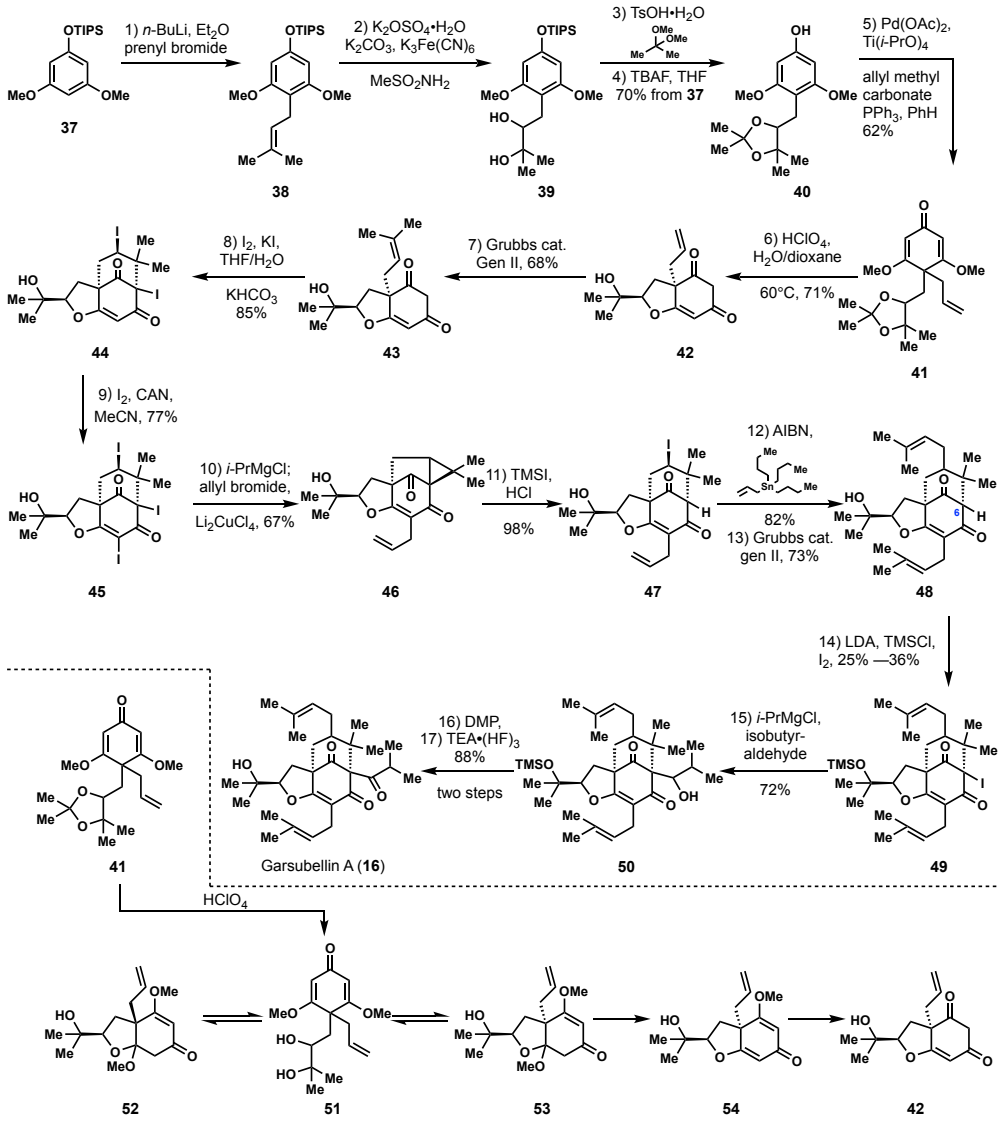
(Scheme 1.2, **17** → **18**).[20b] However, this key intramolecular aldol strategy failed to forge the desired bicyclic intermediate during their synthesis of garsubellin A (**16**) (Scheme 1.2, **19** → **20**). To circumvent this problem, they developed an alternative Claisen rearrangement/ring-closure metathesis (RCM) strategy for the construction of the bicyclo[3.3.1]none. They hypothesized that such a strategy could be beneficial in two ways: i) first, the robust RCM reaction could form the key carbon-carbon bond irreversibly, and ii), the formation of the new bond (between C-1 and C-2, see Scheme 1.2, **30**) is entropically more favorable compared to their previous aldol cyclization strategy.

They began their synthesis of garsubellin A (**16**) with commercially available vinylogous ester **21.** After two steps of functional group interconversions, this vinylogous motif **21** was converted to enone intermediate **22**. A Cu-catalyzed conjugate addition followed by *in-situ* trapping of the resulting enolate with isobutyraldehyde was employed to connect the side chain with the monocyclic core. The newly formed secondary alcohol was then protected with a TIPS group to give the corresponding silyl ether **23**. The pendant prenyl group of **23** was then subjected to a Mukaiyama hydration and the newly formed alcohol protected with MOMCl. This intermediate was then exposed to base (LDA) and reacted with prenyl bromide, which installed the second prenyl group. A regioselective aldol reaction and subsequent dehydration was then employed to forge **25**, which contains the first chiral all-carbon quaternary center. After a series of protecting group manipulations and oxidation state adjustments, the Shibasaki group was able to synthesize 1,3 diketone **26**. This diketone **26** was then subjected to an *O*-allylation by treatment with allyl iodide. The formed allyl enol ether was smoothly isomerized to the diene intermediate **29** upon heating to 200 °C. The RCM reaction delivered the key bicyclic intermediate **30**. This intermediate **30** was then converted to an enone by using Barton's procedure.[23] After several deprotection reactions, the resulting diol was subjected to a Wacker-type oxidation, and tetrahydrofuran intermediate **32** was forged. Finally, racemic garsubellin A (**16**) was obtained by a Stille coupling between vinyl iodide **33** and triprenyl(phenyl)tin (**34**). Shibasaki and coworkers have also reported a formal asymmetric synthesis of garsubellin A (**16**).[24] Starting from silyl enol ether **35**, an asymmetric enolate prenylation was achieved through the use of chiral tetraamine **36**. After two additional steps, a 1,2 addition and a PCC-mediated Dauben oxidative rearrangement, common precursor **22** was achieved with 95% ee.

1.1.3.2 Danishefsky's total synthesis of garsubellin A (16)

Shortly after Shibasaki's synthesis was reported, Danishefsky and Siegel published the second total synthesis of garsubellin A (**16**).[21] The group envisioned a dearomative functionalization strategy to achieve an advanced polyallylated intermediate. Consequently, they began their synthesis with phloroglucinol **37**.[25] This building block was subjected to *ortho*-lithiation and the resulting anion reacted with prenyl bromide to generate **38**. After several steps involving alkene oxidation and protecting group adjustments, phenolic intermediate **40** was obtained and then subjected to a key dearomative *para*-allylation reaction to deliver **41**.[26] Although there are several possible

allylation sites, all the possible isomers could be converted to the thermodynamically stable ketone **41** via an *oxy*-Claisen or/and Cope-like rearrangement. Immediately after this key dearomative allylation reaction, a second thermodynamically driven tandem reaction was executed. The vinylogous carbonate **41** was first transformed into bicyclic intermediate **42** via a four-step sequence consisting of deprotection/*oxy*-Michael reaction/ elimination and hydrolysis of the vinylogous carbonate (71% yield). At the beginning of this reaction, both diastereomers **52** and **53** were present after heating diol **51** at 60 °C.[27] However, the authors found that only **53** was able to further eliminate to yield desired intermediate **54**, which was then hydrolyzed to deliver the key tricyclic intermediate **42**, as a single diastereomer. This newly formed diketone intermediate **42** was then converted to monoprenylated intermediate **43** by an olefin metathesis reaction.

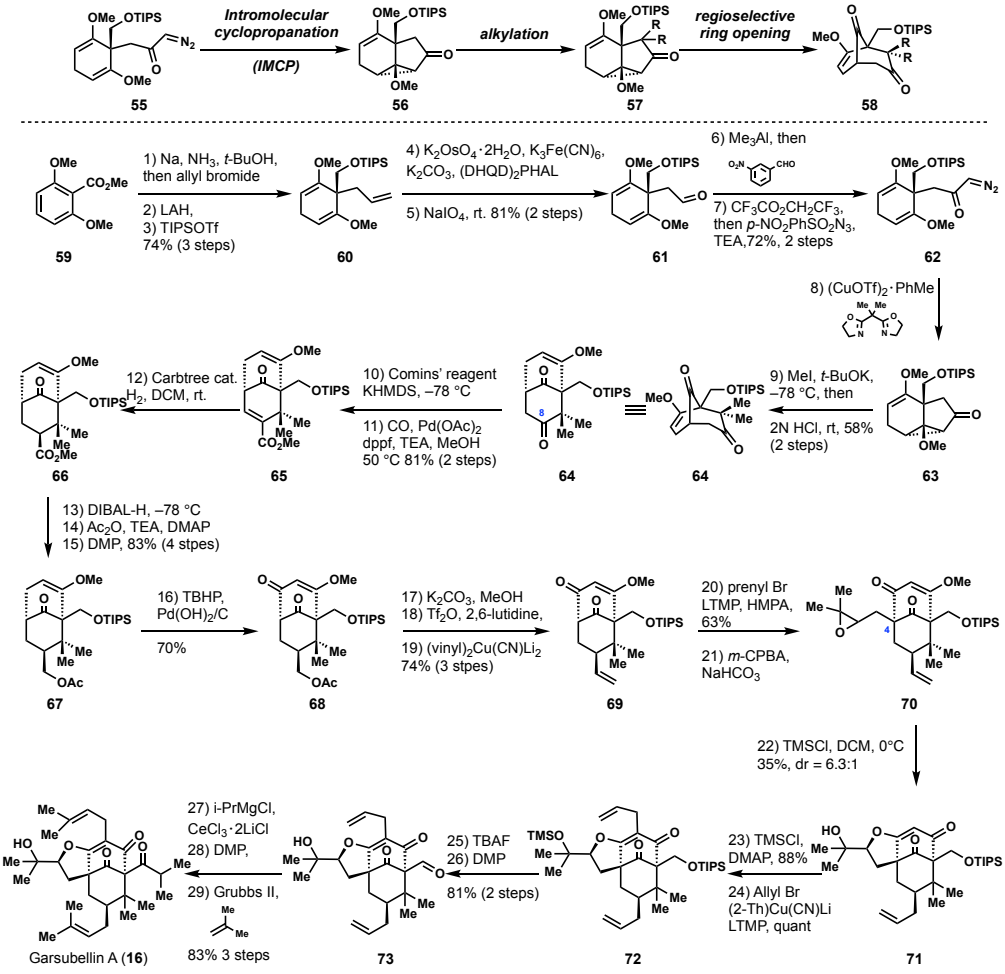


Scheme 1. 3 Danishefsky's total synthesis of garsubellin A (**16**)

With bicycle **43** in hand, the hallmark bicyclo[3.3.1]nonane system was forged via

iodonium-mediated cyclization (I_2) to give diiodinated intermediate **44**. The third allyl group was then installed via a second iodination (see **45**) followed by a magnesium-iodine exchange and an allylation reaction to generate **46**.[28] A transannular Wurtz-type coupling occurred during this process, but the strained cyclopropane formed was easily reopened upon treatment with TMSI giving **47** in 98% yield. The final prenyl group was assembled via a Keck radical allylation and a subsequent olefin metathesis reaction.[29] The bridgehead carbon C-6 was iodinated upon exposure to LDA and iodine generating **49** in modest yield. Magnesium-iodine exchange followed by quenching with isobutyraldehyde then gave neopentyl alcohol **50** from **49**. A final Dess-Martin oxidation and desilyation then delivered garsubellin A (**16**) in 18 steps and with an overall yield of ~1%.

1.1.3.3 Nakada's total synthesis of garsubellin A (16)



Scheme 1. 4 Nakada's total synthesis of garsubellin A (**16**)

Another very interesting and distinct total synthesis of garsubellin A (**16**) was reported by Nakada and coworkers.[22] They developed an impressive intramolecular

cyclopropanation and stereoselective ring opening strategy to construct the bicyclo [3.3.1] nonane system.[22b] In their synthetic plan, they envisioned that resulted ketone and methyl vinyl ether of the bicyclic core **58** could serve as potential reaction handles to introduce the remaining prenyl groups and enable the synthesis of garsubellin A (**16**). To begin, they first converted ester **59** into *bis*-enol ether **60** by a Birch reduction/alkylation sequence followed by ester reduction and protection. Oxidation of the most sterically accessible olefin was accomplished via a Sharpless dihydroxylation reaction, and the resulting diol was cleaved using $NaIO_4$ to give the aldehyde **61**. A one-pot aluminum-mediated methylation/Oppenauer oxidation sequence converted this material to a methyl ketone, which was later subjected to a Regitz diazo transfer reaction to give the diazo compound (**62**).

Diazo compound **62** is the key precursor for the construction of the [3.3.1] core system. With the assistance of a Cu catalyst and BOX ligand, diazo precursor **62** was smoothly converted to tricyclic cyclopropane intermediate **63**. This tricycle was then regioselectively dimethylated. Upon acidic work-up, Nakada and coworkers observed ring opening of the cyclopropane to reveal the bicyclo[3.3.1]nonane intermediate (see **64**). The C-8 ketone was then triflated, and a palladium-catalyzed methoxycarbonylation reaction resulted in ester **65** in 81% yield. A Crabtree reduction of the electron-deficient double bond was chemoselectively accomplished with hydrogen delivered from the sterically most accessible α-face to give **66** as single diastereomer. A subsequent DIBAL reduction was then used to reduce both the ketone and ester functional groups and gave a diol as the product. The newly formed primary alcohol was then protected with an acyl group; and the secondary alcohol was oxidized to give the bicyclic intermediate **67**. The methyl enol ether motif of intermediate **67** was oxidized to vinylogous ester **68**, and with this bicyclic enone **68** in hand, the authors then focused on assembling the periphery of the target. They first converted the primary ester to an allyl group via a three-step sequence of hydrolysis, triflation, and Cu-mediated vinylation, which afforded intermediate **69** in 73% yield. Next, focus was directed toward construction of the western tetrahydrofuran ring. Direct deprotonation of the bridgehead position (C-4 C-H bond) and S_N2 displacement gave the desired prenylated product, which was then subjected to an *m*-CBPA mediated epoxidation to deliver the epoxide **70** as the precursor for constructing the tetrahydrofuran ring. The epoxide ring of **70** was then opened upon treatment with TMSCl, and intermediate **71** was obtained in 35% yield and with 6.3:1 d.r. Before installment of the third prenyl chain, the acidic proton from tertiary alcohol **71** was masked. This vinylogous ester **71** was then subjected to an *ortho*-deprotonation/ allylation to give the allylated intermediate **72** in quantitative yield. To accomplish the total synthesis of garsubellin A (**16**), the tricycle intermediate **72** was globally deprotected, and the resulted primary alcohol was oxidized to give aldehyde **73**. This aldehyde was converted to an alcohol by a Grignard addition, and the neopentyl alcohol was oxidized with Dess-Martin periodinane to forge the desired product. Finally, after global olefin metathesis, Nakada and coworkers achieved the synthesis of garsubellin A (**16**), in 30 steps from commercially available starting materials (1.1% overall yield).

1.2 Our Synthetic Studies towards Garsubellin A (16)

1.2.1 Retrosynthetic analysis of garsubellin A (16)

In summary, the Shibasaki, Danishefsky and Nakada groups have reported three total syntheses of garsubellin A (**16**).[20-22] All of these groups had identified the construction of a highly functionalized bicyclo[3.3.1]nonane ring and the tetrahydrofuran motif as the most challenging synthetic obstacles. To solve these formidable synthetic challenges, multiple creative approaches were executed. Despite these creative solutions, these syntheses required many synthetic steps. Moreover, the key precursors were obtained after considerable efforts of adjusting the protecting groups and oxidation states of intermediates, thus lowering the overall efficiency of the pathways. We thus believed that a more efficient synthesis of garsubellin A (**16**) could be achieved if the precursor for the key reaction could be synthesized in a straightforward fashion. By exploiting our previously described enolate/diketene annulation reaction on a simple ketone, we imagined a very concise construction of the bicyclo[3.3.1]nonane core of garsubellin A could be possible.[30] Although this bicyclic core could be forged by an alternative Robinson annulation, directly introducing the oxidation state of the resulted bicyclo[3.3.1]nonane core could be challenging. This problem could be circumvented by our diketene annulation reaction as a high-oxidation-state variant of the Robinson annulation. Furthermore, we envisioned that a modular strategy toward this core could enable syntheses of several members of the PPAP family.

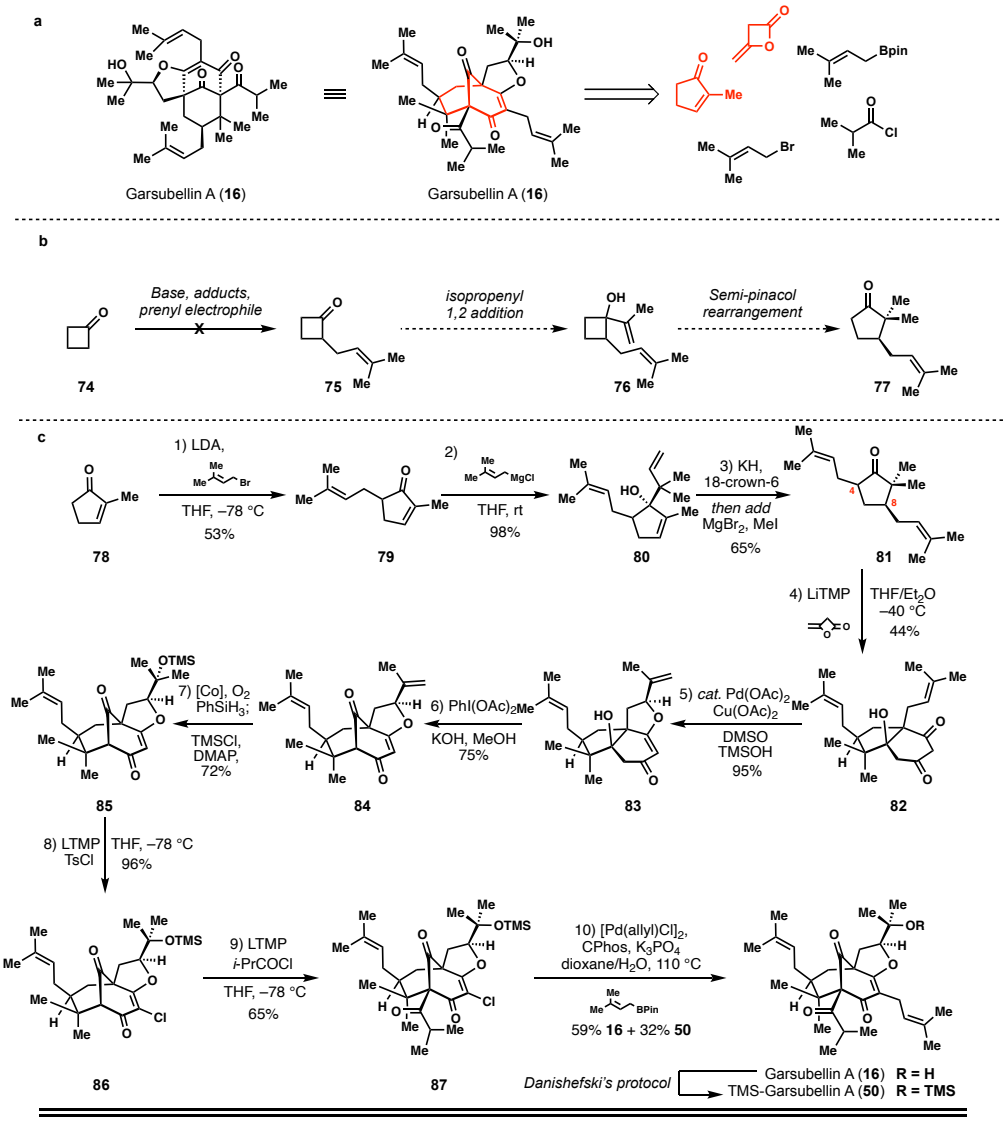
1.2.2 Synthetic efforts towards the diketene annulation precursor

To make this synthesis economic and modular, it must fulfill the following requirements: i) an efficient construction of both the tetrahydrofuran ring and bicyclo [3.3.1] nonane core, and ii) a straightforward and independent strategy for assembling the surrounding functional groups and side chains with minimal oxidation state manipulations.

With those criteria in mind, we first required access to ketone **77**, our diketene cyclization precursor. A cyclobutanone expansion strategy was first envisioned (see Scheme1.5, B), however, multiple attempts of a prenylation reaction of cyclobutanone resulted in only a complex mixture of multi-prenylated regioisomers, and only trace amounts of monoprenylated compound **75** could be isolated.

As a result, we decided to redesign our synthetic plan. It was envisioned that the heavily functionalized cyclopentanone intermediate could be constructed via an *oxy*-Cope rearrangement strategy. Moreover, this *oxy*-Cope strategy could also serve as a potential synthetic solution of other C-8 geranylated BPAP natural products, which aligns with our goal toward a modular and general PPAP synthesis platform. At the same time, this newly formed enolate could be trapped *in-situ* by methyl iodide, which would form two C-C bonds via one tandem reaction, and thus the diketene precursor

could be achieved with high efficiency.[31] To test this idea, commercially available cyclopentenone **78** was subjected to a kinetic deprotonation and mono-prenylation to

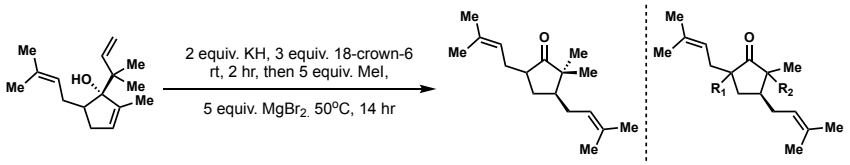


Scheme 1. 5 Our synthetic efforts of garsubellin A. (**16**) A) Retrosynthetic guideline, B) An unsuccessful approach towards cyclopentanone **77**, C) Our total synthesis of garsubellin A (**16**)

give enone **79**. Exposing this material to prenyl magnesium chloride afforded tertiary allylic alcohol **80** by a Grignard 1,2-addition. Although this tertiary alcohol is sensitive to acidic medium, the desired product was obtained in high yield via basic alumina column filtration.

With intermediate **80** in hand, we then focused on the key, one-pot *oxy*-Cope methylation reaction. To realize this tandem reaction, the *oxy*-Cope rearrangement was optimized first. We were pleased to find that with the help of crown ether, this allylic alcohol ether could be converted to the desired rearranged product in 83% yield (Table 1.1, entry 2). This promising result motivated us to try the subsequent one-pot

methylation. However, multiple attempts gave us either over methylated product **90** or protonated product **89**. After carefully analyzing all elementary reactions of this tandem transformation, it was assumed that the over methylated ketone **90** was formed after a secondary deprotonation of the monomethylated ketone (**81**/**88**), and hypothetically this problem could be solved by applying Lewis acids to tune both the nucleophilicity and basicity of the enolate formed after the *oxy*-Cope rearrangement. Meanwhile, we speculated that the sterically demanding deprotonation of the congested tertiary alcohol **80** was relatively slow, potentially resulting in incomplete deprotonation. This newly formed alkoxide species, however, may rapidly convert to an enolate via the *oxy*-Cope rearrangment. The corresponding enolate could then be protonated by the tertiary allylic alcohol **80** to yield compound **89** as an observed side product. This assumption was further supported by applying similar conditions, but with a catalytic amount of LDA, which also resulted in compound **89** (Table 1.1, Entry 3 vs. Entry 2). Hypothetically,



80 **81**

88 R_1 = Me, R_2 = H
89 R_1, R_2 = H
90 R_1, R_2 = Me

Entry	Deviation from standard condition	Result
1	Standard condition	75%, 1:0.15 **81:88**
2	1.2 equiv. LDA and 12-crown-4, 23 °C	83% **89**
3	cat. LDA and 12-crown-4, 23 °C	92% **89**
4	1.2 equiv. KH, 23 °C, 2 hr, then 2 equiv. MeI	mixture of **81** and **89**
5	LiI was added as additive	31% **81** with 10% **88**
6	$ZnBr_2$ was added as additive	complex mixture
7	$In(OAc)_3$ was added as additive	mainly **89**
8	$MgBr_2$ was added as additive	46% **81**, ca. 40% **89**
9	MeOTf was added as methylation reagent	O-methylated pdt.
10	Me_2SO_4 was added as methylation reagent	O-methylated pdt.
11	less KH and MeI	32% **81**
12	LDA was added before addition of MeI	30% **81**
13	MeI was added with three potions.	27% **81**

Table 1. 1 Optimization of the tandem *oxy*-Cope/methylation reaction

this base-catalyzed transformation could be avoided by applying a different base. Therefore, the base was changed from LDA to pre-washed potassium hydride. It was found that the sterically accessible hydride could significantly boost the yield methylated product **81**, presumably because the potassium hydride base could deprotonate the tertiary alcohol at a faster rate (Table 1.1, Entry 4). We also found that addition of anhydrous lithium chloride could provide the monomethylated product as the major product, despite a high ratio of undesired regioisomers (Table 1.1, Entry 5). This result encouraged us to further optimize this reaction by screening different metal salts. After trying various salts (for example, Table 1.1, Entry 6 and Entry 7), it was found that magnesium bromide could suppress the ratio of the undesired isomers of monomethylated products, despite a considerable amount of protonated ketone **89**

(Table 1.1, Entry 8). We thus tried to further optimize this reaction by i) screening different methylating reagents, (Table 1.1, Entry 9 and Entry 10) ii) by adding excess base to prevent aforementioned undesired proton transfer (Table 1.1, Entry 11), and iii) by adding methyl iodide in three portions (Table 1.1, Entry 12); but none of these conditions were successful. Fortunately, formation of protonated product **89** could be avoided by applying excess amounts of methyl iodide and potassium hydride while carefully tuning the addition sequence (Table 1.1, Entry 1, standard condition). Finally, the desired product was obtained as an inseparable mixture of **81** and **88** (**81:85** = 1:0.15). This optimized condition enabled the further synthetic exploration of garsubellin A (**16**).

1.2.3 Substrate screening of the diketene annulation reaction

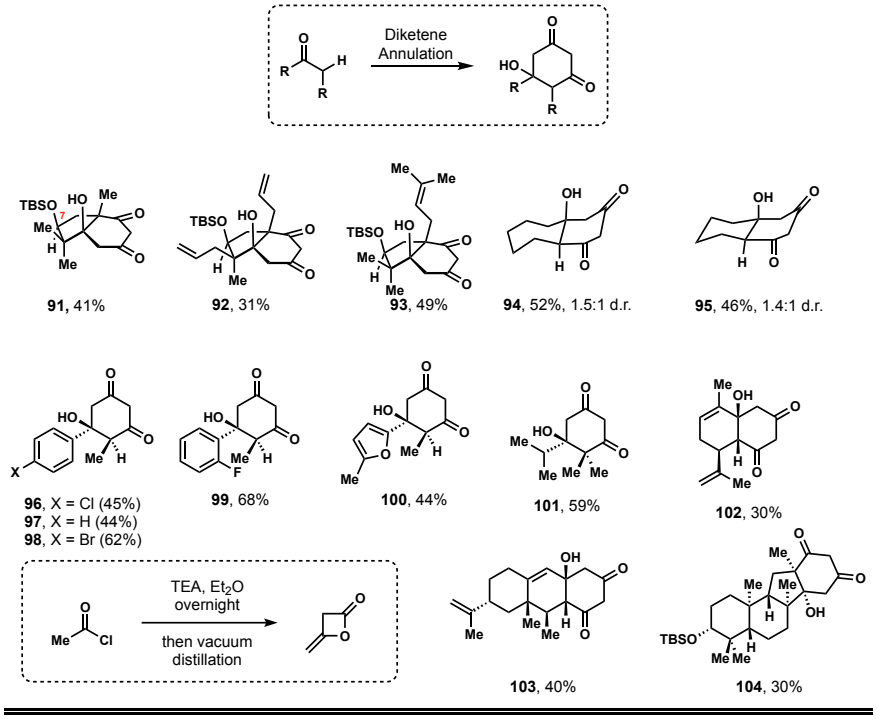


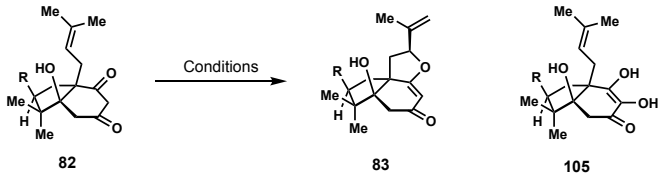
Figure 1. 3 Substrate screening of diketene annulation

As we believed this diketene annulation could serve as a key strategy for a modular synthesis of PPAP natural products, a substrate screen of this key reaction was performed. Fortunately, this diketene reaction works well on several different kinds of substrate. Multiple cyclopentanones with similar PPAP substitution patterns were first examined, largely resulting in the desired annulated products with good yields (**91**-**93**). It is noteworthy that C-7 substitution (see Figure 1.4, **91**) is critical for this annulation, presumably the pendant group could preorganize the substrate for cyclization. It was also found that the diketene annulation could work on 6- or 7- membered ketone ring systems, although the bicyclic diketone was formed in moderate d.r. (**94**, **95**). Meanwhile, diketene annulation reaction worked well on acyclic ketone substrates (**96**-

101). Interestingly, only diethyl ether was required as a solvent. Utilizing THF:Et_2O as solvent only gave acylated product. Finally, using chiral pool starting materials like carvone and nootkatone also afforded desired annulated products (**102-104**). Of note, we also developed a protocol to prepare diketene from acetyl chloride on small scales (see SI for details).

1.2.4 Construction of the tetrahydrofuron motif

Since the relatively high acidity of a 1,3-diketone motif constructed via the diketene annulation reaction might be problematic to forge the [3.3.1] nonane core directly, we decide to focus on the formation of the tetrahydrofuran ring first. This strategy could benefit us in two ways: i) by forming the tetrahydrofuran ring without further substrate manipulation and ii) by converting the 1,3-diketone motif to a vinylogous ester to eliminate the acidic proton. The Nakada's epoxidation/ring formation strategy was first examined. However, this protocol only gave us an inseparable mixture of regioisomers and stereoisomers (Table 1.2, Entry 1). Similar results were also obtained by an OsO_4-catalyzed dihydroxylation/cyclization process (Table 1.2, Entry 2). Attempts of using MMPP tentatively gave **105** as product (Table 1.2, Entry 3).



Entry	Oxidant	Solvent	Result
1	*m*-CPBA	DCM	mixture of isomers
2	OsO_4	DCM	mixture of isomers
3	MMPP	MeOH	tentatively **105**
4	PIDA	TFE	decomp.
5	$PhICl_2$	HFIP	decomp.
6	PIFA	HFIP	decomp.
7 [a]	PhI(OTs)OH	HFIP	22% **83**
8	$Pd(OAc)_2$, Benzoquinone	MeOH	47% **83**, dr. 4:1
9	$Pd(OAc)_2$, $Cu(OAc)_2$	DMSO	77% **83**
10	$Pd(OAc)_2$, $Cu(OAc)_2$	DMSO: TMSOH	> 95% **83**

Table 1. 2 Efforts towards the tetrahydrofuran motif **83**. a) Methyl vinylogous ester was used

As an exhaustive screening of olefin oxidation/cyclization strategies failed to give any promising results, it was questioned if hypervalent iodine mediated cyclization could prove fruitful. Hypothetically, the olefin would be activated by hypervalent iodine, and the subsequent nucleophilic attack could give a tricyclic product. Since the desired 5-*exo*-trig cyclization pathway is kinetically favored, we hoped by activating the olefin, the desired tricycle could be obtained with a better regioselectivity.[32] Unfortunately, applying various of hypervalent iodine reagents only gave us a complex mixture of products (Table 1.2, Entry 4-6). Exposing Koser's reagent to the vinylogous ester gave desired compound **83**, but in low yield (Table 1.2, Entry 7). Inspired by the reactivity

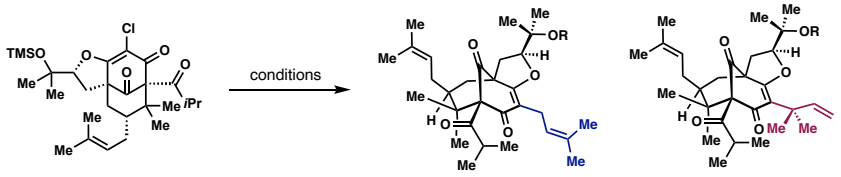
of phenol alcohol, we wondered if a Wacker-type oxidation could be applied to forge this key C-O bond via a vinylogous acid tautomer of **82**.[33] Fortunately, in our initial attempt, it was found that using $Pd(OAc)_2$ as a catalyst and benzoquinone as oxidant, the desired product **83** was obtained as a single regioisomer in 47% yield (Table 1.2, Entry 8), although the diastereoselectivity is moderate (d.r. 4:1). This result greatly encouraged us for further optimizing this novel cyclization reaction. Various oxidants, palladium catalysts, and solvents were explored. We found that a mild oxidant, $Cu(OAc)_2$ could significantly boost the yield of this Wacker-type oxidation (Table 1.2, Entry 9). We have also tried to forge a second C-O bond by *in-situ* trapping of the cyclized C-bound palladium intermediate with water or TMSOH, but all attempts proved to be unfruitful. Surprisingly, it was found that using TMSOH as a cosolvent could significantly increase the yield of Wacker oxidation from 77% to 95% (Table 1.2, Entry 10), possibly due to the enhanced solubility of the copper oxidant. With this tricyclic intermediate **83** in hand, the key [3.3.1] nonane intermediate **84** was obtained by a subsequential PIDA-mediated rearrangement.[34]

After six transformations, commercially available cyclopentenone starting material **78** was converted to vinylogous ester intermediate **84**, which is topologically equivalent to garsubellin A (**16**). To finish this synthesis, the advanced intermediate **83** was first subjected to a one-pot Mukaiyama hydration/silylation sequence to deliver silyl ether **85**. Silyl ether **85** was then converted to a vinyl chloride with TsCl. Applying LTMP as base and isobutyryl chloride as electrophile, the trione intermediate **87** was achieved, and all the quaternary centers assembled.

1.2.5 Development of regioselective prenyl coupling reaction

To regioselectively install the final prenyl group, we first tried all reported similar protocols.[35-38] However, the desired product was not observed from those conditions. Either a protonolysis product (Table 1.3, Entry 1) or, in some rare case, a complex mixture with high polarity was obtained. Based on ^1H NMR spectroscopy, such products were tentatively formed from decomposition of the reverse prenylated product **106** (Table 1.2, Entry 2, 3). For many of the conditions explored, large quantities of starting material were also recovered. Meanwhile, a magnesium-chloride exchange strategy was also attempted, in hopes that the newly formed vinyl magnesium chloride species could convert to garsubellin A (**16**) by a copper mediated S_N2 pathway. However, these conditions led to extensive decomposition.

As all attempts of using known protocols to forge this final C-C bond proved to be unfruitful, a new coupling protocol to solve this problem was required. After testing different combinations of ligands, nucleophiles, solvents, temperature, and salt additives, we were pleased to find that applying Buchwald's CPhos ligand, with 4:1 THF: H_2O as solvent, generated trace amounts of the desired product, TMS-garsubellin A (**50**) (Table 1.3, Entry 6). However, most of the vinyl chloride starting material was recovered. This led us to wonder if oxidative addition of this sterically hindered electronically unmatched vinyl chloride could be problematic, as assumption ultimately proven incorrect. We tried to couple vinyl chloride **87** with a more reactive aryl boronic



Entry	Catalyst/ Ligand	Nucleophile	Solvent	Base	Temp.	Result
1	8% $Pd(OAc)_2$/ 12% *n*-$BuPAd_2$	prenylBF_3K	Tol:H_2O 10:1	Cs_2CO_3	120 ˚C	protonlysized
2	9% $Pd(OAc)_2$/ 18% RuPhos	prenylBF_3K	Dioxane:H_2O 10:1	Cs_2CO_3	120 ˚C	decomp.
3	20% PEPPSI-Pd-iPr	prenylBpin	THF:H_2O 4:1	KOH	70 ˚C	tentitatively **106**
4	10% $Pd(OAc)_2$/ 20% RuPhos	prenylBF_3K	Tol: H_2O 4:1	K_2CO_3	100 ˚C	RSM
5	20% Pd precat/ 20% CPhos	prenylZnBr	THF	—	100 ˚C	decomp.
6[a]	20% $[Pd(allyl)Cl]_2$/ 54% CPhos	prenylBpin	THF:H_2O 1:1	K_3PO_4	100 ˚C	trace **16**
7[a]	20% $[Pd(allyl)Cl]_2$/ 54% CPhos	prenylBpin	Dioxane:H_2O 1:1	K_3PO_4	120 ˚C	~10% **16**
8[a]	20% $[Pd(allyl)Cl]_2$/ 54% CPhos	prenylBpin	Dioxane:H_2O 1:1	K_3PO_4	110 ˚C	23%
9[b]	20% $[Pd(allyl)Cl]_2$/ 54% CPhos	prenylBpin	Dioxane:H_2O 1:1	K_3PO_4	110 ˚C	91% (59% **16**, 32% **50**)
10[b]	10% $[Pd(allyl)Cl]_2$/ 27% CPhos	prenylBpin	Dioxane:H_2O 1:1	K_3PO_4	110 ˚C	73% (57% **16**, 16% **50**)

a: 32 equiv. of K_3PO_4 was used, 12 hr reaction time *b*: 16 equiv. of K_3PO_4 was used, 4 hr reaction time

Table 1. 3 Optimization of regioselective prenyl coupling reaction

ester, and the coupled product was isolated in high yield. This model study clearly suggested that oxidative addition is not the problem. Thus, we turned our attention from oxidative addition toward transmetallation. We found that most of THF was evaporated upon heating. To circumvent this problem, the solvent was switched from THF: H_2O to dioxane: H_2O. This solvent system allowed us to further elevate temperature to 120 ºC without significant evaporation of the organic solvent. It was also found that using less water, in hopes to reduce the protonolysis product, only gave us decomposed product with a characteristic vinyl proton peak in the crude NMR spectrum. After careful analysis, this counter-intuitive result made us believe that increasing the water ratio could significantly activate the prenylBpin, and thus boost the concentration of activated coupling species, despite that water could be the major proton source of protonlysis. Thus, the ratio of organic solvent: H_2O was changed from 4:1 to 1:1 (Table 1.2, Entry 7). In one case, we found that in ^1H NMR spectrum, all starting material was converted, and a characteristic triplet peak at around 5.5 ppm was visible, which corresponds to the coupled prenyl's vinyl proton. However, we were still only able to isolate the product in low yield (23%). By careful NMR analysis, we hypothesized that this decomposition started from the fragile C-O bond of vinylogous ester. To solve this problem, we tried to lower the temperature, shorten the reaction time, and reduce the amount of base utilized (Table 1.2, Entry 8). Finally, the desired natural product **16** was obtained in 59% yield, along with 32% TMS-garsubellin A **40** (Table 1.2, Entry 9). Lower catalyst loading did not significantly lower the yield of this coupling reaction (Table 1.2, Entry 10). Eventually, the total synthesis of garsubellin A (**16**) was accomplished in 10 steps, with an overall yield of 3%.

1.3 Conclusion and Remarks

In conclusion, a concise total synthesis of the PPAP natural product garsubellin A was achieved. The tricyclic core of garsubellin A was constructed by a four-step sequence involving a tandem *oxy*-Cope/methylation reaction, a diketene annulation, a Wacker-type cyclization and a PIDA-mediated rearrangement reaction. Finally, a regioselective prenyl coupling protocol was developed to assemble the final C-C bond of garsubellin A under mild conditions. Additionally, an expanded substrate scope of our diketene annulation process was also surveyed.

This project was conceived by Professor Thomas Maimone and Dr. Chi P. Ting. In Scheme 1.5, both semipinacol ring expansion strategy and *oxy*-Cope rearrangement strategy to synthesize the cyclopentanone were tested by Xingyu Shen (**74**→**77**, **78**→**81**). The synthetic protocols of diketone **82**, tricyclic compound **84**, **86, 87** were developed by Dr. Chi P. Ting. The Wacker oxidation protocol was tested by a collaboration of Dr. Gong Xu and Xingyu Shen. The Mukaiyama hydration reaction for transforming **84** to **86** was developed by Dr. Chi P. Ting and optimized by Xingyu Shen. The regioselective prenyl coupling reaction was developed and optimized by Xingyu Shen. The data was analyzed by Professor Thomas Maimone, Xingyu Shen, Dr. Chi P. Ting and Dr. Gong Xu, and crystal of **86** and **104** was grown by Dr. Gong Xu. All XRD data were obtained and refined with the help of Dr. Antonio DiPasquale and/or Dr. Nicholas Settineri. We gratefully appreciated Dr. Hasan Celik and Dr. Jeffery Pelton for NMR assistance. We also acknowledge the NIH grant GM68933 for funding the 900MHz NMR spectrometer and NIH grant S10OD024998 for funding the AV 600MHz NMR spectrometer.

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Supplementary Information

For

Chapter 1

A Concise Total Synthesis of Garsubellin A

SI 1.1 General procedures:

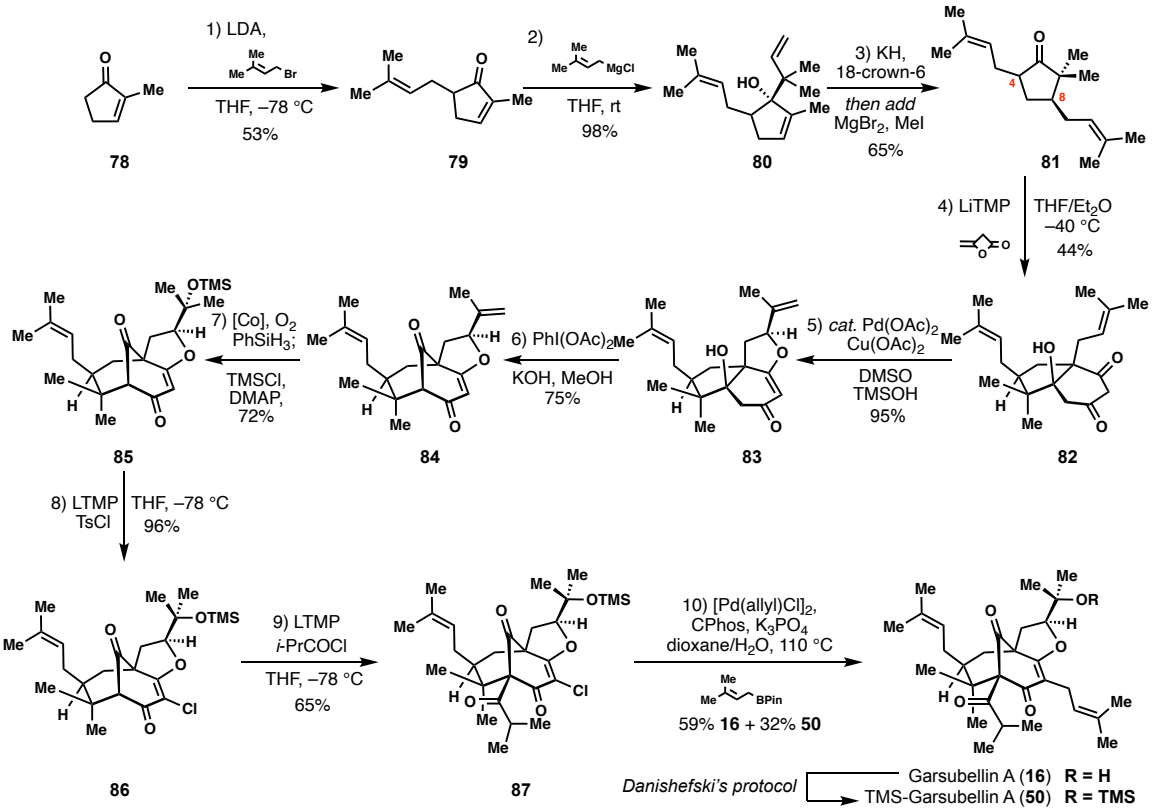
All reactions were performed in flame- or oven-dried glassware under a positive pressure of nitrogen or argon unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe. Volatile solvents were removed under reduced pressure rotary evaporation below 35 °C, DMF was removed under 60 °C. Analytical and preparative thin-layer chromatography (TLC) was performed using glass plates pre-coated with silica gel (0.25-mm, 60-Å pore size, Silicycle SiliaPlate^{TM}) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV), then were stained by submersion in an ethanolic anisaldehyde solution or a basic $KMnO_4$ solution. Flash column chromatography was performed as described by Still et al., employing silica gel purchased from Silicycle (SiliaFlash®, 60 Å, 230-400 mesh, 40-63 μm).

Dry THF, DCM and diethyl ether were obtained by passing these previously degassed solvents through activated alumina columns. TMP and TEA were distilled over calcium hydride prior to use. All other solvents and reagents were used as received without further purification.

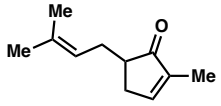
Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Bruker AV 300 (300 MHz, 76 MHz), Bruker AVQ 400 (400 MHz/101 MHz/376 MHz), Bruker AV 400 (400 MHz/101 MHz), Bruker AV 500 (500 MHz/126 MHz), Bruker DRX 500 (500 MHz/126 MHz), Bruker AV 600 (600 MHz/151 MHz) NMR, Bruker AV 700 (700 MHz/176 MHz) NMR or Bruker AV 900 (900 MHz/226 MHz) NMR spectrometers at 23 °C. Proton chemical shifts are expressed as parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.26, C_6D_6: δ 7.16, CD_3OD: δ 3.31). Carbon chemical shifts are expressed as parts per million (ppm, δ scale) and are referenced to the carbon resonance of the NMR solvent ($CDCl_3$: δ 77.2, C_6D_6: δ 128.1, CD_3OD: δ 49.15). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddd = doublet of doublets of doublets, tt = triplet of triplets, m = multiplet, b = broad, app = apparent), coupling constant (*J*) in Hertz (Hz), and integration. Infrared (IR) spectra were recorded on a Bruker Alpha FT-IR spectrometer as thin films and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained at the QB3/Chemistry Mass Spectrometry Facility at University of California, Berkeley using a Thermo LTQ-FT mass spectrometer.

SI 1.2 Compound preparation and characterization data:

SI 1.2.1 Total synthesis of garsubellin A



Supplementary Scheme 1.1 Total synthesis of garsubellin A (**16**)



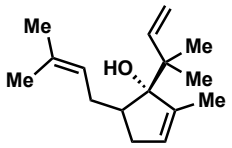
Enone **79**: A 1 L flame-dried round bottom flask was charged with 2-methylcyclopent-2-en-1-one (6.0 mL, 61.2 mmol, 1.0 equiv.). The reaction vessel was evacuated and backfilled with nitrogen and dry THF (500 mL) was added. The flask was cooled to -78 °C and freshly prepared LDA (0.5 M in THF, 135 mL, 67.5 mmol, 1.1 equiv.) was added dropwise. The resulting solution was stirred at -78 °C for 15 minutes and then prenyl bromide (9 mL, 77.5 mmol, 1.3 equiv.) was added. The reaction mixture was slowly warmed to room temperature and stirred overnight and then quenched by the addition of saturated aqueous NH_4Cl solution (500 mL). The mixture was extracted with EtOAc (500 mL), washed with brine, (500 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (3% EtOAc in hexanes) to afford enone **79** (5.3 g, 53% yield) as a yellow oil.

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.27 (m, 1H), 5.05 (m, 1H), 2.66 (dddd, J = 18.8, 8.8, 4.6, 2.2 Hz, 1H), 2.48 (m, 1H), 2.38 (dddd, J = 8.9, 6.6, 4.5, 2.2 Hz, 1H), 2.20 (dq, J = 18.8, 2.4 Hz, 1H), 2.09 (dt, J = 14.4, 8.3 Hz, 1H), 1.77 (td, J = 2.2, 1.4 Hz, 3H), 1.68 (s, 3H), 1.61 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 212.0, 157.2, 141.5, 133.8, 121.1, 45.3, 32.9, 29.9, 26.0, 18.0, 10.5.

IR (thin film) νmax 3420, 3380, 2974, 2922, 1699, 1637, 1441, 1376, 1336, 1230, 1155 cm^{-1}.

HRMS (ESI^+) *m/z* calcd. for $C_{11}H_{17}O$ $[M+H]^+$: 165.1274, found: 165.1274.



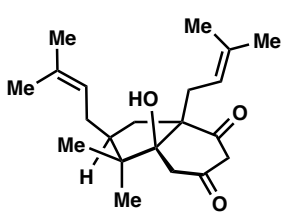
Alcohol **80**: A 250 mL flame-dried round bottom flask was charged with enone **79** (2.3 g, 14 mmol, 1.0 equiv.). The reaction flask was evacuated and backfilled with nitrogen followed by the addition of dry THF (120 mL). Freshly prepared prenylmagnesium chloride (0.67 M, 50 mL, 33.5 mmol, 2.4 equiv.) was then added and the resulting mixture stirred at room temperature for 2 hours. After this period, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution (100 mL), extracted with EtOAc (3 x 200 mL), and concentrated *in vacuo*. The crude product was purified column chromatography on neutral alumina (10% EtOAc in hexanes) to afford allylic alcohol **80** (3.2 g, 98% yield) as a colorless oil.

^{1}H NMR (700 MHz, $CDCl_3$) δ 6.12 (dd, *J* = 18.0, 10.5 Hz, 1H), 5.51 (dt, *J* = 3.1, 1.6 Hz, 1H), 5.13 (tdt, *J* = 6.3, 2.9, 1.4 Hz, 1H), 5.04 (dd, *J* = 10.5, 1.5 Hz, 1H), 5.04 (dd, *J* = 18.0, 1.5 Hz, 1H), 2.38 – 2.25 (m, 2H), 2.21 – 2.15 (m, 1H), 1.95 – 1.81 (m, 2H), 1.74 (dt, *J* = 3.6, 1.8 Hz, 3H), 1.68 (s, 3H), 1.62 (s, 3H), 1.06 (s, 3H), 1.04 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 146.1, 141.9, 132.7, 129.1, 123.8, 112.5, 89.6, 45.5, 43.3, 36.7, 30.7, 26.1, 23.0, 22.4, 18.2, 15.5.

IR (thin film) νmax 3533, 3508, 3080, 3033, 2966, 2920, 2854, 1634, 1445, 1431, 1376, 1362, 1343, 1289, 1174 cm^{-1}.

HRMS (EI) *m/z* calcd. for $C_{16}H_{26}O$ $[M]^+$: 234.1984, found: 234.1982.



Diketone **82**: *i.* A 20 mL flame-dried reaction tube was charged with KH (205 mg, 5.13 mmol, 3.0 equiv.) and 18-crown-6 (1.35 g, 5.13 mmol, 3.0 equiv.). The tube was evacuated and backfilled with nitrogen (three times in total) and THF (5 mL) added. Allylic alcohol **80** (400 mg, 1.7 mmol, 1.0 equiv.) in 1 mL of THF was then added and the resulting solution was stirred at room temperature for 2 hours. After this period, the resulting mixture was transferred to a 100 mL flame-dried round bottom flask that contained a homogenous solution of $MgBr_2$ (1.57 g, 8.54 mmol, 5.0 equiv.) in THF (20 mL) preheated to 50 °C. The resulting brown solution was stirred for 10 mins and then MeI (0.53 mL, 8.54 mmol, 5.0 equiv.) was added. After two hours of stirring at 50 °C, the reaction mixture was slowly cooled to room temperature overnight. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution (25 mL) and extracted with EtOAc (3 x 30 mL). The crude mixture was purified by column chromatography (3% EtOAc in hexanes) to afford an inseparable mixture of the desired methylated ketone (**81**)

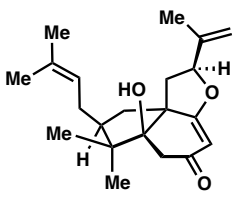
and small amounts of the C-5 methylated isomer and doubly alkylated product as a colorless oil (362 mg, 75% purity as determined by ^{1}H NMR, 65% yield) which were used directly in the next step. *ii*. A 20 mL flame-dried reaction tube was charged with **81** (250 mg, 75% purity, 0.76 mmol, 1 equiv) and the reaction vessel evacuated and backfilled with nitrogen (three times in total). Degassed THF (12.5 mL) and Et_2O (12.5 mL) were added and the reaction vessel cooled to –78 °C. Freshly prepared lithium 2,2,6,6-tetramethylpiperidide (0.45 M in THF, 2 mL, 0.9 mmol, 1.2 equiv.) was added dropwise resulting in a light-yellow colored solution. The reaction mixture was stirred for 30 minutes at –78 °C and then warmed to 0 °C and stirred 60 minutes. After this period, the reaction mixture was cooled to –40 °C and freshly distilled diketene (71 µL, 0.92 mmol, 1.2 equiv.) was added rapidly in one portion resulting in a bright yellow colored solution. The reaction vessel was maintained at this temperature for 90 minutes and then quenched by the addition of aqueous 1 M HCl (20 mL) at this temperature. The reaction mixture was extracted with EtOAc (3 x 35 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (20% EtOAc in hexanes) to afford the annulated product **82** (114 mg, 44% yield) as a red/orange solid: m.p = 109 °C.

^{1}H NMR (700 MHz, $CDCl_3$) δ 5.12 (m, 1H), 4.92 (m, 1H), 3.64 (d, *J* = 18.2 Hz, 1H), 3.12 (d, *J* = 18.2 Hz, 1H), 2.76 (dd, *J* = 13.7, 7.2 Hz, 1H), 2.64 (d, *J* = 15.2 Hz, 1H), 2.53 (dd, *J* =15.1, 7.3 Hz, 1H), 2.41 (dd, *J* = 15.1, 7.1 Hz, 1H), 2.37 (d, *J* = 15.2 Hz, 1H), 2.22 – 2.05 (m, 1H), 1.85 (s, 1H), 1.80 (ddd, *J* = 14.4, 9.6, 7.3 Hz, 1H), 1.69 (s, 6H), 1.59 (dd, *J* = 4.0, 1.3 Hz, 6H), 1.37 (dddd, *J* = 11.4, 10.1, 7.2, 4.0 Hz, 1H), 1.23 (dd, *J* = 13.7, 12.2 Hz, 1H), 0.96 (s, 3H), 0.87 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 206.3, 203.9, 135.2, 132.4, 122.9, 118.3, 83.7, 61.1, 51.9, 50.8, 48.2, 45.2, 35.2, 35.0, 29.0, 26.1, 26.0, 23.7, 18.2, 18.0, 17.9.

IR (thin film) νmax 2971, 2915, 2880, 1732, 1703, 1602, 1452, 1415, 1377, 1325, 1223 cm^{-1}.

HRMS (ESI-) *m/z* calcd. for $C_{21}H_{31}O_3$ $[M-H]^-$: 331.2279, found: 331.2274.



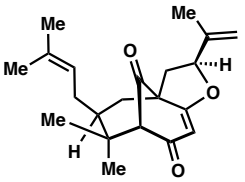
Vinylogous ester **83**: A 100 mL round bottom flask was charged with diketone **82** (100 mg, 0.3 mmol, 1.0 equiv.), $Pd(OAc)_2$ (10 mg, 0.045 mmol, 15 mol%) and $Cu(OAc)_2$ (60 mg, 0.33 mmol, 1.1 equiv.). 14 mL of DMSO and 6 mL of TMSOH were injected and the resulting green solution was allowed to stir at room temperature for 7 hours. The reaction was washed with water (3 x 40 mL) and then combined aqueous solutions extracted with diethyl ether (3 x 40 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (25% EtOAc in hexanes) to give vinylogous ester **83** as a foam (95 mg, 95% yield): m.p. = 140 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.47 (s, 1H), 5.11 (s, 1H), 5.06 (m, 1H), 4.99 (s, 1H), 4.91 (dd, *J* = 11.2, 4.8 Hz, 1H), 2.67 (d, *J* = 17.4 Hz, 1H), 2.40 (d, *J* = 17.4 Hz, 1H), 2.35 (t, *J* = 11.6 Hz, 1H), 2.19 (m, 2H), 2.02 (m, 2H), 1.93 (m, 2H), 1.75 (s, 3H), 1.69 (s, 3H), 1.64 (m, 4H), 0.98 (d, *J* = 1.7 Hz, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 196.7, 183.9, 142.0, 132.9, 122.8, 114.0, 99.8, 85.7, 84.4, 54.5, 46.7, 46.5, 46.0, 41.7, 40.7, 30.9, 25.9, 23.6, 18.8, 18.1, 17.4.

IR (thin film) νmax 2970, 2935, 1627, 1447, 1363, 1230, 1182, 1155 cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{21}H_{31}O_3$ $[M+H]^+$: 331.2268, found: 331.2268.



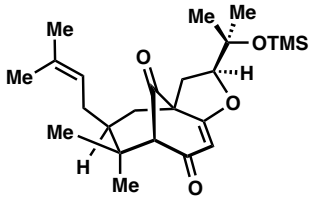
Polycycle **84**: To a 20 mL reaction tube containing vinylogous ester **83** (100 mg, 0.30 mmol, 1.0 equiv.) under nitrogen was added a solution of KOH (5 M in methanol, 6 mL) resulting reddish orange colored solution. The mixture was cooled to –10 °C and PIDA (270 mg, 0.838 mmol, 2.7 equiv.) added as a solid. The reaction mixture was maintained at a temperature of –10–0 °C for 1 hour, quenched with saturated aqueous $NaHCO_3$ (10 mL), and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography (10% EtOAc in hexanes) to give **84** as a pale yellow solid (75 mg, 75% yield). m.p. = 137 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.77 (s, 1H), 5.12 (m, 2H), 5.01 (m, 2H), 2.82 (s, 1H), 2.51 (dd, *J* = 13.1, 11.3 Hz, 1H), 2.21 – 2.15 (m, 1H), 2.13 (dd, *J* = 13.7, 4.6 Hz, 1H), 1.90 (dd, *J* = 13.2, 5.5 Hz, 1H), 1.80 (m, 1H), 1.75 (m, 1H), 1.72 (s, 3H), 1.70 (s, 3H), 1.57 (s, 3H), 1.52 (m, 1H), 1.16 (s, 3H), 0.90 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 204.4, 194.4, 178.8, 141.2, 133.7, 122.3, 114.5, 104.4, 87.6, 73.4, 60.0, 42.8, 40.5, 37.6, 33.6, 27.5, 26.8, 26.0, 20.7, 18.0, 17.2.

IR (thin film) νmax 2969, 2933, 1735, 1651, 1624, 1364, 1250, 1199, 1177, 1055 cm^{-1}.

HRMS (ESI-) *m/z* calcd. for $C_{21}H_{31}O_3$ $[M-H]^-$: 331.2279, found: 331.2274.



Polycycle **85**: A flame-dried reaction tube was charged with olefin **84** (18.6 mg, 0.06 mmol, 1.0 equiv.), (*S,S*)-(+)-*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (3.7 mg, 0.006 mmol, 10 mol%), and dry DMF (0.6 mL). Phenylsilane (8.3 μL, 0.067 mmol, 1.2 equiv.) was then added as a stock solution in DMF (0.2 mL) and the resulting red colored solution was saturated with O_2 by bubbling from a balloon for 10 minutes. The reaction mixture was then stirred at room temperature for 15 hours under an oxygen atmosphere (not bubbling). After that period, TMSCl (72 μL, 0.57 mmol, 10 equiv.), imidazole (39 mg, 0.57 mmol, 10 equiv.), and DMAP (1.4 mg, 0.011 mmol, 20 mol%) were added. The reaction mixture was stirred for 2 days at room temperature, quenched by the addition of saturated aqueous $NaHCO_3$ solution (5 mL), and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (5% EtOAc in hexanes) to give polycycle **85** as a white solid (16.8 mg, 72% yield): m.p. = 82 °C.

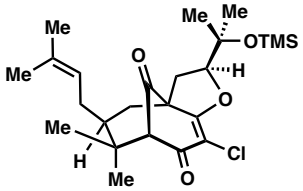
^{1}H NMR (600 MHz, $CDCl_3$) δ 5.73 (s, 1H), 5.00 (m, 1H), 4.48 (dd, *J* = 10.4, 5.8 Hz, 1H), 2.80 (s, 1H), 2.65 (dd, *J* = 13.1, 10.4 Hz, 1H), 2.18 (m, 1H), 2.06 (dd, *J* = 13.7, 4.6 Hz,

1H), 1.79 (m, 1H), 1.72 (m, 1H), 1.70 (s, 3H), 1.67 (m, 1H), 1.57 (s, 3H), 1.49 (dd, *J* = 13.7, 12.2 Hz, 1H), 1.30 (s, 3H), 1.22 (s, 3H), 1.15 (s, 3H), 0.90 (s, 3H), 0.08 (s, 9H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 204.4, 194.6, 179.5, 133.6, 122.4, 104.2, 91.6, 73.8, 73.4, 60.0, 42.6, 40.6, 38.4, 29.3, 27.5, 26.9, 26.7, 26.0, 25.9, 20.7, 18.0, 2.5.

IR (thin film) νmax 2969, 2933, 1735, 1651, 1624, 1451, 1395, 1375, 1360, 1345, 1274, 1240, 1197, 1175, 1146 cm^{-1}.

HRMS (ESI+) *m/z* calc'd for $C_{24}H_{39}O_4Si$ $[M+H]^+$: 419.2612, found: 419.2612.



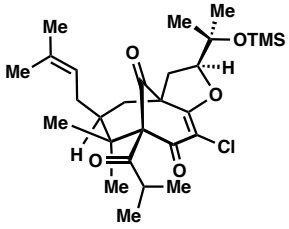
Chloride **86**. A 50 mL flame-dried flask was charged with compound **85** (125 mg, 0.30 mmol, 1.0 equiv.). The reaction vessel was evacuated and backfilled with nitrogen and this process repeated twice. THF (15 mL) was then added, and the solution cooled to -78 °C. A solution of Freshly prepared lithium 2,2,6,6-tetramethylpiperidide (0.50 M in THF, 1.23 mL, 0.62 mmol, 2.1 equiv.) was added dropwise resulting in a light-yellow colored solution. The reaction mixture was stirred for 60 minutes at -78 °C and then *p*-toluenesulfonyl chloride (120 mg, 0.63 mmol, 2.1 equiv.) was added as a solution in THF. The reaction mixture was stirred for 15 minutes at -78 °C, warmed to 0 °C and stirred 15 minutes, and then quenched by the addition of saturated aqueous $NaHCO_3$ solution (10 mL). The reaction mixture was extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (50% DCM in PhMe *then* 20% EtOAc in hexanes) affording **86** (134 mg, 98% yield) as a white solid: m.p. = 115 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48 (m, 1H), 4.61 (dd, J = 10.1, 6.0 Hz, 1H), 3.01 (s, 1H), 2.80 (dd, J = 13.1, 10.1 Hz, 1H), 2.20 (m, 1H), 2.13 (dd, *J* = 13.6, 3.9 Hz, 1H), 1.76 (dd, *J* = 13.2, 6.0 Hz, 1H), 1.70 (s, 3H), 1.69 (m, 2H), 1.56 (s, 3H), 1.51(m, 1H), 1.36 (s, 3H), 1.24 (s, 3H), 1.16 (s, 3H), 0.90 (s, 3H), 0.08 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 202.1, 187.2, 173.2, 133.9, 122.0, 106.8, 92.9, 73.8, 73.4, 61.5, 43.0, 40.6, 38.6, 29.9, 27.5, 26.7, 26.0, 25.9, 20.6, 18.0, 2.4.

IR (thin film) νmax 2967, 2934, 1739, 1669, 1615, 1452, 1385, 1366, 1344, 1249, 1216, 1177, 1051 cm^{-1}.

HRMS (ESI+) *m/z* calc'd for $C_{24}H_{38}O_4ClSi$ $[M+H]^+$: 453.2222, found: 453.2226.



Triketone **87**. Three 20 mL flame-dried reaction tubes were charged with compound **86** (3 x 40 mg, 0.27 mmol, 1.0 equiv.). The reaction vessels were evacuated and backfilled with nitrogen (three times in total) followed by the addition of THF (1 mL each). The reaction mixtures were cooled to -78 °C and a freshly prepared solution of lithium 2,2,6,6-tetramethylpiperidide (0.45 M in THF, 0.64 mL, 0.28 mmol, 3.2 equiv.) was added dropwise to each vessel resulting in a light

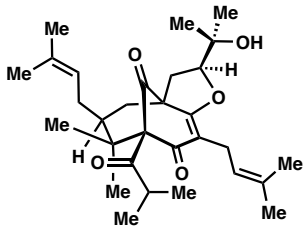
brown colored solution. The reaction mixtures were stirred for 10 minutes at -78°C, warmed to 0 °C and stirred for 5 minutes, and then re-cooled to -78 °C. Isobutyryl chloride (47 μL, 0.44 mmol, 5 equiv.) was then added dropwise to each vessel at -78 °C. The reaction mixtures were slowly warmed to -5 °C over the course of 60 minutes at which point they were quenched with saturated aqueous $NaHCO_3$ solution (5 mL). The contents of the tubes were combined and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (2% → 10% Et_2O in hexanes) to afford **87** (90 mg, 65% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.93 (m, 1H), 4.64 (dd, *J* = 9.9, 6.2 Hz, 1H), 2.93 (dd, *J* = 13.2, 9.9 Hz, 1H), 2.18 (m, 1H), 2.10 (dd, *J* = 11.7, 20.6 Hz, 1H), 2.01 (hept, *J* = 6.5 Hz, 1H), 1.80 (dd, *J* = 13.2, 6.2 Hz, 1H), 1.72 (q, *J* = 8.6 Hz, 1H), 1.68 (s, 3H), 1.58 (m, 1H), 1.55 (s, 3H), 1.43 (s, 3H), 1.31 (m, 1H), 1.27 (s, 3H), 1.24 (s, 3H), 1.08 (d, *J* = 6.6 Hz, 3H), 1.07 (s, 3H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.08 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 207.8, 202.7, 187.1, 172.8, 133.9, 122.1, 106.8, 93.1, 82.9, 73.8, 61.8, 47.0, 42.6, 42.5, 39.5, 30.2, 26.8, 26.7, 26.4, 26.0, 22.7, 21.6, 20.5, 18.1, 16.3, 2.3.

IR (thin film) νmax 2973, 2929, 1736, 1667, 1619, 1445, 1370, 1345, 1251, 1222, 1178 cm^{-1}.

HRMS (ESI+) *m/z* calc'd for $C_{28}H_{44}O_5ClSi$ $[M+H]^+$: 523.2641, found: 523.2642.



Garsubellin A (**16**) and TMS-garsubellin A (**60**). A 10 mL flame-dried reaction tube under nitrogen was charged with compound **87** (10 mg, 0.02 mmol, 1.0 equiv.) and prenylBpin (20 mg, 0.1 mmol, 5.3 equiv.). CPhos (2-Dicyclohexylphosphino-2',6'-bis(*N,N*-dimethylamino)biphenyl (2.2 mg, 0.005 mmol, 25 mol%), and $[Pd(allyl)Cl]_2$ (0.7 mg, 0.002 mmol, 10 mol%) in 0.4 mL of dioxane was injected along with 0.4 mL of an aqueous K_3PO_4 solution (65 mg, 0.30 mmol, 16 equiv. of K_3PO_4). The sealed reaction vessel was heated to 110 °C for 4 hours, cooled to room temperature, quenched with saturated aqueous $NaHCO_3$ (5 mL), and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20 mol% EtOAc in hexanes) to give **16** as a colorless oil (5.5 mg, 57 % yield). Less polar fractions were combined and re-chromatographed (25% DCM in PhMe) to give **60** as a colorless oil (1.8 mg, 17% yield):

Data for garsubellin A **16**: ^{1}H NMR (700 MHz, C_6D_6) δ 5.40 (dd, *J* = 7.4, 5.9 Hz, 1H), 4.96 (dddd, *J* = 7.3, 5.9, 2.9, 1.4 Hz, 1H), 3.91 (dd, *J* = 10.7, 5.8 Hz, 1H), 3.39 (dd, *J* = 14.2, 7.2 Hz, 1H), 3.21 (dd, *J* = 14.2, 7.6 Hz, 1H), 2.73 (dd, *J* = 13.0, 10.7 Hz, 1H), 2.26 (hept, *J* = 6.5 Hz, 1H), 2.09 (m, 1H), 1.93 (dd, *J* = 13.6, 4.5 Hz, 1H), 1.75 (dddd, *J* = 12.5, 10.5, 4.6, 2.8 Hz, 1H), 1.70 (d, *J* = 1.3 Hz, 3H), 1.61 (s, 6H), 1.58 (s, 3H), 1.55 (m, 1H), 1.45 (s, 3H), 1.37 (d, *J* = 6.5 Hz, 3H), 1.31 (d, *J* = 6.5 Hz, 3H), 1.28 (m, 1H), 1.26 (m, 1H), 1.25 (s, 3H), 1.04 (s, 1H), 0.93 (s, 3H), 0.77 (s, 3H).

^{13}C NMR (176 MHz, C_6D_6) δ 208.5, 204.7, 192.9, 173.2, 133.2, 132.5, 123.3, 122.1, 116.7, 90.2, 82.7, 70.3, 59.9, 46.7, 43.1, 42.8, 39.1, 30.3, 27.1, 26.4, 26.0, 25.8, 24.5, 23.2, 22.7, 22.0, 20.9, 17.9, 17.9, 16.5.

IR (thin film) νmax 3444, 2967, 2925, 2854, 1732, 1664, 1622, 1561, 1501, 1451, 1365, 1250, 1213, 1176, 1099, 1054 cm^{-1}.

HRMS (ESI-) *m/z* calc'd for $C_{30}H_{43}O_5$ $[M-H]^-$: 483.3116, found: 483.3127.

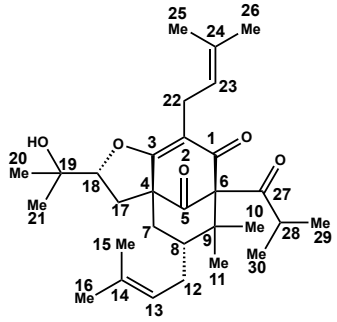
Data for TMS-garsubellin A **(60)**:^{1}H NMR (700 MHz, $CDCl_3$) δ 5.07 (m, 1H), 4.94 (m, 1H), 4.48 (dd, *J* = 10.0, 6.2 Hz, 1H), 3.14 (dd, *J* = 14.2, 7.8 Hz, 1H), 3.01 (dd, *J* = 14.3, 6.8 Hz, 1H), 2.76 (dd, *J* = 13.1, 10.0 Hz, 1H), 2.15 (d, *J* = 14.3 Hz, 1H), 2.02 (dd, *J* = 12.7, 3.7 Hz, 1H), 1.97 (hept, *J* = 6.6 Hz, 1H), 1.72 (m, 4H), 1.68 (s, 3H), 1.66 (m, 1H), 1.61 (s, 3H), 1.55 (s, 3H), 1.543 (m, 1H), 1.48 (m, 1H), 1.35 (s, 3H), 1.27 (s, 3H), 1.25 (s, 3H), 1.07 (d, *J* = 6.5 Hz, 3H), 1.04 (s, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.09 (s, 9H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 209.3, 204.9, 193.0, 173.8, 133.5, 132.4, 122.6, 121.3, 116.1, 91.0, 82.2, 74.1, 59.8, 46.3, 42.6, 42.1, 39.5, 30.1, 29.9, 26.7, 26.6, 26.2, 26.0, 25.8, 22.9, 22.4, 21.5, 20.6, 18.0, 18.0, 16.3, 2.4.

IR (thin film) νmax 2926, 2856, 1733, 1661, 1622, 1455, 1372, 1249, 1231, 1215, 1177, 1121, 1099, 1052 cm^{-1}.

HRMS (ESI-) *m/z* calc'd for $C_{33}H_{52}O_5ClSi$ $[M+Cl]^-$: 591.3278, found: 591.3276.

Natural Product Spectral Comparison:



Peak	This work	Danishefsky et at.	Nakada et al.	Shibasaki et al.	Natural
OH	3444	3444	3458	3448	3499
C=O	1732	1732	1731	1731	1730
Conj. C=O	1622	1626	1626	1627	1626

Table 1.1 IR data for garsubellin A

position	This work	Danishefsky group	Shibasaki Group	Nakada group	natural garsubellin a
7	1.26 (m, 1H)	1.32- 1.30 (m, 2H)			1.30 (dd, *J* = 11.3, 13.6 Hz, 1H)
	1.29 – 1.27 (m, 1H)	1.32- 1.30 (m, 2H)			1.32 (dd, *J* = 5.9, 12.9 Hz, 1H)
8	1.75 (dddd, J = 12.5, 10.5, 4.6, 2.8 Hz, 1H)	1.74 (m, 1H)	1.74 (m, 1H)	1.74 (m, 1H)	1.74 (dddd, *J* = 3.6, 4.5, 7.1, 11.3 Hz, 1H)
10	1.25 (s, 3H)	1.24 (s, 3H)	1.24 (s, 3H)	1.23 (s, 3H)	1.24 (s, 3H)
11	1.61 (s, 6H)	1.61 (s, 6H)	1.60 (s, 3H)	1.60 (s, 3H)	1.60 (s, 3H)
12	1.57 – 1.53 (m, 1H)	1.58 (m, 1H)	1.58 (m, 1H)	1.58 (m, 1H)	1.58 (m, 1H)
	2.15 – 2.02 (m, 1H)	2.09 (m, 1H)	2.08 (m, 1H)	2.09 (m, 1H)	2.09 (ddd, *J* = 3.6, 7.1, 13.4 Hz, 1H)
13	5.07 – 4.89 (m, 1H)	4.97 (dd, *J* = 6.9, 7.0 Hz, 1H)	4.97 (dd, *J* = 7.1, 7.1 Hz, 1H)	4.96 (brd, 1H)	4.96 (dd, *J* = 7.1, 7.1 Hz, 1H)
15	1.45 (s, 3H)	1.45 (s, 3H)	1.44 (s, 3H)	1.44 (s, 3H)	1.45 (s, 3H)
16	1.58 (s, 3H)	1.58 (s, 3H)	1.57 (s, 3H)	1.57 (s, 3H)	1.58 (s, 3H)
17	1.93 (dd, J = 13.6, 4.5 Hz, 1H)	1.93 (dd, *J* = 4.5, 13.6 Hz, 1H)	1.92 (dd, *J* = 4.6, 13.7 Hz, 1H)	1.93 (dd, *J* = 4.5, 14.0 Hz, 1H)	1.93 (dd, *J* = 4.5, 13.6 Hz, 1H)
	2.73 (dd, J = 13.0, 10.7 Hz, 1H)	2.73 (dd, *J* = 10.8, 13.1 Hz, 1H)	2.72 (dd, *J* = 10.8, 13.1 Hz, 1H)	2.73 (dd, *J* = 10.5, 13.0 Hz, 1H)	2.73 (dd, *J* = 10.7, 12.9 Hz, 1H)
18	3.91 (dd, J = 10.7, 5.8 Hz, 1H)	3.92 (dd, *J* = 5.8, 10.6 Hz, 1H)	3.91 (dd, *J* = 6.3, 10.8 Hz, 1H)	3.93 (dd, *J* = 5.5, 11.0 Hz, 1H)	3.92 (dd, *J* = 5.9, 10.7 Hz, 1H)
20	0.93 (s, 3H)	0.94 (s, 3H)	0.93 (s, 3H)	0.95 (s, 3H)	0.94 (s, 3H)
21	0.77 (s, 3H)	0.77 (s, 3H)	0.76 (s, 3H)	0.79 (s, 3H)	0.77 (s, 3H)
22	3.21 (dd, J = 14.2, 7.6 Hz, 1H)	3.21 (dd, *J* = 7.6, 14.3 Hz, 1H)	3.20 (dd, *J* = 7.4, 14.3 Hz, 1H)	3.19 (dd, *J* = 8.0, 14.0 Hz, 1H)	3.21 (dd, *J* = 7.3, 14.2 Hz, 1H)
	3.39 (dd, J = 14.2, 7.2 Hz, 1H)	3.39 (dd, *J* = 7.1, 14.1 Hz, 1H)	3.38 (dd, *J* = 7.4, 14.3 Hz, 1H)	3.36 (dd, *J* = 7.5, 14.0 Hz, 1H)	3.39 (dd, *J* = 7.1, 14.2 Hz, 1H)
23	5.40 (ddt, J = 7.4, 5.9, 1.4 Hz, 1H)	5.40 (dd, *J* = 7.3, 7.3 Hz, 1H)	5.39 (dd, *J* = 7.4, 7.4 Hz, 1H)	5.38 (m, 1H)	5.40 (dd, *J* = 7.1, 7.3 Hz, 1H)
25	1.70 (d, J = 1.3 Hz, 3H)	1.70 (s, 3H)	1.69 (s, 3H)	1.69 (s, 3H)	1.70 (s, 3H)
26	1.61 (s, 6H)	1.61 (s, 6H)	1.60 (s, 3H)	1.58 (s, 3H)	1.61 (s, 3H)
28	2.26 (hept, J = 6.5 Hz, 1H)	2.26 (qq, *J* = 6.6, 6.6 Hz, 1H)	2.25 (qq, *J* = 6.8, 6.8 Hz, 1H)	2.24 (qq, *J* = 6.5, 6.5 Hz, 1H)	2.26 (dq, *J* = 6.6 Hz, 1H)
29	1.31 (d, J = 6.5 Hz, 3H)	1.30 (d, *J* = 6.5 Hz, 3H)	1.30 (d, *J* = 6.8 Hz, 3H)	1.28 (d, *J* = 6.5 Hz, 3H)	1.30 (d, *J* = 6.6 Hz, 3H)
30	1.37 (d, J = 6.5 Hz, 3H)	1.37 (d, *J* = 6.5 Hz, 3H)	1.36 (d, *J* = 6.8 Hz, 3H)	1.34 (d, *J* = 6.8 Hz, 3H)	1.37 (d, *J* = 6.6 Hz, 3H)

Table 1.2 HNMR for garsubellin A

Position	This Work	Danishefsky *et al.*	Nakada *et al.*	Natural
1	193.0	193.3	193.0	192.9
2	116.7	117.1	116.7	116.7
3	173.2	173.6	173.3	173.2
4	59.9	60.2	59.9	59.8
5	204.7	205.0	204.7	204.7
6	82.7	83.0	82.7	82.6
7	39.1	39.4	39.1	39.0
8	43.1	43.3	43.1	43.0
9	46.7	47.0	46.7	46.6
10	16.5	16.9	16.5	16.5
11	23.2	23.5	23.2	23.1
12	27.1	27.4	27.1	27.0
13	123.3	123.6	123.3	123.2
14	133.2	133.5	133.2	133.2
15	17.93	18.2	17.94	17.8
16	26.0	26.3	26.0	25.9
17	30.3	30.6	30.3	30.3
18	90.2	90.5	90.2	90.1
19	70.3	70.6	70.3	70.2
20	26.4	26.7	26.4	26.3
21	24.5	24.8	24.5	24.4
22	22.7	23.0	22.7	22.6
23	122.1	122.4	122.1	122.0
24	132.5	132.8	132.4	132.4
25	17.90	18.3	17.90	17.9
26	25.8	26.1	25.8	25.7
27	208.5	208.9	208.6	208.5
28	42.8	43.1	42.7	42.7
29	22.0	22.3	21.9	21.9
30	20.9	21.3	20.9	20.9

Table 1.3 CNMR for garsubellin

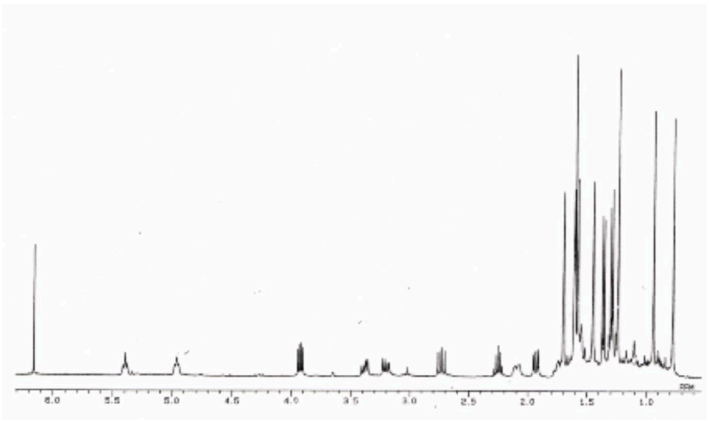


Figure 1.1 Natural Garsubellin A

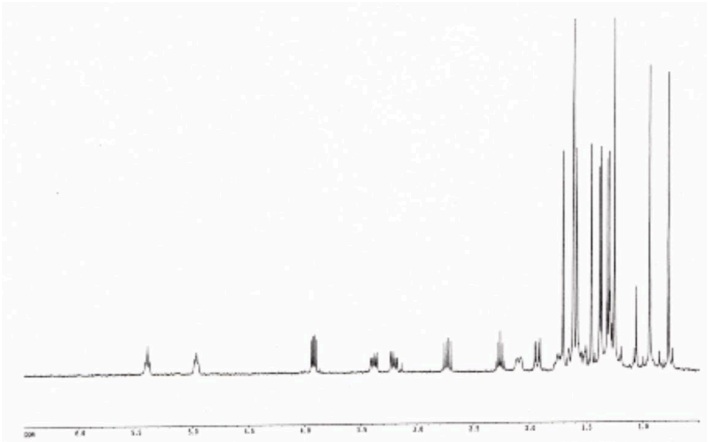


Figure 1.2 Synthetic Garsubellin A reported by Danishefsky *et al.*

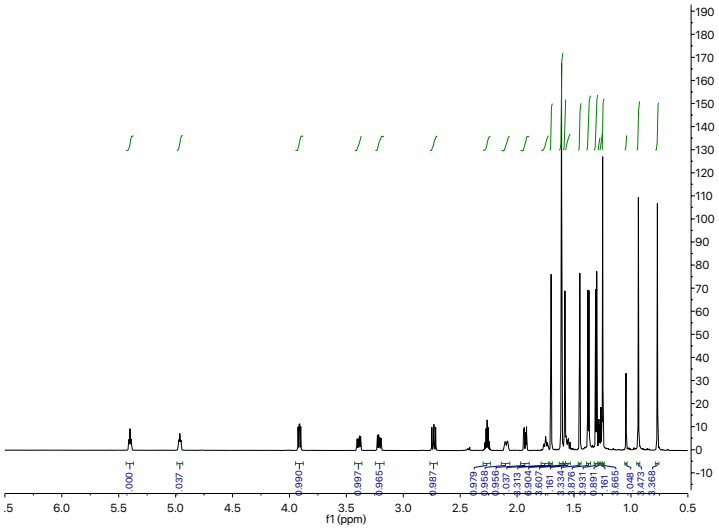
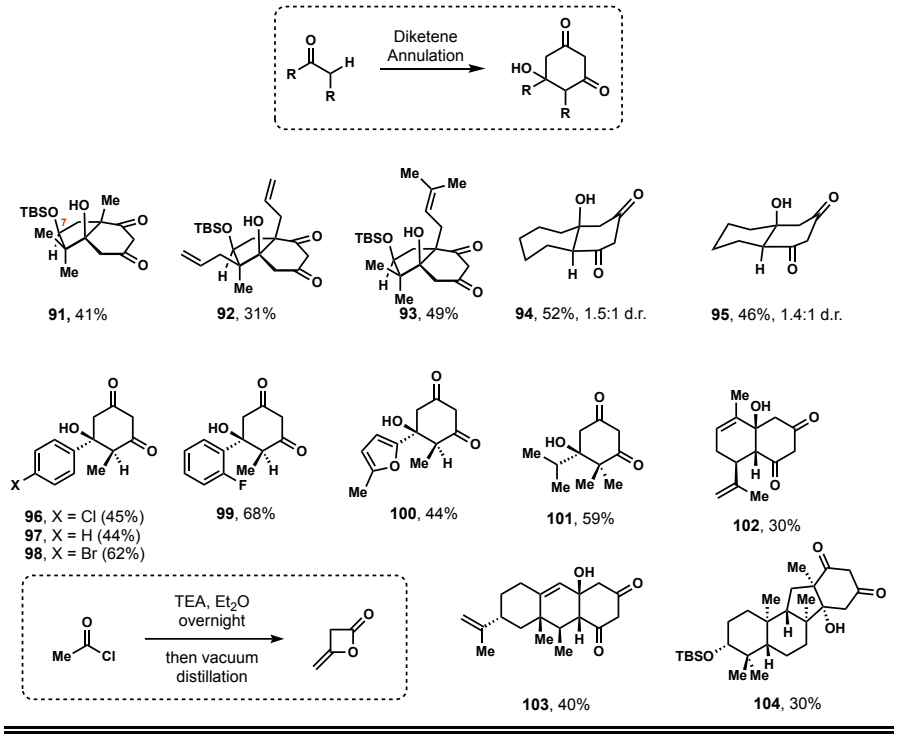


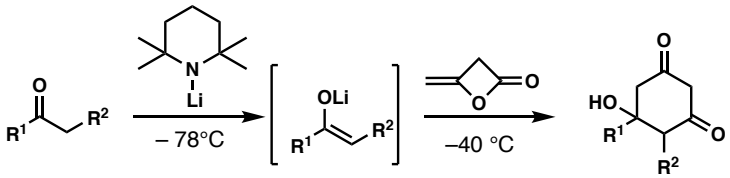
Figure 1.3 Synthetic Garsubellin A

SI 1.2.2 Substrate evaluation of the enolate/diketene annulation reaction.



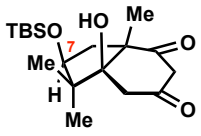
Supplementary Scheme 1.2 Substrate table of diketene annulation

General Procedure for the annulation of lithium enolates with diketene employing enolates generated by ketone deprotonation with Lithium 2,2,6,6-tetramethylpiperidide (LTMP).:



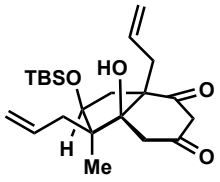
A 20 mL flame-dried reaction tube was charged with 2,2,6,6-tetramethylpiperidine (0.19 mL, 1.1 mmol, 1.1 equiv). The reaction vessel was evacuated and backfilled with nitrogen three times followed by the addition of Et_2O (2.5 mL) or THF (2.5 mL). After cooling the reaction vessel to –78°C, *n*-BuLi (2.5 M in hexanes, 0.42 mL, 1.05 mmol was added dropwise resulting in a light-yellow solution. The reaction mixture was stirred for 30 minutes at -78°C and then 15 minutes at 0 °C. After re-cooling the reaction vessel to –78 °C, the ketone (1.0 mmol, 1.1 equiv) was added dropwise as a solution in Et_2O (2.5 mL). The reaction mixture was stirred for 30 minutes at –78°C and then 30 minutes at 0°C. The reaction mixture was cooled to –40°C and freshly distilled diketene (84 µL, 1.1 mmol, 1.1 equiv) was added rapidly in one portion resulting in the formation of white precipitate. The reaction vessel was maintained at this temperature for 60 minutes then quenched with 1 M HCl (20 mL). The reaction mixture was extracted with EtOAc (3 x 25 mL) and the

combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography to afford the annulated product.



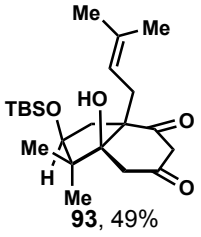
91, 41%

Diketone **91**. Following the general procedure (0.1 mmol scale) and using Et_2O/THF (*v:v* = 1:1) as solvent, the title compound was obtained after column chromatography (20% EtOAc in hexanes) as a white solid (14.3 mg, 41% yield): ^{1}H NMR (700 MHz, $CDCl_3$) δ 4.33 (d, *J* = 1.0 Hz, 1H), 3.74 (d, *J* = 1.1 Hz, 1H), 3.72 (d, *J* = 5.8 Hz, 1H), 3.26 (dd, *J* = 17.0, 2.4 Hz, 1H), 3.13 (dd, *J* = 15.4, 5.9 Hz, 1H), 2.84 (dd, *J* = 16.1, 2.4 Hz, 1H), 2.67 (d, *J* = 16.1 Hz, 1H), 1.57 (d, *J* = 15.4 Hz, 1H), 1.48 (s, 3H), 1.06 (s, 3H), 0.91 (s, 9H), 0.49 (s, 3H), 0.10 (s, 4H), 0.08 (s, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 208.7, 202.0, 83.8, 81.8, 59.8, 54.4, 51.0, 46.6, 42.1, 25.8, 24.1, 22.1, 18.0, 17.9, -4.7, -5.0; IR (thin film) vmax 3464, 2956, 2929, 2884, 1727, 1601 cm^{-1}; HRMS (ESI-) *m/z* calcd. for $C_{18}H_{31}O_4Si$ $[M-H]^-$: 339.1997, found: 339.1997.



92, 31%

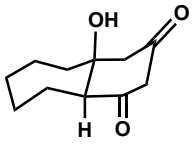
Diketone **92**. Following the general procedure (0.1 mmol scale) and using Et_2O/THF (*v:v* = 1:1) as solvent, the title compound was obtained after column chromatography (50% EtOAc in hexanes) as a light yellow solid (11 mg, 31% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.75 (dt, *J* = 9.8, 5.9 Hz, 1H), 5.21 – 5.07 (m, 2H), 4.40 (s, 1H), 3.87 (d, *J* = 5.5 Hz, 1H), 3.79 – 3.68 (m, 1H), 3.28 (dd, *J* = 17.3, 2.2 Hz, 1H), 3.07 (dd, *J* = 15.6, 5.6 Hz, 1H), 2.92 (dd, *J* = 15.9, 2.2 Hz, 1H), 2.69 (d, *J* = 15.9 Hz, 1H), 2.64 (dd, *J* = 14.1, 5.4 Hz, 1H), 2.11 (dd, *J* = 14.1, 9.2 Hz, 1H), 1.64 (d, *J* = 15.5 Hz, 1H), 0.94 (s, 9H), 0.47 (s, 3H), 0.17 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 208.7, 202.0, 134.2, 118.6, 84.3, 80.3, 60.0, 54.2, 53.3, 47.1, 41.7, 35.0, 25.9, 24.0, 18.8, 17.9, -4.0, -5.0; IR (thin film) vmax 3458, 2952, 2929, 2857, 1592, 1462, 1408, 1390 cm^{-1}; HRMS (ESI-) *m/z* calcd. for $C_{20}H_{33}O_4Si$ $[M-H]^-$: 365.2154, found: 365.2155.



93, 49%

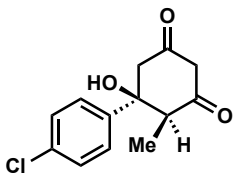
Diketone **93**. Following the general procedure (0.1 mmol scale) and using Et_2O/THF (*v:v* = 1:1) as solvent, the title compound was obtained after column chromatography (20% EtOAc in hexanes) as a white solid (19.1 mg, 49% yield): ^{1}H NMR (600 MHz, CD_2Cl_2) δ 5.07 (td, *J* = 6.9, 3.2 Hz, 1H), 4.29 (s, 1H), 3.75 (d, *J* = 5.7 Hz, 1H), 3.59 (d, *J* = 16.9 Hz, 1H), 3.19 (dd, *J* = 16.9, 2.2 Hz, 1H), 2.96 (dd, *J* = 15.5, 5.8 Hz, 1H), 2.78 (dd, *J* = 16.1, 2.2 Hz, 1H), 2.74 – 2.65 (m, 2H), 2.59 (dd, *J* = 15.0, 6.9 Hz, 1H), 1.70 (d, *J* = 1.5 Hz, 3H), 1.64-1.60 (m, 4H), 1.04 (s, 3H), 0.91 (s, 9H), 0.47 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (151 MHz, CD_2Cl_2) δ 207.9, 202.4, 135.7, 119.5, 84.2, 82.3, 64.0,

56.4, 51.40, 47.7, 40.5, 36.3, 26.1, 25.9, 22.2, 18.1, 18.1, 17.9, -4.7, -5.1; IR (thin film) vmax 3468, 2955, 2929, 2929, 2857, 1736, 1606 cm^{-1}; HRMS (ESI-) *m/z* calcd. for $C_{22}H_{37}O_4Si$ $[M-H]^-$: 393.2467, found: 393.2467.



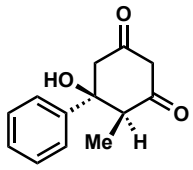
94, 52%, 1.5:1 d.r.

Diketone **94**: Following the general procedure (1.0 mmol scale) using Et_2O as solvent, the title compound (major isomer) was isolated by silica gel column chromatography (30%→40% EtOAc in hexanes) as a brown solid (61 mg, 31% yield). The remaining column fractions were concentrated and re-purified by silica gel column chromatography (0%→7.5% MeOH in CH_2Cl_2) to give the minor diastereomer as a yellow solid (42 mg, 21% yield). Major diastereomer: m.p. = 116-118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.41 (dd, *J* = 18.3, 1.9 Hz, 1H), 3.31 (d, *J* = 18.2 Hz, 1H), 2.89 (d, *J* = 16.2 Hz, 1H), 2.71 – 2.58 (m, 2H), 2.37 – 2.24 (m, 1H), 2.10 (bs, 1H), 2.08 – 1.96 (m, 2H), 1.88 – 1.76 (m, 2H), 1.72 (dd, *J* = 14.3, 10.1 Hz, 1H), 1.53 – 1.41 (m, 2H), 1.41 – 1.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.3, 203.3, 74.4, 60.4, 56.0, 55.3, 42.6, 29.5, 28.1, 22.1, 20.6; IR (thin film) vmax 3391, 2925, 2862, 1726, 1700, 1451 cm^{-1}; HRMS (ESI): *m/z* calcd. for $[C_{11}H_{15}O_3]^-$ $(M-H)^-$: 195.1027, found 195.1055.



96, (45%)

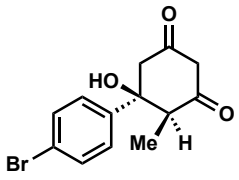
Diketone **96**: Following the general procedure (0.4 mmol scale) using Et_2O as solvent, the title compound was isolated by silica gel column chromatography (50% EtOAc in hexanes) as a light yellow solid (45 mg, 45% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.6 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 2H), 3.82 – 3.48 (m, 2H), 3.22 (d, *J* = 15.7 Hz, 1H), 3.14 (q, *J* = 6.8 Hz, 1H), 2.86 (dd, *J* = 15.7, 1.8 Hz, 1H), 0.94 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 202.5, 201.3, 141.9, 133.9, 129.3, 126.1, 76.0, 57.3, 55.6, 53.3, 8.4; IR (thin film) vmax 3394, 2941, 2349, 1733, 1703, 1606, 1491, 1455 cm^{-1}; HRMS (ESI-): *m/z* calcd. for $C_{13}H_{12}O_3{}^{35}Cl]^-$ (M-H)-: 251.0480, found: 251.0482.



97, (44%)

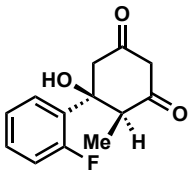
Diketone **97:** Following the general procedure (1.0 mmol scale) using Et_2O as solvent, the title compound was isolated by silica gel column chromatography (20% → 50% EtOAc in hexanes) as a white crystalline solid (138 mg, 63% yield): m.p. = 171-173 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.37 (m, 4H), 7.36 – 7.30 (m, 1H), 3.60 (d, *J* = 20.0 Hz, 1H), 3.55 (d, *J* = 20.0 Hz, 1H), 3.26 (d, *J* = 15.8 Hz, 1H), 3.18 (q, *J* = 6.8 Hz, 1H), 2.88 (dd, *J* = 15.7, 1.6 Hz, 1H), 2.14 (b, 1H), 0.94 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.0, 201.6, 143.3, 129.1, 127.9, 124.5, 76.2, 57.3,

55.8, 53.4, 8.5; IR (thin film) vmax 3379, 3029, 2996, 2899, 1726, 1700 cm^{-1}; HRMS (EI): *m/z* calcd. for $[C_{13}H_{14}O_3]$: 218.0941, found 218.0943



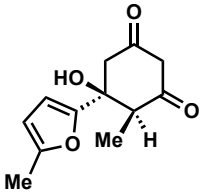
98, (62%)

Diketone **98:** Following the general procedure (1.0 mmol scale) using Et_2O as solvent, the title compound was isolated by silica gel column chromatography (20%→60% EtOAc in hexanes) as an orange solid (184 mg, 62% yield): m.p. = 155-158 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.7 Hz, 2H), 7.28 (d, *J* = 8.7 Hz, 2H), 3.58 (d, *J* = 20.0 Hz, 1H), 3.53 (dd, *J* = 20.0, 1.9 Hz, 1H), 3.22 (d, *J* = 15.7 Hz, 1H), 3.13 (q, *J* = 6.8 Hz, 1H), 2.85 (dd, *J* = 15.8, 1.9 Hz, 1H), 2.38 (bs, 1H), 0.93 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 201.4, 142.5, 132.2, 126.4, 122.0, 76.0, 57.3, 55.5, 53.3, 8.4; IR (thin film) vmax 3569, 3368, 2985, 2903, 1700, 1588 cm^{-1}; HRMS (ESI): *m/z* calcd. for $[C_{13}H_{12}BrO_3]^-$ $(M-H)^-$: 294.9975, found 294.9991.



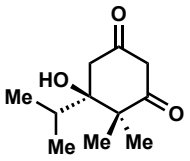
99, 68%

Diketone **99:** Following the general procedure (1.0 mmol scale) using Et_2O as solvent, the title compound was isolated by silica gel column chromatography (20%→50% EtOAc in hexanes) as a white crystalline solid (160 mg, 68% yield): m.p. = 154-158 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (td, *J* = 8.1, 1.8 Hz, 1H), 7.41 – 7.32 (m, 1H), 7.23 (td, *J* = 7.7, 1.3 Hz, 1H), 7.10 (ddd, *J* = 12.2, 8.2, 1.2 Hz, 1H), 3.67 – 3.44 (m, 4H), 2.81 (dd, *J* = 15.8, 2.3 Hz, 1H), 2.42 (bs, 1H), 0.92 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6, 201.8, 158.7 (d, *J* = 244.4 Hz), 130.3 (d, *J* = 8.6 Hz), 130.0 (d, *J* = 12.4 Hz), 127.0 (d, *J* = 3.7 Hz), 125.0 (d, *J* = 3.6 Hz), 116.5 (d, *J* = 23.4 Hz), 74.9 (d, *J* = 4.4 Hz), 57.4, 53.3 (d, *J* = 3.6 Hz), 51.5 (d, *J* = 4.1 Hz), 8.5; IR (thin film) vmax 3391, 2925, 2854, 1730, 1700, 1488 cm^{-1}; HRMS (ESI): *m/z* calcd. for $[C_{13}H_{12}FO_3]^-$ $(M-H)^-$: 235.0776, found 235.0792.



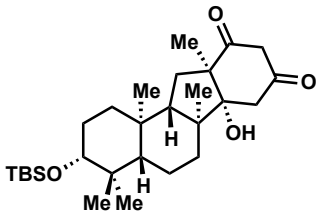
100, 44%

Diketone **100**: Following the general procedure (1.0 mmol scale) using Et_2O as solvent, the title compound was isolated by silica gel column chromatography (50% EtOAc in hexanes) as a brown oil (97 mg, 44% yield): ^1H NMR (500 MHz, $CDCl_3$) δ 6.18 (d, *J* = 3.0 Hz, 1H), 5.93 (d, *J* = 3.0 Hz, 1H), 3.50 (s, 2H), 3.28 (d, *J* = 16.0 Hz, 1H), 3.14 (q, *J* = 6.8 Hz, 1H), 2.90 (d, *J* = 16.0 Hz, 1H), 2.70 (bs, 1H), 2.28 (s, 3H), 1.04 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.1, 201.9, 153.5, 152.5, 107.2, 106.6, 73.3, 57.1, 53.4, 52.3, 13.7, 8.7; IR (thin film) vmax 3357, 2985, 2925, 1707, 1603, 1451 cm^{-1}; HRMS (ESI): *m/z* calcd. for $[C_{12}H_{13}O_4]^-$ $(M-H)^-$: 221.0819, found 221.0830.



101, 59%

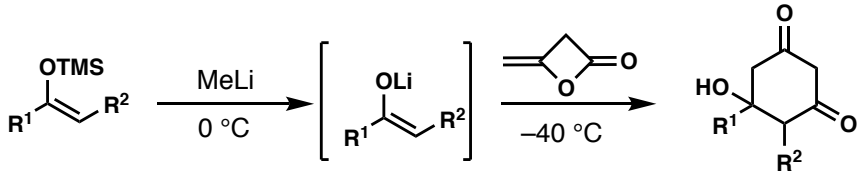
Diketone **101**: Following the general procedure (0.42 mmol scale) and using Et_2O/THF (*v*:*v* = 1:1) as solvent, the title compound was isolated by silica gel column chromatography (50%→60% EtOAc in hexanes) as a white solid (49 mg, 59% yield): m.p. = 108-113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.43 (d, *J* = 20.0 Hz, 1H), 3.38 (d, *J* = 20.0 Hz, 1H), 2.87 (d, *J* = 17.0 Hz, 1H), 2.64 (d, *J* = 17.0 Hz, 1H), 2.10 (sept, *J* = 6.9 Hz, 1H), 2.02 (bs, 1H), 1.30 (s, 3H), 1.26 (s, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.1, 204.3, 77.7, 53.6, 53.1, 43.4, 34.8, 21.9, 19.1, 18.3, 18.0; IR (thin film) vmax 3595, 3473, 2988, 2970, 2571, 1611 cm^{-1}; HRMS (ESI): *m/z* calcd. for $[C_{11}H_{17}O_3]^-$ (M-H)$^-$: 197.1183, found 197.1175.



104, 30%

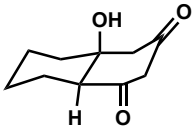
Diketone **104**: Following the general procedure (0.13 mmol scale) and using Et_2O/THF (*v*:*v* = 1:1) as solvent, the title compound was isolated by silica gel column chromatography (2% EtOAc in hexanes → 20% EtOAc in hexanes) as a white solid (18.0 mg, 30% yield, 47% BRSM): m.p. = 205-207 C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.68 (d, *J* = 18.7 Hz, 1H), 3.14 (dd, *J* = 11.5, 4.6 Hz, 1H), 3.11 (d, *J* = 18.5 Hz, 1H), 2.63 (d, *J* = 15.0 Hz, 1H), 2.58 (dd, *J* = 12.9, 6.3 Hz, 1H), 2.43 (d, *J* = 14.9 Hz, 1H), 1.89 (s, 1H), 1.68-1.56 (m, 2H), 1.54-1.42 (m, 4H), 1.40-1.35 (m, 1H), 1.34 (s, 3H), 1.22-1.14 (m, 1H), 1.08 (s, 3H), 1.02-0.93 (m, 2H), 0.92 (s, 3H), 0.88 (s, 12H), 0.76 (s, 3H), 0.66 (dd, *J* = 12.2, 2.3 Hz, 1H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.9, 204.2, 82.1, 79.5, 57.8, 56.4, 54.5, 51.1, 50.8, 48.8, 39.5, 38.6, 36.7, 34.6, 30.2, 28.6, 27.6, 26.1, 24.9, 19.0, 18.3, 16.3, 16.3, 15.9, -3.6, -4.8; IR (thin film) vmax 3406, 2927, 2854, 1726, 1701, 1468, 1387, 1362, 1305, 1254, 1104, 1088, 1062, 1045, 1006, 984, 912, 880, 832, 772 cm^{-1}; HRMS (ESI) *m/z* calcd. for $[C_{28}H_{47}O_4Si]^-$(M-H)$^-$: 475.3249, found 475.3242.

General Procedure for the annulation of lithium enolates with diketene using enolates generated by desilylation of trimethylsilyl enol ethers with methyl lithium.



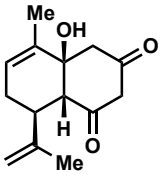
A flame-dried reaction tube was charged with the trimethylsilyl enol ether (0.89 mmol, 1.1 equiv). The reaction vessel was evacuated and backfilled with nitrogen (3 times in total) and Et_2O (4 mL) was added. After cooling the reaction to 0 °C, methyllithium (1.6 M in Et_2O, 0.80 mmol, 1.0 equiv) was added and the reaction mixture stirred for 1 hour. The

reaction mixture was warmed to room temperature and monitored by TLC for consumption of the starting silyl enol ether. The reaction vessel was then cooled to -40 °C and freshly distilled diketene (0.89 mmol, 1.0 equiv) was rapidly added resulting in the formation of white precipitate. The suspension was stirred for 1 hour and then quenched with 1 M HCl (5 mL) and slowly warmed to room temperature. The reaction mixture was diluted in EtOAc (15 mL) and the layers separated. The aqueous layer was extracted with EtOAc (2 x 20 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford a yellow oil. The crude residue was purified by silica gel column chromatography to afford the annulated product.



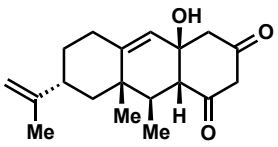
95, 46%, 1.4:1 d.r.

Diketone **95:** Following the general procedure (0.80 mmol scale), the major *trans* diastereomer was isolated by silica gel column chromatography (50%→100% EtOAc in hexanes) as a white solid (40 mg, 27% yield). The remaining column fractions were concentrated and re-purified by silica gel column chromatography (5%→7.5% MeOH in CH_2Cl_2) to afford the *cis* diastereomer as a yellow solid (27 mg, 19% yield). **97** (major diastereomer): m.p. = 145-147 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.43 (dd, *J* = 18.0, 1.6 Hz, 1H), 3.40 (d, *J* = 18.0 Hz, 1H), 2.77 (d, *J* = 15.5 Hz, 1H), 2.72 (dd, *J* = 15.5, 1.5 Hz, 1H), 2.51 (dd, *J* = 12.1, 4.2 Hz, 1H), 2.03 – 1.96 (m, 1H), 1.93 – 1.87 (m, 1H), 1.80 (ddt, *J* = 13.4, 4.0, 1.7 Hz, 1H), 1.72 (bs, 1H), 1.71 – 1.66 (m, 1H), 1.63 – 1.56 (m, 2H), 1.56 – 1.49 (m, 1H), 1.28 (qt, *J* = 13.3, 3.7 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.4, 202.4, 70.8, 57.5, 55.2, 55.1, 38.9, 24.6, 21.3, 21.0; IR (thin film) vmax 3383, 2981, 2936, 2854, 1726, 1700 cm^{-1}; HRMS (ESI): calcd. for $[C_{10}H_{13}O_3]^-$ (M-H)$^-$: *m/z* 181.0870, found 181.0872.



102, 30%

Diketone **102**: Following the general procedure (0.82 mmol scale), the title compound was isolated by silica gel column chromatography (50%→100% EtOAc in hexanes) as a white solid (67 mg, 35% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50 (s, 1H), 4.84 (s, 1H), 4.79 (s, 1H), 3.49 (d, *J* = 16.5Hz, 1H), 3.31 (d, *J* = 16.4, 1H), 2.99 – 2.86 (m, 2H), 2.85 – 2.77 (m, 1H), 2.29 (ddt, *J* =15.6, 10.4, 2.6 Hz, 1H), 2.22 – 2.08 (m, 1H), 1.77 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.2, 201.0, 145.2, 136.5, 123.7, 114.2, 73.3, 60.8, 56.5, 48.5, 45.6, 30.3, 17.5, 16.8.

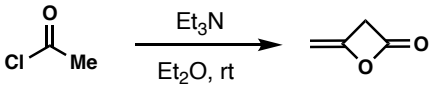


103, 40%

Diketone **103**: Following the general procedure (1.0 mmol scale), the title compound was isolated by silica gel column chromatography (100% EtOAc) as a white solid (121 mg, 40% yield): m.p. = 164-166 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.35 (s, 1H), 4.73 (s, 1H), 4.69 (s, 1H), 3.43 (d, *J* = 16.2 Hz, 1H), 3.36 (d,

J = 16.2 Hz, 1H), 2.91 (d, J = 15.4 Hz, 1H), 2.72 (d, J = 15.4 Hz, 1H), 2.61 (d, J = 12.2 Hz, 1H), 2.39 – 2.32 (m, 1H), 2.28 (t, J = 12.4 Hz, 1H), 2.17 – 2.11 (m, 1H), 2.05 – 1.99 (m, 1H), 1.97 (d, J = 12.7 Hz, 1H), 1.88 (d, J = 12.8 Hz, 1H), 1.72 (s, 3H), 1.30 – 1.18 (m, 1H), 1.08 (s, 3H), 1.02 (t, J = 12.7 Hz, 1H), 0.91 (d, J = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.5, 200.7, 149.4, 145.7, 125.1, 109.3, 71.5, 59.8, 56.9, 50.3, 44.8, 41.8, 40.7, 40.1, 32.8, 32.3, 21.0, 18.3, 12.6; IR (thin film) vmax 3346, 2974, 2933, 2854, 1596, 1529 cm^{-1}; HRMS (ESI): calcd. for $[C_{19}H_{25}O_3]^-$ (M-H)$^-$: *m/z* 301.1809, found 301.1822.

SI 1.2.3 Procedure to prepare diketene from acetyl chloride



A flame-dried 500mL three-neck flask with a fritted side neck (see image **A** below) was charged with acetyl chloride (3 mL, 42 mmol, 1.2 equiv) and dry Et_2O (100 mL) under nitrogen. Freshly distilled triethylamine (5 mL, 36 mmol, 1 equiv.) was added dropwise and the resulting solution stirred vigorously at room temperature for 15 hr. Under positive nitrogen pressure, the white salts were filtered off and the solution collected in a dry three-neck flask (see image **B** below). The salts were washed with additional Et_2O (3 x 50mL) and the combined ether solution concentrated *in vacuo* using a rotary evaporator with an ice-water cooling bath. Upon removal of diethyl ether, the flask was back-filled with nitrogen and a Hickman distillation head with a side port and cooling jacket was attached (see image **C** below). The cooling jacket was cooled to –78 °C (dry ice and acetone) and the diketene was distilled at room temperature using high vacuum wherein a frozen white solid formed in the neck of the Hickman head. The high vacuum was replaced by a nitrogen atmosphere and the dry ice/acetone cooling jacket warmed to room temperature resulting in diketene as a colorless liquid (0.34 mL, 4.4 mmol 24% yield). Spectroscopic data was in agreement with the literature and a commercial sample from Sigma Aldrich.

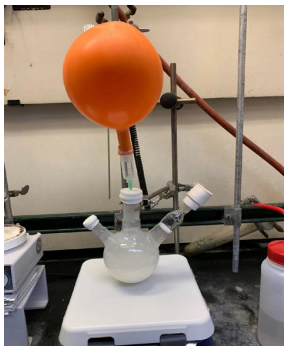


image **A** (reaction set-up)

image **B** (filtration under N_2)

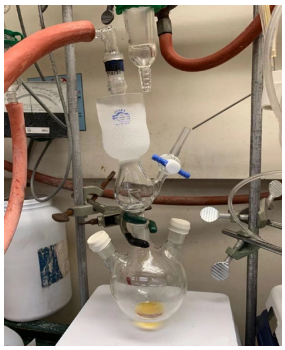


image **C** (Hickman distillation)

Supplementary Figure 2.1 Synthesis of diketene using common laboratory equipment.

Supplementary References

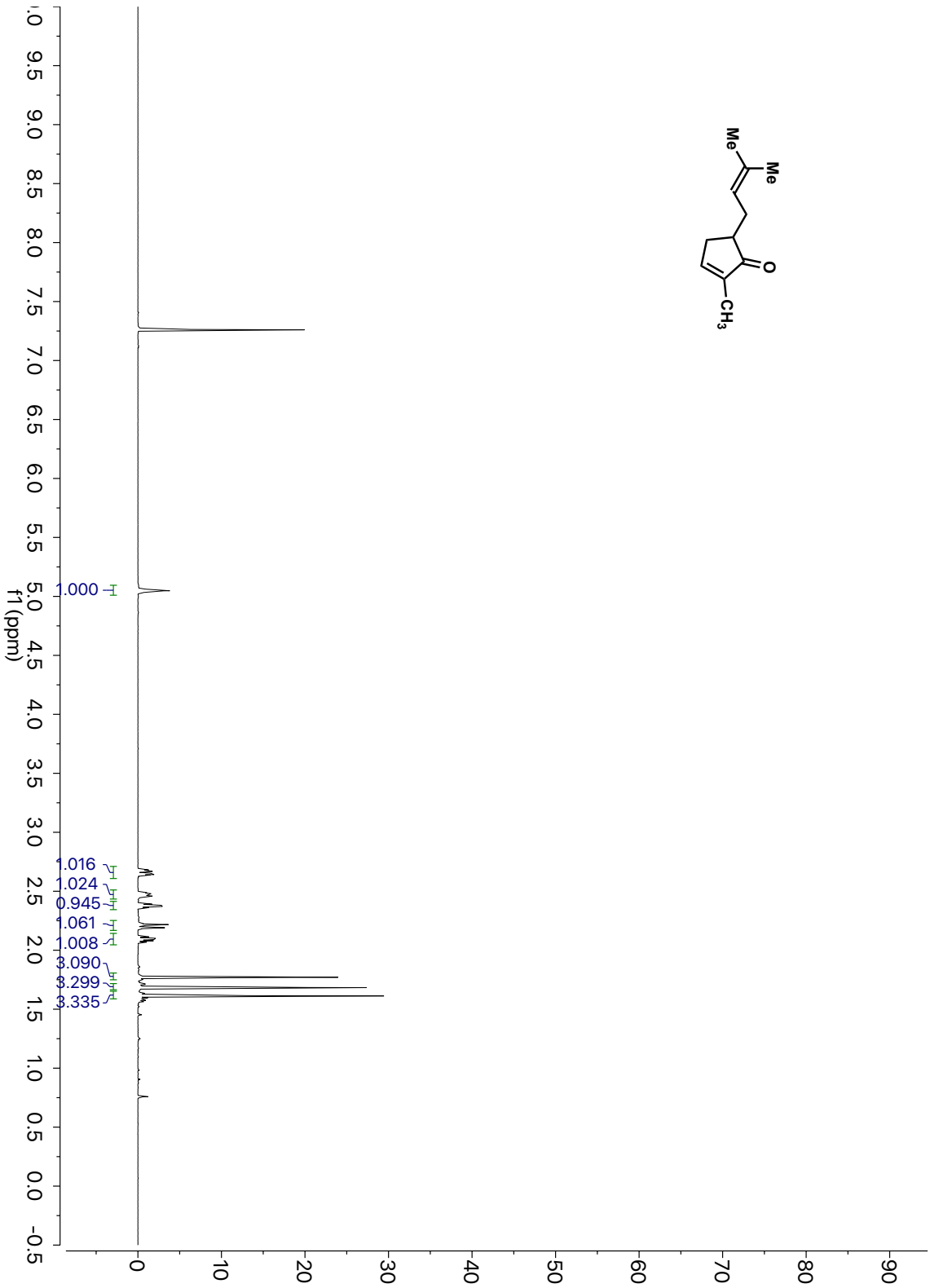
1. Siegel, D. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2016,** 128, 1048.
2. Uwamori, M.; Nakada, M. *J. Antibiot*. **2013**, *66*, 141.
3. Fukuyama, Y.; Kuwayama, A.; Minami, H. *Chem. Pharm. Bull*. **1997,** *45*, 947.
4. Kuramochi, A.; Usuda, H.; Yamatsuga, K.; Kanai M.; Shibasaki, M. *J. Am. Chem. Soc*. **2005**, *127*, 14200.

Appendix I:

NMR Spectra and X-ray Crystallography Data

for

Chapter 1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0.945
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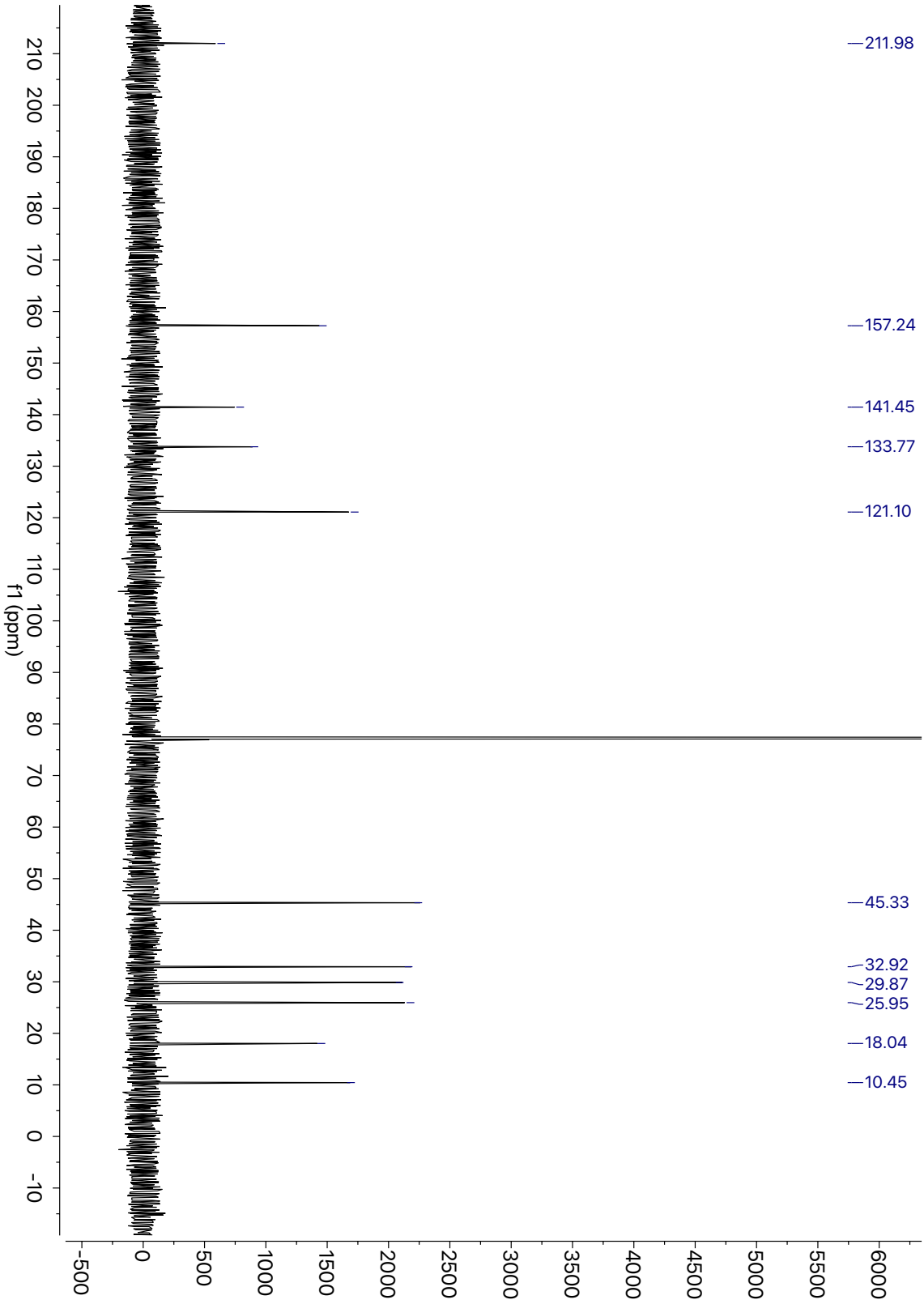
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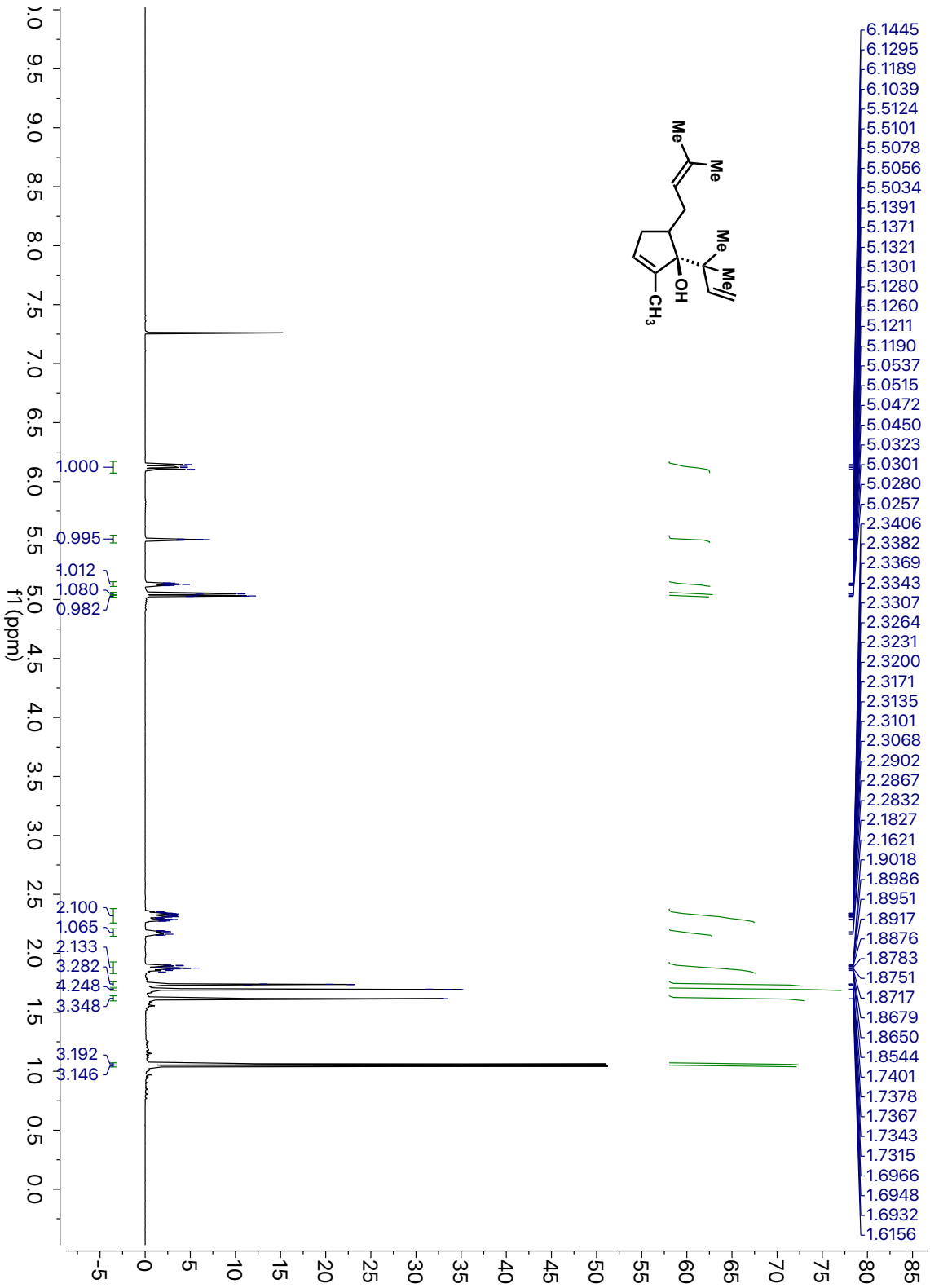
10.45
f1 (ppm)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3.282
4.248
3.348
3.192
3.146
f1 (ppm)
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6.1295
6.1189
6.1039
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5.5101
5.5078
5.5056
5.5034
5.1391
5.1371
5.1321
5.1301
5.1280
5.1260
5.1211
5.1190
5.0537
5.0515
5.0472
5.0450
5.0323
5.0301
5.0280
5.0257
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2.3343
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2.3200
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2.3135
2.3101
2.3068
2.2902
2.2867
2.2832
2.1827
2.1621
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1.8917
1.8876
1.8783
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1.8717
1.8679
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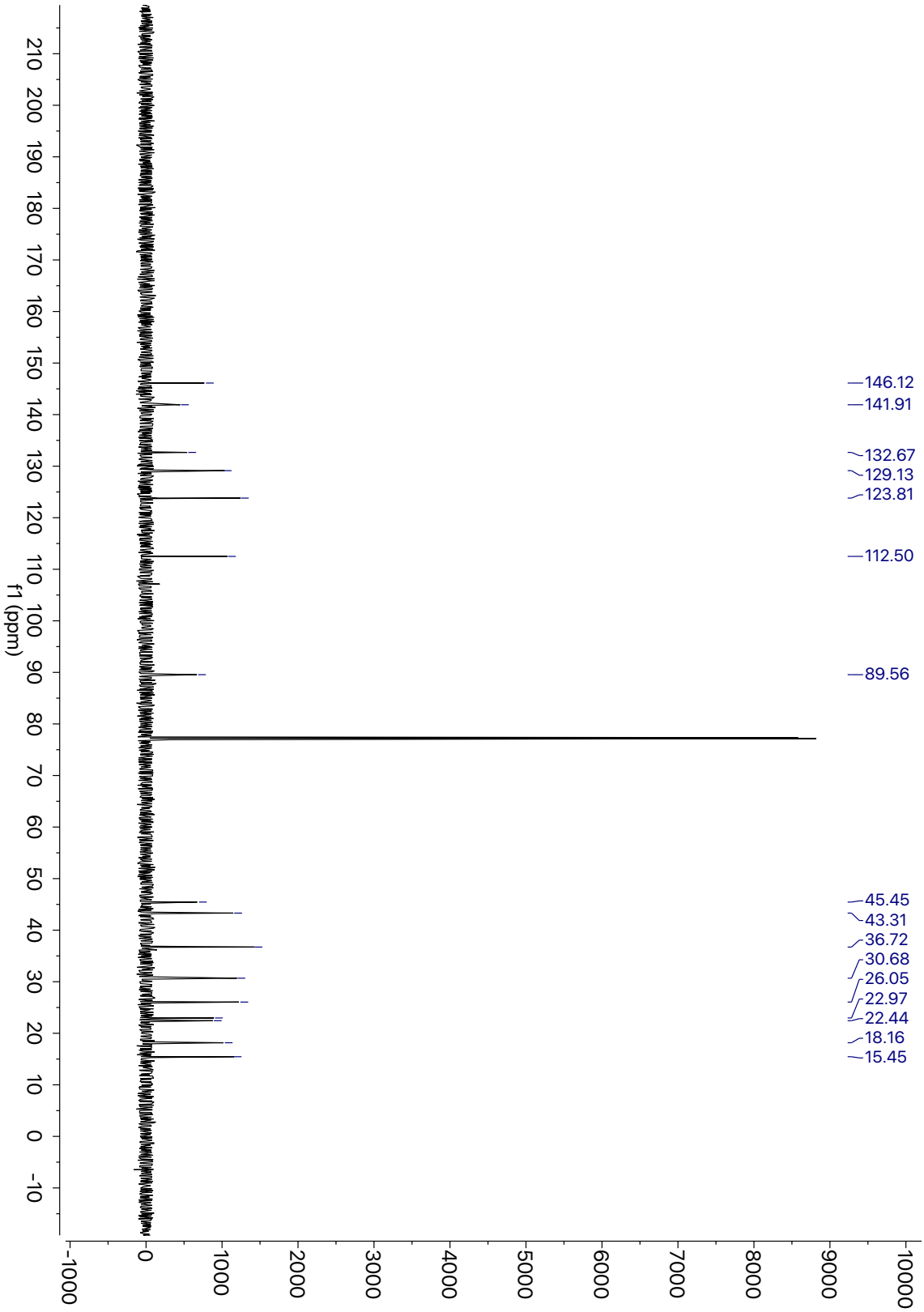
1.6932
1.6156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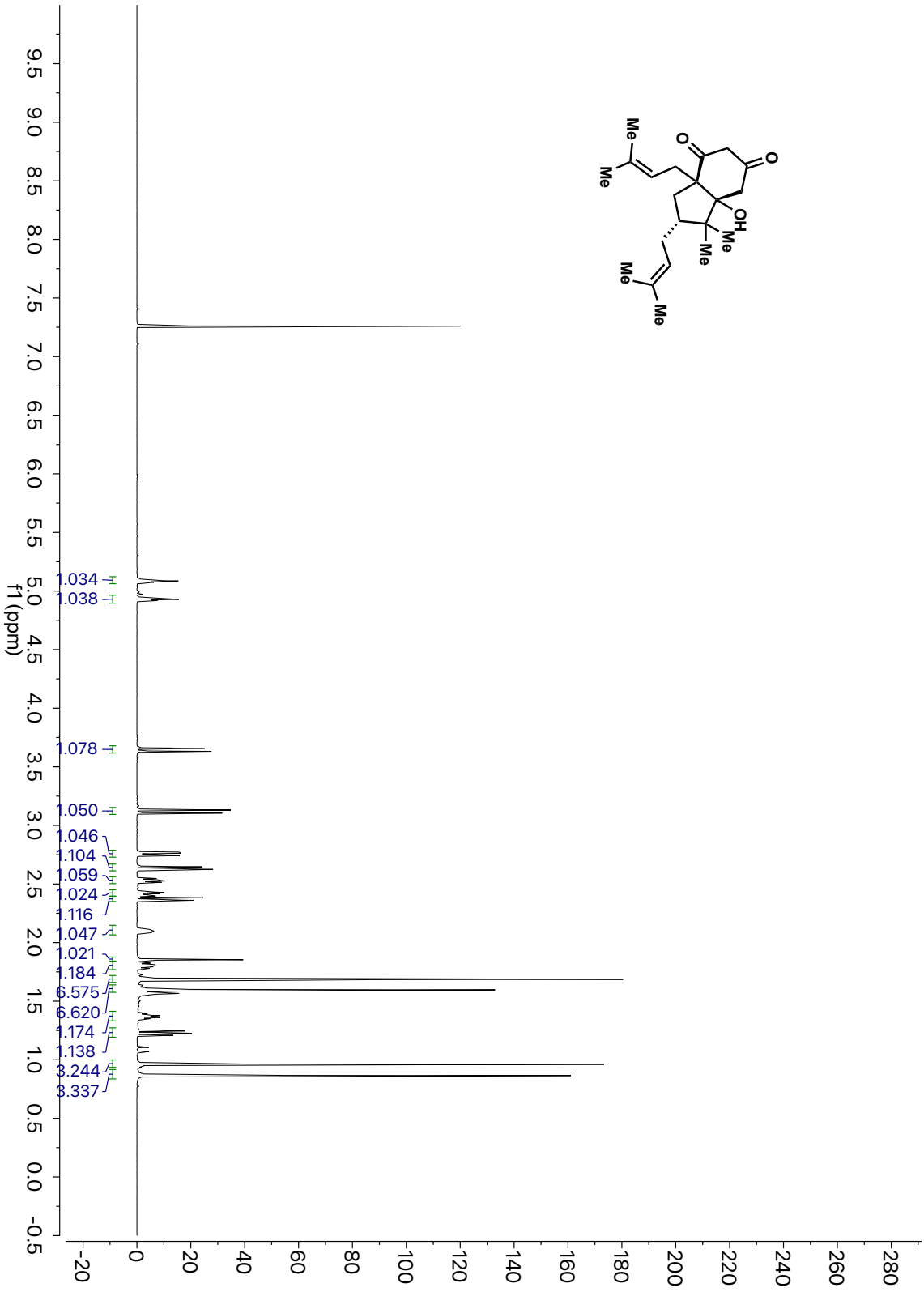
15.45
f1 (ppm)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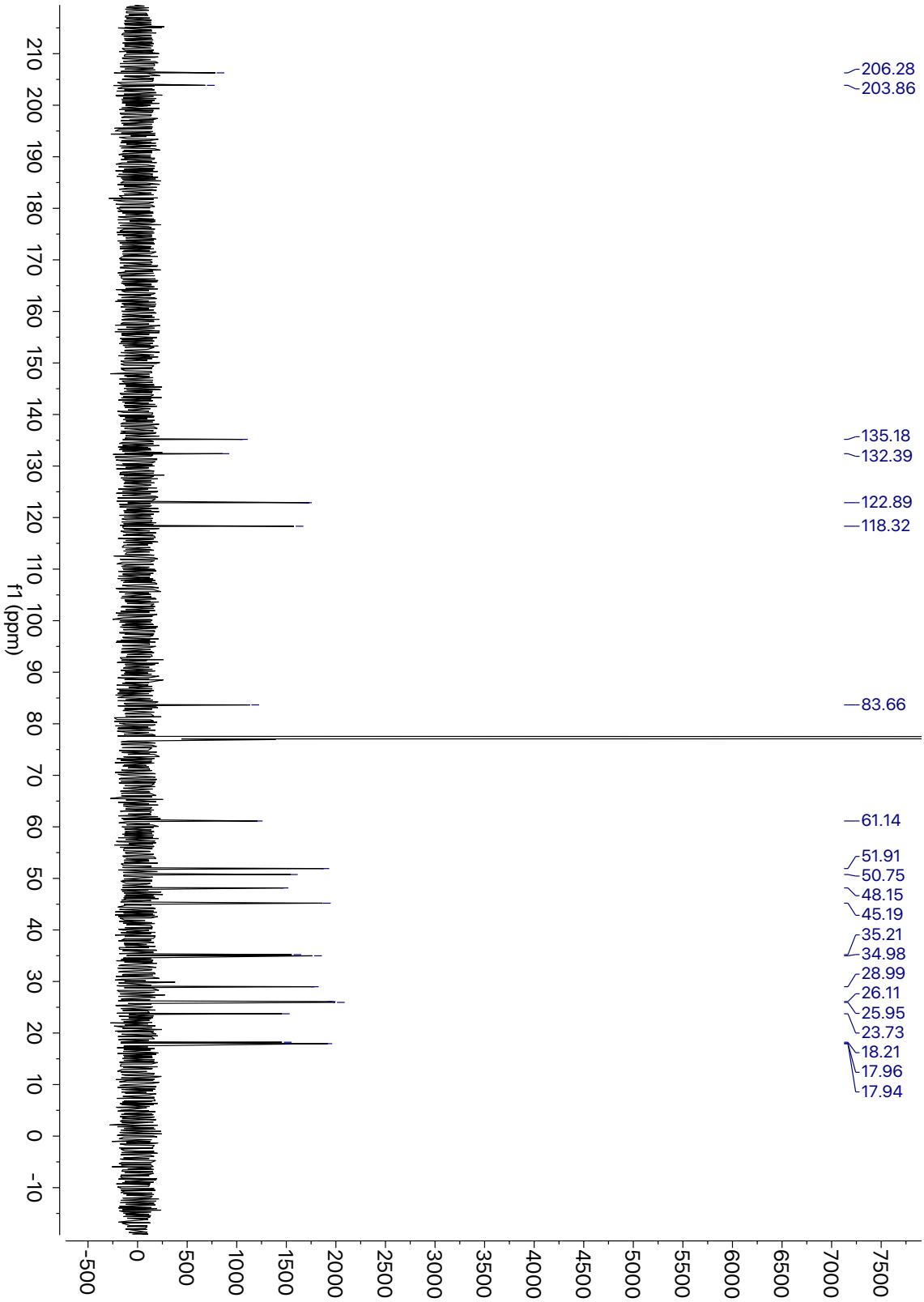
f1 (ppm)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61.14
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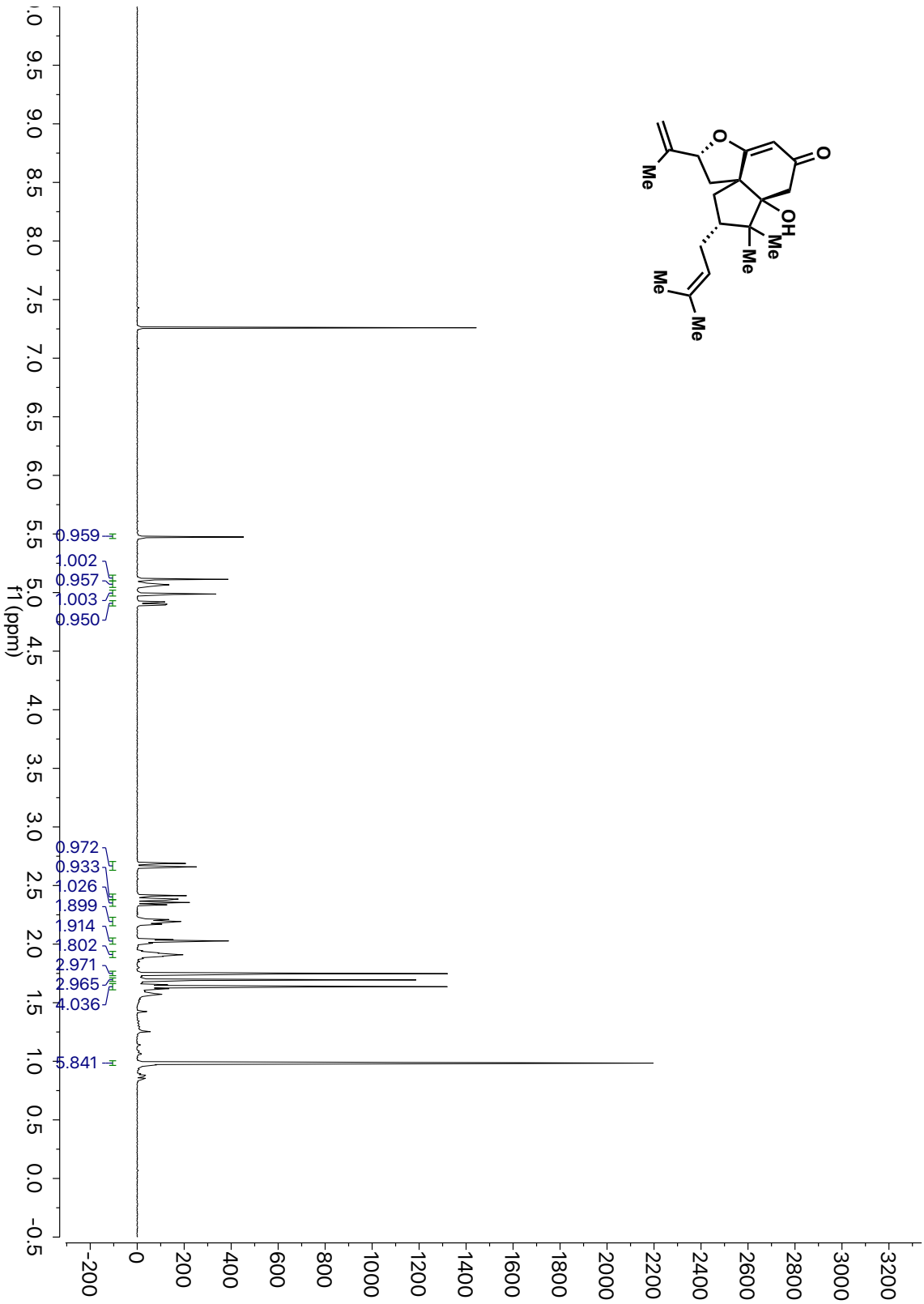
17.94
f1 (ppm)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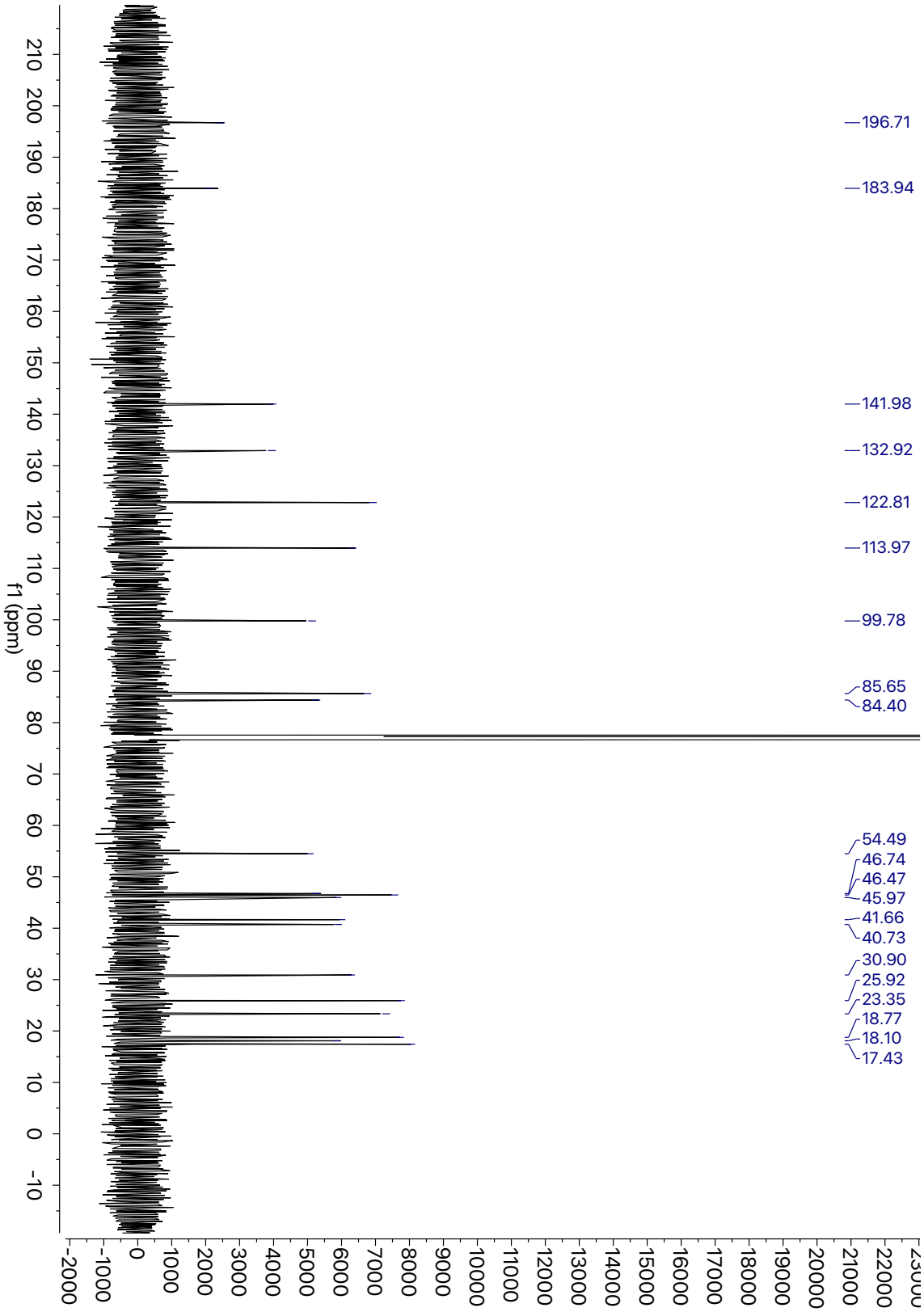
Me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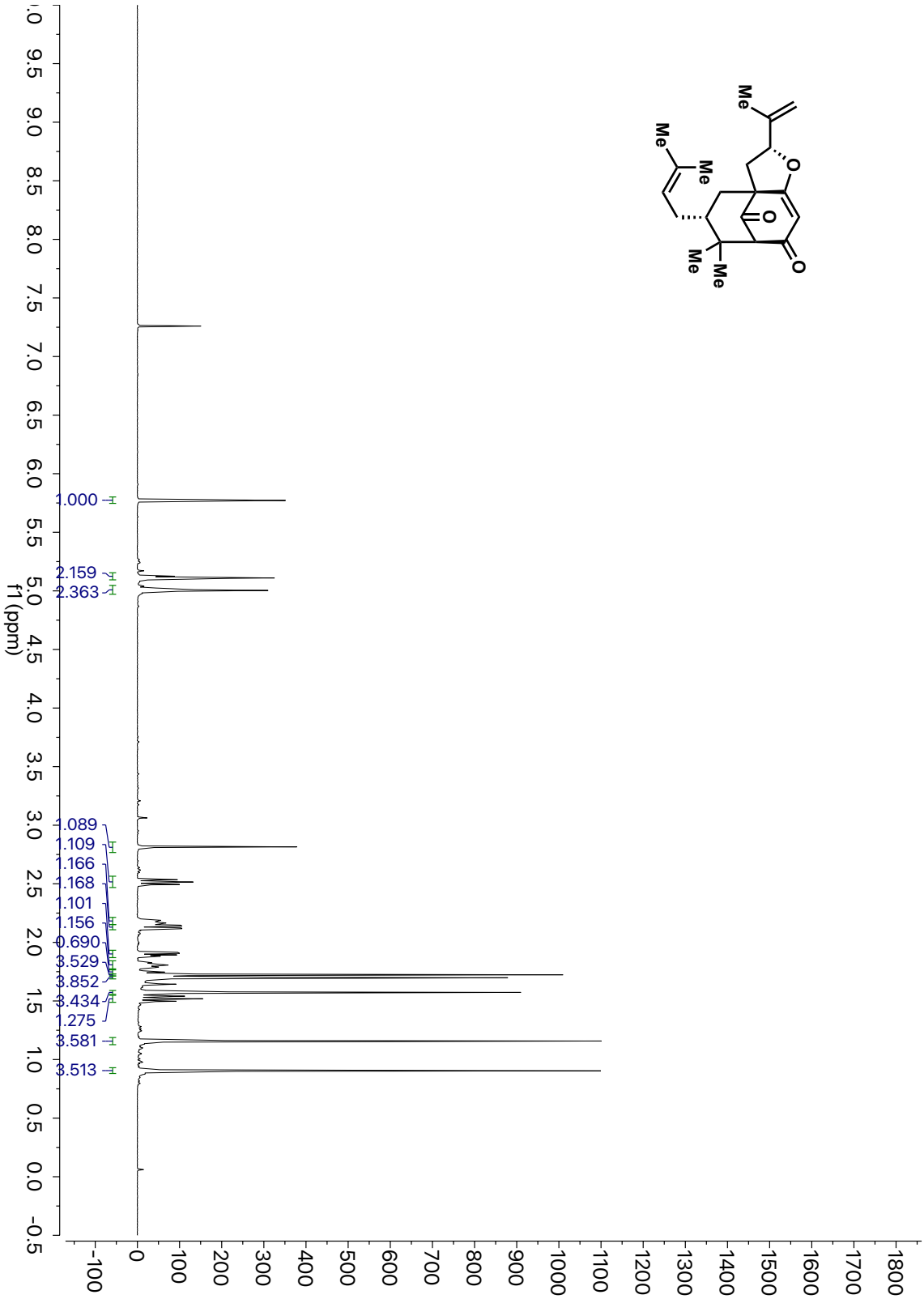
f1 (ppm)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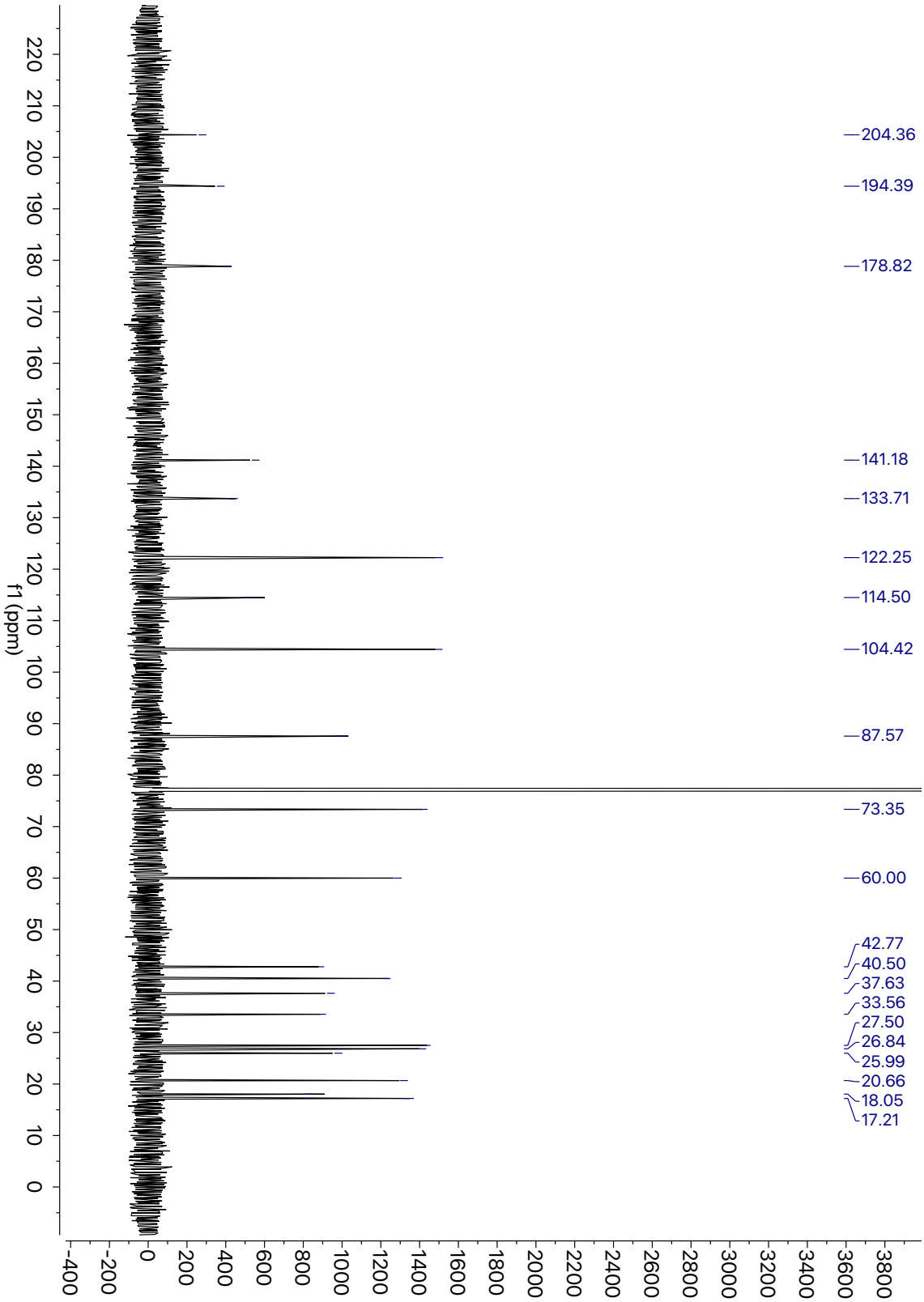
f1 (ppm)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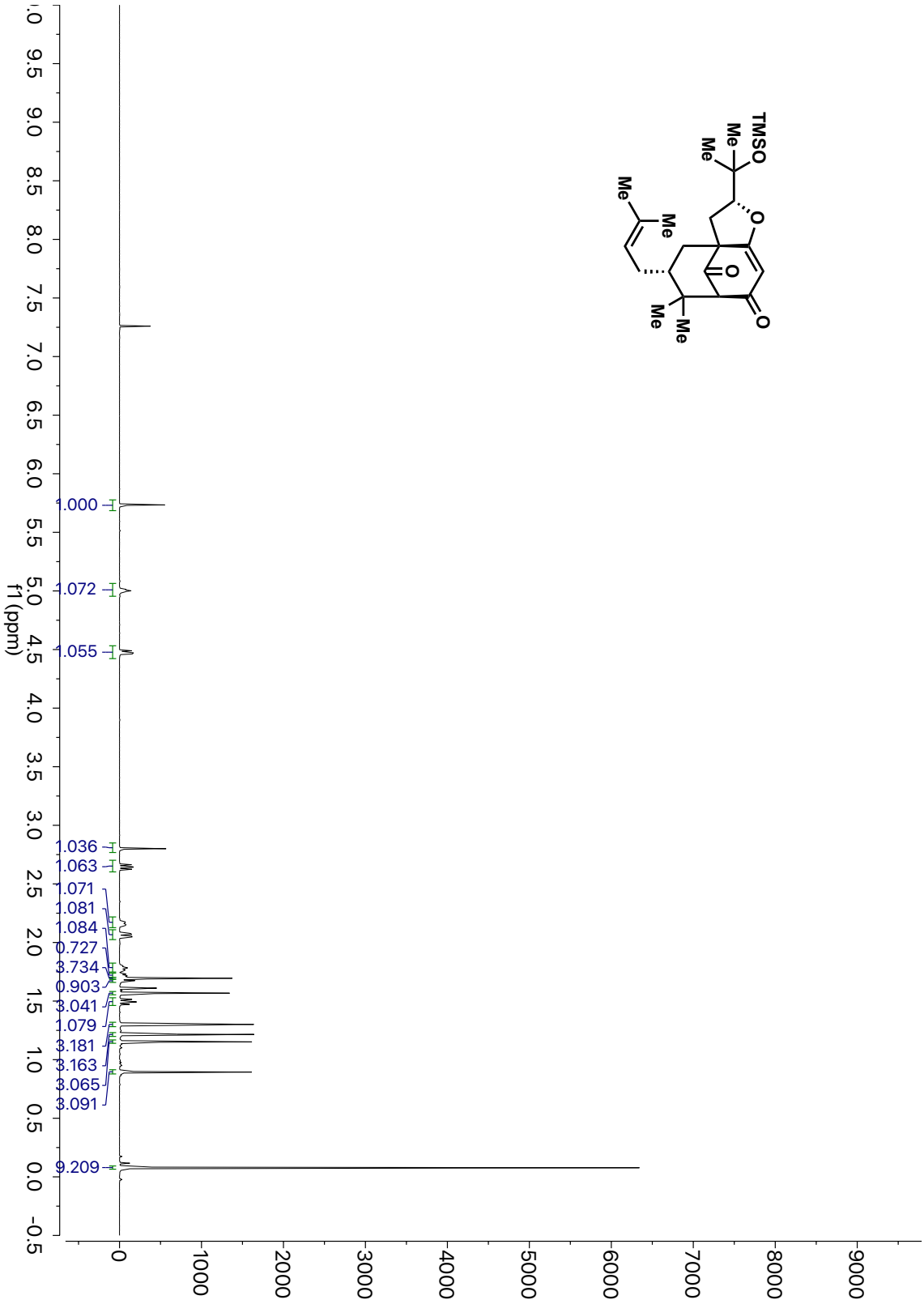
f1 (ppm)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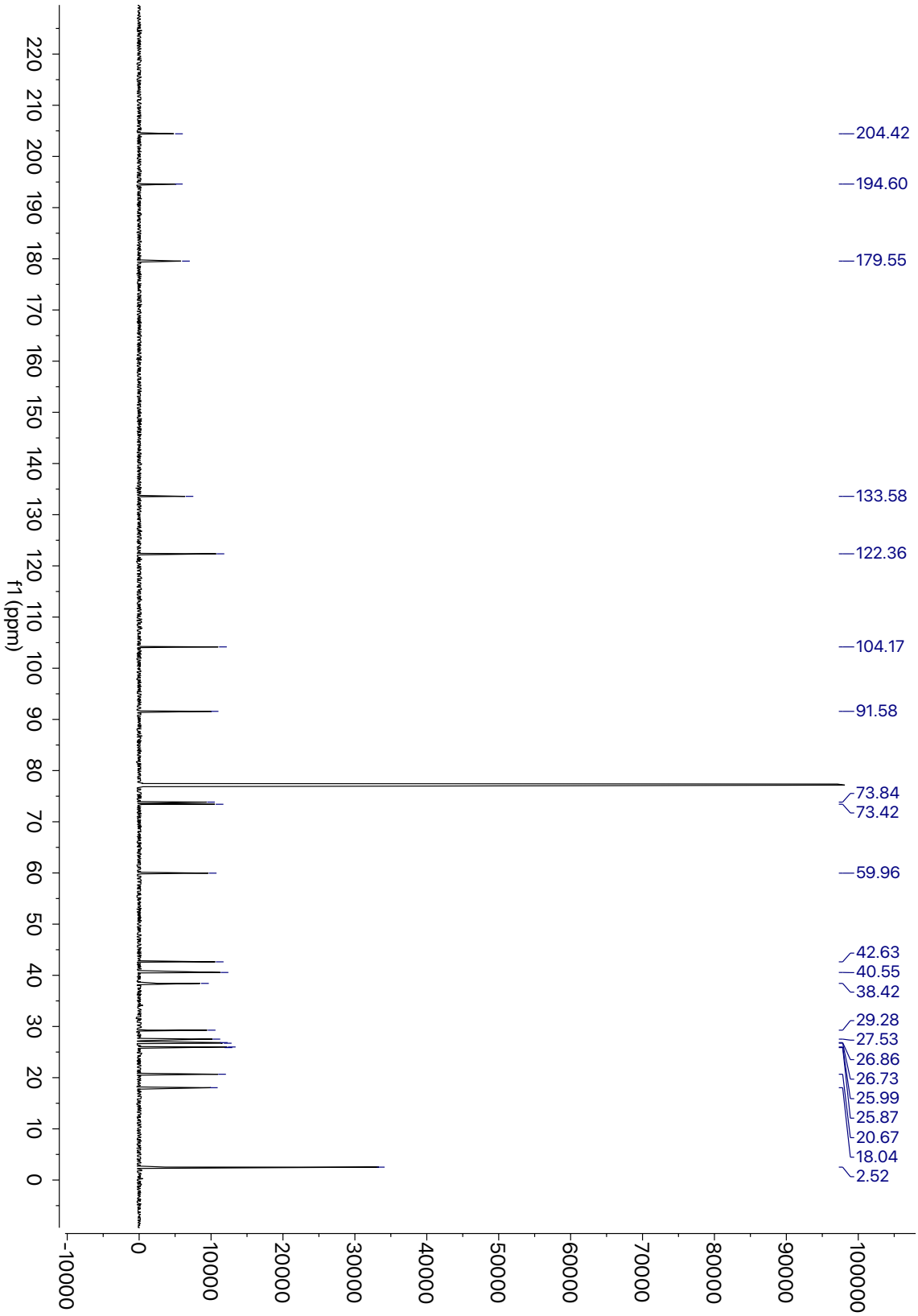
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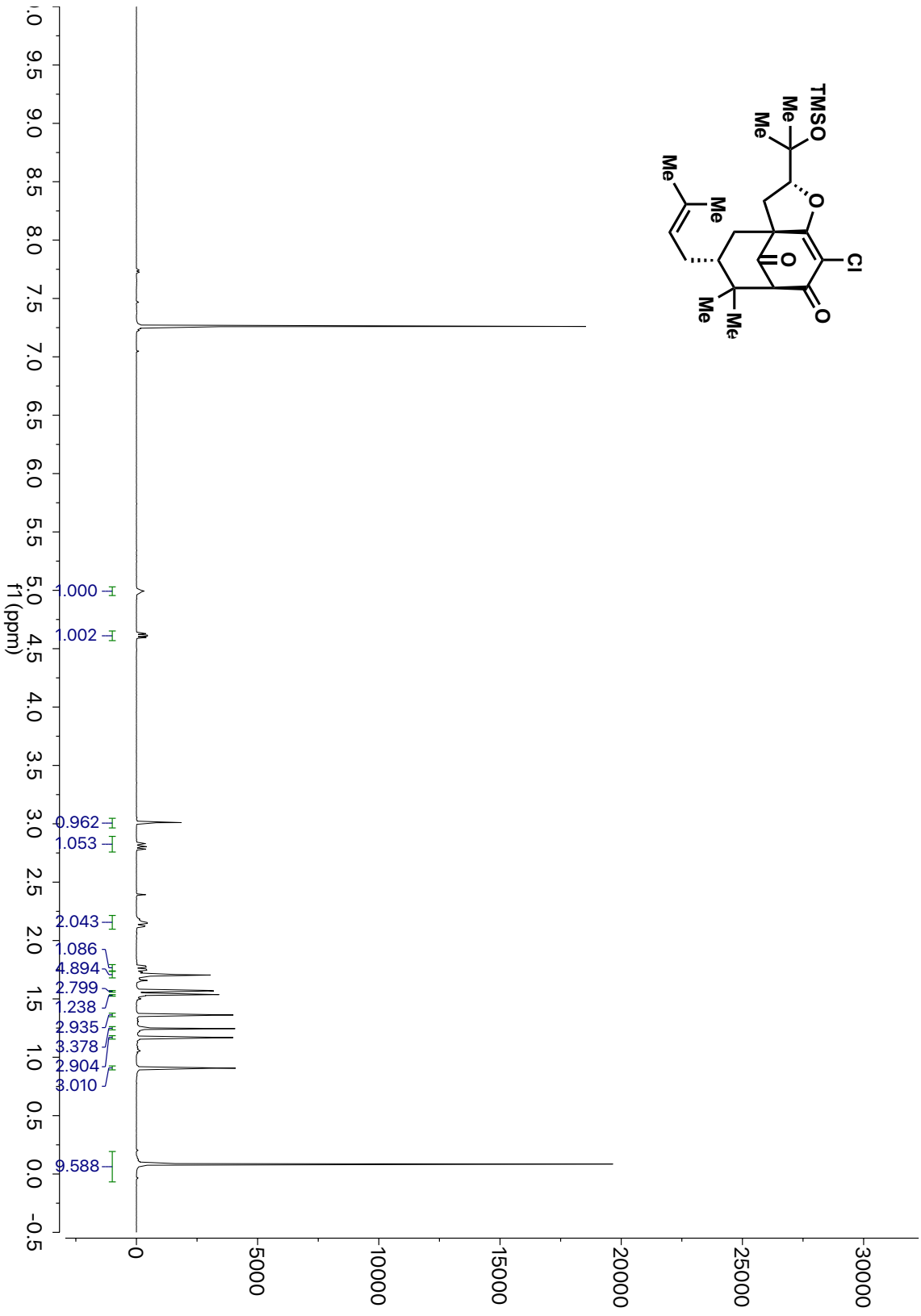
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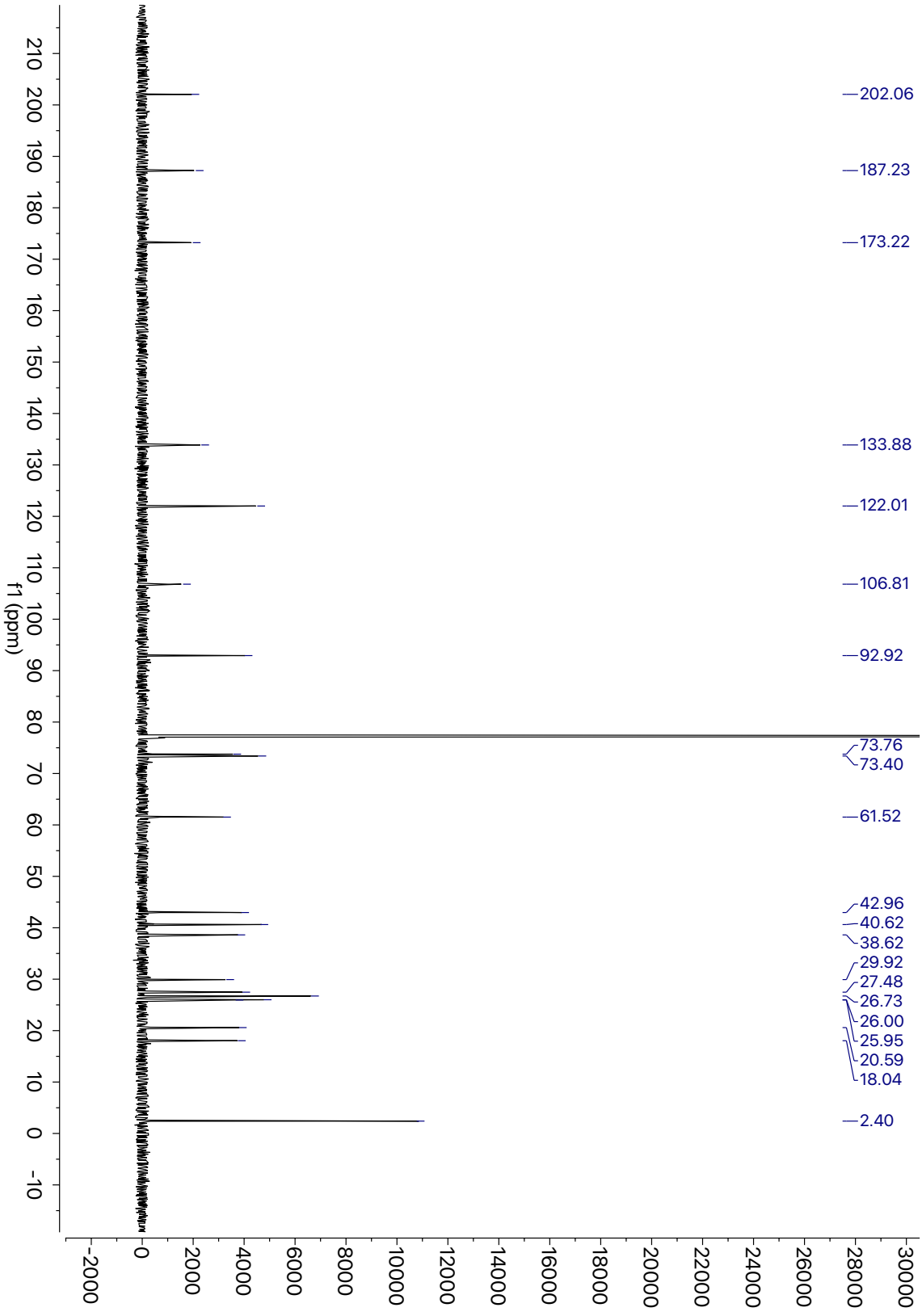
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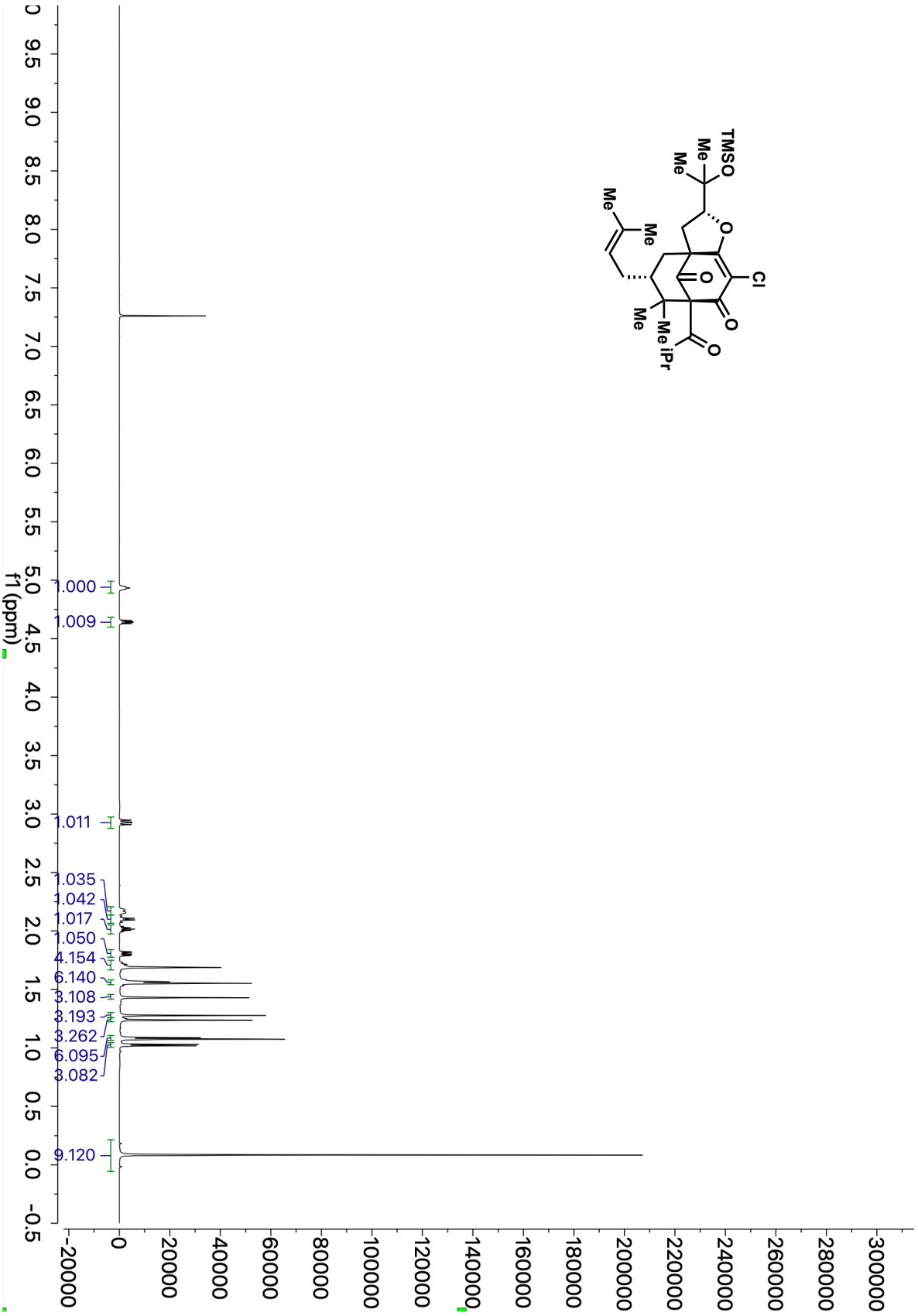
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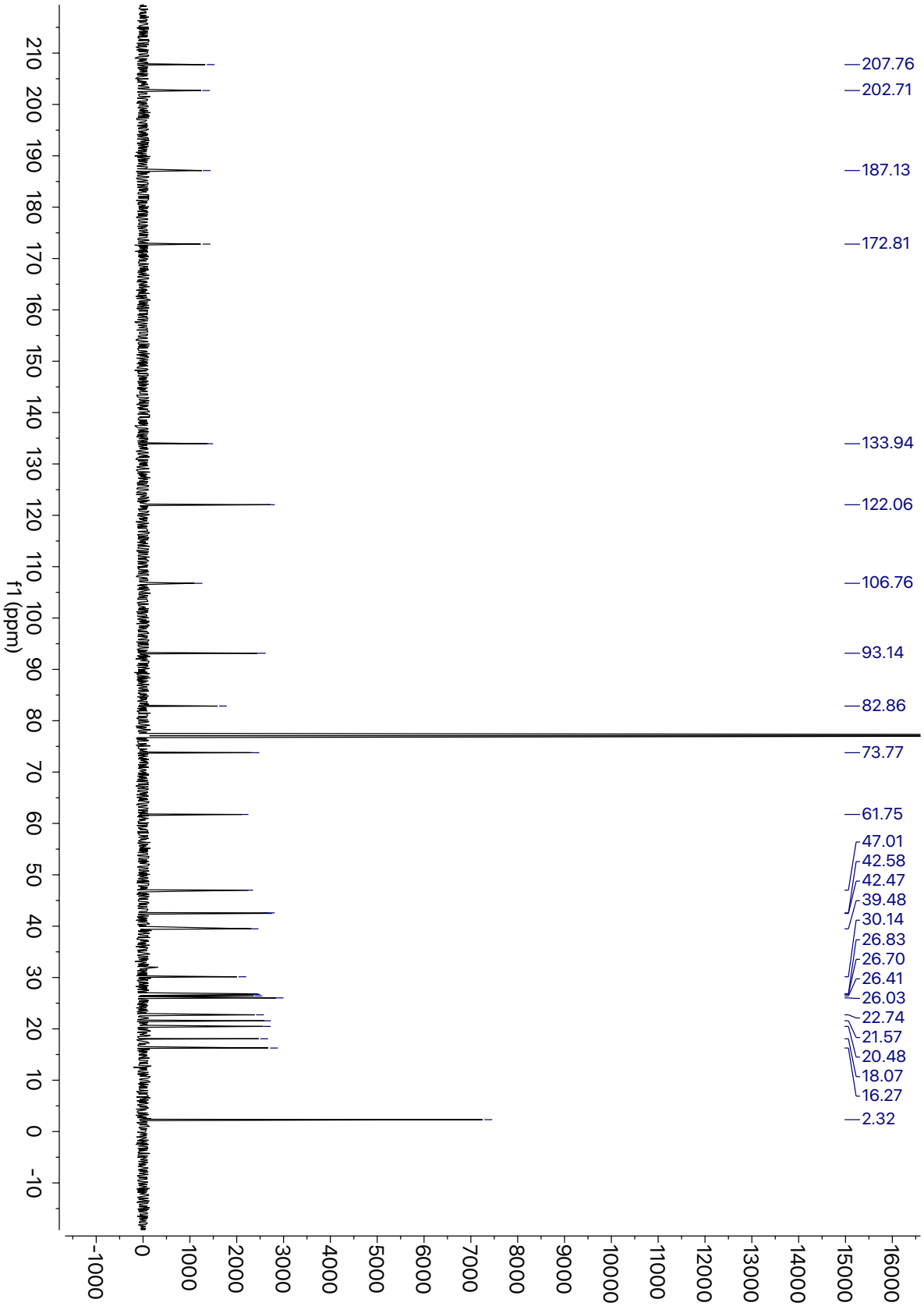
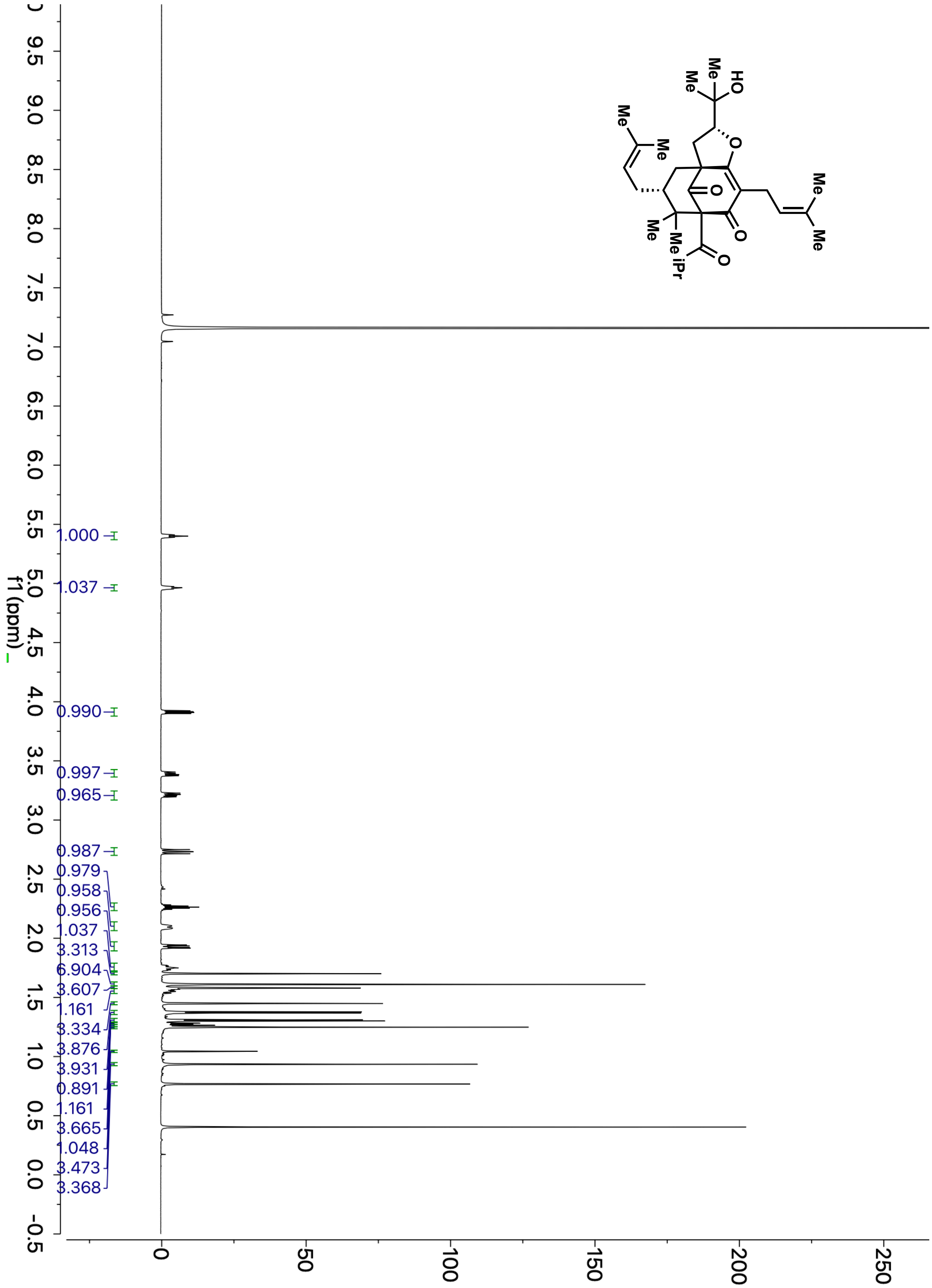
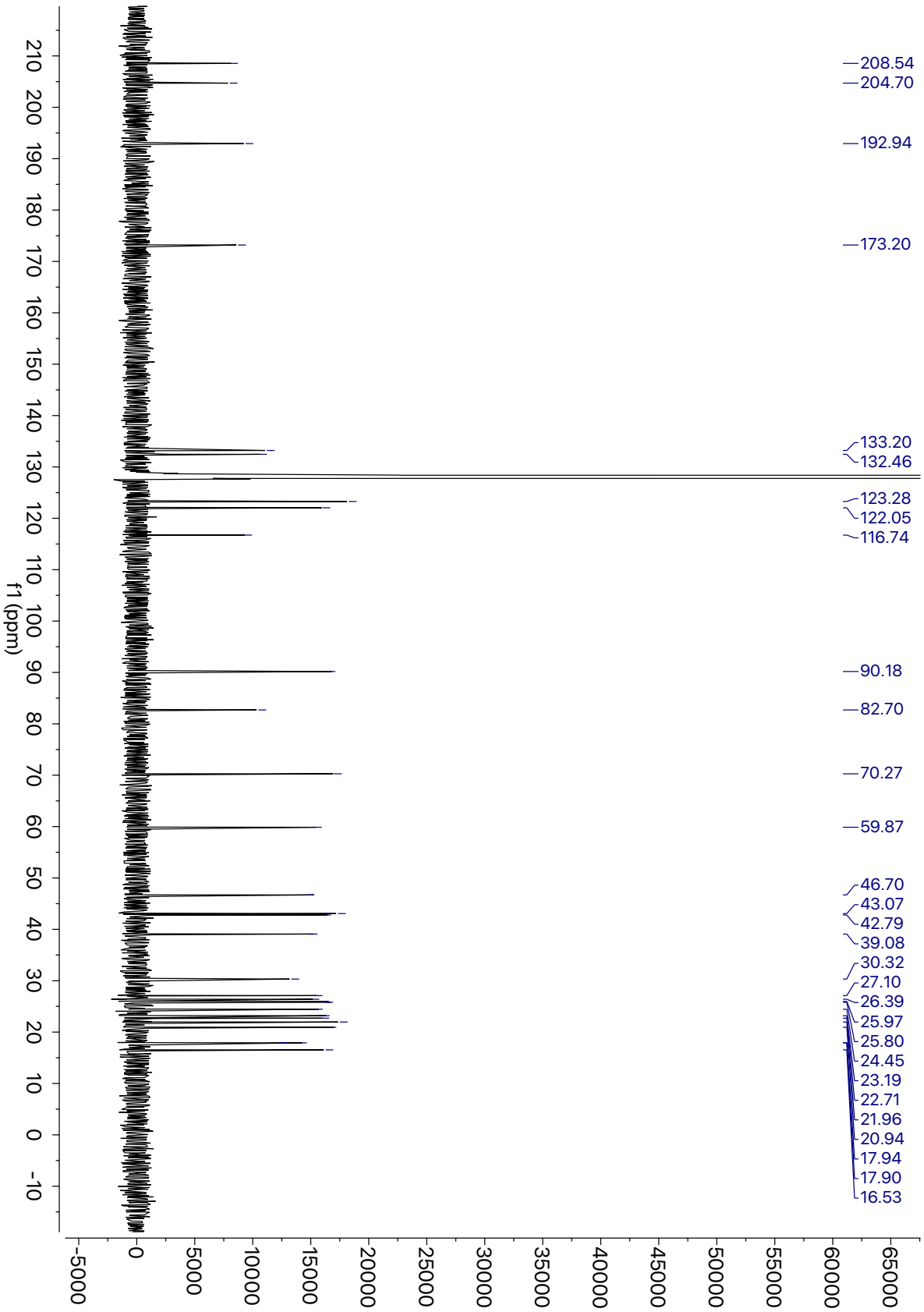
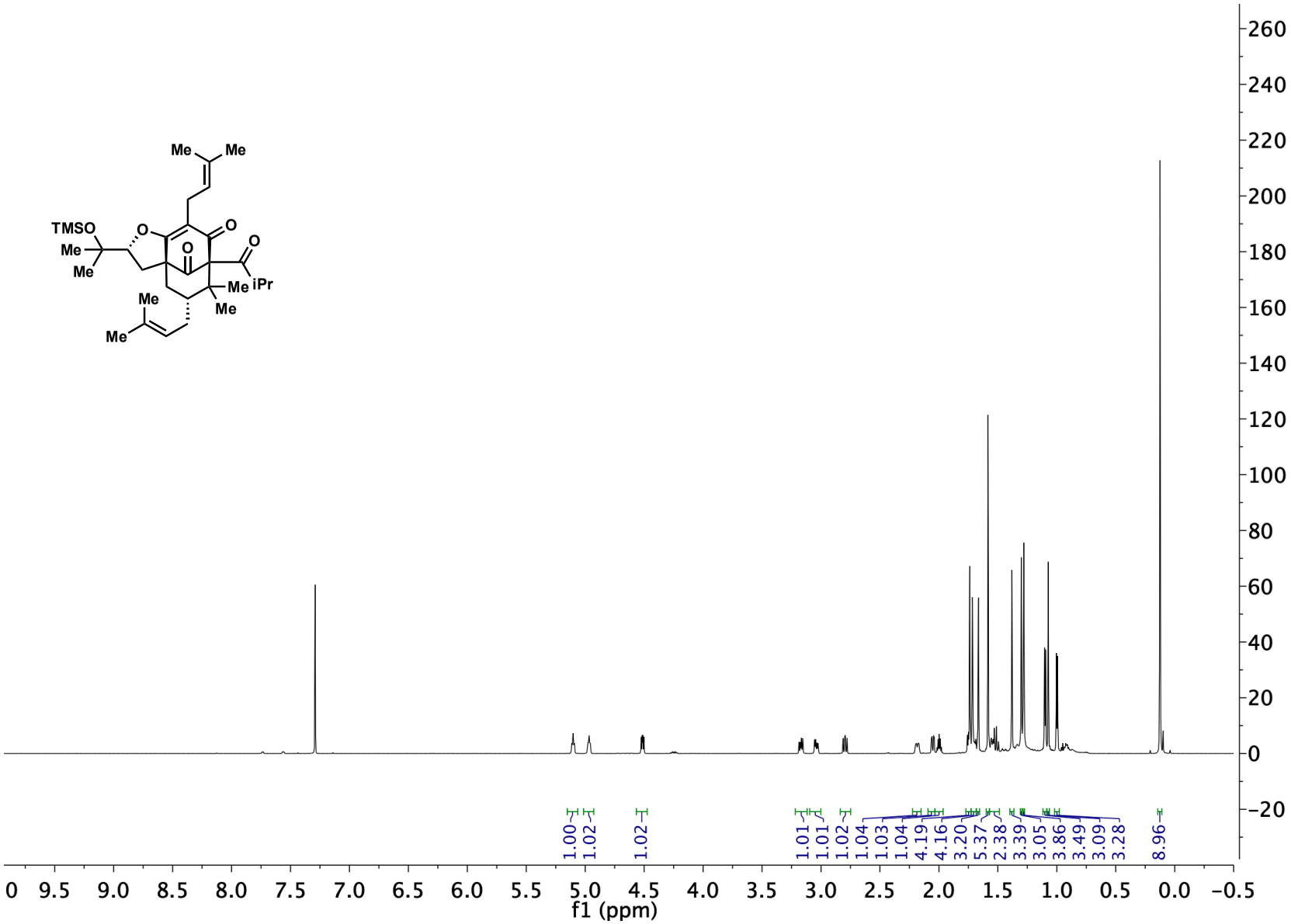
3.082
9.120

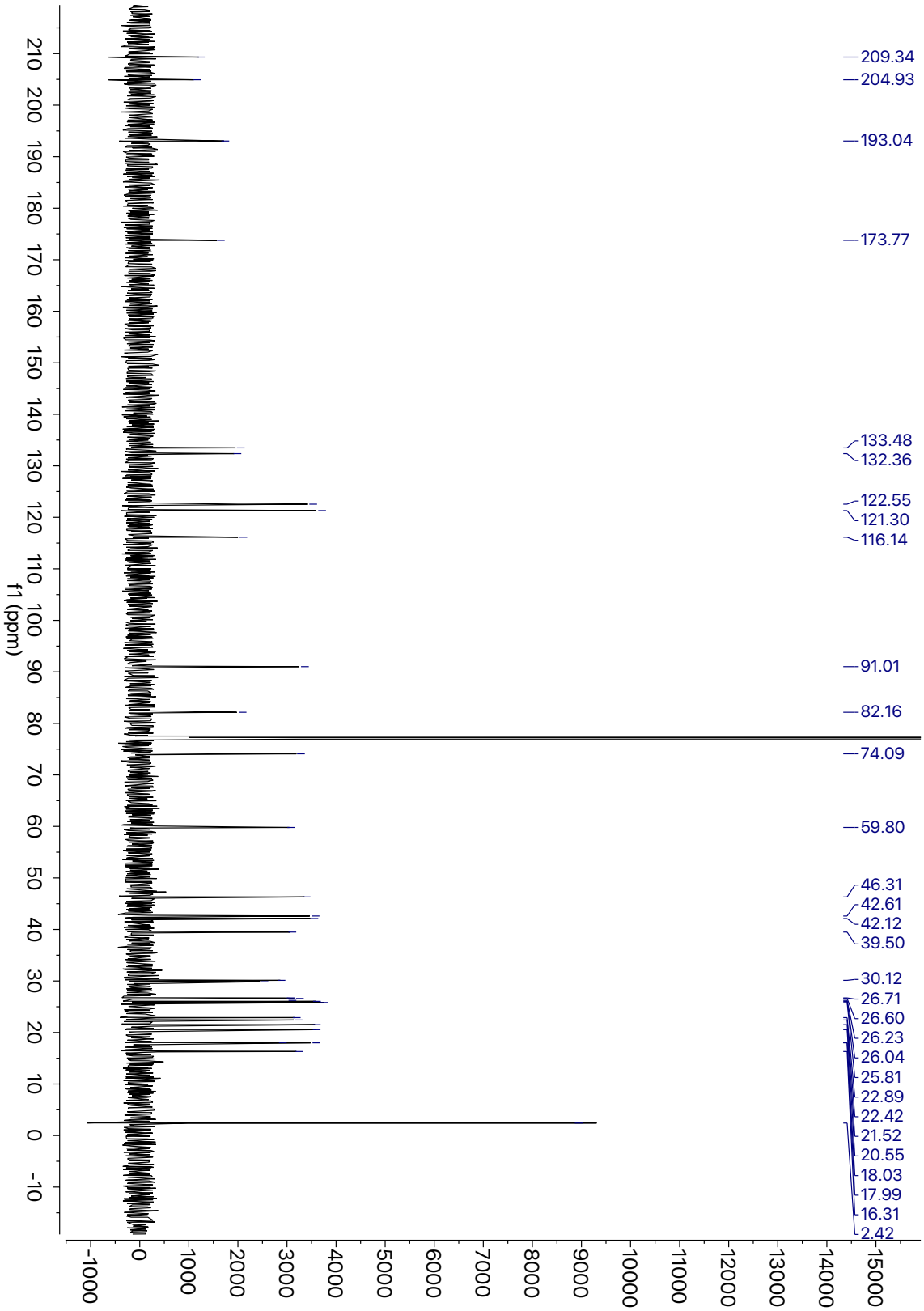

f1 (ppm)
207.76
202.71
187.13
172.81
133.94
122.06
106.76
93.14
82.86
73.77
61.75
47.01
42.58
42.47
39.48
30.14
26.83
26.70
26.41
26.03
22.74
21.57
20.48
18.07
16.27
2.32

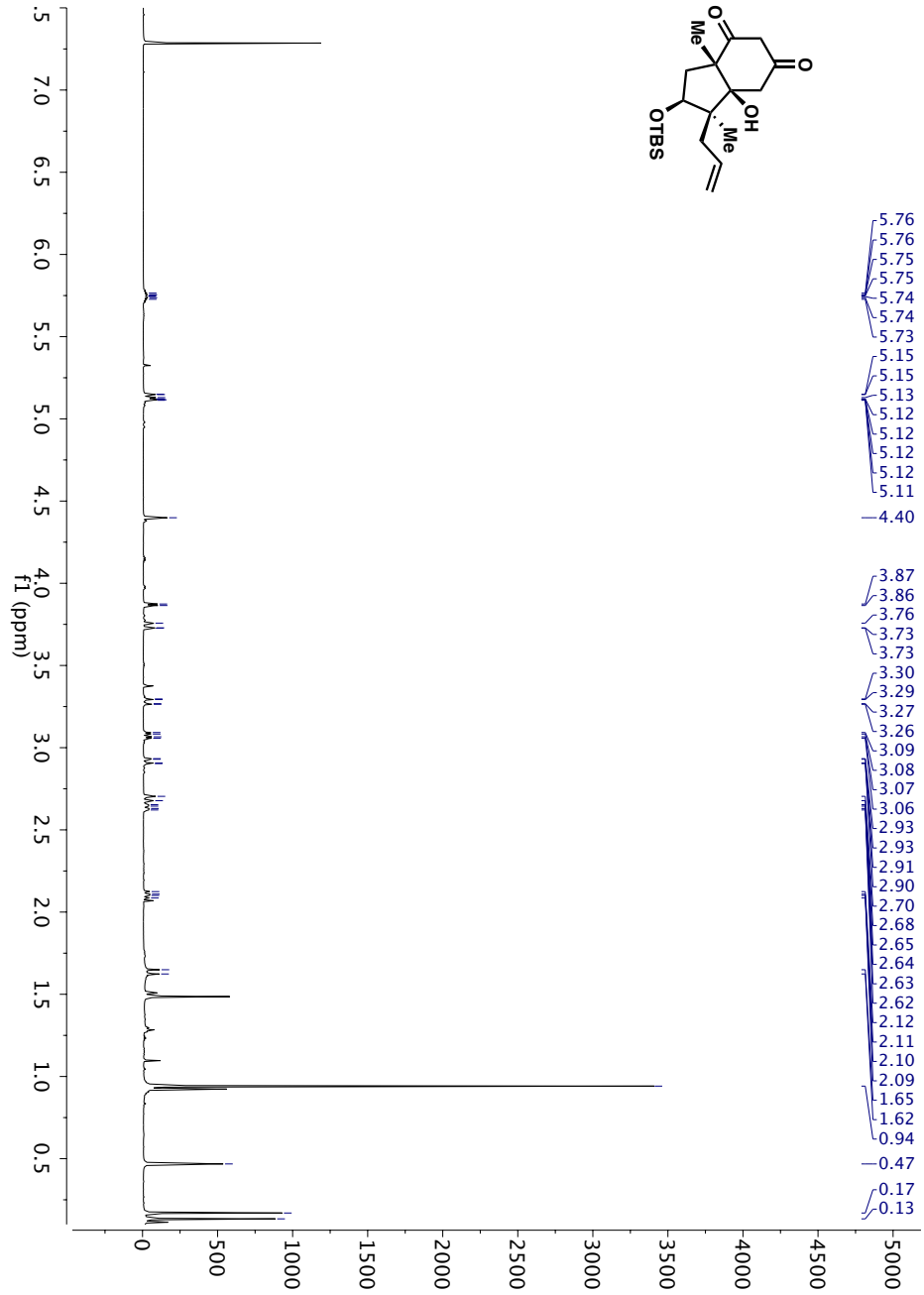


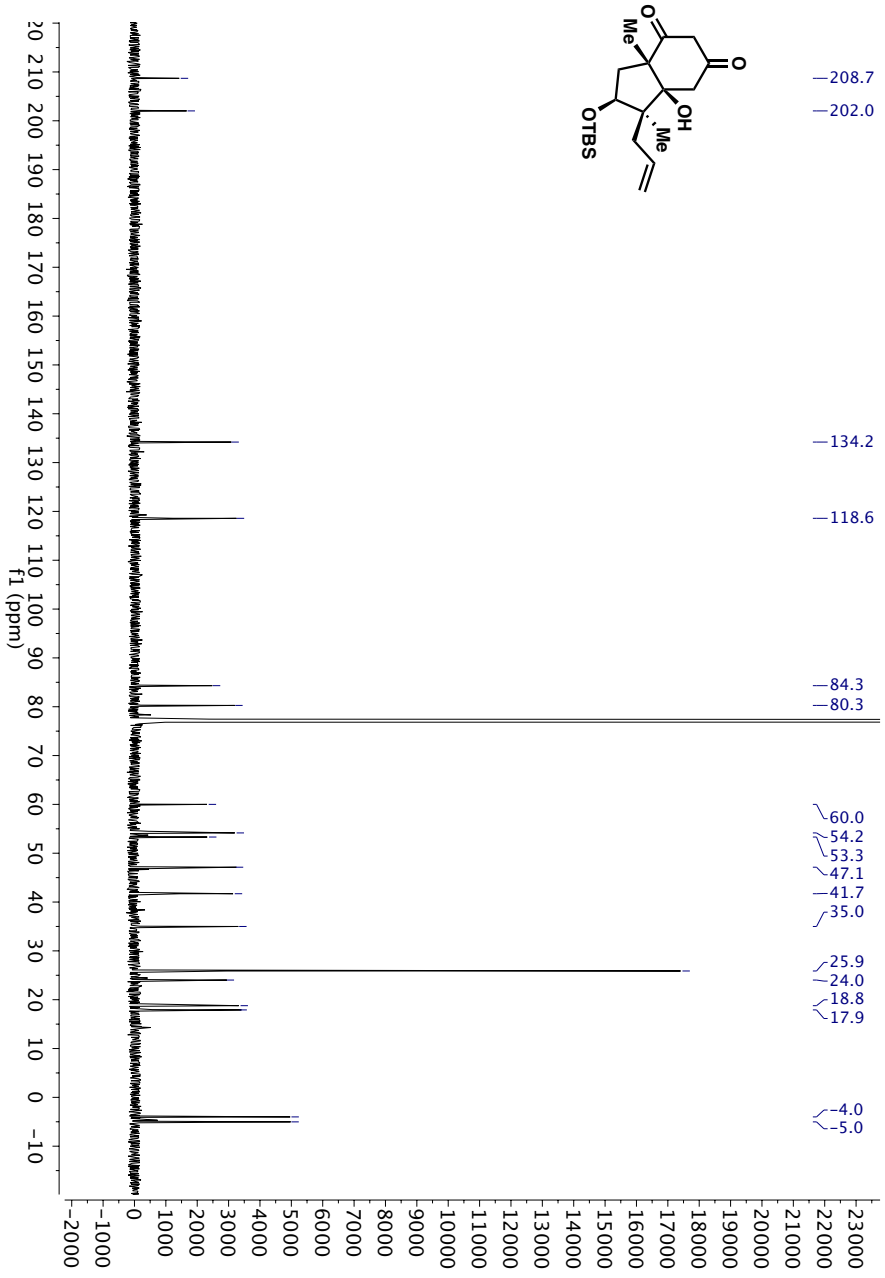
f1 (ppm)
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
0
50
100
150
200
250
1.000
1.037
0.990
0.997
0.965
0.987
0.979
0.958
0.956
1.037
3.313
6.904
3.607
1.161
3.334
3.876
3.931
0.891
1.161
3.665
1.048
3.473
3.368
HO
Me
Me
O
Me
Me
O
O
O
Me
Me
Me
Me
iPr

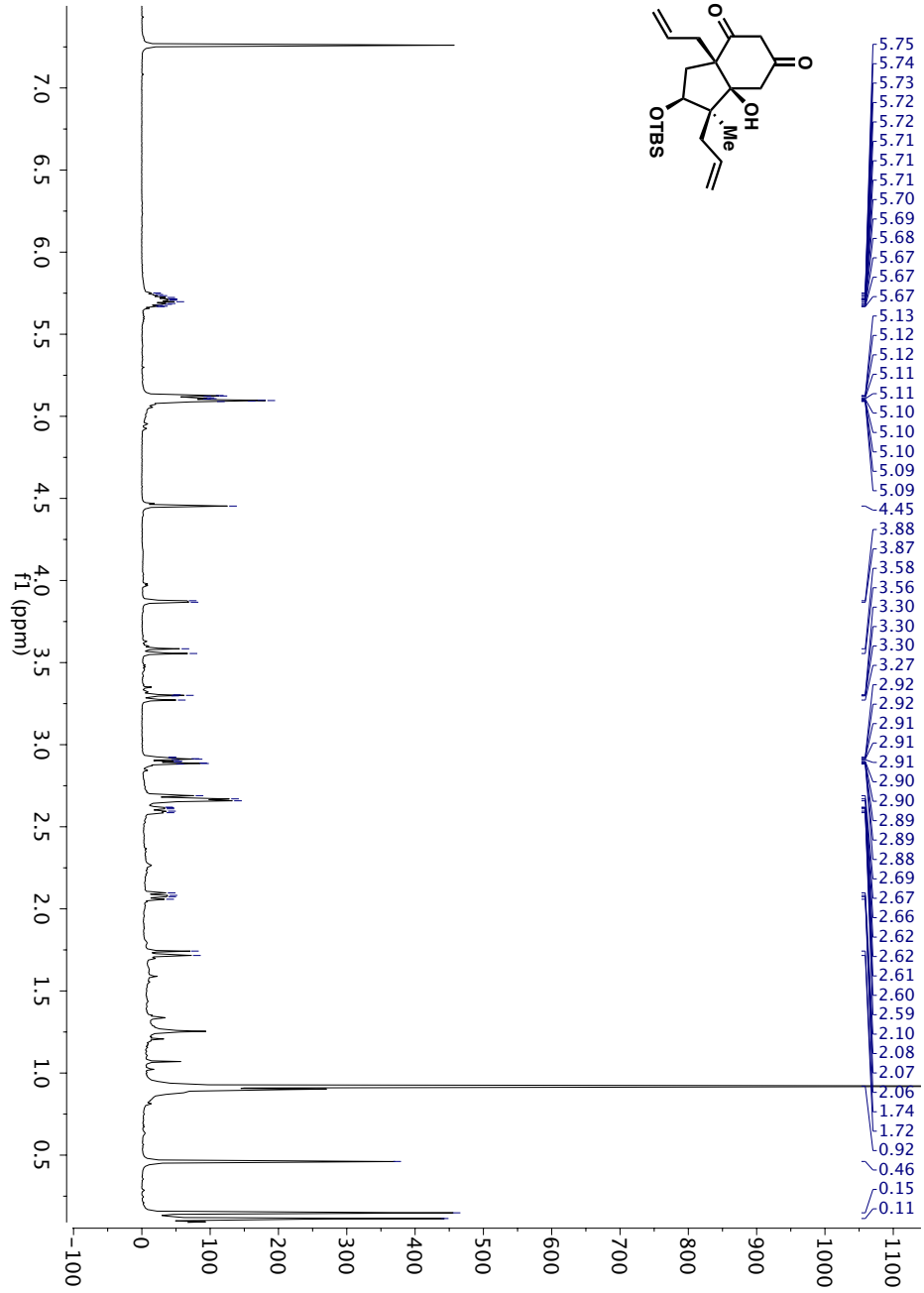

208.54
204.70
192.94
173.20
133.20
132.46
123.28
122.05
116.74
90.18
82.70
70.27
59.87
46.70
43.07
42.79
39.08
30.32
27.10
26.39
25.97
25.80
24.45
23.19
22.71
21.96
20.94
17.94
17.90
16.53
f1 (ppm)

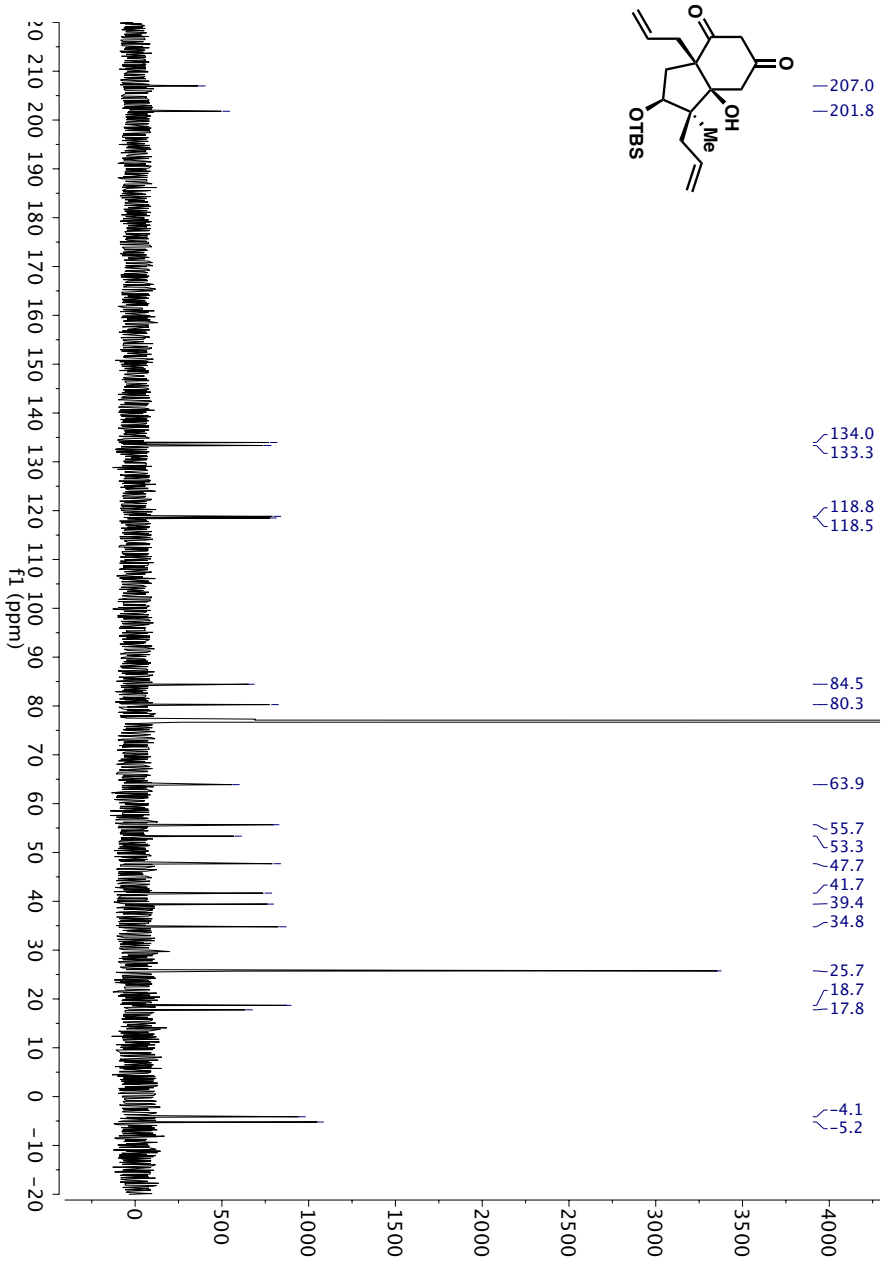

TMSO
Me
Me
Me
Me
Me
Me
Me
Me
iPr
O
O
O
O
1.00
1.02
1.02
1.01
1.01
1.02
1.04
1.03
1.04
4.19
4.16
3.20
5.37
2.38
3.39
3.05
3.86
3.49
3.09
3.28
8.96
f1 (ppm)

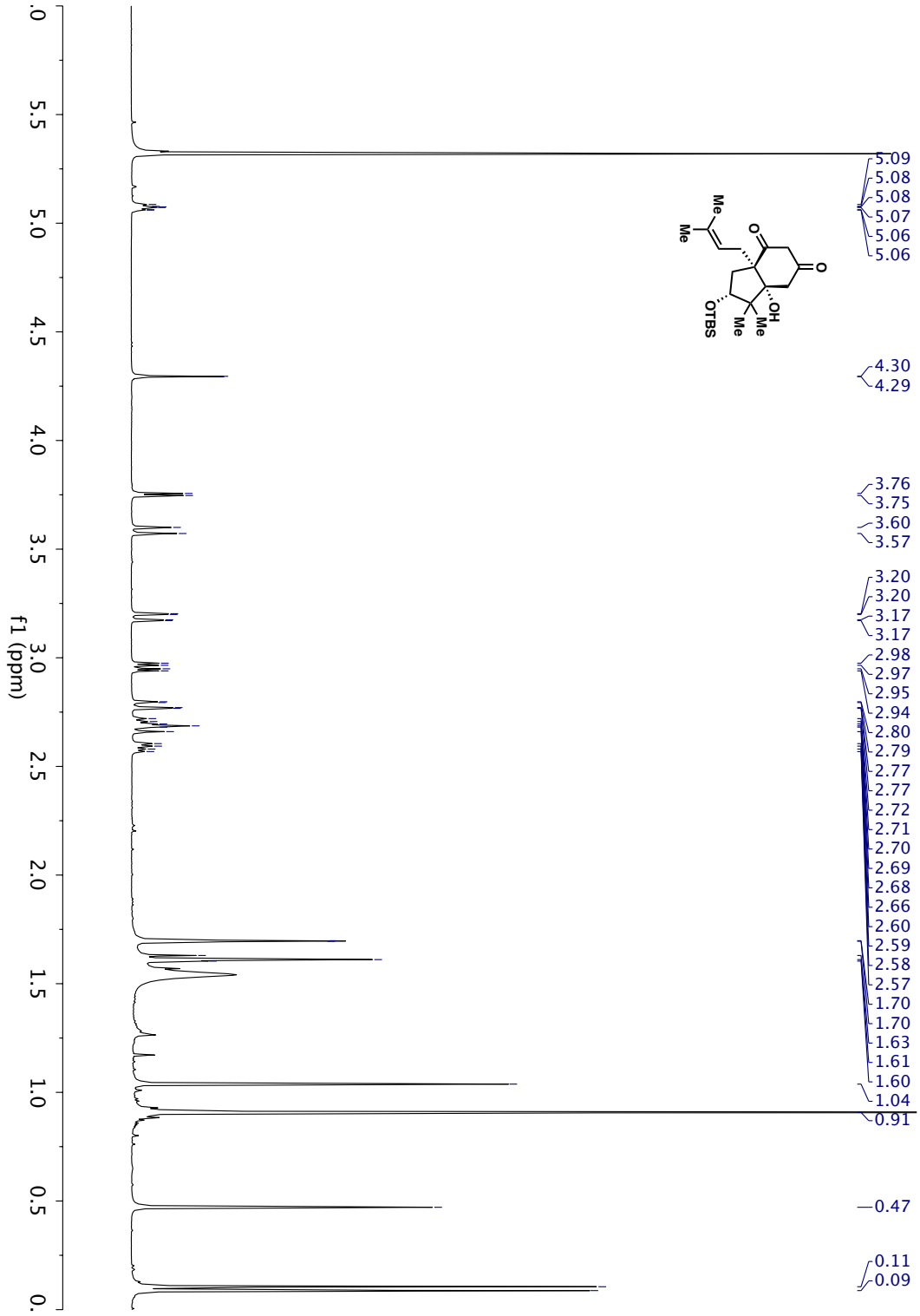

209.34
204.93
193.04
173.77
133.48
132.36
122.55
121.30
116.14
91.01
82.16
74.09
59.80
46.31
42.61
42.12
39.50
30.12
26.71
26.60
26.23
26.04
25.81
22.89
22.42
21.52
20.55
18.03
17.99
16.31
2.42
f1 (ppm)

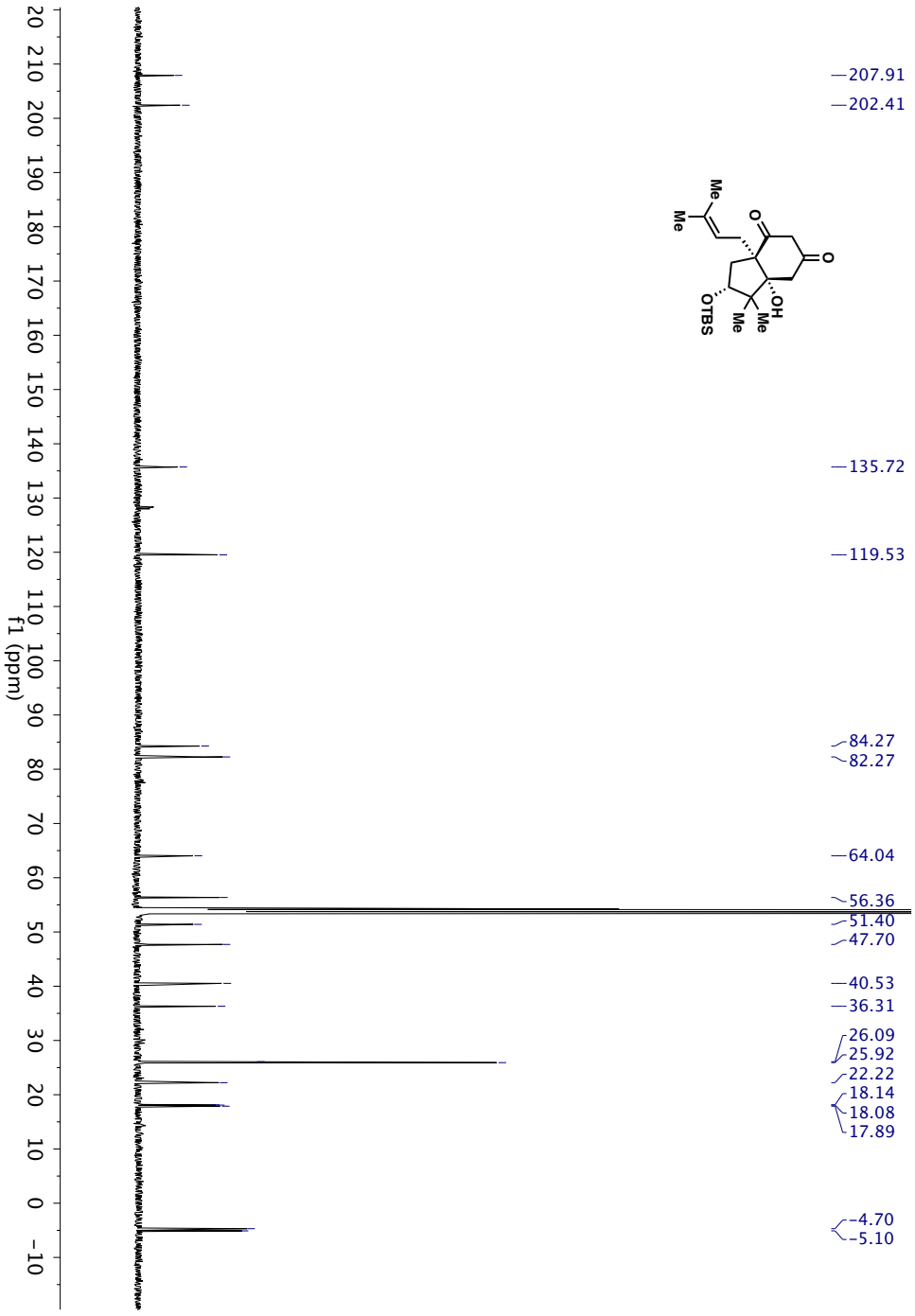

O
Me
O
OH
Me
OTBS
5.76
5.76
5.75
5.75
5.74
5.74
5.73
5.15
5.15
5.13
5.12
5.12
5.12
5.12
5.11
4.40
3.87
3.86
3.76
3.73
3.73
3.30
3.29
3.27
3.26
3.09
3.08
3.07
3.06
2.93
2.93
2.91
2.90
2.70
2.68
2.65
2.64
2.63
2.62
2.12
2.11
2.10
2.09
1.65
1.62
0.94
0.47
0.17
0.13
f1 (ppm)
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
500
1000
1500
2000
2500
3000
3500
4000
4500
5000

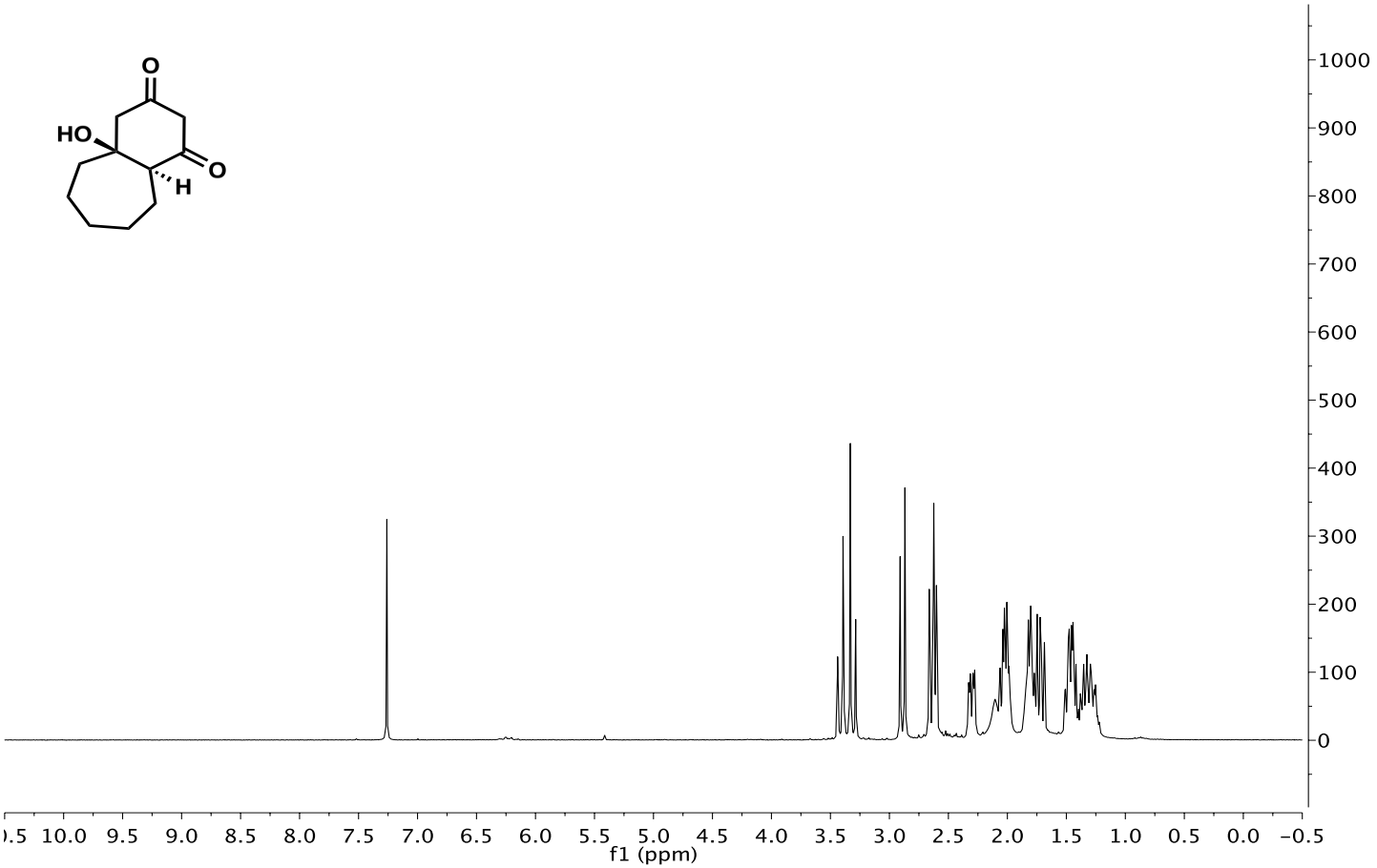

208.7
202.0
134.2
118.6
84.3
80.3
60.0
54.2
53.3
47.1
41.7
35.0
25.9
24.0
18.8
17.9
-4.0
-5.0
f1 (ppm)

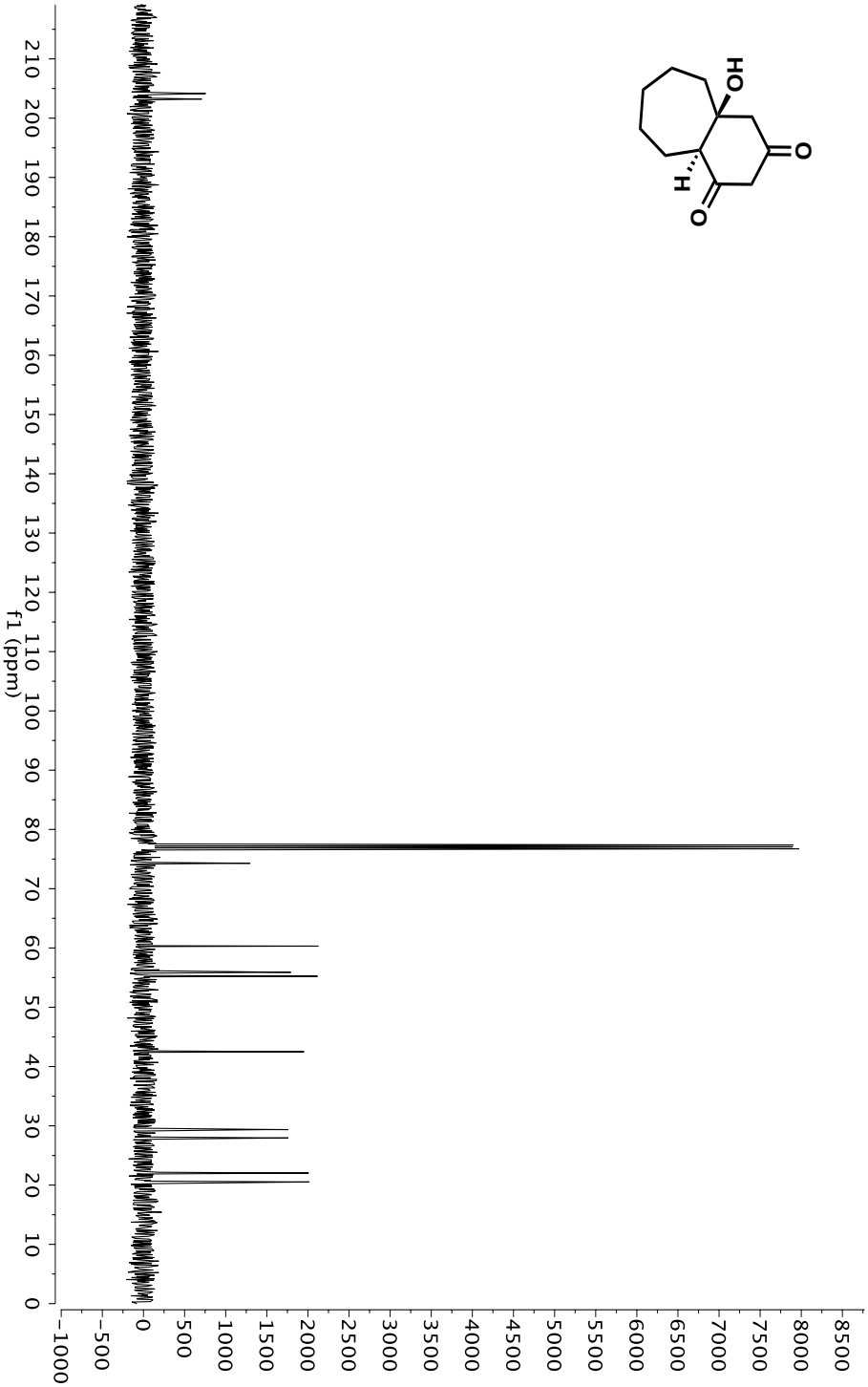

O
O
OH
Me
OTBS
5.75
5.74
5.73
5.72
5.72
5.71
5.71
5.71
5.70
5.69
5.68
5.67
5.67
5.67
5.13
5.12
5.12
5.11
5.11
5.10
5.10
5.10
5.09
5.09
4.45
3.88
3.87
3.58
3.56
3.30
3.30
3.30
3.27
2.92
2.92
2.91
2.91
2.91
2.90
2.90
2.89
2.89
2.88
2.69
2.67
2.66
2.62
2.62
2.61
2.60
2.59
2.10
2.08
2.07
2.06
1.74
1.72
0.92
0.46
0.15
0.11
f1 (ppm)
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
−100
0
100
200
300
400
500
600
700
800
900
1000
1100

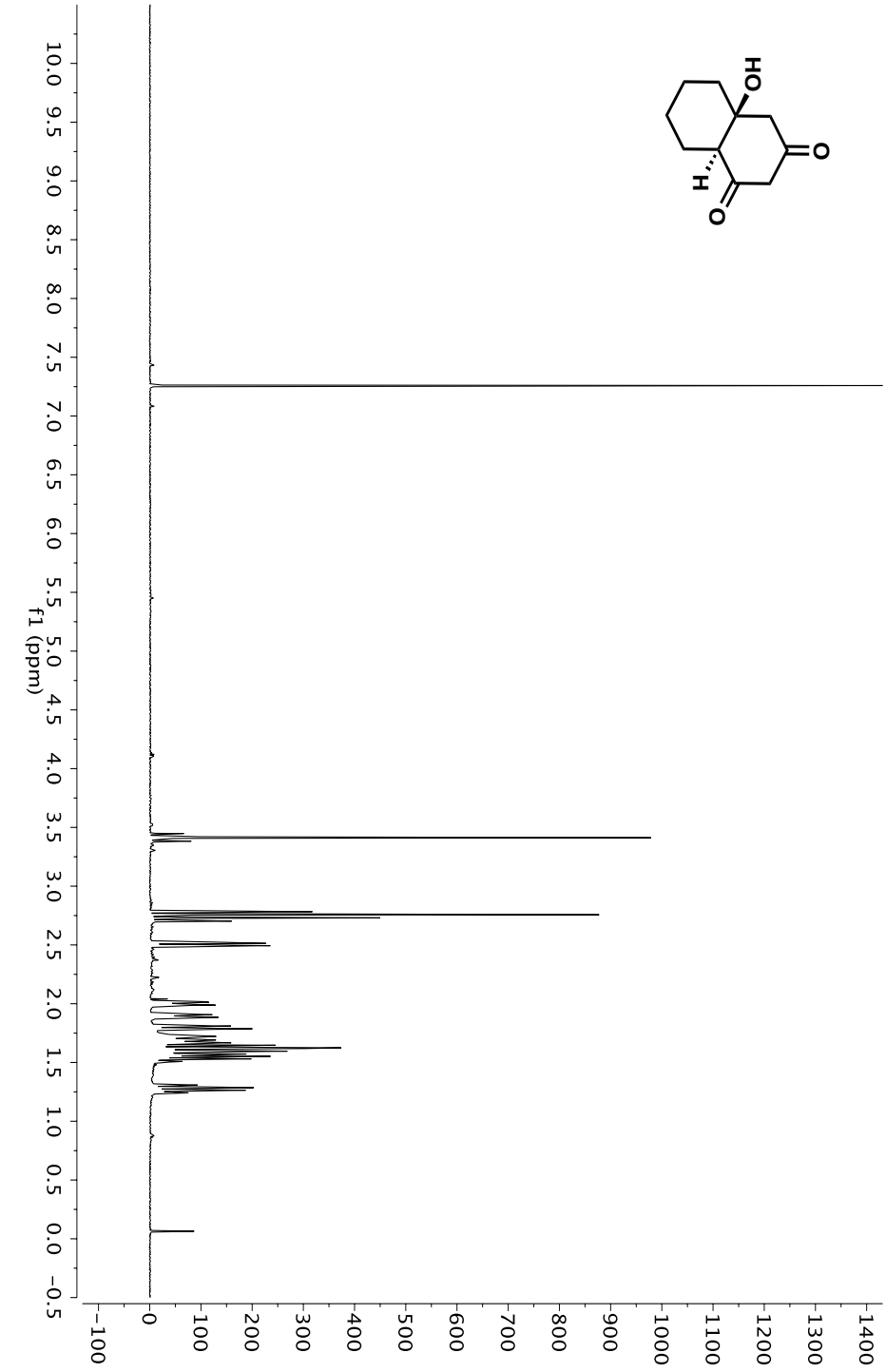

O
O
OTBS
OH
Me
207.0
201.8
134.0
133.3
118.8
118.5
84.5
80.3
63.9
55.7
53.3
47.7
41.7
39.4
34.8
25.7
18.7
17.8
-4.1
-5.2
f1 (ppm)

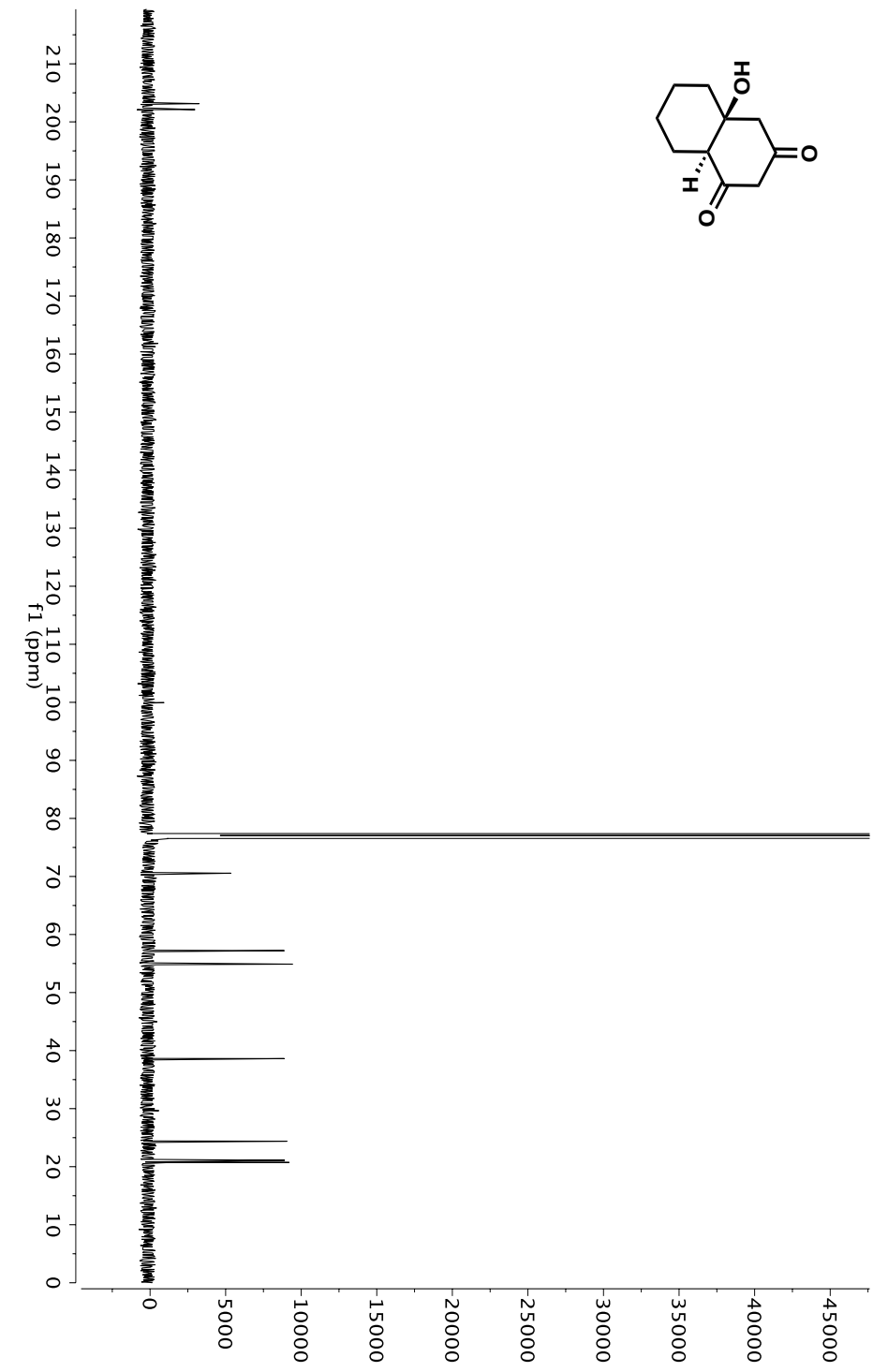

5.09
5.08
5.08
5.07
5.06
5.06
4.30
4.29
3.76
3.75
3.60
3.57
3.20
3.20
3.17
3.17
2.98
2.97
2.95
2.94
2.80
2.79
2.77
2.77
2.72
2.71
2.70
2.69
2.68
2.66
2.60
2.59
2.58
2.57
1.70
1.70
1.63
1.61
1.60
1.04
0.91
0.47
0.11
0.09
f1 (ppm)
Me
Me
O
O
OTBS
OH
Me
Me

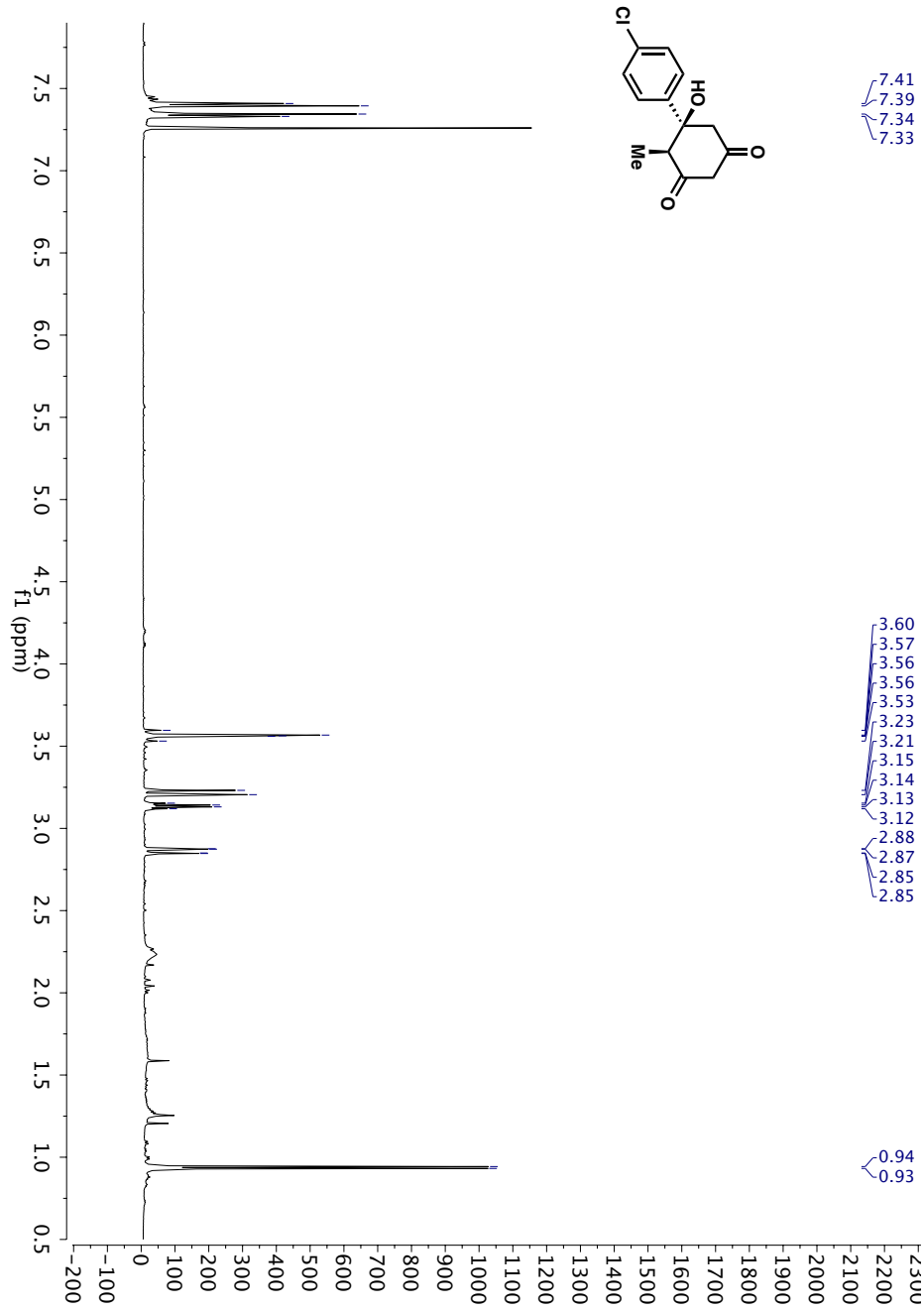

f1 (ppm)
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
207.91
202.41
135.72
119.53
84.27
82.27
64.04
56.36
51.40
47.70
40.53
36.31
26.09
25.92
22.22
18.14
18.08
17.89
-4.70
-5.10
Me
Me
O
O
OTBS
Me
Me
OH

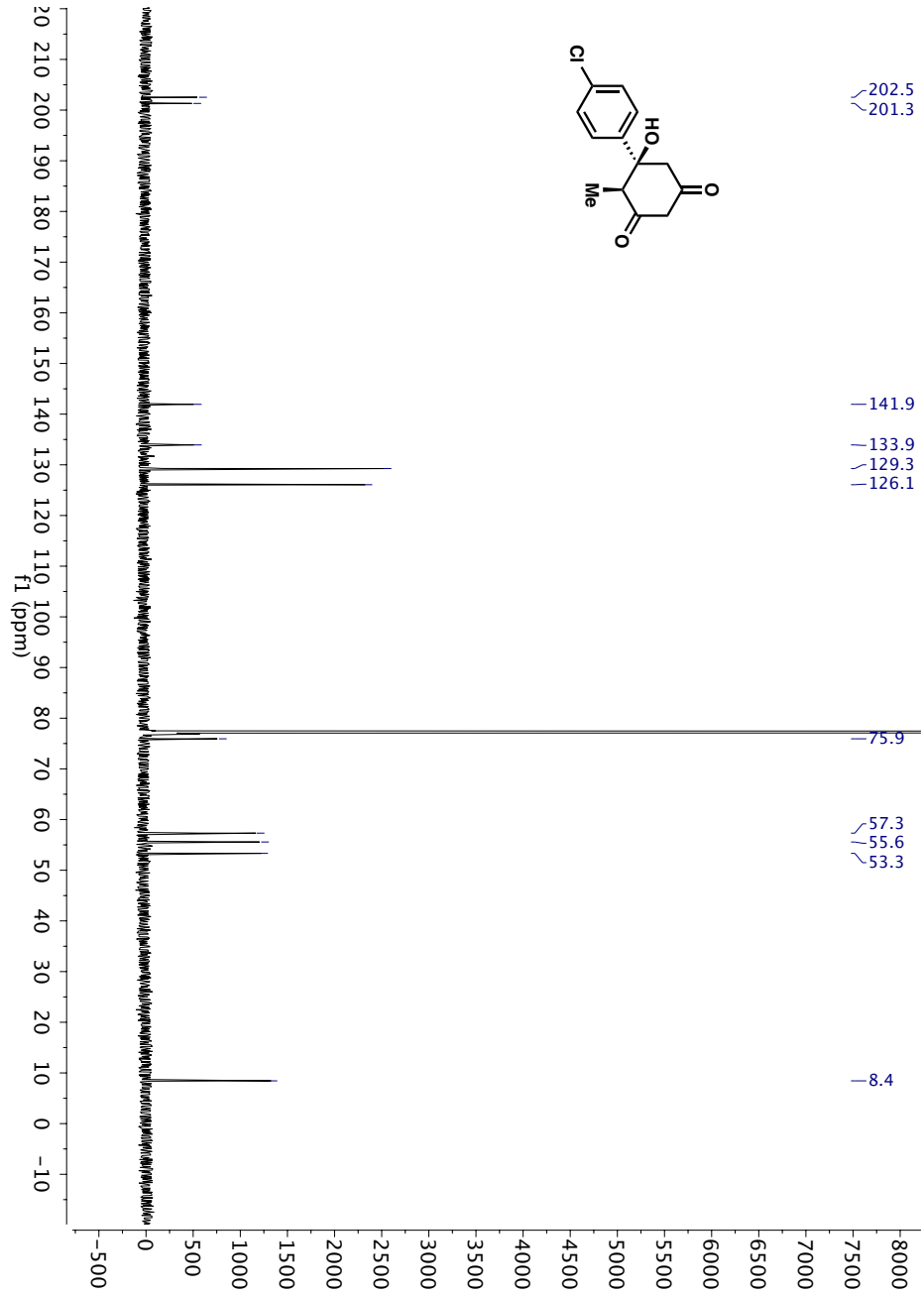

O
HO
O
H
1000
900
800
700
600
500
400
300
200
100
0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

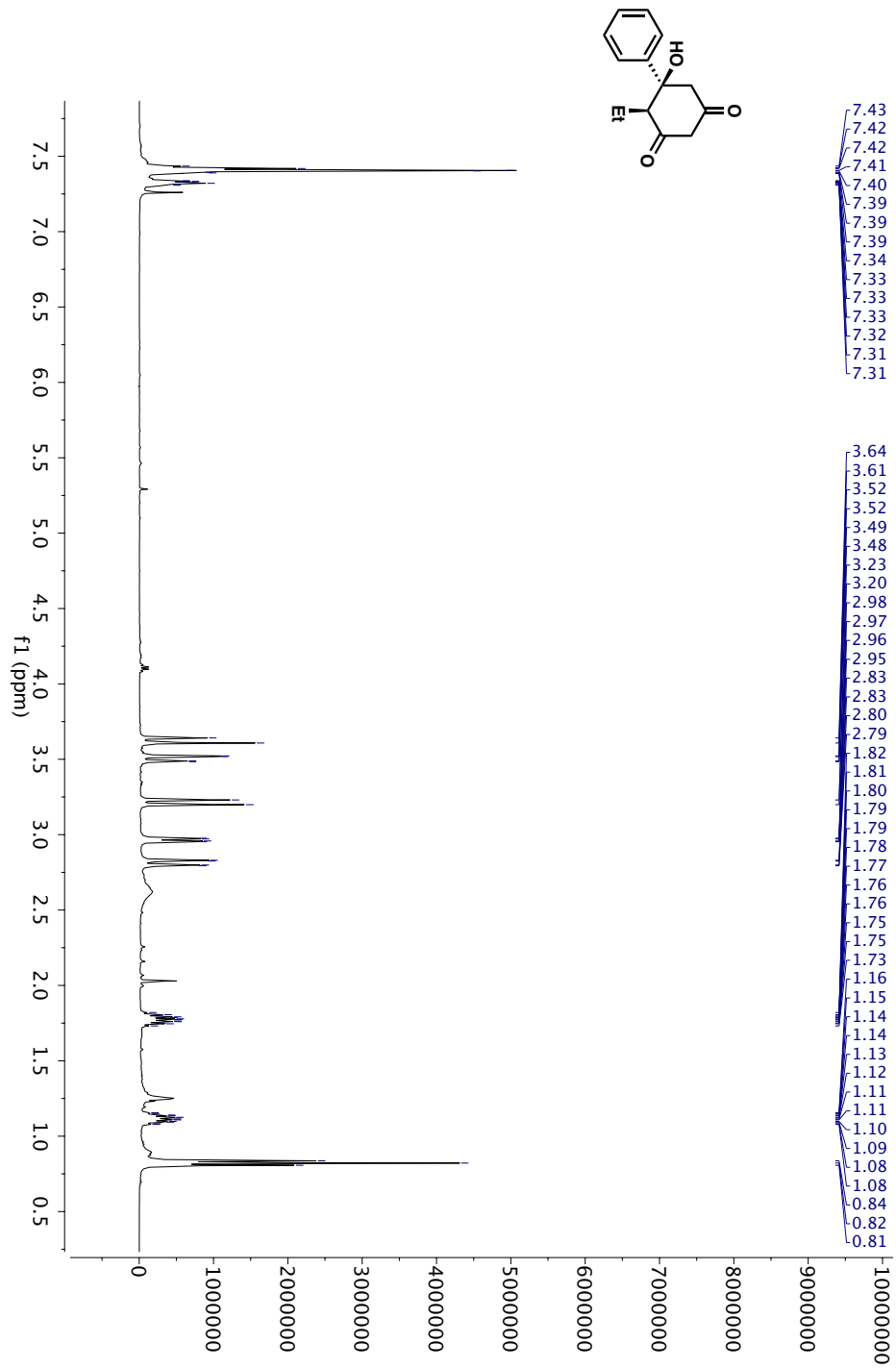

OH
O
H
O
f1 (ppm)

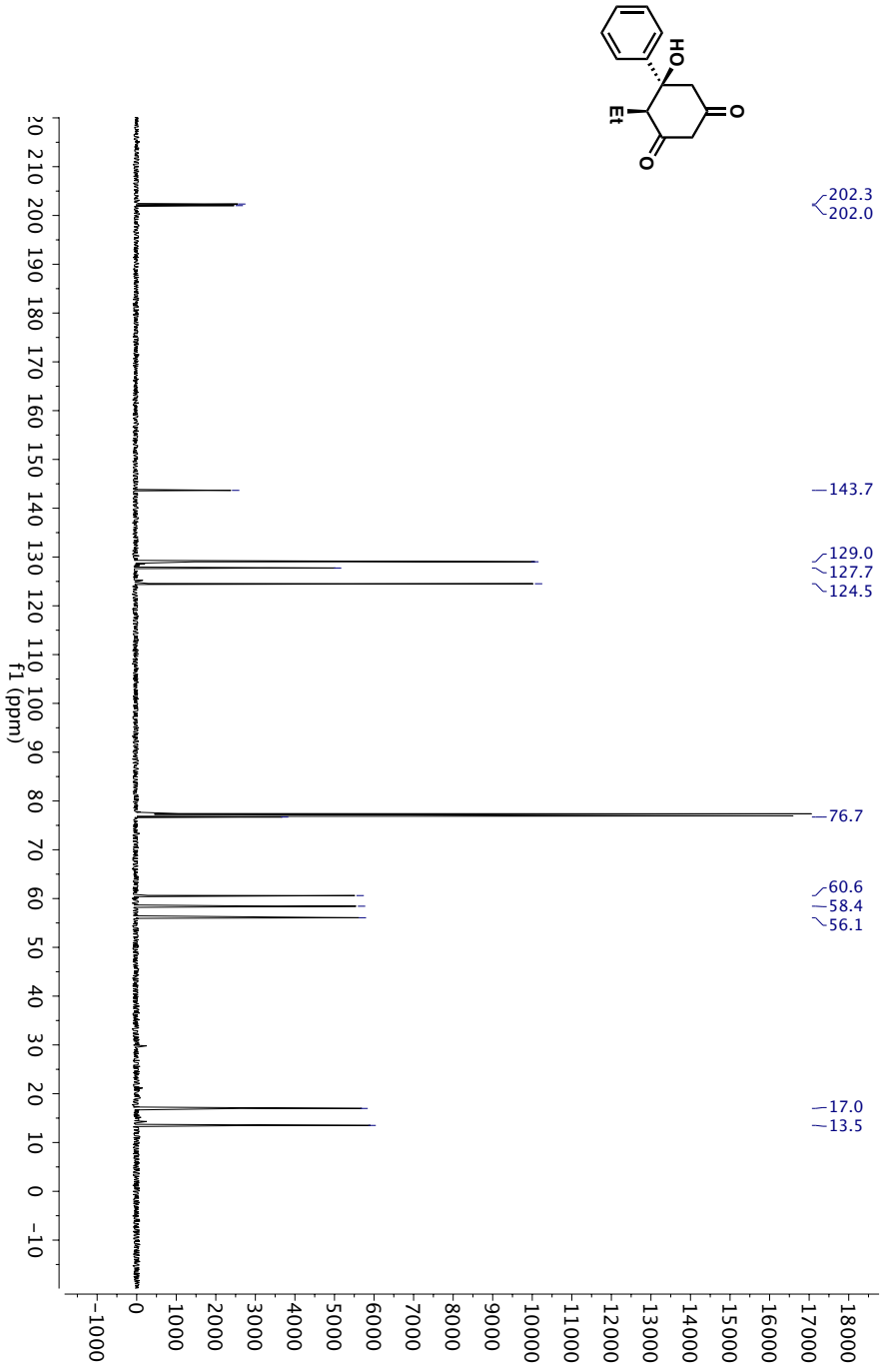

HO
O
H
O
f1 (ppm)
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
−100 0 100 200 300 400 500 600 700 800 900 1000 1100 1200 1300 1400

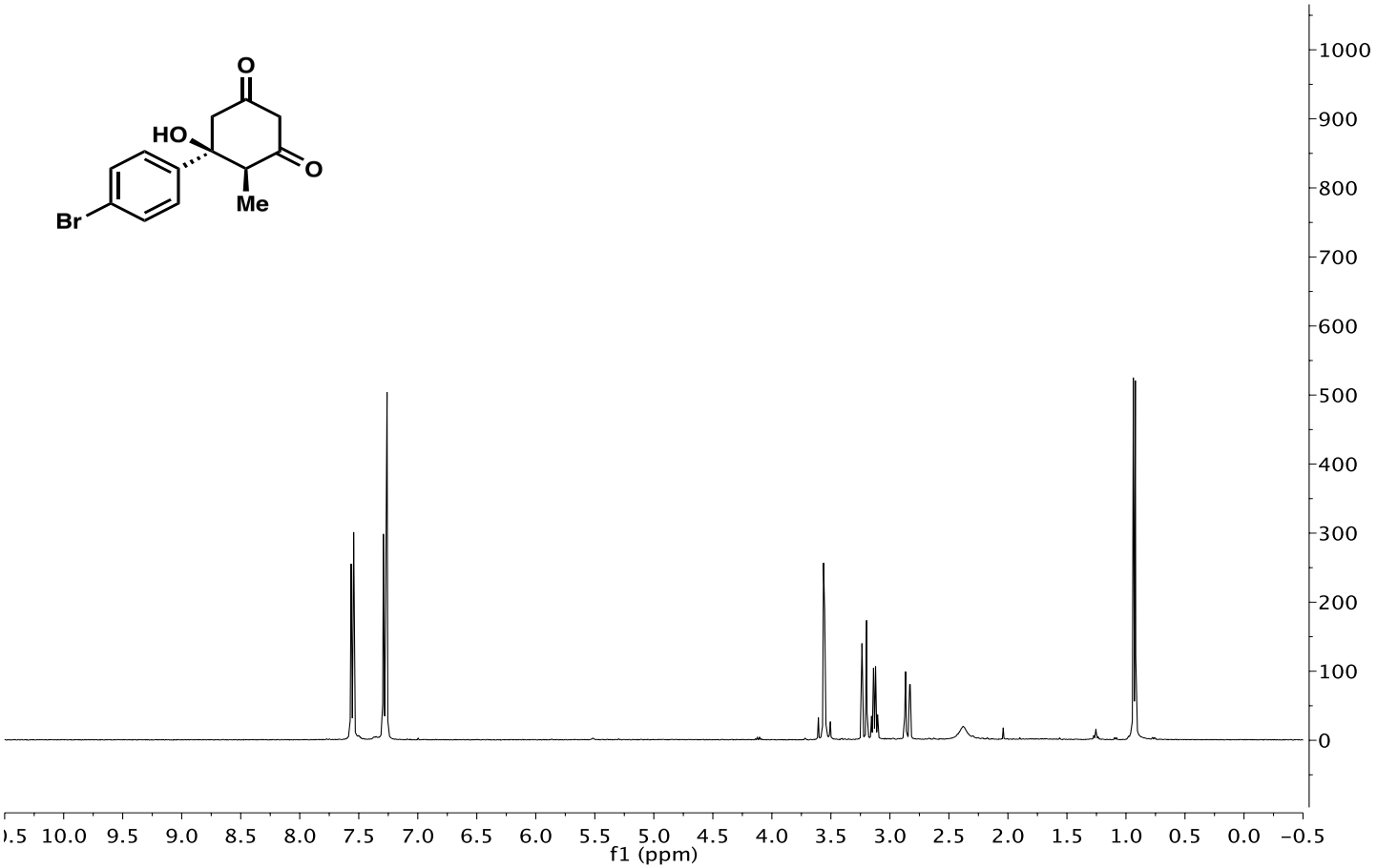

HO
H
O
O
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
0 5000 10000 15000 20000 25000 30000 35000 40000 45000

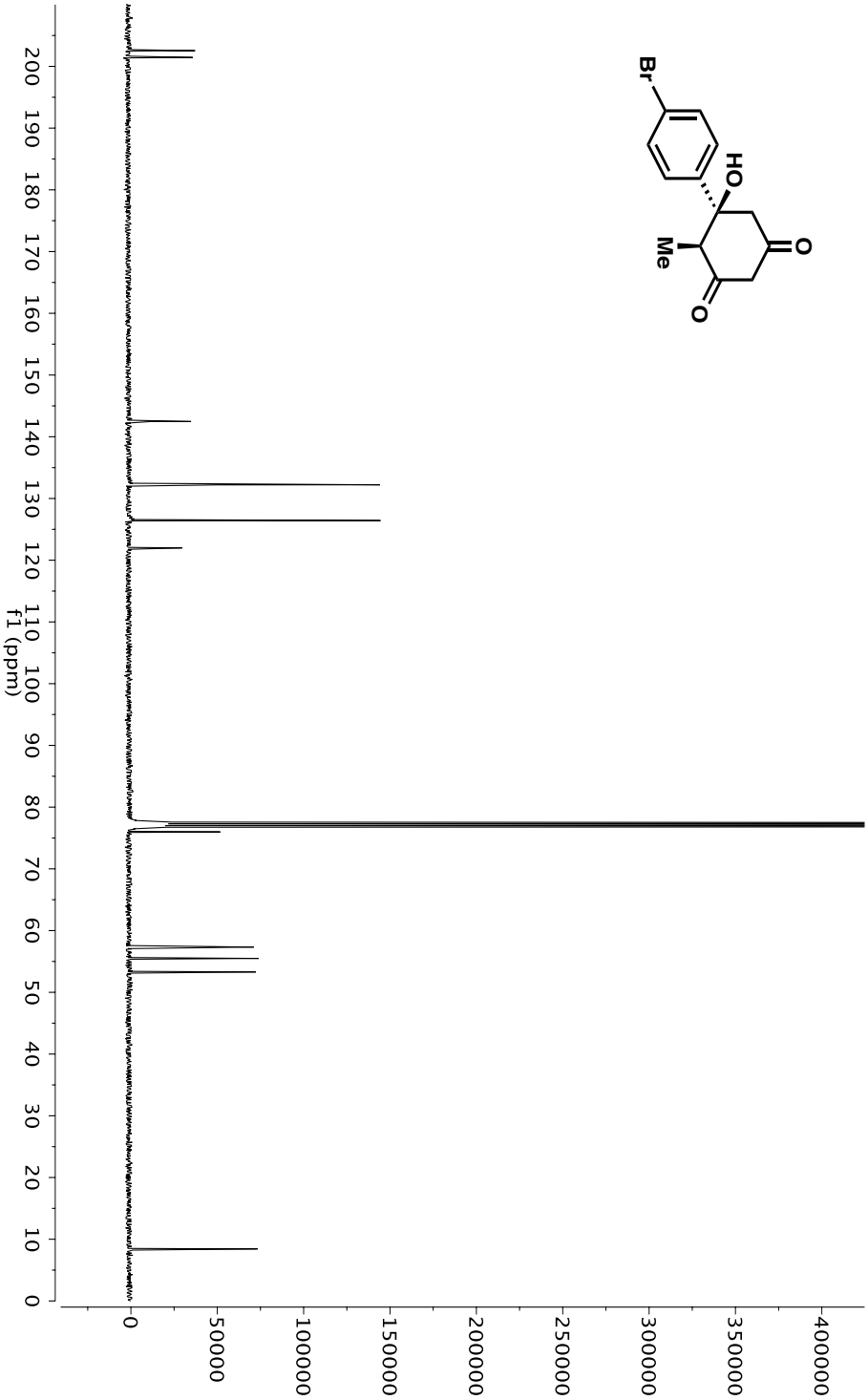

Cl
HO
Me
O
O
7.41
7.39
7.34
7.33
3.60
3.57
3.56
3.56
3.53
3.23
3.21
3.15
3.14
3.13
3.12
2.88
2.87
2.85
2.85
0.94
0.93
f1 (ppm)

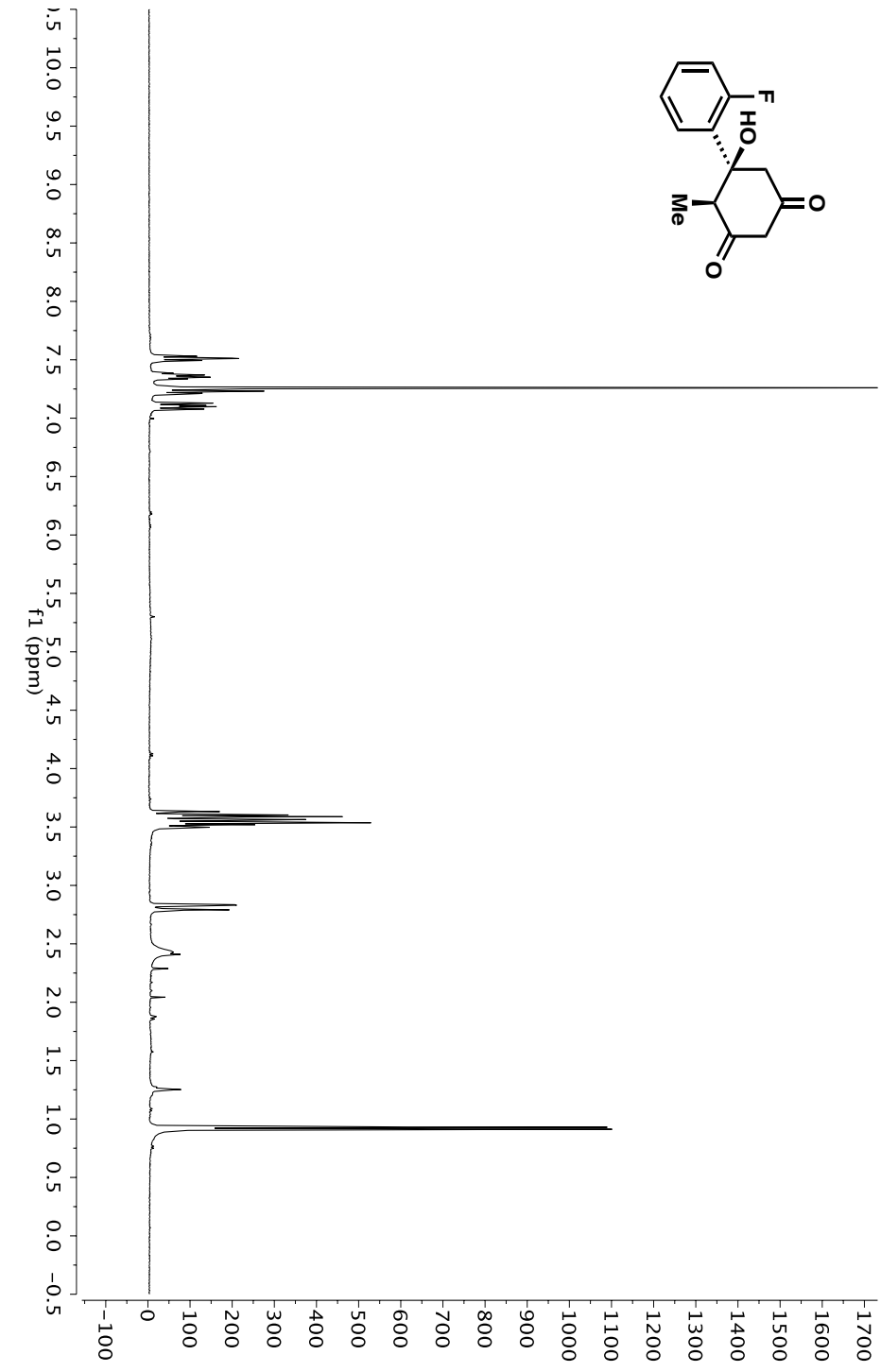

202.5
201.3
141.9
133.9
129.3
126.1
75.9
57.3
55.6
53.3
8.4
Cl
HO
Me
O
O
f1 (ppm)

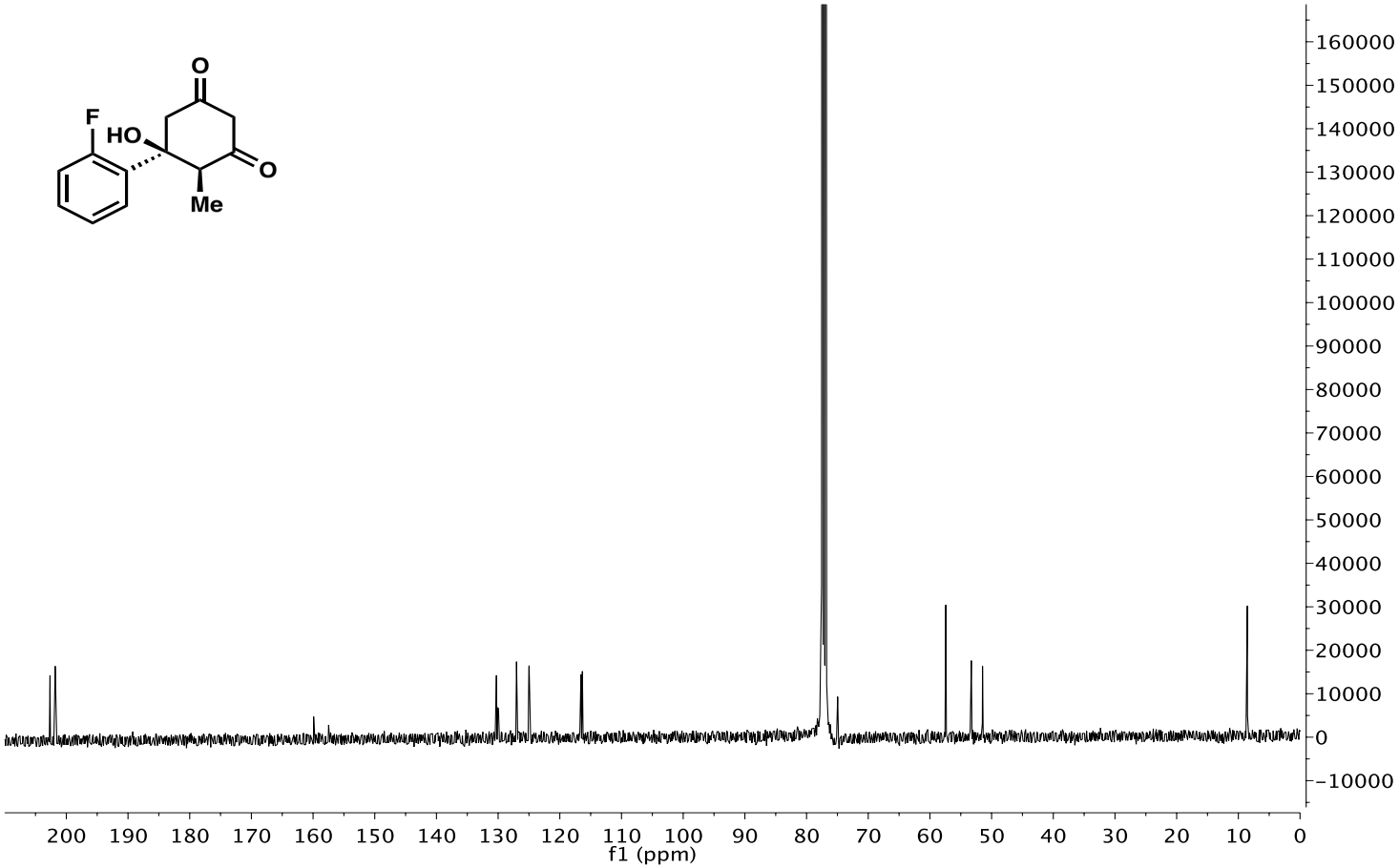

HO
Et
O
O
7.43
7.42
7.42
7.41
7.40
7.39
7.39
7.39
7.34
7.33
7.33
7.33
7.32
7.31
7.31
3.64
3.61
3.52
3.52
3.49
3.48
3.23
3.20
2.98
2.97
2.96
2.95
2.83
2.83
2.80
2.79
1.82
1.81
1.80
1.79
1.79
1.78
1.77
1.76
1.76
1.75
1.75
1.73
1.16
1.15
1.14
1.14
1.13
1.12
1.11
1.11
1.10
1.09
1.08
1.08
0.84
0.82
0.81
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
1000000
2000000
3000000
4000000
5000000
6000000
7000000
8000000
9000000
10000000

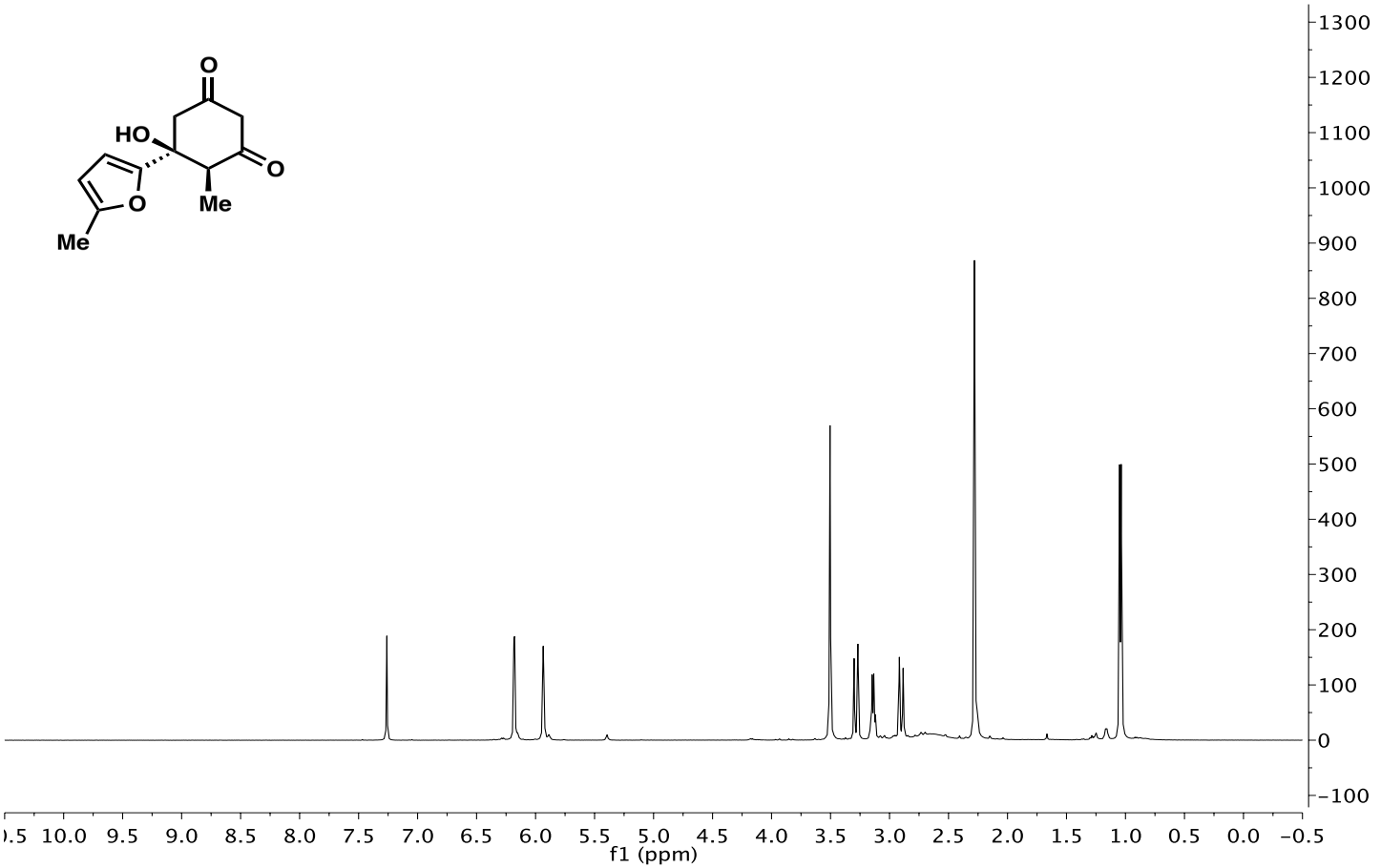

HO
Et
O
O
202.3
202.0
143.7
129.0
127.7
124.5
76.7
60.6
58.4
56.1
17.0
13.5
f1 (ppm)

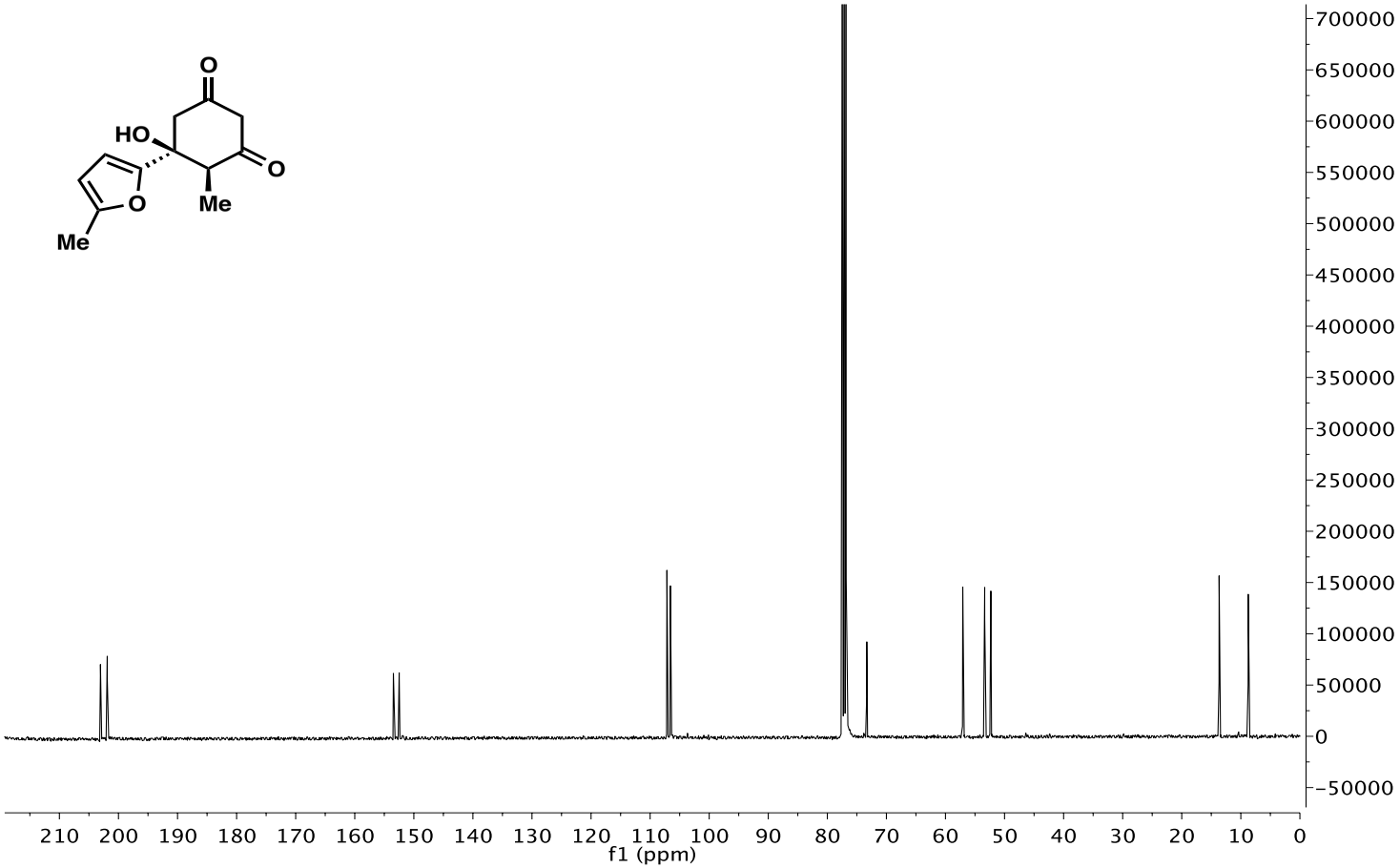

O
HO
O
Me
Br
1000
900
800
700
600
500
400
300
200
100
0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

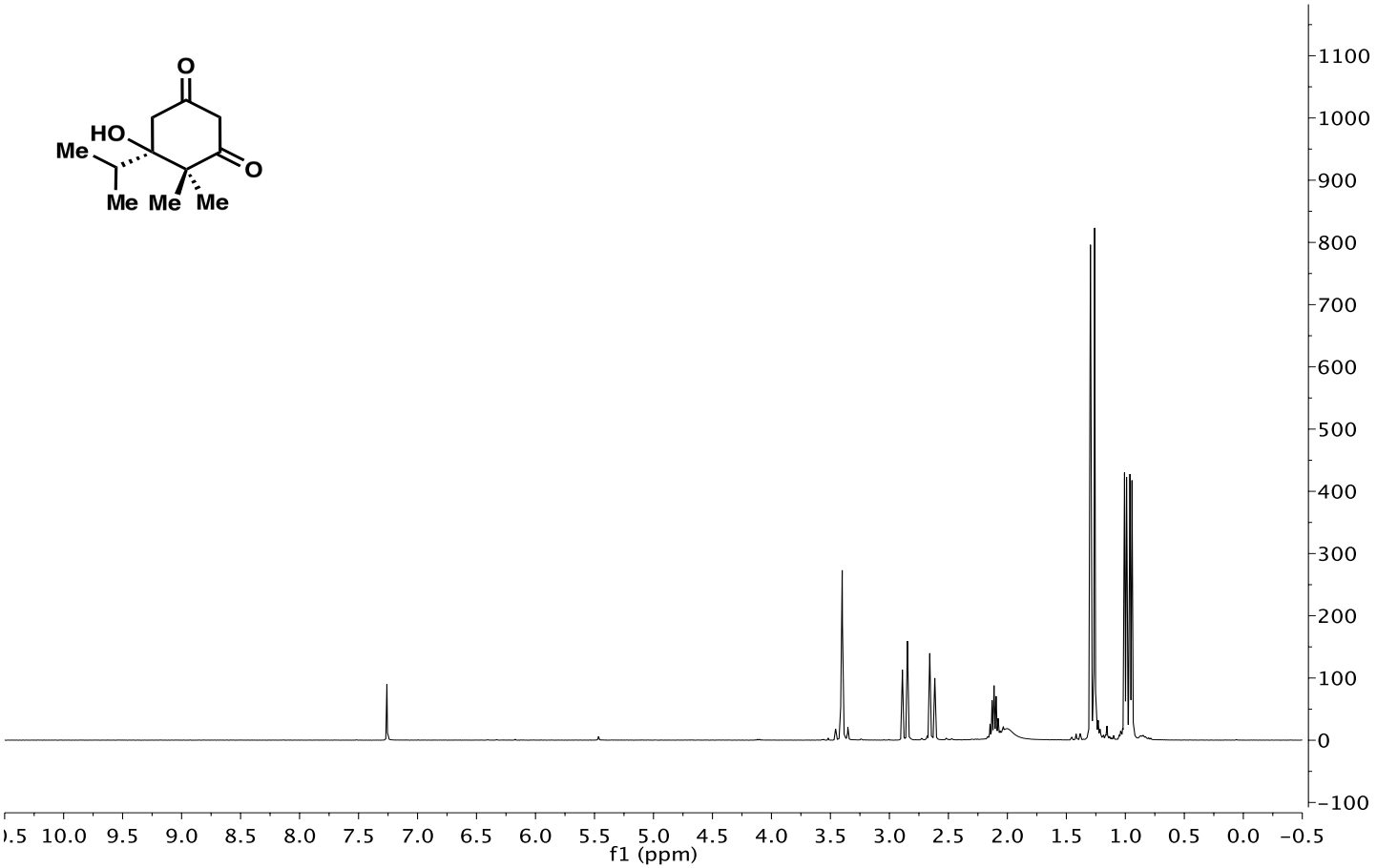

Br
HO
Me
O
O
f1 (ppm)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
0 50000 100000 150000 200000 250000 300000 350000 400000

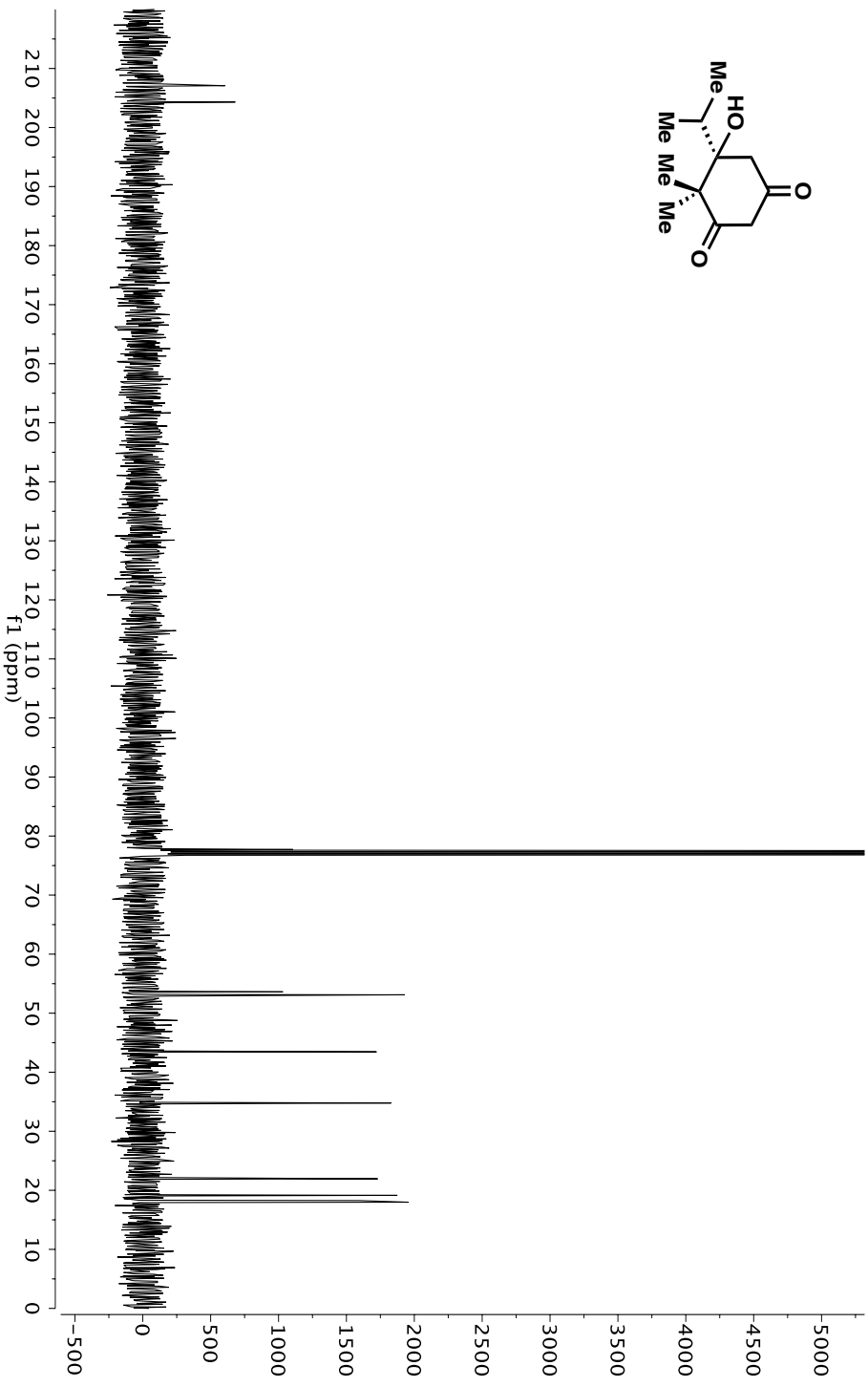

F
HO
Me
O
O
f1 (ppm)

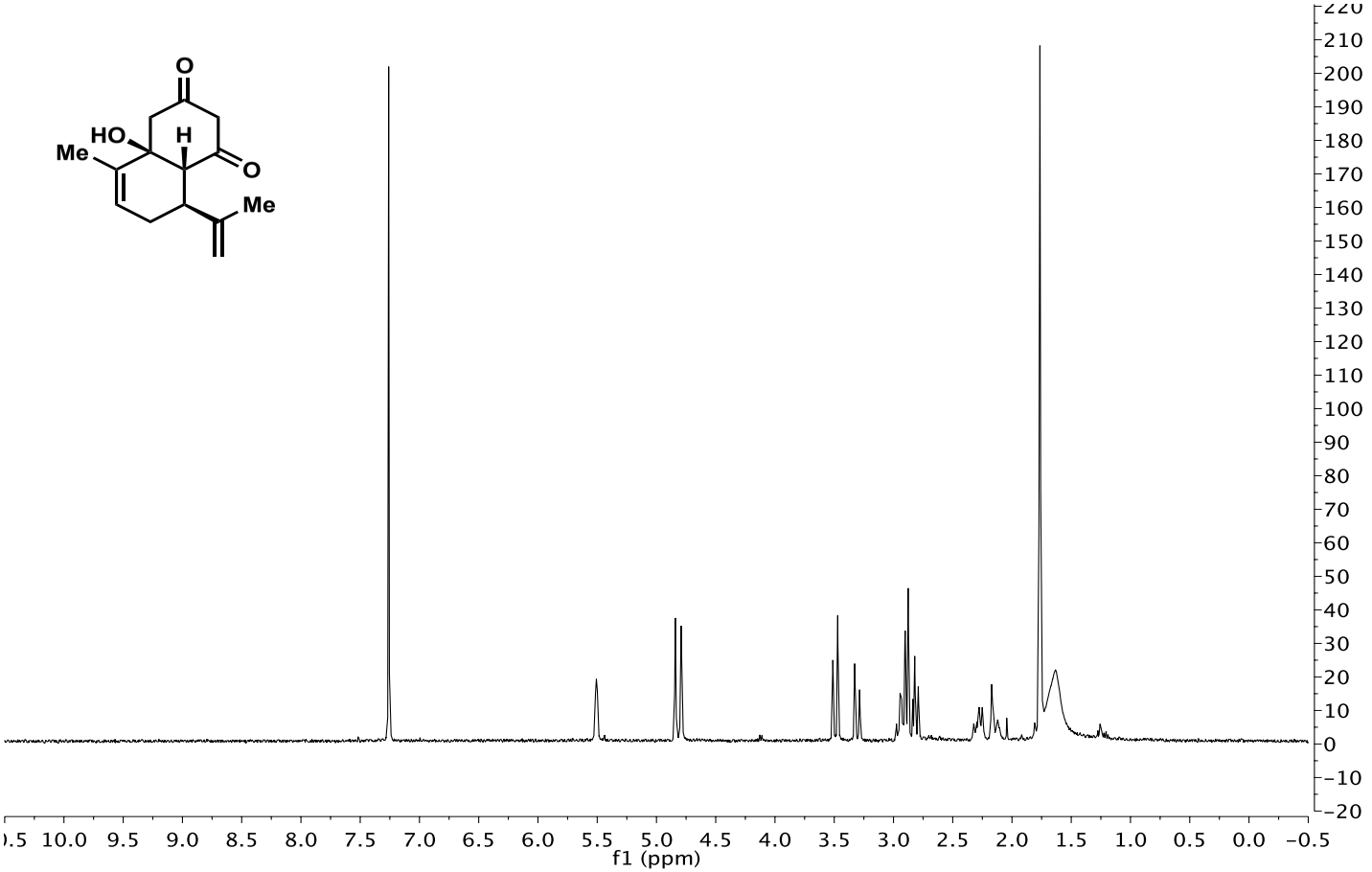

O
F
HO
O
Me
160000
150000
140000
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
−10000
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

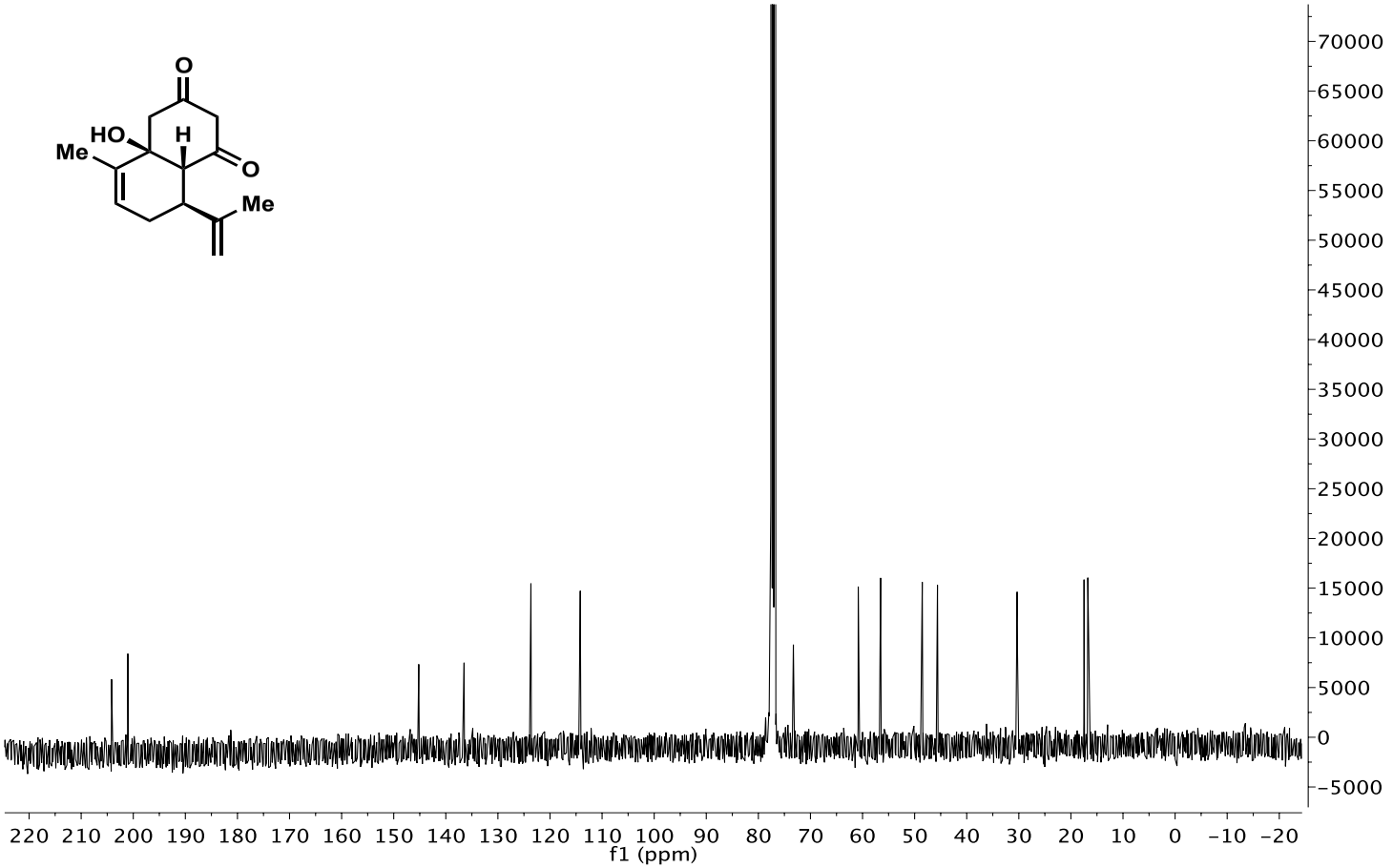

O
HO
O
O
Me
Me
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)


O
HO
O
O
Me
Me
700000
650000
600000
550000
500000
450000
400000
350000
300000
250000
200000
150000
100000
50000
0
−50000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
HO
Me
O
Me Me Me
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)


Me
HO
Me Me Me
O
O
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
−500 0 500 1000 1500 2000 2500 3000 3500 4000 4500 5000


O
HO
H
Me
O
Me
f1 (ppm)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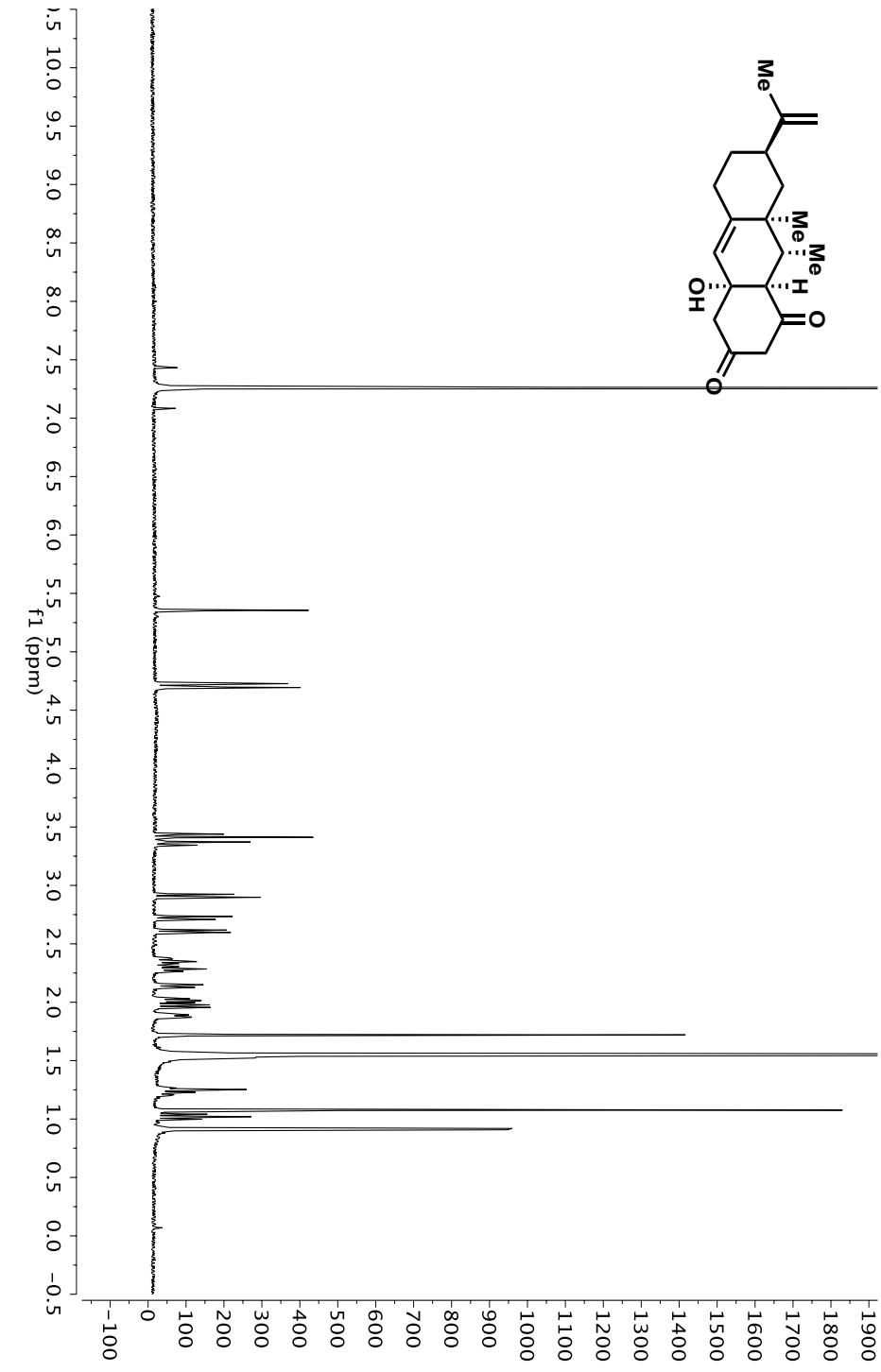
HO
H
Me
O
Me
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
−5000
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10 −20
f1 (ppm)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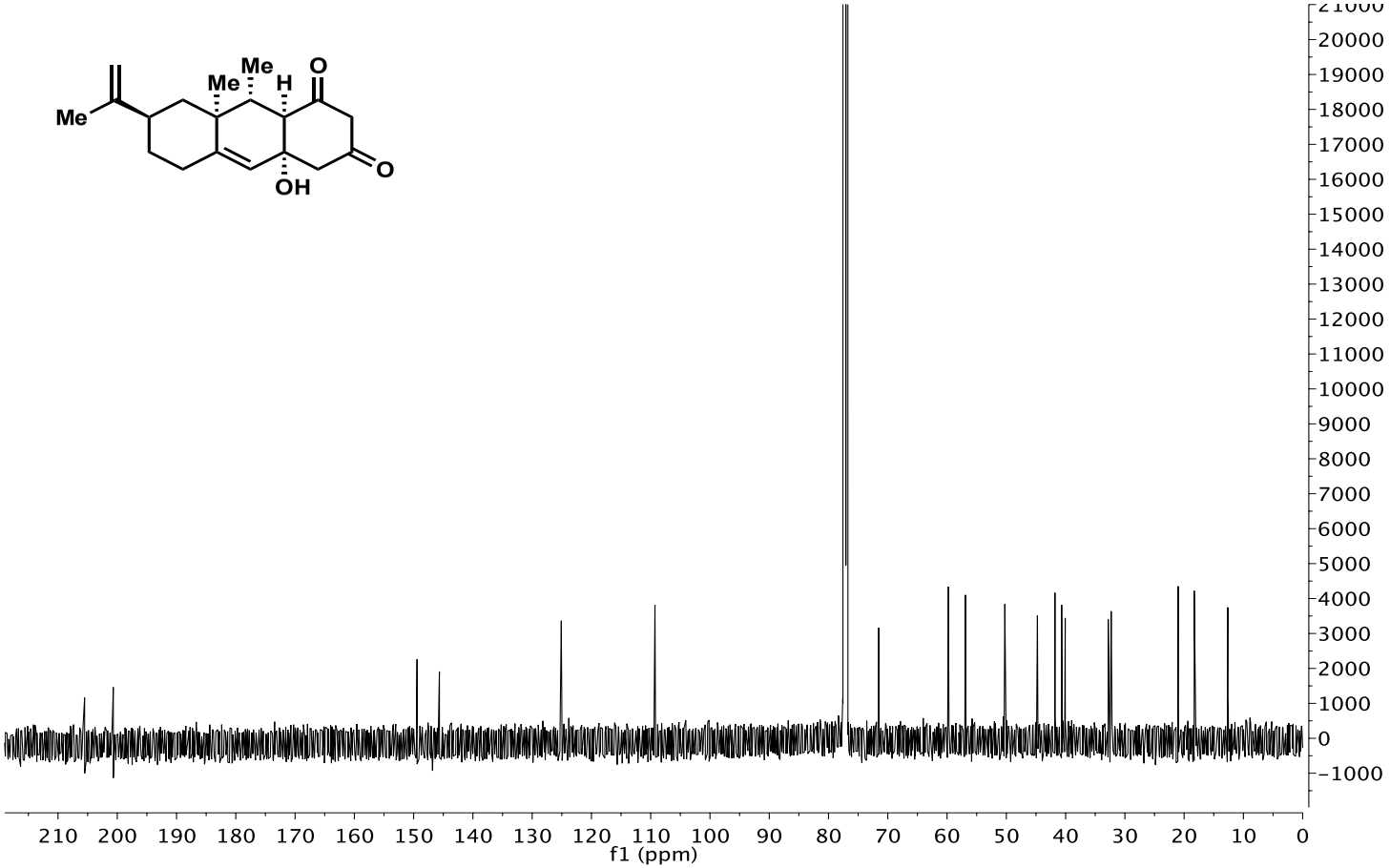
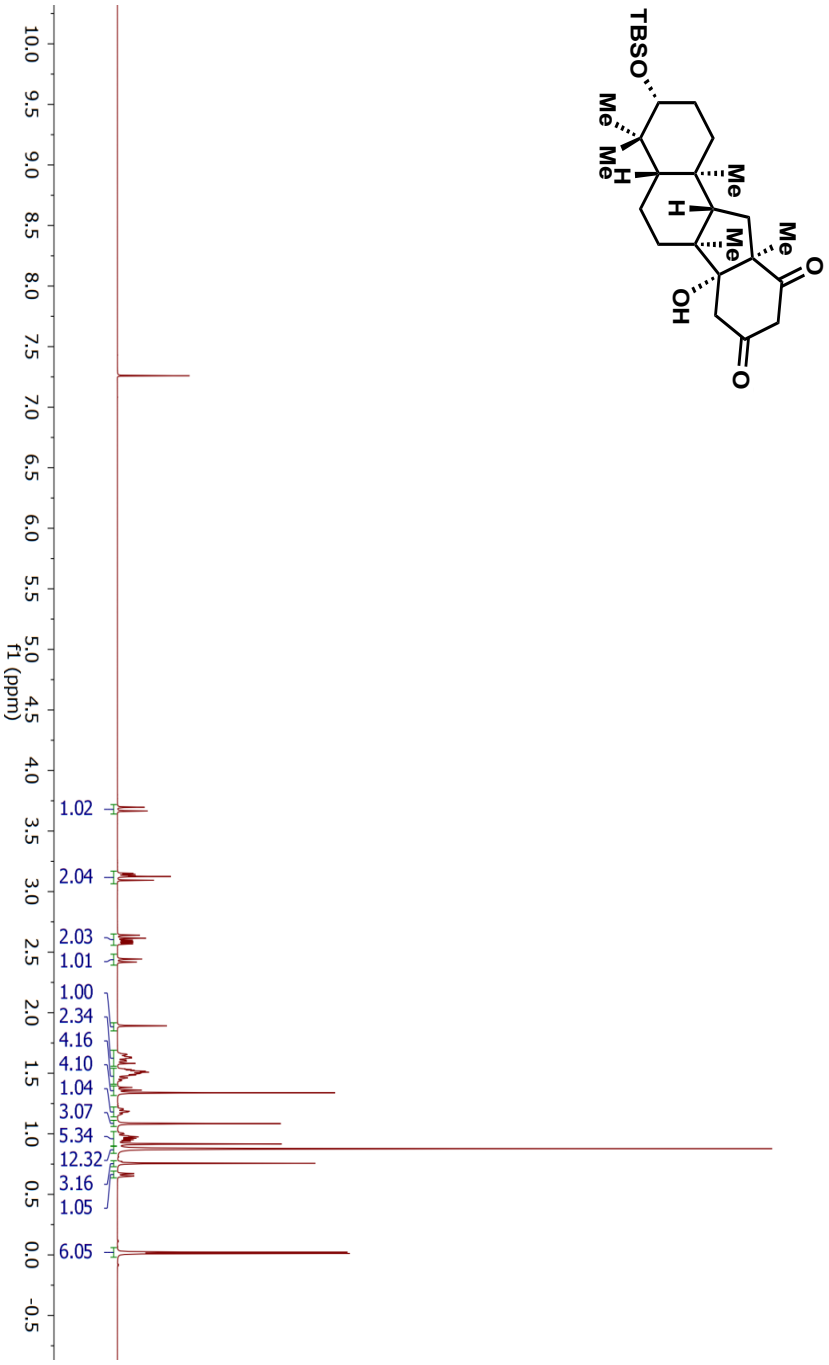
Me
Me
H
O
OH
O
f1 (ppm)


Me
Me
Me
H
O
O
OH
21000
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


TBSO
Me
Me
H
Me
H
Me
Me
OH
O
O
f1 (ppm)
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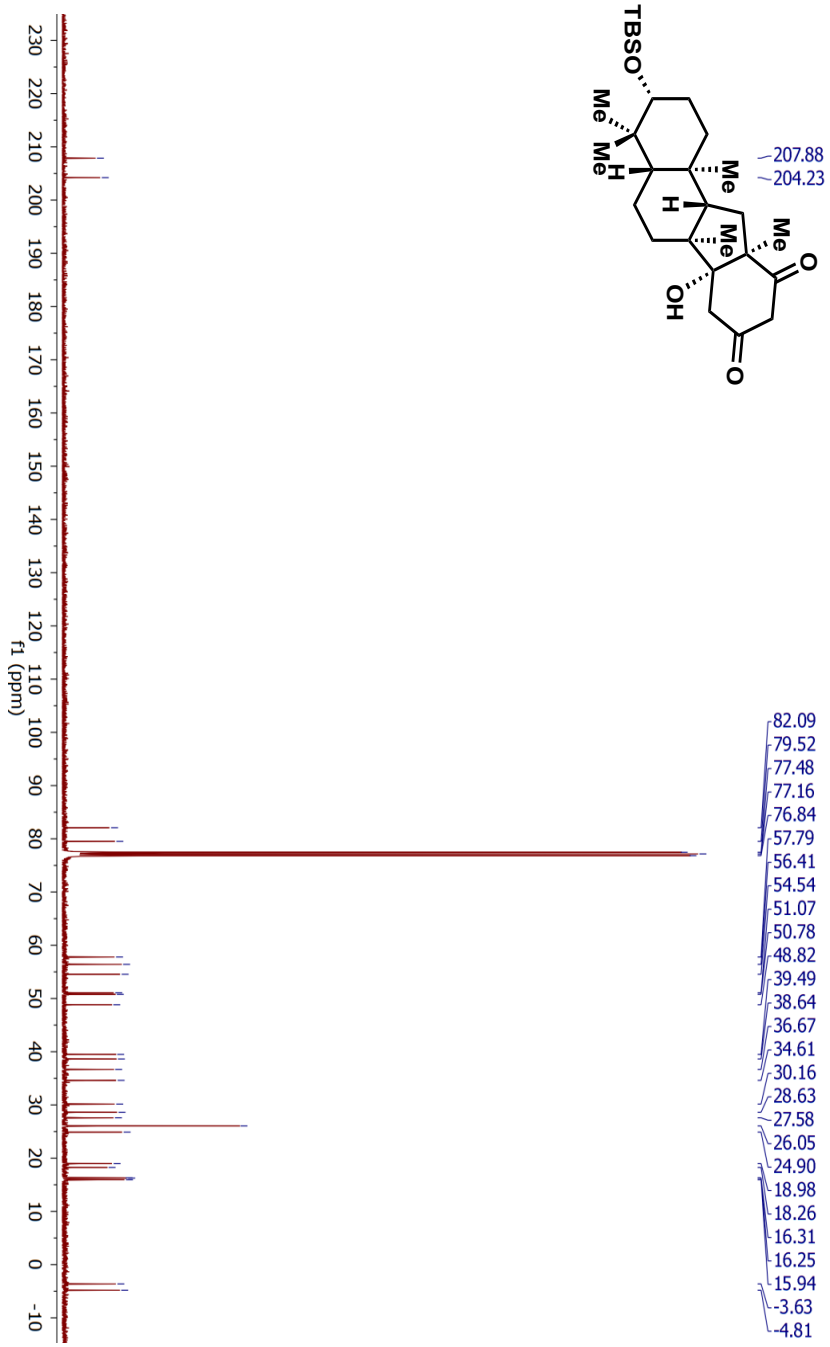
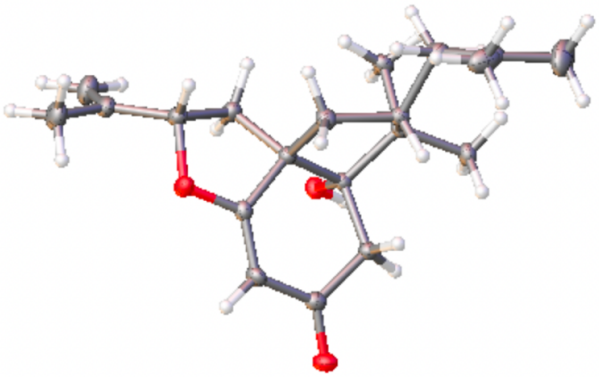
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1.02
2.04
2.03
1.01
1.00
2.34
4.16
4.10
1.04
3.07
5.34
12.32
3.16
1.05
6.05


TBSO
Me
Me
H
Me
H
Me
Me
O
OH
O
207.88
204.23
82.09
79.52
77.48
77.16
76.84
57.79
56.41
54.54
51.07
50.78
48.82
39.49
38.64
36.67
34.61
30.16
28.63
27.58
26.05
24.90
18.98
18.26
16.31
16.25
15.94
-3.63
-4.81
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

X-Ray crystallographic Analysis of Compound 83



A colorless block crystal of 0.300 x 0.200 x 0.100 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K. Data collection was 99.5% complete to 26.356° in θ. A total of 41409 reflections were collected covering the indices -11<=h<=11, -12<=k<=12, -13<=l<=13. 3789 reflections were founded to be symmetry independent, with an R_{int} of 0.0335. Indexing and unit cell refinement indicated a triclinic lattice. The data were integrated using the SAINT and scaled using the SCALE3 SADABS routines Solution by intrinsic phasing (SHELXT-2014) produced a heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2016). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

Table 1 Crystal data and structure refinement for 1879639-2.

Identification code	1879639-2
Empirical formula	$C_{21}H_{30}O_3$
Formula weight	330.45
Temperature/K	100.15
Crystal system	triclinic
Space group	P-1
a/Å	9.0443(19)
b/Å	10.396(2)
c/Å	10.776(2)
α/°	67.725(9)
β/°	84.117(10)
γ/°	84.846(10)
Volume/Å^3	931.2(3)
Z	2
ρ_{calc}g/cm^3	1.178
μ/mm^{-1}	0.077
F(000)	360.0
Crystal size/mm^3	0.3 × 0.2 × 0.1
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.096 to 52.712
Index ranges	-11 ≤ h ≤ 11, -12 ≤ k ≤ 12, -13 ≤ l ≤ 13
Reflections collected	41409
Independent reflections	3789 [R_{int} = 0.0335, R_{sigma} = 0.0144]
Data/restraints/parameters	3789/0/226
Goodness-of-fit on F^2	1.050
Final R indexes [I>=2σ (I)]	R_1 = 0.0407, wR_2 = 0.1043
Final R indexes [all data]	R_1 = 0.0432, wR_2 = 0.1061
Largest diff. peak/hole / e Å^{-3}	0.35/-0.21

Table 2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for 1879639-2. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
C1	8966.4(18)	8329.1(15)	6332.2(16)	33.4(3)
C2	9484.2(16)	6831.3(14)	7010.9(14)	25.3(3)
C3	10229(2)	6520.5(19)	8281.2(17)	44.6(4)
C4	9260.1(14)	5888.2(13)	6499.1(13)	20.2(3)
C5	9588.4(14)	4336.4(13)	7070.2(13)	19.6(3)
C6	8130.0(13)	3579.4(12)	7414.4(12)	16.6(2)
C7	8261.2(13)	1980.7(12)	8165.4(12)	15.6(2)
C8	9552.1(13)	1297.4(13)	7538.7(13)	18.9(3)
C9	8507.5(14)	1573.4(13)	9650.6(12)	20.1(3)
C10	6718.2(13)	1563.4(12)	7932.3(11)	14.6(2)
C11	6482.0(13)	2459.0(12)	6441.4(12)	15.5(2)
C12	7295.3(14)	3815.4(13)	6159.5(12)	19.1(3)
C13	6986.1(14)	1803.8(13)	5382.6(12)	18.3(3)
C14	6121.7(14)	2735.5(13)	4199.6(12)	19.4(3)
C15	5747.9(15)	2163.9(15)	3180.1(13)	23.3(3)
C16	6210.7(18)	906.3(16)	3228.9(15)	30.9(3)
C17	4842.0(18)	3157.0(17)	2085.6(15)	33.1(3)
C18	4861.1(13)	2754.7(12)	6158.2(12)	17.1(2)
C19	3675.4(14)	2647.7(13)	7047.0(13)	19.6(3)
C20	3895.9(13)	2093.4(12)	8456.8(12)	18.0(3)
C21	5474.5(13)	1937.7(13)	8860.8(12)	17.3(2)
O1	6650.5(10)	141.7(9)	8118.2(9)	17.9(2)
O3	4692.8(10)	3068.8(9)	4850.4(9)	20.8(2)
O4	2839.7(10)	1769.7(10)	9326.5(9)	23.3(2)

Table 3 Anisotropic Displacement Parameters ($Å^2×10^3$) for 1879639-2. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	41.3(8)	20.4(7)	38.2(8)	-13.5(6)	11.3(7)	-5.6(6)
C2	30.0(7)	21.7(6)	24.7(7)	-9.8(5)	5.7(5)	-8.4(5)
C3	67.8(12)	37.7(9)	35.7(9)	-17.3(7)	-9.2(8)	-18.0(8)
C4	21.3(6)	18.2(6)	20.2(6)	-5.9(5)	0.1(5)	-3.6(5)
C5	17.9(6)	17.7(6)	23.4(6)	-7.5(5)	-1.4(5)	-3.7(5)
C6	16.0(6)	14.8(6)	18.8(6)	-6.0(5)	-1.5(4)	-0.8(4)
C7	14.2(5)	14.7(6)	17.6(6)	-5.3(5)	-2.2(4)	-1.9(4)
C8	15.8(6)	17.6(6)	23.7(6)	-7.9(5)	-3.4(5)	0.6(4)
C9	20.2(6)	20.8(6)	19.2(6)	-6.4(5)	-5.4(5)	-1.6(5)
C10	14.3(5)	13.6(5)	15.5(5)	-4.6(4)	-2.0(4)	-0.9(4)
C11	15.3(6)	14.8(5)	15.3(6)	-4.6(4)	-1.1(4)	-0.9(4)
C12	20.4(6)	15.8(6)	19.2(6)	-3.4(5)	-2.9(5)	-3.3(5)
C13	18.1(6)	19.6(6)	17.2(6)	-7.1(5)	-2.0(5)	0.8(5)
C14	17.6(6)	22.0(6)	17.8(6)	-7.1(5)	-0.4(5)	-0.2(5)
C15	21.6(6)	30.6(7)	17.7(6)	-8.6(5)	-1.6(5)	-3.4(5)
C16	40.6(8)	31.3(8)	24.9(7)	-14.0(6)	-6.0(6)	-2.5(6)
C17	35.9(8)	41.2(9)	23.5(7)	-12.9(6)	-9.7(6)	4.0(6)
C18	19.2(6)	14.3(5)	17.2(6)	-4.5(4)	-4.7(5)	-0.1(4)
C19	14.8(6)	20.7(6)	21.5(6)	-5.7(5)	-3.8(5)	0.7(5)
C20	17.1(6)	15.0(6)	21.0(6)	-6.1(5)	0.0(5)	-0.8(4)
C21	16.5(6)	18.6(6)	16.2(6)	-5.8(5)	-0.7(4)	-1.9(4)
O1	21.6(4)	13.0(4)	18.2(4)	-3.8(4)	-4.0(3)	-2.2(3)
O3	18.8(4)	25.9(5)	16.7(4)	-7.3(4)	-4.1(3)	4.2(4)
O4	17.9(4)	24.9(5)	21.9(5)	-3.8(4)	1.6(4)	-1.3(4)

Table 4 Bond Lengths for 1879639-2.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
C1	C2	1.502(2)	C11	C12	1.5613(16)
C2	C3	1.499(2)	C11	C13	1.5494(16)
C2	C4	1.3323(19)	C11	C18	1.5087(16)
C4	C5	1.5061(17)	C13	C14	1.5188(17)
C5	C6	1.5368(16)	C14	C15	1.5104(18)
C6	C7	1.5478(16)	C14	O3	1.4833(15)
C6	C12	1.5438(17)	C15	C16	1.320(2)
C7	C8	1.5417(17)	C15	C17	1.5004(19)
C7	C9	1.5274(17)	C18	C19	1.3453(18)
C7	C10	1.5691(16)	C18	O3	1.3425(15)
C10	C11	1.5474(16)	C19	C20	1.4344(18)
C10	C21	1.5502(16)	C20	C21	1.5122(17)
C10	O1	1.4205(14)	C20	O4	1.2407(15)

Table 5 Bond Angles for 1879639-2.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C3	C2	C1	114.43(13)	C13	C11	C12	111.78(10)
C4	C2	C1	120.91(14)	C18	C11	C10	113.06(10)
C4	C2	C3	124.66(14)	C18	C11	C12	112.29(10)
C2	C4	C5	129.06(13)	C18	C11	C13	97.97(9)
C4	C5	C6	110.07(10)	C6	C12	C11	107.07(9)
C5	C6	C7	116.47(10)	C14	C13	C11	101.47(10)
C5	C6	C12	112.75(10)	C15	C14	C13	119.15(11)
C12	C6	C7	105.25(9)	O3	C14	C13	103.29(9)
C6	C7	C10	100.97(9)	O3	C14	C15	107.19(10)
C8	C7	C6	111.82(10)	C16	C15	C14	122.76(12)
C8	C7	C10	110.89(10)	C16	C15	C17	122.70(13)
C9	C7	C6	112.05(10)	C17	C15	C14	114.52(12)
C9	C7	C8	107.93(10)	C19	C18	C11	127.83(11)
C9	C7	C10	113.15(10)	O3	C18	C11	110.85(10)
C11	C10	C7	104.31(9)	O3	C18	C19	121.17(11)
C11	C10	C21	110.17(9)	C18	C19	C20	119.08(11)
C21	C10	C7	109.93(9)	C19	C20	C21	117.62(11)
O1	C10	C7	115.08(9)	O4	C20	C19	121.98(11)
O1	C10	C11	108.16(9)	O4	C20	C21	120.39(11)
O1	C10	C21	109.06(9)	C20	C21	C10	117.10(10)
C10	C11	C12	104.33(9)	C18	O3	C14	108.86(9)
C10	C11	C13	117.71(10)				

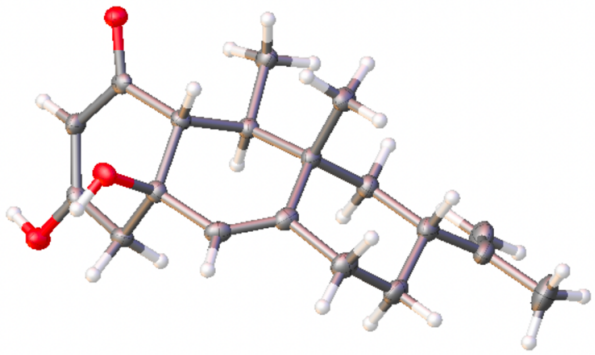
Table 6 Torsion Angles for 1879639-2.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C1	C2	C4	C5	-175.10(13)	C11	C18	O3	C14	11.41(13)
C2	C4	C5	C6	114.35(15)	C12	C6	C7	C8	80.39(11)
C3	C2	C4	C5	4.0(2)	C12	C6	C7	C9	-158.28(10)
C4	C5	C6	C7	-173.12(10)	C12	C6	C7	C10	-37.58(11)
C4	C5	C6	C12	65.06(13)	C12	C11	C13	C14	-77.88(11)
C5	C6	C7	C8	-45.30(14)	C12	C11	C18	C19	-99.79(14)
C5	C6	C7	C9	76.03(13)	C12	C11	C18	O3	84.63(12)
C5	C6	C7	C10	-163.27(10)	C13	C11	C12	C6	-121.06(11)
C5	C6	C12	C11	147.38(10)	C13	C11	C18	C19	142.67(13)
C6	C7	C10	C11	42.37(11)	C13	C11	C18	O3	-32.90(12)
C6	C7	C10	C21	-75.73(11)	C13	C14	C15	C16	-3.83(19)
C6	C7	C10	O1	160.70(9)	C13	C14	C15	C17	177.75(12)
C7	C6	C12	C11	19.42(12)	C13	C14	O3	C18	16.01(12)
C7	C10	C11	C12	-30.73(11)	C15	C14	O3	C18	142.67(10)
C7	C10	C11	C13	93.79(11)	C18	C11	C12	C6	129.96(10)
C7	C10	C11	C18	-153.01(10)	C18	C11	C13	C14	40.05(11)
C7	C10	C21	C20	158.99(10)	C18	C19	C20	C21	12.47(17)
C8	C7	C10	C11	-76.27(11)	C18	C19	C20	O4	-168.71(12)
C8	C7	C10	C21	165.64(9)	C19	C18	O3	C14	-164.51(11)
C8	C7	C10	O1	42.06(13)	C19	C20	C21	C10	-33.83(15)
C9	C7	C10	C11	162.29(10)	C21	C10	C11	C12	87.21(11)
C9	C7	C10	C21	44.19(13)	C21	C10	C11	C13	-148.28(10)
C9	C7	C10	O1	-79.39(13)	C21	C10	C11	C18	-35.08(13)
C10	C11	C12	C6	7.17(12)	O1	C10	C11	C12	-153.68(9)
C10	C11	C13	C14	161.41(10)	O1	C10	C11	C13	-29.17(13)
C10	C11	C18	C19	17.93(17)	O1	C10	C11	C18	84.03(12)
C10	C11	C18	O3	-157.65(10)	O1	C10	C21	C20	-73.98(12)
C11	C10	C21	C20	44.58(13)	O3	C14	C15	C16	-120.45(14)
C11	C13	C14	C15	-154.16(11)	O3	C14	C15	C17	61.13(14)
C11	C13	C14	O3	-35.51(11)	O3	C18	C19	C20	170.00(11)
C11	C18	C19	C20	-5.2(2)	O4	C20	C21	C10	147.33(11)

Table 7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for 1879639-2.

Atom	*x*	*y*	*z*	U(eq)
H1A	8520.01	8452.04	5500.61	50
H1B	9816.67	8917.68	6119.29	50
H1C	8224.43	8595.18	6933.75	50
H3A	10582.19	5538.79	8634.06	67
H3B	9515.65	6709.7	8948.02	67
H3C	11075.21	7109.59	8092.1	67
H4	8833.63	6244.44	5656.01	24
H5A	10130.47	4076.6	7891.24	23
H5B	10228.95	4051.21	6406.45	23
H6	7467.49	3972.98	8000.67	20
H8A	10501.32	1476.38	7790.84	28
H8B	9534.04	1690.33	6557.29	28
H8C	9441.37	291.04	7869.59	28
H9A	9508.42	1807.22	9735.54	30
H9B	8406.03	570.03	10121.89	30
H9C	7765.99	2081.48	10047.41	30
H12A	8006.13	4003.94	5356.71	23
H12B	6565.37	4620.37	5996.03	23
H13A	8073.68	1844.54	5153.51	22
H13B	6707.88	825.19	5698.07	22
H14	6652.98	3612.61	3720.08	23
H16A	5972.25	597.36	2552.87	37
H16B	6782.36	309.92	3940.16	37
H17A	4599.46	2692.33	1498.82	50
H17B	5414.74	3970.07	1557.23	50
H17C	3920.05	3457.21	2486.02	50
H19	2705.39	2935.26	6745.11	24
H21A	5513.35	1208.34	9773.26	21
H21B	5707.71	2822.8	8922.82	21
H1	6810(20)	-400(20)	8930(20)	35(5)

X-Ray crystallographic Analysis of Compound 104



A colorless prism crystal of 0.06 x 0.05 x 0.03 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K. Data collection was 99.2% complete to 68.244° in θ. A total of 16472 reflections were collected covering the indices -8<=h<=7, -10<=k<=10, -32<=l<=31. 2907 reflections were founded to be symmetry independent, with an R_{int} of 0.0323. Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be $P\,2_12_12_1$ (No. 19). The data were integrated using the SAINT and scaled using the SCALE3 SADABS routines Solution by intrinsic phasing (SHELXT-2014) produced a heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2016).All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

Table 1 Crystal data and structure refinement for maimone92.

Identification code	maimone92
Empirical formula	$C_{19}H_{26}O_3$
Formula weight	302.40
Temperature/K	100.15
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	6.6836(2)
b/Å	8.7479(3)
c/Å	27.3717(8)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1600.35(9)
Z	4
ρ_{calc}g/cm^3	1.255
μ/mm^{-1}	0.659
F(000)	656.0
Crystal size/mm^3	0.06 × 0.05 × 0.03
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	6.458 to 136.488
Index ranges	$-8 \leq h \leq 7$, $-10 \leq k \leq 10$, $-32 \leq l \leq 31$
Reflections collected	16472
Independent reflections	2907 [R_{int} = 0.0323, R_{sigma} = 0.0252]
Data/restraints/parameters	2907/0/204
Goodness-of-fit on F^2	1.072
Final R indexes [I>=2σ (I)]	R_1 = 0.0334, wR_2 = 0.0822
Final R indexes [all data]	R_1 = 0.0348, wR_2 = 0.0829
Largest diff. peak/hole / e Å^{-3}	0.18/-0.17
Flack parameter	-0.29(9)

Table 2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for maimone92. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
C1	5410(3)	8039(2)	3171.5(7)	18.4(4)
C2	4198(3)	9455(2)	3323.9(8)	19.8(5)
C3	2362(3)	9717(2)	3028.0(7)	18.9(5)
C4	1610(3)	8660(2)	2715.0(7)	19.5(4)
C5	2493(3)	7185(2)	2673.2(7)	17.9(4)
C6	4056(3)	6701(2)	3039.8(7)	16.9(4)
C7	3087(3)	6001(2)	3502.7(7)	17.9(4)
C8	4723(3)	5346(2)	3848.6(7)	18.5(4)
C9	3741(3)	5133(3)	4357.4(7)	22.3(5)
C10	5178(4)	4751(3)	4772.3(8)	24.4(5)
C11	6758(4)	6013(3)	4803.1(8)	27.5(5)
C12	7880(3)	6164(3)	4318.0(8)	26.8(5)
C13	6474(3)	6450(3)	3894.6(7)	20.8(5)
C14	6779(3)	7610(2)	3587.9(8)	20.8(5)
C15	1466(3)	4837(2)	3371.0(7)	21.4(5)
C16	5499(4)	3794(3)	3659.1(8)	24.6(5)
C17	4128(4)	4468(3)	5257.1(8)	29.8(6)
C18	2168(4)	4537(3)	5320.8(9)	35.0(6)
C19	5465(5)	4077(4)	5677.8(9)	49.1(8)
O1	6517(2)	8344.6(17)	2735.8(5)	22.7(3)
O2	1561(2)	11083.0(17)	3107.1(5)	23.3(3)
O3	1930(2)	6262.4(17)	2350.8(5)	20.7(3)

Table 3 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for maimone92. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	17.7(10)	18.5(11)	18.9(10)	0.2(8)	2.4(8)	-0.3(9)
C2	21.7(11)	17.1(11)	20.6(10)	-2.3(8)	-1.2(9)	-2.4(9)
C3	21.5(11)	16.2(10)	19.0(10)	1.8(8)	4.4(8)	4.1(9)
C4	20.6(10)	19.0(10)	18.9(10)	1.5(8)	-3.7(8)	2.2(9)
C5	18.7(10)	19.5(11)	15.4(10)	1.1(8)	4.1(8)	-4.4(9)
C6	18.3(10)	14.3(10)	18.1(10)	-1.3(8)	0.1(8)	1.6(9)
C7	18.9(10)	17.6(10)	17.1(10)	-1.2(8)	1.0(8)	0.9(9)
C8	20.6(11)	17.1(10)	17.7(10)	0.5(9)	-1.8(8)	2.6(9)
C9	26.3(12)	21.5(11)	19.1(10)	0.8(8)	0.2(9)	0.2(10)
C10	29.4(13)	22.2(11)	21.6(11)	1.3(9)	-3.5(9)	4.1(11)
C11	29.4(12)	31.2(13)	21.7(11)	-0.4(9)	-8.6(9)	4.4(12)
C12	22.2(12)	31.4(13)	26.7(11)	-1.9(10)	-4.8(9)	3.3(11)
C13	18.2(10)	24.0(12)	20.2(10)	-3.5(9)	-1.3(8)	5.1(10)
C14	14.4(10)	24.4(11)	23.5(11)	-6.0(9)	-0.9(9)	0.1(10)
C15	23.3(11)	23.0(11)	18.0(10)	1.2(8)	-0.4(9)	-2.2(10)
C16	29.7(12)	21.4(11)	22.8(11)	-1.1(9)	-4.0(9)	7.0(11)
C17	47.4(17)	22.5(12)	19.5(11)	0.6(9)	-5.2(11)	2.2(12)
C18	47.1(17)	36.9(15)	21.0(12)	4.9(11)	4.1(11)	0.9(13)
C19	57.3(19)	63(2)	26.7(13)	13.4(13)	-8.6(13)	4.1(17)
O1	25.3(8)	21.0(8)	21.8(7)	0.7(6)	5.9(6)	-5.2(7)
O2	25.2(8)	19.5(7)	25.2(8)	-2.4(6)	-5.2(6)	2.3(7)
O3	23.9(8)	19.6(7)	18.6(7)	-2.6(6)	-1.7(6)	0.1(7)

Table 4 Bond Lengths for maimone92.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
C1	C2	1.538(3)	C7	C15	1.530(3)
C1	C6	1.523(3)	C8	C9	1.551(3)
C1	C14	1.509(3)	C8	C13	1.523(3)
C1	O1	1.428(2)	C8	C16	1.543(3)
C2	C3	1.488(3)	C9	C10	1.525(3)
C3	C4	1.357(3)	C10	C11	1.530(3)
C3	O2	1.327(3)	C10	C17	1.522(3)
C4	C5	1.424(3)	C11	C12	1.531(3)
C5	C6	1.509(3)	C12	C13	1.513(3)
C5	O3	1.253(2)	C13	C14	1.333(3)
C6	C7	1.549(3)	C17	C18	1.323(4)
C7	C8	1.556(3)	C17	C19	1.497(3)

Table 5 Bond Angles for maimone92.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C6	C1	C2	111.71(17)	C9	C8	C7	107.05(17)
C14	C1	C2	108.36(17)	C13	C8	C7	110.90(17)
C14	C1	C6	110.35(17)	C13	C8	C9	109.10(17)
O1	C1	C2	110.42(17)	C13	C8	C16	109.10(17)
O1	C1	C6	104.70(16)	C16	C8	C7	110.85(17)
O1	C1	C14	111.31(17)	C16	C8	C9	109.81(18)
C3	C2	C1	114.27(17)	C10	C9	C8	115.38(18)
C4	C3	C2	122.97(19)	C9	C10	C11	108.50(18)
O2	C3	C2	112.50(18)	C17	C10	C9	113.26(19)
O2	C3	C4	124.5(2)	C17	C10	C11	112.81(19)
C3	C4	C5	120.99(19)	C10	C11	C12	110.63(18)
C4	C5	C6	119.18(18)	C13	C12	C11	112.00(18)
O3	C5	C4	121.06(19)	C12	C13	C8	115.84(18)
O3	C5	C6	119.69(19)	C14	C13	C8	123.25(19)
C1	C6	C7	111.02(16)	C14	C13	C12	120.9(2)
C5	C6	C1	110.70(17)	C13	C14	C1	124.9(2)
C5	C6	C7	111.43(16)	C18	C17	C10	124.3(2)
C6	C7	C8	110.48(17)	C18	C17	C19	120.0(2)
C15	C7	C6	111.50(16)	C19	C17	C10	115.6(2)
C15	C7	C8	113.32(17)				

Table 6 Torsion Angles for maimone92.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C1	C2	C3	C4	11.9(3)	C9	C10	C11	C12	-58.1(2)
C1	C2	C3	O2	-168.30(17)	C9	C10	C17	C18	0.2(4)
C1	C6	C7	C8	-62.5(2)	C9	C10	C17	C19	179.6(2)
C1	C6	C7	C15	170.55(17)	C10	C11	C12	C13	56.1(3)
C2	C1	C6	C5	51.5(2)	C11	C10	C17	C18	123.9(3)
C2	C1	C6	C7	-72.8(2)	C11	C10	C17	C19	-56.6(3)
C2	C1	C14	C13	103.5(2)	C11	C12	C13	C8	-51.2(3)
C2	C3	C4	C5	3.6(3)	C11	C12	C13	C14	128.4(2)
C3	C4	C5	C6	10.3(3)	C12	C13	C14	C1	-176.7(2)
C3	C4	C5	O3	-172.77(19)	C13	C8	C9	C10	-50.2(2)
C4	C5	C6	C1	-38.2(3)	C14	C1	C2	C3	-161.38(17)
C4	C5	C6	C7	85.9(2)	C14	C1	C6	C5	172.11(16)
C5	C6	C7	C8	173.62(17)	C14	C1	C6	C7	47.8(2)
C5	C6	C7	C15	46.7(2)	C15	C7	C8	C9	-71.1(2)
C6	C1	C2	C3	-39.6(2)	C15	C7	C8	C13	169.97(17)
C6	C1	C14	C13	-19.1(3)	C15	C7	C8	C16	48.6(2)
C6	C7	C8	C9	162.94(17)	C16	C8	C9	C10	69.3(2)
C6	C7	C8	C13	44.0(2)	C16	C8	C13	C12	-73.6(2)
C6	C7	C8	C16	-77.3(2)	C16	C8	C13	C14	106.7(2)
C7	C8	C9	C10	-170.25(19)	C17	C10	C11	C12	175.5(2)
C7	C8	C13	C12	163.98(18)	O1	C1	C2	C3	76.5(2)
C7	C8	C13	C14	-15.6(3)	O1	C1	C6	C5	-68.0(2)
C8	C9	C10	C11	57.1(3)	O1	C1	C6	C7	167.68(16)
C8	C9	C10	C17	-176.80(19)	O1	C1	C14	C13	-134.9(2)
C8	C13	C14	C1	2.9(3)	O2	C3	C4	C5	-176.14(19)
C9	C8	C13	C12	46.3(2)	O3	C5	C6	C1	144.87(19)
C9	C8	C13	C14	-133.3(2)	O3	C5	C6	C7	-91.1(2)

Table 7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for maimone92.

Atom	*x*	*y*	*z*	U(eq)
H2A	3807.36	9344.2	3671.01	24
H2B	5066.96	10367.52	3297.85	24
H4	477.62	8908.28	2520.85	23
H6	4903.48	5894.8	2884.07	20
H7	2413.99	6854.68	3681.57	21
H9A	3020.3	6085.85	4442.34	27
H9B	2734.75	4306.15	4333.63	27
H10	5884.79	3784.35	4681.26	29
H11A	7719.12	5771.7	5067.28	33
H11B	6102.89	6996.6	4883.32	33
H12A	8845.68	7018.79	4341.12	32
H12B	8645.63	5214.59	4256.27	32
H14	7945.41	8212.61	3635.15	25
H15A	2004.48	4097.84	3136.34	32
H15B	320.81	5368.34	3225.48	32
H15C	1033.85	4299.64	3666.91	32
H16A	5926.69	3901.64	3318.37	37
H16B	4427.96	3031.84	3679.8	37
H16C	6636.45	3462.77	3858.85	37
H18A	1608.64	4338.01	5633.44	42
H18B	1319.97	4784.64	5053.75	42
H19A	6172.94	4997.4	5786.12	74
H19B	6438.74	3303.6	5574.98	74
H19C	4658.27	3673.68	5947.58	74
H1	6907.97	9257.23	2737.78	34
H2	513.81	11174.75	2939.86	35

Chapter 2

Synthetic Studies towards Acutumine Alkaloids

2.1 Background and Introduction

2.1.1 Isolation of the acutumine alkaloids

In 1929, (–)-acutumine (**107**) was first isolated from the leaves of *Sinomenium acutum* by Goto and coworkers.[1] Based on elemental analysis, (–)-acutumine (**107**) was proposed to have a molecular formula of either $C_{20}H_{27}NO_8$ or $C_{21}H_{27}NO_8$. Due to the complexity, the exact structure of (–)-acutumine (**107**) was not able to be elucidated at the time. The authors application of a series of degradative chemical analyses led to the conclusion that (–)-acutumine (**107**) possesses three methoxy groups, one methylated amine and a ketone. At the same time, due to the similar IR absorption spectrum result, the authors also believed that skeleton of (–)-acutumine (**107**) was similar to that of the alkaloid narceine (**108**).

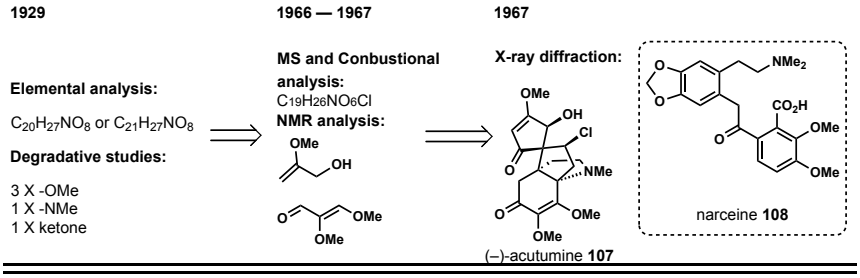
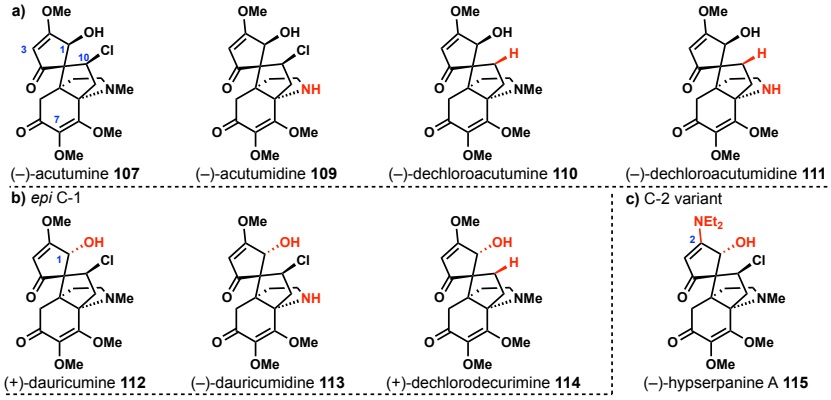


Figure 2. 1 (–)-Acutumine (**107**) and a timeline for its structure determination elucidation

The molecular formula of acutumine was not corrected until 40 years later.[2,3] With the help of mass spectrometry and combustion analysis, Goto and coworkers were the first to correctly identify the molecular formula as $C_{19}H_{24}NO_6Cl$.[2] Additional NMR studies revealed an allylic alcohol along with a vinylogous methyl ester motif, but the total structure of (–)-acutumine (**107**) wasn't fully elucidated until 1967 with the help of X-ray crystallography thus revealing its complex propellane core.[3]



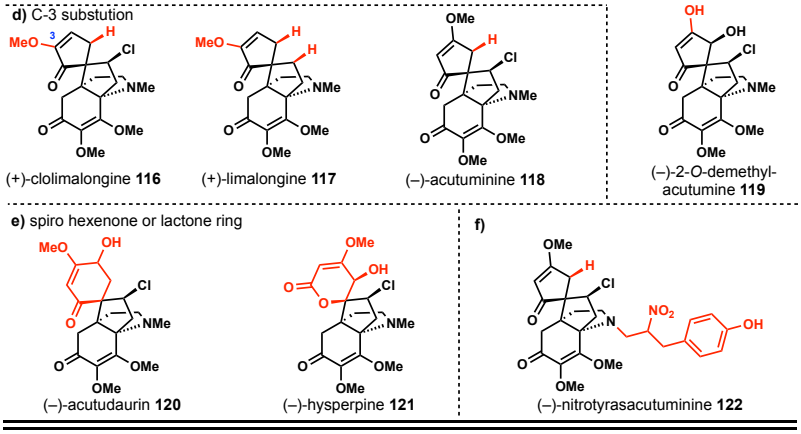


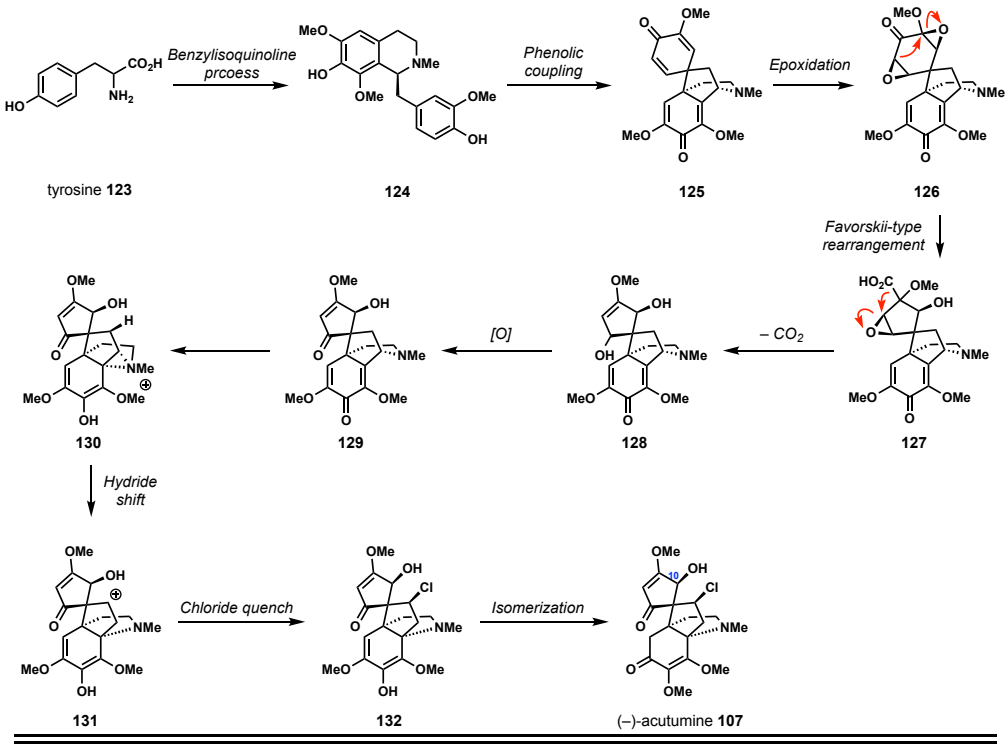
Figure 2. 2 Isolated acutumine-type alkaloids classified based on the substitution pattern of the spirocycle and tertiary amine.

Since the isolation of the flagship natural product acutumine (**107**), fourteen other related natural products from the same family have been isolated from several higher-order plant species[4] (*Sinomenium*[1,8,10,18], *Menispermum*[3,5,6,10-14,16,17,19], *Pachygone*[7] *Hypserpa*[9], and *Limacia*[15]). Among all fifteen acutumine-type alkaloids, ten of them can be isolated from the *Menispermum* plant. These alkaloids are differentiated by their substitution pattern on the spirocycle and substituents on the amine. In addition, four acutumine alkaloids lacking the characteristic neopentyl chloride were isolated after more than 60 years following the isolation of (–)-acutumine (**107**). These include ((–)-dechloroacutumine (**110**), first isolated in 1998,[11] (–)-dechloroacutumidine (**111**), isolated in 2002[12], (+)-dechlorodecurimine (**114**), isolated in 2005[14] and (+)-limalongine (**117**), isolated in 1989.[15]

2.1.2 Biosynthetic proposals for the origins of (–)-acutumine

Owing to its complex ring system and unusual C-10 neopentyl chloride atom, interesting and unusual enzymatic chemistry could be involved in the biosynthesis of these alkaloids (see **107**, Figure 2.2). To date, there have been multiple theories and efforts to elucidate such pathways. In 1968, Barton proposed the first biosynthetic pathway to (–)-acutumine (**107**).[21] He believed that, starting from two equivalents of tyrosine **123**, biaryl intermediate **124** was formed via a classic benzylisoquinoline pathway. A phenolic oxidative coupling then gave the tetracyclic intermediate **125**, also in analogy the biosynthetic phenolic couplings. Oxidation of **125** could then deliver bisepoxide **126** which Barton proposed might undergo a Favorskii-type rearrangement, and subsequential decarboxylation gave the spirocyclic core motif (see **128**). After an oxidation to the vinylogous ester, an aza-Michael addition could convert the tertiary amine **129** to reactive aziridinium **130**. The carbocation formed from a 1,2-hydride shift/aziridinium opening process could then be quenched by a chloride anion to install the neopentyl chloride (**132**). A final isomerization then constructs (–)-acutumine (**107**). This early proposal served as a cornerstone for understanding the biosynthetic origin of acutumine alkaloids and a considerable number of experimentations has been executed

to test the feasibility of various steps in this proposed biosynthetic pathway (see section 2.1.3).[22-29]



Scheme 2. 1 Barton's biosynthetic proposal

2.1.3 Investigation into the proposed biosynthesis

2.1.3.1 Investigation into the benzylisoquinoline process

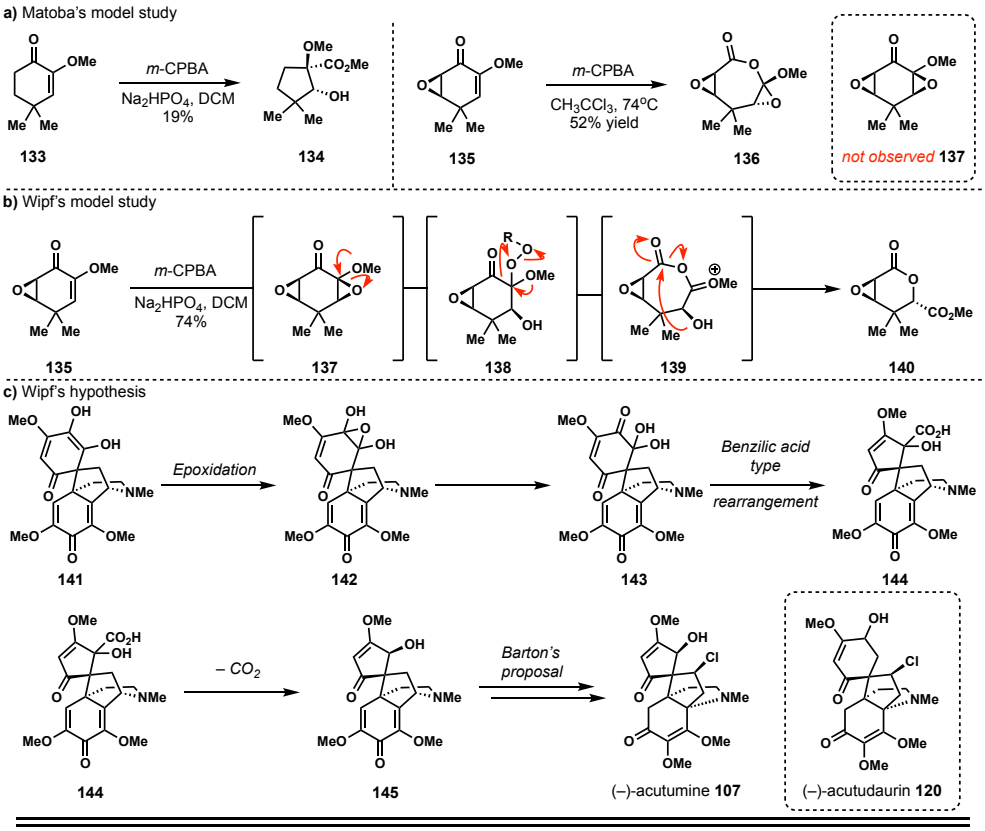
A benzylisoquinoline pathway was proposed as the first step to convert two equivalents of tyrosine **123** to the biaryl intermediate **124**. In support of this putative benzylisoquinoline pathway, Sugimoto and coworkers executed a feeding experiment.[22] The cultured root of *Menispermum dauricum* was fed with ^{14}C labeled tyrosine, extracted under basic condition, and the extraction was then subjected to HPLC analysis. Upon analyzing the *UV* absorption spectrum resulted from the HPLC separation, the authors were able to find an (–)-acutumine (**107)** absorption peak from the radioactive fraction thus confirming the proposed tyrosine-based origins of this natural product.

2.1.3.2 Investigation into the phenolic coupling process

After the first step of the proposed biosynthesis, benzylisoquinoline process, was solidified by aforementioned feeding experiment,[22] the resulting biaryl motif **124** is believed to undergo an oxidative phenolic coupling to furnish **125**. Known for catalyzing such phenolic coupling processes, Cytochrome P450 enzymes were speculated to be involved in the oxidative coupling process to deliver proposed compound **125**.[23] This proposed phenolic coupling process was tested by the Sugimoto

group.[23] By exposing *Menispermum dauricum* root with ketoconazole, a known inhibitor of cytochrome P450 enzyme, Sugimoto and coworkers found that the isolation yield of (–)-acutumine (**107**) was reduced, while an increased amount of early benzoisoquinoline intermediate was isolated. This result suggested that the proposed P450 mediated phenolic coupling process occurred to forge the vicinal quaternary centers of the compound **125**.

2.1.3.3 Investigation into the bisepoxidation/Favorskii type rearrangement



Scheme 2. 2 Synthetic studies of the proposed *bis*-epoxide-mediated biomimetic ring contraction reaction

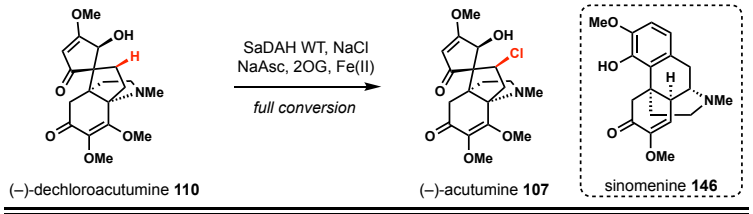
The dienone motif (**125**, see scheme 2.1), produced from the proposed phenolic coupling process, was hypothesized to undergo a bisepoxidation/Farvoskii-type rearrangement to give key spirocyclic compound **127**.[21] To elucidate the feasibility of the proposed ring contraction process chemically, several synthetic model studies have been employed. In 1984, Matoba found that while enone **133** could successfully be converted to cyclopentane **134**, attempts to achieve the synthesis of bisepoxide **137** from enone **135** were unfruitful.[24] An unexpected Baeyer-Villiger oxidation could not be circumvented and only overoxidized lactone **136** was observed. Additionally, the Wipf group executed another model study to test the feasibility of this proposed diepoxidation process.[25] They exposed epoxide **135** to *m*-CPBA, finding that only lactone **140** was isolated under these conditions. It was proposed that the epoxide of proposed intermediate **137** was spontaneously opened by the neighboring methoxy

group, and the formed oxonium intermediate was further oxidized to give acid anhydride **139**. Finally, a transesterification of **139** led to the lactone **140**.

Although an enzymatic epoxidation may differ from the *m*-CPBA-mediated variant, the failure of both epoxidation model studies challenged the feasibility of the proposed cyclopentenone ring formation of (–)-acutumine (**107**), at least in the laboratory. As a result, Wipf and coworkers proposed a revised biosynthetic pathway (Scheme 2.2, c).[25] In this scenario, an epoxidation of the tetracyclic intermediate **141** could take place to give diol epoxide **142**. This diol motif **142** could then undergo a ring contraction reaction and give carboxylic acid **144** as product. A subsequent decarboxylation would then deliver the fully elaborated spiro-fused compound **145**. Currently, this revised biosynthesis of Wipf would also account for the biosynthesis of the related alkaloid (–)-acutudaurin (**120**).

2.1.3.4 Investigation into the proposed chlorination process

Besides the hypothesized ring contraction reaction, the proposed chlorination step has also been called into question. Thirty years after Barton proposed his biosynthetic pathway, Sugimoto and coworkers published their isolation of (–)-dechloroacutumine (**110**),[11] which, at the time, was speculated as the biosynthetic precursor of (–)-acutumine (**107**). As the Barton's proposal could not explain the biosynthetic origin of (–)-dechloroacutumine (**110**), his biosynthetic hypothesis was challenged. Meanwhile, natural products of terrestrial origin are rarely observed to possess halogenated motifs[4,26], leading to speculation that the characteristic neopentyl chloride of (–)-acutumine (**107**) was incorporated into the molecule during the isolation process.[21] This prompted further investigation into the biosynthetic origin of the chlorine atom in the natural product.



Scheme 2. 3 Chlorination of (–)-dechloroacutumine **110** by DAH

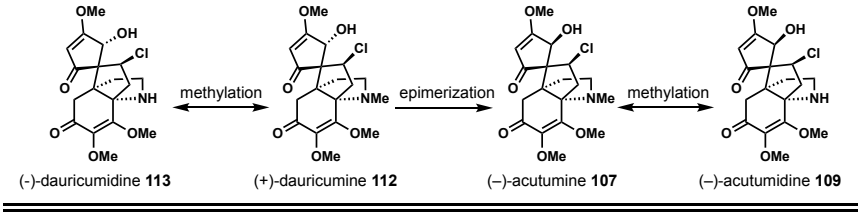
To rule out the possibility that neopentyl chloride was introduced during isolation, Barton first cultivated the plant with ^{36}Cl enriched hydrochloric acid solution[21], expecting to isolate the ^{36}Cl labelled (–)-acutumine (**107**), but they were unable to isolate any incorporation of the unnatural isotope. This result suggested that the chloride was not installed during the isolation procedure. In 1999, Babiker and coworkers demonstrated the possibility that (–)-dechloroacutumine (**110**) could be a biosynthetic precursor of (–)-acutumine (**107**) by a ^{3}H-labeled feeding experiment.[27] They fed *Menispermum dauricum* root with ^{3}H labeled (–)-dechloroacutumine (**110**). It was found that 28% of ^{3}H labeled (–)-dechloroacutumine (**110**) was absorbed, and 5% was converted to (–)-acutumine (**107**). This low conversion rate of (–)-acutumine (**107**) implied that although (–)-dechloroacutumine (**110**) could serve as a precursor of (–)-

acutumine (**107**), the plant might accumulate (–)-dechloroacutumine (**110**), and/or compartmentation of enzymes occurred during the biosynthesis of (–)-acutumine (**107**).

Although the chlorination reaction was tested thoroughly after a set of feeding experiments, the detailed biosynthetic mechanism of this unique chlorination step was not disclosed until recently. In 2020, the Weng group reported the isolation of the dechloroacutumine halogenase (DAH) from *Menispermum dauricum*.[28] Using DAH and NaCl, the authors were able to directly convert (–)-dechloroacutumine (**110**) to (–)-acutumine (**107**) diastereoselectively. On the other hand, attempting this DAH-mediated C-H chlorination with structurally related alkaloid sinomenine (**146**) gave no chlorinated product. This key finding strongly supports the hypothesis that (–)-dechloroacutumine (**110**) is the biosynthetic precursor for (–)-acutumine (**107**), especially considering that DAH appears to be tailored specifically for this transformation.

2.1.3.4 Interconversion between acutumine alkaloids

In 2001, the biosynthetic interconversion between (–)-dauricumidine (**112**), (+)-dauricumine (**113**), (–)-acutumine (**107**) and (–)-adutumidine (**109**) was elucidated by Sugimoto and coworkers (see Scheme 2.4).[29] The authors designed an experiment to study the interconversions between those alkaloids. In this experiment, *Menispermum dauricum* root was exposed to ^{36}Cl labeled (–)-dauricumidine (**112**), (+)-dauricumine (**113**), (–)-acutumine (**107**) and (–)-adutumidine (**109**) under Cl-deficient environment. Sugimogo and coworkers found that the methylation of amine is reversible, as interconversions between (–)-dauricumidine (**112**) and (+)-dauricumine (**113**), (–)-acutumine (**107**) and (–)-adutumidine (**109**) had been observed. They had also found that neopentyl alcohol of (+)-dauricumine (**113**) was irreversibly epimerized to (–)-acutumine (**107**). Moreover, a similar epimerization process between (–)-dauricumidine (**112**) and (–)-acutumidine (**109**) was not observed.



Scheme 2. 4 Interconversion between acutumine alkaloids

2.1.4 Bioactivities of (–)-acutumine (107)

The acutumine alkaloid family of alkaloids also showed a variety of bioactivities, including antiamnesic[30], antiproliferative[12] and anti-hepatitis B virus (HBV) properties[9a]. A 2003 patent disclosed that (–)-acutumine (**107**) could serve as a potential treatment for memory associated diseases like Alzheimer's disease.[30] Acutumine also exhibited an ability of inhibiting proliferation of thymus cells (T-cells),[12] while congeners like (–)-dechloroacutumine (**110**), (–)-acutumidine (**109**) and (–)-dechloroacutumidine (**111**) were tested and didn't show this biological property.[9a]

2.1.5 Previous synthetic studies of (–)-acutumine (107)

The complex structure of the acutumine family of natural products has proven to be a considerable synthetic challenge. (–)-Acutumine (**107**), for example, features a [4.3.3]-propellane core and a spirocycle adjacent to the full carbon quaternary center of the propellane core. (–)-Acutumine (**107**) possesses five contiguous chiral centers (Figure 2.3, highlighted in green dot), and two of them are directly attached to the spiro quaternary carbon: a neopentyl chloride and a neopentyl alcohol. Those quaternary carbon centers from the propellane core and spirocycle significantly boost the difficulty of installing surrounding functional groups, as the trajectories for adjusting those surrounding functional groups are severely limited by steric interactions. Moreover, there are two sets of vinylogous esters on the (–)-Acutumine (**107**) core (Figure 2.3, marked in blue). The repeated functionalities of (–)-Acutumine (**107**) pose a severe regioselectivity problem for any late-stage oxidative stage adjustment. Finally, the (–)-acutumine (**107**) core is densely decorated (Figure 2.3, marked in red), sporting an abnormally high 8:15 heteroatom/carbon ratio, which is significantly higher than most of benzylisoquinoline alkaloids.[4,31]

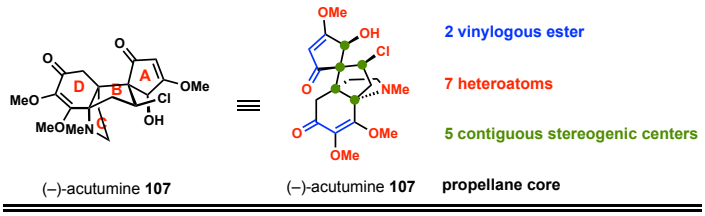
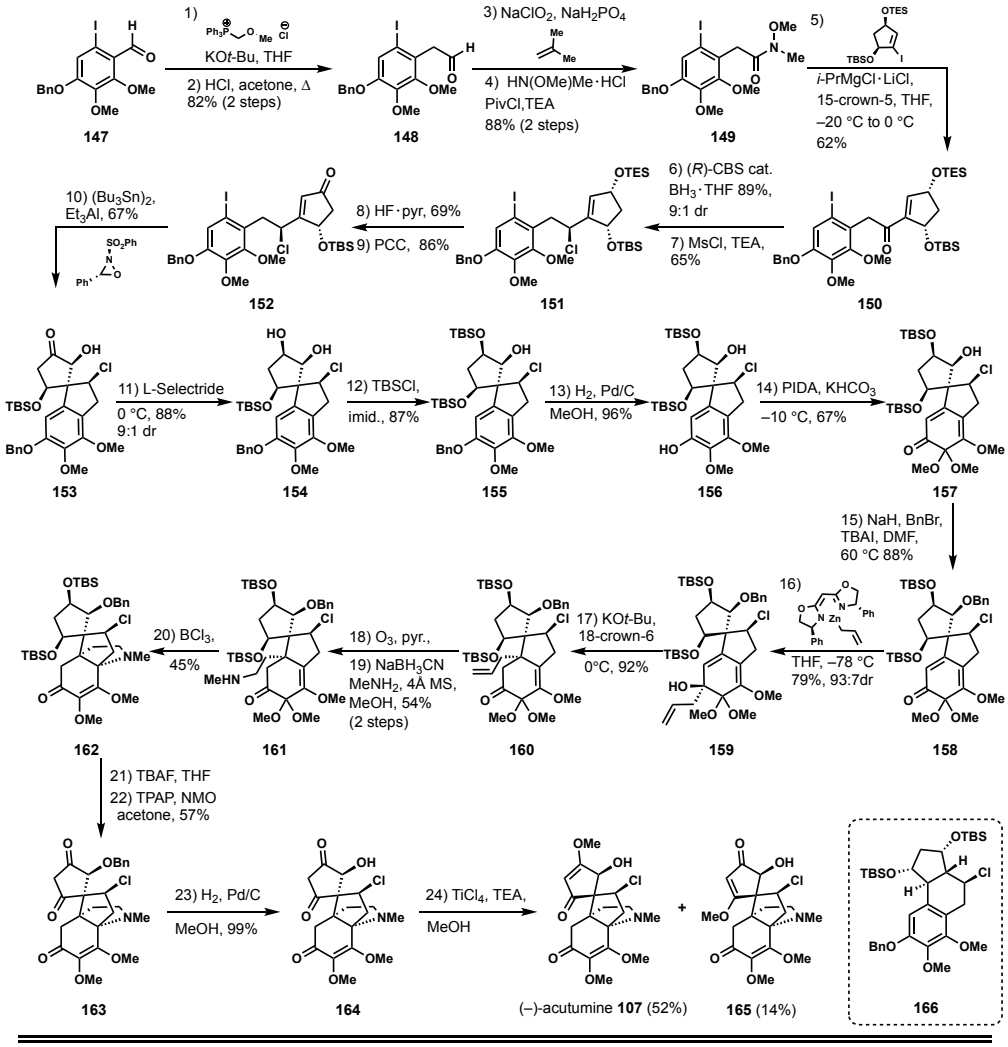


Figure 2. 3 Structural analysis of (–)-acutumine (**107**)

Given their impressive biological properties and enticing molecular structures, it is not surprising that (–)-acutumine (**107**) has obtained considerable attentions from synthetic community. To date, there are two synthetic studies[32,33] and two total syntheses[34,35] of (–)-acutumine (**107**) have been reported.

2.1.4.1 Castle's total synthesis of (–)-acutumine (107)

The first total synthesis of (–)-acutumine **107** was reported by Castle group.[34] During their retrosynthetic analysis, Castle *et al* identified that the steric hindrance associated with the quaternary spiro carbon center could be a problem for the construction of the adjacent quaternary center of the propellane core. Their solution was a thermodynamically favorable *oxy*-Cope rearrangement to install this quaternary allyl group. The intramolecular nature of *oxy*-Cope rearrangement overcomes the disadvantages of constructing this congested neopentyl C-C bond in an intermolecular fashion. Meanwhile, the authors have also imagined that the extremely sterically congested neopentyl chloride could be hard to install at late stage. To circumvent this problem, the C-Cl bond was programmed to be forged prior to the formation of the spirocycle.

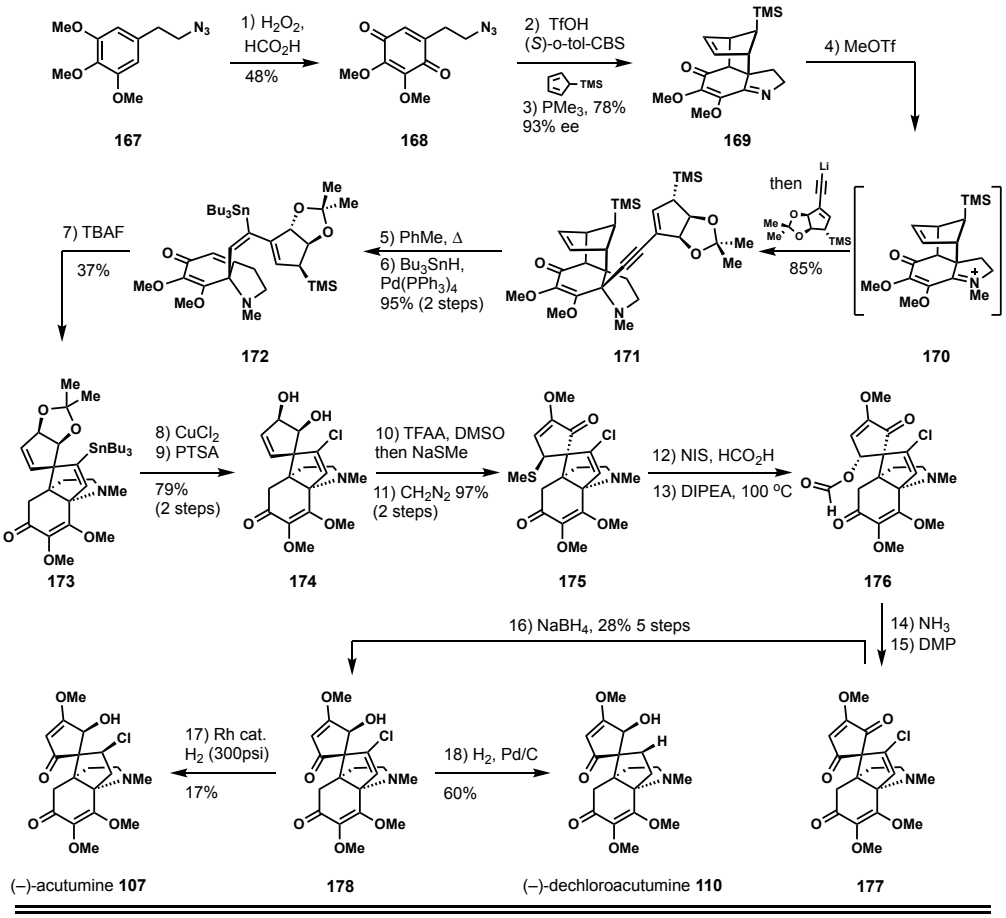


Scheme 2. 5 Castle's total synthesis of (–)-acutumine (**107**)

To realize their synthetic plan, benzaldehyde **147** was chosen as the starting material. This material was first homologated and further oxidized to give Weinreb amide **149**. A Grignard addition of a cyclopentane fragment then generated enone **150** in 62% yield. Before constructing the spiro center, the enone was converted to the allylic chloride (see **151**) by a CBS reduction and an Appel-type chlorination. Direct cyclization of aryl iodide intermediate **151** only generated undesired regioisomer **166** (Scheme 2.5, right bottom box), even though the corresponding 6-*endo*-trig cyclization pathway is kinetically unfavored. To overcome this problem, the silyl ether was converted to enone **152** to electronically bias the reaction towards the kinetically favored 5-*exo*-trig cyclization, generating an α-carbonyl radical which was quenched with Davis oxaziridine to forge the neopentyl alcohol **153**. After oxidation state and protecting group adjustments, the benzyl ether was converted to phenol **156**, and a subsequent PIDA-mediated oxidative dearomatization gave ketone **157** as a key precursor for constructing the final propellane ring system. This ketone was then subjected to an asymmetric allyl addition[36] to form the allylic alcohol intermediate **159**.

This allylic alcohol **159** was then subjected to an *oxy*-Cope rearrangement to deliver intermediate **160**, which possessed the vicinal quaternary centers. This allyl compound **160** was converted to an aldehyde via an ozonolysis reaction. Exposing this aldehyde to methyl amine and sodium cyanoborohydride yielded amine **161**. Such a late-stage amination strategy also helped them avoid potential functional group compatibility issues. Finally, using BCl_3 as catalyst, a S_N2' amination afforded the tetracyclic motif **162**. After several steps of cyclopentene functional group manipulation, the authors were able to achieve (–)-acutumine (**107**) in 29 steps.

2.1.4.2 Herzon's total synthesis of (–)-acutumine (107)

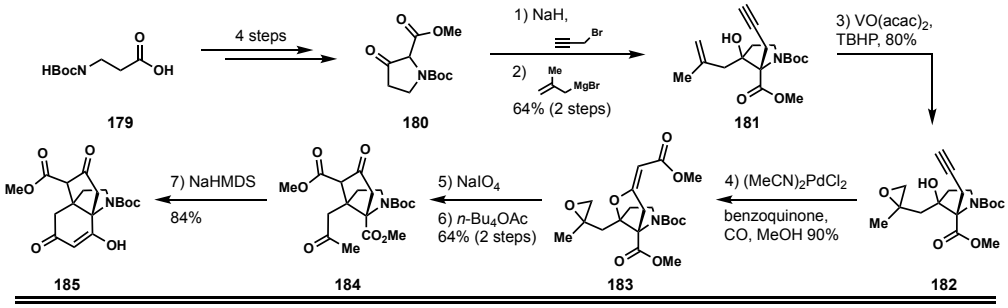


Scheme 2. 6 Herzon's total synthesis of (–)-acutumine (**107**) and (–)-dechloroacutumine (**110**)

Four years after Castle and coworkers reported their total synthesis of (–)-acutumine (**107**), the Herzon group published a total synthesis of (–)-acutumine (**107**).[35] Starting from aryl azide **167**, they were able to synthesize imine intermediate **169** in a three-step sequence consisting of oxidation, an asymmetric Diels-Alder reaction, and a Staudinger-Wittig reaction. The TMS-cyclopentadiene served as a chiral auxiliary and protecting group for the enone olefin. This formed imine compound **169** was then methylated to give a highly reactive iminium **170**, which was treated with an alkynyl

nucleophile to deliver enyne **171** in 85% yield. The cyclopentadiene was cleaved upon retro [4+2] cycloaddition, and a palladium catalyzed hydrostannylation was used to deliver vinyl stannane **172**. This (*E*)-olefin **172** exists in the ideal conformation for the following key Hosomi-Sakurai-Michael addition, which installed the fourth ring and a pair of contiguous full carbon stereogenic centers in one step. The vinyl stannane **173** was converted to vinyl chloride upon exposure of $CuCl_2$. With eight more steps of functional group manipulation, they were able to achieve intermediate **178**, which has all the needed functionality on the spiro cyclopentenone ring assembled. Finally, after an exhaustive condition screen, they were able to reduce the vinyl chloride **178** to (–)-acutumine (**107**), albeit in low yield. Additionally, the authors could also obtain (–)-dechloroacutumine (**120**) in 60% yield via a hydrogenation reaction catalyzed by palladium on carbon.

2.1.4.3 Sorensen's synthetic studies towards acutumine (107)



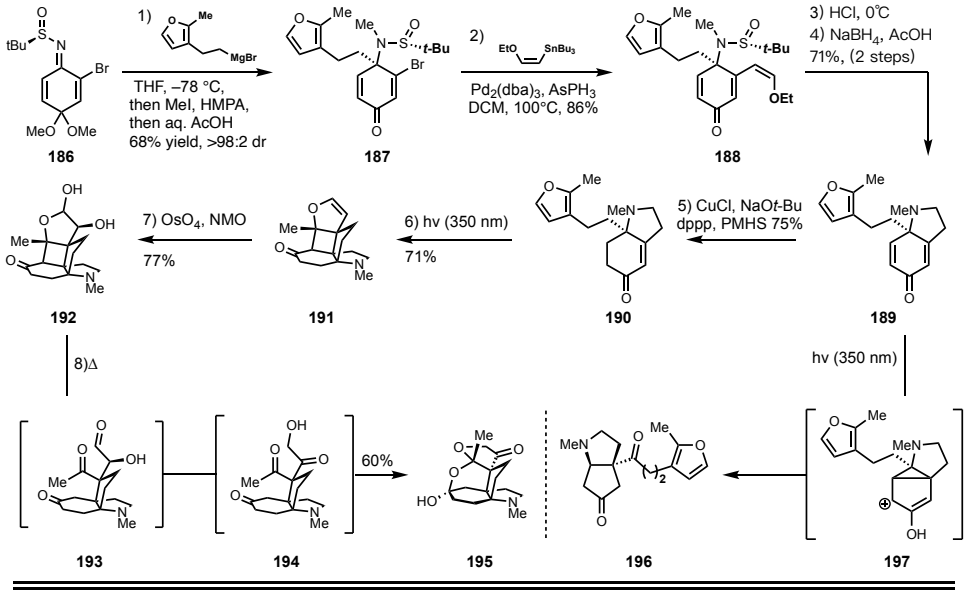
Scheme 2. 7 Sorensen's concise synthesis of the acutumine core

A novel three-carbonyl enabled tandem reaction was reported by Sorensen group to concisely build the propellane core of the acutumine alkaloids.[32] The pyrrolidinone compound **180**, which could be synthesized by known protocol, was subjected to a propargylation and Grignard addition reaction to give homoallylic alcohol **181**. Epoxide **182**, formed by a vanadium catalyzed epoxidation, was then subjected to carbonylative cyclization, affording **183** in 90% yield. The epoxide of oxy bicycle **183** was then exposed to oxidative cleavage conditions to afford a methyl ketone. The formed ketone subsequentially underwent a tandem elimination/ Michael addition reaction upon exposing to the weak base TBA(OAc) and gave the bicyclic intermediate **184**. This bicycle was then treated with NaHMDS to finally give them the propellane core **185**.

2.1.4.4 Reisman's synthetic studies towards acutumine (107)

In 2012, the Reisman group reported a novel [2+2] strategy for the construction of the aza-propellane ring system.[33] To assess the feasibility of their [2+2] strategy, they first synthesized tethered bicycle **187** using Ellman auxiliary chemistry. The vinyl bromide of bicycle intermediate **187** was subjected to a Stille coupling reaction and gave compound **188**. The Ellman sulfonamide was hydrolyzed to form a secondary amine that was cyclized with the vinyl ether upon exposure to acidic condition. After a

sodium borohydride reduction, the tricycle precursor **189** was obtained, and the key [2+2] reaction was tested upon exposing **189** to 350 nm *uv* light. However, this only led to the undesired product **196** via a photon-mediated Nazarov cyclization pathway (**189** → **196**). As a result, the more sterically accessible olefin was masked by reduction and the formed enone **190** was then subjected to the key light-mediated [2+2] reaction to forge the polycyclic intermediate **191**, which contains all the quaternary centers along with the desired propellane core. However, exhaustive screening of transferring compound **191** to the desired spirocycle only led to undesired ketal **195**.

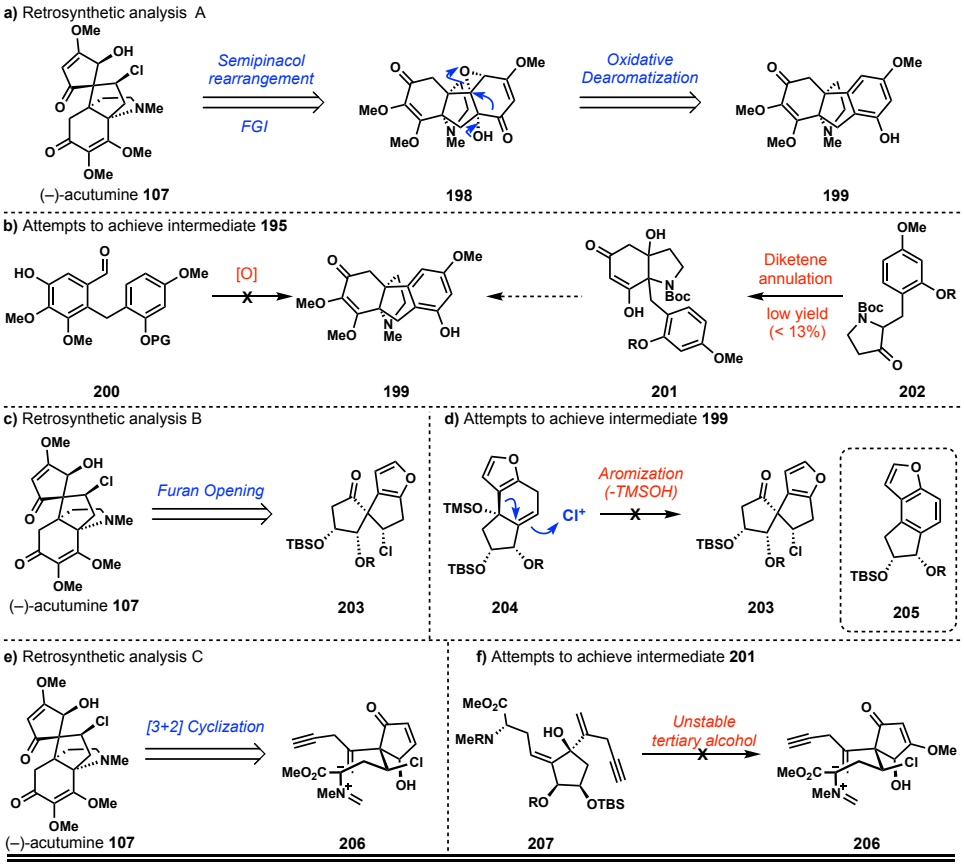


Scheme 2. 8 Reisman's synthetic studies towards of acutumine

2.2 Our Synthetic Study towards (–)-Acutumine (107)

The previously described synthetic studies of (–)-acutumine (**107**) provided different solutions for constructing the vicinal quaternary centers and installing the neopentyl chloride. However, the efficiency of those synthetic studies was undermined by the lengthy functional group manipulations required to prepare key reaction precursors. Moreover, we noticed that both the Herzon and Castle groups needed to employ several steps to install the functional groups and adjust the oxidation state of the spiro cyclopentenone ring.[34,35] We, thus, envisioned a more efficient synthesis of (–)-acutumine (**107**) could be achieved by improving the construction of spiro ring in a more direct sequence.

2.2.8 Our previous synthetic studies of (–)-acutumine (107)



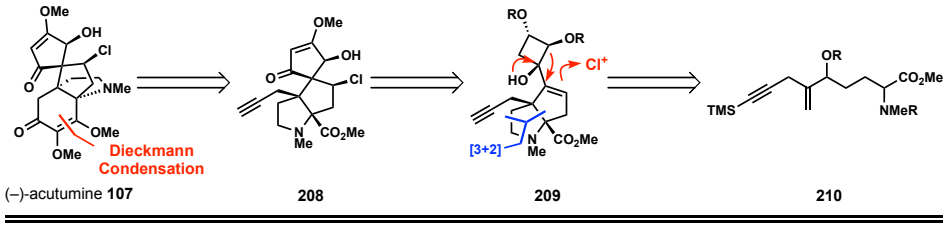
Scheme 2. 9 Our synthetic studies towards (–)-acutumine **103**

To achieve a more concise total synthesis of (–)-acutumine (**107**), we conceived several different strategies over the course of our investigations (Scheme 2.9). We initially envisioned that a semipinacol rearrangement could be applied to forge the spirocycle of (–)-acutumine (see Scheme 2.9, **199** → **107**), which retrosynthetically led back to the key tetracyclic precursor **199**. Yet preparation of tetracyclic compound **199**

was challenging. An oxidative dearomatization strategy was first examined, but heavily functionalized aryl intermediate **200** was incompatible with oxidative conditions and only led to decomposition. We also envisioned that the propellane intermediate **199** could be achieved via a Barton dihydroxylation/radical cyclization reaction. However, the key cyclization reaction was not attempted due to the low yield of the prior pyrrolidinone diketene annulation reaction (**202** → **201**). Additionally, we also tried to forge the neopentyl chloride and the spirocycle at an early stage. We envisioned acutumine alkaloids could be achieved from the tricyclic compound **203**, which possesses both the spirocycle and the neopentyl chloride. However, we could not circumvent the aromatization of **204**, and only benzofuran motif **205** was observed. We also envisioned a [3+2] cycloaddition could construct the core of acutumine alkaloids (see **206** → **107**). But we found the doubly allylic tertiary alcohol motif (**207**) was very unstable and only decomposition of the starting material was observed. All of these initial failures continually evolved our synthetic planning.

2.2.2 Updated retrosynthetic analysis of (–)-acutumine (107)

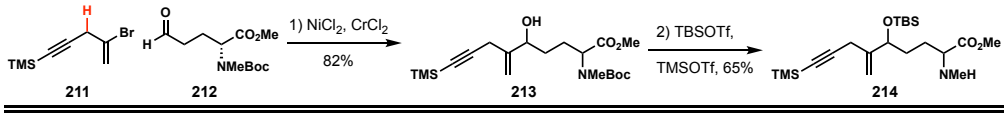
Although all our previous explorations toward (–)-acutumine (**107**) synthesis failed, we had learned many valuable lessons. For example, although a straightforward construction of spiro cycle could significantly boost the efficiency of this synthesis, a lengthy route was required to achieve the cyclopentanol system. It was also found this heavily functionalized cyclopentanol core is very sensitive to acidic/basic condition, and indirectly caused the failure of our previously exploration (see Scheme 2.9, **204** → **203**, **207** → **206**).[37] Additionally, although the diallylic alcohol of compound **207** was fragile, and thus the key [3+2] cycloaddition was not attempted, this problem could be circumvented if the [3+2] cycloaddition was applied prior to the formation of the allylic alcohol, which could construct the aza-bicyclo[3.3.0] core with a high efficiency. With those guidelines in mind, a new retrosynthetic plan was designed. We believed the 6-member ring of (–)-acutumine (**107**) could be formed by a Dieckmann condensation reaction, and the corresponding ketone could be converted from an alkyne. Additionally, we envisioned a directed chlorination/ semipinacol rearrangement of cyclobutanol **209** could be used to construct the neopentyl chloride, a secondary alcohol, and the spiro carbon center. As the spirocycle was planned to be forged by an immediate sequence of 1,2-addition and ring expansion, we envisioned challenges arise from handling the heavily functionalized cyclobutanol could be avoided. The nucleophile for the programmed 1,2-addition could be derived from a neopentyl ketone, and this led to the linear alcohol **210** as a common precursor. If a proper cyclic ketone was used to assemble the proper rearrangement precursor, we imagined this convergent strategy could serve as a potential modular synthesis of acutumine alkaloids (**209** with different substitution on cyclobutanol ring).



Scheme 2. 10 Updated retrosynthetic analysis of (–)-acutumine **107**

2.2.3 Efforts towards the [3.3.0] aza-bicycle

To assess the feasibility of our synthetic plan, we first focused on synthesizing enyne ester **210**. The enyne motif **211** and aldehyde **212** needed to be coupled to give the desired linear allylic alcohol. Although the traditional lithium-halogen exchange or magnesium-halogen reaction failed to provide the desired product in adequate quantities,[38] presumably due an undesired proton transfer between the allylic propargylic proton and the formed vinyl anion, it was found desired allylic alcohol **213** could be achieved via an NHK coupling reaction, in 77% yield. To examine the key [3+2] cycloaddition, the Boc carbamate need to be removed. Additionally, the allylic alcohol might nucleophilic attack the formed iminium and prevent the desired cycloaddition reaction. Therefore, the alcohol was planned to be protected. With those criteria in mind, we were pleased to find that both transformations could be achieved by the sequential addition of TBSOTf and TMSOTf, which gave the silyl ether **214** in 65% yield.



Scheme 2. 11 Towards the [3+2] cyclization precursor

The formation of the methyl amine **214** allowed us to try the key [3+2] cyclization. Our exploration began with applying paraformaldehyde as carbon source to form the iminium ion and molecular sieves to scavenge the water from condensation (Table 2.1, Entry 1), but with no success. We wondered whether this reaction failed during the iminium formation stage or the cyclization stage. As a result, the iminium formation was first monitored by a reported iminium thiophenol trapping protocol.[39] However, mixing the compound **213** with paraformaldehyde and thiophenol only led to recovered starting material (Table 2.1, Entry 2), which suggested that the iminium formation might be problematic. One possible reason for this failure is the volatile nature of the formaldehyde, as the formaldehyde might evaporate out of the reaction mixture. This hypothesis prompted us to use methyl diiodide as the carbon source,[40] but only recovered starting material was isolated (Table 2.1, Entry 3). Additionally, high boiling point aldehydes (ethyl glyoxylate, b.p. 126 ºC and benzaldehyde, b.p. 195 ºC) were applied as model studies to test the feasibility of this [3+2] cyclization (Table 2.1, Entry 4,5). Those conditions only gave unknown mixtures that possess characteristic NMR

peaks from both linear enyne and the aldehyde chain, which was hypothetically derived from condensation of amine **214** and the aldehyde reagent. Thus, we postulated this reaction could be accelerated by an acid catalyzed formation of iminium. Guided by

214 **215** **216** (not observed)

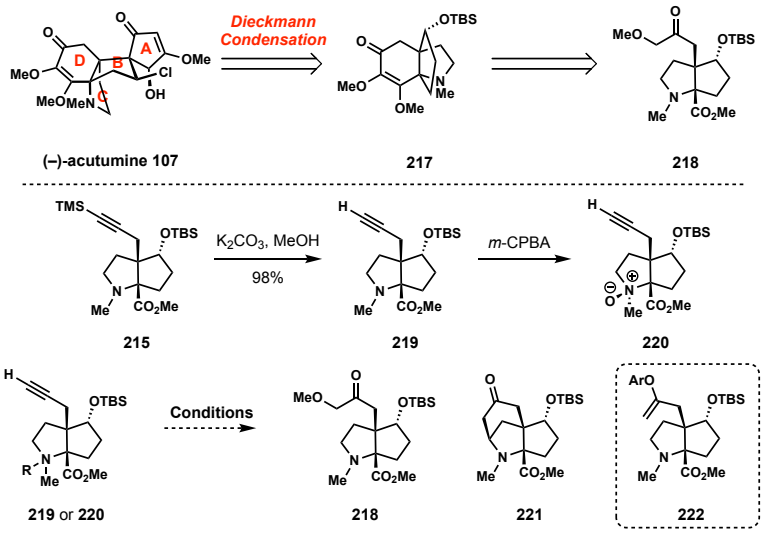
[3+2] cyclization of an unactivated olefin

Entry	Condition	Result
1	4Å MS, paraformaldehyde, Tol, refulx	decomposition
2	paraformaldehyde, PhSH Tol	recovered starting material
3	CH_2I_2, TEA, DCM/Tol/THF	recovered starting material
4	ethyl glyoxylate, TEA, Tol, reflux	no cyclized product
5	PhCHO, Tol, reflux	no cyclized product
6	$(CH_2O)_n$, AcOH, Tol, reflux	trace **213**
7	$(CH_2O)_n$, $CeCl_3$, DCM, reflux, then Tol, reflux	> 5% **213**, single regioisomer
8	$(CH_2O)_3$, $CeCl_3$, DCM, reflux, then Tol reflux	trace **213**
9	formalin, $CeCl_3$, DCM, reflux, then Tol reflux	recovered starting material
10	$(CH_2O)_n$, $CeCl_3$, THF, reflux, then Tol reflux	recovered starting material
11	$(CH_2O)_n$, $CeCl_3$, Tol, reflux	42% **213**
12	$(CH_2O)_n$, Mg_2SO_4, Tol, reflux	20% – 70% **213**
13	two addition of formalin, TEA, Tol. 145°C	77% **213**, 100 mg scale

Table 2.1 Optimization of the key [3+2] cyclization

this observation, AcOH was added as a catalyst and it was found a small amount of desired product **215** was formed regioselectively (as opposed to **216**) (Table 2.1, Entry 6). This result encouraged us to further explore this key [3+2] cyclization, and a screen of formaldehyde sources (Table 2.1, Entry 7-9) and solvent (Table 2.1, Entry 10,11) was performed. Finally, it was found that using magnesium sulfate as an additive provide optimal result, presumably because the magnesium sulfate played two crucial roles: acting as a Lewis acid and scavenging water formed after the condensation (Table 2.1, Entry 12). The desired product was obtained in 70% yield upon exposing **214** to magnesium sulfate and paraformaldehyde (10 mg scale, Table 2.1, Entry 11). However, this condition was very sensitive to scale, as the yield dropped from 70% to 20% when executed on 100 mg scale, again owing to the temperamental nature of formaldehyde as a reagent. This problem could be circumvented if a second portion of formalin was added 12 hours after the initial addition. It was also found this reaction could be further optimized if triethylamine was added as an additive, presumably by facilitating the formation of the 1,3-dipole. Finally, we could obtain this bicyclic compound in 77% yield (100 mg scale, Table 2.1, Entry 13). This protocol enabled us to convert a linear enyne **214** to an advanced bicyclic intermediate **215** that contains an all-carbon quaternary center and a tertiary amine. More importantly, the concavity of **215** would be beneficial to us by rendering future manipulations stereoselective.

2.2.4 Functionalization of the alkyne



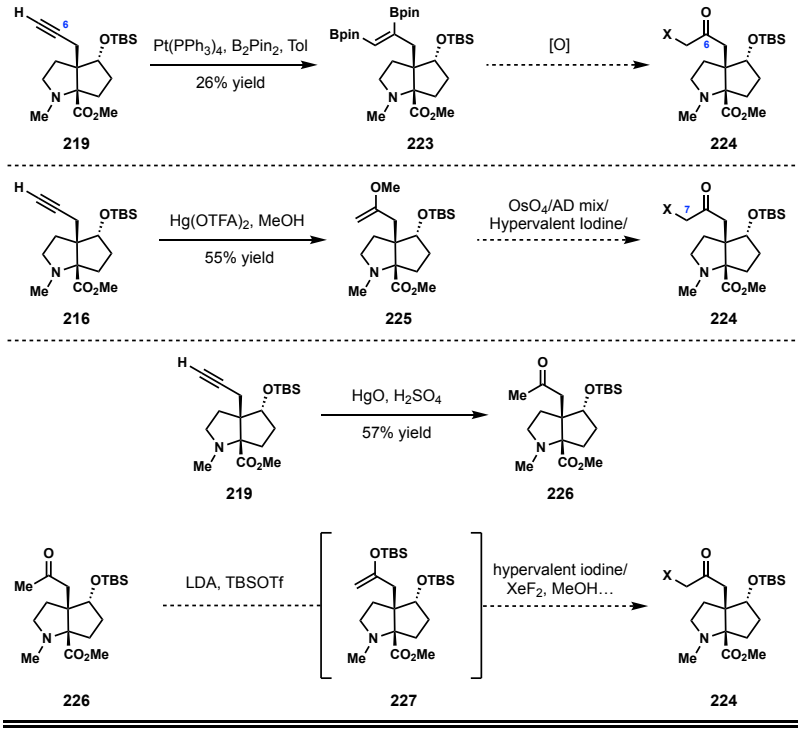
Entry	Substrate	Conditions	Result
1	**219**	$AuPPh_3NTf_2$, 1.2 equiv. pyridine N-Oxide, 1.1 equiv. $HNTf_2$, HFIP, r.t. to 50°C	RSM
2	**219**	$AuPPh_3NTf_2$, 1.2 equiv. pyridine N-Oxide, 2 equiv. $HNTf_2$, HFIP, r.t. to 50°C	RSM
3	**219**	$AuPPh_3NTf_2$, 2.5 equiv. pyridine N-Oxide, 5 equiv. $HNTf_2$, HFIP, r.t. to 50°C	RSM
4	**219**	$AuPPh_3NTf_2$, 1.2 equiv. 8-Me quinoline N-Oxide, AcOH, 50°C	RSM
5	**219**	$AuPPh_3NTf_2$, 2 equiv. $HNTf_2$, DMSO, r.t. to 50°C	RSM
6	**219**	$AuPPh_3NTf_2$, excess NMO, 2 equiv. $HNTf_2$, HFIP, r.t. to 50°C	RSM
7	**220**	$AuPPh_3NTf_2$, DCM, 50 °C, 1 hr	25% **221**
8	**220**	$AuPPh_3NTf_2$, AcOH, DCM,50 °C, 1 hr	ca. 6% **221**
9	**220**	$AuPPh_3NTf_2$, MeONa, DCM, 50 °C, 1 hr	decomp.
10	**219**	HgO, 1.2 equiv. pyridine N-Oxide, 2 equiv. $HNTf_2$, HFIP, r.t. to 50°C	decomp.
11	**219**	$Hg(OTFA)_2$, 1.2 equiv. pyridine N-Oxide, 2 equiv. $HNTf_2$, HFIP, r.t. to 50°C	decomp.
12	**219**	Kosers' reagent, DCM	decomp.

Table 2. 2 Efforts towards α-methoxy ketone **218**

Although forging the cyclohexenone D ring (see Table 2.2, **107**) after the construction of spirocycle C could be beneficial as less redox operations would be required at a late stage, this easily prepared bicyclic intermediate **215** provided us a good platform for studying the construction of the propellane core. We envisioned this propellane system could be made by a reported condensation protocol between a α-methoxy ketone and the neopentyl ester (**217** → **218**).[41] Therefore, silylated alkyne **215** was used as a model for exploring the bisfuncionalizatoin of the alkyne. In 2017, the Zhang group reported a one-pot protocol to convert a terminal alkyne to an α-methoxy ketone,[42] and they applied $HNTf_2$ as an external acid to protonated vinyl gold species. Although this reaction was known for its broad functional group compatibility, it is not

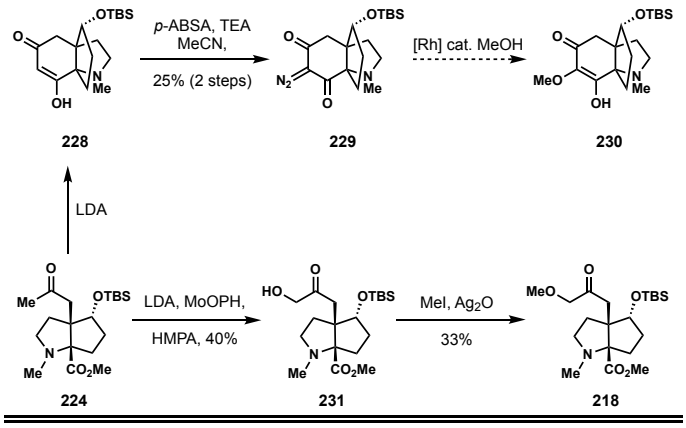
well precedented in the presence of amines.[43] To test this protocol, silylated alkyne was exposed to potassium carbonate, and the resulted terminal alkyne **219** was subjected to the Zhang's alkyne oxidation reaction. Not surprisingly, directly applying their optimal condition to **219**, which contains a tertiary amine, only led to recovered starting material (Table 2.2, Entry 1), presumably because the acid was trapped by the tertiary amine. As a result, the pH environment of the reaction was tuned by varying ratio of acid/pyridine *N*-oxide, and different acid sources were also explored (Table 2.2, Entry 2-4). However, several attempts were unfruitful and only starting material was isolated from the reaction mixture. As the proposed intermediate **222** in this oxidation doesn't possess any additional $A^{1,3}$ or $A^{1,2}$ strain between the pyridine *N*-Oxide motif and the olefin, we hypothesized that the formation of the **222** is kinetically unfavored, as the bicyclic core of **219** sufficiently blocked the approach of the nucleophile. This steric obstacle could be resolved by applying other nucleophiles that feature longer X-O bond lengths, e.g. DMSO (Table 2.2, Entry 4,5).[43] However, those efforts failed to consume any alkyne **219**. Alternatively, this obstacle could be circumvented by an intramolecular delivery of the nucleophilic oxygen anion. To test this idea, the tertiary amine was oxidized smoothly under the action of *m*-CPBA and *N*-Oxide **220** was obtained as a single diastereomer. This freshly prepared *N*-Oxide reacted upon exposing **220** to Au catalyst, but instead of the desired product **216**, only an unexpected tetracyclic product **221** was obtained from the reaction mixture. It was speculated the tetracycle **221** was formed via a hydride ejection/Mannich cyclization pathway.[45] To suppress the formation of tetracycle **221**, we tried to prevent the hydride ejection by masking the formed methyl amine. Additionally, we also tried to quench the potential gold carbenoid with nucleophilic methoxide, but both efforts were unfruitful. (Table 2.2, Entry 7,8). As all attempts of using gold catalyst to functionalize the alkyne failed to give any desired product, we then wondered if this transformation could be achieved upon exposing **220** to other π-Lewis acids. Mercury salts were subsequentially examined for this oxidative methoxylation reaction (Table 2.2, Entry 9, 10). But even under elevated temperature, no desired product **219/222** could be obtained.

Meanwhile, as alkynes are known to be activated by mildly hypervalent iodide reagent,[46] we wondered if this difunctionalization of alkyne could be facilitated by these methods. This idea prompted us to oxidize this alkyne with Koser's reagent, which could form an alkynyl iodinium species and trap it by oxynucleophile to give desired product (Table 2.2, Entry 12). Although it is also known that hypervalent iodine could oxidize the tertiary amine, after exposing the starting material to Koser's reagent for two hours under room temperature, only recovered starting material could be isolated from this reaction mixture, which suggested the tertiary amine is blocked by the nearby quaternary centers. However, after prolonged reaction times and elevated temperatures, it was found all starting material had decomposed.



Scheme 2. 12 Efforts towards the α-methoxy ketone (I)

Hypothetically, the pendant bicyclic motif may effectively block the trajectory for nucleophiles, and thus directly inducing the oxidation state of the alkyne could be challenging. As a result, we decided to overcome this problem by functionalizing the sterically encumbered C-6 position first (see Scheme 2.12, **219**). We tried to introduce the C-6 oxygen by oxidation of a boron-containing intermediate (see **223**) which could be prepared by a Pt-catalyzed diboration of alkyne **219**.[47] The desired product **223** could be obtained from the reaction mixture, however, this highly unstable diboron intermediate failed to convert further to any useful product. At the same time, introducing the C-6 oxygen was also attempted by Hg-catalyzed methyl enol formation, and it was imagined that the highly electron-rich enol ether could be further oxidized at more accessible C-7 to give the desired α-methoxy ketone **224** (X = OMe). Meanwhile, alkyne **219** was also subjected to a hydration reaction to directly introduce the C-6 ketone. Although most of those transformation smoothly delivered the desired product, an organomercury species was occasionally isolated as byproduct. Nevertheless, the methyl enol ether **225** and the methyl ketone motif **226** were obtained. The electrophilic enol **225** and silyl enol ether **227**, which was *in-situ* prepared from ketone **226**, were subjected to various hypervalent iodine oxidation conditions, but all attempts failed to deliver any useful product. Besides, the methyl enol ether **225** was subjected to osmium mediated dihydroxylation reaction, in hopes to give the α-hydroxy ketone. Although even more electron rich olefin was known for such a dihydroxylation,[48] this condition failed to convert **225** to any **224** after prolonged reaction time. A reported methoxylation protocol of α-methoxylation enabled by MeOF[49] was also examined, but exposing **227** to freshly prepared MeOF gave no desired product as well.

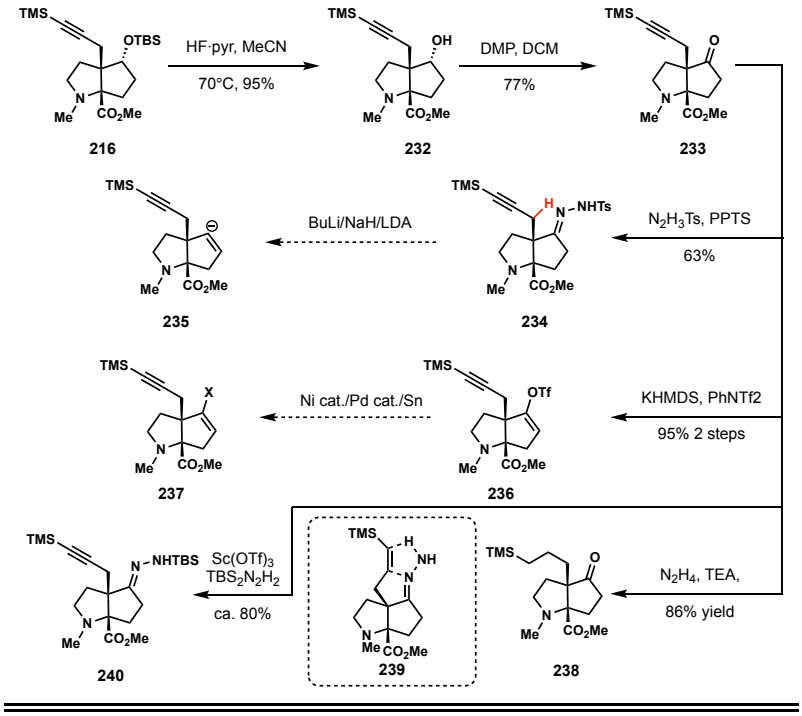


Scheme 2. 13 Our efforts towards the α-methoxy ketone (II)

After exhaustively screening for conditions to oxidizing acyclic intermediates **225, 226** and **227**, we were unable to form the desired product. Those failures made us wondered if, instead of directly oxidizing the enol ether intermediates **225** and **227**, the α-methoxy ketone could be accessed by a carbenoid insertion of methanol. To test this idea, the methyl ketone **224** was intramolecularly condensed with the southern ester group to give vinylogous acid **228**, which was then smoothly converted to diazo motif **229** upon exposure of *p*-ABSA. However, this diazo species **229** failed to further form the methoxylated product. Finally, it was found that treating **224** with MoOPH gave desired alcohol **231** in 40% yield, and desired α-methoxy ketone motif **218** could be formed if alcohol **231** was treated with MeI and freshly prepared Ag_2O.

2.2.5 Construction of the spirocycle: 1,2-addition approach

Despite the unforeseen challenges of the alkyne difunctionalization, we were eventually able to install all desired functional groups by a MoOPH-mediated hydroxylation reaction. As a result, we decided to turn our focus back to the construction of the spiro-fused C-ring, which was designed to be forged by a key semipinacol chlorination strategy (see Scheme 2.10). First, the TBS ether was converted to ketone **233** by selective deprotection and a subsequent Dess-Martin oxidation. With intermediate **233** in hand, we then tried to access the key cyclobutanol precursor for the ring expansion chlorination reaction. The Bamford-Shapiro-Stevens nucleophilic addition reaction was first attempted to forge the C-C bond. Although basic conditions failed to give the desired condensed product, applying pyridinium *p*-toluenesulfonate (PPTS) as a catalyst gave us desired hydrazone **234** for evaluating the Bamford-Shapiro-Stevens reaction. However, screening a variety of Bamford-Shapiro-Stevens conditions failed to give any desired product. Due to the disappearance of the characteristic propargyl methylene on proton NMR, it was believed that this decomposition was caused by the acidic propargyl proton (see Scheme 2.14, **234**, marked in red). Although the acidic nature of the propargyl proton made the vinyl anion



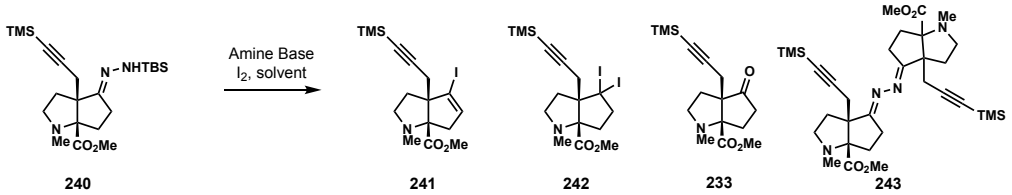
Scheme 2.14 Our synthetic efforts towards the vinyl iodide precursor

thermodynamically unfavored, this proton transfer process might be avoided under low temperature. Therefore, the lithium-halogen exchange was programmed to couple the cyclobutanone electrophile, which required a vinyl iodide compound as the precursor. To achieve the vinyl halide, the ketone **233** was first converted to the vinyl triflate **236** by standard condition. We tried to convert compound **236** to the vinyl iodide by several reported protocols[50,51], but only decomposition was observed.

As our efforts toward synthesizing the vinyl iodide from the vinyl triflate were unfruitful, we decided to try the Barton vinyl iodide synthesis, which required a hydrazone as precursor.[53,54] While PPTS had previously facilitated the condensation of TsN_2H_3 and ketone **233**, several attempts of hydrazine condensation under acidic condition failed to deliver desired hydrazone. It was found that using triethyl amine as base gave us a new product that is slightly less polar than starting material, which was later identified to be an alkyne reduced product **238**. Hypothetically, this reaction might undergo a cyclic transition state (**239**), and the hydrogens were thus able to transfer from hydrazone to the alkyne carbon. Therefore, the TBS protected hydrazine was used for this condensation, as the sterically bulky TBS group might be able to expel the alkyne group and prevent the formation of the bicyclic transition state.[53] This strategy worked well: The TBS hydrazine condensed with neopentyl ketone and gave the hydrazone motif **240** in ca. 80% yield. With no extra purification, hydrazone **240** could be used for forging the vinyl iodide **241**.

Although there are many precedented examples[53,54] of converting hydrazones to vinyl iodides, our initial attempt only gave us an unstable product (Table 2.3, Entry 1),

which could spontaneously convert to the ketone **233** upon purification. As the diiodide was known as one major byproduct for this reaction[54a] and possess similar reactivity[54b], we believed the diiodide **242** was formed. Multiple strategies were then attempted for optimization this reaction to eliminate the formation of this diiodide **242**. For example, we have switched the base to TEA (Table 2.3, Entry 2), or adding a secondary base (DBU, LHMDS or *t*-BuOK) in hope to achieve a one-pot E2 elimination (Table 2.3, Entry 3–5). However, those efforts again resulted primarily in diiodide product **242** or caused decomposition. NIS was also tested as iodination reagent, as the succinimide anion was believed to mediate an elimination reaction more easily, and thus boost the



240 **241** **242** **233** **243**

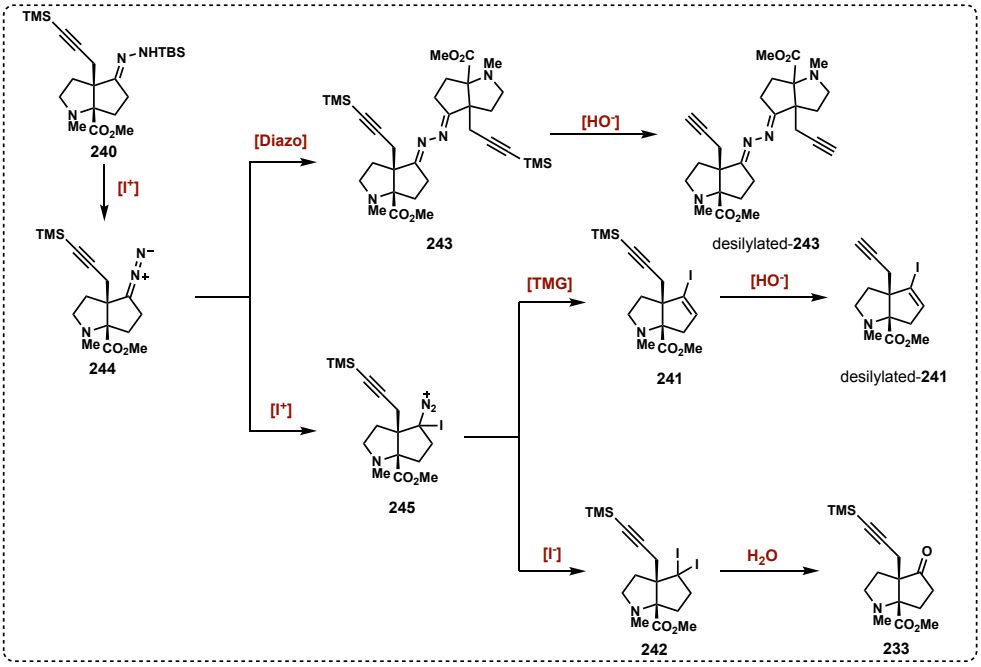
Entry	Condition	Result
1	50 eq. TMG, 8 eq. I_2, THF	diiodide pdt. **242**, trace **241**
2	50 eq. TEA, 8 eq. I_2, THF	diiodide pdt. **242**, trace **241**
3	50 eq. TMG, 8 eq. I_2, THF, then DBU	diiodide pdt. **242**, trace **241**
4	50 eq. TMG, 8 eq. I_2, THF, then *t*-BuOK	decomp.
5	50 eq. TMG, 8 eq. I_2, THF, then LiHMDS	decomp.
6	50 eq. TMG, 8 eq. NIS, THF	bicyclic ketone **233**
7	50 eq. TMG, 8 eq. I_2, DCM	diiodide pdt. **242**, trace **241**
8	50 eq. TMG, 8 eq. I_2, Et_2O	diiodide pdt. **242**, trace **241**
9	50 eq. TMG, 8 eq. I_2, MeCN	diiodide pdt. **242**, trace **241**
10	50 eq. TMG, 8 eq. I_2, DMF	diiodide pdt. **242**, trace **241**
11	50 eq. TMG, 8 eq. I_2, THF, then $AgBF_4$	decomp.
12	5:1 TMG:THF, 8 eq. I_2, r.t., quick injection, r.t. work up	ca. 25% desilylated **241** + diiodide **242**
13	5:1 TMG:THF, 2.5 eq. I_2, 0 °C, slow addition, 0°C work up	Minor **241** + **243** (major)
14	5:1 TMG:THF, 8 eq. I_2, –30 °C, slow addition, 0°C work up.	**243**
15	5:1 TMG:THF, 10 eq. I_2, rt, slow addition, 0°C work up.	ca. 60% **241**, trace **242**, no isolated **243**

Table 2.3 Optimization of the iodination reaction for obtaining **241**

yield of the desired vinyl iodide product **241** (Table 2.3, Entry 6). However, using NIS as an iodination reagent only gave us the ketone precursor **233**. Additionally, a solvent screen was performed (Table 2.3, Entry 7-10) and it was found that no matter whether polar aprotic or nonpolar solvents were applied, only diiodide product **242** could be obtained from the reaction mixture. Attempts of using silver salts, in hope to quench the iodide anion and stop the formation of the undesired diiodide, gave solely decomposition (Table 2.3, Entry 11). Finally, we were pleased to find that using the amine base 1,1,3,3-tetramethylguanidine (TMG) as a cosolvent could significantly increase the yield of the vinyl iodide, while suppressing the formation of diiodide **242** (Table 2.3, Entry 12), despite the terminal alkyne being desilylated. Further suppression of the undesired diiodide **242** was attempted by lowering the reaction temperature to 0 °C. Although no diiodide **242** was observed from this reaction, a new dimerized

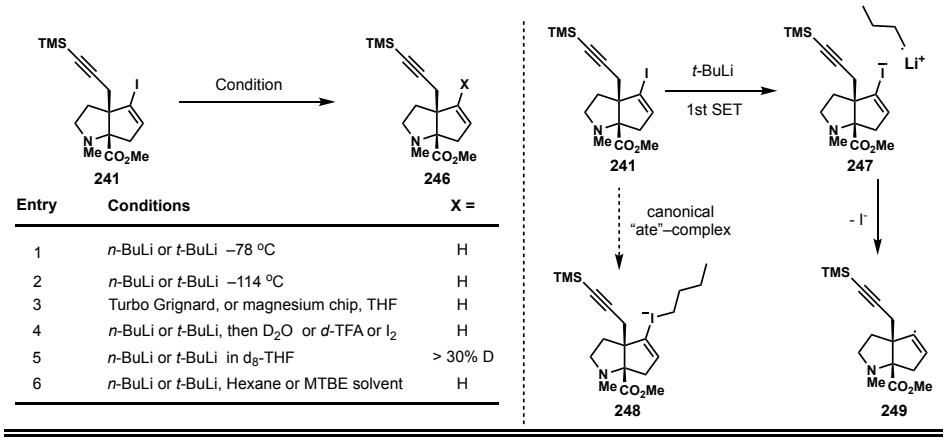
compound **243** was isolated as the major product (Table 2.3, Entry 13).[54] Meanwhile, it was found that if the temperature was lowered to –30 °C, the only highly polar dimerized products **243** was observed, and no desired product **241** or diiodide **242** was formed (Table 2.3, Entry 14).

Based on our observations and previous studies of the Barton vinyl iodide synthesis[54b,c], the following mechanism was proposed as guidance for optimizing this iodination reaction. Hydrazone compound **240** was first oxidized and gave the diazo motif **244**. The diazo intermediate **244** could then undergo two competitive pathways: iodination (**244** → **245**) or dimerization (**244** → **243**). Based on our observation, it was hypothesized the concentration of the iodination reagent is the determining factor. The viscous reaction system formed under low temperature caused a deficient exposure of iodination reagent, and thus the dimerized products were obtained as major product (Table 2.3, Entry 15). Once after the first iodination, the newly formed monoiodinated intermediate **245** could undergo a second set of competitive reactions: E2 elimination (**245** → **241**) or S_N2 substitution (**245** → **242**). Lack of base or excess of iodide anion would cause formation of the undesired diiodide **242**. Therefore, a neat basic reaction would be ideal for the propose of boosting the vinyl iodide yield (Table 2.3, Entry 13). Finally, aqueous work-up of this TMG solution at ambient temperature could cause the undesired TMS deprotection. Consequently, low temperature work-up could be optimal for preventing this undesired desilylation process. With this hypothetical mechanism in mind, it was found that 5:1 TMG: THF was the optimal solvent system, and after a quick extraction with ice-cooled sodium bicarbonate buffered solution, the desired vinyl iodide **241** product was obtained in ca. 60% yield, for two steps (Table 2.3, Entry 15).



Scheme 2.15 Proposed mechanism of iodination reaction

With this desired vinyl iodide in hand, we were able to try to forge the carbon-carbon bond to connect this bicycle **241** and the cyclobutanone building block. Classic conditions for this lithium-halogen exchange were first examined, but all those attempts could only give us protonated product (Entry 1). Both attempts of suppressing this protonated olefin via lowing the temperature (Entry 2) or converting the vinyl iodide to less basic vinyl Grignard reagent (Entry 3) failed to give any desired product. To figure out the exact proton source, series of deuterium and iodine quenching reactions were executed, including using highly acidic *d*-TFA. Hypothetically, the vinyl anion formed after the lithium-halogen exchange, or the propargyl anion formed by an additional intermolecular proton transfer, could be trapped and gave us a product with deuterium or iodide labeled. But to our surprise, after the addition of the lithiate reagent for a short time (5 minutes) and under low temperature (–114 ºC to –78 ºC), the vinyl iodide was fully converted and gave only protonated product **246**, which indicated the hypothetical protonation process was completed prior to the addition of the deuterated reagent or iodine (less than 5 minutes), which left THF as the only possible proton source.



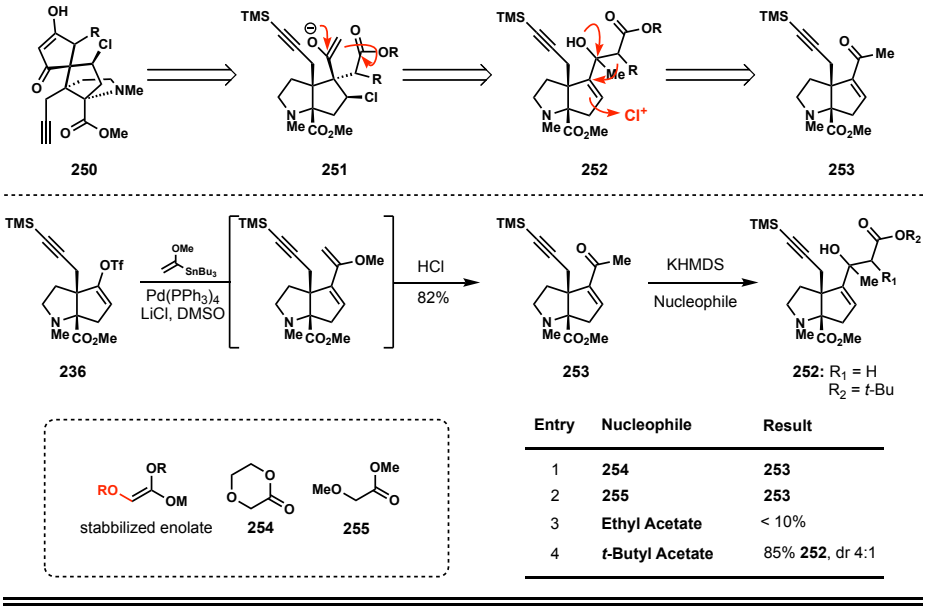
Entry	Conditions	X =
1	*n*-BuLi or *t*-BuLi –78 ºC	H
2	*n*-BuLi or *t*-BuLi –114 ºC	H
3	Turbo Grignard, or magnesium chip, THF	H
4	*n*-BuLi or *t*-BuLi, then D_2O or *d*-TFA or I_2	H
5	*n*-BuLi or *t*-BuLi in d_8-THF	> 30% D
6	*n*-BuLi or *t*-BuLi, Hexane or MTBE solvent	H

Scheme 2.16 Unexpected hydrogenation during the halogen-lithium exchange of vinyl iodide

This unusual results obtained from previous experiments made us suspect if the desired vinyl lithiate specie was not formed, as even the more basic *n*-BuLi was known to be stable in THF at low temperature.[55] Despite that a considerable amount of evidence had suggested the vinyl lithiate was formed through an "ate-complex" by a direct nucleophilic attack,[56] there was also electron spin resonance (ESR) evidence indicating that the lithium halogen exchange is a SET process,[56,57] and the formed vinyl radical could gave the same "protonated" product via a hydrogen atom transfer (HAT) process. To test if this HAT process was involved, the ampule sealed d_8-THF was applied as solvent (Entry 5). Although this expensive NMR d_8-THF solvent contained small amount of water, which could serve as a reactive proton source, it was found the lithium-halogen exchange reaction gave deuterated product **D-246**, as the vinyl proton peak was significantly suppressed on proton NMR. This deuterated olefin product **D-246** made us believe that instead of the most common "ate"-transition state (**241** → **248**), a SET reduction of carbon-iodide bond occurred, and gave vinyl radical **249**. This highly reactive vinyl radical motif **249** then underwent a HAT process and gave the

hydrogenated olefin **246** along with a stabilized α-*oxy* THF radical as product. To overcome this problem, series of solvents with a higher C-H bond BDE were screened for this halogen-lithium exchange reaction, but none of those efforts could give us the desired product (Entry 6). Unable to remedy this reaction, we looked for alternative paths forward.

2.2.6 Construction of the spirocycle: rearrangement approach



Scheme 2.17 Our efforts towards the semipinacol rearrangement precursor

As the lithium-halogen exchange strategy failed to produce the vinyl lithiate cleanly, a new strategy to forge the neopentyl C-C bond for constructing the spirocycle was required. It was envisioned that the spirocycle could be formed by a sequence of spiro center formation and cyclization (**250**→ **251**→ **252**). Although this strategy might not be as efficient as the previous cyclobutanone coupling strategy, it was believed the difficulty of constructing the neopentyl C-C bond would be significantly reduced, as a variety of coupling conditions was reported for highly bulky substrates. To test this idea, a vinyl tin reagent was first attempted to couple with the vinyl triflate **236**. Although the unavoidable $A^{1,2}$ strain of the diene product was suspected to cause problems in the formation of the desired C-C bond, it was found that exposing vinyl triflate **236** to a Stille coupling condition smoothly gave us desired diene product, which was later converted to enone **253** by a one-pot hydrolysis. Ketone **253** could then serve as an aldol acceptor and give us the tertiary allylic alcohol **252** for testing the key chlorination rearrangement reaction. Several aldol reactions (Entry 1, 2) with appropriately functionalized esters were executed first, but only enone **253** was recovered, presumably because the nucleophiles were stabilized by an α-oxygen atom. Therefore, the enolate nucleophile was replaced to the ethyl acetate enolate (Entry 3), and a small amount of the aldol product was observed. Encouraged by this result, a further

optimization of this reaction was undertaken by screening bases, solvents, temperatures, and nucleophiles. Eventually, by applying *t*-butyl acetate as the enolate precursor, the desired tertiary allylic alcohol **252** was obtained in 85% yield with a 4:1 d.r. .

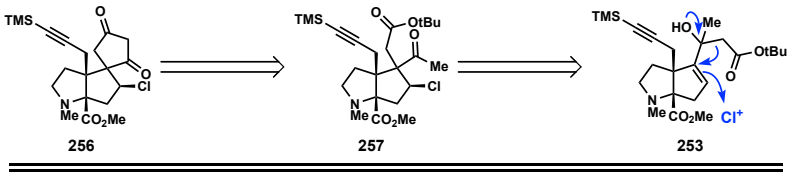


Figure 2. 4 Our plan of installing the neopentyl chloride enabled by a chlorinative rearrangement strategy

With this desired tertiary alcohol **253** in hand, we envisioned both the neopentyl chloride and the neopentyl ketone could be assembled by a chlorinative rearrangement reaction (see Figure 2.4, **256 → 257)**. This reaction could be potentially directed by the tertiary alcohol, and thus the undesired oxidation of the pendant amine could be avoided.

Entry	Conditions	Result
1	TiCl(O*i*-Pr)$_3$, *t*-BuOCl, Hex	RSM
2	TiCl(O*i*-Pr)$_3$, *t*-BuOCl, DCM	decomp.
3	TiCl(O*i*-Pr)$_3$, *t*-BuOCl, THF	decomp.
4	TiCl(O*i*-Pr)$_3$, NCS, Hex	RSM
5	TiCl(O*i*-Pr)$_3$, TCCA, Hex	RSM
6	$CeCl_3$, Bleach, DCM	decomp.
7	$BF_3 \cdot Et_2O$, NCS, Hex	RSM
8	$BF_3 \cdot Et_2O$, TCCA, DCM	RSM
9	$BF_3 \cdot Et_2O$, $Ca(OCl)_2$, THF, 12 hr	RSM + desilylated
10	PIDA, NaCl, 40 °C	decomp.
11	Koser's reagent, HCl, DCM	RSM
12	KHMDS, *t*-BuOCl	**253**
13	HCl, TCCA, PhMe	decomp.
14	HCl, TCCA, THF	decomp.
15	Et_4NCl_3, Hex, BF_3OEt_2	RSM
16	Et_4NCl_3, DCM, BF_3OEt_2	RSM

Table 2.4 Chlorinative semipinacol rearrangement: selective optimization studies

The directed chlorination protocol developed by the Burns group[58] was first examined (Table 2.4, Entry 1), but their optimal condition failed to deliver any product. Additionally, attempts to optimize this reaction by screening solvents (Table 2.4, Entry 2,3) and chlorinating reagents (Table 2.4, Entry 4,5) were not successful. Other than Burn's chlorination strategy, a similar chlorination/Wagner–Meerwein protocol used in Wood's synthesis of welwitindolinone A isonitrile[59] and these conditions were also attempted (Table 2.4, Entry 6). However, exposing the alcohol **252** to $CeCl_3$ and bleach only caused decomposition. A series of Lewis acids were screened, and it was found that BF_3•Et_2O could sufficiently prevent the decomposition process (Table 2.4, Entry

7-9), presumably because the tertiary amine was masked by BF_3•Et_2O. However, no conversion of alcohol **252** could be observed once BF_3•Et_2O was applied as Lewis acid. Moreover, applying a reported chlorination/semipinacol rearrangement protocol[60] failed to bring any desired product as well (Table 2.4, Entry 10,11).

The trisubstituted olefin is deeply buried under the adjacent fully substituted carbon centers, and thus being inaccessible towards organic chlorination reagents. To solve this problem, we tried to chlorinate the olefin in an intramolecular fashion. The alcohol **252** was first exposed to KHMDS and *t*-BuOCl to convert the alcohol to a hypochlorite species. It was envisioned that this fragile O-Cl bond could undergo a homolytic cleavage process, and the *oxy*-radical would initiate an alkyl shift and gave the desired ketone **258** after chloride recombination. However, only ketone **253** was observed from this reaction (Table 2.4, Entry 12). Meanwhile, we also attempted to using small chlorination reagents to facilitate the desired olefin rearrangement reaction. The olefin was first exposed to Cl_2, which was *in situ* prepared by mixing TCCA with hydrochloric acid, but this harsh condition only led to decomposition (Table 2.4, Entry 13, 14). As the Cl_3^+ cation was known for chlorinating inactivated olefins, [61,62] freshly prepared $TEACl_3$ was also examined. However, with the existence of BF_3•Et_2O, only recovered starting material was observed.

2.2.7 Construction of the spirocycle: a condensation approach

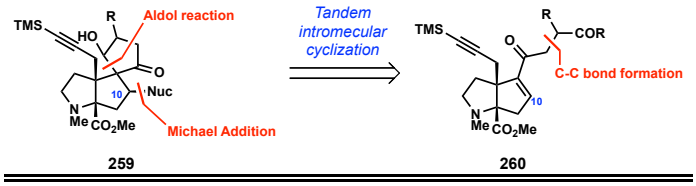
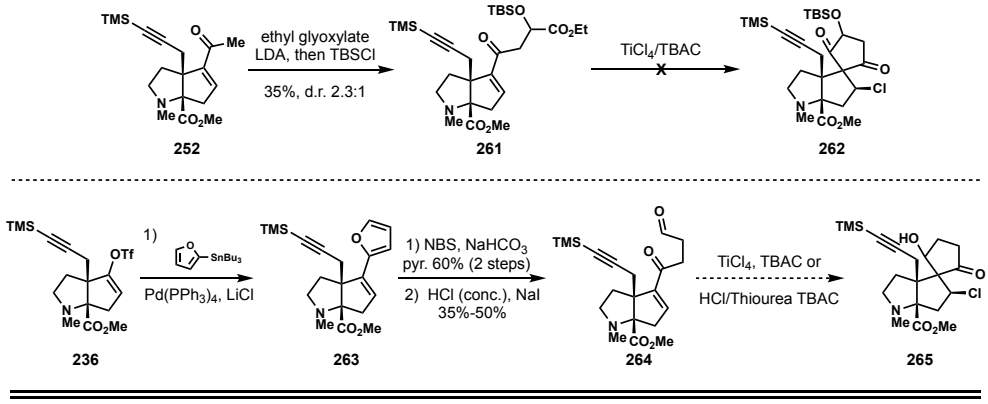


Figure 2.5 Construction of the spiro-fused ring by a Michael addition/condensation reaction

As a series of harsh conditions failed to convert this sterically hindered trisubstituted olefin, our synthetic plan for (–)-acutumine (**107**) needed to be redesigned. While our previous attempts to functionalize the steric inaccessible olefin were not fruitful, we envisioned the electrophilic β position of enone is more accessible, and thus easier to be approached by reagents. Moreover, the intramolecular nature of the subsequent condensation could be beneficial for delivering the electrophile to the congested reactive site. In addition, this strategy also allowed us to install the proper oxidation state prior to the construction of the spirocycle.

In 2012, a cascade chloro-Michael/intramolecular aldol reaction protocol was reported by Miesch group, which was able to convert an enone aldehyde motif to the β-hydroxy ketone with a newly forged C-Cl bond.[64a] Only disubstituted enones were applied as the nucleophile for this tandem reaction, which suggested to us that this reaction is likely very sensitive to sterics; nonetheless, we were still eager to try this protocol on our substrate. We hoped this protocol could forge the spirocycle and install the neopentyl chloride and secondary alcohol in a single step. To attempt this reported cascade reaction, enone ester **261** was first synthesized by a one pot aldol/silylation

reaction. However, exposing ester **261** to the standard condition ($TiCl_4$, DCM) failed to give any cyclized product, and only starting material was recovered. Additionally, our efforts to optimize this reaction, including adding TBAC as external chloride source, raising temperature, screening solvents failed to convert any starting material.

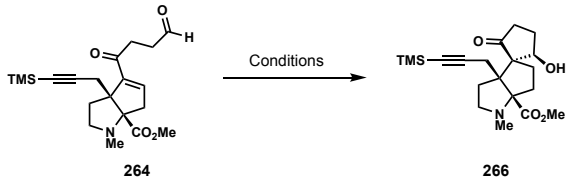


Scheme 2.18 Attempts to forge the spirocycle via a chloro-Michael/Dieckmann condensation or chloro-Michael/aldol condensation reaction.

Although a thorough condition screening of the chloro-Michael/Dieckmann condensation failed to provide any product, we were not sure whether it is because of the steric hindrance arising from the adjacent quaternary center, or the poor electrophilicity of the unsaturated ester. While the steric hindrance is an intrinsic problem for our substrates, the second assumption could be tested if an aldehyde was applied as an electrophile. As a result, the corresponding aldehyde **264** was then synthesized by a Stille coupling of 2-(tributylstannyl) furan and subsequential furan opening reactions.[65,66] However, exposing **264** to $TiCl_4$ again gave only recovered starting material. Additionally, attempts to activate the enone by hydrochloric acid or thiourea were unfruitful.

As efforts to elicit the reported tandem chloro-Michael/intramolecular condensation reaction failed to give any desired cyclized product, we decided to construct the spirocycle first. Although our attempts to perform a L-Selectride-mediated 1,4-reduction unselectively reduced the aldehyde instead, it was found that using Stryker's reagent gave us trace amount of the desired spirocyclic tricycle **266**. The facial selectivity of the aldol reaction and the stereochemistry of the newly formed neopentyl alcohol were revealed by NOESY experiments. Since most of compound **264** was decomposed during this Stryker reagent-mediated reaction, we first tried to circumvent the decomposition by lowering the reaction temperature, but the formation of **266** was diminished under this condition (Table 2.5, Entry 2). Hypothetically, the low yield of this reaction could be caused by the low reactivity of the Cu hexamer, as the enone substrate could be sterically inaccessible to the Cu hexamer. To fix this problem, series of polar solvents were first screened (Table 2.5, Entry 3, 4), but those efforts failed to increase the yield of **266**. It has also been reported that using bis-phosphine ligand to deaggregate the copper hexamer could significantly boost the yield of a Stryker's reagent-mediated 1,4-reduction of a steric congested enone (Table 2.5,

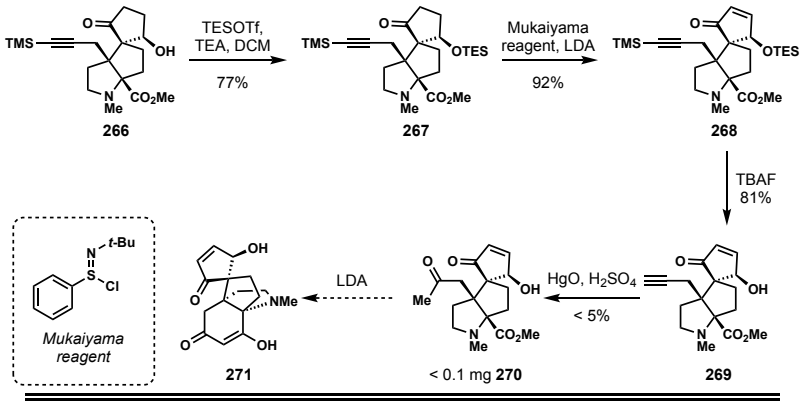
Entry 5).[68] However, no cyclized product **266** could be isolated upon exposing the enone **264** to the BDP ligand. This result made us question if the undesired decomposition was caused by the activated copper hydride monomer. To examine this hypothesis, several nonpolar solvents were then examined (Table 2.5, Entry 6, 7). We were glad to find the decomposition was significantly suppressed, and DCM was determined to be the optimal solvent. Finally, the spiro cycle along with the secondary alcohol was constructed in one step, in 65% yield.



Entry	Condition	Result
1	0.2 eq. Stryker's reagent, Et_2O, 23 °C 3 hr	ca. 25% **266** + decomp.
2	0.2 eq. Stryker's reagent, Et_2O, 0 °C. overnight	trace **266**
3	0.2 eq. Stryker's reagent, DMF 23 °C, 6 hr	decomp.
4	0.2 eq. Stryker's reagent, MeCN, 23 °C, 6 hr	decomp.
5	0.2 eq. Stryker's reagent, 1.2 eq. BDP Et_2O, 23 °C, 3 hr	decomp.
6	0.2 eq. Stryker's reagent, Hex, 23 °C, 6 hr	low conversion
7	0.2 eq. Stryker's reagent, DCM, 23 °C	65% **266**

Table 2.5 Towards the synthesis of spiro-fused tricycle **266**

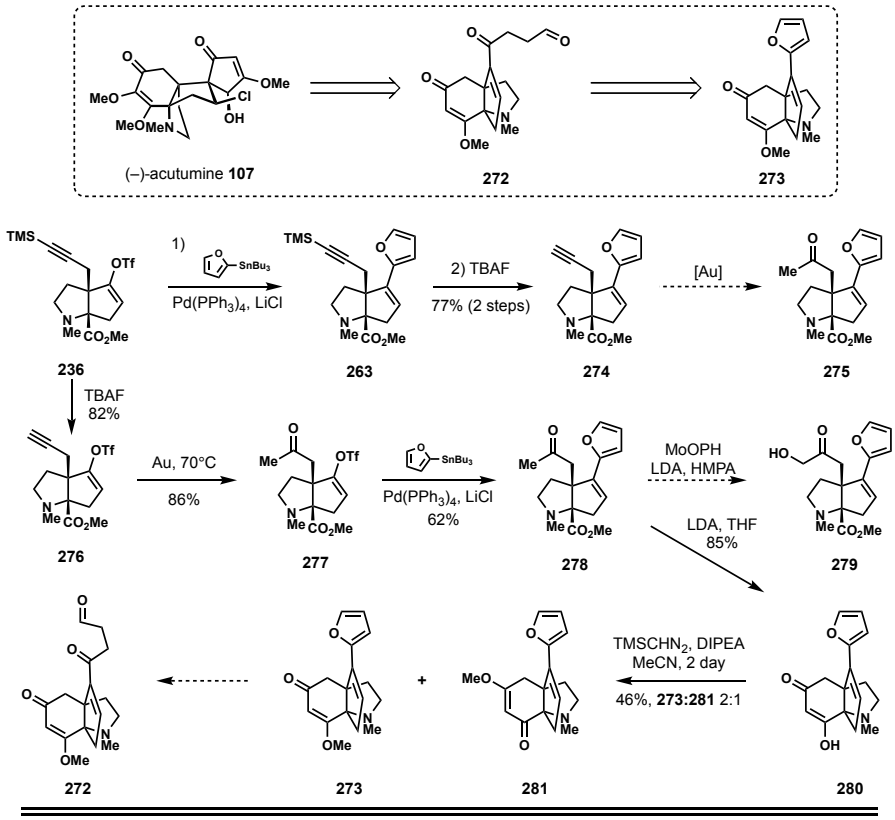
2.2.8 Efforts towards the tetracyclic core of (–)-acutumine (107)



Scheme 2.19 Our efforts towards the tetracycle core of acutumine (**107**)

As the Stryker's reagent could chemoselectively reduced the enone with the existence of aldehyde, we were able to obtain the tricyclic compound **266**. To finish this synthesis, we then focused on the construction of the finally cyclohexenone ring. Before adjusting oxidation state of the alkyne group, the alcohol of tricycle **266** was masked by TES group to remove the active proton. To install the unsaturation of the spiro cycle, the formed silyl ether **267** was subjected to a Mukaiyama dehydrogenation,

and a global desilylation was applied prior to the subsequent hydration of the alkyne and gave terminal alkyne **269** as the product. Although all attempts of using Au catalyst to hydrate the alkyne failed to give desired methyl ketone, upon exposing the terminal alkyne to the H_2SO_4 and HgO under elevated temperature, a small amount (< 0.1mg) of product **270** was isolated. However, we were not able to obtain tetracyclic product **271** by treating compound **270** with LDA, although this condition could forge the cyclohexenone ring of **228** smoothly.



Scheme 2.20 Attempts to obtain the tetracycle core by switching the cyclization sequence.

We hypothesized the spirocycle ketone is more electrophilic than the pendant ester carbonyl, and thus derives side reactions. Supposedly, this problem could be fixed by switching the cyclization sequence and construct the cyclohexenone ring first. We envisioned that the enolate formed after Stryker reduction would not efficiently overlap with the propellane ketone's π* orbital, and thus could give us the desired tetracycle (Scheme 2.19, **273** → **272**→ **107**). With this guideline in mind, the furan intermediate **263** was first desilyated. However, this alkyne **274** was incompatible for the gold catalyzed hydration reaction, presumably because of the pendent furan group. Therefore, the alkyne **236** was first hydrated, and the furan building block was installed by the Stille protocol. As the highly electron rich furan is incompatible with MoOPH oxidation, this methyl ketone **278** was directly cyclized to give vinylogous acid intermediate **280**, which was then methylated with $TMSCHN_2$. With this propellane compound in hand, we then focused on testing our Stryker's reagent-mediated

cyclization reaction to construct the tetracyclic core of acutumine alkaloids. However, our initial attempts of opening the furan only gave decomposed materials. Hypothetically, the excess amount of pyridine required for furan opening deprotonates vinylogous ester of **273**, and thus lead to decomposition. We hope this problem could be fixed by employing a milder condition, and the tetracyclic skeleton of acutumine alkaloids could be achieved from the resulted enone **272**.

2.3 Conclusion and Remarks

In this chapter, the previous studies toward the synthesis of (–)-acutumine (**107**) and its related alkaloids were described, including the isolation, biosynthesis, bioactivities, and previous synthetic studies. Those studies provided us a general understanding of the acutumine natural products, especially the synthetic challenges posed by its unique structure. Meanwhile, we have discussed our synthetic studies of acutumine alkaloids. A [3+2] cycloaddition protocol developed by us enabled a synthesis of [3.3.0] bicycle, and a vicinal stereogenic centers could be installed. Starting from this key intermediate, we were able to obtain several different tricycles and multiple strategies of constructing the tetracyclic core of (–)-acutumine (**107**) were attempted. In parallel routes, we have worked out chemistry to both the address the spirocyclic center and was as the 6-membered rings. Efforts to orchestrate and merge findings from these routes and address the neopentyl chlorine atom are currently underway.

This project was conceived by Professor Thomas Maimone, Xingyu Shen and Dr. Naifeng Hu. Ting. In Scheme 2.9, studies of achieving the tetracyclic compound **199** was conducted by Xingyu Shen. The chlorinative rearrangement and [3+2] cycloaddition strategy was conceived by collaboration of Xingyu, Shen, Professor Thomas Maimone and Dr. Naifeng Hu. In Scheme 2.11, the NHK coupling reaction was developed by Xingyu Shen, and Dr. Naifeng Hu designed the one-opt protocol to adjust the protection groups. The key [3+2] cycloaddition (Table 2.1) and the lithium-halogen exchange (Scheme 2.16) were studied by a collaboration of Xingyu, Shen and Dr. Naifeng Hu. Dr. Naifeng Hu also developed a protocol to convert vinyl triflate **236** to allylic alcohol **252** (Scheme 2,17), The subsequentially studies of functionalization of alkyne (Table 2.2, Scheme 2.12, 2.13), formation of the vinyl iodide (Scheme 2.14, 2.15, Table 2.3), chlorinative rearrangement (Table 2.4) and Stryker's reagent mediated cyclization (Scheme 2.18, 19, 20) were conducted by Xingyu Shen. Data was analyzed by Professor Thomas Maimone, Xingyu Shen and Dr. Naifeng Hu.

We gratefully appreciated Dr. Hasan Celik and Dr. Jeffery Pelton for NMR assistance. We also acknowledge the NIH grant GM68933 for funding the 900MHz NMR spectrometer and NIH grant S10OD024998 for funding the AV 600MHz NMR spectrometer.

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Supplementary Information

For

Chapter 2

Synthetic Studies towards Acutumine Alkaloids

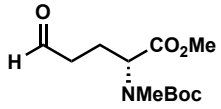
SI 2.1 General procedures:

All reactions were performed in flame- or oven-dried glassware under a positive pressure of nitrogen or argon unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe. Volatile solvents were removed under reduced pressure rotary evaporation below 35 °C, DMF was removed under 60 °C. Analytical and preparative thin-layer chromatography (TLC) was performed using glass plates pre-coated with silica gel (0.25-mm, 60-Å pore size, Silicycle SiliaPlate^{TM}) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV), then were stained by submersion in an ethanolic anisaldehyde solution or a basic $KMnO_4$ solution. Flash column chromatography was performed as described by Still et al., employing silica gel purchased from Silicycle (SiliaFlash®, 60 Å, 230-400 mesh, 40-63 μm).

Dry THF, DCM and diethyl ether were obtained by passing these previously degassed solvents through activated alumina columns. TMP and TEA were distilled over calcium hydride prior to use. All other solvents and reagents were used as received without further purification.

Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Bruker AV 300 (300 MHz, 76 MHz), Bruker AVQ 400 (400 MHz/101 MHz/376 MHz), Bruker AV 400 (400 MHz/101 MHz), Bruker AV 500 (500 MHz/126 MHz), Bruker DRX 500 (500 MHz/126 MHz), Bruker AV 600 (600 MHz/151 MHz) NMR, Bruker AV 700 (700 MHz/176 MHz) NMR or Bruker AV 900 (900 MHz/226 MHz) NMR spectrometers at 23 °C. Proton chemical shifts are expressed as parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.26, C_6D_6: δ 7.16, CD_3OD: δ 3.31). Carbon chemical shifts are expressed as parts per million (ppm, δ scale) and are referenced to the carbon resonance of the NMR solvent ($CDCl_3$: δ 77.2, C_6D_6: δ 128.1, CD_3OD: δ 49.15). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddd = doublet of doublets of doublets, tt = triplet of triplets, m = multiplet, b = broad, app = apparent), coupling constant (*J*) in Hertz (Hz), and integration. Infrared (IR) spectra were recorded on a Bruker Alpha FT-IR spectrometer as thin films and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained at the QB3/Chemistry Mass Spectrometry Facility at University of California, Berkeley using a Thermo LTQ-FT mass spectrometer.

SI 2.2 Compound preparation and characterization data:



212

Aldehyde 212: This aldehyde could be prepared by two different protocols. Method A) A 100 mL flame-dried round bottom flask was charged with dimethyl *N*-(*tert*-butoxycarbonyl)-*N*-methylglutamate (1.0 g, 3.5 mmol, 1 equiv.). The reaction vessel was evacuated and backfilled with nitrogen for three times. 35 mL of THF was added to this round bottom flask and cooled to –94 ºC (liquid N_2/MeOH). DIBAL-H (1.0 M hexane solution, 3.6 mL, 3.6 mmol, 1.05 equiv.) was added dropwise, and this resulted mixture was stirred for 3 hours under –94 ºC. This reaction is carefully monitored by TLC. After all dimethyl *N*-(*tert*-butoxycarbonyl)-*N*-methylglutamate was consumed, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution (50 mL), and saturate aqueous le Rochelle salt solution (100 mL) was subsequentially added. The cloudy mixture was stirred overnight and gave clear biphasic solution as product. The organic phase was extracted with water (2 X 100 mL) and washed with brine solution (150 mL). The collected organic fraction was dried over Na_2SO_4 (30g) and concentrated *in vacuo*. The crude residue was purified by column chromatography (EtOAc:Hex 1:4 to 1:2) to give 310 mg of the desired aldehyde **212** (33% yield).

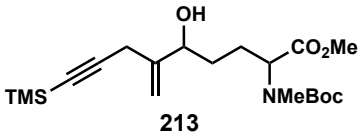
Method B) A 2 L flame-dried round bottom flask was charged with dimethyl *N*-(*tert*-butoxycarbonyl)-*N*-methylglutamate (19.2 g, 66.4 mmol, 1 equiv.). The reaction vessel was evacuated and backfilled with nitrogen for three times. 500 mL of THF was added to this round bottom flask and cooled to –78 ºC (liquid N_2/MeOH). DIBAL-H (1.0 M hexane solution, 132.8 mL, 2.0 equiv.) was added over 30 mins, and this resulted mixture was stirred for 1 hours under –78 ºC. This reaction is carefully monitored by TLC. After all dimethyl *N*-(*tert*-butoxycarbonyl)-*N*-methylglutamate was consumed, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution (200 mL), and saturate aqueous le Rochelle salt solution (1000 mL) was subsequentially added. The cloudy mixture was stirred overnight and gave clear biphasic solution as product. The organic phase was extracted with water (2 X 1000 mL) and washed with brine solution (1000 mL). The collected organic fraction was dried over Na_2SO_4, concentrated *in vacuo* and then was added to a 1 L flame-dried reaction flask. The reaction vessel was evacuated and backfilled with nitrogen, and 300 mL 1:1 DMSO:DCM solution was added. 15.9 g of SO_3·pyr (99.6 mmol, 1.5 equiv.) and 27.6 mL of triethylamine (199.2 mmol, 3 equiv.) was subsequentially added. The resulted mixture was allowed to stir for 12 hour under ambient temperature. The reaction was quenched by the addition of 500 mL saturated $NaHCO_3$ solution. The biphasic mixture was diluted with EtOAc (500 mL) and extracted with water (100 mL) for three times and washed with brine solution (150 mL). The organic phase was collected, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by column chromatography (EtOAc:Hex 1:2) to give 13.7 g desired aldehyde **212** as product (80% yield over 2 steps).

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.78 (d, *J* = 7.9 Hz, 1H), 4.69 (dd, *J* = 10.6, 5.3 Hz, 1H), 4.38 (dd, *J* = 10.4, 5.3 Hz, 1H), 3.72 (s, 3H), 2.85 – 2.75 (m, 3H), 2.60 – 2.43 (m, 2H), 2.35 – 2.26 (m, 1H), 2.08 – 1.98 (m, 1H), 1.50 – 1.39 (m, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 201.0, 200.9, 171.7, 156.4, 155.5, 80.8, 80.6, 59.0, 57.8, 52.3, 52.2, 40.6, 40.3, 32.2, 31.3, 28.5, 22.0, 21.5.

IR (thin film) ν_{max} 2976, 1742, 1692, 1480, 1437, 1392, 1367, 1322, 1250, 1146, 1015 cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{12}H_{21}O_5N_1{}^{23}Na_1$ $[M+H]^+$: 282.1312, found: 282.1315.



213

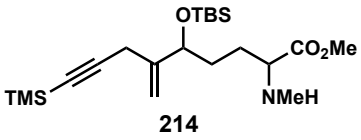
Linear alcohol 213: A 250 mL flame-dried reaction flask was charged with the **aldehyde 212** (1.7 g, 6.6 mmol, 1 equiv.) and enyne **211** (2.85 g, 13.2 mmol, 2.0 equiv.). This reaction vessel was evacuated and backfilled with nitrogen for three times. The vessel was then transferred into glove box and $CrCl_2$ (2.4 g, 19.8 mmol, 3 equiv.) and $NiCl_2$ (85 mg, 0.66 mmol, 10 mol%) were added under inert atmosphere. 65 mL of DMF was carefully degassed and added into the round bottom flask dropwisely at 0 °C. The formed dark green mixture was allowed to stir for 4h at room temperature. After TLC indicated all **aldehyde 212** was consumed, this reaction was quenched by the addition of saturated $NaHCO_3$ solution. The cloudy mixture was filtered by Celite and the resulted biphasic solution was washed was diluted with 100 mL EtOAc for three times, extracted with aqueous $NaHCO_3$ solution (3 X 200 mL) and 150 mL brine solution. The collected organic phase was dried over Na_2SO_4, concentrated *in vacuo*. This concentrated residue was purified by column chromatography to give the desired **linear alcohol 213** in 82% yield, as a mixture of 4 isomers (a pair of diastereomers and a pair of Boc rotamers).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.29 (s, 1H), 5.27 – 5.24 (m, 1H), 5.15 (dt, *J* = 4.0, 1.2 Hz, 1H), 4.79 (q, *J* = 5.1 Hz, 0.6H), 4.36 (s, 0.4H), 4.21 (t, *J* = 6.5 Hz, 1H), 3.70 (s, 3H), 3.20 – 3.04 (m, 1H), 3.00 – 2.93 (m, 1H), 2.87 – 2.71 (m, 3H), 2.09 – 1.99 (m, 1H), 1.58 (d, *J* = 10.3 Hz, 2H), 1.52 – 1.39 (m, 9H), 0.16 (d, *J* = 0.9 Hz, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 172.5, 172.3, 156.6, 155.7, 145.8, 113.0, 112.6, 103.6, 103.5, 88.0, 80.5, 80.4, 80.3, 74.6, 74.2, 73.9, 60.5, 59.7, 59.4, 57.8, 57.3, 53.6, 52.2, 31.5, 31.3, 30.8, 30.5, 28.5, 25.8, 25.5, 25.2, 24.9, 23.0, 22.8, 21.2, 14.3, 0.4, 0.2, -0.0.

IR (thin film) ν_{max} 3455, 2958, 2178, 1744, 1693, 1480, 1436, 1392, 1367, 1327, 1249, 1160 cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{20}H_{35}O_5N_1{}^{23}Na_1{}^{28}Si_1$ $[M+H]^+$: 420.2177, found: 420.2179.



214

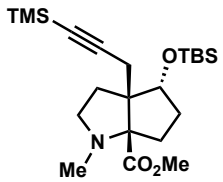
Methylamine 214: A 250 mL flame-dried reaction flask was charged with **213** (3.4 g, 8.6 mmol, 1.0 equiv). This reaction vessel was evacuated and backfilled with nitrogen for three times. 80 mL of DCM was added to this reaction vessel and cooled to –10 °C. After this resulted DCM solution was efficiently cooled, TBSOTf (2.2 mL, 9.4 mmol, 1.1 equiv.) and TEA (4.7 mL, 34.2 mmol, 4.0 equiv.) was added and this reaction mixture was stirred for 1 hour at –10 °C. TMSOTf (2.3 mL, 12.84 mmol, 1.5 equiv.) was then added to the vessel and the reaction mixture was slowly warmed up to ambient temperature over 2 hours. This resulted mixture was quenched by the addition of 100 mL aqueous $NaHCO_3$ solution and diluted with 50 mL EtOAc. The biphasic solution was extracted with $NaHCO_3$ solution (3 X 50 mL) and brine 50 mL solution. The collected organic phase was dried over Na_2SO_4, concentrated *in vacuo*. This concentrated residue was purified by column chromatography (Hex:EtOAc 19:1) to afford desired **214** as a light-yellow oil as two diastereomers.

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.20 (q, *J* = 1.7 Hz, 1H), 5.07 (dp, *J* = 2.6, 1.3 Hz, 1H), 4.19 (dd, *J* = 6.1, 3.0 Hz, 1H), 3.73 (d, *J* = 1.1 Hz, 3H), 3.15 (td, *J* = 6.2, 1.8 Hz, 1H), 3.08 – 3.00 (m, 1H), 2.92 – 2.85 (m, 1H), 2.36 (s, 3H), 1.70 – 1.47 (m, 3H), 0.88 (d, *J* = 1.4 Hz, 9H), 0.16 (s, 9H), 0.04 (s, 1H), 0.03 (s, 2H), 0.01 (s, 1H), 0.01 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 175.7, 145.7, 145.7, 112.2, 104.1, 87.5, 74.9, 74.9, 63.2, 63.2, 51.8, 51.8, 34.9, 34.8, 32.4, 32.4, 29.0, 26.0, 22.4, 22.3, 18.3, 0.2, -4.6, -5.0.

IR (thin film) ν_{max} 2955, 2930, 2897, 2857, 2801, 2178, 1738, 1652, 1361, 1079cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{21}H_{42}O_3N_1{}^{28}Si_1$ $[M+H]^+$: 412.2698, found: 412.2699.



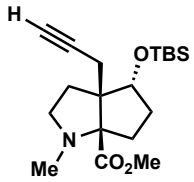
215

Bicycle 215: A high-pressure reaction tube was flame dried and charged with 10 mL of toluene. Enyne alcohol **214** (100 mg, 0.24 mmol, 1 equiv.), formalin (40 µL, 0.48 mmol, 2.0 equiv.) and TEA (40 µL, 0.36 mmol, 1.5 equiv.) was added, and the resulted mixture was stirred at 145 °C for 12 hours. This resulted toluene solution was then cooled down to room temperature and another 40 uL of formalin was added. This reaction vessel was heated again to 145 °C and stirred for another 12 hours. This resulted mixture was then cooled down to room temperature, diluted with 20 mL EtOAc and extracted with aqueous $NaHCO_3$ (3 X 30 mL) solution and 30 mL brine solution. The collected organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The organic residue was purified by column chromatography (Hex:EtOAc 19:1) to deliver desired bicyclic intermediate **215** in 77% yield.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.19 (dd, *J* = 8.7, 5.5 Hz, 1H), 3.70 (s, 3H), 2.94 – 2.87 (m, 1H), 2.67 (ddd, *J* = 8.5, 7.1, 4.6 Hz, 1H), 2.54 (d, *J* = 16.8 Hz, 1H), 2.30 (d, *J* = 16.8 Hz, 1H), 2.25 (dt, *J* = 14.8, 6.7 Hz, 1H), 2.22 (s, 3H), 1.87 – 1.77 (m, 2H), 1.75 – 1.66 (m, 1H), 1.64 – 1.56 (m, 1H), 1.21 (ddd, *J* = 12.8, 6.5, 4.6 Hz, 1H), 0.88 (s, 9H), 0.12 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.5, 104.7, 86.2, 78.6, 76.6, 59.9, 53.6, 51.7, 35.1, 32.6, 31.9, 27.9, 27.1, 25.9, 18.1, 0.1, -4.3, -4.7.
IR (thin film) ν_{max} 2956, 2899, 2858, 2176, 1733, 1472, 1463, 1447, 1251, 1091, 839 cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{22}H_{42}O_3N_1{}^{28}Si_2$ $[M+H]^+$: 424.2698, found: 424.2698.

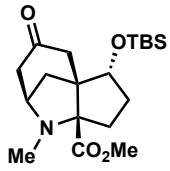


219

Terminal Alkyne 219: A 50 mL reaction tube was charged with 10 mL of MeOH. TMS protected alkyne **215** (100 mg, 0.24 mmol, 1 equiv.) and potassium carbonate (200 mg, 1.45 mmol, 6.0 equiv.) was added into this reaction vessel and the resulted mixture was allowed to stir at room temperature. The reaction was monitored by TLC for the consumption of the starting material. Once all starting material was consumed, the methanol solution was diluted with EtOAc (20 mL), and this resulted cloudy mixture was filtered by a short silica column. The organic solution was concentrated *in vacuo*, and this crude product **219** could be used without further purification. The **219** could also be obtained after column chromatography (19:1 Hex:EtOAc), with 95% yield (80 mg).

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.14 (dd, *J* = 8.6, 5.5 Hz, 1H), 3.72 (s, 3H), 2.67 (ddd, *J* = 8.6, 7.0, 5.3 Hz, 1H), 2.48 (dd, *J* = 16.6, 2.6 Hz, 1H), 2.32 – 2.26 (m, 2H), 2.25 (s, 3H), 1.91 – 1.81 (m, 3H), 1.78 – 1.70 (m, 1H), 1.66 – 1.57 (m, 1H), 1.35 – 1.24 (m, 1H), 0.88 (s, 9H), 0.07 (s, 3H), 0.07 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 173.9, 81.9, 78.8, 77.0, 69.6, 60.0, 53.7, 51.8, 35.2, 32.3, 32.3, 26.9, 26.7, 25.9, 18.1, -4.2, -4.8.
IR (thin film) ν_{max} 2954, 2903, 2858, 2790, 1726, 1255, 1222, 1168, 1092 cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{19}H_{34}O_3N_1{}^{28}Si_1$ $[M+H]^+$: 352.2302, found: 352.2306.



221

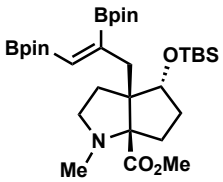
Tricycle 221: *i*) A 6 mL flame-dried reaction tube was charged with *m*-CPBA (77% active, 11.6 mg, 0.052 mmol, 1.5 equiv.), alkyne intermediate **219** (11.6 mg, 0.033 mmol, 1 equiv.). The reaction vessel was evacuated and backfilled with nitrogen for three times and 0.3 mL of DCM was added subsequentially. This mixture was allowed to stir for 30 mins at 0 °C. The suspension was then quenched by the addition of saturate aqueous $NaHCO_3$ solution (ca. 50μL) and saturated $Na_2S_2O_3$ solution (ca. 50μL). The resulted suspension was then filtered, and the filtrate was dried over Na_2SO_4 and concentrated *in vacuo*. To this vessel was added $AuNTf_2PPh_3$ (8mg, 0.11 mmol, 30 mol%) and 0.5 mL MeOH. The suspension was then filtered by a celite column. The resulted MeOH solution was then diluted 5 mL with EtOAc, extracted with aqueous $NaHCO_3$ solution (3 X 2 mL) and 2 mL brine solution. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by a preparative TLC (Hex:EtOAc 3:1) to give the tricycle **221** (2.5 mg, 25% for two steps) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.89 (t, *J* = 8.3 Hz, 1H), 3.64 (s, 3H), 3.36 (d, *J* = 9.5 Hz, 1H), 2.85 – 2.78 (m, 1H), 2.53 – 2.47 (m, 1H), 2.47 (s, 3H), 2.34 (ddd, *J* = 11.7, 5.7, 2.9 Hz, 1H), 2.19 – 2.09 (m, 2H), 2.09 – 2.01 (m, 2H), 1.97 – 1.87 (m, 1H), 1.82 – 1.75 (m, 1H), 1.56 (d, *J* = 11.8 Hz, 1H), 0.87 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 210.0, 176.2, 78.2, 75.9, 60.8, 59.6, 51.5, 48.7, 44.8, 37.1, 34.1, 31.3, 29.5, 25.9, 18.1, -4.3, -4.8.

IR (thin film) ν_{max} 2954, 2928, 2856, 2807, 1718, 1653, 1559, 1472, 1079, 858, 839 cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{19}H_{33}O_4N_1{}^{28}Si_1$ $[M+H]^+$: 368.2252, found: 368.2250.



223

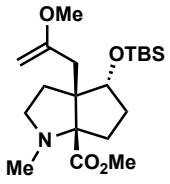
Diboron 223: A 20 mL flame-dried reaction tube was charged with $Pt(PPh)_3$ (2.5 mg, 2.0 μmol, 11 mol%), B_2Pin_2 (5.2 mg, 0.020 mmol, 1.1 equiv.) and alkyne intermediate **219** (6.3 mg, 0.018 mmol, 1equiv.). The reaction vessel was evacuated and backfilled with nitrogen, and mL degassed toluene was added as solvent. This mixture was then heated to 110 °C and stirred for 1.5 hours. The resulted red-orange suspension was cooled to room temperature and directly concentrated *in vacuo*. The residue was then purified by preparative TLC (1:1 Hex:EtOAc) and give the diboron intermediate **223** (2.7 mg, 26% yield) as product. (Notice: this diboron intermediate is highly sensitive to moisture)

^{1}H NMR (600 MHz, C_6D_6) δ 6.17 (s, 1H), 4.23 (t, *J* = 6.0 Hz, 1H), 3.34 (s, 3H), 3.18 – 3.07 (m, 2H), 2.79 (dd, *J* = 12.8, 1.5 Hz, 1H), 2.53 (ddd, *J* = 11.4, 7.2, 3.8 Hz, 1H), 2.31 (d, *J* = 1.0 Hz, 1H), 2.16 – 2.01 (m, 3H), 1.94 – 1.88 (m, 1H), 1.88 – 1.81 (m, 1H), 1.21 (s, 6H), 1.19 (s, 6H), 1.14 (d, *J* = 1.4 Hz, 12H), 1.06 (s, 9H), 0.26 (s, 3H), 0.13 (s, 3H).

^{13}C NMR (151 MHz, C_6D_6) δ 173.9, 128.1, 127.2, 83.2, 82.7, 82.0, 76.6, 62.0, 54.8, 50.2, 47.4, 34.6, 34.3, 31.4, 29.7, 27.4, 26.1, 25.0, 24.7, 24.6, 24.5, 22.7, 20.4, 18.0, 14.0, -4.0, -4.6.

IR (thin film) ν_{max} 2928, 2855, 1725, 1610, 1462, 1435, 1403, 1389, 1372, 1139, 835 cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{31}H_{58}O_7N_1{}^{11}B_2{}^{28}Si_1$ $[M+H]^+$: 606.4163, found: 606.4173.



225

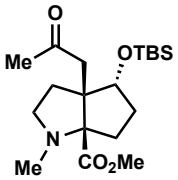
Methyl vinyl ether 225:A 20 mL flame-dried reaction tube was charged with 1 mL of MeOH. To this reaction vessel, **219** (8.3 mg, 0.023 mmol, 1 equiv.), TEA (5.6 μL, 0.040 mmol, 1.8 equiv.) and $Hg(OTFA)_2$ (7.9 mg, 0.019 mmol, 80 mol%) was added. This reaction mixture was stirred at 75 °C for 1.5 hour. Then this suspension was cooled to room temperature and filtered by a celite pad (caution: the mercury salt is highly toxic). The filtrate was concentrated *in vacuo* and the resulted residue was purified by column chromatography (4:1 Hex:EtOAc) to give the methyl vinyl ether **225** (5.1 mg, 58%) as product.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.26 (t, *J* = 4.6 Hz, 1H), 3.91 (d, *J* = 1.9 Hz, 1H), 3.85 (d, *J* = 1.9 Hz, 1H), 3.70 (s, 3H), 3.46 (s, 3H), 2.92 (ddd, *J* = 8.3, 7.2, 2.9 Hz, 1H), 2.64 (td, *J* = 8.7, 6.0 Hz, 1H), 2.25 (s, 3H), 2.16 (d, *J* = 13.7 Hz, 1H), 2.13 – 2.03 (m, 2H), 1.99 (dddd, *J* = 12.2, 8.9, 6.3, 5.0 Hz, 1H), 1.89 – 1.73 (m, 2H), 1.69 – 1.61 (m, 2H), 0.88 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 175.4, 84.1, 82.1, 77.3, 61.9, 54.7, 54.4, 51.6, 42.0, 35.6, 34.7, 32.6, 27.2, 26.0, 26.0, 18.1, -4.2, -4.8.

IR (thin film) ν_{max} 2952, 2934, 2857, 1726, 1255, 1138 cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{20}H_{38}O_4N_1{}^{28}Si_1$ $[M+H]^+$: 384.2565, found: 284.2564.



226

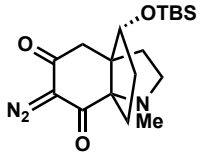
Methyl ketone 226: A 20 mL flame-dried reaction tube was charged with HgO (6 mg, 0.028 mmol, 33 mol%) and alkyne intermediate **219** (30 mg, 0.085 mmol, 1equiv.), then it was evacuated and backfilled with nitrogen for three times. After refilling N_2, 1.2 mL of MeOH and 0.25 mL of 8% H_2SO_4 aqueous solution was added to this reaction vessel. This resulted mixture was stirred at 60 °C for 3 hour and the suspension was diluted with EtOAc. The cloudy solid was filtered by a celite absorption column (caution: the mercury salt is highly toxic) and the filtrate was concentrated *in vacuo*. The resulted residue was purified by column chromatography (4:1 Hex:EtOAc) to give the methyl ketone **226** (17 mg, 54% yield) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.07 (dd, *J* = 8.3, 5.6 Hz, 1H), 3.61 (s, 3H), 2.94 – 2.77 (m, 2H), 2.66 (t, *J* = 14.2 Hz, 2H), 2.31 (dt, *J* = 13.7, 7.2 Hz, 1H), 2.22 (s, 3H), 2.03 (m, 4H), 1.79 (p, *J* = 5.7 Hz, 1H), 1.71 – 1.57 (m, 2H), 1.23 (s, 3H), 0.85 (s, 9H), 0.00 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 208.4, 174.0, 79.1, 58.9, 53.6, 51.3, 49.9, 35.4, 33.0, 32.2, 30.9, 29.8, 27.6, 25.9, 18.1, -4.2, -4.9.

IR (thin film) ν_{max} 2952, 2929, 2856, 1720, 1365, 1258, 1226, 1187 cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{19}H_{36}O_4N_1{}^{28}Si_1$ $[M+H]^+$: 370.2408, found: 270.2408.



229

Diazo 229: *i*) A 6 mL flame-dried reaction tube was charged with methyl ketone **226** (8 mg, 0.022 mmol, 1 equiv.). The reaction vessel was evacuated and backfilled with nitrogen for three times and dry THF (0.5 mL) was added subsequentially. The reaction flask was cooled to –78 °C and freshly prepared LDA (0.133 M, 0.36 mL, 0.048 mmol, 2.2 equiv.) was added dropwise. The resulted solution was stirred at –78 °C for 15 mins and then warmed up to room temperature. This reaction mixture was allowed to stir for another 30 mins and then quenched by the addition of saturated aqueous $NaHCO_3$ solution (50 μL). The biphasic solution was diluted with 5 mL EtOAc and directly dried over Na_2SO_4. The collected

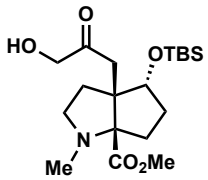
organic fraction was concentrated *in vacuo*. The crude product is highly polar as a zwitterion and could be used for the following diazo transfer reaction without further purification. *ii*) A 6 mL flame-dried reaction tube was charged with tricycle **228** (all from previous step) and *p*-ABSA (10 mg, 0.042 mmol, 1.9 equiv.). The reaction vessel was then evacuated and backfilled with nitrogen for three times. 2.0 mL of MeCM and 50µL of TEA was added to this reaction vessel. This resulted mixture was stirred overnight at room temperature. This resulted suspension was diluted with 10 mL EtOAc, extracted with aqueous $NaHCO_3$ solution (3 X 10 mL) and washed with 15 mL brine solution. The collected organic solution was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified preparative TLC (pure EtOAc) and give the diazo **229** as colorless oil (2.0 mg, 25% two steps).

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.83 (dd, *J* = 7.7, 6.7 Hz, 1H), 3.00 (ddd, *J* = 9.1, 7.9, 3.9 Hz, 1H), 2.69 – 2.60 (m, 2H), 2.50 (d, *J* = 16.4 Hz, 1H), 2.40 (s, 3H), 2.30 (ddd, *J* = 13.2, 8.1, 3.8 Hz, 1H), 2.14 (ddd, *J* = 13.7, 8.5, 4.8 Hz, 1H), 1.86 (dddd, *J* = 12.6, 7.7, 6.6, 4.8 Hz, 1H), 1.76 – 1.69 (m, 1H), 1.55 (td, *J* = 8.1, 4.3 Hz, 3H), 1.48 – 1.41 (m, 1H), 0.92 – 0.85 (m, 9H), 0.05 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 190.1, 189.0, 79.3, 75.8, 55.4, 54.1, 46.2, 35.4, 32.6, 31.8, 25.9, 25.9, 22.9, 18.1, -4.3, -4.8.

IR (thin film) ν_{max} 2954, 2884, 2881, 2791, 2138, 1679, 1648, 1472, 1305, 1284, 1258, 1131, 906, 731cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{18}H_{30}O_3N_3{}^{28}Si_1$ $[M+H]^+$: 364.2051, found: 364.2058.



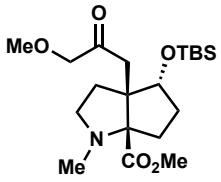
231

α-hydroxy ketone 231: A 6 mL flame-dried reaction tube was charged with methyl ketone **226** (20 mg, 0.057 mmol, 1equiv.). The reaction vessel was evacuated and backfilled with nitrogen for three times and dry THF (0.5 mL) was added subsequentially. The reaction flask was cooled to –78 °C and freshly prepared LDA (0.133 M, 0.5 mL, 0.067, 1.17equiv.) was added dropwise. After stirring for 30 mins, 90 mg of freshly prepared MoOPH (0.21 mmol, 3.6 equiv.) was added directly, and the reaction mixture was slowly warmed up to room temperature. After the reaction was completed as judged by TLC, this mixture was quenched by the addition of aqueous $NaHCO_3$ solution (0.5 mL). This biphasic solution was diluted with 5 mL EtOAc, extracted with aqueous $NaHCO_3$ solution (3 X 5 mL) and 5 mL brine solution. The collected organic fraction was dried over Na_2SO_4 and the residue was concentrated *in vacuo*. The crude mixture was purified by preparative TLC (4:1 Hex:EtOAc) and give the primary alcohol **231** (8.7 mg, 40% yield) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.23 – 4.05 (m, 3H), 3.63 (s, 3H), 2.87 (q, *J* = 7.6 Hz, 1H), 2.78 (d, *J* = 17.2 Hz, 1H), 2.71 (ddd, *J* = 8.7, 6.8, 4.6 Hz, 1H), 2.60 (d, *J* = 17.3 Hz, 1H), 2.33 (dt, *J* = 12.8, 7.2 Hz, 1H), 2.24 (s, 3H), 1.98 (ddd, *J* = 13.0, 10.7, 6.2 Hz, 1H), 1.85 (dtd, *J* = 11.8, 6.0, 3.7 Hz, 1H), 1.75 (ddd, *J* = 13.1, 6.4, 3.7 Hz, 1H), 1.70 – 1.61 (m, 1H), 1.39 – 1.30 (m, 1H), – 0.85 (m, 9H), 0.03 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 209.2, 174.1, 79.2, 68.7, 59.0, 53.6, 51.5, 44.9, 35.4, 32.8, 32.2, 29.9, 27.4, 25.9, 18.1, -4.1, -4.8.
IR (thin film) ν_{max} 2953, 2929, 2856, 1721, 1258, 1227, 1134, 1112, 1094 cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{19}H_{36}O_5N_1{}^{28}Si_1$ $[M+H]^+$: 386.2357, found: 386.2358.

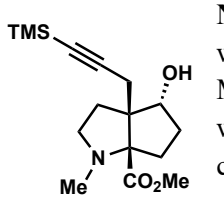


218

α-methoxy ketone 218: A 6 mL flame-dried reaction tube was charged with freshly prepared Ag_2O (15 mg, 0.065 mmol, 3.4 equiv.), and primary alcohol **231** (7 mg, 0.019 mmol, 1 equiv.). The reaction vessel was evacuated and backfilled with nitrogen for three times and dry MeI (1 mL) was added subsequentially. This mixture was allowed to stir for 6 hours at room temperature, and the suspension was filtered by a celite absorption column. The remaining solution was concentrated *in vacuo* (Caution: MeI is carcinogenic), and the crude mixture was then purified by a preparative TLC (4:1 Hex:EtOAc) to give the methoxy ketone **218** (2.5 mg, 33% yield) as a colorless oil.

^{1}H NMR (600 MHz, MeOD) δ 4.16 (dd, *J* = 7.8, 5.5 Hz, 1H), 3.97 (s, 2H), 3.64 (s, 3H), 3.37 (s, 3H), 2.89 (d, *J* = 18.4 Hz, 1H), 2.84 (s, 1H), 2.72 (s, 1H), 2.68 (d, *J* = 18.4 Hz, 1H), 2.35 (dt, *J* = 13.5, 7.2 Hz, 1H), 2.25 (s, 3H), 2.03 (ddd, *J* = 12.8, 9.8, 6.2 Hz, 1H), 1.88 (d, *J* = 5.7 Hz, 1H), 1.76 (s, 1H), 1.70 (d, *J* = 17.9 Hz, 1H), 1.29 (s, 1H), 0.90 (s, 9H), 0.06 (d, *J* = 1.0 Hz, 6H).
^{13}C NMR (151 MHz, MeOD) δ 210.0, 174.9, 78.7, 78.6, 59.9, 59.5, 54.4, 51.8, 49.8, 49.6, 45.8, 35.7, 33.7, 33.2, 28.5, 26.3, -4.2, -4.8.
IR (thin film) ν_{max} 2954, 2938, 2929, 2904, 2856, 1722, 1472, 1448, 1258, 1227, 1094, cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{20}H_{38}O_5N_1{}^{28}Si_1$ $[M+H]^+$: 400.2514, found: 400.2517.



232

Neopentyl alcohol 232: A 40 mL plastic reaction tube was charged with TBS silyl ether **215** (1g, 2.4 mmol, 1 equiv.) and 10 mL of MeCN. 1.0 mL of HF·pyr was then added slowly. The reaction vessel was heated to 70 °C and stirred for 1 hour. Once this reaction was completed as judged by TLC, this reaction mixture was cooled to room temperature and diluted with EtOAc. This formed mixture was then slowly poured into an ice mixture of $NaHCO_3$ solution (50 mL). This mixture was allowed to stir for 30 mins and then this biphasic mixture was diluted with 50 mL of EtOAc. The resulted mixture was then extracted with aqueous $NaHCO_3$ solution (50 mL), water (2 X 50 mL) and washed with brine solution (50 mL). The collected organic fraction was dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by a column chromatography (2:1 Hex:EtOAc) and give the desired product **232** (705 mg, 95% yield) as a light-yellow oil.

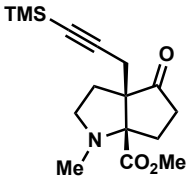
^{1}H NMR (600 MHz, $CDCl_3$) δ 4.08 – 4.03 (m, 1H), 3.70 (s, 3H), 3.00 (q, *J* = 8.1 Hz, 1H), 2.87 (td, *J* = 8.5, 4.0 Hz, 1H), 2.39 – 2.31 (m, 2H), 2.26 (s, 3H), 2.21 (d, *J* = 16.5

Hz, 1H), 2.13 – 2.02 (m, 2H), 1.84 – 1.73 (m, 2H), 1.69 (ddd, *J* = 12.6, 8.3, 4.0 Hz, 1H), 0.14 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 172.7, 104.3, 86.9, 80.9, 79.4, 60.1, 54.2, 51.5, 35.0, 31.9, 29.9, 27.5, 26.9, 0.1.

IR (thin film) ν_{max} 3424, 2957, 2900, 2841, 2790, 2173, 1726, 1447, 1311, 1251, 1215, 1174, 1085, 1041, 1002 cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{16}H_{28}O_4N_1{}^{28}Si_1$ $[M+H]^+$: 310.1833, found: 210.183.

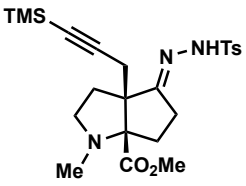


233

ketone 233: To a flame-dried 250 mL round bottom flask was added neopentyl alcohol **232** (500 mg, 1.62 mmol, 1 equiv.). The reaction vessel was evacuated and backfilled with nitrogen for three times, and 50 mL of DCM and 0.75 g of DMP (1.77 mmol, 1.1 equiv.) was added. This reaction was allowed to stir at 0 °C for about 1.5 hours. Once this reaction was completed as judged by TLC, this reaction was quenched by the addition of saturated $Na_2S_2O_3$ solution (50 mL) and $NaHCO_3$ solution (30 mL). The biphasic solution was then diluted by 100 mL EtOAc, extracted with water (3 X 100 mL) and washed with 100 mL brine solution. The collected organic fraction was dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by a column chromatography (5:1 Hex:EtOAc) and give the desired product **233** (382 mg, 77%) as a white wax.

^{1}H NMR (600 MHz, C6D6) δ 2.75 – 2.65 (m, 2H), 2.60 (dt, J = 13.7, 9.9 Hz, 1H), 2.55 (d, J = 17.1 Hz, 1H), 2.46 – 2.36 (m, 2H), 2.33 – 2.22 (m, 2H), 2.05 (s, 3H), 1.96 (ddd, J = 13.7, 9.2, 1.7 Hz, 1H), 1.66 (ddd, J = 13.2, 9.5, 4.0 Hz, 1H), 0.12 (s, 8H).
^{13}C NMR (151 MHz, C_6D_6) δ 217.3, 170.9, 102.8, 87.2, 77.8, 62.6, 52.4, 50.7, 34.6, 34.4, 33.0, 24.3, 24.0, -0.1.
IR (thin film) ν_{max} 2957, 2901, 2844, 2789, 2177, 1742, 1450, 1279, 1250, 1210, 843 cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{16}H_{26}O_3N_1{}^{28}Si_1$ $[M+H]^+$: 308.1676, found: 208.1682



234

Hydrazone 234: To a flame-dried 6 mL reaction tube was added ketone **233**(6 mg, 0.020 mmol, 1equiv.), PPTS (1 mg, 4.0 μmol, 20 mol%) and 7.5 mg of N_2H_3Ts (7.5 mg, 0.040 mmol, 2.0 equiv.). The reaction vessel was evacuated and backfilled with nitrogen and 1 mL of DCM was added. This reaction was allowed to stir overnight at 70 °C. This resulted mixture was then quenched by the addition of 1 mL $NaHCO_3$ solution. The biphasic solution was then diluted with 5 mL EtOAc, extracted with 5 mL water for three times and washed with 5 mL brine solution. The collected organic fraction was dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by a preparative TLC (4:1 Hex:EtOAc) and give the desired product **234** (5.8 mg, 68% yield) as a colorless oil.

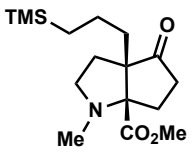
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.29 (dd, *J* = 8.6, 0.7 Hz, 2H), 7.00 (s, 1H), 3.71 (s, 3H), 2.76 (td, *J* = 8.7, 4.4 Hz, 1H), 2.70 (ddd, *J* = 10.1, 8.5, 5.5 Hz, 1H), 2.52 – 2.43 (m, 3H), 2.42 (s, 3H), 2.29 – 2.15 (m, 3H), 2.14 (s, 3H), 1.99 (ddd, *J* = 13.8, 8.6, 1.9 Hz, 1H), 1.88 (ddd, *J* = 12.7, 10.1, 4.4 Hz, 1H), 0.06 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 171.2, 169.5, 144.0, 135.8, 129.6, 128.0, 102.7, 86.6, 79.5, 60.8, 52.4, 51.3, 35.3, 34.7, 27.3, 26.5, 25.5, 21.8, -0.0.

IR (thin film) ν_{max} 3212, 2956, 2900, 2845, 2789, 2176, 1725, 1598, 1449, 1402, 1345, 1324, 1292, 1250, 1214, 1186, 1168, 1093, 1056 cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{23}H_{34}O_4N_3{}^{32}S_1{}^{28}Si_1$ $[M+H]^+$: 476.2034, found: 476.2038.

HRMS (ESI+) *m/z* calcd. for $C_{23}H_{33}O_4N_3{}^{23}Na_1{}^{32}S_1{}^{28}Si_1$ $[M+Na]^+$: 498.1853, found: 498.1856.

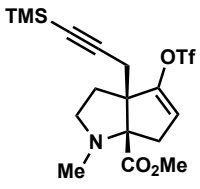


238

Silane 238: To a flame-dried 6 mL reaction tube was added ketone **233** (6 mg, 0.020 mmol, 1equiv.). The reaction vessel was evacuated and backfilled with nitrogen. Then 1 mL of DCM, 27 μL of TEA (0.20 mmol, 10 equiv.) and 24 mg of hydrazine (0.70 mmol, 37.5 equiv.) was subsequentially added. This mixture was allowed to stir overnight at 80 °C. This reaction was then quenched by the addition of aqueous $NaHCO_3$ solution (1 mL). The biphasic solution was then diluted with 10 mL EtOAc, extracted with water (3 X 10 mL) and washed with 15 mL brine solution. The collected organic fraction was dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by a preparative TLC (9:1 Hex:EtOAc) and give the reduced product **238** (5.2 mg, 86% yield) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.75 (s, 3H), 2.96 (td, *J* = 8.7, 4.6 Hz, 1H), 2.80 (ddd, *J* = 10.5, 8.5, 4.7 Hz, 1H), 2.46 – 2.25 (m, 4H), 2.22 (s, 3H), 2.09 – 2.01 (m, 1H), 1.81 (ddd, *J* = 12.6, 10.5, 4.7 Hz, 1H), 1.46 – 1.38 (m, 1H), 1.37 – 1.23 (m, 2H), 1.22 – 1.11 (m, 1H), 0.44 – 0.32 (m, 2H), -0.06 (s, 8H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 218.5, 172.5, 78.3, 64.7, 52.6, 51.3, 35.6, 34.6, 33.5, 30.7, 22.9, 18.9, 17.6, -1.5.
IR (thin film) ν_{max} 2951, 2895, 2848, 2791, 1729, 1449, 1407, 1275, 1247, 861cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{17}H_{25}O_5N_1{}^{28}Si_1$ $[M+H]^+$: 312.1989, found: 312.1987.



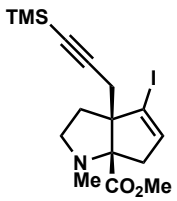
236

Vinyl triflate 236: A 250 mL flame-dried round bottom flask was charged with ketone intermediate **233** (144 mg, 0.47 mmol,1 equiv.). The reaction vessel was evacuated and backfilled with nitrogen for three times and dry THF (100 mL) was added subsequentially. The reaction flask was cooled to –78 °C and KHMDS (0.5 m, 3.76 mL, 1.88 mmol, 4 equiv.) was added dropwise. The resulted solution was stirred at –78 °C for 30 mins and then a 30 mL THF solution of $PhNTf_2$ (670 mg, 1.88 mmol, 4 equiv.) was added dropwise. This reaction mixture was

slowly warmed up to room temperature over 2 hours and then quenched by the addition of aqueous $NaHCO_3$ solution (50 mL). The biphasic solution was then extracted with 50 mL water for three times and then washed with 50 mL brine solution. The collected organic solution was dried over Na_2SO_4 and then concentrated *in vacuo*. The crude product was purified by a column chromatography (9:1 Hex:EtOAc with 3% TEA) and give the desired product **236** (196 mg, 95%) as a brownish chunk.

^{1}H NMR (600 MHz, C_6D_6) δ 5.48 (dd, *J* = 3.1, 2.2 Hz, 1H), 3.35 (s, 3H), 2.94 (dd, *J* = 16.6, 2.2 Hz, 1H), 2.75 (td, *J* = 8.5, 7.5 Hz, 1H), 2.65 – 2.58 (m, 2H), 2.42 (d, *J* = 17.3 Hz, 1H), 2.17 (dd, *J* = 16.6, 3.1 Hz, 1H), 2.05 (s, 3H), 1.95 (dt, *J* = 12.9, 7.8 Hz, 1H), 1.31 (ddd, *J* = 12.9, 8.3, 3.4 Hz, 1H), 0.15 (s, 9H).
^{13}C NMR (151 MHz, C_6D_6) δ 170.5, 149.2, 122.4, 120.2, 119.17 (q, *J* = 320.7 Hz), 118.1, 116.0, 112.3, 102.4, 87.2, 77.5, 62.2, 53.1, 51.0, 34.6, 34.1, 33.2, 25.7, -0.1.
^{19}F NMR (565 MHz, C_6D_6) δ -73.9.
IR (thin film) ν_{max} 2955, 2933, 2850, 2186, 2174, 2155, 1737, 1727, 1667, 1426, 1250, 1213, 1143, 1082, 1054, 1001 cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{17}H_{25}O_5N_1{}^2F_3{}^{32}S_1{}^{2828}Si_1$ $[M+H]^+$: 440.1169, found: 440.1169.



241

Vinyl iodide 214: *i*) To a flame-dried round bottom flask was added ketone **233** (20 mg, 0.067 mmol, 1 equiv.), 1.6 mg of $Sc(OTf)_3$ (0.0032 mmol, 5 mol%) and 3 mL of DCM. The reaction vessel was evacuated and backfilled with nitrogen, and 19 mg of freshly prepared $N_2H_2TBS_2$ (0.072 mmol, 1.1 equiv.) was added. This reaction was allowed to stir at 55 °C for a day. The resulted mixture was diluted with Hexane and quickly filtered by a celite pad. The remaining solvent of this filtrate was removed under reduced pressure, and the resulted crude was then subjected to reduced pressure and heated at 70 °C for 2 hour and give **240** as a colorless oil. This resulted residue could be used directly without further purification. *ii*) A flame-dried round bottom flask was evacuated and backfilled with nitrogen, and 2 mL of TMG and 163 mg of iodine (0.65 mmol, 10 equiv.) was added. This reaction was allowed to stir at room temperature for 20 mins. To this resulted mixture was added 0.4 mL of **240** (20 mg) THF solution. The reaction vessel was covered with aluminum foil and the mixture was allowed to stir for 3 hours at room temperature. The resulted mixture was then poured into 20 mL ice cooled solution of saturated $Na_2S_2O_3$ and 40 mL of EtOAc was added to this diphasic mixture. The biphasic solution was then extracted with 50 mL aqueous $NaHCO_3$ solution, 50 mL of water for twice and washed with 50 mL of brine solution. The collected organic fraction was dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by a column chromatography (4:1 Hex:EtOAc) and give the vinyl iodide **241** (15 mg, 60% for two steps) as an orange oil.

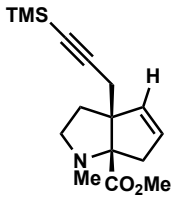
^{1}H NMR (600 MHz, $CDCl_3$) δ 6.08 (dd, *J* = 3.0, 2.1 Hz, 1H), 3.73 (d, *J* = 11.4 Hz, 3H), 3.02 – 2.96 (m, 2H), 2.95 – 2.89 (m, 1H), 2.57 (s, 2H), 2.44 (dd, *J* = 17.0, 3.0 Hz, 1H),

2.27 (s, 3H), 2.07 (dt, *J* = 12.9, 7.8 Hz, 1H), 1.62 (ddd, *J* = 12.5, 8.3, 3.7 Hz, 1H), 0.11 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 171.1, 137.3, 105.8, 102.9, 86.6, 68.2, 53.1, 51.6, 41.1, 35.6, 35.5, 27.6, 25.9, 0.0.

IR (thin film) ν_{max} 2953, 2927, 2854, 2178, 1724, 1447, 1431, 1276, 1249, 1233, 1195 cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{16}H_{25}O_2N_1{}^{127}I_1{}^{28}Si_1$ $[M+H]^+$: 418.0694, found: 418.0700.



246

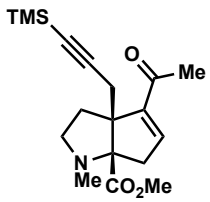
Olefin 246: A flame-dried round bottom flask was added 1 mg of vinyl iodide **241** (2.4 μmol, 1 equiv.). This vinyl iodide was azeotroped with toluene for three times. The reaction vessel was evacuated and backfilled with nitrogen, and 0.3 mL of THF was added. The resulted mixture was cooled to –78 ºC and 3.6 μL of *t*-BuLi (1.6 M, 5.8 μmol, 2.4 equiv.) was added quickly. This reaction was allowed to stir at same temperature for 20 mins and then quenched by the addition of 0.5 mL $NaHCO_3$ solution. The biphasic solution was then diluted by 2 mL EtOAc, extracted with 1 mL aqueous $NaHCO_3$ solution for three times and washed with 1 mL brine solution. The collected organic fraction was dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by a preparative TLC (4:1 Hex:EtOAc) and give the protonated olefin **246** (0.6 mg, 86%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.70 (dt, *J* = 5.8, 2.3 Hz, 1H), 5.60 (dt, *J* = 5.8, 2.1 Hz, 1H), 3.72 (s, 3H), 2.98 (ddd, *J* = 9.0, 8.0, 5.4 Hz, 1H), 2.92 (dt, *J* = 17.4, 2.3 Hz, 1H), 2.77 (ddd, *J* = 9.0, 7.3, 6.1 Hz, 1H), 2.51 (dt, *J* = 17.4, 2.2 Hz, 1H), 2.44 (d, *J* = 16.4 Hz, 1H), 2.37 (d, *J* = 16.3 Hz, 1H), 2.31 (s, 3H), 1.97 (ddd, *J* = 12.6, 7.3, 5.4 Hz, 1H), 1.89 (ddd, *J* = 12.6, 8.0, 6.1 Hz, 1H), 0.13 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.1, 135.7, 128.0, 104.2, 85.7, 79.6, 64.3, 53.0, 51.6, 37.6, 36.0, 35.7, 28.3, -0.0.

IR (thin film) ν_{max} 2953, 2926, 2856, 2177, 1726, 1457, 1250, 842 cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{16}H_{26}O_2N_1{}^{28}Si_1$ $[M+H]^+$: 292.1727, found: 292.1728.



253

Methyl ketone 253: To a flame-dried round bottom flask was added vinyl triflate **236** (200 mg, 0.46 mmol, 1 equiv.), freshly prepared vinyl tin species (308 μL, 0.91 mmol, 2 equiv.), LiCl (115 mg, 2.73 mmol, 6 equiv.), CuCl (225 mg, 2.28 mmol, 5 equiv.) and Pd $(PPh_3)_4$ (52 mg, 0.045 mmol, 10 mol%). The reaction vessel was evacuated and backfilled with nitrogen, and 5 mL of degassed DMSO was added. This resulted mixture was stirred at room temperature for 16 hour. After the reaction was completed, as judged by TLC, the organic solution was diluted with 20 mL EtOAc, washed with 50 mL water. The water phase was washed with EtOAc (3 X 20 mL), and the organic fraction was collected and

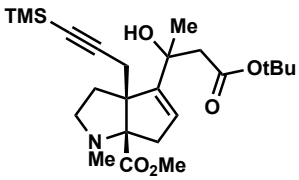
concentrated *in vacuo*. To this crude mixture was added 10 mL of THF and 2 mL of 1N HCl. After the reaction was completed as judged by TLC, this mixture was quenched by the addition of aqueous $NaHCO_3$ solution (30 mL). The biphasic mixture was then diluted by 50 mL EtOAc and extracted with 20 mL aqueous $NaHCO_3$ solution, 50 mL of water for twice and 50 mL brine solution. All collected organic solution was dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was then purified by column chromatography (Hex:EtOAc 3:1) and give methyl ketone **253** as a colorless oil

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.76 (t, *J* = 2.7 Hz, 1H), 3.75 (s, 3H), 3.26 – 3.17 (m, 1H), 3.01 (d, *J* = 17.3 Hz, 1H), 2.98 – 2.86 (m, 2H), 2.67 (d, *J* = 17.3 Hz, 1H), 2.62 – 2.53 (m, 1H), 2.33 (s, 3H), 2.28 (s, 4H), 1.84 (s, 1H), 0.09 (s, 8H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 196.0, 171.1, 147.0, 143.3, 104.3, 85.9, 80.7, 64.0, 53.7, 51.5, 39.4, 35.4, 35.3, 27.4, 26.5, 17.7, 13.7, 0.0.

IR (thin film) ν_{max} 2953, 2841, 2787, 2174, 1723, 1667, 1623, 1447, 1429, 1370, 1338, 1305, 1250, 1194, 1157, 1114 cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{18}H_{28}O_3N_1{}^{28}Si_1$ $[M+H]^+$: 334.1833, found: 334.1833.



252

Allylic alcohol 252: A 6 mL flame-dried reaction tube was charged with *t*-butyl acetate (8 uL, 0.060 mmol, 5 equiv.). The reaction vessel was evacuated and backfilled with nitrogen for three times and dry THF (1 mL) was added subsequentially. The reaction flask was cooled to –78 °C and LiHMDS (1 M Tol solution, 60 μL, 0.060 mmol, 5 equiv.) was added dropwise. The resulted solution was stirred at –78 °C for 30 mins and then a THF solution of methyl ketone **253** (4 mg, 0.012 mmol, 1 equiv. in 0.3 mL THF) was added subsequentially. This reaction mixture was stirred for another 30 mins and then quenched by the addition of aqueous solution of $NaHCO_3$ (1 mL). The biphasic solution was then extracted with 3 mL water for three times and washed with 5 mL brine solution. The collected organic solution was dried over Na_2SO_4 and then concentrated *in vacuo*. The crude product was purified by a column chromatography (4:1 Hex:EtOAc) and give the desired product **252** (4.6 mg, 85%) as a pair of diastereomer with a 4:1 d.r. .

(Major) ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.39 (t, *J* = 2.5 Hz, 1H), 4.17 (s, 1H), 3.72 (s, 3H), 3.19 (d, *J* = 17.4 Hz, 1H), 3.00 – 2.83 (m, 4H), 2.73 (d, *J* = 17.4 Hz, 1H), 2.46 (dt, *J* = 13.3, 8.2 Hz, 1H), 2.41 (d, *J* = 16.2 Hz, 1H), 2.33 (dd, *J* = 17.1, 2.8 Hz, 1H), 2.26 (s, 3H), 1.77 (ddd, *J* = 13.3, 7.9, 3.2 Hz, 1H), 1.51 (s, 1H), 1.48 (s, 9H), 0.10 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 172.9, 172.1, 151.0, 122.8, 106.0, 86.2, 81.9, 80.8, 72.5, 66.9, 53.6, 51.3, 48.9, 38.1, 36.9, 35.8, 31.3, 28.3, 27.2, 0.0.

IR (thin film) ν_{max} 3507, 2977, 2837, 2783, 2175, 1718, 1479, 1449, 1432, 1156, 843 cm^{-1}

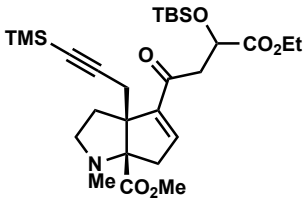
HRMS (ESI+) *m/z* calcd. for $C_{24}H_{40}O_5N_1{}^{28}Si_1$ $[M+H]^+$: 450.2670, found: 450.2673.

(Minor) ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.38 (t, *J* = 2.5 Hz, 1H), 4.10 (s, 1H), 3.75 (s, 3H), 3.10 (d, *J* = 17.3 Hz, 1H), 3.00 – 2.85 (m, 2H), 2.78 (td, *J* = 8.3, 3.1 Hz, 1H), 2.76 – 2.71 (m, 1H), 2.52 (d, *J* = 15.4 Hz, 1H), 2.45 – 2.36 (m, 1H), 2.30 (dd, *J* = 17.1, 2.8 Hz, 1H), 2.22 (s, 3H), 1.73 (ddd, *J* = 13.1, 7.7, 3.1 Hz, 1H), 1.48 (s, 1H), 1.45 (s, 9H), 0.08 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 172.7, 172.0, 149.9, 123.0, 105.7, 85.9, 81.8, 80.4, 72.8, 66.9, 53.4, 51.1, 48.9, 37.9, 36.8, 35.3, 31.8, 28.1, 27.3, -0.1.

IR (thin film) ν_{max} 3483, 2954, 2839, 2785, 2174, 1719, 1456, 1432, 1249, 1153, 842 cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{24}H_{40}O_5N_1{}^{28}Si_1$ $[M+H]^+$: 450.2670, found: 450.2670.



261

Enone 261A 6 mL flame-dried reaction tube was charged with methyl ketone **253**(5 mg, 0.015 mmol, 1 equiv.). The reaction vessel was evacuated and backfilled with nitrogen for three times and dry THF (0.3 mL) was added subsequentially. The reaction flask was cooled to –78 °C and freshly prepared LDA (0.133 M, 0.14 mL, 1.2 equiv.) was added dropwise. The resulted solution was stirred at –78 °C for 30 mins and then an ethyl glyoxalate (50 wt% toluene solution, 6 µL, 0.031 mmol, 2 equiv.) was added dropwise. This reaction mixture was allowed to stir for 30 mins at same temperature. TBSOTf (3.8 µL, 0.017 mmol, 1.1 equiv.) was then added to this mixture. After stirring for another 1 hour at –78 °C, this reaction was quenched by the addition of aqueous solution of $NaHCO_3$ (ca. 1 mL). The biphasic solution was then extracted with water (3 X 3 mL) and washed with 3 mL brine solution. The collected organic solution was dried over Na_2SO_4 and then concentrated *in vacuo*. The crude product was purified by a column chromatography (9:1 Hex:EtOAc) and give the desired product **261** (2.9 mg, 35% yield, d.r. 2.3:1) as a colorless oil

(Major) ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.78 (dd, *J* = 3.1, 2.3 Hz, 1H), 4.78 (dd, *J* = 7.8, 4.0 Hz, 1H), 4.24 – 4.12 (m, 2H), 3.74 (s, 3H), 3.23 – 3.15 (m, 2H), 3.05 – 2.97 (m, 2H), 2.96 – 2.83 (m, 2H), 2.70 (d, *J* = 17.3 Hz, 1H), 2.61 – 2.54 (m, 1H), 2.26 (s, 3H), 2.23 (dt, *J* = 13.4, 4.7 Hz, 1H), 1.84 (ddd, *J* = 13.4, 8.4, 2.9 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.87 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H), 0.07 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 194.3, 173.4, 171.1, 146.8, 143.4, 104.2, 86.0, 80.5, 68.3, 64.1, 61.2, 53.6, 51.5, 44.5, 39.6, 35.4, 35.2, 26.6, 25.9, 18.4, 14.3, 0.0, -4.8, -5.1.

IR (thin film) ν_{max} 2961, 2917, 2794, 1661, 1636, 1601, 1456, 1363, 1220, 1147 cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{28}H_{48}O_6N_1{}^{28}Si_1$ $[M+H]^+$: 550.3015, found: 550.3025.

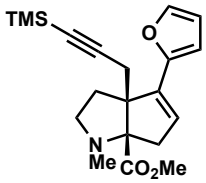
HRMS (ESI+) *m/z* calcd. for $C_{28}H_{47}O_6N_1{}^{23}Na_1{}^{28}Si_1$ $[M+Na]^+$: 572.2834, found: 572.2839.

(Minor) ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.79 (t, *J* = 2.7 Hz, 1H), 4.73 (dd, *J* = 7.8, 4.2 Hz, 1H), 4.19 (qd, *J* = 7.1, 2.9 Hz, 2H), 3.74 (s, 3H), 3.49 (d, *J* = 3.7 Hz, 1H), 3.22 – 3.13 (m, 2H), 2.98 (d, *J* = 17.3 Hz, 1H), 2.92 (q, *J* = 8.4 Hz, 1H), 2.84 (td, *J* = 8.6, 3.2 Hz, 1H), 2.68 (d, *J* = 17.3 Hz, 1H), 2.62 – 2.55 (m, 1H), 2.32 (s, 3H), 1.84 (ddd, *J* = 13.5, 8.4, 3.3 Hz, 1H), 1.28 (t, *J* = 7.2 Hz, 3H), 0.86 (s, 9H), 0.11 (s, 3H), 0.08 (s, 9H), 0.06 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 194.2, 173.3, 171.2, 146.6, 143.4, 104.3, 86.0, 80.5, 68.5, 64.2, 61.2, 53.6, 51.5, 44.4, 39.3, 35.4, 35.2, 26.5, 25.9, 18.3, 14.3, 0.0, -4.8, -5.1.

HRMS (ESI+) *m/z* calcd. for $C_{28}H_{48}O_6N_1{}^{28}Si_1$ $[M+H]^+$: 550.3015, found: 550.3024

HRMS (ESI+) *m/z* calcd. for $C_{28}H_{47}O_6N_1{}^{23}Na_1{}^{28}Si_1$ $[M+Na]^+$: 572.2834, found: 572.2838.

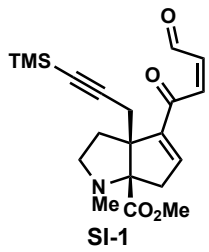


263

Vinyl furan 263: To a flame-dried round bottom flask was added vinyl triflate **236** (100 mg, 0.23 mmol, 1 equiv.), 2-(tributylstannyl)furan (95 mg, 0.28 mmol, 1.2 equiv.), LiCl (25 mg, 0.69 mmol, 3 equiv.) and $Pd(PPh_3)_4$ (25 mg, 0.023 mmol, 10 mol%). The reaction vessel was evacuated and backfilled with nitrogen, and 6 mL of degassed THF was added. This resulted mixture was stirred at 70 °C for 2 hours. The cloudy suspension was then filtered by a short silica column and the solvent of filtrate was removed under reduced pressure. The crude residue then dissolved in hexane and filtered through a glasswool pad to remove undissolved Tin residue. The filtrate was dried over Na_2SO_4 and concentrated *in vacuo* and the crude product was then purified by column chromatography (9:1 Hex:EtOAc with 3% TEA) and give furan compound **263** (78 mg, 95%) as a light-yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (d, *J* = 1.8 Hz, 1H), 6.35 (dd, *J* = 3.4, 1.8 Hz, 1H), 6.25 (d, *J* = 3.3 Hz, 1H), 6.06 (t, *J* = 2.8 Hz, 1H), 3.75 (s, 3H), 3.16 – 3.09 (m, 1H), 3.03 – 2.91 (m, 2H), 2.88 (d, *J* = 17.1 Hz, 1H), 2.83 (d, *J* = 17.1 Hz, 1H), 2.57 – 2.51 (m, 1H), 2.41 (dt, *J* = 12.7, 8.3 Hz, 1H), 2.31 (s, 3H), 1.89 (ddd, *J* = 12.8, 8.3, 3.0 Hz, 1H), 0.09 (s, 9H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 171.6, 150.7, 141.6, 136.6, 123.9, 110.9, 106.3, 104.0, 86.2, 81.0, 64.3, 53.8, 51.4, 38.8, 35.4, 35.1, 27.3, 0.0.
IR (thin film) ν_{max} 2950, 2923, 2849, 2785, 2176, 1721, 1447, 1429, 1306, 1247, 1217, 843cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{20}H_{28}O_3N_1{}^{28}Si_1$ $[M+H]^+$: 358.1833, found: 358.1834.

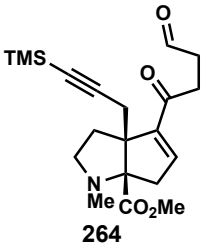


SI-1

Conjugated enal SI-1: To a flame-dried round bottom flask was added NBS (43 mg, 0.24 mmol, 1.1 equiv.) and sodium bicarbonate (37 mg, 0.44 mmol, 2.0equiv.). The reaction vessel was evacuated and backfilled with nitrogen. Then 77 mg vinyl furan **263** (0.22 mmol, 1.0 equiv.) was dissolved in 1 mL of 10:1 acetone/water solution and added to the reaction vessel. This resulted mixture was stirred at –15 °C for 1.5 hours. Then 1 mL of pyridine was added to this the vessel. This mixture was allowed to stir for another 1 hour at 0 °C. The pinkish solution was then diluted by 30 mL of EtOAc. This resulted solution was then extracted with 30 mL of aqueous $NaHCO_3$ solution, 30 mL of water for twice and washed with 50 mL of brine solution. The collected organic fraction was then dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was then purified by column chromatography (4:1 Hex:EtOAc → 2:1 Hex:EtOAc) and give the unsaturated aldehyde **SI-1** (52 mg, 63% yield) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.79 (d, *J* = 7.5 Hz, 1H), 7.44 (d, *J* = 15.7 Hz, 1H), 6.96 (dd, *J* = 3.1, 2.4 Hz, 1H), 6.85 (dd, *J* = 15.7, 7.5 Hz, 1H), 3.76 (s, 3H), 3.32 – 3.25 (m, 1H), 3.04 (d, *J* = 17.4 Hz, 1H), 2.96 (q, *J* = 8.5 Hz, 1H), 2.89 (td, *J* = 8.8, 3.0 Hz, 1H), 2.74 (d, *J* = 17.4 Hz, 1H), 2.71 – 2.65 (m, 1H), 2.32 (dt, *J* = 13.5, 8.3 Hz, 1H), 2.28 (s, 3H), 1.89 (ddd, *J* = 13.6, 8.5, 3.0 Hz, 1H), 0.08 (s, 9H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 192.9, 186.4, 170.8, 147.3, 146.2, 142.6, 137.7, 103.8, 86.4, 80.6, 64.3, 53.5, 51.6, 40.0, 35.2, 35.2, 26.4, 0.0.
IR (thin film) ν_{max} 2954, 2921, 2849, 2174, 1722, 1696, 1656, 1614, 1448, 1430, 1360, 1305, 1250 cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{20}H_{28}O_4N_1{}^{28}Si_1$ $[M+H]^+$: 374.1782, found: 374.1782.



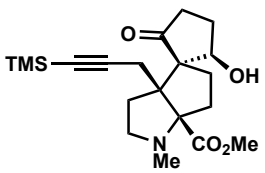
264

Aldehyde 264: To a flame-dried round bottom flask was added sodium iodide (8 mg, 0.053 mmol, 2 equiv.) and aldehyde **SI-1** (10 mg, 0.027 mmol, 1 equiv.). Then a solution of 0.45 uL of 12 M HCl (0.054 mmol H^+, 2 equiv.) in 0.45 mL of acetone was added to this reaction vessel. The resulted mixture was allowed to stir at 0 °C for 3 mins and then 1 mL of aqueous $NaHCO_3$ solution and 1 mL of saturated $Na_2S_2O_3$ solution was added to this mixture to quench the reaction. The resulted biphasic solution was diluted by 5 mL EtOAc, extracted with aqueous 3 mL water for twice and washed with 5 mL brine solution. The collected organic fraction was dried over Na_2SO_4 and concentrated *in vacuo* and purified by a preparative TLC (1:1 Hex:EtOAc) and 5.0 mg of reduced aldehyde **264** (50 % yield) was obtained as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.83 (s, 1H), 6.84 (t, *J* = 2.7 Hz, 1H), 3.74 (s, 3H), 3.24 – 3.17 (m, 1H), 3.12 – 2.98 (m, 2H), 2.96 (d, *J* = 17.3 Hz, 1H), 2.92 (t, *J* = 8.6 Hz, 1H), 2.86 (td, *J* = 8.7, 3.0 Hz, 1H), 2.83 – 2.70 (m, 2H), 2.67 (d, *J* = 17.3 Hz, 1H), 2.63 – 2.56 (m, 1H), 2.27 (s, 3H), 2.25 – 2.20 (m, 1H), 1.82 (ddd, *J* = 13.5, 8.4, 3.0 Hz, 1H), 0.08 (s, 12H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 200.9, 195.9, 171.3, 146.3, 143.1, 104.4, 86.3, 80.7, 64.4, 53.8, 51.7, 39.7, 37.9, 35.6, 35.4, 31.9, 26.7, 0.2.
IR (thin film) ν_{max} 2952, 2928, 2853, 1722, 1668, 1251, 1229, 1095, 1037 cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{20}H_{30}O_4N_1{}^{28}Si_1$ $[M+H]^+$: 376.1939, found: 376.1940.



266

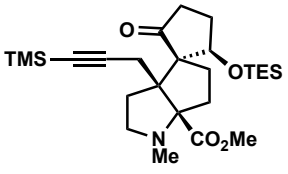
Spirocycle 266: To a flame-dried round bottom flask was added aldehyde **264** (16 mg, 0.043 mmol, 1 equiv.) and Stryker's reagent (16 mg, 8.2 μmol, 20 mol%). The reaction vessel was evacuated and backfilled with nitrogen, and 2.0 mL of DCM was added. This resulted mixture was stirred at room temperature for 8 hours. After the reaction was completed as judged by TLC, this mixture was quenched by the addition of aqueous $NaHCO_3$ solution (ca. 2 mL). This biphasic solution was diluted with 10 mL EtOAc, extracted with 3 mL water for three times and 5 mL brine solution. The collected organic fraction was dried over Na_2SO_4 and the residue was concentrated *in vacuo*. The crude mixture was purified by preparative TLC (1:1 Hex:EtOAc) and give the neopentyl alcohol compound **266** (9.9 mg, 65%) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.16 – 4.12 (m, 1H), 3.71 (s, 3H), 3.15 (ddd, *J* = 10.5, 8.8, 6.1 Hz, 1H), 2.95 – 2.85 (m, 2H), 2.63 – 2.53 (m, 1H), 2.53 – 2.43 (m, 1H), 2.42 – 2.34 (m, 2H), 2.28 (s, 3H), 2.27 – 2.15 (m, 2H), 2.11 – 1.98 (m, 3H), 1.95 (td, *J* = 13.1, 5.8 Hz, 1H), 1.61 – 1.52 (m, 1H), 0.14 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 217.0, 172.2, 107.8, 88.3, 84.3, 78.4, 67.8, 61.4, 53.9, 51.2, 35.3, 35.2, 35.1, 34.5, 30.1, 29.0, 25.6, -0.2.

IR (thin film) ν_{max} 3503, 2951, 2847, 2795, 2172, 1730, 1446, 1407, 1347, 1249, 1219, 1159, 1124, 1078 cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{20}H_{32}O_4N_1{}^{28}Si_1$ $[M+H]^+$: 378.2099, found: 378.2095.



267

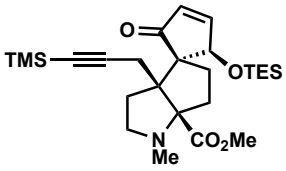
TES ether 267: A 6 mL flame-dried reaction tube was charged with neopentyl alcohol **265** (5 mg, 0.013 mmol, 1 equiv.). The reaction vessel was evacuated and backfilled with nitrogen for three times and dry DCM (0.5 mL) was added subsequentially. The reaction flask was cooled to –78 °C and TEA (10 μL, 0.065 mmol, 5.0 equiv.) and TESOTf (9.3 μL, 0.039 mmol, 3.0 equiv.) was added dropwise. After stirring for another 1 hour at –78 °C, this reaction was quenched by the addition of aqueous solution of $NaHCO_3$ (1 mL). The biphasic solution was then extracted with 1 mL water and washed with 1 mL brine solution. The collected organic solution was dried over Na_2SO_4 and then concentrated *in vacuo*. The crude product was purified by a preparative TLC (4:1 Hex:EtOAc) and give the desired product **267** (5.8 mg, 77%) as clean oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.36 (d, *J* = 3.2 Hz, 1H), 3.75 (s, 3H), 3.24 (ddd, *J* = 10.8, 8.3, 5.2 Hz, 1H), 2.82 (t, *J* = 7.7 Hz, 1H), 2.70 (d, *J* = 17.9 Hz, 1H), 2.63 (d, *J* = 17.8 Hz, 1H), 2.46 – 2.28 (m, 4H), 2.36 (s, 3H), 2.00 – 1.85 (m, 3H), 1.78 (td, *J* = 13.1, 5.8 Hz, 1H), 1.51 (dd, *J* = 13.1, 5.8 Hz, 1H), 1.41 (dd, *J* = 12.7, 6.1 Hz, 1H), 0.98 (t, *J* = 8.0 Hz, 9H), 0.66 (q, *J* = 8.0 Hz, 6H), 0.12 (d, *J* = 1.0 Hz, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 216.0, 173.1, 106.3, 84.8, 82.8, 79.6, 69.8, 59.3, 54.7, 50.7, 35.3, 35.1, 34.8, 30.7, 30.5, 29.4, 27.7, 7.1, 5.3, 0.2.

IR (thin film) ν_{max} 2954, 2908, 2880, 2177, 1735, 1259, 1247, 1162, 1082, 1070cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{26}H_{46}O_4N_1{}^{28}Si_2$ $[M+H]^+$: 492.2960, found: 492.2959.



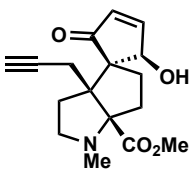
268

Enone 268: A 6 mL flame-dried reaction tube was charged with ketone **267** (7.5 mg, 0.015 mmol, 1 equiv.). The reaction vessel was evacuated and backfilled with nitrogen for three times and dry THF (1 mL) was added subsequentially. The reaction flask was cooled to –78 °C and freshly prepared LDA (0.133 M, 0.13 mL, 0,017 mmol, 1.1 equiv.) was added dropwise. The resulted solution was stirred at –78 °C for 30 mins and then HMPA (13.3 µL, 0.065 mmol, 5.0 equiv.) and Mukaiyama reagent (4.2 mg, 23 µmol, 1.5 equiv.) was added dropwise. This reaction mixture was allowed to stir for another 2 hours while slowly warm up to room temperature. This reaction was quenched by the addition of aqueous solution of $NaHCO_3$ (1 mL). The biphasic solution was then extracted with water (2 X 3 mL) and washed with 3 mL brine solution. The collected organic solution was dried over Na_2SO_4 and then concentrated *in vacuo*. The crude product was purified by a preparative TLC (4:1 Hex:EtOAc) and give the desired product **268** (6.2 mg, 83% yield) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 5.9, 3.0 Hz, 1H), 6.02 (d, *J* = 6.0 Hz, 1H), 4.64 (d, *J* = 3.0 Hz, 1H), 3.77 (s, 3H), 3.23 (ddd, *J* = 11.4, 8.4, 5.0 Hz, 1H), 2.84 (dd, *J* = 8.3, 7.1 Hz, 1H), 2.66 – 2.57 (m, 2H), 2.52 (td, *J* = 13.3, 6.1 Hz, 1H), 2.45 (dd, *J* = 12.4, 4.9 Hz, 1H), 2.36 (s, 3H), 2.03 – 1.96 (m, 1H), 1.89 (td, *J* = 11.9, 7.1 Hz, 1H), 1.52 – 1.43 (m, 2H), 0.98 (t, *J* = 7.9 Hz, 9H), 0.66 (qd, *J* = 7.9, 3.4 Hz, 6H), 0.12 (s, 9H).

HRMS (ESI+) *m/z* calcd. for $C_{26}H_{44}O_4N_1{}^{28}Si_2$ $[M+H]^+$: 490.2803, found: 490.2085.

IR (thin film) ν_{max} 2946, 2896, 2884, 1731, 1259, 1247, 1171, 1085, 1070, 1018 cm^{-1}



269

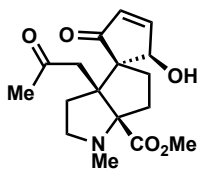
Enone 269: A 6 mL flame-dried reaction tube was charged with TES ether **269** (6 mg, 0.012 mmol, 1equiv.). The reaction vessel was evacuated and backfilled with nitrogen for three times and dry THF (0.5 mL) was added subsequentially. The reaction flask was cooled to 0 °C and 1 M TBAF in THF (0.012 mmol, 1 equiv.) was added subsequentially. After stirring for 15 mins at 0 °C, this reaction was quenched by the addition of aqueous solution of

$NaHCO_3$ (1 mL). The biphasic solution was then extracted with water (2 X 3 mL) and washed with 3 mL brine solution. The collected organic solution was dried over Na_2SO_4 and then concentrated *in vacuo*. The crude product was purified by a preparative TLC (2:1 Hex:EtOAc) and give the desired product **269** (3.1 mg, 81%) as a clean oil.

^{1}H NMR (600 MHz, C_6D_6) δ 7.49 (dd, *J* = 5.9, 2.8 Hz, 1H), 6.13 (dd, *J* = 5.9, 0.9 Hz, 1H), 4.54 (d, *J* = 3.0 Hz, 1H), 3.95 (brd, 1H), 3.75 (s, 3H), 3.11 (ddd, *J* = 11.1, 9.0, 5.6 Hz, 1H), 2.90 (t, *J* = 8.2 Hz, 1H), 2.71 – 2.65 (m, 1H), 2.59 – 2.50 (m, 2H), 2.31 (s, 3H), 2.30 (m, 1H), 2.21 – 2.13 (m, 1H), 2.10 – 2.03 (m, 1H), 2.01 (t, *J* = 2.7 Hz, 1H), 1.78 (ddd, *J* = 12.6, 6.5, 2.4 Hz, 1H), 1.61 – 1.54 (m, 1H).
^{13}C NMR (151 MHz, C_6D_6) δ 208.0, 172.1, 160.5, 132.9, 86.4, 83.9, 80.0, 71.8, 64.1, 61.5, 53.8, 51.3, 36.6, 35.3, 35.1, 30.5, 24.8.
IR (thin film) ν_{max} 2950, 2850, 1728, 1697, 1481, 1445, 1392, 1367, 1321, 1251, 1171, 1147, 1085, 1059, 1018 cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{17}H_{21}O_4N_1{}^{23}Na_1$ $[M+Na]^+$: 326.1363, found: 326.1368.

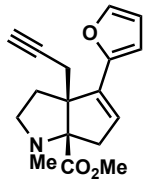
HRMS (ESI+) *m/z* calcd. for $C_{17}H_{22}O_4N_1$ $[M+H]^+$: 304.1543, found: 304.1544.



< 0.1 mg **270**

Methyl Ketone 270: A 6 mL flame-dried reaction tube was charged with 2 mg of alkyne **269** (6.6 µmol, 1 equiv.) and 0.8 mg HgO (3.7 µmol, 60 mol%). The reaction vessel was evacuated and backfilled with nitrogen for three times. To this reaction vassal was added 0.3 mL of MeOH and 17 µL of 1M H_2SO_4 solution (34 µmol H^+, 5.2 equiv.). This mixture was allowed to stir for 2 hours at 60 ºC and then quenched by the addition of 0.1 mL $NaHCO_3$ solution. The biphasic solution was then diluted by 2 mL EtOAc, extracted with 1 mL aqueous $NaHCO_3$ solution for three times and washed with 1 mL brine solution. The collected organic fraction was dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by a preparative TLC (4:1 Hex:EtOAc) and give the protonated olefin **270** (< 0.1 mg). Due to the low yield of this reaction, no C NMR was obtained.

^{1}H NMR (600 MHz, C_6D_6) δ 7.54 (d, *J* = 5.8 Hz, 1H), 6.01 (d, *J* = 5.9 Hz, 1H), 4.59 (s, 1H), 3.79 (s, 3H), 3.49 (d, *J* = 4.6 Hz, 2H), 3.31 – 3.25 (m, 1H), 3.15 (q, *J* = 8.7 Hz, 1H), 2.95 (d, *J* = 8.6 Hz, 1H), 2.72 – 2.63 (m, 2H), 2.54 – 2.46 (m, 1H), 2.30 (s, 3H), 2.17 (s, 1H), 2.05 (s, 3H), 2.00 (d, *J* = 6.9 Hz, 1H), 1.73 (dd, *J* = 13.8, 7.1 Hz, 1H).
HRMS (ESI+) *m/z* calcd. for $C_{17}H_{22}O_4N_1$ $[M+H]^+$: 322.1649, found: 322.1645.



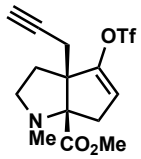
274

Furan 274: A 6 mL flame-dried reaction tube was charged with TMS alkyne **263** (15 mg, 0.042 mmol, 1 equiv.). The reaction vessel was evacuated and backfilled with nitrogen for three times and dry THF (1 mL) was added subsequentially. The reaction flask was cooled to 0 ºC and 1 M TBAF (46µL, 0.046 mmol, 1.1 equiv.) in THF was added subsequentially. After stirring for 15 mins at 0 ºC, this reaction was quenched by the addition of aqueous solution of $NaHCO_3$ (1 mL). The

biphasic solution was then extracted with water (2 X 3 mL) and washed with 3 mL brine solution. The collected organic solution was dried over Na_2SO_4 and then concentrated *in vacuo*. The crude product was purified by a preparative TLC (9:1 Hex:EtOAc) and give the desired product **274** (9.7 mg, 82%) as clean oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (d, *J* = 1.8 Hz, 1H), 6.36 (dd, *J* = 3.4, 1.8 Hz, 1H), 6.27 (dt, *J* = 3.4, 0.6 Hz, 1H), 6.09 (t, *J* = 2.8 Hz, 1H), 3.77 (s, 3H), 3.17 – 3.11 (m, 1H), 3.05 – 2.98 (m, 1H), 2.91 (ddd, *J* = 8.9, 8.1, 3.8 Hz, 1H), 2.89 – 2.78 (m, 2H), 2.61 – 2.54 (m, 1H), 2.40 (dt, *J* = 12.7, 7.8 Hz, 1H), 2.33 (s, 3H), 1.93 (ddd, *J* = 12.4, 8.3, 3.7 Hz, 1H), 1.83 (t, *J* = 2.7 Hz, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 172.1, 150.5, 141.7, 136.3, 124.3, 111.0, 106.3, 81.1, 80.9, 69.8, 64.2, 53.7, 51.5, 38.3, 35.5, 35.1, 25.8.
IR (thin film) ν_{max} 3303, 2923, 2852,1720, 1663, 1599, 1429, 1241, 1156, 1042 cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{17}H_{20}O_3N_1$ $[M+H]^+$: 286.1438, found: 286.1435.



276

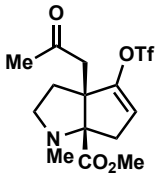
Alkyne 276: A 20 mL flame-dried reaction tube was charged with TMS alkyne **237** (100 mg, 0.227 mmol, 1 equiv.). The reaction vessel was evacuated and backfilled with nitrogen for three times and dry THF (3 mL) was added subsequentially. The reaction flask was cooled to 0 °C and 1 M TBAF in THF (0.23 mL, 0.23 mmol, 1.1 equiv.) was added subsequentially. After stirring for 15 mins at 0 °C, this reaction was quenched by the addition of aqueous solution of $NaHCO_3$ (30 mL). The biphasic solution was then extracted with water (2 X 30 mL) and washed with 30 mL brine solution. The collected organic solution was dried over Na_2SO_4 and then concentrated *in vacuo*. The crude product was purified by a column chromatography (9:1 Hex:EtOAc) and give the desired product **276** (68 mg, 82% yield) as a clean oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.68 (t, *J* = 2.7 Hz, 1H), 3.77 (s, 3H), 3.02 – 2.92 (m, 2H), 2.89 (ddd, *J* = 9.0, 7.7, 4.8 Hz, 1H), 2.66 (dd, *J* = 17.1, 2.7 Hz, 1H), 2.54 (dd, *J* = 17.1, 2.7 Hz, 1H), 2.45 (dd, *J* = 16.9, 3.1 Hz, 1H), 2.30 (s, 3H), 2.13 (ddd, *J* = 12.9, 7.7, 6.4 Hz, 1H), 1.92 (t, *J* = 2.7 Hz, 1H), 1.76 (ddd, *J* = 12.9, 8.1, 4.7 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 171.3, 148.3, 121.8, 119.7, 117.5, 115.4, 112.7, 79.1, 77.3, 70.8, 61.8, 53.0, 51.9, 35.0, 33.2, 33.2, 24.2.

IR (thin film) ν_{max} 3307, 2921, 2849, 2791, 1725, 1666, 1423, 1300, 1213, 1142, 1102, 1052, 1020 cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{14}H_{17}O_5N_1F_3{}^{23}S_1$ $[M+H]^+$: 368.0774, found: 368.0779.

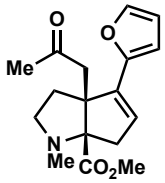


277

Methyl ketone 277: A 20 mL flame-dried round bottom flask was charged with $AuSPhosNTf_2$ (10 mg, 0.011 mmol, 5 mol%) and alkyne **276** (84 mg, 0.228 mmol, 1 equiv.), then it was evacuated and backfilled with nitrogen for three times.0.3 mL of MeOH and 17 uL of water (0.94 mmol, 4 equiv.) was then added to this reaction vessel. This resulted mixture was stirred overnight at 100 °C. The resulted solution was concentrated *in vacuo* and the resulted residue was purified by column chromatography (2:1 Hex:EtOAc) to give desired methyl ketone **277** (75 mg, 86% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.59 (dd, *J* = 3.1, 2.3 Hz, 1H), 3.66 (s, 3H), 3.20 (dd, *J* = 16.8, 2.3 Hz, 1H), 3.16 (d, *J* = 0.7 Hz, 1H), 2.98 (td, *J* = 18.5, 1.5 Hz, 1H), 2.89 (dt, *J* = 9.2, 7.3 Hz, 1H), 2.81 (ddd, *J* = 9.1, 7.3, 4.3 Hz, 1H), 2.48 (dd, *J* = 16.8, 3.1 Hz, 1H), 2.30 (s, 3H), 2.11 (dt, *J* = 12.7, 7.3 Hz, 1H), 2.06 (s, 3H), 1.72 (ddd, *J* = 12.7, 7.4, 4.3 Hz, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 206.2, 171.3, 148.1, 113.9, 76.6, 59.2, 52.3, 51.5, 47.4, 35.3, 35.0, 33.5, 30.4. (Triflate carbon not shown)
IR (thin film) ν_{max} 2949, 2849, 2792, 1724, 1667, 1421, 1366, 1302, 1246, 1211, 1142, 1102, 1052 cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{14}H_{19}O_6N_1F_3{}^{23}S_1$ $[M+H]^+$: 386.0880, found: 386.0883.

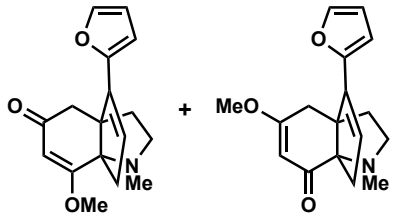


278

Methyl ketone 280: To a flame-dried round bottom flask was added vinyl triflate **277** (20 mg, 0.052 mmol, 1 equiv.), 2-(tributylstannyl)furan (22 mg, 0.062 mmol, 1.2 equiv.), LiCl (6 mg, 0.16 mmol, 3 equiv.) and $Pd(PPh_3)_4$ (6 mg, 5.2 µmol, 10 mol%). The reaction vessel was evacuated and backfilled with nitrogen, and 1 mL of degassed THF was added. This resulted mixture was stirred at 70 °C for 2 hours. The cloudy suspension was then filtered by a short silica column and the solvent of filtrate was removed under reduced pressure. The crude residue then dissolved in hexane and filtered by glasswool to remove undissolved Tin residue. The filtrate was dried over Na_2SO_4 and concentrated *in vacuo* and the crude product was then purified by column chromatography (2:1 Hex:EtOAc with 3% TEA) and give furan compound **278** (9.7 mg, 62% yield) as a light-yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (d, *J* = 1.8 Hz, 1H), 6.36 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.29 (d, *J* = 3.4 Hz, 1H), 5.98 (t, *J* = 2.8 Hz, 1H), 3.69 (s, 3H), 3.34 (d, *J* = 16.4 Hz, 1H), 3.21 – 3.14 (m, 2H), 2.98 – 2.88 (m, 1H), 2.86 (ddd, *J* = 9.0, 7.9, 3.1 Hz, 1H), 2.58 – 2.51 (m, 1H), 2.36 (dt, *J* = 12.6, 8.1 Hz, 1H), 2.31 (s, 3H), 1.94 – 1.90 (m, 2H), 1.89 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 208.1, 171.9, 150.8, 141.7, 136.2, 124.4, 111.0, 106.4, 80.1, 62.4, 52.9, 51.1, 48.7, 38.5, 36.7, 35.8, 31.4.
IR (thin film) ν_{max} 2947, 2845, 1721, 1447, 1430, 1244, 1222, 1196, 1182, 1154 cm^{-1}

HRMS (ESI+) *m/z* calcd. for $C_{17}H_{22}O_4N_1$ $[M+H]^+$: 304.1543 , found: 303.1544.



273 281

Methyl Vinylogous ester 273, 281: *i*) A 6 mL flame-dried reaction tube was charged with methyl ketone **288** (10 mg, 0.033 mmol, 1 equiv.). The reaction vessel was evacuated and backfilled with nitrogen for three times and dry THF (1 mL) was added subsequentially. The reaction flask was cooled to –78 ºC and freshly prepared LDA (0.133 m, 0.55 mL, 0.073 mmol, 2.2 equiv.) was added dropwise. The resulted solution was stirred at –78 ºC for 15 mins and then warmed up to room temperature. This reaction mixture was allowed to stir for another 30 mins and then quenched by the addition of saturated aqueous $NaHCO_3$ solution (50µL). The biphasic solution was diluted with 5 mL EtOAc and directly dried over Na_2SO_4. The collected organic fraction was concentrated *in vacuo*. The crude product is highly polar as a zwitterion and could be used for the following methylation reaction without further purification. *ii*) A 6 mL flame-dried reaction tube was charged with vinylogous ester **280** (10 mg, 0.037 mmol, 1 equiv.). The reaction vessel was evacuated and backfilled with nitrogen for three times and a mixed solvent of MeOH:MeCN (0.4 mL: 1.6 mL) was added subsequentially. DIPEA (10 µL, 0.057 mmol, 1.5 qduiv) and $TMSCHN_2$ (2 M hexane solution, 28 µL, 2 equiv.) was then added. The $TMSCHN_2$ solution (3 * 2 M hexane solution, 28 µL, 2 equiv.) was added into this reaction twice a day and the resulted solution was allowed to stir for 2 days. After most of the vinylogous ester **280** was consumed, as judged by TLC, the reaction was quenched by the addition of aqueous $NaHCO_3$ solution (1 mL). The biphasic solution was diluted by 3 mL EtOAc and extracted with 3 mL water for twice and washed with 3 mL brine solution. The collected organic solution was dried over Na_2SO_4 and then concentrated *in vacuo*. The crude residue was then purified by preparative TLC (pure EtOAc) to two methylated regioisomers as clean oil.

(**273**: 3.2 mg, 33% yield) ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 (d, *J* = 1.8 Hz, 1H), 6.38 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.29 (d, *J* = 3.4 Hz, 1H), 5.98 (t, *J* = 2.8 Hz, 1H), 5.38 (s, 1H), 3.73 (s, 3H), 3.06 – 2.99 (m, 2H), 2.73 (ddd, *J* = 9.0, 7.1, 5.0 Hz, 1H), 2.65 (dt, *J* = 9.0, 6.9 Hz, 1H), 2.62 – 2.56 (m, 1H), 2.51 (s, 3H), 2.48 (d, *J* = 15.8 Hz, 1H), 2.38 (ddd, *J* = 12.1, 6.6, 5.0 Hz, 1H), 1.83 (dt, *J* = 12.6, 7.1 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 198.0, 176.7, 149.9, 142.1, 138.6, 122.0, 111.2, 106.9, 100.7, 72.0, 59.9, 55.8, 53.9, 53.6, 46.6, 37.6, 36.4, 34.1.

HRMS (ESI+) *m/z* calcd. for $C_{17}H_{20}O_3N_1$ $[M+H]^+$: 286.1438, found: 286.1436.

IR (thin film) ν_{max} 2954, 2930, 2900, 2788, 2175, 1755, 1726, 1668, 1622, 1464, 1447, 1431, 1374, 1250, 1191, 841 cm^{-1}

(**281**: 1.7mg, 18% yield) ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (d, *J* = 1.8 Hz, 1H), 6.39 (dd, *J* = 3.4, 1.8 Hz, 1H), 6.30 (d, *J* = 3.4 Hz, 1H), 6.02 (t, *J* = 2.7 Hz, 1H), 5.45 (d, *J* = 1.7 Hz, 1H), 3.73 (s, 3H), 2.93 – 2.86 (m, 2H), 2.74 (ddd, *J* = 9.0, 7.2, 4.7 Hz, 1H), 2.67 (dt, *J* = 8.9, 6.9 Hz, 1H), 2.63 – 2.52 (m, 2H), 2.48 (s, 3H), 2.43 (ddd, *J* = 11.8, 6.6, 4.7 Hz, 1H), 1.89 (dt, *J* = 12.5, 7.2 Hz, 1H).

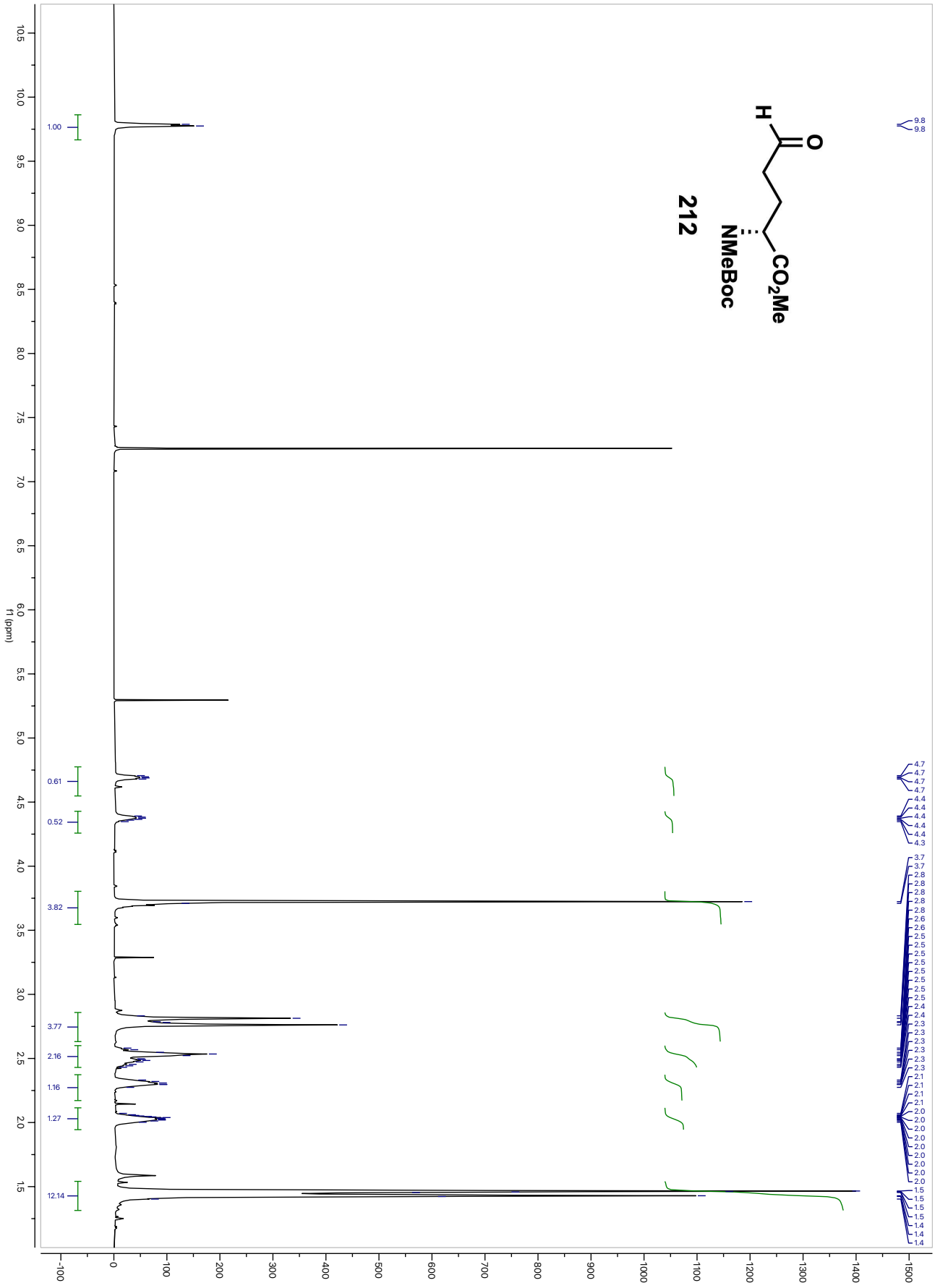
^{13}C NMR (151 MHz, $CDCl_3$) δ 197.2, 174.1, 150.2, 141.8, 137.8, 123.7, 111.0, 106.4, 101.5, 75.3, 58.5, 56.0, 53.8, 53.4, 38.2, 35.8, 34.0.

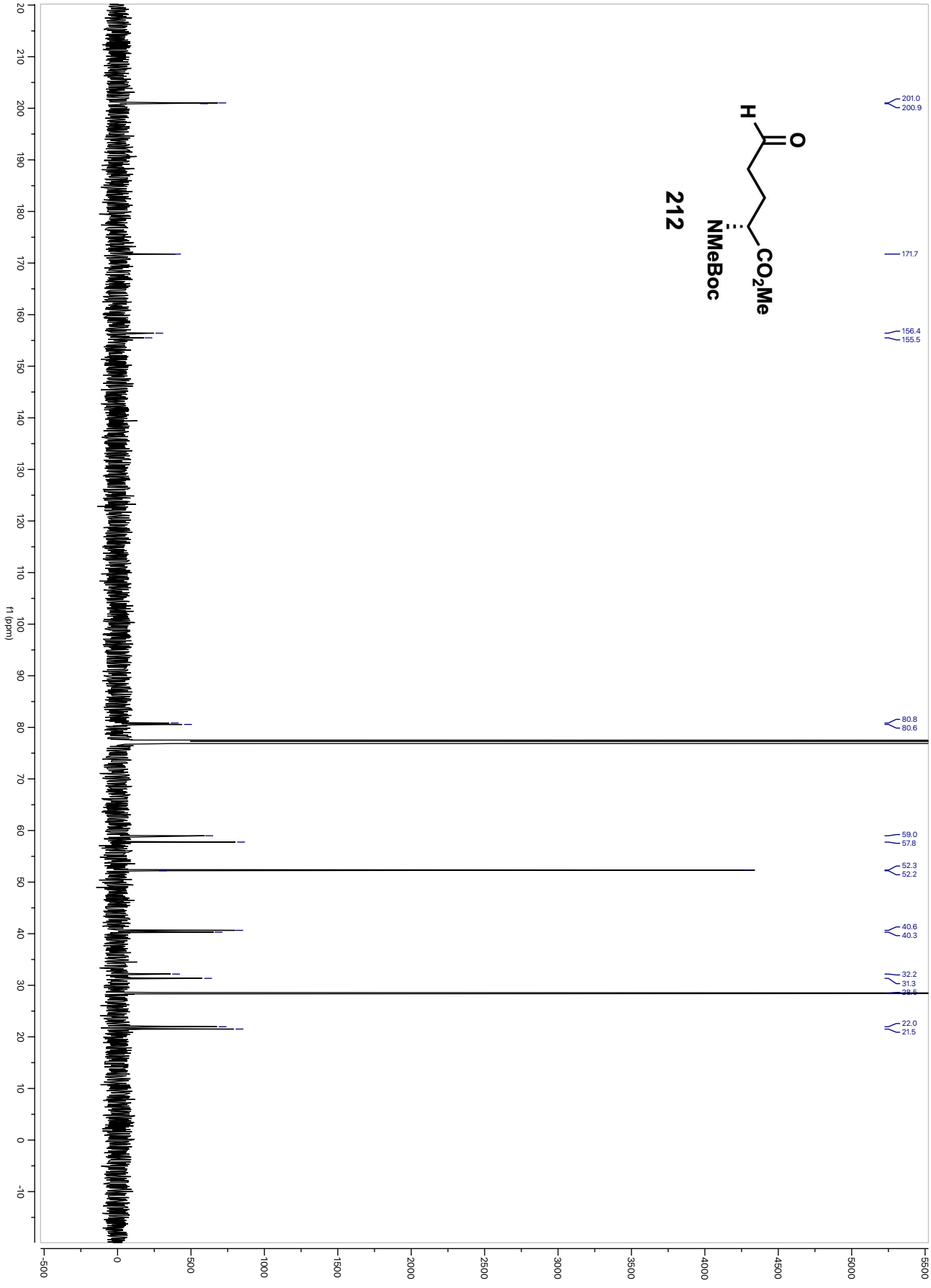
IR (thin film) ν_{max} 2954, 2929, 2856, 2176, 1754, 1727, 1669, 1464, 1447, 1432, 1251, 841 cm^{-1}

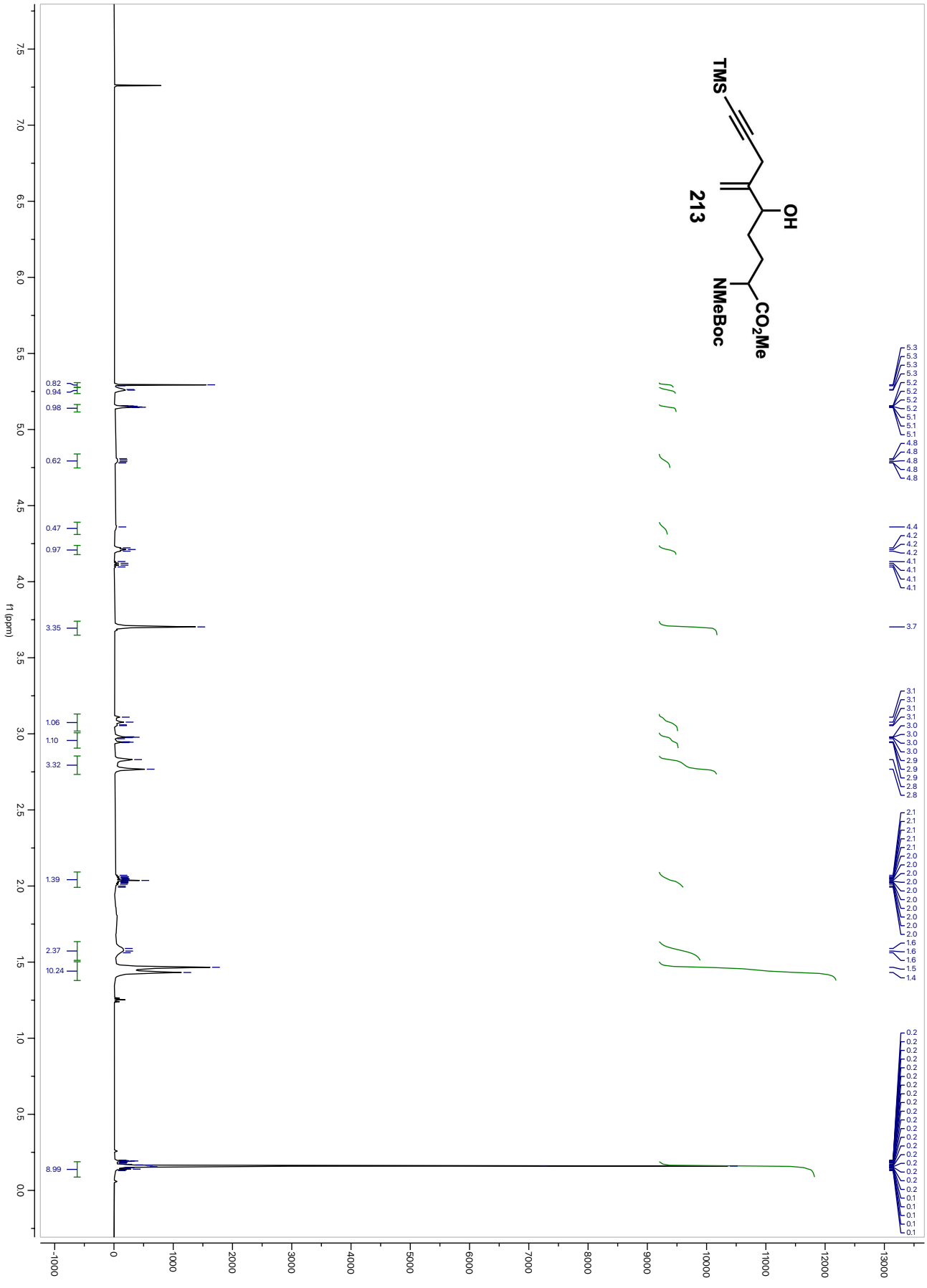
HRMS (ESI+) *m/z* calcd. for $C_{17}H_{20}O_3N_1$ $[M+H]^+$: 286.1438, found: 286.1437.

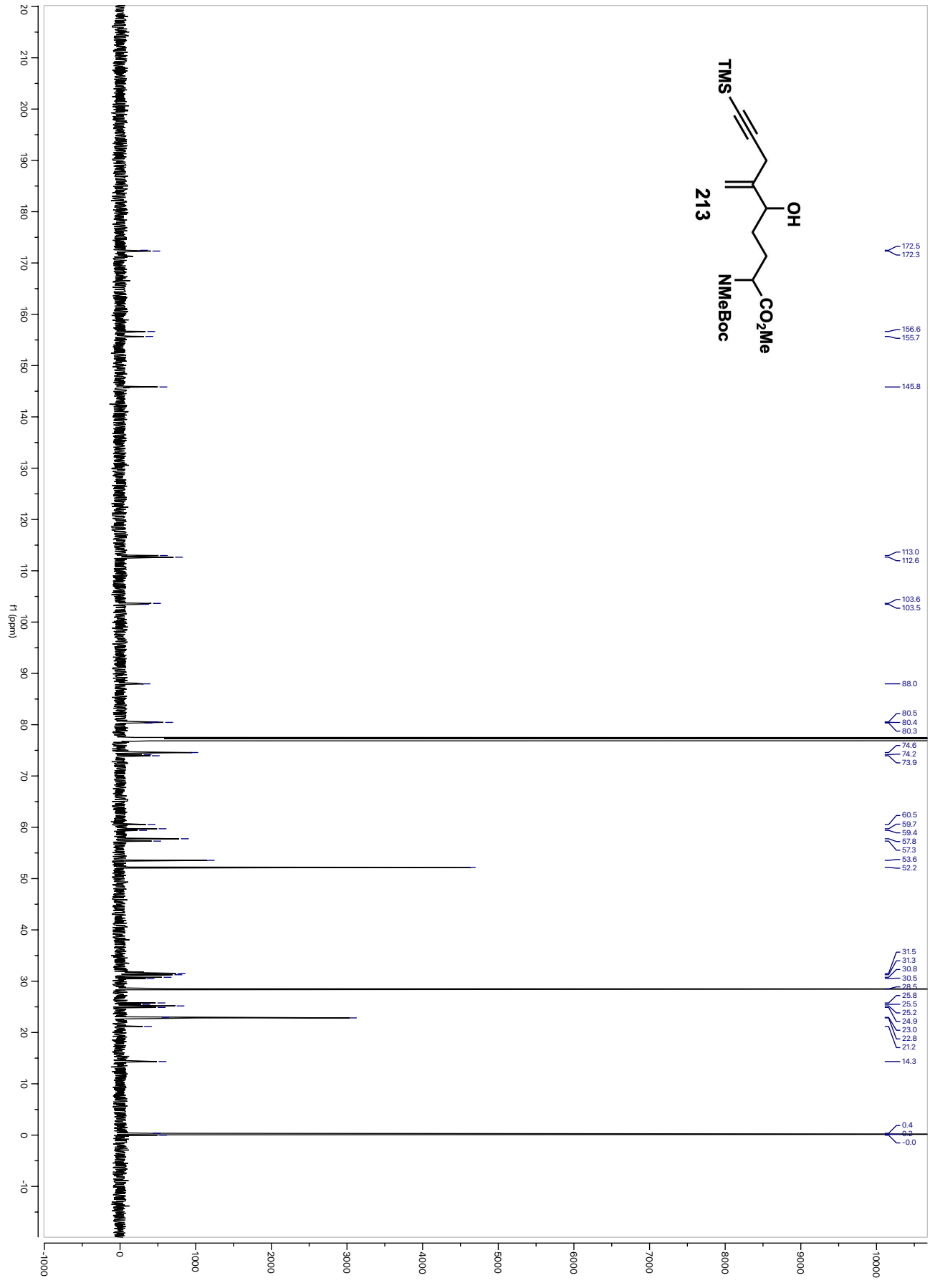
Appendix II:

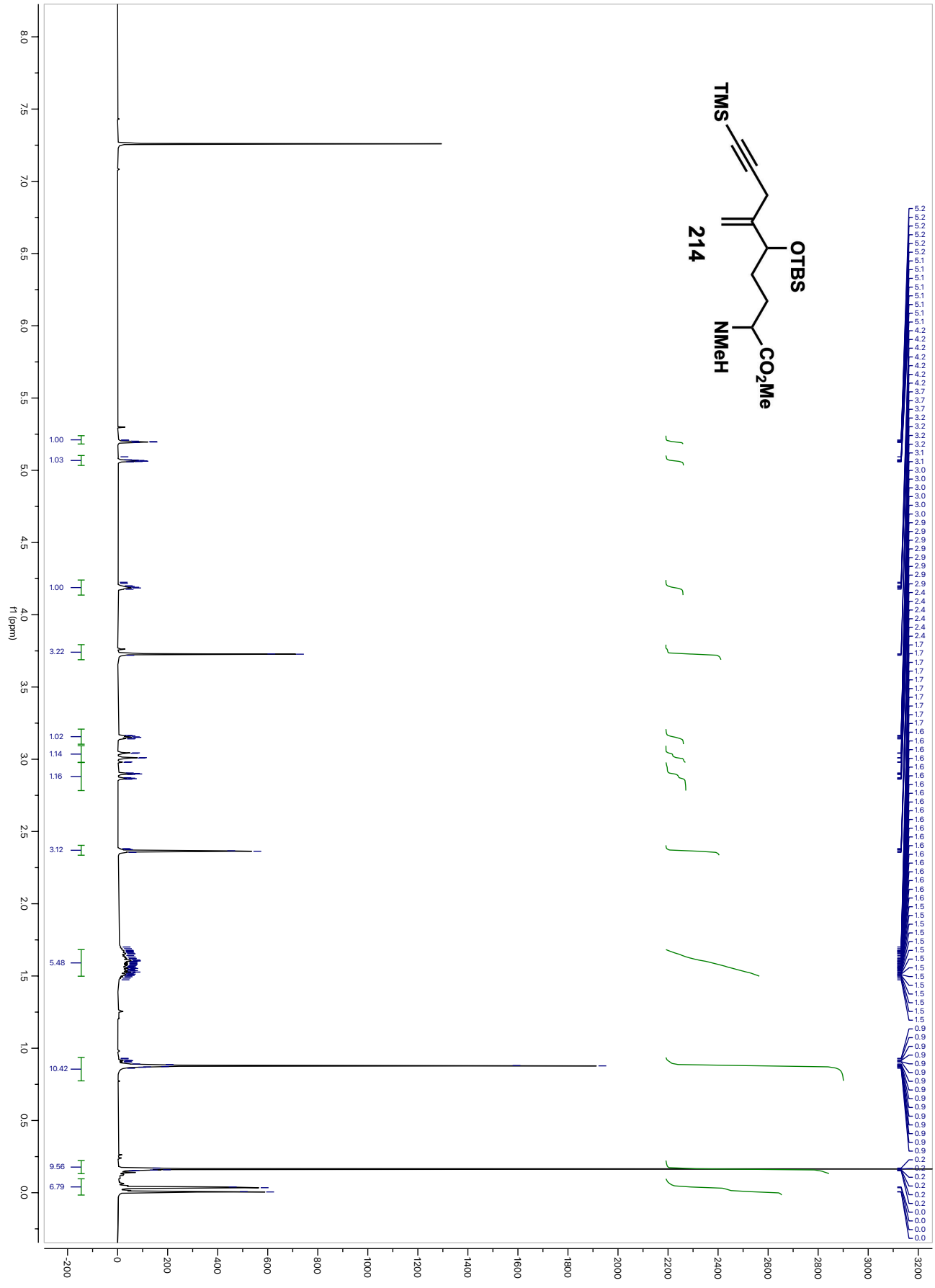
NMR Spectra for Chapter 2

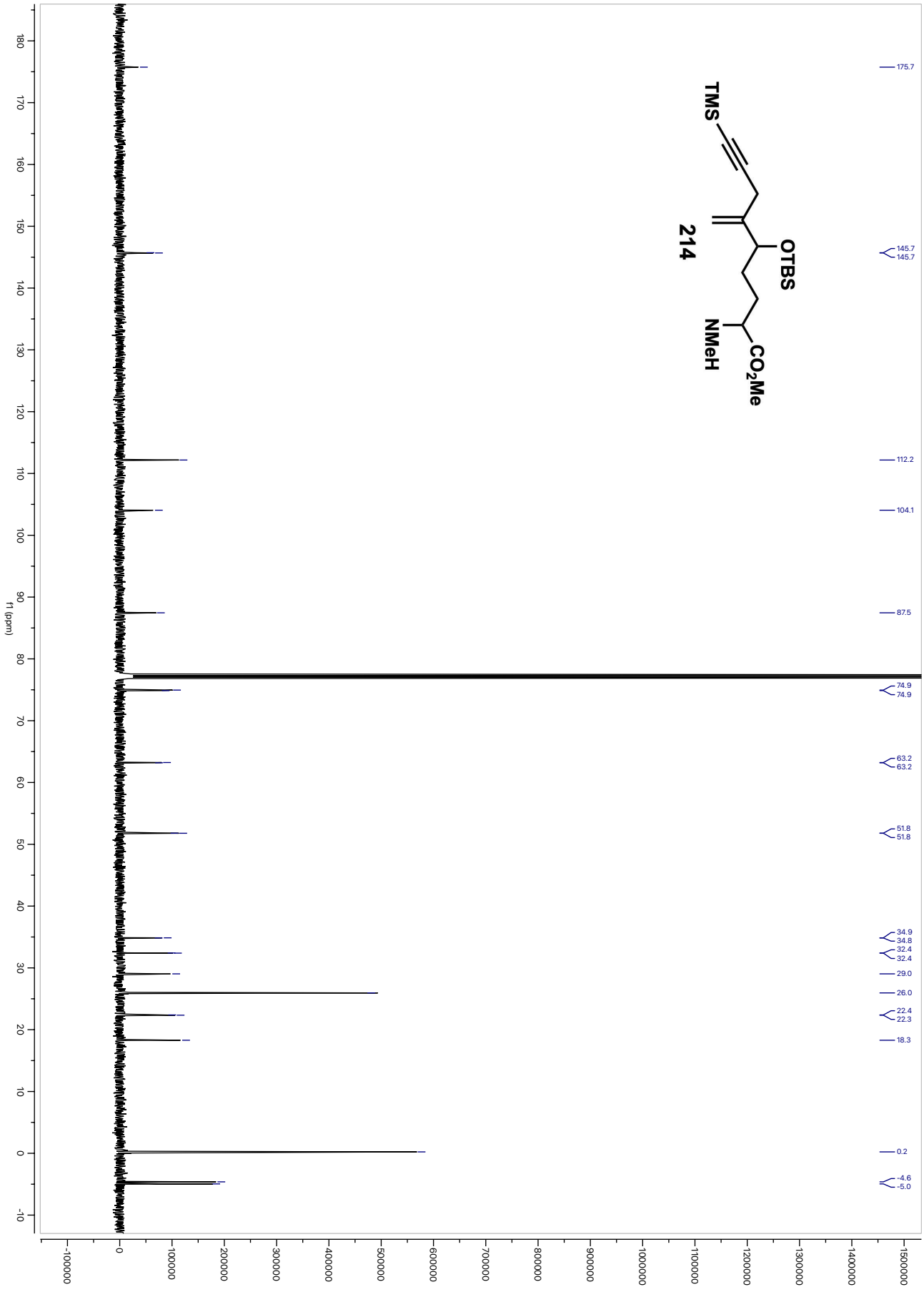

212
NMeBoc
CO2Me
f1 (ppm)

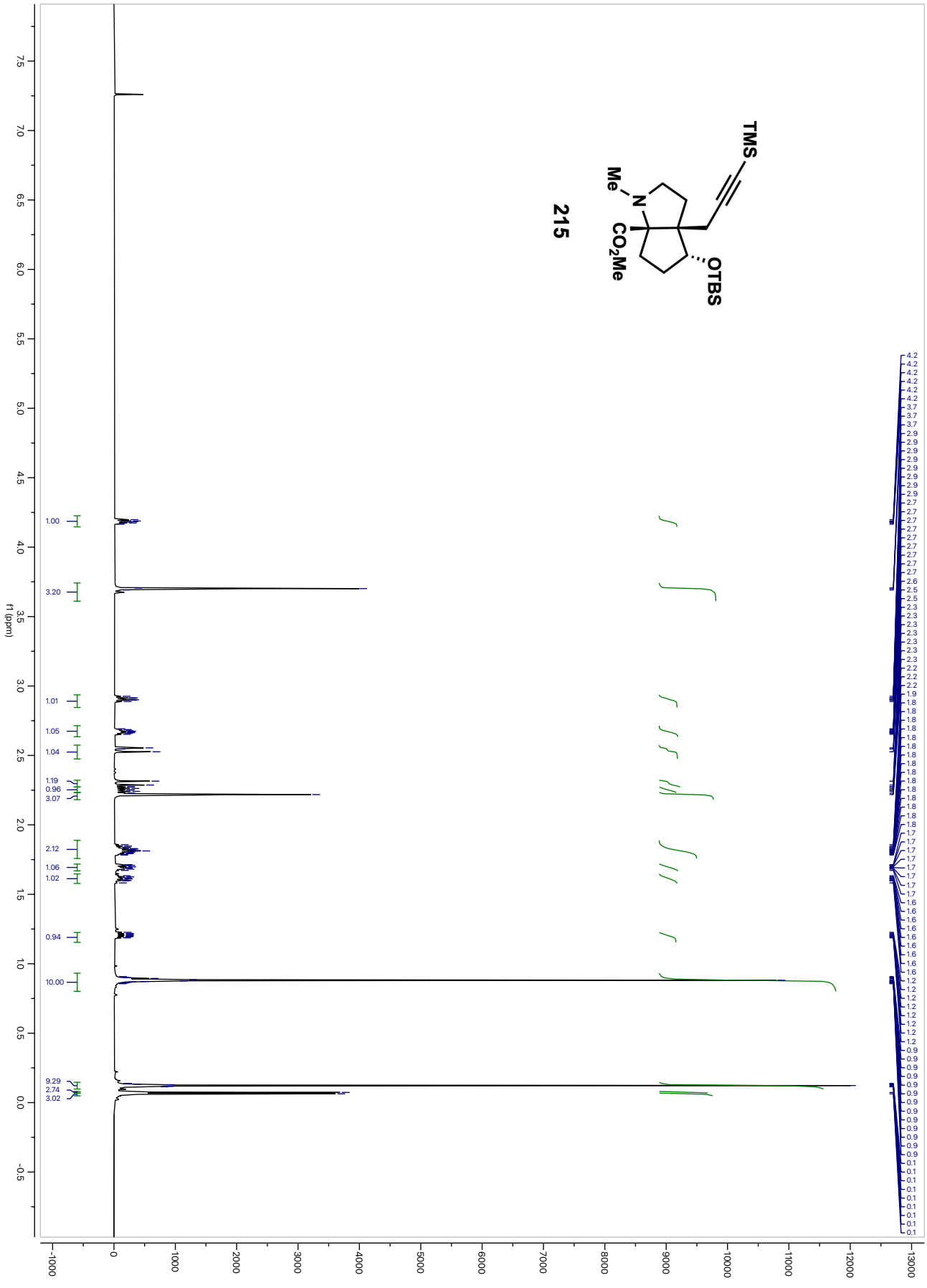

212
NMeBoc
CO2Me
201.0
200.9
171.7
156.4
155.5
80.8
80.6
59.0
57.8
52.3
52.2
40.6
40.3
32.2
31.3
22.0
21.5
f1 (ppm)

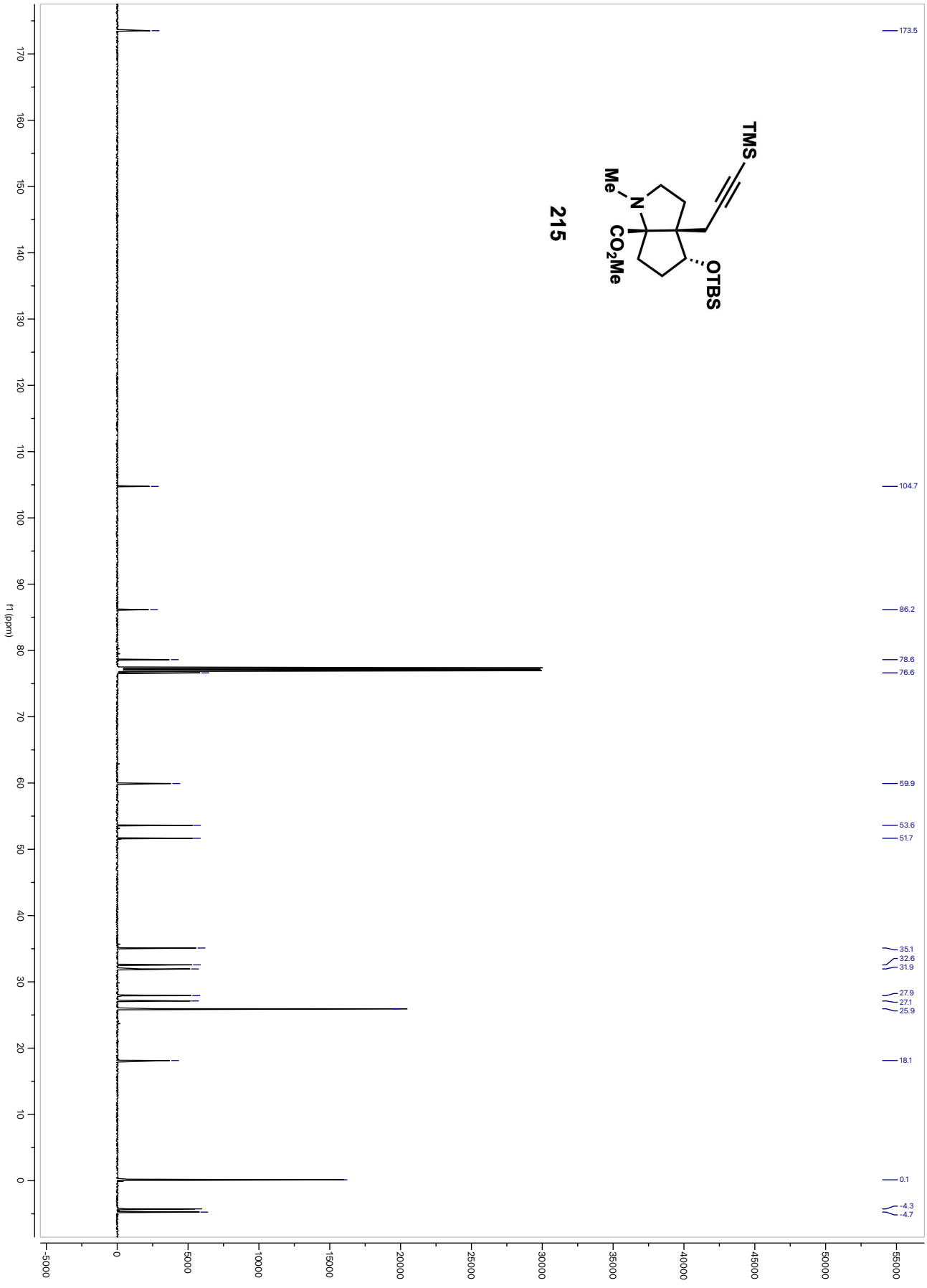

TMS
OH
213
NMeBoc
CO2Me
f1 (ppm)

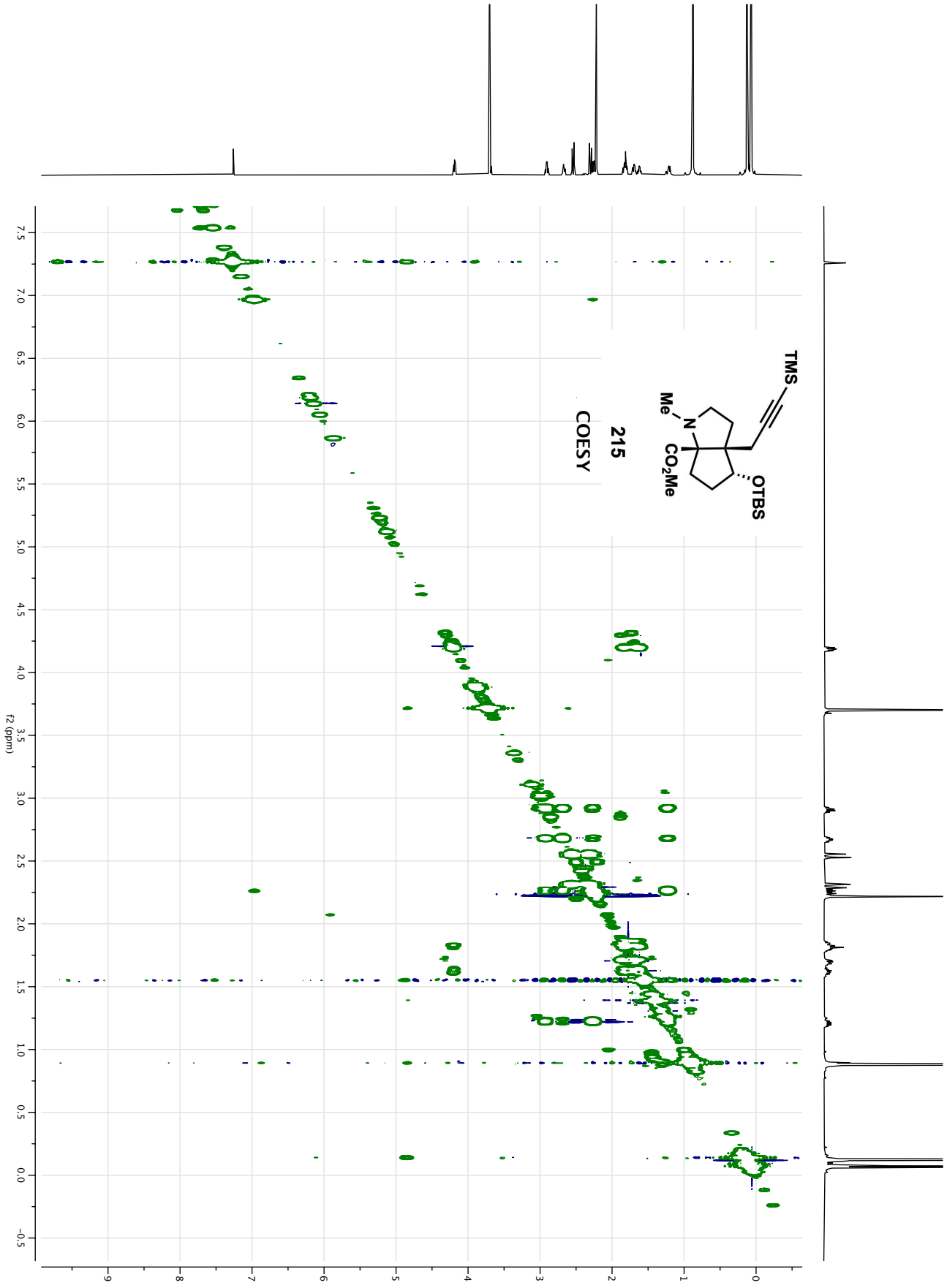

TMS
OH
213
NMeBoc
CO2Me
172.5
172.3
156.6
155.7
145.8
113.0
112.6
103.6
103.5
88.0
80.5
80.4
80.3
74.6
74.2
73.9
60.5
59.7
59.4
57.8
57.3
53.6
52.2
31.5
31.3
30.8
30.5
28.5
25.8
25.5
25.2
24.9
23.0
22.8
21.2
14.3
0.4
0.2
-0.0
f1 (ppm)

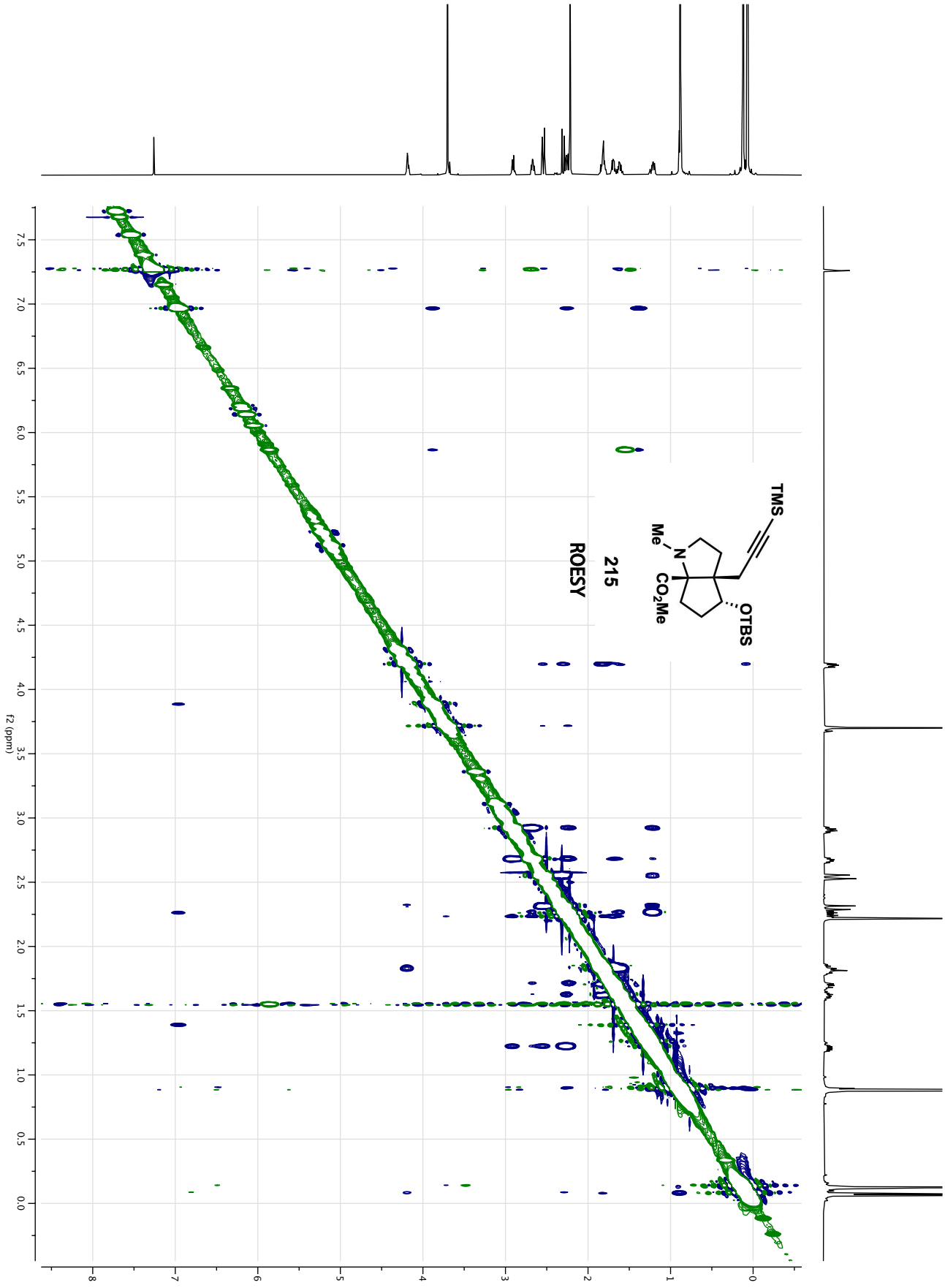

TMS
OTBS
NMeH
CO2Me
214
f1 (ppm)
1.00
1.03
1.00
3.22
1.02
1.14
1.16
3.12
5.48
10.42
9.56
6.79

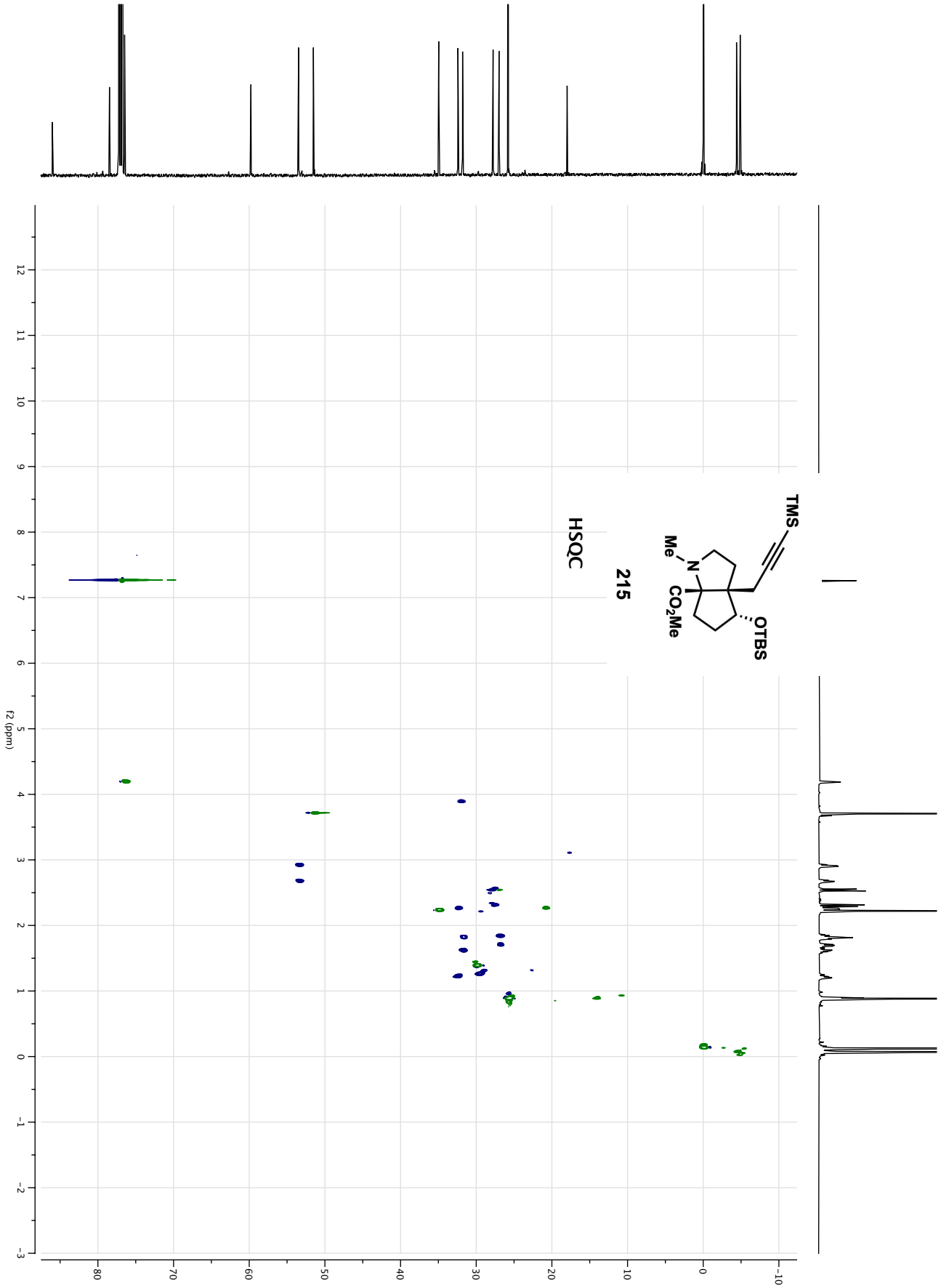

TMS
OTBS
NMeH
CO2Me
214
175.7
145.7
145.7
112.2
104.1
87.5
74.9
74.9
63.2
63.2
51.8
51.8
34.9
34.8
32.4
32.4
29.0
26.0
22.4
22.3
18.3
0.2
-4.6
-5.0
f1 (ppm)

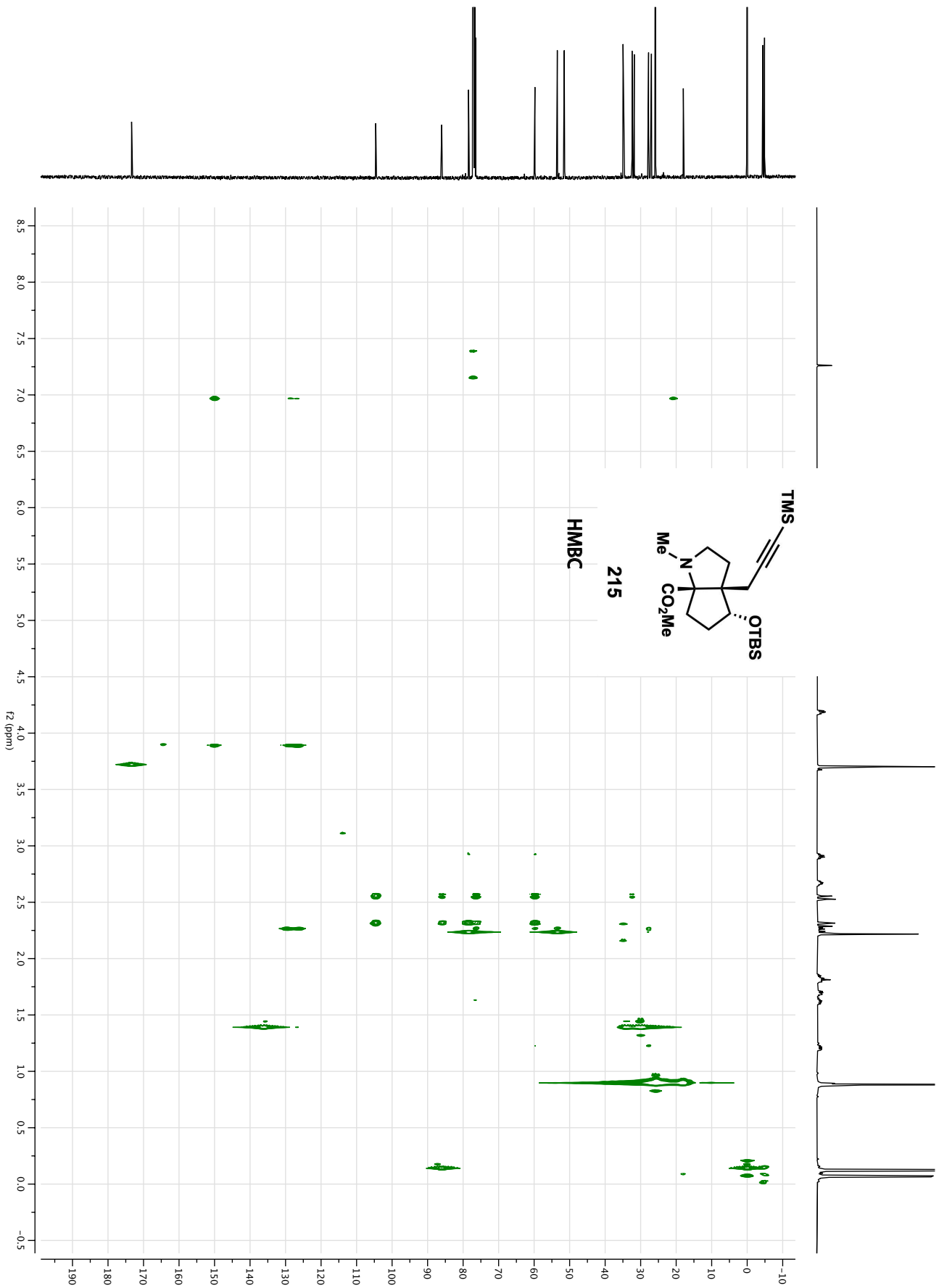

TMS
Me
N
CO2Me
OTBS
215
f1 (ppm)
1.00
3.20
1.01
1.05
1.04
1.19
0.96
3.07
2.12
1.06
1.02
0.94
10.00
9.29
2.74
3.02

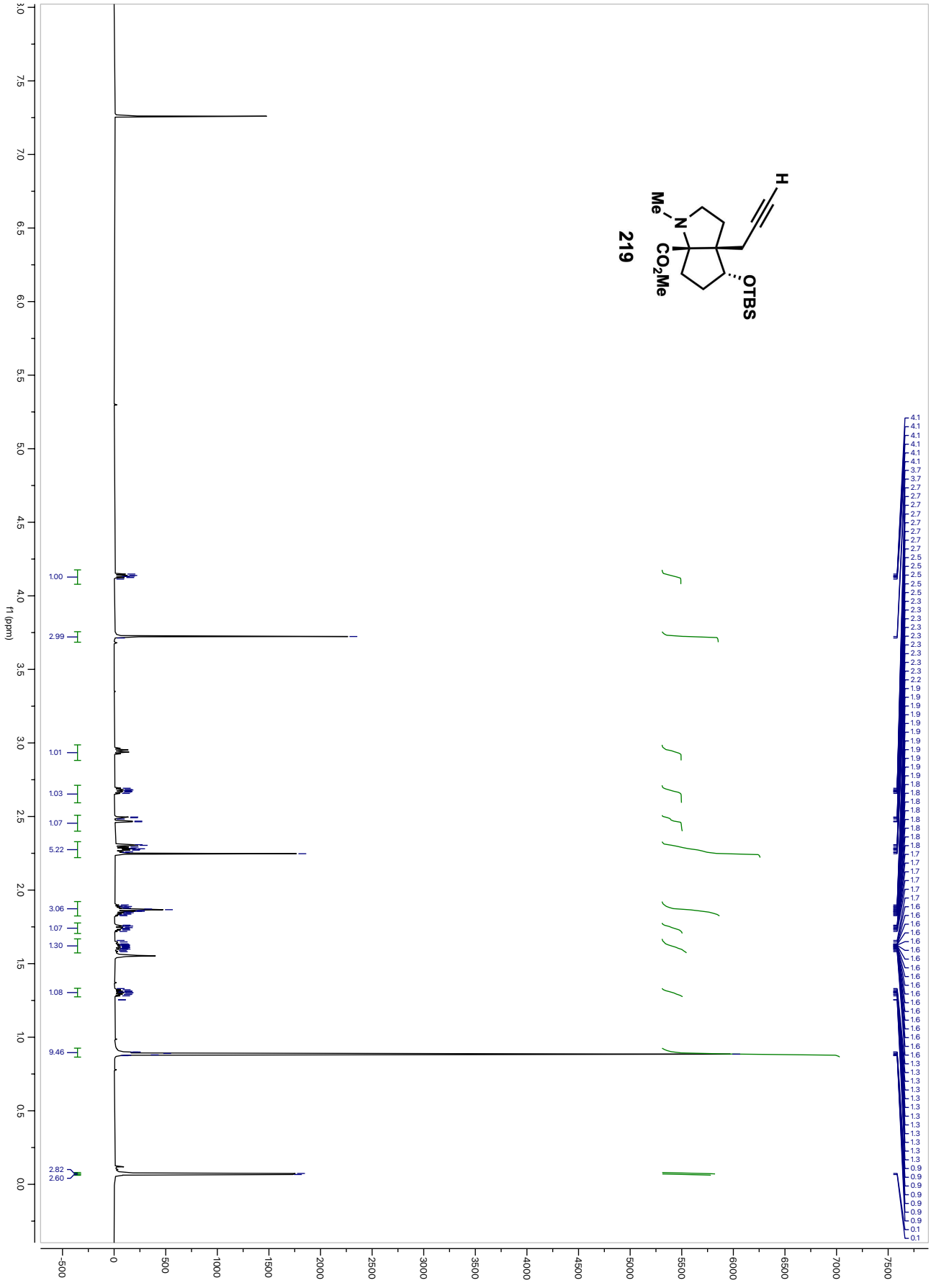

215
TMS
Me
N
CO2Me
OTBS
f1 (ppm)
173.5
104.7
86.2
78.6
76.6
59.9
53.6
51.7
35.1
32.6
31.9
27.9
27.1
25.9
18.1
0.1
-4.3
-4.7

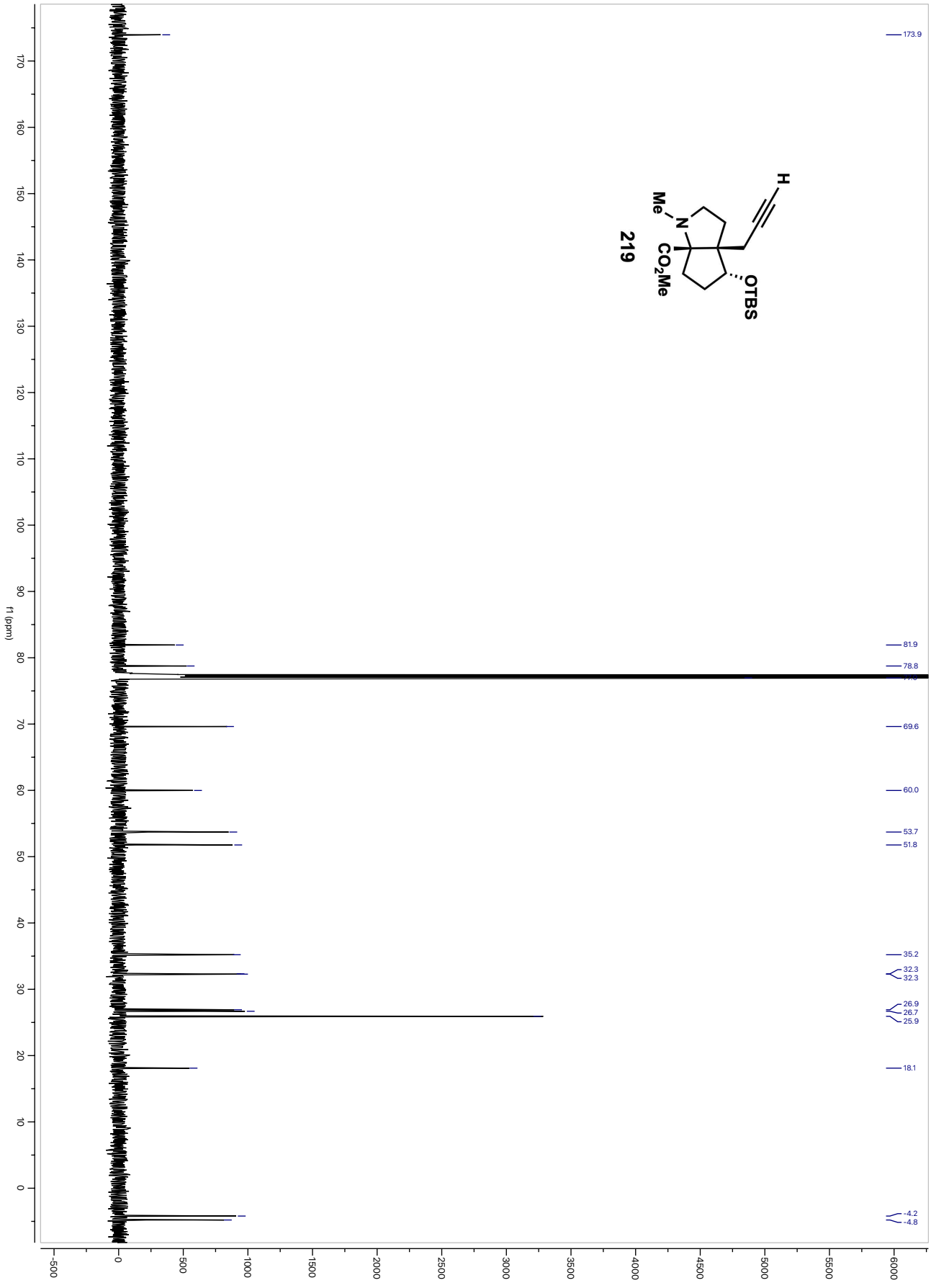

TMS
Me
N
CO2Me
OTBS
215
COESY
f2 (ppm)
f1 (ppm)

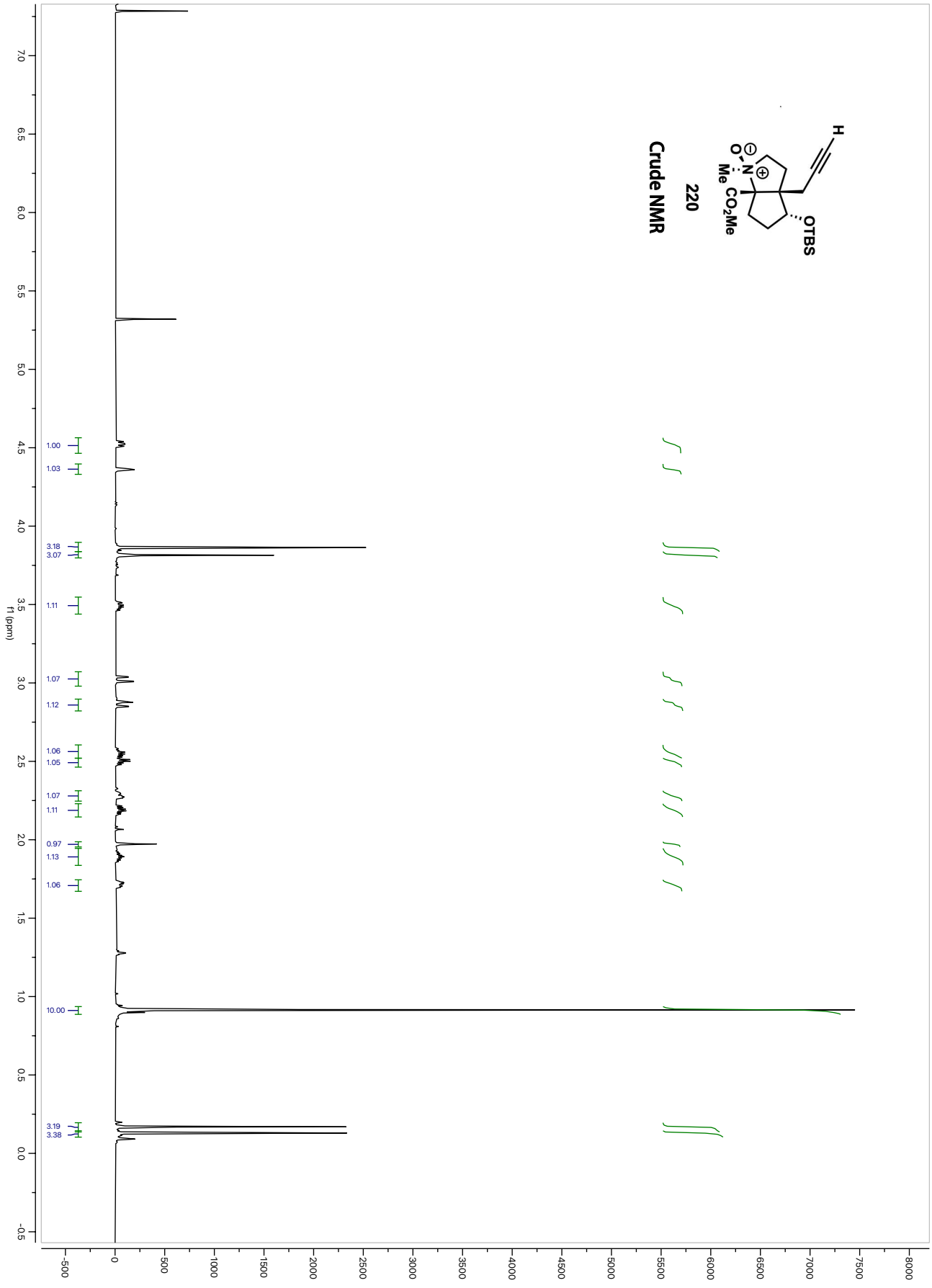

TMS
Me
N
CO2Me
OTBS
215
ROESY
f2 (ppm)
f1 (ppm)

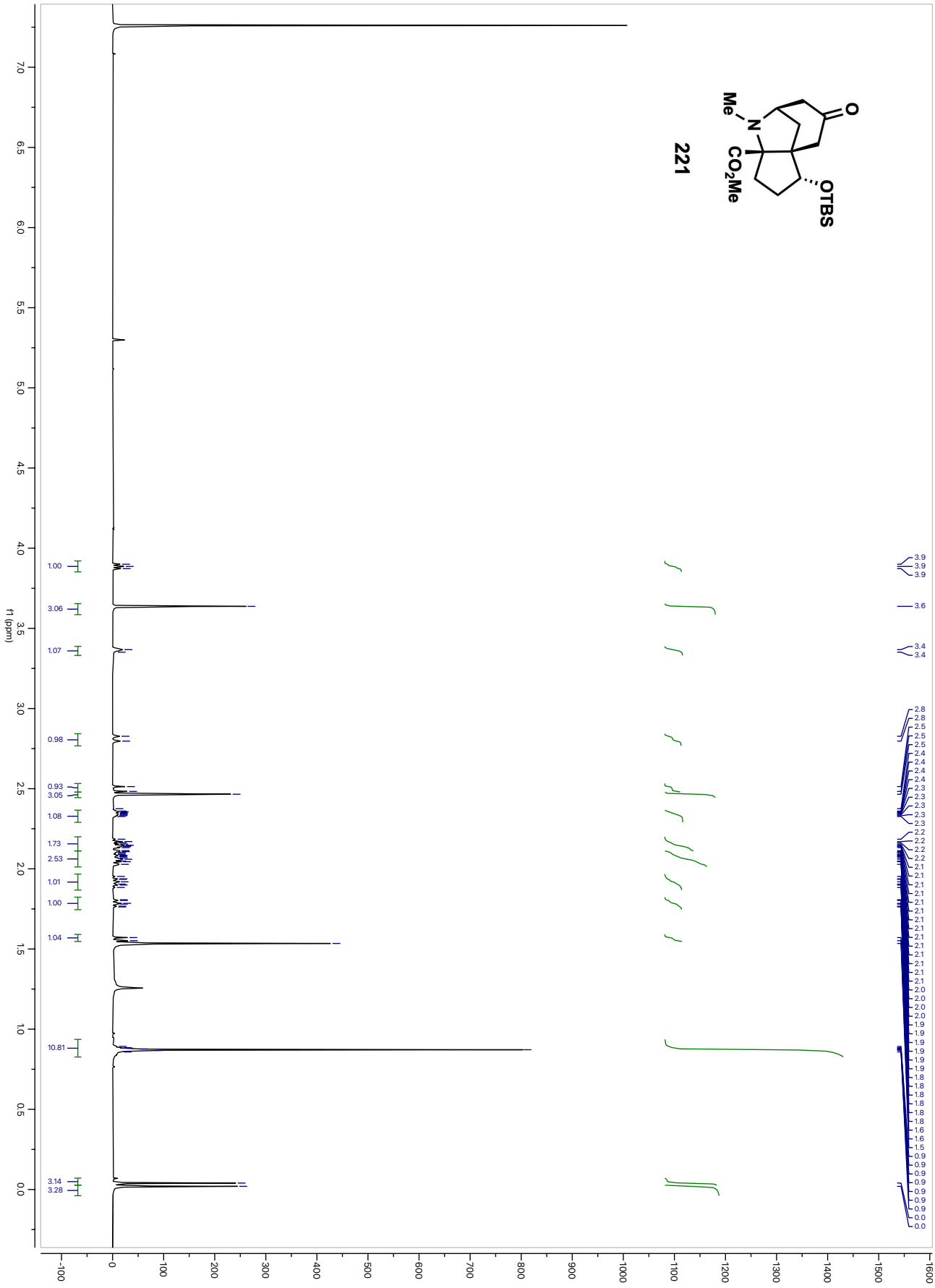

HSQC
215
TMS
Me
N
CO2Me
OTBS
f2 (ppm)
f1 (ppm)

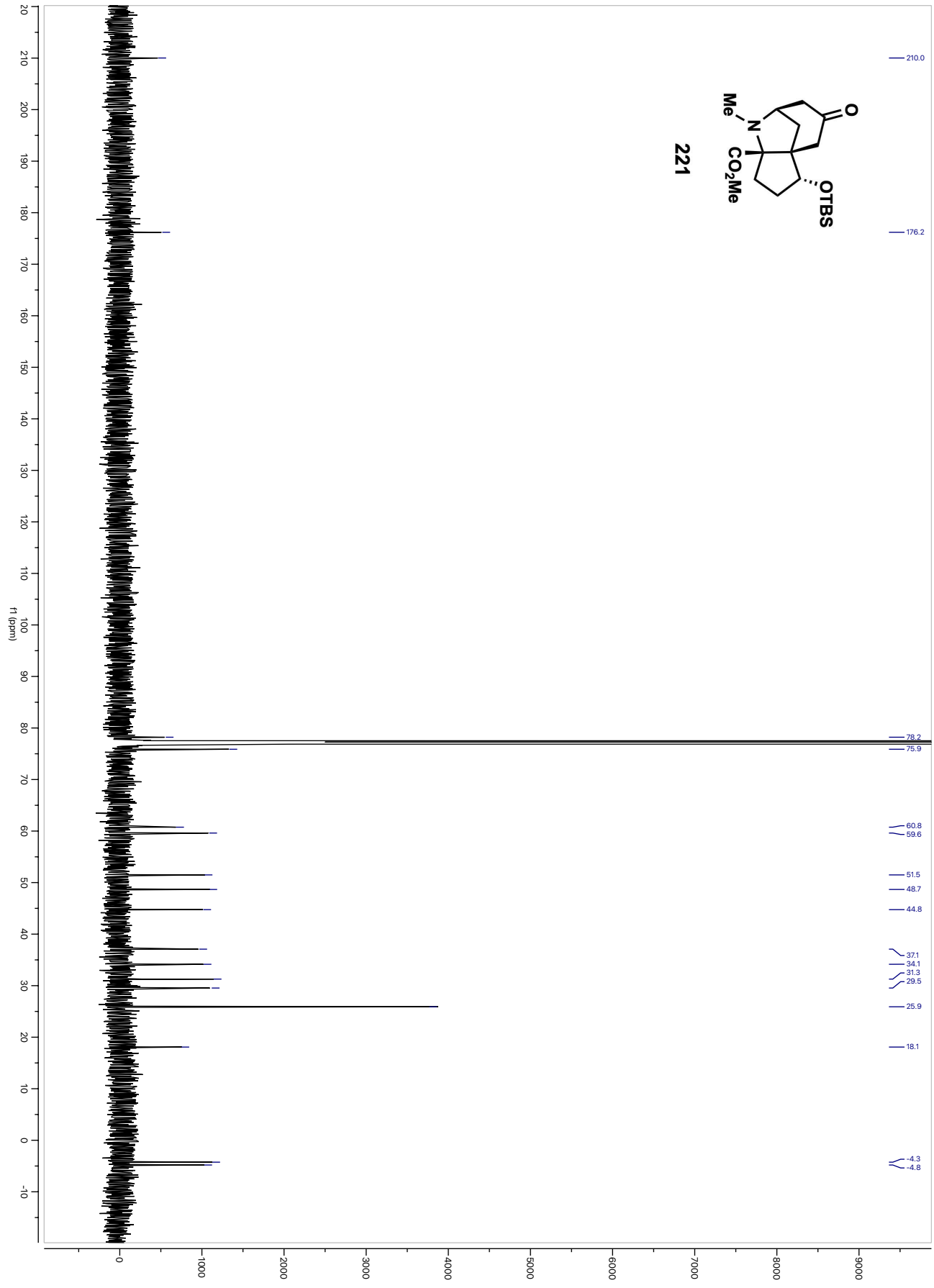

HMBC
215
TMS
Me
N
CO2Me
OTBS
f2 (ppm)
f1 (ppm)

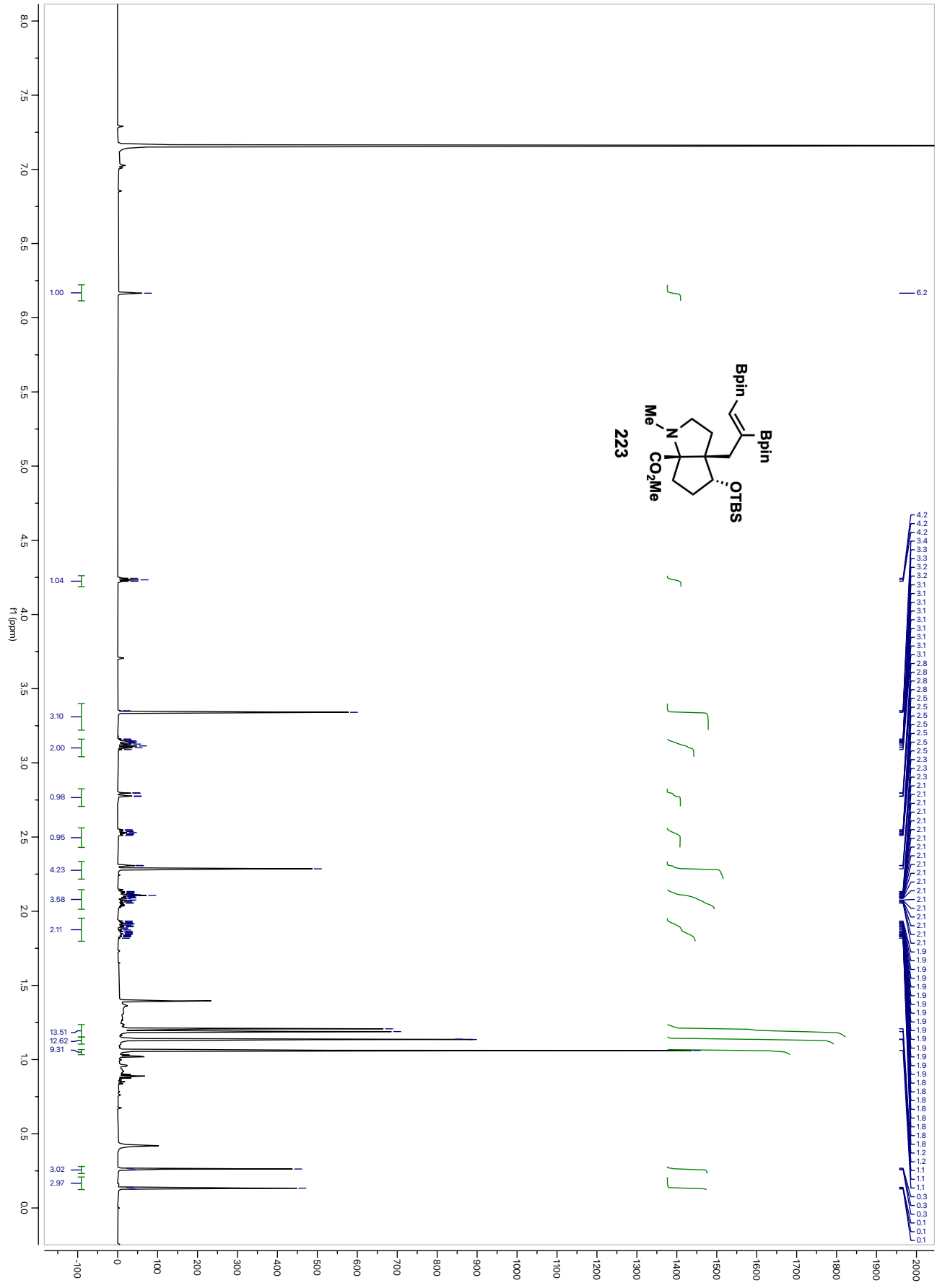

219
H
Me
N
CO2Me
OTBS
f1 (ppm)
1.00
2.99
1.01
1.03
1.07
5.22
3.06
1.07
1.30
1.08
9.46
2.82
2.60

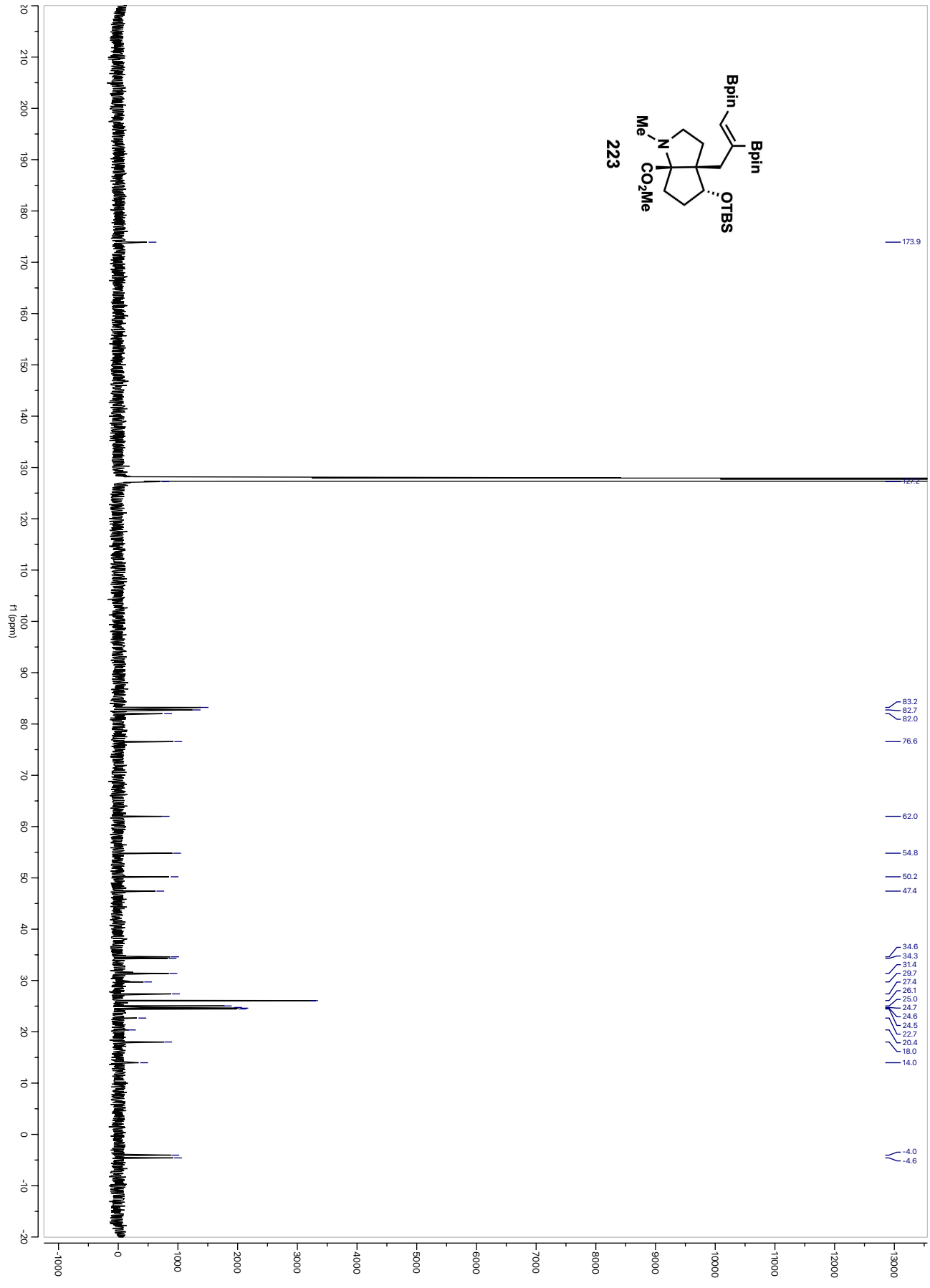

173.9
81.9
78.8
69.6
60.0
53.7
51.8
35.2
32.3
32.3
26.9
26.7
25.9
18.1
-4.2
-4.8
f1 (ppm)
H
Me
N
CO2Me
OTBS
219

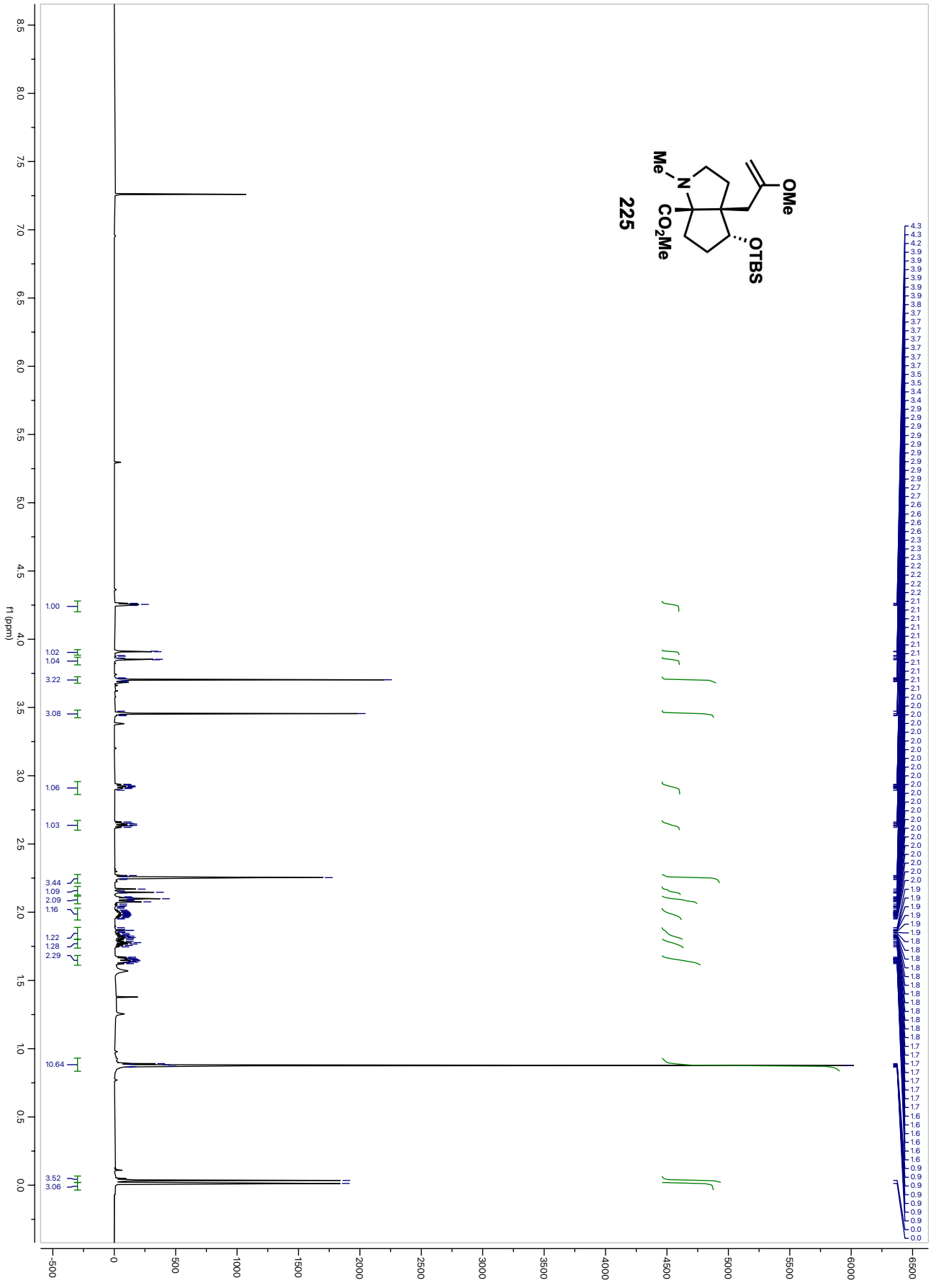

Crude NMR
220
OTBS
CO2Me
Me
H
f1 (ppm)
1.00
1.03
3.18
3.07
1.11
1.07
1.12
1.06
1.05
1.07
1.11
0.97
1.13
1.06
10.00
3.19
3.38

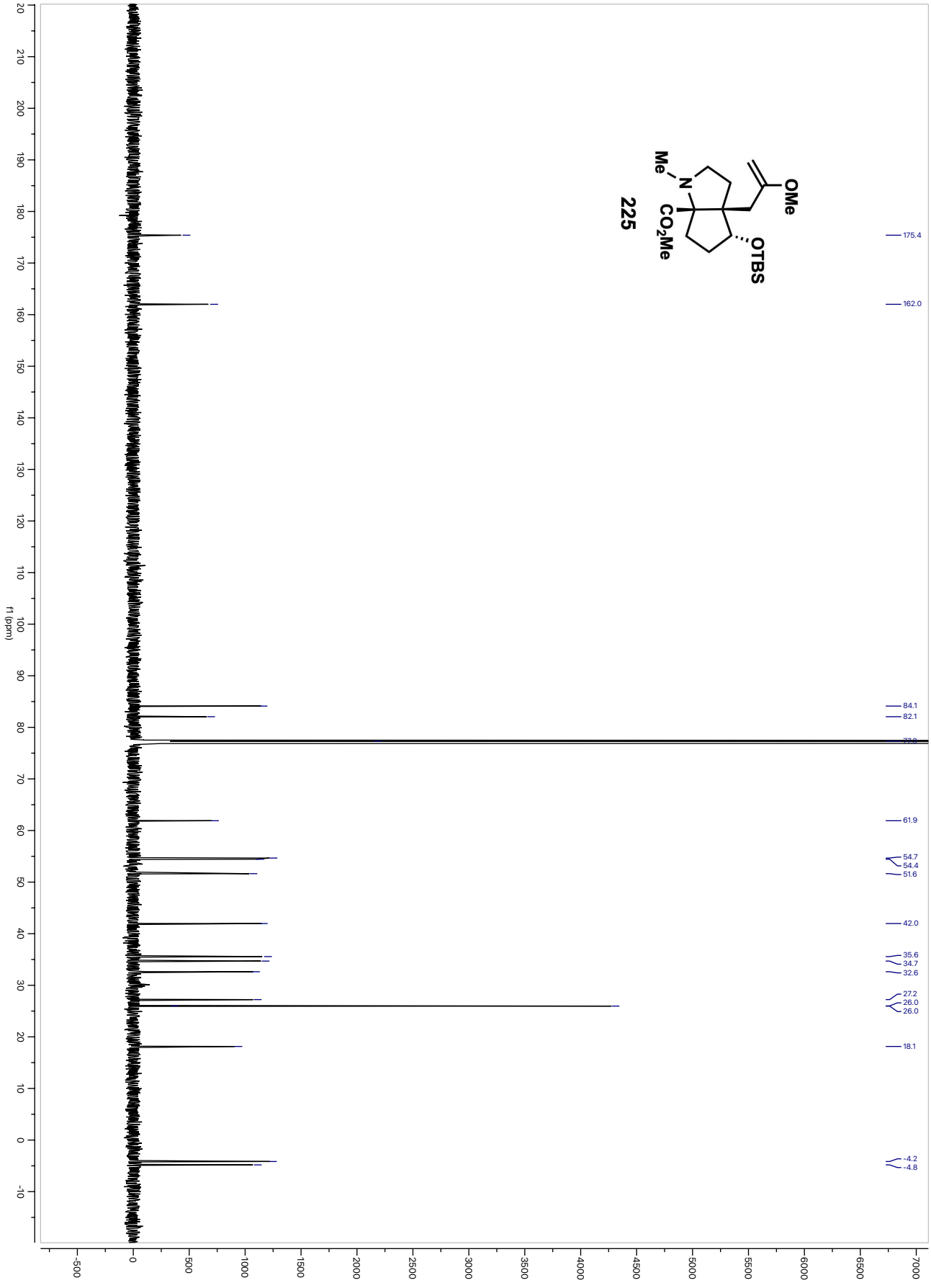

221
Me
N
CO2Me
O
OTBS
f1 (ppm)
1.00
3.06
1.07
0.98
0.93
3.05
1.08
1.73
2.53
1.01
1.00
1.04
10.81
3.14
3.28
3.9
3.6
3.4

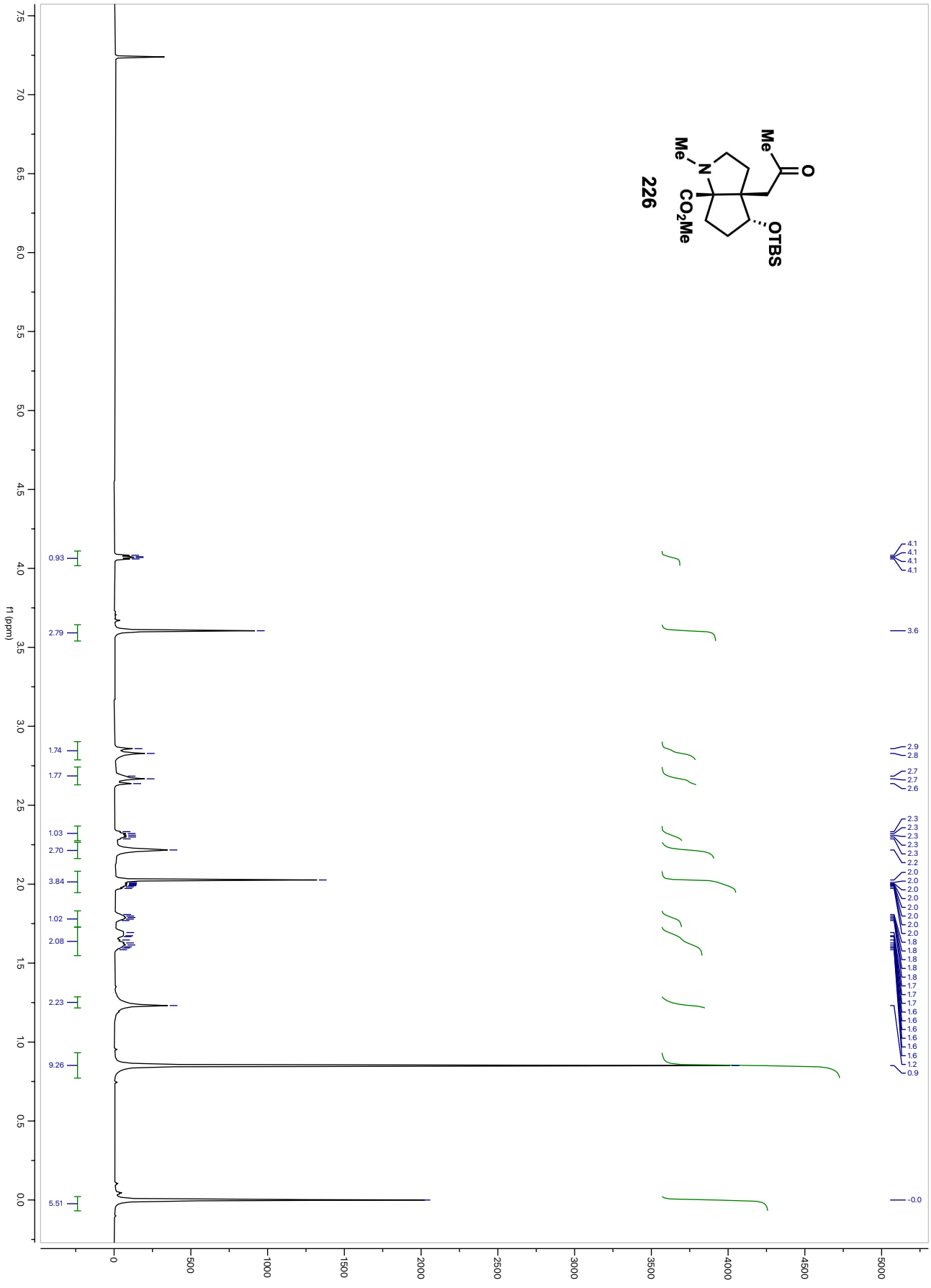

221
Me
N
CO2Me
O
OTBS
f1 (ppm)
210.0
176.2
78.2
75.9
60.8
59.6
51.5
48.7
44.8
37.1
34.1
31.3
29.5
25.9
18.1
-4.3
-4.8

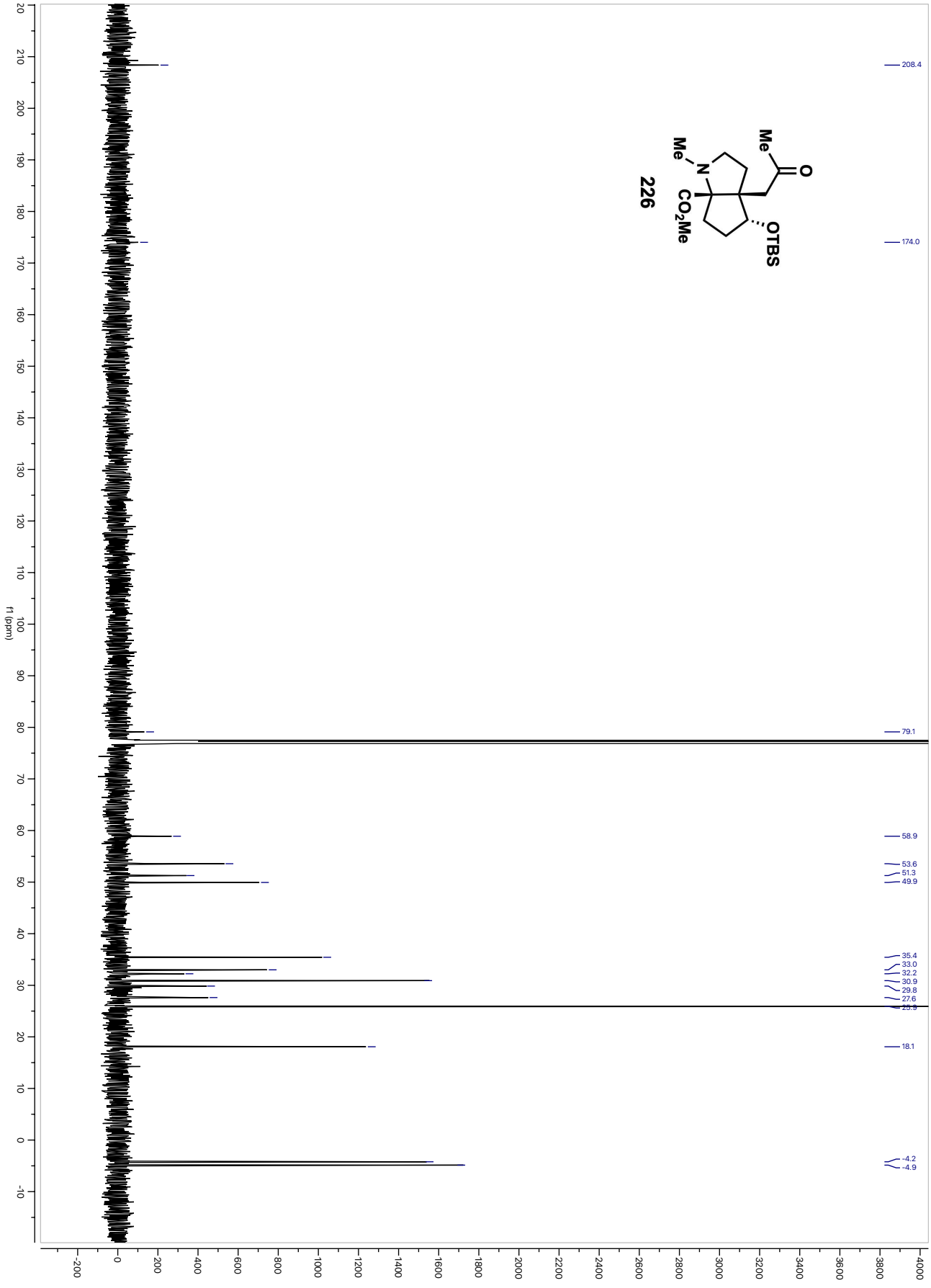

Bpin
Bpin
Me
N
CO2Me
OTBS
223
f1 (ppm)

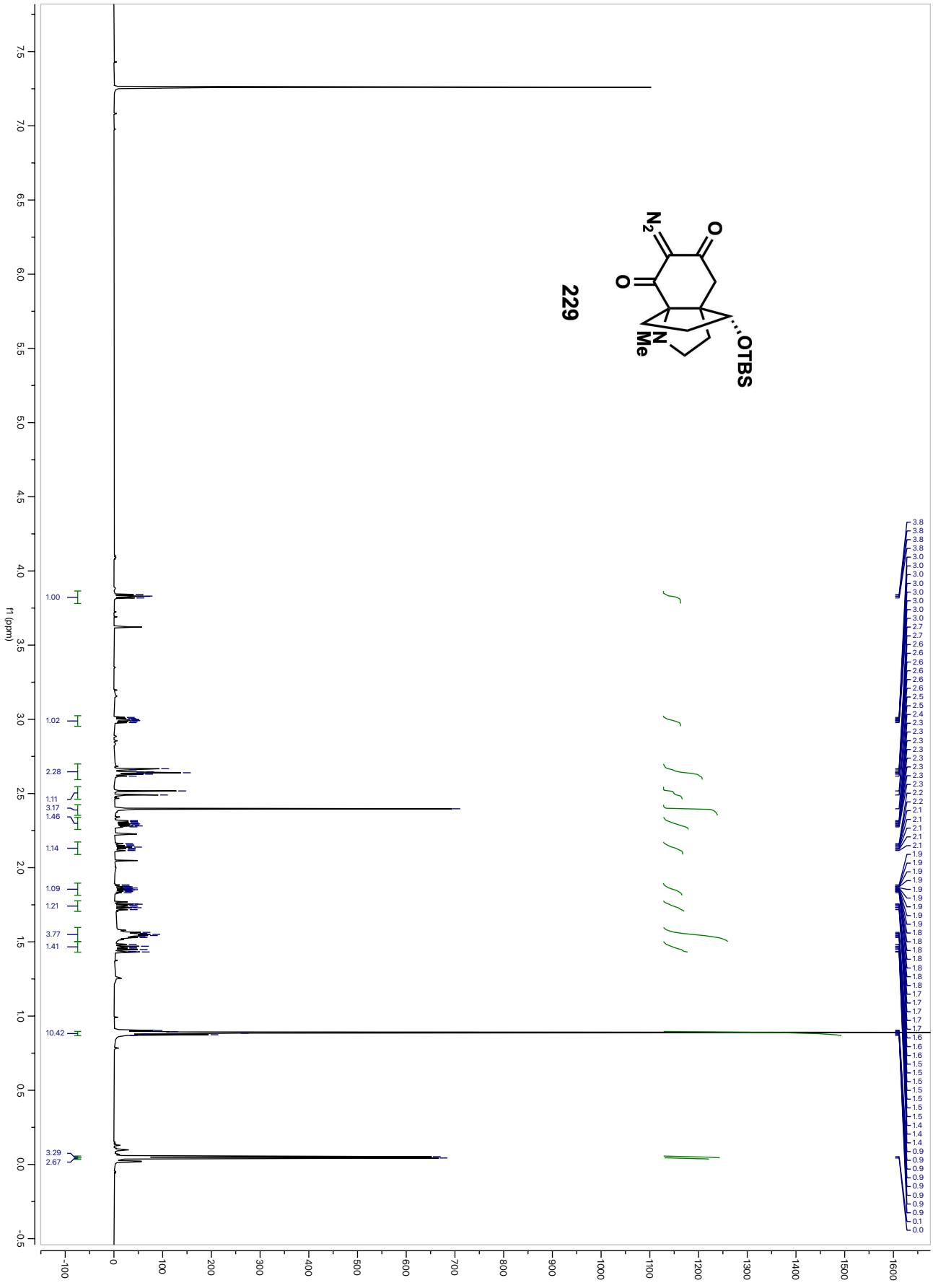

Bpin
Bpin
Me
N
CO2Me
OTBS
223
173.9
127.2
83.2
82.7
82.0
76.6
62.0
54.8
50.2
47.4
34.6
34.3
31.4
29.7
27.4
26.1
25.0
24.7
24.6
24.5
22.7
20.4
18.0
14.0
-4.0
-4.6
f1 (ppm)

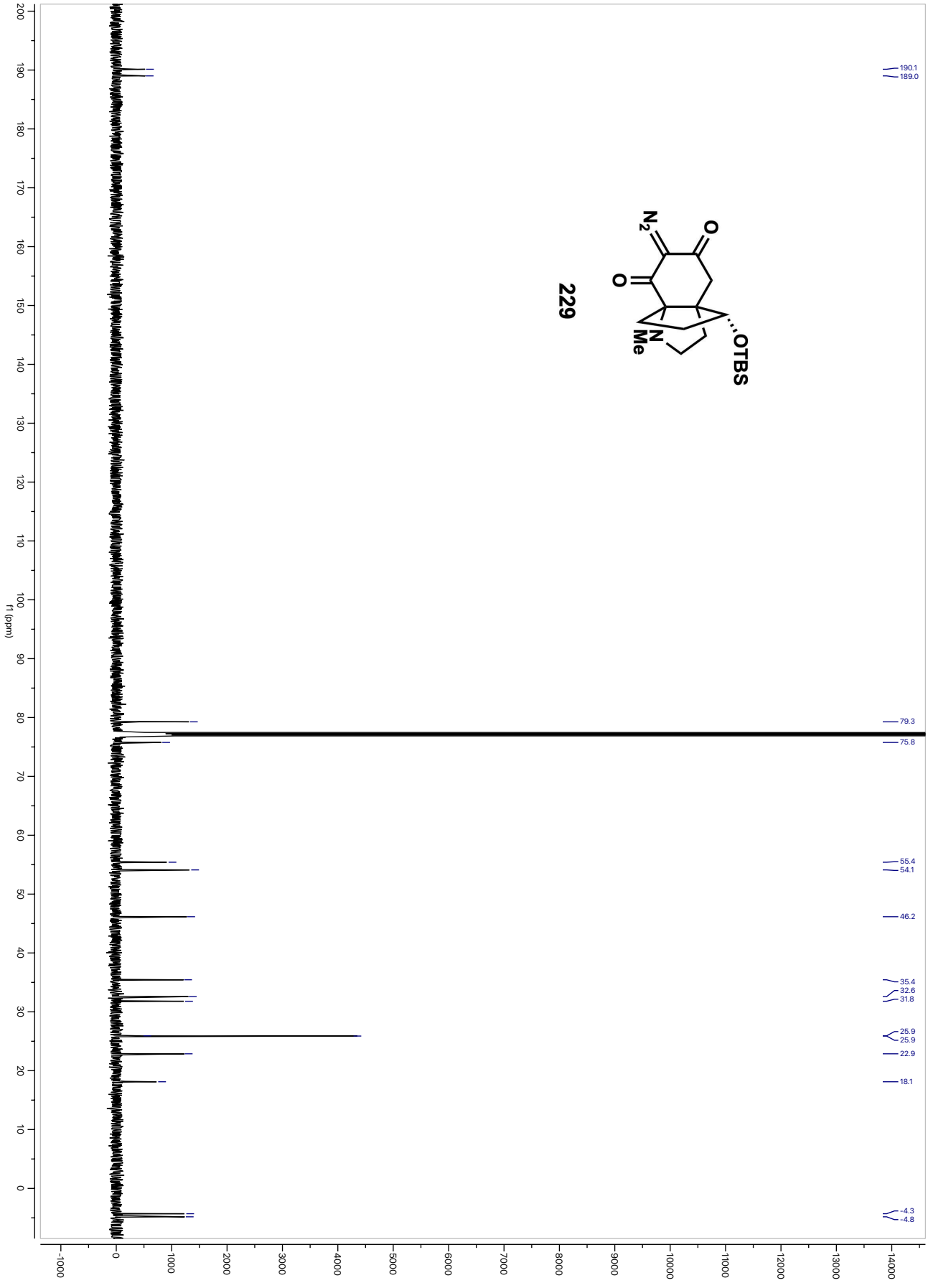

OMe
OTBS
Me
N
CO2Me
225
f1 (ppm)
1.00
1.02
1.04
3.22
3.08
1.06
1.03
3.44
1.09
2.09
1.16
1.22
1.28
2.29
10.64
3.52
3.06

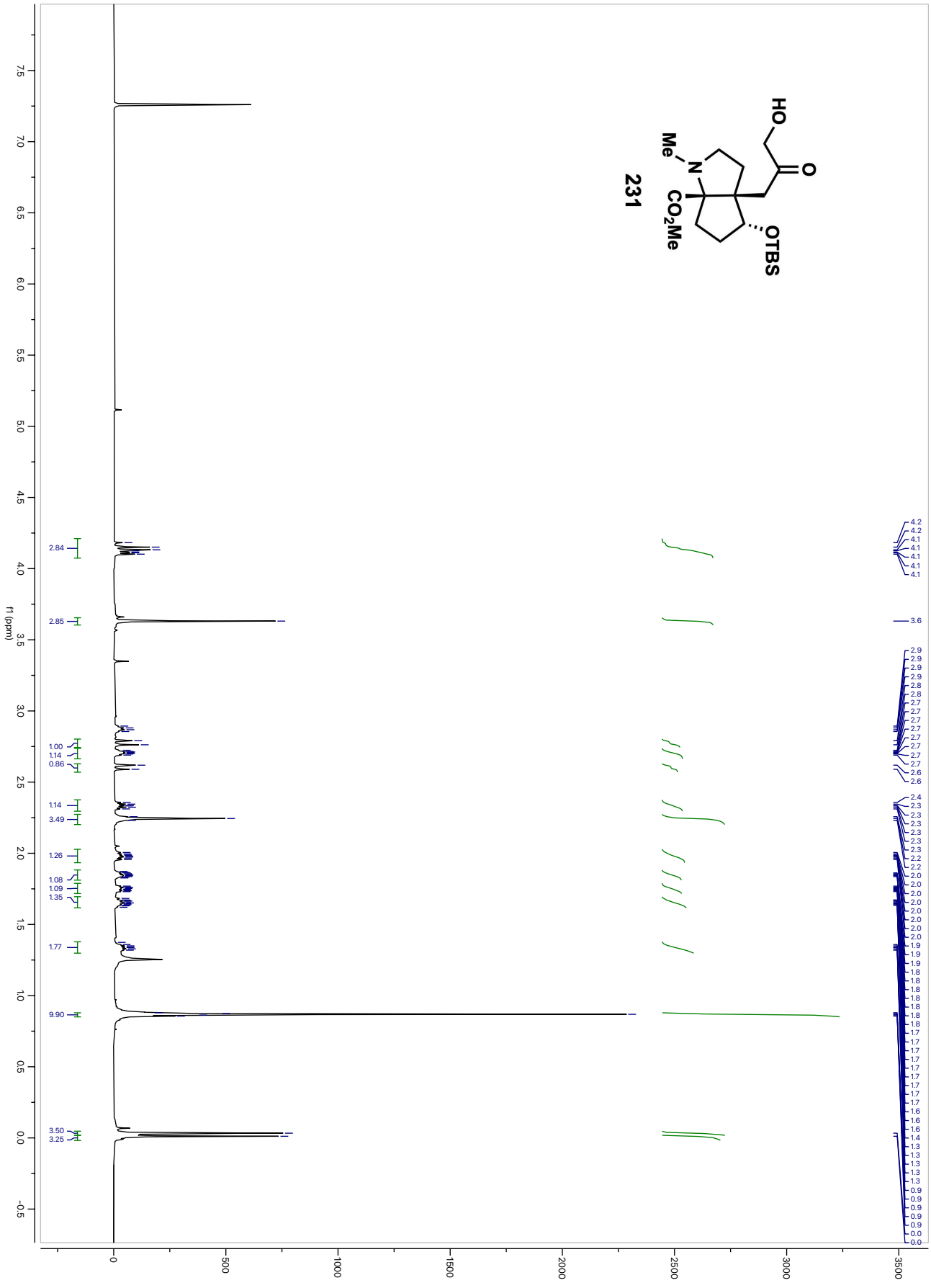

225
OMe
OTBS
CO2Me
Me
N
175.4
162.0
84.1
82.1
77.9
61.9
54.7
54.4
51.6
42.0
35.6
34.7
32.6
27.2
26.0
26.0
18.1
-4.2
-4.8
f1 (ppm)

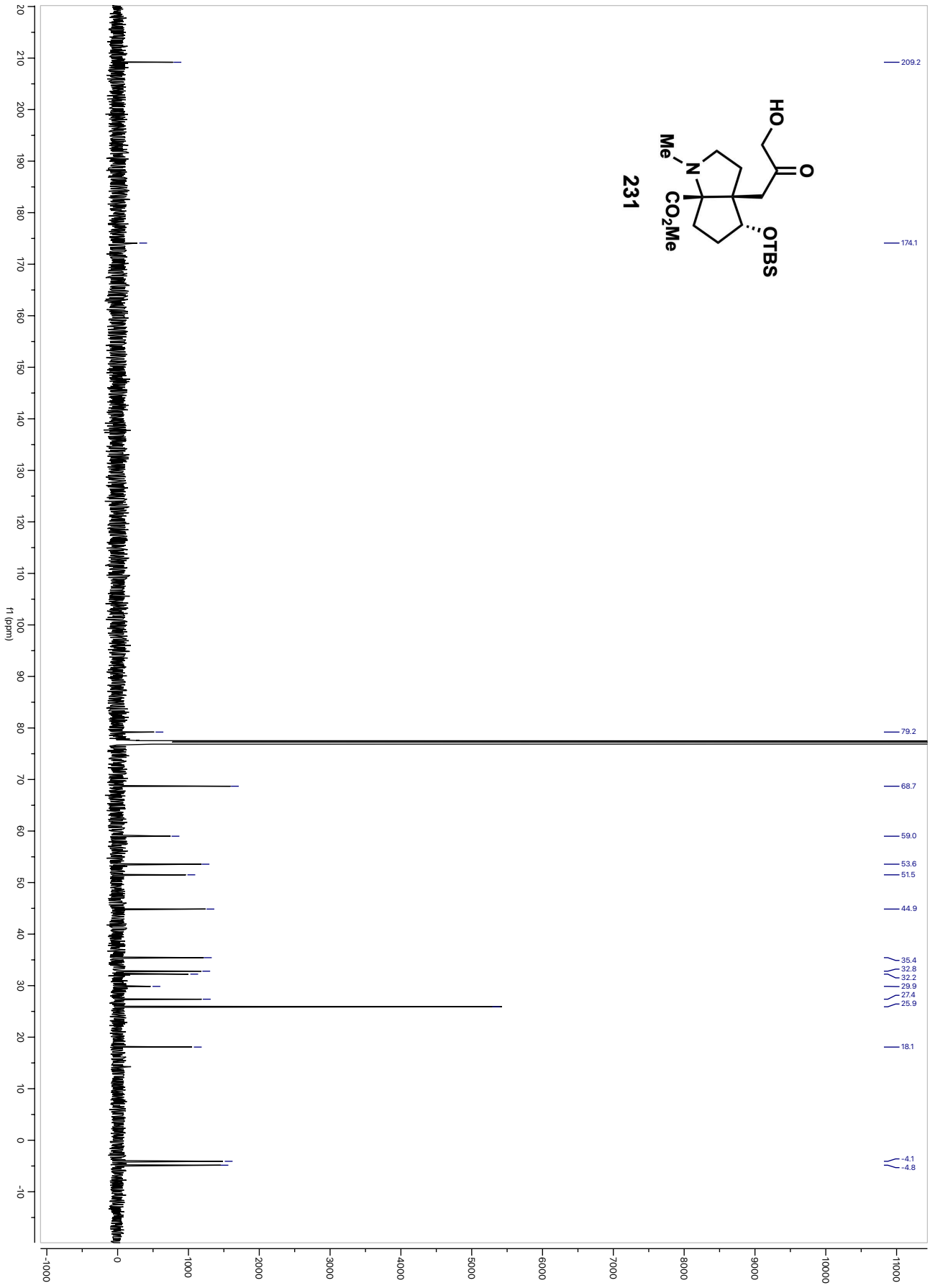

226
Me
O
Me
N
CO2Me
OTBS
f1 (ppm)
0.93
2.79
1.74
1.77
1.03
2.70
3.84
1.02
2.08
2.23
9.26
5.51
4.1
3.6
2.9
2.8
2.7
2.6
2.3
2.2
2.0
1.8
1.7
1.6
1.2
0.9
-0.0

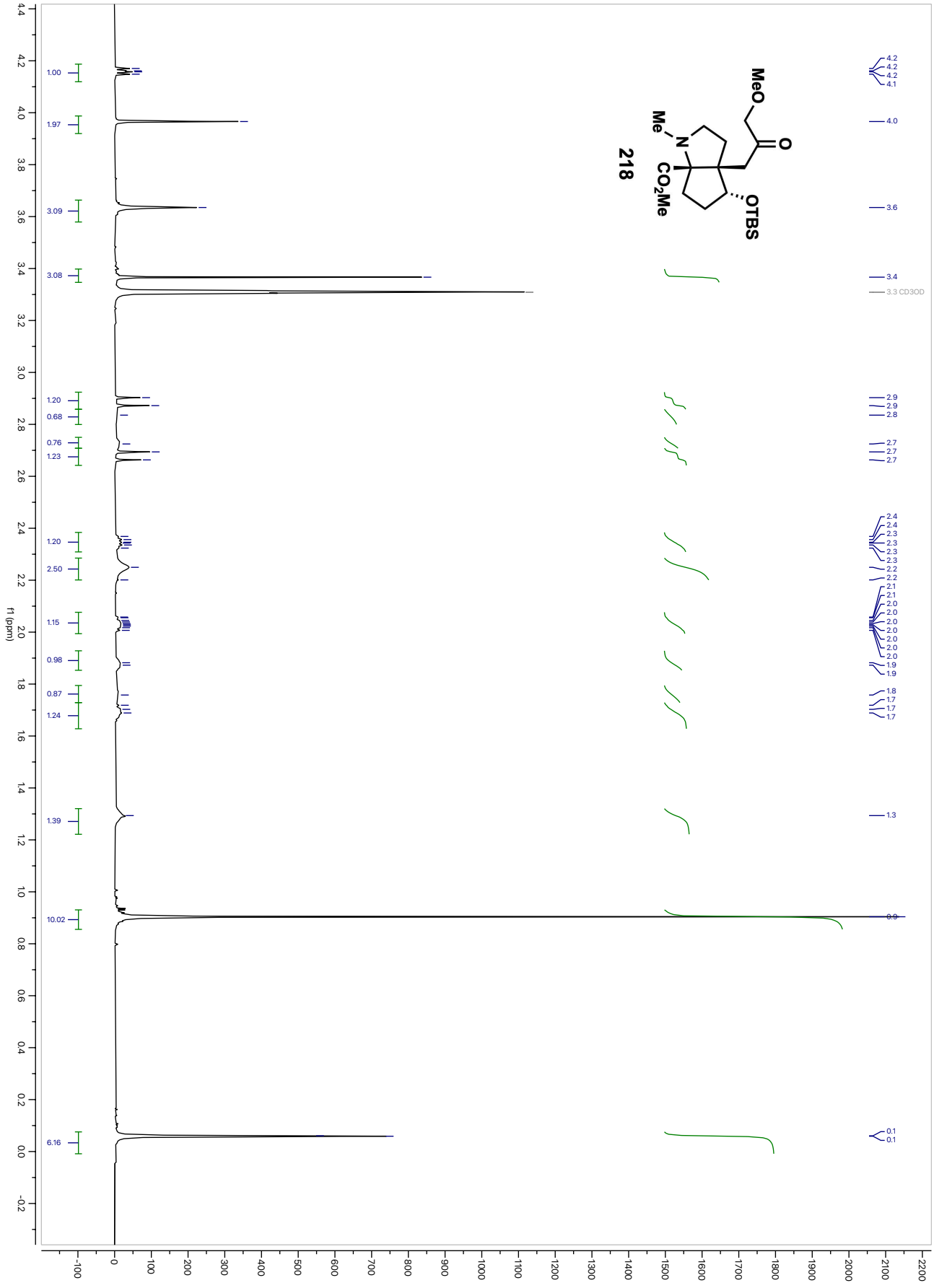

208.4
174.0
79.1
58.9
53.6
51.3
49.9
35.4
33.0
32.2
30.9
29.8
27.6
25.9
18.1
-4.2
-4.9
f1 (ppm)
226
Me
N
Me
CO2Me
O
OTBS

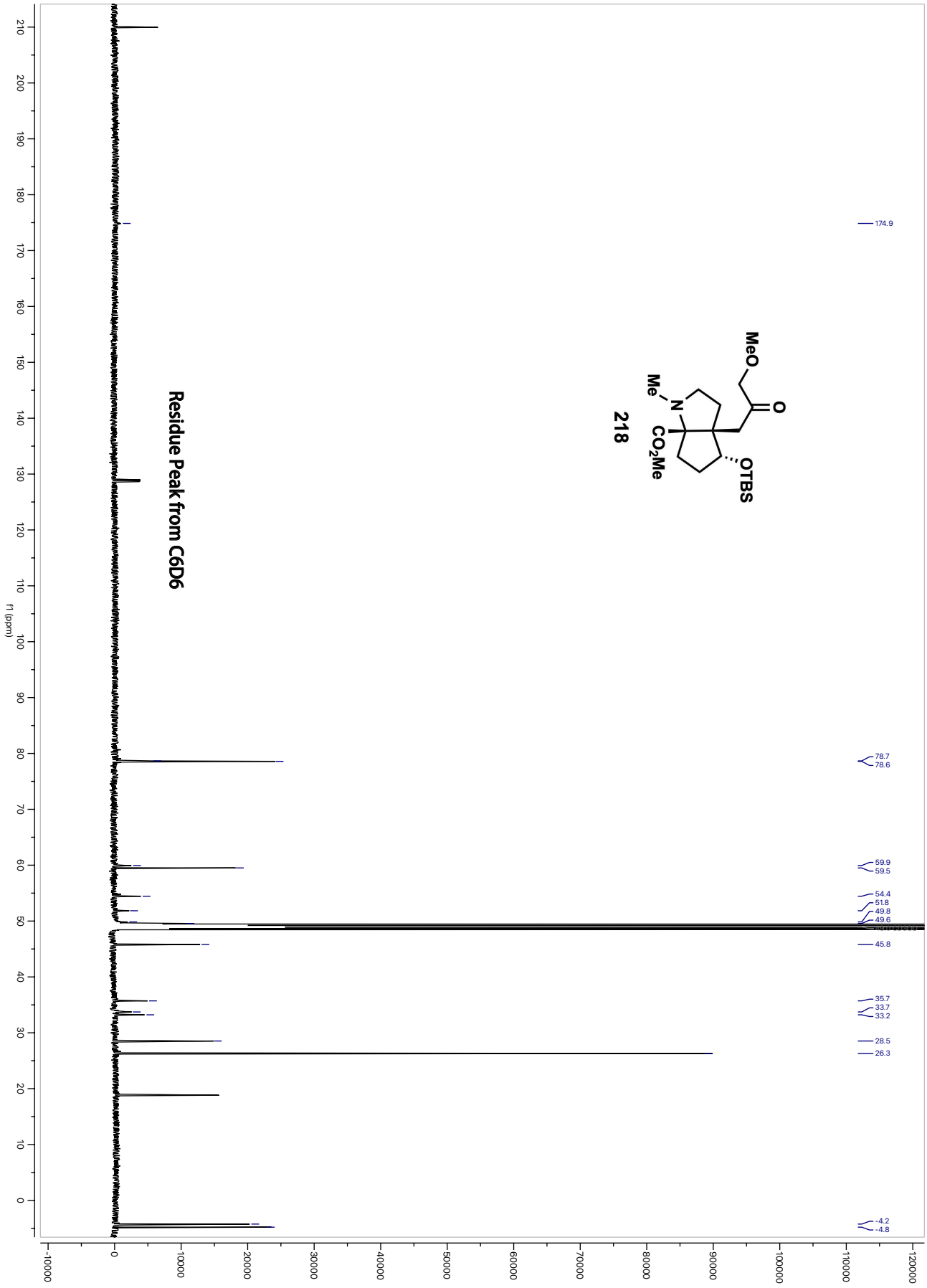

229
N2
O
O
N
Me
OTBS
f1 (ppm)
1.00
1.02
2.28
1.11
3.17
1.46
1.14
1.09
1.21
3.77
1.41
10.42
3.29
2.67

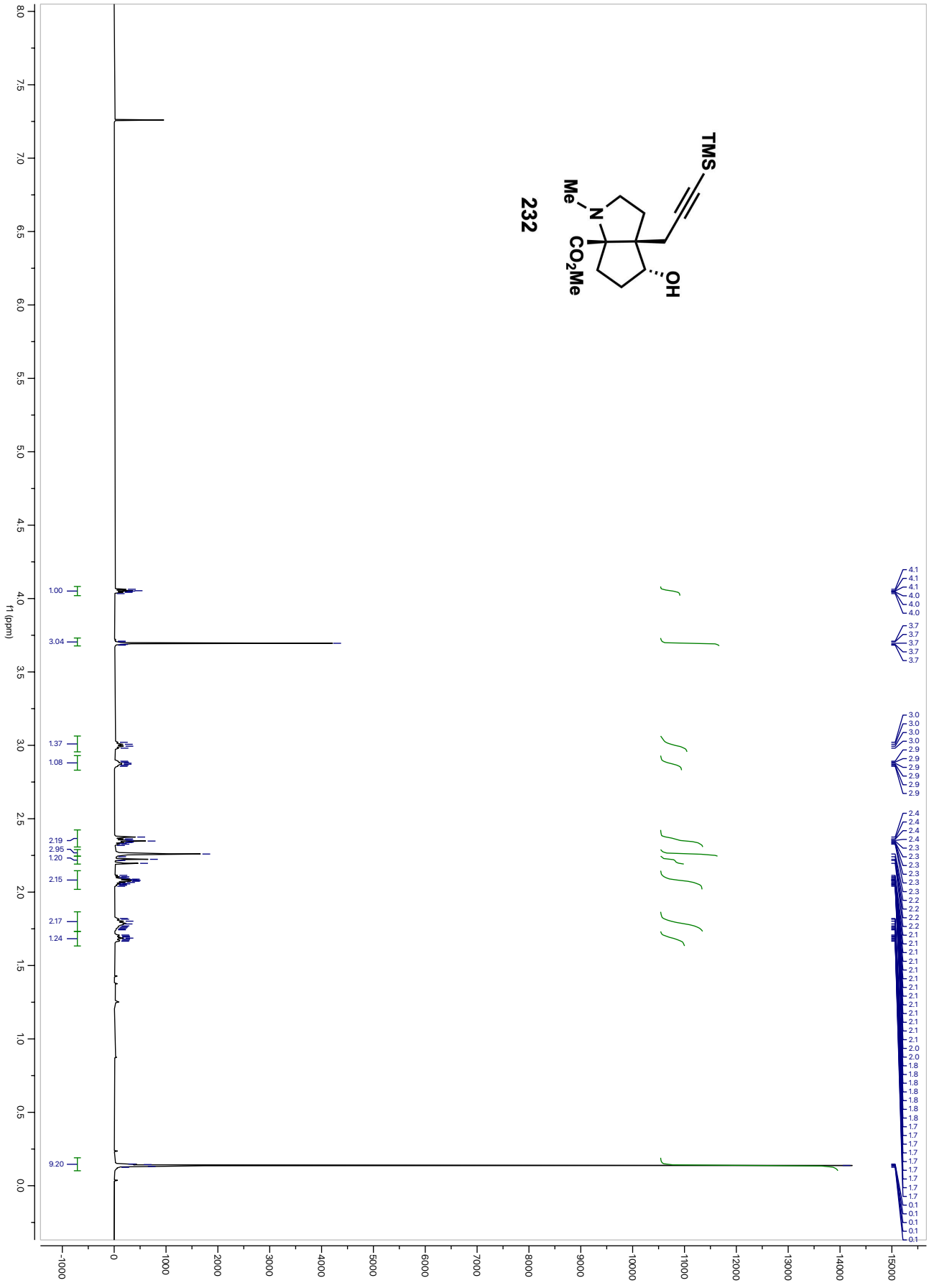

229
N2
O
O
N
Me
OTBS
190.1
189.0
79.3
75.8
55.4
54.1
46.2
35.4
32.6
31.8
25.9
25.9
22.9
18.1
-4.3
-4.8
f1 (ppm)

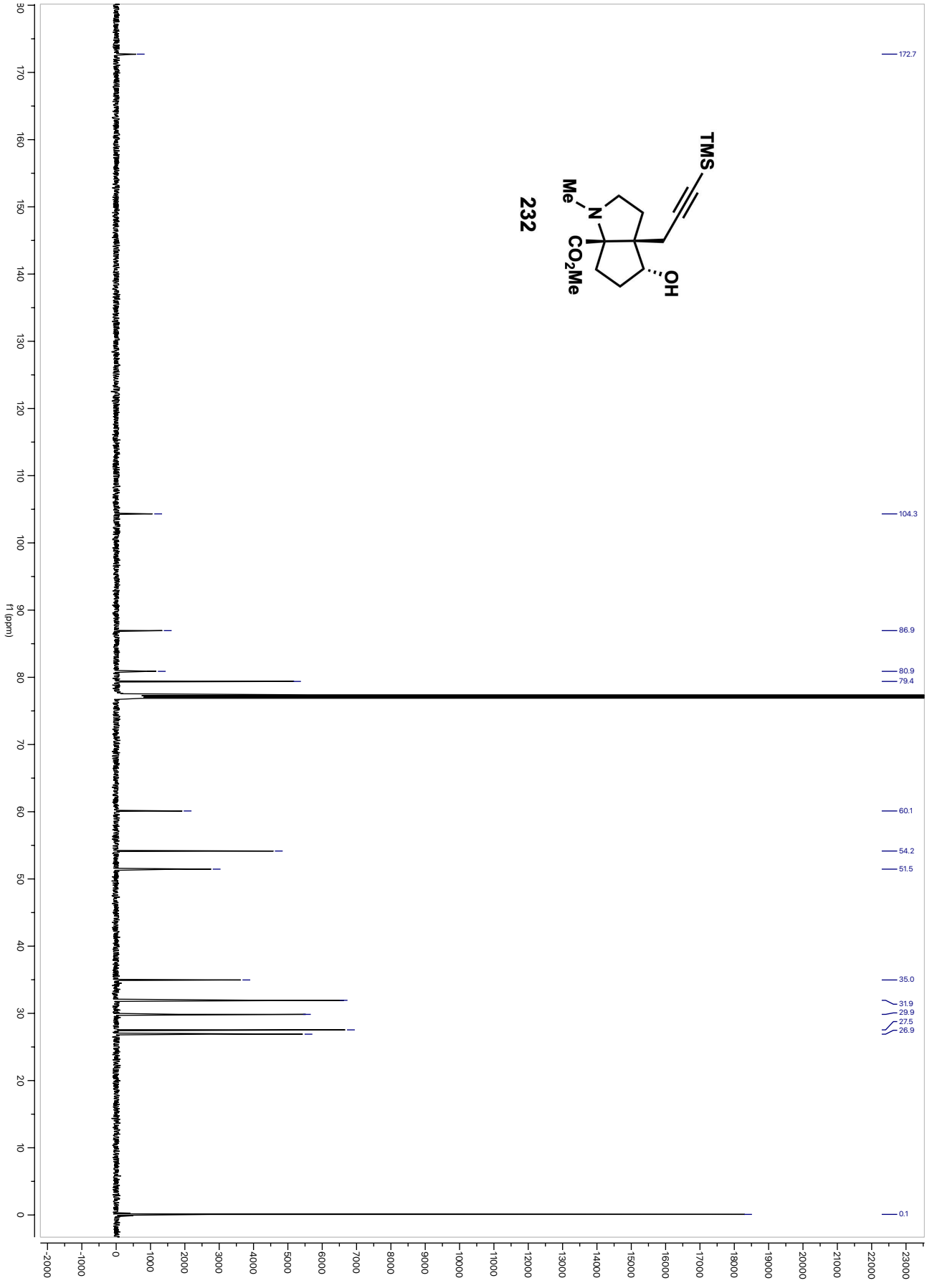

231
HO
O
Me
N
CO2Me
OTBS
f1 (ppm)
2.84
2.85
1.00
1.14
0.86
1.14
3.49
1.26
1.08
1.09
1.35
1.77
9.90
3.50
3.25
3.6

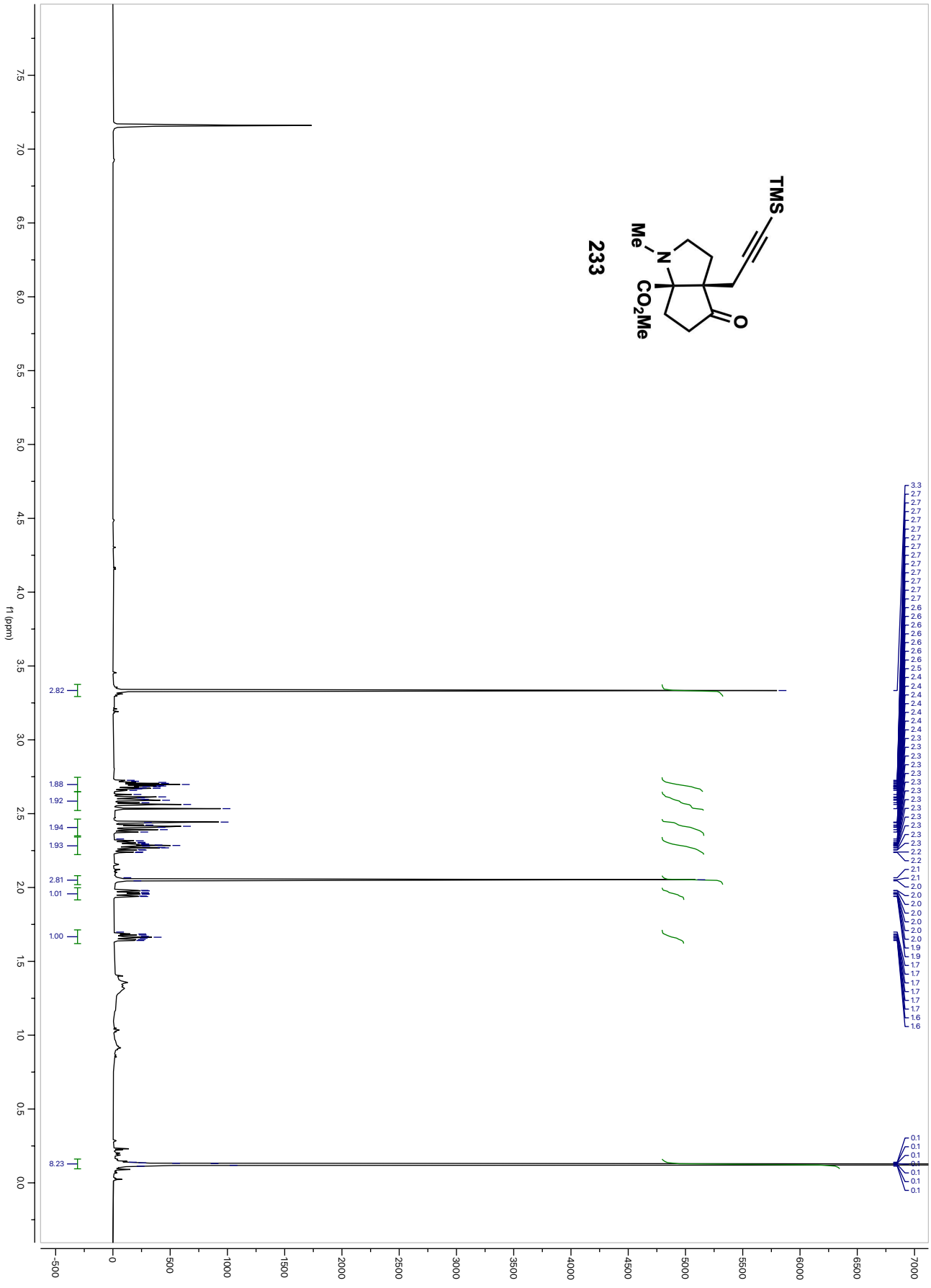

209.2
174.1
79.2
68.7
59.0
53.6
51.5
44.9
35.4
32.8
32.2
29.9
27.4
25.9
18.1
-4.1
-4.8
f1 (ppm)
231
HO
O
Me
N
CO2Me
OTBS

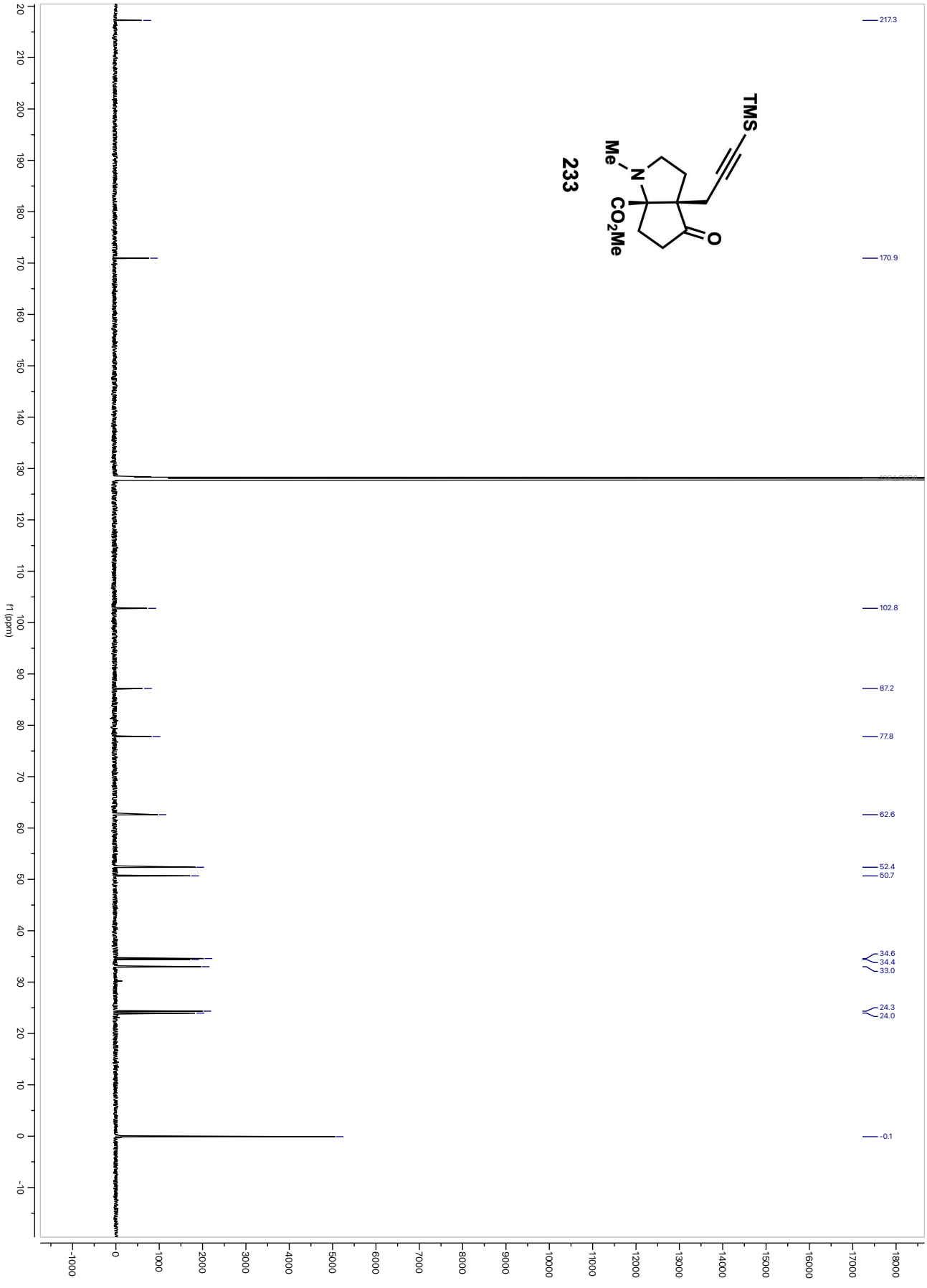

218
MeO
O
Me
N
CO2Me
OTBS
f1 (ppm)
3.3 CD3OD

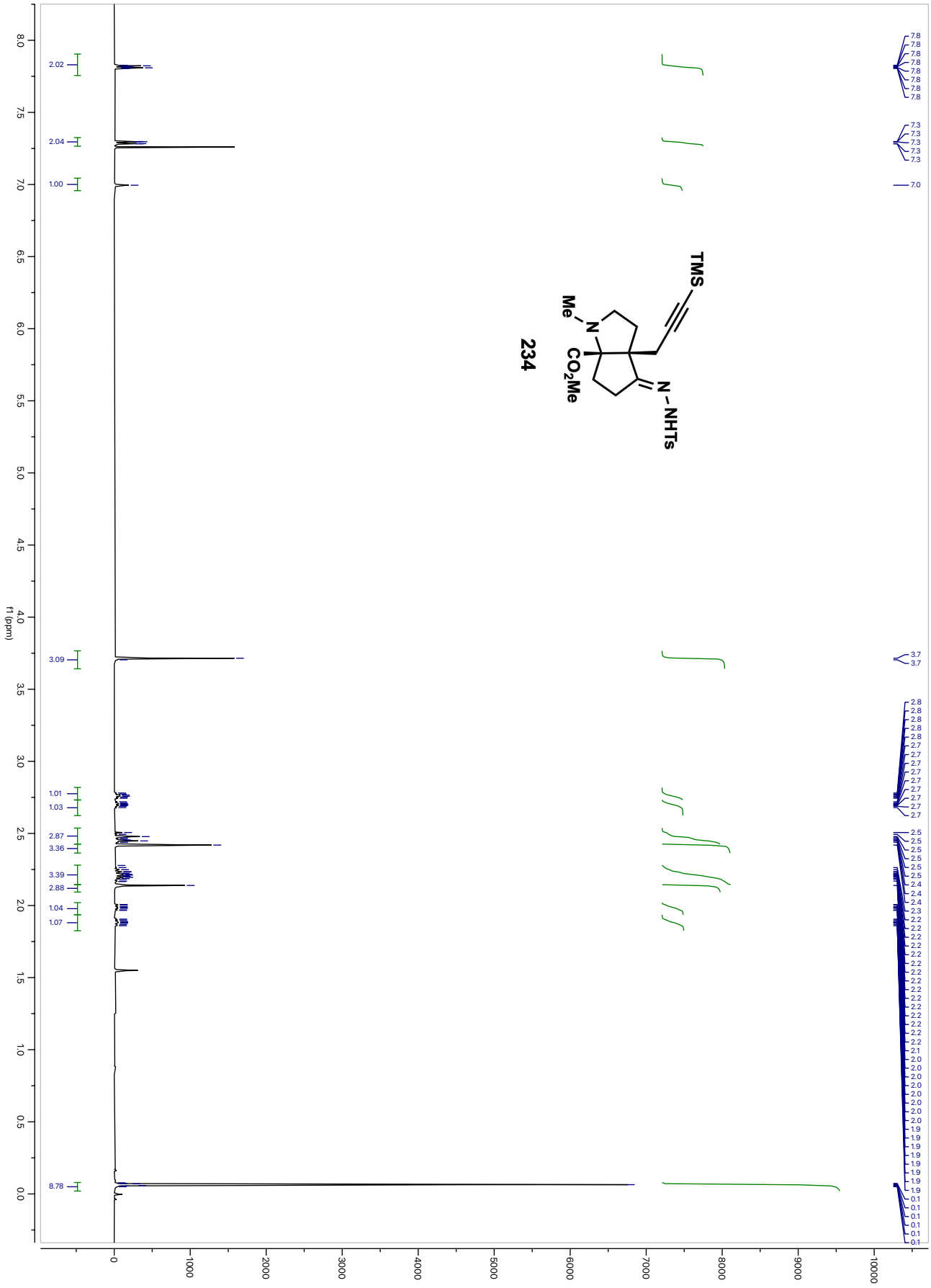

Residue Peak from C6D6
218
MeO
O
Me
N
CO2Me
OTBS
174.9
78.7
78.6
59.9
59.5
54.4
51.8
49.8
49.6
45.8
35.7
33.7
33.2
28.5
26.3
-4.2
-4.8
f1 (ppm)

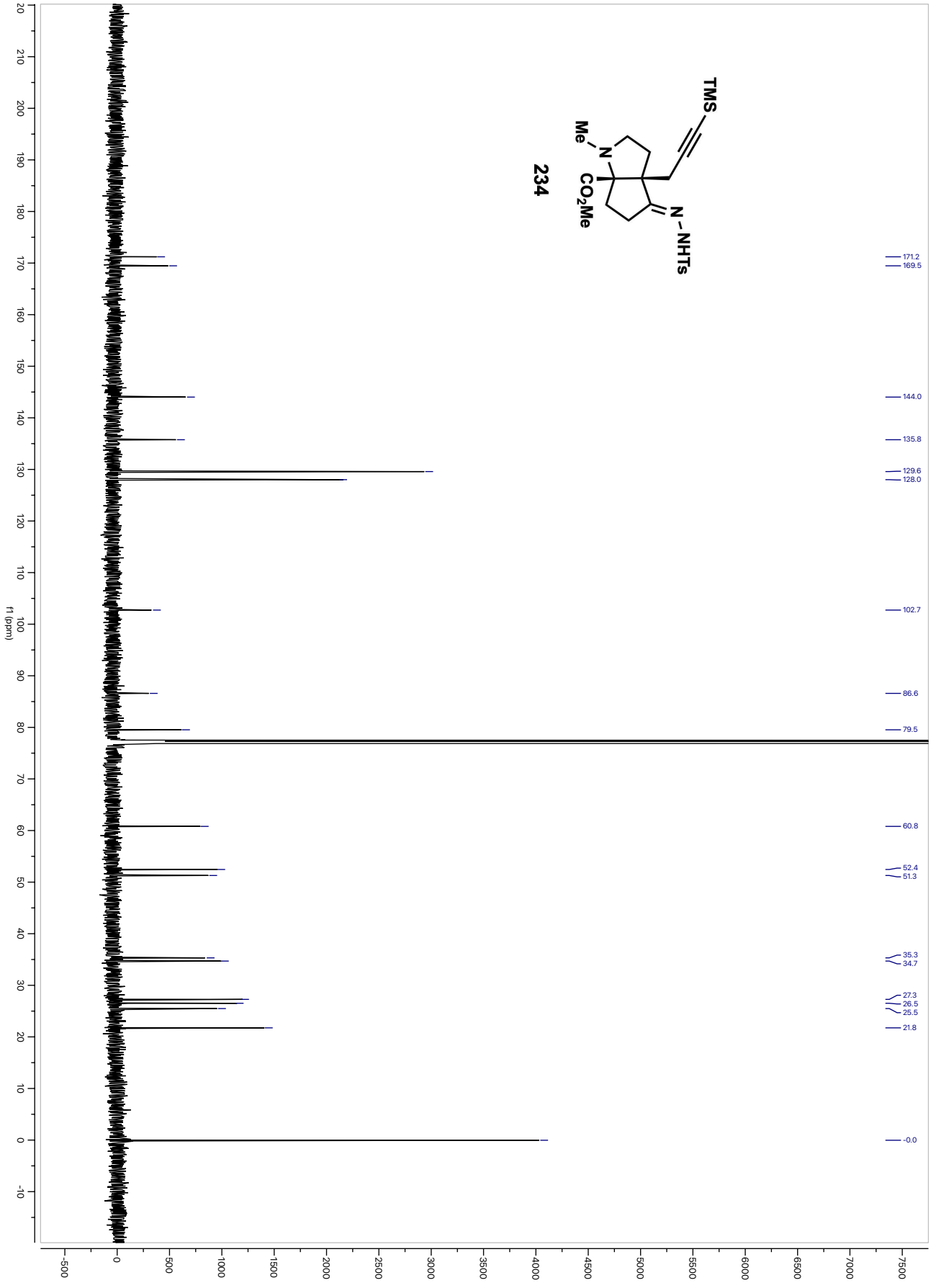

232
TMS
Me
N
CO2Me
OH
f1 (ppm)
1.00
3.04
1.37
1.08
2.19
2.95
1.20
2.15
2.17
1.24
9.20

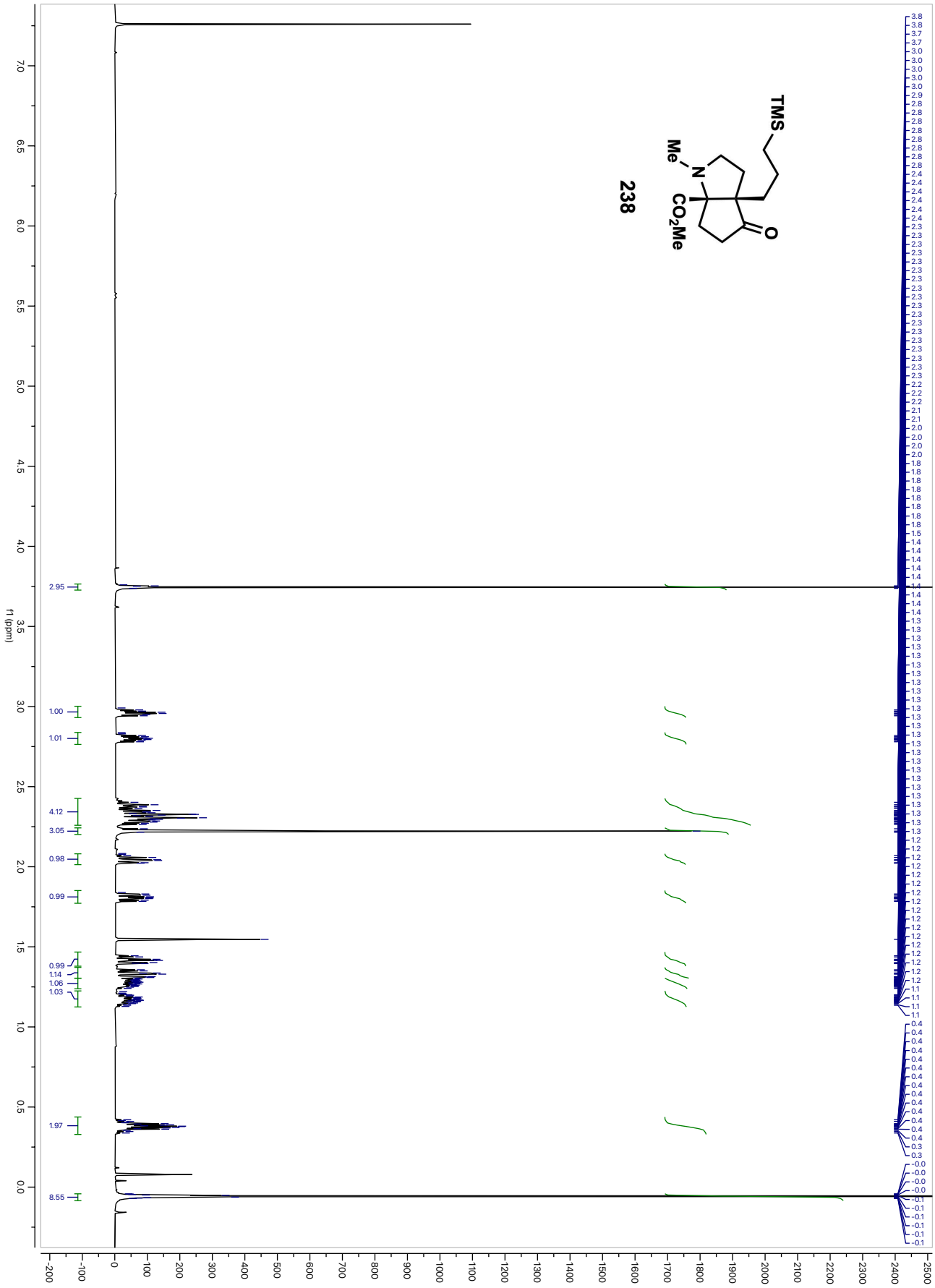

232
TMS
Me
N
CO2Me
OH
172.7
104.3
86.9
80.9
79.4
60.1
54.2
51.5
35.0
31.9
29.9
27.5
26.9
0.1
f1 (ppm)

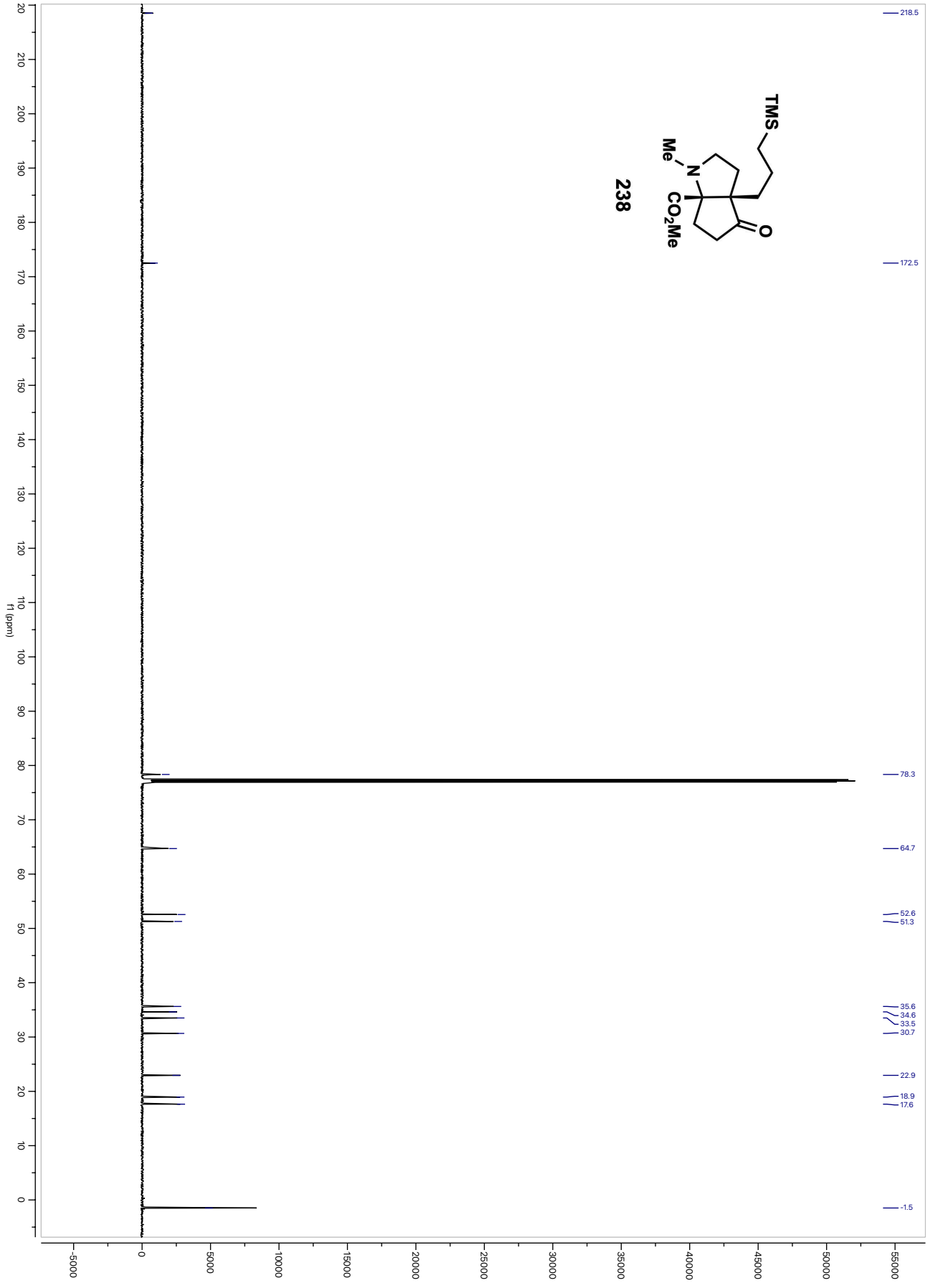

233
TMS
Me
N
CO2Me
O
f1 (ppm)
2.82
1.88
1.92
1.94
1.93
2.81
1.01
1.00
8.23

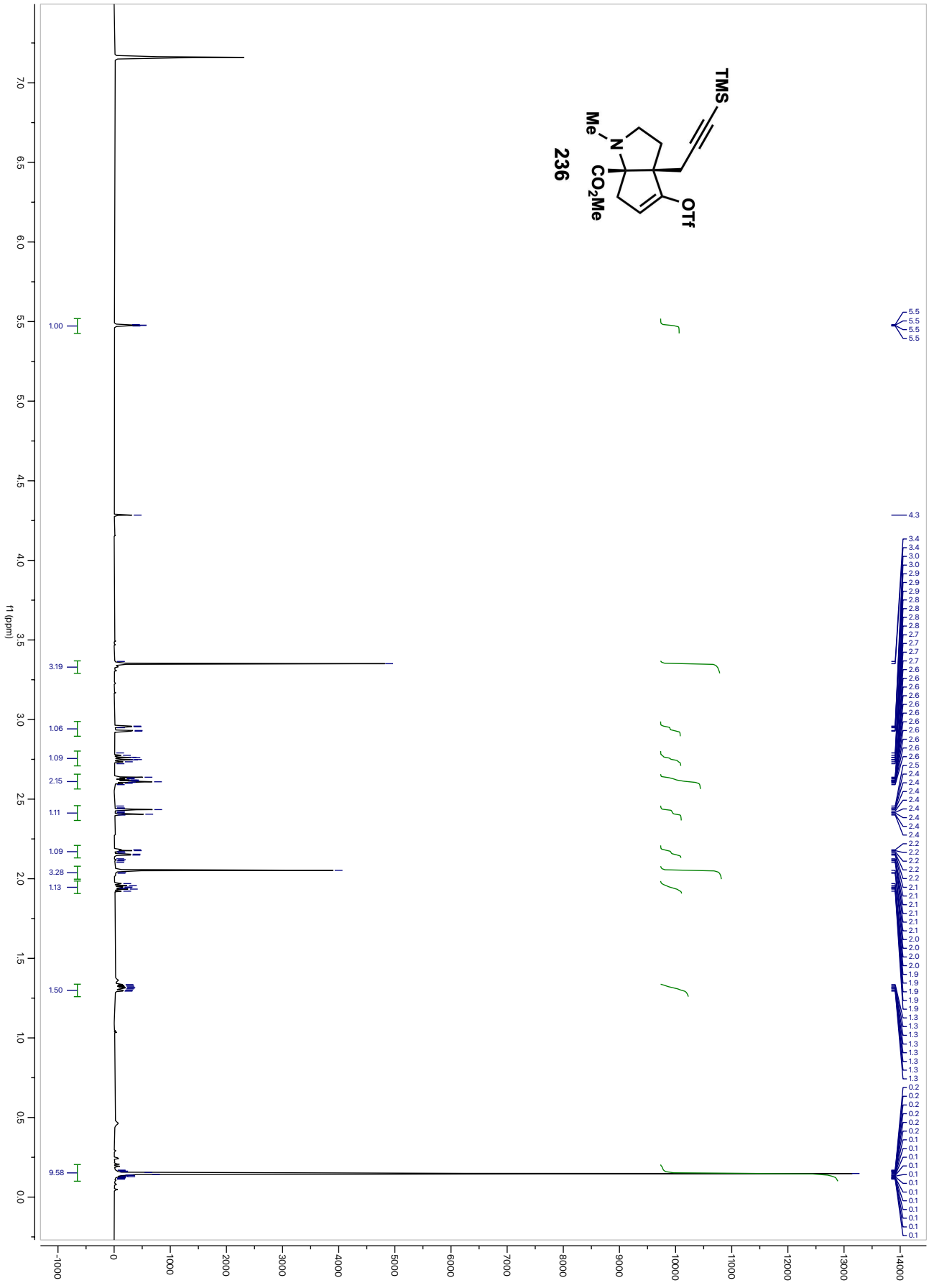

TMS
Me
N
CO2Me
O
233
217.3
170.9
102.8
87.2
77.8
62.6
52.4
50.7
34.6
34.4
33.0
24.3
24.0
-0.1
f1 (ppm)

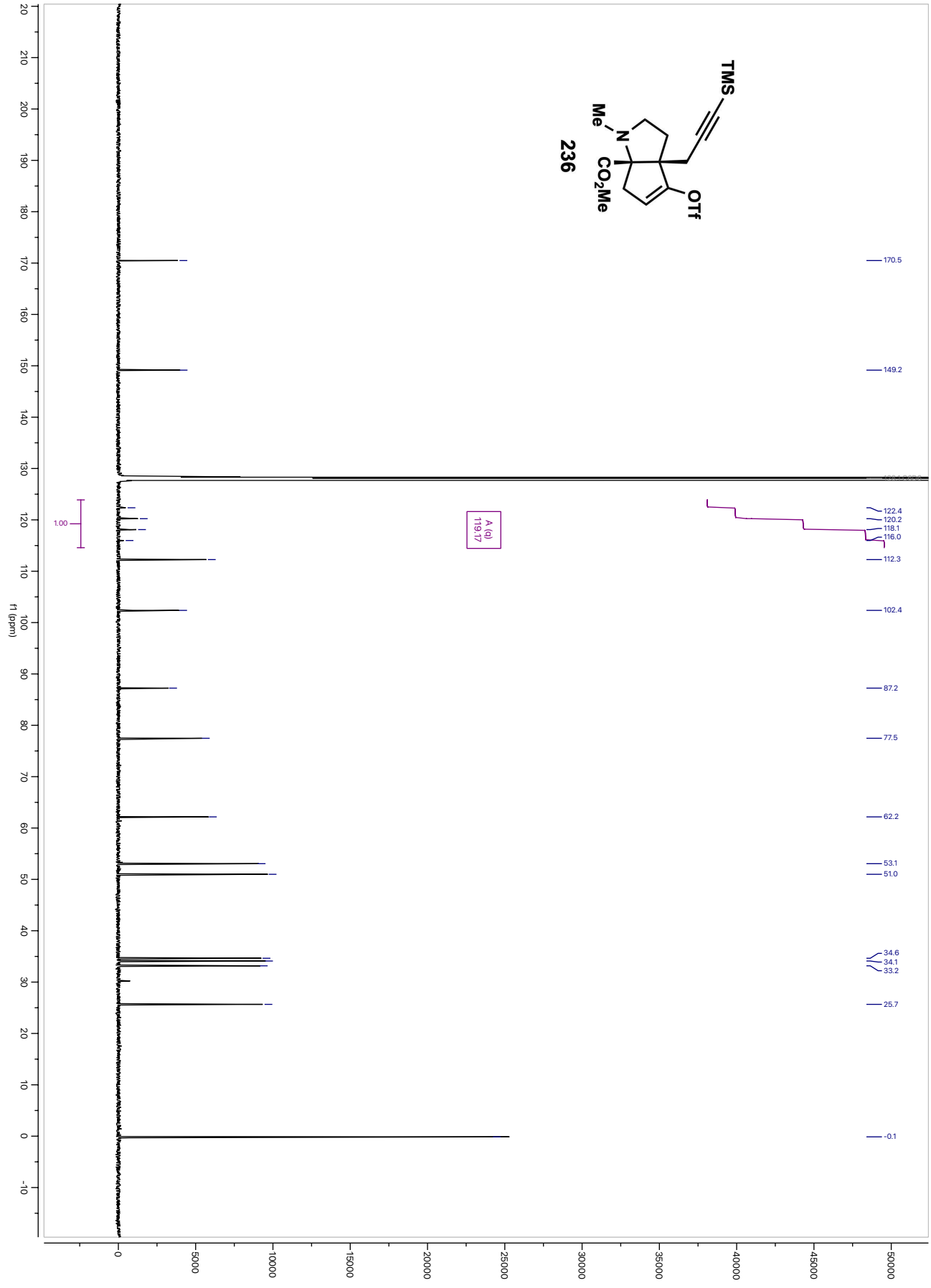

234
TMS
Me
N
CO2Me
N–NHTs
f1 (ppm)

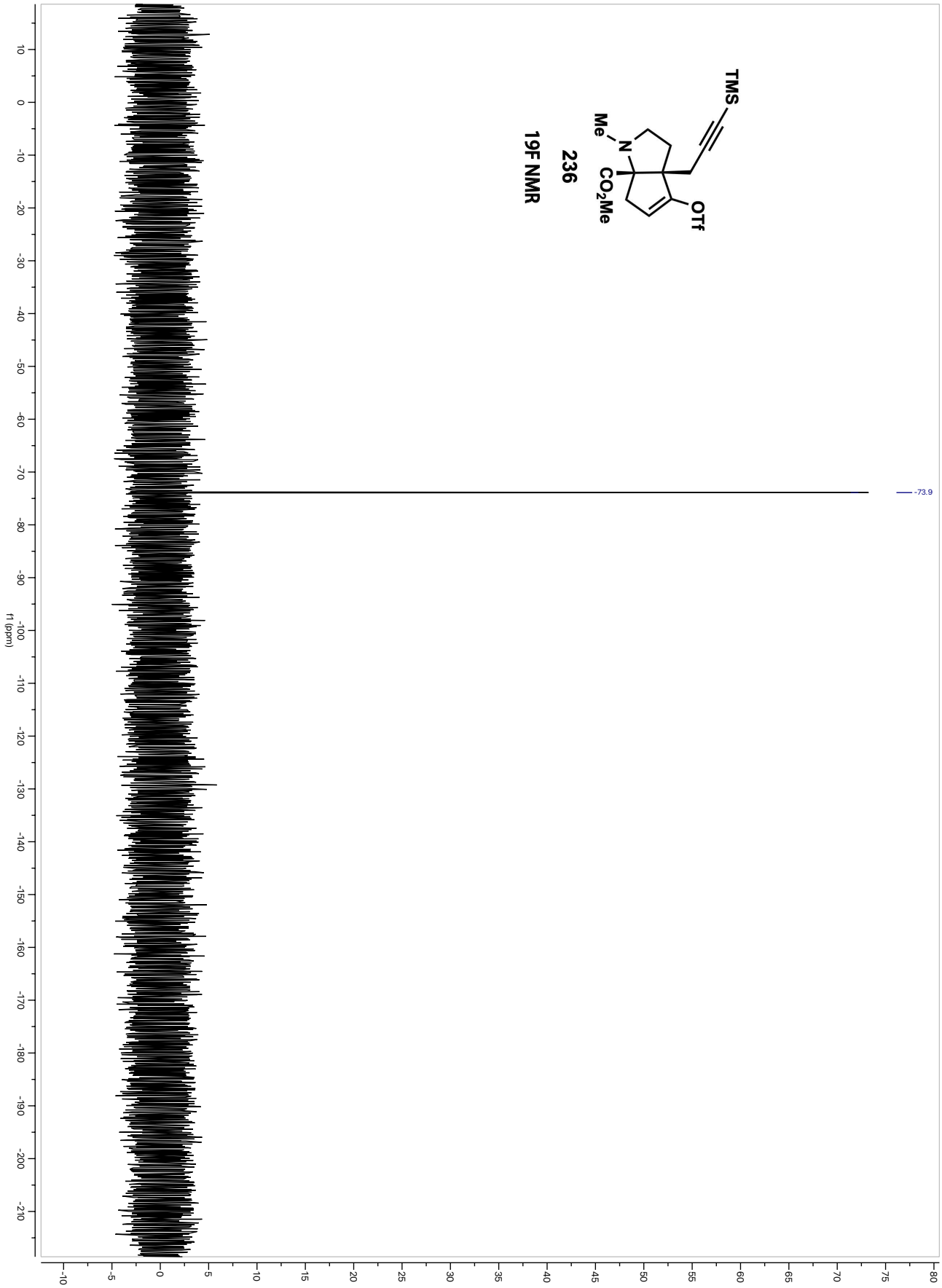

234
TMS
Me
N
CO2Me
N
NHTs
171.2
169.5
144.0
135.8
129.6
128.0
102.7
86.6
79.5
60.8
52.4
51.3
35.3
34.7
27.3
26.5
25.5
21.8
-0.0
f1 (ppm)

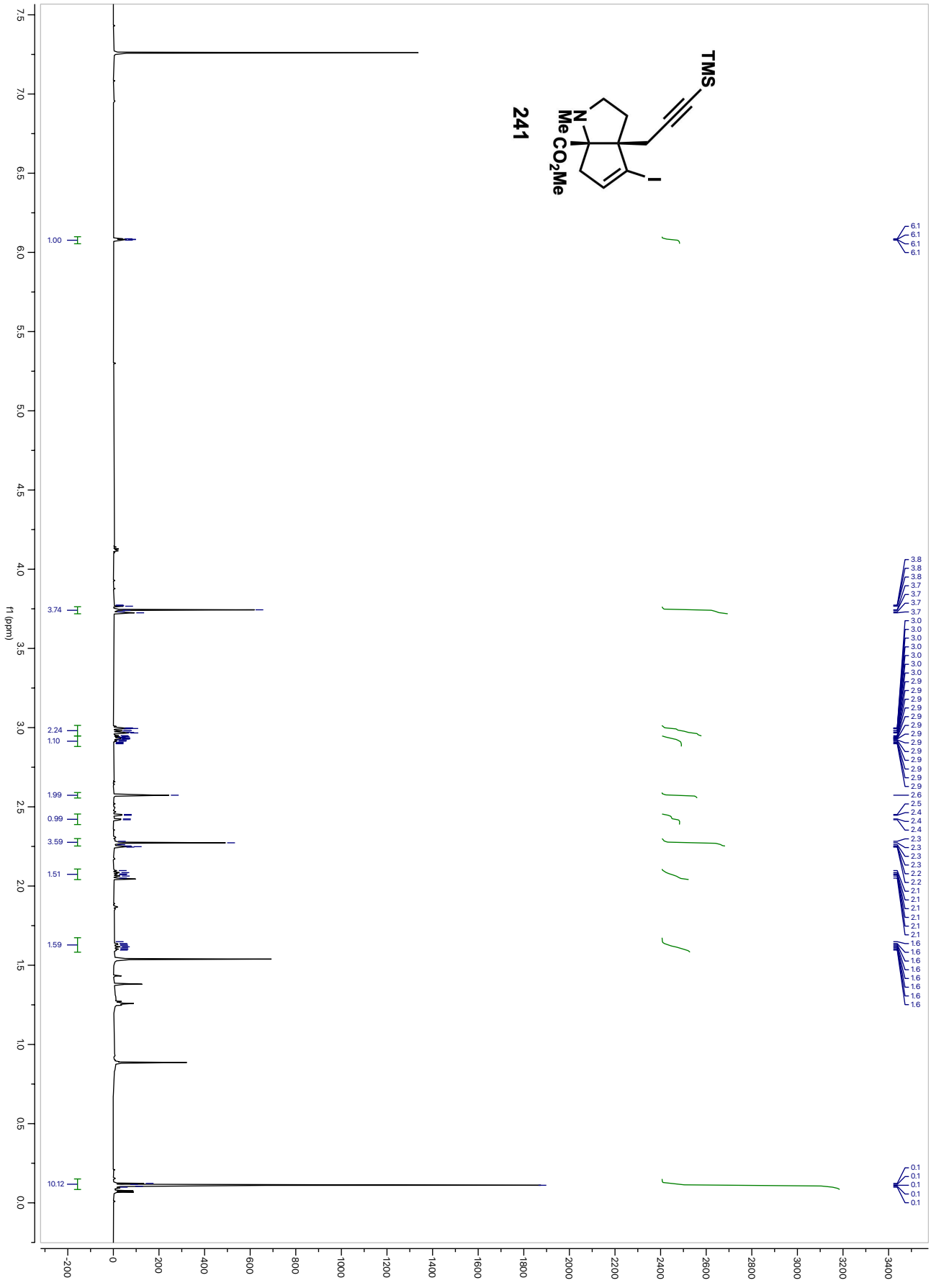

238
TMS
Me
N
CO2Me
O
f1 (ppm)
2.95
1.00
1.01
4.12
3.05
0.98
0.99
0.99
1.14
1.06
1.03
1.97
8.55

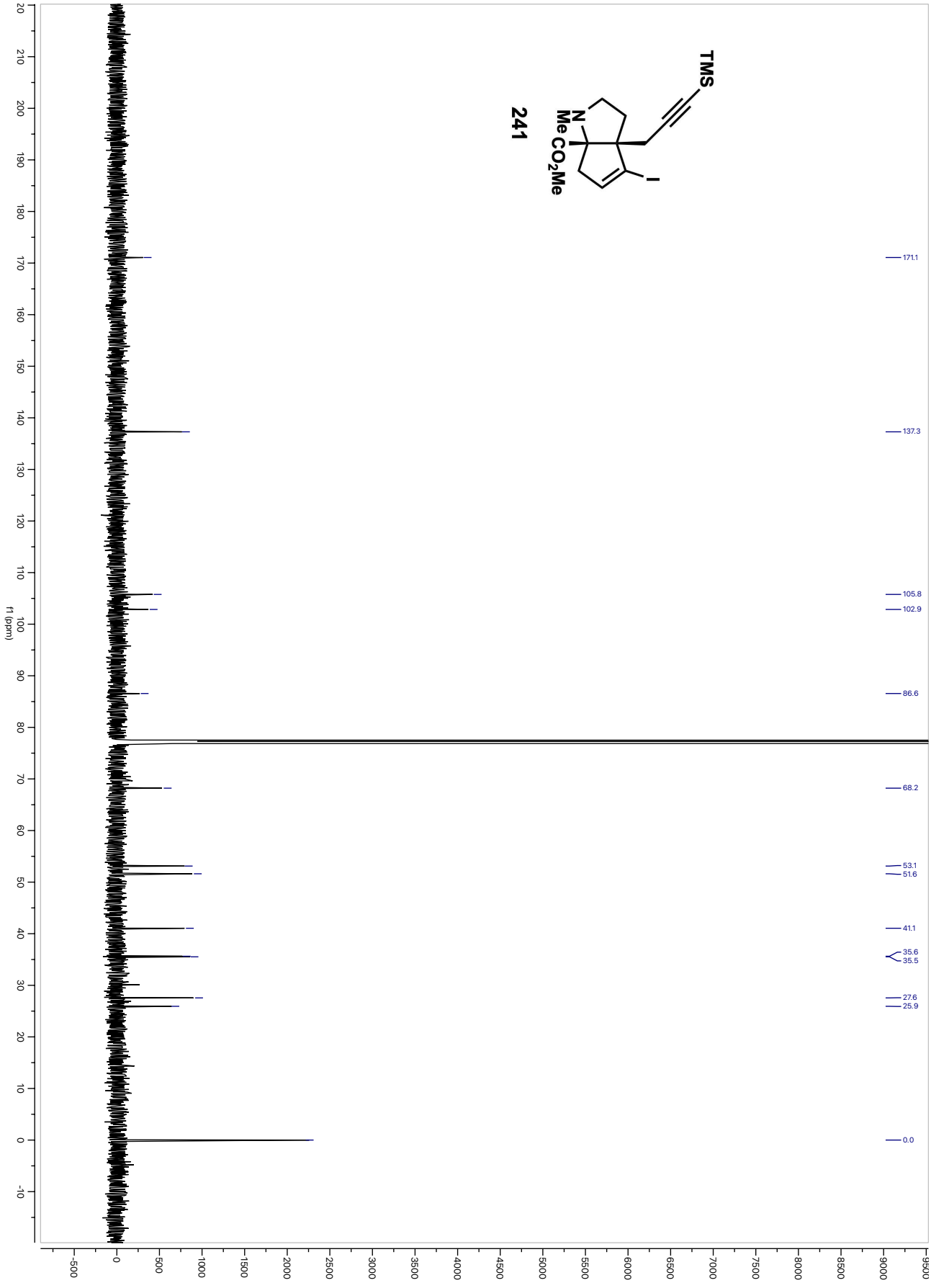

238
TMS
Me
N
CO2Me
O
218.5
172.5
78.3
64.7
52.6
51.3
35.6
34.6
33.5
30.7
22.9
18.9
17.6
-1.5
f1 (ppm)

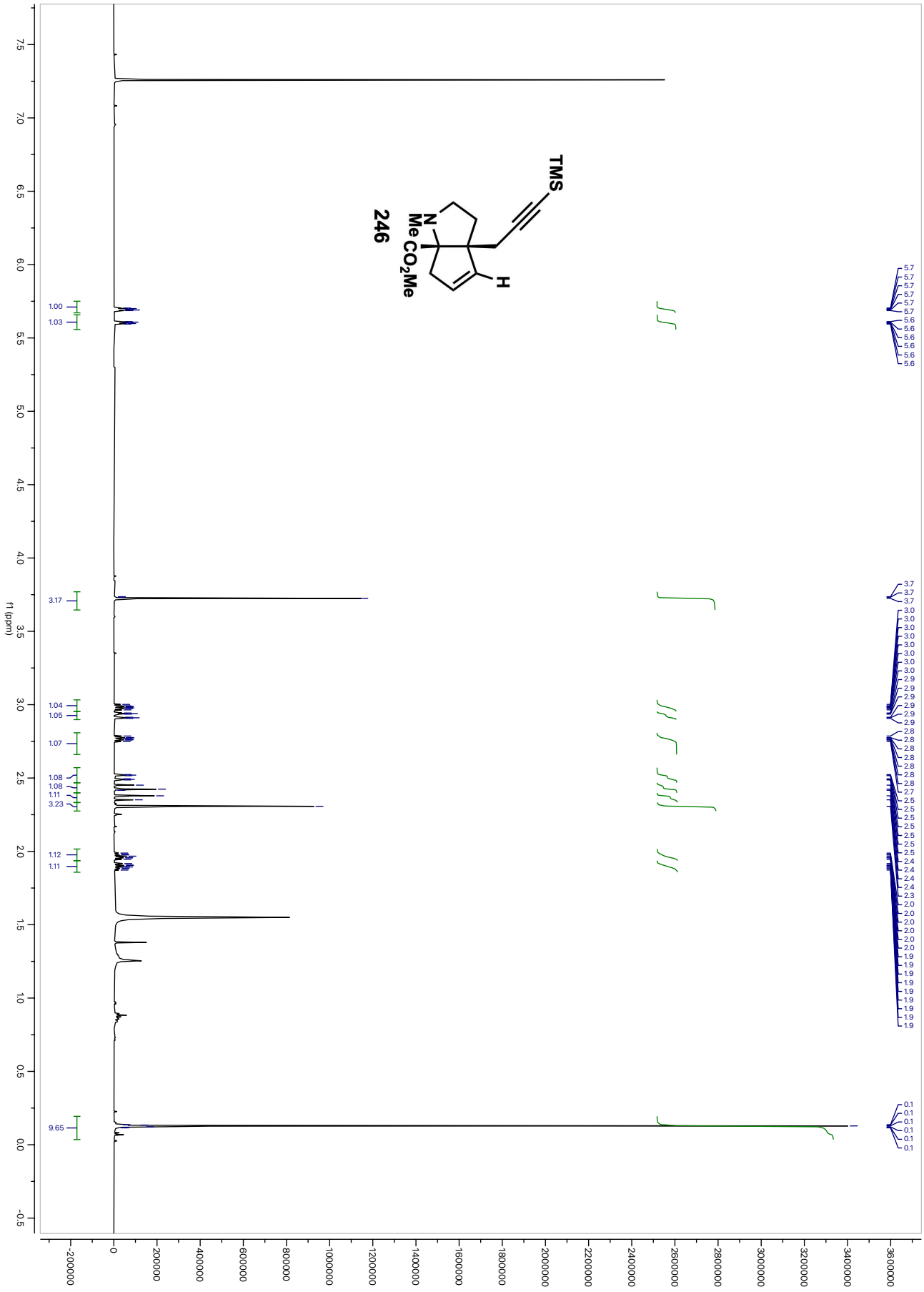

TMS
Me
N
CO2Me
OTf
236
f1 (ppm)

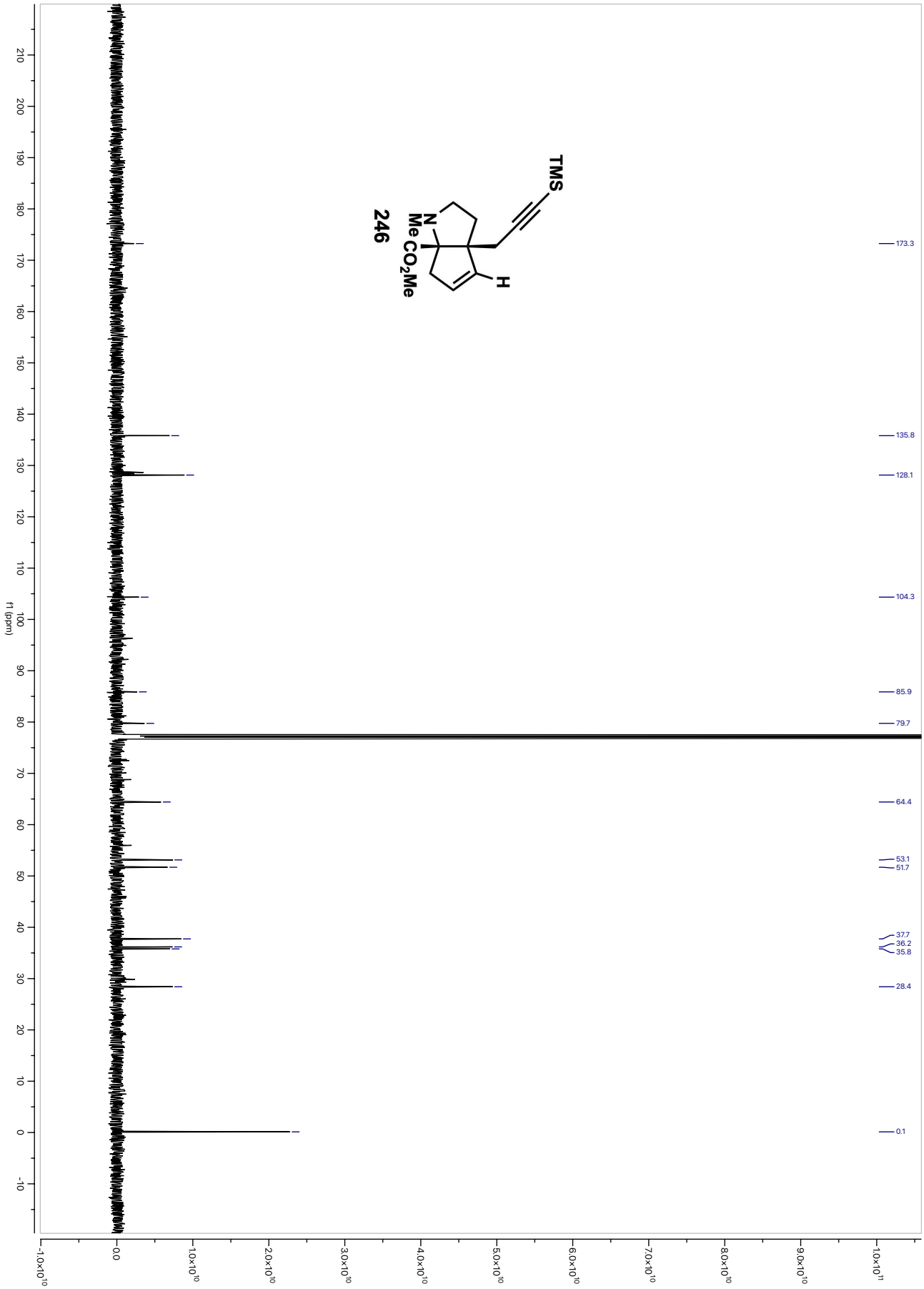

TMS
Me
N
CO2Me
OTf
236
170.5
149.2
122.4
120.2
118.1
116.0
112.3
102.4
87.2
77.5
62.2
53.1
51.0
34.6
34.1
33.2
25.7
-0.1
1.00
A (q)
119.17
f1 (ppm)

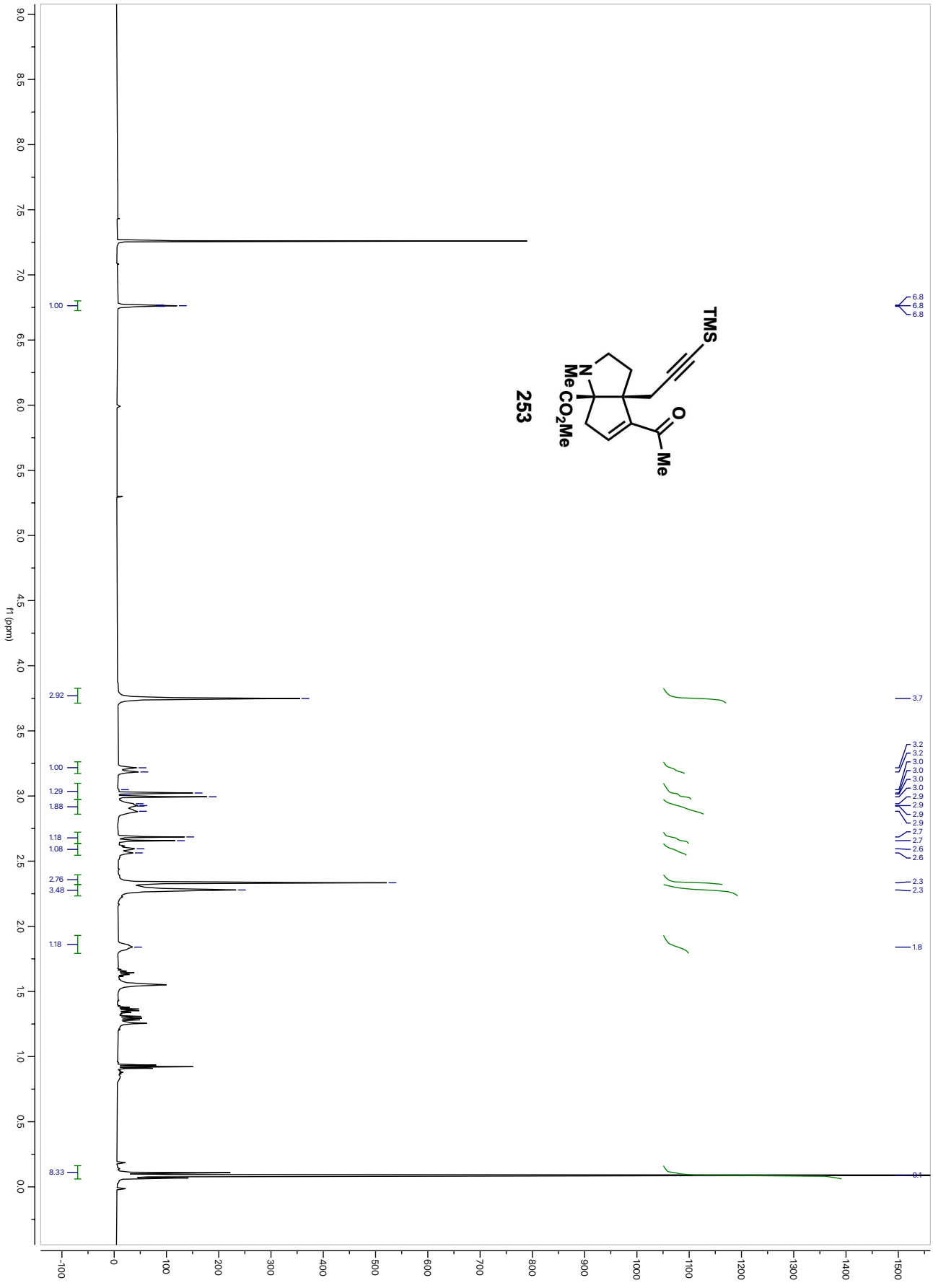

TMS
Me
N
CO2Me
OTf
236
19F NMR
-73.9
f1 (ppm)

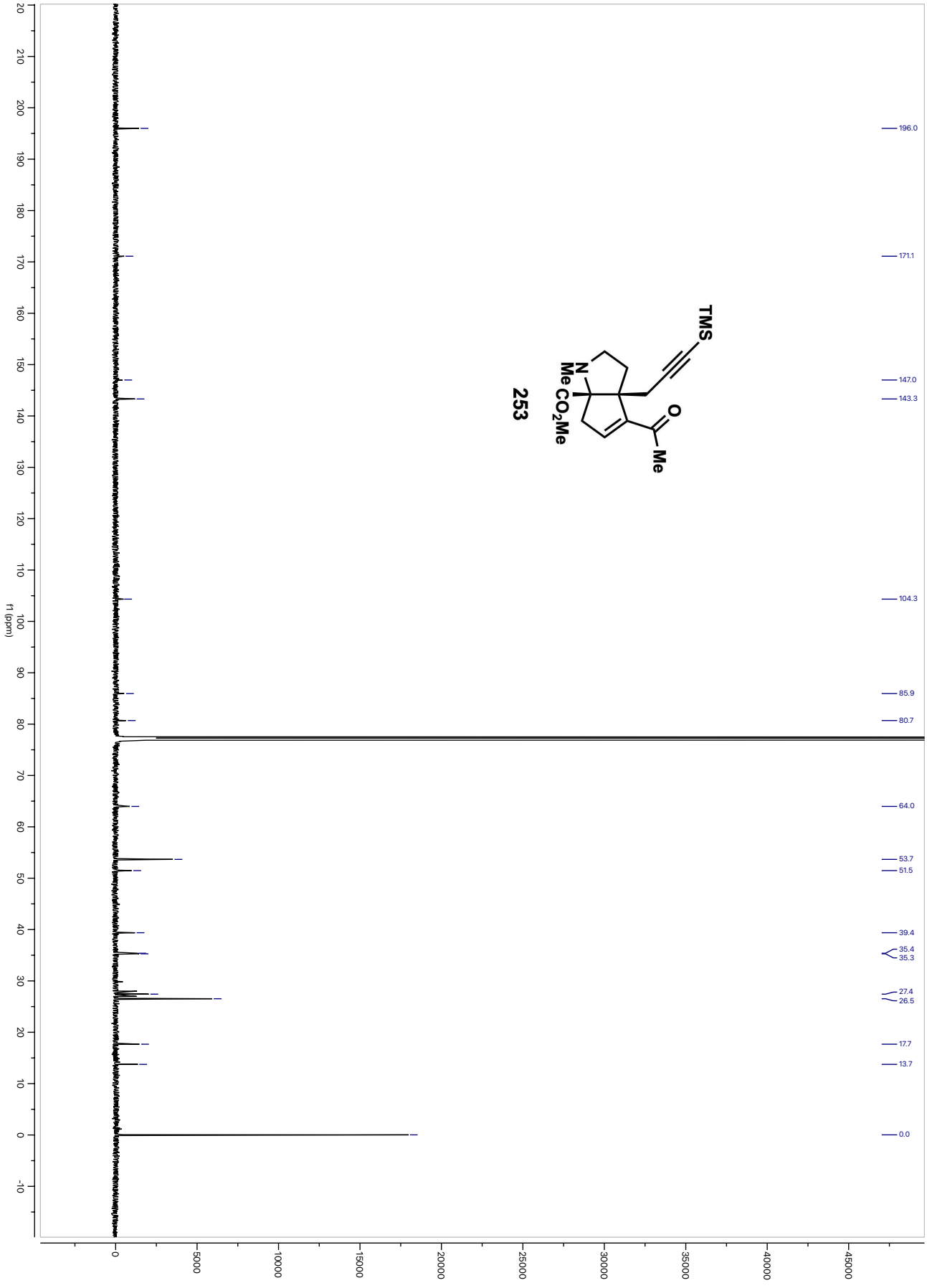

TMS
N
Me
CO2Me
I
241
f1 (ppm)
1.00
3.74
2.24
1.10
1.99
0.99
3.59
1.51
1.59
10.12

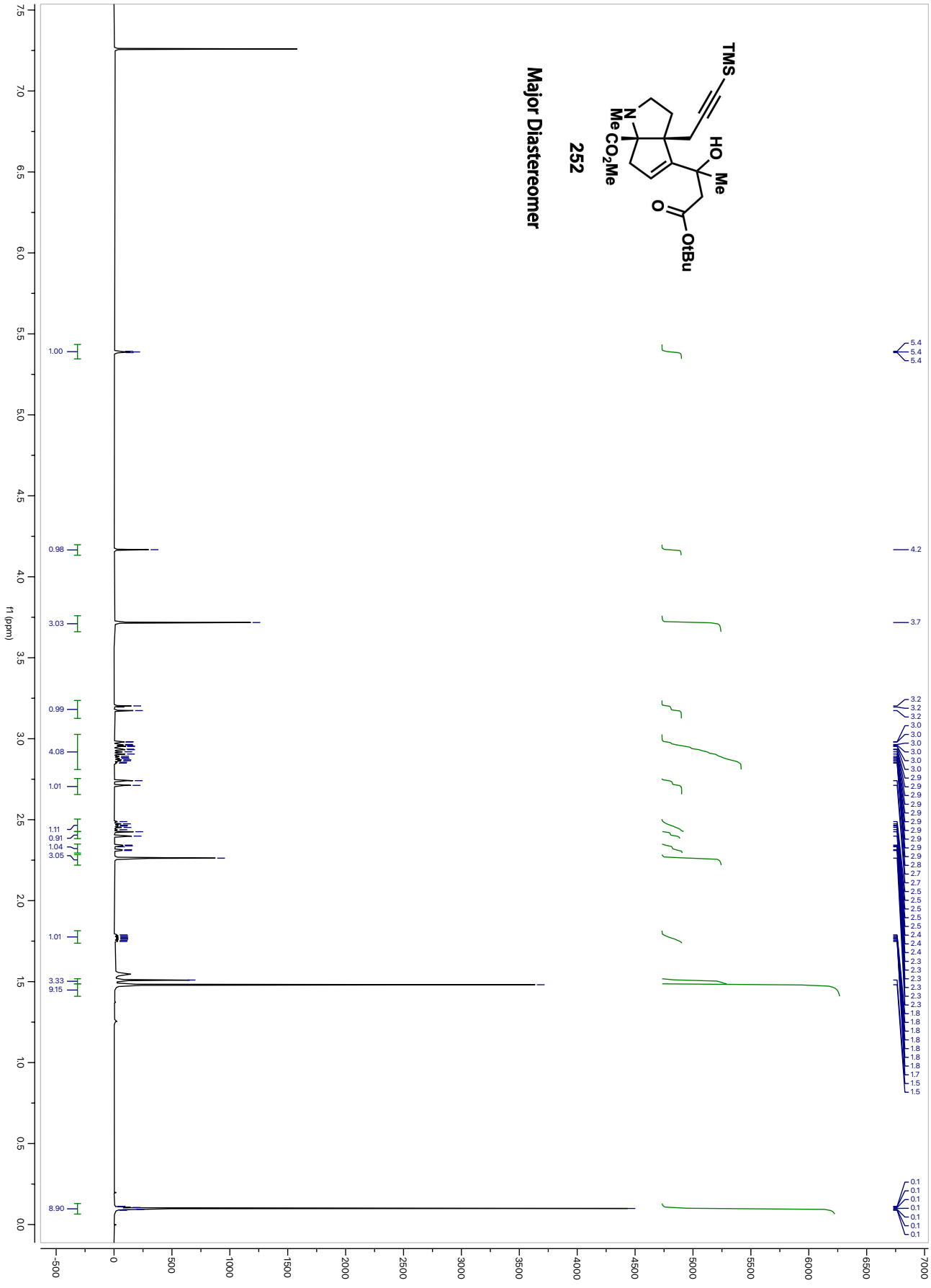

TMS
N
Me
CO2Me
I
241
171.1
137.3
105.8
102.9
86.6
68.2
53.1
51.6
41.1
35.6
35.5
27.6
25.9
0.0
f1 (ppm)

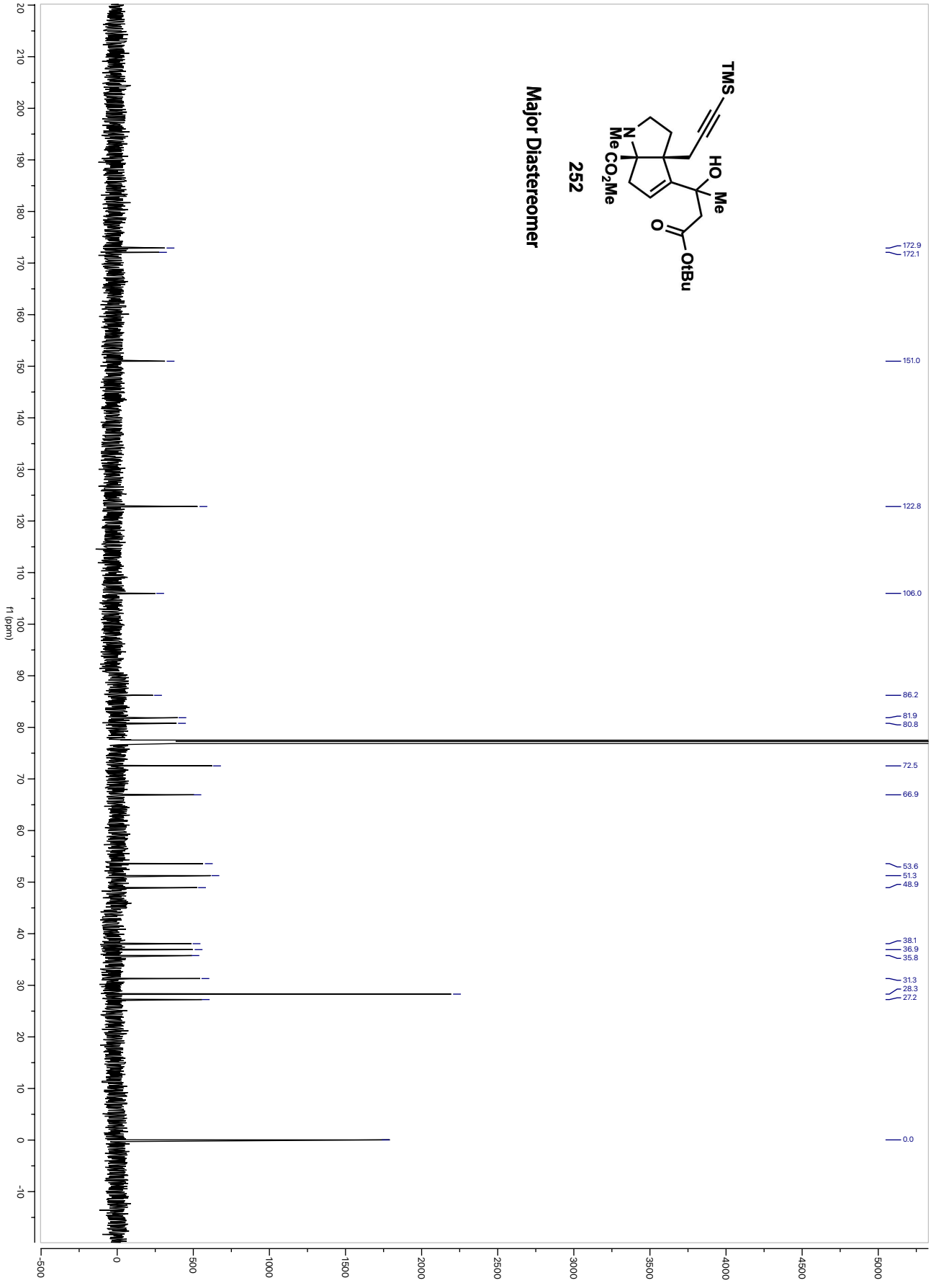

TMS
N
Me
CO2Me
H
246
f1 (ppm)

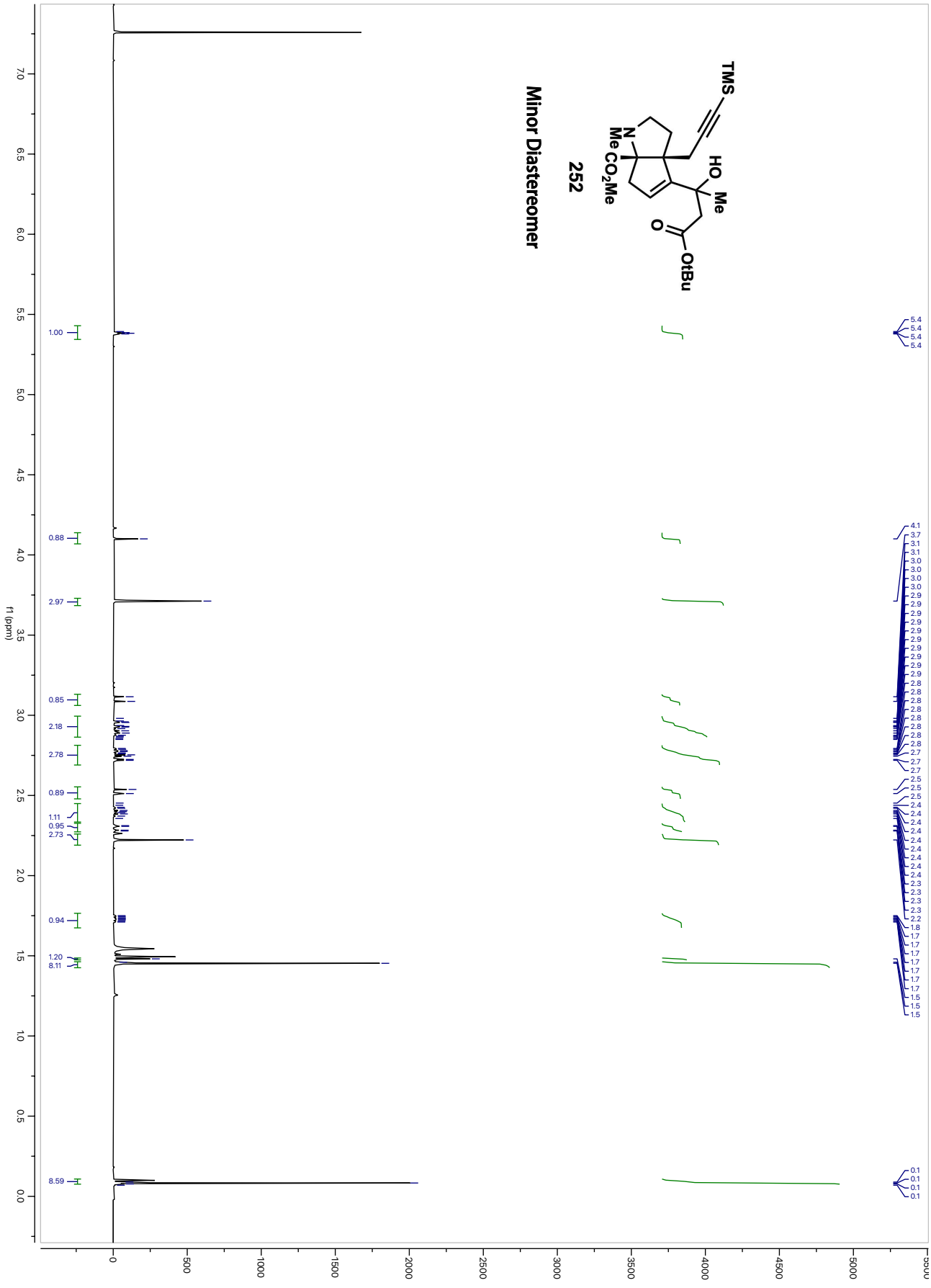

TMS
N
Me
CO2Me
H
246
173.3
135.8
128.1
104.3
85.9
79.7
64.4
53.1
51.7
37.7
36.2
35.8
28.4
0.1
f1 (ppm)

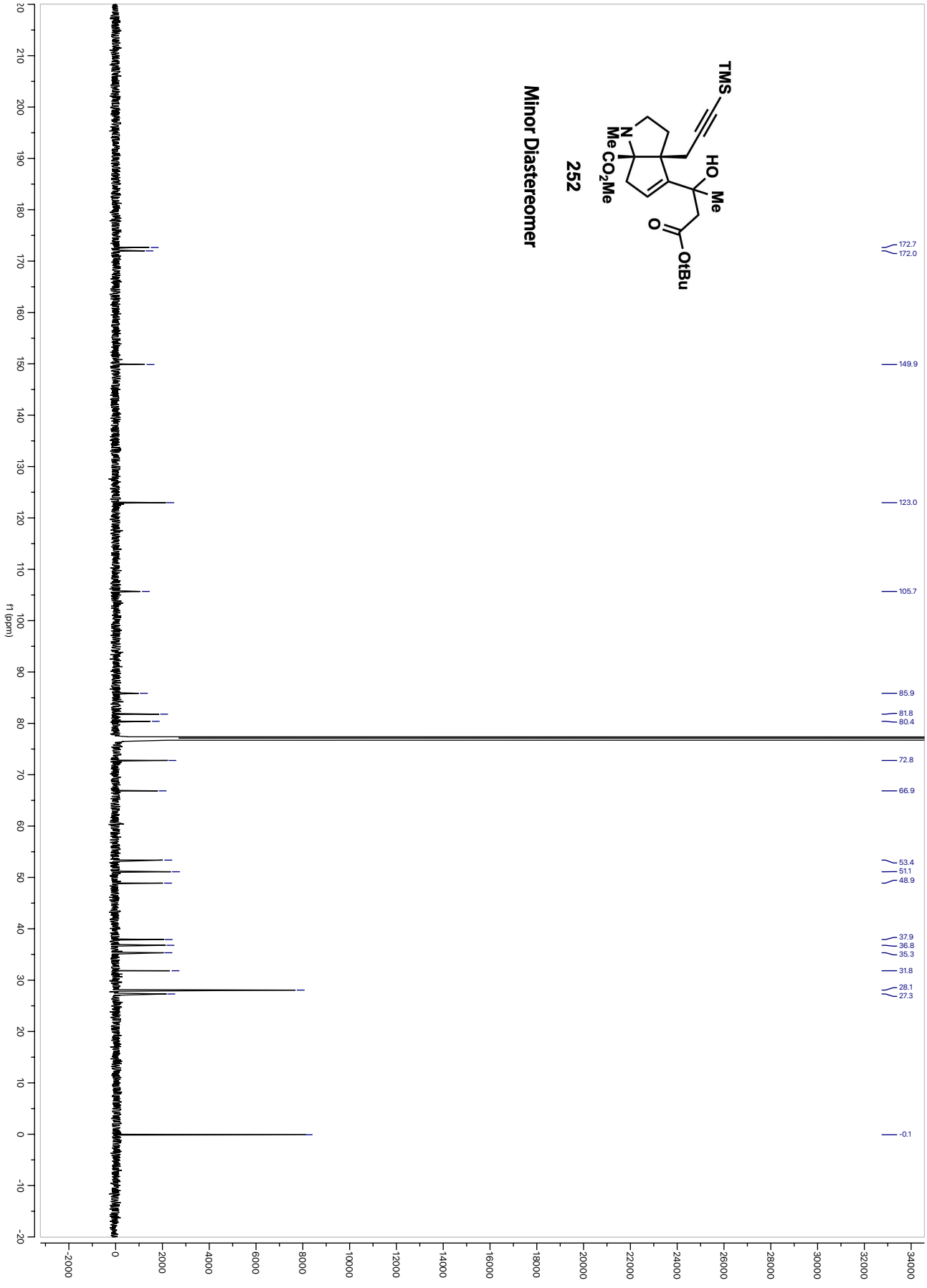

TMS
N
Me
CO2Me
O
Me
253
f1 (ppm)

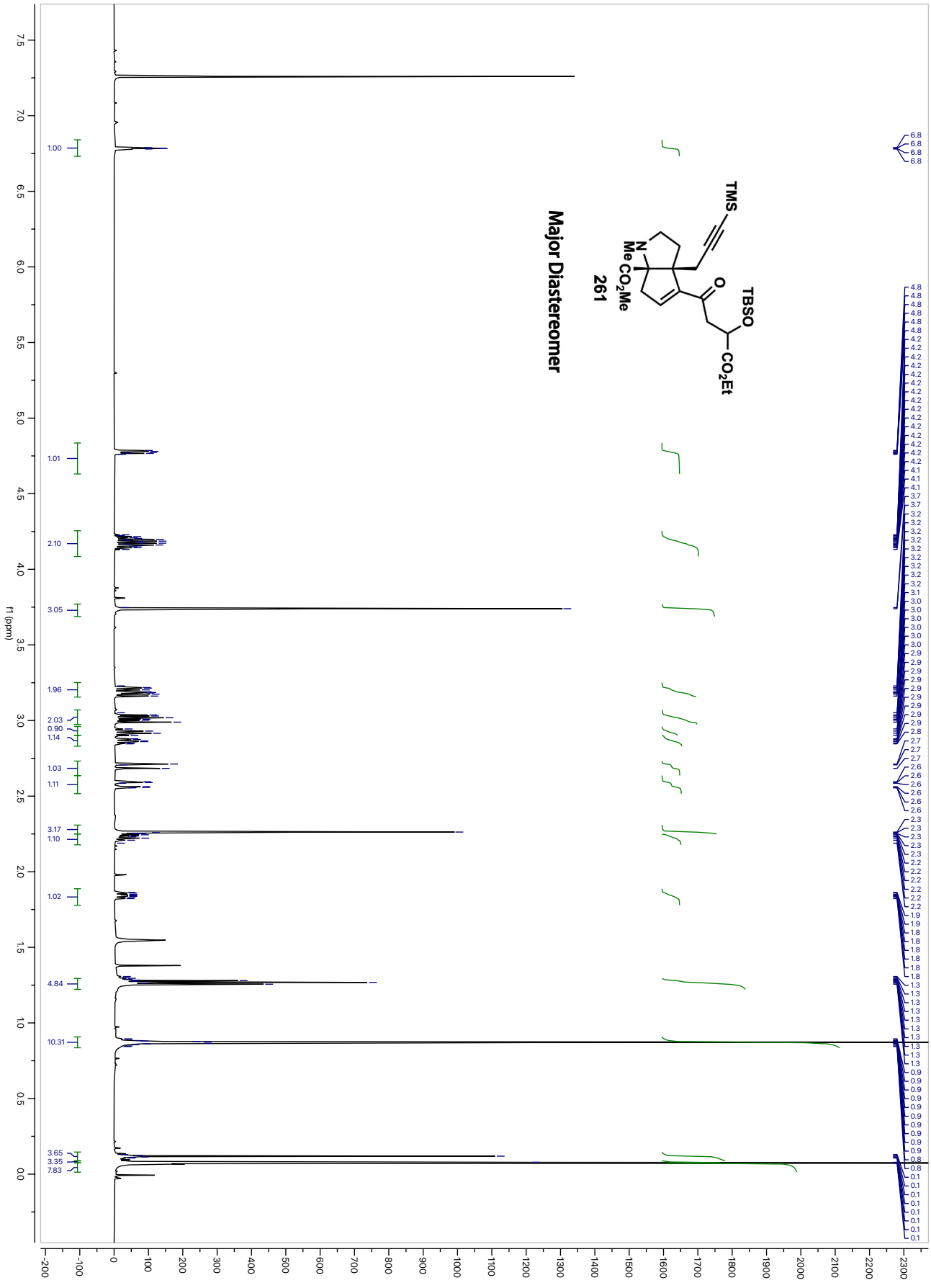

TMS
N
Me
CO2Me
O
Me
253
196.0
171.1
147.0
143.3
104.3
85.9
80.7
64.0
53.7
51.5
39.4
35.4
35.3
27.4
26.5
17.7
13.7
0.0
f1 (ppm)

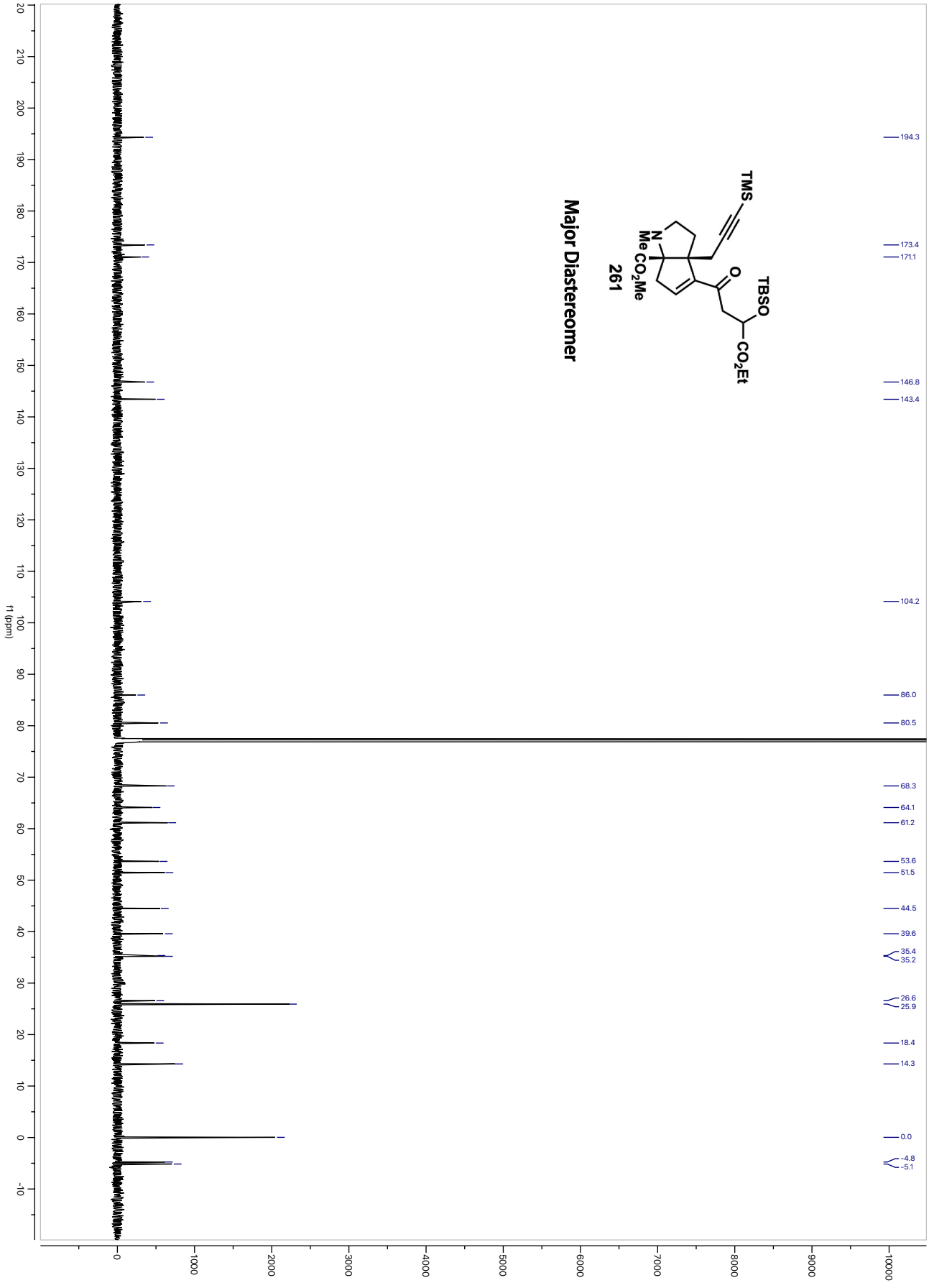

Major Diastereomer
252
TMS
HO
Me
N
Me
CO2Me
O
OtBu
f1 (ppm)

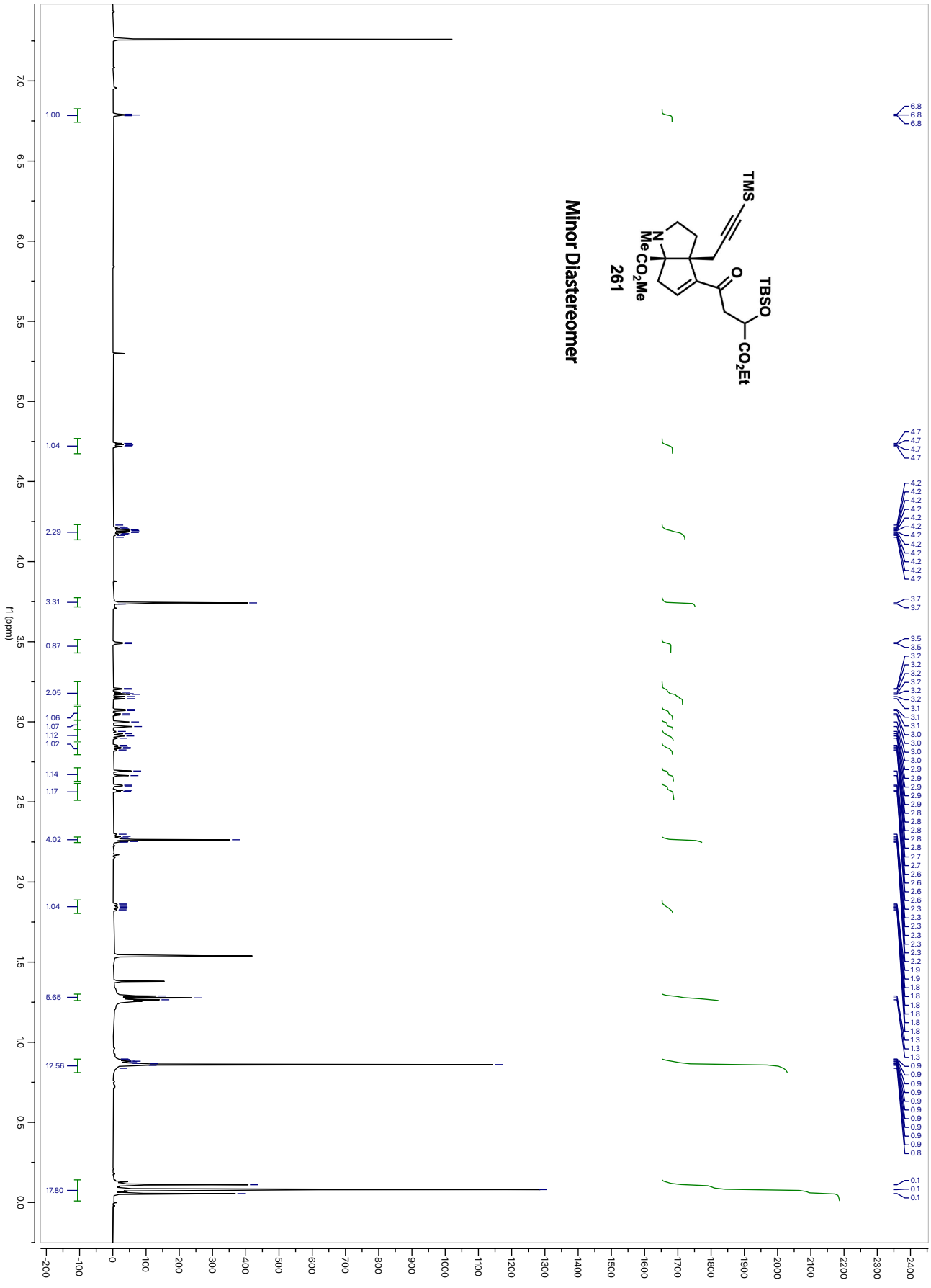

Major Diastereomer
252
TMS
HO
Me
N
Me
CO2Me
O
OtBu
172.9
172.1
151.0
122.8
106.0
86.2
81.9
80.8
72.5
66.9
53.6
51.3
48.9
38.1
36.9
35.8
31.3
28.3
27.2
0.0
f1 (ppm)

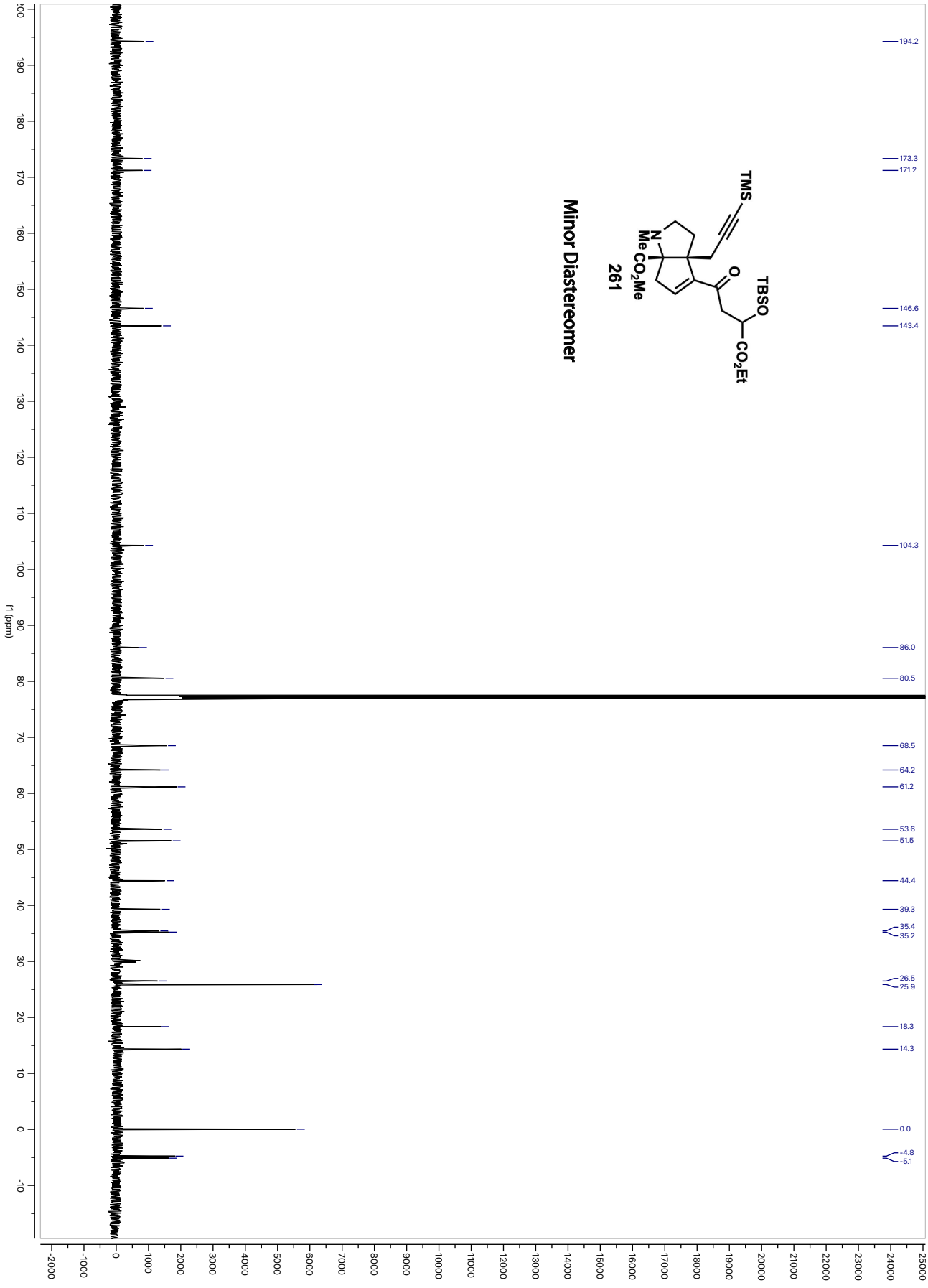

Minor Diastereomer
252
TMS
HO
Me
N
Me
CO2Me
O
OtBu
f1 (ppm)

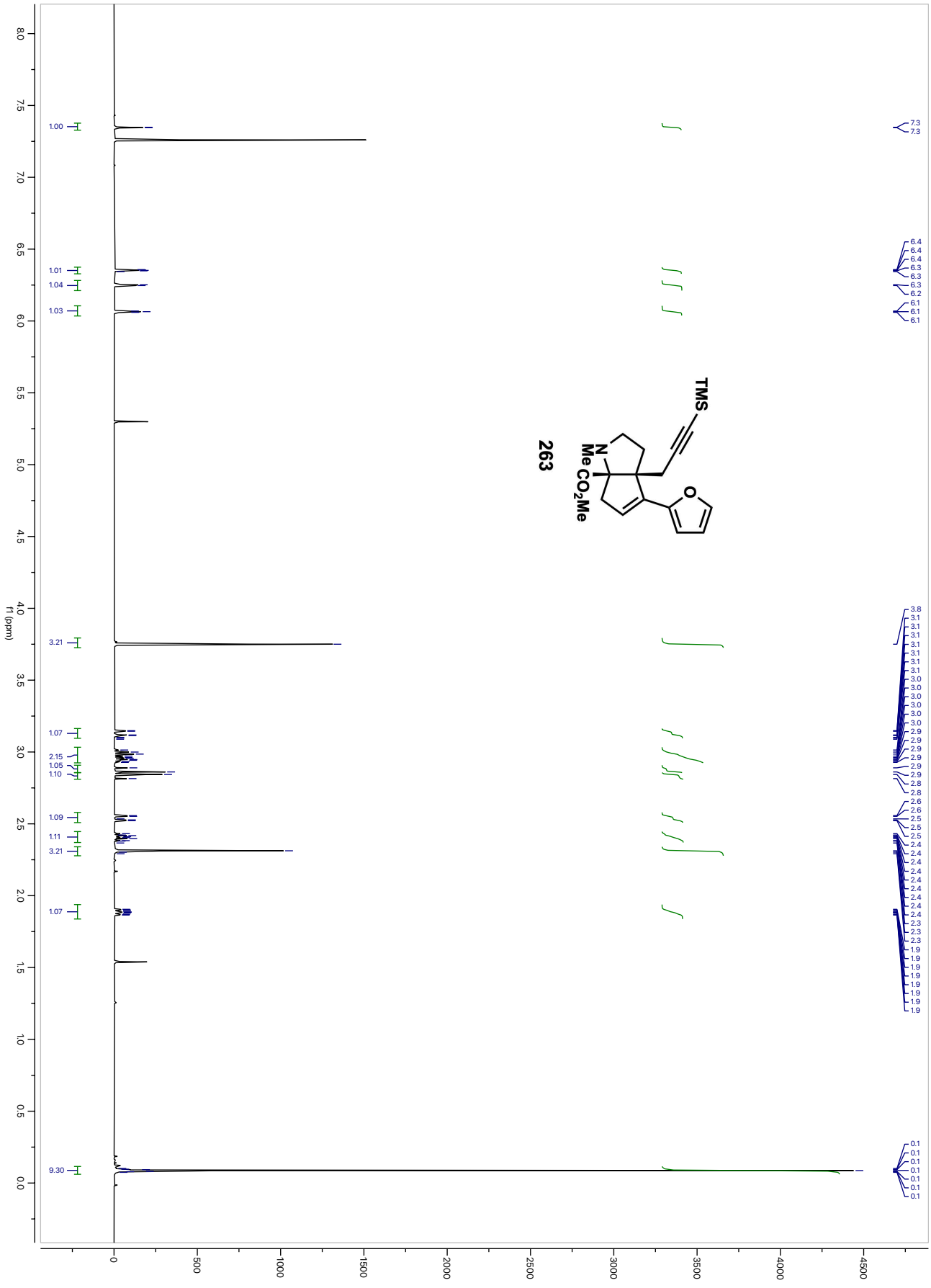

Minor Diastereomer
252
TMS
HO
Me
N
Me
CO2Me
O
OtBu
172.7
172.0
149.9
123.0
105.7
85.9
81.8
80.4
72.8
66.9
53.4
51.1
48.9
37.9
36.8
35.3
31.8
28.1
27.3
-0.1
f1 (ppm)

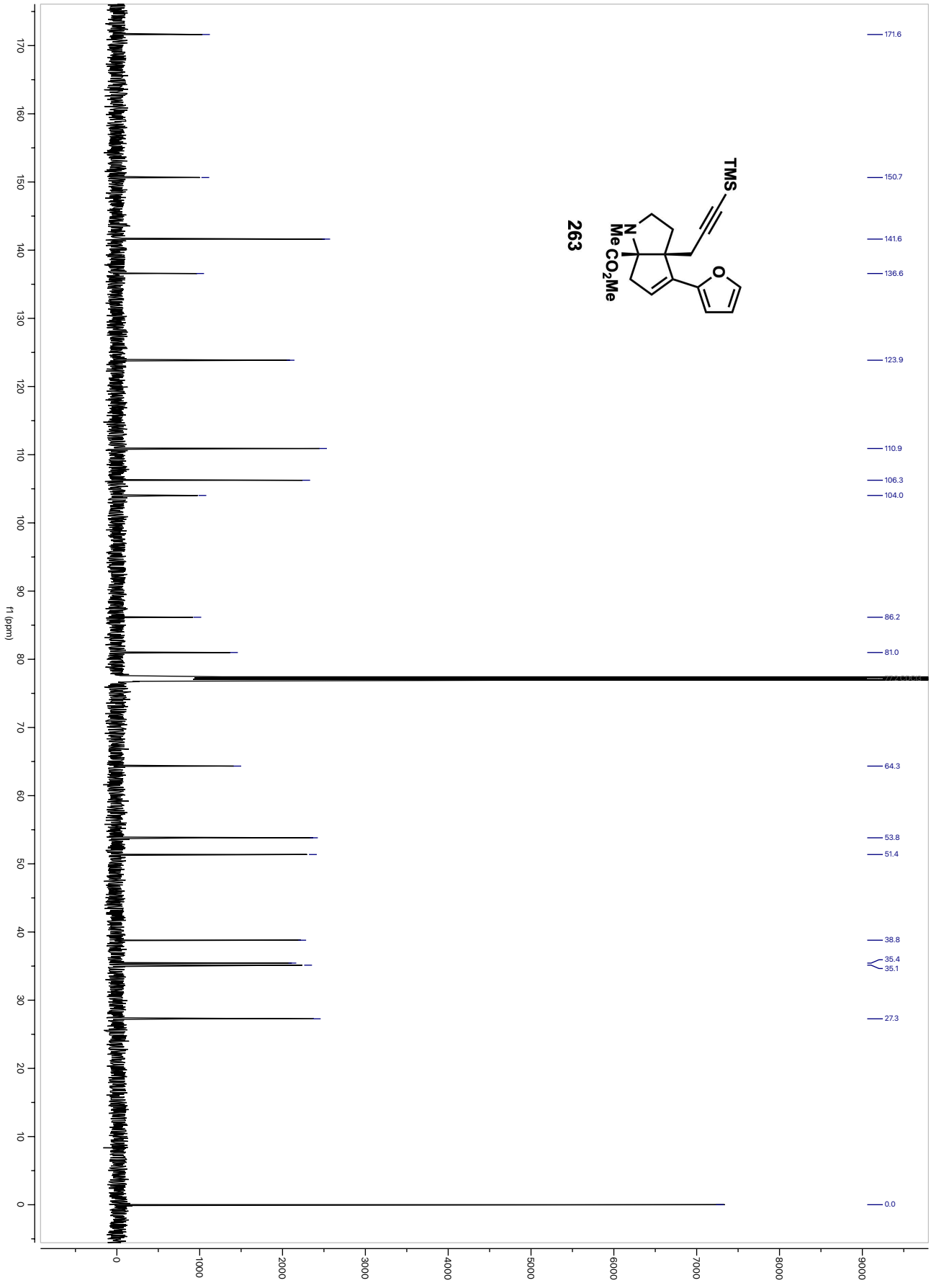

Major Diastereomer
261
TMS
TBSO
CO2Et
N
Me
CO2Me
O
f1 (ppm)

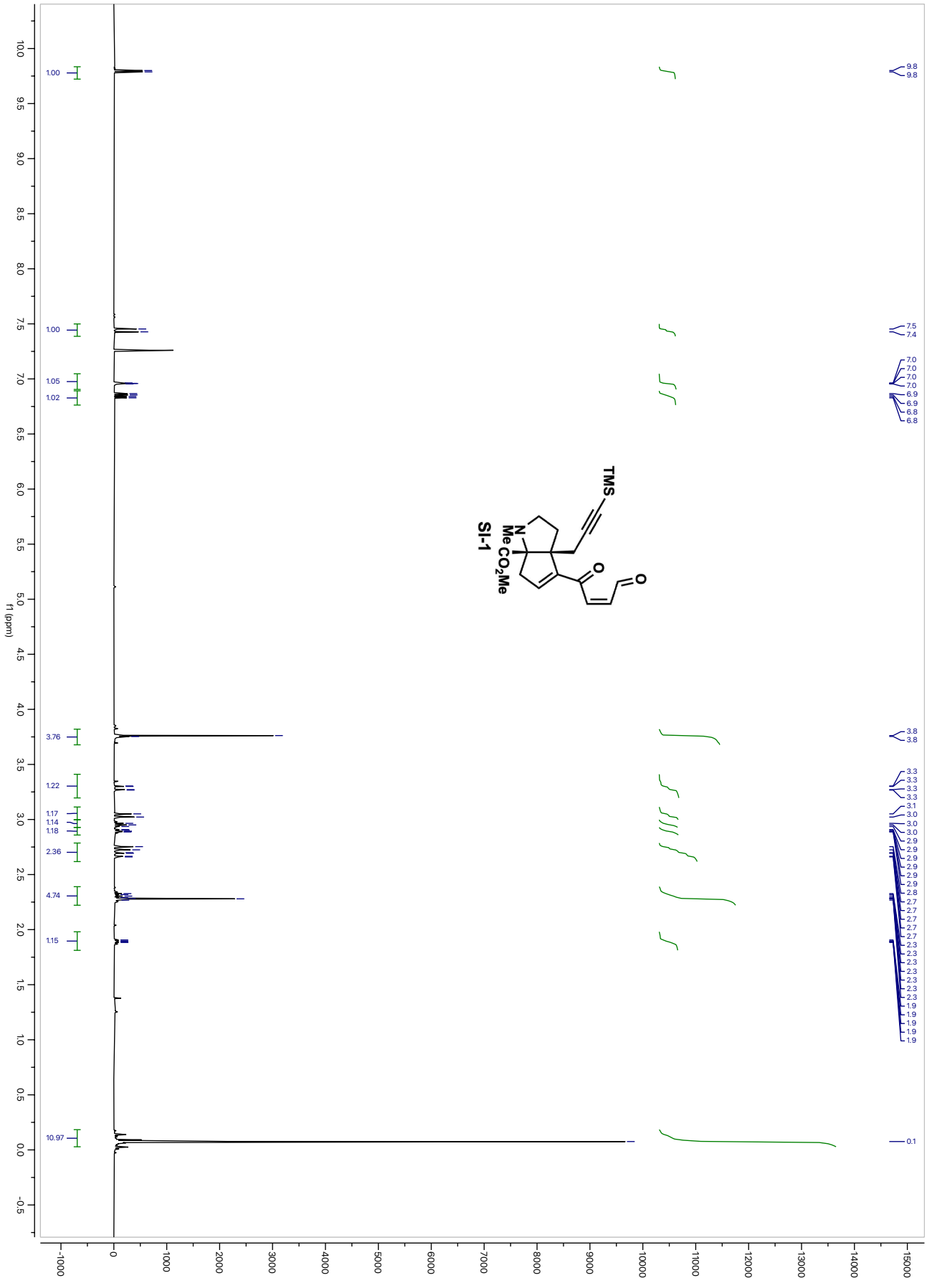

Major Diastereomer
261
TMS
N
Me
CO2Me
O
TBSO
CO2Et
194.3
173.4
171.1
146.8
143.4
104.2
86.0
80.5
68.3
64.1
61.2
53.6
51.5
44.5
39.6
35.4
35.2
26.6
25.9
18.4
14.3
0.0
-4.8
-5.1
f1 (ppm)

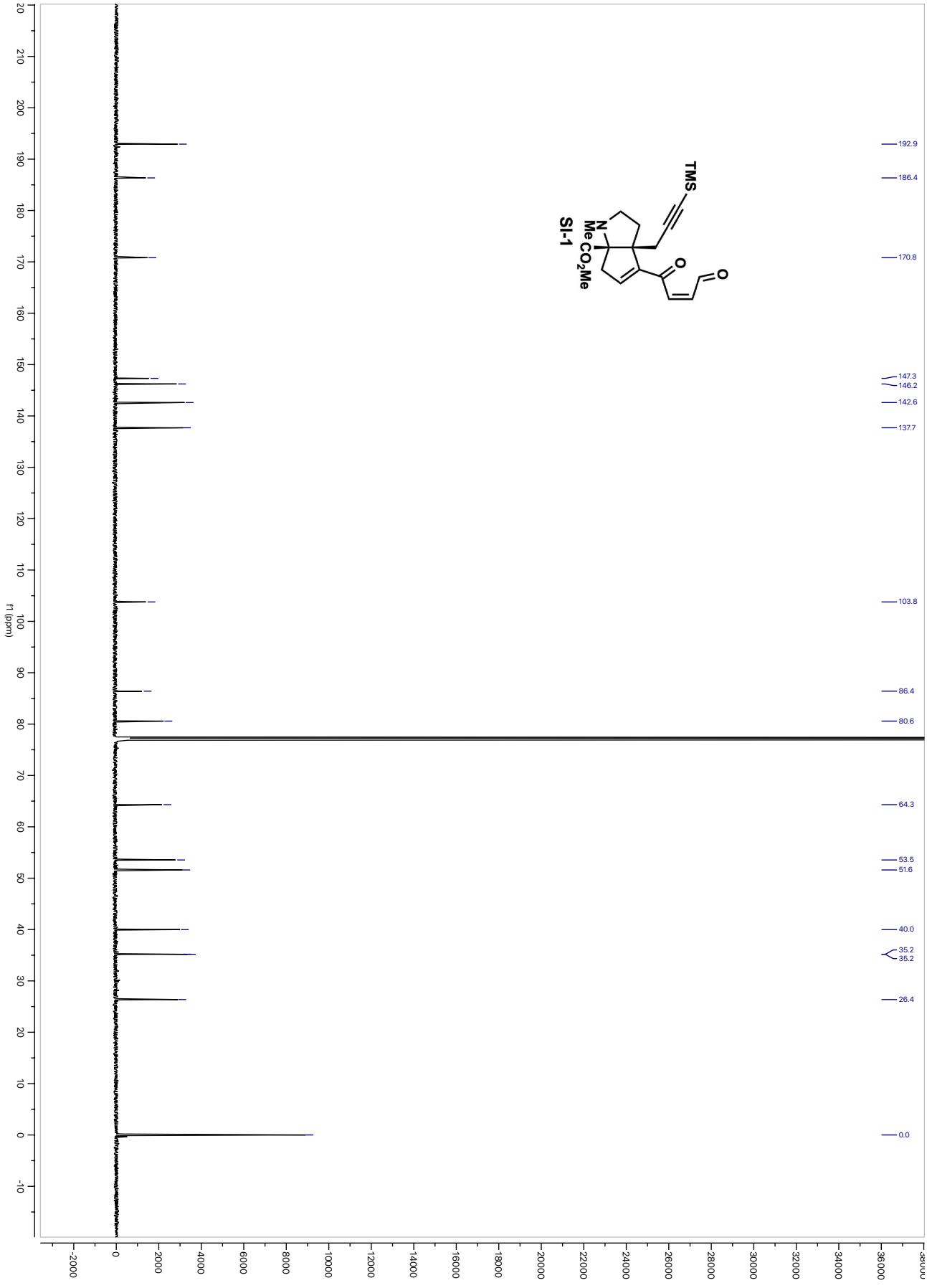

Minor Diastereomer
261
TMS
N
Me
CO2Me
O
TBSO
CO2Et
f1 (ppm)

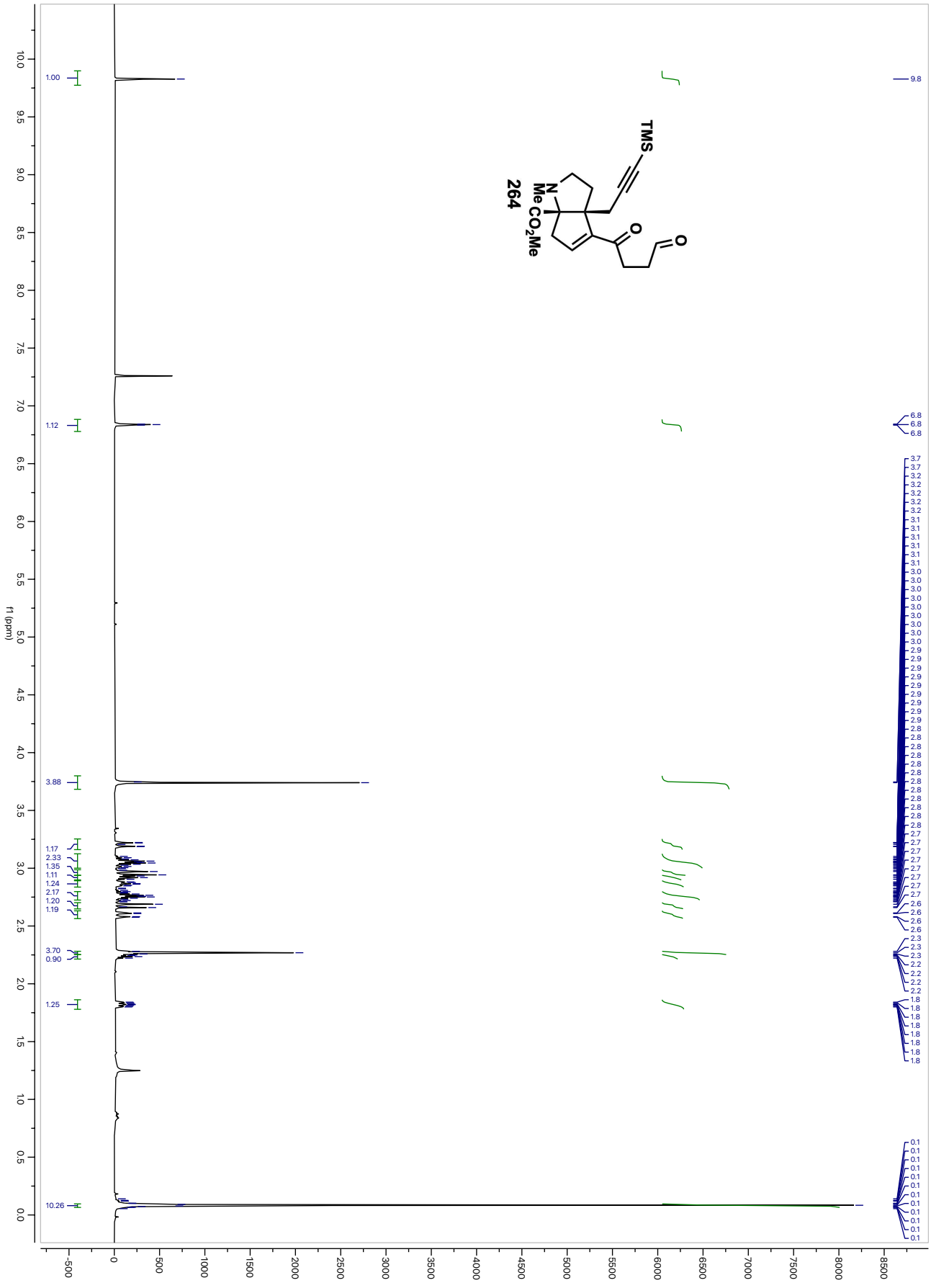

Minor Diastereomer
261
TMS
N
Me
CO2Me
O
TBSO
CO2Et
194.2
173.3
171.2
146.6
143.4
104.3
86.0
80.5
68.5
64.2
61.2
53.6
51.5
44.4
39.3
35.4
35.2
26.5
25.9
18.3
14.3
0.0
-4.8
-5.1
f1 (ppm)

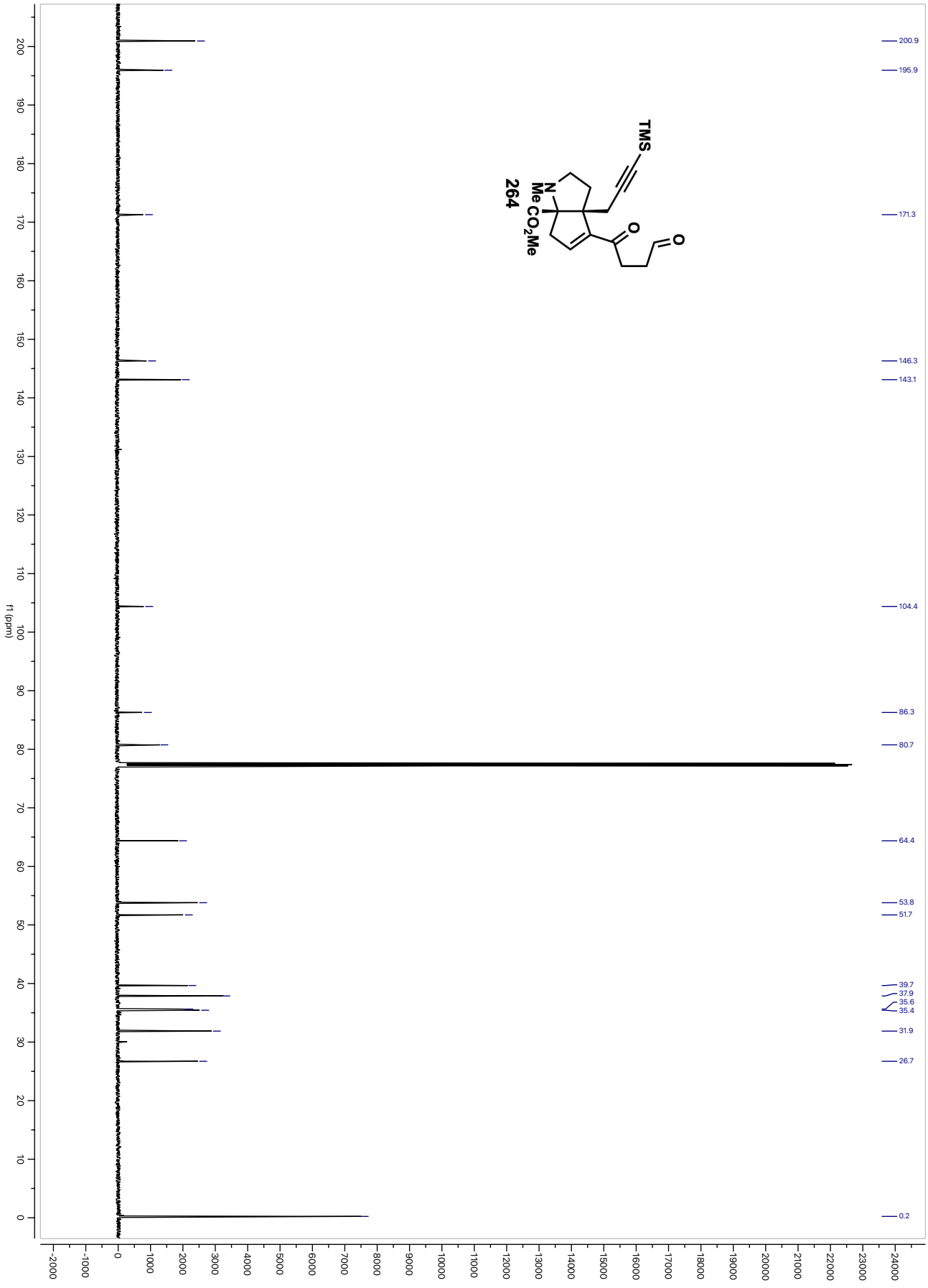

263
TMS
N
Me
CO2Me
O
f1 (ppm)

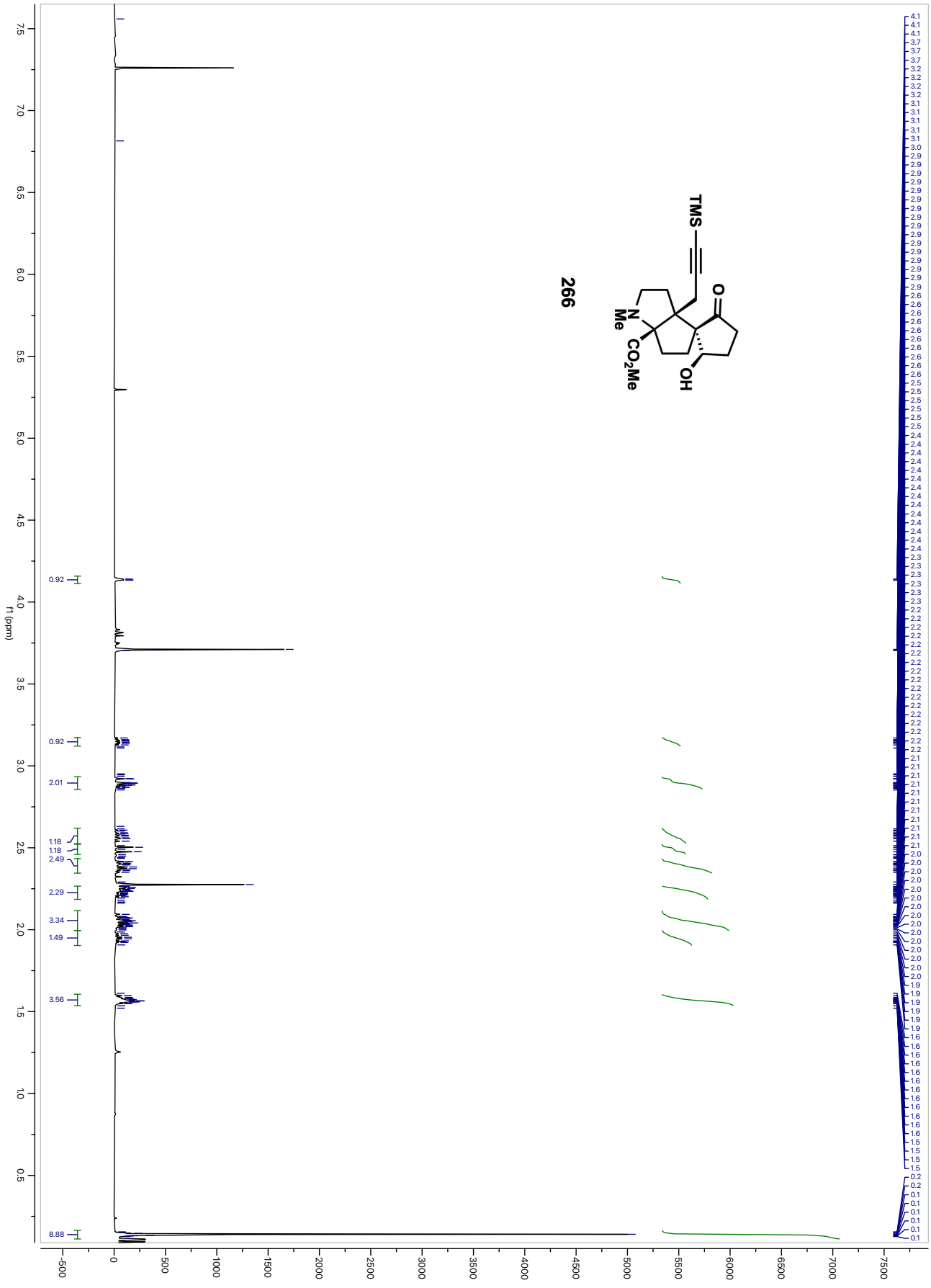

263
TMS
N
Me
CO2Me
O
171.6
150.7
141.6
136.6
123.9
110.9
106.3
104.0
86.2
81.0
64.3
53.8
51.4
38.8
35.4
35.1
27.3
0.0
f1 (ppm)

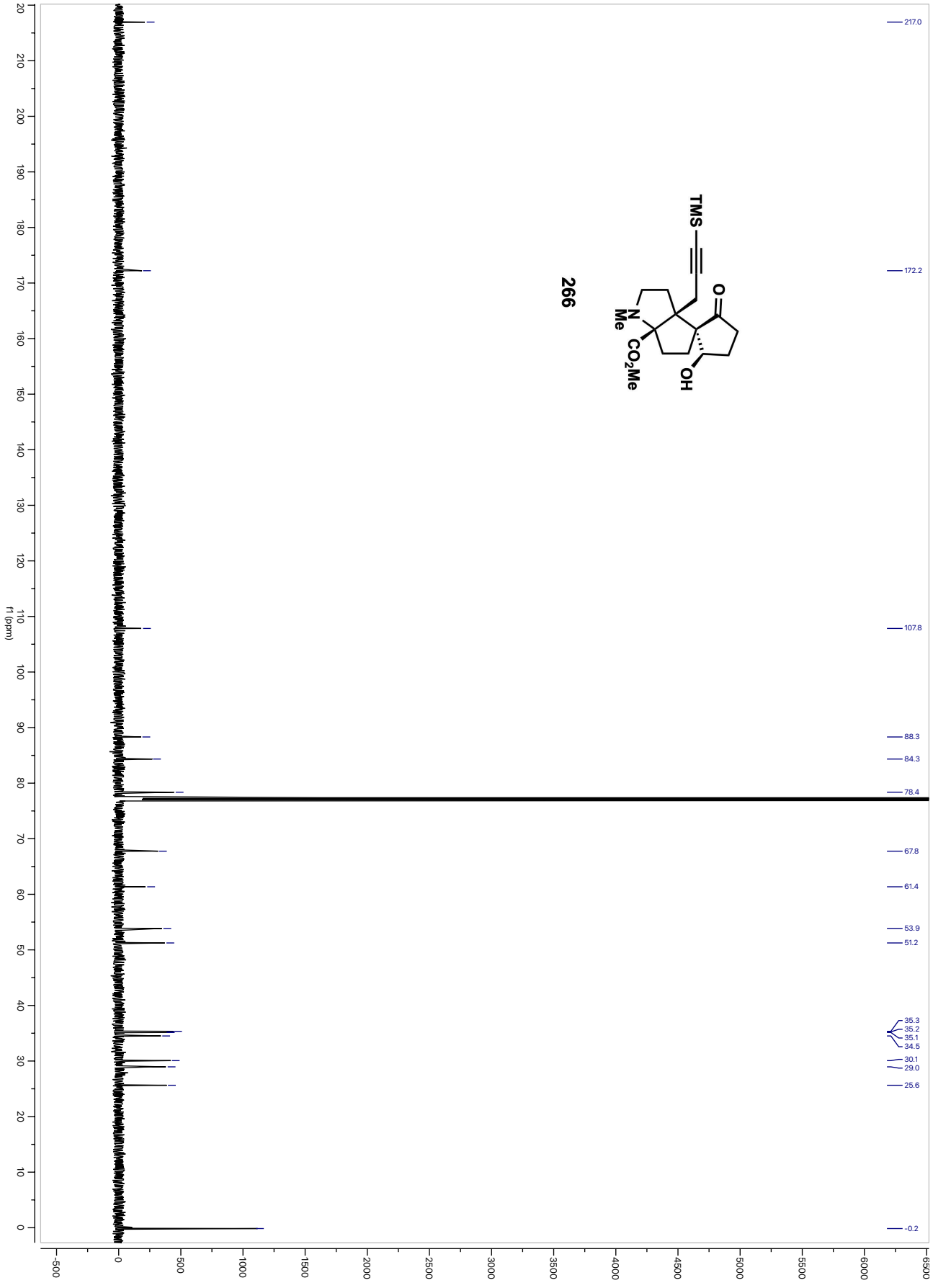

TMS
N
Me
CO2Me
O
O
SI-1
f1 (ppm)

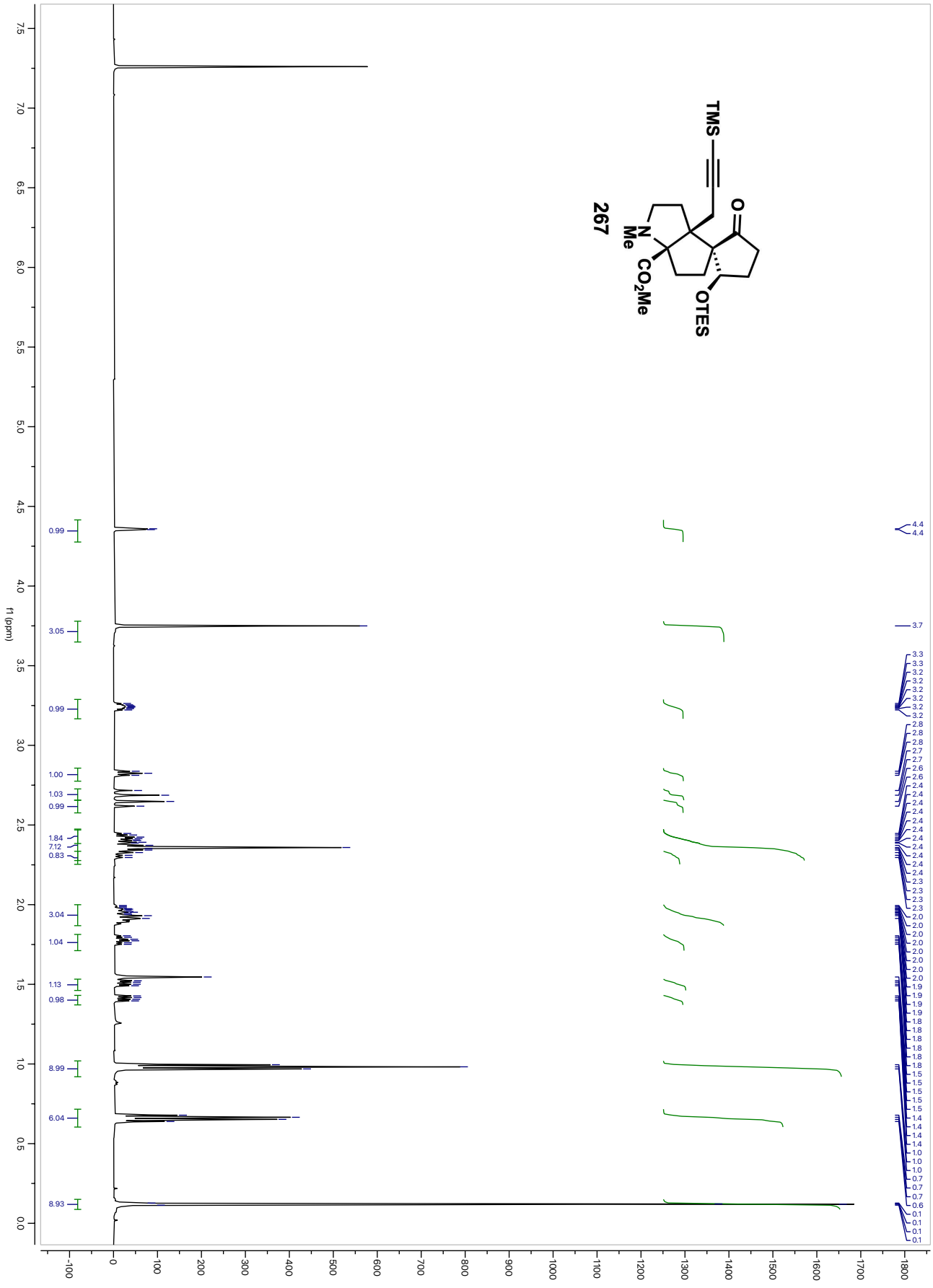

TMS
N
Me
CO2Me
SI-1
O
O
192.9
186.4
170.8
147.3
146.2
142.6
137.7
103.8
86.4
80.6
64.3
53.5
51.6
40.0
35.2
35.2
26.4
0.0
f1 (ppm)

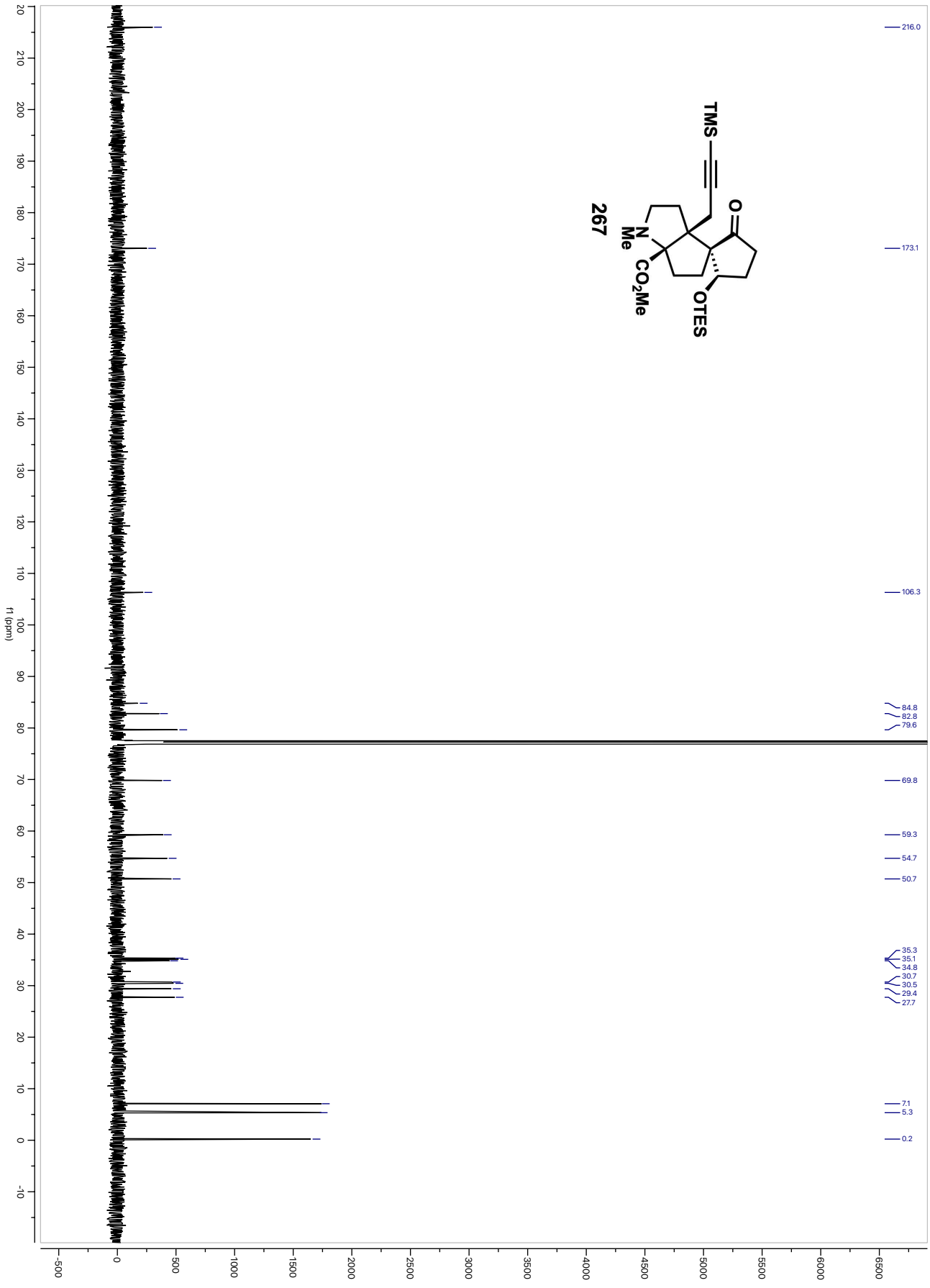

TMS
N
Me
CO2Me
O
O
264
f1 (ppm)

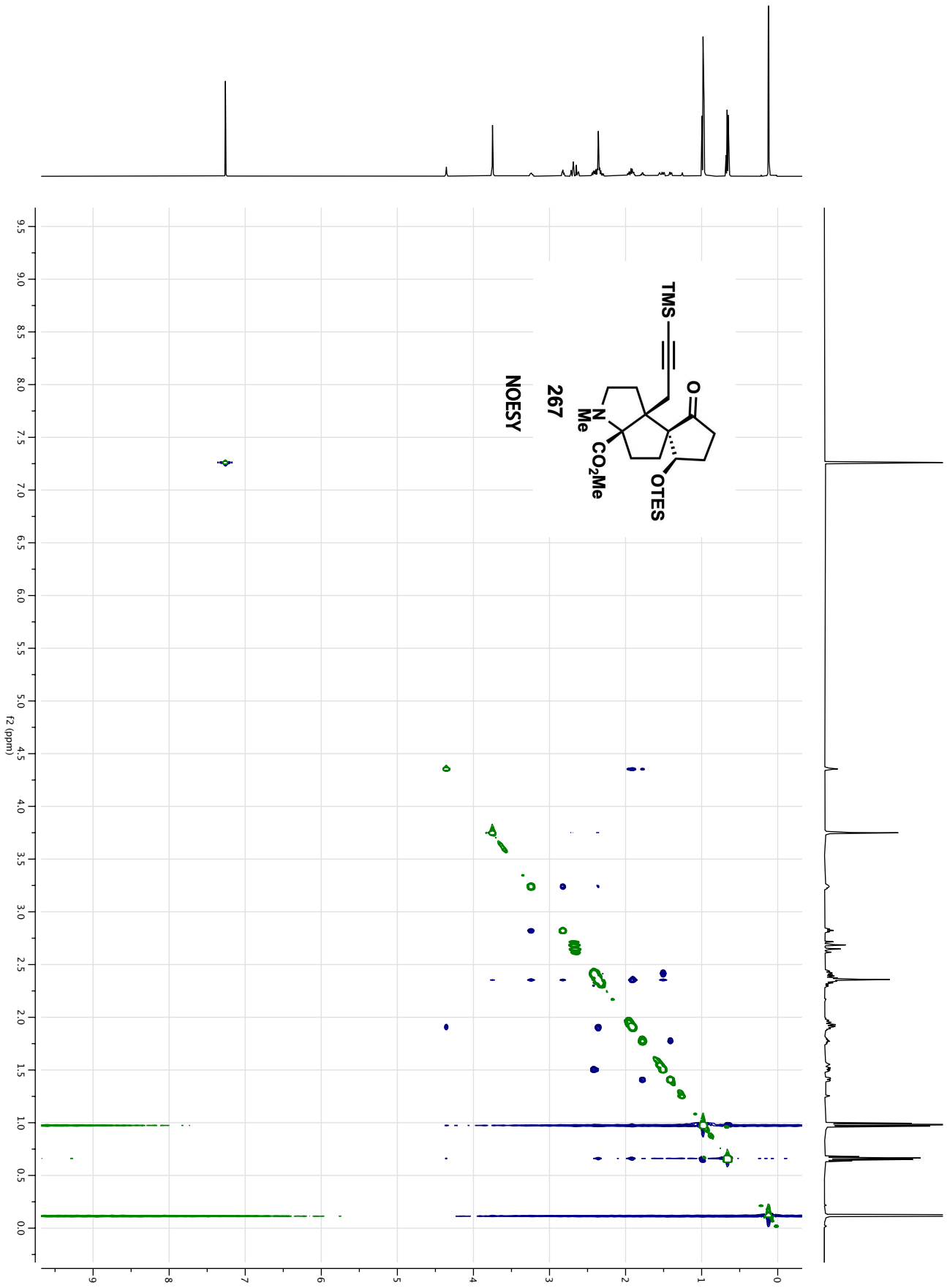

TMS
N
Me
CO2Me
O
O
264
200.9
195.9
171.3
146.3
143.1
104.4
86.3
80.7
64.4
53.8
51.7
39.7
37.9
35.6
35.4
31.9
26.7
0.2
f1 (ppm)

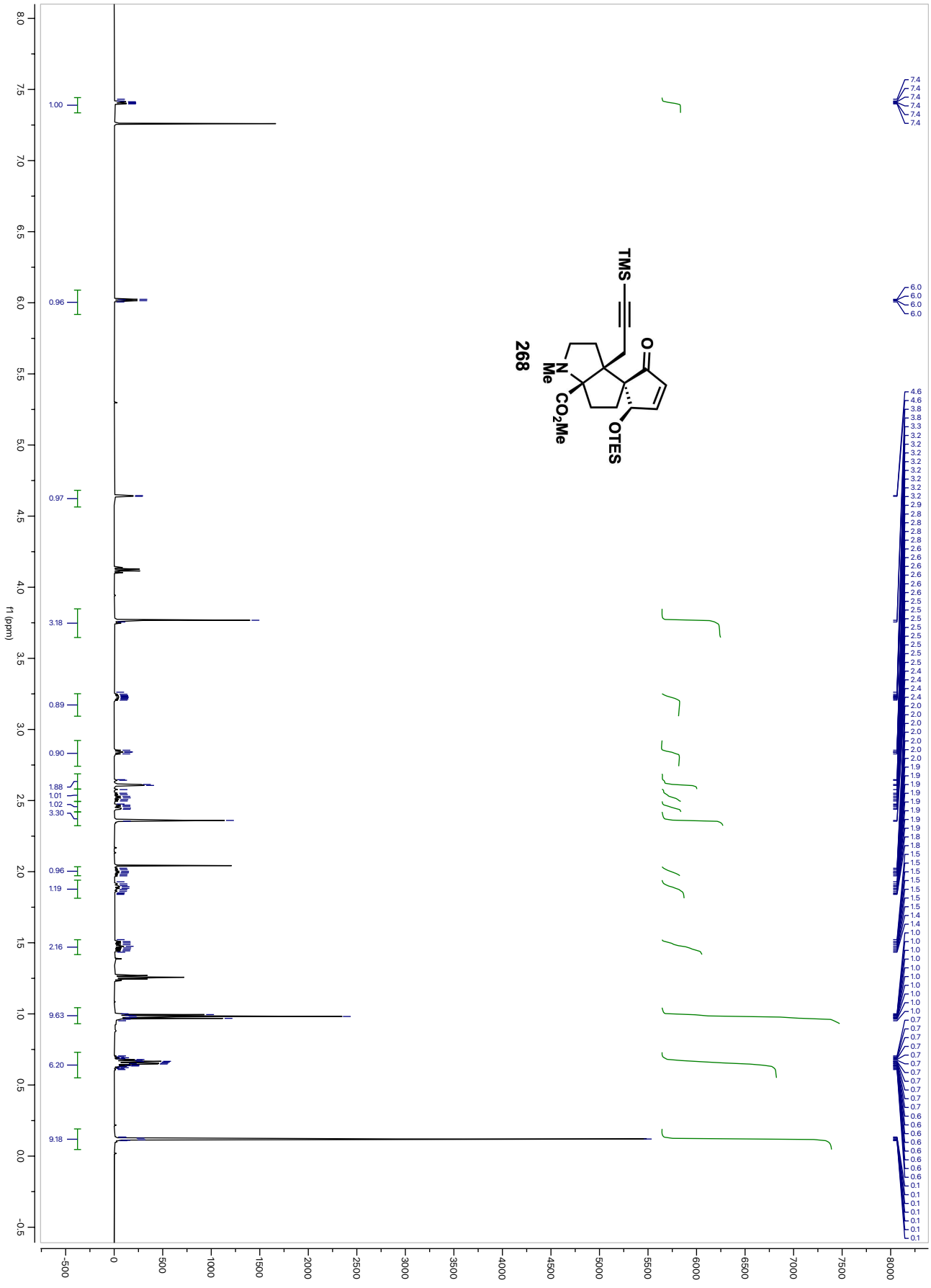

266
TMS
O
N
Me
CO2Me
OH
f1 (ppm)
0.92
0.92
2.01
1.18
1.18
2.49
2.29
3.34
1.49
3.56
8.88

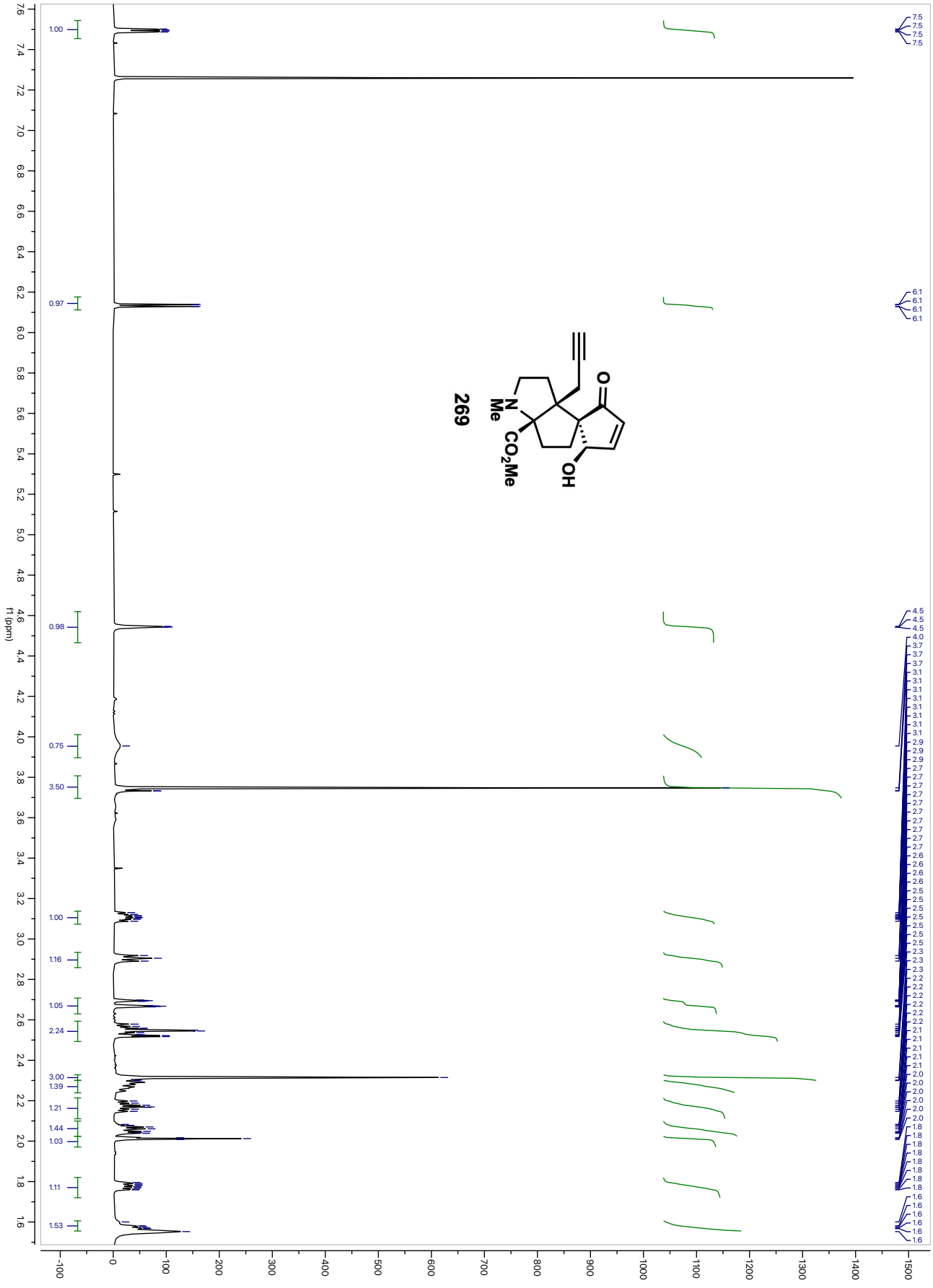

217.0
172.2
107.8
88.3
84.3
78.4
67.8
61.4
53.9
51.2
35.3
35.2
35.1
34.5
30.1
29.0
25.6
-0.2
f1 (ppm)
TMS
O
N
Me
CO2Me
OH
266

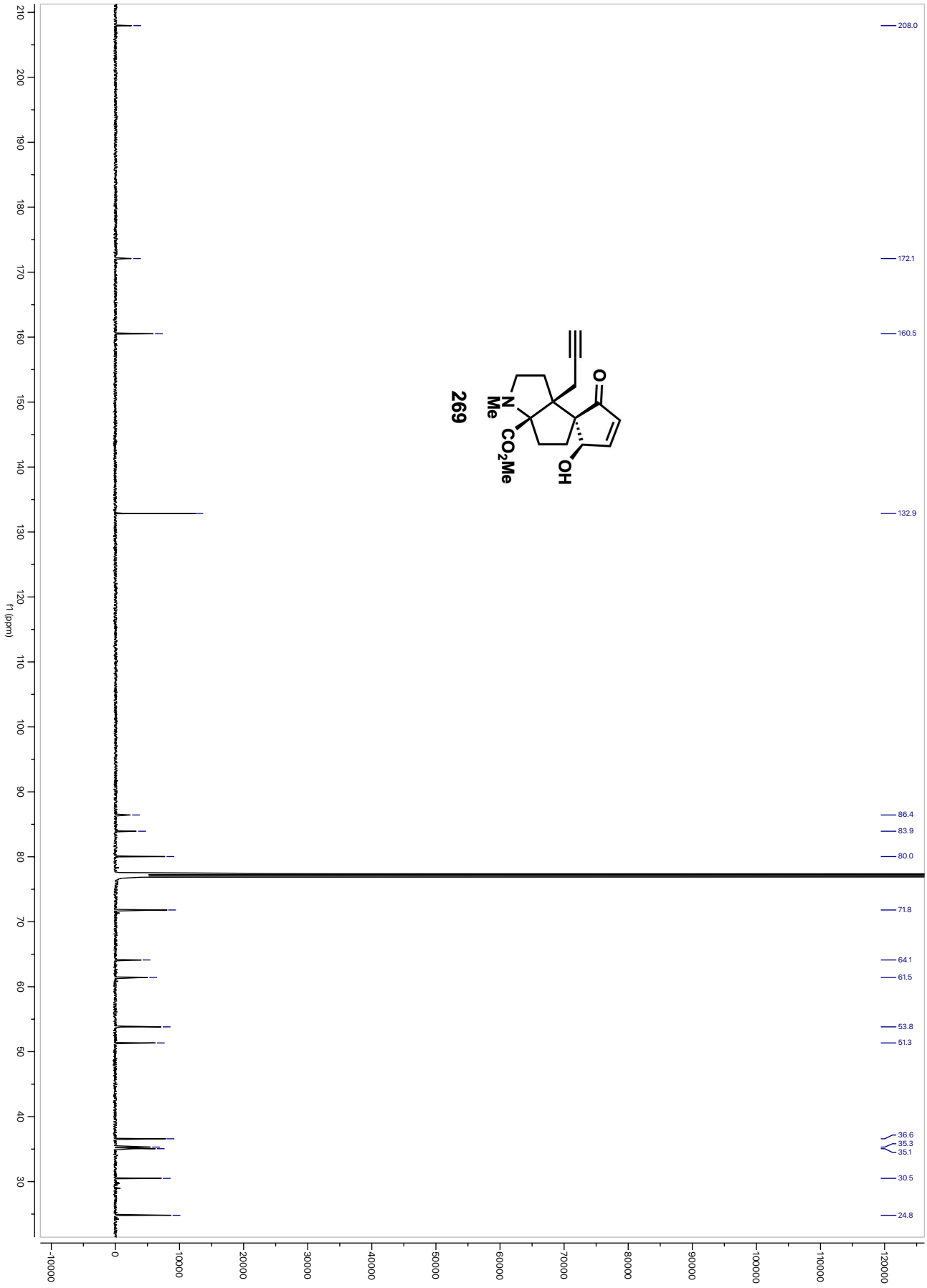

TMS
O
N
Me
CO2Me
OTES
267
f1 (ppm)

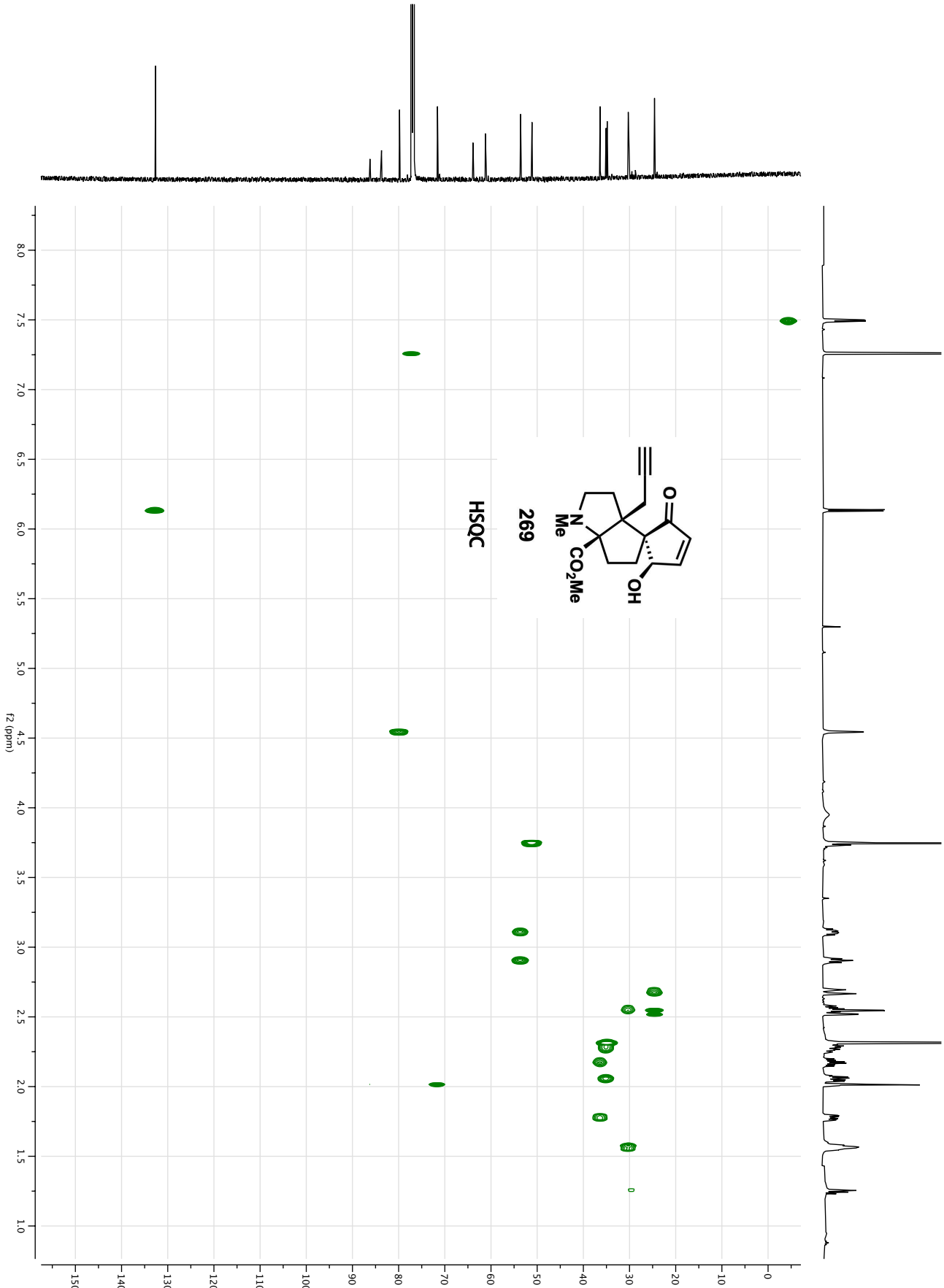

TMS
O
N
Me
CO2Me
OTES
267
216.0
173.1
106.3
84.8
82.8
79.6
69.8
59.3
54.7
50.7
35.3
35.1
34.8
30.7
30.5
29.4
27.7
7.1
5.3
0.2
f1 (ppm)

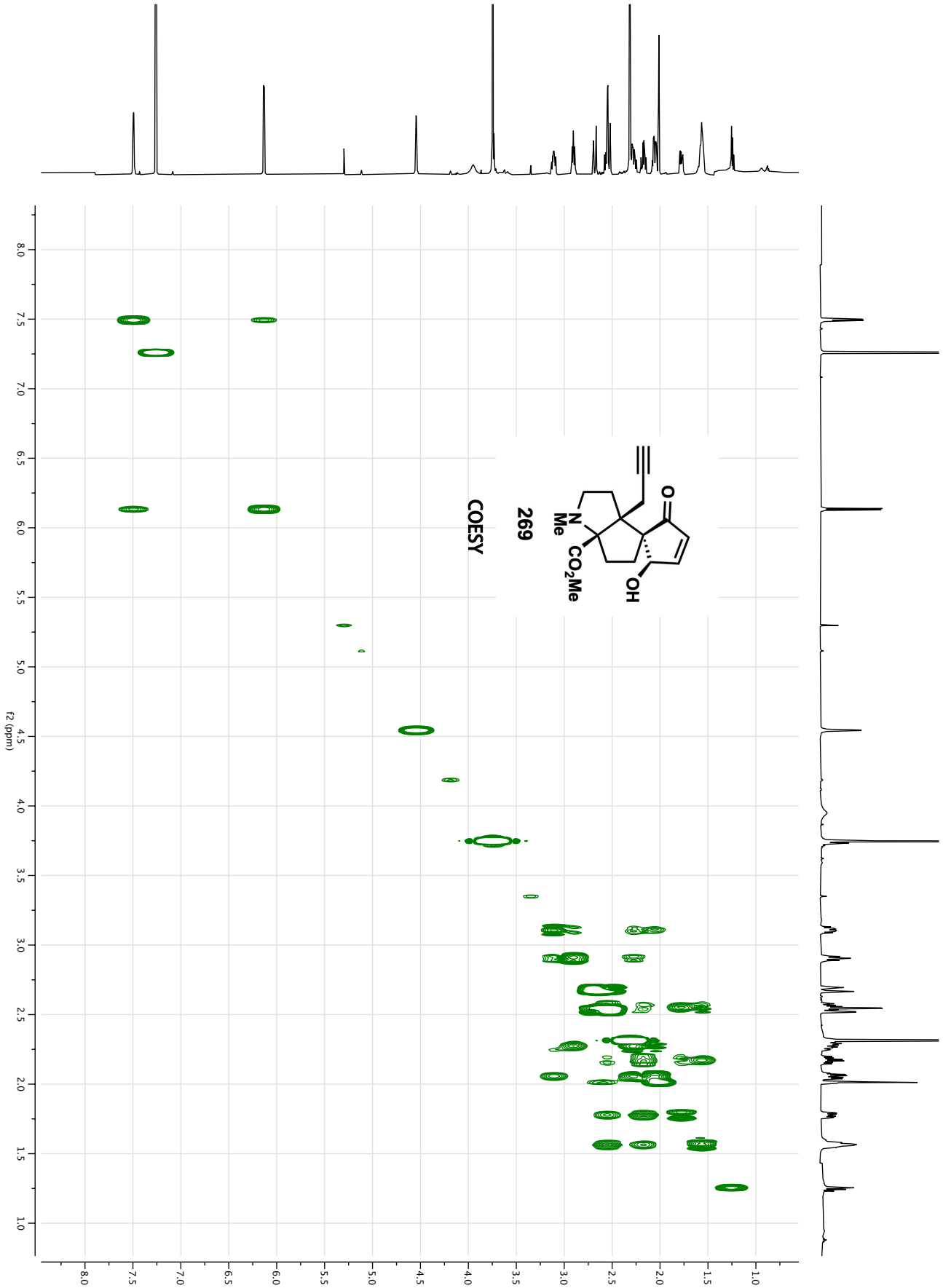

NOESY
267
TMS
O
N
Me
CO2Me
OTES
f2 (ppm)
f1 (ppm)

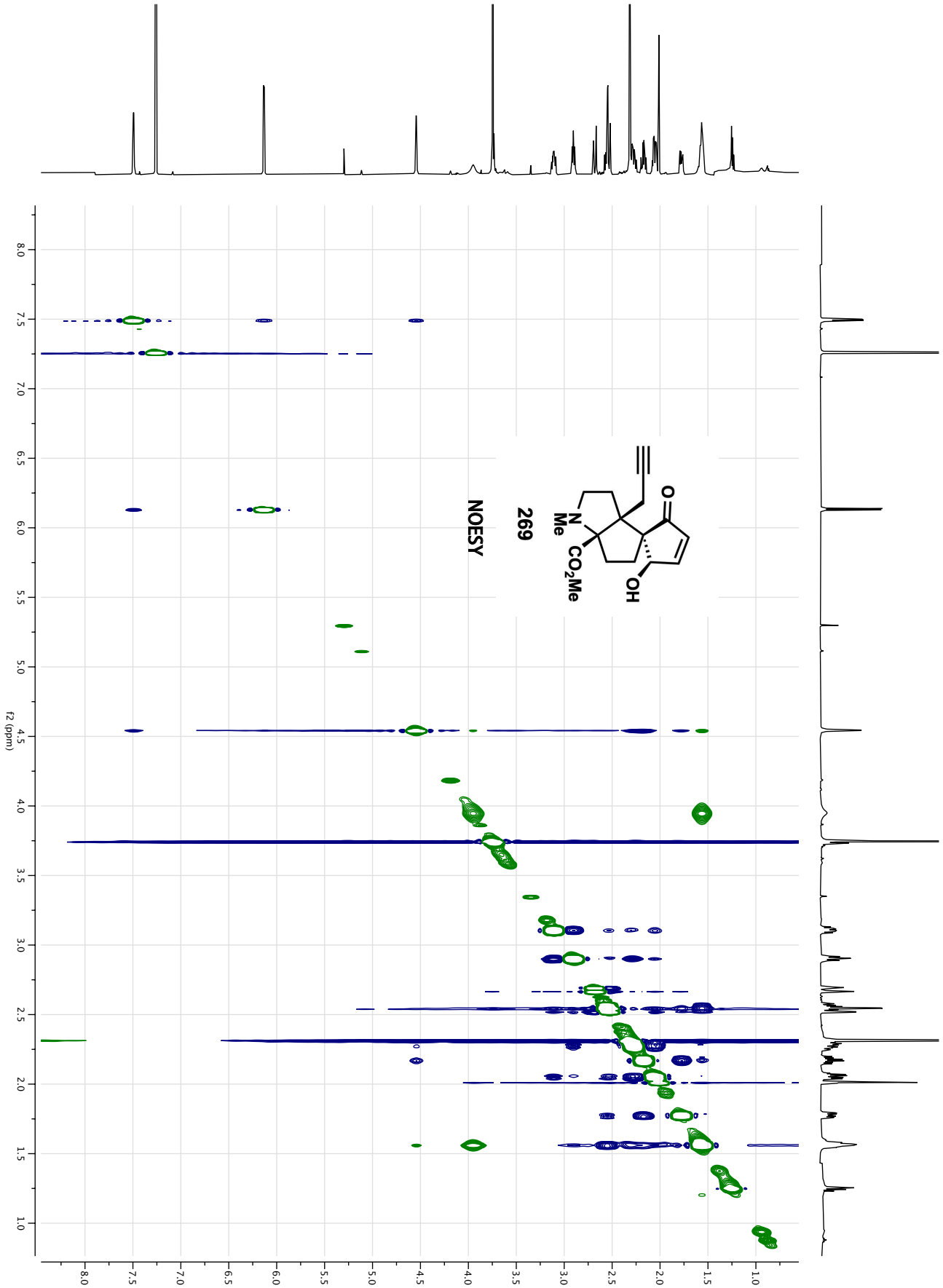

TMS
O
N
Me
CO2Me
OTES
268
f1 (ppm)

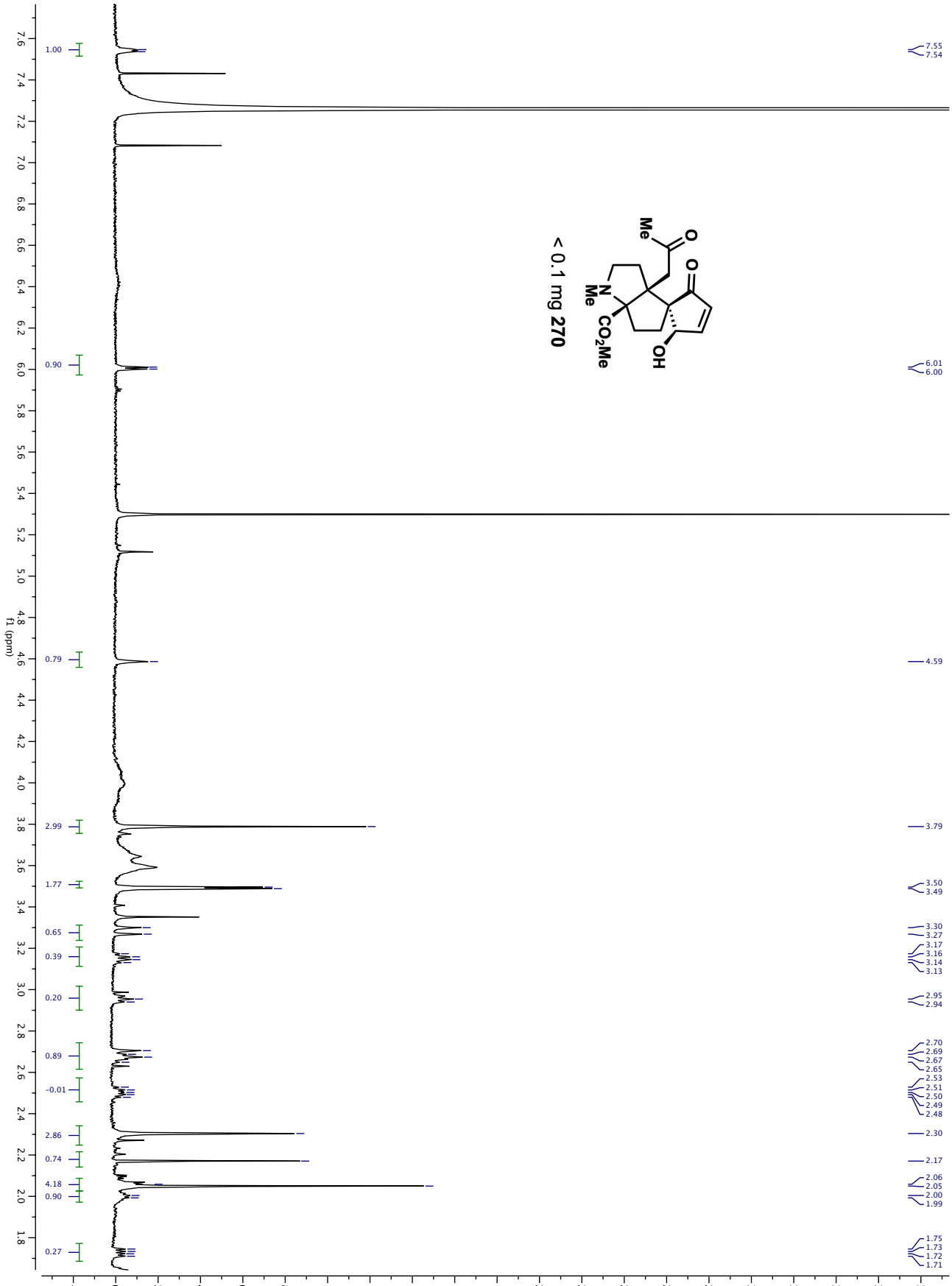

269
N
Me
CO2Me
OH
O
f1 (ppm)

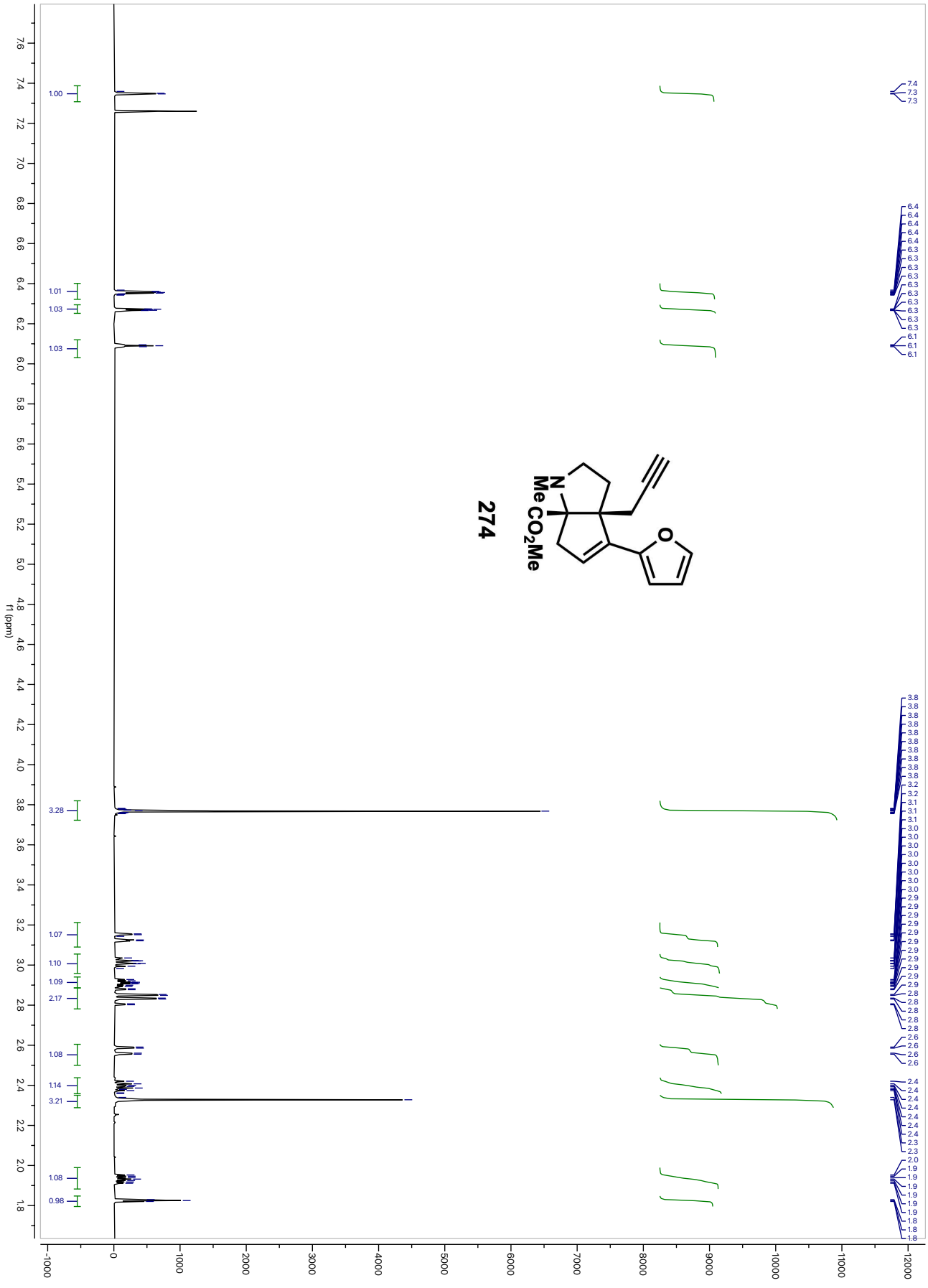

208.0
172.1
160.5
132.9
86.4
83.9
80.0
71.8
64.1
61.5
53.8
51.3
36.6
35.3
35.1
30.5
24.8
f1 (ppm)
269
N
Me
CO2Me
OH
O

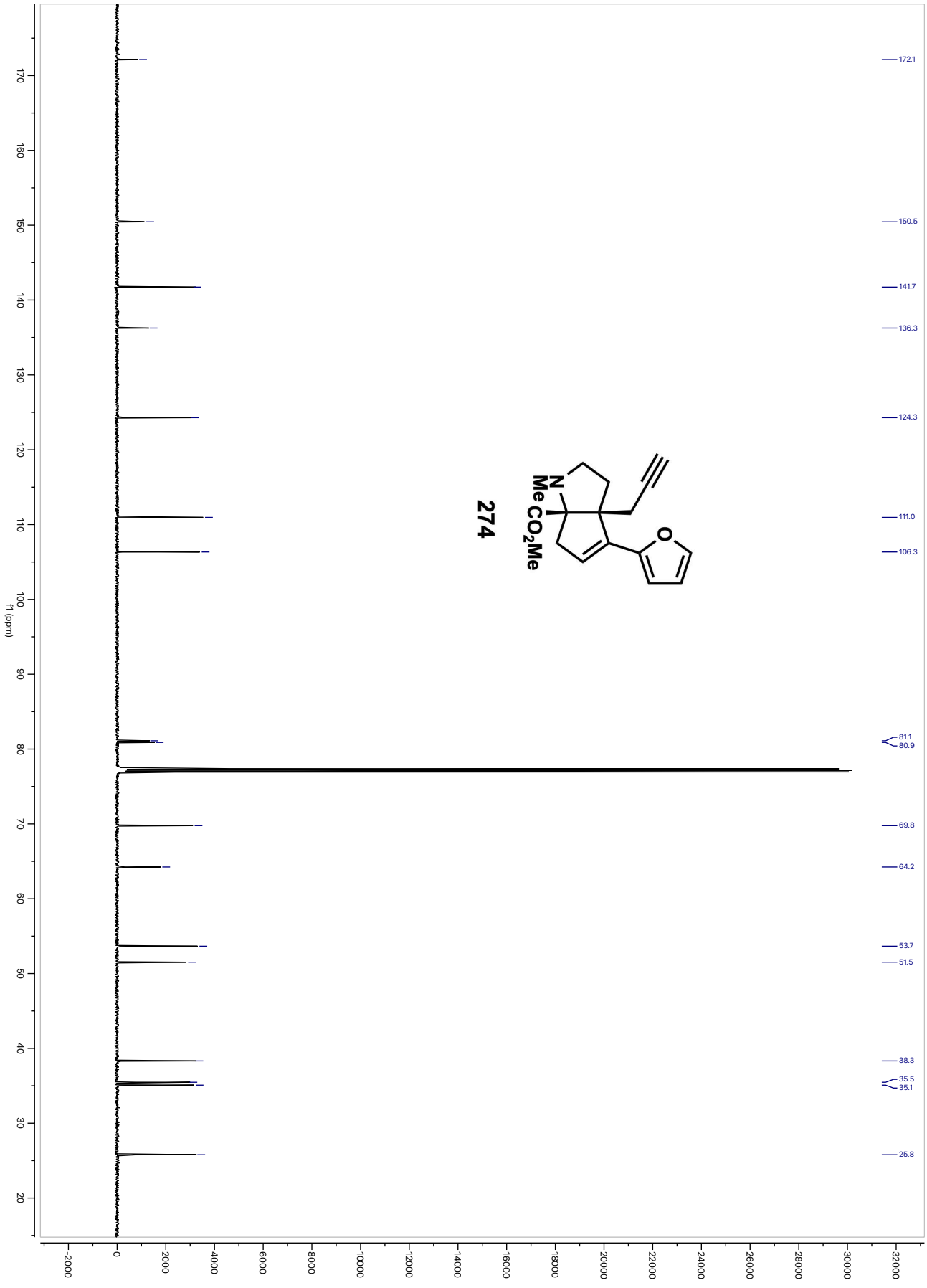

HSQC
269
N
Me
CO2Me
OH
O
f2 (ppm)
f1 (ppm)

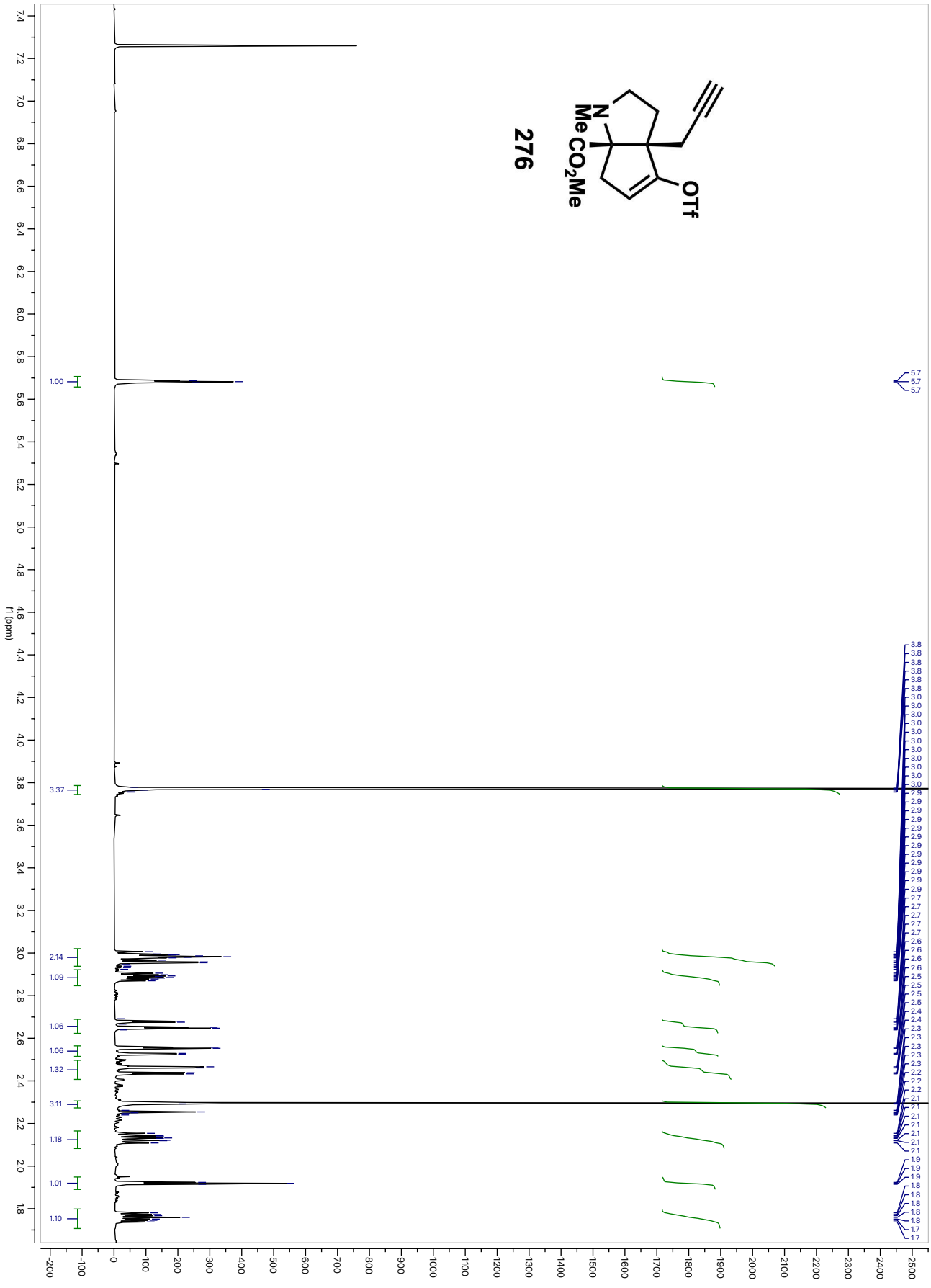

COESY
269
N
Me
CO2Me
OH
O
f2 (ppm)
f1 (ppm)

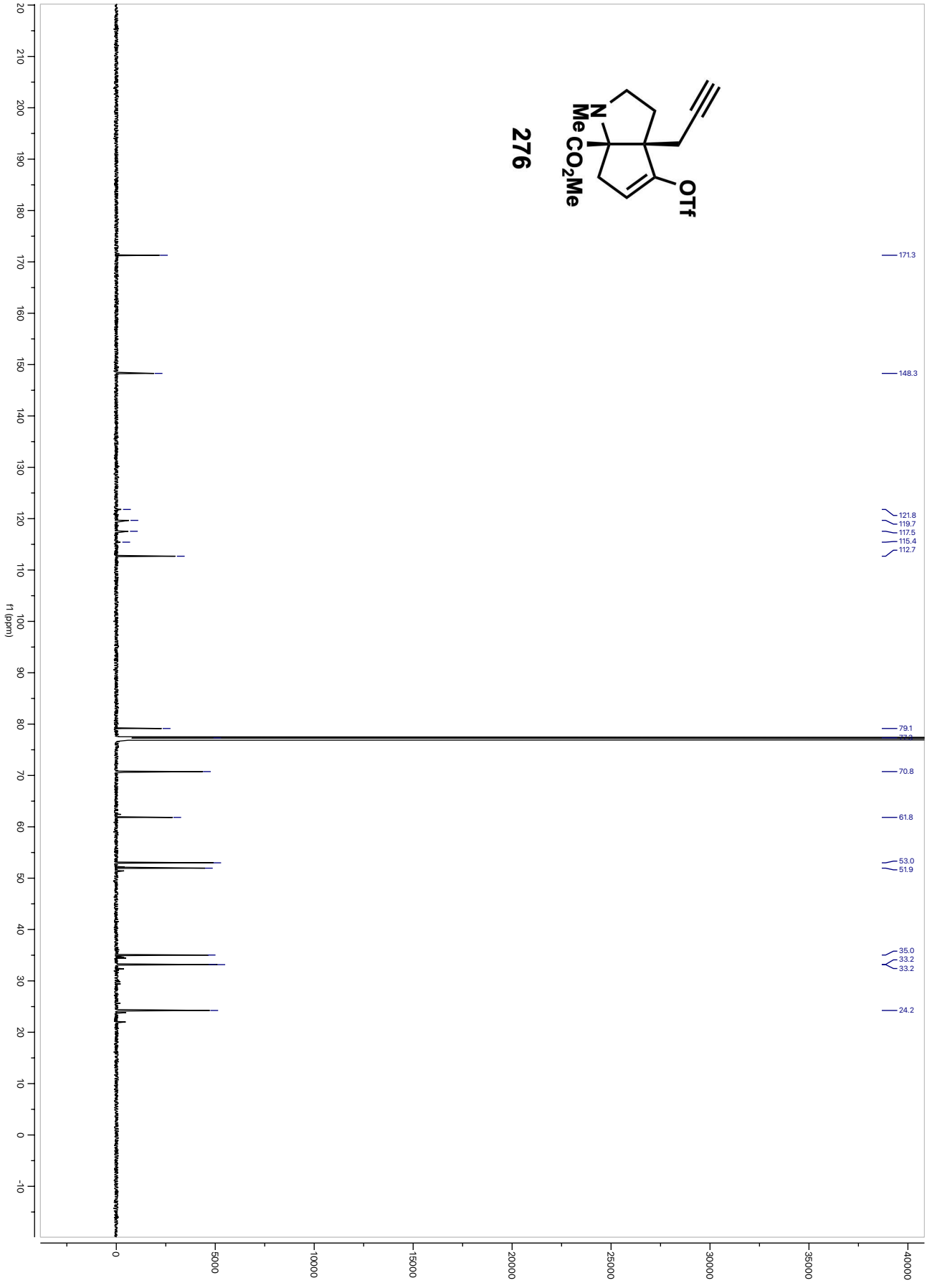

NOESY
269
N
Me
CO2Me
O
OH
f2 (ppm)
f1 (ppm)

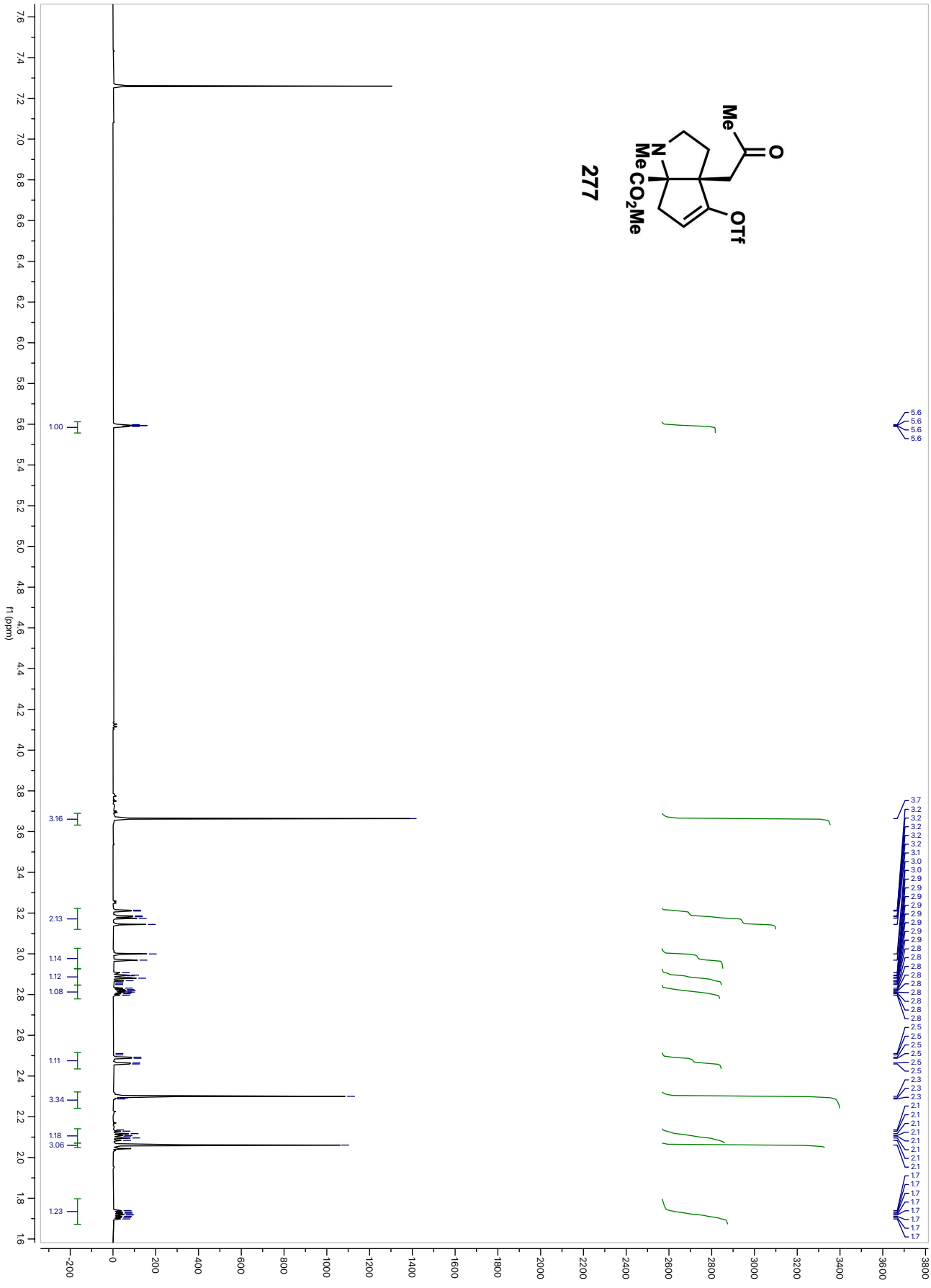

< 0.1 mg 270
Me
O
O
N
Me
CO2Me
OH
f1 (ppm)
1.00
0.90
0.79
2.99
1.77
0.65
0.39
0.20
0.89
-0.01
2.86
0.74
4.18
0.90
0.27
7.55
7.54
6.01
6.00
4.59
3.79
3.50
3.49
3.30
3.27
3.17
3.16
3.14
3.13
2.95
2.94
2.70
2.69
2.67
2.65
2.53
2.51
2.50
2.49
2.48
2.30
2.17
2.06
2.05
2.00
1.99
1.75
1.73
1.72
1.71

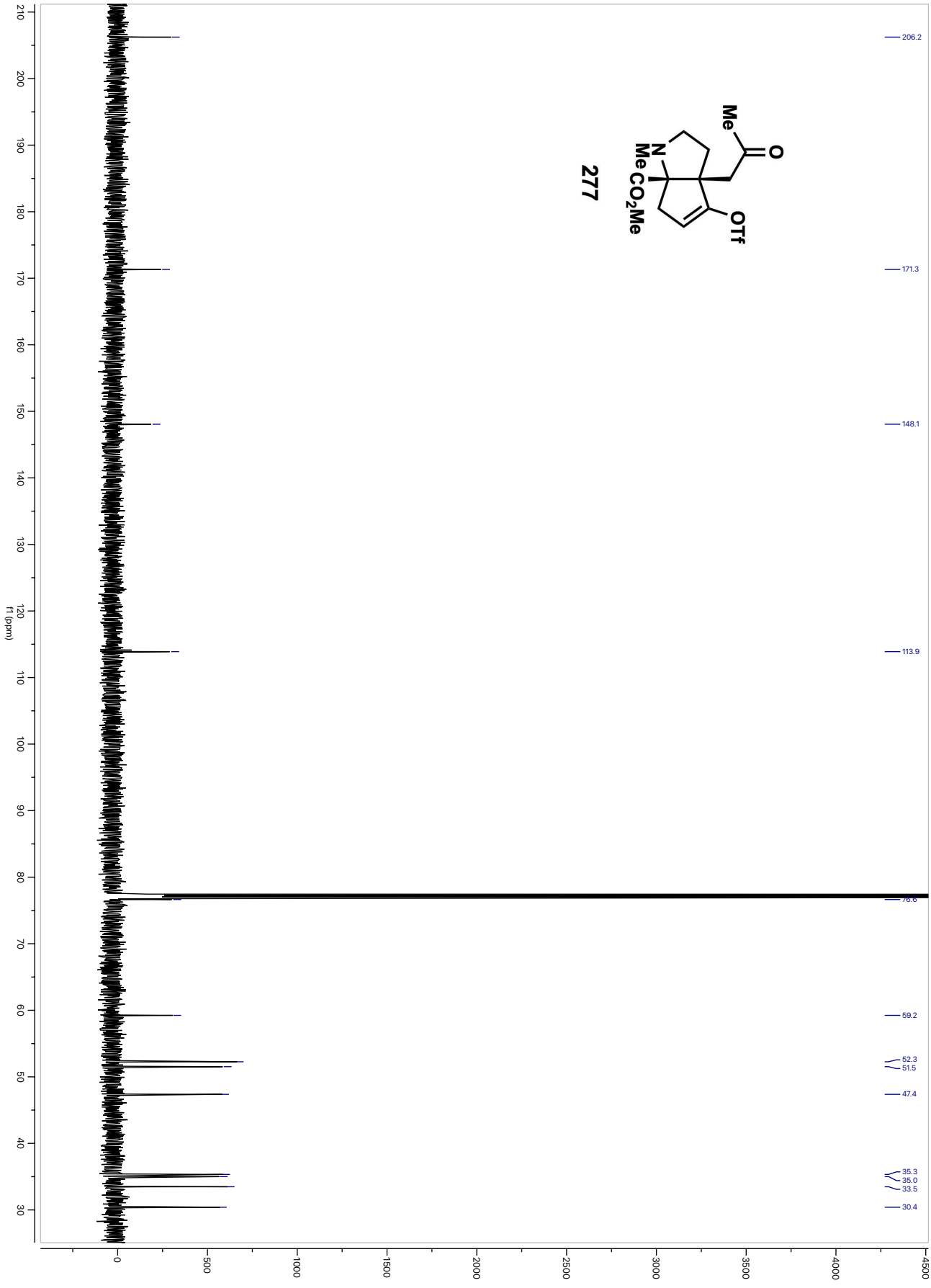

f1 (ppm)
1.00
1.01
1.03
1.03
3.28
1.07
1.10
1.09
2.17
1.08
1.14
3.21
1.08
0.98
N
Me
CO2Me
O
274

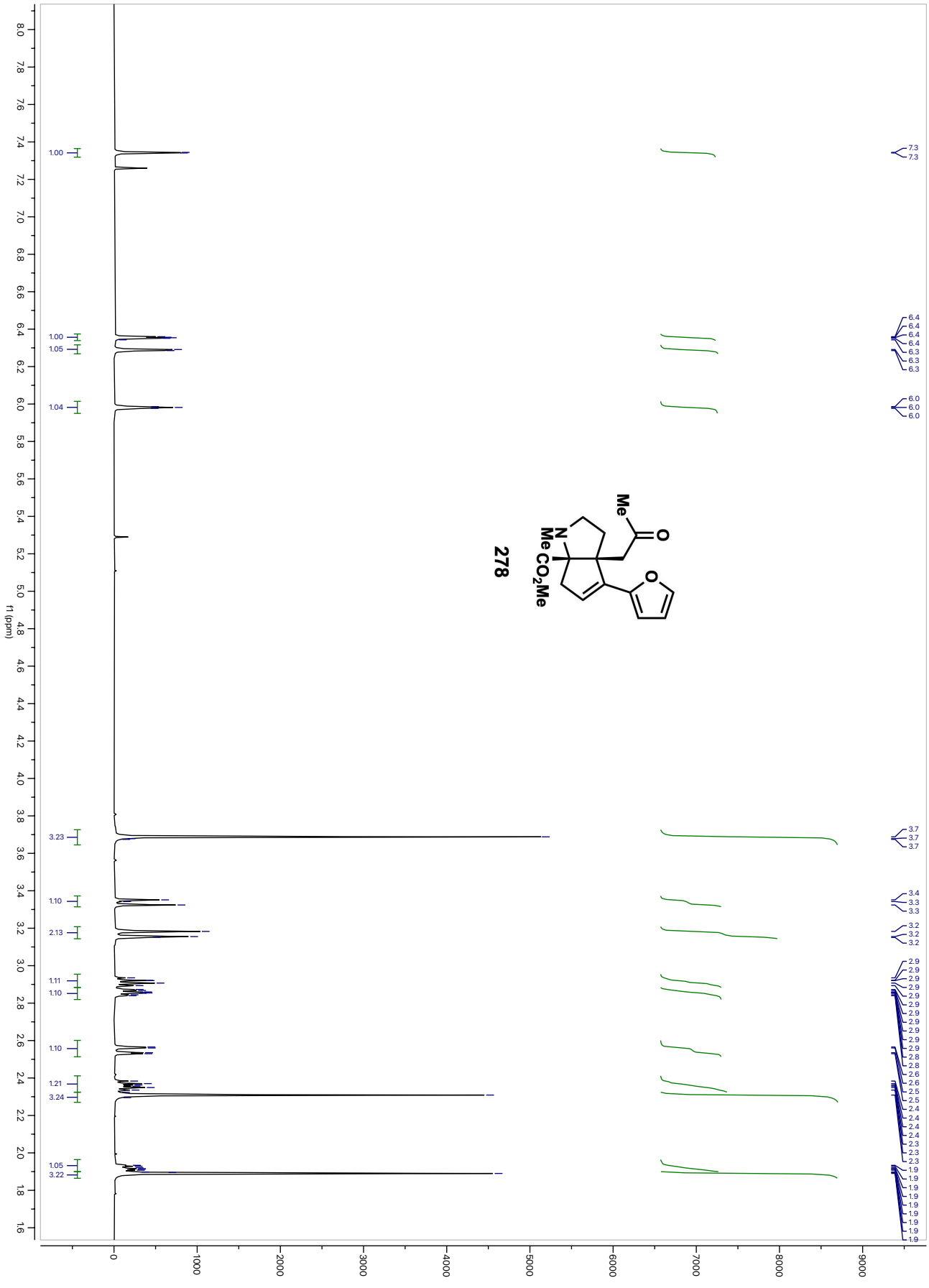

172.1
150.5
141.7
136.3
124.3
111.0
106.3
81.1
80.9
69.8
64.2
53.7
51.5
38.3
35.5
35.1
25.8
f1 (ppm)
274
N
Me
CO2Me
O

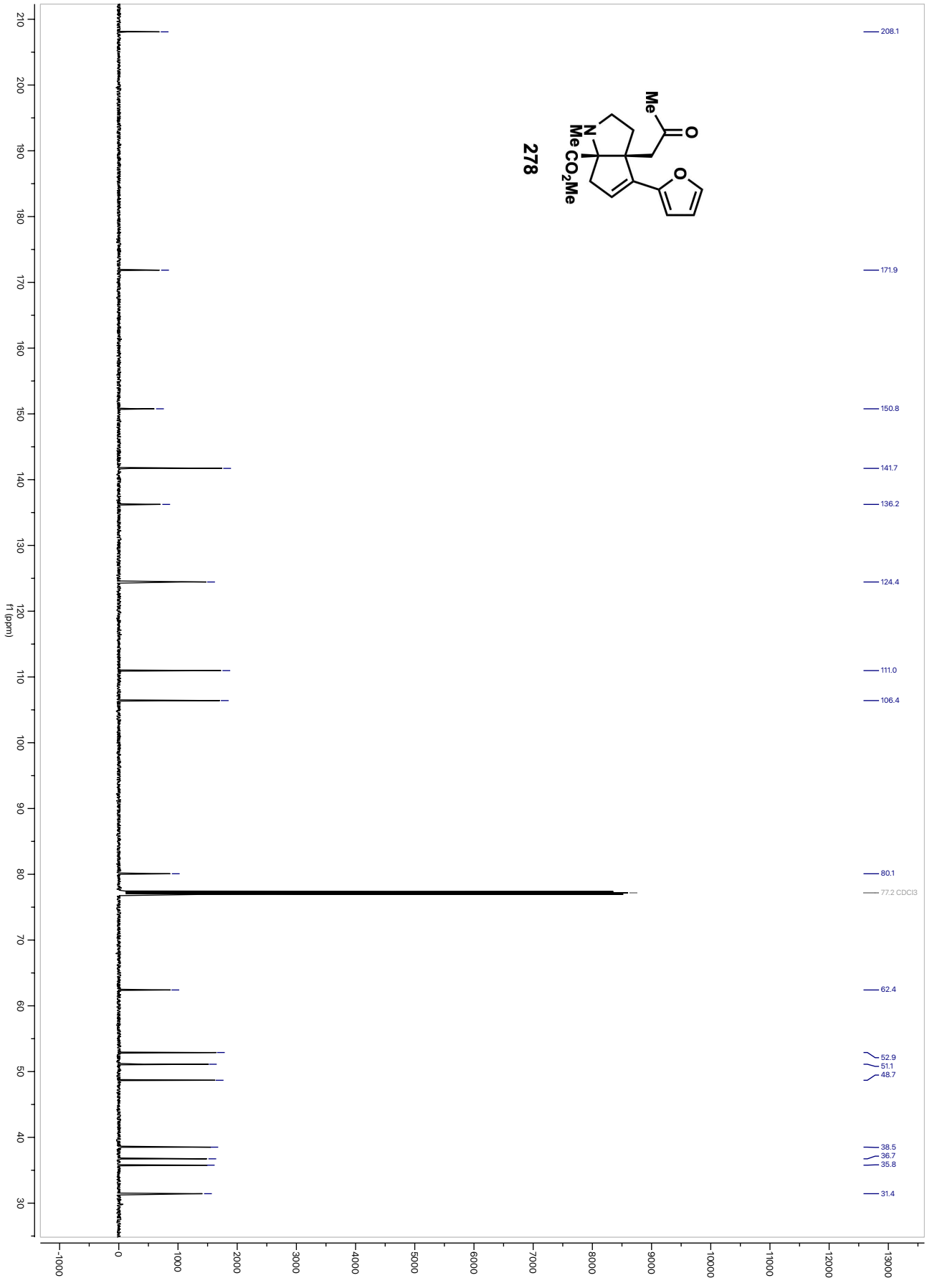

276
N
Me
CO2Me
OTf
f1 (ppm)
1.00
3.37
2.14
1.09
1.06
1.06
1.32
3.11
1.18
1.01
1.10

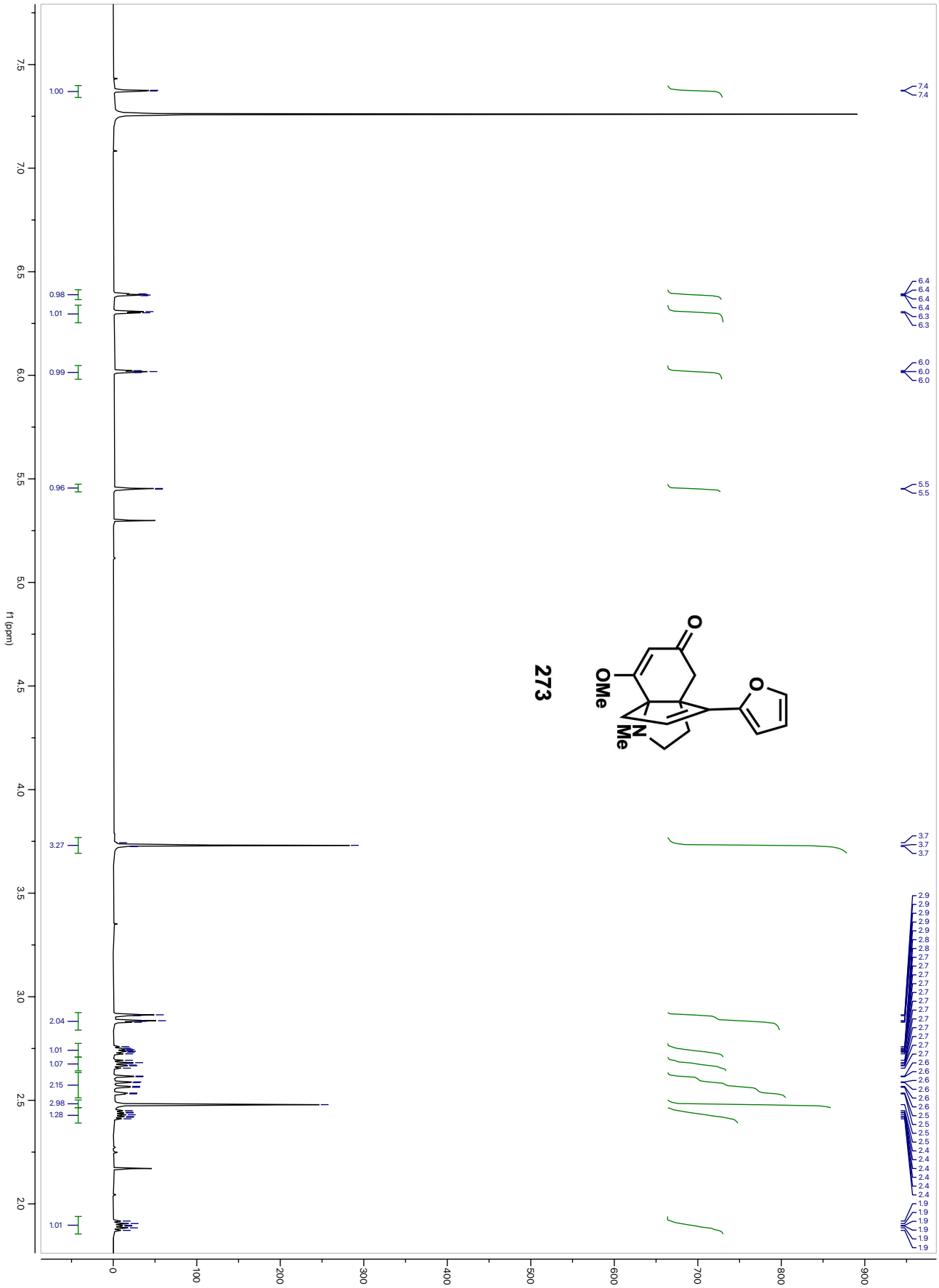

276
N
Me
CO2Me
OTf
171.3
148.3
121.8
119.7
117.5
115.4
112.7
79.1
77.9
70.8
61.8
53.0
51.9
35.0
33.2
33.2
24.2
f1 (ppm)

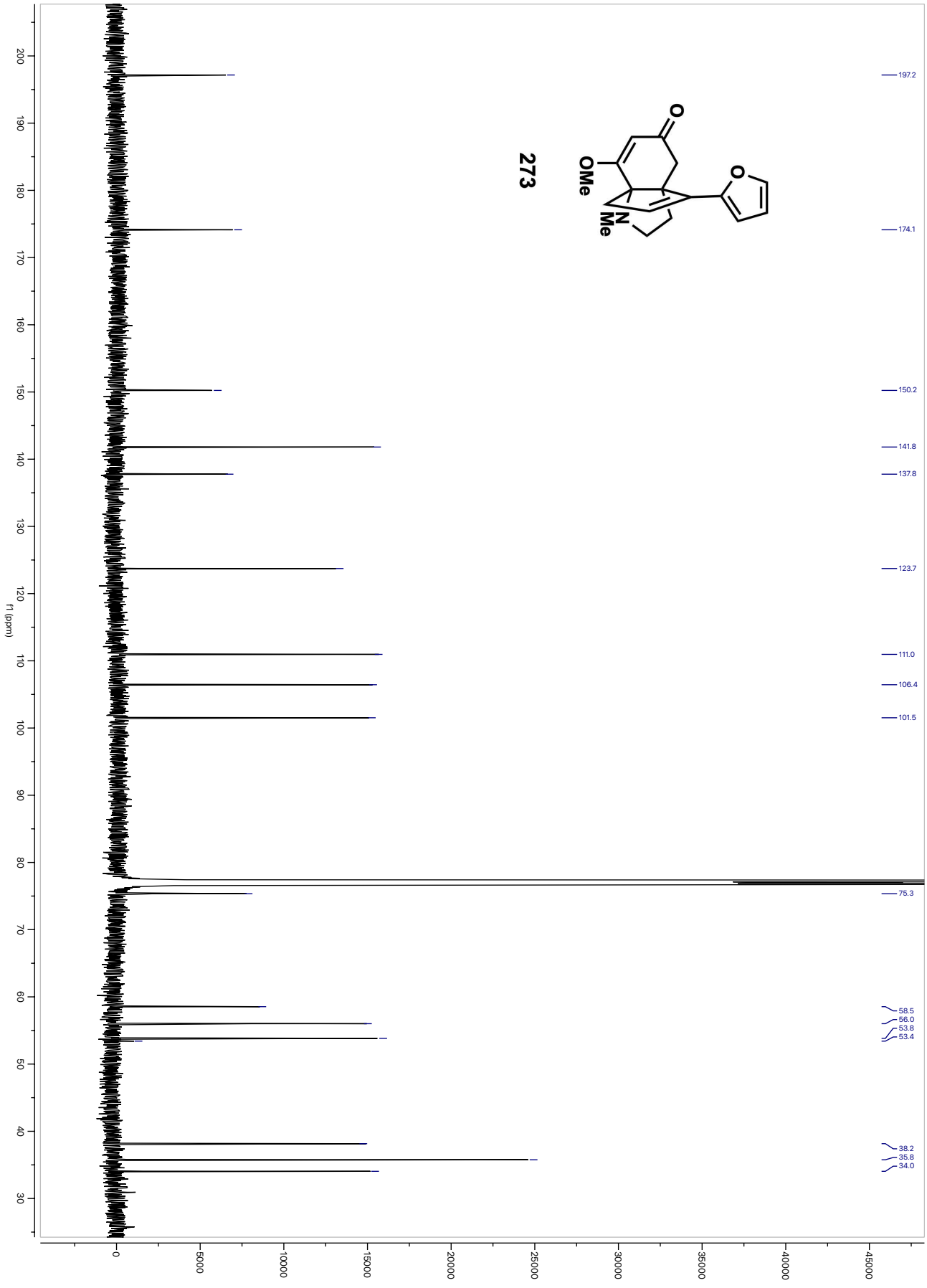

277
Me
O
N
Me
CO2Me
OTf
f1 (ppm)
1.00
3.16
2.13
1.14
1.12
1.08
1.11
3.34
1.18
3.06
1.23

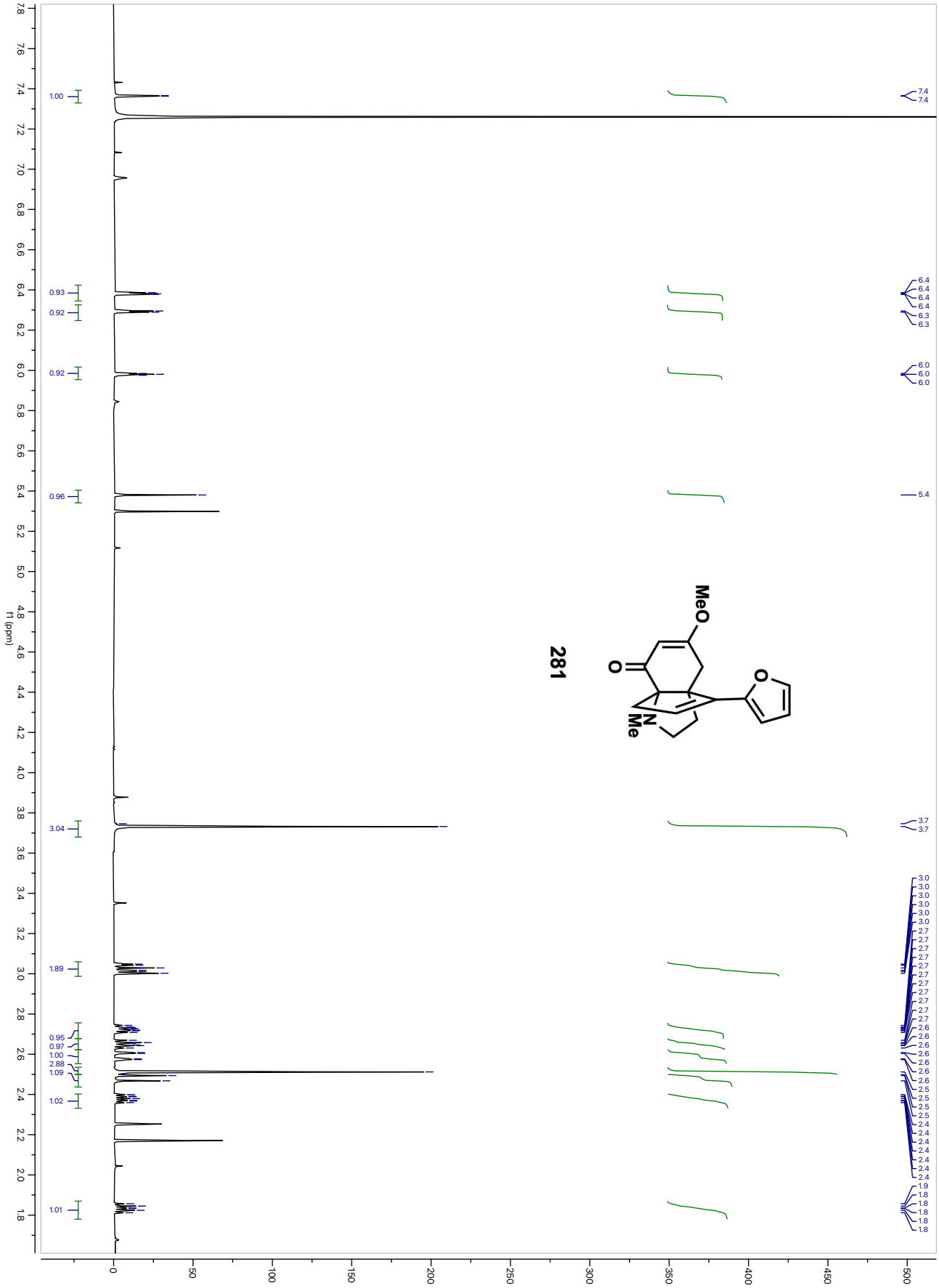

277
Me
O
N
Me
CO2Me
OTf
206.2
171.3
148.1
113.9
76.6
59.2
52.3
51.5
47.4
35.3
35.0
33.5
30.4
f1 (ppm)

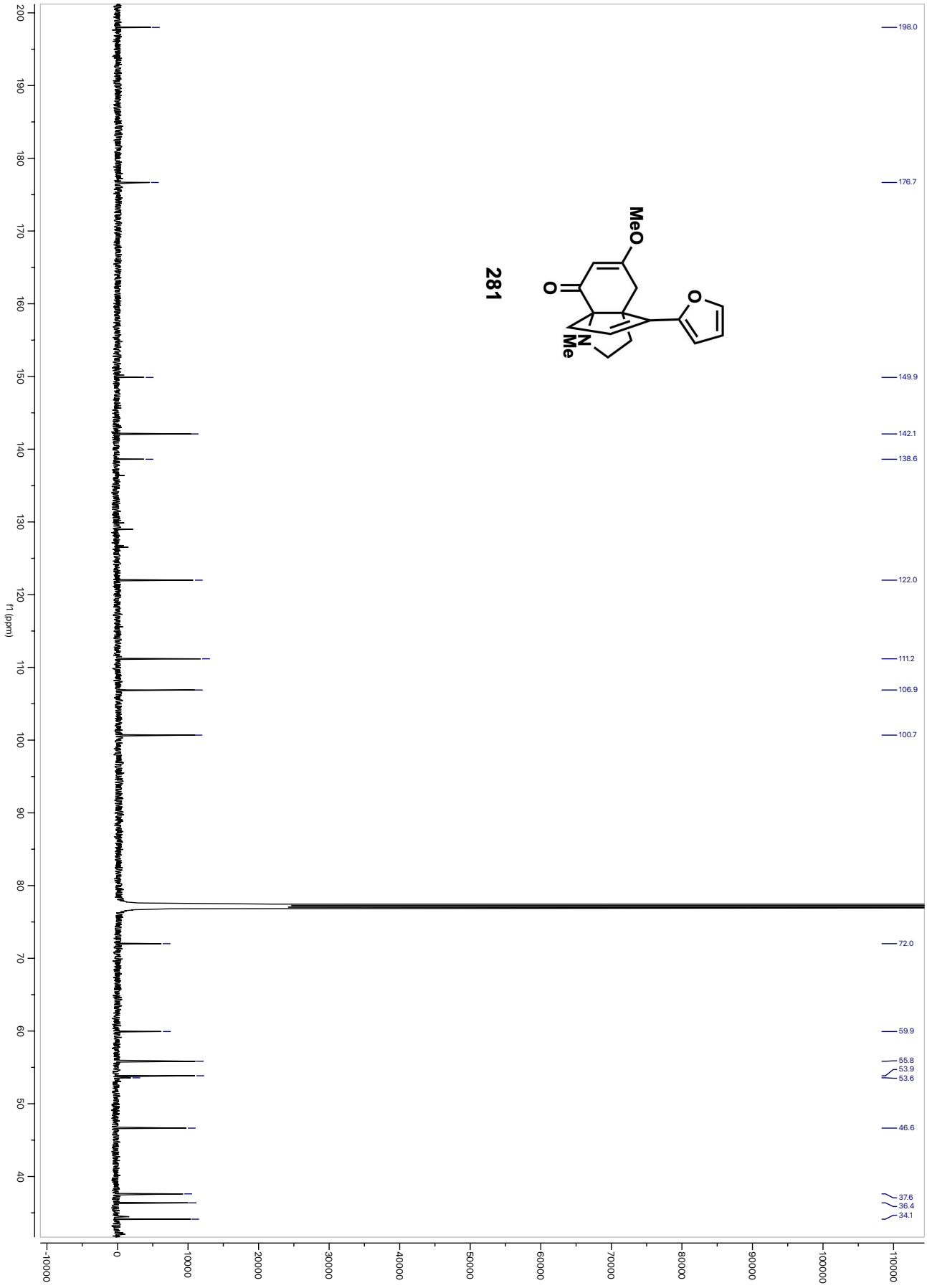

278
Me
O
N
Me
CO2Me
O
f1 (ppm)
1.00
1.00
1.05
1.04
3.23
1.10
2.13
1.11
1.10
1.10
1.21
3.24
1.05
3.22
7.3
7.3
6.4
6.4
6.4
6.4
6.3
6.3
6.3
6.0
6.0
6.0
3.7
3.7
3.7
3.4
3.3
3.3
3.2
3.2
3.2
2.9
2.9
2.9
2.9
2.9
2.9
2.9
2.9
2.9
2.9
2.9
2.8
2.8
2.6
2.6
2.5
2.5
2.4
2.4
2.4
2.4
2.3
2.3
2.3
1.9
1.9
1.9
1.9
1.9
1.9
1.9
1.9
1.9
1.9
1.9
0
1000
2000
3000
4000
5000
6000
7000
8000
9000


278
Me
O
N
Me
CO2Me
O
208.1
171.9
150.8
141.7
136.2
124.4
111.0
106.4
80.1
77.2 CDCl3
62.4
52.9
51.1
48.7
38.5
36.7
35.8
31.4
f1 (ppm)


273
OMe
N
Me
O
O
f1 (ppm)


273
OMe
N
Me
O
O
197.2
174.1
150.2
141.8
137.8
123.7
111.0
106.4
101.5
75.3
58.5
56.0
53.8
53.4
38.2
35.8
34.0
f1 (ppm)


281
MeO
O
O
N
Me
f1 (ppm)


281
MeO
O
O
N
Me
198.0
176.7
149.9
142.1
138.6
122.0
111.2
106.9
100.7
72.0
59.9
55.8
53.9
53.6
46.6
37.6
36.4
34.1
f1 (ppm)