THE TRANSANNULAR BIS-MICHAEL REACTION IN THE SYNTHETIC STUDIES OF CELASTROL AND THE DEVELOPMENT OF NOVEL PALLADIUM-CATALYZED REACTIONS

A Dissertation

by

THOMAS MAXWELL KAISER

Submitted to the Office of Graduate and Professional Studies of
Texas A&M University
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Chair of Committee,	Jiong Yang
Committee Members,	Michael Manson
	Karen Wooley
	Daniel Romo
Head of Department,	David Russell

December 2013

Major Subject: Chemistry

ABSTRACT

Pharmaceutical R&D is currently undergoing a productivity crisis. Also, the loss of activity of established medicines continues to reduce the pool of agents capable of treating infectious diseases. Small molecule synthesis and synthetic methodology development continue to be essential scientific endeavors due to the ability of synthetic chemistry to create new starting points for the development of medicines. Therefore, in order to increase the ability to discover new medicines, more efficient synthetic strategies and transformations capable of generating structurally complex drug-like molecules are required.

This work explored the transannular *bis*-Michael reaction (TMR) as a potential method to access polycyclic natural products in an efficient manner. We sought to develop an expedient route to an all-carbon *Z,E* macrocyclic precursor to the TMR and we then evaluated whether the *Z,E* isomer would follow our proposed model for the TMR. Our strategy relied on a 1,3-dipolar cycloaddition to access the TMR precursor. However, this 1,3-dipolar synthetic route had a low synthetic efficiency.

Consistent with our other studies, this *Z,E*-macrocyclic *bis*-enone was found to be inactive in the transannular *bis*-Michael reaction cascade for the conditions evaluated. *En route*, we also discovered that our 1,3-dipolar cycloaddition gave a rare 3,4-disubstituted isoxazole under kinetic reaction conditions. We also demonstrated that the dipolar cycloaddition is reversible and the thermodynamic 3,5-disubstituted isoxazole can be obtained through isomerization of its 3,4-disubstituted isomer under elevated

temperature. Our initial mechanistic studies support the role of hydrogen-bonding in accelerating the isomerization process.

Our work in developing new palladium-catalyzed reactions resulted in a novel palladium-catalyzed enamine Heck reaction. This reaction is capable of generating α,β-unsaturated ketones directly from aldehydes and vinyl iodides. However, the limitations of scope in both vinyl iodide and aldehyde severely limit the synthetic utility of the reaction described herein.

Also, our work clearly demonstrated a novel enantioconvergent approach to 3-allyl-3-alykl-indolenines through the use of a chiral palladium/trialkylborane dual catalyst system. We suggest a greater role of trialkyl borane beyond allylic alcohol activation in previous allylation examples employing R_3B/allyl alcohol as the allyl source.

Finally, we extended or understanding of the role of Et_3B to the Tamaru allylation. The Lewis acid, Et_3B, facilitates enolization and behaves as a co-catalyst to effect the allylation of aldehydes. We have also begun developing an enantioselective version of this reaction that suffers from low enantioselectivity. This reaction was shown to be selective for aldehydes as ketones did not react under the described conditions.

DEDICATION

To my wife

ACKNOWLEDGEMENTS

I would like to thank my committee chair, Dr. Jiong Yang for providing the resources and environment necessary to conduct this research. I would also like to thank my committee members, Dr. Romo and Dr. Wooley for their guidance and support throughout the course of this research.

I would especially like to thank Dr. Mike Manson for the late-night discussions of life, in general, and science, in particular. Some of my best memories in graduate school are of his porch or took place in his car. I am grateful to Drs. Christopher Dorsey, Arjun Raghuraman, Guo-Qiang Tian, Houston Perry, Dave Herbert and Casey Wade for their guidance. Their experience and character served to make my endeavor far less painful. Also, my friends Ryan Kuppler, Dr. Trevor Makal, Morgan Shirley, Tyler Hood, Joon Kim, Henri Priest and Jon White always gave support when it was needed.

Finally, I am grateful for my family: both in blood and in law. Their aid and support helped my wife and me greatly. And, I am especially grateful to my wife, Michelle, for all of her work and love. I could not have done this without her support.

NOMENCLATURE

4 Å MS	4 Angstrom Molecular Sieves
9-BBN	9-Borabicyclo[3.3.1]nonane
AIBN	Azobisisobutyronitrile
Ar-	Aryl
B	Base
Bn	Benzyl
BOMO	Benzyloxymethyl-O-
dba	Dibenzylideneacetone
Cat.	Catalytic
CBS	Corey-Bakshi-Shibata
Cp	Cyclopentadienyl
1,2-DCE	1,2-Dichloroethane
DCM	Dichloromethane
dia	Diastereomer
DIBAL	Diisobutylaluminum Hydride
DIOP	2,3-*O*-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DIPA	Diisopropylamine
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine

DME	Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
dppb	1,2-*bis*(Diphenylphosphino)Butane
dppe	1,2-*bis*(Diphenylphosphino)Ethane
dppf	1,2-*bis*(Diphenylphosphino)ferrocene
dppp	1,2-*bis*(Diphenylphosphino)propane
dr	Diastereomeric Ratio
DYKAT	Dynamic Kinetic Asymmetric Transformation
ee	Enantiomeric Excess
ent	Enantiomer
FMO	Frontier Molecular Orbital
h, hr, hrs	Hour/Hours
HOMO	Highest Occupied Molecular Orbital
hv	Photon Irradiation
HMPA	Hexamethylphosphoramide
IBX	2-Iodoxy-Benzoic Acid
i-Pr	Isopropyl
L_n	Any Number of Ligands
LDA	Lithium Diisopropylamide
LiHMDS	Lithium *bis*(Trimethylsilyl)Amide
LUMO	Lowest Unoccupied Molecular Orbital

M	Metal Atom
Me	Methyl
n-Bu	Butyl
NCS	*N*-Chloro-Succinimide
NF-κB	Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells
NHK	Nozaki-Hiyama-Kishi
NIS	*N*-Iodo-Succinimide
NMO	*N*-Methylmorpholine *N*-Oxide
NMR	Nuclear Magnetic Resonance
Nu	Nucleophile
OAc	Acetate
OTf	Trifluoromethanesulfonate
Ph	Phenyl
PHOX	2-[2-(Diphenylphosphino)Phenyl]-2-Oxazoline
PMB	*para*-Methoxybenzyl
R	Any Alkyl, Aryl, Vinyl, or Alkynyl Group
r.t.	Room Temperature
(*S*)-BINAP	(*S*)-(−)-2,2′-*bis*(Diphenylphosphino)-1,1′-Binaphthyl
T	Temperature
TBAC	Tetrabutylammonium Chloride
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl

t-Bu	*tert*-Butyl
TBAF	Tetra-*n*-Butylammonium Fluoride
TEMPO	(2,2,6,6-Tetramethyl-Piperidin-1-yl)Oxyl
TES	Triethylsilyl
TFA	Trifluoroacetic Acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMR	Transannular *bis*-Michael Reaction
TMS	Trimethylsilyl
Tol-BINAP	2,2′-Bis(di-*p*-tolylphosphino)-1,1′-binaphthyl
TPAP	Tetrapropylammonium Perruthenate
Ts	Tosyl
X-	Any Halide

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF SCHEMES

LIST OF TABLES

CHAPTER I

INTRODUCTION AND LITERATURE REVIEW

Our world is faced with many challenges, not the least of which are the productivity crisis in drug discovery[1] and the emergence of drug-resistant pathogens.[2] Faced with the diminishing returns of pharmaceutical R&D and the loss of activity of established medicines, small molecule synthesis continues to be an essential scientific endeavor. However, new tools for the expedient exploration of diverse chemical space are in dire need. Most small molecule libraries used in drug discovery contain molecules comprised of extended sp^2 systems with little to no stereochemical complexity.[3,4] Therefore, in order to increase the ability to discover new medicines, more efficient synthetic strategies and transformations capable of generating structurally complex drug-like molecules are required. It is through this light that the following research should be viewed. The progress described within not only focused on the development of a new synthetic strategy to access biologically relevant, stereochemically complex natural products; the research also dealt with new palladium-catalyzed bond-forming strategies with the aim of eventual application in synthesis.

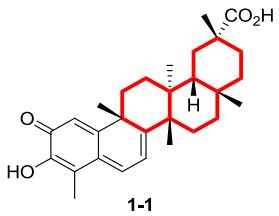
The Transannular bis-*Michael Reaction and Synthetic Studies of Celastrol*

Chemical Structure and Biology of Celastrol

The extracts of the *Trypterygium wilfordii* (Lei Gong Teng), have been used in traditional Chinese medicine to treat rheumatoid arthritis, an autoimmune disease, for

hundreds of years. Recent interest in the extracts' therapeutic effects has led to eleven clinical trials in various stages of completion.[5] One of the active components in the extracts of *T. wilfordii* is celastrol **1-1** (Figure **1-1**).[6,7] Of special interest is the molecular biology of celastrol. In animal models of lupus, arthritis, amyotrophic lateral sclerosis and Alzheimer's disease, celastrol was found to inhibit the inflammatory response.[8] Celastrol was also shown to induce multiple biological effects at the molecular level, such as NF-κB pathway perturbation, proteasome inhibition, topoisomerase II inhibition and heat shock response activation.8 While it is known that celastrol can alter these pathways, the exact molecular target(s) remains unknown.

With the opportunity to explore novel biology as well as develop new chemistry, we turned our attention to the structure of **1-1**. Celastrol is representative of a small group of quinone methide triterpenoids isolated from the families Celastraceae and Hippocrateaceae.[9] These molecules feature an *o*-hydroxy substituted *p*-quinone methide ring system embedded within a **D**:**A**-*freido-nor-oleanane* skeleton which contains a perhydrophenanthrene ring system (highlighted red in Figure **1-1**). As of yet there is no total synthesis of celastrol in the literature.



1-1

Figure 1-1. Celastrol

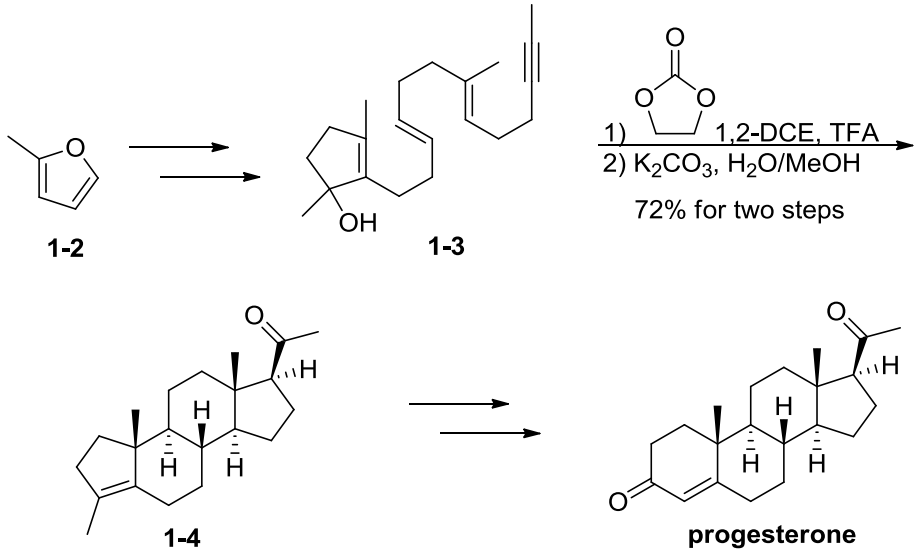
Methods of Perhydrophenanthrene Construction in Total Synthesis

The construction of the perhydrophenanthrene ring system of **1-1** is the key synthetic challenge in the total synthesis of celastrol. This is due to the large array of all-carbon quaternary stereocenters without obvious functional group handles for their construction. Therefore, a brief examination of previous efforts to synthesize similar systems serves to give a setting to our strategy for the perhydrophenanthrene ring system of **1-1**. The focus is on cascade or intramolecular reactions and these reactions have been divided into four categories: cationic cyclization cascades, radical cyclization cascades, pericyclic reactions, and Michael reactions.

Cationic Cyclization Cascade Reactions

Fused carbocyclic systems abound in natural products and have captured the imagination of synthetic organic chemists for decades. One of the earliest proving grounds for synthetic methodology was the collection of natural products known as steroids which contain a complex carbocyclic core. One of the first major breakthroughs in the synthesis of these steroid molecules was the biomimetic total synthesis of progesterone by Johnson and coworkers (Scheme **1-1**).[10] The development of Stork-Eschenmoser hypothesis,[11] describing the stereochemical relationship between linear polyunsaturated systems and the cyclization product resulting from the cationic cyclization cascade, allowed for the controlled formation of **1-4** from **1-3** using TFA to generate the cationic intermediate from **1-3**. This two part sequence of cationic cyclization cascade/trapping followed by hydrolysis of the resulting ethylene carbonium cation generated **1-4** in 72% yield. It is important to note that the cationic cascade

generated three carbocycles and set 6 stereocenters of which two are all-carbon quaternary centers.



Scheme 1-1. The Johnson synthesis of progesterone

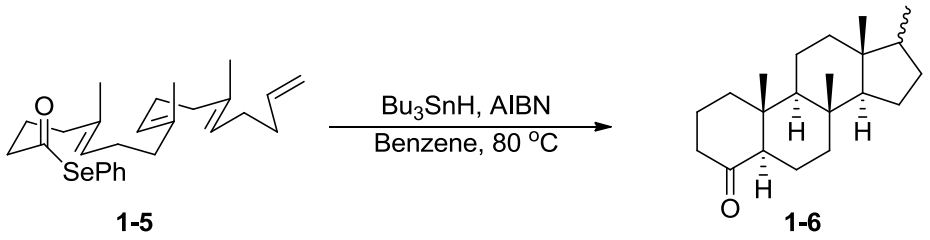
Major advances in this strategy include the development of mild and/or enantioselective Lewis acid catalysts to effect this transformation. Current examples abound in the literature with Corey's synthesis of lupeol in 2009 being noteworthy for the rapid enantioselective construction of the polycyclic core.[12]

Despite the history of synthetic achievement for cationic cyclizations, there are limitations to this strategy. Chief among these is the requisite formation of a reactive carbocationic species *in situ*. These high energy species are subject to rearrangement and hydride shifting and therefore substrates where these side reactions can occur are not suitable for the cationic cyclization cascade.

Radical Cyclization Cascade Reactions

Over the past few decades, many new methods have been developed to generate stereochemically complex polycycles. One of the most versatile has proven to be radical cyclization cascades. These cascade reactions take advantage of the generation of a carbon radical in close proximity to an array of unsaturated groups so that a series of free-radical bond-forming and bond-breaking processes give rise to a desired carbocyclic system in a highly controlled manner. One of the earliest natural product total synthesis strategies to take advantage of this process was the total synthesis of hirsutene by Curran and coworkers.[13]

It was not until 1996 that a strategy of generating a complex polycyclic system from an entirely linear precursor was developed. Pattenden and coworkers developed a means of accessing polycyclic systems in good yields by using polyunsaturated phenyl selenoates as precursors.[14] In a representative example from this methodology, compound **1-5** was exposed to Bu_3SnH and AIBN which generated **1-6** in 78% yield by means of a radical cyclization cascade (Scheme **1-2**). This reaction set six stereocenters, of which three were quaternary, and formed four C-C bonds all with a high degree of diastereoselectivity for the carbocyclic core.



Scheme **1-2**. Radical cyclization cascade to synthesize **1-6**

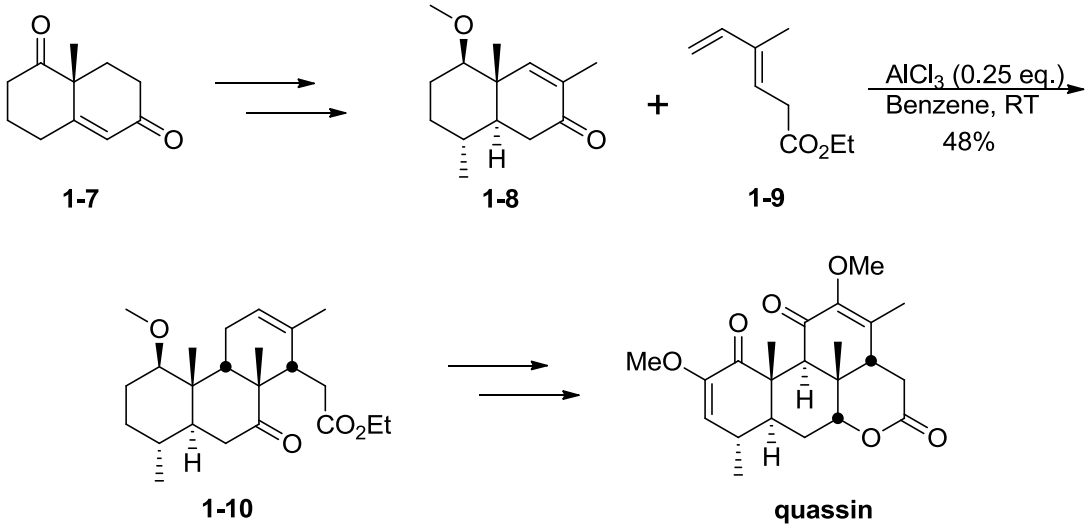
One of the major advantages of radical cyclization cascades is the low propensity of the radical intermediates to undergo rearrangements compared to carbocations. However, radical intermediates are still high energy species and premature termination as well as polymerization are major side reactions that can be problematic when conducting radical reaction cascades.

Pericyclic Cyclization Reactions

Pericyclic reactions have been one of the most versatile sets of transformations available to organic chemistry. These reactions include one of the most widely used reactions in total synthesis: the Diels-Alder reaction.[15] Other members of the pericyclic family merit mention as useful strategies to construct polycyclic carbocycles especially the [2+2+2]-carbocylization and the intramolecular ene reaction. Many of these reaction types have allowed for the rapid construction of all-carbon ring systems in a highly efficient manner.

One of the classic examples of a Diels-Alder strategy in the synthesis of perhydrophenanthrenes is the synthesis of quassin in 1980 by Grieco (Scheme **1-3**).[16] In this synthesis, a key intermolecular Diels-Alder between **1-8** and **1-9** was conducted

using a catalytic amount of $AlCl_3$. The highly substituted perhydrophenanthrene derivative **1-10** was generated in 48% yield. The stereoselectivity for the Diels-Alder reaction arises because of the *endo* transition state being favored.

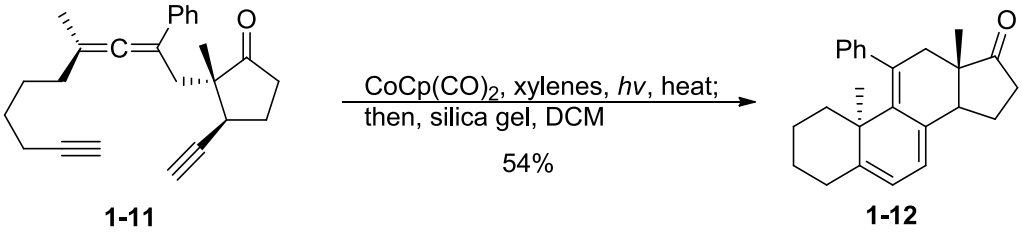


Scheme **1-3**. The Grieco synthesis of quassin

Diels-Alder reactions represent a classic method for the construction of polycyclic ring systems through either an intramolecular or intermolecular strategy. These reactions also benefit from mild reaction conditions and a well studied stereoselectivity.

Another type of pericyclic reaction capable of polycycle construction is the transition metal-mediated [2+2+2] carbocyclization. In 2004, the Malacria group reported the cobalt(I)-facilitated [2+2+2] intramolecular cyclization cascade of

allenediyne **1-11** to generate **1-12** in 54% yield with only one diastereomer generated (Scheme **1-4**).[17]



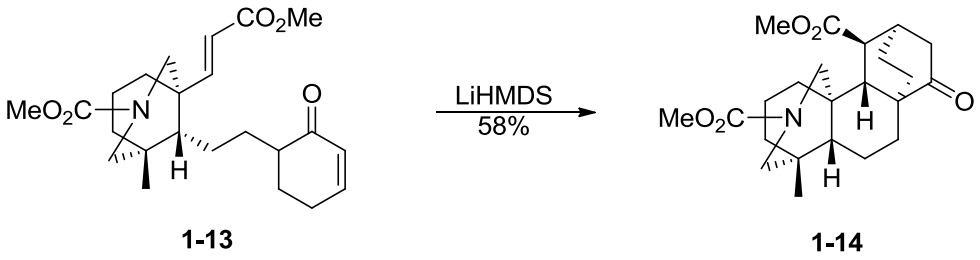
1-11 **1-12**

Scheme **1-4**. The Co-mediated [2+2+2]

As these examples show, pericyclic reactions provide many routes to a diverse family of carbon polycycles. Pericyclic reactions also have the major advantage of milder conditions than cationic and radical cyclization cascades. Also, no reactive intermediates are formed and, thus, the possibility for rearrangements and side reactions is reduced.

Michael Cyclization Cascade Reactions

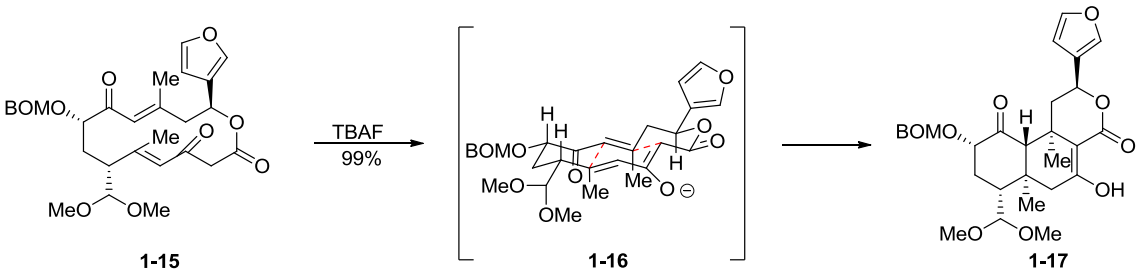
Conjugate additions have long been a major tool for synthetic chemists to construct carbocyclic ring systems.[18] Especially with the advent of tandem intramolecular processes, Michael cyclization cascade reactions have been demonstrated to be highly diastereoselective in addition to being able to form complex polycycles. An illustrative example developed by Fukumoto and coworkers involves treatment of **1-13** with LiHMDS to generate **1-14** in 58% yield and as a single isomer (Scheme **1-5**).[19] This intramolecular process generated a high degree of structural complexity in a single step.



1-13 **1-14**

Scheme **1-5**. The Fukumoto Michael cyclization cascade

In 2007, a new type of Michael cascade reaction was reported by Evans and coworkers in the course of their total synthesis of salvinorin A: the transannular *bis*-Michael reaction.[20] This reaction is astonishing both in the mild conditions required for the reaction (TBAF in THF at -78 ^{o}C) and in the 99% yield reported of **1-17** from **1-15** (Scheme **1-6**). Furthermore, only one diastereomer was isolated. The high diastereoselectivity of the transannular *bis*-Michael reaction (TMR) arises from a highly ordered transition state, **1-16**, with a proposed chair-like conformation adopted in transition state.



Scheme **1-6**. The transannular *bis*-Michael reaction

The initial alkene geometries of **1-15** are translated into the relative stereochemistry of the angular methyls in **1-17**. However, the Evans example is only one isomer of the four possible double bond isomers that could react under the TMR conditions. Furthermore, the TMR had only been demonstrated in a macrolide setting. We were curious if an all-carbon macrocycle could undergo the TMR and give a perhydrophenanthrene ring system. In addition, a knowledge gap existed regarding the complete relationship between the stereochemical structure of the four precursors and that of their cyclized products. We therefore proposed a stereochemical model to address this knowledge gap and we sought to test the scope of the TMR and evaluate if the TMR could be used in the construction of a perhydrophenanthrene ring system.

The Transannular *bis*-Michael Reaction

Advantages of Transannular Reactions

Transannular is a term applied to chemical reactions that involve two or more groups reacting "across the ring". Transannular reactions are intramolecular reactions by definition and, as such, have several key advantages over intermolecular reactions (Figure **1-2**). The first of which is transannular reactions can take advantage of the

conformational preference of ring systems in order to direct the stereochemistry of the reaction.[18] Medium and large ring systems (8-14 atom rings) have well defined conformations and the ability of conformations to direct the stereochemical outcome of reactions has long been known in organic chemistry as macrocyclic stereocontrol. Secondly, transannular reactions have the advantage of rate acceleration due to the proximal nature of the reacting groups. The third key advantage is the ability of transannular reactions to form multiple smaller rings in one step from reacting functional

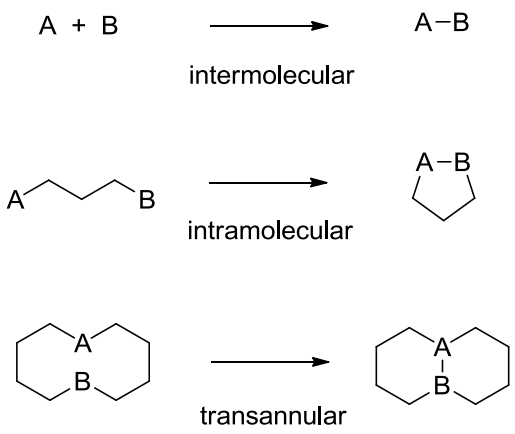


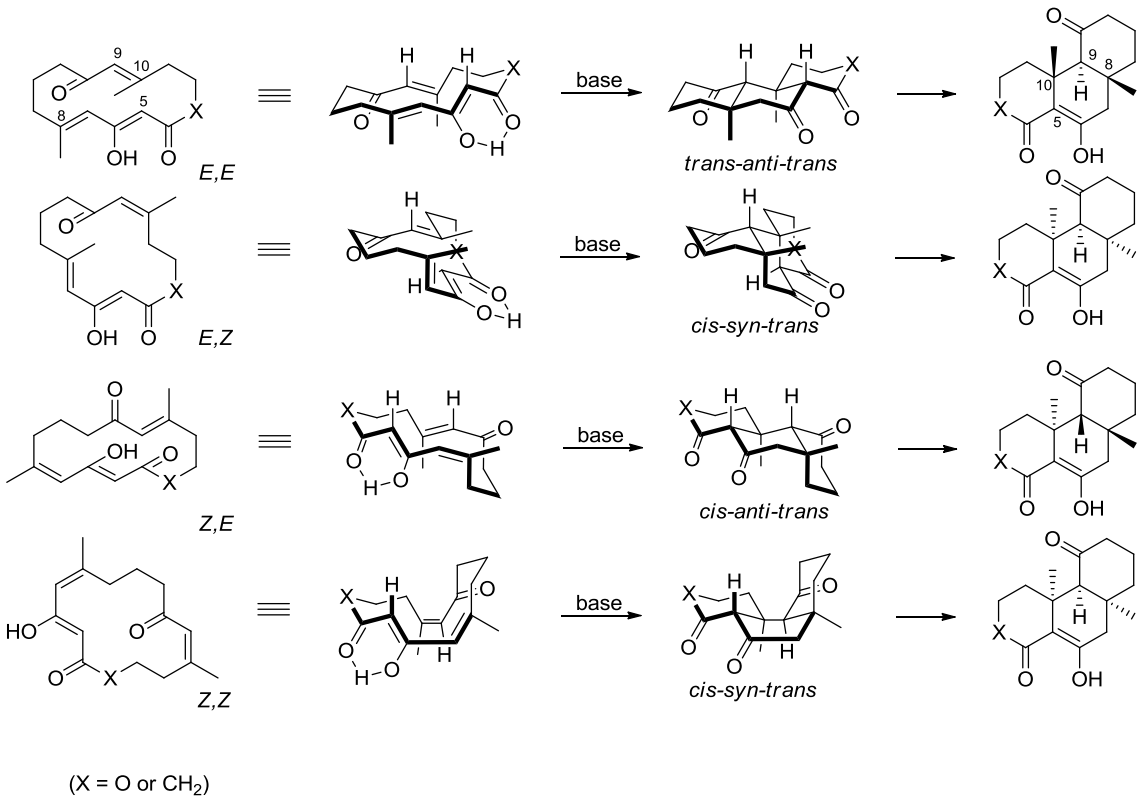
Figure **1-2**. Types of reactions

groups that are kept in close proximity. The efficiency of the constructing many rings with stereocontrol in one step is of high value to modern organic synthesis.[21]

The Stereochemical Model of the Transannular bis-*Michael Reaction*

We set about to compose a model that would allow chemists to predict the product of the TMR given the double bond geometry of hypothetical starting material of

either macrolide or all-carbon character. We proposed a model analogous to the Stork-Eschenmoser hypothesis of cationic polyene cyclization whereby the transannular bis-Michael reaction cascade would proceed through a tight, chair-like transition state whenever possible and the initial alkene geometries would translate into the relative stereochemistry of the products (Scheme **1-7**).



Scheme **1-7**. A proposed stereochemical model for the TMR

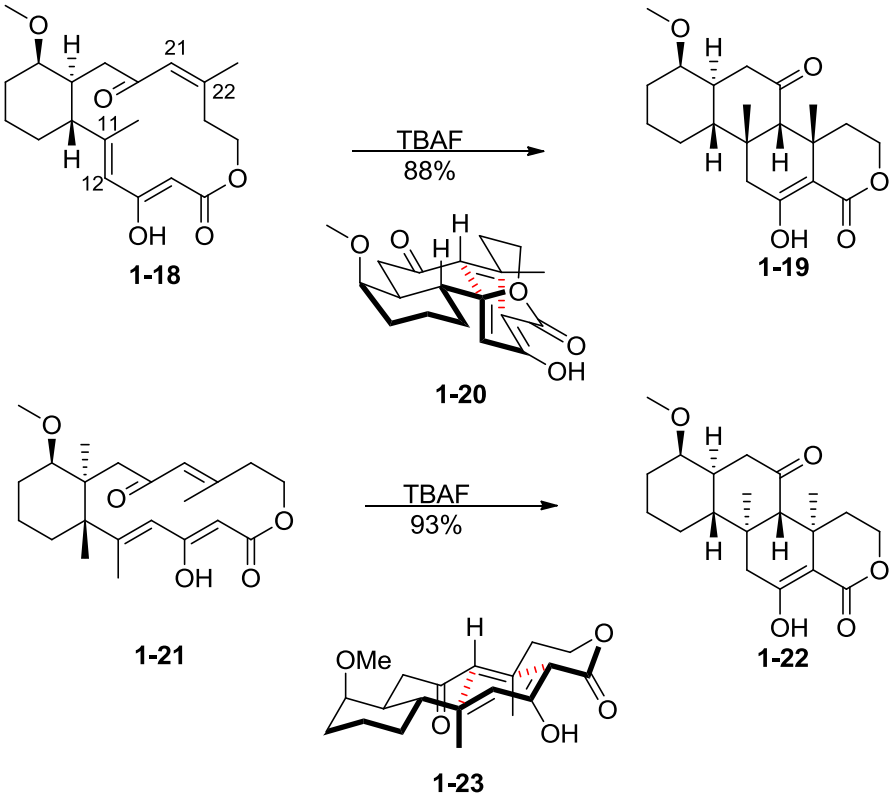
We expect that a 9,10-anti perhydrophenanthrene will be generated when the macrocyclic bisenone contains a C9-C10 *E* double bond. Also, our model predicts a

9,10-syn perhydrophenanthrene ring system when the C9-C10 double bond is *Z*. We hypothesize that the transition state conformations of the macrocyclic substrates are largely determined by the configurations of the C5-C6, C7-C8, and C9-C10 double bonds. Also, we expect that the C5-C6 double bond will be *Z* across all substrates due to the favorable hydrogen bond formed between the enol and the adjacent carbonyl oxygen. With this model in place, our investigations of the TMR began in the context of eventual application in the total synthesis of norzoanthamine (not pictured) and **1-1**. We designed two classes of TMR precursors: the norzoanthamine class (X=O in Scheme **1-7**) and the celastrol class ($X=CH_2$ in Scheme **1-7**) that would serve the purpose of testing the stereochemical model with the appropriate functionality to continue with the respective synthesis.

The Evaluation of the Stereochemical Model of the Transannular bis-*Michael Reaction*

Initially, our model was applied to substrates **1-18** and **1-21** of the norzoanthamine class (Scheme **1-8**).[22] Gratifyingly, these substrates underwent the TMR reaction according to our predictions and gave the desired products **1-19** and **1-22** respectively as characterized by NMR and X-Ray analysis. We hypothesize that the three-dimensional structures **1-20** and **1-23** are the reactive conformations of substrates **1-18** and **1-21**. Because of the constraint of the macrocycle in structure **1-18**, the C11-C12 double bond must adopt a pseudo-axial orientation to the incipient ring formed by the bond between C21 and C11. In addition, the C21-C22 double bond assumes a pseudo-equatorial orientation in the transition state. As a result of these orientations, the

cyclization of **1-18** proceeds to give structure **1-19**. These same structural analyses can be made for **1-21** and yield the same result: our hypothesis holds.

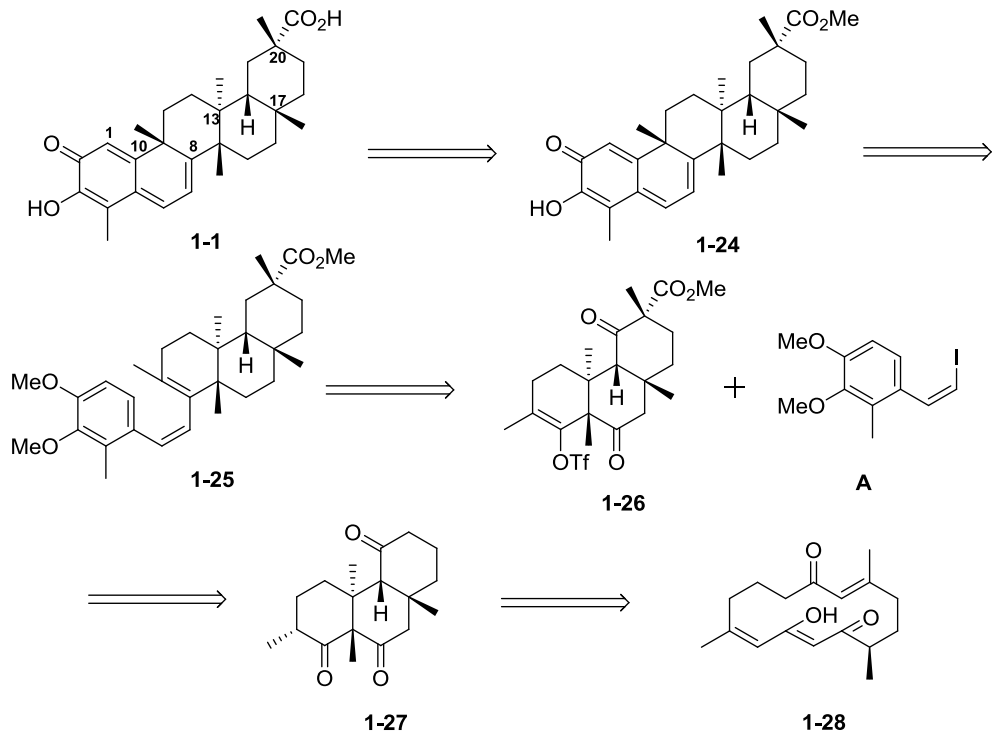


Scheme **1-8**. Preliminary results of the stereochemical model of the TMR

The Transannular *bis*-Michael Reaction in the Total Synthesis of Celastrol

Encouraged by our initial results in the evaluation of our model, we turned our attention to completing the model with an eye on using the resulting perhydrophenanthrenes in the total synthesis of **1-1**. As a result of this planning, we devised a retrosynthesis as follows (Scheme **1-9**). We envisioned that with ester

hydrolysis of **1-24** we could synthesize **1-1**. The methyl ester **1-24**, itself a natural product named pristimerin, is expected to come from **1-25** after BCl_3 mediated cleavage of the methyl ethers followed by oxidative cyclization to form the requisite *p*-quinone methide functionality. Diene **1-25** is expected to be synthesized from **1-26** and **A** through a Pd-mediated cross-coupling followed by functional group manipulations. Selective enolization and subsequent transformation of the selectively generated enolates is expected to give **1-26** from **1-28**. The key transformation in this retrosynthetic plan is



Scheme **1-9**. Retrosynthetic analysis of **1-1**

the use of the TMR to generate **1-27** from **1-28** followed by methylation. We therefore set out to synthesize **1-28** in order to confirm our stereochemical model and provide a synthetic route to celastrol. The course of our experimentation in this endeavor is outlined in chapters II and III of this dissertation.

The Development of Novel Palladium-Catalyzed Reactions

Organic chemists spend a great deal of time forming C-C bonds and new transformations that allow the ready formation of these bond types often revolutionize the field of organic synthesis. One of the most extraordinary developments of 20th century chemistry was the discovery that palladium reagents could catalyze the formation of a myriad of C-C and C-X bond types in an efficient and predictable manner.[23] In fact, the developments of palladium chemistry had such a broad impact beyond the organic chemistry community, the early pioneers of palladium chemistry Heck, Negishi and Suzuki were awarded the 2010 Nobel Prize for their work.

Introduction to Pd-Catalyzed Cross-coupling Reactions

In 1968 and 1969 Heck reported the coupling of alkenes with Ar-Hg-X derivatives to give arylated alkenes mediated by a stoichiometric Pd(II) salts.[24] These communications are some of the earliest examples of what would later be known as cross-coupling reactions. Any cross-coupling reaction is defined by the combination of one molecule with another coupling partner to form a new bond. Some common types of palladium catalyzed cross-coupling reactions employed in organic synthesis are outlined in Figure **1-3**.[25]

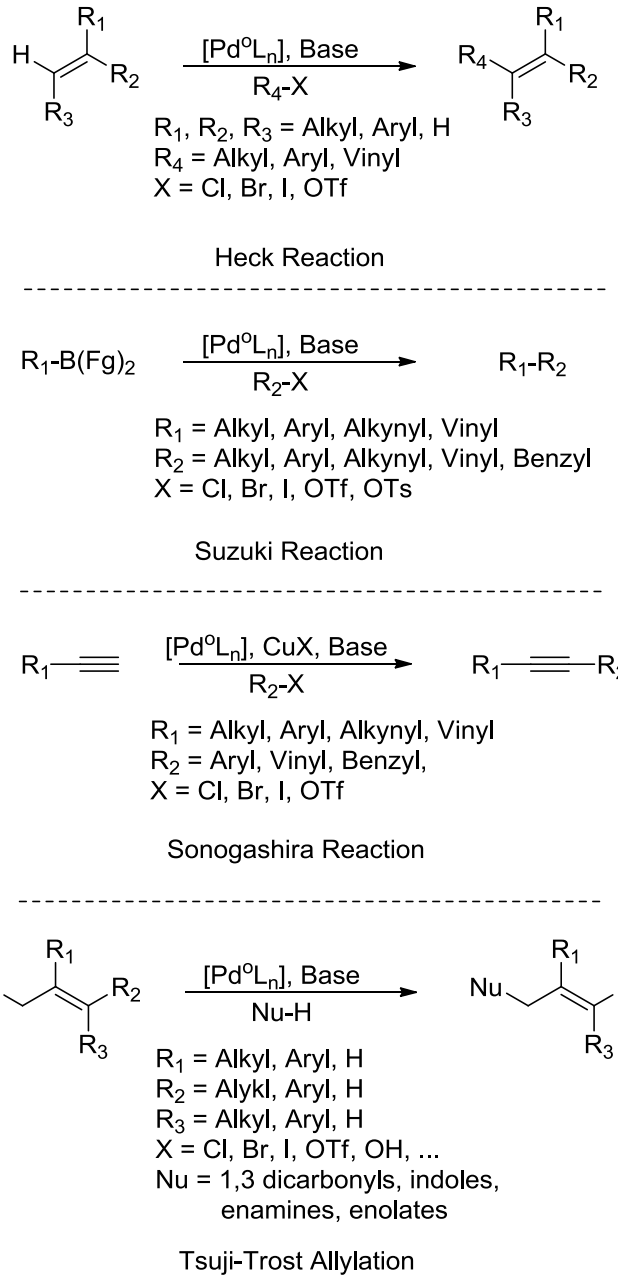


Figure **1-3**. Some common Pd-catalyzed cross-coupling reactions

The reaction types given in Figure **1-3** all give access to new C-C bonds and all have limitations on the R groups attached to the coupling partners. New advancements in

the field of Pd-catalyzed C-C bond formation focus on two main areas: new C-C bond forming reaction types and the expansion of substrate scope for the current classes of cross-coupling reactions. This research focuses on the expansion of substrate scope for two coupling reaction types: the Heck reaction and the Tsuji-Trost allylation.

The Heck Reaction

Introduction to the Catalytic Heck Reaction

As was previously stated, in 1968 and 1969 Heck reported the coupling of alkenes with Ar-Hg-X derivatives to give arylated alkenes mediated by a stoichiometric amount of a Pd(II) salt.[24] However, research into the modern catalytic Heck reaction as represented in Figure **1-3** was not possible until the work of Mizoroki and co-workers in 1971.[26] This work was the first to report a catalytic, ligand-free palladium system that used iodobenzene to arylate alkenes. However, these reaction conditions required a high temperature (125 ^{o}C) autoclave. Also, the reported scope of the reaction was limited to iodobenzene and simple alkenes as coupling partners. Despite these limitations, the development of a catalytic version using iodobenzene was a significant improvement.

The next key improvement for the Heck reaction was the discovery that phosphine ligands could improve the catalytic activity of the proposed Pd^0 species. This realization came about with the work of Dieck and Heck in 1974.[27] The catalytic system involved $Pd(OAc)_2$ as the Pd source with the addition of PPh_3 as a ligand. The addition of PPh_3 substantially increased the rate of reaction for aryl iodides, and aryl bromides were also found to react, albeit at higher temperatures (100-135 ^{o}C). These two

developments (catalytic palladium and phosphine ligands) gave rise to the modern Heck reaction.

Mechanism of the Heck Reaction

Heck and Nolley proposed the first mechanism for the Pd-catalyzed Heck reaction in 1972.[28] However, a mechanism including phosphine ligands was not described until 1974 by Dieck and Heck.[27] The proposed catalytic cycle is comprised of four steps: oxidative addition, migratory insertion, β-hydride elimination, and reductive elimination of HX. These four steps are outlined in Figure **1-4**.

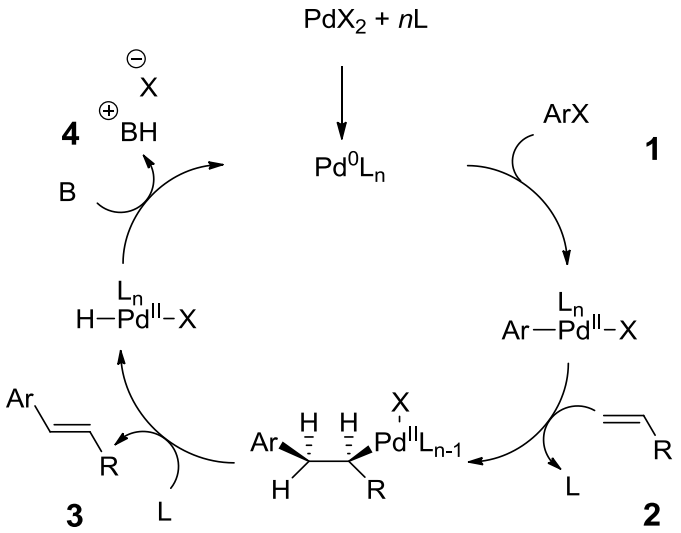


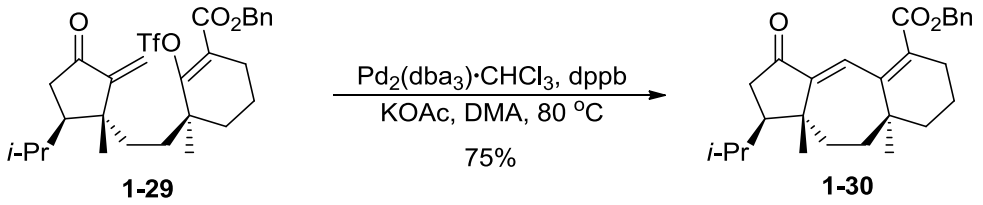
Figure **1-4**. General mechanism for the Heck reaction

The mechanism begins with a Pd^0-ligand complex (Pd^0L_n) with Pd^0 being formed *in situ* or preformed. Step **1** in Figure **1-4** is the oxidative addition of Pd^0L_n to the Ar-X bond with aryl iodides and aryl bromides reacting much faster than aryl chlorides. Step **2**

involves loss of one ligand molecule (L) and the coordination of an alkene. This is followed by *syn* addition of the Ar-$Pd^{II}(L_n)$-X across the C-C double bond as a migratory insertion step. Step **3** consists of rotation about the C-C bond, *syn* β-hydride elimination, disassociation of the product, and binding of a ligand molecule L. Finally, step **4** invovles the reductive elemination of HX from H-$Pd^{II}L_n$-X to regenerate Pd^0L_n. The reaction is driven by base (B) quenching the HX produced as a byproduct.

Modern Developments of the Heck Reaction

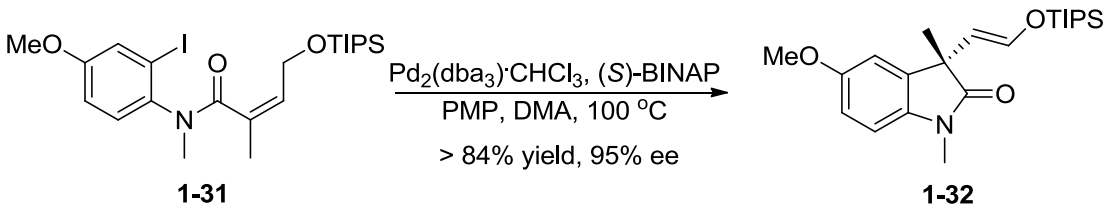
The modern phosphine-Pd catalytic system has seen wide application in both academic and industrial synthesis.[29] One of the prime uses for the Heck reaction is in the construction of carbocycles. An especially interesting use of the Heck reaction was in a rare 7-*endo*-trig cyclization employed by Overman and co-workers in the total synthesis of (+)-guanacastepene (Scheme **1-10**).[30] The tricycle **1-30** was formed in 75% yield when **1-29** was exposed to Heck conditions.



Scheme **1-10**. The 7-*endo*-trig cyclization of **1-29**

One of the most important developments of the Heck reaction has been the introduction of an asymmetric version capable of synthesizing quaternary stereocenters.

This area of research has been largely driven by the groups of Shibasaki and Overman.[31,32] An excellent use of the asymmetric Heck reaction was in the total synthesis of (-)-physostigmine by Overman and co-workers (Scheme **1-11**).[33] This transformation proceeded in greater than 84% yield and afforded **1-32** in 95% ee. Many examples of asymmetric Heck reactions in total synthesis have been demonstrated.[29]



1-31 **1-32**

Scheme **1-11**. Asymmetric Heck reaction

In addition to the asymmetric Heck reaction, many other modifications and advancements exist. Microwave-assisted Heck reactions have been developed[34] as well as Heck conditions where water[35] is the solvent. Other major developments include the use of an oxidative Heck reaction, the Fujiwara-Moritani reaction.[36] This palladium-catalyzed process is capable of coupling aryl and alkenyl systems without the aryl component containing any halide functional group as an activator (i.e. X=H in Figure **1-3**). Finally, the development of large cone angle ligands by Fu and others (i.e. P(*t*-Bu)$_3$) has allowed for the use of previously unreactive aryl chlorides as coupling partners in the Heck reaction.[37] All of these improvements described allow for an improvement in the scope of the Heck reaction and serve to make the Heck reaction a robust synthetic

tool. However, many types of coupling partners have yet to be shown capable of participating in the Heck reaction. These types, specifically where R_1, R_2 or R_3 in Figure **1-3** is $-NR_2$, provide a means of directly accessing conjugated enamines (and presumably enones after hydrolysis) efficiently should simple enamines be demonstrated as viable coupling partners. Chapter IV deals with an exploration of this idea and the development of a new type of Heck reaction: the enamine-Heck reaction (Figure **1-5**).

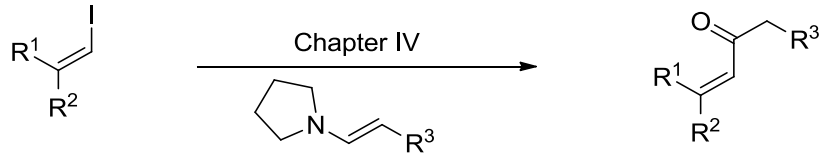


Figure **1-5**. Research into substrate scope expansion for the Heck reaction

The Tsuji-Trost Reaction

Introduction to the Tsuji-Trost Reaction

The first report of a π-allylpalladium electrophile reacting with soft nucleophiles like *N*,*N*-dimethylcyclohexenamine or the enolates derived from diethyl malonate and ethyl acetoacetate was by Tsuji and co-workers in 1965.[38] The allylation described involved the stoichiometric use of preformed π-allylpalladium chloride; however, this limitation was overcome by the work of Atkins and co-workers when they developed a catalytic version.[39] One of the seminal contributions in the early Tsuji-Trost reaction was by Trost and Fullerton whereby they demonstrated that alkyl substituted π-allylpalladium intermediates could react with soft nucleophiles to give products with

high regioselectivity.[40] Also, Trost and Fullerton demonstrated that hard nucleophiles like Grignard reagents and organolithium reagents did not attack the alkyl substituted π-allylpalladium intermediates. Taken together, these works established the Tsuji-Trost reaction outlined in Figure **1-3**.

One of the unique features of the Tsuji-Trost reaction is the wide substrate scope for allyl-X as seen in Figure **1-3**. A survey of some of the more common allylating reagents is given in Figure **1-6**. All of the examples given in Figure **1-6** are capable of forming π-allylpalladium complexes under mild reaction conditions.

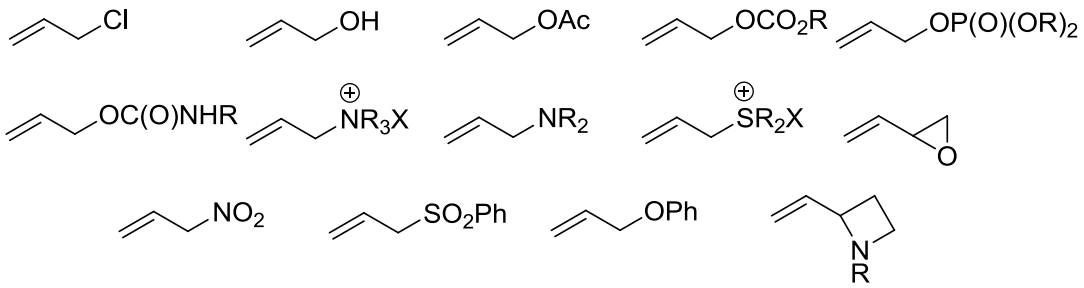


Figure **1-6**. Some common allylating reagents for the Tsuji-Trost reaction

The Tsuji-Trost reaction can be divided into two main reaction types: the intermolecular allylation and the intramolecular allylation.[18] Both reaction types have seen the development of enantioselective versions and both have been broadly applied in organic synthesis.

Mechanism for the Tsuji-Trost Reaction

The first mechanistic description of π-allylpalladium intermediates in the Tsuji-Trost reaction was by Kurosawa in 1987.[41] The current most general mechanism is the result of intensive effort and is outlined in Figure **1-7**.

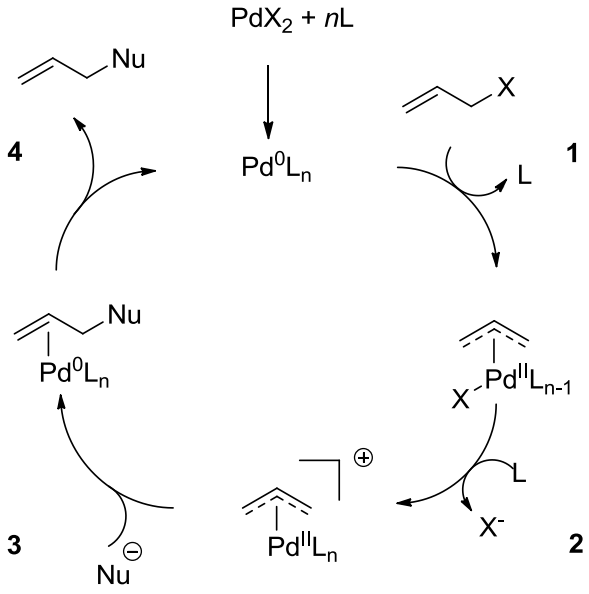


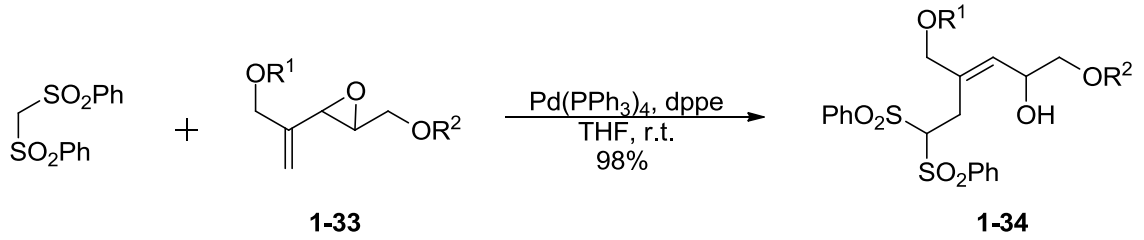
Figure **1-7**. Mechanism for the Tsuji-Trost reaction

Following ligand complexation to the Pd^0 atom, there are four main steps to the catalytic cycle. Step **1** in Figure **1-7** is coordination of allyl-X to the palladium center with displacement of one molecule of ligand L followed by oxidative addition of Pd^0 to the C-X bond to give an allyl-$Pd^{II}L_{n-1}$ complex. Step **2** involves displacement of X^- with L to give a cationic $(allyl\text{-}Pd^{II}L_n)^+$ complex which is attacked by Nu^- in step **3**. This

generates the allyl-NuPd^{0}L$_n$ complex which dissociates in step **4** to regenerate the catalyst and gives product.

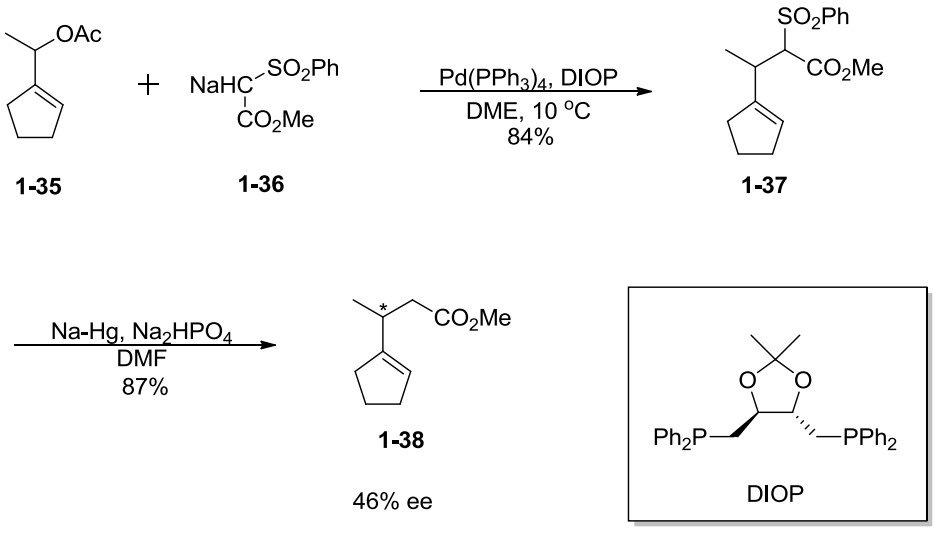
The Intermolecular Allylation

One of the applications of the intermolecular allylation was in the synthesis of cristatic acid by Fürstner and Gastner.[42] The Tsuji-Trost reaction was used to couple *bis*-(phenylsulfonyl)methane with **1-33** through the use of palladium catalysis (Scheme **1-12**).



Scheme **1-12**. The use of the Tsuji-Trost reaction in the synthesis of cristatic acid

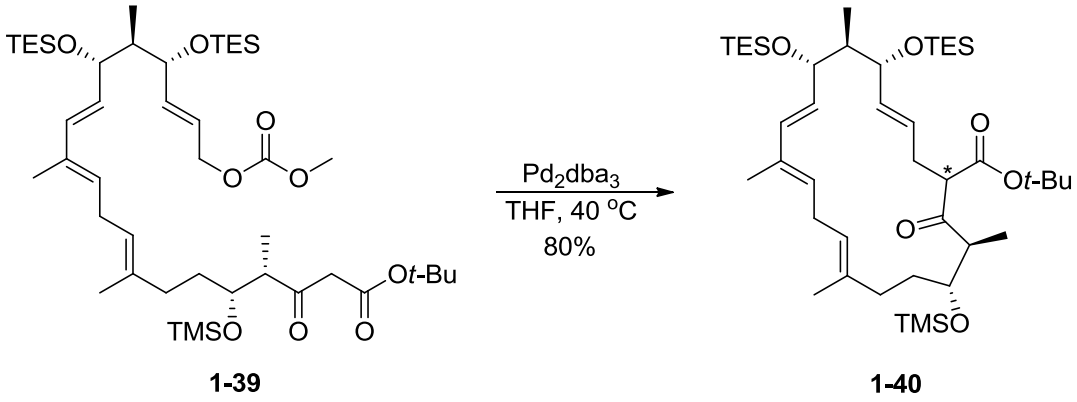
In this example, **1-34** was formed in 98% yield from **1-33** through the action of Pd-dppe formed *in situ*. Also, the reaction conditions were mild compared to conditions normally required to open an oxirane through conjugate addition.[29] However, the broadest utility of the intermolecular Tsuji-Trost reaction is found in the enantioselective version first described by Trost and Strege in 1977.[43] The initial reaction described involved the use of a C_2-symmetric DIOP ligand and afforded low enantioselectivities (Scheme **1-13**). Enantioselectivities as high as 99% have been demonstrated in the literature with more modern ligands (*i.e.* PHOX-type).[44]



Scheme **1-13**. First example of the enantioselective Tsuji-Trost reaction

The Intramolecular Allylation

In the intramolecular Tsuji-Trost allylation, the nucleophile and the allylating reagent are part of the same molecule. One of the classic examples of this strategy was in the total synthesis of (+)-FR182877 by Sorensen and co-workers (Scheme **1-14**).[45] The macrocylization of **1-39** employed an intramolecular Tsuji-Trost allylation using mild conditions (10 mol % Pd_2dba_3 and 40 ^oC in THF) to give **1-40** in 80% yield. This reaction demonstrates

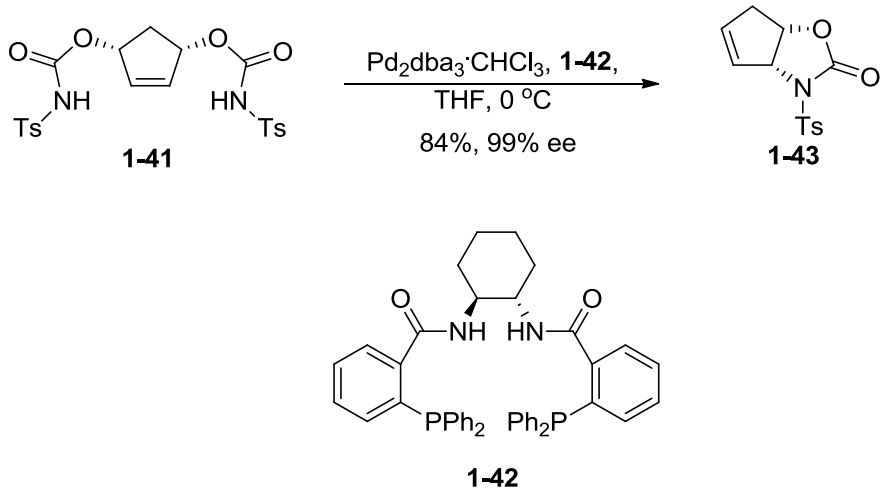


1-39 **1-40**

Scheme **1-14**. Intramolecular Tsuji-Trost reaction

the high diastereoselectivity achievable in the Tsuji-Trost reaction as only one diastereomer was detected (stereocenter not assigned). Also, a high degree of functional group tolerance is demonstrated for the Tsui-Trost reaction in the conversion of **1-39** to **1-40**.

Enantioselective conditions have been developed for the intramolecular Tsuji-Trost reaction. One of the first examples to obtain high ee was the enantioselective intramolecular allylation of tosyl carbamates to generate tosyl oxazolidinones developed by Trost and Patterson in 1998 (Scheme **1-15**).[46] The high enantionselectivity was imparted by a new class of ligand synthesized by 2-(diphenylphosphino)benzoate and cyclohexane-1,2-diamine (**1-42** in Scheme **1-15**). This class of ligand has seen many



Scheme **1-15**. The desymmetrization of **1-41**

developments that have led to it becoming a ligand class with broad application in the synthetic community.[47] However, the main feature of this reaction is that it is one of the early examples of a catalytic desymmetrization of a racemic or, in this case, a prochiral molecule. The conditions employed by Trost and Patterson were capable of forming **1-43** in 84 % yield but in greater than 99% ee from **1-41**. The work presented in this dissertation focuses on the desymmetrization process in the Tsuji-Trost reaction and a discussion of desymmetrization is therefore merited.

Desymmetrization in the Tsuji-Trost Reaction

There are many examples of desymmetrization in organic chemistry.[48] Desymmetrization reactions can either be conversion of achiral molecules into chiral molecules or the transformation of a racemate into a chiral product.[49] This is outlined in Figure **1-8**.

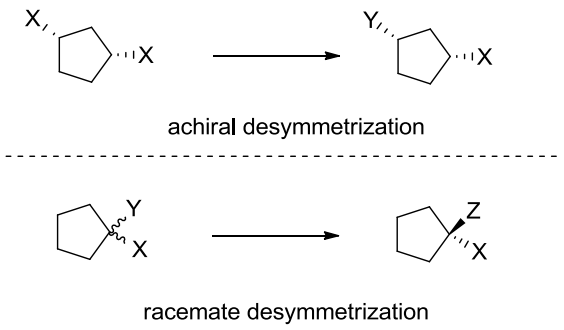


Figure **1-8**. The two types of desymmetrization reactions

Examples of the Tsuji-Trost reaction used to desymmetrize molecules abound[49] and this dissertation presents two new developments in that area: a catalytic enantioconvergent decarboxylative allylic alkylation of allyl indolenine-3-carboxylates and a catalytic enantioconvergent allylic α-alkylation of aldehydes to give enantioenriched quaternary all-carbon centers (Figure **1-9**). These two areas are discussed in chapters V and VI respectively.

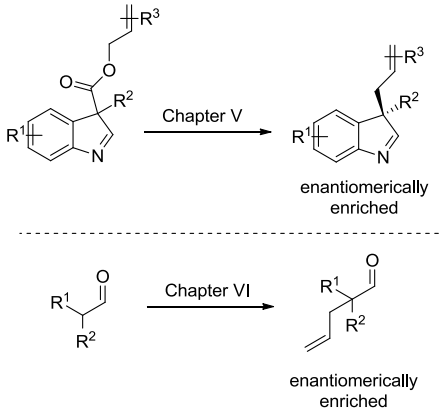


Figure **1-9**. Research into the desymmetrizing Tsuji-Trost reaction

CHAPTER II

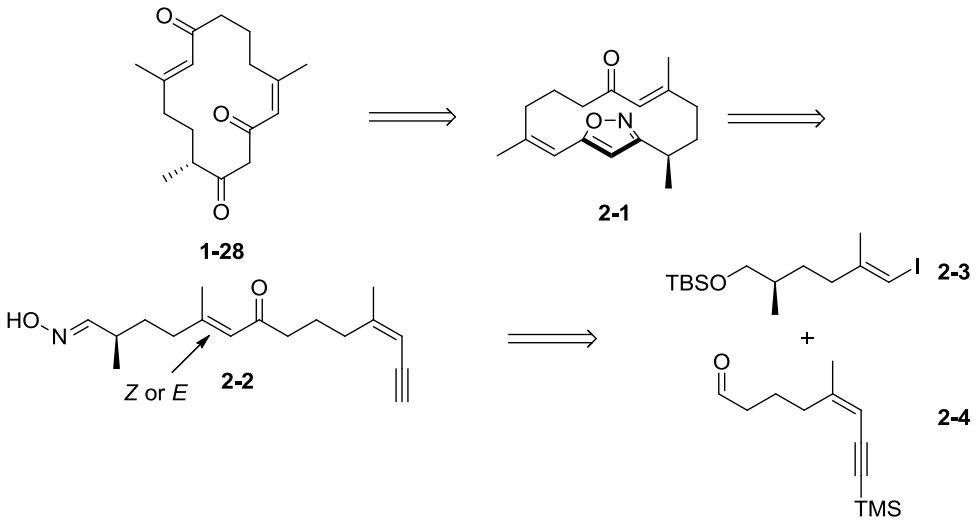
THE INTRAMOLECULAR 1,3 DIPOLAR ROUTE TO TMR MACROCYCLIC PRECURSOR

Our synthesis of celastrol (**1-1**) hinged on an efficient route to an all carbon marcyocyclic skeleton (**1-28** in Scheme **1-9**). A complicating feature of this macrocycle is the 1,3-diketone functionality which would have to be concealed for the majority of the multi-step synthesis due to the high acidity of 1,3-diketones. We therefore envisioned a strategy that would involve not only keeping the 1,3-diketone masked until the TMR, but also involve a dual purpose macrocylization and masked 1,3-diketone construction step. An intramolecular [3+2] isoxazole synthesis was selected as the means to effect this strategy as isoxazoles are known to easily be cleaved to reveal 1,3-diketones under mild conditions.[50]

*First Generation Intramolecular [3+2] Synthetic Strategy to Access **1-28***

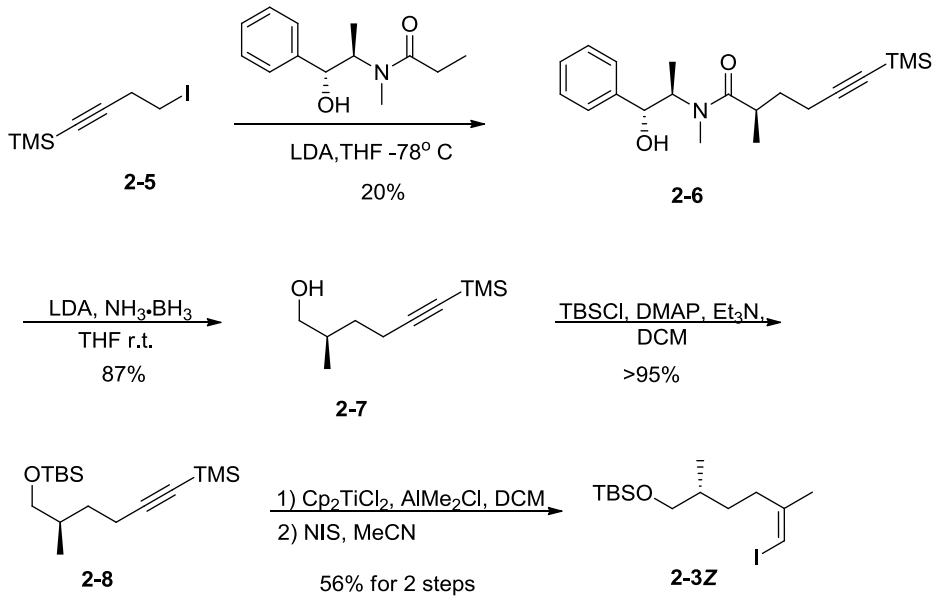
Accordingly, we envisaged **1-28** coming from isoxazole **2-1** by reducing the isoxazole ring and hydrolyzing the resulting vinylogous amide to generate **1-28** (Scheme **2-1**). We expected **2-1** to come from an intramolecular 1,3-dipolar cycloaddition using a terminal alkyne and a nitrile oxide as the coupling partners on opposite ends of the molecule. This disconnection led us to **2-2** which we anticipated would come from the intermolecular coupling of vinyl iodide **2-3** with aldehyde **2-4**. Oxidation, protecting group removal and condensation with hydroxylamine would yield **2-2**. The olefin

geometry of **2-3** would either be *Z* or *E* to provide either the *Z,Z* or *Z,E* model substrate (Scheme **1-7**).



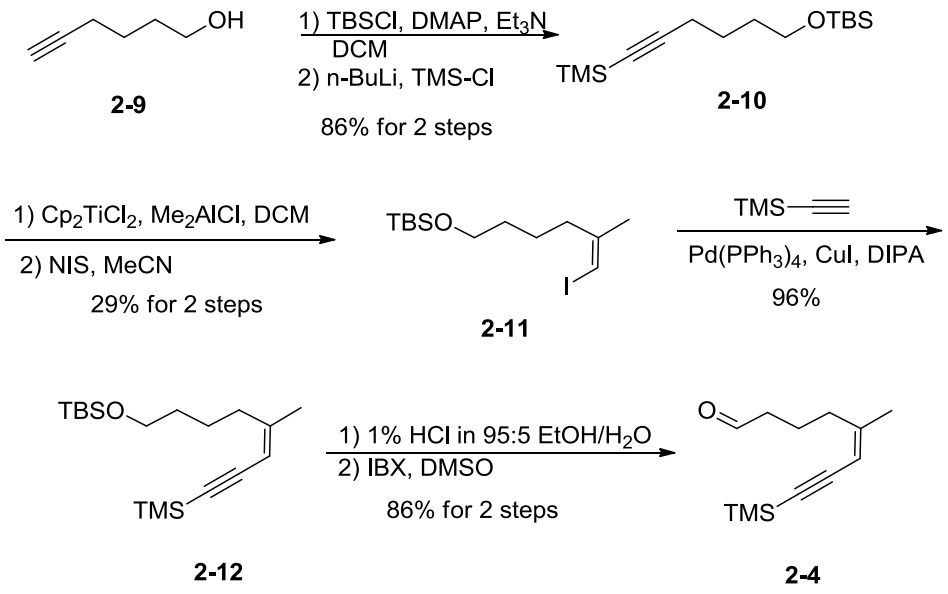
Scheme **2-1**. First generation retrosynthesis strategy

Our synthesis of the *Z,Z* model substrate began with the Myers asymmetric alkylation of pseudoephedrine proplyamide with **2-5** (Scheme **2-2**).[51] Interestingly, this reaction gave only 20% conversion even upon exposure to longer reaction times (20 hours). Despite this, amide **2-6** was reduced to primary alcohol **2-7** which was protected with a TBS group in quantitative conversion to give silyl ether **2-8**. The TMS alkyne was carbometallated according to Snider's procedure to give a *Z* vinyl silane. This *Z* vinyl silane was then iodinated with retention of olefin geometry to give vinyl iodide **2-3*Z*** in 56% yield for two steps from **2-8**.[52]



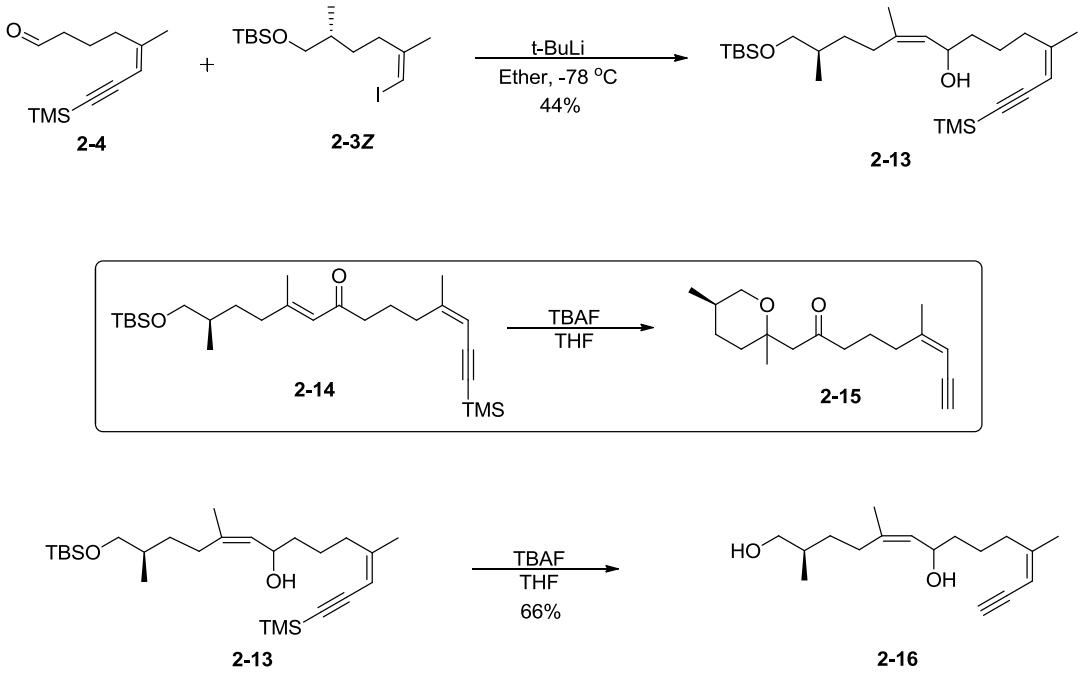
Scheme **2-2**. Synthesis of **2-3*Z***

The synthesis of aldehyde **2-4** commences with silyation of commercially available **2-9** by first TBS protecting the alcohol followed by installation of a TMS group on the alkyne to generate **2-10** in 86% yield for two steps (Scheme **2-3**). Again, use of Snider's proceedure gave the *Z* vinyl silane (35% yield 6.25:1 *Z*:*E*) which underwent iodinolysis with NIS to give vinyl iodide **2-11**. Sonogashira cross-coupling of **2-11** with TMS-acetylene gave enyne **2-12**. The TBS group was removed and the resulting primary alcohol was oxidized with IBX to generate the requisite aldehyde **2-4** in 24% overall yield from **2-10**.



Scheme **2-3**. Synthesis of **2-4**

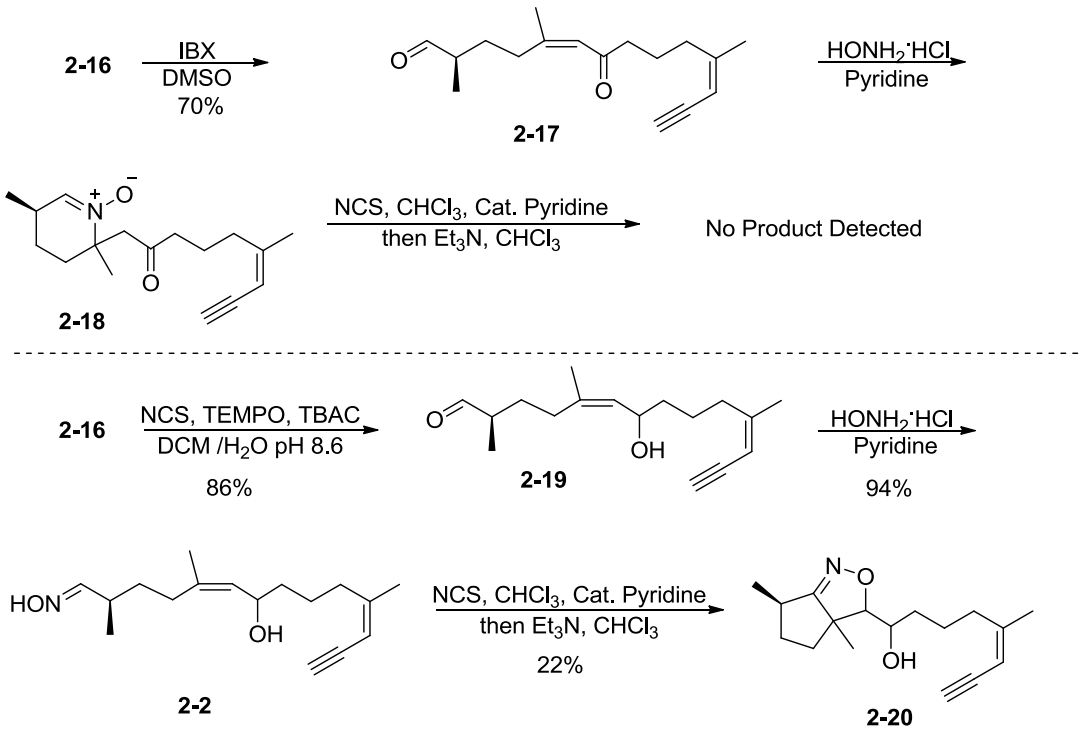
We then attempted to couple **2-3*Z*** with **2-4** using Nozaki-Hiyama-Kishi conditions (Scheme **2-4**).[53] We initially chose the NHK because of its mild conditions. However, all attempts along this line were met with failure as vinyl iodide **2-3*Z*** was reduced by Cr(II) to the disubstituted olefin without any coupling product formed. We switched to a *t*-BuLi mediated coupling and found the reaction worked to give **2-13** in moderate yield. Our original plan was to oxidize the allylic alcohol to the α,β-unsaturated ketone. However, when this was done on the *Z,E* precursor **2-14** (synthesis not shown), the desilylation step would only give the oxy-Michael product **2-15**. We therefore left the allylic alcohol present and globally desilylated **2-13**. Treatment of **2-13** with TBAF in THF gave **2-16** in 66%. A stepwise procedure in which the protecting groups were removed through the action of basic methanol followed by acid-catalyzed ethanolysis failed to improve the yield.



Scheme **2-4.** Synthesis of **2-16**

Both alcohol functionalities of **2-16** were oxidized to give the dicarbonyl species **2-17** (Scheme **2-5**). The aldehyde of **2-17** was selectively converted to the oxime using hydroxylamine hydrochloride. To our dismay, this reaction quantitatively produced nitrone **2-18**. We believe **2-18** was synthesized in a cascade reaction that began by first forming the oxime by condensation of hydroxylamine with the aldehyde of **2-17**. The nitrogen of the resulting oxime then added in a 1,4-addition to the α,β-unsaturated ketone. This provides the structure **2-18**. We expected the 1,4-addition to be reversible so that *N*-chlorosuccinimide would be able to react with the oxime and form the hydroximinoyl chloride. Presumably, the hydroximinoyl chloride would then undergo

base-induced elimination to generate the nitrile oxide required for the 1,3-dipolar cycloaddition. However, no product was detected when this reaction was run.

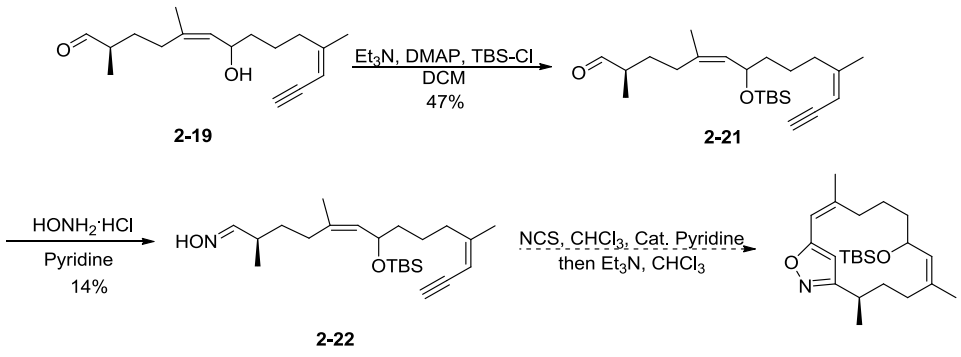


Scheme **2-5**. End stages of first strategy to access **1-28**

To avoid formation of the electrophilic α, β-unsaturated ketone functionality in **2-17**, we selectively oxidized the primary alcohol. We employed the TEMPO/NCS reagent system to oxidize diol **2-16** to aldehyde **2-19** in 86% yield.[54] Oxime **2-2** was then formed in 94% yield. Initially, it was expected that the terminal alkyne to be significantly more reactive than the trisubstituted alkene. Therefore, we presumed that the *in situ* generated

nitrile oxide would react preferentially with the alkyne to form the isoxazole. To our surprise, the 1,3 dipolar cyclization gave isoxazoline **2-20** as the exclusive product.

We believed that adding a bulky group to the allylic alcohol would block the kinetic accessibility of the olefin and thereby drive the nitrile oxide to react with the alkyne. Initially, it was thought that a PMB protecting group on the allylic alcohol of **2-13** would be able to alter the regioselectivity of the nitrile oxide. We attempted the PMB protection of **2-13** with 4-methoxybenzyl trichloroacetimidate and were surprised to find only allylic alcohol elimination products. After repeated attempts to perform the protection using mild conditions, we turned our attention to installing a bulky silyl group on the allylic alcohol.



Scheme **2-6**. Attempts to alter the regioselectivity of the [3+2] cycloaddition

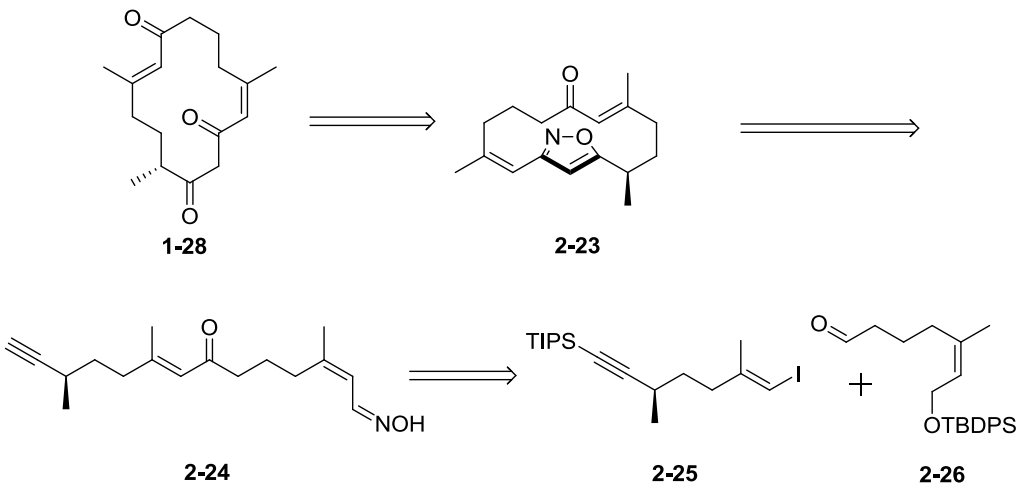
We explored TIPS protection of the allylic alcohol group in **2-19**, however, there was no conversion of starting material after 20 hours. We then attempted a TBS protection of **2-19** and were able to form **2-21** in 47% yield (Scheme **2-6**). Oxime **2-22** was then

synthesized in 14% yield. With **2-22** in hand, we attempted the 1,3-dipolar cycloaddition and were unable to find any detectable cycloaddition product by NMR.

At the conclusion of the experiments of Scheme **2-6** it became clear to us that this synthetic route had many insurmountable difficulties. Placing the oxime functionality four carbons from the α, β-unsaturated ketone resulted in several problems: the susceptibility of the primary alcoholic oxygen to cyclization (Scheme **2-4**), the susceptibility of the oxime to undergo a 1,4-addition to irreversibly generate a nitrone (Scheme **2-5**), the selectivity of the nitrile oxide for the proximal alkene (Scheme **2-5**), and the inability to block the reactivity of the proximal alkene by adding bulky protecting groups (Scheme **2-6**). As a result, we devised an alternate synthetic scheme with the hope of resolving these problems.

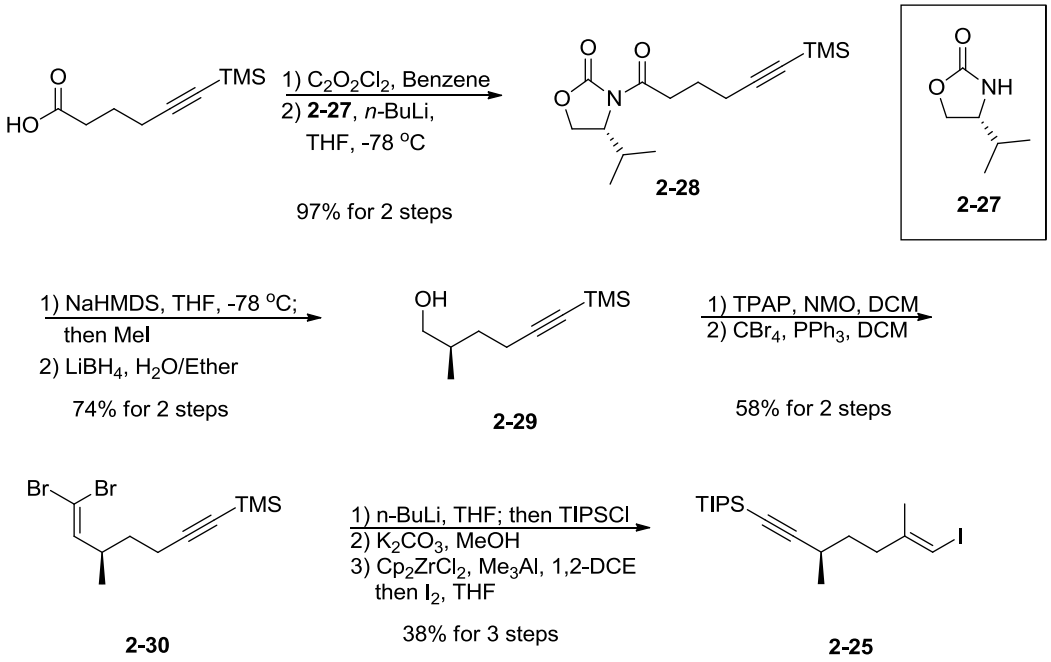
*Second Generation Intramolecular [3+2] Synthetic Strategy to Access **1-28***

We continued to believe that the best route to access the TMR precursors was the late stage intramolecular 1,3-dipolar cycloaddition to both form the macrocycle and install the masked 1,3 diketone in one step. Learning from previous experiments we switched the position of the alkyne and the oxime. We therefore expected **1-28** to come from **2-23** via reduction of the N-O bond and hydrolysis of the vinylogous amide (Scheme **2-7**). Isoxazole **2-23** would then come from **2-24** through the intramolecular 1,3-dipolar cycloaddition and **2-24** was expected to be formed through the *t*-BuLi coupling of **2-25** and **2-26** followed by global deprotection, oxidation and selective oxime formation.



Scheme **2-7**. Second generation retrosynthetic strategy

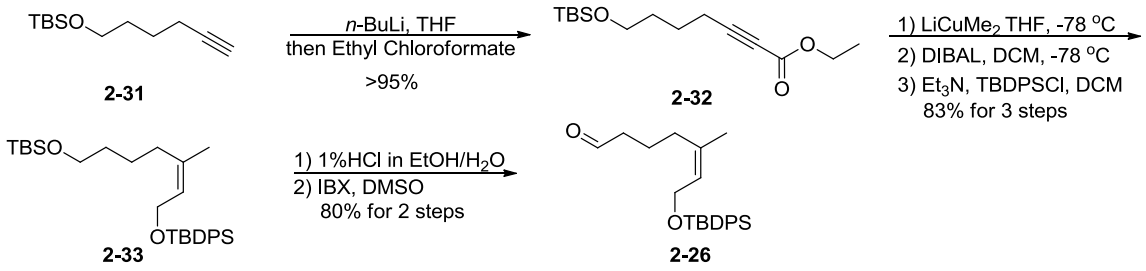
Our synthesis of the *Z,E* model substrate begins with the conversion of 6-(trimethylsilyl)hex-5-ynoic acid[55] to the corresponding acid chloride using oxalyl chloride (Scheme **2-8**). The acid chloride was coupled with lithiated (*R*)-(+)-4-isopropyl-2-oxazolidinone to give **2-28** in 97% yield for two steps. Substrate **2-28** then underwent Evans alkylation (83% yield, 11:1 dr) followed by reduction to give primary alcohol **2-29**. This opening sequence replaced the Meyer's alkylation conditions employed in the first generation synthesis.



Scheme **2-8**. Synthesis of **2-25**

Alcohol **2-29** was oxidized with TPAP/NMO and the resulting aldehyde was converted to *gem*-dibromo olefin **2-30** in 58% yield for two steps**.** We completed the Corey-Fuchs alkyne synthesis by lithiating **2-30** and trapping the intermediate lithium acetylide with TIPSCl. The crude reaction mixture was selectively desilylated by basic methanol. Vinyl iodide **2-25** was obtained in 38% yield from **2-30** through the use of Negishi's carbometallation conditions.[56]

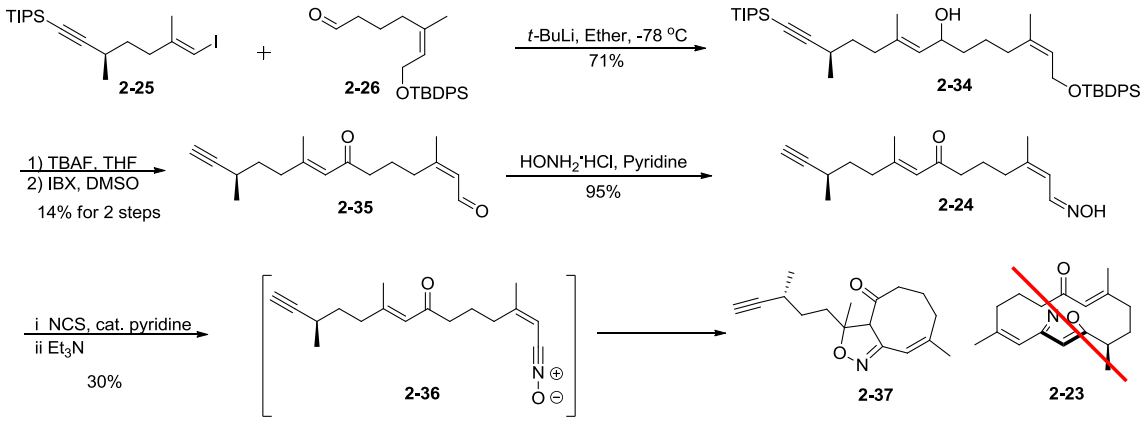
To synthesize aldehyde **2-26**, we coupled the lithium acetylide derived from **2-31** with ethyl chloroformate to generate alkynyl ester **2-32** quantitatively (Scheme **2-9**). Cupration to install the *Z* trisubstituted olefin (17:1 *Z*:*E*) followed by reduction and TBDPS protection generated **2-33** in three steps in an 83% yield. Protonolysis of the TBS ether and IBX oxidation gave the desired aldehyde **2-26** in 80% yield for two steps.



Scheme **2-9**. Synthesis of **2-26**

With vinyl iodide **2-25** and aldehyde **2-26** in hand, we attempted the *t*-BuLi coupling (Scheme **2-10**). We were pleased to find that the coupling proceeded well in a 71% yield (3.4:1 dr) to give allylic alcohol **2-34**. Alcohol **2-34** was globally desilylated with TBAF in 14% yield. This low yield was due to poor conversion and is unoptimized. The resulting diol was converted to dicarbonyl **2-35** using IBX as the oxidant in 95% yield from **2-34**. Finally. Aldehyde **2-35** was converted into oxime **2-24** in 95 % yield through the action of hydroxylamine hydrochloride and pyridine.

We then tested the intramolecular 1,3-dipolar cycloaddition using NCS and triethylamine to generate the intermediate nitrile oxide **2-36**. Unexpectedly, this nitrile oxide did not cyclize at the terminal alkyne to give **2-23**. The cyclization happened at the



Scheme **2-10**. End stage for second generation intramolecular [3+2] cycloaddition

previously problematic olefin to give [6.3.0] bicycle **2-37**! We had predicted that the cyclization would occur to generate the 14-membered ring rather than the 8-membered ring due to strain typically associated in an 8-membered transition state.

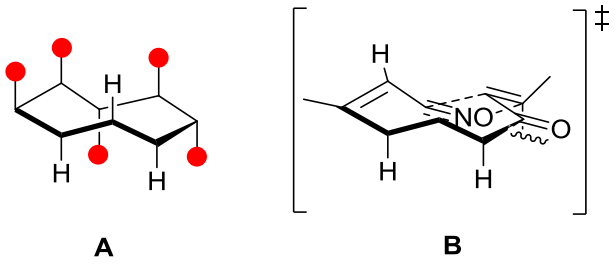


Figure **2-1**. Transition state geometry in the reaction of **2-36**

This result can be analyzed by examining our proposed transition state for the 1,3-dipolar cycloaddition (Figure **2-1**). Much of the strain in a fully saturated 8-membered ring comes from the diaxial interactions of the axial protons.[57] As can be seen

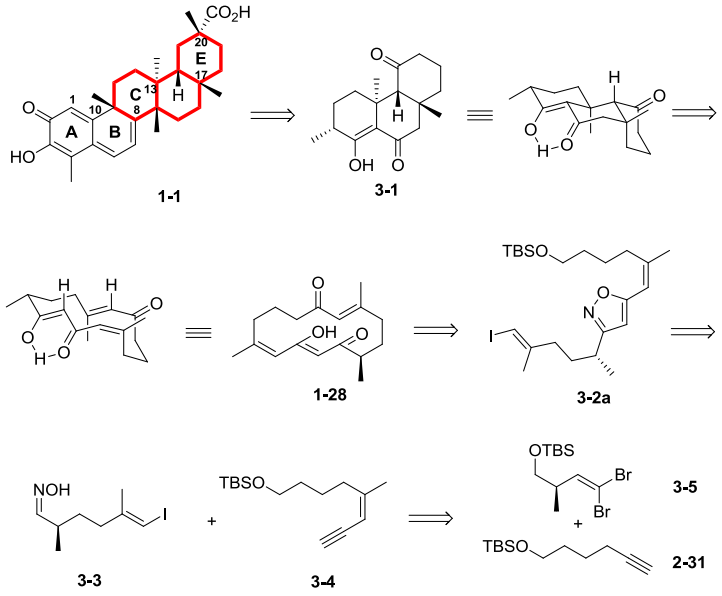
in Figure **2-1**, the protons labeled with red circles in **A** are either not present or severely distorted in the unsaturated **B** such that these interactions do not take place. This lowers the overall strain in the 8-membered transition state so that it becomes kinetically favored. As a result of the 8-membered ring being kinetically favored, we had to abandon this synthetic sequence.

With the failures of both generations of intramolecular [3+2] strategies to access **1-28**, we sought other means of pursuing our synthetic goals. We still believed that the isoxazole was the best way to not only construct the requisite 1,3-diketone moiety, but also to conceal it until the TMR. Therefore, we switched to an intermolecular strategy to construct the isoxazole *en route* to the macrocyclic precursor. This work is detailed in Chapter III.

CHAPTER III

THE INTERMOLECULAR 1,3 DIPOLAR CYCLOADDITION ROUTE TO TMR MACROCYCLIC PRECUSOR *

After the failure of the intramolecular 1,3-dipolar cycloaddition strategy outlined in Chapter II, we decided to shift the timing of our synthetic strategy. We retained the use of the 1,3-dipolar cycloaddition; however, this reaction would be used to intermolecularly couple two fragments instead. Therefore, we envisioned that **1-1** could

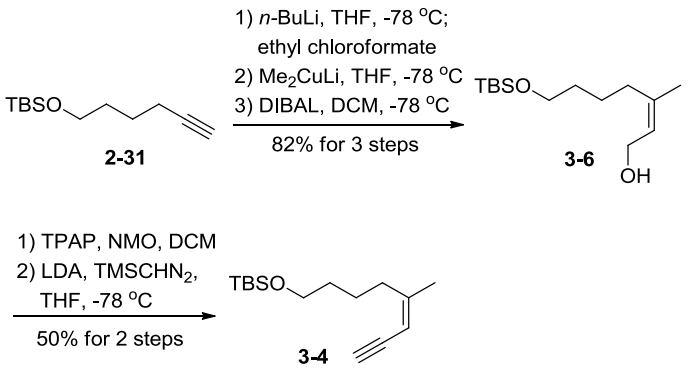


Scheme **3-1**. The new retrosynthetic strategy to celastrol

---

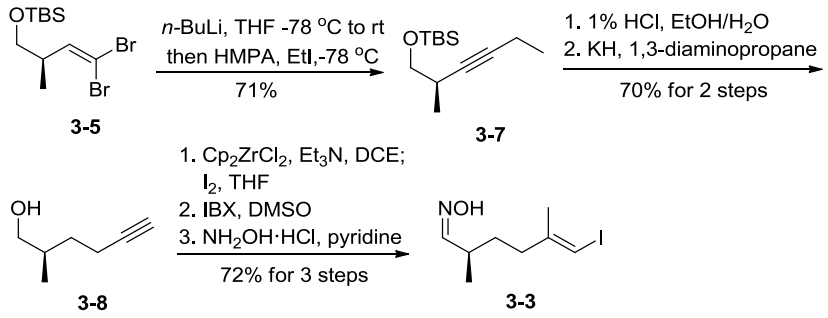
* Reprinted with permission from "Regiochemistry discoveries in the use of isoxazole as a handle for the rapid construction of an all-carbon macrocyclic precursor in the synthetic studies of celastrol" by Kaiser, T.: Huang, J.; Yang, J., **2013**. *J. Org. Chem., 78*, 6297-6302. Copyright 2013 American Chemical Society.

be accessed by functional group manipulation and installation of the *p*-quinone methide ring system using **1-28** as the core as explained in Chapter I (Scheme **3-1**). We still planned to synthesize the perhydrophenanthrene system **3-1** anticipating that the stereochemistry of the angular methyls would be dictated by the olefin geometry of **1-28** through an all-chair transition state during the transannular *bis*-Michael reaction. Our retrosynthesis of **1-28** focused on the use of an isoxazole to rapidly construct the requisite 1,3-diketone through the use of a 1,3-dipolar cycloaddition. Therefore, **1-28** was envisaged to come from **3-2a** by desilylation and oxidation of the alcohol to give an aldehyde, intramolecular coupling of that aldehyde with the vinyl iodide, and oxidation to the ketone. This sequence would be followed by reduction and hydrolysis of the isoxazole to generate the desired 1,3-diketone functionality. Isoxazole **3-2a** is expected to come from the intermolecular 1,3-dipolar cycloaddition of the nitrile oxide derived from oxime **3-3** and enyne **3-4**. Oxime **3-3** will be synthesized from the known *gem*-dibromo olefin **3-5**[58] and enyne **3-4** will be generated from known TBS silyl ether **2-31**.[59]



Scheme **3-2**. Synthesis of **3-4**

We began our synthesis by constructing the two 1,3-dipolar cycloaddition coupling partners **3-3** and **3-4**. Our synthesis of **3-4** started with the addition of the lithium acetylide derived from **2-31** to ethyl chloroformate to generate an alkynyl ester followed by cupration to install the *Z*-trisubstituted olefin (Scheme **3-2**). These steps were followed with DIBAL reduction to give **3-6** in 82% yield for 3 steps. The resulting allylic alcohol **3-6** was oxidized to an aldehyde using the TPAP/NMO system and then converted to **3-4** using LDA and $TMSCHN_2$ in 50% yield over two steps.[60]

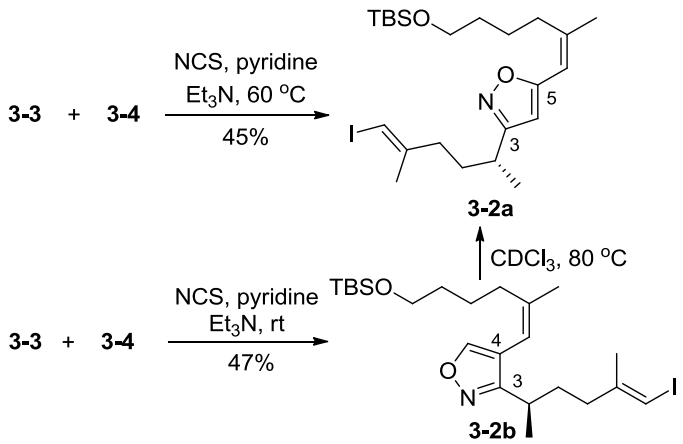


Scheme **3-3**. Synthesis of **3-3**

The synthesis of oxime **3-3** began with the known *gem*-dibromo olefin **3-5** (Scheme **3-3**) which was lithiated with *n*-BuLi to form the lithium acetylide. The addition of the resulting acetylide to ethyl iodide required the presence of 2 equivalents of HMPA. With the desired internal alkyne synthesized, we performed the KAPA-mediated alkyne zipper reaction using KH and 1,3-diaminopropane. This reaction was uncharacteristically slow with **3-7** and produced only degradation products. It is known that internal alkynes with a free alcohol are capable of undergoing the KAPA-mediated isomerization.[20,61] We therefore removed the TBS group and conducted the isomerization reaction on the crude product. External alkyne **3-8** was obtained in 70% over 2 steps from internal alkyne **3-7**. Negishi's carbometallation procedure was then used to install the vinyl iodide.[56] This was followed by IBX oxidation and oxime formation to form the desired oxime **3-3** in 72% yield from **3-8**.

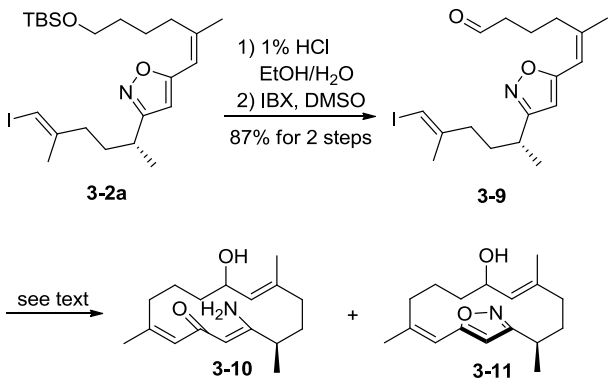
With **3-3** and **3-4** synthesized, we turned to the 1,3-dipolar cycloaddition for the synthesis of **3-2a** (Scheme **3-4**). In the course of our evaluation of the reaction, it was discovered that the outcome of the reaction was highly temperature dependent. Conducting the reaction at room temperature led to only the 3,4-disubstituted isomer **3-2b** in 47% yield. However, elevating the reaction temperature to 60 ^{o}C resulted in the production of **3-2a** in 45% yield with approximately 20% of **3-2b**. Curious if we could isomerize **3-2b** to **3-2a** given limited examples of reversible 1,3-dipolar cylcoadditions,[62] we heated **3-2b** to 80 ^{o}C. Even though the isomerization was accompanied by partial scrabbling of the C-5 alkene (~3:1 desired to undesired), complete conversion of **3-2b** to the regio-isomeric **3-2a** was observed after 92 hours.

Both the temperature-dependent regioselectivity of the 1,3-dipolar cycloaddition and the isomerizability of the reaction at elevated temperature are surprising.[63] Sharpless and Fokin, in their study of Cu-catalyzed 1,3-dipolar cylcoadditions, examined the activation energies for the formation of regioisomeric 3,4- and 3,5-disubstituted isoxazoles by the uncatalyzed cycloaddition of acetonitrile oxide and propyne.[64] The calculations predicted a 2.8 kcal/mole energy difference in the transition states with the 3,5-regioisomer being strongly favored. Indeed, formation of 3,4-disubstituded isoxazoles by the 1,3-dipolar cycloaddition of nitrile oxides and alkynes is rare, if not completely unprecedented. However, only the 3,4-disbustituted **3-2b** was obtained upon reaction of **3-3** and **3-4** at room temperature. We speculate that the reversal of regioselectivity is likely due to a substantial increase in the LUMO coefficient at the terminal acetylene carbon of **3-4** and a concomitant lowering of the LUMO energy due to conjugation of the alkyne.[65] Therefore, due to both the largest orbital coefficient of the nitrile oxide HOMO residing on the oxygen and the largest orbital coefficient of the enyne LUMO residing on the terminal carbon, simple FMO analysis predicts the 3,4-regioisomer to be favored kinetically.



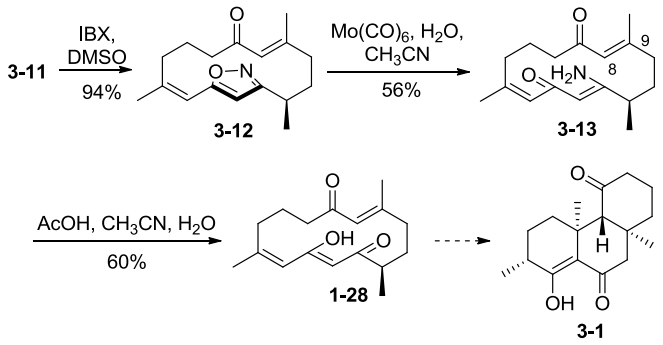
Scheme **3-4**. Synthesis of **3-2a** and **3-2b** and isomerization of **3-2b** to **3-2a**

In order to explain the surprising temperature dependence of the regiochemistry of the 1,3-dipolar cycloaddition as well as the slow isomerization of **3-2b** to **3-2a** at elevated temperatures, we hypothesize that by-products from the nitrile oxide synthesis are responsible for this unusual behavior. The work of Chen *et al.* discovered that hydrogen bond catalysis not only imparted enantiocontrol in the 1,3-dipolar cycloaddition of cyclic enones, it also substantially improved the reactivity of the substrate.[66] We postulate that participation of a hydrogen bond donor (*i.e. in situ* generated succinimide) is leading to activation of the 3,4-regioisomer and providing a lower energy pathway for the thermodynamically driven isomerization to take place. In order to investigate this hypothesis, we compared the rates of isomerization of **3-2b** both in the presence of succinimide and without succinimide. Indeed, we found a 1.87 fold increase in the rate of isomerization of **3-2b** to **3-2a** in the presence of succinimide at 70 ^{o}C.[67]



Scheme **3-5**. Synthesis of **3-11**

With a robust means of synthesizing **3-2a**, we continued in our synthetic studies. We were able to synthesize aldehyde **3-9** in 87% yield for two steps from **3-2a** (Scheme **3-5**). Using the Nozaki-Hiyama-Kishi reaction,[53] allylic alcohol **3-10** was formed in 6-12% yield from **3-9**. The poor yield of this reaction can be attributed to the formation of a 14-membered macrocycle with a high degree of strain imparted by the alkene functionalities present in the molecule. Also, $CrCl_2$ reductively cleaved the isoxazole in **3-9** generating a vinylogous amide **3-10**. Seeking to keep the isoxazole intact, the number of equivalents of $CrCl_2$ was reduced from 10 equivalents to 5 equivalents. Under such reaction conditions, allylic alcohol **3-11** was generated in slightly improved yield (12-26%).

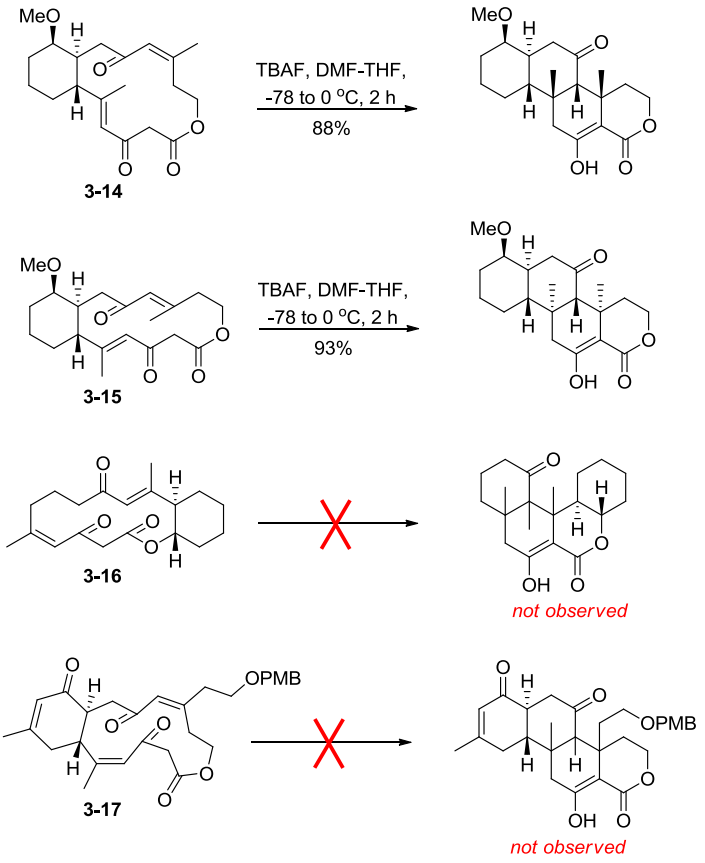


Scheme **3-6.** The synthesis of **1-28**

Following the coupling reaction, **3-11** was oxidized to α,β-unsaturated ketone **3-12** in 94% yield using IBX (Scheme **3-6**). We turned our attention to revealing the 1,3-diketone functional group through reduction and hydrolysis of the isoxazole functionality in **3-12**. We were pleased to find that the treatment of **3-12** with $Mo(CO)_6$ in CH_3CN generated the desired vinylogous amide **3-13** in 56% yield (2.2:1 mixture of *E*:*Z* isomers of the C8-C9 double bond, tentatively assigned by NMR).[68] Alternatively, **3-13** could be prepared directly from **3-10** through the action of IBX in 55% yield. The hydrolysis of **3-13** to give **1-28** proved to be difficult. The use of $Cu(OAc)_2$, HOAc/NaOAc, $Mn(OAc)_3$, and $CeCl_3/Et_3N$ all failed to hydrolyze the vinylogous amide. It was only when vinylogous amide **3-13** was dissolved in a 2:2:1 solution of $AcOH:CH_3CN:H_2O$ did the desired molecule **1-28** form in 60% yield (2.7:1 mixture of *E*:*Z* isomers of the C8-C9 double bond, tentatively assigned by NMR).

Our investigation of the transannular *bis*-Michael reaction cascade could now proceed with **1-28** accessed. In contrast to the smooth transannular Michael reactions when the *E,E*- or *E,Z*-macrocyclic *bis*-enones were employed,[22] the starting material was

fully recovered when **1-28** was treated with TBAF in THF/DMF at -78 °C. Also, we did not detect any **3-1** when the reaction was carried out at ambient temperature. We attempted the transannular Michael reactions on vinylogous amide **3-13** by treatment with NaOMe in DMF. Again, no desired transannular reaction product was detected even when elevated temperatures were applied. These experimental results were later corroborated by our work in 2012 concerning the evaluation of the stereochemical model of the transannular *bis*-Michael reaction in 14-membered macrolide systems.[22]



Scheme **3-7**. The full scope of the transannular *bis*-Michael reaction

In this work, macrolides **3-14** through **3-17** were prepared and each substrate was evaluated for an ability to undergo the transannular *bis*-Michael reaction (Scheme **3-7**). It was discovered that the *E,Z* and *E,E* macrocycles (**3-14** and **3-15** respectively) were smoothly transformed into the desired diastereomeric macrocycles in good yield and excellent diastereoselectivity (only one diastereomer was detected for each substrate). However, the *Z,E* and *Z,Z* substrates (**3-16** and **3-17** respectively) were found to be inert to the reaction conditions. Even if the reactions were conducted at elevated temperatures, no product was detected. Given that our all-carbon macrocycle falls under the *Z,E*-isomer category, it is not surprising that the transannular *bis*-Michael reactions of both **1-28** and **3-13** failed to take place.

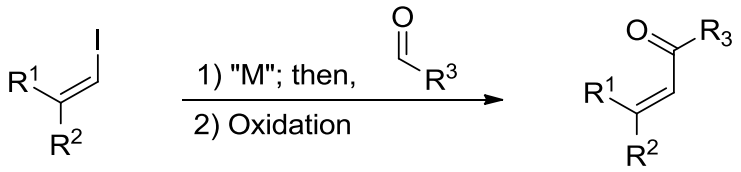
In summary, as part of our synthetic studies toward celastrol, we have developed a synthetic route making use of a 1,3-dipolar cycloaddition for the convergent synthesis of a 1,3-diketone-containing macrocycle. Consistent with our other studies, this *Z,E*-macrocyclic *bis*-enone was found to be inactive in the transannular *bis*-Michael reaction cascade for the conditions evaluated. We discovered that the 1,3-dipolar cycloaddition of **3-3** and **3-4** gave the rare 3,4-disubstituted isoxazole under kinetic reaction conditions. We also demonstrated that the dipolar cycloaddition is reversible and the thermodynamic 3,5-disubstituted isoxazole can be obtained through isomerization of its 3,4-disubstituted isomer under elevated temperature. Our initial mechanistic studies support the role of hydrogen-bonding in accelerating the isomerization process.

CHAPTER IV

THE DIRECT ACYLATION OF VINYL IODIDES TO GENERATE A,B-UNSATURATED KETONES BY MEANS OF PALLADIUM CATALYSIS

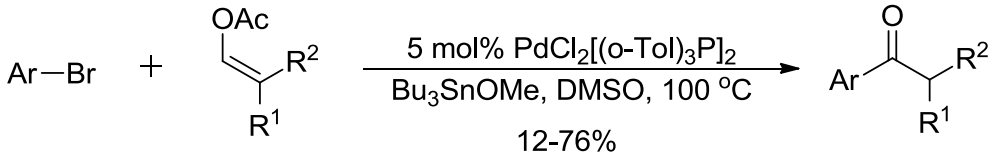
Over the course of our synthetic studies of celastrol we encountered many limitations of current reaction methodologies; but, none was more staggering than the low-yielding Nozaki-Hiyama-Kishi reaction of Chapter III. Faced with a very low-yielding reaction in our macrocyclization strategy, we wondered if better ways of forming the desired α,β-unsaturated ketone were possible (i.e. a one-step reaction). We felt that this exploration of new methodology to access α,β-unsaturated ketones in a one-step strategy would not only improve the synthetic efficiency of our route to access celastrol, this exploration would serve to improve the overall accessibility of the versatile α,β-unsaturated ketone[69] in the body of synthetic chemistry.

One of the most common methods to access α,β-unsaturated ketones (and ketones in general) is a two-step sequence of, first, 1,2-addition of an *in situ* generated vinyl-M species to an aldehyde (M = Mg, Li, Zn, Ti...) followed by a second step where the resulting allylic alcohol from the first step is oxidized to the requisite α,β-unsaturated ketone (Scheme **4-1**). This method of synthesis is limited in the strongly basic and reducing conditions employed to effect the 1,2-addition. This limitation significantly constrains the functional groups available for use in a synthetic strategy and often necessitates the use of protecting groups.



Scheme **4-1**. Two-step sequence to accessing α,β-unsaturated ketones

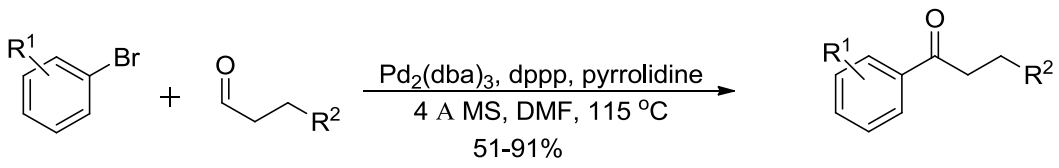
However, new catalytic methods beyond the traditional two-step ketone synthesis have been under development for the construction of aliphatic and aryl ketones from aldehyde precursors in one step. The two main categories of these methods are a C-H activation strategy and a palladium-mediated cross-coupling strategy. However, the C-H activation method is limited to only intramolecular reactions.[70] Of special interest is the intermolecular acylation strategy first described by Uriac and co-workers.[71] In this work, prepared enol esters are cross-coupled with aryl bromides to give aryl ketones (Scheme **4-2**). This report was the first demonstration of a direct route to aryl ketones prepared from a cross-coupling reaction using activated aldehydes.



Scheme **4-2**. Acylation of aryl bromides developed by Uriac and co-workers

However, the reaction developed by Uriac is still two steps with the activation of aldehydes requiring the formation of enol esters before the acylation reaction can be

performed. We believed that it would be possible to cross-couple aldehydes with a coupling partner directly in one pot without the need to activate the aldehyde for cross-coupling in a separate step. This concept was clearly demonstrated by Xiao and co-workers when they discovered a method for the direct acylation of aryl bromides through the use of a palladium/pyrrolidine system (Scheme **4-3**).[72]

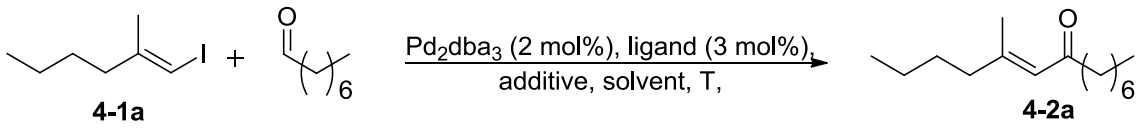


Scheme **4-3**. Direct acylation of aldehydes by Xiao and co-workers

This reaction centered around the reaction of pyrrolidine with the aldehyde coupling partner to form an enamine. The resulting enamine reacted with the aryl bromide in the presence of a palladium catalyst analogous to the traditional Heck reaction to give an aryl enamine which hydrolyzed upon workup to give the desired acyl aromatic group in one step. With this precedent, we set out to extend the substrate scope to include vinyl halides in addition to aryl bromides.

We set out to first attempt the coupling between **4-1a** and octanal (Table **4-1**). We began with the conditions disclosed by Xiao and co-workers[72] (entry 1, Table **4-1**) and found that no desired molecule **4-2a** was formed. When the molecular sieves were replaced with 5 equivalents of K_2CO_3 and the loading of pyrrolidine was reduced to 0.5

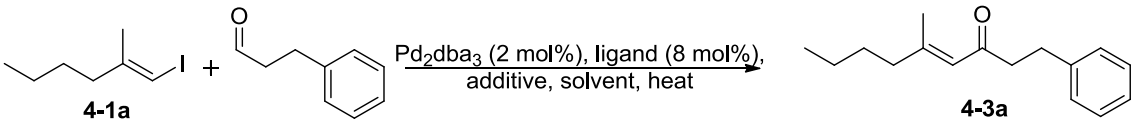
equivalents, **4-2a** was generated in 20% yield. Conducting the reaction at 50 °C and using 8 mol% of P(*t*-Bu)$_3$ generated **4-2a** in 71% yield (entry 8, Table **4-1**).



4-1a **4-2a**

Entry	L	Additive	Solvent	*T* (°C)	%Yield
1	dppp	4 Å MS / 2 eq. pyrrolidine	DMF	60	0
2	Tol-BINAP	4 Å MS / 2 eq. pyrrolidine	DMF	60	0
3	dppf	4 Å MS / 2 eq. pyrrolidine	DMF	60	0
4	dppe	4 Å MS / 2 eq. pyrrolidine	DMF	60	0
5	dppp	5 eq. K_2CO_3 / 2 eq. pyrrolidine	DMF	60	trace
6	dppp	5 eq. K_2CO_3 / 0.5 eq. pyrrolidine	DMF	23	20
7	dppp (6 mol%)	5 eq. K_2CO_3 / 0.5 eq. pyrrolidine	DMF	50	55
8	P(*t*-Bu)$_3$ (8 mol%)	5 eq. K_2CO_3 / 0.5 eq. pyrrolidine	DMF	50	71

Table **4-1**. Initial screening of conditions to generate **4-2a**



Entry	L	Additive	Solvent	*T* (°C)	%Yield
1	P(*t*-Bu)$_3$ (8 mol%)	5 eq. K_2CO_3 / 0.5 eq. pyrrolidine	DMF	50	30
2	P(*t*-Bu)$_3$ (8 mol%)	5 eq. K_2CO_3 / 0.5 eq. pyrrolidine	DMF	80	42
3	P(*t*-Bu)$_3$ (8 mol%)	5 eq. K_2CO_3 / 0.5 eq. pyrrolidine	DMF	100	34
4	P(*t*-Bu)$_3$ (8 mol%)	5 eq. K_2CO_3 / 0.2 eq. pyrrolidine	DMF	80	15
5	P(*t*-Bu)$_3$ (8 mol%)	5 eq. K_2CO_3 / 0.5 eq. pyrrolidine	NMP	80	17
6	P(*t*-Bu)$_3$ (8 mol%)	5 eq. K_2CO_3 / 0.5 eq. pyrrolidine	Toluene	80	13
7	P(*t*-Bu)$_3$ (8 mol%)	5 eq. K_2CO_3 / 0.5 eq. pyrrolidine	THF	80	11
8	P(*t*-Bu)$_3$ (8 mol%)	5 eq. K_2CO_3 / 0.5 eq. pyrrolidine	DMA	80	65
9	P(*t*-Bu)$_3$ (8 mol%)	5 eq. K_2CO_3 / 0.5 eq. morpholine	DMA	80	trace
10	DavePhos (8 mol%)	5 eq. K_2CO_3 / 0.5 eq. pyrrolidine	DMA	80	16
11	TangPhos (8 mol%)	5 eq. K_2CO_3 / 0.5 eq. pyrrolidine	DMA	80	0

Table **4-2**. Optimization for **4-3a**

We then sought to test the scope of our conditions by coupling **4-1a** with hydrocinnamaldehyde (entry 1, Table **4-2**). However, we were surprised to find that these conditions resulted in only 30% yield for **4-3a**. The yield of the reaction improved when the temperature was raised to 80 ^{o}C (entry 2, Table **4-2**). Substantial olefin isomerization was detected along with a reduced yield if the reaction was run at 100 ^{o}C (entry 3, Table **4-2**). After screening solvents, we found that a 65% yield of **4-3a** could be obtained when DMA was used as the solvent (entry 8, Table **4-2**). We explored morpholine as a possible replacement for pyrrolidine and found that only trace yield could be obtained (entry 9, Table **4-2**). Given the success of P(*t*-Bu)$_3$ in this reaction, we were curious if the yield could be improved with other sterically demanding ligands.[73] Therefore, we tested DavePhos and TangPhos (entries 10 and 11, Table **4-2**) and found that the yield dropped substantially in both cases.

We then turned our attention to exploring the substrate scope of the enamine Heck reaction. Our exploration began by evaluating the tolerance of the reaction to various changes with the vinyl iodide coupling partner. We found that aliphatic and electron-neutral conjugated vinyl iodides were well tolerated in the reaction (Figure **4-1**). Vinyl iodides **4-1a** and **4-1b** gave the resulting cross-coupling products in 65% and 64% yield. However, the reaction did not tolerate electron-poor vinyl iodides, **4-1c (**0% yield), or vinyl-iodides of the type of **4-1d** (~10% yield). Also, disubstituted vinyl iodides did not undergo cross-coupling (**4-1e**) and vinyl bromides did not prove react as smoothly as vinyl iodides (**4-1f**).

Curious if the aldehyde coupling partner would be less constraining, we evaluated the scope of the reaction for the aldehyde component (Figure **4-2**). We found that the ability of the aldehyde to participate in the cross-coupling was highly dependent on the solvent used. Hydrocinnamaldehyde worked well in DMA **4-3a**) but octanal

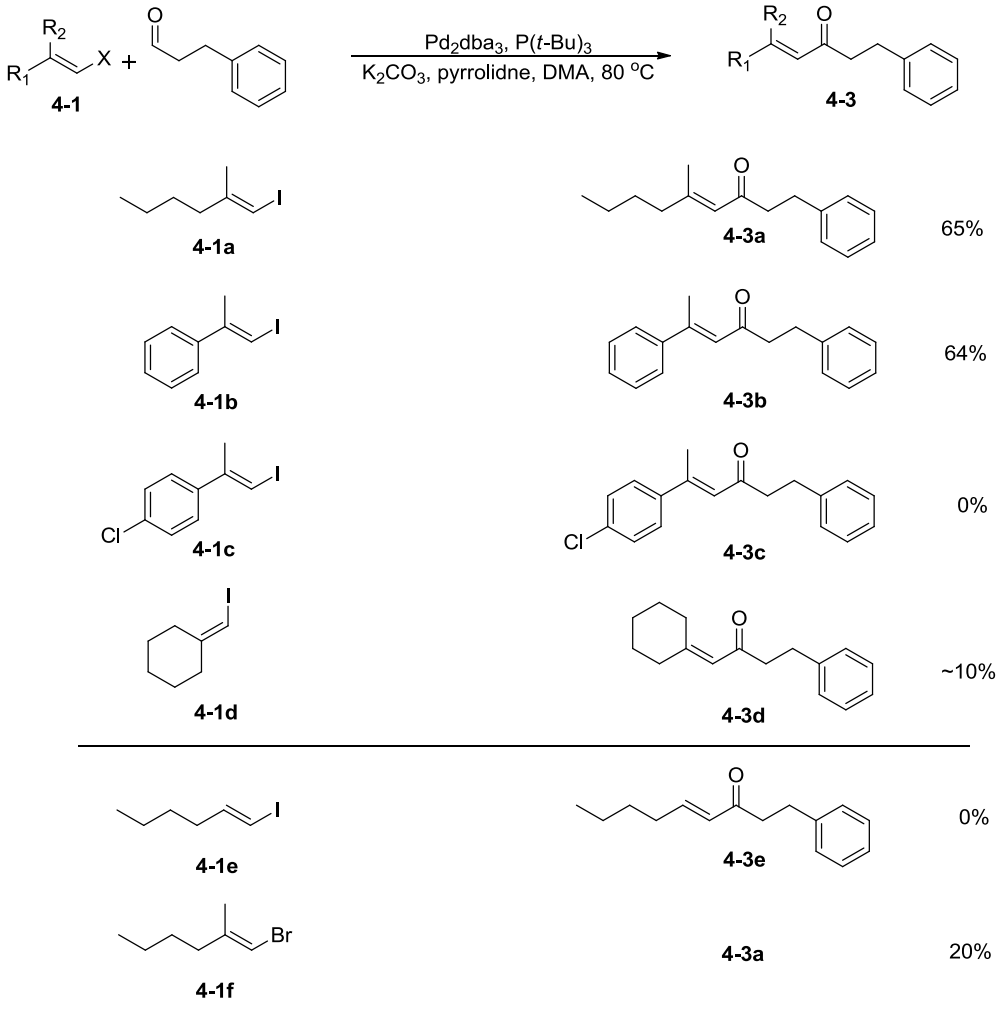


Figure **4-1**. Vinyl iodide substrate scope for the enamine-Heck reaction

required the use of DMF (**4-2a**). Also, decanal and hexanal (**4-2b** and **4-2c**) did not react smoothly in DMA whereas, in DMF, decanal reacted to give the desired product in <50% yield.

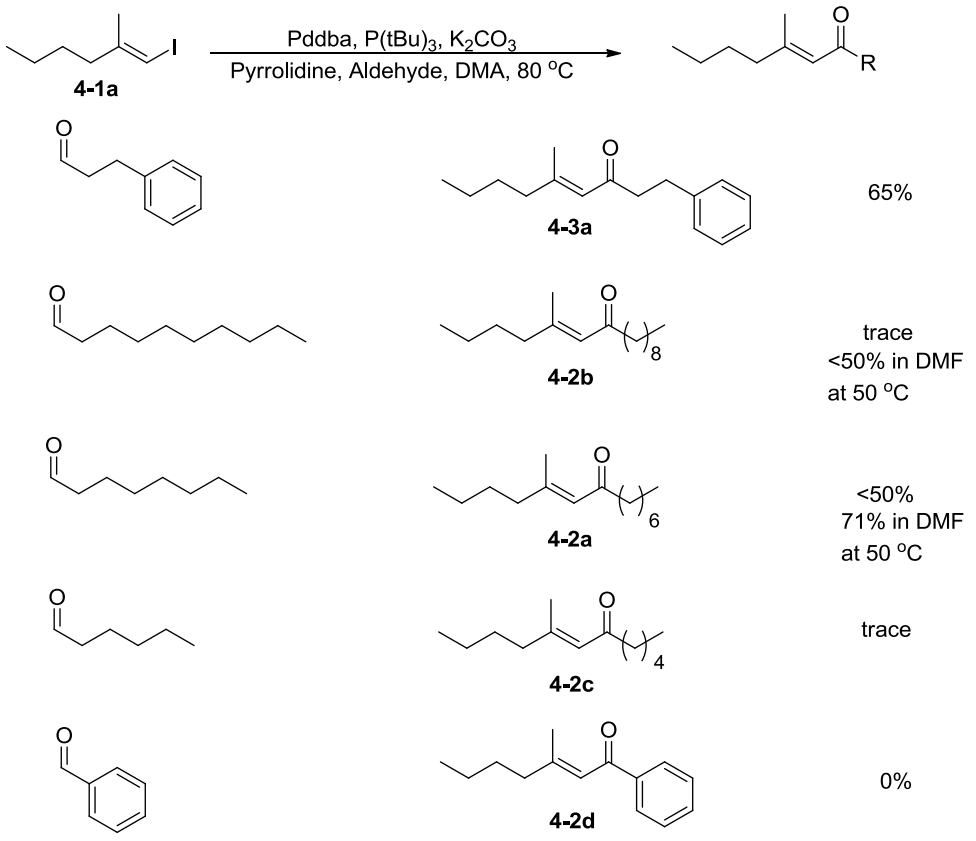


Figure **4-2**. Aldehyde substrate scope for the enamine-Heck reaction

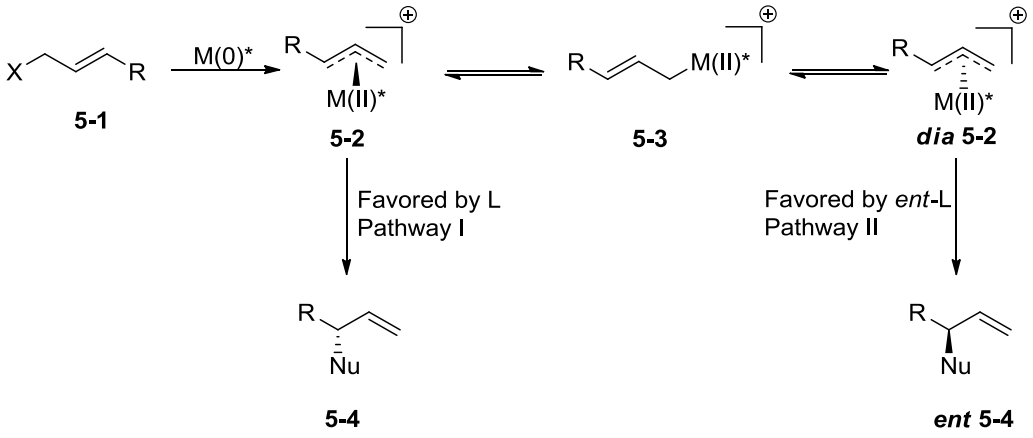
Taken together, the limitations of scope in both vinyl iodide and aldehyde severely limit the synthetic utility of the reaction described herein. However, the possibility exists that significant improvements in yield could be achieved by evaluating other transition metal systems as catalysts. Also, new synthetic technologies like

microwave reactors could enable the current catalytic system to be more broad in substrate scope.[74]

CHAPTER V

CATALYTIC ENANTIOCONVERGENT DECARBOXYLATIVE ALLYLIC ALKYLATION OF ALLYL 3-ALYKL-INDOLENIN-3-CARBOXYLATES *

One of the strengths of the Tsuji-Trost reaction is the ability to use prochiral sp^2 intermediates to generate chiral products through the use of chiral ligands. This feature of chiral induction on a prochiral substrate based on rates of equilibration between two possible diastereomeric intermediates was first described by Trost and co-workers as dynamic kinetic asymmetric transformation, or DYKAT (Scheme **5-1**).[75] In the DYKAT, an initial prochiral **5-1** is reacted with the chiral metal-ligand complex, M(0)*, to



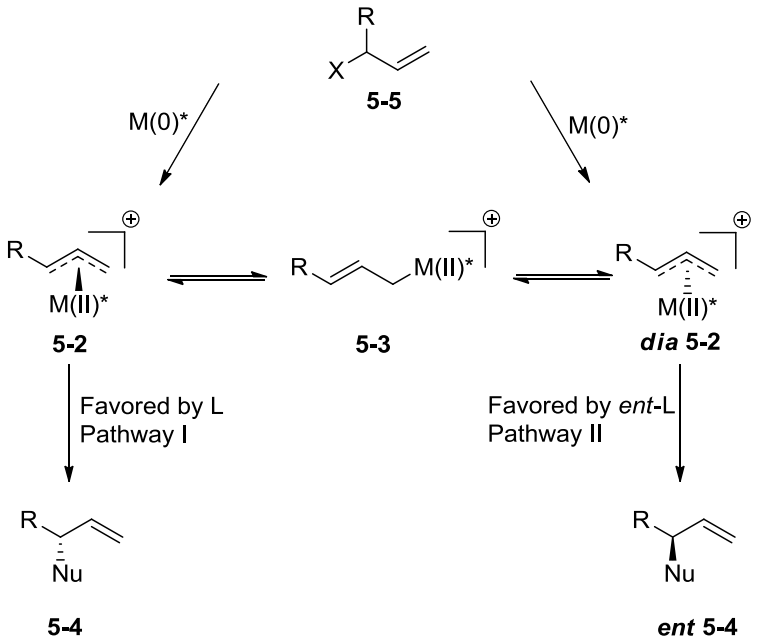
Scheme **5-1**. The DYKAT process with prochiral **5-1**

---

* Reprinted with permission from "Catalytic enantioconvergent decarboxylative allylic alkylation of allyl indolenin-3-carboxylates" by Kaiser, T.; Yang, J., **2013**. *Eur. J. Org. Chem., 2013*, 3983-3987. Copyright 2013 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

generate a mixture of **5-2** and ***dia* 5-2**. The relative concentrations of **5-2** and ***dia* 5-2** are dictated by the energetics of the two diastereomeric complexes, and the equilibrium proceeds through σ-complex **5-3**. Therefore, if M(0)* consists of a metal complex with L, the concentration of **5-2** is higher and the reaction proceeds to give **5-4**. However, if M(0)* consists of a metal complex with *ent*-L, the concentration of ***dia* 5-2** is higher and the reaction proceeds to give ***dia* 5-4**.

The DYKAT is also theoretically capable of using a racemic starting material and relying on an intermediate equilibration to set the stereocenter (Scheme **5-2**). In this case, racemic **5-5** reacts with the chiral metal-ligand complex, M(0)*, to give a similar equilibrium in Scheme **5-1**.



Scheme **5-2**. The DYKAT process with racemic **5-5**

Both of the processes outlined in Schemes **5-1** and **5-2** offer ready access to enantiomerically enriched intermediates starting from prochiral or racemic intermediates. However, we wished to focus on the enantioconvergent DYKAT process outlined in Scheme **5-2**. This enantioconvergent DYKAT process requires ready access to racemic starting materials in order for the DYKAT to be synthetically useful. Also, we were specifically interested if homoallylic chiral centers could be constructed in this manner rather than the allylic chiral centers presented in the original DYKAT work in Schemes **5-1** and **5-2**. We therefore selected allyl 3-alkyl-indolenin-3-carboxylates as the ideal starting material due to the direct synthesis of these racemic starting materials having been recently described by our group (Figure **5-1**).[76]

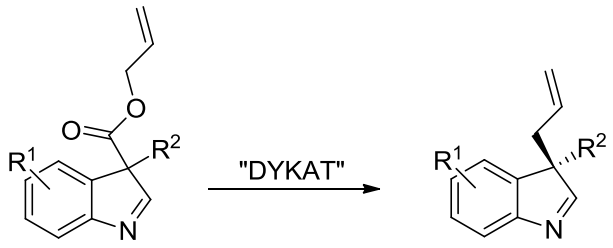


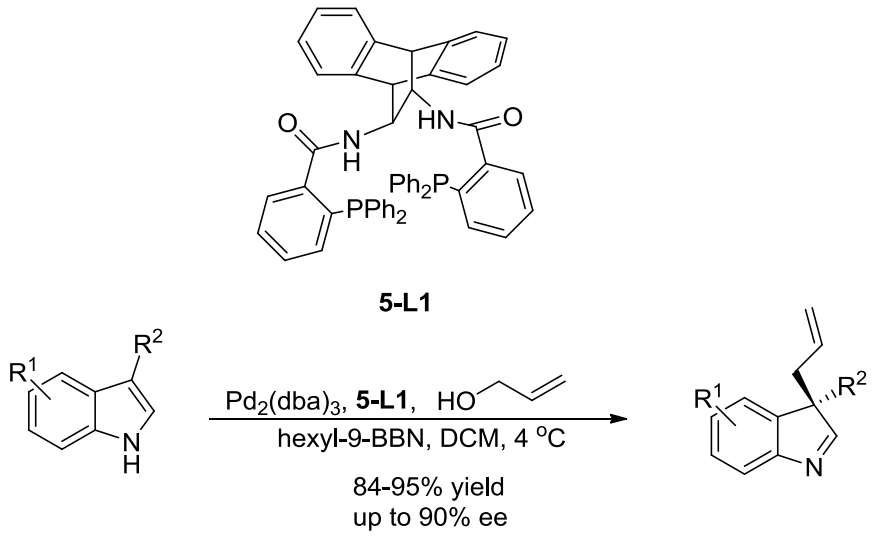
Figure **5-1**. DYKAT of selected allyl 3-alkyl-indolenin-3-carboxylates

Introduction to the C-3 Allylation of Indoles

Enantiomerically enriched 3-allyl-3-alkylindolenines are valuable intermediates in the synthesis of biologically relevant small molecules.[77] As such, robust means of

accessing these useful structures are in demand. However, a strategy of direct allylation of the indole core often is beset with significant challenges such as *N*-allylation, C2 allylation, inadequate nucleophilicity of the indolyl nucleophile to generate the C3-quaternary center, unfavorable energetics due to loss of aromaticity and so on.[78] In spite of potential shortcomings, many examples of allylation and benzylation of indole or oxindole cores are known.

The first example of a dearomatizing enantioselective allylation of 3-substituted indoles was reported in 2006 by Trost and co-worker.[79] In this work, allyl alcohols were activated with hexyl-9-BBN and cross-coupled with 3-substituted indoles to give 3-allyl-3-alkylindolenines in 84-95% yield and up to 90% ee (Scheme **5-3**). The catalytic system was generated from $Pd_2(dba)_3$ and **5-L1**.

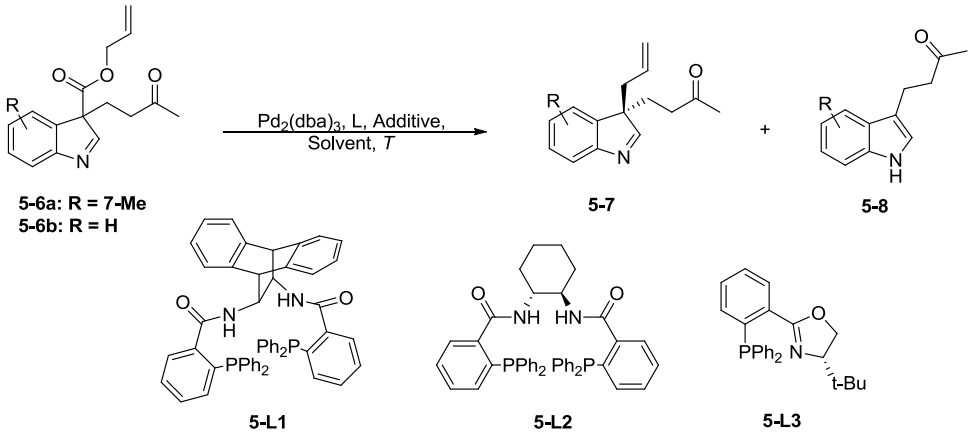


Scheme **5-3**. Enantioselective allylation of 3-substituted indoles by Trost

Several other examples of intermolecular dearomatizing reactions have been reported recently;[80] however, we sought to extend the utility of these 3-allyl-3-alkylindolenines by developing an intramolecular decarboxylative allylation strategy to access these substrates.

The Decarboxylative Allylic Alkylation of Allyl 3-Alykl-Indolenin-3-Carboxylates

Our foray into developing such a process started by testing its feasibility by using common Pd catalyzed allylic alkylation systems with **5-6a** as a model substrate (Table **5-1**).[81] Following the precedent of Rawal and co-workers for the intermolecular decarboxylative allylic alkylation of indoles,[80a] we treated **5-6a** with $Pd_2(dba)_3$/(2-furyl)$_3$P in CH_2Cl_2. Although decarboxylation product **5-8a** was isolated as the major product (56% yield), we were pleased to find that desired 3-allyl-3-alkyl indolenine **5-7a** was also formed (34% yield; Table **5-1**, entry 1). The effect of additives was then explored. For example, whereas only decarboxylation product **5-8a** was formed when HOAc was used as an additive (Table **5-1**, entry 2), the reaction proceeded essentially quantitatively to convert **5-6a** into **5-7a** and **5-8a** in 30 and 70% yield, respectively, in



Entry	Substrate	L	Additive	Solvent	*T* (°C)	%Yield **5-7** / **5-8**	%ee
1	**5-6a**	$(2\text{-furyl})_3P$	None	CH_2Cl_2	23	34:56	n.a.
2	**5-6a**	$(2\text{-furyl})_3P$	AcOH	CH_2Cl_2	23	0:85	n.a.
3	**5-6a**	$(2\text{-furyl})_3P$	MeOH	CH_2Cl_2	23	30:70	n.a.
4	**5-6a**	$(2\text{-furyl})_3P$	CuI	CH_2Cl_2	23	92:0	n.a.
5	**5-6b**	$(2\text{-furyl})_3P$	CuI	CH_2Cl_2	23	0:0	n.a.
6	**5-6b**	**5-L1**	none	CH_2Cl_2	23	0:37	n.a.
7	**5-6b**	**5-L1**	Et_3B	CH_2Cl_2	23	62:16	49
8	**5-6b**	**5-L1**	$C_{12}H_{27}BO_2$	CH_2Cl_2	23	0:21	n.a.
9	**5-6b**	**5-L1**	Hexyl-9-BBN	CH_2Cl_2	0	44:20	55
10	**5-6b**	**5-L1**	Hexyl-9-BBN	Toluene	0	48:14	56
11	**5-6b**	**5-L1**	Hexyl-9-BBN	$(CH_2Cl)_2$	0	44:23	64
12	**5-6b**	**5-L1**	Hexyl-9-BBN	Dioxane	0	48:19	48
13	**5-6b**	**5-L1**	Hexyl-9-BBN	THF	0	43:20	65
14	**5-6b**	**5-L1**	Hexyl-9-BBN	THF	-20	35:12	n.d.
15	**5-6b**	**5-L2**	Hexyl-9-BBN	THF	0	44:21	57
16	**5-6b**	**5-L3**	Hexyl-9-BBN	THF	0	0:13	n.d.
17	**5-6b**	**5-L1**	Ph_3B	THF	0	33:14	n.d.
18	**5-6b**	**5-L1**	$(F_5C_6)_3B$	THF	0	0:0	n.d.
19*	**5-6b**	**5-L1**	Hexyl-9-BBN	THF	0	80:0	77

Unless noted otherwise, the following conditions were used for the reactions: $Pd_2(dba)_3$ (2.5 mol-%), ligand (7.5 mol-%), and R_3B (0.5 eq.) when applicable. n.a.: not applicable, n.d.: not determined. *$Pd_2(dba)_3$ (2.3 mol-%), **5-L1** (11.25 mol-%), and hexyl-9-BBN (1.05 equiv.).

Table **5-1**. Optimization of the decarboxylative allylation

the presence of MeOH (Table **5-1**, entry 3). The highest reaction efficiency was achieved when CuI was used as the additive; **5-7a** was formed in 92% yield while only a trace amount of **5-7b** was generated under these same conditions (Table 1, entries 4 and 5). The effect of CuI appears to be specific to **5-6a**, as no reaction was observed when unsubstituted allyl indolenin-3-carboxylate (**5-6b**) was treated under the same reaction conditions. These results were corroborated by computational work by Wheeler and Lu whereby the presence of a 7-methyl group leads to a 5 kcal/mol stronger binding of Cu at nitrogen (Figure **5-2**).[82]

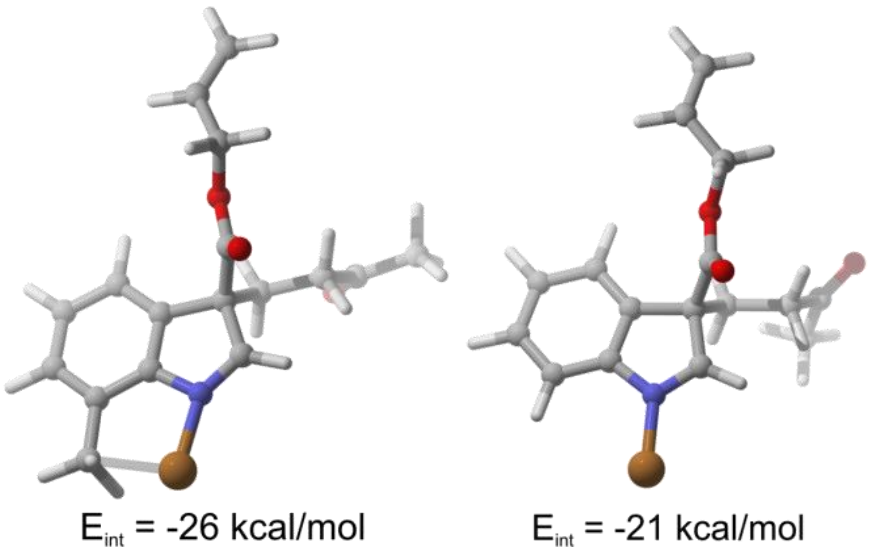


Figure **5-2**. Calculated structures of Cu(II) binding to **5-6a**(left) and **5-6b**(right)

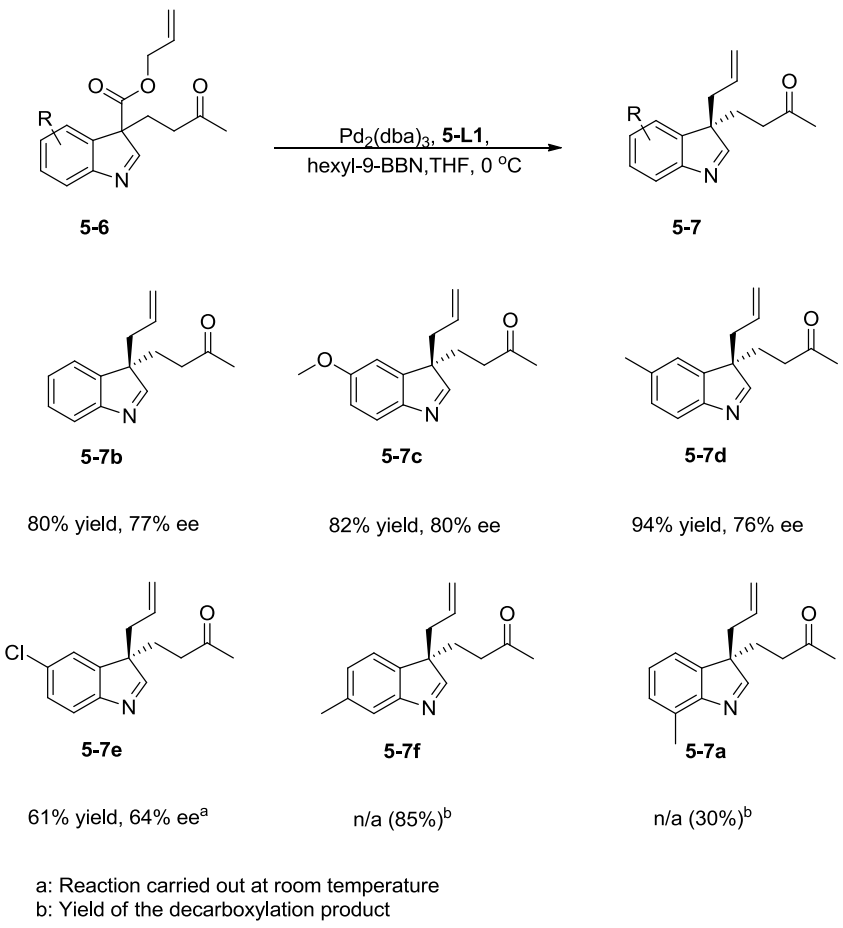
Having established the feasibility of the racemic reaction, we turned to chiral catalytic systems to develop an enantioconvergent variant of the transformation. Initial experiments with the use of $Pd_2(dba)_3$ and Trost ligand (*R*,*R*)-**5-L1** and **5-6b** as the

substrate proved to be ineffective, as only decarboxylation product **5-8b** was formed, in 37% yield (Table **5-1**, entry 6). Being aware of the positive influence of trialkylboranes in Pd-catalyzed intermolecular allylation and benzylation reactions of indoles,[83,79] we tested triethylborane (0.5 equiv.) as the reaction additive. Indeed, this led to the formation of **5-7b** in 62% yield with 49% ee (Table **5-1**, entry 7). Encouraged by this result, we also tested *n*-hexylcatecholborane and *n*-hexyl-9-BBN. Whereas only decarboxylation product **5-8b** was formed when *n*-hexylcatecholborane was used (Table **5-8b**, entry 8), the addition of hexyl-9-BBN led to the formation of **2b** in 44% yield with 55% ee (Table **5-1**, entry 9). Subsequent testing with Ph_3B and $(F_5C_6)_3B$ as the reaction additive showed that they were not as effective (Table **5-1**, entries 17 and 18).

Further screening of the reaction conditions revealed THF to be the solvent of choice at 0 °C (Table **5-1**, entries 13, 15, and 16). We found that lower temperatures such as –20 °C resulted in poor conversion (Table **5-1**, entry 14). Trost ligand **5-L2** also catalyzed this Pd-catalyzed enantioconvergent transformation albeit with slightly reduced enantioselectivity (Table **5-1**, entry 15). However, other common catalytic systems, such as $Pd_2(dba)_3$–**5-L3** (Table **5-1**, entry 16) were found to be ineffective. Finally, we were pleased to find that formation of decarboxylation product **5-8b** could be suppressed if a stoichiometric amount of hexyl-9 BBN (1.05 equivalents) was used, and the enantioselectivity could be improved to 77% ee if 11 mol-% of **5-L1** was employed (Table **5-1**, entry 19).[84] The absolute stereochemical configuration of **2b** was assigned as shown by comparing its optical rotation with that of the literature value.[79]

Exploration of Substrate Scope

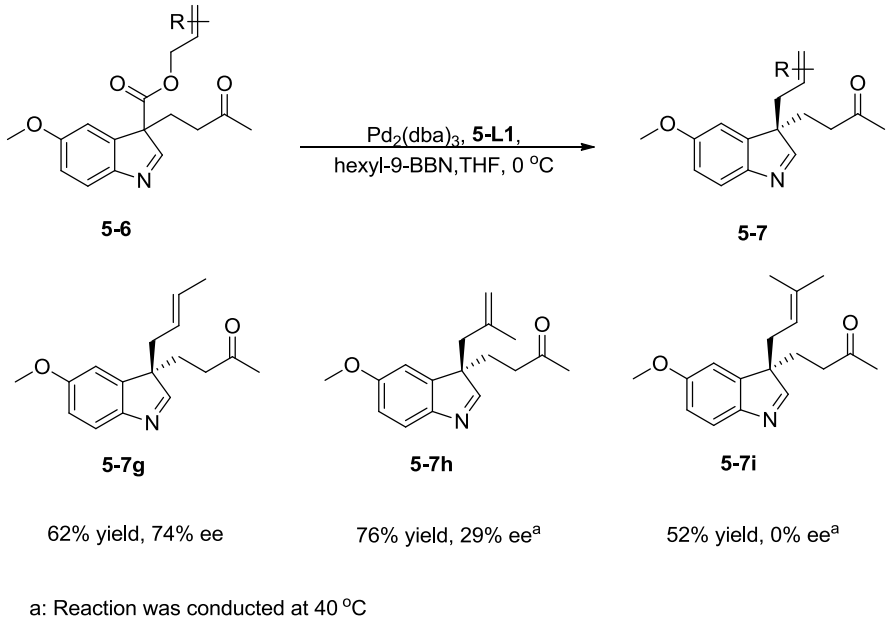
With an enantioconvergent process developed for **5-6a**, we sought to test the substrate scope of the reaction. We discovered that substitution at the C5 position of the aromatic ring was well tolerated in the reaction. For example, 5-methoxy- and 5-methyl-substituted substrates underwent the decarboxylative allylic alkylation to give the corresponding products (i.e., **5-7c** and **5-7d**) in high yields (82 and 94%) with ee values (80 and 76%) similar to that of **5-7b** (Scheme **5-4**). An electron-withdrawing chloride at the C5 position was also compatible even though the yield (61%) and *ee* (64%) of the product (i.e., **5-7e**) were somewhat reduced. However, methyl substitution at positions C6 and C7 of the aromatic ring was found to be incompatible with the reaction, as only the decarboxylation products (i.e., **5-8a** and **5-8f**) were formed.



Scheme **5-4**. Initial substrate scope of the enantioconvergent decarboxylative allylation

We were also capable of introducing different allyl groups for the decarboxylative allylation. We were pleased to observe that **5-7g** was formed in 62% yield with 74% ee from the corresponding crotyl indolenin-3-carboxylate (Scheme **5-5**). A reaction temperature of 40 °C was necessary for the reaction of the less-reactive methallyl ester to give **2h** in 76% yield with a low ee of 29%. When we attempted an enantioconvergent decarboxylative prenylation, only racemic indolenine **2i** was formed

in 52% yield after the corresponding prenyl ester was subjected to the reaction conditions at 40 °C.



a: Reaction was conducted at 40 °C

Scheme **5-5**. Effects of substitution on the allyl group

Our initial substrate pool was limited by the method of synthesis available for the precursor. We were relying on previous work by our laboratory to access the allyl 3-alykl-indolenin-3-carboxylates which constrained the 3-alkyl substituent to a butan-3-onyl group (Figure **5-3**).[76] We therefore sought additional methods of synthesis so that we could explore the effects of varying the alkyl substituent on the reaction.

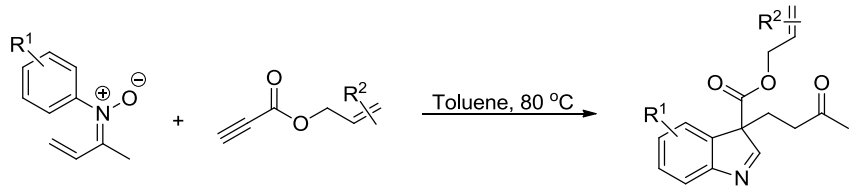
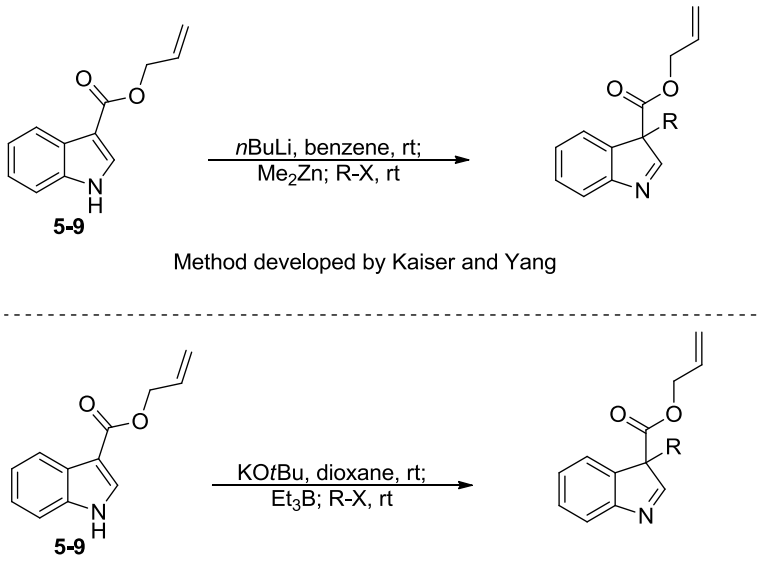


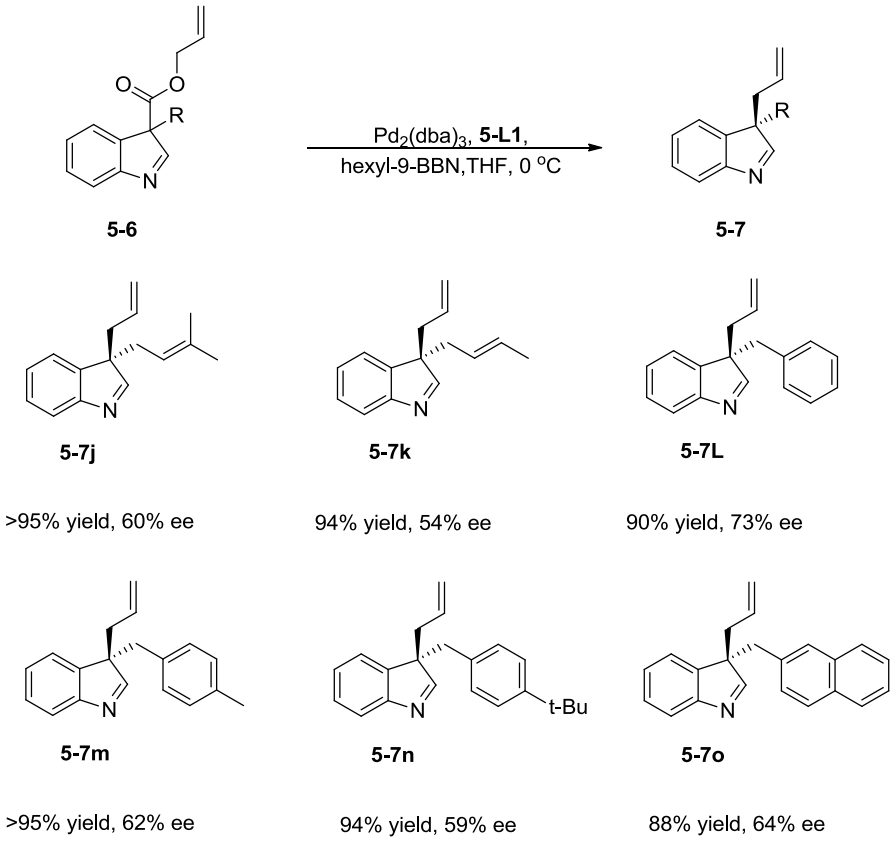
Figure **5-3**. Initial method of substrate construction

We explored many strategies to diversify our substrate pool. These methods included the oxidative coupling of allyl indole-3-carboxylate with electrophiles, intramolecular oxidative dimerization of (*Z*)-but-2-ene-1,4-diyl bis(1H-indole-3-carboxylate) and the C3 alkylation of allyl indole-3-carboxylate with electrophiles. Fortunately, we found that the C3 alkylation of allyl indole-3-carboxylate with benzyl and allyl halides could be effected when allyl indole-3-carboxylate, **5-9**, was deprotonated with *n*BuLi and the resulting lithium amide was transmetallated to a zinc amide (Scheme **5-6**). We later adapted a process by Lin, Hashim and Yang in our group's publication of the dearomatizing C3 alkylation of C3 alkyl indoles with alkyl halides to give C3 quaternary indolenines.[85] This was the first instance of direct C3 alkylation on indole-3-carboxylates to generate C3 quaternary indolenines.



Scheme **5-6**. Conditions to alkylate the C3 position of **5-9**

With a method capable of accessing substrates with a diverse C3 alkyl substituent, we continued our substrate scope analysis. Allyl indolenine-3-carboxylates with C3 allyl or C3 aryl substitution gave uniformly high yields (>88%) upon decarboxylative allylic alkylation even though lower ee values were observed as compared to the butan-3-onyl containing substrates (Scheme **5-7**). For example, prenyl-substituted indolenine **5-7k** was formed in 60% ee upon decarboxylative allylic alkylation, and



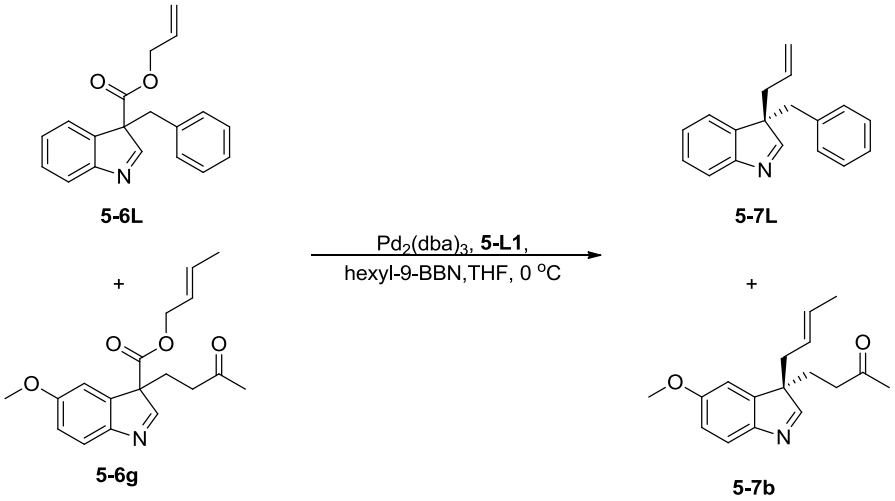
Scheme **5-7**. Enantioconvergent decarboxylative allylation of C3 allyl and aryl substrates

crotyl-substituted indolenine **5-7f** was formed with slightly lower enantioselectivity of 54% ee. Similar enantioselectivities (59–73% ee) were seen with various benzyl-substituted C3-quaternary indolenines (i.e., **5-7L** to **5-7o**) upon reaction of the corresponding allyl indolenin-3-carboxylates.

Mechanistic Discussion

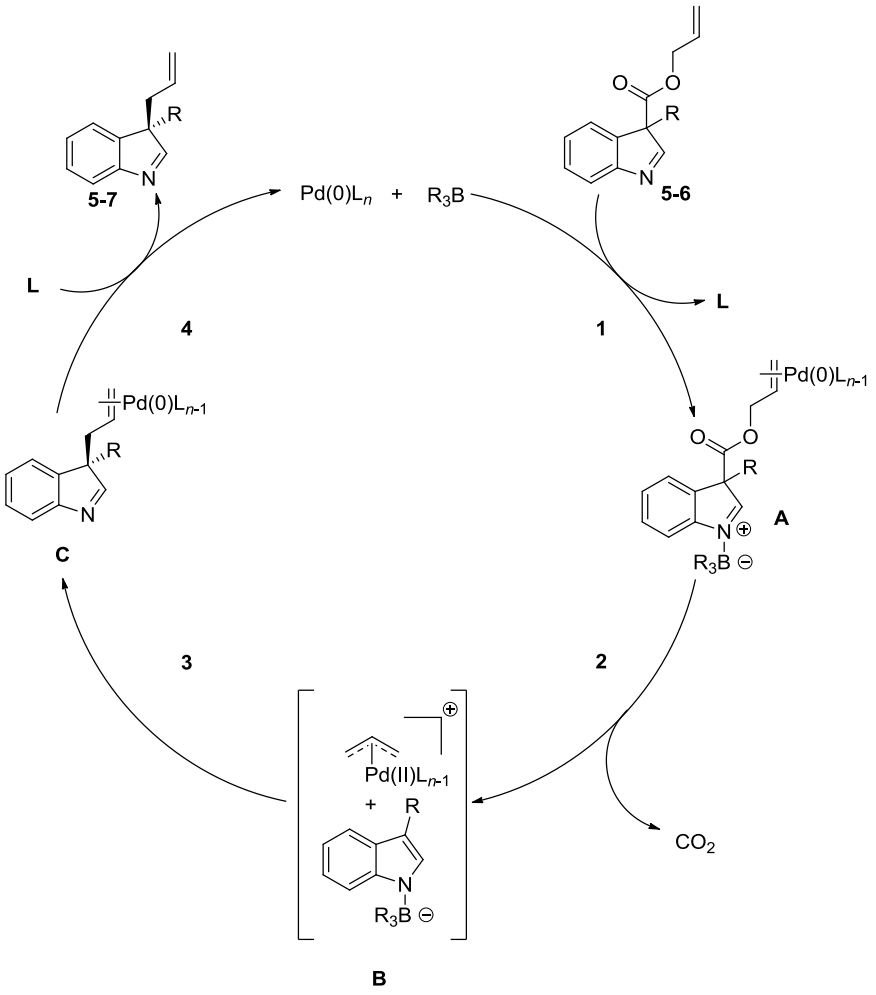
In order to better understand the mechanism of the enantioconvergent decarboxylative allylation, a crossover experiment was carried out in which a 1:1

mixture of **5-6g**/**5-6L** was subjected to the reaction conditions (Scheme **5-8**). Only **5-7g** and **5-7L** were detected by crude NMR thus indicating that the reactive species that were formed from each of the substrates remained closely associated as a tight ion pair during the process and recombined to give the products.



Scheme **5-8**. Crossover experiment of **5-6g** and **5-6L**

Our aggregate experimental findings suggest that the trialkylborane participates in the reaction both as a Lewis acid to facilitate decarboxylative elimination of the C3 esters and as part of a strongly π-nucleophilic *N*-indolyltrialkylborate species for dearomatizing C3-allylic alkylation to form the quaternary carbon center. A proposed reaction mechanism that accounts for these effects is depicted in Scheme **5-9**.[86] First,



Scheme **5-9**. Proposed mechanism of the enantioconvergent decarboxylative allylation

N–B coordination of indolenine (**5-6**) and trialkylborane forms electron-deficient 3*H*-indolium intermediate **A**. This leads to activation of the allyl ester towards oxidative addition of Pd(0) and facilitates decarboxylation of the resulting C3 carboxylate to give tightly associated ion pair **B**.[87] Subsequent C3 allylation of the solvent-caged *N*-indolyltrialkylborate and the chiral cationic Pd–π–allyl complex gives **C**, which dissociates to form enantiomerically enriched C3- quaternary indolenine **5-7**. Formation

of the electron-rich *N*-indolyltrialkylborate species is required to increase the π-nucleophilicity for the dearomatizing C3 allylation reactions. Consistent with this hypothesis, only the decarboxylation product (i.e., **5-8a**) was formed when **5-6a** was subjected to the reaction conditions, likely due to impeded N–B coordination as a result of 7-Me substitution, which prevented formation of the nucleophilic *N*-indolyltrialkylborate species.[88]

Conclusions

This work clearly demonstrated a novel enantioconvergent approach to 3-allyl-3-alykl-indolenines through the use of a chiral palladium/trialkylborane dual catalyst system. Also, we suggest a greater role of trialkyl borane beyond allylic alcohol activation in previous allylation examples employing R_3B/allyl alcohol as the allyl source. It was suggested that formation of strongly π-nucleophilic *N*-indolylborate species for the dearomatizing allylic alkylation was integral to the success of the reaction.

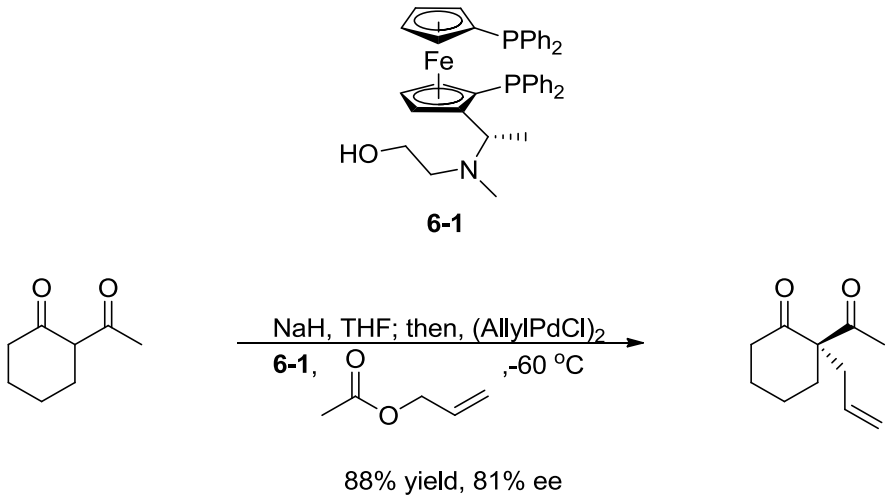
CHAPTER VI

ASYMMETRIC ALLYLATION OF ALDEHYDES EMPLOYING BORANE ACTIVATION

The key observation of substrate activation by a trialkyl borane came out of our efforts to develop an asymmetric decarboxylative allylation of allyl 3-alkyl-indolenin-3-carboxylates described in Chapter V. With this strategy to effect an asymmetric allylic alkylation on an *in situ* generated nucleophile, we were curious if we could apply this strategy to give an asymmetric allylic alkylation of *in situ* activated aldehydes and ketones using a trialkyl borane as the activating reagent.

Introduction to the Tsuji-Trost Reaction on Carbonyl Compounds

The enolate was one of the earliest nucleophiles explored in the development of the Tsuji-Trost reaction when enolates formed from diethyl malonate and ethyl acetoacetate were allylated by Tsuji and co-workers in 1965.[38] However, it was not until the work of Hayashi in 1988 that a reaction capable of asymmetric allylation of 1,3-diketones was developed.[89] It was found that chiral ferrocene ligand **6-1** and palladium were capable of enantioselectively allylating 2-acetyl-cyclohexanone with allyl acetate in 88% yield and with 81% ee (Scheme **6-1**). The reaction proceeded through an intermediate stabilized prochiral enolate generated by initial treatment of the 1,3-diketone with NaH.



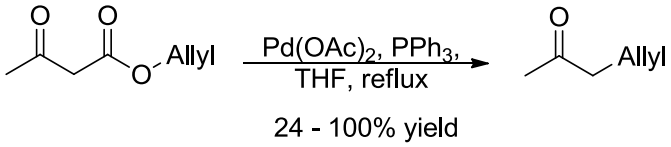
Scheme **6-1**. Enantioselective allylation of 1,3 diketones by Hayashi and co-workers

Many other examples of enantioselective allylation using 1,3-dicarbonyl species have been reported with several substrates and catalytic systems giving greater than 95% ee.[90]

One of the major limitations of this method is that the allylation reaction involves an intermediate enolate which must be generated using strongly basic conditions. Therefore, the substrates capable of undergoing this reaction must have other acidic functional groups protected. Also, the substrate must either have only one enolizable center or have a large difference in acidity between the sites of deprotonation. Therefore, a new method of selective allylation was developed simultaneously to address these limitations.

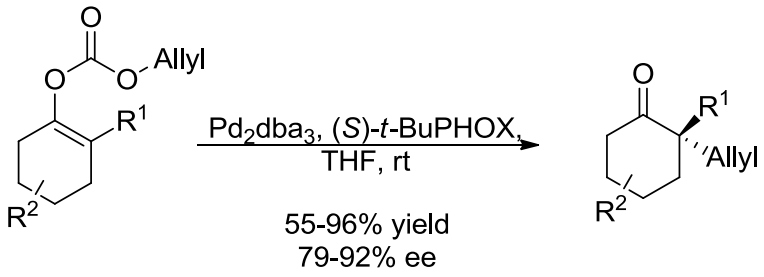
The first instance of unstabilized enolates undergoing an allylation reaction was reported by Tsuji and co-workers in 1980 (Scheme **6-2**).[91] This reaction is also one of the first instances of a decarboxylative allylation strategy and it involved allyl β-

ketoesters reacting with a palladium catalyst to generate homoallylic ketones as the reaction product.



Scheme **6-2**. The allylation of unstabilized ketones by Tsuji and co-workers

Different examples abound for the allylation of unstabilized enolates[92] but it was not until 2004 when Stoltz and co-worker disclosed an enantioselective Tsuji-Trost allylation using allyl enol carbonate substrates (Scheme **6-3**).[93] This work involved the generation of an allyl enol carbonate that underwent enantioselective decarboxylative allylation in the presence of palladium and (*S*)-tert-butyl phosphinooxazoline as the ligand. This catalytic system was capable of forming quaternary carbon centers in 55-96% yield and 79-92% ee. Also of note is the first highly enantioselective synthesis of 2-allyl-2-methylcyclohexanone in 89% ee.

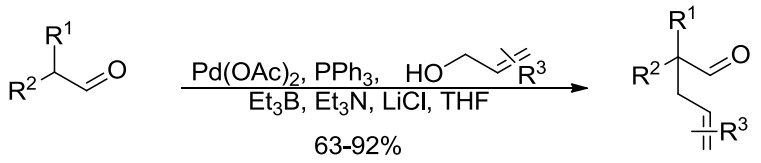


Scheme **6-3**. Enantioselective allylation of unstabilized ketones by Stoltz and co-woker

Other methods developed to enantioselectively allylate carbonyl compounds include the allylation of silyl enol ethers[93] and the enantionselective decarboxylation of allyl β-ketoesters[94] with both methods capable of good yields and excellent enantioselectivities. However, the current methodologies for the allylation of unstabilized enolates all require the preactivation of the substrate by formation of allyl enol carbonates, silyl enol ethers and allyl β-ketoesters. This adds a potentially low-yielding step to the synthetic sequence that reduces the synthetic efficiency of the synthesis. Therefore, methods that can directly and enantioselectively allylate aldehydes and ketones are in high demand.

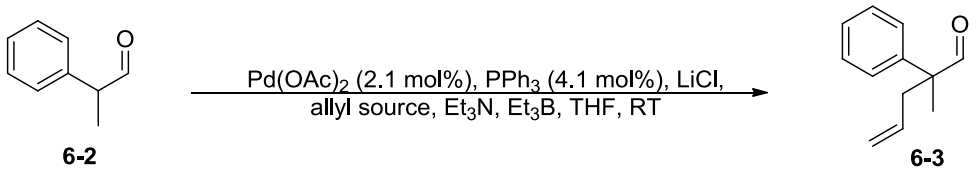
The Enantioselective Allylic Alkylation of Unactivated, Unstabilized Aldehydes

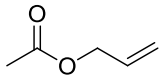
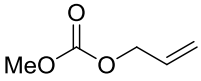
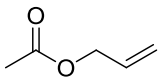
The first report of a reaction capable of allylic alkylation of unactivated, unstabilized aldehydes was by Tamaru and co-workers in 2001.[95] Their methodology involved the use of an allylic alcohol as an allylating reagent with Et_3B as the activating reagent capable coordinating to the allylic alcohol and thereby facilitating the allylic alkylation of aldehydes (Scheme **6-4**). This reaction proceeded in 63-92% yield.



Scheme **6-4**. Allylic alkylation of unactivated, unstabilized aldehydes by Tamaru

We believed we could use the experience gained in our work outlined in Chapter V to create an enantioselective version of this reaction. Initial efforts were directed at screening conditions for the allylation of 2-phenyl-propanal (**6-2** in Table **6-1**). We began by first exploring the role of Et_3B in the allylation reaction reported by Tamaru. It is known that trialkyl boranes can activate allylic alcohols for oxidative addition by Pd(0) (Chapter V) and we were curious if Et_3B had another role in the reaction.



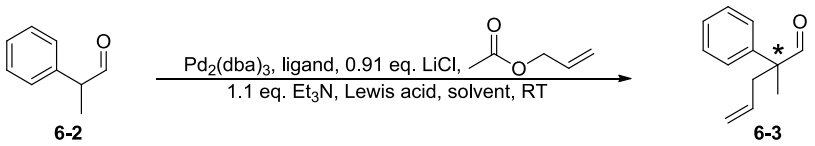
entry	allyl source	yield	time
1		81%	40 min
2		62%	16 hours
3		0%	24 hours

Note: Entry 3 was conducted without Et_3B

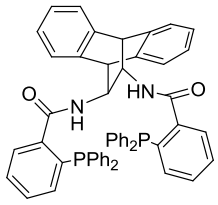
Table **6-1**. Conditions screen for racemic allylic alkylation of aldehydes

Therefore, we switched to allylating reagents that do not require boranes for activation. The first two allylating reagents we explored were allyl acetate (entry 1, Table **6-1**) and allyl methyl carbonate (entry 2, table **6-1**). To our delight, allyl acetate gave a 81% yield with only a 40 minute reaction time while the conditions of entry 2 gave only 62% yield after 16 hours. Also, when the reaction was conducted without Et_3B, there was no product detected after 24 hours (entry 3, Table **6-1**).

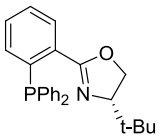
With a robust racemic allylation demonstrated, we turned our attention to developing an enantioselective version. Our conditions screen began by evaluating various ligands (entries 1-5, Table **6-2**). We found that phosphoramidite ligand **6-L3** performed the best of the ligand classes evaluated and gave **6-3** in 91% yield and in 26% ee at rt (entry 3, Table **6-2**). Our next efforts were focused on the Lewis acid. Previous work of ours (Chapter V) had demonstrated that, for the enantioselective decarboxylative allylation of allyl 3-alkyl-indolenine-3-carboxylates, the size of the trialkyl borane influenced the enantioselectivity of the reaction. Therefore, we screened the larger hexyl-9-BBN and we also explored the CBS reagent (*S*)-Bu-CBS. While hexyl-9-BBN gave a similar enantioselectivity (25% entry 6, Table **6-2**), the yield of the reaction was substantially decreased to <70%. Also, (*S*)-Bu-CBS failed to give any product after 20 hours (entry 8, Table **6-2**). We also explored the ability of Zn Lewis acids to catalyze this reaction and found that $Zn(OTf)_2$ failed to facilitate the allylation (entry 9, Table **6-2**).



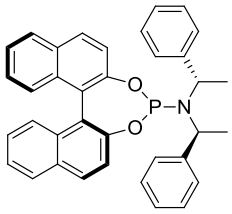
6-2 6-3



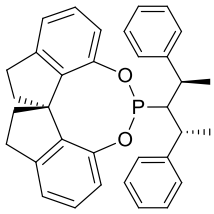
6-L1



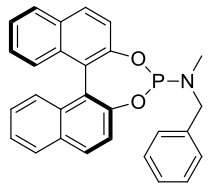
6-L2



6-L3



6-L4



6-L5

Entry	L	Lewis Acid	Solvent	%Yield	%ee	Time
1	**6-L1**	2.2 eq. Et_3B	THF	97	12	24 hrs
2	**6-L2**	2.2 eq. Et_3B	THF	97	9	1 hr
3	**6-L3**	2.2 eq. Et_3B	THF	91	26	1 hr
4	**6-L4**	2.2 eq. Et_3B	THF	67	-8	18 hrs
5	**6-L5**	2.2 eq. Et_3B	THF	60	-1	18 hrs
6	**6-L3**	1.09 eq. 9-hexyl-BBN	THF	<70	25	24 hrs
7	**6-L3**	1.09 eq. Et_3B	THF	95	24	20 hrs
8	**6-L3**	2.2 eq. (*S*)-Bu-CBS	THF	0	n/a	20 hrs
9	**6-L3**	2.2 eq. $Zn(OTf)_2$	THF	0	n/a	20 hrs
10	**6-L3**	2.2 eq. Et_3B	DCM	>95	19	1.5 hrs
11	**6-L3**	2.2 eq. Et_3B	Dioxane	82	23	20 min
12	**6-L3**	2.2 eq. Et_3B	Toluene	93	18	30 min
13[a]	**6-L3**	2.2 eq. Et_3B	THF	>95	21	1 hr
14[b]	**6-L3**	2.2 eq. Et_3B	THF	83	25	24 hrs

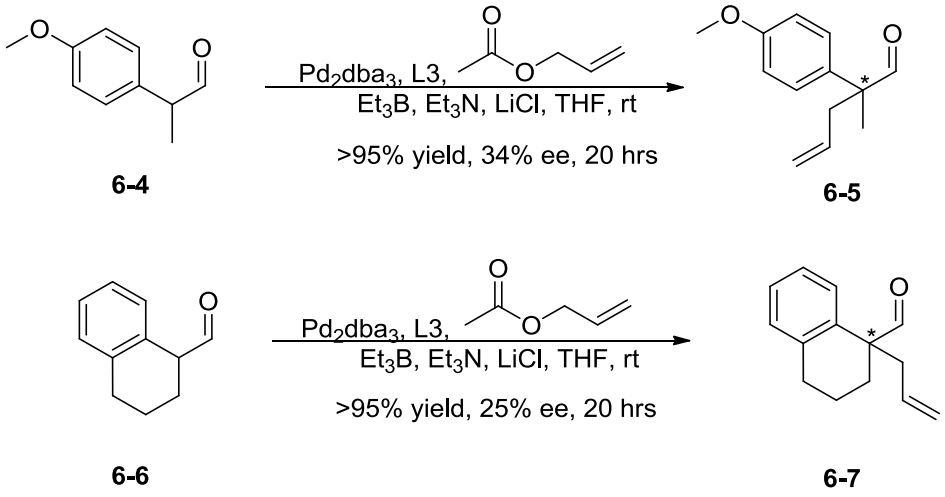
a) reaction was conducted without LiCl; b) allyl methylcarbonante was used as the allyl source

Table **6-2**. Conditions screen for the enantioselective allylation of aldehydes

We next looked at solvents (entries 10, 11 and 12) and found that none performed better than THF. Also, the role of LiCl was explored and it was found that the ee dropped to 21% without LiCl added to the reaction (entry 13). Finally, we were curious if the allyl source would affect the enantioselectivity of the reaction and we used allyl methyl carbonate instead of allyl acetate and found that there was no change in selectivity (entry 14).

With our screening complete, we found that current ligand classes were unable to impart substantial selectivity of the allylation of **6-2**. Curious the substrate class could influence the enantioselectivity, we prepared two substrates to explore how changes to the electronics and sterics of the intermediate enolate would affect the reaction.

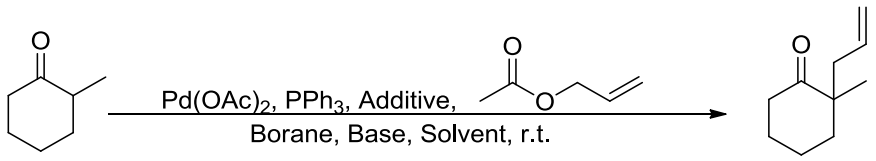
In order to study how the electronics of the enolate governed the enantioselectivity of the allylation, the electron rich substrate **6-4** was subjected to the reaction conditions (Scheme **6-5**). It was found that the allylated product **6-5** was formed in >95% yield and in 34% ee. This results suggests that the enantioselectivity of the



Scheme **6-5**. The role of structure and electronics in the enantioselective allylation

reaction depends on the electronic nature of the intermediate enolate more so than the steric bulk of the two substituents. Also, ridged substrate **6-6** was shown to undergo allylation to give **6-7** in >95% yield and in 25% ee. Reaction of **6-6** gave similar results to that of **6-2** which suggests that increasing the rigidity of the starting material does not influence the enantioselectivity of the reaction.

Finally, we sought to apply these methods to ketone substrates in order to develop a method that was capable of directly allylating ketones to give enantiopure, quaternary centers α to the ketone. We began our screen with 2-methyl-cyclohexanone and our conditions from the racemic allylation of aldehydes (entry 1, Table **6-3**). After



6-8 **6-9**

Entry	Additive	Borane	Base	Solvent	% yield
1	0.91 eq. LiCl	2.2 eq. Et_3B	1.1 eq. Et_3N	THF	0
2	0.91 eq. LiCl	none	1.1 eq. Et_3N	THF	0
3	0.91 eq. LiCl	2.2 eq. Et_3B	1.1 eq. Cs_2CO_3	THF	0
4	0.91 eq. LiCl	2.2 eq. Et_3B	1.1 eq. NaOH	THF	0
5	0.91 eq. LiCl	2.2 eq. Et_3B	1.1 eq. KO*t*-Bu	THF	0
6	0.91 eq. LiCl	2.2 eq. Et_3B	1.1 eq. K_3PO_4	THF	0
7	0.91 eq. LiCl	2.2 eq. Et_3B	1.1 eq. K_3PO_4	DMF	0
8	0.91 eq. LiCl	2.2 eq. Et_3B	1.1 eq. KO*t*-Bu	Dioxane	0
9	none	2.2 eq. Et_3B	1.1 eq. K_3PO_4	THF	0
10	0.91 eq. LiCl	0.3 eq. $(F_5\text{-}Ph)_3B$	1.1 eq. Et_3N	THF	0

Table **6-3**. Screen to optimize the direct allylation of ketones

24 hours, no product was detected. We examined if the reaction would happen without the addition of borane (entry 2, Table **6-3**) and again found no reactivity. Realizing that the p*K*a of protons α to ketones is higher than protons α to aldehydes, we attempted the reaction with stronger bases and still found no product detectible by NMR (entries 3 - 6). Also, solvent (entries 7 and 8), the presence/absence of LiCl (entry 9) and a more powerful Lewis acid (entry 10) all failed to generate product. The strategy of trialkyl borane activation of ketones for direct allylation had been demonstrated not to work.

However, the fact that ketones do not undergo the reaction can be useful. The direct allylation of aldehydes using Et_3B is selective for aldehydes over ketones. This

results in a synthetic method that is capable of functionalizing the α position of aldehydes while theoretically not having to protect ketone functional groups in the molecule due to lack of ketone reactivity under these reaction conditions.

Conclusions

In closing, we have developed an understanding of the role of Et_3B in the Tamaru allylation that goes beyond activation of allyl alcohol. The Lewis acid Et_3B facilitates enolization and behaves as a co-catalyst to effect the allylation of aldehydes. We have also begun developing an enantioselective version of this reaction that suffers from low enantioselectivity. Finally, this reaction is selective for aldehydes as ketones have been demonstrated to not react under the described conditions.

CHAPTER VII

CONCLUSIONS

Our work presented on the transannular *bis*-Michael reaction was two-fold in nature. We sought to develop an expedient route to an all-carbon *Z*,*E* macrocyclic precursor to the TMR and we then evaluated whether the *Z*,*E* isomer would follow our proposed model for the TMR. At the conclusion of the experiments of Chapter II, it became clear to us our initial intramolecular 1,3-dipolar synthetic route had many insurmountable difficulties. No matter the placement of the requisite oxime and alkyne functionalities, no desired isoxazole product was formed. As a result, we devised an alternate synthetic scheme with the hope of resolving these problems.

We still believed that the isoxazole was the best way to construct the requisite 1,3-diketone moiety. Therefore, we switched to an intermolecular strategy to construct the isoxazole in our synthesis of the macrocyclic precursor. This work is detailed in Chapter III. While the synthetic efficiency was demonstrated to be low, we developed a synthetic route making use of a 1,3-dipolar cycloaddition for the convergent synthesis of a 1,3-diketone-containing macrocycle. Consistent with our other studies, this *Z*,*E*-macrocyclic *bis*-enone was found to be inactive in the transannular *bis*-Michael reaction cascade for the conditions evaluated. The combined efforts of our lab to explore the utility and stereoselectivity of the TMR led to the discovery that two of the four possible olefin isomers (*Z*,*E* and *Z*,*Z*) were not acceptable substrates for the TMR due to their lack of reactivity. As a result of this work, the synthetic utility of the TMR has been

increased due to the knowledge gained of not only the stereochemical outcome of the *E*,*Z* and *E*,*E* isomers, but also of the limitations of substrate scope: the *Z*,*E* and *Z*,*Z* substrates cannot participate in the reaction. Therefore, retrosynthetic strategies making use of this disconnection can appropriately plan for the limitations described herein.

We also discovered that our 1,3-dipolar cycloaddition gave a rare 3,4-disubstituted isoxazole under kinetic reaction conditions. We demonstrated that the dipolar cycloaddition is reversible and the thermodynamic 3,5-disubstituted isoxazole can be obtained through isomerization of its 3,4-disubstituted isomer under elevated temperature. Our initial mechanistic studies support the role of hydrogen-bonding in accelerating the isomerization process. This discovery sets the stage for a possible direct route to access 3,4-disubstituted isoxazoles.

Our work in developing new palladium-catalyzed reactions resulted in a novel palladium-catalyzed enamine Heck reaction. This reaction is capable of generating α,β-unsaturated ketones directly from aldehydes and vinyl iodides. However, the limitations of scope in both vinyl iodide and aldehyde severely limit the synthetic utility of the reaction described herein. The possibility exists that significant improvements in yield could be achieved by evaluating other transition metal systems as catalysts or through the use of new synthetic techniques such as microwave acceleration.

In addition, our work clearly demonstrated a novel enantioconvergent approach to 3-allyl-3-alykl-indolenines through the use of a chiral palladium/trialkylborane dual catalyst system. We suggest a greater role of trialkyl borane beyond allylic alcohol activation in previous allylation examples employing R_3B/allyl alcohol as the allyl

source. It was suggested that formation of strongly π-nucleophilic *N*-indolylborate species for the dearomatizing allylic alkylation was necessary for the success of the reaction. While this reaction had good to excellent yields across the substrate pool, the enantioselectivity was at most good. However, the maximum *ee* we observed is consistent with other literature reports of reactions to access this type of substrate.

Finally, we extended or understanding of the role of Et_3B to the Tamaru allylation. The Lewis acid Et_3B facilitates enolization and behaves as a co-catalyst to effect the allylation of aldehydes. We have also begun developing an enantioselective version of this reaction that suffers from low enantioselectivity. This reaction was shown to be selective for aldehydes as ketones did not react under the described conditions.

Taken together, this research has explored a diverse area of chemical transformations and has provided insight into their respective limitations. It is hoped that future work in the area of complex molecule synthesis can avail itself of some of the methods and models that are described in the previous chapters.

REFERENCES

1. Pammolli, F.; Magazzini, L.; Riccaboni, M. *Nat. Rev. Drug Disc.* **2011**, *10*, 428-438.

2. a) Neu, H. C. *Science* **1992**, *257*, 1064-1073.; b) Arias, C. A.; Murray, B. E. *Nat. Rev. Microbio.* **2012**, *10*, 266-278.

3. Huigens III, R. W.; Morrison, K.C.; Hicklin, R. W.; Flood, T. A.; Richter, M. F.; Hergenrother, P. J. *Nat. Chem*. **2013**, *5*, 195-202.

4. MacLellan, P.; Selson, A. *Chem. Commun.* **2013**, *49*, 2383-2393.

5. United States Clinical Trials Online Registry http://clinicaltrials.gov/ct2/results?term=tripterygium+wilfordii (accessed February 12, 2013 and is a list of all clinical trials for *T. wilfordii*)

6. Chou, T. Q.; Mei, P. E. *Zhongguo Shenglixue Zazhi* **1936**, *10*, 529-534.

7. Harada, R.; Kakisawa, H.; Kobayashi, S.; Musya, M.; Nakanishi, K.; Takahashi, Y. *Tetrahedron Lett.* **1962**, *14*, 603-607.

8. Sethi, G.; Ahn, K. S.; Pandey, M. K.; Aggarwal, B. B. *Blood* **2007**, *109*, 2727-2735.

9. a) Setzer, W. N.; Setzer, M. C. *Mini Rev. Med. Chem.* **2003**, *3*, 540-556.; b) Alvarenga, N.; Ferro, E. A. *Studies Nat. Prod. Chem.* **2005**, *30*, 635-702.; c) Zhou, Q. "Natural diterpene and triterpene quinone methides: Structures, synthesis, and biological potentials" in Rokita, S. E. ed. "Quinone Methides" John Wiley & Sons, Inc., **2009** (Hoboken, New Jersey).

10. Johnson, W. S.; Gravestock, M, B.; McCarry, B. E.; *J. Am. Chem. Soc.* **1971**, *93*, 4332-4334.

11. a) Stork, G.; Burgstahler, A.W. *J. Am. Chem. Soc.* **1955**, *77,* 5068-5077.; b) Eschenmoser, A; Ruzicka, L; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1957**, *40*, 2191-2198.

12. Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2009**, *131*, 13928–13929.

13. Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 1448-1449.

14. Batsanov, A.; Chen, L.; Gill, G. B.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1996**, *1*, 45-55.

15. Nicolaou, K. C.; Snyder, S. A; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668-1698.

16. Grieco, P. A.; Ferrino, S.; Vidaro, G. *J. Am. Chem. Soc.* **1984**, *102*, 7586-7587.

17. Petit, M.; Aubert, C.; Malacria, M. *Org. Lett.* **2004**, *6*, 3937–3940.

18. Carreira, E. M.; Kvaerno, L. "Classics in Stereoselective Synthesis" Wiley-VCH Verlag GmbH &Co., **2009** (Weinheim, Germany)

19. Ihara, M.; Suzuki, M.; Fukumoto, K.; Kabuto, C. *J. Am. Chem. Soc.* **1990**, *112*, 1164-1171.

20. Scheerer, J. R.; Lawrence, J. F.; Wang, G. C.; Evans, D. A. *J. Am. Chem. Soc.* **2007**, *129*, 8968-8969.

21. Hudlicky, T.; Reed, J. W. "The Way of Synthesis" Wiley-VCH Verlag GmbH &Co., **2007** (Weinheim, Germany)

22. Xue, H.; Peddabuddi, G.; Yang, J. *J. Org. Chem.* **2012**, *77*, 8933-8945.

23. Tsuji, J. "Palladium Reagents and Catalysts" John Wiley & Sons Ltd, **2004** (Hoboken, New Jersey)

24. a) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518-5526.; b) Heck, R. F. *J. Am. Chem. Soc.* **1969**, *91*, 6707-6714.

25. Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442-4489.

26. Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Soc. Chem. Jpn.* **1971**, *44*, 581.

27. Dieck, A.H.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 1133-1136.

28. Heck, R.F.; Nolley, J.P. *J. Org. Chem.* **1972**, *37*, 2320-2322.

29. Kurti, L.; Czako, B. "Strategic Applications of Named Reactions in Organic Synthesis" Elsevier Academic Press, **2005** (Burlington, Massachusetts)

30. Iimura, S.; Overman, L. E.; Paulini, R; Zakarian, A. *J. Am. Chem. Soc.* **2006**, *128*, 13095-13101.

31. Sato, Y.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 4738-4739.

32. Carpenter, N. E., Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5846-5848.

33. Ashimori, A.; Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Org. Chem.* **1993**, *58*, 6949-6951.

34. Larhed, M.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 9582-9584.

35. Jeffery, T. *Tetrahedron Lett.* **1994**, *35*, 3051-3054.

36. Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633-639.

37. Littke, A.; Fu, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176-4211.

38. Tsuji, L.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett*. **1965**, *6*, 4387-4388.

39. Atkins, K. E.; Walker, W., E; Manyik, R. M. *Tetrahedron Lett*. **70**, *11*, 3821-3824.

40. Trost, B. M., Fullerton, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 292-294.

41. Kurosawa, H. *J. Organomet. Chem.* **1987**, *334*, 243-253.

42. Fürstner, A; Gastner, T. *Org. Lett.* **2000**, *2*, 2467-2470.

43. Trost, B. M.; Strege, P. E. *J. Am. Chem. Soc.* **1077**, *99*, 1649-1651.

44. a) Von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1993**, *32*, 566-568.; b) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.***1993**, *34*, 1769-1772.; c) Dawson, G. J.; Frost, C. G.; Williams, J.M.J. *Tetrahedron Lett.* **1993**, *34*, 3149-3150.

45. Vosburg, D. A.; Vanderwal, C. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 4552-4553.

46. Trost, B. M.; Patterson, D. E. *J. Org. Chem.* **1998**, *63*, 1339-1341.

47. Trost, B.M. *J. Org. Chem.* **2004**, *69*, 5813-5837.

48. Corey, E. J.; Kurti, L. "Symmetry-breaking reactions" in *Enantioselective Chemical Synthesis* Direct Book Publishing, **2010**. (Cambridge, Massachusetts)

49. Rovis, T. Recent advances in catalytic asymmetric desymmetrization reactions in *New Frontiers in Asymmetric Catalysis*, Mikami, K. and Lautens M. Editors; John Wiley & Sons Inc., **2007**. (Hoboken, New Jersey)

50. Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Simoni, D. *Synthesis* **1987**, 857-869.

51. Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997,** *119,* 6496-6511.

52. Snider, B. B. *Journal of Organometallic Chemistry* **1979**, *179*, C37-C41.

53. Pospisil, J.; Muller, C.; Fürstner, A. *Chem. Eur. J.* **2009**, *15,* 5956-5968.

54. Einhorn, J.; Einhorn, C.; Ratajczak, F.; Pierre, J.-L. *J. Org. Chem.* **1996,** *61,* 7452-7454.

55. Duan, M.; Paquette, L. A.; *Angew. Chem., Int. Ed.* **2001**, *40*, 3632-3636.

56. Negishi, E.; Van Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc*. **1985**, *107,* 6639-6647.

57. Anslyn, E.; Dougherty, D. *Modern Physical Organic Chemistry*, 1st ed.; University Science Books: Sausalito, **2006**. (Sausalito, California)

58. Kalesse, M.; Khandavalli, P. C.; Quitschalle, M.; Burzlaff, A.; Kasper, C.; Scheper, T. *Chem. Eur. J.* **2003**, *9*, 1129-1136.

59. Negishi, E.; Pour, M.; Cederbaum, F.E.; Kotora, M. *Tetrahedron* **1998**, *54*, 7057-7074.

60. Nicolaou, K. C.; Nold, A. L.; Milburn, R. R.; Schindler, C. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 6527-6532.

61. Lindhoudt, J. C.; van Mourik, G. L.; Pabon, H. J. J. *Tetrahedron Lett.* **1976**, *17*, 2565.

62. a) Kritchenkov, A. S.; Bokach, N. A.; Kuznetsov, M. L.; Dolgushin, F. M.; Tung, T. Q.; Molchanov, A. P.; Kukushkin, V. Y. *Organometallics* **2012**, *31*, 687-699.; b) Nakayama, J.; Kaneko, A.; Sugihara, Y.; Ishii, A.; Oishi, A.; Shibuya, I. *Hetero. Chem.* **2000**, *11*, 434-440.

63. Heaney, F. *Eur. J. Org. Chem.* **2012**, 3043-3058.

64. Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V.V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *117*, 210-216.

65. Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361-369.

66. Chen, W.; Du, W.; D, Y.-Z.; Wu, Y.; Yang, S.-Y.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 7667-7670.

67. The experimental design is as follows. Two NMR tubes were each charged with 0.5 mL of CDCl3 containing 6.5 mg of **5b** (0.013 mmol). To one of the tubes was added succinimide (6.2 mg, 0.063 mmol). Both NMR tubes were sealed and heated to 70 ^{o}C for 2 days. The reaction progress was analyzed by NMR at 2, 4, 18, 25, and 41 hours. The relative abundance of **5a** for each tube was determined and the rate enhancement was calculated by dividing the relative abundance of **5a** in the presence of succinimide by the relative abundance of **5a** in only $CDCl_3$.

68. Nitta, M.; Kobayashi, T. *J. Chem. Soc. Perkin Trans. 1* **1985**, 1401-1406.

69. a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Elsevier: Oxford, 1992.; b) Basavaiah, D.; Jaganmohan Rao, A.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811-892.

70. Alvarez-Bercedo, P.; Flores-Gaspar, A.; Correa, A.; Martin, R. *J. Am. Chem. Soc.* **2010**, *132*, 466-467.

71. Jean, M.; Renault, J.; Uriac, P.; Capet, M.; van de Weghe, P. *Org. Lett.* **2007**, *9*, 3623-3625.

72. Ruan, J.; Saidi, O.; Iggo, J. A.; Xiao, J. *J. Am. Chem. Soc.* **2008**, *130*, 10510-10511.

73. Martin, R.; Buchwald, S. *Acc. Chem. Res.*, **2008**, *41*, 1461–1473.

74. Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284.

75. a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 3543–3544.; b) Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968–5976.

76. Huehls, C. B.; Hood, T.; Yang, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 5110–5113.

77. a) He, F; Bo, Y.; Altom, J. D.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771–6772.; B) Kozmin, S. A. ; Iwama, T. ; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628–4641.

78. a) Roche, S. P.; Porco, J. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 4068–4093.; b) Zhuo, C.-X.; Zhang, W.; You, S.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 12662–12686.

79. Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314-6315.

80. a) Kagawa, N.; Malerich, J. P.; Rawal, V. H. *Org. Lett.* **2008**, *10*, 2381–2384.; b) Liu, Y.; Du, H. *Org. Lett.* **2013**, *15*, 740–743.; c) Chen, J.; Cook, M. J. *Org. Lett.* **2013**, *15*, 1088–1091.; d) Montgomery, T. D.; Zhu, Y.; Kagawa, N.; Rawal, V. H. *Org. Lett.* **2013**, *15*, 1140–1143.

81. a) Weaver, J. D.; Recio III, A.; Grenning, A. J.; Tunge, J. A.; *Chem. Rev.* **2011**, *111*, 1846–1913.; b) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258–297.; c) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921–2944.; d) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395–422.

82. These calculations were carried out by Prof. Steven Wheeler and Dr. Tongxiang Lu. The level of theory was BP86 DFT functional, with the 6-31G*/SDD basis set, and a PCM model to account for solvent effects

83. Zhu, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2012**, *134*, 111–114.

84. See the Supporting Information for a list of the conditions that were tested

85. Lin, A.; Yang, J.; Hashim, M. *Org. Lett.* **2013**, *15*, 1950–1953.

86. Related trialkylborane effects have been known. However, to the best of our knowledge, the nature of such effects has not been clearly defined. See Kimura,

M.; Horino, Y.; Mukai, R.; Tanaka, S.; Tamaru, Y. *J. Am. Chem. Soc.* **2001**, *123*, 10401–10402.

87. An alternative pathway for Lewis acidic activation through O–B coordination of the trialkylborane and the carbonyl group of **5-6** is less likely because of the sterically congested environment.

88. It is unclear why C6-methyl-substituted indolenine (i.e., **5-6f**) also failed to form under the reaction conditions.

89. Hayashi, T.; Kanehira, K.; Hagihara, T.; Kumada M. *J. Org. Chem.* **1988**, *53*, 113-120.

90. a) Kuwano, R.; Ito, Y. *J. Am. Chem. Soc.*, **1999**, *121*, 3236-3237.; b) Trost, B. M.; Schroeder, G. M.; Kristensen, J. *Angew. Chem., Int. Ed*, **2002**, *41*, 3492-3495.; c) You, S.-L.; Hou, X.-L.; Dai, L.-X.; Cao, B.-X.; Sun, J. *Chem. Commun.* **2000**, 1933-1934.

91. Shimizu, I.; Yamada, T.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 3199-3202.

92. Tune, J. A.; Burger, E. C. *Eur. J. Org. Chem.* **2005**, 1715-1726.

93. Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044-15045.

94. Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924-6927.

95. Kimura, M.; Horino, Y.; Mukai, R.; Tanaka, S.; Tamaru, Y. *J. Am. Chem. Soc.* **2001**, *123*, 10401-10402.

APENDIX A

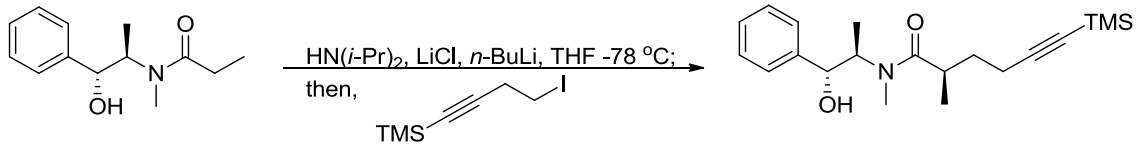
EXPERIMENTAL PROCEDURES

General Information

All solvents were degassed for by bubbling N_2 through the solvent for several hours. The solvents were then dried by passing through an alumina column before use. Thin-layer chromatography was done on TLC Silica gel 60 F_{254} commercial plates (EMD chemicals). ^{1}H NMR spectra were recorded on Varian Inova 500 (500 MHz) and Mercury 300 (300 MHz) spectrometers. All spectra are referenced to the residual solvent peak (7.26 ppm for $CHCl_3$). The chemical shift (δ) of each signal is reported in parts per million (ppm) and all coupling constants (*J*) are reported in Hertz (Hz). ^{13}C NMR spectra were recorded on Varian Inova 500 (125 MHz) and Mercury 300 (75 MHz) spectrometers. All spectra are referenced to the residual solvent peak (7.26 ppm for $CHCl_3$). The chemical shift (δ) of each signal is reported in parts per million (ppm). Chiral HPLC analyses were preformed either on a Shimadzu Prominence SiL-20A UFLC or an Agilent Technologies 1200 Series HPLC using Daicel Chemical Industries CHIRALPAK® columns (IA, IB, IC, ASH, and AD) eluting with hexane / *iso*-propanol mixtures as indicated. The Laboratory for Biological Mass Spectrometry at Texas A&M University recorded low and high resolution mass spectra.

Proceedures

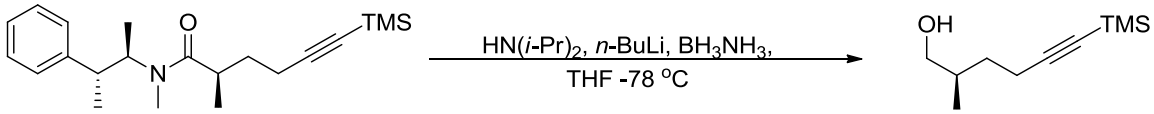
CHAPTER II



(*R*)-*N*,2-dimethyl-*N*-((2*R*,3*R*)-3-phenylbutan-2-yl)-6-(trimethylsilyl)hex-5-ynamide (2-6).

n-BuLi (32.3 mL, 51.6 mmol, 1.6 M in hexanes) was added dropwise to a solution of HN(*i*-Pr)$_2$ (7.8 mL, 55.7 mmol) and LiCl (6.95 g, 164 mmol) in THF (37 mL) at -78 °C under N_2. The resulting suspension was held at -78 °C for 5 minutes, transferred to an ice bath (~ 4 °C) for 5 minutes and then cooled to -78 °C. *N*-methyl-*N*-((2*R*,3*R*)-3-phenylbutan-2-yl)propionamide[1] (6.0 g, 27.1 mmol) in THF (81 mL) was added via cannula and the mixture was stirred for 1 hour at -78 °C, warmed to 0 °C for 15 minutes, and then stirred at RT for 3 minutes. The flask was then cooled to 0 °C and (4-iodobut-1-yn-1-yl)trimethylsilane[2] (3.26 g, 12.9 mmol) was added. The reaction was stirred for 2 hours and quenched with saturated NH_4Cl (130 mL). The mixture was extracted 4x with EtOAc (4x 130 mL). The combined organics were dried over $MgSO_4$ and concentrated. The crude material was purified by column chromatography (Hexanes:EtOAc 60:40) to give **2-6** (0.86 g, 20%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39-7.27 (m, 5H), 4.65-4.56 (m,

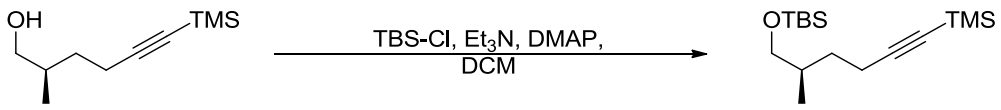
1H), 2.89 (s, 3H), 2.29-2.08 (m, 2H), 1.86-1.74 (m, 1H), 1.64 -1.44 (m, 3H), 1.14 (d, J = 6.9 Hz, 3H), 1.11 (d, J = 6.9 Hz, 3H), 0.12 (s, 9H). LRMS (EI+) m/z calculated for $C_{20}H_{32}NO_2Si$ $[M+H]^+$: 346.22, found: 346.14.



(*R*)-2-methyl-6-(trimethylsilyl)hex-5-yn-1-ol (2-7).

n-BuLi (5.0 mL, 8.0 mmol, 1.6 M in hexanes) was added dropwise to a solution of HN(*i*-Pr)$_2$ (1.2 mL, 8.7 mmol) in THF (8.7 mL) at -78 ^oC under N_2. The resulting solution was stirred at -78 ^oC for 10 minutes and warmed to 0 ^oC and stirred for 10 minutes. BH_3NH_3 (0.28 g, 8.2 mmol) was added and the suspension was stirred for 15 minutes at 0 ^oC, warmed to RT and stirred for 15 minutes and cooled to 0 ^oC. **2-6** (0.71 g, 2.1 mmol) in THF (5.2 mL) was added dropwise and the reaction was warmed to RT. The reaction was followed by TLC and was complete after 3 hours. The reaction cooled to 0 ^oC and was quenched with the addition of 3M HCl (21 mL) and stirred for 30 minutes at 0 ^oC. The mixture was extracted 3x with diethyl ether (3x 20 mL). The combined organic phases were washed 2x with 3M HCl (2x 8.5 mL), 1x with saturated $NaHCO_3$ (8.5 mL), 1x with $CuSO_4$ and 1x with brine (8.5 mL). The extract was dried over $MgSO_4$, filtered and concentrated to give **2-7** (0.332 g, 87%). ^1H NMR ($CDCl_3$, 300 MHz) δ 3.55-3.45 (m, 2H), 2.37-2.17 (m, 2H), 1.81-1.60 (m, 2H), 1.49 (brs, 1H), 1.44-1.33 (m, 1H), 0.93 (d, J = 6.9 Hz, 3H), 0.14 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 107.6, 84.7, 67.8, 35.1,

32.1, 17.6, 16.4, 0.27. LRMS (EI+) m/z calculated for $C_{10}H_{20}LiOSi$ $[M+Li]^+$: 191.1438, found: 191.1394.

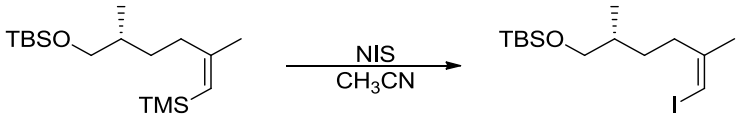


(*R*)-tert-butyldimethyl((2-methyl-6-(trimethylsilyl)hex-5-yn-1-yl)oxy)silane (2-8). **2-7** (0.291 g, 1.58 mmol) was dissolved in DCM (2.1 mL) under N_2 and Et_3N (0.33 mL, 2.4 mmol) and DMAP (19 mg, 0.16 mmol) were added. TBS-Cl (0.297 g, 1.97 mmol) was then added at RT and the reaction was stirred overnight. The reaction was quenched with the addition of 5 mL of H_2O and the organic layer was separated. The organic phase was washed 2x with H_2O (2x 5 mL), dried over $MgSO_4$, filtered and concentrated. The crude material was purified by column chromatography (Hexanes:EtOAc 90:10) to give **2-8** (0.526 g, >95%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.48-3.37 (m, 2H), 2.35-2.16 (m, 2H), 1.77-1.60 (m, 2H), 1.37-1.24 (m, 1H), 0.89 (m, 12H), 0.14 (s, 9H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 107.8, 84.4, 68.1, 35.1, 32.4, 26.1, 18.5, 17.8, 16.5, 0.3, 0.2. LRMS (EI+) m/z calculated for $C_{16}H_{35}OSi_2$ $[M+H]^+$: 299.2221, found: 299.2054.

(*R*,*Z*)-tert-butyl((2,5-dimethyl-6-(trimethylsilyl)hex-5-en-1-yl)oxy)dimethylsilane (2-8a).

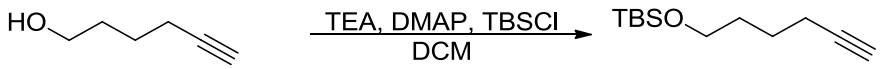
Cp_2TiCl_2 (0.78 g, 3.1 mmol) was placed in a flame-dried flask under N_2 and DCM (6.8 mL) was added. To this suspension was added Me_2AlCl (0.29 mL, 3.1 mmol) and the reaction was stirred for 30 minutes at RT. **2-8** (0.47 g, 1.6 mmol) in a flask under N_2 was added via cannula. The flask containing **2-8** was rinsed with 1 mL of DCM which was cannulated to the reaction. The reaction was stirred for 4.5 hours. KOH (11.6 g) was dissolved in H_2O (35 mL) and this solution was placed in an flask with stir bar under AMBIENT atmosphere. When TLC indicated that the carbometallation of **2-8** was complete after 4.5 hours, the reaction was slowly cannulated to the vigorously stirred solution of KOH in H_2O. The reaction flask and cannula were rinsed with DCM. The resulting biphasic mixture was then filtered over a celite pad and the pad was washed with DCM (50 mL). The organic phase was separated and the aqueous phase was extracted 3x with DCM (3x 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude material was purified by column chromatography (Hexanes:EtOAc 100:0) to give **2-8a** (0.329 g, 67%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.18-5.17 (m, 1H), 3.47-3.37 (m, 2H), 2.21-2.00 (m, 2H), 1.82 (d, J = 1.2 Hz, 3H), 1.62-1.50 (m 2H), 1.22-1.10 (m, 1H), 0.90 (m, 12 H), 0.09 (s, 9H), 0.04 (s, 6H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.6, 124.5, 68.3, 36.5, 35.5, 32.6, 26.7, 26.1, 28.5, 16.9, 0.5, -5.2. LRMS (EI+) m/z calculated for $C_{17}H_{38}LiOSi_2$ $[M+Li]^+$: 321.2621, found: 321.2702.



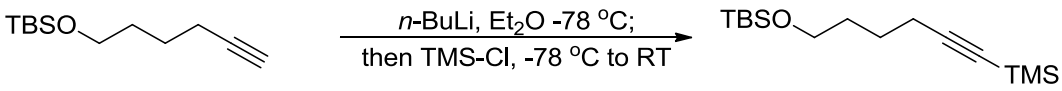
(*R*,*Z*)-tert-butyl((6-iodo-2,5-dimethylhex-5-en-1-yl)oxy)dimethylsilane (2-3*Z*).

2-8a (0.257 g, 0.82 mmol) was dissolved in CH_3CN (4.9 mL) under N_2. The reaction was wrapped in foil and NIS (0.295 g, 1.31 mmol) was added in one portion. The reaction was stirred for 18 hours and quenched the addition of saturated $NaHCO_3$ (2.5 mL) and saturated $Na_2S_2O_3$ (2.5 mL). The reaction was stirred for 10 minutes and extracted 3x with Et_2O (3x 10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated. The crude material was purified by column chromatography (Hexanes:EtOAc 98:2) to give **2-3*Z*** (0.250 g, 83%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.81-5.80 (m, 1H), 3.46-3.41 (m, 2H), 2.27-2.18 (m, 2H), 1.88 (d, *J* = 1.5 Hz, 3H), 1.63-1.52 (m, 2H), 1.25-1.13 (m, 1H), 0.93 (d, *J* = 9.0 Hz, 3H), 0.90 (s, 9H), 0.05 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.1, 73.9, 68.1, 36.5, 35.7, 30.4, 26.1, 23.3, 18.5, 16.8, -5.2. LRMS (EI+) m/z calculated for $C_{14}H_{29}IOSi_2$ $[M+H]^+$: 369.1105, found: 369.0915.



***tert*-Butyl(hex-5-yn-1-yloxy)dimethylsilane (2-31).**

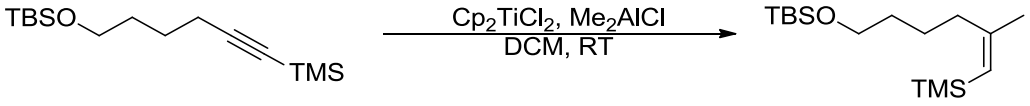
To a solution of hex-5-yn-1-ol (7.73 mL, 71.3 mmol), triethylamine (15 mL, 107 mmol), and DMAP (0.44 g, 3.67 mmol) in DCM (95 mL) under N_2 was added TBSCl (13.4 g, 89 mmol). The reaction was stirred at RT overnight. The reaction was quenched with water (75 mL) and the organic phase was separated. The organic phase was washed with water (25 mL), saturated NH_4Cl (25 mL), and 2x with saturated $NaHCO_3$ (75 mL). The organic phase was then dried over $MgSO_4$ and concentrated. The crude material was purified by column chromatography (Hexanes:EtOAc 90:10) to give **2-31** (13.9 g, 92%). The spectra were identical to those reported in the literature.[3] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.65 (t, *J*= 6.0 Hz, 2H), 2.24-2.18 (m, 2H), 1.94 (t, *J* = 2.7 Hz, 1H), 1.67-1.54 (m, 4H), 0.89 (s, 9H), 0.05 (s, 6H).



***tert*-butyldimethyl((6-(trimethylsilyl)hex-5-yn-1-yl)oxy)silane (2-10).**

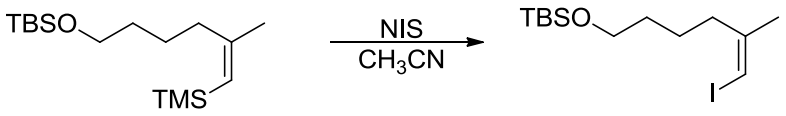
To a solution of **2-31** (2.3 g, 10.8 mmol) in Et_2O (7.3 mL) was added drop wise *n*-BuLi (6.9 mL, 11.1 mmol, 1.6 M in hexanes) at -78 °C. The reaction was stirred for 30 minutes at -78 °C. TMS-Cl (1.42 mL, 11.1 mmol) was added dropwise and the reaction was allowed to warm to RT and then stirred for 2 hours. The reaction was quenched with

H_2O (20 mL) and the mixture was extracted 3x with Et_2O (3x 20 mL). The extracts were dried over $MgSO_4$, filtered and concentrated. The crude material was purified by column chromatography (Hexanes:EtOAc 90:10) to give **2-10** (2.91 g, 94%). The spectra were identical to those reported in the literature.[4] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.63 (t, *J* = 6.0 Hz, 2H), 2.24 (t, *J* = 6.9 Hz, 2H), 1.64-1.52 (m, 4H), 0.89 (s, 9H), 0.14 (s, 9H), 0.05 (s, 6H).



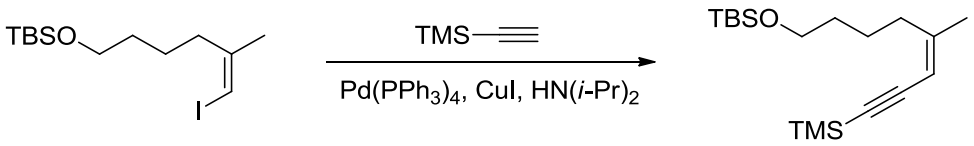
(*Z*)-*tert*-butyldimethyl((5-methyl-6-(trimethylsilyl)hex-5-en-1-yl)oxy)silane (2-10a). Cp_2TiCl_2 (5.03 g, 20.5 mmol) was placed in a flame-dried flask under N_2 and DCM (45 mL). Me_2AlCl (1.9 mL, 20.5 mmol) was added dropwise at RT and the reaction was stirred for 30 minutes. **2-10** (2.91 g, 10.23 mmol) was cannulated over and the canula was rinsed with DCM (2 mL). The reaction was stirred for 20 hours. KOH (37.5 g) was dissolved in H_2O (113 mL) and this solution was placed in an flask with stir bar under AMBIENT atmosphere. The carbometallation reaction was slowly cannulated to the vigorously stirred solution of KOH in H_2O. The reaction flask and cannula were rinsed with DCM. The resulting biphasic mixture was then filtered over a celite pad and the pad was washed with DCM (150 mL). The organic phase was separated and the aqueous phase was extracted 3x with DCM (3x 100 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude material was purified by column

chromatography (Hexanes:EtOAc 100:0 to 99:1 to 98:2) to give **2-10a** (1.07 g, 35%, *Z*:*E* 86:14). The spectra were identical to those reported in the literature.[5] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.19-5.18 (m, 1H), 3.61 (t, *J* = 6.3 Hz, 2H), 2.14-2.09 (m, 2H), 1.81 (d, *J* = 1.2 Hz, 3H), 1.53-1.42 (m, 4H), 0.89 (s, 9H), 0.08 (s, 9H), 0.05 (s, 6H).

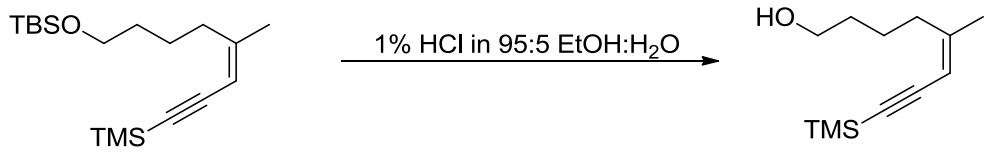


(*Z*)-tert-butyl((6-iodo-5-methylhex-5-en-1-yl)oxy)dimethylsilane (2-11).

2-10a (1.00 g, 3.33 mmol) was dissolved in CH_3CN (20 mL) under N_2. The reaction was wrapped in foil and NIS (1.20 g, 5.32 mmol) was added in one portion. The reaction was stirred for 18 hours and quenched the addition of saturated $NaHCO_3$ (10 mL) and saturated $Na_2S_2O_3$ (10 mL). The reaction was stirred for 10 minutes and extracted 3x with Et_2O (3x 25 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated. The crude material was purified by column chromatography (Hexanes:EtOAc 98:2) to give **2-11** (0.985 g, 84%). The spectra were identical to those reported in the literature.5 ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.83-5.82 (m, 1H), 3.63 (t, *J* = 6.3 Hz, 2H), 2.22 (t, *J* = 7.8 Hz, 2H), 1.87 (d, *J* = 1.2 Hz, 3H), 1.57-1.43 (m, 4H), 0.90 (s, 9H), 0.05 (s, 6H).

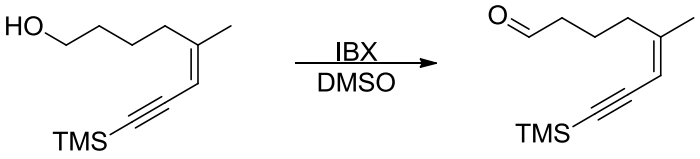


(*Z*)-*tert*-butyldimethyl((5-methyl-8-(trimethylsilyl)oct-5-en-7-yn-1-yl)oxy)silane (2-12). $Pd(PPh_3)_4$ (0.30 g, 0.26 mmol) and CuI (98 mg, 0.52 mmol) were combined under N_2 and $HN(i\text{-}Pr)_2$ (9.2 mL) was added with stirring at 0 ^oC. **2-10** (0.91 g, 2.58 mmol) was dissolved in $HN(i\text{-}Pr)_2$ (18.4 mL) under N_2 and added to the reaction. Trimethylsilylacetylene (0.55 mL, 3.87 mmol) was added and the reaction was taken out of the ice-bath. After 30 minutes of stirring, the reaction was quenched with the addition of saturated NH_4Cl (10 mL) and extracted 3x with Et_2O (3x 50 mL). The organics were washed with 230 mL of a mixture of saturated $CuSO_4$ (30 mL) and H_2O (200 mL). The organic phase was separated and the aqueous phase was extracted 3x with Et_2O (3x 100 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated to **2-12** (0.805 g, 96%). ^1H NMR ($CDCl_3$, 300 MHz) δ 5.30 (s, 1H), 3.63 (t, J = 6.0 Hz, 2H), 2.33 (t, J = 7.2 Hz, 2H), 1.77 (d, J = 1.2 Hz, 3H), 1.55-1.47 (m , 4H), 0.89 (s, 9H), 0.18 (s, 9H), 0.05 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.4, 105.8, 103.6, 96.2, 63.1, 34.6, 32.6, 26.1, 23.8, 22.6, 18.5, 0.3, -5.1. LRMS (EI+) m/z calculated for $C_{18}H_{37}OSi_2$ $[M+H]^+$: 325.2377, found: Not Observed.



(*Z*)-5-methyl-8-(trimethylsilyl)oct-5-en-7-yn-1-ol (2-12a).

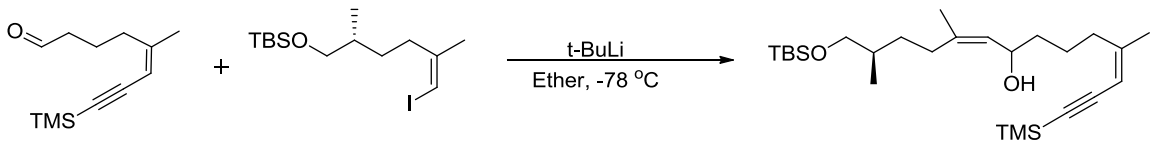
2-12 (0.745 g, 2.29 mmol) was dissolved in 1% HCl in 95:5 EtOH:H_2O (33 mL) and the reaction was stirred at RT for 5 minutes. The reaction was quenched with the addition of saturated $NaHCO_3$ (55 mL) and the mixture was extracted 3x with Et_2O (55 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated. The crude material was purified by column chromatography (Hexanes:EtOAc 75:25) to give **2-12a** (0.48 g, 94%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.3 (s, 1H), 3.67 (t, *J* = 6.0 Hz, 2H), 2.34 (t, *J* = 7.2 Hz, 2H), 1.77 (d, *J* = 1.5 Hz, 3H), 1.60-1.48 (m, 4H), 0.17 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.1, 105.9, 103.5, 96.4, 62.8, 34.4, 32.3, 23.7, 22.6, 0.2. LRMS (EI+) m/z calculated for $C_{12}H_{22}LiOSi$ $[M+Li]^+$: 217.16, found: 217.18.



(*Z*)-5-methyl-8-(trimethylsilyl)oct-5-en-7-ynal (2-4).

2-12a (0.454 g, 2.16 mmol) was dissolved in DMSO (11 mL) and IBX (2.30 g, 8.2 mmol) was added at RT. The reaction was stirred for 3 hours and quenched with the addition of H_2O (22 mL). The slurry was stirred for 5 minutes and filtered through celite. The celite was rinsed with Et_2O (50 mL) and the filtrate was separated. The aqueous

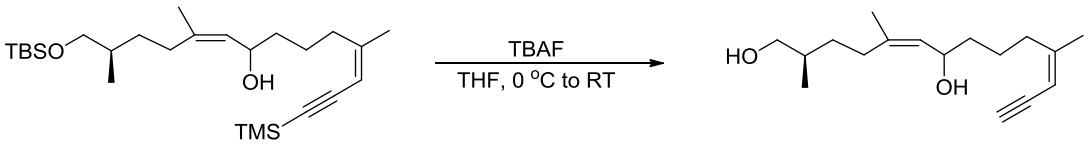
phase was extracted 2x with Et_2O (2x 50 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated. The crude material was purified by column chromatography (Hexanes:EtOAc 85:15) to give **2-4** (0.408 g, 91%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.79 (t, *J* = 1.5 Hz, 1H), 5.34 (s, 1H), 2.48-2.43 (m, 2H), 2.36 (t, *J* = 7.5 Hz, 2H), 1.85-1.75 (m, 4H), 1.78 (d, *J* = 1.5 Hz, 3H), 0.17 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.4, 152.8, 106.9, 103.2, 96.8, 43.1, 33.9, 22.5, 19.9, 0.2.



(2*R*,5*Z*,11*Z*)-1-((*tert*-butyldimethylsilyl)oxy)-2,11-dimethyl-14-(trimethylsilyl)tetradeca-5,11-dien-13-yn-7-ol (2-13).

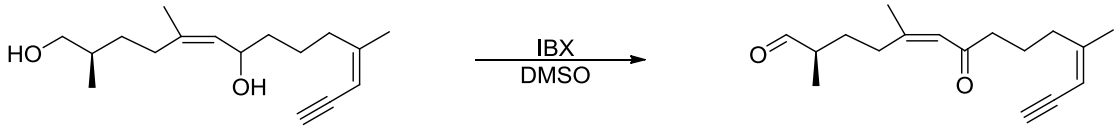
2-3*Z* (0.337 g, 0.91 mmol) and **2-4** (0.153 g, 0.73 mmol) were combined in a flame dried flask and azeotroped to dryness with toluene. The flask was placed under N_2 and Et_2O (2.6 mL) was added. The reaction was cooled to -78 °C and *t*-BuLi (1.2 mL, 2.1 mmol, 1.7M in hexanes) was added dropwise. After the addition of *t*-BuLi, the reaction was pulled out of the -78 °C bath and let warm to RT. The reaction was stirred for 75 minutes and quenched with the addition of saturated NH_4Cl (5 mL). The reaction was diluted with H_2O (10 mL) and extracted 3x with EtOAc (3x 10 mL). The material was dried over Na_2SO_4, filtered and concentrated. The crude material was purified by column chromatography (Hexanes:EtOAc 94:6) to give **2-13** (0.140 g, 44%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.30 (s, 1H), 5.16 (d, *J* = 8.1 Hz, 1H), 4.39-4.32 (m, 1H), 3.42 (d, *J* = 5.7

Hz, 2H), 2.40-2.27 (m, 2H), 2.12-2.03 (m, 2H), 1.77 (s, 3H), 1.71 (s, 3H), 1.61-1.25 (m, 7H), 0.89 (s, 9H), 0.18 (s, 9H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.3, 15.1, 139.7, 128.6, 128.5, 105.9, 103.6, 79.8, 68.3, 68.2, 68.2, 37.6, 36.0, 35.8, 34.8, 34.7, 32.1, 32.0, 31.1, 30.0, 29.9, 26.1, 25.8, 25.0, 23.6, 23.6, 22.6, 18.5, 16.9, 16.8, 0.3, 0.1, -5.2. LRMS (EI+) m/z calculated for $C_{26}H_{50}LiO_2Si_2$ $[M+Li]^+$: 457.3504, found: 457.3662.



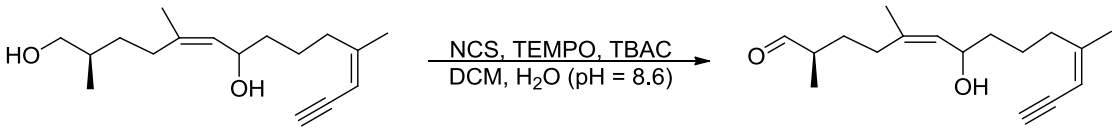
(2*R*,5*Z*,11*Z*)-2,5,11-trimethyl-14-(trimethylsilyl)tetradeca-5,11-dien-13-yne-1,7-diol (2-16).

2-13 (0.111g, 0.248 mmol) was dissolved in THF (2.5 mL) and cooled to 0 °C. TBAF was added dropwise (1.0 mL, 1.0 mmol, 1M in THF) and the reaction was allowed to warm to RT. After stirring for 22 hours at RT, the reaction was quenched with the addition of water (10 mL) and the mixture was extracted 3x with EtOAc (3x 15 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated. The crude material was purified by column chromatography (Hexanes:EtOAc 55:45) to give **2-16** (43 mg, 66%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.26 (s, 1H), 5.18-5.14 (m, 1H), 4.39-4.32 (m, 1H), 3.53-3.40 (m 2H), 2.97 (d, *J* = 2.1 Hz, 1H), 2.37-2.32 (m, 2H), 2.27-1.97 (m 2H), 1.78 (s, 3H), 1.71 (s, 3H), 1.68-1.39 (m 6H), 1.33-1.12 (m, 1H), 0.95-0.91 (m, 3H).



(*R*,5*Z*,11*Z*)-2,5,11-trimethyl-7-oxotetradeca-5,11-dien-13-ynal (2-17).

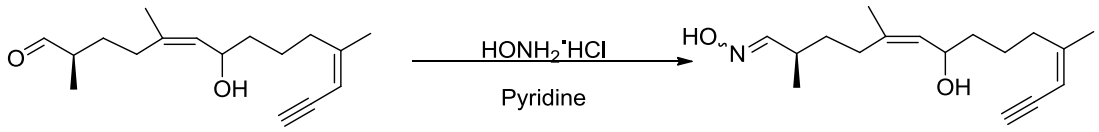
2-16 (9.6 mg, 0.036 mmol) was dissolved in DMSO (1.9 mL) and IBX (30.5 mg, 0.109 mmol) was added at RT. The reaction was stirred for 16 hours and the reaction was concentrated. The crude material was purified by column chromatography (Hexanes:EtOAc 80:20) to give **2-17** (6.5 mg, 70%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.68 (d, *J* = 1.8 Hz, 1H), 6.08 (s, 1H), 5.28 (s, 1H), 2.95 (d, *J* = 2.4 Hz, 1H), 2.61-2.55 (m, 3H), 2.46-2.31 (m, 6 H), 1.88 (d, *J* = 1.5 Hz, 3H), 1.79 (d, *J* = 1.2 Hz, 3H), 1.78-1.70 (m, 2H), 1.15 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.5, 130.9, 128.8, 124.2, 105.0, 79.3, 68.2, 46.3, 43.5, 38.7, 33.9, 31.3, 30.4, 28.9, 28.8, 25.4, 23.8, 23.0, 22.3, 21.8, 14.1, 13.4, 11.0. LRMS (EI+) m/z calculated for $C_{17}H_{24}LiO_2$ $[M+Li]^+$: 267.1931, found: 267.1925.



(2*R*,5*Z*,11*Z*)-7-hydroxy-2,5,11-trimethyltetradeca-5,11-dien-13-ynal (2-19).

A solution at pH = 8.6 was prepared by dissolving $NaHCO_3$ (420 mg) and K_2CO_3 (69 mg) in 10 mL of H_2O. **2-16** (12.4 mg, 0.047 mmol) was dissolved in DCM (0.4 mL) and the pH = 8.6 solution was added (0.4 mL). TEMPO (1.7 mg, 0.01 mmol) and TBAC (2.6 mg, 0.09 mmol) were added. Then NCS (12.6 mg, 0.096 mmol) was added and the

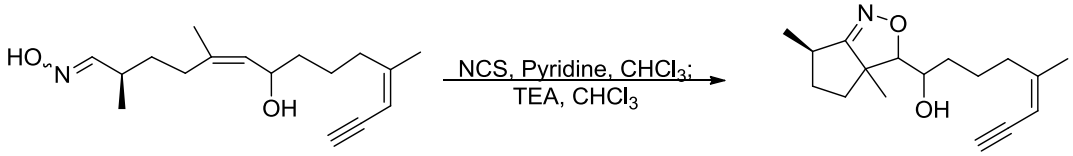
reaction was stirred for 1 hour. The reaction was directly loaded on a column and the crude material was purified by column chromatography (Hexanes:EtOAc 75:25) to give **2-19** (10.6 mg, 86%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.61-9.59 (m, 1H), 5.26 (s, 1H), 5.23-5.19 (m, 1H), 4.36-4.27 (m, 1H), 2.98 (d, *J* = 2.1 Hz, 1H), 2.37-2.33 (m, 2H), 2.21-2.01 (m, 2H), 1.78 (d, *J* = 1.5 Hz, 3H), 1.73-1.72 (m, 3H), 1.64-1.38 (m, 7H), 1.13 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.3, 138.1, 137.7, 129.9, 129.6, 104.8, 81.8, 79.4, 68.1, 67.8, 46.4, 45.9, 37.3, 34.5, 29.9, 29.5, 29.0, 23.5, 23.5, 22.5, 13.8, 13.7. LRMS (EI+) m/z calculated for $C_{17}H_{26}LiO_2$ $[M+Li]^+$: 269.2087, found: 269.2111.



(2*R*,5*Z*,11*Z*)-7-hydroxy-2,5,11-trimethyltetradeca-5,11-dien-13-ynal oxime (2-2).

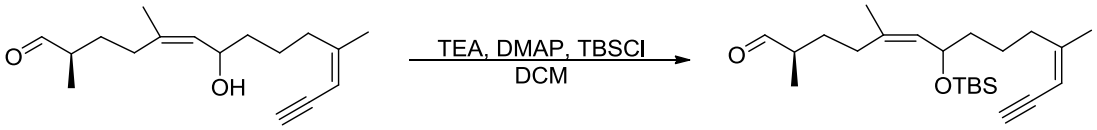
2-19 (4.2 mg, 0.016 mmol) was dissolved in pyridine (130 μL) and hydroxylamine hydrochloride (1.5 mg, 0.021 mmol) was added at RT. The reaction was stirred for 25 minutes and the pyridine was removed *en vacuo*. The crude reaction was directly loaded on a column and the crude material was purified by column chromatography (Hexanes:EtOAc 60:40) to give **2-2** (4.1 mg, 94% as a mixture of C1 *E/Z* isomers). NMR for the *Z* isomer ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.18 (d, *J* = 8.4 Hz, 1H), 5.26-5.22 (m, 2H), 4.39-4.31 (m, 1H), 2.99 (d, *J* = 2.7 Hz, 1H), 2.45-2.28 (m, 4H), 1.92-1.83 (m, 1H), 1.78 (d, *J* = 1.2 Hz, 3H), 1.68 (d, *J* = 1.2 Hz, 3H), 1.53-1.38 (m, 6H), 1.08 (d, *J* = 6.9 Hz, 3H). NMR for the *E* isomer ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 (d, *J* = 6.9 Hz,

1H), 5.27 (s, 1H), 5.18 (d, *J* = 9 Hz, 1H), 4.40-4.33 (m, 1H), 3.00-2.98 (m, 1H), 2.41-2.30 (m, 4H), 2.09-2.00 (m, 1H), 1.78 (d, *J* = 1.5 Hz, 3H), 1.72-1.70 (m, 3H), 1.63-1.42 (m, 6H), 1.10 (d, *J* = 6.9 Hz, 3H). LRMS (EI+) m/z calculated for $C_{17}H_{28}NO_2$ $[M+H]^+$: 278.2115, found: 278.1981.



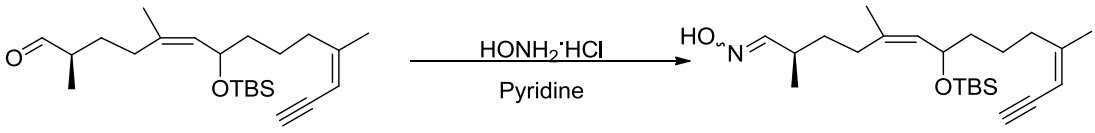
(*Z*)-1-((6*R*)-3a,6-dimethyl-3a,4,5,6-tetrahydro-3H-cyclopenta[c]isoxazol-3-yl)-5-methyloct-5-en-7-yn-1-ol (2-20).

2-2 (4.1 mg, 0.015 mmol) was dissolved in $CHCl_3$ (200 μL) and NCS (2.0 mg, 0.0145 mmol) and pyridine (0.1 μL) were added at RT. The reaction was stirred for 30 minutes and the reaction was diluted with $CHCl_3$ (1.3 mL). Et_3N (2.1 μL, 0.015 mmol) was then addedabd tge reactuib was sturred fir 20 hours at RT. The crude reaction concentrated and directly loaded on a column and the crude material was purified by column chromatography (Hexanes:EtOAc 75:25 to 50:50) to give **2-20** (0.9 mg, 22%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.27 (s, 1H), 3.94 (d, *J* = 4.5 Hz, 0.2 H), 3.89 (d, *J* = 5.7 Hz, 3H), 3.57-3.50 (m, 1H), 2.97 (d, *J* = 2.1 Hz, 1H), 1.79 (m, 3H) (NOTE: due to the amount of material analyzed, the proton NMR data set is incomplete). LRMS (EI+) m/z calculated for $C_{17}H_{26}NO_2$ $[M+H]^+$: 276.1958, found: 276.1882.



(2*R*,5*Z*,11*Z*)-7-((*tert*-butyldimethylsilyl)oxy)-2,5,11-trimethyltetradeca-5,11-dien-13-ynal (2-21).

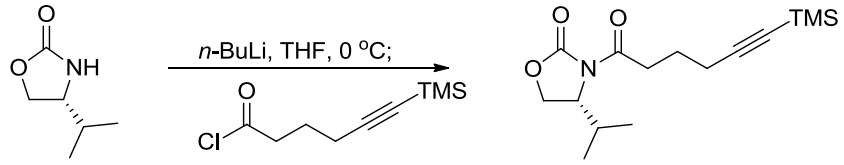
2-19 (10.6 mg, 0.04 mmol) was azeotroped with toluene and dissolved in DCM (0.5 mL) under N_2 in a flame-dried flask. TEA (40 μL, 0.28 mmol), DMAP (1 mg), and TBSCl (30.4 mg, 0.20 mmol) were added and the reaction was stirred for 19 hours at RT. The reaction was directly loaded on a column and the crude material was purified by column chromatography (Hexanes:EtOAc 93:7) to give **2-21** (7.2 mg, 47%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.63 (s, 1H), 5.25 (s, 1H), 5.17-5.11 (m, 1H), 4.35-4.26 (m, 1H), 2.97 (d, *J* = 2.1 Hz, 1H), 2.35-2.31 (m, 2H), 2.03-1.92 (m, 1H), 1.77 (s, 3H), 1.68 (s, 3H), 1.58-1.29 (m, 8H), 1.13 (m, 3H), 0.86 (s, 9H), -0.01 (s, 6H). LRMS (EI+) m/z calculated for $C_{23}H_{41}O_2Si$ $[M+H]^+$: 377.2870, found: 377.3446.



(2*R*,5*Z*,11*Z*)-7-((tert-butyldimethylsilyl)oxy)-2,5,11-trimethyltetradeca-5,11-dien-13-ynal oxime (2-22).

2-21 (7.1 mg, 0.019 mmol) was dissolved in pyridine (300 μL) and hydroxylamine hydrochloride (1.8 mg, 0.025 mmol) was added at RT. The reaction was stirred for 60 minutes and the pyridine was removed *en vacuo*. The crude reaction was directly loaded

on a column and the crude material was purified by column chromatography (Hexanes:EtOAc 80:20) to give **2-22** (1.0 mg, 14%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.77 (d, *J* = 9.9 Hz, 1H), 5.26 (s, 1H), 5.13 (d, *J* = 9.0 Hz, 1H), 4.36-4.28 (m, 1H), 2.99 (s, 1H), 2.37-2.30 (m, 3H), 2.14-1.91 (m, 2H), 1.91 (s, 3H), 1.7* (d, *J* = 1.5 Hz, 3H), 1.50-1.30 (m, 6H), 1.10 (d, *J* = 6.9 Hz, 3G), 0.87 (s, 9H), 0.01 (s, 6H). LRMS (EI+) m/z calculated for $C_{17}H_{26}NO$ $[M\text{-}HOTBS]^+$: 260.2009, found: 260.2027.

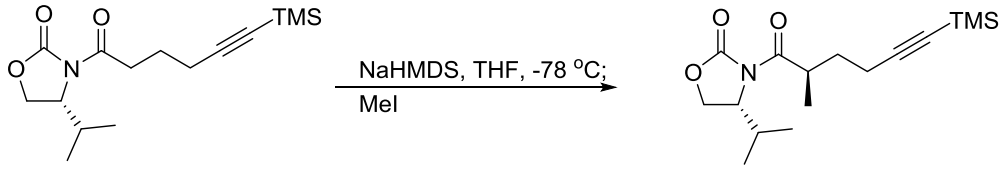


(*R*)-4-isopropyl-3-(6-(trimethylsilyl)hex-5-ynoyl)oxazolidin-2-one (2-28).

Two drops of DMF were added to a solution of 6-(trimethylsilyl)hex-5-ynoic acid[6] (5.27 g, 28.6 mmol) in dry benzene (40 mL) under N_2. To this reaction was added dropwise oxalyl chloride (4.84 mL, 57.2 mmol) and the reaction was stirred at RT for 2 hours. After 2 hours, the reaction was concentrated *en vacuo* and the crude acid chloride was used in the next step without further purification.

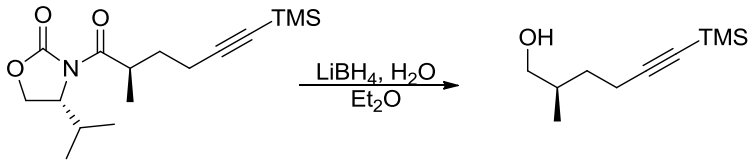
(*R*)-4-isopropyloxazolidin-2-one (2.46 g, 19.1 mmol) was dissolved in THF (24.6 mL) and cooled to 0 °C. *n*-BuLi (11.2 mL, 1.6 M in hexanes) was added dropwise and the reaction was stirred at 0 °C for 5 minutes. 6-(trimethylsilyl)hex-5-ynoyl chloride (28.6 mmol) was added and the reaction was stirred and followed by TLC. After 14 hours, the reaction was quenched with the addition of saturated NH_4Cl (10 mL) and diluted with H_2O (10 mL). The mixture was then extracted 3x with EtOAc (3x 50 mL). The orgs

were dried over Na_2SO_4, filtered and concentrated. The crude material was purified by column chromatography (Hexanes:EtOAc 90:10) to give **2-28** (5.45 g, 97%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.45-4.40 (m, 1H), 4.30-4.18 (m, 2H), 3.14-2.94 (m, 2H), 2.41-2.29 (m, 3H), 1.92-1.82 (m, 2H), 0.92-0.86 (m, 6H), 0.14-0.12 (m, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.8, 154.1, 106.2, 85.6, 63.5, 58.5, 34.4, 28.5, 23.3, 19.3, 18.1, 14.8, 0.2. LRMS (EI+) m/z calculated for $C_{15}H_{25}LiNO_3Si$ $[M+Li]^+$: 302.1758, found: 302.1651.



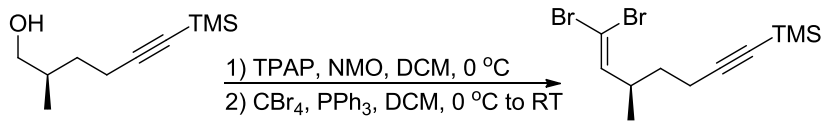
(*R*)-4-isopropyl-3-((*R*)-2-methyl-6-(trimethylsilyl)hex-5-ynoyl)oxazolidin-2-one (2-28a). To a solution of NaHMDS (11.1 mL, 1.0 M in THF) in THF (38 mL) at -78 °C was added **2-28** (2.95 g, 10 mmol) in THF (18 mL) under N_2. The reaction was stirred at -78 °C for 30 minutes and MeI (3.11 mL, 50 mmol) was added dropwise. After addition of MeI, the reaction was stirred for 5 minutes at -78 °C, warmed to -40 °C and stirred for 1.5 hours. Saturated NH_4Cl (15 mL) was added to quench the reaction and the resulting mixture was diluted with H_2O (20 mL). The mixture was extracted 3x with EtOAc (3x 50 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated. The crude material was purified by column chromatography (Hexanes:EtOAc 80:20) to give **2-28a** (2.50 g, 83%, 11:1 dr). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.45-4.42 (m, 1H), 4.26 (t, *J* = 9.0 Hz, 1H), 4.21-4.18 (m, 1H), 3.95-3.84 (m, 1H), 2.36-2.29 (m, 1H), 2.26-2.23 (m, 2H), 2.00-1.93 (m, 1H), 1.64-1.57 (m, 1H), 1.22 (d, *J* = 7.0 Hz, 3H), 0.91-0.86 (m, 6H),

0.13 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.5, 153.6, 106.3, 85.4, 63.4, 58.5, 37.0, 31.6, 28.6, 18.1, 18.0, 17.8, 14.8, 0.2. LRMS (EI+) m/z calculated for $C_{15}H_{27}LiNO_3Si$ $[M+Li]^+$: 316.1915, found: 316.1727.



(*R*)-2-methyl-6-(trimethylsilyl)hex-5-yn-1-ol (2-29).

2-28a (2.51 g, 8.12 mmol) was dissolved in Et_2O (95 mL) under N_2 and H_2O (0.16 mL) was added. The reaction was cooled to 0 ^oC and $LiBH_4$ (0.198 g, 9.1 mmol) was added. The reaction was stirred for 1 hour at 0 ^oC and quenched with the addition of NaOH (10 mL, 1M in H_2O). The reaction was then extracted 3x with Et_2O (3x 10 mL). The organics were dried over $MgSO_4$, filtered and concentrated to give **2-29** (0.997 g, 67%, yields ranged from 67-89%). The material was used without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.53-3.46 (m, 2H), 2.34-2.19 (m, 2H), 1.78-1.72 (m, 1H), 1.69-1.62 (m, 1H), 1.57 (brs, 1H), 1.42-1.35 (m, 1H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.13 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 107.6, 84.7, 67.8, 35.1, 32.1, 17.6, 16.4, 0.3. LRMS (EI+) m/z calculated for $C_{10}H_{21}OSi$ $[M+H]^+$: 185.1356, found: 185.1337.

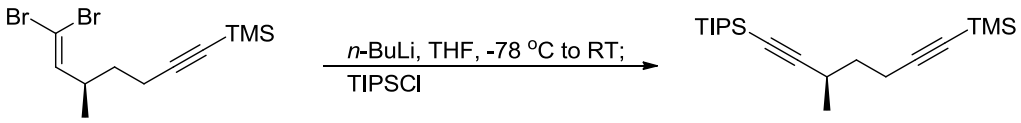


(*R*)-(7,7-dibromo-5-methylhept-6-en-1-yn-1-yl)trimethylsilane (2-30).

To a solution of **2-29** (0.184 g, 1 mmol) in DCM (20 mL) under N_2 was added NMO (0.176 g, 1.5 mmol) and 4Å molecular sieves (0.267 g). The reaction was cooled to 0 °C and stirred for 1 hour. TPAP (10.5 mg, 0.03 mmol) was added and the reaction was stirred for 16 hours. The reaction mixture was filtered through a short pad of silica gel and the silica gel was rinsed with 150 mL of DCM. The organics were concentrated to ~2 mL *en vacuo* due to the high volatility of the aldehyde and used in the next step without further purification.

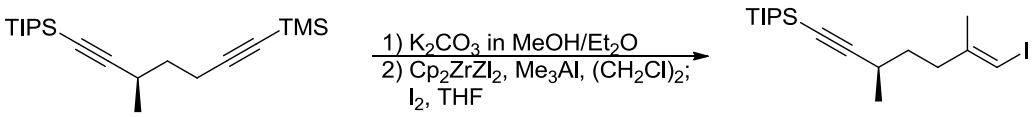
PPh_3 (1.12 g, 4.28 mmol) was added to a solution of CBr_4 (0.71 g, 2.14 mmol) in DCM (7.2 mL) at 0 °C under N_2. The solution was stirred at 0 °C for 10 minutes and **2-29a** (from the previous step in ~1.6 mL of DCM) was added by cannula and the cannula was rinsed with DCM (1.6 mL). The reaction was allowed to warm to RT and stirred for 70 minutes. The reaction was quenched with saturated $NaHCO_3$ (3.6 mL) and the organic layer was separated. The aqueous phase was extracted 3x with DCM (3x 18 mL) and the combined organics were dried over $MgSO_4$, filtered and concentrated. The crude material was purified by column chromatography (100% Hexanes) to give **2-30** (0.1947 g, 58% over 2 steps). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.17 (d, J = 9.5 Hz, 1H), 2.64-2.57 (m, 1H), 2.23 (t, J = 7.0 Hz, 2H), 1.63-1.52 (m, 2H), 1.03 (d, J = 7.0 Hz, 3H), 0.14 (s,

9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.3, 106.7, 88.4, 85.1, 37.7, 35.0, 19.0, 18.0, 0.3. LRMS (EI+) m/z calculated for $C_{11}H_{19}Br_2Si$ $[M+H]^+$: 336.9617, found: Not Observed.



(*R*)-triisopropyl(3-methyl-7-(trimethylsilyl)hepta-1,6-diyn-1-yl)silane (2-30a).

2-30 (0.189 g, 0.558 mmol) was dissolved in THF (4.1 mL) under N_2 and cooled to -78 °C. *n*-BuLi (0.77 mL, 1.6 M in hexanes) was added dropwise and the reaction was stirred for 1 hour at -78 °C. After 1 hour, the reaction was warmed to RT and stirred for 1 hour. The reaction was then cooled to 0 °C and TIPSCl (0.15 mL, 0.725 mmol) was added and the reaction was stirred for 16 hours. Saturated NH_4Cl (6 mL) was added to quench the reaction and the slurry was diluted with water (6 mL). The mixture was then extracted 3x with EtOAc (3x 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude material was purified by column chromatography (100% Hexanes) to give **2-30a** (0.130 g, 70%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.65-2.57 (m, 1H), 2.45-2.33 (m, 2H), 1.68-1.61 (m, 2H), 1.19 (d, J = 7.0 Hz, 3H), 1.08-0.98 (m, 21H), 0.14 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 112.6, 107.1, 84.7, 80.7, 36.0, 26.4, 21.2, 18.8, 18.1, 11.4, 0.30. LRMS (EI+) m/z calculated for $C_{20}H_{39}Si_2$ $[M+H]^+$: 335.2585, found: Not Observed.

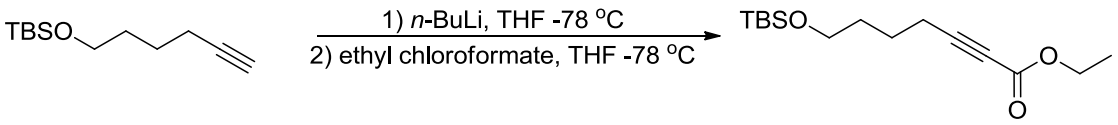


(*R*,*E*)-(7-iodo-3,6-dimethylhept-6-en-1-yn-1-yl)triisopropylsilane (2-25).

2-30a (0.1222 g, 0.365 mmol) was dissolved in Et_2O (0.6 mL) and saturated K_2CO_3 in MeOH (1.2 mL) was added. The reaction was stirred vigorously for 3 hours and quenched with the addition of saturated NH_4Cl (18 mL) and extracted 3x with hexanes (3x 20 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated to give **2-30b** (0.0995 g, 104 %) which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.70-2.57 (m, 1H), 2.43-2.30 (m, 2H), 1.94 (t, *J* = 2.7 Hz, 1H), 1.69-1.59 (m, 2H), 1.20 (d, *J* = 6.9 Hz, 3H), 1.09-0.97 (m, 21H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 112.5, 84.2, 80.8, 68.5, 36.0, 26.3, 21.2, 18.8, 16.7, 11.4.

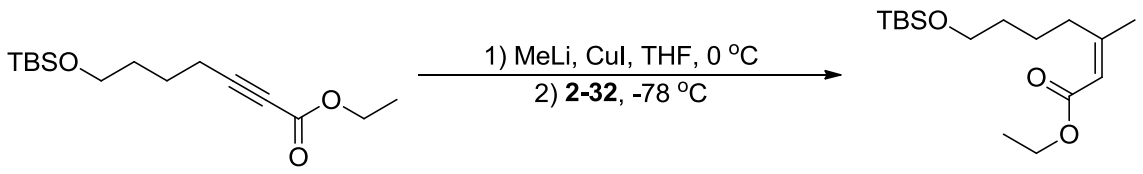
To a suspension of Cp_2ZrCl_2 (0.111 g, 0.38 mmol) in $(CH_2Cl)_2$ (0.5 mL) was added Me_3Al (0.38 mL, 2.0 M in hexanes) under N_2. The reaction was stirred for 15 minutes at which point the mixture became homogeneous. To this solution was added **2-30b** (0.0995 g, 0.38 mmol) in $(CH_2Cl)_2$ (0.5 mL) and the reaction was stirred at RT for 7.5 hours. Then, the reaction was cooled to 0 ^{o}C and I_2 (0.1155 g, 0.46 mmol) in THF (0.6 mL) was added via cannula and the reaction was stirred overnight. The reaction was quenched with the addition of water (1 mL) and saturated NH_4Cl (2 mL) and stirred for 10 minutes. The resulting slurry was filtered through celite and the pad was washed with Et_2O. The mixture was then diluted with water (10 mL) and extracted 3x with Et_2O (3x 20 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated. The crude material was purified by column chromatography (100% Hexanes) to give **2-25**

(0.1111 g, 72%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.92 (s, 1H), 2.47-2.33 (m, 3H), 1.84 (s, 3H), 1.61-1.48 (m, 2H), 1.19 (d, *J* = 7.0 Hz, 3H), 1.07-1.00 (m, 21H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.8, 113.0, 80.7, 75.1, 37.5, 35.3, 26.6, 24.0, 21.4, 19.0, 11.4.



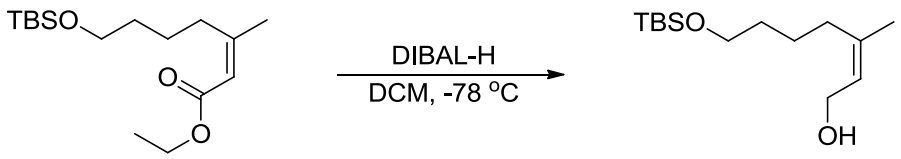
Ethyl 7-((tert-butyldimethylsilyl)oxy)hept-2-ynoate (2-32).

n-BuLi (3.0 mL of 1.6 M in hexanes, 4.76 mmol) was added dropwise to a solution of **2-31** (1.0 g, 4.71 mmol) in THF (4.7 mL) under N_2 at -78 °C. The reaction was stirred at -78 °C for 10 min and cannulated over 15 minutes to a solution of ethyl chloroformate (0.9 mL, 9.4 mmol) in THF (18.8 mL) at -78 °C. The reaction was stirred for 1 hr and quenched with the addition of saturated NH_4Cl (4 mL) and allowed to warm to RT. The reaction was diluted with water (15 mL) and extracted with ether 3x (20 mL). The organics were dried over $MgSO_4$ and concentrated to give **2-32** (1.32 g, 100%). The crude product was used in the next reaction without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.22 (q, *J* = 7.0 Hz, 2H), 3.63 (t, *J* = 6.0 Hz, 2H), 2.36 (t, *J* = 7.0 Hz, 2H), 1.69-1.56 (m, 4H), 1.30 (t, *J* = 7.5 Hz, 2H), 0.89 (s, 9H), 0.04 (s, 6H). The spectra were identical to those reported in the literature.[7]



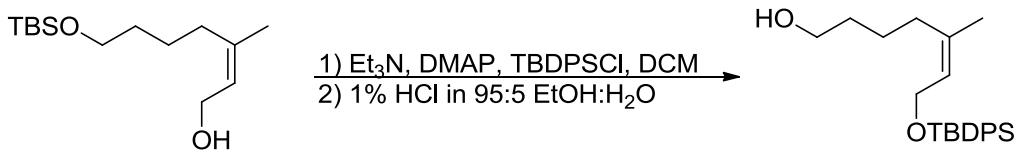
(Z)-ethyl 7-((tert-butyldimethylsilyl)oxy)-3-methylhept-2-enoate (2-32a).

MeLi (11.8 mL, 18.8 mmol) was added slowly to a suspension of CuI (1.79 g, 9.42 mmol) in THF (5 mL) at 0 °C. The mixture was stirred at 0 °C until colorless and homogeneous. The reaction was then cooled to -78 °C and **2-32** (1.34 g, 4.71 mmol) was added. The reaction was then stirred for 1 hr at - 78 °C and quenched with the dropwise addition of a saturated solution of NH_4Cl in 4:1 EtOH:H_2O (10 mL). The reaction was further quenched with 10 mL sat (aq.) NH_4Cl and allowed to warm to RT. Air was then bubbled into the reaction over 1 hr. The reaction was dituled with water (30 mL) and extracted 3x with EtOAc (50 mL). The orgs were dried over $MgSO_4$, filtered and concentrated. The organics were then flashed through a pad of silica gel (hexanes:EtOAc 90:10) to give **2-32a** and used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.65 (s, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.64-3.59 (m, 2H), 2.63 (t, *J* = 7.5 Hz, 2H), 1.87 (d, *J* = 1.2 Hz, 3H), 1.68-1.45 (m, 4H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H).



(Z)-7-((tert-butyldimethylsilyl)oxy)-3-methylhept-2-en-1-ol (3-6).

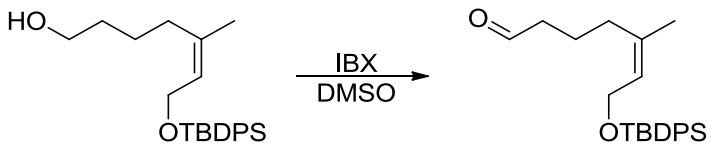
2-32a (4.2 mmol crude from the preveous step) was azeotroped to dryness with toluene and dissolved in DCM (7.5 mL) under N_2. The reaction was cooled to -78 ^{o}C and DIBAL-H (1.0 M in THF) was added dropwise (10.4 mL, 10.4 mmol). The reaction was stirred for 2 hrs and quenched with the careful addition of water (2.5 mL). The mixture was then stirred for 10 minutes and a 15 % solution of NaOH in water (10 mL) was added and the reaction was stirred for an additional 10 minutes. Water was again added (7.5 mL) and the reaction was stirred for 15 minutes, filtered through a plug of celite and dried over $MgSO_4$. The Organic phase was then filtered, concentrated and the material was purified by column chromatography (Hexanes:EtOAc 88:12) to give **3-6** (1.00 g, 82% for 3 steps). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.41 (t, *J* = 8.5 Hz, 1H), 4.11 (d, *J* = 7 Hz, 2H), 3.60 (t, *J* = 6 Hz, 2H), 2.07 (t, *J* = 7.5 Hz, 2H), 1.72 (s, 3H), 1.51-1.39 (m, 4H), 0.88 (s, 9H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.3, 124.4, 63.1, 59.1, 32.6, 31.7, 26.1, 24.6, 23.5, 18.5. LRMS (EI+) m/z calculated for $C_{14}H_{31}O_2Si$ $[M+H]^+$: 259.2088, found: 259.2049.



(*Z*)-7-((tert-butyldiphenylsilyl)oxy)-5-methylhept-5-en-1-ol (2-33a).

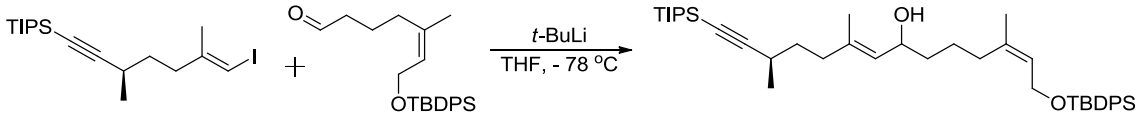
2-32b (1.00 g, 3.88 mmol) was dissolved in DCM (5.2 mL) under N_2 at RT. Et_3N (0.82 mL, 5.82 mmol), DMAP (24 mg, 0.19 mmol), and TBDPSCl (1.26 mL, 4.85 mmol) were added. The reaction was stirred overnight. The reaction was quenched with saturated NH_4Cl (25 mL) and diluted with water (30 mL). The organic phase was separated, dried over $MgSO_4$, filtered and concentrated to give **2-33**. The crude material was used in the next step without further purification.

2-33 (~3.88 mmol) was dissolved in a 1% HCl solution in 95:5 EtOH:H_2O (25 mL). The reaction was stirred for 20 minutes and quenched with the careful addition of saturated $NaHCO_3$ (25 mL) and diluted with water (30 mL). The mixture was extracted 3x with EtOAc (3x 50 mL). The organics were dried over $MgSO_4$, filtered and concentrated. The crude material was purified by column chromatography (Hexanes:EtOAc 85:15 to 80:20) to give **2-33a** (1.41 g, 95%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71-7.69 (m, 4H), 7.45-7.37 (m, 6H), 5.42 (t, *J* = 6.5 Hz, 1H), 4.20 (d, *J* = 7.5 Hz, 2H), 3.55 (t, *J* = 6.5 Hz, 2H), 1.89 (t, *J* = 7.5 Hz, 2H), 1.71-1.70 (m, 3H), 1.46-1.31 (m, , 4H), 1.05 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.7, 135.7, 134.1, 129.6, 127.7, 125.0, 62.9, 60.8, 32.5, 31.8, 27.0, 24.2, 23.4, 19.3. LRMS (EI+) m/z calculated for $C_{24}H_{36}O_2Si$ $[M+H]^+$: 383.2401, found: Not Observed.



(*Z*)-7-((tert-butyldiphenylsilyl)oxy)-5-methylhept-5-enal (2-26).

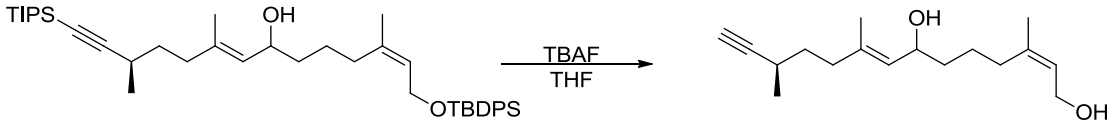
2-33a (200 mg, 0.52 mmol) was dissolved in DMSO (2.6 mL) and IBX (0.366 g, 1.31 mmol) was added. The reaction was stirred for 14 hours and quenched with the addition of water (3.5 mL). The slurry was stirred for 15 minutes and filtered through celite and the celite plug was washed with EtOAc. After concentration, the crude material was purified by column chromatography (Hexanes:EtOAc 95:5) to give **2-26** (0.158 g, 80%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.67 (t, *J* = 1.8 Hz, 1H), 7.74-7.68 (m, 4H), 7.46-7.36 (m, 6H), 5.45 (t, *J* = 6.6 Hz, 1H), 4.17 (d, *J* = 6.6 Hz, 2H), 2.28 (dt, *J* = 1.5, 7.5 Hz, 2H), 1.90 (t, *J* = 7.2 Hz, 2H), 1.70 (s, 3H), 1.66-1.56 (m, 2H), 1.05 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.4, 136.7, 135.7, 134.0, 129.7, 127.9, 127.8, 125.9, 60.7, 43.4, 31.2, 27.0, 23.2, 20.3, 19.3.



(2*Z*,8*E*,12*R*)-1-((tert-butyldiphenylsilyl)oxy)-3,9,12-trimethyl-14-(triisopropylsilyl)tetradeca-2,8-dien-13-yn-7-ol (2-34).

2-25 (0.111g, 0.275 mmol) and **2-26** (0.0954 g, 0.25 mmol) were combined in a flame-dried flask and azeotroped with benzene and placed under N_2. The material was dissolved in THF (2.5 mL) and cooled to -78 °C. To this solution was added *t*-BuLi (0.55

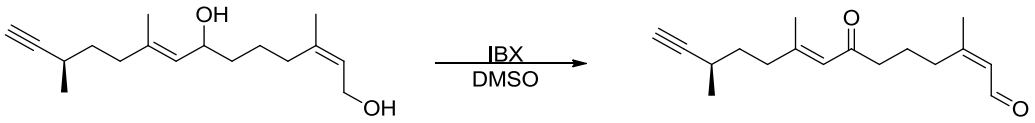
mL, 1.1 M in hexanes, 0.6 mmol) and the reaction was stirred for 45 minutes. The reaction was quenched with the addition of saturated NH_4Cl at -78 ^oC and the reaction was slowly warmed to RT. The slurry was then diluted with water (10 mL) and the mixture was extracted 3x with EtOAc (3x 20 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated. The crude material was purified by column chromatography (Hexanes:EtOAc 90:10) to give **2-34** (0.1169 g, 71%, 3.4:1 dr). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.73-7.67 (m, 4H), 7.45-7.35 (m, 6H), 5.41(t, *J* = 6.3 Hz, 1H), 5.17-5.13 (m, 1H), 4.31-4.23 (m, 1H), 4.19 (d, *J* = 7.8 Hz, 2H), 2.47-2.38 (m, 1H), 2.26-2.03 (m, 3H), 1.87 (t, *J* = 7.5 Hz, 2H), 1.69-1.69 (m, 3H), 1.64 (t, *J* = 1.5 Hz, 3H), 1.56-1.43 (m, 2H), 1.35-1.23 (m, 3H), 1.22 (d, *J* = 6.9 Hz, 3H), 1.09-1.02 (m, 30H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.6, 138.5, 137.7, 137.7, 135.8, 134.1, 129.6, 128.3, 128.1, 127.7, 125.1, 113.6, 113.5, 68.6, 60.8, 37.5, 37.4, 35.5, 35.4, 32.2, 32.0, 31.7, 27.0, 26.8, 26.7, 25.8, 25.6, 23.9, 23.5, 23.4, 21.5, 21.4, 19.3, 18.8, 16.8, 16.6, 11.4.



(2*Z*,8*E*,12*R*)-3,9,12-trimethyltetradeca-2,8-dien-13-yne-1,7-diol (2-34a).

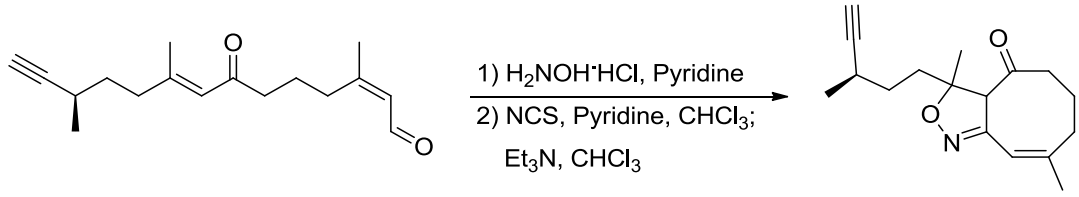
2-34 (0.1169 g, 0.177 mmol) was dissolved in THF (0.1 mL) at RT and TBAF (0.885 mL, 1.0 M in THF) was added. The reaction was stirred for 90 minutes and quenched with 1/3 saturated NaCl (3 mL). The mixture was extracted 3x with EtOAc (3x 20 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated. The crude

material was purified by column chromatography (Hexanes:EtOAc 60:40) to give **2-34a** (7.2 mg, 15%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.44 (t, *J* = 8.5 Hz, 1H), 5.21-5.18 (m, 1H), 4.39-4.34 (m, 1H), 4.15-4.08 (m, 2H), 2.44-2.37 (m, 1H), 2.22-2.07 (m, 3H), 2.05 (d, *J* = 1.5 Hz, 1H), 1.7.-1.73 (m, 3H), 1.69 (t, *J* = 1.0 Hz, 3H), 1.58-1.52 (m, 3H), 1.46-1.37 (m, 4H), 1.20 (d, *J* = 6.5 Hz, 3H).



(*R*,2*Z*,8*E*)-3,9,12-trimethyl-7-oxotetradeca-2,8-dien-13-ynal (2-35).

2-34a (7.2 mg, 0.0277 mmol) was dissolved in DMSO (1 mL) at RT and IBX (23.2 mg, 0.0762 mmol) was added. The reaction was stirred for 17 hours and the DMSO was pulled off *en vacuo*. The crude material was purified using a pipette silica gel column (Hexanes:EtOAc 90:10) to give **2-35** (6.8 mg, 95%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.93 (d, *J* = 8.0 Hz, 1H), 6.06 (s, 1H), 5.90 (d, *J* = 8.5 Hz, 1H), 2.59 (t, *J* = 7.5 Hz, 2H), 2.48 (t, *J* = 7.0 Hz, 2H), 2.45-2.40 (m, 1H), 2.37-2.31 (m, 1H), 2.25-2.19 (m, 1H), 2.14 (s, 3H), 2.08 (d, *J* = 2.0 Hz, 1H), 1.99 (s, 3H), 1.88-1.82 (m, 2H), 1.62-1.57 (m, 2H), 1.21 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 190.9, 159.1, 158.8, 129.0, 123.3, 88.2, 69.2, 43.2, 39.0, 34.6, 31.9, 25.6, 25.0, 22.8, 21.1, 19.6, 18.8.



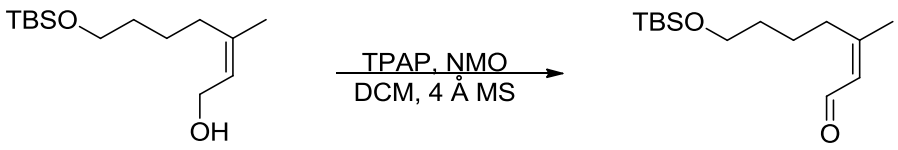
(*Z*)-3,8-dimethyl-3-((*R*)-3-methylpent-4-yn-1-yl)-3,3a,6,7-tetrahydrocycloocta[c]isoxazolin-4(5H)-one (2-37).

2-35 (6.8 mg, 0.026 mmol) was dissolved in pyridine (1 mL) and $H_2NOH{\cdot}HCl$ (2.8 mg, 0.031 mmol) was added at RT. the reaction was stirred for 30 minutes and the pyridine was removed *en vacuo*. The residue was then partitioned between EtOAc (5 mL) and water (3 mL). The organic phase was removed and the aqueous phase was extracted 1x with EtOAc (1x 10 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated to give **2-24** (6.8 mg, 95% yield).

2-24 (6.8 mg, 0.0247 mmol) was dissolved in $CHCl_3$ (0.1 mL) and NCS (3.4 mg, 0.0247 mmol) was added. To this solution was added pyridine (40 μL) and the reaction was stirred for 20 minutes. The reaction was diluted with $CHCl_3$ (9.7 mL) and Et_3N (35 μL) was added. The reaction was stirred for 6.5 hours and quenched with the addition of saturated $NaHCO_3$ (15 mL). The mixture was diluted with DCM (5 mL) and the organic phase was separated. The aqueous phase was extracted 3x with DCM (3x 25 mL) and the combined organics were dried over Na_2SO_4, filtered and concentrated. The crude material was purified using a pipette silica gel column (Hexanes:EtOAc 90:10) to give **2-37** (2.2 mg, 30%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.45 (s, 1H), 3.84-3.82 (m, 1H), 3.08-2.87 (m, 1H), 2.51-2.28 (m, 4H), 2.15-2.08 (m, 2H), 2.07-2.05 (m, 1H), 1.97 (s, 3H),

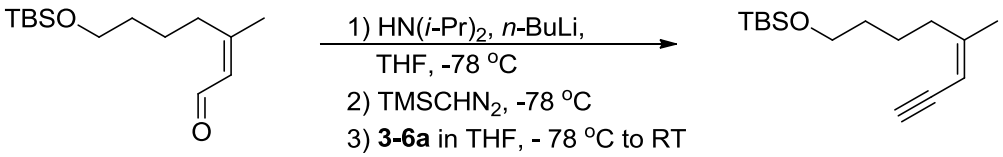
1.95-1.88 (m, 2H), 1.50-1.39 (m, 2H), 1.23-1.20 (m, 3H), 1.19 (s, 3H). LRMS (EI+) m/z calculated for $C_{17}H_{23}NO_2$ $[M+H]^+$: 274.1802, found: 274.1636.

CHAPTER III



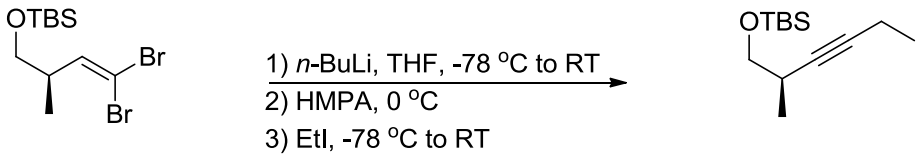
(Z)-7-((tert-butyldimethylsilyl)oxy)-3-methylhept-2-enal (3-6a).

3-6 (0.41 g, 1.58 mmol) was dissolved under N_2 in DCM (32 mL) at RT and NMO (0.28 g, 2.4 mmol) and 4 Å molecular sieves (0.44 g) were added. The reaction was cooled to 0 ^oC and the reaction was stirred for 1 hr. TPAP (16.7 mg, 0.048 mmol) was added and the reaction was stirred for 15 hrs and flashed over a silica gel plug (Hexanes:EtOAc 80:20) until all product was off. The product was concentrated to give **3-6a** (0.405 g, 100 %) and was used in the next step without further purification. ^1H NMR ($CDCl_3$, 500 MHz) δ 9.95 (d, *J* = 8.0 Hz, 1H), 5.88 (d, *J* = 8.0 Hz, 1H), 3.63 (t, *J* = 6.0 Hz, 2H), 2.59 (t, *J* = 7 Hz, 2H), 1.97 (s, 3H), 1.65-1.52 (m, 4H), 0.88 (s, 9H), 0.04 (s, 6H).^{13}C NMR ($CDCl_3$, 125 MHz) δ 190.7, 160.6, 128.5, 62.6, 32.4, 32.3, 25.9, 25.1, 24.9, 18.3, 0.0.



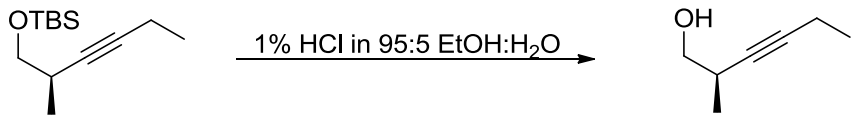
(Z)-tert-butyldimethyl((5-methyloct-5-en-7-yn-1-yl)oxy)silane (3-4).

Diisopropylamine (0.13 mL, 0.94 mmol) was dissolved in THF (6.2 mL) under N_2 and cooled to -78 °C. *n*-BuLi (1.6 M in hexanes, 0.59 mL, 0.94 mmol) was added dropwise and the reaction was stirred for 15 minutes. Trimethylsilyldiazomethane (2.0 M in hexanes, 0.47 mL, 0.94 mmol) was added dropwise and the mixture was stirred at -78 °C for 30 minutes. **3-6a** (0.2 g, 0.78 mmol) in THF (1.6 mL) was added dropwise and the reaction was left to slowly warm to RT over the course of an hour. After 10 minutes at RT the reaction was quenched with water (6 mL) and stirred for 10 minutes. The mixture was then extracted 3x with EtOAc (25 mL). The organics were dried over $MgSO_4$, filtered and concentrated. The material was purified by column chromatography (Hexanes:EtOAc 97:3) to give **3-4** (120 mg, 50% for 2 steps). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.26 (s, 1H), 3.63 (t, *J* = 6.0 Hz, 2H), 2.96 (s, 1H), 2.34 (t, *J* = 7.5 Hz, 2H), 1.79 (d, *J* = 1 Hz, 3H), 1.57-1.48 (m, 4H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.7, 104.6, 81.8, 79.3, 63.0, 34.4, 32.5, 26.1, 23.8, 22.5, 18.5, 0.2. LRMS (EI+) m/z calculated for $C_{15}H_{29}OSi$ $[M+H]^+$: 253.1988, found: 253.1925.



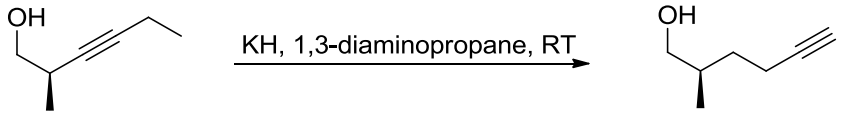
(±)-tert-butyldimethyl((2-methylhex-3-yn-1-yl)oxy)silane (3-7).

3-5 (0.25 g, 0.7 mmol) was dissolved in THF (6.5 mL) and cooled to -78 °C under N_2. *n*-BuLi (0.96 mL, 1.54 mmol, 1.6 M in hexanes) was added dropwise and the reaction was stirred at -78 °C for 1 hour. The reaction was then stirred at RT for 1 hour. The reaction was cooled to 0 °C and HMPA (0.24 mL, 1.4 mmol) was added. The reaction was cooled to -78 °C and ethyl iodide (0.28 mL, 3.5 mmol) was added and the reaction was stirred for 6 hours while warming to RT. The reaction was quenched with sat. NH_4Cl (1 mL) and diluted with water. The mixture was then extracted 3x with EtOAc (30 mL) and the organics were dried over $MgSO_4$, filtered and concentrated. The material was purified by column chromatography (Hexanes:EtOAc 96:4) to give **3-7** (113 mg, 71%).^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.67-3.64 (m, 1H), 3.41-3.38 (m, 1H), 2.55-2.50 (m, 1H), 2.18-2.13 (m, 2H), 1.13-1.09 (m, 6H), 0.89 (s, 9H), 0.06 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 82.6, 81.5, 67.6, 29.1, 25.9, 26.0, 18.6, 17.7, 14.3, 12.4. LRMS (EI+) m/z calculated for $C_{13}H_{26}LiOSi$ $[M+H]^+$: 233.1913, found: 233.2026



(±)-hex-3-yn-2-ol (3-7a).

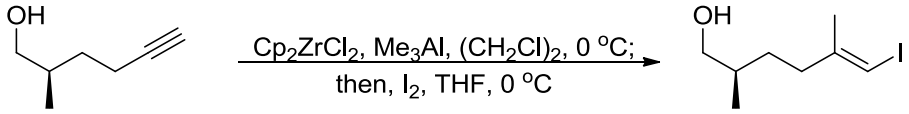
3-7 (0.46 g, 2.0 mmol) was dissolved in 1% HCl in 95:5 EtOH:H_2O (29 mL). The reaction was stirred for 20 minutes and quenched with sat. $NaHCO_3$ (20 mL). The mixture was diluted with H_2O (50 mL) and extracted 3x with ether (70 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated to give 0.39 g of **3-7a**. The material was used in the next step without purification.



(±)-2-methylhex-5-yn-1-ol (3-8).

In a glovebox, a flask was charged with KH (0.97 g) that had been washed with hexanes to rid the KH of mineral oil. This flask was taken from the glovebox and placed under N_2 on a Schlenk line. 1,3-Diaminopropane (20.2 mL) was added to the flask and the reaction was heated with a heat gun until foaming occurred. The reaction was then stirred at RT for 1 hour. **3-7a** (~2.0 mmol from previous step) in 1 mL of 1,3 diaminopropane was added to the reaction at RT and the reaction was stirred for 19 hours with monitoring by NMR. After NMR indicated the reaction was complete, the reaction was cooled to 0 ^oC and quenched with the careful addition of sat. NH_4Cl (20 mL). The mixture was diluted with H_2O (20 mL) and extracted 3x with EtOAc (50 mL).

The organics were dried over $MgSO_4$, filtered and concentrated. The material was purified by column chromatography (Hexanes:EtOAc 60:40) to give **3-8** (158 mg, 70% for 2 steps). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.54-3.46 (m, 2H), 2.32-2.18(m, 2H), 1.94 (t, *J* = 3.0 Hz, 1H), 1.82-1.76 (m, 1H), 1.72-1.65 (m, 1H), 1.46 (brs, 1H), 1.41-1.34 (m, 1H), 0.94 (d, *J*= 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 84.6, 68.5, 67.8, 34.9, 31.9, 16.3, 16.2. LRMS (EI+) m/z calculated for $C_7H_{13}O$ $[MH+]^+$: 113.0961, found: 113.1089.



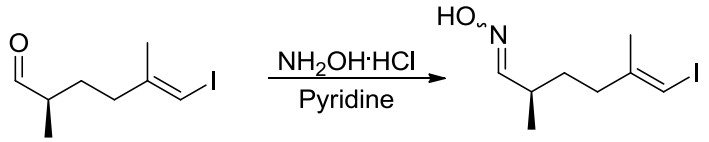
(±)-(*E*)-6-iodo-2,5-dimethylhex-5-en-1-ol (3-8a).

Cp_2ZrCl_2 (0.39 g, 1.3 mmol) was dissolved in $(CH_2Cl)_2$ (2 mL) under N_2 and Me_3Al (2.0 M in toluene, 1.9 mL, 3.8 mmol) was added at RT. The reaction was stirred for 15 minutes and **3-8** (0.15 g, 1.3 mmol) in $(CH_2Cl)_2$ (0.4 mL) was added dropwise at 0 °C. The reaction was stirred and allowed to warm to RT over 2 hours. After TLC indicated carbometallation was complete, the reaction was cooled to 0 °C and I_2 (0.42 g, 1.66 mmol) in THF (2 mL) was added dropwise. The reaction was warmed to RT and stirred for 10 minutes. The reaction was quenched with the dripwise addition of NH_4Cl (20 mL). Water (10 mL) was then added and the mixture was extracted 3x with diethyl ether (3x 50 mL). The organics were dried over $MgSO_4$, filtered and concentrated. The material was then flashed over a short silica gel plug to remove inorganic impurities (Hexanes:Et_2O 40:60). The material was then concentrated and used in the next step without further purification. Yields varied from 76 - 34%. ^{1}H NMR ($CDCl_3$, 500 MHz) δ

5.90-5.89 (m, 1H), 3.53-3.44 (m, 2H), 2.31-2.18 (m, 1H), 1.84 (d, *J* = 1.0 Hz, 3H), 1.63 - 1.56 (m, 2H), 1.28-1.21 (m, 2H), 0.93 (d, *J* = 6.5 Hz, 3H).

(±)-(*E*)-6-iodo-2,5-dimethylhex-5-enal (3-8b).

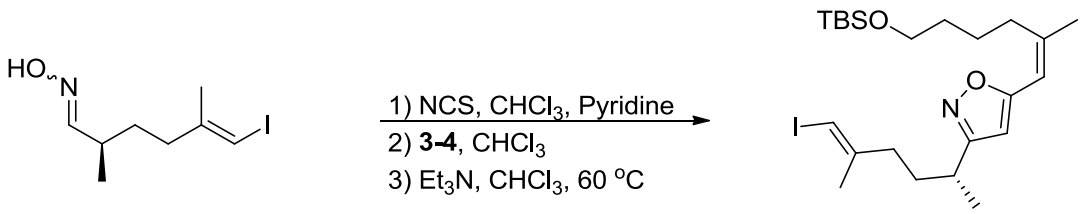
3-8a (1.20 g, 4.71 mmol) was dissolved in DMSO (87 mL) and IBX (1.98 g, 7.07 mmol) was added. The reaction was stirred for 15 hours and quenched with the addition of H_2O (100 mL) and stirred for 8 minutes. The slurry was filtered over a pad of celite and the celite was rinsed wit ether (100 mL). The filtrate was diluted with brine (20 mL) and the organic phase was removed. The aqueous phase was extracted with ether (75 mL) and the organics were combined, dried over Na_2SO_4, filtered and concentrated. The material was used for the next step without further purification.



(±)-(5*E*)-6-iodo-2,5-dimethylhex-5-enal oxime (3-3).

3-8a (~1.20 g, 4.71 mmol) was dissolved in pyridine (13 mL) and $NH_2OH{\cdot}HCl$ (0.43 g, 6.12 mmol) was added at RT. The reaction was stirred for 30 minutes and poured into ether (12 mL). The organic mixture was washed with a saturated solution of $CuSO_4$ and

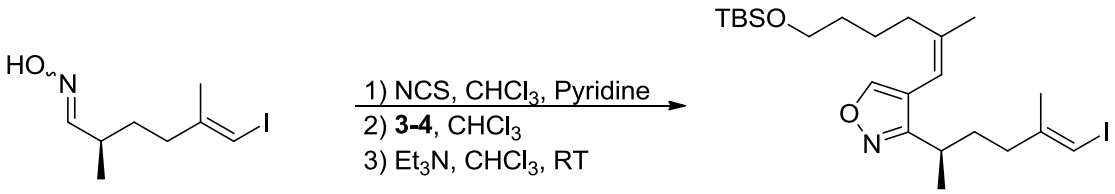
water. The organic phase was then dried over Na_2SO_4, filtered and concentrated to give **3-3** (1.17 g, 95% yield for 2 steps). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 (d, *J* = 6.9 Hz, 0.8H), 6.49 (d, *J* = 7.8 Hz, 0.2H) 5.92-5.90 (m, 1H), 2.39-2.30 (m, 1H), 1.84-1.83 (m, 3H), 2.23 (t, *J* = 7.2 Hz, 2H), 1.67-1.25 (m, 2H), 1.25 (brs, 1H), 1.10-1.08 (d, *J* = 6.9 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.9, 155.9, 147.4, 75.4, 37.3, 37.0, 34.0, 32.8, 32.6, 29.8, 29.1, 24.0, 18.1, 17.6. LRMS (EI+) m/z calculated for $C_8H_{15}INO_2$ $[M+H]^+$: 268.0193, found: 268.0240.



(±)-5-((*Z*)-6-((tert-butyldimethylsilyl)oxy)-2-methylhex-1-en-1-yl)-3-((*E*)-6-iodo-5-methylhex-5-en-2-yl)isoxazole (3-2a).

3-3 (1.17 g, 4.38 mmol) was dissolved in $CHCl_3$ (2.8 mL) and added dropwise to a solution of NCS (0.585 g, 4.38 mmol) and pyridine (7 μL, 0.09 mmol) in $CHCl_3$ (2.8 mL). The reaction was stirred until the solid disappeared (~20 minutes) and **3-4** (1.33 g, 5.3 mmol) in $CHCl_3$ (2.8 mL) was added in one portion. A solution of Et_3N (0.62 mL, 4.38 mmol) in $CHCl_3$ (11.4 mL) was added slowly and the reaction was heated to 60 °C overnight. The reaction was then cooled to RT and washed with water, $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4, filtered and concentrated. The material was purified by column chromatography (Hexanes:EtOAc 90:10) to give **3-2a** (1.01 g,

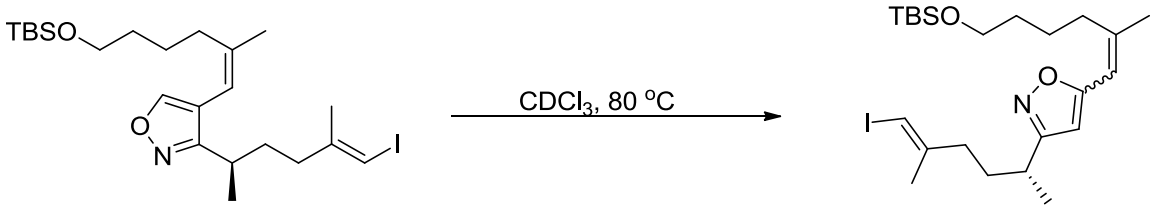
45%).[1]H NMR ($CDCl_3$, 300 MHz) δ 6.11 (s, 1H), 5.88-5.87 (m, 2H), 3.65-3.61 (m, 2H), 2.91-2.83 (m, 1H), 2.49-2.42 (m, 2H), 2.24-2.14 (m, 2H), 1.93 (d, *J* = 1.2 Hz, 3H), 1.82 (d, *J* = 1.2 Hz, 3H), 1.80-1.68 (m, 2H), 1.60-1.51 (m, 4H), 1.27 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H). [13]C NMR ($CDCl_3$, 75 MHz) δ 168.7, 167.8, 147.8, 147.5, 112.0, 99.6, 75.3, 63.0, 37.2, 34.4, 34.3, 33.6, 32.6, 31.3, 26.1, 24.6, 24.2, 24.1, 20.2, 18.5, -5.1. LRMS (EI+) m/z calculated for $C_{23}H_{41}INO_2Si$ $[M+H]^+$: 518.1951, found: 518.1999.



(±)-4-((*Z*)-6-((tert-butyldimethylsilyl)oxy)-2-methylhex-1-en-1-yl)-3-((*E*)-6-iodo-5-methylhex-5-en-2-yl)isoxazole (3-2b).

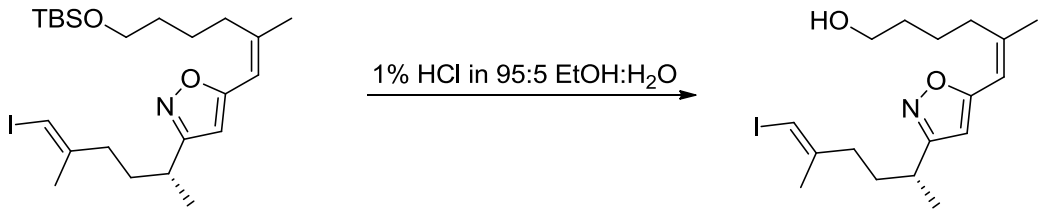
3-3 (134 mg, 0.51 mmol) was dissolved in $CHCl_3$ (0.33 mL) and added dropwise to a solution of NCS (68 mg, 0.51 mmol) and pyridine (1 μL, 0.01 mmol) in $CHCl_3$ (0.33 mL). The reaction was stirred until the solid disappeared (~20 minutes) and **3-4** (0.154 g, 0.61 mmol) in $CHCl_3$ (0.33 mL) was added in one portion. A solution of Et_3N (72 μL, 0.51 mmol) in $CHCl_3$ (1.3 mL) was added slowly and the reaction was stirred overnight at RT. The reaction was then washed with water, $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4, filtered and concentrated. The material was purified by column chromatography (Hexanes:EtOAc 80:20) to give **3-2b** (0.125 g, 47%).[1]H NMR ($CDCl_3$, 300 MHz) δ 8.02 (brs, 1H), 5.90-5.88 (m, 1H), 5.23 (d, *J* = 1.5 Hz, 1H), 3.64-3.60 (m,

2H), 2.61-2.37 (m, 3H), 2.19 (t, *J* = 7.5 Hz, 2H), 1.86 (d, *J* = 1.2 Hz, 3H), 1.82 (d, *J* = 0.9 Hz, 3H), 1.81-1.69 (m, 1H), 1.57-1.50 (m, 5H), 1.17 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.6, 148.1, 147.5, 104.7, 100.6, 75.3, 63.1, 38.8, 38.1, 37.2, 35.2, 32.8, 32.7, 32.4, 26.1, 24.1, 23.9, 23.0, 19.0, 18.5. LRMS (EI+) m/z calculated for $C_{23}H_{41}INO_2Si$ $[M+H]^+$: 518.1951, found: 518.2119.



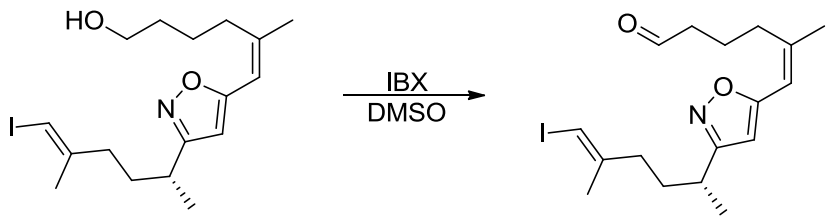
Thermal Isomerization of 3-2b to 3-2a.

3-2b (8.3 mg, 0.016 mmol) was dissolved in $CDCl_3$ (0.7 mL) and placed in an NMR tube. The tube was wrapped thoroughly with parafilm. The reaction was heated to 80 °C and followed by NMR. Analysis by NMR indicated that conversion of **3-2b** to **3-2a** was complete after 92 hours. Also, it was observed that olefin isomerization occurred with a distribution of 3:1 desired to undesired. TLC analysis indicated that the olefin isomers were inseparable.



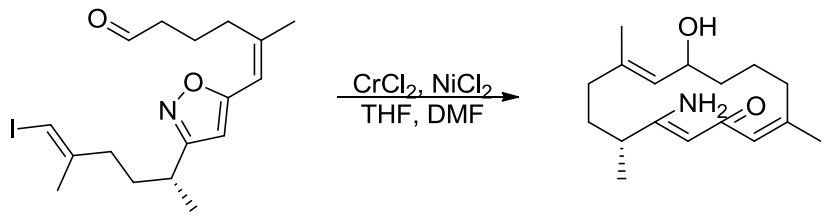
(±)-(*Z*)-6-(3-((*E*)-6-iodo-5-methylhex-5-en-2-yl)isoxazol-5-yl)-5-methylhex-5-en-1-ol (3-2ab).

3-2a (0.125 g, 0.24 mmol) was dissolved in 3.3 mL of 1% HCl in 95:5 EtOH:$H_2O$and the reaction was stirred for 20 minutes. The reaction was quenched with the addition of saturated $NaHCO_3$ (1.5 mL) and diluted with water (7 mL). The aqueous phase was extracted 3x with EtOAc (3x 20 mL) and the organics were dried over Na_2SO_4, filtered, and concentrated. The crude material was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.10 (s, 1H), 5.89-5.87 (m, 2H), 3.71-3.67 (m, 2H), 2.90-2.83 (m, 1H), 2.49-2.45 (m, 2H), 2.23-2.13 (m, 2H), 1.94 (d, *J* = 1.2 Hz, 3H), 1.81 (d, *J* = 0.9 Hz, 3H), 1.79-1.68 (m, 3H), 1.66-1.55 (m, 6H), 1.26 (d, *J* = 7.2 Hz, 3H).



(±)-(*Z*)-6-(3-((*E*)-6-iodo-5-methylhex-5-en-2-yl)isoxazol-5-yl)-5-methylhex-5-enal (3-9).

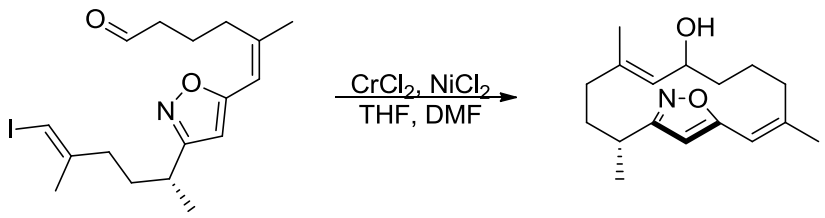
3-2ab (0.24 mmol from the previous step) was dissolved in DMSO (0.7 mL) and IBX (102 mg, 0.36 mmol) was added. The reaction was stirred for 20 hours and quenched with the addition of water (2 mL). The slurry was stirred for 15 minutes and then filtered over celite. The celite was washed 3x with EtOAc (3x 10 mL). The filtrate was dried over $MgSO_4$ and concentrated. The material was purified by column chromatography (first neutralization with 1% Et_3N in Hexanes, then the column was run in Hexanes:EtOAc 85:15) to give **3-9** (84 mg, 87% for 2 steps). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.80-9.79 (m, 1H), 6.13(s, 1H), 5.98 (s, 1H), 5.87 (s, 1H), 2.91-2.84 (m, 1H), 2.56-2.45 (m, 4H), 2.26-2.13 (m, 2H), 2.94 (s, 3H), 1.90-1.65 (m, 4H), 1.81 (s, 3H), 1.27 (d, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.2, 168.3, 138.0, 147.5, 146.3, 112.6, 100.1, 75.3, 43.6, 37.2, 34.2, 33.3, 31.2, 24.9, 24.1, 20.2, 20.1. LRMS (EI+) m/z calculated for $C_{17}H_{25}INO_2$ $[M+H]^+$: 402.0924, found: 402.1143.



(±)-(2*Z*, 7*E*,13*Z*)-3-amino-9-hydroxy-4,7,13-trimethylcyclotetradeca-2,7,13-trienone (3-10).

In a glovebox, $CrCl_2$ (0.255 g, 2.09 mmol) and $NiCl_2$ (2.7 mg, 0.021 mmol) were combined in a flame-dried flask. The flask was placed under N_2 on a Schlenk line. THF (0.24 mL) was added to the mixture of $CrCl_2$ and $NiCl_2$. **3-9** (84 mg, 0.21 mmol) was dissolved in DMF (21 mL) and the resulting solution was cannulated at RT to the flask containing $CrCl_2$, $NiCl_2$, and THF. The reaction was then stirred at RT for 20 hours and quenched with the addition of a potassium serinante solution (7 mL).[viii] The reaction was stirred for 1 hour and the DMF was removed *in vacuo*. The resulting solids were partitioned between 50 mL of water and 125 mL EtOAc. The organic phase was separated and the aqueous phase was extracted 2x with EtOAc (2x 125). The combined organics were dried over Na_2SO_4, filtered and concentrated. The material was purified by column chromatography (Hexanes:EtOAc 50:50 to 40:60) to give **3-10** (7 mg, 12% as a 1:1.5 mixture of diastereomers). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.95 (brs, 1H), 5.75 (s, 0.6 H), 5.72 (s, 0.4H), 5.39 (d, *J* = 8.1 Hz, 0.4 H), 5.24 (d, *J* = 8.7 Hz, 0.6H), 5.13 (s, 0.6H), 5.11 (s, 0.4H), 4.99 (brs, 1H) 4.44-4.35 (m, 1H), 22.55-1.96 (m, 4H), 1.93-1.45 (m, 7H), 1.78-1.77 (m, 3H), 1.72 (s, 1.2H), 1.65 (s, 1.8 H), 1.33 (brs, 1H), 1.18-1.15 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 193.23, 193.17, 169.5, 168.1, 144.2, 144.1, 139.8,

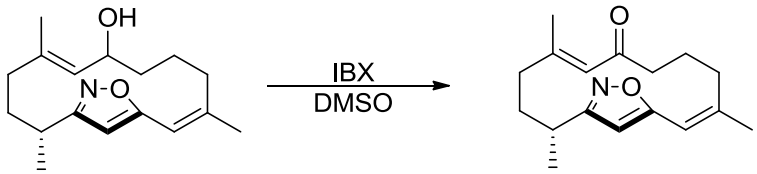
139.5, 129.8, 129.3, 129.2, 129.1, 97.1, 96.7, 67.9, 67.2, 45.9, 41.2, 40.2, 39.1, 37.0, 36.8, 36.4, 35.2, 33.6, 31.7, 31.0, 24.4, 24.1, 23.3, 21.7, 15.5, 8.8. LRMS (EI+) m/z calculated for $C_{17}H_{28}NO_2$ $[M+H]^+$: 278.2115, found: 278.2467.



(±)-(5*E*,11*Z*)-2,5,11-trimethyl-14-oxa-15-azabicyclo[11.2.1]hexadeca-1(15),5,11,13(16)-tetraen-7-ol (3-11).

In a glovebox, $CrCl_2$ (46 mg, 0.37 mmol) and $NiCl_2$ (~1 mg, 0.008 mmol) were combined in a flame-dried flask. The flask was placed under N_2 on a Schlenk line. THF (84 μL) was added to the mixture of $CrCl_2$ and $NiCl_2$. **3-9** (30 mg, 0.075 mmol) was dissolved in DMF (7.5 mL) and the resulting solution was cannulated at RT to the flask containing $CrCl_2$, $NiCl_2$, and THF. The reaction was then stirred at RT for 21 hours and quenched with the addition of a potassium serinante solution (2.5 mL).[ix] The reaction was stirred for 1 hour and the DMF was removed *in vacuo*. The resulting solids were partitioned between 18 mL of water and 45 mL EtOAc. The organic phase was separated and the aqueous phase was extracted 2x with EtOAc (2x 45). The combined organics were dried over Na_2SO_4, filtered and concentrated. The material was purified by column chromatography (Hexanes:EtOAc 70:30 to 50:50) to give **3-11** (4.7 mg, 23% as a 1:2.1 mixture of diastereomers). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.09 (s, 0.3 H), 6.06 (s, 0.7H),

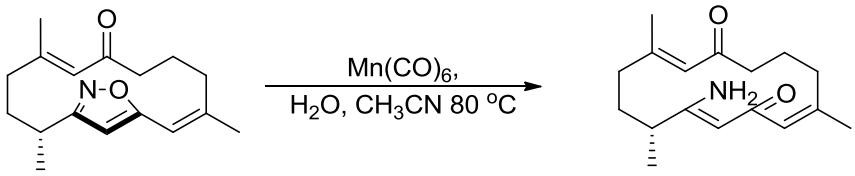
6.00 (s, 0.3H), 5.91 (s, 0.7H) 5.13 (d, *J* = 9.0 Hz 0.3H), 5.03 (d, *J* = 9.0 Hz, 0.7 H), 4.32-4.19 (m, 1H), 3.11-3.00 (m, 0.3H), 2.92-2.81 (m, 0.7H), 2.52-2.31 (m, 1H), 2.19-1.64 (m, 5H), 1.92-1.90 (m, 3H), 1.52 (s, 2.1 H), 1.47 (s, 0.9 H), 1.45-1.15 (m, 4H), 1.30-1.26 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.9, 167.7, 149.0, 148.5, 140.1, 139.5, 128.3, 127.5, 112.3, 112.1, 101.4, 101.2, 68.1, 68.0, 39.0, 36.9, 36.6, 35.1, 34.3, 34.1, 33.9, 32.9, 32.2, 32.1, 26.1, 25.9, 22.6, 22.3, 21.7, 20.1, 17.8, 15.9. LRMS (EI+) m/z calculated for $C_{17}H_{24}NO$ $[M-H_2O]^+$: 258.1852, found: 258.2101.



(±)-(5*E*,11*Z*)-2,5,11-trimethyl-14-oxa-15-azabicyclo[11.2.1]hexadeca-1(15),5,11,13(16)-tetraen-7-one (3-12).

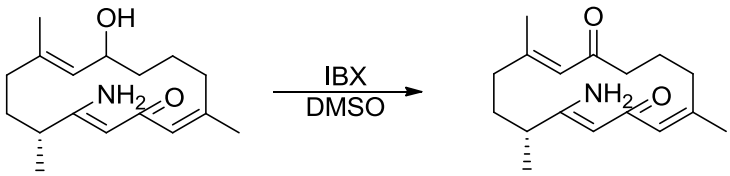
3-11 (24 mg, 0.087 mmol) was dissolved in DMSO (1.0 mL) and IBX (36.5 mg, 0.13 mmol) was added in one portion. The reaction was stirred at RT for 16 hrs. The reaction was quenched with the addition of H_2O (1.2 mL) and stirred for 15 minutes. The slurry was filtered through a plug of celite and the plug was washed with EtOAc. The filtrate was dried over Na_2SO_4 and concentrated. The material was purified by column chromatography (Hexanes:EtOAc 90:10 to 80:20) to give **3-12** (22.4 mg, 94%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.09 (s, 1H), 5.84 (s, 1H), 5.54 (s, 1H), 2.99-2.87 (m, 1H), 2.34-2.17 (m, 5H), 2.08 (d, *J* = 0.9 Hz, 3H), 2.08-1.98 (m, 1H), 1.91 (d, *J* = 1.5 Hz, 3H), 1.86-1.67 (m, 4H), 1.27 (d, *J*= 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.1, 168.0,

167.3, 158.8, 147.9, 124.2, 112.9, 101.9, 42.0, 38.9, 32.8, 32.4, 31.9, 24.5, 23.1, 21.1, 19.3. LRMS (EI+) m/z calculated for $C_{17}H_{24}NO_2$ $[M+H]^+$: 274.1802, found: 274.1937.



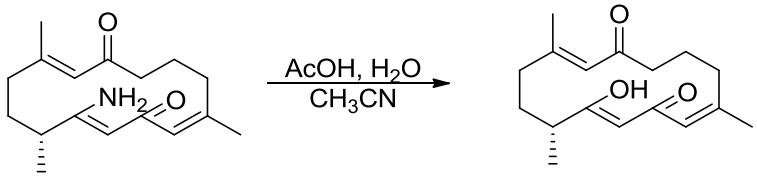
(±)-(2*Z*,8*E*,13*Z*)-13-amino-3,9,12-trimethylcyclotetradeca-2,8,13-triene-1,7-dione (3-13).

3-12 (9.5 mg, 0.035 mmol) was dissolved in CH_3CN (0.7 mL) under N_2 in a 1.5 mL flame dried bomb. To this solution was added H_2O (1 μL) followed by $Mn(CO)_6$ (4.7 mg, 0.018 mmol). The reaction was sealed and heated to 80 ^oC and stirred for 40 minutes. The solution was concentrated and the material was purified by column chromatography (Hexanes:EtOAc 60:40) to give **3-13** (3.7 mg, 56% 2.2:1 mixture of *E*:*Z* isomers by NMR). The spectra were consistent with material previously prepared using the alternate synthesis of **3-13**. See alternate synthesis of **3-13** for spectral analysis.



Alternate synthesis of 3-13.

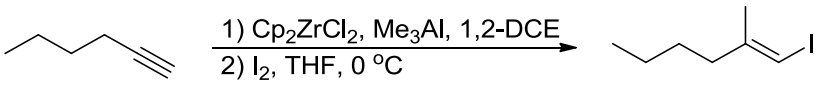
3-10 (6.1 mg, 0.022 mmol) was dissolved in DMSO (0.35 mL) at RT and IBX (9.2 mg, 0.033 mmol) was added. The reaction was stirred for 8 hours and quenched with the addition of 0.36 mL of water. The reaction was stirred for 15 minutes and then the slurry was filtered over celite. The celite was washed with EtOAc and the aqueous phase was extracted 3 x with EtOAc (3x 10 mL). The organic phases were dried over Na_2SO_4, filtered and concentrated. The material was purified by column chromatography (Hexanes:EtOAc 60:40) to give **3-13** (4.7 mg, 55%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.97 (brs, 1H), 6.15 (s, 1H), 5.85 (s, 1H), 5.13 (s, 1H), 4.91 (brs, 1H), 2.15-2.27 (m, 5H), 2.26-2.08 (m, 2H), 2.15 (s, 3H), 1.89-1.65 (m, 4H), 1.79 (s, 3H), 1.17 (d, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.9, 192.4, 167.7, 156.9, 145.0, 129.9, 125.1, 97.3, 43.4, 40.4, 39.8, 32.2, 30.1, 24.3, 23.4, 21.4, 18.1. LRMS (EI+) m/z calculated for $C_{17}H_{26}NO_2$ $[M+H]^+$: 276.1958, found: 276.1739.



(±)-(2*Z*,8*E*,13*Z*)-13-hydroxy-3,9,12-trimethylcyclotetradeca-2,8,13-triene-1,7-dione (1-28).

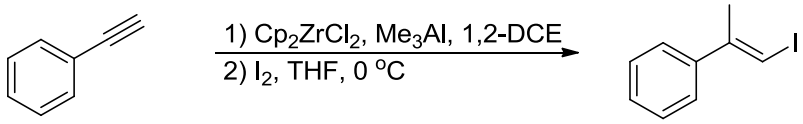
3-13 (3.0 mg, 0.012 mmol) was dissolved in AcOH (0.1 mL). To this solution was added H_2O (50 μL) followed by CH_3CN (0.1 mL). The reaction was stirred at RT for 6 hours and diluted with DCM (1mL) and water (1 mL). The aqueous phase was washed with 3x with DCM (3x 3 mL) and the organic phases were combined, dried over Na_2SO_4 and concentrated. The material was purified by column chromatography (Hexanes:EtOAc 88:12) to give **1-28** (1.7 mg, 60% 2.7:1 mixture of *E:Z* isomers). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 15.63-15.54 (m, 1H), 5.97 (s, 1H), 5.81 (s, 0.7H), 5.78 (s, 0.3H), 5.50 (s, 1H), 2.75-2.65 (m, 1H), 2.38-2.20 (m, 5H), 2.16 (d, *J* = 1.2 Hz, 2H), 2.10-1.94 (m 3H), 1.87 (d, *J* = 1.2 Hz, 1H), 1.83 (d, *J* = 1.2 Hz, 3H), 1.71-1.61 (m, 2H), 1.13-1.08 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.2, 199.8, 158.7, 151.0, 125.0, 124.5, 124.2, 123.7, 101.4, 100.9, 43.6, 43.5, 42.1, 41.6, 40.8, 39.8, 32.5, 31.3, 31.1, 31.0, 30.8, 29.8, 27.9, 26.1, 24.5, 24.4, 22.7, 22.0, 19.5, 19.1, 18.4. LRMS (EI+) m/z calculated for $C_{17}H_{25}O_3$ $[M+H]^+$: 277.1798, found: 277.2102.

CHAPTER IV



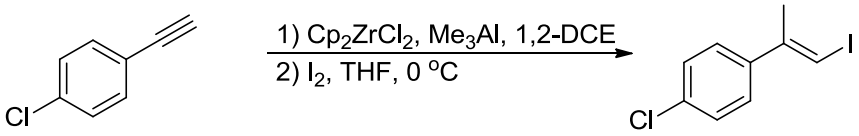
(*E*)-1-iodo-2-methylhex-1-ene (4-1a).

This molecule was prepared according to the method of Negishi *et al*.[x] Isolated material: 1.35 g, 60% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.86-5.85 (m, 1H), 2.20 (t, *J* = 8.0 Hz, 2H), 1.82 (d, *J* = 1 Hz, 3H0, 1.44-1.38 (m, 2H), 1.32-1.25 (m, 2H), 0.90 (t, *J* = 7.5 Hz, 3H).



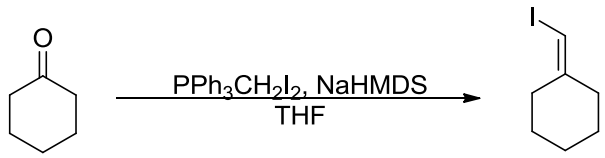
(*E*)-(1-iodoprop-1-en-2-yl)benzene (4-1b).

This molecule was prepared according to the method of Negishi *et al*.x Isolated material: 2.13 g, 87% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36-7.27 (m, 5H), 6.52-6.52 (m, 1H), 2.28 (d, *J* = 1.5 Hz, 3H).



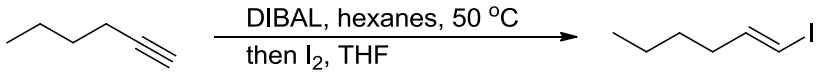
(*E*)-1-chloro-4-(1-iodoprop-1-en-2-yl)benzene (4-1c).

To a suspension of Cp_2ZrCl_2 (2.92 g, 10 mmol) in 1,2-DCE (25 mL) was added Me_3Al (1.92 mL, 20 mmol) under N_2. The rection was stirred for 10 minutes and 1-chloro-4-ethynylbenzene[xi] (1.37 g, 10 mmol) in 1,2 DCE (5 mL) was added. The reaction was stirred overnight at r.t. After 17 hours, the reaction was cooled to 0 °C and I_2 (3.04 g, 12 mmol) in THF (15 mL) was added dropwise. The reaction was stirred for 10 min and then worked up as in Negishi *et al*.x A yellow oil was isolated (2.12 g, 76% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.32-7.26 (m, 4H), 6.56-6.55 (m, 1H), 2.27 (d, J = 1.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.3, 140.1, 134.0, 128.9, 127.6, 80.1, 24.6.



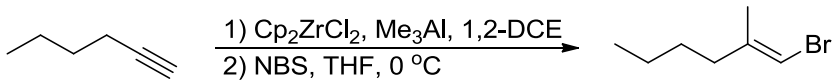
(iodomethylene)cyclohexane (4-1d).

This substrate was prepared according to the method of Stork and Zhao.[xii] Isolated material: 0.670 g, 44% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.78-5.76 (m, 1H), 2.31-2.23 (m, 4H), 1.57-1.49 (m, 6H).



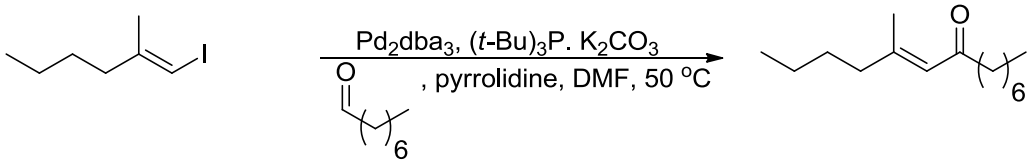
(*E*)-1-iodohex-1-ene (4-1e).

This substrate was prepared according to the method of Liu *et al*.[xiii] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.56-6.46 (m, 1H), 6.00-5.94 (m, 1H), 2.09-2.02 (m, 2H), 1.43-1.23 (m, 4H), 0.92-0.86 (m, 3H).



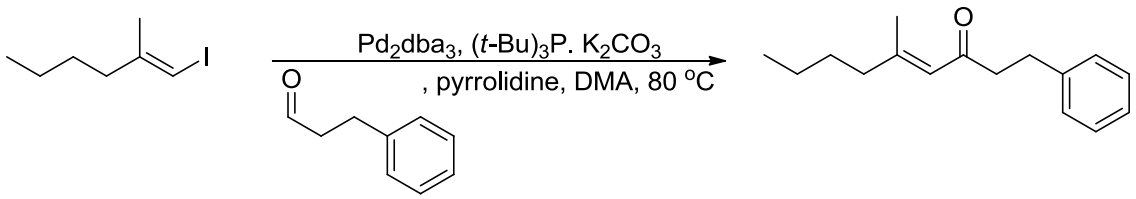
(*E*)-1-bromo-2-methylhex-1-ene (4-1f).

To a suspension of Cp_2ZrCl_2 (2.92 g, 10 mmol) in 1,2-DCE (25 mL) was added Me_3Al (1.92 mL, 20 mmol) under N_2. The rection was stirred for 10 minutes and 1-hexyne was added (1.15 mL, 10 mmol). The reaction was stirred overnight at r.t. After 17 hours, the reaction was cooled to 0 °C and NBS (2.14 g, 12 mmol) in THF (30 mL) was added dropwise. The reaction was stirred for 1 hour and then worked up as in Negishi *et al*.x A yellow oil was isolated (0.82 g, 46% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.88-5.87 (m, 1H), 2.12-2.08 (m, 2H), 1.78 (d, J = 1.5 Hz, 3H), 1.44-1.38 (m, 2H), 1.32-1.25 (m, 2H), 0.90 (t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.1, 101.0, 38.2, 29.8, 22.3, 19.2, 14.0.



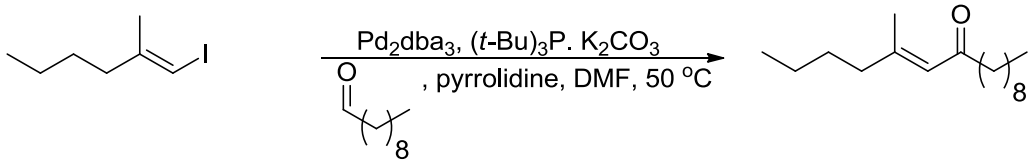
Direct Acylation Method A (DMF). **The synthesis of (*E*)-5-methyltetradec-5-en-7-one (4-2a) is representative.**

To a flame-dried flask in a glove box were added dry K_2CO_3 (172 mg, 1.25 mmol), Pd_2dba_3 (4.6 mg, 0.005 mmol) and (t-Bu)$_3$P (4.0 mg, 0.02 mmol). The flask was capped with a rubber septum and placed on a Schlenk line. DMF (1 mL), (*E*)-1-iodo-2-methylhex-1-ene (56 mg, 0.25 mmol), octanal (48 μL, 0.3 mmol), and pyrrolidine (10 μL, 0.125 mmol) were added and the reaction was heated to 50 °C. The reaction was stirred for 6 hours and then diluted with EtOAc. The reaction was filtered and the solid was washed with EtOAc (15 mL). The organics were concentrated and a column was run (Hexanes:EtOAc 99.5:0.5) to give **4-2a** as a yellow oil (40 mg, 71%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.04-6.04 (m, 1H), 2.41-2.38 (m, 2H), 2.11 (d, J = 1.0 Hz, 3H), 1.60-1.53 (m, 4H), 1.47-1.41 (m, 2H), 1.33-1.23 (m, 10H), 0.92-0.85 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.7, 158.7, 123.2, 44.6, 41.0, 31.8, 29.8, 29.4, 29.3, 24.4, 22.7, 22.5, 19.4, 14.2, 14.0.



Direct Acylation Method B (DMA). **The synthesis of (*E*)-5-methyl-1-phenylnon-4-en-3-one (4-3a) is representative.**

To a flame-dried flask in a glove box were added dry K_2CO_3 (172 mg, 1.25 mmol), Pd_2dba_3 (4.6 mg, 0.005 mmol), (t-Bu)$_3$P (4.0 mg, 0.02 mmol), DMA (1 mL), (*E*)-1-iodo-2-methylhex-1-ene (56 mg, 0.25 mmol), hydrocinnamaldehyde (40.2 mg, 0.3 mmol), and pyrrolidine (10 μL, 0.125 mmol) were added. The flask was capped with a rubber septum, placed on a Schlenk line and the reaction was heated to 80 °C. The reaction was stirred for 3 hours and then diluted with EtOAc. The reaction was filtered and the solid was washed with EtOAc (15 mL). The organics were concentrated and a column was run (Hexanes:EtOAc 99.5:0.5) to give **4-3a** as a light red oil (35.6 mg, 65%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31-7.15 (m, 5H), 6.05-6.03 (m, 1H), 2.95-2.90 (m, 2H), 2.78-2.71 (m, 2H), 2.14 (d, J = 1.2 Hz, 3H), 1.64-1.25 (m, 6H), 0.91 (t, J = 7.2 Hz, 3H). The proton spectrum was consentient with the literature.[xiv]

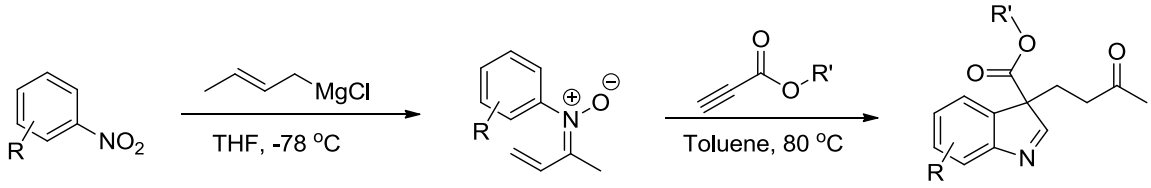


(*E*)-5-methylhexadec-5-en-7-one (4-2b).

Following direct acylation method A, the crude material crude product was purified by flash chromatography on silica gel (Hexanes/EtOAc, 99.5:0.5) to give **4-2b** (31.8 mg) as a yellow oil NMR analysis suggests that the yield is far less than 50%. See NMR labeled **4-2b**.

CHAPTER V

Preparation of 3,3 Disubstituted 3*H*-Indole Starting Materials

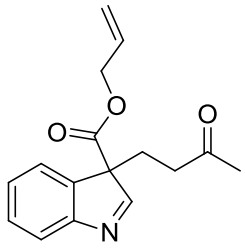


General procedure A for the synthesis of 3-(3-oxobutyl)-3*H*-indole-3-carboxylates. The synthesis of (±)-allyl 7-methyl-3-(3-oxobutyl)-3*H*-indole-3-carboxylate (5-6a) is representative.

2-Nitrotoluene (0.59 mL, 5 mmol) was dissolved in THF (30 mL) and cooled to -78 °C under N_2. A solution of freshly prepared (*E*)-but-2-en-1-ylmagnesium chloride was added dropwise (1.5 M in THF, 4.33 mL). The reaction was stirred at -78 °C for 30

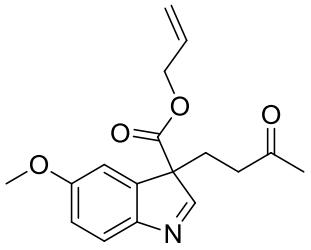
minutes and quenched with the addition of saturated aqueous NH_4Cl (5 mL). The mixture was then allowed to warm to rt. The mixture was diluted with water (30 mL) and extracted three times with ethyl acetate (3x 40 mL). The organic phases were combined and dried over Na_2SO_4, filtered and concentrated to give crude (*E*)-*N*-(but-3-en-2-ylidene)-2-methylaniline oxide. The residue was used in the next reaction without further purification.

(*E*)-N-(but-3-en-2-ylidene)-2-methylaniline oxide was dissolved in toluene (23 mL) and allyl propiolate (0.78 g, 7.1 mmol) was added. The reaction was heated to 80 ^oC for 14 hours. After cooling to rt, the reaction was concentrated and a silica gel column (Hexanes/EtOAc, 73:27) was run to give (±)-allyl 7-methyl-3-(3-oxobutyl)-3*H*-indole-3-carboxylate, **5-6a** (0.185 g, 51 %) as a dark yellow oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 8.11 (s, 1H), 7.32-7.17 (m, 3H), 5.88-5.75 (m, 1H), 5.24-5.17 (m, 2H), 4.62-4.50 (m, 2H), 2.61-2.37 (m, 2H), 2.59 (s, 3H), 2.19-2.04 (m, 2H), 1.98 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.8, 170.2, 169.2, 153.7, 135.8, 131.3, 131.2, 130.6, 126.9, 120.8, 118.8, 66.9, 66.3, 37.7, 30.0, 27.4, 16.8. HRMS (EI+) m/z calculated for $C_{17}H_{20}NO_3$ $[M+H]^+$: 286.1438, found: 286.1441.



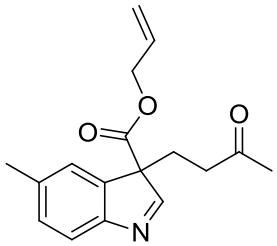
(±)-Allyl 3-(3-oxobutyl)-3*H*-indole-3-carboxylate (5-6b).

Following general procedure A for the synthesis of **5-6a** with the exception of a 1 day stir at rt instead of overnight at 80 ^{o}C, the crude product was purified by flash chromatography on silica gel (Hexanes/EtOAc, 73:27) to give **5-6b** (0.109 g, 13 %) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.14 (s, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 8 Hz, 1H), 7.41 (t, *J* = 6.5 Hz, 1H), 7.30 (t, J = 7.5 Hz, 1H), 5.86-5.78 (m, 1H), 5.22-5.18 (m, 2H), 4.60-4.52 (m, 2H), 2.60-2.54 (m, 1H), 2.46-2.40 (m, 1H), 2.14-2.01 (m, 2H), 1.96 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.7, 171.4, 169.0, 155.1, 135.9, 131.1, 129.2, 127.0, 123.5, 121.4, 118.9, 66.7, 66.3, 37.6, 30.0, 27.3. HRMS (EI+) m/z calculated for $C_{16}H_{18}NO_3$ $[M+H]^+$: 272.1281, found: 272.1292.



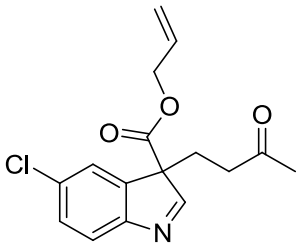
(±)-Allyl 5-methoxy-3-(3-oxobutyl)-3*H*-indole-3-carboxylate (5-6c).

Following general procedure A for the synthesis of **5-6a**, the crude product was purified by flash chromatography on silica gel (Hexanes/EtOAc, 73:27) to give **5-6c** allyl 5-methoxy-3-(3-oxobutyl)-3H-indole-3-carboxylate (0.23 g, 16 %) as a dark yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.99 (s, 1H), 7.52 (d, *J* = 8.5, Hz, 1H), 7.03 (d, *J* = 2.5 Hz, 1H), 6.91 (dd, *J* = 2.5, 8.5 Hz, 1H) 5.86-5.76 (m, 1H), 5.23-5.17 (m, 2H), 4.61-4.51 (m, 2H), 3.82 (s, 3H) 2.60-2.52 (m, 1H), 2.41-2.35 (m, 1H), 2.14-1.99 (m, 2H), 1.96 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.8, 169.3, 169.2, 159.2, 148.9, 137.7, 131.3, 121.9, 119.0, 114.3, 109.7, 66.9, 66.4, 55.9, 37.6, 30.1, 27.6. HRMS (EI+) m/z calculated for $C_{17}H_{19}NO_4Na$ $[M+Na]^+$: 324.1206, found: 324.1208.



(±)-Allyl 5-methyl-3-(3-oxobutyl)-3*H*-indole-3-carboxylate (5-6d).

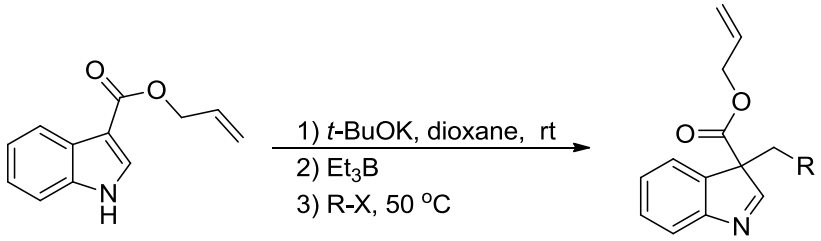
Following general procedure A for the synthesis of **5-6a**, the crude product was purified by flash chromatography on silica gel (Hexanes/EtOAc, 73:27) to give **5-6d** (0.330 g, 25 %) as a dark yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.03 (s, 1H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.26 (s, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 5.81-5.74 (m, 1H), 5.18-5.13 (m, 2H), 4.56-4.48 (m, 2H), 2.55-2.49 (m, 1H), 2.39-2.33 (m, 1H), 2.36 (s, 3H), 2.12-1.97 (m, 2H), 1.93 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.7, 170.4, 169.2, 152.9, 137.0, 136.0, 131.2, 129.8, 124.1, 120.9, 118.7, 66.5, 66.2, 37.6, 29.9, 27.4, 21.5. HRMS (EI+) m/z calculated for $C_{17}H_{20}NO_3$ $[M+H]^+$: 286.1438, found: 286.1447.



(±)-Allyl 5-chloro-3-(3-oxobutyl)-3*H*-indole-3-carboxylate (5-6e).

Following general procedure A for the synthesis of **5-6a**, the crude product was purified by flash chromatography on silica gel (Hexanes/EtOAc, 73:27) to give **5-6e** (0.151 g, 12

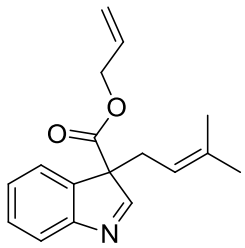
%) as a dark yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.14 (s, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 3.5 Hz, 1H), 7.39 (dd, *J* = 3.5, 8.0 Hz, 1H), 5.88-5.79 (m, 1H), 5.27-5.22 (m, 2H), 4.65-4.55 (m, 2H), 2.61-2.55 (m, 1H), 2.43-2.38, (m, 1H), 2.13-2.10 (m, 2H), 2.01 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.3, 171.6, 168.4, 153.7, 137.7, 132.9, 131.0, 129.5, 124.1, 122.3, 119.3, 67.1, 66.6, 37.6, 30.0, 27.5. HRMS (EI+) m/z calculated for $C_{16}H_{17}ClNO_3$ $[M+H]^+$: 306.0891, found: 306.0893.



General procedure B for the synthesis of 3-alkyl-3*H*-indole-3-carboxylates. The synthesis of (±)-(*E*)-allyl 3-(but-2-en-1-yl)-3H-indole-3-carboxylate (5-6k).

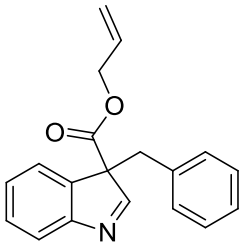
Allyl 1H-indole-3-carboxylate (0.30 g, 1.5 mmol) is dissolved in 1,4 dioxane (4.5 mL) under N_2 at rt. To this solution is added *t*-BuOK (0.185 mg, 1.65 mmol). The reaction is stirred at rt for 15 minutes. A solution of Et_3B in THF (0.165 mL, 1.65 mmol) is then added dropwise and the reaction is stirred for 30 minutes. *trans*-crotyl bromide (0.24 mL, 3 mmol at 85% purity) is added and the reaction is stirred at 50 °C for 16 hours. The reaction was quenched with the careful addition of saturated aqueous ammonium chloride (2 mL) and the mixture was diluted with water (10 mL). The aqueous phase was extracted 3x with EtOAc (15 mL) and the organic phases were combined, dried (Na_2SO_4) and concentrated. Silica gel chromatography (Hexanes/EtOAc 85:15) was run

to yield **5-6k** (0.280 g, 35 %) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22 (s, 1H), 7.63 (d, *J* = 7.5 Hz, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.43-7.27 (m, 2H), 5.91-5.78 (m, 1H), 5.59-5.47 (m, 1H), 5.30-5.18 (m, 3H), 4.65-4.52 (m, 2H), 2.93-2.85 (m, 1H), 2.63-2.55 (m, 1H), 1.59 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.9, 169.2, 155.1, 136.8, 131.5, 130.8, 129.1, 126.8, 124.0 ,123.6, 121.4, 118.8, 67.8, 66.3, 38.2, 18.0. HRMS (EI+) m/z calculated for $C_{16}H_{17}NO_2$ $[M+H]^+$: 256.1338, found: 256.1343.



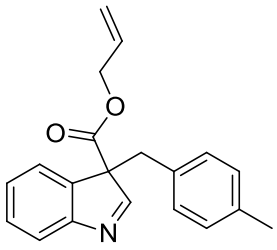
(±)-allyl 3-(3-methylbut-2-en-1-yl)-3*H*-indole-3-carboxylate (5-6j).

Following general procedure B for the synthesis of **5-6k,** the crude product was purified by flash chromatography on silica gel (Hexanes/EtOAc, 90:10) to give **5-6j** (0.160 g, 39 %) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.21 (s, 1H), 7.62 (d, *J* = 7.5 Hz, 1H), 7.55 (d, *J* = 7 Hz, 1H), 7.39 (dt, *J* = 1.5, 8.0 Hz, 1H), 7.8 (t, *J* = 7.0, 1H), 5.87-5.79 (m, 1H), 5.24-5.19 (m, 2H), 4.98-4.94 (m, 1H), 4.63-4.53 (m, 2H), 2.94 (dd, *J* = 7.5, 14 Hz, 1H), 2.60 (dd, *J* = 7.5, 14 Hz, 1H), 1.63 (s, 3H), 1.54 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.1, 169.3, 155.1, 136.9, 136.7, 131.5, 129.0, 126.7, 123.5, 121.3, 118.7, 117.2, 67.8, 66.2, 33.7, 25.9, 18.1. HRMS (EI+) m/z calculated for $C_{17}H_{19}LiNO_2$ $[M+Li]^+$: 276.1576, found: 276.1493.



(±)-(*E*)-allyl 3-(but-2-en-1-yl)-3*H*-indole-3-carboxylate (5-6L).

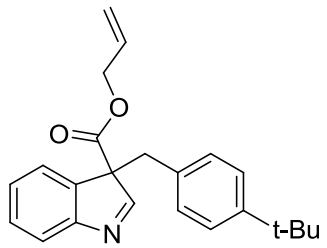
Following general procedure B for the synthesis of **5-6k**, the crude product was purified by flash chromatography on silica gel (Hexanes/EtOAc, 90:10) to give **5-6L** (183 mg, 42 %) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22 (s, 1H), 7.56 (t, *J* = 8.1 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 1H) 7.33-7.19 (m, 4H), 7.08-7.04 (m, 2H), 5.84-5.71 (m, 1H), 5.19-5.13 (m, 2H), 4.61-4.49 (m, 2H), 3.57 (d, *J* = 13.5 Hz, 1H), 3.11 (d, *J* = 13.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.5, 169.0, 154.9, 136.5, 134.2, 131.1, 1297, 129.1, 128.3, 127.3, 126.6, 123.7, 121.4, 118.8, 68.3, 66.2, 41.3. HRMS (EI+) m/z calculated for $C_{19}H_{17}NO_2$ $[M+H]^+$: 292.1338, found: 292.1348.



(±)-allyl 3-(4-methylbenzyl)-3*H*-indole-3-carboxylate (5-6m).

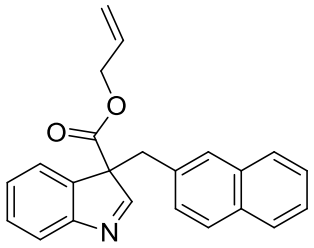
Following general procedure B for the synthesis of **5-6k,** the crude product was purified by flash chromatography on silica gel (Hexanes/EtOAc, 90:10) to give **5-6m** (0.170 g,

37 %) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.21 (s, 1H), 7.58-7.54 (m, 2H), 7.39 (dt, *J* = 1.0, 7.5 Hz, 1 H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 8 Hz, 2 H), 6.94 (d, *J* = 8 Hz, 2 H), 5.82-5.74 (m, 1H), 5.19-5.14 (m, 2H), 4.59-4.51 (m, 2H), 3.55 (d, *J* = 13.5 Hz, 1H), 3.09 (d, *J* = 13.5 Hz, 1H), 2.29 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.8, 169.2, 155.1, 137.1, 136.7, 132.2, 131.3, 129.6, 129.2, 129.1, 126.7, 123.8, 121.5, 118.9, 68.5, 66.3, 41.1, 21.2. HRMS (EI+) m/z calculated for $C_{20}H_{19}NO_2$ $[M+H]^+$: 306.1494, found: 306.1508.



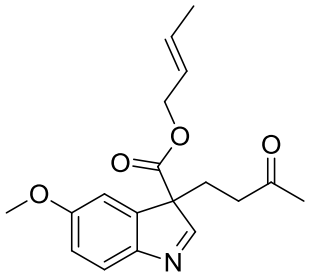
(±)-allyl 3-(4-(tert-butyl)benzyl)-3*H*-indole-3-carboxylate (5-6n).

Following general procedure B for the synthesis of **5-6k,** the crude product was purified by flash chromatography on silica gel (Hexanes/EtOAc, 90:10) to give **5-6n** (0.201 g, 37 %) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.23 (s, 1H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.40 (dt, *J* = 1.5, 7.5 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.25 (d, *J* = 8 Hz, 2H), 7.02 (d, *J* = 8 Hz, 2H), 5.79-5.71 (m, 3H), 5.16-5.10 (m, 2H), 4.60-4.49 (m, 2H), 3.56 (d, *J* = 13.5 Hz, 1H), 3.03 (d, *J* = 13.5 Hz, 1H), 1.29 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.9, 169.2, 155.0, 150.3, 136.8, 132.4, 131.3, 129.5, 129.2, 126.8, 125.4, 123.8, 121.5, 118.8, 68.5, 66.3, 51.2, 34.6, 31.4. HRMS (EI+) m/z calculated for $C_{23}H_{25}NO_2$ $[M+H]^+$: 348.1964, found: 348.1977.



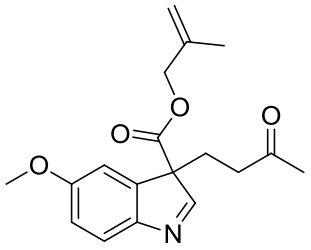
(±)-allyl 3-(naphthalen-2-ylmethyl)-3*H*-indole-3-carboxylate (5-6o).

Following general procedure B for the synthesis of **5-6k,** the crude product was purified by flash chromatography on silica gel (Hexanes/EtOAc, 90:10) to give **5-6o** (0.190 g, 37 %) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.28 (s, 1H), 7.80-7.78 (m, 1H), 7.74-7.0 (m, 2H), 7.59-7.57 (m, 3 H) 7.47-7.43 (m, 2H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.32 (t, *J* = 8.5 Hz, 1H), 7.18 (dd, *J* = 1.5, 7 Hz, 1H), 5.78-5.70 (m, 1H), 5.14-5.10 (m, 2H), 4.59-4.51 (m, 2H), 3.77 (d, *J* = 13.5 Hz, 1H), 3.27 (d, *J* = 13.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.6, 169.2, 155.1, 136.7, 133.3, 133.0, 132.6, 131.2, 129.3, 128.8, 128.1, 127.8, 127.8, 127.7, 126.8, 126.3, 126.0, 123.8, 121.6, 119.0, 68.6, 66.4, 41.7. HRMS (EI+) m/z calculated for $C_{23}H_{20}NO_2$ $[M+H]^+$: 342.1494, found: 342.1513.



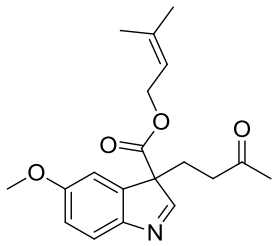
(±)-(*E*)-But-2-en-1-yl 5-methoxy-3-(3-oxobutyl)-3*H*-indole-3-carboxylate (5-6g).

Following general procedure A for the synthesis of **5-6a**, the crude product was purified by flash chromatography on silica gel (Hexanes/EtOAc, 73:27) to give **5-6g** (0.154 g, 20 %) as a dark yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.01 (s, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.06 (d, *J* = 2.4 Hz, 1H), 6.92 (dd, *J* = 2.4, 8.4 Hz, 1H), 5.80-5.68 (m, 1H), 5.55-5.46 (m, 1H), 4.59-4.43 (m, 2H), 3.85 (s, 3H), 2.66-2.52 (m, 1H), 2.44-2.34 (m, 1H), 2.17-2.03 (m, 2H), 1.99 (s, 3H), 1.70 (d, *J* = 8.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.8, 169.4, 169.2, 159.1, 148.7, 137.6, 132.2, 124.2, 121.8, 114.2, 109.7, 66.8, 66.6, 55.8, 37.6, 30.0, 27.6, 17.8. HRMS (EI+) m/z calculated for $C_{18}H_{22}NO_4$ $[M+H]^+$: 316.1543, found: 316.1489.

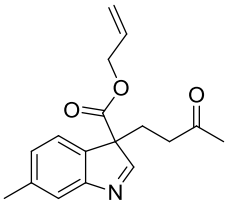


(±)-2-Methylallyl 5-methoxy-3-(3-oxobutyl)-3*H*-indole-3-carboxylate (5-6h).

Following general procedure A for the synthesis of **5-6a** with the exception of a 4 day stir at rt instead of overnight at 80 ^{o}C, the crude product was purified by flash chromatography on silica gel (Hexanes/EtOAc, 73:27) to give **5-6h** (0.341 g, 26 %) as a dark yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.00 (s, 1H), 7.52 (d, *J* = 8.5Hz, 1H), 7.03 (d, *J* = 2.5 Hz, 1H), 6.91 (dd, *J* = 2.5, 8.5 Hz, 1H), 4.87 (s, 1H), 4.84 (s, 1H), 4.48 (s, 2H), 3.82 (s, 3H), 2.60-2.54 (m, 1H), 2.43-2.37 (m, 1H), 2.15-1.99 (m, 2H), 1.97 (s, 3H), 1.65 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.8, 169.3, 169.1, 159.2, 148.9, 139.1, 137.7, 121.9, 114.4, 113.6, 109.6, 69.0, 55.9, 37.7, 30.1, 27.5, 25.7, 19.4. HRMS (EI+) m/z calculated for $C_{18}H_{22}NO_4$ $[M+H]^+$: 316.1543, found: 316.1725.



(±)-3-Methylbut-2-en-1-yl 5-methoxy-3-(3-oxobutyl)-3*H*-indole-3-carboxylate (5-6i). Following general procedure A for the synthesis of **5-6a** with the exception of a 3 day stir at rt instead of overnight at 80 ^{o}C, the crude product was purified by flash chromatography on silica gel (Hexanes/EtOAc, 73:27) to give **5-6i** (0.185 g, 30 %) as a dark yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.00 (s, 1H), 7.50 (d, *J* = 8.5 Hz, 1H), 7.04 (d, *J* = 2.5 Hz, 1H), 6.91 (dd, *J* = 2.5, 8.5 Hz, 1H), 5.28-5.24 (m, 1H), 4.63-4.51 (m, 2H), 3.84 (s, 3H), 2.58-2.52 (m, 1H), 2.41-2.35 (m, 1H), 2.15-2.04 (m, 2H), 1.98 (s, 3H), 1.72 (s, 3H), 1.65 (s, 3H) . ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.8, 269.5, 169.4, 159.1, 148.7, 140.0, 137.7, 121.7, 117.8, 114.2, 109.7, 66.9, 62.8, 55.8, 37.6, 30.0, 27.7, 25.7, 18.1. HRMS (EI+) m/z calculated for $C_{19}H_{24}NO_4$ $[M+H]^+$: 330.1705, found: 330.1536.



(±)-Allyl 6-methyl-3-(3-oxobutyl)-3*H*-indole-3-carboxylate (5-6f).

Following general procedure A for the synthesis of **5-6a**, the crude product was purified by flash chromatography on silica gel (Hexanes/EtOAc, 73:27) to give **5-6f** (0.185 g, 10

%) as a dark yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.11 (s, 1H), 7.45 (s, 1H), 7.36 (d, *J* = 7.5 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 1H), 5.82-5.78 (m, 1H), 5.23-5.17 (m, 2H), 4.60-4.52 (m, 2H), 2.57-2.51 (m, 1H), 2.45-2.39 (m, 1H), 2.42 (s, 3H), 2.15-2.01 (m, 2H), 1.97 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.8, 171.6, 169.2, 155.5, 139.4, 132.9, 131.2, 127.7, 123.1, 122.1, 118.8, 66.4, 66.3, 37.7, 30.0, 27.3, 21.6. HRMS (EI+) m/z calculated for $C_{17}H_{20}NO_3$ $[M+H]^+$: 286.1438, found: 286.1432.

III. Decarboxylative Allylic Alkylation of Allyl Indolenine-3-Carboxylates

Scheme S1. General reaction and ligands.

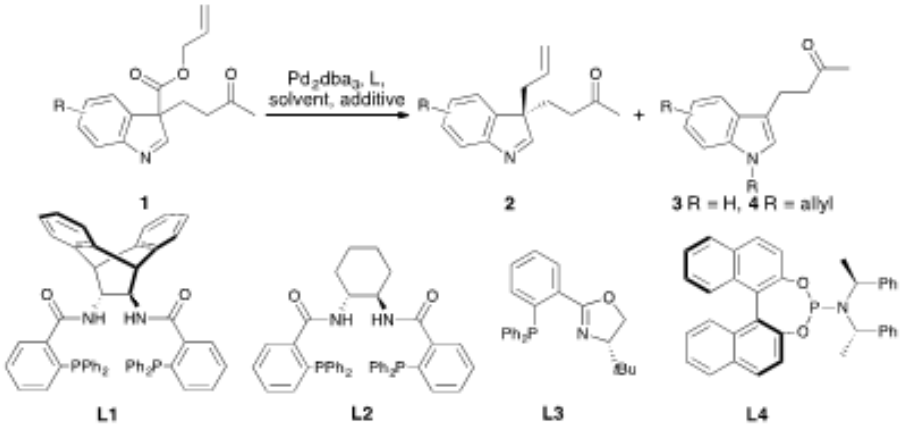
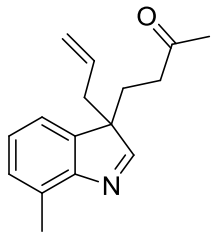


Table S1. Extended Reaction Conditions.

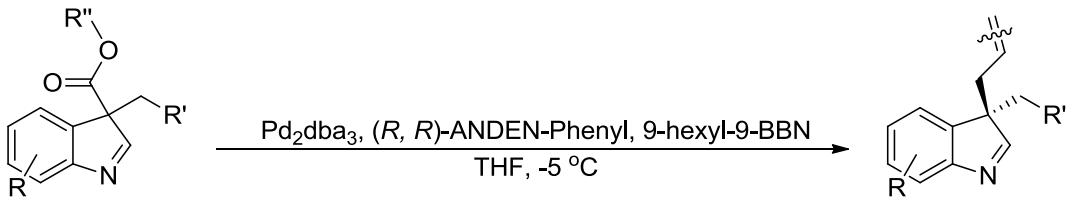
entry	R	ligand	additive	solvent	T (°C)	**2** / **3** / **4**	%ee
1	7-Me (**5-6a**)	Ph_3P	none	toluene	60	(44) / (38) / (23)	n/a
2	7-Me (**5-6a**)	$(2\text{-furyl})_3P$	none	CH_2Cl_2	23	(34) / (56) / 0	n/a
3	7-Me (**5-6a**)	$(2\text{-furyl})_3P$	AcOH	CH_2Cl_2	23	0 / 85 / 0	n/a
4	7-Me (**5-6a**)	$(2\text{-furyl})_3P$	MeOH	CH_2Cl_2	23	30 / 70 / 0	n/a
5	7-Me (**5-6a**)	$(2\text{-furyl})_3P$	CuI	CH_2Cl_2	23	(92) / 0 / 0	n/a
6	H (**5-6b**)	$(2\text{-furyl})_3P$	CuI	CH_2Cl_2	23	0 / 0 / 0	n/a
7	H (**5-6b**)	$(2\text{-furyl})_3P$	CuI	toluene	23	0 / 0 / 0	n/a
8	H (**5-6b**)	$(2\text{-furyl})_3P$	Et_3B (1eq.)	toluene	23	82 / 17 / 0	n/a
9	H (**5-6b**)	L1	Et_3B (1eq.)	toluene	23	(95) / 0 / 0	48
10	H (**5-6b**)	L1	hexyl-9-BBN[a]	toluene	0	48 / 14 / 0	56
11	H (**5-6b**)	L1	hexyl-9-BBN[a]	CH_2Cl_2	0	44 / 20 / 0	55
12	H (**5-6b**)	L1	hexyl-9-BBN[a]	1,4-dioxane	0	48 / 19 / 0	48
13	H (**5-6b**)	L1	hexyl-9-BBN[a]	DCE	0	44 / 23 / 0	64
14	H (**5-6b**)	L1	hexyl-9-BBN[a]	THF	0	43 / 20 / 0	65
17	H (**5-6b**)	L2	hexyl-9-BBN[a]	THF	0	44 / 21 / 0	57
18	H (**5-6b**)	L3	hexyl-9-BBN[a]	THF	0	0 / 13 / 0	N.D.
15	H (**5-6b**)	L1	hexyl-9-BBN[a]	toluene	-20	35 / 12 / 0	N.D.
16	H (**5-6b**)	L1	hexyl-9-BBN[a]	THF	-20	35 / 12 / 0	N.D.
17	H (**5-6b**)	L1	hexyl-9-BBN[b]	THF	0	48 / 13 / 0	72
20	5-MeO (**5-6c**)	L1	hexyl-9-BBN[b]	THF	0	(70) / 30 / 0	70
21	5-MeO (**5-6c**)	L1	hexyl-9-BBN[c]	THF	0	32 / 37 / 0	70
22	5-MeO (**5-6c**)	L1	hexyl-9-BBN[d]	THF	0	(92) / 12 / 0	74
23	5-MeO (**5-6c**)	L1	hexyl-9-BBN[e]	THF	0	(82) / 12 / 0	80
24	5-MeO (**5-6c**)	L4	None[f]	THF:propyl amine:dioxane (1:18)	50	0/trace	N/A
25	5-MeO (**5-6c**)	L4	hexyl-9-BBN[g]	THF:propyl amine:dioxane (1:18)	50	0/0	N/A

a) 0.025 eq. of Pd_2dba_3, 0.075 eq. L, 0.525 eq. hexyl-9-BBN
b) 0.0375 eq. of Pd_2dba_3, 0.1125 eq. L, 0.525 eq. hexyl-9-BBN
c) 0.0375 eq. of Pd_2dba_3, 0.1125 eq. L, 0.25 eq. hexyl-9-BBN
d) 0.0375 eq. of Pd_2dba_3, 0.1125 eq. L, 1.05 eq. hexyl-9-BBN
e) 0.023 eq. of Pd_2dba_3, 0.1125 eq. L, 1.05 eq. hexyl-9-BBN
f) 0.02 eq. of $Ir(cod)Cl_2$, 0.04 eq. L4, 0 eq. hexyl-9-BBN
g) 0.02 eq. of $Ir(cod)Cl_2$, 0.04 eq. L4, 1.05 eq. hexyl-9-BBN



Synthesis of 4-(3-allyl-7-methyl-3*H*-indol-3-yl)butan-2-one 5-7a.

A flame-dried flask was charged under N_2 with Pd_2dba_3 (4.1 mg, 0.0045 mmol), tri(2-furyl)phosphine (2.1 mg, 0.009 mmol) and dissolved in DCM (0.3 mL). This solution was then added to CuI (8.6 mg, 0.045 mmol) under N_2. A solution of 0.15 mmol (42.8 mg) of Allyl 7-methyl-3-(3-oxobutyl)-3H-indole-3-carboxylate, **5-6a**, in DCM (3 mL) was then added to the reaction flask and the reaction was then stirred overnight at RT. The reaction was then concentrated and a silica gel column (Hexanes/EtOAc, 65:35) was run to give 4-(3-allyl-7-methyl-3H-indol-3-yl)butan-2-one (33 mg, 90 %) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.95 (s, 1H), 7.20-7.11, (m, 2H), 7.09-7.03, (m, 1H), 5.52-5.38 (m, 1H), 5.07-4.90 (m, 2H), 2.64-2.44 (m, 2H), 2.59 (s, 3H), 2.35-2.25 (m, 1H), 2.18-2.09 (m, 1H), 1.96-1.70 (m, 2H), 1.89 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 207.8, 176.6, 154.1, 140.5, 132.3, 130.9, 129.5, 126.3, 119.5, 118.8, 60.9, 39.9, 37.9, 30.0, 27.5, 16.8. HRMS (EI+) m/z calculated for $C_{16}H_{20}NO$ $[M+H]^+$: 242.1545, found: 242.1534.



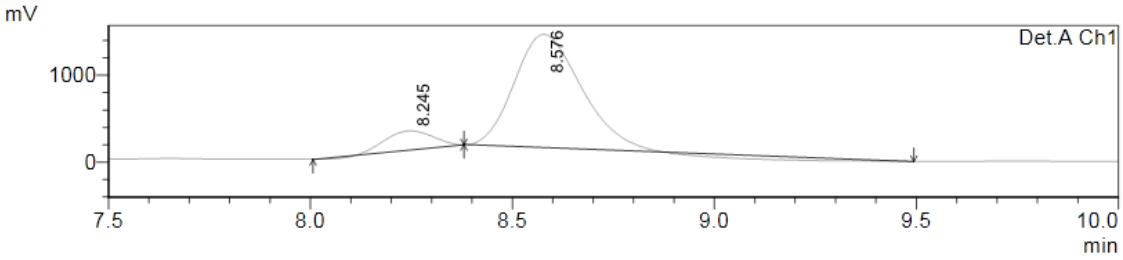
General procedure C for the synthesis of 3-alkyl-3*H*-indole-3-carboxylates. The synthesis of (*R*)-4-(3-allyl-3H-indol-3-yl)butan-2-one (5-7b) is representative.

Borane generation: A flame-dried 3 mL conical flask was placed under nitrogen and charged with a solution of 9-BBN in THF (0.5 M, 0.63 mL, 0.315 mmol). This solution was then diluted with THF (0.63 mL) and 1-hexene (93 μL, 0.75 mmol) was added. The reaction was stirred at RT for 4 hrs.

Enantioconvergent decarboxylative allylic alkylation: A flame-dried 10 mL flask was charged with Pd_2dba_3 (4.0 mg, 0.004 mmol) and (*R*,*R*)-ANDEN-phenyl Trost ligand L1 (17.4 mg, 0.0214 mmol). It was placed under nitrogen and THF (4.4 mL) was added. The solution was cannulated to a flask containing (±)-allyl indolenin-3-carboxylate (0.19 mmol) under nitrogen atmosphere at 0 °C. The reaction was stirred for 2 min at 0 °C and 0.8 mL of the aforementioned borane solution was added. The reaction was sealed with parafilm and stirred at 0 °C for 16 hrs. *Workup A*: The reaction was quenched with the addition of saturated $NaHCO_3$ (3 mL) and the mixture was vigorously stirred for 2 hrs. The mixture was then diluted with 5 mL water and extracted with EtOAc (15 mLx3). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. *Workup B*: The reaction was quenched with the addition of 2 N NaOH (2 mL) and diluted with EtOAc (3 mL). The mixture was then vigorously stirred for 2 hrs before it was diluted

with 5 mL water and extracted with EtOAc (15 mLx3). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. *Workup C*: Ethanolamine (35 µL, 0.57 mmol) was added to the reaction and the solution was stirred vigorously for 2 hrs. The resulting mixture was filtered and the filtrate was washed with EtOAc (15 mL). The combined organic phase was washed with sat. Na_2CO_3 (5 mL) and brine (5 mL) before it was dried over Na2SO4, filtered, and concentrated. Workup A was used for the synthesis of **5-7b** and the crude product was purified by flash chromatography on silica gel (Hexanes/EtOAc, 73:27) to give **5-7b** (35 mg, 80 % yield) as a light yellow oil. The spectra of **5-7b** were consistent with the reported literature values.[xv] $[\alpha_D]^{20}$ (c 1.0, CH_2Cl_2) = 20.4°. The ee was determined to be 77 % by chiral HPLC (Chiralpak IA, 90:10 hexane:*i*PrOH, 1.0 mL/min, 8.58 min major, 8.25 min minor).

Chiral Chromatogram for **5-7**.

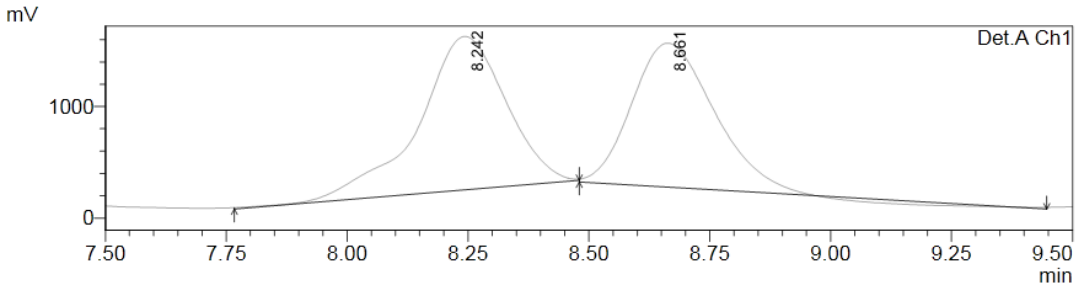


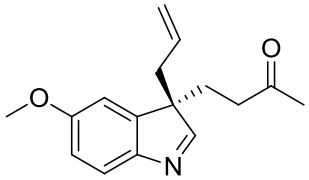
PeakTable

Detector A Ch1 210nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.245	1799201	220291	11.311	14.457
2	8.576	14107558	1303481	88.689	85.543
Total		15906760	1523772	100.000	100.000

Racemic Chromatogram for **5-7b**.

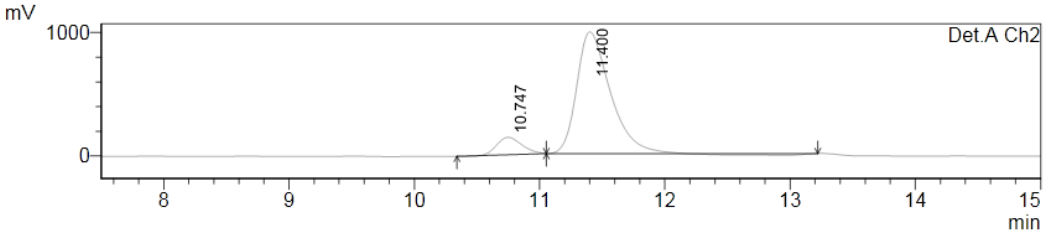




(*R*)-4-(3-allyl-5-methoxy-3*H*-indol-3-yl)butan-2-one (5-7c).

Following general procedure C with Workup A was used for **5-7c**. A silica gel column was then run (Hexanes/EtOAc 73:27) to give **5-7c** (40.0 mg, 82 % yield) as a light yellow oil. The spectra of **5-7c** were consistent with the reported literature values.[xv] $[\alpha_D]^{20}$ (c .047, CH_2Cl_2) = 8.5°. The ee was determined to be 80 % by chiral HPLC (Chiralpak IA, 90:10 hexane:*i*PrOH, 1.0 mL/min, 11.37 min major, 10.75 min minor).

Chiral Chromatogram for **5-7c.**

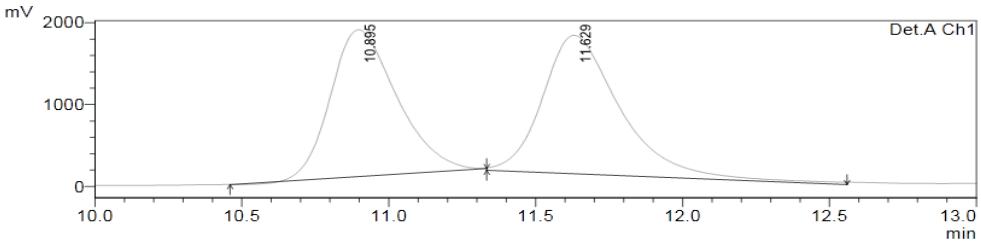


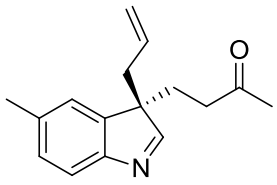
PeakTable

Detector A Ch2 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.747	1955934	141484	9.813	12.550
2	11.400	17976811	985850	90.187	87.450
Total		19932745	1127334	100.000	100.000

Racemic Chromatogram for **5-7c.**



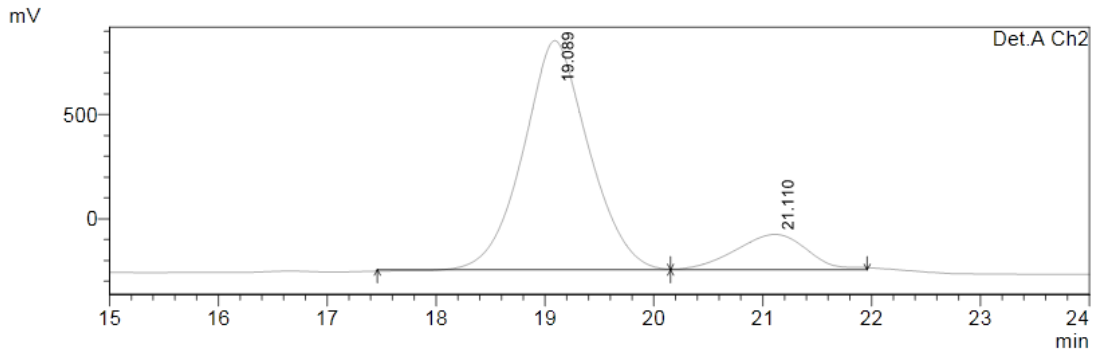


(*R*)-4-(3-allyl-5-methyl-3*H*-indol-3-yl)butan-2-one (5-7d).

Following general procedure C with Workup A for the synthesis of **5-7b**, the crude product was purified by flash chromatography on silica gel (Hexanes/EtOAc, 73:27) to give **5-7d** (41 mg, 94 %) as a light yellow oil. $[\alpha_D]^{20}$ (c 1.0, CH_2Cl_2) = 19.8°. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.89 (s, 1H), 7.49 (d, *J* = 8 Hz, 1H), 7.14 (d, *J* = 8 Hz, 1H), 7.04 (s,

1H), 5.48-5.40 (m, 1H), 5.02-4.94 (m, 2H), 2.60-2.46 (m, 2H), 2.39 (s, 3H), 2.32-2.26 (m, 1H), 2.15-2.08 (m, 1H), 1.93-1.87 (m, 1H), 1.89 (s, 3H), 1.80-1.74 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 207.9, 176.9, 153.4, 140.7, 136.3, 132.3, 128.8, 122.8, 120.7, 118.8, 60.6, 39.9, 37.8, 30.0, 27.5, 21.5. HRMS (EI+) m/z calculated for $C_{16}H_{19}LiNO$ $[M+Li]^+$: 248.1627, found: 248.1639. The ee was determined to be 76 % by chiral HPLC (Chiralpak IC, 95:5 hexane:*i*PrOH, 1.0 mL/min, 19.09 min major, 21.11 min minor).

Chiral Chromatogram for **5-7d**.

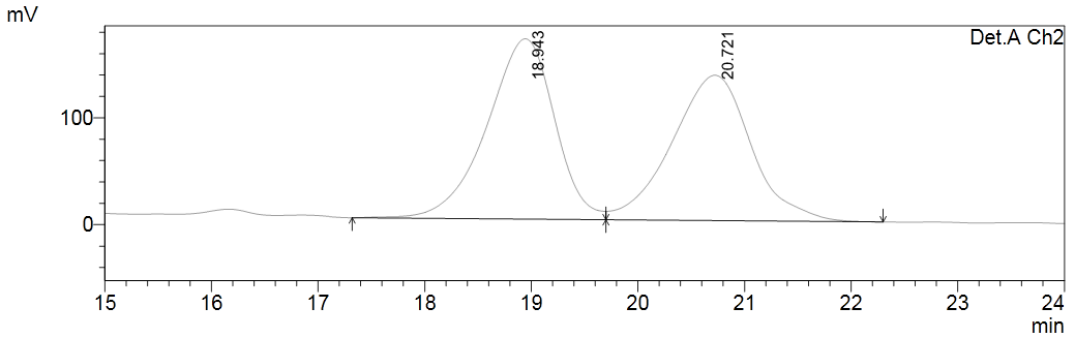


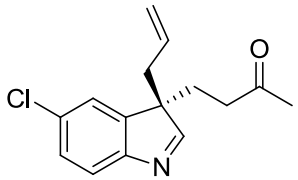
PeakTable

Detector A Ch1 210nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	18.927	167981816	3966606	88.047	88.352
2	21.107	22805727	522932	11.953	11.648
Total		190787543	4489539	100.000	100.000

Racemic Chromatogram for **5-7d**.

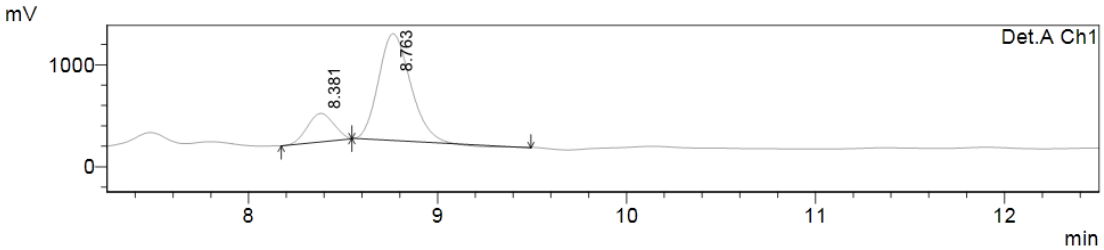




(*R*)-4-(3-allyl-5-chloro-3*H*-indol-3-yl)butan-2-one (5-7e).

Following general procedure C with Workup A for the synthesis of **5-7b** except conducting the reaction at RT, the crude product was purified by flash chromatography on silica gel (Hexanes/EtOAc, 73:27) to give **5-7e** (30.5 mg, 61 %) as a light yellow oil. $[\alpha_D]^{20}$ (c 0.5, CH_2Cl_2) = 8.3°. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.96 (s, 1H), 7.55 (d, *J* = 8.5 Hz, 1), 7.34 (dd, *J* = 2, 8 Hz, 1H), 7.23 (d, *J* = 2 Hz, 1H), 5.47-5.39 (m, 1H), 5.04-4.98 (m, 2H), 2.57-2.48 (m, 2H), 2.36-2.30 (m, 1H), 2.15-2.09 (m, 1H), 1.93 (s, 3H), 1.92 - 1.79 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 207.6, 178.5, 154.5, 142.9, 123.7, 131.9, 128.8, 123.0, 122.5, 119.7, 61.7, 40.0, 38.1, 30.3, 27.5. HRMS (EI+) m/z calculated for $C_{15}H_{17}ClNO$ $[M+H]^+$: 262.0999, found: 262.0996. The ee was determined to be 64 % by chiral HPLC (Chiralpak IA, 90:10 hexane:*i*PrOH, 1.0 mL/min, 8.76 min major, 8.38 min minor).

Chiral Chromatogram for **5-7e**.

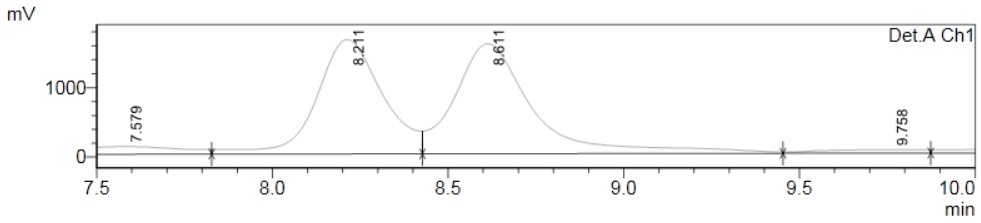


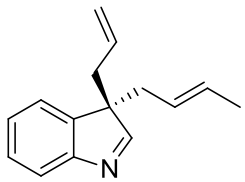
PeakTable

Detector A Ch2 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.382	1039928	107282	18.123	20.943
2	8.764	4698224	404985	81.877	79.057
Total		5738152	512267	100.000	100.000

Racemic Chromatogram for **5-7e**.



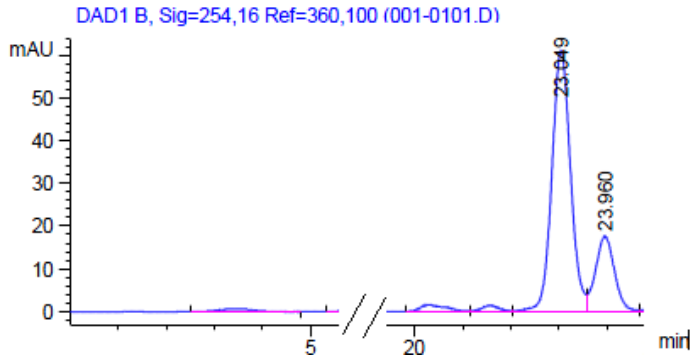


(*S*,*E*)-3-allyl-3-(but-2-en-1-yl)-3*H*-indole 5-7k.

Following general procedure C with Workup B[xvi] for the synthesis of **5-7b,** the crude product was purified by flash chromatography on silica gel (Hexanes/EtOAc, 90:10) to give **5-7k** (38 mg, 94 %) as a colorless oil. $[\alpha_D]^{20}$ (c 1.0, CH_2Cl_2) = -8.1°. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.03 (s, 1H), 7.62 (d, *J* = 7.5 Hz, 1H), 7.34 (dt, *J* = 1.5, 6 Hz, 1 H), 7.30 - 7.23 (m, 2H), 5.47-5.38 (m, 2H), 5.15-5.09 (m, 1H), 5.01-4.92 (m, 2H), 2.57-2.40 (m, 4H), 1.56 (d, *J* = 8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.2, 155.6, 141.8, 132.6, 129.5, 127.9, 126.0, 124.9, 122.4, 121.2, 118.6, 61.2, 38.5, 37.6, 18.0. HRMS (EI+) m/z calculated for $C_{15}H_{17}N$ $[M+H]^+$: 212.1439, found: 212.1447. The ee was

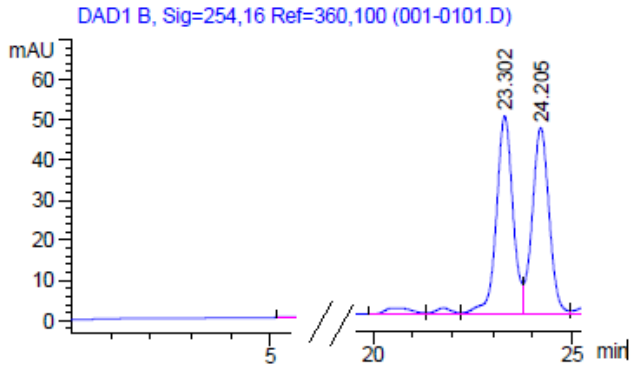
determined to be 54 % by chiral HPLC (Chiralpak AD, 99:1 hexane:*i*PrOH, 0.5 mL/min, 23.05 min major, 23.96 min minor).

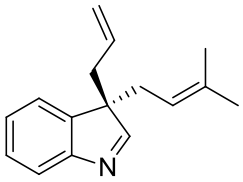
Chiral Chromatogram for **5-7k**.



Peak	Retention Time (min)	Area (mAU's)	Area %
1	23.049	1648.22668	77.28
2	23.960	484.45633	22.72
Total		2132.68	100.00

Racemic Chromatogram for **5-7k**.

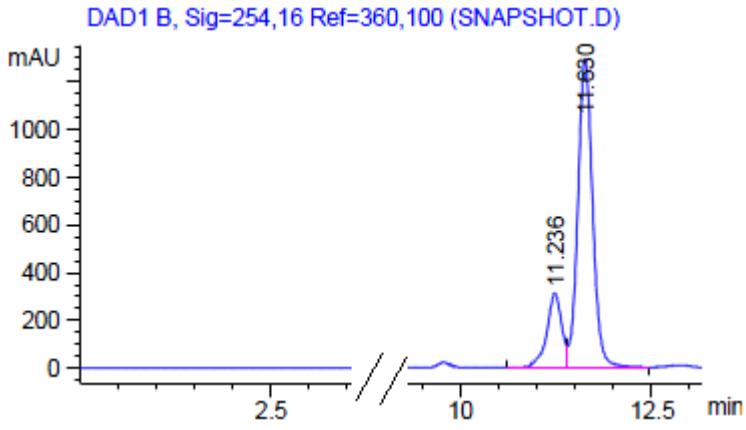




(*S*)-3-allyl-3-(3-methylbut-2-en-1-yl)-3*H*-indole (5-7j).

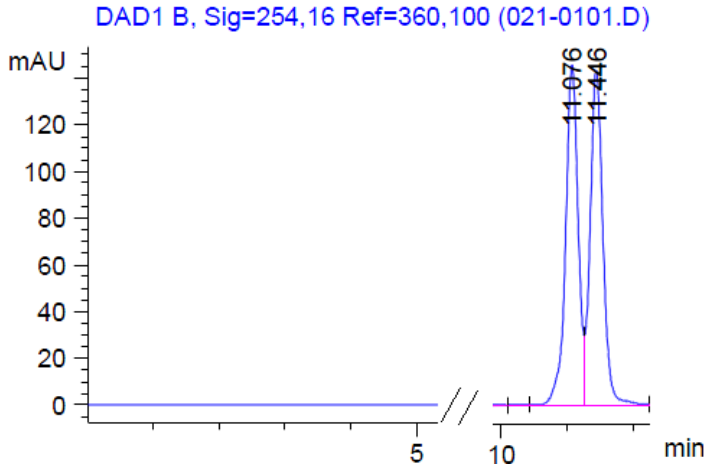
Following general procedure C with Workup B[xvi] for the synthesis of **5-7b,** the crude product was purified by flash chromatography on silica gel (Hexanes/EtOAc, 90:10) to give **5-7j** (46.5 mg, >95 %) as a colorless oil. $[\alpha_D]^{20}$ (c 1.0, CH_2Cl_2) = -7.6°. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.02 (s, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.36 - 7.29 (m, 2H), 7.26 - 7.23 (m, 1H), 5.45 - 5.37 (m, 1H), 5.01 - 4.91(m, 2H), 4.88 - 4.83 (m, 1H), 2.60 - 2.49 (m, 3H), 2.43 - 2.39 (m, 1H), 1.60 (s, 3H), 1.53 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.2, 155.5, 141.8, 135.1, 132.7, 127.8, 125.9, 1222.2, 121.1, 118.4, 118.1, 62.6, 38.4, 32.9, 25.8, 18.0. HRMS (EI+) m/z calculated for $C_{16}H_{20}N$ $[M+H]^+$: 226.1596, found: 226.1588. The ee was determined to be 60 % by chiral HPLC (Chiralpak AD, 95:5 hexane:*i*PrOH, 0.5 mL/min, 11.63 min major, 11.24 min minor).

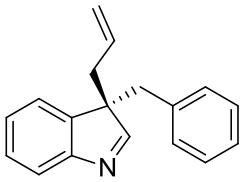
Chiral Chromatogram for **5-7j**.



Peak	Retention Time (min)	Area (mAU's)	Area %
1	11.236	4348.13086	19.94
2	11.630	1.74538e4	80.06
Total		21798	100.00

Racemic Chromatogram for **5-7j**.



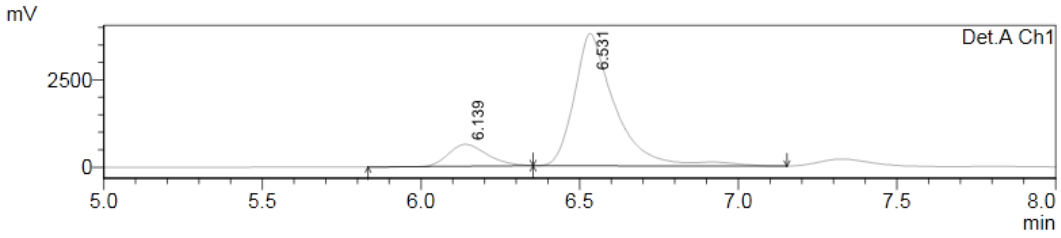


(*S*)-3-allyl-3-benzyl-3*H*-indole (5-7L).

Following general procedure C with workup B[xvi] for the synthesis of **5-7b,** the crude product was purified by flash chromatography on silica gel (Hexanes/EtOAc, 90:10) to give **5-7L** (43 mg, 92 %) as a colorless oil. $[\alpha_D]^{20}$ (c 0.5, CH_2Cl_2) = -86.5°. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.08 (s, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.33-7.30 (m, 1H), 7.28-7.24

(m, 2H), 7.17-7.14 (m, 3H), 6.96-6.94 (m, 2H), 5.43-5.34 (m, 1H), 5.01-4.92 (m, 2H), 3.12 (d, J = 13.5 Hz, 1H), 3.03 (d, J = 13.5 Hz, 1H), 2.65-2.57 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.4, 136.1, 132.3, 129.8, 128.0, 127.9, 126.7, 125.8, 122.6, 121.2, 118.7, 61.8, 41.1, 38.7. HRMS (EI+) m/z calculated for $C_{18}H_{18}N$ $[M+H]^+$: 248.1434, found: 248.1431. The ee was determined to be 73 % by chiral HPLC (Chiralpak IB, 90:10 hexane:*i*PrOH, 1.0 mL/min, 6.53 min major, 6.14 min minor).

Chiral Chromatogram for **5-7L**.

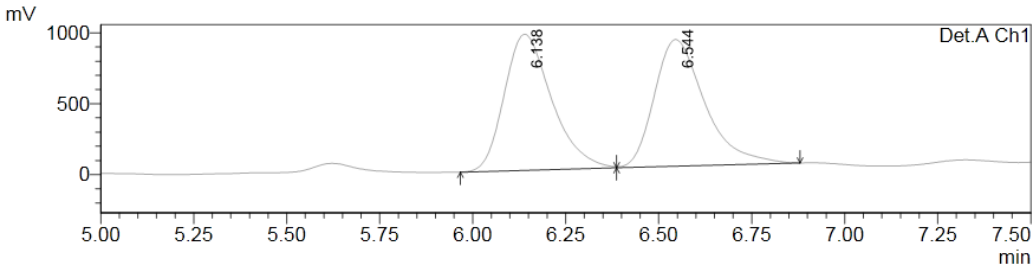


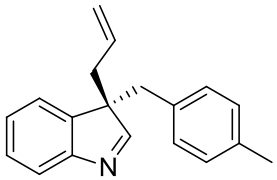
PeakTable

Detector A Ch1 210nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.139	5316424	623268	13.587	14.139
2	6.531	33812346	3785030	86.413	85.861
Total		39128770	4408298	100.000	100.000

Racemic Chromatogram for **5-7L**.

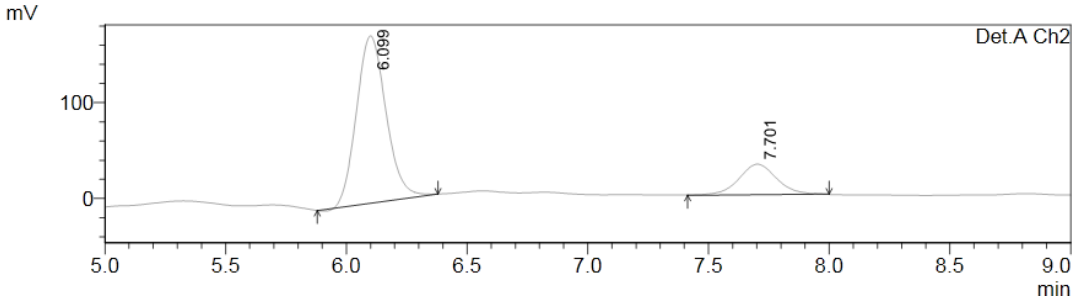




(*S*)-3-allyl-3-(4-methylbenzyl)-3*H*-indole (5-7m).

Following general procedure C with workup B[xvi] for the synthesis of **5-7b,** the crude product was purified by flash chromatography on silica gel (Hexanes/EtOAc, 90:10) to give **5-7m** (50 mg, >95 %) as a colorless oil. $[\alpha_D]^{20}$ (c 1.0, CH_2Cl_2) = 3.9°. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.07 (s, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.34-7.30 (m, 1 H), 7.28 - 7.24 (m, 2H), 6.97 (d, *J* = 7.5 Hz, 2H), 6.84 (d, *J* = 8 Hz, 2H), 5.42-5.33 (m, 1H), 5.00 - 4.90 (m, 2H), 3.08 (d, *J* = 13.5 Hz, 1H), 2.99 (d, *J* = 13.5 Hz, 1H), 2.64 - 2.56 (m 2H), 2.58 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.7, 155.7, 141.4, 136.4, 133.2, 132.5, 129.8, 128.8, 128.0, 125.9, 122.7, 121.3, 118.8, 62.0, 40.9, 38.7, 21.2. HRMS (EI+) m/z calculated for $C_{19}H_{20}N$ $[M+H]^+$: 262.1590, found: 262.1591. The ee was determined to be 54 % by chiral HPLC (Chiralpak IA, 95:5 hexane:*i*PrOH, 1.0 mL/min, 6.10 min major, 7.70 min minor).

Chiral Chromatogram for **5-7m**.

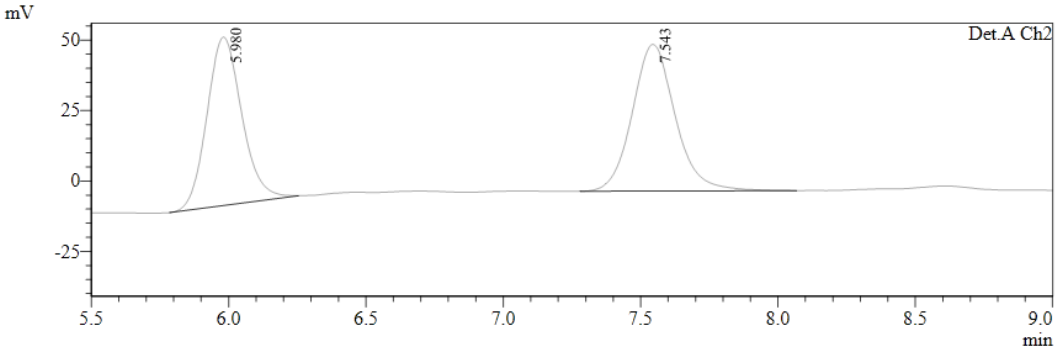


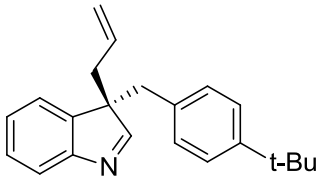
PeakTable

Detector A Ch2 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.099	1489110	174590	81.229	84.616
2	7.701	344123	31742	18.771	15.384
Total		1833233	206332	100.000	100.000

Racemic Chromatogram for **5-7m**.



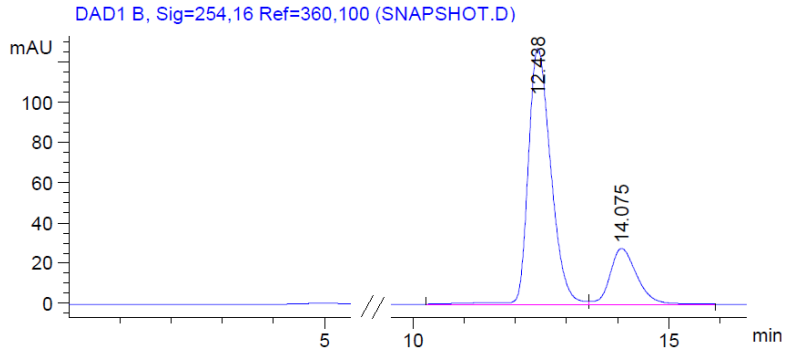


(*S*)-3-allyl-3-(4-(tert-butyl)benzyl)-3*H*-indole (5-7n).

Following general procedure C with Workup B[xvi] for the synthesis of **5-7b,** the crude product was purified by flash chromatography on silica gel (Hexanes/EtOAc, 90:10) to give **5-7n** (55 mg, 96 %) as a colorless oil. $[\alpha_D]^{20}$ (c 1.0, CH_2Cl_2) = -63.7°. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.07 (s, 1H), 7.56 (d, *J* = 8.5 Hz, 1H), 7.35-7.32 (m, 1 H), 7.28 - 7.26 (m, 2H), 7.20 (d, *J* = 8.5 Hz, 2H), 6.92 (d, *J* = 8.5 Hz, 2H), 5.38-5.29 (m, 1H), 4.95 (m, 2H), 3.06 (d, *J* = 13.5 Hz, 2H), 2.97 (d, *J* = 13.5 Hz, 1H), 2.61 (d, *J* = 9.5 Hz, 1H),

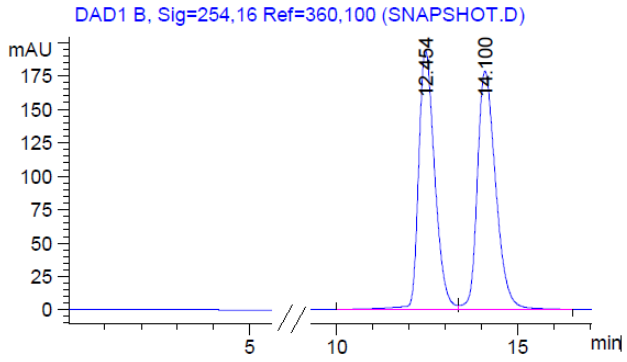
1.27 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.8, 155.7, 149.7, 141.6, 133.3, 132.5, 129.7, 128.0, 126.0, 125.1, 122.7, 121.3, 118.7, 62.9, 40.8, 38.5, 34.5, 31.5, 31.5. HRMS (EI+) m/z calculated for $C_{22}H_{25}N$ $[M+H]^+$: 304.2065, found: 304.2067. The ee was determined to be 59 % by chiral HPLC (Chiralpak ASH, 99:1 hexane:*i*PrOH, 0.5 mL/min, 12.44 min major, 14.07 min minor).

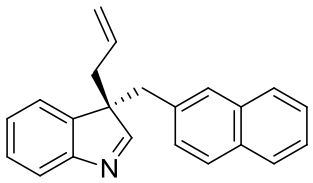
Chiral Chromatogram for **5-7n**.



Peak	Retention Time (min)	Area (mAU's)	Area %
1	12.438	3898.81177	79.5387
2	14.075	1002.96954	20.4613
Total		4901.78131	100.00

Racemic Chromatogram for **5-7n**.



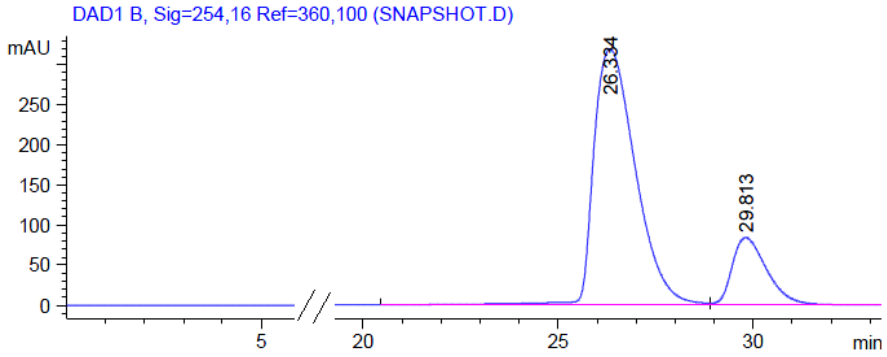


(*S*)-3-allyl-3-(naphthalen-2-ylmethyl)-3*H*-indole (5-7o).

Following general procedure C with Workup B[xvi] for the synthesis of **5-7b,** the crude product was purified by flash chromatography on silica gel (Hexanes/EtOAc, 90:10) to give **5-7o** (49.6 mg, 88 %) as a colorless oil. $[\alpha_D]^{20}$ (c 1.0, CH_2Cl_2) = -108.0°. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.08 (s, 1H), 7.72-7.65 (m, 2H), 7.60 (d, *J*= 8.5, 1H), 7.48 (d, *J* = 8.0 Hz 1H), 7.41-7.37 (m, 3H), 7.29-7.21 (m, 3H), 7.02 (d, *J* = 8.0 Hz, 1H), 5.40-5.32 (m, 1H), 4.97-4.89 (m, 2H), 3.23 (d, *J* = 13.5 Hz, 1H), 3.14 (d, *J* = 13.5 Hz, 1H), 2.64-2.58 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.4, 155.5, 141.2, 133.8, 133.1, 132.3, 132.2, 128.5, 128.2, 128.0, 127.6, 127.57, 127.51, 126.0, 125.9, 125.6, 122.6, 121.3, 118.8, 117.4, 61.9, 41.3, 38.7. HRMS (EI+) m/z calculated for $C_{22}H_{20}N$ $[M+H]^+$:

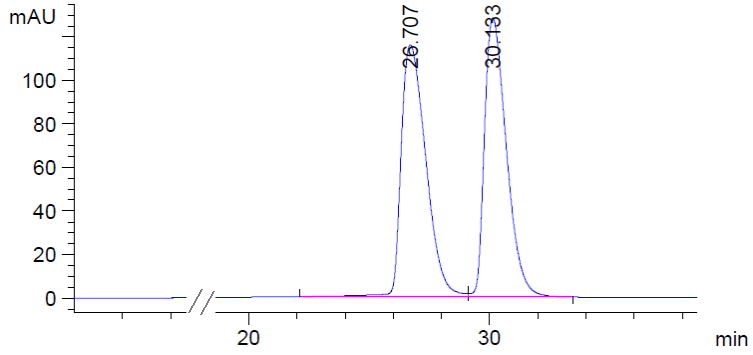
298.1590, found: 298.1604. The ee was determined to be 64 % by chiral HPLC (Chiralpak ASH, 99:1 hexane:*i*PrOH, 0.5 mL/min, 26.33 min major, 29.81 min minor).

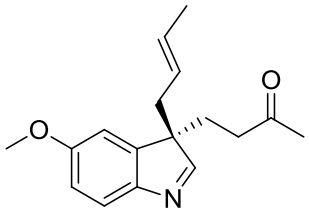
Chiral Chromatogram for **5-7o**.



Peak	Retention Time (min)	Area (mAU's)	Area %
1	26.334	2.37747e4	82.0034
2	29.813	5217.63428	17.9966
Total		2.89924e4	100.00

Racemic Chromatogram for **5-7o**.

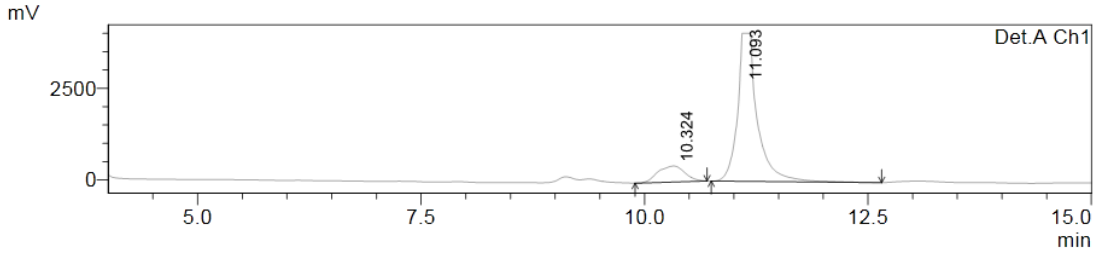




(*R*,*E*)-4-(3-(but-2-en-1-yl)-5-methoxy-3*H*-indol-3-yl)butan-2-one (5-7g).

Following general procedure C with Workup B for the synthesis of **5-7b**, the crude product was purified by flash chromatography on silica gel (Hexanes/EtOAc, 73:27) to give **5-7g** (32 mg, 62 %) as a colorless oil. $[\alpha_D]^{20}$ (c 1.0, CH_2Cl_2) = 9.86°.^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.83, (s, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 6.87 (dd, *J* = 2.5, 8.0 Hz, 1H), 6.7 (d, *J* = 2.5 Hz, 1H), 5.47-5.40 (m, 1H), 5.16-5.10 (m, 1H), 3.83 (s, 3H), 2.45-2.36 (m, 2H), 2.30-2.24 (m, 1H), 2.12-2.05 (m, 1H), 1.93-1.87 (m, 1H), 1.90 (s, 3H), 1.80-1.73 (m, 1H), 1.55 (d, *J* = 7.5 Hz, 3H).^{13}C NMR ($CDCl_3$, 125 MHz) δ 207.9, 176.1, 158.7, 129.6, 124.6, 121.5, 121.4, 116.7, 112.7, 108.6, 55.7, 38.8, 37.9, 30.0, 27.4, 26.6, 17.8. HRMS (EI+) m/z calculated for $C_{17}H_{22}NO_2$ $[M+H]^+$: 242.1651, found: 242.1647. The ee was determined to be 74 % by chiral HPLC (Chiralpak IA, 90:10 hexane:*i*PrOH, 1.0 mL/min, 11.09 min major, 10.32 min minor).

Chiral Chromatogram for **5-7g**.

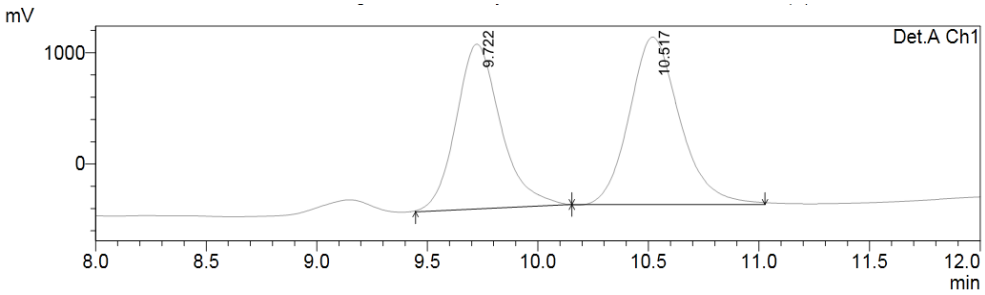


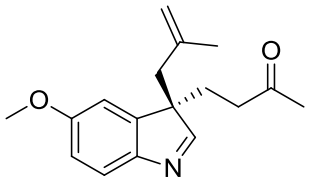
PeakTable

Detector A Ch1 210nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.324	9230638	434415	12.838	9.712
2	11.093	62669694	4038541	87.162	90.288
Total		71900333	4472956	100.000	100.000

Racemic Chromatogram for **5-7g**.



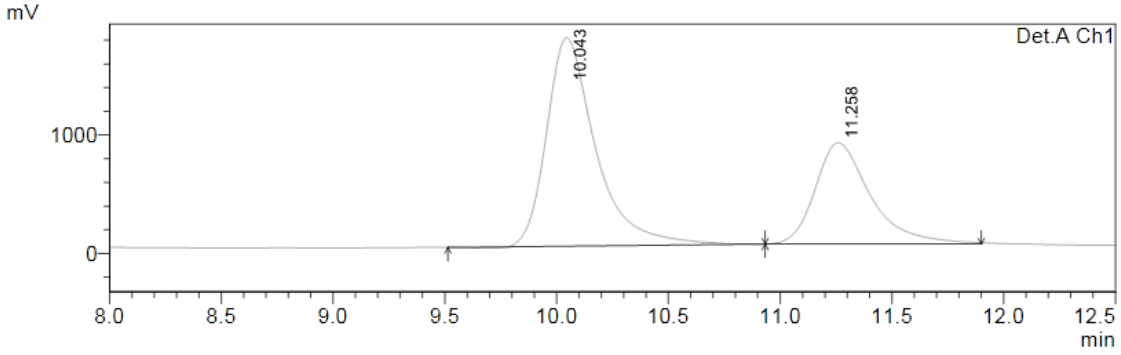


(*R*)-4-(5-methoxy-3-(2-methylallyl)-3*H*-indol-3-yl)butan-2-one (5-7h).

Following general procedure C with Workup A for the synthesis of **5-7b** with the exception of conduction the reaction at 40 ^{o}C overnight, the crude product was purified by flash chromatography on silica gel (Hexanes/EtOAc, 73:27) to give **5-7h** (40 mg, 76 %) as a light yellow oil. $[\alpha_D]^{20}$ (c 1.0, CH_2Cl_2) = -7.45^{o}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.90 (s, 1H), 7.51 (d, *J* = 8.5 Hz, 1H), 6.86 (dd, *J* = 2.5, 8.5 Hz, 1 H), 6.78 (d, *J* = 2.5 Hz, 1H), 4.68, (s, 1H), 4.57 (s, 1H), 3.83 (s, 1H), 2.70 (d, *J* = 14 Hz, 1 H), 2.47 (d, *J* = 14 Hz, 1H), 2.33-2.28 (m, 1H), 2.12-2.10 (m, 1H), 1.91-1.84 (m, 1H), 1.89 (s, 3H), 1.78-1.70 (m, 1H), 1.44 (s, 3H) .^{13}C NMR ($CDCl_3$, 125 MHz) δ 207.9, 176.2, 158.9, 149.4,

142.7, 140.7, 121.7, 115.2, 112.9, 108.8, 61.3, 55.9, 44.4, 37.8, 30.2, 28.9, 24.2. HRMS (EI+) m/z calculated for $C_{17}H_{22}NO_2$ $[M+H]^+$: 272.1651, found: 272.1662. The ee was determined to be 29 % by chiral HPLC (Chiralpak IA, 90:10 hexane:*i*PrOH, 1.0 mL/min, 10.04 min major, 11.26 min minor).

Chiral Chromatogram for **5-7h**.

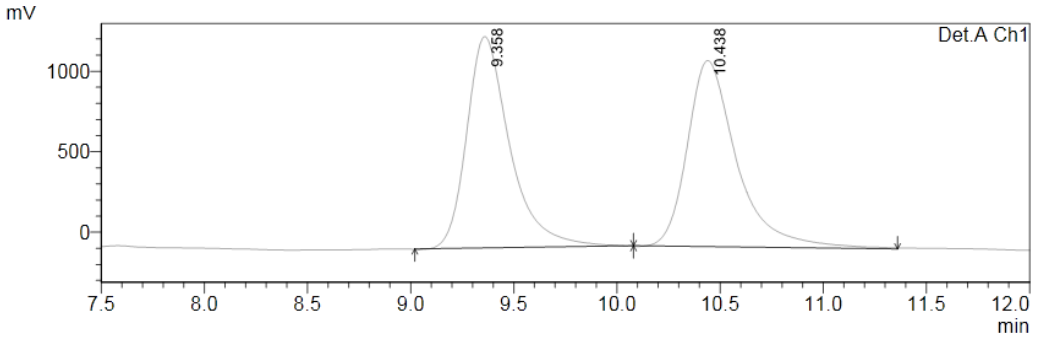


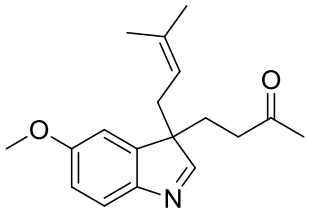
PeakTable

Detector A Ch1 210nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.043	26934533	1761333	64.469	67.269
2	11.258	14844262	857015	35.531	32.731
Total		41778795	2618348	100.000	100.000

Racemic Chromatogram for **5-7h**.

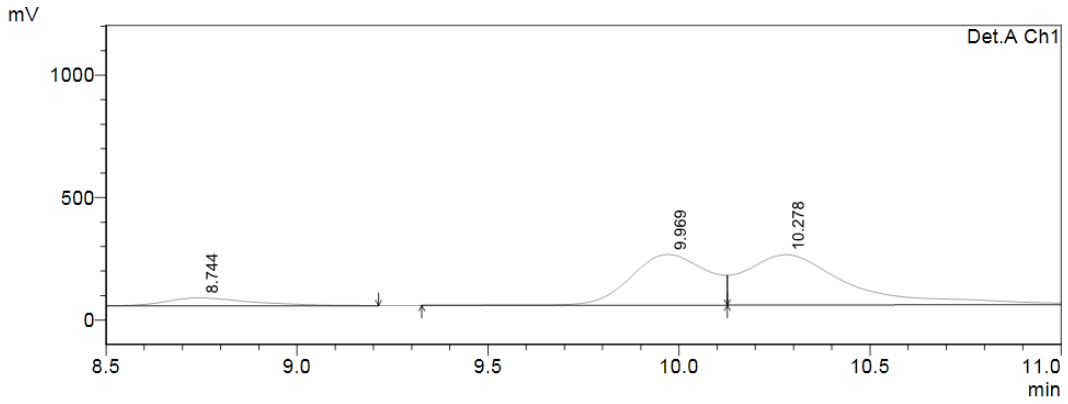




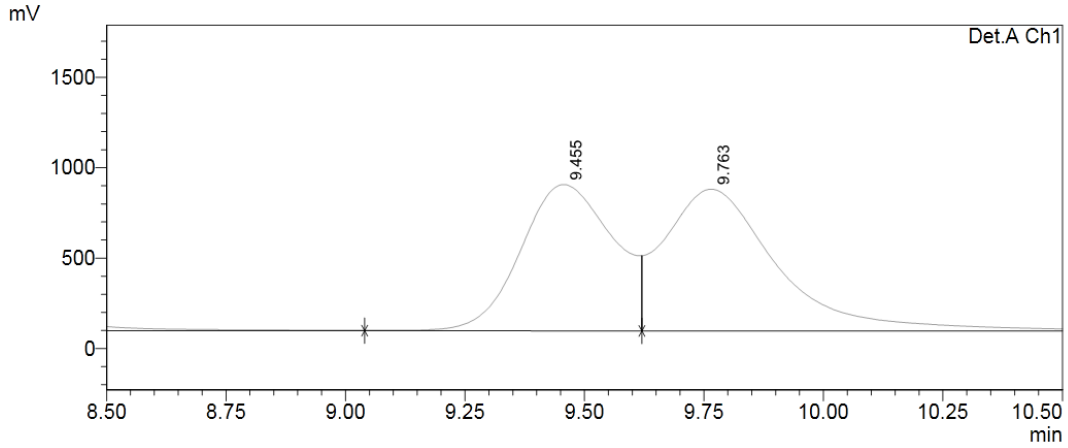
(±)-4-(5-methoxy-3-(3-methylbut-2-en-1-yl)-3*H*-indol-3-yl)butan-2-one (5-7i).

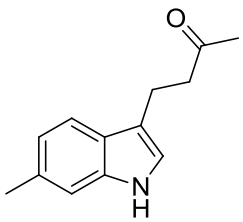
Following general procedure C using Workup B for the synthesis of **5-7b** with the exception of conduction the reaction at 45 ^{o}C overnight, the crude product was purified by flash chromatography on silica gel (Hexanes/EtOAc, 73:27) to give **5-7i** (28 mg, 52 %) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.82, (s, 1H), 7.52 (d, J = 8.4 Hz, 1H), 6.87 (dd, J = 2.7, 8.4 Hz, 1H), 6.7 (d, J = 2.7 Hz, 1H), 4.86 (t, J = 7.5 Hz, 1H), 3.83 (s, 3H), 2.47-2.26 (m, 3H), 2.17-2.06 (m, 1H), 1.95-1.73 (m, 2H), 1.89 (s, 3H), 1.60 (s, 3H), 1.53 (s, 3H).^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.9, 176.2, 158.7, 149.2, 142.9, 135.2, 121.4, 118.0, 112.7, 108.5, 61.6, 55.7, 37.9, 34.2, 30.0, 27.4, 25.8, 17.9. HRMS (EI+) m/z calculated for $C_{18}H_{24}NO_2$ $[M+H]^+$: 286.1802, found: 286.1808. The ee was determined to be 0 % by chiral HPLC (Chiralpak IA, 90:10 hexane:*i*PrOH, 1.0 mL/min, 9.97 min, 10.28 min for both enantiomers).

Chiral Chromatogram for **5-7i**.



Racemic Chromatogram for **5-7i**.

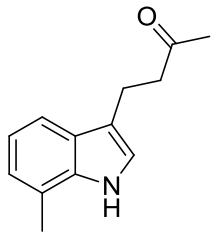




4-(6-methyl-1*H*-indol-3-yl)butan-2-one (5-8f).

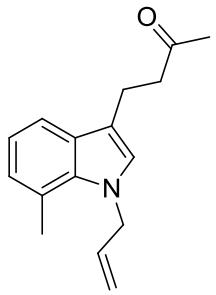
Following general procedure C for the synthesis of **5-7b,** the crude product was purified by flash chromatography on silica gel (Hexanes/EtOAc, 90:10) to give **5-8f** (38 mg, 89 %) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.92 (brs, 1H), 7.46 (d, J = 8.0 Hz,

1H), 7.06 (t, *J* = 7.0 Hz, 1H), 7.02-7.00 (m, 2H), 3.06 (t, *J* = 7.0 Hz, 2 H), 2.85 (t, *J* = 7.5 Hz, 2 H), 2.48 (s, 3H), 2.15 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 208.8, 135.9, 126.7, 122.6, 121.2, 120.4, 119.5, 116.4, 115.7, 44.1, 30.1, 19.5, 16.6. HRMS (EI+) m/z calculated for $C_{13}H_{14}NO$ $[M-H]^-$: 200.1081, found: 200.1083.



4-(7-methyl-1*H*-indol-3-yl)butan-2-one (5-8a).

Product was isolated by flash chromatography on silica gel (Hexanes/EtOAc, 73:27) as a beige solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.94 (brs, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.09-6.99 (m, 3 H), 3.06 (t, *J* = 7.8 Hz, 2H), 2.85 (t, *J* = 7.8 Hz, 2H), 2.48 (s, 3H), 2.15 (s, 3H).



4-(1-allyl-7-methyl-1*H*-indol-3-yl)butan-2-one.

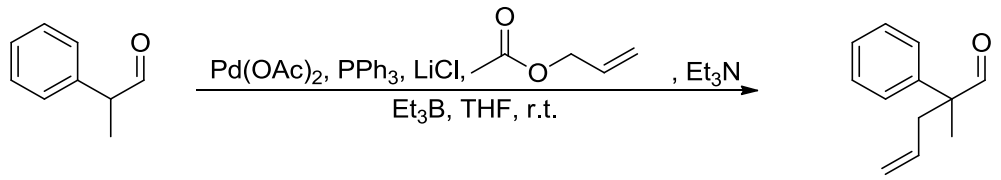
Product was isolated by flash chromatography on silica gel (Hexanes/EtOAc, 73:27) as a beige solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42 (d, *J* = 7.8 Hz, 1H), 7.00 (t, *J* = 7.2 Hz, 1H), 6.92 (d, *J* = 7.2 Hz, 1H), 6.80 (s, 1H), 6.08-5.96 (m, 1H), 5.11 (d, *J* = 10.5 Hz, 1H), 4.90-4.87 (m, 1H), 4.77 (d, *J* = 17.1 Hz, 1H), 3.02 (t, *J* = 7.8 Hz, 2H), 2.83 (t, *J* = 7.8 Hz, 2H), 2.66 (s, 3H), 2.14 (s, 3H).

Synthesis of the Racemic HPLC standards.

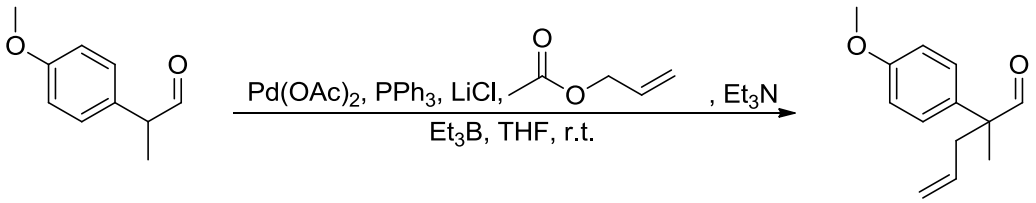
A flame-dried flask was charged under N_2 with Pd_2dba_3 (3.8 mg, 0.0047 mmol), tri(2-furyl)phosphine (2.1 mg, 0.00834 mmol) and **1a-o** (0.14 mmol). Toluene (2.8 mL) was then added at RT to the reaction flask and Et_3B (0.14 mL, 0.14 mmol, 1M in THF) was added. The reaction was sealed by wrapping with parafilm and stirred overnight (14 hours) at RT. The reaction was then concentrated and a silica gel column (same polarity as chiral **2a-o**) was run to give racemic **2a-o** in 50-78% yield. The materials were identical in appearance and spectral analysis to the chiral **2a-o**.

CHAPTER VI

General Proceedure A. The Racemic Palladium-Catalyzed Allylic Alkylation of Aldehydes. The Synthesis of 2-methyl-2-phenylpent-4-enal (6-3) is Representative.

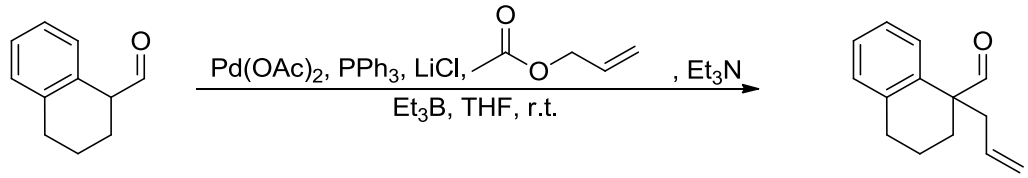


A flame-dried flask was charged with $Pd(OAc)_2$ (4.7 mg, 0.021 mmol), PPh_3 (10.9 mg, 0.041 mmol), and dried LiCl (8.9 mg, 0.21 mmol). The flask was placed under N_2 and THF (1 mL) was added. To this solution was added **6-2** (30.9 μL, 0.23 mmol), allyl acetate (26 μL, 0.24 mmol), Et_3N (35 μL, 0.25 mmol), and Et_3B (0.51 mL, 0.51 mmol, 1M in hexanes) at room temperature. The reaction was stirred and monitored by TLC. The reaction was complete after 40 minutes and was concentrated *en vacuo*. The material was then loaded onto a pasture pipette silica column that had been neutralized by suspending the silica gel in a 1% Et_3N in hexanes solution. The column was run with ~7 mL of 90:10 hexanes:EtOAc to give **6-3** (30.5 mg, 81% yield) as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 9.52 (s, 1H), 7.41-7.37 (m, 2H), 7.31-7.28 (m, 1H), 7.27-7.24 (m 2H), 5.59-5.51 (m, 1H), 5.08-5.02 (m, 2H), 2.72-2.61 (m, 2H), 1.45 (s, 3H). The spectra were consistent with the literature.[xvii]



2-(4-methoxyphenyl)-2-methylpent-4-enal (6-5)

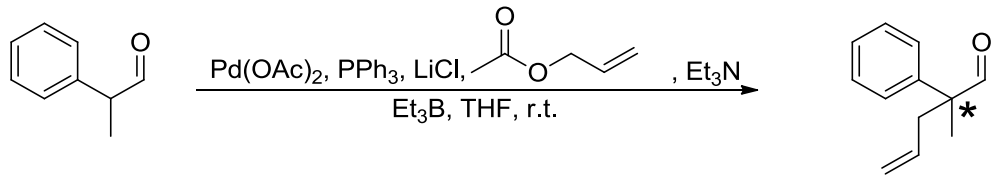
The starting material **6-4** was prepared according to the literature.[xviii] **6-5** was prepared according to general proceedure A and the reaction was run for 18 hours (38.7 mg, 82% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.46 (s, 1H), 7.18 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 5.62-5.48 (m, 1H), 5.08-5.01 (m, 2H), 3.81 (s, 3H), 2.71-2.56 (m, 2H), 1.42 (s, 3H). The spectra were consistent with the literature.[xix]



1-allyl-1,2,3,4-tetrahydronaphthalene-1-carbaldehyde (6-7)

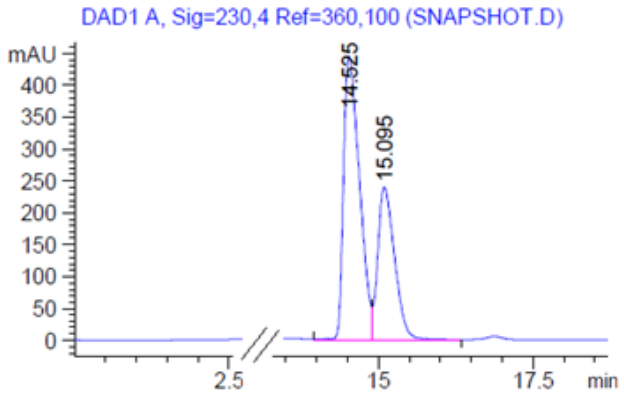
The starting material **6-6** was prepared according to the literature.[xviii] **6-7** was prepared according to general proceedure A and the reaction was run for 18 hours (41.5 mg, 90% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.56 (s, 1H), 7.21-7.14 (m, 4H), 5.64-5.56 (m, 1H), 5.09-5.03 (m, 2H), 2.80-2.77 (m, 2H), 2.64-2.62 (m, 2H), 2.12-2.07 (m, 1H), 1.90-1.74 (m, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.4, 139.0, 134.3, 134.0, 130.2, 128.6, 127.3, 126.7, 118.8, 53.4, 41.4, 30.2, 28.2, 19.5. HRMS (EI+) m/z calculated for $C_{14}H_{17}O$ $[M+H]^+$: 201.1274, found: Not Found.

General Proceedure B. The Racemic Palladium-Catalyzed Allylic Alkylation of Aldehydes. The Synthesis of Enantioenriched 2-methyl-2-phenylpent-4-enal (6-3) is Representative.



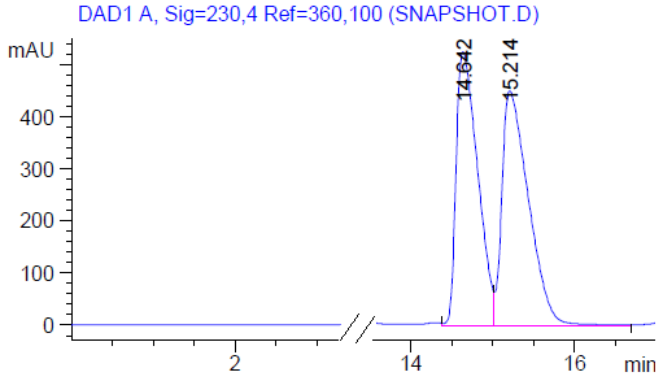
A flame-dried flask was charged with $Pd_2(dba)_3$ (6.3 mg, 0.0069 mmol), **6-L3** (7.4 mg, 0.0138 mmol), and dried LiCl (8.9 mg, 0.21 mmol). The flask was placed under N_2 and THF (1 mL) was added. The reaction was stirred for 10 minutes at r.t. To this solution was added **6-2** (30.9 μL, 0.23 mmol), allyl acetate (26 μL, 0.24 mmol), Et_3N (35 μL, 0.25 mmol), and Et_3B (0.51 mL, 0.51 mmol, 1M in hexanes) at room temperature. The reaction was stirred and monitored by TLC. The reaction was complete after 1 hour and was concentrated *en vacuo*. The material was then loaded onto a pasture pipette silica column that had been neutralized by suspending the silica gel in a 1% Et_3N in hexanes solution. The column was run with ~7 mL of 90:10 hexanes:EtOAc to give **6-3** (36.6 mg, 91% yield) as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 9.52 (s, 1H), 7.41-7.37 (m, 2H), 7.31-7.28 (m, 1H), 7.27-7.24 (m 2H), 5.59-5.51 (m, 1H), 5.08-5.02 (m, 2H), 2.72-2.61 (m, 2H), 1.45 (s, 3H). The spectra were consistent with the literature.[xvii] The ee was determined to be 26% by chiral HPLC (Chiralpak AS-H, 99:1 hexane:*i*PrOH, 0.5 mL/min, 14.53 min major, 15.10 min minor).

Chiral Chromatogram for **6-3**

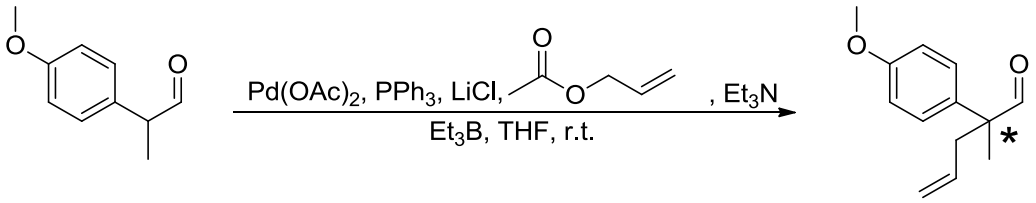


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.525	VV	0.2872	8067.55957	445.72638	63.3922
2	15.095	VV	0.2977	4658.86182	240.79857	36.6078
Totals :				1.27264e4	686.52495	

Racemic Chromatogram for **6-3**



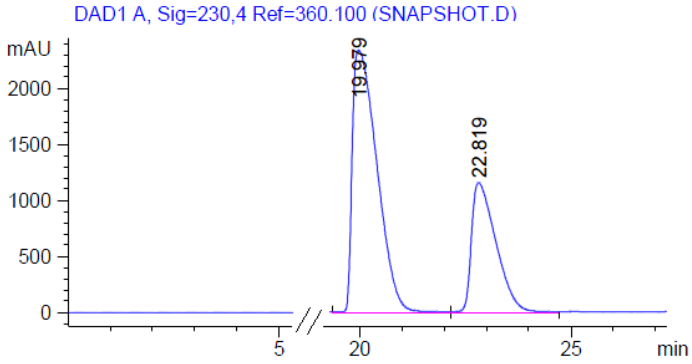
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.642	VV	0.2893	9592.92578	524.62201	48.5657
2	15.214	VV	0.3467	1.01595e4	451.19696	51.4343
Totals :				1.97525e4	975.81897	



Enantioenriched 2-(4-methoxyphenyl)-2-methylpent-4-enal (6-5)

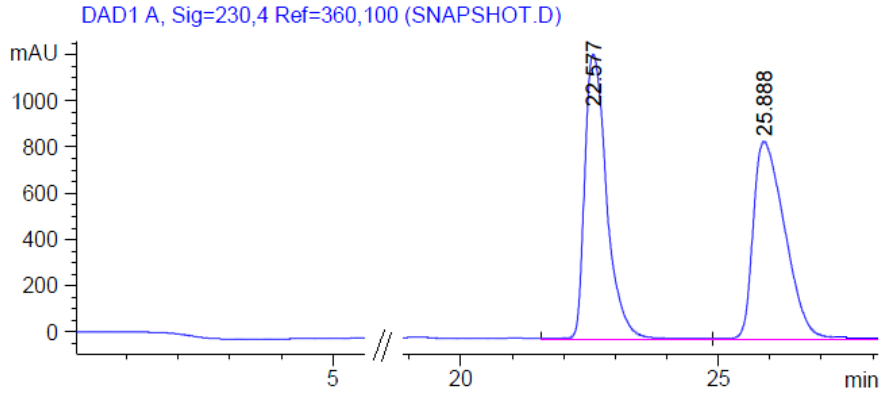
The starting material **6-4** was prepared according to the literature.[xviii] **6-5** was prepared according to general proceedure B and the reaction was run for 19 hours (50.3 mg, >95% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.46 (s, 1H), 7.18 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 5.62-5.48 (m, 1H), 5.08-5.01 (m, 2H), 3.81 (s, 3H), 2.71-2.56 (m, 2H), 1.42 (s, 3H). The spectra were consistent with the literature.[xix] The ee was determined to be 34% by chiral HPLC (Chiralpak AS-H, 99:1 hexane:*i*PrOH, 0.5 mL/min, 19.98 min major, 22.82 min minor).

Chiral Chromatogram for **6-5**.

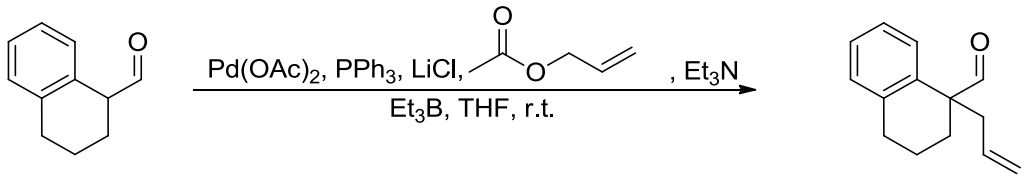


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.979	VV	0.6468	9.52737e4	2340.85547	67.0192
2	22.819	VV	0.6242	4.68850e4	1158.33472	32.9808
Totals :				1.42159e5	3499.19019	

Racemic Chromatogram for **6-5**.



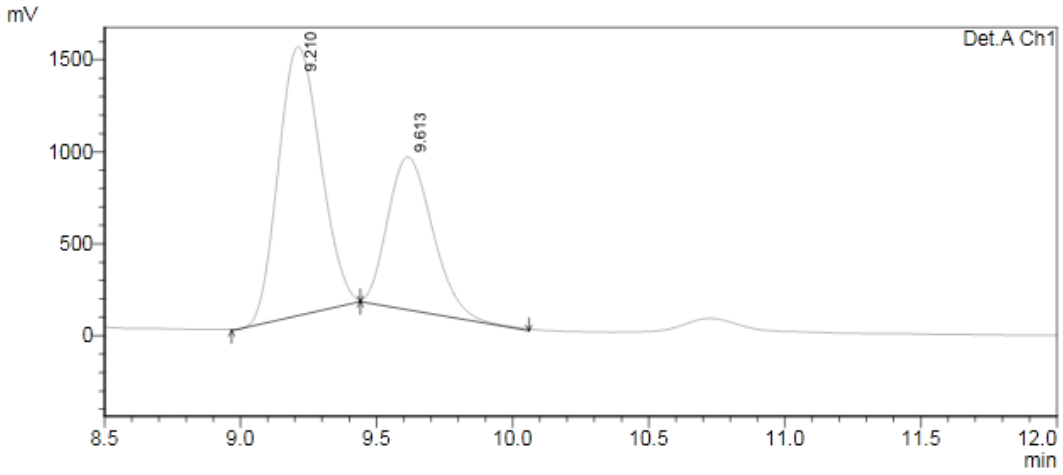
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.577	VV	0.4752	3.65660e4	1228.79443	50.0466
2	25.888	VBA	0.6835	3.64979e4	852.44196	49.9534
Totals :				7.30639e4	2081.23639	



Enantioenriched 1-allyl-1,2,3,4-tetrahydronaphthalene-1-carbaldehyde (6-7)

The starting material **6-6** was prepared according to the literature.[xviii] **6-7** was prepared according to general proceedure B and the reaction was run for 20 hours (48.0 mg, >95% yield). Proton and carbon NMR were consistent with the racemic sample. The ee was determined to be 25% by chiral HPLC (Chiralpak IB, 97:3 hexane:*i*PrOH, 0.5 mL/min, 9.21 min major, 9.61 min minor).

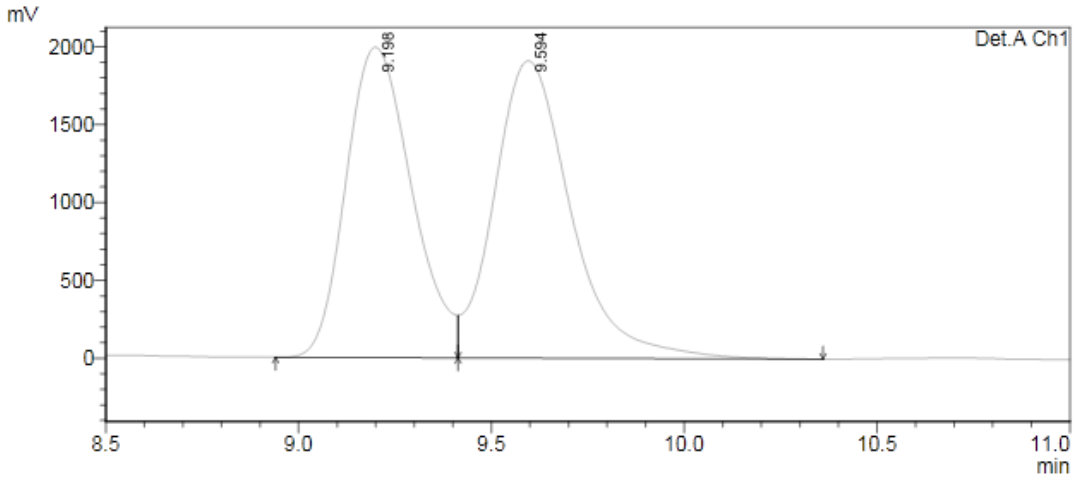
Chiral Chromatogram for **6-7**.



Detector A Ch1 210nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.210	15805618	1462094	62.171	63.783
2	9.613	9617026	830197	37.829	36.217
Total		25422644	2292291	100.000	100.000

Racemic Chromatogram for **6-7**.



Detector A Ch1 210nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.198	23650510	1992468	47.281	51.085
2	9.594	26370643	1907822	52.719	48.915
Total		50021152	3900290	100.000	100.000

---

i. This material was prepared according to the method of Myers *et al. J. Am. Chem. Soc.* **1997**, *119*, 6496-6511.

ii. This material was prepared according to the method of Pattenden *et al. Synlett* **2001**, 365-368.

iii. Negishi, E.; Pour, M.; Cederbaum, F.E.; Kotora, M. *Tetrahedron* **1998**, *54*, 7057-7074.

iv. McIntosh, M. C.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 4823-4832.

v. Yakelis, N. A.; Roush, W. R. *Org. Lett.* **2001**, *3*, 957-960.

vi. Duan, M.; Paquette, L. A.; *Angew. Chem., Int. Ed.*, **2001**, *40*, 3632-3636.

vii. Guo, H.; Mortensen, M. S.; O'Doherty, G. A. *Org. Lett*. **2008**, *10*, 3149-3152.

viii. The potassium serinate solution was prepared by mixing 6.59 g of serine, 4.71 g of $KHCO_3$ and 3.25 g of K_2CO_3 in 55 mL of H_2O.

ix. The potassium serinate solution was prepared by mixing 6.59 g of serine, 4.71 g of $KHCO_3$ and 3.25 g of K_2CO_3 in 55 mL of H_2O.

x. Negishi, E.; Van Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc*. **1985**, *107,* 6639-6647.

xi . Musso, D. L.; Clarke, M. J.; Kelley, J. L.; Boswell, G. E.; Chen, G. *Org. and Biomol. Chem.*, **2003**, *1*, 498-506.

xii. Stork, G; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173-2174.

xiii. Chen, M.-J.; Narkunan, K.; Liu, R.-S. *J. Org. Chem.* **1999**, *64*, 8311-8318.

xiv. Tanaka, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 8862–8863.

xv. Trost, B. M. ; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314-6315.

xvi. This workup was developed for substrates **2f**-**2k** as Workup B occasionally gave borane contamination in the product. Workup C was developed on **2i** and did not result in a decrease in yield.

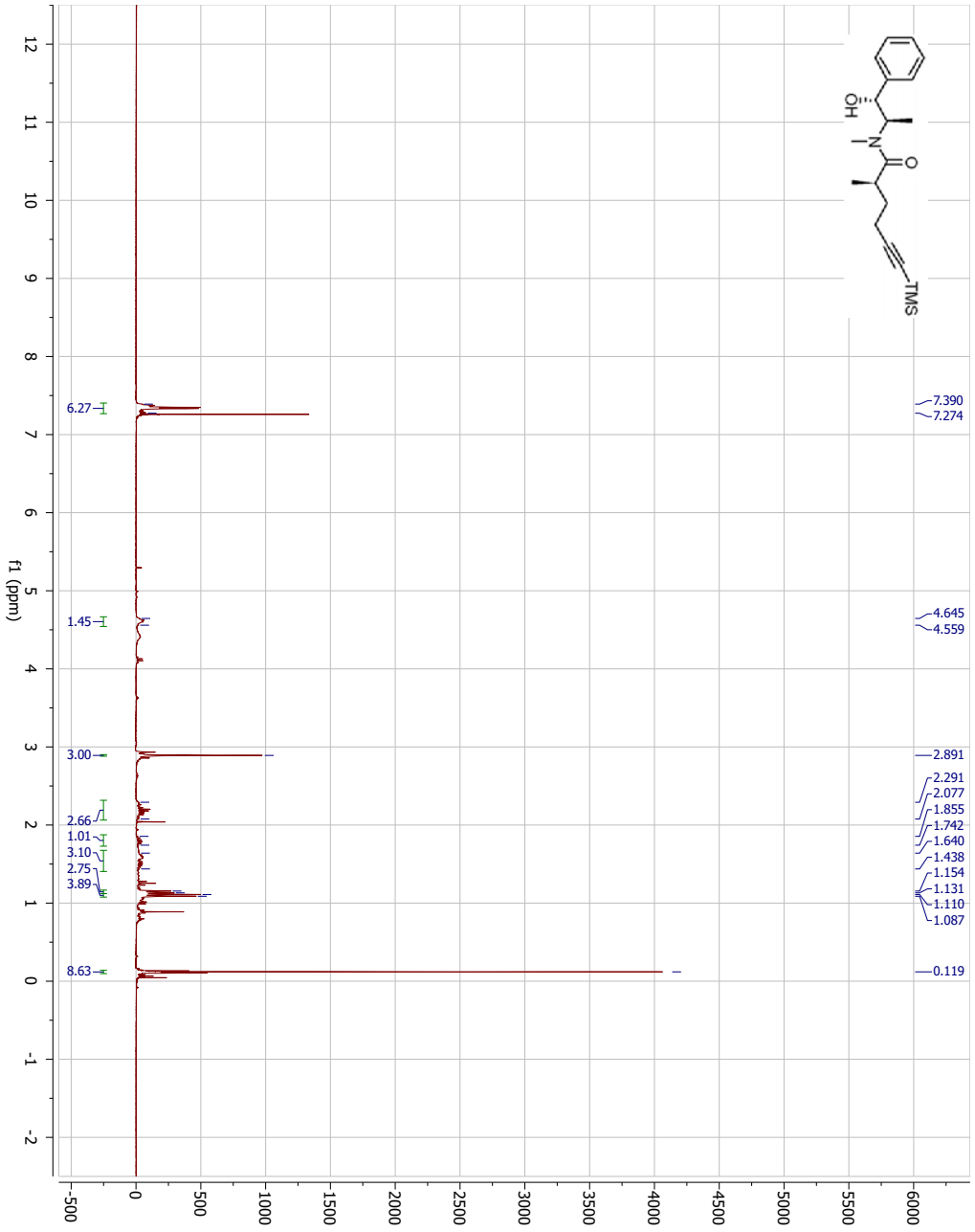
xvii. Kimura, M.; Horino, Y.; Mukai, R.; Tanaka, S.; Tamaru, Y. *J. Am. Chem. Soc.* **2001**, *123*, 10401-10402.

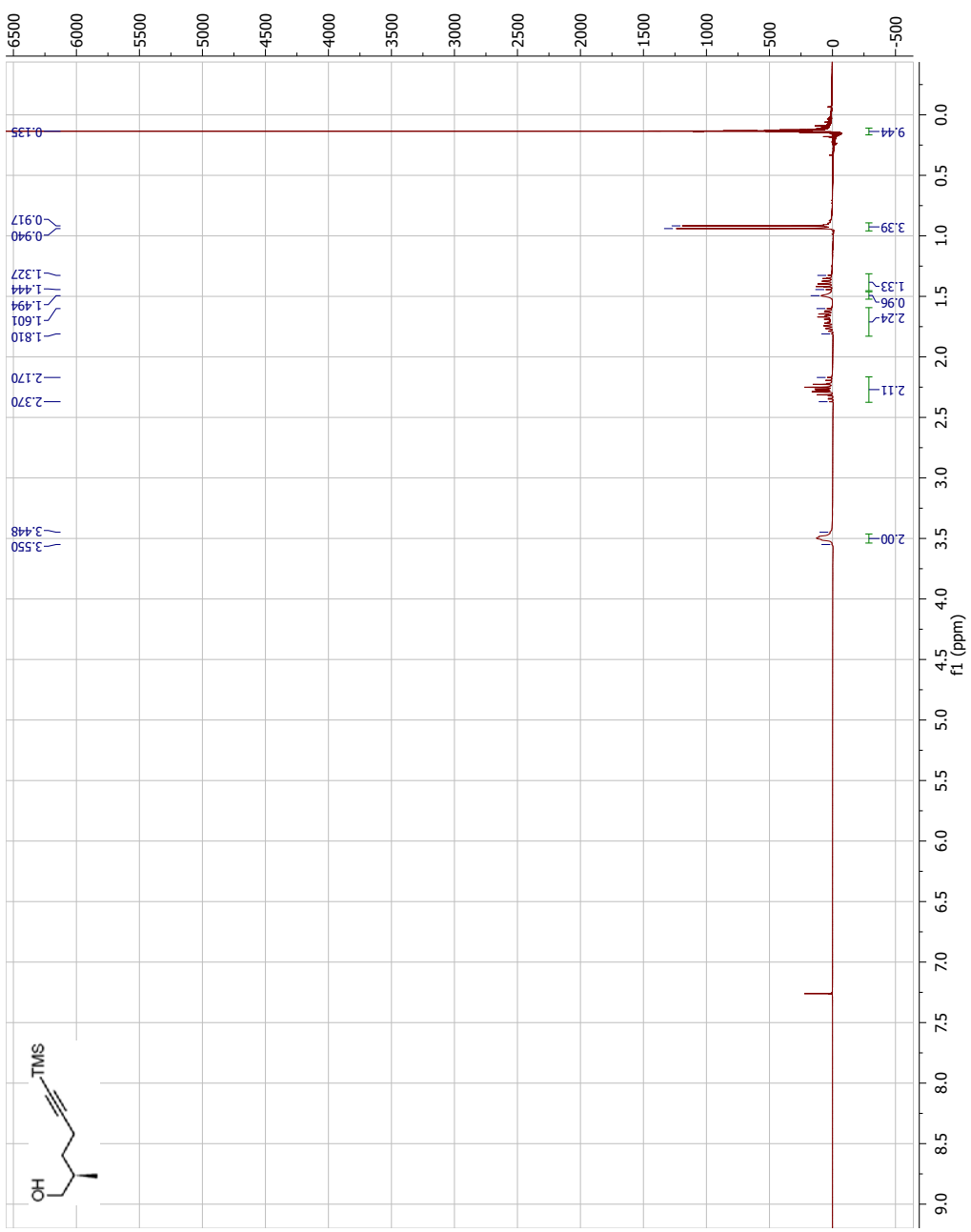
xviii. Havare, N.; Plattner, D. A. *Org. Lett*. **2012**, *14*, 5078-5081.

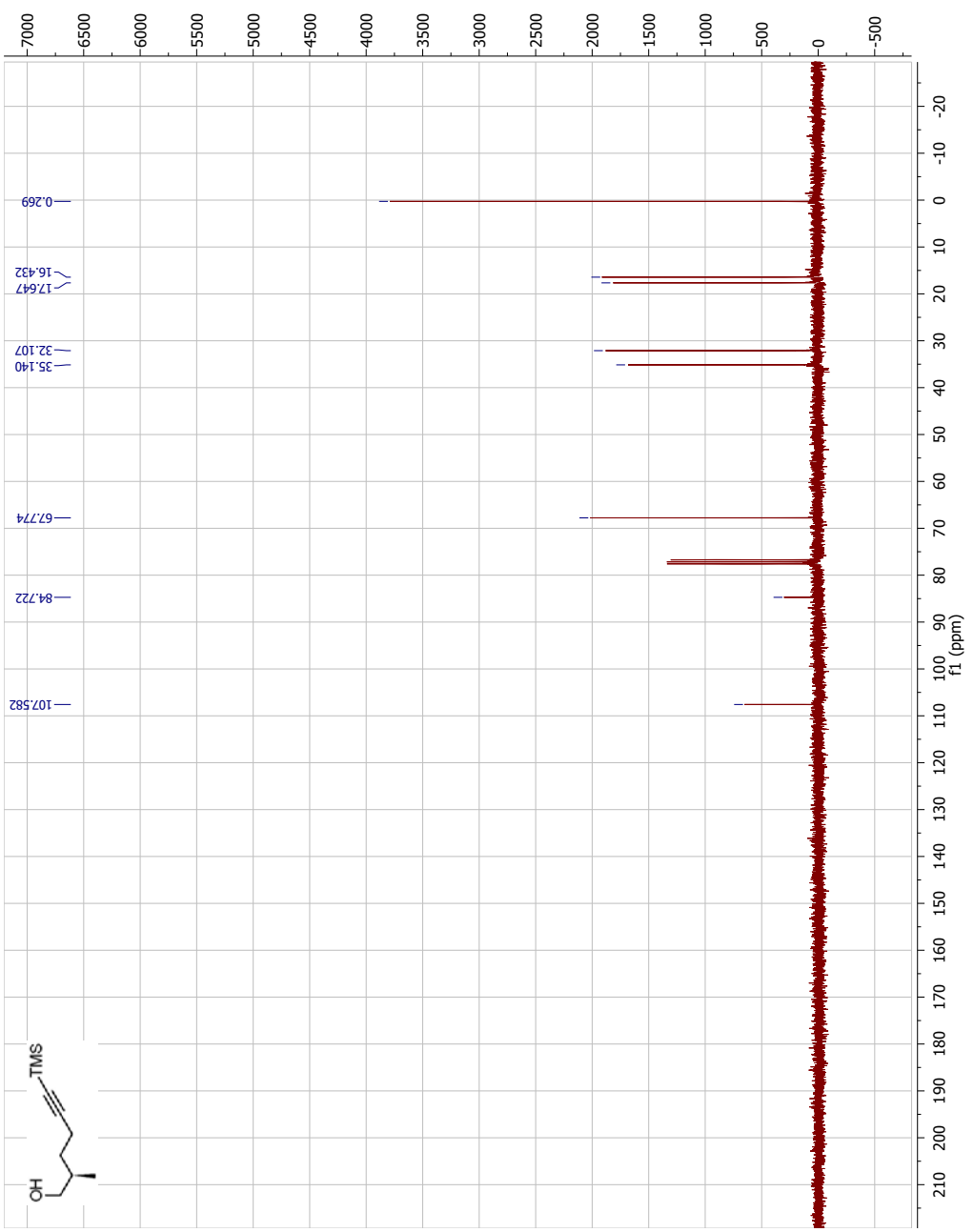
xix. Jiang, G.; List, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 9471-9474.

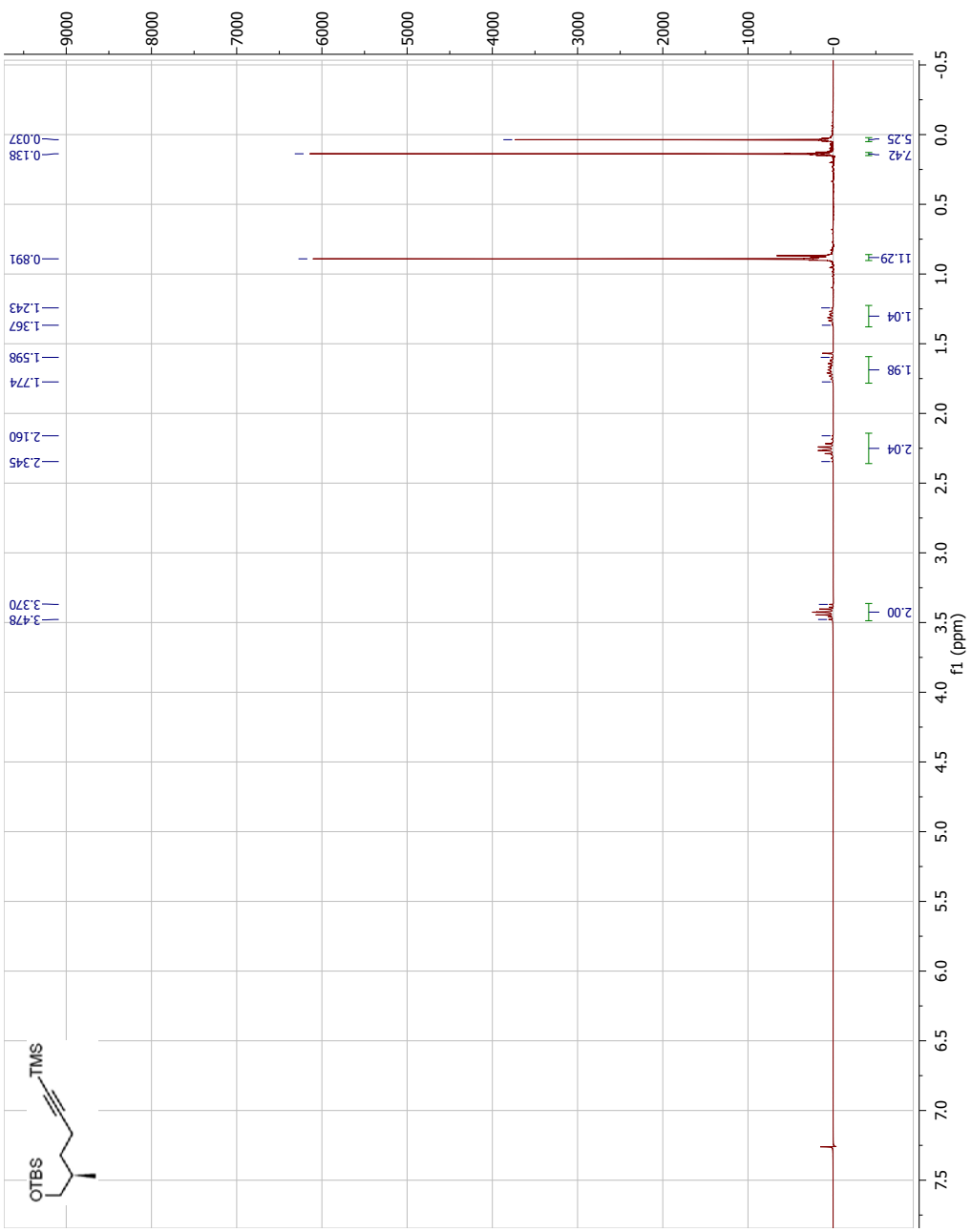
APENDIX B

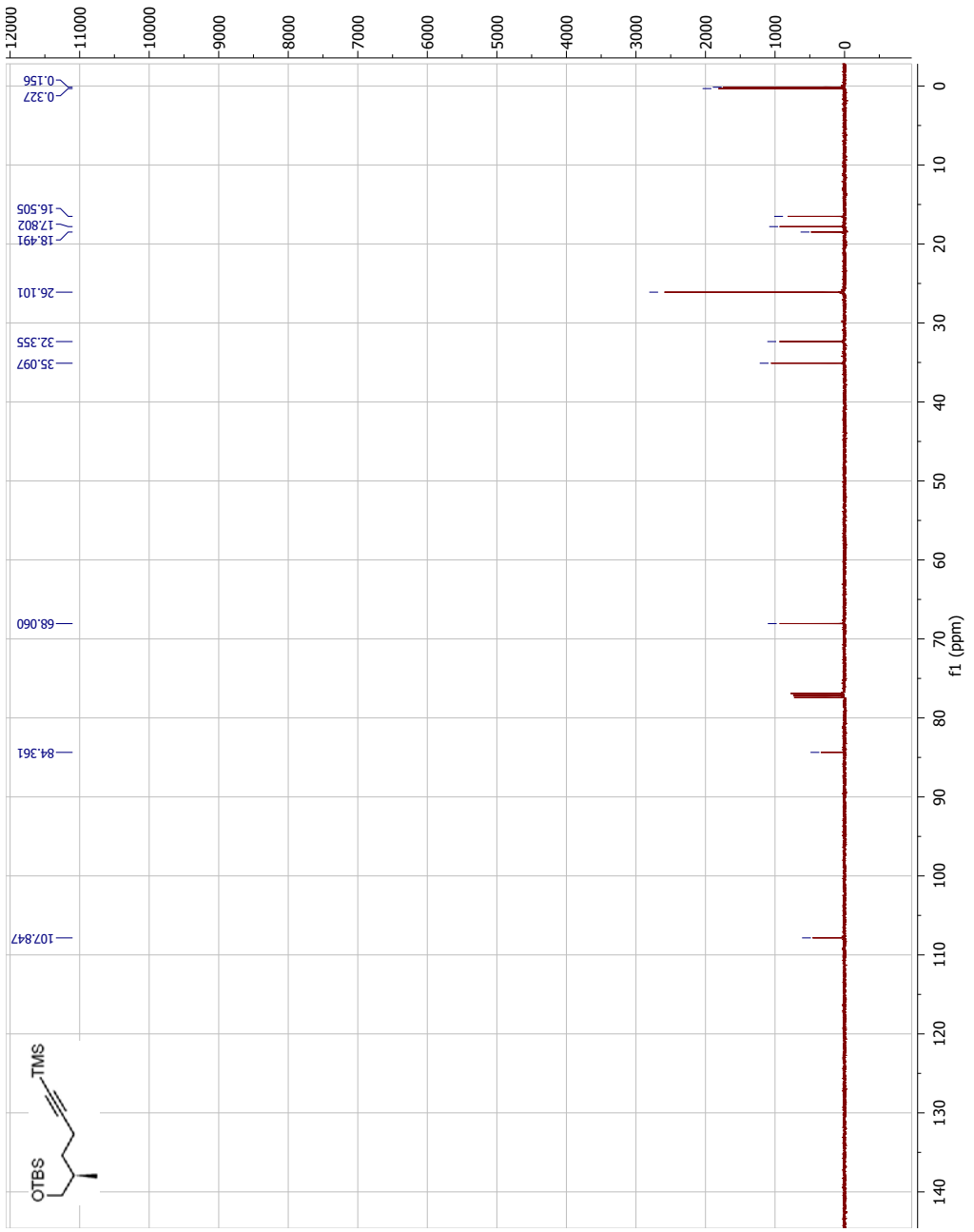
NMR SPECTRA

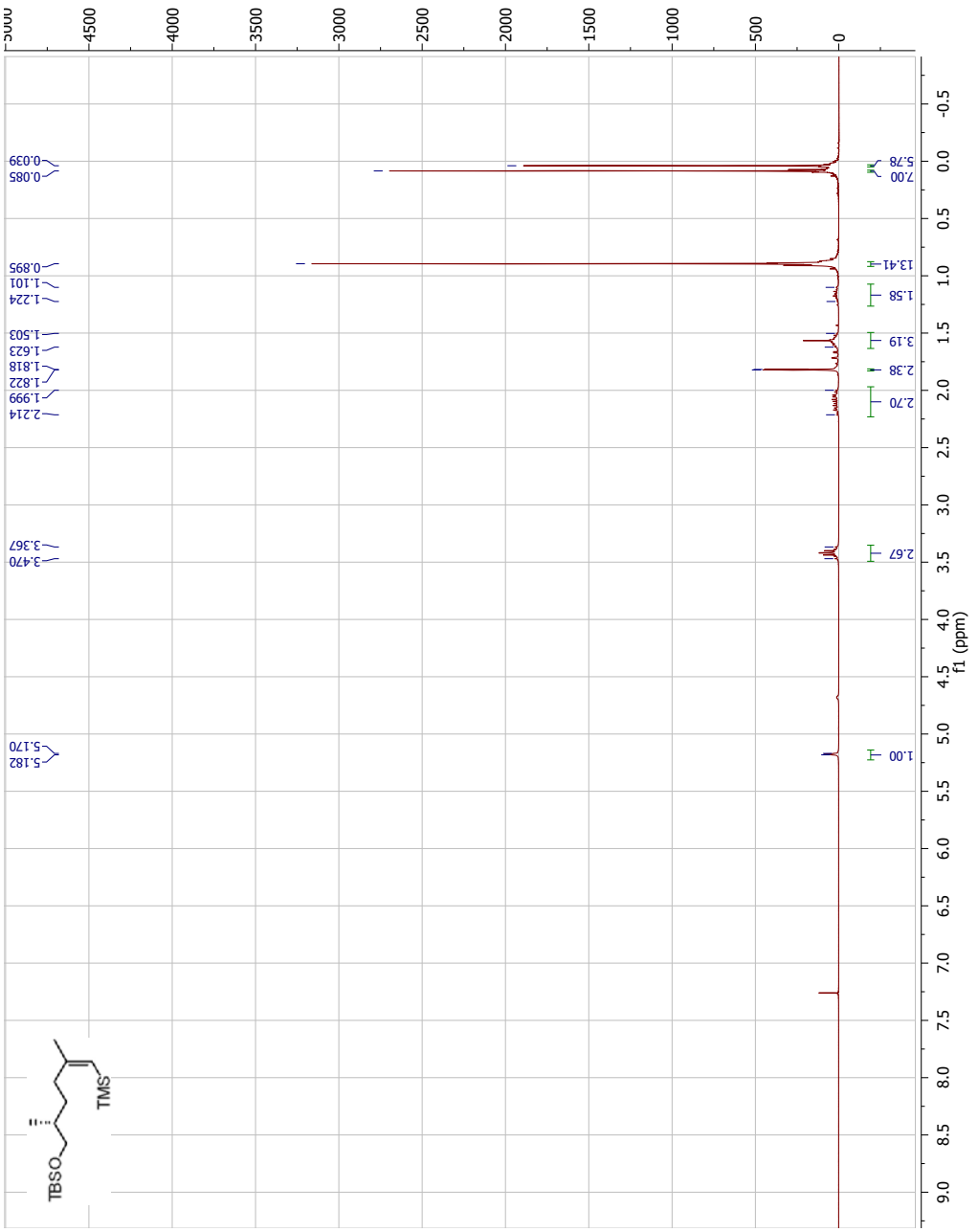

f1 (ppm)
6.27
1.45
3.00
2.66
1.01
3.10
2.75
3.89
8.63
7.390
7.274
4.645
4.559
2.891
2.291
2.077
1.855
1.742
1.640
1.438
1.154
1.131
1.110
1.087
0.119
OH
N
O
TMS

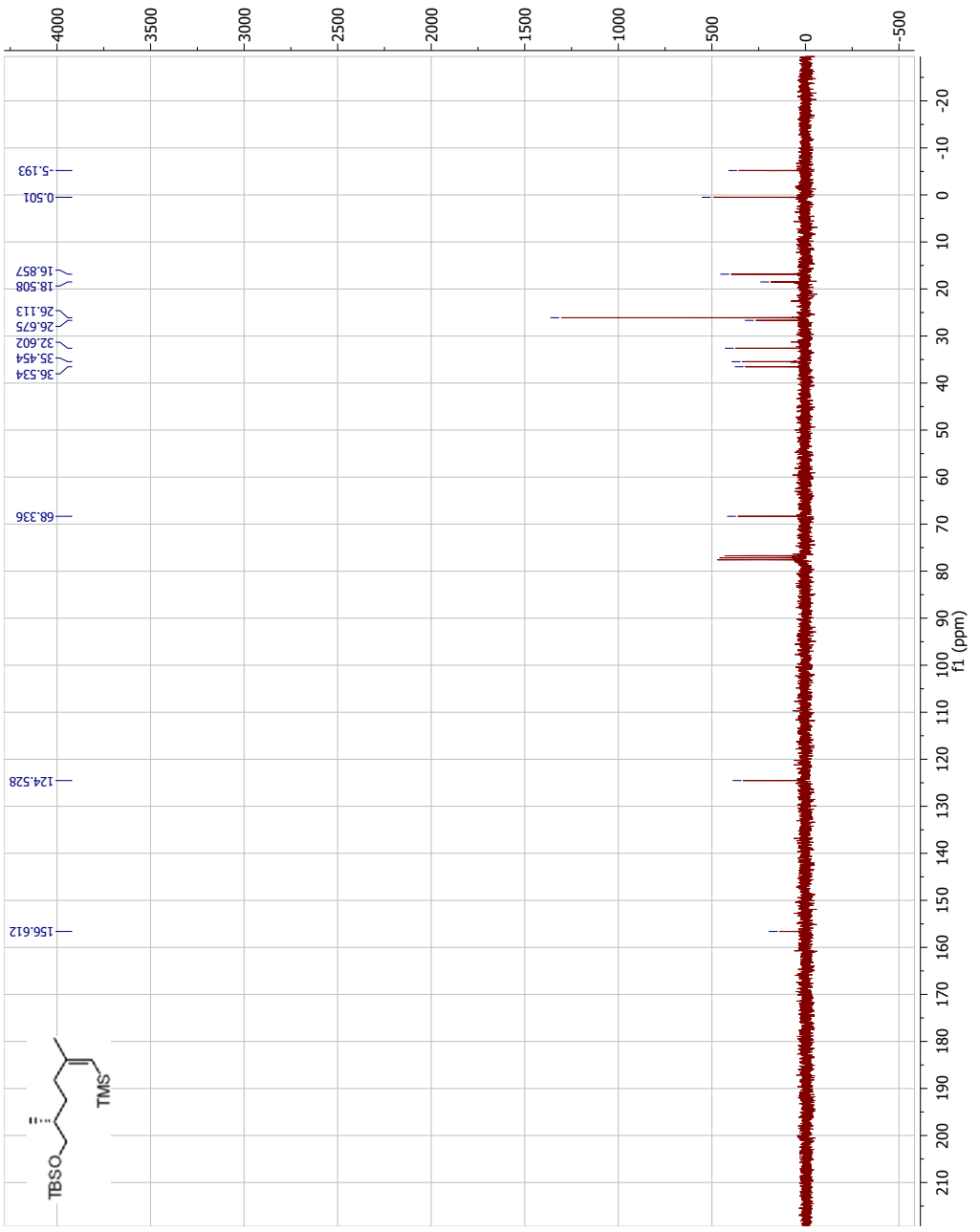

TMS
OH
f1 (ppm)

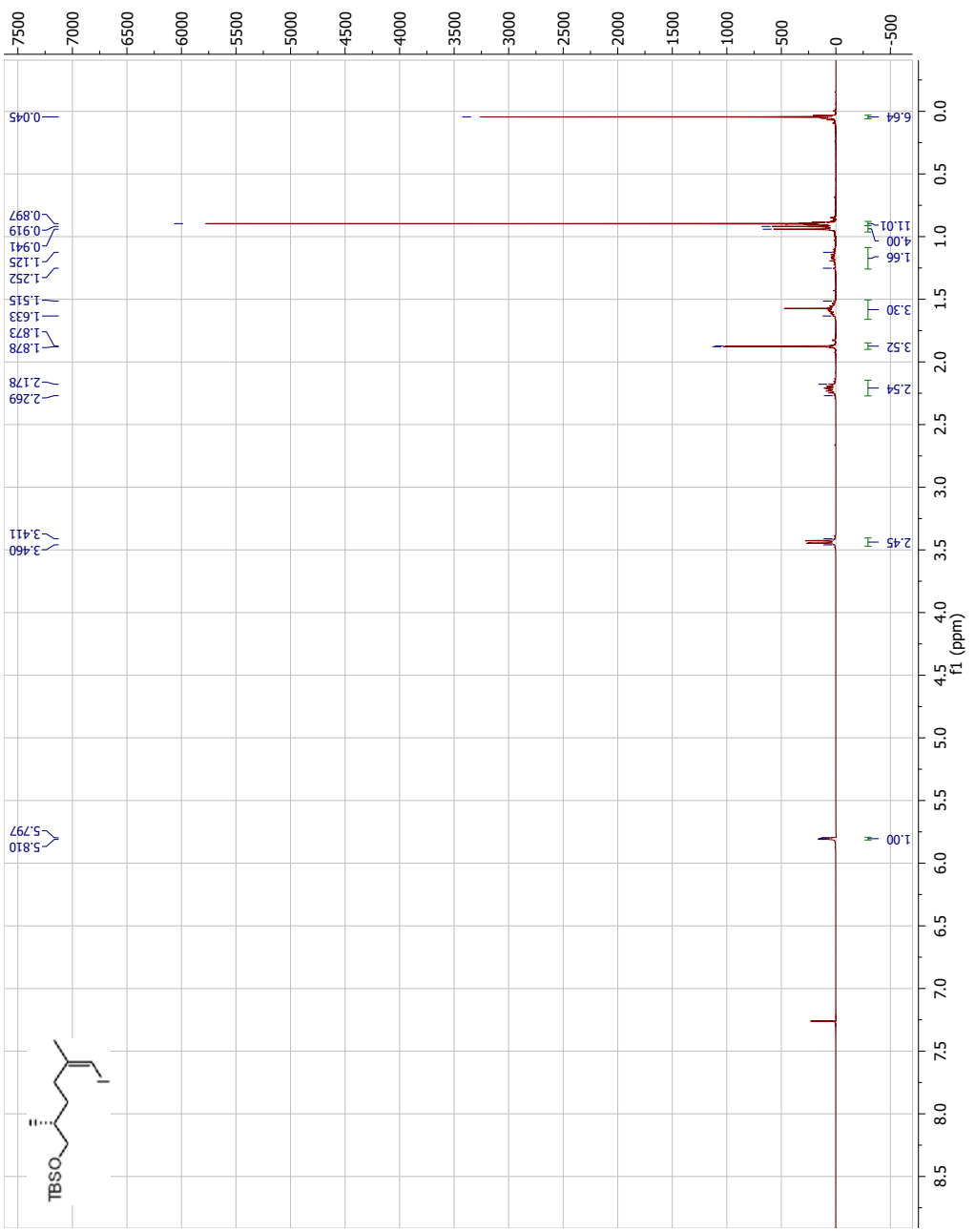

0.269
16.432
17.647
32.107
35.140
67.774
84.722
107.582
TMS
OH
f1 (ppm)

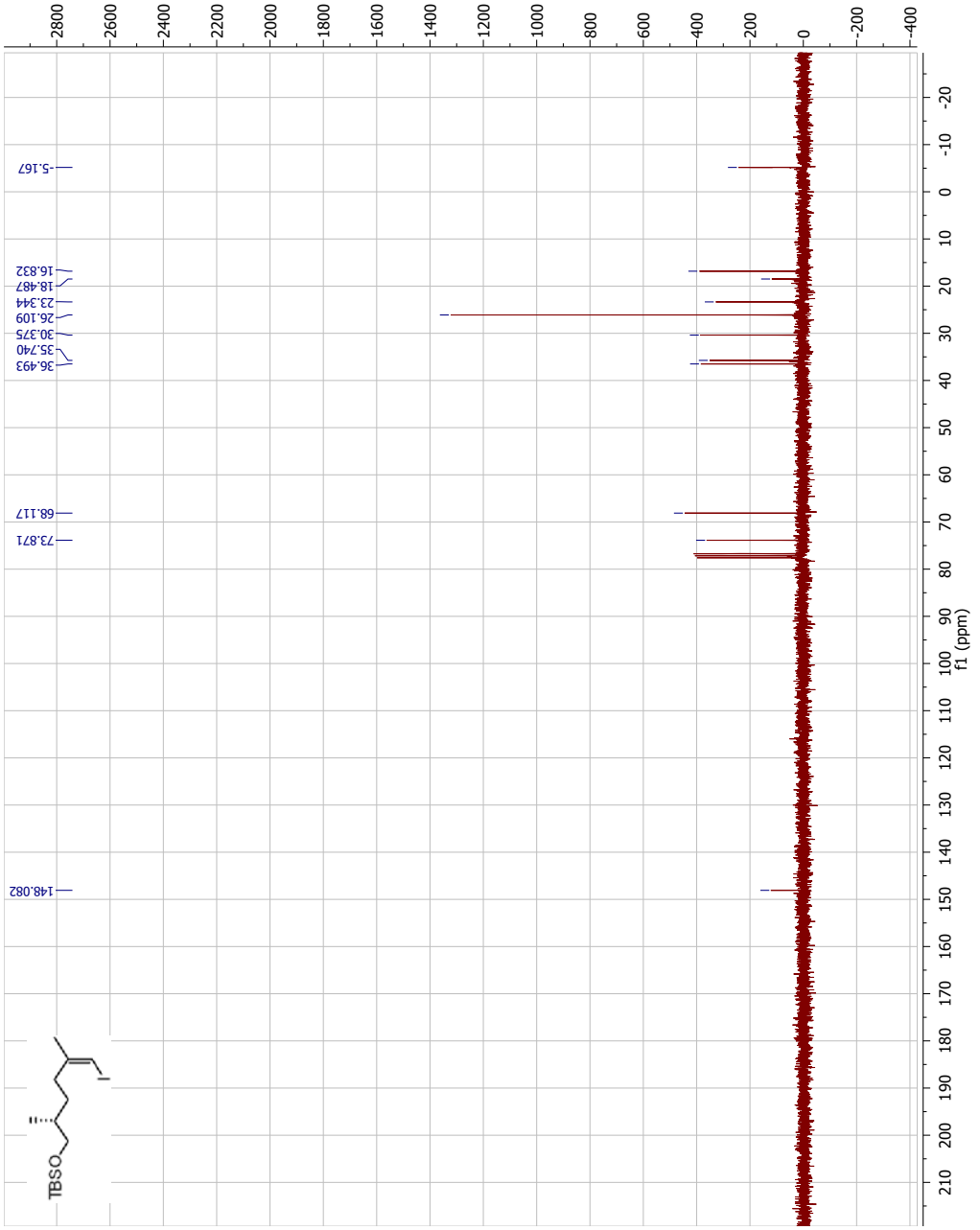

TMS
OTBS
f1 (ppm)
5.25
7.42
11.29
1.04
1.98
2.04
2.00
0.037
0.138
0.891
1.243
1.367
1.598
1.774
2.160
2.345
3.370
3.478

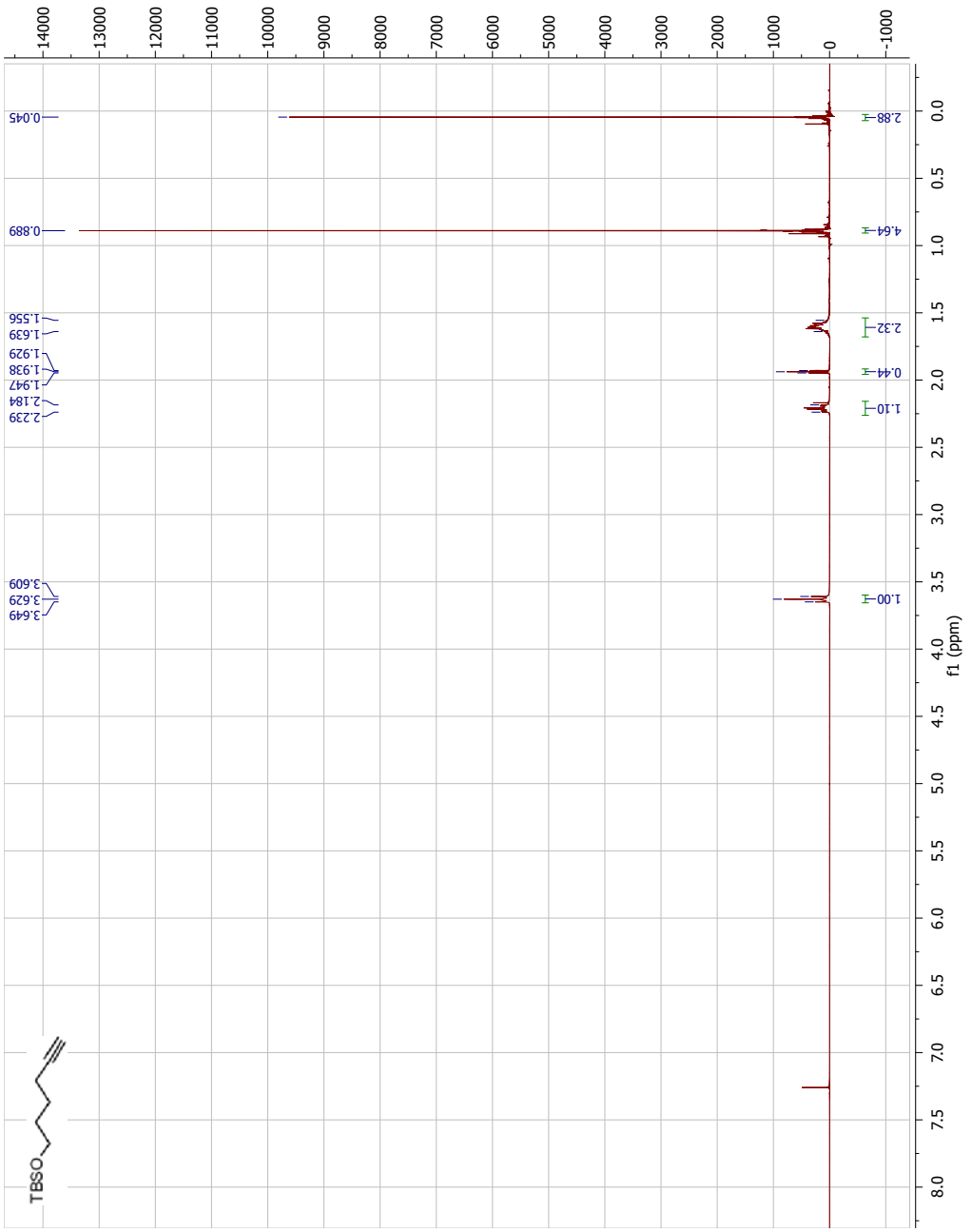

0.156
0.327
16.505
17.802
18.491
26.101
32.355
35.097
68.060
84.361
107.847
OTBS
TMS
f1 (ppm)

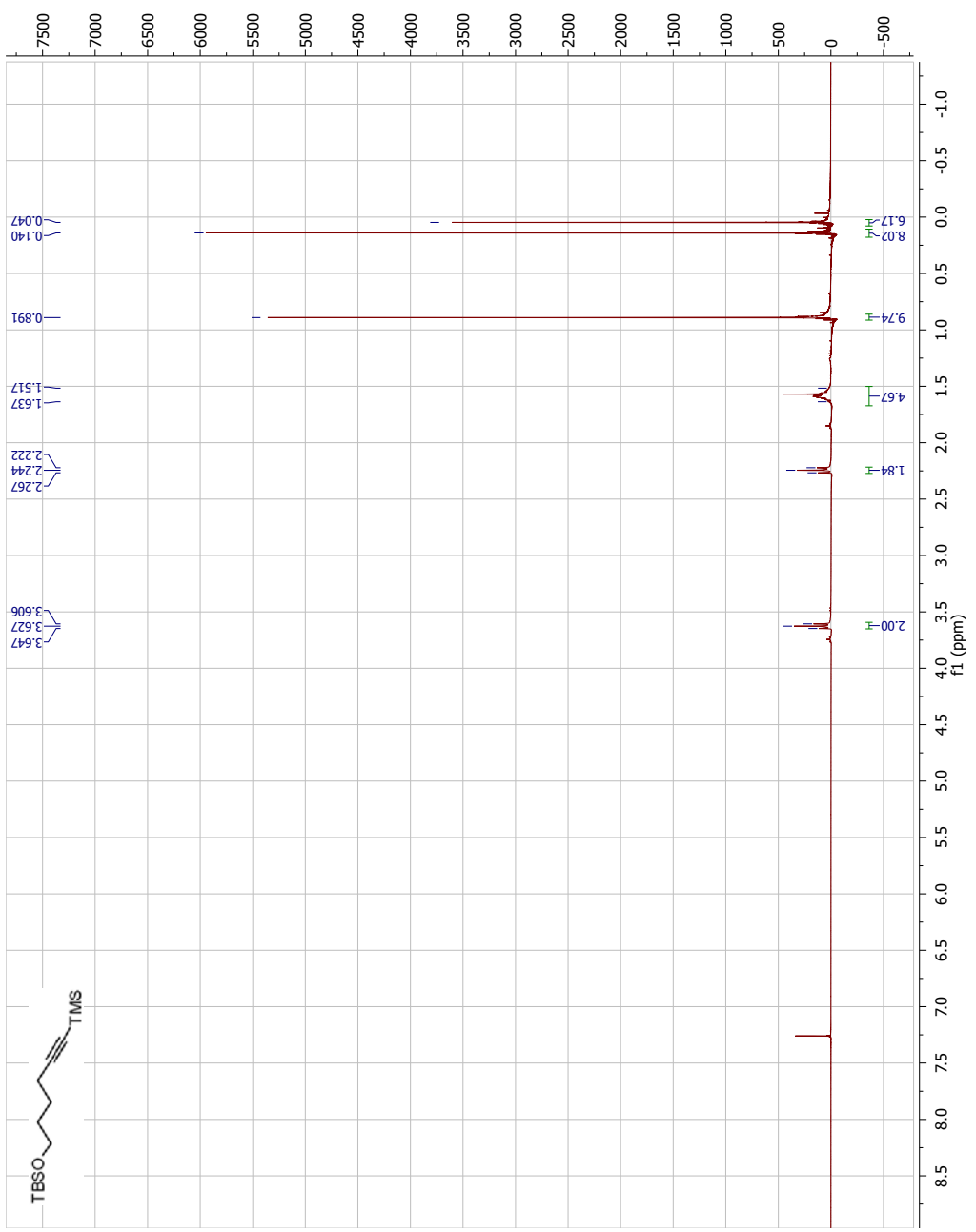

TBSO
TMS
f1 (ppm)

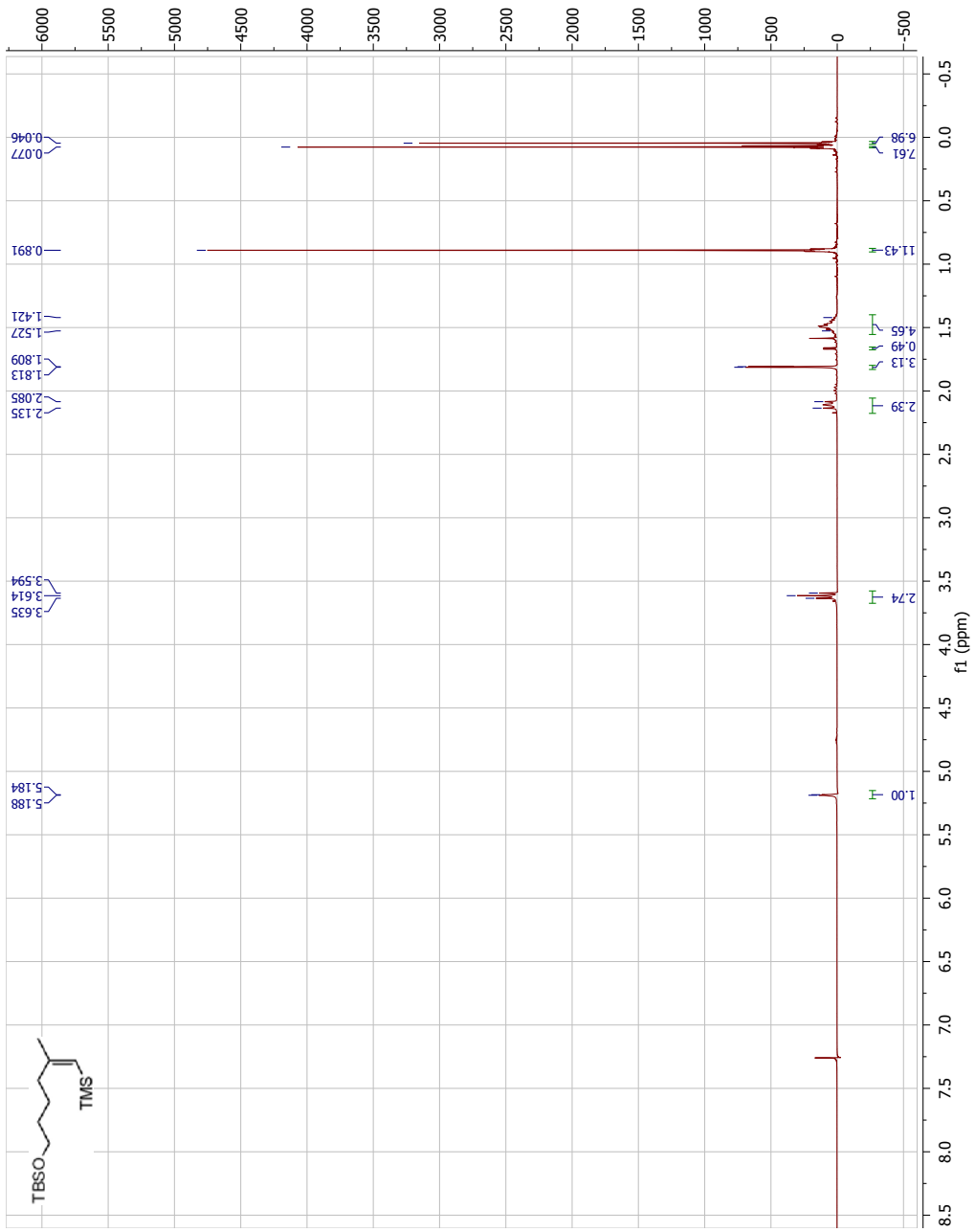

-5.193
0.501
16.857
18.508
26.113
26.675
32.602
35.454
36.534
68.336
124.528
156.612
TBSO
TMS
f1 (ppm)

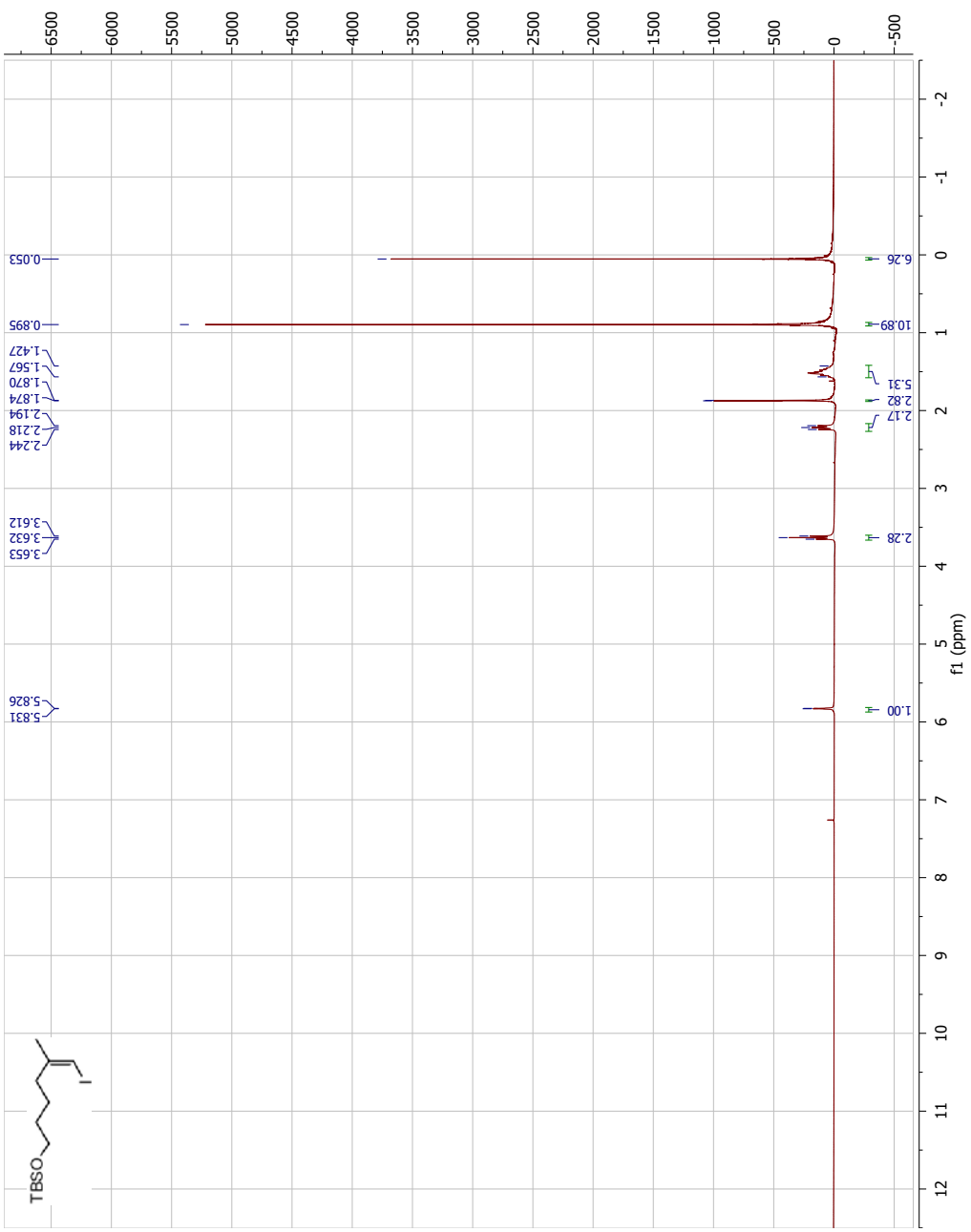

TBSO
f1 (ppm)

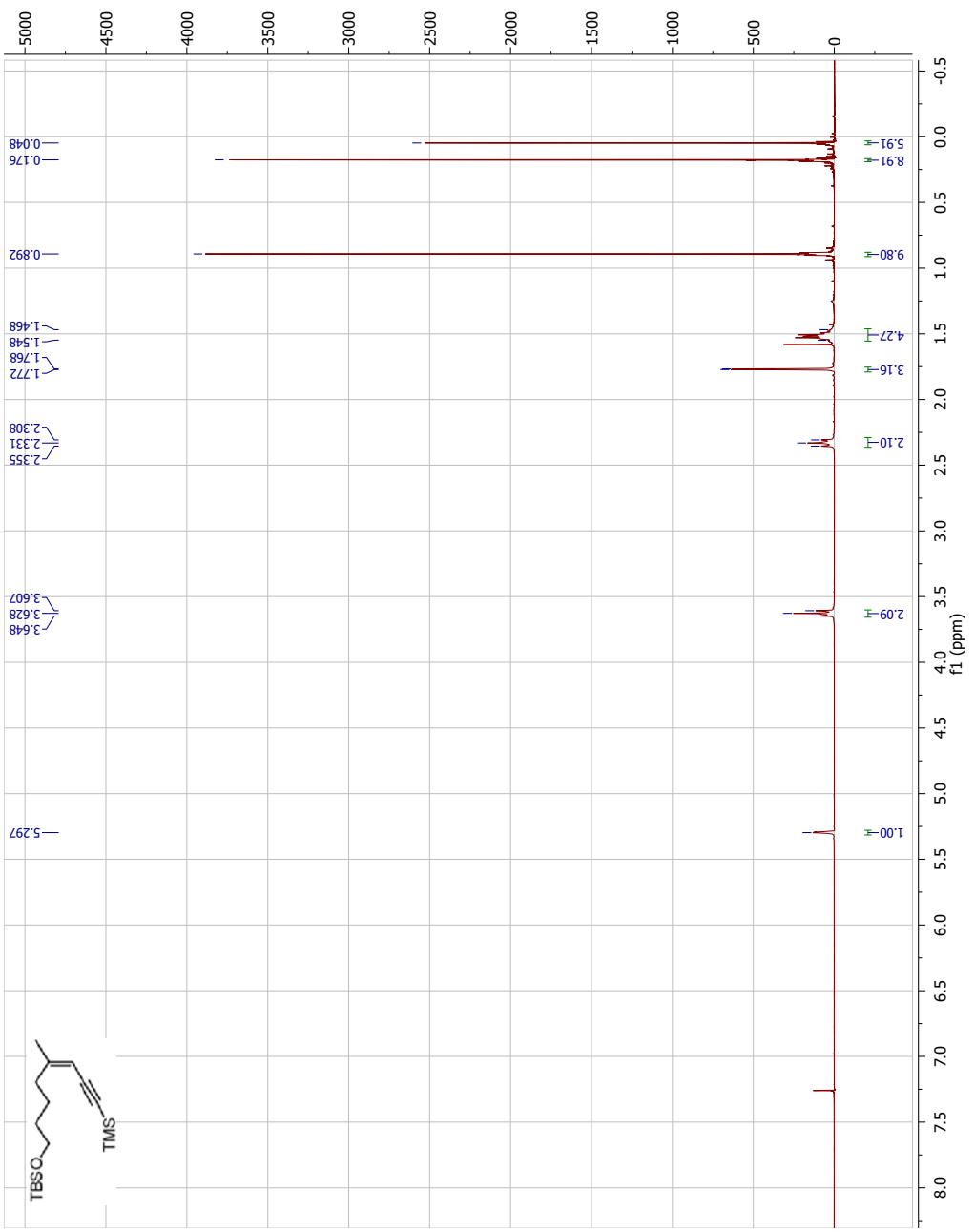

148.082
73.871
68.117
36.493
35.740
30.375
26.109
23.344
18.487
16.832
-5.167
TBSO
f1 (ppm)

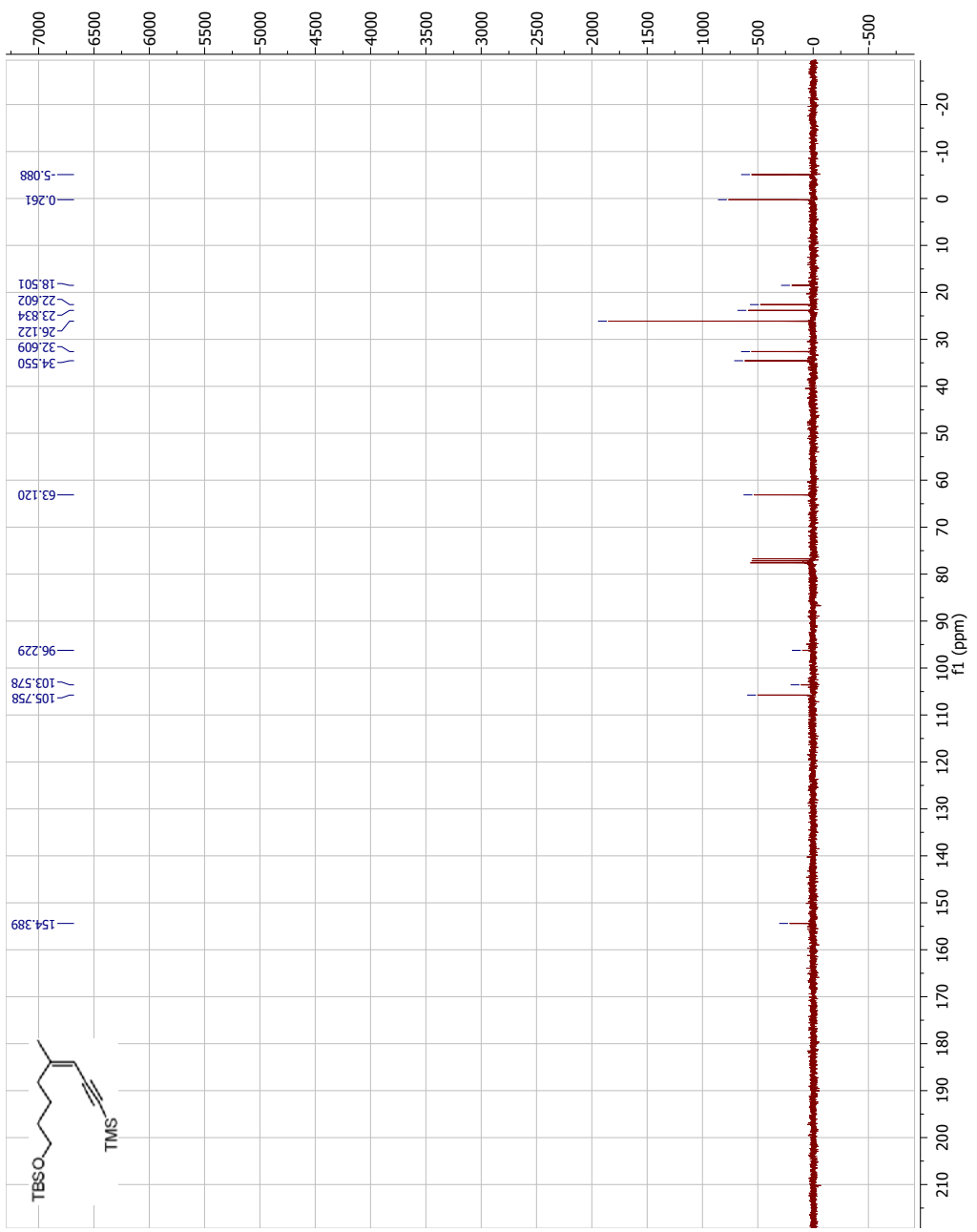

TBSO
f1 (ppm)
0.045
0.889
1.556
1.639
1.929
1.938
1.947
2.184
2.239
3.609
3.629
3.649
2.88
4.64
2.32
0.44
1.10
1.00

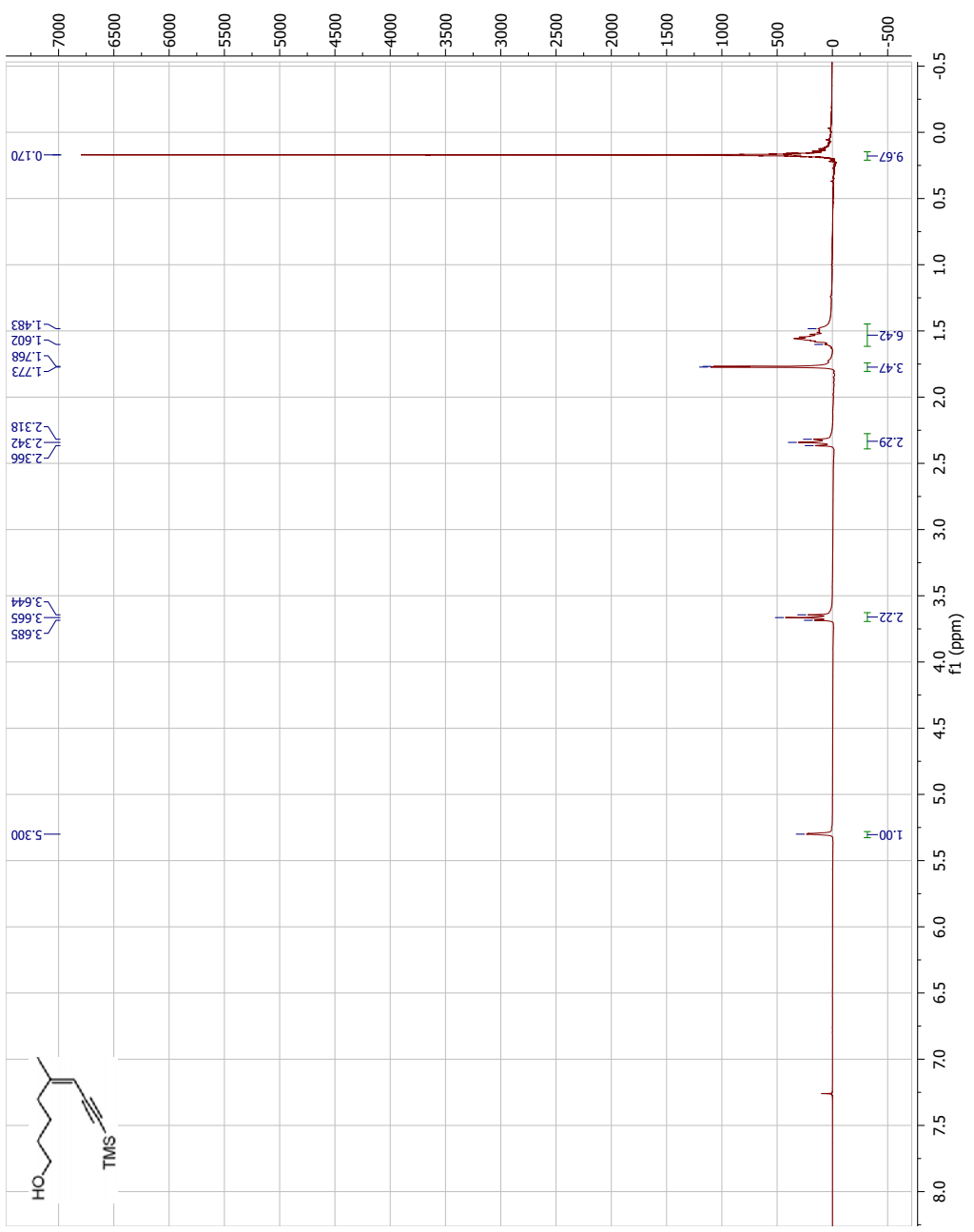

TBSO
TMS
f1 (ppm)
0.047
0.140
0.891
1.517
1.637
2.222
2.244
2.267
3.606
3.627
3.647
2.00
1.84
4.67
9.74
8.02
6.17

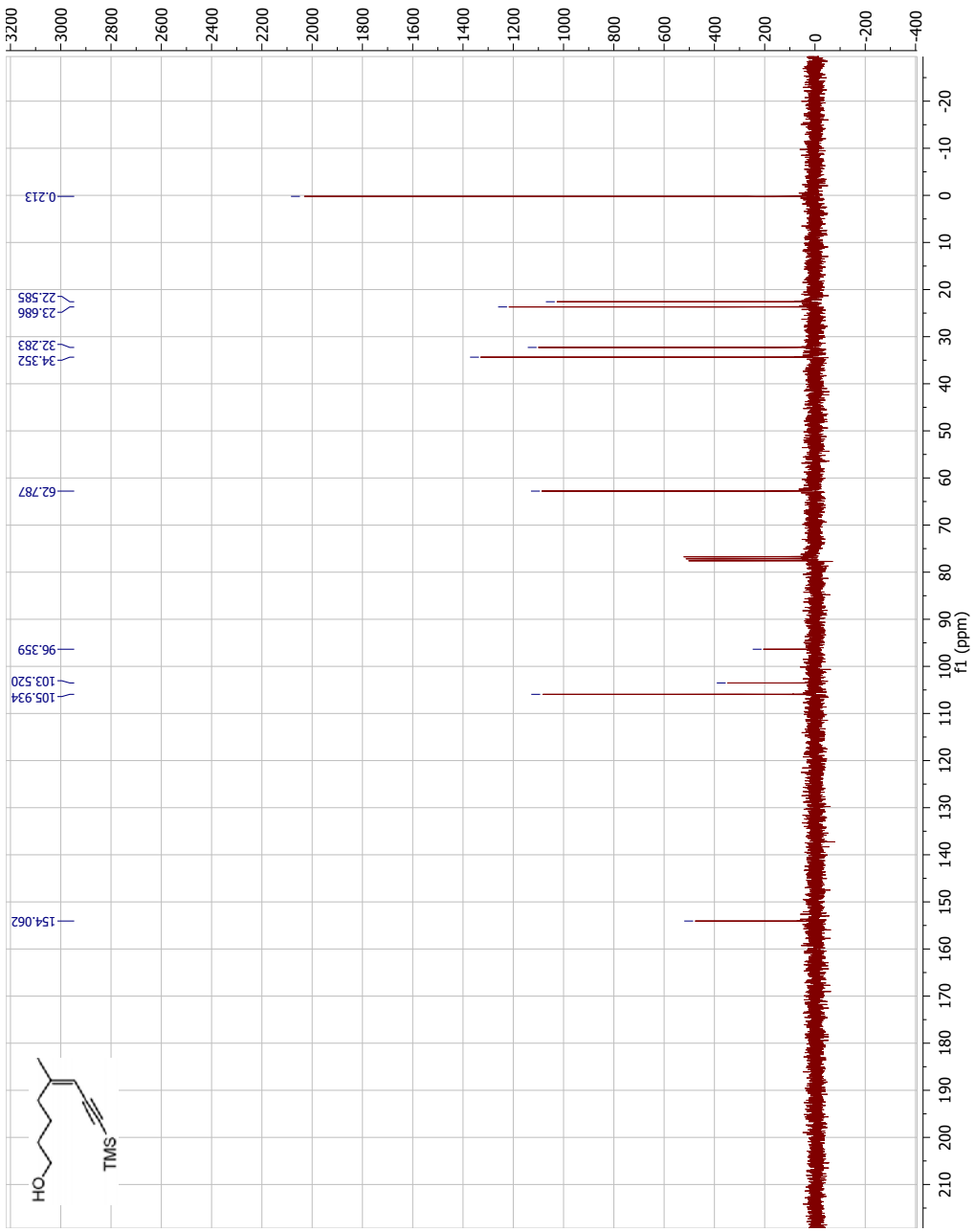

TBSO
TMS
f1 (ppm)
0.046
0.077
0.891
1.421
1.527
1.809
1.813
2.085
2.135
3.594
3.614
3.635
5.184
5.188
1.00
2.74
2.39
3.13
0.49
4.65
11.43
6.98
7.61

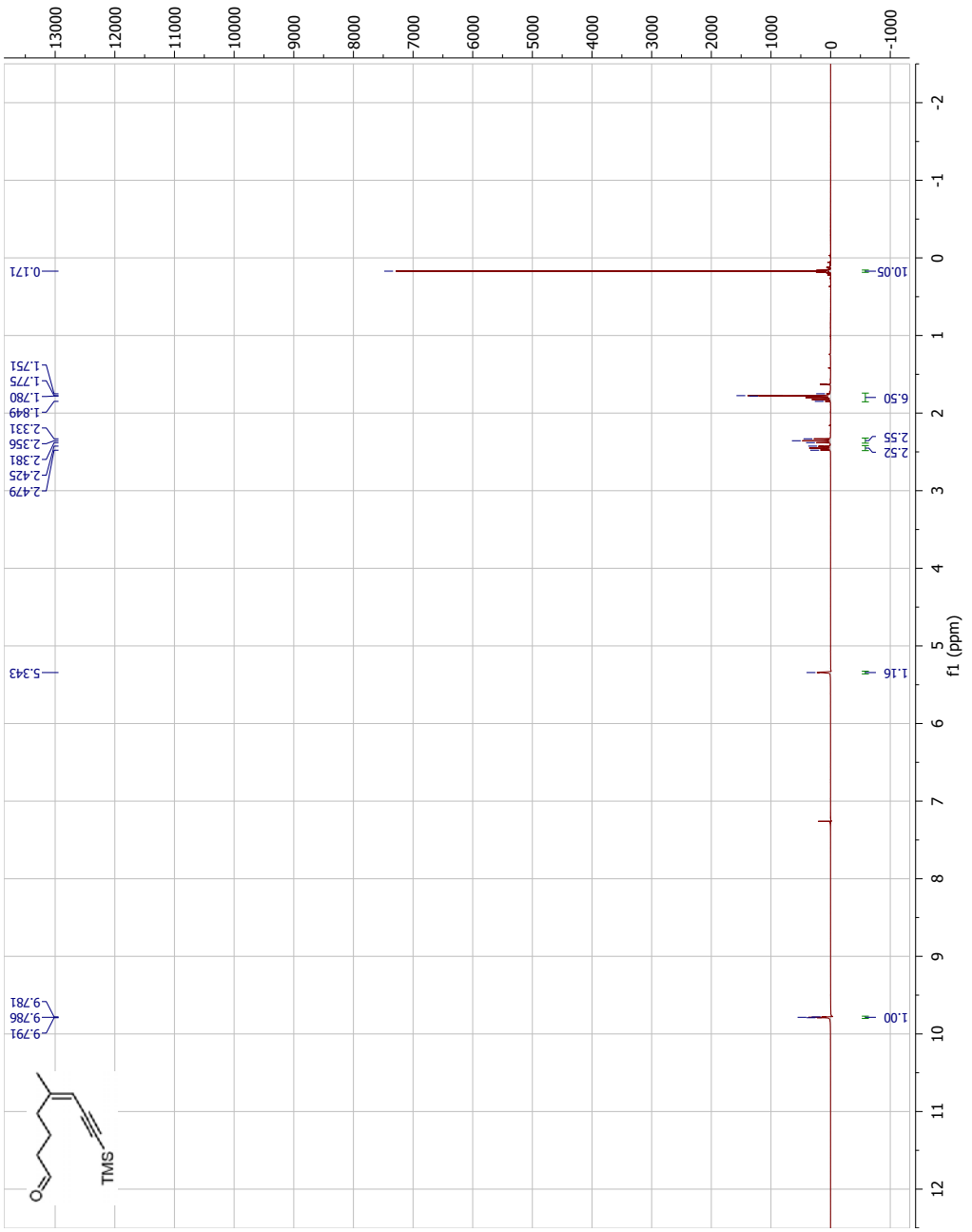

TBSO
I
f1 (ppm)
0.053
0.895
1.427
1.567
1.870
1.874
2.194
2.218
2.244
3.612
3.632
3.653
5.826
5.831
1.00
2.28
5.31
2.82
2.17
10.89
6.26

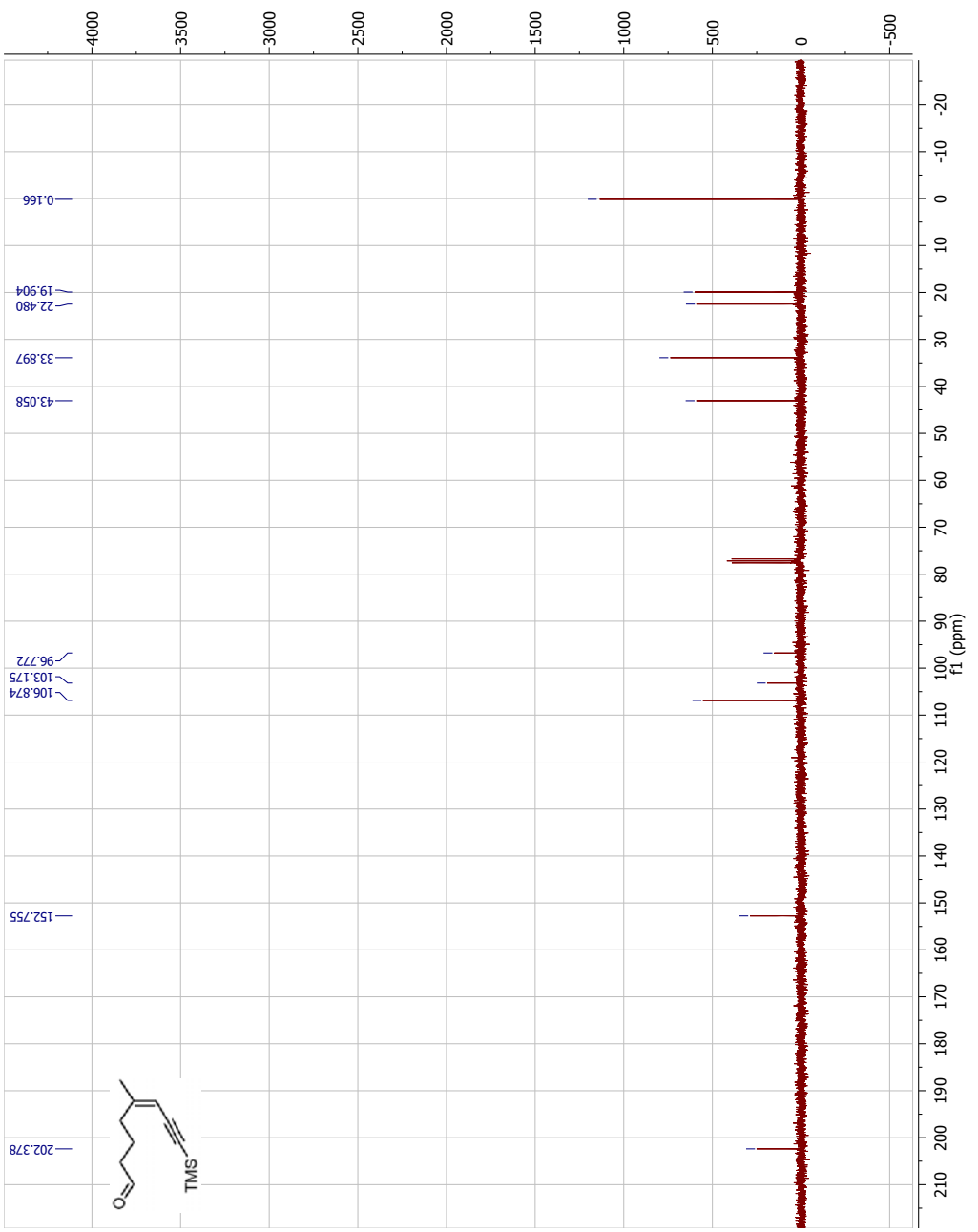

TBSO
TMS
f1 (ppm)

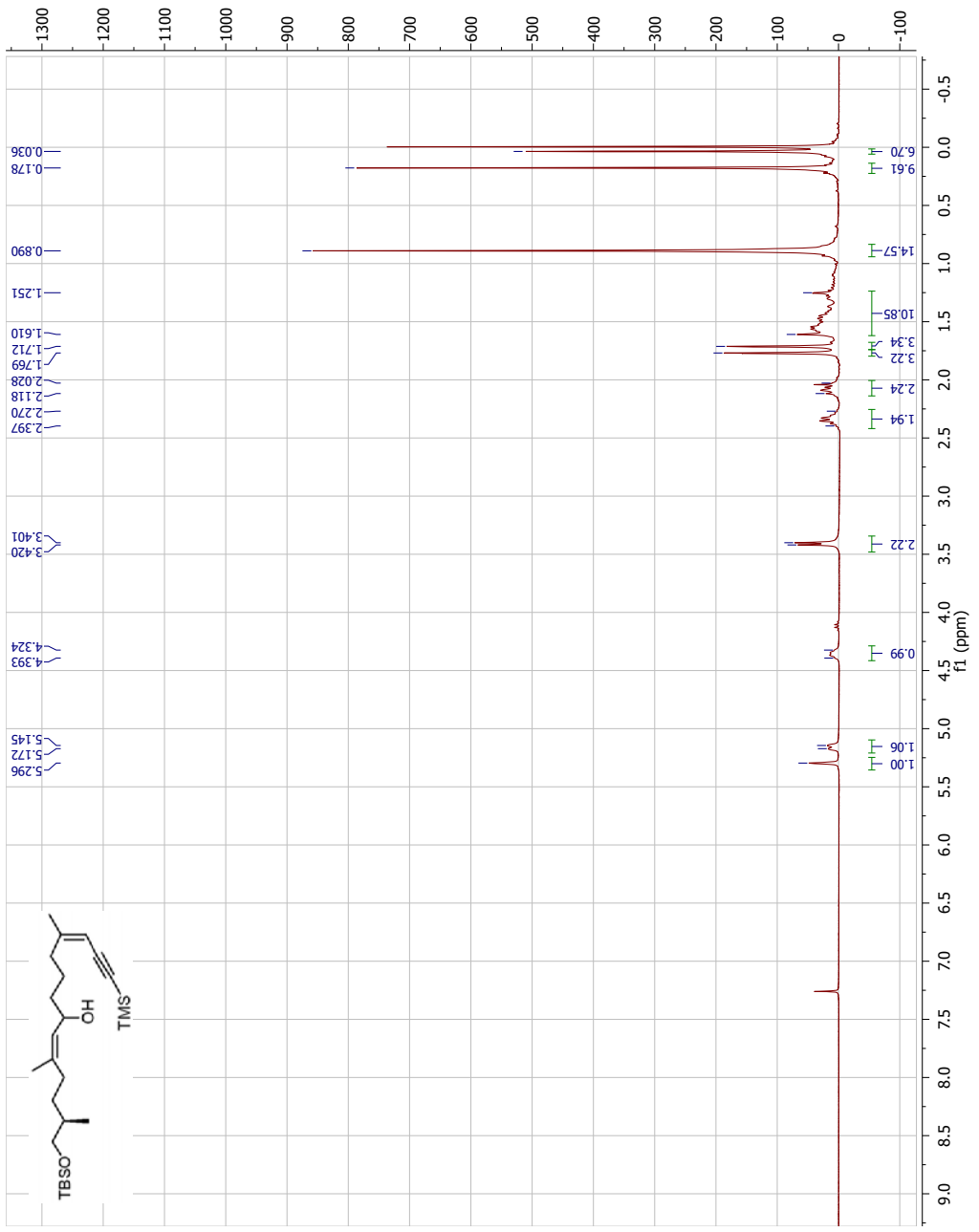

154.389
105.758
103.578
96.229
63.120
34.550
32.609
26.122
23.834
22.602
18.501
0.261
-5.088
TBSO
TMS
f1 (ppm)

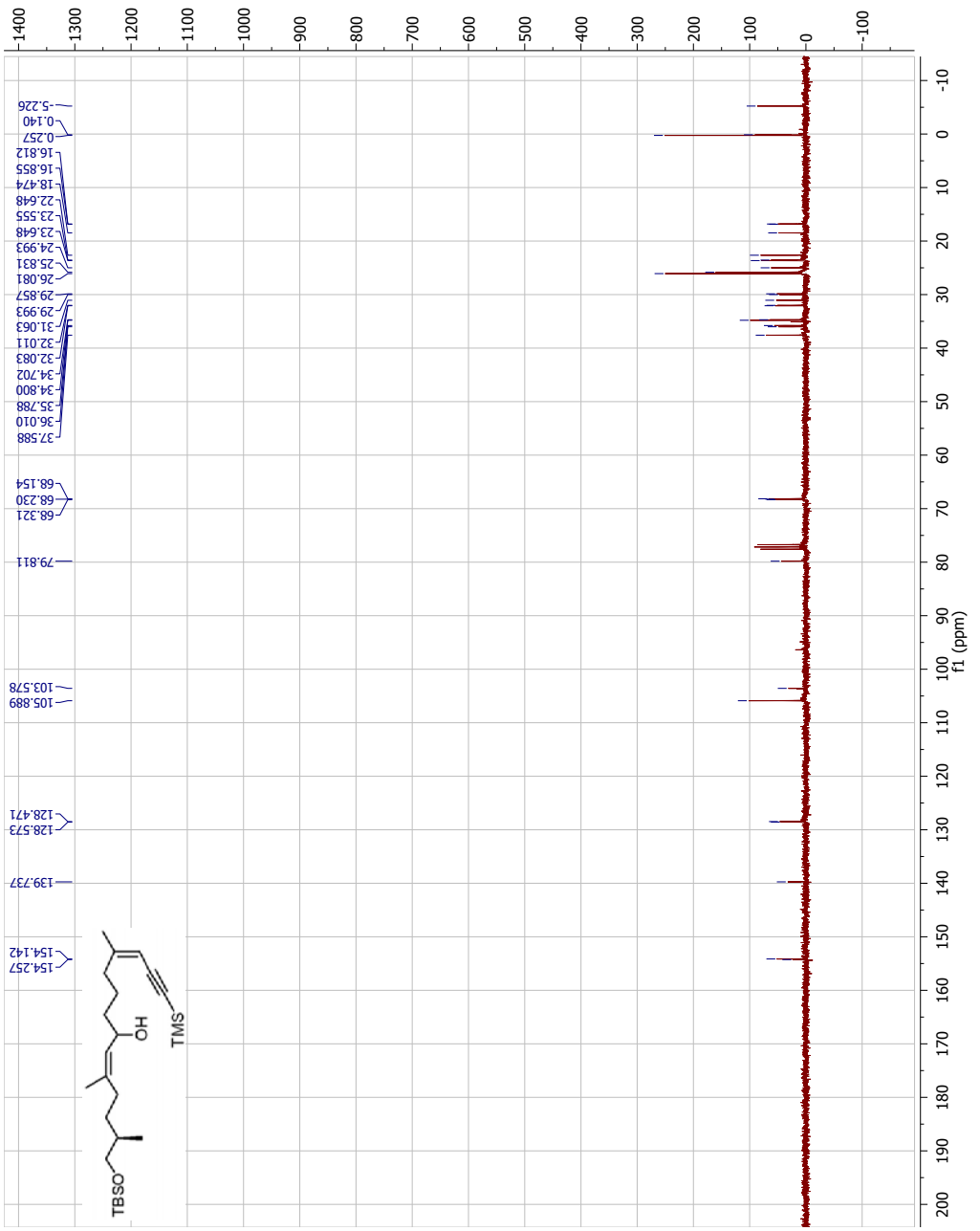

0.170
1.483
1.602
1.768
1.773
2.318
2.342
2.366
3.644
3.665
3.685
5.300
9.67
6.42
3.47
2.29
2.22
1.00
HO
TMS
f1 (ppm)

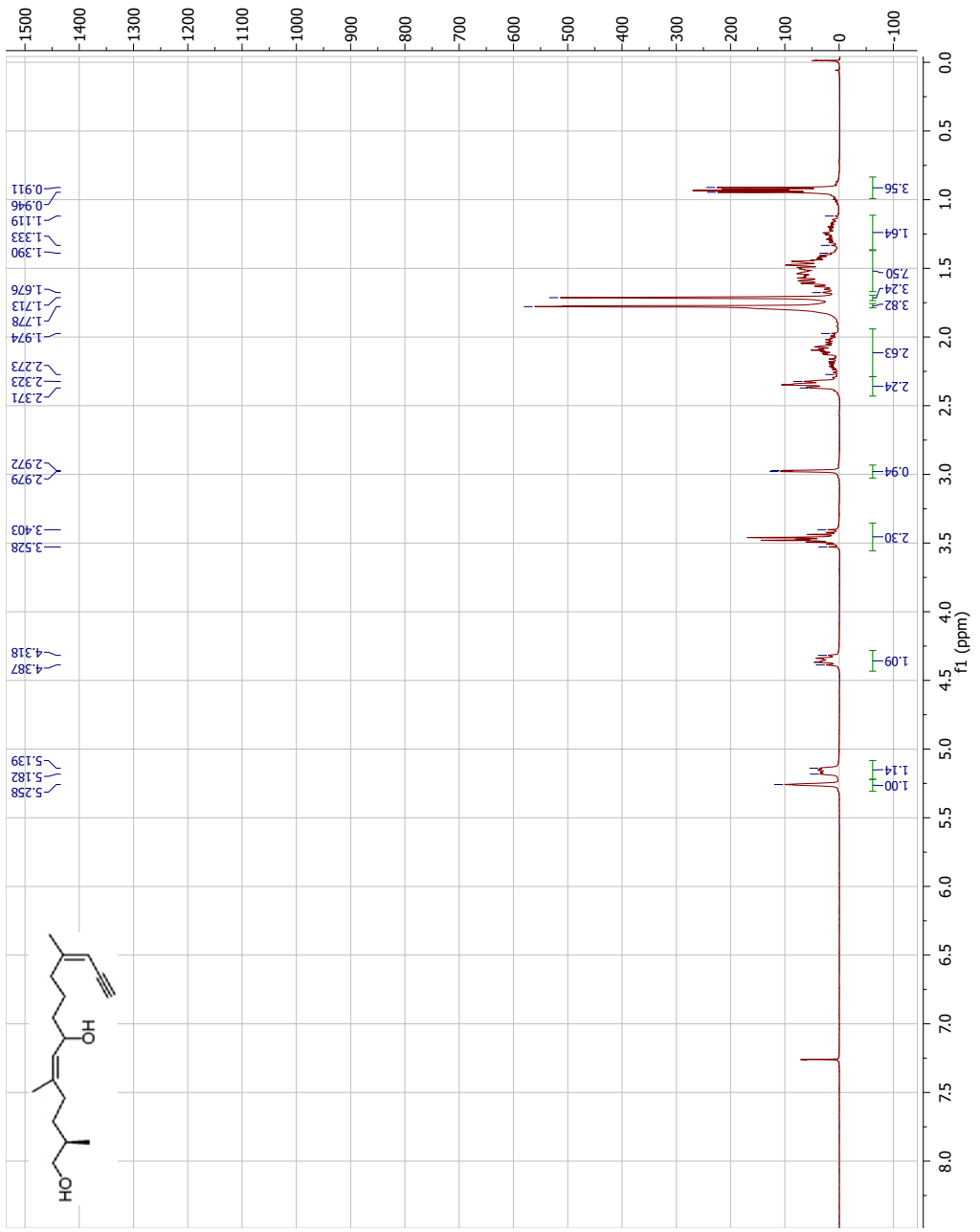

0.213
22.585
23.686
32.283
34.352
62.787
96.359
103.520
105.934
154.062
HO
TMS
f1 (ppm)

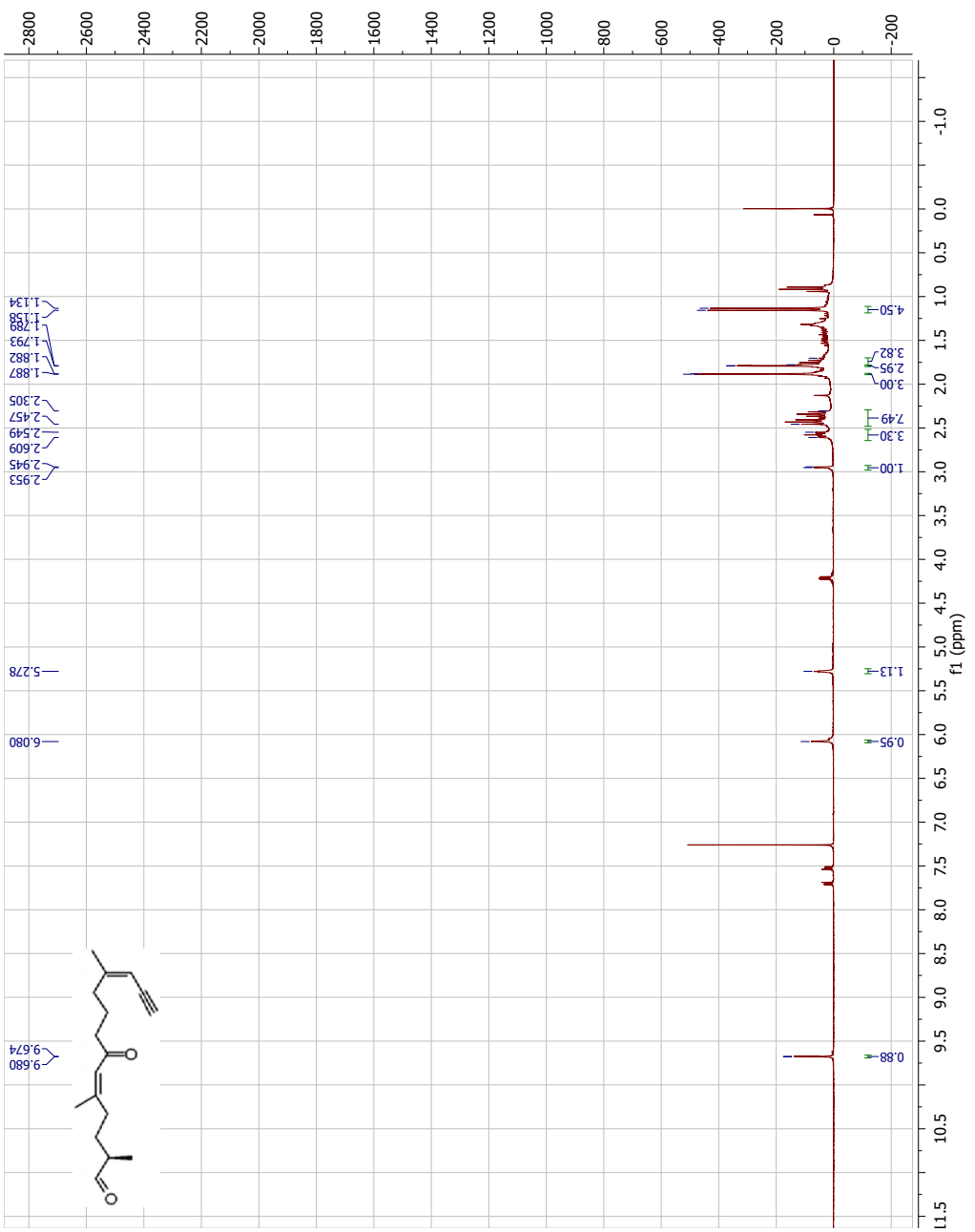

9.791
9.786
9.781
5.343
2.479
2.425
2.381
2.356
2.331
1.849
1.780
1.775
1.751
0.171
1.00
1.16
2.52
2.55
6.50
10.05
TMS
f1 (ppm)

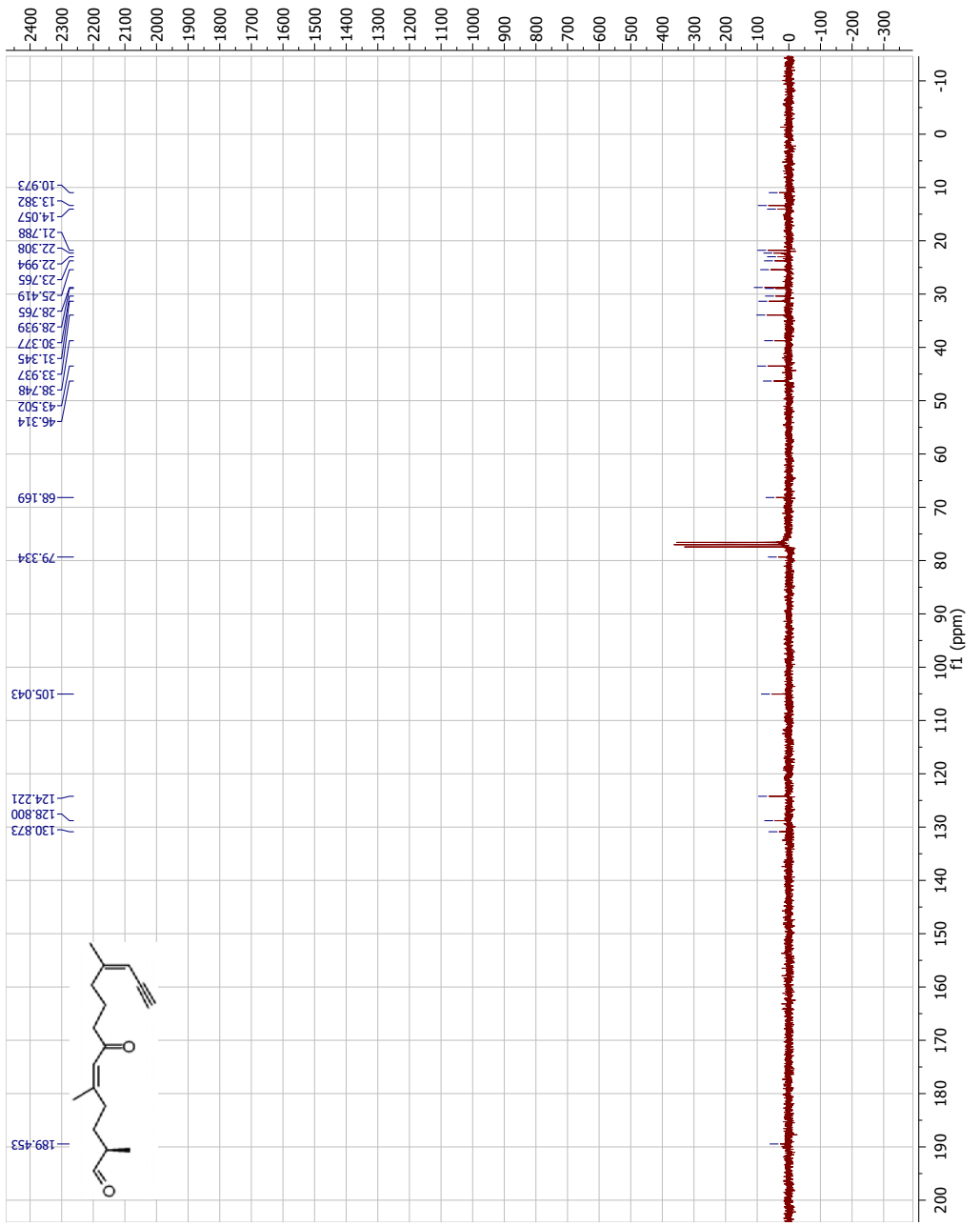

202.378
152.755
106.874
103.175
96.772
43.058
33.897
22.480
19.904
0.166
TMS
O
f1 (ppm)

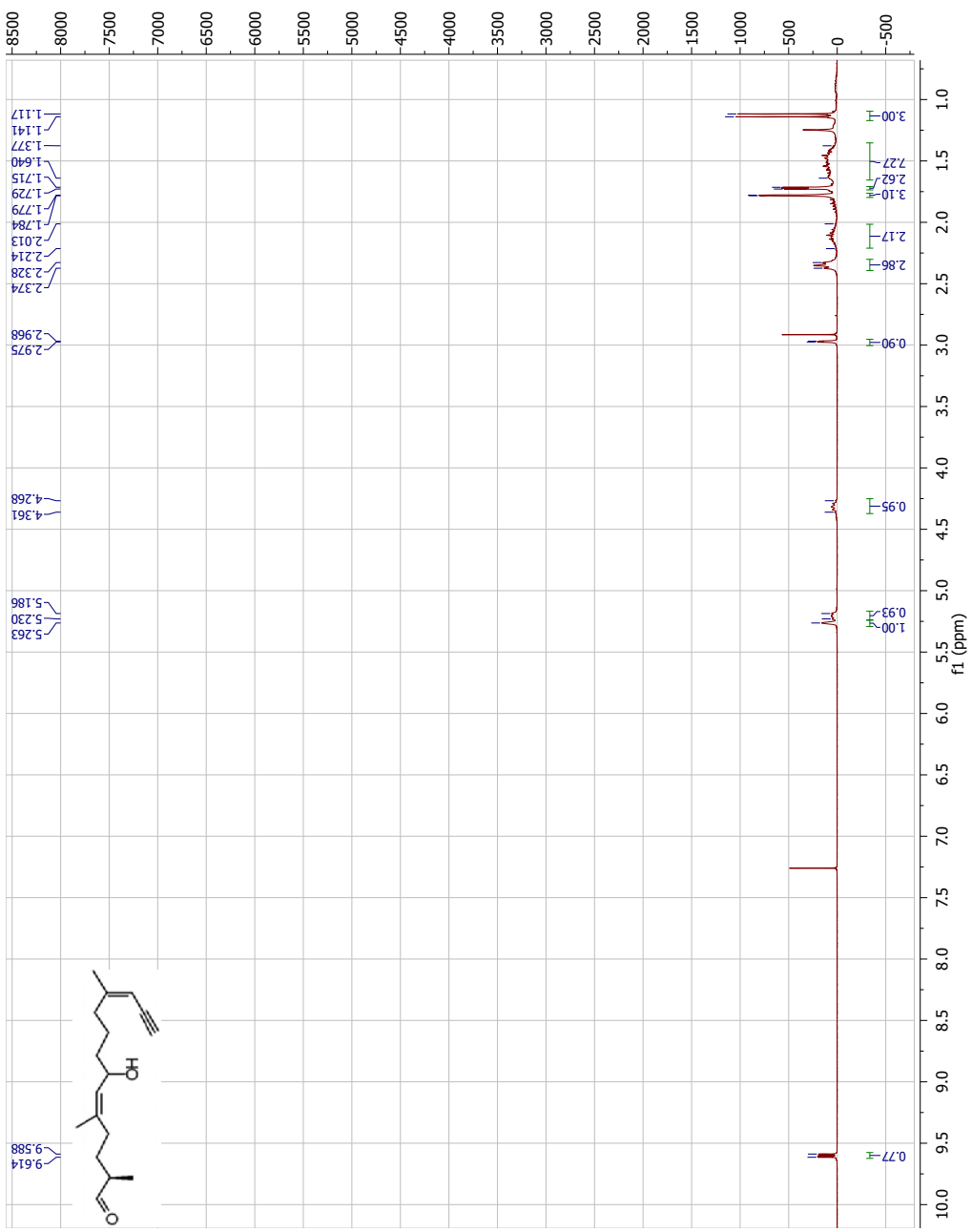

TBSO
OH
TMS
f1 (ppm)

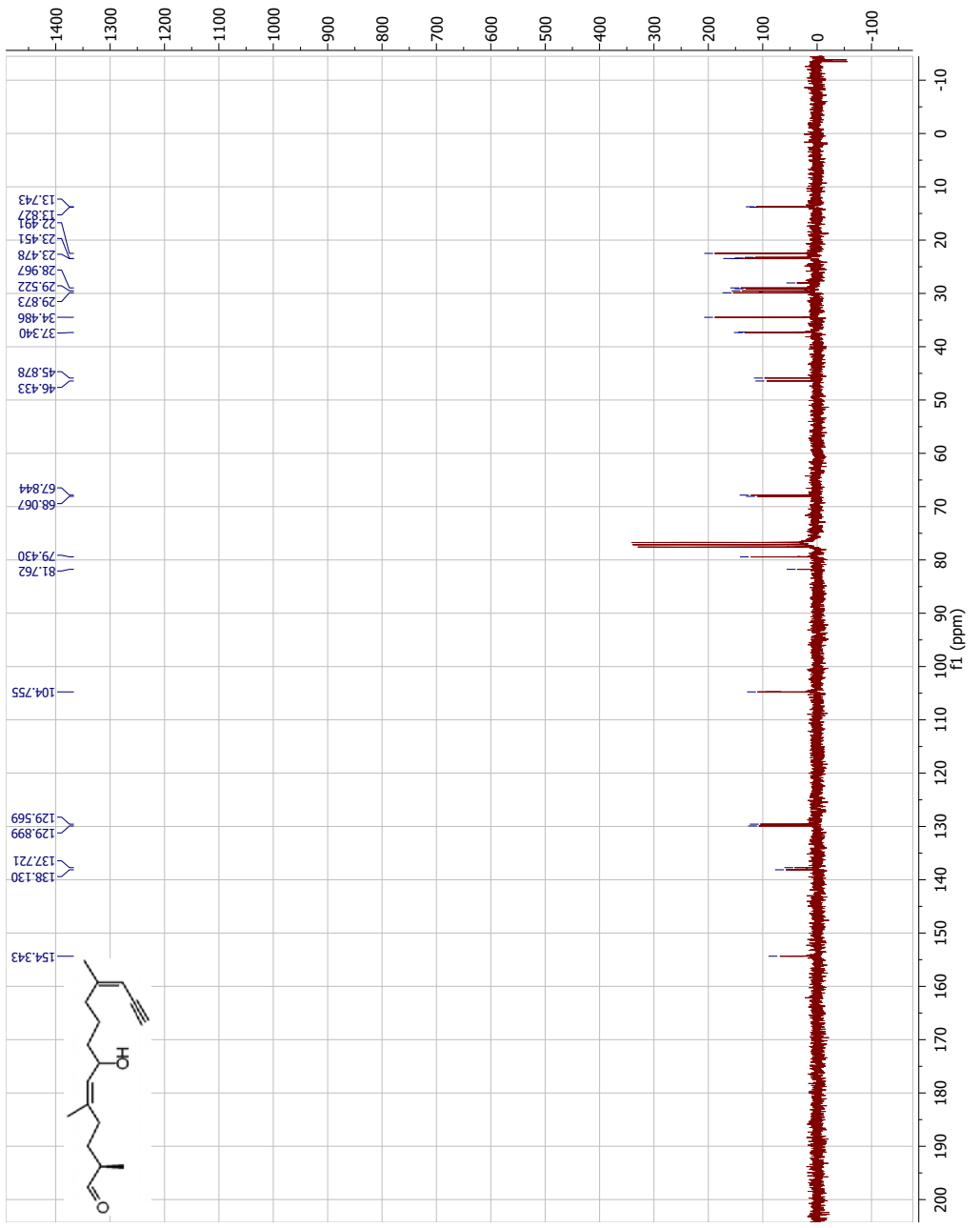

TBSO
OH
TMS
154.257
154.142
139.737
128.573
128.471
105.889
103.578
79.811
68.321
68.230
68.154
37.588
36.010
35.788
34.800
34.702
32.083
32.011
31.063
29.993
29.857
26.081
25.831
24.993
23.648
23.555
22.648
18.474
16.855
16.812
0.257
0.140
-5.226
f1 (ppm)

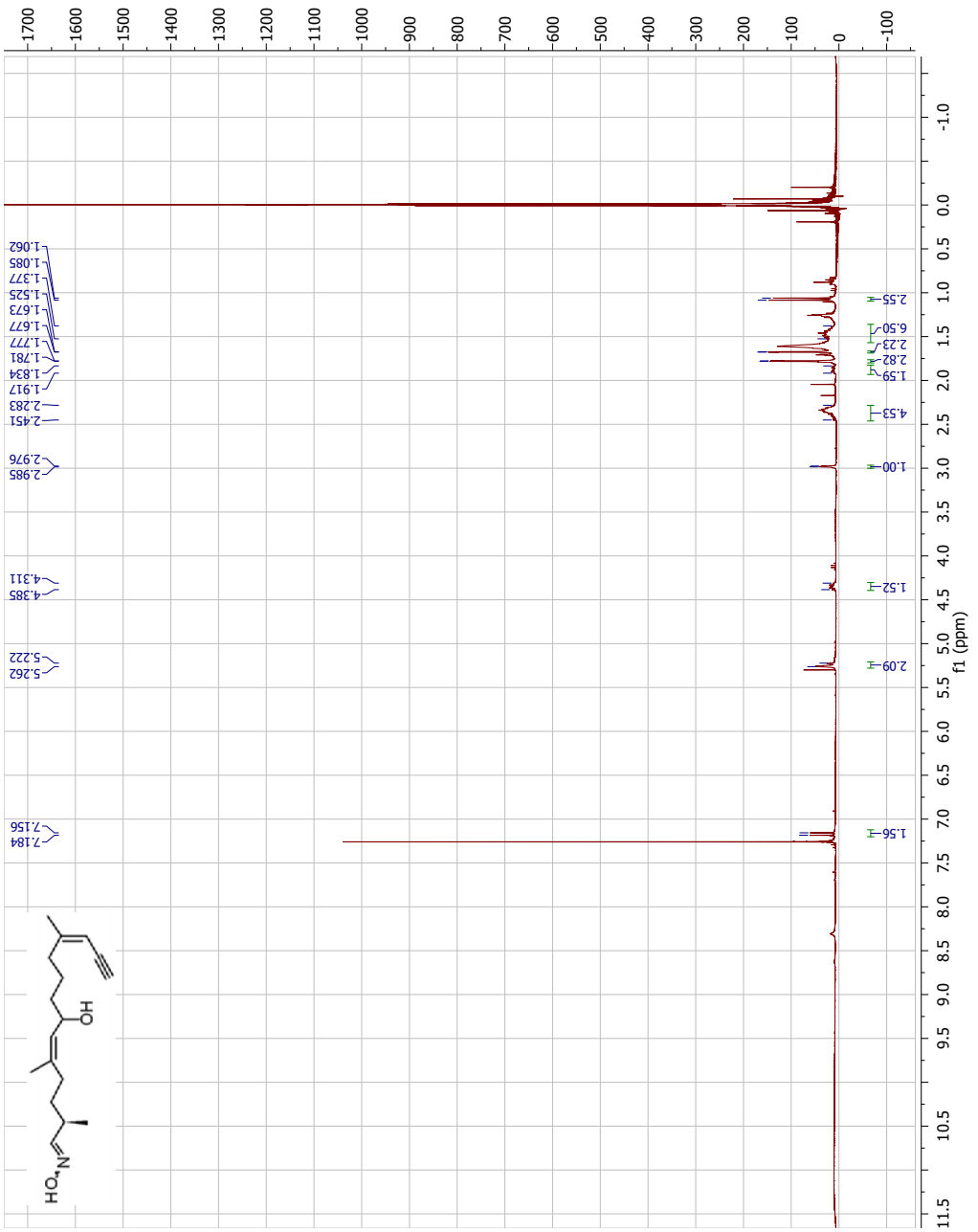

f1 (ppm)
OH
HO

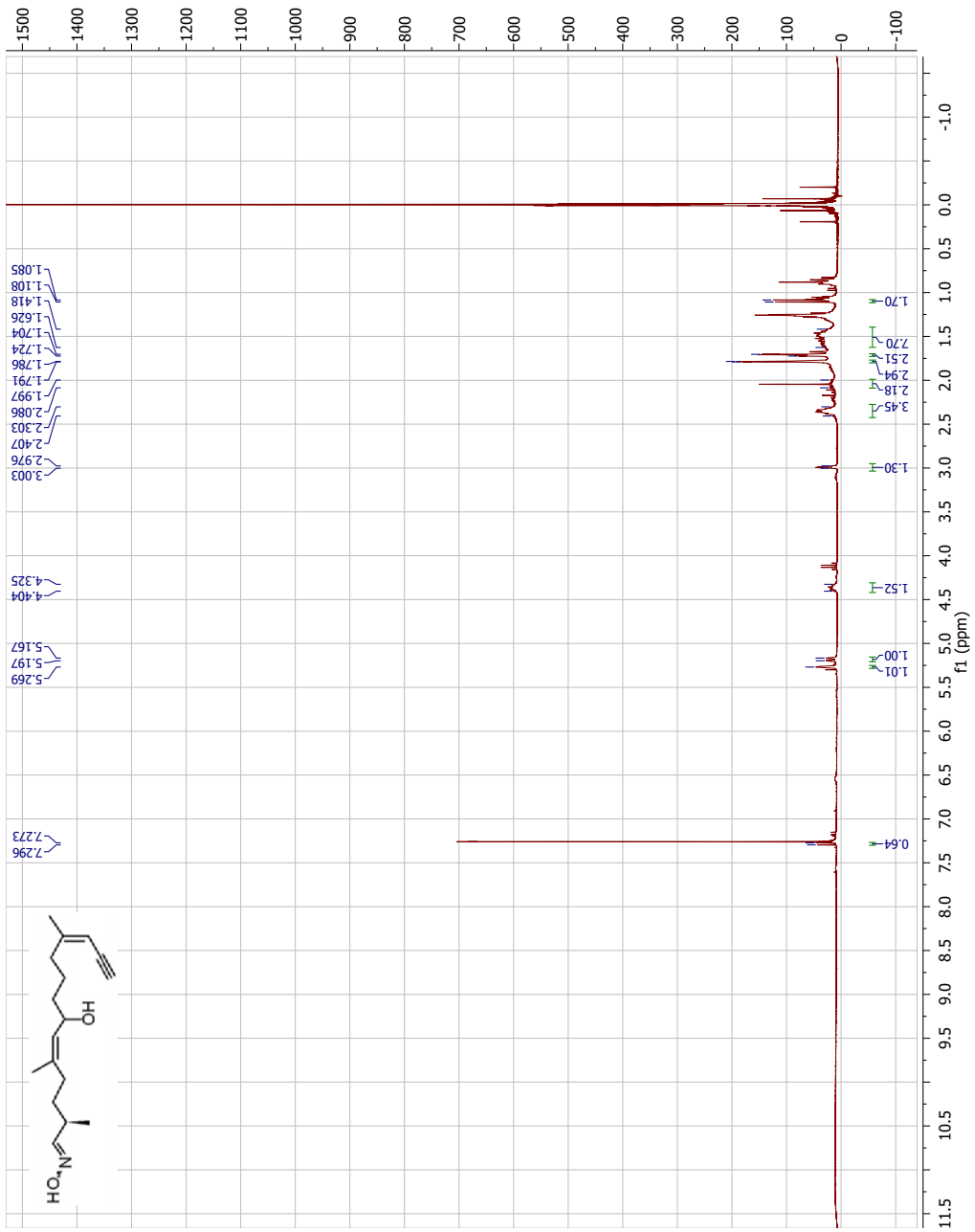

9.680
9.674
5.278
6.080
2.953
2.945
2.609
2.549
2.457
2.305
1.887
1.882
1.793
1.789
1.158
1.134
4.50
3.82
2.95
3.00
7.49
3.30
1.00
1.13
0.95
0.88
f1 (ppm)

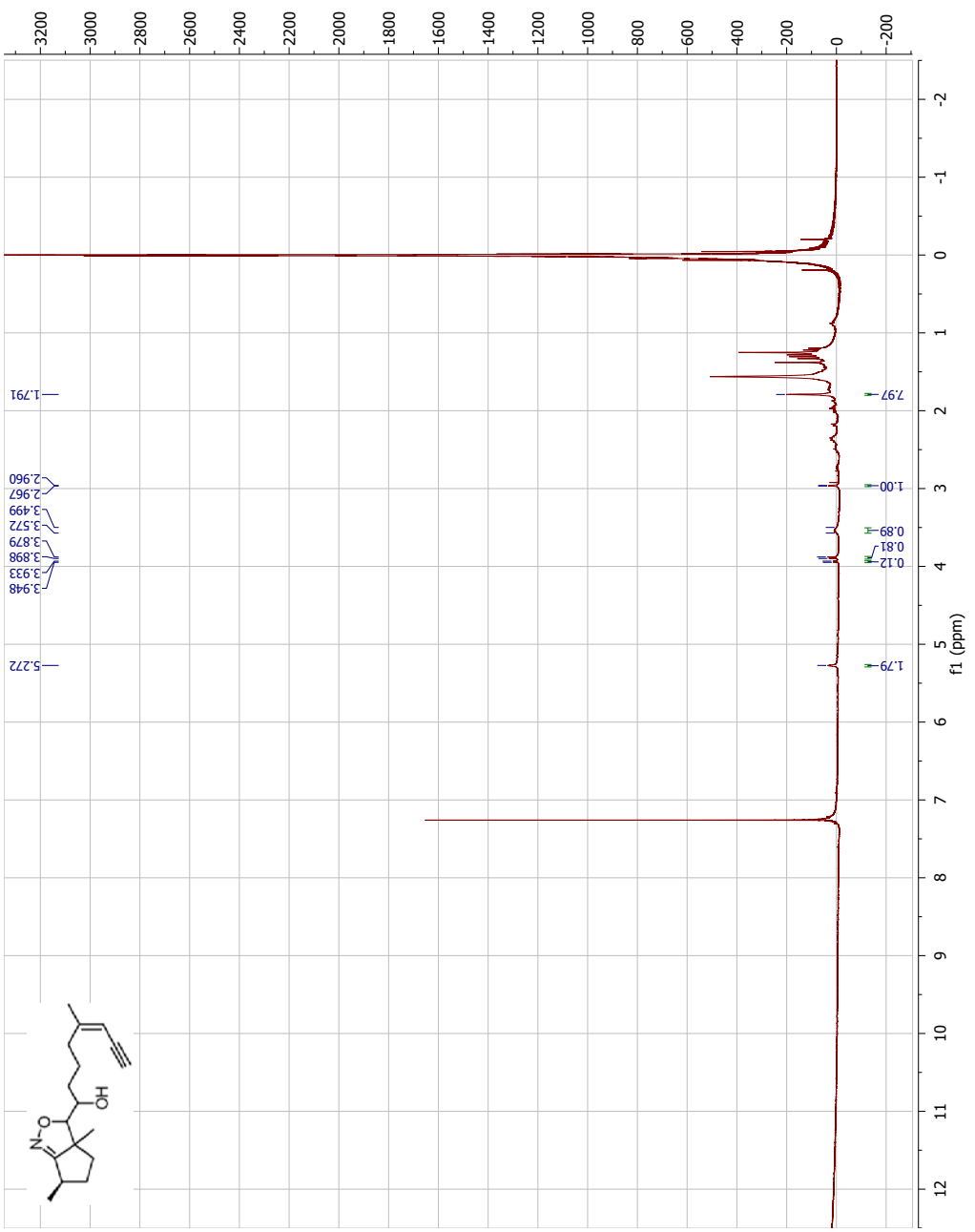

189.453
130.873
128.800
124.221
105.043
79.334
68.169
46.314
43.502
38.748
33.937
31.345
30.377
28.939
28.765
25.419
23.765
22.994
22.308
21.788
14.057
13.382
10.973
f1 (ppm)

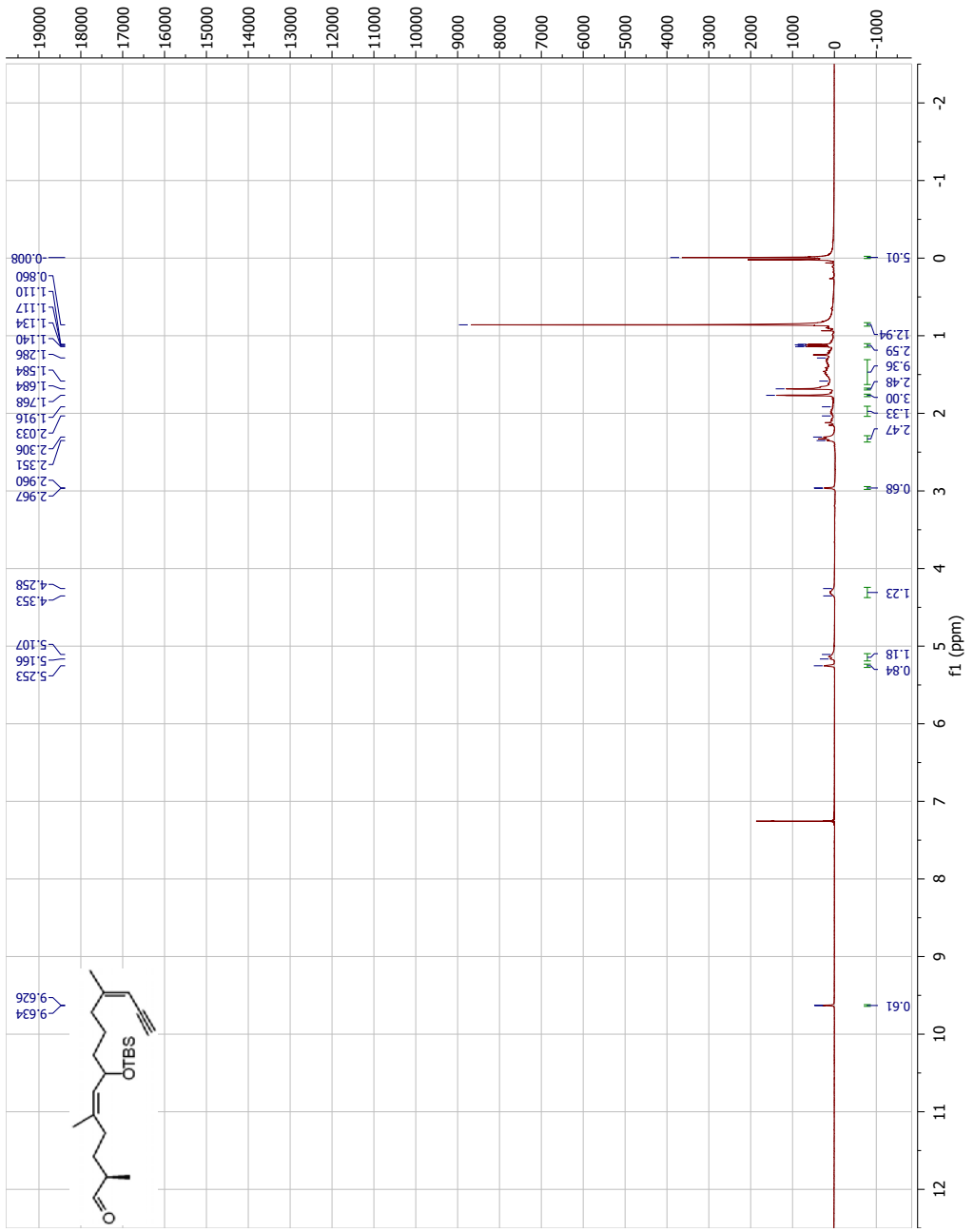

f1 (ppm)
9.614
9.588
5.263
5.230
5.186
4.361
4.268
2.975
2.968
2.374
2.328
2.214
2.013
1.784
1.779
1.729
1.715
1.640
1.377
1.141
1.117
0.77
1.00
0.93
0.95
3.00
7.27
2.62
3.10
2.17
2.86
0.90

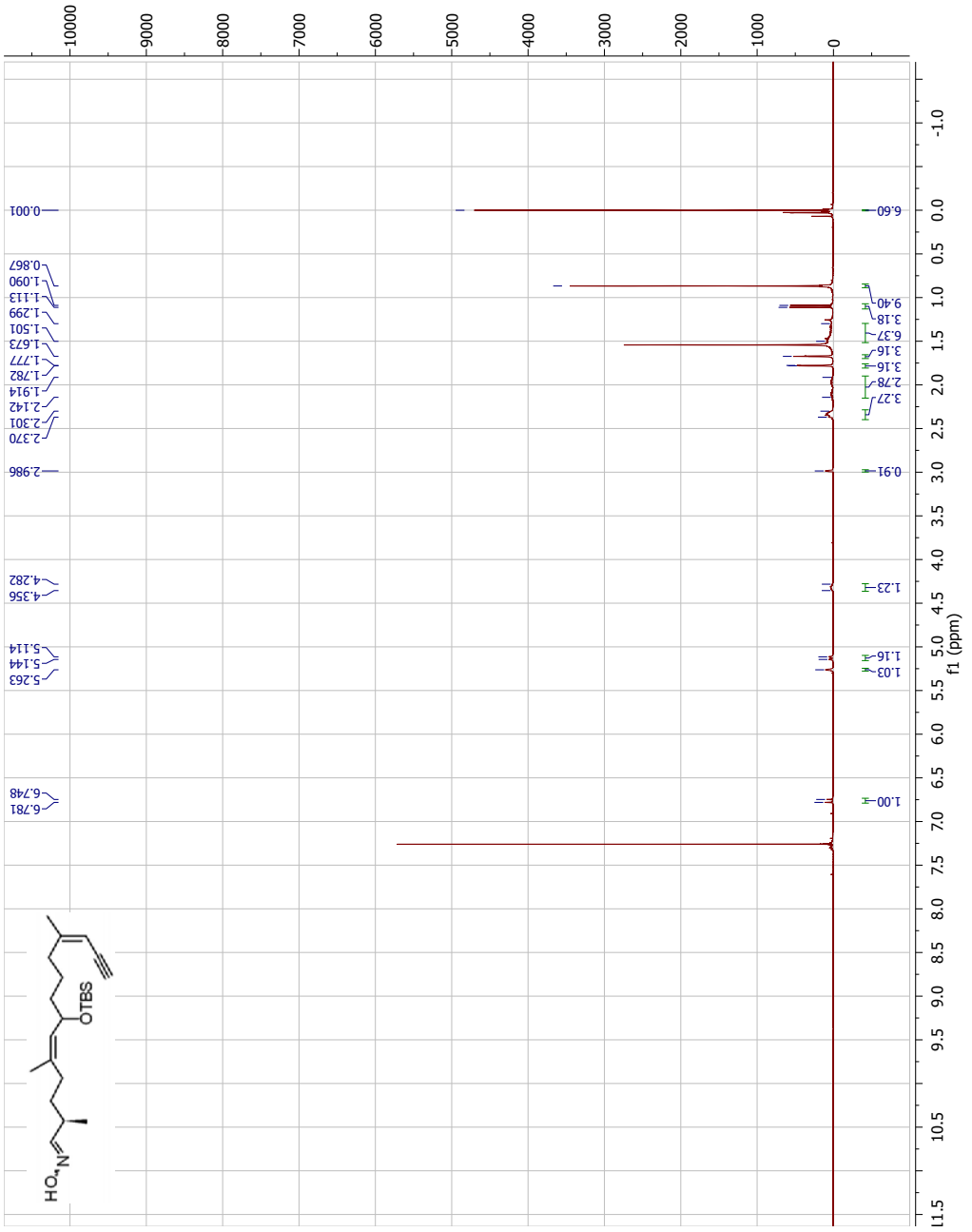

154.343
138.130
137.721
129.899
129.569
104.755
81.762
79.430
68.067
67.844
46.433
45.878
37.340
34.486
29.873
29.522
28.967
23.478
23.451
22.491
13.827
13.743
f1 (ppm)

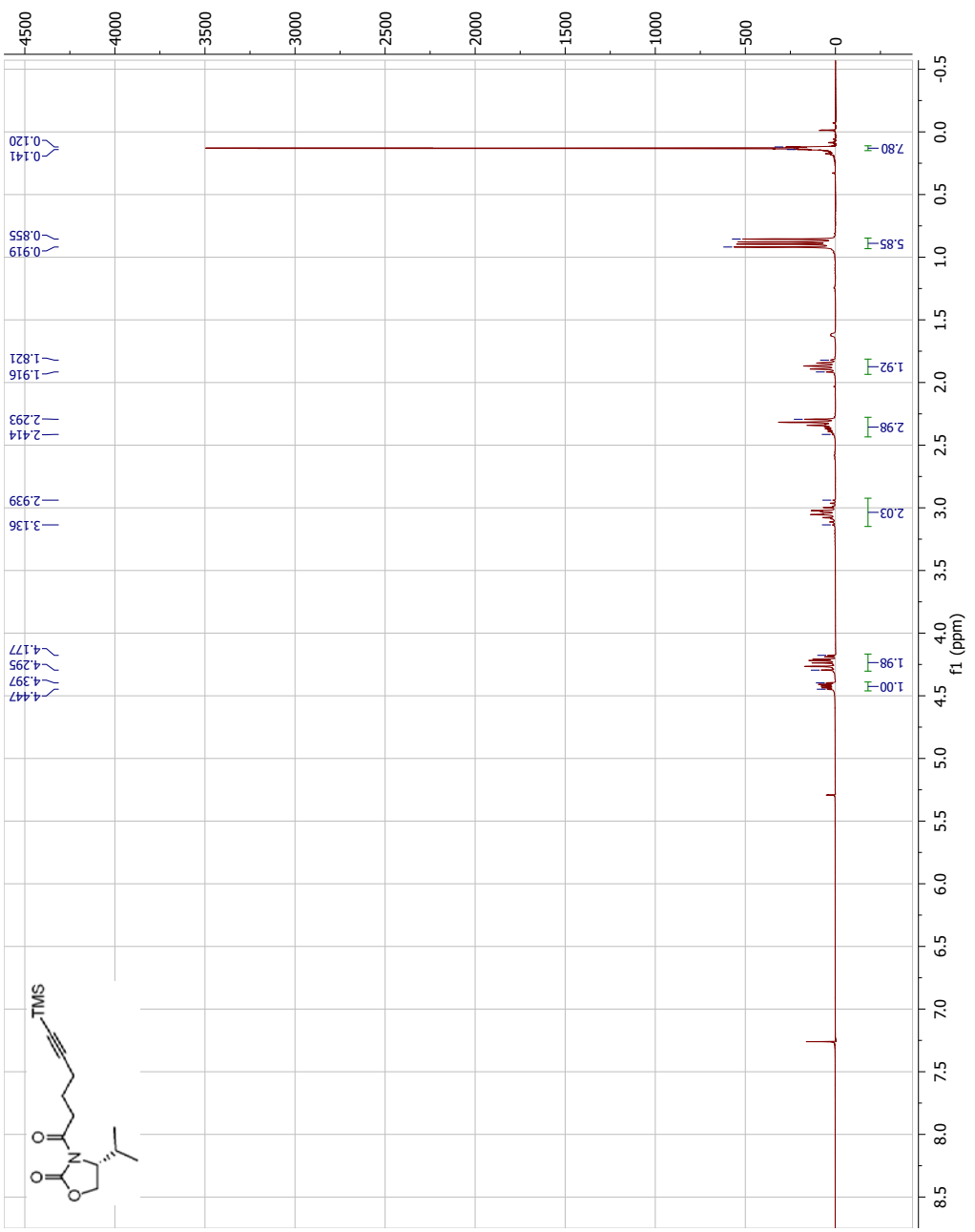

f1 (ppm)
HO
N
OH

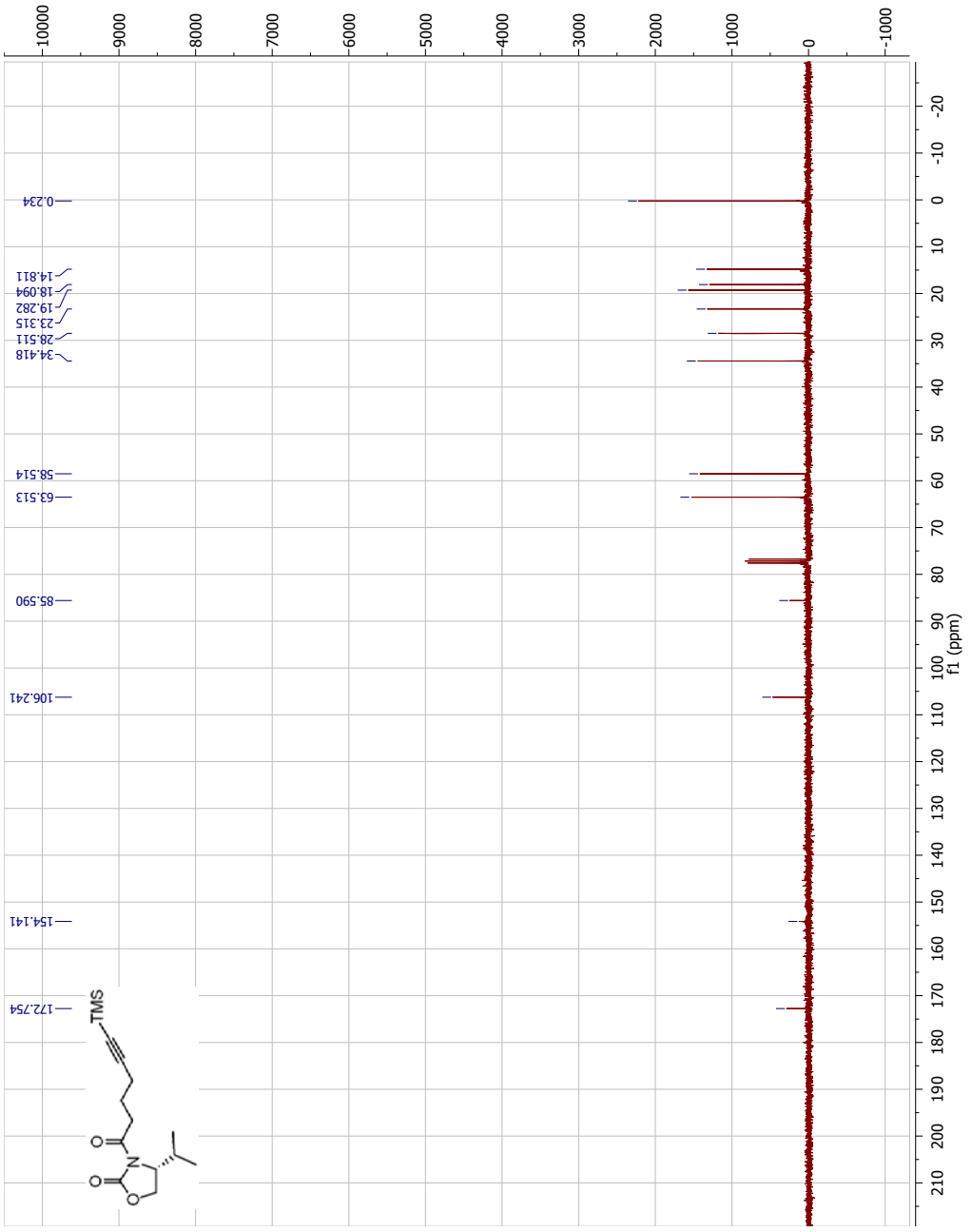

7.296
7.273
5.269
5.197
5.167
4.404
4.325
3.003
2.976
2.407
2.303
2.086
1.997
1.791
1.786
1.724
1.704
1.626
1.418
1.108
1.085
0.64
1.01
1.00
1.52
1.30
3.45
2.18
2.94
2.51
7.70
1.70
HO
N
OH
f1 (ppm)

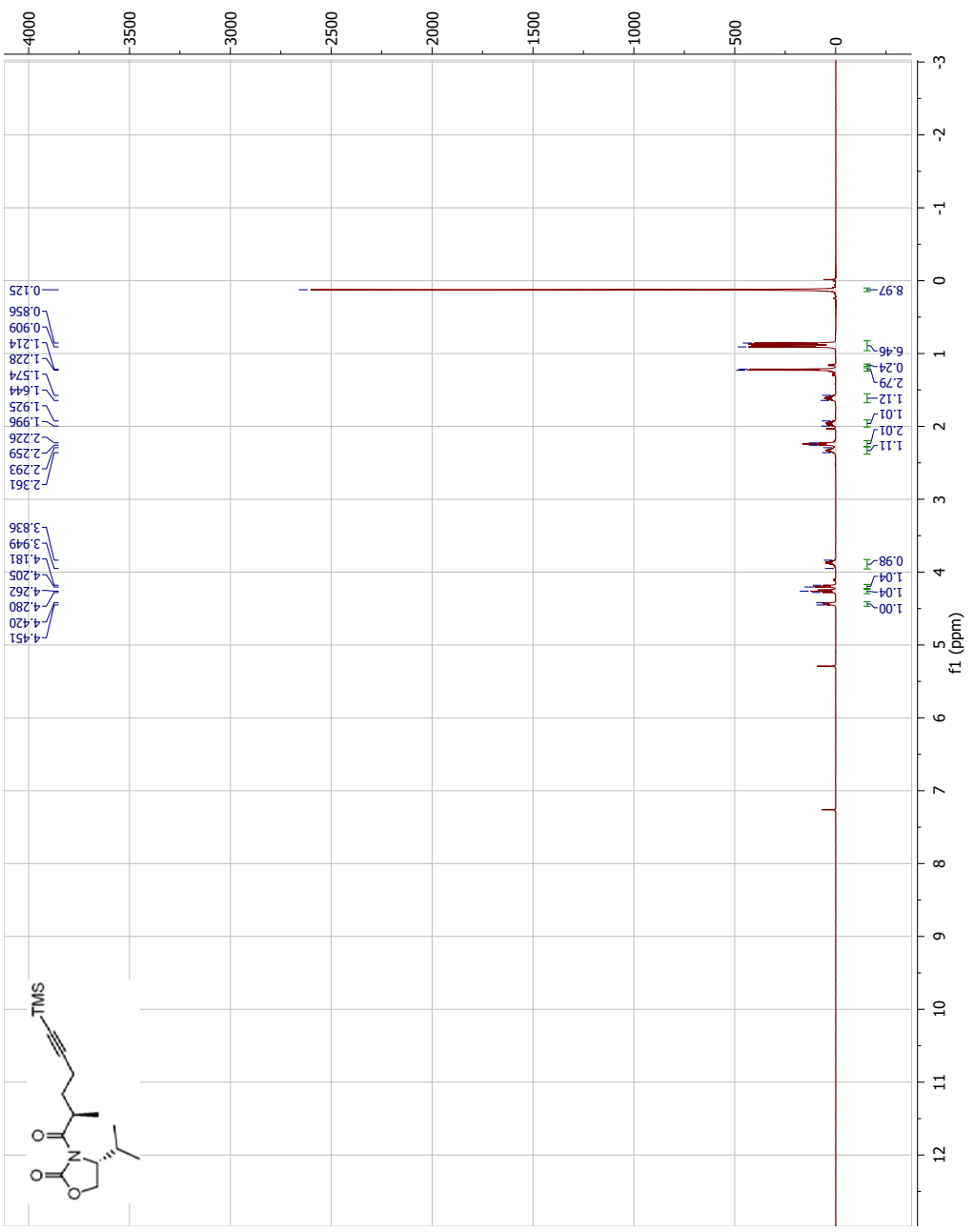

f1 (ppm)
7.97
1.00
0.89
0.81
0.12
1.79
5.272
3.948
3.933
3.898
3.879
3.572
3.499
2.967
2.960
1.791
HO
N
O

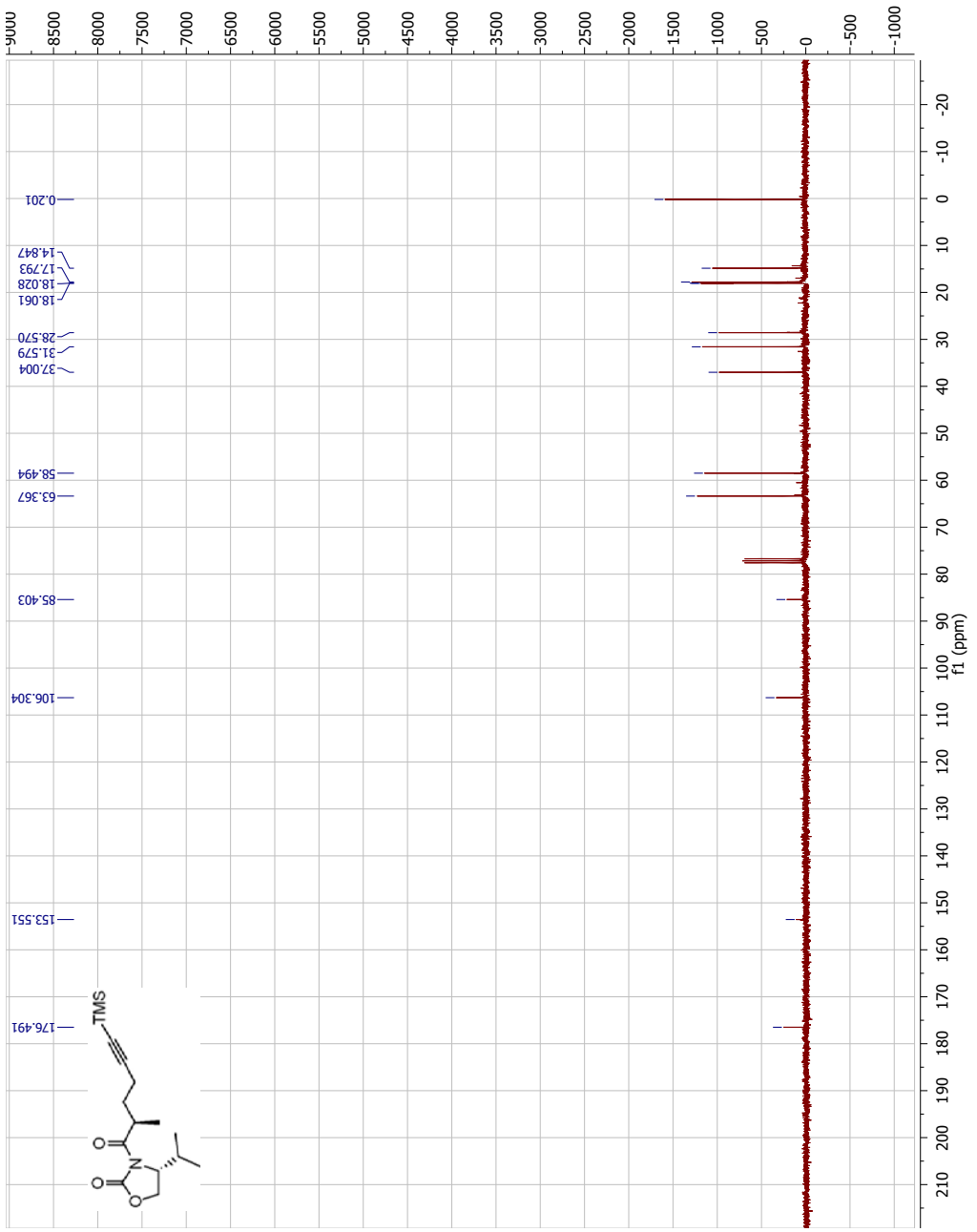

OTBS
O
9.634
9.626
5.253
5.166
5.107
4.353
4.258
2.967
2.960
2.351
2.306
2.033
1.916
1.768
1.684
1.584
1.286
1.140
1.134
1.117
1.110
0.860
0.008
5.01
12.94
2.59
9.36
2.48
3.00
1.33
2.47
0.68
1.23
0.84
1.18
0.61
f1 (ppm)

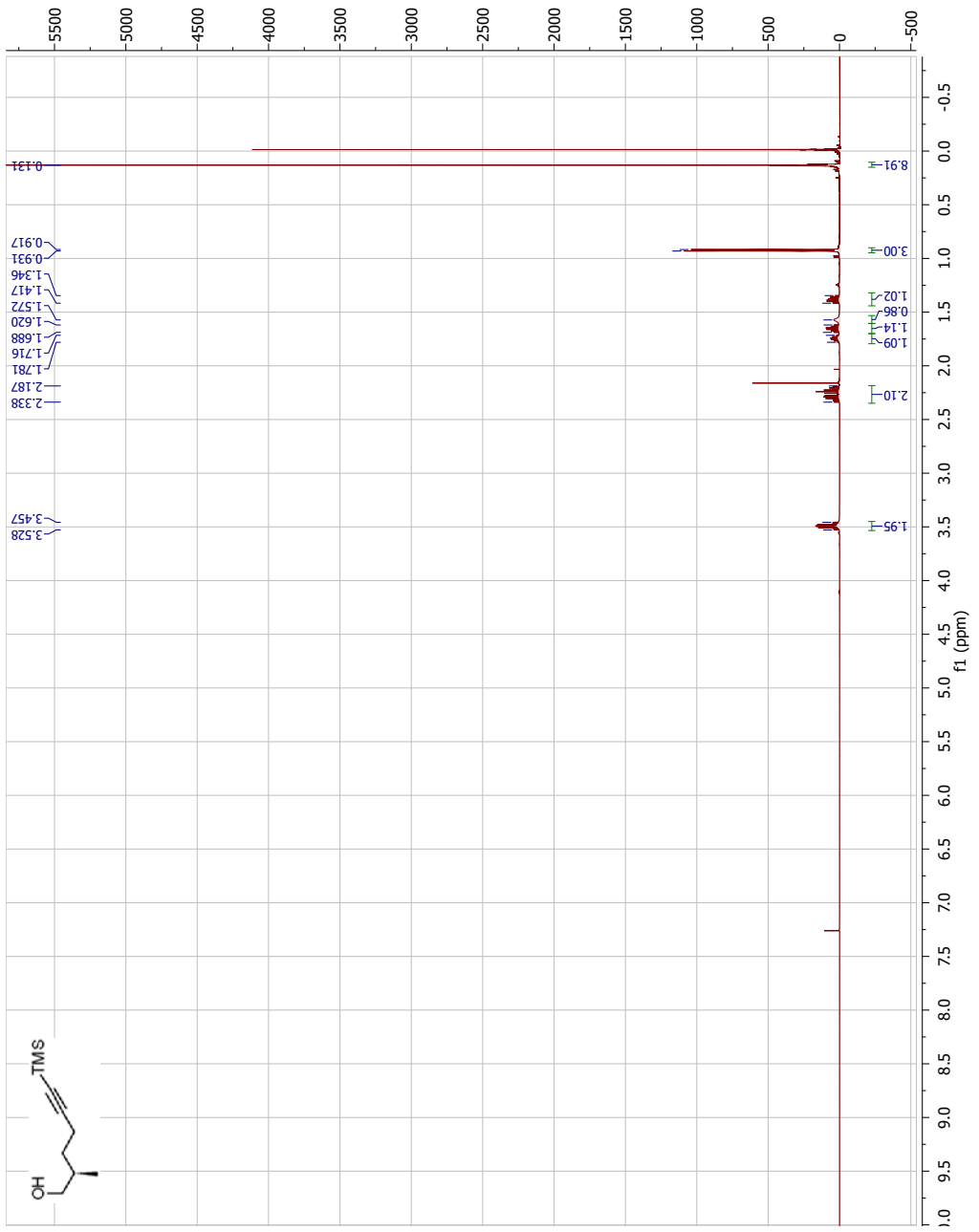

OTBS
HO
N
f1 (ppm)

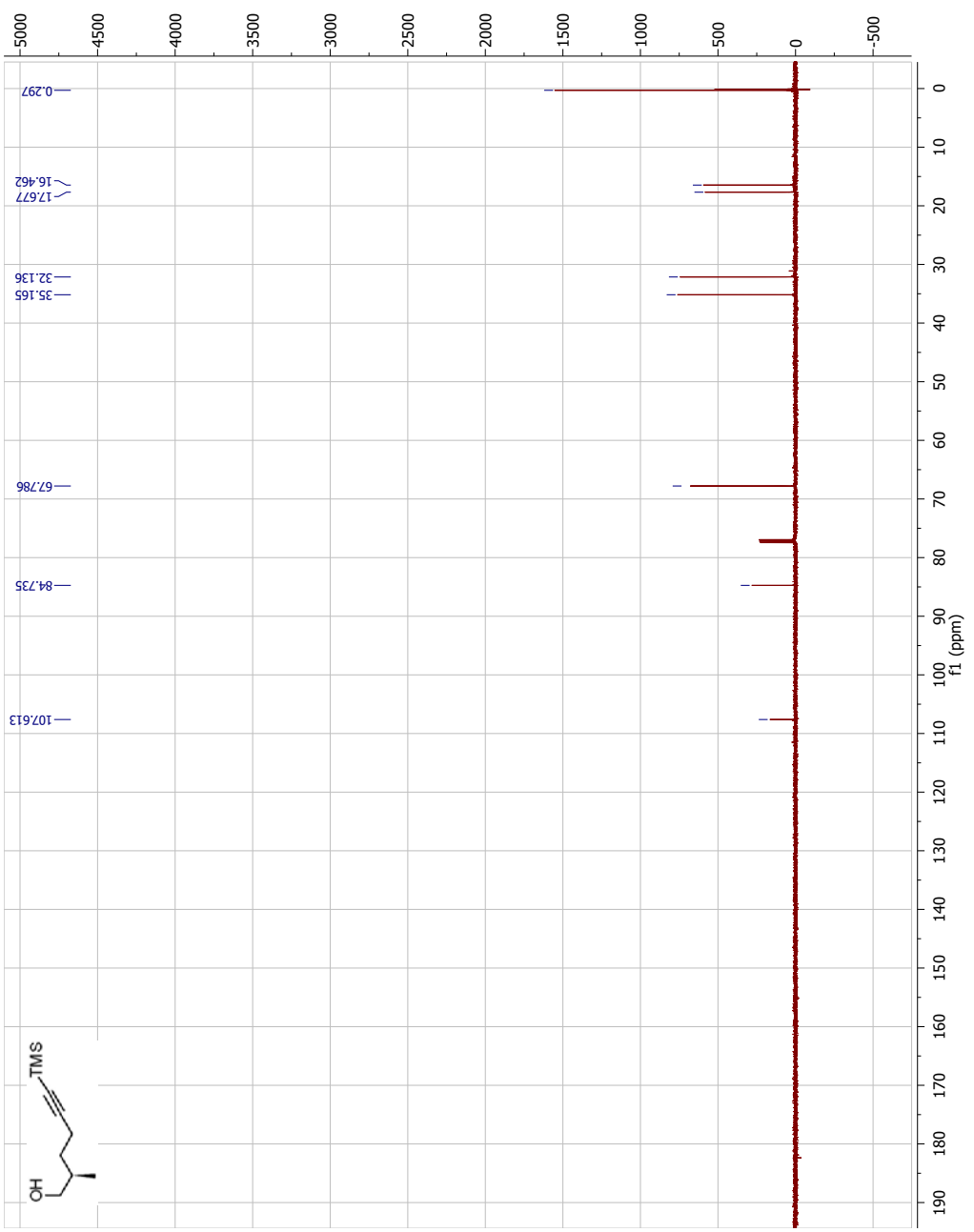

4500
4000
3500
3000
2500
2000
1500
1000
500
0
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
f1 (ppm)
0.120
0.141
0.855
0.919
1.821
1.916
2.293
2.414
2.939
3.136
4.177
4.295
4.397
4.447
7.80
5.85
1.92
2.98
2.03
1.98
1.00
TMS
O
N
O
O

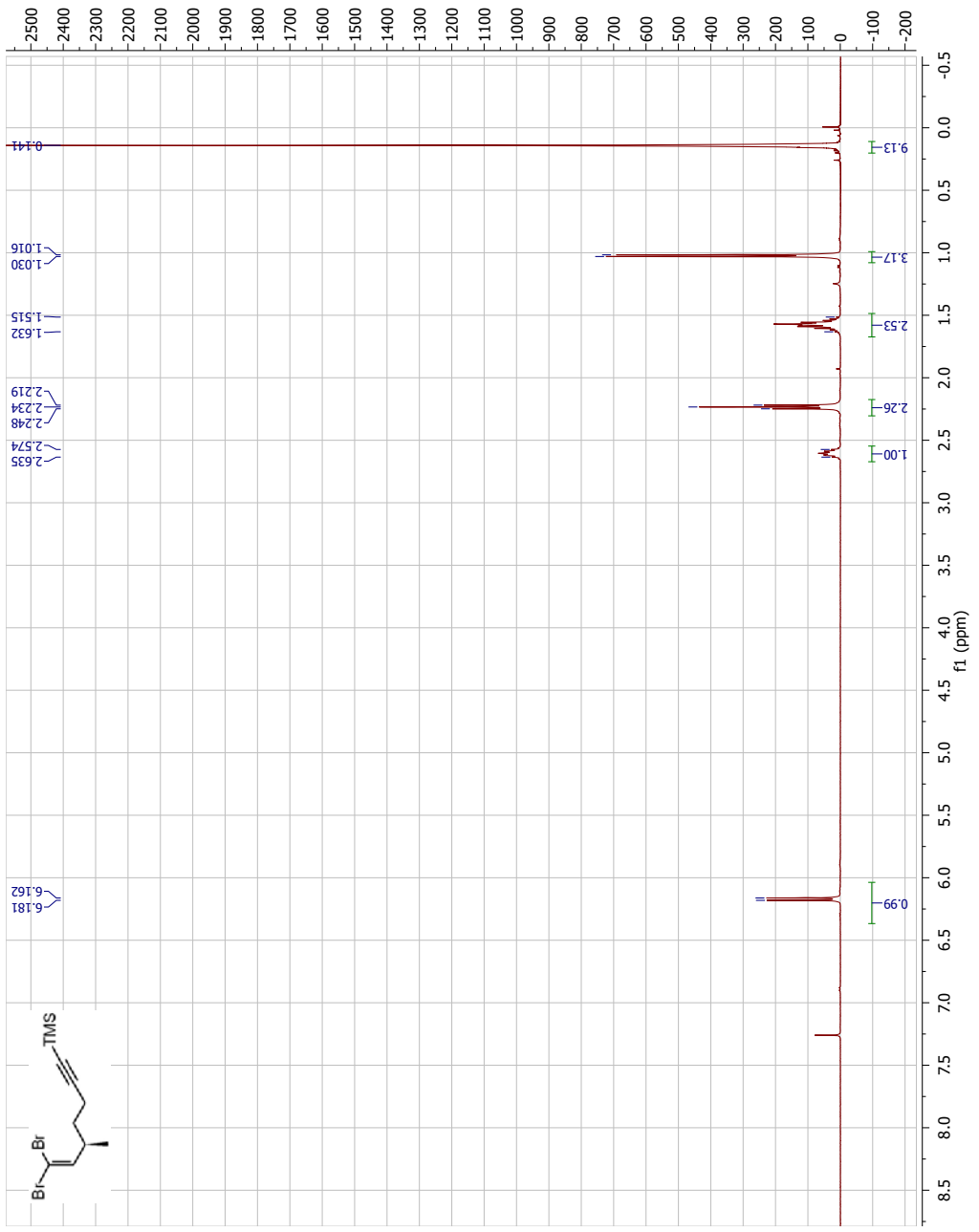

172.754
154.141
106.241
85.590
63.513
58.514
34.418
28.511
23.315
19.282
18.094
14.811
0.234
TMS
f1 (ppm)

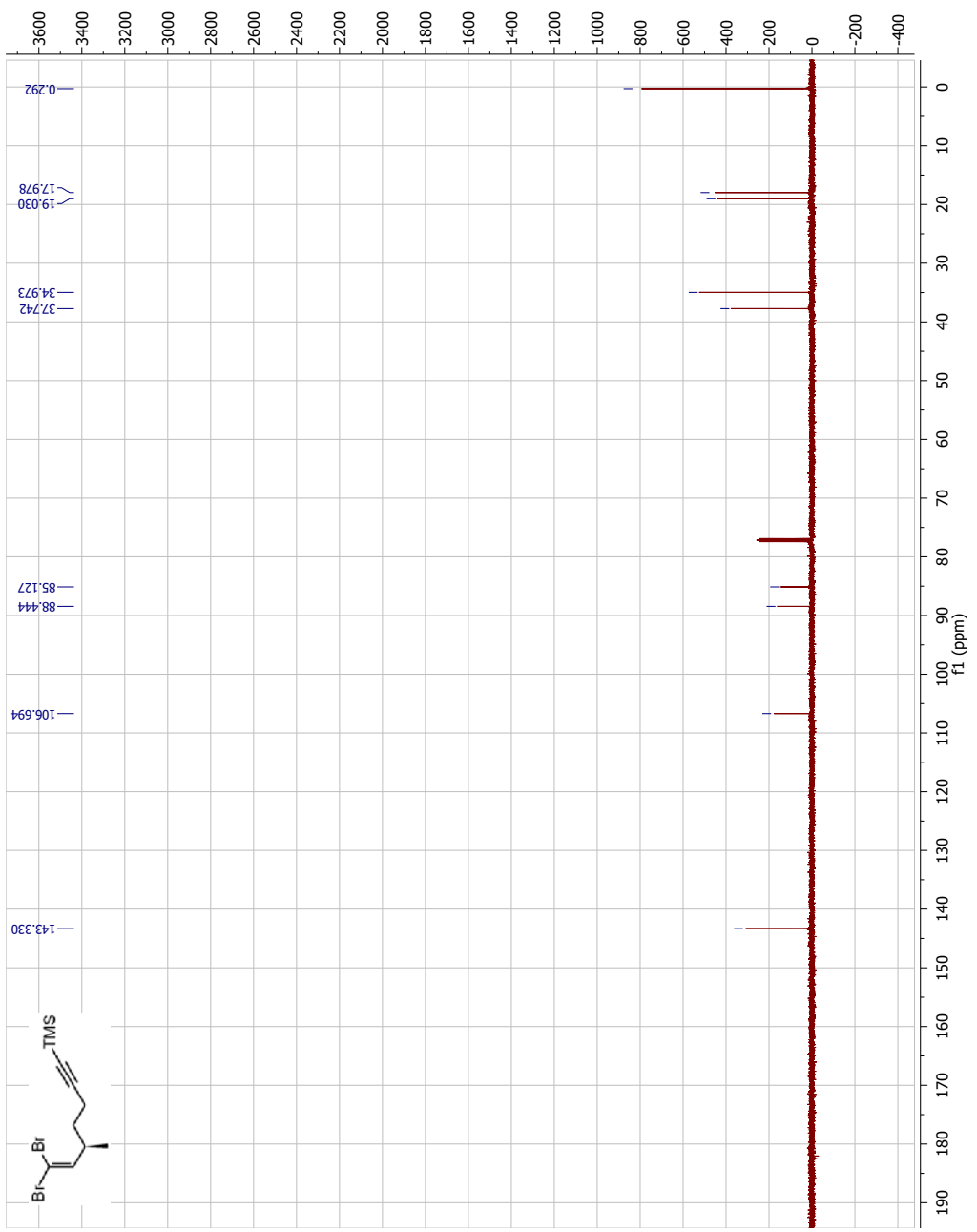

TMS
f1 (ppm)

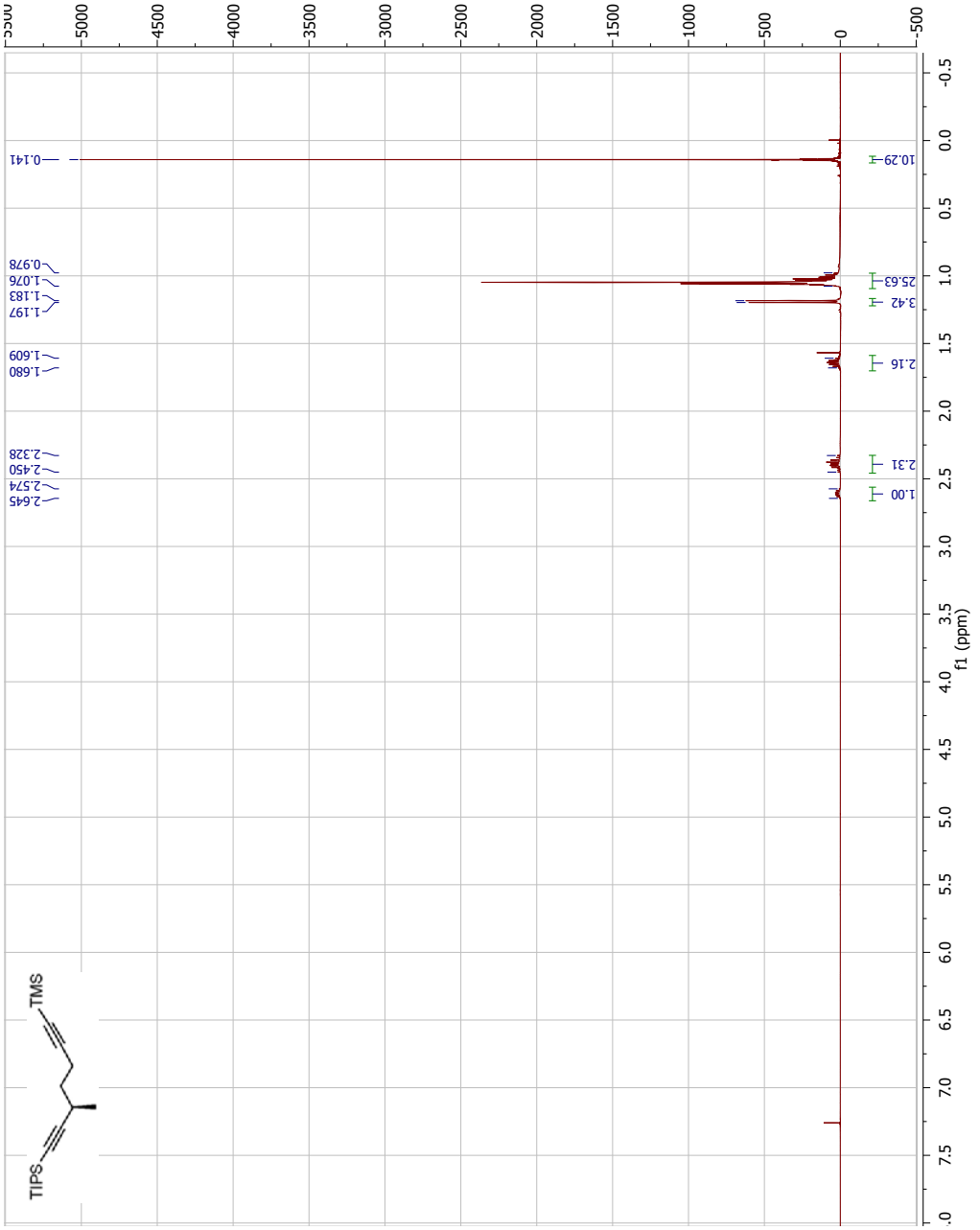

0.201
14.847
17.793
18.028
18.061
28.570
31.579
37.004
58.494
63.367
85.403
106.304
153.551
176.491
TMS
f1 (ppm)

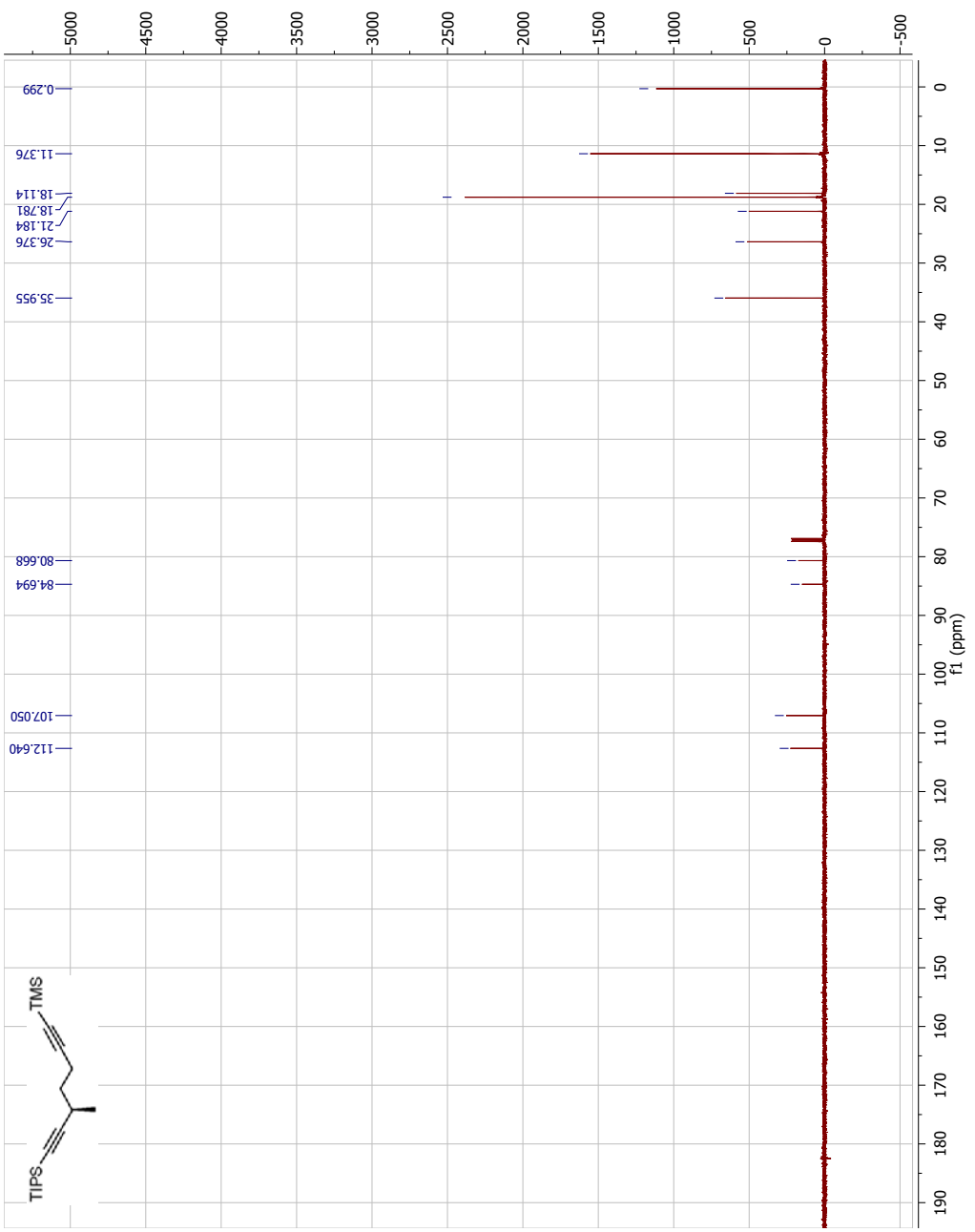

TMS
OH
f1 (ppm)

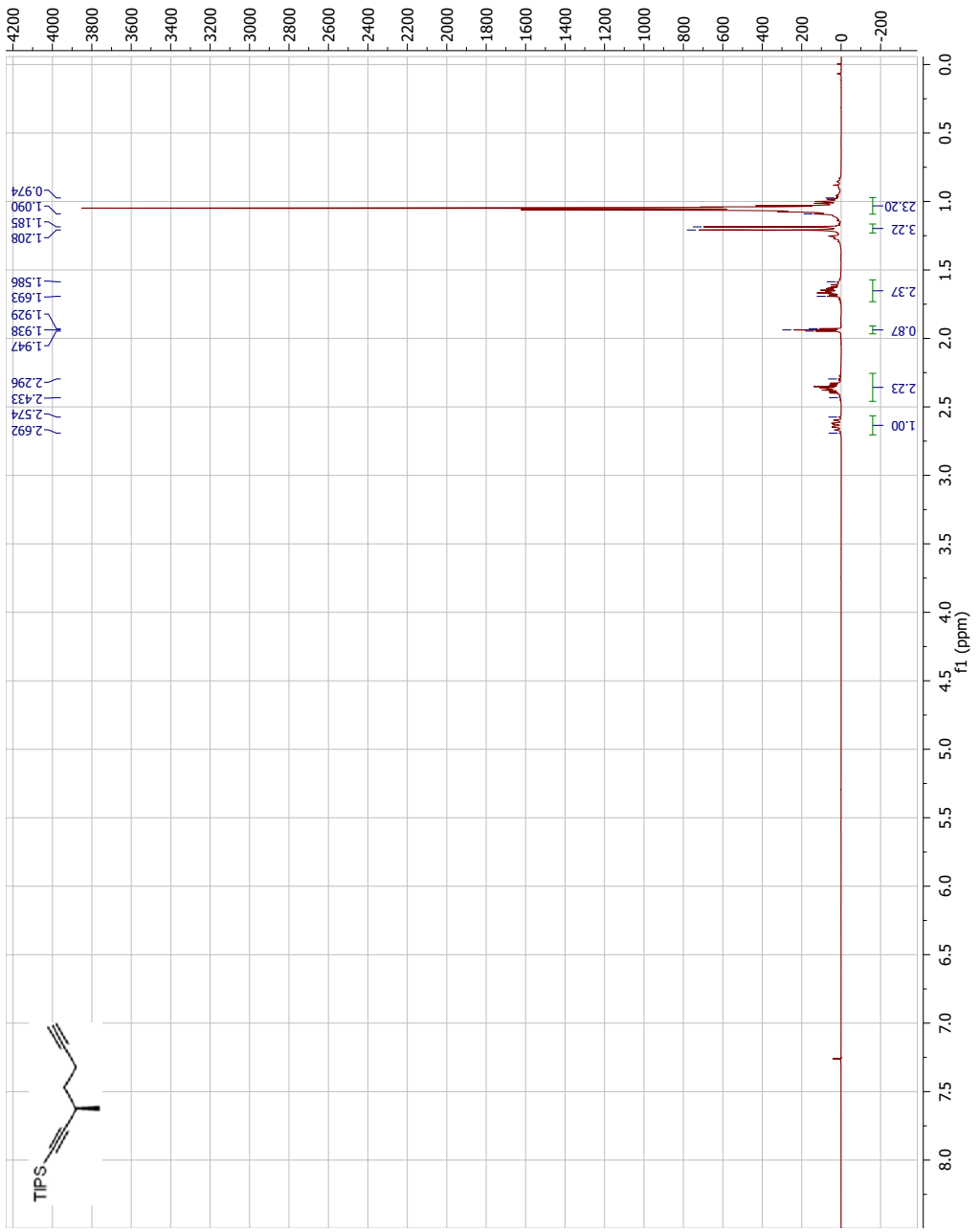

0.297
16.462
17.677
32.136
35.165
67.786
84.735
107.613
TMS
OH
f1 (ppm)

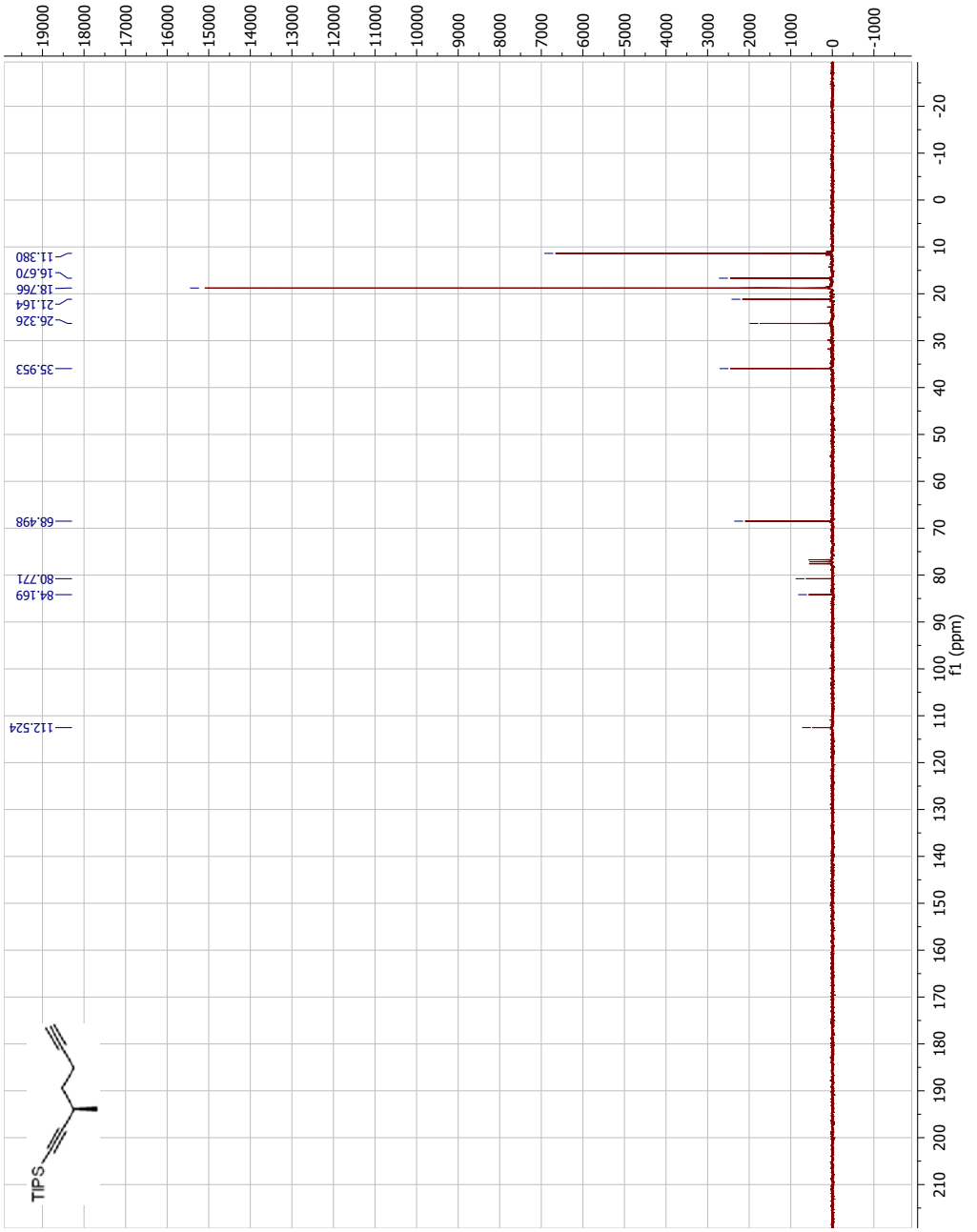

TMS
Br
Br
0.141
1.016
1.030
1.515
1.632
2.219
2.234
2.248
2.574
2.635
6.162
6.181
9.13
3.17
2.53
2.26
1.00
0.99
f1 (ppm)

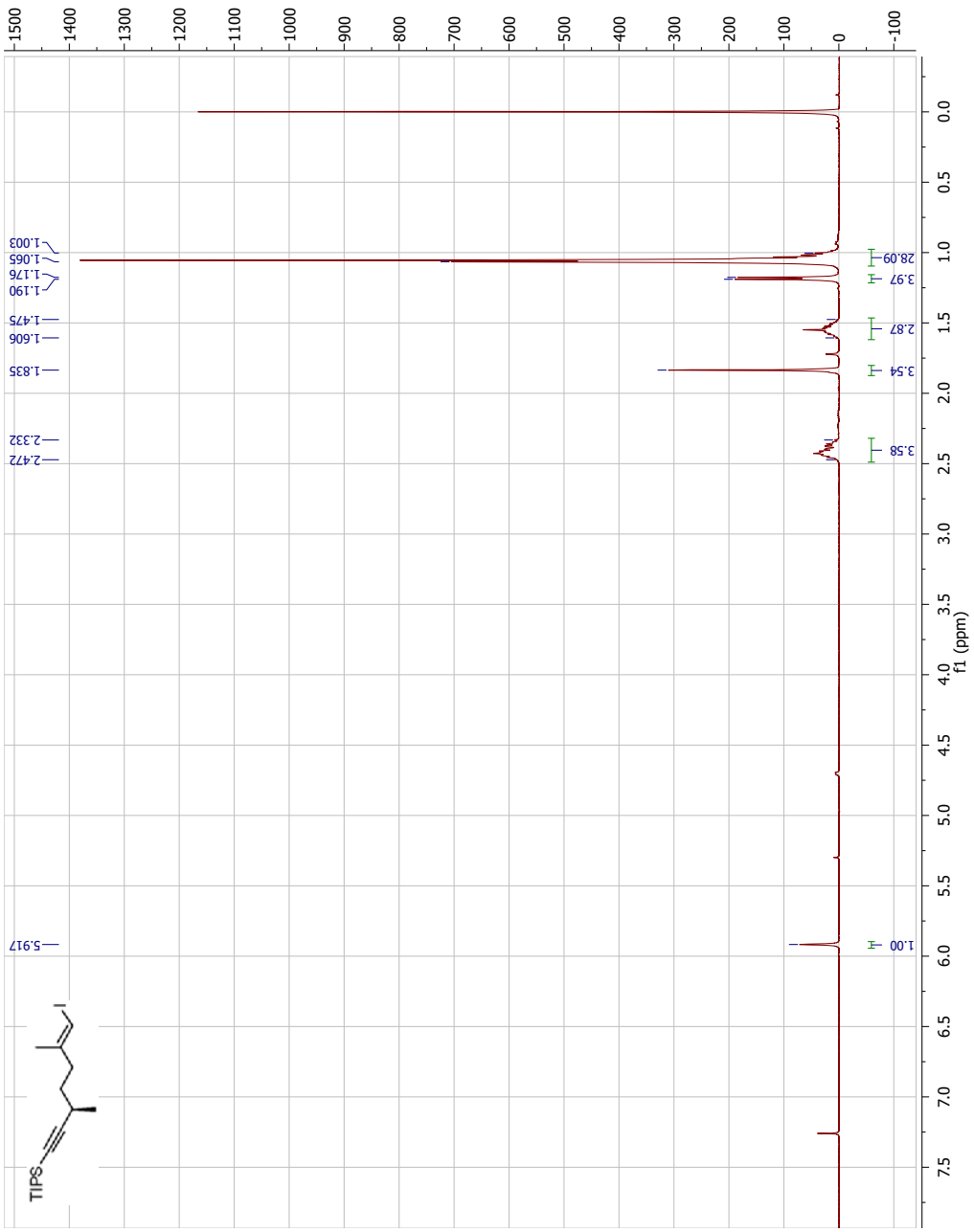

143.330
106.694
88.444
85.127
37.742
34.973
19.030
17.978
0.292
TMS
Br
Br
f1 (ppm)

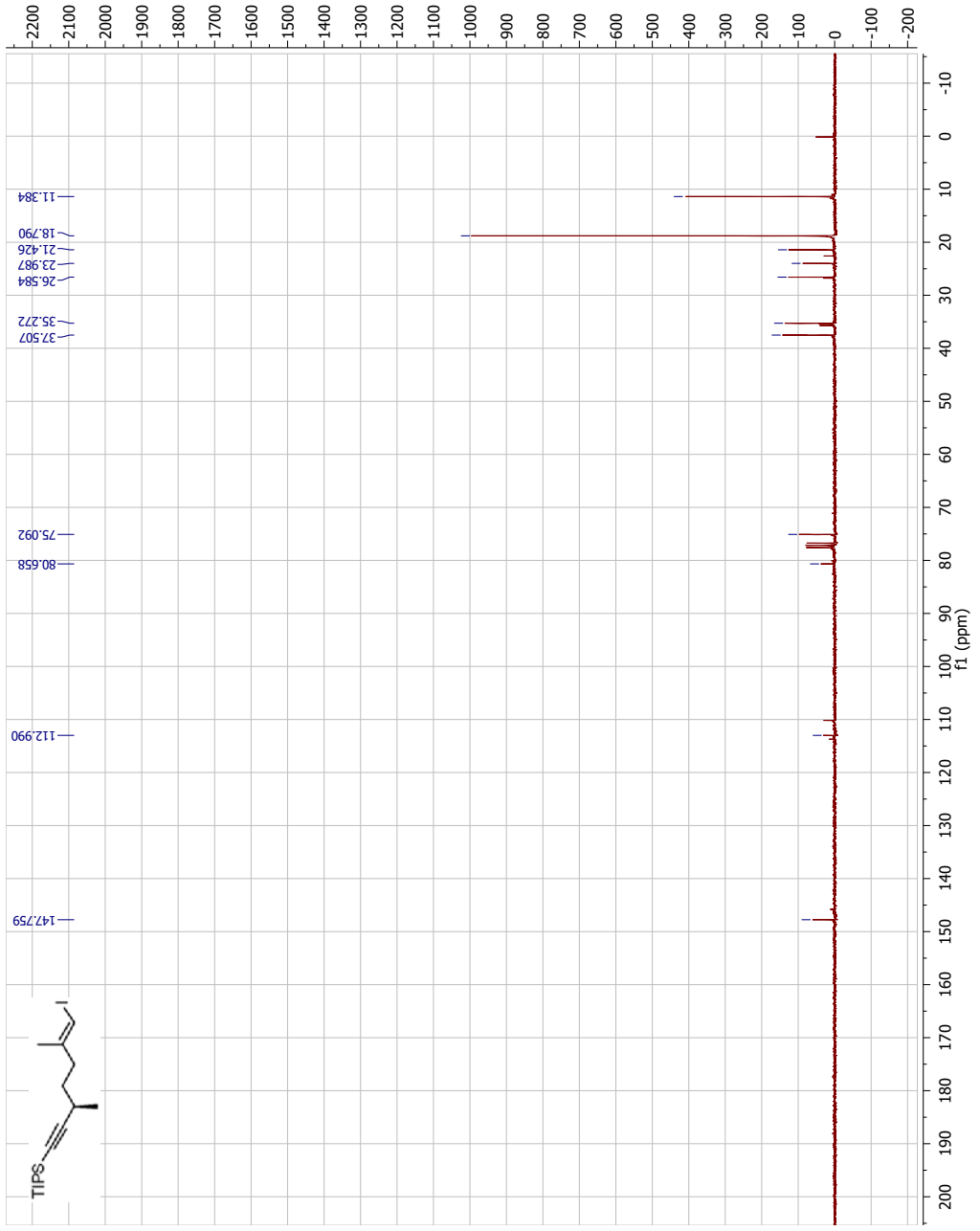

TMS
TIPS
0.141
0.978
1.076
1.183
1.197
1.609
1.680
2.328
2.450
2.574
2.645
10.29
25.63
3.42
2.16
2.31
1.00
f1 (ppm)

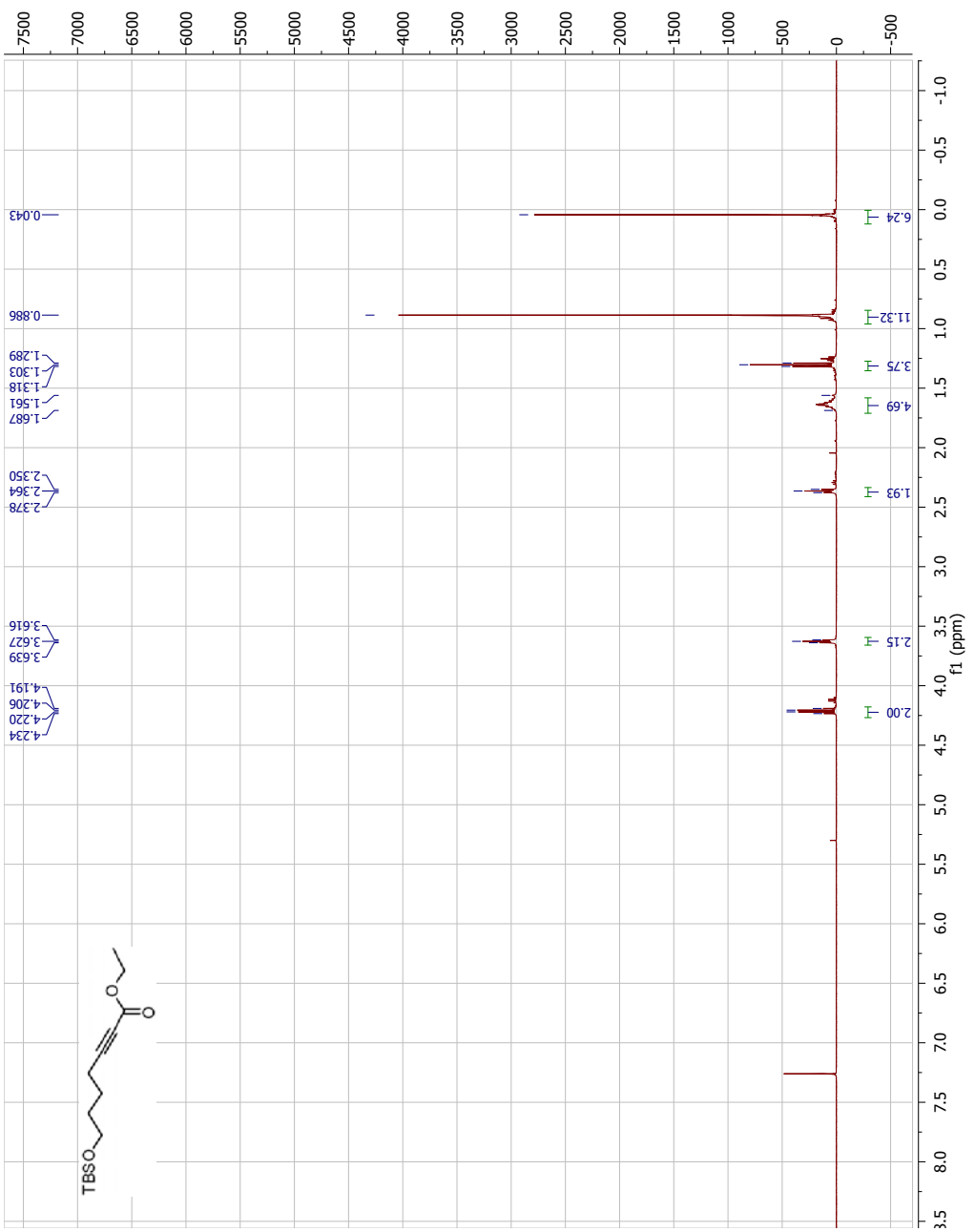

0.299
11.376
18.114
18.781
21.184
26.376
35.955
80.668
84.694
107.050
112.640
TMS
TIPS
f1 (ppm)

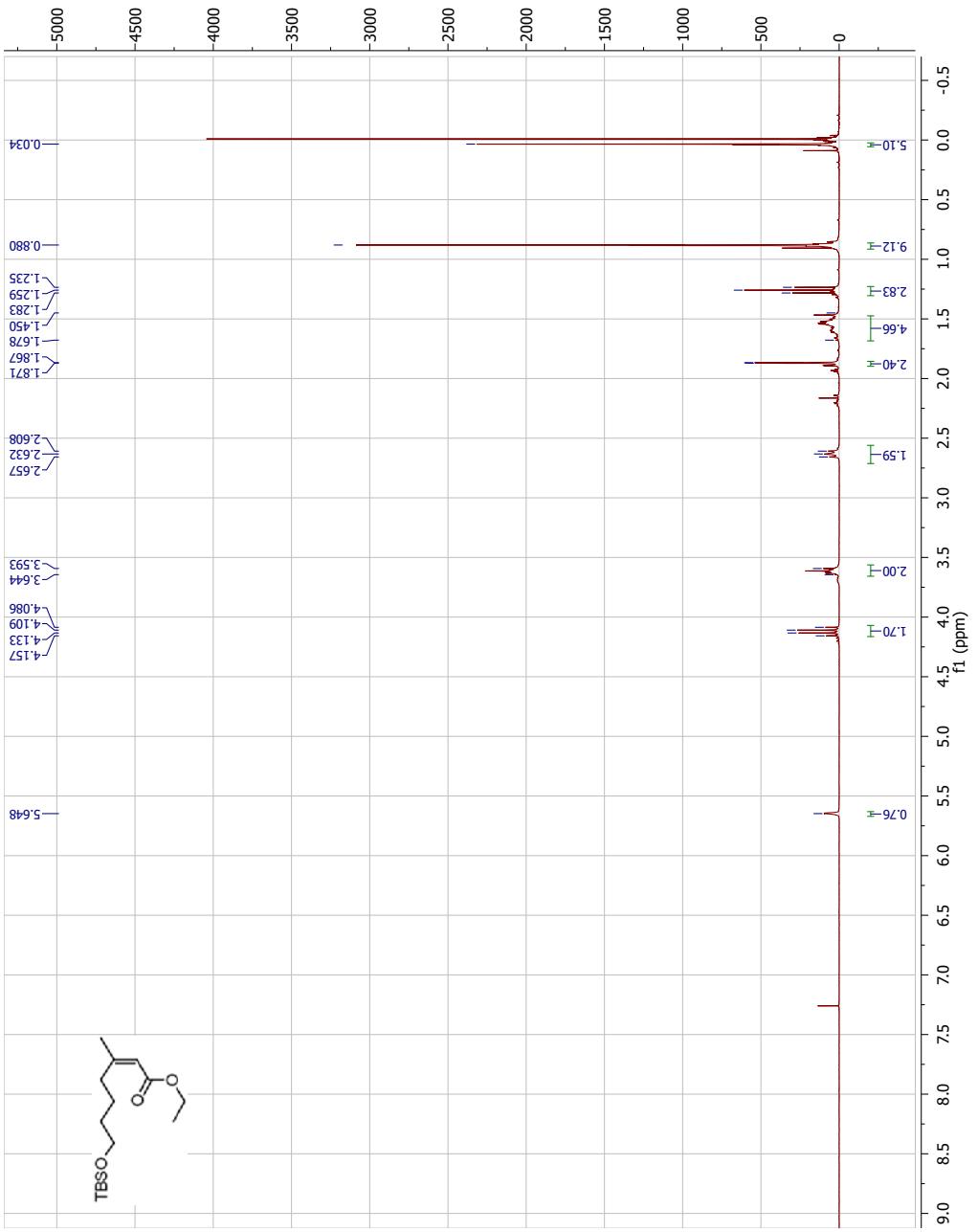

TIPS
f1 (ppm)
0.974
1.090
1.185
1.208
1.586
1.693
1.929
1.938
1.947
2.296
2.433
2.574
2.692
23.20
3.22
2.37
0.87
2.23
1.00

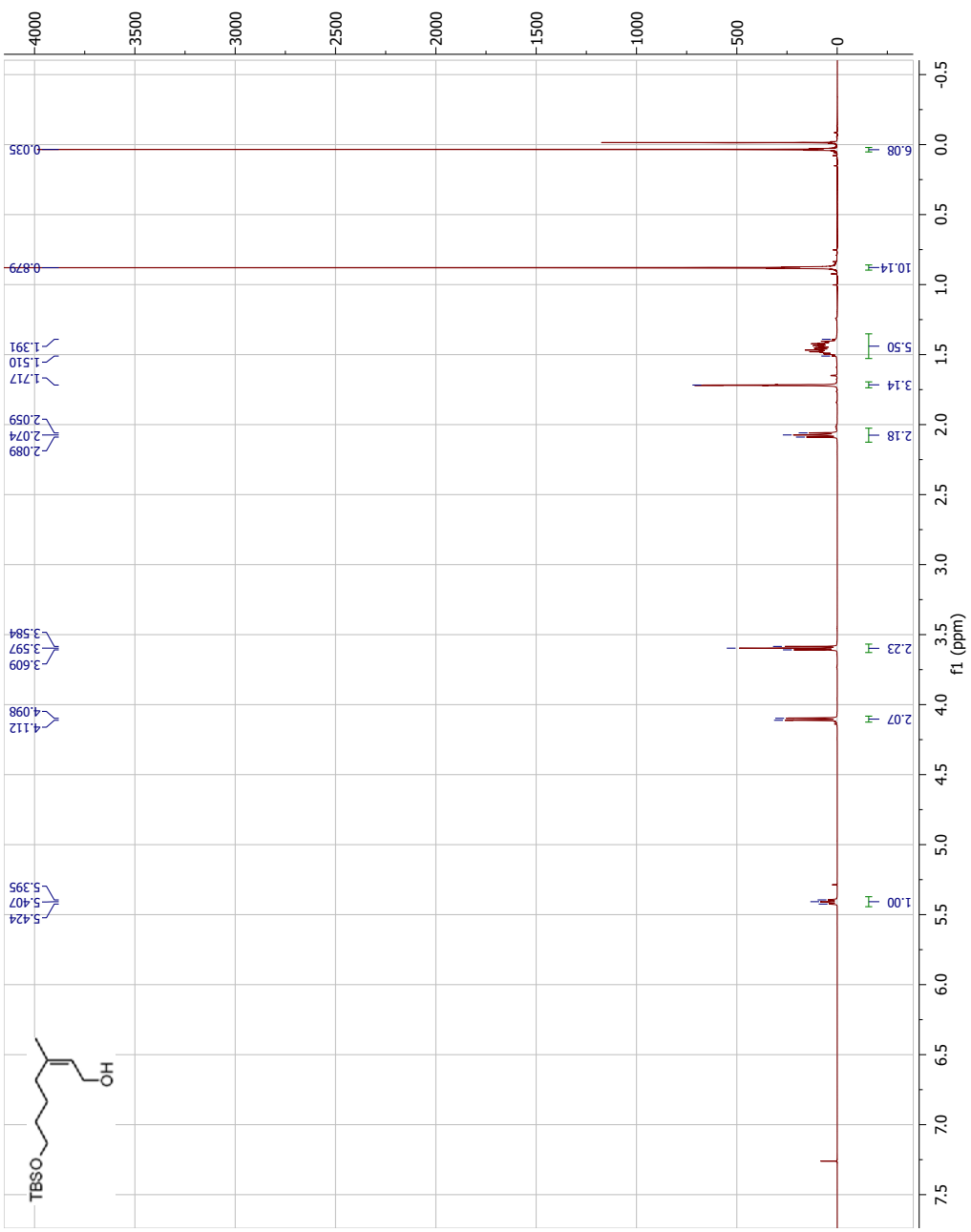

11.380
16.670
18.766
21.164
26.326
35.953
68.498
80.771
84.169
112.524
TIPS
f1 (ppm)

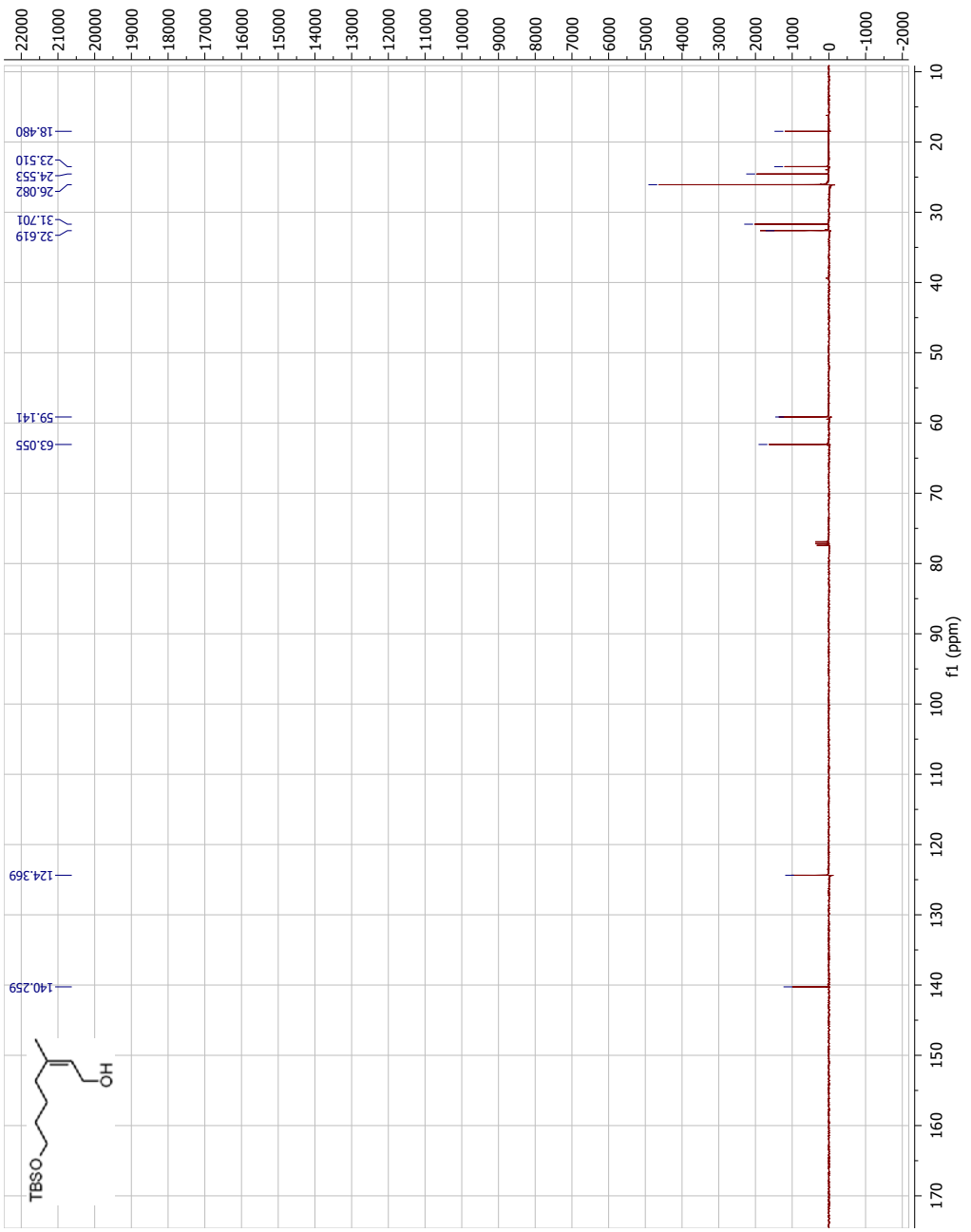

TIPS
I
5.917
2.472
2.332
1.835
1.606
1.475
1.190
1.176
1.065
1.003
1.00
3.58
3.54
2.87
3.97
28.09
f1 (ppm)

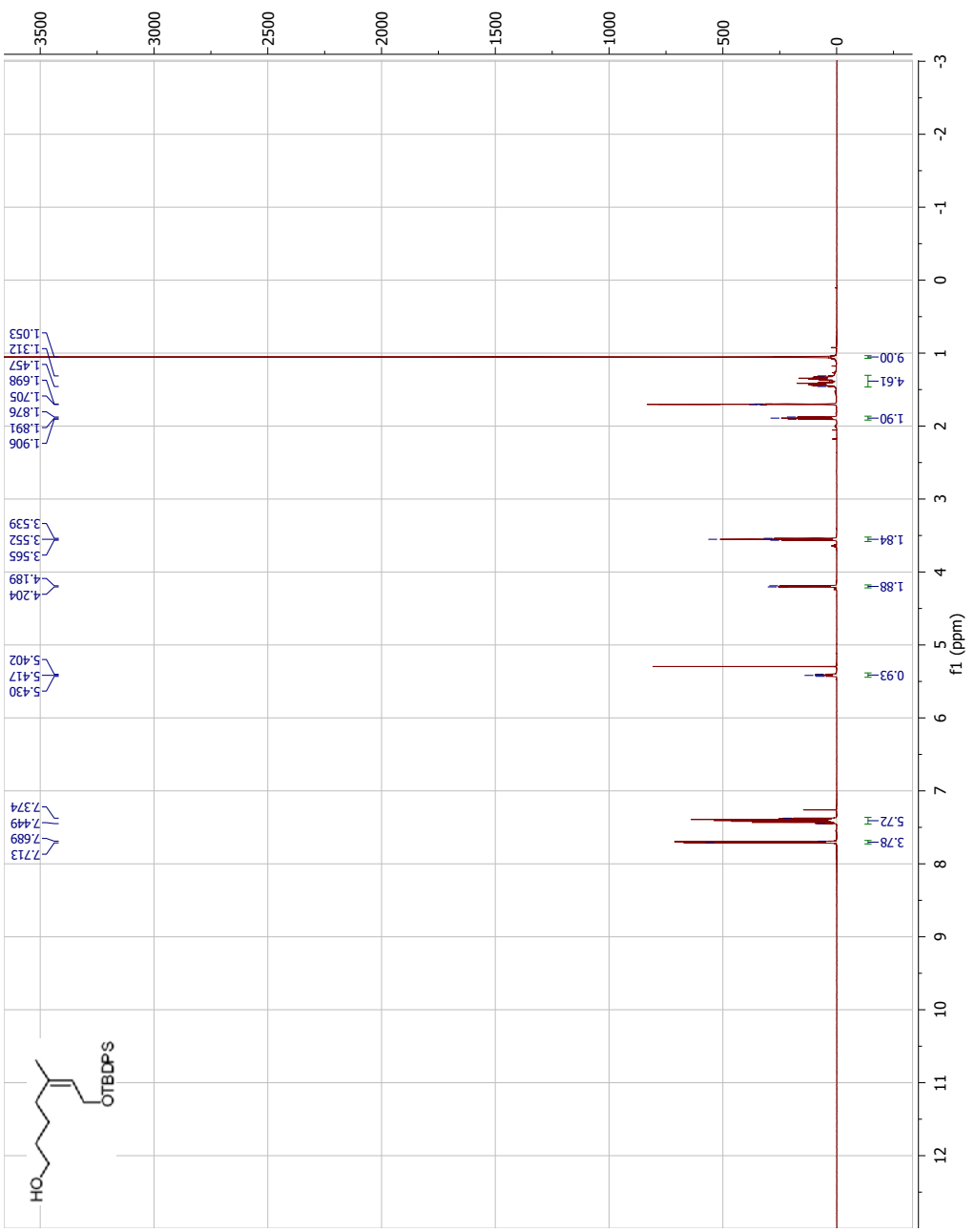

11.384
18.790
21.426
23.987
26.584
35.272
37.507
75.092
80.658
112.990
147.759
TIPS
f1 (ppm)

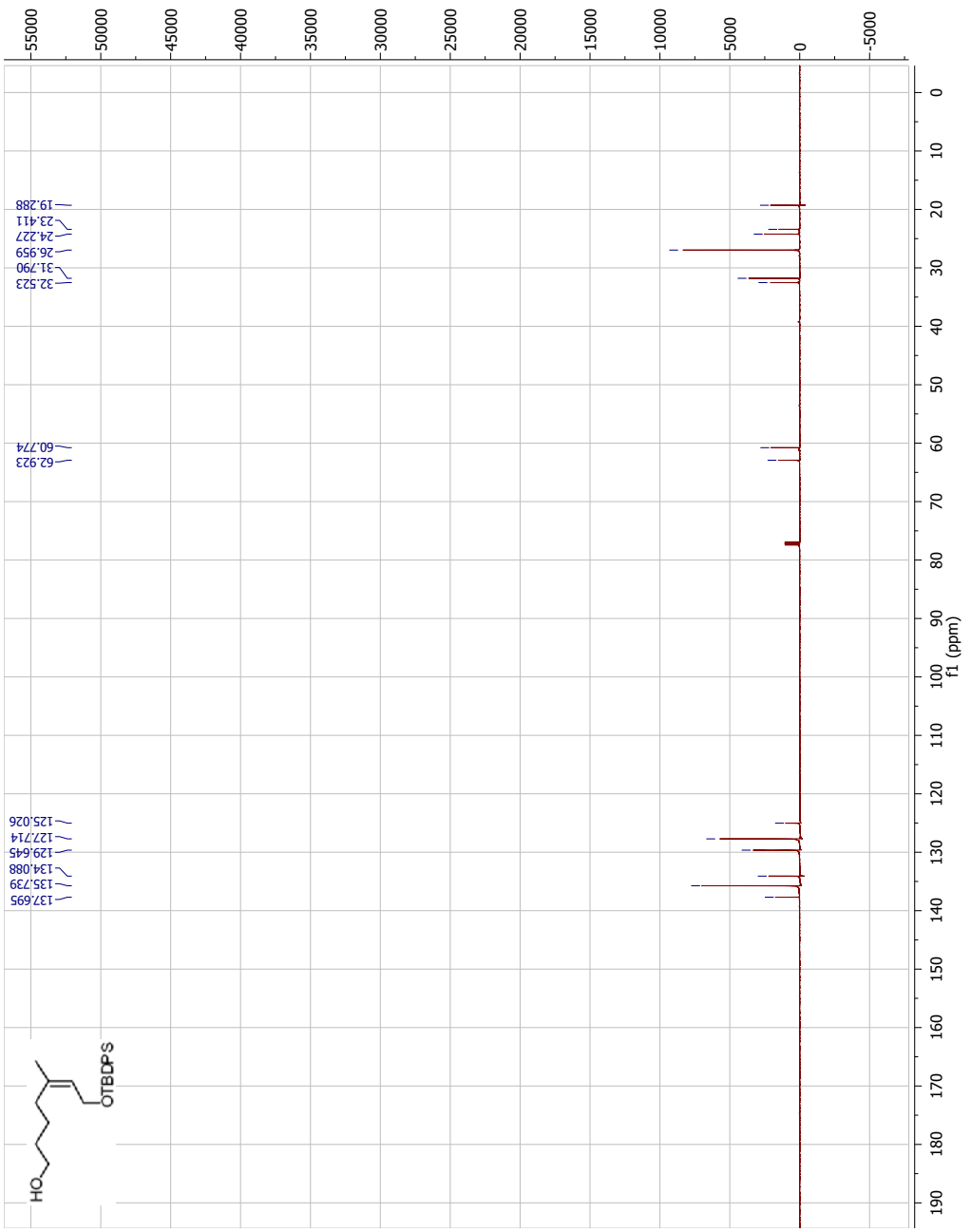

TBSO
O
O
f1 (ppm)
6.24
11.32
3.75
4.69
1.93
2.15
2.00
0.043
0.886
1.289
1.303
1.318
1.561
1.687
2.350
2.364
2.378
3.616
3.627
3.639
4.191
4.206
4.220
4.234

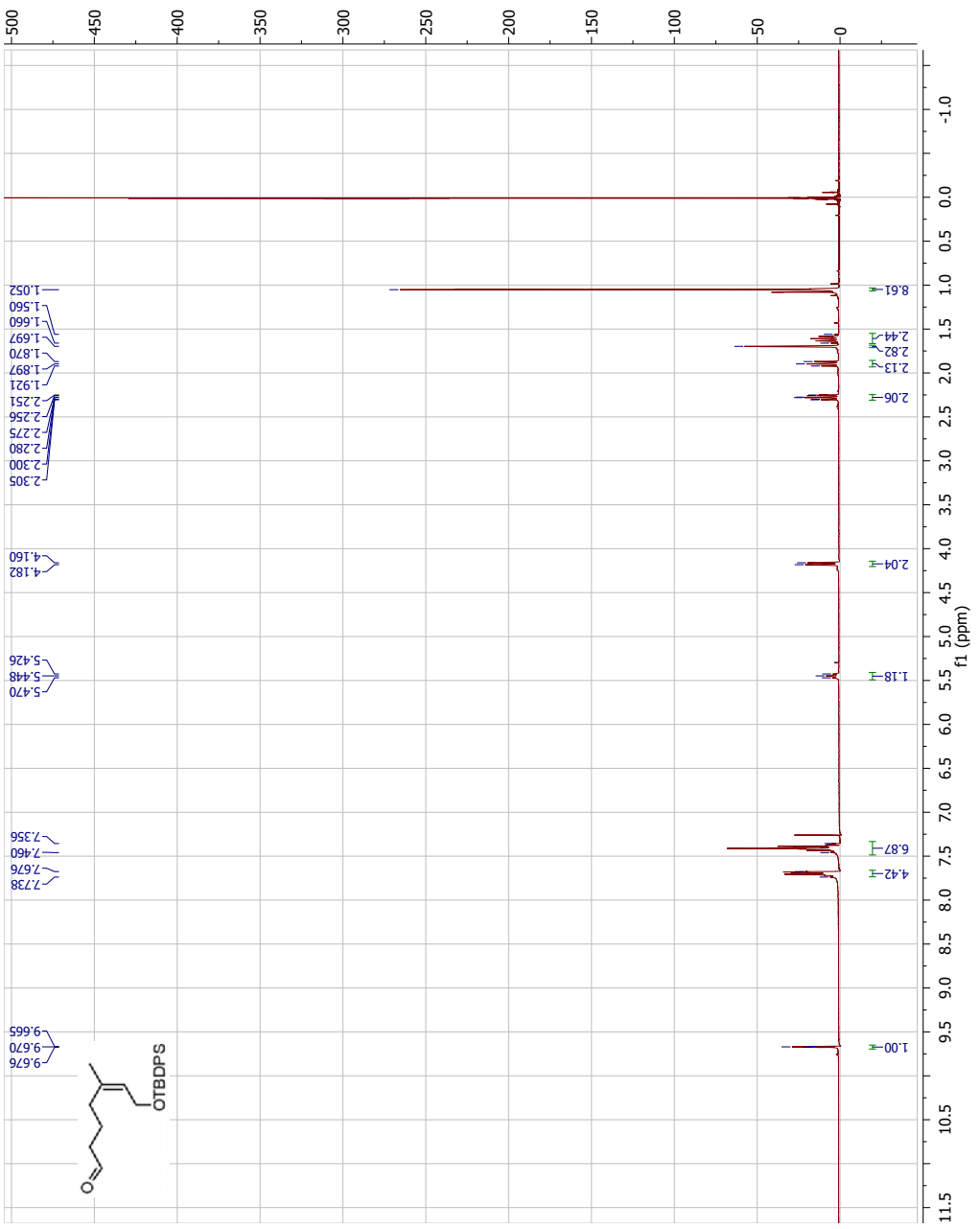

TBSO
O
O
0.034
0.880
1.235
1.259
1.283
1.450
1.678
1.867
1.871
2.608
2.632
2.657
3.593
3.644
4.086
4.109
4.133
4.157
5.648
5.10
9.12
2.83
4.66
2.40
1.59
2.00
1.70
0.76
f1 (ppm)

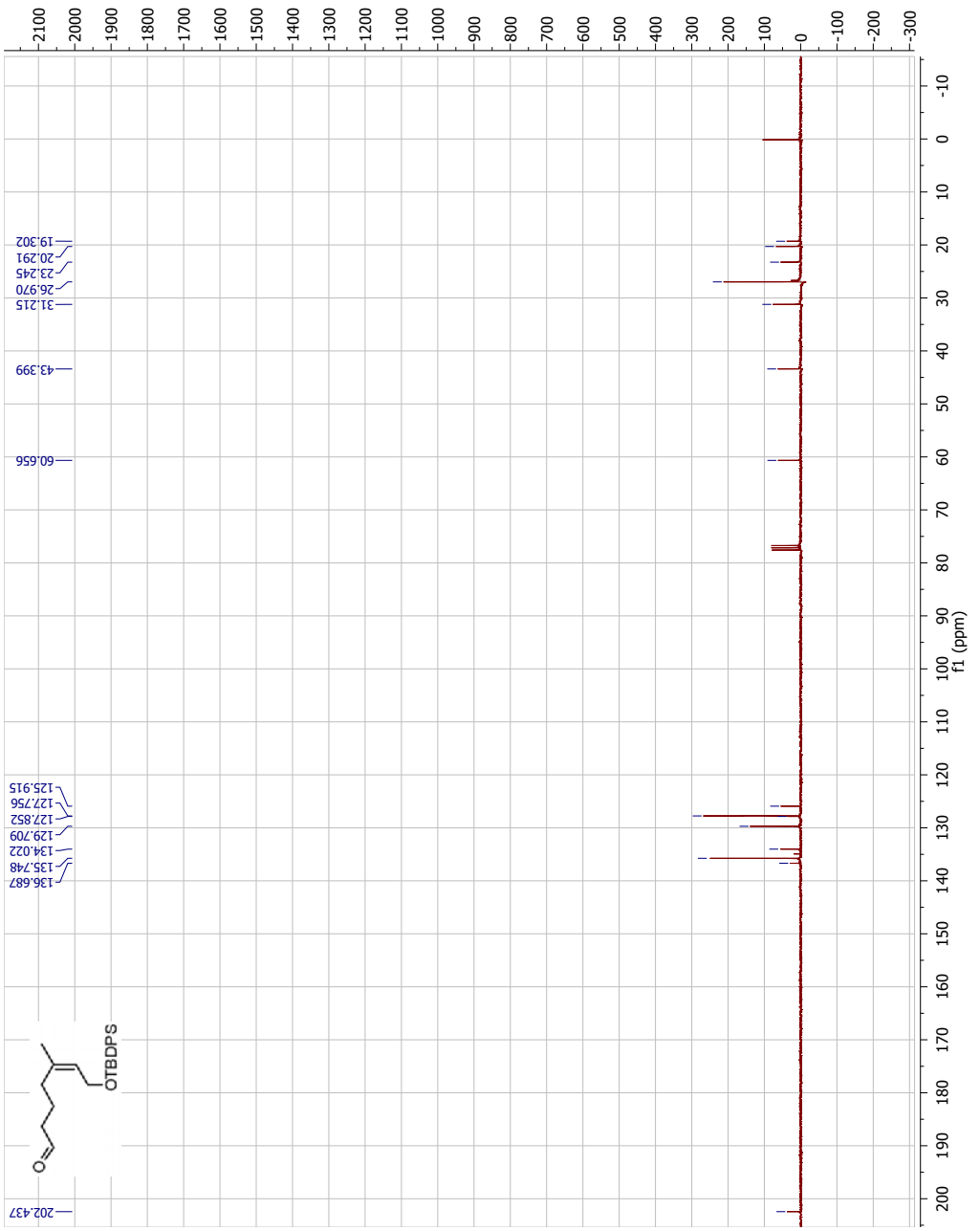

4000
3500
3000
2500
2000
1500
1000
500
0
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
f1 (ppm)
0.035
0.879
1.391
1.510
1.717
2.059
2.074
2.089
3.584
3.597
3.609
4.098
4.112
5.395
5.407
5.424
6.08
10.14
5.50
3.14
2.18
2.23
2.07
1.00
TBSO
OH

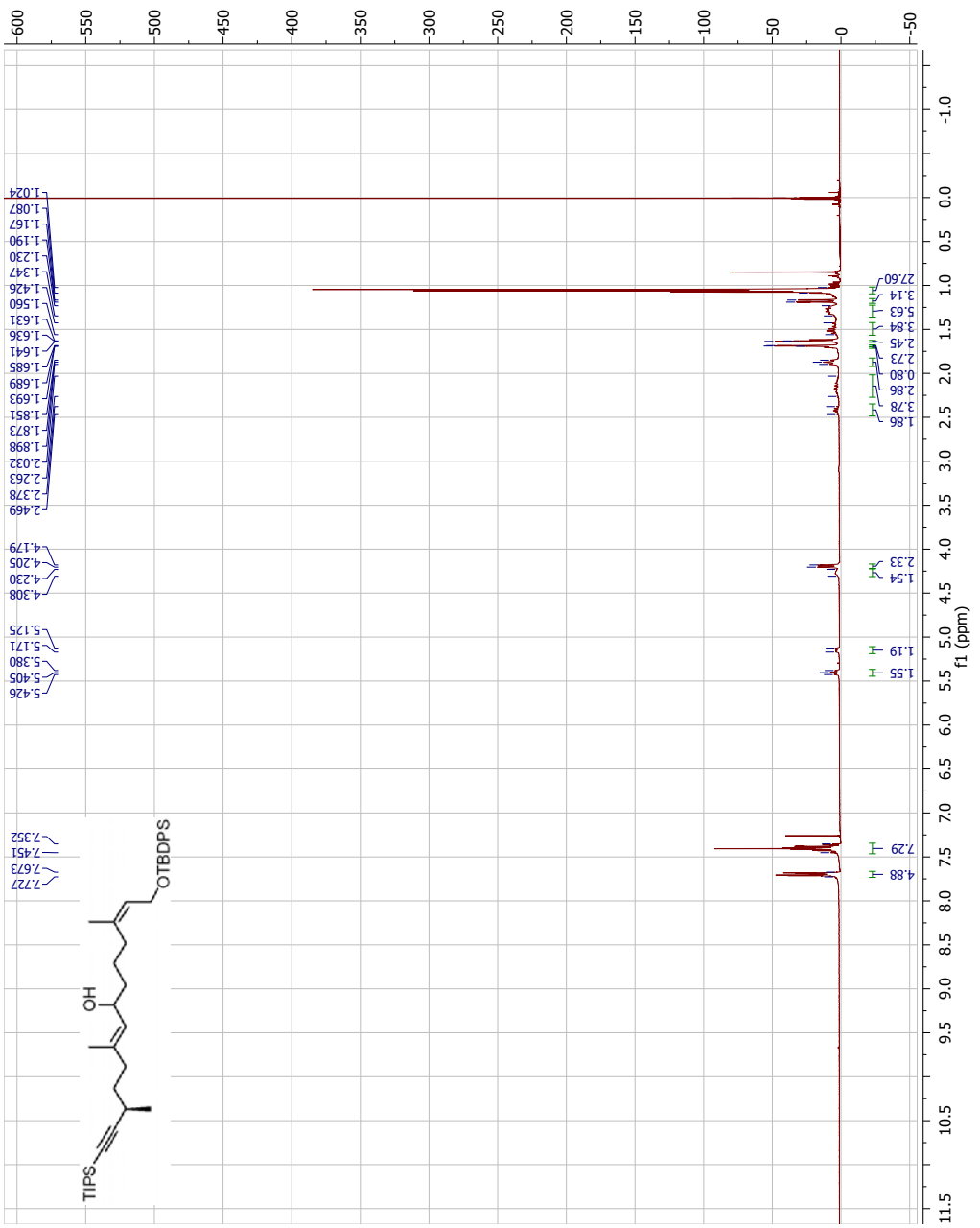

140.259
124.369
63.055
59.141
32.619
31.701
26.082
24.553
23.510
18.480
TBSO
OH
f1 (ppm)

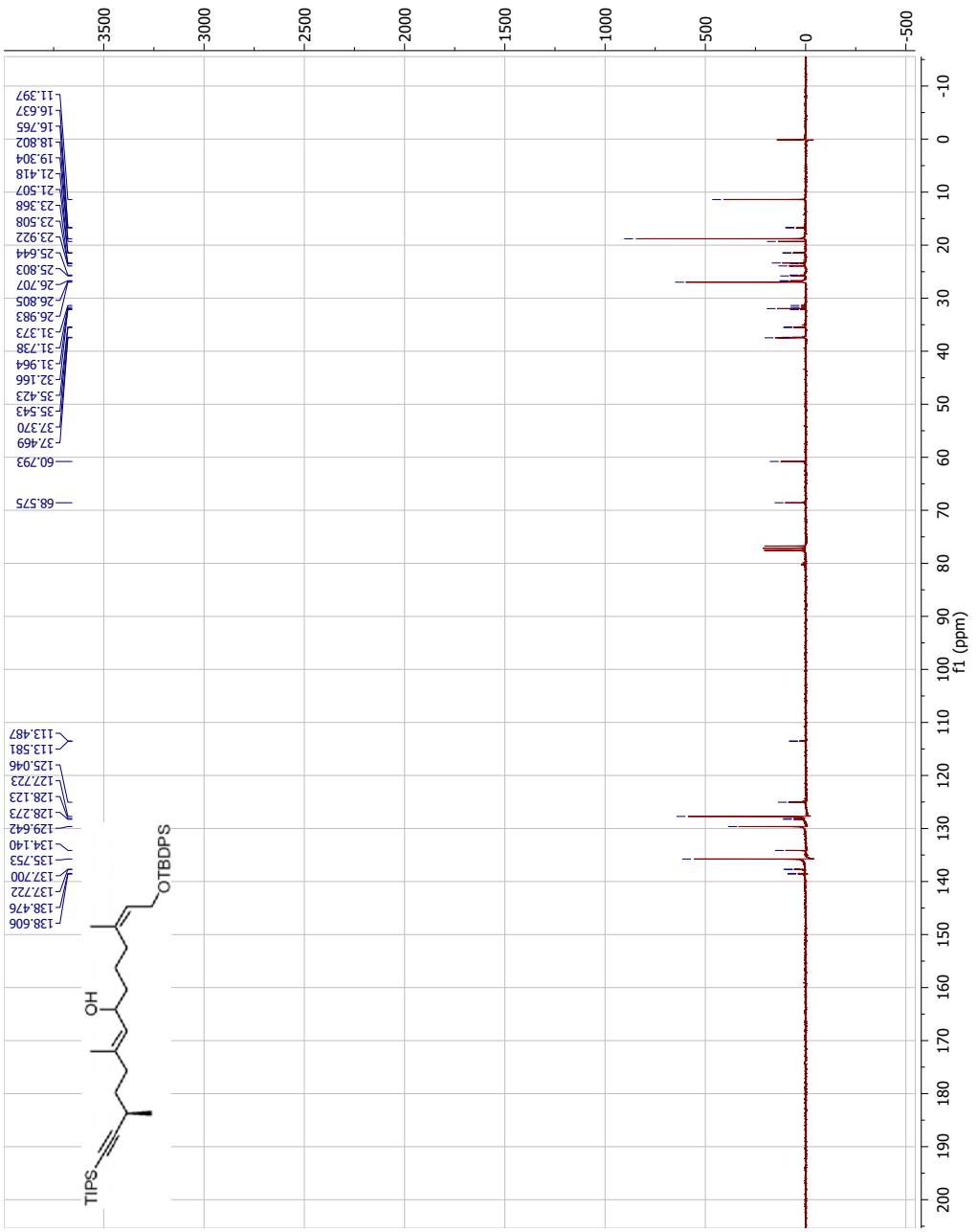

HO
OTBDPS
f1 (ppm)

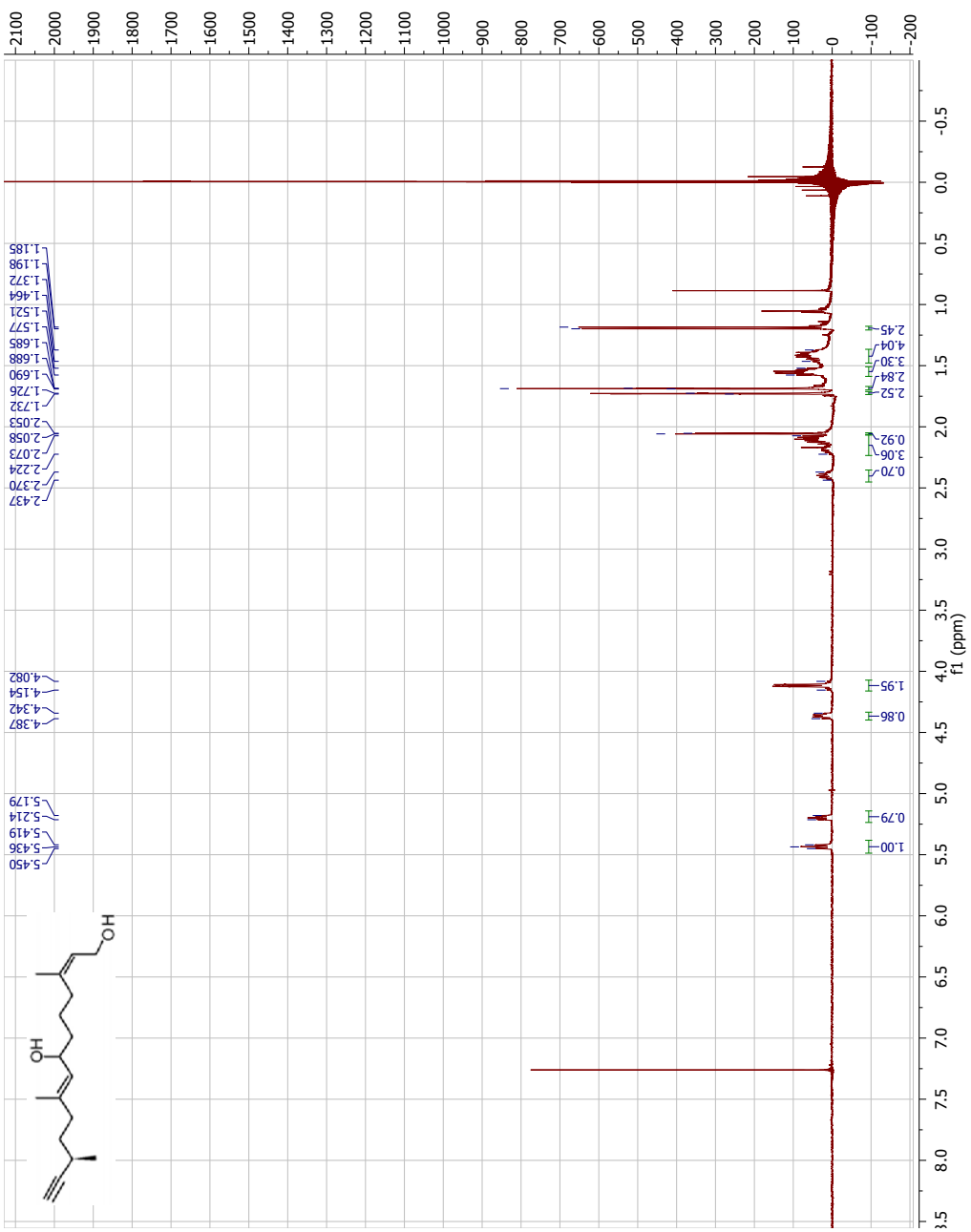

137.695
135.739
134.088
129.645
127.714
125.026
62.923
60.774
32.523
31.790
26.959
24.227
23.411
19.288
OH
OTBDPS
f1 (ppm)

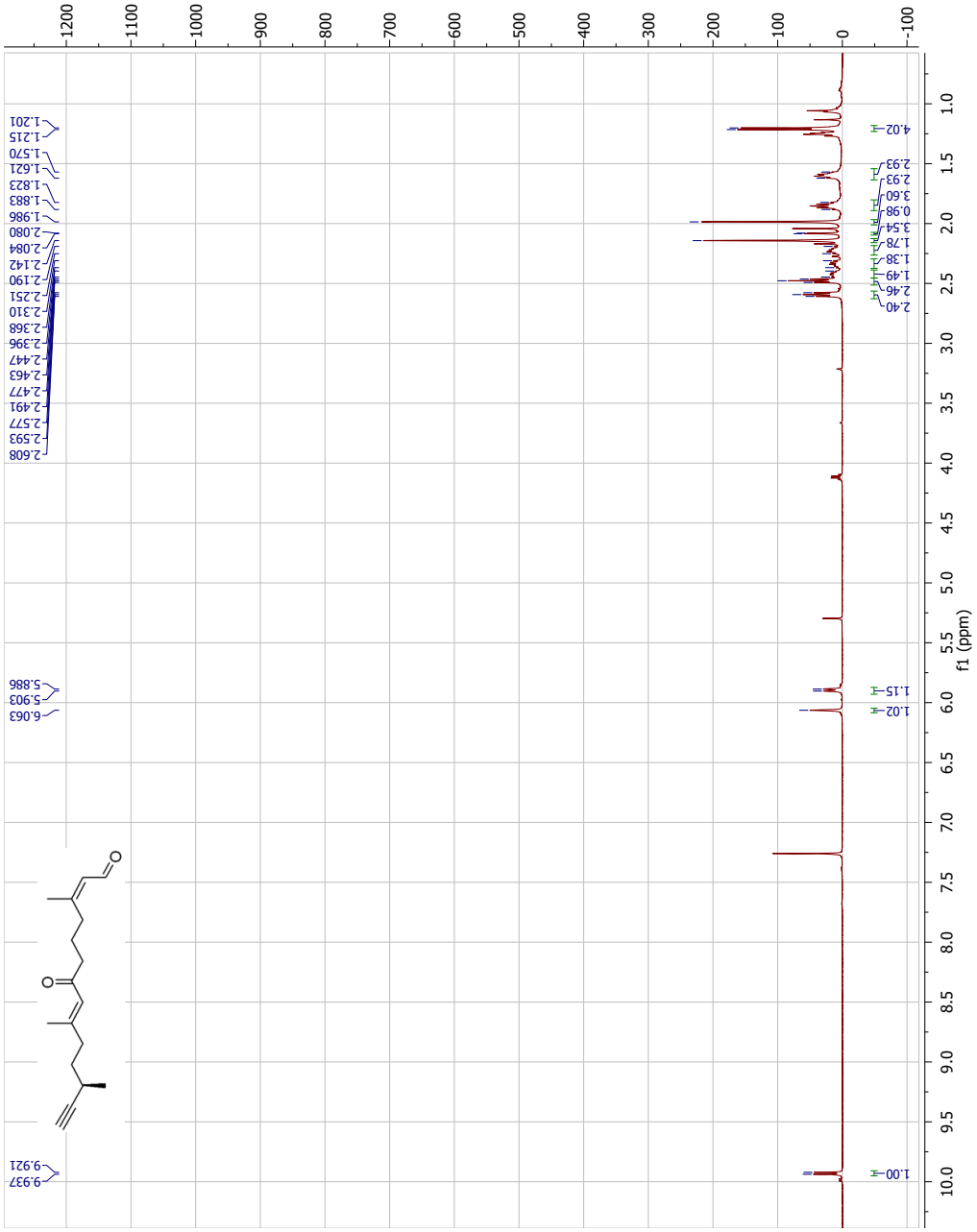

OTBDPS
f1 (ppm)

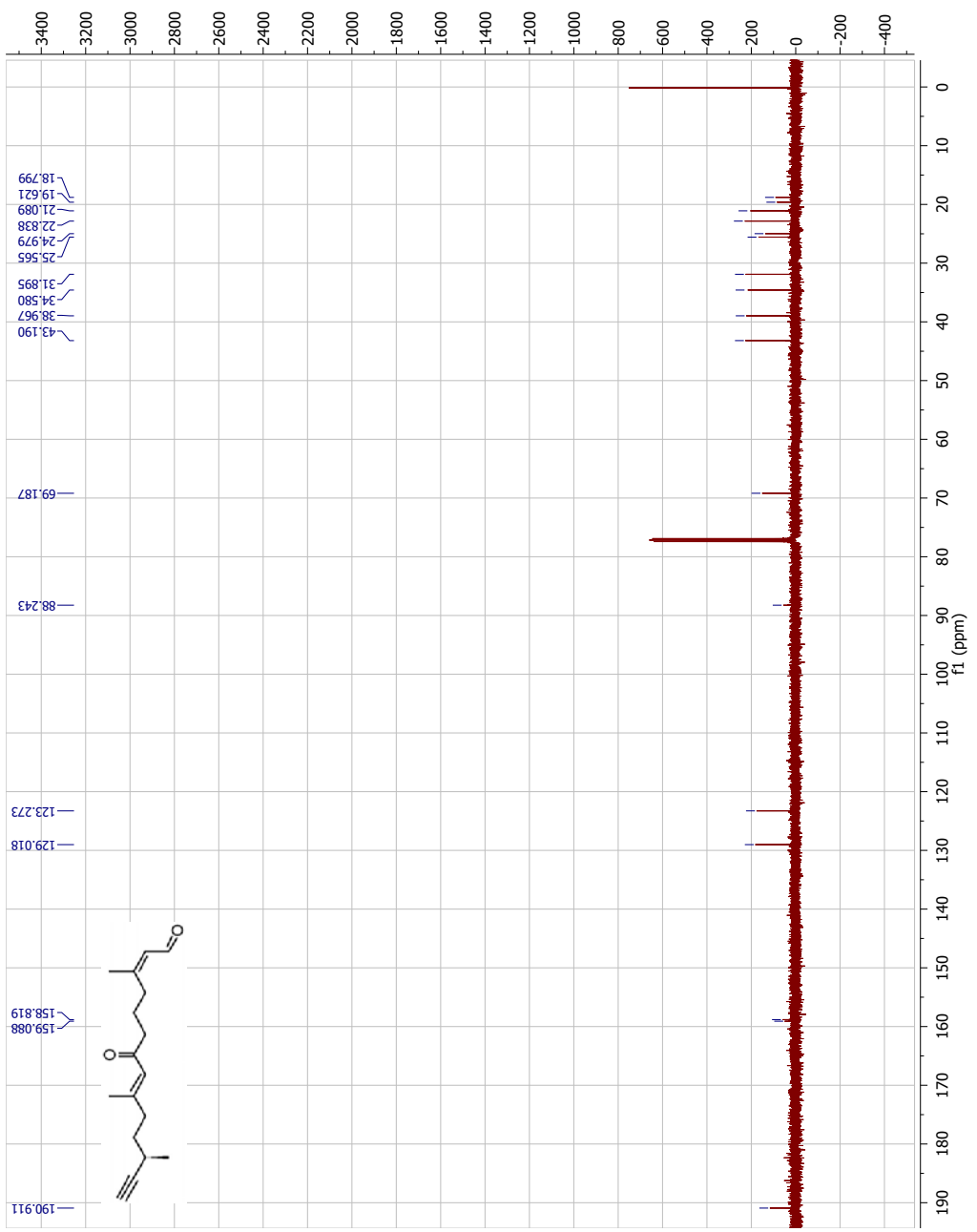

OTBDPS
202.437
136.687
135.748
134.022
129.709
127.852
127.756
125.915
60.656
43.399
31.215
26.970
23.245
20.291
19.302
f1 (ppm)

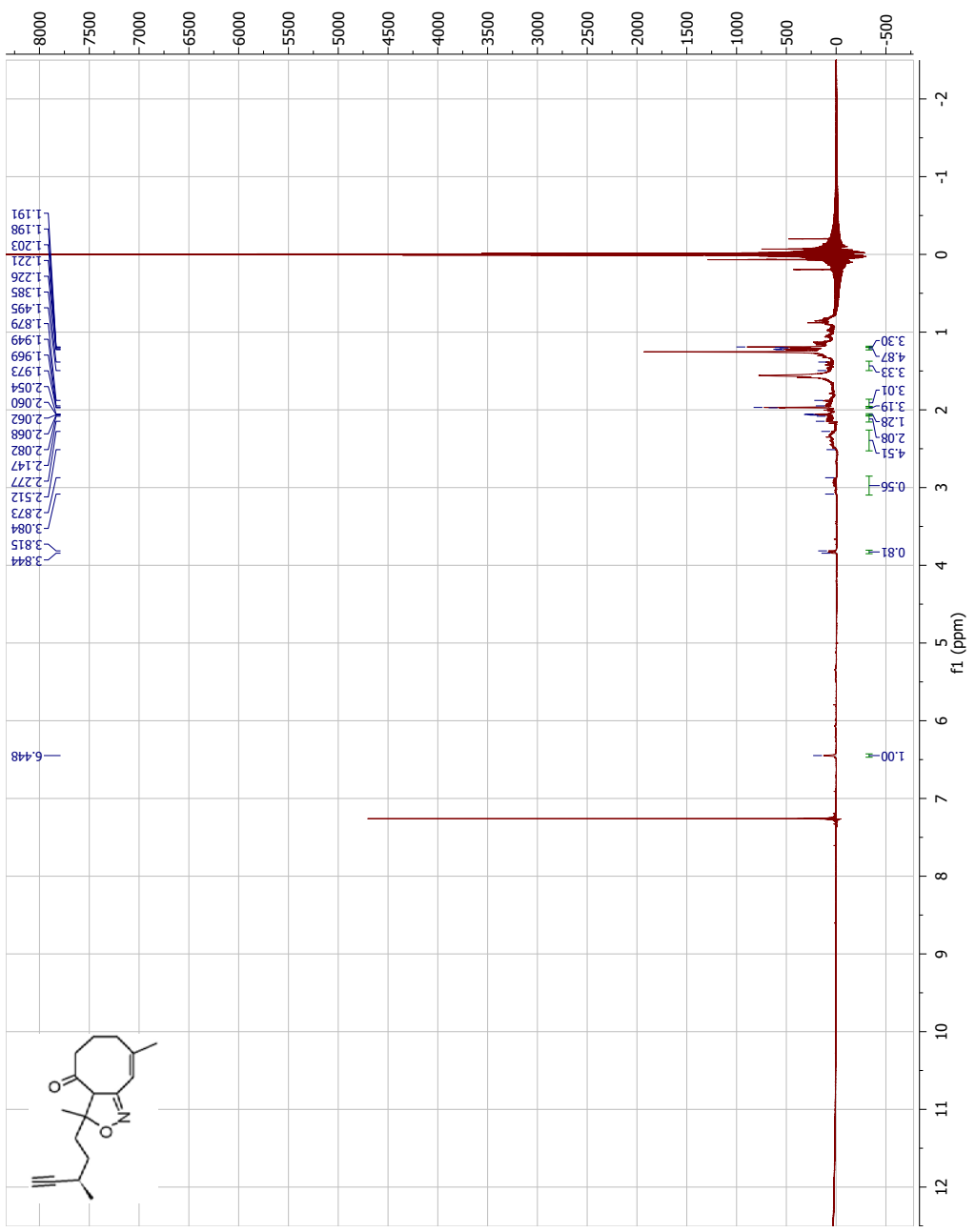

OTBDPS
OH
TIPS
f1 (ppm)

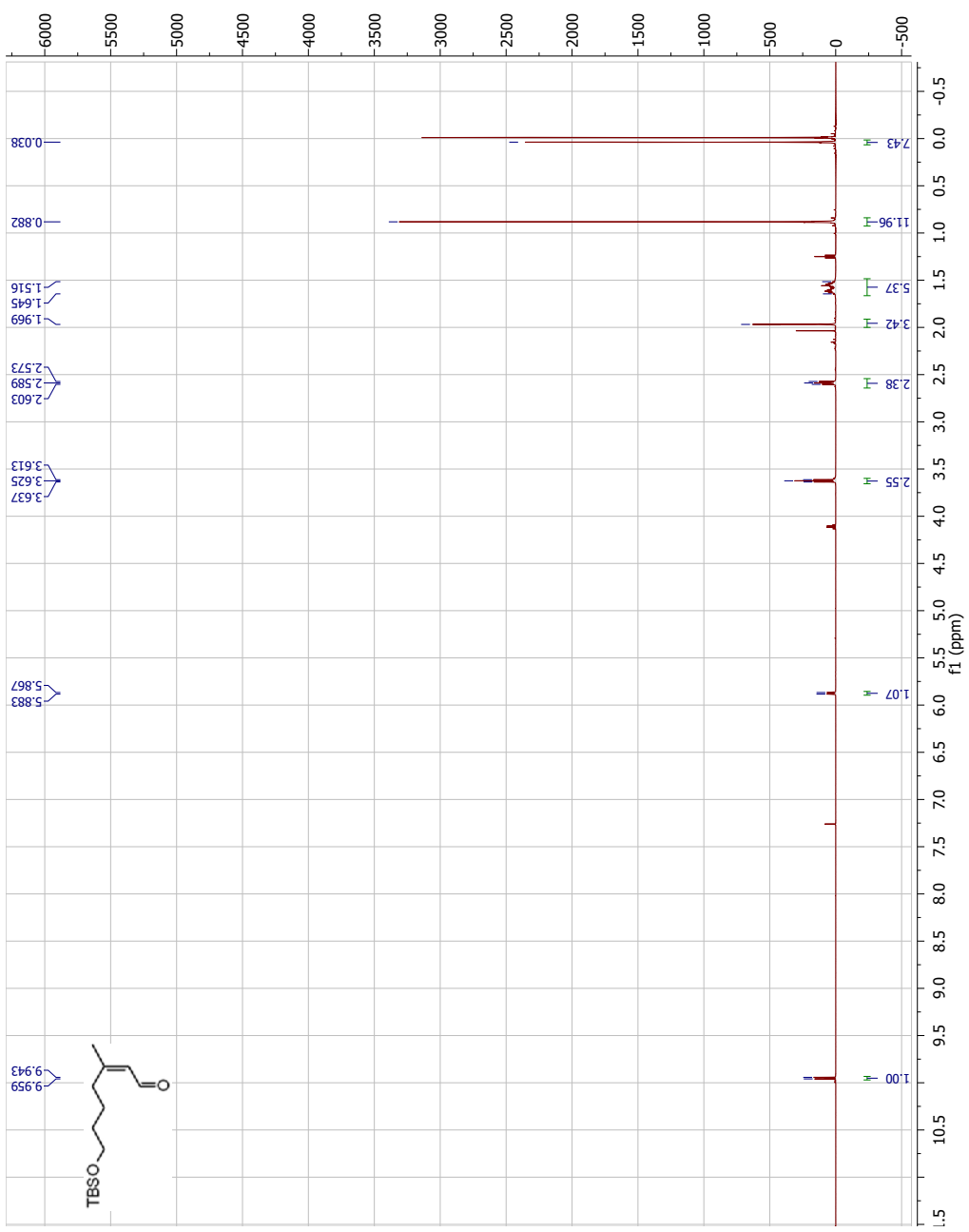

138.606
138.476
137.722
137.700
135.753
134.140
129.642
128.273
128.123
127.723
125.046
113.581
113.487
68.575
60.793
37.469
37.370
35.543
35.423
32.166
31.964
31.738
31.373
26.983
26.805
26.707
25.803
25.644
23.922
23.508
23.368
21.507
21.418
19.304
18.802
16.765
16.637
11.397
OTBDPS
OH
TIPS
f1 (ppm)

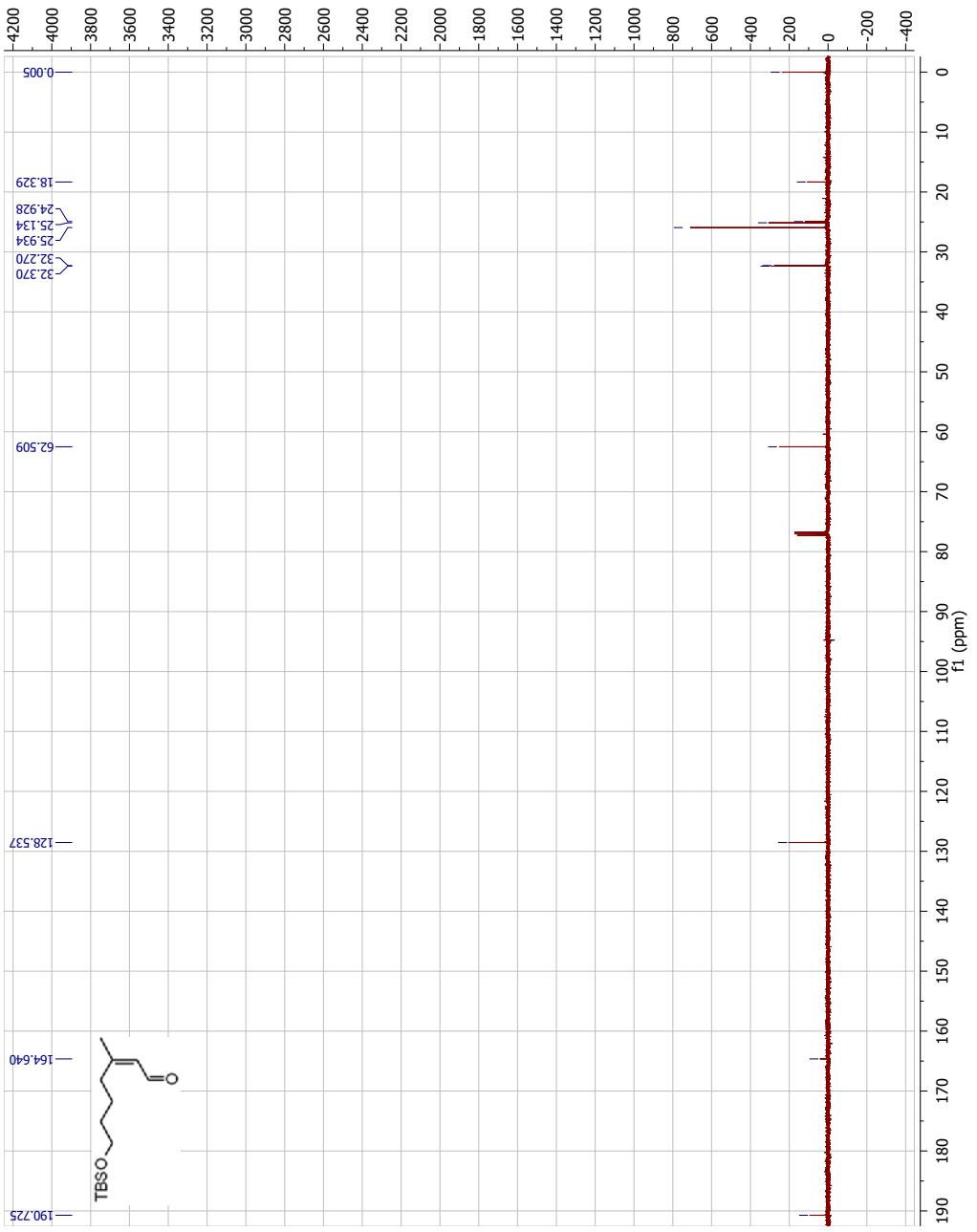

f1 (ppm)
OH
OH

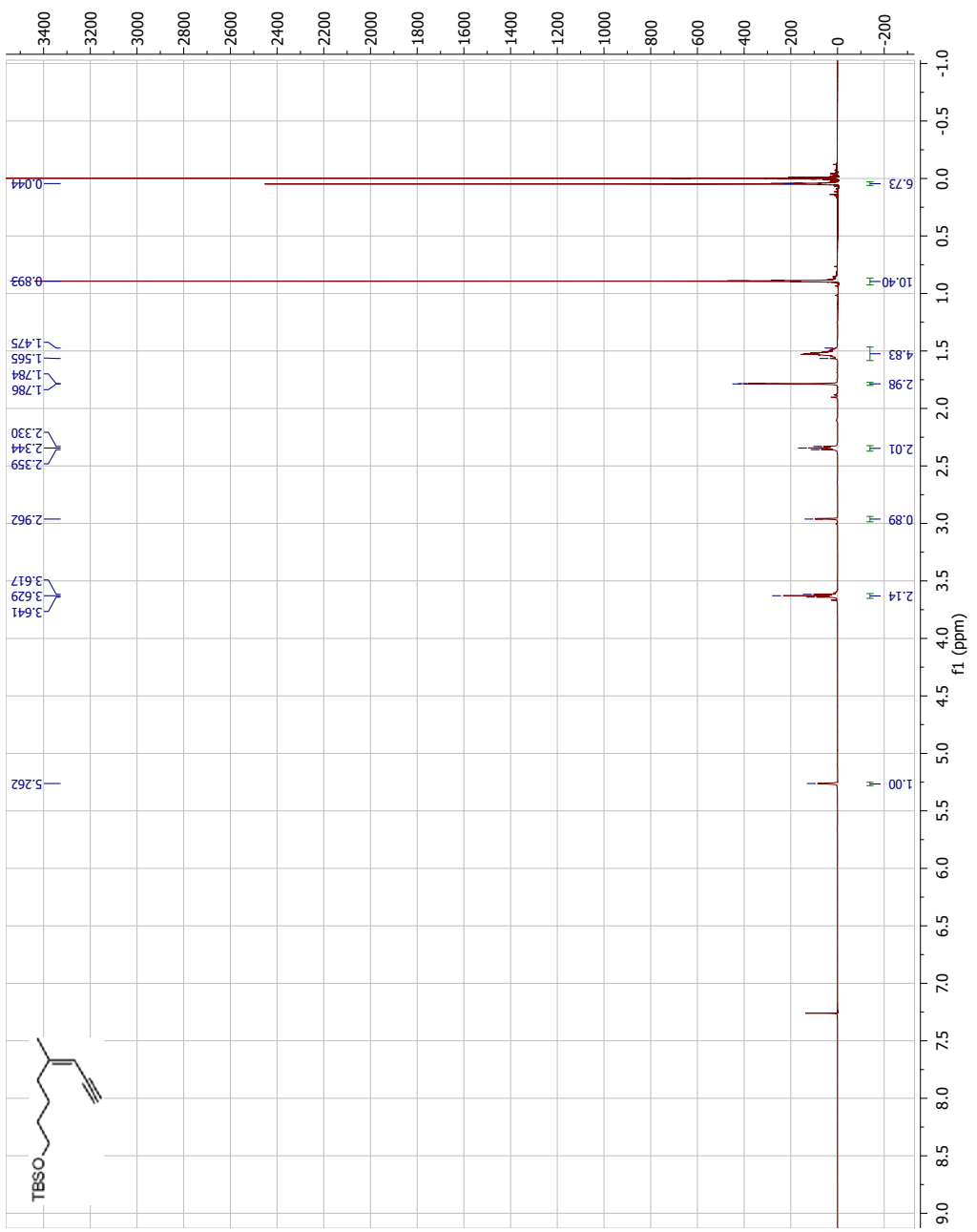

9.937
9.921
6.063
5.903
5.886
2.608
2.593
2.577
2.491
2.477
2.463
2.447
2.396
2.368
2.310
2.251
2.190
2.142
2.084
2.080
1.986
1.883
1.823
1.621
1.570
1.215
1.201
4.02
2.93
2.93
3.60
0.98
3.54
1.78
1.38
1.49
2.46
2.40
1.15
1.02
1.00
f1 (ppm)

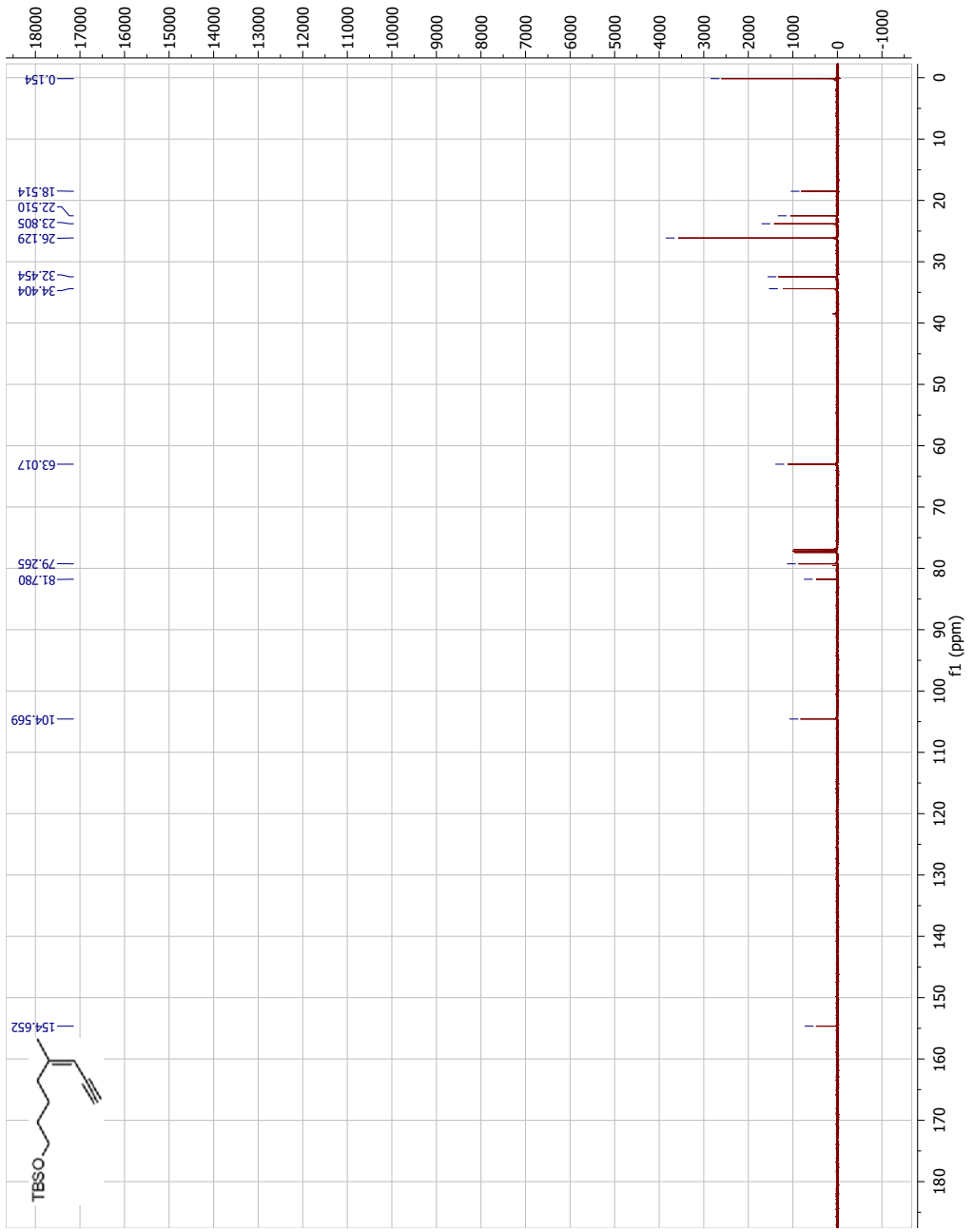

190.911
159.088
158.819
129.018
123.273
88.243
69.187
43.190
38.967
34.580
31.895
25.565
24.979
22.838
21.089
19.621
18.799
f1 (ppm)

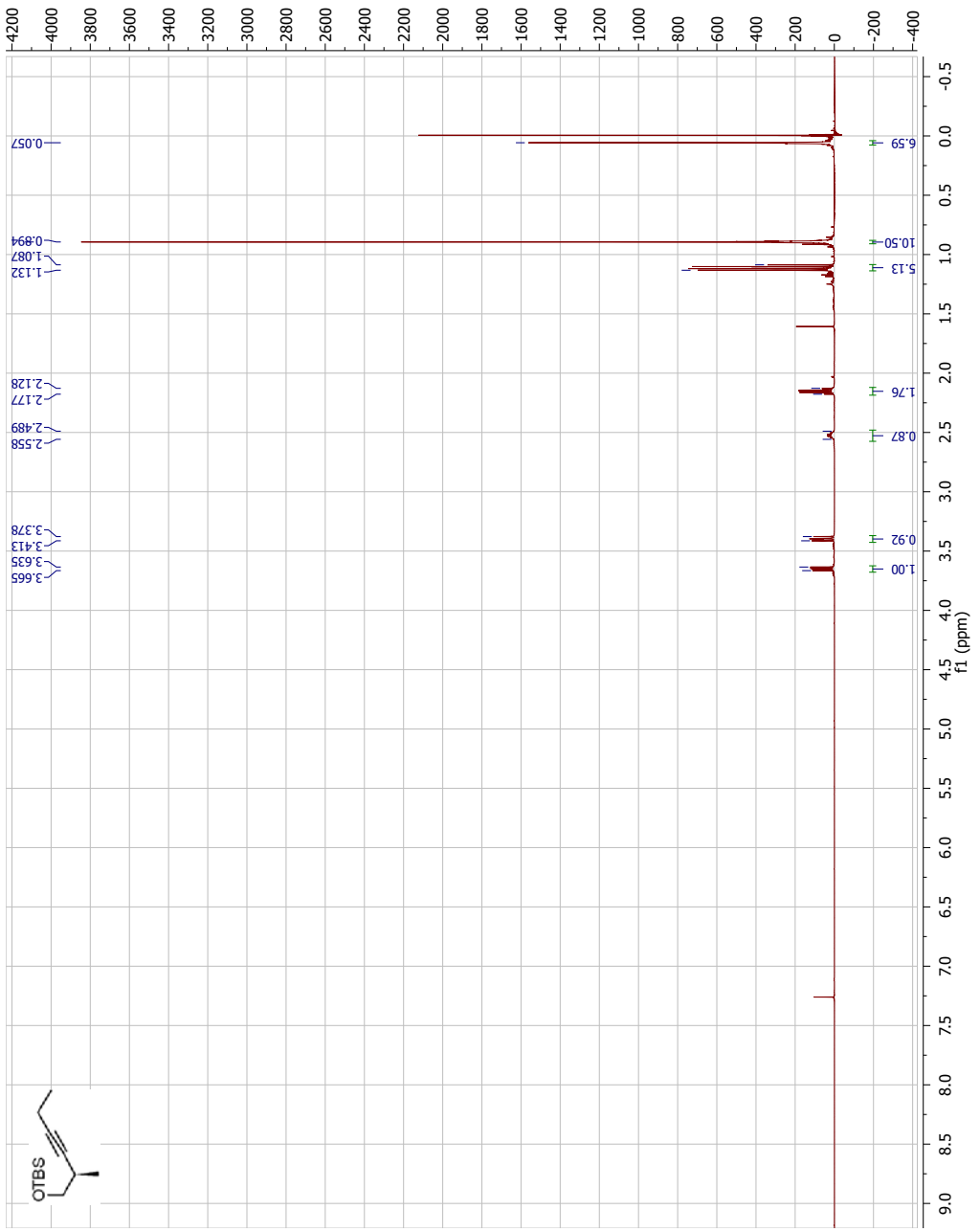

f1 (ppm)
1.191
1.198
1.203
1.221
1.226
1.385
1.495
1.879
1.949
1.969
1.973
2.054
2.060
2.062
2.068
2.082
2.147
2.277
2.512
2.873
3.084
3.815
3.844
6.448
3.30
4.87
3.33
3.01
3.19
1.28
2.08
4.51
0.56
0.81
1.00

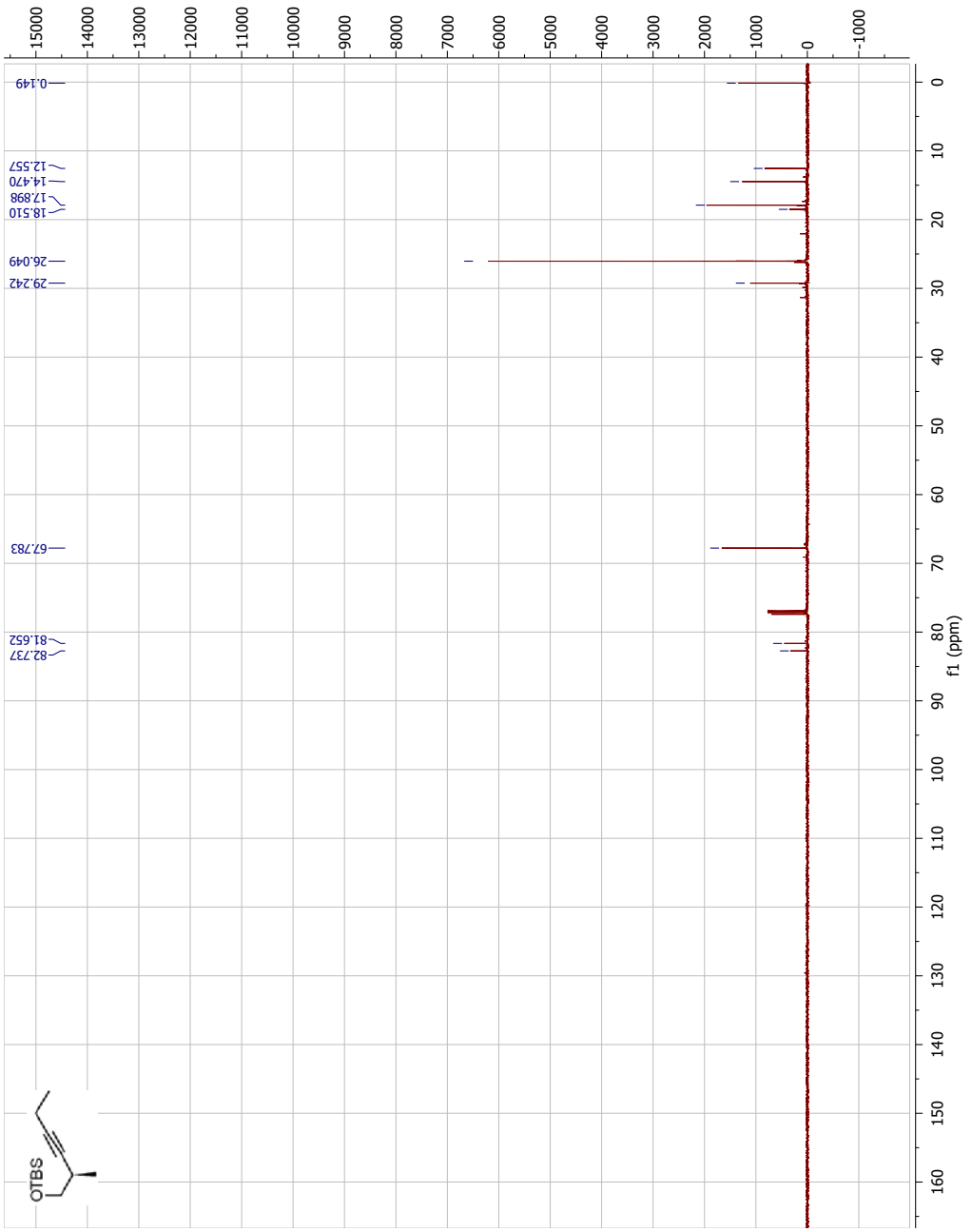

9.959
9.943
5.883
5.867
3.637
3.625
3.613
2.603
2.589
2.573
1.969
1.645
1.516
0.882
0.038
1.00
1.07
2.55
2.38
3.42
5.37
11.96
7.43
TBSO
O
f1 (ppm)

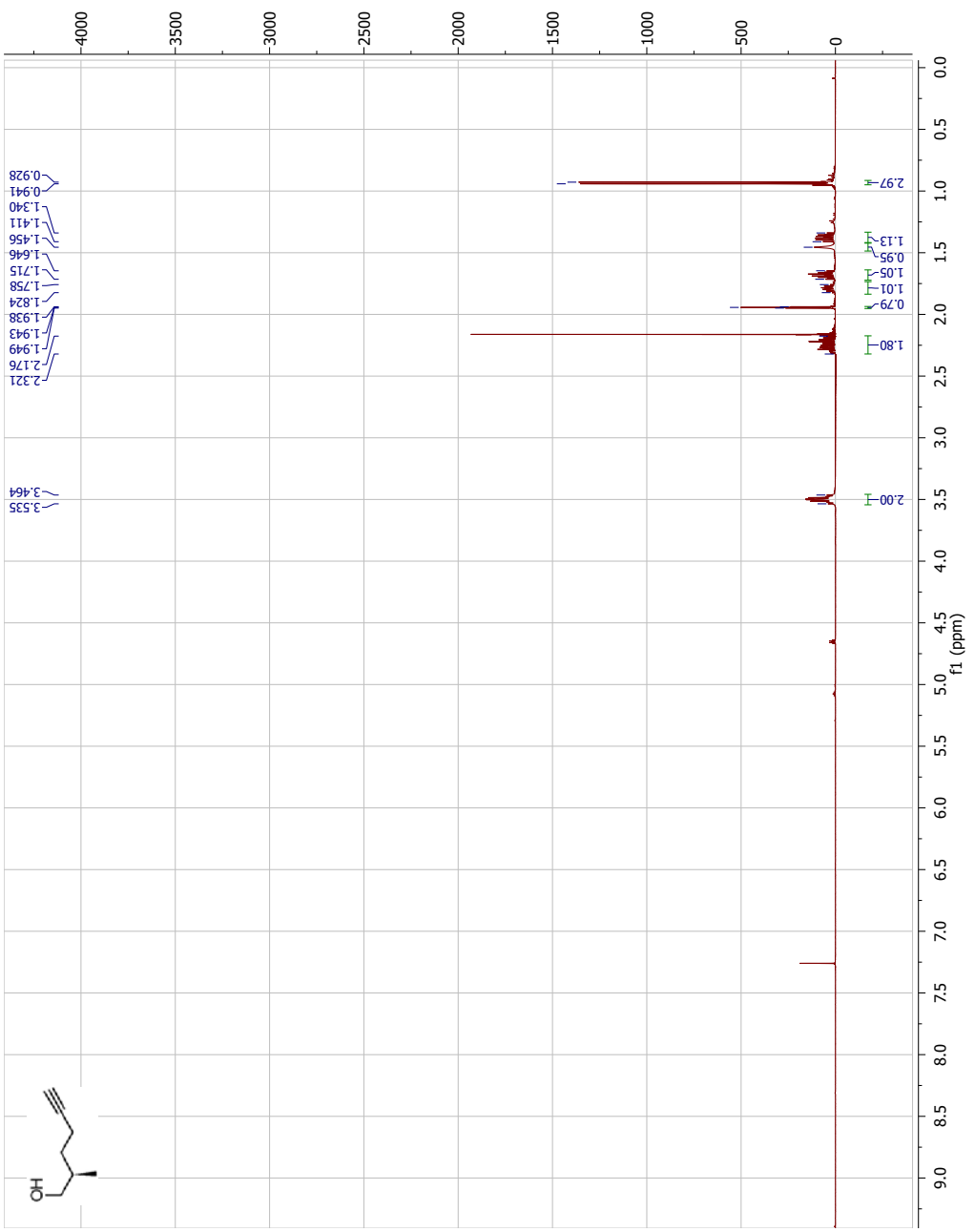

190.725
164.640
128.537
62.509
32.370
32.270
25.934
25.134
24.928
18.329
0.005
TBSO
f1 (ppm)

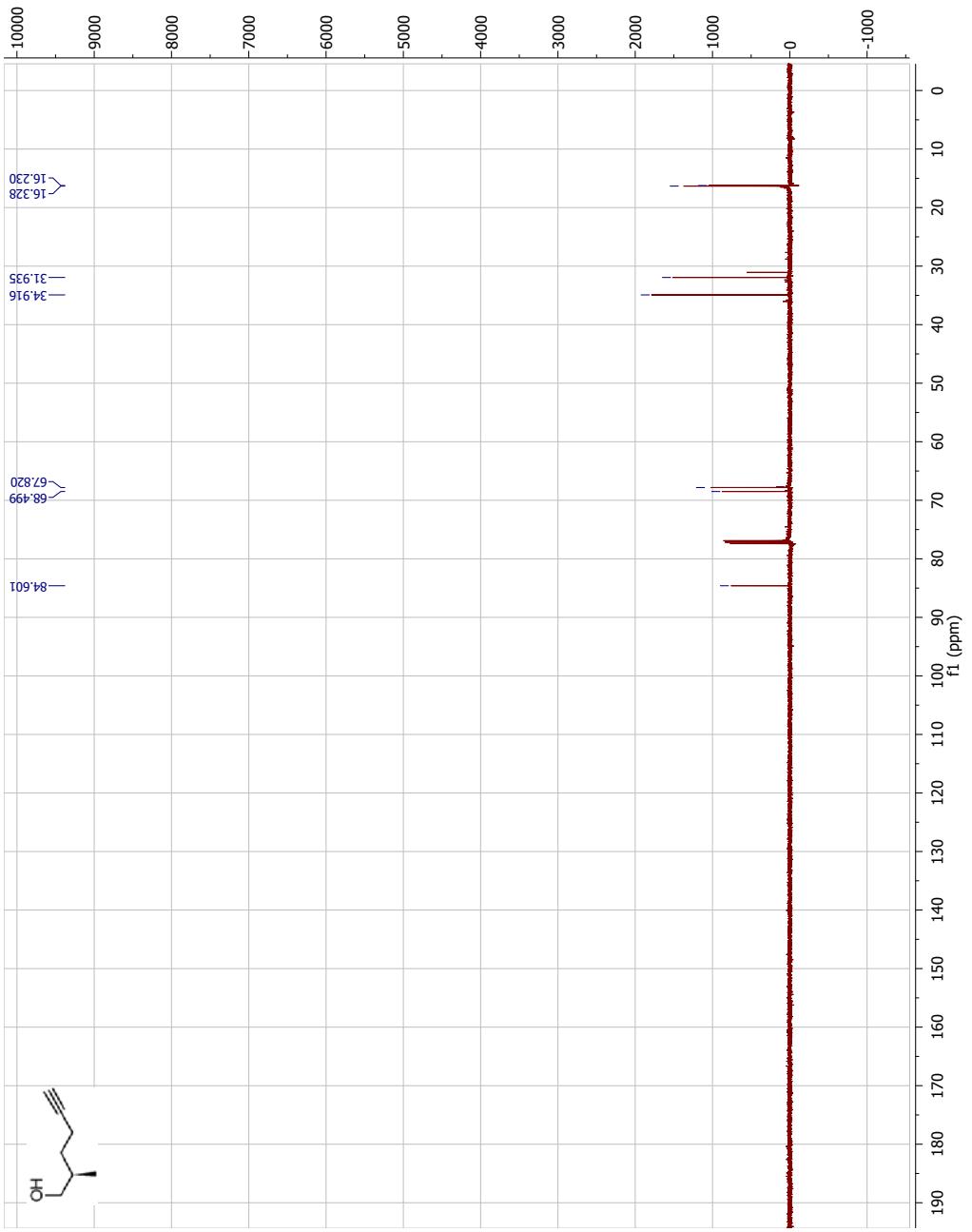

TBSO
f1 (ppm)
0.044
0.893
1.475
1.565
1.784
1.786
2.330
2.344
2.359
2.962
3.617
3.629
3.641
5.262
6.73
10.40
4.83
2.98
2.01
0.89
2.14
1.00

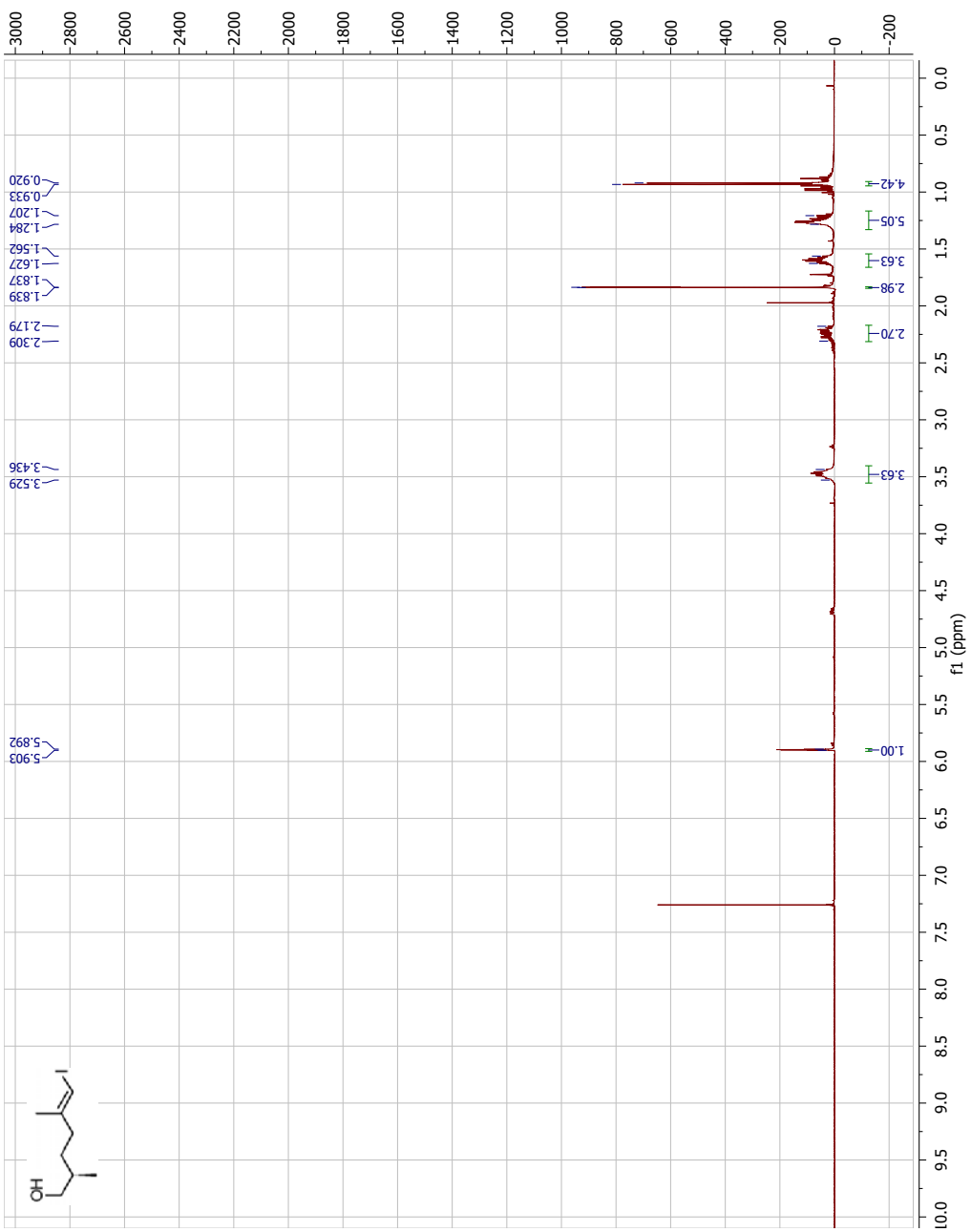

154.652
104.569
81.780
79.265
63.017
34.404
32.454
26.129
23.805
22.510
18.514
0.154
TBSO
f1 (ppm)

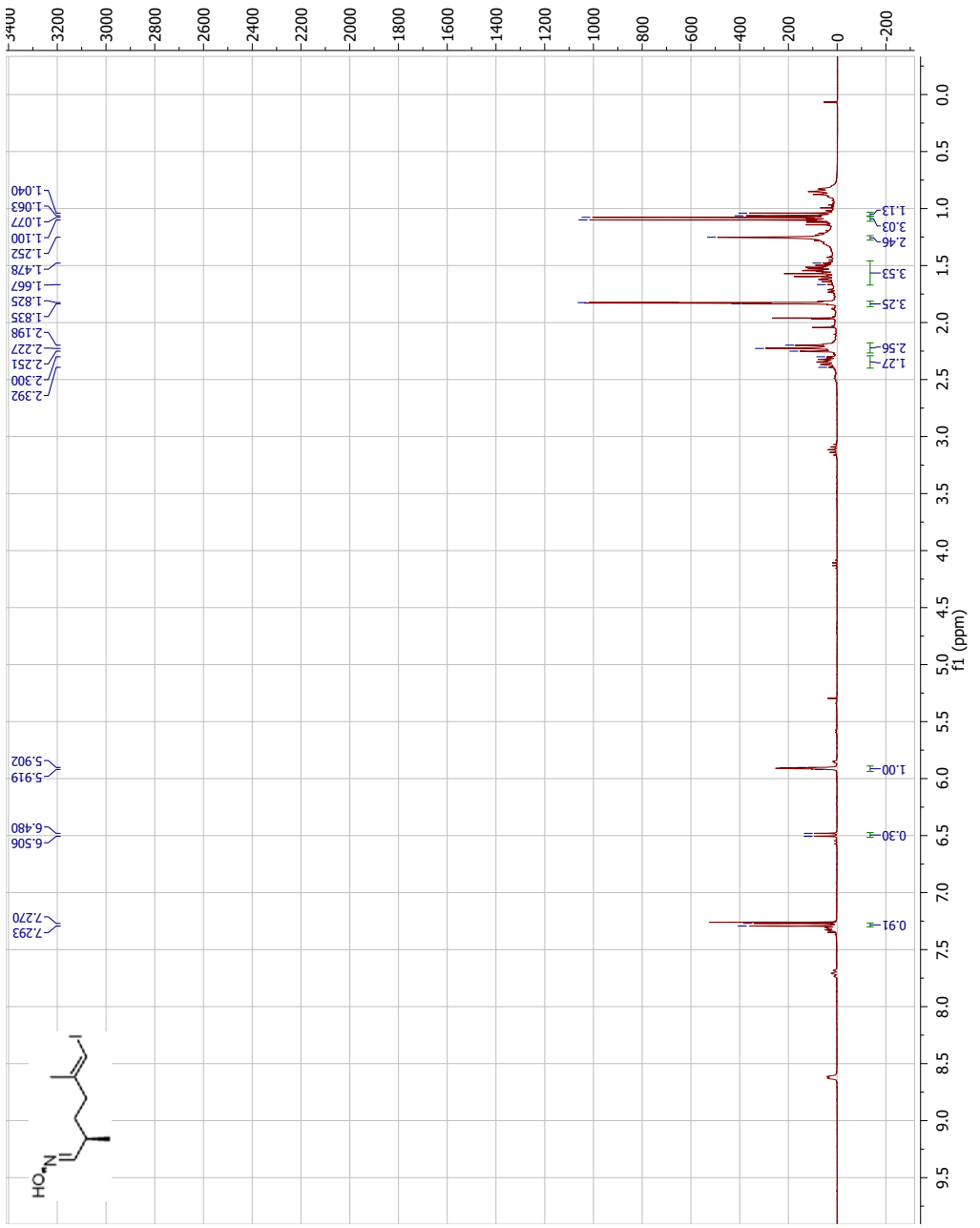

OTBS
f1 (ppm)
0.057
0.894
1.087
1.132
2.128
2.177
2.489
2.558
3.378
3.413
3.635
3.665
1.00
0.92
0.87
1.76
5.13
10.50
6.59

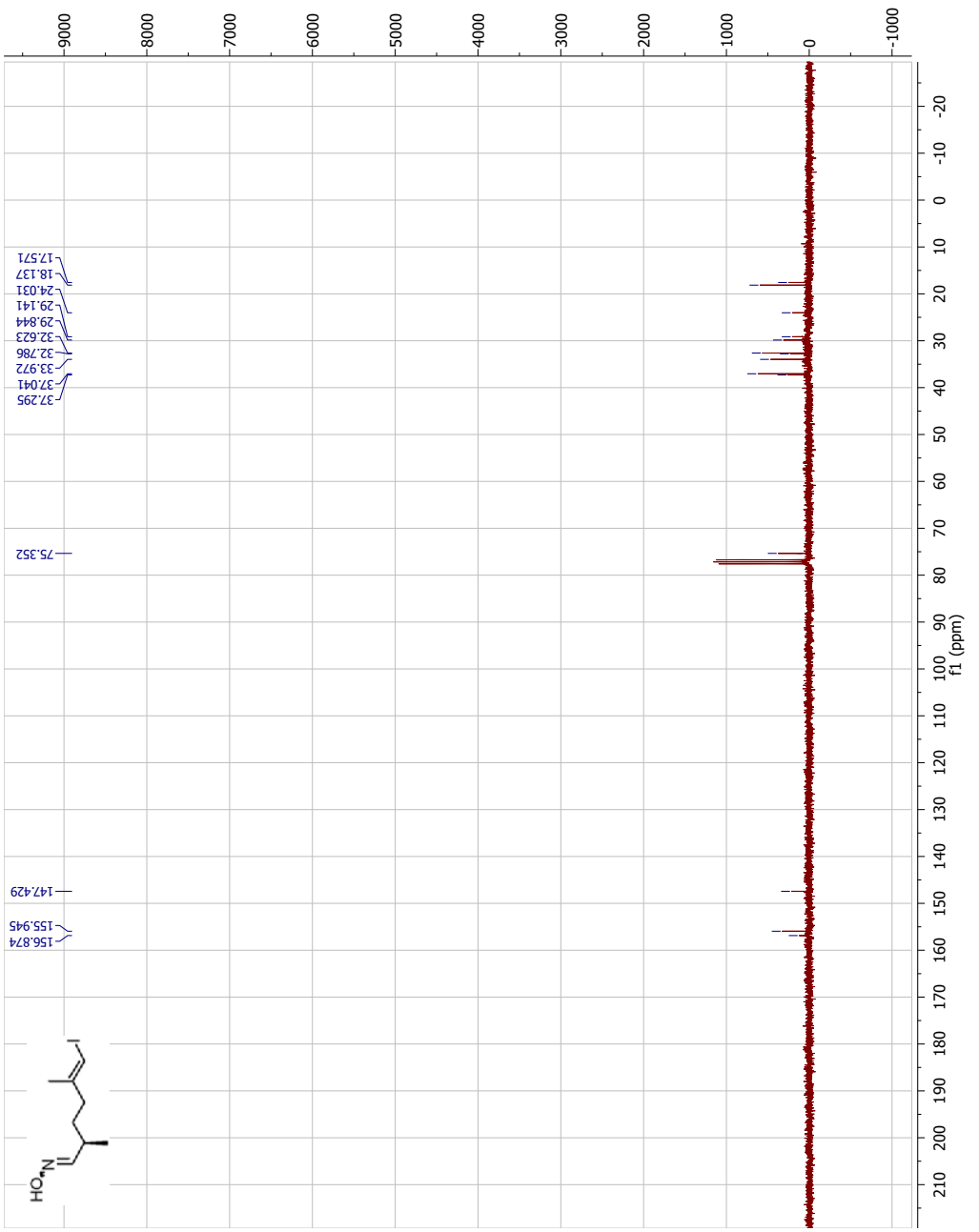

0.149
12.557
14.470
17.898
18.510
26.049
29.242
67.783
81.652
82.737
OTBS
f1 (ppm)

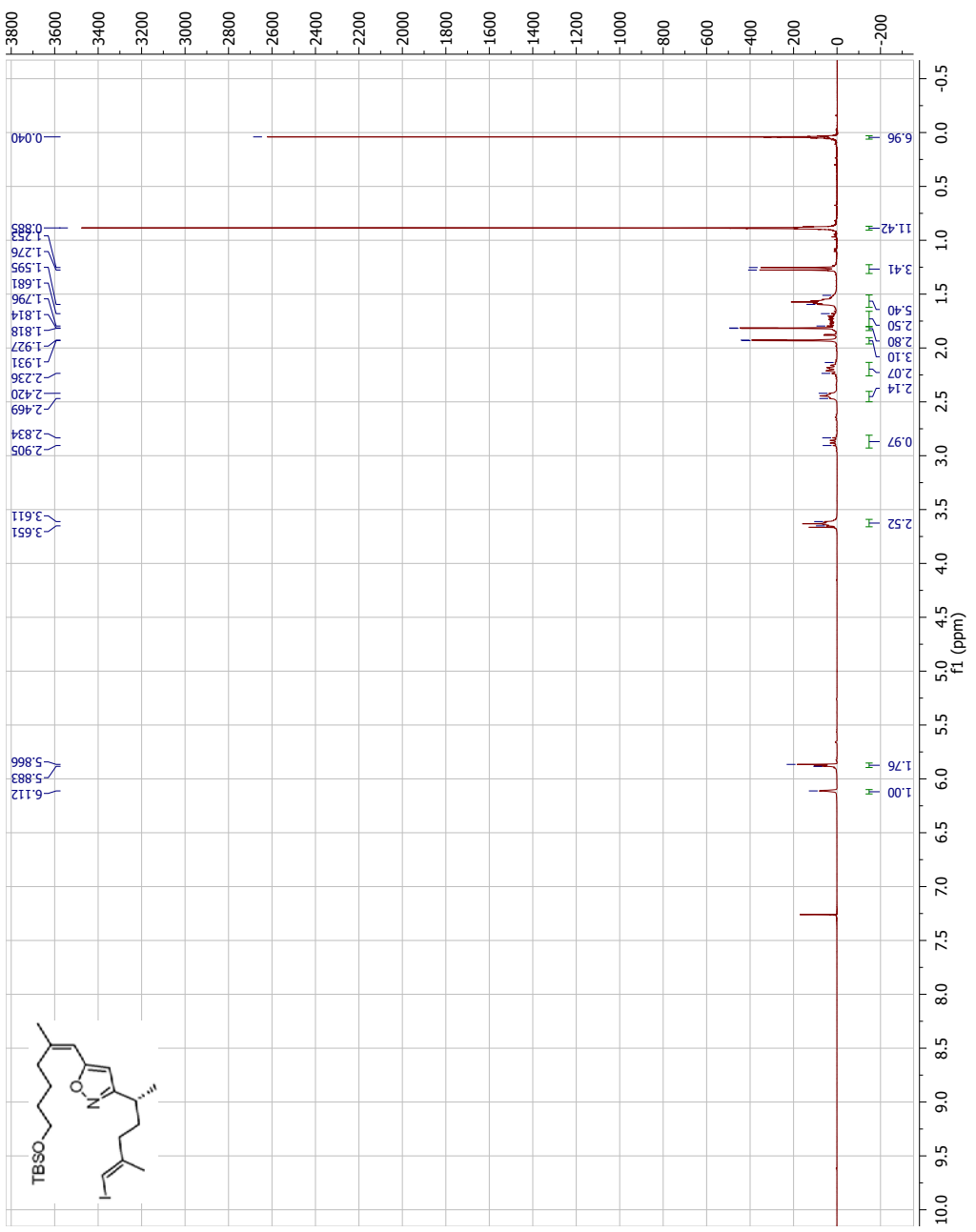

4000
3500
3000
2500
2000
1500
1000
500
0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
f1 (ppm)
2.97
1.13
0.95
1.05
1.01
0.79
1.80
2.00
0.928
0.941
1.340
1.411
1.456
1.646
1.715
1.758
1.824
1.938
1.943
1.949
2.176
2.321
3.464
3.535
HO

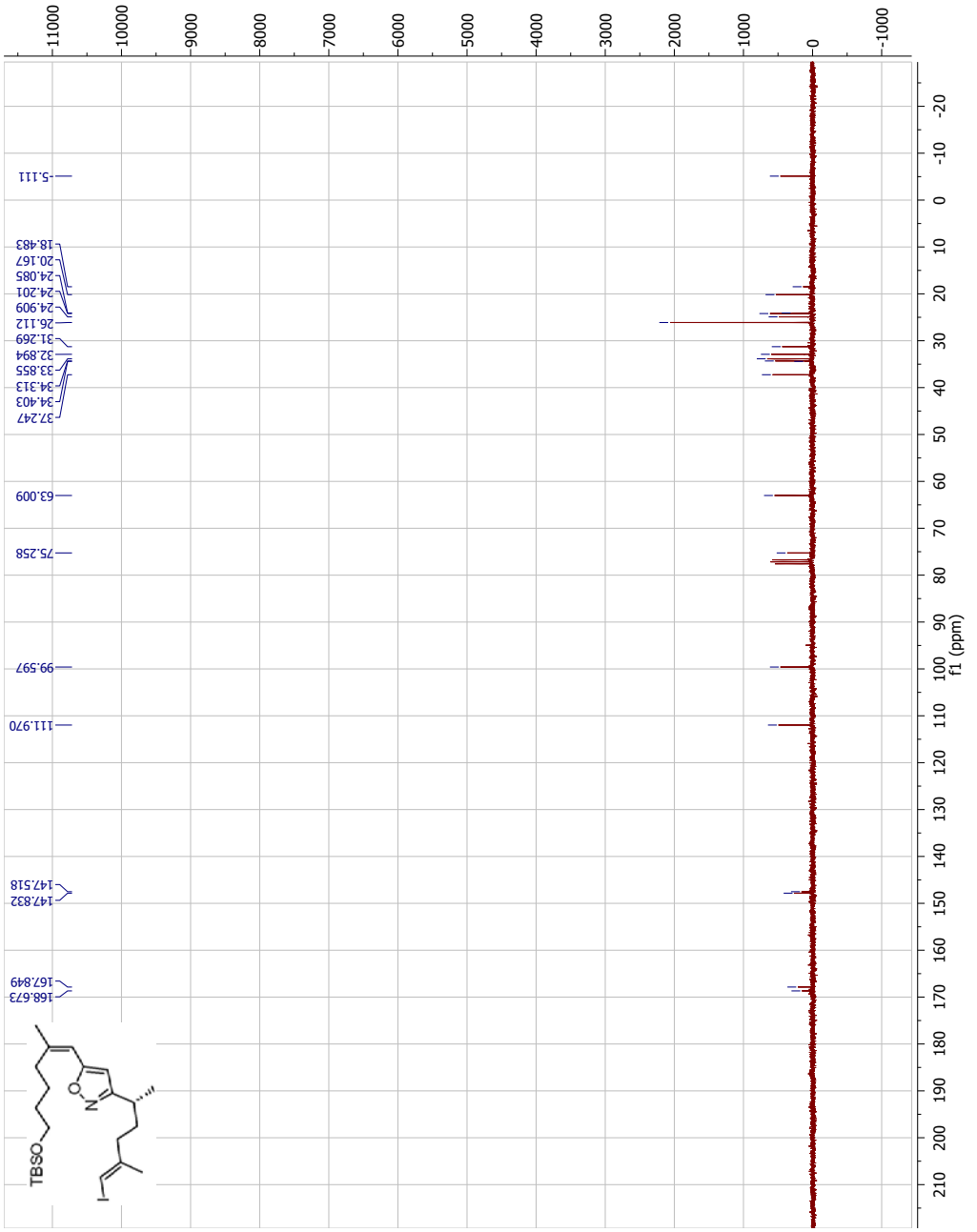

16.328
16.230
31.935
34.916
67.820
68.499
84.601
f1 (ppm)

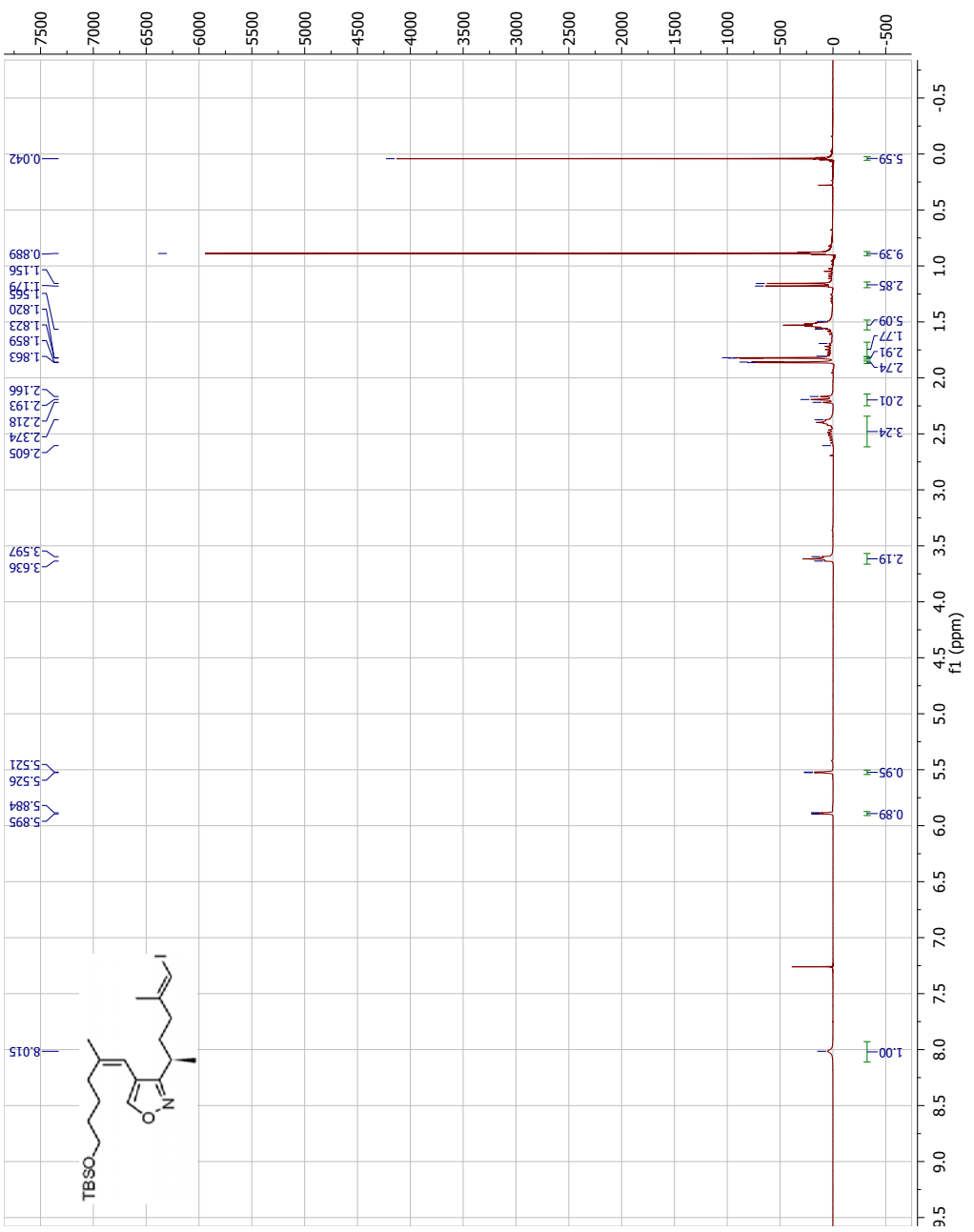

f1 (ppm)
1.00
4.42
5.05
3.63
2.98
2.70
3.63
5.903
5.892
3.529
3.436
2.309
2.179
1.839
1.837
1.627
1.562
1.284
1.207
0.933
0.920

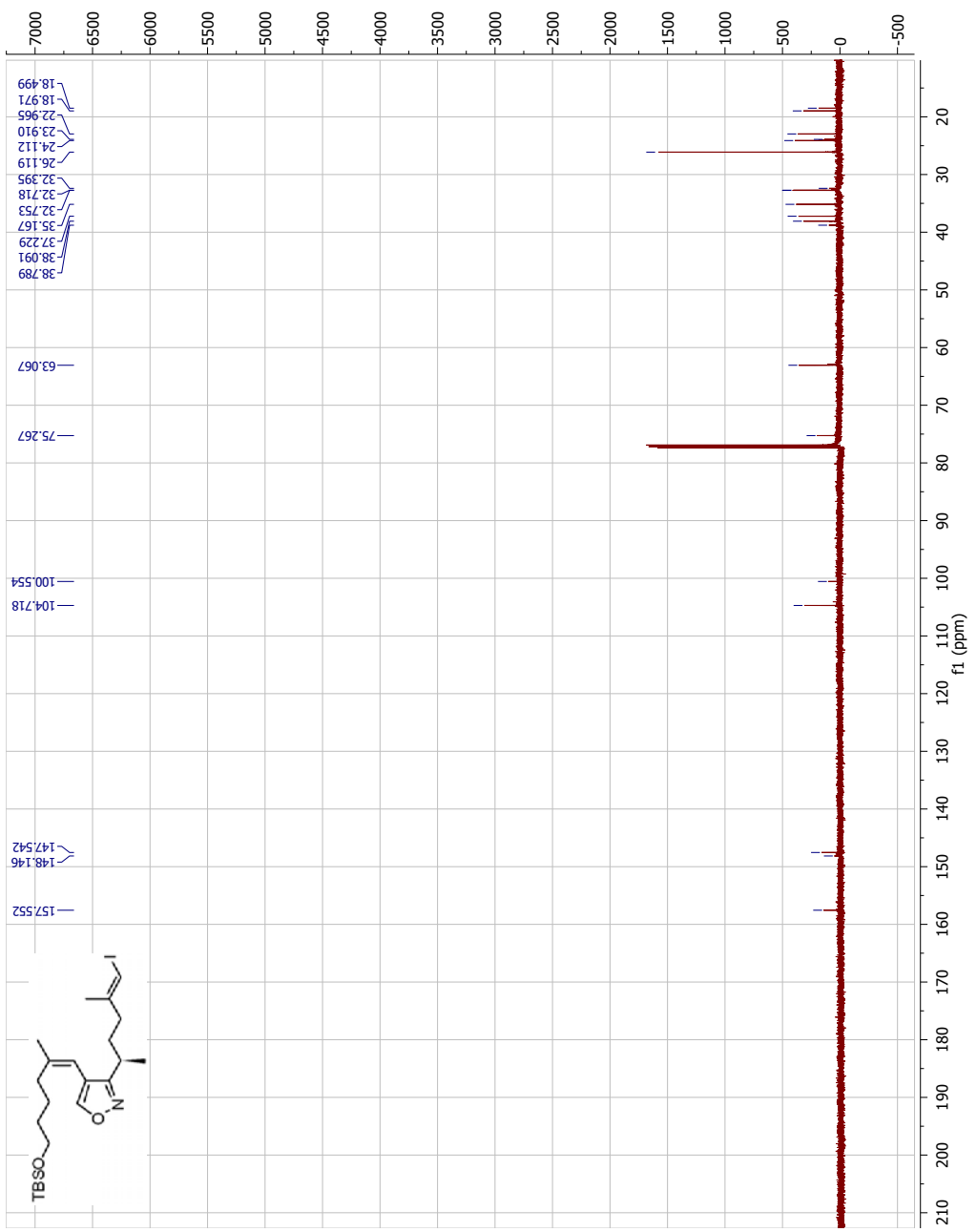

7.293
7.270
6.506
6.480
5.919
5.902
2.392
2.300
2.251
2.227
2.198
1.835
1.825
1.667
1.478
1.252
1.100
1.077
1.063
1.040
1.27
2.56
3.25
3.53
2.46
3.03
1.13
1.00
0.30
0.91
f1 (ppm)

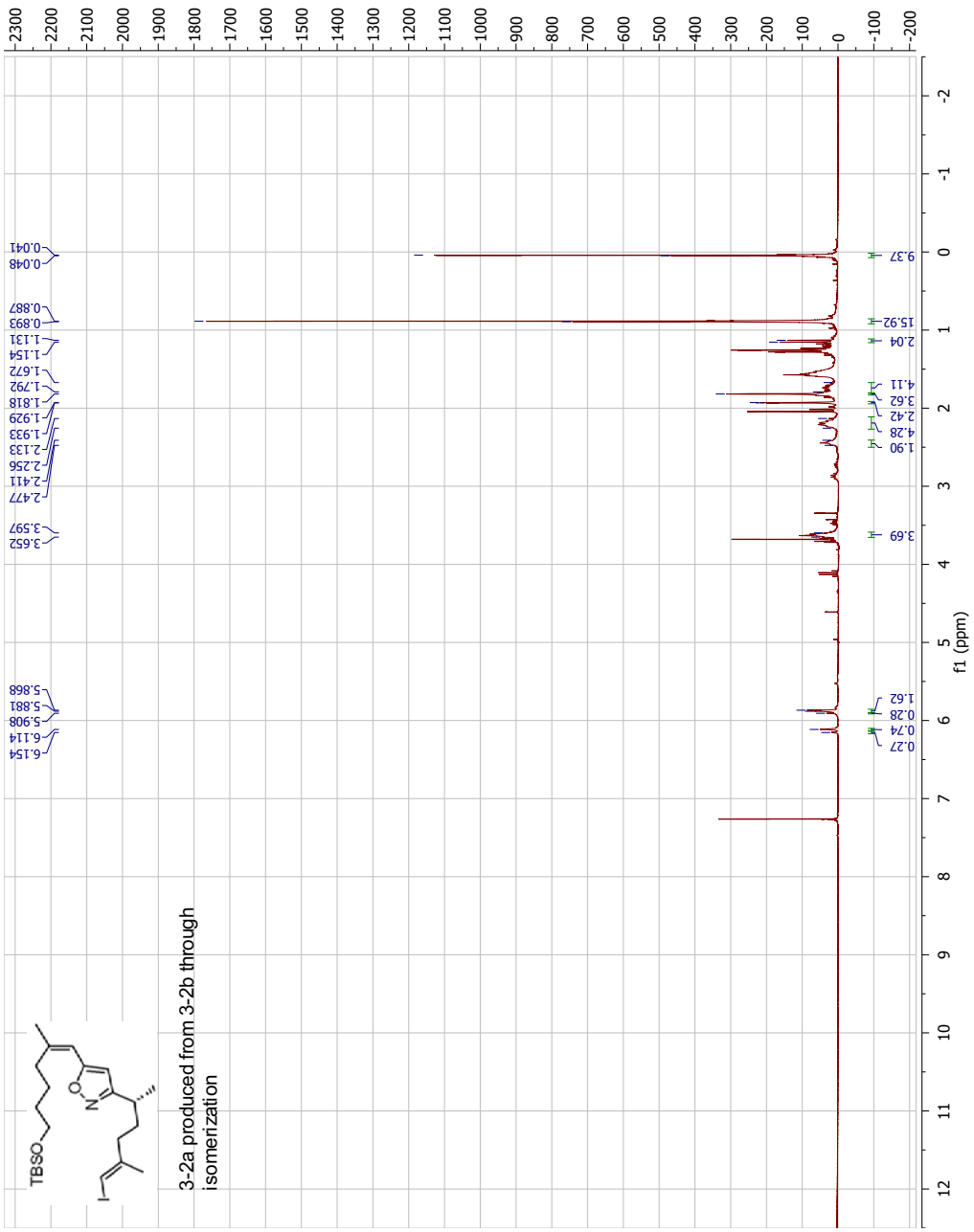

156.874
155.945
147.429
75.352
37.295
37.041
33.972
32.786
32.623
29.844
29.141
24.031
18.137
17.571
f1 (ppm)

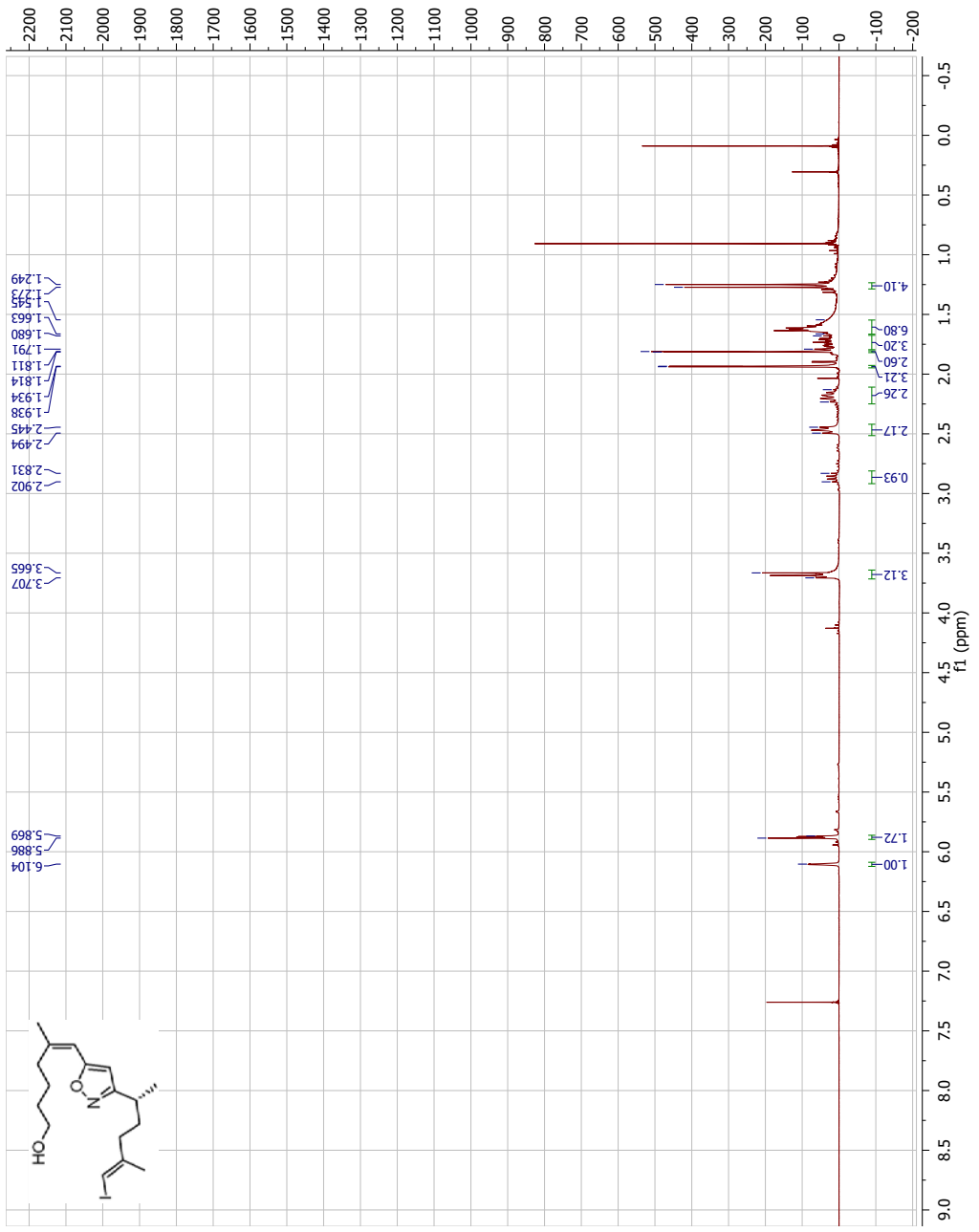

f1 (ppm)
TBSO
O
N
I

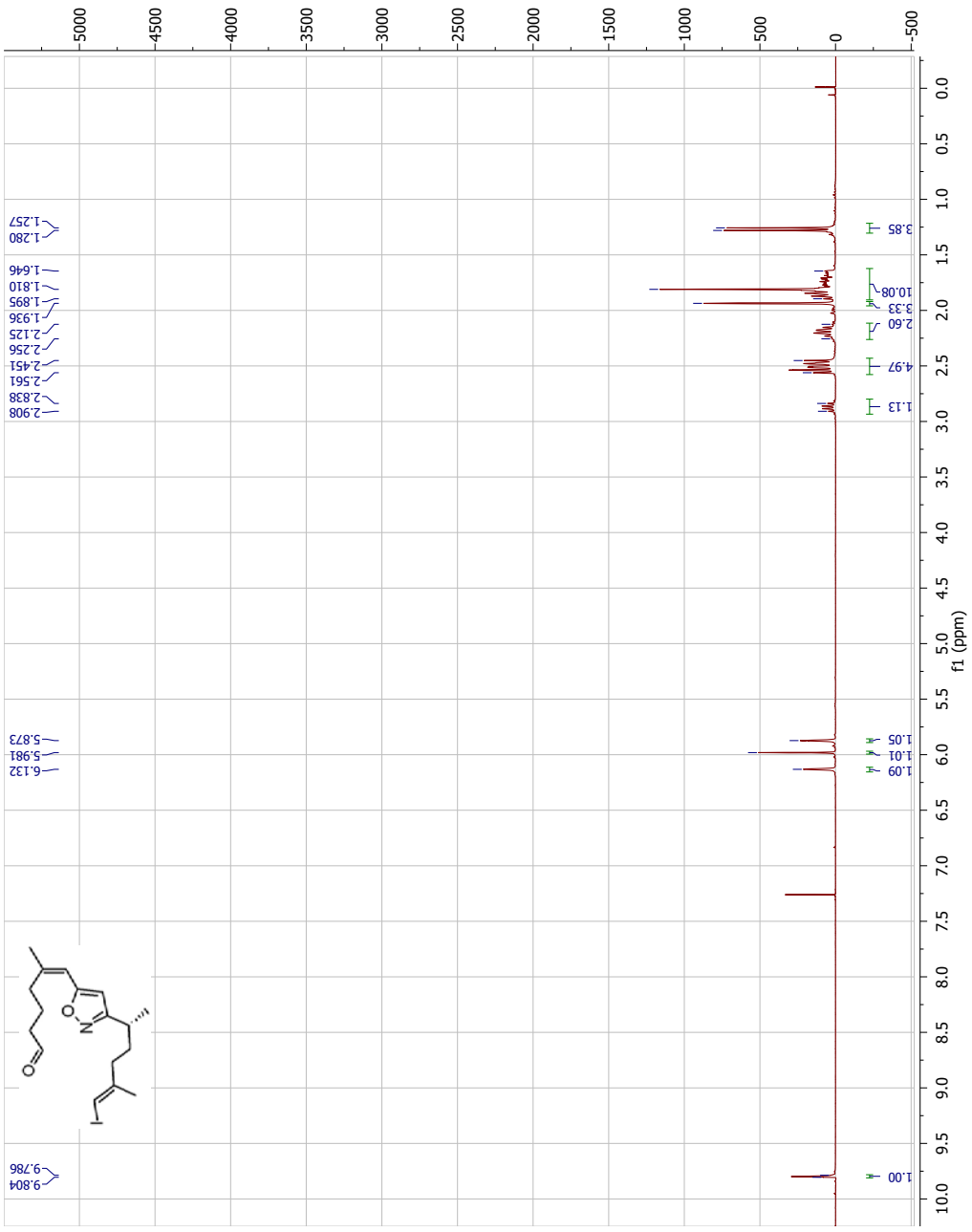

168.673
167.849
147.832
147.518
111.970
99.597
75.258
63.009
37.247
34.403
34.313
33.855
32.894
31.269
26.112
24.909
24.201
24.085
20.167
18.483
-5.111
TBSO
f1 (ppm)

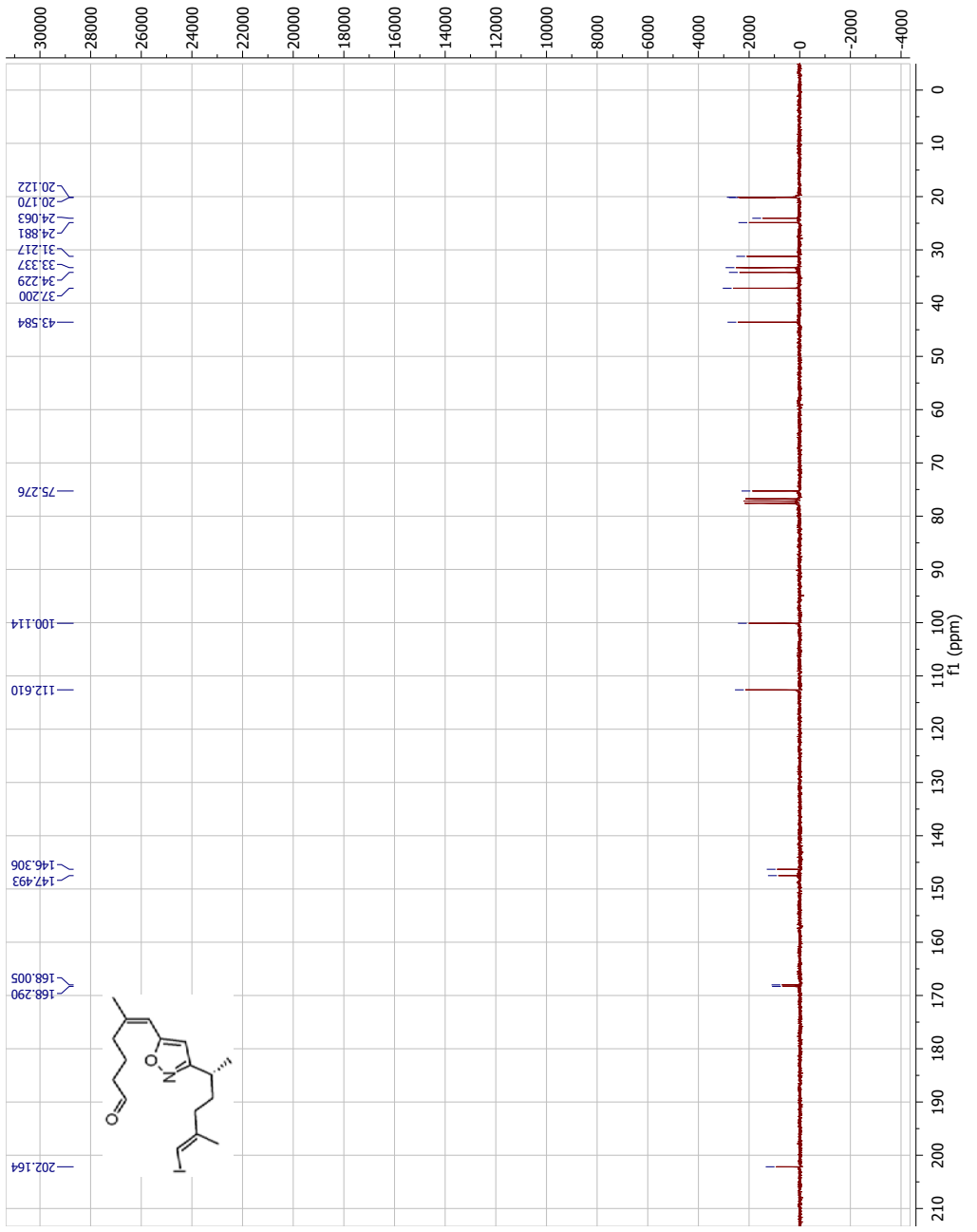

f1 (ppm)
TBSO
I
O
N

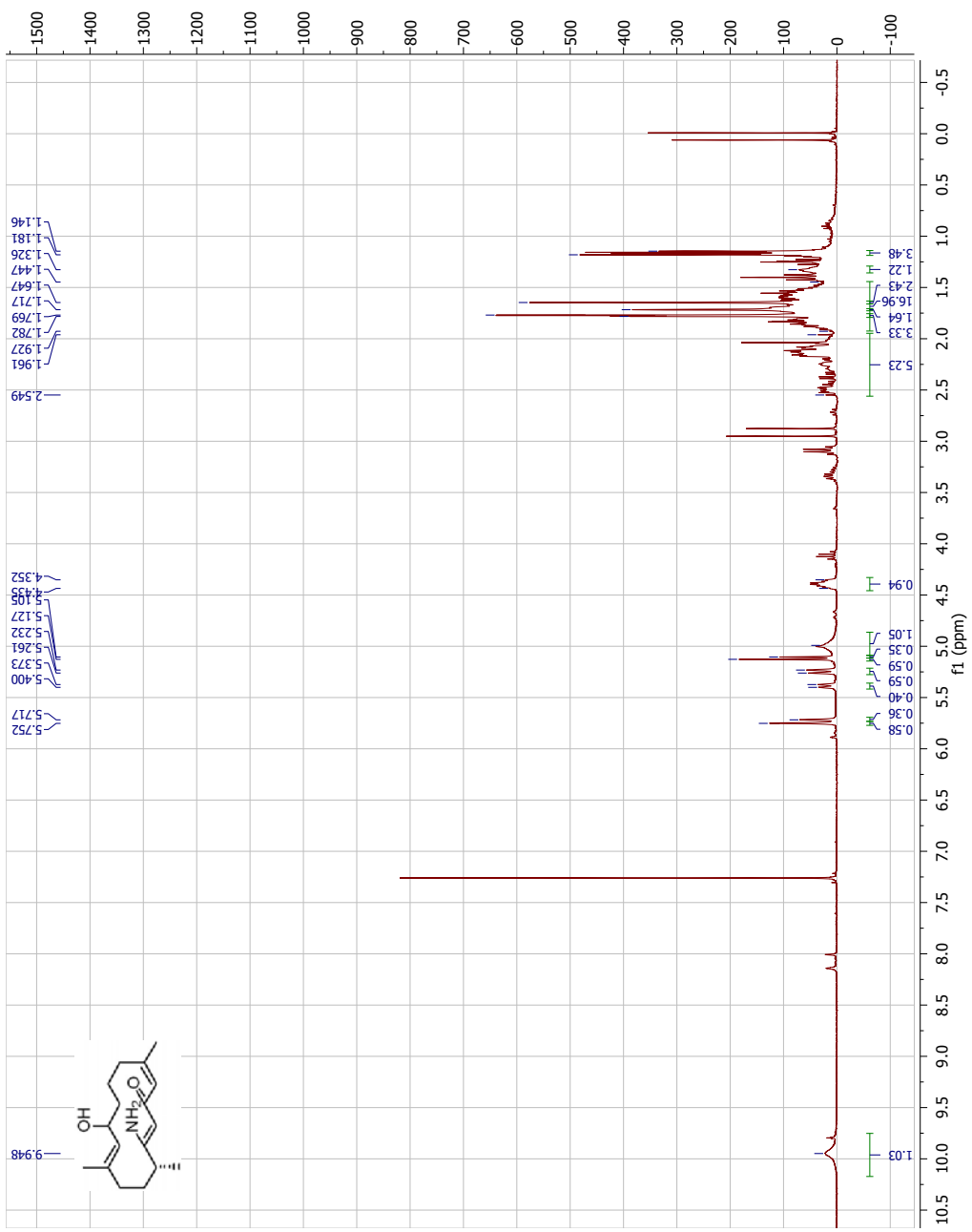

157.552
148.146
147.542
104.718
100.554
75.267
63.067
38.789
38.091
37.229
35.167
32.753
32.718
32.395
26.119
24.112
23.910
22.965
18.971
18.499
TBSO
f1 (ppm)

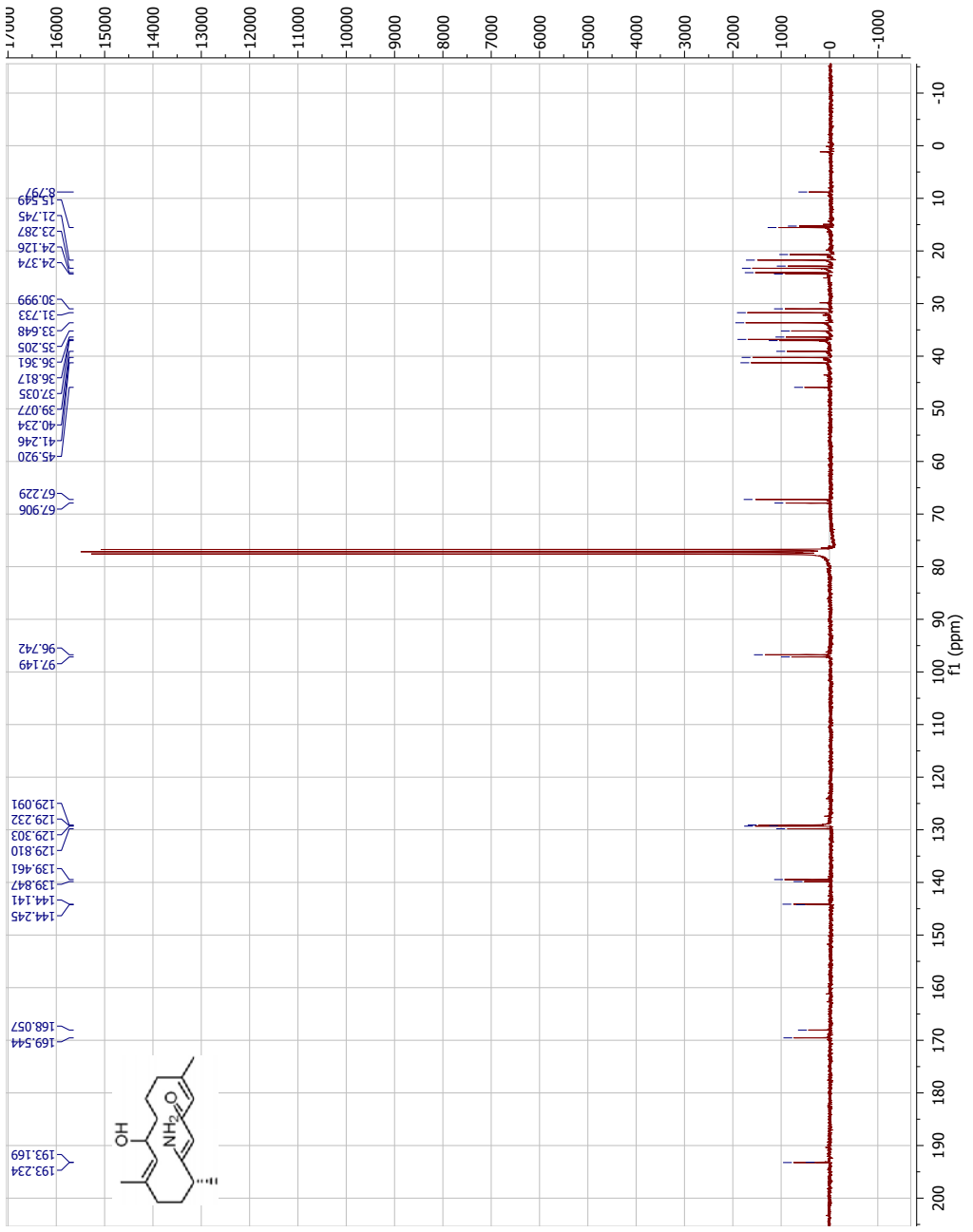

3-2a produced from 3-2b through isomerization
TBSO
f1 (ppm)

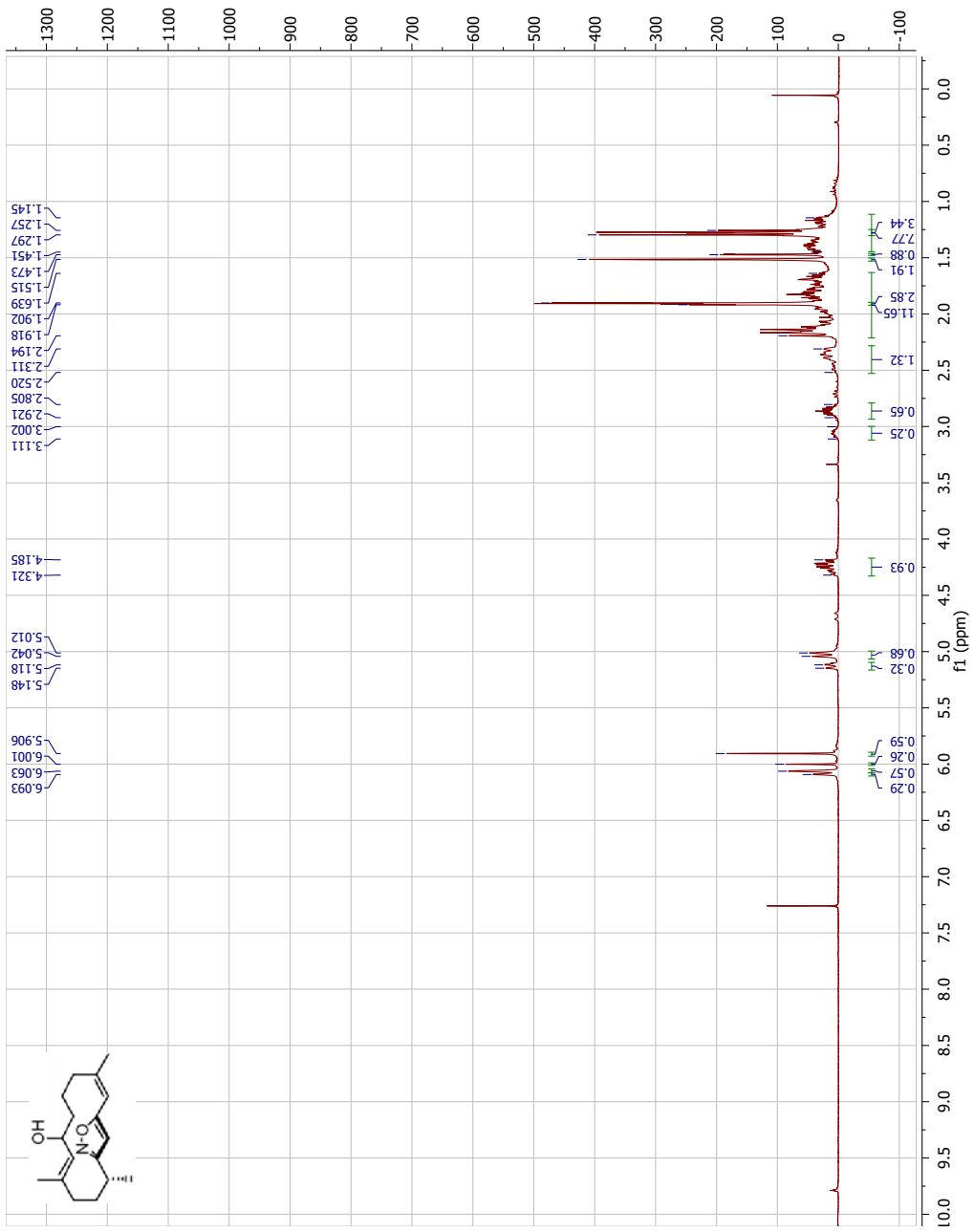

f1 (ppm)
6.104
5.886
5.869
3.707
3.665
2.902
2.831
2.494
2.445
1.938
1.934
1.814
1.811
1.791
1.680
1.663
1.545
1.273
1.249
4.10
6.80
3.20
2.60
3.21
2.26
2.17
0.93
3.12
1.72
1.00
HO
O
N
I

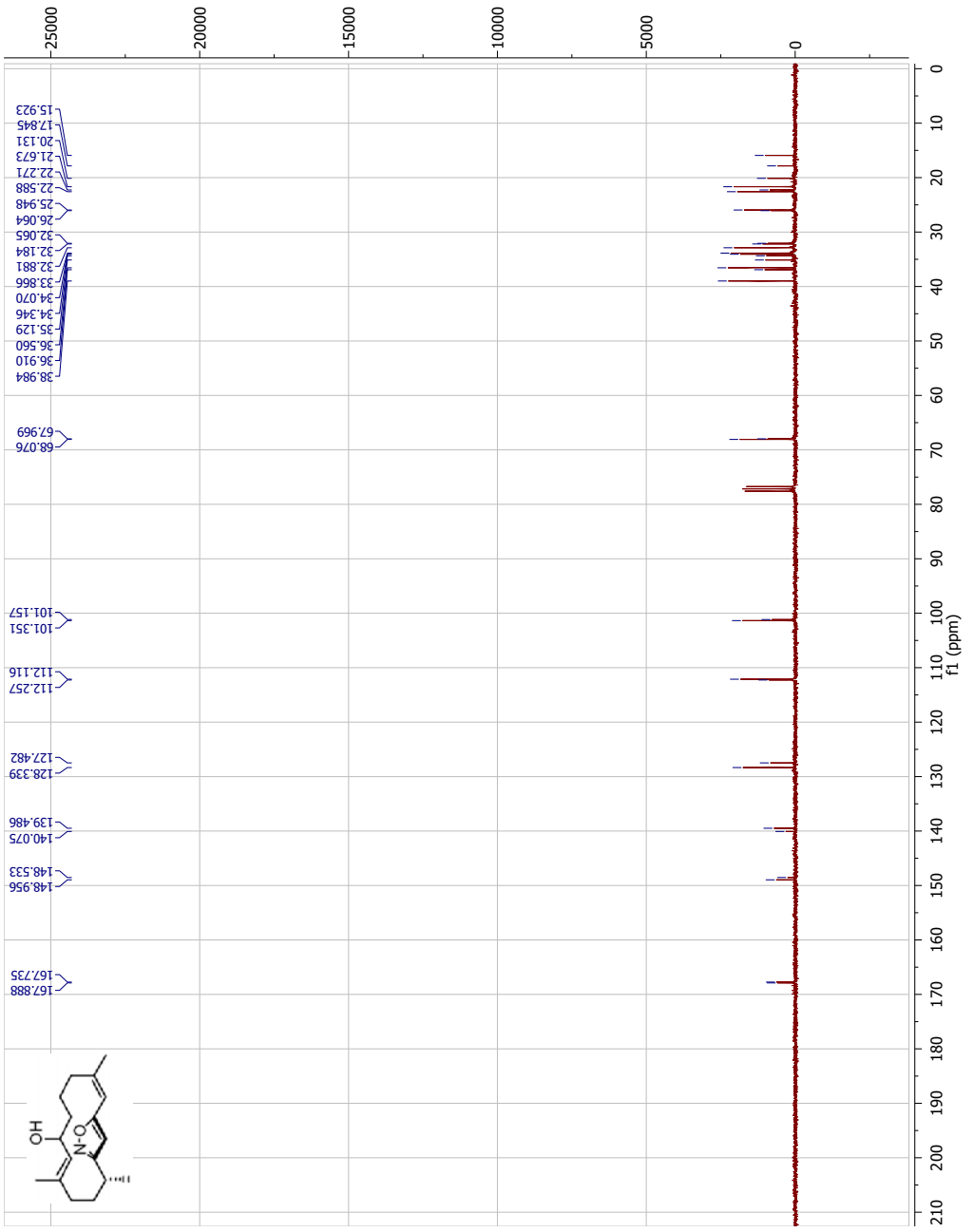

9.804
9.786
6.132
5.981
5.873
2.908
2.838
2.561
2.451
2.256
2.125
1.936
1.895
1.810
1.646
1.280
1.257
1.00
1.05
1.01
1.09
1.13
4.97
2.60
3.33
10.08
3.85
f1 (ppm)

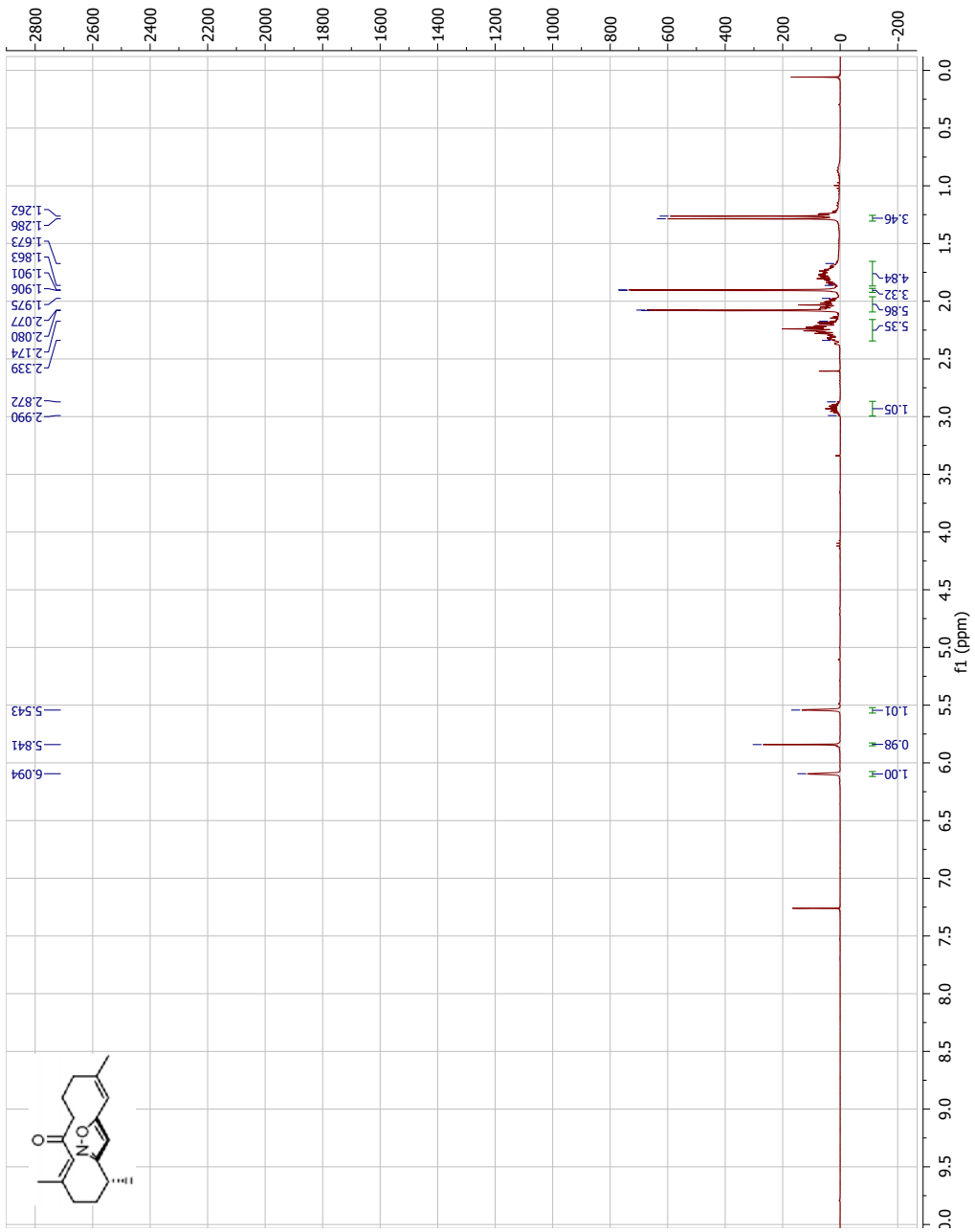

202.164
168.290
168.005
147.493
146.306
112.610
100.114
75.276
43.584
37.200
34.229
33.337
31.217
24.881
24.063
20.170
20.122
f1 (ppm)

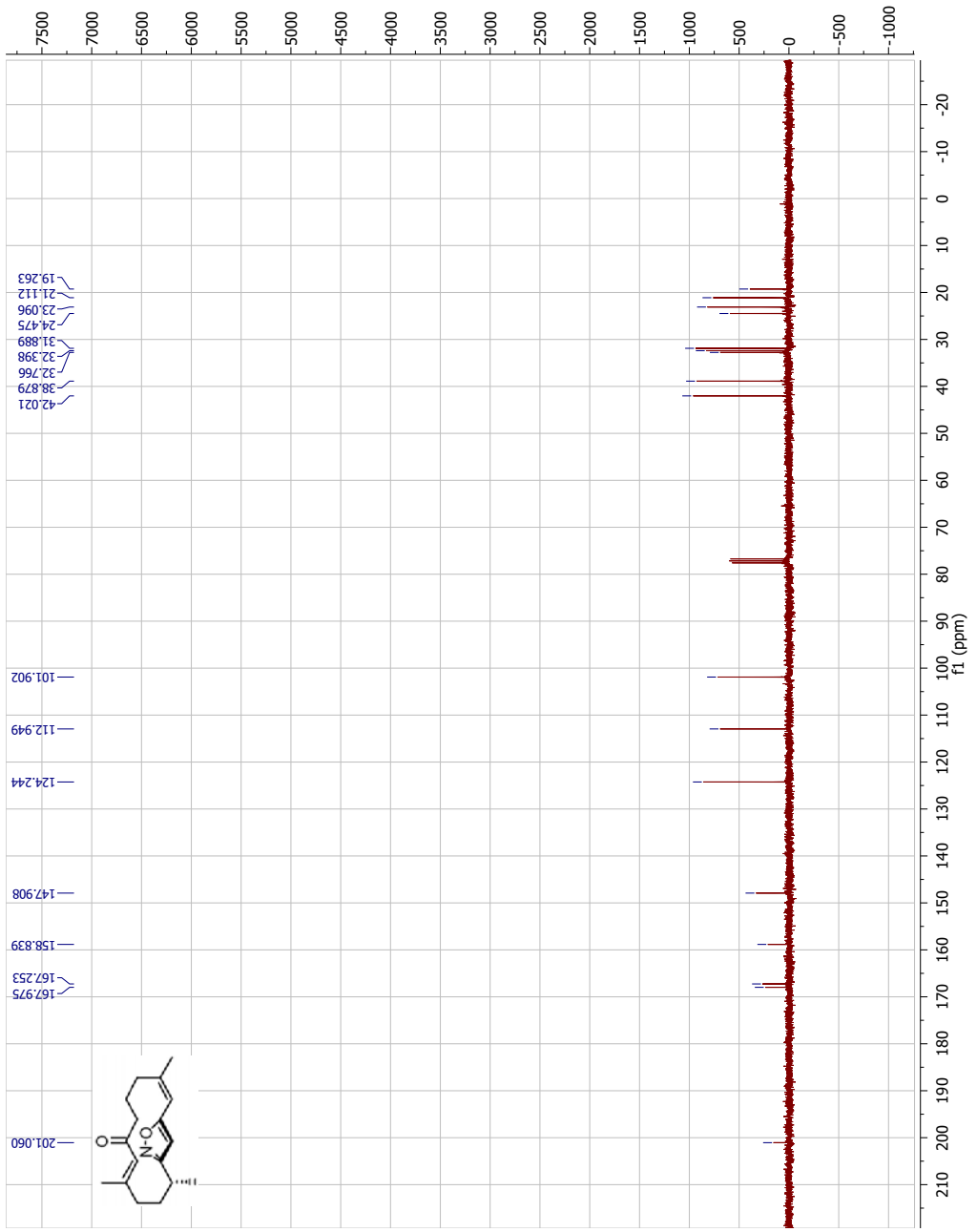

f1 (ppm)
9.948
5.752
5.717
5.400
5.373
5.261
5.232
5.127
5.106
4.435
4.352
2.549
1.961
1.927
1.782
1.769
1.717
1.647
1.447
1.326
1.181
1.146
1.03
0.94
5.23
3.48
1.22
2.43
16.96
1.64
3.33
0.58
0.36
0.40
0.59
0.59
0.35
1.05
OH
NH2
O

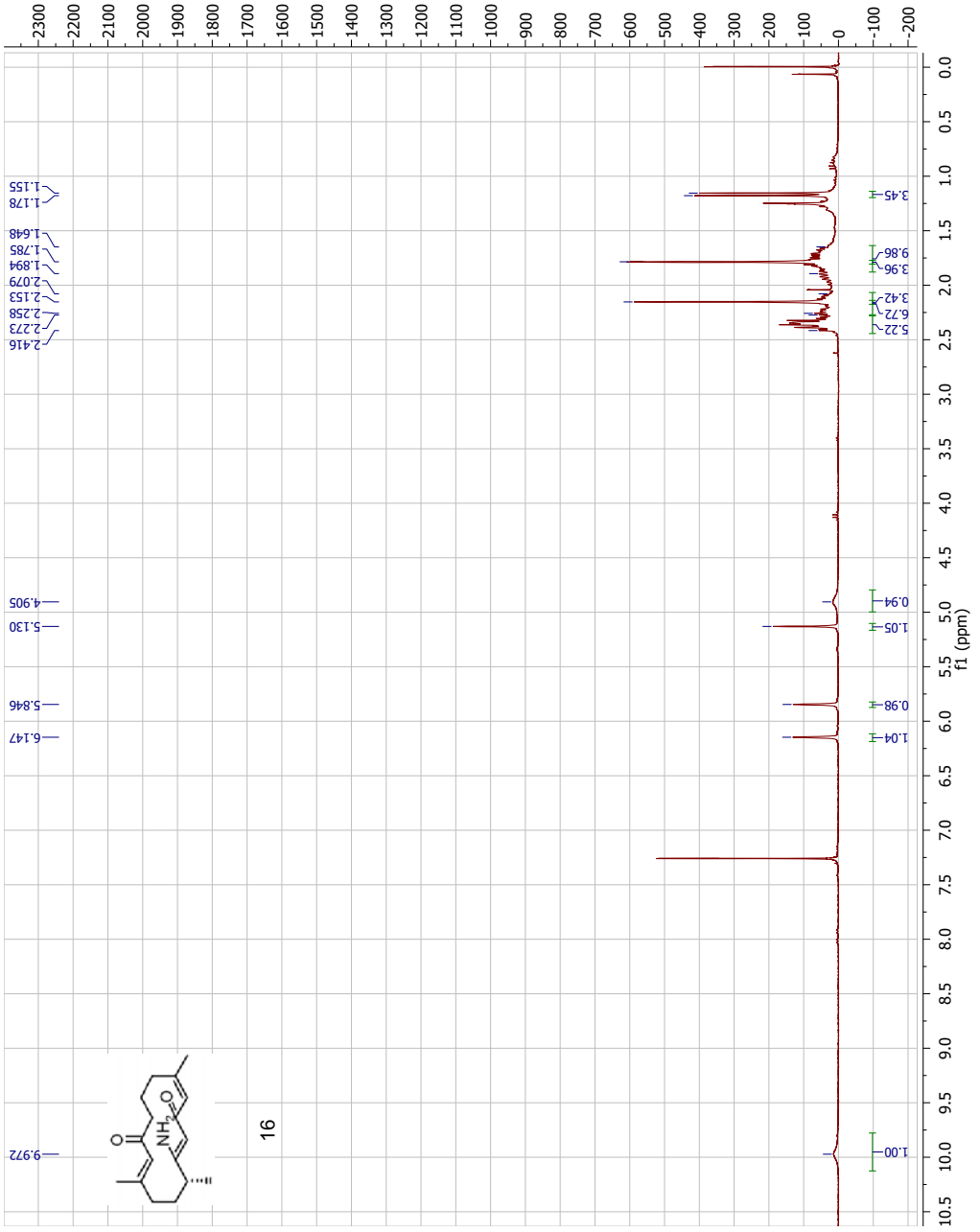

193.234
193.169
169.544
168.057
144.245
144.141
139.847
139.461
129.810
129.303
129.232
129.091
97.149
96.742
67.906
67.229
45.920
41.246
40.234
39.077
37.035
36.817
36.361
35.205
33.648
31.733
30.999
24.374
24.126
23.287
21.745
15.549
8.797
f1 (ppm)

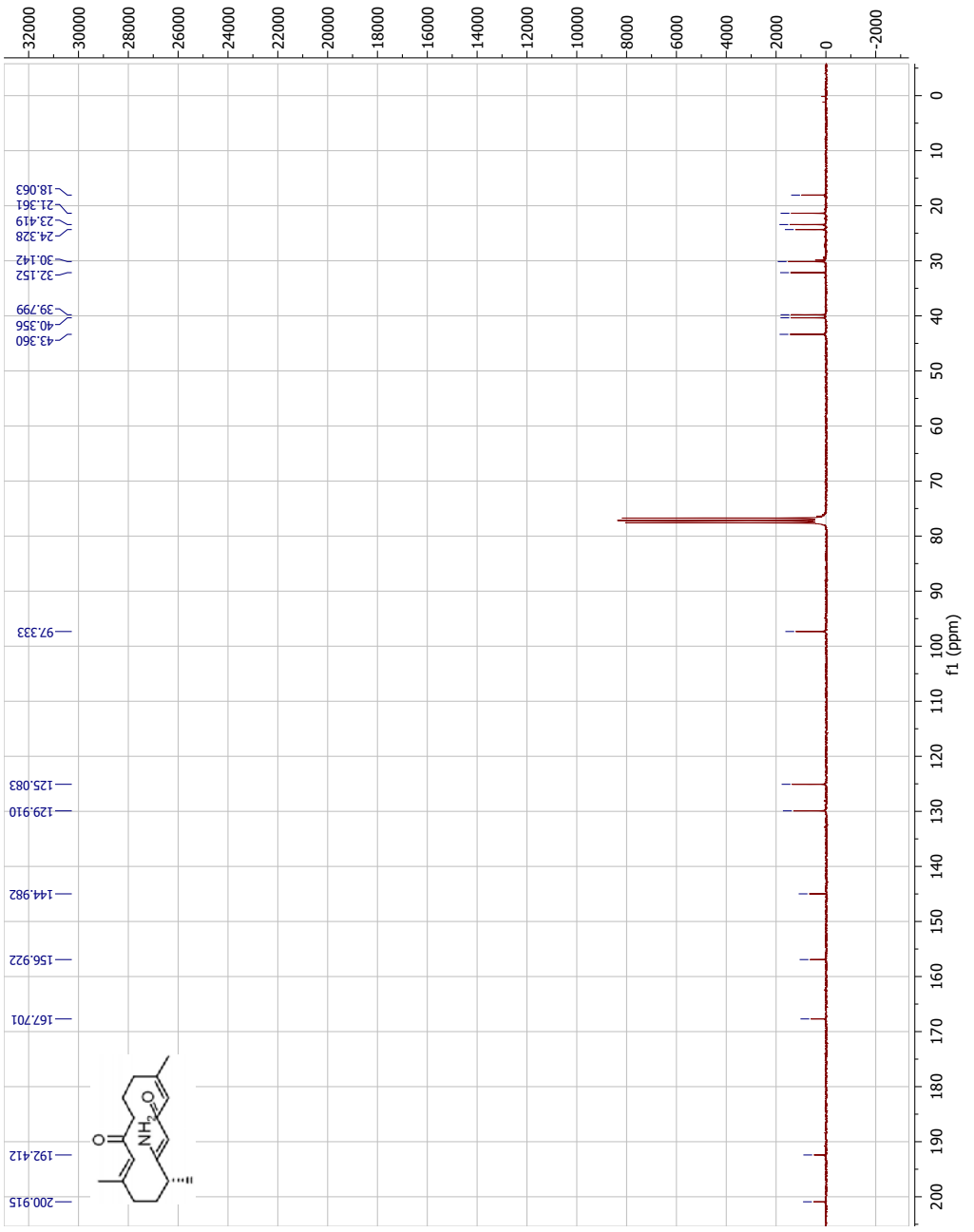

f1 (ppm)
OH
N-O

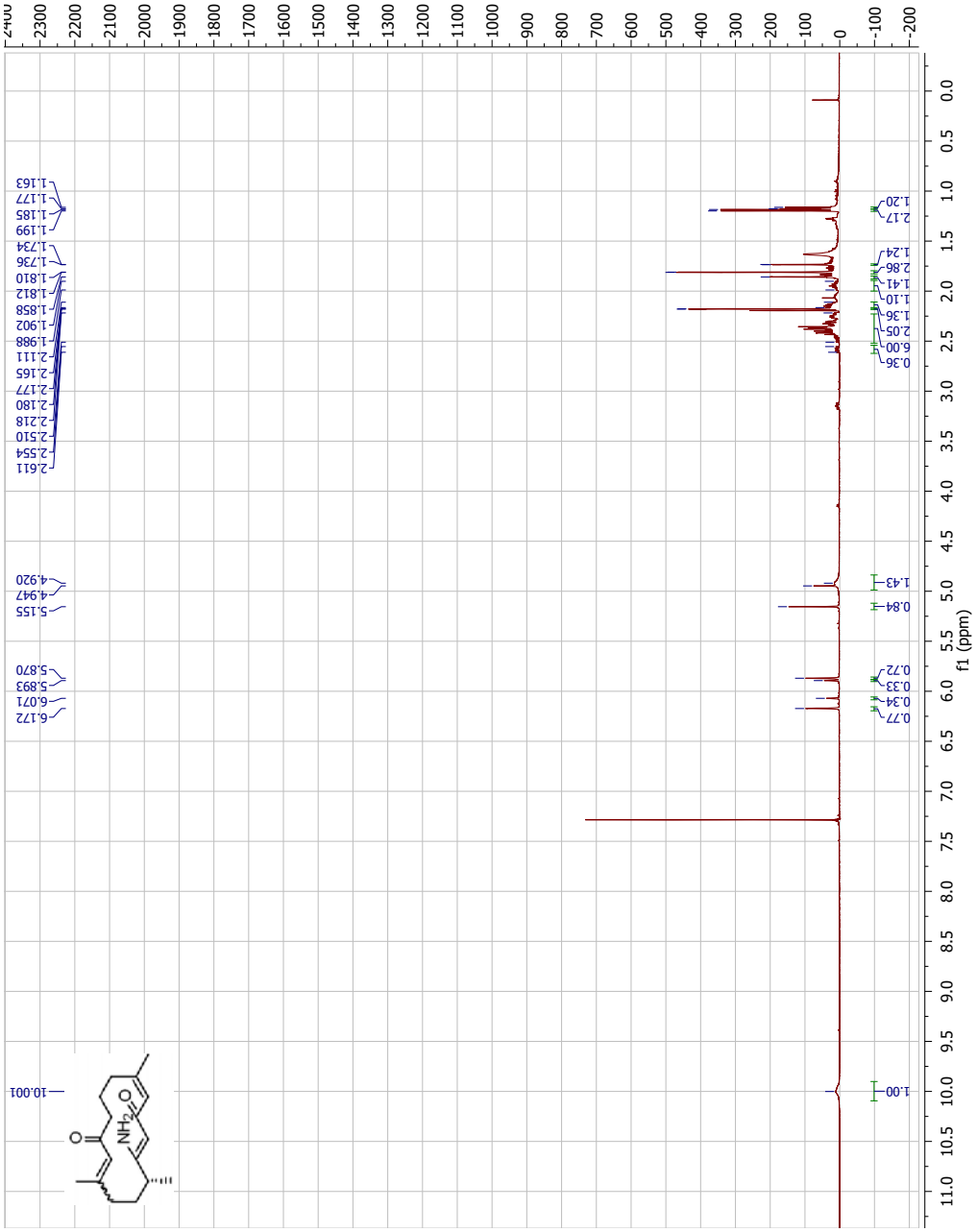

15.923
17.845
20.131
21.673
22.271
22.588
25.948
26.064
32.065
32.184
32.881
33.866
34.070
34.346
35.129
36.560
36.910
38.984
68.076
67.969
101.351
101.157
112.257
112.116
127.482
128.339
139.486
140.075
148.533
148.956
167.735
167.888
OH
N
O
f1 (ppm)

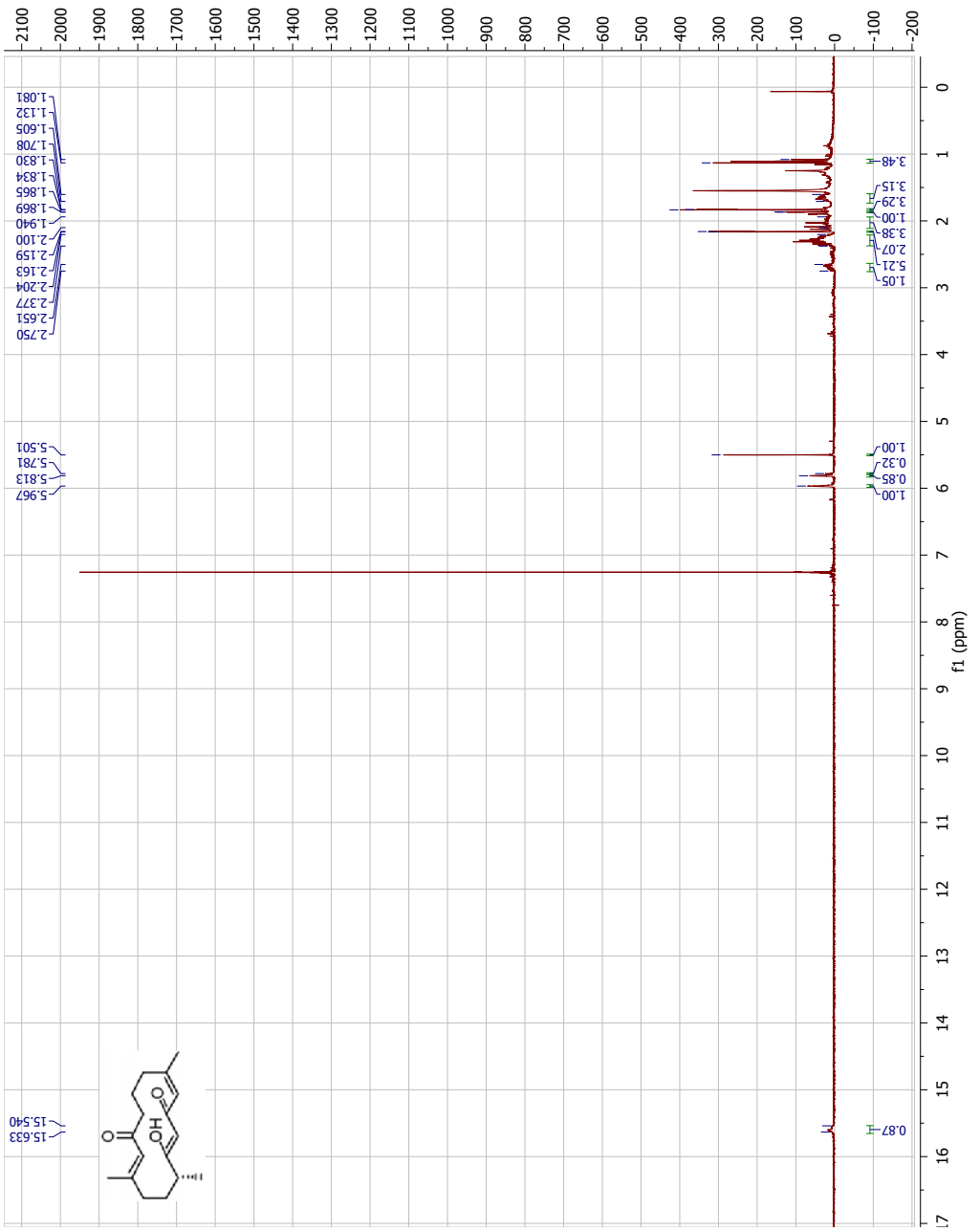

f1 (ppm)
1.262
1.286
1.673
1.863
1.901
1.906
1.975
2.077
2.080
2.174
2.339
2.872
2.990
5.543
5.841
6.094
3.46
4.84
3.32
5.86
5.35
1.05
1.01
0.98
1.00

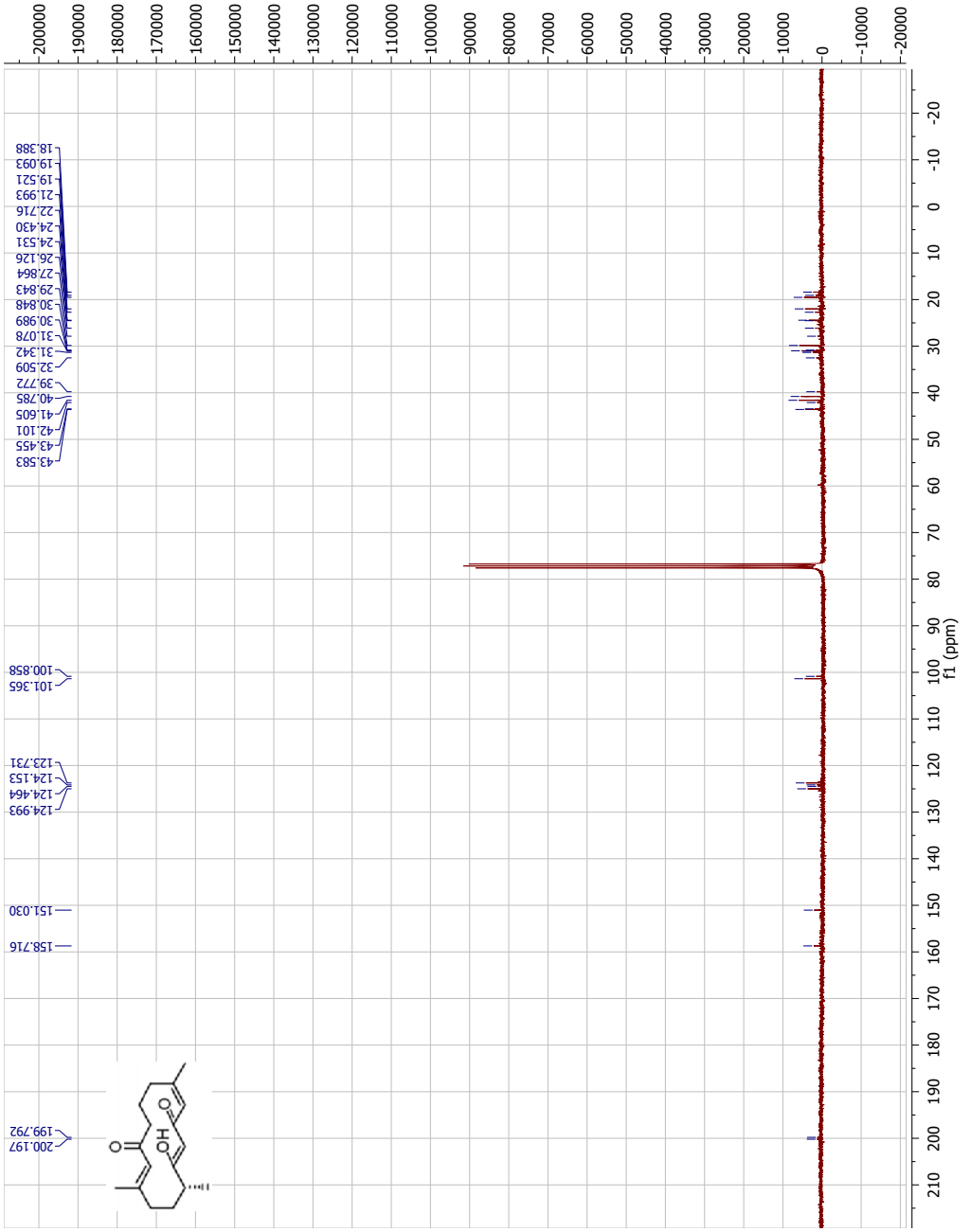

201.060
167.975
167.253
158.839
147.908
124.244
112.949
101.902
42.021
38.879
32.766
32.398
31.889
24.475
23.096
21.112
19.263
f1 (ppm)

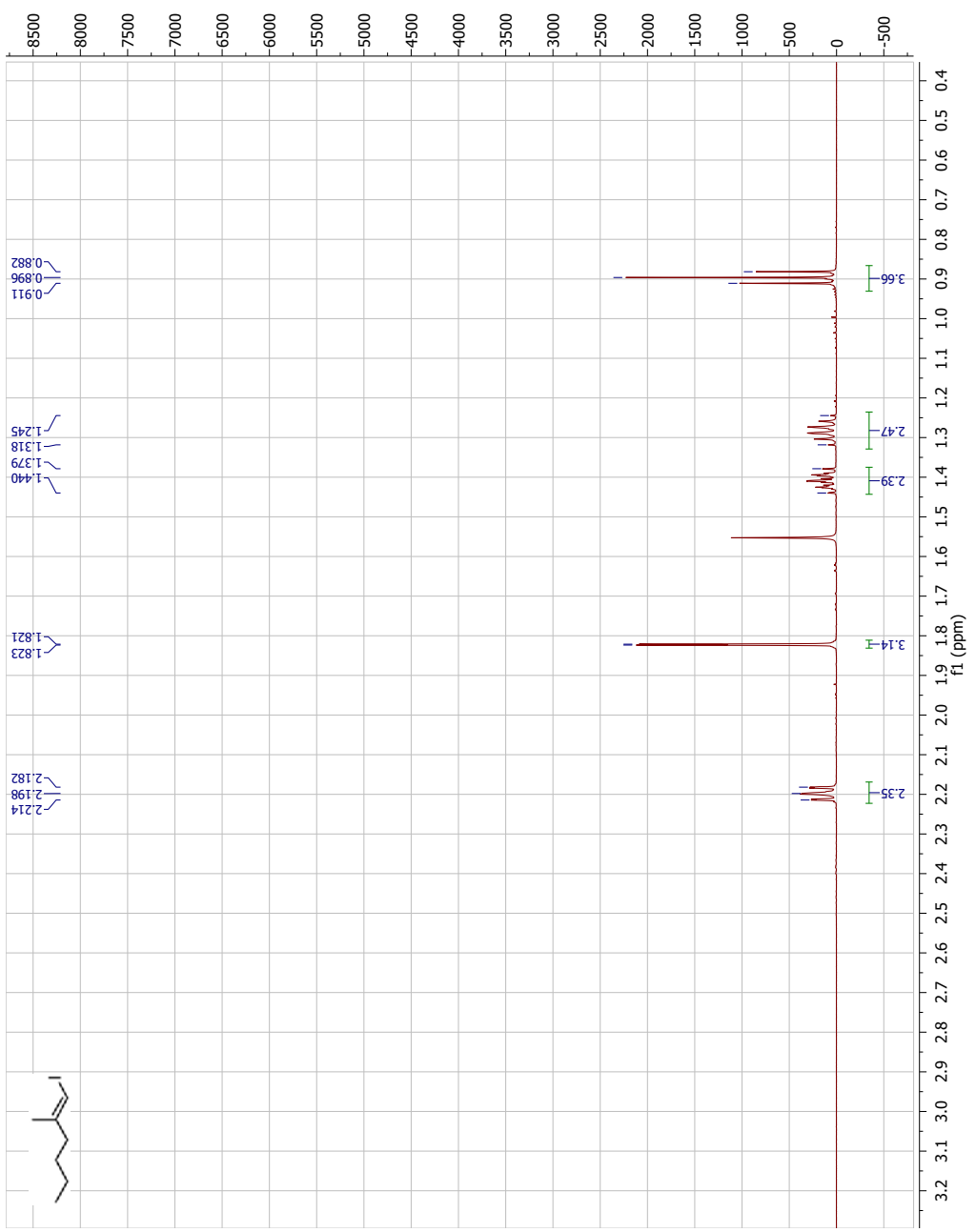

16
f1 (ppm)

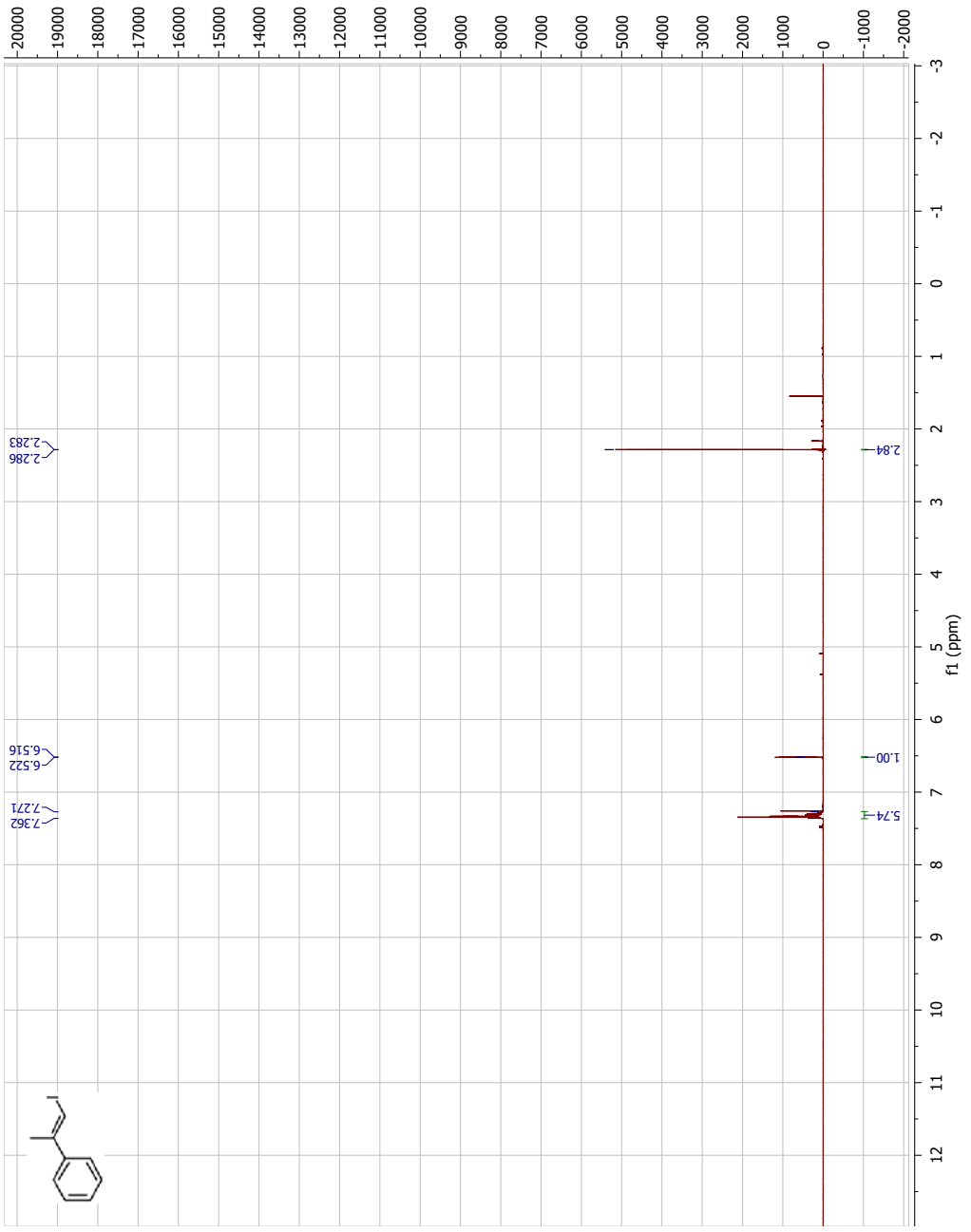

200.915
192.412
167.701
156.922
144.982
129.910
125.083
97.333
43.360
40.356
39.799
32.152
30.142
24.328
23.419
21.361
18.063
f1 (ppm)

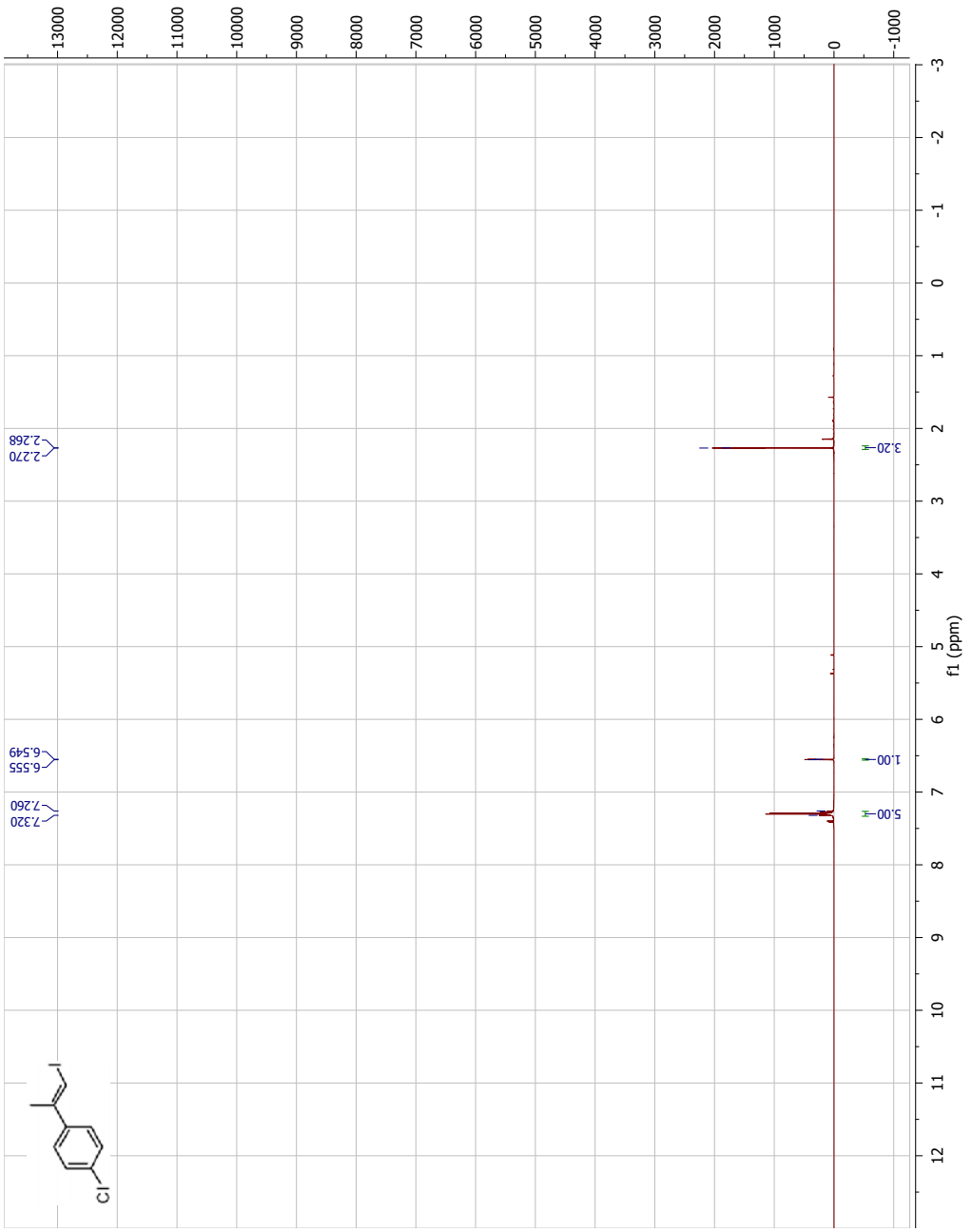

f1 (ppm)
10.001
6.172
6.071
5.893
5.870
5.155
4.947
4.920
2.611
2.554
2.510
2.218
2.180
2.177
2.165
2.111
1.988
1.902
1.858
1.812
1.810
1.736
1.734
1.199
1.185
1.177
1.163
1.00
0.77
0.34
0.33
0.72
1.43
0.84
0.36
6.00
2.05
1.36
1.10
1.41
2.86
1.24
2.17
1.20

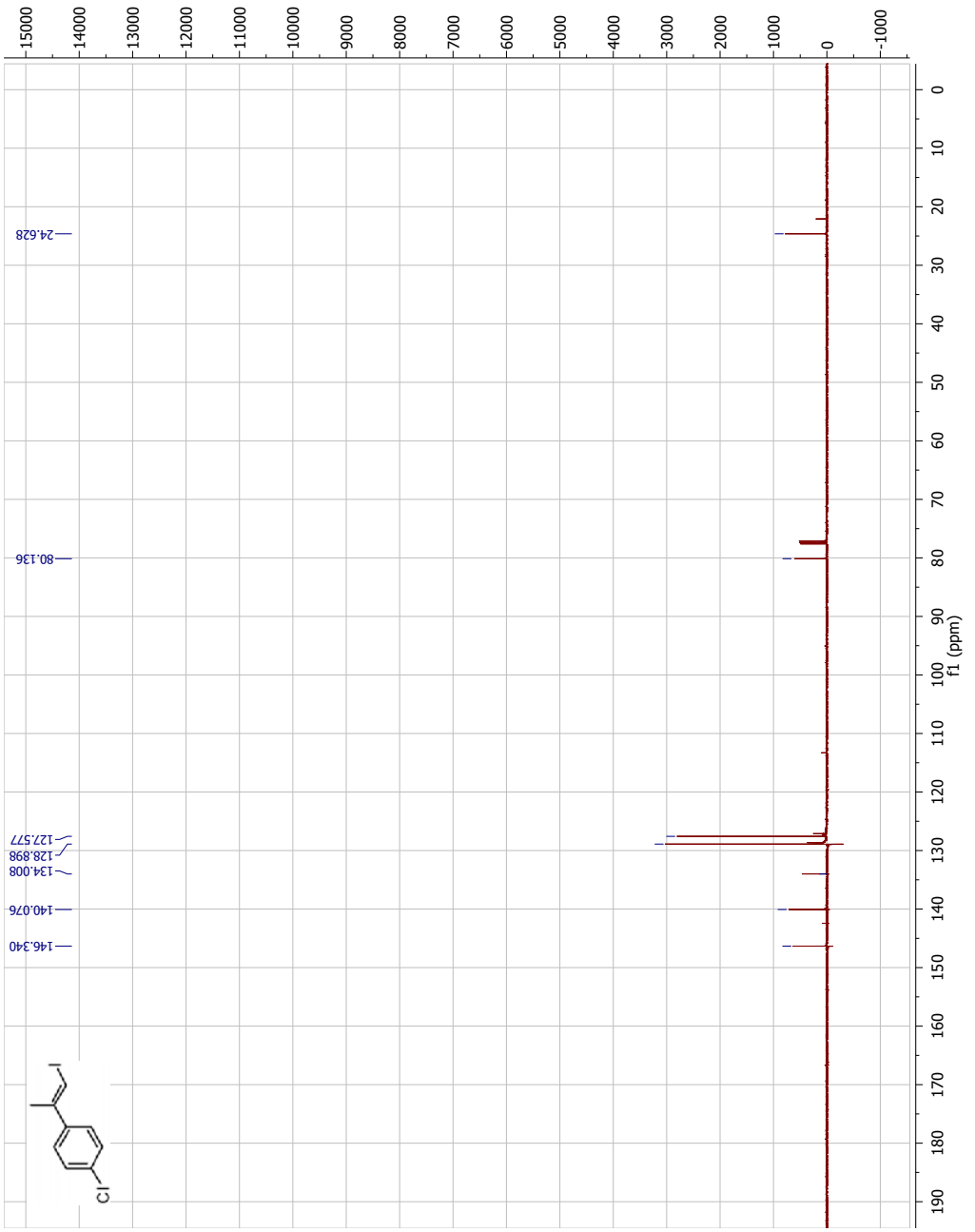

f1 (ppm)
15.633
15.540
5.967
5.813
5.781
5.501
2.750
2.651
2.377
2.204
2.163
2.159
2.100
1.940
1.869
1.865
1.834
1.830
1.708
1.605
1.132
1.081
3.48
3.15
3.29
1.00
3.38
2.07
5.21
1.05
1.00
0.85
0.32
1.00
0.87

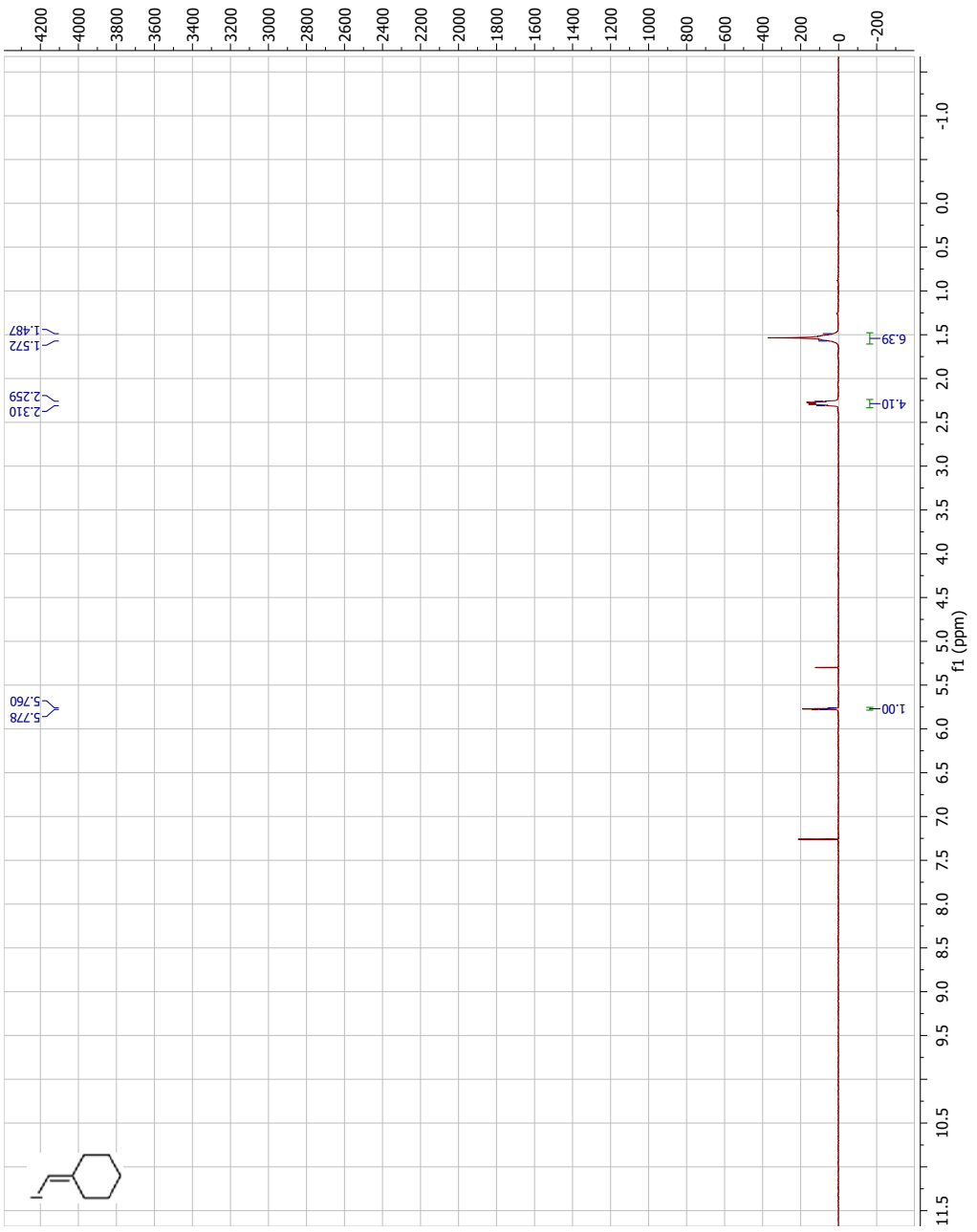

200.197
199.792
158.716
151.030
124.993
124.464
124.153
123.731
101.365
100.858
43.583
43.455
42.101
41.605
40.785
39.772
32.509
31.342
31.078
30.989
30.848
29.843
27.864
26.126
24.531
24.430
22.716
21.993
19.521
19.093
18.388
f1 (ppm)

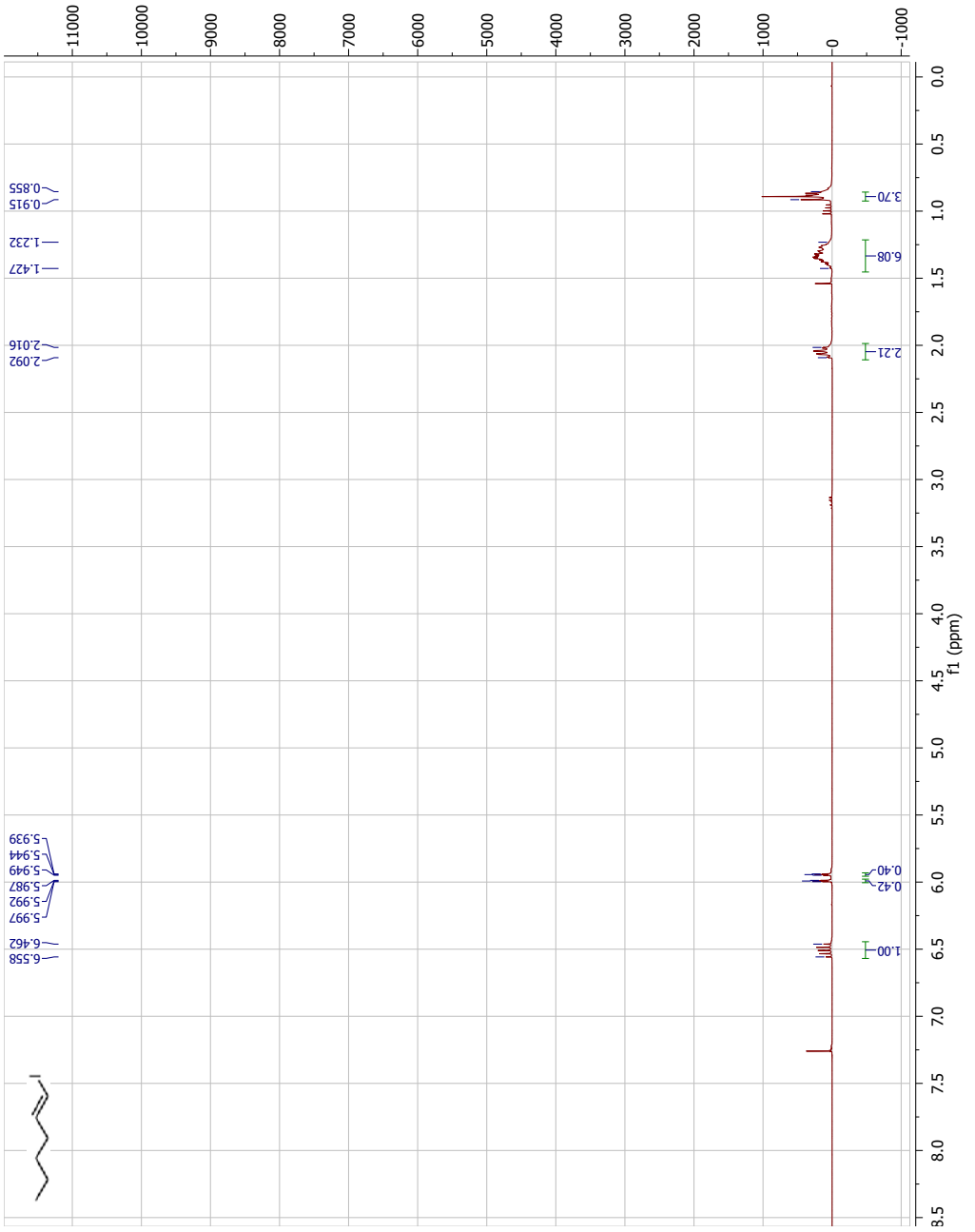

f1 (ppm)
0.882
0.896
0.911
1.245
1.318
1.379
1.440
1.821
1.823
2.182
2.198
2.214
3.66
2.47
2.39
3.14
2.35

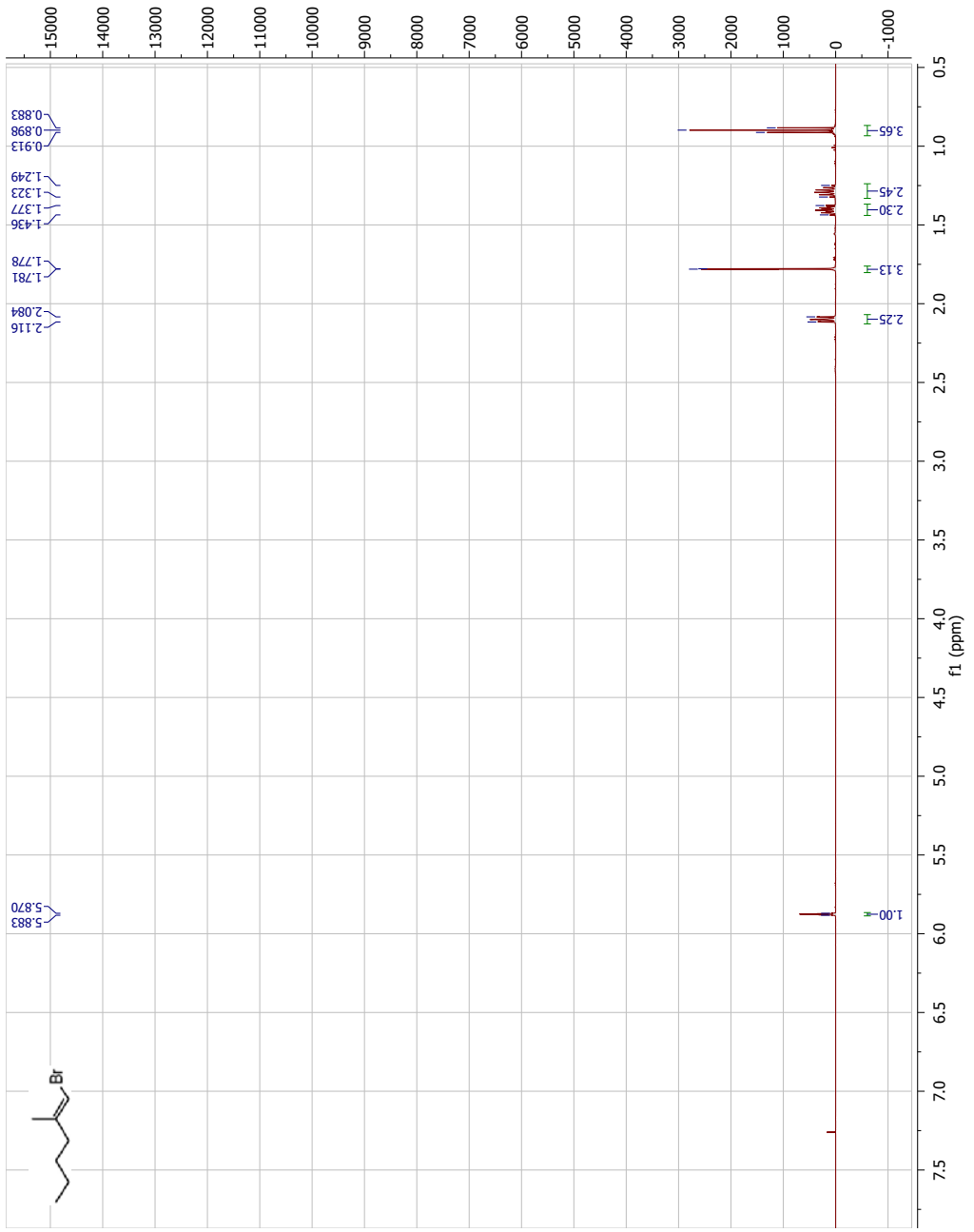

2.286
2.283
6.522
6.516
7.362
7.271
2.84
1.00
5.74
f1 (ppm)

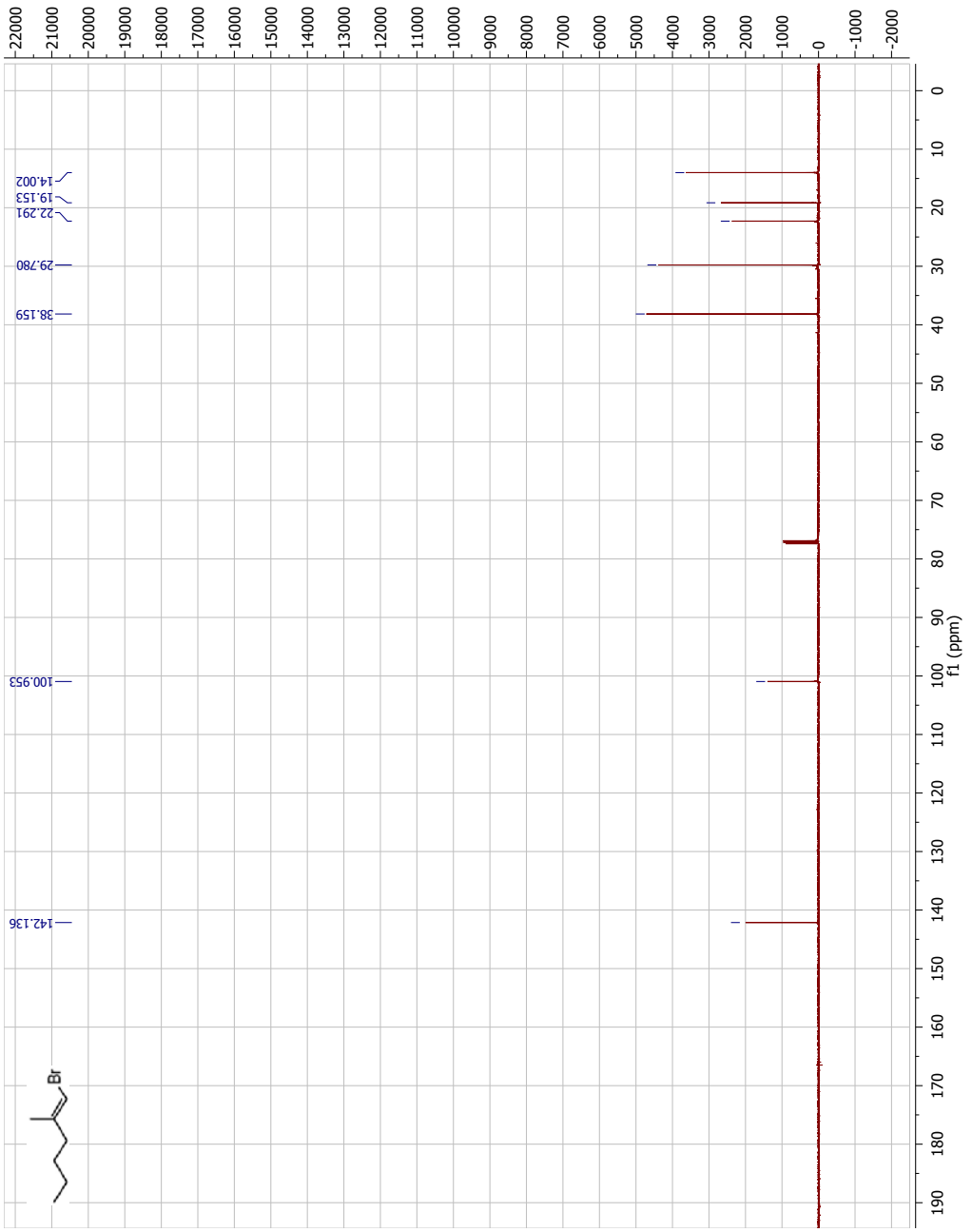

7.320
7.260
6.555
6.549
2.270
2.268
5.00
1.00
3.20
f1 (ppm)
Cl

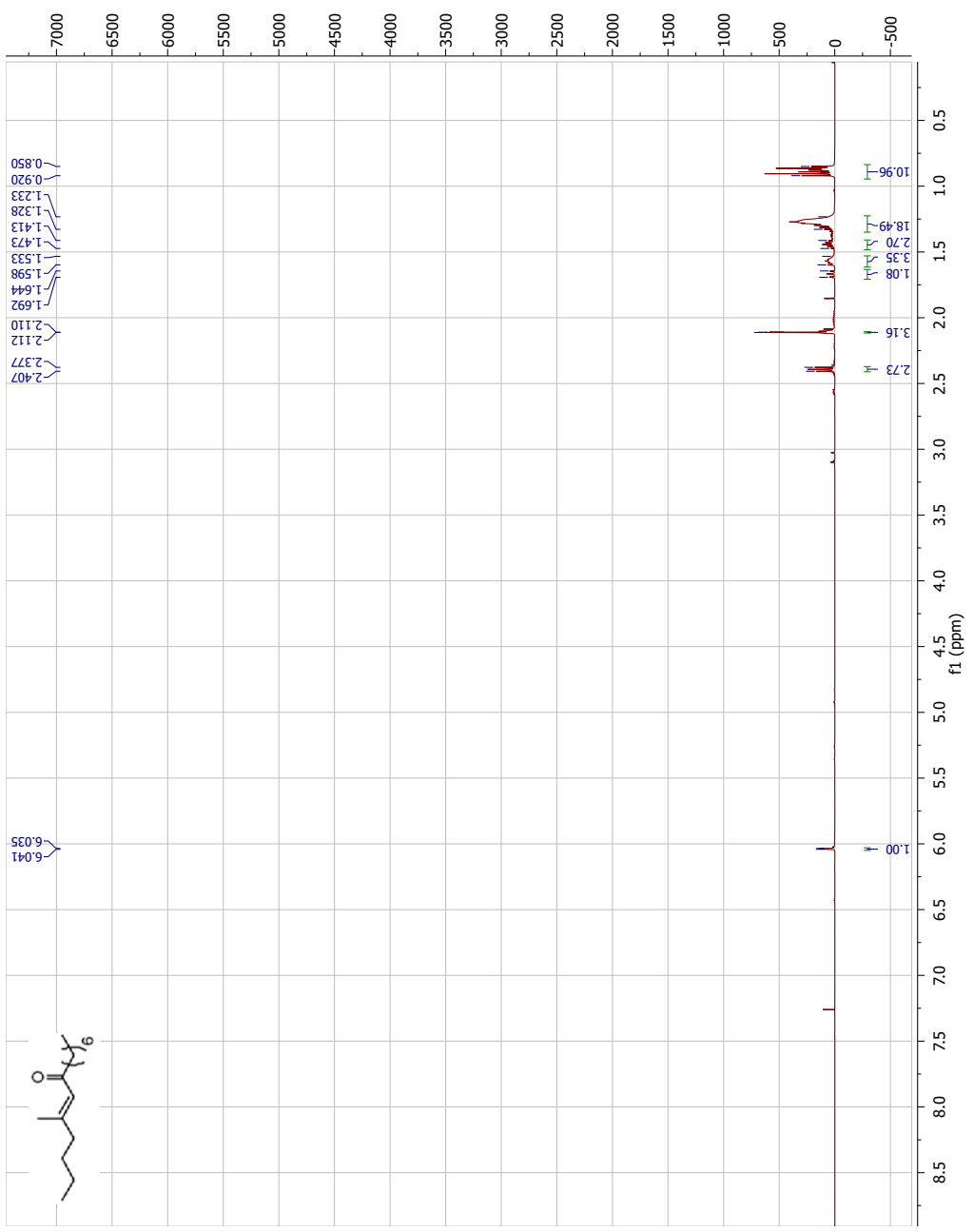

24.628
80.136
127.577
128.898
134.008
140.076
146.340
Cl
f1 (ppm)

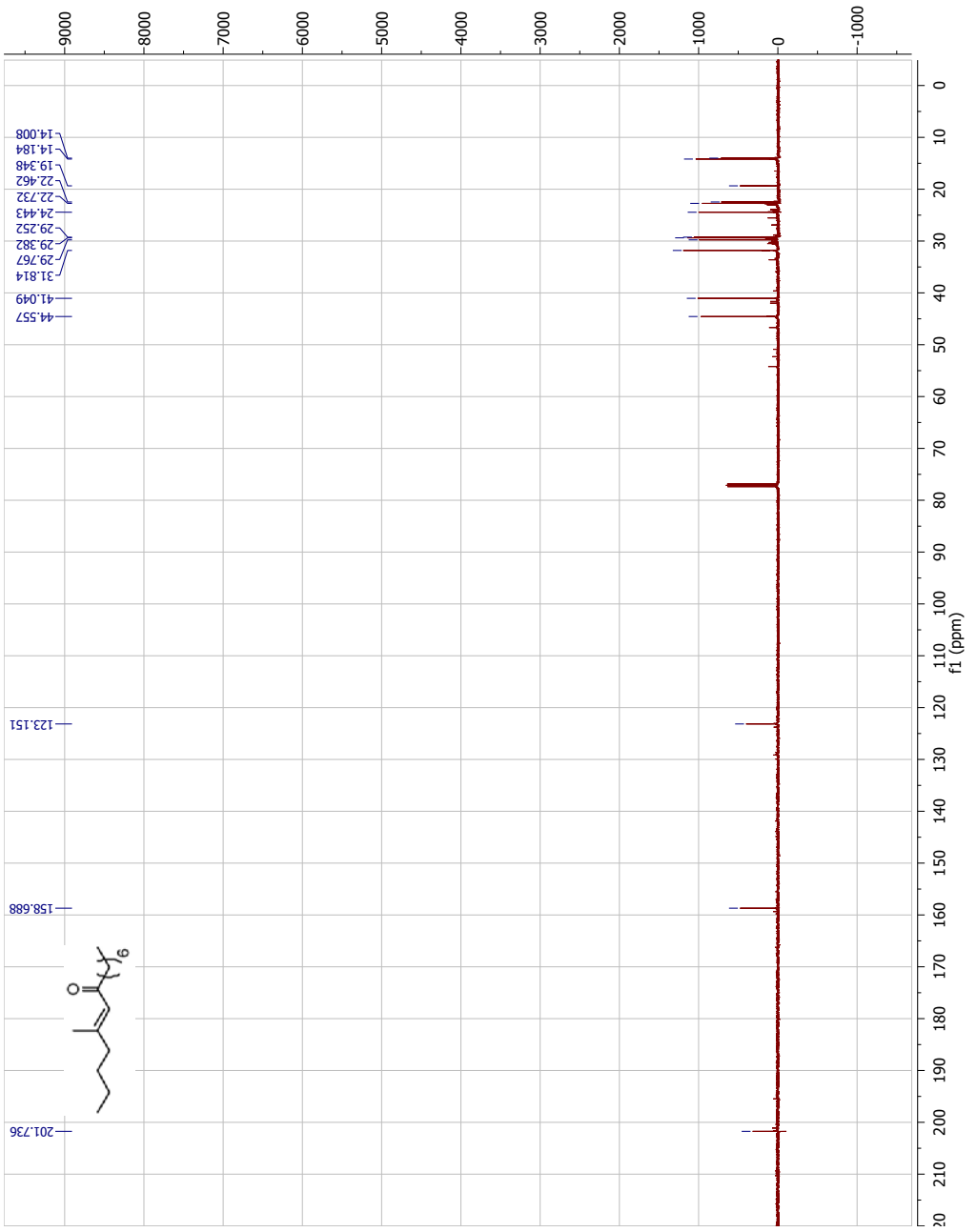

5.778
5.760
2.310
2.259
1.572
1.487
1.00
4.10
6.39
f1 (ppm)

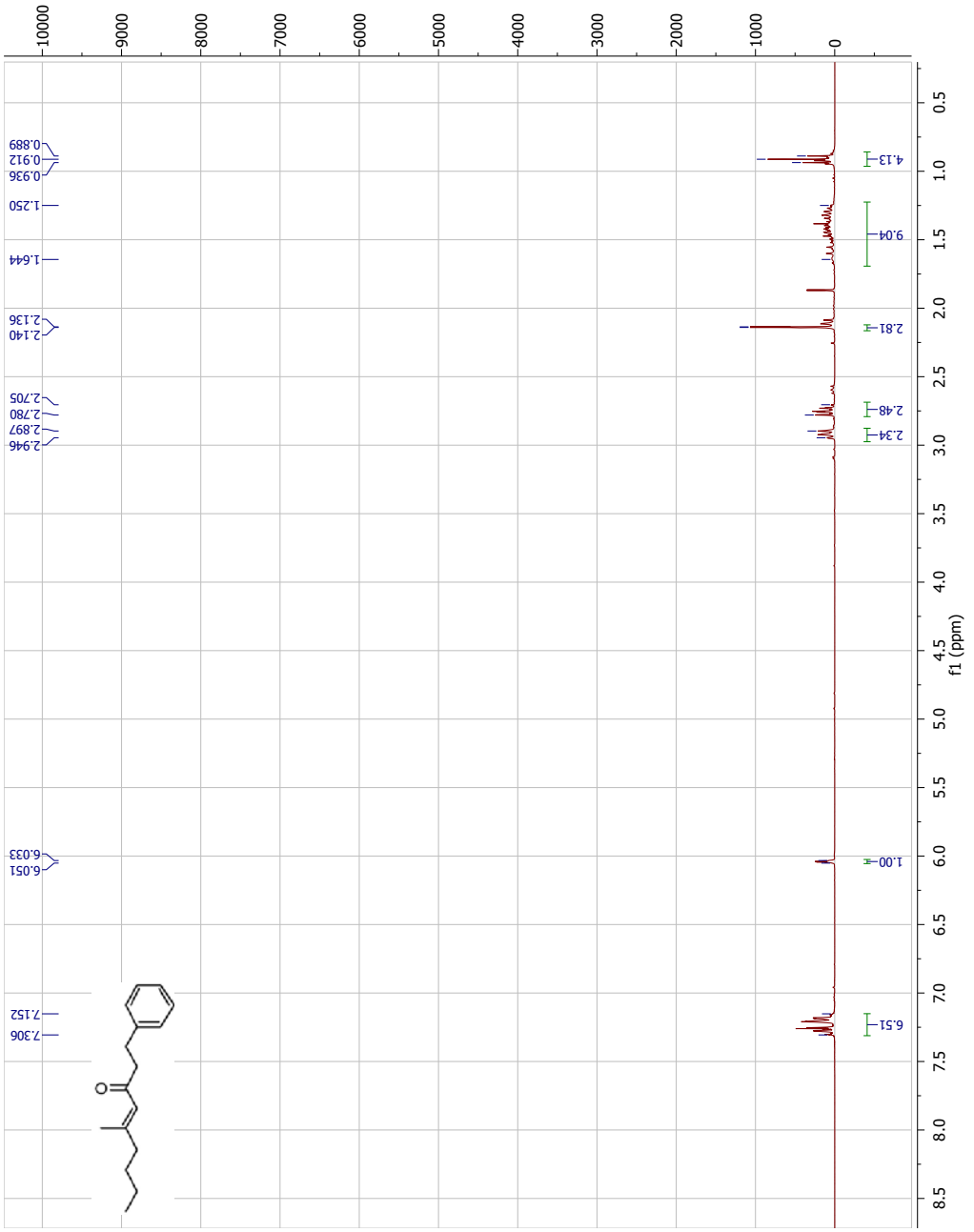

11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
f1 (ppm)
0.855
0.915
1.232
1.427
2.016
2.092
5.939
5.944
5.949
5.987
5.992
5.997
6.462
6.558
3.70
6.08
2.21
0.40
0.42
1.00

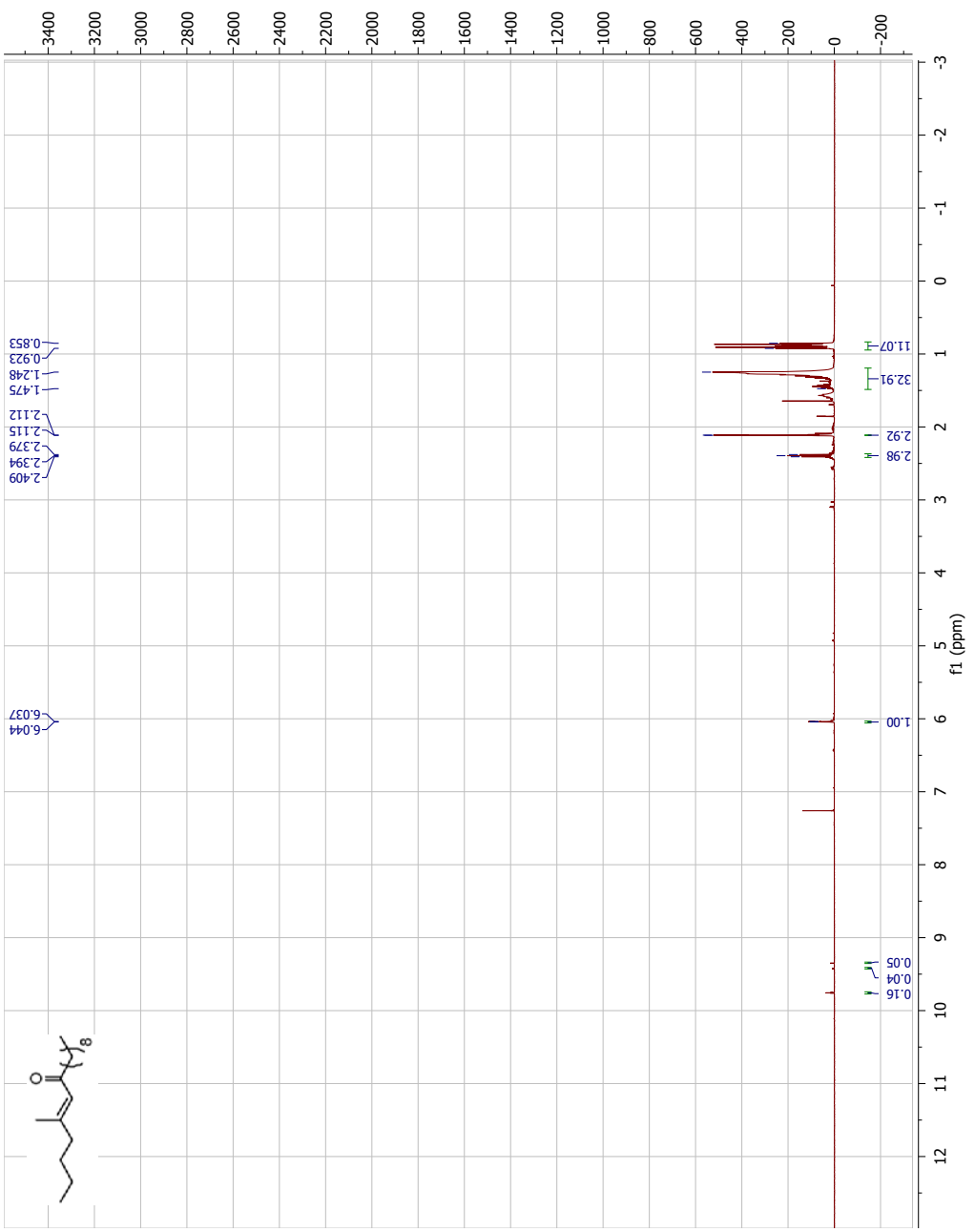

Br
5.883
5.870
2.116
2.084
1.781
1.778
1.436
1.377
1.323
1.249
0.913
0.898
0.883
1.00
3.13
2.45
2.30
2.25
3.65
f1 (ppm)

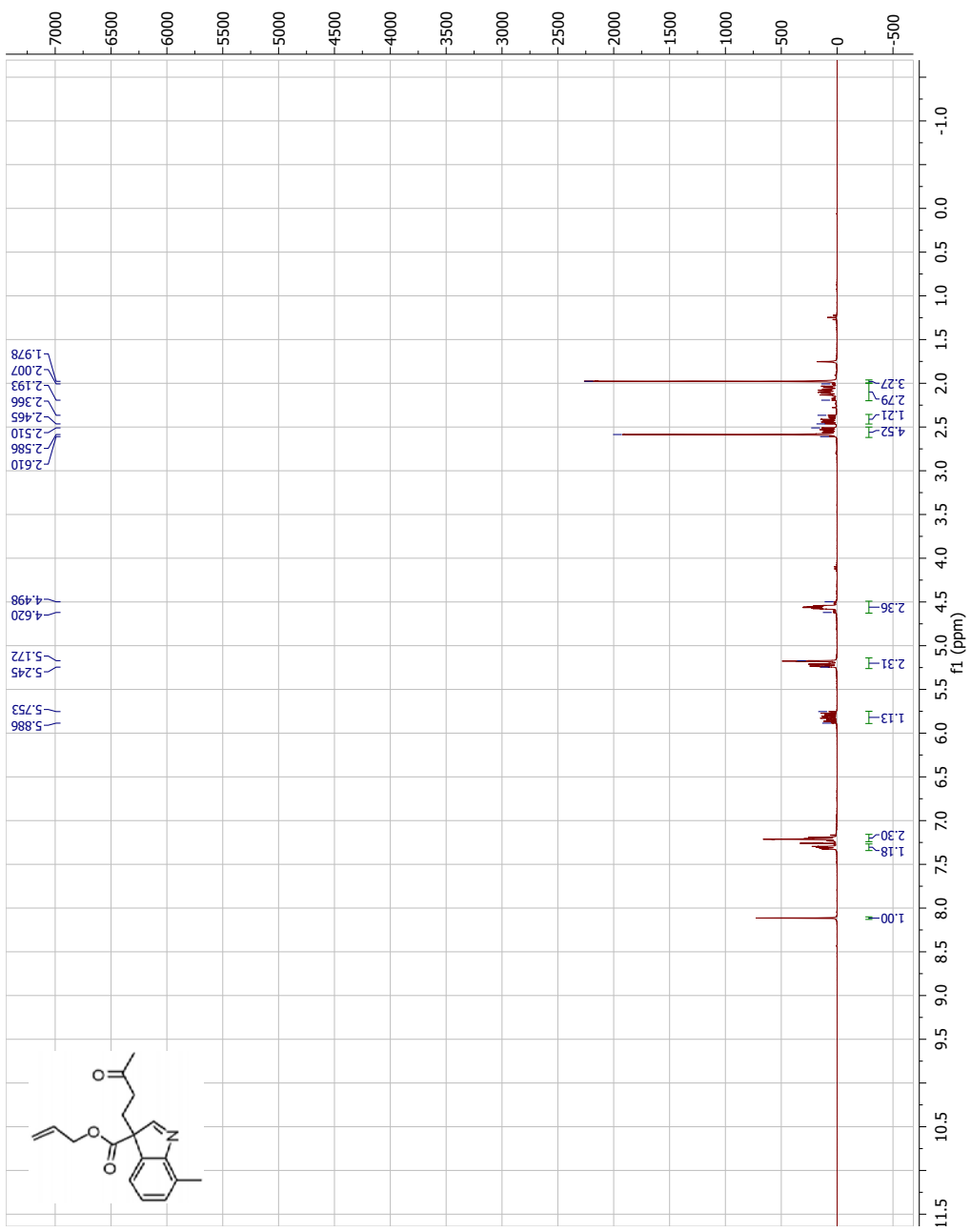

142.136
100.953
38.159
29.780
22.291
19.153
14.002
Br
f1 (ppm)

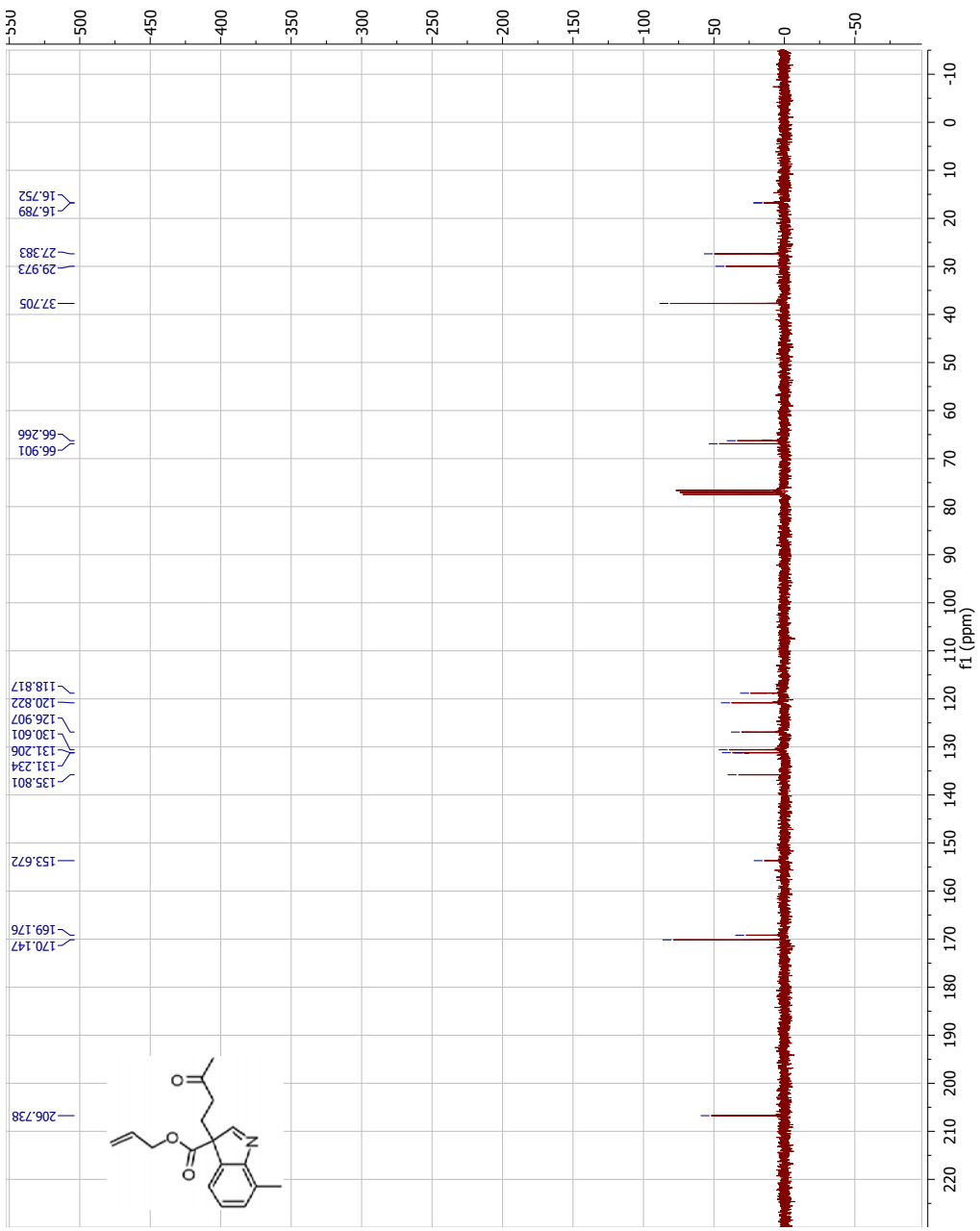

6.041
6.035
2.407
2.377
2.112
2.110
1.692
1.644
1.598
1.533
1.473
1.413
1.328
1.233
0.920
0.850
1.00
2.73
3.16
10.96
1.08
3.35
2.70
18.49
f1 (ppm)

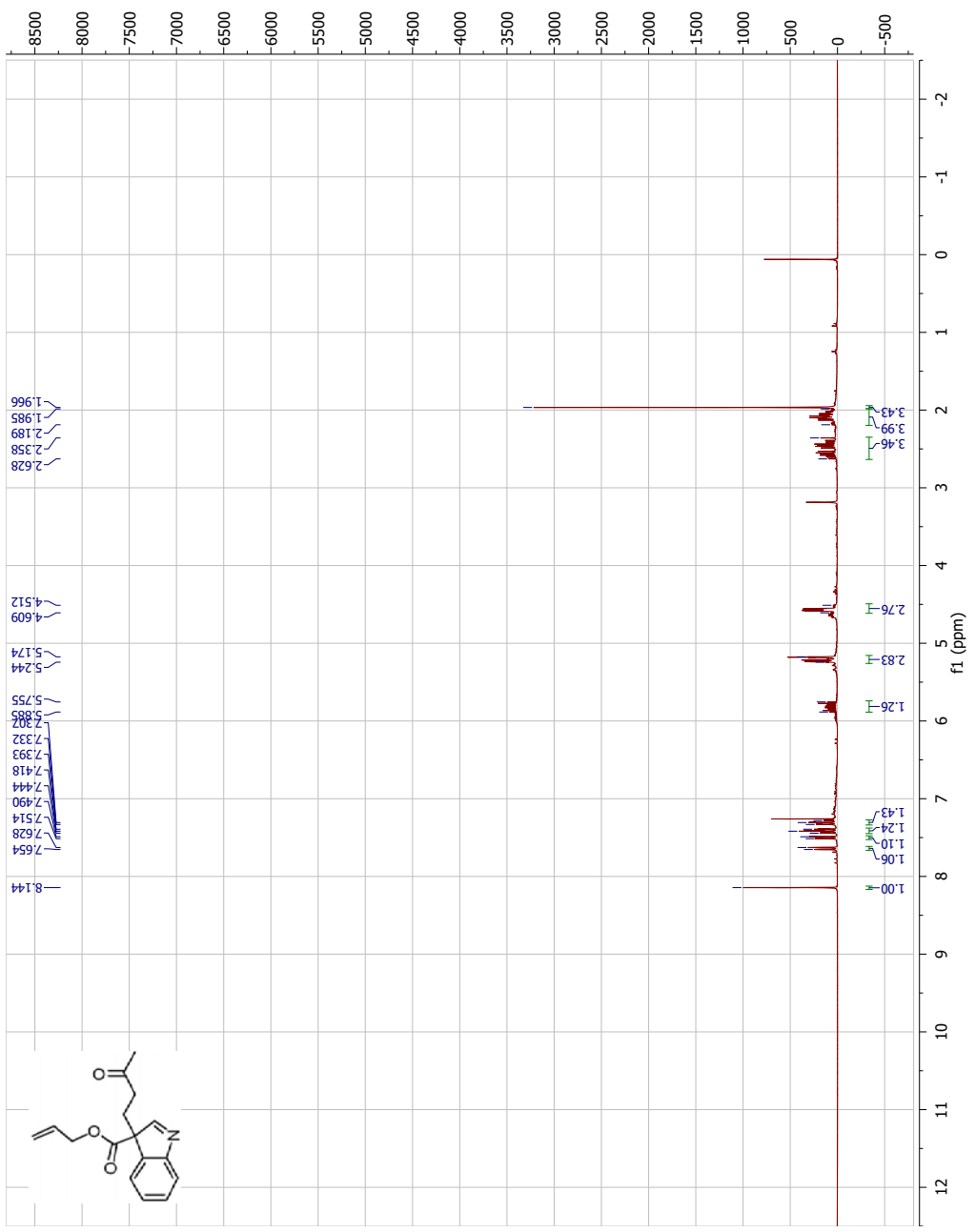

14.008
14.184
19.348
22.462
22.732
24.443
29.252
29.382
29.767
31.814
41.049
44.557
123.151
158.688
201.736
f1 (ppm)

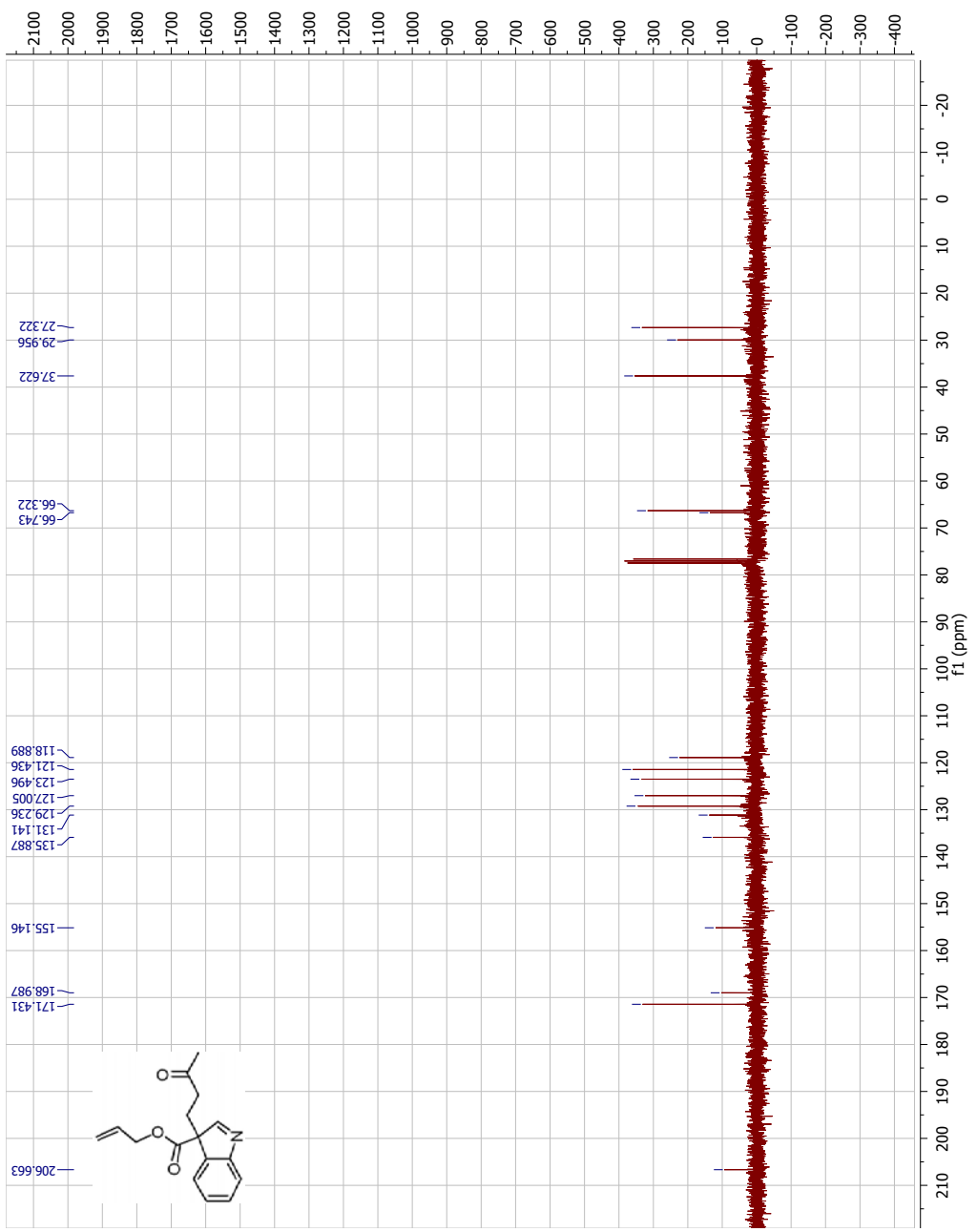

f1 (ppm)
7.306
7.152
6.051
6.033
2.946
2.897
2.780
2.705
2.140
2.136
1.644
1.250
0.936
0.912
0.889
6.51
1.00
2.81
2.48
2.34
9.04
4.13

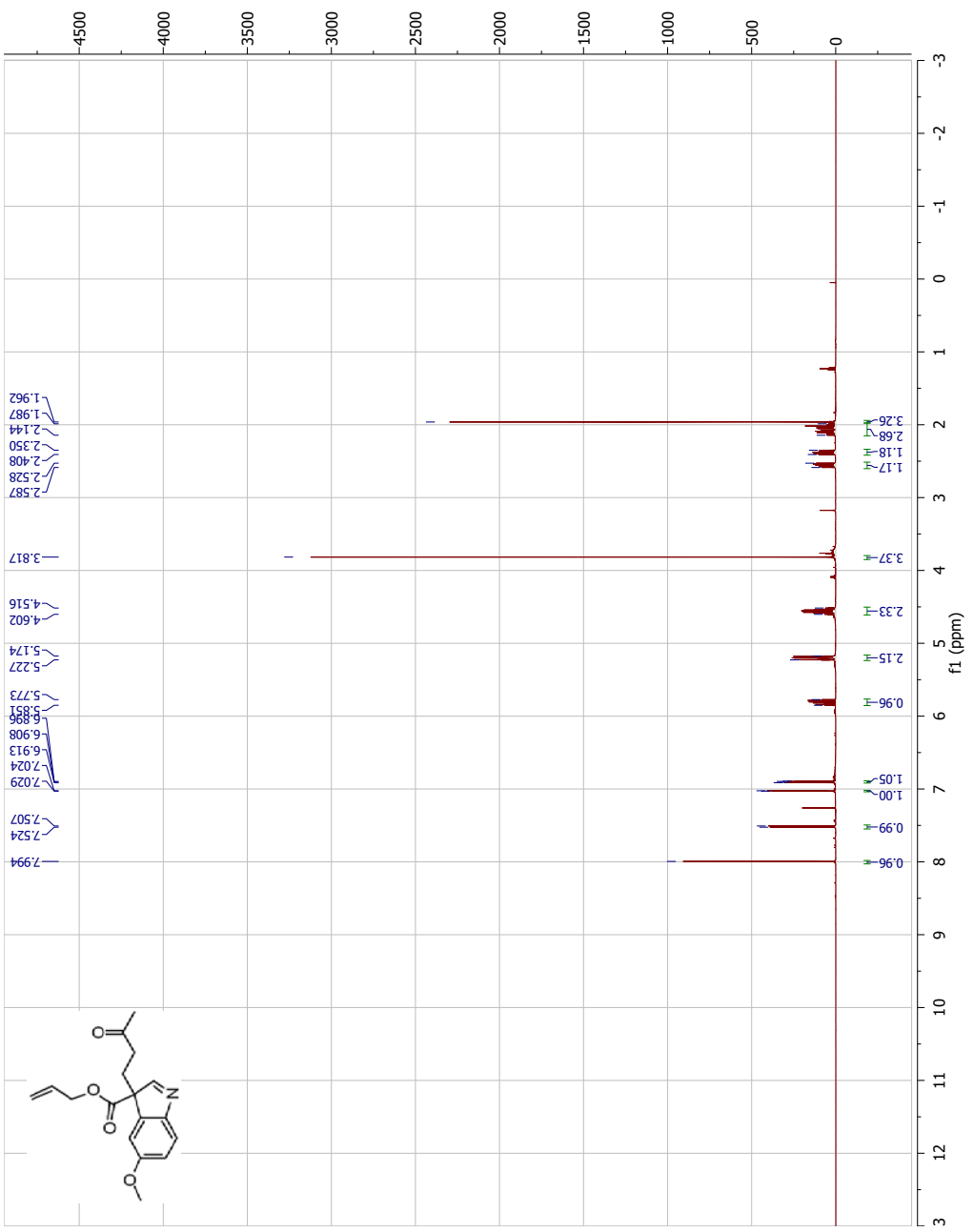

f1 (ppm)
0.853
0.923
1.248
1.475
2.112
2.115
2.379
2.394
2.409
6.037
6.044
0.05
0.04
0.16
1.00
2.98
2.92
32.91
11.07

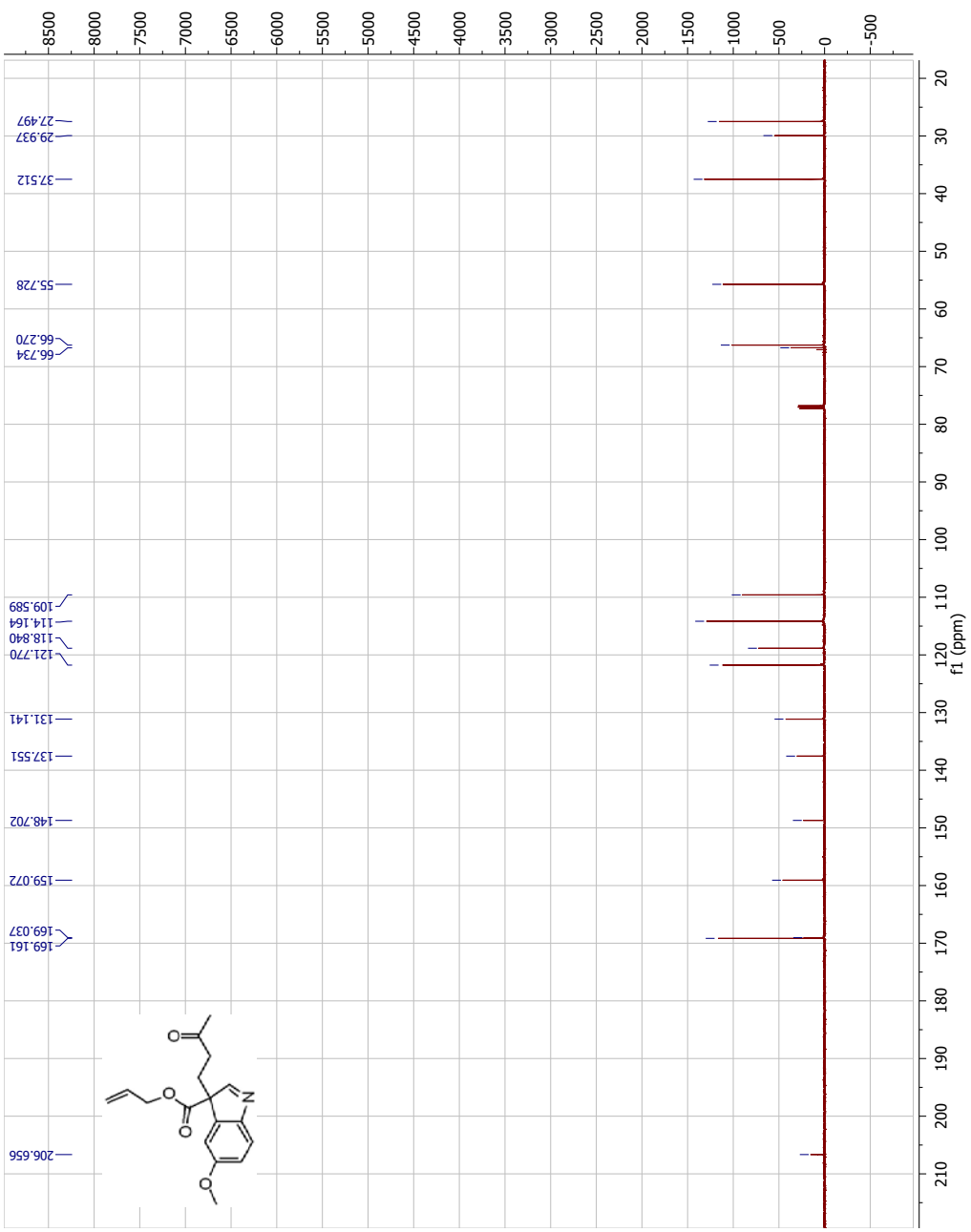

f1 (ppm)
1.978
2.007
2.193
2.366
2.465
2.510
2.586
2.610
4.498
4.620
5.172
5.245
5.753
5.886
1.00
1.18
2.30
1.13
2.31
2.36
4.52
1.21
2.79
3.27

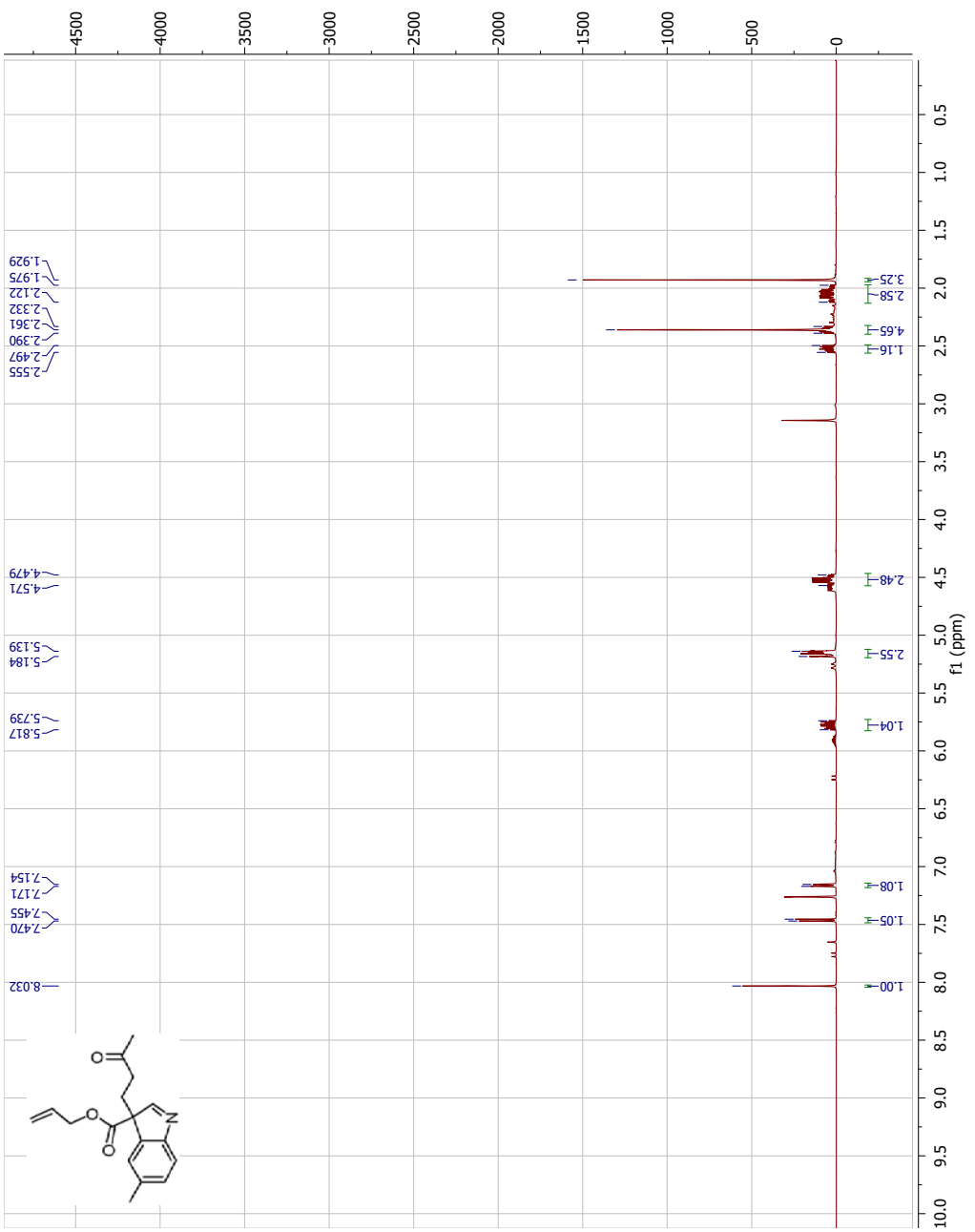

16.789
16.752
27.383
29.973
37.705
66.901
66.266
118.817
120.822
126.907
130.601
131.206
131.234
135.801
153.672
169.176
170.147
206.738
f1 (ppm)

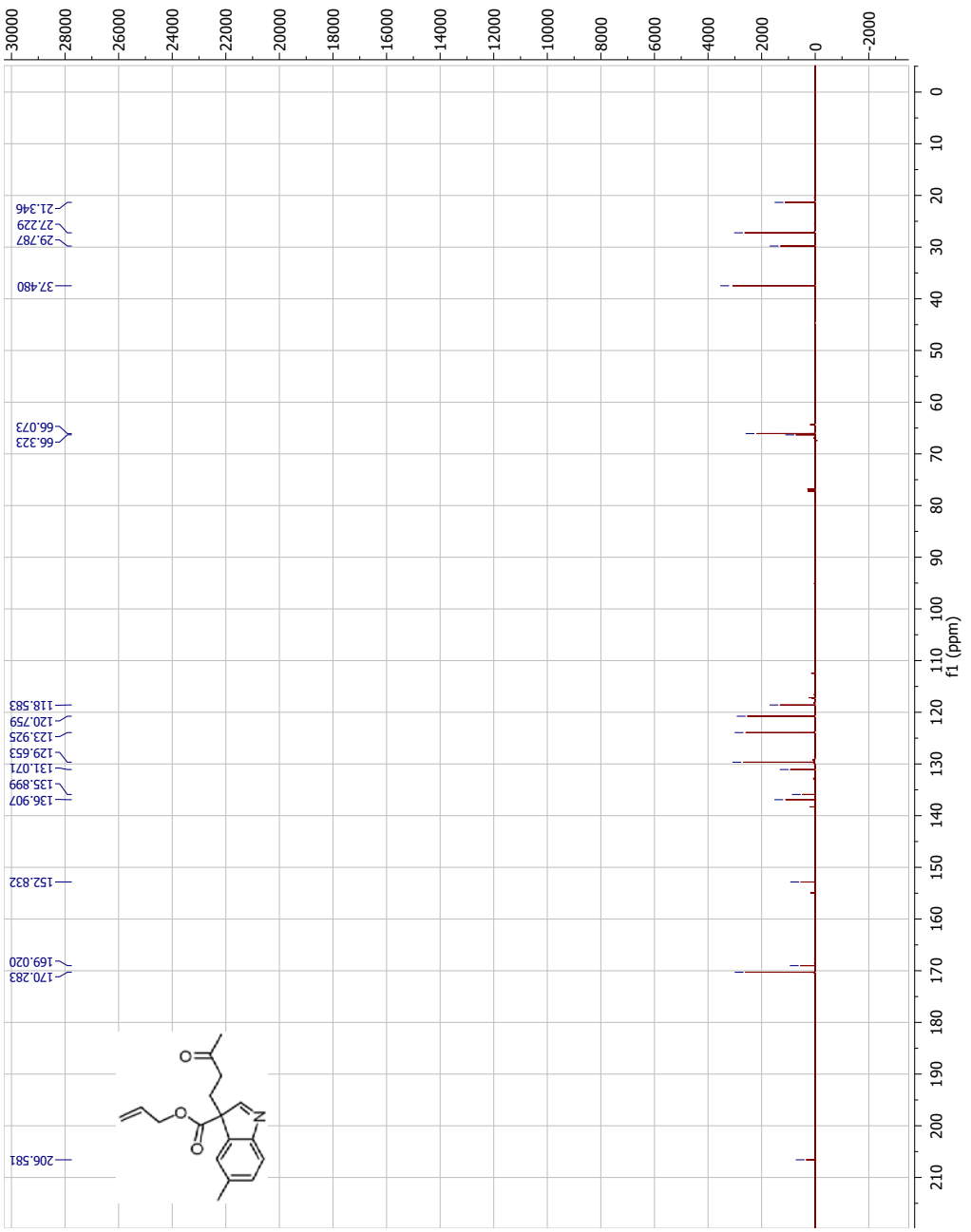

8.144
7.654
7.628
7.514
7.490
7.444
7.418
7.393
7.332
7.302
5.885
5.755
5.244
5.174
4.609
4.512
2.628
2.358
2.189
1.985
1.966
1.00
1.06
1.10
1.24
1.43
2.76
2.83
1.26
3.43
3.99
3.46
f1 (ppm)

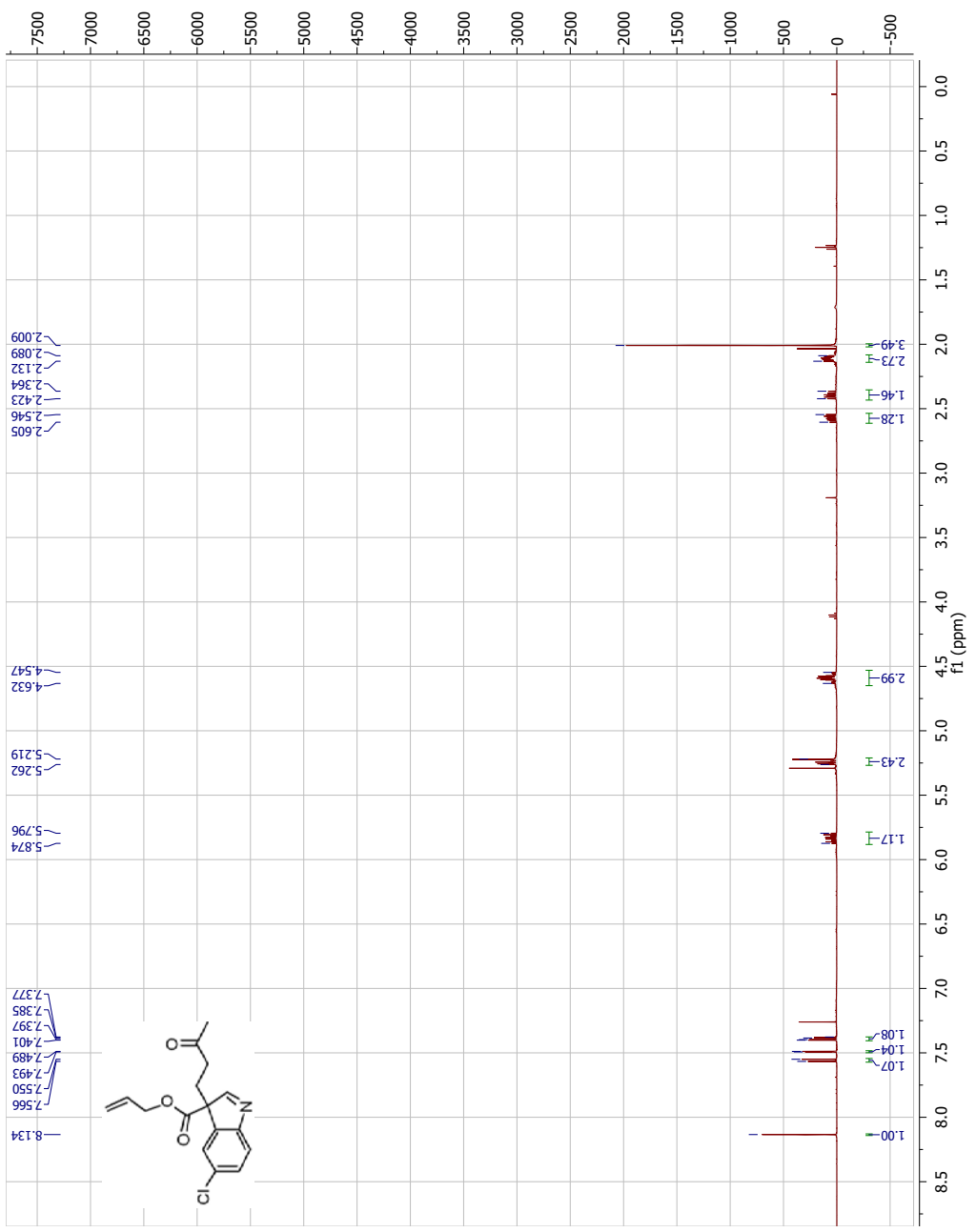

206.663
171.431
168.987
155.146
135.887
131.141
129.236
127.005
123.496
121.436
118.889
66.743
66.322
37.622
29.956
27.322
f1 (ppm)

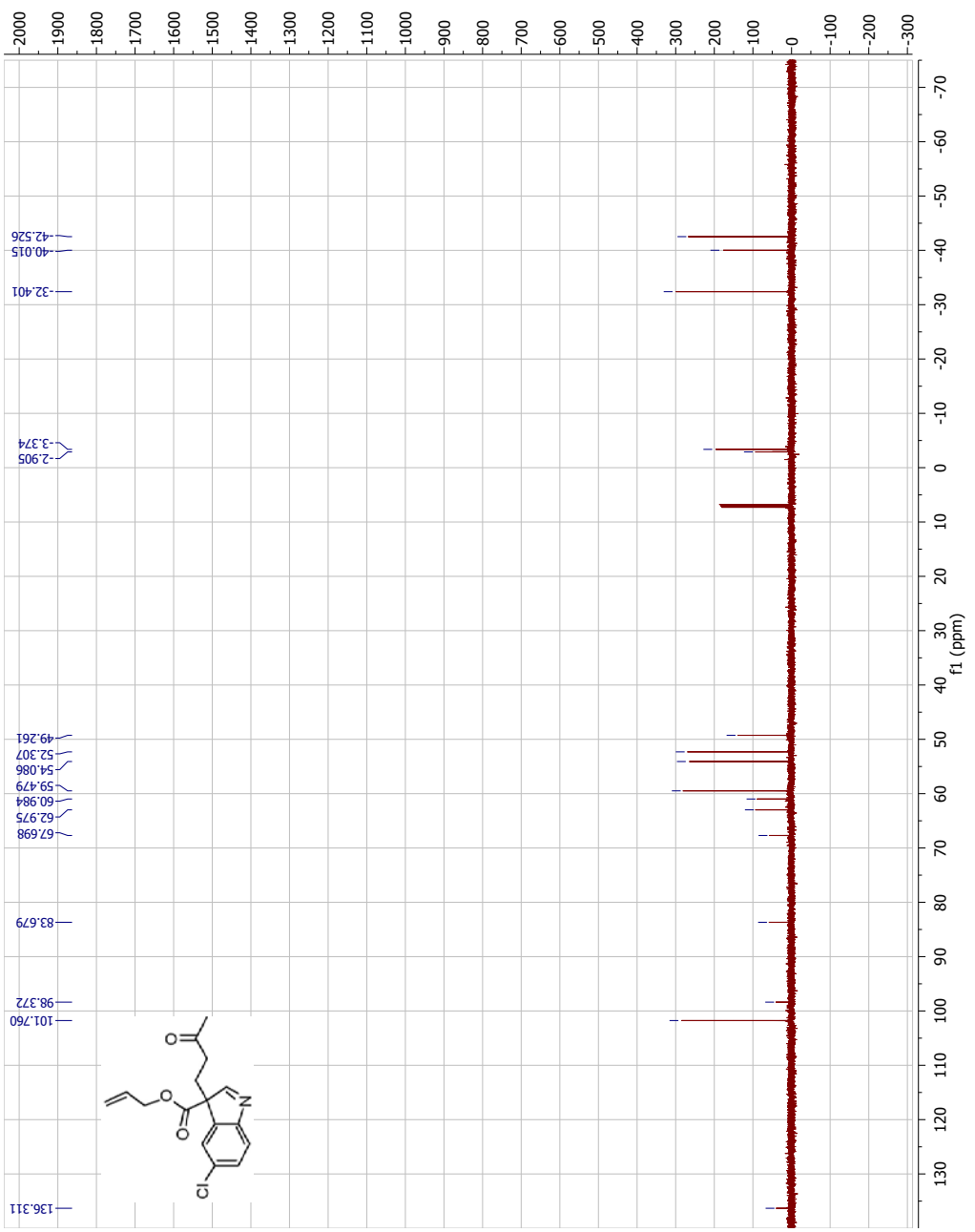

f1 (ppm)

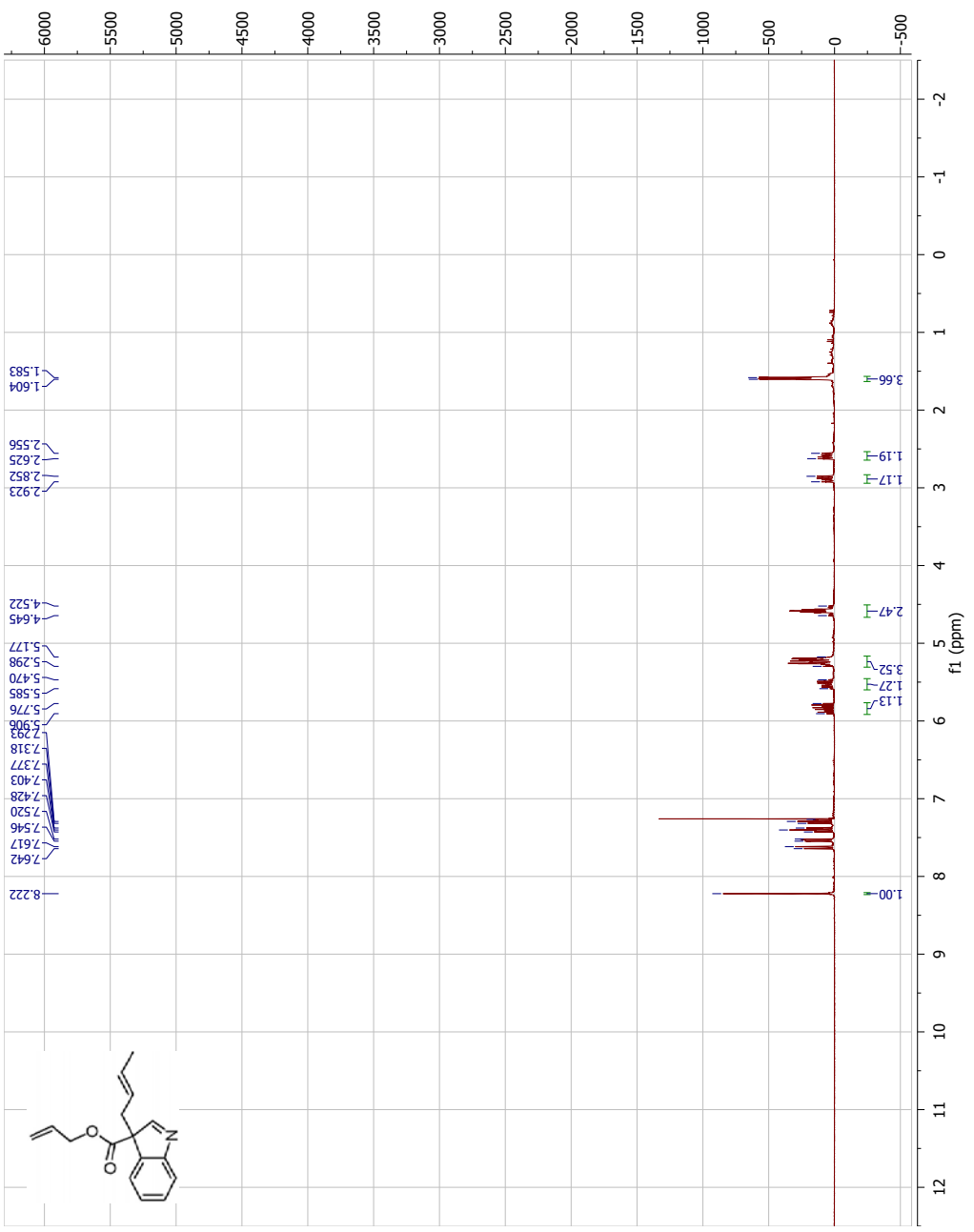

206.656
169.161
169.037
159.072
148.702
137.551
131.141
121.770
118.840
114.164
109.589
66.734
66.270
55.728
37.512
29.937
27.497
f1 (ppm)

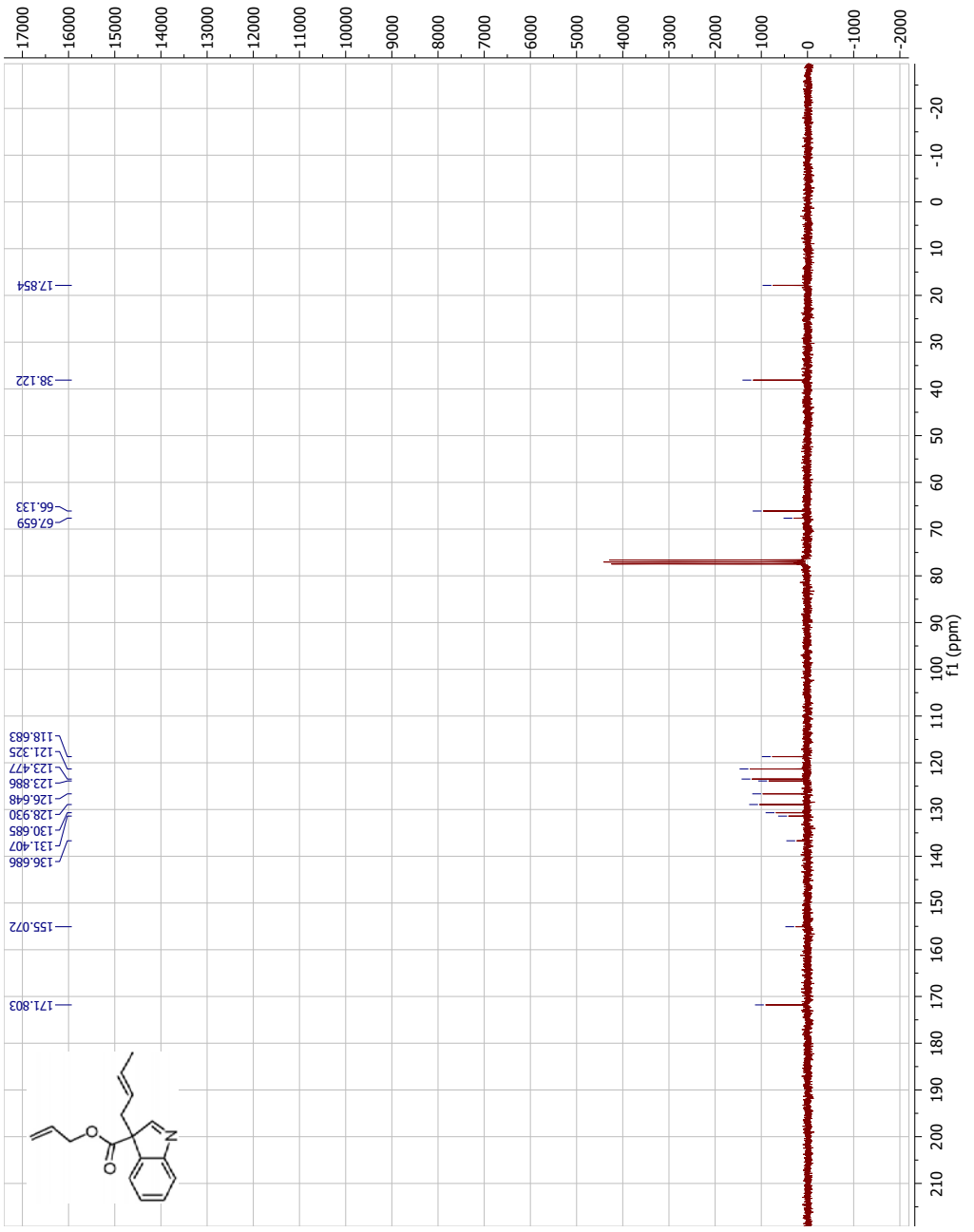

8.032
7.554
7.471
7.455
7.170
7.154
5.817
5.739
5.184
5.139
4.571
4.479
2.555
2.497
2.390
2.361
2.332
2.122
1.975
1.929
1.00
1.05
1.08
1.04
2.55
2.48
1.16
4.65
2.58
3.25
f1 (ppm)

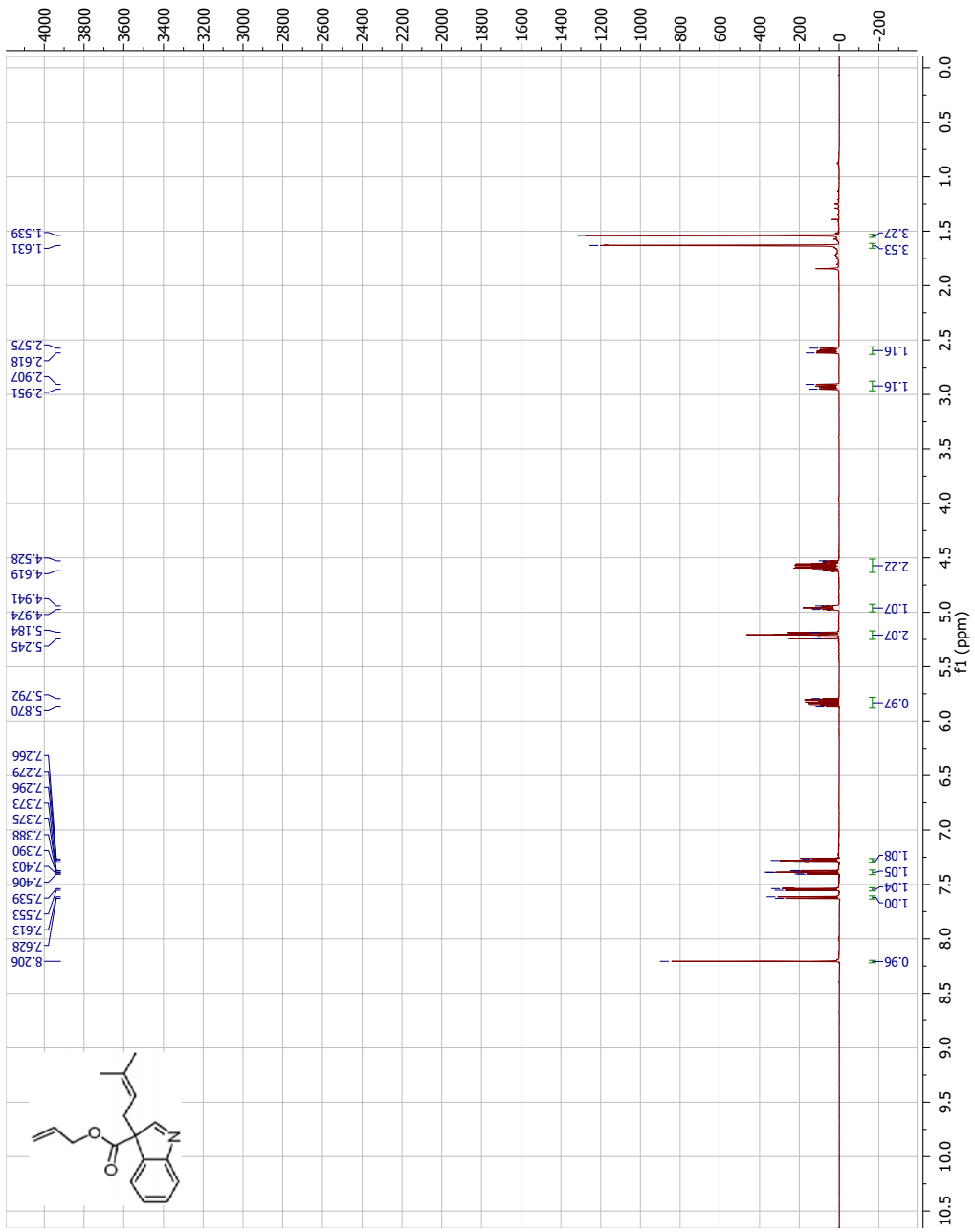

206.581
170.283
169.020
152.832
136.907
135.899
131.071
129.653
123.925
120.759
118.583
66.323
66.073
37.480
29.787
27.229
21.346
f1 (ppm)

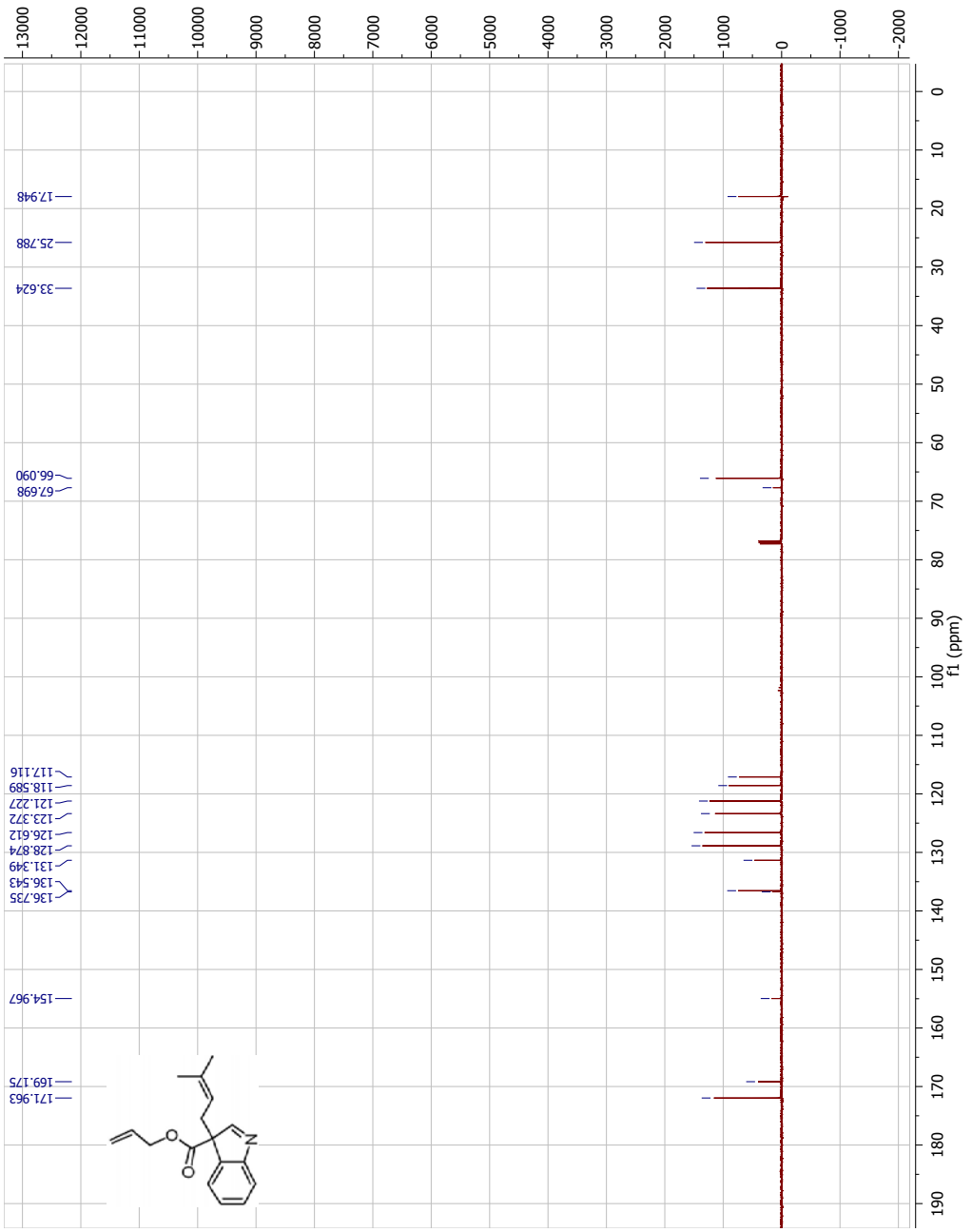

f1 (ppm)
8.134
7.566
7.550
7.493
7.489
7.401
7.397
7.385
7.377
5.874
5.796
5.262
5.219
4.632
4.547
2.605
2.546
2.423
2.364
2.132
2.089
2.009
3.49
2.73
1.46
1.28
2.99
2.43
1.17
1.08
1.04
1.07
1.00
O
O
O
N
Cl


-42.526
-40.015
-32.401
-3.374
-2.905
49.261
52.307
54.086
59.479
60.984
62.975
67.698
83.679
98.372
101.760
136.311
f1 (ppm)

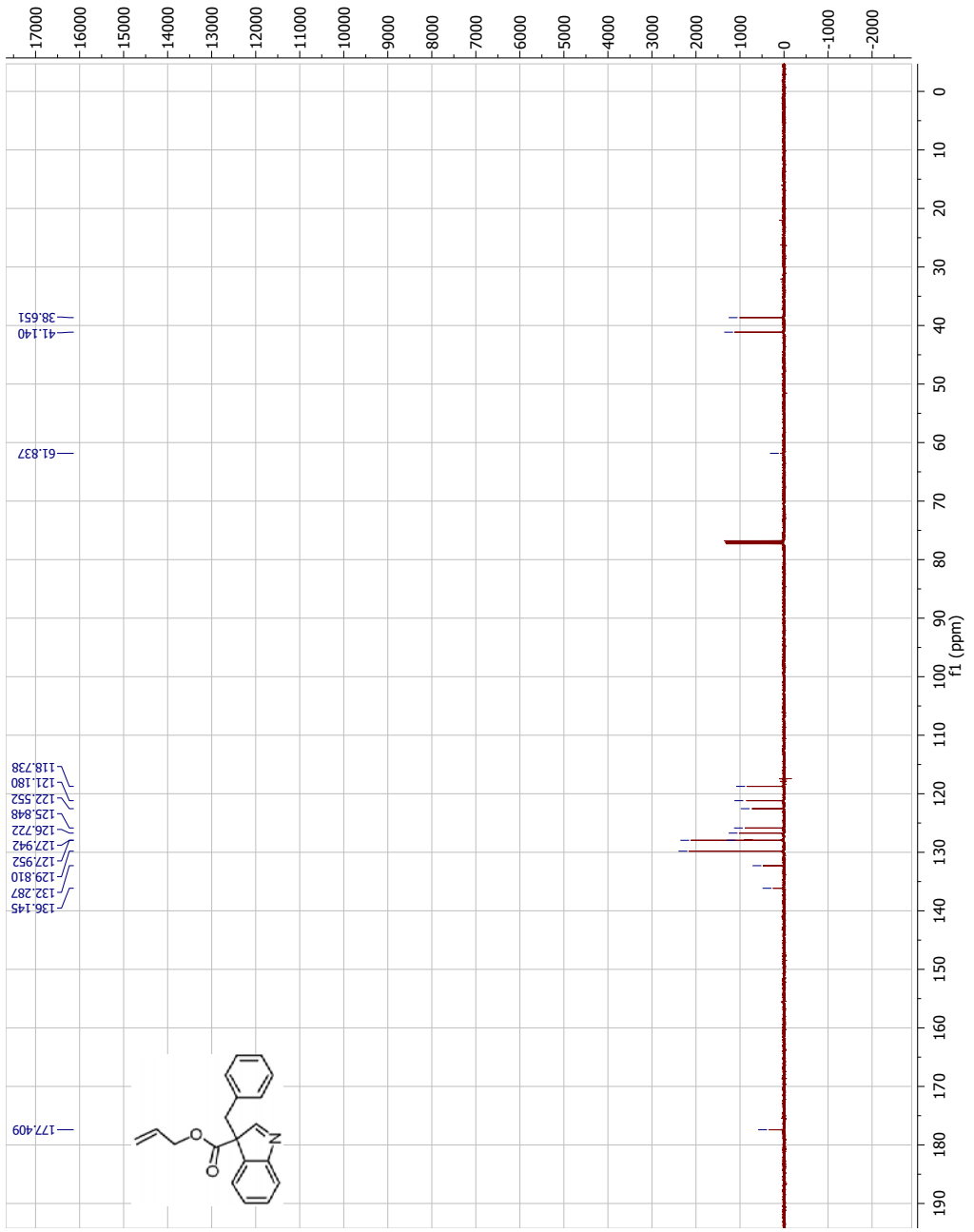

8.222
7.642
7.617
7.546
7.520
7.428
7.403
7.377
7.318
7.293
5.906
5.776
5.585
5.470
5.298
5.177
4.645
4.522
2.923
2.852
2.625
2.556
1.604
1.583
1.00
2.47
3.52
1.27
1.13
1.19
1.17
3.66
f1 (ppm)

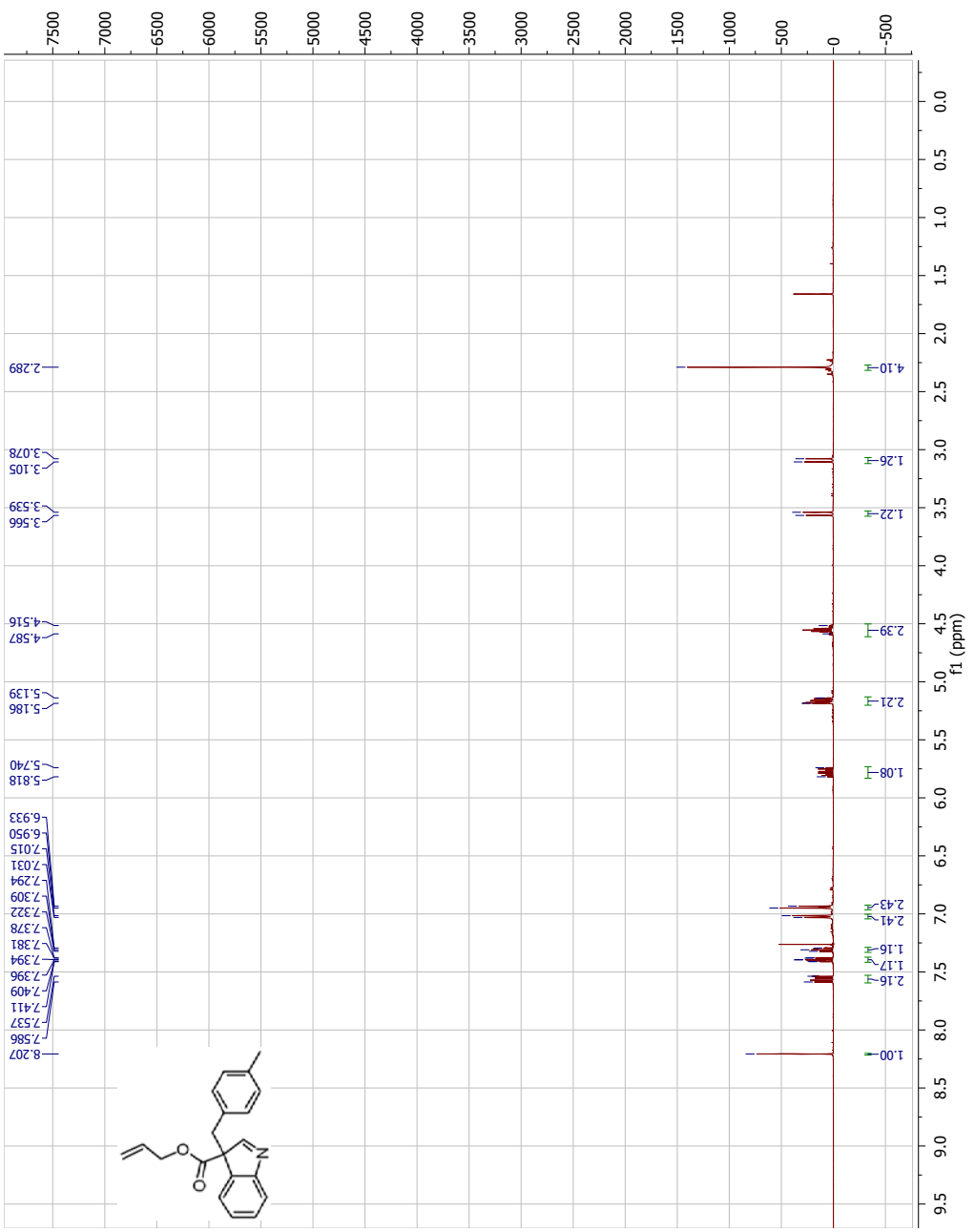

17.854
38.122
66.133
67.659
118.683
121.325
123.477
123.886
126.648
128.930
130.685
131.407
136.686
155.072
171.803
f1 (ppm)

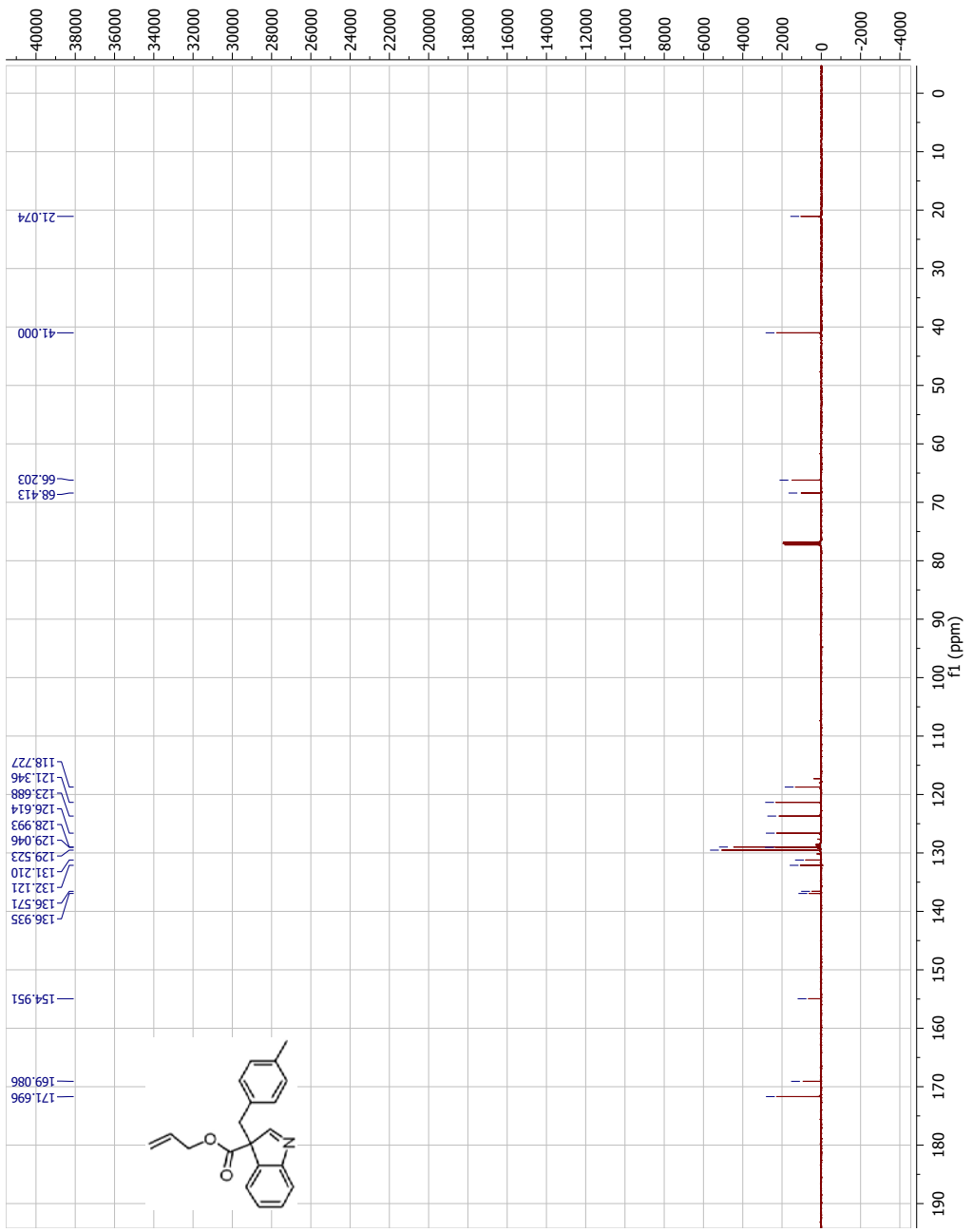

f1 (ppm)

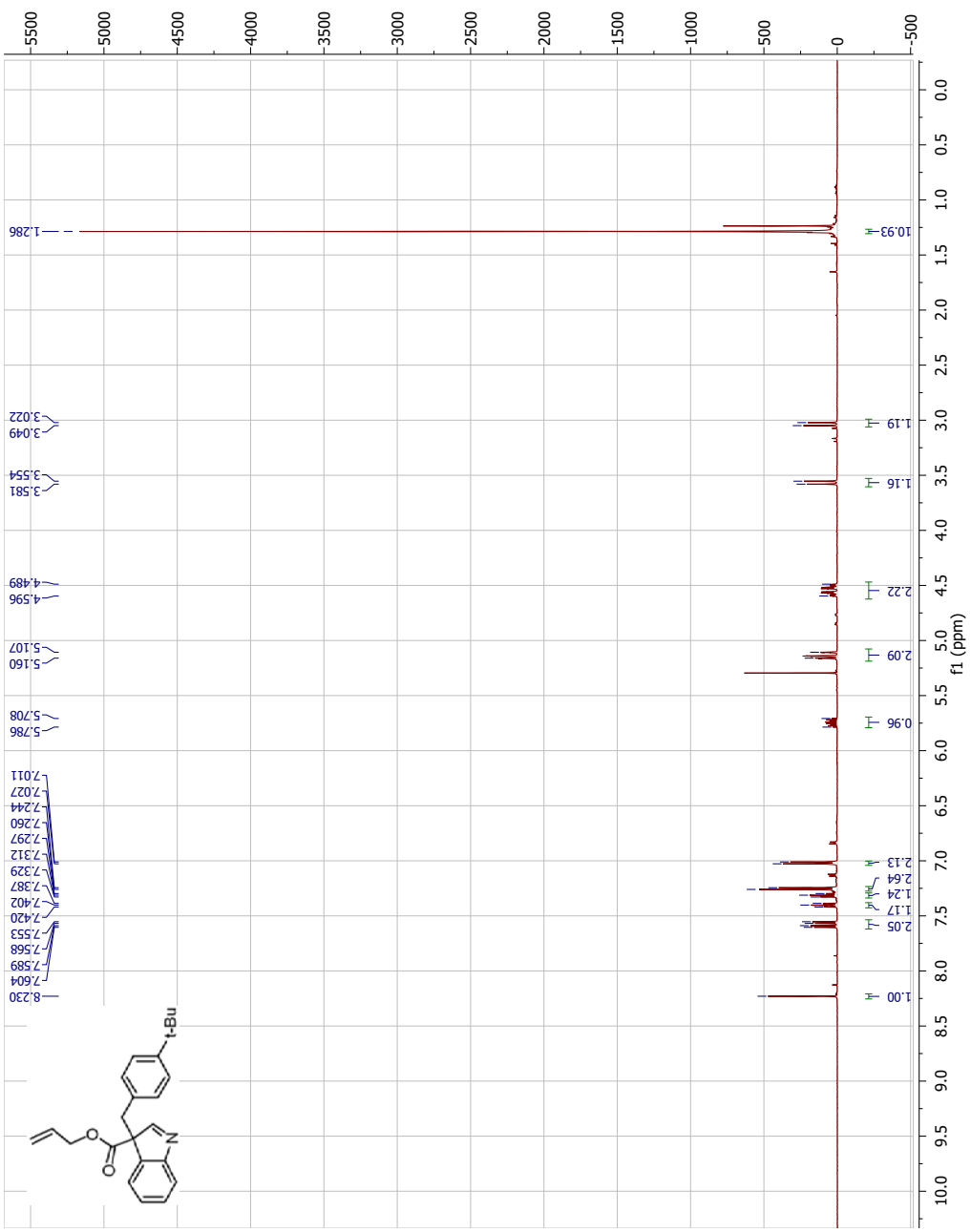

17.948
25.788
33.624
66.090
67.698
117.116
118.589
121.227
123.372
126.612
128.874
131.349
136.543
136.735
154.967
169.175
171.963
f1 (ppm)

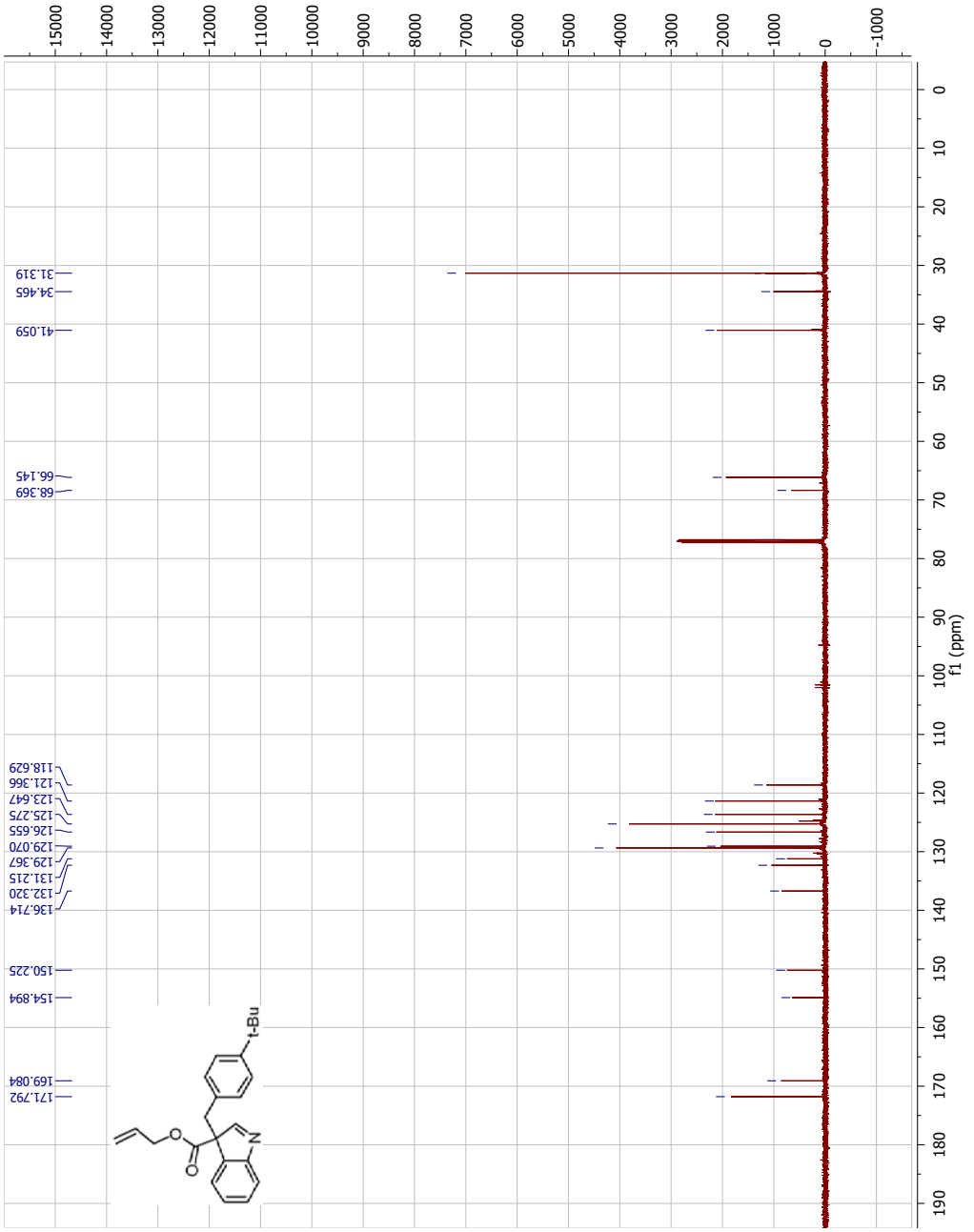

8.075
7.531
7.516
7.331
7.298
7.277
7.236
7.168
7.138
5.428
5.344
5.005
4.916
3.131
3.104
3.042
3.015
2.649
2.571
2.97
2.66
2.26
1.12
1.12
2.16
1.06
1.04
1.00
1.02
f1 (ppm)

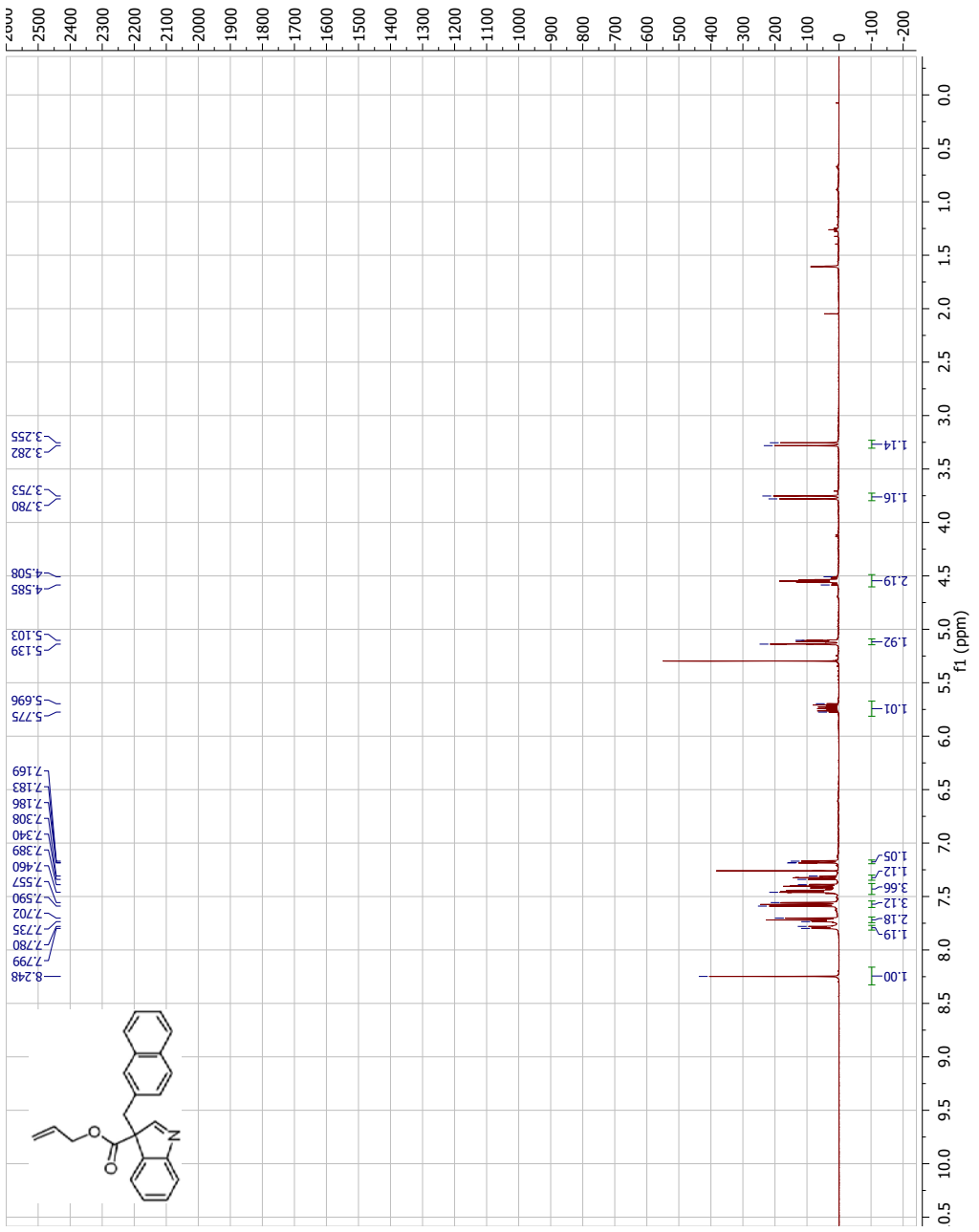

17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-2000
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)
38.651
41.140
61.837
118.738
121.180
122.552
125.848
126.722
127.942
127.952
129.810
132.287
136.145
177.409

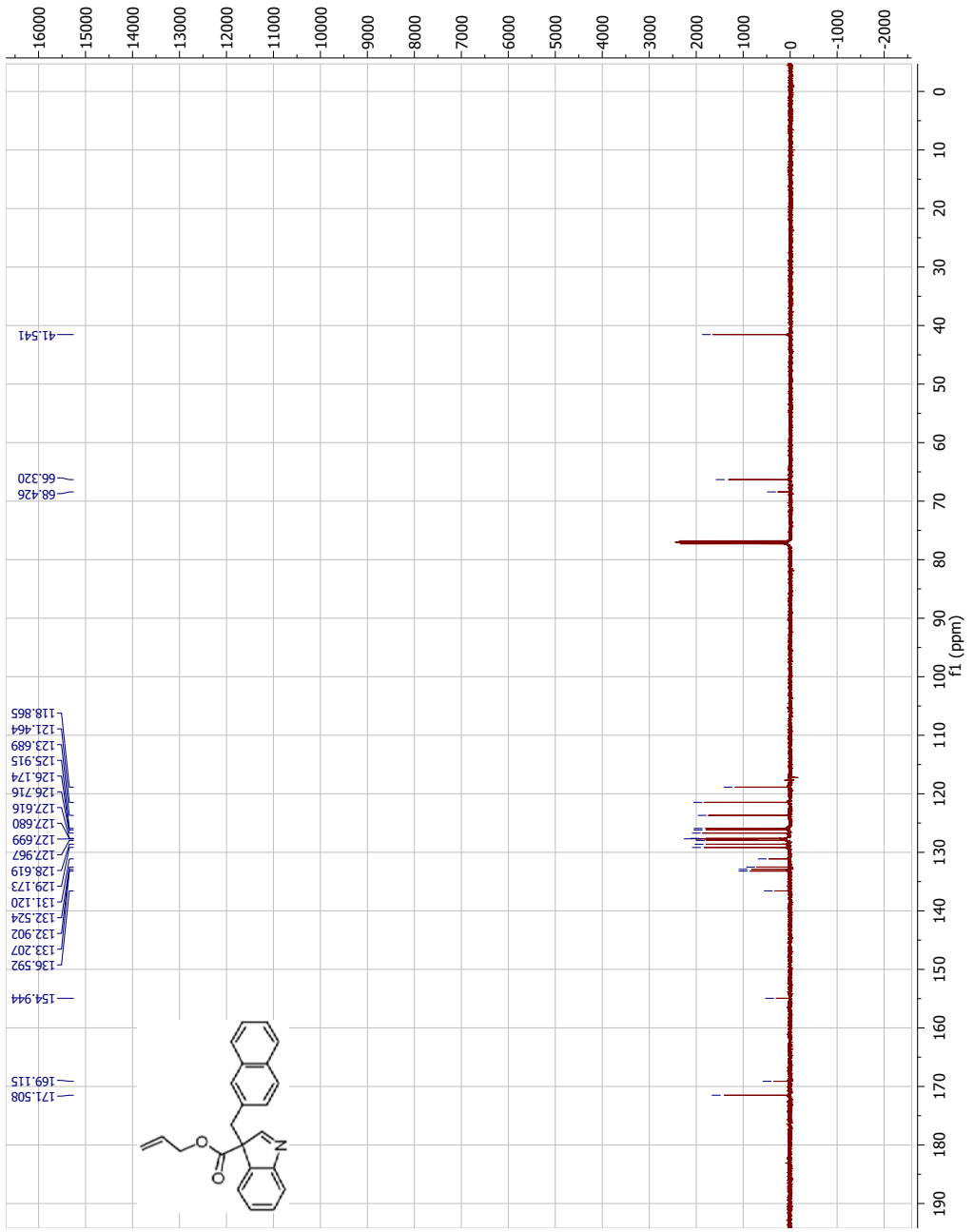

f1 (ppm)
8.207
7.586
7.537
7.411
7.409
7.396
7.394
7.381
7.378
7.322
7.309
7.294
7.031
7.015
6.950
6.933
5.818
5.740
5.186
5.139
4.587
4.516
3.566
3.539
3.105
3.078
2.289
1.00
2.16
1.17
1.16
2.41
2.43
1.08
2.21
2.39
1.22
1.26
4.10

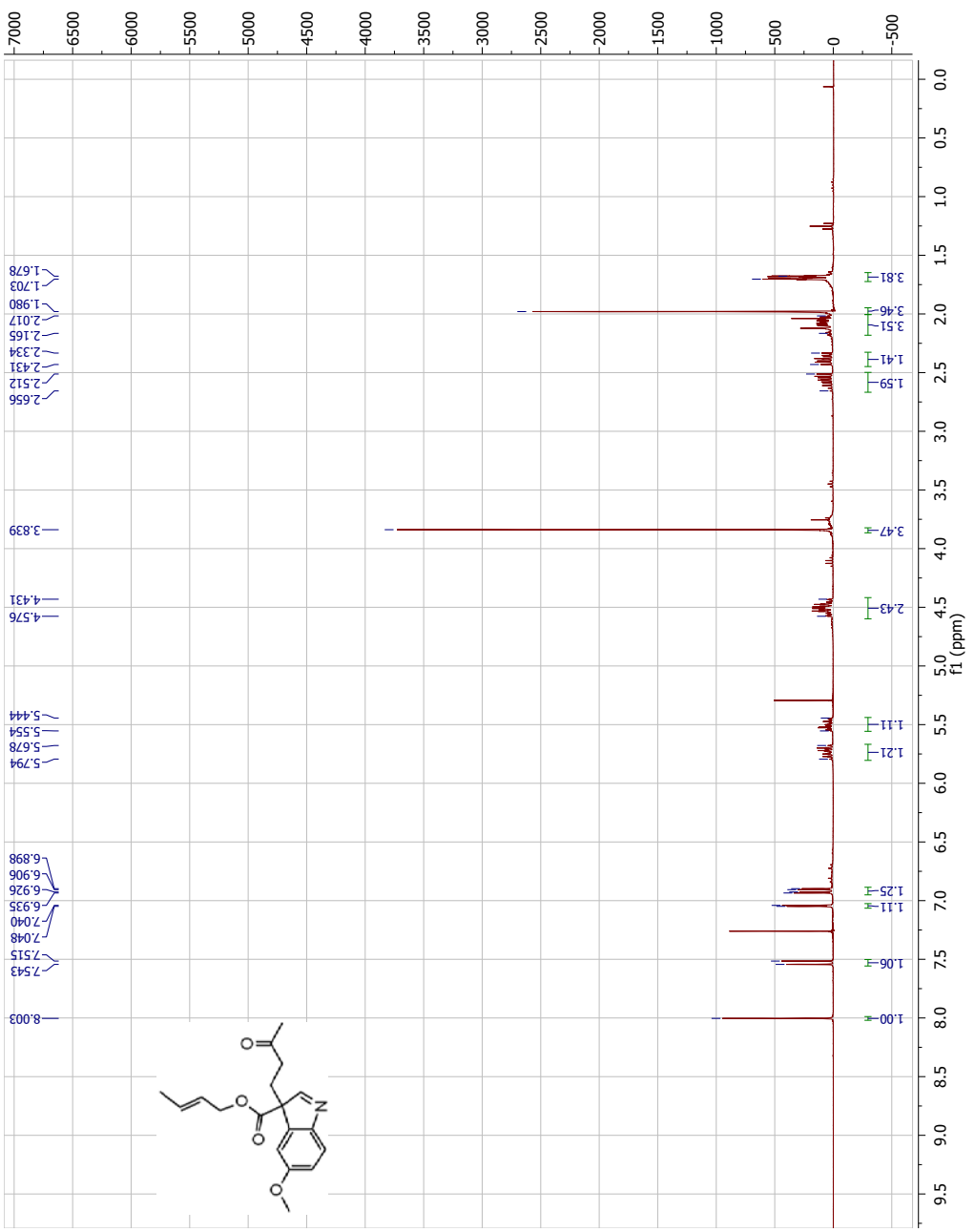

171.696
169.086
154.951
136.935
136.571
132.121
131.210
129.523
129.046
128.993
126.614
123.688
121.346
118.727
68.413
66.203
41.000
21.074
f1 (ppm)

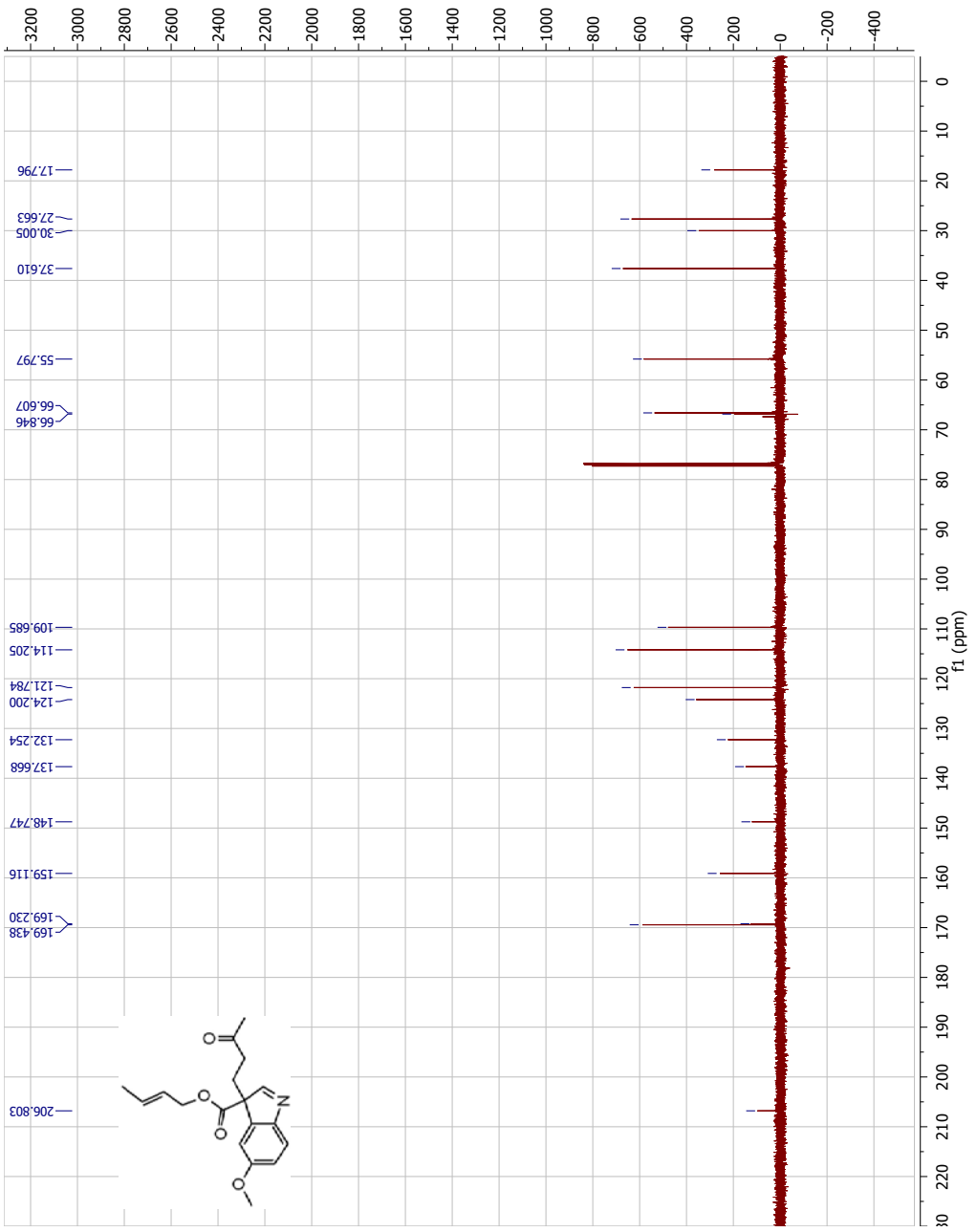

1.286
3.022
3.049
3.554
3.581
4.489
4.596
5.107
5.160
5.708
5.786
7.011
7.027
7.244
7.260
7.297
7.312
7.329
7.387
7.402
7.420
7.553
7.568
7.589
7.604
8.230
10.93
1.19
1.16
2.22
2.09
0.96
2.13
2.64
1.24
1.17
2.05
1.00
t-Bu
N
O
O
f1 (ppm)

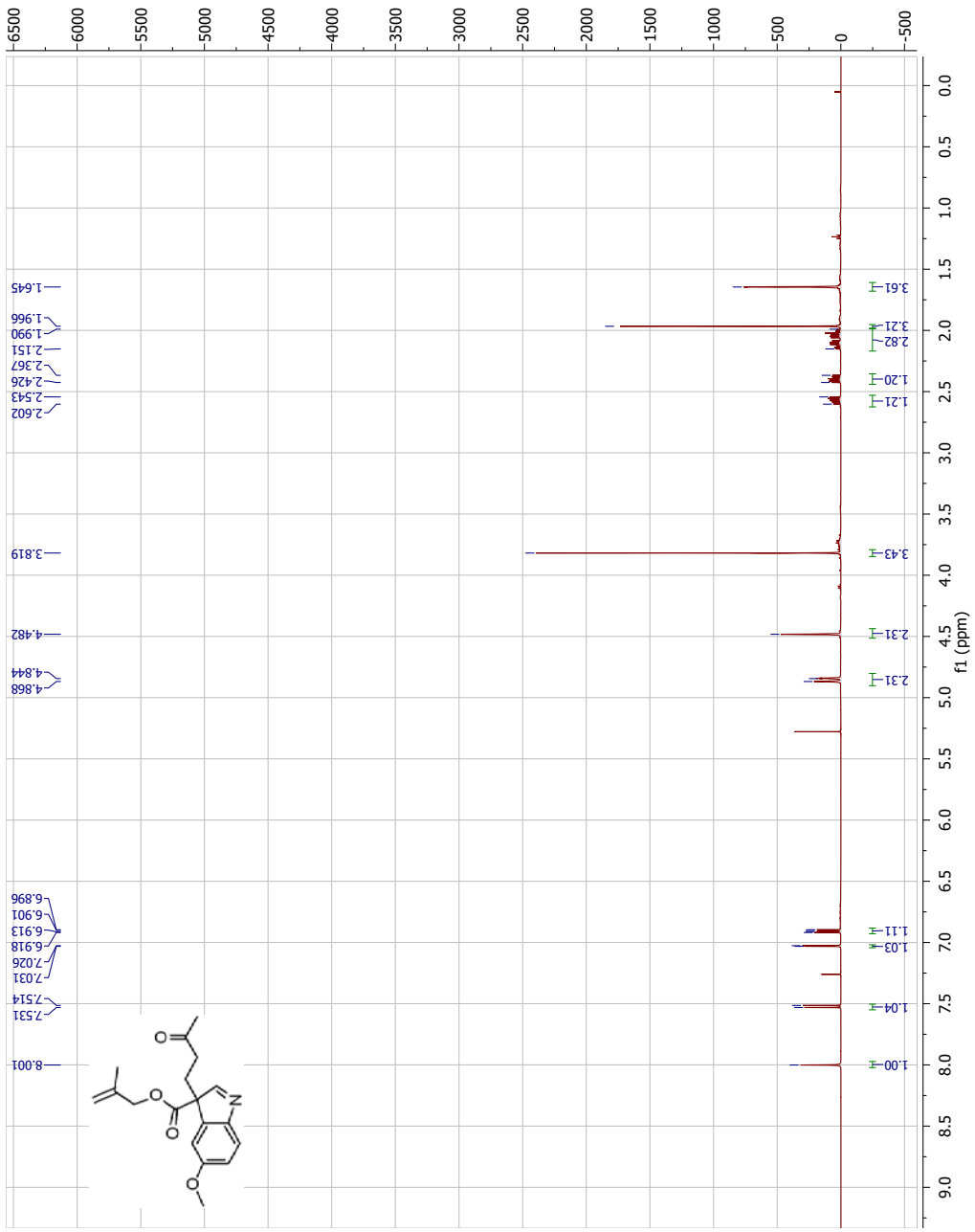

31.319
34.465
41.059
66.145
68.369
118.629
121.366
123.647
125.275
126.655
129.070
129.367
131.215
132.320
136.714
150.225
154.894
169.084
171.792
t-Bu
f1 (ppm)

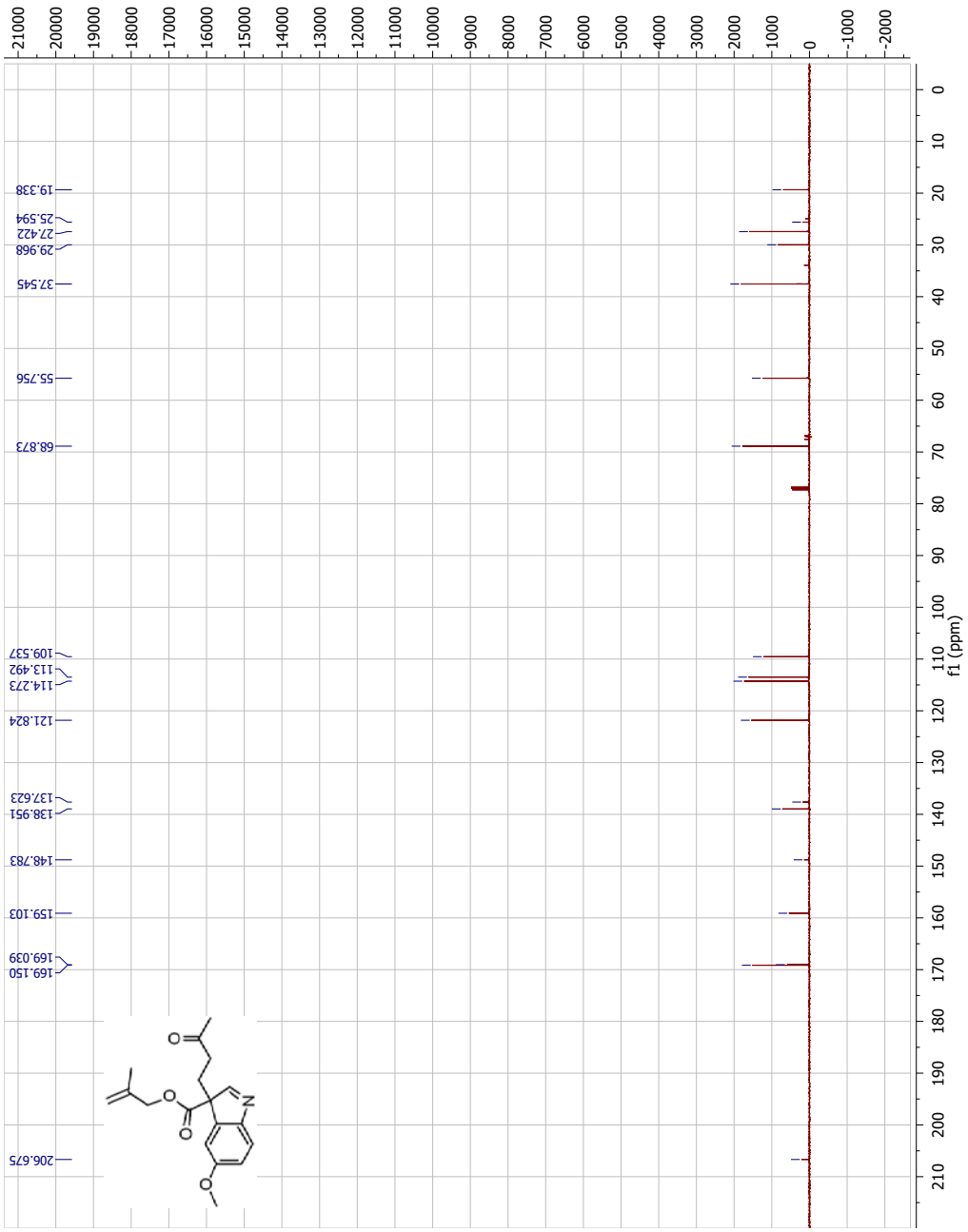

f1 (ppm)

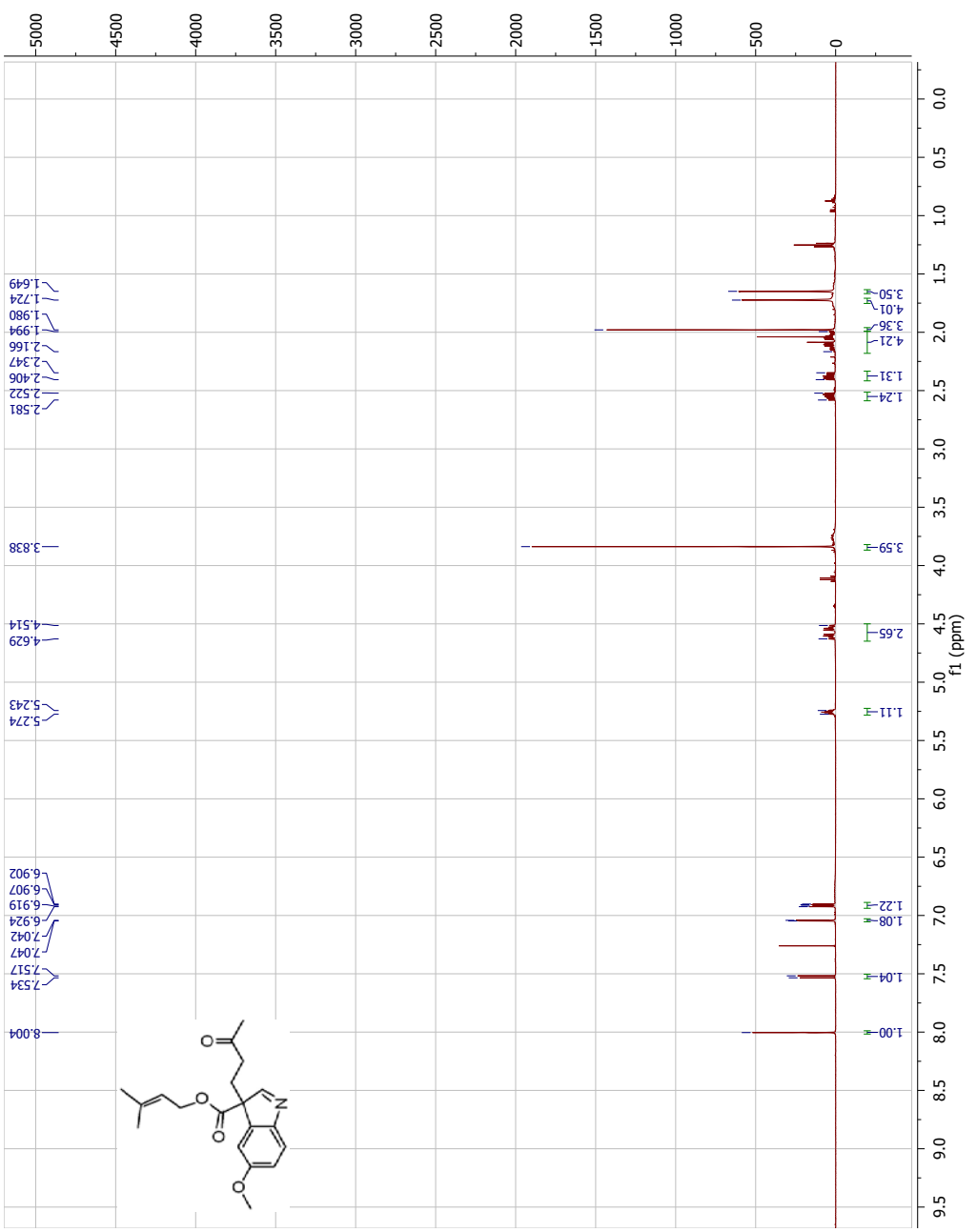

171.508
169.115
154.944
136.592
133.207
132.902
132.524
131.120
129.173
128.619
127.967
127.699
127.680
127.616
126.716
126.174
125.915
123.689
121.464
118.865
68.426
66.320
41.541
f1 (ppm)

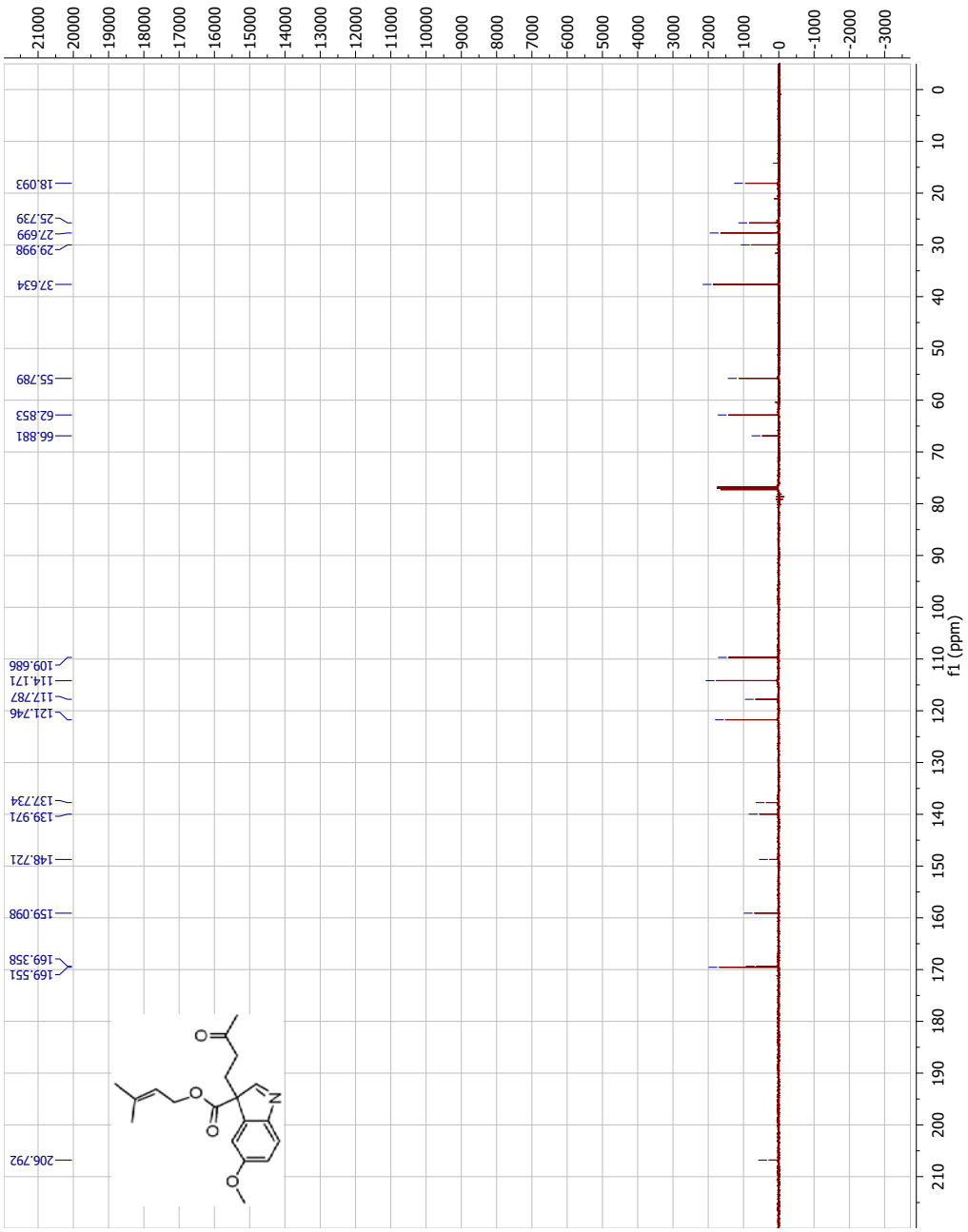

8.003
7.543
7.515
7.048
7.040
6.935
6.926
6.906
6.898
5.794
5.678
5.554
5.444
4.576
4.431
3.839
2.656
2.512
2.431
2.334
2.165
2.017
1.980
1.703
1.678
1.00
1.06
1.11
1.25
2.43
1.21
1.11
3.47
1.59
1.41
3.51
3.46
3.81
f1 (ppm)

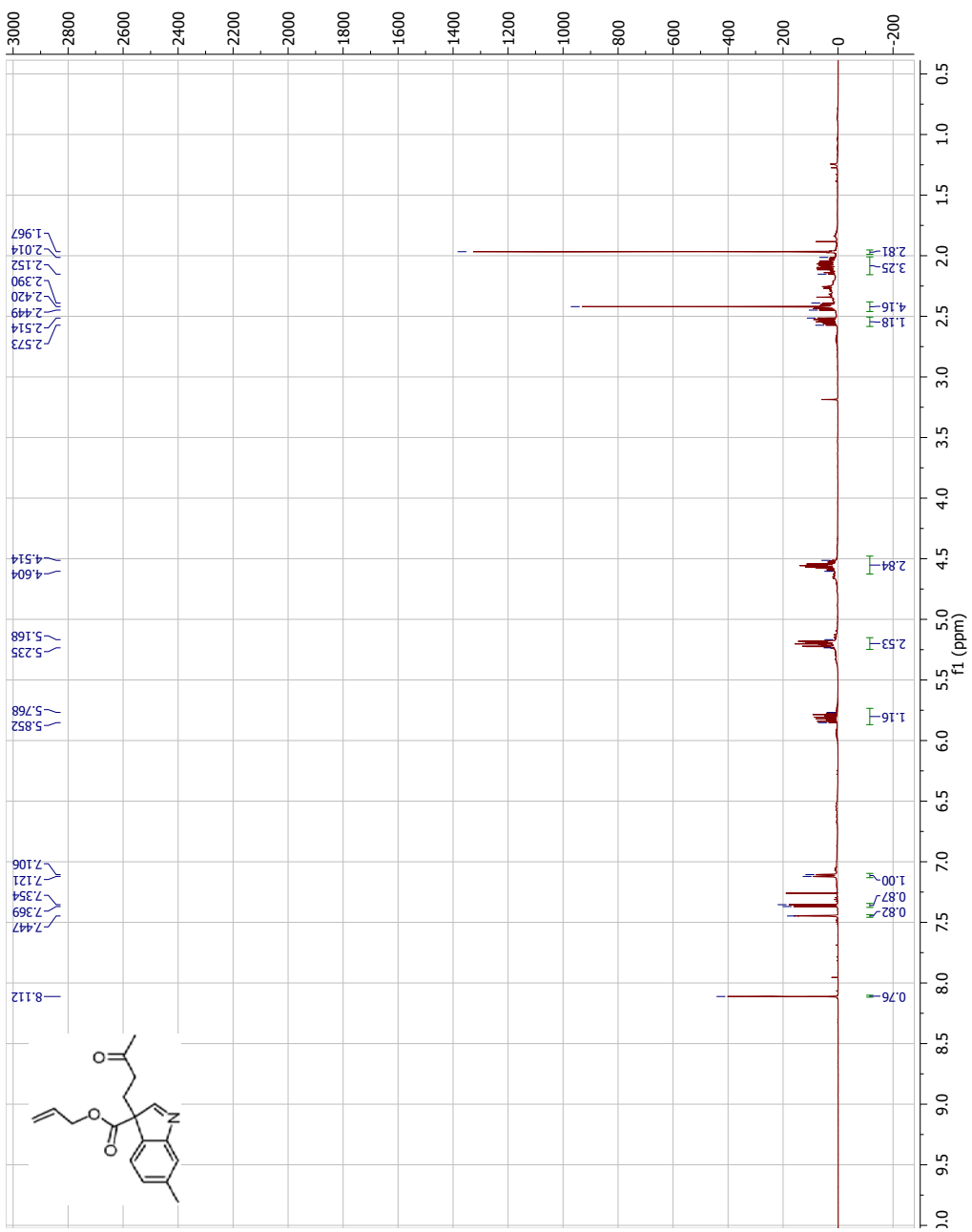

17.796
27.663
30.005
37.610
55.797
66.607
66.846
109.685
114.205
121.784
124.200
132.254
137.668
148.747
159.116
169.230
169.438
206.803
f1 (ppm)

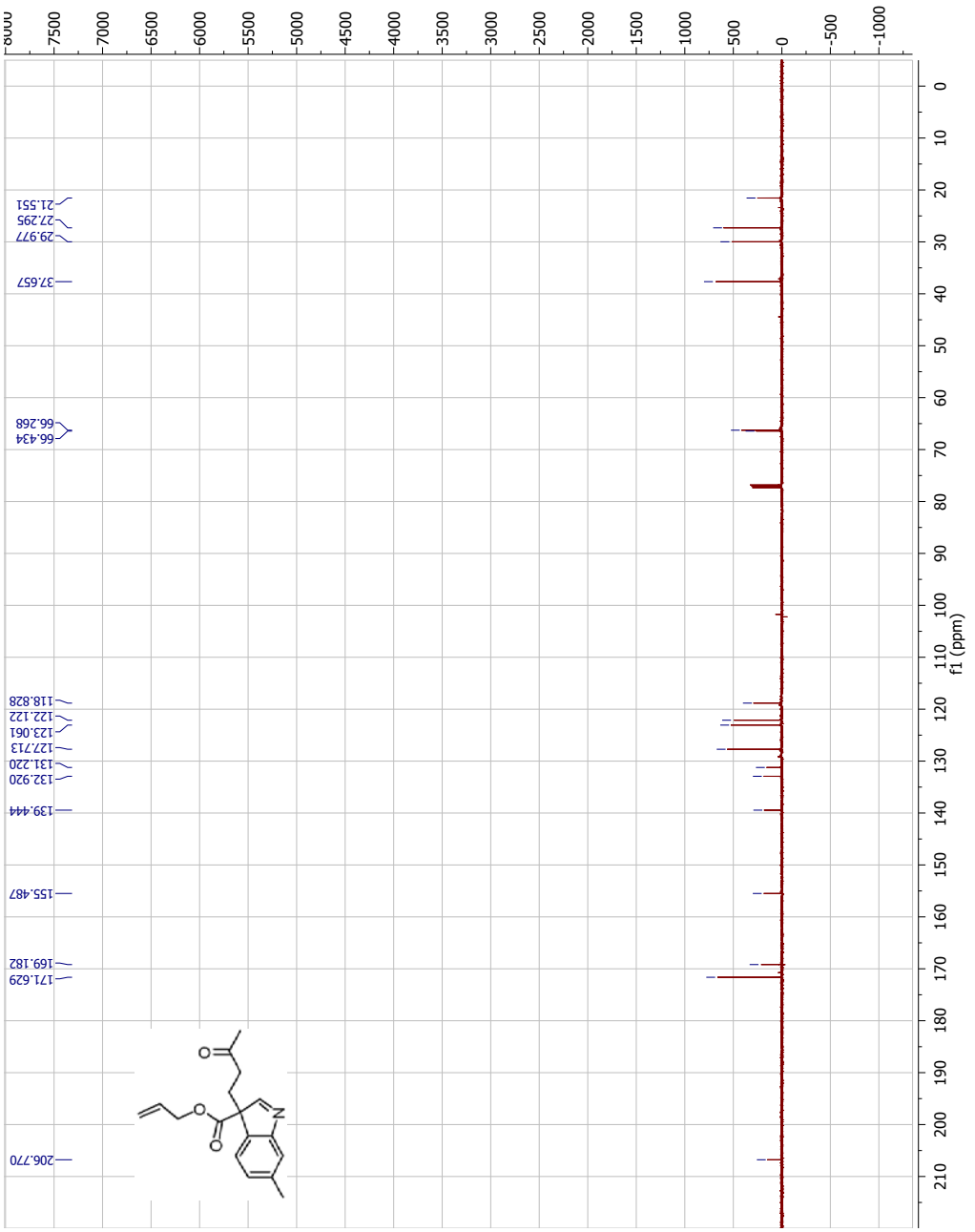

8.001
7.531
7.514
7.031
7.026
6.918
6.913
6.901
6.896
4.868
4.844
4.482
3.819
2.602
2.543
2.426
2.367
2.151
1.990
1.966
1.645
3.61
3.21
2.82
1.20
1.21
3.43
2.31
2.31
1.11
1.03
1.04
1.00
f1 (ppm)

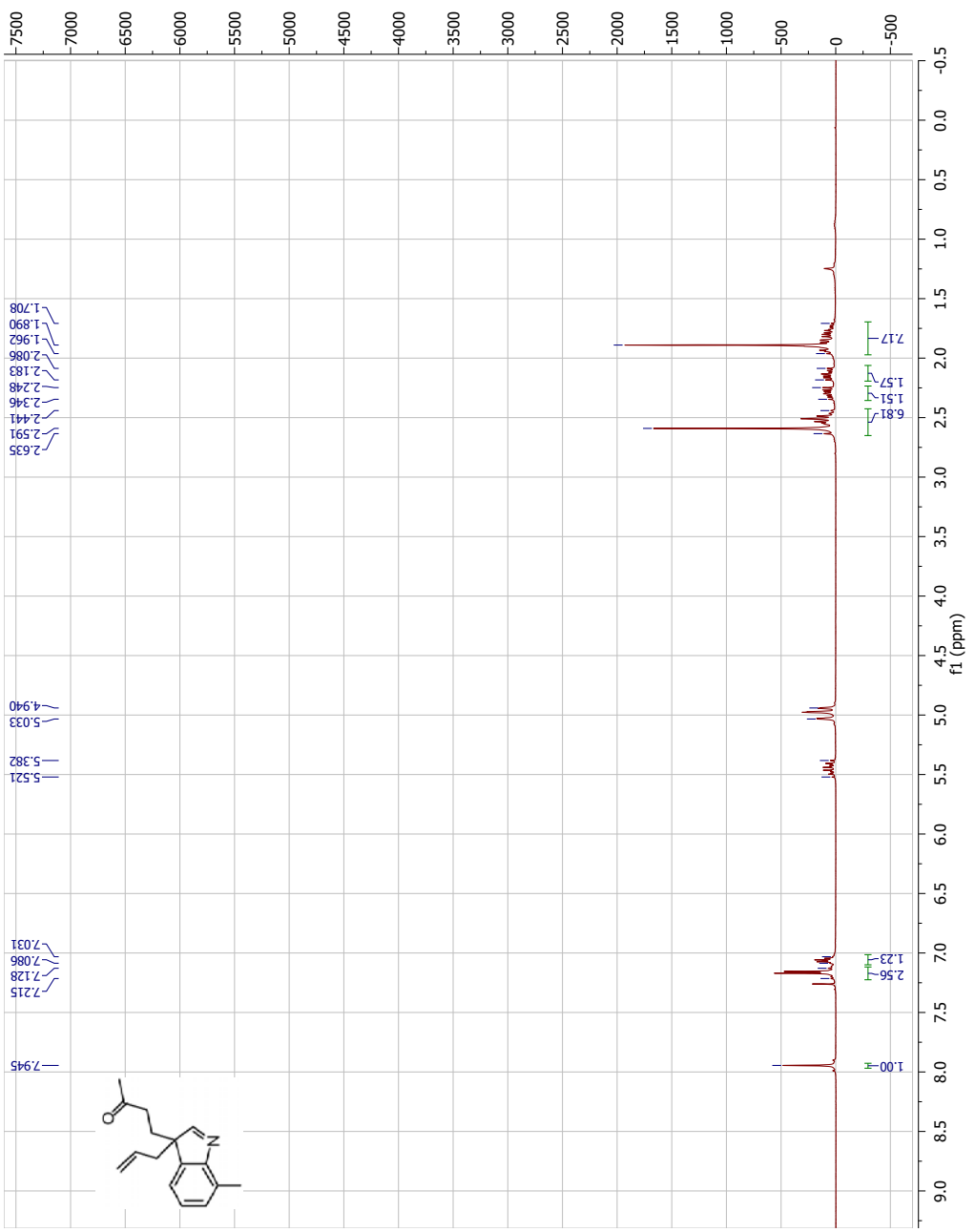

206.675
169.150
169.039
159.103
148.783
138.951
137.623
121.824
114.273
113.492
109.537
68.873
55.756
37.545
29.968
27.422
25.594
19.338
f1 (ppm)

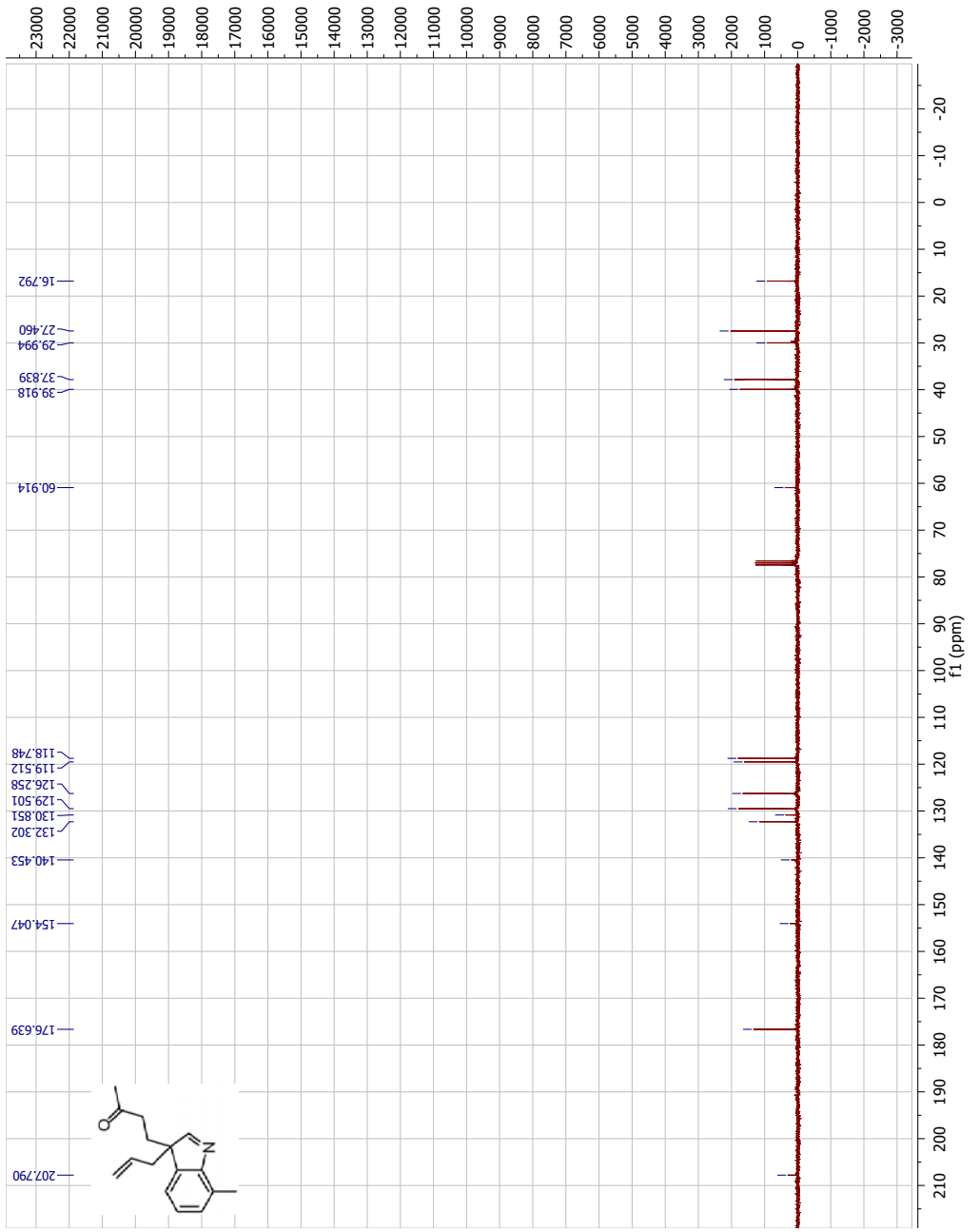

8.004
7.534
7.517
7.047
7.042
6.924
6.919
6.907
6.902
5.274
5.243
4.629
4.514
3.838
2.581
2.522
2.406
2.347
2.166
1.994
1.980
1.724
1.649
1.00
1.04
1.08
1.22
1.11
3.59
2.65
1.24
1.31
4.21
3.36
4.01
3.50
f1 (ppm)

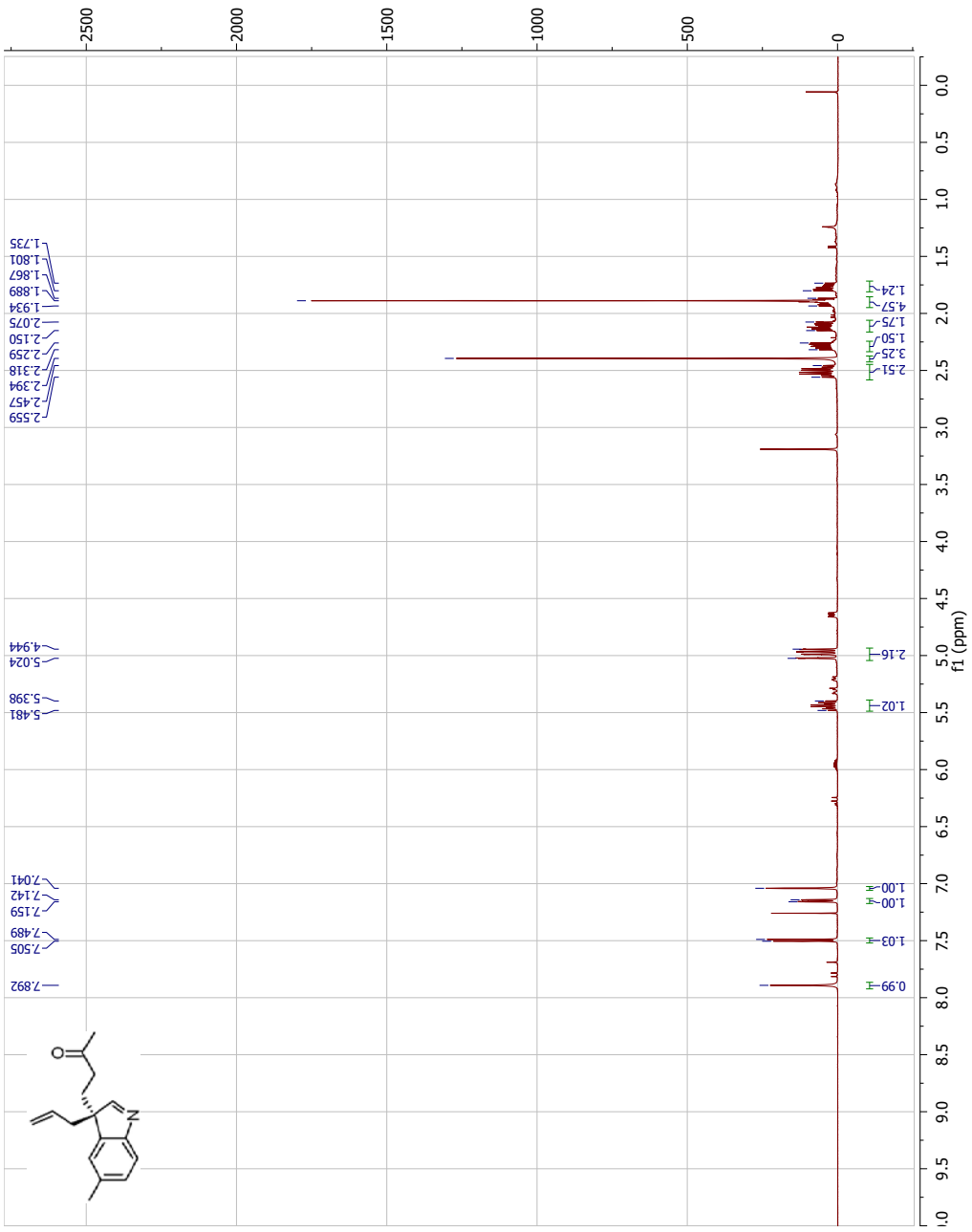

206.792
169.551
169.358
159.098
148.721
139.971
137.734
121.746
117.787
114.171
109.686
66.881
62.853
55.789
37.634
29.998
27.699
25.739
18.093
f1 (ppm)

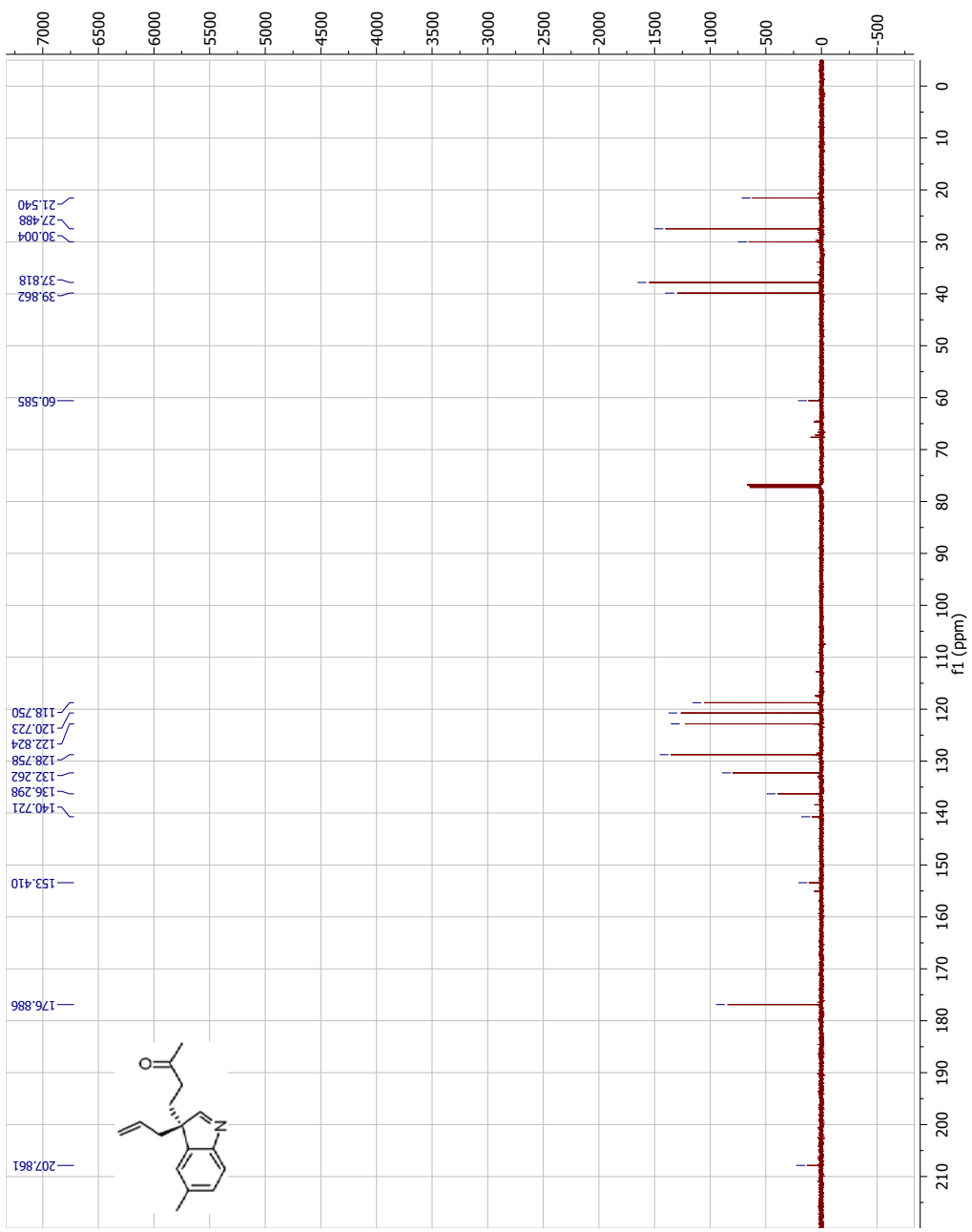

8.112
7.447
7.369
7.354
7.121
7.106
5.852
5.768
5.235
5.168
4.604
4.514
2.573
2.514
2.449
2.420
2.390
2.152
2.014
1.967
0.76
1.00
0.87
0.82
1.16
2.53
2.84
4.16
1.18
2.81
3.25
f1 (ppm)

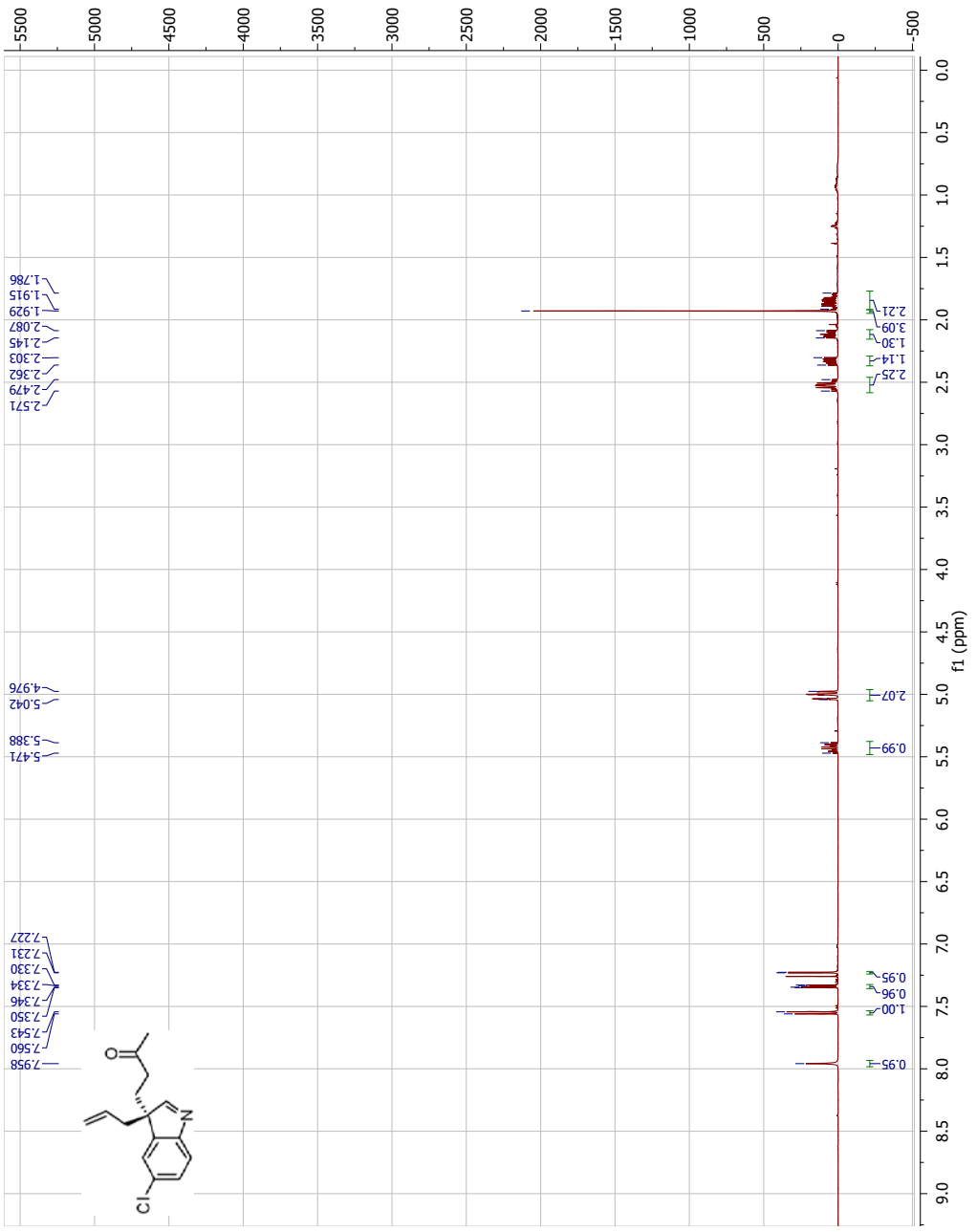

206.770
171.629
169.182
155.487
139.444
132.920
131.220
127.713
123.061
122.122
118.828
66.434
66.268
37.657
29.977
27.295
21.551
f1 (ppm)

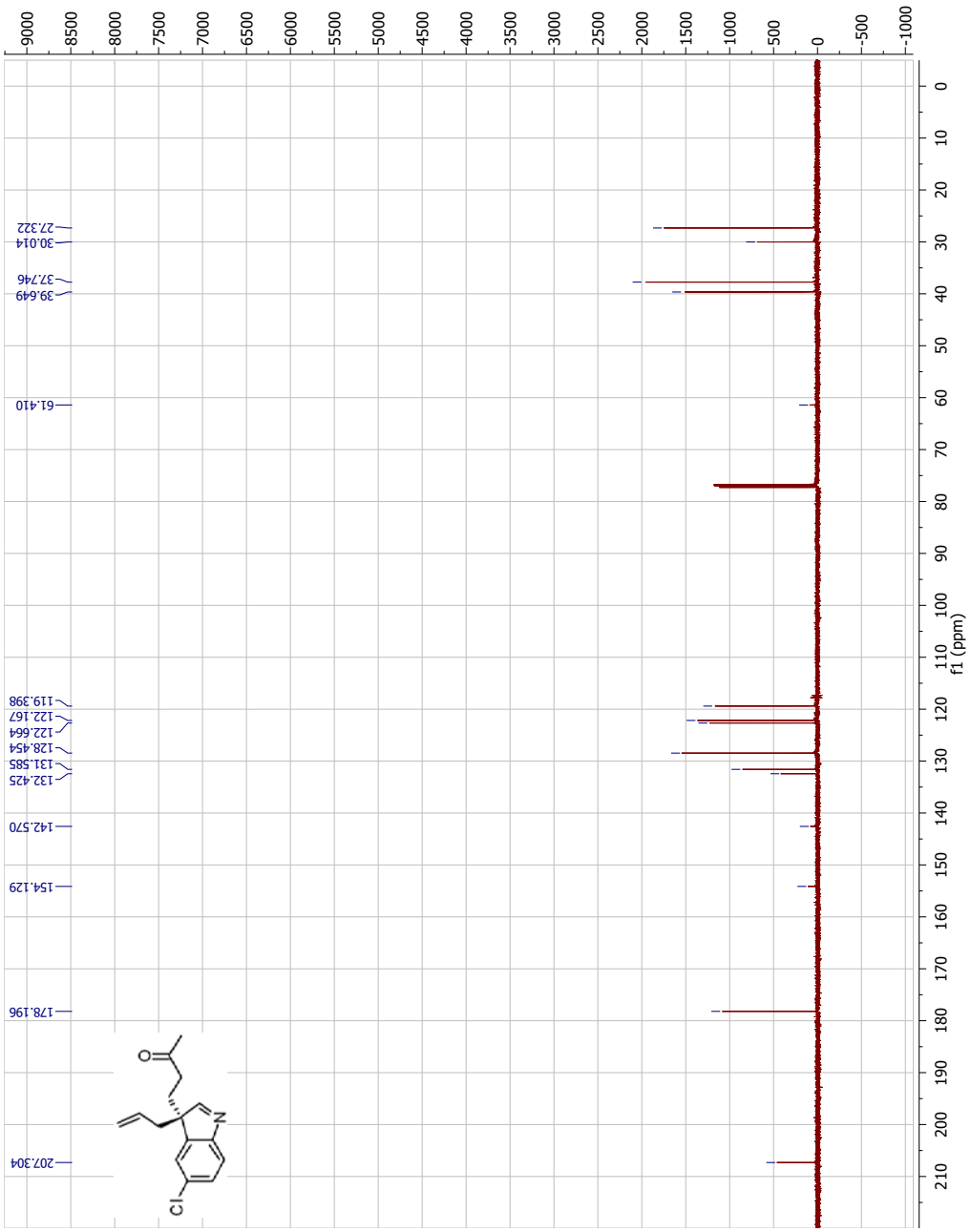

7.945
7.215
7.128
7.086
7.031
5.382
5.033
4.940
2.635
2.591
2.441
2.346
2.248
2.183
2.086
1.962
1.890
1.708
1.00
2.56
1.23
6.81
1.51
1.57
7.17
f1 (ppm)

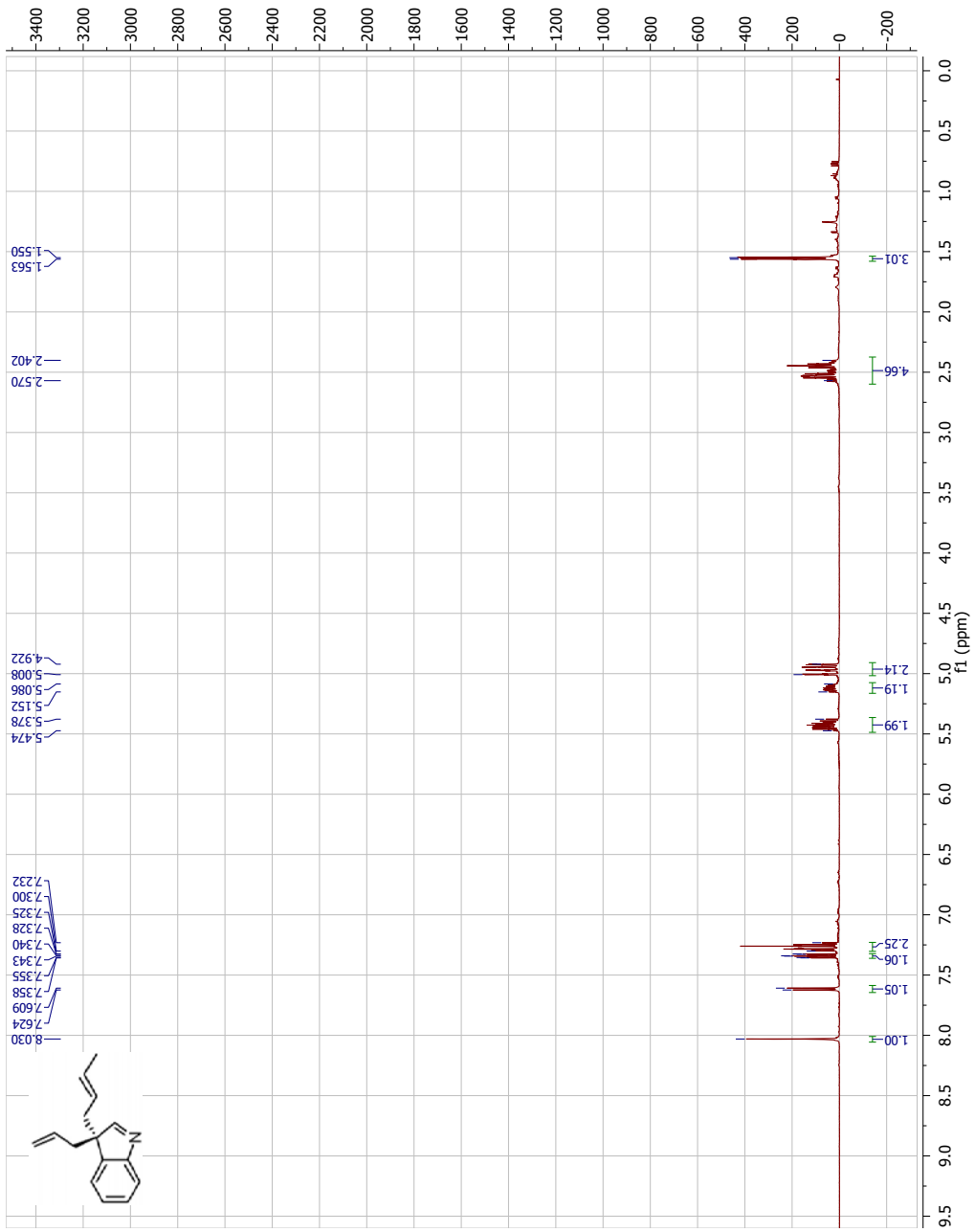

16.792
27.460
29.994
37.839
39.918
60.914
118.748
119.512
126.258
129.501
130.851
132.302
140.453
154.047
176.639
207.790
f1 (ppm)

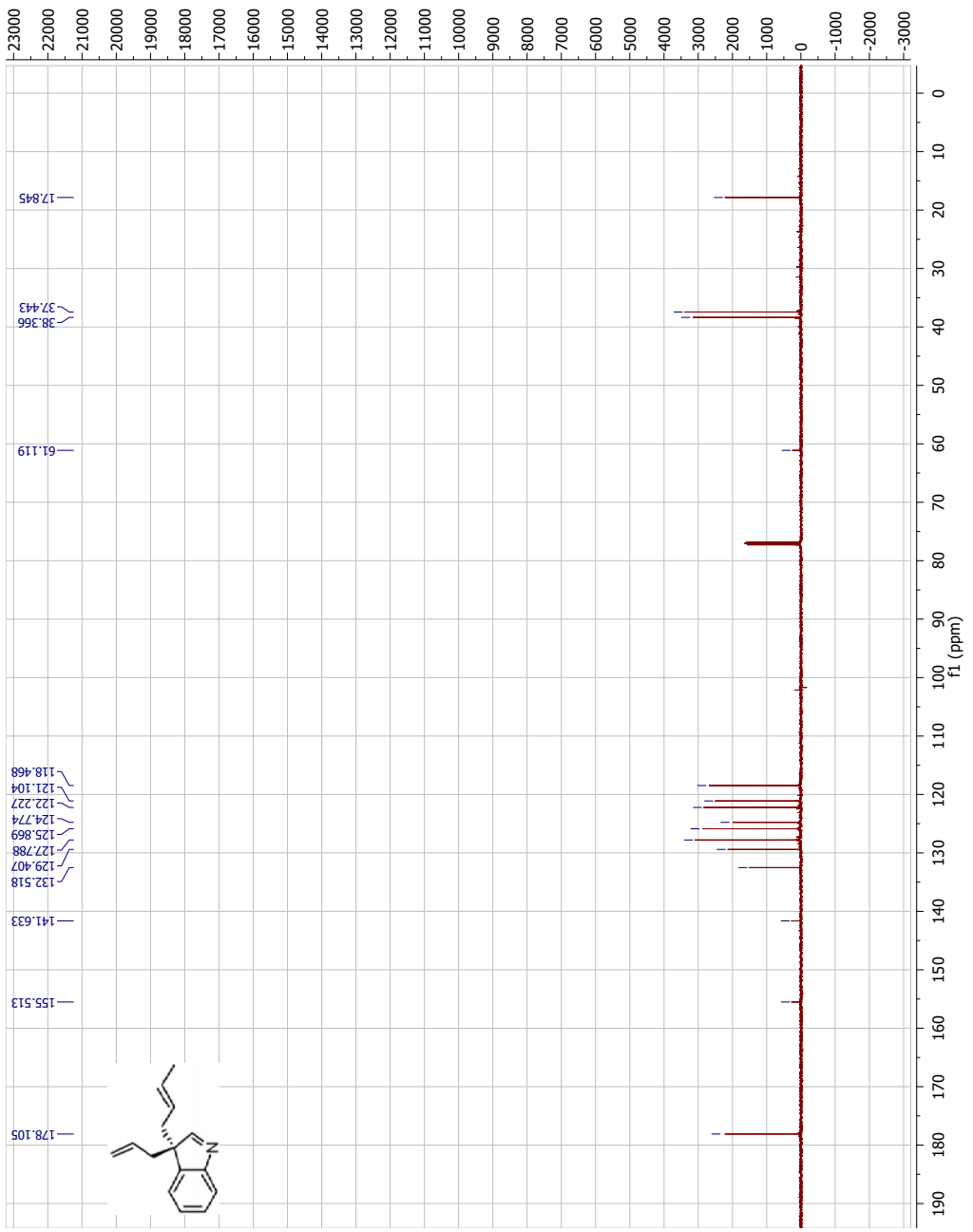

2500
2000
1500
1000
500
0
f1 (ppm)
7.892
7.505
7.489
7.159
7.142
7.041
5.481
5.398
5.024
4.944
2.559
2.457
2.394
2.318
2.259
2.150
2.075
1.934
1.889
1.867
1.801
1.735
0.99
1.03
1.00
1.00
1.02
2.16
2.51
3.25
1.50
1.75
4.57
1.24

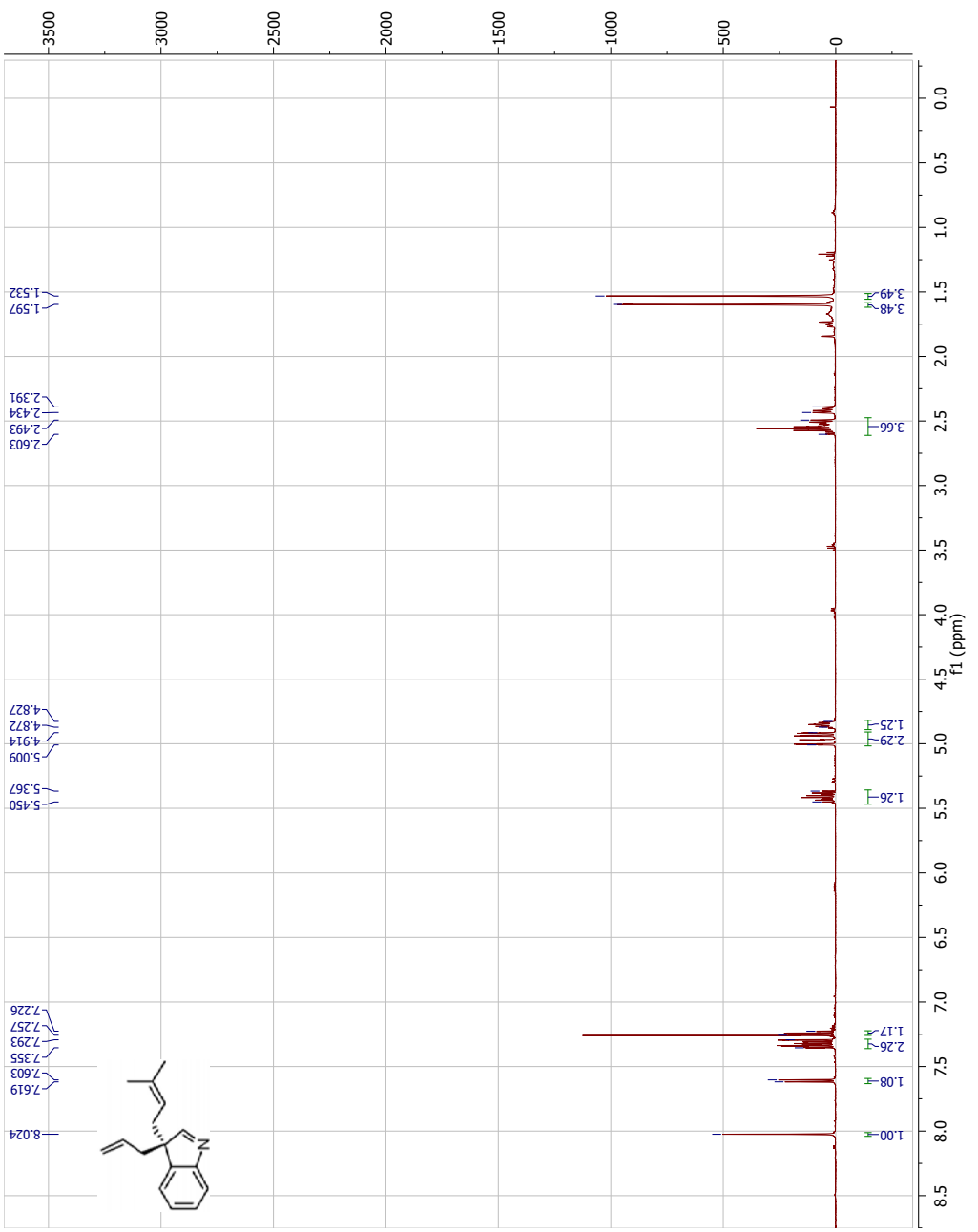

207.861
176.886
153.410
140.721
136.298
132.262
128.758
122.824
120.723
118.750
60.585
39.862
37.818
30.004
27.488
21.540
f1 (ppm)

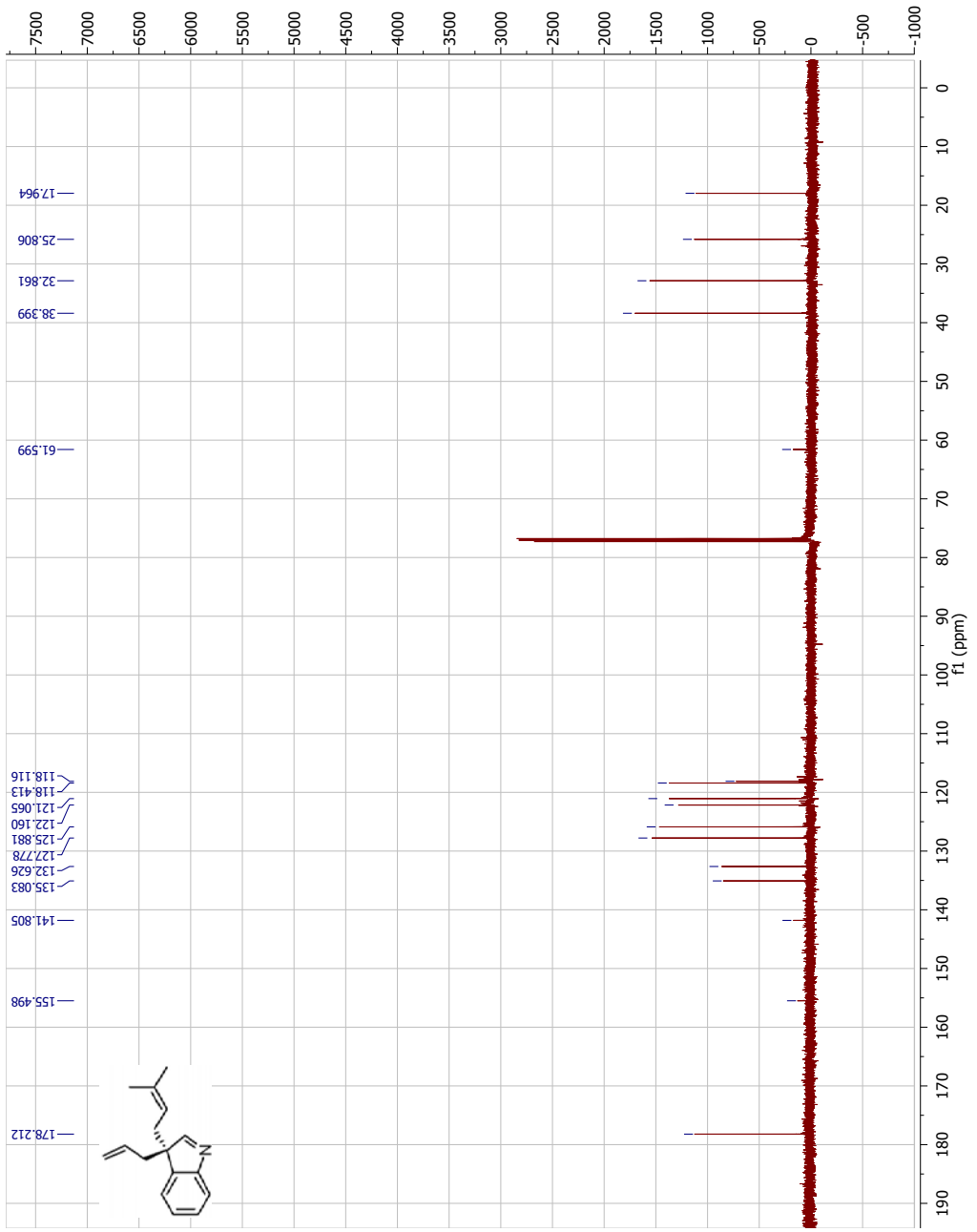

7.958
7.560
7.543
7.350
7.346
7.334
7.330
7.231
7.227
5.471
5.388
5.042
4.976
2.571
2.479
2.362
2.303
2.145
2.087
1.929
1.915
1.786
0.95
1.00
0.96
0.95
2.07
0.99
2.25
1.14
1.30
3.09
2.21
f1 (ppm)
O
N
Cl

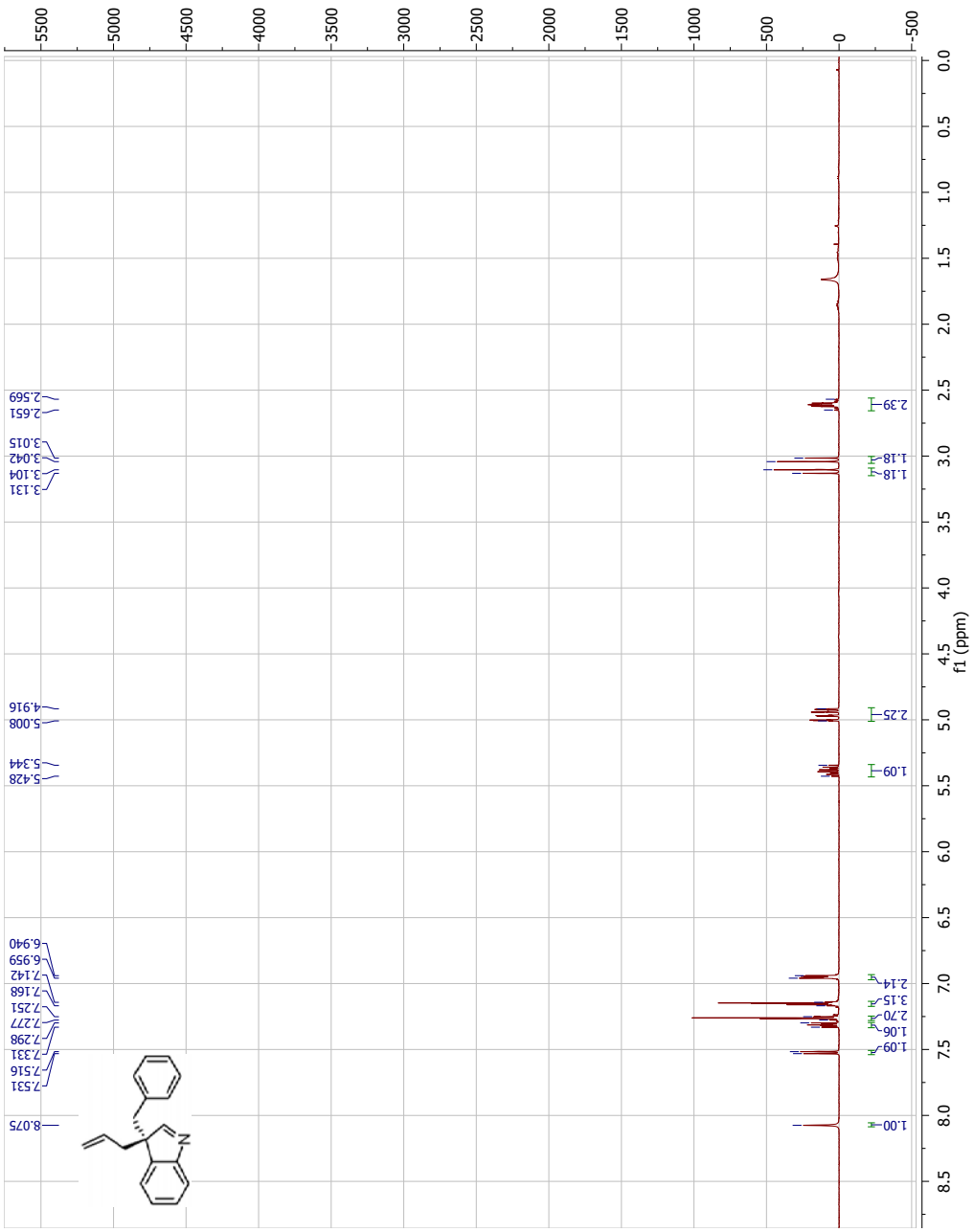

207.304
178.196
154.129
142.570
132.425
131.585
128.454
122.664
122.167
119.398
61.410
39.649
37.746
30.014
27.322
f1 (ppm)

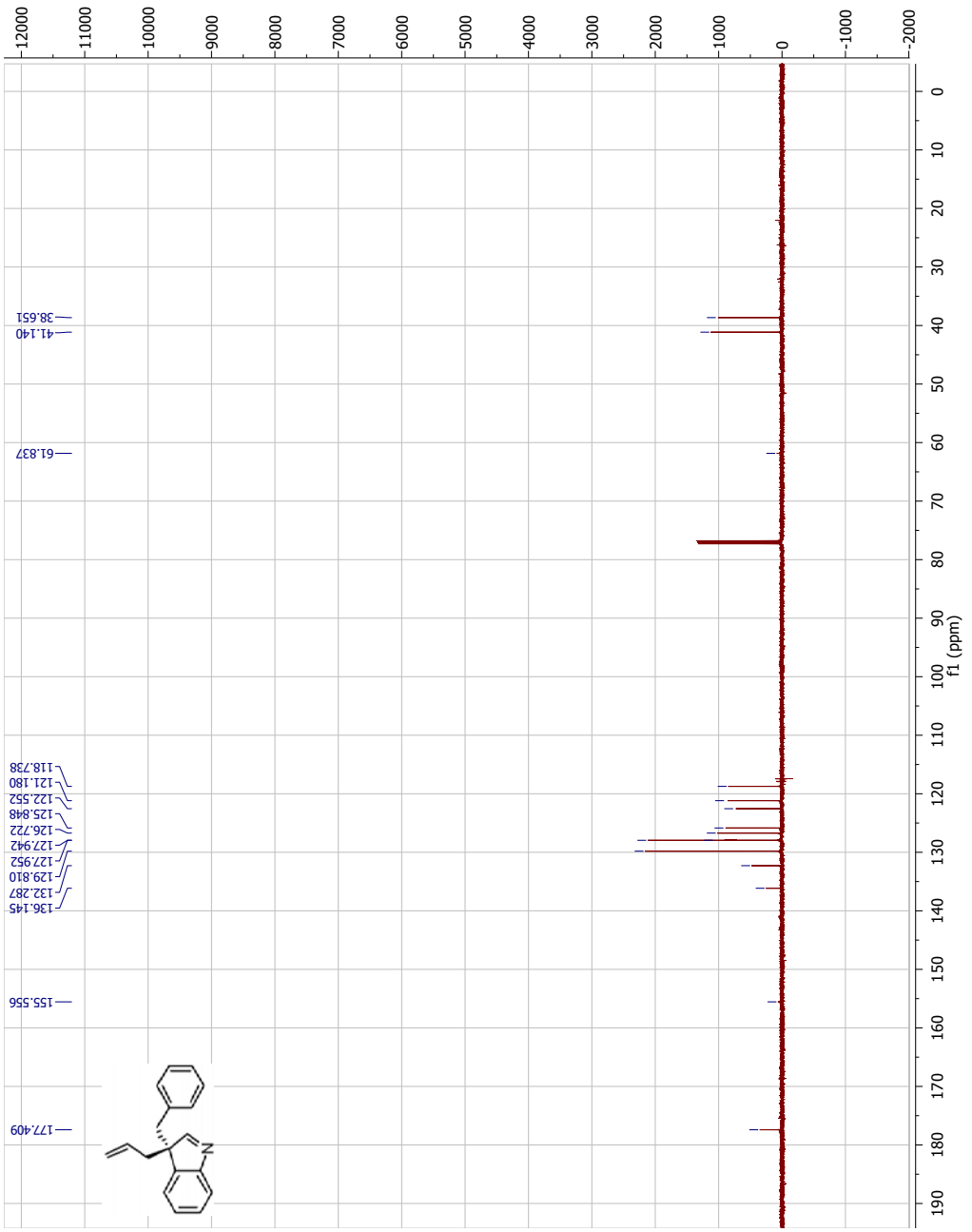

f1 (ppm)
8.030
7.624
7.609
7.358
7.355
7.343
7.340
7.328
7.325
7.300
7.232
5.474
5.378
5.152
5.086
5.008
4.922
2.570
2.402
1.563
1.550
1.00
1.05
1.06
2.25
1.99
1.19
2.14
4.66
3.01

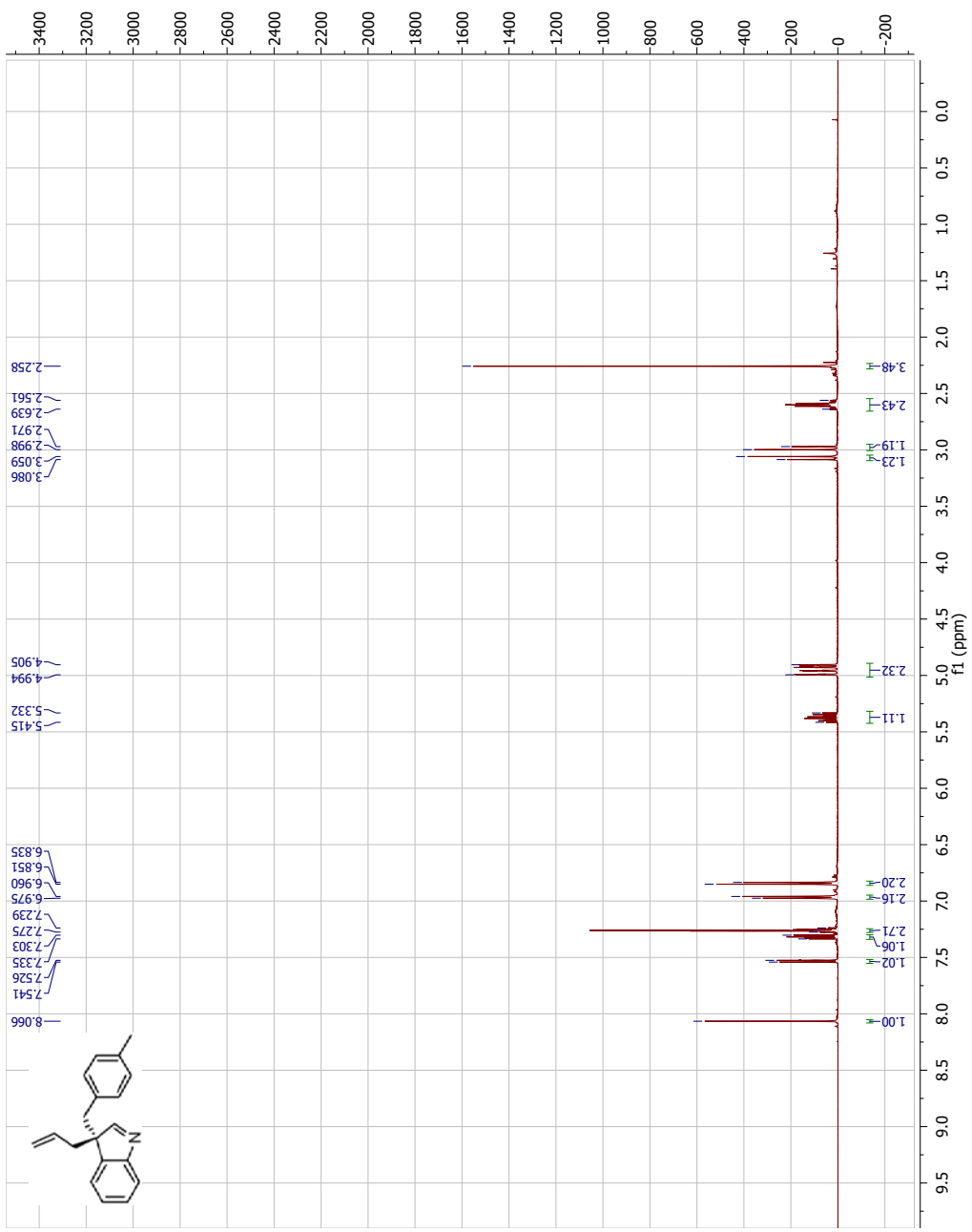

178.105
155.513
141.633
132.518
129.407
127.788
125.869
124.774
122.227
121.104
118.468
61.119
38.366
37.443
17.845
f1 (ppm)

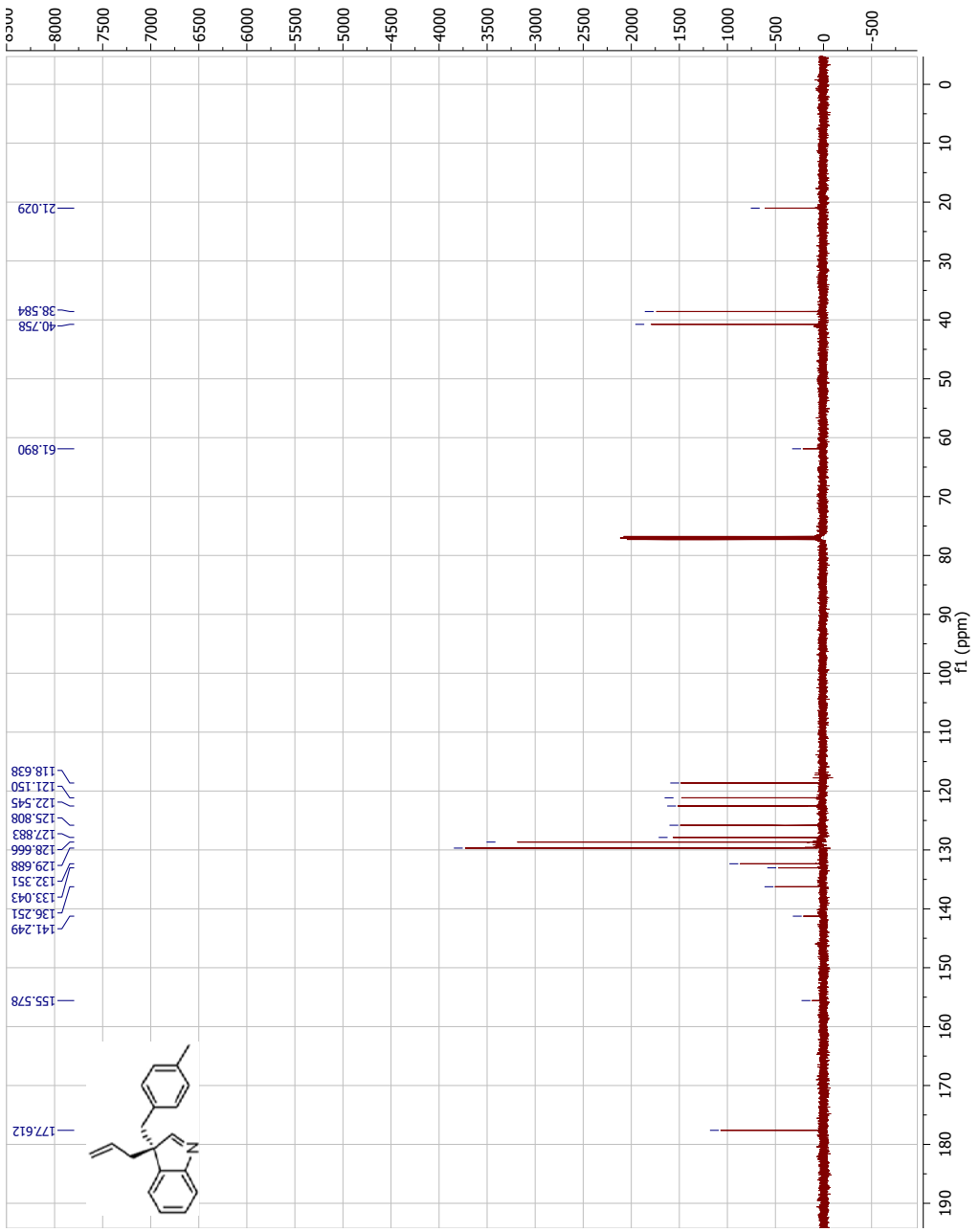

8.024
7.619
7.603
7.355
7.293
7.257
7.226
5.450
5.367
5.009
4.914
4.872
4.827
2.603
2.493
2.434
2.391
1.597
1.532
1.00
1.08
2.26
1.17
2.29
1.25
1.26
3.66
3.48
3.49
f1 (ppm)

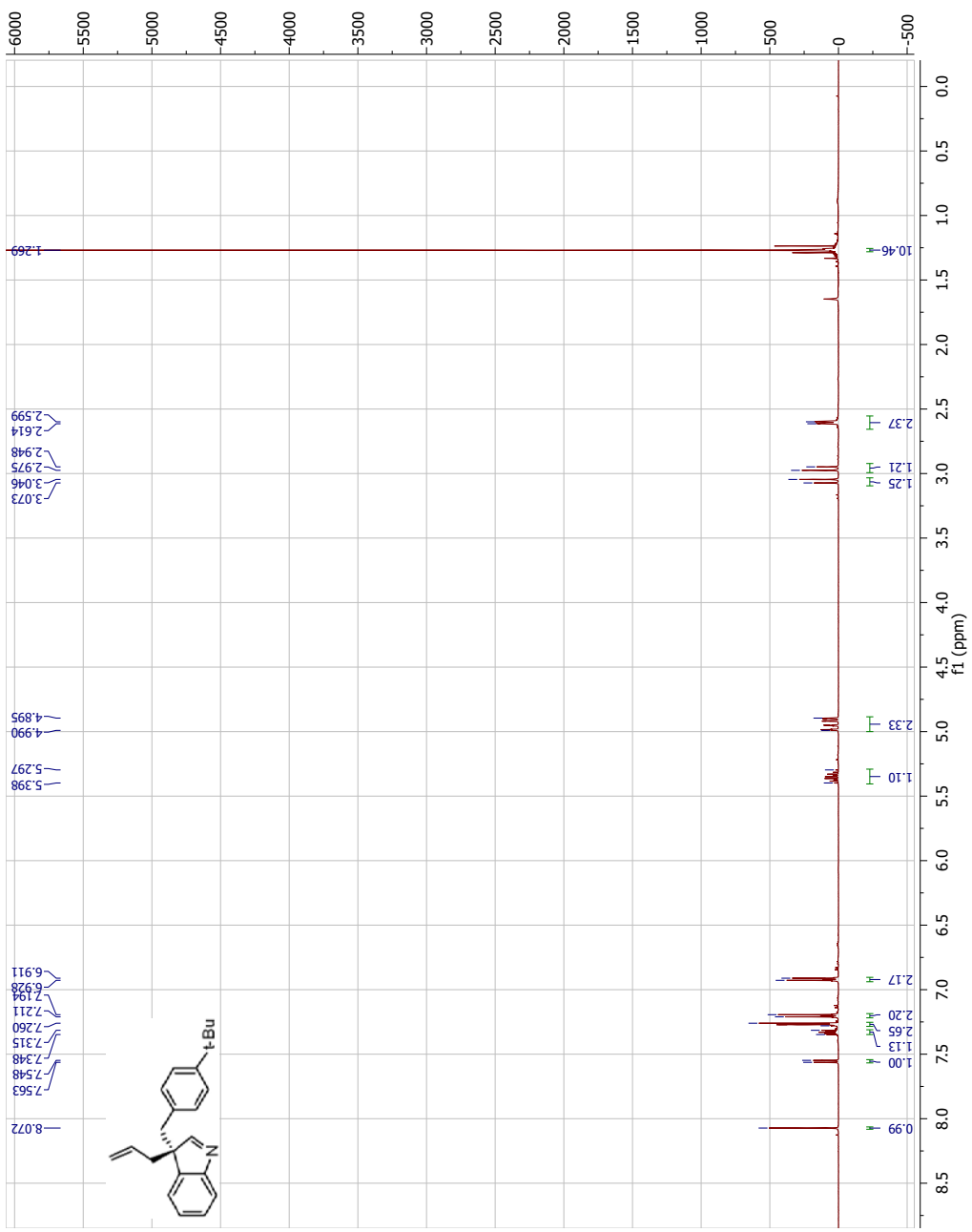

178.212
155.498
141.805
135.083
132.626
127.778
125.881
122.160
121.065
118.413
118.116
61.599
38.399
32.861
25.806
17.964
f1 (ppm)

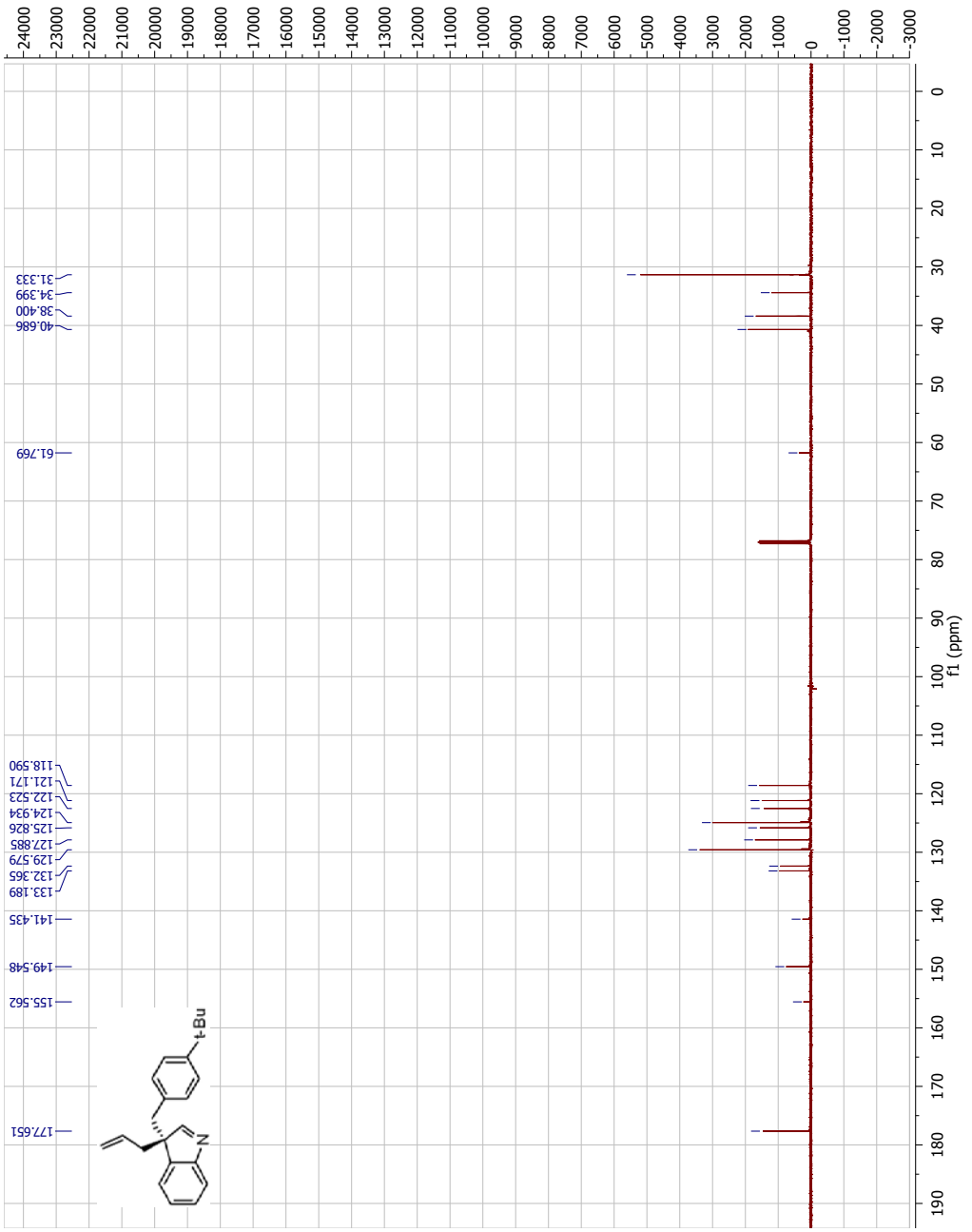

f1 (ppm)
8.075
7.531
7.516
7.331
7.298
7.277
7.251
7.168
7.142
6.959
6.940
5.428
5.344
5.008
4.916
3.131
3.104
3.042
3.015
2.651
2.569
1.00
1.09
2.14
3.15
2.70
1.06
1.09
2.25
1.09
1.18
1.18
2.39

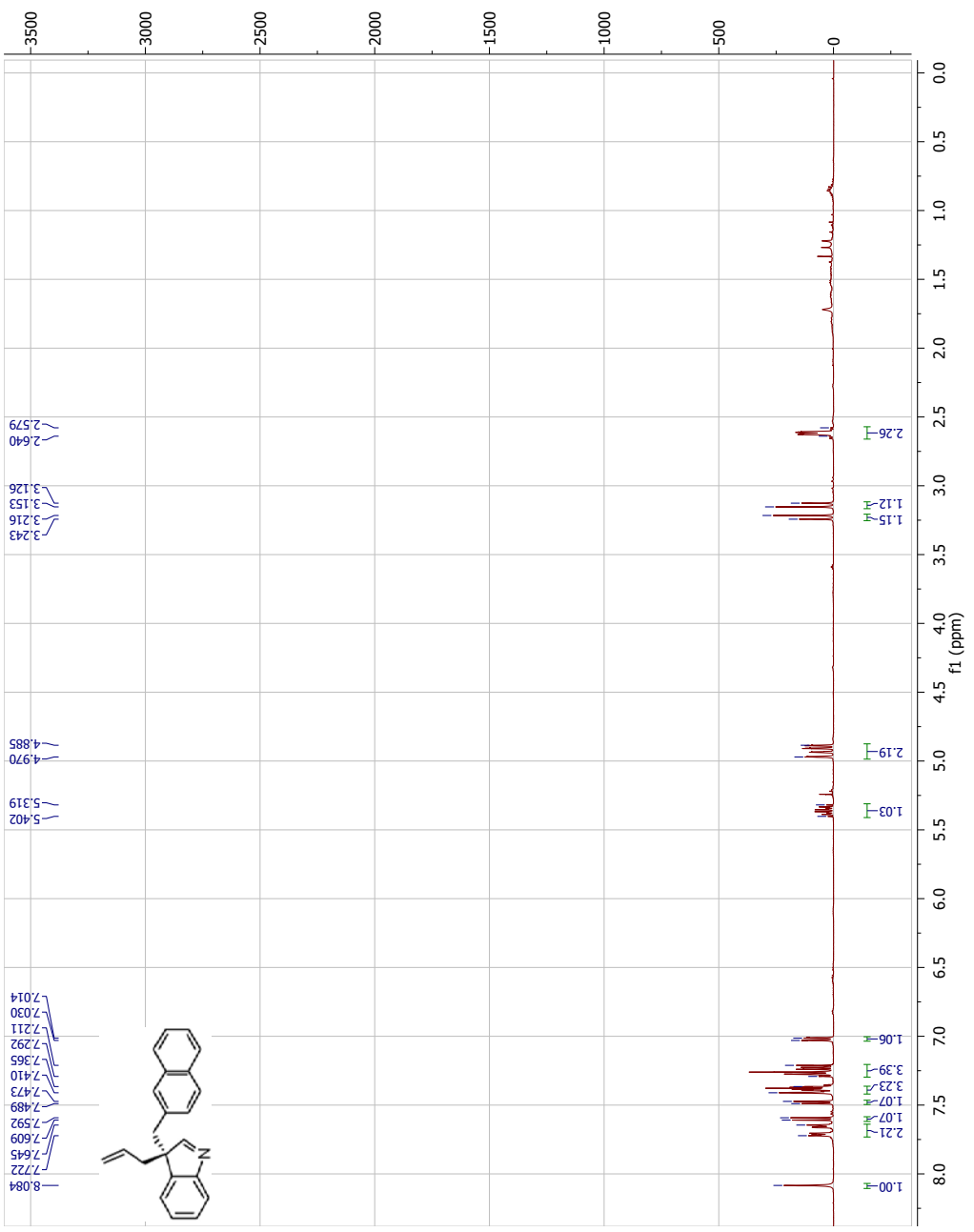

177.409
155.556
136.145
132.287
129.810
127.952
127.942
126.722
125.848
122.552
121.180
118.738
61.837
41.140
38.651
f1 (ppm)

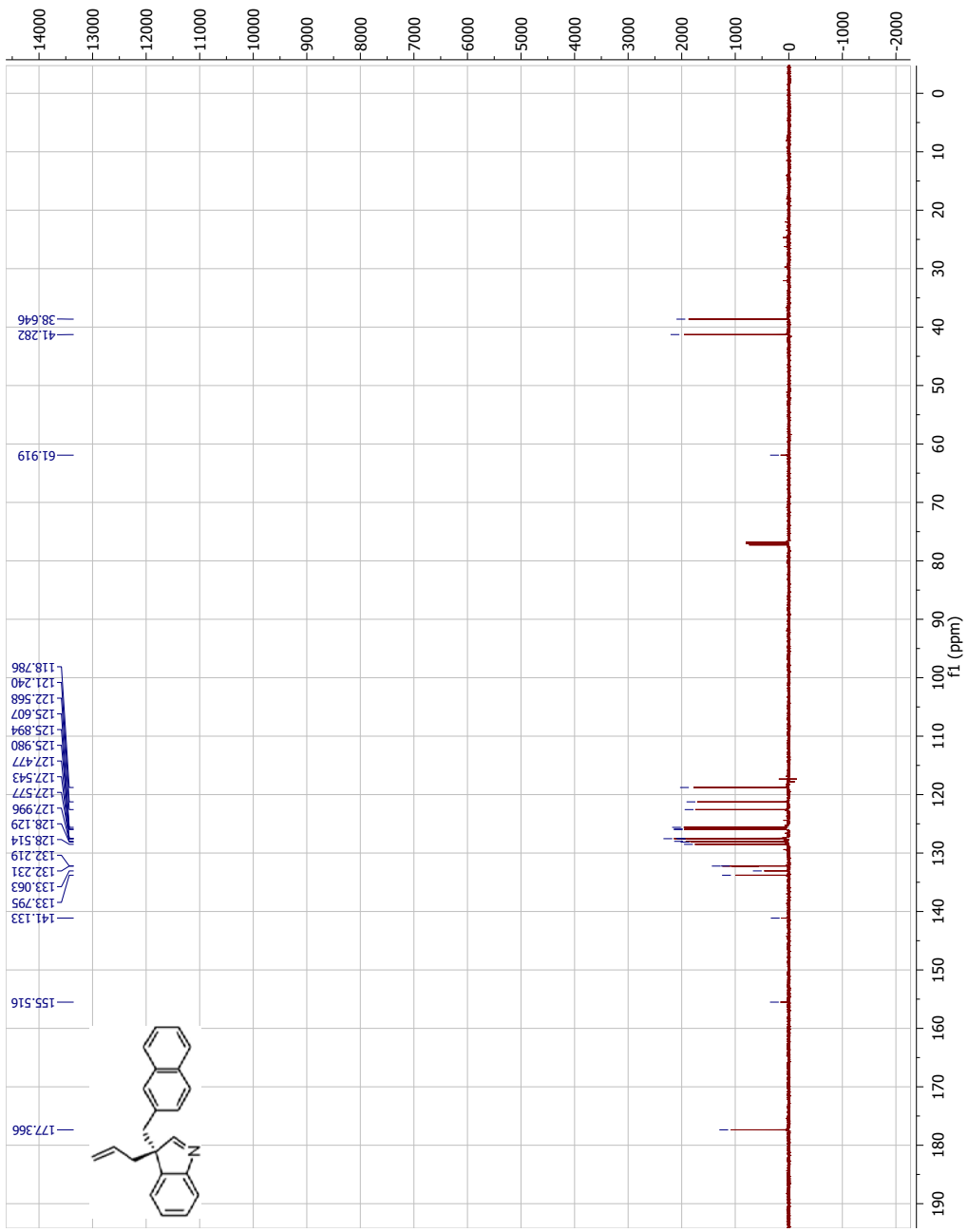

8.066
7.541
7.526
7.335
7.303
7.275
7.239
6.975
6.960
6.851
6.835
5.415
5.332
4.994
4.905
3.086
3.059
2.998
2.971
2.639
2.561
2.258
3.48
2.43
1.23
1.19
2.32
1.11
2.20
2.16
2.71
1.06
1.02
1.00
f1 (ppm)

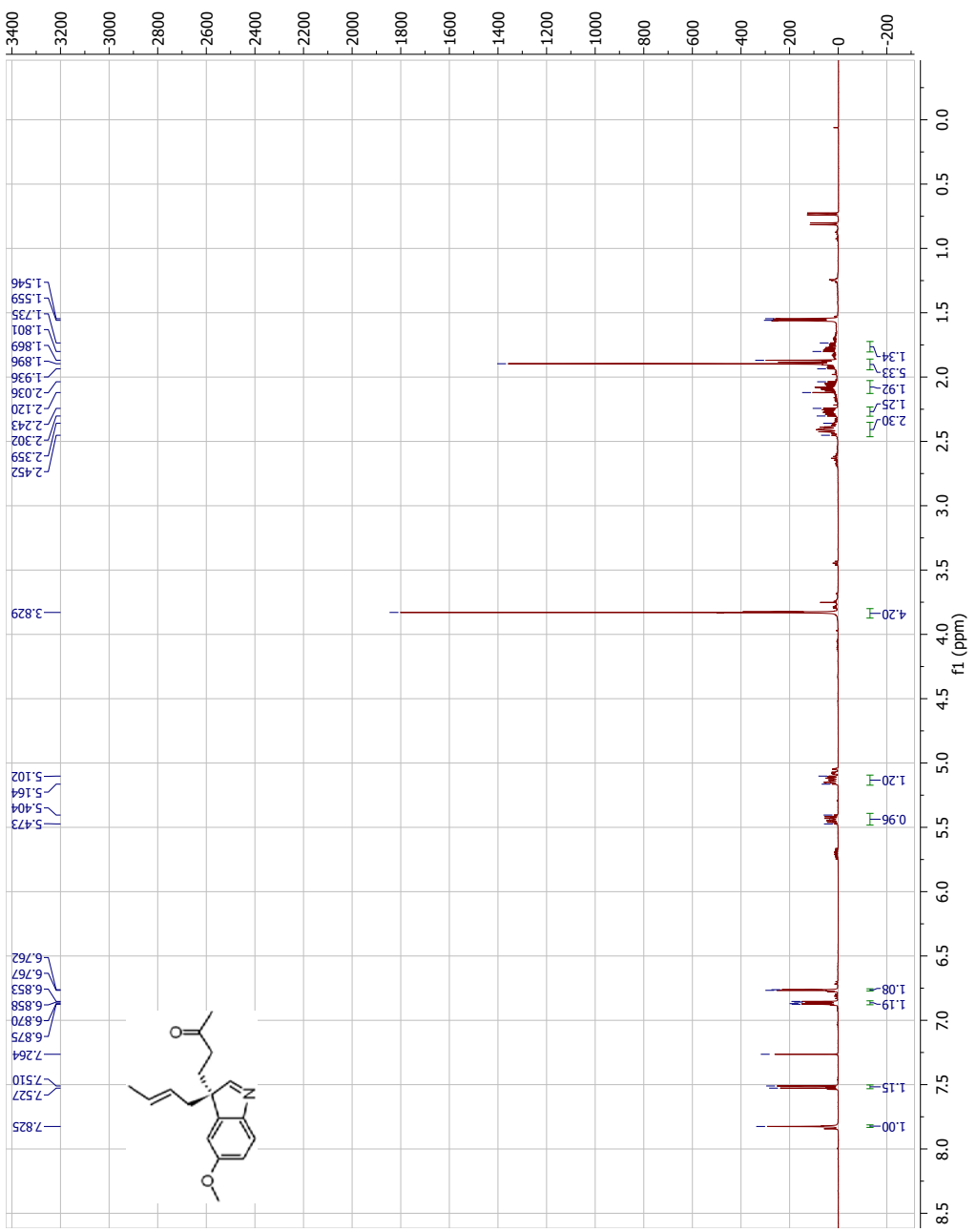

177.612
155.578
141.249
136.251
133.043
132.351
129.688
128.666
127.883
125.808
122.545
121.150
118.638
61.890
40.758
38.584
21.029
f1 (ppm)

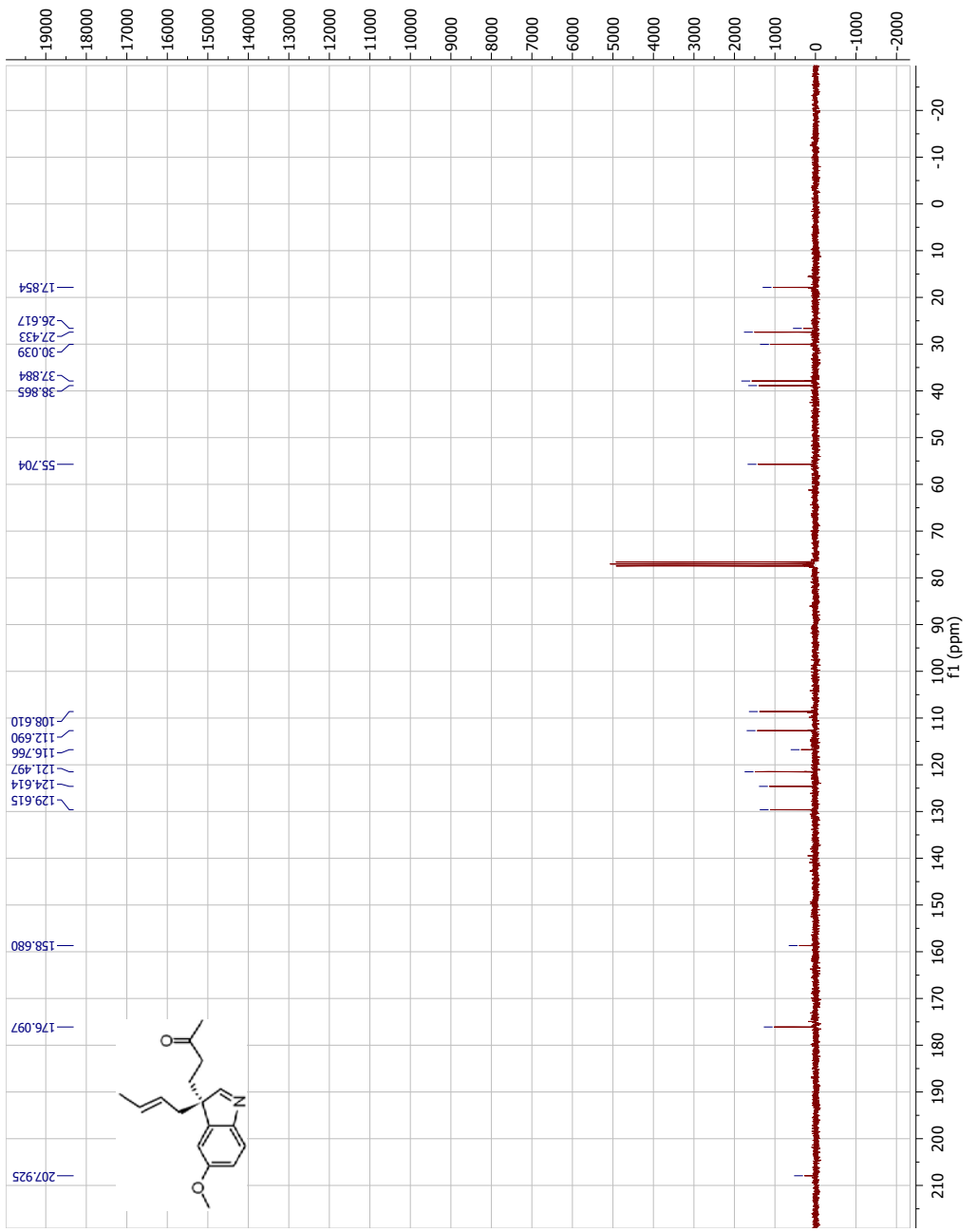

8.072
7.563
7.548
7.348
7.315
7.260
7.211
7.194
6.928
6.911
5.398
5.297
4.990
4.895
3.073
3.046
2.975
2.948
2.614
2.599
1.269
10.46
2.37
1.25
1.21
2.33
1.10
2.17
2.20
2.65
1.13
1.00
0.99
t-Bu
N
f1 (ppm)

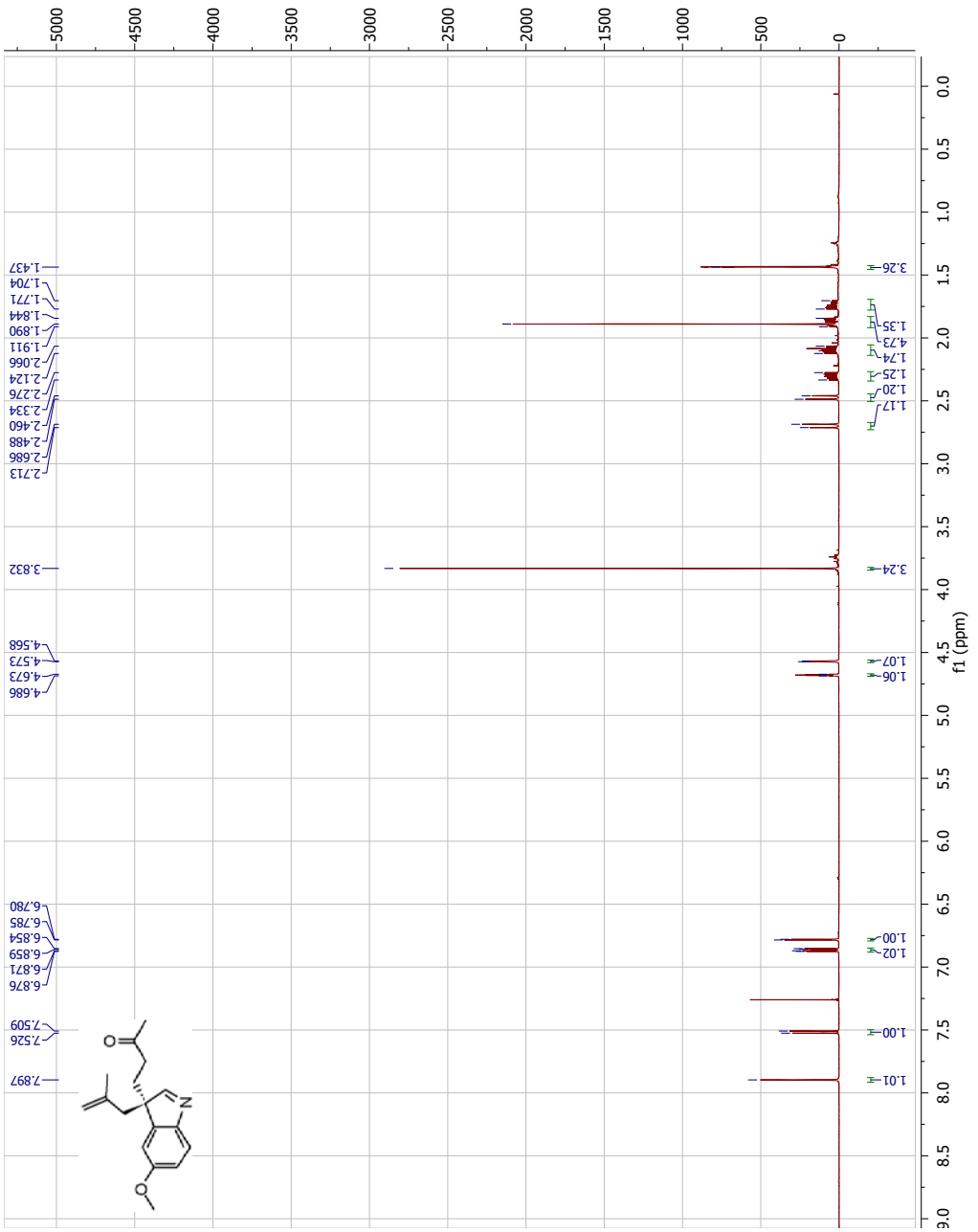

177.651
155.562
149.548
141.435
133.189
132.365
129.579
127.885
125.826
124.934
122.523
121.171
118.590
61.769
40.686
38.400
34.399
31.333
t-Bu
N
f1 (ppm)

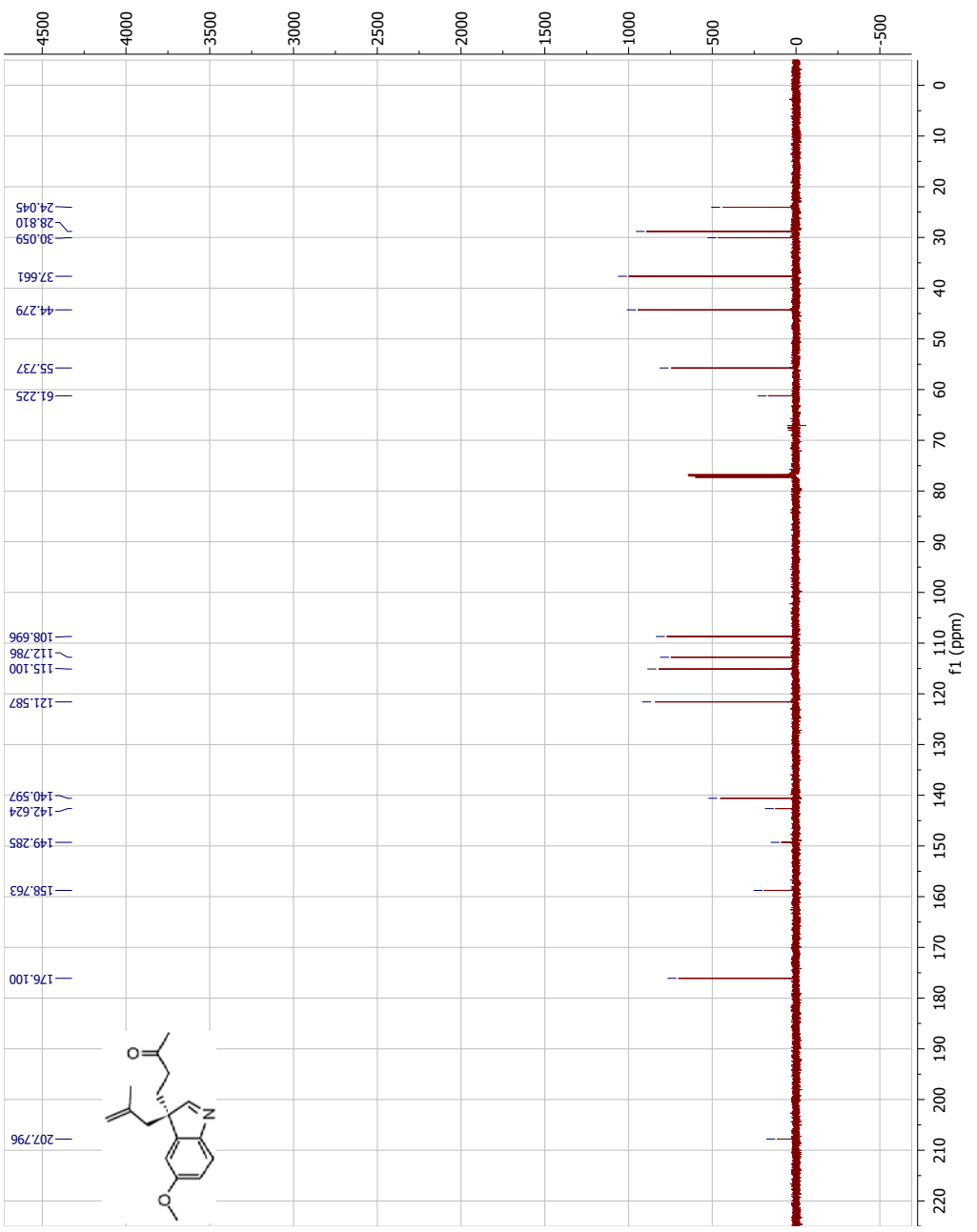

8.084
7.722
7.645
7.609
7.592
7.489
7.473
7.410
7.365
7.292
7.211
7.030
7.014
5.402
5.319
4.970
4.885
3.243
3.216
3.153
3.126
2.640
2.579
1.00
2.21
1.07
1.07
3.23
3.39
1.06
2.19
1.03
2.26
1.12
1.15
f1 (ppm)

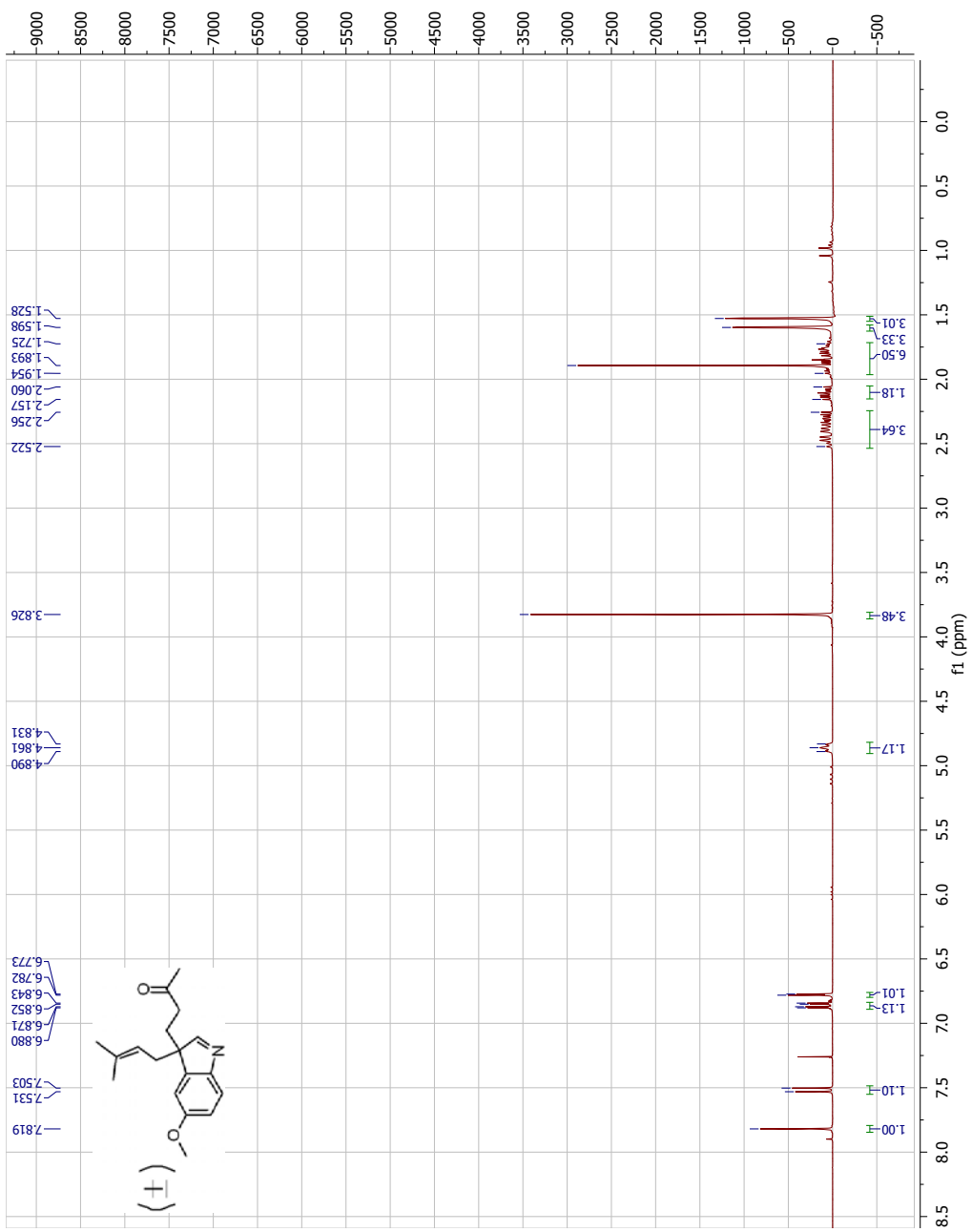

177.366
155.516
141.133
133.795
133.063
132.231
132.219
128.514
128.129
127.996
127.577
127.543
127.477
125.980
125.894
125.607
122.568
121.240
118.786
61.919
41.282
38.646
f1 (ppm)

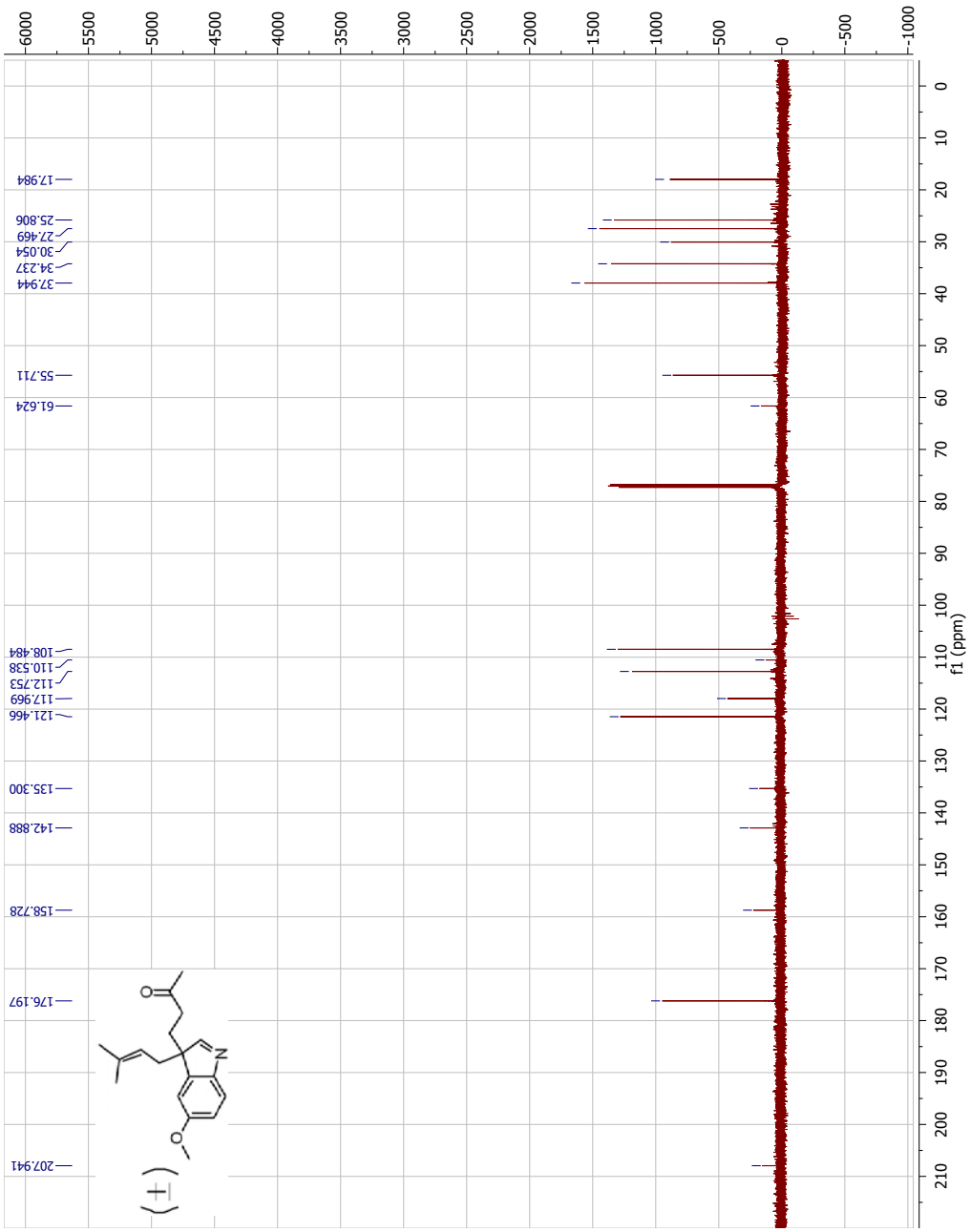

f1 (ppm)
1.546
1.559
1.735
1.801
1.869
1.896
1.936
2.036
2.120
2.243
2.302
2.359
2.452
3.829
5.102
5.164
5.404
5.473
6.762
6.767
6.853
6.858
6.870
6.875
7.264
7.510
7.527
7.825
1.34
5.33
1.92
1.25
2.30
4.20
1.20
0.96
1.08
1.19
1.15
1.00

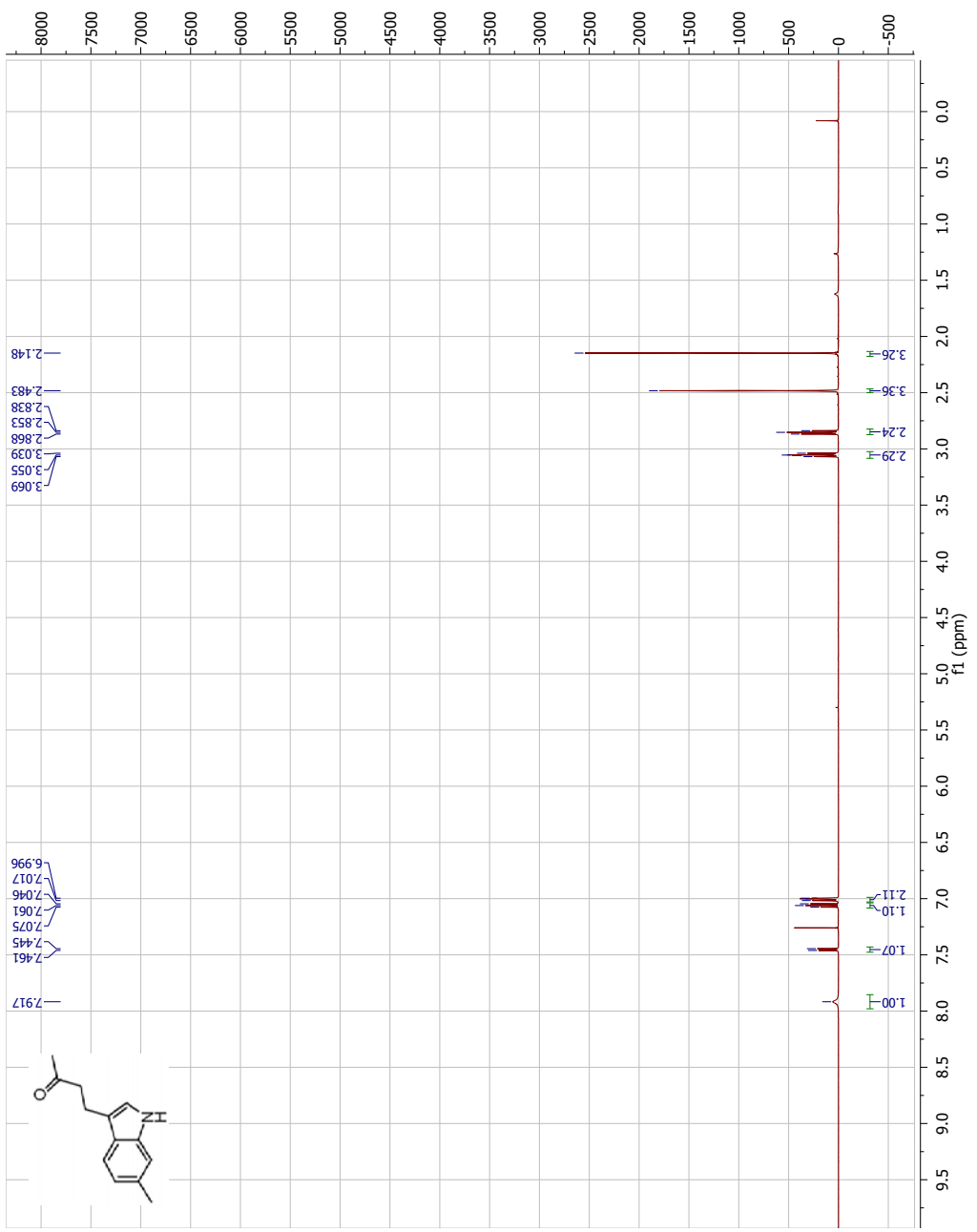

207.925
176.097
158.680
129.615
124.614
121.497
116.766
112.690
108.610
55.704
38.865
37.884
30.039
27.433
26.617
17.854
f1 (ppm)

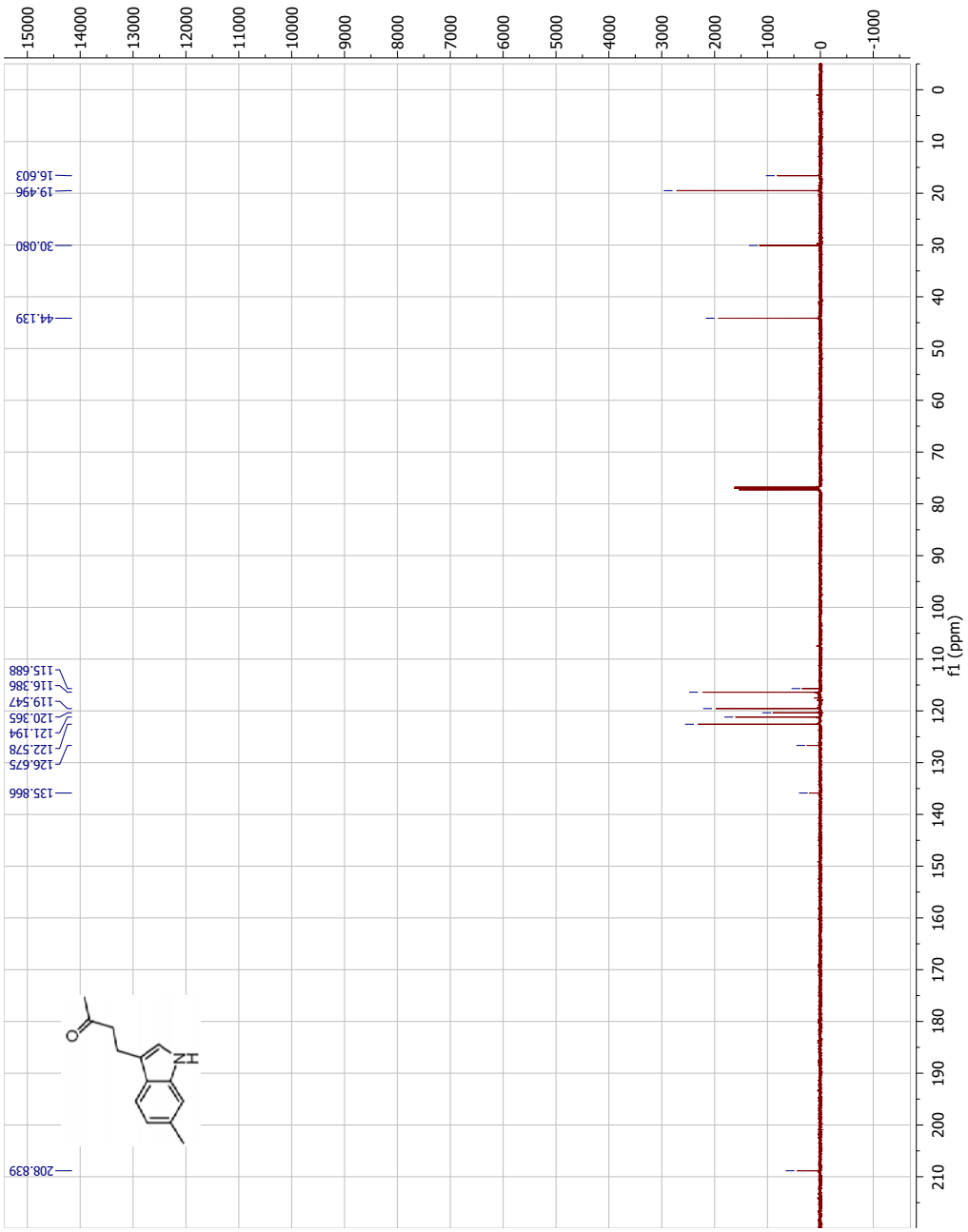

f1 (ppm)
1.437
1.704
1.771
1.844
1.890
1.911
2.066
2.124
2.276
2.334
2.460
2.488
2.686
2.713
3.832
4.568
4.573
4.673
4.686
6.780
6.785
6.854
6.859
6.871
6.876
7.509
7.526
7.897
3.26
1.35
4.73
1.74
1.25
1.20
1.17
3.24
1.07
1.06
1.00
1.02
1.00
1.01

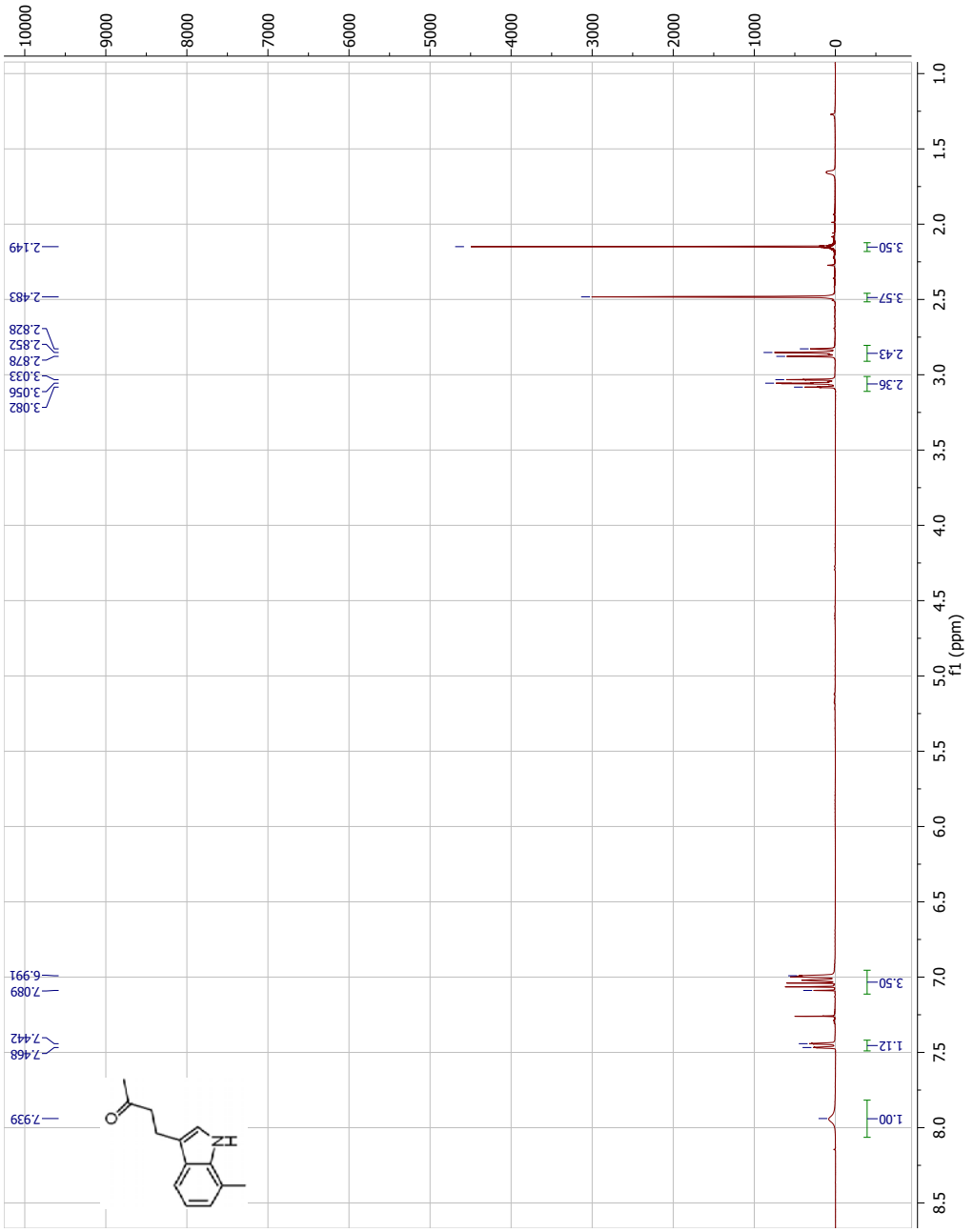

207.796
176.100
158.763
149.285
142.624
140.597
121.587
115.100
112.786
108.696
61.225
55.737
44.279
37.661
30.059
28.810
24.045
f1 (ppm)

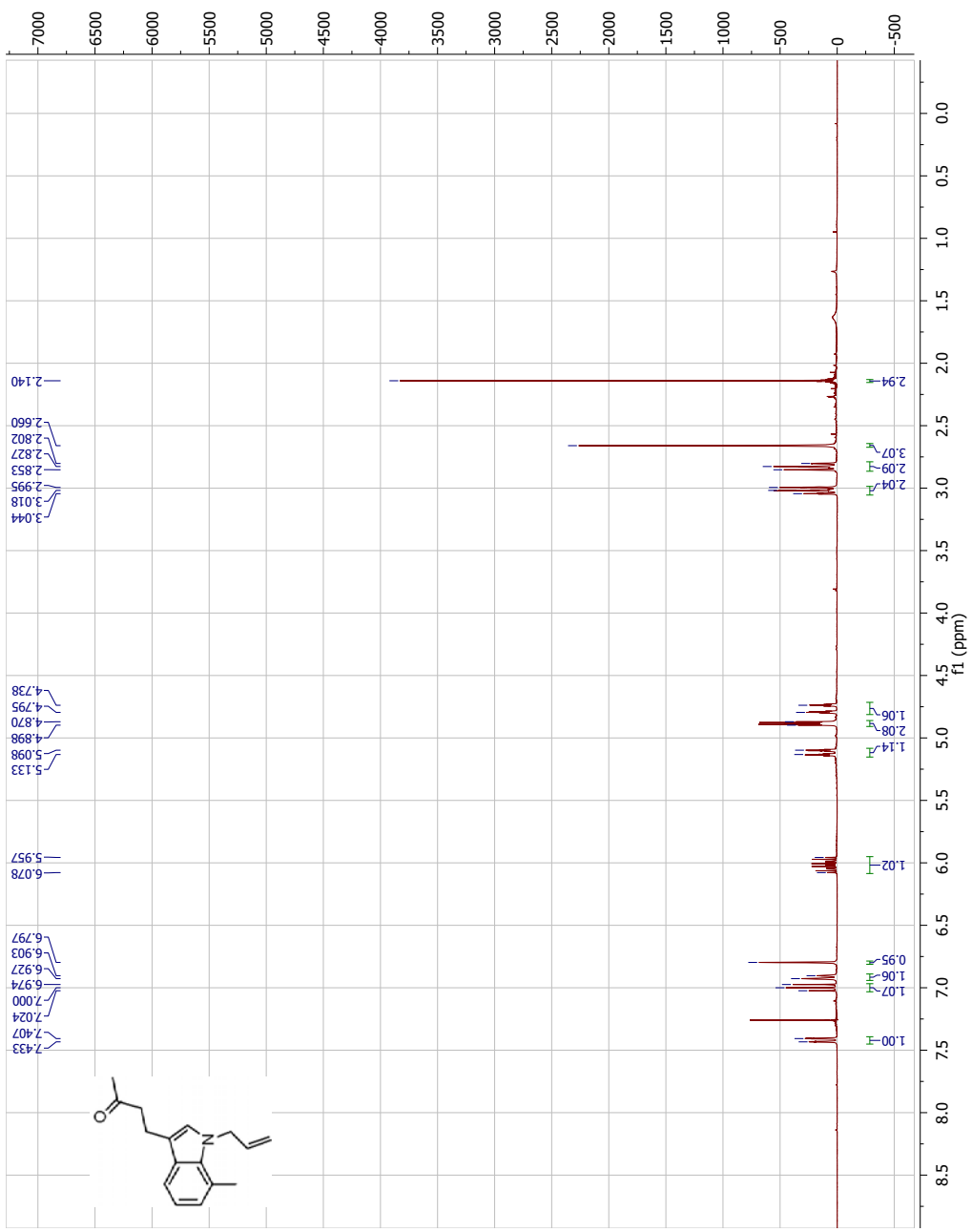

f1 (ppm)
7.819
7.531
7.503
6.880
6.871
6.852
6.843
6.782
6.773
4.890
4.861
4.831
3.826
2.522
2.256
2.157
2.060
1.954
1.893
1.725
1.598
1.528
1.00
1.10
1.01
1.13
1.17
3.48
1.18
3.64
6.50
3.33
3.01

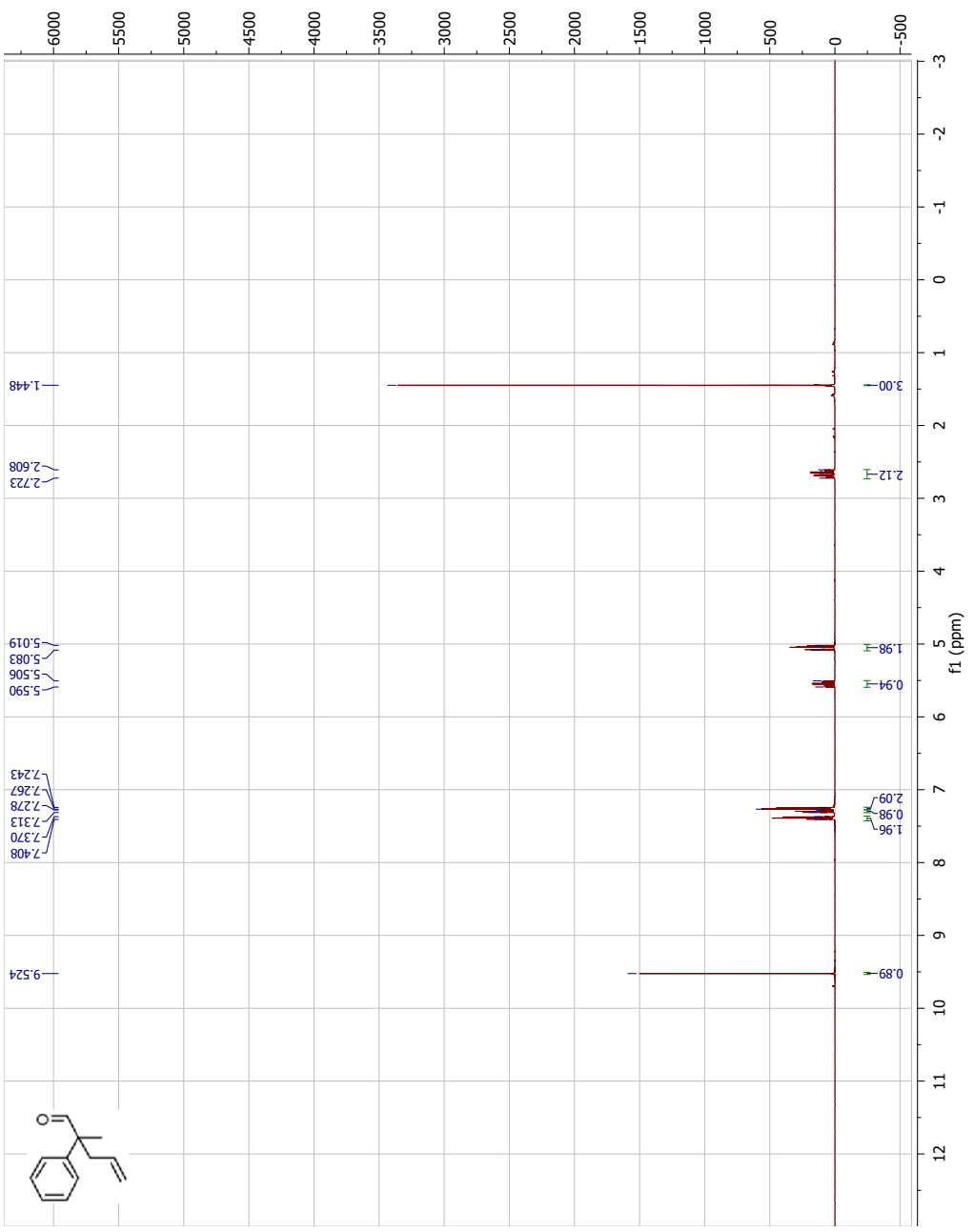

207.941
176.197
158.728
142.888
135.300
121.466
117.969
112.753
110.538
108.484
61.624
55.711
37.944
34.237
30.054
27.469
25.806
17.984
f1 (ppm)

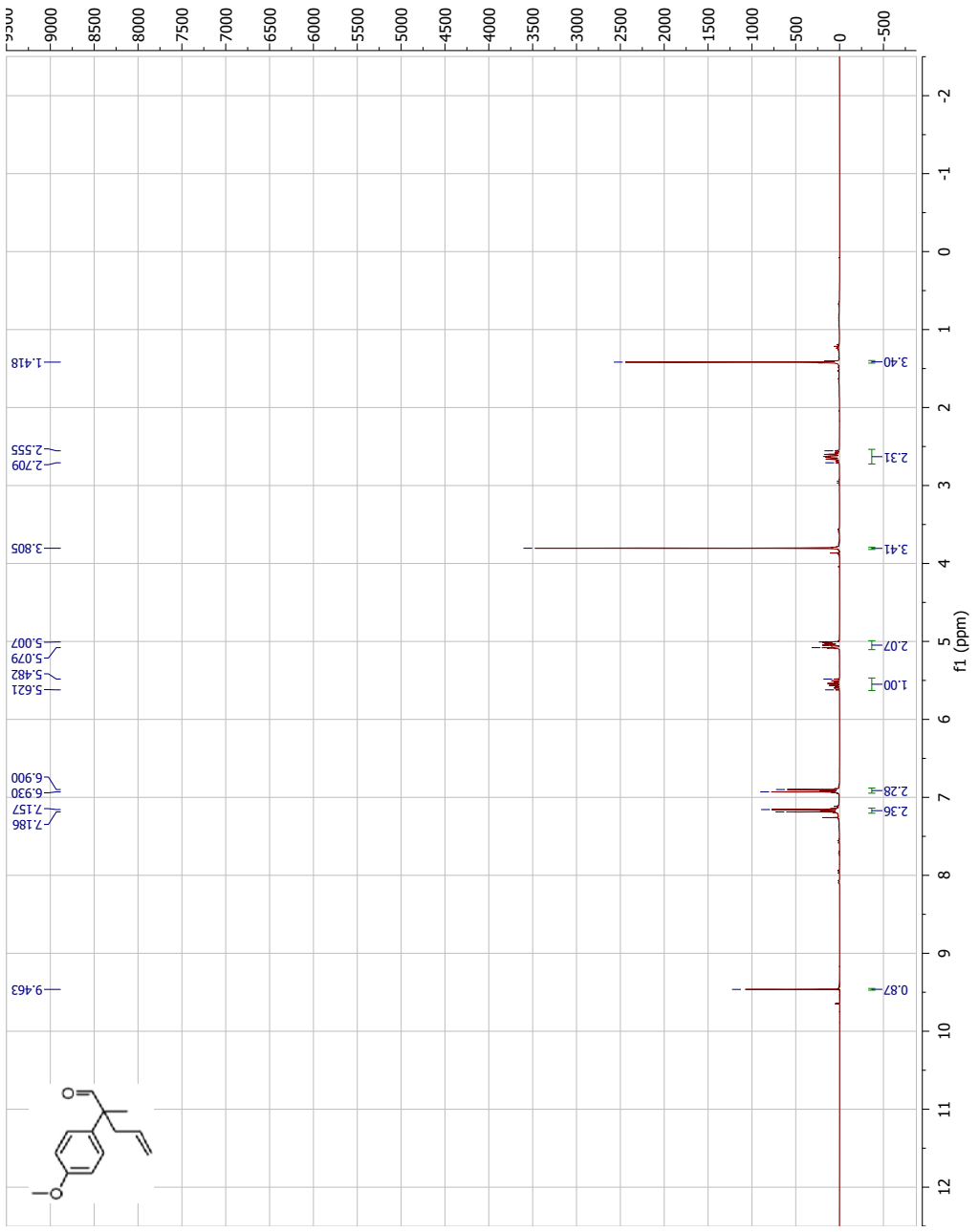

f1 (ppm)
3.26
3.36
2.24
2.29
2.11
1.10
1.07
1.00
2.148
2.483
2.838
2.853
2.868
3.039
3.055
3.069
6.996
7.017
7.046
7.061
7.075
7.445
7.461
7.917

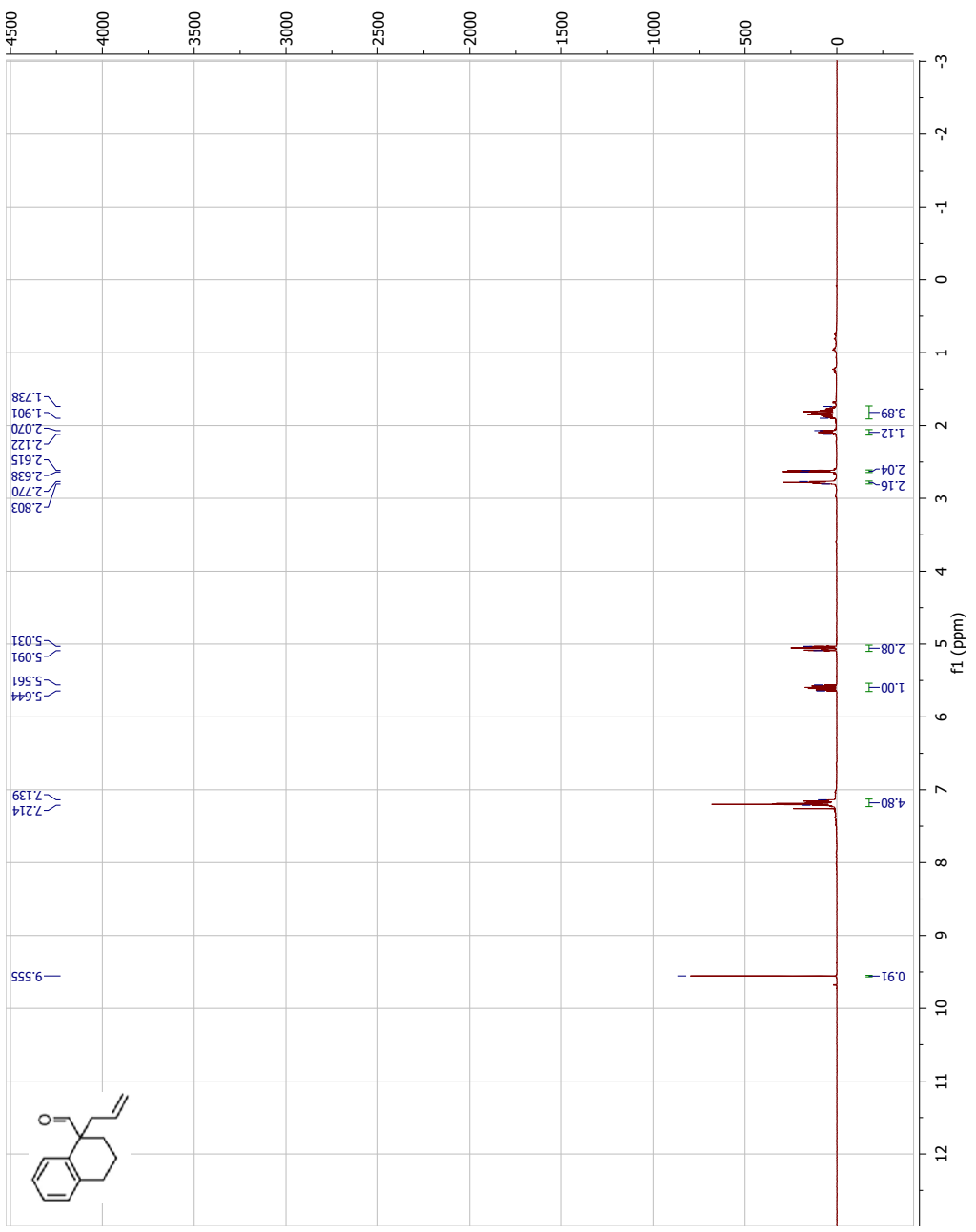

208.839
135.866
126.675
122.578
121.194
120.365
119.547
116.386
115.688
44.139
30.080
19.496
16.603
f1 (ppm)

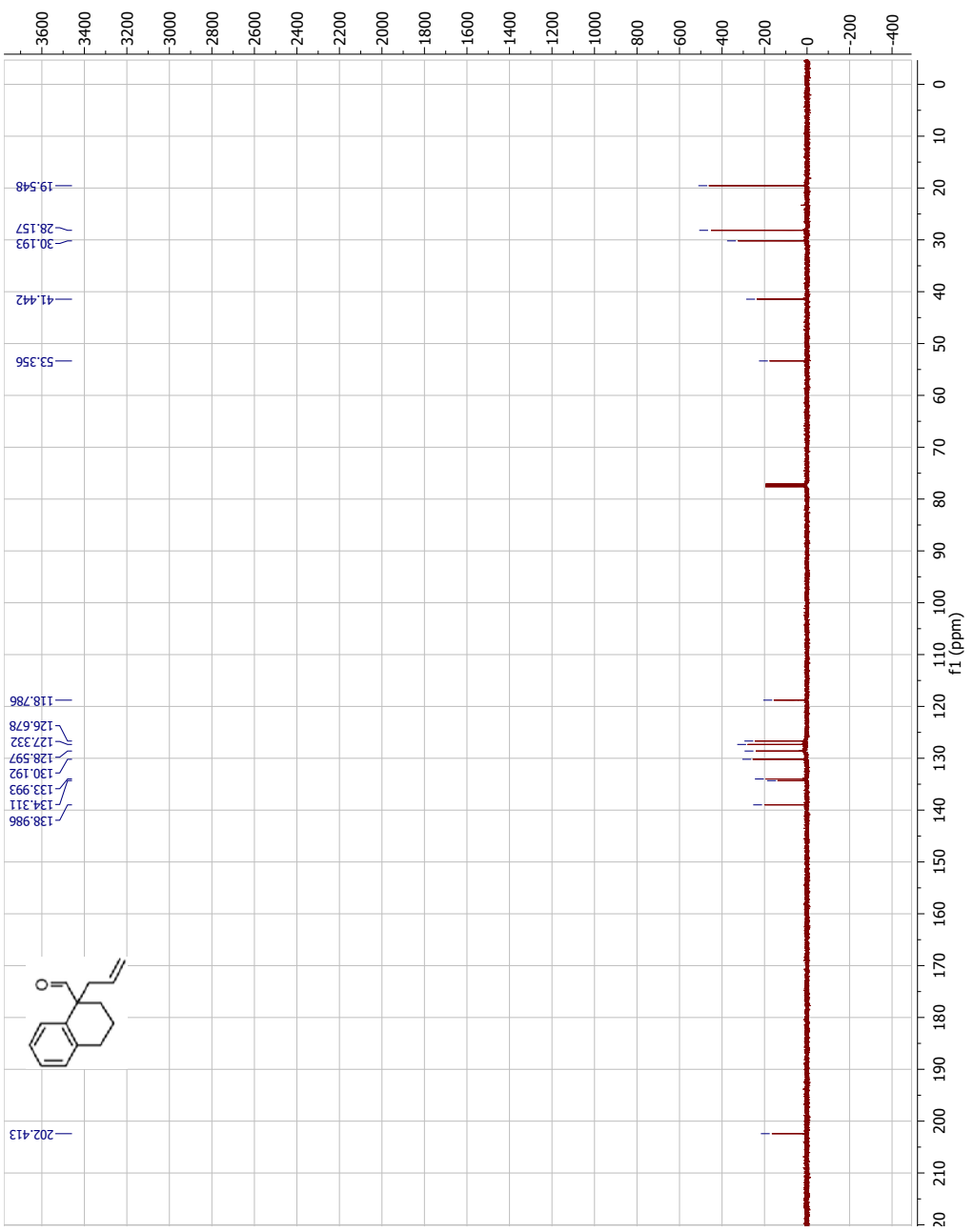

10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
f1 (ppm)
2.149
2.483
2.828
2.852
2.878
3.033
3.056
3.082
6.991
7.089
7.442
7.468
7.939
3.50
3.57
2.43
2.36
3.50
1.12
1.00
O
NH


7.433
7.407
7.024
7.000
6.974
6.927
6.903
6.797
6.078
5.957
5.133
5.098
4.898
4.870
4.795
4.738
3.044
3.018
2.995
2.853
2.827
2.802
2.660
2.140
1.00
1.07
1.06
0.95
1.02
1.14
2.08
1.06
2.04
2.09
3.07
2.94
f1 (ppm)


f1 (ppm)
9.524
7.408
7.370
7.313
7.278
7.267
7.243
5.590
5.506
5.083
5.019
2.723
2.608
1.448
0.89
1.96
0.98
2.09
0.94
1.98
2.12
3.00


9.463
7.186
7.157
6.930
6.900
5.621
5.482
5.079
5.007
3.805
2.709
2.555
1.418
0.87
2.36
2.28
1.00
2.07
3.41
2.31
3.40
f1 (ppm)


9.555
7.214
7.139
5.644
5.561
5.091
5.031
2.803
2.770
2.638
2.615
2.122
2.070
1.901
1.738
0.91
4.80
2.08
1.00
3.89
1.12
2.04
2.16
f1 (ppm)


202.413
138.986
134.311
133.993
130.192
128.597
127.332
126.678
118.786
53.356
41.442
30.193
28.157
19.548
f1 (ppm)