SYNTHESIS OF POLYCYCLIC RING SYSTEMS VIA C-H BOND INSERTION

AND

ENANTIOSELECTIVE CONJUGATE ADDITION

A Dissertation Presented to

The Faculty of the Department of Chemistry

University of Houston

In Partial Fulfillment

Of the Requirements for the Degree

Doctor of Philosophy

By

Santa Jansone-Popova

May 2014

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APPROVED:

Dr. Jeremy A. May, Chairman

Dr. Scott R. Gilbertson

Dr. Olafs Daugulis

Dr. Zachary T. Ball

Dr. Shoujun Xu

Dean, College of Natural Sciences and Mathematics

ACKNOWLEDGEMENTS

I would like to thank my doctoral advisor, Professor Jeremy May, for his guidance and support throughout these five years. I value your passion for chemistry, it is contagious. Your door has been always open for the scientific discussion. I am also very grateful for the independence that I have had for the last five years. I would also like to thank my PhD committee members, especially, Dr. Gilbertson and Dr. Daugulis for many insightful discussions, suggestions and most of all encouragement.

I am very thankful to my former and current group members: Cristabel, Brian, Betty, Miguel, DK, Phong, Thien, Ravi, Edward, Emma, Allan and Krit. I will miss greatly my two very close pals, Edward and Emma. I hope the distance, whenever I move to another city, will not change a thing and we will keep in touch. The former and current undergraduate students from our lab are absolutely the best: Ron, Tho, Chris, Ashar and Stephanie. They all are very talented, smart, young people and I wish them all the best. Gino and Jessica, you both are amazing, thank you for always keeping me informed about what is happening around me.

I am very thankful to my family, my mom Alda and sister Džita (Gita). Their support was incredibly important throughout the years. Although, my godmother Lilita was a little bit upset about me leaving Latvia, she has been very supportive and caring all this time.

The biggest thank you goes to Ilja, my best friend, my role model for a scientist, mentor and teacher. I would not have achieved so much without you. I will continue to keep up with you.

I would also like to thank Professor Huw Davies for sending us some of the chiral rhodium catalysts; Professor Dean J. Tantillo and his students: Stephanie, Phil and Hoby, for doing the DFT calculations, to have an insight on the selective C-H bond insertion; Dr. James Korp for solving X-ray crystal structures in a short period of time; and Dr. Charles Anderson for helping with NMR spectroscopy.

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ABSTRACT

This dissertation presents three main projects. The first discusses synthetic strategies towards the total synthesis of the natural product Maoecrystal V. The second part presents an efficient way to construct complex polycyclic ring systems. The third project describes an organocatalytic asymmetric conjugate addition of organoboronates to indole-appended enones.

A structurally complex natural product, Maoecrystal V, possesses potent biological activity against the HeLa cancer cell line. An efficient synthetic route would allow access to larger quantities of this compound. Our approach is based on a rhodium-catalyzed bridgehead C-H bond insertion method to construct a γ-lactone. Substitution of the molecule's methylene hydrogens with deuterium or fluorine atoms allows selective functionalization of the methine C-H bond. Installation of two more rings in the molecule will finish the total synthesis of Maoecrystal V.

The alkyne/carbene cascade reaction is highly efficient and predictable in transforming simple, commercially available materials into complex polycyclic molecules, which represent the core structures of many natural products. Subsequently, we discovered an alkyne/carbamate-derived nitrene cascade reaction that leads to the formation of complex polycyclic molecules containing nitrogen atoms. Two products are produced during the reaction and their identity and ratio can be controlled by the relative size of the silyl substituent on the alkyne.

Lastly, an efficient method for the organocatalytic conjugate addition of alkenylboronic acids to indole-appended enones was developed. Most importantly, unprotected indoles can be used as substrates, which further increases the applicability of this method.

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LIST OF ABBREVIATIONS

Ac	acetyl, acetate
AIBN	Azobisisobutyronitrile
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
BHT	Butylated hydroxytoluene
BOM	benzyloxymethyl
Cap	caprolactamate
Cod	cyclooctadiene
CI	chemical ionization
D	doublet
DMSO	dimethyl sulfoxide
DMAP	4-dimethylaminopyridine
DBU	1,8-Diazabicycloundec-7-ene
DMP	Dess–Martin periodinane
DIBAL	Diisobutylaluminium hydride
DMDO	Dimethyldioxirane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DDQ	2,3-Dichloro-5,6-Dicyanobenzoquinone
DMA	dimethylaniline
DIAD	Diisopropyl azodicarboxylate
DCC	*N*,*N'*-Dicyclohexylcarbodiimide
DMF	*N*,*N*-dimethylformamide
Et	ethyl

Esp	α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid
ESI	electrospray ionization
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
HRMS	high resolution mass spectroscopy
HPLC	high performance liquid chromotography
IR	infrared (spectroscopy)
J	coupling constant
LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
m	multiplet or milli
m/z	mass to charge ratio
Me	methyl
MS	molecular sieves
mCPBA	*meta*-Chloroperoxybenzoic acid
Ms	methanesulfonyl (mesyl)
MOM	methoxymethyl
NBS	N-bromosuccinimide
NMR	nuclear magnetic resonance
nOe	Nuclear Overhauser Effect
NCS	*N*-chlorosuccinimide
pABSA	*p*-Acetamidobenzenesulfonyl Azide
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Py	pyridine
Ph	phenyl
q	quartet

s	singlet
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxy
TBS	tert-butyldimethylsilyl
TBAF	tetrabutylammonium fluoride
Ts	p-toluenesulfonyl
TMS	trimethylsilyl
TMP	2,2,6,6-Tetramethylpiperidine
TM	transition metal
TPA	triphenylacetate

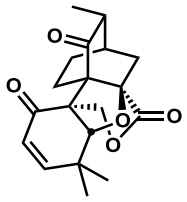
1. STUDIES TOWARD THE SYNTHESIS OF MAOECRYSTAL V

1.1. Background

1.1.1. Natural Product Maoecrystal V

Maoecrystal V (**1**) was isolated from the leaves of the Chinese medicinal herb *Isodon eriocalyx* and characterized in 2004 by Sun and coworkers. Natural product **1** was tested for its cytotoxicity against five human tumor cell lines (K252, A549, BGC-823, CNE, HeLa). Interestingly, it only exhibited potent cytotoxicity against gynecological cancer cells and was almost inert toward the remaining cell lines (Figure 1)

Figure 1. Cytotoxicity of natural product Maoecrystal V (**1**).



Maoecrystal V (1)

Isolated from Isodon eriocalyx
(5 mg from 11.9 kg dried plant leaves)

	IC_{50} (μg/mL)				
	K252	A549	BGC-823	CNE	HeLa
Maoecrystal V	6.43×10^4	2.63×10^5	1.47×10^4	nd	**0.02**
cis-platin	0.38	1.61	0.25	2.31	0.99

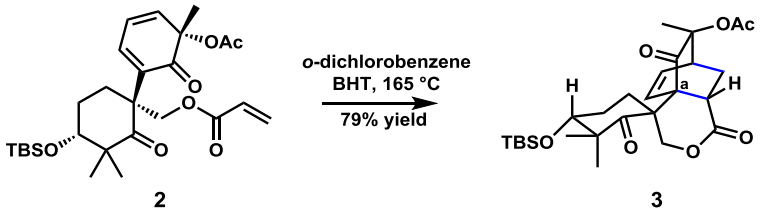
Its structural complexity combined with highly potent biological activity and scarce available quantities has attracted significant attention from synthetic organic chemists worldwide.

1.1.2. Synthetic Studies Toward Maoecrystal V

To date, nine different research groups have published synthetic studies toward the core structure of Maoecrystal V[2a-i]. A late-stage intra- or intermolecular Diels-Alder reaction to form the bicyclo[2.2.2]octane ring is a common element in these syntheses

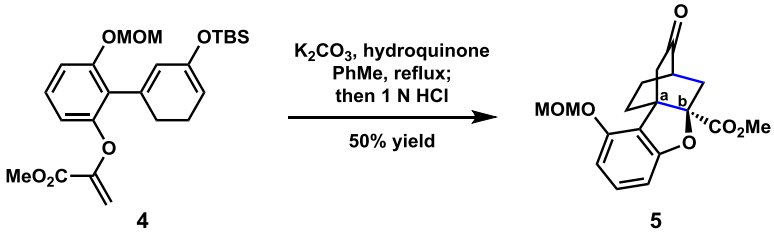
(Figure 2). This transformation allows the installation of the quaternary center **a**, which is challenging to access any other way.

Figure 2. Intramolecular Diels-Alder reaction reported by Baran and co-workers[2a].



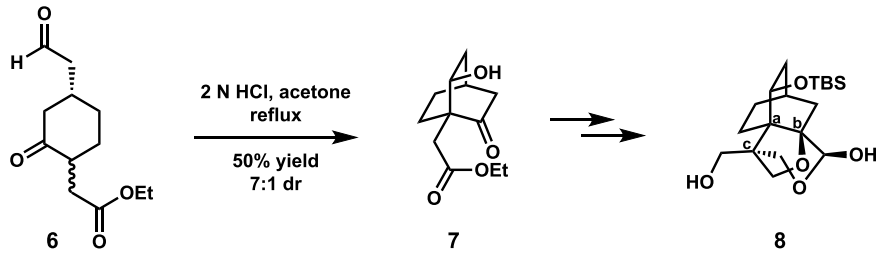
An appropriate choice of dienophile for the intramolecular Diels-Alder reaction, as reported by Nicolaou and co-workers, allows access to the fully substituted carbons **a** and **b** in single step[2d] (Figure 3). This reaction is highly efficient and allows constructing the functionalized Maoecrystal V core structure in a straightforward manner.

Figure 3. Intramolecular Diels-Alder reaction reported by Nicolaou and co-workers.



An alternative synthetic strategy to construct the Maoecrystal V core structure has been published by Trauner et al. (Figure 4)[2g]. Intramolecular aldol addition afforded a bicycle[2.2.2]octane **7** as a 7:1 mixture of isomers. The major isomer was further transformed into the advanced intermediate **8**, which features two contiguous quaternary centers **a** and **c**, as well as fully substituted carbon **b** (Figure 4).

Figure 4. Intramolecular Diels-Alder reaction reported by Trauner and co-workers.



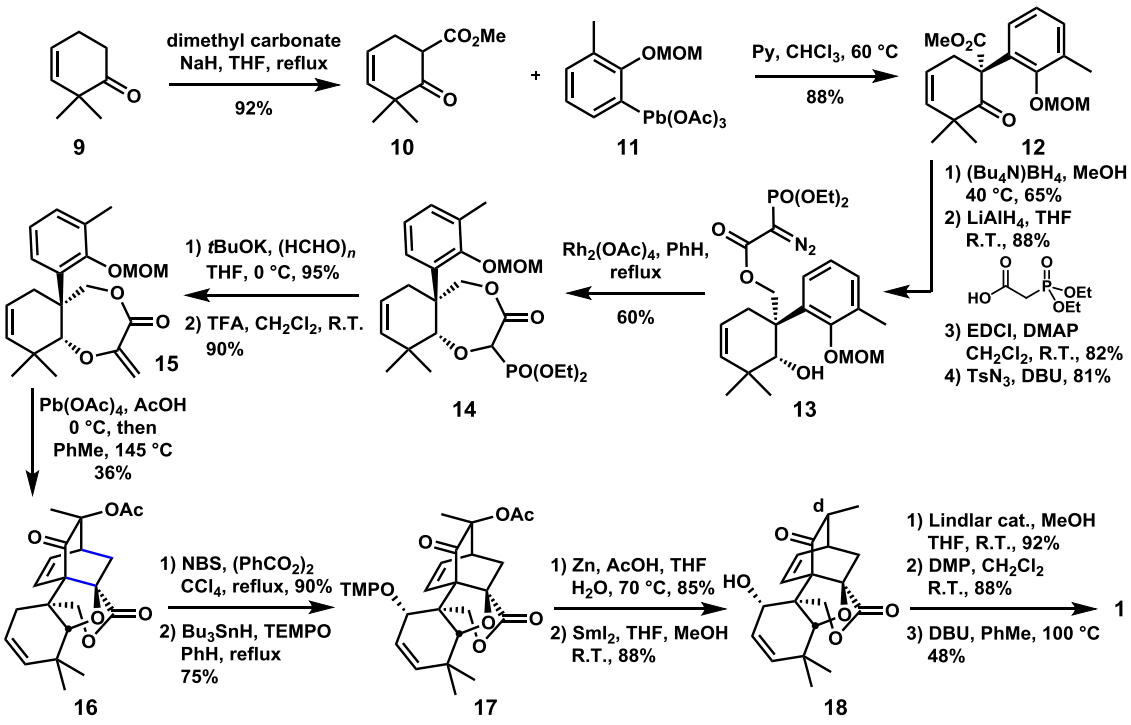
1.1.3. Total Synthesis of Maoecrystal V

To date, three total syntheses of Maoecrystal V have been reported, the first by the Yang group[3] in 2010, the second by the Danishefsky group[4] in 2012, and the third by the Zakarian group[5] in 2013.

1.1.3.1. By Yang et al.

Yang and co-workers worked out the first total synthesis of Maoecrystal V by employing a rhodium(II) catalyzed carbene O-H bond insertion (Figure 5)[3]. The intermediate **14** allowed access to the desired dienophile **15** for the intramolecular Diels-Alder reaction. After the cyclization, a mixture of *endo* and *exo* isomers was obtained. The desired *endo* product **16** was separated from the mixture in 36% yield. Afterwards, an interesting oxidation of cyclohexene **16** was conducted to form the allylic alcohol in **18**. Lastly, an epimerization at carbon **d** was required, since unfortunately the reduction of the acetate in **17** yielded the incorrect stereochemistry. Still, after the epimerization a 1:1 mixture of isomers was produced, and only half of the material corresponded to the natural product **1**. The total synthesis of Maoecrystal V was completed in 21 total steps with a 0.33% overall yield.

Figure 5. First total synthesis of Maoecrystal V.

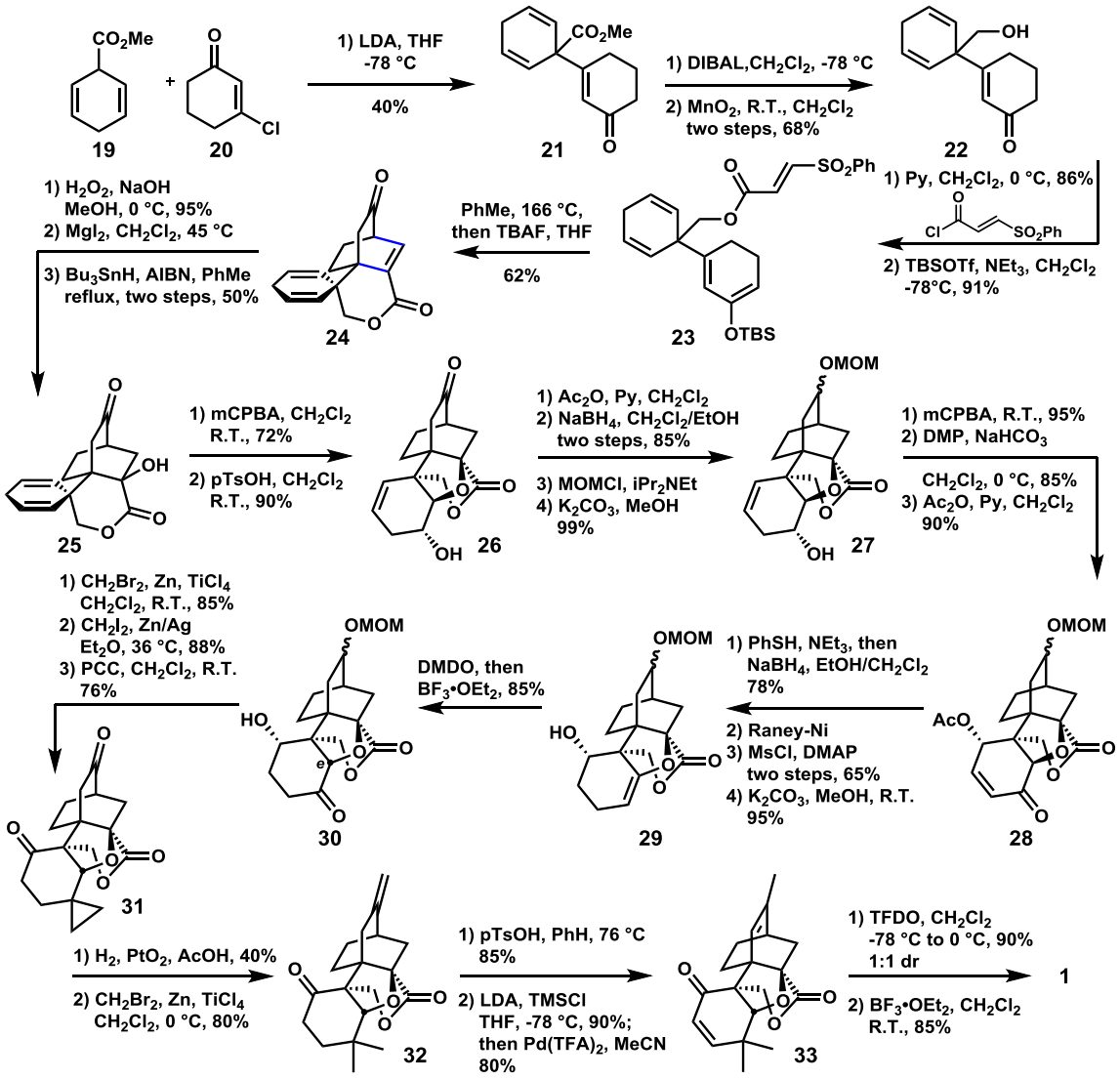


1.1.3.2. By Danishefsky et al.

After two years Danishefsky's group published a full article describing the second total synthesis of Maoecrystal V[4]. Their first synthetic approach unfortunately generated the undesired diastereomer after the intramolecular Diels-Alder reaction. They successfully modified the synthetic strategy, which allowed accessing the natural product **1** in 38 steps with a <0.04% overall yield. The synthetic scheme is outlined below (Figure 6). Many more steps were required to finish the synthesis, and the need to carry the mixture of isomers **27** throughout the later part of the synthesis did make this task even more challenging. Interesting oxidative manipulations were implemented in the synthesis in order to obtain the desired result; for example, the oxidation of vinyl ether **29** into

compound **30**. Epoxidation of the alkene takes place from the bottom-face of the molecule, which leads to the installation of the correct stereochemistry at carbon **e** after the 1,2-hydride shift.

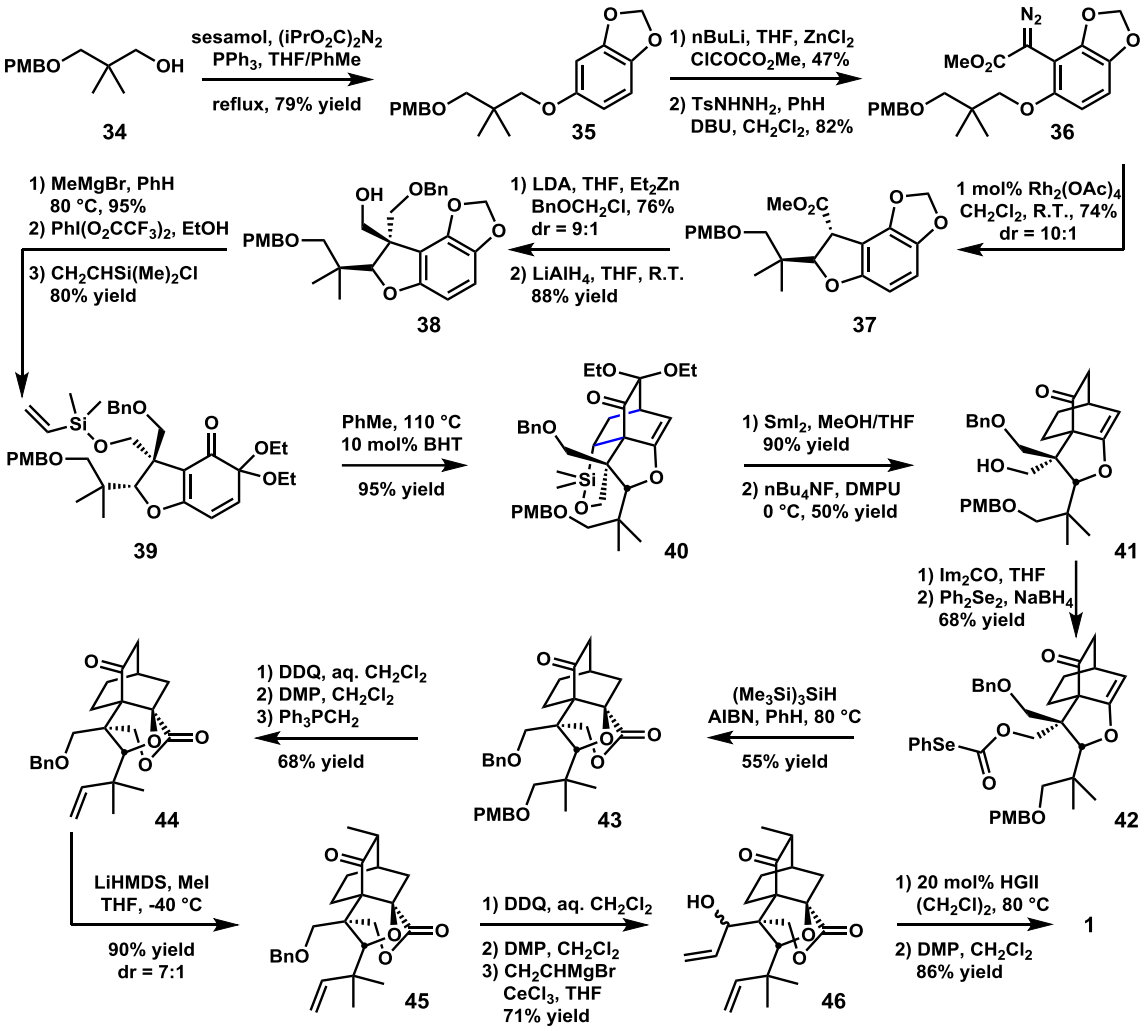
Figure 6. Second total synthesis of Maoecrystal V.



1.1.3.3. By Zakarian et al.

The third total synthesis was reported almost a year later by the Zakarian group (Figure 7)[5]. In this work, the cyclic five membered ether was generated prior to the intramolecular inverse demand Diels-Alder reaction. The [4+2] cyclization beautifully generated the bicylo[2.2.2]octene core **40** employing a tethered vinylsilanol as a dienophile. The six membered lactone was formed via radical cyclization, starting with selenocarbonate **42** in the presence of AIBN as a radical initiator and $(Me_3Si)_3SiH$ as a less efficient hydrogen atom donor in order to prevent the fast radical hydrogen recombination prior to the cyclization step. Lastly, a ring closing metathesis followed by oxidation to an enone furnished Maoecrystal V in 25 steps with 0.3% overall yield, starting from commercially available 1-chloro-3-methyl but-2-ene.

Figure 7. Third total synthesis of Maoecrystal V.



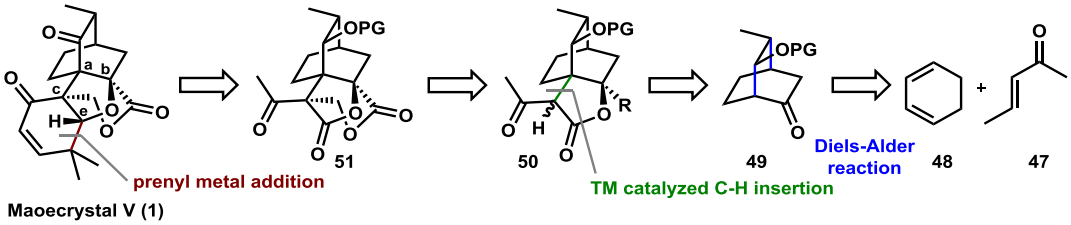
1.2. Synthetic Plan for Maoecrystal V

1.2.1. Retrosynthesis

Our proposed strategy differs from all other known proposals. We propose the stepwise introduction of the ring systems after the synthesis of bridged bicycle **49**. First, γ-lactone **50** would be formed via a transition metal catalyzed carbene C-H bond insertion at

the bridgehead position, as illustrated in the Figure 8. The δ-lactone in structure **51** would be formed during the cyclization between a primary alcohol and an ester or acid chloride.

Figure 8. Proposed retrosynthesis.



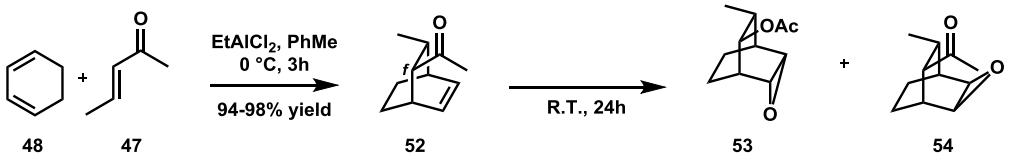
Lastly, the cyclohexenone quaternary carbon center could be accessed by using a prenyl metal addition to the in-situ generated oxocarbenium ion from the corresponding lactol in the presence of a Lewis acid. Installment of the required stereochemistry at carbons **b**, **c** and **e** would be controlled by the large protecting group (PG) which provides diastereoselectivity through steric hindrance.

1.2.2. Synthesis of the 1st Advanced Intermediate 60

The forward synthesis of Maoecrystal V starts with an intermolecular Diels-Alder reaction between 1,3-cyclohexadiene (**48**) and 3-penten-2-one (**47**) (Scheme 1). The cyclization generates the *endo* product **52** as well as introduces the methyl group with the correct stereochemistry. Next, the bicyclo[2.2.2]octene **52** was subjected to Baeyer-Villiger oxidation in order to obtain the necessary oxidation state at carbon **f**. As expected, epoxidation competed with Bayer-Villiger oxidation, generating the doubly oxidized products **53** and **54** predominantly. A change of oxidants to H_2O_2, magnesium monoperoxyphthalate, *t*BuOOH, $(TMSO)_2$, or urea hydroperoxide in combination with

different additives (acid or base) and solvents did not provide selectivity for the Baeyer-Villiger reaction. We realized that compound **53** could be readily transformed into the target ketone **60** (Scheme 2). Importantly, we noticed a much cleaner formation of **53** by using pure mCPBA instead of the commercially available reagent, which contains up to 30% of H_2O and benzoic acid. Using pure mCPBA as an oxidant and benzene or pentane as a reaction solvent led to the highest product **53**:**54** ratio. For safety reasons we chose pentane over benzene as an optimal reaction solvent, leading to 75-85% isolated yields for doubly oxidized product **53**.

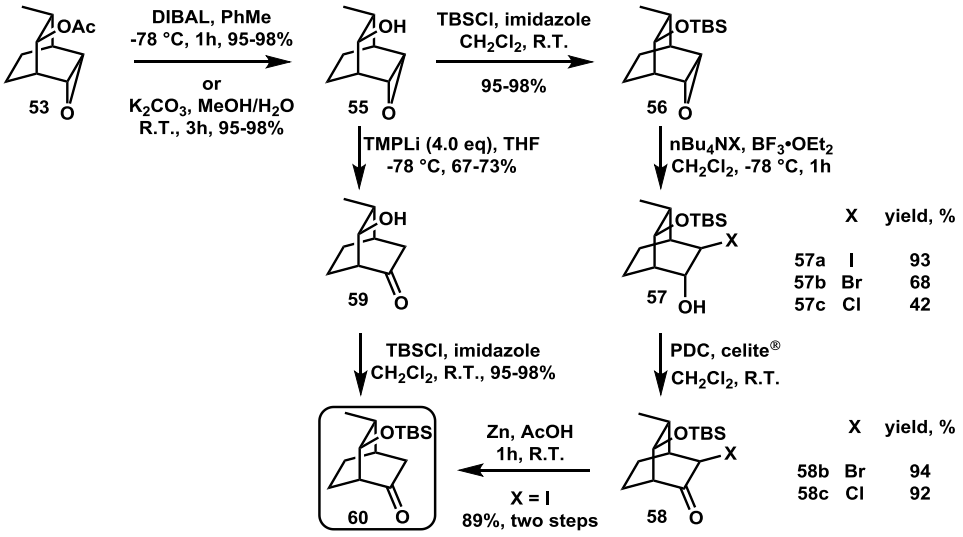
Scheme 1. Baeyer-Villiger oxidation and epoxidation of bicycle **52**.



Oxidant	*Additive*	*Solvent*	*Ratio of products by ^{1}HNMR:*	
mCPBA	AcOH	CH_2Cl_2	1	1.2
mCPBA	$NaHCO_3$	CH_2Cl_2	1.5	1
mCPBA	-	CH_2Cl_2	1.7	1
mCPBA	-	H_2O	1.4	1
mCPBA	-	PhH	3.5	1
mCPBA	-	pentane	3.9 (75-85% isolated)	1

The acetate group in compound **53** was changed to a larger *t*-butyldimethylsilyl (TBS) group. The acetate group can be cleaved under reducing or basic conditions. Although the yields are very high for both reactions, the latter is more practical. Silylation proceeds cleanly to generate silyl ether **56**.

Scheme 2. Two synthetic pathways for synthesis of advanced intermediate **60**.

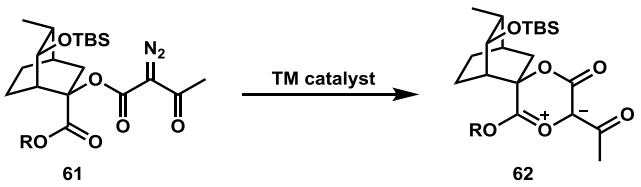


Next, we proposed two pathways to access the advanced intermediate **60** (Scheme 2). The longer route requires a nucleophilic epoxide opening with a halide, oxidation of the secondary alcohol to the α-halo ketone **58**, and the reduction of the halide to generate product **60** with 67% overall yield. On the other hand, when compound **55** is treated with 4 equivalents of the strong base TMPLi, the deprotonated alkoxide directs the base for the deprotonation of the closest epoxide hydrogen, which generates an enolate upon the epoxide opening via elimination. After the protonation of the enolate with aqueous acid, the desired product **60** was isolated as a single regioisomer. It is important to note that the weaker base LDA does not work, and other solvents like Et_2O and PhMe are not suitable due to poor solubility of the deprotonated species. If less than 4 equivalents of TMPLi base is used, the reaction does not go to completion and starting material is recovered. An overall 61% yield can be obtained for the second and more shorter route.

1.2.3. Introduction of Latent Carboxylate Functionality in Compound 63

With the first important intermediate in our hands, we started to prepare for the next important transformation – C-H bond insertion. It is known that carbenoids in the presence of carbonyls generate dipoles[6], like that which is illustrated in Figure 9. For us this transformation is unproductive. In order to avoid the formation of dipole **62**, the R group in compound **63** (Scheme 3) must be unreactive towards the in-situ generated metal carbene during the C-H bond insertion step. Preferably the R group can be easily transformed into the carboxylate group.

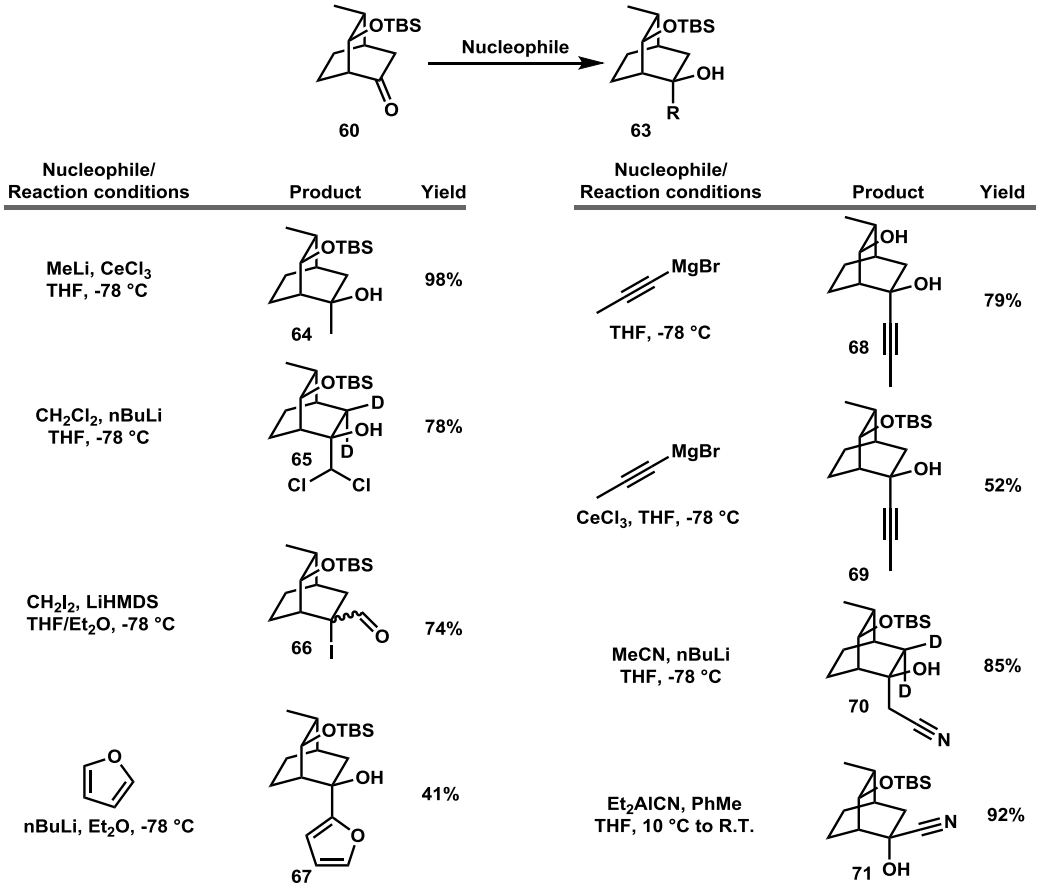
Figure 9. Dipole formation.



We started to examine different nucleophiles (Scheme 3). As expected, the large silyl group prevented the nucleophile addition from the β-face, which led to the generation of the desired stereoisomer. Compound **71** was an exception. The opposite stereoisomer (cyanohydrine **71**) was formed when ketone **60** was reacted with Nagata's reagent (Et_2AlCN). The cyanide addition under these reaction conditions is known to be a reversible process[7], and the formation of the thermodynamic product is observed. Trauner et al. observed the same stereoselectivity when reacting a ketone with cyanide in their studies for Maoecrystal V synthesis[2g].

All attempts to add the trichloromethyl anion to ketone **60** were unsuccessful. Interestingly, the in situ generated dichloromethyl anion cleanly adds to ketone **60** to generate product **65**. However, when the diiodomethane is used instead, the α-iodo aldehyde **66** is isolated. Presumably, the diiodomethyl alcohol intermediate is more prone to generating an epoxide, which then rearranges into the observed structure **66** via 1,2-iodide migration. We encountered cleavage of the silyl protecting group when reacting propynylmagnesium bromide with ketone **60**. Switching to the less basic organocerium reagent[8] allowed the isolation of the desired product **69** in acceptable yield. The tertiary alcohol **64** was chosen as a model substrate for the initial C-H bond insertion screening. The reactivity of most of the other tertiary alcohols will be discussed in the next section.

Scheme 3. Syntheses of different latent carboxylate groups.



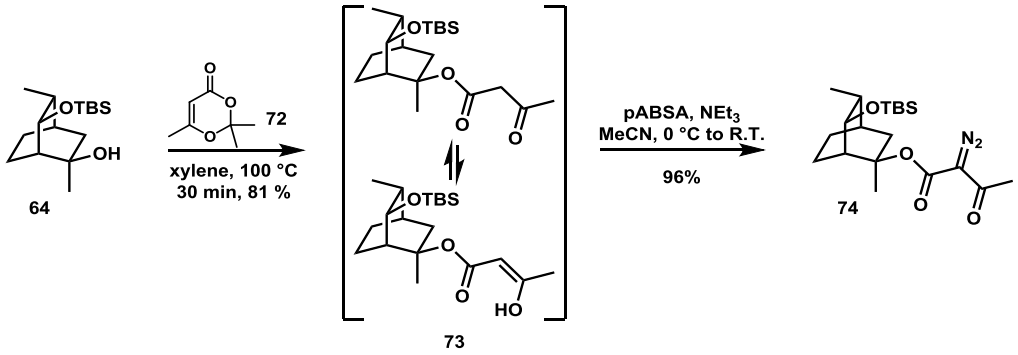
1.2.4. Synthesis of Different Diazo-Precursos

This section will include syntheses of different diazo-compounds. The reason why these particular substrates were made will be discussed in detail in section 1.2.6.

Pyrolysis of dioxinone **72** takes place above 100 ˚C providing acetylketene[9], which in the presence of alcohol **64** generated β-ketoester as a mixture of keto-, enol-tautomers (Scheme 4). Diazo-acetoacetate **74** was formed by reacting β-ketoester **73** with diazo-

transfer reagent pABSA, which is a well-established method[10]. It served as an initial test compound.

Scheme 4. Synthesis of diazo-acetoacetate **74**.

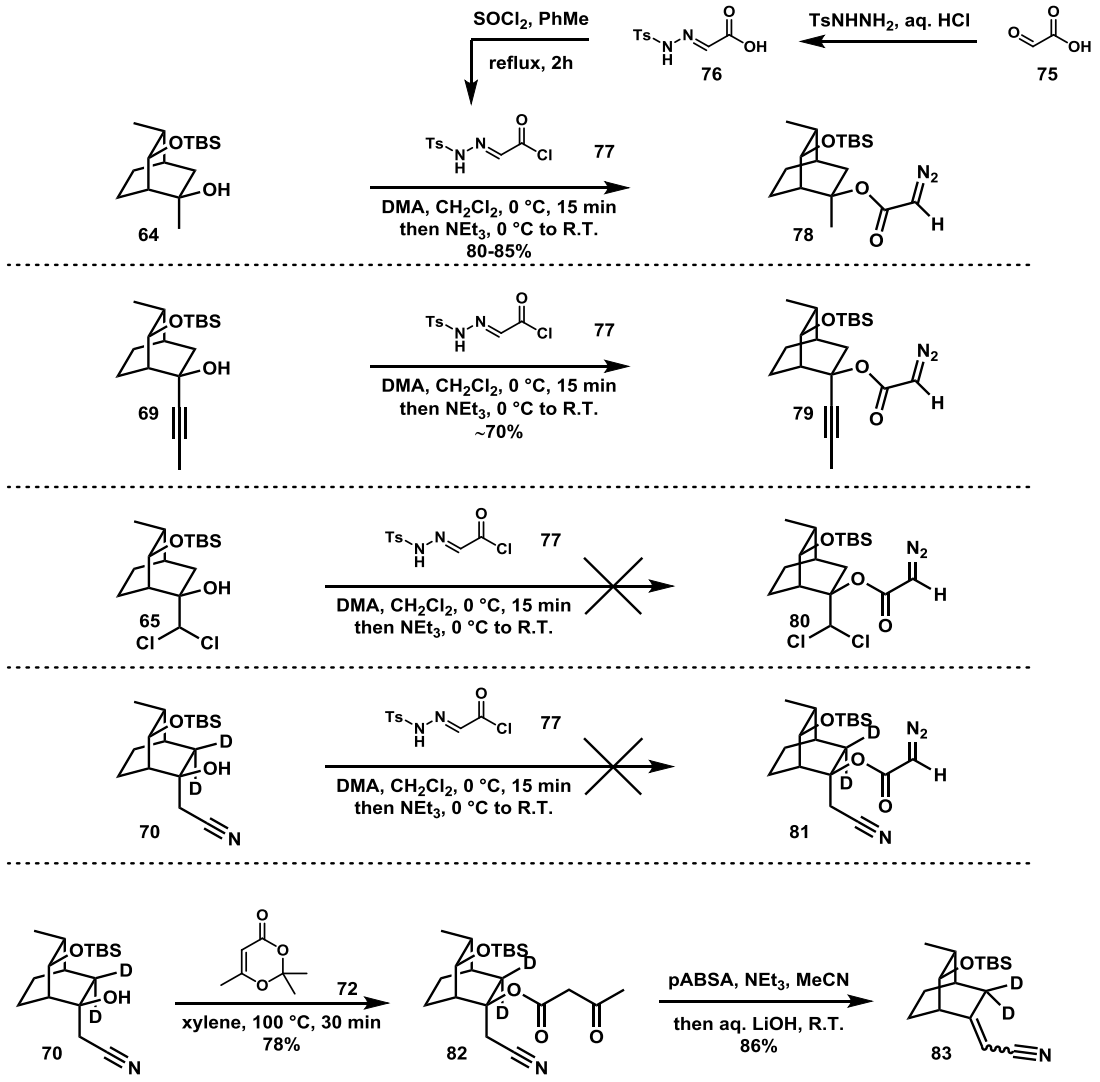


The diazo-acetate group can be introduced using the very useful protocol written by House and Blankley[11]. The diazo-transfer reagent (**77**) is not commercially available. In order to access larger amounts of **77** without being exposed to benzene, the reaction solvent was changed to toluene. This change greatly simplified the recrystallization step. Due to very high solubility of **77** in benzene at room temperature, the filtration of crystalized product was performed while the solution was still cold. Benzene, however, freezes below 5 ˚C, which complicated the isolation process. Thus the toluene (mp = -95 ˚C) was chosen as an optimal solvent. Diazo-acetates **78** and **79** were isolated in good yields (Scheme 5).

The steric hindrance around the tertiary alcohols **65** and **70** prevented the formation of diazo-acetates **80** and **81**. We attempted the stepwise formation of diazo-acetate **81**. Under thermal reaction conditions we were able to access β-ketoester **82**. The diazo-acetoacetate formation went cleanly. Next, we envisioned a deacetylation step to generate

diazo-acetate **81**. However, under basic reaction conditions, deprotonation of the more acidic nitrile α-hydrogen facilitated an elimination step to form α,β-unsaturated nitrile **83** instead.

Scheme 5. Syntheses of different diazo-acetates.



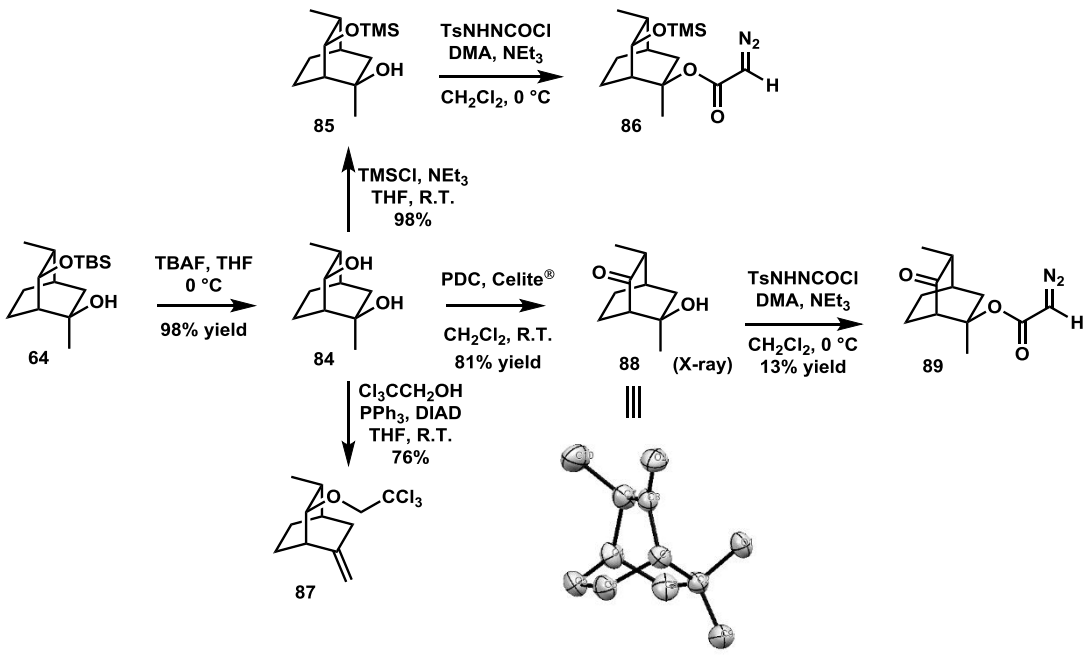
To test the influence of the large TBS group on C-H bond insertion, we attempted to synthesize a diazo-acetate with a smaller protecting group on the secondary alcohol. The

smaller trimethylsilyl ether **85** in the reaction with diazo-transfer reagent generated an inseperable mixture of products.

The methyl ether C-H bonds might be activated for the insertion reaction, thus we attempted to synthesize trichloroethyl ether instead. Due to strong electronwithdrawing nature of chlorine the methylene C-H bonds next to oxygen should be deactivated for the C-H bond insertion. We subjected the diol **84** to Mitsunobu reaction conditions. Unsaturated trichloroethyl ether **87** was isolated in 76% yield. A migration of the trichloroethyl group from the secondary alcohol to the tertiary might be taking place via a six member transition state. The tertiary ether then gets activated for elimination and generates the disubstituted olefin **87**.

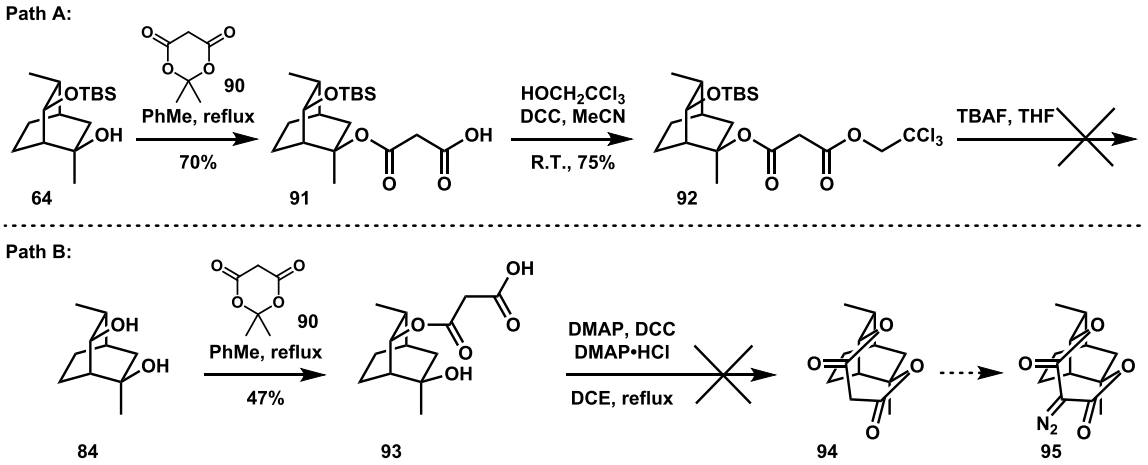
A free alcohol would not be suitable for the C-H bond insertion reaction, as it would undergo insertion in the O-H bond instead. Thus, after the oxidation of the secondary alcohol, we synthesized diazo-acetate **89** in a low 13% yield. The structure of tertiary alcohol **88** was confirmed by X-ray diffraction analysis. The crystal structure allowed confirmation of the stereochemistry in compound **64**, which had been previously assigned by 1D nOe studies.

Scheme 6. Elimination of steric hindrance for C-H insertion step.



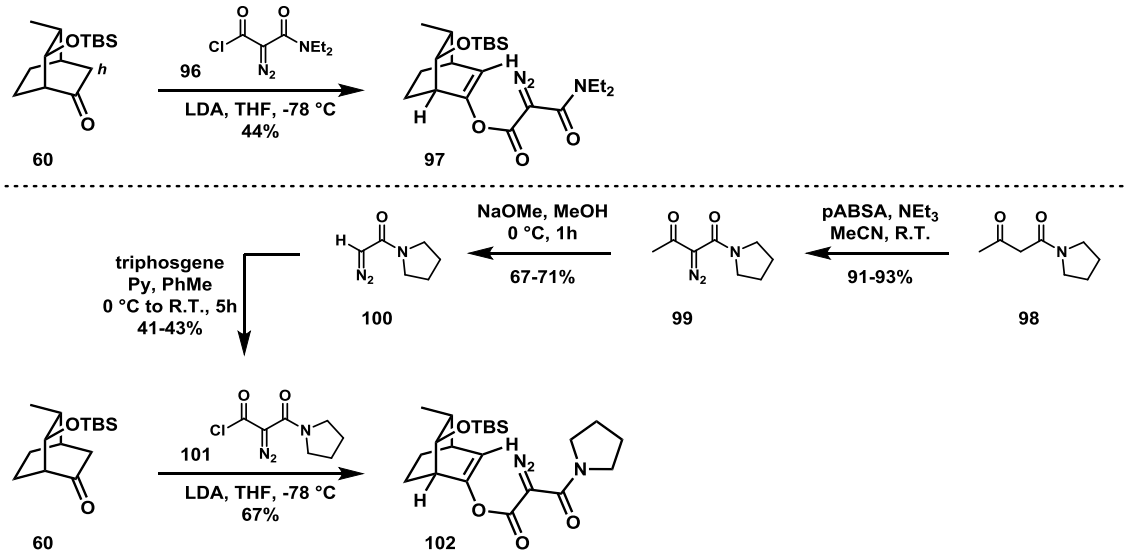
Another proposal was to link both alcohols together (structure **95**) and then perform an intramolecular C-H bond insertion (Scheme 7). Unfortunately, due to the moderately high ring strain energy of the expected eight membered cycle **94** (~9.6 kcal/mol greater than cyclohexane[12]), neither of the pathways A or B produced the desired product **94**. The reaction with Meldrum's acid with **64** and **84** afforded the corresponding carboxylic acids **91** and **93**. The deprotection of the silyl group was unsuccessful in ester **92**. For compound **93**, the Keck macrolactonization did not produce the expected result, and instead a complex mixture of products was obtained.

Scheme 7. Attempts to synthesize diazo-compound **95**.



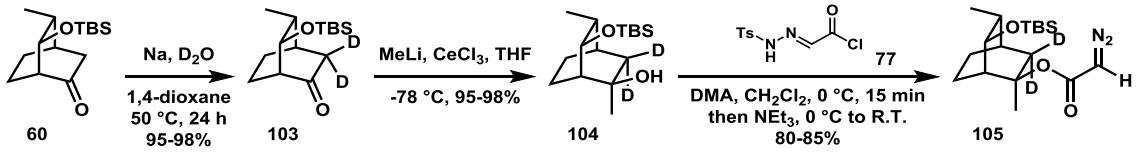
Next, we proposed to change the carbon **h** hybridization in **60** from sp^3 to sp^2, ending with enol diazo-acetates **97** and **102** as our substrates (Scheme 8). The preparation of acetyl chloride **96** has been described in the literature[13]; reagent **101** was synthesized using the same strategy.

Scheme 8. Synthesis of enol diazo-acetates **97** and **102**.



A strategic use of deuterium kinetic isotope effect to favor the desired functionalization step, in the total synthesis of the Welwitindolinone class of compounds, has been reported by Garg et al.[14] Similarly, we proposed to use deuterium as a blocking group for the methylene carbon in **60** (Scheme 9). Usage of NaOD in D_2O[15] for deuterium incorporation in the ketone **103** was superior to other exchange conditions ($KOtBu/D_2O$; $TBD/CDCl_3$[17]), leading to 99% substitution. Diazoester **105** was synthesized in 80-85% yield.

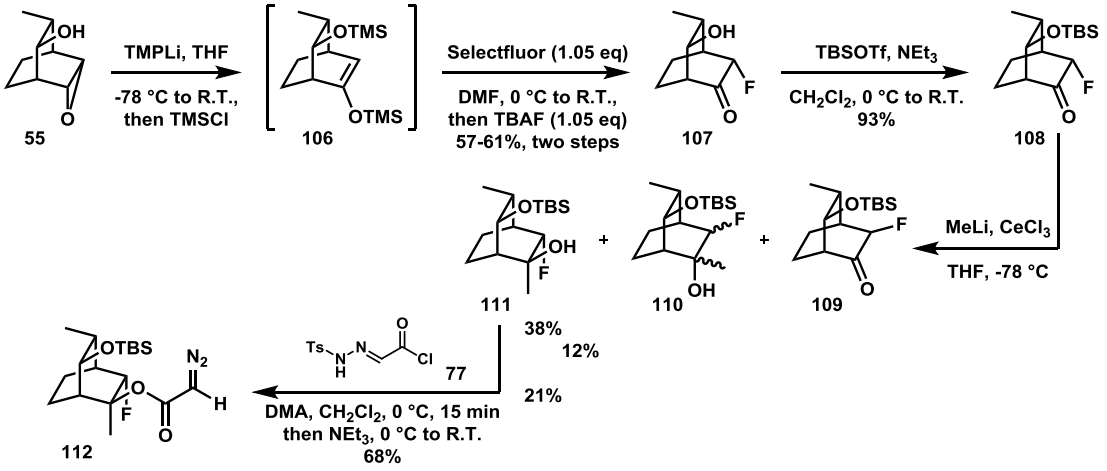
Scheme 9. Synthesis of α-deuterated diazo-acetate **105**.



Next, we proposed to use different blocking groups at the α-position to the diazo-acetate functional group. α-Iodo and α-bromo ketones **58a** and **58b** from Scheme 2, are not suitable starting material for the formation of the corresponding α-iodo or α-bromo diazo-acetates. α-Iodo, α-bromo ketones are readily converted into the cerium enolates when treated with cerium reagent[8], as a result, 1,2-addition product is not obtained. α-Chloro ketone **58c** can be transformed into α-chloro diazo-acetate, however, the formation of **58c** from epoxide **56** is low yielding (39% yield for two steps). Thus, we chose the smallest and the most electron withdrawing halogen – fluorine. We assumed that introducing a fluorine *trans* to the hydroxyl (see **112**) might lead to a productive result (Scheme 10). First, the diazo-acetate formation would be manageable; second, the C-H bond would be deactivated towards the insertion due to the electron withdrawing nature of the fluorine.

The attempted fluorination of ketone **60** (starting material from the previous Scheme) with Selectfluor produced a mixture of products. In order to eliminate the side reactions, we started with the epoxide **55**. After the deprotonation/rearrangement, both the alkoxide and enolate were protected as TMS ethers (**106**). Only then was the silyl enol ether **106** subjected to α-fluorination, which worked in 57-61% yield. Next, the secondary alcohol in compound **107** was protected with a TBS group. The milder TBSCl/imidazole conditions did not work for this particular substrate. Due to steric hindrance around the ketone, a mixture of products **109**, **110** and **111** was produced in the reaction with methyl cerium. Still, enough material was obtained to carry on diazoester formation from **111**. Diazoacetate **112** was isolated in 68% yield.

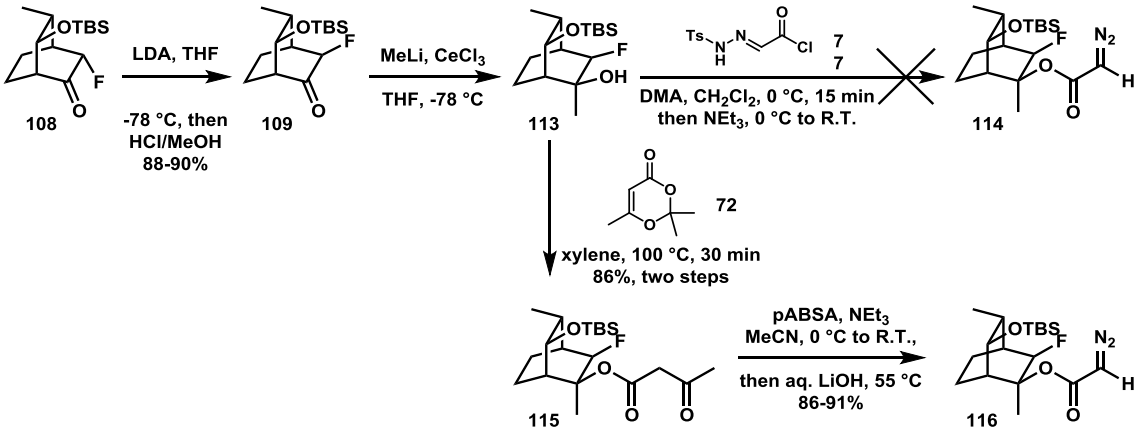
Scheme 10. Synthesis of *trans* α-fluoro diazoacetate **112**.



We asked ourselves a question: would the selectivity for C-H insertion change with *cis*-fluorodiazo-acetate **116** (Scheme 11)? To provide an answer, we prepared compound **109** through epimerization. Direct diazo-ester transfer reaction did not work on alcohol

113. We then looked at a stepwise alternative. Indeed, when the diazo-acetoacetate generated from β-ketoester **115** was heated in aqueous base solution, deacetylation took place. Product **116** was isolated in 86-91% yield.

Scheme 11. Synthesis of *cis* α-fluoro diazoacetate **116**.

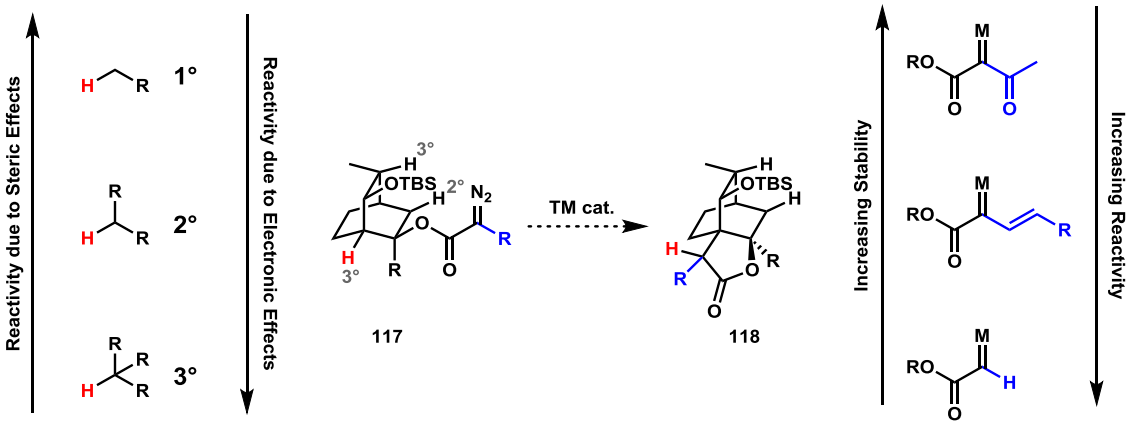


1.2.5. Background for C-H Insertion

Metal carbene C-H bond insertion is a well studied transformation. Rhodium(II) catalysts are very effective for diazo decomposition[18]. Site-selectivity for C-H bond insertion is controlled by electronic and steric effects. Sites that can stabilize a positive charge buildup in the transition state are more reactive towards C-H bond activation. However, steric hindrance might change this selectivity by favoring the 2˚ or 1˚ C-H bonds over 3˚ (Figure 11)[18]. It is also known that the electrophilicity of the metal carbenoid has a marked influence on the selectivity of C-H bond activation. Acceptor/acceptor and acceptor substituted carbenoids are more electrophilic than acceptor/donor metal carbenes.

Five membered ring formation is a favored process for intramolecular insertion due to entropic factors and transition state geometry.

Figure 11. Considerations for C-H insertion step.

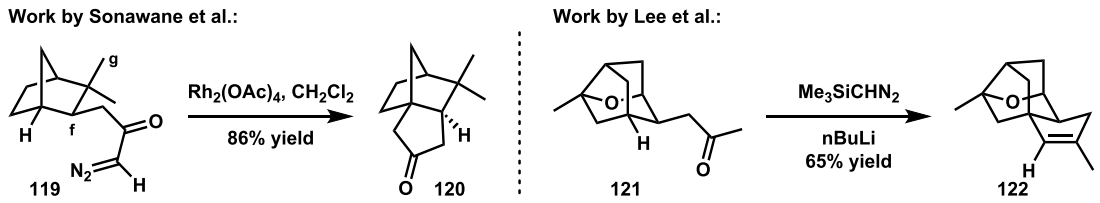


This information allows us to examine our substrate for the key C-H insertion step. The molecule **117** has two tertiary and one secondary C-H bonds that would be accessible to the carbene. Based on the trend presented on the left side of Figure 11 – the bridgehead tertiary C-H bond should be more reactive with metal carbene. It would also generate a preferred five membered ring. On the other hand, an electron withdrawing inductive effect of silyl ether oxygen might deactivate the site for C-H bond insertion, which might reverse the selectivity.

There are very few reports in the literature that correspond to our proposed bridgehead C-H bond insertion. Sonawane and co-workers showed a very selective insertion into a bridgehead methine, generating a five membered ring **120**[19]. The 4- and 6-membered ring formation by insertion into **f** or **g**, respectively, was not observed (Figure

12). In more recent work, Lee and co-workers reported a very selective insertion into the more electron rich methine (product **122**), with no methylene insertion being observed[20]. These findings support our proposal.

Figure 12. Literature examples of insertion in bridgehead C-H bonds.

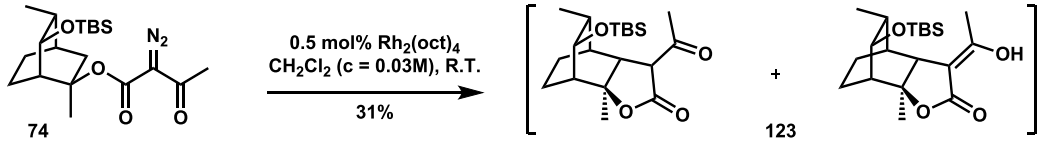


1.2.6. Reactivity of Different Diazo-Compounds

In this section, the reactivity of all the synthesized diazo-esters will be discussed in detail. The data will be presented in chronological order, which will lead to the best system for selective bridgehead C-H bond insertion to date.

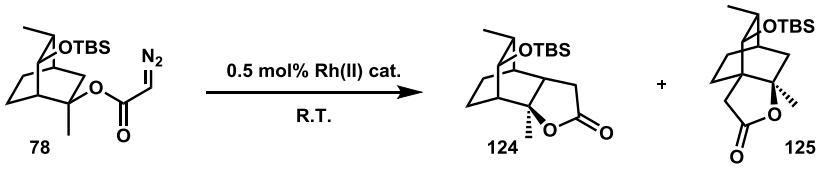
We started the C-H bond insertion study with substrate **74**. Unfortunately, when diazo-compound **74** was subjected to catalytic amounts of $Rh_2(oct)_4$, none of the desired methine C-H insertion product was observed (Scheme 12). Presumably, the less selective acceptor/acceptor carbene is more sensitive towards the steric hindrance (provided by large silyl group) or the methine C-H bond is less activated than the methylene C-H bond due to the electron withdrawing inductive effect of oxygen, thus favoring the insertion in methylene C-H bond.

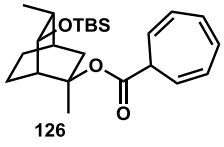
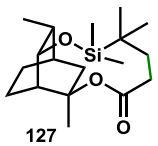
Scheme 12. C-H insertion with diazo-acetoacetate **74**.



We thought the smaller and more reactive diazo-acetate group might change the selectivity, favoring methine over methylene C-H bond insertion. Unfortunately, the smaller diazo-acetate **78** produced methine insertion product **125** in a very low yield when reacted with catalytic amounts of $Rh_2(oct)_4$ (Scheme 13). The smaller, highly reactive metal carbene still preferred to insert in the methylene C-H bond (product **124**).

Scheme 13. Reactivity of diazo-esters.



Entry	Catalyst	Solvent	Conc., M	Yield	Yield	
1	$Rh_2(oct)_4$	CH_2Cl_2	0.03	24%	8%	
2	$Rh_2(esp)_2$	CH_2Cl_2	0.01	32%	25%	
3	$Rh_2(esp)_2$	CH_2Cl_2	0.005	35%	26%	
4	$Rh_2(esp)_2$	PhH	0.01	14%	12%	 126 53%
5	$Rh_2(TPA)_4 \cdot CH_2Cl_2$	CH_2Cl_2	0.01	-	-	 127 87%

It is known that changing the carboxylate or carboxamide ligands yields dirhodium(II) complexes with different physical and chemical properties, which accordingly leads to different observed selectivity's for C-H bond insertion and/or cyclopropanation[21]. No reaction was observed when using the more electrophilic $Rh_2(tfa)_4$. Interestingly, when using the Du Bois catalyst, $Rh_2(esp)_2$, greater selectivity for methine C-H insertion was observed than before (entry 2, Scheme 13). $Rh_2(esp)_2$ has been developed and extensively used for C-H amination reactions[22]. Recently, this rhodium(II) catalyst has been the catalyst of choice for some C-H insertion reactions as well[23]. Bidentate esp ligands provide higher kinetic stability for the complex compared to tetracarboxylate ligands.

The unproductive homodimerization of starting material **78** always competes with C-H bond insertion under the given reaction conditions. However, decrease in concentration (0.005M versus 0.01M) did not improve the overall yield of insertion products (entry 3, Scheme 13).

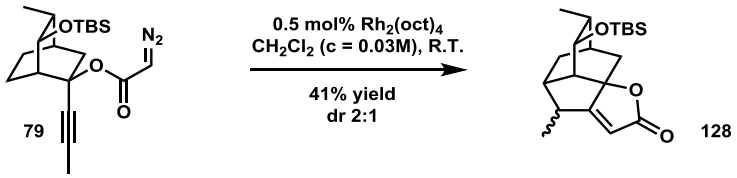
Next, another common solvent for C-H bond insertion reactions, benzene, was used. Unfortunately, the cyclopropanation of the reaction solvent, followed by ring expansion (known as the Buchner reaction), was faster than C-H bond insertion, generating cycloheptatriene **126** as a major product (entry 4, Scheme 13).

Using the more sterically hindered dirhodium(II) tetra(triphenylacetate), $Rh_2(tpa)_4$, chemoselectivity for C-H insertion was changed. Exclusive C-H insertion in one of the

tert-butyl methyl groups from the TBS protecting group was observed. The ten-membered lactone **127** was isolated with 87% yield (entry 5, Scheme 13).

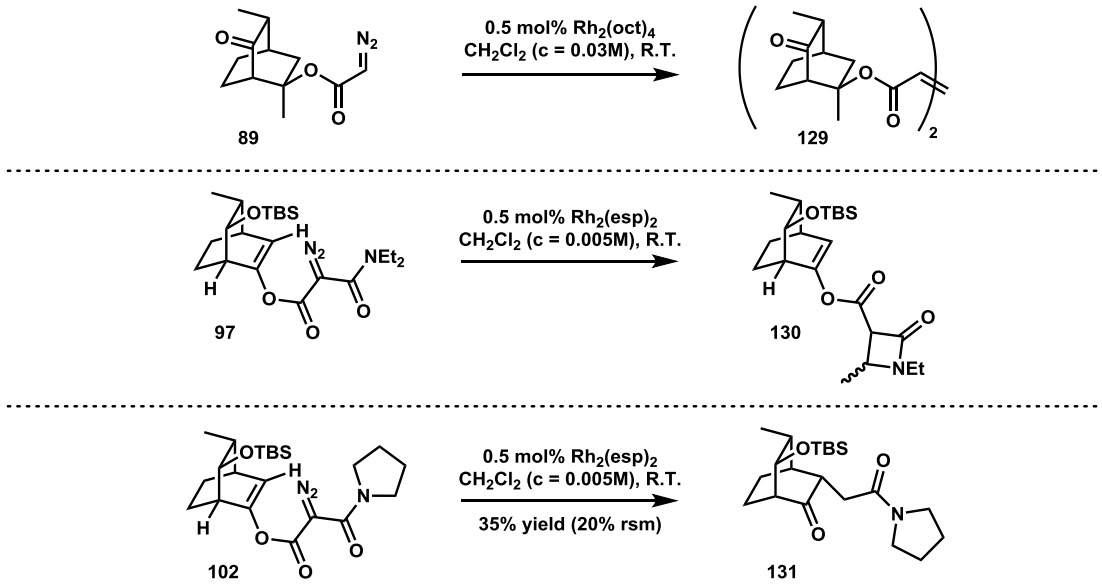
We decided to test the reactivity of alkynyl diazo-ester **79**; alkyne group could be readily transformed into carboxylate, a productive intermediate for Maoecrystal V synthesis. In a reaction with dirhodium(II) complex more polar compound was isolated (Scheme 14). After extensive characterization, the structure was elucidated to be polycycle **128**. This initially unexpected result gained our attention. We saw this reaction as a versatile way to access complex polycyclic systems. This study will be discussed in detail in Chapter 2.

Scheme 14. Reactivity of alkynyl diazo-acetate **79**.



Next, we proposed to test ketone **89** for the C-H bond insertion reaction (Scheme 15). Due to the inductive electron withdrawing effect of the carbonyl group, the methine C-H bond should be deactivated for the insertion reaction. However, insufficient orbital overlap between the methine C-H bond and the π^* of the carbonyl group might decrease the electron withdrawing effect. When carbonyl compound **89** was treated with $Rh_2(oct)_4$, a mixture of products was formed, with homodimerization being the most dominant.

Scheme 15. Reactivity of different diazo-compounds.



The only success that had been observed in these early studies was the synthesis of compound **125** in diminishing 25% yield (Scheme 13). In order to prevent the methylene C-H bond insertion, we proposed to deactivate that site by introducing an sp^2 carbon. Vinyl C-H bond is deactivated for insertion reaction and alkene should be geometrically protected from cyclopropanation. Thus, we tested the diazo-diethylamide **97** (Scheme 15). The insertion into the amide ethyl group generated a mixture of diastereomers of β-lactam **130**.

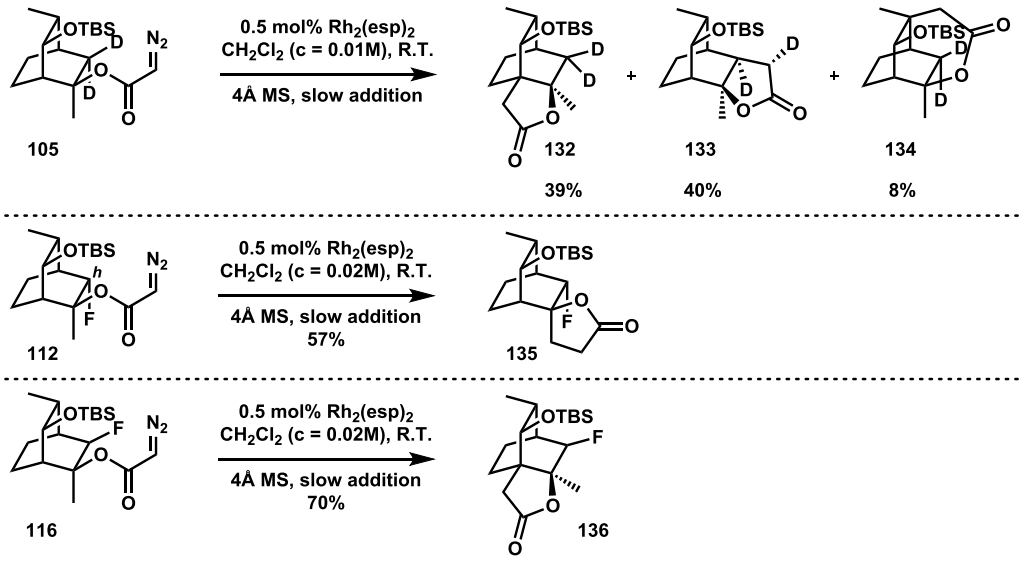
We proposed to test the reactivity of diazo-pyrrolidine amide **102**. The metal carbene would not insert in pyrrolidine C-H bond to generate the [2.0.3] fused ring system. Even though we prevented the insertion in the amide group, we did not observe the formation of our desired bridgehead C-H insertion product when enol diazo-acetate **102** was reacted with $Rh_2(esp)_2$. Under the given reaction conditions, the in situ generated

electrophilic metal carbene derived from **102** underwent intramolecular cyclization with the enol, generating product **131** (Scheme 15). Although this particular type of cyclization has not been described in the literature, there are simpler ways to access the same functionality.

The results discussed above suggest that the methylene carbon must be blocked or its C-H bond deactivated towards functionalization in order to obtain the desired regioselectivity – insertion in the methine C-H bond.

Due to the increased mass of deuterium relative to hydrogen, the rate of reaction involving C-H bonds could be faster than with the corresponding C-D bonds[24]. Thus, the deuterated diazo-acetate **105** was reacted with $Rh_2(esp)_2$ (Scheme 16). The desired methine insertion product **132** was isolated in 39% yield. The rate of insertion in to the C-H and C-D bonds was almost equal, while in the previous example (**78** to **125**, Scheme 13) insertion into the methylene C-H bond was faster than into methine C-H bond.

Scheme 16. Reactivity of α-functionalized diazo-acetates.



This is why we proposed to introduce a halide α to diazo-ester. Halides are inert towards rhodium carbenes, which have singlet character. Moreover, the C-H bond at carbon **h** in *trans* α-fluoro diazoacetate **112** would be deactivated towards the insertion due to the strong electron withdrawing nature of the halogen. To our surprise, when compound **112** was reacted with catalytic amounts of $Rh_2(esp)_2$ (Scheme 16), the insertion into the C-H bond of the methyl group produced the major product **135**. Only trace amounts of the bridgehead C-H bond insertion product was observed. The regioselectivity is not entirely clear, but it might be that the methyl C-H bond is activated due to the strong inductive effects of fluorine. Through space activation cannot be ruled out either.

To obtain different reactivity from that of *trans* α-fluoro diazoacetate **112**, we synthesized *cis* α-fluoro diazoacetate **116** (Scheme 16). Diazo-acetate **116** was reacted with catalytic amounts of $Rh_2(esp)_2$. After full characterization, the product's structure was

confirmed to match lactone **136**. C-H bond insertion was very selective, and product **136** was isolated as the only regioisomer in 70% yield.

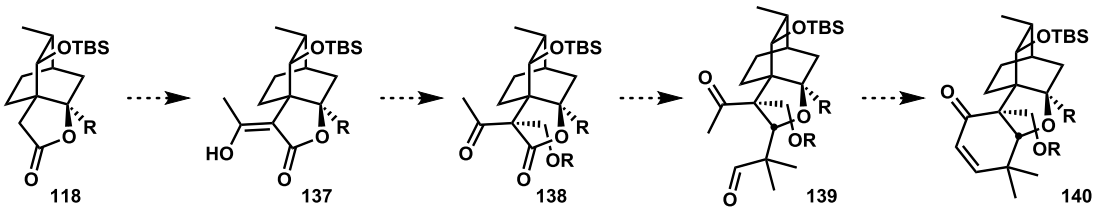
The desire to achieve selective C-H insertion in a complex system led to new, interesting, and valuable results. The last example in Scheme **16**, of course, is the most productive for the further studies towards the synthesis of Maoecrystal V. Even though the core structure of Maoecrystal V contains fluorine (**136**), at the end it might be a beneficial instalment. Introduction of fluorine in the drug-like molecule can have an intense effect on its biological activity. Fluorinated molecules have higher metabolic stability and increased lipophilicity, which facilitates the bioavailability of the molecule, when compared to the non-fluorinated counterparts[25]. 15% of the top 20 drugs have a fluorine atom introduced in the molecule; more commonly used are fluorinated aromatic systems, including Lipitor, Crestor, and Lexapro. However, selective introduction of the fluorine in the molecule might not be as straightforward. Nevertheless, more fluorine containing pharmaceuticals are entering the market[26].

1.2.7. Cyclohexenone Ring Formation in Maoecrystal V

1.2.7.1. Approach I. Nucleophile Addition to Oxocarbenium Ion

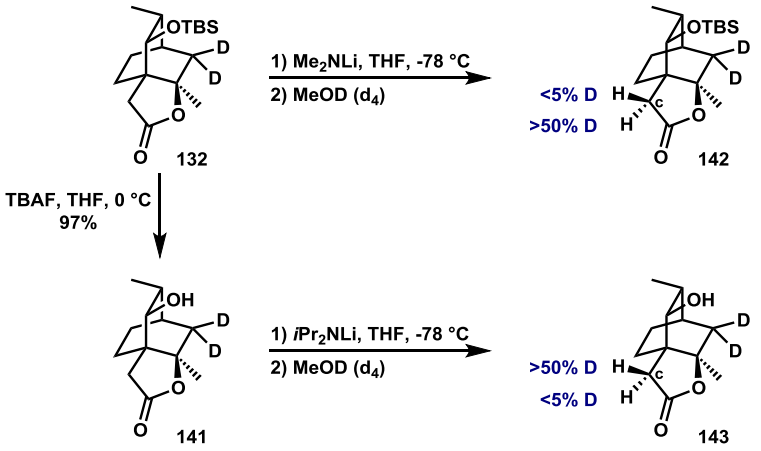
More straightforward access to larger quantities of lactones **132** and **136** (Scheme 16) allowed us to study the forward synthesis. Reacting enolate of **118** with acetaldehyde, followed by oxidation, would generate β-ketoester **137**. Intermediate **139** could be accessed either through silylenol ether or through prenylmetal addition to an oxocarbenium ion, followed by ozonolysis (Scheme 17). The cyclohexenone **140** could be formed through intramolecular aldol condensation of a methyl ketone and an appropriate aldehyde.

Scheme 17. Proposed pathway for the formation of **140**.



First, we attempted to test the influence of the large silyl group on diastereoselectivity at carbon **c** (see **142**, Scheme 18). Two parallel reactions were performed, enolate deuturation in compounds **132** and **141**. The results were as expected; the large protecting group on the secondary alcohol prevents the enolate from being approached by the electrophile from the β-face.

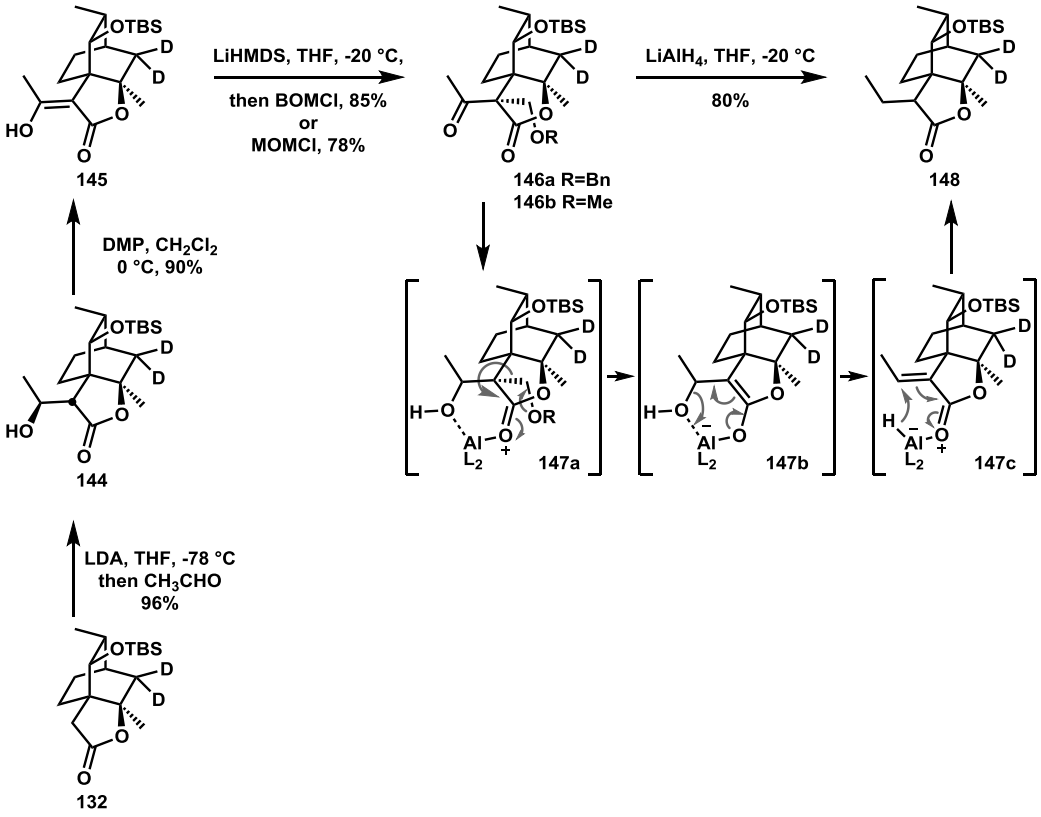
Scheme 18. Influence of TBS group on stereochemistry at carbon **c**.



To access β-ketoester **145**, first, the lactone **132** was deprotonated to form enolate, which was reacted with acetaldehyde. Alcohol was isolated in 96% yield (Scheme 19). Next, secondary alcohol **144** was oxidized with Dess-Martin periodinane, **145** was isolated

in 90% yield and consisted of a mixture of keto, enol tautomers. With the TBS ether in ketoester **145**, the correct stereochemistry at carbon **c** was generated in the reaction between the enolate and BOM- or MOM-chloride (Scheme 19). All attempts to use formaldehyde as an electrophile failed. Next, we subjected the dicarbonyl compound **146a** to reducing conditions. Reduction of the ketone carbonyl likely took place; however, reduction did not occur at the lactone to form the desired diol. Most likely, a retro aldol reaction, followed by 1,4-hydride addition to enone took place (**147a-c**), generating compound **148** instead. The same result was obtained with methyl ether **146b**.

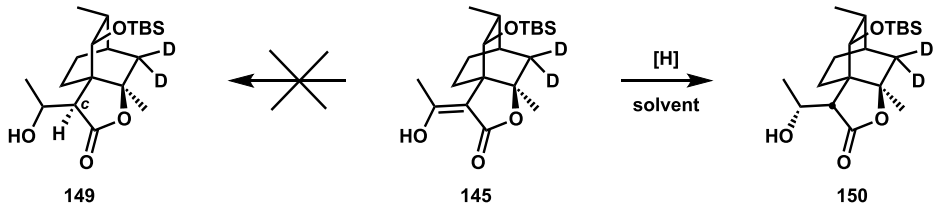
Scheme 19. Quaternary center formation, reduction of compound **146**.



Given the problems with degradation of the quaternary carbon center, we decided to identify conditions for its formation after the construction of cyclohexenone ring. This already has been shown to work on a Maoecrystal V model substrate by Chen et al.[2h]

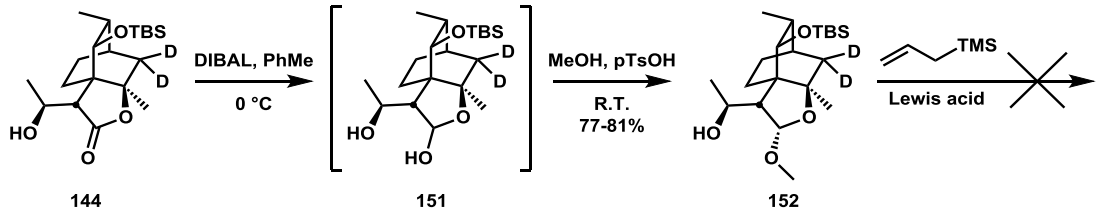
In order to obtain the desired stereochemistry at carbon **c**, in structure **149**, β-ketoester **145** was reacted with a small hydride source (Scheme 20). However, diasteromer **150**, was obtained at all instances of changing the hydride source (DIBAL, Red-Al, Super-H, L-selectride) or solvent (PhMe, Et_2O, CH_2Cl_2).

Scheme 20. Reduction of compound **145**.



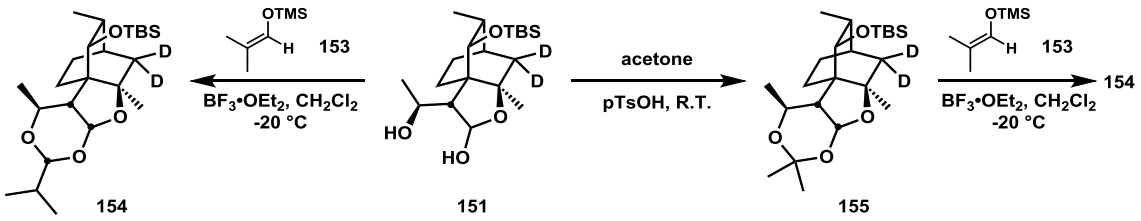
While thinking of alternatives for the cyclohexenone ring formation, we decided to try nucleophilic (trimethylsilyl-enol ether and allyltrimethylsilane) addition to an oxocarbenium ion. Diol **151** was accessed through the reduction of lactone **144** (Scheme 21). Lactol **151** was carried on without purification to the next step, acetal formation (see **152**). Unfortunately, the allyl addition under Lewis acidic conditions did not work in acetal **154**; instead, lactol **151** was identified in the crude ^{1}H NMR spectrum after the work-up.

Scheme 21. Reaction with allyltrimethylsilane.



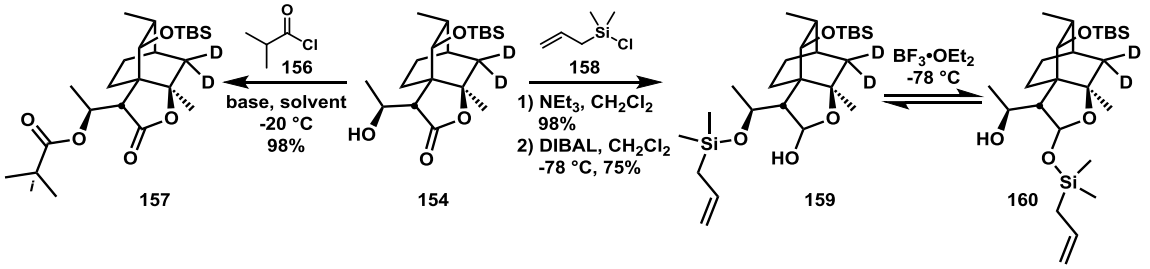
Reaction of the diol **151** with silyl-enol ether **153** generated a mixture of products, the major product, acetal **154,** was isolated in a low xx% yield. We thought protection of both alcohols as acetonide **155** would prevent the formation of acetal **154** with silyl-enol ether **153**; however, the formation of **154** was observed (Scheme 22).

Scheme 22. Reactivity of diol **151**.



We turned our attention to an intramolecular reaction (Scheme 23). The syntheses of the precursors **157** and **159** were straightforward. For compound **157**, the silyl-enol ether formation failed. Deprotonation at carbon **i** with LiHMDS or LDA, followed by the addition of silyl electrophile, only produced trace amounts of silyl enol ether. The allylsilyl migration in compound **159** was observed at low temperatures in the presence of Lewis acid; the allylation of the lactol **159** was not detected.

Scheme 23. Reactivity of compounds **157** and **159**.

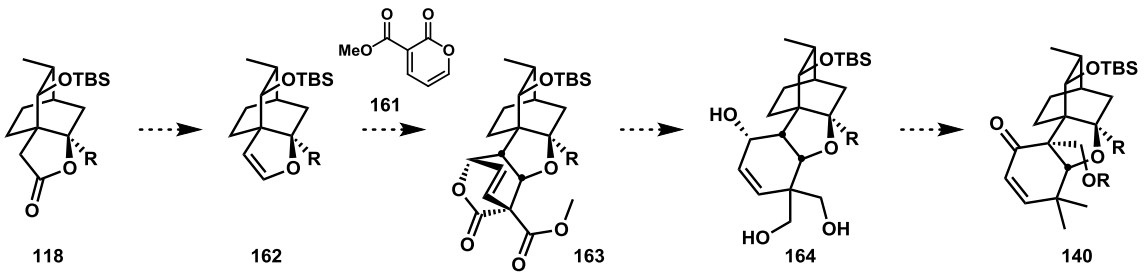


From the study above, we learned that allyldimethylsilane and trimethylsilyl-enol ether addition to an oxocarbenium ion is not a productive pathway for this particular substrate. Complementing our observations, Trauner et al. were unable to affect a prenylation of an aldehyde for their Maoecrystal V synthesis, either[2g].

1.2.7.2. Approach II. Inverse Electron Demand Diels-Alder Reaction

Similar cyclohexene ring systems to those in compound **140** (Scheme 24) can be accessed through Diels-Alder reactions[27]. 3-Carbomethoxy-2-pyrone (**161**) would be used as a diene for the formation of bis bridged bicycle **163**. This would allow accessing the gem-dimethyl group in the cyclohexenone ring of **140**. Dihydrofuran **162** would act as a dienophile in an inverse demand Diels-Alder reaction. Weaker Lewis acids would be used, like $Yb(OTf)_3$ or $Eu(hfc)_3$[28] in order to prevent decarboxylation. Decarboxylation in compound **163** takes place in the presence of strong Lewis acids[29].

Scheme 24. 2nd proposed pathway for the formation of compound **140**.

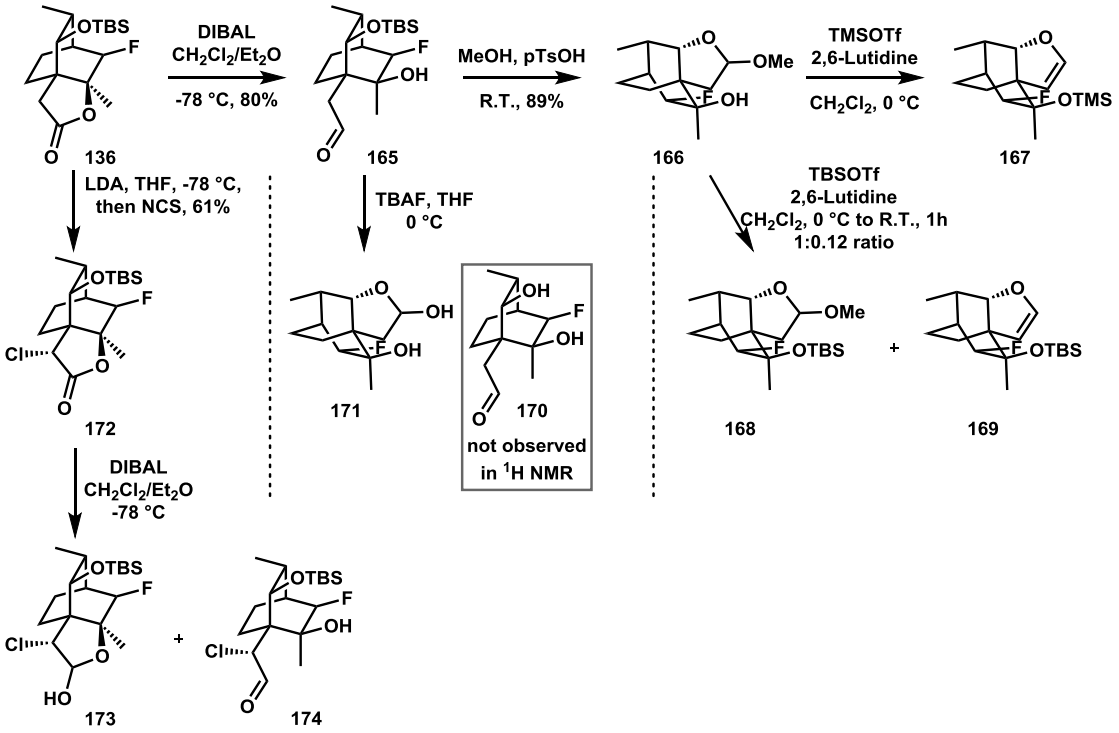


Vinyl ethers can be accessed by reduction of a lactone to a lactol, followed by the formation of a good leaving group, like a mesylate, and then elimination. In our system, acyclic aldehyde **165** is isolated after the reduction of **136** (Scheme 25). Ring opened product formation might be due to additional strain in the five membered ring, which is fused to bridged bicyclic backbone. Attempts to cyclize aldehyde back onto the tertiary alcohol in **165** and reform an acetal failed. Instead, silyl group cleavage, followed by acetal formation with the secondary alcohol, took place. Acetal **166** was carefully characterized by 1D and 2D NMR experiments. Elimination worked nicely to form cyclic vinyl ether **167**. Although it is not productive for the synthesis, we tested the reactivity of compound **167** with pyrone **161** (from Scheme 24). No reaction was observed at room temperature in the presence of $Yb(OTf)_3$ or $Eu(hfc)_3$ catalysts. Under thermal conditions (PhMe, reflux), decomposition of compound **167** took place.

We thought introduction of a halide to the lactol (see **172**) would prevent the ring opening. Indeed, the formation of lactol **173** was observed; however, a significant amount of aldehyde **174** was produced as well (Scheme 25).

The acetal formation with the secondary alcohol **170** could be prevented by simply oxidizing it to the ketone. However, during the deprotection of the silyl group of **165** with TBAF lactol **171** was generated.

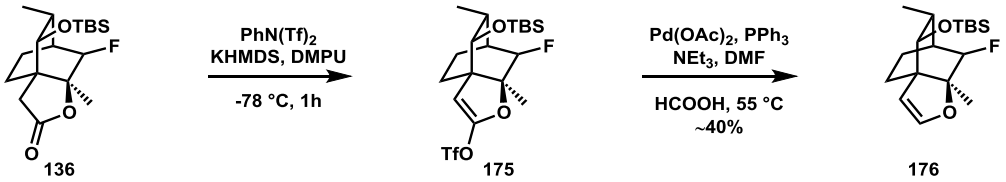
Scheme 25. Cyclic vinyl ether formation.



Another, less common, way to access vinyl ethers is through hydrometallation of vinyl ether triflates or phosphonates (Scheme 26). Formation of **175** was very clean as shown by ^{1}H NMR spectroscopy of the crude material. However, the isolation of **175** was problematic, due to its instability. Thus, crude **175** was subjected to the next step, hydrometallation. Only the conditions shown in Scheme 26 produced the product, which was obtained in ~40% yield. The isolation of **176** from the crude mixture was very difficult due to its similar R_f value to that of the starting material **175**. The product was decomposing

during the purification as well. Other hydride sources, like Et_3SiH or Bu_3SnH, were ineffective. No reaction was observed in toluene or THF, and a Pd^0 catalyst ($Pd(PPh_3)_4$) was ineffective as well. This reaction requires extensive optimization to reach the desired goal.

Scheme 26. Cyclic vinyl ether formation.

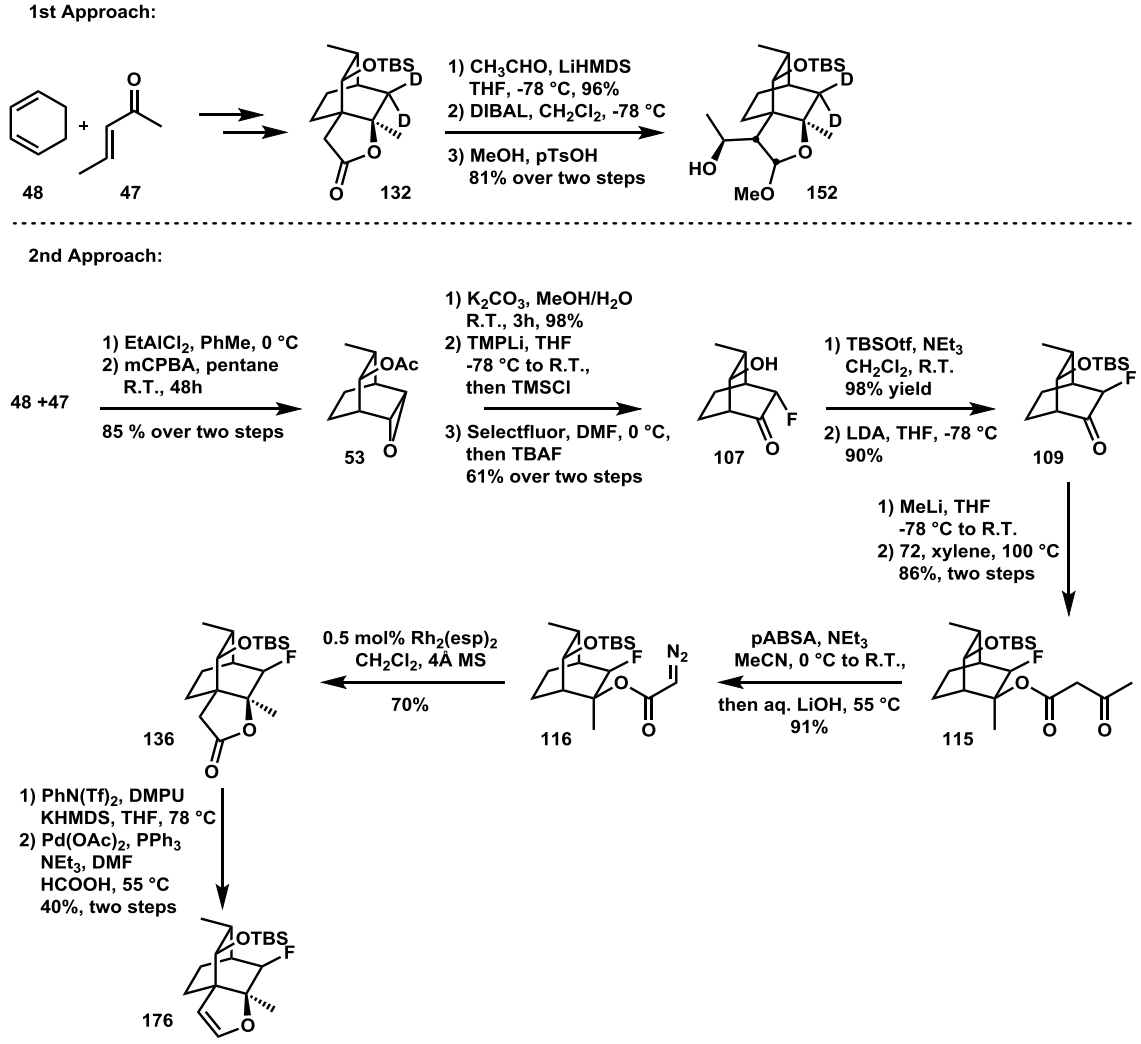


1.3. Conclusions

Despite all the obstacles, we have synthesized two advanced intermediates for the core structure of Maoecrystal V. We encountered a selectivity problem for the C-H bond insertion step. Eventually, by introducing a fluorine in the molecule, we overcame that challenge. Throughout the C-H bond insertion study we learned many valuable lessons. We found a very nice way to access complex polycyclic systems when reacting an alkynyl diazo-acetate with a Rh(II) catalyst. This finding allowed us to expand the study to access other even more complex policyclic systems.

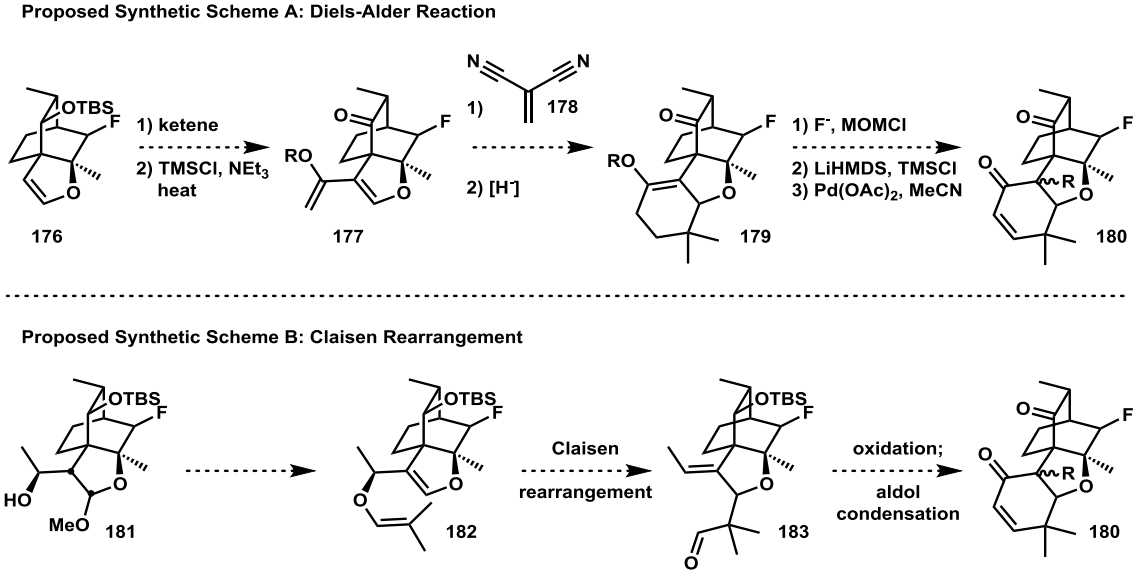
The synthetic approaches are highlighted bellow in Scheme 27. The first advanced intermediate **152** was synthesized in 12 steps with 15.0% overall yield. The second advanced intermediate **176** was synthesized in 13 steps with 9.8% overall yield.

Scheme 26. Overall Synthetic Scheme



Both intermediates are valuable starting points for the construction of cyclohexenone, the remaining ring, as it is highlighted in Scheme 28. Although we have not been successful in generating this ring system so far, the Diels-Alder reaction in Scheme 28 might yield a positive result. The Claisen rearrangement in **182** would be another efficient way how to introduce a gem-dimethyl group in **180**.

Scheme 28. Proposed further studies for the synthesis of **180**.



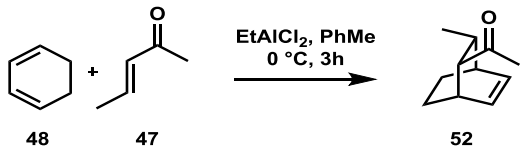
1.4. Experimental

1.4.1. Material and Methods

General Considerations

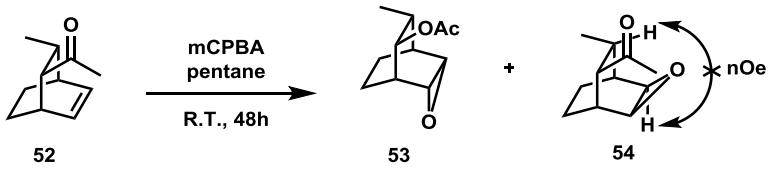
All reactions were carried out in flame- or oven-dried glassware. THF, toluene and CH_2Cl_2 were purged with argon and dried over activated alumina columns. Flash chromatography was performed on 60Å silica gel (Sorbent Technologies). Analytical thin layer chromatography was performed on EMD silica gel/TLC plates with fluorescent indicator 254 nm. The ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a JEOL ECA-500 or ECX-400P spectrometer using residual solvent peak as an internal reference ($CDCl_3$: 7.25 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR; DMSO-d_6: 2.50 ppm for ^{1}H NMR and 39.51 ppm for ^{13}C NMR; benzene-d_6: 7.16 ppm for ^{1}H NMR). Hexafluorobenzene (δ = -164.9 ppm) was employed as an internal standard in ^{19}F NMR spectra. For ^{13}C NMR, multiplicities were distinguished using DEPT experiments: methyl and methine carbons appear positive (up); methylene carbons appear negative. IR spectra were obtained using a ThermoNicolet Avatar 370 FT-IR instrument. HRMS analyses were performed under contract by UT Austin's mass spectrometric facility via positive mode ESI method and US10252005 instrument. Commercially available compounds were purchased from Aldrich Chemical Co., Acros Organics, Alfa Aesar or TCI America and were used without further purification.

1.4.2. Syntheses of Compounds



48 47 52

1-((1S,4R,7S,8R)-8-Methylbicyclo[2.2.2]oct-2-en-7-yl)ethanone (52). A flame-dried one liter round-bottom flask was charged with 1,4-cyclohexadiene (**48**) (9.8 ml, 0.10 mol) and penten-2-one (**47**) (10.0 ml, 0.10 mol, 70% purity). Anhydrous PhMe (0.20 L, 0.5M) was added and the flask was cooled in an ice/water bath. $EtAlCl_2$ (113 ml, 0.11 mol) was then added, the reaction mixture was stirred at 0 ˚C for 3 hours. Afterward, 1N HCl solution was added slowly to the reaction mixture, until the evolution of gas has ceased. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. Acetone was added to the residue, the white precipitate formed was removed by filtration through the small plug of Celite® and rinsed with acetone. Solvent was removed via rotary evaporation. The obtained yellow oil was subjected to the next step without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.41-6.33 (m, 1H), 6.10-6.03 (m, 1H), 2.81-2.73 (m, 1H), 2.29-2.22 (m, 1H), 2.10 (s, 3H), 2.03 (dd, J = 6.4 Hz, 1.8 Hz, 1H), 1.91-1.81 (m, 1H), 1.79-1.69 (m, 1H), 1.56-1.46 (m, 1H), 1.34-1.24 (m, 1H), 1.12-1.01 (m, 1H), 1.07 (d, J = 6.9 Hz, 1H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 210.0, 136.9, 130.6, 60.6, 36.0, 33.8, 32.9, 28.4, 26.2, 20.0, 18.2.

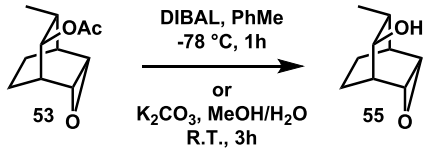


A one liter round-bottom flask was charged with the crude material from the previous reaction. Reagent grade pentane (0.5 L, 0.2M) was added, followed by pure mCPBA (37.0 g, 0.30 mol). The order of the addition is important! The reaction mixture was stirred at room temperature for 48 hours. To the reaction mixture saturated $NaHCO_3$ solution was added slowly, until the benzoic acid dissolves. The mixture was extracted with EtOAc (3x), the organic phases were combined and washed with saturated $Na_2S_2O_3$ solution and brine, then dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The residue was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent.

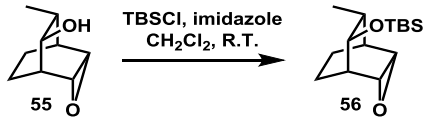
7-Methyl-3-oxatricyclo[3.2.2.0^{2,4}]non-6-yl acetate (53) was obtained as a clear oil (12.5 g, 88%) with the corresponding spectroscopic data: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.54 (t, J = 3.4 Hz, 1H), 3.33 (t, J = 4.6 Hz, 1H), 3.24 (t, J = 4.6 Hz, 1H), 2.33-2.29 (m, 1H), 2.04 (s, 3H), 2.01-1.97 (m, 1H), 177-1.64 (m, 2H), 1.52-1.44 (m, 1H), 1.33-1.24 (m, 1H), 1.19-1.10 (m, 1H), 1.14 (d, J = 6.9 Hz, 3H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 170.8, 80.9, 54.0, 50.4, 37.0, 34.6, 33.4, 21.5, 21.0, 18.0, 16.5. **HRMS**-CI m/z: [M+H], calculated for $C_{11}H_{16}O_3$, 197.1178; found 197.1183. **R_f**: 0.41 in 20% EtOAc/hexanes.

1-(7-Methyl-3-oxatricyclo[3.2.2.0^{2,4}]non-6-yl)ethanone (54) was obtained as a clear oil, with the corresponding spectroscopic data: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.23 (t, J = 4.6 Hz, 1H), 3.18 (t, J = 4.6 Hz, 1H), 2.73-2.69 (m, 1H), 2.29-2.22 (m, 1H), 2.16 (s, 3H), 2.02-

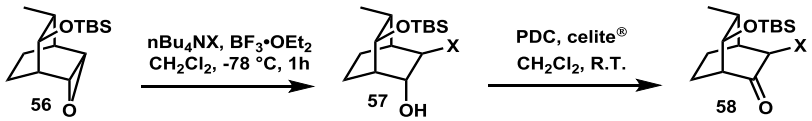
1.97 (m, 1H), 1.80-1.72 (m, 1H), 1.67-1.58 (m, 1H), 1.54-1.50 (m, 1H), 1.49-1.42 (m, 1H), 1.40-1.31 (m, 1H), 1.07 (d, J = 6.9 Hz, 3H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 209.2, 58.3, 53.2, 51.0, 33.6, 30.5, 29.9, 27.0, 21.7, 21.1, 16.6. **HRMS**-CI m/z: [M+H], calculated for $C_{11}H_{16}O_2$, 181.1229; found 181.1237. **R_f**: 0.20 in 20% EtOAc/hexanes. 1D nOe analysis revealed the stereochemistry of epoxide in **54**.

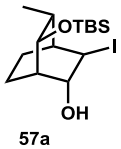


7-Methyl-3-oxatricyclo[3.2.2.0^{2,4}]nonan-6-ol (55). A round-bottom flask was charged with **53** (2.00 g, 0.01 mol). Reagent grade MeOH (51 ml, 0.2M), water (22 ml, 0.45M) and K_2CO_3 (4.20 g, 0.03 mol) were added. The reaction mixture was stirred at room temperature overnight. MeOH was removed via rotary evaporation. To the residue 1N HCl solution was added, the product was extracted with Et_2O (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered through short silica gel plug and rinsed with Et_2O. Solvent was removed via rotary evaporation to yield clean product as a white solid (1.53 g, 97%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.53-3.47 (m, 1H), 3.36-3.29 (m, 1H), 2.25-2.18 (m, 1H), 2.00-1.93 (m, 1H), 1.72 (d, J = 3.2 Hz, 1H), 1.71-1.59 (m, 2H), 1.50-1.39 (m, 1H), 1.27-1.18 (m, 1H), 1.13-0.99 (m, 1H), 1.11 (d, J = 7.3Hz, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 79.4, 54.4, 50.8, 39.8, 36.4, 34.8, 21.4 (CH_2), 18.1, 16.5 (CH_2). **HRMS**-CI m/z: [M+H], calculated for $C_9H_{13}O_2$, 154.0994; found 154.0990. **R_f**: 0.29 in 50% EtOAc/hexanes.



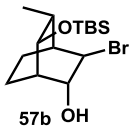
***tert*-Butyldimethyl({7-methyl-3-oxatricyclo[3.2.2.0^{2},^{4}]nonan-6-yl}oxy)silane (56).** A round-bottom flask was charged with **55** (1.25 g, 8.1 mmol). Anhydrous CH_2Cl_2 (32 ml, 0.25M) was added, followed by the addition of imidazole (1.93 g, 28.3 mmol) and TBSCl (3.05 g, 20.2 mmol). The reaction mixture was stirred overnight at room temperature. CH_2Cl_2 was removed via rotary evaporation. To the residue 5% EtOAc in hexanes solution was added, the mixture was filtered through short silica gel plug and rinsed with 5% EtOAc in hexanes solution. Solvent was removed via rotary evaporation to yield clean product as a colorless oil (2.15 g, 99%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.39 (t, J = 2.9 Hz, 1H), 3.30 (t, J = 4.6 Hz, 1H), 3.26 (t, J = 4.6 Hz, 1H), 2.14-2.09 (m, 1H), 1.95-1.90 (m, 1H), 1.70-1.58 (m, 2H), 1.47-1.38 (m, 1H), 1.25-1.17 (m, 1H), 1.07-0.97 (m, 1H), 1.05 (d, J = 6.9 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 79.7, 54.3, 51.4, 40.1, 36.7, 34.7, 25.9, 21.3, 18.1, 16.5, -4.5. **HRMS**-CI m/z: [M+H], calculated for $C_{15}H_{28}O_2Si$, 269.1937; found 269.1927. **R$_f$**: 0.69 in 20% EtOAc/hexanes.





(1S,2R,4S,5R,6S)-6-(tert-Butyldimethylsilyloxy)-3-iodo-5-methylbicyclo-[2.2.2]octan-2-ol (57a). A flame-dried round-bottom flask was charged with **56** (2.15 g, 8.00 mmol) and Bu_4NI (3.85 g, 10.4 mmol). Anhydrous CH_2Cl_2 (80.0 ml, 0.1M) was added and the flask was cooled to -78 ˚C in a dry ice/acetone bath. $BF_3 \cdot OEt_2$

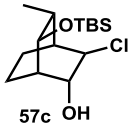
(1.3 ml, 10.4 mmol) was then added dropwise, the reaction mixture was stirred at -78 ˚C for 30 minutes, then allowed to warm to room temperature. CH_2Cl_2 was removed via rotary evaporation. To the residue saturated NH_4Cl solution was added, product was extracted with Et_2O (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The obtained yellow oil was subjected to the next step without further purification. The residue was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a white solid (2.54 g, 80%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.75-4.66 (m, 1H), 4.10 (dd, J = 5.0 Hz and 1.8 Hz, 1H), 3.15 (dd, J = 5.5 Hz and 2.3 Hz, 1H), 2.30-2.21 (m, 1H), 1.84-1.74 (m, 1H), 1.59-1.55 (m, 1H), 1.55-1.50 (m, 1H), 1.48 (s, 1H), 1.31-1.16 (m, 2H), 1.06 (s, 9H), 1.09-0.92 (m, 1H), 0.94 (d, J = 6.9 Hz, 3H), 0.14 (s, 3H), 0.09 (s, 3H). **^{13}C NMR** (125.76 MHz, benzene-d_6) δ 78.0, 77.1, 44.5, 44.2, 43.2, 38.8, 26.4, 21.3, 18.5, 18.1, 16.2, -4.1. **R_f**: 0.14 in 5% EtOAc/hexanes.



57b

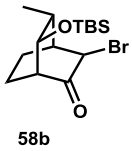
(1S,2R,4S,5R,6S)-6-(tert-Butyldimethylsilyloxy)-3-bromo-5-methyl-bicyclo[2.2.2]octan-2-ol (57b). A flame-dried round-bottom flask was charged with **56** (0.51 g, 1.90 mmol) and Bu_4NBr (0.80 g, 2.49 mmol). Anhydrous CH_2Cl_2 (19.0 ml, 0.1M) was added and the flask was cooled to -78 ˚C in a dry ice/acetone bath. $BF_3{\cdot}OEt_2$ (0.3 ml, 2.49 mmol) was then added dropwise. The reaction mixture was stirred at -78 ˚C for 30 minutes, then allowed to warm to room temperature. CH_2Cl_2 was removed via rotary evaporation. To the residue saturated NH_4Cl solution was added, product was extracted with Et_2O (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The obtained

yellow oil was subjected to the next step without further purification. The residue was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a white solid (0.45 g, 68%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.50-4.43 (m, 1H), 4.00 (dd, J = 5.0 Hz and 1.8 Hz, 1H), 3.27 (dd, J = 5.5 Hz and 2.3 Hz, 1H), 2.06-1.96 (m, 1H), 1.93 (s, 1H), 1.84-1.73 (m, 1H), 1.69-1.56 (m, 3H), 1.53-1.43 (m, 1H), 1.29-1.19 (m, 1H), 1.02 (d, J = 6.9 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H). **R_f**: 0.26 in 10% EtOAc/hexanes.



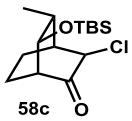
(1S,2R,4S,5R,6S)-6-(tert-Butyldimethylsilyloxy)-3-chloro-5-methyl-bicyclo[2.2.2]octan-2-ol (57c). A flame-dried round-bottom flask was charged with **56** (100 mg, 0.37 mmol) and Bu_4NCl (207 mg, 0.74 mmol). Anhydrous CH_2Cl_2 (3.7 ml, 0.1M) was added and the flask was cooled to -78 ˚C in a dry ice/acetone bath. $BF_3{\cdot}OEt_2$ (0.4 ml, 1.11 mmol) was then added dropwise, the reaction mixture was stirred at -78 ˚C for 30 minutes, then allowed to warm to room temperature. CH_2Cl_2 was removed via rotary evaporation. To the residue saturated NH_4Cl solution was added, product was extracted with Et_2O (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The obtained yellow oil was subjected to the next step without further purification. The residue was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a white solid (48 mg, 42%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.33-4.28 (m, 1H), 3.85 (dd, *J* = 4.6 Hz and 1.7 Hz, 1H), 3.28 (dd, *J* = 5.7 Hz and 2.3 Hz, 1H), 2.02-1.91 (m, 2H), 1.81-1.72 (m, 1H), 1.69-1.66 (m, 1H), 1.66-1.54 (m, 2H), 1.47-1.38 (m, 1H), 1.29-1.20 (m, 1H), 1.02 (d, *J* = 7.4 Hz, 3H), 0.88 (s, 9H), 0.05 (s,

3H), 0.03 (s, 3H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 77.3, 75.0, 69.6, 43.4, 42.0, 35.3, 25.9, 20.1, 18.1, 17.4, 16.5, -4.5.



58b

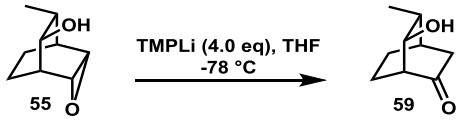
(1R,4S,5R,6S)-3-Bromo-6-(tert-butyldimethylsilyloxy)-5-methyl-bicyclo[2.2.2]octan-2-one (58b). A round-bottom flask was charged with **57b** (0.45 g, 1.29 mmol). Anhydrous CH_2Cl_2 (13 ml, 0.1M) was added, followed by the addition of Celite® (1.45g) and PDC (1.45 g, 3.80 mmol). The reaction mixture was stirred overnight at room temperature. Heterogeneous solution was filtered through short silica gel plug and rinsed with CH_2Cl_2. After the removal of solvent via rotary evaporation and drying under high vacuum for few hours, product solidified. Product as a light yellow solid was collected in 94% yield (0.42 g). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.32 (d, J = 2.9 Hz, 2H), 3.45-3.40 (m, 1H), 2.39 (q, J = 2.9 Hz, 1H), 2.35-2.27 (m, 1H), 2.11-2.06 (m, 1H), 1.99-1.91 (m, 1H), 1.79-1.70 (m, 1H), 1.70-1.61 (m, 1H), 1.61-1.52 (m, 1H), 1.13 (d, J = 6.9 Hz, 3H), 0.86 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 207.3, 52.7, 51.4, 42.3, 37.1, 25.7, 19.6, 19.0, 18.3, 17.9, -4.6. **HRMS**-CI m/z: [M+H], calculated for $C_{15}H_{27}O_2SiBr$, 349.1021; found 349.1031. **R_f**: 0.22 in 5% EtOAc/hexanes.



58c

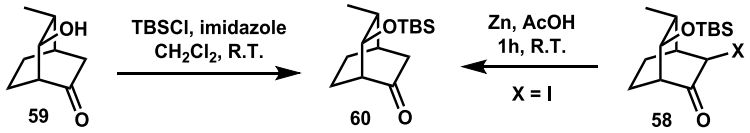
(1R,4S,5R,6S)-3-Chloro-6-(tert-butyldimethylsilyloxy)-5-methylbicyclo-[2.2.2]octan-2-one (58c). A round-bottom flask was charged with **57c** (35 mg, 0.11 mmol). Anhydrous CH_2Cl_2 (2.0 ml, 0.1M) was added, followed by the addition of Celite® (0.22 g) and PDC (0.22 g, 0.57 mmol). The reaction mixture was stirred overnight at room temperature. Heterogeneous solution was filtered through short silica gel plug and rinsed with CH_2Cl_2. After the removal of solvent via rotary evaporation and drying under high vacuum for few hours, product solidified. Product as a light yellow solid was collected

in 91% yield (32 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.12 (d, J = 2.8 Hz, 1H), 3.50 (t, J = 3.7 Hz, 1H), 2.41-2.37 (m, 1H), 2.28-2.20 (m, 1H), 2.07 (quintet, J = 2.8 Hz, 1H), 2.00-1.90 (m, 1H), 1.80-1.62 (m, 2H), 1.60-1.50 (m, 1H), 1.14 (d, J = 7.3 Hz, 3H), 0.85 (s, 9H), 0.04 (s, 3H), 0.04 (s, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 207.2, 78.0, 61.5, 51.4, 42.2, 36.4, 25.8, 25.7, 19.1, 18.9, 17.9, -4.6. **R$_f$**: 0.51 in 20% EtOAc/hexanes.



(1R,4R,5R,6S)-6-Hydroxy-5-methylbicyclo[2.2.2]octan-2-one (59). A flame-dried round-bottom flask was charged with TMPH (4.6 ml, 27.2 mmol) under an argon atmosphere. Anhydrous THF (25.0 ml, 0.26 M) was added, and the flask was cooled to -78 ˚C in a dry ice/acetone bath. 2.5M nBuLi solution (10.4 ml, 25.9 mmol) was then added. After 15 minutes at -78 ˚C alcohol **55** (1.00 g, 6.48 mmol), dissolved in 7.0 ml of anhydrous THF (0.9M), was added dropwise to the base solution. The reaction mixture was allowed to warm to room temperature and stir for 2 more hours. After completion, saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 50% EtOAc in hexanes as an eluent. The product was obtained as a viscous oil (0.64 g, 64%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.61 (t, J = 3.7 Hz, 1H), 2.99 (bs, 1H), 2.38-2.33 (m, 1H), 2.30-2.16 (m, 2H), 1.95-1.89 (m, 1H), 1.81-1.61 (m, 4H), 1.43-1.33 (m, 1H), 1.15 (d, J = 7.3 Hz, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 216.6, 51.5, 45.6, 41.5, 33.7,

20.1, 18.8, 18.2. **HRMS**-CI m/z: [M+H], calculated for $C_9H_{13}O_2$, 154.0994; found 154.0993. **R_f**: 0.20 in 50% EtOAc/hexanes.



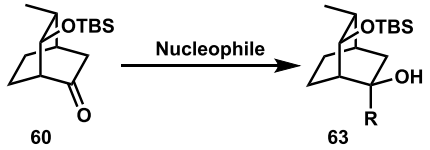
(1R,4R,5R,6S)-6-(tert-Butyldimethylsilyloxy)-5-methylbicyclo[2.2.2]octan-2-one (60).

Methode A: A round-bottom flask was charged with **58** (3.62 g, 9.2 mmol. Glacial AcOH (50.0 ml, 0.18M) and Zn dust (1.71 g, 26.1 mmol) were added. Solution was stirred at room temperature and monitored by TLC. After completion, the reaction mixture was filtered through the short plug of Celite® and rinsed with CH_2Cl_2. To the ice cold solution of filtrate, saturated $NaHCO_3$ solution was added slowly dropwise, until the pH paper indicate a neutral media. The mixture was extracted with CH_2Cl_2 (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (2.42 g, 98%).

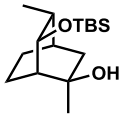
Methode B: A round-bottom flask was charged with **59** (0.64 g, 4.15 mmol). Anhydrous CH_2Cl_2 (21 ml, 0.2M) was added, followed by the addition of imidazole (0.56 g, 8.30 mmol) and TBSCl (0.94 g, 6.22 mmol). The reaction mixture was stirred overnight at room temperature. CH_2Cl_2 was removed via rotary evaporation. To the residue 5% EtOAc in hexanes solution was added, the mixture was filtered through the short silica gel plug and

rinsed with 5% EtOAc in hexanes solution. Solvent was removed via rotary evaporation to yield clean product as a colorless oil (1.02 g, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.52 (t, J = 3.2 Hz, 1H), 2.31-2.14 (m, 3H), 1.96-1.91 (m, 1H), 1.80-1.56 (m, 4H), 1.40-1.30 (m, 1H), 1.11 (d, J = 7.3 Hz, 1H), 0.83 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 214.8, 51.6, 45.6 (CH_2), 42.6, 33.7, 25.8, 20.1, 18.9 (CH_2), 18.5, 18.0 (CH_2), -4.6. **HRMS**-CI m/z: [M+H], calculated for $C_{15}H_{28}O_2Si$, 269.1937; found 269.1932. **R_f**: 0.34 in 10% EtOAc/hexanes.



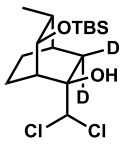
60 63



64

(1R,2R,4R,5R,6S)-6-(tert-Butyldimethylsilyloxy)-2,5-dimethylbicyclo-[2.2.2]octan-2-ol (64). Anhydrous $CeCl_3$ was obtained by dehydrating $CeCl_3 \cdot 7H_2O$) (5.41 g, 14.5 mmol) under high vacuum at 165 ˚C for 2 hours. After 2 hours the flask was allowed to cool to room temperature and then filled with inert gas. To the $CeCl_3$ anhydrous THF (100.0 ml) was added and the suspension was stirred for 2 hours at room temperature. 1.6M MeLi solution (9.1 ml, 14.5 mmol) was added to the above solution at -78 ˚C. After 30 minutes ketone **60** (1.95 g, 7.26 mmol) dissolved in anhydrous THF (21.0 ml) was added slowly. After 1 hour at -78 ˚C, the reaction mixture was quenched with saturated NH_4Cl solution and allowed to warm to room temperature. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes

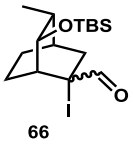
as an eluent. The product was obtained as a colorless oil, which, when stored at low temperatures, solidified (2.00 g, 97%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.07 (s, 1H), 3.50-3.46 (m, 1H), 1.80-1.55 (m, 5H), 1.52-1.48 (m, 1H), 1.47-1.39 (m, 1H), 1.26-1.18 (m, 1H), 1.22 (s, 3H), 1.16-1.07 (m, 1H), 1.01 (d, J = 7.4 Hz, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.09 (s, 3H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 80.8, 71.2, 47.0, 42.9, 41.6, 32.4, 30.0, 25.9, 20.9, 18.9, 17.9, -4.5. **HRMS**-CI m/z: [M+H], calculated for $C_{16}H_{32}O_2Si$, 285.2250; found 285.2243. **R$_f$**: 0.48 in 10% EtOAc/hexanes.



65

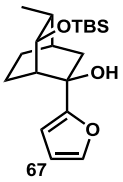
6-[(tert-Butyldimethylsilyl)oxy]-2-(dichloromethyl)-5-methyl(3,3-D_2) bicyclo[2.2.2]octan-2-ol (65). A flame-dried round-bottom flask was charged with anhydrous CH_2Cl_2 (35.0 µl, 0.55 mmol) and anhydrous THF (0.75 ml, 0.5M) under an argon atmosphere. The flask was cooled to -78 ˚C in a dry ice/acetone bath. 2.5M nBuLi solution (0.18 ml, 0.44 mmol) was then added. After 15 minutes at -78 ˚C alcohol **103** (100 mg, 0.37 mmol) dissolved in 1.0 ml of anhydrous THF was added dropwise to the above solution. After 1 hour at -78 ˚C, saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (131.0 mg, 78%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.68 (s, 1H), 5.44 (s, 1H), 3.47-3.42 (m, 1H), 2.08-2.03 (m, 1H), 1.90-1.83 (m, 1H), 1.61-1.57 (m, 1H), 1.54-1.39 (m, 2H), 1.39-1.30 (m, 1H), 1.17-1.08 (m, 1H), 1.04 (d, J = 7.4 Hz, 3H), 0.90 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 80.3, 80.0, 77.4 (CH_0), 76.2 (CH_0), 40.3, 39.3, 31.9, 25.8,

19.8 (CH_2), 18.2, 17.9 (CH_2), -4.5. **HRMS**-CI m/z: [M+H], calculated for $C_{16}H_{28}D_2O_2SiCl_2$, 355.1596; found 355.1592. **R_f**: 0.66 in 20% EtOAc/hexanes.



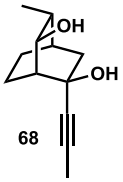
66

(1R,4R,5R,6S)-6-(tert-Butyldimethylsilyloxy)-2-iodo-5-methylbicyclo-[2.2.2]octane-2-carbaldehyde (66). A flame-dried round-bottom flask, covered by aluminum foil, was charged with 1.0M LiHMDS solution (0.59 ml, 0.59 mmol), anhydrous THF (1.60 ml, 0.11M) and anhydrous Et_2O (1.00 ml, 0.19M) under an argon atmosphere. The flask was cooled to -78 ˚C in a dry ice/acetone bath. CH_2I_2 (54.0 µl, 0.67 mmol) dissolved in anhydrous THF (0.40 ml) was then added. After 20 minutes ketone **60** (50.0 mg, 0.19 mmol), dissolved in 0.80 ml of anhydrous THF, was added dropwise to the above solution. After 20 minutes at -78 ˚C, saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 2.5% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (56.0 mg, 74%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 3.44 (t, *J* = 3.7 Hz, 1H), 2.97 (dt, *J* =15.6 HZ and 2.8 Hz, 1H), 2.18 (dd, *J* = 15.6 Hz and 3.2 Hz, 1H), 2.15-2.05 (m, 2H), 1.76-1.52 (m, 3H), 1.46-1.39 (m, 1H), 1.38-1.29 (m, 1H), 0.96 (d, *J* = 7.3 Hz, 3H), 0.86 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 189.2, 77.6, 62.7, 45.4, 41.0, 38.4, 31.4, 25.9, 24.2, 18.9, 18.3, 18.0, -4.4, -4.4. **R_f**: 0.43 in 5% EtOAc/hexanes.



67

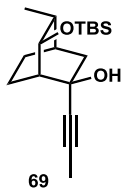
(1R,2R,4R,5R,6S)-2-(Furan-2-yl)-5-methylbicyclo[2.2.2]octane-2,6-diol (67). A flame-dried round-bottom flask was charged with furan (80 µl, 1.08 mmol) under an argon atmosphere. Anhydrous Et_2O (3.0 ml) was added, and the flask was cooled to 0 ˚C in an ice/water bath. 2.5M nBuLi solution (0.3 ml, 0.72 mmol) was then added. After 30 minutes at 0 ˚C ketone **60** (96 mg, 0.36 mmol), dissolved in 3.0 ml of anhydrous Et_2O, was added dropwise to the above solution. The reaction mixture was allowed to warm to room temperature and stirred overnight. Saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a light yellow solid (50.0 mg, 41%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37-7.35 (m, 1H), 6.31-6.27 (m, 2H), 5.50 (s, 1H), 3.55 (dd, J = 4.6 Hz and 2.3 Hz, 1H), 2.39 (dd, J = 14.3 Hz and 2.9 Hz, 1H), 2.14 (q, J = 2.9 Hz, 1H), 1.99 (dt, J = 14.3 Hz and 2.9 Hz, 1H), 1.93-1.86 (m, 1H), 1.64-1.60 (m, 1H), 1.46-1.38 (m, 1H), 1.27-1.13 (m, 3H), 1.06 (d, J = 6.9 Hz, 3H), 0.92 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H). **R_f**: 0.51 in 20% EtOAc/hexanes.



68

(1R,2R,4R,5R,6S)-5-Methyl-2-(prop-1-ynyl)bicyclo[2.2.2]octane-2,6-diol (68). A flame-dried round-bottom flask was charged with ketone **60** (200.0 mg, 0.74 mmol) under an argon atmosphere. Anhydrous THF (3.7 ml) was added, and the flask was cooled to -78 ˚C in a dry ice/aceone bath. 0.5M propynyl magnesium bromide solution (4.5 ml, 2.23 mmol) was then added. After 30 minutes the reaction mixture was allowed to warm to room temperature and stirred overnight. Saturated NH_4Cl

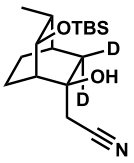
solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 50% EtOAc in hexanes as an eluent. The product was obtained as a white solid (114.0 mg, 79%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.38 (bs, 2H), 3.27 (dd, J = 5.7 Hz and 1.7 Hz, 1H), 2.09-2.02 (m, 1H), 2.00-1.96 (m, 1H), 1.94-1.88 (m, 1H), 1.82 (s, 3H), 1.78-1.63 (m, 2H), 1.51-1.36 (m, 2H), 1.25-1.14 (m, 1H), 1.05 (d, J = 7.4 Hz, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 84.3, 79.0, 78.3, 70.7, 46.7, 43.3, 41.4, 31.7, 21.5, 18.3, 17.9, 3.7. **R_f**: 0.09 in 20% EtOAc/hexanes.



69

(1R,2R,4R,5R,6S)-6-(tert-Butyldimethylsilyloxy)-5-methyl-2-(prop-1-ynyl)bicyclo[2.2.2]octan-2-ol (69). Anhydrous $CeCl_3$ was obtained by dehydrating $CeCl_3 \cdot 7H_2O$ (0.83 g, 2.23 mmol) under high vacuum at 165 ˚C for 2 hours. After 2 hours the flask was allowed to cool to room temperature and then filled with inert gas. To the $CeCl_3$ anhydrous THF (11.0 ml) was added and the suspension was stirred for 2 hours at room temperature. 0.5M propynyl magnesium bromide solution (4.5 ml, 2.23 mmol) was added to the above solution at 0 ˚C. After 30 minutes ketone **60** (0.30 g, 1.12 mmol) dissolved in anhydrous THF (8.0 ml) was added slowly. After 2.5 hours at 0 ˚C, the reaction mixture was quenched with saturated NH_4Cl solution. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a white solid (0.18 g, 52%). Product **69** was

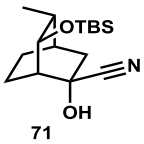
isolated in 12 % yield (26.8 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.22 (s, 1H), 3.51-3.46 (m, 1H), 2.15 (dd, J = 14.3 Hz and 2.9 Hz, 1H), 1.92-1.81 (m, 2H), 1.83 (s, 3H), 1.76-1.69 (m, 1H), 1.53-1.49 (m, 1H), 1.47-1.39 (m, 1H), 1.35-1.21 (m, 2H), 1.02 (d, J = 7.4 Hz, 3H),0.88 (s, 9H), 0.09 (s, 3H), 0.09 (s, 3H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 84.5, 79.6, 77.9, 69.3, 48.1, 42.8, 41.1, 31.6, 25.9, 21.2, 18.7, 17.8, 17.7, 3.9, -4.5, -4.6. **HRMS**-CI m/z: [M+H], calculated for $C_{18}H_{32}O_2Si$, 309.2250; found 309.2239. **R_f**: 0.63 in 20% EtOAc/hexanes.



70

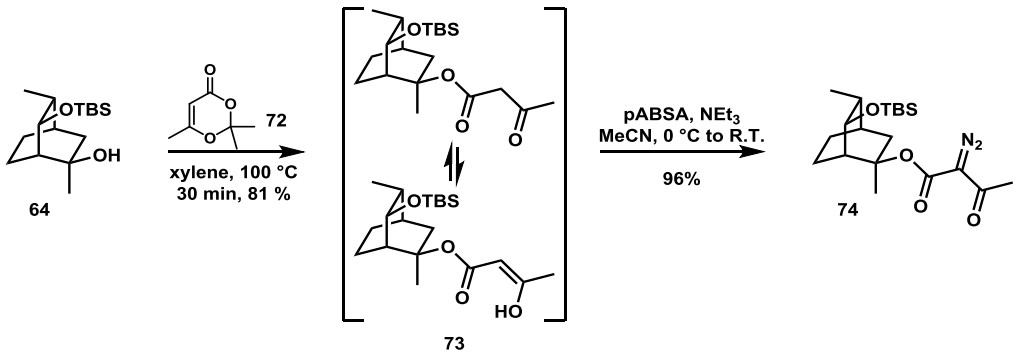
2-{6-[(tert-Butyldimethylsilyl)oxy]-2-hydroxy-5-methyl(3,3-D_2) bicyclo[2.2.2]octan-2-yl}acetonitrile (70). A flame-dried round-bottom flask was charged with 2.5M nBuLi solution (0.35 ml, 0.89 mmol) under an argon atmosphere. Anhydrous THF (4.0 ml) was added, and the flask was cooled to -78 ˚C in a dry ice/acetone bath. MeCN (0.19 ml, 3.70 mmol) was then added. After 20 minutes at -78 ˚C ketone **103** (200 mg, 0.74 mmol), dissolved in 3.0 ml of anhydrous THF, was added dropwise to the above solution. After 1 hour at -78 ˚C, saturated NH_4Cl solution was added and reaction mixture was allowed to warm to room temperature. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (161.0 mg, 70%). 21.5 mg of starting material **103** was recovered (11%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.42 (s, 1H), 3.52-3.49 (m, 1H), 2.59 (d, J = 16.0 Hz, 1H), 2.43 (dd, J = 16.0 Hz and 1.2 Hz, 1H), 1.91-1.86 (m, 1H), 1.83-1.75 (m, 1H), 1.58-1.54 (m, 1H), 1.54-1.44 (m, 2H), 1.42-1.33 (m, 1H), 1.15-1.07 (m, 1H),

1.04 (d, J = 7.4 Hz, 3H), 0.90 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 117.9, 79.9, 71.4 (CH_0), 41.1, 40.2, 31.6, 31.3 (CH_2), 25.8, 20.5 (CH_2), 18.5, 17.9 (CH_0), 17.8 (CH_0), -4.5, -4.6. **HRMS**-CI m/z: [M+H], calculated for $C_{17}H_{29}D_2NO_2Si$, 312.2328; found 312.2329. **R_f**: 0.37in 20% EtOAc/hexanes.



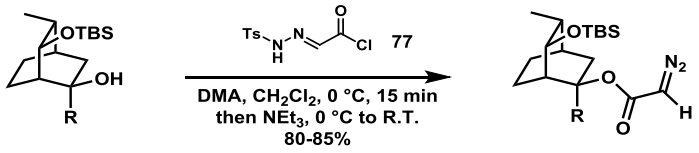
71

(1R,2S,4R,5R,6S)-6-(tert-Butyldimethylsilyloxy)-2-hydroxy-5-methyl-bicyclo[2.2.2]octane-2-carbonitrile (71). A flame-dried round-bottom flask was charged with ketone **60** (0.24 g, 0.88 mmol) under an argon atmosphere. Anhydrous PhMe (5.0 ml) was added, and the flask was cooled to 0 ˚C in an ice/water bath. 1.0M Et_2AlCN solution (1.3 ml, 1.32 mmol) was then added. After 30 minutes the reaction mixture was diluted with EtOAc and saturated Rochelle's solution was added. After stirring at room temperature for 30 minutes, the layers were separated, aqueous layer was extracted with EtOAc (2x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a white solid (245 mg, 95%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.47 (t, J = 3.4 Hz, 1H), 2.35 (dt, J = 14.3 Hz and 2.3 Hz, 1H), 2.28 (s, 1H), 2.06-2.01 (m, 1H), 1.96-1.88 (m, 1H), 1.79 (dd, J = 14.3 Hz and 3.4 Hz, 1H), 1.68-1.61 (m, 1H), 1.60-1.55 (m, 1H), 1.54-1.45 (m, 1H), 1.39-1.31 (m, 1H), 1.25-1.16 (m, 1H), 1.04 (d, J = 7.4 Hz, 3H), 0.92 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 123.9, 76.3, 65.4, 43.6, 43.4, 41.5, 31.0, 26.0, 18.6, 18.3, 17.7, 17.7, -4.3, -4.6. **HRMS**-CI m/z: [M+H], calculated for $C_{16}H_{29}NO_2Si$, 296.2046; found 296.2046. **R_f**: 0.48 in 20% EtOAc/hexanes.



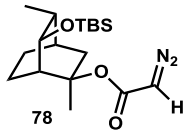
(1R,2R,4R,5R,6S)-6-(tert-Butyldimethylsilyloxy)-2,5-dimethylbicyclo[2.2.2]octan-2-yl 3-oxobutanoate (73). A flame-dried round-bottom flask was charged with tertiary alcohol **64** (85.0 mg, 0.30 mmol) and dioxinone **72** (0.16 ml, 1.20 mmol) under an argon atmosphere. Xylene (60 µl, 5.0M) was added, and the flask was placed in a preheated (100 ˚C) oil bath. After 30 minutes the reaction mixture was allowed to cool to room temperature. Afterwards, the crude reaction mixture was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a white solid (86 mg, 81%). ^{1}H NMR spectrum revealed that a product consists of a 1:0.2 mixture of keto, enol tautomers. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 12.26 (s, 1H, minor), 4.89 (s, 1H, minor), 3.37 (d, J = 14.9 Hz, 1H, major), 3.37-3.33 (m, 2H, minor), 3.23 (d, J = 14.9 Hz, 1H, major), 2.45-2.42 (m, 1H, minor), 2.42-2.38 (m, 1H, major), 2.25 (s, 3H, major), 2.06-1.96 (m, major/minor), 1.85 (s, 3H, minor), 1.78-1.69 (m, major/minor), 1.60 (s, 3H, minor), 1.60 (s, 3H, major), 0.53-1.36 (m, major/minor), 1.18-1.10 (m, major/minor), 1.00 (d, J = 6.9 Hz, 3H, major), 1.00-0.97 (d, 3H, minor), 0.88 (s, 9H, major), 0.85 (s, 9H, minor), 0.04 (s, 3H, major), 0.03 (s, 3H, major), 0.01 (s, 3H, minor), -0.01 (s, 3H, minor). **R_f**: 0.57 in 20% EtOAc/hexanes.

(1R,2R,4R,5R,6S)-6-(tert-Butyldimethylsilyloxy)-2,5-dimethylbicyclo[2.2.2]octan-2-yl 2-diazo-3-oxobutanoate (74). A flame-dried round-bottom flask was charged with β-ketoester **73** (86 mg, 0.23 mmol) under an argon atmosphere. MeCN (0.60 ml, 0.4M) was added and the flask was cooled to 0 ˚C in an ice/water bath. NEt_3 (0.10 ml, 0.69 mmol) followed by pABSA (62 mg, 0.25 mmol) were then added. After 10 minutes the reaction mixture was allowed to warm to room temperature and stir overnight. MeCN was removed via rotary evaporation. To the residue DI water was added, the product was extracted with Et_2O (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a white solid (85 mg, 92%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.37 (dd, J = 7.3 Hz and 1.8 Hz, 1H), 2.53-2.47 (m, 1H), 2.41 (s, 3H), 1.96-1.88 (m, 1H), 1.69 (s, 3H), 1.67-1.58 (m, 1H), 1.54-1.41 (m, 5H), 1.21-1.11 (m, 1H), 1.01 (d, J = 7.3 Hz, 3H), 0.83 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 191.1, 160.8, 84.8, 79.5, 44.8, 40.4, 40.0, 32.7, 28.2, 26.5, 26.2, 22.4, 19.0, 18.6, 18.1, -4.0, -4.8. **R_f**: 0.48 in 5% EtOAc/hexanes. **FTIR** (neat, cm^{-1}): 2927, 2136, 1713, 1644, 1362, 1140, 1082, 1004.

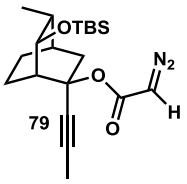


General procedure A for diazo-acetate synthesis: A flame-dried round-bottom flask was charged with tertiary alcohol (1.0 eq) under an argon atmosphere. Anhydrous CH_2Cl_2 (0.17

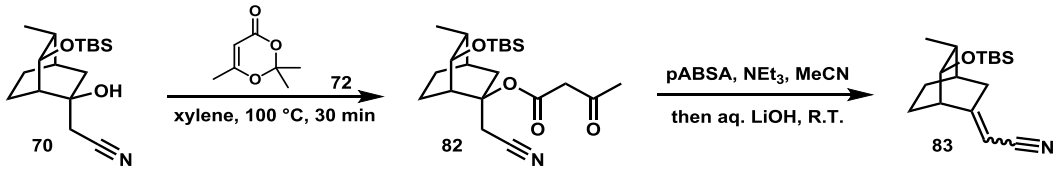
M) was added, and the flask was cooled to 0 ˚C. Glyoxylic acid chloride *p*-toluenesulfonylhydrazone (**77**) (2.0 eq) was added in one portion followed by *N*,*N*-dimethyl aniline (1.8 eq). The reaction mixture was stirred for 15 minutes before adding triethylamine (5.0 eq) and was stirred for 10 more minutes at 0 ˚C. The reaction was concentrated under reduced pressure. A concentrated citric acid solution and an EtOAc/hexanes mixture were added to the residue. The layers were separated, and the aqueous layer was extracted two times with the EtOAc/hexanes mixture. The combined organic phases were washed with concentrated citric acid solution and brine, dried over $MgSO_4$, filtered through a short silica gel plug, and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel.



(1R,2R,4R,5R,6S)-6-(tert-Butyldimethylsilyloxy)-2,5-dimethyl-bicyclo[2.2.2]octan-2-yl 2-diazoacetate (78) was synthesized from tertiary alcohol **64** (0.22 g, 0.77 mmol) following general procedure A. 10% EtOAc/hexanes mixture was used to extract the product. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a yellow oil (0.22 g, 81% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.53 (s, 1H), 3.34 (dd, J = 6.9 Hz and 1.7 Hz, 1H), 2.47-2.42 (m, 1H), 1.73-1.66 (m, 1H), 1.62 (s, 3H), 1.52-1.35 (m, 4H), 1.17-1.10 (m, 1H), 0.99 (d, J = 6.9 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 187.9, 135.6, 83.2, 79.5, 47.3, 40.8, 39.8, 32.6, 26.2, 26.1, 22.5, 21.8, 19.1, 18.5, 18.1, -4.0, -4.8. **R_f**: 0.54 in 20% EtOAc/hexanes. **FTIR** (neat, cm^{-1}): 2952, 2102, 1693, 1472, 1342, 1140, 1090.

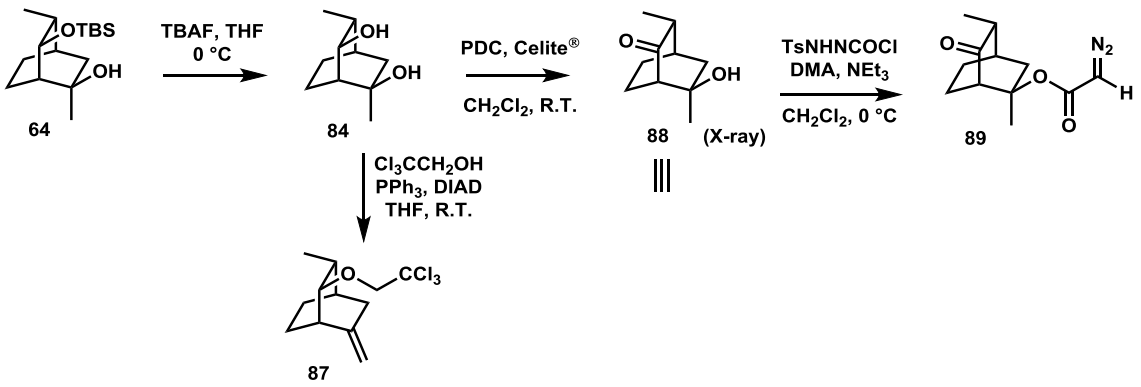


(1R,2R,4R,5R,6S)-6-(tert-Butyldimethylsilyloxy)-5-methyl-2-(prop-1-ynyl)bicyclo[2.2.2]octan-2-yl 2-diazoacetate (79) was synthesized from propargyl alcohol **69** (80 mg, 0.26 mmol) following general procedure A. 10% EtOAc/hexanes mixture was used to extract the product. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a yellow oil (75 mg, 77% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.61 (s, 1H), 3.35 (dd, J = 7.3 Hz and 1.4 Hz, 1H), 2.62-2.58 (m, 1H), 2.16-2.08 (m, 1H), 2.01-1.94 (m, 1H), 1.87-1.75 (m, 1H), 1.85 (s, 3H), 1.69-1.60 (m, 1H), 1.53-1.38 (m, 3H), 1.28-1.83 (m, 1H), 0.99 (d, J = 7.3 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.03 (s, 3H). **R_f**: 0.51 in 20% EtOAc/hexanes.

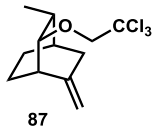


2-((1S,4R,7S,8R)-7-(tert-Butyldimethylsilyloxy)-8-methylbicyclo[2.2.2]octan-2-ylidene)acetonitrile (82). A flame-dried round-bottom flask was charged with tertiary alcohol **70** (62.0 mg, 0.20 mmol) and dioxinone **72** (40 µl, 0.30 mmol) under an argon atmosphere. Xylene (40 µl, 5.0M) was added, and the flask was placed in a preheated (100 ˚C) oil bath. After 30 minutes the reaction mixture was allowed to cool to room temperature. Afterwards, the crude reaction mixture was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (61 mg, 78%). ^{1}H NMR spectrum revealed that a product consists of a 1:0.2 mixture of keto, enol tautomers. **R_f**: 0.48 in 20% EtOAc/hexanes.

2-((1S,4R,7S,8R)-7-(tert-Butyldimethylsilyloxy)-8-methylbicyclo[2.2.2]octan-2-ylidene)acetonitrile (83). A flame-dried round-bottom flask was charged with β-ketoester **82** (49 mg, 0.12 mmol) under an argon atmosphere. Anhydrous MeCN (1.2 ml, 0.1M) was added and the flask was cooled to 0 ˚C in an ice/water bath. NEt_3 (26 µl, 0.18 mmol) followed by pABSA (33 mg, 0.13 mmol) were then added. After 10 minutes the reaction mixture was allowed to warm to room temperature and stir for 1 hour. After 1 hour LiOH (13 mg, 0.30 mmol) and water (0.12 ml, 1.0M) were added to the above solution. The reaction mixture was stirred overnight at room temperature. Saturated NH4Cl solution was added, the product was extracted with Et_2O (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (31 mg, 86%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.08 (s, 1H), 3.37 (t, J = 3.4 Hz, 1H), 2.25 (q, J = 2.9 Hz, 1H), 1.71-1.68 (m, 1H), 1.66-1.46 (m, 4H), 1.31-1.23 (m, 1H), 1.03 (d, J = 7.4 Hz, 3H), 0.83 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 169.4, 117.1, 93.4, 77.6, 45.6, 42.5, 31.6, 25.9, 25.8, 22.5, 18.6, 18.6, 18.0, -4.4. **HRMS**-CI m/z: [M+H], calculated for $C_{17}H_{27}D_2NOSi$, 294.2222; found 294.2219. **R_f**: 0.63 in 20% EtOAc/hexanes.

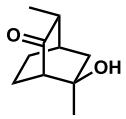


(1R,2R,4R,5R,6S)-2,5-Dimethylbicyclo[2.2.2]octane-2,6-diol (84). A flame-dried round-bottom flask was charged with TBS-ether **64** (0.47 g, 1.65 mmol) under an argon atmosphere. Anhydrous THF (2.20 ml) was added and the flask was cooled to 0 ˚C in an ice/water bath. Then TBAF (1.96 ml, 1.98 mmol) was added dropwise. The reaction mixture was warmed to room temperature. After 10 minutes, TLC analysis showed no starting material. Saturated $NaHCO_3$ solution was added, the mixture was extracted with Et_2O (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 30% EtOAc in hexanes as an eluent. The product was obtained as a white solid (0.27 g, 97%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.35-3.26 (m, 2H), 2.68 (s, 1H), 1.77-1.66 (m, 3H), 1.65-1.59 (m, 1H), 1.56-1.41 (m, 3H), 1.40-1.30 (m, 1H), 1.29 (s, 3H), 1.16-1.05 (m, 1H), 1.07 (d, J = 7.3 Hz, 3H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 79.5, 73.5, 46.2, 43.0, 41.6, 32.5, 30.5, 21.4, 18.6, 18.1. **HRMS**-CI m/z: [M+H], calculated for $C_{10}H_{18}O_2$, 171.1385; found 171.1387. **R_f**: 0.14 in 40% EtOAc/hexanes.



87

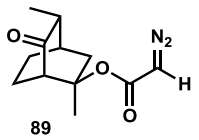
(1R,2R,3S,4S)-2-Methyl-5-methylene-3-(2,2,2-trichloroethoxy)bicycle-[2.2.2]octane (87). A flame-dried round-bottom flask was charged with diol **84** (54 mg, 0.32 mmol), Cl_3CH_2OH (0.14 ml, 0.66 mmol) and PPh_3 (0.39 g, 0.66 mmol) under an argon atmosphere. Anhydrous THF (7.3 ml, 0.04M) was added followed by DIAD (0.29 ml, 0.66 mmol). The reaction mixture was stirred until TLC analysis showed no starting material. To the reaction mixture DI H_2O was added, the mixture was extracted with EtOAc (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a light yellow oil (68 mg, 70%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.85 (t, J = 2.3 Hz, 1H), 3.34-3.27 (m, 1H), 2.29-2.38 (m, 2H), 2.18-2.12 (m, 1H), 1.73 (s, 2H), 1.70-1.51 (m, 4H), 1.40-1.27 (m, 2H), 1.07 (d, J = 7.3 Hz, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 146.3, 110.5, 99.5, 77.6, 76.4, 44.3, 43.3, 36.5, 32.4, 23.4, 19.1, 18.6. **R_f**: 0.51 in 20% EtOAc/hexanes.



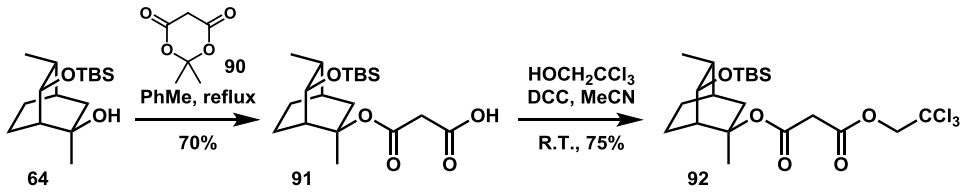
88

(1S,3R,4R,6R)-6-Hydroxy-3,6-dimethylbicyclo[2.2.2]octan-2-one (86). A round-bottom flask was charged with diol **84** (0.29 g, 1.73 mmol). Anhydrous CH_2Cl_2 (17 ml, 0.1M) was added, followed by the addition of Celite® (1.3 g) and PDC (1.3 g, 3.46 mmol). The reaction mixture was stirred overnight at room temperature. Heterogeneous solution was filtered through a short plug of Celite® and rinsed with CH_2Cl_2. After the removal of solvent via rotary evaporation, the crude product was purified by column chromatography on silica gel using 40% EtOAc in hexanes as an eluent. The product was obtained as a white solid (0.24 g, 81%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.43-

2.35 (m, 1H), 2.19-2.15 (m, 1H), 2.01-1.96 (m, 1H), 1.90-1.83 (m, 1H), 1.82 (s, 1H), 1.79-1.64 (m, 4H), 1.43-1.33 (m, 1H), 1.37 (s, 3H), 1.11 (d, J = 7.4 Hz, 3H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 218.4, 72.1, 55.9, 45.0, 44.0, 34.7, 28.9, 20.6, 19.3, 13.3. **HRMS**-CI m/z: [M+H], calculated for $C_{10}H_{16}O_2$, 169.1229; found 169.1229. **R_f**: 0.48 in 40% EtOAc/hexanes.



(1S,2R,4R,5R)-2,5-Dimethyl-6-oxobicyclo[2.2.2]octan-2-yl 2-diazo-acetate (89) was synthesized from tertiary alcohol **88** (90 mg, 0.53 mmol) following general procedure A. 20% EtOAc/hexanes mixture was used to extract the product. The crude product was purified by column chromatography on silica gel using 1% EtOAc in hexanes as an eluent. The product was obtained as a yellow oil (40 mg, 32% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.59 (bs, 1H), 2.65-2.60 (m, 1H), 2.36-2.29 (m, 1H), 2.29-2.22 (m, 1H), 2.00-1.95 (m, 1H), 1.89-1.77 (m, 2H), 1.76-1.66 (m, 2H), 1.68 (s, 3H), 1.46-1.38 (m, 1H), 1.12 (d, J = 7.4 Hz, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 216.3, ~165, 83.8, 52.9, 47.1, 45.2, 42.3, 34.5, 24.2, 19.7, 19.1, 13.4. **R_f**: 0.17 in 20% EtOAc/hexanes. **FTIR** (neat, cm^{-1}): 2933, 2105, 1721, 1682, 1366, 1180.

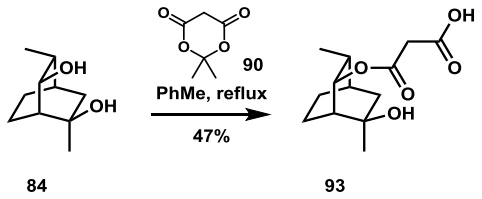


3-((1R,2R,4R,5R,6S)-6-(tert-Butyldimethylsilyloxy)-2,5-dimethylbicyclo[2.2.2]octan-2-yloxy)-3-oxopropanoic acid (91). A round-bottom flask was charged with tertiary alcohol **64** (0.21 g, 0.73 mmol) and Meldrum's acid (0.12 g, 0.80 mmol). The reaction

mixture was refluxed in anhydrous PhMe (2.5 ml, 0.28M) for 3 hours. After the removal of solvent via rotary evaporation, the crude product was purified by column chromatography on silica gel using 40% EtOAc in hexanes as an eluent. The product was obtained as a white solid (0.19 g, 68%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 12-11 (bs, 1H), 3.43 (dd, J = 7.4 Hz and 1.1 Hz, 1H), 3.34 (dd, J = 32.1 Hz and 18.9 Hz, 2H), 2.50-2.46 (m, 1H), 2.07-2.01 (m, 1H), 1.84-1.76 (m, 1H), 1.63 (s, 3H), 1.53-1.42 (m, 5H), 1.21-1.13 (m, 1H), 1.03 (d, J = 6.9 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H, 3H, overlap). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 169.2, 167.0, 86.2, 80.2, 43.9, 43.3, 40.7, 40.3, 39.1, 32.7, 26.4, 25.3, 22.4, 19.0, 18.0, -4.7. **HRMS**-CI m/z: [M+H], calculated for $C_{19}H_{34}O_5Si$, 371.2254; found 371.2246. **R_f**: 0.20 in 40% EtOAc/hexanes.

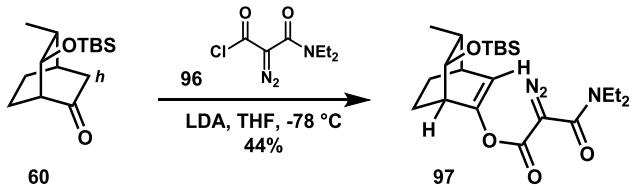
(1R,2R,4R,5R,6S)-6-(tert-Butyldimethylsilyloxy)-2,5-dimethylbicyclo[2.2.2]octan-2-yl 2,2,2-trichloroethyl malonate (92). A round-bottom flask was charged with carboxylic acid **91** (50 mg, 0.13 mmol) and Cl_3CCH_2OH (15 µl, 0.15 mmol). MeCN (1.7 ml, 0.08M) followed by DCC (28 mg, 0.13 mmol) were added. The reaction mixture was stirred overnight at room temperature. CH_2Cl_2 was removed via rotary evaporation. The heterogeneous reaction mixture was filtered through short plug of Celite® and rinsed with CH_2Cl_2. After the removal of solvent via rotary evaporation, the crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (51 mg, 75%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.77 (dd, J = 26.1 Hz and 11.9 Hz, 2H), 3.39 (dd, J = 45.8 Hz and 15.6 Hz, 2H), 3.37 (d, J = 1.4 Hz, 1H), 2.44-2.39 (m, 1H), 2.04-1.95 (m, 1H), 1.80-1.71 (m, 1H), 1.61 (s, 3H), 1.51-1.38

(m, 5H), 1.18-1.09 (m, 1H), 1.00 (d, J = 7.3 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). **R_f**: 0.46 in 20% EtOAc/hexanes.



84 93

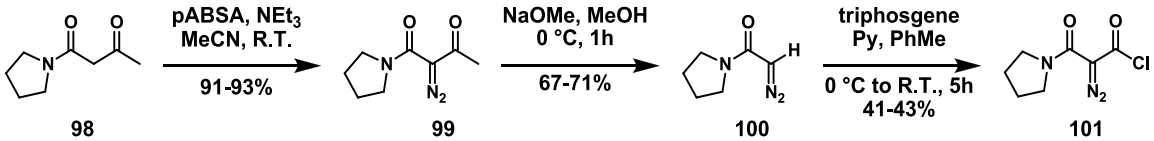
3-((1R,2S,3R,4R,6R)-6-Hydroxy-3,6-dimethylbicyclo[2.2.2]octan-2-yloxy)-3-oxopropanoic acid (93). A round-bottom flask was charged with diol **84** (0.18 g, 0.64 mmol) and Meldrum's acid (0.10 g, 0.70 mmol). The reaction mixture was refluxed in anhydrous PhMe (2.3 ml, 0.28M) for 3 hours. After the removal of solvent via rotary evaporation, the crude product was purified by column chromatography on silica gel using 40% EtOAc in hexanes as an eluent. The product was obtained as a white solid (0.10 g, 44%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ~13 (bs, 1H), 4.30 (d, *J* = 5.9 Hz, 1H), 3.33 (s, 2H), 2.04-1.88 (m, 1H), 1.71-1.31 (m, 8H), 1.14 (s, 3H), 0.94 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 169.3, 166.3, 82.2, 72.6, 44.9, 41.6, 40.6, 37.2, 32.3, 29.6, 21.4, 18.3, 18.1. **HRMS**-CI m/z: [M+H], calculated for $C_{13}H_{20}O_5$, 257.1389; found 257.1395. **R_f**: 0.06 in 40% EtOAc/hexanes.



60 97

(1R,4S,7S,8R)-7-(tert-Butyldimethylsilyloxy)-8-methylbicyclo[2.2.2]oct-2-en-2-yl 2-diazo-3-(diethylamino)-3-oxopropanoate (97). A flame-dried round-bottom flask was

charged with iPr_2NH (0.10 ml, 0.74 mmol) under an argon atmosphere. Anhydrous THF (3.0 ml) was added, and the flask was cooled to 0 ˚C in an ice/H_2O bath. 2.5M nBuLi solution (0.30 ml, 0.74 mmol) was then added. After 30 minutes the above solution was cooled to -78 ˚C in a dry ice/acetone bath, ketone **60** (100 mg, 0.37 mmol) dissolved in 2.0 ml of anhydrous THF was added. After another 30 minutes, Diazo-acetyl chloride **96** (152 mg, 0.74 mmol) dissolved in 2.0 ml of anhydrous THF was added. After stirring the reaction mixture for 1 hour at 0 ˚C, saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a yellow oil (72 mg, 44%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.93 (dd, J = 7.3 Hz and 2.3 Hz, 1H), 3.46-3.33 (m, 4H), 3.29 (t, J = 2.8 Hz, 1H), 2.40-2.34 (m, 1H), 2.34-2.26 (m, 1H), 1.73-1.61 (m, 1H), 1.61-1.52 (m, 1H), 1.48-1.38 (m, 1H), 1.36-1.27 (m, 1H), 1.17 (t, J = 7.3 Hz, 6H), 1.00 (d, J = 7.3 Hz, 3H), 1.20-1.06 (m, 1H), 0.83 (s, 9H), 0.01 (s, 3H), 0.01 (s, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 160.8, 160.5, 149.9, 117.3, 79.0, 66.5, 43.5, 43.4, 42.2, 35.9, 25.8, 21.9, 18.6, 18.0, 18.0, 13.4, -4.4, -4.5. **R_f**: 0.28 in 10% EtOAc/hexanes.



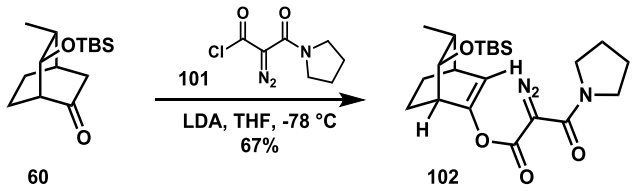
2-Diazo-1-(pyrrolidin-1-yl)butane-1,3-dione (99). A flame-dried round-bottom flask was charged with β-ketoester **98** (1.60 g, 10.3 mmol) under an argon atmosphere. MeCN (15.0 ml, 0.7M) was added and the flask was cooled to 0 ˚C in an ice/water bath. NEt_3 (1.60

ml, 11.3 mmol) followed by pABSA (2.72 g, 11.3 mmol) were then added. After 10 minutes the reaction mixture was allowed to warm to room temperature and stir overnight. MeCN was removed via rotary evaporation. To the residue DI water was added, the product was extracted with Et_2O (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified twice by column chromatography on silica gel using 70% Et_2O in pentane as an eluent. The product was obtained as a yellow solid (1.74 g, 93%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.53-3.35 (m, 4H), 2.38 (s, 3H), 1.96-1.87 (m, 4H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ ~190, 159.4, 73.8, 47.7, 27.9, 25.5.

2-Diazo-1-(pyrrolidin-1-yl)ethanone (100). A flame-dried round-bottom flask was charged with diazo-compound **99** (0.32 g, 1.77 mmol) under an argon atmosphere. Anhydrous MeOH (97.0 mg, 3.0M) was added and the flask was cooled to 0 ˚C in an ice/water bath. NaOMe (1.60 ml, 1.79 mmol) was then added in small portions. The reaction mixture was stirred at 0 ˚C for 1 hour. Afterwords, DI water was added, the product was extracted with Et_2O (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was subjected to the next step without any further purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.80 (s, 1H), 3.62-3.05 (m, 4H), 2.05-1.74 (m, 4H).

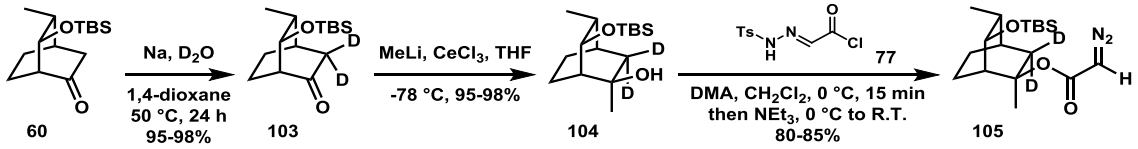
2-Diazo-3-oxo-3-(pyrrolidin-1-yl)propanoyl chloride (101). A flame-dried round-bottom flask was charged with triphosgene (0.43 g, 1.45 mmol) under an argon atmosphere. Anhydrous PhMe (2.0 ml, 1.8M) was added and the flask was cooled to 0 ˚C in an ice/water bath. Py (0.90 µl, 1.08 mmol) was added. A white precipitate was formed. To the reaction

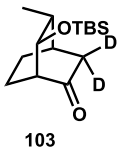
flask the crude material from the above reaction (3.23 mmol) was added drompwise. The reaction mixture was warmed to room temperature and stirred for 6 hours. After the filtration through a short plug of Celite, filtrate was concentrated to yield crude product. The crude product was purified fast by column chromatography on silica gel using 70% Et_2O in pentane as an eluent. The product was obtained as a yellow solid (0.28 g, 43%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.60-3.36 (m, 4H), 2.00-1.81 (m, 4H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 156.7, 154.2, 78.8, (48.6, 47.6), (26.1, 24.2). **R_f**: 0.34 in 60% Et_2O/pentane. **FTIR** (neat, cm^{-1}): 2978, 2139, 1735, 1714, 1643, 1614, 1410, 1254.



(1R,4S,7S,8R)-7-(tert-Butyldimethylsilyloxy)-8-methylbicyclo[2.2.2]oct-2-en-2-yl 2-diazo-3-oxo-3-(pyrrolidin-1-yl)propanoate (102). A flame-dried round-bottom flask was charged with iPr_2NH (34 μl, 0.24 mmol) under an argon atmosphere. Anhydrous THF (1.0 ml) was added, and the flask was cooled to 0 ˚C in an ice/H_2O bath. 2.5M nBuLi solution (0.10 ml, 0.24 mmol) was then added. After 30 minutes the above solution was cooled to -78 ˚C in a dry ice/acetone bath, ketone **60** (50 mg, 0.19 mmol) dissolved in 1.5 ml of anhydrous THF was added. After another 30 minutes, diazo-acetyl chloride **101** (53 mg, 0.26 mmol) dissolved in 1.0 ml of anhydrous THF was added. The reaction mixture was allowed to warm to room temperature, saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The

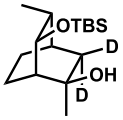
crude product was purified by column chromatography on silica gel using 15% EtOAc in hexanes as an eluent. The product was obtained as a yellow oil (46 mg, 57%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.94 (dd, J = 7.4 Hz and 2.3 Hz, 1H), 3.58-3.45 (m, 1H), 3.31-3.28 (m, 1H), 2.40-2.35 (m, 1H), 2.33-2.27 (m, 1H), 1.95-1.79 (m, 4H), 1.72-1.62 (m, 1H), 1.62-1.53 (m, 1H), 1.47-1.39 (m, 1H), 1.37-1.28 (m, 1H), 1.17-1.07 (m, 1H), 1.01 (d, J = 7.4 Hz, 3H), 0.84 (s, 9H), 0.01 (s, 3H, 3H, overlap). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 160.4, 159.6, 149.9, 117.4, 79.0, 67.3, ~47, 43.5, 43.4, 35.9, 26.2, 25.8, 21.9, 18.6, 18.0, 18.0, -4.4. **R_f**: 0.09 in 10% EtOAc/hexanes. **FTIR** (neat, cm^{-1}): 2950, 2930, 2136, 1714, 1641, 1625, 1408, 1154.





6-[(tert-Butyldimethylsilyl)oxy]-5-methyl(3,3-D_2)bicyclo[2.2.2]octan-2-one (103). To a stirred solution of 2.2 ml 1,4-dioxane (0.6M) and 3.8 ml D_2O (0.7M) under an inert atmosphere was added Na metal (73 mg, 3.17 mmol) in small pieces. After the Na had reacted, ketone **60** (0.71 g, 2.64 mmol) dissolved in 2.0 ml of 1,4-dioxane was added and the resulting solution was heated at 50 ˚C for 24 hours. The reaction mixture was cooled to room temperature, saturated NH_4Cl solution was added. The reaction mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (717 mg, 99%). 99% Substitution of hydrogen to deuterium was obtained after analyzing the ^{1}H

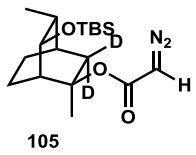
NMR spectrum of clean product. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.55-3.50 m, 1H), 2.31-2.27 (m, 1H), 1.95-1.90 (m, 1H), 1.79-1.67 (m, 3H), 1.66-1.57 (m, 1H), 1.40-1.31 (m, 1H), 1.11 (d, J = 7.4 Hz, 3H), 0.83 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 215.0, 51.6, 42.5, 33.6, 33.5, 25.8, 20.1, 18.9, 18.5, 18.0, -4.6. **HRMS**-CI m/z: [M+H], calculated for $C_{15}H_{26}D_2O_2Si$, 271.2062; found 271.2065. **R_f**: 0.66 in 20% EtOAc/hexanes.



104

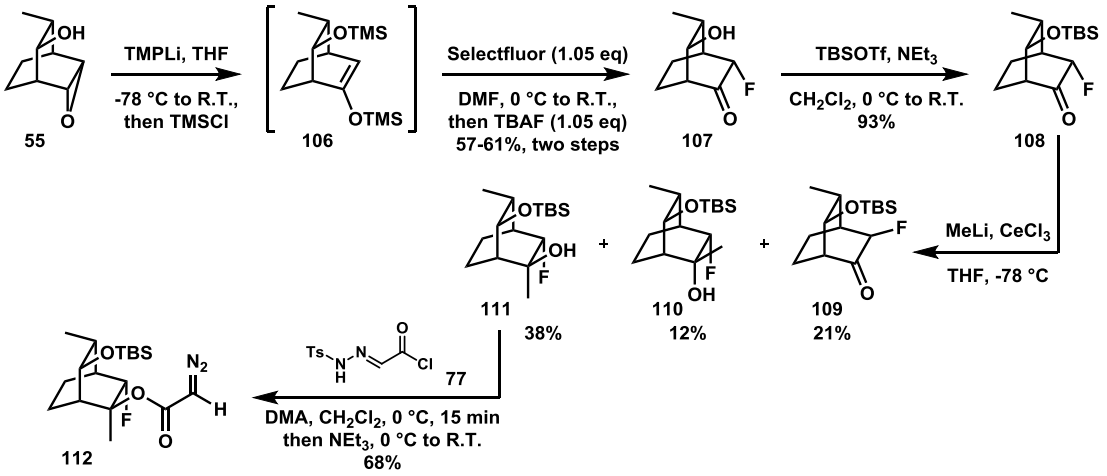
6-[(tert-Butyldimethylsilyl)oxy]-2,5-dimethyl(3,3-D_2)bicyclo[2.2.2]octan-2-ol (104). Anhydrous $CeCl_3$ was obtained by dehydrating $CeCl_3 \cdot 7H_2O$ (4.52 g, 12.1 mmol) under high vacuum at 165 ˚C for 2 hours. After 2 hours the flask was allowed to cool to room temperature and then filled with inert gas. To the $CeCl_3$ anhydrous THF (60.0 ml) was added and the suspension was stirred for 2 hours at room temperature. 1.6M MeLi solution (7.6 ml, 12.1 mmol) was added to the above solution at -78 ˚C. After 30 minutes ketone **103** (1.64 g, 6.06 mmol) dissolved in anhydrous THF (16.0 ml) was added slowly. After 1 hour at -78 ˚C, the reaction mixture was quenched with saturated NH_4Cl solution and allowed to warm to room temperature. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil, which, when stored at low temperatures, solidified (1.71 g, 98%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.05 (s, 1H), 3.49-3.45 (m, 1H), 1.76-1.69 (m, 5H), 1.62-1.54 (m, 2H), 1.50-1.46 (m, 1H), 1.46-1.38 (m, 1H), 1.26-1.18 (m, 1H), 1.21 (s, 3H), 1.15-1.07 (m, 1H), 1.01 (d, J = 7.4 Hz, 3H), 0.88 (s, 9H),

0.09 (s, 3H), 0.08 (s, 3H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 80.8, 71.0, ~48, 42.9, 41.6, 32.2, 30.0, 25.9, 20.9, 18.9, 17.9, 17.8, -4.5. **HRMS**-CI m/z: [M+H], calculated for $C_{16}H_{30}D_2O_2Si$, 287.2375; found 287.2375. **R_f**: 0.66 in 20% EtOAc/hexanes.

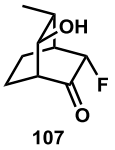


105

6-[(tert-Butyldimethylsilyl)oxy]-2,5-dimethyl(3,3-D_2) bicyclo[2.2.2] octan-2-yl 2-diazoacetate (105). Diazo-acetate **105** was synthesized from tertiary alcohol **104** (1.00 g, 0.49 mmol) following general procedure A. 10% EtOAc/hexanes mixture was used to extract the product. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a yellow oil (1.06 g, 85% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.53 (s, 1H), 3.34 (dd, J = 6.9 Hz and 1.4 Hz, 1H), 2.48-2.42 (m, 1H), 1.74-1.64 (m, 1H), 1.62 (s, 3H), 1.53-1.36 (m, 4H), 1.18-1.08 (m, 1H), 0.99 (d, J = 6.9 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). **^{13}C NMR** (100.53 MHz, $CDCl_3$) δ ~165, 83.2, 79.5, 47.4, 40.7, 39.8, 32.5, 26.2, 26.1, 22.5, 19.1, 18.5, 18.1, -4.0, -4.8. **R_f**: 0.34 in 10% EtOAc/hexanes. **FTIR** (neat, cm^{-1}): 2949, 2929, 2103, 1711, 1366, 1112, 858.



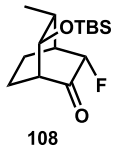
(1R,3S,4S,5R,6S)-3-Fluoro-6-hydroxy-5-methylbicyclo[2.2.2]octan-2-one (107).



Step I: A flame-dried round-bottom flask was charged with TMPH (9.27 ml, 54.5 mmol) under an argon atmosphere. Anhydrous THF (33.0 ml) was added, and the flask was cooled to -78 ˚C in a dry ice/acetone bath. 2.5M nBuLi solution (20.8 g, 51.9 mmol) was then added. After 15 minutes at -78 ˚C alcohol **55** (2.00 g, 13.0 mmol), dissolved in 10.0 ml of anhydrous THF, was added dropwise to the base solution. The reaction mixture was allowed to warm to room temperature and stir for 1 hours. Afterwards, TMSCl (7.08 ml, 55.7 mmol) was added to the above solution at -78 C and warmed to room temperature. After being stirred for 1 hour at room temperature, cold saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with cold saturated $NaHCO_3$ solution, brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. Crude product was subjected to the next step without any further purification.

Step II: A flame-dried round-bottom flask was charged with Selectfluor (7.6 g, 21.4 mmol) under an argon atmosphere. Anhydrous DMF (25.0 ml) was added, and the flask was

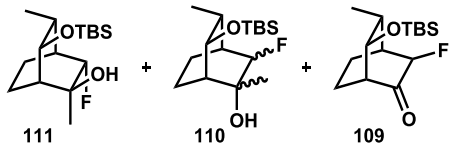
cooled to 0 ˚C in an ice/H_2O bath. Crude product xx from the previous reaction was dissolved in 14 ml of anhydrous DMF and added to the above solution via cannula. After the addition reaction mixture was stirred 0 ˚C for 30 minutes. 1.0M TBAF solution (21.0 ml, 19.5 mmol) then was added. Reaction mixture was allowed to warm to room temperature, saturated NaCl solution was added. The mixture was extracted with Et_2O (5x), and the organic phases were combined and dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 40% EtOAc in hexanes as an eluent. The product was obtained as a white foam (1.99 g, 60%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.74-4.53 (m, 1H), 3.72-3.61 (m, 1H), 2.57-2.47 (m, 1H), 2.33-2.24 (m, 1H), 2.21 (s, 1H), 1.96-1.79 (m, 2H), 1.79-1.59 (m, 3H), 1.23 (d, J = 7.3 Hz, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ (210.4, 210.3), (92.3, 90.4), 75.2, 50.9, (39.7, 39.5), (39.1, 39.0), 21.2, 18.5, 12.4. **R_f**: 0.51 in 40% EtOAc/hexanes.



108

(1R,3S,4S,5R,6S)-6-(tert-Butyldimethylsilyloxy)-3-fluoro-5-methyl-bicyclo[2.2.2]octan-2-one (108). A round-bottom flask was charged with **107** (1.62 g, 9.41 mmol). Anhydrous CH_2Cl_2 (19.0 ml, 0.5M) was added, and the flask was cooled to 0 ˚C in an ice/H_2O bath. NEt_3 (1.97 ml, 14.1 mmol), followed by TBSOTf (2.38 ml, 10.3 mmol) were added. The reaction mixture was allowed to warm to room temperature and stir for 20 minutes. Solvent was removed via rotary evaporation. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (2.53 g, 94%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.76-4.61 (m, 1H), 3.54 (d, *J* = 4.0 Hz, 1H), 2.49-2.43 (m, 1H),

2.31-2.23 (m, 1H), 1.99-1.91 (m, 1H), 1.87-1.77 (m, 1H), 1.75-1.58 (m, 3H), 1.18 (d, *J* = 7.4 Hz, 3H), 0.82 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ (209.9, 209.8), (92.6, 91.1), 75.2, 50.9, (40.8, 40.7), (39.8, 39.7), 25.7, 21.1, (18.4, 17.9), 12.7, -4.7. **^{19}F NMR** (470.62 MHz, $CDCl_3$) δ -189.19 (dt, *J* = 52.0 Hz and 6.5 Hz, 1F)**.** **HRMS**-CI m/z: [M+H], calculated for $C_{15}H_{27}O_2FSi$, 287.1843; found 287.1850. **R_f**: 0.60 in 20% EtOAc/hexanes.



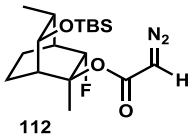
Anhydrous $CeCl_3$ was obtained by dehydrating $CeCl_3 \cdot 7H_2O$ (1.14 g, 3.02 mmol) under high vacuum at 165 ˚C for 2 hours. After 2 hours the flask was allowed to cool to room temperature and then filled with inert gas. To the $CeCl_3$ anhydrous THF (20.0 ml) was added and the suspension was stirred for 2 hours at room temperature. 1.6M MeLi solution (1.9 ml, 3.02 mmol) was added to the above solution at -78 ˚C. After 30 minutes ketone **108** (0.43 g, 1.51 mmol) dissolved in anhydrous THF (5.0 ml) was added slowly. After 1 hour at -78 ˚C, the reaction mixture was quenched with saturated NH_4Cl solution and allowed to warm to room temperature. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified twice by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent.

(1R,2S,3S,4S,5R,6S)-6-(tert-Butyldimethylsilyloxy)-3-fluoro-2,5-dimethylbicyclo-[2.2.2]octan-2-ol (110) was obtained as a white solid (55 mg, 12% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.20-5.16 (m, 1H), 4.61 (dd, J = 50.8 Hz and 3.7 Hz, 1H), 3.44 (dd, J = 4.1 Hz and 2.3 Hz, 1H), 1.84-1.69 (m, 2H), 1.68-1.59 (m, 2H), 1.55-1.44 (m, 1H), 1.34-1.20 (m, 5H), 1.10-1.05 (m, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.09 (s, 3H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ (101.5, 100.0), 79.8, (74.4, 74.2), 43.7, (39.3, 39.2), (37.5, 37.4), 25.8, (22.1, 22.0), 20.3, (17.9, 17.8), (11.3, 11.2), -4.7. **R_f**: 0.53 in 10% EtOAc/hexanes.

(1R,2R,3S,4S,5R,6S)-6-(tert-Butyldimethylsilyloxy)-3-fluoro-2,5-dimethylbicyclo-[2.2.2]octan-2-ol (111) was obtained as a colorless oil (182 mg, 38% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.40-4.25 (m, 1H), 3.35 (dd, J = 5.2 Hz and 2.3 Hz, 1H), 2.57 (d, J = 10.9 Hz, 1H), 2.02-1.93 (m, 1H), 1.78-1.72 (m, 1H), 1.65-1.56 (m, 2H), 1.58-1.46 (m, 1H), 1.42 (d, J = 1.7 Hz, 3H), 1.37-1.28 (m, 1H), 1.19-1.10 (m, 1H), 1.05 (d, J = 8.0 Hz, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 97.0, 95.2, 77.9, 69.3, 69.2, 44.6, 39.2, 39.1, 37.5, 37.4, 30.9, 25.9, 25.7, 19.5, 18.0, 17.8, 11.9, 11.8, -4.2, -4.7. **^{19}F NMR** (470.62 MHz, $CDCl_3$) δ -197.10 (d, *J* = 52.0 Hz, 1F)**. HRMS**-ESI m/z: [M+Na], calculated for $C_{16}H_{31}FO_2Si$, 325.19700; found 325.19760. **R_f**: 0.46 in 10% EtOAc/hexanes.

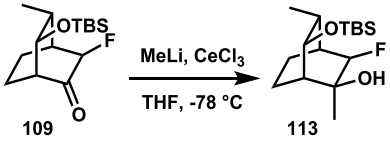
(1R,4S,5R,6S)-6-(tert-Butyldimethylsilyloxy)-3-fluoro-5-methylbicyclo[2.2.2]octan-2-one (109) was obtained as a white solid (89 mg, 21% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.56 (dd, J = 48.7 Hz and 2.9 Hz, 1H), 3.52 (dd, J = 5.2 Hz and 2.3 Hz, 1H), 2.30 (quintet, J = 2.9 Hz, 1H), 2.14-2.08 (m, 1H), 2.08-2.01 (m, 1H), 1.95-1.85 (m, 1H), 1.75-1.63 (m, 2H), 1.59-1.51 (m, 1H), 1.13 (d, J = 6.9 Hz, 3H), 0.85 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 208.2-208.1, 92.3-90.7, 78.9, 51.0, 39.3-39.2, 36.2,

25.7, 19.0, 18.0, 17.2, 16.4, -4.4. **HRMS**-CI m/z: [M+H], calculated for $C_{15}H_{27}O_2FSi$, 287.1843; found 287.1841. **R_f**: 0.29 in 10% EtOAc/hexanes.



112

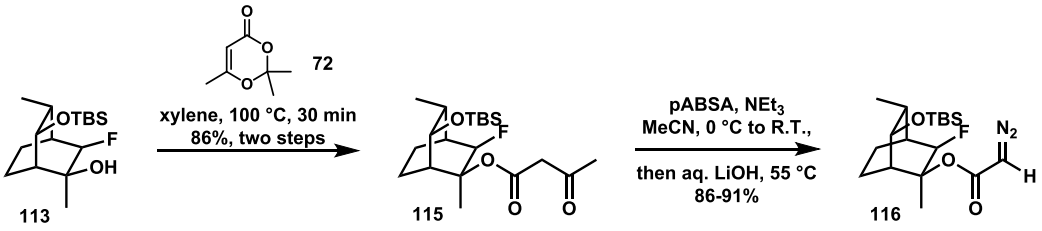
(1R,2S,3S,4S,5R,6S)-6-(tert-Butyldimethylsilyloxy)-3-fluoro-2,5-dimethylbicyclo[2.2.2]octan-2-yl 2-diazoacetate (112) was synthesized from tertiary alcohol **111** (70 mg, 0.23 mmol) following general procedure A. 20% EtOAc/hexanes mixture was used to extract the product. The crude product was purified by column chromatography on silica gel using 1% EtOAc in CH_2Cl_2 as an eluent, then purified one more time using 2.5% EtOAc in hexanes as an eluent. The product was obtained as a yellow oil (86 g, 68% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.69 (s, 1H), 4.63-4.49 (m, 1H), 3.35 (dd, J = 6.3 Hz and 2.3 Hz, 1H), 2.10-2.04 (m, 1H), 1.84-1.73 (m, 2H), 1.80 (d, J = 1.7 Hz, 3H), 1.66-1.57 (m, 1H), 1.57-1.49 (m, 1H), 1.39-1.29 (m, 1H), 1.27-1.15 (m, 1H), 1.05 (d, J = 6.9 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.05 (s, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ ~165, 95.1, 93.2, 80.6, 80.5, 77.4, 46.8, 43.2, 38.1, 38.0, 37.5, 37.3, 26.4, 25.9, 25.8, 19.6, 18.0, 17.5, 12.3, 12.3, -4.3, -4.7. **R_f**: 0.28 in 10% EtOAc/hexanes. **FTIR** (neat, cm^{-1}): 2930, 2106, 1709, 1642, 1366, 1226.



109 113

(1R,2S,4S,5R,6S)-6-(tert-Butyldimethylsilyloxy)-3-fluoro-2,5-dimethylbicyclo-[2.2.2]octan-2-ol (113). A flame-dried round-bottom flask was charged with ketone **109** (0.30 g, 1.05 mmol) under an argon atmosphere. Anhydrous THF (12.0 ml) was added, and the flask was cooled to -78 ˚C in a dry ice/acetone bath. 1.6M MeLi solution (1.30 ml, 2.10

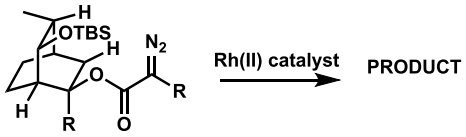
mmol) was then added. The reaction mixture was warmed to room temperature and stirred for 2 hours before saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered through short silica gel plug and concentrated to yield crude product. Crude product was subjected to the next step without any further purification. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.86 (s, 1H), 4.22 (dd, *J* = 51.0 Hz and 3.4 Hz, 1H), 3.46 (t, *J* = 3.4 Hz, 1H), 2.18-2.11 (m, 1H), 1.85-1.79 (m, 1H), 1.66-1.62 (m, 1H), 1.61-1.48 (m, 2H), 1.26 (s, 3H), 1.28-1.13 (m, 2H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 96.0, 94.4, 79.8, 70.7, 70.6, 43.0, 37.7, 37.5, 33.4, 28.6, 25.8, 20.2, 18.0, 17.9, 15.9, 15.8, -4.5, -4.6. **^{19}F NMR** (470.62 MHz, $CDCl_3$) δ -197.21 (d, *J* = 50.9 Hz, 1F)**. R_f**: 0.51 in 20% EtOAc/hexanes.

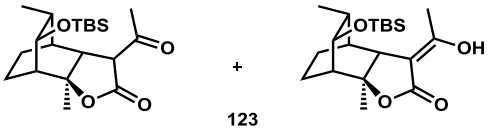


6-[(tert-Butyldimethylsilyl)oxy]-3-fluoro-2,5-dimethylbicyclo[2.2.2]octan-2-yl 3-oxobutanoate (115). A flame-dried round-bottom flask was charged with the tertiary alcohol **113** (1.05 mmol) from the previous reaction and dioxinone **72** (0.22 ml, 1.58 mmol) under an argon atmosphere. Xylene (0.21 ml, 5.0M) was added, and the flask was placed in a preheated (100 ˚C) oil bath. After 30 minutes the reaction mixture was allowed to cool to room temperature. Afterwards, the crude reaction mixture was purified by column

chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a white solid (349 mg, 86%). **R_f**: 0.51 in 20% EtOAc/hexanes.

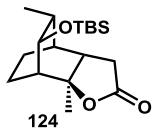
(1R,2S,4S,5R,6S)-6-(tert-Butyldimethylsilyloxy)-3-fluoro-2,5-dimethylbicyclo-[2.2.2]octan-2-yl 2-diazoacetate (116). A flame-dried round-bottom flask was charged with β-ketoester **115** (1.00 g, 2.59 mmol) under an argon atmosphere. Anhydrous MeCN (26.0 ml, 0.1M) was added and the flask was cooled to 0 ˚C in an ice/water bath. NEt_3 (0.54 ml, 3.88 mmol) followed by pABSA (0.68 g, 2.85 mmol) were then added. After 10 minutes the reaction mixture was allowed to warm to room temperature and stir for 1 hour (monitored by TLC). After 1 hour LiOH (1.09 g, 25.9 mmol) and water (3.5 ml, 0.7M) were added to the above solution. The reaction mixture was heated at 55 ˚C for 24 hours (monitored by TLC). After completion, the reaction mixture was cooled to room temperature before adding saturated NH_4Cl solution. The product was extracted with Et_2O (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a yellow oil (0.82 g, 86%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.61 (bs, 1H), 4.16 (dd, J = 49.0 Hz and 1.8 Hz, 1H), 3.35-3.29 (m, 1H), 2.56-2.50 (m, 1H), 2.17-2.08 (m, 1H), 1.72 (s, 3H), 1.70-1.53 (m, 2H), 1.43-1.34 (m, 2H), 1.30-1.20 (m, 1H), 1.02 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.04 (s, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ ~165, 97.5, 95.6, 80.1, 80.0, 78.8, 47.7, 41.3, 38.7, 38.5, 33.3, 26.2, 25.7, 24.3, 21.6, 18.5, 17.3, 17.1, -4.8. **R_f**: 0.31 in 5% EtOAc/hexanes. **FTIR** (neat, cm^{-1}): 2955, 2928, 2104, 1695, 1369, 1241.



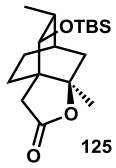


123

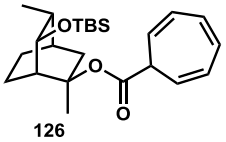
(2R)-5-Acetyl-9-[(tert-butyldimethylsilyl)oxy]-2,8-dimethyl-3-oxatricyclo[5.2.2.0^{2},^{6}]undecan-4-one (123). A flame dried round-bottom flask was charged with diazo-acetate **74** (100.0 mg, 0.25 mmol) under an argon atmosphere. Anhydrous CH_2Cl_2 (9.0 ml, 0.03M) was added. The reaction mixture was vigorously stirred at room temperature while adding $Rh_2(oct)_4$ (1.0 mg, 0.5 mol%) in one portion. After 20 minutes, TLC analysis showed no starting material. The reaction was concentrated under reduced pressure and the residue was purified by flash column chromatography using 5% EtOAc in hexanes as an eluent. The product was obtained as a white solid (28.9 mg, 31% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.54 (s, 1H, major), 3.65 (d, J = 4.0 Hz, 1H, minor), 3.34 (dd, J = 5.2 Hz and 2.3 Hz, 1H, minor), 3.31 (dd, J = 5.2 Hz and 2.3 Hz, 1H, major), 2.70 (t, J = 3.4 Hz, 1H, minor), 2.60 (d, J = 2.3 Hz, 1H, major), 2.45 (s, 3H, minor), 1.92 (s, 3H, major), 1.84 (q, J = 2.9 Hz, 1H, minor), 1.83-1.80 (m, 1H, major), 1.71-1.51 (m, major/minor), 1.44-1.35 (m, major/minor), 1.39 (s, 3H, minor), 1.38 (s, 3H, major), 1.34-1.21 (m, major/minor), 1.02 (d, J = 6.9 Hz, 3H, minor), 0.96 (d, J = 6.9 Hz, 3H, major), 0.89 (s, 9H, minor), 0.88 (s, 9H, major), 0.04 (s, 3H, minor), 0.03 (s, 3H, major), 0.02 (s, 3H, minor), 0.00 (s, 3H, major). **^{13}C NMR** (100.25 MHz, $CDCl_3$) δ 200.8, 175.6, 171.3, 168.4, 99.7, 85.9, 85.4, 78.3, 77.9, 59.9, 48.0, 44.6, 41.7, 41.6, 37.1, 36.8, 36.4, 36.0, 29.5, 27.7, 27.3, 25.8, 25.8, 21.9, 21.7, 19.0, 18.8, 18.7, 18.6, 18.0, -4.3, -4.3, -4.6, -4.7. **HRMS**-CI m/z: [M+H], calculated for $C_{20}H_{32}O_5Si$, 381.2097; found 381.2098. **R_f**: 0.68 in 20% EtOAc/hexanes.



(2R)-9-[(tert-Butyldimethylsilyl)oxy]-2,8-dimethyl-3-oxatricyclo [5.2.2.0^{2},^{6}]undecan-4-one (124). A flame dried round-bottom flask was charged with diazo-acetate **78** (163.0 mg, 0.46 mmol) under an argon atmosphere. Anhydrous CH_2Cl_2 (15.4 ml, 0.03M) was added. The reaction mixture was vigorously stirred at room temperature while adding $Rh_2(oct)_4$ (1.8 mg, 0.5 mol%) in one portion. After 20 minutes, TLC analysis showed no starting material. The reaction was concentrated under reduced pressure and the residue was purified by flash column chromatography using 10% EtOAc in hexanes as an eluent. The product was obtained as a white solid (36.0 mg, 24% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.32 (dd, J = 5.7 Hz and 2.3 Hz, 1H), 2.79 (dd, J = 18.9 Hz and 10.9 Hz, 1H), 2.39 (dd, J = 18.9 Hz and 2.9 Hz, 1H), 2.10 (dt, J = 10.9 Hz and 2.9 Hz, 1H), 1.84-1.81 (m, 1H), 1.70-1.51 (m, 3H), 1.47-1.36 (m, 2H), 1.40 (s, 3H), 1.28-1.19 (m, 1H), 1.02 (d, J = 6.9 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 176.7, 86.4, 78.0, 43.6, 42.0, 37.3, 35.3, 32.9, 27.5, 25.8, 22.0, 19.3, 18.5, 18.0, -4.6. **R_f**: 0.23 in 20% EtOAc/hexanes.



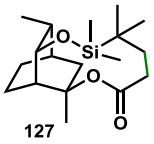
(5R)-9-[(tert-Butyldimethylsilyl)oxy]-5,8-dimethyl-4-oxatricyclo [5.2.2.0^{1},^{5}]undecan-3-one (125). From the above reaction, product **125** was obtained as a white solid (12.5 mg, 8% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.29-2.25 (m, 1H), 2.26 (dd, J = 109.4 Hz and 16.9 Hz, 2H), 2.04 (d, J = 13.3 Hz, 1H), 1.90 (dd, J = 13.3 Hz and 5.0 Hz, 1H), 1.83-1.69 (m, 2H), 1.68-1.50 (m, 4H), 1.40 (s, 3H), 1.34-1.21 (m, 1H), 1.03 (d, J = 7.3 Hz, 3H), 0.87 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 176.6, 84.7, 82.6, 44.4, 44.3, 39.3, 37.6, 32.1, 27.9, 25.9, 23.8, 19.4, 19.0, 17.8, -4.0, -4.8. **R_f**: 0.31 in 20% EtOAc/hexanes.



126

(1R,2R,4R,5R,6S)-6-(tert-Butyldimethylsilyloxy)-2,5-dimethyl-bicyclo[2.2.2]octan-2-yl cyclohepta-2,4,6-trienecarboxylate (126). A flame dried round-bottom flask was charged with diazo-acetate **78** (21.5 mg, 0.06 mmol) under an argon atmosphere. Anhydrous PhH (11.5 ml, 0.005M) was added. The reaction mixture was vigorously stirred at room temperature while adding $Rh_2(esp)_2$ (0.4 mg, 1 mol%) in one portion. After 20 minutes, TLC analysis showed no starting material. The reaction was concentrated under reduced pressure and the residue was purified by flash column chromatography using 5% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (24.6 mg, 53% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.63-6.59 (m, 2H), 6.22-6.15 (m, 2H), 5.62-5.49 (m, 2H), 3.39-3.34 (m, 1H), 2.52-2.48 (m, 1H), 2.47-2.42 (m, 1H), 2.10-2.03 (m, 1H), 1.83-1.74 (m, 1H), 1.62 (s, 3H), 1.53-1.38 (m, 5H), 1.20-1.11 (m, 1H), 1.00 (d, J = 6.9 Hz, 3H), 0.82 (s, 9H), -0.01 (s, 3H), -0.02 (s, 3H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 171.6, 131.1, 130.9, 124.9, 120.6, 120.4, 83.0, 79.7, 45.6, 44.3, 40.8, 39.6, 32.9, 26.5, 25.5, 22.7, 19.3, 18.8, 18.1, -3.8, -4.5. **HRMS**-ESI m/z: [M+Na], calculated for $C_{24}H_{38}O_3Si$, 425.24820; found 425.24810. **R_f**: 0.63 in 20% EtOAc/hexanes.

2,5,5,6,6,11-Hexamethyl-4,10-dioxa-5-silatricyclo[9.3.1.0^{3,12}] pentadecan-9-one (127).



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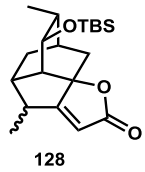
A flame dried round-bottom flask was charged with diazo-acetate **78** (50.0 mg, 0.14 mmol) under an argon atmosphere. Anhydrous CH_2Cl_2 (20.0 ml, 0.007M) was added. The reaction mixture was vigorously stirred at room temperature while adding $Rh_2(TPA)_4 \cdot CH_2Cl_2$ complex (1.9 mg, 1 mol%) in one portion. After 20 minutes, TLC analysis showed no starting material. The reaction was concentrated under reduced pressure and the residue was purified by flash column chromatography using 10%

EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (40.0 mg, 87% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.22-3.18 (m, 1H), 2.66-2.62 (m, 1H), 2.33-2.18 (m, 2H), 2.07-2.00 (m, 1H), 1.93 (dt, J = 14.3 Hz and 3.4 Hz, 1H), 1.79-1.72 (m, 1H), 1.59 (s, 3H), 1.52-1.28 (m, 5H), 1.16-1.07 (m, 2H), 0.94 (d, J = 6.9 Hz, 3H), 0.92 (s, 3H), 0.77 (s, 3H), 0.09 (s, 3H), -0.04 (s, 3H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 175.6, 81.5, 78.1, 45.3, 40.4, 37.2, 36.4, 32.2, 32.2, 26.2, 23.0, 21.5, 21.0, 19.0, 17.8, -4.3. **HRMS**-CI m/z: [M+H], calculated for $C_{18}H_{32}O_3Si$, 325.2199; found 325.2187. **R_f**: 0.60 in 20% EtOAc/hexanes.

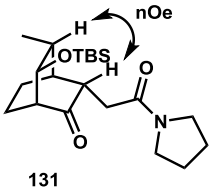
11-[(tert-Butyldimethylsilyl)oxy]-6,10-dimethyl-2-oxatetracyclo[7.3.1.0^{1,5}.0^{7,12}]



128

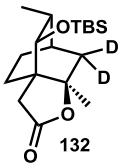
tridec-4-en-3-one (128). A flame dried round-bottom flask was charged with diazo-acetate **79** (42.0 mg, 0.11 mmol) under an argon atmosphere. Anhydrous CH_2Cl_2 (11.7 ml, 0.01M) was added. The reaction mixture was vigorously stirred at room temperature while adding $Rh_2(oct)_4$ (0.9 mg, 1 mol%) in one portion. After 20 minutes, TLC analysis showed no starting material. The reaction was concentrated under reduced pressure and the residue was purified by flash column chromatography using 10% EtOAc in hexanes as an eluent. The product was obtained as a white solid (16.1 mg, 41% yield). The diastereomeric ratio was measured to be 2:1 in ^{1}H NMR spectrum after isolation. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.56 (d, J = 1.4 Hz, 1H, major), 5.57 (d, J = 2.3 Hz, 1H, minor), 3.53 (dd, J = 5.0 Hz and 2.3 Hz, 1H, major), 3.47 (dd, J = 5.0 Hz and 2.3 Hz, 1H, minor), 3.01-2.90 (m, 1H, major), 2.60-2.51 (m, 1H, minor), 2.42-2.32 (m, 1H, major), 2.17-2.04 (m, 1H major, 1H minor), 2.00-1.93 (m, 1H, minor), 1.90-1.77 (m, 1H minor, 1H major), 1.72-1.44 (m, major/minor), 1.23 (d, J = 7.3 Hz, 3H, major), 1.22 (d, J = 7.3 Hz, 3H, minor), 1.04 (d, J = 7.3 Hz, 3H, major), 1.02 (d, J = 7.3 Hz, 3H, minor), 0.88

(s, 9H, minor), 0.87 (s, 9H, major), 0.02 (s, 3H major, 3H minor), -0.01 (s, 3H major, 3H minor). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 185.3, 175.7, 109.7, 90.0, 74.1, 48.4, 42.7, 39.9, 38.9, 34.6, 31.4, 25.8, 18.7, 18.2, 18.0, 14.4, -4.3, -4.4. **R_f**: 0.26 in 20% EtOAc/hexanes.

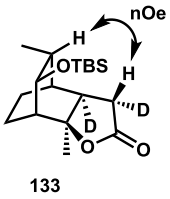


131

(1R,3S,4S,5R,6S)-6-(tert-Butyldimethylsilyloxy)-5-methyl-3-(2-oxo-2-(pyrrolidin-1-yl)ethyl)bicyclo[2.2.2]octan-2-one (131). A flame dried round-bottom flask was charged with diazo-acetate **102** (49.0 mg, 0.11 mmol) under an argon atmosphere. Anhydrous CH_2Cl_2 (3.8 ml, 0.03M) was added. The reaction mixture was vigorously stirred at room temperature while adding $Rh_2(esp)_2$ (0.4 mg, 0.5 mol%) in one portion. After 2 hours, TLC analysis showed no starting material. The reaction was concentrated under reduced pressure and the residue was purified by flash column chromatography using 20% to 40% EtOAc in hexanes as an eluent. The product was obtained as a white solid (18.0 mg, 32% yield). 10 mg of the starting material xx were recovered (20% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.57-3.52 (m, 1H), 3.49-3.33 (m, 4H), 2.89 (dd, J = 16.0 Hz and 3.2 Hz, 1H), 2.86-2.79 (m, 1H), 2.36-2.30 (m, 1H), 2.20 (dd, J = 16.0 Hz and 10.1 Hz, 1H), 2.06-1.88 (m, 4H), 1.88-1.79 (m, 2H), 1.69-1.55 (m, 3H), 1.44-1.34 (m, 1H), 1.11 (d, J = 7.3 Hz, 3H), 0.82 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 216.9, 170.1, 76.5, 51.5, 49.7, 46.7, 45.9, 43.6, 37.6, 31.9, 26.2, 25.8, 24.5, 21.2, 19.1, 18.0, 14.4, -4.5, -4.7. **HRMS**-CI m/z: [M+H], calculated for $C_{21}H_{37}NO_3Si$, 380.2621; found 380.2623. **R_f**: 0.51 in 50% EtOAc/hexanes.

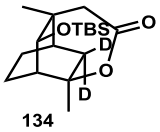


(5R)-9-[(tert-Butyldimethylsilyl)oxy]-5,8-dimethyl(6,6-D_2)-4-oxatricyclo [5.2.2.0^{1,5}]undecan-3-one (132). A round-bottom flask charged with 4Å molecular sieves (~3g/mmol) was flame-dried under high vacuum. A flask was allowed to cool to room temperature then it was purged with an argon atmosphere. $Rh_2(esp)_2$ (3.2 mg, 0.5 mol%) was added followed by anhydrous CH_2Cl_2 (36.0 ml, 0.02M). Diazo-acetate **105** (0.25 g, 0.72 mmol) dissolved in anhydrous CH_2Cl_2 (8.0 ml, 0.1M) was added dropwise slowly (20 ml/h) via syringe pump. After the addition, the TLC analysis showed no starting material. The reaction was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a white solid (94 mg, 39% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.30-3.25 (m, 1H), 2.25 (dd, J = 109.4 Hz and 16.5 Hz, 2H), 1.82-1.69 (m, 2H), 1.67-1.47 (m, 3H), 1.40 (s, 3H), 1.34-1.22 (m, 1H), 1.03 (d, J = 7.3 Hz, 3H), 0.87 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 176.6, 84.6, 82.6, 44.3, 44.2, 37.6, 31.9, 27.8, 25.9, 23.8, 19.4, 18.9, 17.8, -4.0. **HRMS**-CI m/z: [M+H], calculated for $C_{18}H_{30}D_2O_3Si$, 327.2325; found 327.2323. **R_f**: 0.28 in 20% EtOAc/hexanes.



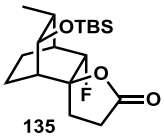
(2S,5S,6R)-9-[(tert-Butyldimethylsilyl)oxy]-2,8-dimethyl(5,6-D_2)-3-oxatricyclo[5.2.2.0^{2,6}]undecan-4-one (133). From the above reaction, product **133** was obtained as a white solid (94 mg, 39% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.31 (dd, J = 5.7 Hz and 2.3 Hz, 1H), 2.39-2.33 (m, 1H), 1.84-1.79 (m, 1H), 1.69-1.49 (m, 3H), 1.49-1.34 (m, 2H), 1.39 (s, 3H), 1.26-1.18 (m, 1H), 1.01 (d, J = 6.9 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 176.6, 86.3, 78.0, 41.9, 37.1, 35.3, 27.4, 25.8, 22.0, 19.2, 18.5, 18.0, -4.3. **HRMS**-CI m/z:

[M+H], calculated for $C_{18}H_{30}D_2O_3Si$, 327.2325; found 327.2336. **R**$_f$: 0.23 in 20% EtOAc/hexanes.



134

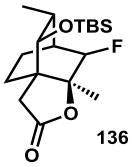
8-[(tert-Butyldimethylsilyl)oxy]-3,7-dimethyl(2,2-D$_2$)-4-oxatricyclo [5.4.0.0^{3,9}]undecan-5-one (134). From the above reaction, product **134** was obtained as a white solid (19 mg, 8% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.57 (s, 1H), 2.54 (dd, J = 32.5 Hz and 17.9 Hz, 2H), 1.76-1.72 (m, 1H), 1.68-1.52 (m, 3H), 1.46-1.30 (m, 2H), 1.35 (s, 3H), 0.99 (s, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 173.6, 80.8, 78.1, 44.1, 43.6, 38.2, 36.5, 26.8, 25.8, 25.7, 24.6, 22.3, 21.1, 18.1, -4.4. **HRMS**-CI m/z: [M+H], calculated for $C_{18}H_{30}D_2O_3Si$, 327.2325; found 327.2325. **R**$_f$: 0.20 in 20% EtOAc/hexanes.



135

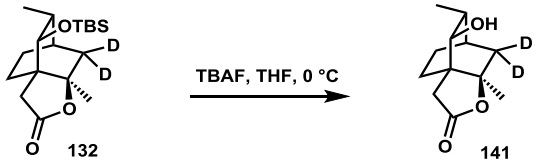
(1R,2S,3S,4S,5R,6S)-6-(tert-Butyldimethylsilyloxy)-3-fluoro-5-methyl-3'H-spiro[bicyclo[2.2.2]octane-2,2'-furan]-5'(4'H)-one (135). A round-bottom flask charged with 4Å molecular sieves (~3g/mmol) was flame-dried under high vacuum. A flask was allowed to cool to room temperature then it was purged with an argon atmosphere. $Rh_2(esp)_2$ (0.5 mg, 0.5 mol%) was added followed by anhydrous CH_2Cl_2 (7.0 ml, 0.02M). Diazo-acetate **112** (51.0 mg, 0.14 mmol) dissolved in anhydrous CH_2Cl_2 (1.4 ml, 0.1M) was added dropwise slowly (10 ml/h) via syringe pump. After the addition, the TLC analysis showed no starting material. The reaction was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (25 mg, 54% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.59-4.40 (m, 1H), 3.40 (t, J = 3.2 Hz, 1H), 2.70-2.57 (m, 1H), 2.49-2.38 (m, 1H), 2.37-2.21 (m, 2H), 2.07-1.97 (m, 1H), 1.93-1.81 (m,

2H), 1.81-1.69 (m, 1H), 1.63-1.52 (m, 1H), 1.43-1.32 (m, 1H), 1.20-1.10 (m, 1H), 1.08 (d, J = 7.3 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 176.8, (95.8, 93.8), (83.9, 83.7), 76.8, 43.6, (40.9, 40.8), 37.9, (37.1, 37.0), 28.5, 26.0, 19.0, 18.3, 18.0, 11.6, -4.4, -4.6. **HRMS**-CI m/z: [M+H], calculated for $C_{18}H_{31}O_3FSi$, 343.2105; found 343.2106. **R_f**: 0.14 in 5% EtOAc/hexanes.

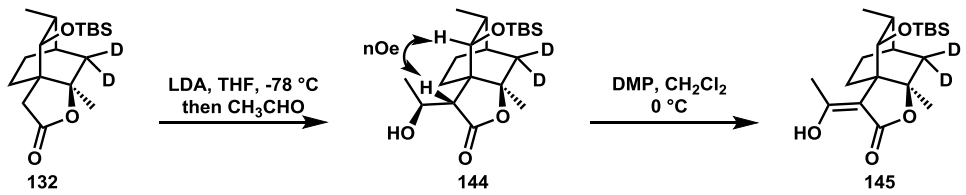


(5S)-9-[(tert-Butyldimethylsilyl)oxy]-6-fluoro-5,8-dimethyl-4-oxatricyclo [5.2.2.0^{1,5}]undecan-3-one (136). A round-bottom flask charged with 4Å molecular sieves (~3g/mmol) was flame-dried under high vacuum. A flask was allowed to cool to room temperature then it was purged with an argon atmosphere. $Rh_2(esp)_2$ (13.8 mg, 0.6 mol%) was added followed by anhydrous CH_2Cl_2 (160 ml, 0.017M). Diazo-acetate **116** (0.99 g, 2.67 mmol) dissolved in anhydrous CH_2Cl_2 (24 ml, 0.11M) was added dropwise slowly (45 ml/h) via syringe pump. After the addition, the TLC analysis showed no starting material. The reaction was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel using 30% EtOAc in hexanes as an eluent. The product was obtained as a white solid (0.62 g, 68% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.60 (dd, J = 52.1 Hz and 5.2 Hz, 1H), 3.26 (d, J = 1.7 Hz, 1H), 2.40 (d, J = 16.6 Hz, 1H), 2.19 (d, J = 16.6 Hz, 1H), 2.32-2.24 (m, 1H), 2.12-2.06 (m, 1H), 1.80-1.70 (m, 1H), 1.61-1.53 (m, 1H), 1.4-1.28 (m, 2H), 1.38 (d, J = 2.3 Hz, 3H), 1.06 (d, J = 7.4 Hz, 3H), 0.87 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 175.6, (91.9, 90.3), (81.2, 81.0), 53.6, 44.4, 37.3, (37.1, 36.9), (33.8, 33.8), (26.5, 26.5), 25.8, 23.3, 18.5, 18.0, 17.0, -4.0, -4.7. **^{19}F NMR** (470.62 MHz,

$CDCl_3$) δ –197.97 (d, *J* = 52.0 Hz)**. HRMS**-CI m/z: [M+H], calculated for $C_{18}H_{31}O_3SiF$, 343.2105; found 343.2113. **R_f**: 0.14 in 20% EtOAc/hexanes.

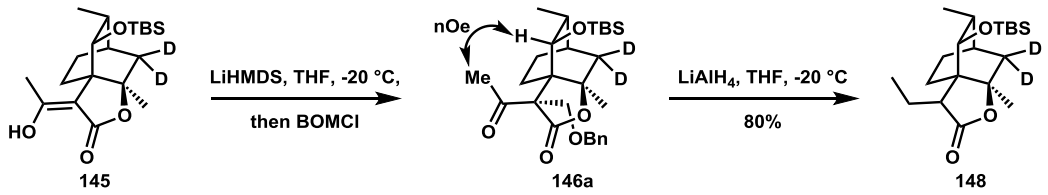


(5R)-9-Hydroxy-5,8-dimethyl(6,6-$^2H_2$)-4-oxatricyclo[5.2.2.0^1,^{5}]undecan-3-one (141). A flame-dried round-bottom flask was charged with TBS-ether **132** (35.2 mg, 0.11 mmol) under an argon atmosphere. Anhydrous THF (1.10 ml, 0.1M) was added and the flask was cooled to 0 ˚C in an ice/water bath. Then TBAF (0.13 ml, 0.13 mmol) was added dropwise. The reaction mixture was warmed to room temperature. After 10 minutes, TLC analysis showed no starting material. Saturated $NaHCO_3$ solution was added, the mixture was extracted with Et_2O (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 30% to 40% EtOAc in hexanes as an eluent. The product was obtained as a white solid (22 mg, 97%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.90 (d, J = 2.8 Hz, 1H), 2.60 (d, J = 16.9 Hz, 1H), 2.24-2.15 (m, 1H), 2.15 (d, J = 16.9 Hz, 1H), 1.78-1.66 (m, 2H), 1.60-1.54 (m, 1H), 1.44-1.33 (m, 1H), 1.27 (s, 3H), 1.15 (d, J = 6.9 Hz, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 178.0, 90.3, 73.6, 45.4, 36.4, 35.3, 32.9, 28.2, 26.2, 20.8, 18.1. **R_f**: 0.23 in 50% EtOAc/hexanes.



(2S,5R)-9-[(tert-Butyldimethylsilyl)oxy]-2-[(1S)-1-hydroxyethyl]-5,8-dimethyl(6,6-D_2)-4-oxatricyclo[5.2.2.0^{1,5}]undecan-3-one (144). A flame-dried round-bottom flask was charged with *i*Pr_2NH (0.33 ml, 2.35 mmol) under an argon atmosphere. Anhydrous THF (3.6 ml) was added, and the flask was cooled to 0 ˚C. 2.5M *n*BuLi solution (0.90 ml, 2.24 mmol) was added, and the reaction mixture was stirred for 15 minutes at 0 ˚C. Lactone **132** (183.0 mg, 0.56 mmol) dissolved in 2.0 ml of anhydrous THF was added dropwise to the above solution at -78 ˚C and stirred for 30 minutes. Acetaldehyde (0.16 ml, 2.80 mmol) was then added and the reaction mixture was allowed to warm to room temperature. After completion, saturated NH_4Cl solution was added. The reaction mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 30% EtOAc in hexanes as an eluent. Product was obtained as a white solid (0.20 g, 97% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.17-4.09 (m, 1H), 3.90 (s, 1H), 3.20 (s, 1H), 2.18 (d, J = 9.7 Hz, 1H), 1.86-1.78 (m, 1H), 1.78-1.73 (m, 1H), 1.73-1.63 (m, 2H), 1.56-1.46 (m, 1H), 1.48 (s, 3H), 1.27 (d, J = 5.7 Hz, 3H), 1.28-1.20 (m, 1H), 1.04 (d, J = 7.4 Hz, 3H), 0.86 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 179.5, 85.5, 84.3, 66.6, 54.4, 46.1, 43.8, 31.2, 30.2, 25.8, 23.9, 22.0, 19.3, 18.9, 17.8, -3.9. **R_f**: 0.14 in 20% EtOAc/hexanes.

(2Z,5R)-9-[(tert-Butyldimethylsilyl)oxy]-2-(1-hydroxyethylidene)-5,8-dimethyl(6,6-D_2)-4-oxatricyclo[5.2.2.0^{1,5}]undecan-3-one (145). A flame-dried round-bottom flask was charged with alcohol **144** (0.24 g, 0.65 mmol) under an argon atmosphere. Anhydrous CH_2Cl_2 (12.0 ml, 0.05M) was added and the flask was cooled to 0 ˚C in an ice/water bath, then DMP (0.33 g, 0.78 mmol) was added. The reaction mixture was warmed to room temperature. After 3 hours, TLC analysis showed no starting material. Saturated $NaHCO_3/Na_2SO_3$ (1:1) solution was added, the mixture was extracted with CH_2Cl_2 (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a white solid (195 mg, 82%). Mixture of keto, enol tautomers (3.5:3.0 ratio) was observed in ^{1}H NMR spectrum after isolation. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.15 (s), 4.25 (s), 3.36-3.16 (m), 2.49 (s), 2.32 (s), 2.08-1.98 (m), 1.92 (s), 1.84-1.43 (m), 1.41 (s), 4.39 (s), 1.37 (s), 1.06 (d, J = 7.3 Hz), 1.05 (d, J = 7.3 Hz), 1.04 (d, J = 7.3 Hz), 0.87 (s), 0.83 (s), 0.10 (s), 0.07 (s), 0.07 (s), 0.02 (s), -0.11 (s), -0.12 (s). **R_f**: 0.37 in 20% EtOAc/hexanes.

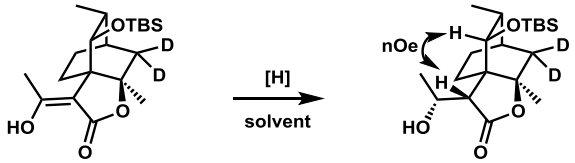


(2S,5R)-2-Acetyl-2-[(benzyloxy)methyl]-9-[(tert-butyldimethylsilyl)oxy]-5,8-dimethyl(6,6-$^2H_2$)-4-oxatricyclo[5.2.2.0^{1,5}]undecan-3-one (146a). A flame-dried round-bottom flask was charged with **145** (30 mg, 0.08 mmol) under an argon atmosphere.

Anhydrous THF (1.0 ml, 0.08M) was added and the flask was cooled to -10 ˚C and 1.0M LiHMDS solution (0.10 ml, 0.10 mmol) was added. After 1 hour BOMCl (17 µl, 0.12 mmol) was added. The reaction mixture was allowed to warm to room temperature and stir overnight. Saturated NH_4Cl solution was added, the mixture was extracted with Et_2O (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 20% EtOAc in hexanes as an eluent. The product was obtained as a white solid (34 mg, 85%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39-7.23 (m, 5H), 5.20 (dd, J = 63.2 Hz and 7.3 Hz, 2H), 4.73 (dd, J = 33.4 Hz and 11.9 Hz, 2H), 3.39-3.36 (m, 1H), 2.07 (s, 3H), 1.84-1.71 (m, 3H), 1.68-1.48 (m, 3H), 1.31 (s, 3H), 1.05 (d, J = 7.3 Hz, 3H), 0.86 (s, 9H), 0.03 (s, 3H), -0.05 (s, 3H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 169.3, 159.5, 137.4, 128.6, 128.2, 128.0, 113.4, 92.3, 81.2, 81.0, 70.7, 48.6, 44.3, 31.5, 29.3, 26.0, 25.8, 24.7, 19.5, 19.1, 17.8, 16.4. **HRMS**-CI m/z: [M+H], calculated for $C_{28}H_{40}D_2O_5Si$, 489.3005; found 489.3005. **R_f**: 0.20 in 20% EtOAc/hexanes.

(5R)-9-[(tert-Butyldimethylsilyl)oxy]-2-ethyl-5,8-dimethyl(6,6-$^2H_2$)-4-oxatricyclo[5.2.2.0^{1,5}]undecan-3-one (148). A round-bottom flask was charged with **146a** (10.0 mg, 0.02 mmol). Anhydrous THF (0.5 ml) and Et_2O (0.5 ml) were added, and the flask was cooled to 0 ˚C in an ice/H_2O bath. $LiAlH_4$ (7.0 mg, 0.14 mmol) was then added in one portion. After 30 min TLC analysis showed no starting material. To the reaction mixture 1N HCl solution was added dropwise until evolution of H_2 has ceased. Mixture was extracted with Et_2O (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product. The crude

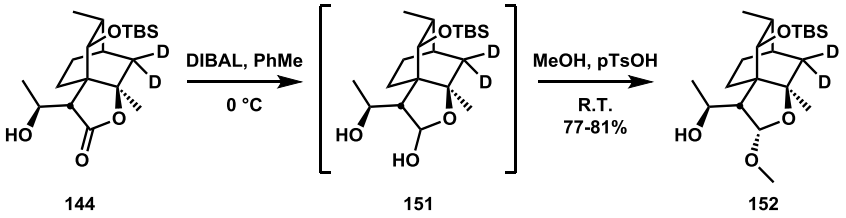
product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (5.8 mg, 80% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.47 (s, 1H), 2.28 (dd, J = 8.2 Hz and 5.5 Hz, 1H), 1.94-1.77 (m, 2H), 1.75-1.69 (m, 1H), 1.62-1.46 (m, 4H), 1.41 (s, 3H), 1.39-1.29 (m, 1H), 1.08-1.00 (m, 6H), 0.86 (s, 9H), 0.11 (s, 3H), 0.05 (s, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 177.6, 81.4, 77.3, 46.5, 45.9, 43.1, 30.7, 26.8, 25.8, 23.0, 19.1, 18.1, 17.6, 17.5, 12.8, -3.3, -4.8. **R_f**: 0.46 in 20% EtOAc/hexanes.



145 150

(2S,5R)-9-[(tert-Butyldimethylsilyl)oxy]-2-[(1R)-1-hydroxyethyl]-5,8-dimethyl(6,6-D_2)-4-oxatricyclo[5.2.2.0^{1,5}]undecan-3-one (150). A flame-dried round-bottom flask was charged with **145** (15 mg, 0.04 mmol) under an argon atmosphere. Anhydrous CH_2Cl_2 (2.0 ml, 0.02M) was added and the flask was cooled to -78 ˚C in a dry ice/acetone bath. 3.3M REDAL solution (0.06 ml, 0.20 mmol) was added. After 1 hour 1N HCl solution was added dropwise until the evolution of H_2 gas has ceased. Mixture was extracted with Et_2O (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 30% EtOAc in hexanes as an eluent. The product was obtained as a white solid (14 mg, 90%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.28-4.19 (m, 1H), 3.26 (s, 1H), 2.19 (d, J = 9.2 Hz, 1H), 1.95-1.87 (m, 1H), 1.83-1.75 (m, 1H), 1.75-1.71 (m, 1H), 1.71-1.62 (m, 1H), 1.56-1.37 (m, 3H), 1.45 (s, 3H), 1.43 (d, J = 6.3 Hz, 3H), 1.03 (d,

J = 7.4 Hz, 3H), 0.86 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). **HRMS**-CI m/z: [M+H], calculated for $C_{20}H_{34}D_2O_4Si$, 371.2587; found 371.2589. **R_f**: 0.43 in 40% EtOAc/hexanes.



144 151 152

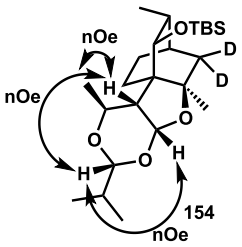
General procedure B, step I:

(5R)-9-[(tert-Butyldimethylsilyl)oxy]-2-[(1S)-1-hydroxyethyl]-5,8-dimethyl(6,6-D_2)-4-oxatricyclo[5.2.2.0^{1,5}]undecan-3-ol (151). A flame-dried round-bottom flask was charged with alcohol **144** (100.0 mg, 0.27 mmol) under an argon atmosphere. Anhydrous PhMe (2.7 ml, 0.1M) was added and the flask was cooled to -78 ˚C in a dry ice/acetone bath. 1.0M DIBAL solution (2.0 ml, 2.16 mmol) was added. After 1 hour 1N HCl solution was added dropwise until the evolution of H_2 gas has ceased. Mixture was extracted with Et_2O (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product.

Step II:

(1S)-1-[(5R)-9-[(tert-Butyldimethylsilyl)oxy]-3-methoxy-5,8-dimethyl(6,6-D_2)-4-oxatricyclo[5.2.2.0^{1,5}]undecan-2-yl]ethan-1-ol (152). In the 2 dram glass vial, the crude product was dissolved in anhydrous MeOH (1.30 ml, 0.2M) and catalytic amount of pTsOH was added. After stirring the reaction mixture at room temperature overnight, saturated NaCl solution was added. Product was extracted with Et_2O (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and

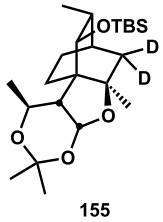
concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product **152** was obtained as a white solid (78 mg, 75%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.08 (d, J = 6.9 Hz, 1H), 4.32 (s, 1H), 4.13-4.01 (m, 1H), 3.37 (s, 3H), 3.05 (s, 1H), 2.16 (dd, J = 9.6 Hz and 6.9 Hz, 1H), 1.76-1.67 (m, 1H), 1.67-1.39 (m, 4H), 1.42 (s, 3H), 1.19 (d, J = 5.9 Hz, 3H), 1.15-1.03 (m, 1H), 0.99 (d, J = 7.3 Hz, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H). **R_f**: 0.51 in 20% EtOAc/hexanes.



Step I: Crude Diol **151** was synthesized from lactone **144** (20 mg, 0.05 mmol) following the general procedure B.

Step II: tert-Butyldimethyl{[(2S,3S,5R,7R,9R)-3,9,12-trimethyl-5-(propan-2-yl)(10,10-$^2H_2$)-4,6,8-trioxatetracyclo[9.2.2.0^1,^{9}.0^2,^{7}]pentadecan-13-yl]oxy}silane (154). A flame-dried round-bottom flask was charged with diol **151** (0.05 mmol) under an argon atmosphere. Anhydrous CH_2Cl_2 (1.10 ml, 0.05M) and TMS vinyl ether (20.0 µl, 0.10 mmol) were added and the flask was cooled to -78 ˚C in a dry ice/acetone bath. $BF_3{\cdot}OEt_2$ (20.0 µl, 0.15 mmol) then was added dropwise. The reaction was monitored by TLC, very slow reaction was observed at -78 C, and thus it was warmed to 0 C. After 1 hour, saturated NaCl solution was added, product was extracted with Et_2O (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product. From the compelex mixture the major product was isolated by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. Small amount of product **154** was obtained. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.22 (d, J = 6.4 Hz, 1H), 4.54 (d, J = 3.7 Hz, 1H), 3.98 (m, J = 5.5 Hz, 1H),

3.06 (s, 1H), 1.90 (dd, J = 11.0 Hz and 6.4 Hz, 1H), 1.84-1.67 (m, 2H), 1.67-1.61 (m, 1H), 1.61-1.46 (m, 3H), 1.50 (s, 3H), 1.15 (d, J = 6.0 Hz, 3H), 1.17-1.02 (m, 1H), 0.99 (d, J = 7.3 Hz, 3H), 0.92 (d, J = 2.8 Hz, 3H), 0.91 (d, J = 2.8 Hz, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 197.1, 104.3, 99.4, 84.6, 84.1, 66.8, 54.7, 48.7, 44.3, 33.9, 32.1, 30.0, 29.9, 26.0, 22.4, 21.1, 19.6, 18.8, 18.0, 16.5, 16.4, -3.8, -4.5. **R_f**: 0.57 in 20% EtOAc/hexanes.

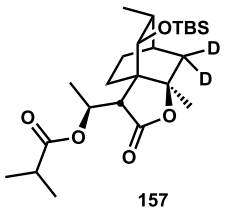


155

Step I: Crude diol **151** was synthesized from lactone **152** (50 mg, 0.13 mmol) following the general procedure B.

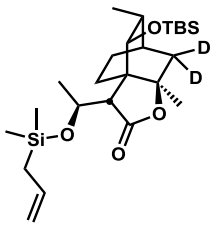
Step II: tert-Butyldimethyl{[(2S,3S,7R,9R)-3,5,5,9,12-pentamethyl (10,10-$^2H_2$)-4,6,8-trioxatetracyclo[9.2.2.0^{1,9}.0^{2,7}]pentadecan-13-yl]oxy}silane (155). In the 2 dram glass vial, the crude product was dissolved in anhydrous acetone (1.30 ml, 0.1M) and catalytic amount of pTsOH was added. After stirring the reaction mixture at room temperature overnight, saturated NaCl solution was added. Product was extracted with Et_2O (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product **155** was obtained as a white solid (35 mg, 63%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.40 (d, J = 5.9 Hz, 1H), 3.98 (m, J = 5.9 Hz, 1H), 3.08-3.03 (m, 1H), 1.96 (dd, J = 11.0 Hz and 6.4 Hz, 1H), 1.76-1.67 (m, 1H), 1.66-1.61 (m, 1H), 1.60-1.47 (m, 3H), 1.51 (s, 3H), 1.35 (s, 3H), 1.34 (s, 3H), 1.16 (d, J = 5.9 Hz, 3H), 1.17-1.06 (m, 1H), 0.99 (d, J = 7.3 Hz, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 100.3, 99.2, 84.8, 83.9, 66.3, 55.6, 48.3, 44.3, 32.1, 30.0, 26.9, 26.0, 25.0, 22.5, 21.1,

19.6, 18.8, 18.0, -3.8, -4.5. **HRMS**-CI m/z: [M+H], calculated for $C_{23}H_{40}D_2O_4Si$, 413.3056; found 413.3049. **R_f**: 0.54 in 20% EtOAc/hexanes.



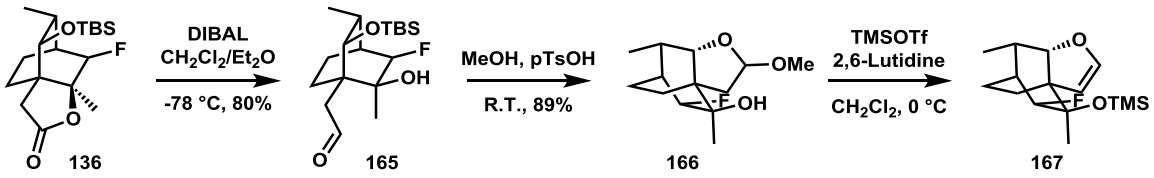
157

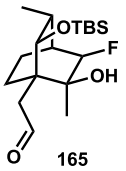
(1S)-1-[(5R)-9-[(tert-Butyldimethylsilyl)oxy]-5,8-dimethyl-3-oxo(6,6-$^2H_2$)-4-oxatricyclo[5.2.2.0^{1,5}]undecan-2-yl]ethyl 2-methylpropanoate (157). A round-bottom flask was charged with alcohol **144** (37.0 mg, 0.10 mmol). Anhydrous CH_2Cl_2 (1.0 ml, 0.1M) was added, followed by the addition of DMAP (12.0 mg, 0.10 mmol) and NEt_3 (21.0 µl, 0.15 mmol). Isobutyryl chloride (12 µl, 0.12 mmol) was added to the above mixture at 0 ˚C. The reaction mixture was allowed to warm to room temperature and stir overnight. Solvent was removed via rotary evaporation to yield crude product. The crude product was purified by column chromatography on silica gel using 7.5% EtOAc in hexanes as an eluent. The product was obtained as a white solid (38 mg, 86%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.30-5.22 (m, 1H), 3.18 (s, 1H), 2.56 (m, J = 6.9 Hz, 1H), 2.28 (d, J = 8.6 Hz, 1H), 1.83-1.76 (m, 1H), 1.76-1.51 (m, 4H), 1.58 (s, 3H), 1.32 (d, J = 6.3 Hz, 3H), 1.15 (d, J = 7.4 Hz, 3H), 1.14 (d, J = 6.9 Hz, 3H), 1.03 (d, J = 7.4 Hz, 3H), 0.86 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 176.9, 174.7, 84.4, 83.6, 67.2, 52.2, 46.4, 44.0, 34.1, 31.3, 29.7, 25.9, 21.9, 21.6, 19.3, 19.2, 18.9, 18.8, 17.8, -3.9, -4.8. **HRMS**-CI m/z: [M+H], calculated for $C_{24}H_{40}D_2O_5Si$, 441.3005; found 441.3008. **R_f**: 0.48 in 20% EtOAc/hexanes.



(5R)-9-[(tert-Butyldimethylsilyl)oxy]-2-[(1S)-1-{[dimethyl(prop-2-en-1-yl)silyl]oxy}ethyl]-5,8-dimethyl(6,6-$^2H_2$)-4-oxatricyclo [5.2.2.0^{1,5}]undecan-3-one. A round-bottom flask was charged with alcohol **144** (50.0 mg, 0.13 mmol). Anhydrous CH_2Cl_2 (0.9 ml, 0.1M)

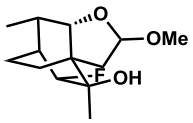
was added, followed by the addition of DMAP (1.5 mg, 0.01 mmol) and NEt_3 (30.0 µl, 0.20 mmol). Allyldimethylsilyl chloride (30.0 µl, 0.20 mmol) was added to the above mixture at 0 ˚C. The reaction mixture was allowed to warm to room temperature and stir overnight. Saturated $NaHCO_3$ solution was added, product was extracted with CH_2Cl_2 (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a white solid (63 mg, 98%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.81-5.69 (m, 1H), 4.91-4.80 (m, 2H), 4.19-4.10 (m, 1H), 3.14 (s, 1H), 2.23 (d, J = 4.0 Hz, 1H), 1.83-1.71 (m, 2H), 1.67-1.51 (m, 5H), 1.41 (d, J = 6.3 Hz, 3H), 1.84-1.10 (m, 1H), 1.01 (d, J = 7.4 Hz, 3H), 0.86 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 175.9, 134.2, 114.0, 84.7, 83.4, 66.8, 54.4, 46.5, 44.0, 31.3, 30.4, 25.9, 25.8, 25.3, 24.9, 20.7, 19.3, 18.8, 17.8, -1.4, -1.4, -3.9, -4.9. **R_f**: 0.40 in 10% EtOAc/hexanes.





2-((1S,2S,4S,5R,6S)-6-(tert-butyldimethylsilyloxy)-3-fluoro-2-hydroxy-2,5-dimethylbicyclo[2.2.2]octan-1-yl)acetaldehyde (165). A flame-dried round-bottom flask was charged with lactone **136** (100.0 mg, 0.29 mmol) under an argon atmosphere. Anhydrous CH_2Cl_2 (1.4 ml) and Et_2O (1.4 ml) were added and the flask was cooled to -78 ˚C in a dry ice/acetone bath. 1.0M DIBAL solution (0.58 ml, 0.58

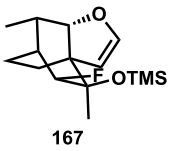
mmol) was added. After 1 hour 1N HCl solution was added dropwise until the evolution of H_2 gas has ceased. Mixture was extracted with Et_2O (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product. Crude product was purified by column chromatography on silica gel using 20% EtOAc in hexanes as an eluent. The product was obtained as a white solid (85 mg, 84%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.89 (t, J = 2.3 Hz, 1H), 4.47-4.44 (m, 1H), 4.35 (dd, J = 52.1 Hz and 4.0 Hz, 1H), 3.73 (d, J = 2.3 Hz, 1H), 2.98 (dd, J = 16.6 Hz and 2.3 Hz, 1H), 2.38 (dd, J = 16.6 Hz and 2.3 Hz, 1H), 2.55-2.17 (m, 1H), 1.99-1.93 (m, 1H), 1.72-1.61 (m, 1H), 1.58-1.48 (m, 1H), 1.44-1.37 (m, 1H), 1.26-1.16 (m, 1H), 1.20 (s, 3H), 1.08 (d, J = 7.4 Hz, 3H), 0.90 (s, 9H), 0.15 (s, 3H), 0.08 (s, 3H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 203.0, (96.2, 94.7), 80.6, (72.2, 72.1), 44.6, 42.6, (36.5, 36.3), (34.0, 33.9), 25.8, 25.5, 24.5, 18.5, 17.9, (15.9, 15.8), -3.9. **^{19}F NMR** (470.62 MHz, $CDCl_3$) δ -192.38 (dd, *J* = 52.0 Hz and 5.4 Hz, 1F). **HRMS**-CI m/z: [M+H], calculated for $C_{18}H_{33}O_3SiF$, 345.2261; found 345.2252. **R_f**: 0.43 in 30% EtOAc/hexanes.



166

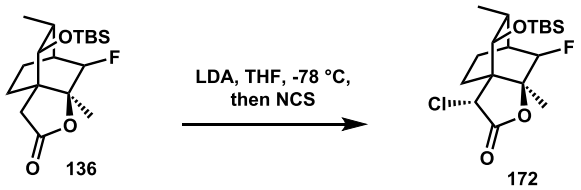
(5S)-8-Fluoro-3-methoxy-6,9-dimethyl-4-oxatricyclo[5.2.2.0^{1,5}] undecan-9-ol (166). A flame-dried round-bottom flask was charged with aldehyde **165** (50.0 mg, 0.14 mmol) under an argon atmosphere. Anhydrous MeOH (0.8 ml, 0.2M) and catalytic amount of pTsOH were added. After stirring the reaction mixture at room temperature overnight, saturated NaCl solution was added. Product was extracted with Et_2O (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using

20% EtOAc in hexanes as an eluent. The product was obtained as a white solid (29 mg, 82%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.16-5.09 (m, 1H), 4.24 (d, J = 50.8 Hz, 1H), 3.53 (d, J = 7.8 Hz, 1H), 3.26 (s, 3H), 2.86 (d, J = 3.2 Hz, 1H), 2.43 (dd, J = 14.2 Hz and 5.9 Hz, 1H), 2.32 (m, J = 6.9 Hz, 1H), 1.80-1.57 (m, 3H), 1.46-1.38 (m, 1H), 1.36-1.20 (m, 2H), 1.23 (s, 3H), 1.13 (d, J = 6.9 Hz, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 106.9, (96.2, 94.3), 87.0, (73.0, 72.9), 55.8, 47.5, (39.1, 38.9), 38.5, 29.3, 27.3, 24.3, 17.8, (17.6, 17.5). **HRMS**-ESI m/z: [M+Na], calculated for $C_{13}H_{21}FO_3$, 267.13670; found 267.13700. **R_f**: 0.51 in 30% EtOAc/hexanes.



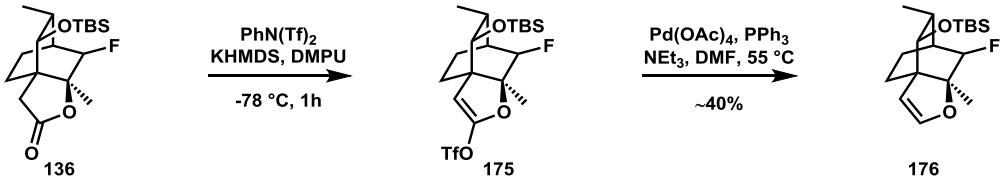
167

{[(5S)-8-Fluoro-6,9-dimethyl-4-oxatricyclo[5.2.2.0^{1,5}]undec-2-en-9-yl]oxy}trimethylsilane (167). A flame-dried round-bottom flask was charged with acetal **166** (48.0 mg, 0.20 mmol) under an argon atmosphere. Anhydrous CH_2Cl_2 (2.0 ml, 0.1M) and the flask was cooled to 0 ˚C in an ice/H_2O bath. 2,6-Lutidine (0.11 ml, 1.00 mmol) followed by TMSOTf (0.14 ml, 0.60 mmol) were added. The reaction mixture was warmed to room temperature and stirred for 4 hours. Afterwards, saturated NaCl solution was added, product was extracted with Et_2O (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product. The crude product was dissolved in Et_2O and filtered through short plug of Celite®. After the removal of solvent via rotary evaporation, product was obtained as a light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.48 (d, J = 2.9 Hz, 1H), 4.85 (d, J = 2.9 Hz, 1H), 4.09 (dd, J = 51.0 Hz and 1.7 Hz, 1H), 3.56 (d, J = 9.2 Hz, 1H), 2.75-2.65 (m, 1H), 1.72-1.62 (m, 2H), 1.57-1.48 (m, 1H), 1.38-1.21 (m, 2H), 1.19 (s, 3H), 1.10 (d, J = 6.9 Hz, 3H), 0.06 (s, 9H). **R_f**: 0.71 in 30% EtOAc/hexanes.



(2R,5S)-9-[(tert-Butyldimethylsilyl)oxy]-2-chloro-6-fluoro-5,8-dimethyl-4-oxatricyclo[5.2.2.0^{1,5}]undecan-3-one (172). A flame-dried round-bottom flask was charged with *i*Pr_2NH (20.0 µl, 0.14 mmol) under an argon atmosphere. Anhydrous THF (0.5 ml) was added, and the flask was cooled to 0 ˚C. 2.5M *n*BuLi solution (50.0 µl, 0.12 mmol) was added, and the reaction mixture was stirred for 15 minutes at 0 ˚C. Mixture of lactone **136** (30.0 mg, 0.09 mmol) and TMSCl (17 µl, 0.14 mmol) dissolved in 1.0 ml of anhydrous THF were added dropwise to the above solution at -78 ˚C and stirred for 30 minutes. N-Chlorosucinimide (15.0 mg, 0.12 mmol) dissolved in 1.0 ml of anhydrous THF was then added and the reaction mixture was allowed to warm to room temperature. After completion, saturated NH_4Cl solution was added. The reaction mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 30% EtOAc in hexanes as an eluent. Product was obtained as a white solid (20 mg, 61% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.56 (dd, J = 52.7 Hz and 5.2 Hz, 1H), 4.19 (s, 1H), 3.41 (s, 1H), 2.33-2.25 (m, 1H), 2.18-2.12 (m, 1H), 1.90 (dd, J = 13.8 Hz and 10.9 Hz, 1H). 1.86-1.75 (m, 1H), 1.64 (d, J = 2.3 Hz, 3H), 1.49-1.39 (m, 1H), 1.34-1.20 (m, 2H), 1.08 (d, J = 7.4 Hz, 3H), 0.86 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 172.0, (92.6, 91.0), 82.2, (82.1,

82.0), (37.0, 36.9), (33.9, 33.9), 27.8, 25.7, 21.0, (18.3, 18.0), (16.7, 16.7), -4.0, -4.7. **R_f**: 0.14 in 20% EtOAc/hexanes.



(5S)-9-[(tert-Butyldimethylsilyl)oxy]-6-fluoro-5,8-dimethyl-4-oxatricyclo[5.2.2.0^{1},^{5}] undec-2-en-3-yl trifluoromethanesulfonate (175). A flame-dried round-bottom flask was charged with lactone **136** (30.0 mg, 0.09 mmol), $PhN(Tf)_2$ (37.0 mg, 0.11 mmol) under an argon atmosphere. Anhydrous THF (0.9 ml, 0.1M) was added and the flask was cooled to -78 ˚C in a dry ice/acetone bath. DMPU (11.0 µl, 0.09 mmol) followed by 1.0M KHMDS (0.11 ml, 0.12 mmol) were added. The reaction mixture was warmed to room temperature and stirred for 1 hours. Afterwards, solvent was removed via rotary evaporation. To the crude product Et_2O was added and the mixture was filtered through short plug of Celite®. After the removal of solvent via rotary evaporation a light yellow oil was obtained. The crude material was used directly in the next step without any further purifications. **R_f**: 0.43 in 10% EtOAc/hexanes.

tert-Butyl({[(5S)-6-fluoro-5,8-dimethyl-4-oxatricyclo[5.2.2.0^{1},^{5}]undec-2-en-9-yl]oxy})dimethylsilane (176). A flame-dried round-bottom flask was charged with the crude vinyl triflate **175** (30.0 mg, 0.09 mmol), deoxyganated DMF (1.80 ml, 0.05M), NEt_3 (0.14 ml, 1.08 mmol), PPh_3 (18.4 mg, 0.08 mmol), $Pd(OAc)_2$ (8.0 mg, 0.04 mmol), and 98% formic acid (26.0 µl, 0.72 mmol) under an argon atmosphere. The reaction mixture was heated at 55 ˚C for 10 minutes. Mixture turned black during the first few minutes.

When cooled to room temperature, product was extracted with hexanes (3x). The organic phases were combined, dried over anhydrous $MgSO_4$, filtered through the pad of Celite®, and concentrated to yield crude product. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.33 (d, J = 2.8 Hz, 1H), 4.72 (dd, J = 52.7 Hz and 5.5 Hz, 1H), 4.58 (d, J = 2.8 Hz, 1H), 2.92 (s, 1H), 2.31-2.21 (m, 1H), 2.07-1.99 (m, 1H), 1.75-1.59 (m, 2H), 1.50-1.38 (m, 1H), 1.33 (s, 3H), 1.27-1.14 (m, 1H), 1.04 (s, 3H), 0.86 (s, 9H), 0.02 (s, 3H), -0.05 (s, 3H). **R_f**: 0.48 in 10% EtOAc/hexanes.

1.4.3. Crystalographic Data

Crystal data and structure refinement for 88.

Empirical formula	$C_{10}H_{16}O_2$	
Formula weight	168.23 g/mol	
Crystallization solvent	EtOAc	
Crystal habit	prismatic block	
Crystal size	0.40 x 0.30 x 0.12 mm^3	
Crystal color	colorless	
Data Collection		
Type of diffractometer	Bruker APEX II CCD	
Wavelength	0.71073 Å MoKα	
Data collection temperature	223(2) K	
Unit cell dimensions	a = 9.3942(4) Å	α = 90.00 °
	b = 10.5409(5) Å	β = 98.553(1) °
	c = 9.5041(4) Å	γ = 90.00 °
Volume	930.70(7) $Å^3$	
Z	4	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Density	1.201 Mg/m^3	
F(000)	368	
Reflections collected	1745	
Absorption coefficient	0.082	

1.5. References and Notes

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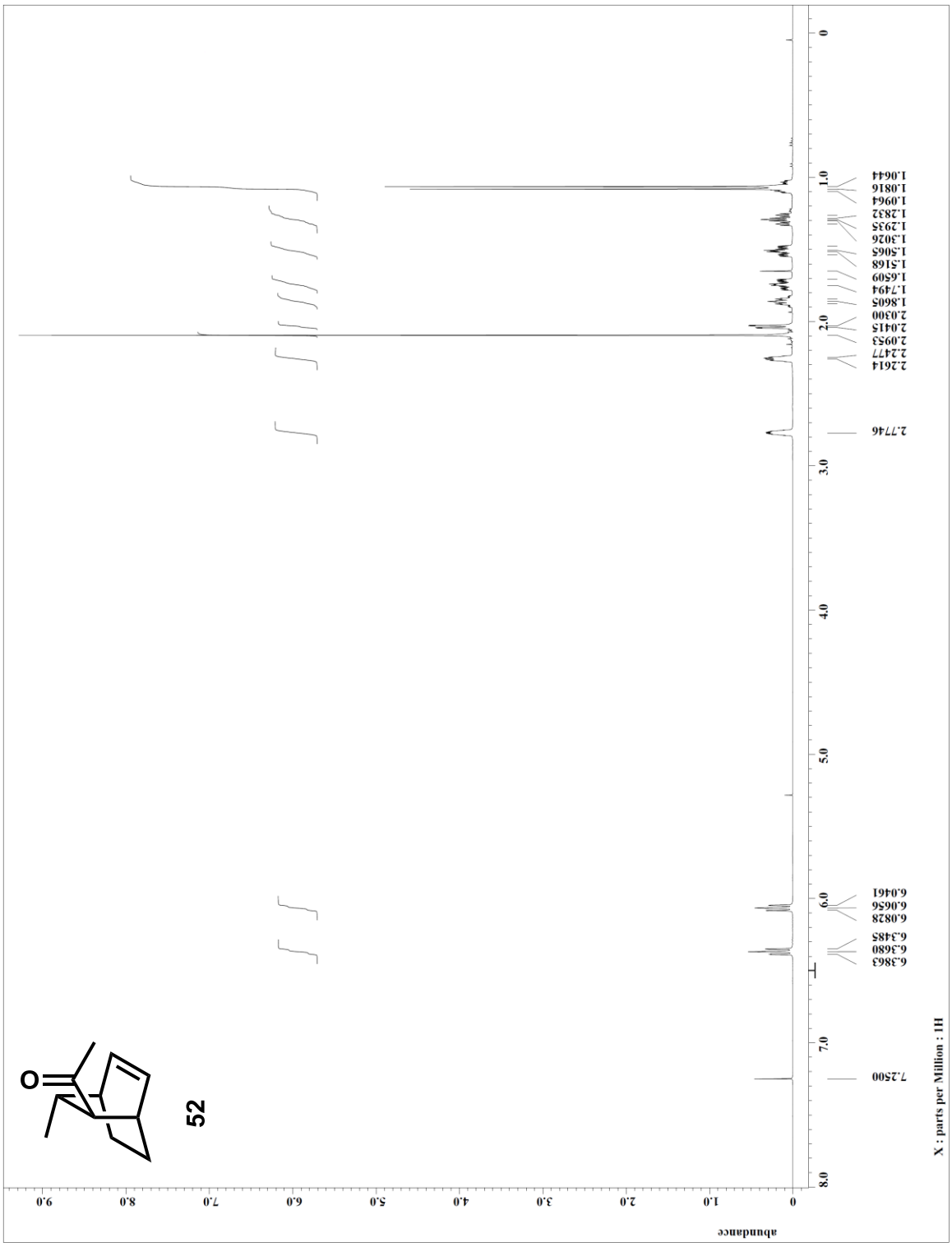
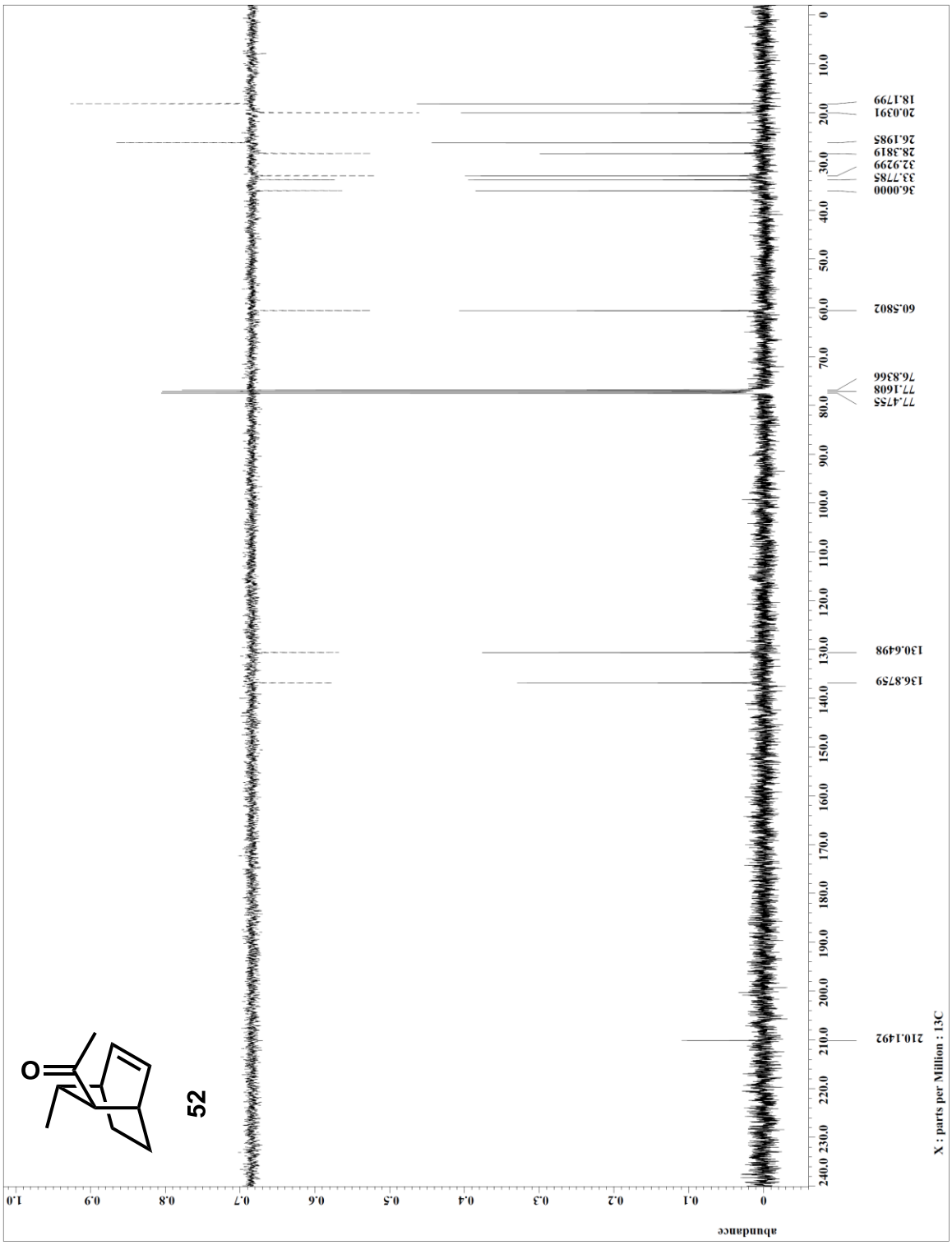
APPENDIX ONE

Spectra Relevant to Chapter 1



^{1}H NMR for compound **52**



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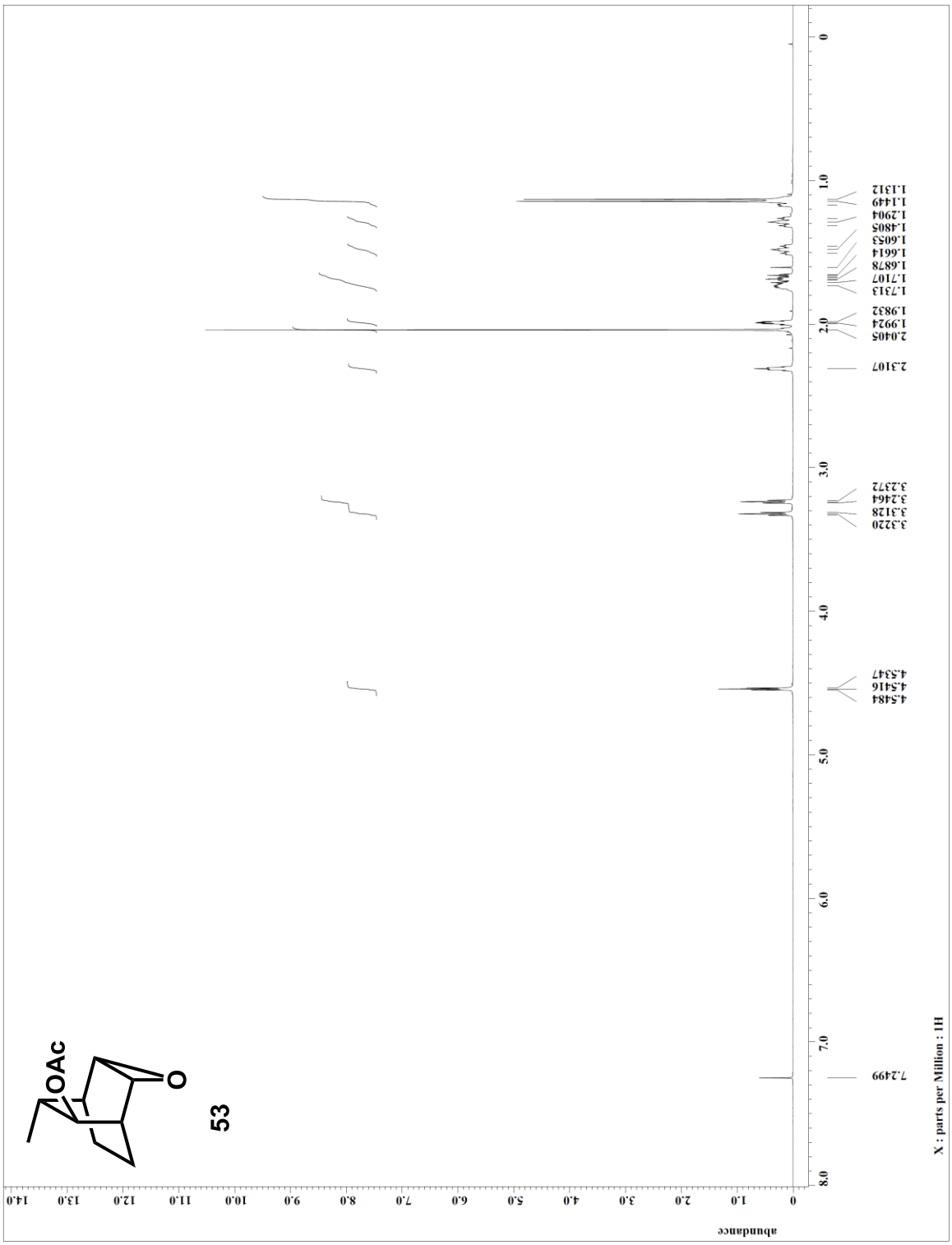

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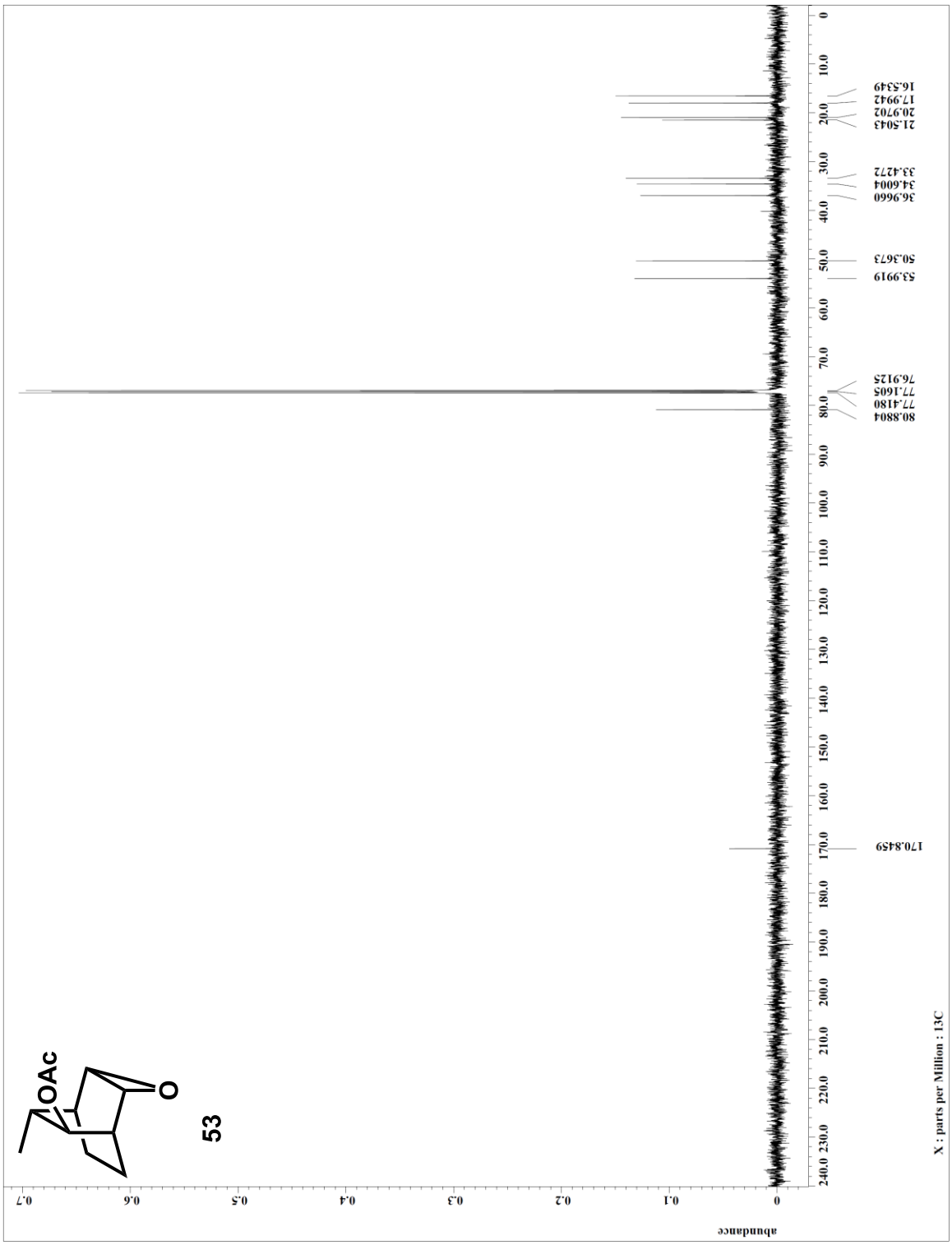

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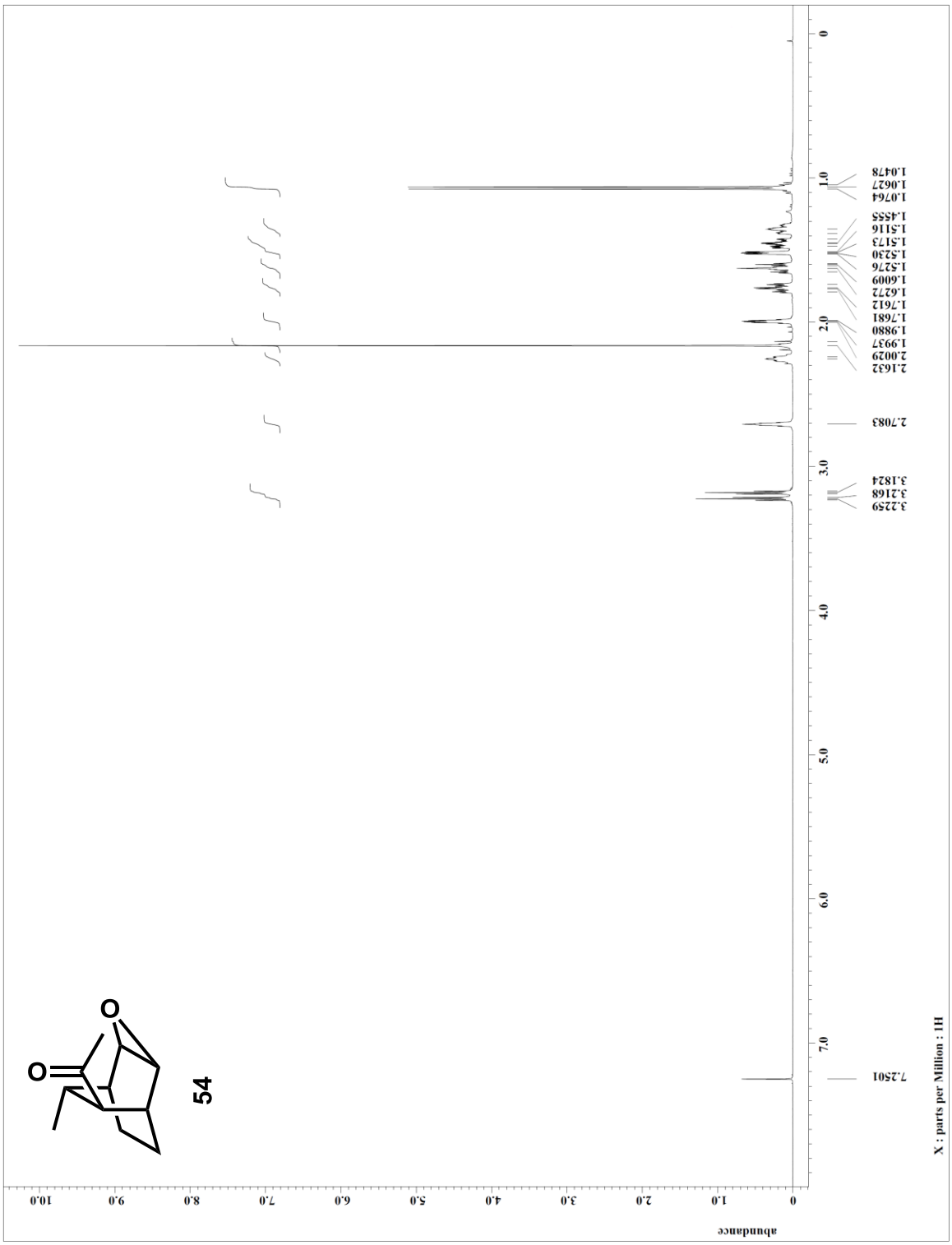

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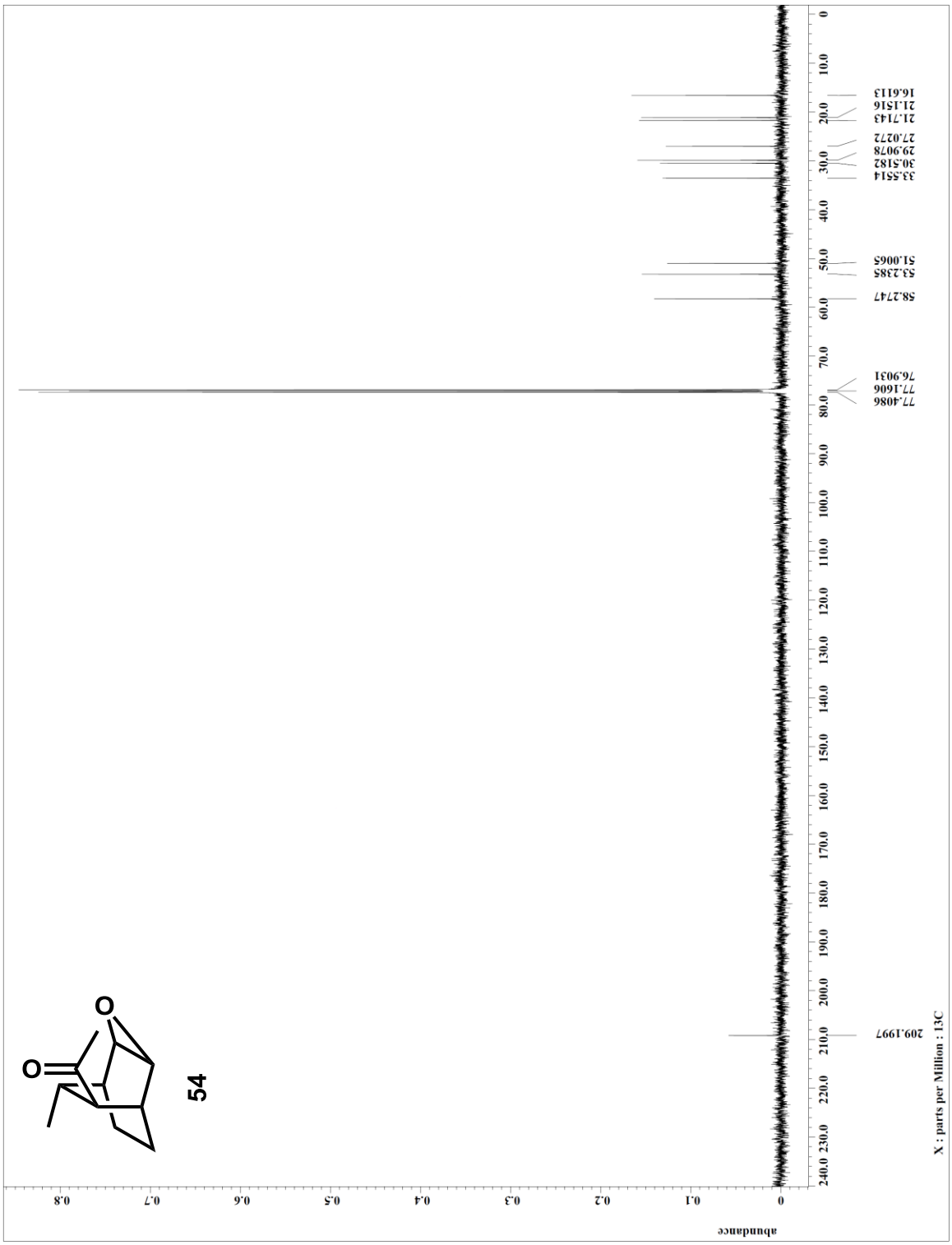

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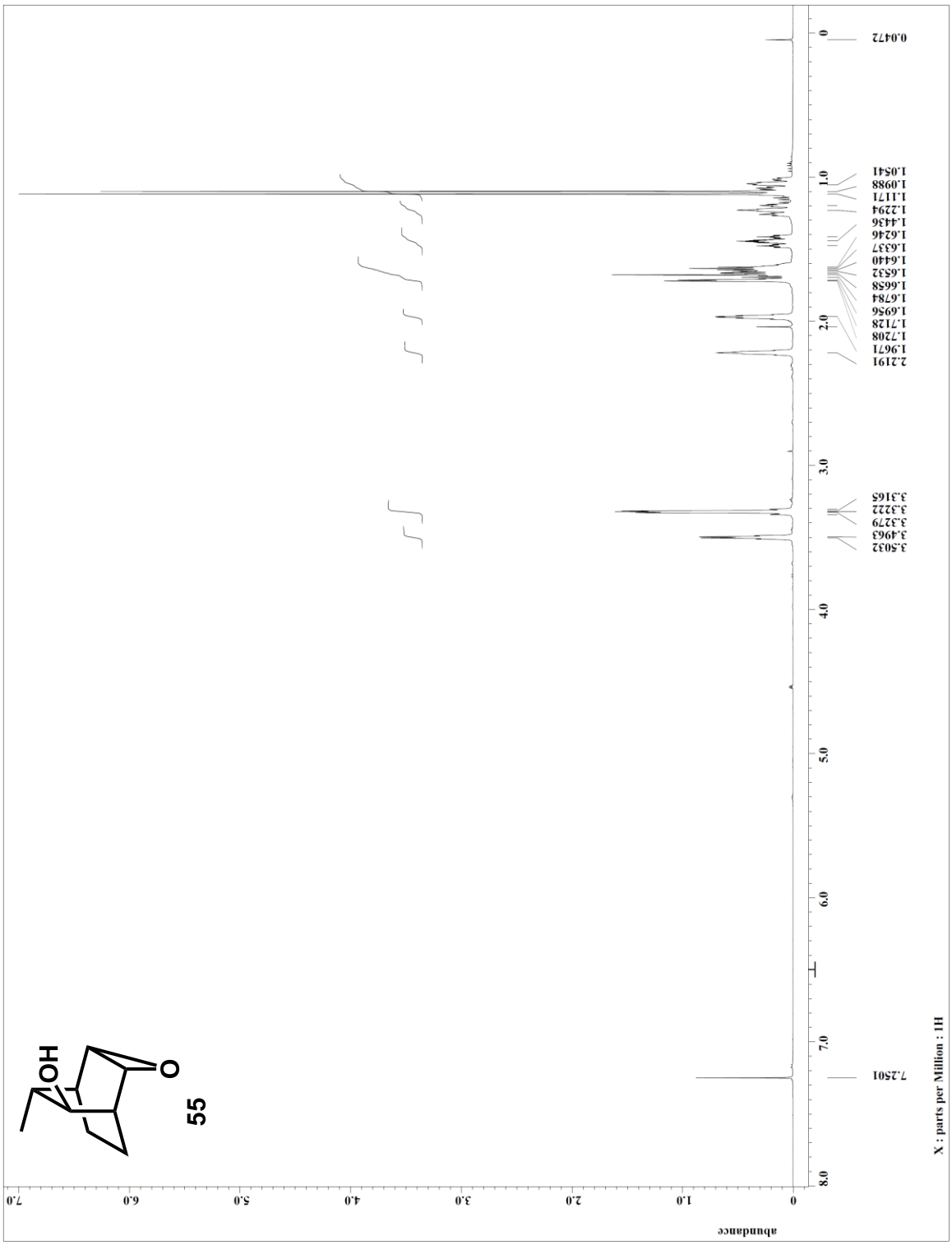

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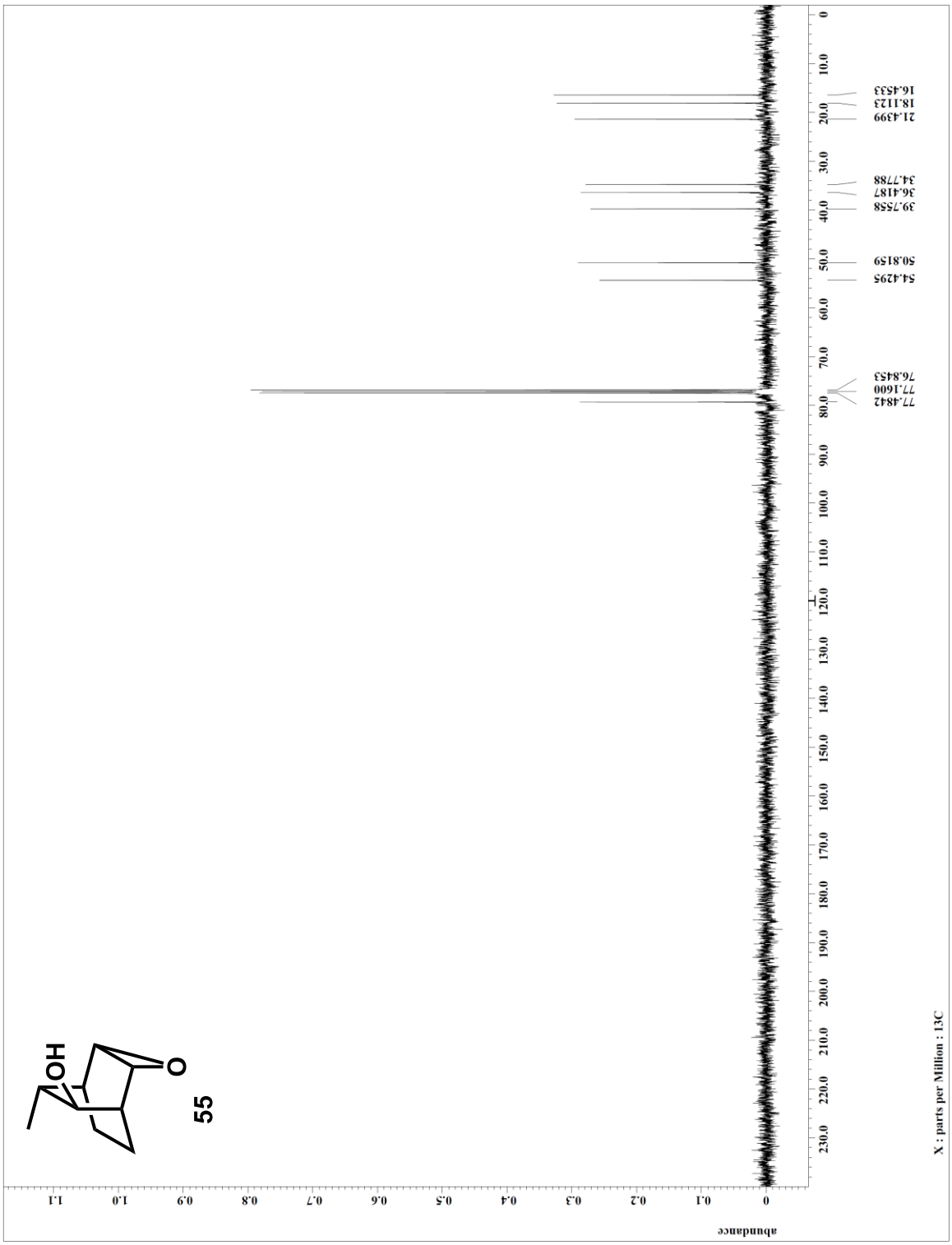

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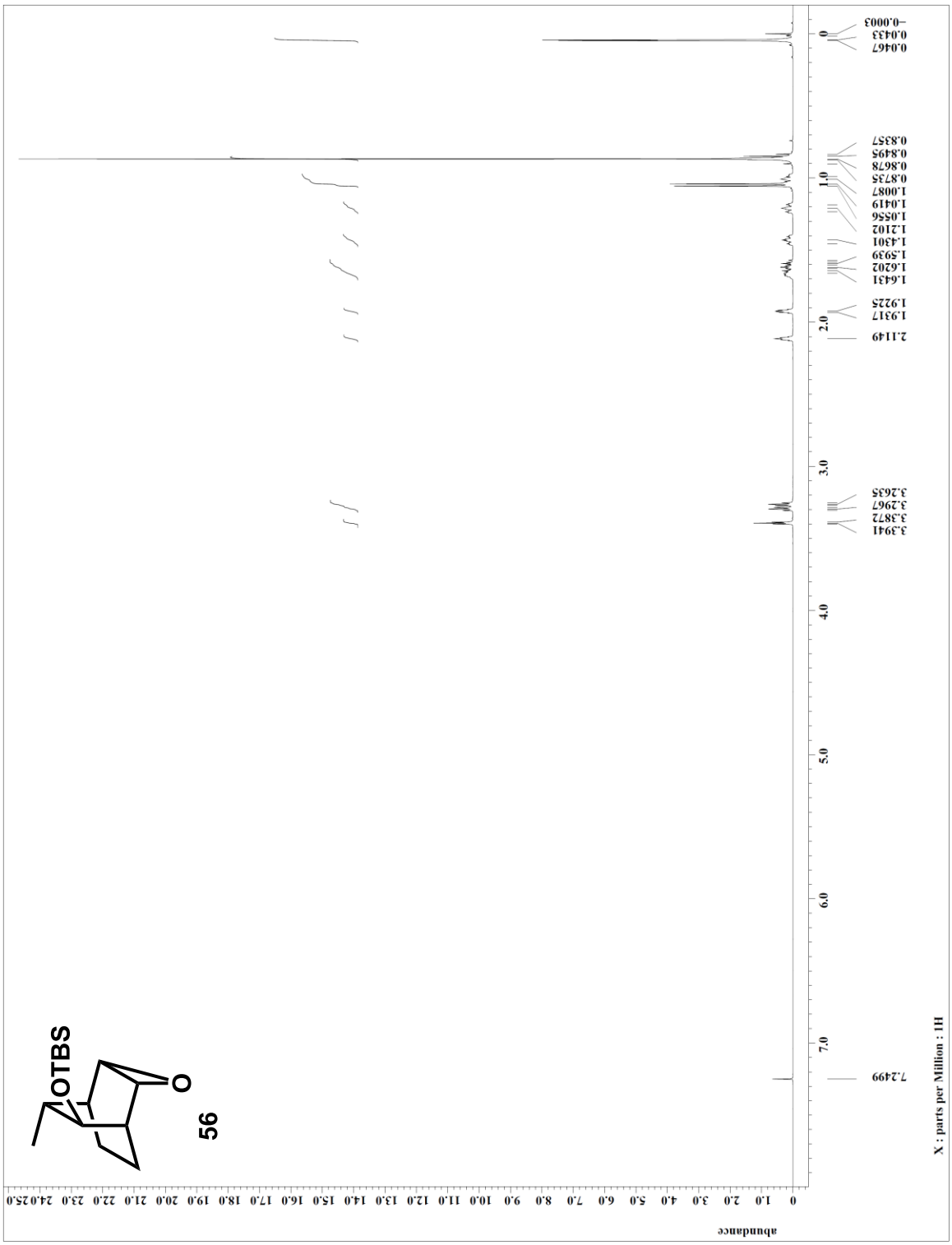

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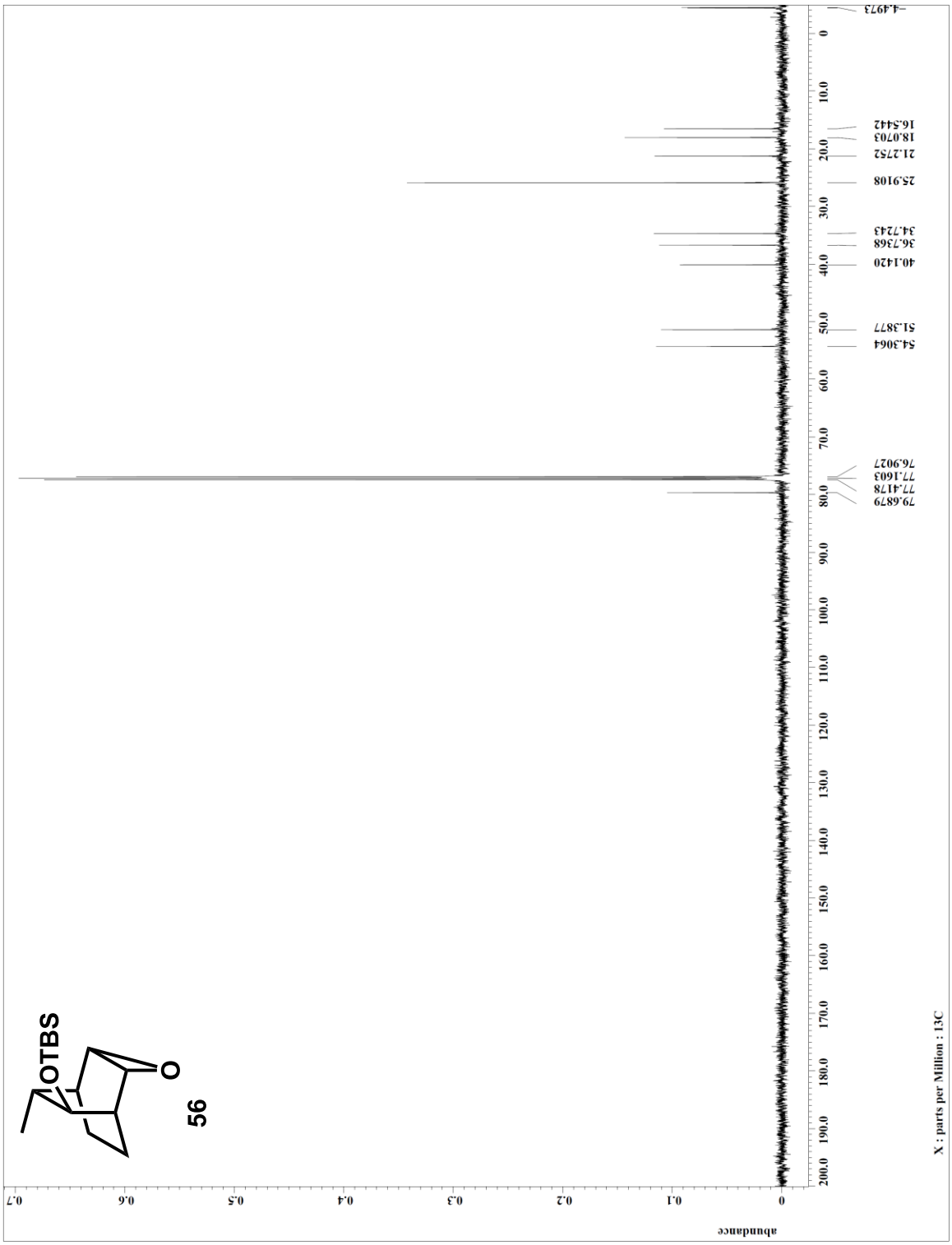

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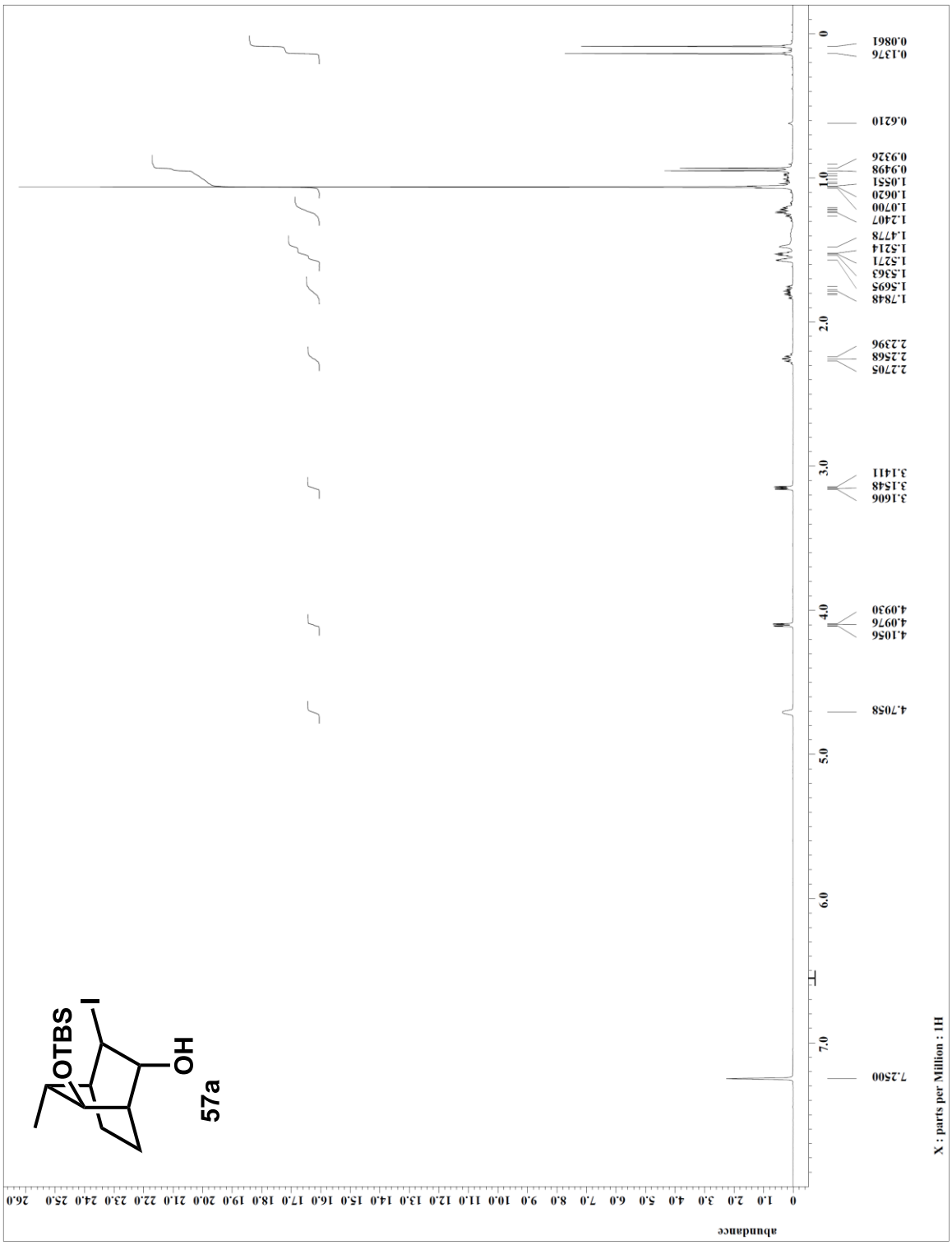

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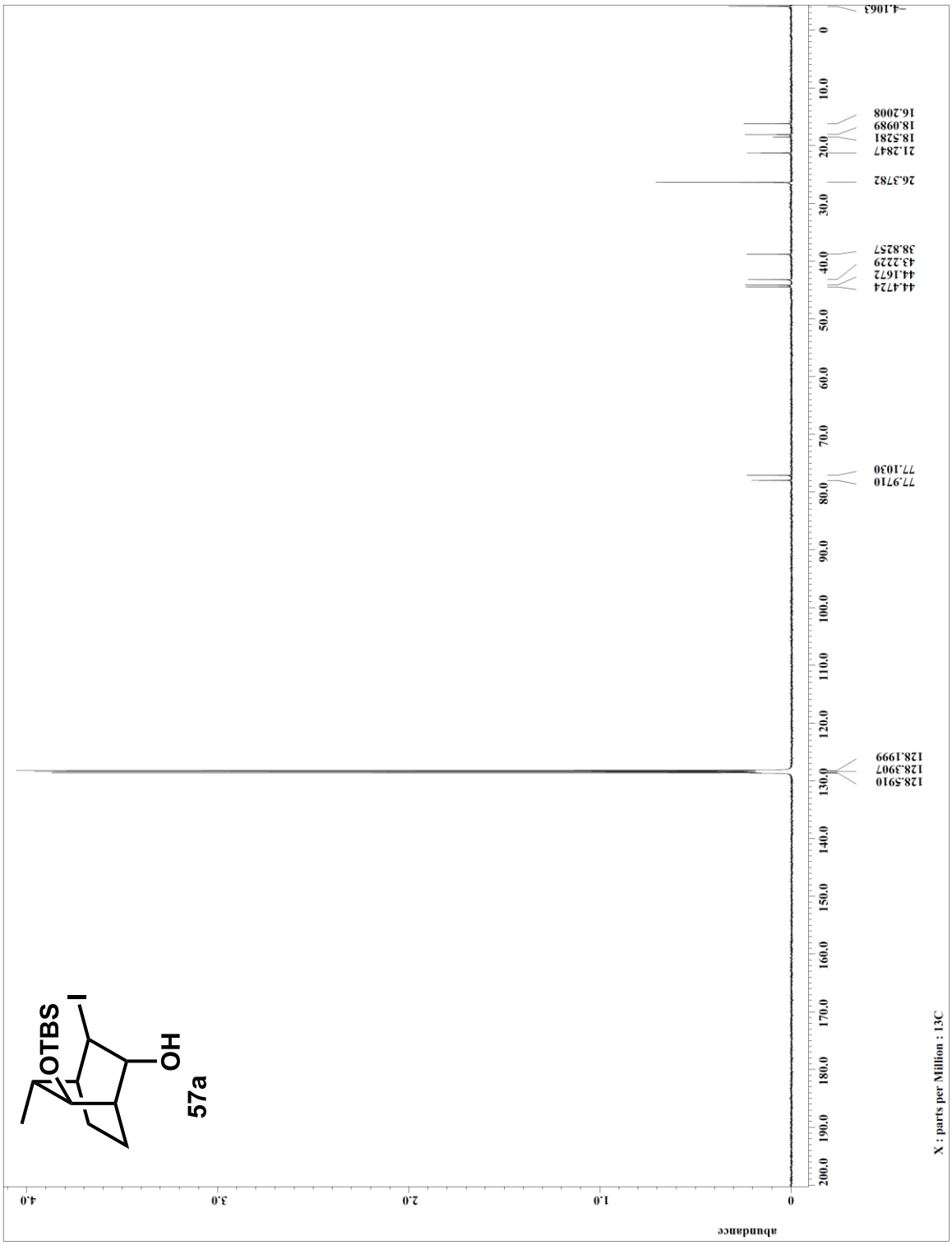

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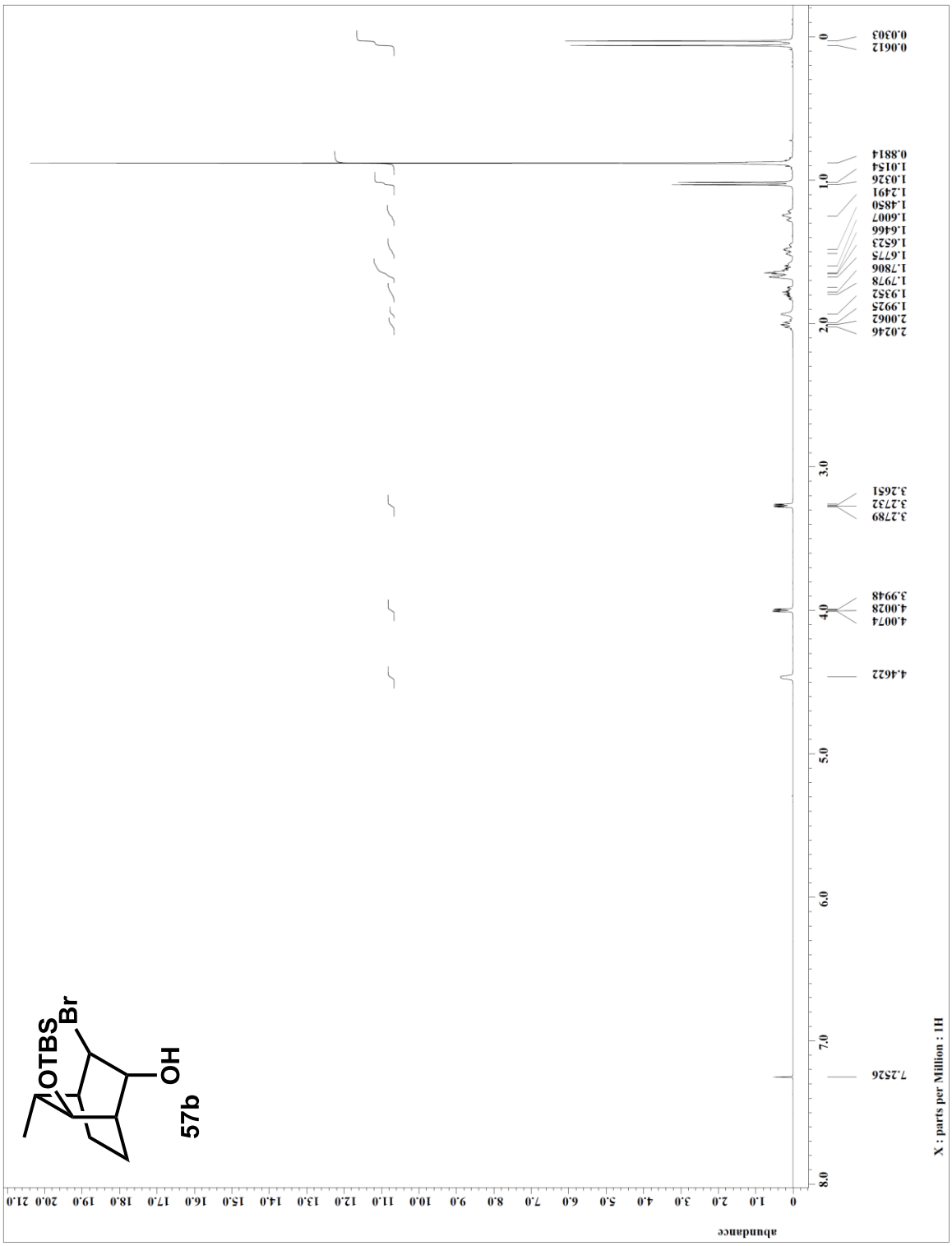

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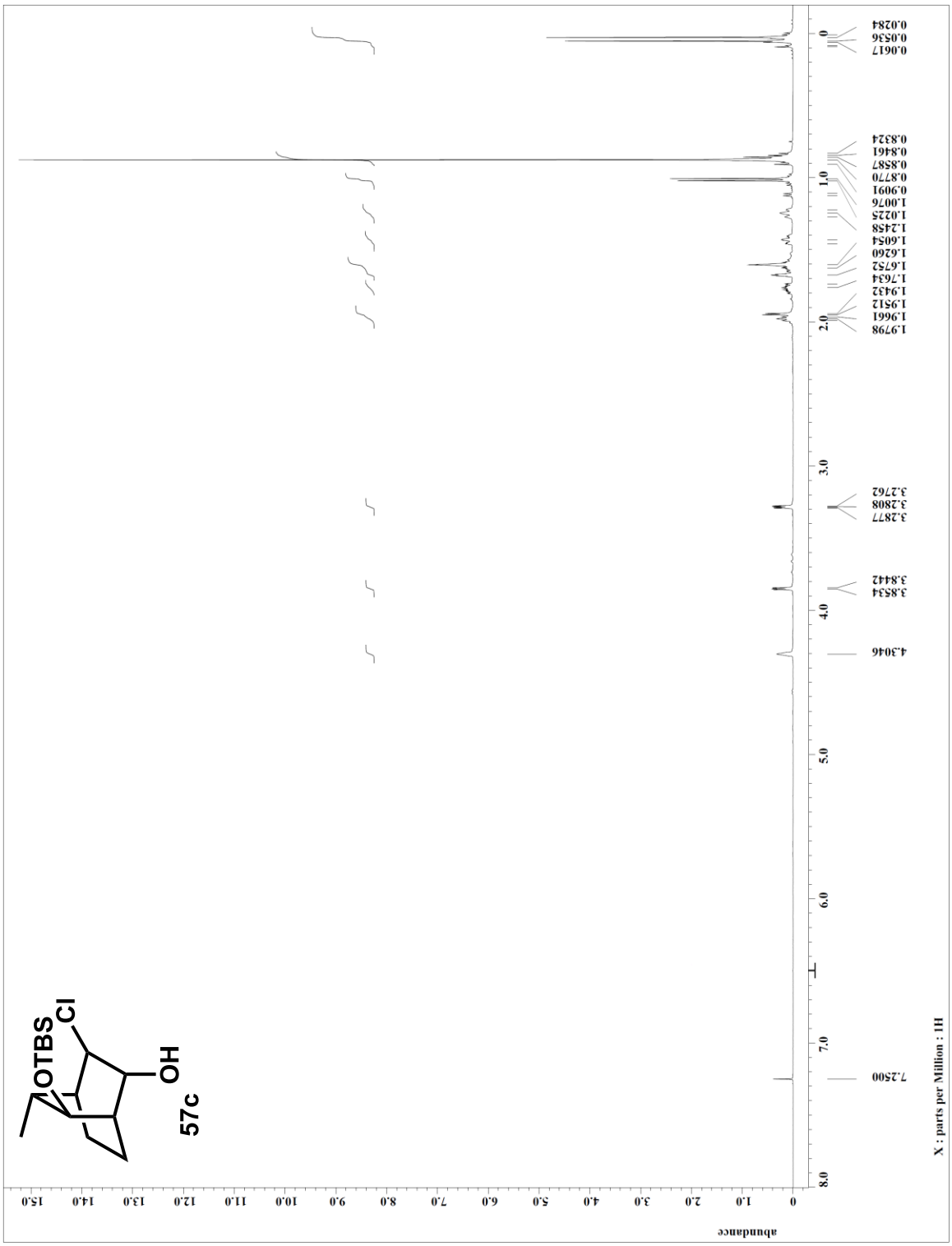

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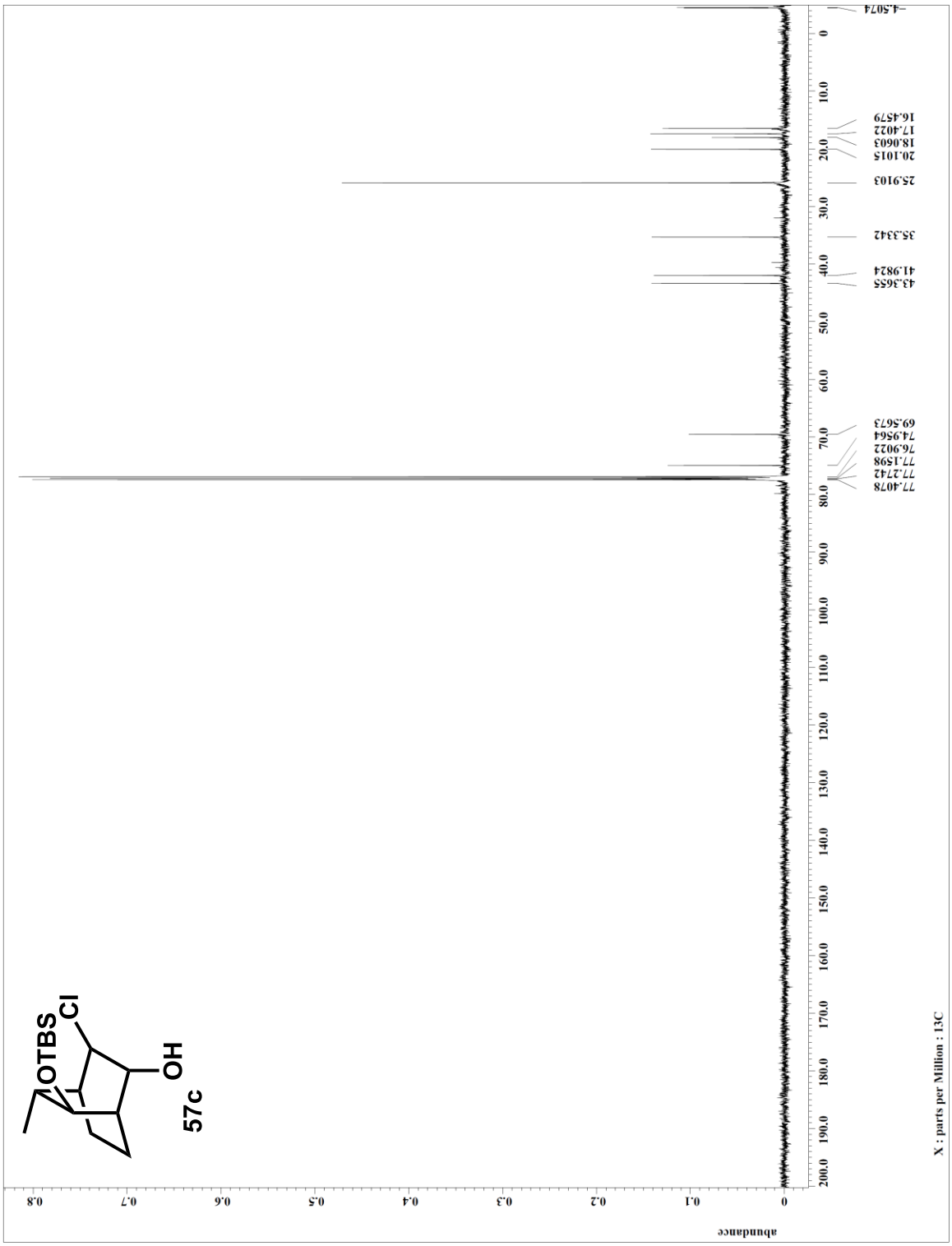
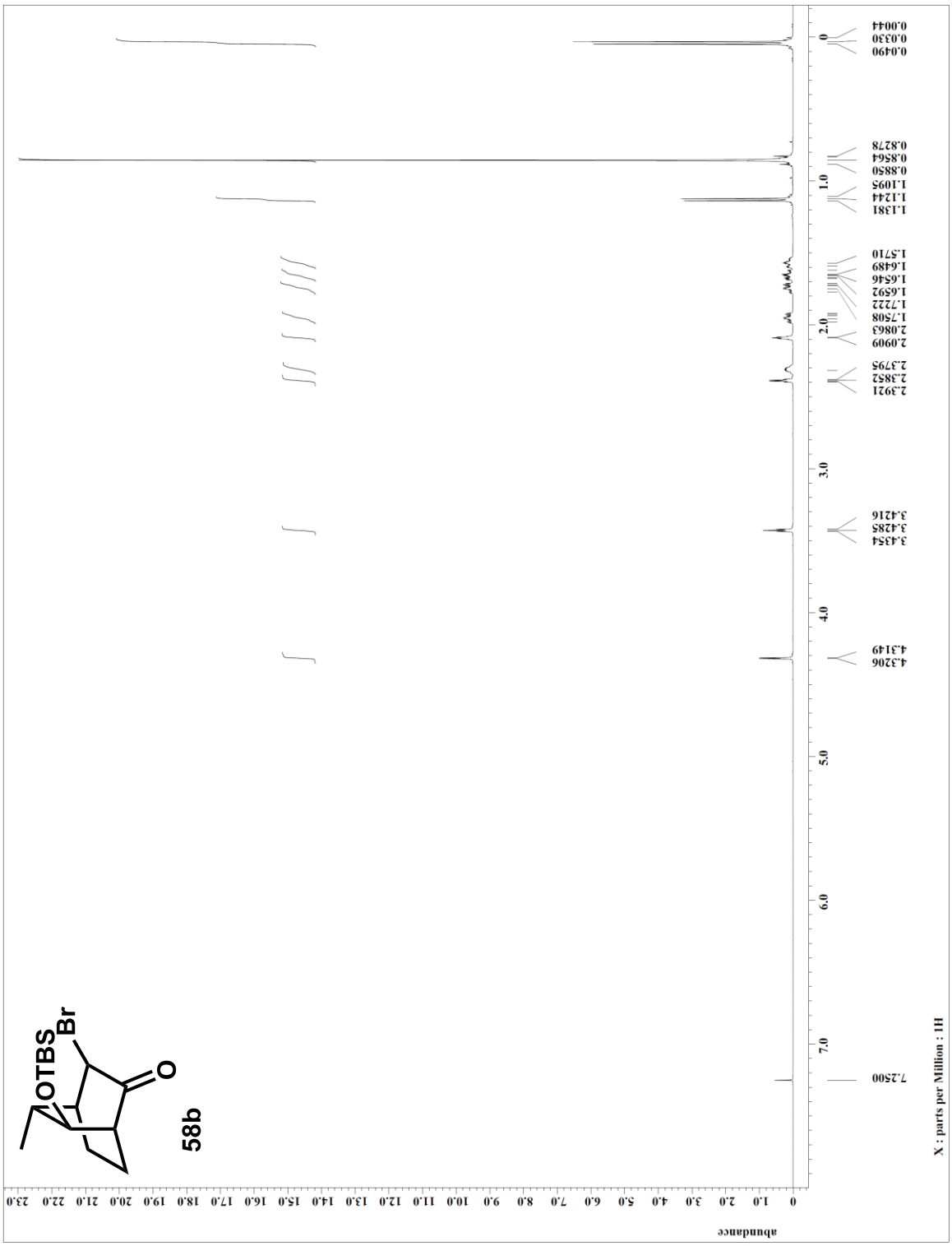
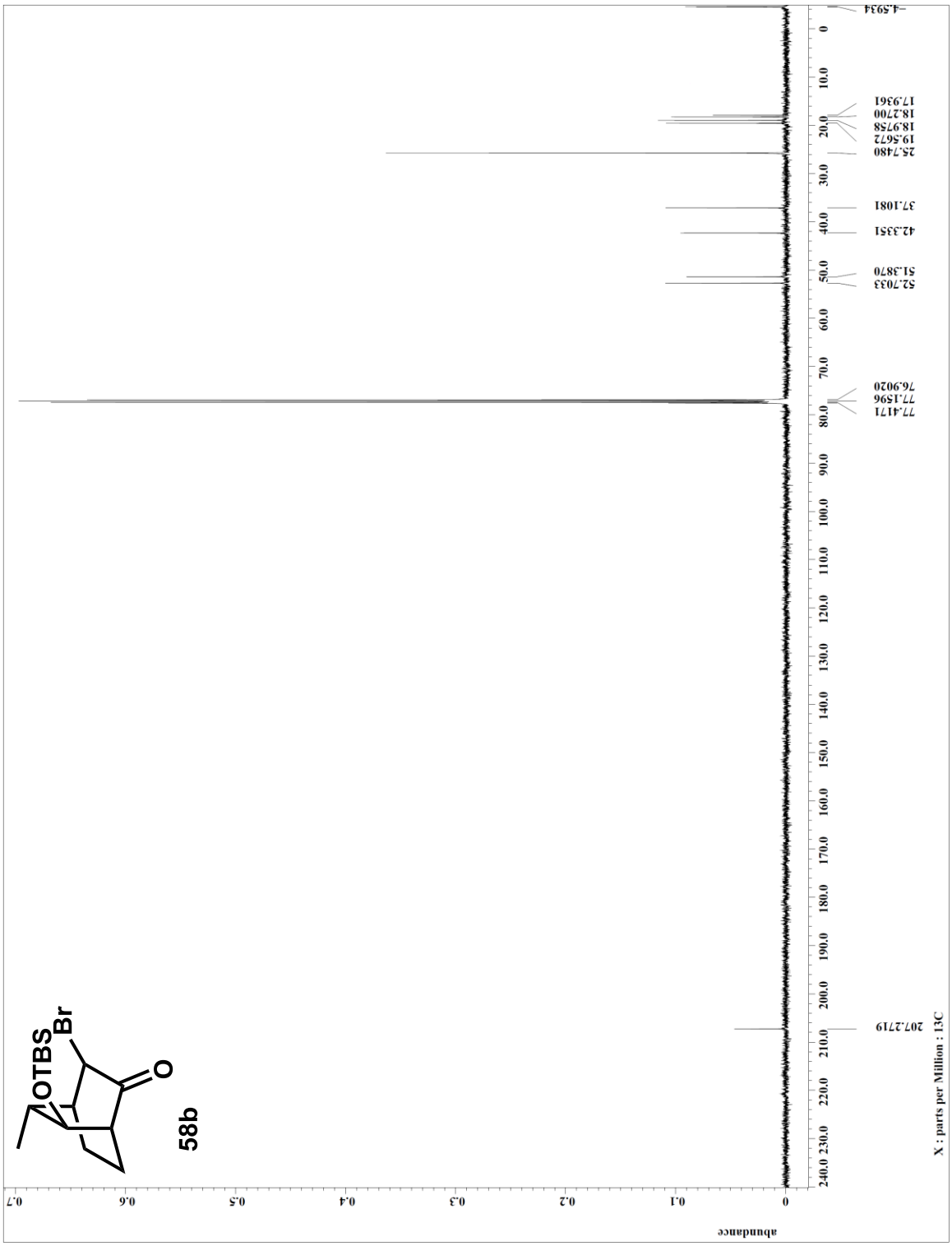


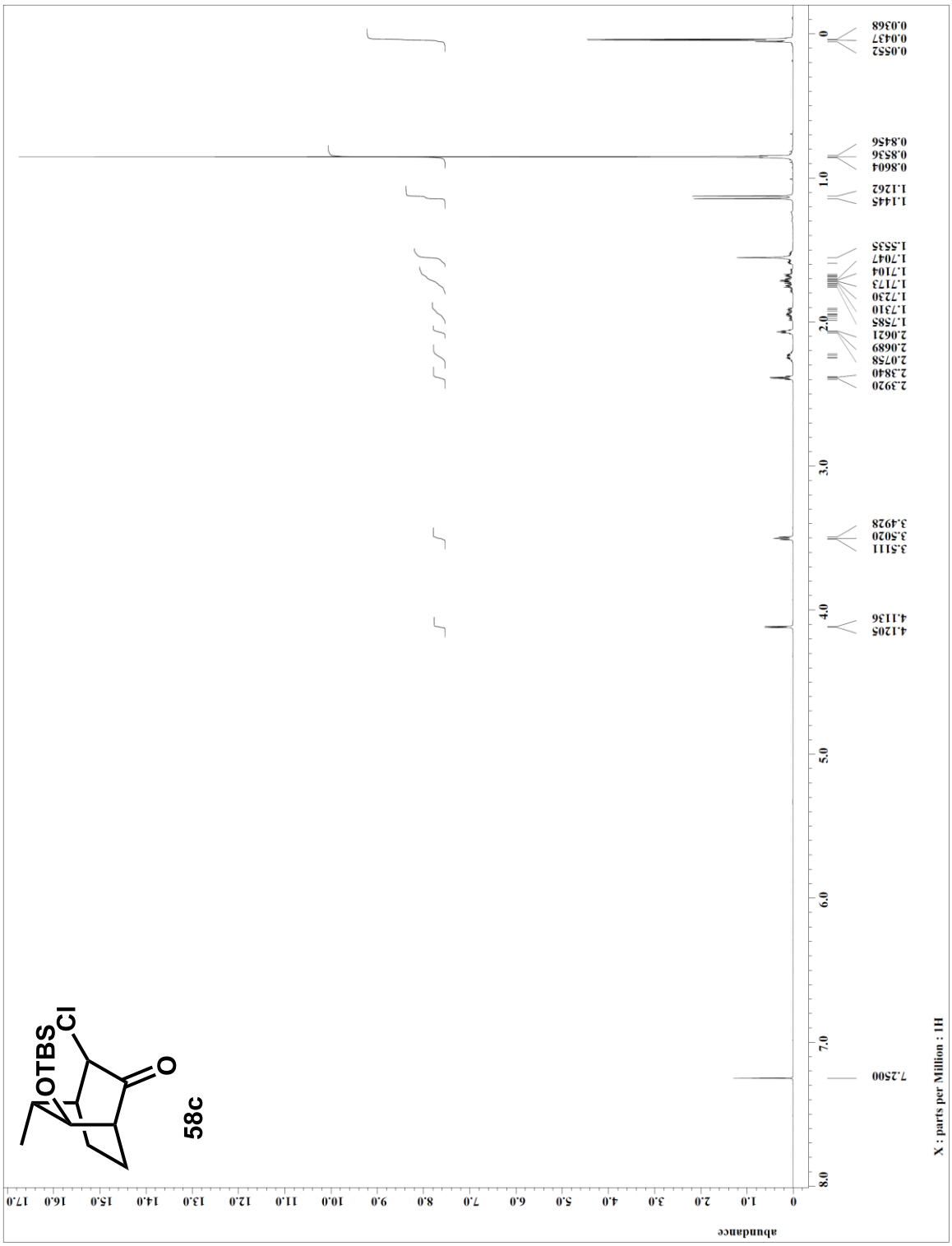
^{13}C NMR for compound **57c**



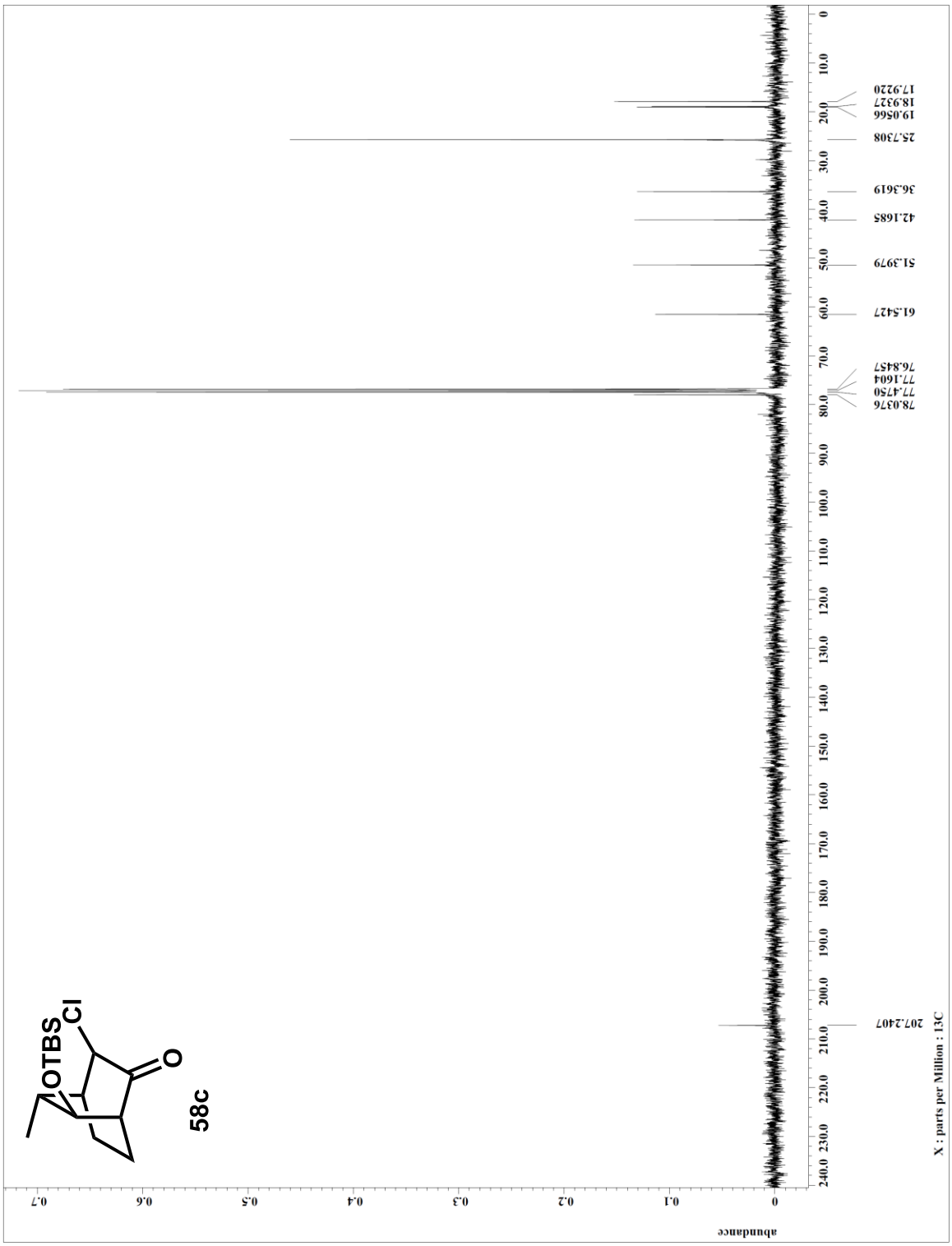
^{1}H NMR for compound **58b**



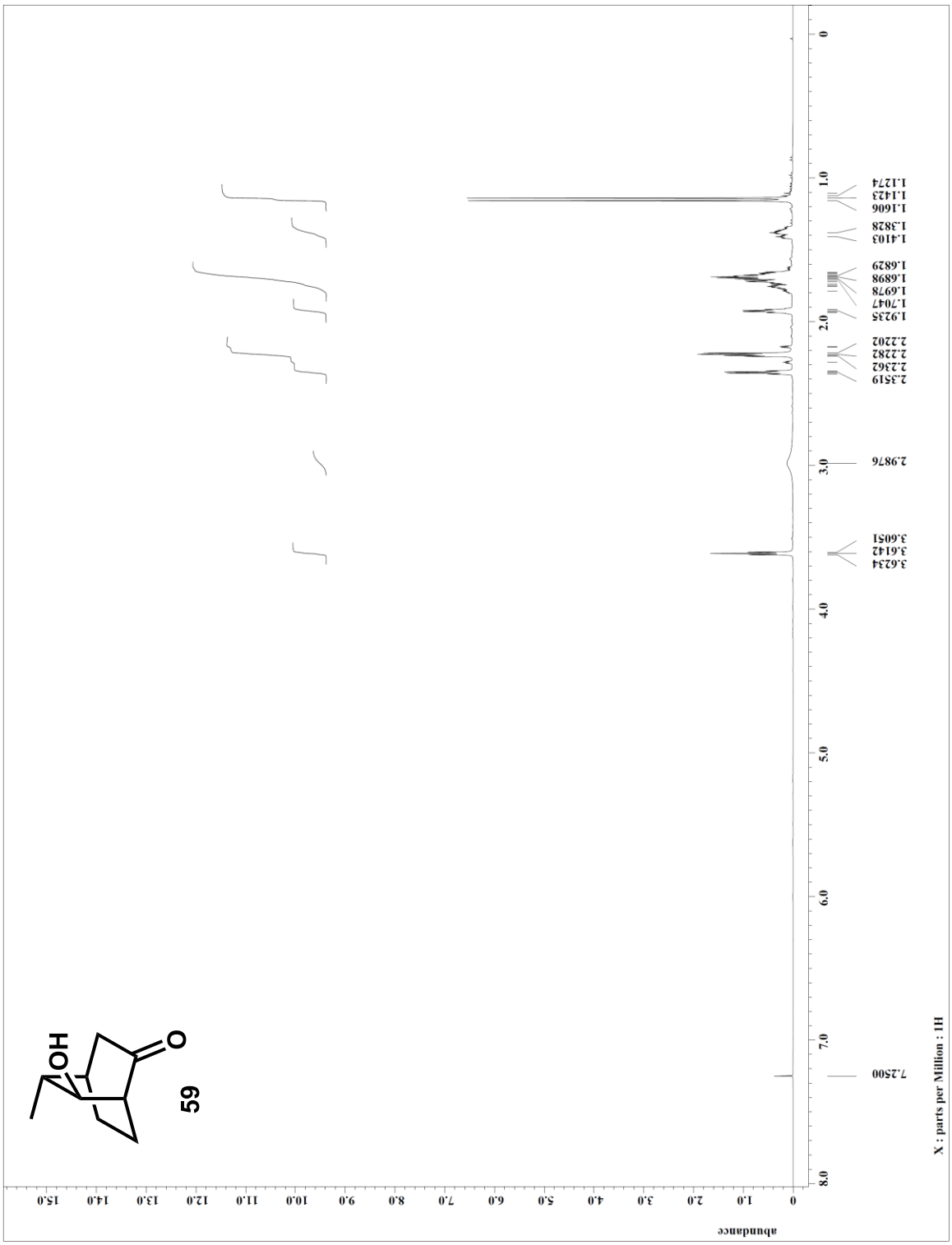
^{13}C NMR for compound **58b**



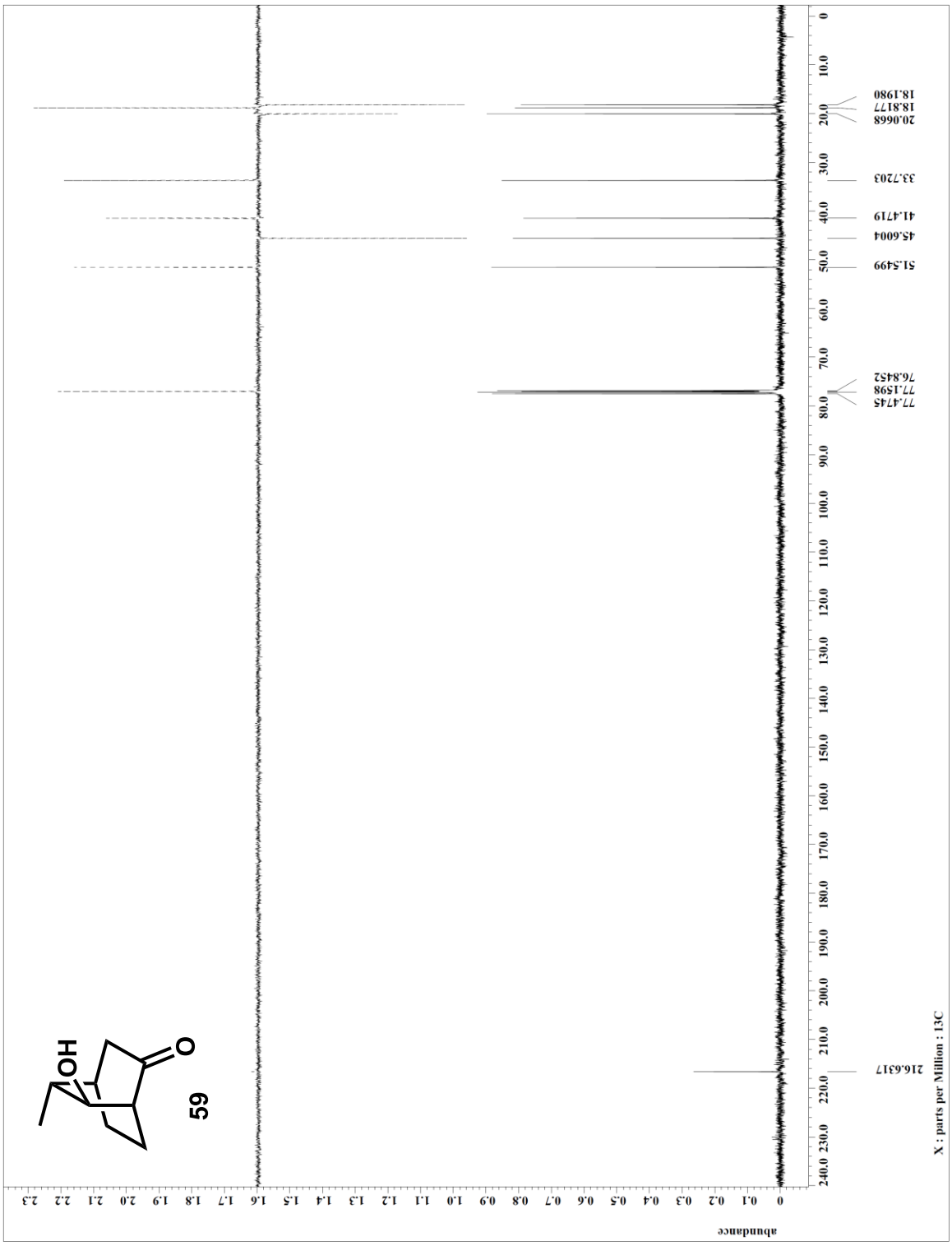
^{1}H NMR for compound **58c**



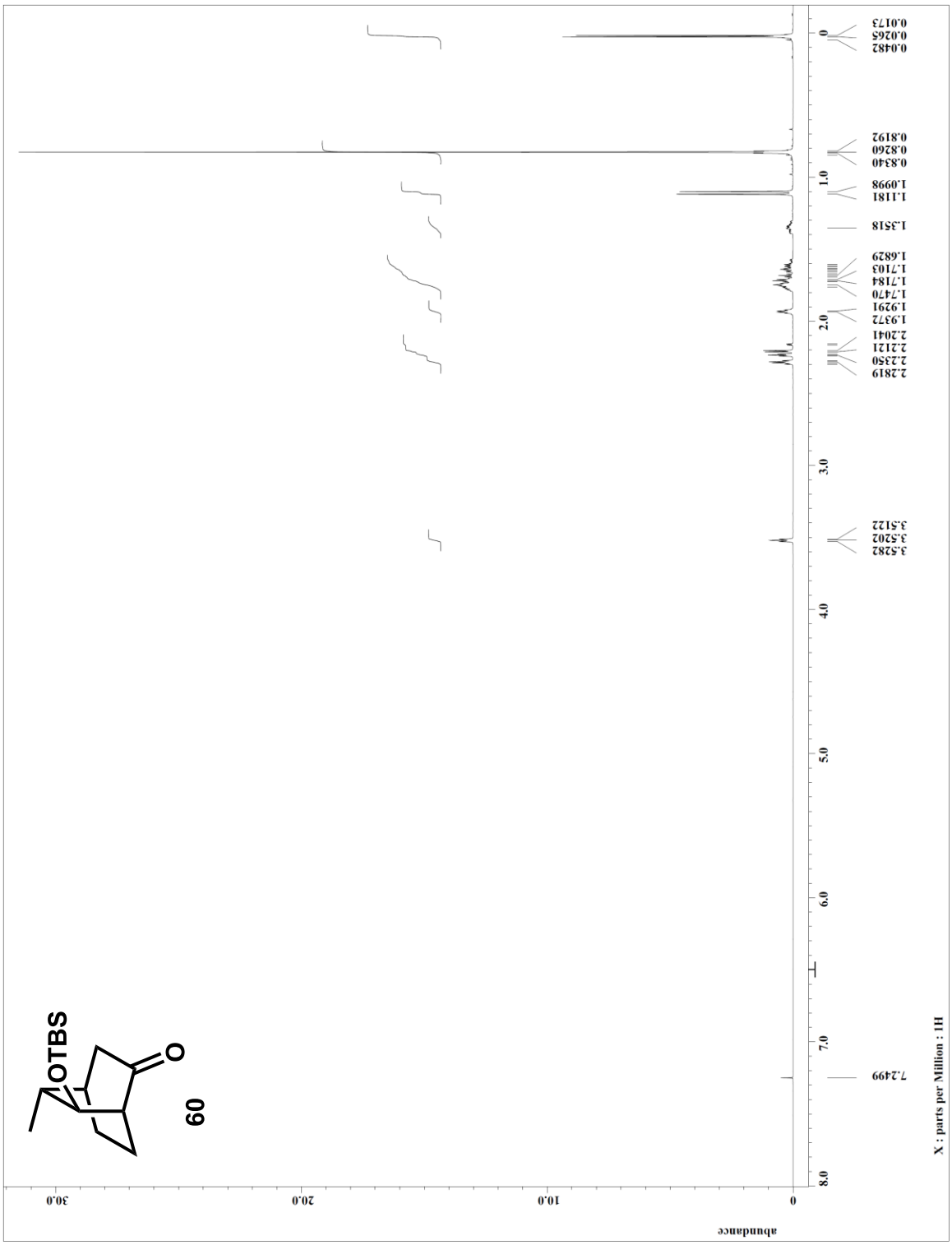
^{13}C NMR for compound **58c**



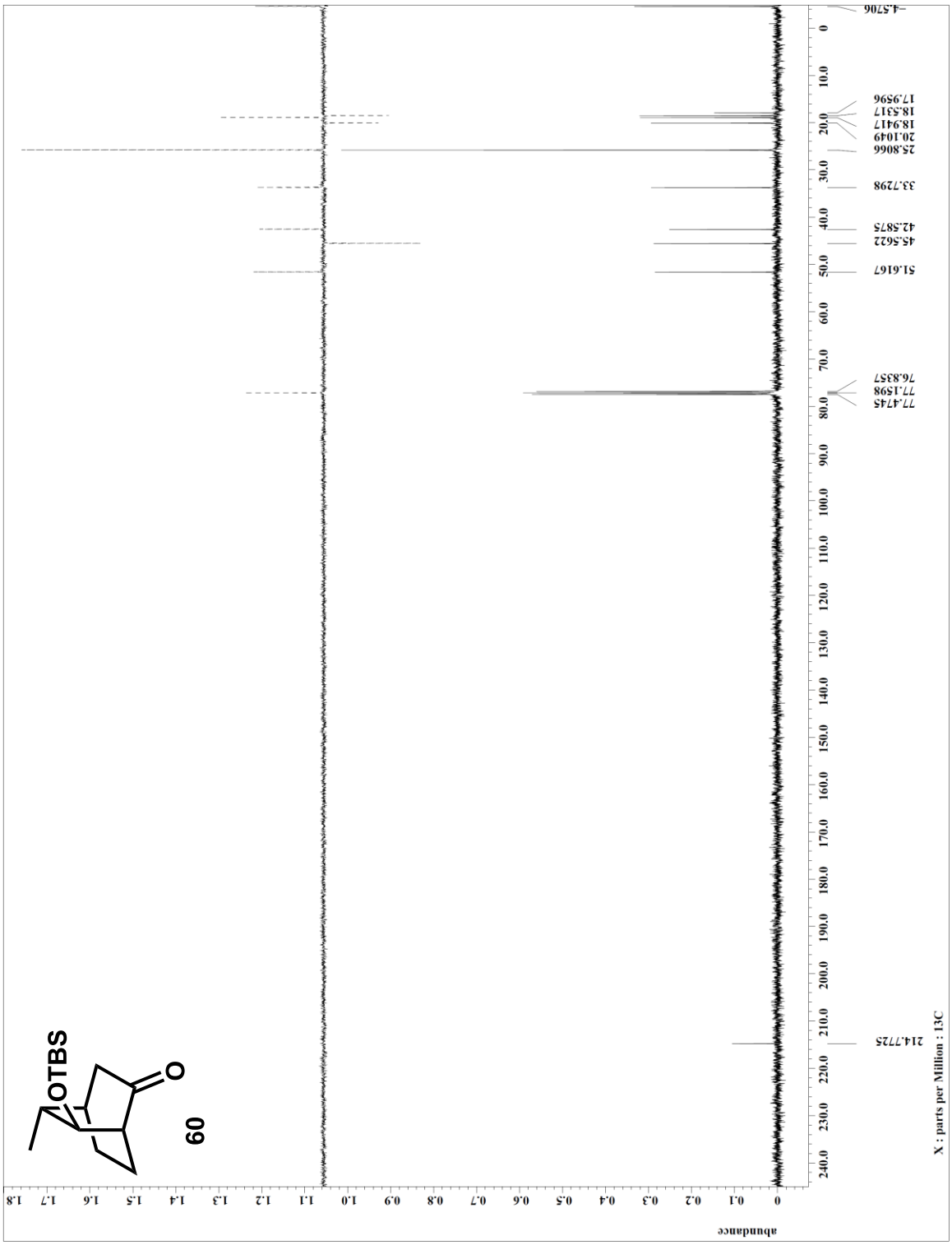
^{1}H NMR for compound **59**



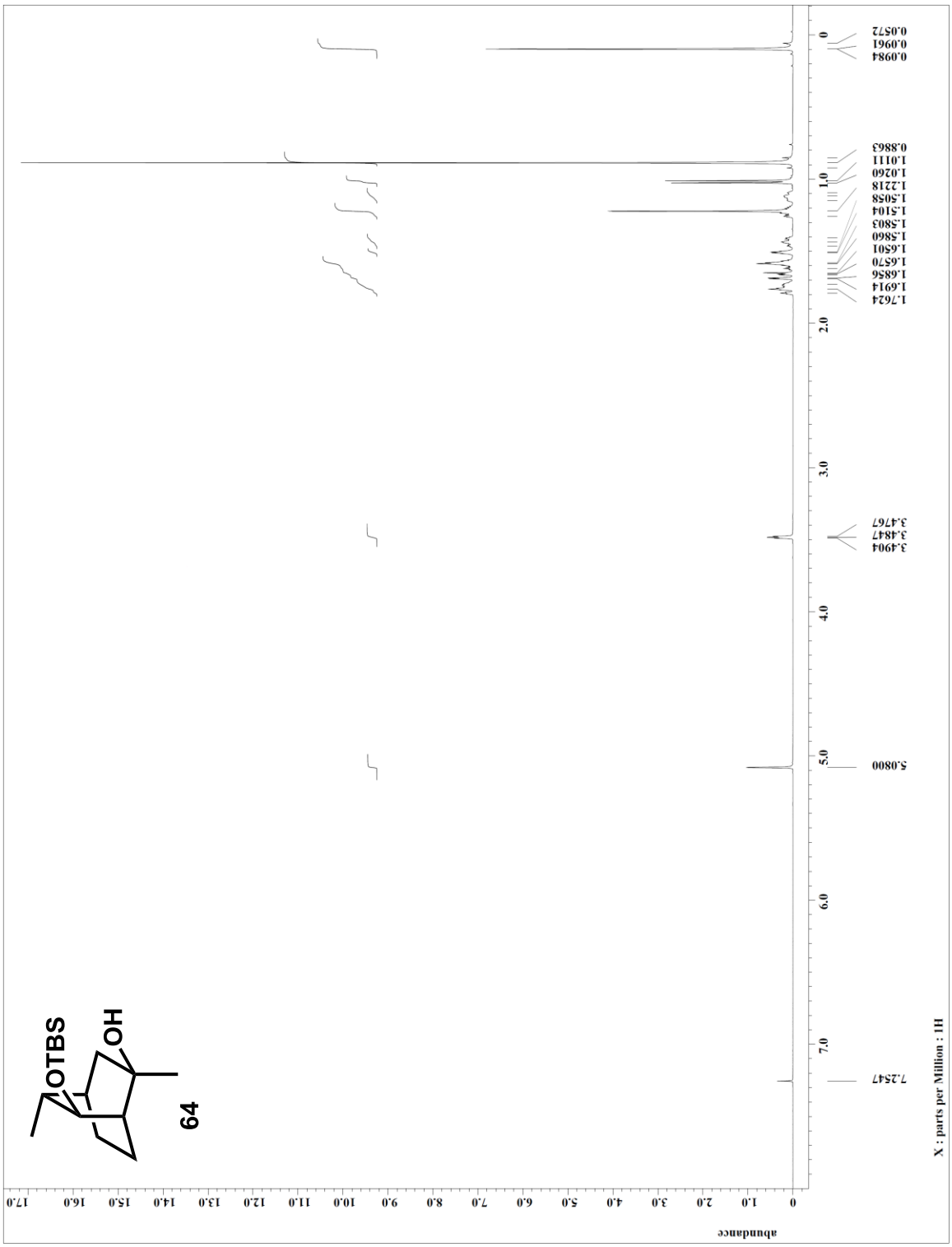
^{13}C NMR and DEPT for compound **59**



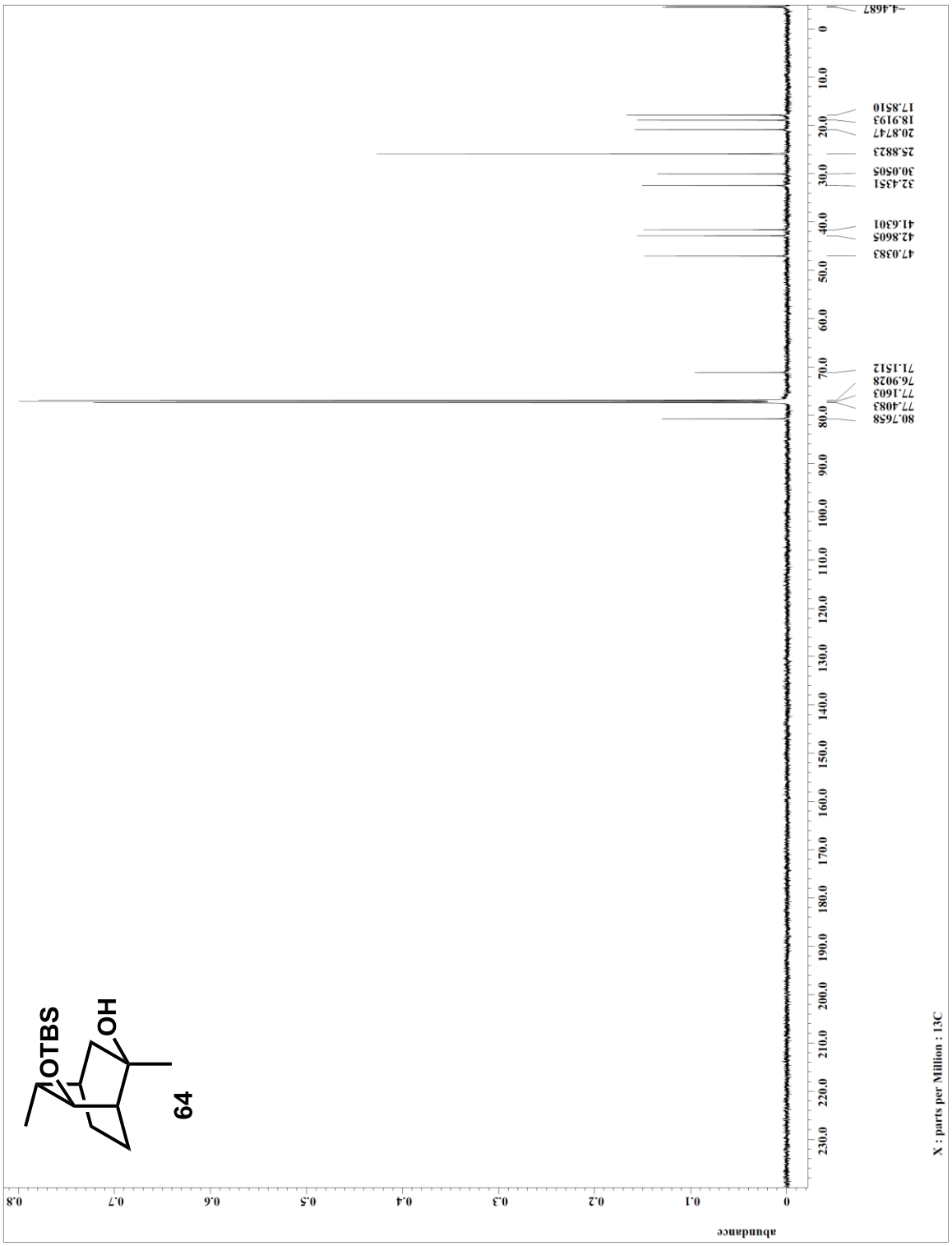
^{1}H NMR for compound **60**



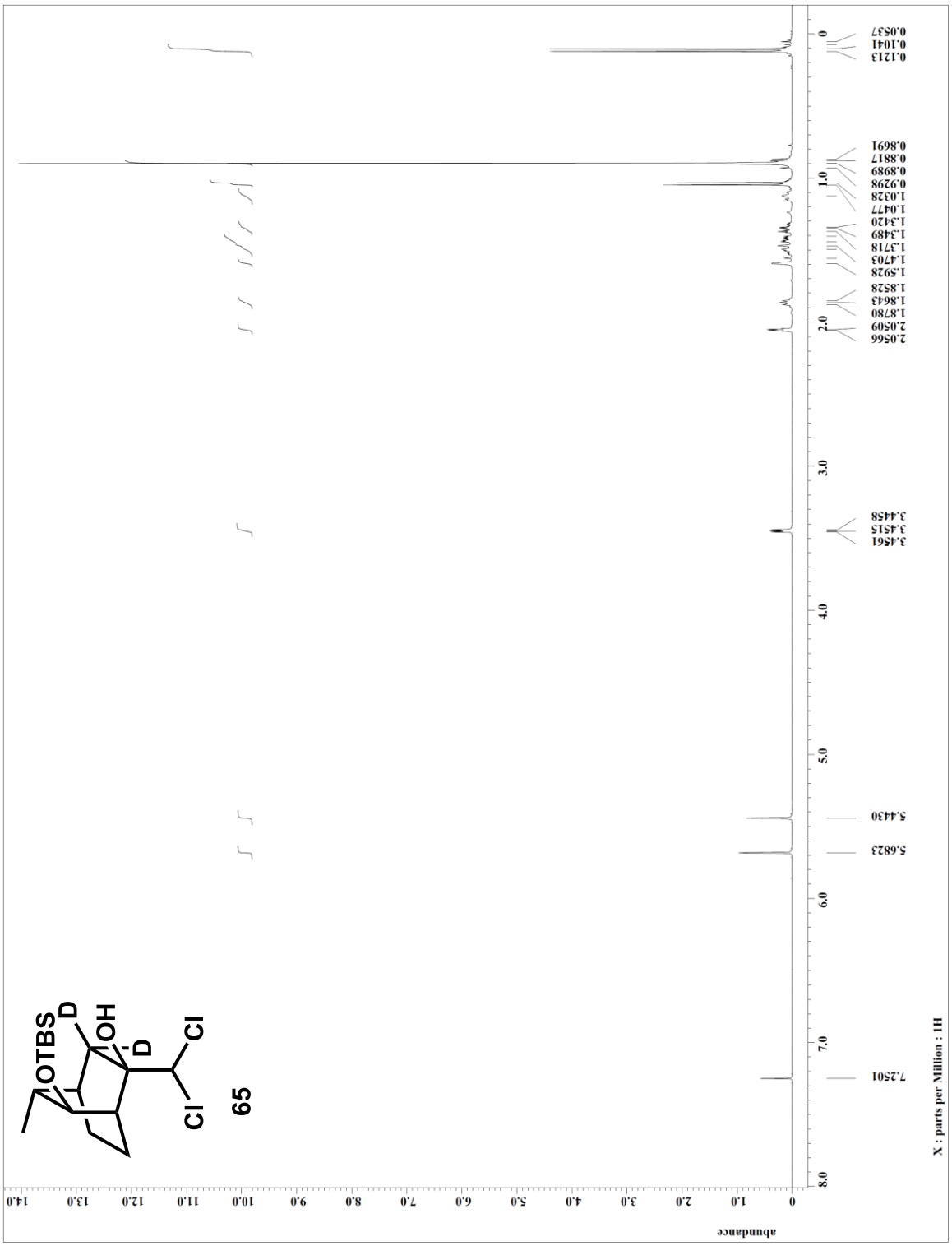
^{13}C NMR and DEPT for compound **60**



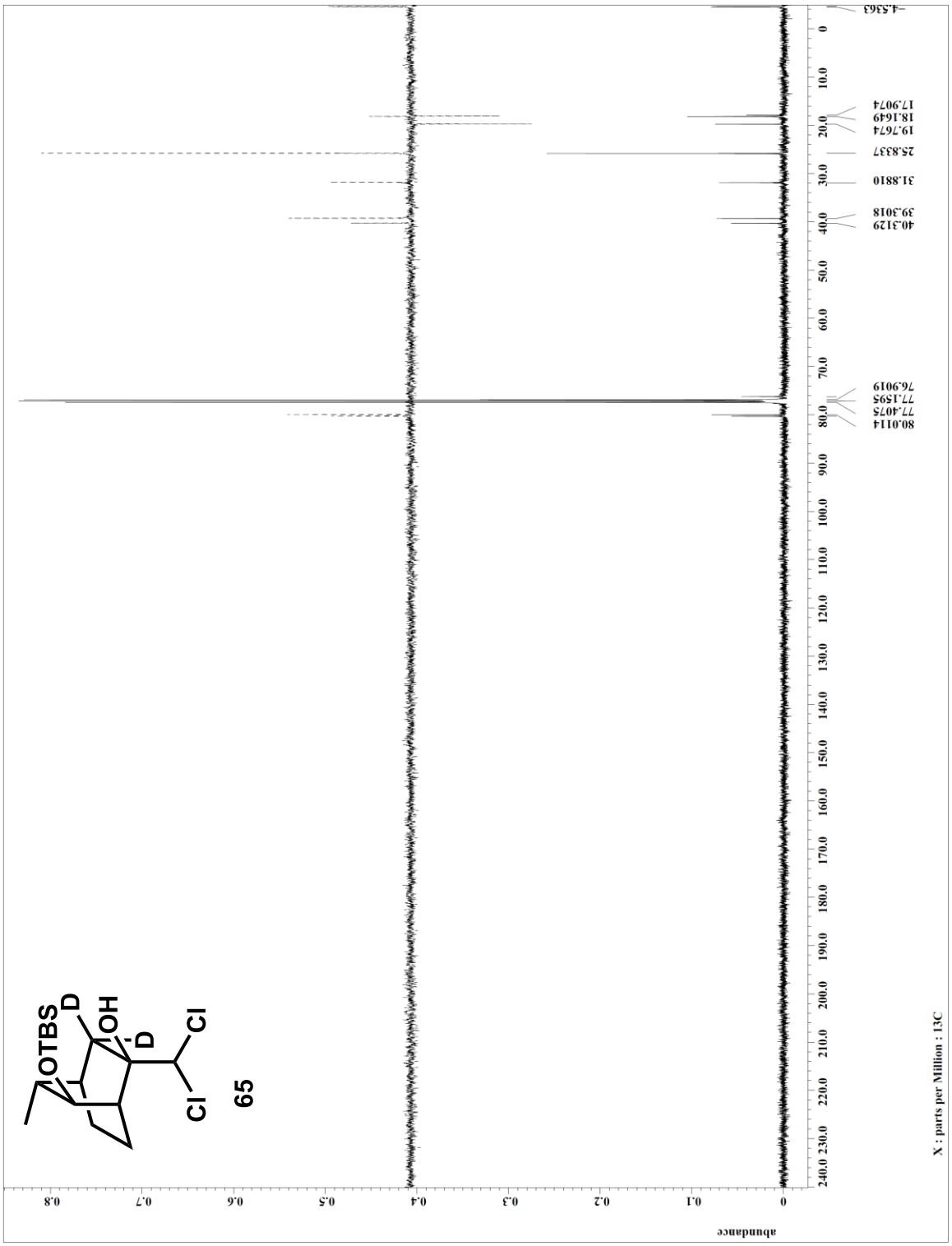
^{1}H NMR for compound **64**



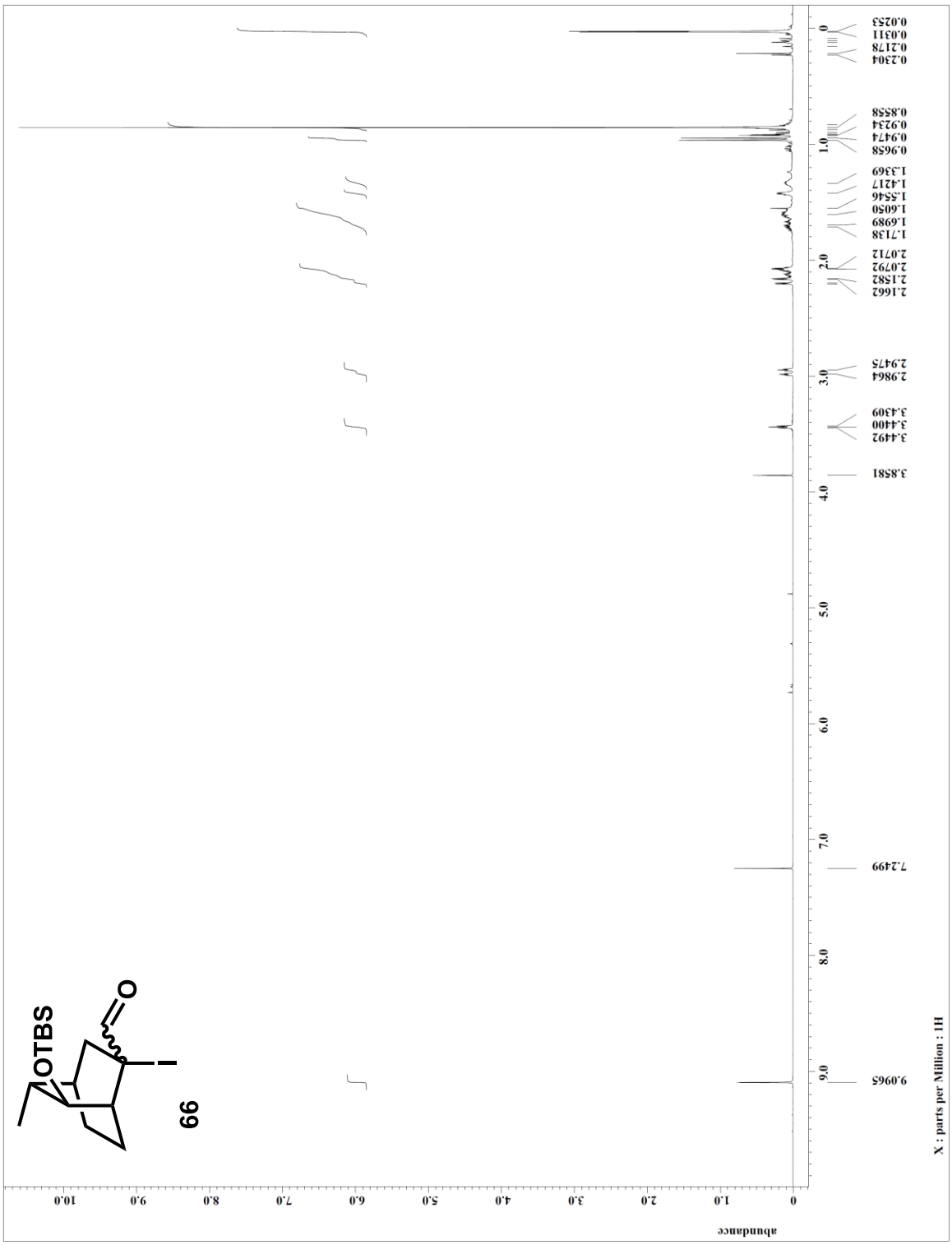
^{13}C NMR for compound **64**



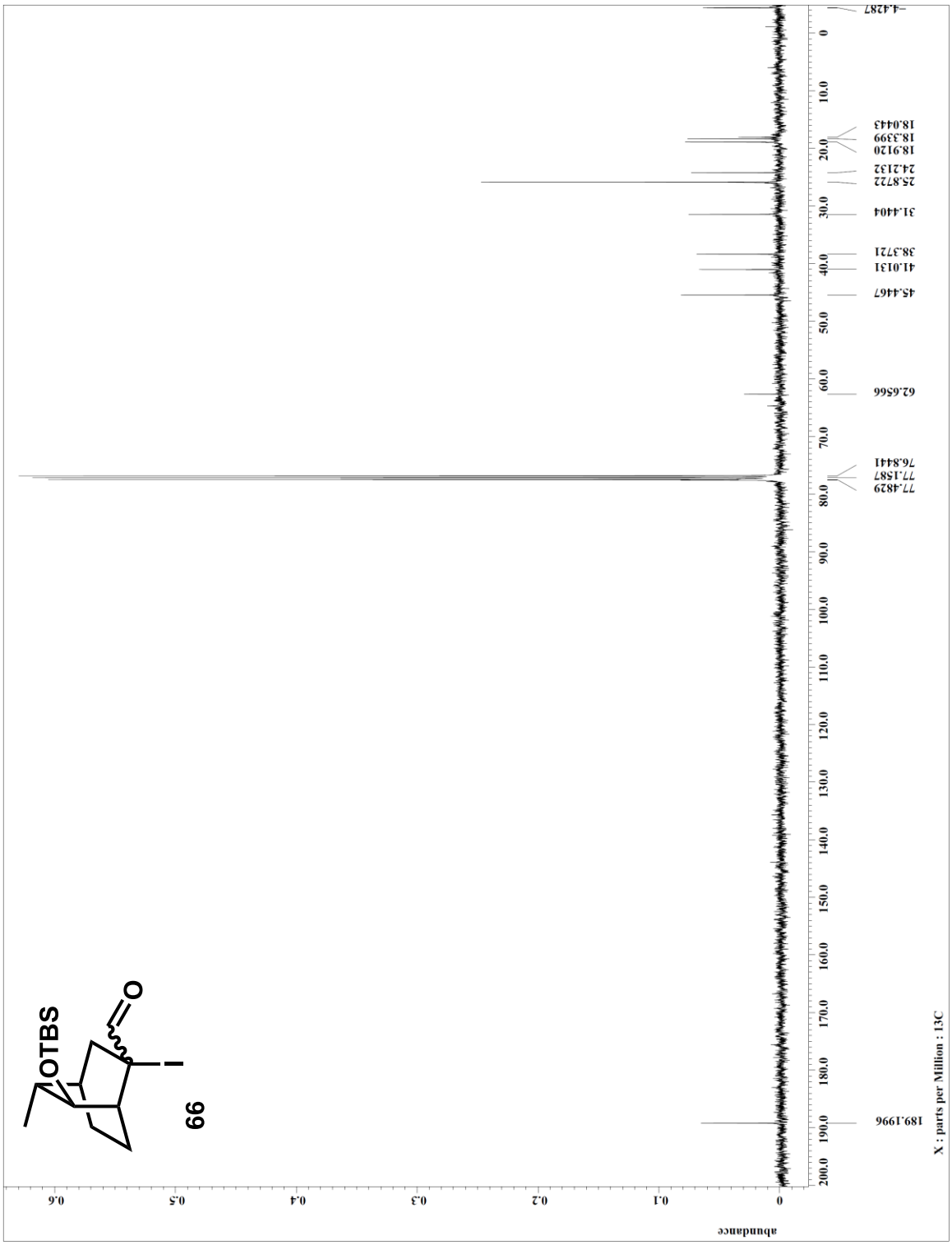
^{1}H NMR for compound **65**



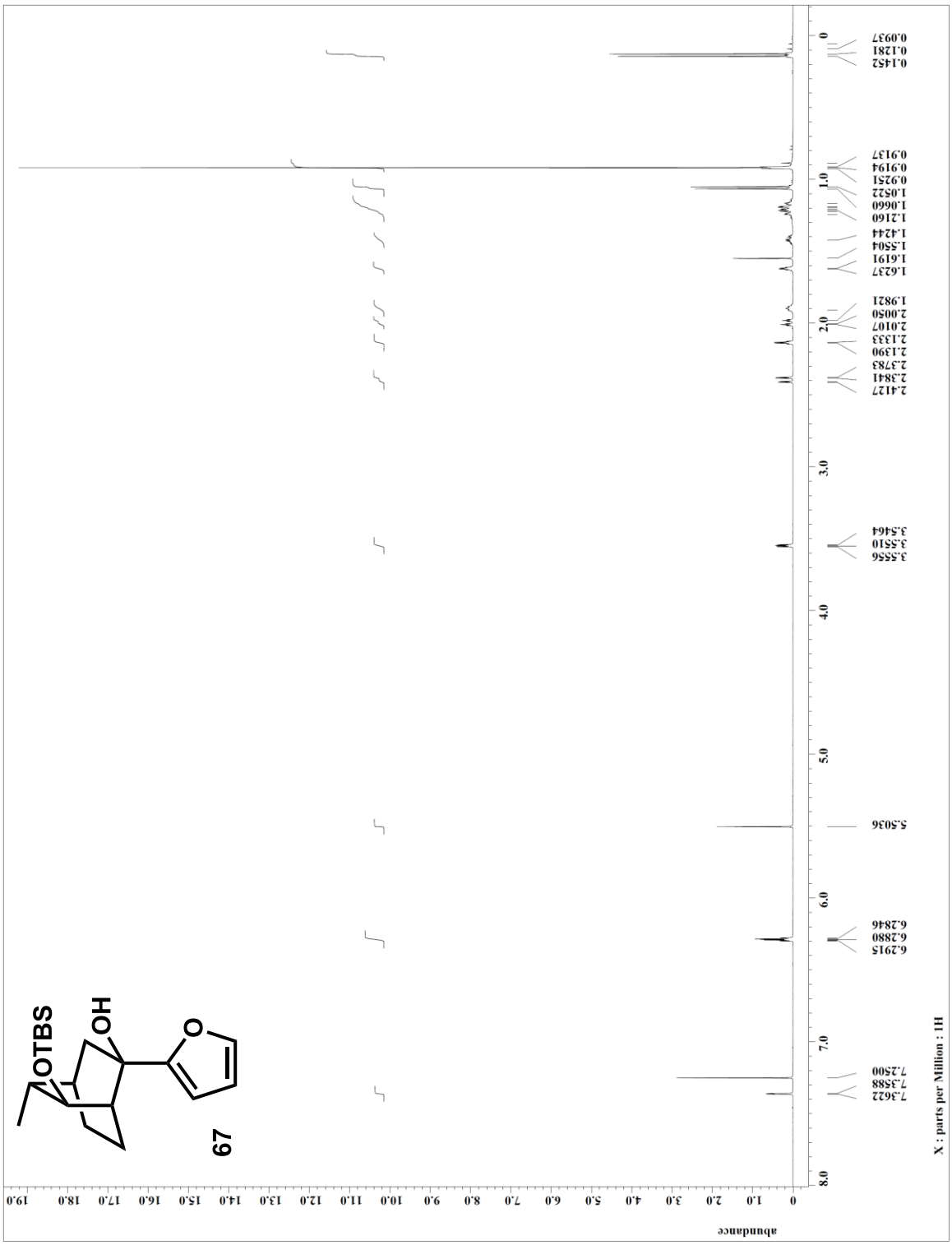
^{13}C NMR for compound **65**



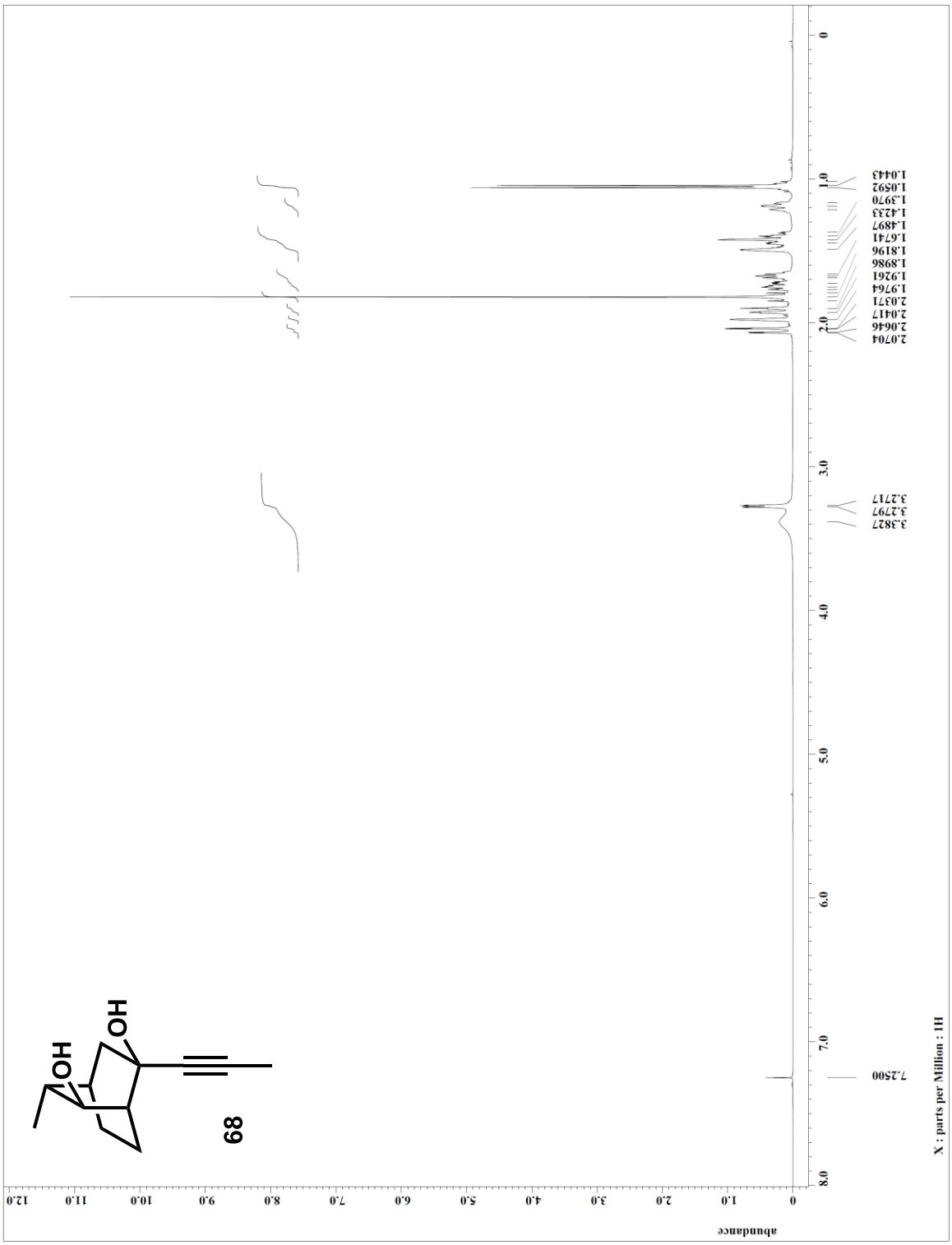
^{1}H NMR for compound **66**



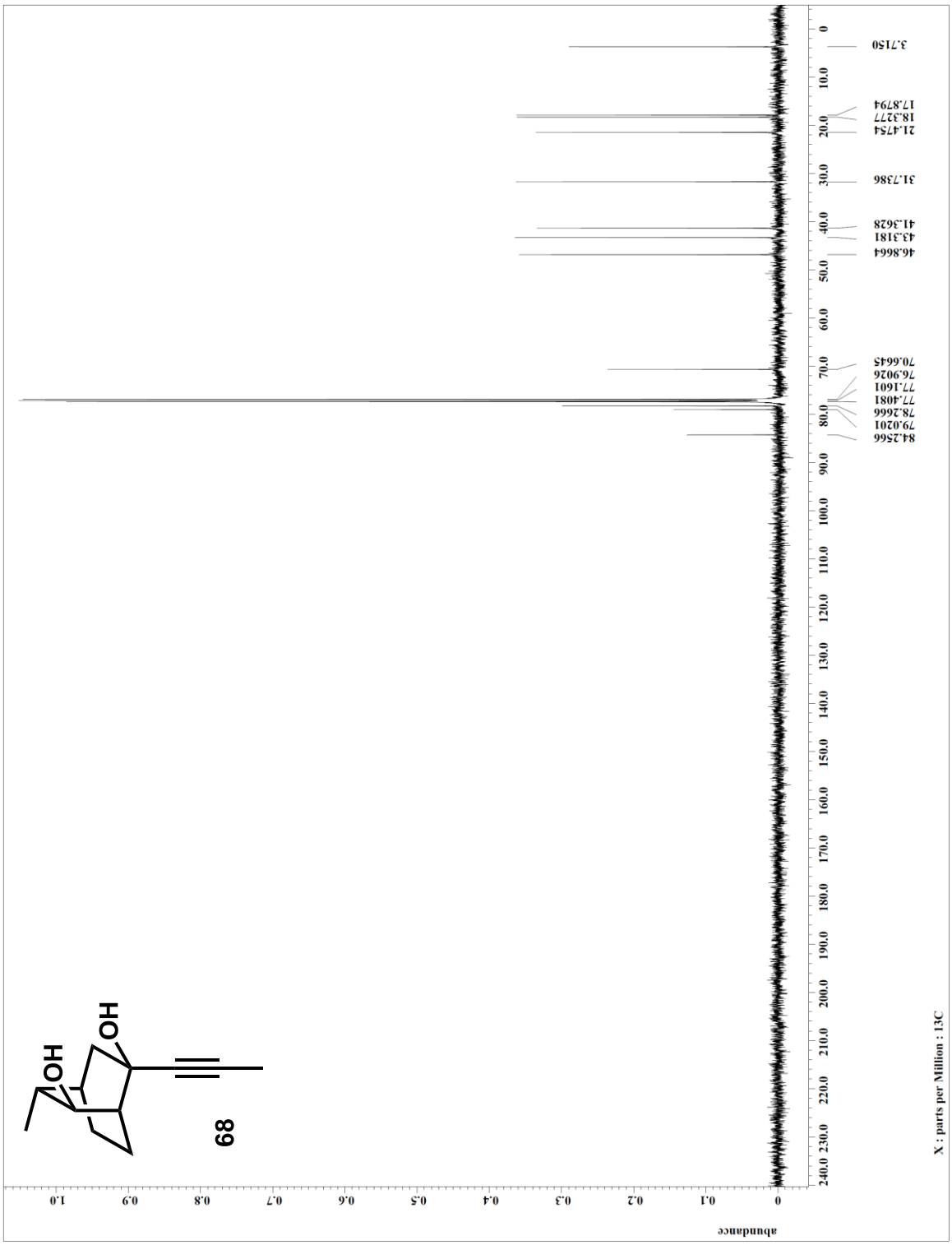
^{13}C NMR for compound **66**



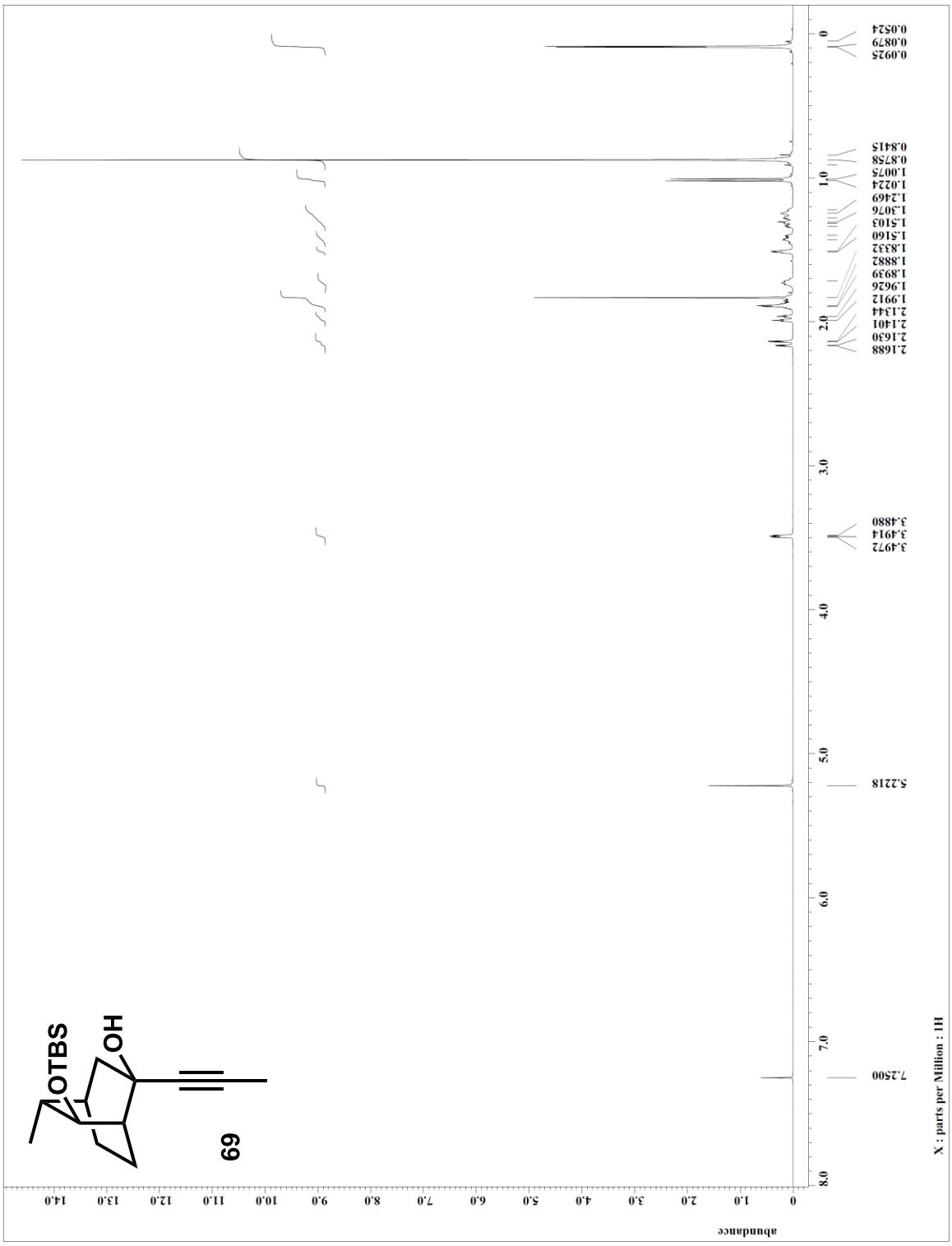
^{1}H NMR for compound **67**



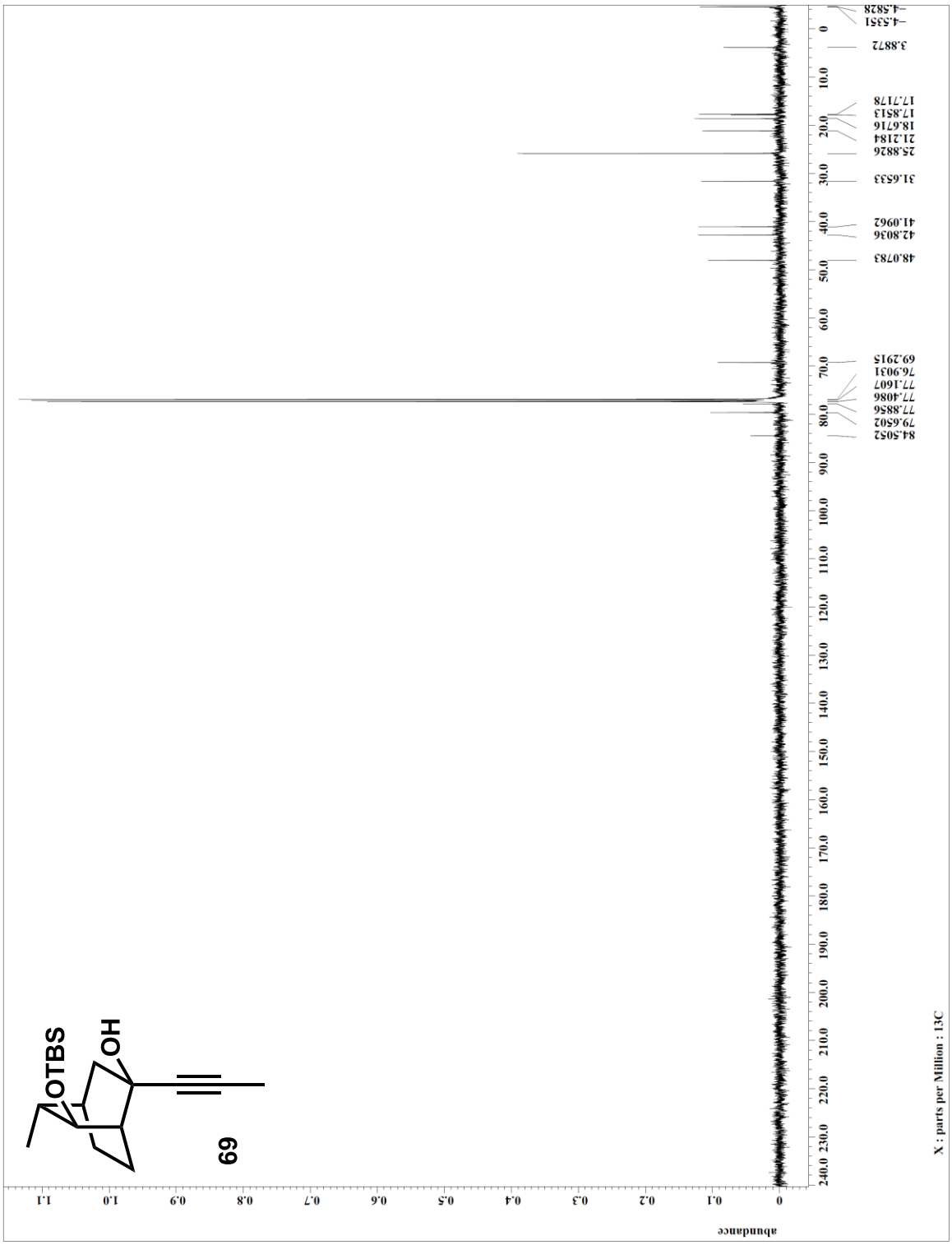
^{1}H NMR for compound **68**



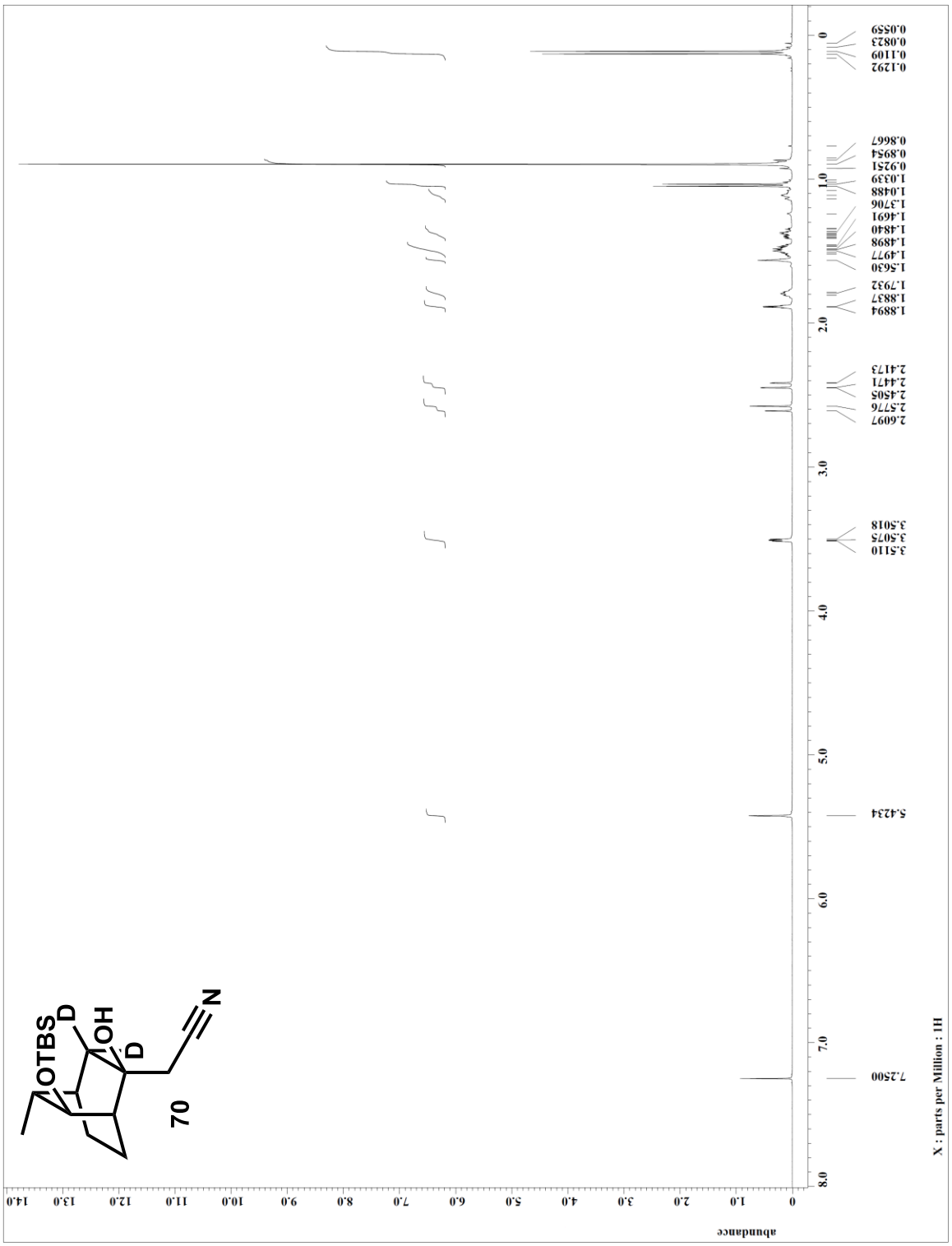
^{13}C NMR for compound **68**



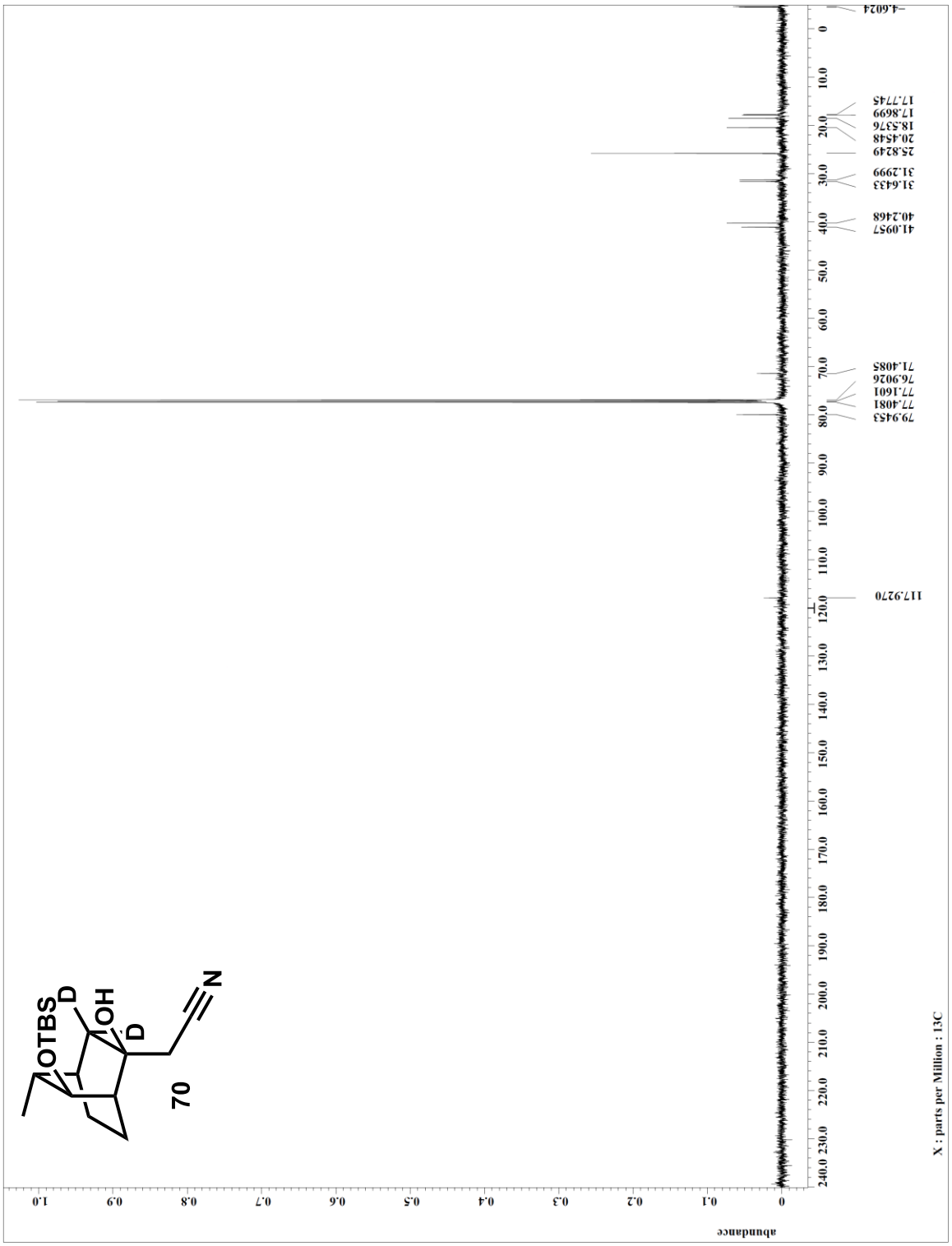
^{1}H NMR for compound **69**



^{13}C NMR for compound **69**



^{1}H NMR for compound **70**



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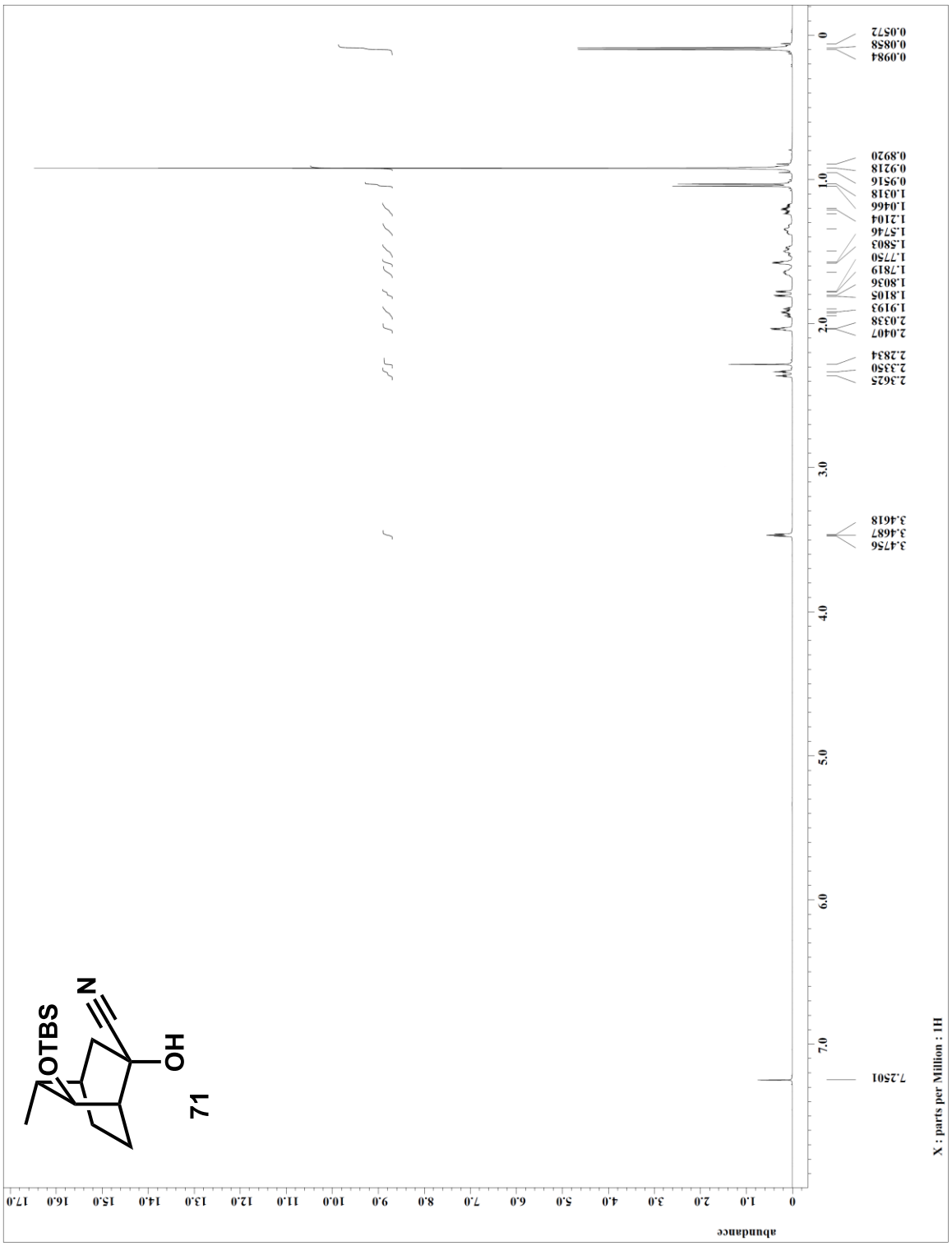
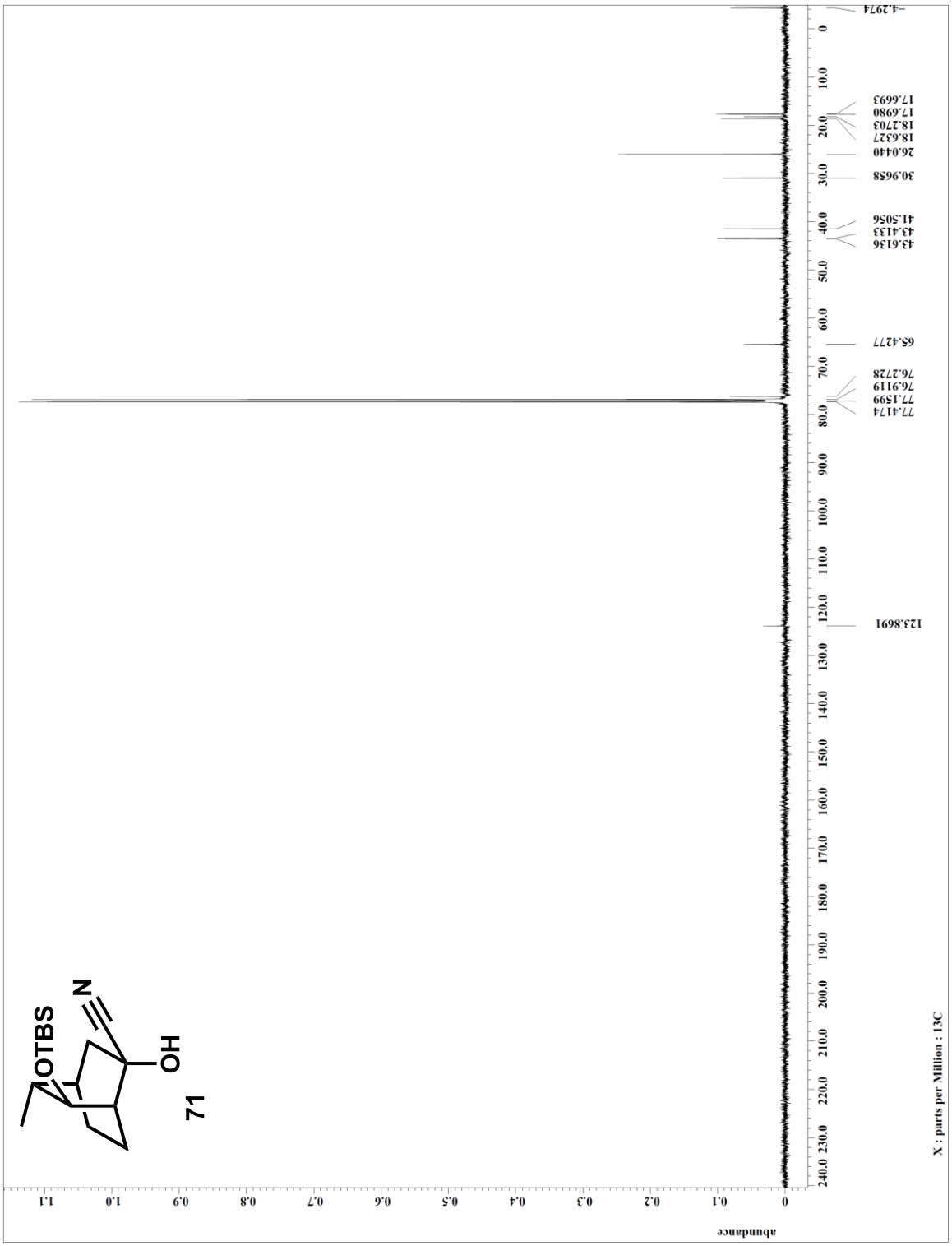
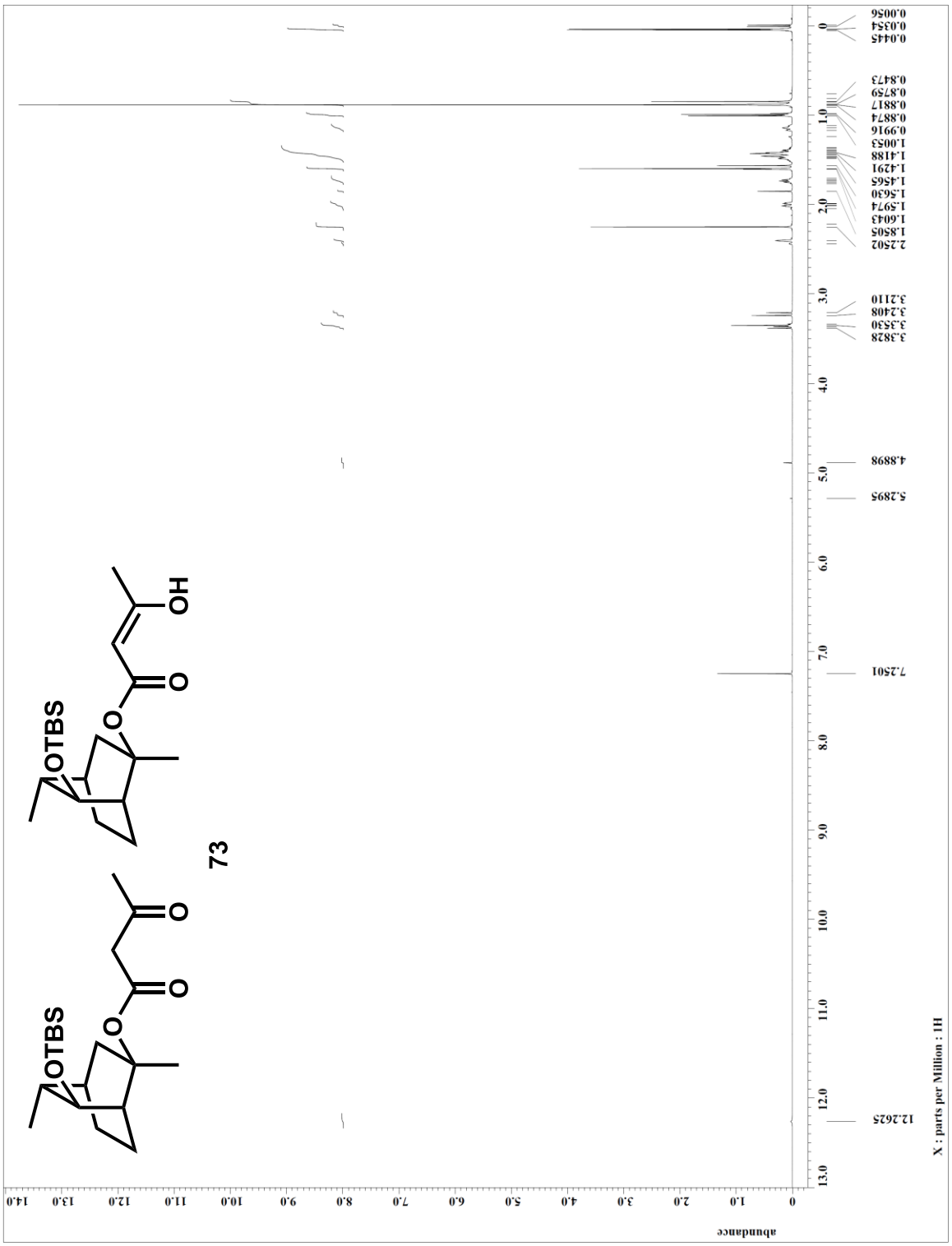


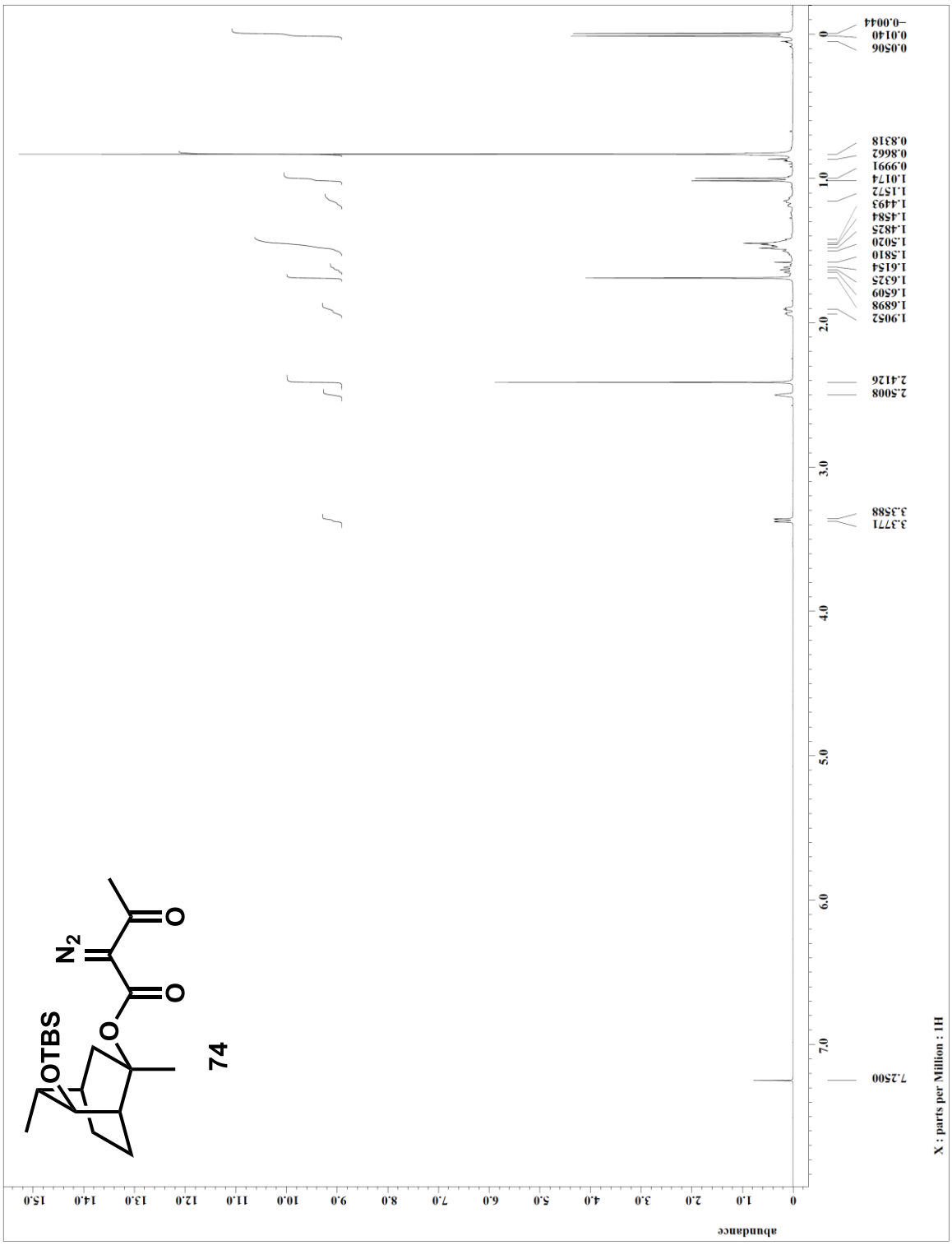
^{1}H NMR for compound **71**



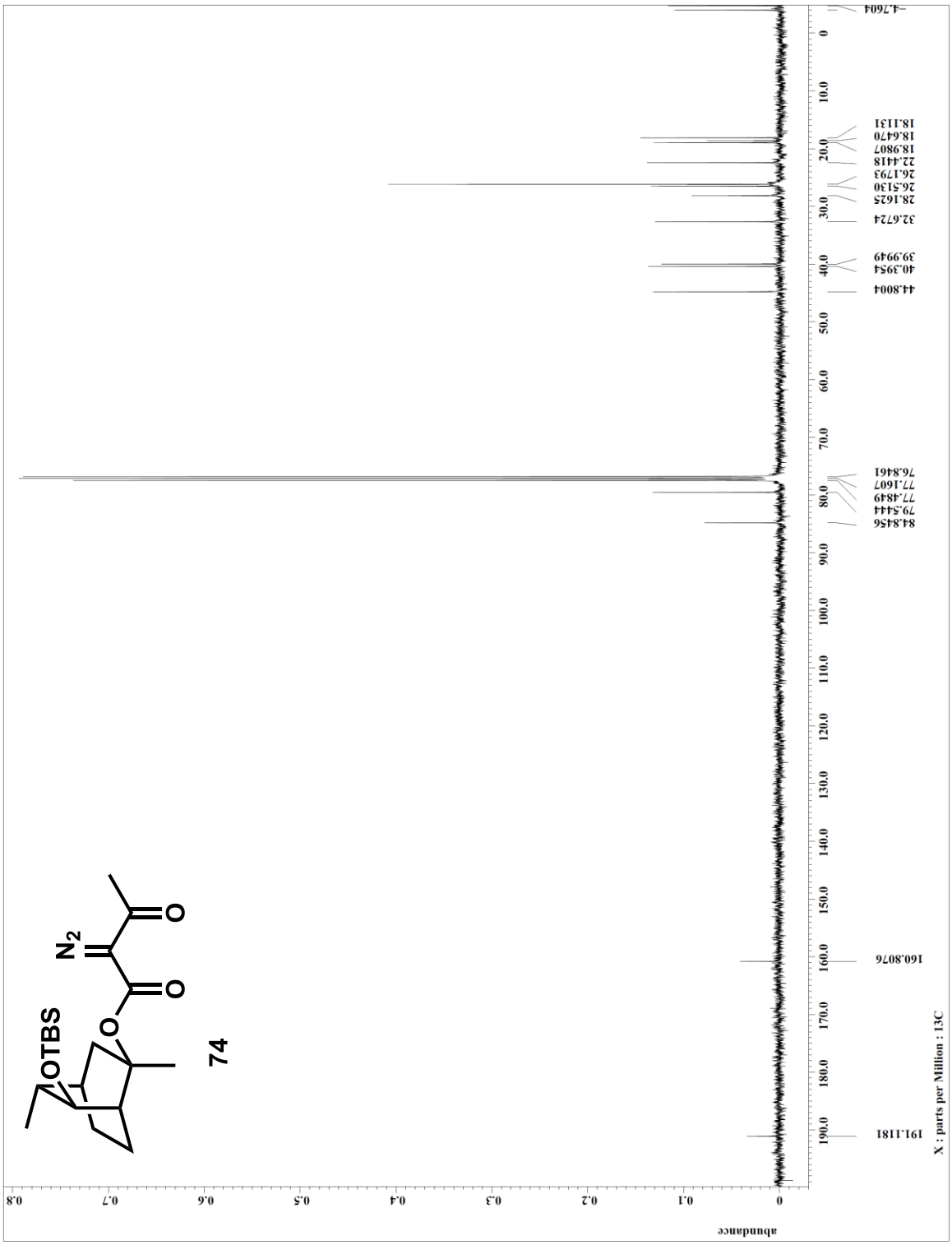
^{13}C NMR for compound **71**



^{1}H NMR for compound **73**



^{1}H NMR for compound **74**



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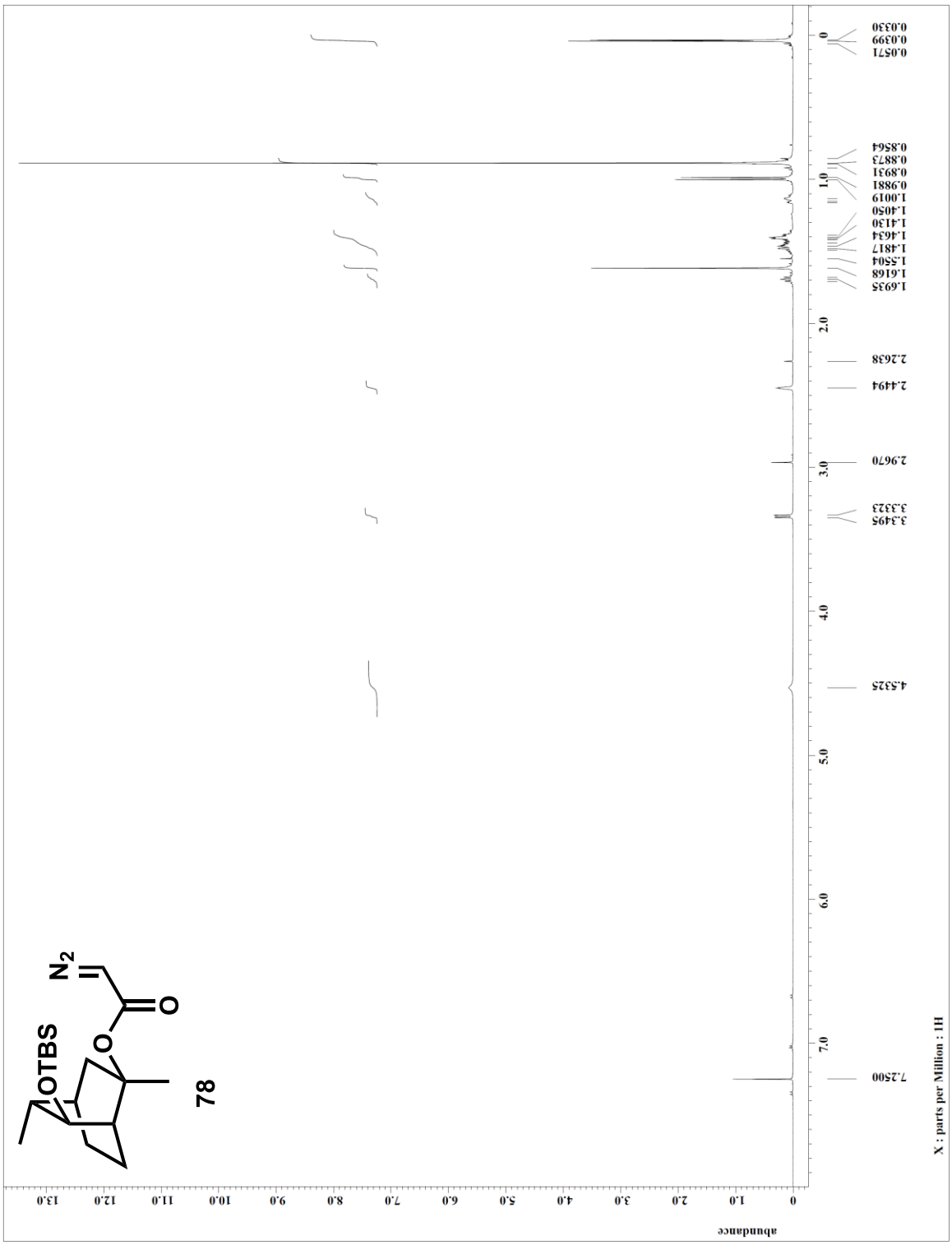
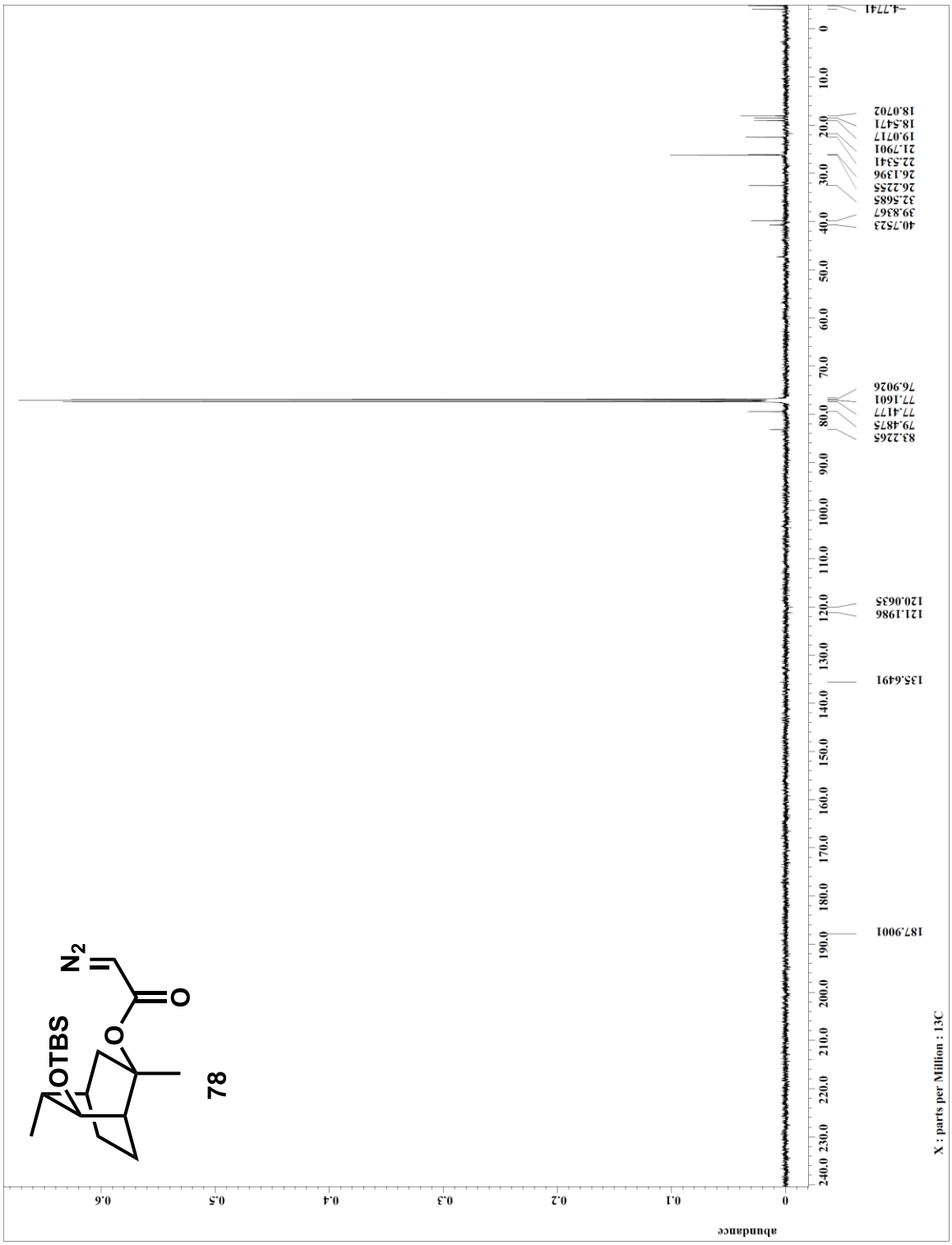


^{1}H NMR for compound **78**



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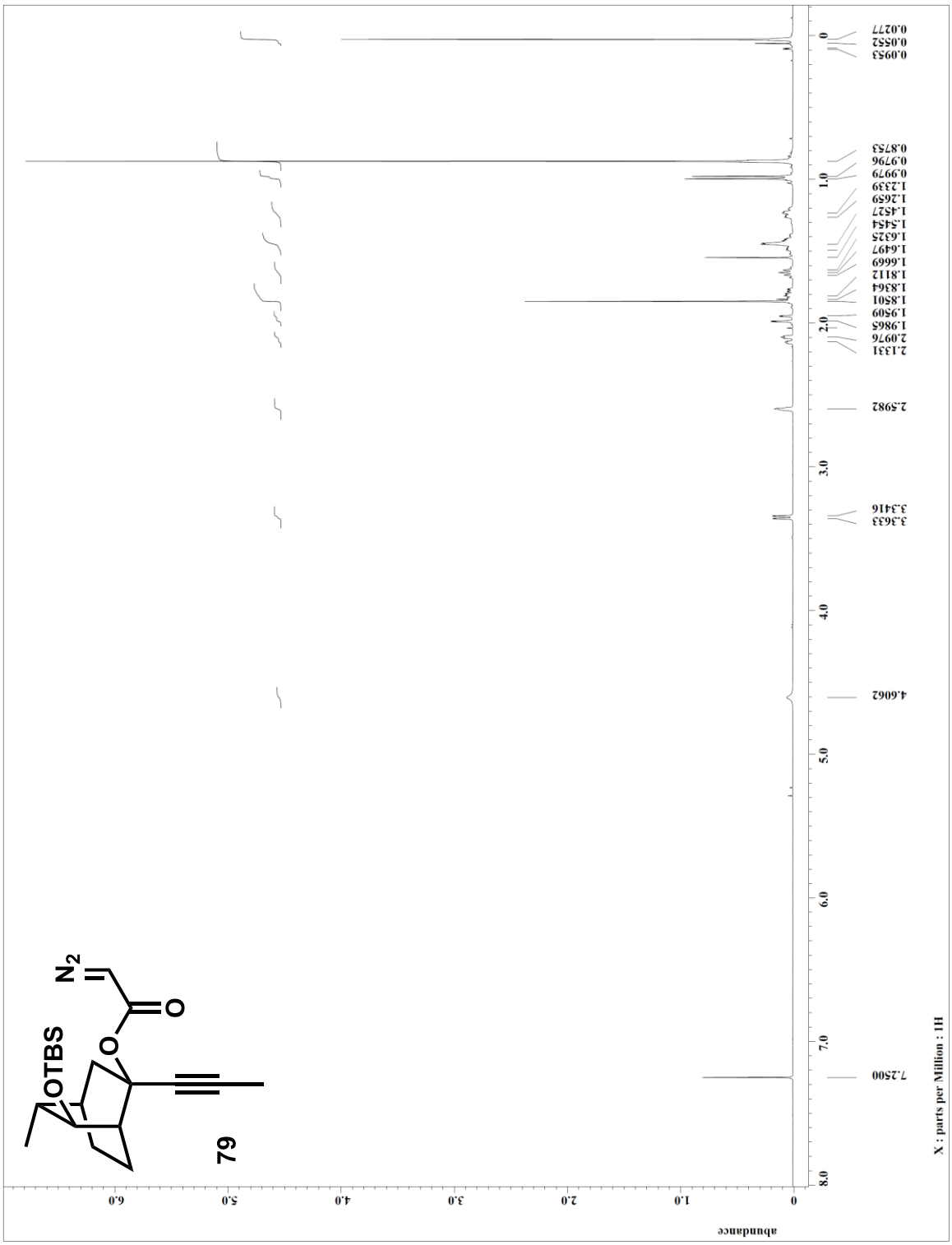
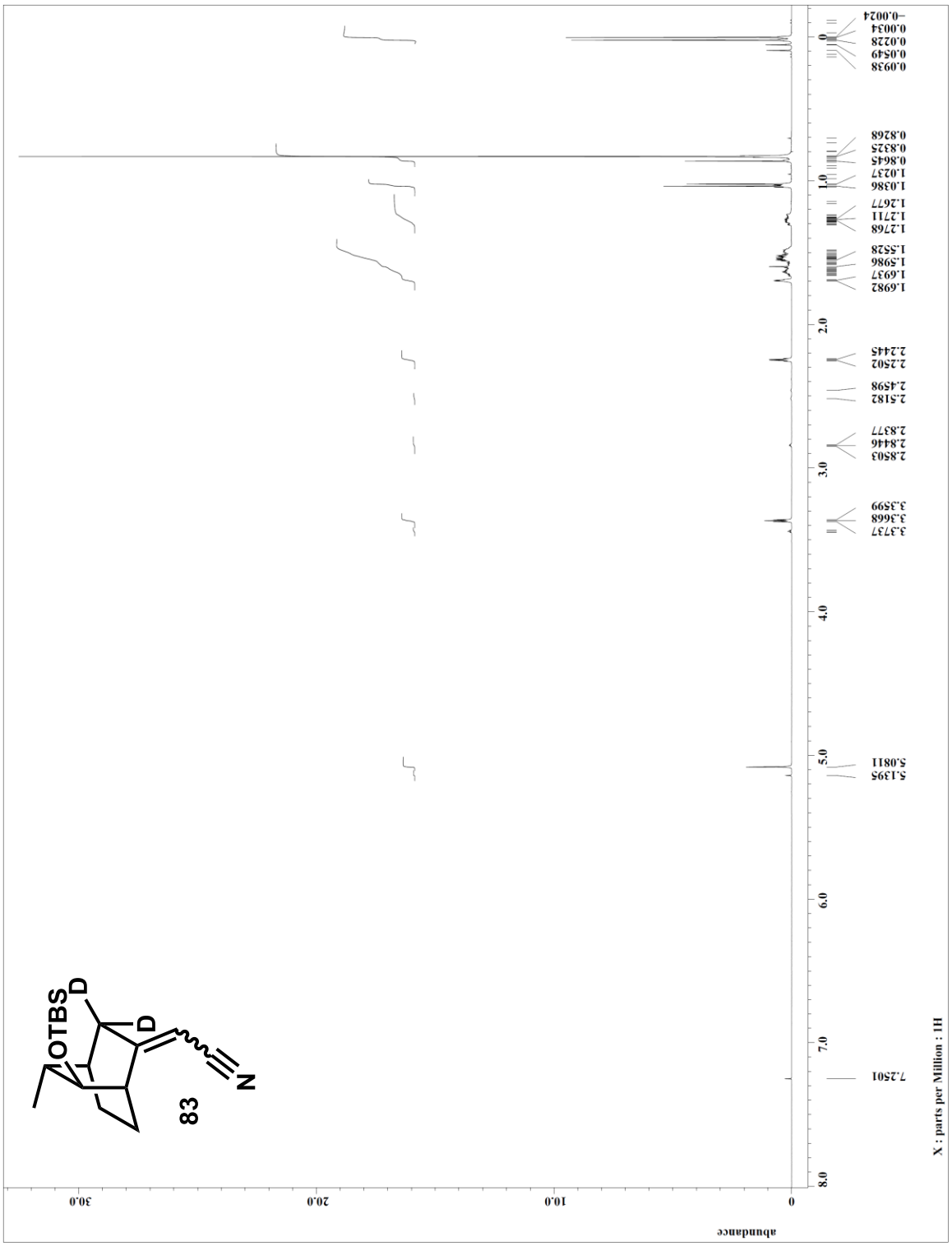
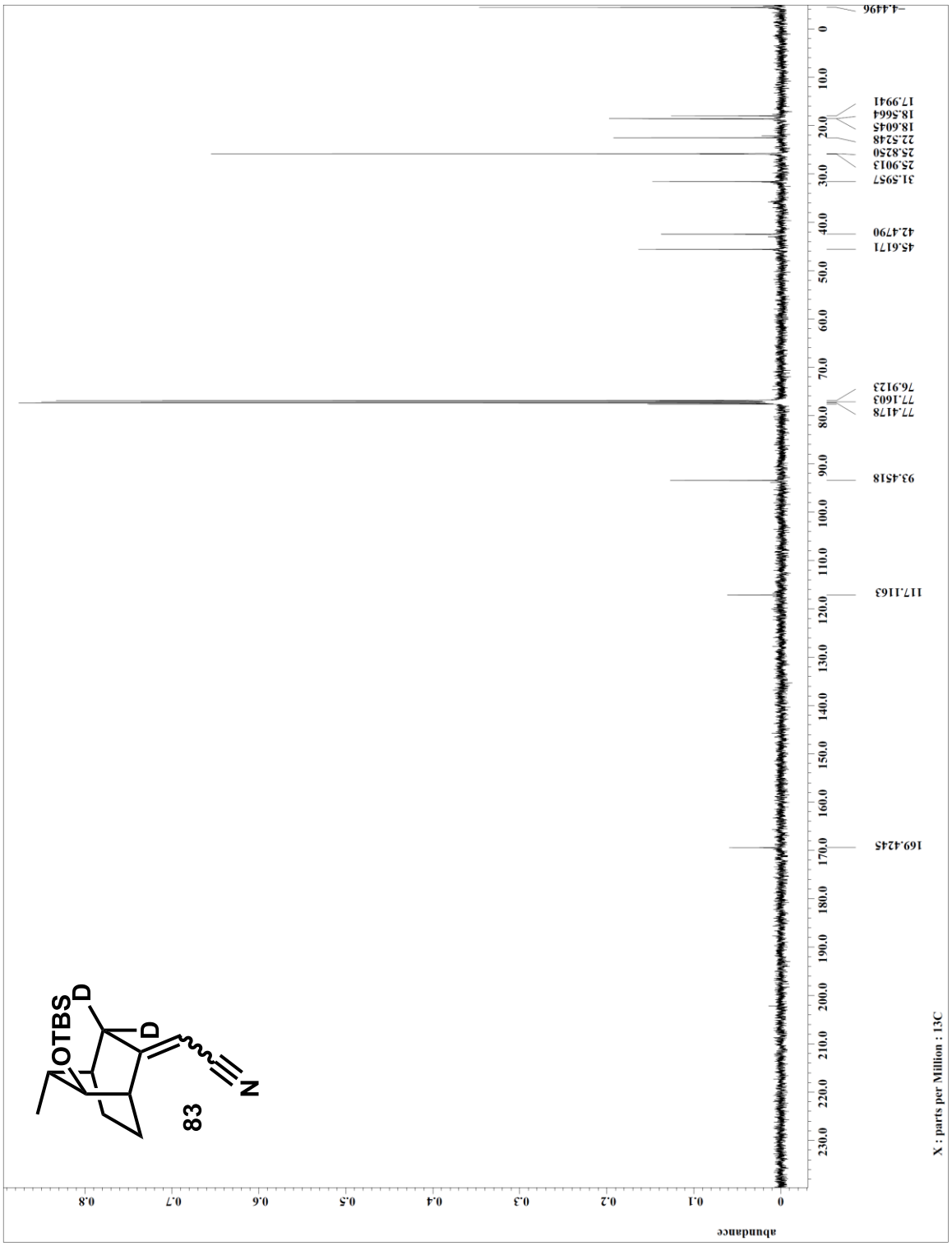


^{1}H NMR for compound **79**



^{1}H NMR for compound **83**



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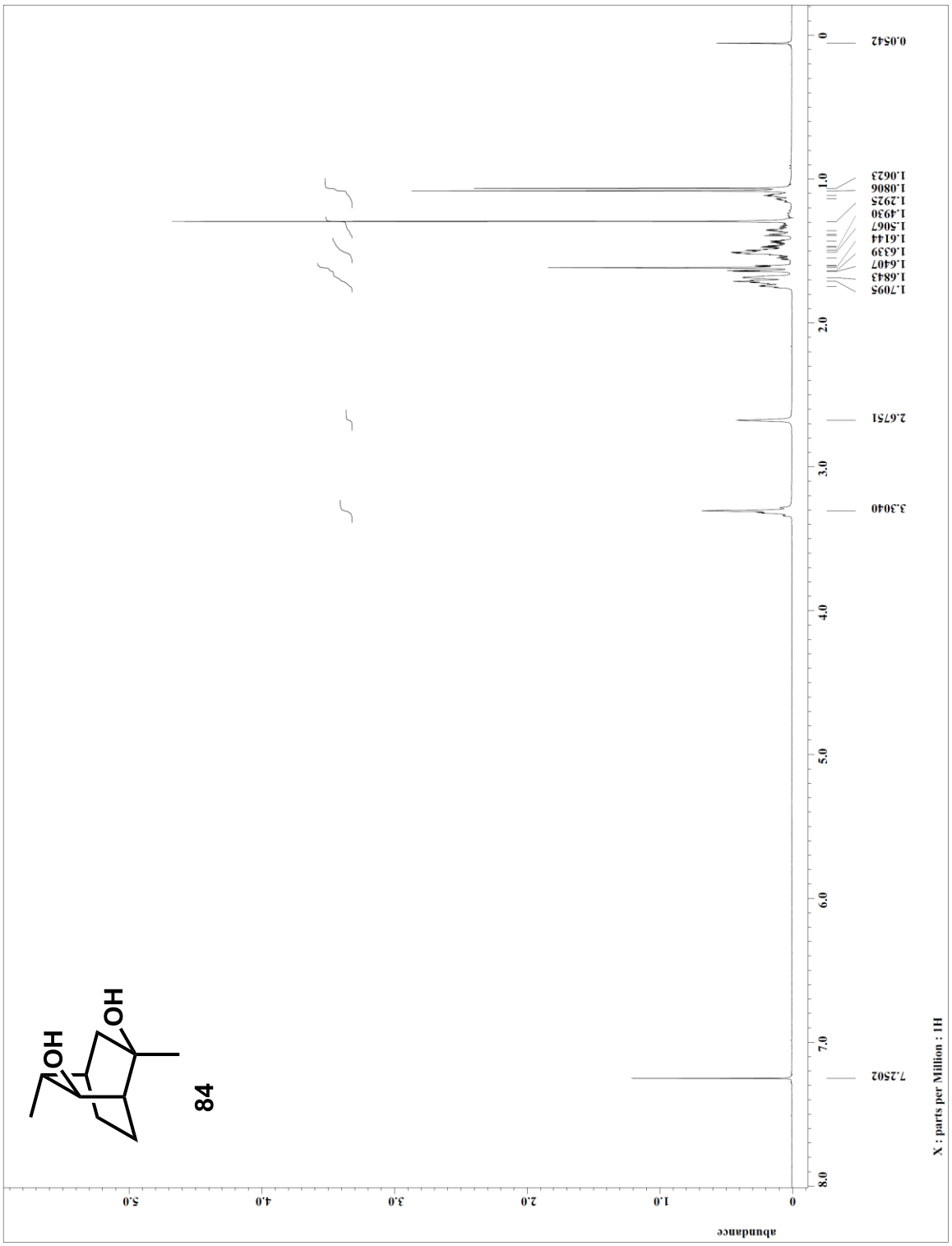

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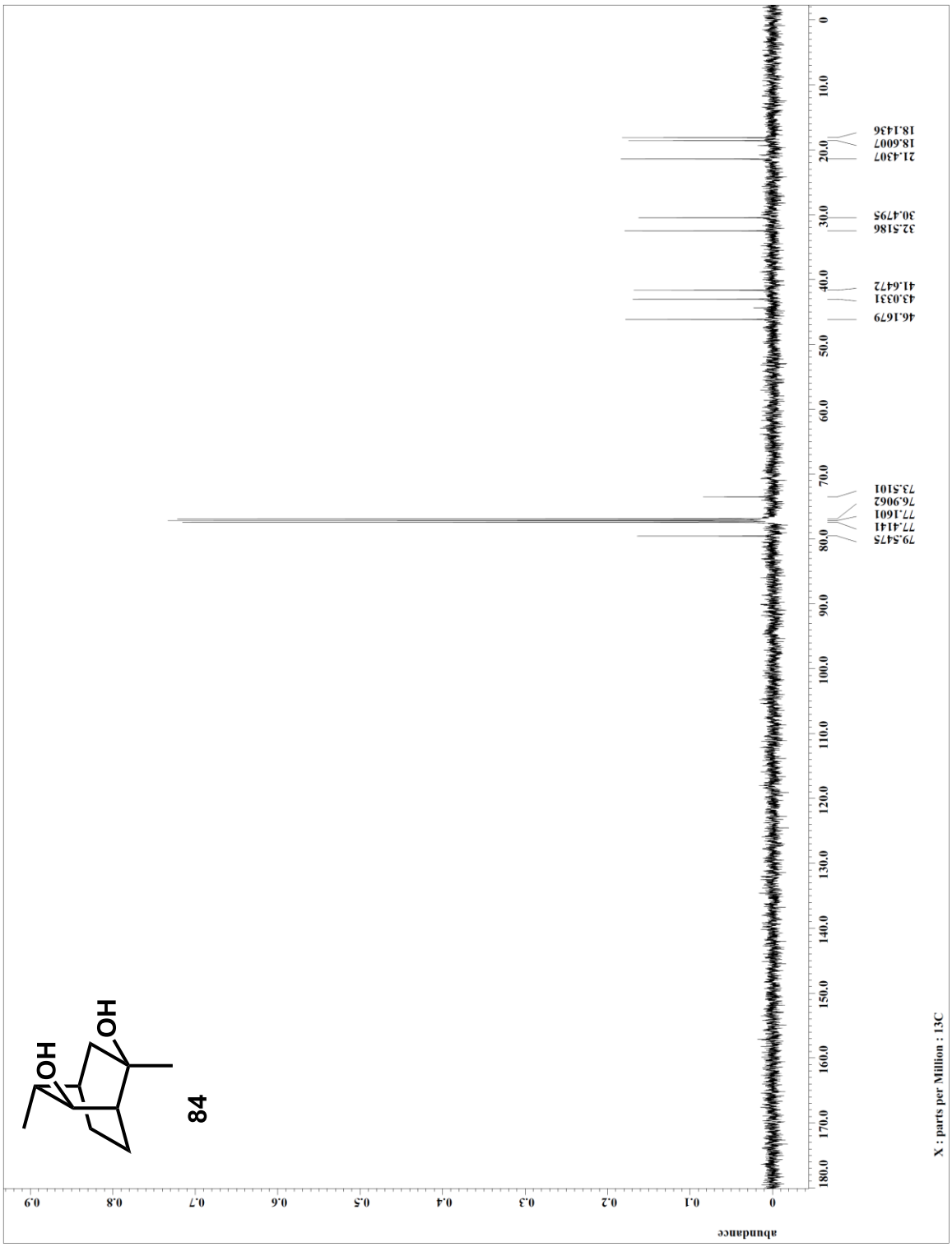
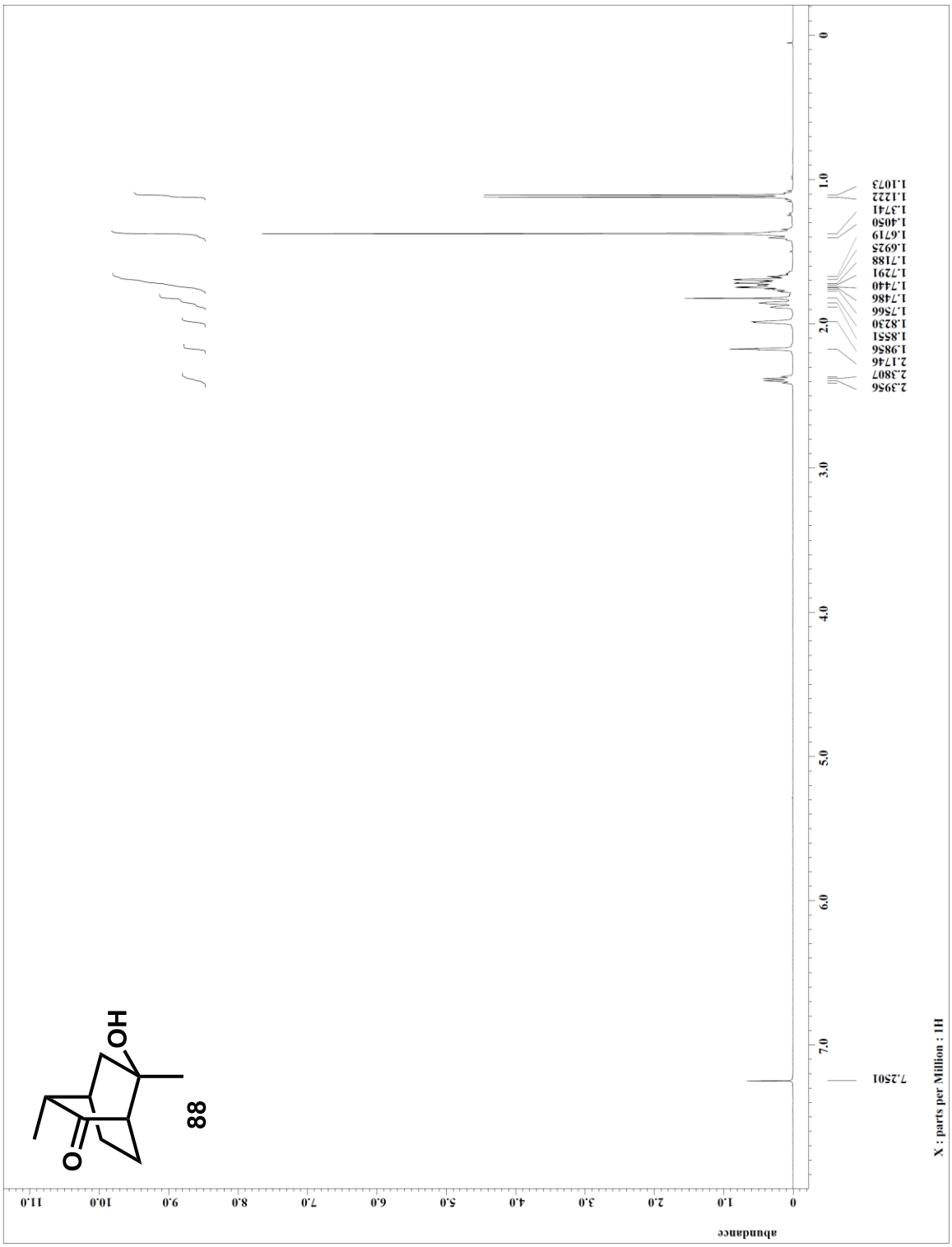
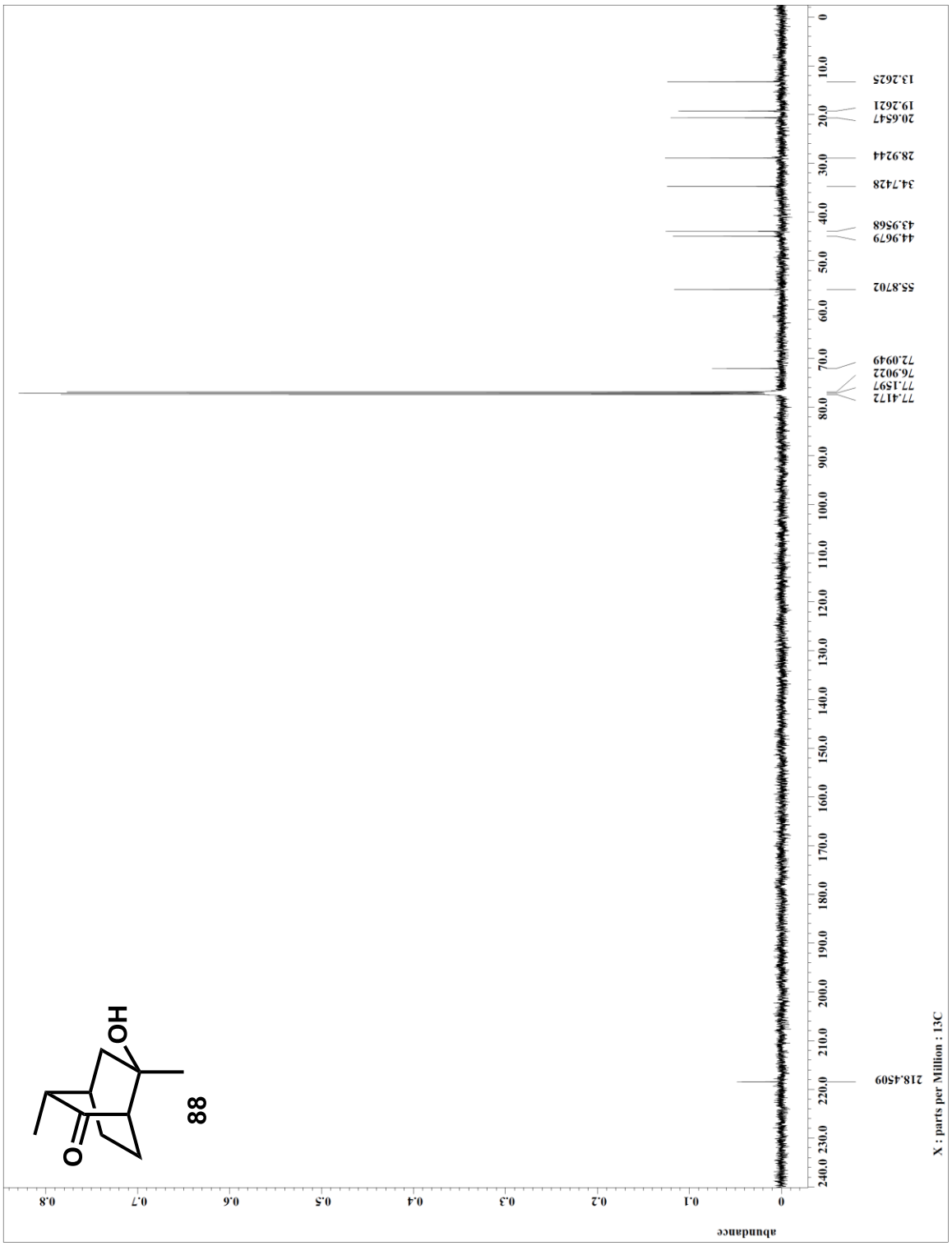


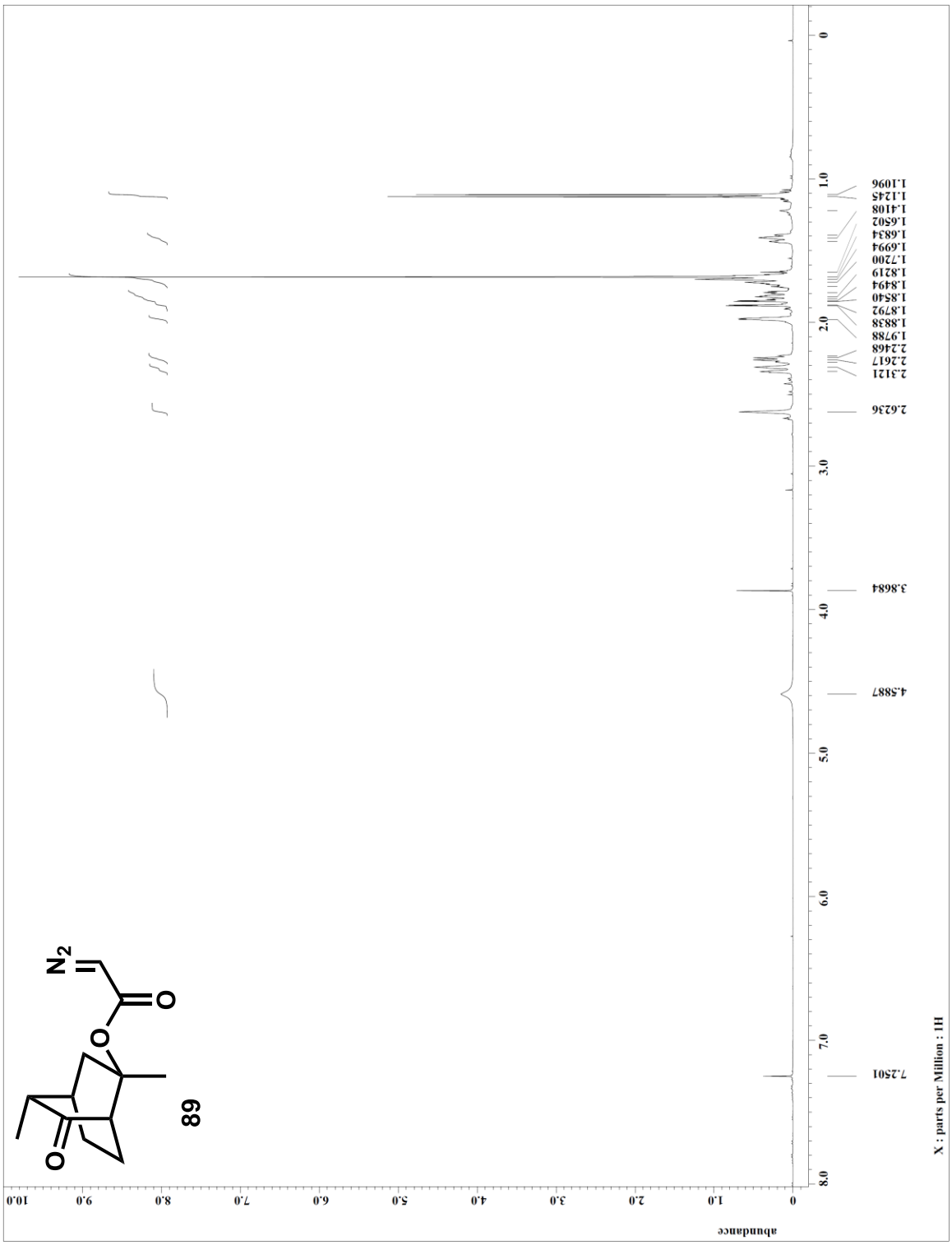
^{13}C NMR for compound **84**



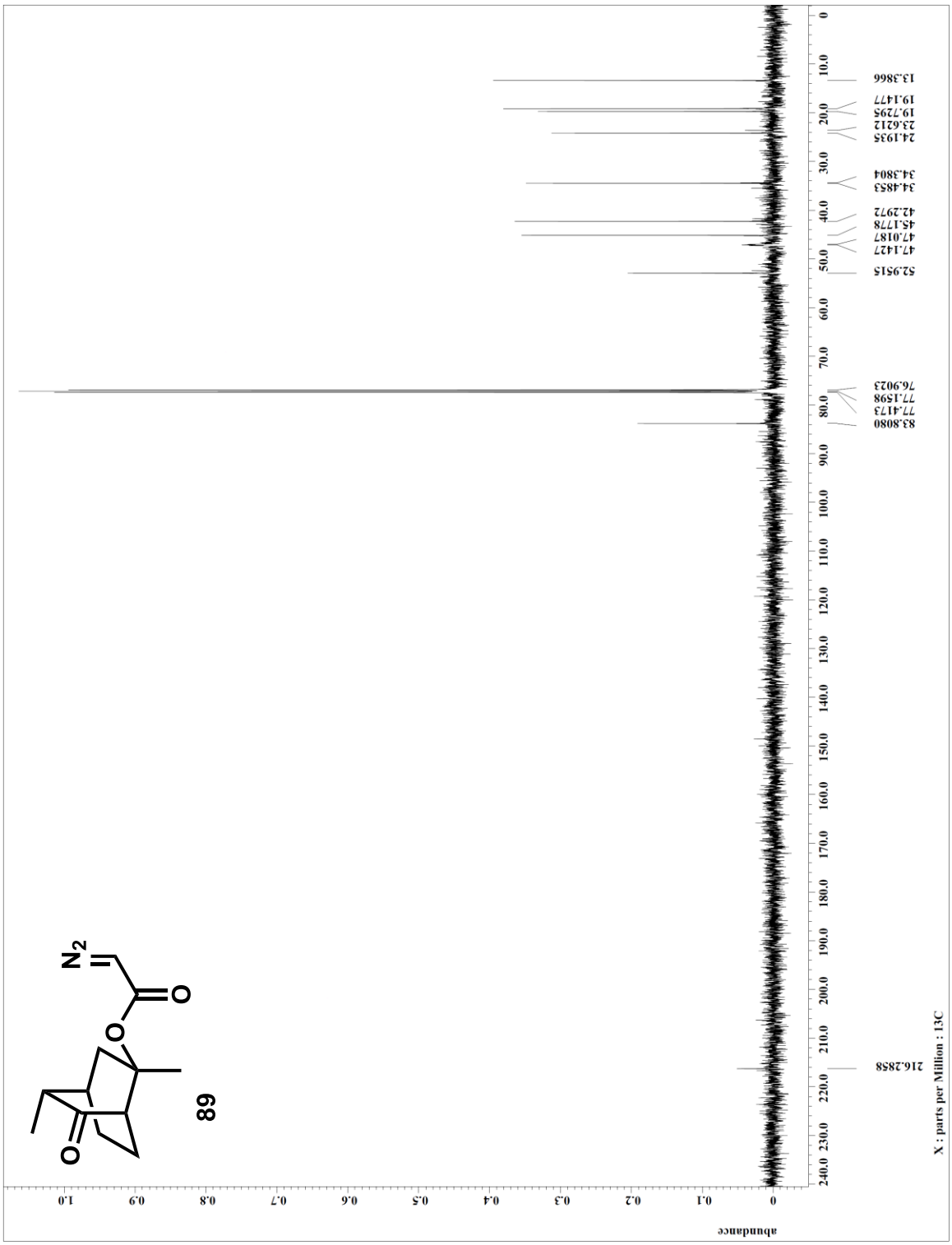
^{1}H NMR for compound **88**



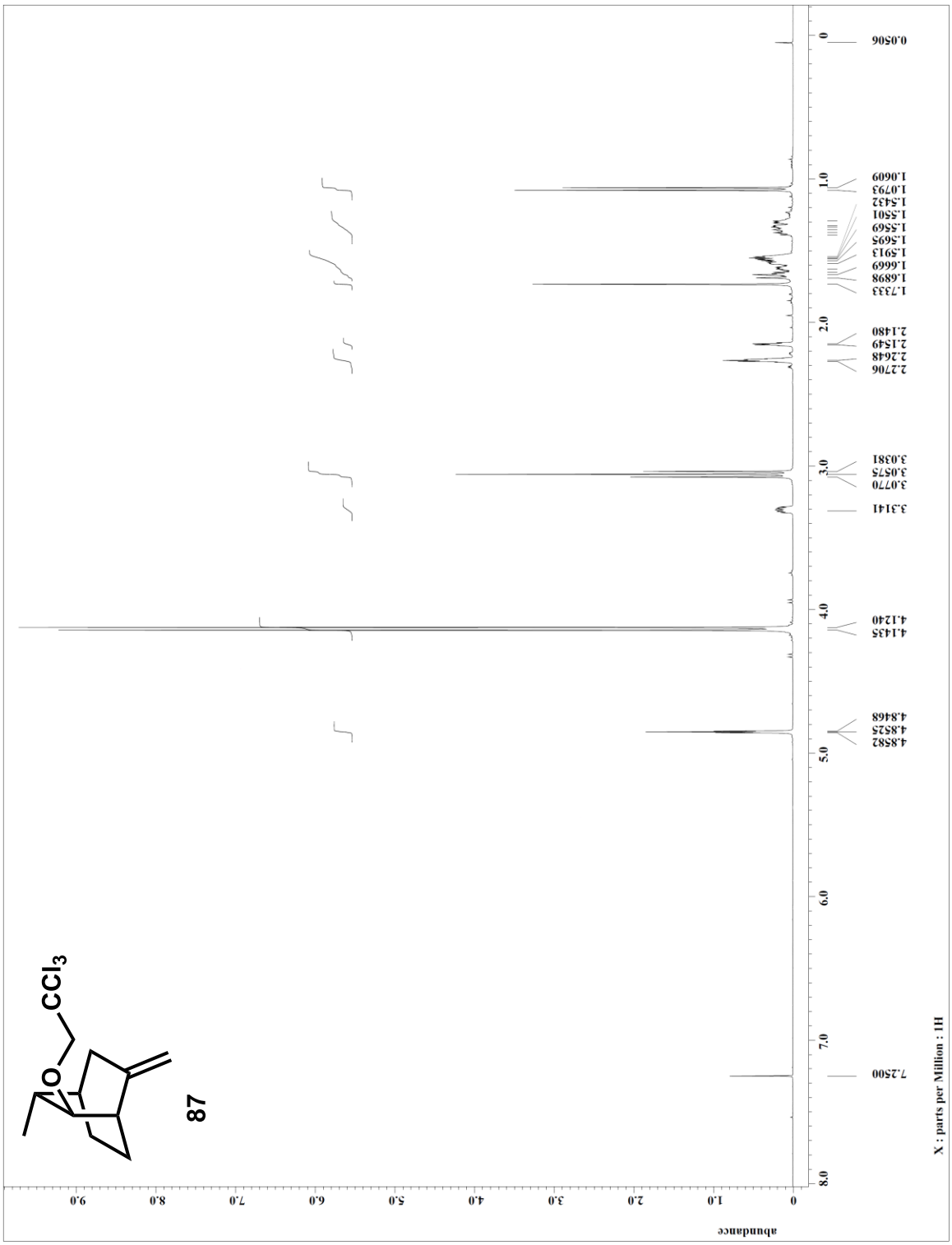
^{13}C NMR for compound **88**



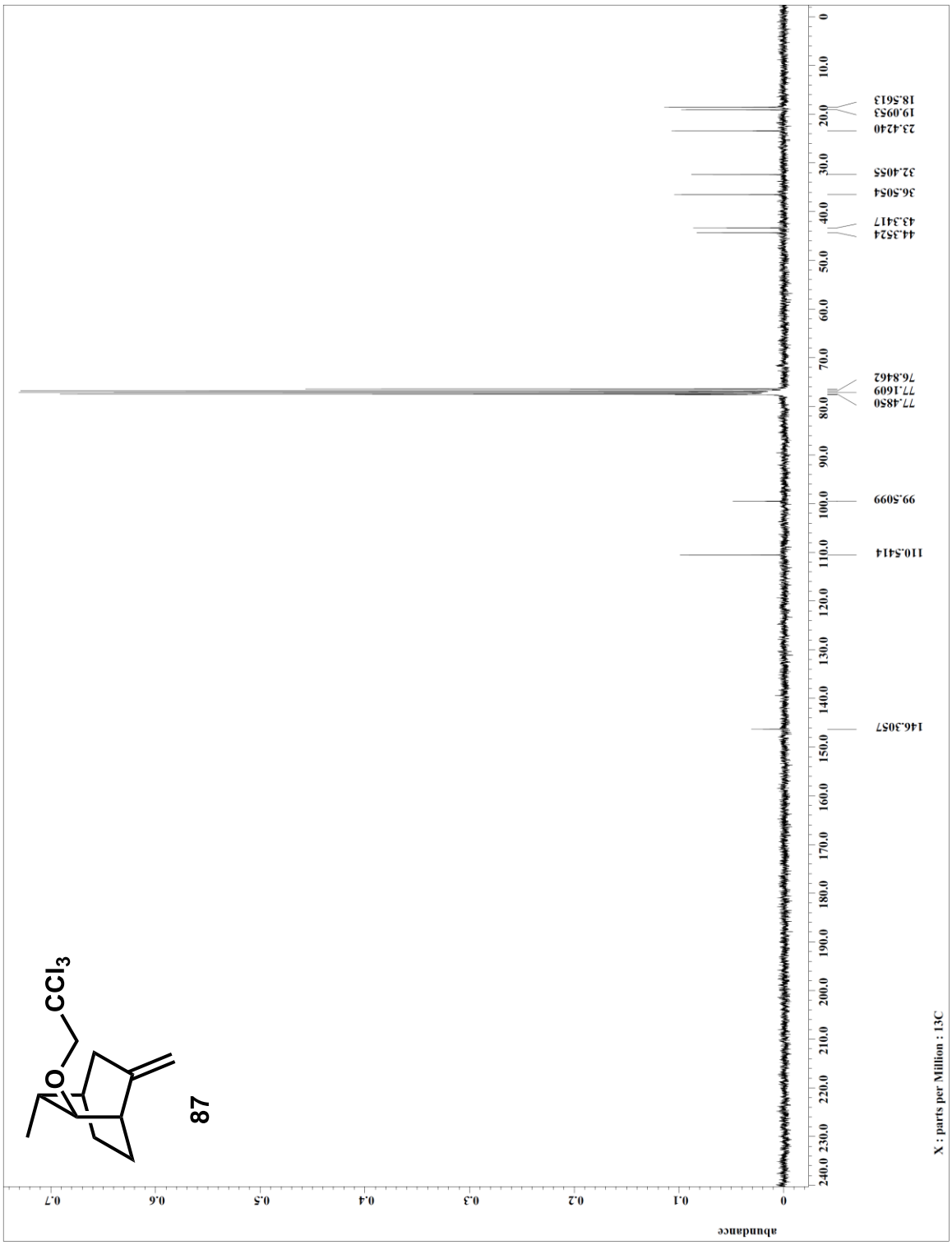
^{1}H NMR for compound **89**



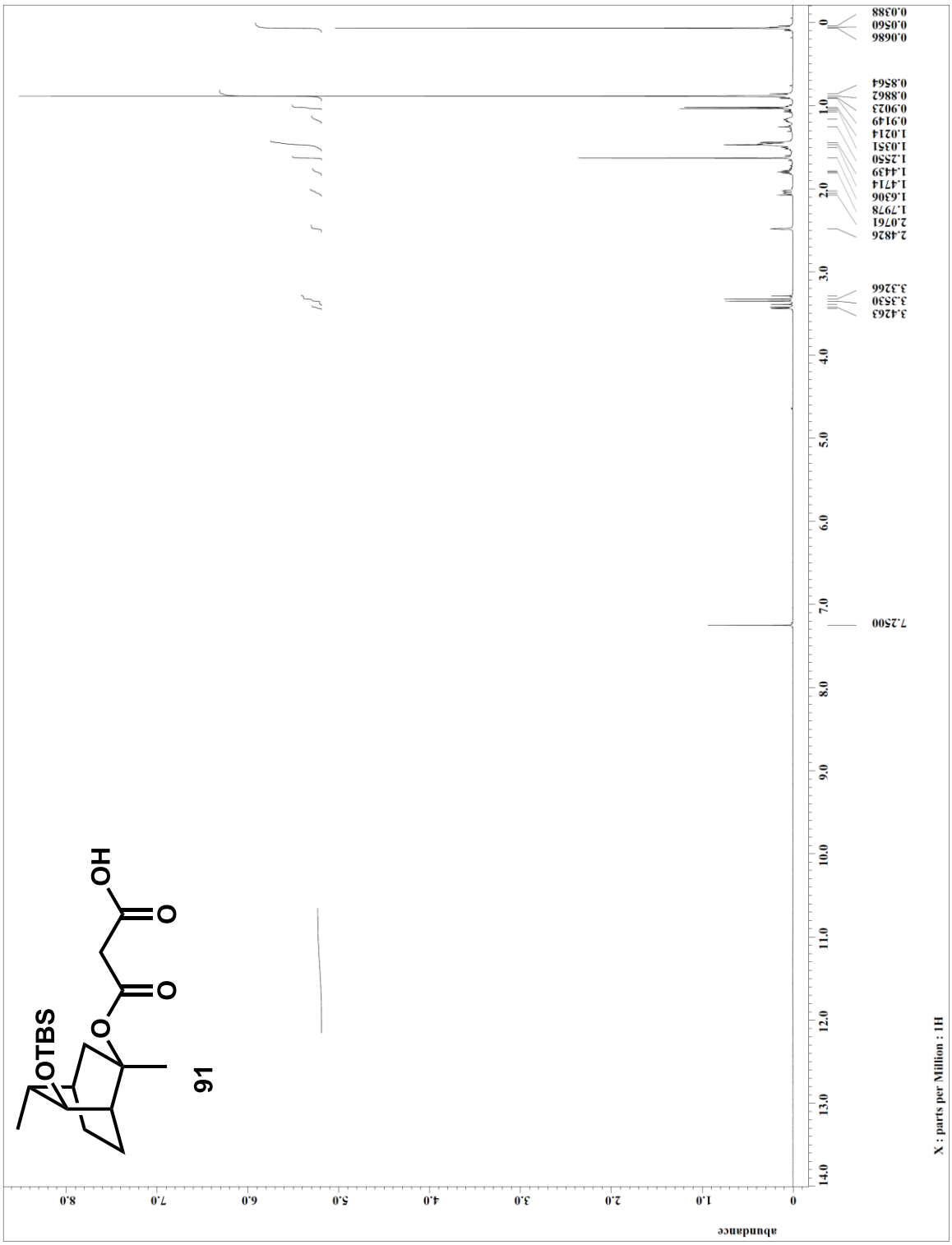
^{13}C NMR for compound **89**



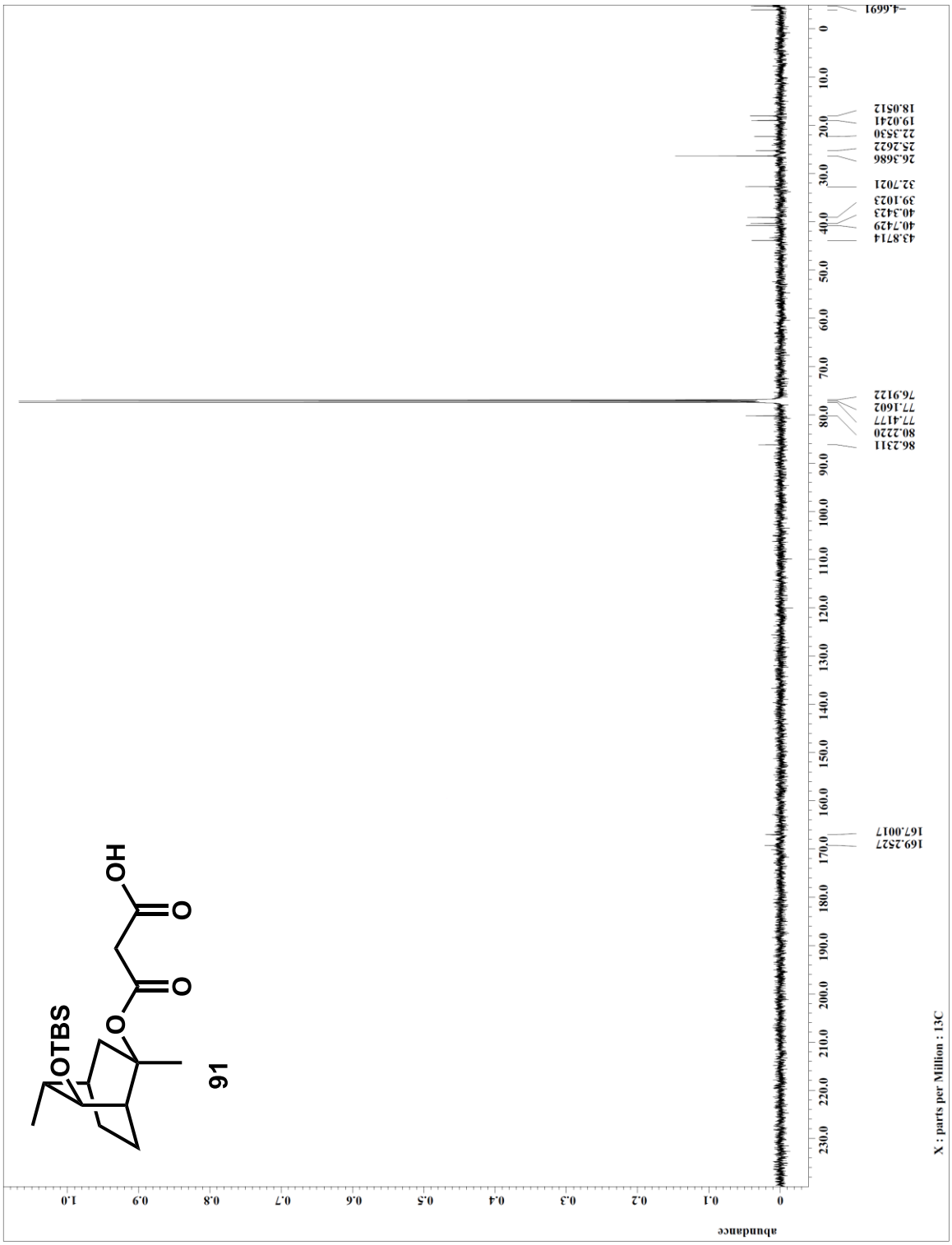
^{1}H NMR for compound **87**



^{13}C NMR for compound **87**



^{1}H NMR for compound **91**



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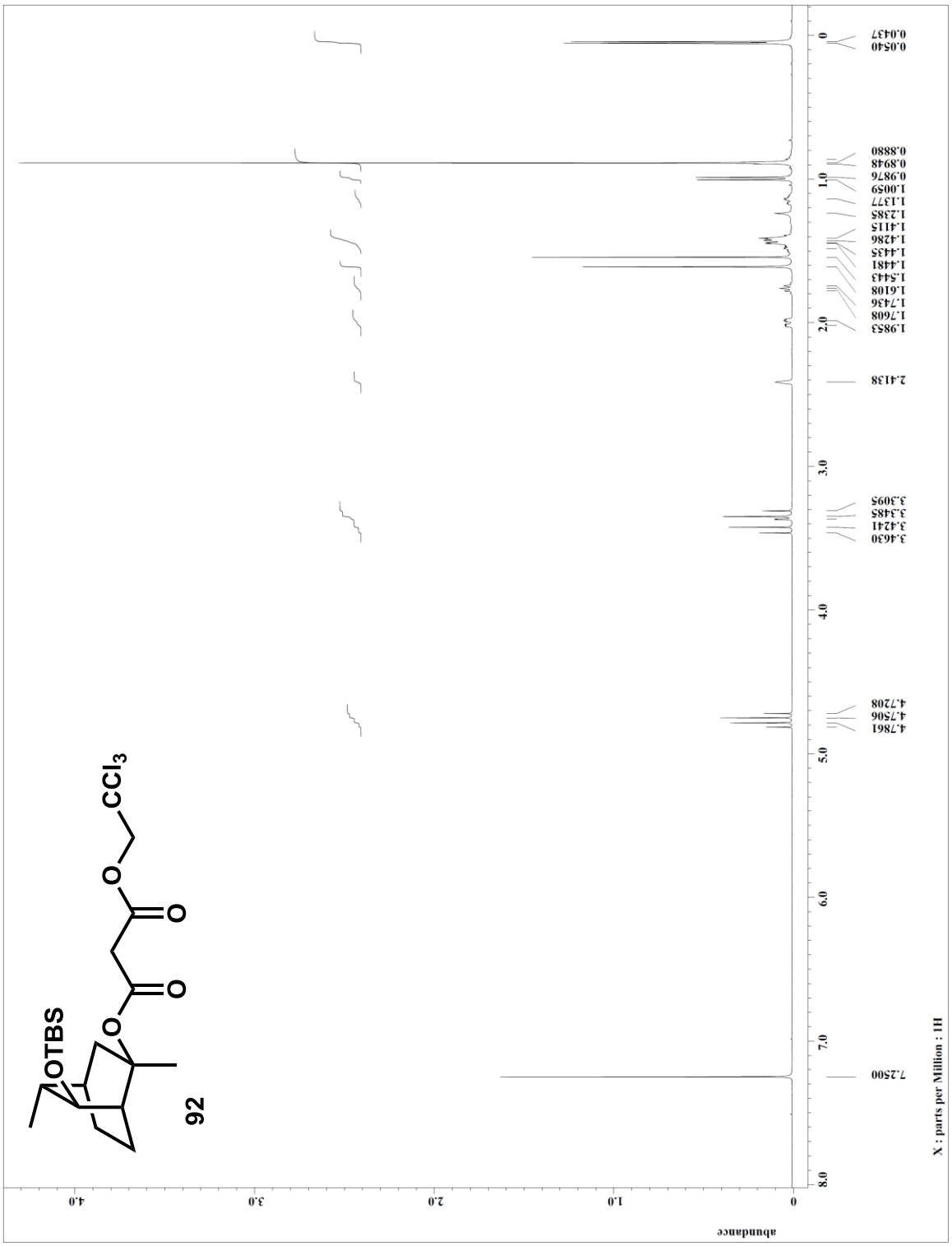
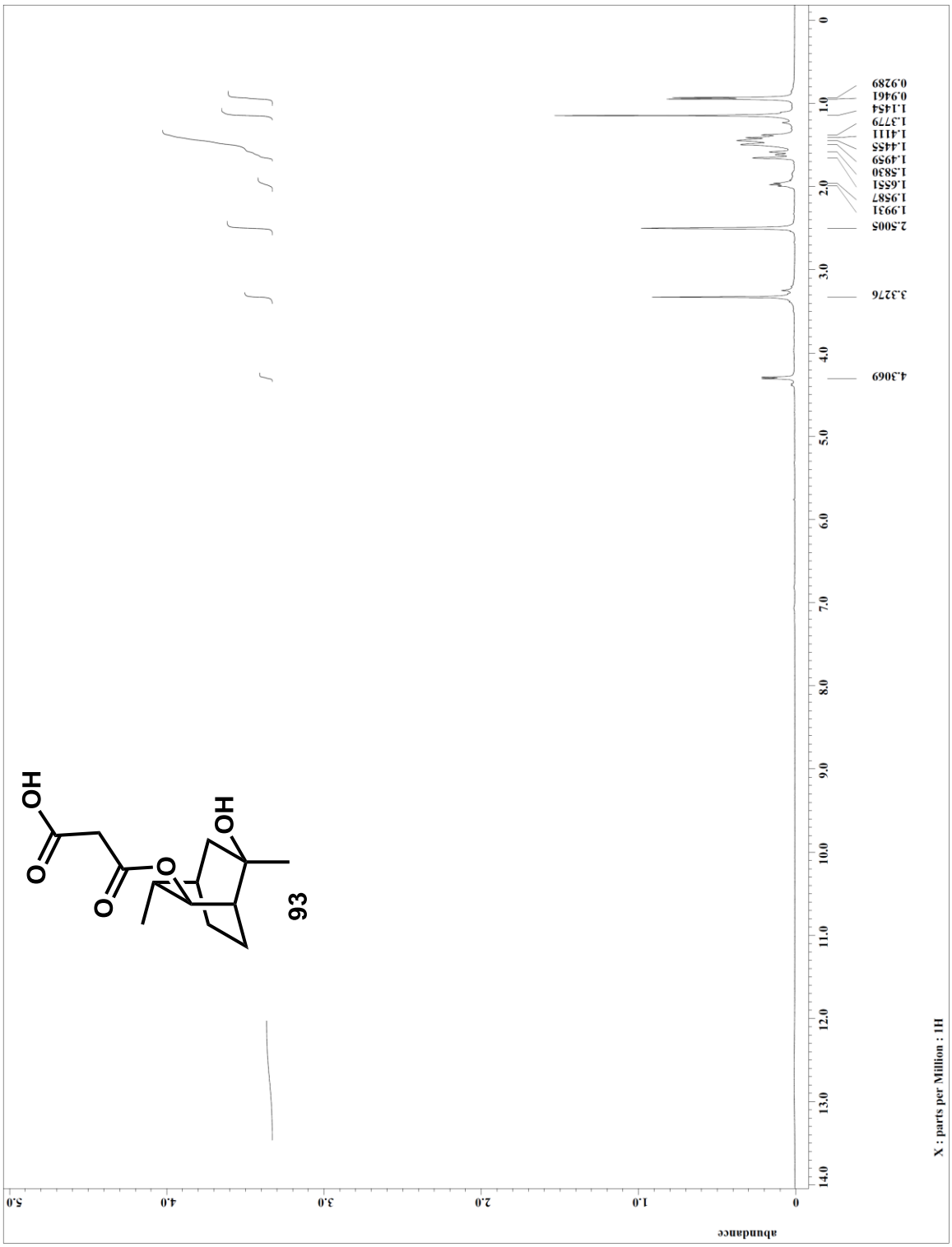
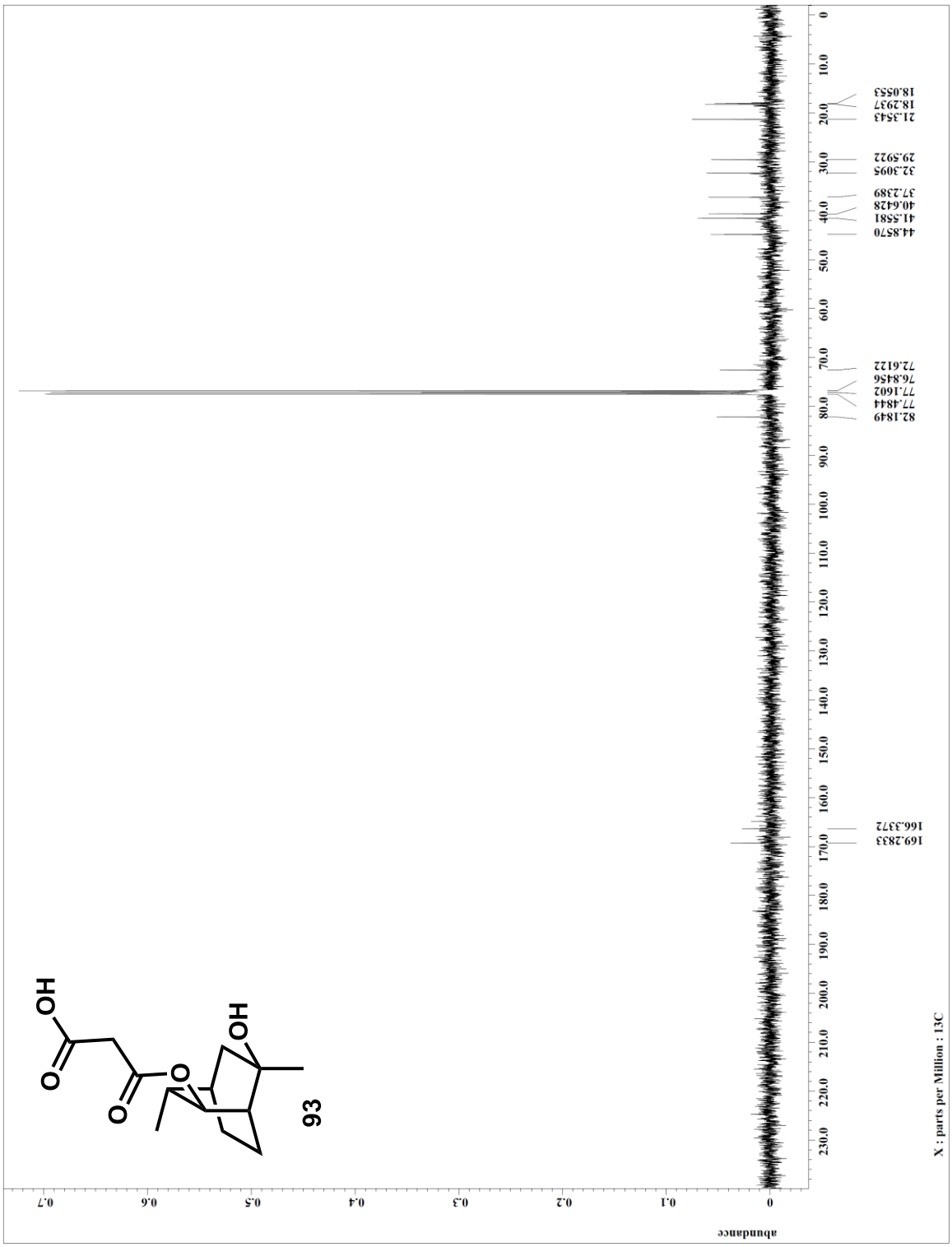


^{1}H NMR for compound **92**

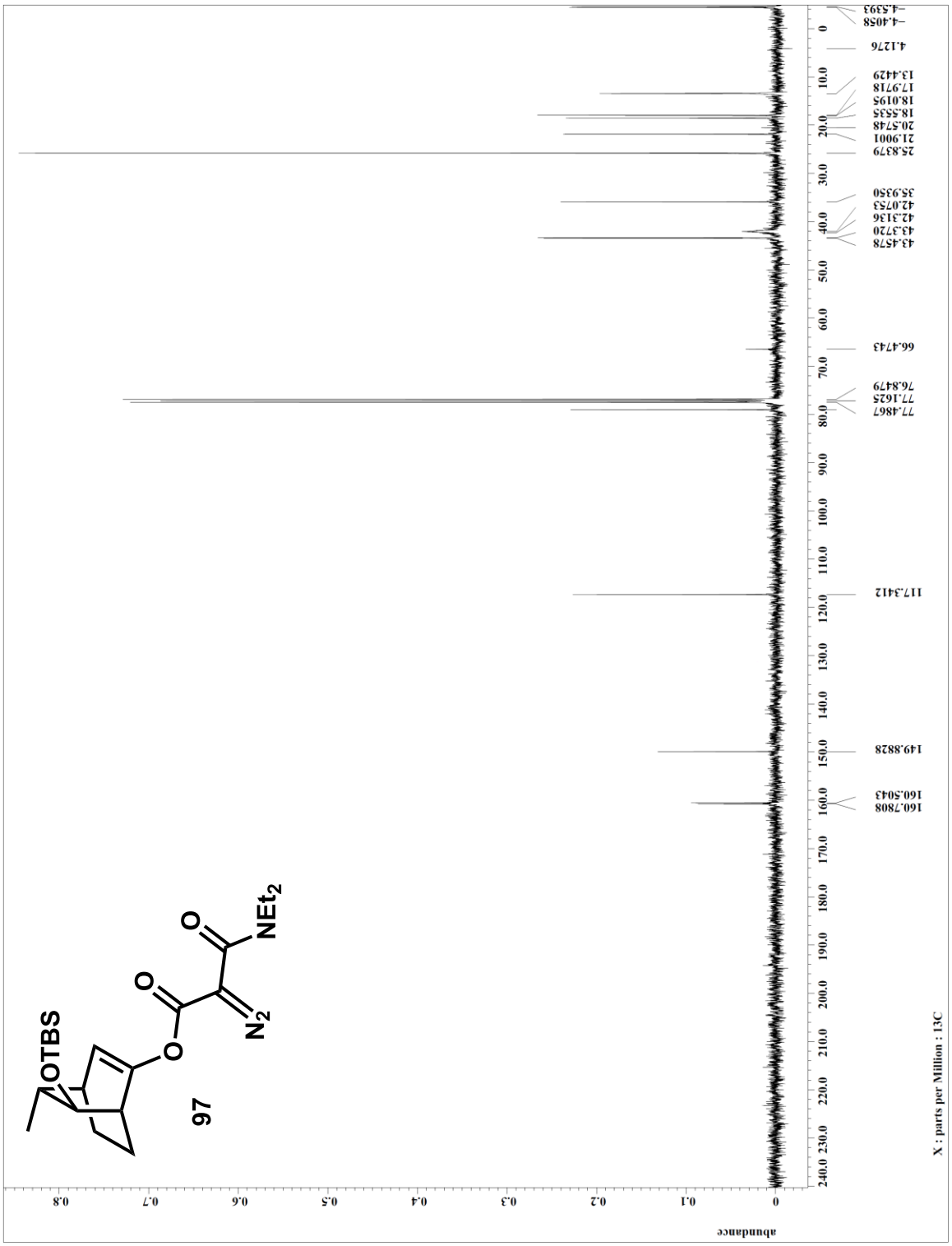


^{1}H NMR for compound **93**

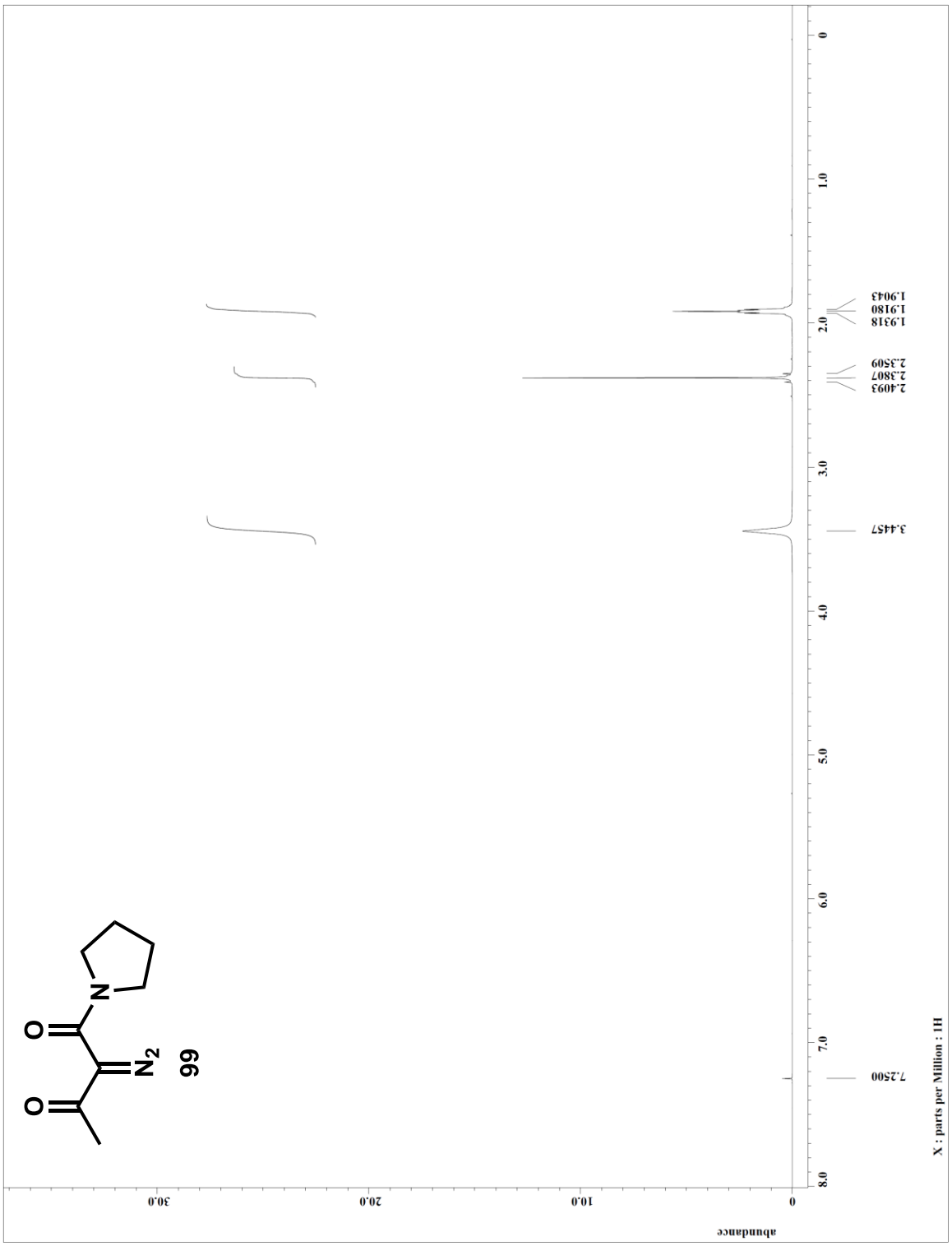


^{13}C NMR for compound **93**

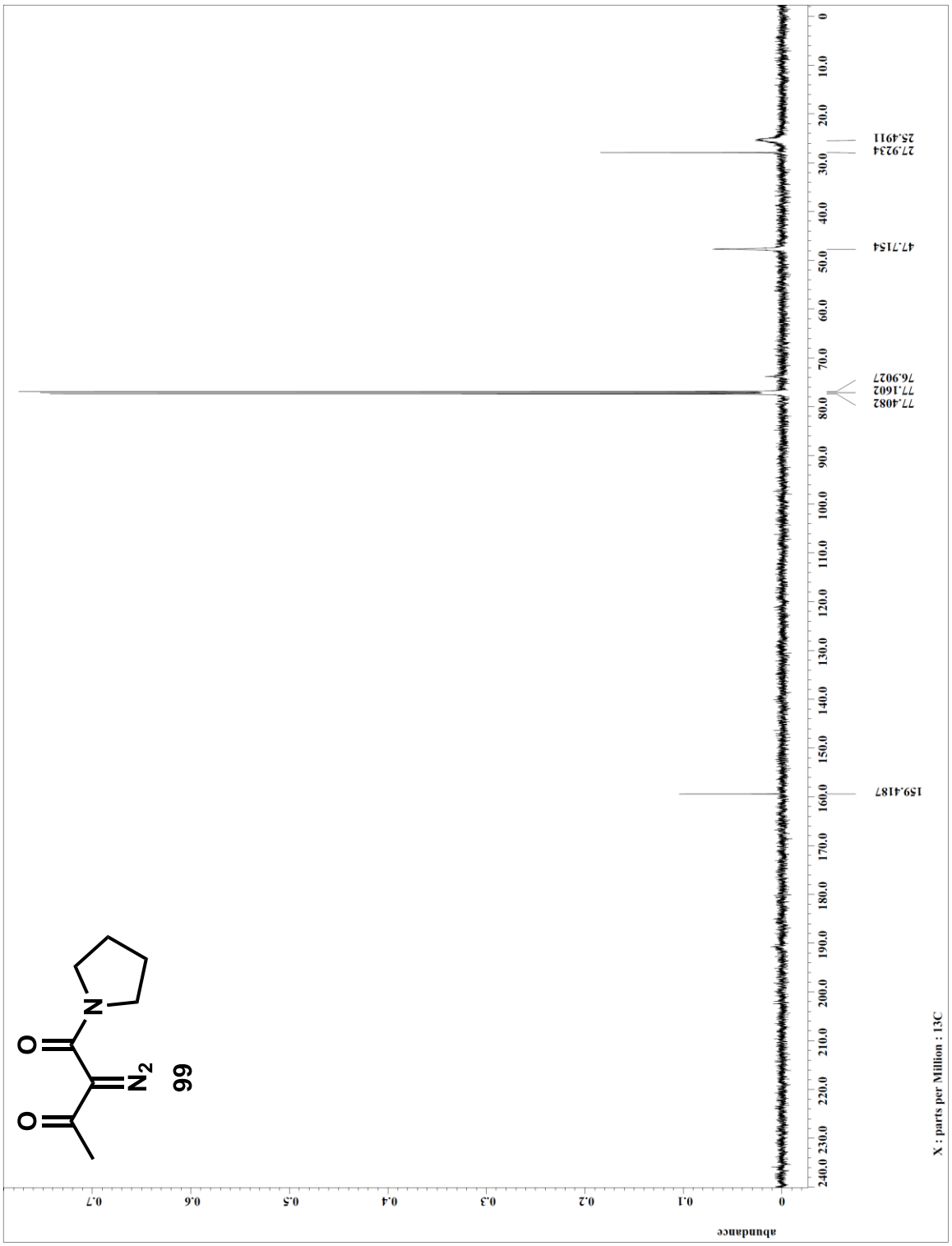
^{1}H NMR for compound **97**



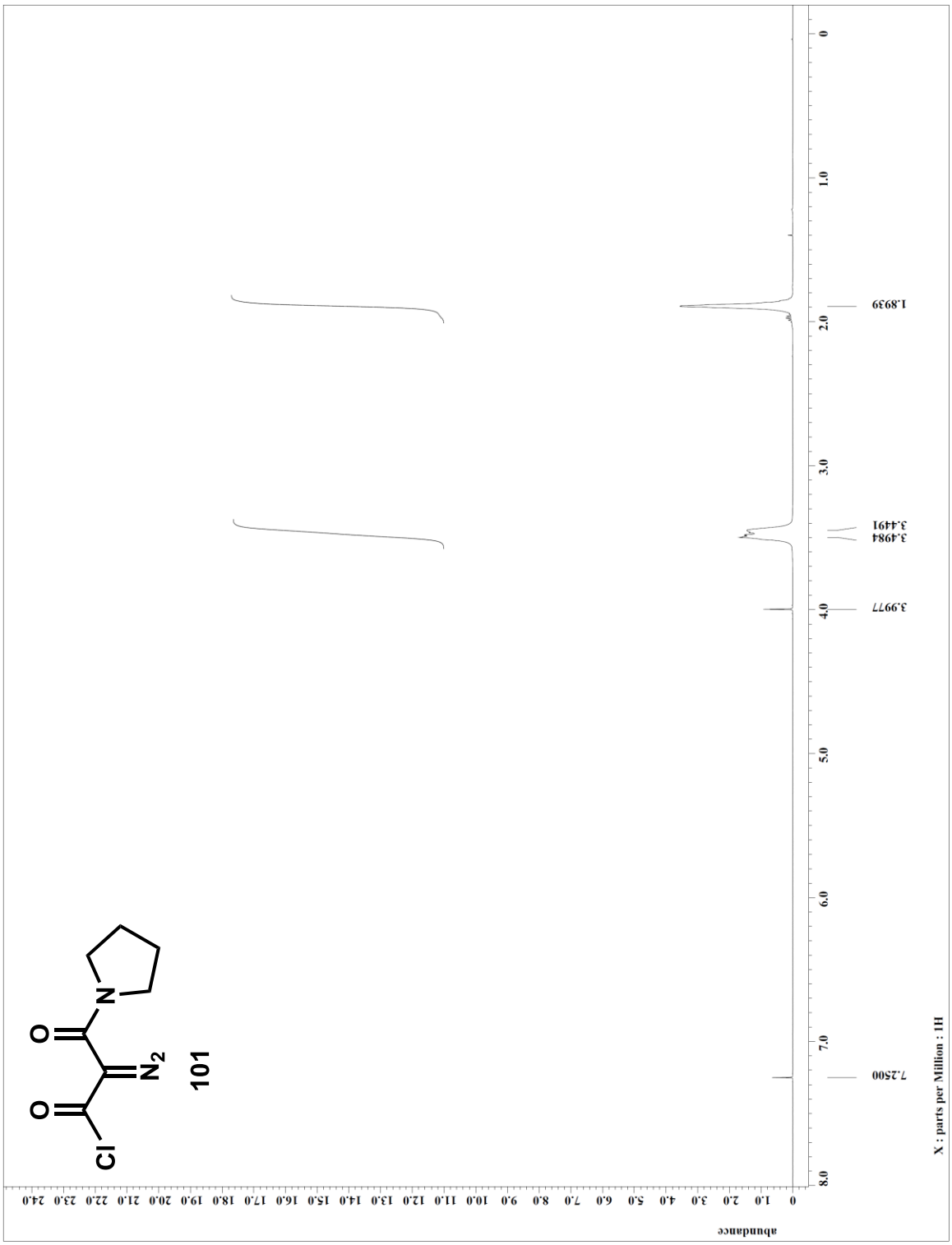
^{13}C NMR for compound **97**



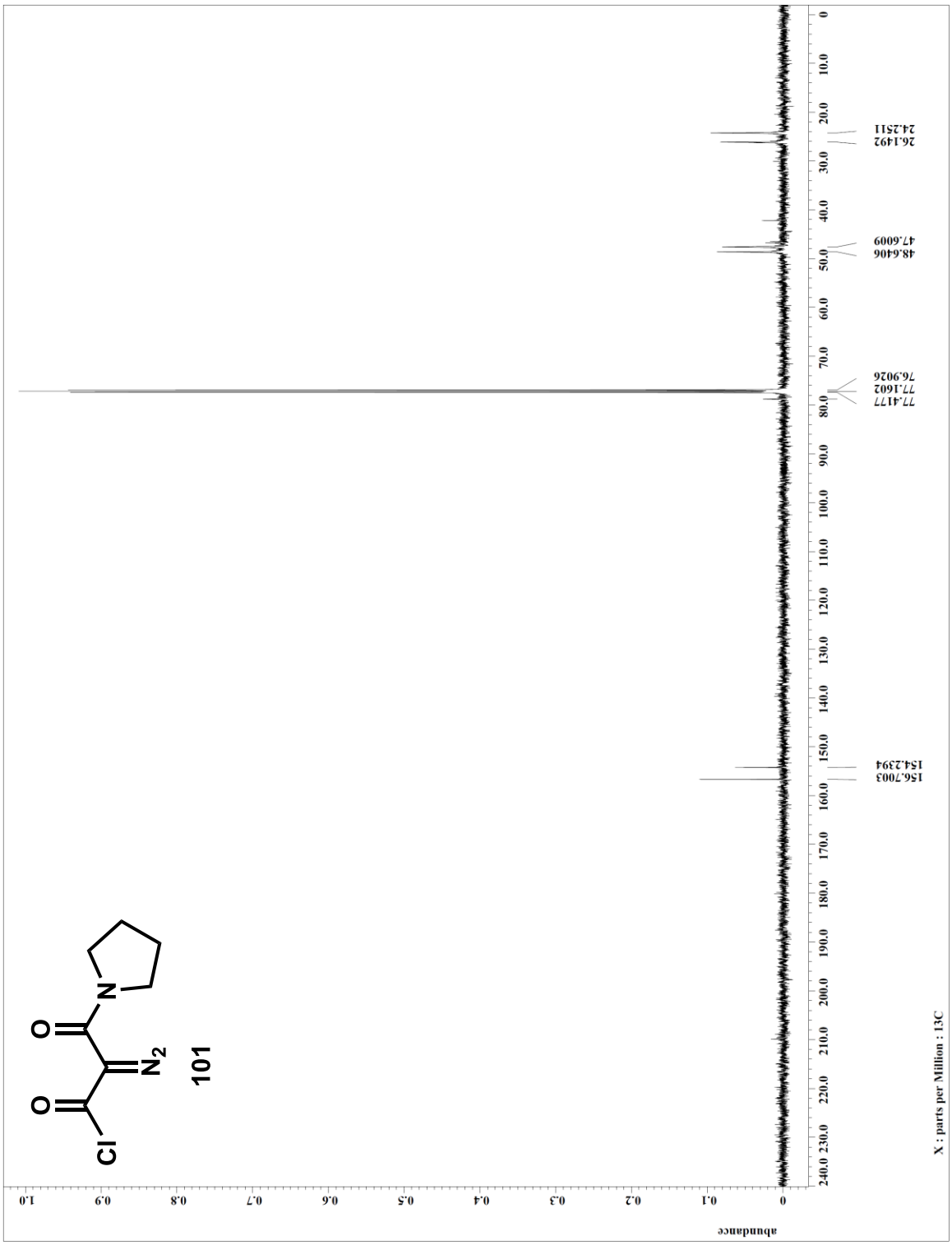
^{1}H NMR for compound **99**



^{13}C NMR for compound **99**

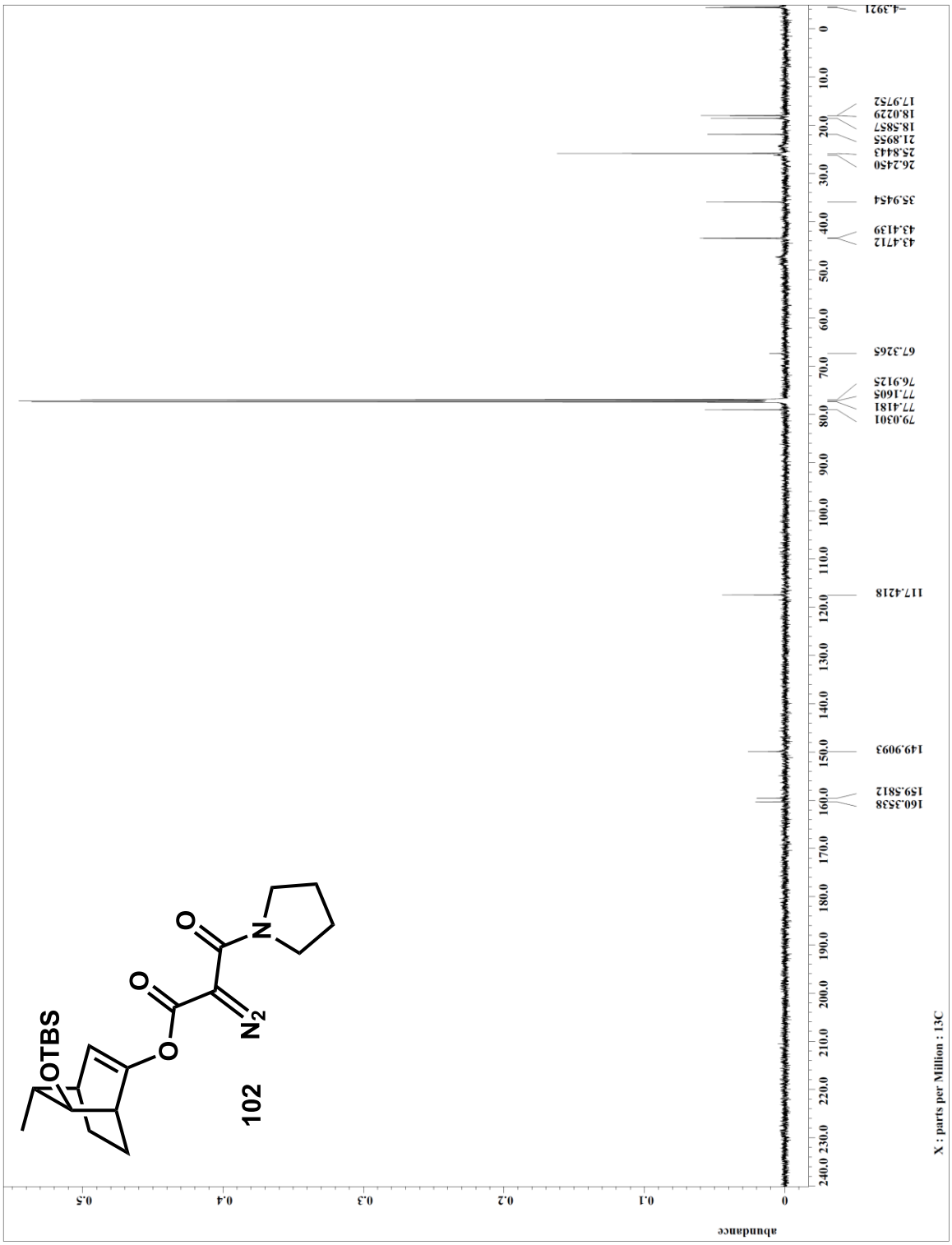


^{1}H NMR for compound **101**

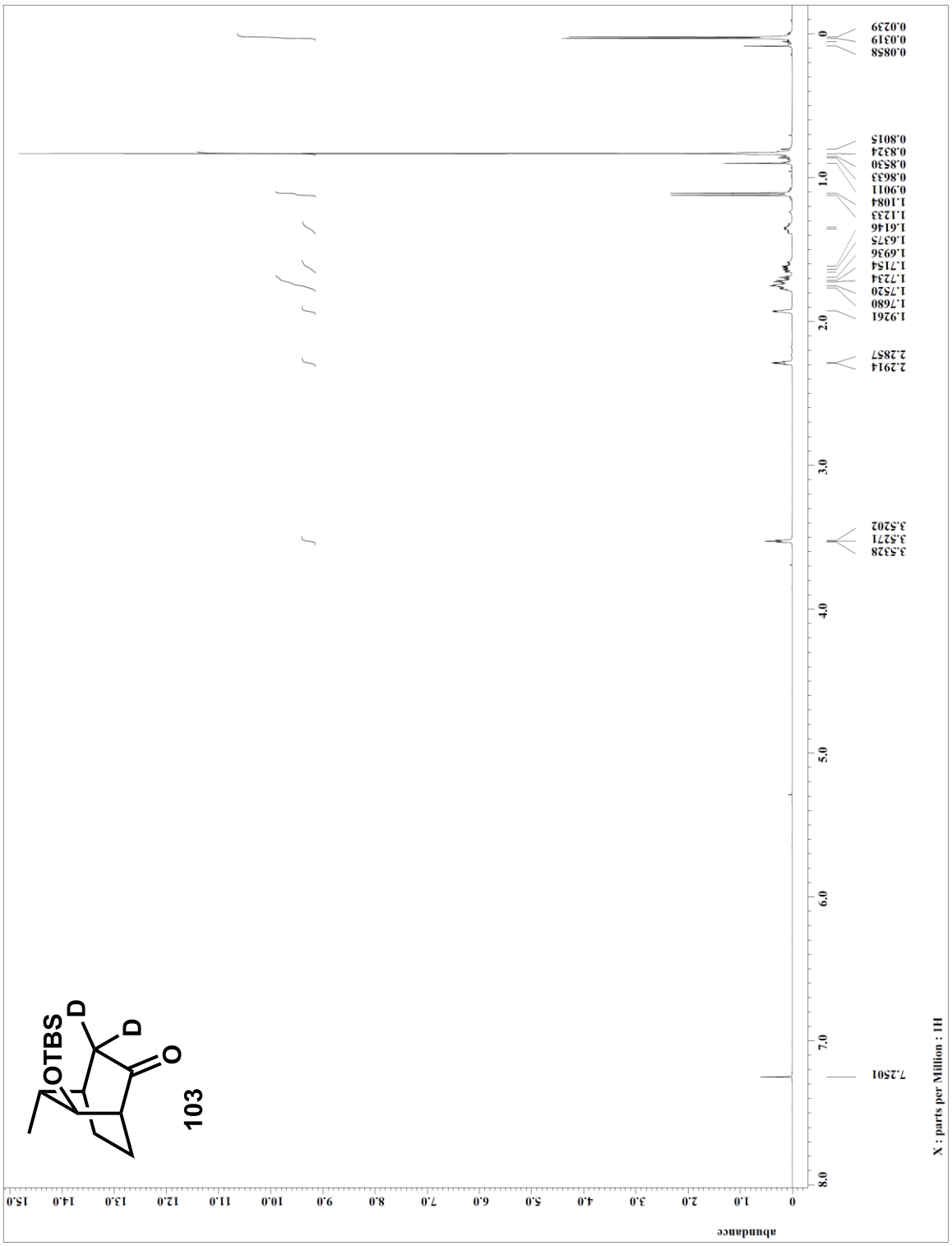


^{13}C NMR for compound **101**

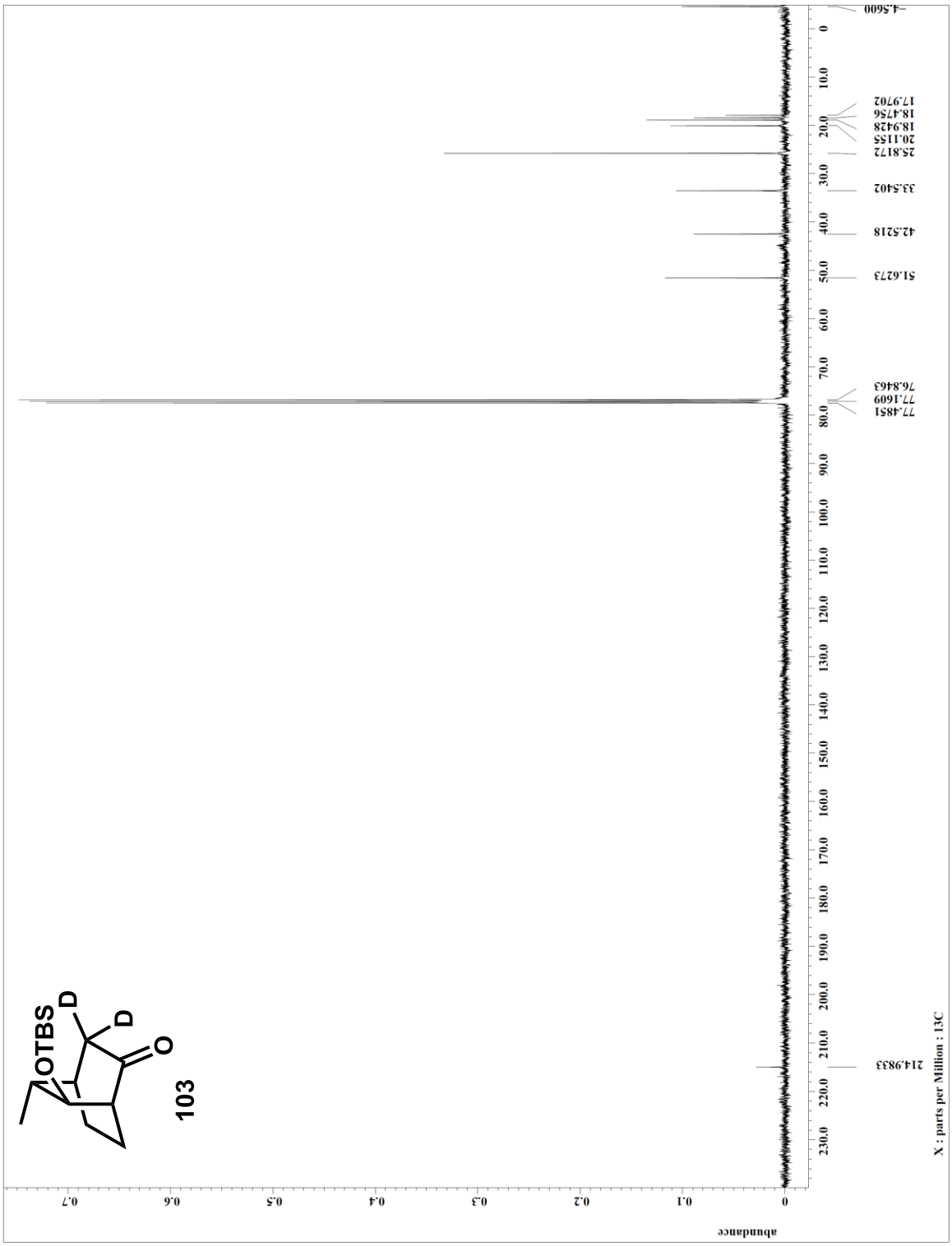
^{1}H NMR for compound **102**



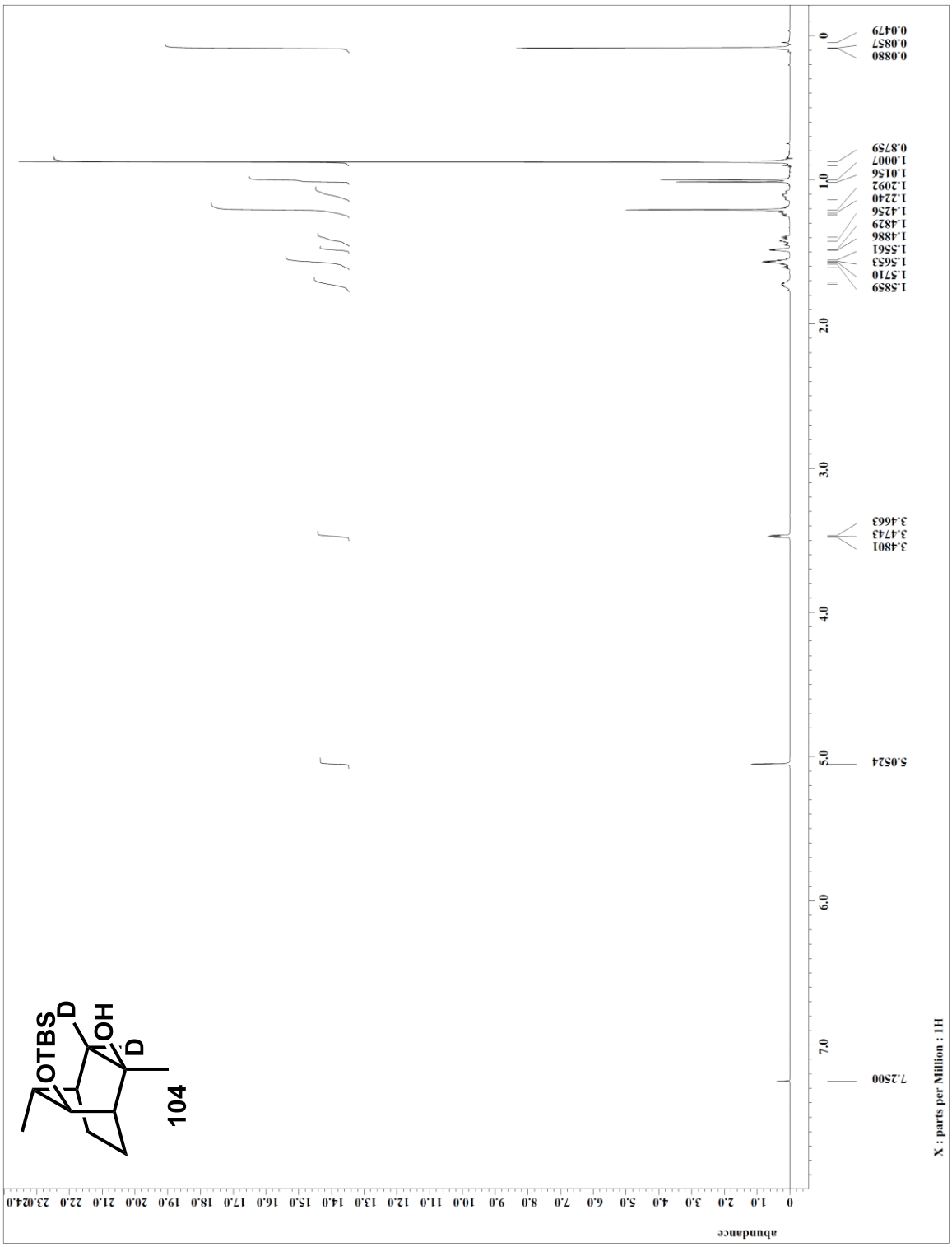
^{13}C NMR for compound **102**



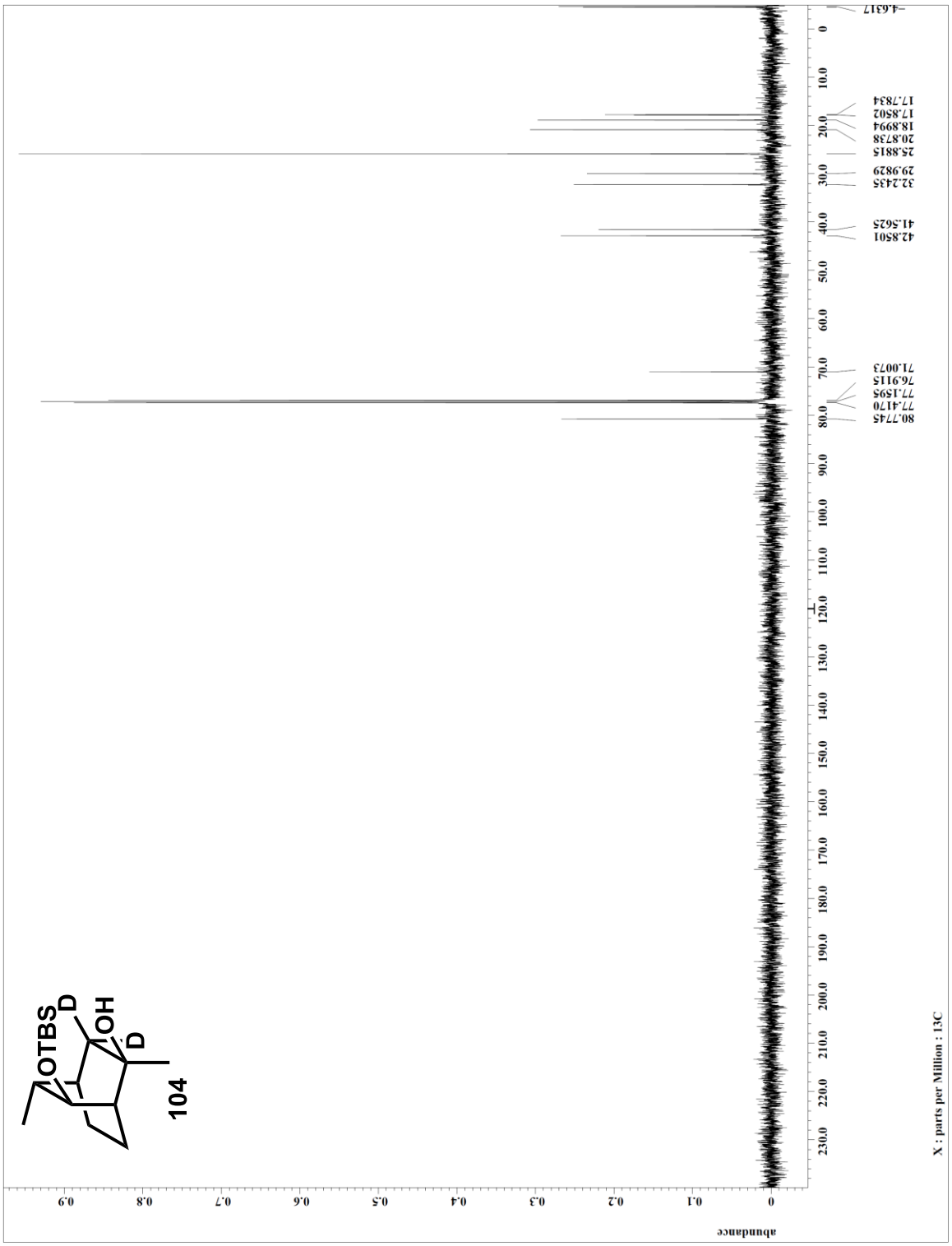
^{1}H NMR for compound **103**



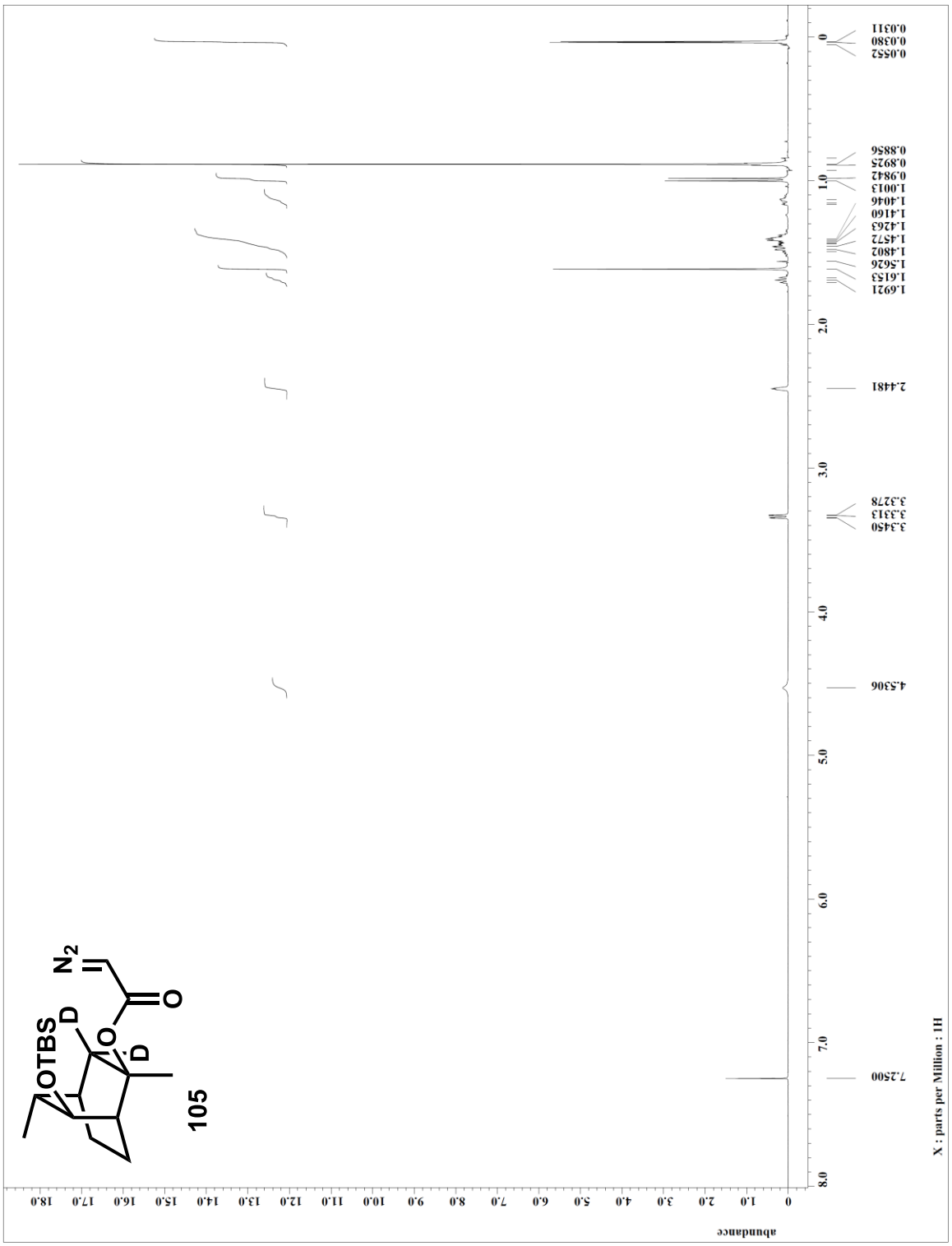
^{13}C NMR for compound **103**



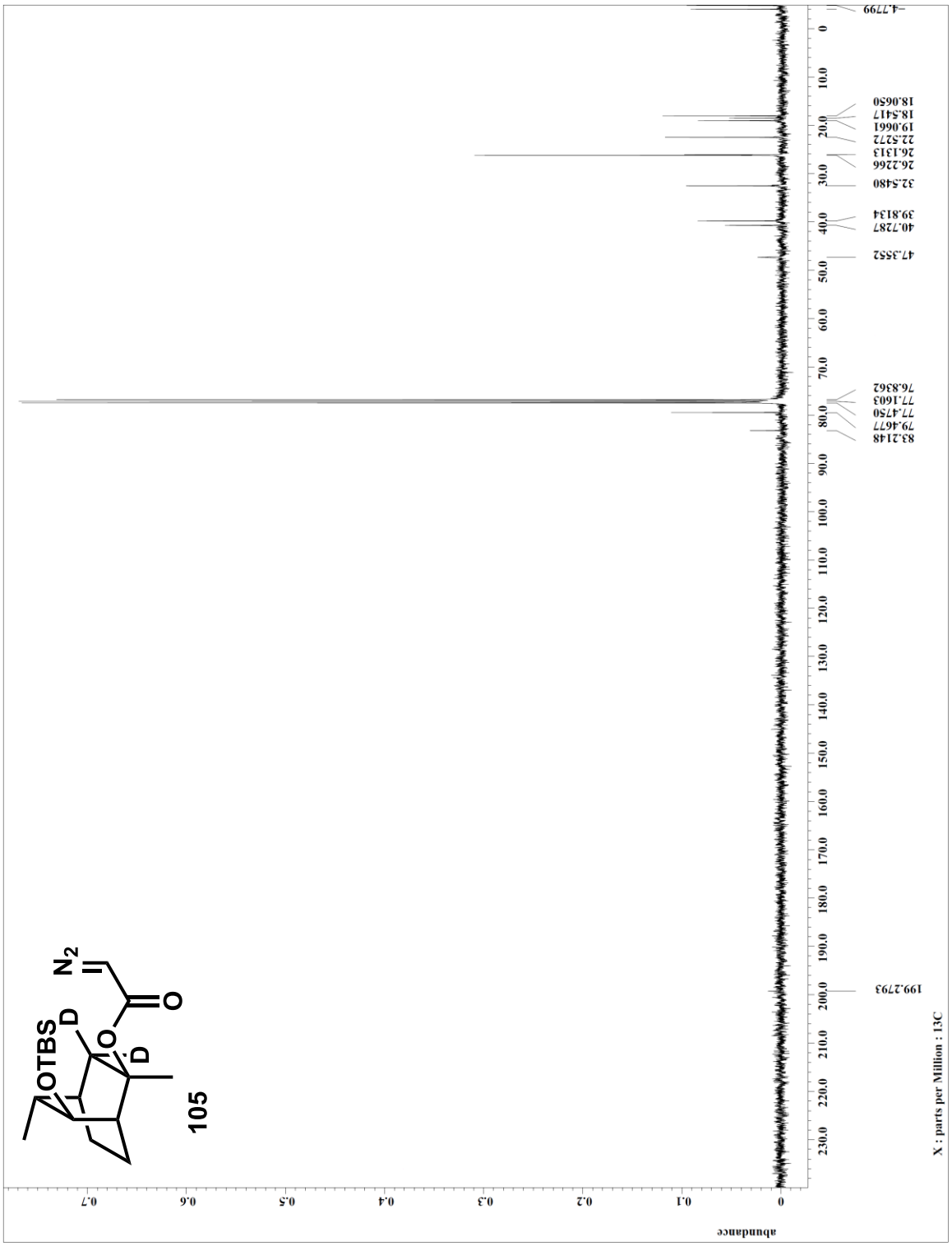
^{1}H NMR for compound **104**



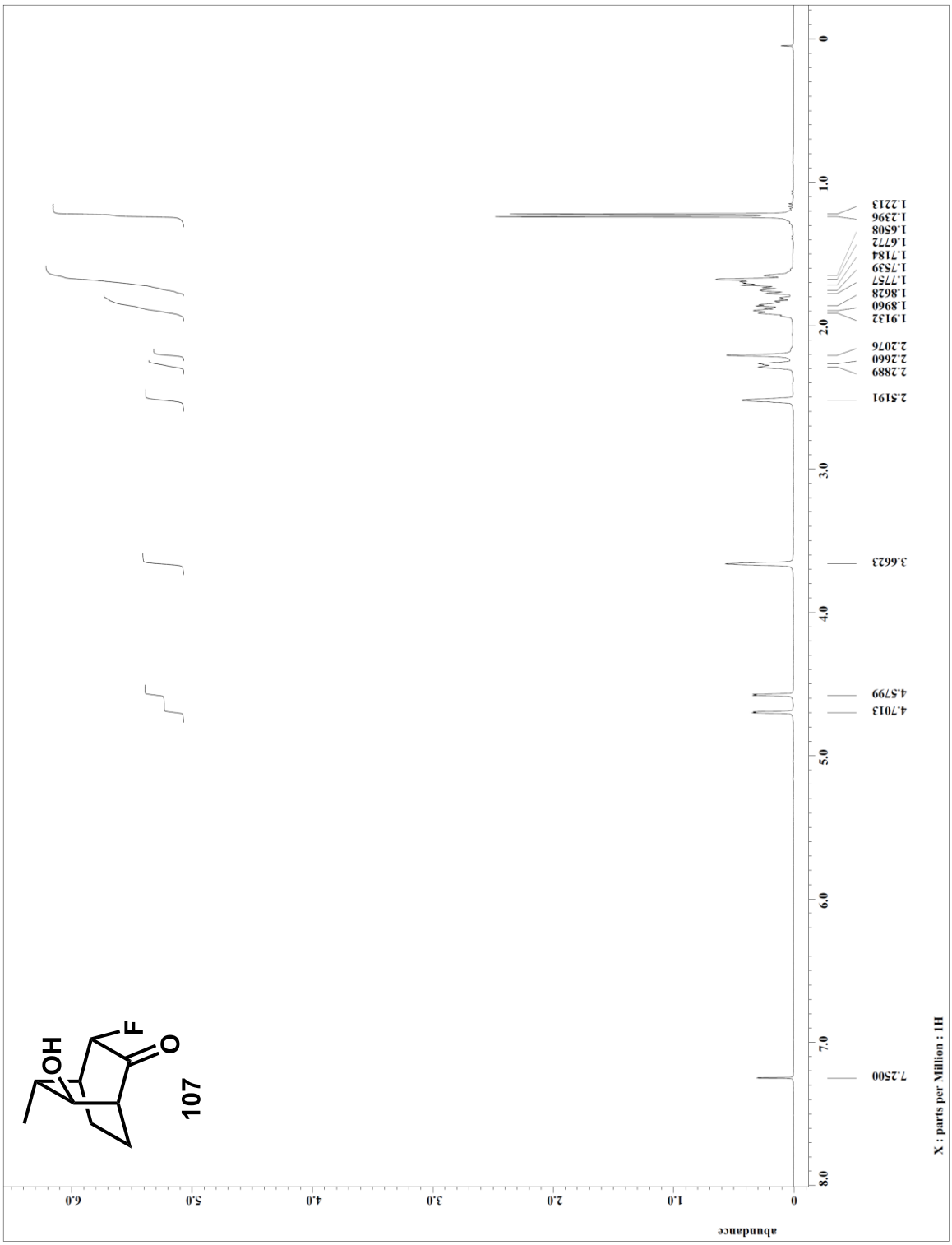
^{13}C NMR for compound **104**



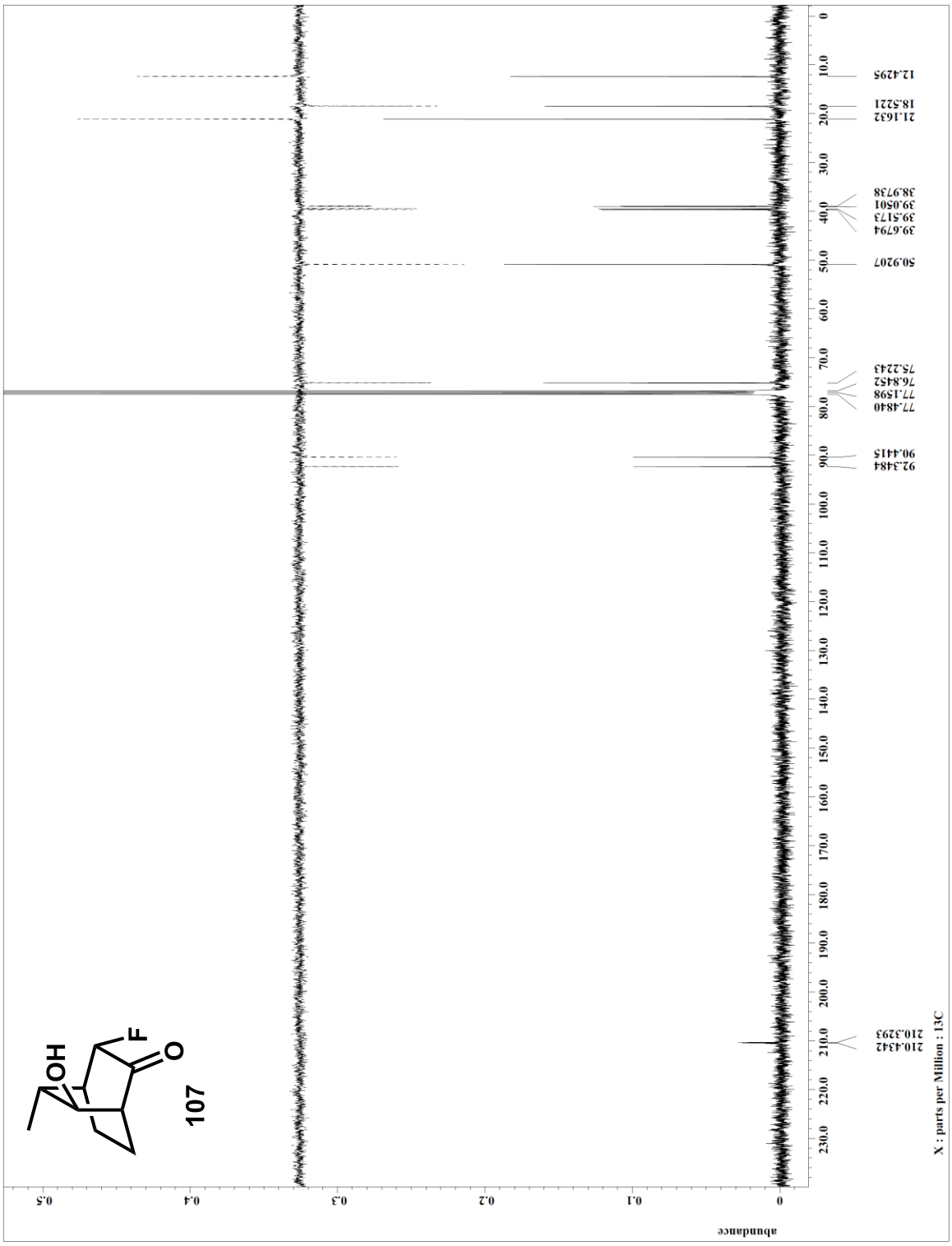
^{1}H NMR for compound **105**



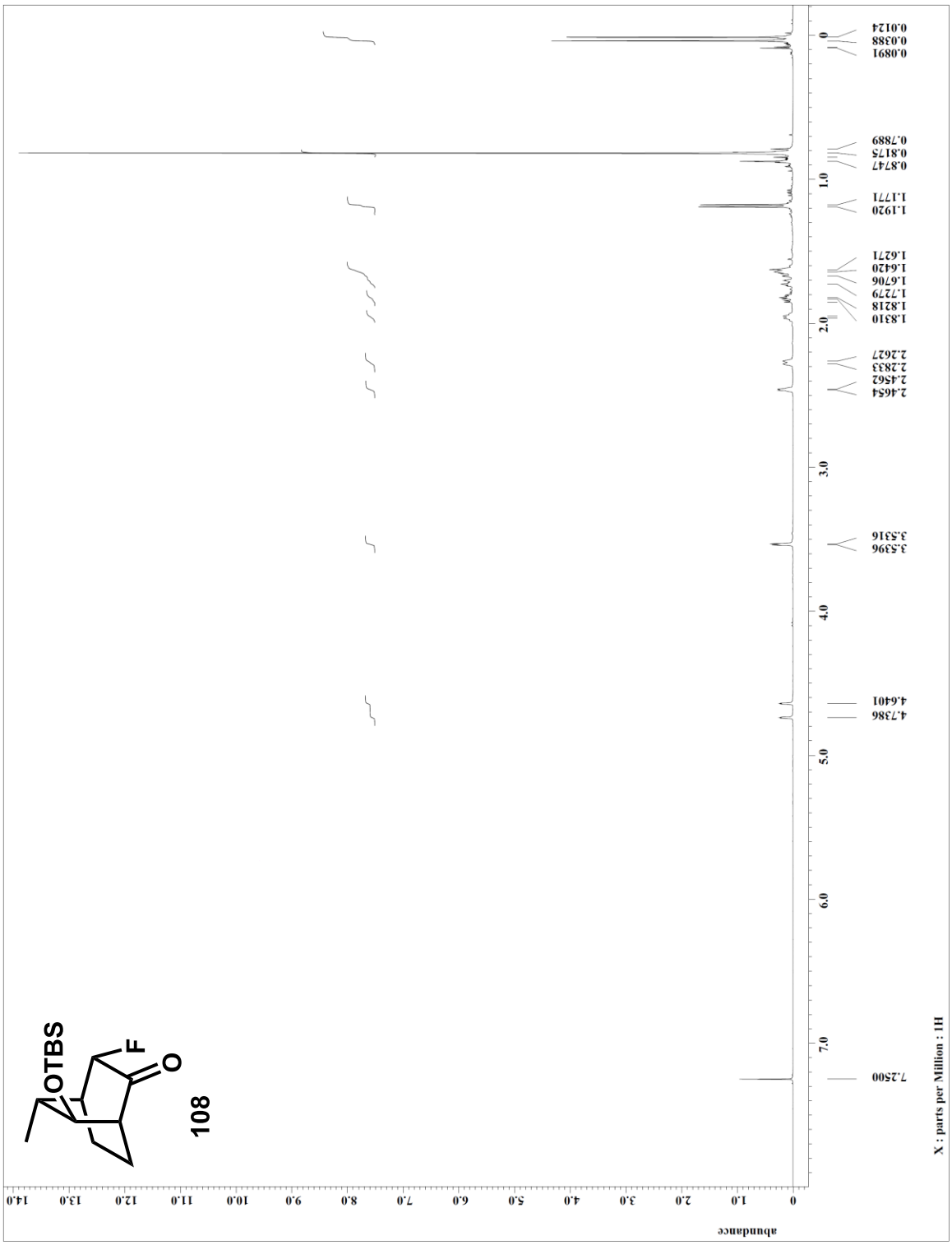
^{13}C NMR for compound **105**



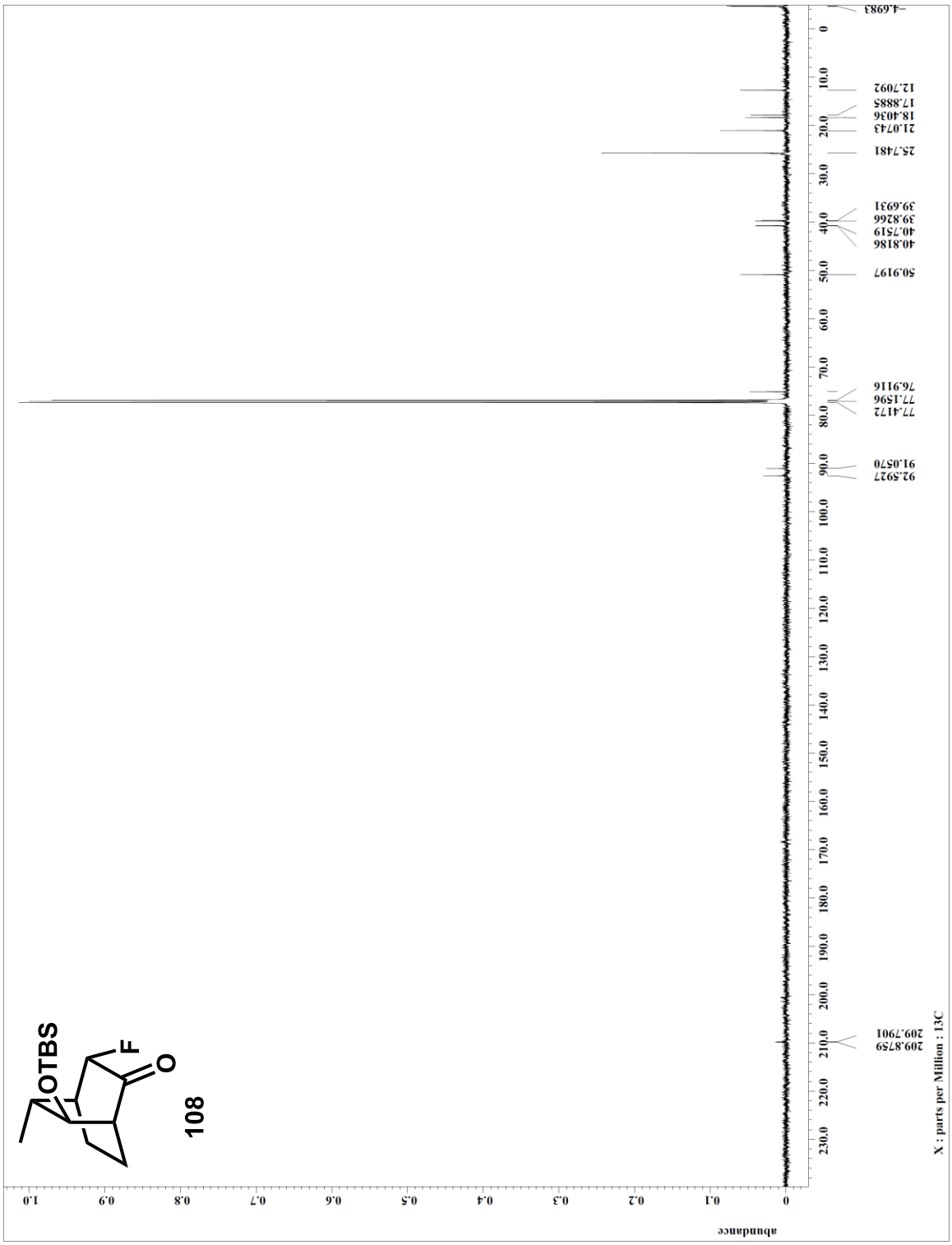
^{1}H NMR for compound **107**



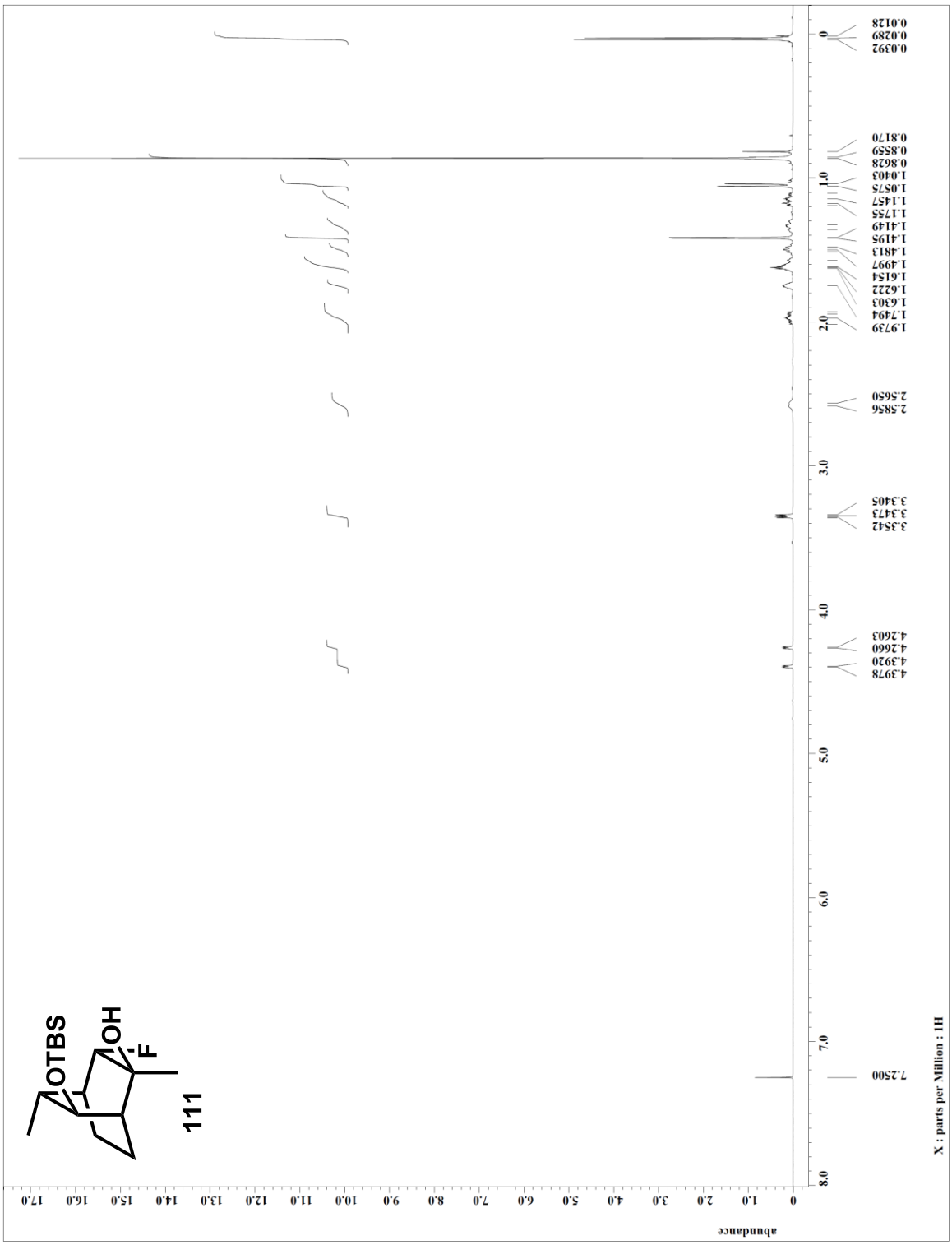
^{13}C NM and DEPT for compound **107**



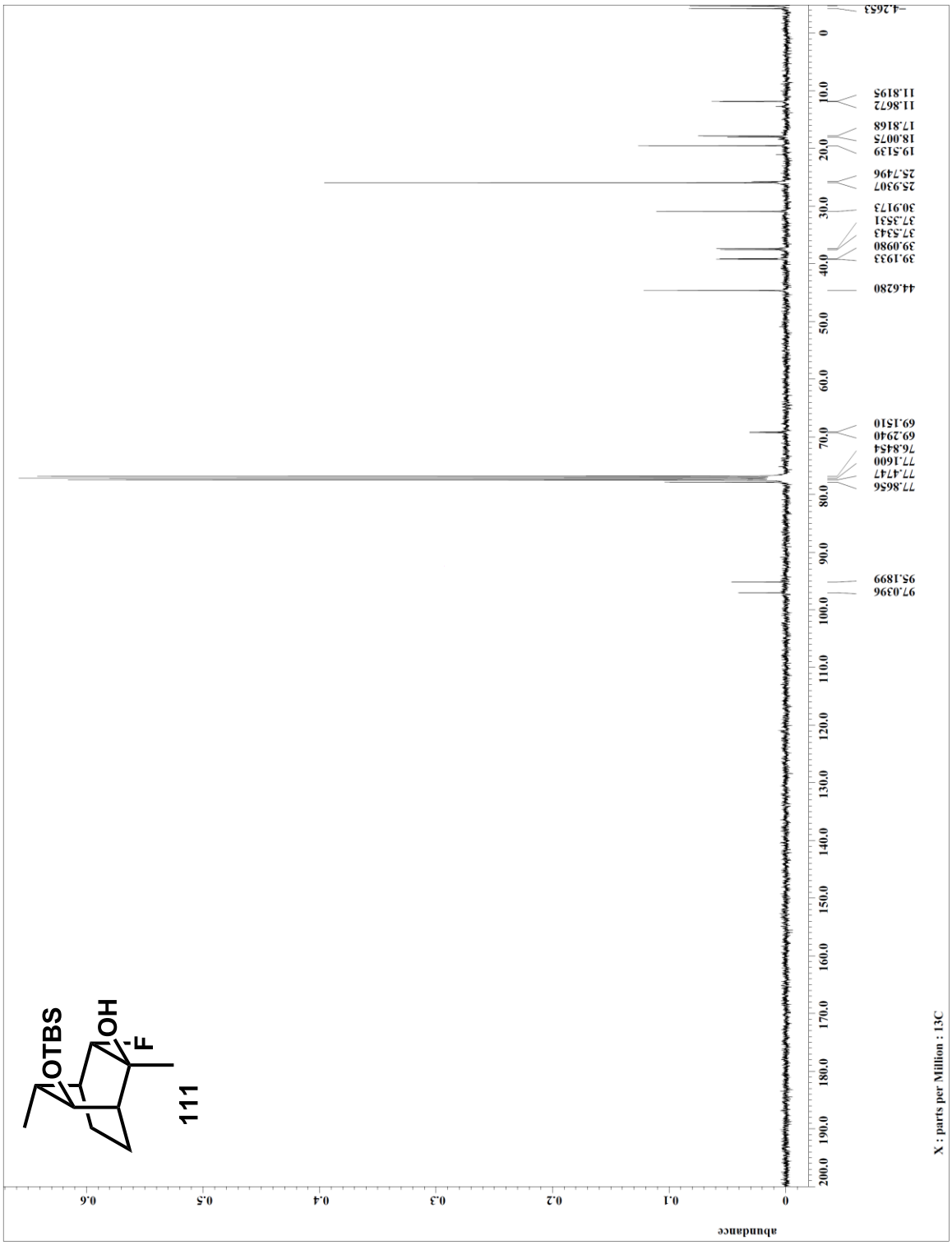
^{1}H NMR for compound **108**



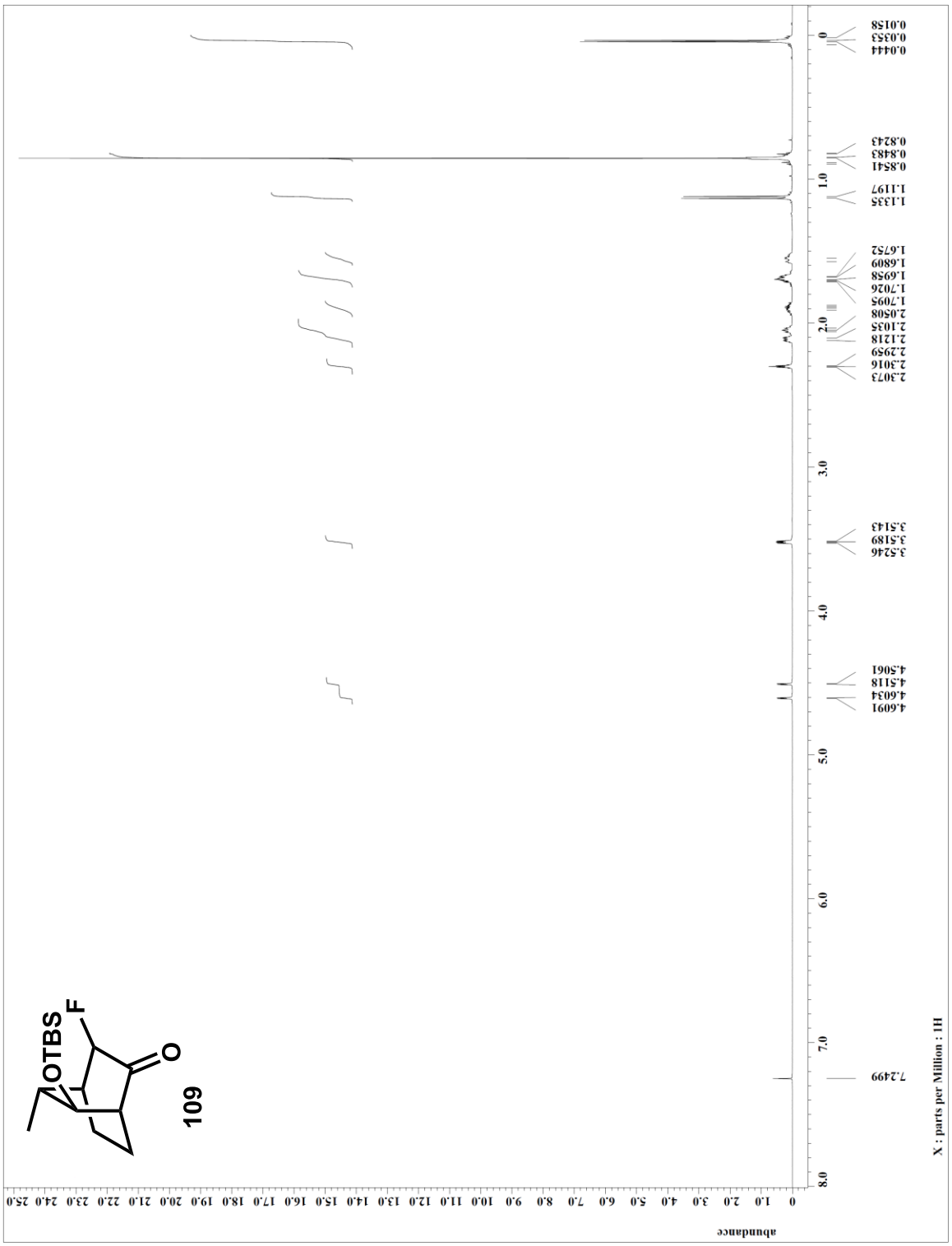
^{13}C NMR for compound **108**



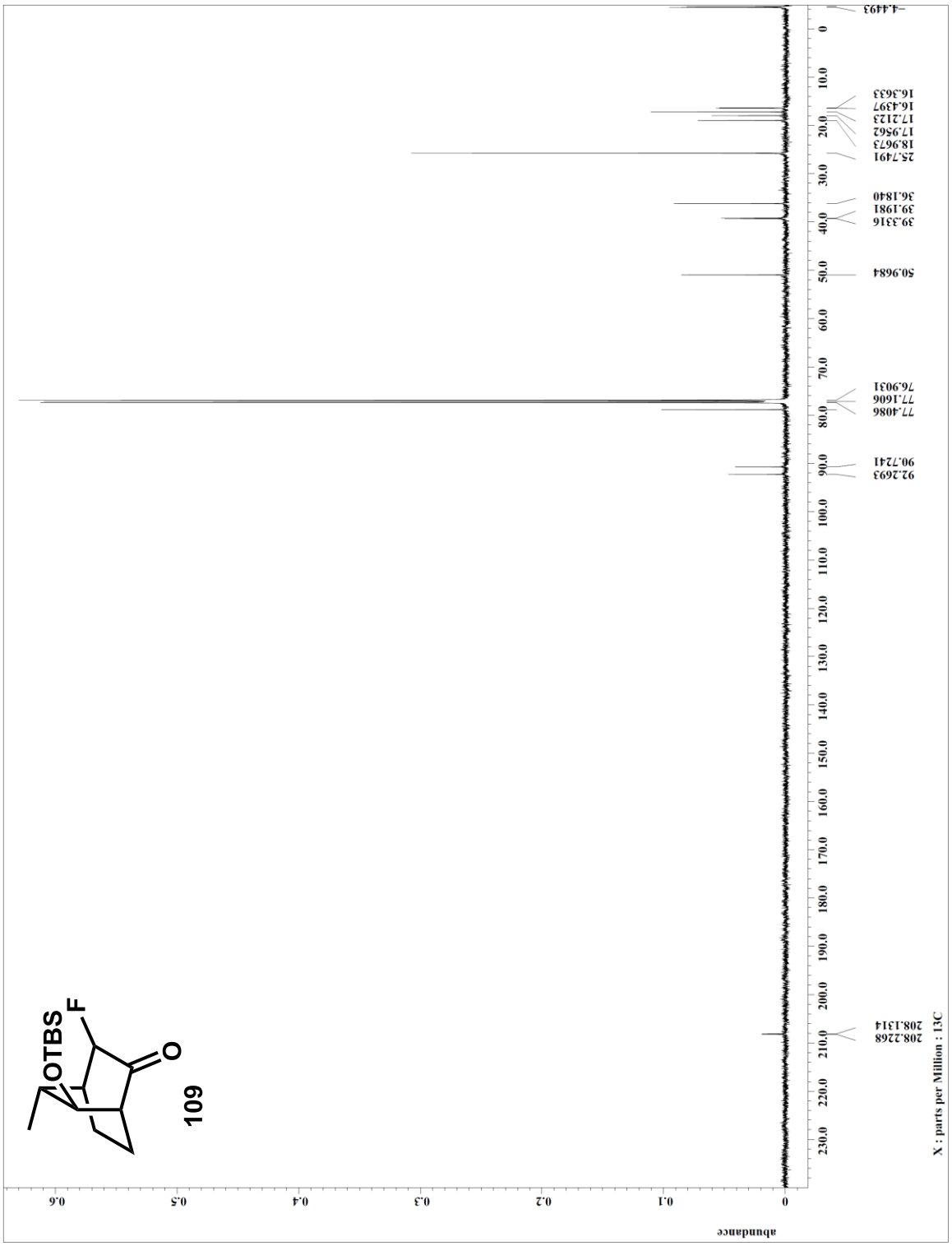
^{1}H NMR for compound **111**



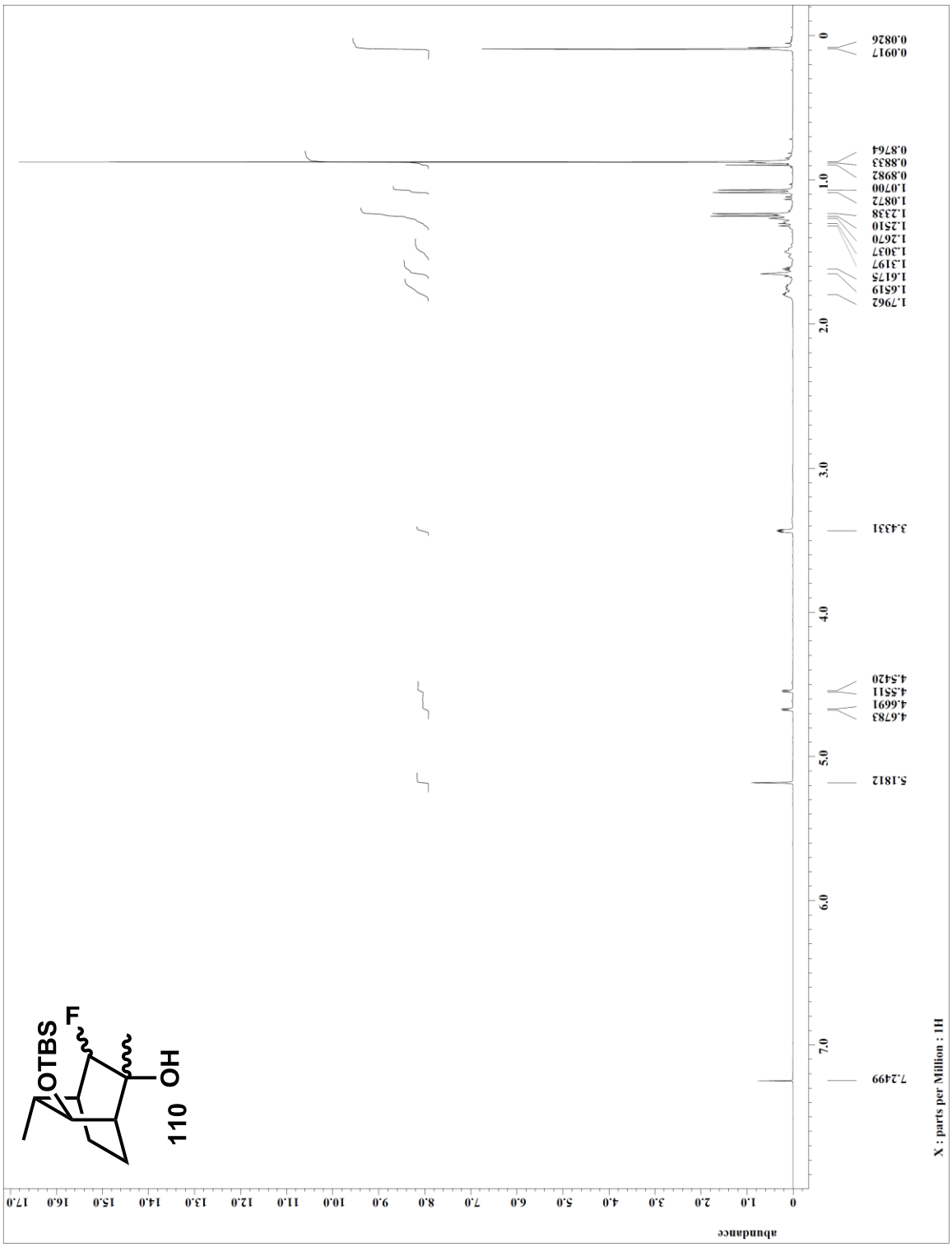
^{13}C NMR for compound **111**



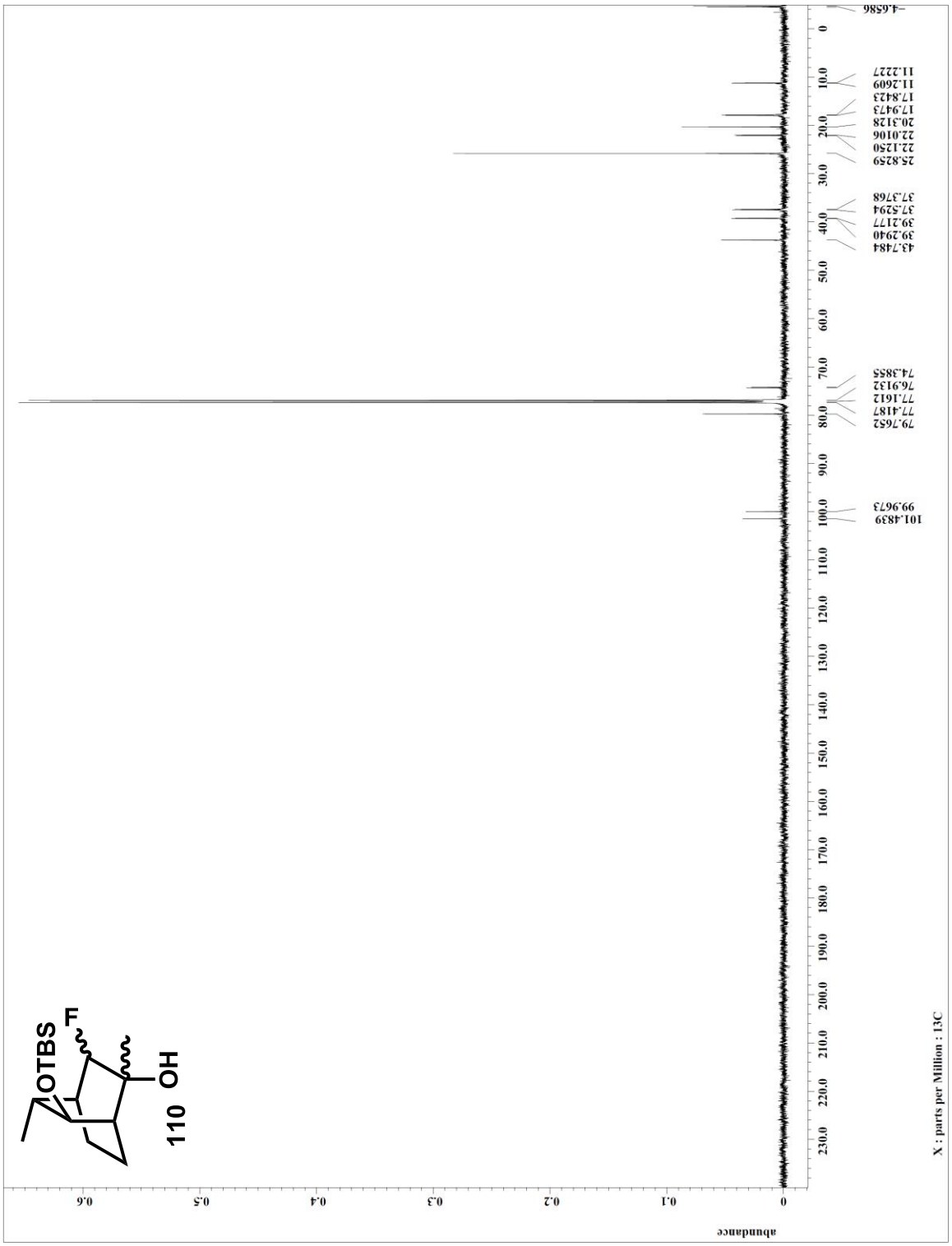
^{1}H NMR for compound **109**



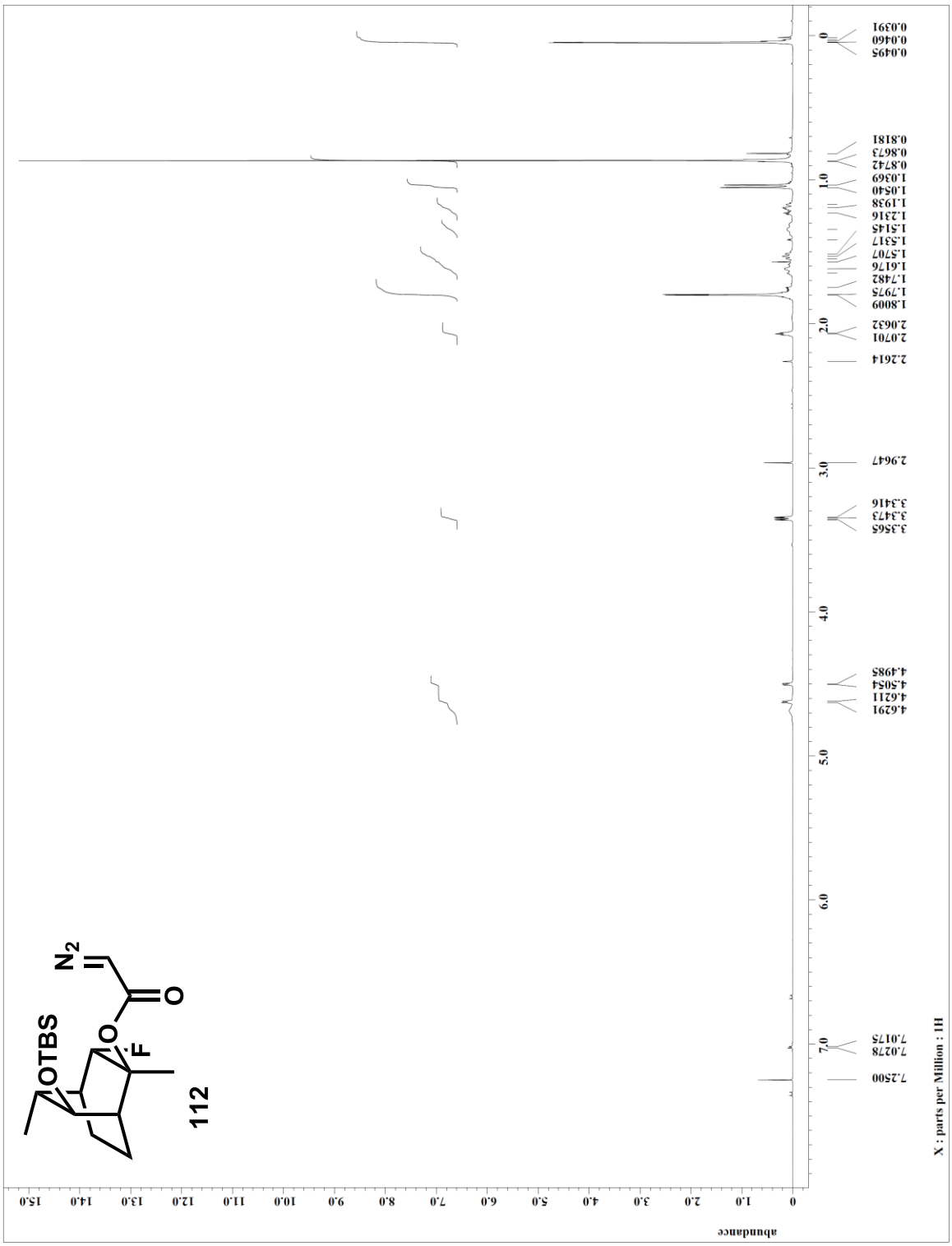
^{13}C NMR for compound **109**



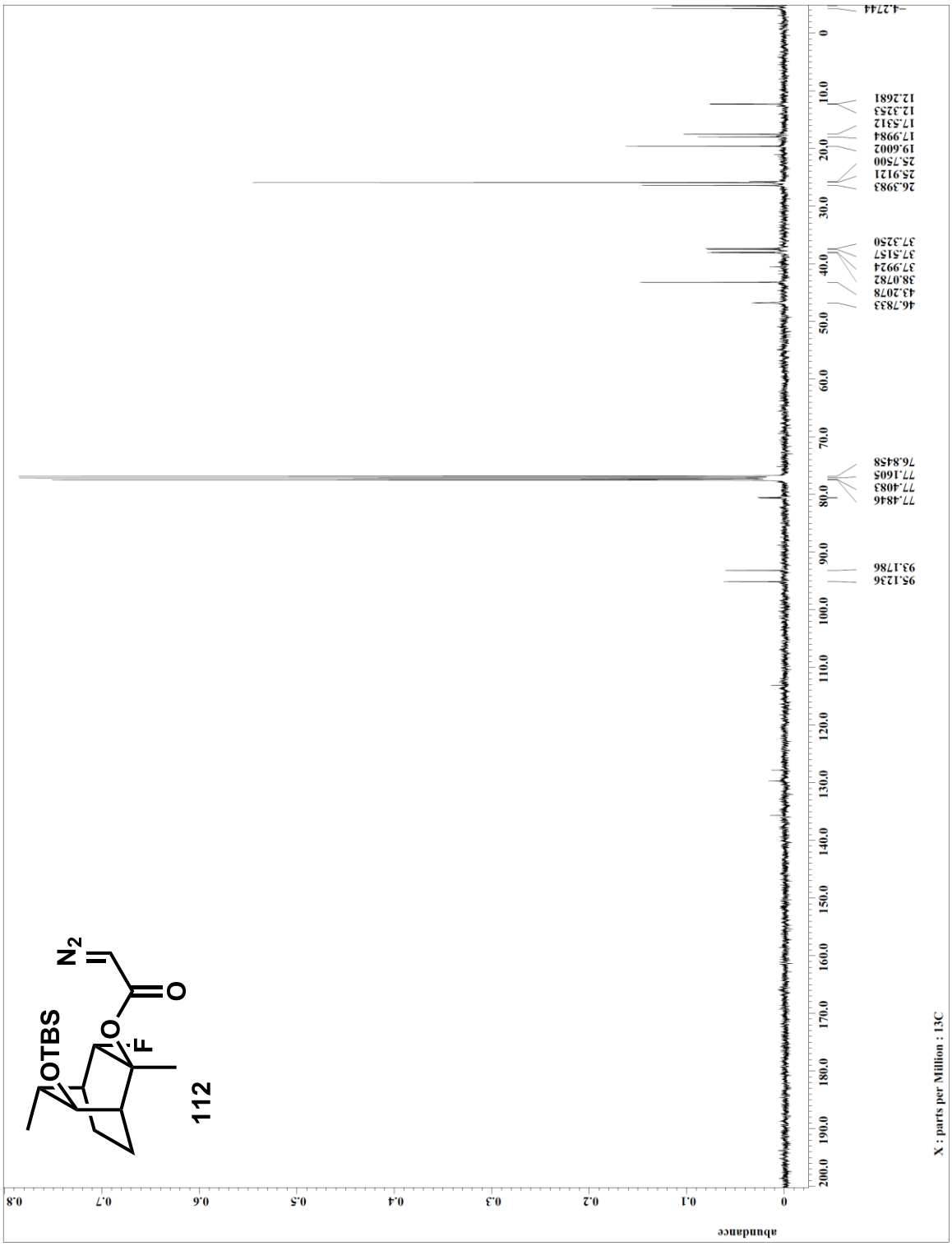
^{1}H NMR for compound **110**



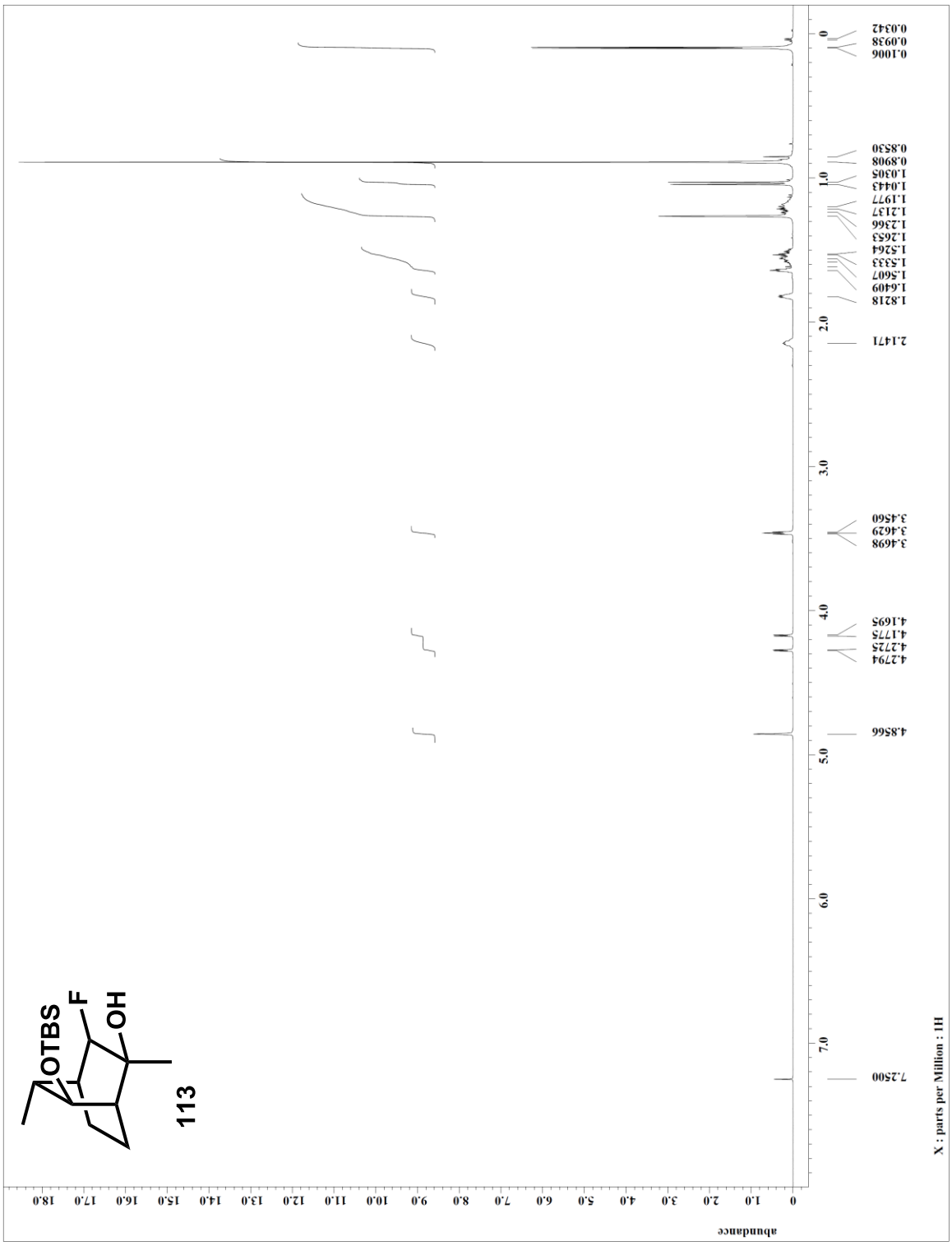
^{13}C NMR for compound **110**



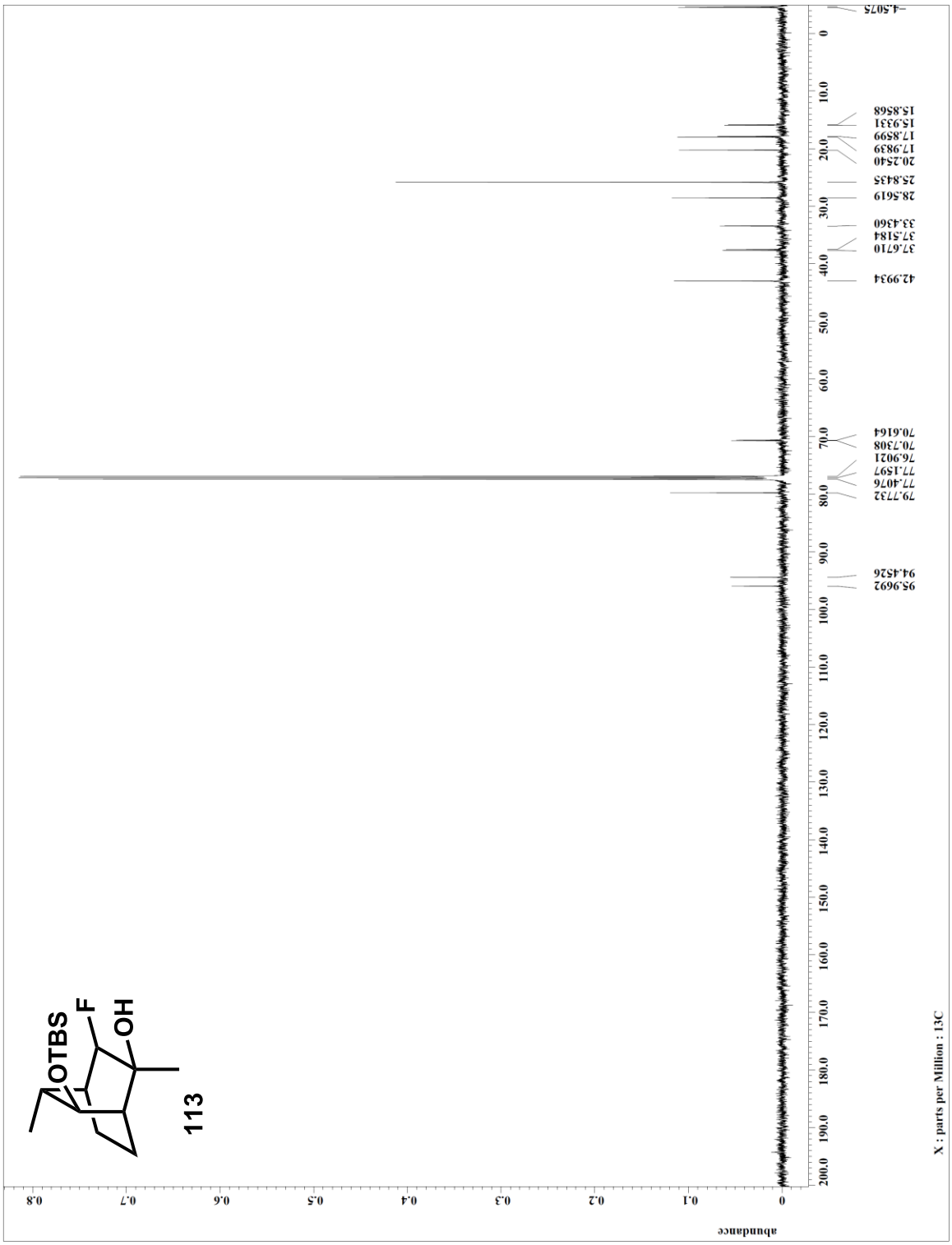
^{1}H NMR for compound **112**



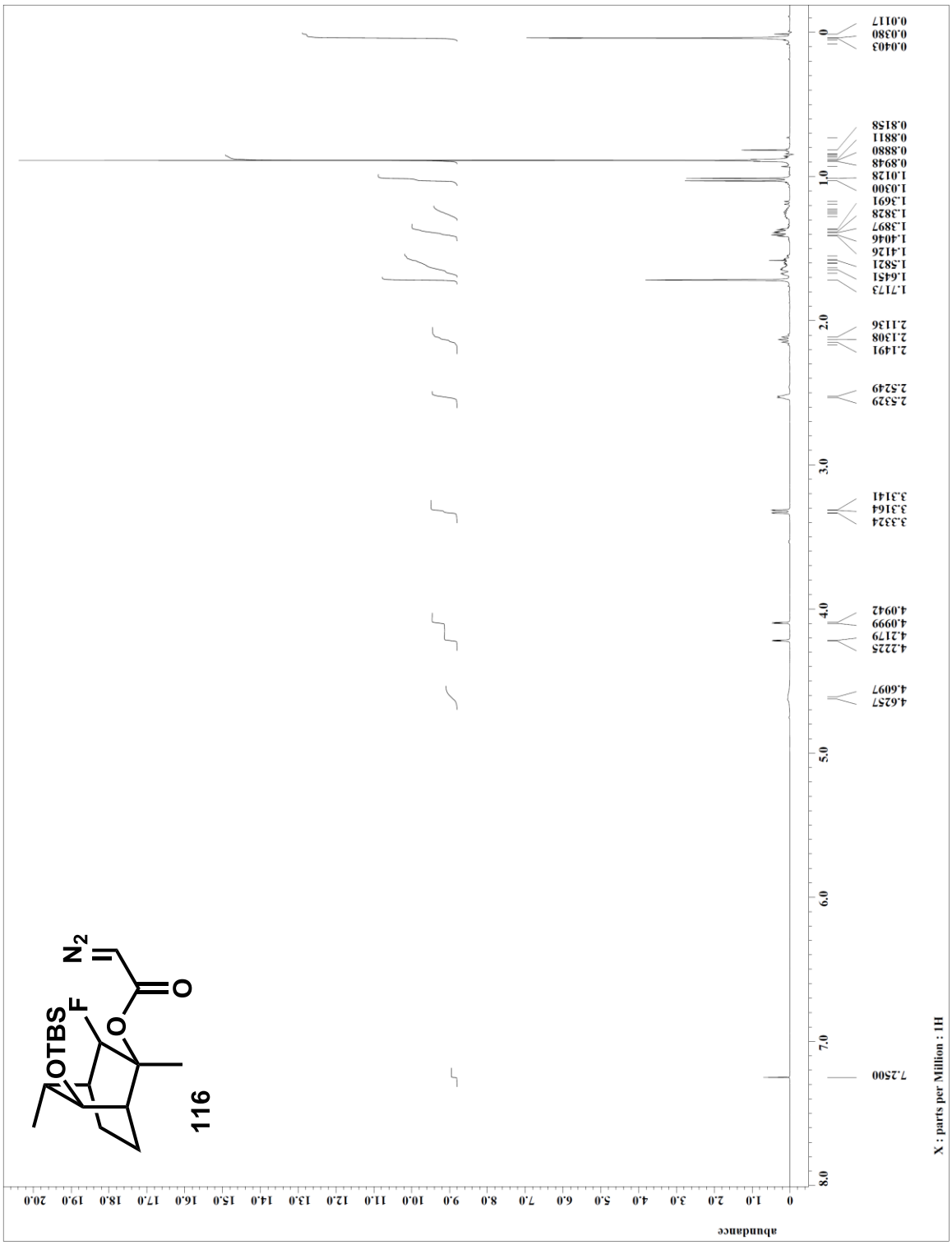
^{13}C NMR for compound **112**



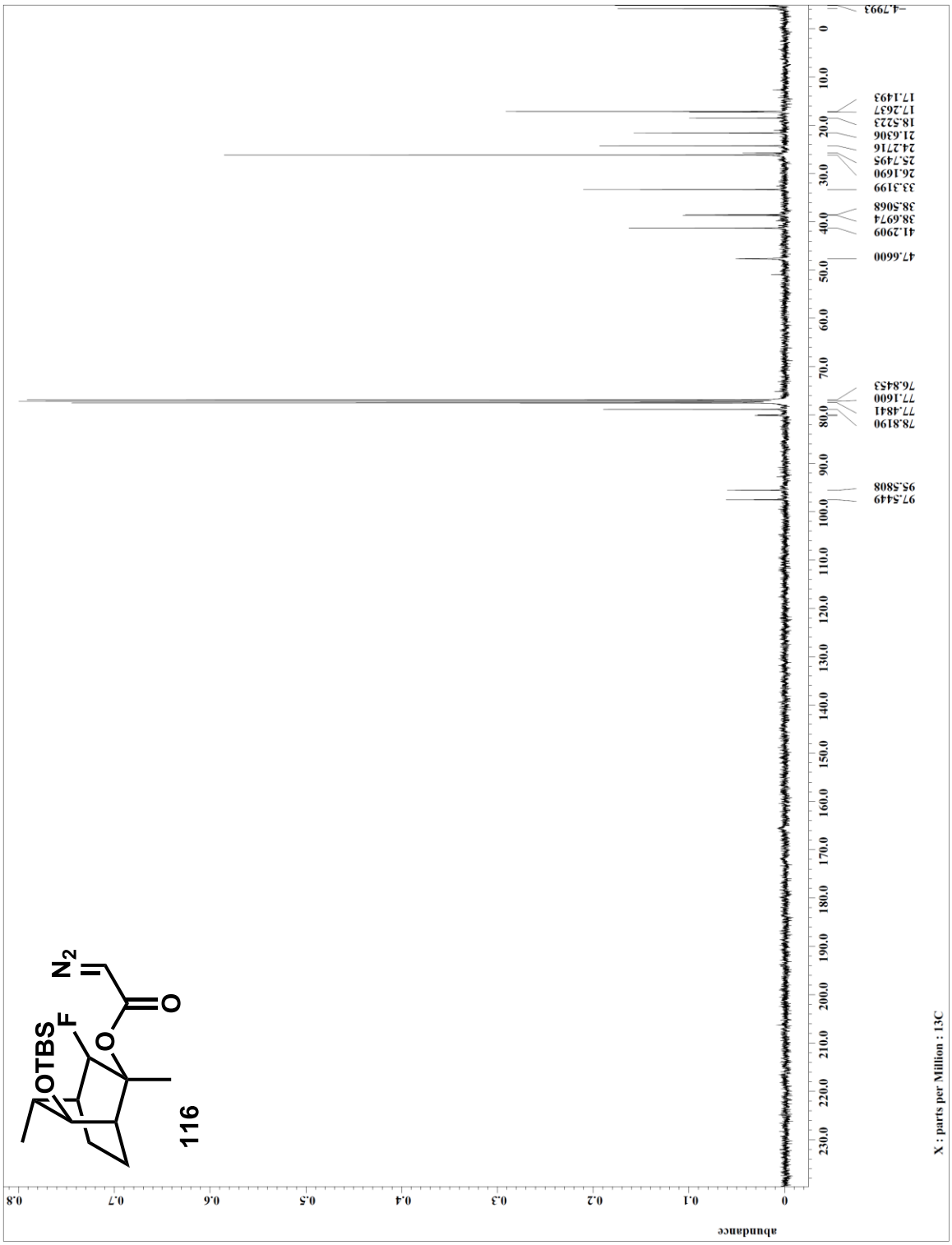
^{1}H NMR for compound **113**



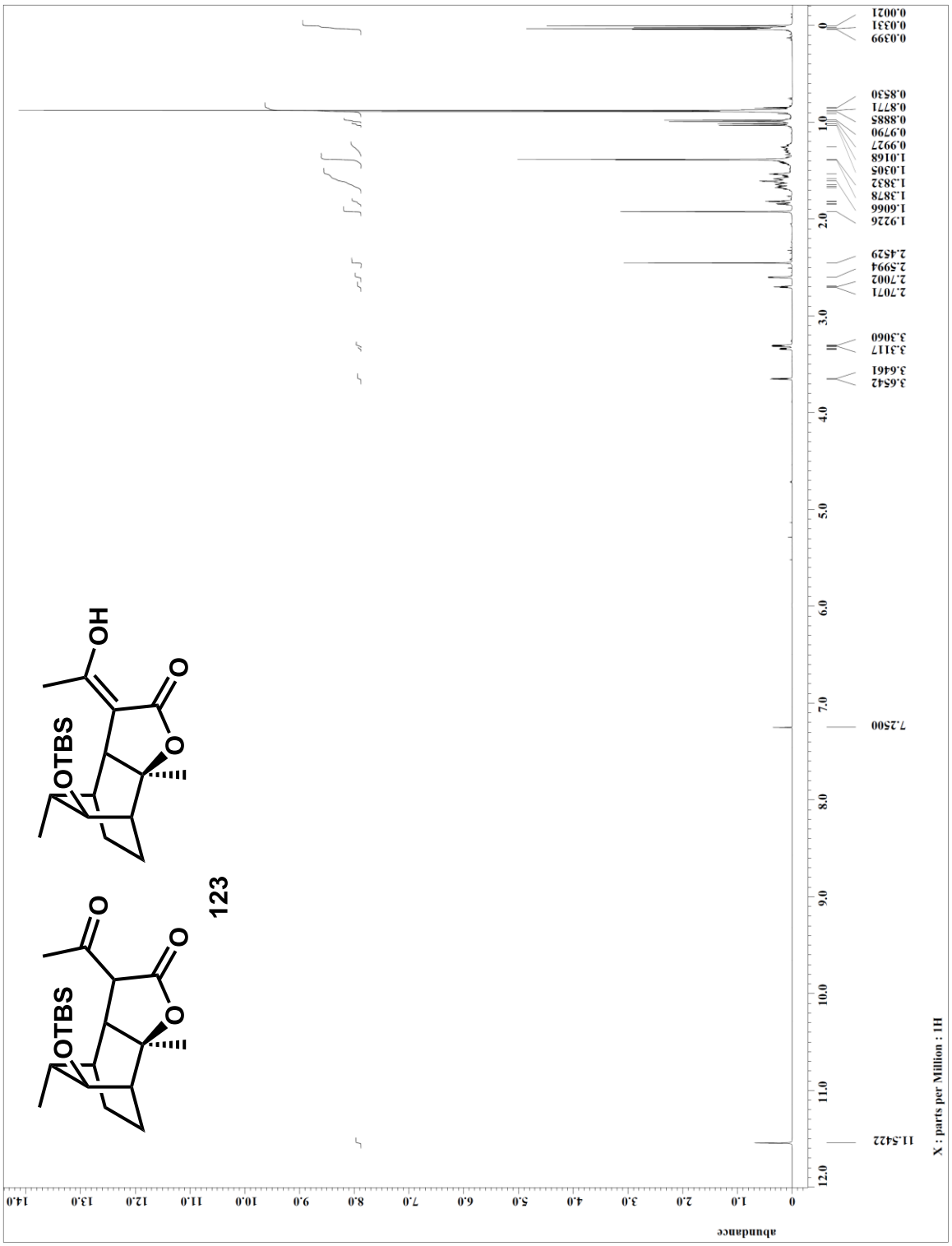
^{13}C NMR for compound **113**



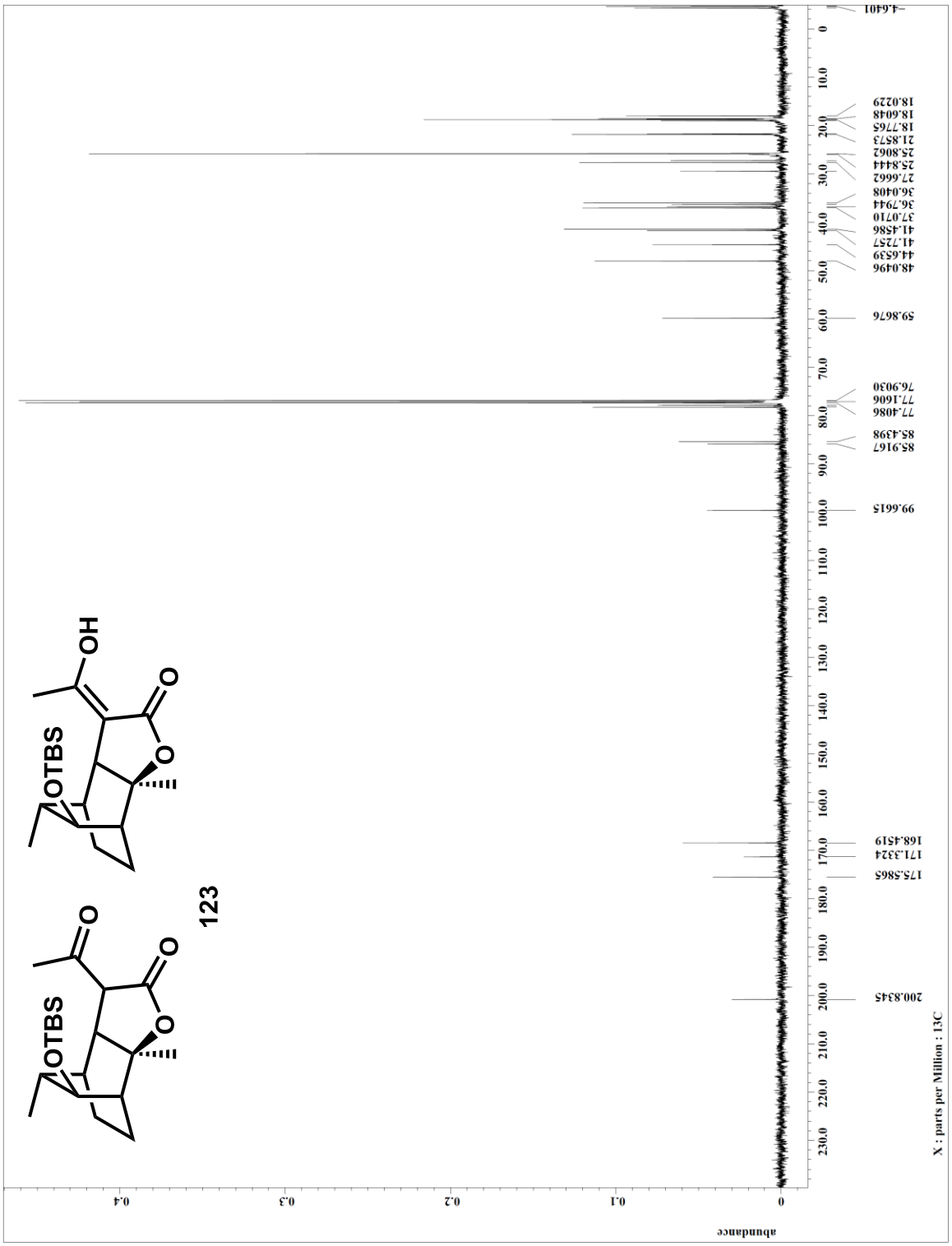
^{1}H NMR for compound **116**



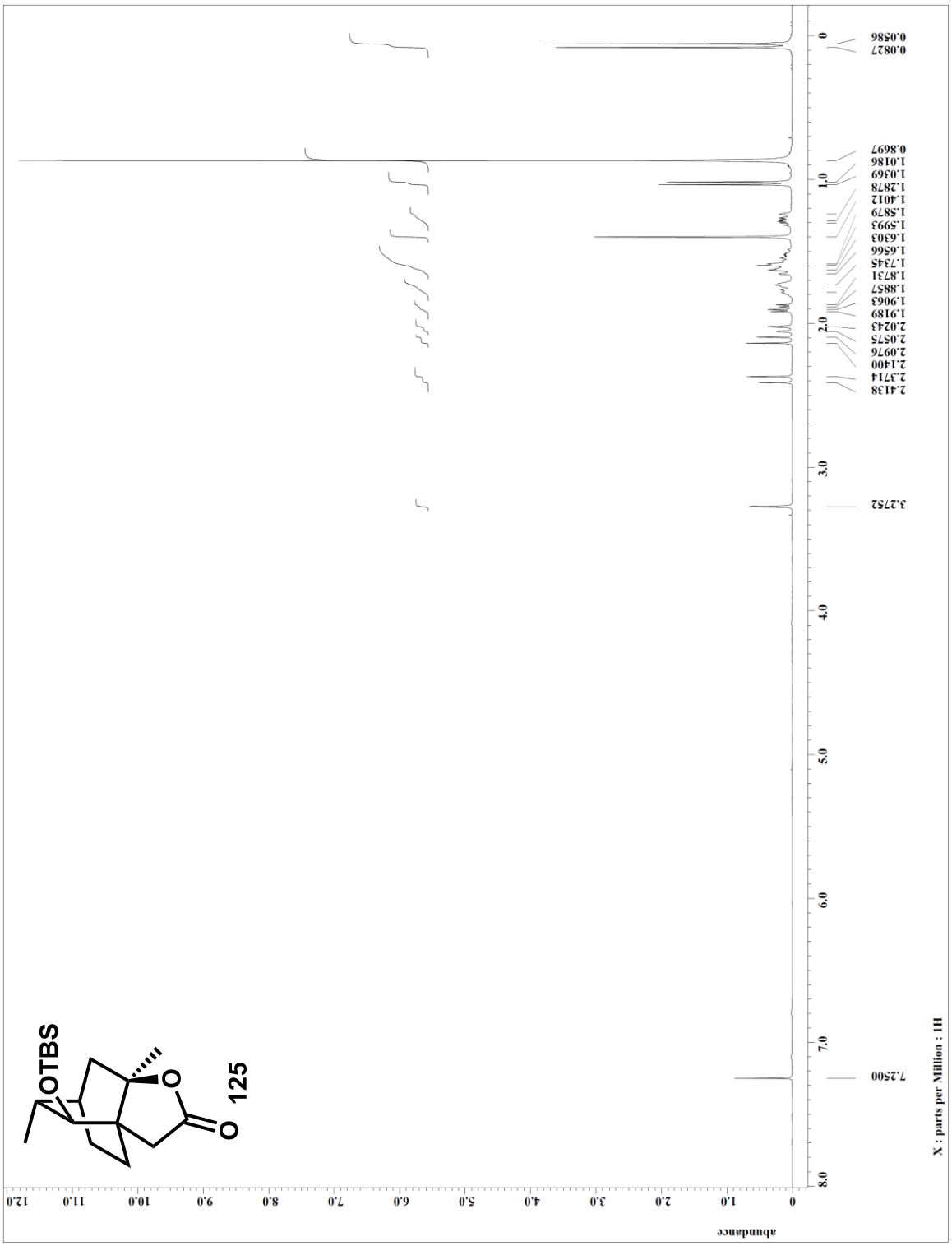
^{13}C NMR for compound **116**



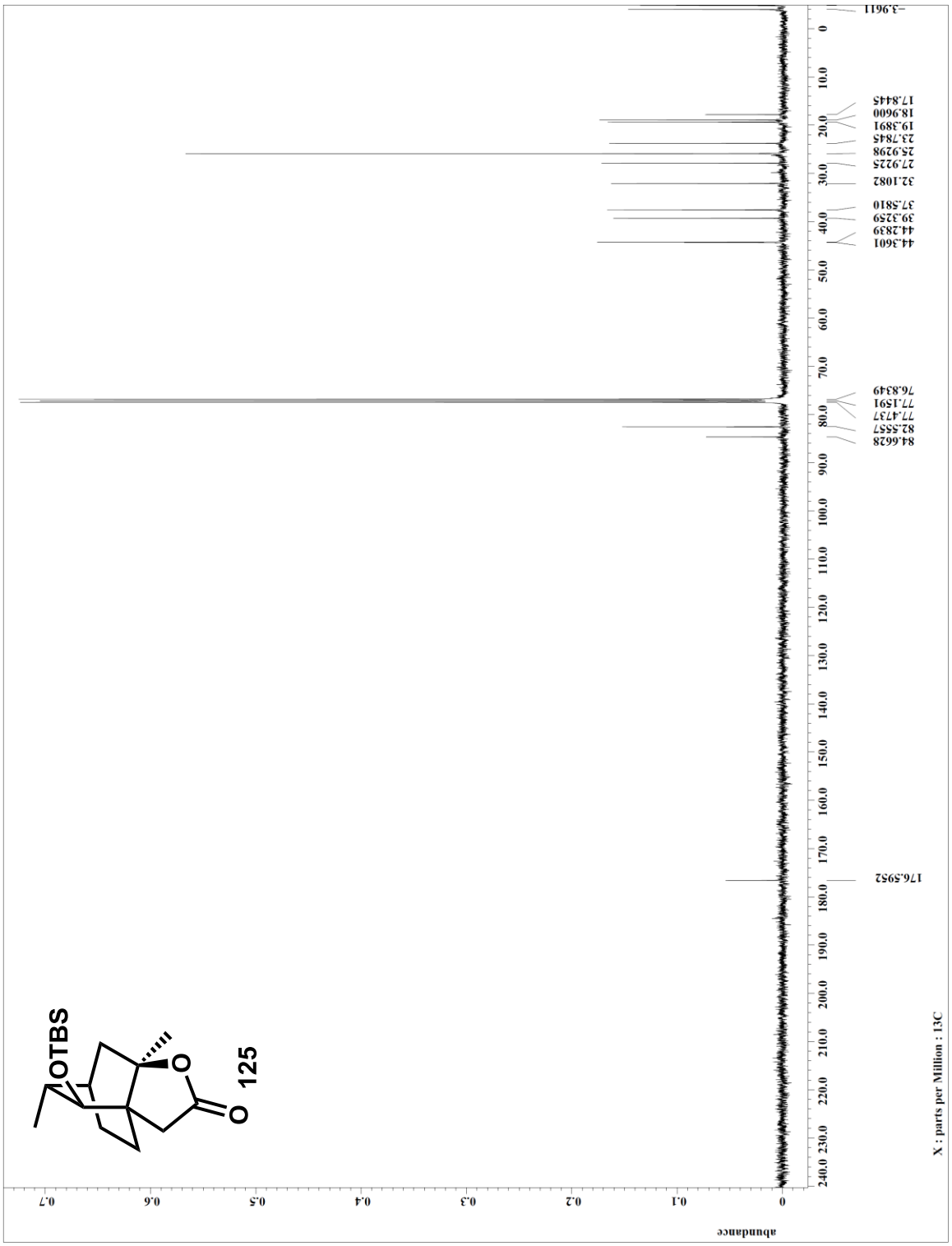
^{1}H NMR for compound **123**



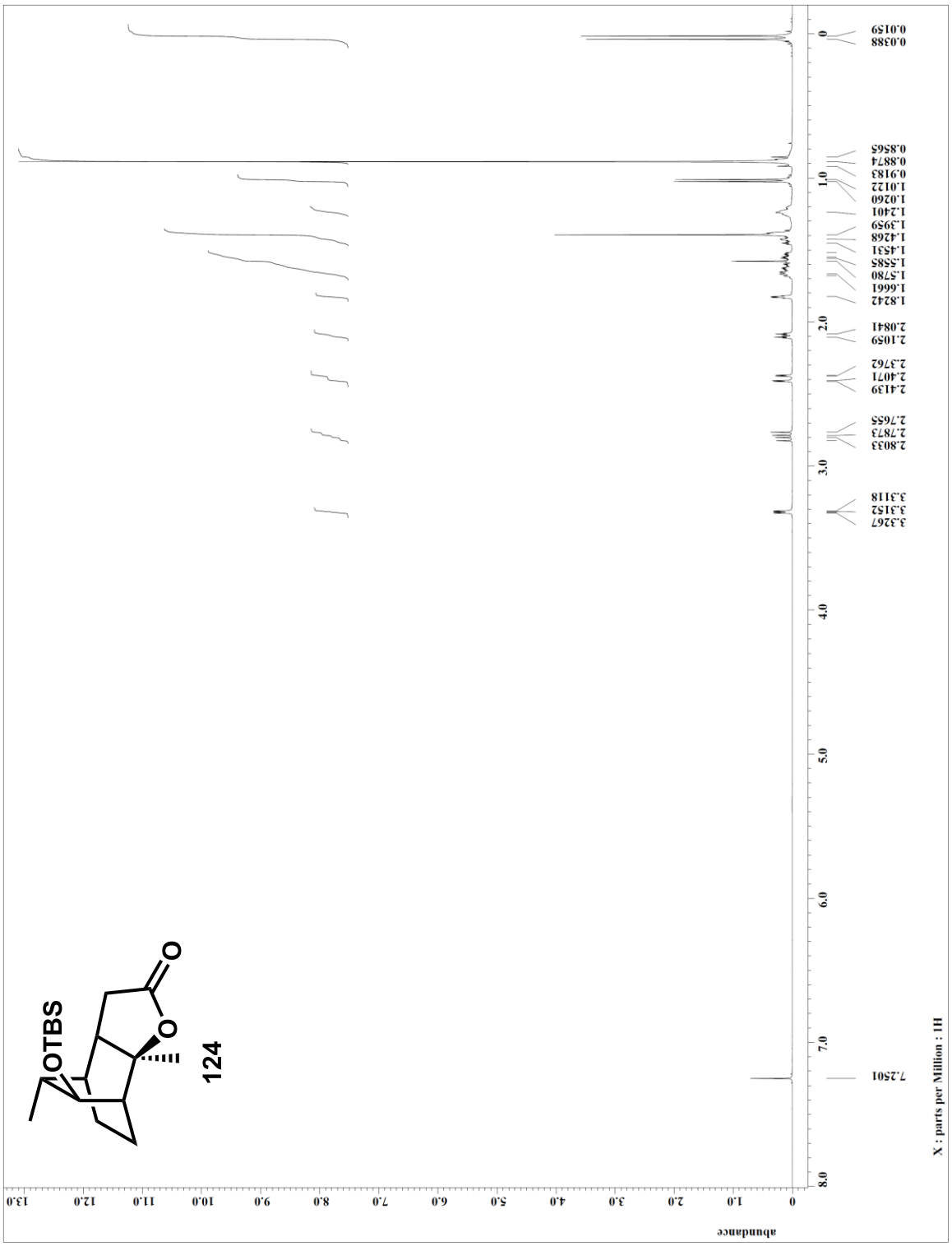
^{13}C NMR for compound **123**



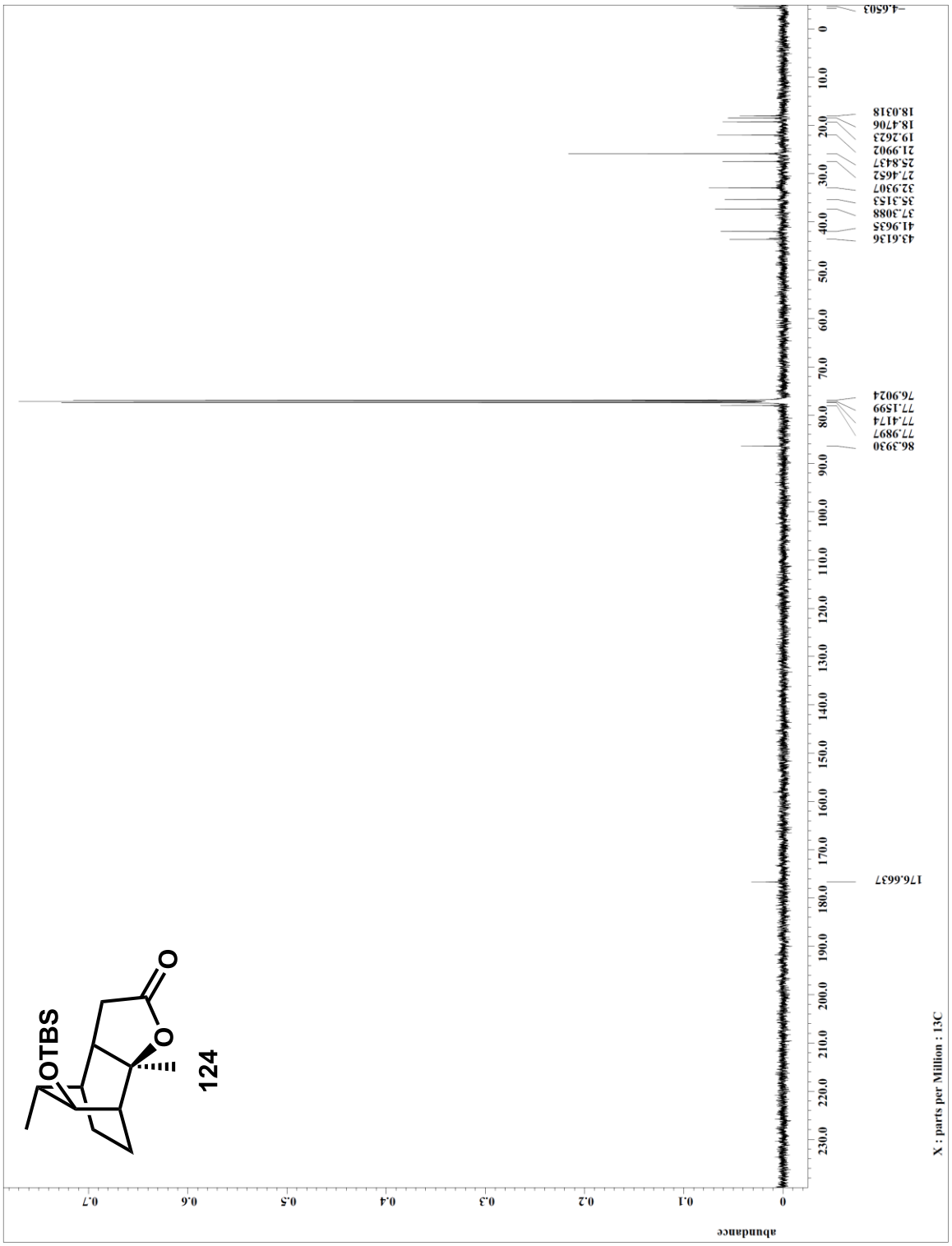
^{1}H NMR for compound **125**



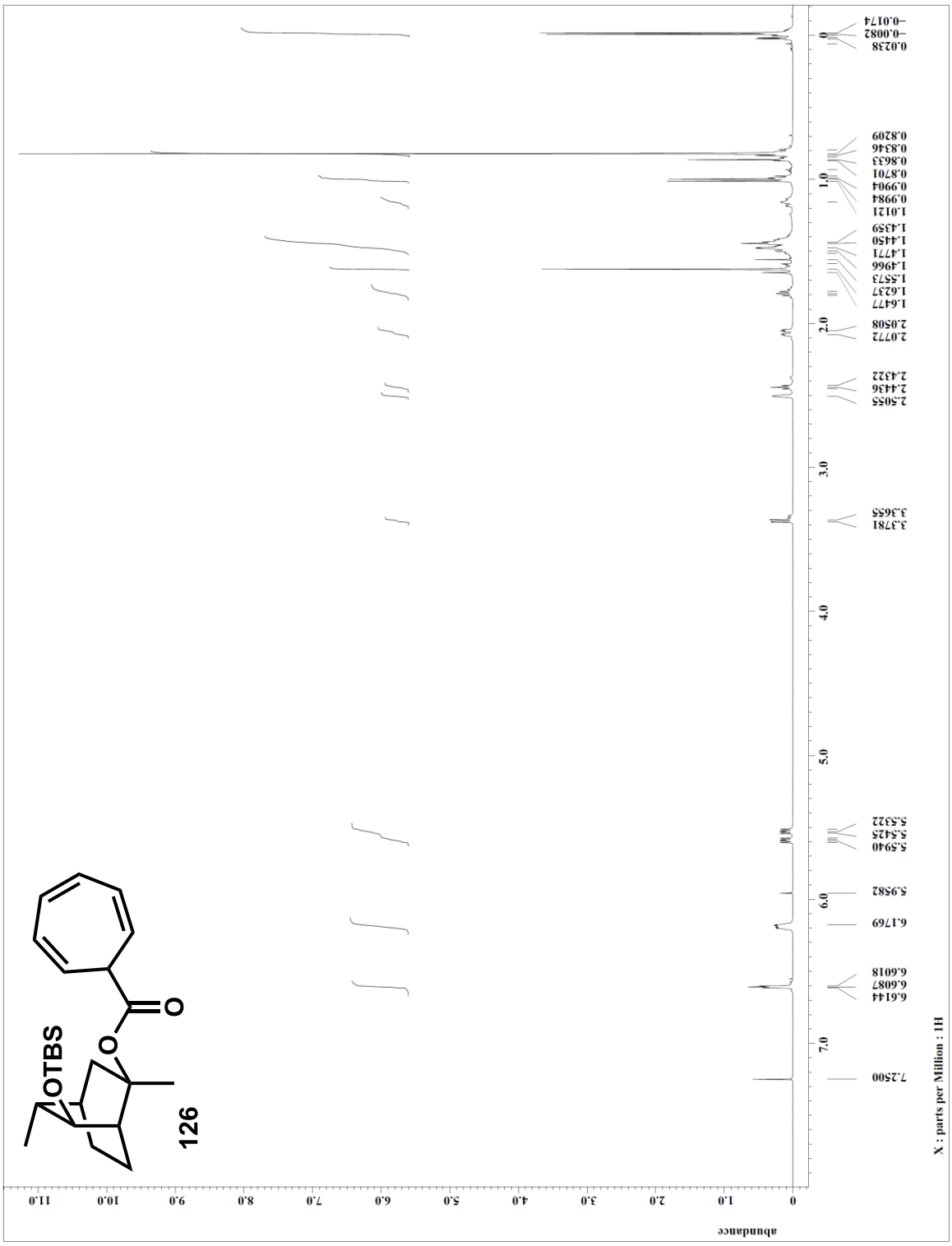
^{13}C NMR for compound **125**



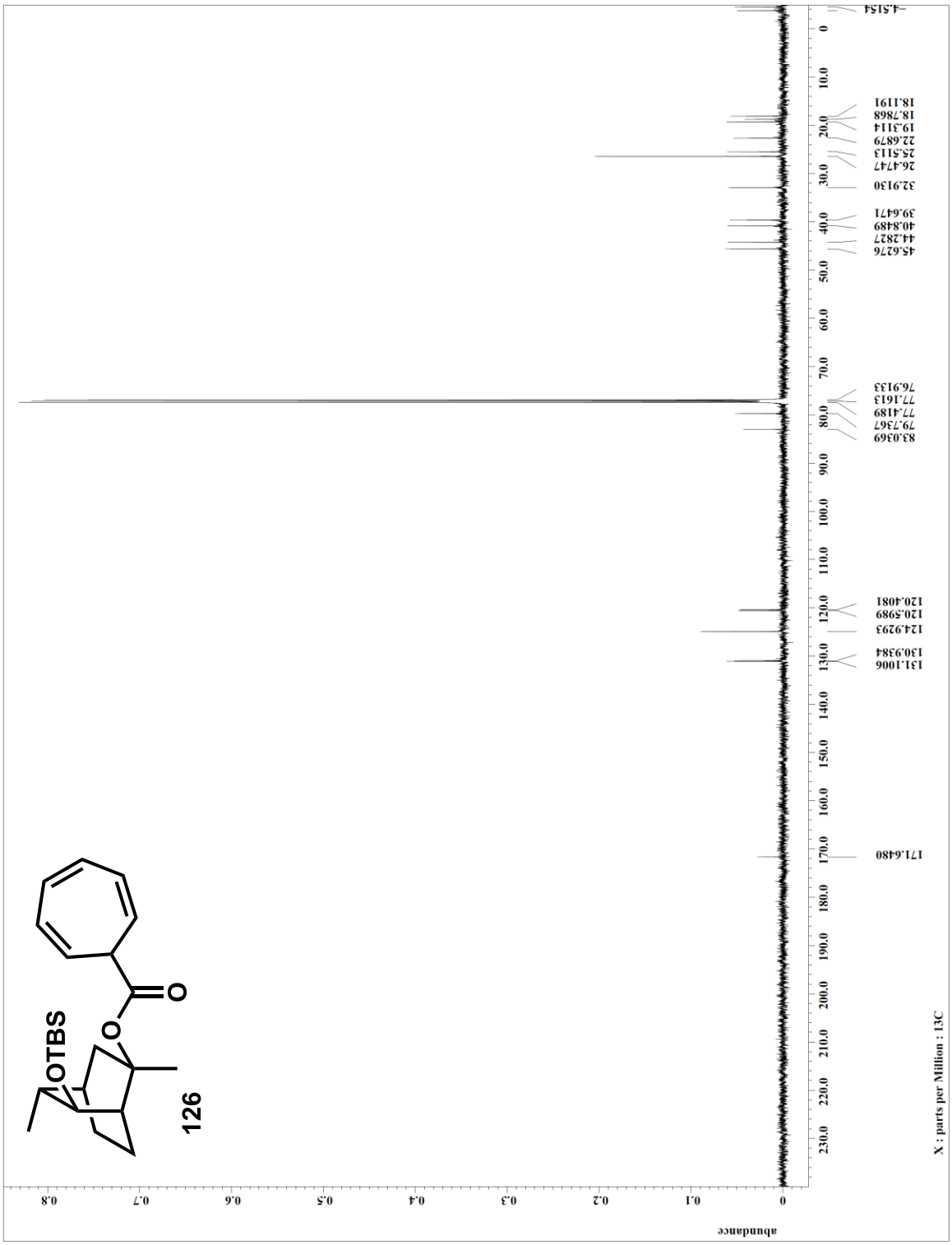
^{1}H NMR for compound **124**



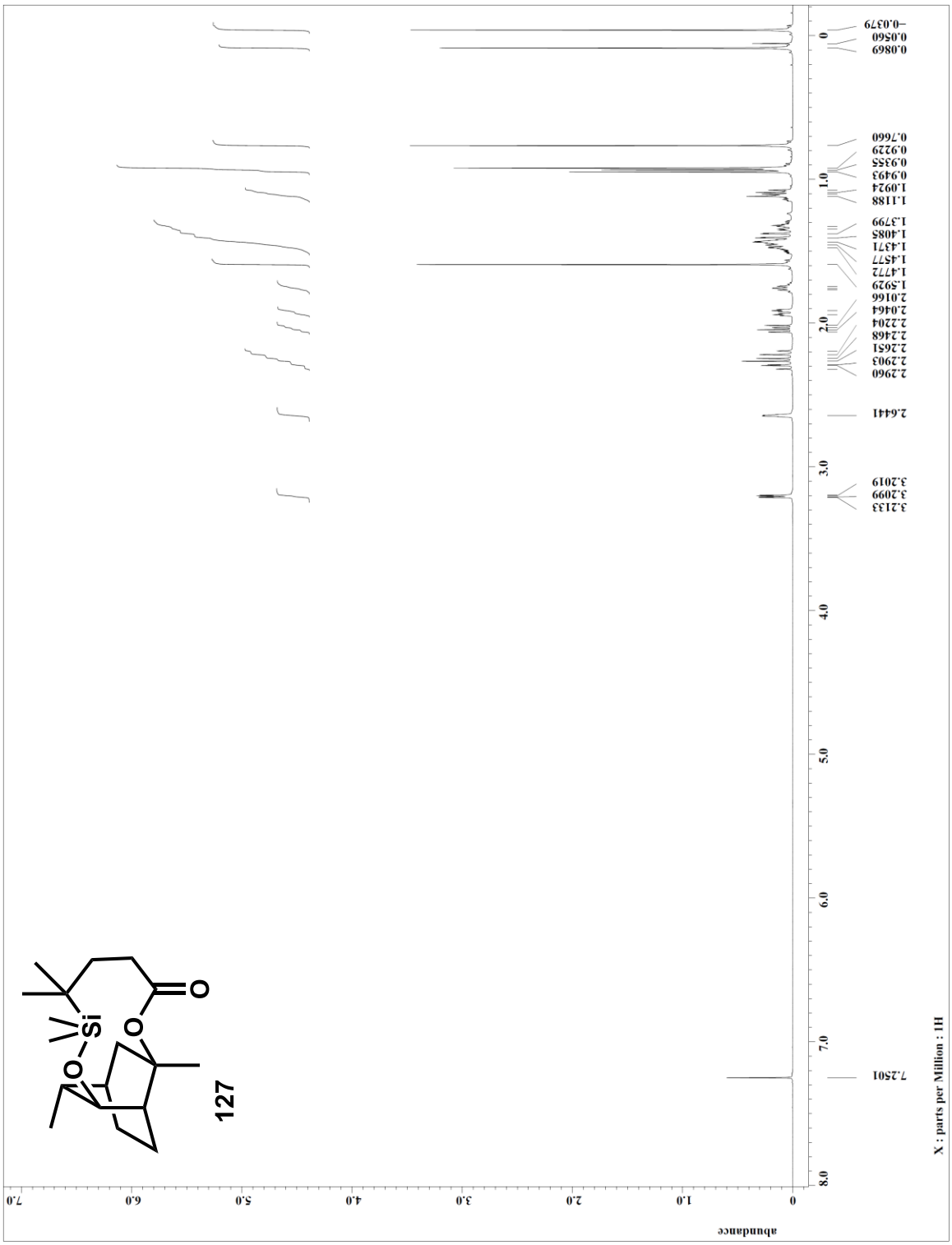
^{13}C NMR for compound **124**



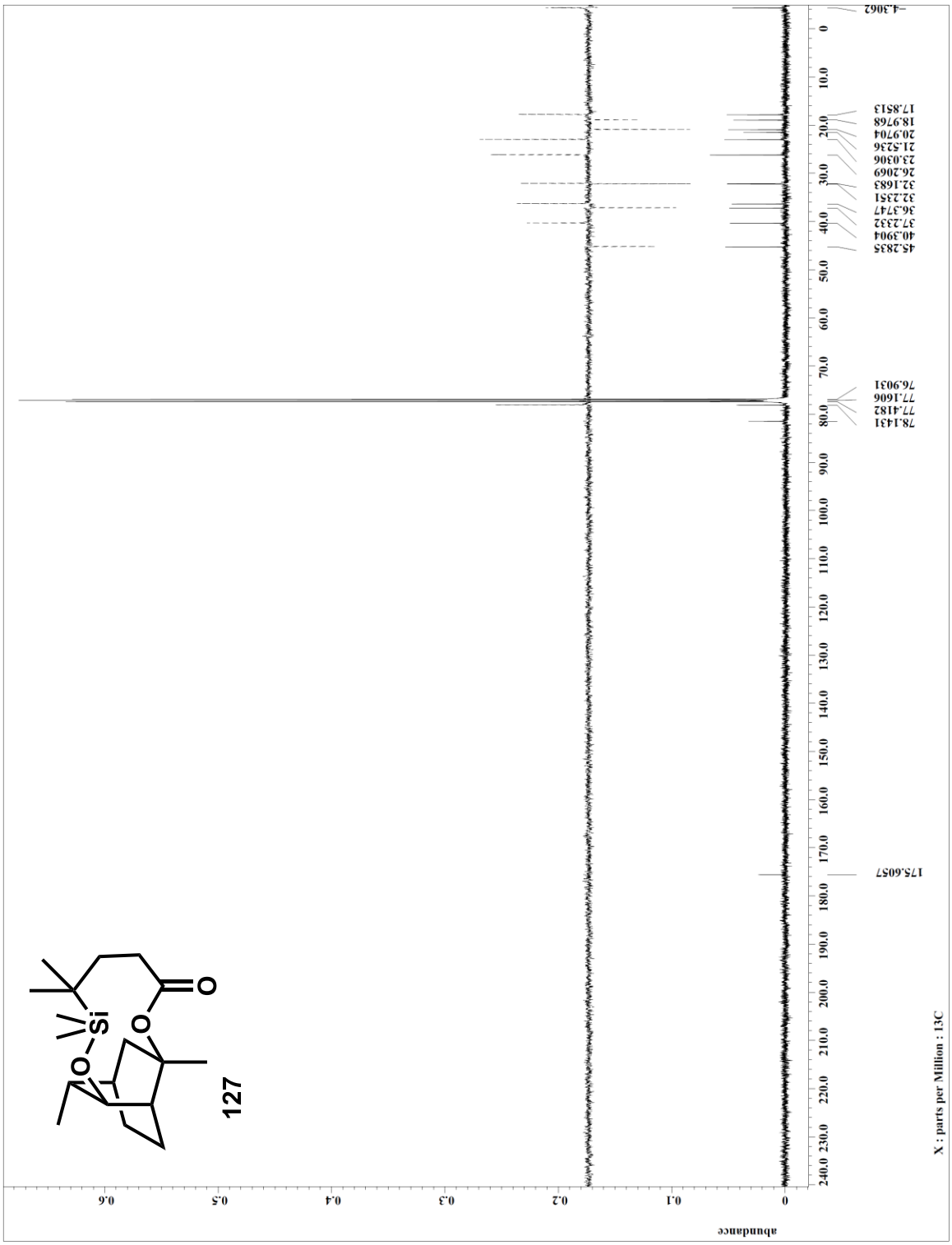
^{1}H NMR for compound **126**



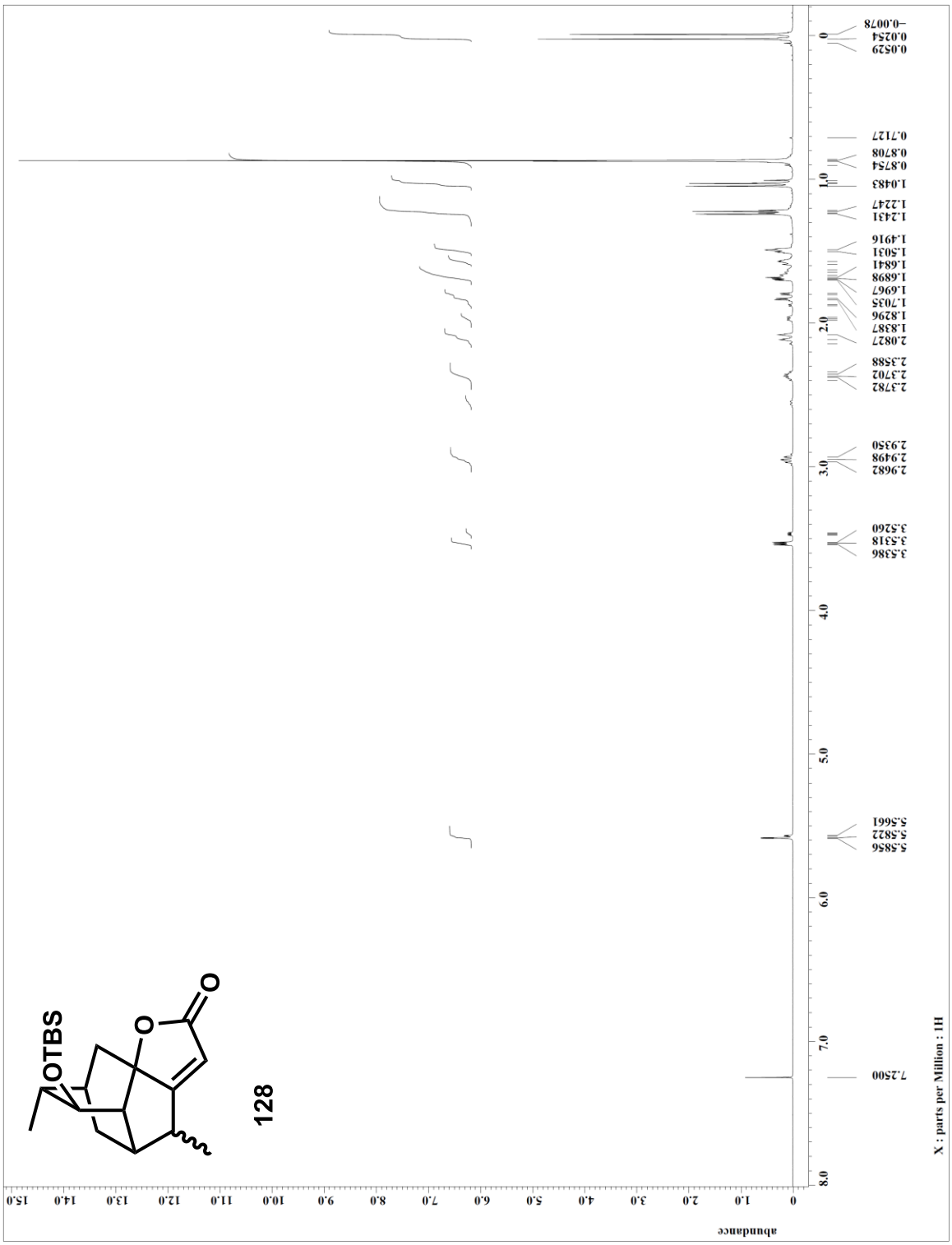
^{13}C NMR for compound **126**



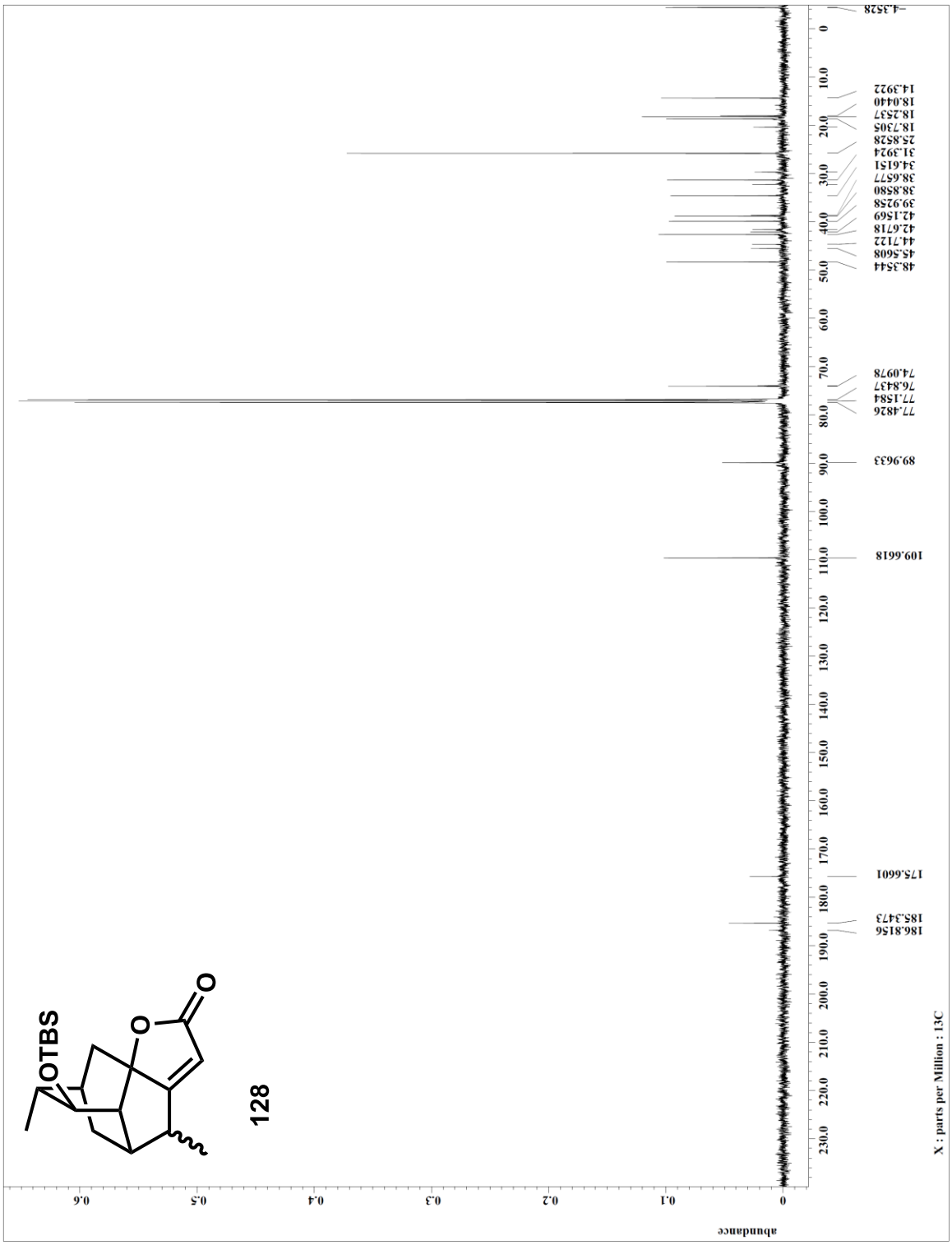
^{1}H NMR for compound **127**



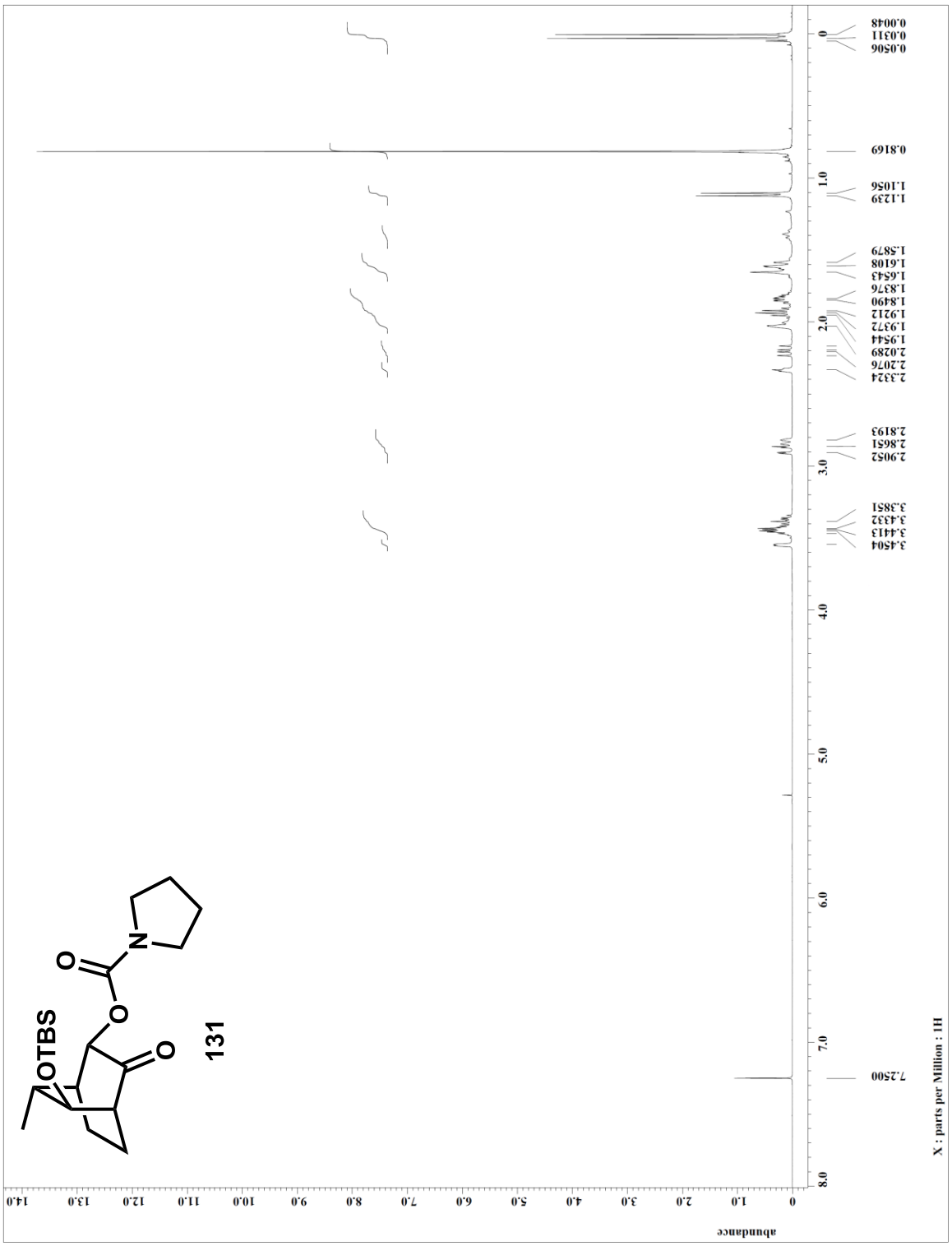
^{13}C NMR and DEPT for compound **127**



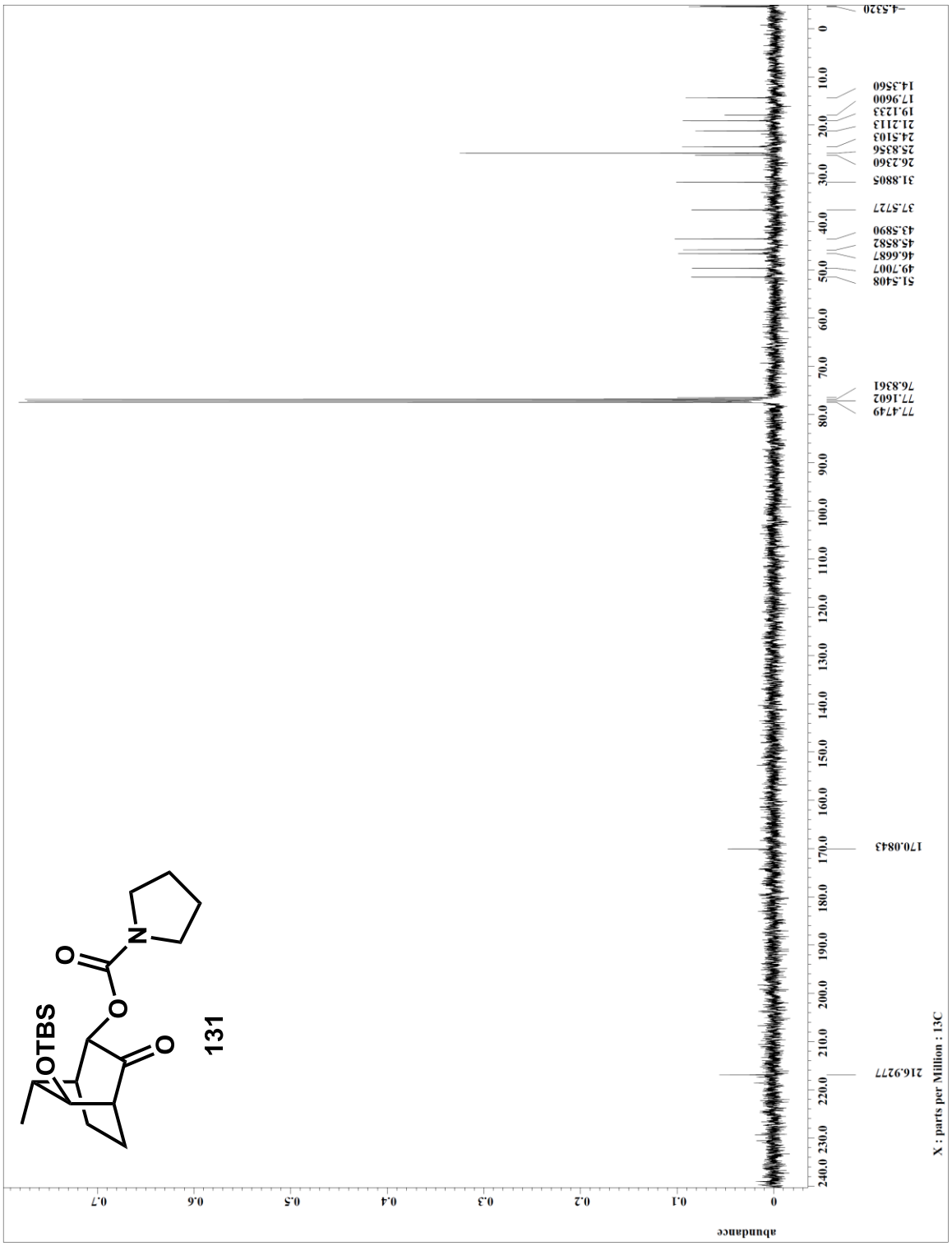
^{1}H NMR for compound **128**



^{13}C NMR for compound **128**



^{1}H NMR for compound **131**



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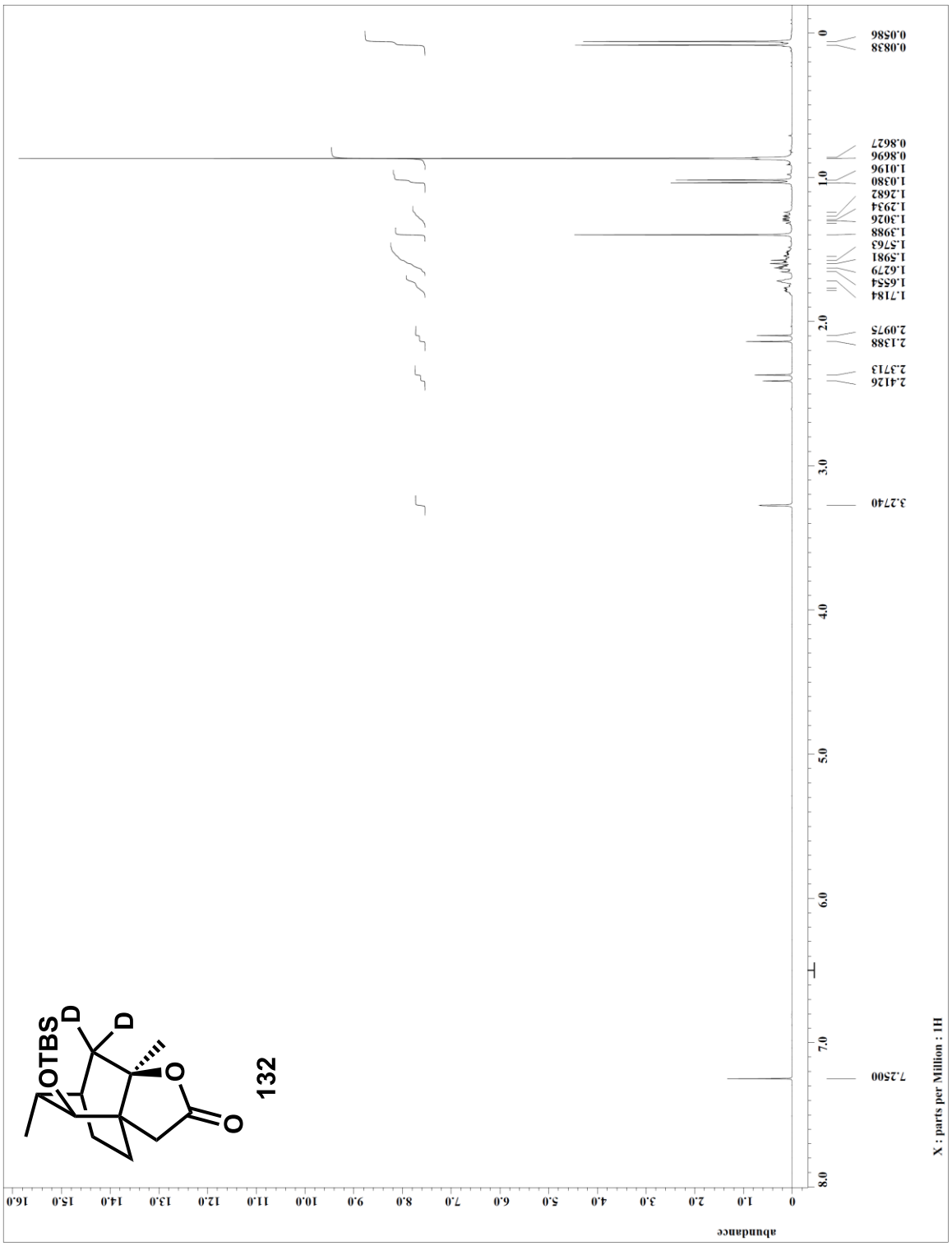

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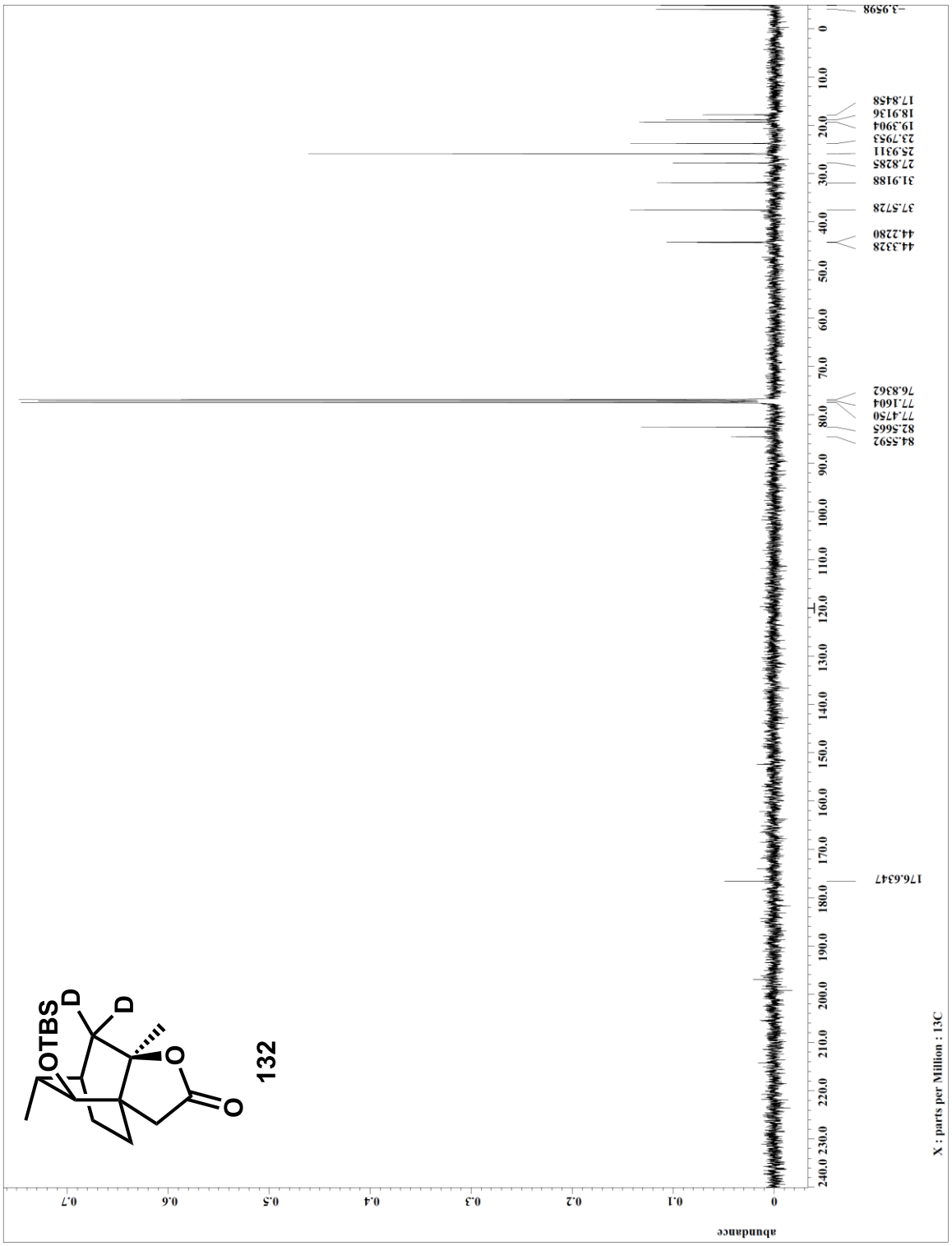

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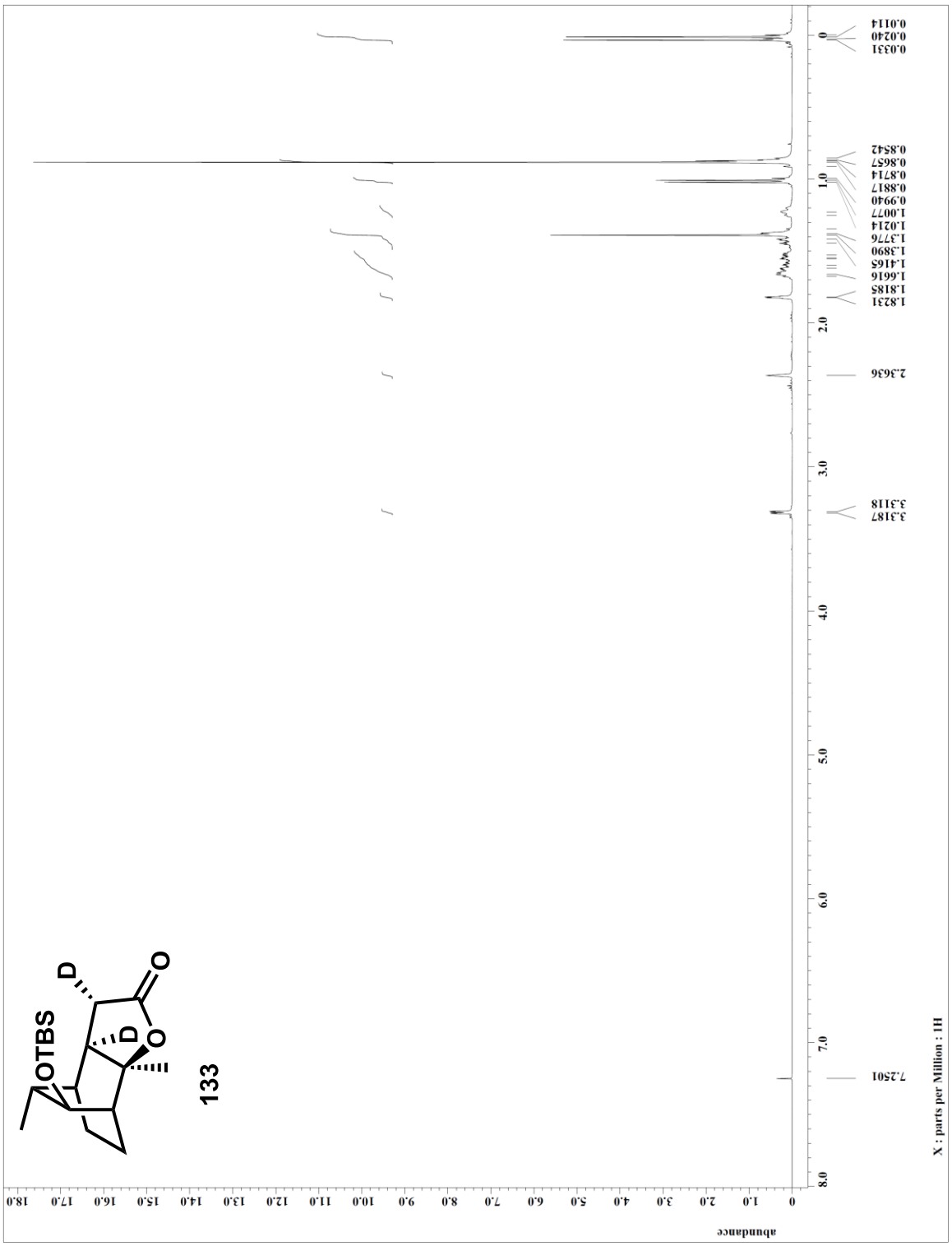
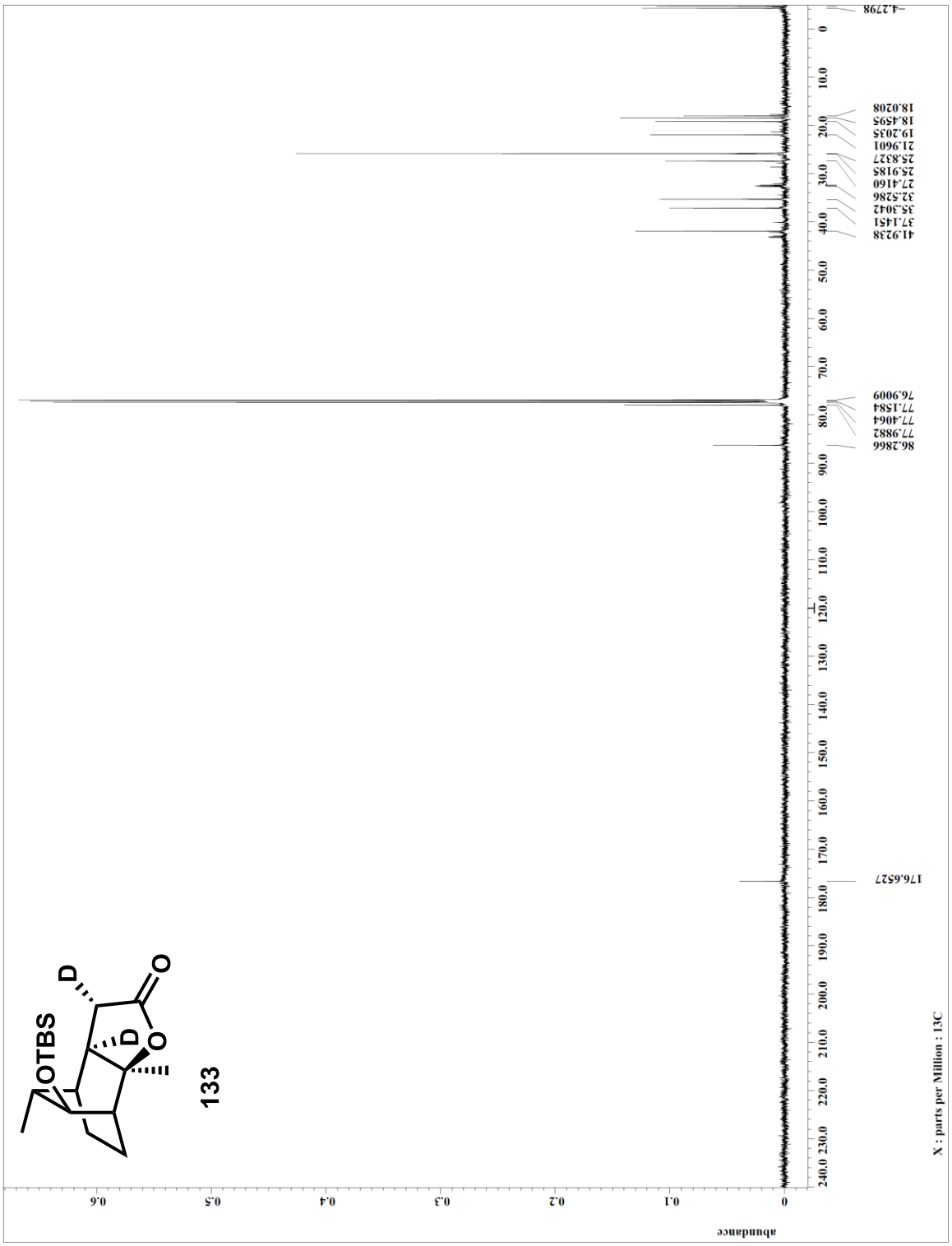
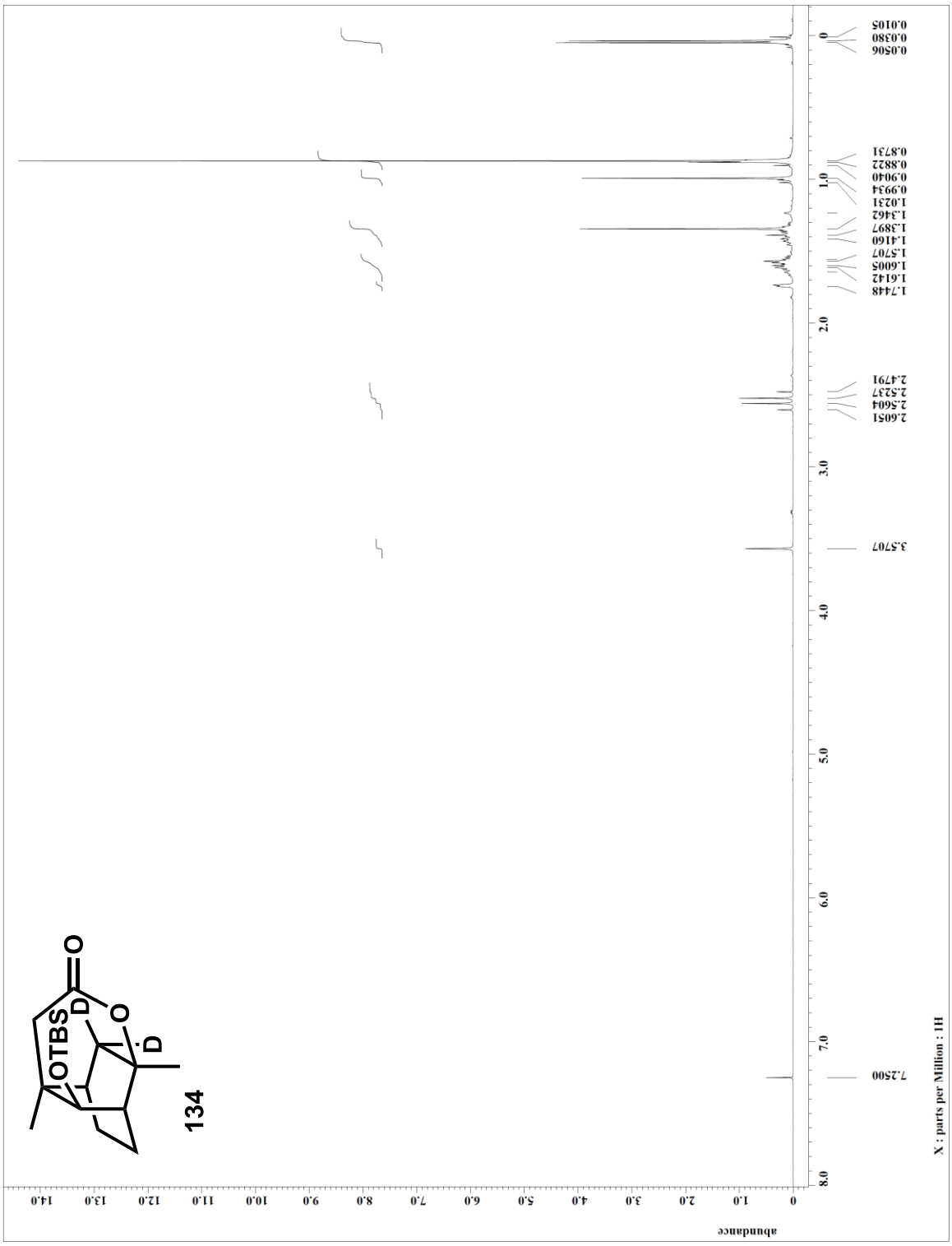


^{1}H NMR for compound **133**



^{13}C NMR for compound **133**



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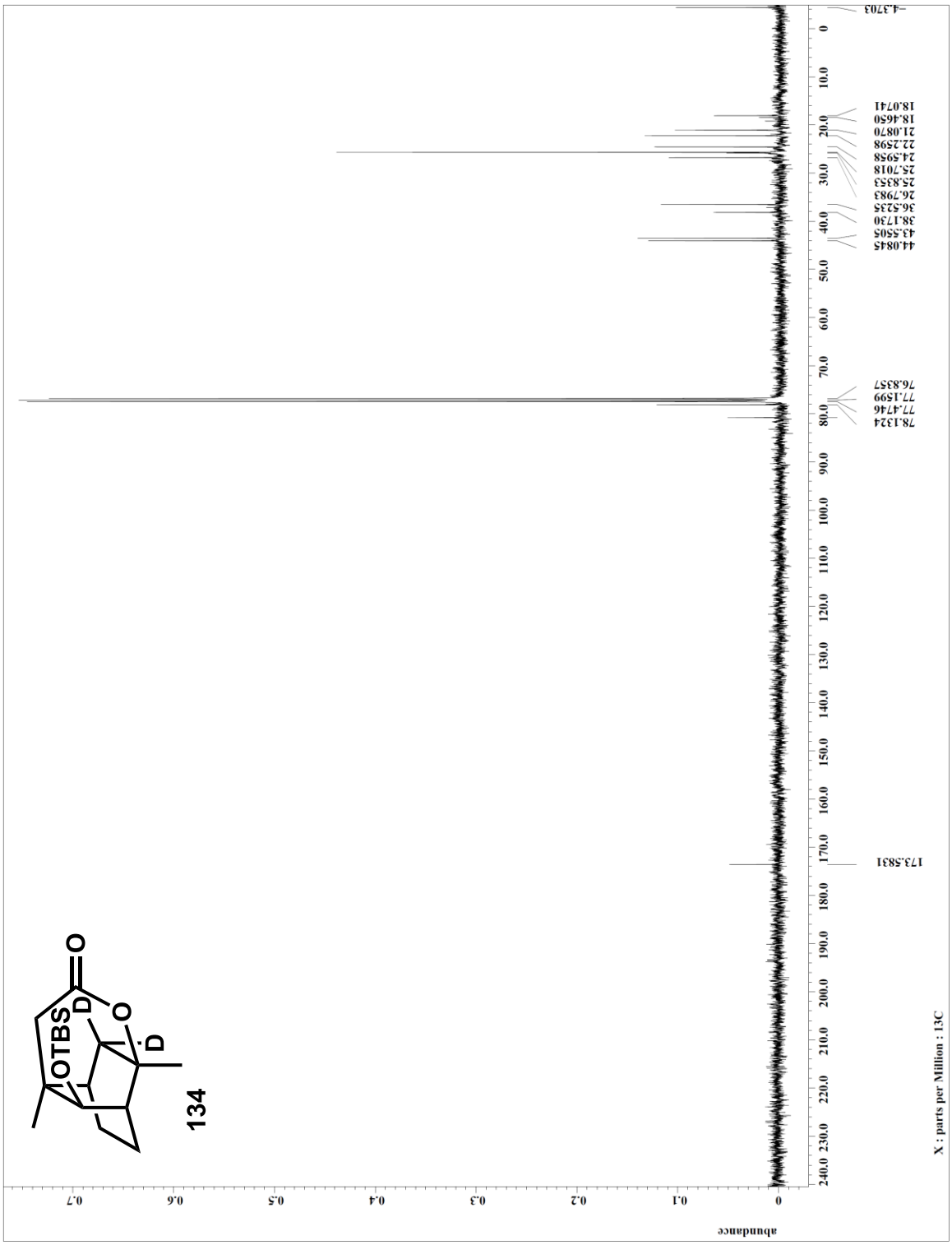

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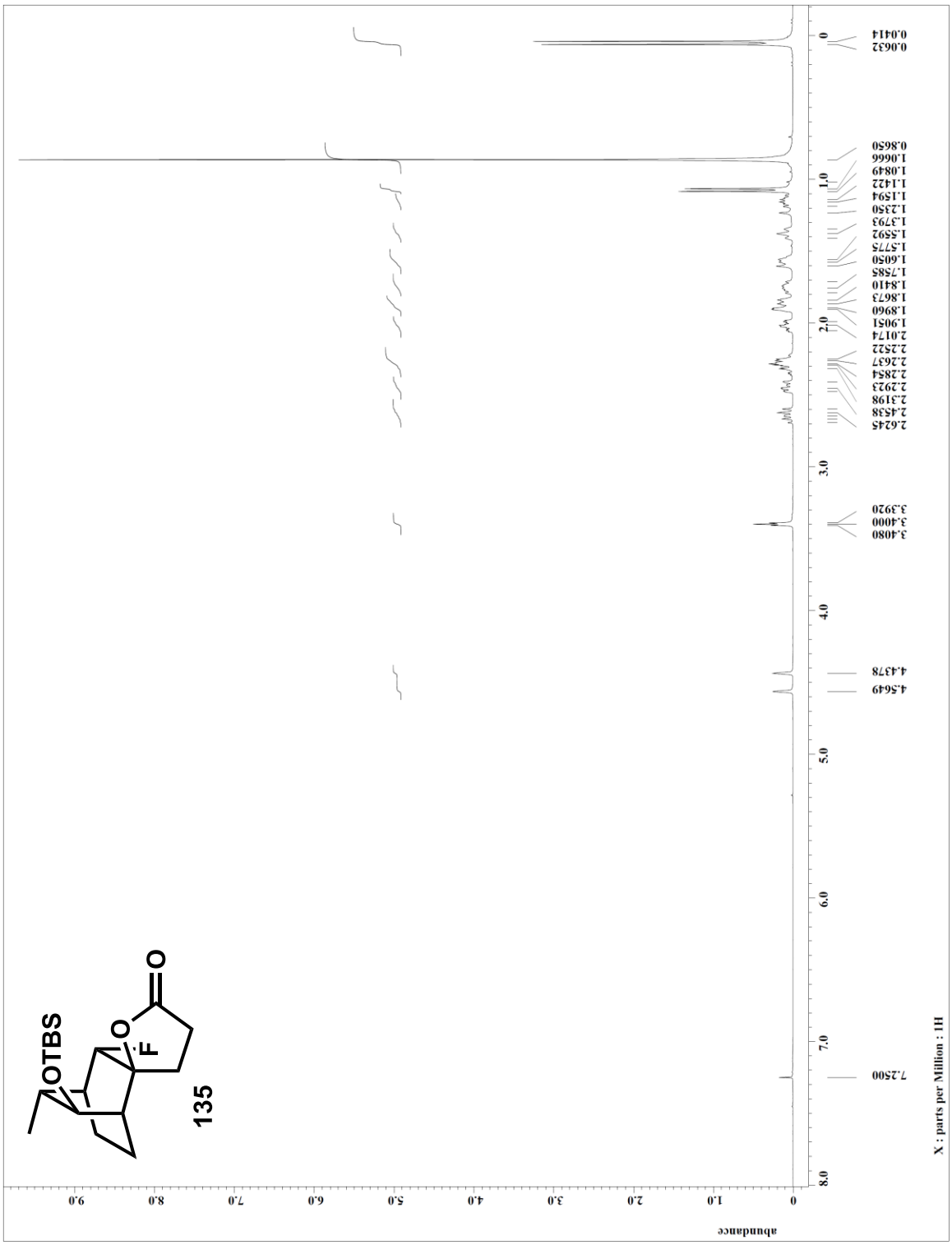
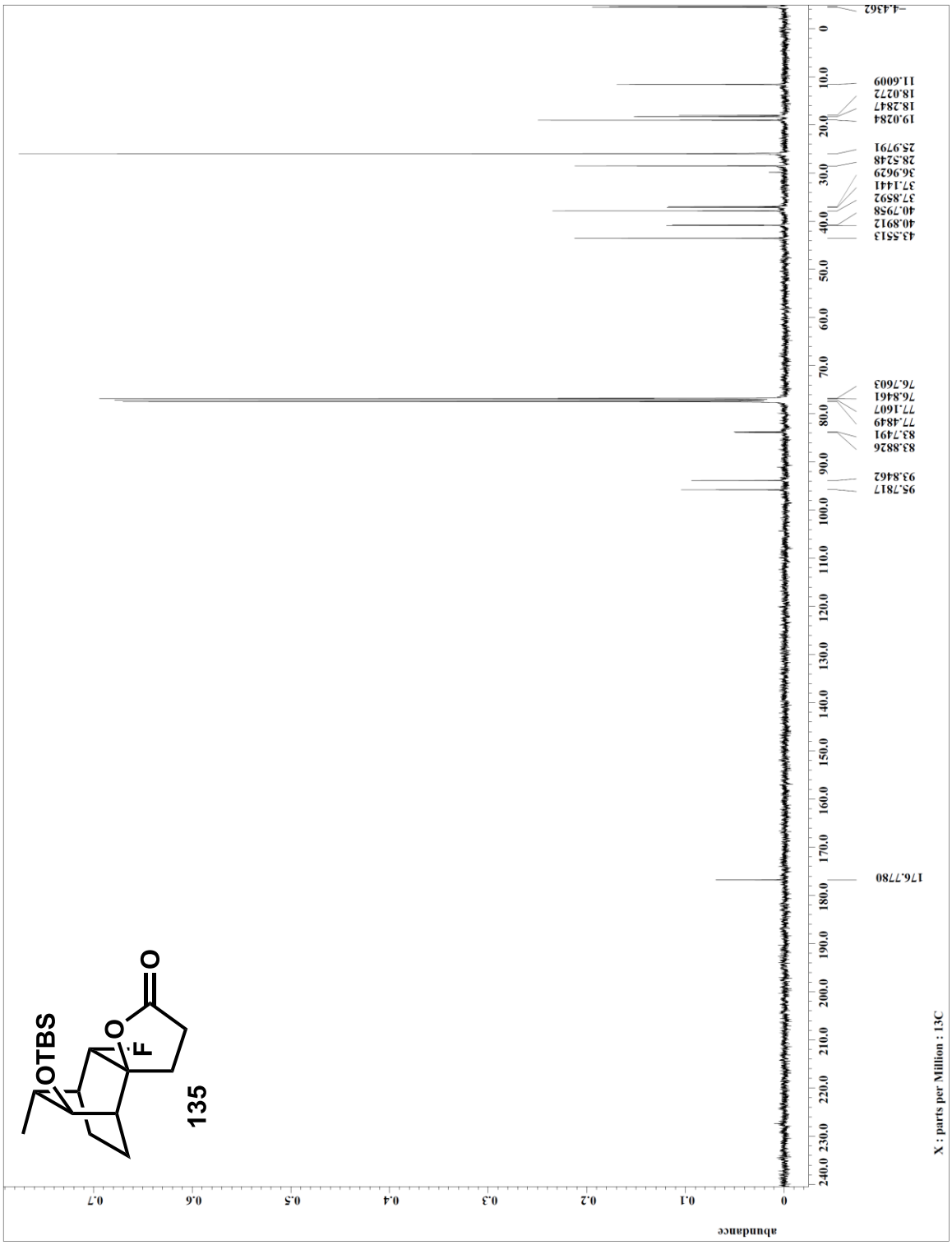
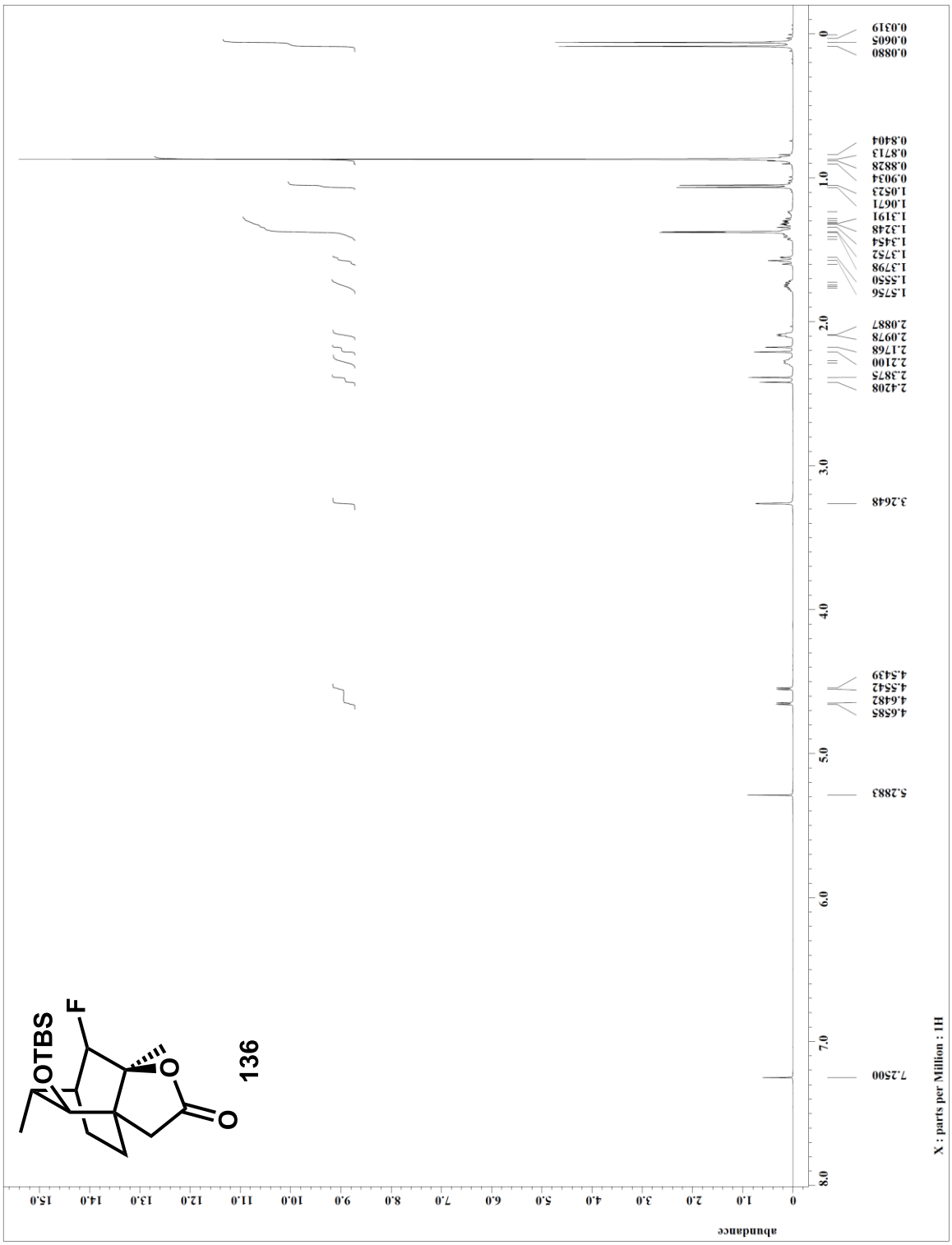


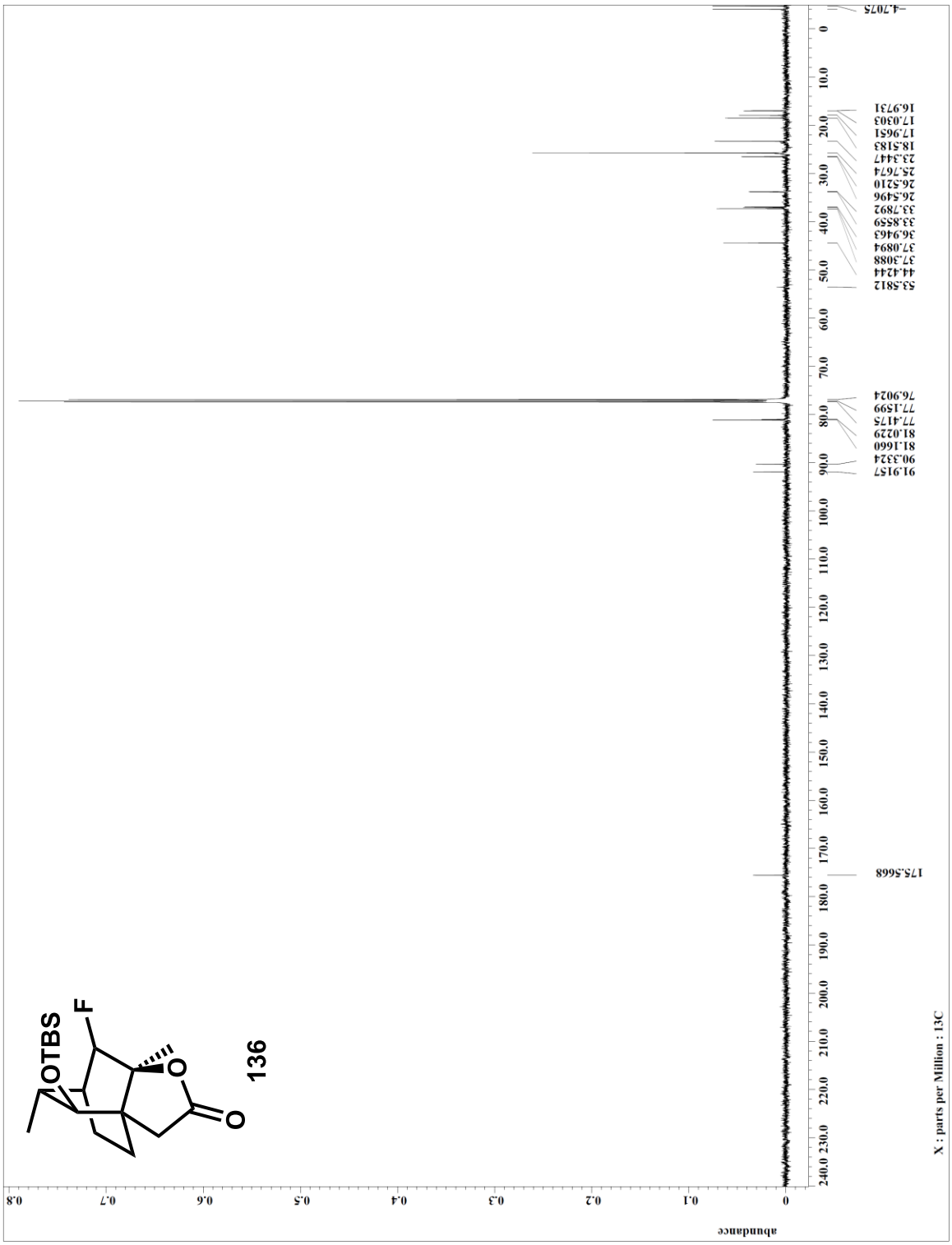
^{1}H NMR for compound **135**



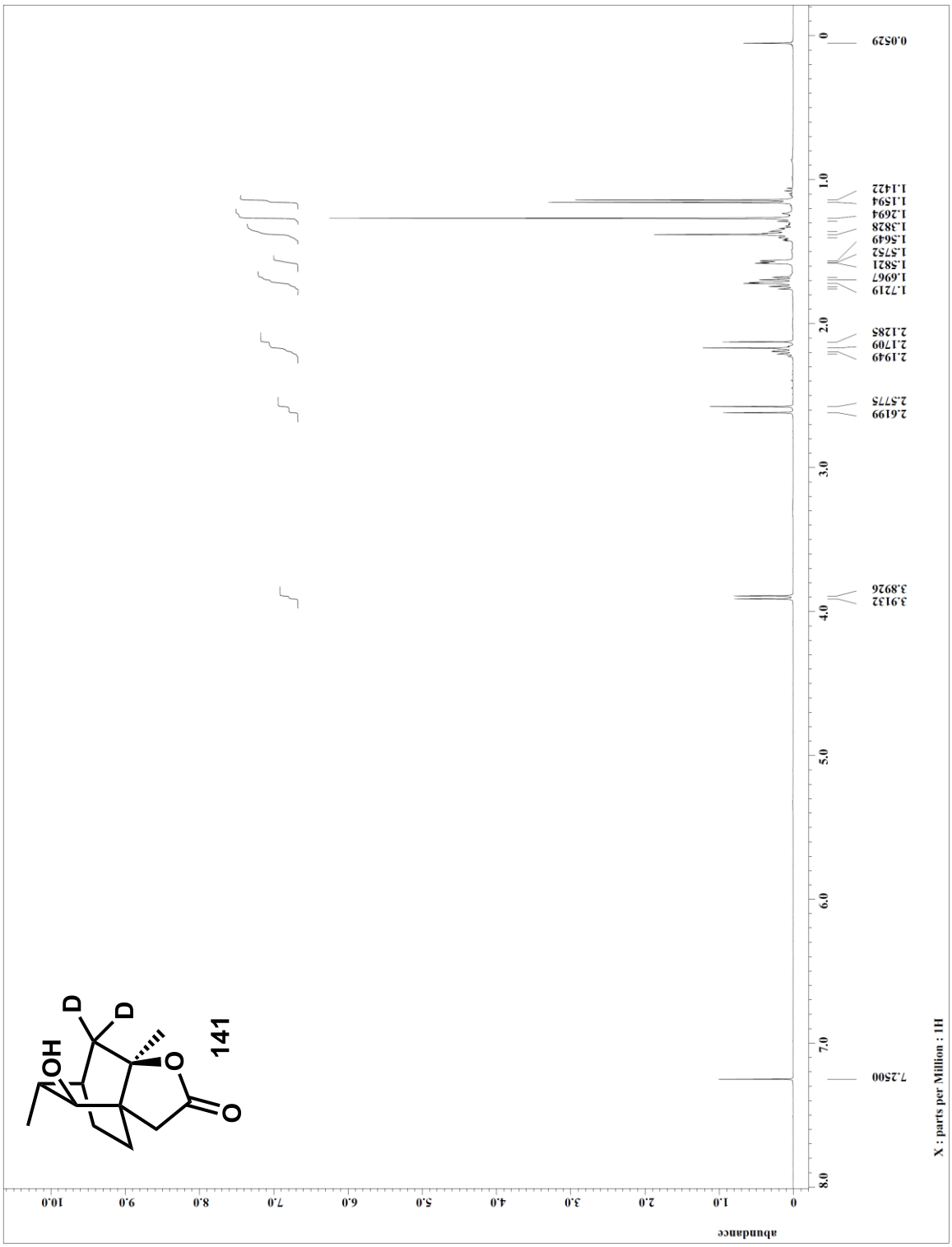
^{13}C NMR for compound **135**



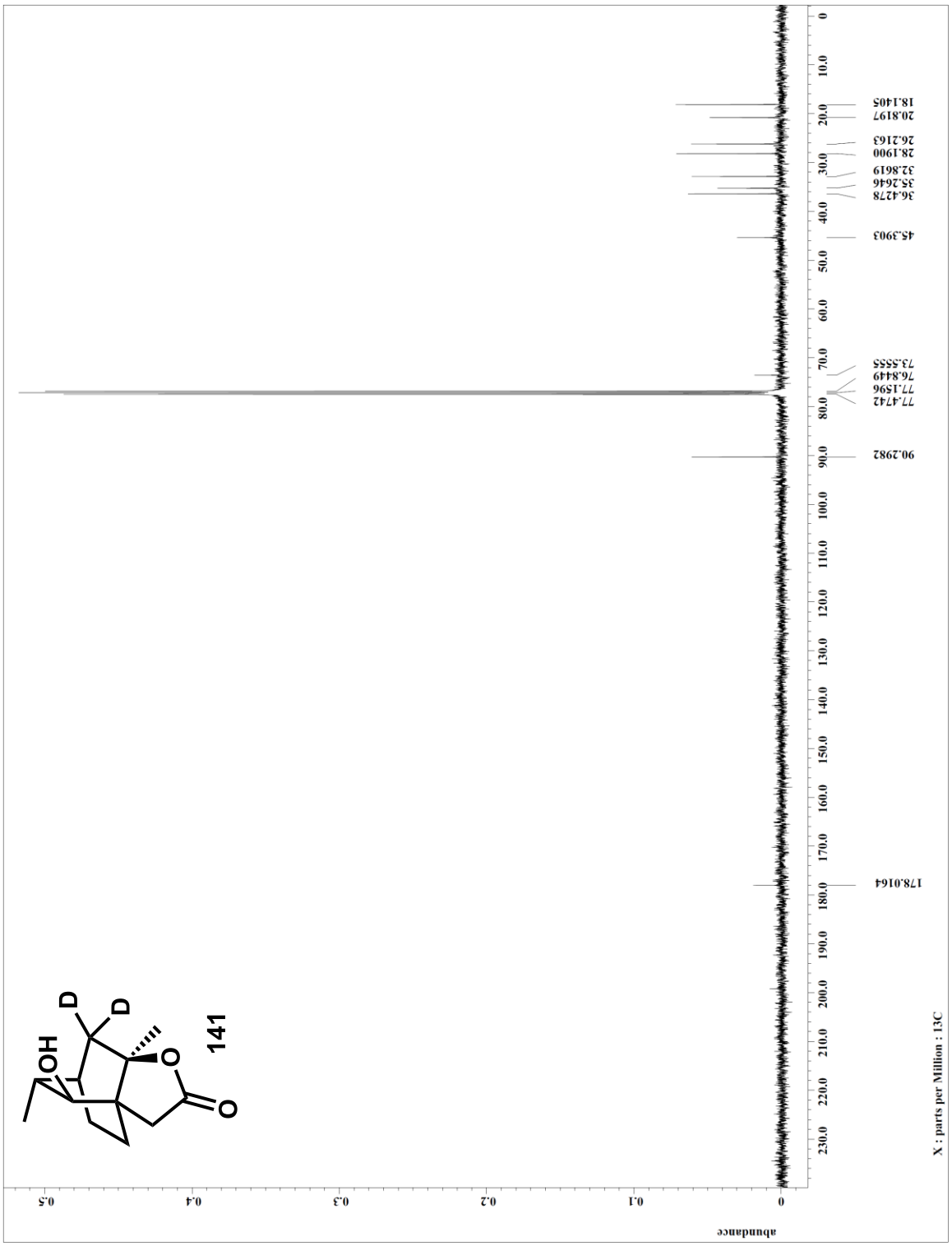
^{1}H NMR for compound **136**



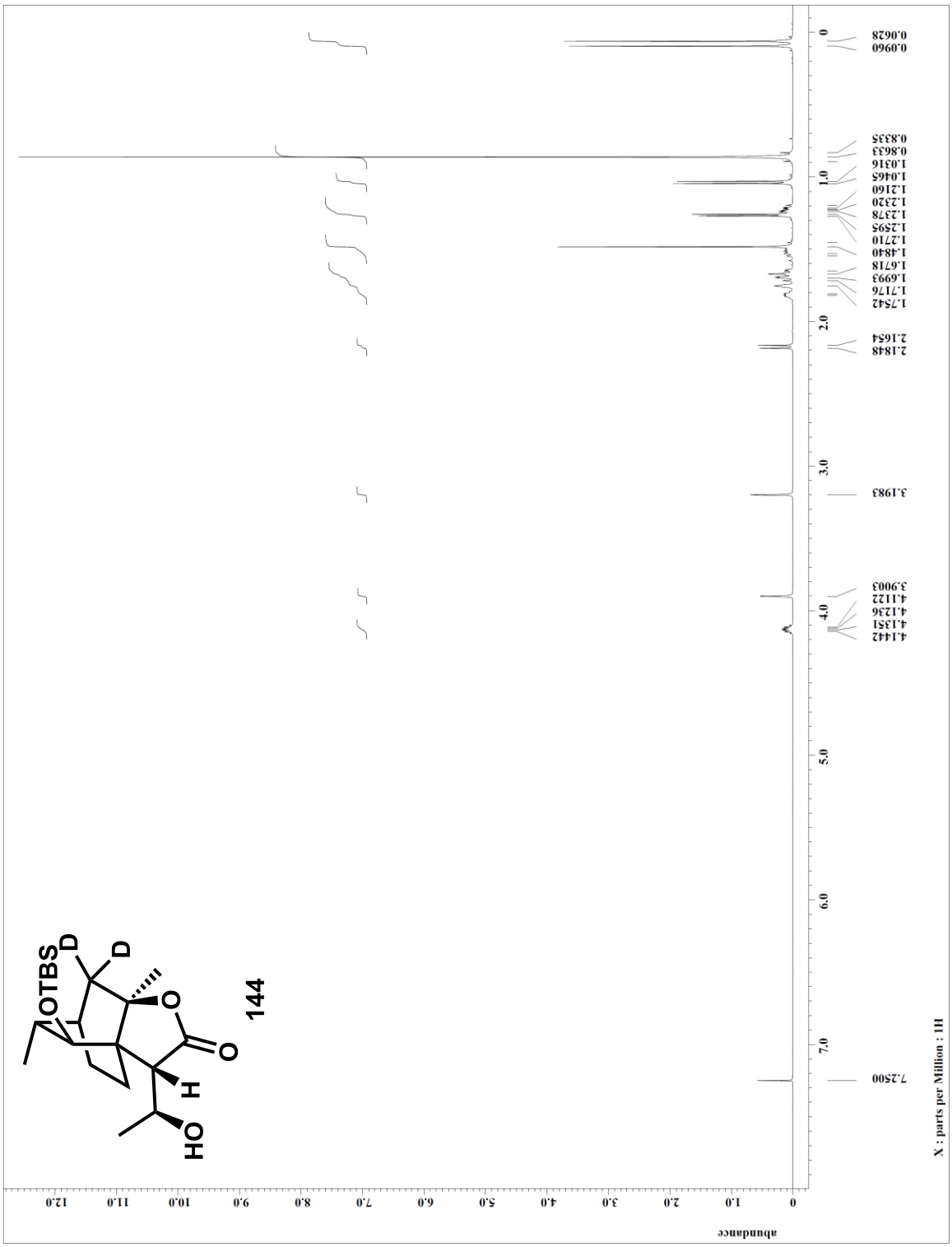
^{13}C NMR for compound **136**



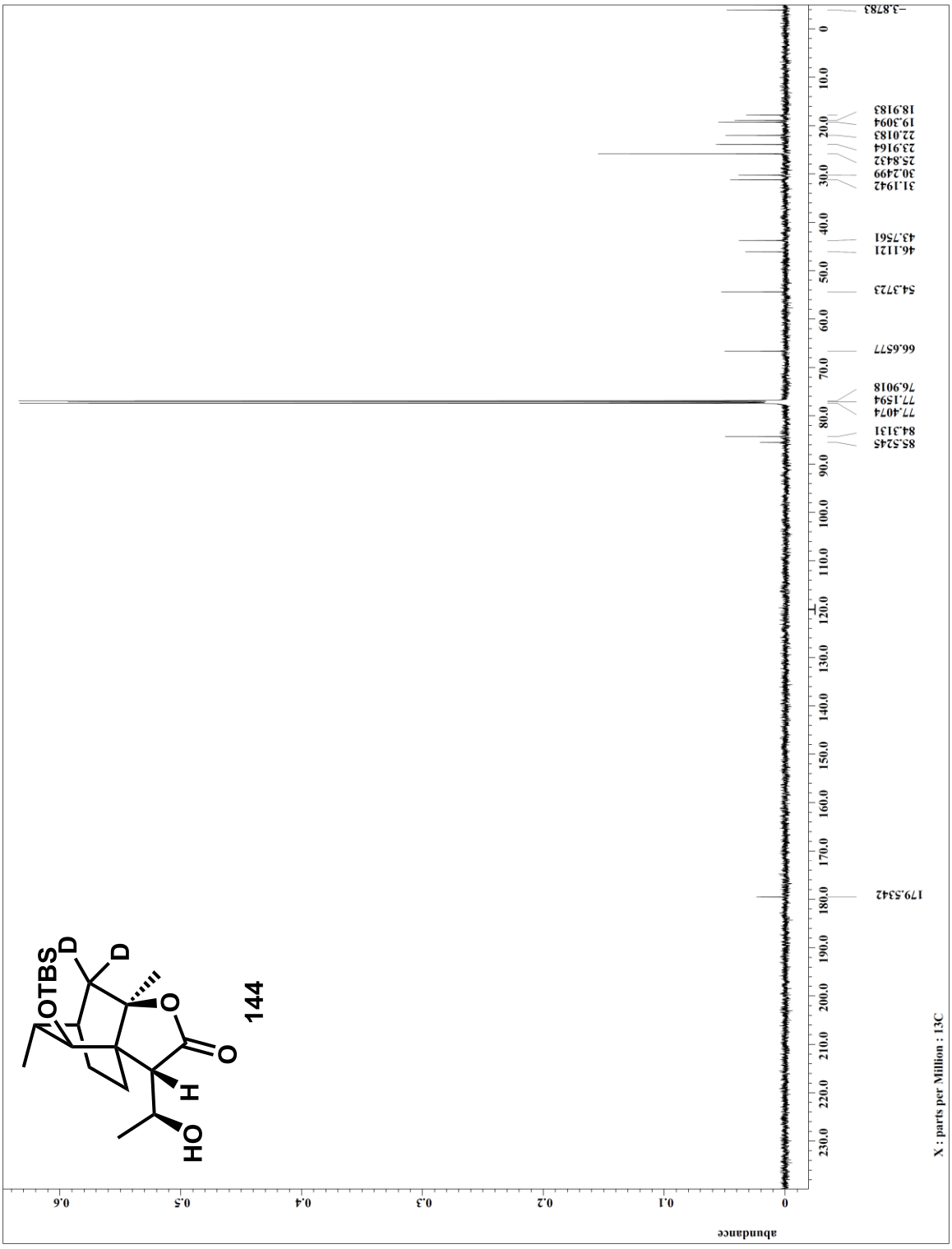
^{1}H NMR for compound **141**



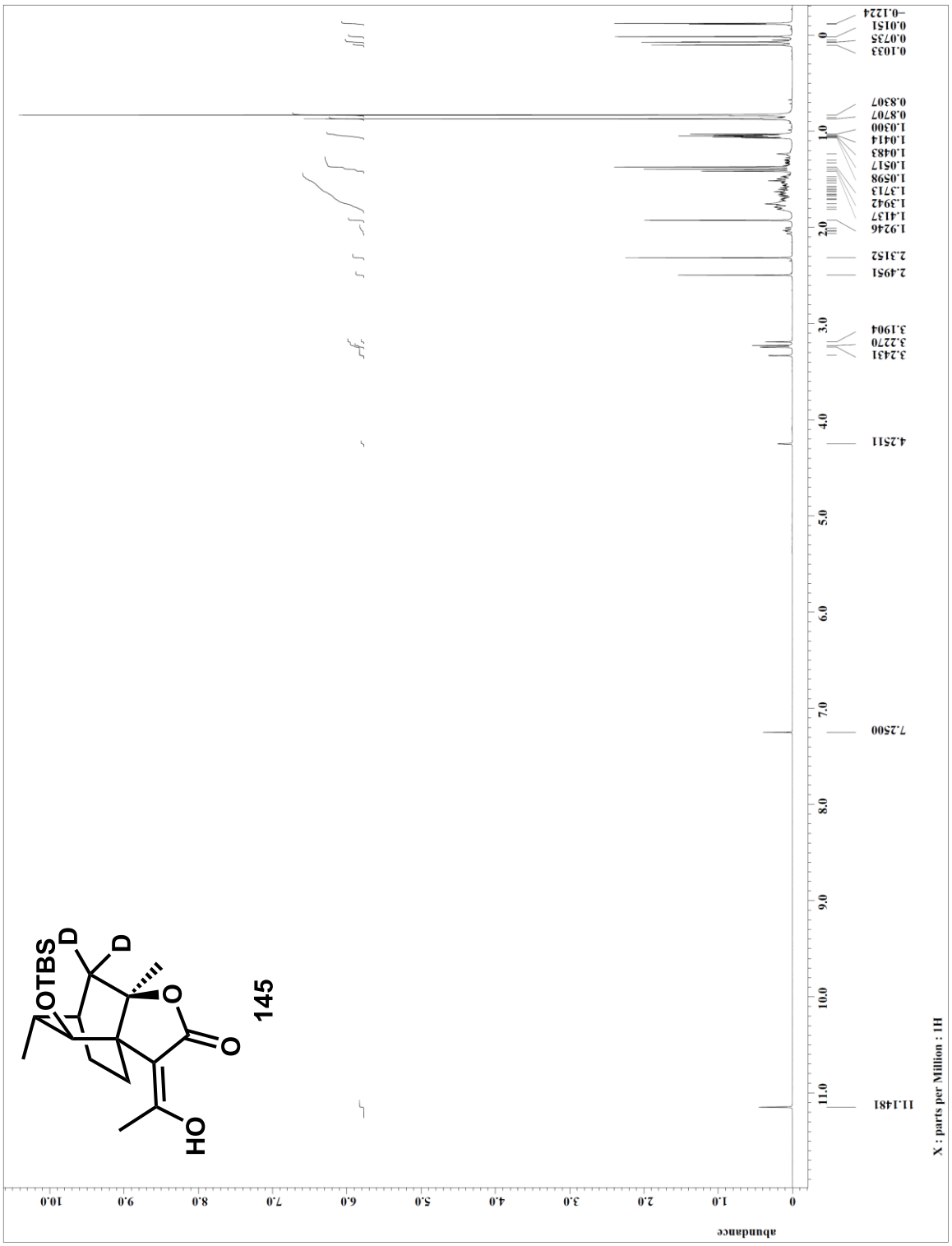
^{13}C NMR for compound **141**



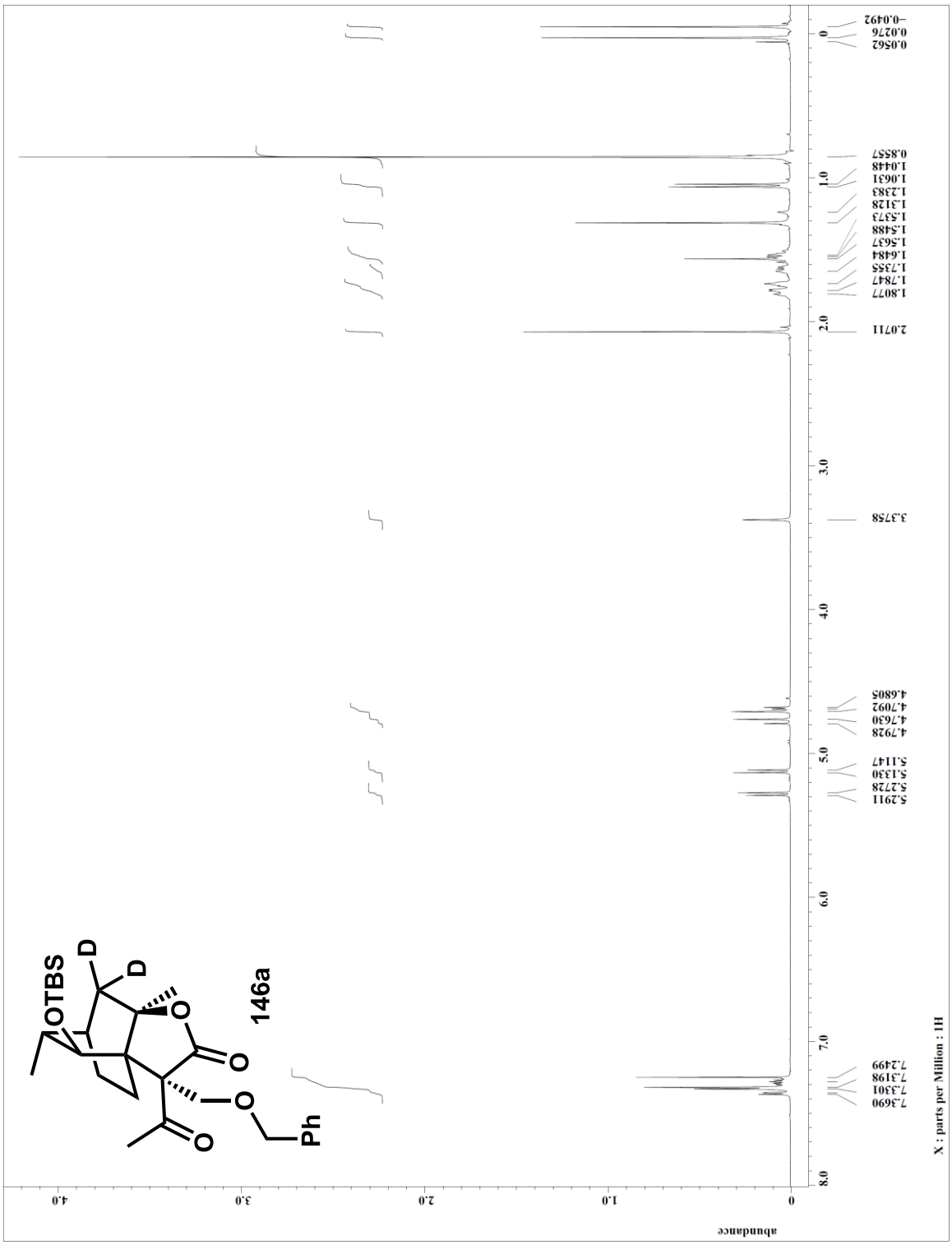
^{1}H NMR for compound **144**



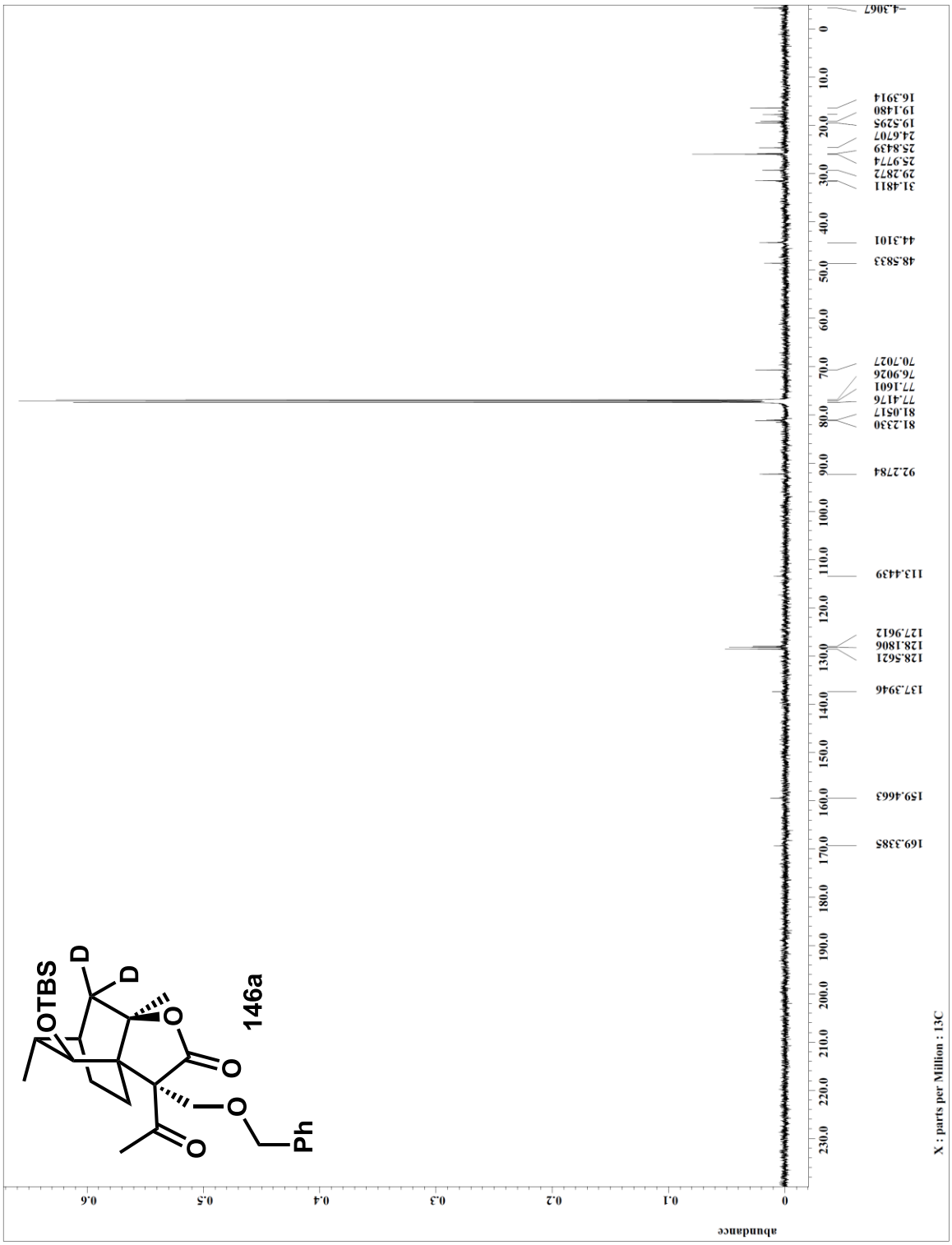
^{13}C NMR for compound **144**



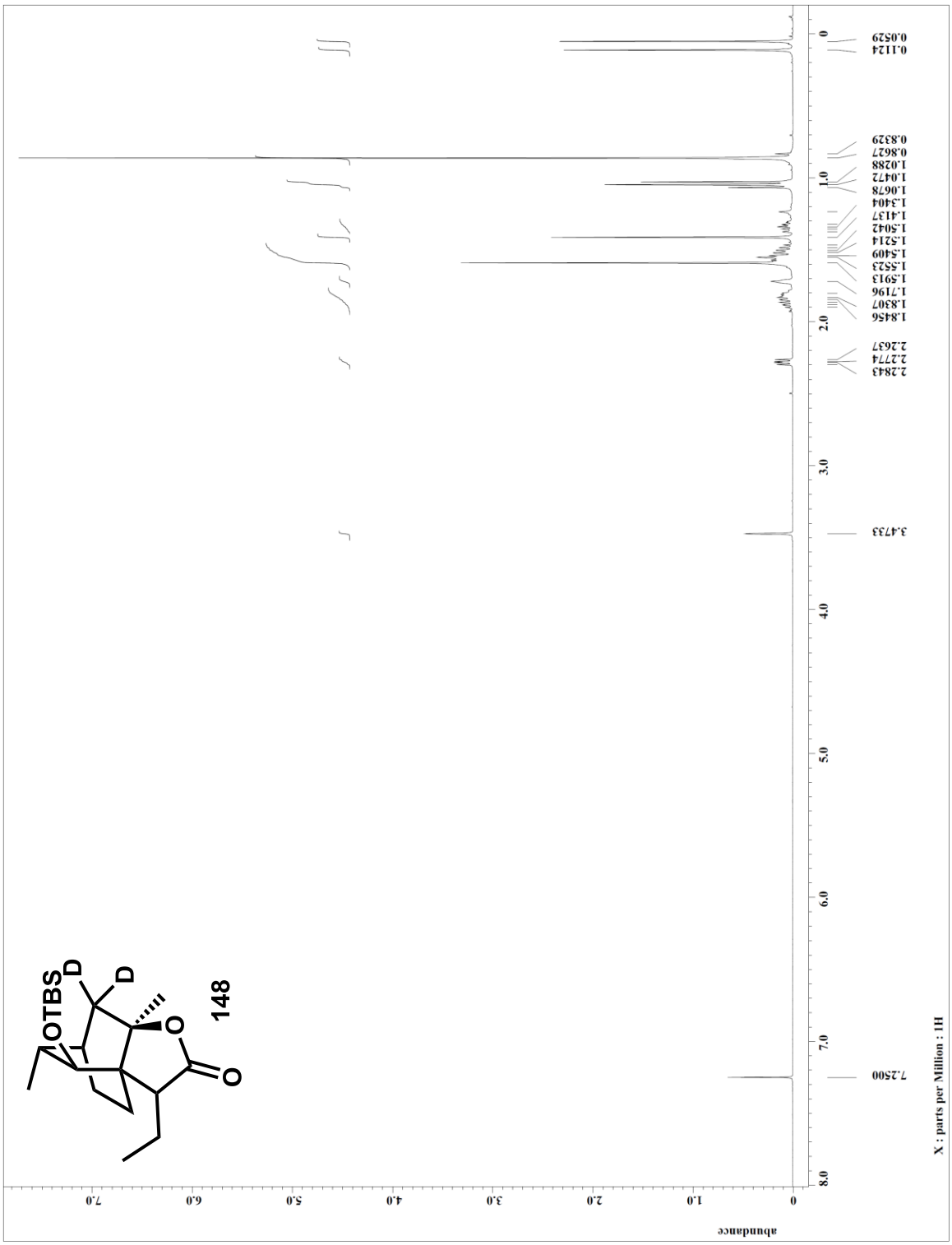
^{1}H NMR for compound **145**



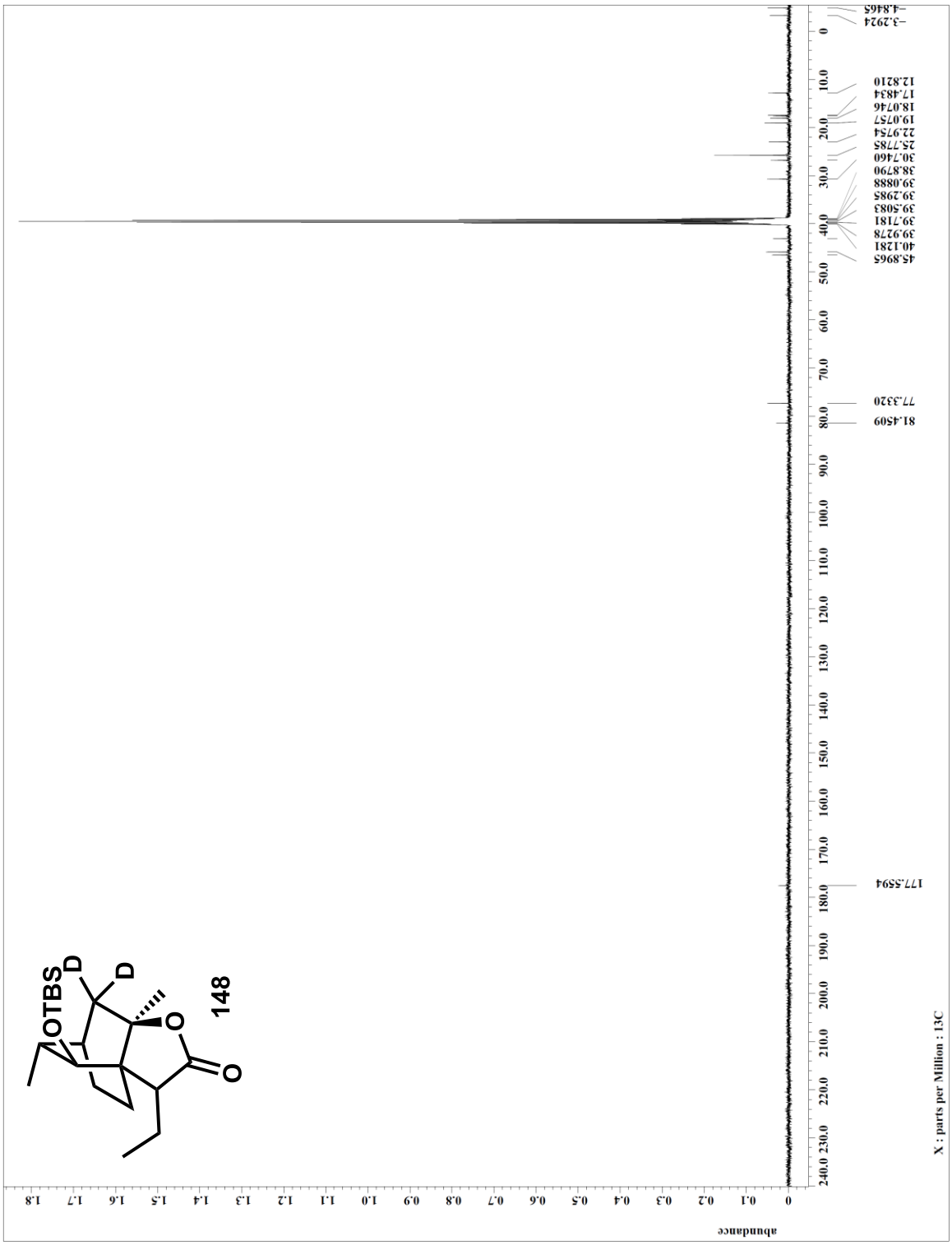
^{1}H NMR for compound **146a**



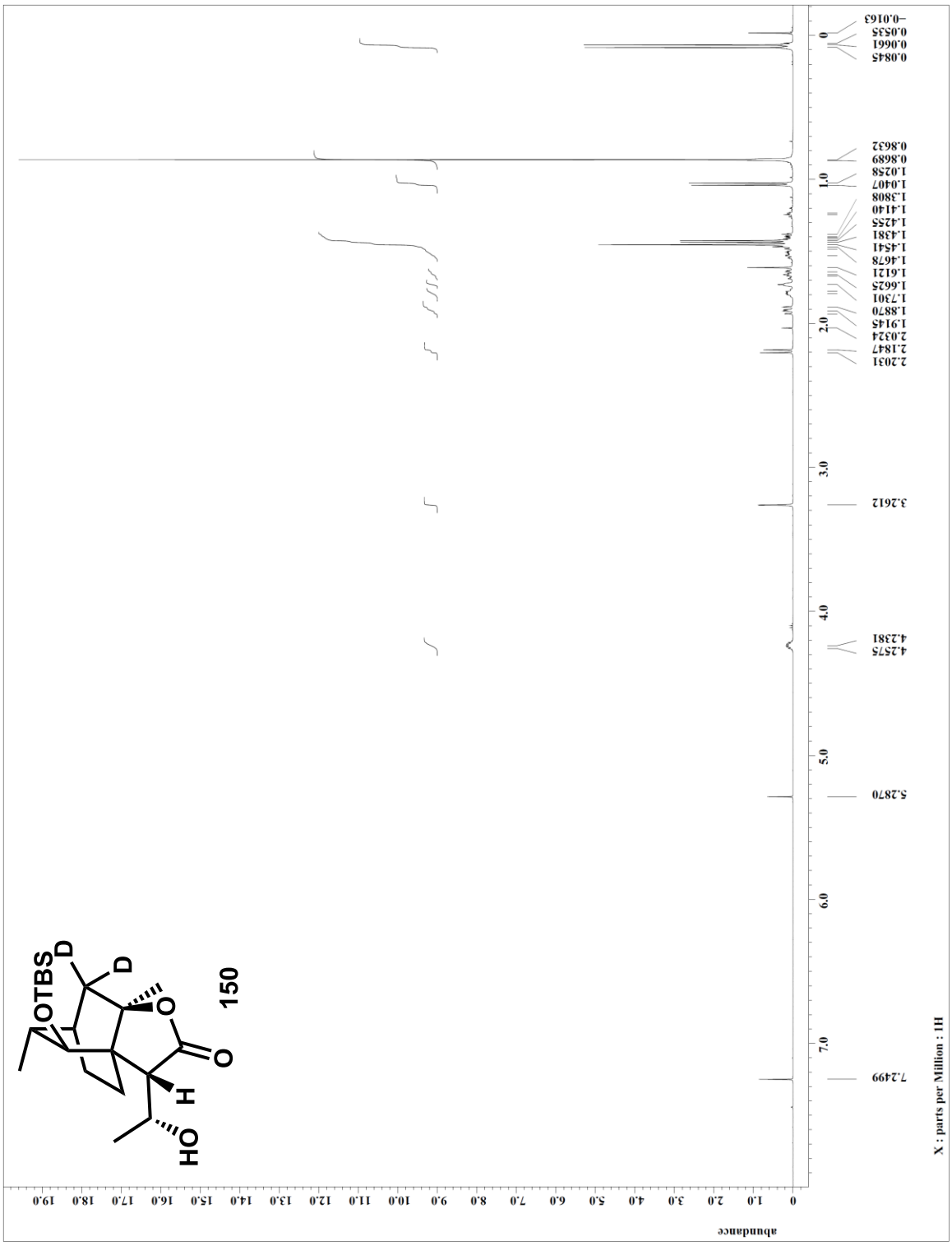
^{13}C NMR for compound **146a**



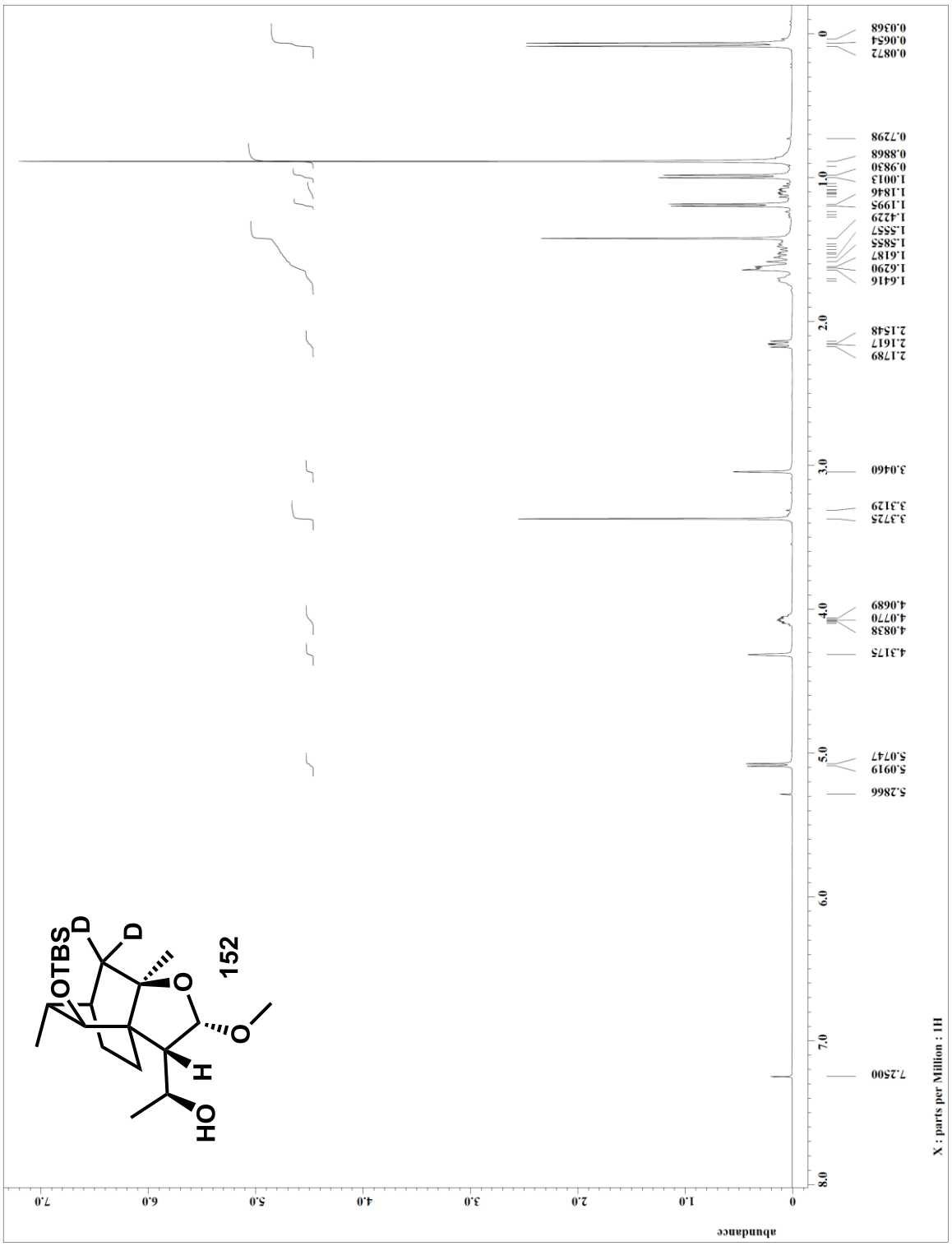
^{1}H NMR for compound **148**



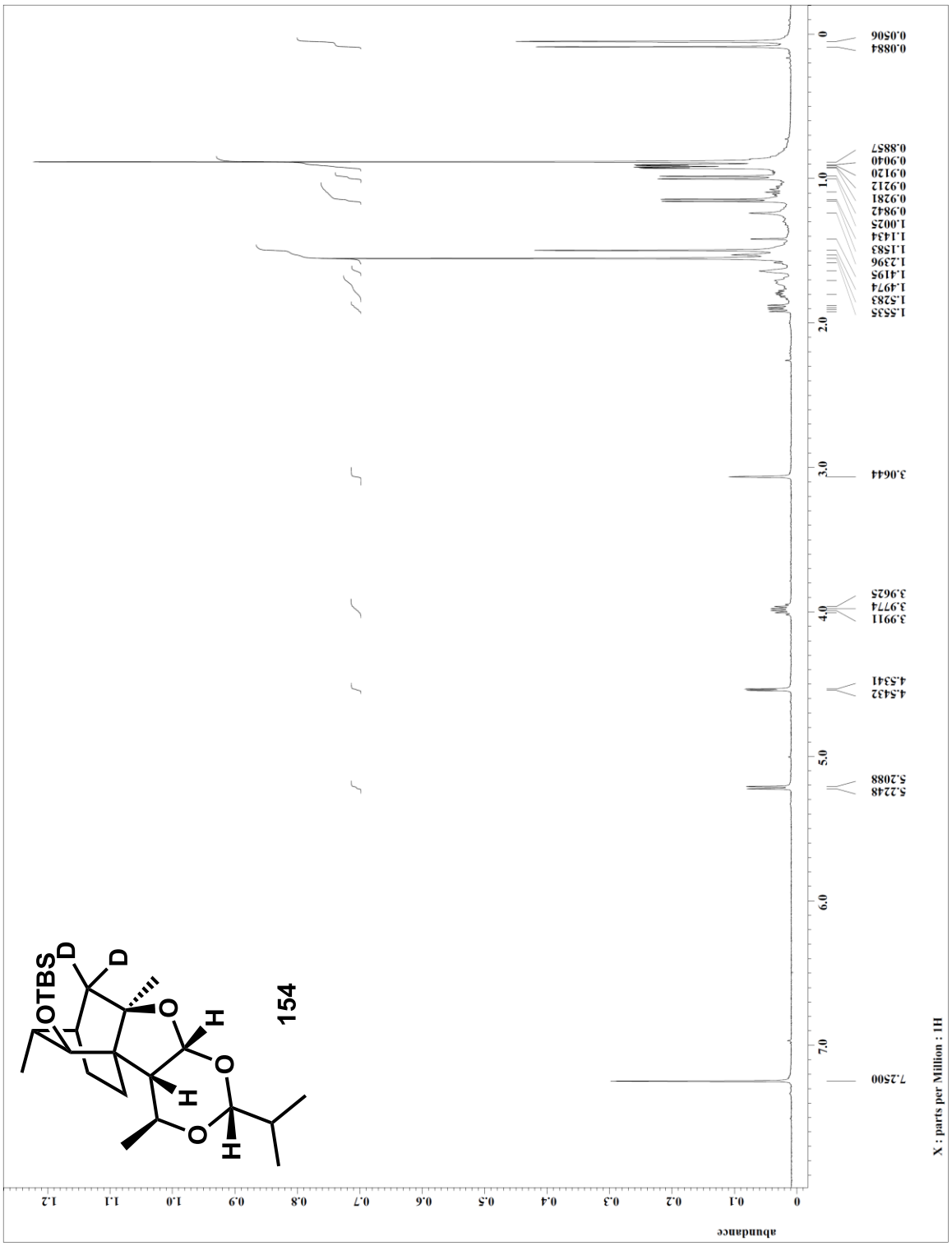
^{13}C NMR for compound **148**



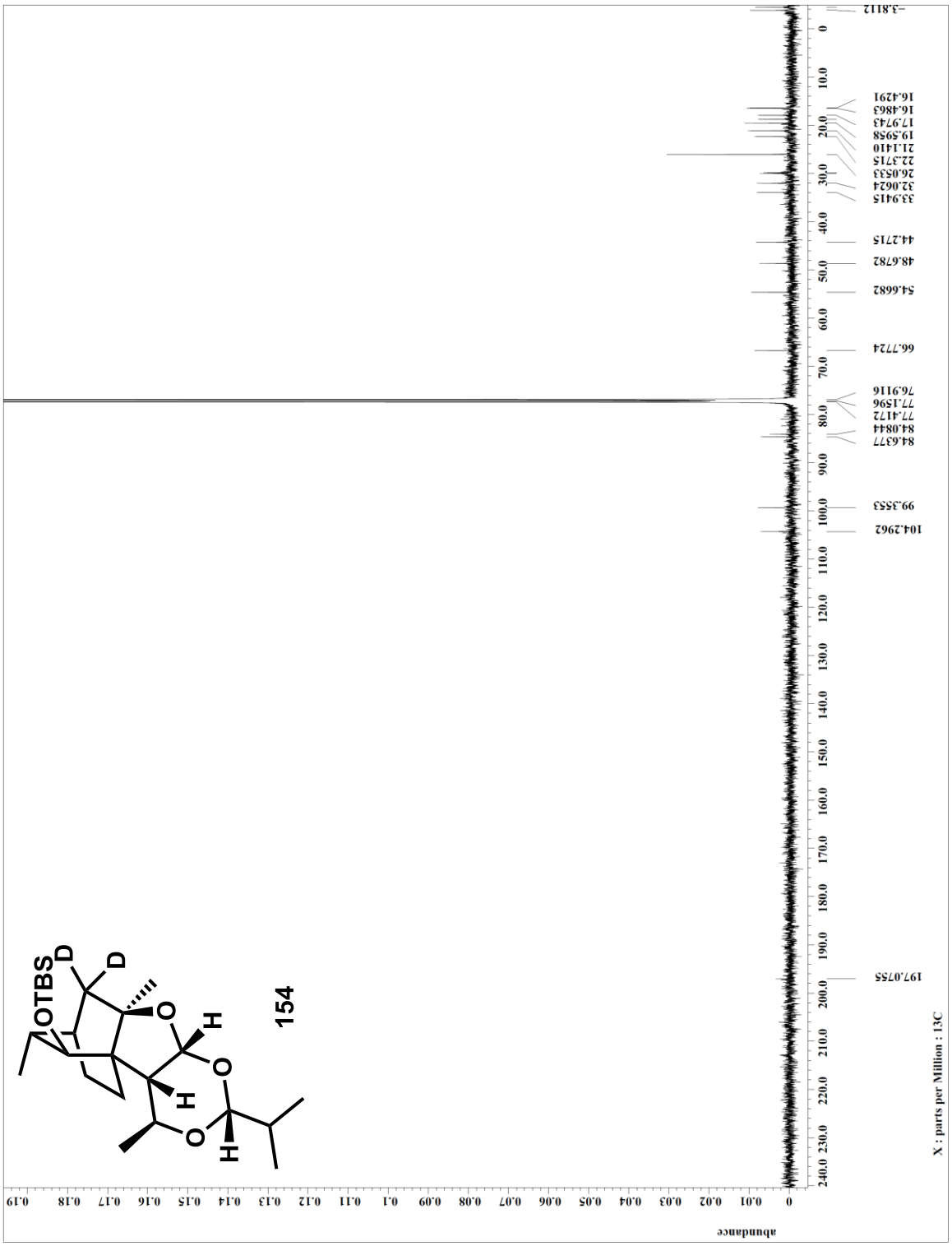
^{1}H NMR for compound **150**



^{1}H NMR for compound **152**



^{1}H NMR for compound **154**



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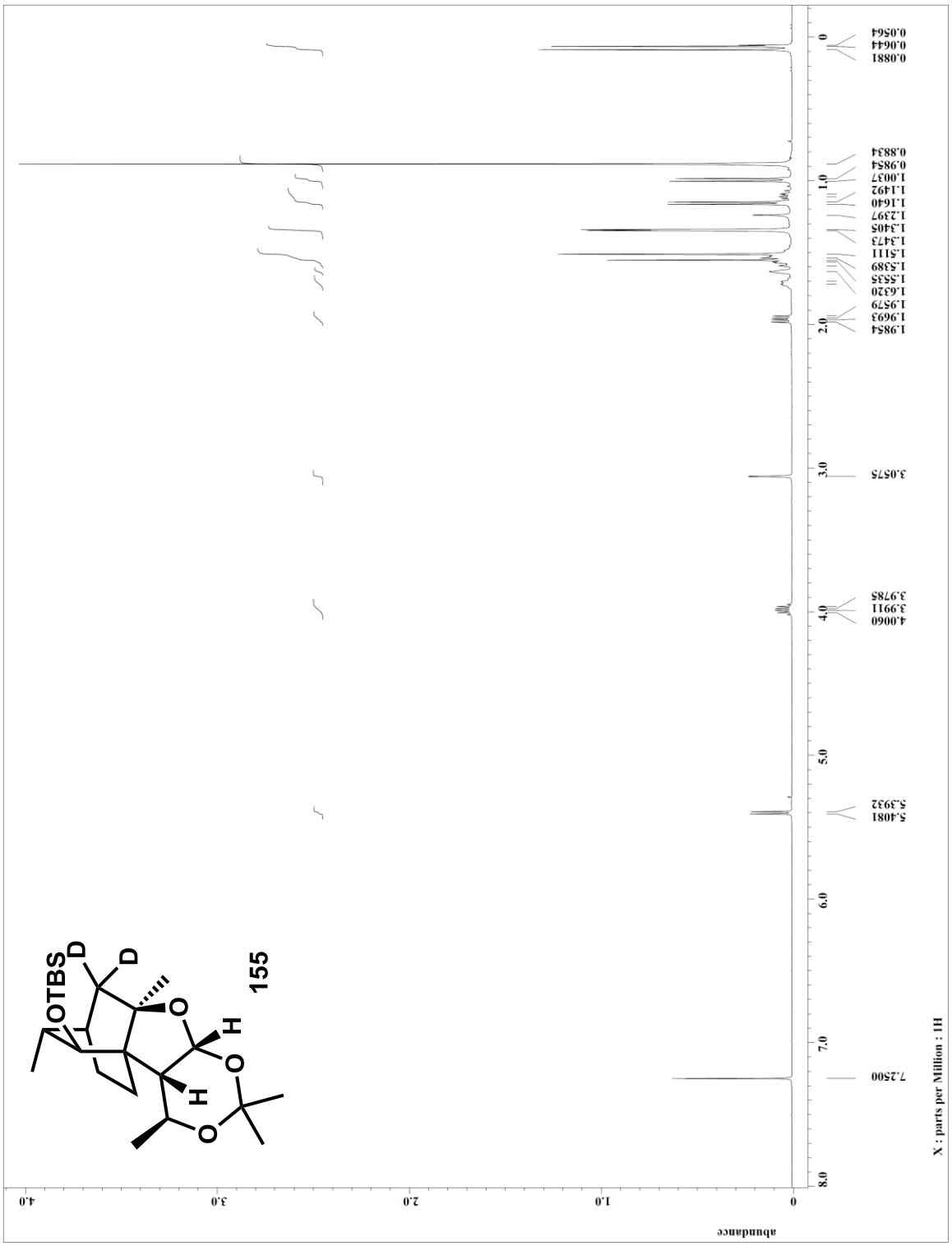
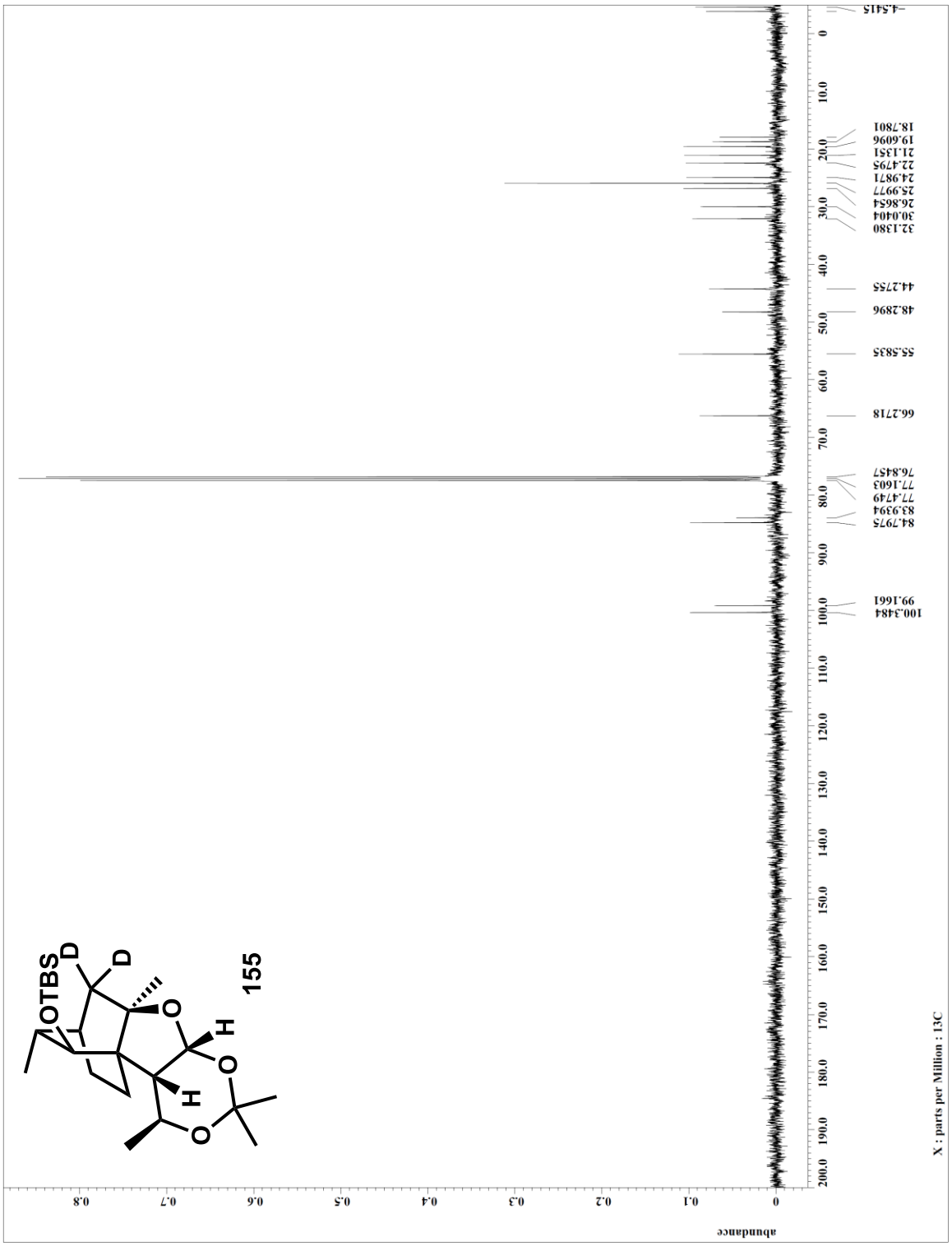
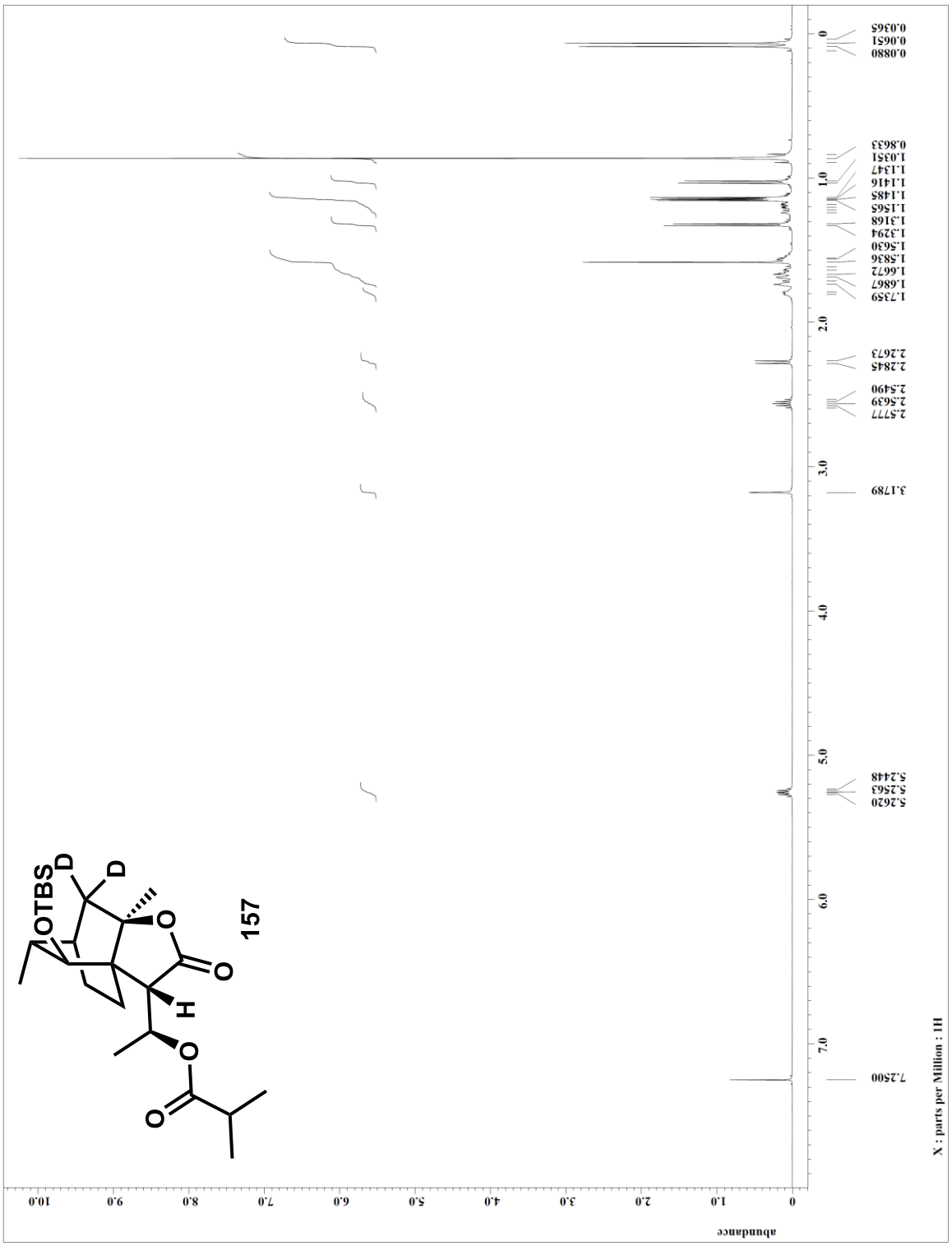


^{1}H NMR for compound **155**



^{13}C NMR for compound **155**



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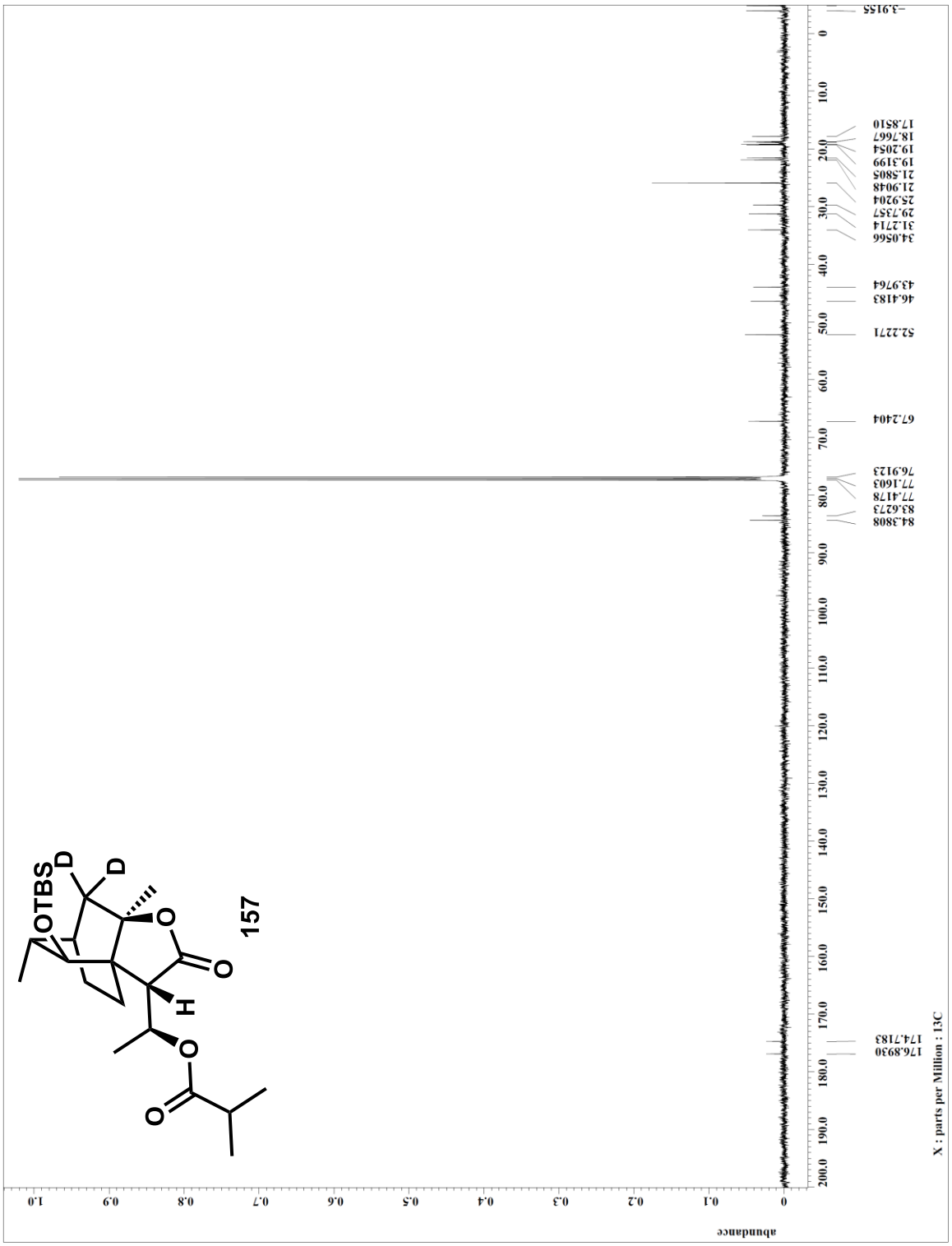
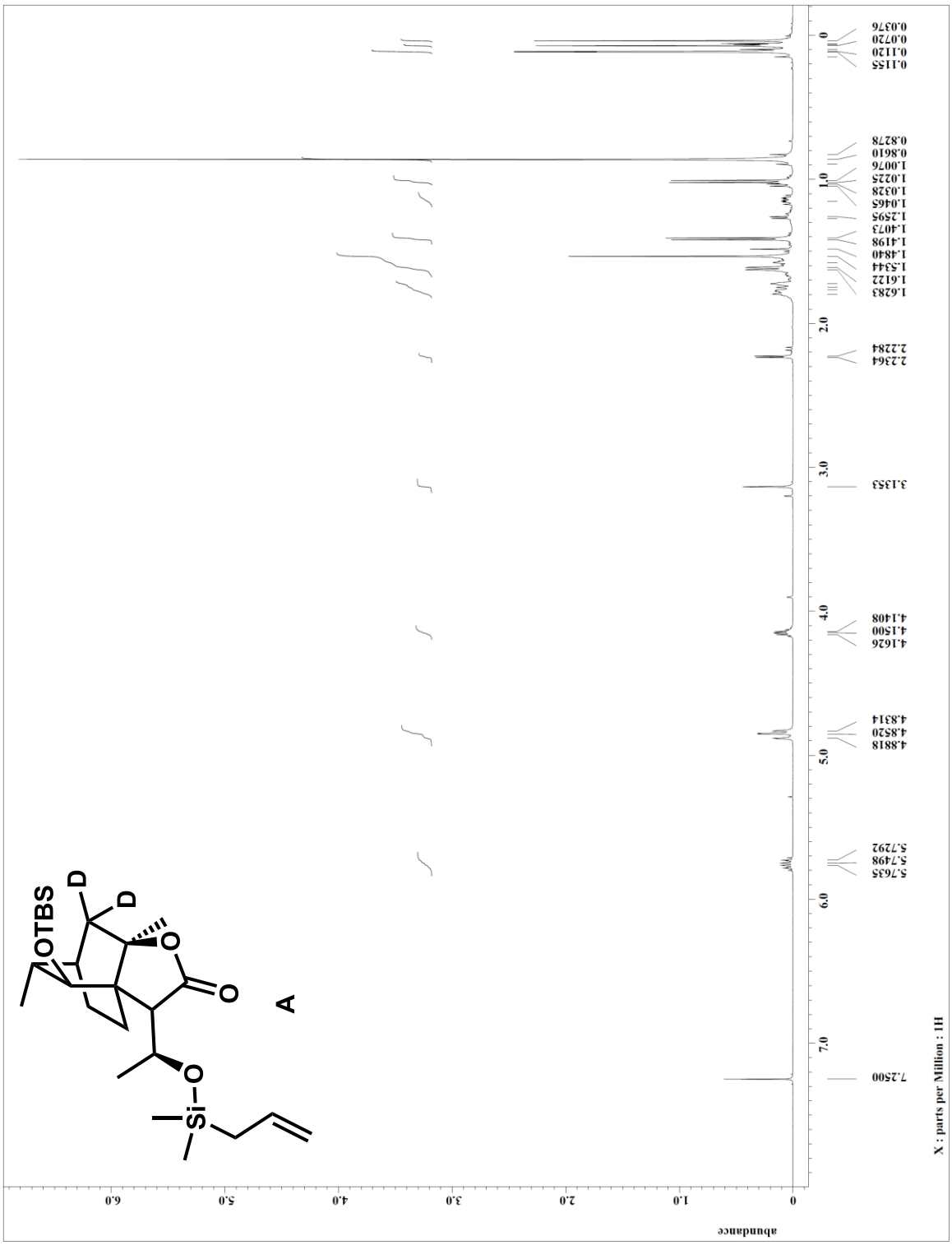
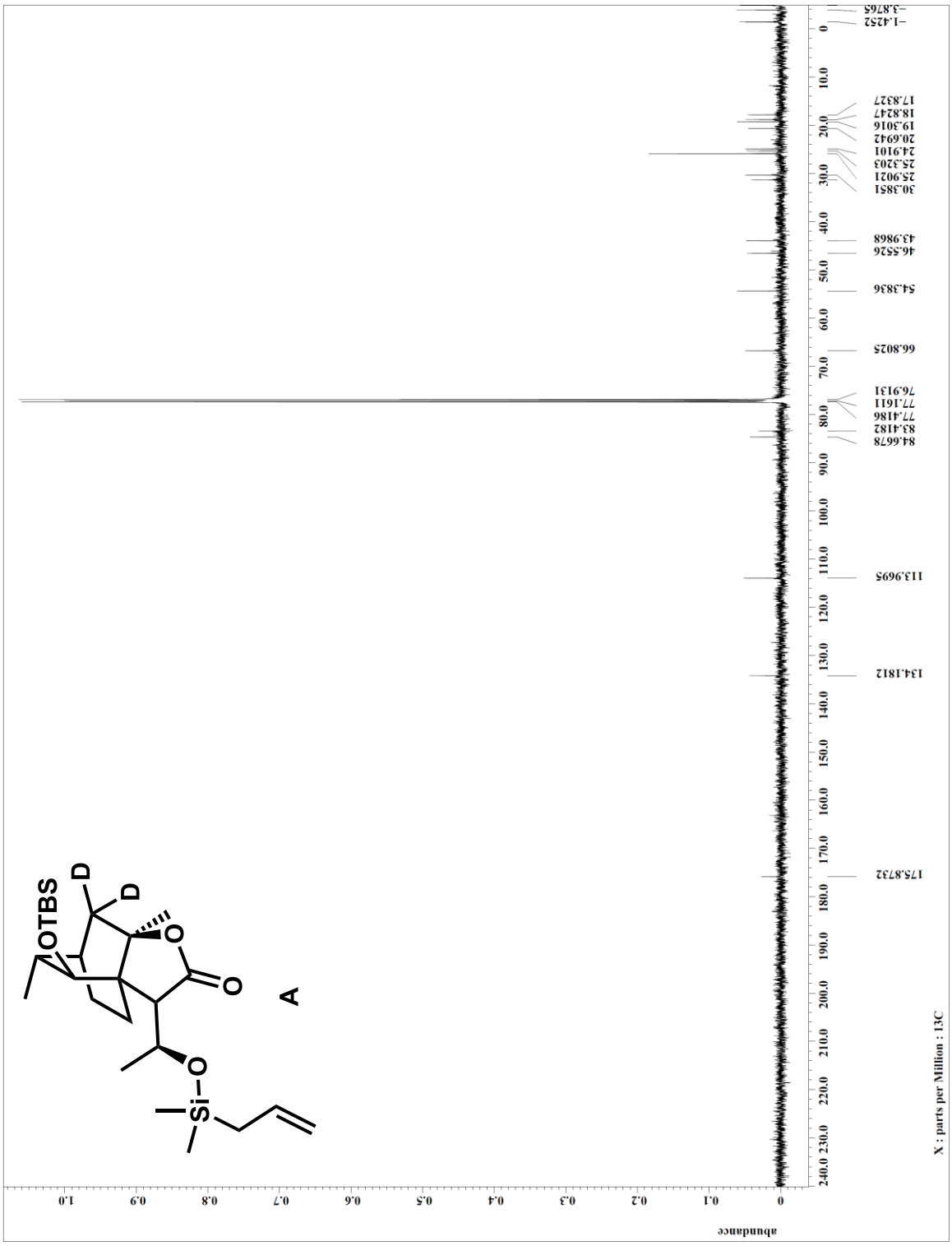


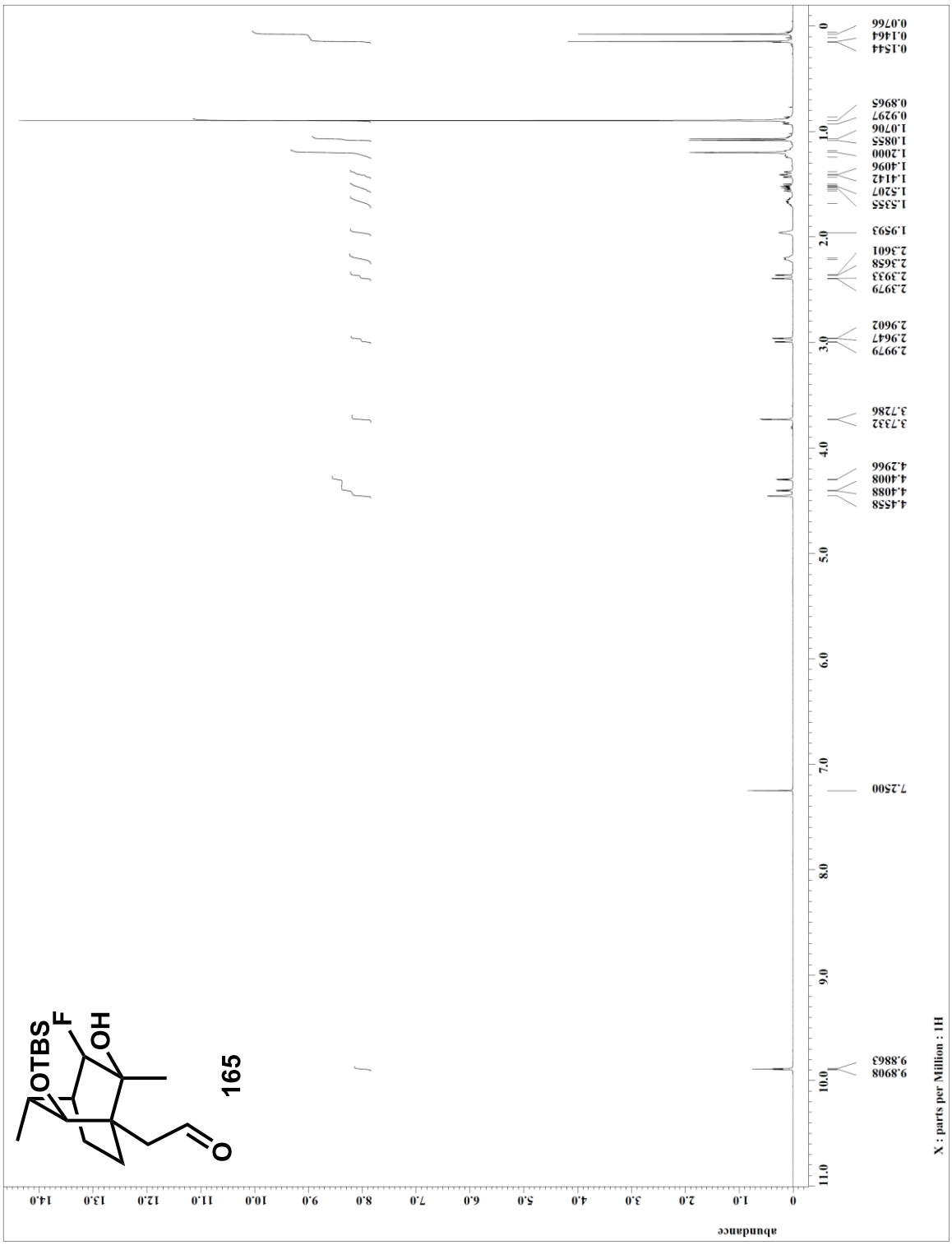
^{13}C NMR for compound **157**



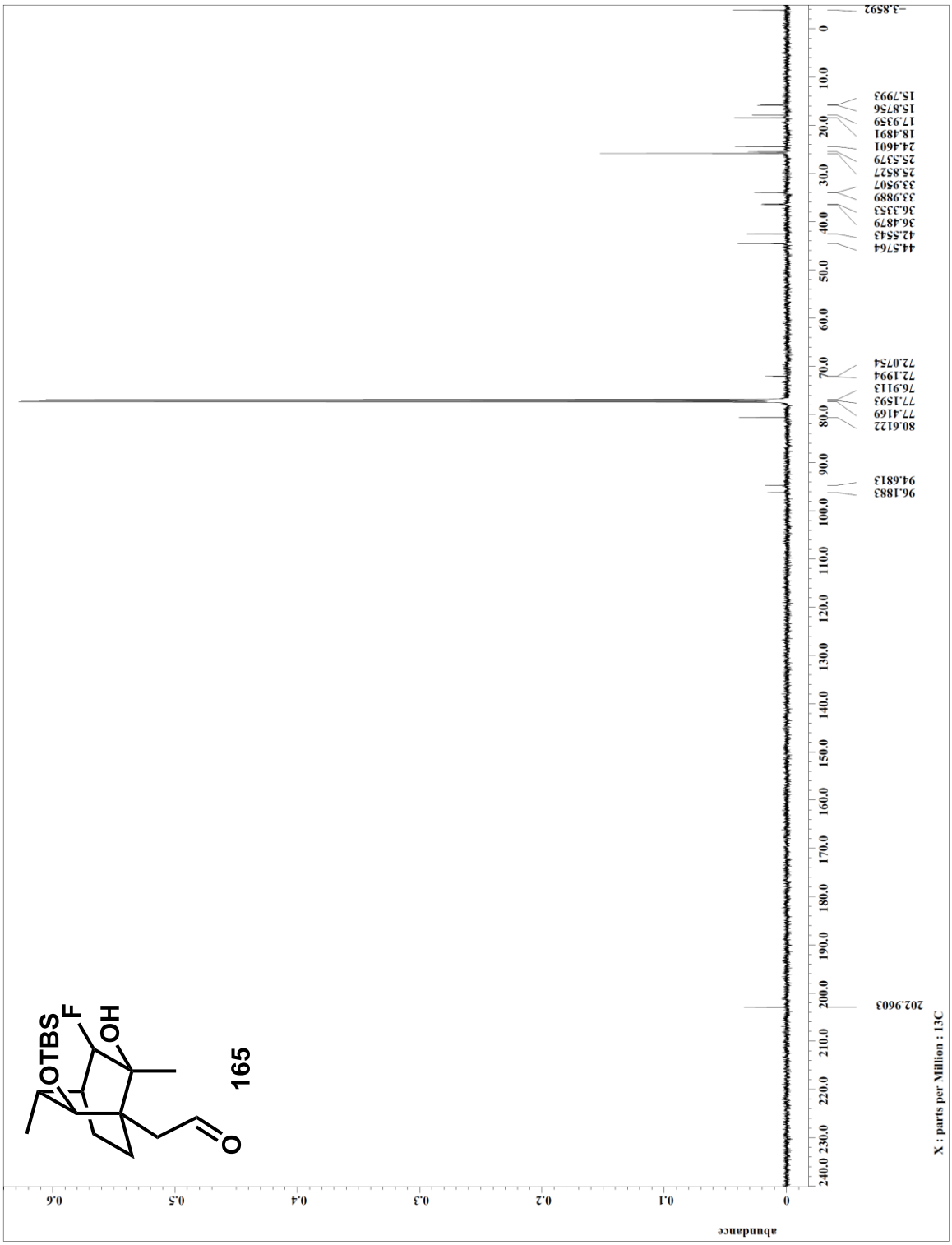
^{1}H NMR for compound **A**



^{13}C NMR for compound **A**



^{1}H NMR for compound **165**



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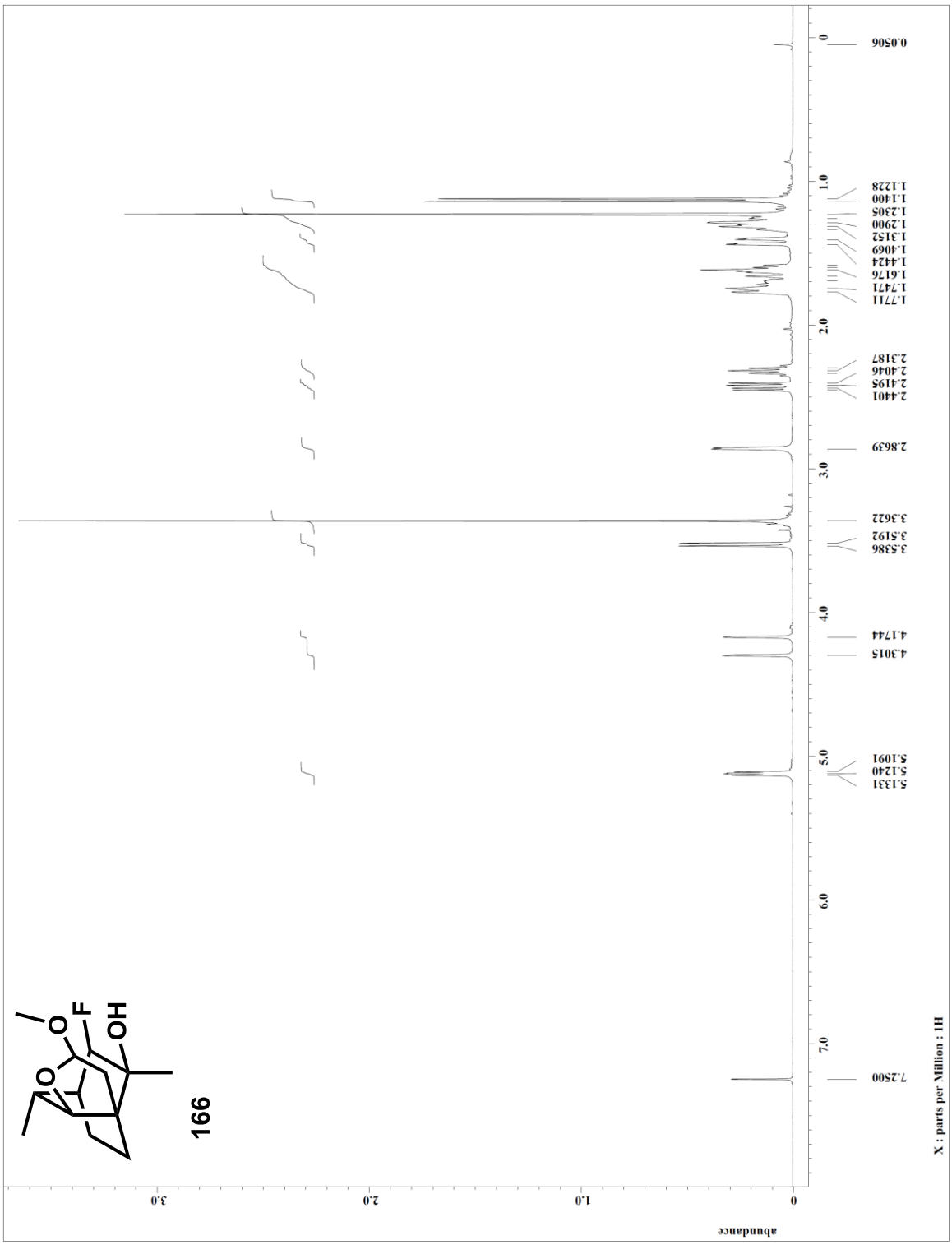

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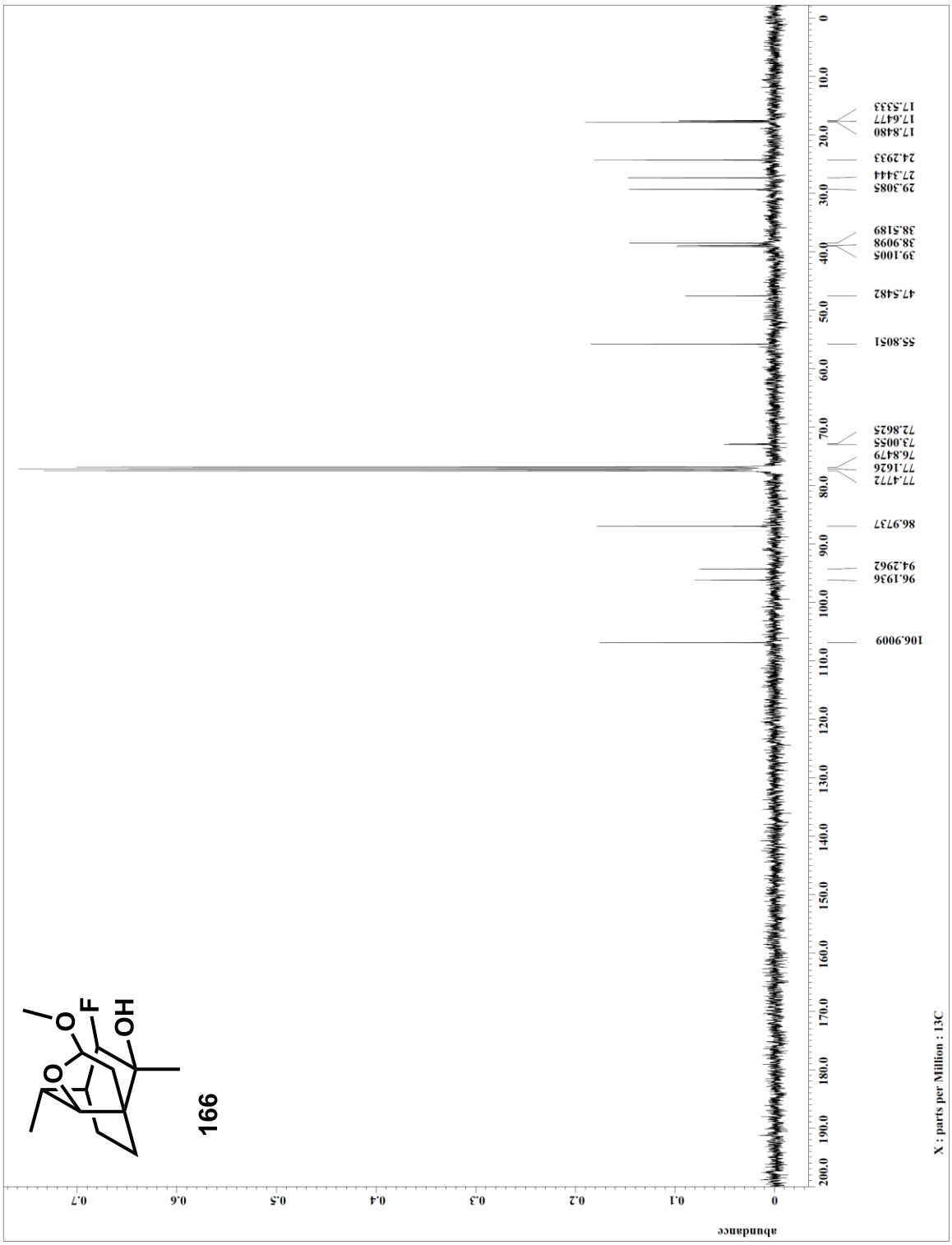

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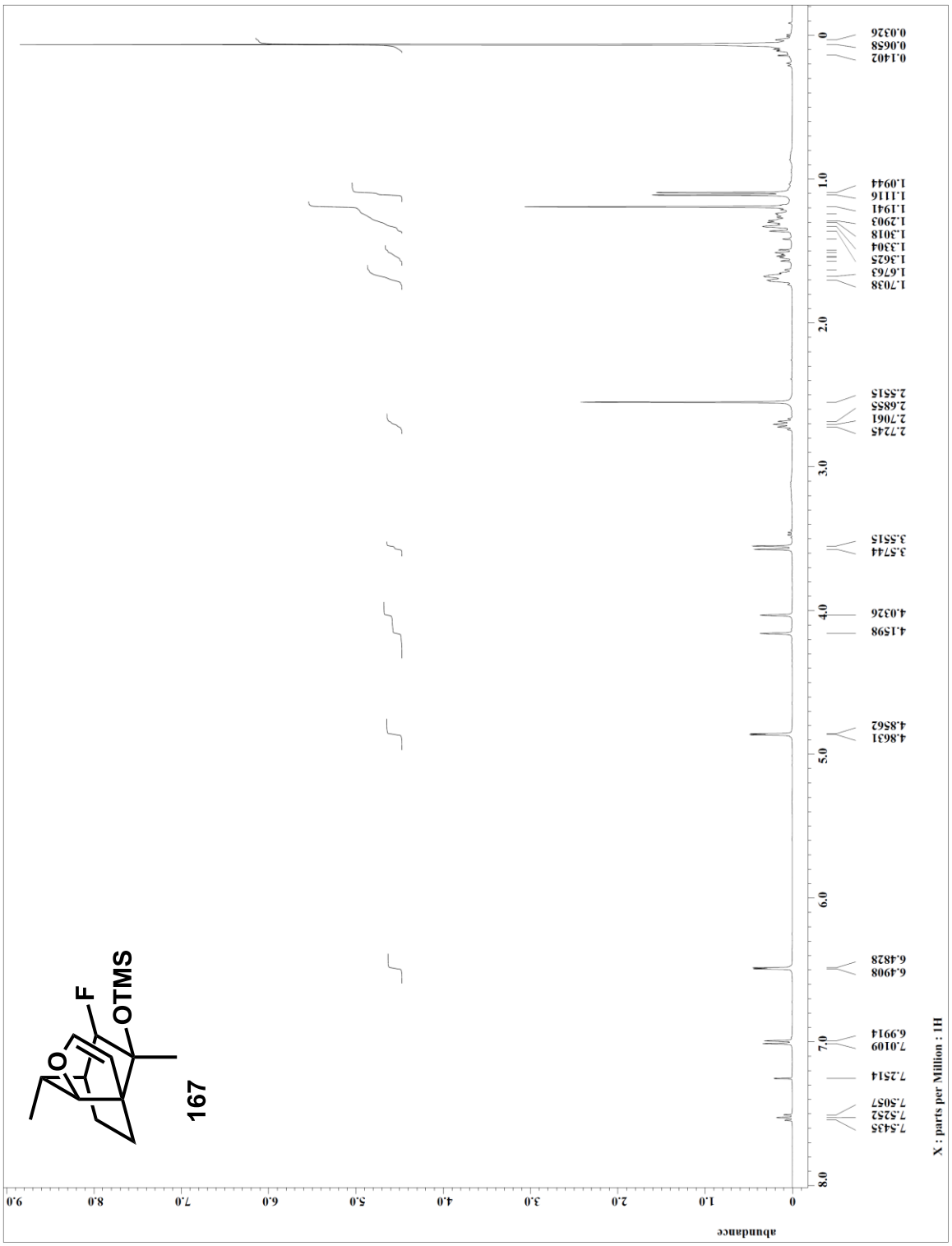
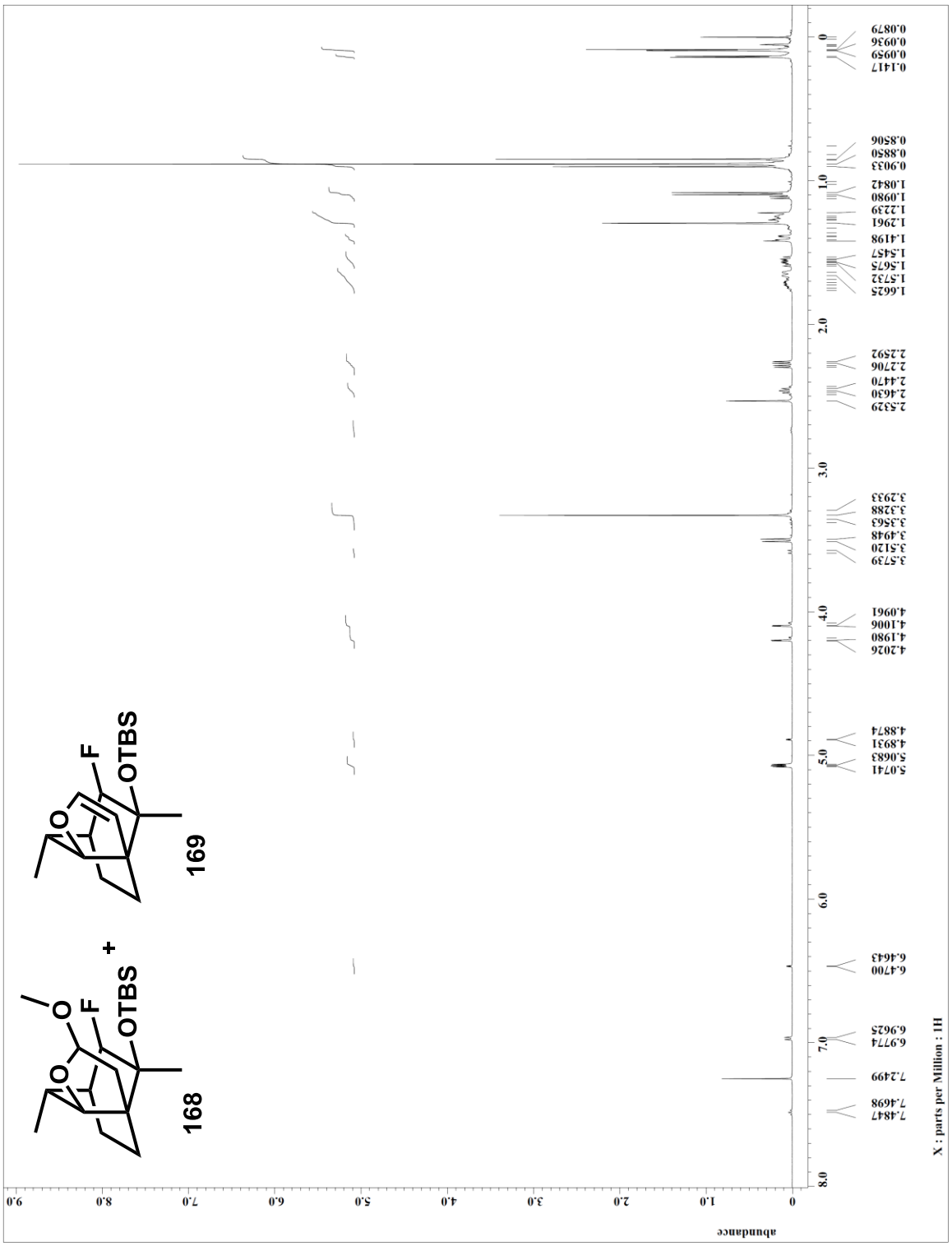
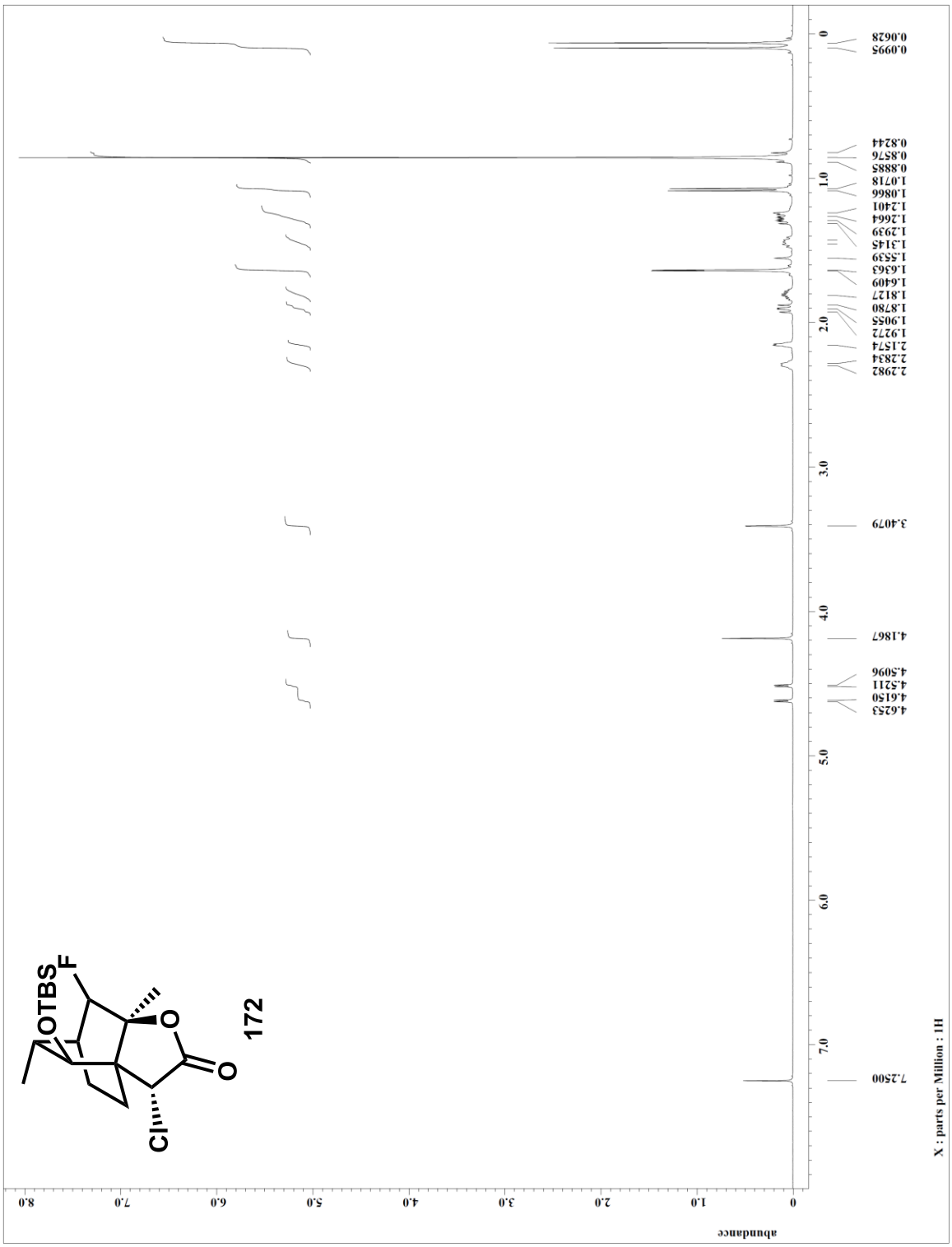


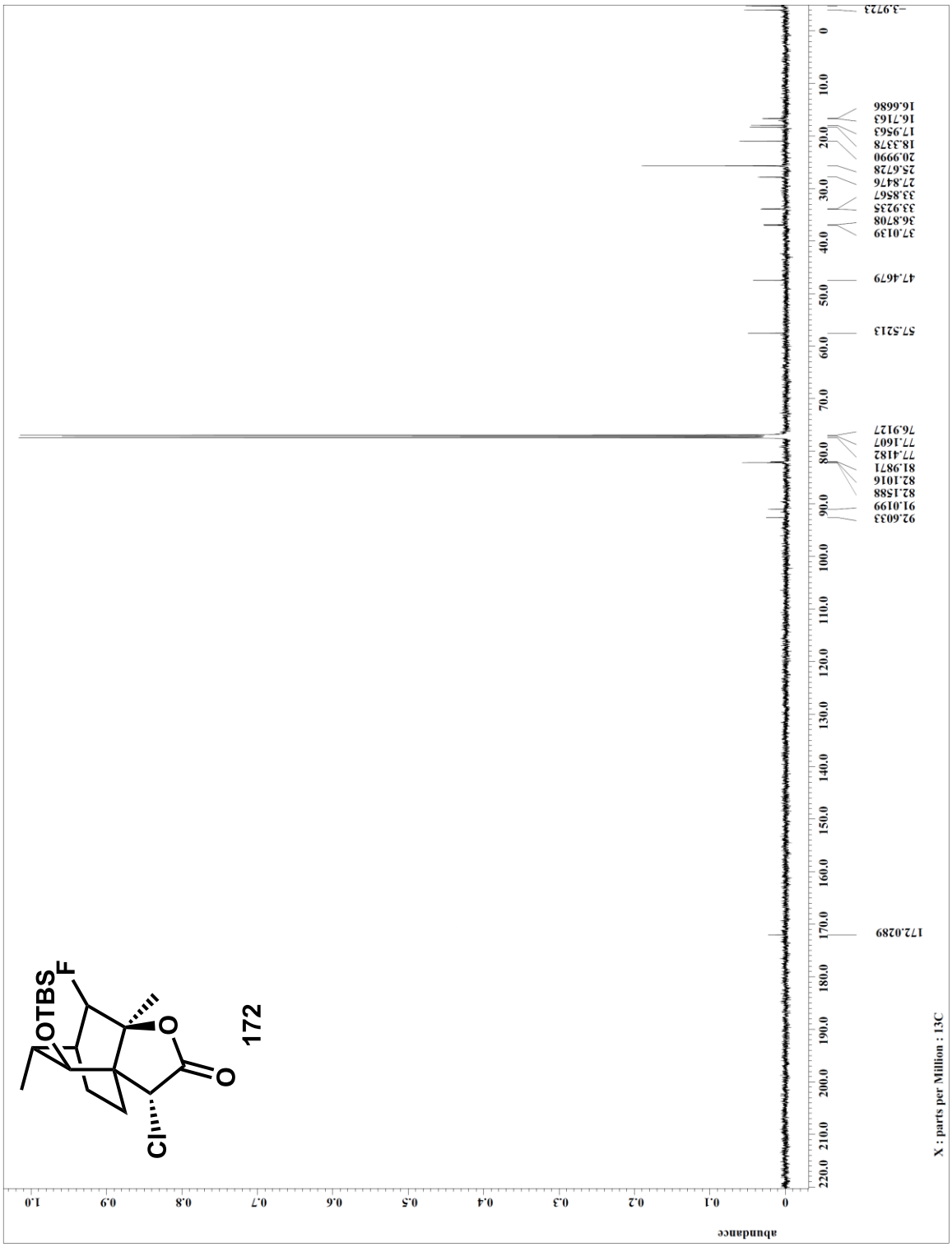
^{1}H NMR for compound **167**



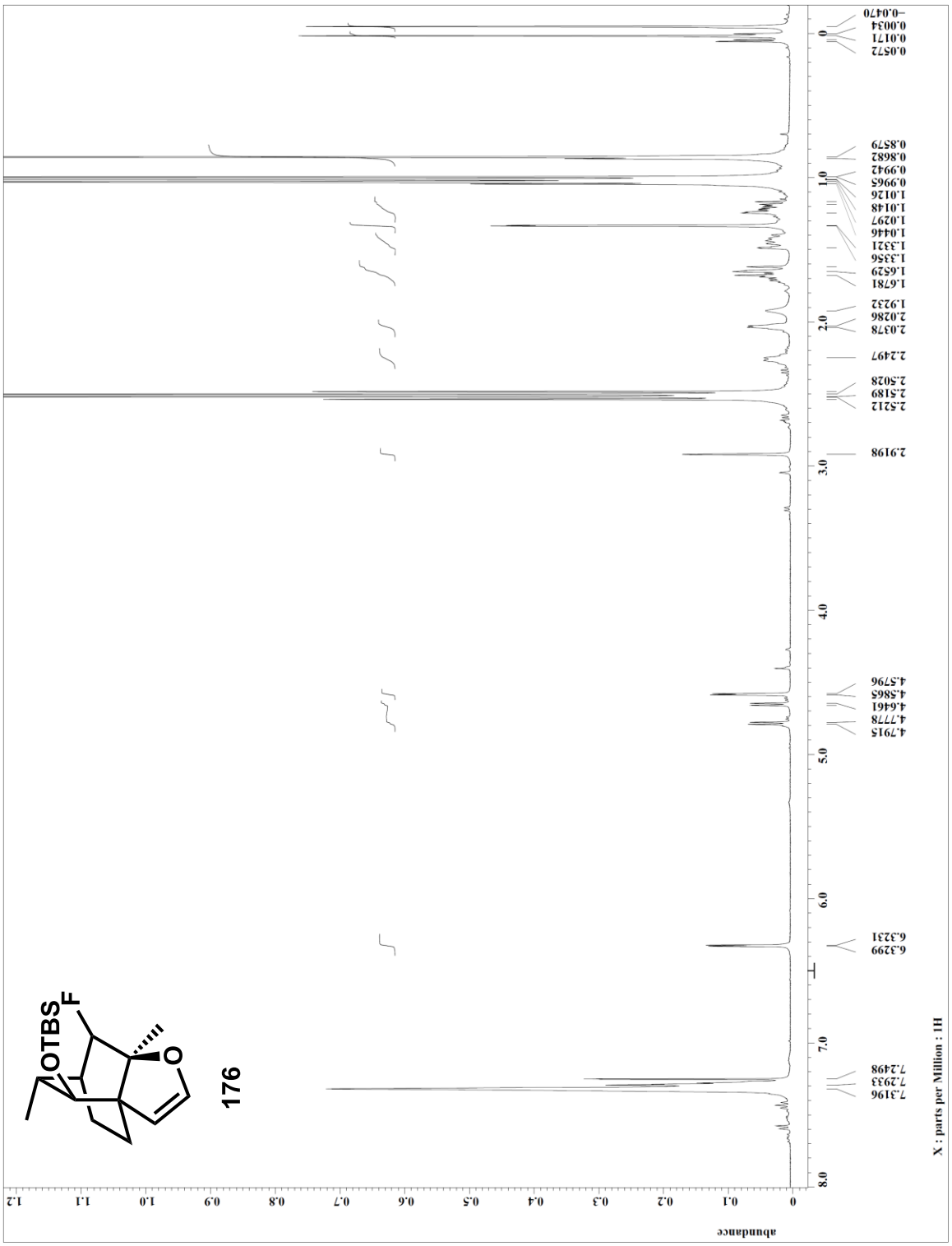
^{1}H NMR for compounds **168** and **169**



^{1}H NMR for compound **172**



^{13}C NMR for compound **172**



^{1}H NMR for compound **176**

2. SYNTHESIS OF POLYCYCLIC RING SYSTEMS VIA CARBENE CASCADES

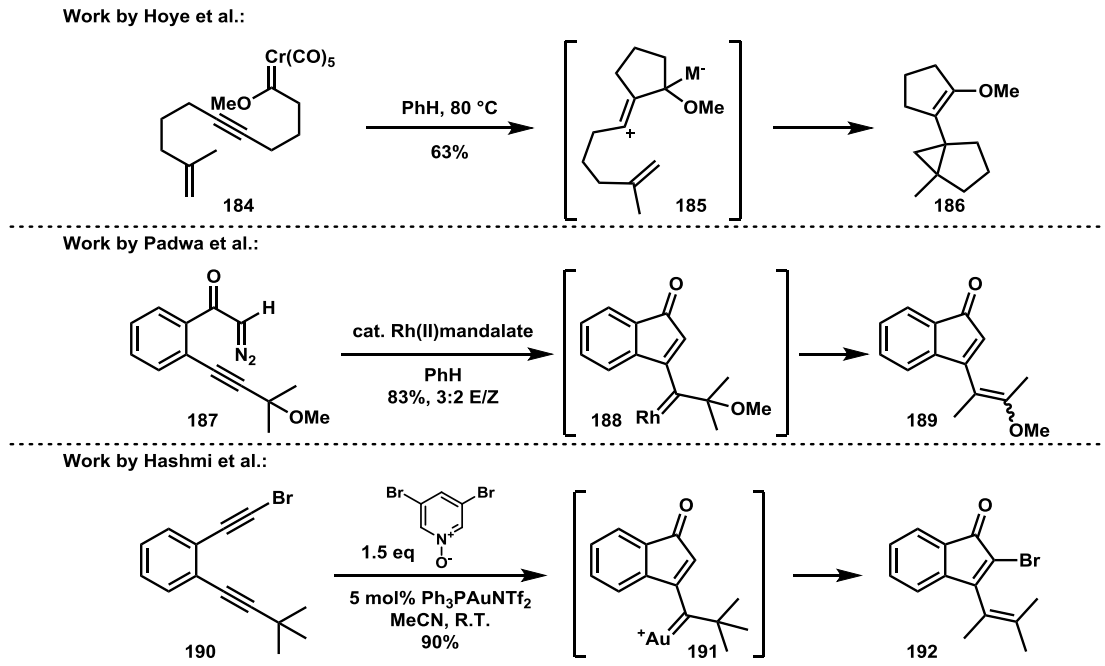
2.1. Background

2.1.1. Alkyne/Carbene Cascade Reactions

The first examples of carbene alkyne metathesis cascade reactions were reported by the Hoye[1] and Padwa[2] groups in 1988 and 1990 respectively (Figure 13). Cascade reactions are very powerful transformations. A diazo-compound forms a metal carbene with loss of dinitrogen when exposed to TM catalyst. The reaction of the transition metal carbene onto the alkyne π-bond generates an allyl carbenoid-like intermediate, whose reactivity is like that in **186** or **189**. This resulting transition metal carbenoid complex can undergo a wide assortment of transformations, like C–H insertion, X–H insertion, cyclopropanation (product **184**), 1,2-hydride or alkyl migration (product's **187** and **190**), and ylide formation. In more recent work by Hashmi et al.[3], gold was used to catalyze the oxidative cyclization of diynes, which yields the same general indene-one structure.

The reported examples represent the application of the alkyne/carbene metathesis for the construction of fused ring systems.

Figure 13. Representative examples of carbene/alkyne cascades.

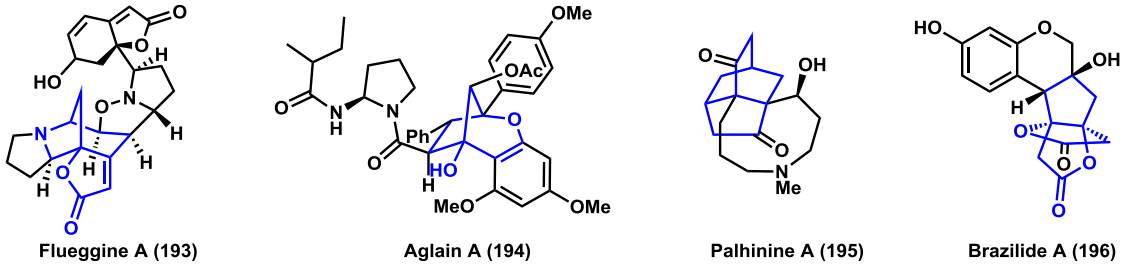


2.2. Polycyclic Ring Formation

2.2.1. Importance

Bridged bicycles and polycycles are common structural motifs in natural products, many of which have impressive bioactivities. A few examples are highlighted in Figure 14. A general method with a common starting point could allow access to many different polycyclic core structures.

Figure 14. Policyclic natural products.

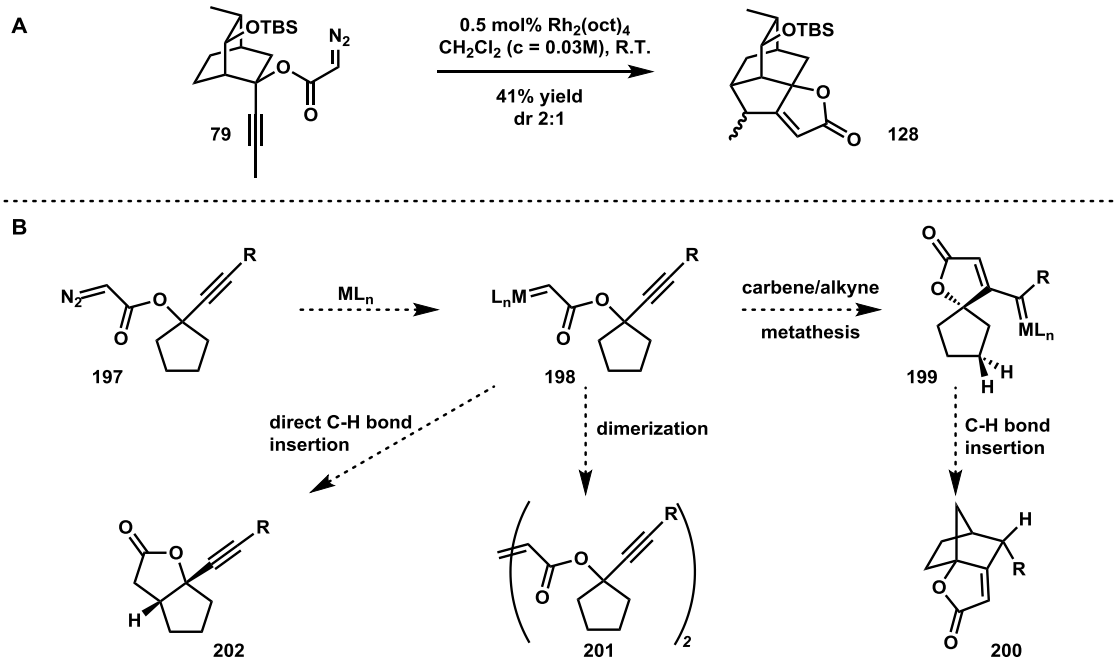


2.2.2. Formation of Bridged Bicyclic Ring Systems

As previously described in Chapter 1 for the toward synthesis of Maoecrystal V, we observed a selective formation of caged polycycle **128**, when alkynyl diazo-acetate **79** was reacted with Rh(II) catalyst (part A, Figure 15). We envisioned this transformation being an efficient way to access different bridged polycycles, where multiple C-C bonds are formed in a single reaction.

After the extrusion of a dinitrogen molecule from diazo-acetate **197** with metal catalysts (ML_n), a metal carbene **198** is generated (path B, Figure 15). The starting carbenoid cyclizes with a nearby alkyne in **198** to form a new metal carbene **199**. Further insertion in the most available C-H bond takes place to terminate the metal carbene in **199**, and bridged polycyle **200** is formed. Carbenoid **198** can also react with **197**, which leads to undesired homodimer product **201**. The metal carbene in **198** could possibly insert in the nearby C-H bond as well, generating a fused [3.3.0]bicycle **202**.

Figure 15. The carbene cascade.

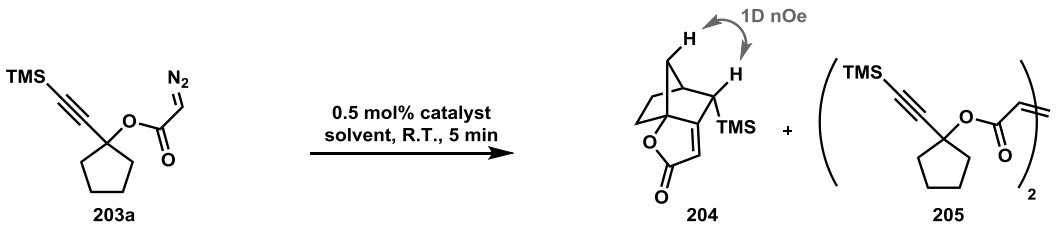


2.2.3. Reaction Optimization

We started to examine the reactivity of diazo-ester **198** with different transition metal catalysts (Table 1). Copper and silver catalysts were ineffective to catalyze the cascade reaction. From all the tested rhodium complexes: $Rh_2(esp)_2$ was the most effective, generating the [3.2.1]bicycle **199** in 77% isolated yield. Dichloromethane was chosen as an optimal reaction solvent. Interestingly, homodimer **200** formation was the most dominant when using a less polar solvent, pentane (entry 10). The reaction was much slower at 0 ˚C than the corresponding reaction at room temperature. A higher concentration was detrimental to the formation of bridged bicycle, since more dimers were formed (entry 12). The dimerization process can be completely eliminated by performing a slow addition

of substrate to the rhodium(II) catalyst (entry 14). Due to the simple reaction set-up and short reaction time we chose conditions from entry 9 as most practical.

Table 1. Reaction optimization.



203a 204 205

Entry	Catalyst	Solvent	Conc., M	Yield, %[a]	Yield, %[a]
1	$Rh_2(OAc)_4$	CH_2Cl_2	0.005	28	32
2	$Rh_2(oct)_4$	CH_2Cl_2	0.005	50	24
3	$Rh_2(TPA)_4$	CH_2Cl_2	0.005	36	18
4	$Rh_2(TFA)_4$	CH_2Cl_2	0.005	trace	41
5	$Rh_2(cap)_4$	CH_2Cl_2	0.005	trace	trace
6	AgOTf	CH_2Cl_2	0.01	-	-
7	$(CuOTf)_2$•PhH	CH_2Cl_2	0.005	trace	trace
8	$Cu(MeCN)_4$•PF_6	CH_2Cl_2	0.005	trace	trace
9	$Rh_2(esp)_2$	CH_2Cl_2	0.005	77	16
10	$Rh_2(esp)_2$	pentane	0.005	38	60
11	$Rh_2(esp)$	$(CH_2Cl)_2$	0.005	46	5
12	$Rh_2(esp)_2$	CH_2Cl_2	0.01	63	27
13[b]	$Rh_2(esp)_2$	CH_2Cl_2	0.005	55	23
14[c]	$Rh_2(esp)_2$	CH_2Cl_2	0.005	70	trace

Isolated yields; [a] 0 °C; [c] Slow addition of x to $Rh_2(esp)_2$

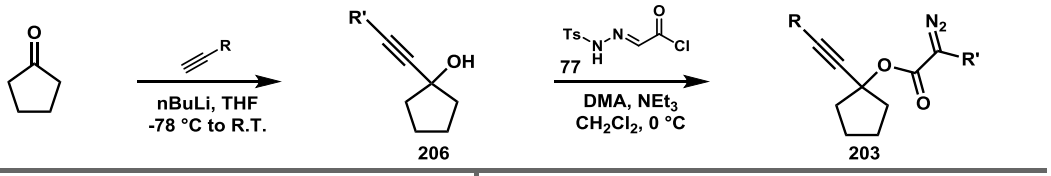
2.2.4. Syntheses of Starting Materials

2.2.4.1. Tertiary Alcohol Synthesis and Diazo-Acetate Synthesis

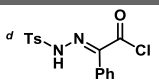
It is important to emphasize the simplicity of the preparation of the cascade starting materials. The diazo-esters can be prepared in just two steps, starting with commercially

available ketones. Different lithium acetalydes can be reacted with ketones to generate propargylic alcohols**,** like **206** in Table 2. These propargylic alcohols are then subjected to reaction with diazo-ester reagent **77**. The diazo-compounds were isolated in decent to good yields. No decomposition of diazo-esters was observed even after twelve months when stored at low temperatures.

Table 2. Synthesis of different alkyne substituted diazo-esters.

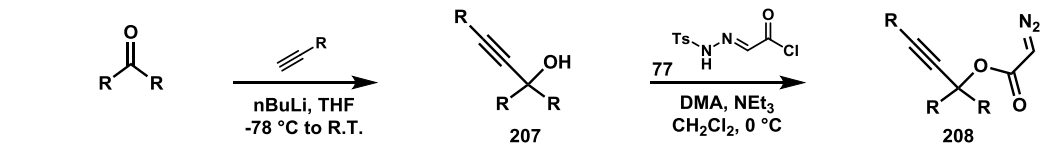


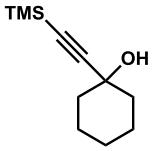
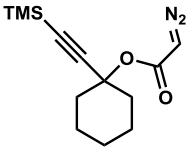
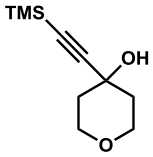
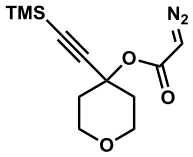
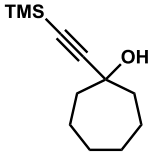
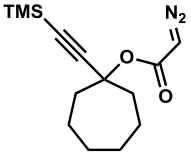
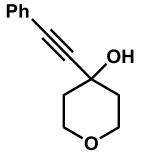
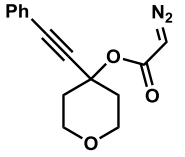
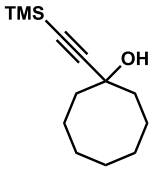
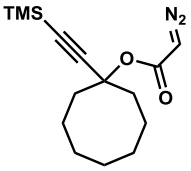
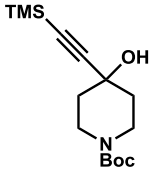
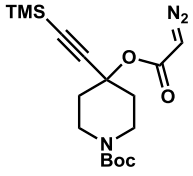
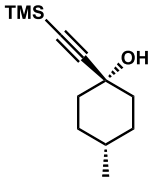
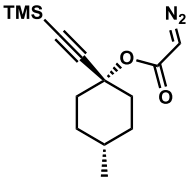
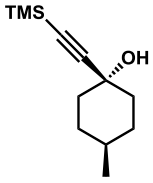
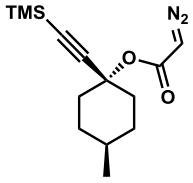
Entry	Product 206a-f	Yield	Product 203a-f	Yield	Entry	Product 206g-l	Yield	Product 203g-l	Yield
1	R = TMS	97%	R' = H	78%	7	R = Ph(*p*-OMe)	96%	R' = H	52%
2	R = TIPS	88%	R' = H	80%	8	R = Ph(*p*-CF_3)	99%	R' = H	44%
3	R = nBu	96%	R' = H	61%	9	R = Ph(*m*-OMe)	88%	R' = H	71%
4	R = tBu	75%	R' = H	73%	10	R = Ph(*m*-Br)[c]	92%	R' = H	68%
5	R = CF_3[a]	61%	R' = H	20%	11	R = Ph(*m*-CO_2Me)[c]	99%	R' = H	53%
6	R = Br[b]	97%	R' = H	53%	12	R = TMS	97%	R' = Ph[d]	32%

[a] , LDA [b] xx + $AgNO_3$, NBS, acetone, 0 °C [c] LDA [d] 

A mixture of diastereomers was produced when reacting substituted cyclohexanone's with lithium acetalydes. The axial addition of the small nucleophile to the carbonyl is preferred[4].

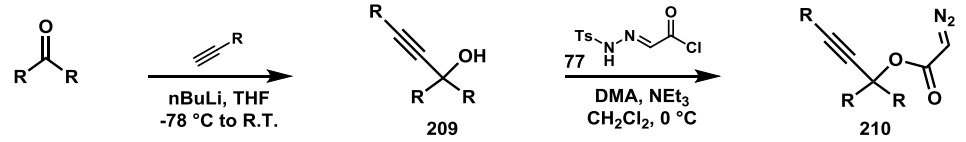
Table 3. Preparation of different diazo-esters.

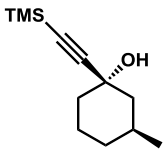
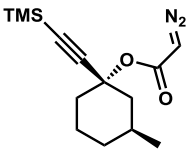
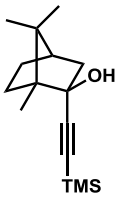
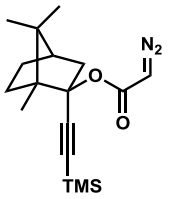
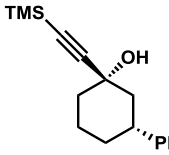
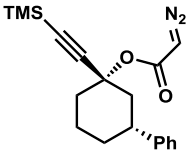
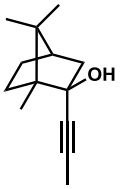
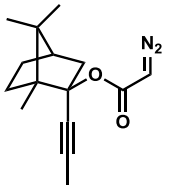
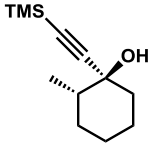
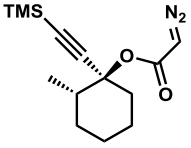
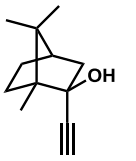
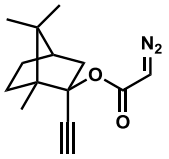
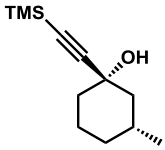
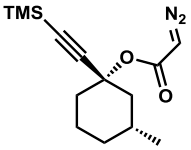
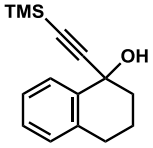
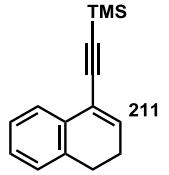
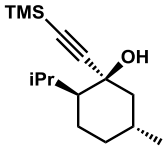
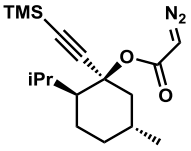
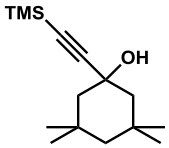
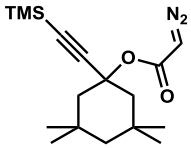


Entry	Product 207a-d	Yield	Product 208a-d	Yield	Entry	Product 207e-h	Yield	Product 208e-h	Yield
1		94%		68%	5		94%		45%
2		97%		64%	6		96%		42%
3		99%		61%	7		87%		47%
4		12%		70%	8		78%		67%

Diazo-acetate formation of a naphthalenol was unsuccessful (Table 4, entry 9). Enyne **211** was isolated as a major product from a complex reaction mixture. Most likely, this product is formed through an E1 mechanism, since in this substrate a highly stabilized carbocation intermediate can be generated.

Table 4. Preparation of different diazo-esters.

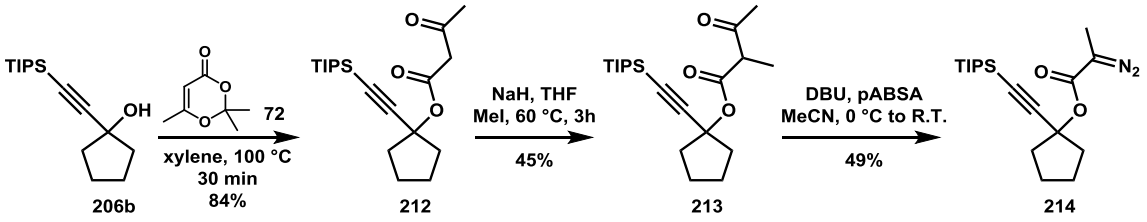


Entry	Product 209a-e	Yield	Product 210a-e	Yield	Entry	Product 209f-j	Yield	Product 210f-j	Yield
1		18%		67%	6		XX%		51%
2		78%		44%	7		79%		57%
3		XX%		43%	8		XX%		35%
4		71%		71%	9		25%		24%
5		70%		50%	10		92%		65%

The methyl diazo-acetate formation was more challenging (Scheme 29). First, β-keto-ester **212** was generated in the reaction of propargyl alcohol **206b** with dioxinone **72**. Mono-alkylation of **212** had to compete with dialkylation, which led to a lower isolated yield of mono-methyl acetoacetate **213**. In **213**, deacetylation took place in the presence of

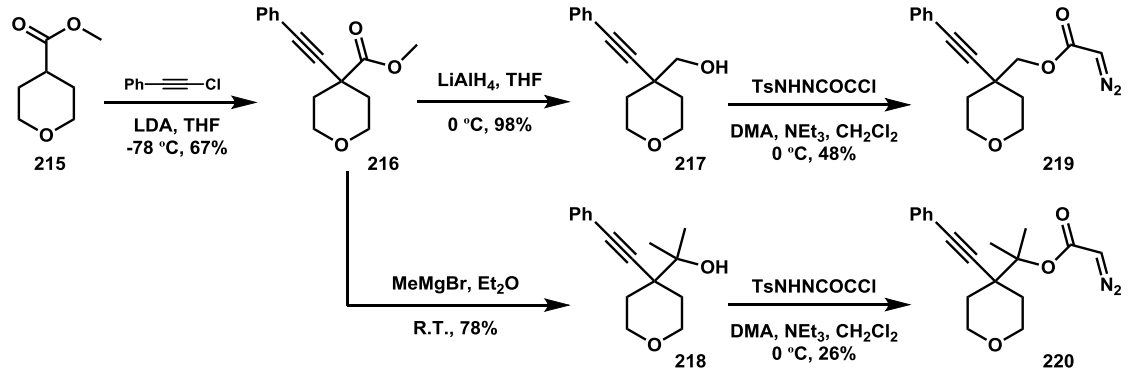
base, followed by diazotization with pABSA, generating the methyl diazo-ester **214** with 49% isolated yield.

Scheme 29. Synthesis of diazo-propionate.



Homo-propargylic alcohols **217** and **218** were prepared following a reported protocol[5] for a similar substrate (Scheme 30). The diazo-esters **219** and **220** were isolated in 48% and 26% yield, respectively.

Scheme 30. Preparation of diazo-esters **215** and **216**.



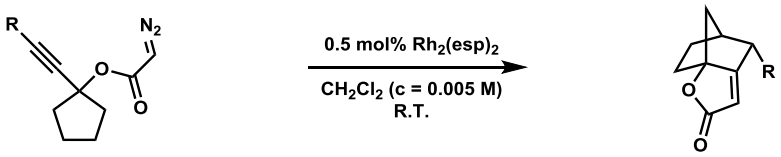
2.2.5. Tolerance of Various Functional Groups on Alkyne

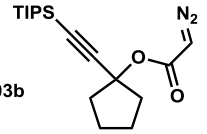
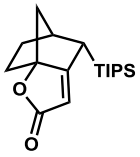
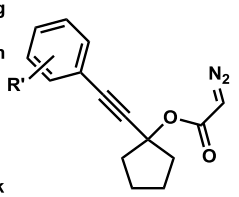
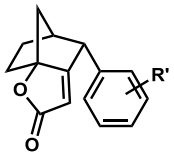
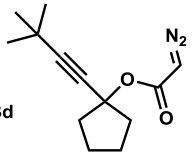
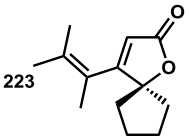
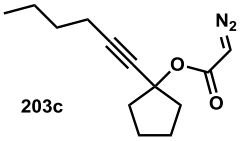
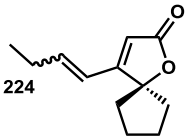
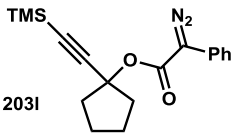
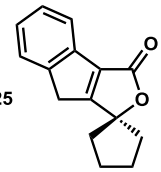
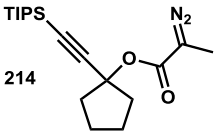
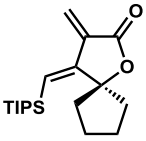
We started with an examination of the reactivity and compatibility of different functional groups on the alkyne for the cascade reaction (Table 5).

Silyl groups generally worked well. The advantage of using a silyl group is the ease of its removal or the ability of being further functionalized, for example, oxidized via Tamao-Fleming oxidation.

The cascade reaction with aryl substituted alkynes required higher reaction temperature. Electron neutral or deficient aromatic systems worked well. However, electron rich systems worked poorly (entry 2). It might be that after the carbene/alkyne metathesis reaction (as illustrated by **199** in Figure 15), the generated metal carbenoid is less electrophilic because it is resonance stabilized by the electron rich aromatic system, and no further reactivity is observed.

Table 5. Alkyne substitution and diazo-ester substitution.



Entry	Diazoester	Product		Yield
1	203b 	221 		55%
2	203g	222g	R' = p-OMe	7% [a]
3	203h	222h	R' = p-CF_3	64% [a]
4	203i 	 222i	R' = m-OMe	63% [a]
5	203j	222j	R' = m-Br	56% [a]
6	203k	222k	R' = m-CO_2Me	65% [a]
7	 203d	 223		75%
8	 203c	 224		67% 1:1.4 cis/trans 50% 2:1 cis/trans
9	 203l	 225		85%
10	 214	 226		xx% [b]

[a] Reaction perfomed at 45 °C for 30 min.

[b] Yield based on integration of 1H NMR spectrum compared to internal starndart.

The metal cabenoids formed in the metathesis reaction with alkyl substituted alkynes were terminated by a 1,2-hydride or 1,2-methyl shift instead of being terminated by C-H bond insertion. Spirocyclic structures **223** and **224** were isolated. Padwa et al. have reported similar migrations when employing aliphatic alkynes in the metathesis reaction[6]. Interestingly, a 1,2-hydride shift with different *cis*/*trans* ratio was observed when the reaction solvent was switched to pentane. In the work reported by Padwa's group, no migration was observed when pentane was used on a similar reaction system[7]. This observation illustrates the increased barrier for C-H bond insertion in our system due to additional ring strain in the product.

Trifluoromethyl and bromo alkyne diazo-esters in the presence of catalytic $Rh_2(esp)_2$ produced a mixture of products. It might be due to the instability of these functional groups next to the metal carbene after the metathesis reaction.

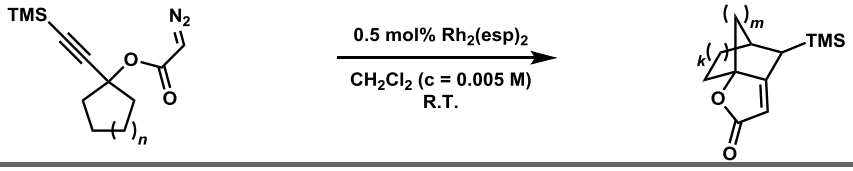
Diazo-aceoacetates are known to form furan rings[8], so their reactivity for the cascade reaction was not examined. We looked at the reactivity of aryl and methyl substituted diazo-esters (entry 9-10 in Table 5). After the carbene/alkyne metathesis reaction, 1,5-electrocylization with the nearby aromatic system of **203l** took place to form indene **225**, similarly as described in the literature by Padwa et al.[9] Bridged polycyclic system was not generated. The reactivity of the methyl diazo-ester was unclear. A mixture of products was generated, with the diene **226** being the most dominant.

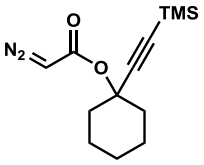
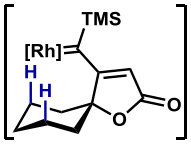
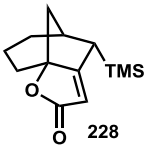
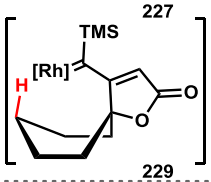
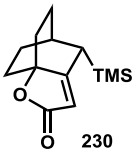
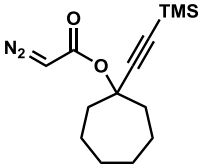
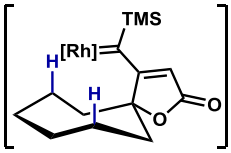
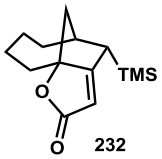
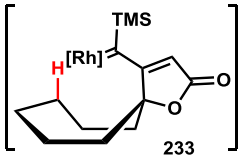
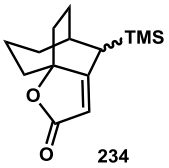
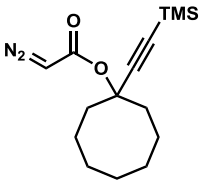
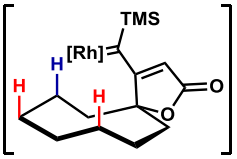
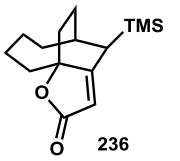
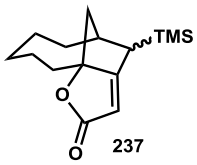
2.2.6. Ring Variations

The initial ring system in the alkynyl diazo-ester has a crucial impact on the bridged bicycle that is formed as an end product of the cascade reaction. The metal carbene derived from diazo-acetate must be located in the pseudoaxial position for the productive C-H bond insertion event. The probable conformations are presented in the following tables for each substrate with the most likely C-H bond insertion sites colored in blue, read, or green.

In the cyclohexane ring of **208a**, there are two different possible sites for C-H bond insertion as demonstrated in entry 1, Table 6. Bicyclo[3.2.1]octane **228** and bicycle[2.2.2]octane **230** were isolated in a 1.5 to 1 ratio. The C-H bond insertion in larger ring systems was more selective. Bicyclo[4.2.1]nonane **232** and bicyclo[4.2.2]decane **236** were isolated in 64% and 55% yields respectively.

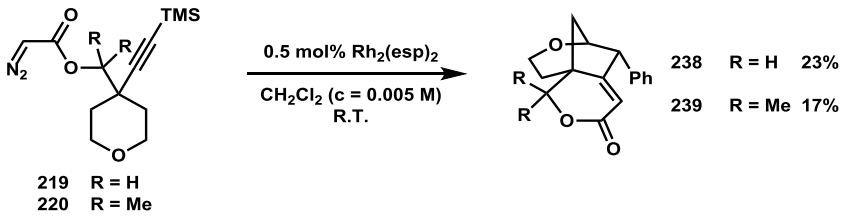
Table 6. Ring variation.



Entry	Diazoester	Conformer	Product	Yield
1	 208a	 227	 228	41% 1.1:1 dr
		 229	 230	28%
2	 208b	 231	 232	64% 2.3:1 dr
		 233	 234	8%
3	 208c	 235	 236	55%
			 237	10%

The formation of the γ-lactone did not work as well as we hoped (Scheme 31). Little formation of bicycles **238** and **239** was observed.

Scheme 31. Length of diazo-acetate.



2.2.6.1. Substituent Effect

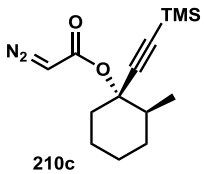
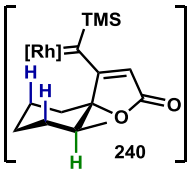
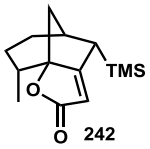
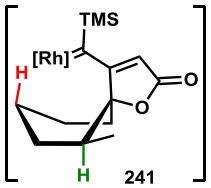
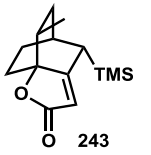
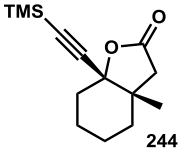
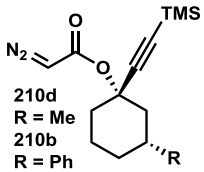
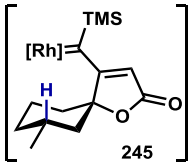
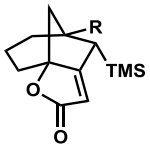
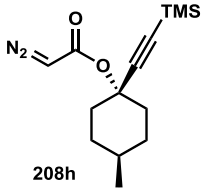
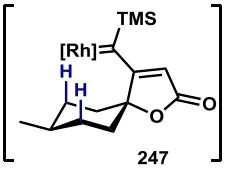
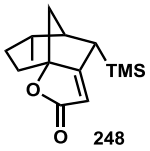
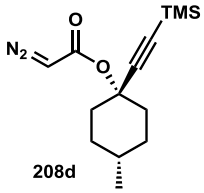
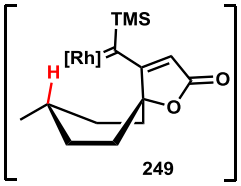
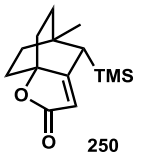
Substituents on the ring dictate the point of C-H bond insertion. Electronic and/or conformational effects have to be considered. The sites which can stabilize a positive charge built-up in the transition state are more susceptible towards the C-H bond functionalization. The trend for C-H bond insertion customarily follows the trend: methine>methylene>methyl.

The metal carbene **210c** with the methyl substituent at the 2-position in the cyclohexane ring prefers to insert in the axial blue C-H bond to form distantly substituted bicyclic product **242**. Because in **210c** the methyl group and alkyne are cis to each other, the insertion in the methine C-H bond happens as well; however, it is slower than the metathesis reaction of carbene and alkyne.

Methine position in **210d** and **210b**, where alkyne and substituent at the 3-position are trans to each other, is activated for the C-H bond insertion (entry 2 in Table 7). Indeed, products **246a** and **246b** were isolated in good yields.

Methyl substituent at the ring's 4-position dictates the formation of the bicycle. If methyl group and alkyne are in the cis stereochemical relationship (entry 3), bicyclo[3.2.1]octane **248** is generated. Bicyclo[2.2.2]octane **250** is formed, when methyl group and alkyne are in trans configuration with respect to each other (entry 4).

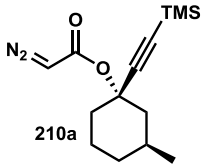
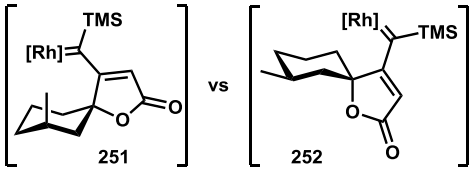
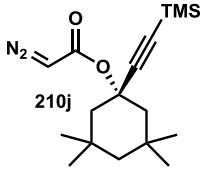
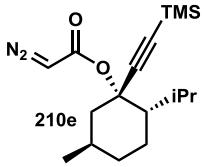
Table 7. Substitution effect.

Entry	Diazoester	Conformer	Product	Yield
1	 210c	 240	 242	58% 2.4:1 dr
		 241	 243	14% 1.3:1 dr
			 244	14%
2	 210d R = Me 210b R = Ph	 245	 246a R = Me 246b R = Ph	49% 1.5:1 dr 54% 1.9:1 dr
3	 208h	 247	 248	67% 1.6:1 dr
4	 208d	 249	 250	56%

Reaction conditions: 0.5 mol% $Rh_2(esp)_2$, 0.005 M CH_2Cl_2, R.T.

The transition state should not be too stericly crowded. No reaction was observed when reacting 3-substituted cyclohexanes (entry 1-3 in Table 8) with $Rh_2(esp)_2$, even after refluxing in CH_2Cl_2. For a productive result, the metal carbene should be located close to the functionalized site (conformer **251**); however, the axially positioned methyl group prevents this from happening. An interesting observation is that nothing besides the starting material is recovered: no product of C-H bond insertion into the methyl group, and no dimers.

Table 8. Substitution effect.

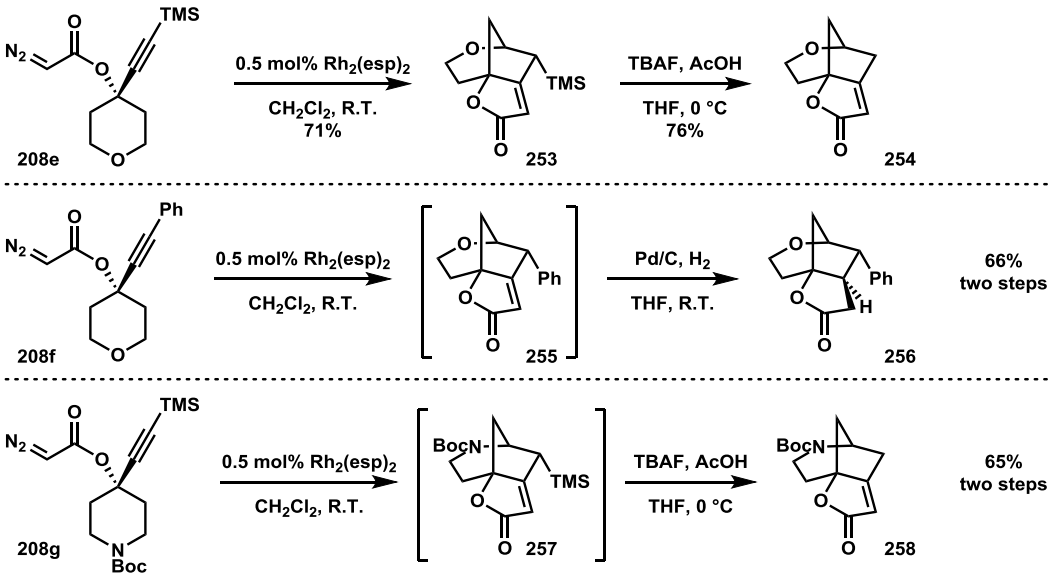
Entry	Diazoester	Conformer	Yield
1	 210a	 251 vs 252	no reaction
2	 210j		no reaction
3	 210e		no reaction

Reaction conditions: 0.5 mol% $Rh_2(esp)_2$, 0.005 M CH_2Cl_2, R.T., then reflux

C-H sites α to heteroatoms are very reactive in C-H bond insertion reactions. Functionalized pyrone **208e** and piperidine **208g** selectively generated polycyclic structures **254** and **258** when subjected to the cascade reaction conditions (Scheme 32). It

is worth noting that when phenyl substituted alkyne **208f** was used in the cascade reaction, **255** was formed as a single diastereomer. In all the other examples when a silyl substituted alkynyl diazo-ester and a cyclohexane ring is used, a mixture of diastereomers was always observed. During the isolation process, bicycle **255** was decomposing, so it was subjected to hydrogenation right after the cascade reaction. Saturated compound **256** was isolated in 66% yield over two steps.

Scheme 32. Reactivity of heterocyclic diazo-esters.

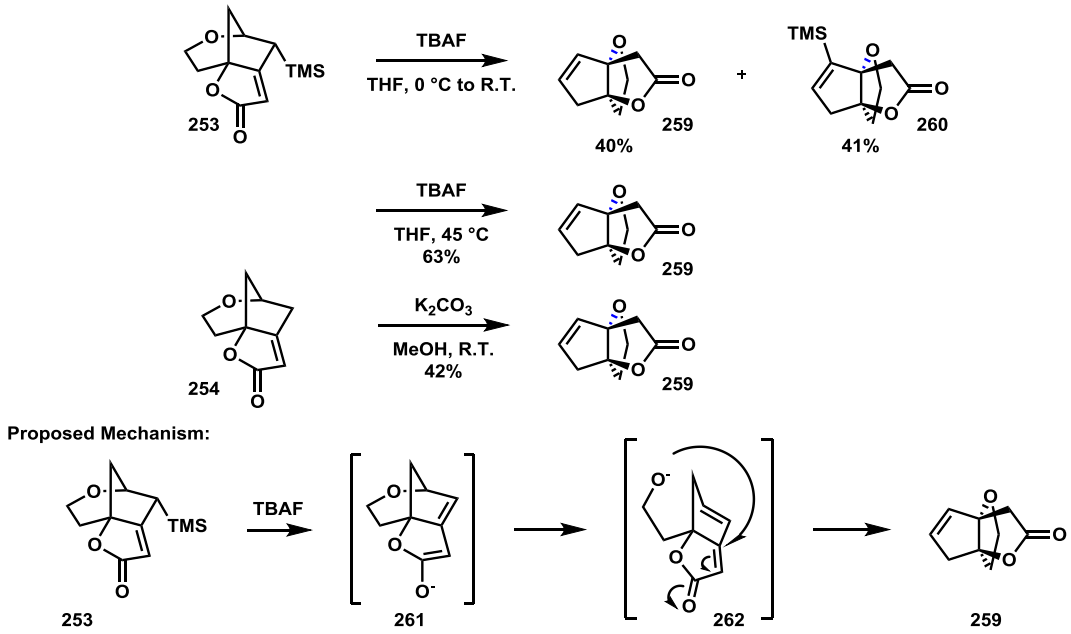


2.2.6.2. Rearrangement into Propellane Structure

The decomposition of **255** (Scheme 32) during the isolation process was initially puzzling. Additionally, whenever we tried to cleave the silyl group in **253** with TBAF a mixture of products was produced. A single product was formed when the reaction temperature was increased. After careful examination of several 2D NMR experiments, we

eventually assigned the structure to be propellane **259** (Scheme 33). A plausible explanation for its formation is as follows: in the presence of TBAF, desilylation and/or deprotonation is taking place, generating a conjugated enolate **261**. After alkoxide elimination, the ring strain in the system is released. It further reacts with the α,β-unsaturated carbonyl in a 1,4-addition as illustrated in **262**. The isolation of propellane structure was very exciting. The rearranged product is reminiscent of the core structure in brazilide A (Figure 14). The desilylation can be affected without the rearrangement as well. In that instance, the desilylation must be performed under buffered TBAF/AcOH conditions. We also showed that under basic reaction conditions, bicycle **254** can be rearranged into propellane **259**.

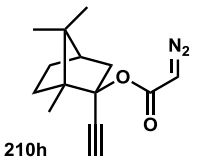
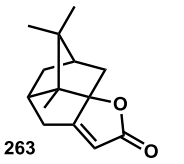
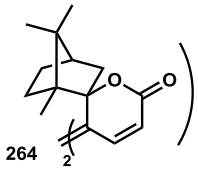
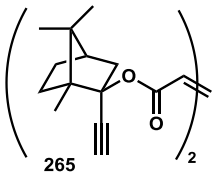
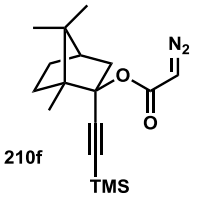
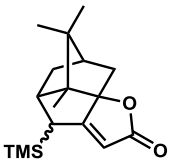
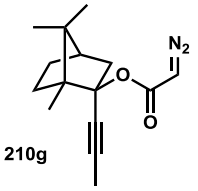
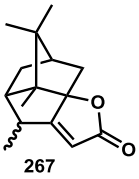
Scheme 33. Post-cascade modification.



2.2.7. Formation of Caged Polycyclic Products

Caged systems, like the ones presented in Table 9, can be accessed using this cascade reaction. The terminal alkynes are known to be prone to 6-endo-dig cyclization[10] and that is exactly what we observed (formation of product **264**, entry 1). Trimethylsilyl alkyne **210f** produced caged product **266** in excellent yield. The natural product palhinine A (Figure 14) bears a similar caged core structure.

Table 9. Caged polycyclic products.

Entry	Diazoester	Product	Yield
1	 210h	 263	48%
		 264	16%
		 265	17%
2	 210f TMS	 TMS 266	90% 2:1 dr
3	 210g	 267	>47% 1.5:1 dr

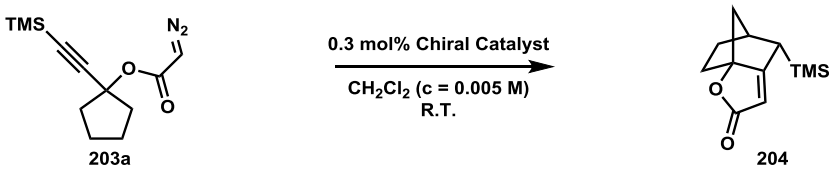
Reaction conditions: 0.5 mol% $Rh_2(esp)_2$, 0.005 M CH_2Cl_2, R.T.

2.2.8. Approach Toward the Enantioselective Transformation

While in the process of studying the racemic transformation, we decided to test chiral catalysts to see if enantiopure products could be generated. From all the chiral rhodium(II) catalysts tested (Table 10), Rh_2(S-PTAD)$_4$ produced the best result in the terms of enantioselectivity (23% ee). The bidentate Rh_2(biTISP)$_2$ (the most geometrically similar

to achiral $Rh_2(esp)_2$) produced the product in lower yield but similar enantiopurity. Clearly, there is a room for improvement.

Table 10. Enantioselective catalysis.



Chiral catalyst	Yield, %	ee, %
Rh_2(*S*-PTAD)$_4$	31	23
Rh_2(*S*-DOSP)$_4$	19	12
Rh_2(*S*-*t*BuSP)$_4$	40	16
Rh_2(*S*-BTPCP)$_4$	21	6
Rh_2(*S*-biTISP)$_2$	~10	21

2.3. Conclusions

This rhodium(II) catalyzed carbene/alkyne cascade reaction allows rapid access to a diverse pool of differently substituted polycyclic structures as well as propellanes in a short, highly efficient manner. Presented bridged ring systems are common structural motifs in natural products, many of which have impressive bioactivities. Our presented work on carbene/alkyne cascade reaction exemplify that the connectivity in bridged bicycles can be predicted, considering conformational and stereoelectronic effects of the system[11].

2.4. Experimental

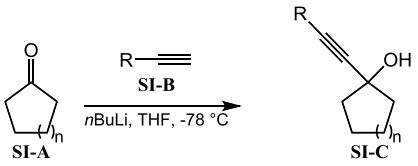
2.4.1. Material and Methods

General Considerations

All reactions were carried out in flame- or oven-dried glassware. THF, toluene and CH_2Cl_2 were purged with argon and dried over activated alumina columns. Flash chromatography was performed on 60Å silica gel (Sorbent Technologies). Analytical thin layer chromatography was performed on EMD silica gel/TLC plates with fluorescent indicator 254 nm. The ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a JEOL ECA-500 or ECX-400P spectrometer using residual solvent peak as an internal reference ($CDCl_3$: 7.25 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR; DMSO-d_6: 2.50 ppm for ^{1}H NMR). Hexafluorobenzene (δ = -164.9 ppm) was employed as an internal standard in ^{19}F NMR spectra. For ^{13}C NMR, multiplicities were distinguished using DEPT experiments: methyl and methine carbons appear positive (up); methylene carbons appear negative. NMR yields were determined by addition of 0.5 equivalent of methyl (4-nitrophenyl) carboxylate as an internal standard to the crude reaction mixture. IR spectra were obtained using a ThermoNicolet Avatar 370 FT-IR instrument. GCMS analyses were performed on a Shimadzu GCMS-QP2010S chromatographer equipped with a Shimadzu column (SHRXI-5MS, 0.25 mm x 0.25 u x 30 M). HRMS analyses were performed under contract by UT Austin's mass spectrometric facility via positive mode ESI method and US10252005 instrument. Commercially available compounds were purchased from Aldrich Chemical Co., Acros Organics, Alfa Aesar or TCI America and were used without further purification.

2.4.2. Syntheses of the Starting Materials

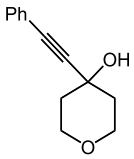
2.4.2.1. Synthesis of Propargyl Alcohols



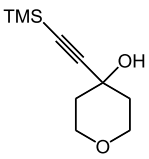
General Procedure A: A flame-dried round-bottom flask was charged with *n*BuLi (1.3 eq, 2.5 M) under an argon atmosphere. Anhydrous THF (0.5 M) was added, and the flask was cooled to -78 ˚C in a dry ice/acetone bath. The terminal acetylene **SI-B** (1.3 eq) was then added dropwise. After 30 minutes at -78 ˚C, the cyclic ketone **SI-A** (1.0 eq) was added dropwise (if a solid, prior to addition it was dissolved in anhydrous THF). The reaction mixture was allowed to warm to room temperature and stir overnight. After completion, saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel.

General Procedure B: A flame-dried round-bottom flask was charged with *i*Pr_2NH (1.3 eq) under an argon atmosphere. Anhydrous THF (0.5 M) was added, and the flask was cooled to 0 ˚C. *n*BuLi (1.3 eq, 2.5 M) was added, and the reaction mixture was stirred for 30 minutes at 0 ˚C and then cooled to -78 ˚C in a dry ice/acetone bath. The terminal acetylene **SI-B** (1.3 eq) was then added dropwise. After 30 minutes at -78 ˚C, the cyclic ketone **SI-A** (1.0 eq) was added dropwise (if a solid, prior to addition it was dissolved in anhydrous THF). The reaction mixture was allowed to warm to room temperature and stir

overnight. After completion, saturated NH_4Cl solution was added. The reaction mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel.

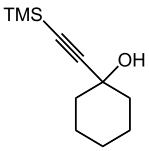


4-(Phenylethynyl)tetrahydro-2H-pyran-4-ol (207f) was synthesized from tetrahydro-4-pyranone (1.00 ml, 10.83 mmol) and phenylacetylene following general procedure A. The crude product was purified by column chromatography on silica gel using 30-50% gradient of Et_2O in pentane as an eluent. The product was obtained as a light yellow oil which solidifies on standing (2.11 g, 96% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44-7.40 (m, 2H), 7.33-7.28 (m, 3H), 3.98-3.90 (m, 2H), 3.76-3.67 (m, 2H), 2.46 (s, 1H), 2.06-1.98 (m, 2H), 1.93-1.83 (m, 2H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 131.8 (CH_1), 128.7 (CH_1), 128.5 (CH_1), 122.4 (CH_0), 91.3 (CH_0), 85.3 (CH_0), 66.4 (CH_0), 65.1 (CH_2), 40.2 (CH_2). **MS** (EI) m/z (M^+): calculated for $C_{13}H_{14}O_2$: 202.10; found: 202. **R_f**: 0.22 in 30% EtOAc/hexanes.

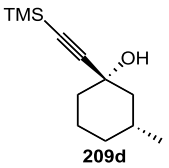


4-((Trimethylsilyl)ethynyl)tetrahydro-2H-pyran-4-ol (207e) was synthesized from tetrahydro-4-pyranone (1.50 ml, 16.24 mmol) and trimethylsilylacetylene following general procedure A. The crude product was purified by column chromatography on silica gel using 30-40% gradient of EtOAc in hexanes as an eluent. The product was obtained as a light yellow solid (3.02 g, 94% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.88 (dt, *J* = 11.9, 4.6 Hz, 2H), 3.62 (dd, *J* = 9.2, 2.8 Hz, 2H), 2.38 (s, 1H), 1.93-1.85 (m, 2H), 1.76 (dd, *J* = 9.6, 4.1 Hz, 2H), 0.16 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 108.0 (CH_0), 89.7 (CH_0), 66.2 (CH_0), 65.1 (CH_2), 40.0 (CH_2), 0.0

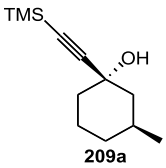
(CH_3). **MS** (EI) m/z (M^+): calculated for $C_{10}H_{18}O_2Si$: 198.11; found: 198. **R_f**: 0.09 in 20% EtOAc/hexanes.



1-((Trimethylsilyl)ethynyl)cyclohexanol (207a) was synthesized from cyclohexanone (1.00 ml, 9.65 mmol) and trimethylsilylacetylene following general procedure A. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a white solid (1.78 g, 94% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.96 (s, 1H), 1.92-1.82 (m, 2H), 1.72-1.62 (m, 2H), 1.58-1.46 (m, 5H), 1.27-1.15 (m, 1H), 0.15 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 109.6 (CH_0), 88.6 (CH_0), 69.1 (CH_0), 40.0 (CH_2), 25.3 (CH_2), 23.5 (CH_2), 0.1 (CH_3). **MS** (EI) m/z (M^+-Me): calculated for $C_{11}H_{20}OSi$: 196.13; found: 181. **R_f**: 0.43 in 20% EtOAc/hexanes.



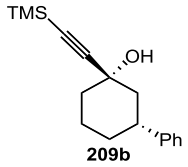
209d



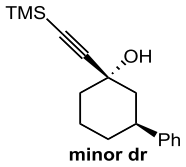
209a

(*syn*)-3-Methyl-1-((trimethylsilyl)ethynyl)cyclohexanol (209d) and (*anti*)-3-methyl-1-((trimethylsilyl)ethynyl)cyclohexanol (209a) were synthesized from 3-methylcyclohexanone (1.00 ml, 8.14 mmol) and trimethylsilylacetylene following general procedure A. The diastereomeric ratio was measured to be 2.4:1 by GCMS. The products were separated by flash column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The major diasteroemer (**209d**) was obtained as a colorless oil (1.22 g, 71% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.05 (s, 1H), 1.97-1.88 (m, 2H), 1.74-1.48 (m, 4H), 1.40-1.30 (m, 1H), 1.00 (t, J = 11.9 Hz, 1H), 0.91 (d, J = 6.4 Hz, 3H), 0.83-0.71 (m, 1H), 0.14 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 109.3 (CH_0), 89.1 (CH_0), 69.9 (CH_0), 48.6

(CH_2), 40.0 (CH_2), 34.2 (CH_2), 30.6 (up), 23.8 (CH_2), 22.2 (up), 0.2 (CH_3). **MS** (EI) m/z (M^+-Me): calculated for $C_{12}H_{22}OSi$: 210.14; found: 195. **R_f**: 0.51 in 20% EtOAc/hexanes. The minor diastereomer (**209a**) was obtained as a white solid (0.30 g, 18% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.95-1.83 (m, 2H), 1.79-1.66 (m, 1H), 1.69 (s, 1H), 1.66-1.50 (m, 4H), 1.34-1.25 (m, 1H), 0.90-0.78 (m, 1H), 0.86 (d, *J* = 6.9 Hz, 3H), 0.14 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 111.4, 86.0, 67.2, 47.2, 38.5, 34.0, 27.2, 22.3, 21.0, 0.14. **MS** (EI) m/z (M^+-Me): calculated for $C_{12}H_{22}OSi$: 210.14; found: 195. **R_f**: 0.60 in 20% EtOAc/hexanes.



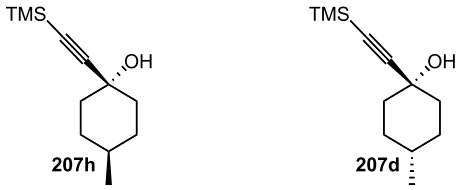
209b



minor dr

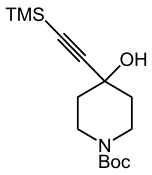
(*syn*)-3-Phenyl-1-((trimethylsilyl)ethynyl)cyclohexanol (209b) and (*anti*)-3-phenyl-1-((trimethylsilyl)ethynyl)cyclohexanol (minor dr) were synthesized from 3-phenylcyclohexanone (0.50 g, 2.87 mmol) and trimethylsilylacetylene following general procedure A. The diastereomeric ratio was measured to be 3.8:1 by GCMS. The products were separated by flash column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The major diastereomer (**209b**) was obtained as a colorless oil (0.61 g, 78% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32-7.28 (m, 2H), 7.22-7.18 (m, 3H), 2.87 (tt, *J* = 12.6, 3.4 Hz, 1H), 2.18-2.12 (m, 2H), 2.07-2.02 (m, 1H), 1.90-1.83 (m, 2H), 1.72 (qt, *J* = 13.2, 3.4 Hz, 1H), 1.67 (t, *J* = 12.6 Hz, 1H) 1.52 (dd, *J* = 13.2, 3.4 Hz, 1H), 1.33 (qd, *J* = 12.6, 3.4 Hz, 1H), 0.20 (s, 9H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 145.9 (CH_0), 128.6 (CH_1), 127.1 (CH_1), 126.4 (CH_1), 108.9 (CH_0), 90.0 (CH_0), 70.1 (CH_0), 47.3 (CH_2), 42.1 (CH_1), 39.7 (CH_2), 33.4 (CH_2), 24.1 (CH_2), 0.2 (CH_3). **MS** (EI) m/z (M^+-H): calculated for

$C_{17}H_{24}OSi$: 272.16; found: 271. **R_f**: 0.44 in 20% EtOAc/hexanes. The minor diastereomer (**minor dr**) was obtained as a colorless oil (0.12 g, 15% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31-7.26 (m, 2H), 7.22-7.16 (m, 3H), 2.95 (tt, *J* = 12.6, 3.4 Hz, 1H), 2.16-2.10 (m, 1H), 2.02-1.96 (m, 1H), 1.89-1.77 (m, 3H), 1.74 (s, 1H), 1.77-1.67 (m, 2H) 1.42 (dd, *J* = 12.6, 3.4 Hz, 1H), 0.14 (s, 9H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 146.4 (CH_0), 128.6 (CH_1), 127.1 (CH_1), 126.3 (CH_1), 110.8 (CH_0), 86.5 (CH_0), 67.2 (CH_0), 46.3 (CH_2), 38.6 (CH_1), 38.4 (CH_2), 33.0 (CH_2), 21.4 (CH_2), 0.1 (CH_3). **MS** (EI) m/z (M^+-H): calculated for $C_{17}H_{24}OSi$: 272.16; found: 271. **R_f**: 0.56 in 20% EtOAc/hexanes.

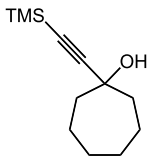


(*anti*)-4-Methyl-1-((trimethylsilyl)ethynyl)cyclohexanol (207h) and (*syn*)-4-methyl-1-((trimethylsilyl)ethynyl)cyclohexanol (207d) were synthesized from 4-methylcyclohexanone (1.50 ml, 12.22 mmol) and trimethylsilylacetylene following general procedure A. The products were separated by flash column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The major diastereomer (**207h**) was obtained as a white solid (1.94 g, 75% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.01 (s, 1H), 1.95-1.90 (m, 2H), 1.68-1.62 (m, 2H), 1.54-1.46 (m, 2H), 1.37-1.20 (m, 3H), 0.90 (d, *J* = 5.7 Hz, 3H) 0.16 (s, 9H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 109.2, 89.5, 69.7, 40.0, 32.6, 31.8, 22.0, 0.1. **MS** (EI) m/z (M^+-Me): calculated for $C_{12}H_{22}OSi$: 210.39; found: 195. **R_f**: 0.20 in 20% EtOAc/hexanes. The minor diastereomer (**207d**) was obtained as a white solid (0.31 g, 12% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.92-1.85 (m, 2H), 1.73-1.64 (m, 2H), 1.66 (s, 1H), 1.55-1.48 (m, 2H), 1.45-1.36 (m, 1H), 1.34-1.23 (m, 2H), 0.89 (d, *J* = 6.3 Hz,

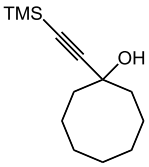
3H) 0.14 (s, 9H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 111.1 (CH_0), 86.4 (CH_0), 66.7 (CH_0), 38.3 (CH_2), 31.0 (up), 29.6 (CH_2), 21.8 (up), 0.1 (CH_3). **MS** (EI) m/z (M^+-Me): calculated for $C_{12}H_{22}OSi$: 210.39; found: 195. **R_f**: 0.31 in 20% EtOAc/hexanes.



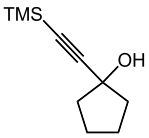
***tert*-Butyl 4-((trimethylsilyl)ethynyl)-4-hydroxypiperidine-1-carboxylate (207g)** was synthesized from *tert*-butyl-4-oxopiperidine-1-carboxylate (1.50 g, 7.53 mmol) and trimethylsilylacetylene following general procedure A. The crude product was purified by flash column chromatography on silica gel using 20-30% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white solid (1.94 g, 87% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.86-3.70 (m, 2H), 3.24-3.14 (m, 2H), 2.24 (s, 1H), 1.89-1.79 (m, 2H), 1.70-1.60 (m, 2H), 1.44 (s, 9H), 0.15 (s, 9H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 154.7 (CH_0), 107.7 (CH_0), 89.9 (CH_0), 79.8 (CH_0), 67.2 (CH_0), ~40.5 (CH_2), 39.1 (CH_2), 28.6 (CH_3), 0.1 (CH_3). **MS** (EI) m/z (M^+-CMe_3): calculated for $C_{15}H_{27}NO_3Si$: 297.18; found: 240. **R_f**: 0.29 in 20% EtOAc/hexanes.



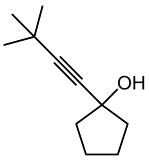
1-((Trimethylsilyl)ethynyl)cycloheptanol (207b) was synthesized from cycloheptanone (0.64 ml, 5.43 mmol) and trimethylsilylacetylene following general procedure A. The crude product was purified by flash column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a white solid (1.10 g, 97% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.02-1.94 (m, 2H), 1.88 (s, 1H), 1.84-1.74 (m, 2H), 1.68-1.48 (m, 8H), 0.15 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 110.6 (CH_0), 87.7 (CH_0), 72.1 (CH_0), 43.1 (CH_2), 28.0 (CH_2), 22.4 (CH_2), 0.1 (CH_3). **MS** (EI) m/z (M^+): calculated for $C_{12}H_{22}OSi$: 210.14; found: 210. **R_f**: 0.43 in 20% EtOAc/hexanes.



1-((Trimethylsilyl)ethynyl)cyclooctanol (207c) was synthesized from cyclooctanone (0.68 g, 5.39 mmol) and trimethylsilylacetylene following general procedure A. The crude product was purified by flash column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (1.19 g, 99% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.98-1.82 (m, 4H), 1.74 (s, 1H), 1.67-1.56 (m, 7H), 1.52-1.41 (m, 3H), 0.15 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 110.6 (CH_0), 87.3 (CH_0), 71.7 (CH_0), 38.3 (CH_2), 28.0 (CH_2), 24.6 (CH_2), 22.2 (CH_2), 0.2 (CH_3). **MS** (EI) m/z (M^+-H): calculated for $C_{13}H_{24}OSi$: 224.16; found: 223. **R_f**: 0.52 in 20% EtOAc/hexanes.

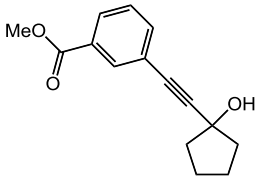


1-((Trimethylsilyl)ethynyl)cyclopentanol (206a) was synthesized from cyclopentanone (1.00 ml, 11.30 mmol) and trimethylsilylacetylene following general procedure A. The crude product was purified by flash column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a white solid (2.49 g, 97% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.99-1.85 (m, 5H), 1.85-1.65 (m, 4H), 0.14 (s, 9H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 109.7 (CH_0), 87.2 (CH_0), 74.9 (CH_0), 42.7 (CH_2), 23.7 (CH_2), 0.1 (CH_3). **MS** (EI) m/z (M^+): calculated for $C_{10}H_{18}OSi$: 182.11; found: 182. **R_f**: 0.48 in 20% EtOAc/hexanes.

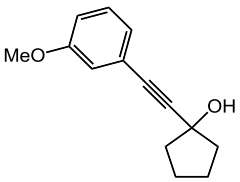


1-(3,3-Dimethylbut-1-ynyl)cyclopentanol (206d) was synthesized from cyclopentanone (0.50 ml, 5.65 mmol) and *t*-butylacetylene following general procedure A. The crude product was purified by flash column chromatography on silica gel using 5% Et_2O in pentane as an eluent. The product was obtained as a white solid (0.71 g, 75% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.94-1.63 (m,

9H), 1.19 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 91.9 (CH_0), 82.4 (CH_0), 74.8 (CH_0), 42.8 (CH_2), 31.2 (CH_3), 27.4 (CH_0), 23.6 (CH_2). **MS** (EI) m/z (M^+-H): calculated for $C_{11}H_{18}O$: 166.14; found: 165. **R_f**: 0.46 in 20% EtOAc/hexanes.

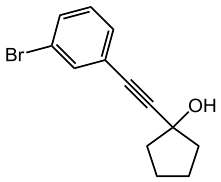


Methyl 3-((1-hydroxycyclopentyl)ethynyl)benzoate (206k) was synthesized from cyclopentanone (0.30 ml, 3.39 mmol) and methyl-3-ethynylbenzoate following general procedure B. The crude product was purified by flash column chromatography on silica gel using 20-30% gradient of EtOAc in hexanes as an eluent. The product was obtained as a light yellow oil (0.82 g, 99% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10-8.06 (m, 1H), 7.98-7.92 (m, 1H), 7.61-7.55 (m, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 3.91 (s, 3H), 2.11-1.97 (m, 4H), 1.93-1.73 (m, 4H), 1.89 (s, 1H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 166.6 (CH_0), 135.9 (CH_1), 132.9 (CH_1), 130.4 (CH_0), 129.3 (CH_1), 128.6 (CH_1), 123.5 (CH_0), 93.9 (CH_0), 82.3 (CH_0), 75.0 (CH_0), 52.4 (CH_3), 42.7 (CH_2), 23.6 (CH_2). **MS** (EI) m/z (M^+-H): calculated for $C_{15}H_{16}O_3$: 244.11; found: 243. **R_f**: 0.21 in 20% EtOAc/hexanes.

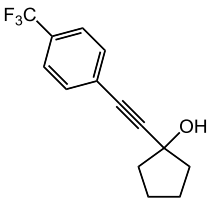


1-((3-Methoxyphenyl)ethynyl)cyclopentanol (206i) was synthesized from cyclopentanone (0.25 ml, 2.83 mmol) and *m*-methoxyphenylacetylene following general procedure A. The crude product was purified by flash column chromatography on silica gel using 20-30% EtOAc in hexanes as an eluent. The product was obtained as a light yellow oil (0.54 g, 88% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19 (t, *J* = 7.8 Hz, 1H), 7.02-6.98 (m, 1H), 6.95-6.92 (m, 1H), 6.87-6.82 (m, 1H), 3.78 (s, 3H), 2.11-1.97 (m, 5H), 1.92-1.72 (m, 4H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 159.3 (CH_0), 129.4 (CH_1), 124.3 (CH_1), 124.0 (CH_0), 116.5 (CH_1), 115.0 (CH_1), 92.8 (CH_0), 83.1 (CH_0), 75.0 (CH_0), 55.4 (CH_3), 42.6 (CH_2), 23.6 (CH_2). **MS**

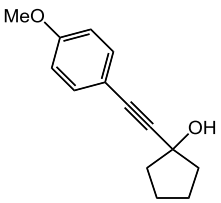
(EI) m/z (M^+-H): calculated for $C_{14}H_{16}O_2$: 216.12; found: 215. **R_f**: 0.29 in 20% EtOAc/hexanes.



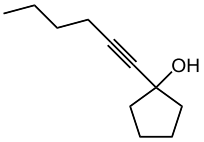
1-((3-Bromophenyl)ethynyl)cyclopentanol (206j) was synthesized from cyclopentanone (0.3 ml, 3.39 mmol) and *m*-bromophenylacetylene following general procedure B. The crude product was purified by flash column chromatography on silica gel using 25% Et_2O in pentane as an eluent. The product was obtained as a light yellow oil (0.83 g, 92% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58-7.55 (m, 1H), 7.44-7.40 (m, 1H), 7.35-7.31 (m, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 2.09-1.96 (m, 4H), 1.92-1.72 (m, 5H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 134.5 (CH_1), 131.5 (CH_1), 130.3 (CH_1), 129.8 (CH_1), 125.0 (CH_0), 122.2 (CH_0), 94.3 (CH_0), 81.8 (CH_0), 75.0 (CH_0), 42.6 (CH_2), 23.6 (CH_2). **MS** (EI) m/z (M^+-H): calculated for $C_{13}H_{13}BrO$: 264.01; found: 263. **R_f**: 0.34 in 20% EtOAc/hexanes.



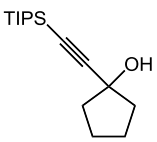
1-((4-(Trifluoromethyl)phenyl)ethynyl)cyclopentanol (206h) was synthesized from cyclopentanone (0.40 ml, 4.52 mmol) and *p*-trifluoromethylphenylacetylene following general procedure A. The crude product was purified by flash column chromatography on silica gel using 20% Et_2O in pentane as an eluent. The product was obtained as a white solid (1.14 g, 99% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58-7.48 (m, 4H), 2.12-1.97 (m, 4H), 1.97-1.73 (m, 5H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 132.0 (CH_1), 129.9 (CH_0), 126.8 (CH_0), 125.3 (CH_1), 122.7 (CH_0), 95.5 (CH_0), 82.0 (CH_0), 75.0 (CH_0), 42.6 (CH_2), 23.6 (CH_2). **^{19}F NMR** (400 MHz, $CDCl_3$) δ -66.01. **MS** (EI) m/z (M^+-H): calculated for C14H13F_3O: 254.09; found: 253. **R_f**: 0.34 in 20% EtOAc/hexanes.



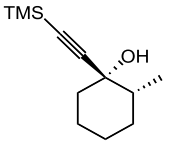
1-((4-Methoxyphenyl)ethynyl)cyclopentanol (206g) was synthesized from cyclopentanone (0.2 ml, 2.26 mmol) and *p*-methoxyphenylacetylene following general procedure A. The crude product was purified by column chromatography on silica gel using 20% Et_2O in pentane as an eluent. The product was obtained as a light yellow oil (0.47 g, 96% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37-7.32 (m, 2H), 6.84-6.79 (m, 2H), 3.79 (s, 3H), 2.10-1.96 (m, 4H), 1.91-1.71 (m, 4H), 1.89 (s, 1H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 159.6 (CH_0), 133.2 (CH_1), 115.1 (CH_0), 114.0 (CH_1), 91.5 (CH_0), 83.1 (CH_0), 75.1 (CH_0), 55.4 (CH_3), 42.7 (CH_2), 23.6 (CH_2). **MS** (EI) m/z (M^+-H): calculated for $C_{14}H_{16}O_2$: 216.12; found: 215. **R_f**: 0.28 in 20% EtOAc/hexanes.



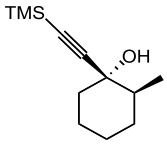
1-(Hex-1-ynyl)cyclopentanol (206c) was synthesized from cyclopentanone (0.6 ml, 6.78 mmol) and 1-hexyne following general procedure A. The crude product was purified by column chromatography on silica gel using 10% Et_2O in pentane as an eluent. The product was isolated as a colorless oil (1.08 g, 96% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.18 (t, *J* = 7.3 Hz, 2H), 1.95-1.82 (m, 4H), 1.82-1.75 (m, 2H), 1.74 (s, 1H), 1.75-1.64 (m, 2H), 1.51-1.33 (m, 4H), 0.89 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 84.1 (CH_0), 83.7 (CH_0), 74.8 (CH_0), 42.7 (CH_2), 30.9 (CH_2), 23.5 (CH_2), 22.1 (CH_2), 18.5 (CH_2), 13.8 (CH_3). **MS** (EI) m/z (M^+): calculated for $C_{11}H_{18}O$: 166.14; found: 166. **R_f**: 0.34 in 20% EtOAc/hexanes.



1-((Triisopropylsilyl)ethynyl)cyclopentanol (206b) was synthesized from cyclopentanone (0.3 ml, 3.39 mmol) and triisopropylsilylacetylene following general procedure A. The crude product was purified by flash column chromatography on silica gel using 10% Et_2O in pentane as an eluent. The product was obtained as a white solid (0.79 g, 88% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.02-1.95 (m, 2H), 1.95-1.88 (m, 2H), 1.86-1.68 (m, 5H), 1.09-0.99 (m, 21H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 112.0 (CH_0), 83.3 (CH_0), 75.1 (CH_0), 42.8 (CH_2), 23.6 (CH_2), 18.7 (up), 11.3 (up). **MS** (EI) m/z (M^+-H): calculated for $C_{16}H_{30}OSi$: 266.21; found: 265. **R_f**: 0.34 in 10% Et_2O/pentane.



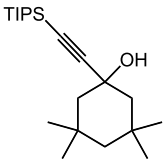
minor dr



209c

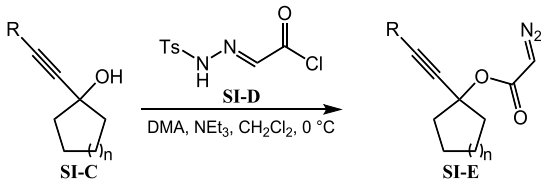
(*syn*)-2-Methyl-1-((trimethylsilyl)ethynyl)cyclohexanol (minor dr) and (*anti*)-2-methyl-1-((trimethylsilyl)ethynyl)cyclohexanol (209c) were synthesized from 2-methylcyclohexanone (1.00 ml, 8.24 mmol) and trimethylsilylacetylene following general procedure A. The diastereomeric ratio was measured to be 1.4:1 by GCMS. The products were separated by flash column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The major diasteroemer (**209c**) was obtained as a colorless oil (0.89 g, 51% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.10 (s, 1H), 2.00-1.93 (m, 1H), 1.71-1.64 (m, 1H), 1.64-1.40 (m, 5H), 1.28-1.12 (m, 2H), 1.01 (d, J = 6.3 Hz, 3H), 0.16 (s, 9H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 106.9 (CH_0), 90.8 (CH_0), 73.6 (CH_0), 42.7 (CH_1 or CH_3), 40.8 (CH_2), 32.4 (CH_2), 25.7 (CH_2), 24.4 (CH_2), 16.2 (CH_1 or CH_3), 0.2 (CH_3). **MS** (EI) m/z (M^+-Me): calculated for $C_{12}H_{22}OSi$: 210.14; found: 195. **R_f**: 0.51 in 20% EtOAc/hexanes. The minor diastereomer (**minor dr**) was obtained as a colorless oil (0.52 g, 30% yield). **^{1}H**

NMR (500 MHz, $CDCl_3$) δ 1.99-1.92 (m, 1H), 1.68 (s, 1H), 1.69-1.44 (m, 6H), 1.35-1.19 (m, 2H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.14 (s, 9H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 110.7 (CH_0), 87.1 (CH_0), 69.9 (CH_0), 40.6 (CH_1 or CH_3), 39.3 (CH_2), 29.3 (CH_2), 25.2 (CH_2), 21.2 (CH_2), 16.2 (CH_1 or CH_3), 0.1 (CH_3). **MS** (EI) m/z (M^+-Me): calculated for $C_{12}H_{22}OSi$: 210.14; found: 195. **R_f**: 0.60 in 20% EtOAc/hexanes.



3,3,5,5-Tetramethyl-1-((triisopropylsilyl)ethynyl)cyclohexanol (209j) was synthesized from 3,3,5,5-tetramethylcyclohexanone (0.7 ml, 4.00 mmol) and trimylsilylacetylene following general procedure A. The crude product was purified by flash column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a white solid (0.93 g, 92% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.88 (s, 1H), 1.74 (d, *J* = 12.6 Hz, 2H), 1.49 (d, *J* = 13.2 Hz, 2H), 1.24-1.13 (m, 2H), 1.10 (s, 3H), 1.01 (s, 3H), 0.13 (s, 9H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 112.0 (CH_0), 88.0 (CH_0), 68.2 (CH_0), 51.5 (CH_2), 51.0 (CH_2), 33.4 (CH_3), 32.0 (CH_0), 30.6 (CH_3), -0.1 (CH_3). **R_f**: 0.57 in 20% EtOAc/hexanes.

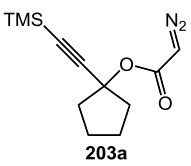
2.4.2.2. Synthesis of Diazo-Alkynyl Esters



General Procedure C: A flame-dried round-bottom flask was charged with propargyl alcohol **SI-C** (1.0 eq) under an argon atmosphere. Anhydrous CH_2Cl_2 (0.17 M) was added, and the flask was cooled to 0 ˚C. Glyoxylic acid chloride *p*-toluenesulfonylhydrazone (**SI-D**) (2.0 eq) was added in one portion followed by *N*,*N*-dimethyl aniline (1.8 eq). The

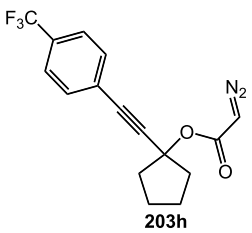
reaction mixture was stirred for 15 minutes before adding triethylamine (5.0 eq) and was stirred for 10 more minutes at 0 ˚C. The reaction was concentrated under reduced pressure. A concentrated citric acid solution and an EtOAc/hexanes mixture were added to the residue. The layers were separated, and the aqueous layer was extracted two times with the EtOAc/hexanes mixture. The combined organic phases were washed with concentrated citric acid solution and brine, dried over $MgSO_4$, filtered through a short silica gel plug, and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel.

*Glyoxylic acid chloride p-toluenesulfonylhydrazone (**SI-D**) was synthesized according to the procedure described in literature. All properties were identical to those reported (*House, H. O.; and Blenkley, C. J. *J. Org. Chem.* **1968**, *33*, 53–60*).*



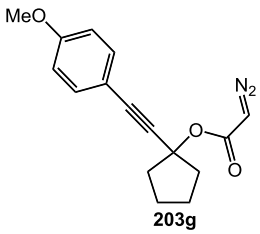
203a

1-((Trimethylsilyl)ethynyl)cyclopentyl 2-diazoacetate was synthesized from propargyl alcohol **206a** (0.60 g, 3.29 mmol) following general procedure C. 10% EtOAc/hexanes mixture was used to extract the product. The crude product was purified by column chromatography on silica gel using 5% Et_2O in pentane as an eluent. The product was obtained as a yellow solid (0.64 g, 78% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.68 (s, 1H), 2.27-2.17 (m, 2H), 2.17-2.06 (m, 2H), 1.77-1.66 (m, 4H), 0.14 (s, 9H). **^{13}C NMR** (100.52 MHz, CDCl3) δ 165.1 (CH_0), 105.6 (CH_0), 89.5 (CH_0), 81.7 (CH_0), 46.8 (CH_1), 40.8 (CH_2), 23.5 (CH_2), 0.0 (CH_3). **FTIR** (neat, cm^{-1}): 3093, 2961, 2111, 1681, 1376, 1158, 843. **R_f**: 0.37 in 10% Et_2O/pentane.



203h

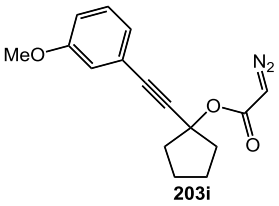
1-((4-(Trifluoromethyl)phenyl)ethynyl)cyclopentyl 2-diazoacetate was synthesized from propargyl alcohol **206h** (0.50 g, 1.97 mmol) following general procedure C. 10% EtOAc/hexanes mixture was used to extract the product. The crude product was purified by column chromatography on silica gel using 5-8% gradient of Et_2O in pentane as an eluent followed by another column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a light yellow solid (0.28 g, 44% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 (s, 4H), 4.73 (s, 1H), 2.39-2.29 (m, 2H), 2.29-2.18 (m, 2H), 1.85-1.74 (m, 4H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 165.2 (CH_0), 132.2 (CH_1), 130.3 (CH_0), 126.7 (CH_0), 125.2 (CH_1), 122.7 (CH_0), 92.1 (CH_0), 83.7 (CH_0), 81.6 (CH_0), 46.9 (CH_1), 40.8 (CH_2), 23.5 (CH_2). **^{19}F NMR** (376.17 MHz, $CDCl_3$) δ -66.01. **FTIR** (neat, cm^{-1}): 3085, 2115, 1684, 1381, 1325, 1161, 1127, 841. **R_f**: 0.48 in 20% EtOAc/hexanes.



203g

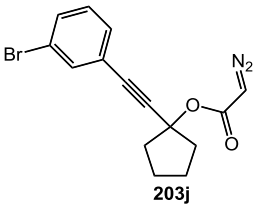
1-((4-Methoxyphenyl)ethynyl)cyclopentyl 2-diazoacetate was synthesized from propargyl alcohol **206g** (0.25 g, 1.97 mmol) following general procedure C. 20% EtOAc/hexanes mixture was used to extract the product. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent followed by another column chromatography on silica gel using 15% Et_2O in pentane as an eluent. The product was obtained as a light yellow solid (0.17 g, 52% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39-7.34 (m, 2H), 6.82-6.77 (m, 2H), 4.71 (s, 1H), 3.78 (s, 3H), 2.37-2.27 (m, 2H), 2.27-2.17 (m, 2H), 1.83-1.72 (m, 4H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 165.4 (CH_0), 159.7 (CH_0), 133.5 (CH_1), 115.0 (CH_0), 113.9 (CH_1), 88.2 (CH_0), 84.9 (CH_0), 82.2 (CH_0),

55.4 (CH_3), 46.9 (CH_1), 40.9 (CH_2), 23.5 (CH_2). **FTIR** (neat, cm^{-1}): 3089, 2966, 2109, 1673, 1379, 1247, 1158, 834. **R_f**: 0.26 in 10% EtOAc/hexanes.



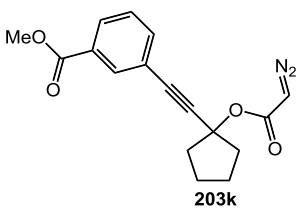
203i

1-((3-Methoxyphenyl)ethynyl)cyclopentyl 2-diazoacetate was synthesized from propargyl alcohol **206i** (0.20 g, 0.92 mmol) following general procedure C. 20% EtOAc/hexanes mixture was used to extract the product. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a yellow oil (0.19 g, 71% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.8 Hz, 1H), 7.05-6.99 (m, 1H), 6.97-6.93 (m, 1H), 6.87-6.81 (m, 1H), 4.72 (s, 1H), 3.78 (s, 3H), 2.38-2.28 (m, 2H), 2.28-2.18 (m, 2H), 1.83-1.74 (m, 4H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ ~165 (CH_0), 159.3 (CH_0), 129.3 (CH_1), 124.6 (CH_1), 123.8 (CH_0), 116.5 (CH_1), 115.3 (CH_1), 89.4 (CH_0), 84.9 (CH_0), 81.9 (CH_0), 55.4 (CH_3), 46.9 (CH_1), 40.8 (CH_2), 23.5 (CH_2). **FTIR** (neat, cm^{-1}): 2960, 2109, 1698, 1369, 1168. **R_f**: 0.37 in 20% EtOAc/hexanes.



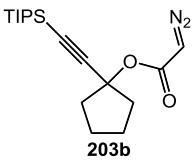
203j

1-((3-Bromophenyl)ethynyl)cyclopentyl 2-diazoacetate was synthesized from propargyl alcohol **206j** (0.40 g, 1.51 mmol) following general procedure C. 10% EtOAc/hexanes mixture was used to extract the product. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a yellow solid (0.34 g, 68% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59-7.56 (m, 1H), 7.43-7.38 (m, 1H), 7.37-7.32 (m, 1H), 7.14 (t, *J* = 7.8 Hz, 1H), 4.72 (s, 1H), 2.38-2.27 (m, 2H), 2.27-2.16 (m, 2H), 1.84-1.73 (m, 4H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ ~165, 134.7, 131.6, 130.5, 129.7, 124.8, 122.1, 91.0, 83.5, 81.7, 46.8, 40.8, 23.5. **FTIR** (neat, cm^{-1}): 3094, 2973, 2112, 1676, 1375, 1154, 785. **R_f**: 0.46 in 20% EtOAc/hexanes.



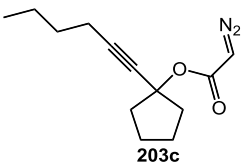
203k

Methyl 3-((1-(2-diazoacetoxy)cyclopentyl)ethynyl)benzoate was synthesized from propargyl alcohol **206k** (0.30 g, 1.23 mmol) following general procedure C. 20% EtOAc/hexanes mixture was used to extract the product. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a yellow oil (0.20 g, 53% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.11-8.08 (m, 1H), 7.98-7.92 (m, 1H), 7.63-7.57 (m, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 4.73 (s, 1H), 3.90 (s, 3H), 2.39-2.28 (m, 2H), 2.28-2.18 (m, 2H), 1.85-1.73 (m, 4H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 166.6, 159.2, 136.2, 133.1, 130.4, 129.4, 128.4, 123.3, 90.6, 84.0, 81.7, 52.4, 46.9, 40.8, 23.5. **FTIR** (neat, cm^{-1}): 3115, 2954, 2110, 1725, 1699, 1369, 1300, 1245, 1169, 754. **R_f**: 0.31 in 20% EtOAc/hexanes.



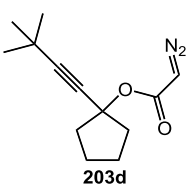
203b

1-((Triisopropylsilyl)ethynyl)cyclopentyl 2-diazoacetate was synthesized from propargyl alcohol **206b** (0.40 g, 1.50 mmol) following general procedure C. 10% EtOAc/hexanes mixture was used to extract the product. The crude product was purified by column chromatography on silica gel using 5% Et_2O in pentane as an eluent. The product was obtained as a yellow oil (0.40 g, 80% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.67 (s, 1H), 2.24-2.14 (m, 4H), 1.78-1.69 (m, 4H), 1.08-1.00 (m, 21H). **^{13}C NMR** (100.52 MHz, CDCl3) δ 164.9 (CH_0), 107.9 (CH_0), 85.8 (CH_0), 81.7 (CH_0), 46.6 (CH_1), 40.9 (CH_2), 23.4 (CH_2), 18.7 (CH_3), 11.3 (CH_1). **FTIR** (neat, cm^{-1}): 2943, 2866, 2109, 1705, 1369, 1169. **R_f**: 0.51 in 10% Et_2O/pentane.



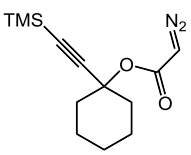
203c

1-(Hex-1-ynyl)cyclopentyl 2-diazoacetate was synthesized from propargyl alcohol **206c** (0.50 g, 3.00 mmol) following general procedure C. 10% EtOAc/hexanes mixture was used to extract the product. The crude product was purified by column chromatography on silica gel using 5% Et_2O in pentane as an eluent followed by another column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a yellow oil (0.43 g, 61% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.67 (s, 1H), 2.26-2.17 (m, 2H), 2.20 (t, *J* = 6.9 Hz, 2H), 1.76-1.66 (m, 4H), 1.51-1.32 (m, 4H), 0.88 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 165.4 (CH_0), 85.8 (CH_0), 82.1 (CH_0), 80.5 (CH_0), 46.8 (CH_1), 40.8 (CH_2), 30.8 (CH_2), 23.3 (CH_2), 22.1 (CH_2), 18.6 (CH_2), 13.8 (CH_3). **FTIR** (neat, cm^{-1}): 3103, 2959, 2108, 1699, 1368, 1173. **R_f**: 0.46 in 20% EtOAc/hexanes.



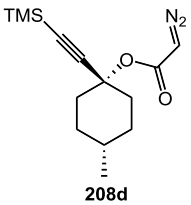
203d

1-(3,3-Dimethylbut-1-ynyl)cyclopentyl 2-diazoacetate was synthesized from propargyl alcohol **206d** (0.40 g, 2,41 mmol) following general procedure C. 10% EtOAc/hexanes mixture was used to extract the product. The crude product was purified by column chromatography on silica gel using 5% Et_2O in pentane as an eluent. The product was obtained as a light yellow solid (0.41 g, 73% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.66 (s, 1H), 2.25-2.14 (m, 2H), 2.10-1.99 (m, 2H), 1.76-1.63 (m, 4H), 1.18 (s, 9H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 165.1, 93.9, 82.1, 79.0, 46.7, 40.9, 31.0, 27.5, 23.3. **FTIR** (neat, cm^{-1}): 3084, 2965, 2109, 1682, 1378, 1197, 1160. **R_f**: 0.48 in 20% EtOAc/hexanes.



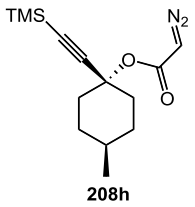
208a

1-((Trimethylsilyl)ethynyl)cyclohexyl 2-diazoacetate was synthesized from propargyl alcohol **207a** (0.60 g, 3.06 mmol) following general procedure C. 10% EtOAc/hexanes mixture was used to extract the product. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a yellow solid (0.55 g, 68% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.67 (s, 1H), 2.15-2.03 (m, 2H), 1.91-1.78 (m, 2H), 1.64-1.54 (m, 4H), 1.54-1.44 (m, 1H), 1.36-1.23 (m, 1H), 0.16 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ ~165 (CH_0), 105.3 (CH_0), 91.2 (CH_0), 76.7 (CH_0), 46.7 (CH_1), 37.4 (CH_2), 25.2 (CH_2), 22.8 (CH_2), 0.1 (CH_3). **FTIR** (neat, cm^{-1}): 2938, 2108, 1702, 1370, 863, 843. **R_f**: 0.46 in 20% EtOAc/hexanes.

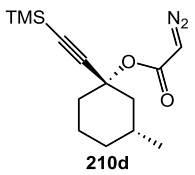


208d

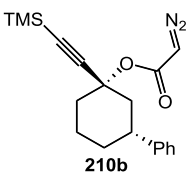
(*syn*)-4-Methyl-1-((trimethylsilyl)ethynyl)cyclohexyl 2-diazoacetate was synthesized from propargyl alcohol **207d** (100 mg, 0.48 mmol) following general procedure C. 10% EtOAc/hexanes mixture was used to extract the product. The crude product was filtered through the plug of silica gel using CH_2Cl_2 as an eluent followed by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a yellow oil (93 mg, 70% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.68 (s, 1H), 2.47-2.38 (m, 2H), 1.73-1.62 (m, 2H), 1.59-1.50 (m, 2H), 1.49-1.37 (m, 1H), 1.19-1.06 (m, 2H), 0.89 (d, J = 6.4 Hz, 3H), 0.15 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 165.5 (CH_0), 106.3 (CH_0), 89.2 (CH_0), 74.6 (CH_0), 46.7 (CH_1), 36.5 (CH_2), 31.0 (up), 29.7 (CH_2), 22.0 (up), 0.1 (CH_3). **FTIR** (neat, cm^{-1}): 2953, 2928, 2108, 1703, 1370, 858, 843. **R_f**: 0.54 in 20% EtOAc/hexanes.



(*anti*)-4-Methyl-1-((trimethylsilyl)ethynyl)cyclohexyl 2-diazoacetate was synthesized from propargyl alcohol **207h** (0.40 g, 1.90 mmol) following general procedure C. 10% EtOAc/hexanes mixture was used to extract the product. The crude product was filtered through the plug of silica gel using CH_2Cl_2 as an eluent followed by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a yellow oil (0.36 g, 67% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.66 (s, 1H), 2.37-2.30 (m, 2H), 1.69-1.56 (m, 4H), 1.40-1.27 (m, 3H), 0.90 (d, *J* = 6.0 Hz, 3H), 0.17 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 164.9 (CH_0), 104.8 (CH_0), 92.5 (CH_0), 77.6 (CH_0), 46.8 (CH_1), 37.3 (CH_2), 31.9 (CH_2), 31.8 (up), 22.0 (up), 0.1 (CH_3). **FTIR** (neat, cm^{-1}): 2953, 2109, 1703, 1370, 858, 842. **R_f**: 0.51 in 20% EtOAc/hexanes.

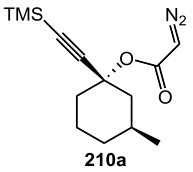


(*syn*)-3-Methyl-1-((trimethylsilyl)ethynyl)cyclohexyl 2-diazoacetate was synthesized from propargyl alcohol **209d** (0.50 g, 2.38 mmol) following general procedure C. 10% EtOAc/hexanes mixture was used to extract the product. The crude product was purified by column chromatography on silica gel using 5-10% gradient of Et_2O in pentane as an eluent. The product was obtained as a yellow oil (0.47 g, 71% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.65 (s, 1H), 2.40-2.30 (m, 2H), 1.82-1.59 (m, 4H), 1.46 (td, *J* = 12.4, 4.6 Hz, 1H), 1.20 (t, *J* = 12.4 Hz, 1H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.88-0.76 (m, 1H), 0.16 (s, 9H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 164.8 (CH_0), 104.9 (CH_0), 92.1 (CH_0), 77.9 (CH_0), 46.8 (CH_1), 45.5 (CH_2), 37.4 (CH_2), 34.2 (CH_2), 30.0 (up), 23.1 (CH_2), 22.1 (up), 0.1 (CH_3). **FTIR** (neat, cm^{-1}): 2953, 2109, 1703, 1369, 1170, 864, 842. **R_f**: 0.54 in 20% EtOAc/hexanes.



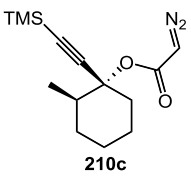
210b

(*syn*)-3-Methyl-1-((trimethylsilyl)ethynyl)cyclohexyl 2-diazoacetate was synthesized from propargyl alcohol **209b** (0.20 g, 0.74 mmol) following general procedure C. 10% EtOAc/hexanes mixture was used to extract the product. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a light yellow solid (0.11 g, 44% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32-7.26 (m, 2H), 7.22-7.17 (m, 3H), 4.67 (s, 1H), 3.01-2.90 (m, 1H), 2.59-2.45 (m, 2H), 1.92-1.73 (m, 3H), 1.75 (t, *J* = 12.4 Hz, 1H), 1.66-1.57 (m, 1H), 1.45-1.33 (m, 1H), 0.22 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ ~165 (CH_0), 145.5 (CH_0), 128.6 (CH_1), 127.1 (CH_1), 126.4 (CH_1), 104.5 (CH_0), 92.9 (CH_0), 77.8 (CH_0), 46.8 (CH_1), 44.7 (CH_2), 41.4 (CH_1), 37.1 (CH_2), 33.2 (CH_2), 23.5 (CH_2), 0.2 (CH_3). **FTIR** (neat, cm^{-1}): 3098, 2106, 1700, 1682, 1350, 1236, 843. **R_f**: 0.48 in 20% EtOAc/hexanes.



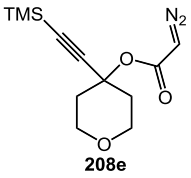
210a

(*anti*)-3-Methyl-1-((trimethylsilyl)ethynyl)cyclohexyl 2-diazoacetate was synthesized from propargyl alcohol **209a** (0.20 g, 0.95 mmol) following general procedure C. 10% EtOAc/hexanes mixture was used to extract the product. The crude product was purified by column chromatography on silica gel using 5% Et_2O in pentane as an eluent. The product was obtained as a light yellow solid (0.18 g, 67% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.67 (s, 1H), 2.51-2.43 (m, 2H), 1.68-1.40 (m, 5H), 1.31-1.22 (m, 1H), 0.93-0.82 (m, 1H), 0.87 (d, *J* = 6.4 Hz, 3H), 0.14 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ ~165, 106.5, 88.9, 75.2, 46.6, 45.0, 36.6, 33.8, 27.4, 22.2, 21.2, 0.1. **FTIR** (neat, cm^{-1}): 2953, 2108, 1703, 1370, 1183, 1147, 860, 843. **R_f**: 0.43 in 10% Et_2O/pentane.



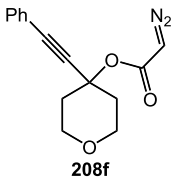
210c

(*anti*)-2-Methyl-1-((trimethylsilyl)ethynyl)cyclohexyl 2-diazoacetate was synthesized from propargyl alcohol **209c** (0.30 g, 1.43 mmol) following general procedure C. A 10% EtOAc/hexanes mixture was used to extract the product. The crude product was filtered through a plug of silica gel using 40-50% gradient of CH_2Cl_2 in hexanes as an eluent followed by column chromatography on silica gel using 5-7.5% gradient of EtOAc in hexanes as an eluent. The product was obtained as a light yellow solid (0.17 g, 43% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.66 (s, 1H), 2.74-2.64 (m, 1H), 1.89-1.80 (m, 1H), 1.69-1.53 (m, 5H), 1.41-1.31 (m, 1H), 1.26-1.16 (m, 1H), 0.98 (d, *J* = 6.3 Hz, 3H), 0.17 (s, 9H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ ~165 (CH_0), 102.4 (CH_0), 93.4 (CH_0), 82.1 (CH_0), 46.8 (CH_1), 41.1 (CH_1), 36.7 (CH_2), 31.8 (CH_2), 25.3 (CH_2), 23.9 (CH_2), 16.4 (CH_3), 0.1 (CH_3). **FTIR** (neat, cm^{-1}): 2931, 2119, 1680, 1370, 1189, 1170, 1007, 846. **R_f**: 0.46 in 50% CH_2Cl_2/hexanes.



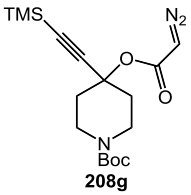
208e

4-((Trimethylsilyl)ethynyl)tetrahydro-2H-pyran-4-yl 2-diazoacetate was synthesized from propargyl alcohol **207e** (0.50 g, 2.52 mmol) following general procedure C. 20% EtOAc/hexanes mixture was used to extract the product. The crude product was purified by column chromatography on silica gel using 1-2% gradient of EtOAc in CH_2Cl_2 as an eluent. The product was obtained as a yellow oil (0.30 g, 45% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.70 (s, 1H), 3.88-3.77 (m, 2H), 3.75-3.64 (m, 2H), 2.25-2.15 (m, 2H), 2.06-1.95 (m, 2H), 0.18 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ ~165 (CH_0), 103.6 (CH_0), 92.6 (CH_0), 73.7 (CH_0), 64.6 (CH_2), 46.8 (CH_1), 37.9 (CH_2), 0.0 (CH_3). **FTIR** (neat, cm^{-1}): 2963, 2110, 1702, 1369, 1149, 859, 843. **R_f**: 0.23 in 20% EtOAc/hexanes; **R_f**: 0.51 in 5% EtOAc/CH_2Cl_2.



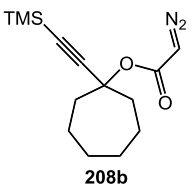
208f

4-(Phenylethynyl)tetrahydro-2H-pyran-4-yl 2-diazoacetate was synthesized from propargyl alcohol **207f** (0.31 g, 1.53mmol) following general procedure C. 20% EtOAc/hexanes mixture was used to extract the product. The crude product was purified by column chromatography on silica gel using 25% Et_2O in pentane as an eluent. The product was obtained as a yellow oil (0.17 g, 42% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.47-7.44 (m, 2H), 7.32-7.28 (m, 3H), 4.75 (s, 1H), 3.88 (dt, *J* = 12.6, 4.0 Hz, 2H), 3.79 (dd, *J* = 9.2, 2.9 Hz, 2H), 2.36-2.30 (m, 2H), 2.12 (dd, *J* = 9.2, 4.0 Hz, 2H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ ~165 (CH_0), 132.1 (CH_1), 128.8 (CH_1), 128.4 (CH_1), 122.3 (CH_0), 87.6 (CH_0), 87.4 (CH_0), 73.9 (CH_0), 64.7 (CH_2), 46.9 (CH_1), 38.1 (CH_2). **FTIR** (neat, cm^{-1}): 2110, 1698, 1369, 1180, 1143. **R_f**: 0.26 in 30% Et_2O/pentane.



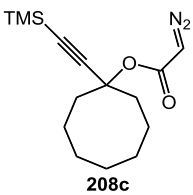
208g

***tert*-Butyl 4-(2-diazoacetoxy)-4-((trimethylsilyl)ethynyl)piperidine-1-carboxylate** was synthesized from propargyl alcohol **207g** (0.50 g, 1.68 mmol) following general procedure C. 20% EtOAc/hexanes mixture was used to extract the product. The crude product was purified by column chromatography on silica gel using 2% EtOAc in CH_2Cl_2 as an eluent. The product was obtained as a yellow oil (0.29 g, 47% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.70 (s, 1H), 3.83-3.59 (m, 2H), 3.36-3.20 (m, 2H), 2.20-2.08 (m, 2H), 1.96-1.82 (m, 2H), 1.44 (s, 9H), 0.16 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ ~165 (CH_0), 154.6 (CH_0), 103.3 (CH_0), 92.7 (CH_0), 79.9 (CH_0), 74.6 (CH_0), 46.8 (CH_1), ~40.5 (CH_2), 36.8 (CH_2), 28.5 (CH_3), 0.0 (CH_3). **FTIR** (neat, cm^{-1}): 2110, 1698, 1367, 1248, 1151, 1030, 858, 844. **R_f**: 0.43 in 5% EtOAc/CH_2Cl_2.



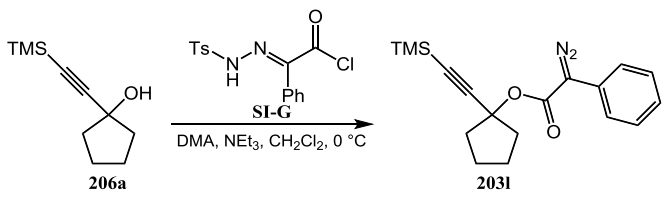
208b

1-((Trimethylsilyl)ethynyl)cycloheptyl 2-diazoacetate was synthesized from propargyl alcohol **208b** (0.40 g, 1.90 mmol) following general procedure C. 5% EtOAc/hexanes mixture was used to extract the product. The crude product was purified by column chromatography on silica gel using 2-4% gradient of EtOAc in hexanes as an eluent. The product was obtained as a yellow solid (0.34 g, 64% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.66 (s, 1H), 2.26-2.15 (m, 2H), 2.15-2.03 (m, 2H), 1.65-1.49 (m, 8H), 0.15 (s, 9H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 164.8 (CH_0), 106.4 (CH_0), 90.4 (CH_0), 80.2 (CH_0), 46.8 (CH_1), 40.5 (CH_2), 28.2 (CH_2), 22.4 (CH_2), 0.1 (CH_3). **FTIR** (neat, cm^{-1}): 2934, 2105, 1701, 1678, 1371, 1179, 843. **R_f**: 0.54 in 20% EtOAc/hexanes.



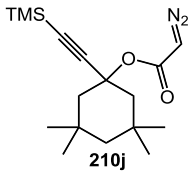
208c

1-((Trimethylsilyl)ethynyl)cyclooctyl 2-diazoacetate was synthesized from propargyl alcohol **208c** (0.40 g, 1.78 mmol) following general procedure C. 10% EtOAc/hexanes mixture was used to extract the product. The crude product was purified by column chromatography on silica gel using 5% gradient of EtOAc in hexanes as an eluent. The product was obtained as a yellow solid (0.32 g, 61% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.65 (s, 1H), 2.27-2.16 (m, 2H), 2.16-2.06 (m, 2H), 1.69-1.40 (m, 10H), 0.15 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 164.8 (CH_0), 106.1 (CH_0), 90.4 (CH_0), 80.2 (CH_0), 46.8 (CH_1), 35.5 (CH_2), 27.9 (CH_2), 24.7 (CH_2), 21.9 (CH_2), 0.1 (CH_3). **FTIR** (neat, cm^{-1}): 2920, 2104, 1677, 1378, 1184, 840. **R_f**: 0.52 in 20% EtOAc/hexanes.



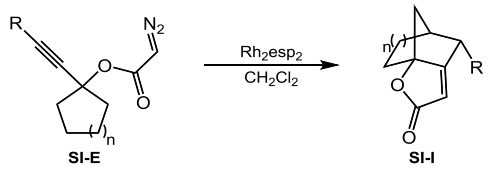
1-((Trimethylsilyl)ethynyl)cyclopentyl 2-diazo-2-phenylacetate (203l). A flame-dried round-bottom flask was charged with propargyl alcohol **206a** (150 mg, 0.82 mmol) under an argon atmosphere. Anhydrous CH_2Cl_2 (4.8 ml) was added, and the flask was cooled to 0 ˚C. Phenylglyoxylic acid chloride *p*-toluenesulfonylhydrazone (**SI-G**) (0.55 g, 1.64 mmol) was added in one portion followed by *N*,*N*-dimethyl aniline (0.19 ml, 1.48 mmol). The reaction mixture was stirred for 15 minutes before adding triethylamine (0.57 ml, 4.1 mmol) and was stirred for 10 more minutes at 0 ˚C. The reaction was concentrated under reduced pressure. A concentrated citric acid solution and a 20% EtOAc in hexanes mixture was added to the residue. The layers were separated, and the aqueous layer was extracted two times with a 20% EtOAc in hexanes mixture. The combined organic phases were washed with concentrated citric acid solution and brine, dried over $MgSO_4$, filtered through a short silica gel plug, and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as an orange solid (87 mg, 32% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.50-7.46 (m, 2H), 7.39-7.34 (m, 2H), 7.18-7.14 (m, 1H), 2.35-2.27 (m, 2H), 2.22-2.13 (m, 2H), 1.81-1.70 (m, 4H), 0.16 (s, 9H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 163.4 (CH_0), 129.0 (CH_1), 125.9 (CH_0), 125.8 (CH_1), 124.0 (CH_1), 105.6 (CH_0), 89.8 (CH_0), 82.0 (CH_0), 63.6 (CH_0), 40.9 (CH_2), 23.6 (CH_2), 0.1 (CH_3). **FTIR** (neat, cm^{-1}): 2927, 2085, 1707, 1245, 1150, 848, 758. **R_f**: 0.66 in 20% EtOAc/hexanes.

*Phenylglyoxylic acid chloride p-toluenesulfonylhydrazone (**SI-G**) was synthesized according to the procedure described in literature. All properties were identical to those reported (*Zimmerman, H. E.; Bunce, R. A. *J. Org. Chem.* **1982**, *47*, 3377–3396*).*



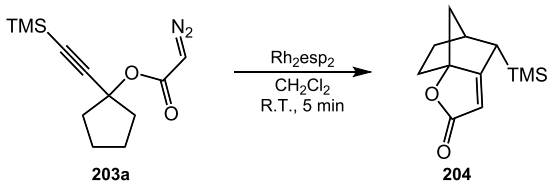
3,3,5,5-Tetramethyl-1-((trimethylsilyl)ethynyl)cyclohexyl 2-diazoacetate was synthesized from propargyl alcohol **209j** (0.30 g, 1.19 mmol) following general procedure C. 10% EtOAc/hexanes mixture was used to extract the product. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as an orange solid (0.25 g, 65% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.64 (s, 1H), 2.04 (d, *J* = 13.7 Hz, 2H), 1.79 (d, *J* = 13.7 Hz, 2H), 1.29-1.17 (m, 2H), 1.02 (d, *J* = 8.7 Hz, 12H), 0.14 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ ~165 (CH_0), 107.2 (CH_0), 89.6 (CH_0), 76.7 (CH_0), 51.2 (CH_2), 48.0 (CH_2), 46.8 (CH_1), 32.9 (CH_3), 31.6 (CH_0), 30.9 (CH_3), -0.1 (CH_3). **FTIR** (neat, cm^{-1}): 2955, 2112, 1711, 1693, 1333, 1192, 990, 842. **R_f**: 0.57 in 20% EtOAc/hexanes.

2.4.2.3. Synthesis of Bridged Polycyclic Compounds



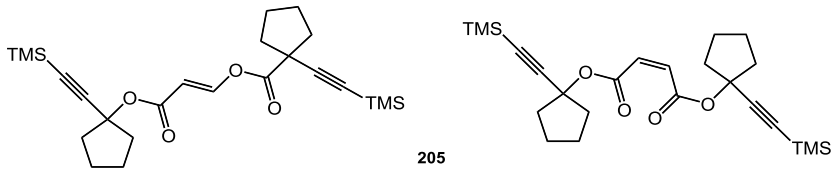
General Procedure D: A flame-dried round-bottom flask was charged with diazoacetate **SI-E** (1.0 eq) under an argon atmosphere. Anhydrous CH_2Cl_2 (0.005 M) was added. The reaction mixture was vigorously stirred at room temperature while adding $Rh_2(esp)_2$ catalyst (0.5 mol%) in one portion. After 5 minutes, the TLC analysis showed no starting material. The reaction was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel.

General Procedure E: A flame-dried round-bottom flask equipped with a condenser was charged with diazoacetate **SI-E** (1.0 eq) under an argon atmosphere. Anhydrous CH_2Cl_2 (0.005 M) was added, and the reaction mixture was heated to 45 ˚C. When it started to reflux $Rh_2(esp)_2$ catalyst (0.5 mol%) dissolved in anhydrous CH_2Cl_2 (2 ml) was added dropwise slowly through the condenser using a syringe equipped with a long needle. After 30 minutes, the reaction mixture was allowed to cool down to room temperature. The reaction was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel.



203a 204

6-(Trimethylsilyl)-2-oxatricyclo[5.2.1.0^{1,5}]dec-4-en-3-one (204) was synthesized from diazoacetate **203a** (75 mg, 0.30 mmol) following general procedure D. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a white solid (51 mg, 76% yield). The stereochemistry of the TMS-group was assigned by 1D nOe correlation experiments (see page SI212). A similar experiment starting with 38 mg (0.15 mmol) of **203a** gave 27 mg (80% yield) of **204** and dimers were isolated together as a light yellow solid (5 mg, 16% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.40 (d, *J* = 2.3 Hz, 1H), 2.69-2.64 (m, 1H), 2.28-2.24 (m, 1H), 2.20-2.12 (m, 1H), 2.05-2.01 (m, 1H), 1.91-1.82 (m, 1H), 1.69-1.62 (m, 1H), 1.49-1.44 (m, 1H), 1.37-1.30 (m, 1H), 0.13 (s, 9H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 185.1 (CH_0), 175.9 (CH_0), 104.9 (CH_1), 95.0 (CH_0), 45.0 (CH_2), 39.5 (CH_1), 36.5 (CH_1), 27.0 (CH2), 25.9 (CH2), -1.5 (CH_3). **HRMS**-ESI m/z: [M+Na], calculated for $C_{12}H_{18}NaO_2Si$, 245.0968; found 245.0967. **R_f**: 0.31 in 20% EtOAc/hexanes.

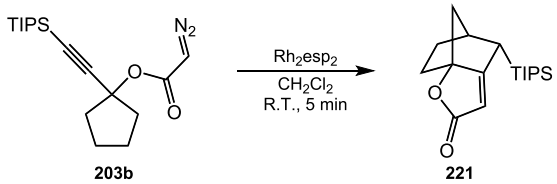


205

Homodimers (cis/trans) were separated by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The minor dimer **205** was isolated as a white solid: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.76 (s, 2H), 2.30-2.20 (m, 4H), 2.20-2.09 (m, 4H), 1.79-1.68 (m, 8H), 0.14 (s, 18H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 163.4 (CH_0), 134.3 (CH_1), 104.8

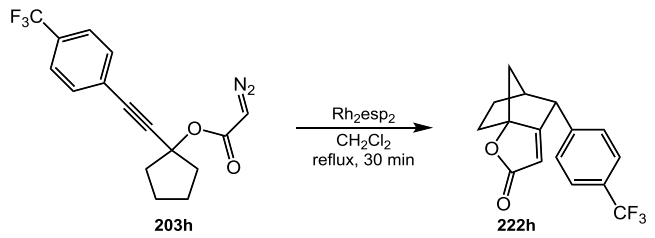
(CH_0), 90.0 (CH_0), 82.1 (CH_0), 40.6 (CH_2), 23.5 (CH_2), 0.0 (CH_3). **HRMS**-ESI m/z: [M+Na], calculated for $C_{24}H_{36}NaO_4Si_2$, 467.2044; found 467.2044. **R_f**: 0.31 in 5% EtOAc/hexanes.

The major dimer **205** was isolated as a white solid: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.12 (s, 2H), 2.35-2.25 (m, 4H), 2.17-2.07 (m, 4H), 1.80-1.67 (m, 8H), 0.14 (s, 18H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 163.3 (CH_0), 130.0 (CH_1), 105.4 (CH_0), 89.7 (CH_0), 82.1 (CH_0), 40.6 (CH_2), 23.6 (CH_2), 0.0 (CH_3). **HRMS**-ESI m/z: [M+Na], calculated for $C_{24}H_{36}NaO_4Si_2$, 467.2044; found 467.2042. **R_f**: 0.23 in 5% EtOAc/hexanes.

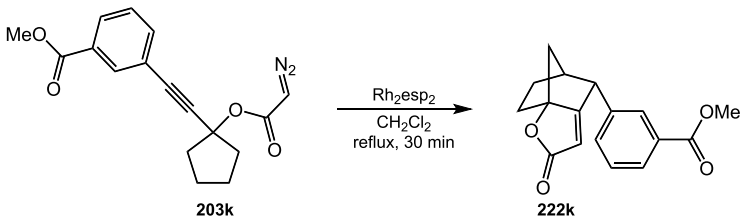


203b **221**

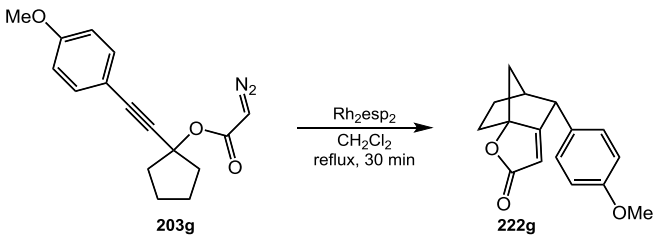
6-(Triisopropylsilyl)-2-oxatricyclo[5.2.1.0^{1,5}]dec-4-en-3-one (221) was synthesized from diazoacetate **203b** (68 mg, 0.20 mmol) following general procedure D. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a white solid (34 mg, 55% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.42 (d, *J* = 2.3 Hz, 1H), 2.69-2.64 (m, 1H), 2.24-2.14 (m, 2H), 2.05-1.95 (m, 1H), 1.95-1.90 (m, 1H), 1.62-1.52 (m, 2H), 1.50-1.41 (m, 1H), 1.24-1.12 (m, 3H), 1.12-1.02 (m, 18H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 184.9 (CH_0), 176.0 (CH_0), 105.5 (CH_1), 94.4 (CH_0), 40.0 (CH_2), 39.0 (CH_1), 32.4 (CH_1), 30.9 (CH_2), 28.0 (CH_2), 19.0 (CH_3 or CH_1), 11.3 (CH_1 or CH_3). **HRMS**-ESI m/z: [M+Na], calculated for $C_{18}H_{30}NaO_2Si$, 329.1907; found 329.1906. **R_f**: 0.46 in 20% EtOAc/hexanes.



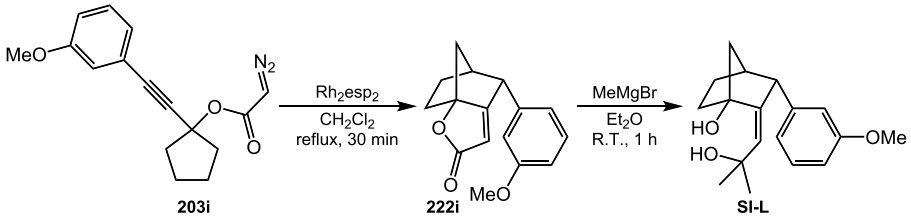
6-((4-(Trifluoromethyl)phenyl)-2-oxatricyclo[5.2.1.0^{1,5}]dec-4-en-3-one (222h) was synthesized from diazoacetate **203h** (66 mg, 0.20 mmol) following general procedure E. The crude product was filtered through the plug of silica gel using 30% EtOAc in hexanes as an eluent followed by column chromatography on silica gel using 1-2% gradient of EtOAc in CH_2Cl_2 as an eluent. The product was obtained as a white solid (40 mg, 66% yield). A similar experiment starting with 65 mg (0.20 mmol) of **203h** gave 38 mg (62% yield) of **222h**. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 5.81 (d, *J* = 1.7 Hz, 1H), 4.24-4.20 (m, 1H), 2.87-2.83 (m, 1H), 2.25 (dd, *J* = 9.2 Hz, 1.7 Hz, 1H), 2.24 (td, *J* = 12.6, 4.6 Hz, 1H), 1.73-1.65 (m, 2H), 1.42-1.36 (m, 1H), 1.30-1.22 (m, 1H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 179.2 (CH_0), 175.0 (CH_0), 141.5 (CH_0), 128.1 (CH_1), 126.0 (CH_1), 111.2 (CH_1), 94.7 (CH_0), 47.8 (CH_1), 42.1 (CH_1), 41.3 (CH_2), 27.4 (CH_2), 22.1 (CH_2). **^{19}F NMR** (376.17 MHz, $CDCl_3$) δ -65.78. **HRMS**-ESI m/z: [M+Na], calculated for $C_{16}H_{13}F_3NaO_2$, 317.0760; found 317.0760. **R_f**: 0.14 in 20% EtOAc/hexanes.



Methyl-3-(3-oxo-2-oxatricyclo[5.2.1.0^{1,5}]dec-4-en-6-yl)benzoate (222k) was synthesized from diazoacetate **203k** (40 mg, 0.13 mmol) following general procedure E. The crude product was filtered through the plug of silica gel using 20% EtOAc in hexanes as an eluent followed by column chromatography on silica gel using 2% EtOAc in CH_2Cl_2 as an eluent. The product was obtained as a white solid (24 mg, 65% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.99-7.94 (m, 1H), 7.84-7.81 (m, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.36-7.32 (m, 1H), 5.82 (d, *J* = 1.7 Hz, 1H), 4.23-4.19 (m, 1H), 3.92 (s, 3H), 2.87-2.82 (m, 1H), 2.24 (dd, *J* = 9.2, 1.7 Hz, 1H), 2.25-2.18 (m, 1H), 1.71-1.61 (m, 2H), 1.44-1.37 (m, 1H), 1.30-1.22 (m, 1H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 179.5 (CH_0), 175.2 (CH_0), 166.8 (CH_0), 137.8 (CH_0), 132.0 (CH_1), 131.0 (CH_0), 129.2 (CH_1), 128.7 (CH_1), 128.7 (CH_1), 111.1 (CH_1), 94.8 (CH_0), 52.5 (up), 47.8 (up), 42.0 (up), 41.2 (CH_2), 27.5 (CH_2), 22.1 (CH_2). **HRMS**-ESI m/z: [M+Na], calculated for $C_{17}H_{16}NaO_4$, 307.0941; found 307.0940. **R_f**: 0.36 in 2% EtOAc/CH_2Cl_2.

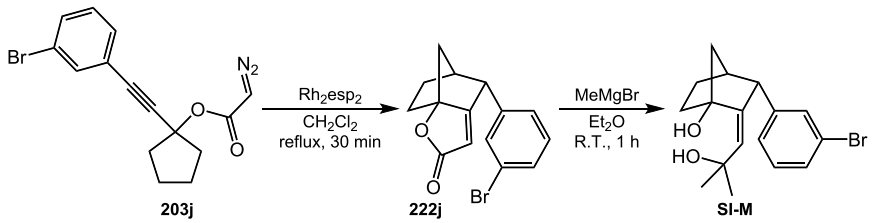


6-(4-Metoxyphenyl)-2-oxatricyclo[5.2.1.0^{1,5}]dec-4-en-3-one (222g) was synthesized from diazoacetate **203g** (26 mg, 0.09 mmol) following general procedure E. The yield was measured to be 7% by integration of internal standard and vinyl proton in the crude ^{1}H NMR spectrum.



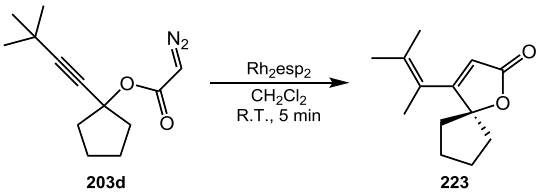
6-(3-Metoxyphenyl)-2-oxatricyclo[5.2.1.0^{1,5}]dec-4-en-3-one (222i) was synthesized from diazoacetate **203i** (51 mg, 0.18 mmol) following general procedure E. Purification of the crude product by column chromatography was insufficient, as it led to epimerization of **222i** and product decomposition. Thus, the yield was measured to be 63% by integration of an internal standard and the vinyl proton of **222i** in the crude ^{1}H NMR spectrum. In order to obtain an analytically pure sample for structural elucidation, the crude product was dissolved in anhydrous Et_2O (1.8 ml) and methylmagnesiumbromide (0.2 ml, 3.3 eq) was added dropwise slowly at room temperature. After 1 h, saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product. The crude product was filtered through a plug of silica gel using 30% EtOAc

in hexanes as an eluent followed by column chromatography on silica gel using 15% EtOAc in CH_2Cl_2 as an eluent. The product was obtained as a colorless oil (22 mg, 41% yield for two steps). Spectral data for **(2E)-2-(2-hydroxy-2-methylpropylidene)-3-(3-methoxyphenyl)bicycle[2.2.1]heptan-1-ol (SI-L): ^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22 (t, *J* = 8.2 Hz, 1H), 6.82-6.73 (m, 3H), 5.22 (d, *J* = 2.8 Hz, 1H), 3.95-3.91 (m, 1H), 3.79 (s, 3H), 2.17-2.12 (m, 1H), 1.88-1.73 (m, 4H), 1.63-1.53 (m, 1H), 1.49-1.37 (m, 1H), 1.44 (s, 3H), 1.41 (s, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 159.6 (CH_0), 146.3 (CH_0), 144.4 (CH_0), 129.3 (CH_1), 128.6 (CH_1), 121.3 (CH_1), 114.7 (CH_1), 111.4 (CH_1), 85.4 (CH_0), 72.0 (CH_0), 56.0 (CH_1), 55.3 (CH_1), 46.7 (CH_2), 40.4 (CH_1), 35.9 (CH_2), 32.0 (CH_3), 31.8 (CH_3), 24.2 (CH_2). **HRMS**-ESI m/z: [M+Na], calculated for $C_{18}H_{24}NaO_3$, 311.1618; found 311.1620. **R_f**: 0.09 in 2% EtOAc/CH_2Cl_2.



6-(3-Bromophenyl)-2-oxatricyclo[5.2.1.0^{1,5}]dec-4-en-3-one (222j) was synthesized from diazoacetate **203j** (50 mg, 0.15 mmol) following general procedure E. Purification of the crude product by column chromatography was insufficient, which led to epimerization of **222j** and product decomposition. Thus, the yield was measured to be 56% by integration of an internal standard and the vinyl proton of **222j** in the crude ^{1}H NMR spectrum. In order to obtain an analytically pure sample for structural elucidation, the crude product was dissolved in anhydrous Et_2O (1.5 ml) and methylmagnesiumbromide (165 µl, 3.3 eq) was added dropwise slowly at room temperature. After 1 h, saturated NH_4Cl solution was

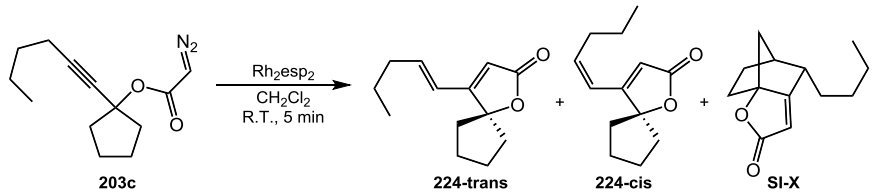
added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product. The crude product was filtered through a plug of silica gel using 30% EtOAc in hexanes as an eluent followed by column chromatography on silica gel using 20% EtOAc in CH_2Cl_2 as an eluent. The product was obtained as a colorless oil (27 mg, 53% yield for two steps). Spectral data for **(2E)-2-(2-hydroxy-2-methylpropylidene)-3-(3-bromophenyl)bicycle[2.2.1]heptan-1-ol (SI-M): ^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35-7.31 (m, 2H), 7.20-7.10 (m, 2H), 5.16 (d, *J* = 2.3 Hz, 1H), 3.93-3.88 (m, 1H), 2.17-2.12 (m, 1H), 1.90-1.72 (m, 4H), 1.65-1.55 (m, 1H), 1.45-1.36 (m, 1H), 1.43 (s, 3H), 1.41 (s, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 146.1 (CH_0), 145.2 (CH_0), 132.0 (CH_1), 129.9 (CH_1), 129.5 (CH_1), 128.8 (CH_1), 127.5 (CH_1), 122.5 (CH_0), 85.3 (CH_0), 72.1 (CH_0), 55.7 (CH_1), 46.7 (CH_2), 40.3 (CH_1), 35.8 (CH_2), 32.0 (CH_3), 31.8 (CH_3), 24.0 (CH_2). **HRMS**-ESI m/z: [M+Na], calculated for $C_{17}H_{21}BrNaO_2$, 359.0617; found 359.0616. **R_f**: 0.20 in 30% EtOAc/hexanes.



203d **223**

4-(3-methylbut-2-en-2-yl)-1-oxaspiro[4.4]non-3-en-2-one (223) was synthesized from diazoacetate **203d** (70 mg, 0.30 mmol) following general procedure D. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a white solid (47 mg, 76% yield). A similar experiment starting with 70 mg (0.30 mmol) of **33** gave 45 mg (73% yield) of **34**. **^{1}H NMR** (400 MHz,

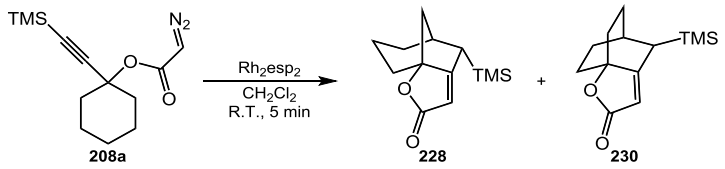
$CDCl_3$) δ 5.64 (s, 1H), 2.01-1.86 (m, 4H), 1.85-1.75 (m, 7H), 1.75-1.71 (m, 3H), 1.62-1.58 (m, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 175.4 (CH_0), 172.4 (CH_0), 132.4 (CH_0), 120.4 (CH_0), 117.3 (CH_1), 99.0 (CH_0), 37.0 (CH_2), 24.2 (CH_2), 22.7 (CH_3), 20.2 (CH_3), 19.1 (CH_3). **R_f**: 0.34 in 20% EtOAc/hexanes.



4-[(1E)-pent-1-en-1-yl]-1-oxaspiro[4.4]non-3-en-2-one (224-trans) and **4-[(1Z)-pent-1-en-1-yl]-1-oxaspiro[4.4]non-3-en-2-one (224-cis)** were synthesized from diazoacetate **203c** (71 mg, 0.30 mmol) following general procedure D. The ratio of cis/trans isomer was measured to be 1:1.4 in the crude ^{1}H NMR spectrum. The yield of product **SI-X** was measured to be 9% by integration of an internal standard and the vinyl proton of **SI-X** in the crude ^{1}H NMR spectrum. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. Both isomers were isolated together as a light yellow oil (42 mg, 67% yield). A similar experiment was performed using pentane instead of CH_2Cl_2 as a reaction solvent: A flame dried round-bottom flask was charged with $Rh_2(esp)_2$ catalyst (1.1 mg) under an argon atmosphere. Anhydrous pentane (50 ml) was added. The reaction mixture was vigorously stirred at room temperature while adding 1-(hex-1-ynyl)cyclopentyl 2-diazoacetate (**203c**) (71 mg, 0.30 mmol) dissolved in anhydrous pentane (10 ml) dropwise slowly (5 ml/h) via syringe pump. After 2 hours, TLC analysis showed no starting material. The reaction was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using 10%

EtOAc in hexanes as an eluent. Both isomers were isolated together as a light yellow oil (31 mg, 50% yield). The product **SI-X** was not detected in the crude ^{1}H NMR spectrum. Isomers were separated by column chromatography on silica gel using a 5-10% gradient of EtOAc in hexanes as an eluent. The separation was repeated twice for each of the isomer. Spectral data for product **224-trans**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.32 (dt, *J* = 16.0, 6.9 Hz, 1H), 6.07-6.00 (m, 1H), 5.86 (s, 1H), 2.24-2.17 (m, 2H), 2.06-1.95 (m, 4H), 1.94-1.72 (m, 4H), 1.49 (sextet, *J* = 7.3 Hz, 2H), 0.94 (t, *J* = 7.3 Hz, 3 H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 172.6 (CH_0), 167.5 (CH_0), 142.9 (CH_1), 120.1 (CH_1), 113.1 (CH_1), 96.6 (CH_0), 37.7 (CH_2), 35.8 (CH_2), 25.5 (CH_2), 22.0 (CH_2), 13.8 (CH_3). **HRMS**-ESI m/z: [M+H], calculated for $C_{13}H_{19}O_2$, 207.1380; found 207.1380. **R_f**: 0.29 in 20% EtOAc/hexanes.

Spectral data for product **224-cis**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.15 (dt, *J* = 11.9, 7.3 Hz, 1H), 5.89 (s, 1H), 5.85-5.79 (m, 1H), 2.30-2.23 (m, 2H), 2.03-1.74 (m, 8H), 1.50 (sextet, *J* = 7.3 Hz, 2H), 0.94 (t, *J* = 7.3 Hz, 3 H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 172.9 (CH_0), 165.9 (CH_0), 144.8 (CH_1), 117.8 (CH_1), 115.5 (CH_1), 97.7 (CH_0), 37.0 (CH_2), 32.1 (CH_2), 25.4 (CH_2), 22.4 (CH_2), 13.9 (CH_3). **HRMS**-ESI m/z: [M+H], calculated for $C_{13}H_{19}O_2$, 207.1380; found 207.1379. **R_f**: 0.34 in 20% EtOAc/hexanes.

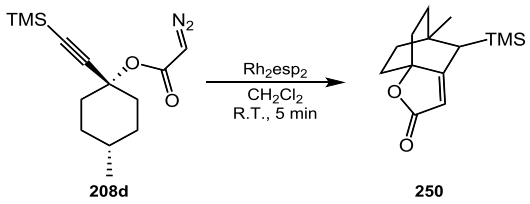


6-Trimethylsilyl-2-oxatricyclo[5.3.1.0^{1,5}]undec-4-en-3-one (228-endo), 6-Trimethylsilyl-2-oxatricyclo[5.3.1.0^{1,5}]undec-4-en-3-one (228-exo) and 6-Trimethylsilyl-2-oxatricyclo[5.2.2.0^{1,5}]undec-4-en-3-one (230) were synthesized from diazoacetate **208a** (98 mg, 0.37 mmol) following general procedure D. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. All three products were isolated together as colorless oil which crystalized on standing (61 mg, 69% yield). The ratio of **228-endo**/**228-exo**/**230** was measured to be 0.8:0.7:1 in the ^{1}H NMR spectrum after isolation. All three products were separated by column chromatography on silica gel using 5-10% gradient of EtOAc in hexanes as an eluent. Spectral data for **228-endo** (stereochemistry of the TMS-group was assigned by 1D nOe correlation experiments, see page SI213): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.53 (d, *J* = 2.3 Hz, 1H), 2.84-2.77 (m, 1H), 2.36-2.31 (m, 1H), 2.22-2.12 (m, 1H), 1.90 (d, *J* = 10.1 Hz, 1H), 1.84-1.50 (m, 6H), 0.20 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 185.9 (CH_0), 174.6 (CH_0), 109.6 (CH_1), 94.0 (CH_0), 45.1 (CH_2), 40.6 (CH_1), 37.1 (CH_2), 35.8 (CH_1), 28.5 (CH_2), 20.6 (CH_2), -0.2 (CH_3). **HRMS**-ESI m/z: [M+H], calculated for $C_{13}H_{21}O_2Si$, 237.1305; found 237.1304. **R_f**: 0.31 in 20% EtOAc/hexanes.

Spectral data for **228-exo** (stereochemistry of the TMS-group was assigned by 1D nOe correlation experiments, see page SI214): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.55 (d, *J* = 2.8 Hz, 1H), 2.68-2.62 (m, 1H), 2.19-2.09 (m, 1H), 1.95-1.90 (m, 1H), 1.84-1.72 (m, 3H), 1.69-

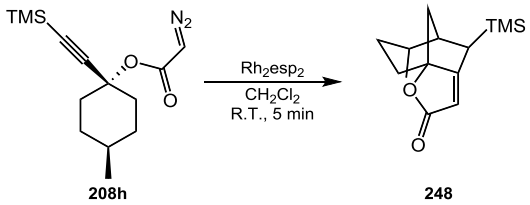
1.62 (m, 1H), 1.61-1.51 (m, 3H), 0.08 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 183.7 (CH_0), 175.2 (CH_0), 109.0 (CH_1), 92.8 (CH_0), 40.8 (CH_2), 39.8 (CH_1), 37.1 (CH_2), 31.6 (CH_1), 31.2 (CH_2), 19.9 (CH_2), -2.4 (CH_3). **HRMS**-ESI m/z: [M+H], calculated for $C_{13}H_{21}O_2Si$, 237.1305; found 237.1304. **R_f**: 0.34 in 20% EtOAc/hexanes.

Spectral data for **230**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.46 (d, *J* = 2.3 Hz, 1H), 2.38-2.34 (m, 1H), 2.22-2.10 (m, 2H), 2.08-2.03 (m, 1H), 1.94-1.84 (m, 1H), 1.80-1.73 (m, 2H), 1.72-1.62 (m, 1H), 1.54 (dt, *J* = 11.9, 3.7 Hz, 1H), 1.51-1.41 (m, 1H), 0.14 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 180.3 (CH_0), 174.6 (CH_0), 106.5 (CH_1), 84.8 (CH_0), 36.5 (CH_1), 29.9 (CH_2), 29.1 (CH_2), 28.5 (CH_1), 28.3 (CH_2), 24.3 (CH_2), -1.5 (CH_3). **HRMS**-ESI m/z: [M+H], calculated for $C_{13}H_{21}O_2Si$, 237.1305; found 237.1303. **R_f**: 0.23 in 20% EtOAc/hexanes.



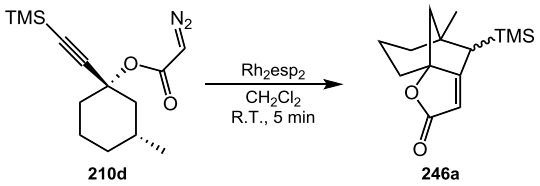
6-Trimethylsilyl-7-methyl-2-oxatricyclo[5.2.2.0^{1,5}]undec-4-en-3-one (250) was synthesized from diazoacetate **208d** (52 mg, 0.19 mmol) following general procedure D. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a white solid (27 mg, 57% yield). A similar experiment starting with 41 mg (0.15 mmol) of **208d** gave 21 mg (56% yield) of **250**. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.48 (d, *J* = 2.3 Hz, 1H), 2.30-2.26 (m, 1H), 2.23-2.11 (m, 2H), 1.74-1.44 (m, 6H), 1.04 (s, 3H), 0.18 (s, 9H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 180.5 (CH_0), 174.5 (CH_0), 107.2 (CH_1), 85.1 (CH_0), 42.4 (up), 38.3 (CH_2), 34.4 (CH_0),

31.6 (CH_2), 31.0 (CH_2), 28.3 (CH_2), 27.3 (up), 0.7 (CH_3). **HRMS**-ESI m/z: [M+Na], calculated for $C_{14}H_{22}NaO_2Si$, 273.1281; found 273.1284. $\mathbf{R_f}$: 0.26 in 20% EtOAc/hexanes.



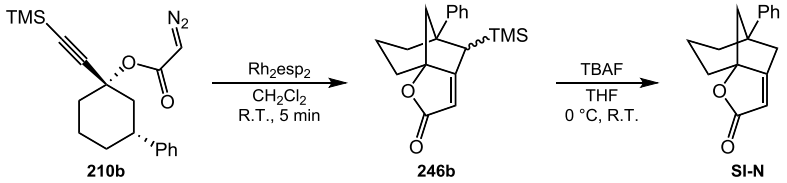
***anti*-6-(Trimethylsilyl)-8-methyl-2-oxatricyclo[5.3.1.0^{1,5}]undec-4-en-3-one (248-exo)** and ***syn*-6-(Trimethylsilyl)-8-methyl-2-oxatricyclo[5.3.1.0^{1,5}]undec-4-en-3-one (248-endo)** were synthesized from diazoacetate **208h** (34 mg, 0.12 mmol) following general procedure D. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The major diastereomer (**248-exo**) was obtained as a white solid (13 mg, 42% yield) and the minor diastereomer (**248-endo**) was obtained as a waxy gray solid (8 mg, 26% yield). A similar experiment starting with 81 mg (0.29 mmol) of **208h** gave 47 mg (65% yield) of **248-exo** and **248-endo** isolated together. Spectral data for **248-exo** (stereochemistry of the TMS-group was assigned by 1D nOe correlation experiments): **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.54 (d, *J* = 2.3 Hz, 1H), 2.34-2.30 (m, 1H), 2.20-2.12 (m, 1H), 2.05-2.01 (m, 1H), 1.86-1.78 (m, 2H), 1.76-1.66 (m, 2H), 1.51-1.45 (m, 1H), 1.40-1.30 (m, 1H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.08 (s, 9H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 183.7 (CH_0), 175.2 (CH_0), 108.7 (CH_1), 92.7 (CH_0), 46.0 (up), 41.2 (CH_2), 36.3 (CH_2), 35.0 (up), 28.1 (CH_2), 26.5 (up), 19.3 (up), -2.4 (CH_3). **HRMS**-ESI m/z: [M+Na], calculated for $C_{14}H_{22}NaO_2Si$, 273.1281; found 273.1284. $\mathbf{R_f}$: 0.46 in 20% EtOAc/hexanes.

Spectral data for **248-endo**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.55 (d, *J* = 2.3 Hz, 1H), 2.63-2.58 (m, 1H), 2.33-2.29 (m, 1H), 2.23-2.14 (m, 1H), 1.98 (d, *J* = 10.3 Hz, 1H), 1.88-1.79 (m, 2H), 1.71-1.64 (m, 1H), 1.56-1.49 (m, 1H), 1.40-1.30 (m, 1H), 1.03 (d, *J* = 7.4 Hz, 3H), 0.26 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 186.1 (CH_0), 174.7 (CH_0), 109.3 (CH_1), 94.0 (CH_0), 47.3 (up), 46.3 (CH_2), 36.4 (CH_2), 36.0 (up), 35.1 (up), 28.3 (CH_2), 21.0 (up), 0.8 (CH_3). **HRMS**-ESI m/z: [M+Na], calculated for $C_{14}H_{22}NaO_2Si$, 273.1281; found 273.1281. **R_f**: 0.40 in 20% EtOAc/hexanes.



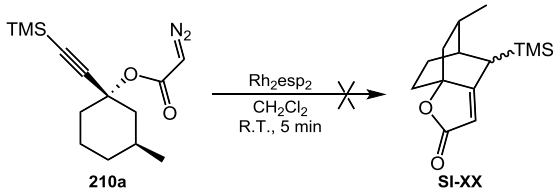
6-(Trimethylsilyl)-7-methyl-2-oxatricyclo[5.3.1.0^{1,5}]undec-4-en-3-one (246a) was synthesized from diazoacetate **210d** (55 mg, 0.20 mmol) following general procedure D. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The inseparable mixture of four isomers was obtained as a light yellow oil (25 mg, 55% yield). The two major products are diastereomers of **246a**, as for both products methyl group is observed as a singlet instead of the doublet in ^{1}H NMR spectrum. Integration of the vinyl and methyl protons in the ^{1}H NMR spectrum after isolation, allowed calculation of the yield (46%) and diastereomeric ratio (1.4:1) of **246a**. A similar experiment starting with 84 mg (0.30 mmol) of **210d** gave 45 mg (60% yield) of inseparable mixture of four isomers. Integration of the vinyl and methyl protons in the ^{1}H NMR spectrum after isolation, allowed calculation of the yield (51%) and diastereomeric

ratio (1.6:1) of **246a**. **HRMS**-ESI m/z for four isomer mixture: [M+H], calculated for $C_{14}H_{23}O_2Si$, 251.1462; found 251.1462. $\mathbf{R_f}$: 0.33 in 20% EtOAc/hexanes.

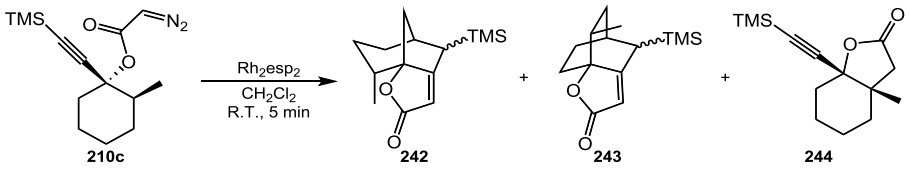


6-(trimethylsilyl)-7-phenyl-2-oxatricyclo[5.3.1.0^{1,5}]undec-4-en-3-one (246b) was synthesized from diazoacetate **210b** (68 mg, 0.20 mmol) following general procedure D. Purification of the crude product by column chromatography was insufficient to yield a clean ^{1}H NMR spectrum of the four isomer mixture. Integration of an internal standard and the vinyl protons of the four isomers in the crude ^{1}H NMR spectrum, allowed measurement of the yield (52%) and diastereomeric ratio (1.9:1) of **246b**. A similar experiment starting with 32 mg (0.09 mmol) of **210b** gave an inseparable mixture of four isomers. Integration of an internal standard and the vinyl protons of the four isomers in the crude ^{1}H NMR spectrum, allowed measurement of the yield (56%) and diastereomeric ratio (1.9:1) of **246b**. In order to obtain an analytically pure sample and to demonstrate that the two major products in the crude ^{1}H NMR spectrum are the diastereomers of **246b**, the crude product was carefully purified by column chromatography on silica gel using a 10-15% gradient of EtOAc in hexanes as an eluent. The mixture of the two major products (1:1 ratio) was observed in ^{1}H NMR spectrum. The TMS-group was cleaved for this mixture using TBAF (1.1 eq) in THF as a reaction solvent. Indeed, only one product was observed in the crude ^{1}H NMR spectrum after the reaction was completed (monitored by TLC analysis). The crude product was purified by column chromatography on silica gel using 20% EtOAc in hexanes as an eluent. **7-phenyl-2-oxatricyclo[5.3.1.0^{1,5}]undec-4-en-3-one (SI-N)** was

obtained as a white solid with a corresponding spectral data: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37-7.31 (m, 2H), 7.26-7.17 (m, 3H), 5.72 (t, *J* = 1.8 Hz, 1H), 3.08-3.00 (m, 1H), 2.82-2.74 (m, 1H), 2.28-2.18 (m, 2H), 2.07-2.01 (m, 1H), 2.01-1.65 (m, 5H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 179.3 (CH_0), 174.1 (CH_0), 147.6 (CH_0), 128.8 (CH_1), 126.8 (CH_1), 125.4 (CH_1), 112.8 (CH_1), 92.7 (CH_0), 50.9 (CH_0), 46.0 (CH_2), 40.7 (CH_2), 35.6 (CH_2), 35.3 (CH_2), 21.1 (CH_2). **HRMS**-ESI m/z: [M+Na], calculated for $C_{16}H_{16}NaO_2$, 263.1042; found 263.1043. **R_f**: 0.18 in 20% EtOAc/hexanes.



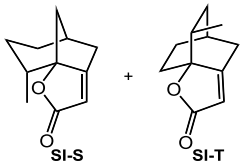
6-(Trimethylsilyl)-8-methyl-2-oxatricyclo[5.2.2.0^{1,5}]undec-4-en-3-one (SI-XX) could not be detected in the crude ^{1}H NMR spectrum using diazoacetate **210a** (52 mg, 0.19 mmol) as a starting material, following either general procedure D or general procedure E. In both cases, unreacted starting material **44** was observed in the crude ^{1}H NMR spectra.



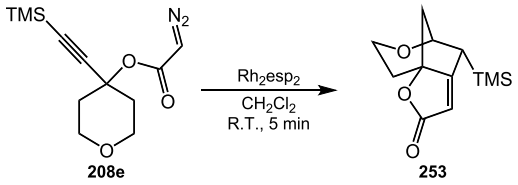
6-Trimethylsilyl-10-methyl-2-oxatricyclo[5.3.1.0^{1,5}]undec-4-en-3-one (242), 6-Trimethylsilyl-9-methyl-2-oxatricyclo[5.2.2.0^{1,5}]undec-4-en-3-one (243) and **(3aS,7aS)-3a-methyl-7a-[2-(trimethylsilyl)ethynyl]-octahydro-1-benzofuran-2-one (244)** were synthesized from diazoacetate **210c** (84 mg, 0.30 mmol) following general procedure D. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. Product **244** was isolated as a light yellow oil

(11 mg, 14% yield): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.58 (d, *J* = 16.5 Hz, 1H), 2.28 (d, *J* = 16.5 Hz, 1H), 2.14-2.05 (m, 1H), 1.91-1.80 (m, 1H), 1.59-1.37 (m, 6H), 1.26 (s, 3H), 0.16 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 176.0, 103.0, 92.8, 84.0, 43.8, 41.8, 33.9, 33.2, 21.7, 20.9, 20.8, -0.1. **HRMS**-ESI m/z: [M+H], calculated for $C_{14}H_{23}O_2Si$, 251.1467; found 251.1467. **R_f**: 0.46 in 20% EtOAc/hexanes. Products **242-endo/exo** and **243-endo/exo** were isolated together as a colorless oil (56 mg, 72% yield). **R_f**: 0.37 in 20% EtOAc/hexanes. Products could not be separated by column chromatography under any of the eluents analyzed. In order to obtain the product ratio as well as the diastereomeric ratios, the TMS- group was cleaved to limit the mixture to only two products. The corresponding procedure was followed: the mixture of **242-endo/exo** and **243-endo/exo** (56 mg, 0.22 mmol) was dissolved in anhydrous THF (2.20 ml) under an argon atmosphere, and the reaction vessel was cooled to 0 ˚C. TBAF (0.27 ml, 1.2 eq) was added dropwise slowly. The reaction was warmed to room temperature. After 10 minutes, TLC analysis showed no starting material. Deionized water was added, the mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The inseparable mixture of products **SI-S** and **SI-T** was obtained as a colorless oil (31.5 mg, 79% yield). The ratio of **SI-S** and **SI-T** was measured to be 4.0:1 in the crude ^{1}H NMR spectrum, which allowed assigning the diastereomer pairs for the previous reaction. The diastereomeric ratios were measured to be 2.4:1 for **47** and 1.3:1 for **48** accordingly. The product mixture was carefully purified by column chromatography on silica gel using a 5-

10% gradient of EtOAc in hexanes as an eluent twice in order to obtain clean **SI-S** for analysis.

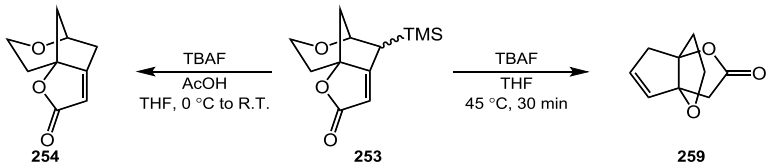


Spectral data for **SI-S**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.74 (t, *J* = 1.8 Hz, 1H), 2.59 (dd, *J* = 19.2, 7.3 Hz, 1H), 2.41-2.33 (m, 2H), 2.21-2.11 (m, 1H), 2.00-1.92 (m, 1H), 1.85-1.56 (m, 5H), 0.72 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 179.3 (CH_0), 175.1 (CH_1), 113.8 (CH_1), 95.1 (CH_0), 45.4 (CH_1), 43.7 (CH_1), 37.5 (CH_2), 31.9 (CH_2), 26.7 (CH_2), 20.2 (CH_2), 12.0 (CH_3). **HRMS**-ESI m/z: [M+H], calculated for $C_{11}H_{15}O_2$, 179.1072; found 179.1072. **R_f**: 0.23 in 20% EtOAc/hexanes.



6-(Trimethylsilyl)-2,8-dioxatricyclo[5.3.1.0^{1,5}]undec-4-en-3-one (253) was synthesized from diazoacetate **208a** (80 mg, 0.30 mmol) following general procedure D. The crude product was purified by column chromatography on silica gel using 20% EtOAc in hexanes as an eluent. The inseparable mixture of diastereomers was obtained as a white solid (51 mg, 71% yield). The *endo*-product **253** is the major diastereomer assigned by similarity to **255**. The diastereomeric ratio was measured to be 1.4:1 in ^{1}H NMR spectrum after isolation. A similar experiment starting with 61 mg (0.23 mmol) of **208a** gave 39 mg (72% yield) of **253**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.64 (d, *J* = 2.3 Hz, 1H, minor), 5.58 (d, *J* = 1.8 Hz, 1H, major), 4.80-4.76 (m, 1H, major), 4.66-4.63 (m, 1H, minor), 4.00-3.88 (m, 2H,

major/minor), 3.77-3.68 (m, 2H, major/minor), 2.50-2.38 (m, 4H, major/minor), 2.37-2.34 (m, 1H, major), 2.13-2.08 (m, 1H, minor), 1.82-1.73 (m, 1H, major), 1.68-1.57 (m, 2H, major/minor), 1.53-1.46 (m, 1H, minor), 0.22 (s, 9H, major), 0.13 (s, 9H, minor). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 183.3 (CH_0), 179.9 (CH_0), 174.5 (CH_0), 174.2 (CH_0), 109.4 (CH_1), 109.1 (CH_1), 91.2 (CH_0), 91.1 (CH_0), 80.1 (CH_1), 79.8 (CH_1), 60.4 (CH_2), 60.2 (CH_2), 42.2 (CH_2), 42.0 (CH_2), 38.3 (CH_1), 37.5 (CH_2), 36.3 (CH_2), 32.6 (CH_1), -0.8 (CH_3), -2.3 (CH_3). **R_f**: 0.14 in 20% EtOAc/hexanes.

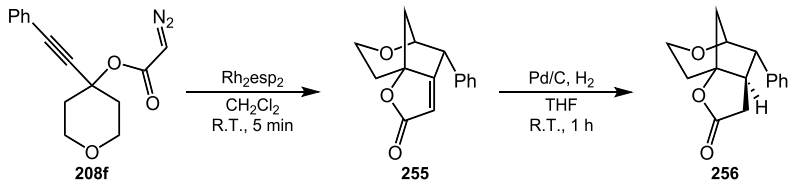


2,8-dioxatricyclo[5.3.1.0^{1,5}]undec-4-en-3-one (254) was synthesized according to the following procedure: **253** (21 mg, 0.09 mmol) was dissolved in anhydrous THF (1.0 ml) under an argon atmosphere, and the reaction vessel was cooled to 0 ˚C. AcOH (6 µl, 1.1 eq) followed by TBAF (96 µl, 1.1 eq) were added dropwise. The reaction was allowed to warm to room temperature. After 10 minutes, TLC analysis showed no starting material. Deionized water was added, the mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 30% EtOAc in hexanes as an eluent. The product **254** was obtained as a white solid (11 mg, 76% yield). A similar experiment starting with 13 mg (0.05 mmol) of **253** gave 7 mg (78% yield) of **254**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.80 (t, *J* = 1.8 Hz, 1H), 4.75 (t, *J* = 4.6 Hz, 1H), 4.04-3.98 (m, 1H), 3.90-3.81 (m, 1H), 2.96 (dt, *J* = 19.7, 2.3 Hz, 1H), 2.80-2.72 (m, 1H), 2.47 (td, *J* = 12.4, 6.7 Hz, 1H), 2.16 (dd, *J* = 11.0,

1.8 Hz, 1H), 1.66 (dt, *J* = 11.0, 3.2 Hz, 1H), 1.59-1.53 (m, 1H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 176.8 (CH_0), 173.9 (CH_0), 113.3 (CH_1), 91.1 (CH_0), 77.4 (CH_1), 60.8 (CH_2), 42.9 (CH_2), 36.7 (CH_2), 29.4 (CH_2). **HRMS**-ESI m/z: [M+Na], calculated for $C_9H_{10}NaO_3$, 189.0522; found 189.0520. **R_f**: 0.09 in 20% EtOAc/hexanes.

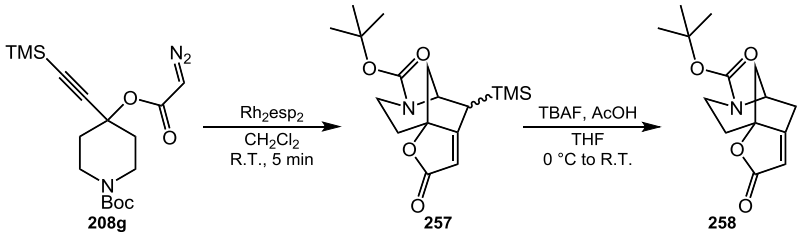
2,6-dioxatricyclo[3.3.3.0^{1,5}]undec-10-en-3-one (259) was synthesized according to the following procedure: **253** (19 mg, 0.08 mmol) was dissolved in anhydrous THF (0.80 ml) under an argon atmosphere, and the reaction vessel was cooled to 0 ˚C. TBAF (0.12 ml, 1.5 eq) was added dropwise slowly. The reaction was warmed to 45 ˚C for 30 minutes. After 30 minutes, TLC analysis showed no starting material. Deionized water was added, the mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 30% EtOAc in hexanes as an eluent. The product **259** was obtained as a colorless oil (8 mg, 63% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.87-5.83 (m, 1H), 5.79-5.75 (m, 1H), 3.99-3.93 (m, 1H), 3.87-3.81 (m, 1H), 2.90 (d, *J* = 18.9 Hz, 1H), 2.81-2.79 (m, 2H), 2.77 (d, *J* = 18.9 Hz, 1H), 2.40-2.33 (m, 1H), 2.18-2.11 (m, 1H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 176.0 (CH_0), 133.0 (CH_1), 131.0 (CH_1), 99.1 (CH_0), 98.5 (CH_0), 67.2 (CH_2), 44.2 (CH_2), 40.5 (CH_2), 40.1 (CH_2). **HRMS**-ESI m/z: [M+Na], calculated for $C_9H_{10}NaO_3$, 189.0522; found 189.0519. **R_f**: 0.13 in 20% EtOAc/hexanes. Product **259** can also be synthesized from compound **254** following this procedure: **254** (7 mg, 0.04 mmol) was dissolved in MeOH (0.4 ml) and K_2CO_3 (6 mg, 1.1 eq) was added in one portion. The

reaction mixture was allowed to stir at room temperature overnight. After purification (as described above), product **259** was obtained as a colorless oil (3 mg, 42% yield).



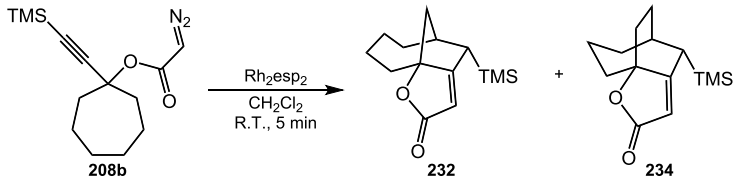
6-(Phenyl)-2,8-dioxatricyclo[5.3.1.0^{1,5}]undec-4-en-3-one (255) was synthesized from diazoacetate **208f** (40 mg, 0.15 mmol) following general procedure D. Only one diastereomer (**255**) was detected in in the crude ^{1}H NMR spectrum. The stereochemistry of the phenyl group was assigned using 1D nOe correlation experiments (see page SI216). Purification of the crude product by column chromatography was insufficient, leading to product decomposition. Thus, the yield was measured to be 62% by integration of an internal standard and the vinyl proton of **255** in the crude ^{1}H NMR spectrum. In order to obtain an analytically pure sample for structural elucidation, the crude product was dissolved in anhydrous THF (0.6 ml) under an argon atmosphere. 10% Pd/C (20 mg, 13 mol%) was added in one portion. The reaction vessel was evacuated and backfilled with hydrogen gas twice. After 1 h 30 min, TLC analysis showed no starting material. The mixture was filtered through a short plug of Celite® and washed with EtOAc. The reaction was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using a 20-30% gradient of EtOAc in hexanes as an eluent. The product **256** was obtained as a white solid (25 mg, 66% yield for two steps). Only one diastereomer was detected in the crude ^{1}H NMR spectrum. The stereochemistry of the *β*-hydrogen to the carbonyl group was assigned by 1D nOe correlation experiments. Spectral

data for **6-(Phenyl)-2,8-dioxatricyclo[5.3.1.0^{1,5}]undecan-3-one (256)**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38-7.33 (m, 4H), 7.30-7.24 (m, 1H), 4.87-4.83 (m, 1H), 3.81 (dd, *J* = 11.9, 6.4 Hz, 1H), 3.37-3.28 (m, 2H), 3.16 (dd, *J* = 17.9, 10.1 Hz, 1H), 2.85-2.77 (m, 1H), 2.56 (dd, *J* = 17.9, 10.1 Hz, 1H), 2.40-2.30 (m, 1H), 2.15-2.09 (m, 1H), 2.05-1.98 (m, 1H), 1.66 (dt, *J* = 11.9, 3.7 Hz, 1H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 176.2 (CH_0), 138.2 (CH_0), 128.7 (CH_1), 127.0 (CH_1), 126.9 (CH_1), 90.2 (CH_0), 78.4 (CH_1), 61.3 (CH_2), 54.6 (CH_1), 45.6 (CH_1), 43.7 (CH_2), 38.4 (CH_2), 36.7 (CH_2). **HRMS**-ESI m/z: [M+H], calculated for $C_{15}H_{17}O_3$, 245.1172; found 245.1173. **R_f**: 0.18 in 20% EtOAc/hexanes.



***tert*-Butyl-6-(trimethylsilyl)-3-oxo-2-oxa-8-azatricyclo[5.3.1.0^{1,5}]undec-4-ene-8-carboxylate (257)** was synthesized from diazoacetate **208g** (74 mg, 0.20 mmol) following general procedure D. Integration of both diastereomers in the crude ^{1}H NMR spectrum or ^{1}H NMR spectrum after purification was not feasible. In order to obtain an analytically pure sample for structural confirmation, the crude product was dissolved in anhydrous THF (2.00 ml) under an argon atmosphere, and the reaction vessel was cooled to 0 ˚C. AcOH (13 µl, 1.1 eq) followed by TBAF (0.22 ml, 1.1 eq) were added dropwise slowly. The reaction was allowed to warm to room temperature. After 10 minutes, TLC analysis showed no starting material. Deionized water was added, the mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product. The crude product

was purified by column chromatography on silica gel using 30% EtOAc in hexanes as an eluent. The product **258** was obtained as a white solid (35 mg, 65% yield for two steps). Spectral data for ***tert*-Butyl-3-oxo-2-oxa-8-azatricyclo[5.3.1.0^{1,5}]undec-4-ene-8-carboxylate (258)**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.81 (t, *J* = 1.8 Hz, 1H), 5.18-4.85 (bm, 1H), 4.28-3.99 (bm, 1H), 3.21-3.01 (bm, 1H), 2.92-2.81 (m, 1H), 2.66 (d, *J* = 19.2 Hz, 1H), 2.33 (td, *J* = 12.4, 7.3 Hz, 1H), 1.98 (dd, *J* = 11.0, 1.8 Hz, 1H), 1.77-1.67 (m, 1H), 1.62-1.52 (m, 1H), 1.46 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 177.2 (CH_0), 173.8 (CH_0), 113.6 (CH_1), 91.7 (CH_0), 80.7 (CH_1), ~55 (CH_1) 41.8 (CH_2), ~39 (CH_2), 34.4 (CH_2), 30.3 (CH_2), 29.8 (CH_0), 28.5 (CH_3). **HRMS**-ESI m/z: [M+Na], calculated for $C_{14}H_{19}NNaO_4$, 288.1206; found 288.1209. **R_f**: 0.24 in 30% EtOAc/hexanes.



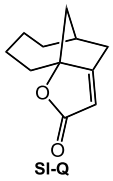
6-(Trimethylsilyl)-2-oxatricyclo[5.4.1.0^{1,5}]dodec-4-en-3-one (232-endo), 6-(Trimethylsilyl)-2-oxatricyclo[5.4.1.0^{1,5}]dodec-4-en-3-one (232-endo) and **6-(Trimethylsilyl)-2-oxatricyclo[5.3.2.0^{1,5}]dodec-4-en-3-one (234)** were synthesized from diazoacetate **208b** (84 mg, 0.30 mmol) following general procedure D. The crude product was purified by column chromatography on silica gel using a 5-15% gradient of EtOAc in hexanes as an eluent. The major diastereomer **232-endo** was obtained as a white solid (34 mg, 45% yield). The stereochemistry of the TMS-group was assigned by 1D nOe correlation experiments. The minor diastereomer **232-exo** was obtained as a white solid

(14 mg, 19% yield). A single diastereomer of product **234** was obtained as a white solid (6 mg, 8% yield).

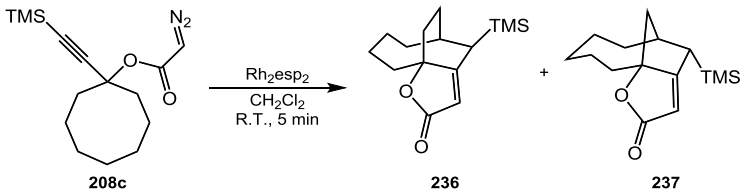
Spectral data for **232-endo**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.54 (d, *J* = 2.8 Hz, 1H), 2.70-2.63 (m, 1H), 2.24-2.14 (m, 1H), 2.09 (d, *J* = 12.4 Hz, 1H), 1.83-1.47 (m, 9H), 0.07 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 185.7 (CH_0), 174.9 (CH_0), 109.6 (CH_1), 95.4 (CH_0), 40.3 (CH_1), 38.7 (CH_2), 35.1 (CH_2), 34.2 (CH_2), 32.5 (CH_1), 24.5 (CH_2), 23.2 (CH_2), -2.9 (CH_3). **HRMS**-ESI m/z: [M+H], calculated for $C_{14}H_{23}O_2Si$, 251.1462; found 251.1460. **R_f**: 0.37 in 20% EtOAc/hexanes.

Spectral data for **232-exo**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.55 (d, *J* = 2.3 Hz, 1H), 2.35-2.18 (m, 4H), 1.93-1.86 (m, 1H), 1.78-1.61 (m, 5H), 1.58-1.47 (m, 2H), 0.13 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 179.5, 173.8, 108.8, 88.3, 39.3, 37.7, 36.2, 30.5, 29.1, 22.0, 21.0, -1.1. **HRMS**-ESI m/z: [M+Na], calculated for $C_{14}H_{22}NaO_2Si$, 273.1281; found 273.1282. **R_f**: 0.29 in 20% EtOAc/hexanes.

Spectral data for **234**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.51 (d, *J* = 2.3 Hz, 1H), 2.50-2.45 (m, 1H), 2.45-2.36 (m, 1H), 2.30-2.15 (m, 2H), 1.87-1.51 (m, 8H), 0.17 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 180.7 (CH_0), 173.9 (CH_0), 108.2 (CH_1), 87.9 (CH_0), 36.2 (CH_1), 35.6 (CH_2), 32.1 (CH_1), 31.6 (CH_2), 30.5 (CH_2), 24.6 (CH_2), 20.9 (CH_2), -0.8 (CH_3). **HRMS**-ESI m/z: [M+Na], calculated for $C_{14}H_{22}NaO_2Si$, 273.1281; found 273.1282. **R_f**: 0.24 in 20% EtOAc/hexanes.



In order to demonstrate that both products **232-endo** and **232-exo** are diastereomers, the TMS-group was cleaved for the ~1:1 mixture of **232-endo** and **232-exo** using TBAF (1.1 eq) in THF as a reaction solvent. Indeed, only one product was observed in the crude ^{1}H NMR spectrum after the reaction was completed (monitored by TLC analysis). The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. **2-Oxatricyclo[5.3.2.0^{1,5}]dodec-4-en-3-one (SI-Q)** was obtained as a white solid with a corresponding spectral data: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.65 (d, *J* = 1.8 Hz, 1H), 2.90-2.79 (m, 2H), 2.41-2.30 (m, 1H), 2.22-2.12 (m, 1H), 2.10 (d, *J* = 13.3 Hz, 1H), 1.79-1.46 (m, 8H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 182.7 (CH_0), 174.2 (CH_0), 112.4 (CH_1), 94.6 (CH_0), 37.5 (CH_2), 36.5 (CH_1), 36.2 (CH_2), 33.7 (CH_2), 31.2 (CH_2), 24.4 (CH_2), 23.1 (CH_2). **HRMS**-ESI m/z: [M+H], calculated for $C_{11}H_{15}O_2$, 179.1072; found 179.1074. **R_f**: 0.17 in 20% EtOAc/hexanes.

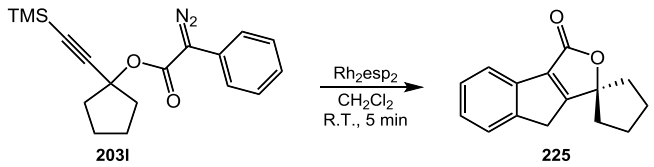


6-(Trimethylsilyl)-2-oxatricyclo[5.4.2.0^{1,5}]tridec-4-en-3-one (236) and **6-(Trimethylsilyl)-2-oxatricyclo[5.5.1.0^{1,5}]tridec-4-en-3-one (237)** were synthesized from diazoacetate **208c** (102 mg, 0.35 mmol) following general procedure D. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The major product **236** was obtained as a white solid (52 mg, 56% yield). The stereochemistry of the TMS-group in product **236** was assigned by 1D nOe correlation experiments (see page SI219). The minor product **237** was obtained as a white solid (11

mg, 11% yield). The stereochemistry of the TMS-group in product **237** was assigned by 1D nOe correlation experiments. A similar experiment starting with 88 mg (0.30 mmol) of **208c** gave 43 mg (54% yield) of **236** and 7mg (9% yield) of **237**.

Spectral data for **236**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.59 (d, *J* = 2.3 Hz, 1H), 2.75-2.66 (m, 1H), 2.19-1.95 (m, 4H), 1.92-1.69 (m, 6H), 1.65-1.47 (m, 2H), 1.46-1.35 (m, 1H), 0.09 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 184.8 (CH_0), 174.6 (CH_0), 111.6 (CH_1), 95.5 (CH_0), 41.3 (CH_2), 40.9 (CH_1), 37.2 (CH_2), 35.6 (CH_2), 29.4 (CH_1), 26.64 (CH_2), 26.56 (CH_2), 26.3 (CH_2), -2.6 (CH_3). **HRMS**-ESI m/z: [M+Na], calculated for $C_{15}H_{24}NaO_2Si$, 287.1438; found 287.1436. **R_f**: 0.43 in 20% EtOAc/hexanes.

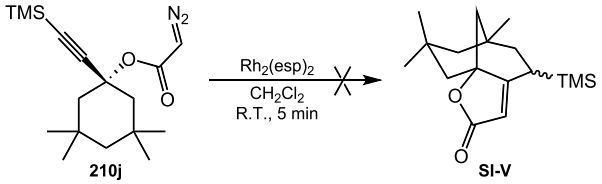
Spectral data for **237**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.46 (d, *J* = 1.8 Hz, 1H), 2.88-2.77 (m, 1H), 2.61-2.54 (m, 2H), 2.34-2.23 (m, 1H), 1.92-1.66 (m, 6H), 1.55-1.36 (m, 3H), 1.19-1.05 (m, 1H), 0.20 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 187.8 (CH_0), 175.2 (CH_0), 108.9 (CH_1), 94.7 (CH_0), 38.7 (CH_1), 37.6 (CH_1), 34.8 (CH_2), 34.6 (CH_2), 32.3 (CH_2), 31.2 (CH_2), 25.3 (CH_2), 24.0 (CH_2), 0.1 (CH_3). **HRMS**-ESI m/z: [M+Na], calculated for $C_{15}H_{24}NaO_2Si$, 287.1438; found 287.1439. **R_f**: 0.34 in 20% EtOAc/hexanes.



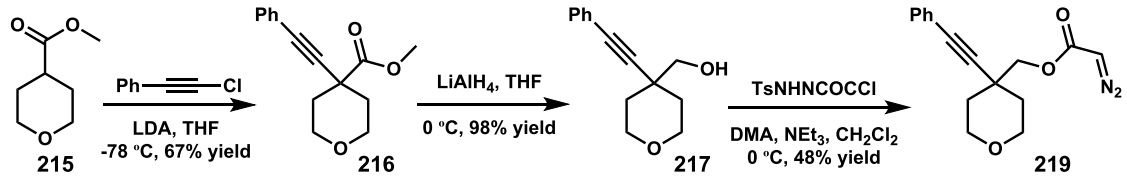
203l **225**

Spiro[cyclopentane-1,1'-indeno[2,1-c]furan]-3'(8'H)-one (225) was synthesized from diazoacetate **203l** (33 mg, 0.10 mmol) following general procedure D. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (19 mg, 85% yield).**^{1}H NMR** (400 MHz,

$CDCl_3$) δ 7.72-7.67 (m, 1H), 7.52-7.47 (m, 1H), 7.39-7.33 (m, 1H), 7.31-7.25 (m, 1H), 3.58 (s, 2H), 2.15-1.98 (m, 6H), 1.96-1.84 (m, 2H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 177.1 (CH_0), 166.8 (CH_0), 146.4 (CH_0), 137.0 (CH_0), 135.4 (CH_0), 127.5 (CH_1), 126.4 (CH_1), 125.1 (CH_1), 121.1 (CH_1), 95.2 (CH_0), 38.0 (CH_2), 33.8 (CH_2), 24.9 (CH_2). **HRMS**-ESI m/z: [M+Na], calculated for $C_{15}H_{14}NaO_2$, 249.0886; found 249.0886. **R_f**: 0.31 in 20% EtOAc/hexanes.



Only trace amounts of **6-(Trimethylsilyl)-8,10,10-trimethyl-2-oxatricyclo[6.3.1.0^{1,5}]undec-4-en-3-one (SI-V)** were detected in the crude ^{1}H NMR spectra using diazoacetate **210j** (65 mg, 0.20 mmol) as a starting material and following either general procedure D or general procedure E. In both cases, unreacted starting material **210j** was observed in the crude ^{1}H NMR spectra (see page SI227).



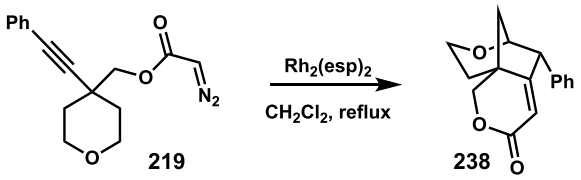
Methyl 4-(phenylethynyl)tetrahydro-2H-pyran-4-carboxylate (216) A flame-dried round-bottom flask was charged with *i*Pr_2NH (0.63 ml, 4.5 mmol) under an argon atmosphere. Anhydrous THF (4.0 ml) was added, and the flask was cooled to 0 ˚C. 2.5 M *n*BuLi (1.8 ml, 4.5 mmol) was added, and the reaction mixture was stirred for 30 minutes at 0 ˚C and then cooled to -78 ˚C in a dry ice/acetone bath. Ester **215** (0.4 ml, 3.0 mmol)

was then added dropwise followed by a dropwise addition of (chloroethynyl)benzene (0.65 g, 4.8 mmol) dissolved in 2.0 ml of THF. The reaction mixture was allowed to warm to room temperature slowly. After completion, saturated NH_4Cl solution was added. The reaction mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a white solid (0.49 g, 67% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47-7.41 (m, 2H), 7.33-7.28 (m, 3H), 3.89-3.83 (m, 4H), 3.80 (s, 3H), 2.15-2.05 (m, 2H), 1.99-1.92 (m, 2H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 172.8, 131.9, 128.5, 128.4, 122.8, 80.0, 85.4, 64.4, 53.1, 41.8, 34.7. **MS** (EI) m/z (M^+): calculated for $C_{11}H_{20}OSi$: 244; found: 244. **R$_f$**: 0.29 in 20% EtOAc/hexanes.

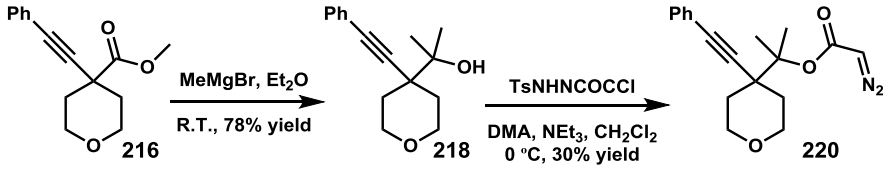
(4-(Phenylethynyl)tetrahydro-2H-pyran-4-yl)methanol (217) A flame-dried round-bottom flask was charged with ester **216** (51 mg, 0.2 mmol) under an argon atmosphere. Anhydrous THF (2.0 ml) was added, and the flask was cooled to 0 ˚C. $LiAlH_4$ (23 mg, 0.6 mmol) was added in one portion, and the reaction mixture was stirred for 30 minutes at 0 ˚C. After completion, 1N HCl solution was added. The reaction mixture was extracted with EtOAc (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered through short silica gel plug and concentrated to yield pure product as a white solid (45 mg, 98% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45-7.39 (m, 2H), 7.33-7.28 (m, 3H), 3.93 (dd, *J* = 11.5 Hz, *J* = 2.9 Hz, 2H), 3.82 (td, *J* = 12.0 Hz, *J* = 1.7 Hz, 2H), 3.56 (d, *J* = 6.3 Hz, 2H), 1.88 (t, *J* = 6.9 Hz, 1H), 1.79-1.73 (m, 2H), 1.68-

1.60 (m, 2H). **^{13}C NMR** (125.75 MHz, $CDCl_3$) δ 131.9, 128.5, 128.4, 123.0, 91.0, 85.6, 71.4, 65.0, 38.7, 34.3. **R_f**: 0.11 in 20% EtOAc/hexanes.

(4-(Phenylethynyl)tetrahydro-2H-pyran-4-yl)methyl 2-diazoacetate (219) A flame-dried round-bottom flask was charged with alcohol **217** (0.20 g, 0.93 mmol) under an argon atmosphere. Anhydrous CH_2Cl_2 (0.17 M, 5.5 ml) was added, and the flask was cooled to 0 ˚C. Glyoxylic acid chloride *p*-toluenesulfonylhydrazone (0.49 g, 1.8 mmol) was added in one portion followed by *N*,*N*-dimethyl aniline (0.21 ml, 1.7 mmol). The reaction mixture was stirred for 15 minutes before adding triethylamine (0.65 ml, 4.6 mmol) and was stirred for 10 more minutes at 0 ˚C. The reaction was concentrated under reduced pressure. A concentrated citric acid solution and 20% EtOAc/hexanes mixture were added to the residue. The layers were separated, and the aqueous layer was extracted two times with the 20% EtOAc/hexanes mixture. The combined organic phases were washed with concentrated citric acid solution and brine, dried over $MgSO_4$, filtered through a short silica gel plug, and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a yellow oil (0.13 g, 48% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44-7.37 (m, 2H), 7.33-7.27 (m, 3H), 4.80 (s, 1H), 4.19 (s, 2H), 3.96-3.79 (m, 4H), 1.78-1.64 (m, 4H). **^{13}C NMR** (100.52 MHz, CDCl3) δ 166.7, 131.8, 128.4, 128.3, 123.1, 90.1, 85.0, 71.0, 64.6, 46.4, 36.2, 34.1. **R_f**: 0.18 in 20% EtOAc/hexanes.



7-Phenyl-3,9-dioxatricyclo[6.3.1.0^{1,6}]dodec-5-en-4-one (238) A flame-dried round-bottom flask was charged with diazoacetate **219** (43 mg, 0.15 mmol) under an argon atmosphere. Anhydrous CH_2Cl_2 (0.005 M, 31.0 ml) was added. The reaction mixture was vigorously stirred at room temperature while adding $Rh_2(esp)_2$ (0.5 mol%, 0.6 mg) in one portion. After 5 minutes, the TLC analysis showed no starting material. The yield of product **238** was measured to be 23% by integration of an internal standard and the vinyl proton of **238** in the crude ^{1}H NMR spectrum, the yield of dimers was measured to be 16%.

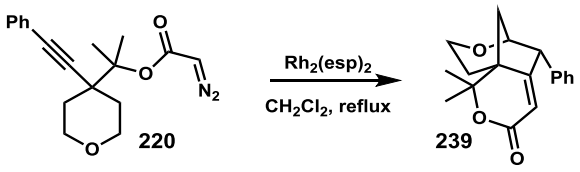


2-(4-(Phenylethynyl)tetrahydro-2H-pyran-4-yl)propan-2-ol (218) A flame-dried round-bottom flask was charged with 3.0 M MeMgBr solution (1.1 ml, 3.3 mmol) under an argon atmosphere. Anhydrous Et_2O (1.8 ml) was added. Ester **216** (0.25 g, 1.0 mmol) dissolved in 1.0 ml of dry THF was added dropwise over 30 min at room temperature, after addition reaction mixture was stirred for one more hour at room temperature. After completion, the reaction mixture was cooled to 0 ˚C and 1N HCl solution was added. The reaction mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using

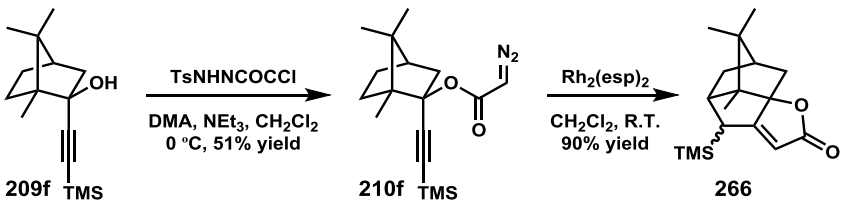
30% EtOAc in hexanes as an eluent. The product was obtained as a white solid (0.20 g, 78% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46-7.39 (m, 2H), 7.34-7.27 (m, 3H), 3.96 (dd, *J* = 11.5 Hz, *J* = 4.6 Hz, 2H), 3.88-3.80 (m, 2H), 1.89-1.80 (m, 2H), 1.81 (s, 1H), 1.70-1.64 (m, 2H), 1.35 (s, 6H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 131.7 (CH_1), 128.5 (CH_1), 128.3 (CH_1), 123.2 (CH_0), 91.6 (CH_0), 86.8 (CH_0), 74.1 (CH_0), 65.5 (CH_2), 45.2 (CH_0), 31.8 (CH_2), 25.1 (CH_3). **MS** (EI) m/z (M^+-Me): calculated for $C_{11}H_{20}OSi$: 244; found: 229. **R_f**: 0.06 in 20% EtOAc/hexanes.

2-(4-(Phenylethynyl)tetrahydro-2H-pyran-4-yl)propan-2-yl 2-diazoacetate (220) A flame-dried round-bottom flask was charged with propargyl alcohol **218** (0.15 g, 0.61 mmol) under an argon atmosphere. Anhydrous CH_2Cl_2 (0.17 M, 3.6 ml) was added, and the flask was cooled to 0 ˚C. Glyoxylic acid chloride *p*-toluenesulfonylhydrazone (0.32 g, 1.22 mmol) was added in one portion followed by *N*,*N*-dimethyl aniline (0.14 ml, 1.10 mmol). The reaction mixture was stirred for 15 minutes before adding triethylamine (0.43 ml, 3.05 mmol) and was stirred for 30 more minutes at 0 ˚C. The reaction was concentrated under reduced pressure. A concentrated citric acid solution and 20% EtOAc/hexanes mixture were added to the residue. The layers were separated, and the aqueous layer was extracted two times with the 20% EtOAc/hexanes mixture. The combined organic phases were washed with concentrated citric acid solution and brine, dried over $MgSO_4$, filtered through a short silica gel plug, and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a yellow oil (57 mg, 30% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44-7.38 (m, 2H), 7.34-7.28 (m, 3H), 4.68 (s, 1H), 3.99-3.90 (m, 2H), 3.90-3.79

(m, 2H), 1.99-1.87 (m, 2H), 1.74 (s, 6H), 1.69-1.61 (m, 2H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ ~166, 131.7, 128.5, 128.3, 123.3, 90.8, 86.4, 85.7, 65.3, 47.1, 45.2, 31.2, 21.8. **R_f**: 0.28 in 20% EtOAc/hexanes.



2,2-Dimethyl-7-phenyl-3,9-dioxatricyclo[6.3.1.0^{1,6}]dodec-5-en-4-one (239) A flame-dried round-bottom flask was charged with diazoacetate **220** (32 mg, 0.10 mmol) under an argon atmosphere. Anhydrous CH_2Cl_2 (0.005 M, 20.5 ml) was added. The reaction mixture was vigorously stirred at room temperature while adding $Rh_2(esp)_2$ (0.5 mol%, 0.4 mg) in one portion. After 5 minutes, the TLC analysis showed no starting material. The yield of product **239** was measured to be 17% by integration of an internal standard and the vinyl proton of **239** in the crude ^{1}H NMR spectrum, the yield of dimers was measured to be 4%.



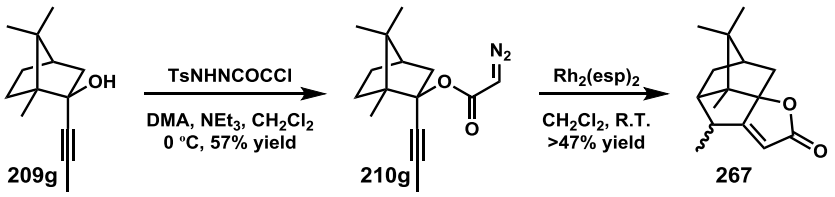
(1S,2R,4R)-1,7,7-Trimethyl-2-((trimethylsilyl)ethynyl)bicyclo[2.2.1]heptan-2-yl 2-diazoacetate (210f) A flame-dried round-bottom flask was charged with propargyl alcohol **209f** (0.5g, 2.0 mmol) under an argon atmosphere. Anhydrous CH_2Cl_2 (0.17 M, 12.0 ml) was added, and the flask was cooled to 0 ˚C. Glyoxylic acid chloride *p*-toluenesulfonylhydrazone (1.04g, 4.0 mmol) was added in one portion followed by *N*,*N*-

dimethyl aniline (0.46 ml, 3.6 mmol). The reaction mixture was stirred for 15 minutes before adding triethylamine (1.4 ml, 10.0 mmol) and was stirred for 10 more minutes at 0 ˚C. The reaction was concentrated under reduced pressure. A concentrated citric acid solution and 10% EtOAc/hexanes mixture were added to the residue. The layers were separated, and the aqueous layer was extracted two times with the 10% EtOAc/hexanes mixture. The combined organic phases were washed with concentrated citric acid solution and brine, dried over $MgSO_4$, filtered through a short silica gel plug, and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a yellow oil (0.32 g, 51% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.64 (bs, 1H), 2.53-2.45 (m, 1H), 2.10-2.01 (m, 2H), 1.77-1.72 (m, 1H), 1.72-1.61 (m, 1H), 1.49-1.39 (m, 1H), 1.21-1.12 (m, 1H), 0.94 (s, 3H), 0.93 (s, 3H), 0.89 (s, 3H), 0.15 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 164.0 (CH_0), 105.3 (CH_0), 89.2 (CH_0), 84.4 (CH_0), 54.8 (CH_1), 48.4 (CH_0), 47.0 (CH_2), 46.9 (CH_0), 45.5 (CH_1), 32.1 (CH_2), 26.6 (CH_2), 21.4 (CH_3), 20.8 (CH_3), 10.9 (CH_3), 0.1 (CH_3). **R_f**: 0.47 in 20% EtOAc/hexanes.

10,10,11-trimethyl-6-(trimethylsilyl)-2-oxatetracyclo[7.2.1.0^{1,5}.0^{7,11}]dodec-4-en-3-one (266). A flame-dried round-bottom flask was charged with diazoacetate **210f** (50 mg, 0.16 mmol) under an argon atmosphere. Anhydrous CH_2Cl_2 (0.005 M, 31.0 ml) was added. The reaction mixture was vigorously stirred at room temperature while adding $Rh_2(esp)_2$ (1.0 mol%, 1.2 mg) in one portion. After 5 minutes, the TLC analysis showed no starting material. The reaction was concentrated under reduced pressure, and the crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent.

The product was obtained as a white solid (41 mg, 90% yield). The diastereomeric ratio was measured to be 2:1 in the ^{1}H NMR spectrum after isolation. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.54 (d, *J* = 2.3 Hz, 1H, minor), 5.50 (d, J = 1.8 Hz, 1H, major), 2.47-2.41 (m, 1H, minor), 2.39-2.29 (m, major/minor), 2.21-2.15 (m, 1H, minor), 2.10-2.00 (m, 1H, major), 1.91 (t, J = 3.7 Hz, 1H, minor), 1.87 (t, J = 3.7 Hz, 1H, major), 1.87-1.83 (m, 1H, minor), 1.70 (d, J = 13.7 Hz, 1H, minor), 1.64 (d, J = 13.7 Hz, 1H, major), 1.26-1.19 (m, 1H, major), 1.05 (s, 3H, minor), 1.04 (s, 3H, major), 1.03-0.97 (m, 1H, minor), 0.89 (s, 3H, major), 0.88 (s, 3H, minor), 0.69 (s, 3H, major), 0.64 (s, 3H, minor), 0.16 (s, 9H, major), 0.11 (s, 9H, minor). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 185.7, 183.5, 176.1, 175.7, 108.2, 108.1, 99.3, 98.9, 61.1, 56.8, 50.0, 48.7, 48.69, 48.2, 45.5, 45.0, 42.1, 41.3, 40.0, 35.6, 33.9, 33.4, 20.5, 20.4, 19.8, 19.6, 8.2, 6.9, -0.5, -1.7. **HRMS**-CI m/z: [M+H], calculated for $C_{17}H_{27}O_2Si$, 291.1780; found 291.1780. **R_f**: 0.41 in 20% EtOAc/hexanes. The TMS-group was cleaved for this mixture using TBAF (1.1 eq) in THF as a reaction solvent. Only one product was observed in the crude ^{1}H NMR spectrum after the reaction was completed (monitored by TLC analysis). The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. **10,10,11-trimethyl-2-oxatetracyclo[7.2.1.0^{1},^{5}.0^{7},^{11}]dodec-4-en-3-one (263)** was obtained as a white solid with the spectral data: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.68 (t, *J* = 1.8 Hz, 1H), 2.75-2.66 (m, 1H), 2.43 (dt, *J* = 13.3, *J* = 3.7 Hz, 1H), 2.41-2.34 (m, 1H), 2.32-2.64 (m, 2H), 1.90-1.86 (m, 1H), 1.67 (d, *J* = 13.7 Hz, 1H), 1.05 (s, 3H), 1.02-0.94 (m, 1H), 0.89 (s, 3H), 0.67 (s, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 180.9 (CH_0), 175.6 (CH_0), 111.6 (CH_1), 98.8 (CH_0), 58.0 (CH_0), 49.6 (CH_0), 45.4 (CH_3), 45.2 (CH_3), 40.8 (CH_2), 39.4 (CH_2), 30.8 (CH_2),

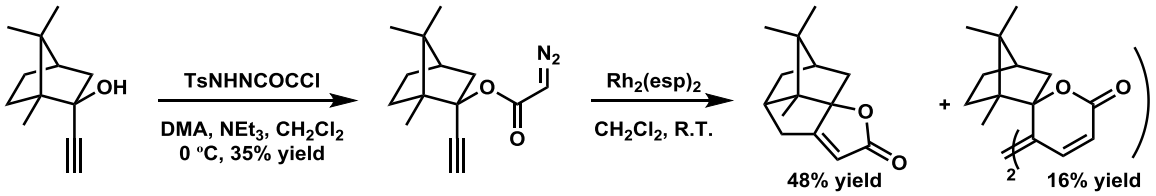
20.5 (CH_3), 19.6 (CH_3), 7.2 (CH_3). **HRMS**-CI m/z: [M+H], calculated for $C_{14}H_{19}O_2$, 219.1385; found 219.1384. **R_f**: 0.26 in 20% EtOAc/hexanes.



(1S,2S,4R)-1,7,7-Trimethyl-2-(prop-1-ynyl)bicyclo[2.2.1]heptan-2-yl 2-diazoacetate (210g) A flame-dried round-bottom flask was charged with propargyl alcohol **209g** (0.30 g, 1.6 mmol) under an argon atmosphere. Anhydrous CH_2Cl_2 (0.17 M, 9.2 ml) was added, and the flask was cooled to 0 ˚C. Glyoxylic acid chloride *p*-toluenesulfonylhydrazone (0.81 g, 3.2 mmol) was added in one portion followed by *N*,*N*-dimethyl aniline (0.36 ml, 2.9 mmol). The reaction mixture was stirred for 15 minutes before adding triethylamine (1.1 ml, 8.0 mmol) and was stirred for 10 more minutes at 0 ˚C. The reaction was concentrated under reduced pressure. A concentrated citric acid solution and 10% EtOAc/hexanes mixture were added to the residue. The layers were separated, and the aqueous layer was extracted two times with the 10% EtOAc/hexanes mixture. The combined organic phases were washed with concentrated citric acid solution and brine, dried over $MgSO_4$, filtered through a short silica gel plug, and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 5% Et_2O in pentane as an eluent, followed by another column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a yellow oil (0.23 g, 57% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.64 (s, 1H), 2.55-2.47 (m, 1H), 2.07-1.96 (m, 2H), 1.86 (s, 3H), 1.77-1.71 (m, 1H), 1.71-1.62 (m, 1H), 1.47-1.38 (m, 1H), 1.20-1.11 (m, 1H), 0.94 (s,

3H), 0.93 (s, 3H), 0.89 (s, 3H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ ~165, 84.9, 80.8, 79.1, 54.8, 48.3, 47.0, 45.4, 32.1, 26.6, 21.5, 20.8, 10.9, 3.9. **R_f**: 0.34 in 20% EtOAc/hexanes.

6,10,10,11-tetramethyl-2-oxatetracyclo[7.2.1.0^{1},^{5}.0^{7},^{11}]dodec-4-en-3-one (267). A flame-dried round-bottom flask was charged with diazoacetate **210g** (52 mg, 0.20 mmol) under an argon atmosphere. Anhydrous CH_2Cl_2 (0.005 M, 40.0 ml) was added. The reaction mixture was vigorously stirred at room temperature while adding $Rh_2(esp)_2$ catalyst (0.5 mol%, 0.8 mg) in one portion. After 5 minutes, the TLC analysis showed no starting material. The reaction was concentrated under reduced pressure, and the crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a white solid (>22 mg, >47% yield). The diastereomeric ratio was measured to be 1.5:1 in the ^{1}H NMR spectrum after isolation. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.67 (d, *J* = 1.4 Hz, 1H, major), 5.64 (d, *J* = 1.8 Hz, 1H, minor) 2.98-2.87 (m, 1H, major), 2.69-2.59 (m, 1H, minor), 2.46-2.23 (m, major/minor), 1.93-1.74 (m, major/minor), 1.64 (dd, *J* = 27.5 Hz, *J* = 13.7 Hz, 2H, major), 1.38-1.32 (m, 1H, major), 1.24 (d, *J* = 7.3 Hz, 3H, minor), 1.22 (d, *J* = 8.2 Hz, 3H, major), 1.08-1.02 (m, 1H, minor), 1.03 (s, 3H, major), 1.02 (s, 3H, minor), 0.91 (s, 3H, major), 0.86 (s, 3H, minor), 0.72 (s, 3H, minor), 0.68 (s, 3H, major). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 186.3, 184.9, 175.7, 175.5, 111.3, 110.4, 98.7, 98.6, 58.5, 57.9, 53.9, 50.1, 49.8, 49.4, 45.4, 44.5, 40.9, 40.4, 39.8, 39.4, 32.3, 28.3, 20.8, 20.6, 20.4, 19.5, 15.5, 8.7, 7.2. **HRMS**-CI m/z: [M+H], calculated for $C_{15}H_{21}O_2$, 233.1542; found 233.1542. **R_f**: 0.34 in 20% EtOAc/hexanes.



209h 210h 263 264

(1S,2S,4R)-2-Ethynyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 2-diazoacetate (210h)

A flame-dried round-bottom flask was charged with propargyl alcohol **209h** (0.50 g, 2.8 mmol) under an argon atmosphere. Anhydrous CH_2Cl_2 (0.17 M, 16.5 ml) was added, and the flask was cooled to 0 ˚C. Glyoxylic acid chloride *p*-toluenesulfonylhydrazone (1.46 g, 5.6 mmol) was added in one portion followed by *N*,*N*-dimethyl aniline (0.64 ml, 5.0 mmol). The reaction mixture was stirred for 15 minutes before adding triethylamine (1.9 ml, 14.0 mmol) and was stirred for 10 more minutes at 0 ˚C. The reaction was concentrated under reduced pressure. A concentrated citric acid solution and 10% EtOAc/hexanes mixture were added to the residue. The layers were separated, and the aqueous layer was extracted two times with the 10% EtOAc/hexanes mixture. The combined organic phases were washed with concentrated citric acid solution and brine, dried over $MgSO_4$, filtered through a short silica gel plug, and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a yellow oil (0.24 g, 35% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.68 (s, 1H), 2.56-2.48 (m, 1H), 2.53 (s, 1H), 2.11 (d, *J* = 14.6 Hz, 1H), 2.10-2.01 (m, 1H), 1.80-1.75 (m, 1H), 1.75-1.64 (m, 1H), 1.53-1.42 (m, 1H), 1.23-1.13 (m, 1H), 0.96 (s, 3H), 0.95 (s, 3H), 0.90 (s, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 84.0, 83.6, 73.1, 54.6, 48.4, 47.0, 45.4, 32.0, 26.5, 21.4, 20.7, 10.8.

Compounds 263/264 A flame-dried round-bottom flask was charged with diazoacetate **210h** (49 mg, 0.20 mmol) under an argon atmosphere. Anhydrous CH_2Cl_2 (0.005 M, 40.0 ml) was added. The reaction mixture was vigorously stirred at room temperature while adding $Rh_2(esp)_2$ (0.5 mol%, 0.8 mg) in one portion. After 5 minutes, the TLC analysis showed no starting material. The reaction was concentrated under reduced pressure, and the crude mixture was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. Homodimerization products (cis/trans) **265** were isolated together (7.6 mg, 17% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.72 (s, 1H, minor), 6.13 (s, 1H, major), 2.66 (dt, *J* = 14.3, *J* = 4.0 Hz, 1H, major), 2.51 (s, 1H, minor), 2.47 (s, 1H, major), 2.48-2.41 (m, 1H, minor), 2.14 (d, *J* = 14.3 Hz, 1H, minor), 2.12 (d, *J* = 14.9 Hz, 1H, major), 2.11-2.02 (m), 1.81-1.64 (m), 1.55-1.44 (m), 1.26-1.14 (m), 1.03 (s, 3H, minor), 0.98 (s, 3H, major), 0.95 (s, 3H, minor), 0.95 (s, 3H, major), 0.92 (s, 3H, minor), 0.89 (s, 3H, major). Products **263** and **264** were isolated together (28 mg). Integration of signals in ^{1}H NMR allowed the calculation of the corresponding yields, for **263**-48% and **264**-16% (two vinyl signals integrated). The ^{1}H NMR spectrum of the major product in the crude mixture matched the desilylated product **263** spectrum: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.68 (t, *J* = 1.8 Hz, 1H), 2.75-2.66 (m, 1H), 2.43 (dt, *J* = 13.3, *J* = 3.7 Hz, 1H), 2.41-2.34 (m, 1H), 2.32-2.64 (m, 2H), 1.90-1.86 (m, 1H), 1.67 (d, *J* = 13.7 Hz, 1H), 1.05 (s, 3H), 1.02-0.94 (m, 1H), 0.89 (s, 3H), 0.67 (s, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 180.9 (CH_0), 175.6 (CH_0), 111.6 (CH_1), 98.8 (CH_0), 58.0 (CH_0), 49.6 (CH_0), 45.4 (CH_3), 45.2 (CH_3), 40.8 (CH_2), 39.4 (CH_2), 30.8 (CH_2), 20.5 (CH_3), 19.6 (CH_3), 7.2 (CH_3). **HRMS**-CI m/z: [M+H], calculated for $C_{14}H_{19}O_2$, 219.1385; found 219.1384. **R_f**: 0.26 in 20% EtOAc/hexanes.

The spectral data of compounds **203-267** have been previously reported[11].

2.5. References and Notes

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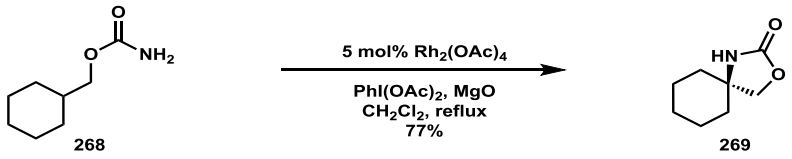
3. SYNTHESIS OF SUBSTITUTED VINYL NITRILES AND BRIDGED POLYCYCLIC RING SYSTEMS VIA ALKYNE/NITRENE CASCADES

3.1. Background

3.1.1. Nitrene Precursors

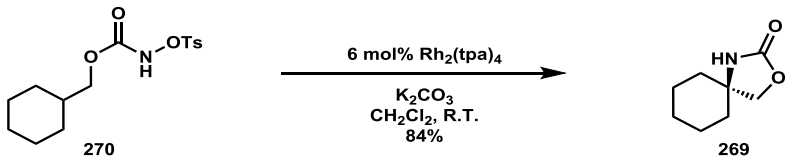
Nitrenes are isoelectronic to carbenes and display similar reactivity: rearrangements (Wolff versus Lossen rearrangement); insertions into to C-H or C-heteroatom bonds, and cycloadditions to C=C, C≡C bonds. Metal nitrenes can be generated from azides, *N*-haloamines, or iminoiodanes. Iminoiodanes are formed by ligand exchange between an iodine(III) oxidant and a carbamate or sulfamate. As an oxidant, iodosylbenzene (PhI=O) or $PhI(OAc)_2$ can be used. The latter one requires the addition of base, MgO, to scavenge the in situ released acetic acid[1]. The Du Bois oxidation method (represented in Figure 15) has been widely adopted for the generation of metal nitrenes for C-H bond aminations[2].

Figure 15. Oxidative cyclization of carbamates to oxazolidinones.



N-tosyloxycarbamate can be used as a metal nitrene precursor (Figure 16)[3]. Iodine(III) oxidant is not needed. Instead, base (K_2CO_3) facilitates the formation of metal nitrene in the presence of a Rh(II) catalyst. Potassium tosylate is produced as a byproduct and is easily removed by the filtration of the reaction mixture through Celite®.

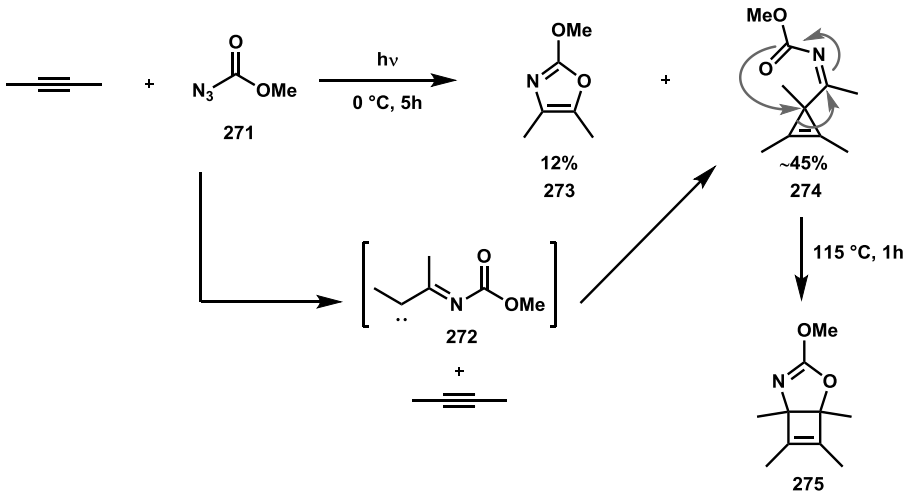
Figure 16. Cyclization of *N*-tosyloxycarbamates to oxazolidinones.



3.1.2. Reactivity of Carbamate-Derived Nitrenes with Alkynes

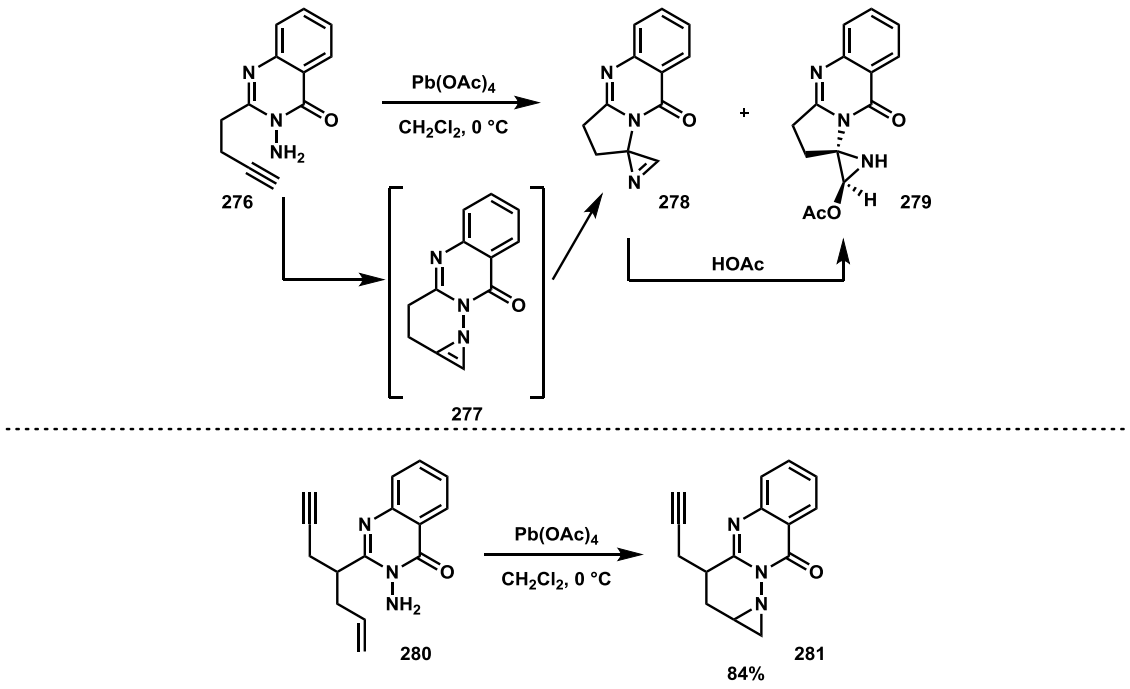
Cyclopropanation of alkynes with metal carbenes is a well-established transformation[4]. However, there are very few examples in the literature on the addition of nitrenes to alkynes. One of the first studies was reported by Meinwald and Aue on the photochemical addition of methyl azidoformate to 2-butyne (Figure 17)[5]. Azirine formation was not detected, instead the isomeric product, oxazole **273**, was isolated, along with large amounts of cyclopropene **274**. Two molecules of alkyne and one molecule of nitrene are incorporated in **274**. The authors proposed the initial formation of imine carbene **272**, followed by the cyclopropanation of another 2-butyne molecule. Attempts to purify the product using simple distillation led to the formation of new rearranged product **275**.

Figure 17. Intermolecular reaction of nitrene with alkyne.



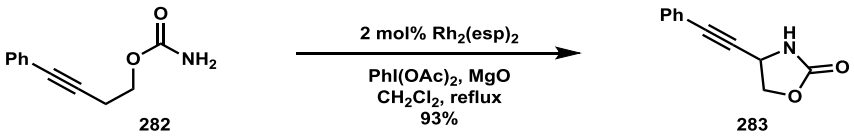
The intramolecular reaction of nitrenes with alkynes was studied by Atkinson and Grimshire[6]. The oxidation of aminoquinazolone **276** gave the azirine product **277**, which rearranged rapidly to azirine **278** (Figure 18). Its structure was confirmed by X-ray analysis. During the prolonged reaction, the azirine **278** further reacts with acetic acid, the byproduct of the oxidation with $Pb(OAc)_4$, generating aziridine **279**. In comparison, oxidation of aminoquinazolone **280** only formed aziridine **281**, and no addition to alkyne was observed.

Figure 18. Azirine formation.



Intramolecular cyclization was not observed when reacting carbamate-derived nitrenes and alkynes in the work by Schomaker et al. Instead, a very selective propargylic C-H bond amination was accomplished[7], which is presented in Figure 19.

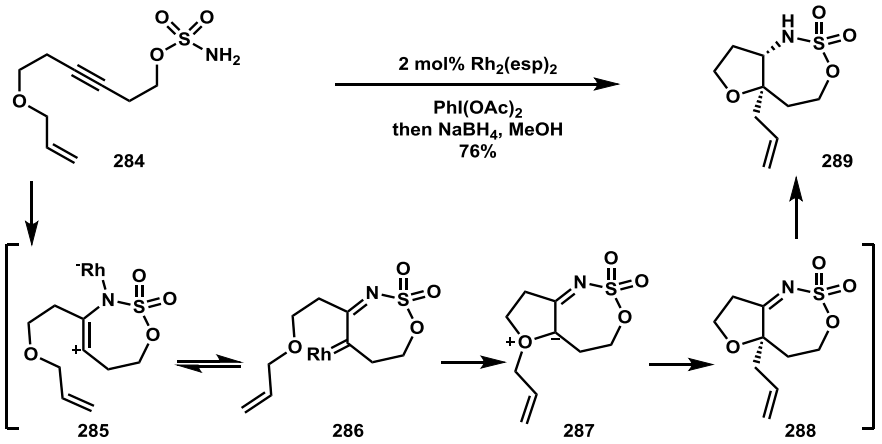
Figure 19. Intramolecular propargylic C-H bond amination.



Pioneering work on reactivity of sulfamate-derived nitrenes and alkynes has been presented by Blakey et al.[8]. A rhodium nitrene cyclizes with the tethered alkyne, and a

seven membered carbenoid **286** is formed. The metal carbene **286** can react differently: by ylide formation with subsequent rearrangement (as presented in Figure 20); cyclopropanation of the alkene; Friedel-Crafts reaction with a substituted benzene. Interestingly, propargylic C-H bonds were not aminated. This observation highlights the importance of the functional group on nitrene's reactivity.

Figure 20. Sulfamate-derived nitrene/alkyne cascade reaction.



3.2. Intramolecular Alkyne/Carbamate-Derived Nitrene Cascades

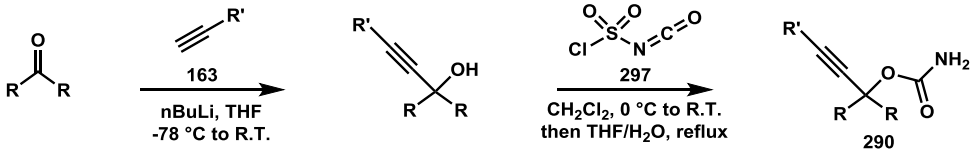
3.2.1. Importance

The reactivity of nitrenes with alkynes is not well explored. The reactivity of alkyne and carbamate-derived nitrenes in intramolecular reactions is not described in the literature. Influenced by our own report on an alkyne/metal carbene cascade reaction (Chapter 2), we proposed to test the cascade with the nitrene derived from propargyl carbamate **290a** in Scheme 35.

3.2.2. Synthesis of Starting Materials

The propargylic carbamates are formed by reacting propargyl alcohols with chlorosulfonyl isocyanate **297**[9]. The polar nature of carbamate allows using recrystallization as a purification method. The column chromatography is not required for a two-step synthesis of carbamates starting with commercially available ketones.

Table 11. Synthesis of carbamates.

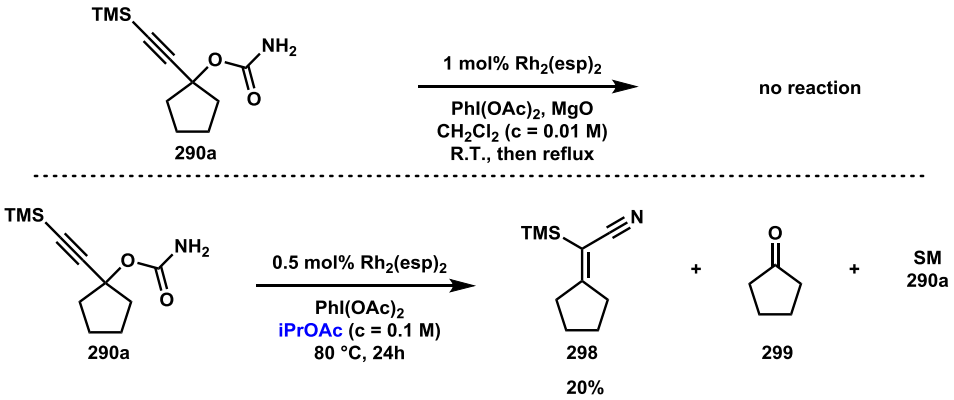


Entry	Product	Yield	Product 290a-f	Yield	Entry	Product	Yield	Product 290g-i	Yield
1	206a			75%	8	294	98%		mixture
2					9	295			56%
3	291 R = H		R = H	97%					
4	207f R = Ph		R = Ph	68%					
5	207e R = TMS		R = TMS	89%					
6	292 R = TIPS	98%	R = TIPS	70%					
7	293 R = TBS	98%	R = TBS	80%					

3.2.3. Reaction Optimization

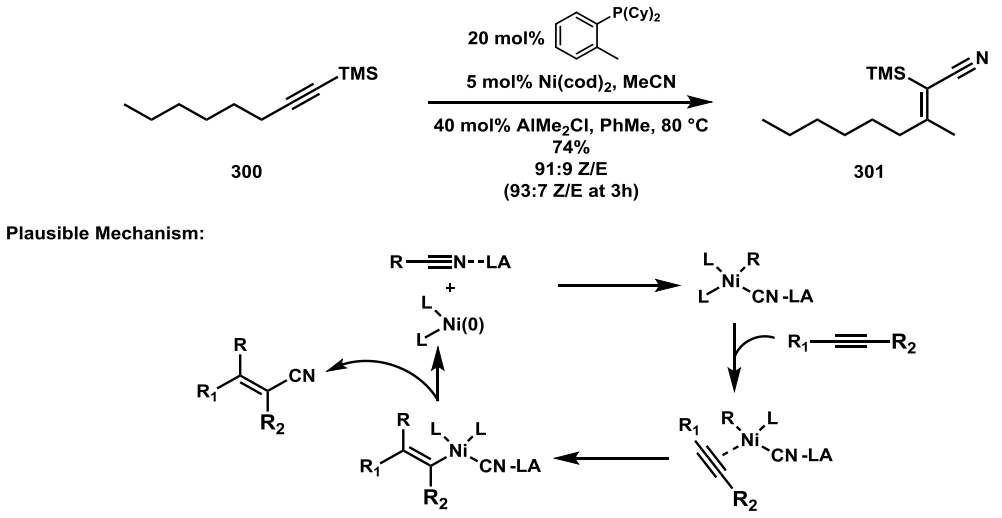
The oxidation of propargyl carbamate **290a** was tested. Initially, the widely used Du Bois reaction conditions were applied (Scheme 35). After heating the reaction mixture in CH_2Cl_2 for 21 hours, only unreacted starting material was observed in the ^1H NMR spectrum of the crude material. CH_2Cl_2 was changed to the polar solvent, iPrOAc. After refluxing the reaction mixture for 21 hours, a nonpolar product was formed. The rest of the material consisted of unreacted starting material **290a** and cyclopentanone **299**. ^1H and ^{13}C NMR spectra of the new product were too simple to conclusively assign the structure. As an additional analysis method, IR spectroscopy was used. The characteristic signal of the nitrile functional group was present in the IR spectrum. This information allowed us to assign the structure to be TMS-vinyl nitrile **298**. A plausible mechanism of the formation of product **298** will be discussed later in this chapter (Scheme 36). The solvents PhMe and EtOAc did not improve the yield of nitrile **298**.

Scheme 35. Initial reaction screening.



Very few examples are described in the literature on the formation of silyl vinyl nitriles. In a report by Hiyama and co-workers, a nickel-catalyzed carbocyanation of alkynes was performed to access highly substituted vinyl nitriles[10]. The transformation is presented in Figure 21. Lewis acid accelerates the oxidative addition of nickel(0) into C-CN bond. Afterwards, migratory insertion followed by reductive elimination releases the cyano product and active catalyst. The regioselectivity observed in the product arises from the coordination of the alkyne with the metal center, in which the steric repulsion between large R_2 and R groups is avoided. Under the given reaction conditions the final product tend to isomerize.

Figure 21. Nickel-catalyzed carbocyanation of alkynes.

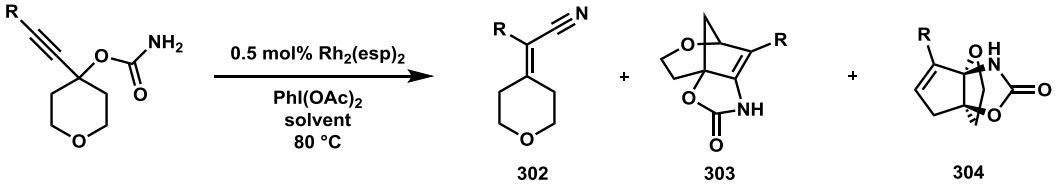


We find the formation of the TMS-vinyl nitrile **298** (from Scheme 35) mechanistically very interesting. We decided to test the oxidation on a different substrate – tetrahydropyran **290d** (entry 1, Table 12). We anticipated that a product more valuable

could be generated. The C-H bonds α to heteroatoms are highly active for C-H bond insertion. Unfortunately, the bridged bicycle formation was not observed when the TMS-alkynyl carbamate **290d** was oxidized. TMS-vinyl nitrile **302a** was isolated in 25% yield; the rest of the material consisted of starting material (**290d**) and tetrahydro-pyran-4-one **311** (presented in Scheme 36). We decided to test the reactivity of different substituted alkynyl carbamates on the formation of substituted vinyl nitriles. We subjected TIPS-propargyl carbamate **290e** to oxidizing conditions; iPrOAc was used as a reaction solvent. After heating the reaction mixture for 21 hours, formation of two new products was observed in addition to the vinyl nitrile **302b**, unreacted starting material, and tetrahydro-pyran-4-one **311**. The structures were assigned to be [3.2.1]bicycle **303** and propellane **304**. The switch to the larger silyl substituent on the alkyne changed the pathway dramatically (6-endo-dig versus 5-exo-dig cyclization).

The initial reaction solvent, CH_2Cl_2, was tested once more (entry 3 in Table 12). TIPS-alkynyl carbamate **290e** was refluxed vigorously in CH_2Cl_2. After 21 hours the products **302b** and **304** were observed, albeit in a lower combined yield. The reaction in dichloroethane did not work significantly better than in CH_2Cl_2 (compere entries 3 and 4). Importantly, increased solvent concentration led to the higher isolated yield of **304** (entry 5). Interestingly, the reaction in hexanes worked as well as in dichloroethane at high 0.5 M concentration (entry 6).

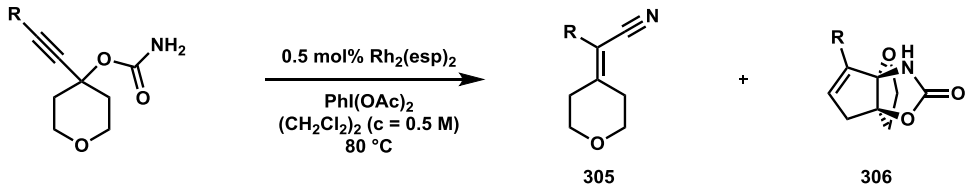
Table 12. Reactivity of tetrahydropyran carbamate.



Entry		R	Solvent	Conc.		Yield	Yield	Yield
1	290d	TMS	iPrOAc	0.1M	302a	25%	-	-
2		TIPS	iPrOAc	0.1 M		16%	12%	27%
3		TIPS	CH_2Cl_2	0.1 M		9%	-	18%
4	290e	TIPS	$(CH_2Cl)_2$	0.1 M	302b	10%	-	21%
5		TIPS	$(CH_2Cl)_2$	0.5 M		17%	-	45%
6		TIPS	hexanes	0.5 M		13%	-	39%

We also tested the reactivity of the other substituted alkynyl carbamates (Table 13). Carbamates **290b** and **290c** were unreactive for oxidative cyclization (entry 1 and 2). The TBS-substituted alkynyl carbamate in entry 3 was slightly less selective for 5-exo-dig cyclization; propellane **306** was isolated in 35% yield. For comparison on reactivity with TIPS-substituted alkynyl carbamate see entry 5 from Table 12.

Table 13. Oxidation of different substituted alkyne carbamates.



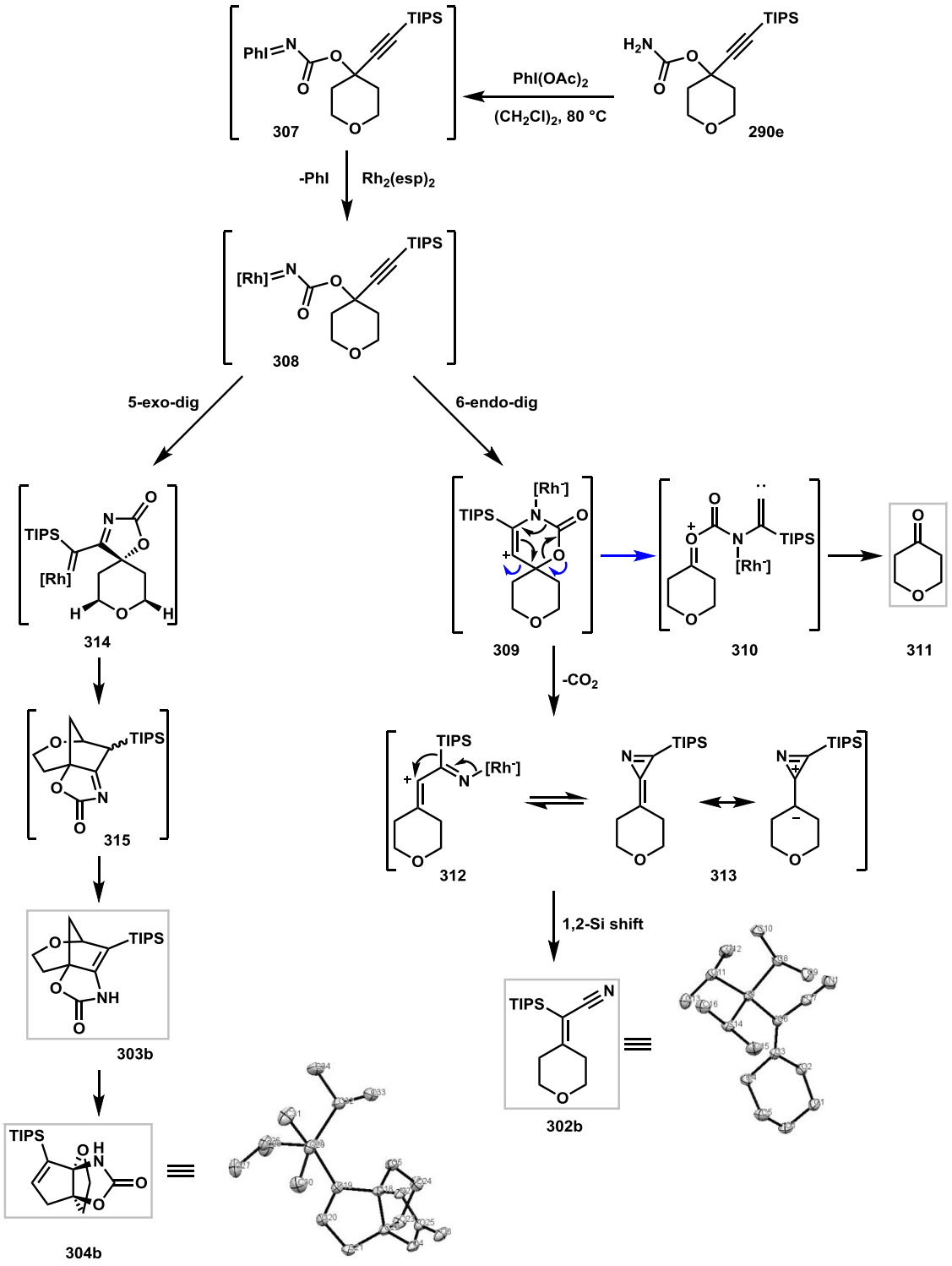
305 306

Entry		Carbamate	Yield	Yield
1	290b	R = H	-	-
2	290c	R = Ph	-	-
3	290f	R = TBS	18%	35%

3.2.4. Proposed Mechanism

A plausible mechanism for the formation of vinyl nitrile **302b** and propellane **304** is presented in Scheme 36. The rhodium nitrene **308** is generated by the reaction of $Rh_2(esp)_2$ with iminoiodine **307**, which is formed by ligand exchange between carbamate **290e** and the iodine(III) oxidant, $PhI(OAc)_2$. Two competing pathways are taking place for TIPS-propargyl nitrene **308**: the 6-endo-dig cyclization as and 5-exo-dig cyclization.

Scheme 36. Plausible mechanism.



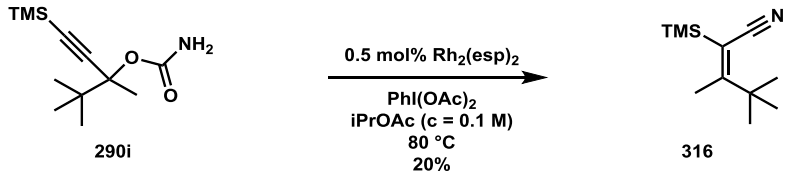
The 6-endo-dig cyclization leads to the formation of vinyl cation **309**, which might be stabilized via a β-silicon effect. A retro [4+2] reaction releases neutral CO_2 and generates vinyl cation **312** and/or vinyl azirine **313**. A short lived vinyl azirine has been observed spectroscopicaly in ^{13}C NMR and IR spectra by Banert and Hagedorn[11]. 1,2-silyl migration in **312** and/or **313** generates TIPS-vinyl nitrile **302b**. The product's structure was confirmed by X-ray analysis. A byproduct, pyranone **311**, could be generated through the 6-endo-dig cyclization pathway as well. Alkylidine carbene could be eliminated in **309** to form oxocarbenium **310** (illustrated by the blue arrows in Scheme 36), and further elimination could generate isocyanate and ketone **311**.

The 5-exo-dig cyclization leads to the formation of the metal carbene **314**. The carbenoid inserts into the C-H bond α to oxygen generating oxabicyclo[3.2.1]octane **315**. Olefin isomerization in **315** forms cyclic carbamate **303**, which has been isolated and characterized spectroscopcally. Under the given reaction conditions, **303** further rearranges into propellane **304**. The propellane's structure was confirmed by single-crystal X-ray analysis.

We do not have evidence for the proposed intermediates in Scheme 36. We know that the oxidation of propargylic carbamate **290e** does not produce the observed products in the absence of the rhodium(II) catalyst. The addition of the acetic acid scavengers MgO and K_2CO_3 generated less of the vinyl nitrile **302b** and propellane **304**. The only other products observed spectroscopically were unreacted starting material and ketone **311**. Because the reaction works so well in a non-polar solvent, hexane, charged species like **309** and **312** are unlikely intermediates.

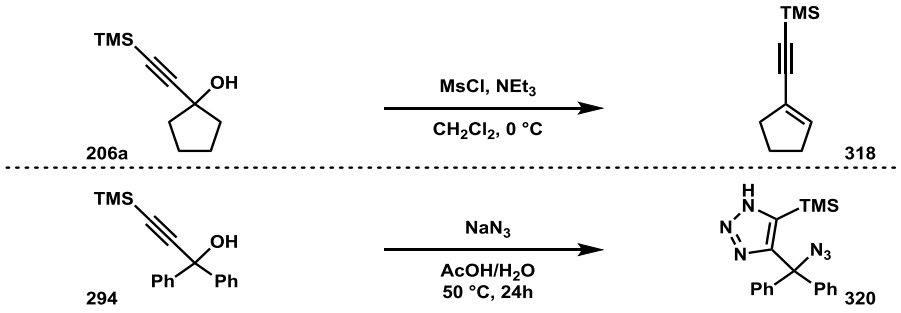
The oxidation of unsymmetrical propargylic carbamate **290i** in Scheme 37 led to the formation of tetra-substituted *E*-olefin exclusively. Thus, thermodynamic products **316** was isolated.

Scheme 37. Regioselectivity in unsymmetrical systems.



We attempted to form silyl allenyl azide, a possible nitrene precursor, which would represent the intermediate **312** and **313** in Scheme 36. Unfortunatelly, the enyne **318** was isolated when propargyl alcohol **206a** was reacted with MsCl and NEt_3. Triazine **320** was formed when propargyl alcohol **294** was reacted with NaN_3 in aqueous acetic acid.

Scheme 38. Attempts to generate allenyl azide.



3.3. Conclusians

We have discovered a novel transformation employing an intramolecular alkyne/carbamate derived-nitrene cascade reaction, which leads to either substituted vinyl nitrile or propellane products. A detailed mechanism of this transformation has not been determined, but a few general guidelines are provided. The steric environment of the alkyne silyl substituent dictates the mode of cyclization between the nitrene and the alkyne. When a small silyl group is used, a 6-endo-dig cyclization happens, and vinyl nitriles are isolated. On the contrary, 5-exo-dig cyclization dominates when a large silyl group is employed, which leads to the formation of highly complex polycyclic systems.

3.4. Experimental

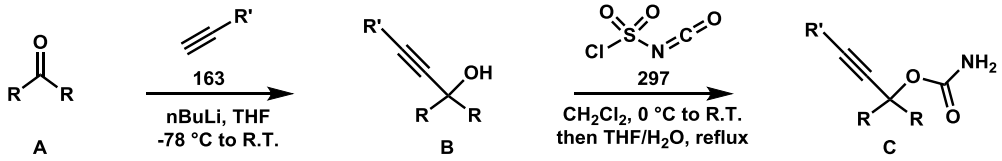
3.4.1. Material and Methods

General Considerations

All reactions were carried out in flame- or oven-dried glassware. THF, toluene and CH_2Cl_2 were purged with argon and dried over activated alumina columns. Flash chromatography was performed on 60Å silica gel (Sorbent Technologies). Analytical thin layer chromatography was performed on EMD silica gel/TLC plates with fluorescent indicator 254 nm. The ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a JEOL ECA-500 or ECX-400P spectrometer using residual solvent peak as an internal reference ($CDCl_3$: 7.25 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR; DMSO-d_6: 2.50 ppm for ^{1}H NMR). For ^{13}C NMR, multiplicities were distinguished using DEPT experiments: methyl and methine carbons appear positive (up); methylene carbons appear negative. IR spectra were obtained using a ThermoNicolet Avatar 370 FT-IR instrument. GCMS analyses were performed on a Shimadzu GCMS-QP2010S chromatographer equipped with a Shimadzu column (SHRXI-5MS, 0.25 mm x 0.25 u x 30 M). Commercially available compounds were purchased from Aldrich Chemical Co., Acros Organics, Alfa Aesar or TCI America and were used without further purification.

3.4.2. Synthesis of Compounds

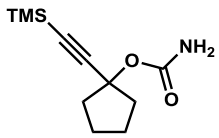
3.4.2.1. Synthesis of Alkynyl-Carbamates



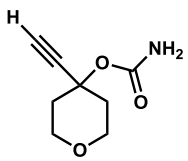
General Procedure. Step I. A flame-dried round-bottom flask was charged with *n*BuLi (1.3 eq, 2.5 M) under an argon atmosphere. Anhydrous THF (0.5 M) was added, and the flask was cooled to -78 ˚C in a dry ice/acetone bath. The terminal acetylene (1.3 eq) was then added dropwise. After 30 minutes at -78 ˚C, the cyclic ketone **A** (1.0 eq) was added dropwise (if a solid, prior to addition it was dissolved in anhydrous THF). The reaction mixture was allowed to warm to room temperature and stir overnight. After completion, saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered through short silica gel plug and concentrated to yield crude product. The crude product was subjected to the next step without any further purification.

Step II. A flame-dried round-bottom flask was charged with chlorosulfonyl isocyanate **297** (1.5 eq) under an argon atmosphere. Anhydrous CH_2Cl_2 (0.1M) was added, and the flask was cooled to 0 ˚C in an ice/H_2O bath. The crude product **B** (1.0 eq) dissolved in anhydrous CH_2Cl_2 (0.3M) was then added dropwise. The reaction mixture was allowed to warm to room temperature. After 30 minutes, H_2O (1/10 of the total volume of CH_2Cl_2 added) and THF (1/5 of the total volume) were added. The reaction mixture was refluxed (45 ˚C oil bath) for 30 minutes. Then saturated NaCl solution was added, layers were separated.

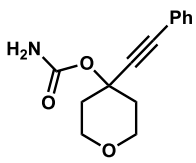
Aqueous layere was extracted with CH_2Cl_2 (2x), and the organic phases were combined, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel, or recrystallized from EtOAc/hexanes mixture.



1-[2-(trimethylsilyl)ethynyl]cyclopentyl carbamate (290a) was synthesized from propargyl alcohol **206a** (0.39 g, 2.17 mmol) following general procedure, step II. The crude product was purified by column chromatography on silica gel using 30% EtOAc in hexanes as an eluent. The product was obtained as a white solid (0.34 g, 75% yield). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 155.3, 106.0, 88.9, 81.1, 40.8, 23.5, 0.1.

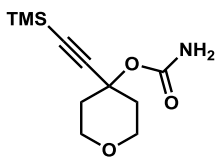


4-ethynyloxan-4-yl carbamate (290b) was synthesized from propargyl alcohol **291** (100 mg, 0.26 mmol) following general procedure, step II. The crude product was purified by column chromatography on silica gel using 60% EtOAc in hexanes as an eluent. The product was obtained as a white solid (130 mg, 97% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.80 (s, 2H), 3.91-3.78 (m, 2H), 3.78-3.64 (m, 2H), 2.67 (s, 1H), 2.28-2.16 (m, 2H), 2.09-1.95 (m, 2H). **^{13}C NMR** (125.75 MHz, $CDCl_3$) δ 154.9, 82.7, 72.3, 64.4, 37.7.

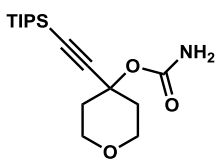


4-(2-phenylethynyl)oxan-4-yl carbamate (290c) was synthesized from tetrahydropyranone (0.50 ml, 0.26 mmol) following general procedure. The crude product was recrystallized from EtOAc/hexanes mixture. After filtration product was collected (0.89 g, 68% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52-7.41 (m, 2H), 7.36-7.22 (m, 2H), 4.71 (s, 2H), 3.97-3.85 (m, 2H), 3.85-3.72 (m, 2H), 2.40-

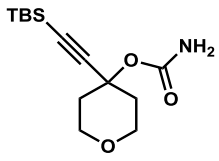
2.27 (m, 2H), 2.17-2.04 (m, 2H). **^{13}C NMR** 154.9, 132.0, 128.7, 128.4, 122.4, 87.9, 87.0, 73.1, 64.7, 38.0.



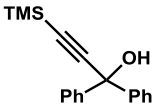
4-[2-(trimethylsilyl)ethynyl]oxan-4-yl carbamate (290d) was synthesized from propargyl alcohol **207e** (0.30 g, 0.85 mmol) following general procedure, step II. The crude product was purified by column chromatography on silica gel using 35% EtOAc in hexanes as an eluent. The product was obtained as a white solid (0.30 g, 89% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.64 (s, 2H), 3.91-3.77 (m, 2H), 3.75-3.62 (m, 2H), 2.25-2.13 (m, 2H), 2.06-1.92 (m, 2H), 0.17 (s, 9H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 154.7, 104.0, 92.1, 73.0, 64.7, 37.9, 0.0.



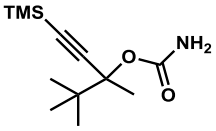
4-{2-[tris(propan-2-yl)silyl]ethynyl}oxan-4-yl carbamate (290e) was synthesized from propargyl alcohol **292** (0.31 g, 0.26 mmol) following general procedure, step II. The crude product was purified by column chromatography on silica gel using 30% EtOAc in hexanes as an eluent. The product was obtained as a white solid (0.24g, 70% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.60 (s, 2H), 3.87 (dt, J = 12.0 Hz and 4.0 Hz, 2H), 3.77-3.68 (m, 2H), 2.28-2.20 (m, 2H), 2.03-1.93 (m, 2H), 1.11-1.00 (m, 3H), 1.06 (s, 18H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 154.6, 105.9, 88.3, 73.2, 64.9, 38.1, 18.7, 11.2.



4-[2-(tert-butyldimethylsilyl)ethynyl]oxan-4-yl carbamate (290f) was synthesized from propargyl alcohol **293** (0.30 g, 1.25 mmol) following general procedure, step II. The crude product was purified by column chromatography on silica gel using 30% EtOAc in hexanes as an eluent. The product was obtained as a white solid (0.28 g, 80% yield).

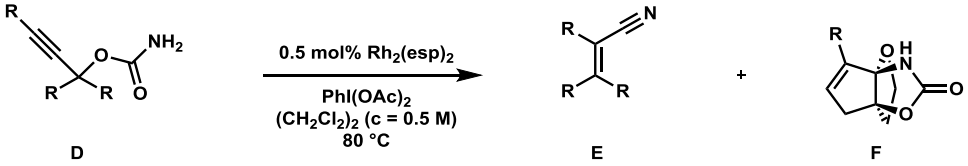


1,1-diphenyl-3-(trimethylsilyl)prop-2-yn-1-ol (294) was synthesized from benzophenone (2.0 g, 11.0 mmol) following general procedure, step I. The product was obtained as a colorless oil (3.0 g, 98% yield). Step II produced a complex mixture. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.64-7.59 (m, 4H), 7.36-7.30 (m, 4H), 7.30-7.24 (m, 2H), 2.83 (s, 1H), 0.25 (s, 9H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 144.9, 128.4, 128.0, 126.1, 107.8, 92.2, 74.8, 0.0.

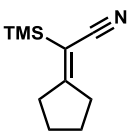


3,4,4-trimethyl-1-(trimethylsilyl)pent-1-yn-3-yl carbamate (290h) was synthesized from propargyl alcohol **295** (0.50 g, 2.52 mmol) following general procedure, step II. The crude product was purified by column chromatography on silica gel using 30% EtOAc in hexanes as an eluent. The product was obtained as a white solid (0.34 g, 56% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.54 (s, 2H), 1.67 (s, 3H), 1.04 (s, 9H), 0.15 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 155.3, 105.2, 90.1, 80.8, 39.1, 25.2, 20.9, 0.1.

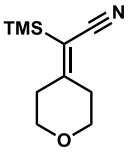
3.4.2.2 Synthesis of Substituted Vinyl Nitriles and Bridged Polycyclic Compounds



General Procedure: A 1 dram or 2 dram vial was charged with magnetic stirbar, alkynyl carbamate **D** (1.0 eq), $PhI(OAc)_2$ (1.2 eq) and $Rh_2(esp)_2$ (0.5 mol%). Solvent (0.1M or 0.5M) was added and the vial was sealed. The reaction mixture was heated at 80 ˚C for 21 hours. When cooled to room temperature, solvents were remoed via rotary evapouration and the residue was purified by flash column chromatography on silica gel.

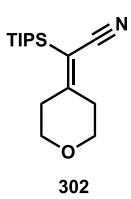


2-[cyclopentylidene]-2-(trimethylsilyl)acetonitrile (298) was synthesized from carbamate **290a** (25 mg, 0.10 mmol) following general procedure. The crude product was purified by column chromatography on silica gel using 2.5% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (4 mg, ~20% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.67 (t, J = 6.9 Hz, 2H), 2.42 (t, J = 6.9 Hz, 2H), 1.85-1.67 (m, 4H), 0.24 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 182.9, 37.7, 34.6, 27.2, 25.4, -0.9.



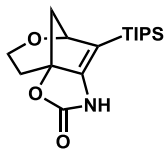
302

2-(oxan-4-ylidene)-2-(trimethylsilyl)acetonitrile (302a) was synthesized from carbamate **209d** (48 mg, 0.20 mmol) following general procedure. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (10 mg, 25% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.78 (t, J = 5.7 Hz, 2H), 3.72 (t, J = 5.7 Hz, 2H), 2.72 (t, J = 5.7 H, 2H), 2.47 (t, J = 5.7 Hz, 2H), 0.28 (s, 9H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 171.1, 119.5, 107.8, 68.9, 68.4, 37.7, 35.8, -0.03.



302

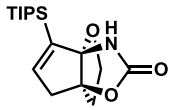
2-(oxan-4-ylidene)-2-[tris(propan-2-yl)silyl]acetonitrile (302b) was synthesized from carbamate **290e** (65 mg, 0.20 mmol) following general procedure. The crude product was purified by column chromatography on silica gel using 5%-20% EtOAc in hexanes as an eluent. The product **302** was obtained as a white solid (9 mg, 16% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.80 (t, J = 5.7 Hz, 2H), 3.74 (t, J = 5.7 Hz, 2H), 2.82 (t, J = 5.7 Hz, 2H), 2.47 (t, J = 5.7 Hz, 2H), 1.41-1.31 (m, 3H), 1.11 (m, 18H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 172.4, 120.5, 104.2, 69.0, 68.5, 38.0, 36.6, 18.7, 13.0.

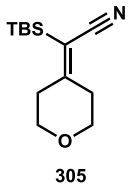


303

6-[tris(propan-2-yl)silyl]-2,8-dioxa-4-azatricyclo[5.3.1.0^{1},^{5}]undec-5-en-3-one (303) was obtained as a white solid (8 mg, 12% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.06 (s, 1H), 4.98 (d, J = 2.9 Hz, 1H), 4.09-4.01 (m, 1H), 3.88 (dd, J = 10.9 Hz and 6.9 H, 1H), 2.34-2.26 (m, 2H), 2.18 (d, J = 9.2 Hz, 1H), 1.69-1.63 (m, 1H), 1.19-1.10 (m, 3H), 1.09-1.04 (m, 18H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 158.6, 156.5, 98.2, 91.9, 84.9, 60.6, 52.3, 32.6, 31.1, 18.8, 18.6, 11.8.

(1R,5R)-11-[tris(propan-2-yl)silyl]-2,6-dioxa-4-azatricyclo[3.3.3.0^{1},^{5}]undec-10-en-3-one (304) was obtained as a white solid (17 mg, 27% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.02 (t, J = 2.3 Hz, 1H), 5.54 (s, 1H), 4.10-4.05 (m, 1H), 3.98-3.91 (m, 1H), 2.97-2.80 (m, 2H), 2.52-2.45 (m, 1H), 1.98-1.88 (m, 1H), 1.19-1.01 (m, 21H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 157.8, 144.2, 139.8, 112.1, 97.4, 67.4, 45.1, 38.9, 18.8, 18.7, 18.7, 11.4.

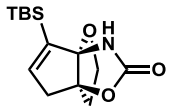




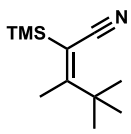
305

2-(tert-butyldimethylsilyl)-2-(oxan-4-ylidene)acetonitrile (305) was synthesized from carbamate **290f** (43 mg, 0.15 mmol) following general procedure. The crude product was purified by column chromatography on silica gel using 5%-20% EtOAc in hexanes as an eluent. The product **305** was obtained as a white solid (6 mg, 18% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.79 (t, J = 5.7 Hz, 2H), 3.72 (t, J = 5.7 Hz, 2H), 2.76 (t, J = 5.7 Hz, 2H), 2.47 (t, J = 5.7 Hz, 2H), 0.95 (s, 9H), 0.28 (s, 3H), 0.28 (s, 3H).

(1R,5R)-11-(tert-butyldimethylsilyl)-2,6-dioxa-4-azatricyclo[3.3.3.0^{1},^{5}]undec-10-en-

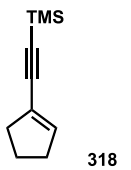


3-one (306) was obtained as a white solid (15 mg, 35% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.00 (t, J = 2.3 Hz, 1H), 5.90 (s, 1H), 2.86 (qd, J = 18.9 Hz and 2.3 Hz, 2H), 4.11-4.05 (m, 1H), 3.98-3.91 (m, 1H), 2.50-2.44 (m, 1H), 1.98-1.90 (m, 1H), 0.89 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 158.1, 143.5, 142.0, 112.1, 97.3, 67.4, 45.3, 39.0, 26.7, 26.2, 16.6.



316

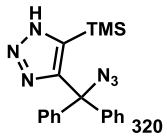
(2E)-3,4,4-trimethyl-2-(trimethylsilyl)pent-2-enenitrile (316) was synthesized from carbamate **290h** (50 mg, 0.21 mmol) following general procedure. The crude product was purified by column chromatography on silica gel using 1% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.98 (s, 3H), 1.31 (s, 9H), 0.28 (s, 9H).**^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 181.7, 121.0, 106.5, 40.2, 29.5, 22.5, 0.2



318

[2-(cyclopent-1-en-1-yl)ethynyl]trimethylsilane (318) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12-6.08 (m, 1H), 2.48-2.36 (m, 4H), 1.93-1.83 (m, 2H), 0.18 (s,

9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 139.6, 124.7, 102.7, 95.4, 36.5, 33.4, 23.5, 0.2.



320

4-(azidodiphenylmethyl)-5-(trimethylsilyl)-1H-1,2,3-triazole (320) ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.89 (s, 1H), 7.37-7.26 (m, 10H), 0.31 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 156.0, 142.2, 128.4, 128.3, 128.2, 77.5, 72.8, -0.4.

3.4.3. Crystallographic Data

Crystal data and structure refinement for 302e.

Empirical formula	$C_{16}H_{29}NOSi$	
Formula weight	279.49	
Crystallization solvent	EtOAc/hexanes	
Crystal habit	Plate	
Crystal size	0.30 x 0.30 x 0.10 mm^3	
Crystal color	colorless	
Data Collection		
Type of diffractometer	Bruker DUO APEX II CCD	
Wavelength	1.54178 Å MoKα	
Data collection temperature	123(2) K	
Unit cell dimensions	a = 7.5883(2) Å	α = 90.00 ˚
	b = 30.7424(8) Å	β = 107.783(1) ˚
	c = 7.7047(2) Å	γ = 90.00 ˚
Volume	1711.49(8) $Å^3$	
Z	4	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Density	1.085 Mg/m^3	
F(000)	616	
Reflections collected	2929	

Crystal data and structure refinement for 303.

Empirical formula	$C_{17}H_{29}NO_3Si$
Formula weight	323.50 g/mol
Crystallization solvent	EtOAc/hexanes
Crystal habit	flat column
Crystal size	0.40 x 0.20 x 0.08 mm^3
Crystal color	colorless

Data Collection

Type of diffractometer	Bruker DUO APEX II CCD	
Wavelength	1.54178 Å MoKα	
Data collection temperature	123(2) K	
Unit cell dimensions	a = 8.9713(3) Å	α = 90.00 ˚
	b = 12.6161(3) Å	β = 90.00 ˚
	c = 31.4987(8) Å	γ = 90.00 ˚
Volume	3565.11(17) $Å^3$	
Z	8	
Crystal system	Orthorombic	
Space group	P21 21 21	
Density	1.205 Mg/m^3	
F(000)	1408	
Reflections collected	6085	

3.5. References and Notes

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[9] see SI: Grigg, R. D.; Rigoli, J. W.; Pearce, S. D.; Schomaker, J. M. *Org. Lett.* **2012**, *14*, 280–283.

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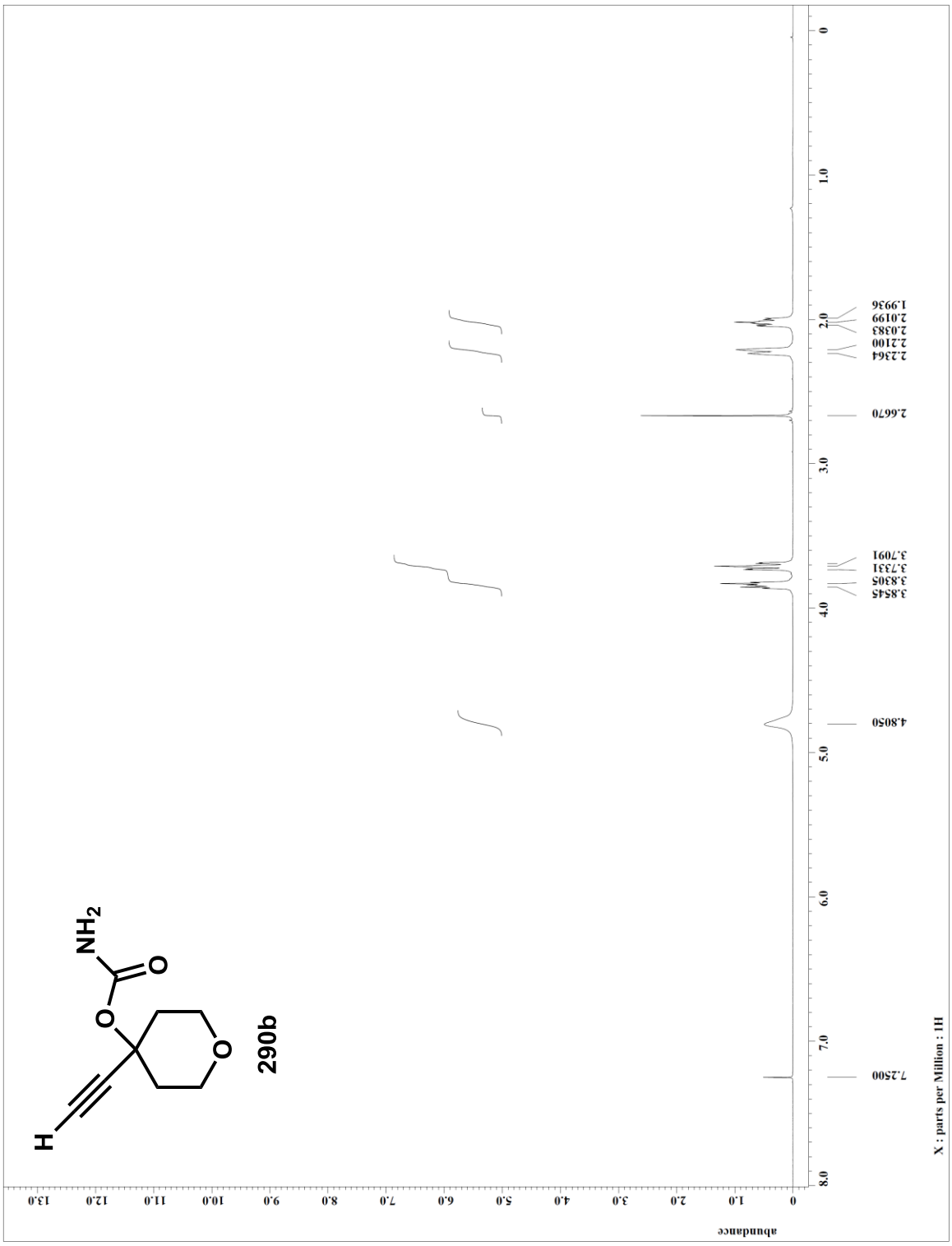
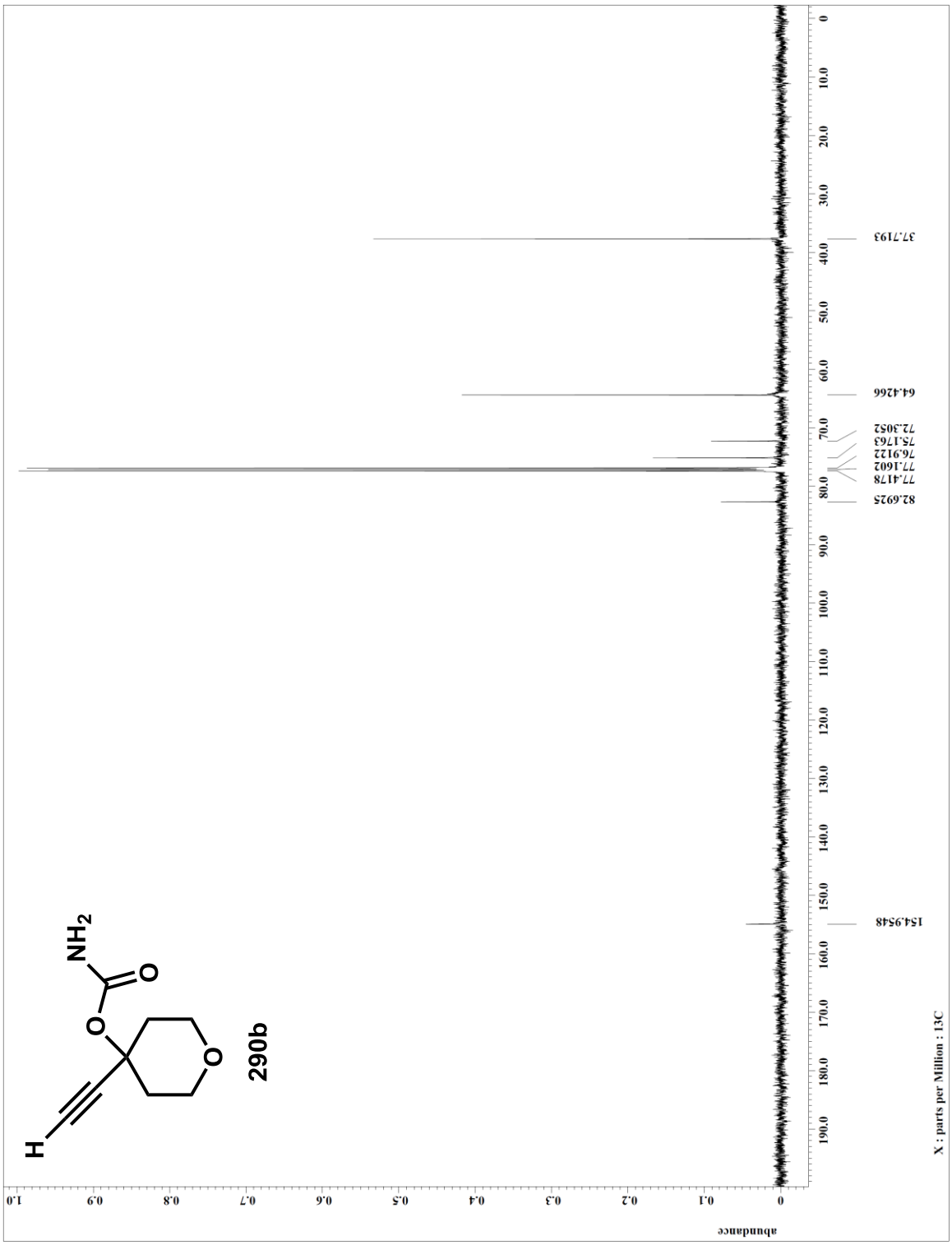
APPENDIX TWO

Spectra Relevant to Chapter 3



^{1}H NMR for compound **290b**



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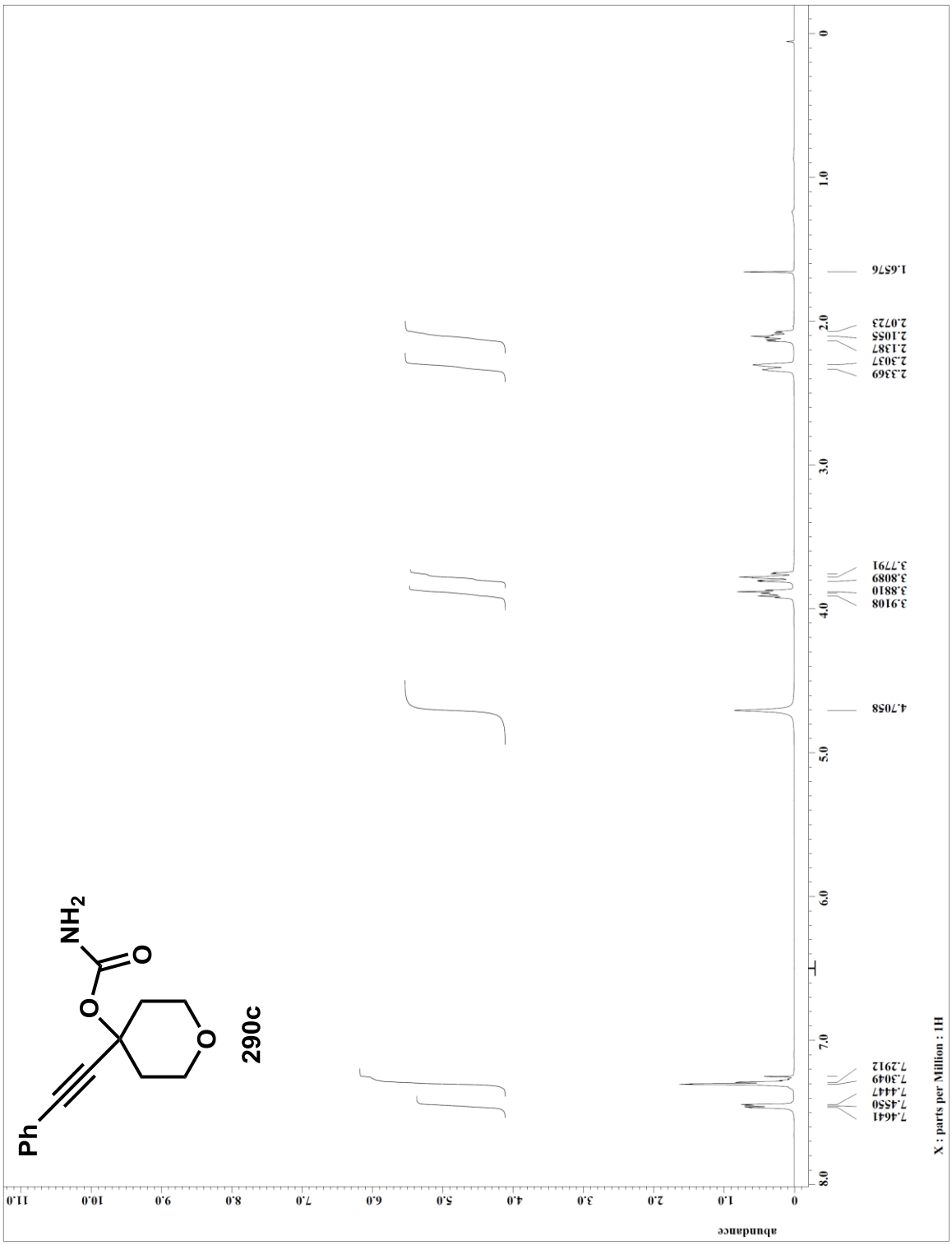

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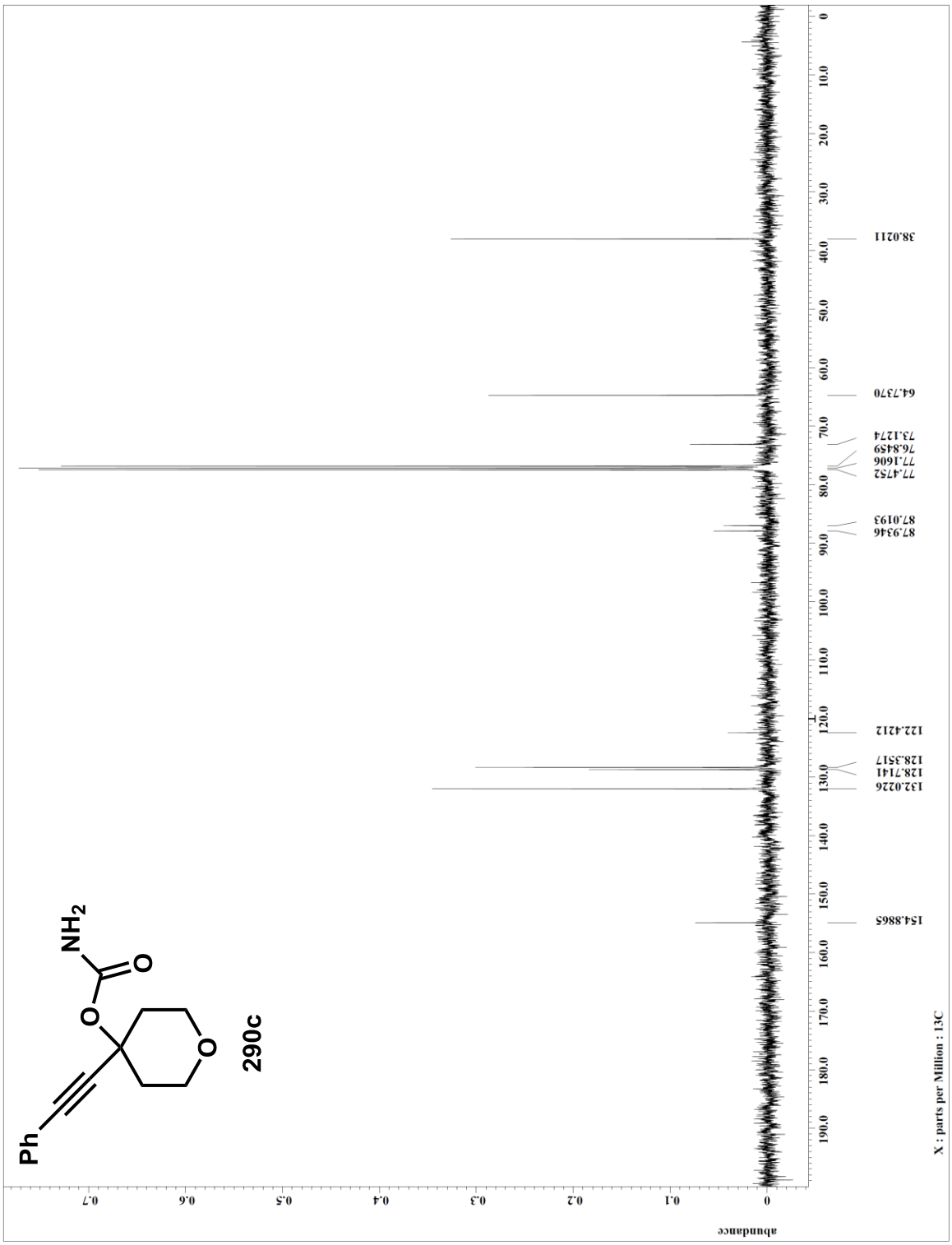

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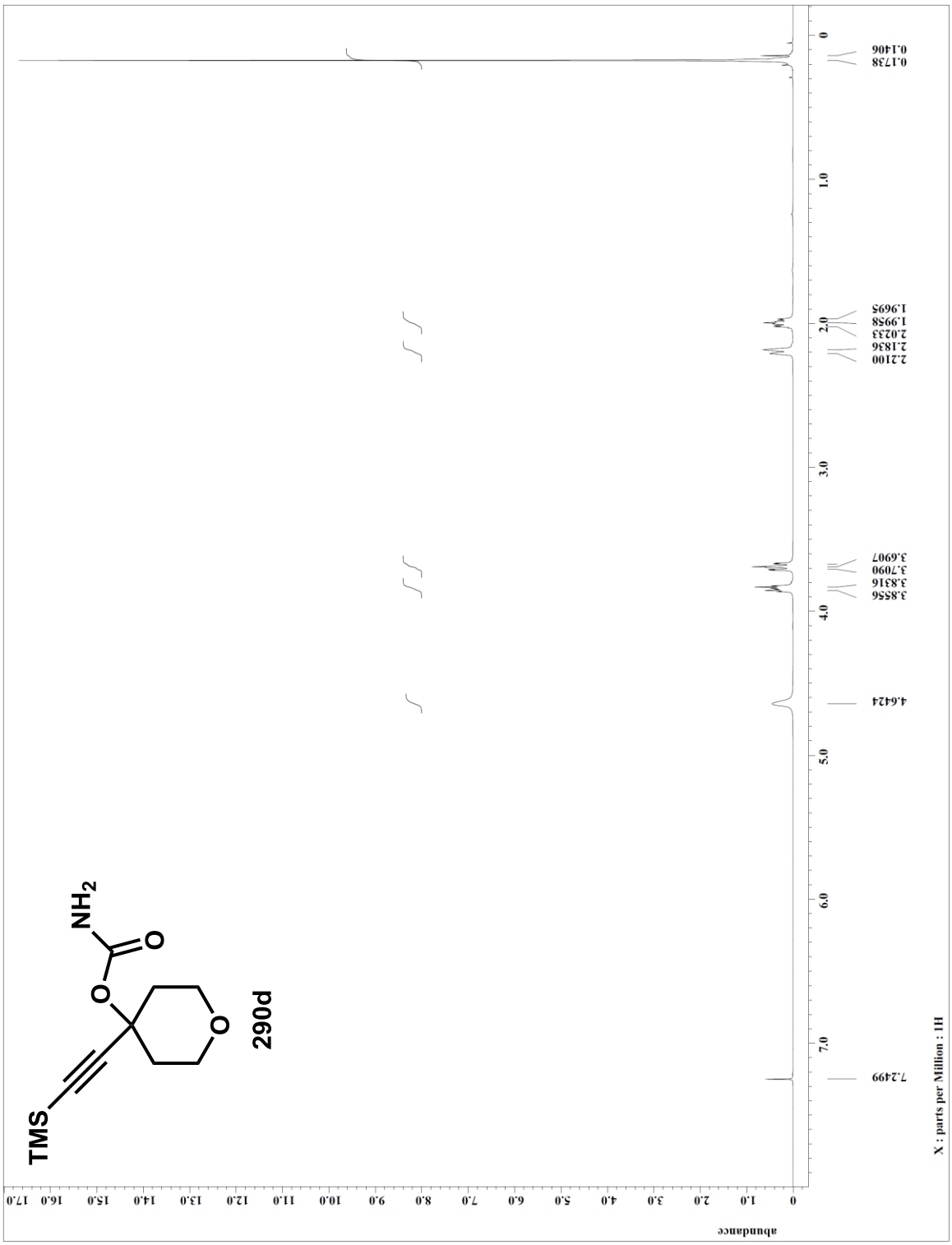

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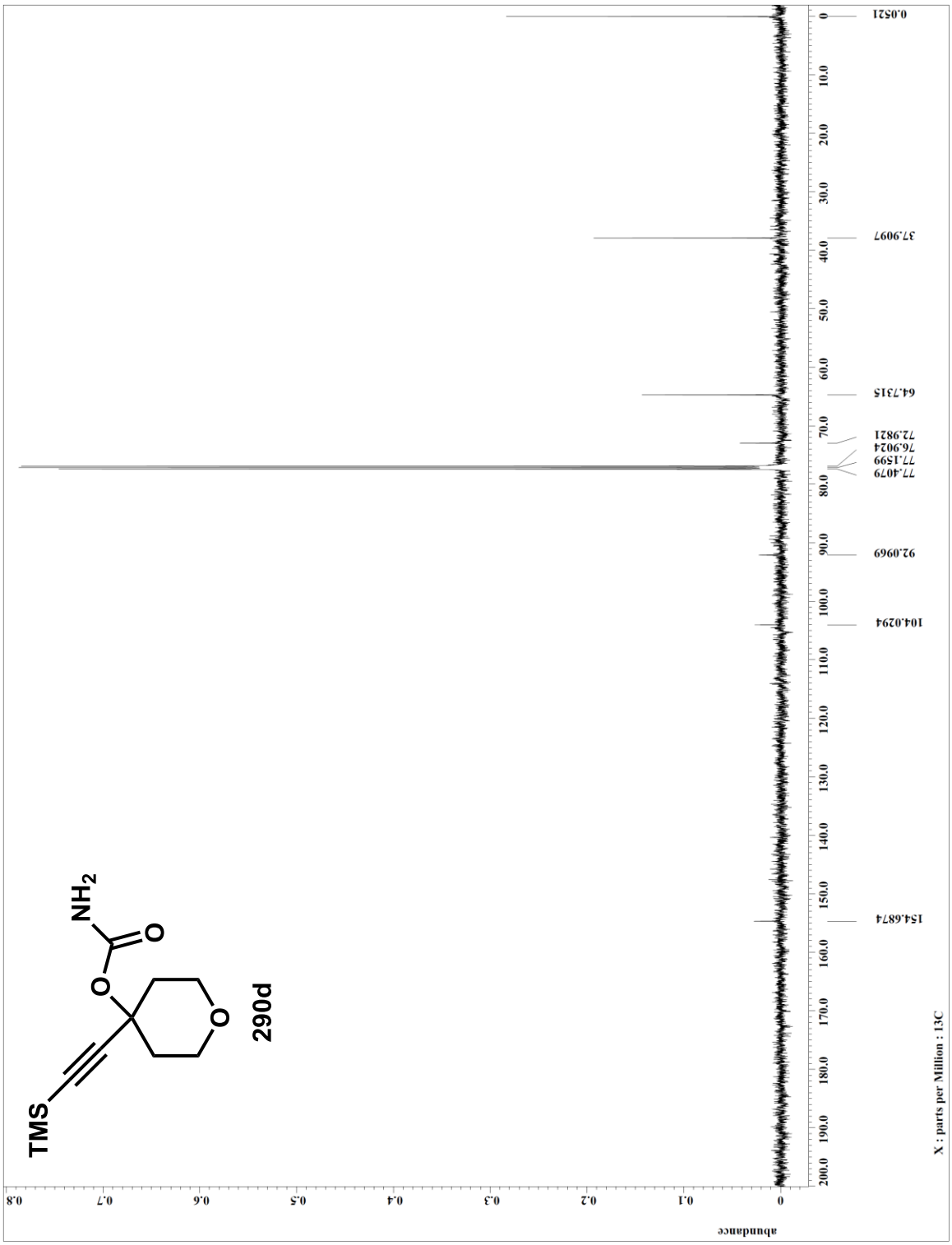

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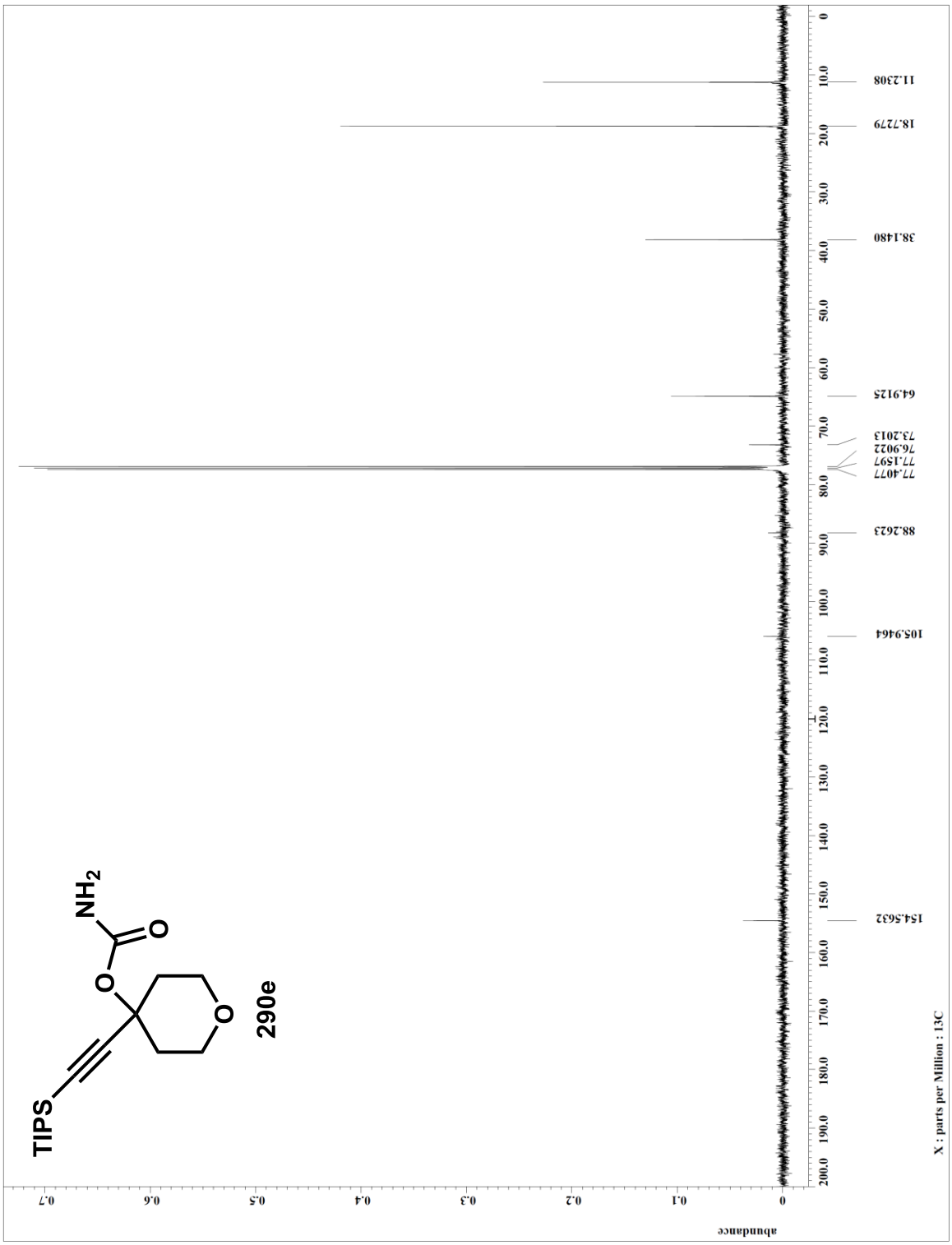

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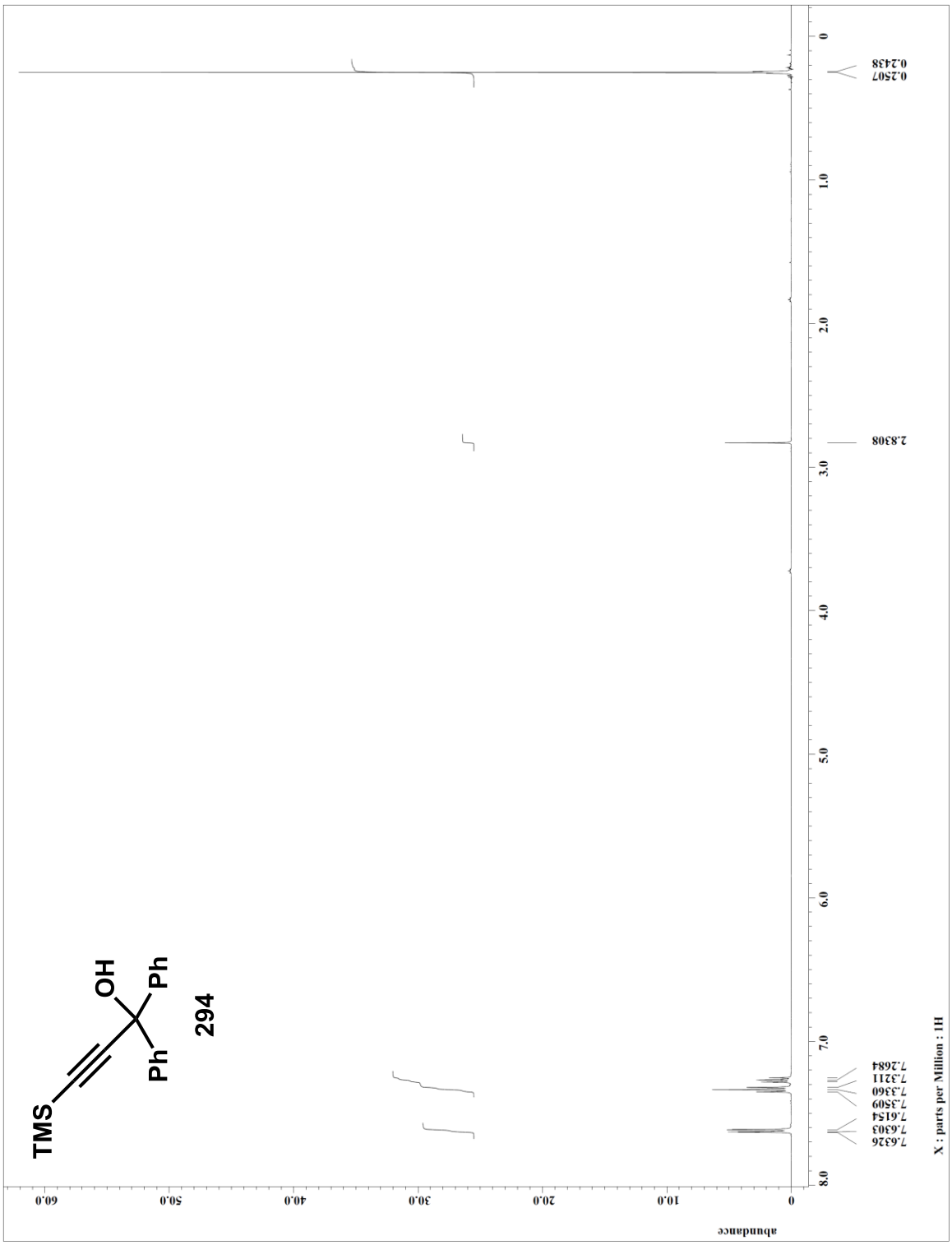

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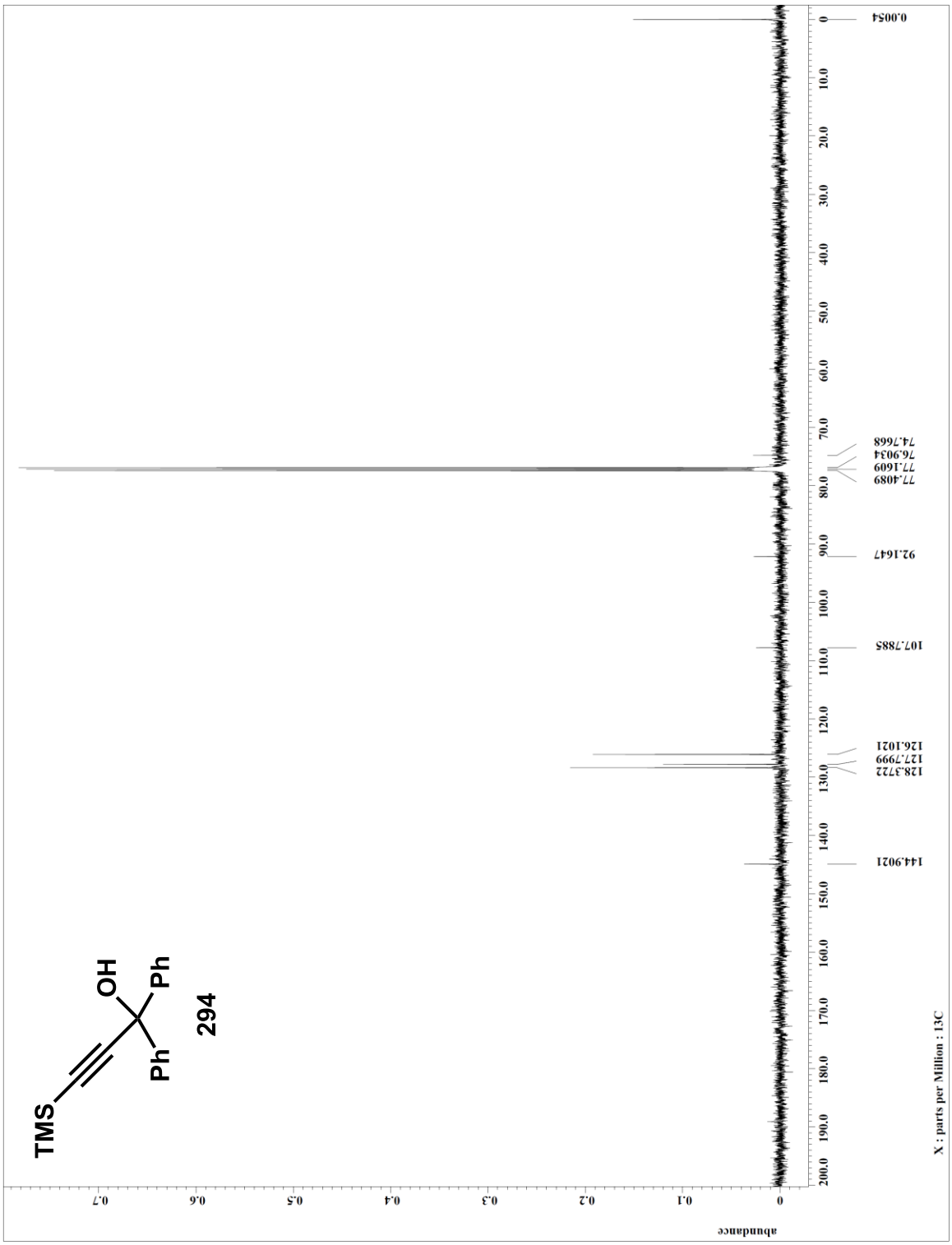

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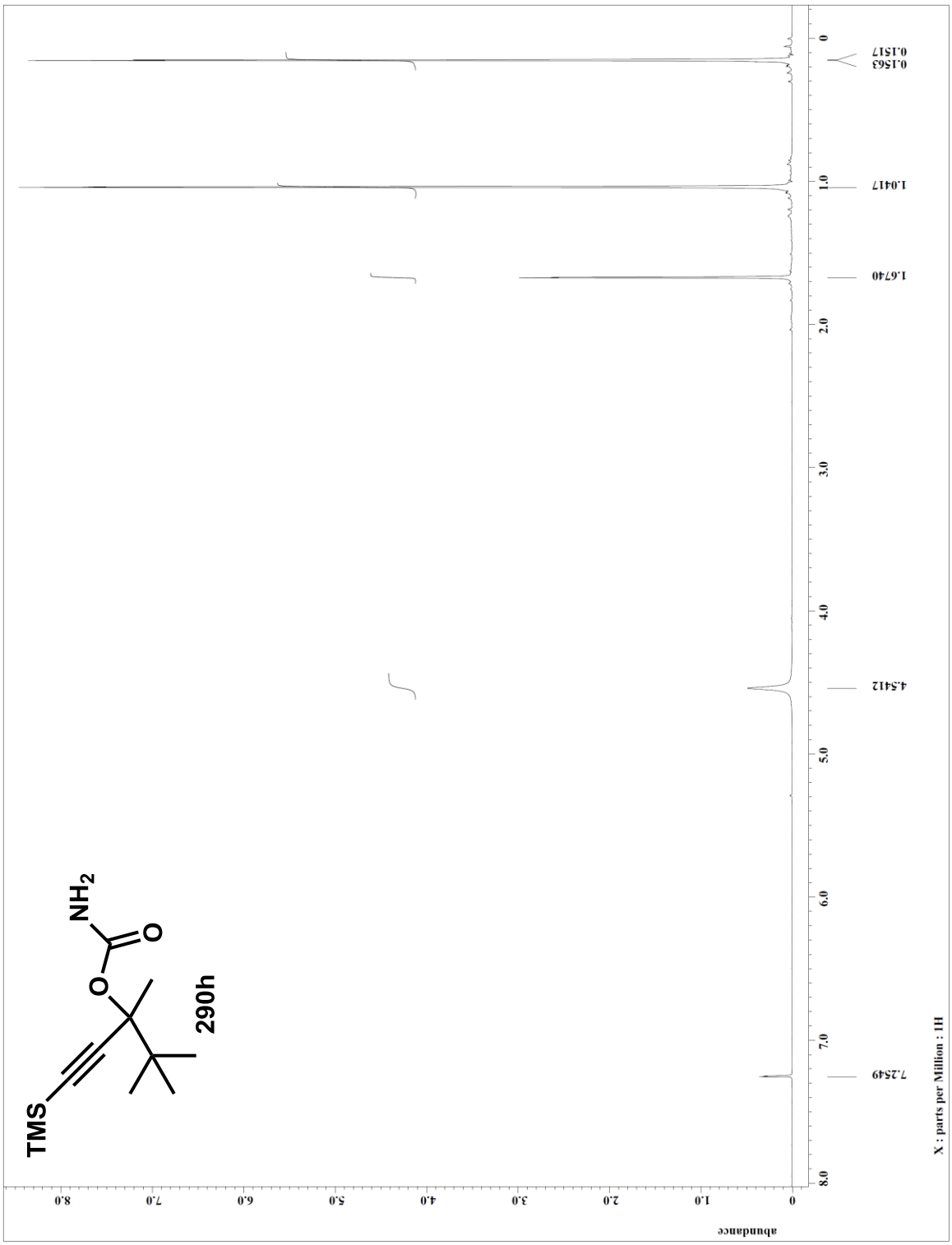

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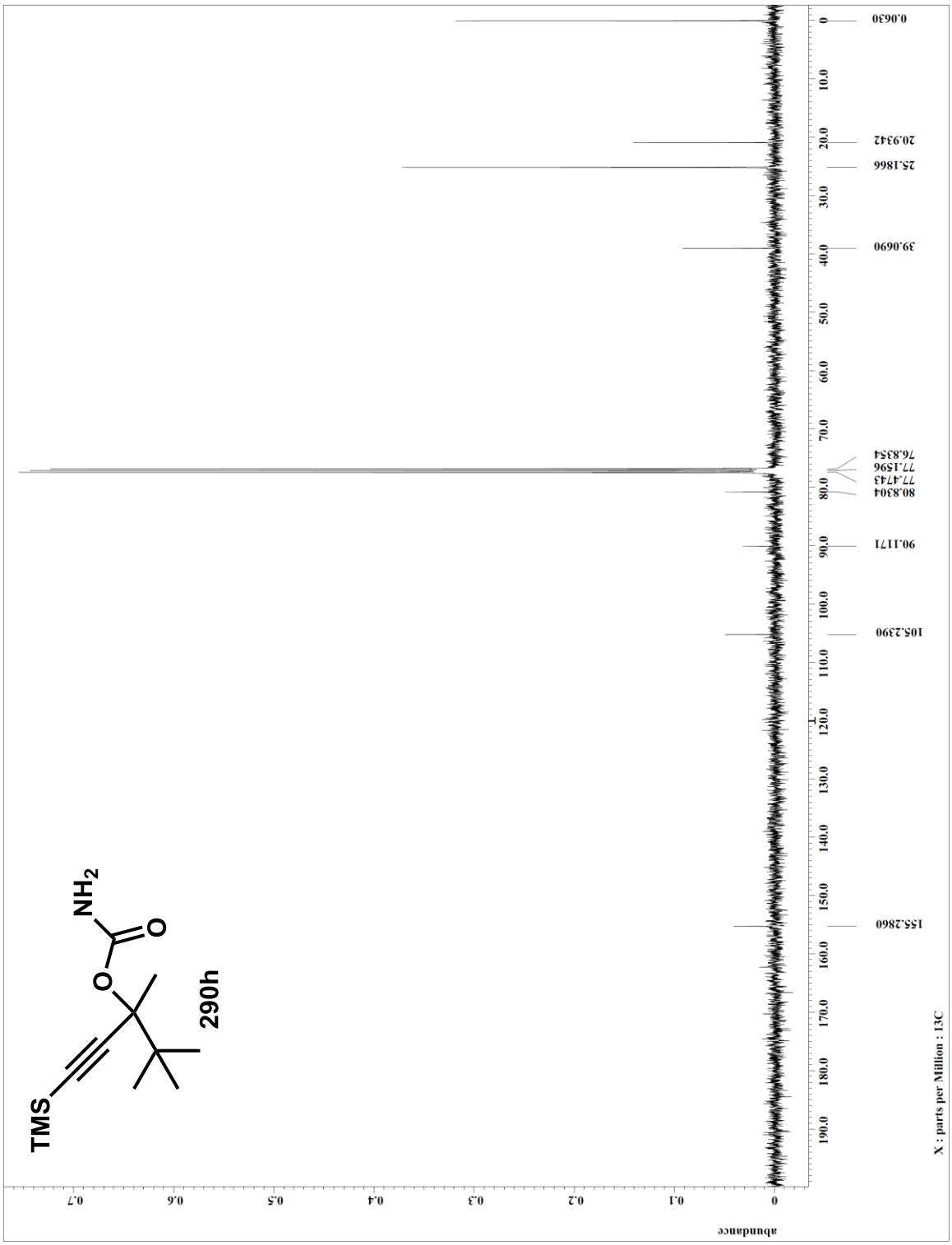

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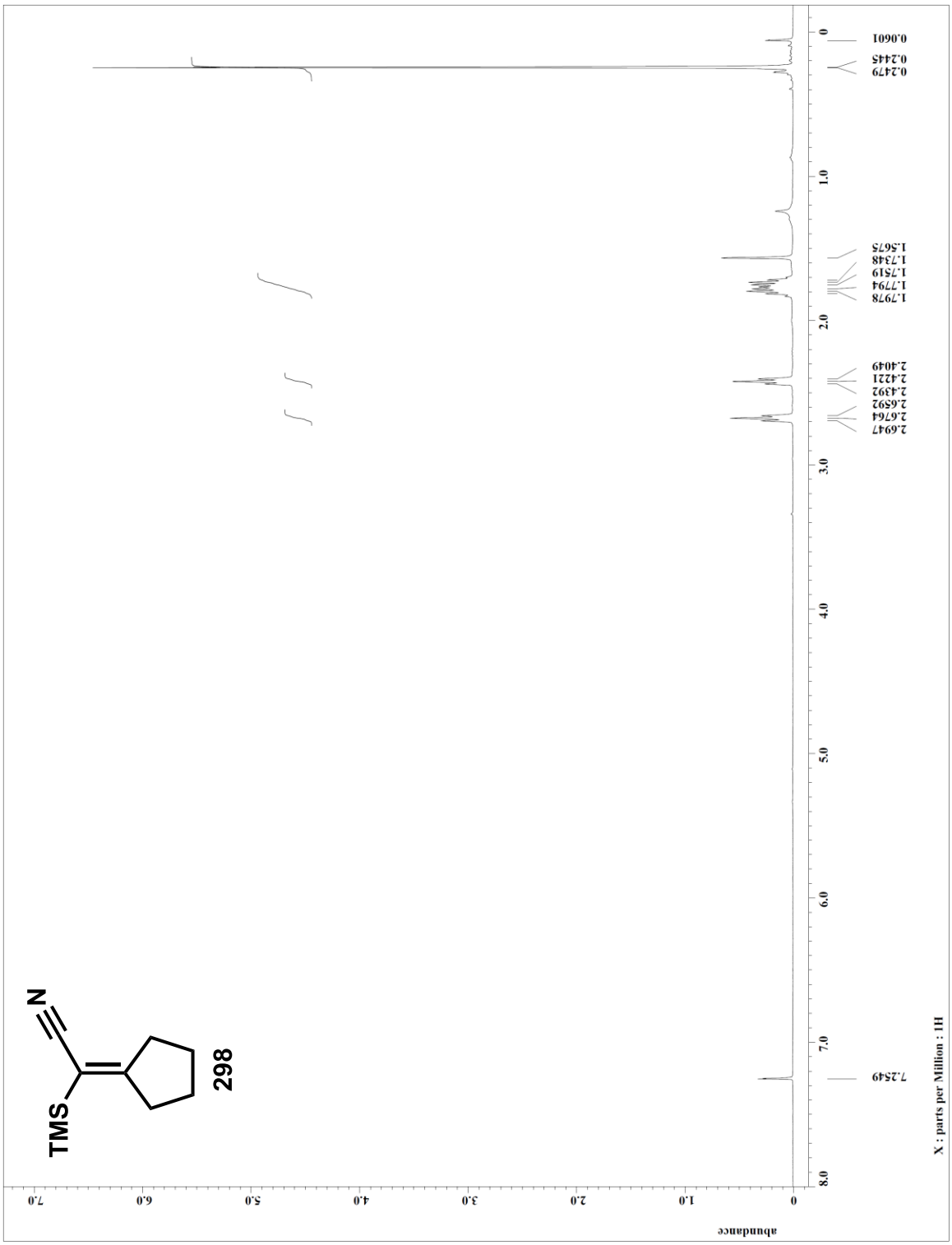

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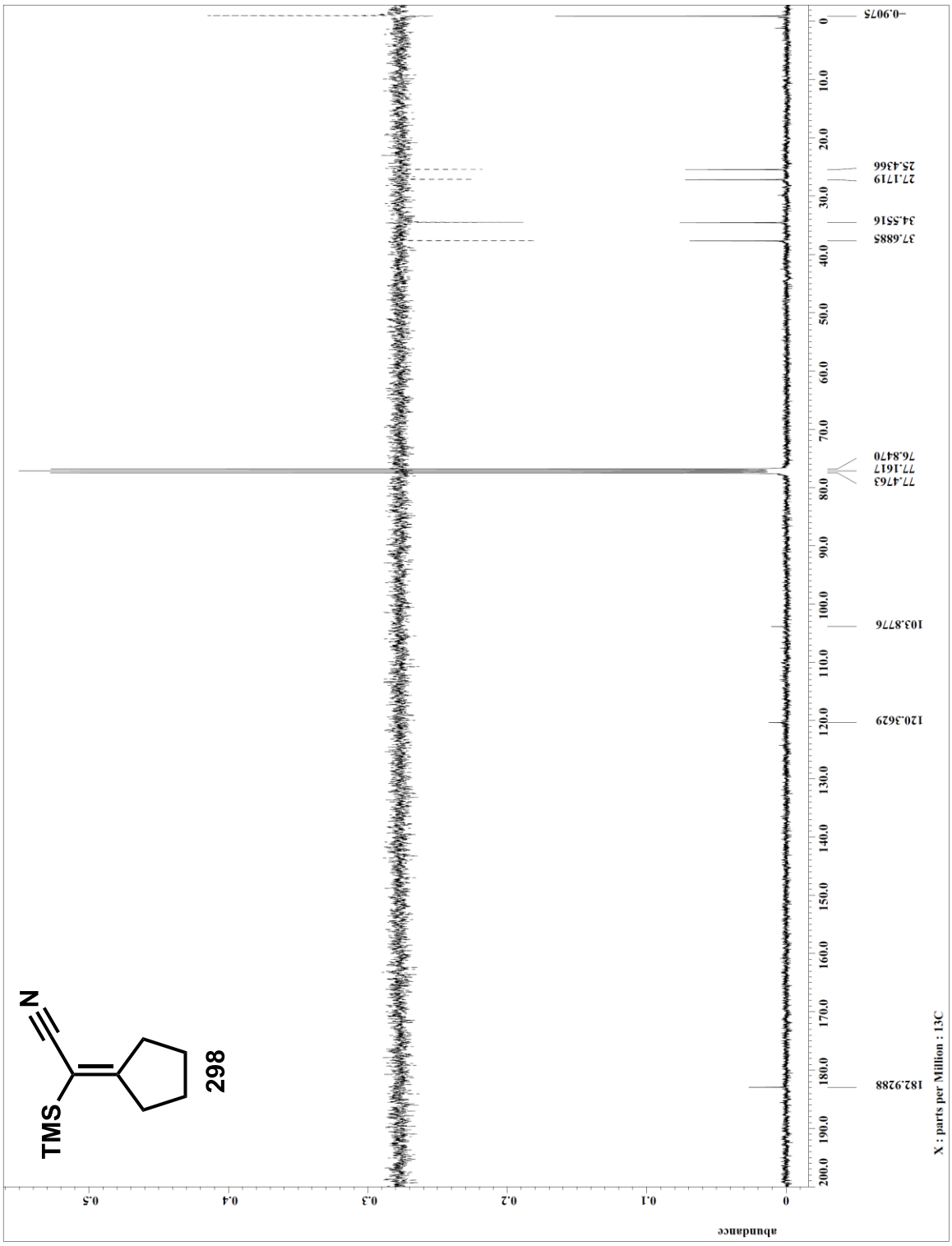
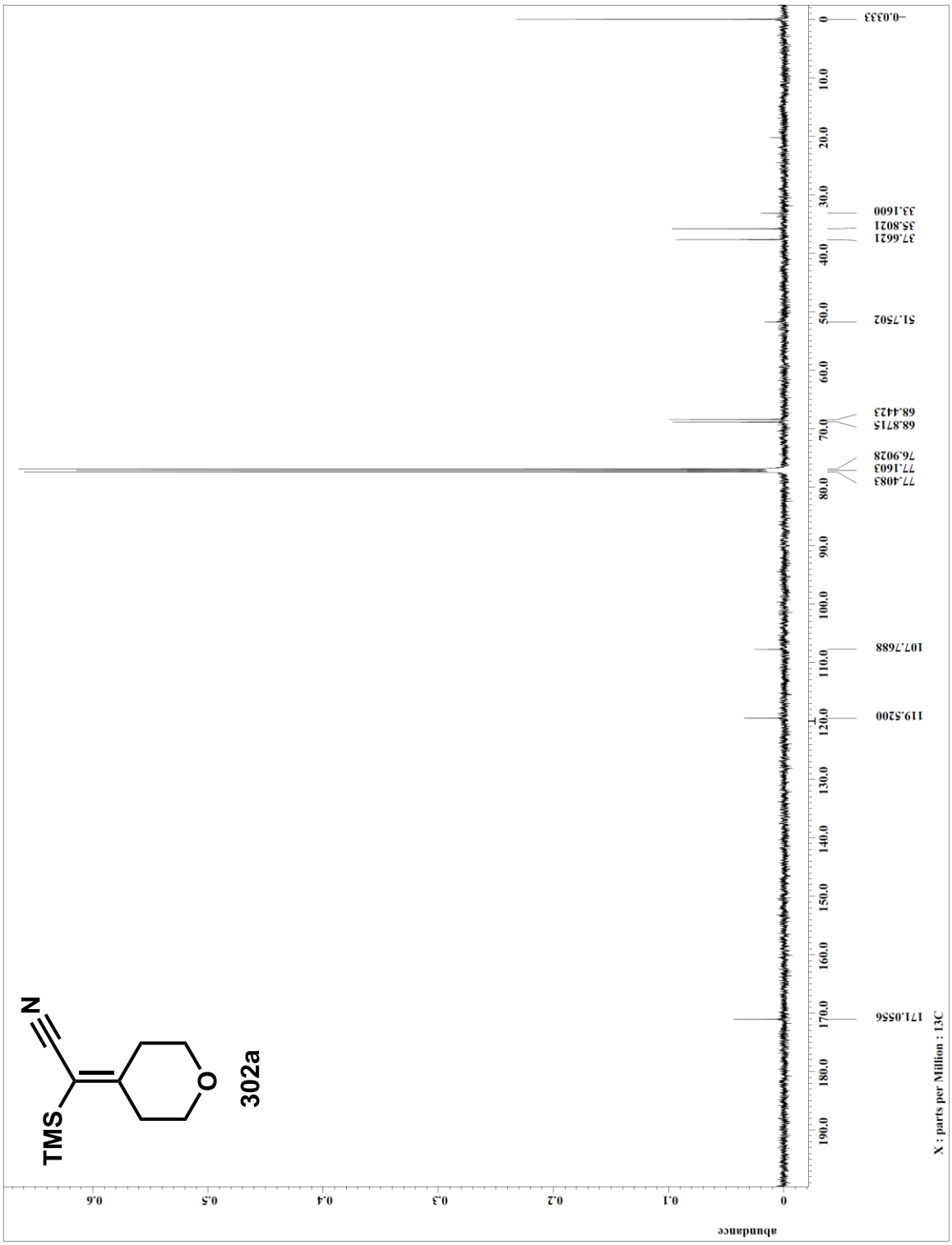


^{13}C NMR and DEPT for compound **298**

^{1}H NMR for compound **302a**



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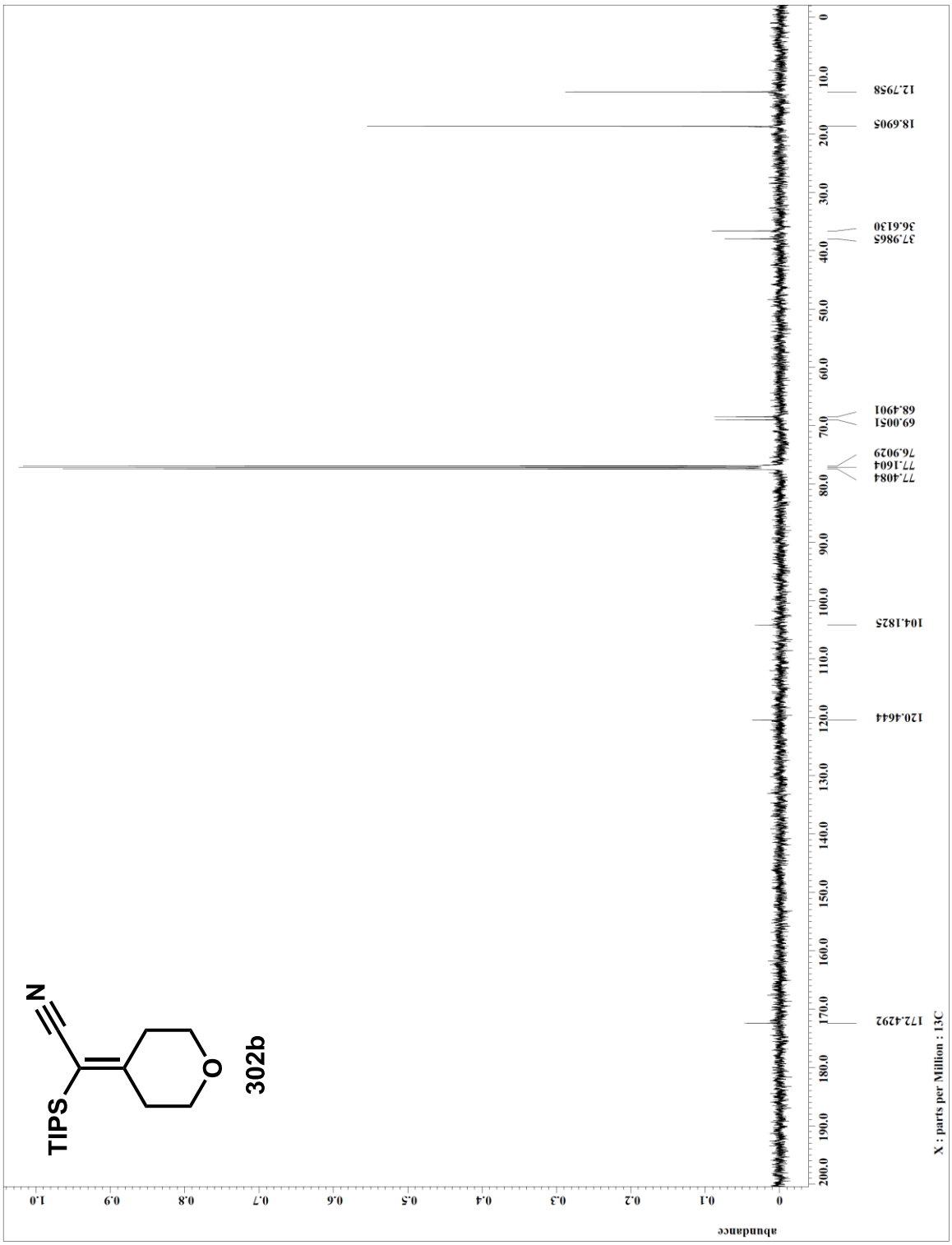

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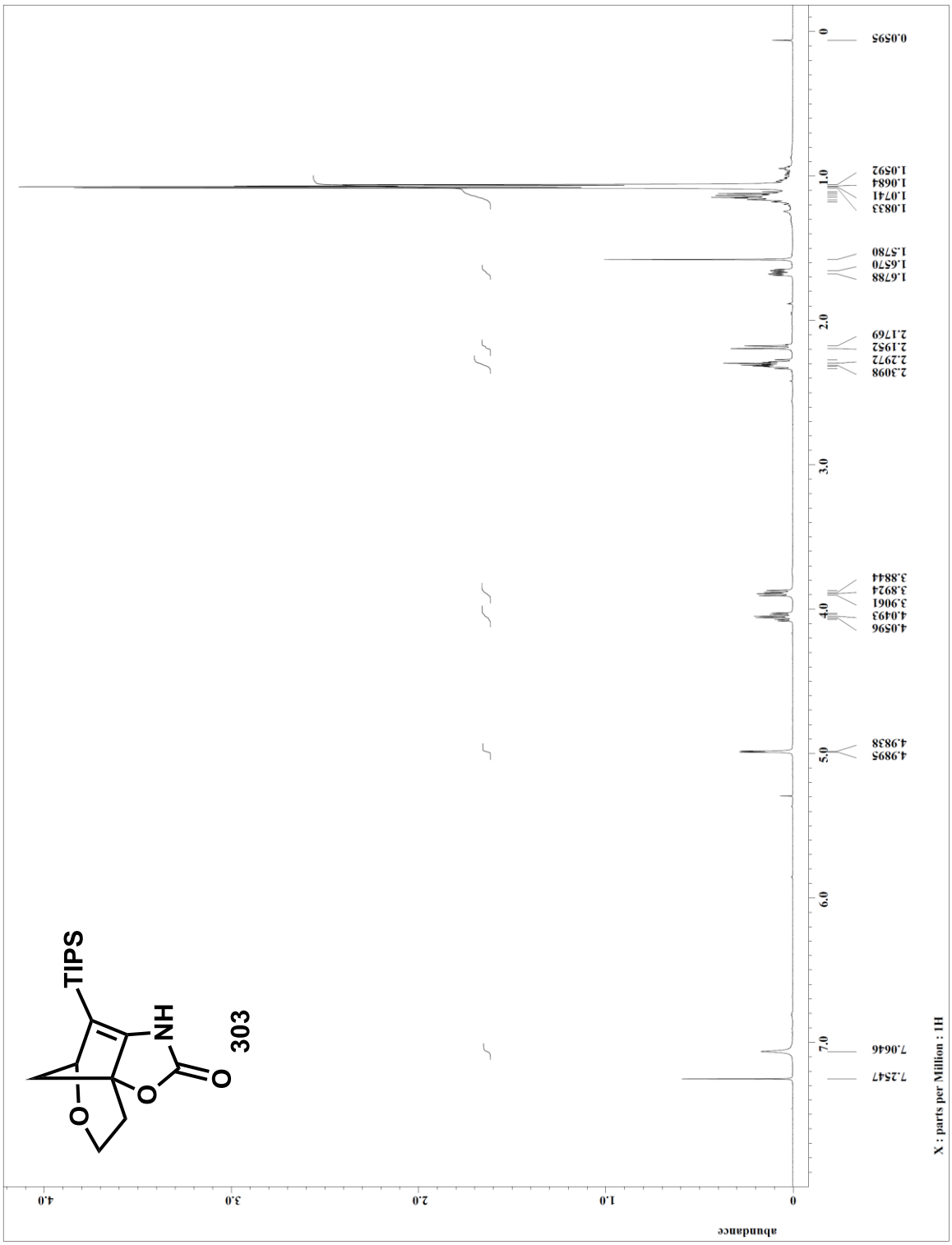

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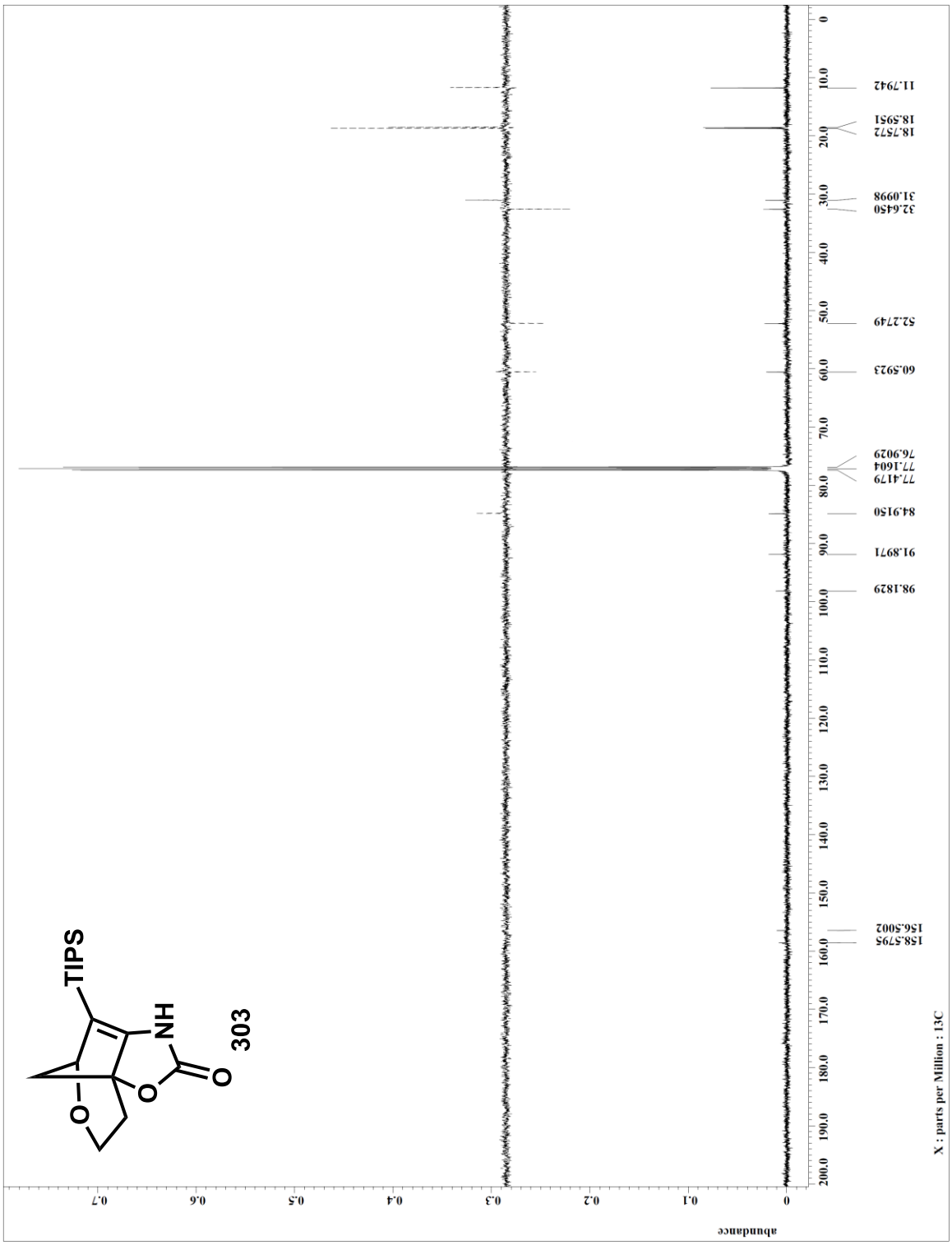
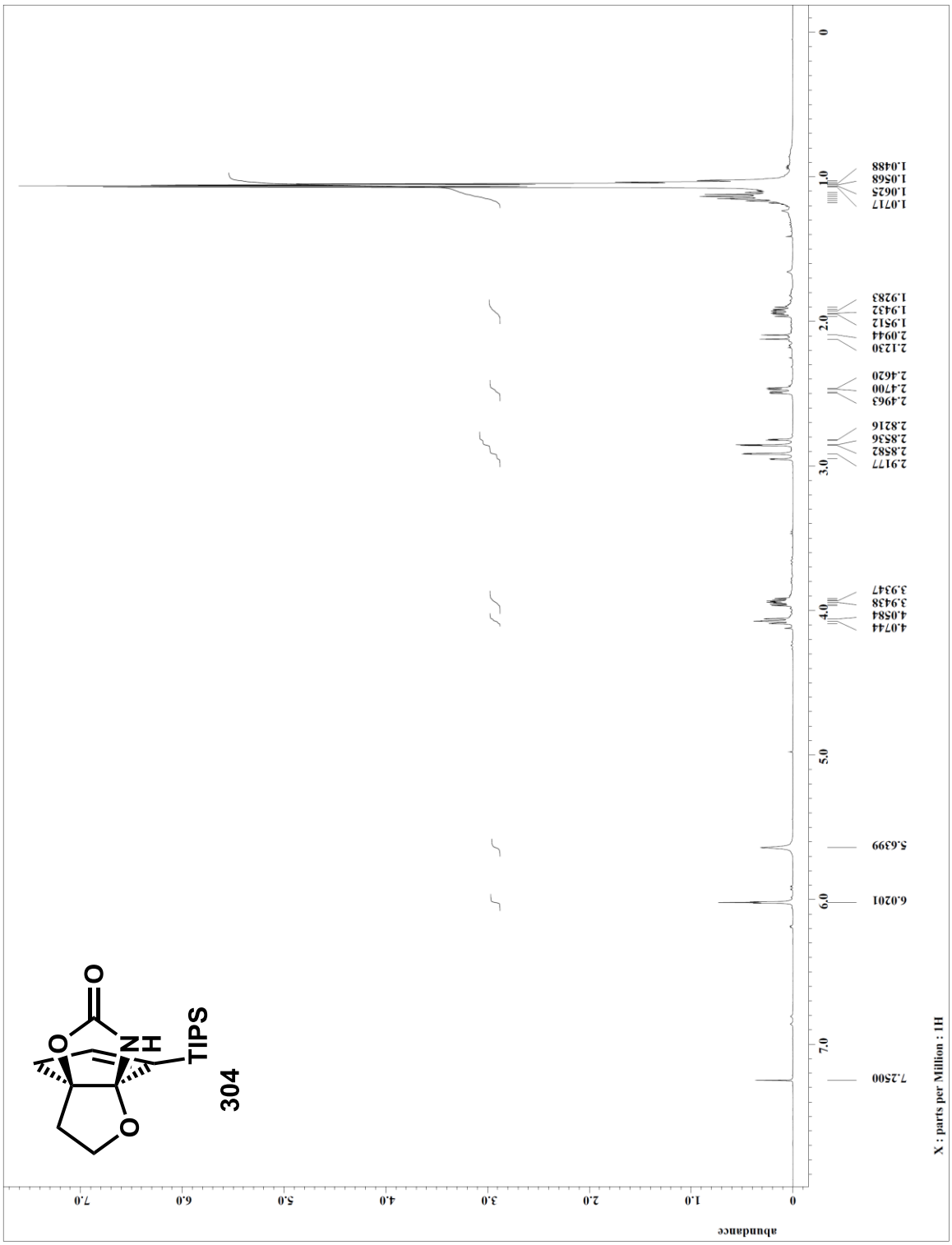


^{13}C NMR and DEPT for compound **303**



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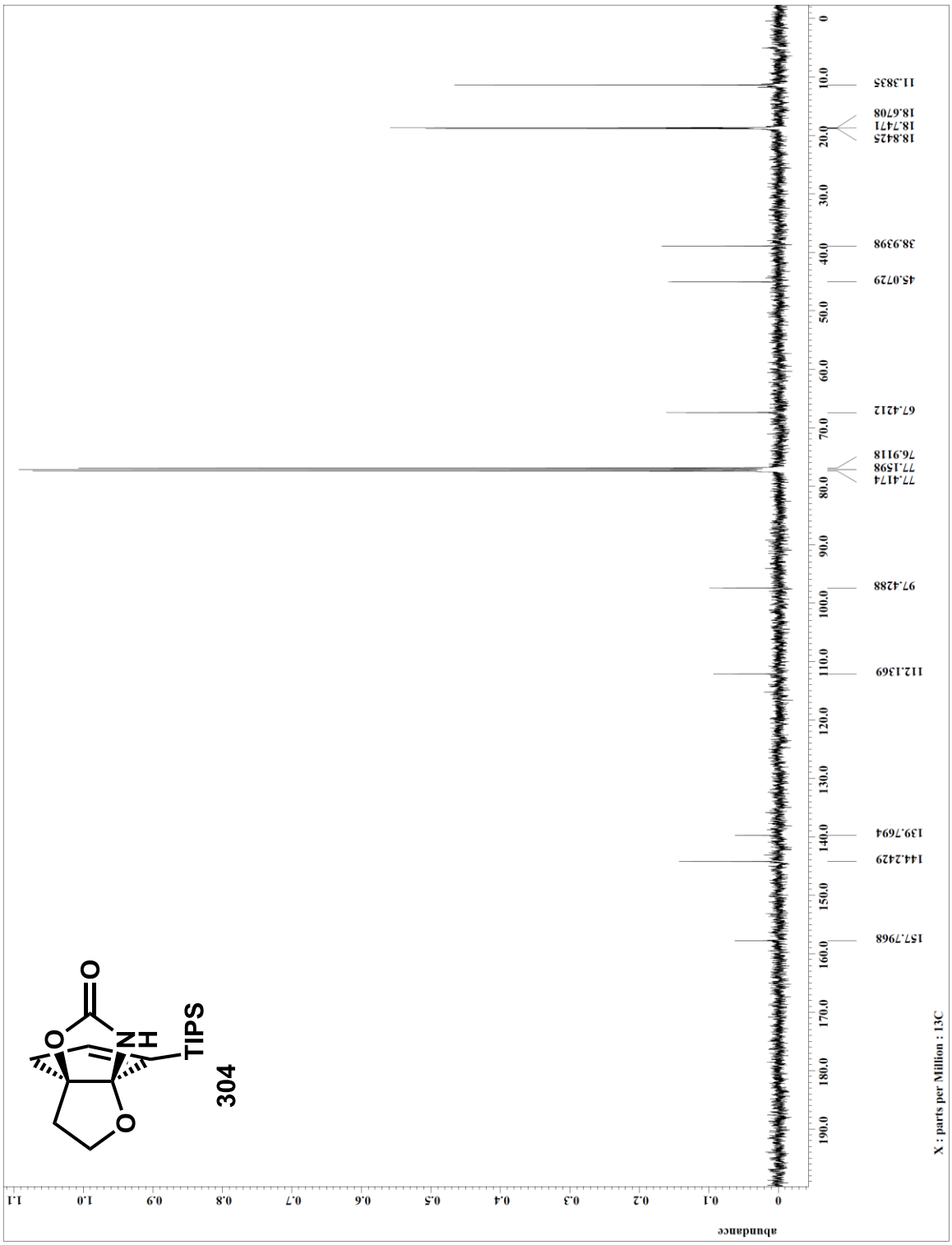

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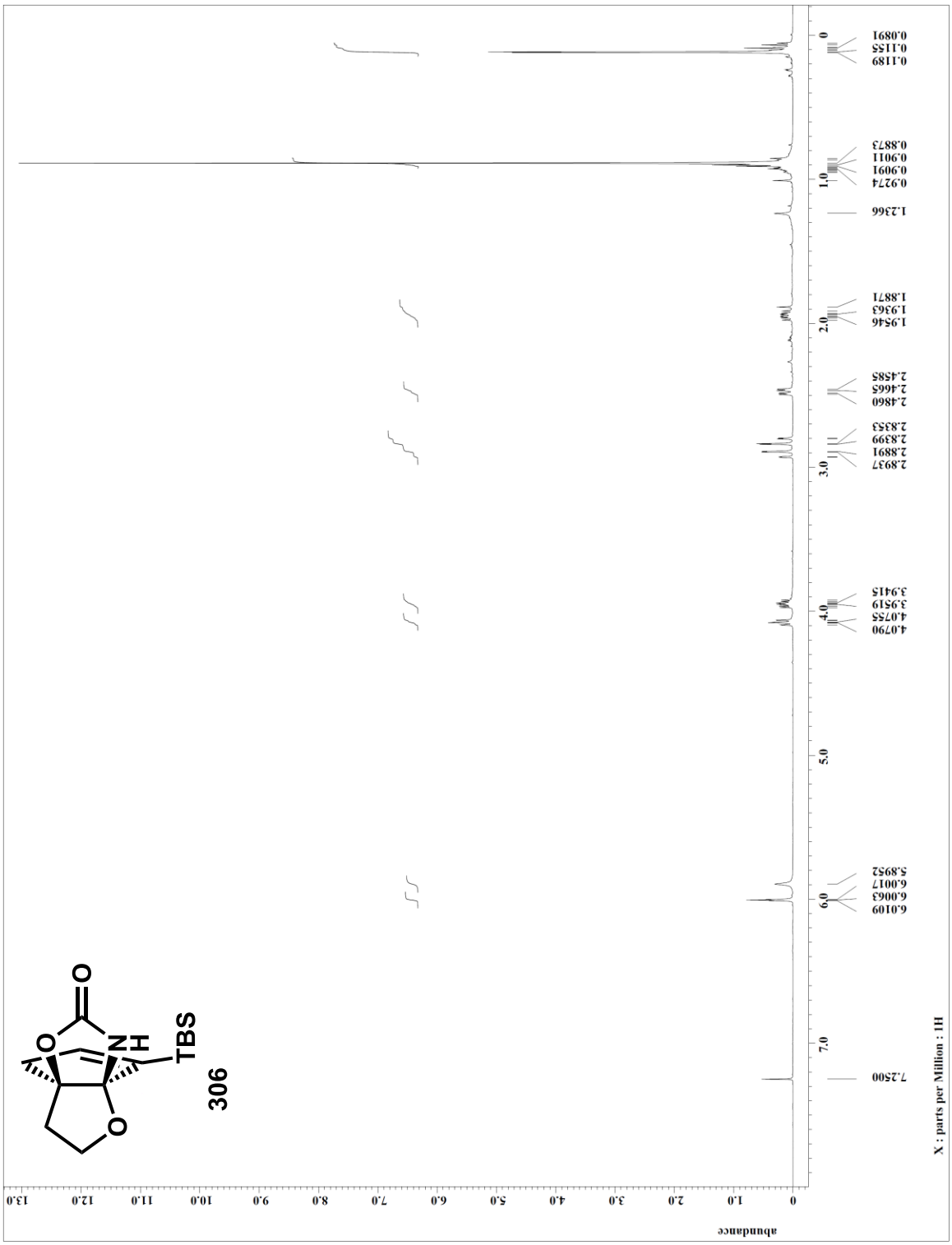

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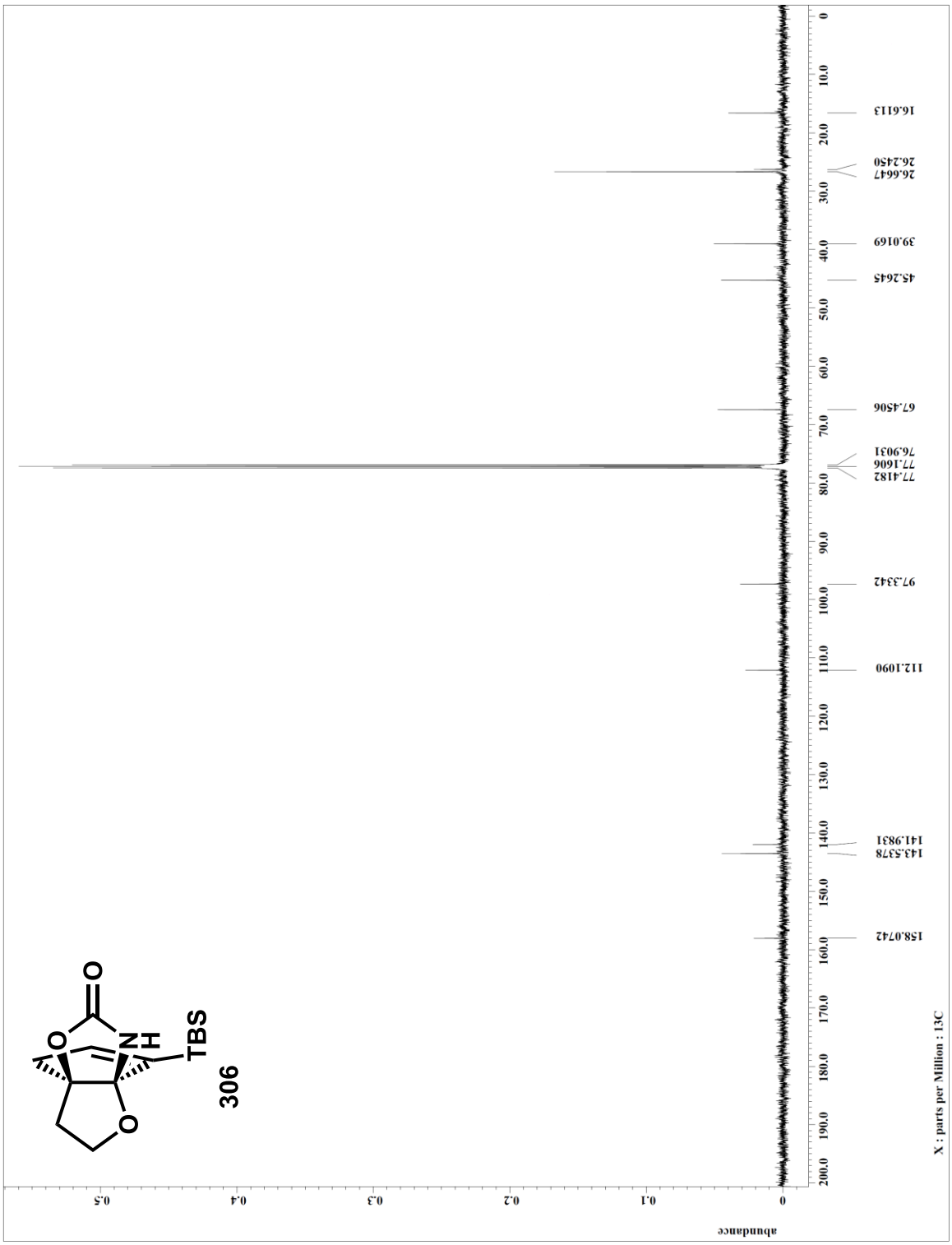

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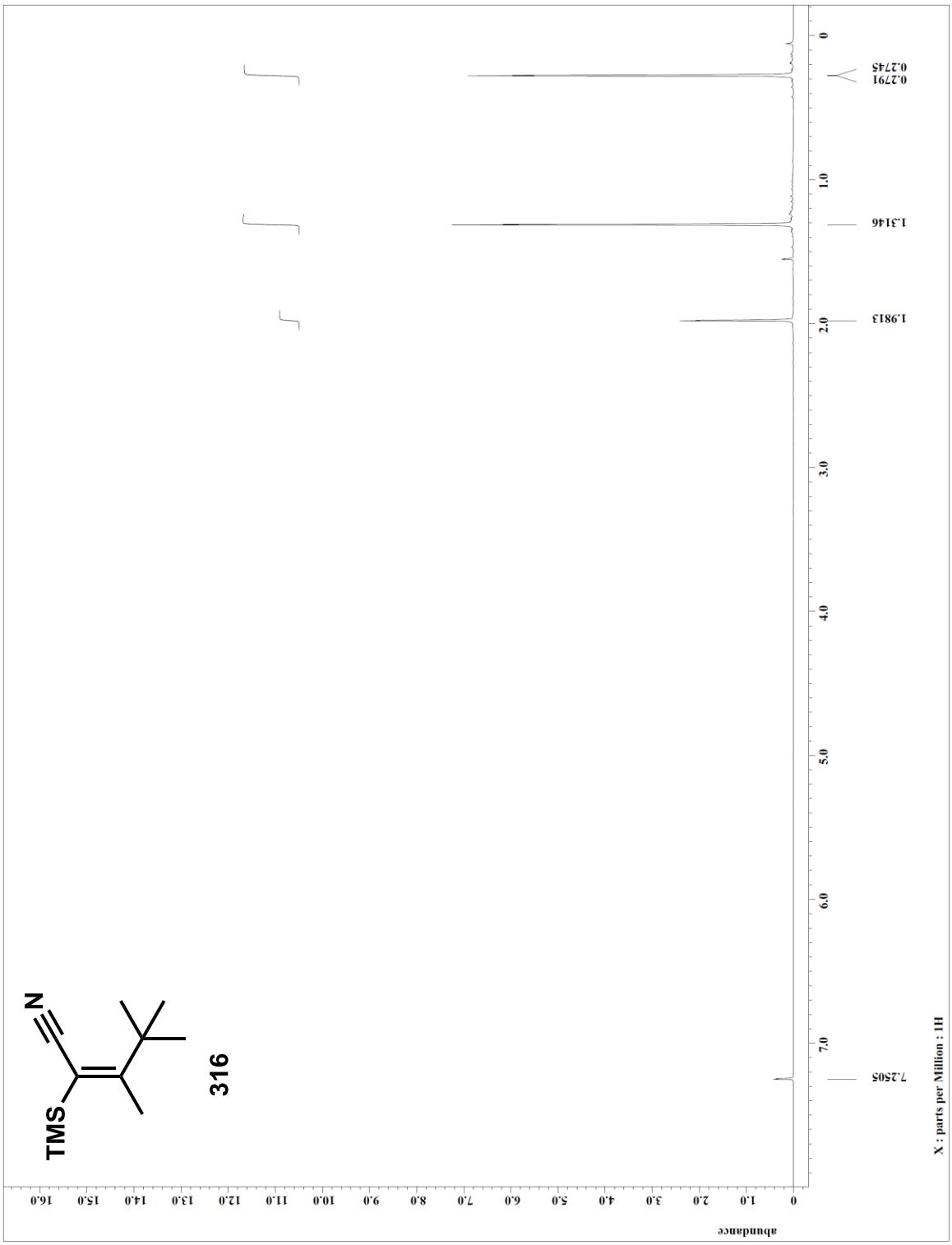

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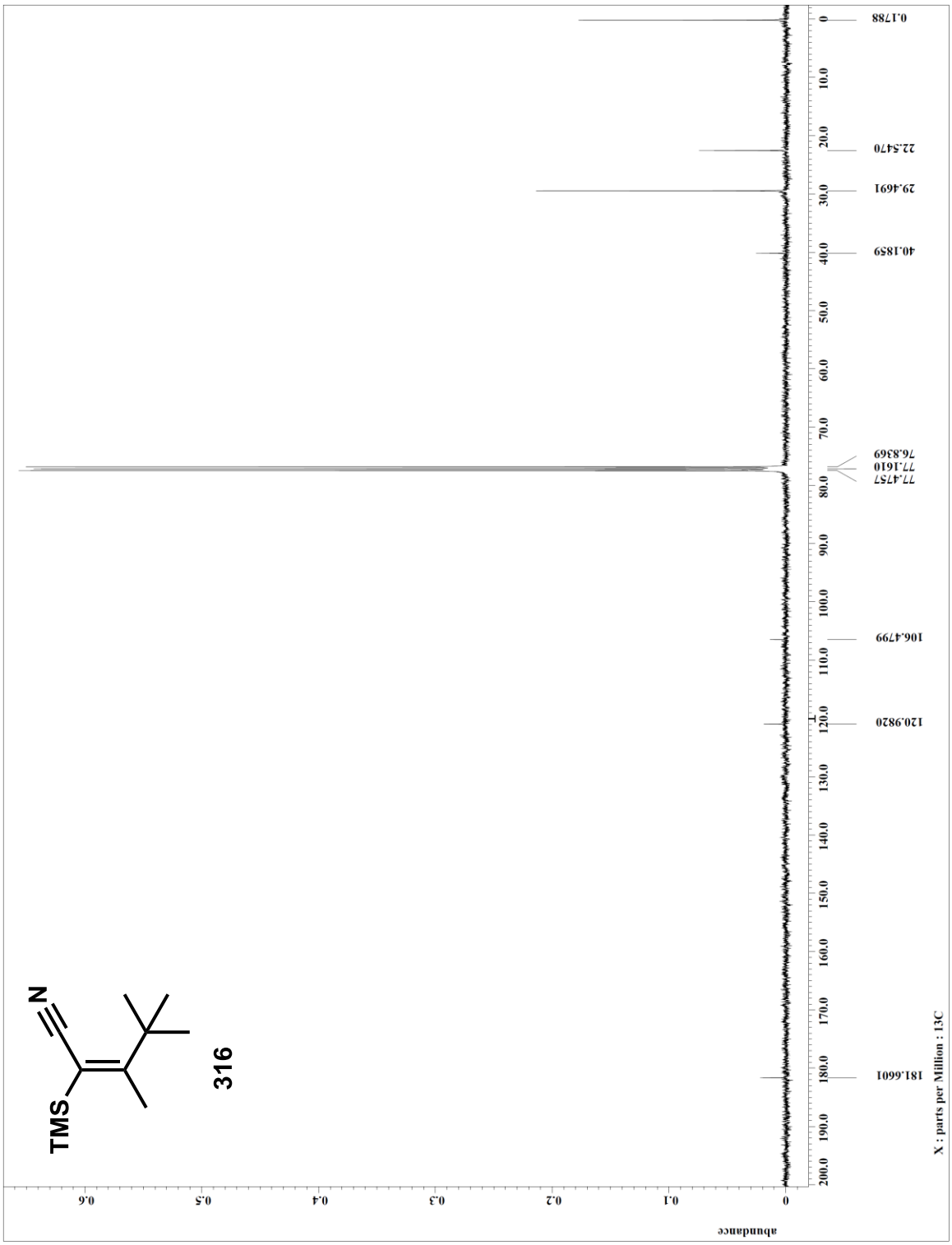

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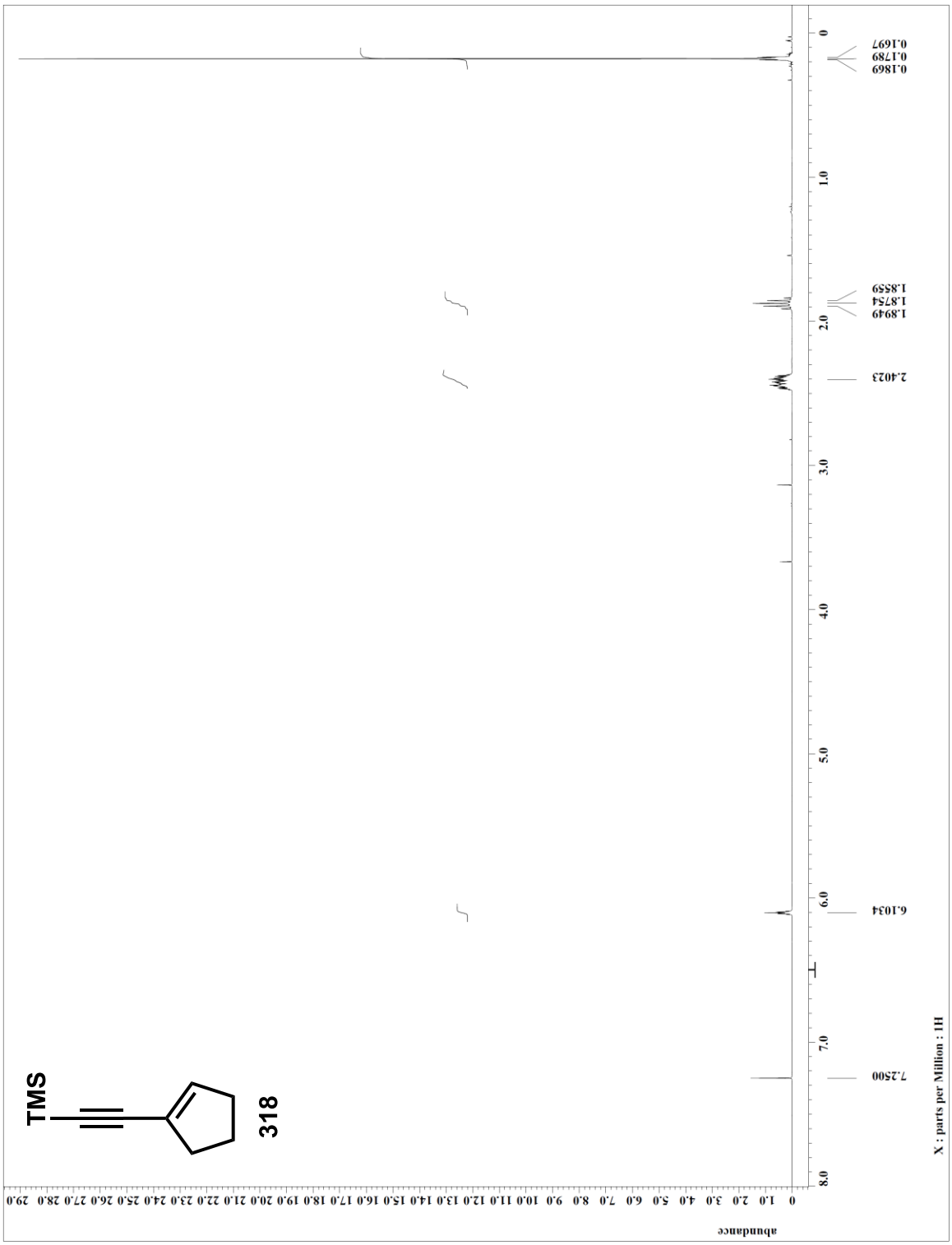
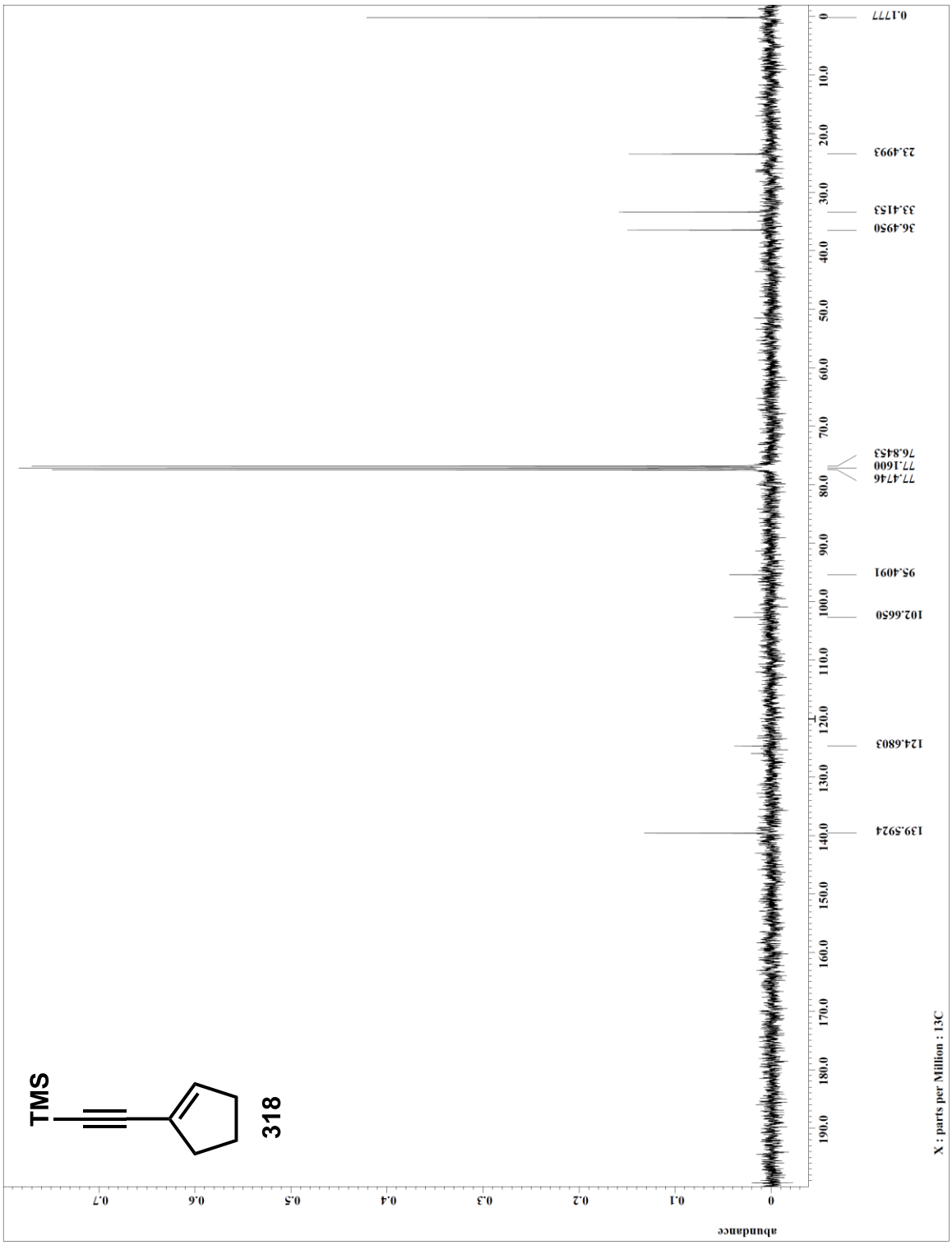


^{1}H NMR for compounds **318**



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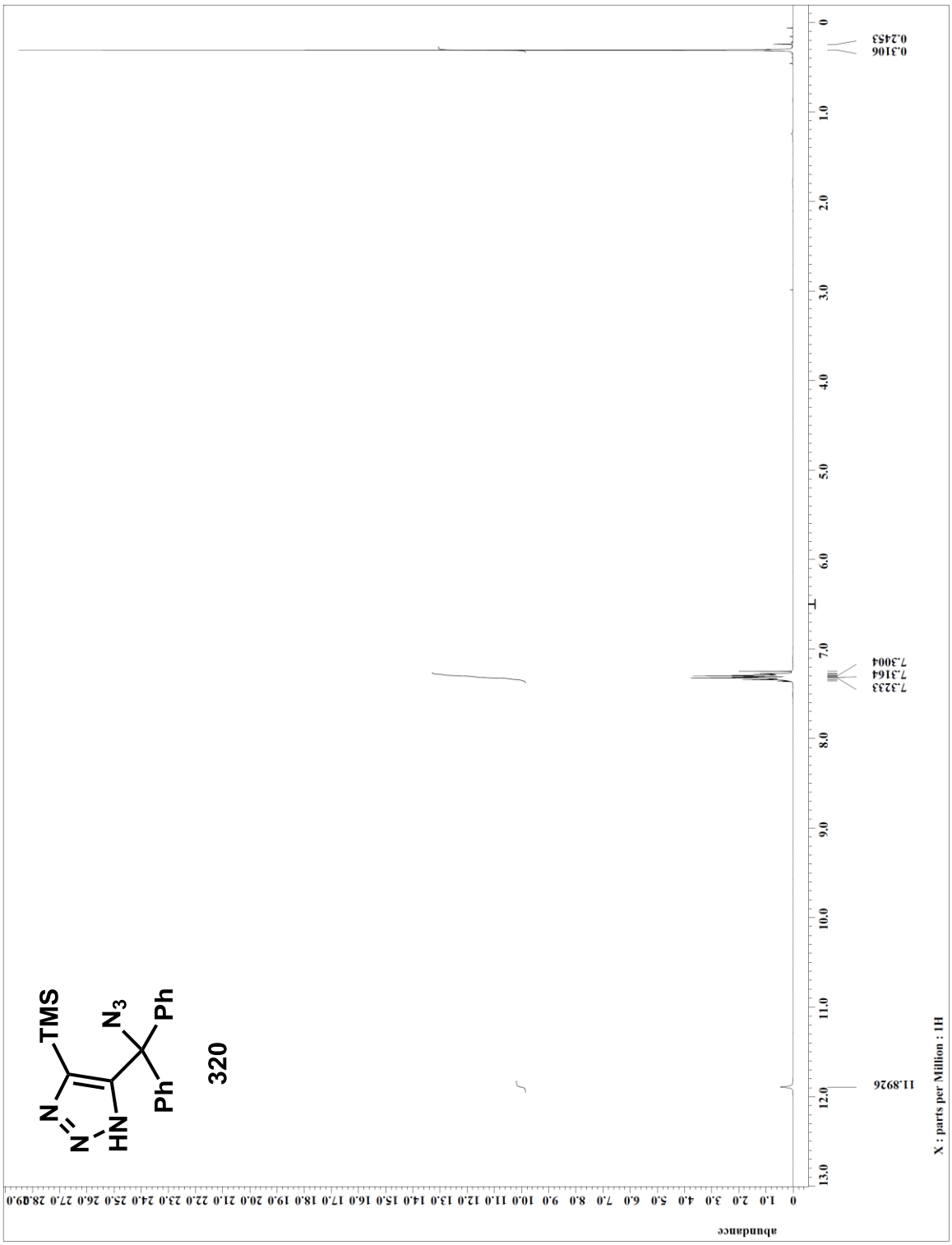

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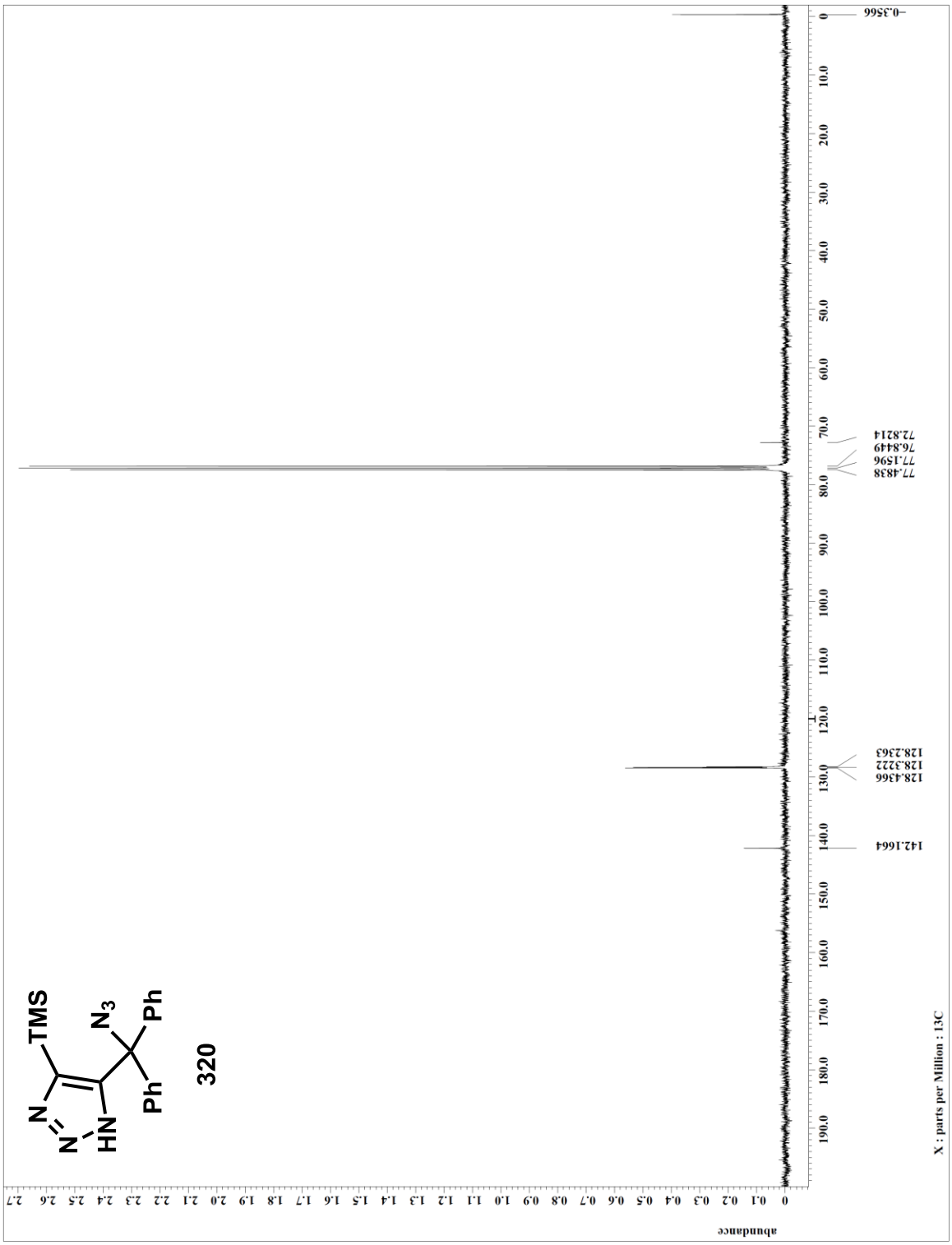


^{13}C NMR for compound **320**

4. CHAPTER IV: Enantioselective Conjugate Addition of Alkenylboronic Acids to Indole-Appended Enones

4.1. Background

4.1.1. Asymmetric Conjugated Addition of Organoboronates to Enones

Asymmetric conjugate addition of organoboronic acids and esters to α,β-unsaturated carbonyl compounds is an efficient method to construct C-C bonds. Many chiral transition metal catalysts (Cu, Rh, Pd, Zn, etc.) are known to promote the Michael-type addition of nucleophiles to α,β-unsaturated carbonyls[1]. Alternatively, chiral organocatalysts like 3,3′-disubstituted biphenol derivatives, thioureas, tartaric acids, and secondary amines can be used to facilitate this transformation to produce γ-substituted carbonyls as well.

Hayashi and coworkers were the first to report the rhodium-catalyzed asymmetric conjugate addition of organoboronic acids to enones[2].

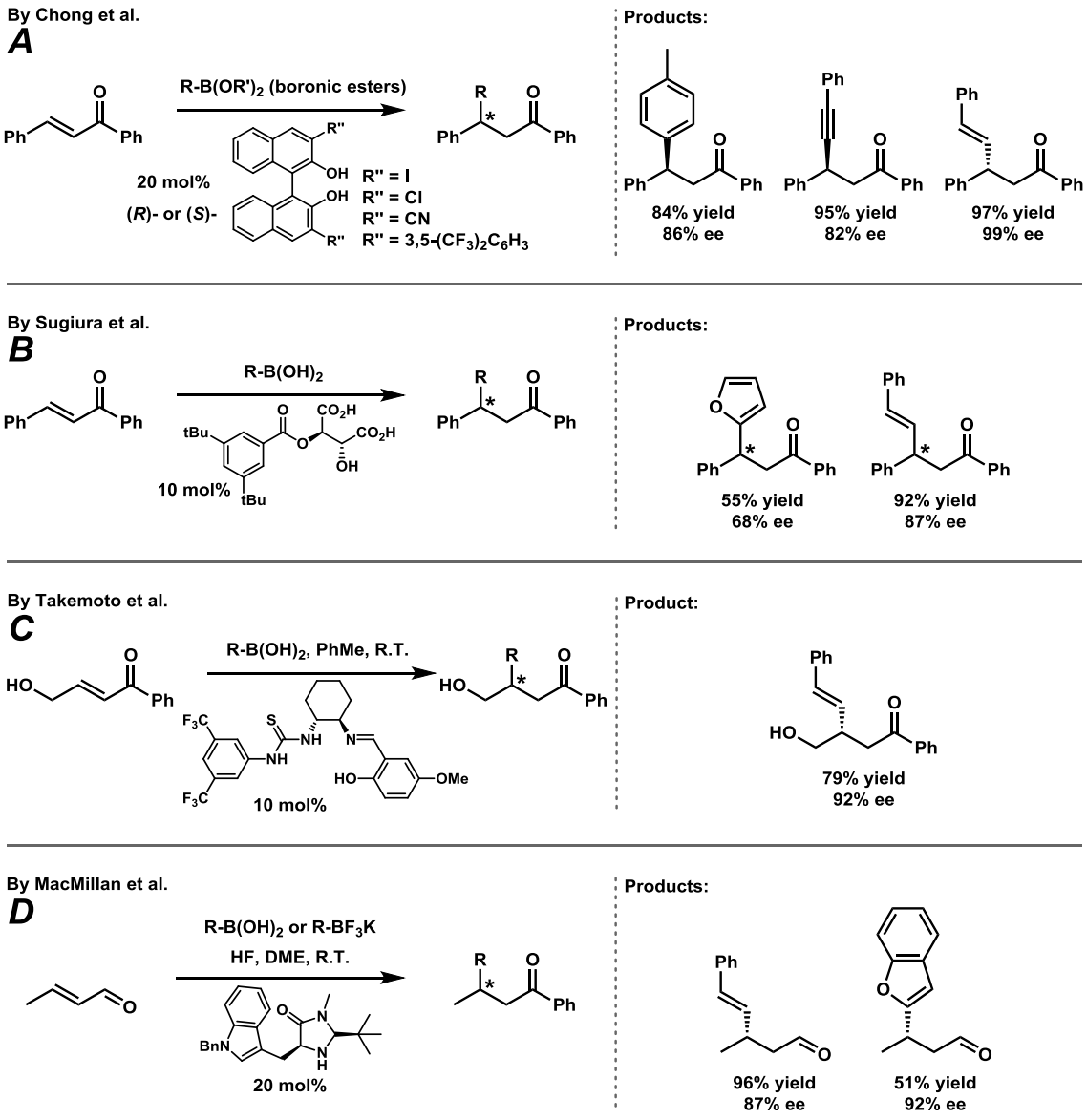
The asymmetric organocatalytic methods of 1,4-addition of organoboronates to α,β-unsaturated carbonyls are highlighted in Figure 22. Chong and coworkers used chiral BINOL derivatives to catalyze the conjugate addition of organoboronate esters to α,β-unsaturated carbonyls. Electron withdrawing groups at BINOL's 3,3′-positions are crucial for the reactivity. Alkenyl, alkynyl[3] and aryl boronic esters[4] are reactive substrates to provide enantiopure β-substituted carbonyl compounds (part **A**).

O-Monoacyl-(*L*)-tartaric acid is capable of activating boronic acids for asymmetric conjugate alkenylboration of enones. This work has been reported by the Sugiura group

(part **B**, Figure 22)[5]. Boronic acids and boronic esters are stable in the presence of water unlike Grignard reagents and organolithium compounds. They are commonly used in conjugate addition reactions to enones.

The Takemoto group reported a Michael-type addition of alkenylboronic acids to α,β-unsaturated ketones bearing a hydroxyl group[6]. The reaction requires the use of γ-hydroxy enones to ensure activation of the organoboron center via formation of tethered boronate nucleophile. Alkylated carbonyl compounds were isolated in good yields and high enantioselectivities (part **C**).

Figure 22. Examples of asymmetric conjugate addition to enones.



An asymmetric amine catalyzed conjugate addition of vinyl, heteroaryl trifluoroborate salt and boronic acid has been reported by MacMillan group[7]. Electron deficient heteroaromatic compounds are traditionally inert to iminium catalysis, unlike the heteroaromatic trifluoroborate salts or boronic acids (part **D**, presented in Figure 22).

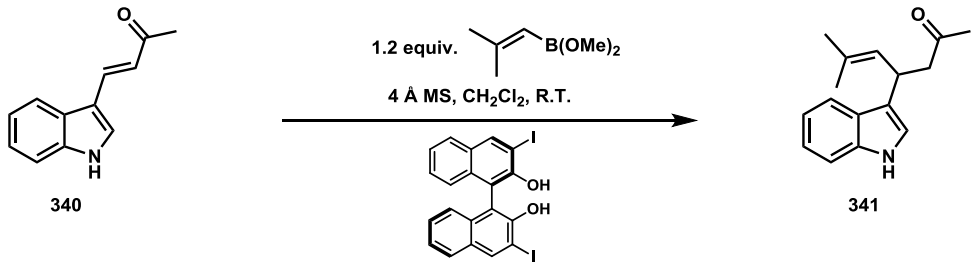
4.1.2. Importance

Many natural products have stereocenters attached to the indole core. Moreover, our group members Christabel Tanifum and Ravikrishna Vallakati were looking for an efficient method to install an alkenyl group α to an indole for the enantioselective synthesis of flinderol C, a natural product. Thus, we proposed to develop an asymmetric conjugate addition of organoboron nuchleophiles to unprotected indole-appended enones, which had not been previously described in the literature. The method was accomplished by working with Brian Lundy, another group member. Brian's part of the work has been described in detail in his Ph. D. thesis.

4.1.3. Syntheses of 3,3′-Disubstituted Binaphthols

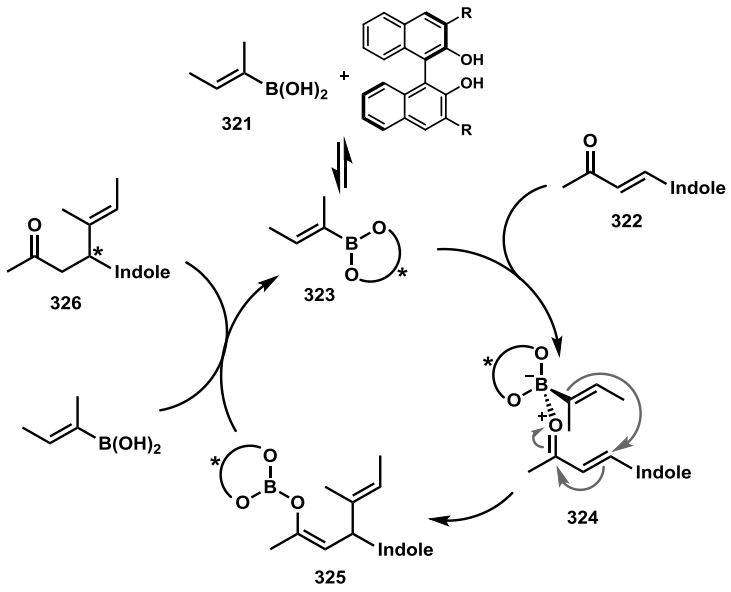
The first attempts of conjugate addition of vinyl boronic esters to unprotected indole enones did not work (Scheme 39). Changes to the nucleophile, dimethylvinyl boronic acid, produced small amounts of β-substituted carbonyl compound (entry 1, Table 14). The sluggish conjugate addition of the vinyl boronic acid to the indole-appended enone using a 3,3′-disubstituted binaphthol catalyst prompted us to try other catalysts with stronger electron withdrawing groups in the 3,3′-positions of BINOL.

Scheme 39. Conjugate addition of dimethylvinylboronic acid to indole-appended enone.



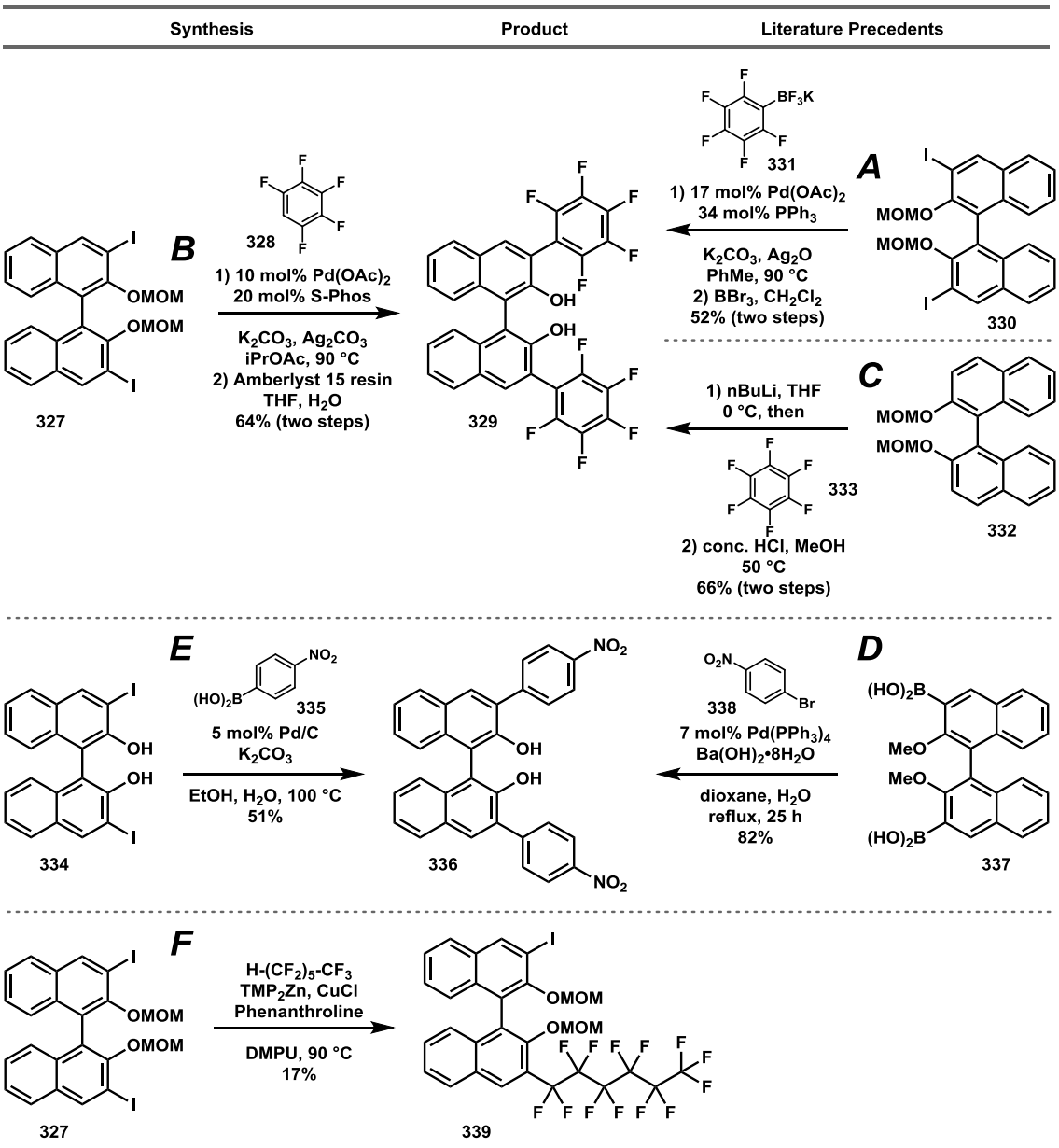
The mechanism proposed by Chong et al. for the asymmetric conjugate addition of alkenylboronates to enones is presented in Figure 23. Reaction between boronic acids and 3,3′-disubstituted binaphthol generates chiral boronic ester intermediate **323** (Figure 23). After the coordination of an indole-appended enone **322** to the boron center, 1,4-addition takes place yielding boron enolate **325**. The exchange of ligands regenerates chiral boronic ester **323** and delivers the alkylated product **326** after the protonation. The presence of electron withdrawing groups in the 3 and 3′ positions of the aromatic system is very important. Presumably, the stronger EWG withdrew the electron density from the oxygens in **323**, rendering the boron center in the boronate ester more Lewis acidic.

Figure 23. Proposed mechanism.



Thus, we attempted to synthesize 3,3′-bis(pentafluorophenyl)-BINOL (**329**), as well as 3,3′-bis(4-nitrophenyl)-BINOL (**336**). Syntheses of these two catalysts were previously described in the literature[8,9]. In order to improve the overall utility of the system, we attempted to access BINOL catalysts **329** and **336** in a more straightforward manner compared to that reported (part **A** and **D**, Scheme 40).

Scheme 40. Syntheses of 3,3′-disubstituted binaphthols.



3,3′-Bis(pentafluorophenyl)-binaphthol **329** was formed through cross-coupling 3,3'-diiodo-binaphthol **327** and pentafluorobenzene (**328**) using the protocol reported by Fagnou and coworkers[10]. After the acidic deprotection of the MOM-group, BINOL **329**

was isolated in 64% overall yield over two steps (part **B** in Scheme 40). An even better approach to this catalyst was reported, where nucleophilic aromatic substitution by an aryl lithium of **332** with hexafluorobenzene (**333**) was employed (part **C**).

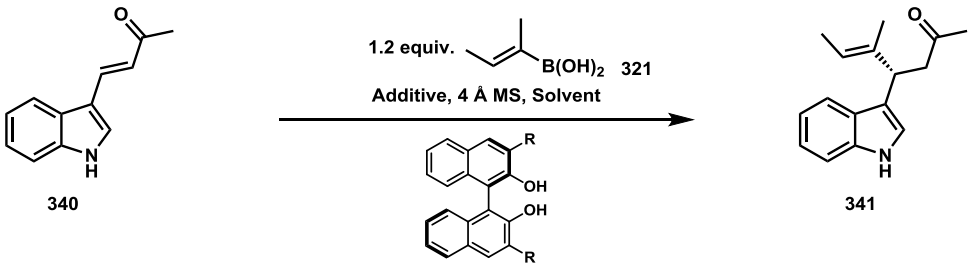
The synthesis of 3,3′-bis(4-nitrophenyl)-binaphthol **336** was straightforward (part **E**), and did not require protection of the BINOL hydroxyls[11].

We also attempted to synthesize a perfluoroalkyl BINOL catalyst as well. After testing different methods, the only conditions that allowed formation of the mono(perfluoroalkyl) BINOL **339** in low yield were from the method reported by the Daugulis group[12] (part **F**, Scheme 40).

4.1.4. Reaction Optimization

We tested the reactivity of 3,3′-bis(pentafluorophenyl)binaphthol **329** and 3,3'-bis(4-nitrophenyl)binaphthol **336** (Table 14). The reaction catalyzed by **336** was sluggish due to the poor solubility of the nitrophenyl catalyst in chlorinated solvents (entry 5). The pentafluorophenyl catalyst **329** was even more reactive than diiodo-BINOL catalyst **334** (compare entries 6 and 4). Dichloroethane was chosen as a reaction solvent due to the good solubility of reactants and worked very well for many different alkenyl boronic acids, with the exception of 2-cis-butenylboronic acid. The switch to toluene as a reaction solvent increased the yield of the alkenylated product **341** significantly (entry 11).

Table 14. Optimization of the BINOL-catalyzed conjugate addition.

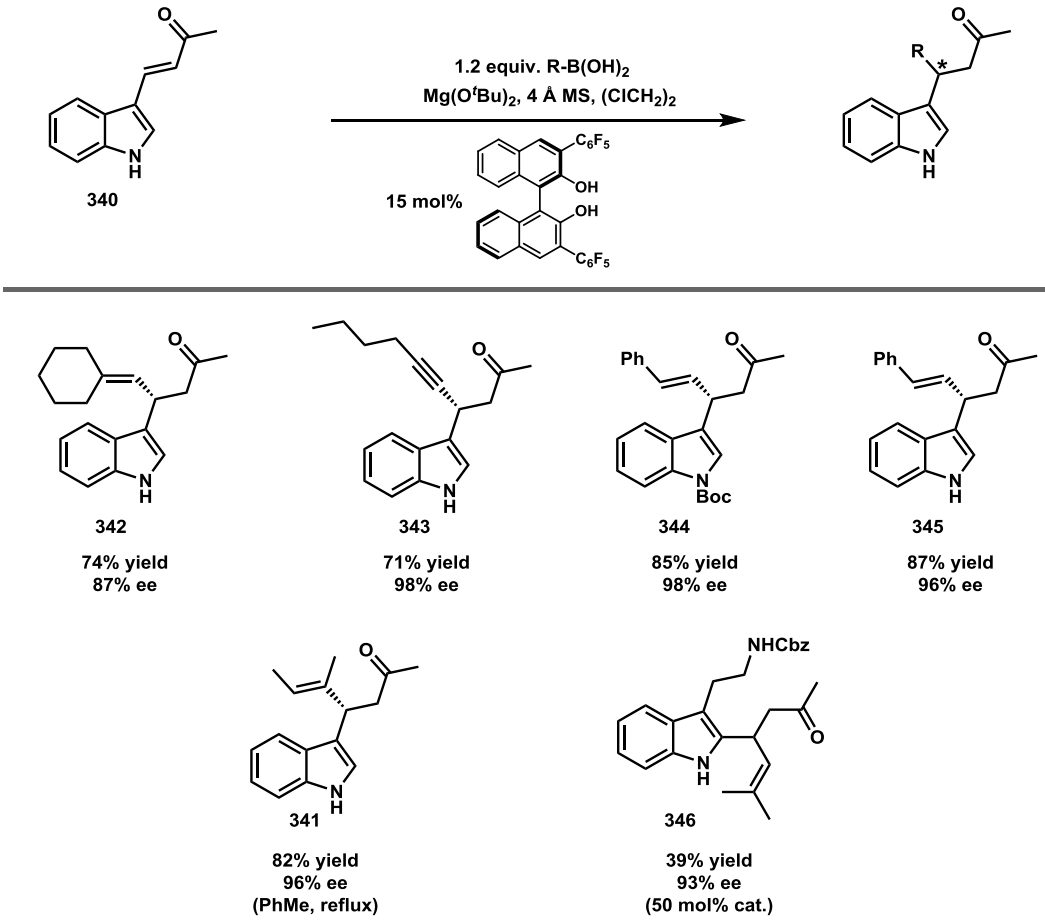


Entry	Solvent	Temp., °C	Cat. R, 20 mol%	Additive, 0.1 equiv.	Yield (SM)	ee
1	CH_2Cl_2	R.T.	I	-	<2% (85%)	-
2	THF	reflux	I	-	<2% (96%)	-
3	PhMe	70	I	-	22% (67%)	-
4	$(CH_2Cl)_2$	70	I	-	21% (77%)	-
5	$(CH_2Cl)_2$	70	4-$NO_2C_6H_4$	-	-	-
6	$(CH_2Cl)_2$	70	C_6F_5	-	32% (63%)	98%
7	$(CH_2Cl)_2$	70	C_6F_5	Cs_2CO_3	11% (81%)	-
8	$(CH_2Cl)_2$	70	C_6F_5	LiCl	38% (54%)	99%
9	$(CH_2Cl)_2$	70	C_6F_5	$Mg(OtBu)_2$	48% (51%)	99%
10	$(CH_2Cl)_2$	reflux	C_6F_5	$Mg(OtBu)_2$	49% (36%)	98%
11	PhMe	reflux	C_6F_5	$Mg(OtBu)_2$	82%	96%

4.1.5. Asymmetric Conjugate Addition to Indole-Appended Enones

Most importantly, unprotected indoles were compatible with the reaction conditions and provided functionalized indole products in good yields and high enantioselectivities. The reactivity of protected indole appended enones was also good. An alkynyl nucleophile was tested as well; alkynylated product **343** was isolated in good yield.

Scheme 41. The 1,4-addition products of indolo enones.



The only problematic substrate that we encountered was the 2-substituted indole **346**. The formation of the product was slow, and prolonged reaction times led to decomposition. It is possible that the electronics of the 2-substituted indole might negatively affect the conjugated system and the steric bulk of the nearby group at the indoles 3-position might hinder the conjugate addition of vinyl boronate as well.

4.2. Conclusions

We have developed an efficient method for the conjugate addition of different alkenyl and alkynyl boronic acids catalyzed by a chiral binaphthol catalyst[13]. Many indole-appended enones provided enantioenriched conjugate addition products. Importantly, substrates containing an unprotected indole nitrogen work very well, further increasing the applicability of our method.

4.3. Experimental

4.3.1. Materials and Methods

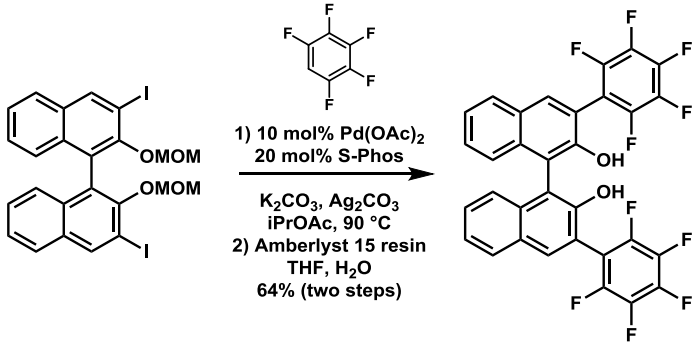
General considerations.

All the reactions were performed in flame- or oven-dried glassware. THF, Et_2O, toluene, MeCN and CH2Cl2 were purged with argon and dried over activated alumina columns. Flash chromatography was performed on 60Å silica gel (Sorbent Technologies). Preparative plate chromatography was performed on EMD silica gel plates, 60Å, with UV-254 indicator. Analysis by HPLC was performed on a Shimadzu Prominence LC (LC-20AB) equipped with a SPD-20A UV-Vis detector and a Varian Dynamax (250 mm x 21.4 mm) column. The 1H, 13C and 19F NMR spectra were recorded on a JEOL ECA-500 or ECX-400P spectrometer using TMS or residual solvent peak as an internal standard. Hexafluorobenzene (δ = -164.9) was employed as an external standard in 19F NMR spectra. Elemental analyses were performed by Atlantic Microlab Inc. of Norcross, GA. IR spectra were obtained using a ThermoNicolet Avatar 370 FT-IR instrument. Analytical thin layer chromatography was performed on EMD silica gel/TLC plates with fluorescent indicator 254 nm.

Commercially available compounds were purchased from Aldrich, Acros, and Alfa Aesar and were used without further purification.

4.3.2. Synthesis of Compounds

4.3.2.1. Synthesis of BINOL Catalysts



(*R*)-2,2'-bis(methoxymethoxy)-3,3'-bis(perfluorophenyl)-1,1'-binaphthyl

To the flame-dried Kontes flask equipped with magnetic stirbar K_2CO_3 (830 mg, 6.00 mmol), Ag_2CO_3 (414 mg, 1.50 mmol), S-Phos (148 mg, 24 mol%) and $Pd(OAc)_2$ (40.4 mg, 12 mol%) was added. The flask was evacuated and back filled with Argon (3x). To this mixture pentafluorobenzene (0.5 mL, 4.50 mmol) and *i*PrOAc (1.5 mL) was added. Reaction mixture was allowed to stir for 1 min at R.T. before the addition of 3,3'-diiodo-2,2'-bis(methoxymethoxy)-1,1'-binaphtyl (**SI-25**) (940 mg, 1.50 mmol). Reaction temperature was increased to 80 °C and stirred at this temperature for 12 h. Reaction mixture was then cooled to R.T., passed through the plug of Celite® washed with EtOAc. After the removal of solvents, reaction mixture was purified by column chromatography on silica gel using 5% EtOAc in hexanes as eluent. Product was obtained as a white solid (524 mg, 0.742 mmol, 50% yield) and the spectra data was in agreement with reported data. **^{19}F NMR** (376.17 MHz, $CDCl_3$) δ -142.39 (dd, *J* = 22.5, 8.7 Hz, 2F), -142.98 (dd, *J* = 22.5, 8.7 Hz, 2F), -158.00 (t, *J* = 20.8 Hz, 2F), -165.43 − -165.74 (m, 4F). **Elemental**

Analysis: Anal. Calcd. for $C_{36}H_{20}F_{10}O_4$: C, 61.20; H, 2.85; F, 26.89. Found: C, 61.01; H, 2.84; F, 26.63.

(*R*)-3,3'-bis(perfluorophenyl)-1,1'-binaphthyl-2,2'-diol (329)

To starting material **327** (2.25 g, 3.59 mmol, 1.0 equiv) was added MeOH (8 mL) and THF (8 mL). Amberlyst 15 resin (0.08 g) was then added and the reaction was refluxed overnight. After completion, the resin was filtered off and the solvent removed via rotary evaporation. The reaction mixture was then purified by column chromatography on silica gel using 5% ethyl acetate in hexanes as eluent. The product was a white solid (542 mg, 0.742 mmol, 98% yield). All spectral properties were identical to those reported.

4.3.2.2. Conjugated Addition Protocol

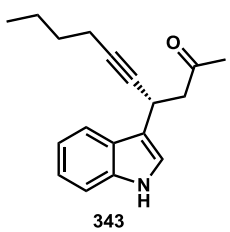
General procedure for the reaction optimiation:

A 2-dram vial was charged with a magnetic stir bar and 4Å molecular sieves and was flame-dried under high vacuum. Indole enone **SI-1**, catalyst, additive and solvent were added under Argon atmosphere. The vial was sealed, and reaction mixture was vigorously stirred at indicated temperature for 20 h. After cooling the reaction mixture to R.T., MeOH was added. The reaction mixture was filtered through the plug of Celite® and washed with MeOH. Then, 151 µL (c=0.06 M, n=0.009 mmol) of MeOH solution of 1,3,5-trimethoxybenzene (internal standard) was added. After the removal of solvents under reduced pressure, the reaction mixture was dissolved in $CDCl_3$ and transferred into the NMR tube. NMR data was collected using a relaxation delay of 30 sec. The singlet corresponding to the internal standard at 2.69 ppm was integrated as 1. Integration of the

vinyl hydrogens in the starting material (6.71 ppm) and product (5.47 ppm) gave the corresponding NMR yields, which are summarized in the optimization table. The product enantiomeric ratio was determined using analytical HPLC – Shimadzu Prominence LC (LC-20AB) equipped with UV/VIS photodiode array detector SPD-M20A with Chiralcel column. As eluent *i*PrOH in hexanes was used.

General Procedure for 1,4-Conjugate Addition

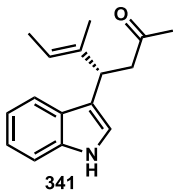
To a flask equipped with a stir bar and a condenser was added 4Å powdered molecular sieves (100 mg) and the flask was flamed-dried under high vacuum. The flask was then back filled with argon. Indole enone (0.22 mmol, 1.0 equiv), $Mg(O\textit{t}Bu)_2$ (3.8 mg, 0.022 mmol, 0.1 equiv), boronic acid (39 mg, 0.26 mmol, 1.2 equiv), and BINOL catalyst (20.4 mg, 0.033 mmol, 0.15 equiv) were then added. Freshly distilled dichloroethane (4.4 mL) was added and the reaction was heated to 70 ºC and allowed to stir at this temperature (see each product for specific reaction times). After completion, methanol was added and the reaction mixture was concentrated via rotary evaporation. The crude reaction mixture was then dry-loaded onto silica gel and purified via column chromatography on silica gel with ethyl acetate in hexanes (see each product for eluent concentrations) as eluent.



343

4-(1*H*-indol-3-yl)dec-5-yn-2-one (343). See the general procedure for 1,4-conjugate addition reaction above. The reaction time for this substrate was 24 hours. 3 Equivalents of boronic ester were used in this reaction. The crude reaction mixture was purified via column chromatography with a 10–25% gradient of ethyl acetate in hexanes as eluent on silica

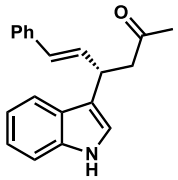
gel. (Trial 1: 43.0 mg, 0.161 mmol, 73% yield, 98.6:1.4 er; Trial 2: 40.2 mg, 0.150 mmol, 68% yield, 98.8:1.2 er). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.93 (bs, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.15-7.10 (m, 1H), 7.09-7.03 (m, 2H), 4.37-4.36 (m, 1H), 2.92 (d, *J* = 7.4 Hz, 2H), 2.12 (td, *J* = 6.9, 2.3 Hz, 2H), 2.09 (s, 3H), 1.45-1.37 (m, 2H), 1.37-1.28 (m, 2H), 0.83 (app. t, *J* = 7.4, 6.9 Hz, 3H) ppm. **^{13}C NMR** (125.77 MHz, $CDCl_3$): δ 207.3, 137.0, 125.9, 122.5, 122.1, 119.8, 119.6, 116.6, 111.6, 82.4, 81.1, 51.0, 31.4, 31.0, 25.2, 22.3, 18.8, 14.0 ppm. **IR** (neat): 3362, 2933, 1713, 1458, 1404, 1369, 1164, 1104, 741, 660, 613 $^{cm-1}$. Anal. Calcd. for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24; O, 5.98. Found: C, 80.63; H, 7.92; N, 5.16; O, 6.29. **R_F**: 0.44 in 40% ethyl acetate in hexanes.



341

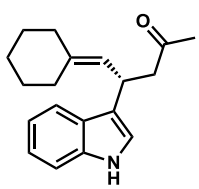
(*E*)-4-(1*H*-indol-3-yl)-5-methylhept-5-en-2-one (341). See the general procedure for 1,4-conjugate addition reaction above. The reaction time for this substrate is 18 hours. This reaction ran with toluene as solvent in a sealed tube at reflux. The crude reaction mixture was purified via column chromatography with 20% ethyl acetate in hexanes as eluent on silica gel. (Trial 1: 46.9 mg, 0.194 mmol, 88% yield, 98.7:1.3 er; Trial 2: 39.7 mg, 0.164 mmol, 75% yield, 97.5:2.5 er). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.93 (bs, 1H), 7.55 (d, *J* = 6.9 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.10 (ddd, *J* = 6.9, 1.2 Hz, 1H), 7.01 (ddd, *J* = 8.0, 1.2 Hz, 1H), 6.88 (d, *J* = 2.3 Hz, 1H), 5.52-5.45 (m, 1H), 4.09 (app. t, *J* = 8.0, 7.4 Hz, 1H), 2.87 (dd, *J* = 2.3, 1.7 Hz, 2H), 2.04 (s, 3H), 1.54 (d, *J* = 6.9 Hz, 3H), 1.44 (d, *J* = 1.2 Hz, 3H) ppm. **^{13}C NMR** (125.77 MHz, $CDCl_3$): δ 208.9, 137.0, 136.8, 127.2, 122.3, 121.7, 119.9, 119.8,

119.6, 117.8, 111.4, 47.9, 42.1, 30.3, 14.0, 13.8 ppm. **IR** (neat): 3314, 2923, 1689, 1457, 1361, 1267, 1106, 748, 647 $^{cm-1}$. $\mathbf{R_F}$: 0.42 in 40% ethyl acetate in hexanes.



345

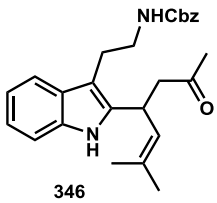
(*E*)-4-(1*H*-indol-3-yl)-6-phenylhex-5-en-2-one (345). See the general procedure for 1,4-conjugate addition reaction above. The reaction time for this substrate was 18 hours. The crude reaction mixture was purified via column chromatography with a 10–30% gradient of ethyl acetate in hexanes as eluent on silica gel. (Trial 1: 57.6 mg, 0.199 mmol, 90% yield, 98.1:1.9 er; Trial 2: 54.7 mg, 0.189 mmol, 86% yield, 98.6:1.4 er; 53.4 mg, 0.184 mmol, 84% yield, 97.7:2.3 er). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.95 (bs, 1H), 7.60 (d, *J* = 7.4 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.25 (app. d, *J* = 7.4 Hz, 2H), 7.20 (app. t, *J* = 7.4 Hz, 2H), 7.14-7.10 (m, 2H), 7.03 (app. t, *J* = 7.4 Hz, 1H), 6.98 (d, *J* = 2.2 Hz, 1H), 6.42-6.33 (m, 2H), 4.32 (dd, *J* = 14.3, 6.8 Hz, 1H), 3.03-2.92 (m, 2H), 2.06 (s, 3H) ppm. **^{13}C NMR** (125.77 MHz, $CDCl_3$): δ 208.0, 137.6, 136.9, 132.5, 130.1, 128.8, 127.5, 126.7, 126.6, 122.5, 121.5, 119.8, 117.8, 111.6, 49.4, 36.1, 30.9 ppm**. IR** (neat): 3385, 1703, 1337, 1104, 930, 772, 756, 699, 650 cm-1. $\mathbf{R_F}$: 0.55 in 50% ethyl acetate in hexanes.



342

5-cyclohexylidene-4-(1*H*-indol-3-yl)pentan-2-one (342). See the general procedure for 1,4-conjugate addition reaction above. The reaction time for this substrate was 24 hours. The crude reaction mixture was purified via column chromatography with a 10–25% gradient of ethyl acetate in hexanes on silica gel. Trial 1: 45.8 mg, 0.135 mmol, 74% yield; 93.2:6.8 er Trial 2: 38.0 mg, 0.163 mmol, 61% yield; 93.7:6.3 er. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (bs, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.26 (d, *J* = 7.8 Hz, 1H), 7.14-7.00 (m, 2H), 6.88

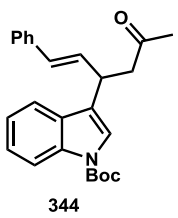
(d, *J* = 1.8 Hz, 1H), 5.17 (d, *J* = 9.6 Hz, 1H), 4.40-4.30 (m, 1H), 2.89 (dd, *J* = 15.1, 6.0 Hz, 1H), 2.69 (dd, *J* = 15.1, 8.7 Hz, 1H), 2.36-2.13 (m, 2H), 2.04 (s, 3H), 2.02-1.96 (m, 2H), 1.54-1.37 (m, 6H). **^{13}C NMR** (125.77 MHz, CDCl3) δ 208.8, 140.2, 136.8, 126.7, 124.0, 122.3, 120.8, 119.8, 119.6, 119.5, 111.6, 50.6, 37.5, 31.4, 31.0, 29.5, 28.9, 28.1, 27.1 **IR** (neat): 3343, 2926, 2859, 1700, 1459, 1444, 1340, 1260, 1107, 1015, 741 cm-1 **Elemental Analysis:** Anal. Calcd. for $C_{19}H_{23}O$: C, 81.10; H, 8.24; N, 4.98; O, 5.69. Found: C, 80.83; H, 8.38; N, 4.90; O, 5.89. **R_F:** 0.45 in 40% ethyl acetate in hexaness.



346

Synthesis of benzyl 2-(2-(2-methyl-6-oxohept-2-en-4-yl)-1*H*-indol-3-yl)ethylcarbamate (346). See the general procedure for 1,4-conjugate addition reaction above. 3 Equivalents of boronic acid and 20 mol % of 3,3'-I_2-BINOL catalyst were used in this reaction. The reaction time for this substrate was 48 hours. The crude reaction mixture was purified via column chromatography with a 10–30% gradient of ethyl acetate in hexanes as eluent on silica gel. This substrate was not dry-loaded. (Trial 1: 19.3 mg, 0.046 mmol, 61% yield (based on recovered starting material); 12.0 mg, 0.029 mmol, 30% starting material recovered, 97.1:2.9 er; Trial 2: 36.8 mg, 0.088 mmol, 57% yield (based on recovered starting material); 23.3 mg, 0.064 mmol, 29% starting material recovered; 96.6:3.4 er). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.40 (bs, 1H), 7.43 (d, *J* = 7.7 Hz, 1H), 7.26-7.19 (m, 5H), 7.05 (td, *J* = 7.7, 0.9 Hz, 1H), 6.98 (td, *J* = 7.7, 0.9 Hz, 1H), 5.35 (d, *J* = 9.1 Hz, 1H), 5.05-4.98 (m, 2H), 4.81 (bt, *J* = 5.5 Hz, 1H), 4.20-4.15 (m, 1H), 3.44-3.34 (m, 2H), 2.91-2.81 (m, 3H), 2.71 (dd, *J* = 16.9, 5.5 Hz, 1H), 2.00 (s, 3H), 1.59 (s, 3H), 1.57 (s, 3H) ppm. **^{13}C NMR** (125.77 MHz, $CDCl_3$): δ 208.4, 156.7, 138.2, 135.7, 134.7, 128.8, 128.5, 128.4, 124.1, 121.8, 119.7, 118.6, 111.0, 107.6, 66.9, 49.7, 41.8, 31.9, 31.1, 26.0, 25.1, 18.3

ppm. **IR** (neat): 3357, 2920, 1699, 1517, 1460, 1247, 1138, 1032, 742 cm-1. $\mathbf{R_F}$: 0.10 in 40% ethyl acetate in hexanes.



344

Synthesis of (*E*)-*tert*-butyl 3-(5-oxo-1-phenylhex-1-en-3-yl)-1*H*-indole-1-carboxylate (344). See the general procedure for 1,4-conjugate addition reaction above. The reaction time for this substrate was 18 hours. The crude reaction mixture was purified via column chromatography with a 10–20% gradient of ethyl acetate in hexanes as eluent on silica gel. (Trial 1: 73.5 mg, 0.189 mmol, 86% yield, 99.0:1.0 er; 72.5 mg, 0.186 mmol, 84% yield, 99.0:1.0 er). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.05 (bs, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.36 (bs, 1H), 7.24-7.11 (m, 7H), 6.39 (d, *J* = 16.0 Hz, 1H), 6.29 (dd, *J* = 16.0, 7.4 Hz, 1H), 4.26 (app. dd, *J* = 7.4, 6.8 Hz, 1H), 3.01-2.92 (m, 2H), 2.09 (s, 3H), 1.60 (s, 9H) ppm. **^{13}C NMR** (125.77 MHz, CDCl3): δ 207.1, 150.2, 137.3, 131.3, 131.0, 129.9, 128.8, 127.7, 126.6, 124.8, 122.8, 122.6, 122.4, 120.0, 115.7, 84.0, 48.6, 35.4, 31.1, 28.6 ppm. **IR** (neat): 2979, 1724, 1452, 1370, 1256, 1156, 1090, 766, 745, 694 cm-1. $\mathbf{R_F}$: 0.39 in 20% ethyl acetate in hexanes.

The spectral data for compounds **327-346** have been previously reported[13].

4.4. References and Notes

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