THE UNIVERSITY OF CHICAGO

STRATEGIES TOWARD THE TOTAL SYNTHESIS OF (+)-WAIHOENSENE

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To my family and friends

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LIST OF ABBREVIATIONS

°C	Celsius
AIBN	Azobisisobutyronitrile
DA	Diels-Alder
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DEAD	Diethyl azo dicarboxylate
DMF	Dimethyl formamide
DIAD	Diisopropyl azo dicarboxylate
DIBAL-H	Diisobutylaluminum hydride
DIPEA	Diisopropyl ethyl amine
DMAP	Dimethyl amino pyridine
DMP	Dess–Martin periodinane
DMSO	Dimethyl sulfoxide
DOSP	Tetrakis[(R)-(+)-N-(p-dodecylphenylsulfonyl)prolinato
Esp	α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid
EtOAc	Ethyl acetate
HAT	Hydrogen atom transfer
HMPA	Hexamethyl phosphoramide
IBX	Iodoxy benzoic acid
KHMDS	Potassium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
LEA	Lithium diethylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
LiTMP	Lithium 2,2,6,6-tetramethylpiperidide

L-selectride	Lithium trisec-butyl borohydride
Mander's	Methyl cyanoformate
mCPBA	m-Chloroperbenzoic acid
NaHMDS	Sodium bis(trimethylsilyl)amide
NBS	N-Bromo succinimide
Nu	Nucleophile
PDC	Pyridinium dichromate
PhS^-	Thiophenolate
PhSH	Thiophenol
PIDA	Phenyl iodo diacetate
PIFA	Phenyl iodo bis(trifluoroacetate)
TBAF	Tetra n-butyl ammonium fluoride
TBDPS	tert-Butyl diphenylsilyl
t-BuOH	tert-butanol
t-BuOK	Potassium tert-butoxide
TES	Triethylsilane
Tf	Trifyl
TFA	Trifluoro acetic acid
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Ts	Tosyl

Chapter 1

Introduction

1.1 Terpenes and terpenoids

Terpenes and terpenoids are a very large and diverse class of hydrocarbons which are produced by a wide variety of plants primarily for protection against herbivores.[1,2] They are molecules composed of repeating, rearranged units of isoprene with the general formula $(C_5H_8)_n$. Nature has bestowed these exciting molecules with a vast array of carbocyclic frameworks with a diverse array of ring systems and functional groups. Because of this complex diversity, terpenes have long attracted the attention of the synthetic community due to the challenges posed by their intriguing frameworks.[3–6]

1.2 Angular polyquinanes

Among this huge library of terpenes and terpenoids, a particularly small group of molecules has piqued the interest of the synthetic community. These molecules are angular polyquinanes which contain fused five membered rings arranged in an angular fashion (Figure 1.1). The structures of such natural products present a lot of synthetic challenge due to their highly congested frameworks and the presence of an array of quaternary centers.[7] The first natural product to be isolated with an angular polyquinane framework was isocomenes in 1977.[8,9] Since then, many

other angular triquinanes have since been isolated like silphinenes,[10,11] pentalenanes,[12,13] silphiperfolanes,[10,14] crinipellins,[15] conidiogenones,[16–18] rippertenol,[19] presilphiperfolanes,[20,21] retigeranic acid[22], bipolarolides[23] and many more.

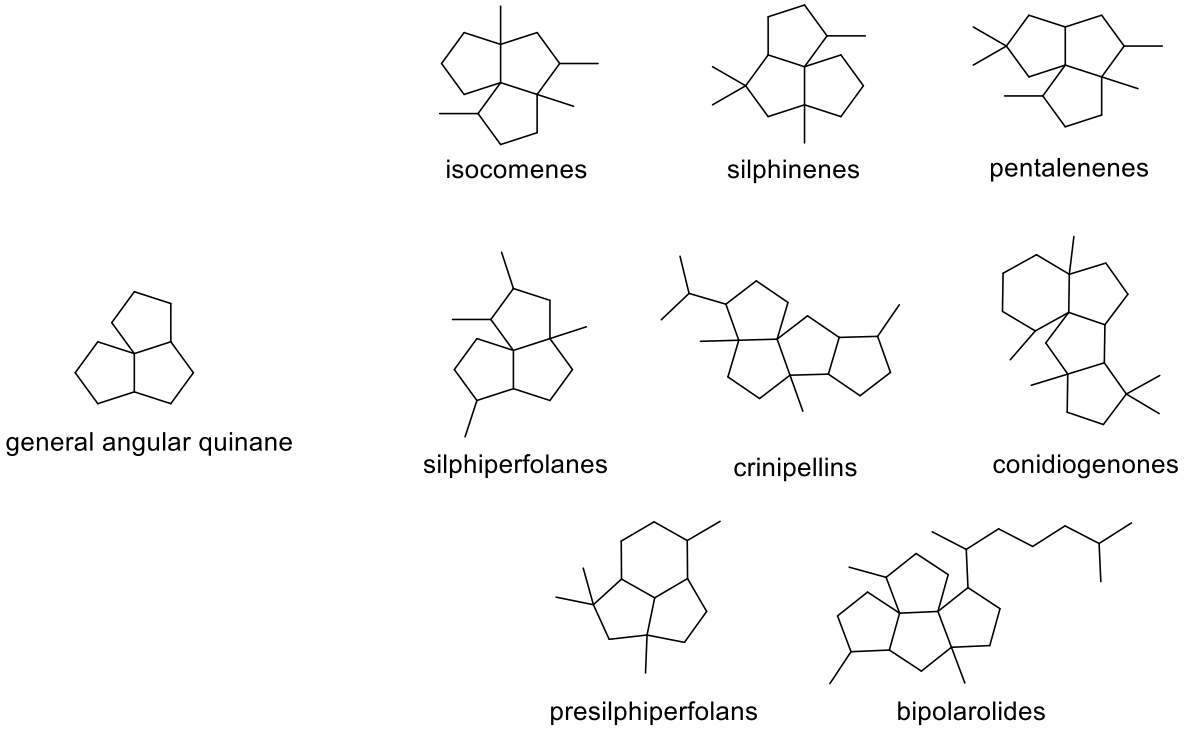
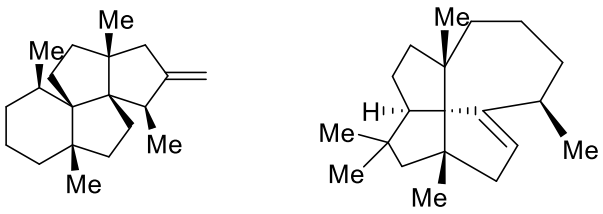


Figure 1.1: Some examples of angular polyquinanes

1.3 Waihoensene and related natural products

In 1997, the research group of Weavers isolated a very small quantity of a novel diterpene waihoensene **(1)** from the New Zealand podocarp , *Podocarpus totara var waihoensis.*[24,25] Its tetracyclic pentaleno indene carbon framework is decorated with six contiguous stereocenters and four chiral all-carbon quaternary centers. Its structure is closely related to the natural product laurenene isolated by the same group in 1979.[26,27] Laurenene **(2)** is decorated with three chiral all-carbon quaternary centers. Many angular triquinane natural products possess three all-

carbon quarternary centers (Figure 1.2). But waihoensene is the only known natural product with four contiguous all-carbon chiral quaternary center which accounts for 20% of its carbons.



1: waihoensene **2:** laurenene

Figure 1.2: Waihoensene and laurenene

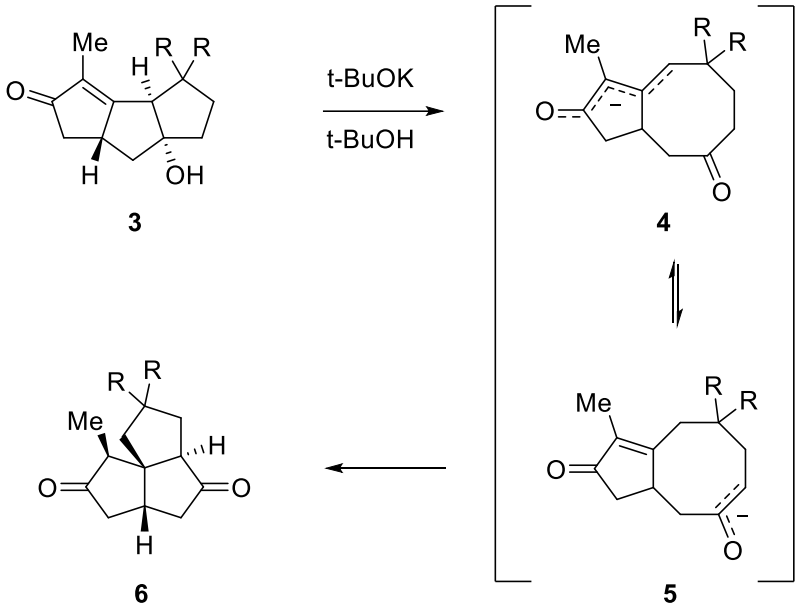
Because of its intriguing structure and the high number of quaternary centers, waihoensene has garnered a lot of interest from the synthetic community. In the next section, we will discuss some of the efforts toward its total synthesis.

1.4 Synthetic efforts toward waihoensene

Even though the unique and highly dense carbon framework of waihoensene attracted the attention of the synthetic community, its total synthesis remained elusive for two decades when finally, in 2017, Lee and co-workers (KAIST, Korea) reported the first racemic route to the natural product.[28] Before this report, a study towards the ring system of waihoensene was undertaken by Moore and co-workers (UC, Irvine) in 1999.[29] Lee's synthesis was followed by an equally creative approach from the Yang group (Peking, China)[30] and our group (Chicago)[31] in 2020 and a model study from the Wang and Tu group (China).[32]

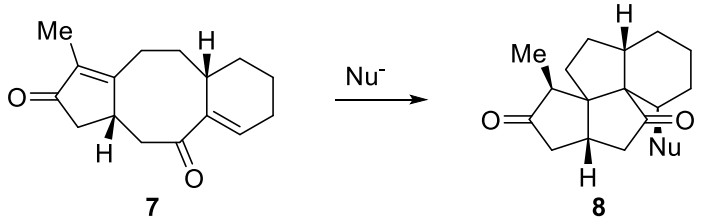
1.4.1 Moore's synthesis of the waihoensene ring system

The first synthesis of the waihoensene ring system was reported by Moore and co-workers in 1997.[29] Their analysis relied on a previously published method that certain linear triquinanes upon treatment with strong base like t-BuOk rearranged into their angular versions via a retro-aldol mechanism to give enolates **4** and **5** in equilibrium which then undergo a transannular Michael addition to give the angularly fused ring system (Scheme 1.1).[33,34]



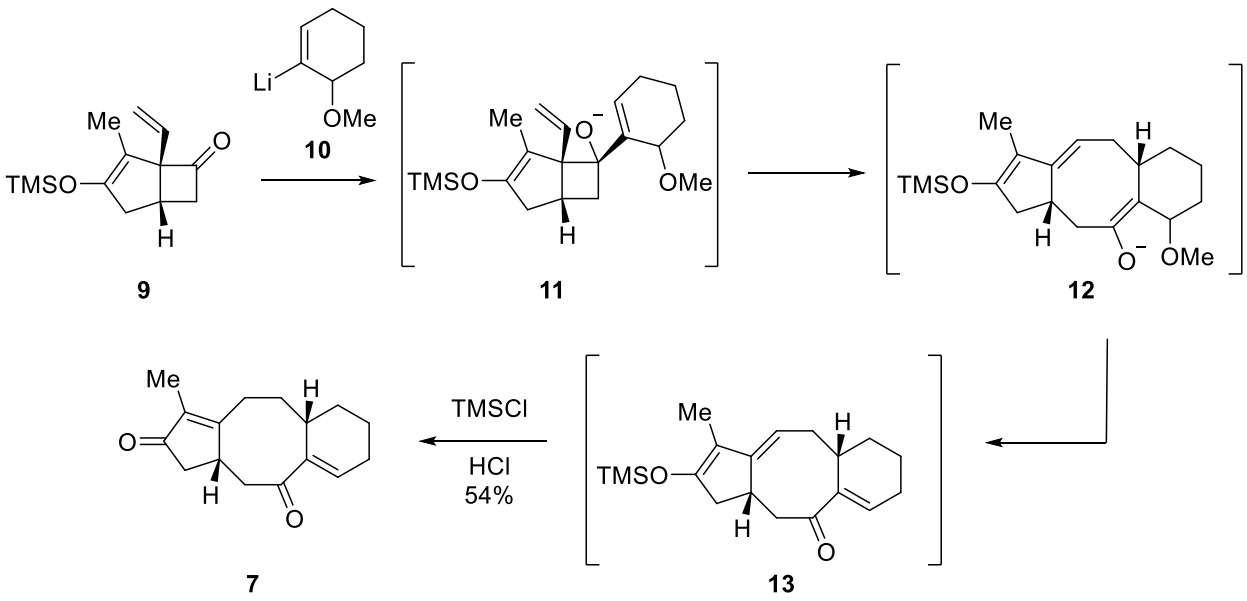
Scheme 1.1: Rearrangement of linear triquinanes

The group envisioned using a similar strategy on the compound **7** using a nucleophile to construct the tetracyclic ring system of waihoensene (Scheme 1.2).



Scheme 1.2: Strategy for the synthesis of the waihoensene ring system

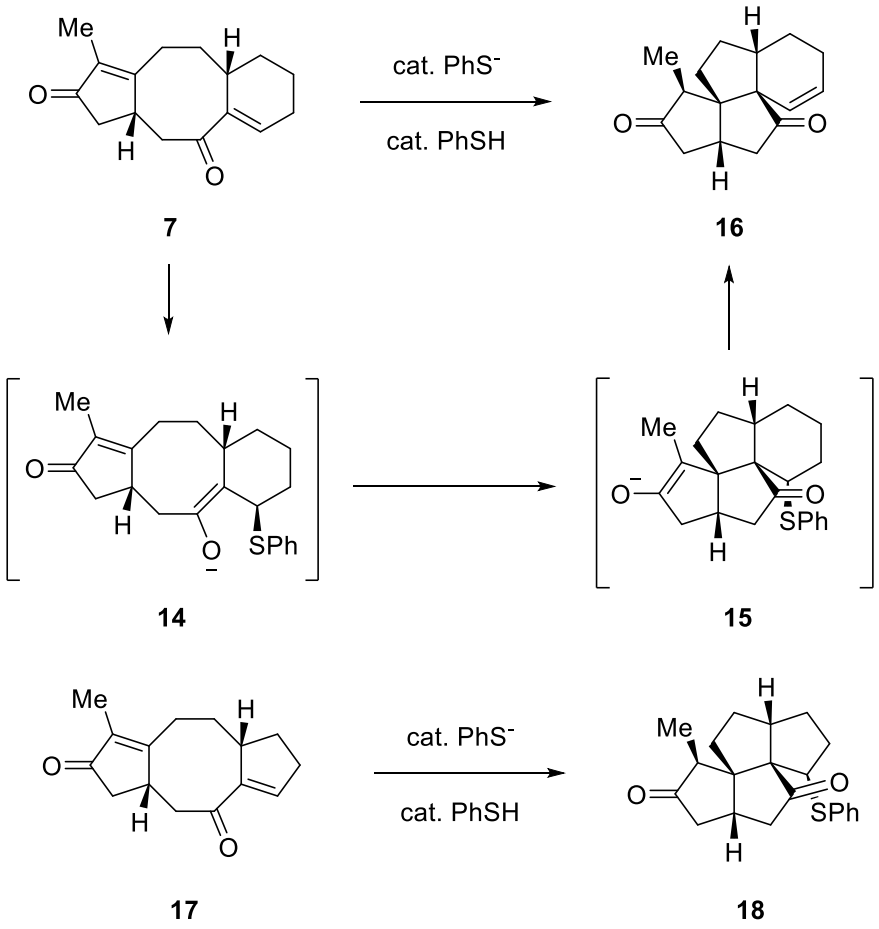
The synthesis of the key precursor **7** started with the known bicyclic compound **9**.[35] Subjecting this compound to the lithiated compound **10** generated the enolate **11** which underwent an anionic oxy-Cope rearrangement to the tricyclic compound **13** after elimination of the methoxy group of enolate **12**.[36] Acidic hydrolysis of this compound using TMSCl and HCl gave **7**, the precursor to the key retro aldol rearrangement (Scheme 1.3).



Scheme 1.3: Synthesis of the key precursor **7**

When the key precursor **7** was exposed to a catalytic amount of thiophenol and thiophenolate, the compound cleanly rearranged itself to the angularly fused tetraquinane **16** which represents the ring system of the waihoensene. This unusual transformation is hypothesized to involve a 3-step tandem sequence of events. First, the initial Michael attack of the thiophenolate anion to the more readily accessible enone from the β-face, then the attack of the thus formed enolate onto the other enone to undergo a transannular ring closure to form **15** and finally the abstraction of the β-proton anti to the thiophenol group by the enolate to effect an intramolecular E2 trans-diaxial elimination of the thiophenolate to form the tetracyclic ring

system of waihoensene and regenerate the nucleophile. When **17**, the homo analogue of the compound **7** was exposed to similar conditions, no elimination of the thiophenolate was observed and compound **18** was isolated instead. Molecular models revealed that the β-proton anti to the thiophenol group wasn't proximally located to the enone to be easily extracted (Scheme 1.4).



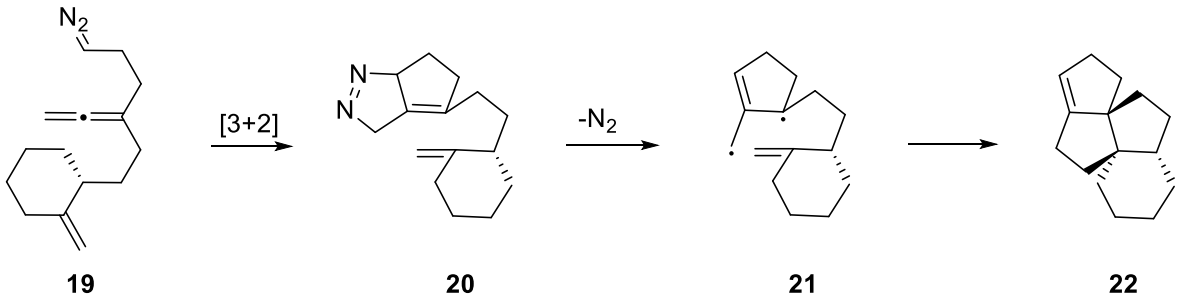
Scheme 1.4: Rearrangement to the angular triquinane

1.4.2 Lee's approach to waihoensene

Waihoensene finally succumbed to total synthesis after two decades since its isolation in 1997[24] when in 2017, Lee and co-workers finally reported a racemic approach to the molecule through

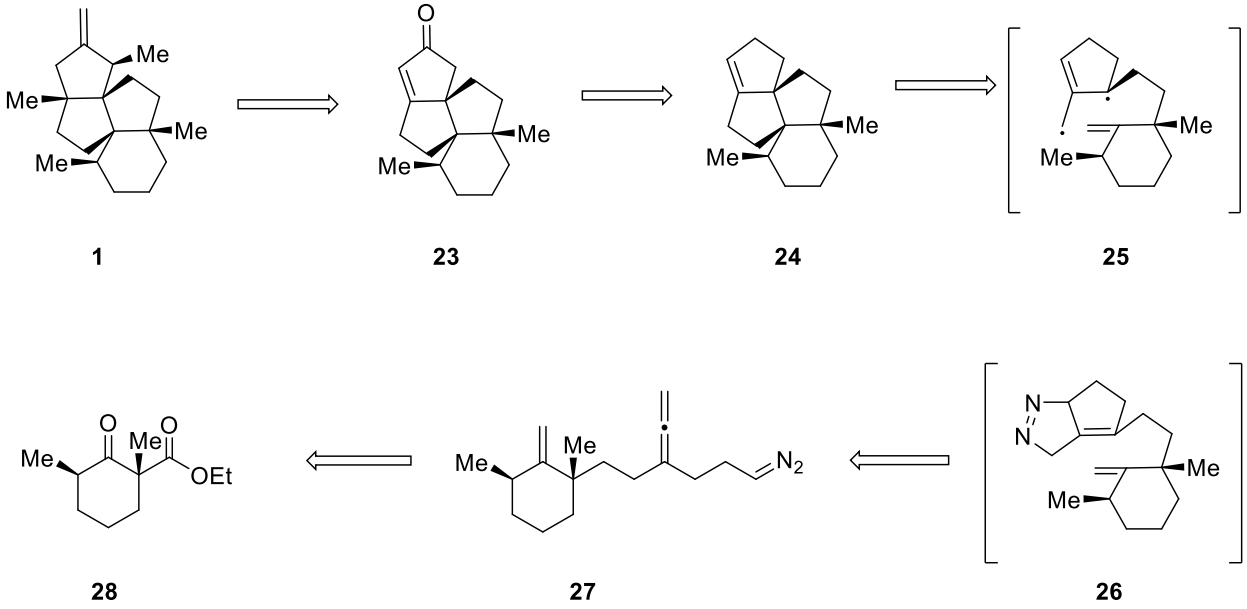
a tandem cycloaddition reaction of a diazo substrate via a trimethylenemethane diyl intermediate.

The key disconnection in the Lee strategy was the formation of the C10-C11 and the C18-C19 bonds via a [3+2] cycloaddition reaction between an alkene and a diyl intermediate **21** formed after a nitrogen extrusion from intermediate **20**[37] which in turn is formed via a [3+2] cycloaddition of diazo group and allene in intermediate **19** (Scheme 1.5).[38]



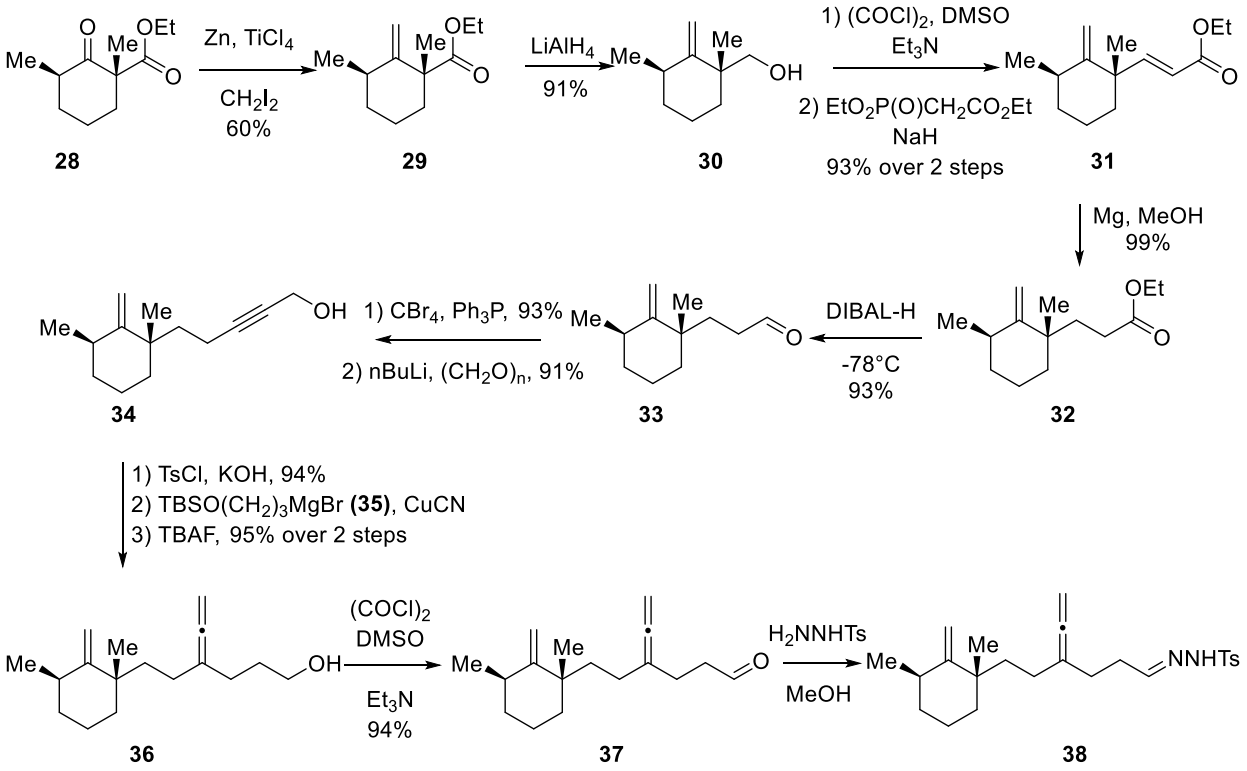
Scheme 1.5: Tandem cycloaddition strategy via diyl intermediate

In the retrosynthetic analysis, waihoensene was proposed to arise from the enone **23** (via two methyl addition steps followed by a Wittig type homologation) which in turn could be synthesized through allylic oxidation of the olefin **24**. The olefin was envisioned to be generated through the tandem cycloaddition strategy described above starting from the diazo compound **27** which is very similar to the diazo compound **19** with two additional methyl groups. The diazo compound **27** could in turn be formed from the ester **28** which can be synthesized from commercially available materials in 2 steps (Scheme 1.6).[39]



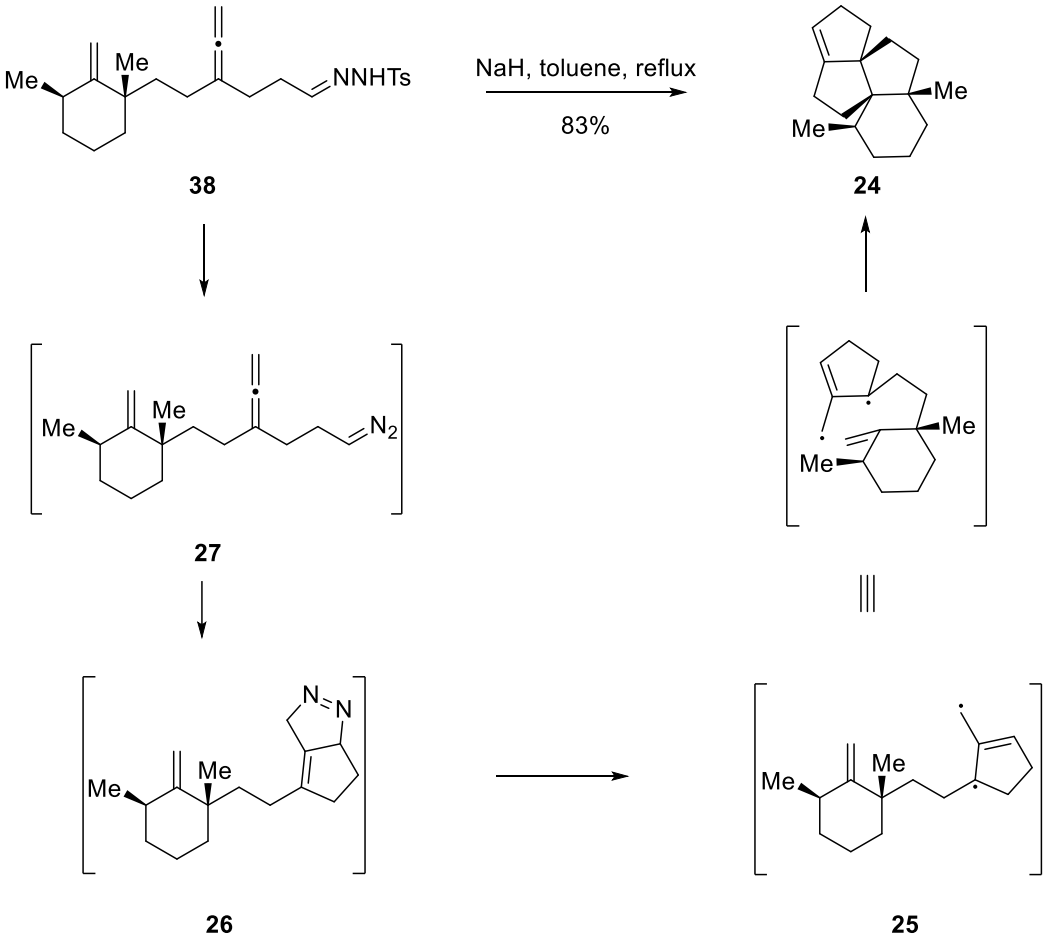
Scheme 1.6: Lee's retrosynthetic analysis

Starting from ketone **28**, a Lombardo-Takai olefination[40,41] to give ester **29** followed by lithium aluminum hydride gave the alcohol **30**. Swern oxidation followed by a Horner-Wadsworth-Emmons reaction delivered the α,β-unsaturated ester **31**. Reduction of the α,β-unsaturated ester under radical conditions using Mg in MeOH delivered the saturated ester **32** which was partially reduced using diisobutyl aluminum hydride at -78°C to produce the aldehyde **33**. Using the Corey-Fuchs procedure,[42] the aldehyde **33** was converted to the dibromide followed by formation of the alkynyl anion and hydromethylation with formaldehyde, thus furnishing the propargyl alcohol **34**. This was then converted to the allenyl alcohol **36** by tosylation of the alcohol **34** followed by an S_N2' attack of the Grignard reagent **35** and TBAF deprotection. Swern oxidation to give the aldehyde **37** followed by conversion of the aldehyde to the hydrazone gave the key precursor **38** for the tandem cycloaddition reaction to form the carbon ring framework of waihoensene (Scheme 1.7).



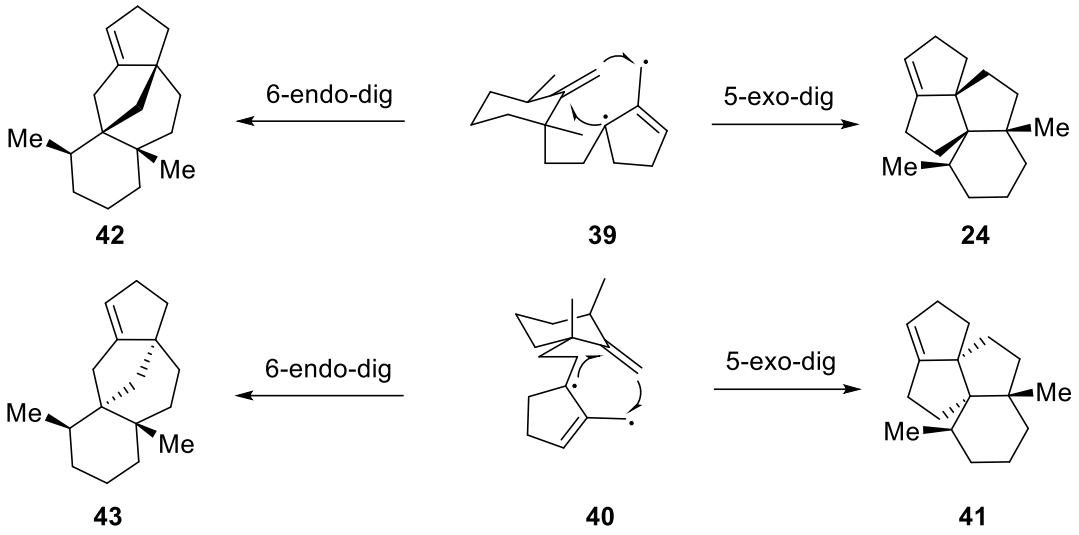
Scheme 1.7: Synthesis of the key hydrazone presursor **38**

With the key precursor for the tandem cycloaddition reaction in hand, the group endeavored to construct the tetracyclic carbon framework of the natural product. Thus, heating the hydrazone **38** with NaH under reflux conditions in toluene converted it into the diazo compound **27**[43] which underwent a [3+2] cycloaddition reaction with the allene moiety to furnish the tetrahydropyrazole **26**. Elimination of the nitrogen molecule formed the highly reactive diyl intermediate **25** which underwent another [3+2] cycloaddition with the exocyclic olefin to furnish the desired tetraquinane **24** along with other isomers (Scheme 1.8).



Scheme 1.8: Tandem cycloaddition reaction

Among all the possible isomers from the tandem cycloaddition reaction, the desired product was found to be the major product with the ratio of the desired to the undesired products being 3.3:1. This selectivity was explained by transition state analysis (Scheme 1.9). The transition state **39** which gives rise to the major product after a 5-exo-dig cyclization was presumed to be favored over the other transition state **40** because of the equatorial positioning of most substituents on the six-membered ring. The favorable 5-exo-dig cyclization then gives the desired tetraquinane product **24**.

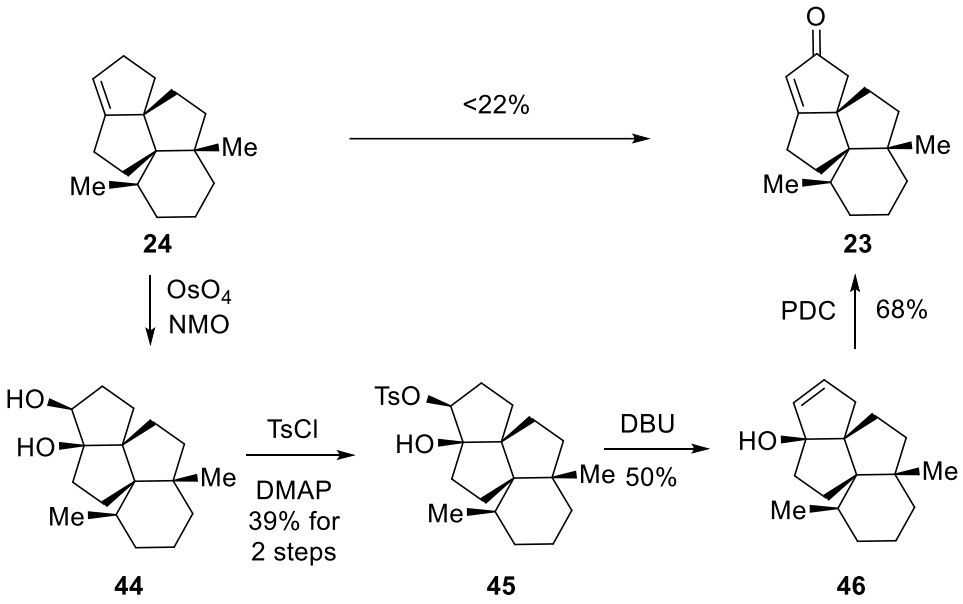


42 **39** **24**

43 **40** **41**

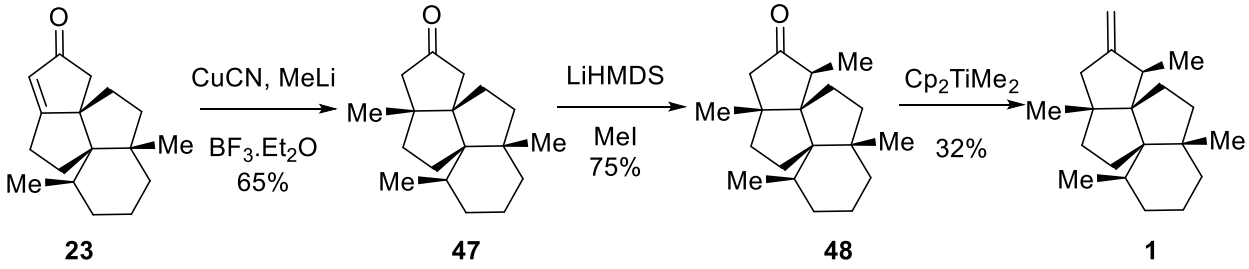
Scheme 1.9: Transition state analysis

With the tetraquinane **24** in hand, the next step involved the oxidation of the olefin to the enone **23**. Repeating the conditions from their previous synthesis of crinipellin A[44] using PDC and TBHP, along with other oxidation conditions turned out to be very troublesome producing yields of only ~22%. Therefore, they had to resort to a four-step sequence for the installation of the oxo group. Dihydroxylation of the alkene to the diol **44**, tosylation of the secondary alcohol followed by elimination gave the allylic alcohol **46**. Babler oxidation[45] of **46** then delivered the desired enone **23** (Scheme 1.10).



Scheme 1.10: Synthesis of enone **23**

The endgame of the synthesis involved the introduction of two methyl groups. Attempting the α-methylation under various conditions did not yield any fruitful results. Performing the Michael addition first, however, fortuitously delivered the ketone **47** which underwent the α-methylation reaction smoothly using lithium hexamethyldisilazane as the base giving the correct regio and stereoselectivity because of the ease of abstraction of the axial proton at the correct position. Finally, the methylenation of the ketone **48** using Petasis reagent furnished waihoensene **(1)** thus completing the total synthesis in a total of 22 steps (Scheme 1.11).

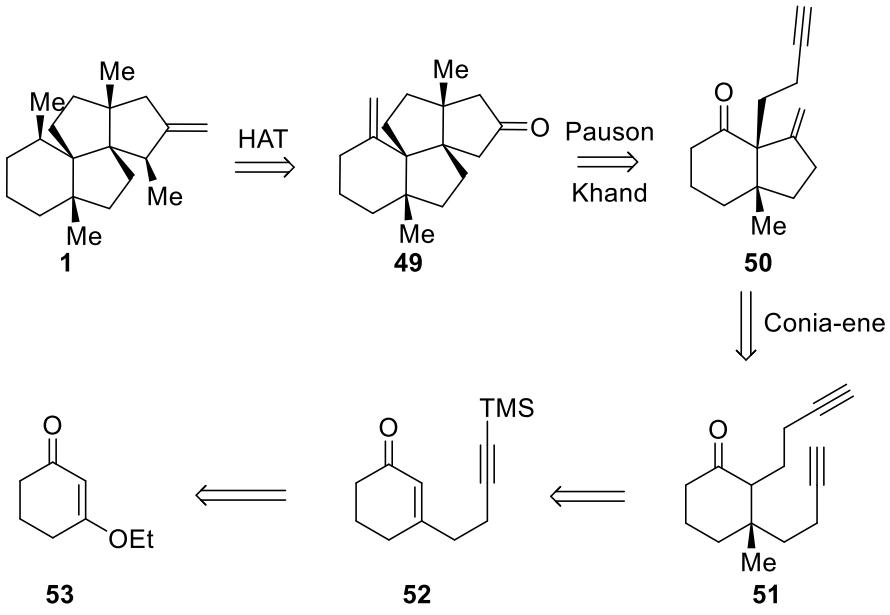


Scheme 1.11: Endgame of Waihoensene

1.4.3. Yang's strategy for waihoensene

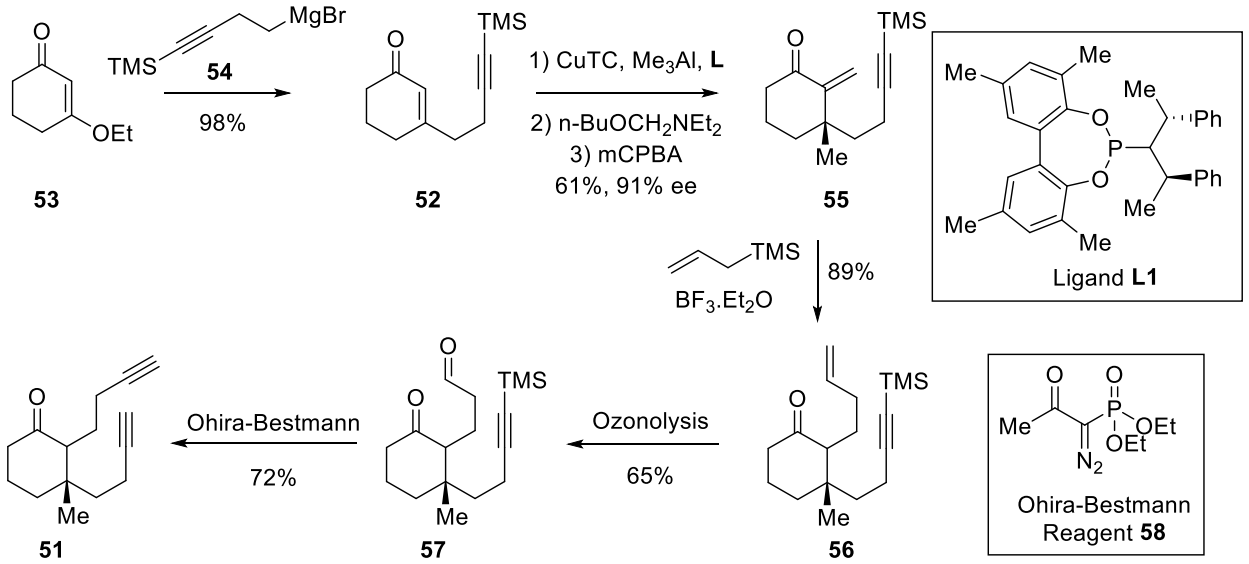
In 2020, Yang and co-workers reported the first enantioselective total synthesis of waihoensene.[30] Their approach involved a Pauson-Khand reaction to construct the tetracyclic core of the molecule and a diasteroselective hydrogenation of an exocyclic olefin via hydrogen atom transfer process.[46,47]

The retrosynthetic analysis starts with envisioning the construction of waihoensene **(1)** via a diastereoselective hydrogen atom transfer process on the exocyclic olefin **49**. This tetracyclic olefin **49** can be constructed by an intramolecular Pauson-Khand reaction[48] of the alkene **50**. This intermediate could in turn be synthesized via a Conia-ene reaction[49] starting from the dialkyne **51** which can be generated from enone **52** via a asymmetric Michael addition to set the first stereocenter of the molecule (Scheme 1.12).



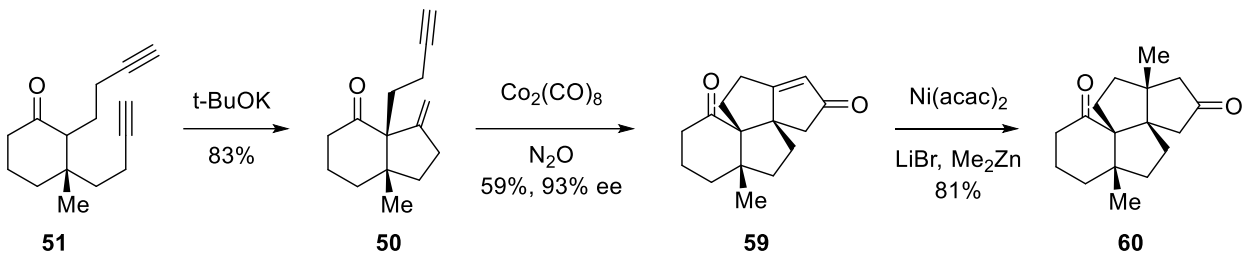
Scheme 1.12: Yang's retrosynthetic analysis

In the forward sense, starting from the commercially available vinyl ethoxide **53**, reaction with the Grignard reagent **54** provides the enone **52**.[50] Then, using the asymmetric strategy developed by Alexakis,[51] asymmetric methylation was effected on the enone **52** using the phosphine based catalyst **L1**, followed by trapping of the thus formed aluminum enolate with Eschenmoser salt to give an amino-methyl substituent at the α-position which is then eliminated to give the α,β-unsaturated enone **55**. Sakurai reaction[52] followed by ozonolysis of the formed olefin **56** delivers the aldehyde **57**. Subjecting **57** to Ohira-Bestmann reagent **58** converts the aldehyde to the alkyne and deprotects the TMS group in-situ to deliver the chiral dialkyne **51** (Scheme 1.13).



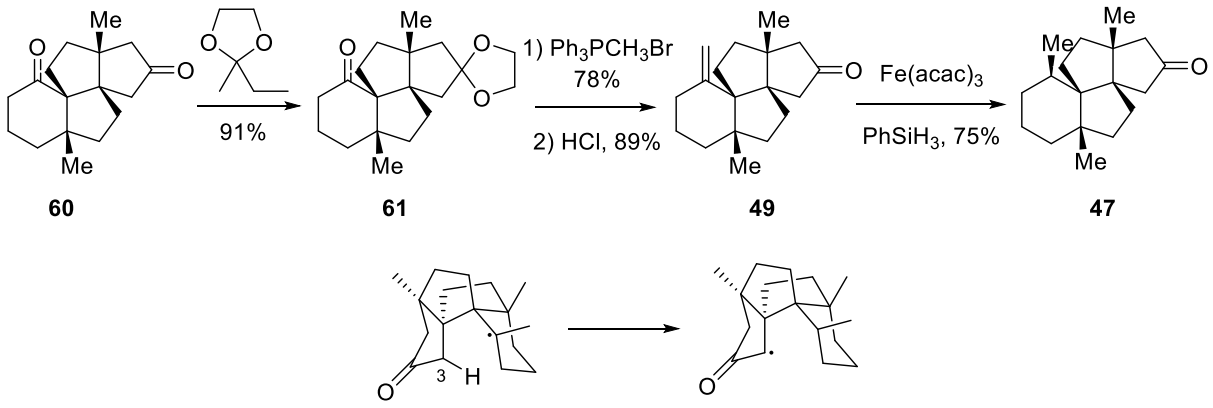
Scheme 1.13: Synthesis of Conia-ene precursor

With ketone **51** in hand, the Conia-ene reaction was achieved diastereoselectively using a strong base like t-BuOK[53] to deliver the bicyclic precursor **50** for the key Pauson-Khand reaction. After extensive experimentation, using $Co_2(CO)_8$ in N_2O atmosphere[54] delivered the desired angular tetraquinane **59** in 59% yield. Then, a Ni-catalyzed methylation[55] of enone **59** delivered the diketone **60** (Scheme 1.14).



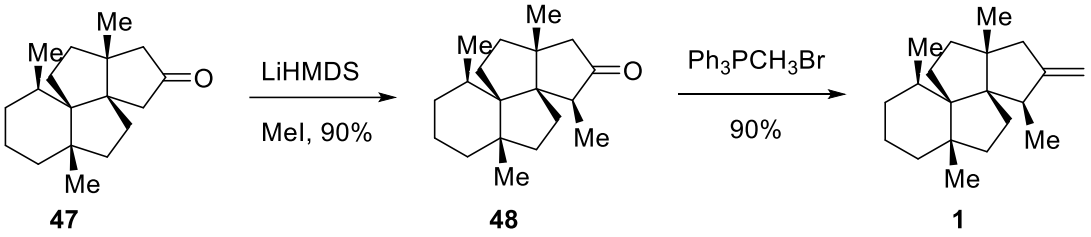
Scheme 1.14: The key Pauson-Khand reaction

The next step was the stereo and regioselective installation of the methyl groups at the C3 and C9 positions. To that end, protection of the unhindered ketone[56] followed by wittig olefination delivered the olefin **49**. Hydrogenation of the double bond using conventional transition metal catalysts delivered the compound with the wrong stereochemistry. Using HAT chemistry, however, the correct stereoisomer was achieved because the radical at C9 (formed after reduction) abstracts a proton from the C3 position present on the concave face due to its proximity thus only giving the methyl group at the top face (Scheme 1.15).



Scheme 1.15: HAT reaction

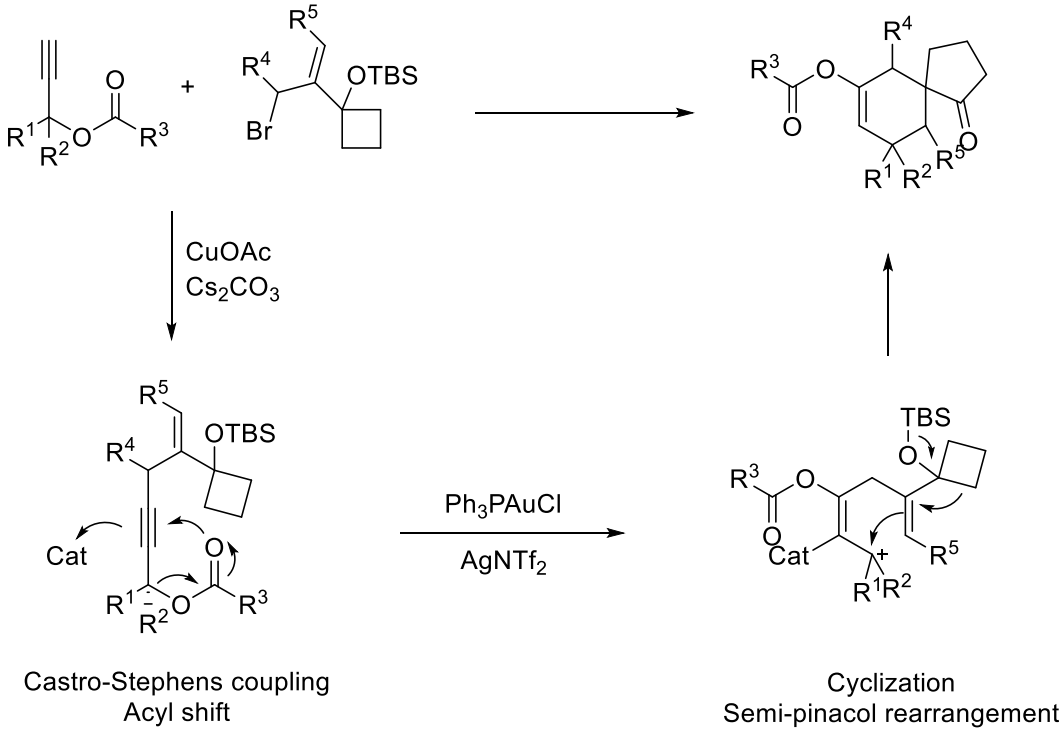
For the final synthesis, following the protocol developed by Lee[28], the ketone **47** was converted to **48** via α-methylation. Finally, a wittig homologation gave the natural product **1** in 15 steps with 3.8% overall yield (Scheme 1.16).



Scheme 1.16: Final Synthesis

1.4.4 Tu and Wang's model study

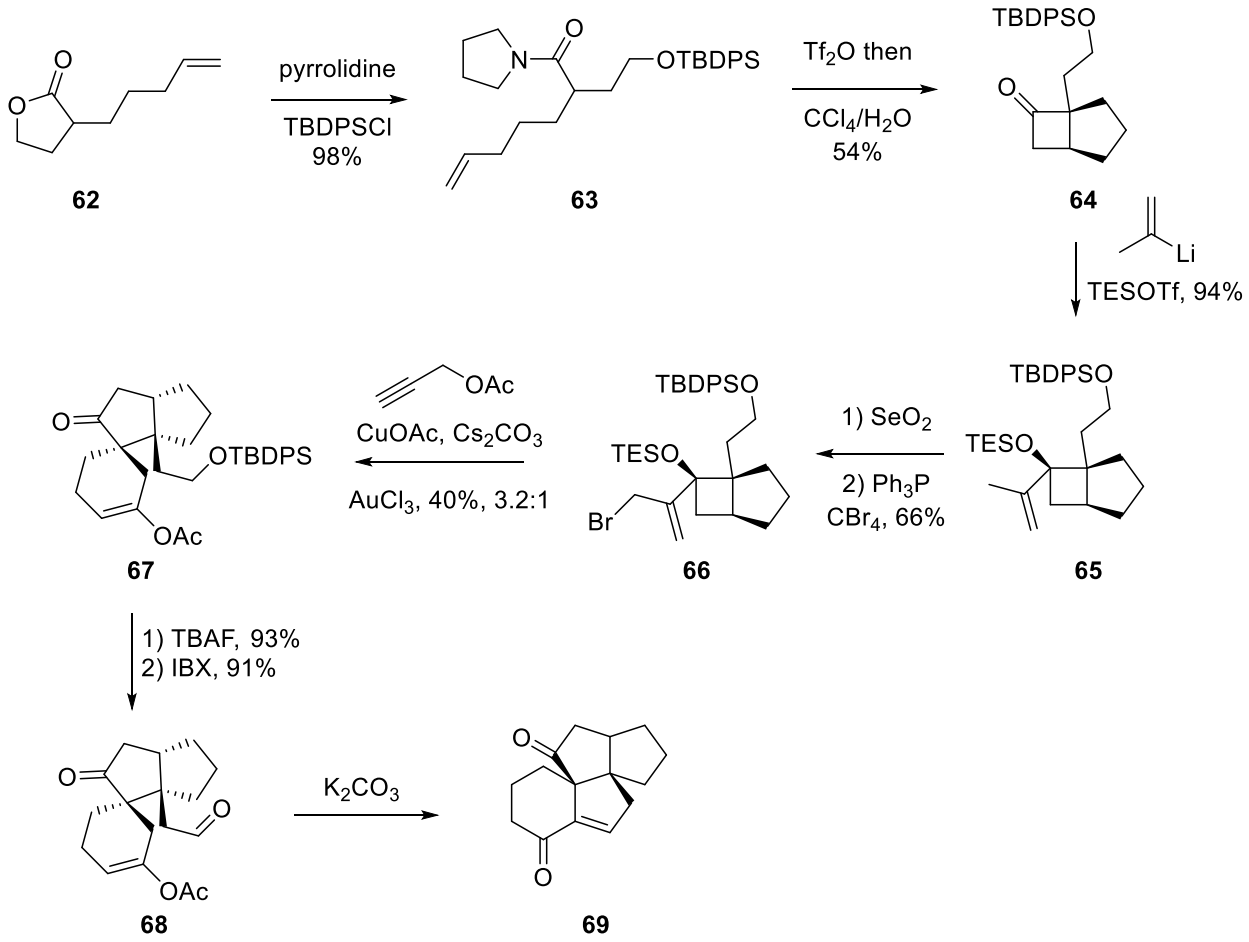
In 2020, Tu and Wang published a method for the construction of spiro bicyclic compounds using a Castro-Stephens coupling[57], acyloxy shift, cyclization and semi-pinacol rearrangement sequence (Scheme 1.17).[32]



Scheme 1.17: Strategy towards spirocyclic compounds

The group applied the same strategy towards the model study of the waihoensene ring system. Starting from compound **62**, compound **66** was synthesized in 6 steps as described in Scheme

1.18. Subjecting **66** to the developed conditions with prop-2-yn-1-yl acetate, the tricyclic compound **67** was obtained in 40% yield with a dr ratio of 3.2:1. Compound **67** was then converted to **68** via TBAF deprotection followed by IBX oxidation. Then a tandem hydrolysis, intramolecular aldol cyclization/elimination reaction induced by K_2CO_3 enabled a quick construction of the carbon ring framework of waihoensene.



Scheme 1.18: Synthesis of the waihoensene ring system

1.4.5 Our approaches to waihoensene

In this thesis, we will be presenting three different synthetic strategies we attempted to achieve the total synthesis of waihoensene.

In chapter 1, we describe our attempts at an oxidative coupling approach towards waihoensene which uses a hypervalent iodine mediated oxidative coupling reaction as the key step for constructing the tetraquinane ring structure followed by a ring expansion to get the carbon ring framework of the natural product.

In chapter 2, we describe our attempts toward a Rhodium catalyzed C-H insertion strategy to the natural product. Here, we attempted a SmI_2 mediated reductive coupling to construct a bicyclic structure followed by a C-H insertion reaction of a diazo compound to generate the tetraquinane structure.

In chapter 3, we describe our final and successful attempt toward the natural product. In this route, we employ a Pauson-Khand reaction to construct the carbon ring framework of the natural product and use quaternary centers as a guide to set the correct stereochemistry at all the chiral centers of the molecule.

Before our synthesis began, there were no reported synthesis of waihoensene and only Moore's synthesis of the waihoensene ring system was published. During our synthetic attempts, Lee's first total synthesis was published. Yang's total synthesis and Tong and Wu's model study was published while our manuscript was under review.

1.5 References

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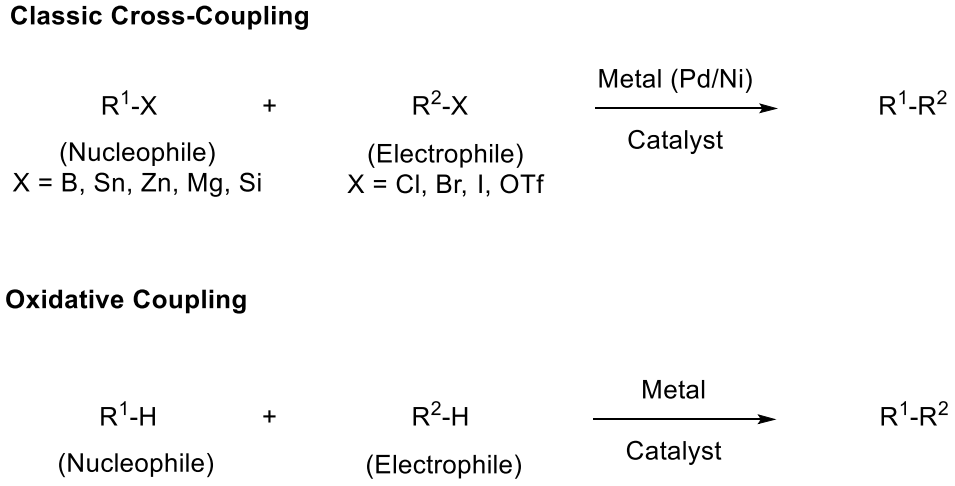
Chapter 2

Oxidative coupling strategy towards waihoensene

2.1 Introduction

In the recent decades, significant advances have been made in the field of oxidative coupling which still continues to fascinate and bewilder chemists. Despite the advent of many modern C-H activation techniques, oxidative coupling is still the methodology of choice for C-C coupling reactions for the synthesis of complex molecules.[1,2] Oxidative coupling has several benefits over the traditional cross-coupling procedures. First, cross-coupling methodology depends on the coupling of two different electronic centers, an electron-rich nucleophilic center and an electron-deficient electrophilic center. This requires the need for the pre-installation of functional groups in the substrates which increases the steps involved in the synthesis. The other involves the use of electropositive atoms like boron, tin, zinc, magnesium, silicon etc. to be bound to the nucleophilic center. These reagents are usually air and moisture sensitive therefore quite difficult to handle or harmful to both human and environmental health. Also, as these atoms are not incorporated in the final substrates and are eliminated as metallic wastes, they contribute to poor atom economy of the reaction. These issues render this process somewhat unsustainable in the long run. Oxidative coupling offers a solution to both these problems. It utilizes two nucleophilic centers which can be carbon, nitrogen or oxygen which is bound to a hydrogen atom.

Thus, the need for pre-functionalization is circumvented. Also, since the substrates are mostly just hydrocarbons, there is no requirement for additional atoms like boron, tin, zinc etc. which renders the whole process much more environmental-friendly, safer and easier to handle and atom-economical. (Scheme 2.1).

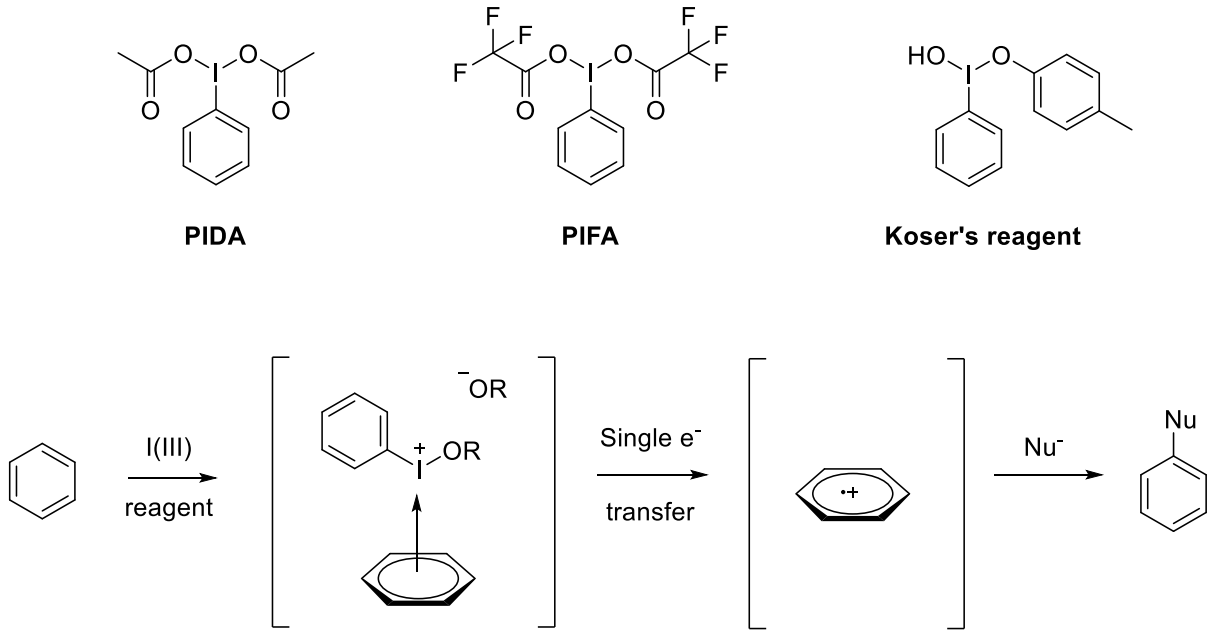


Scheme 2.1: Cross vs oxidative coupling

2.1.1 Hypervalent iodine mediated oxidative coupling

Transition metals have traditionally been the choice of oxidants in the last few decades for the construction of diverse and complex molecular scaffolds via oxidative coupling. The highly electropositive nature, low reduction potential and the general basic nature of the salts of these transition metals make them the option of choice for the activation of the C-H bonds in oxidative coupling.[3] However, the high-costs associated with the use of rare transition metals, their relatively toxic nature and high environmental impact again makes this methodology relatively undesirable. Therefore, processes that can achieve the same transformation without the use of any rare metals have a high level of attraction for chemists worldwide. In this regard, the use of

hypervalent iodine reagents has emerged as a very viable alternative. Recent years have seen an enormous and tremendous growth in the development of hypervalent iodine chemistry for their use in modern synthetic tools. The ease of availability, heavily reduced cost, low toxicity and environmental benignity are some of the characteristics of these reagents that make them a much better alternative.[4–6] Many hypervalent iodine reagents like phenyliodine(III) diacetate (PIDA), phenyliodine(III) bis(trifluoroacetate) (PIFA), Koser's reagent etc. have been developed that have achieved success in achieving oxidative couplings (Scheme 2.2). Their mode of action is explained in Scheme 2.2.[7,8]

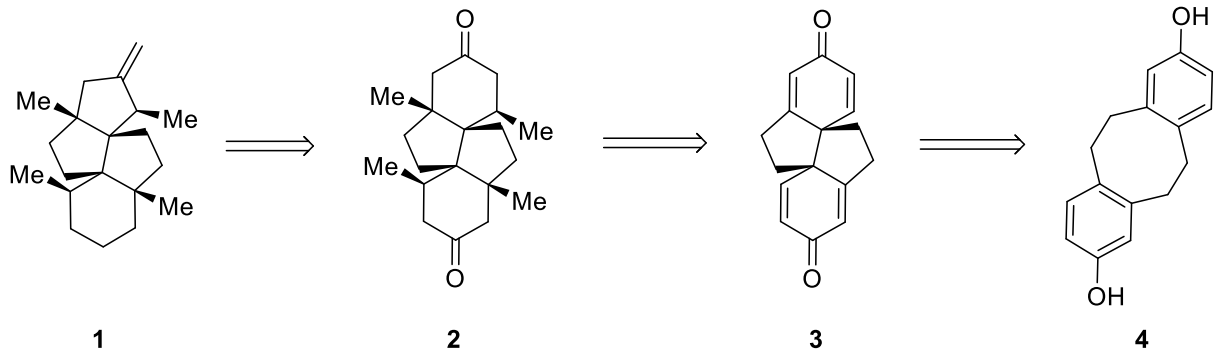


Scheme 2.2: Hypervalent iodine reagents and mode of action

2.2 Retrosynthetic Analysis

Given the potential symmetry of the carbon framework of waihoensene **(1)**, we envisioned a synthetic route towards waihoensene **(1)** that took this element of symmetry into account. Thus,

the tetracyclic [5, 5, 5, 6] ring system of waihoensene **(1)** could be synthesized via a ring contraction reaction from the C2 symmetric tetracyclic [6, 5, 5, 6] di-ketone compound **2**.[9–13] The four methyl groups of molecule **2** could be installed via two different Michael addition reactions from the tetracyclic enone **3**. In this regard, the use of nickel to catalyze the Michael addition of aluminum or titanium based methylating agents to sterically hindered α,β-unsaturated enones has been known.[14,15] The stereochemistry of the incoming methyl groups could be explained by the stereochemistry of the enone **3**. Due to the up-up configuration of the two five-membered rings, the two six-membered rings have to face downwards blocking the bottom face. Thus, all the incoming methyl groups should approach from the top face setting the desired stereochemistry. Also, attack of the methyl groups on the 5 and 11 positions (waihoensene numbering) from the bottom face would generate a highly strained trans-fused five-membered ring. This key intermediate **3** in turn, could be synthesized using a hypervalent iodine mediated oxidative coupling reaction from the eight-membered ring compound **4**,[4–8,16,17] a molecule whose seemingly simple structure masked the challenges in its synthesis (Scheme 2.3).



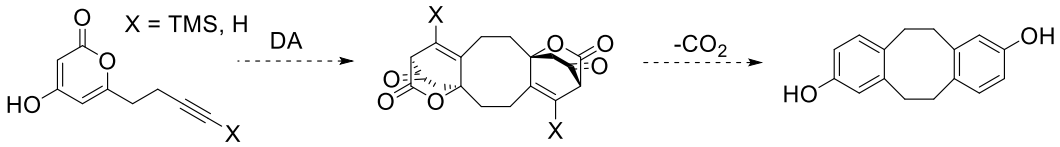
Scheme 2.3: Retrosynthetic analysis of waihoensene **(1)**

2.3 Synthesis of compound 4

Our synthetic efforts began with the synthesis of the diphenolic compound **4**. Seemingly simple, this compound turned out to be quite difficult to synthesize than anticipated. We tried various approaches for the synthesis of this compound including pyrone Diels-Alder, metathesis, formation of Kagan ether followed by breaking open the oxygen bridge[18] etc.

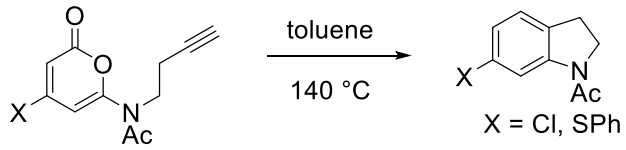
2.3.1 Pyrone Diels-Alder strategy

Initially, we thought that the symmetric eight-membered ring compound **4** could be synthesized via dimerization of the alkyne-pyrone **5** or **6** using a double Diels-Alder reaction (Scheme 2.4).[19–23]



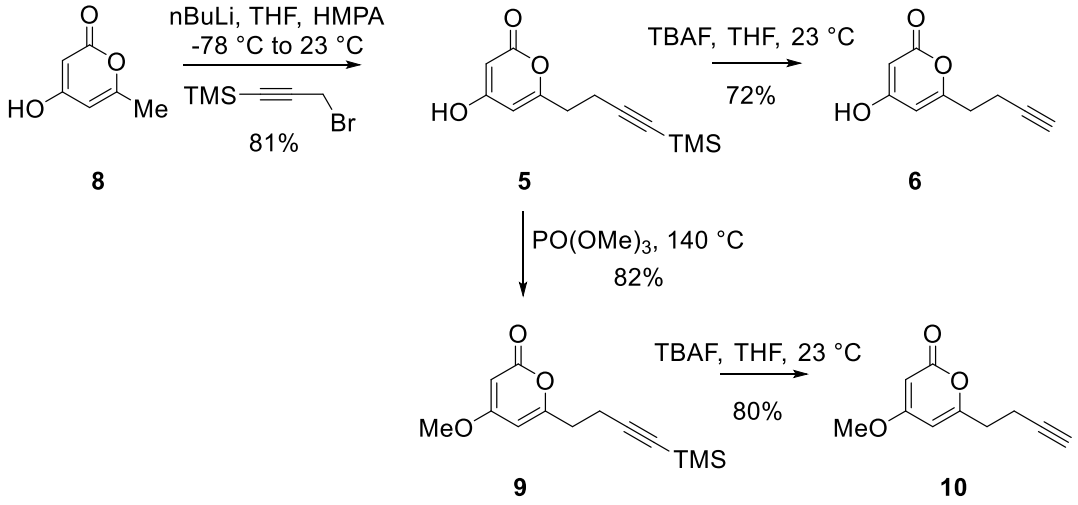
Scheme 2.4: Diels- Alder approach

Previously from our lab, pyrone Diels-Alder routes have been used for the synthesis of indolines and hydroindolines.[24] Intramolecular Diels-Alder between a pyrone and a pendant alkyne delivered the desired indoles in high yields (Scheme 2.5). Keeping this result in mind, we thought we could affect an intermolecular Diels-Alder reaction between two alkyne-pyrone moieties to synthesize the desired molecule **4.**



Scheme 2.5: Diels-Alder reaction of pyrone with tethered alkyne

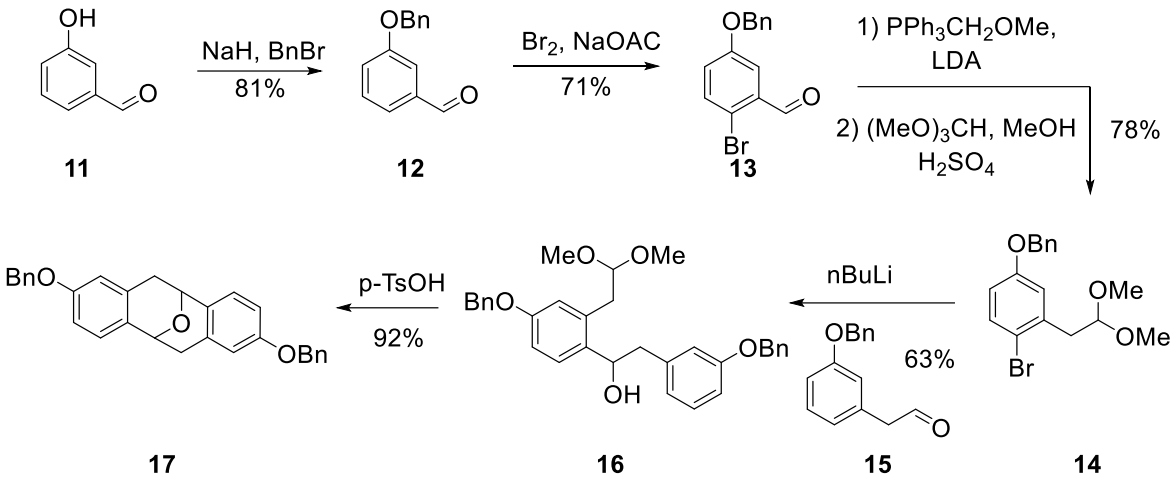
The alkyne-pyrones **5** and **6** were efficiently synthesized starting from the commercially available 4-hydroxy 6-methyl pyrone **8** using Hsung's procedure for the alkylation of **8** (Scheme 2.6).[25] But, subjecting these pyrones to microwave conditions never generated the desired Diels-Alder product; instead, they gave a messy and un-characterizable reaction mixture. We believe the lactone must be hydrolyzing due to the presence of the free alcohol. Thus, the alcohol was methylated with trimethylphosphate. Upon subjecting the pyrones **9** and **10** to microwave irradiation up to 250 °C, no reaction was observed. We finally concluded that the pyrone and alkyne were too inactive as intermolecular Diels-Alder partners.



Scheme 2.6: Synthesis of the Diels-Alder precursors

2.3.2 Kagan ether route

The group of Harmata, in 1999, reported an efficient synthesis of 2,8-bis(benzyloxy)-5,6,11,12-tetrahydro-5,11-epoxydibenzo[a,e]cyclooctene **17**, a compound which is an analogue of the Kagan ether.[18] Their synthesis featured a cyclic acetal formation followed by an intramolecular Friedel-Crafts alkylation to generate the eight-membered ring with the oxygen bridge (Scheme 2.7).

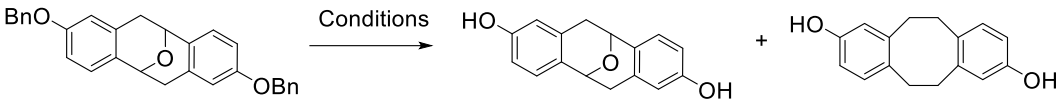


Scheme 2.7: Harmata's synthesis of Kagan ether analogue

Hoping that the oxygen bridge of **17** being benzylic on both sides could be easily removed, we followed the protocol to synthesize this intermediate.

Hydrogenation attempts to cleave the oxygen bridge

With the Kagan ether **17** in hand, we sought out to use hydrogenation to cleave both the benzyl protecting group and the oxygen bridge. However, several attempts with various palladium catalysts and Lewis acids just effected deprotection and could not reduce the oxygen bridge.



17 18 4

Conditions	18	4
H_2, Pd/C, TFA, MeOH, 60 °C	43%	0%
H_2, Pd/C, $BF_3.Et_2O$, MeOH, 60 °C	52%	0%
H_2, $Pd(OH)_2$/C, TFA, MeOH, 60 °C	59%	0%
H_2, $Pd(OH)_2$/C, $BF_3.Et_2O$, MeOH, 60 °C	68%	0%

Table 2.1: Hydrogenation attempts with H_2

With the failure in reduction using H_2, we thought of using Et_3SiH as both an in-situ generator of H_2 using a Pd-catalyst[26,27] and as a hydride donor to effect the reduction of the bridge.[28,29] Here again, use of several different Lewis acids in a variety of solvents proved unfruitful and either only the debenzylated product was isolated or decomposition of the material was observed.

Conditions	18	4
Et_3SiH, Pd/C, BBr_3, MeOH-CH_2Cl_2, 60 °C	32%	0%
Et_3SiH, Pd/C, $BF_3.Et_2O$, MeOH-CH_2Cl_2, 60 °C	65%	0%
Et_3SiH, $Pd(OH)_2$/C, BBr_3, Acetone, 60 °C	18%	0%
Et_3SiH, $Pd(OH)_2$/C, $BF_3.Et_2O$, Acetone, 60 °C	49%	0%
Et_3SiH, BBr_3, CH_2Cl_2, 60 °C	Decomposition	
Et_3SiH, $BF_3.Et_2O$, CH_2Cl_2, 60 °C	Decomposition	
Et_3SiH, TFA, CH_2Cl_2, 60 °C	Decomposition	

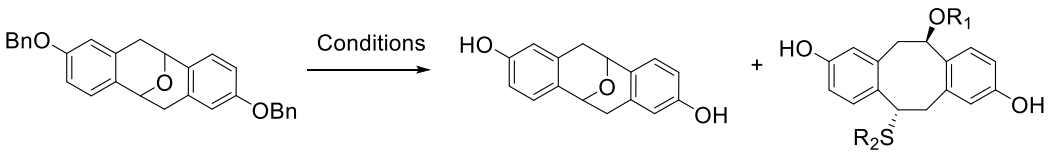
Table 2.2: Hydrogenation attempts with Et_3SiH

With a significant amount of the debenzylated product **18** in hand, we thought of attempting the bridge reduction on the free alcohol. Repeating the same conditions on **18** were not successful and we did not observe the product **4**, recovering only the starting material.

We attributed the failure of all the above hydrogenation conditions to the geometry of the oxygen bridge in these Kagan ether molecules. Since the oxygen atom is present on a bridge, it can never be on the same plane as the aromatic rings. Because of this, the formation of a π-complex with the Pd is prohibited and there is no efficient orbital overlap between the benzylic C-O bond and the Pd for the metal to insert into it.[30–33] Hence, hydrogenation was incapable in removing the benzylic bridge head O atom.

Nucleophilic attack to reduce the bridge

After the failure in reducing the bridge by hydrogenation conditions, we thought of opening up the oxygen bridge using a nucleophilic attack of a thiol using a Lewis acid as an activator. We thought using a strong Lewis acid like Meerwein's salt (Me_3OBF_4) or Et_2AlCl could make the bridgehead carbon electrophilic enough to be attacked by a strong nucleophile like thiol. But, here too, we did not have any success. In all the conditions attempted with the Et_2AlCl, we could only isolate the debenzylated product in very good yields, whereas Meerwein's salt resulted in decomposition of the starting material. (Table 2.3)



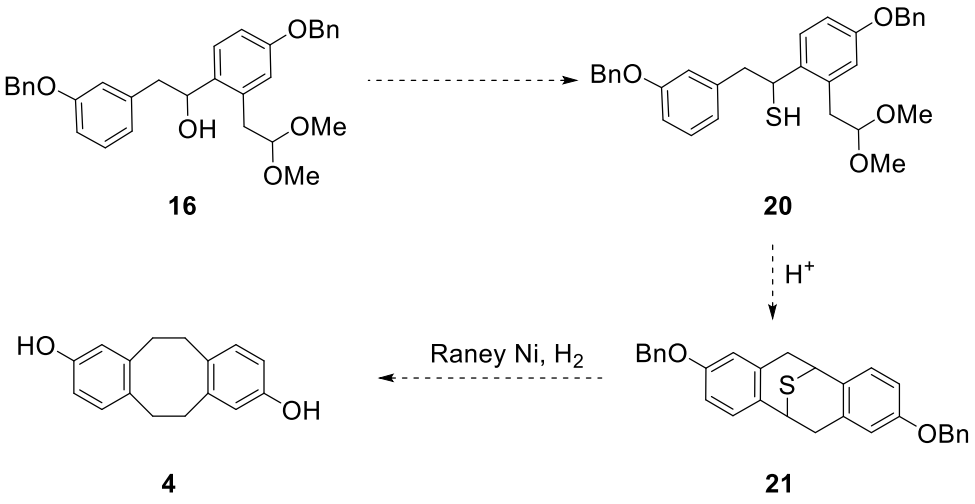
17 18 19

Conditions	18	19
Et_2AlCl, EtSH, THF, reflux (R_1 = H, R_2 = Et)	100%	0%
Et_2AlCl, PhSH, THF, reflux (R_1 = H, R_2 = Ph)	80%	0%
Me_3OBF_4, EtSH, THF, reflux (R_1 = Me, R_2 = Et)	Decomposition	
Me_3OBF_4, PhSH, THF, reflux (R_1 = Me, R_2 = Ph)	Decomposition	

Table 2.3: Attempts at nucleophilic attack

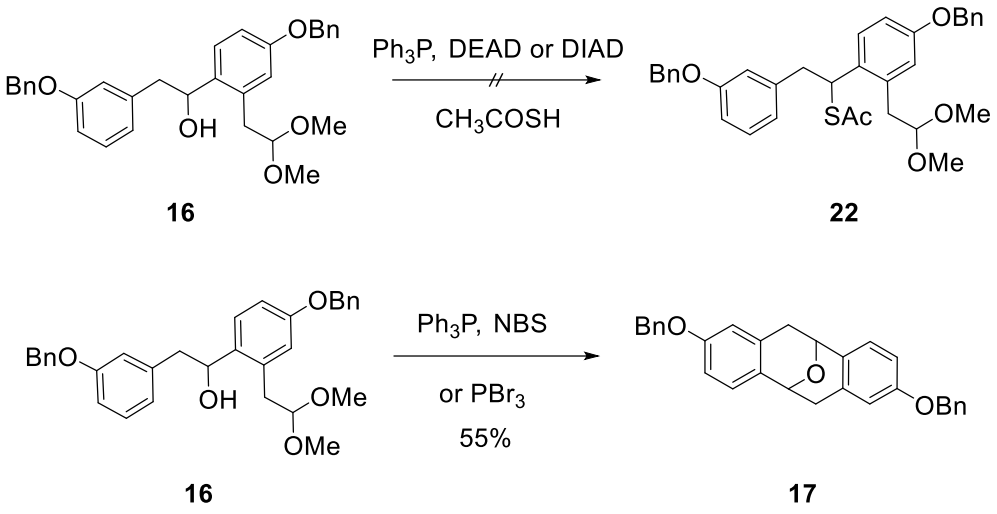
Sulfur bridge formation

Because of the difficulties faced in reducing the oxygen bridge, we next thought of constructing a sulfur bridge which might give us an opportunity to reduce the bridge easily using Raney Ni. To replace the oxygen bridge with sulfur, we had to convert **16** into a thiol **20** (Scheme 2.8).



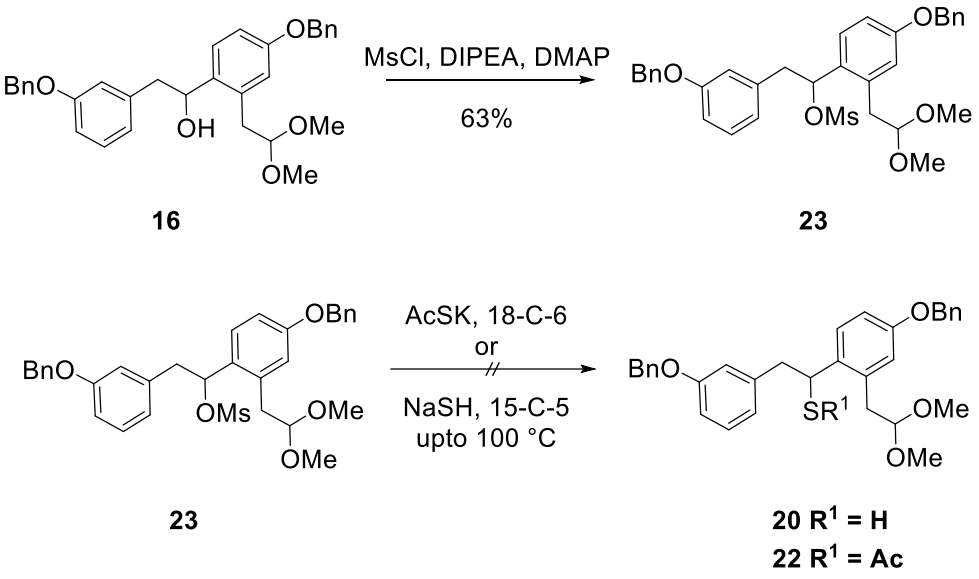
Scheme 2.8: Conversion of O bridge to S bridge

In theory, this could be achieved using Mitsonobu conditions to directly convert the alcohol **16** to the thioacetate **22** followed by hydrolysis to give thiol **20**. This however, cleaved the dimethyl acetal and triggered the decomposition of the alcohol because of the strong acidic conditions. Attempts to convert the hydroxy group into a bromide using PBr_3 or Ph_3P, NBS delivered instead the Kagan ether **17** in 55% yield. The mild acidic nature of the reagents was enough to effect the cyclic acetal formation and intramolecular Friedel-crafts alkylation (Scheme 2.9).



Scheme 2.9: Attempted Mitsonobu and bromination

Conversion of the alcohol **16** to a mesylate **23** was successful using Hunig's base in the presence of catalytic DMAP. However, attempts to replace the mesylate **23** with a thiol **20** or a thioacetate **22** using AcSK or NaSH in the presence of crown ethers failed with quantitative recovery of the starting material (Scheme 2.10).



16 **23**

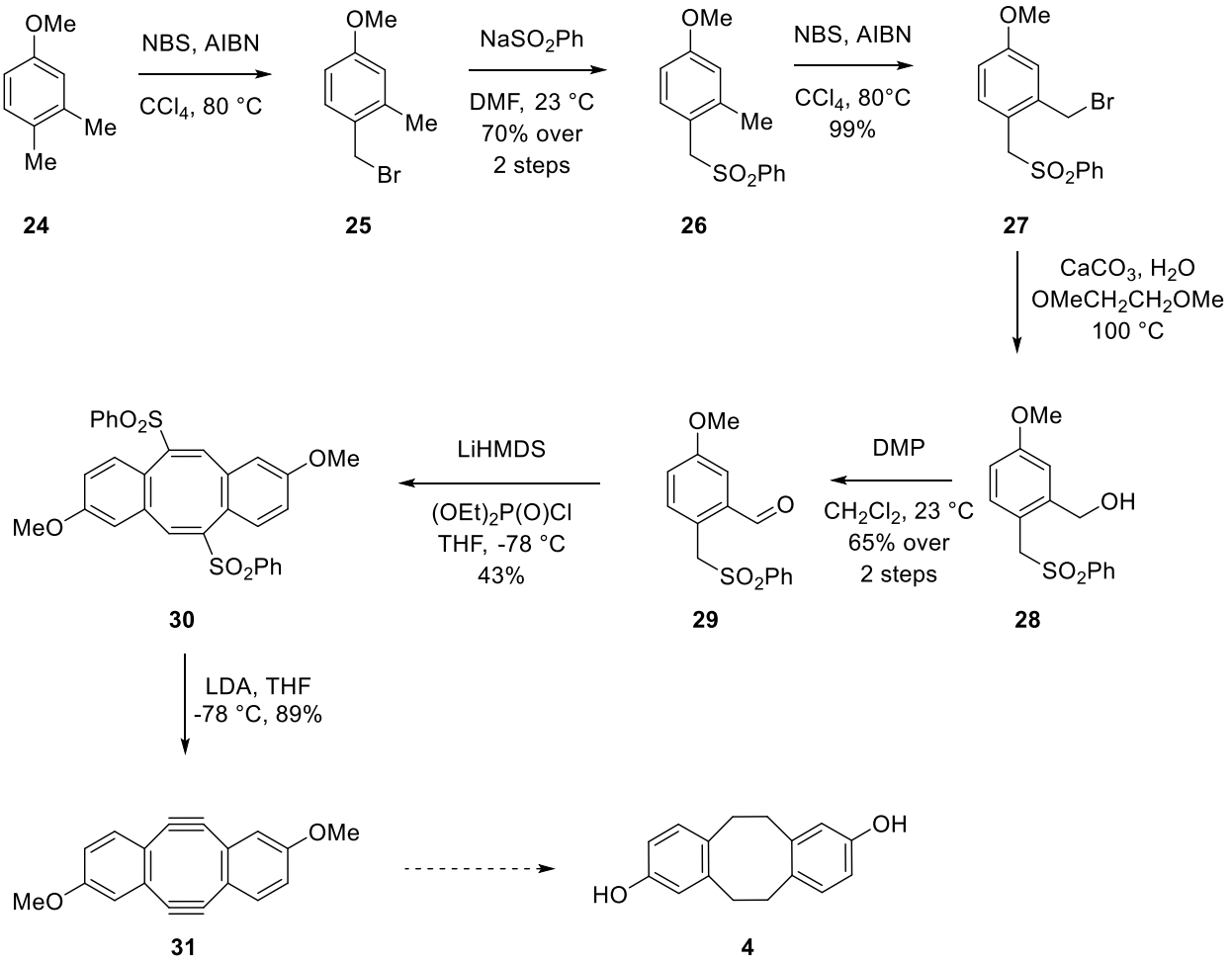
23 **20 R^1 = H**
22 R^1 = Ac

Scheme 2.10: Attempted displacement of the mesylate

2.3.3 Orita's strategy for the eight-membered ring formation

After repeated failed attempts, we decided to follow Orita's strategy for the construction of the eight-membered ring compound **4** via the formation of the alkyne intermediate **31** (Scheme 2.11).[34] Following the procedure followed by Orita for the synthesis of compound **31**, we started with radical bromination of 3,4-dimethyl anisole using NBS, AIBN to give bromide **25** which was converted to the sulfone **26** via SN_2 displacement. A second radical bromination of the methyl group at the meta-position gives the bromide **27**. Nucleophilic hydroxylation using calcium carbonate followed by oxidation of the resulting alcohol **28** using Dess-Martin Periodinane delivered the aldehyde **29** (Scheme 2.11).

With the formyl sulfone **29** in hand, employing an intermolecular and intramolecular Horner-Wadsworth-Emmons olefination protocol provides the cyclic vinyl sulfone **30** which undergoes sulfone elimination under LDA conditions to deliver the diyne **31**. Hydrogenation of this compound should then give us the key precursor **4** for the oxidative coupling step (Scheme 2.11).

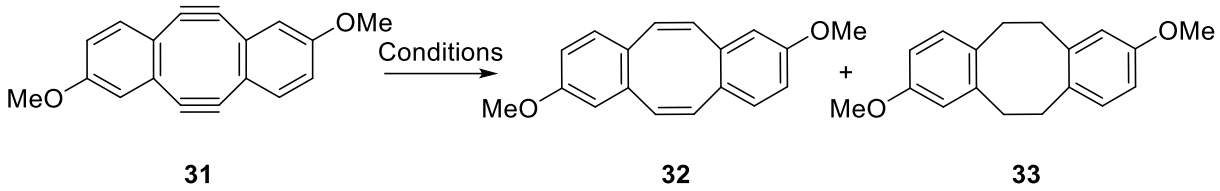


Scheme 2.11: Orita's strategy for the synthesis of the eight-membered ring

2.3.4 Hydrogenation of the diyne 31

The next step, hydrogenation of the alkynes to the alkane, required some experimentation. Simple hydrogenation conditions using Pd/C as the catalyst reduced the alkyne **31** down to the alkene **32** but the reaction did not proceed any further. The reaction preformed under various solvents like methanol, ethyl acetate, dichloromethane and dichloroethane and even under reflux conditions did not yield different results and the reaction stopped at the alkene stage. Homogenous catalysis using Wilkinson's catalyst or Crabtree's catalyst under reflux conditions in dichloroethane also gave us the same result and only the alkene **32** could be isolated.

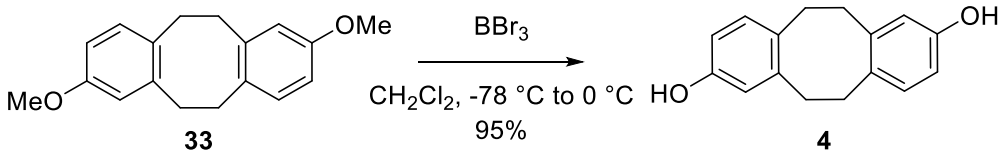
Fortunately, using Pearlman's catalyst in chloroform at ambient temperatures[35] delivered us the desired compound **33**. Deprotection of the methoxy group using boron tribromide produced the precursor **4** for the key oxidative coupling step (Scheme 2.12).



31 **32** **33**

Conditions	Results
H_2, Pd/C, MeOH, 23 °C	Only **32** isolated
H_2, Pd/C, EtOAc, 23 °C	Only **32** isolated
H_2, Pd/C, CH_2Cl_2, 23 °C	Only **32** isolated
H_2, Pd/C, $ClCH_2CH_2Cl$, reflux	Only **32** isolated
H_2, Pd/C, $CHCl_3$, reflux	Only **32** isolated
H_2, Crabtree's catalyst, CH_2Cl_2, reflux	Only **32** isolated
H_2, Wilkinson's catalyst, CH_2Cl_2, reflux	Only **32** isolated
H_2, $Pd(OH)_2$/C, $CHCl_3$, 23 °C	79% yield of **33**

Table 2.4: Hydrogenation attempts



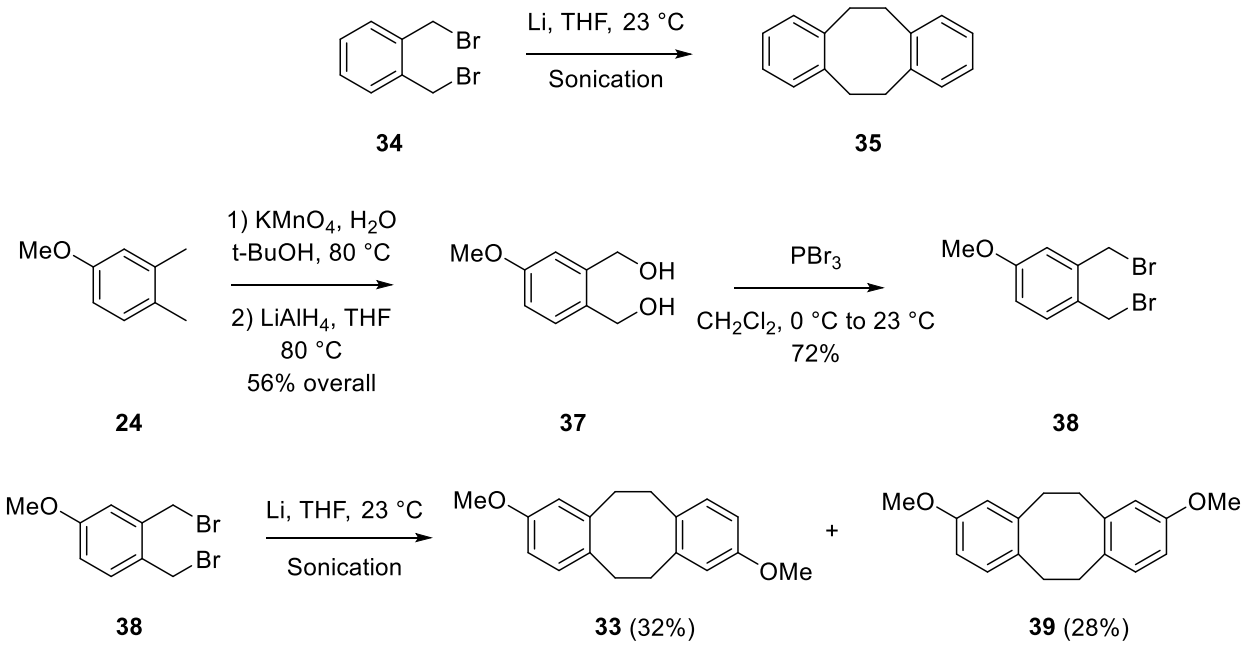
33 **4**

Scheme 2.12: Synthesis of key precursor **4**

2.3.5 Dimerization of dibromide

Considering the length and poor yields of some of the steps involved in the previous route towards key precursor **4**, we thought of a quicker route involving lesser steps which involved dimerization of the benzylic dibromide **38** to give the eight membered ring key precursor **33**.[36,37] Therefore, starting from 3,4-dimethyl anisole **24**, oxidation using $KMnO_4$ produced the acid **36** which is then reduced under $LiAlH_4$ conditions to deliver the diol **37**.[38] Conversion of the diols using phosphorous tribromide to the dibromide **38**[39] gave the precursor for the dimerization (Scheme 2.13).

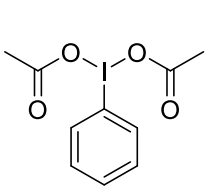
Subjecting the dibromide **38** to lithium under sonication conditions in THF then delivered the desired compound **33** in 32% yield along with the undesired regioisomer **39** in 28% yield. This route although had steps which were very low-yielding, it was much efficient in terms of step count and overall yield (Scheme 2.13).



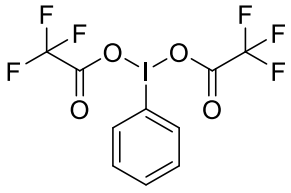
Scheme 2.13: A different strategy towards **33**

2.4 Oxidative coupling attempts

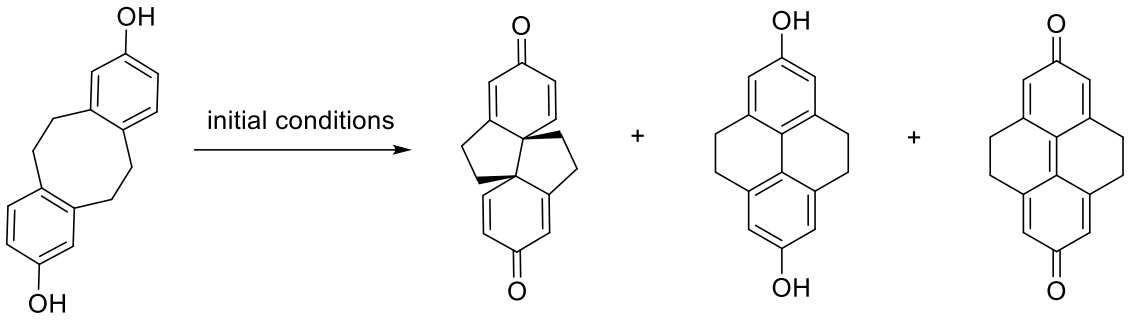
With the key precursor **4** in hand, we endeavored to attempt the key oxidative coupling step. According to the literature, we figured that the use of hypervalent iodine reagents would be a good start for the reaction.[4,40–45] Therefore, for our initial attempt, we decided to use PIDA and PIFA reagents in acetonitrile as the solvent. Under these conditions, instead of getting our desired product we isolated a mixture of compounds **40** and **41** (Table 2.5). These initial results were exciting as it showed that the reaction does form the key C-C bond connection we were hoping to construct. We hypothesized, however, that after formation of the product, it undergoes a dienone-phenol rearrangement to give the tetracyclic compounds **40** and **41**. As these types of rearrangements are usually catalyzed by acid, we thought that the trace amounts of acid generated by the hypervalent iodine reagents were responsible for the rearrangement of the product. So, to circumvent this issue, we decided to add a base to the reaction mixture which could sequester the residual acid formed and stop the reaction at the product stage. To our delight, simply adding solid sodium bicarbonate did the trick for us and the reaction stopped before the rearrangement to deliver us the desired product **3** in 25% yield. Adding $BF_3.Et_2O$ to the reaction mixture to further activate the hypervalent iodine reagent bumped the yield upto 50%. Using several metal oxidants in this case was ineffective as none of the oxidants we tried were able to deliver us the coupling product **3**.



PIDA



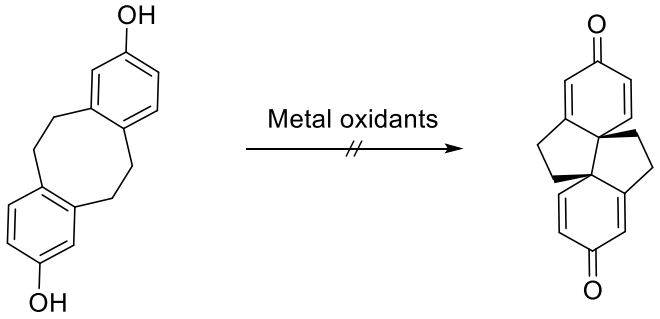
PIFA



4 **3** **40** **41**

Conditions	Results
PIDA (1.1 eq), CH_3CN, -40 °C	**40** + **41** observed
PIFA (1.1 eq), CH_3CN, -40 °C	**40** + **41** observed
PIDA (2.2 eq), CH_3CN, -40 °C	**41** observed
PIFA (2.2 eq), CH_3CN, -40 °C	**41** observed
PIDA (1.1 eq), $NaHCO_3$, CH_3CN, -40 °C	20% **3**
PIFA (1.1 eq), $NaHCO_3$, CH_3CN, -40 °C	25% **3**
PIFA (1.1 eq), $NaHCO_3$, $BF_3.Et_2O$, CH_3CN, -40 °C	50% **3**

Table 2.5: Oxidative coupling

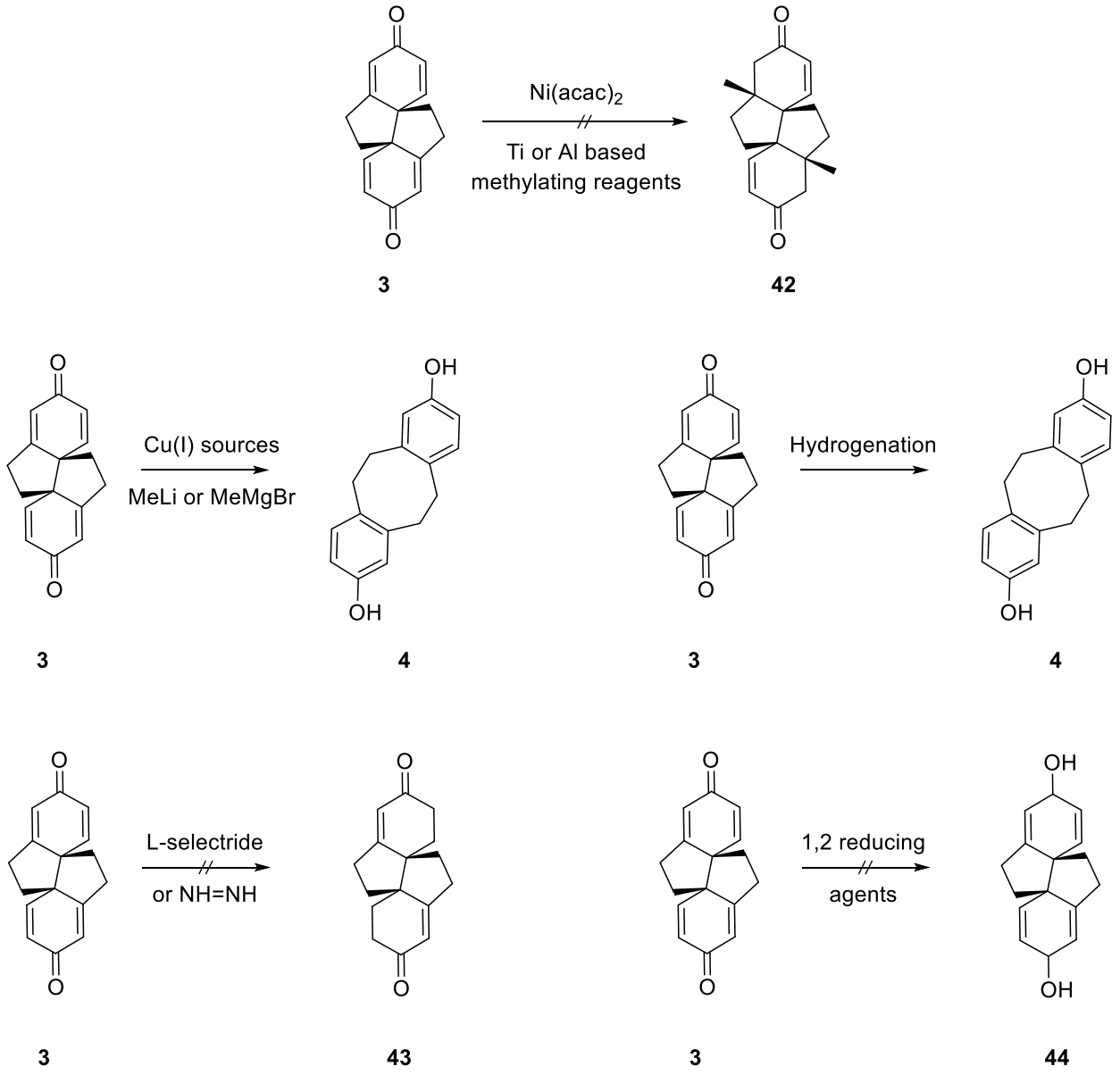


4 **3**

Scheme 2.14: Oxidative coupling attempts

2.5 Installation of the methyl groups

With the oxidative coupling product **3** in hand, the next task was the installation of the methyl groups via a conjugate addition on the enones. As previously mentioned, the role of nickel catalysts to install methyl groups on to very hindered enones using aluminum or titanium-based reagents is known.[14,15] However, using various different methylating reagents, the desired product was never isolated, instead we could only observe decomposition of the product. Switching to copper catalysis, we observed very interesting results. Subjecting the compound to any copper conditions, the compound reverted back to the diphenol compound **4**. This result was very surprising and it showed the lability of the newly formed C-C bond and the propensity of the molecule to attain a highly stable aromatic state. The same result was also obtained when the compound was subjected to hydrogenation under various conditions. Instead of the reduction of the double bonds, we once again observed the reduction of the new C-C bond and the compound **4** was cleanly isolated. Many other attempts, for example, reduction of the double bonds using L-selectride or di-imide, reduction of the ketone using sodium borohydride also did not bear any fruitful attempts and only decomposition was observed (Scheme 2.15).



Scheme 2.15: Attempts at conjugate addition

2.6 Conclusion

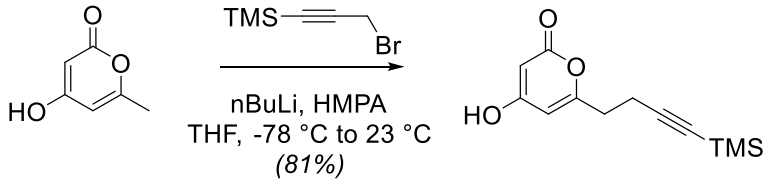
We were able to achieve the key oxidative coupling step and synthesized the tetracyclic ring framework of the natural product waihoensene. However, we were not able to achieve any transformations on compound **3** to reach the final target. Any attempts to install the four methyl groups on the compound either led to decomposition or reverted the compound back to the

tricyclic oxidative coupling precursor **4**. Since, we hypothesized that the presence of the double bonds increased the propensity of the molecule to achieve the aromatic state, we had to come up with a new route that eliminated this issue while still taking the inherent symmetry of the molecule into account.

2.7 Experimental Procedures

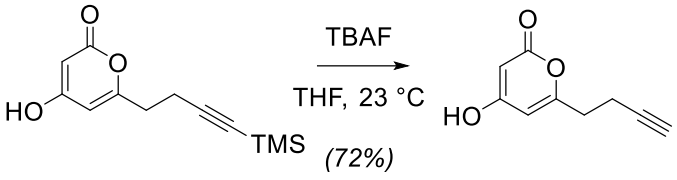
All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, diethyl ether (Et_2O), acetonitrile (CH_3CN) and dichloromethane (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Anhydrous MeOH was purchased from Sigma-Aldrich and was used without further purification. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent, and an ethanolic solution of phosphomolybdic acid and cerium sulfate and vanillin, and heat as developing agents. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker 500 MHz and 400 MHz instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m =

multiplet, app = apparent. IR spectra were recorded on a Perkin-Elmer 1000 series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on Agilent 6244 TOF-MS using ESI (Electrospray Ionization) at the University of Chicago Mass Spectroscopy Core Facility.



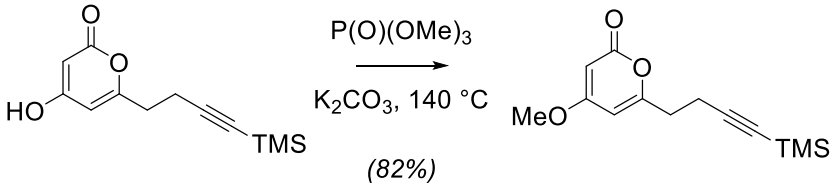
8 **5**

TMS-protected hydroxy alkyne pyrone 5: A 100 mL, flame-dried round bottom flask, equipped with a magnetic stir bar, is charged with hydroxy pyrone **8** (1.0 g, 7.93 mmol, 1.0 equiv), THF (24 mL) and HMPA (4 mL). The reaction mixture is cooled down to -78 °C followed by the dropwise addition of n-BuLi (7.3 mL, 2.5 M in hexanes, 18.24 mmol, 2.3 equiv) and stirred for an hour. TMS-protected propargyl bromide (3.03 g, 2.6 mL, 15.86 mmol, 2.0 equiv) is then added and the stirring is continued for another 15 h at 23 °C. After the reaction is complete, the reaction mixture is quenched by the addition of 1 N HCl (20 mL). The reaction contents are transferred to a separatory funnel and the layers are separated. The aqueous layer is extracted with Et_2O (3 x 20 mL) and the combined organic layer is washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. Flash column chromatography (silica gel, hexanes/EtOAc, 2/1) of the resultant residue gave TMS-protected alkyne hydroxy pyrone **5** (1.52 g, 81% yield) as a white solid. **5**: R_f = 0.30 (silica gel, hexanes/EtOAc, 1/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.07 (d, *J* = 2.0 Hz, 1 H), 5.61 (d, *J* = 2.1 Hz, 1 H), 2.69 (t, *J* = 7.2 Hz, 2 H), 2.57 (t, *J* = 6.9 Hz, 2 H), 0.13 (s, 9 H).



5 **6**

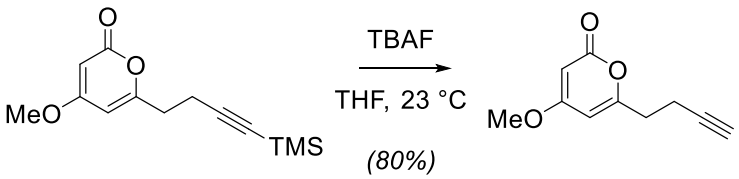
Hydroxy Alkyne pyrone 6: To a 100 mL, flame-dried round bottom flask equipped with a magnetic stir bar, a solution of TMS-protected alkyne hydroxy pyrone **5** (1.0 g, 4.23 mmol, 1.0 equiv) in THF (42 mL) is added. The reaction contents are cooled down to 0 °C and a solution of TBAF (5.1 mL, 1 M in THF, 5.1 mmol, 1.2 equiv) is added dropwise. The reaction mixture is warmed to 23 °C and stirred for 2 h. Upon completion, the reaction is quenched by the addition of a saturated aqueous solution of NH_4Cl (30 mL). The reaction contents are then transferred to a separatory funnel and the layers are separated. The aqueous layer is extracted with EtOAc (3 x 30 mL) and the combined organics are washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. Flash column chromatography (silica gel, hexanes/EtOAc, 2/1) of the resultant residue gave hydroxy alkyne pyrone **6** (500 mg, 72% yield) as a white solid. **6**: R_f = 0.26 (silica gel, hexanes/EtOAc, 1/1).



5 **9**

TMS-protected alkyne methoxy pyrone 9: A 50 mL round bottom flask, equipped with a magnetic stir bar is charged with TMS-protected alkyne hydroxy pyrone **5** (590 mg, 2.5 mmol, 1.0 equiv). K_2CO_3 (415 mg, 3 mmol, 1.2 equiv) and trimethyl orthophosphate (1.09 g, 900 µL, 5.6

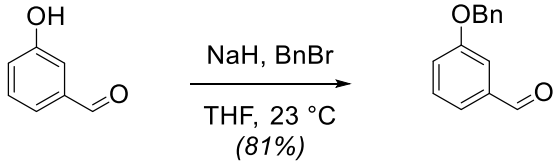
mmol, 2.1 equiv) is added and the reaction mixture is heated to 140 °C and stirred for 2h. Upon completion, the reaction mixture is cooled down to 23 °C and quenched by the addition of water (20 mL) and diluted by the addition of EtOAc (50 mL). The reaction contents are then transferred to a separatory funnel and the layers are separated. The aqueous layer is extracted with EtOAc (3 x 50 mL) and the combined organic layers are washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. Flash column chromatography (silica gel, hexanes/EtOAc, 2/1) of the resultant residue gave TMS-protected alkyne methoxy pyrone **9** (513 mg, 82% yield) as a white solid. **9**: R_f = 0.42 (silica gel, hexanes/EtOAc, 1/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (d, *J* = 2.2 Hz, 1 H), 5.40 (d, *J* = 2.2 Hz, 1 H), 3.78 (s, 3 H), 2.61 (t, *J* = 7.2 Hz, 2 H), 2.54 (t, *J* = 7.0 Hz, 2 H), 0.09 (s, 9 H).



9 **10**

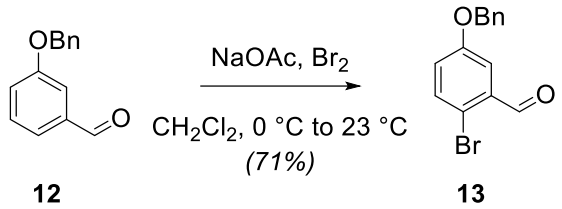
Methoxy alkyne pyrone 10: To a 100 mL, flame-dried round bottom flask equipped with a magnetic stir bar, a solution of TMS-protected alkyne methoxy pyrone **9** (500 mg, 2.0 mmol, 1.0 equiv) in THF (20 mL) is added. The reaction contents are cooled down to 0 °C and a solution of TBAF (2.4 mL, 1 M in THF, 2.4 mmol, 1.2 equiv) is added dropwise. The reaction mixture is warmed to 23 °C and stirred for 2 h. Upon completion, the reaction is quenched by the addition of a saturated aqueous solution of NH_4Cl (20 mL). The reaction contents are then transferred to a separatory funnel and the layers are separated. The aqueous layer is extracted with EtOAc (3 x 20 mL) and the combined organics are washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. Flash column chromatography (silica gel, hexanes/EtOAc, 2/1) of the resultant

residue gave methoxy alkyne pyrone **10** (285 mg, 80% yield) as a white solid. **10**: R_f = 0.35 (silica gel, hexanes/EtOAc, 1/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (d, *J* = 2.1 Hz, 1 H), 5.43 (d, *J* = 2.3 Hz, 1 H), 3.80 (s, 3 H), 2.66 (t, *J* = 7.1 Hz, 2 H), 2.55 (tdd, *J* = 7.2, 2.7, 0.9 Hz, 2 H), 2.00 (t, *J* = 2.6 Hz, 1 H).



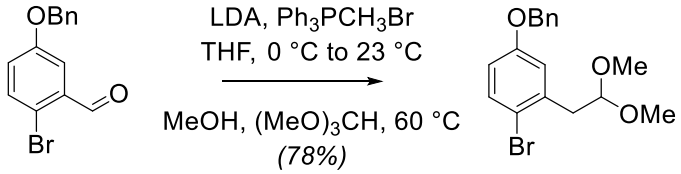
11 **12**

3-benzyloxy benzaldehyde 12 was prepared using the procedure reported by Lee.[46] To a 250 mL, flame-dried round bottom flask equipped with a magnetic stir bar, NaH (4.29 g, 60% dispersion in mineral oil, 98.3 mmol, 1.2 equiv) was added and washed with dry hexanes (3 x 25 mL) to remove the oil. THF (120 mL) was added followed by the addition of 3-hydroxy benzaldehyde **11** (10.0 g, 122.1 mmol, 1.0 equiv) as a solid in small portions at 23 °C. BnBr (20.87 g, 14.5 mL, 171.0 mmol, 1.5 equiv) is added over 30 min and stirring is continued for 3 h. After completion, the reaction is quenched by the addition of saturated aqueous NH_4Cl solution (100 mL) and diluted with EtOAc (100 mL). The reaction contents were transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined organics were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. Flash column chromatography (silica gel, hexanes/EtOAc, 4/1) of the resultant residue gave 3-benzyloxy benzaldehyde **12** (14.6 g, 81% yield) as a white solid. **12**: R_f = 0.35 (silica gel, hexanes/EtOAc, 4/1); ^{1}H NMR and ^{13}C NMR matched those reported by the Lee group.[46]



12 **13**

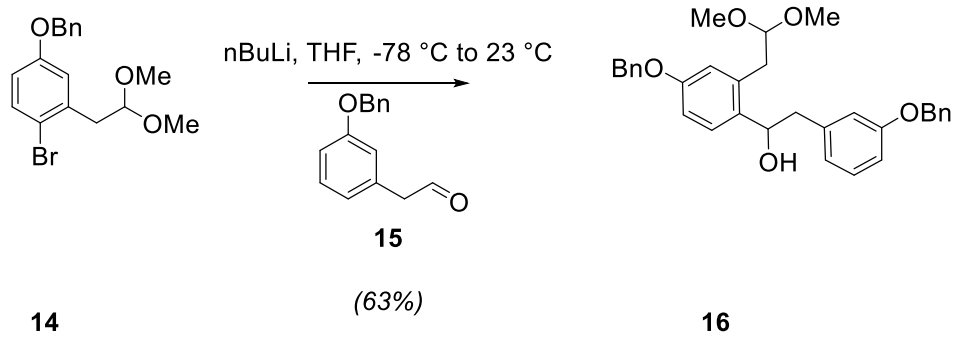
2-bromo 5-benzyloxy benzaldehyde 13 was prepared using the procedure reported by Lipshutz.[47] To a 250 mL, flame-dried round bottom flask equipped with a magnetic stir bar, NaOAc (27.1 g, 329.8 mmol, 7.0 equiv) was added. CH_2Cl_2 (120 mL) was added followed by the addition of 3-benzyloxy benzaldehyde **12** (10.0 g, 47.1 mmol, 1.0 equiv) as a solid in small portions at 23 °C. Br_2 (37.60 g, 12.1 mL, 235.6 mmol, 5.0 equiv) is added over 45 min at 0 °C and stirring is continued for 3 h at 23 °C. After completion, the reaction is quenched by the addition of saturated aqueous NaS_2O_3 solution (100 mL) and diluted with EtOAc (100 mL). The reaction contents were transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined organics were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. Flash column chromatography (silica gel, hexanes/EtOAc, 4/1) of the resultant residue gave 2-bromo 5-benzyloxy benzaldehyde **13** (9.7 g, 71% yield) as a white solid. **13**: R_f = 0.41 (silica gel, hexanes/EtOAc, 4/1); ^{1}H NMR and ^{13}C NMR matched those reported by the Lipshutz group.[47]



13 **14**

Bromoacetal 14 was prepared according to the procedure developed by Harmata.[18] To a 1000 mL, flame-dried, round bottom flask equipped with a magnetic stir bar, freshly distilled

diisopropylamine (1.5 g, 2.1 mL, 14.8 mmol, 1.5 equiv) and dry THF (40 mL). The flask was cooled to 0 °C in an ice bath. To this flask, n-BuLi (9.3 mL, 14.8 mmol, 1.6 M in hexane) was added dropwise. Powdered (methoxymethyl)- triphenylphosphonium chloride (5.1 g, 14.8 mmol, 1.5 equiv) was added as a solid, resulting in a blood-red-colored solution. The mixture was allowed to stir at 23 °C for 2 h. To this solution was then added a solution of 2-bromo 5-benzyloxy benzaldehyde **13** (2.12 g, 9.9 mmol, 1.0 equiv) in 50 mL of dry THF via a syringe over 15 min. The reaction mixture was stirred at 23 °C for 8 h. Upon completion, the reaction mixture was quenched with the addition of brine (100 mL). The reaction contents were transferred into a separatory funnel and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 100 mL) and the combined organics were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. To the crude residue, methanol (90 mL), trimethyl orthoformate (20.9 g, 21.6 mL, 197.1 mmol, 20 equiv), and 2 mL of concentrated sulfuric acid were added, and the mixture was stirred at 60 °C for 4 h. Upon completion, the reaction contents are cooled down to 23 °C and the flask was concentrated on a rotary evaporator to remove the methanol. The resulting residue was then transferred into a separatory funnel and diluted with EtOAc (200 mL). It was washed with water and brine, dried ($MgSO_4$), filtered and concentrated. Flash column chromatography (silica gel, hexanes/EtOAc/Et_3N, 4/1/0.01) of the resultant residue gave acetal **14** (1.9 g, 78% yield) as a white solid. **14**: R_f = 0.36 (silica gel, hexanes/EtOAc, 4/1); ^1H NMR and ^{13}C NMR matched those reported by the Harmata group.[18]

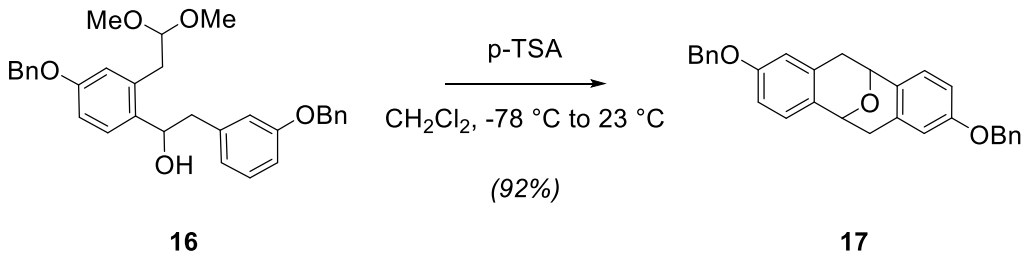


15

(63%)

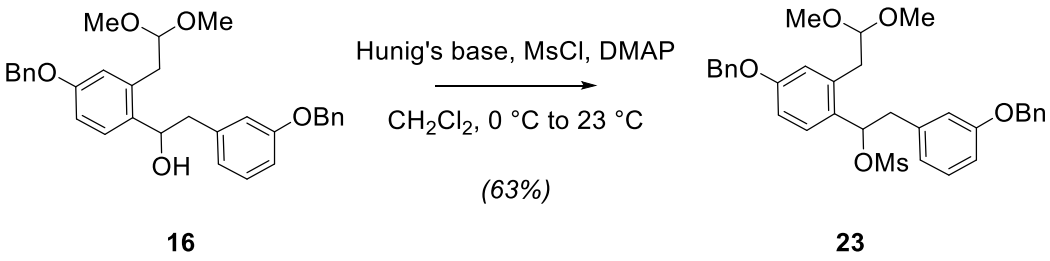
14 **16**

Alcohol 16 was prepared according to the procedure developed by Harmata.[18] To a 500 mL flame-dried, round bottom flask equipped with a magnetic stir bar, was added bromoacetal **15** (1.45 g, 4.1 mmol, 1.0 equiv) and THF (180 mL). The flask was cooled down to -78 °C and n-BuLi (2.8 mL, 4.5 mmol, 1.6 M solution in hexane) was added via a syringe over 5 min, and the mixture was allowed to stir at -78 °C for 1 h. To the resulting yellow solution was added the 3-benzyloxy phenyl acetaldehyde **15** (1.06 g, 4.7 mmol, 1.15 equiv) as a solution in THF (5 mL). The reaction was stirred at -78 °C for 1 h. The mixture warmed to the 23 °C and stirred for 2 h. After completion, the reaction is quenched by the addition of saturated aqueous NH_4Cl solution (100 mL) and diluted with EtOAc (100 mL). The reaction contents were transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined organics were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. Flash column chromatography (silica gel, hexanes/EtOAc, 4/1) of the resultant residue gave alcohol **16** (1.29 g, 63% yield) as a colorless oil. **16**: R_f = 0.12 (silica gel, hexanes/EtOAc/Et_3N, 4/1/0.01); ^1H NMR and ^{13}C NMR matched those reported by the Harmata group.[18]



16 **17**

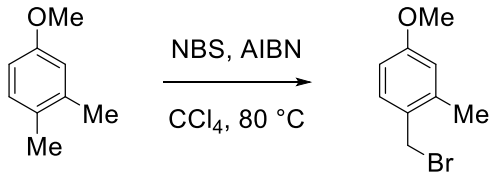
Kagan ether 17 was prepared according to the procedure developed by Harmata.[18] To a 100 mL flame-dried, round bottom flask equipped with a magnetic stir bar, alcohol **16** (1.72 g, 3.4 mmol, 1.0 equiv) and CH_2Cl_2 (69 mL) is added. Temperature is brought down to -78 °C and p-toluenesulfonic acid (59 mg, 0.31 mmol, 0.09 equiv) is added as a solid in one portion. The solution is allowed to come to 23 °C and stirred for 8h. Upon completion, solid K_2CO_3 is added and stirring is continued for 10 min. The reaction mixture is filtered and concentrated. Flash column chromatography (silica gel, hexanes/EtOAc, 6/1) of the resultant residue gave Kagan ether **17** (1.38 g, 92% yield) as a white solid. **17**: R_f = 0.42 (silica gel, hexanes/EtOAc, 6/1); ^{1}H NMR and ^{13}C NMR matched those reported by the Harmata group.[18]



16 **23**

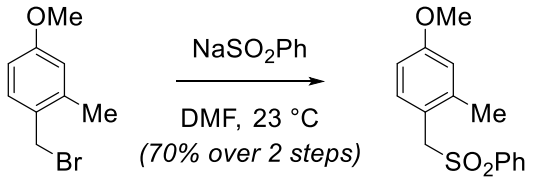
Mesylate 23: A 10 mL, flame-dried round bottom flask equipped with a magnetic stir bar, is charged with alcohol **16** (47 mg, 94 µmol, 1.0 equiv), CH_2Cl_2 (0.2 mL), Hunig's base (15 mg, 20 µL, 113 µmol, 1.2 equiv) and a single crystal of DMAP. The reaction mixture is cooled down to 0 °C and MsCl (13 mg, 9 µL, 113 µL, 1.2 equiv) is added. Stirring is continued at 0 °C for 2 h and at 23 °C for 4 h. Upon completion, the reaction system is quenched with water (2 mL) and diluted with

CH_2Cl_2 (2 mL) and the contents are transferred to a separatory funnel. The layers are extracted and the aqueous layer is extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layer is washed with water, dried ($MgSO_4$), filtered and concentrated. Flash column chromatography (silica gel, hexanes/EtOAc, 4/1) of the resultant residue gave mesylate **23** (34 mg, 63% yield) as a light yellow oil. **23**: R_f = 0.52 (silica gel, hexanes/EtOAc, 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52–7.25 (m, 11 H), 7.24–7.13 (m, 1 H), 6.96 (ddd, *J* = 8.5, 4.8, 2.8 Hz, 1 H), 6.88–6.82 (m, 2 H), 6.82–6.73 (m, 2 H), 5.09 (d, *J* = 4.1 Hz, 2 H), 5.01 (dd, *J* = 11.0, 6.7 Hz, 2 H), 4.72 (dd, *J* = 7.5, 5.5 Hz, 1 H), 4.30 (q, *J* = 5.5, 5.0 Hz, 1 H), 3.35–3.30 (m, 3 H), 3.30–3.25 (m, 3 H), 3.21–3.15 (m, 3 H), 3.07 (dt, *J* = 13.5, 5.9 Hz, 1 H), 2.92–2.83 (m, 1 H), 2.77 (tt, *J* = 14.0, 7.7 Hz, 2 H).



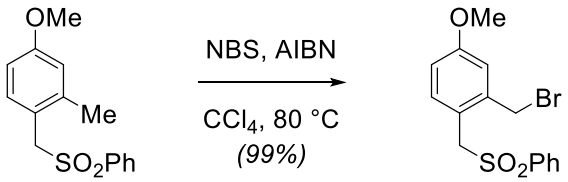
24 **25**

Bromide 25 was prepared according to the procedure developed by Gilligan[48]. To a 500 mL, flame-dried round bottom flask, equipped with a magnetic stir bar, a solution of 3,4 dimethyl anisole **24** (13.62 g, 100.0 mmol, 1.0 equiv) in carbon tetrachloride (200 mL) is added followed by the addition of N-bromo succinimide (17.8 g, 100.0 mmol, 1.0 equiv) and azobisisobutyronitrile (164 mg, 1 mmol, 0.01 equiv). The reaction mixture is heated to 80 °C and stirred for 3 h. Upon completion, the reaction contents are allowed to cool down to ambient temperature and is filtered and washed with CH_2Cl_2. Concentration on a rotary evaporator gave a yellow oily residue which was directly used for the next step.



25 **26**

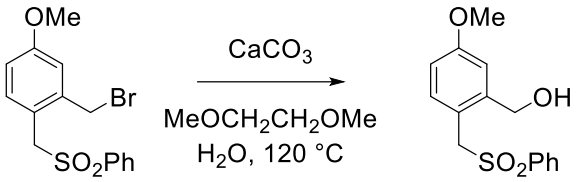
Sulphone 26 was prepared according to the procedure developed by Ghera.[49] To the crude mixture of the previous bromide **25** (100.0 mmol, 100% yield assumed), DMF (50 mL) is added followed by the addition of benzene sulfinic acid sodium salt (19.7 g, 120.0 mmol, 1.2 equiv). The reaction is allowed to stir for 4 h at 23 °C after which the reaction is quenched with water (50 mL) and diluted with Et_2O (200 mL). The reaction contents are transferred to a separatory funnel and the layers are separated. The aqueous layer is extracted with Et_2O (4 x 100 mL) until TLC showed no presence of product in the aqueous layer. The combined organic layer is then washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. Flash column chromatography (silica gel, hexanes/EtOAc, 2/1) of the resultant residue gave sulphone **26** (19.3 g, 70% yield over 2 steps) as a white solid. **26**: R_f = 0.30 (silica gel, hexanes/EtOAc, 2/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (dq, *J* = 14.9, 7.5, 6.8 Hz, 3 H), 7.47 (t, *J* = 7.7 Hz, 2 H), 6.94 (d, *J* = 8.2 Hz, 1 H), 6.64 (d, *J* = 9.3 Hz, 2 H), 4.31 (s, 2 H), 3.78 (s, 3 H), 2.06 (s, 3 H).



26 **27**

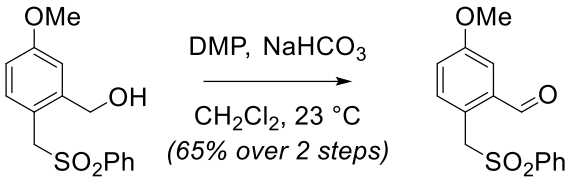
Bromo sulphone 27 was prepared according to the procedure developed by Ghera.[49] To a 2000 mL, flame-dried round bottom flask, equipped with a magnetic stir bar, a solution of sulphone **26**

(19.3 g, 70.0 mmol, 1.0 equiv) in carbon tetrachloride (700 mL) is added followed by the addition of N-bromo succinimide (12.5 g, 70.0 mmol, 1.0 equiv) and azobisisobutyronitrile (574 mg, 3.5 mmol, 0.05 equiv). The reaction mixture is heated to 80 °C and stirred for 3 h. Upon completion, the reaction contents are allowed to cool down to ambient temperature and is filtered and washed with CH_2Cl_2. Concentration on a rotary evaporator gave a yellow oily residue which was purified by flash column chromatography (silica gel, hexanes/EtOAc, 2/1) to give bromo sulphone **27** (24.7 g, 99% yield) as a white solid. **27:** R_f = 0.30 (silica gel, hexanes/EtOAc, 2/1); ^{1}H NMR and ^{13}C NMR spectra match those reported by Ghera.[49]



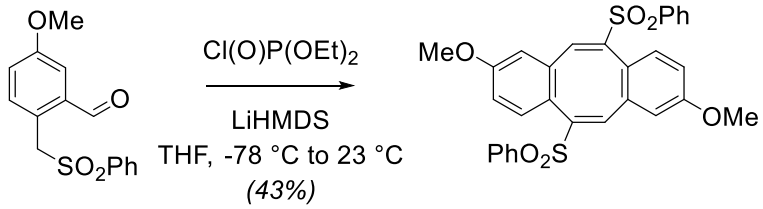
27 **28**

Alcohol 28: To a 1000 mL round bottom flask equipped with a magnetic stir bar, bromo sulphone **27** (24.7 g, 69.5 mmol, 1.0 equiv), $CaCO_3$ (69.5 g, 695 mmol, 10.0 equiv), 1,2-dimethoxy ethane (210 mL) and water (210 mL) is added and heated to 120 °C and stirred for 12 h. The solution is neutralized by the slow addition of 2 N HCl until gas evolution ceases and then diluted with CH_2Cl_2 (200 mL). The reaction contents are transferred to a separatory funnel and the layers are separated. The aqueous layer is extracted with CH_2Cl_2 (3 x 100 mL) and the combined organics is washed with brine, dried ($MgSO_4$), filtered, concentrated and directly used for the next step.



28 **29**

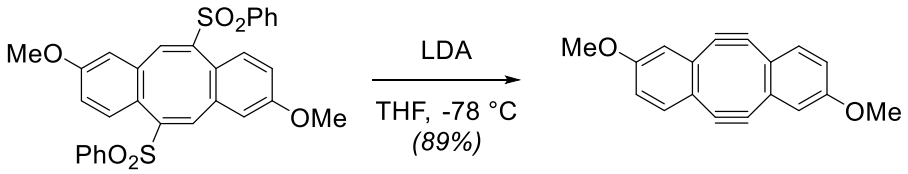
Aldehyde 29: To the crude mixture of the alcohol **28** (69.5 mmol, 100% yield assumed), CH_2Cl_2 (350 mL) is added followed by Dess-Martin periodinane (35.4 g, 83.4 mmol, 1.2 equiv) and $NaHCO_3$ (29.2 g, 347.5 mmol, 5.0 equiv) and the reaction is stirred at 23 °C for 2 h. After completion, the reaction mixture is concentrated and loaded directly onto a column for flash column chromatography (silica gel, hexanes/EtOAc, 2/1) to give aldehyde **29** (13.1 g, 65% yield over 2 steps) as a white solid. **29:** R_f = 0.24 (silica gel, hexanes/EtOAc, 2/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.80 (s, 1 H), 7.69 – 7.65 (m, 2 H), 7.60 (ddt, *J* = 8.7, 7.1, 1.3 Hz, 1 H), 7.49–7.43 (m, 2 H), 7.30 (d, *J* = 8.4 Hz, 1 H), 7.26 (s, 1 H), 7.09 (dd, *J* = 8.4, 2.8 Hz, 1 H), 4.90 (s, 2 H), 3.88 (d, *J* = 0.8 Hz, 3 H).



29 **30**

Vinyl sulphone dimer 30: To a 2000 mL, flame-dried round bottom flask equipped with a magnetic stir bar was added the aldehyde **29** (13.1 g, 45.2 mmol, 1.0 equiv), THF (675 mL) and $Cl(O)P(OEt)_2$ (9.4 g, 54.2 mmol, 1.2 equiv). The reaction mixture was then cooled down to -78 °C and LiHMDS (90.4 mL, 1 M in THF, 90.4 mmol, 2.0 equiv) is added dropwise. The reaction contents

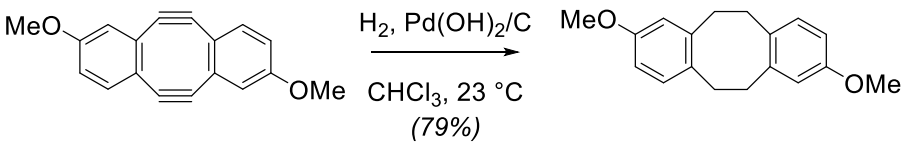
are stirred for 30 min at -78 °C and for 90 min at 23 °C. Upon completion, the reaction is quenched by the addition of saturated NH_4Cl solution (200 mL). The contents are transferred to a separatory funnel and the layers are separated. The aqueous layer is extracted with EtOAc (3 x 200 mL) and the combined organics is washed with water and brine, dried ($MgSO_4$), filtered and concentrated. Flash column chromatography (silica gel, hexanes/EtOAc, 2/1) of the resultant residue gave vinyl sulphone dimer **30** (5.3 g, 43% yield) as a white solid. **30**: R_f = 0.42 (silica gel, hexanes/EtOAc, 2/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (t, *J* = 7.4 Hz, 2 H), 7.51–7.38 (m, 10 H), 6.80 (dd, *J* = 8.7, 2.7 Hz, 2 H), 6.48 (d, *J* = 2.7 Hz, 2 H), 3.74 (d, *J* = 0.9 Hz, 6 H).



30 **31**

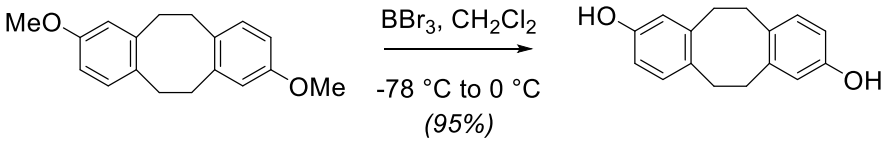
Dialkyne 31: In a 100 mL, flame-dried round bottom flask equipped with a magnetic stir bar, n-BuLi (15.4 mL, 2.5 M solution in hexanes, 38.5 mmol, 5.0 equiv) is added to a solution of di-isopropyl amine (3.9 g, 5.4 mL, 38.5 mmol, 5.0 equiv) in THF (18 mL, 1 M solution of LDA) at -78 °C and the temperature is raised to 0 °C and stirred for 15 min. A separate 250 mL, flame-dried round bottom flask equipped with a magnetic stir bar, was charged with vinyl sulphone dimer **30** (5.3 g, 9.7 mmol, 1.0 equiv) and THF (40 mL). To this, the fresh LDA solution prepared above (1 M, 5.0 equiv) is added dropwise at -78 °C. After stirring at that temperature for 2 h, the reaction is quenched by the addition of saturated NH_4Cl solution (50 mL). The contents are transferred to a separatory funnel and the layers are separated. The aqueous layer is extracted with EtOAc (3 x 50 mL) and the combined organics is washed with water and brine, dried ($MgSO_4$), filtered and

concentrated. Flash column chromatography (silica gel, hexanes/CH_2Cl_2, 5/2) of the resultant residue gave dialkyne **31** (2.25 g, 89% yield) as a yellow solid. **31**: R_f = 0.53 (silica gel, hexanes/CH_2Cl_2, 3/2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.68 (d, *J* = 8.4 Hz, 2 H), 6.39 (dd, *J* = 8.4, 2.7 Hz, 2 H), 6.34 (d, *J* = 2.6 Hz, 2 H), 3.72 (s, 6 H).



31 **33**

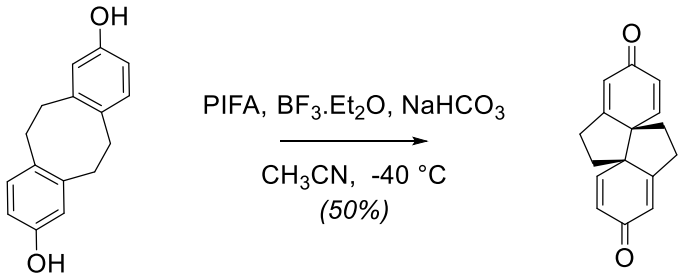
Cyclooctane 33: To a 100 mL, round bottom flask equipped with a magnetic stir bar, a solution of the dialkyne **31** (2.25 g, 8.6 mmol, 1.0 equiv) in chloroform (43 mL) is added followed by Pearlman's catalyst $Pd(OH)_2/C$ (10%, 200 mg). The system is bubbled with H_2 gas for 45 min and stirred for 3 h at 23 °C. Upon completion as judged by TLC, the system is filtered through celite, concentrated and purified by flash column chromatography (silica gel, hexanes/EtOAc, 6/1) to give cyclooctane **33** (1.90 g, 79% yield) as a white solid. **33:** R_f = 0.38 (silica gel, hexanes/EtOAc, 6/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90 (dd, *J* = 8.0, 2.5 Hz, 2 H), 6.58–6.53 (m, 4 H), 3.73 (s, 6 H), 3.03–2.98 (m, 8 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.75, 141.78, 132.96, 130.56, 115.62, 110.74, 55.10, 35.33, 34.51.



33 **4**

Diphenol 4: To a 250 mL, flame-dried round bottom flask equipped with a magnetic stir bar, a solution of the cyclooctane **33** (1.90 g, 6.9 mmol, 1.0 equiv) in CH_2Cl_2 (69 mL) is added. The

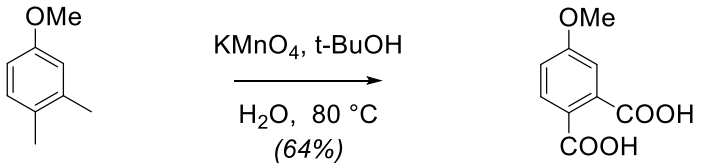
temperature of the reaction is lowered to -78 °C and BBr_3 (17.3 mL, 1 M solution in CH_2Cl_2, 17.3 mmol, 2.5 equiv) is added. The temperature is brought back up to 0 °C and stirred for 2 h. Upon completion, the reaction is quenched with the dropwise addition of saturated $NaHCO_3$ solution until gas evolution ceases. The reaction contents are transferred to a separatory funnel and the layers are separated. The aqueous layer is extracted with CH_2Cl_2 (3 x 50 mL) and the combined organics are dried ($MgSO_4$), filtered, and concentrated. Flash column chromatography (silica gel, hexanes/EtOAc, 1/1) of the resultant residue gave diphenol **4** (1.58 g, 95% yield) as a white amorphous solid. **4**: R_f = 0.25 (silica gel, hexanes/EtOAc, 1/1); ^{1}H NMR (500 MHz, Acetone-d_6) δ 7.86 (s, 2 H), 6.80 (d, *J* = 7.9 Hz, 2 H), 6.50 (d, *J* = 2.6 Hz, 2 H), 6.46 (dd, *J* = 8.1, 2.6 Hz, 2 H), 3.01–2.98 (m, 8 H); ^{13}C NMR (126 MHz, Acetone-d_6) δ 155.85, 142.15, 131.59, 130.98, 117.11, 112.92, 35.54, 34.27.



4 **3**

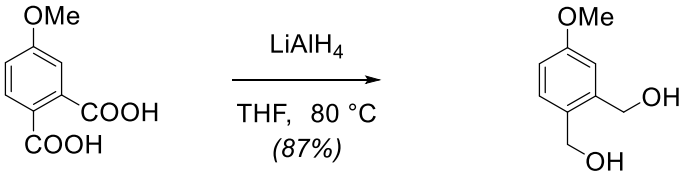
Tetracyclic tetra-enone 3: A 250 mL, flame-dried round bottom flask equipped with a magnetic stir bar is charged with PIFA (3.4 g, 7.9 mmol, 1.2 equiv), $NaHCO_3$ (2.76 g, 32.9 mmol, 5.0 equiv), $BF_3.Et_2O$ (1.87 g, 1.6 mL, 13.2 mmol, 2.0 equiv) and CH_3CN (132 mL). The reaction mixture is cooled down to -40 °C and diphenol **4** (1.58 g, 6.6 mmol, 1.0 equiv) is added as a solid in one shot and stirred at -40 °C for 2 h. Upon completion, the reaction system is concentrated and loaded directly onto a column for flash column chromatography (silica gel, hexanes/EtOAc, 1/3) to give

tetracyclic tetra-enone **3** (786 mg, 50% yield) as a white solid. **3:** R_f = 0.32 (silica gel, hexanes/EtOAc, 1/3); ^{1}H NMR (500 MHz, CDCl3) δ 6.63 (d, J = 9.8 Hz, 1 H), 6.26 (dd, J = 2.6, 1.3 Hz, 1 H), 6.17 (dd, J = 9.9, 1.7 Hz, 1 H), 3.09 (dddd, J = 17.8, 11.2, 5.4, 2.3 Hz, 1 H), 2.80 (dddd, J = 17.7, 9.6, 6.2, 1.3 Hz, 1 H), 2.32 (ddd, J = 14.2, 11.2, 6.1 Hz, 1 H), 2.07 (ddd, J = 14.5, 9.5, 5.3 Hz, 1 H); ^{13}C NMR (126 MHz, CDCl3) δ 207.12, 168.72, 147.25, 128.69, 124.43, 58.78, 35.64, 28.56. HRMS (ESI) calcd for $C_{16}H_{15}O_2$+ [M + H+] 239.1067, found 239.1076.



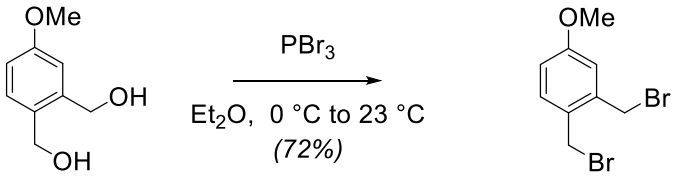
24 **36**

4-methoxy phthalic acid 36 was prepared according to the procedure developed by Wentzel.[38] A 1000 mL round bottom flask is charged with 3,4-dimethylanisole **24** (13.6 g, 100.0 mmol, 1.0 equiv), potassium permanganate (94.8 g, 600.0 mmol, 6.0 equiv), t-BuOH (160 mL) and water (400 mL), and refluxed at 80 °C for 20 h. Excess potassium permanganate is destroyed by adding EtOH (100 mL). The mixture is filtered through celite to remove MnO_2 and then concentrated on a rotary evaporator to remove excess EtOH. The mixture is then acidified by the addition of 3 N HCl and filtered to get 4-methoxy phthalic acid **36** (12.6 g, 64% yield) as a white solid. ^{1}H NMR and ^{13}C NMR spectra match those reported by Wentzel.[38]



36 **37**

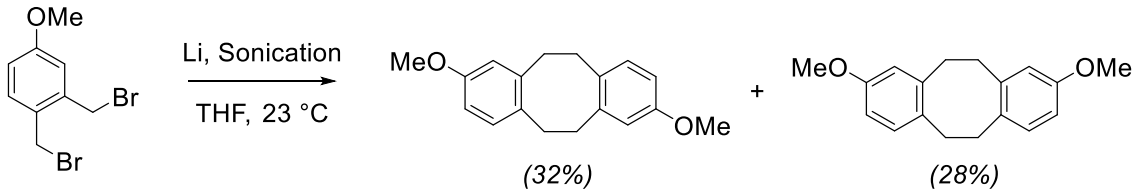
(2-hydroxymethyl-5-methoxy-phenyl)-methanol 37 was prepared according to the procedure developed by Haubrich.[50] A 500 mL, flame-dried round bottom flask equipped with a magnetic stir bar, is charged with 4-methoxy phthalic acid **36** (12.6 g, 64.0 mmol, 1.0 equiv) and THF (128 mL). Temperature is reduced to 0 °C and $LiAlH_4$ (5.8 g, 153.6 mmol, 2.4 equiv) is added to the mixture in batches. After the addition is complete, temperature is increased to 80 °C and stirred for 2 h. Upon completion, the temperature is brought back down to 0 °C and water (5.8 mL) is added very slowly followed by aqueous NaOH solution (5.8 mL, 15 g in 100 mL) and water (17.4 mL). The resulting solution is stirred for 15 min at 23 °C followed by the addition of $MgSO_4$. After 5 min, the mixture is filtered and concentrated. Flash column chromatography (silica gel, hexanes/EtOAc, 1/1) of the resultant residue gave (2-hydroxymethyl-5-methoxy-phenyl)-methanol **37** (9.42 g, 87% yield) as a colorless oil. **37**: R_f = 0.30 (silica gel, hexanes/EtOAc, 1/1); ^1H NMR and ^{13}C NMR spectra match those reported by Haubrich.[50]



37 **38**

1,2-bis(bromomethyl)-4-methoxybenzene 38 was prepared according to the procedure developed by Gleason.[39] To a 500 mL flame-dried round bottom flask charged with a magnetic stir bar, (2-hydroxymethyl-5-methoxy-phenyl)-methanol **37** (9.42 g, 56.0 mmol, 1.0 equiv) and Et_2O (280 mL), is added phosphorous tribromide (37.9 g, 16.1 mL, 140.0 mmol, 2.5 equiv) dropwise at 0 °C. Temperature is then raised to 23 °C and stirring is continued for 2 h. Upon

completion, the reaction is quenched by the addition of water (100 mL). The reaction contents are transferred to a separatory funnel and the layers are separated. The aqueous layer is extracted with Et_2O (3 x 100 mL) and the combined organic layer is washed with water and brine, dried ($MgSO_4$), filtered and concentrated. Flash column chromatography (silica gel, hexanes/EtOAc, 9/1) of the resultant residue gave 1,2-bis(bromomethyl)-4-methoxybenzene **38** (11.8 g, 72% yield) as a colorless oil. **38**: R_f = 0.48 (silica gel, hexanes/EtOAc, 9/1); ^1H NMR and ^{13}C NMR spectra match those reported by Gleason.[39]



38 *(32%)* **33** *(28%)* **39**

Cyclooctane 33 was prepared according to the sonication procedure developed by Han.[36] To a 250 mL, flame-dried round bottom flask equipped with a magnetic stir bar, a solution of 1,2-bis(bromomethyl)-4-methoxybenzene **38** (11.8 g, 40.1 mmol, 1.0 equiv) in THF (80 mL) is added. Li pieces (675 mg, 96.3 mmol, 2.4 equiv) are then added at 0 °C and the reaction mixture is subjected to sonication at 23 °C for 12 h. After completion, the reaction is quenched by very slow addition of water and diluted with Et_2O (50 mL). The reaction contents are then transferred to a separatory funnel and the layers are separated. The aqueous layer is then extracted with Et_2O (3 x 50 mL) and the combined organic layer is washed with water and brine, dried ($MgSO_4$), filtered and concentrated. Flash column chromatography (silica gel, hexanes/EtOAc, 6/1) of the resultant residue gave cyclooctane **33** (1.72 g, 32% yield) as a white solid and cyclooctane **39** (1.51 g, 28% yield) as a white solid. **39:** R_f = 0.36 (silica gel, hexanes/EtOAc, 6/1); ^1H NMR (500 MHz, $CDCl_3$) δ

7.25 (dd, *J* = 9.0, 6.9 Hz, 2 H), 6.89 (dt, *J* = 6.9, 2.2 Hz, 2 H), 6.79 (dq, *J* = 8.3, 2.7 Hz, 2 H), 3.85 (d, *J* = 2.5 Hz, 6 H), 2.98 (t, *J* = 16.6 Hz, 8 H).

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2.9 NMR's of selected intermediates

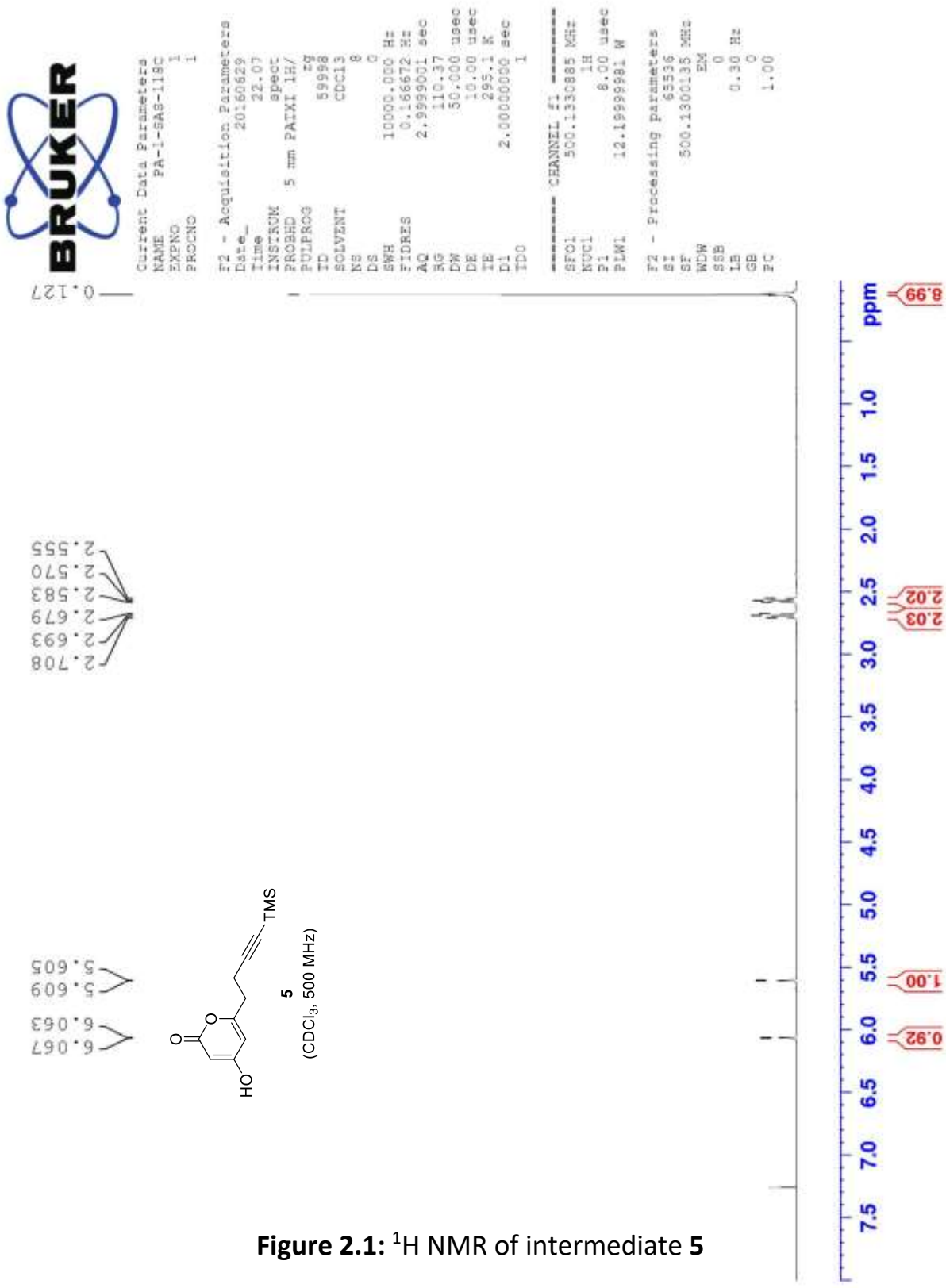


Figure 2.1: ^{1}H NMR of intermediate **5**

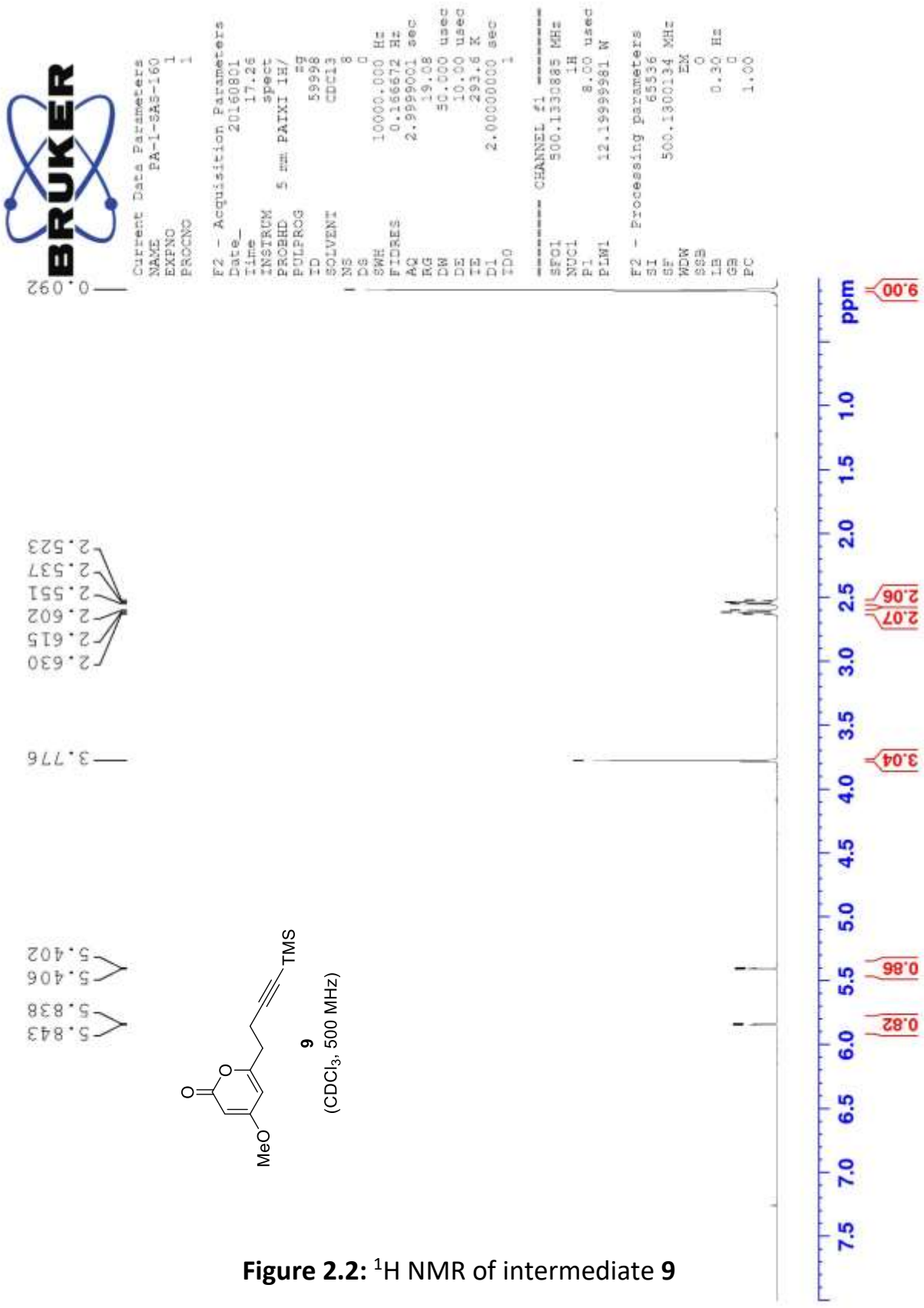


Figure 2.2: ^{1}H NMR of intermediate **9**

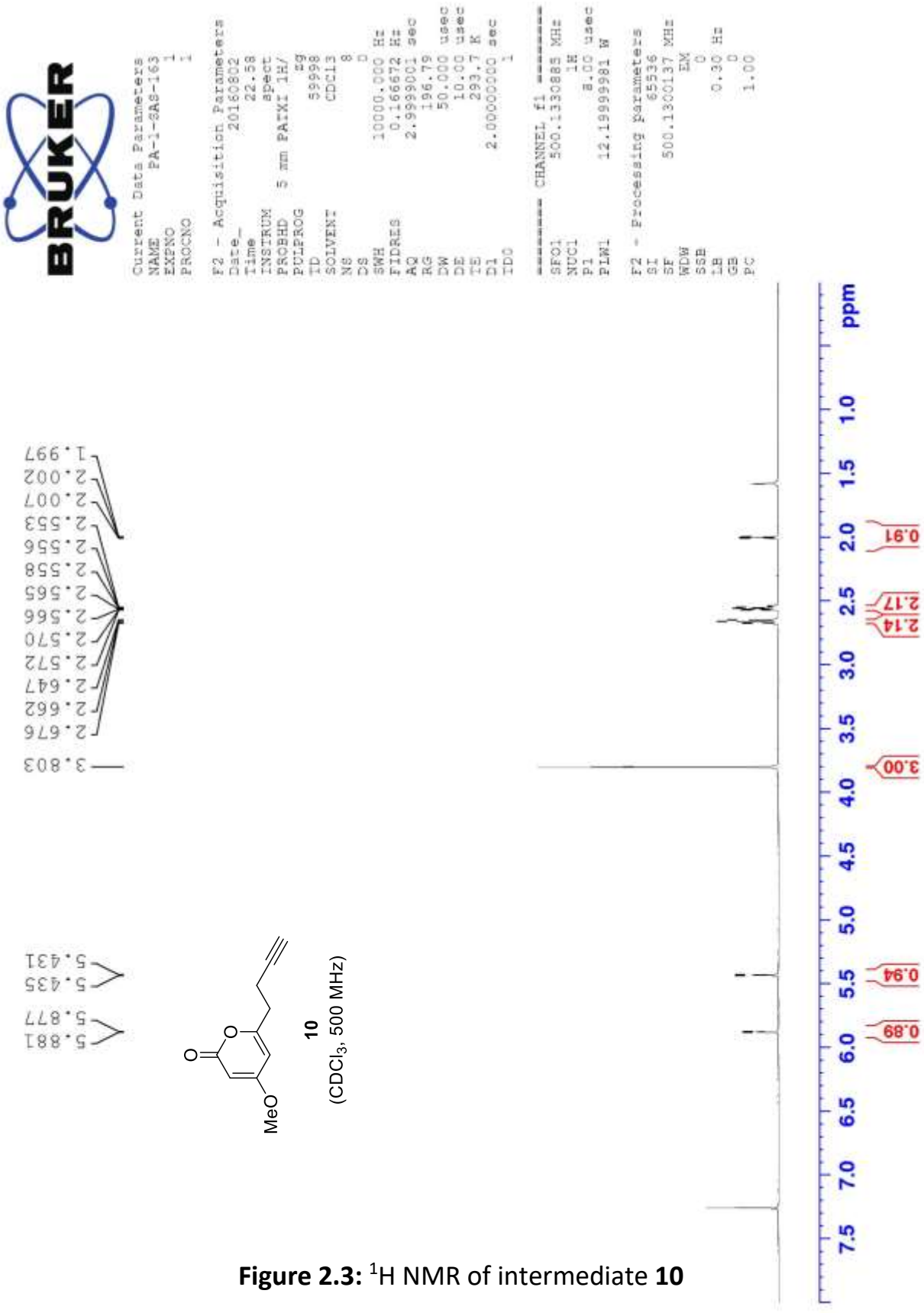


Figure 2.3: ^{1}H NMR of intermediate **10**

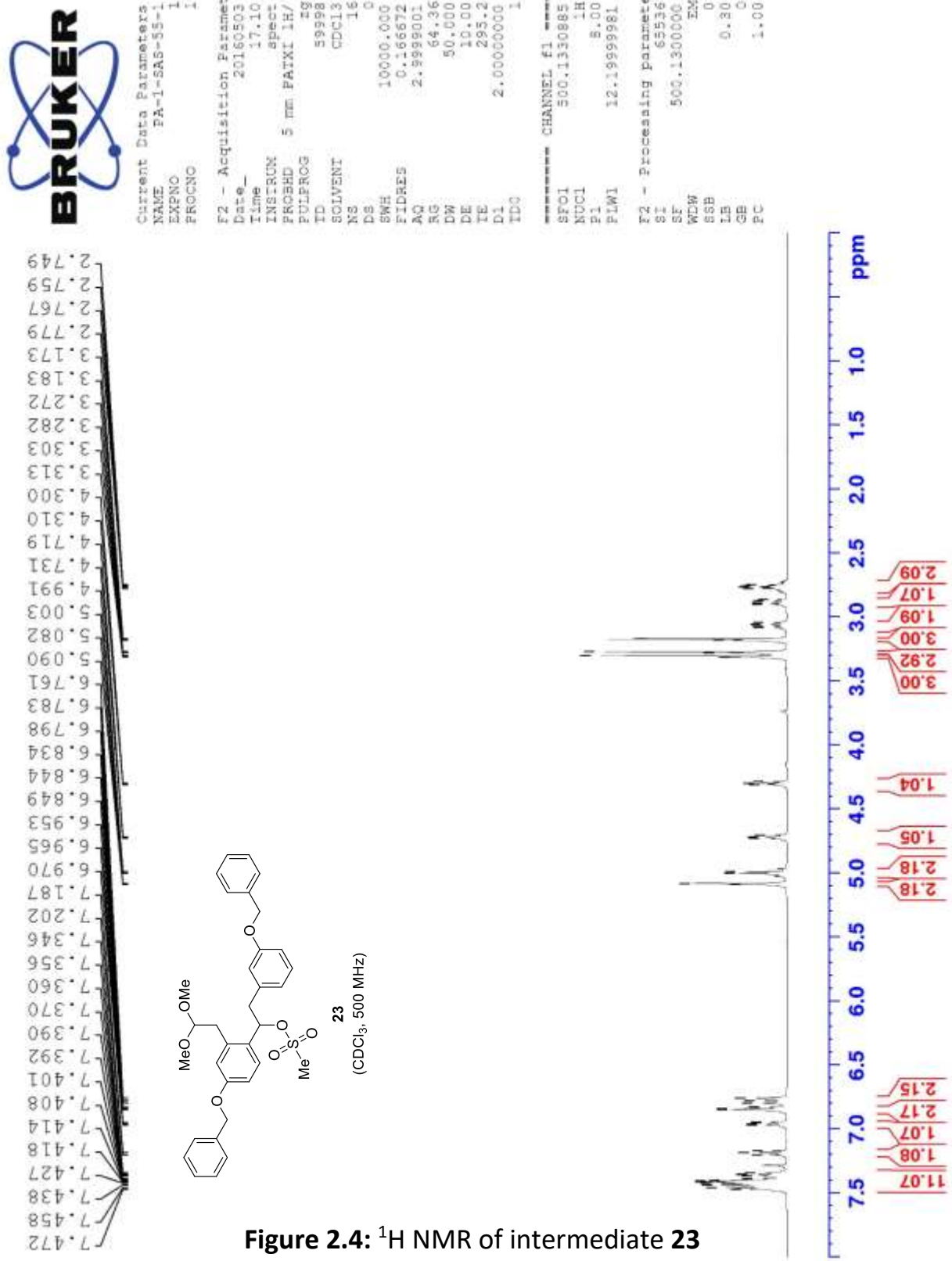


Figure 2.4: ^{1}H NMR of intermediate **23**

Figure 2.5: ^{1}H NMR of intermediate **26**

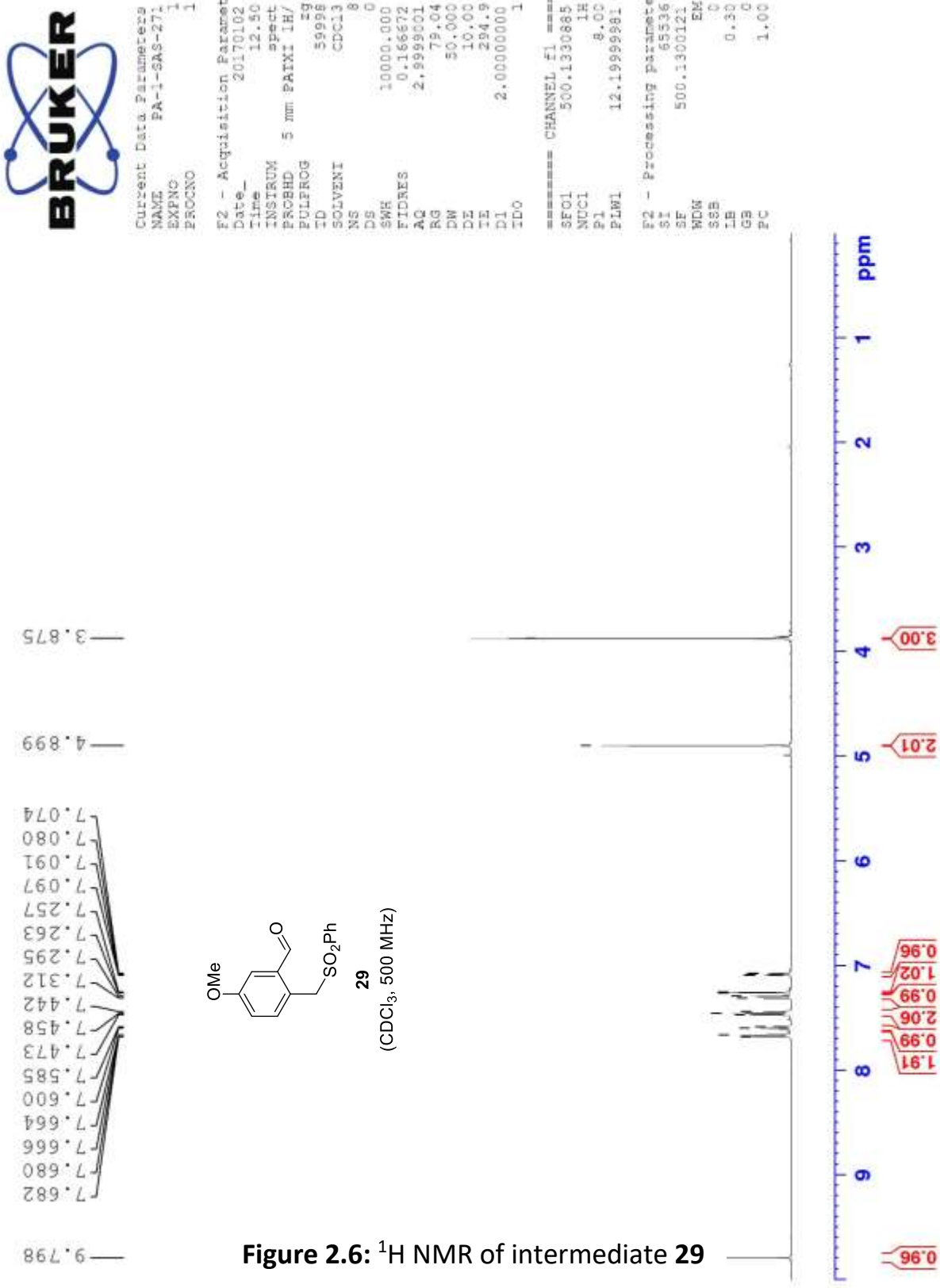


Figure 2.6: ^{1}H NMR of intermediate **29**

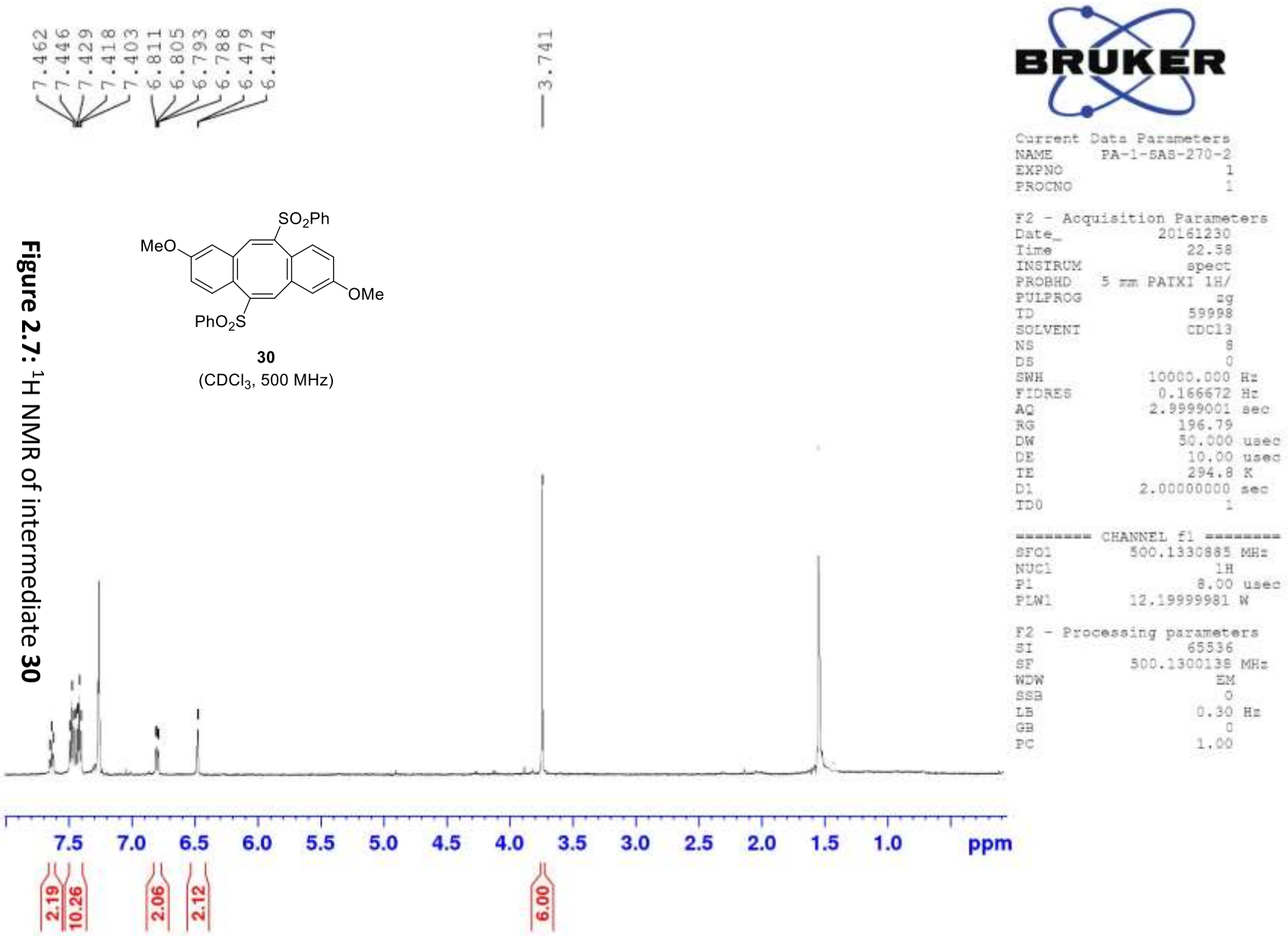


Figure 2.7: ^{1}H NMR of intermediate **30**

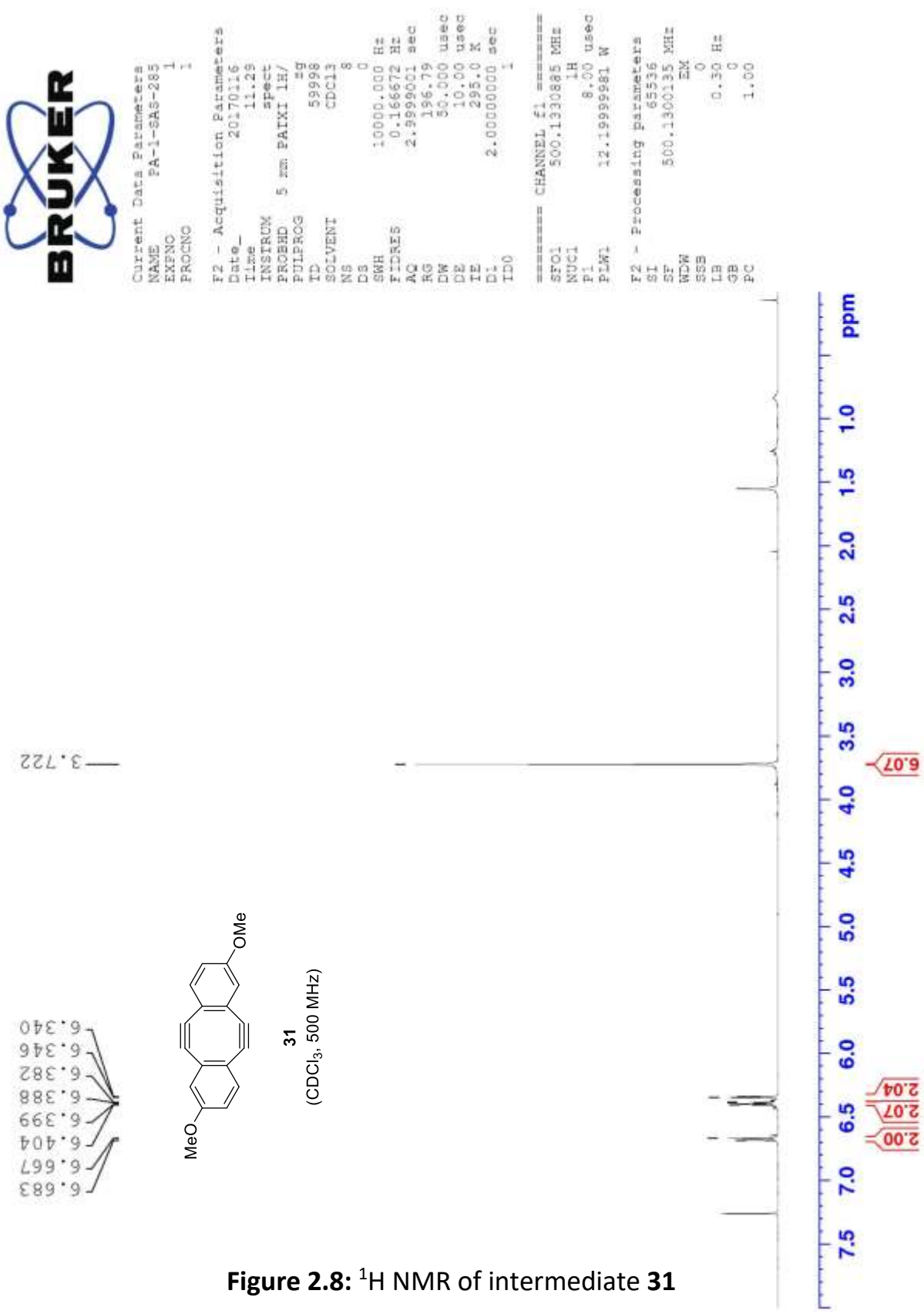


Figure 2.8: ^{1}H NMR of intermediate **31**

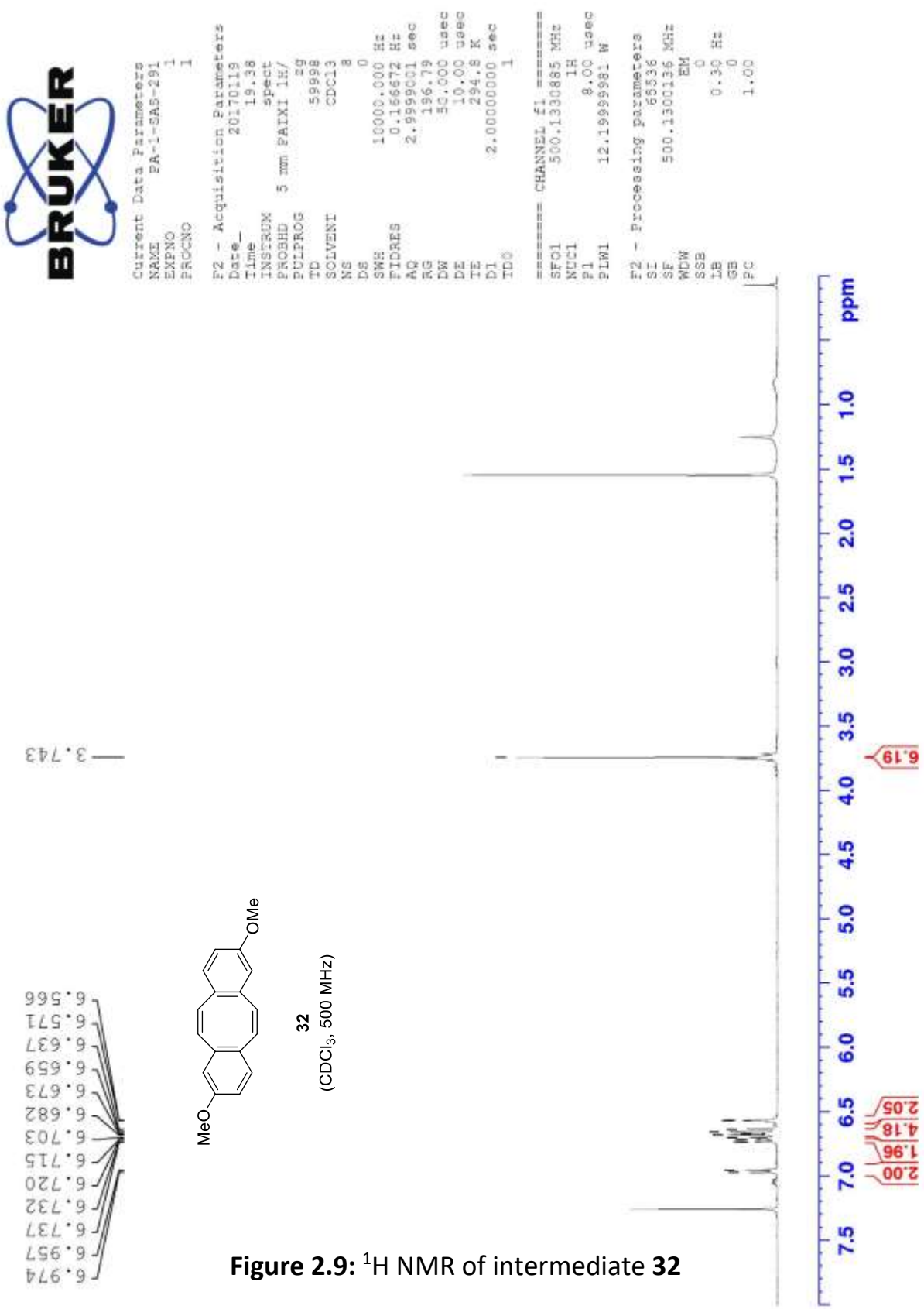


Figure 2.9: ^{1}H NMR of intermediate **32**

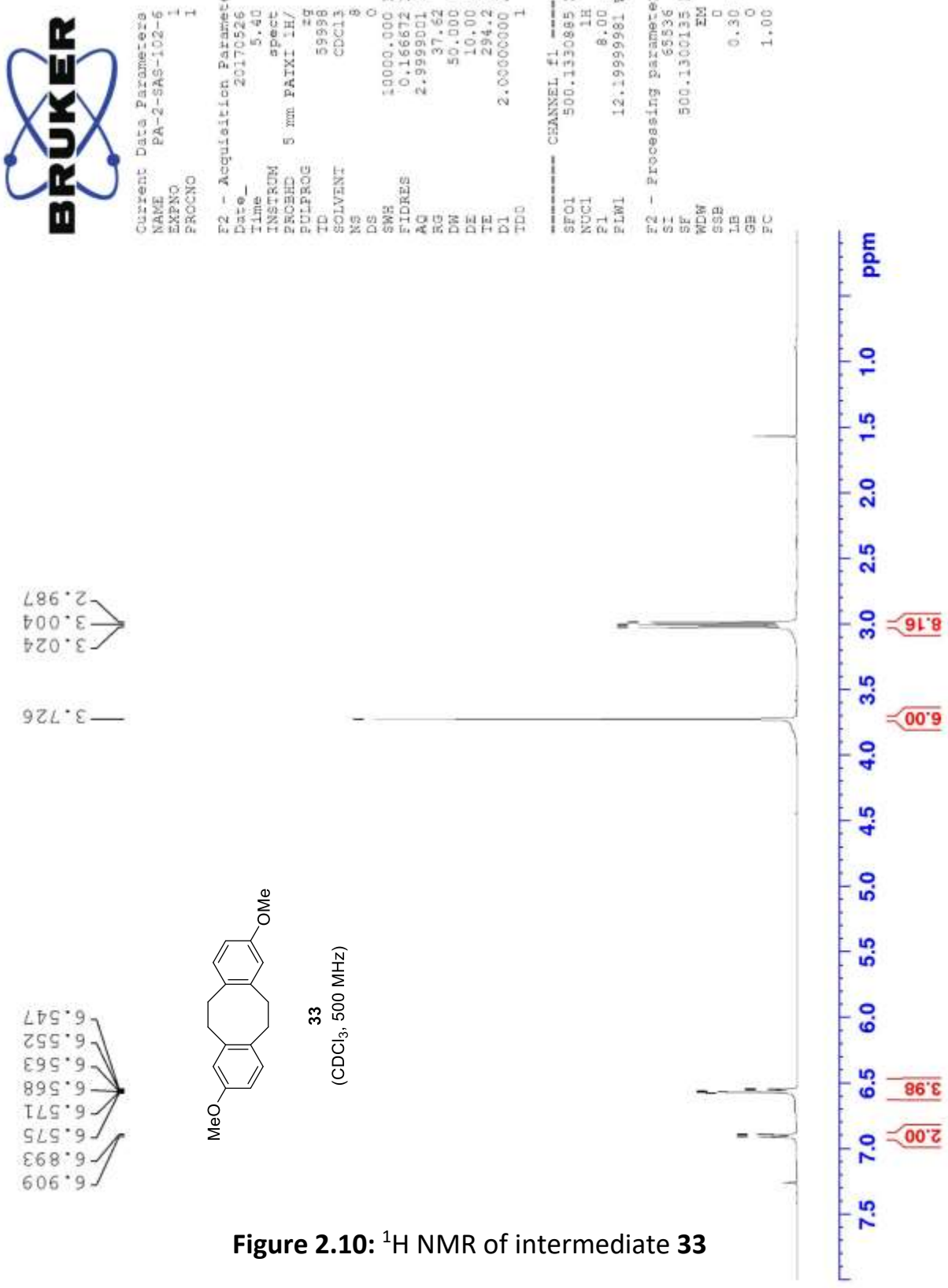
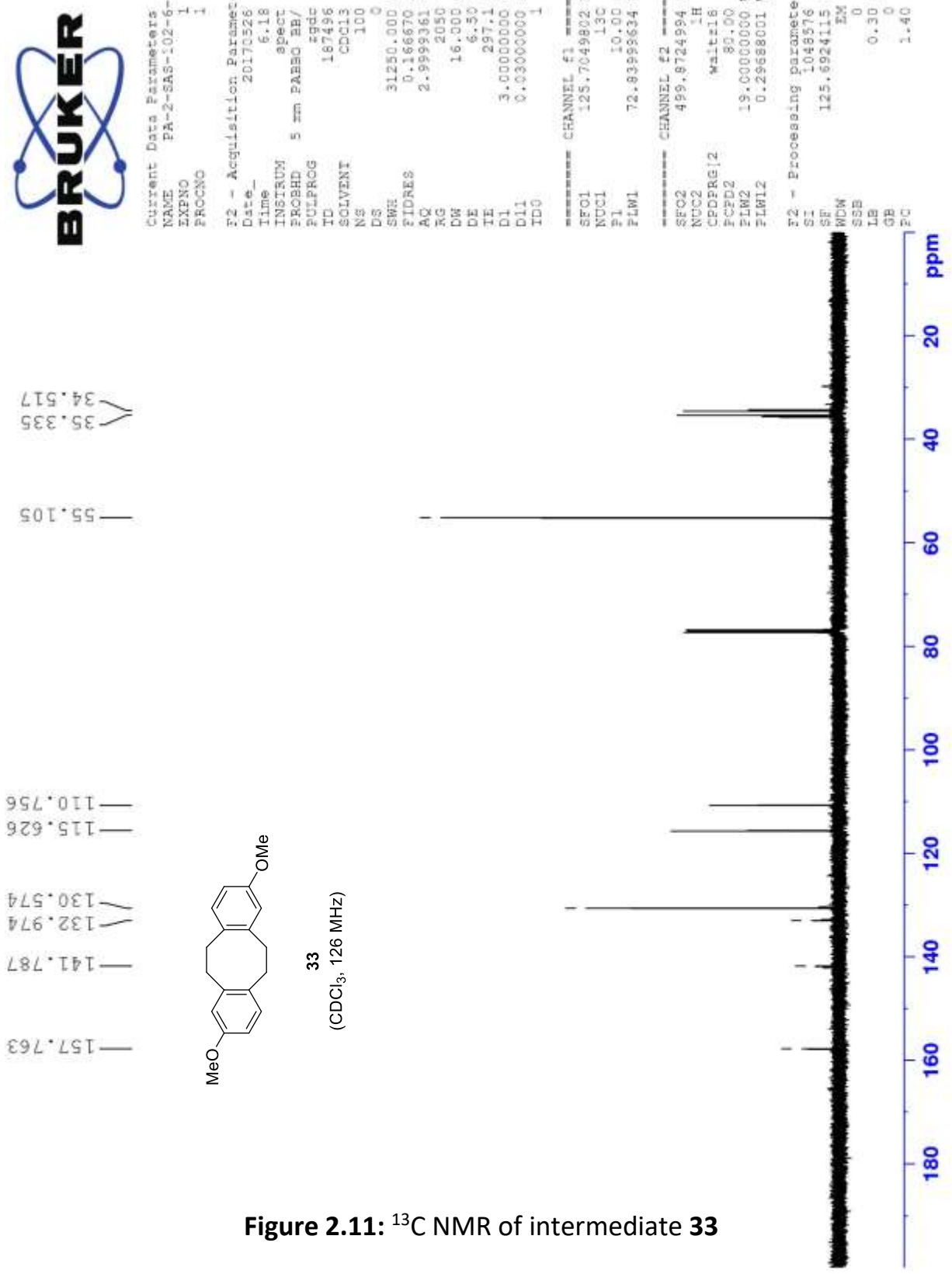


Figure 2.10: ^{1}H NMR of intermediate **33**



33
($CDCl_3$, 126 MHz)

Figure 2.11: ^{13}C NMR of intermediate **33**

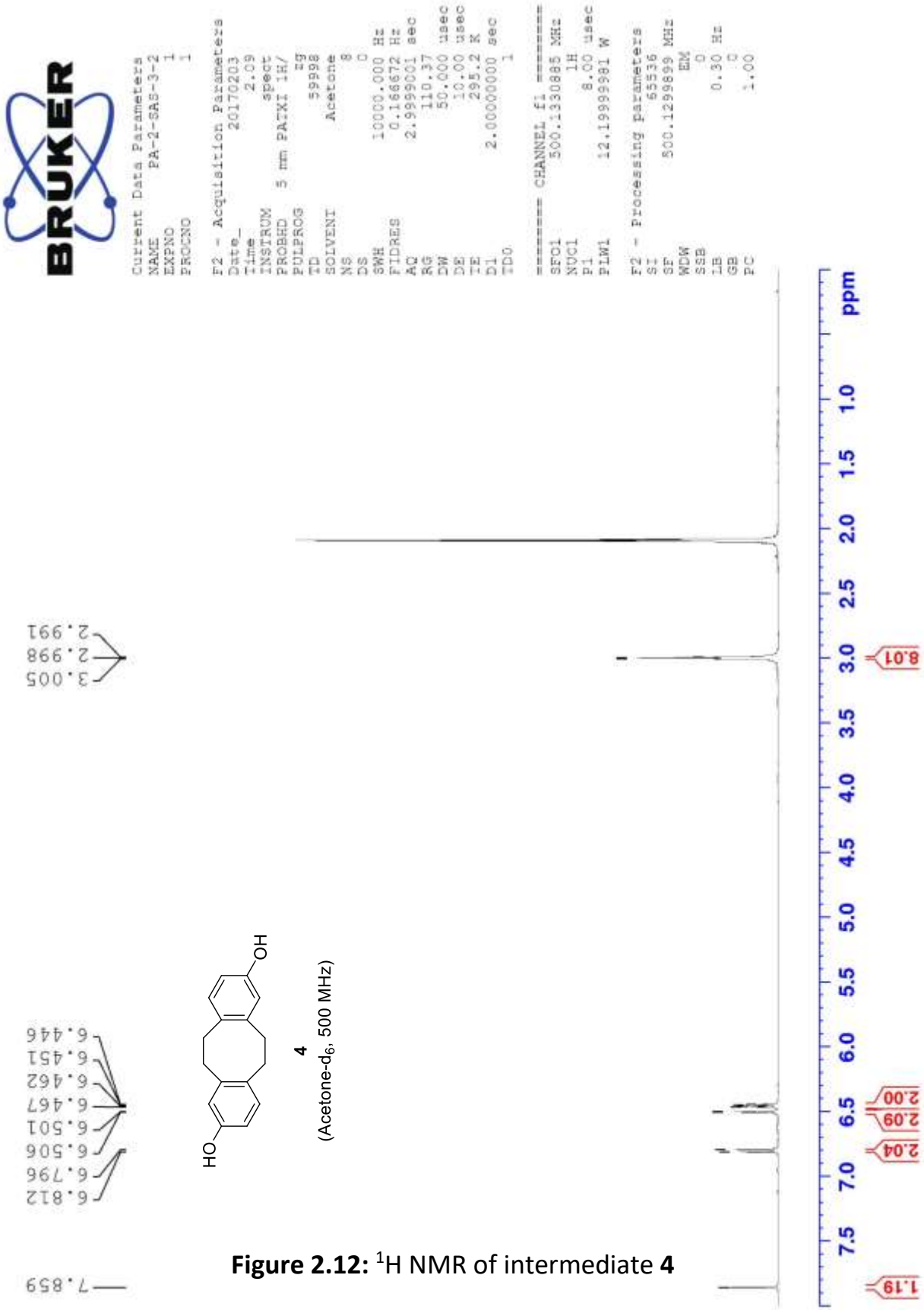


Figure 2.12: ^{1}H NMR of intermediate **4**

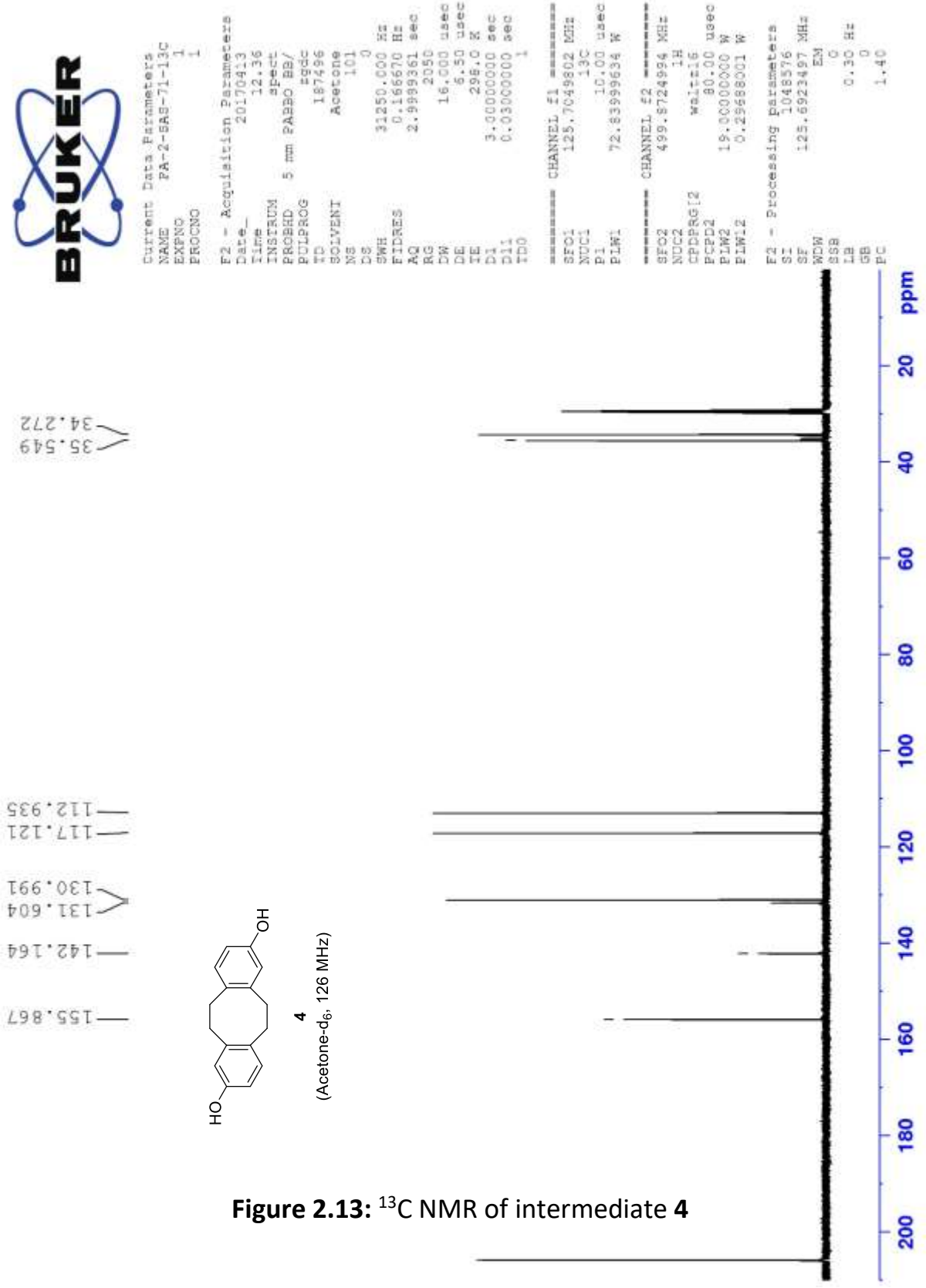


Figure 2.13: ^{13}C NMR of intermediate **4**

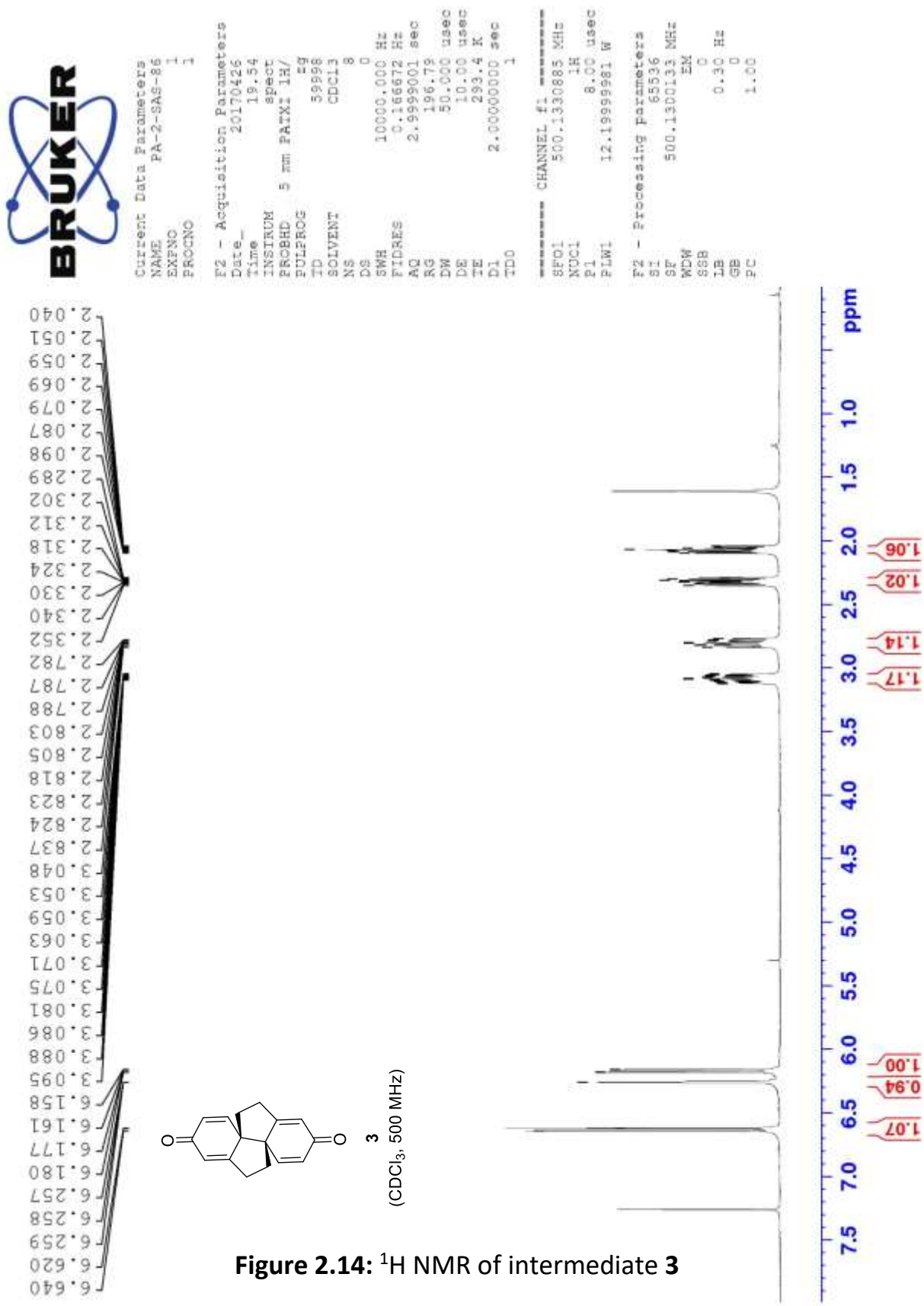


Figure 2.14: ^{1}H NMR of intermediate **3**

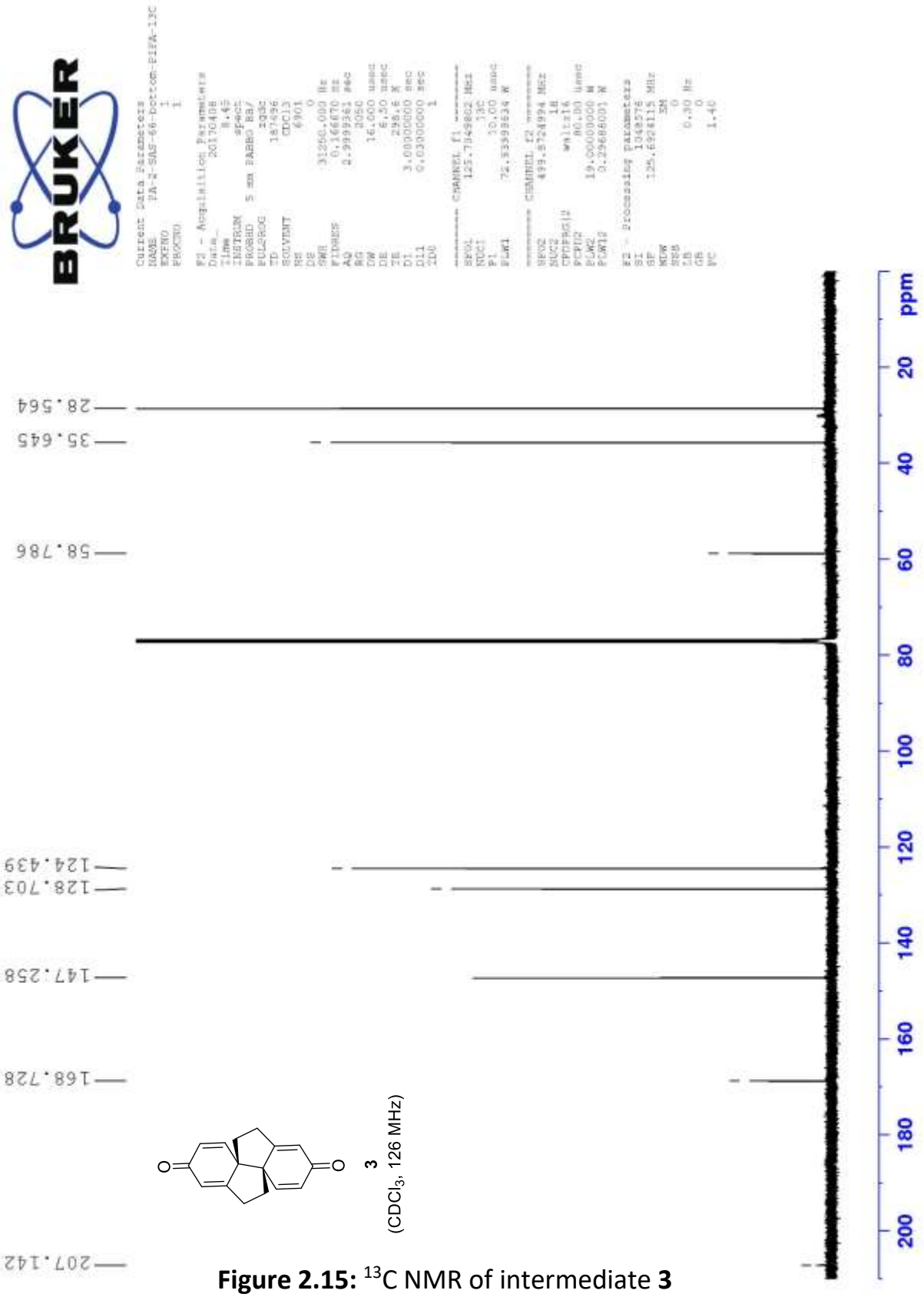


Figure 2.15: ^{13}C NMR of intermediate **3**

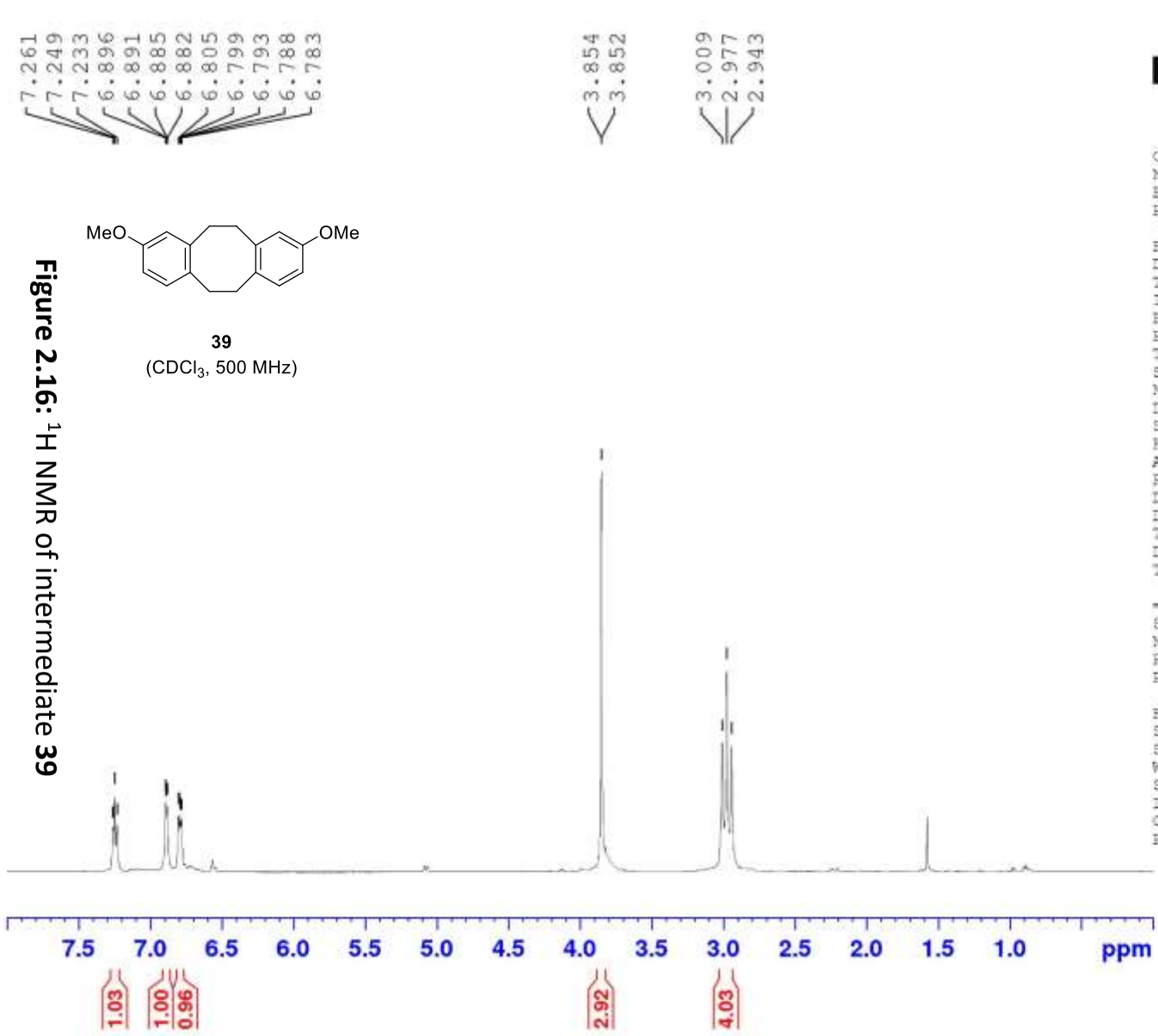


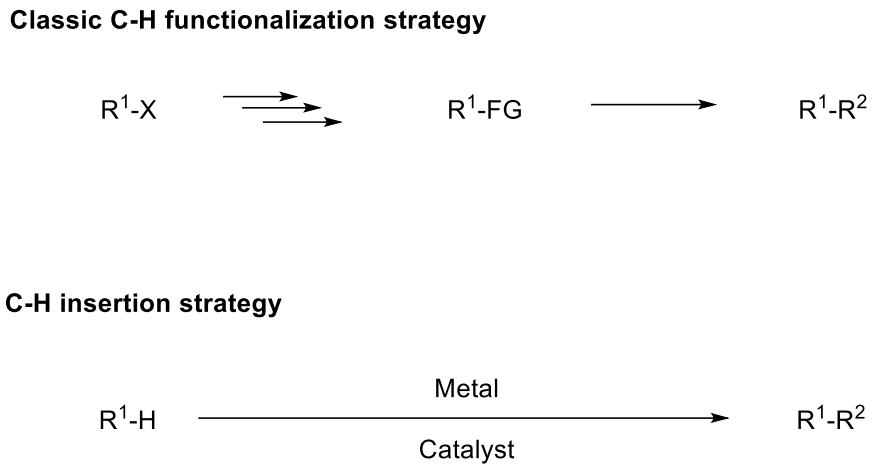
Figure 2.16: ^{1}H NMR of intermediate **39**

Chapter 3

C-H insertion strategy towards waihoensene

3.1 Introduction

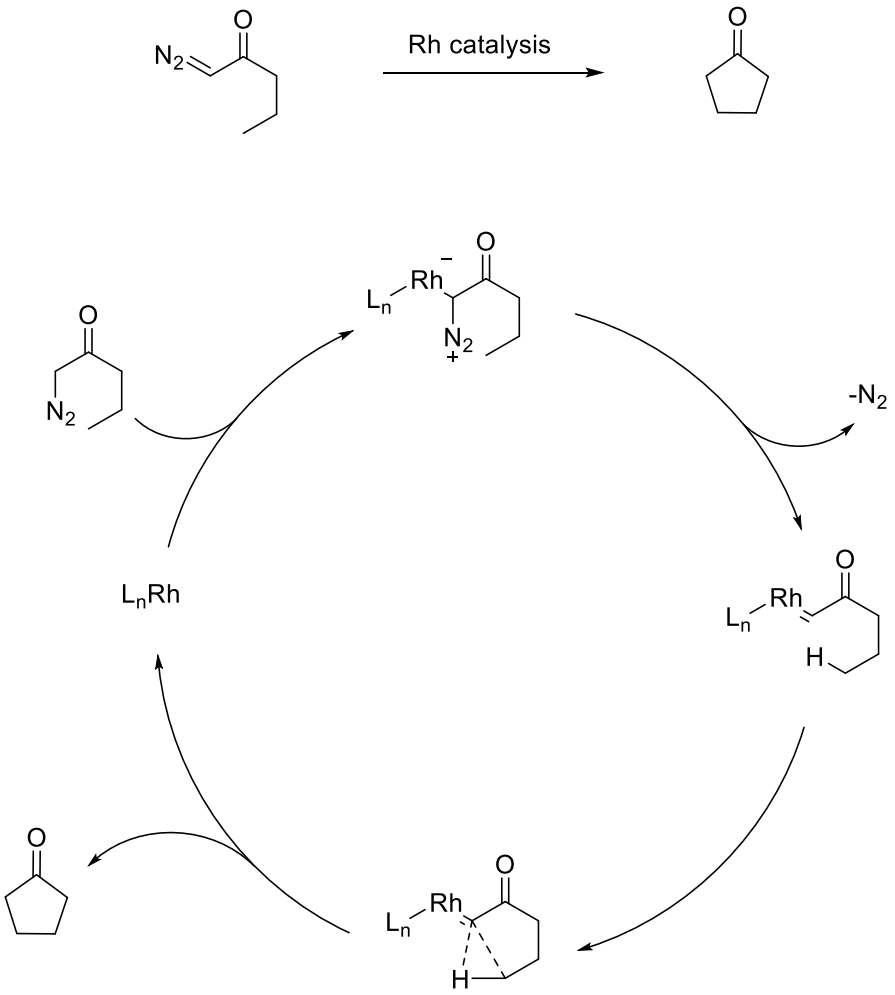
C-H insertion has emerged as a very powerful tool in the field of molecular synthesis with its varied applications in the fields of drug discovery, medicinal chemistry, pharmaceutical sciences and materials engineering.[1–6] Isolated C-H bonds, although ubiquitous in organic molecules, are very unreactive owing to their large kinetic barriers due to a very high bond dissociation energy and very non-polar nature of the bond. Therefore, the capability of directly functionalizing such a ubiquitous bond in nature is considered the Holy Grail in organic synthesis. For that reason, selectively activating such a non-functional group has actively been studied for several decades now. C-H insertion strategy allows for the synthesis of very complex molecules in a very step-economical, environmental-friendly and non-toxic fashion which does not necessitate the pre-installation of functional groups for coupling of C-C or C-heteroatom bonds.



Scheme 3.1: C-H insertion strategy

3.1.1 Rh-catalyzed insertion of diazo compounds

Insertion of a carbene into C-H bonds has attracted immense attention from the synthetic community because of its potential to construct difficult C-C bonds.[7,8] In this respect, the use of diazo compounds for the in-situ carbene generation has become a very popular method of forming carbenes. While, free carbenes are generated using thermal or photochemical reactions, carbenoids i.e. carbenes bonded to transition metals are generated from reactions with transition metals.[9–12] Extensive studies on the reactivities and properties of these carbenoids has been undertaken and the potential of this particular methodology is under investigation by the synthetic community at large.[13,14] The working mechanism of this reaction (Scheme 3.2) and some natural products synthesized using this methodology[15–17] is discussed in Figure 3.1.



Scheme 3.2: Mechanism of Rh-catalyzed C-H insertion

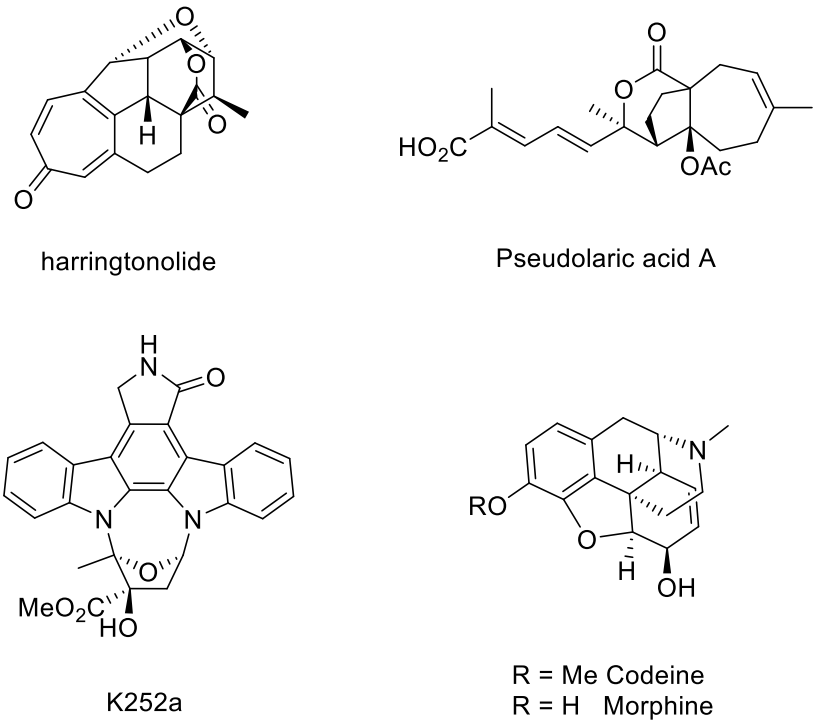
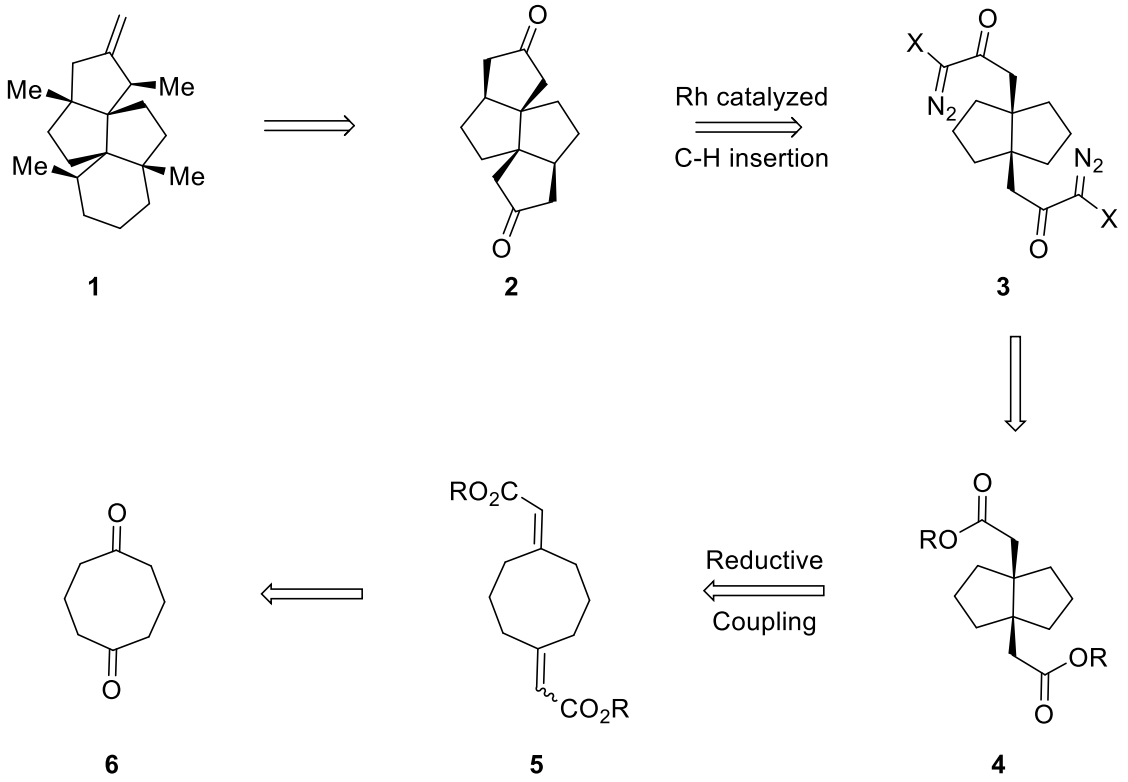


Figure 3.1: Natural products synthesized using Rh-catalyzed C-H insertion

3.2 Retrosynthetic Analysis

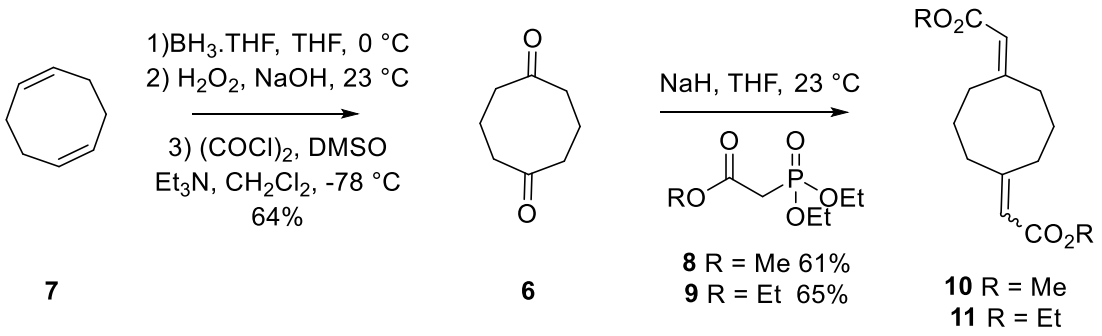
Still keeping with the possibility of a symmetrical element in the retrosynthetic analysis of the molecule, we envisioned the natural product waihoensene **(1)** to arise from the symmetric tetracyclic compound **2** through de-symmetrization via a ring expansion reaction[18–22] followed by installation of the methyl groups. The tetracyclic ketone **2** could be synthesized via a Rh-catalyzed C-H insertion reaction on the diazo compound **3**. This compound can be generated from the ester compound **4** which is synthesized using a samarium mediated reductive coupling reaction[23–31] starting from the α,β-unsaturated ester **5**. Horner-Wadsworth-Emmons reaction on the previously known 1,5-cyclooctadione **6** could deliver the α,β-unsaturated ester **5** (Scheme 3.3).



Scheme 3.3: Retrosynthetic analysis

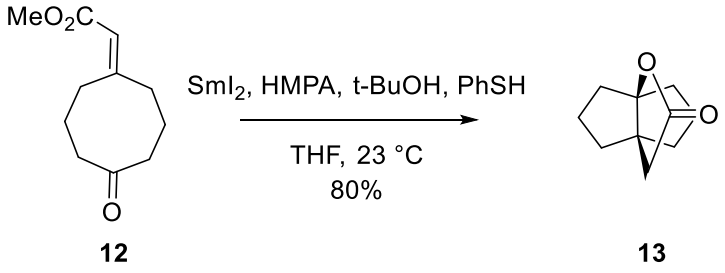
3.3 Reductive Coupling

Our synthesis commenced with the synthesis of 1,5-cyclooctadione. According to the literature procedure, 1,5-cyclooctadiene **7** was subjected to hydroboration-oxidation reaction to give the diol which was oxidized via Swern oxidation to generate the 1,5-cyclooctadione **6**.[32] Subjecting this compound to Horner-Wadsworth-Emmons conditions with carboxylate phosphonates **8** and **9** using sodium hydride as the base in THF, gave the α,β-unsaturated esters **10** and **11** with yields ranging from 60-65% (Scheme 3.4).[33] Other olefination conditions such as Wittig olefination, Julia olefination or Peterson olefination gave either no product or only the mono esters as the major product. With this, the stage was set for attempting the first key step, samarium mediated reductive coupling to forge the bicyclic structure **4**.

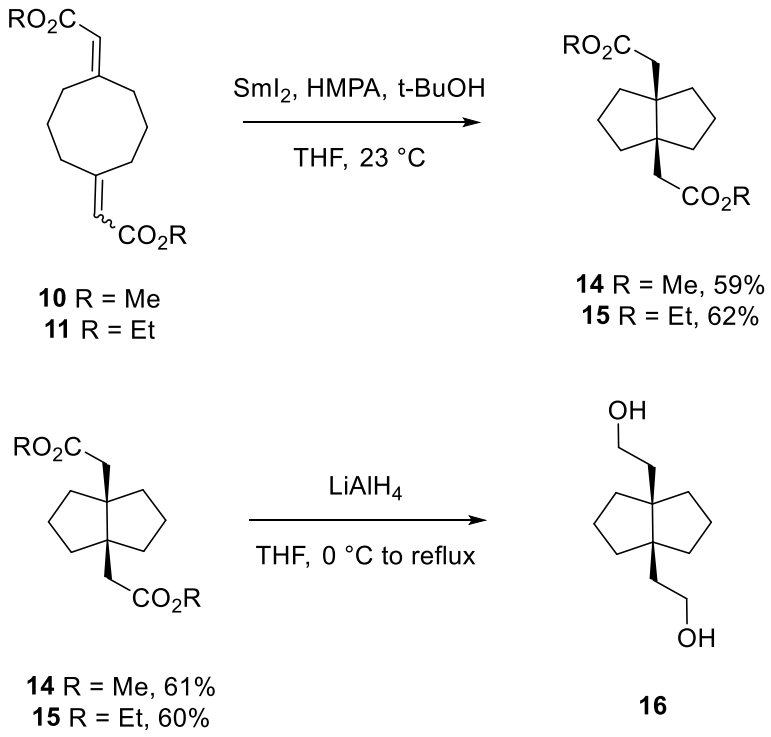


Scheme 3.4: Synthesis of reductive coupling precursors

For the reductive coupling step, we decided to first employ the conditions used by Molander[28] (SmI_2, HMPA, t-BuOH, PhSH, THF, 23 °C) for the intramolecular reductive coupling of ketone **12** to give the fused bicyclic compound **13** (Scheme 3.5). Fortunately, on our initial attempts we were able to convert both the α,β-unsaturated esters **10** and **11** to the fused five-membered bicyclic esters **14** and **15** in ~60% yields (Scheme 3.6). In our case, we found that the use of PhSH was inconsequential as the yields did not vary in its absence. To confirm the stereochemistry of the reductive coupling products both the bicyclic esters **14** and **15** were reduced using excess lithium aluminum hydride to the bicyclic diol **16** which was recrystallized from CH_2Cl_2/hexane system. X-ray crystallography on the diol **16** confirmed the cis nature of the two ester groups on the bicyclic system (Scheme 3.6).

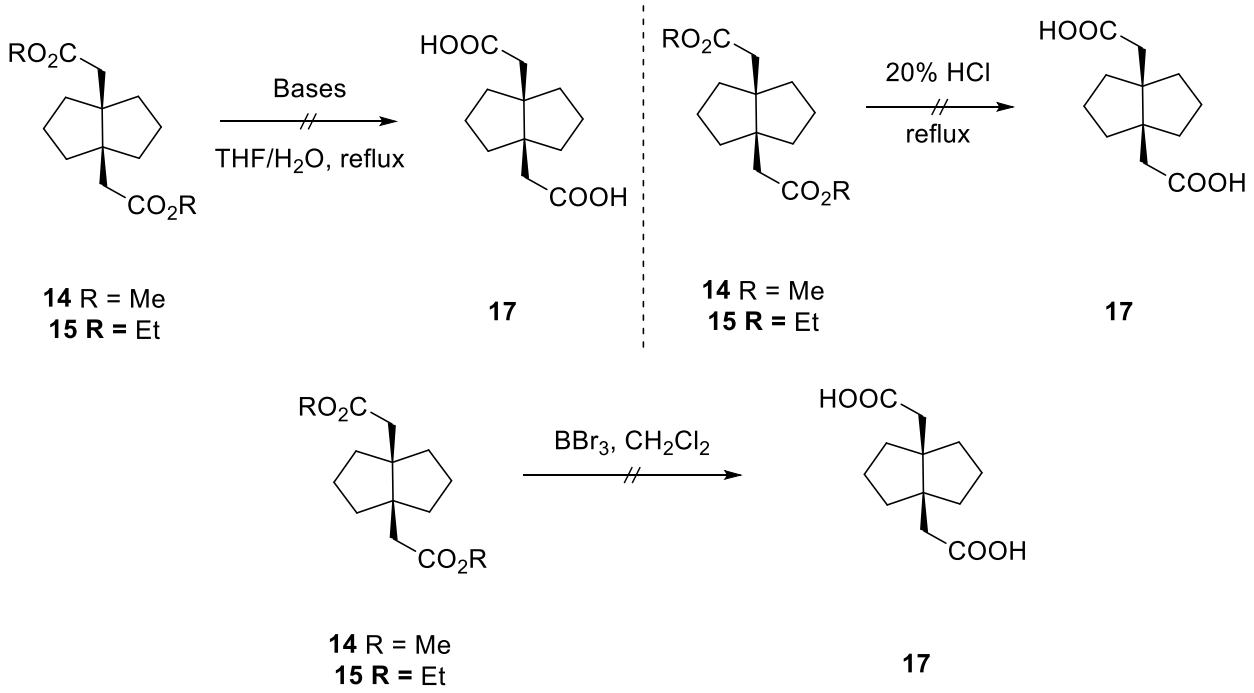


Scheme 3.5: Molander's conditions for reductive coupling



Scheme 3.6: SmI_2 mediated reductive coupling

With one of the key steps of the route solved, we turned our attention towards the Rh-catalyzed C-H insertion step. For that, the ester groups of the compounds **14** and **15** needed to be converted to the α-diazo compound **3** for which the ester groups needed to be hydrolyzed to the corresponding acid **17**. However, various basic hydrolysis conditions using a variety of bases like LiOH, NaOH, CsOH, K_2CO_3, Cs_2CO_3 etc did not affect any reaction even under reflux conditions. The use of acidic conditions like refluxing in 20% HCl or treating with boron tribromide was also not fruitful and no reaction was observed at all. We hypothesized, that the presence of the neo-pentyl system next to the carbonyl center was causing too much steric hindrance and that the alkyl groups were not active enough to undergo any reaction.

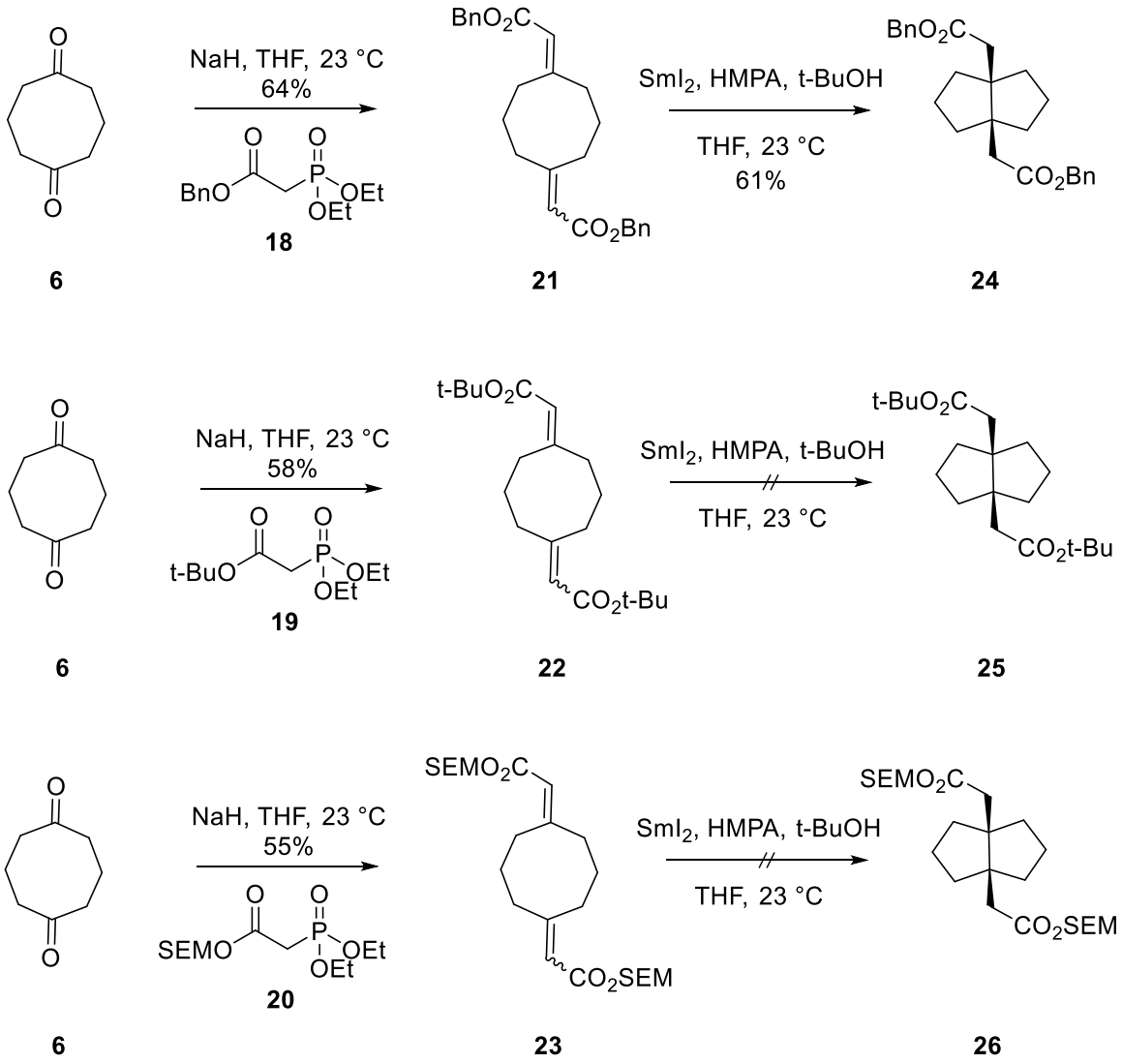


Scheme 3.7: Attempts at hydrolysis

3.4 Change in ester group

Since, we were unable to hydrolyze the esters **14** and **15** under standard acidic or basic conditions, we thought of changing the ester group to something that can be removed using a completely different set of conditions. To that end, we thought of synthesizing the benzyl, the tert-butyl and the SEM ester versions of compound **4** which could be easily removed by hydrogenation, very mild acidic conditions like acetic acid or by fluoride. Therefore, we synthesized the benzyl ester **21**, tert-butyl ester **22** and SEM ester **23** of the α,β-unsaturated esters **5** using the corresponding Horner-Wadsworth-Emmons reagents **18**,[34] **19**[35] and **20**[36,37] respectively.[33] Repeating the previously used conditions for the reductive coupling using SmI_2,[28] we were able to convert the

benzyl ester **21** to the desired product **24**. However, under the same conditions the tert-butyl ester **22** and the SEM ester **23** failed to deliver any reductive coupling product (Scheme 3.8).

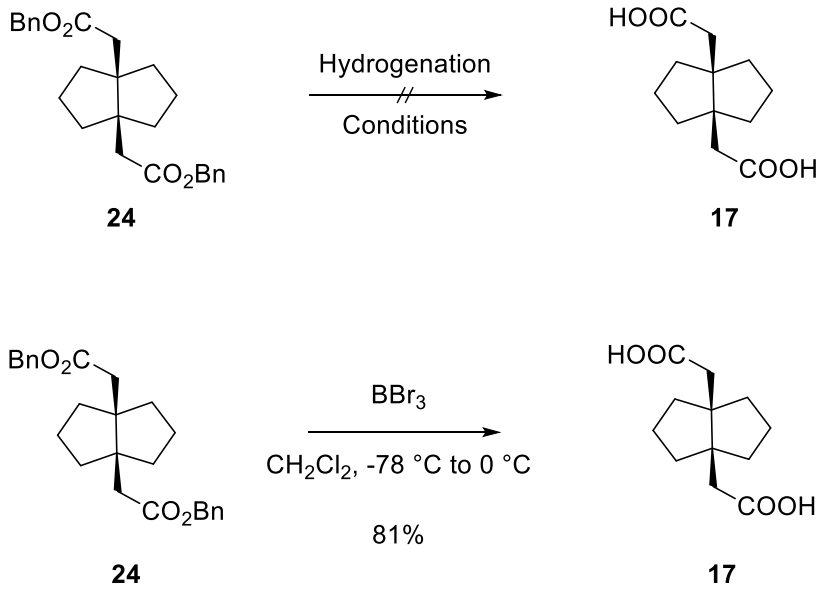


Scheme 3.8: Change in ester group

3.5 Hydrogenation attempts

With the benzyl ester reductive coupling product **24** in hand, we proceeded to remove the benzyl group via hydrogenation. However, here too, we had to face disappointment. All the different

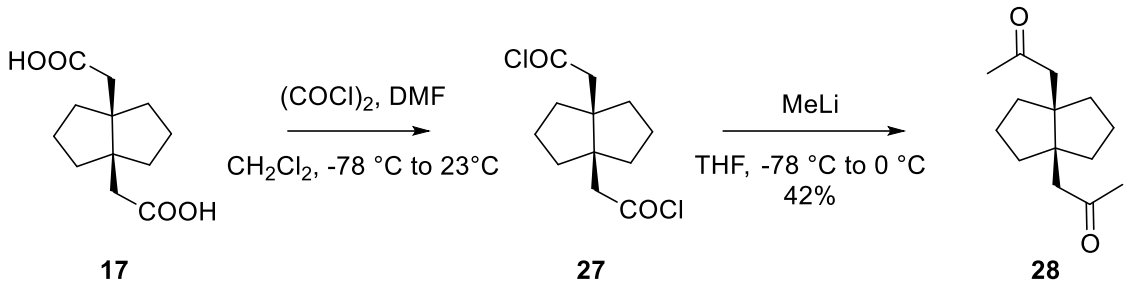
hydrogenation conditions we tried were unable to remove the benzyl group on the compound to deliver us the acid. Fortunately, the use of BBr_3 worked in this instance, and we could isolate the desired diacid **17** in 81% yield (Scheme 3.9).



Scheme 3.9: Hydrolysis of benzyl ester

3.6 Synthesis of diazo compound

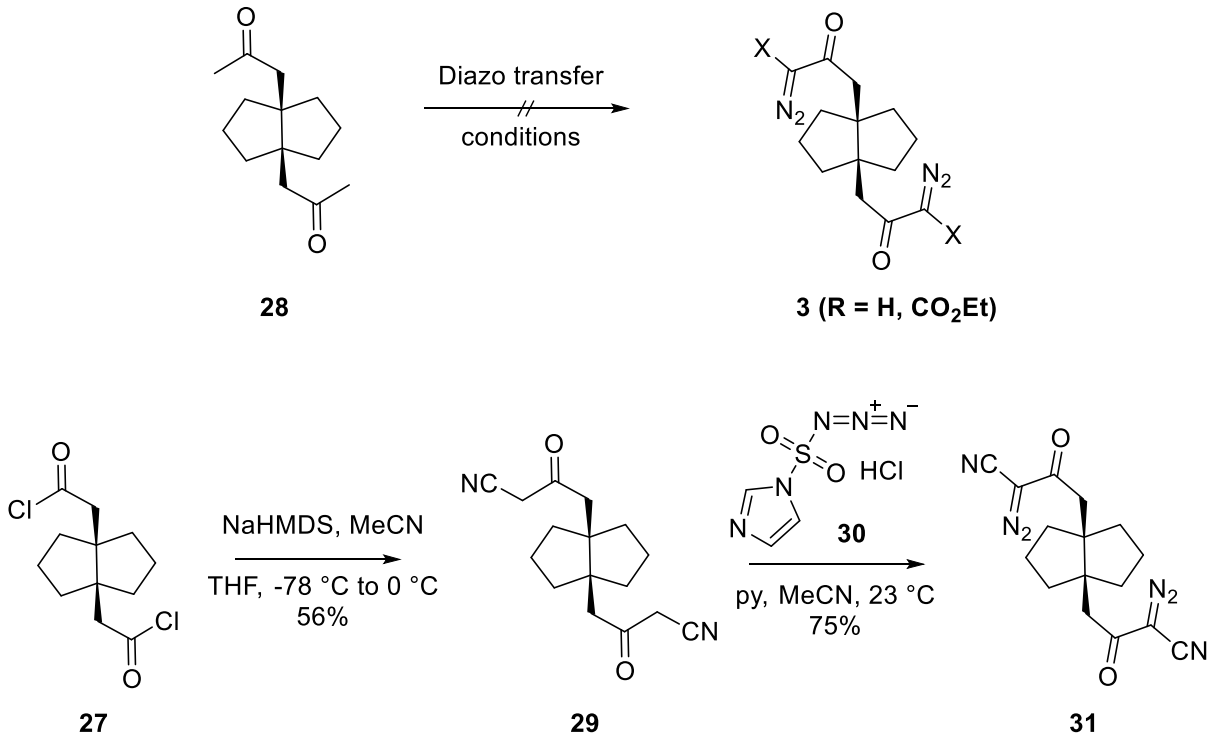
With the diacid finally in hand, we next had to convert the compound **17** to the α-diazo compound **3.** Initially, we first thought of synthesizing the ketone **28** and then installing the diazo group via a diazo transfer reagent. To that end, the acid was first converted to the acyl chloride **27** using the Vilsmeier-Haack conditions[38] and then directly converted to the ketone **28** using methyl lithium as the methylating reagent (Scheme 3.10).



17 **27** **28**

Scheme 3.10: Synthesis of diazo precursor

Then, we tried several conditions for the installation of the diazo group on to the compound **28**. However, all of our conditions to install the diazo group on to the ketone **28** did not fruit any results (Scheme 3.11). We then switched to using Reisman's procedure for installing the diazo group on to α-nitrile ketones.[39] Therefore, generating the nucleophile from acetonitrile using NaHMDS as the base and then reacting it with the acyl chloride **27** generated the α-nitrile ketone compound **29**. This compound upon reaction with imidazolinium sulphonyl azide hydrochloride salt **30**[40] produced the desired diazo compound **31** setting the stage for the key Rh-catalyzed C-H insertion step (Scheme 3.11).

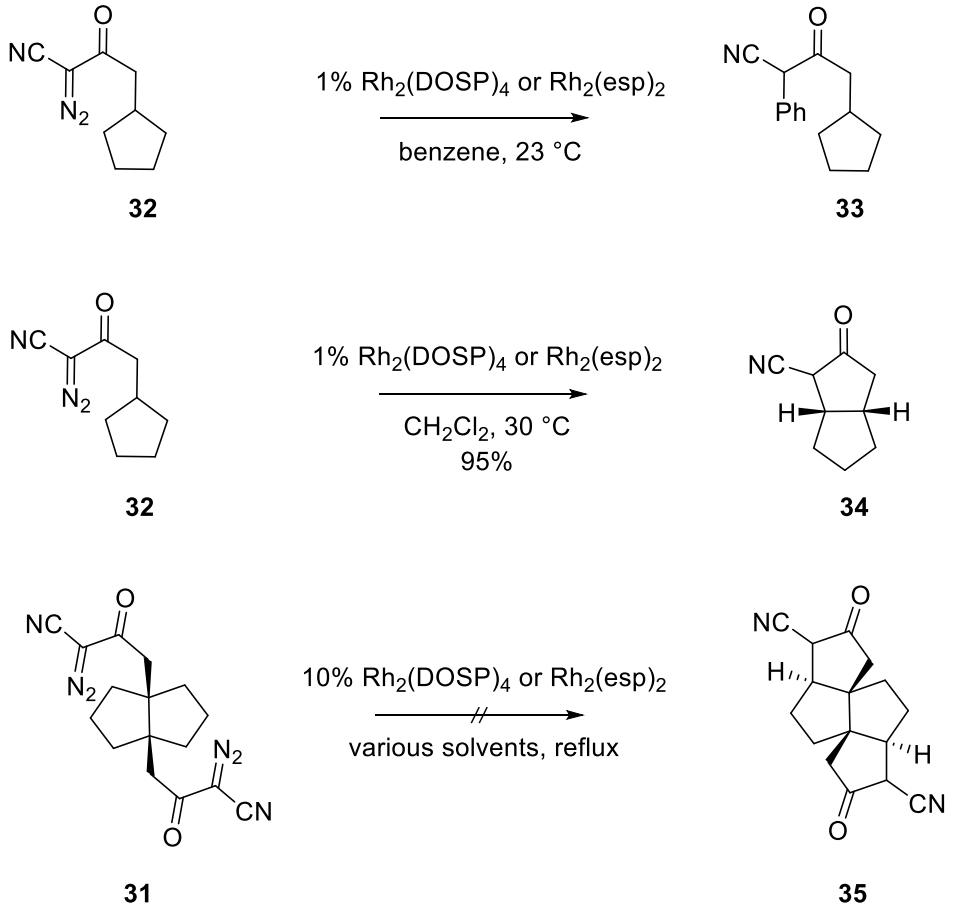


Scheme 3.11: Synthesis of diazo compound

3.7 C-H insertion

With the stage set for the key step, we set out to attempt the Rh catalyzed C-H insertion step. Before trying it out on our actual substrate, however, we decided to first attempt on a model substrate (Scheme 3.12). Therefore, initial attempts were made on the α-nitrile ketone compound **32**. In our initial attempts using benzene as the solvent, we did achieve the C-H insertion reaction but the compound instead of reacting intramolecularly, reacted with the benzene solvent and we isolated the α-phenyl ketone compound **33**. Switching the solvent from benzene to dichloromethane at a slightly elevated temperature of 30 °C, we observed the formation of our desired product **34**[41] in almost 95% yields on a gram scale. Elated with this result, we switched back to trying this condition out on our actual substrate. To our disappointment,

however, at 30 °C we observed the loss of the diazo group but no insertion of the Rh-carbenoid into the C-H bond. Switching to higher boiling solvent like dichloroethane and running the reaction at reflux temperatures was also not helpful and the same results were obtained. We envisioned that, due to the geometry of the molecule, the five- membered rings and the Rh-carbenoid formed point in completely different directions and therefore are very far from each other to engage in a C-H insertion reaction. Therefore, the reaction does not proceed further than the carbenoid formation and instead follows a decomposition pathway (Scheme 3.12).



Scheme 3.12:: Attempts at C-H insertion

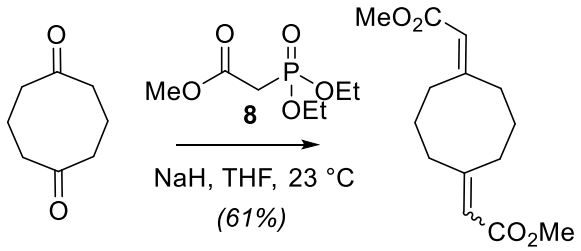
3.8 Conclusion

We were unable to construct the core ring framework of the molecule via C-H insertion strategy. After the failure of this route, we thought of dropping the idea of using a symmetrical route to construct the molecule in a quick fashion and instead use a linear approach to the molecule which takes into account the presence of quaternary centers in the molecule and uses them as guides for the construction for the other quaternary centers.

3.9 Experimental Procedures

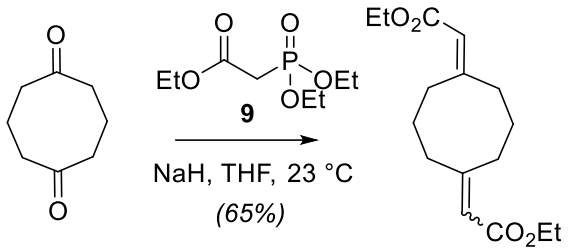
All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, acetonitrile (CH_3CN) and dichloromethane (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Anhydrous MeOH was purchased from Sigma-Aldrich and was used without further purification. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent, and an ethanolic solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker 500 MHz and 400 MHz instruments and calibrated using residual undeuterated solvent as

an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet, app = apparent. IR spectra were recorded on a Perkin-Elmer 1000 series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on Agilent 6244 TOF-MS using ESI (Electrospray Ionization) at the University of Chicago Mass Spectroscopy Core Facility.



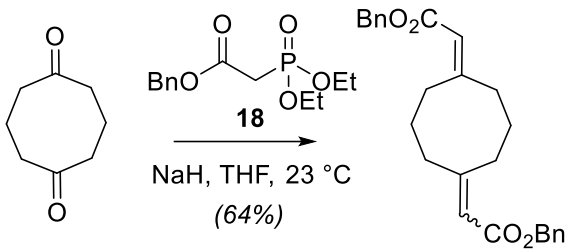
α,β-unsaturated ester 10: A flame-dried, 500 mL round bottom flask equipped with a magnetic stir bar at 23 °C was charged with methyl diethylphosphonoacetate **8** (30.0 g, 142.7 mmol, 4.0 equiv) and THF (105 mL). NaH (60% dispersion in mineral oil, 5.6 g, 139.1 mmol, 3.9 equiv) is then added in one portion at 23 °C and the resultant solution is stirred for an hour. The 1,5 cyclo-octadione **6** (5.0 g, 35.7 mmol, 1.0 equiv) is then added dropwise as a solution in THF (70 mL) and the resultant solution is stirred for 48 h. Upon completion, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (100 mL). The contents were then transferred to a separatory funnel and diluted with EtOAc (100 mL) and H_2O (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 $\times$ 100 mL). The combined organic layers were washed with saturated aqueous NH_4Cl solution (50 mL), H_2O and brine, dried ($MgSO_4$), filtered, and concentrated. Flash column chromatography (silica gel, hexanes/EtOAc, 9/1) of the resultant

residue gave α,β-unsaturated ester **10** (5.5 g, 61% yield) as a light yellow oil. **10**: R_f = 0.88 (silica gel, hexanes/EtOAc, 3/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63 (s, 2 H), 3.64 (d, *J* = 10.2 Hz, 6 H), 2.84–2.61 (m, 4 H), 2.37–2.23 (m, 4 H), 2.12–1.92 (m, 4 H).

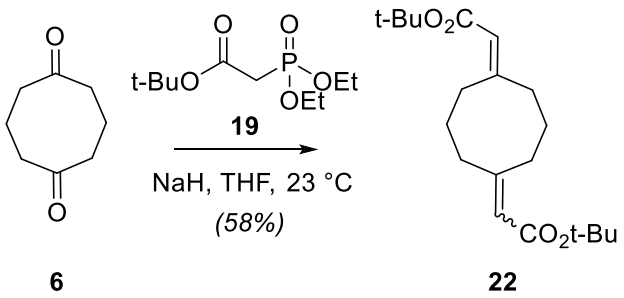


6 **11**

α,β-unsaturated ester 11: A flame-dried, 500 mL round bottom flask equipped with a magnetic stir bar at 23 °C was charged with triethylphosphonoacetate **9** (32.0 g, 142.7 mmol, 4.0 equiv) and THF (105 mL). NaH (60% dispersion in mineral oil, 5.6 g, 139.1 mmol, 3.9 equiv) is then added in one portion at 23 °C and the resultant solution is stirred for an hour. The 1,5 cyclo-octadione **6** (5.0 g, 35.7 mmol, 1.0 equiv) is then added dropwise as a solution in THF (70 mL) and the resultant solution is stirred for 48 h. Upon completion, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (100 mL). The contents were then transferred to a separatory funnel and diluted with EtOAc (100 mL) and H_2O (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with saturated aqueous NH_4Cl solution (50 mL), H_2O and brine, dried ($MgSO_4$), filtered, and concentrated. Flash column chromatography (silica gel, hexanes/EtOAc, 9/1) of the resultant residue gave α,β-unsaturated ester **11** (6.5 g, 65% yield) as a light yellow oil. **11**: R_f = 0.89 (silica gel, hexanes/EtOAc, 3/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.61 (s, 2 H), 4.09 (p, J = 7.1 Hz, 4 H), 2.73 (dt, J = 52.1, 6.2 Hz, 4 H), 2.29 (dt, J = 21.6, 6.4 Hz, 4 H), 2.04–1.92 (m, 4 H), 1.29–1.17 (m, 6 H).

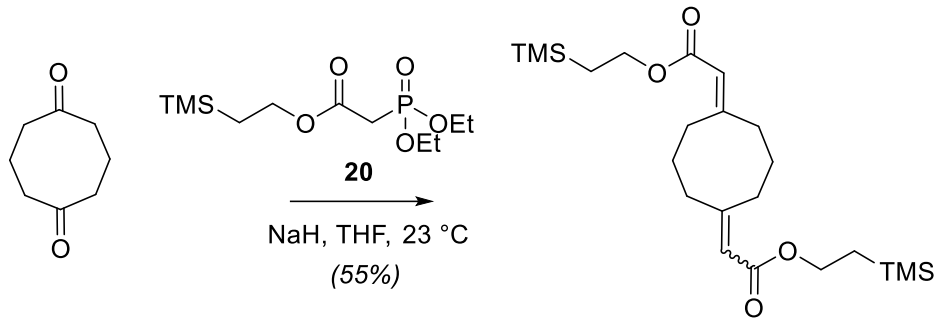


α,β-unsaturated ester 21: A flame-dried, 500 mL round bottom flask equipped with a magnetic stir bar at 23 °C was charged with benzyl diethylphosphonoacetate **18**[34] (40.8 g, 142.7 mmol, 4.0 equiv) and THF (105 mL). NaH (60% dispersion in mineral oil, 5.6 g, 139.1 mmol, 3.9 equiv) is then added in one portion at 23 °C and the resultant solution is stirred for an hour. The 1,5 cyclo-octadione **6** (5.0 g, 35.7 mmol, 1.0 equiv) is then added dropwise as a solution in THF (70 mL) and the resultant solution is stirred for 48 h. Upon completion, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (100 mL). The contents were then transferred to a separatory funnel and diluted with EtOAc (100 mL) and H_2O (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 $\times$ 100 mL). The combined organic layers were washed with saturated aqueous NH_4Cl solution (50 mL), H_2O and brine, dried ($MgSO_4$), filtered, and concentrated. Flash column chromatography (silica gel, hexanes/EtOAc, 9/1) of the resultant residue gave α,β-unsaturated ester **21** (9.2 g, 64% yield) as a colorless oil. **21**: R_f = 0.92 (silica gel, hexanes/EtOAc, 3/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.25 (m, 10 H), 5.71 (d, *J* = 13.1 Hz, 2 H), 5.08 (d, *J* = 24.1 Hz, 4 H), 2.86–2.66 (m, 4 H), 2.38–2.24 (m, 4 H), 2.17–1.93 (m, 4 H).



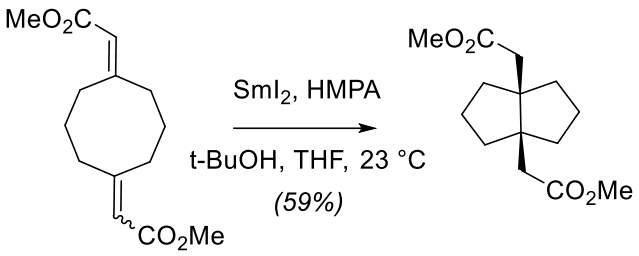
6 **22**

α,β-unsaturated ester 22: A flame-dried, 500 mL round bottom flask equipped with a magnetic stir bar at 23 °C was charged with tert-butyl diethylphosphonoacetate **19**[35] (36.0 g, 142.7 mmol, 4.0 equiv) and THF (105 mL). NaH (60% dispersion in mineral oil, 5.6 g, 139.1 mmol, 3.9 equiv) is then added in one portion at 23 °C and the resultant solution is stirred for an hour. The 1,5 cyclo-octadione **6** (5.0 g, 35.7 mmol, 1.0 equiv) is then added dropwise as a solution in THF (70 mL) and the resultant solution is stirred for 48 h. Upon completion, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (100 mL). The contents were then transferred to a separatory funnel and diluted with EtOAc (100 mL) and H_2O (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 $\times$ 100 mL). The combined organic layers were washed with saturated aqueous NH_4Cl solution (50 mL), H_2O and brine, dried ($MgSO_4$), filtered, and concentrated. Flash column chromatography (silica gel, hexanes/EtOAc, 9/1) of the resultant residue gave α,β-unsaturated ester **22** (7.0 g, 58% yield) as a colorless oil. **22**: R_f = 0.92 (silica gel, hexanes/EtOAc, 3/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.59–5.45 (s, 2 H), 2.69 (dt, *J* = 59.6, 6.1 Hz, 4 H), 2.25 (dt, *J* = 23.7, 6.1 Hz, 4 H), 2.09–1.88 (m, 4 H), 1.43 (s, 18 H).



6 **23**

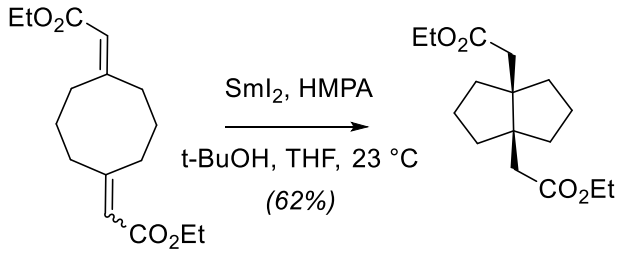
α,β-unsaturated ester 23: A flame-dried, 500 mL round bottom flask equipped with a magnetic stir bar at 23 °C was charged with 2-trimethylsilyl ethyl diethylphosphonoacetate **20**[36,37] (42.3 g, 142.7 mmol, 4.0 equiv) and THF (105 mL). NaH (60% dispersion in mineral oil, 5.6 g, 139.1 mmol, 3.9 equiv) is then added in one portion at 23 °C and the resultant solution is stirred for an hour. The 1,5 cyclo-octadione **6** (5.0 g, 35.7 mmol, 1.0 equiv) is then added dropwise as a solution in THF (70 mL) and the resultant solution is stirred for 48 h. Upon completion, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (100 mL). The contents were then transferred to a separatory funnel and diluted with EtOAc (100 mL) and H_2O (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 $\times$ 100 mL). The combined organic layers were washed with saturated aqueous NH_4Cl solution (50 mL), H_2O and brine, dried ($MgSO_4$), filtered, and concentrated. Flash column chromatography (silica gel, hexanes/EtOAc, 9/1) of the resultant residue gave α,β-unsaturated ester **23** (8.3 g, 55% yield) as a colorless oil. **23**: R_f = 0.92 (silica gel, hexanes/EtOAc, 3/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65–5.56 (s, 2 H), 4.18–4.06 (m, 4 H), 2.74 (dt, *J* = 52.4, 6.1 Hz, 4 H), 2.30 (dt, *J* = 19.9, 6.3 Hz, 4 H), 2.11–1.93 (m, 4 H), 1.04–0.89 (m, 4 H), 0.07 (s, 18 H).



10 **14**

Bicyclic methyl ester 14: A flame-dried, 1 L flask equipped with a magnetic stir bar is charged with Samarium powder (14.7 g, 100.0 mmol, 10.0 equiv) and degassed THF (100 ml, argon-bubbling for 45 min) at 23 °C. Then, a partial amount (~5 mL) of a solution of diiodo ethane (14.1 g, 50.0 mmol, 5.0 equiv) in degassed THF (100 mL) is added at 23 °C. After the solution turns navy blue, degassed THF (300 mL) is added followed by the rest of the solution of diiodo ethane in degassed THF and the resultant solution is allowed to stir for 12 h. Another flame-dried, 1 L flask equipped with a magnetic stir bar is charged with HMPA (36.4 g, 35.4 mL, 200 mmol, 20.0 equiv) at 23 °C. The freshly prepared SmI_2 solution is then transferred via cannula to the HMPA at 23 °C. After the transfer is complete, a solution of the α,β-unsaturated ester **10** (2.52 g, 10 mmol, 1.0 equiv) and t-BuOH (3.5 g, 4.5 mL, 20.0 mmol, 2.0 equiv) in degassed THF (100 mL) is added via cannula at 23 °C and the resultant solution is stirred for 3 h. After completion, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (200 mL) and stirred for another 10 min. The contents were then transferred to a separatory funnel and diluted with Et_2O (300 mL) and H_2O (100 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3×100 mL). The combined organic layers were washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated. Flash column chromatography (silica gel, hexanes/EtOAc, 9/1) of the resultant residue gave bicyclic methyl ester **14** (1.5 g, 59% yield) as a light-yellow oil. **14**: $R_f = 0.42$

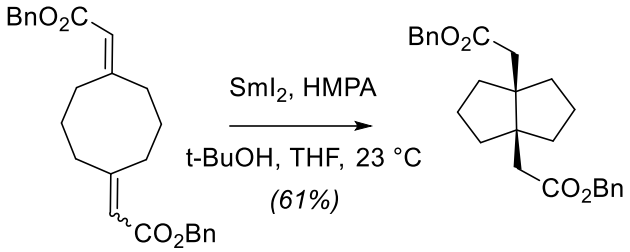
(silica gel, hexanes/EtOAc, 9/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.77 (s, 6 H), 2.47 (s, 4 H), 1.73–1.62 (m, 2 H), 1.57 (qd, *J* = 8.4, 7.6, 3.9 Hz, 6 H), 1.52–1.44 (m, 4 H).



11 **15**

Bicyclic ethyl ester 15: A flame-dried, 1 L flask equipped with a magnetic stir bar is charged with Samarium powder (14.7 g, 100.0 mmol, 10.0 equiv) and degassed THF (100 ml, argon-bubbling for 45 min) at 23 °C. Then, a partial amount (~5 mL) of a solution of diiodo ethane (14.1 g, 50.0 mmol, 5.0 equiv) in degassed THF (100 mL) is added at 23 °C. After the solution turns navy blue, degassed THF (300 mL) is added followed by the rest of the solution of diiodo ethane in degassed THF and the resultant solution is allowed to stir for 12 h. Another flame-dried, 1 L flask equipped with a magnetic stir bar is charged with HMPA (36.4 g, 35.4 mL, 200 mmol, 20.0 equiv) at 23 °C. The freshly prepared SmI_2 solution is then transferred via cannula to the HMPA at 23 °C. After the transfer is complete, a solution of the α,β-unsaturated ester **11** (2.80 g, 10 mmol, 1.0 equiv) in and t-BuOH (3.5 g, 4.5 mL, 20.0 mmol, 2.0 equiv) in degassed THF (100 mL) is added via cannula at 23 °C and the resultant solution is stirred for 3 h. After completion, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (200 mL) and stirred for another 10 min. The contents were then transferred to a separatory funnel and diluted with Et_2O (300 mL) and H_2O (100 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with H_2O and brine, dried ($MgSO_4$), filtered, and

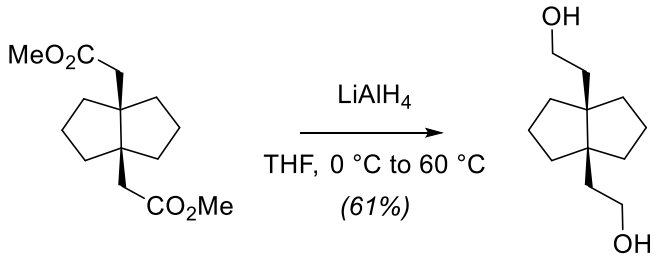
concentrated. Flash column chromatography (silica gel, hexanes/EtOAc, 9/1) of the resultant residue gave bicyclic ethyl ester **15** (1.75 g, 62% yield) as a light-yellow oil. **15**: R_f = 0.41 (silica gel, hexanes/EtOAc, 9/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.25 (q, *J* = 7.1 Hz, 4 H), 2.49 (s, 4 H), 1.80–1.65 (m, 2 H), 1.65–1.55 (m, 6 H), 1.55–1.44 (m, 4 H), 1.32 (t, *J* = 7.1 Hz, 6 H);



21 **24**

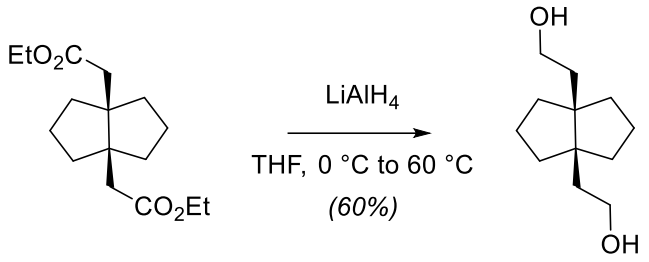
Bicyclic benzyl ester 24: A flame-dried, 1 L flask equipped with a magnetic stir bar is charged with Samarium powder (14.7 g, 100.0 mmol, 10.0 equiv) and degassed THF (100 ml, argon-bubbling for 45 min) at 23 °C. Then, a partial amount (~5 mL) of a solution of diiodo ethane (14.1 g, 50.0 mmol, 5.0 equiv) in degassed THF (100 mL) is added at 23 °C. After the solution turns navy blue, degassed THF (300 mL) is added followed by the rest of the solution of diiodo ethane in degassed THF and the resultant solution is allowed to stir for 12 h. Another flame-dried, 1 L flask equipped with a magnetic stir bar is charged with HMPA (36.4 g, 35.4 mL, 200 mmol, 20.0 equiv) at 23 °C. The freshly prepared SmI_2 solution is then transferred via cannula to the HMPA at 23 °C. After the transfer is complete, a solution of the α,β-unsaturated ester **21** (4.04 g, 10 mmol, 1.0 equiv) and t-BuOH (3.5 g, 4.5 mL, 20.0 mmol, 2.0 equiv) in degassed THF (100 mL) is added via cannula at 23 °C and the resultant solution is stirred for 3 h. After completion, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (200 mL) and stirred for another 10 min. The contents were then transferred to a separatory funnel and diluted with Et_2O (300 mL) and

H_2O (100 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated. Flash column chromatography (silica gel, hexanes/EtOAc, 9/1) of the resultant residue gave bicyclic benzyl ester **24** (2.48 g, 61% yield) as a light-yellow oil. **24**: R_f = 0.45 (silica gel, hexanes/EtOAc, 9/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.29 (m, 10 H), 5.24 (s, 4 H), 2.48 (s, 4 H), 1.77–1.69 (m, 2 H), 1.61–1.55 (m, 6 H), 1.52–1.47 (m, 4 H).



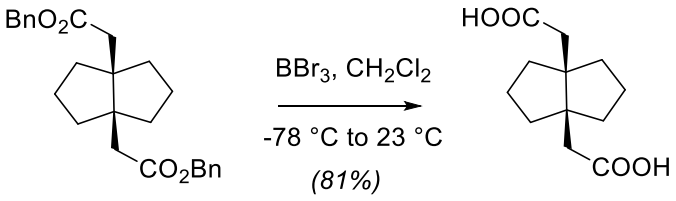
14 **16**

Diol 16: A 25 mL, flame-dried round bottom flask equipped with a magnetic stir bar, is charged with bicyclic methyl ester **14** (51 mg, 0.2 mmol, 1.0 equiv) and THF (2 mL). $LiAlH_4$ (76 mg, 2.0 mmol, 10.0 equiv) is added to the mixture. After the addition is complete, temperature is increased to 70 °C and stirred for 5 h. Upon completion, the temperature is brought back down to 0 °C and water (75 µL) is added slowly followed by aqueous NaOH solution (75 µL, 15 g in 100 mL) and water (230 µL). The resulting solution is stirred for 15 min at 23 °C followed by the addition of $MgSO_4$. After 5 min, the mixture is filtered and concentrated. Recrystallization of the crude solid with CH_2Cl_2/hexanes gave diol **16** (24 mg, 61% yield) as a white crystalline solid. **16**: R_f = 0.40 (silica gel, hexanes/EtOAc, 1/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.83–3.60 (s, 4 H), 1.58 (d, *J* = 7.8 Hz, 4 H), 1.56–1.53 (m, 2 H), 1.50 (s, 10 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 62.24, 54.05, 41.66, 39.84, 25.09.



15 **16**

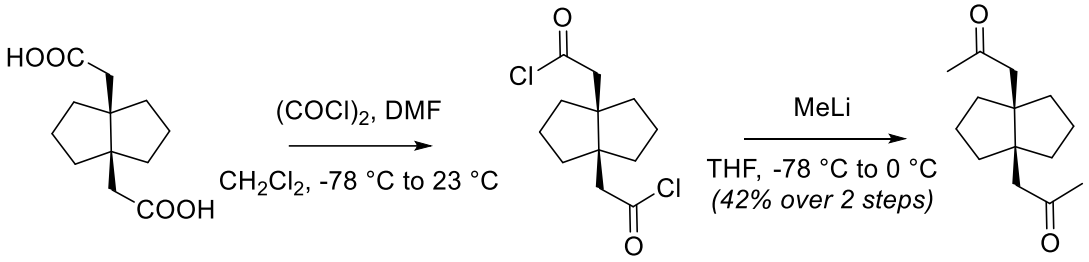
Diol 16: A 25 mL, flame-dried round bottom flask equipped with a magnetic stir bar, is charged with bicyclic ethyl ester **15** (56 mg, 0.2 mmol, 1.0 equiv) and THF (2 mL). $LiAlH_4$ (76 mg, 2.0 mmol, 10.0 equiv) is added to the mixture. After the addition is complete, temperature is increased to 70 °C and stirred for 5 h. Upon completion, the temperature is brought back down to 0 °C and water (75 µL) is added slowly followed by aqueous NaOH solution (75 µL, 15 g in 100 mL) and water (230 µL). The resulting solution is stirred for 15 min at 23 °C followed by the addition of $MgSO_4$. After 5 min, the mixture is filtered and concentrated. Recrystallization of the crude solid with CH_2Cl_2/hexanes gave diol **16** (23 mg, 60% yield) as a white crystalline solid.



24 **17**

Diacid 17: A flame-dried, 100 mL round bottom flask equipped with a magnetic stir bar is charged with bicyclic benzyl ester **24** (2.03 g, 5 mmol, 1 equiv) and CH_2Cl_2 (50 mL). The temperature is reduced down to -78 °C and a 1M solution of BBr_3 (12.5 mL, 12.5 mmol, 2.5 equiv) is added

dropwise. The temperature is raised to 23 °C and stirring is continued for 2 h. Upon completion, the reaction is cooled down to 0 °C and quenched via dropwise addition of water (25 mL). The reaction mixture is transferred to a separatory funnel and the layers are separated. The aqueous layer is extracted with CH_2Cl_2 (3 x 25 mL) and the combined organic layer is washed with H_2O (20 mL). The organic layer is then extracted with 5 N NaOH solution (3 x 25 mL). The combined basic layer is then washed with CH_2Cl_2 (3 x 25 mL) and acidified with 6 N HCl until the pH of the solution is 2-3. The acidic layer is then extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layer is washed with 1 N HCl (25 mL) and H_2O (25 mL), dried ($MgSO_4$) and concentrated to give the diacid **17** (916 mg, 81% yield) as a yellow solid. **17**: R_f = 0.34 (silica gel, CH_2Cl_2/MeOH, 9/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.29 (s, 2 H), 2.51 (s, 4 H), 1.80–1.71 (m, 2 H), 1.60 (tt, *J* = 11.1, 4.1 Hz, 6 H), 1.51 (dtd, *J* = 11.4, 7.1, 2.9 Hz, 4 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.83, 55.74, 47.41, 41.35, 39.55, 25.56.

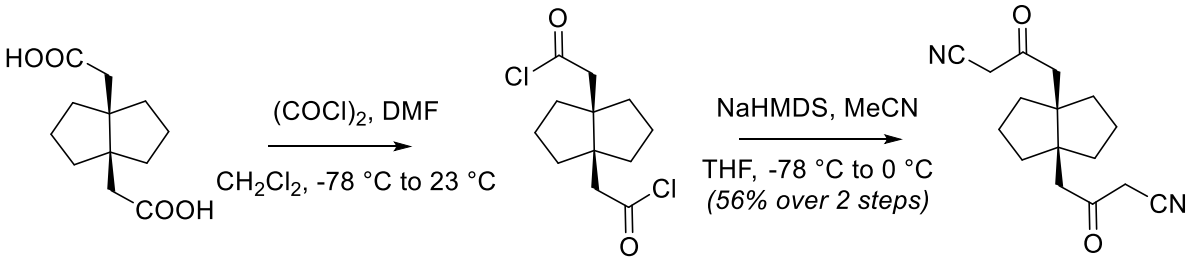


17 **27** **28**

Methyl ketone 28: To a 25 mL, flame-dried round bottom flask equipped with a magnetic stir bar, a solution of diacid **17** (226 mg, 1.0 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) is added followed by a drop of DMF. The temperature is reduced to -78 °C and oxalyl chloride (380.8 mg, 257 µL, 3.0 mmol, 3.0 equiv) is added dropwise. Temperature is then raised to 23 °C and stirring is continued

for 2 h. The resultant solution is then concentrated on a rotary evaporator and directly taken for the next step without further purification.

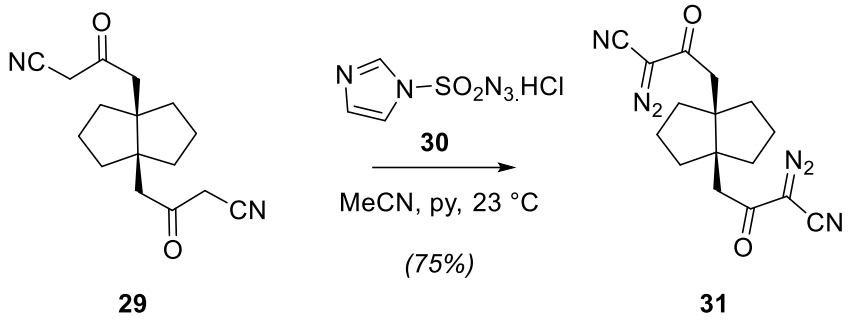
Next, to a 50 mL, flame-dried round bottom flask equipped with a magnetic stir bar, a solution of the previous crude acyl chloride **27** (1.0 mmol, 100% yield assumed) in THF (10 mL) is added. The temperature of the reaction mixture is reduced to -78 °C followed by the dropwise addition of MeLi (6.25 mL, 1.6 M solution in THF, 10.0 mmol, 10.0 equiv). The temperature is gradually increased to 0 °C and stirring is continued for 2 h. After the reaction is complete, the reaction is quenched by the addition of saturated NH_4Cl (10 mL). The contents were then transferred to a separatory funnel and diluted with EtOAc (20 mL) and H_2O (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 $\times$ 10 mL). The combined organic layers were washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated. Flash column chromatography (silica gel, hexanes/EtOAc, 6/1) of the resultant residue gave methyl ketone **28** (93 mg, 42% yield) as a light-yellow oil. **28**: R_f = 0.70 (silica gel, hexanes/EtOAc, 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.70 (s, 4 H), 2.48 (s, 6 H), 1.75–1.65 (m, 4 H), 1.63–1.56 (m, 4 H), 1.47 (dddd, *J* = 12.4, 10.9, 5.5, 3.5 Hz, 4 H).



17 **27** **29**

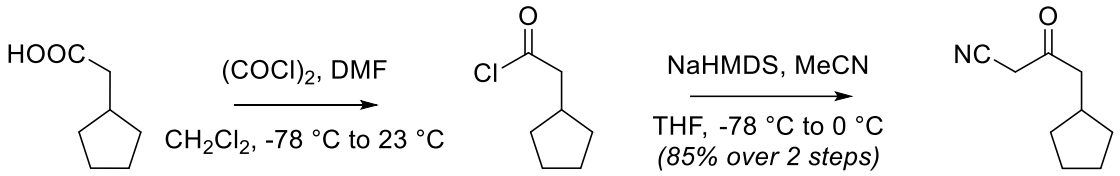
α-nitrile ketone 29: To a 25 mL, flame-dried round bottom flask equipped with a magnetic stir bar, a solution of diacid **17** (226 mg, 1.0 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) is added followed by a drop of DMF. The temperature is reduced to -78 °C and oxalyl chloride (380.8 mg, 257 µL, 3.0 mmol, 3.0 equiv) is added dropwise. Temperature is then raised to 23 °C and stirring is continued for 2 h. The resultant solution is then concentrated on a rotary evaporator and directly taken for the next step without further purification.

Next, a 50 mL, flame-dried round bottom flask equipped with a magnetic stir bar, was charged with NaHMDS (5 mL, 1 M solution in THF, 5 mmol, 5.0 equiv) and THF (10 mL). The reaction mixture was cooled down to -78 °C and anhydrous MeCN (246 mg, ~315 µL, 6.0 mmol, 6.0 equiv) was added and stirred for 30 min. Then, a solution of the previous crude acyl chloride **27** (1.0 mmol, 100% yield assumed) in THF (5 mL) is added. The temperature is gradually increased to 0 °C and stirring is continued for 2 h. After the reaction is complete, the reaction is quenched by the addition of saturated NH_4Cl (10 mL). The contents were then transferred to a separatory funnel and diluted with EtOAc (20 mL) and H_2O (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 $\times$ 10 mL). The combined organic layers were washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated. Flash column chromatography (silica gel, hexanes/EtOAc, 6/1) of the resultant residue gave α-nitrile ketone **29** (152 mg, 56% yield) as a light-yellow oil. **29**: R_f = 0.32 (silica gel, hexanes/EtOAc, 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.00 (s, 4 H), 2.76 (s, 4 H), 1.72 (hept, *J* = 6.7 Hz, 4 H), 1.65–1.54 (m, 4 H), 1.48 (tq, *J* = 12.4, 6.1 Hz, 4 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.36, 113.54, 56.80, 55.32, 41.01, 39.38, 33.48, 25.32.



29 **31**

α-nitrile diazo ketone 31: A 25 mL, flame-dried flask equipped with a magnetic stir bar, was charged with imidazolinium sulphonyl azide hydrochloride salt **30**[40] (87 mg, 0.41 mmol, 2.6 equiv). Then, a solution of α-nitrile ketone **29** (43 mg, 0.16 mmol, 1.0 equiv) in CH_3CN (5 mL) was added followed by pyridine (138 mg, 140 µL, 1.75 mmol, 11.0 equiv). The resulting orange solution was stirred at 23 °C for 5 h. Upon completion, the solution was directly concentrated on a rotary evaporator. Flash column chromatography (silica gel, hexanes/EtOAc, 6/1) of the resultant residue gave α-nitrile diazo ketone **31** (39 mg, 75% yield) as a deep yellow oil. **31**: R_f = 0.48 (silica gel, hexanes/EtOAc, 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.65 (s, 4 H), 1.88 (dt, *J* = 14.7, 5.5 Hz, 2 H), 1.60 (qd, *J* = 10.0, 8.8, 6.0 Hz, 8 H), 1.56–1.47 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.47, 107.89, 71.49, 59.24, 53.53, 41.28, 38.30, 25.59.

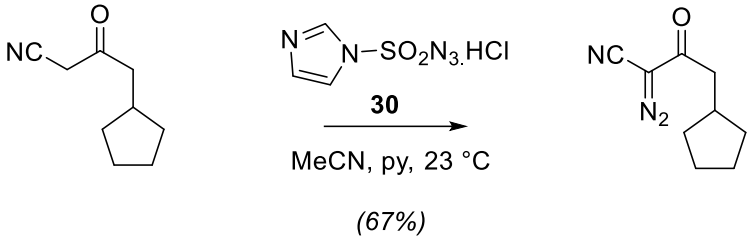


36 **37** **38**

α-nitrile ketone 38: To a 500 mL, flame-dried round bottom flask equipped with a magnetic stir bar, a solution of cyclopentylacetic acid **36** (2.56 g, 20.0 mmol, 1.0 equiv) in CH_2Cl_2 (200 mL) is added followed by DMF (73 mg, 77 µL, 1 mmol, 0.05 equiv). The temperature is reduced to -78

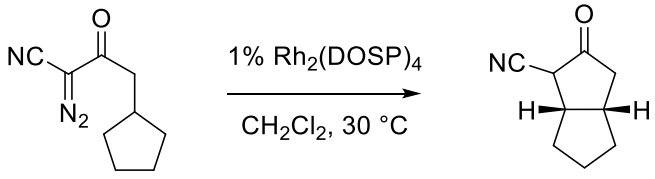
°C and oxalyl chloride (3.05 g, 2.1 mL, 24.0 mmol, 1.2 equiv) is added dropwise. Temperature is then raised to 23 °C and stirring is continued for 2 h. The resultant solution is then concentrated on a rotary evaporator and directly taken for the next step without further purification.

Next, a 500 mL, flame-dried round bottom flask equipped with a magnetic stir bar, was charged with NaHMDS (24 mL, 1 M solution in THF, 24 mmol, 1.2 equiv) and THF (200 mL). The reaction mixture was cooled down to -78 °C and anhydrous MeCN (1.23 g, 1.6 mL, 30.0 mmol, 1.5 equiv) was added and stirred for 30 min. Then, a solution of the previous crude acyl chloride **37** (20.0 mmol, 100% yield assumed) in THF (50 mL) is added. The temperature is gradually increased to 0 °C and stirring is continued for 2 h. After the reaction is complete, the reaction is quenched by the addition of saturated NH_4Cl (100 mL). The contents were then transferred to a separatory funnel and diluted with EtOAc (200 mL) and H_2O (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 $\times$ 100 mL). The combined organic layers were washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated. Flash column chromatography (silica gel, hexanes/EtOAc, 6/1) of the resultant residue gave α-nitrile ketone **38** (2.57 g, 85% yield) as a light-yellow oil. **38**: R_f = 0.30 (silica gel, hexanes/EtOAc, 9/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.44 (s, 2 H), 2.63 (d, *J* = 7.1 Hz, 2 H), 2.25 (hept, *J* = 7.6 Hz, 1 H), 1.85 (dq, *J* = 15.7, 6.1, 5.7 Hz, 2 H), 1.65–1.58 (m, 2 H), 1.55 (tt, *J* = 7.8, 3.0 Hz, 2H), 1.15–1.04 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.58, 114.14, 48.66, 35.50, 32.79, 32.41, 25.24.



38 **32**

α-nitrile diazo ketone 32: A 500 mL, flame-dried flask equipped with a magnetic stir bar, was charged with imidazolinium sulphonyl azide hydrochloride salt **30**[40] (3.2 g, 15.2 mmol, 1.2 equiv). Then, a solution of α-nitrile ketone **38** (1.916 mg, 12.68 mmol, 1.0 equiv) in CH_3CN (250 mL) was added followed by pyridine (5.0 g, 5.1 mL, 63.4 mmol, 5.0 equiv). The resulting orange solution was stirred at 23 °C for 5 h. Upon completion, the solution was directly concentrated on a rotary evaporator. Flash column chromatography (silica gel, hexanes/EtOAc, 9/1) of the resultant residue gave α-nitrile diazo ketone **32** (1.5 g, 67% yield) as a deep yellow oil. **32**: R_f = 0. 48(silica gel, hexanes/EtOAc, 9/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.64 (d, *J* = 7.3 Hz, 2 H), 2.30 (hept, *J* = 7.7 Hz, 1 H), 1.85 (dq, *J* = 11.8, 6.4 Hz, 2 H), 1.64 (tq, *J* = 9.5, 5.0, 3.9 Hz, 2 H), 1.61–1.50 (m, 2 H), 1.23–1.11 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 108.59, 45.43, 36.21, 32.40, 24.83.

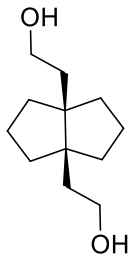


32 **34**

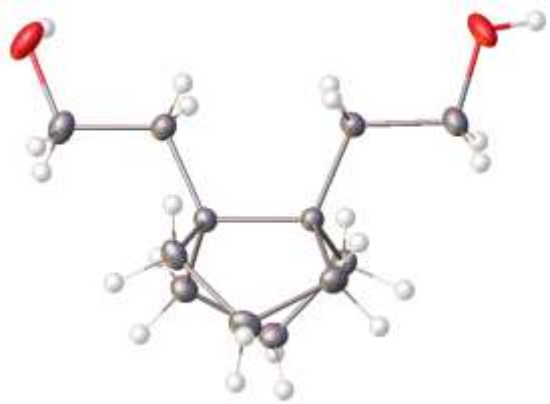
Bicyclic α-nitrile ketone 34: A 250 mL, flame-dried round bottom flask equipped with a magnetic stir bar is charged with a solution of α-nitrile diazo ketone **32** (1.50 g, 8.46 mmol, 1.0 equiv) in CH_2Cl_2 (84 mL). The solution is then purged with argon for 45 min before the addition of $Rh_2(DOSP)_4$ (160.8 mg, 0.085 mmol, 0.01 equiv). The resultant solution is then stirred for 90 min

before being concentrated directly on a rotary evaporator. Flash column chromatography (silica gel, hexanes/EtOAc, 19/1) of the resultant residue gave bicyclic α-nitrile ketone **34**[41] (1.20 g, 95% yield) as a colorless oil. **34**: R_f = 0. 55(silica gel, hexanes/EtOAc, 9/1); ^{1}H NMR (500 MHz, $CDCl_3$, reported for a 1 : 1 ratio of two diastereomers) δ 3.57 (dd, *J* = 8.7, 1.0 Hz, 1 H), 3.05–2.87 (m, 3 H), 2.79 (dddd, *J* = 20.0, 16.0, 10.7, 6.4 Hz, 3 H), 2.72–2.62 (m, 2 H), 2.28 (dd, *J* = 19.2, 4.6 Hz, 1 H), 2.13–1.98 (m, 6 H), 1.84–1.75 (m, 3 H), 1.75–1.66 (m, 3 H), 1.54 (dtd, *J* = 17.3, 6.9, 6.1, 3.2 Hz, 2 H), 1.39 (dq, *J* = 14.5, 7.4 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.47, 116.91, 116.07, 45.80, 45.20, 45.12, 43.30, 42.78, 42.69, 38.52, 38.09, 33.73, 33.23, 32.20, 30.17, 25.27, 25.21.

3.10 ORTEP structure of 16



16



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3.12 NMR's of selected intermediates

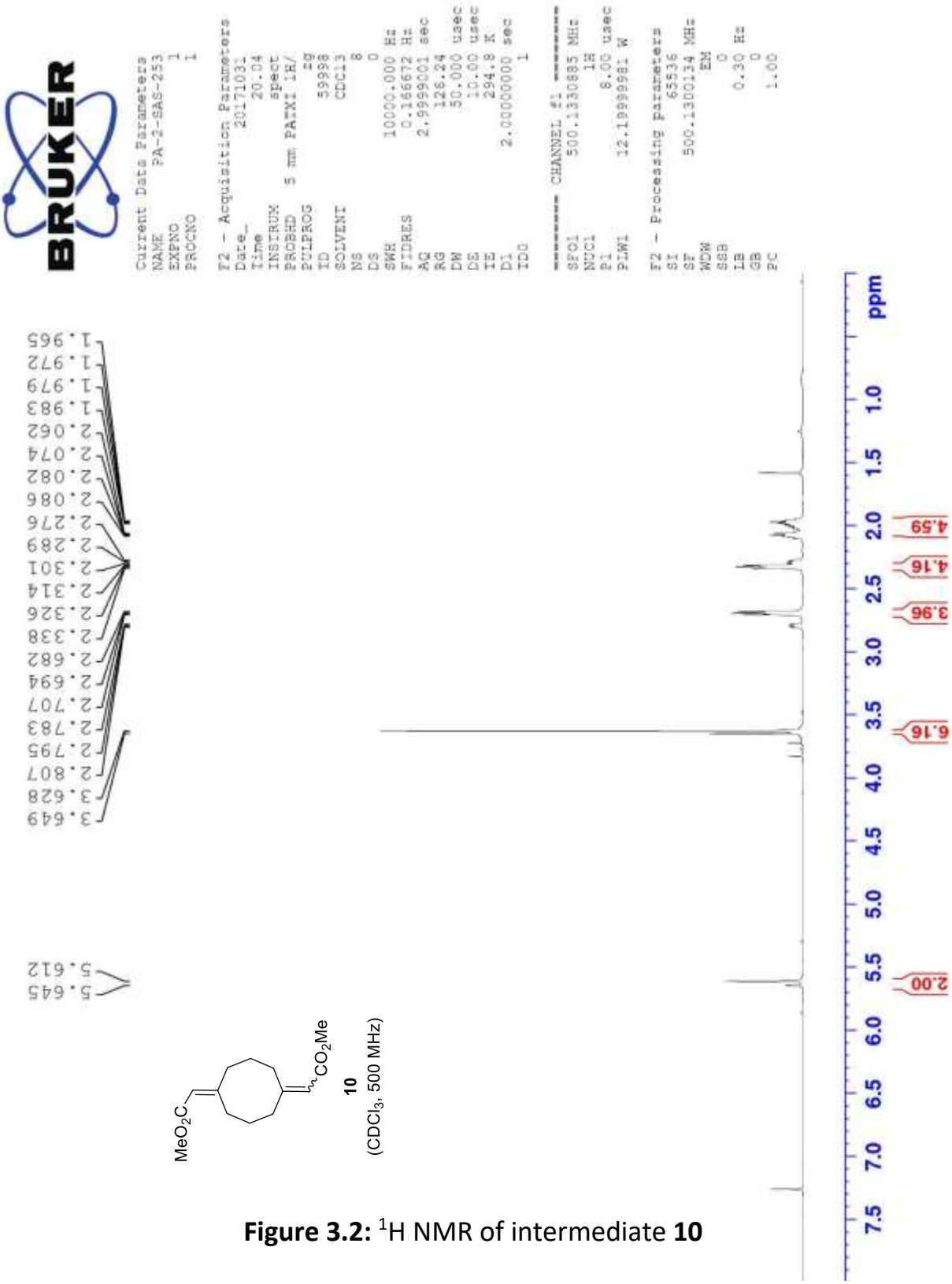


Figure 3.2: ^{1}H NMR of intermediate **10**

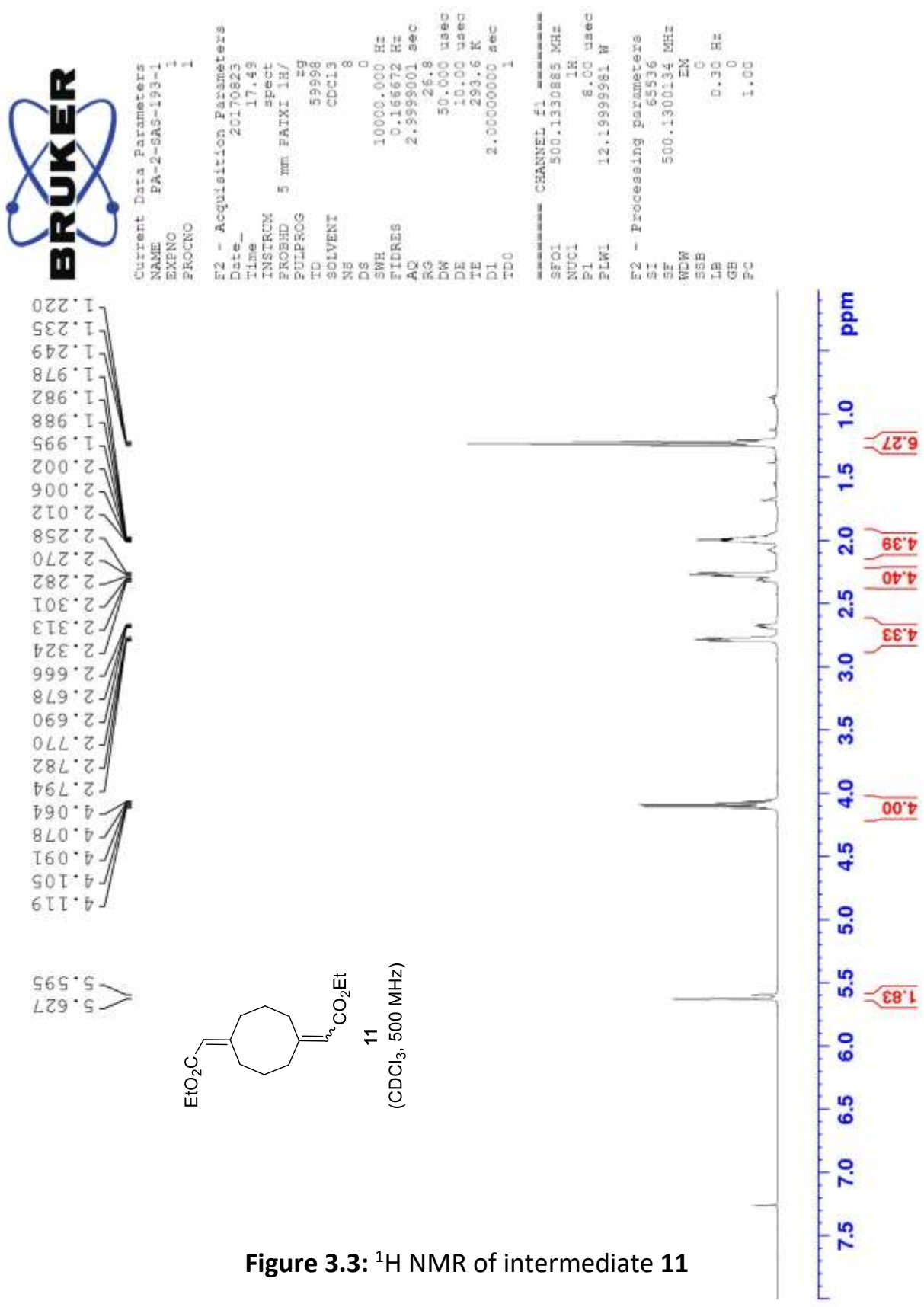


Figure 3.3: ^{1}H NMR of intermediate **11**

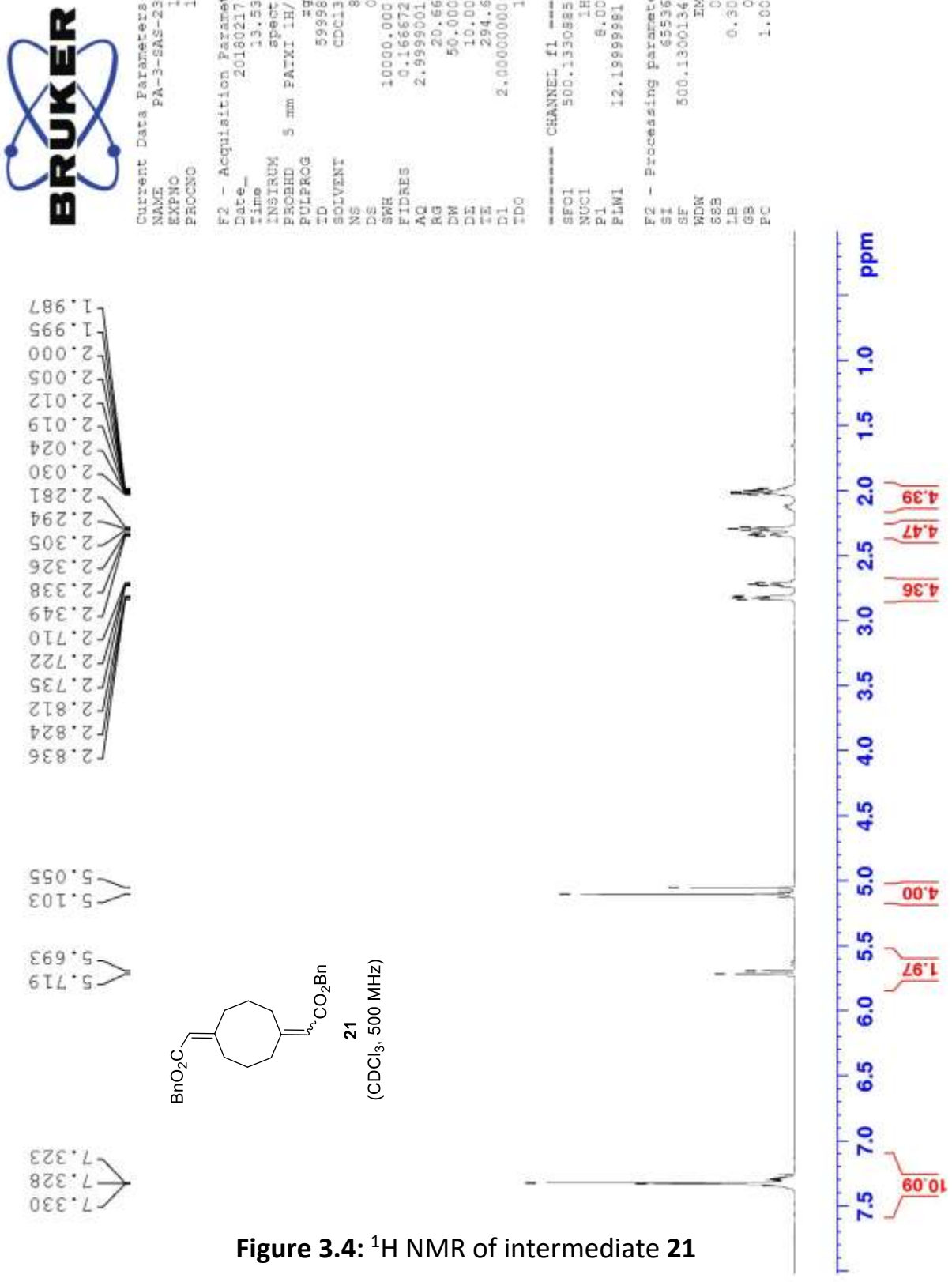


Figure 3.4: ^{1}H NMR of intermediate **21**

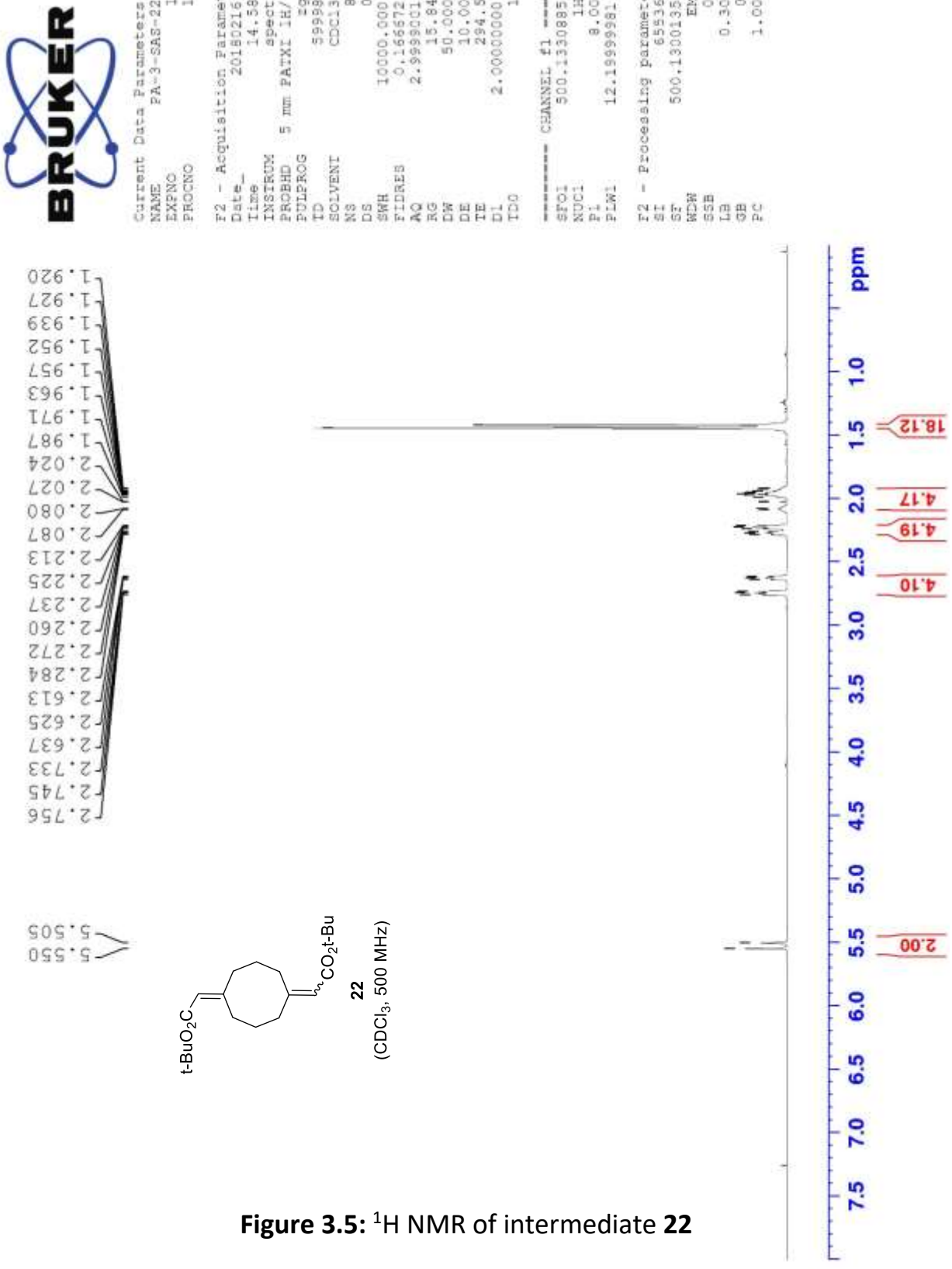


Figure 3.5: ^{1}H NMR of intermediate **22**

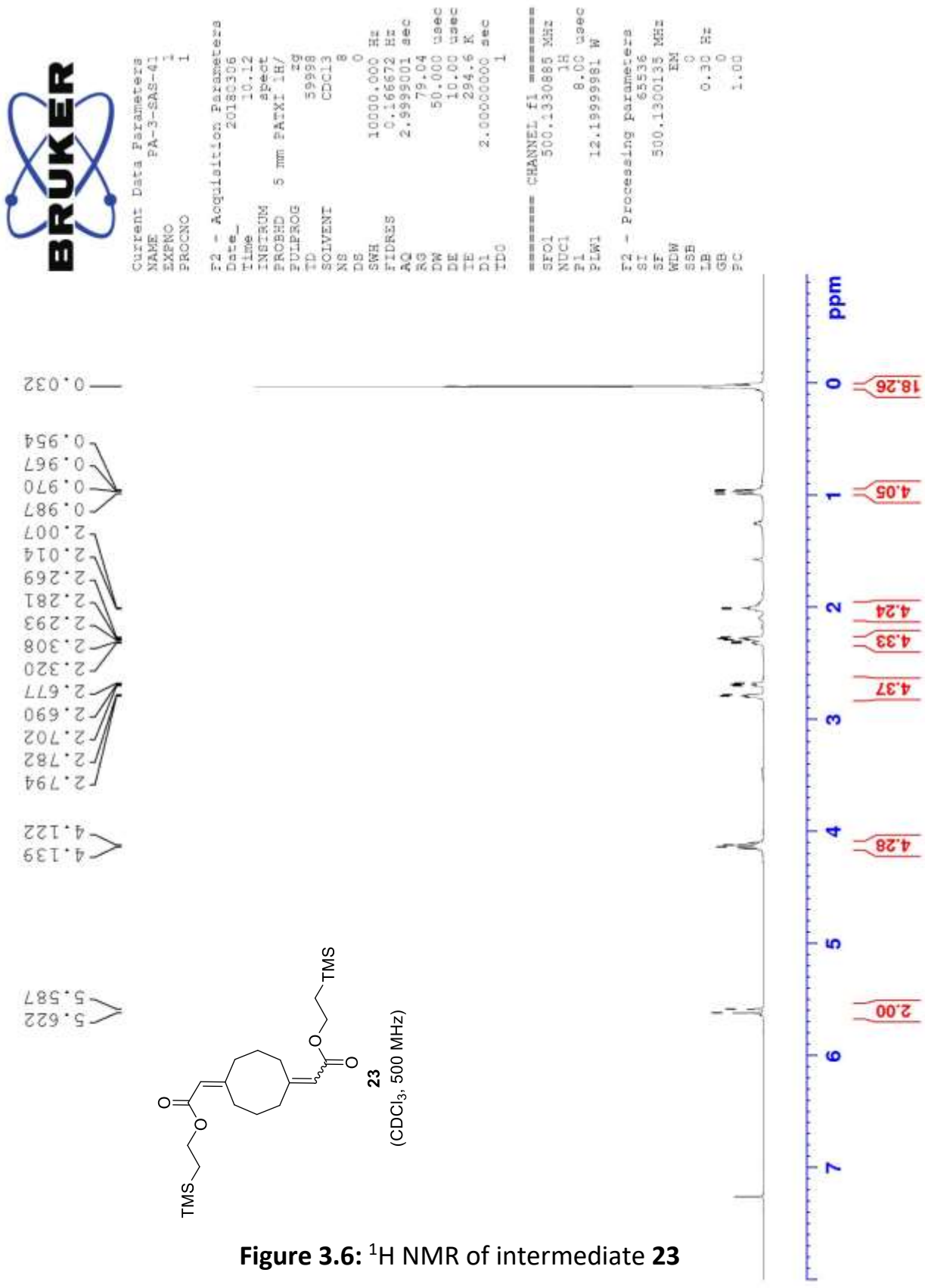
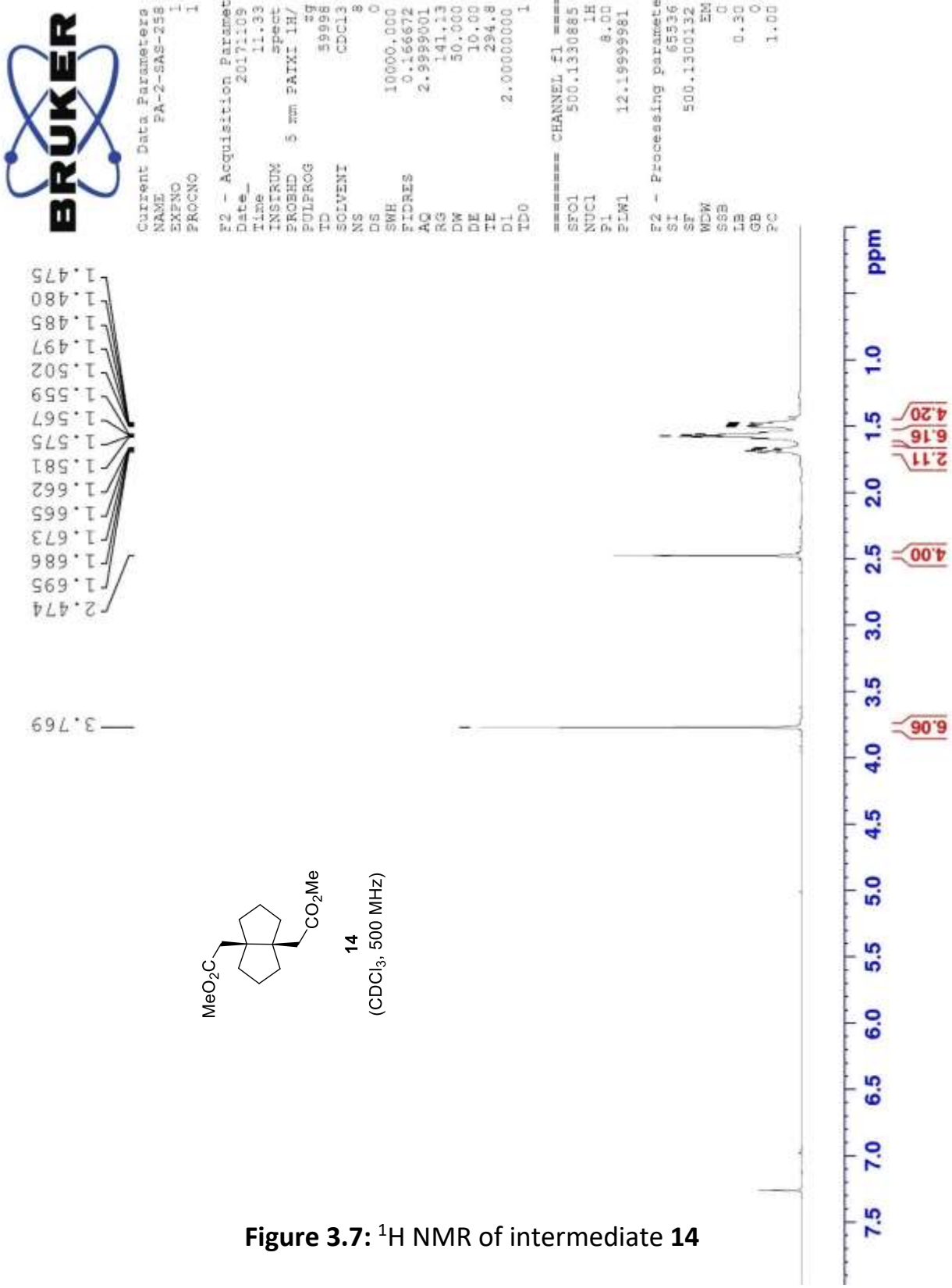


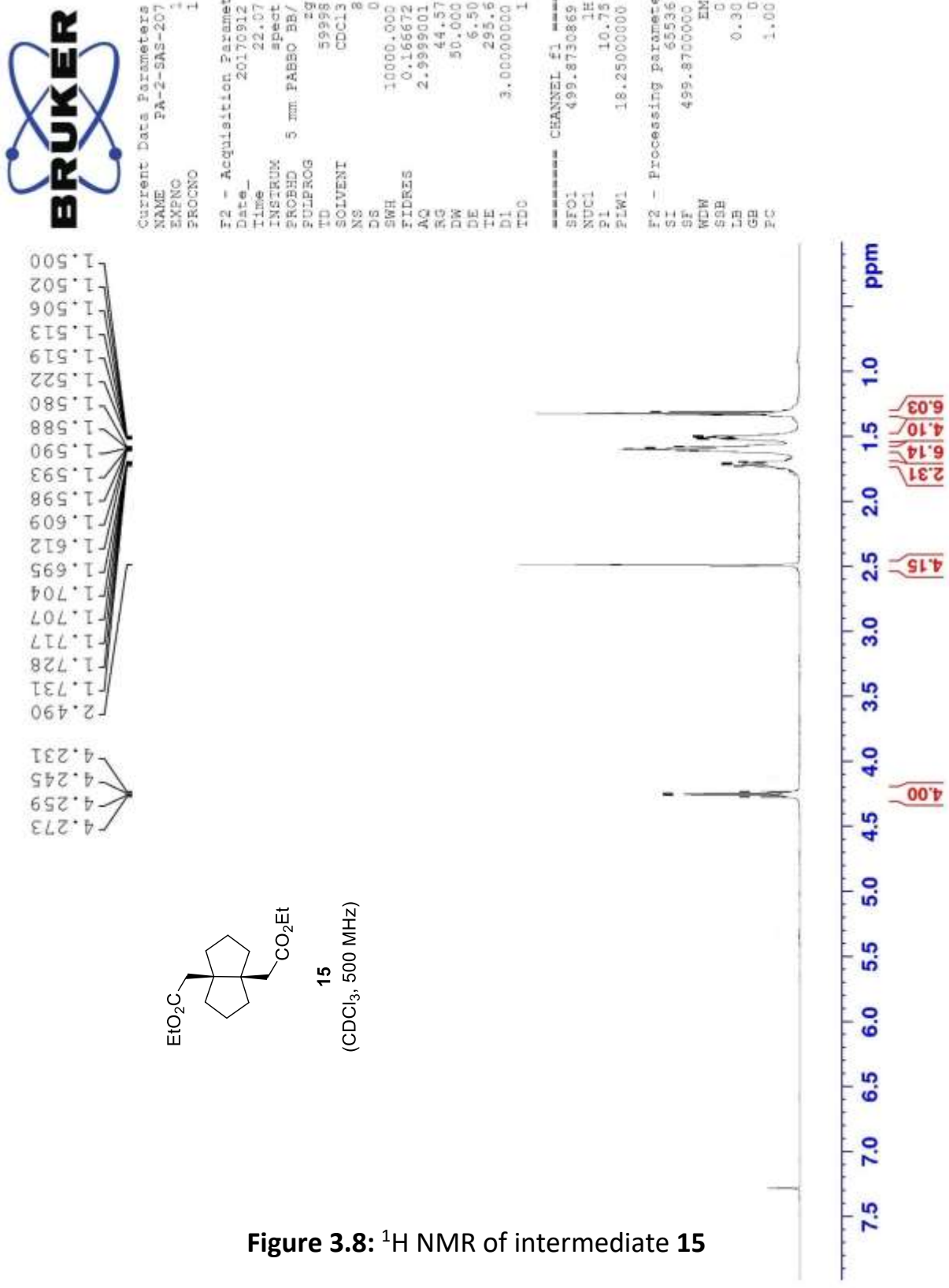
Figure 3.6: ^{1}H NMR of intermediate **23**



14

($CDCl_3$, 500 MHz)

Figure 3.7: ^{1}H NMR of intermediate **14**



EtO_2C CO_2Et

15

($CDCl_3$, 500 MHz)

Figure 3.8: ^{1}H NMR of intermediate **15**

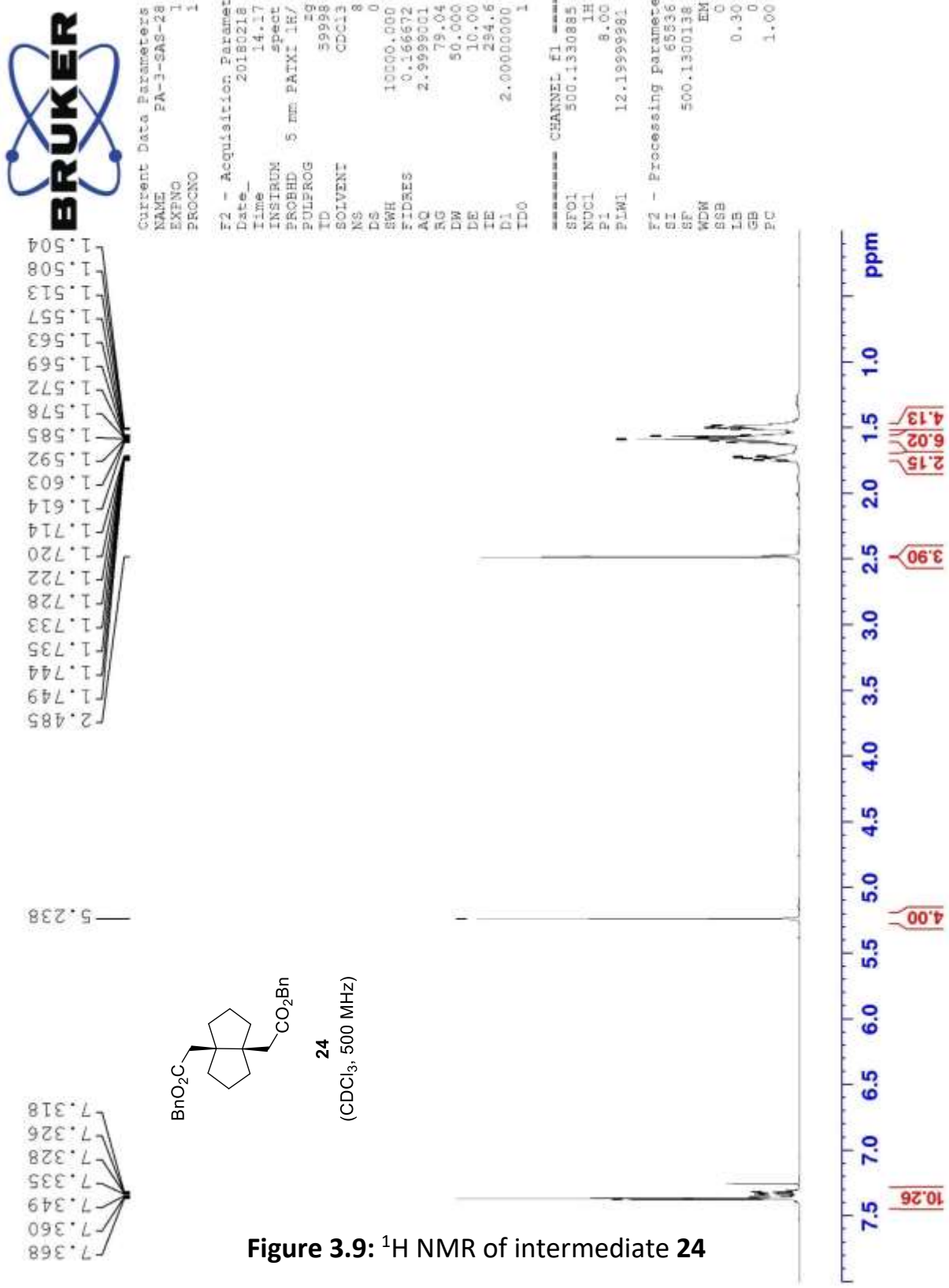


Figure 3.9: ^{1}H NMR of intermediate **24**

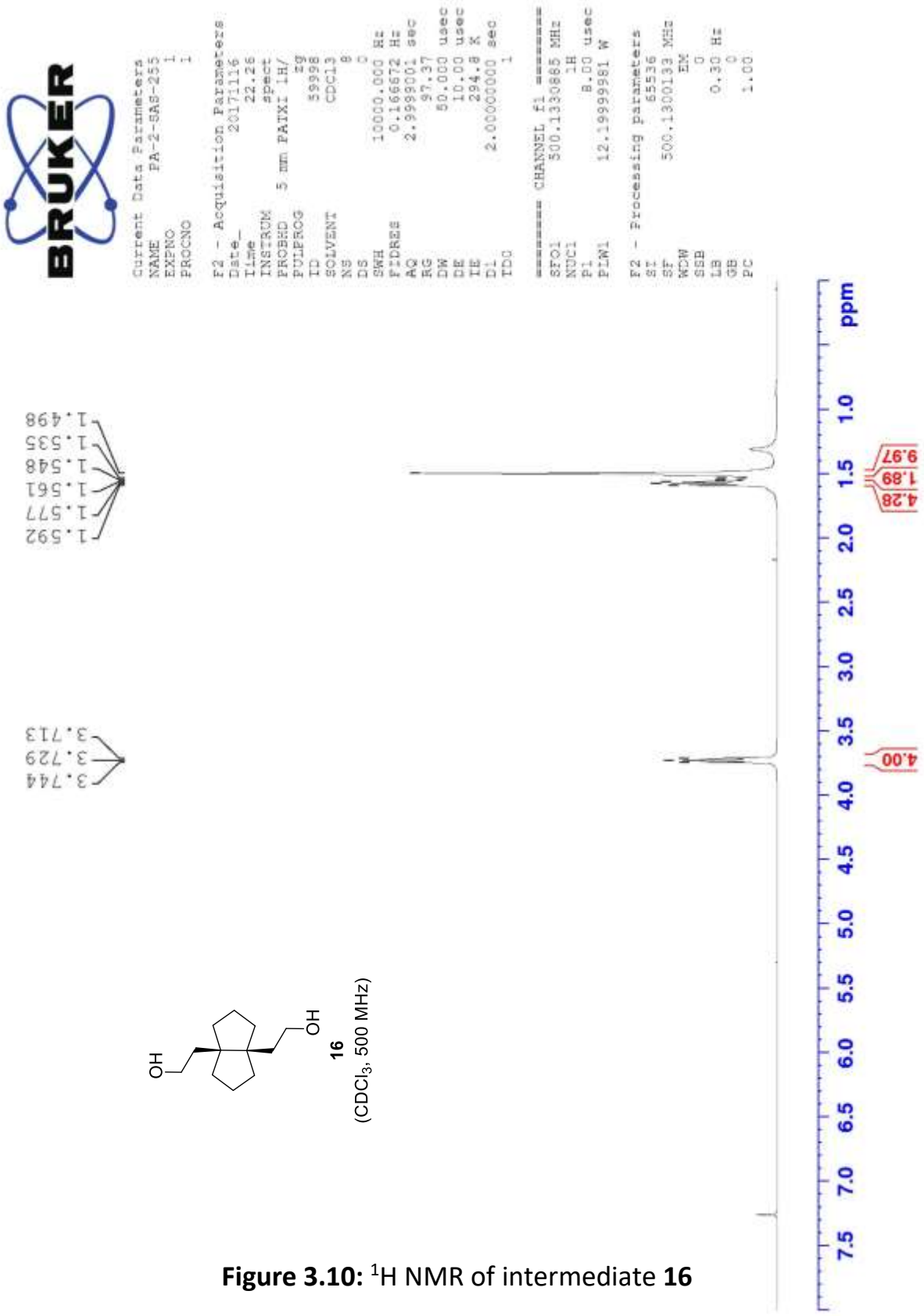
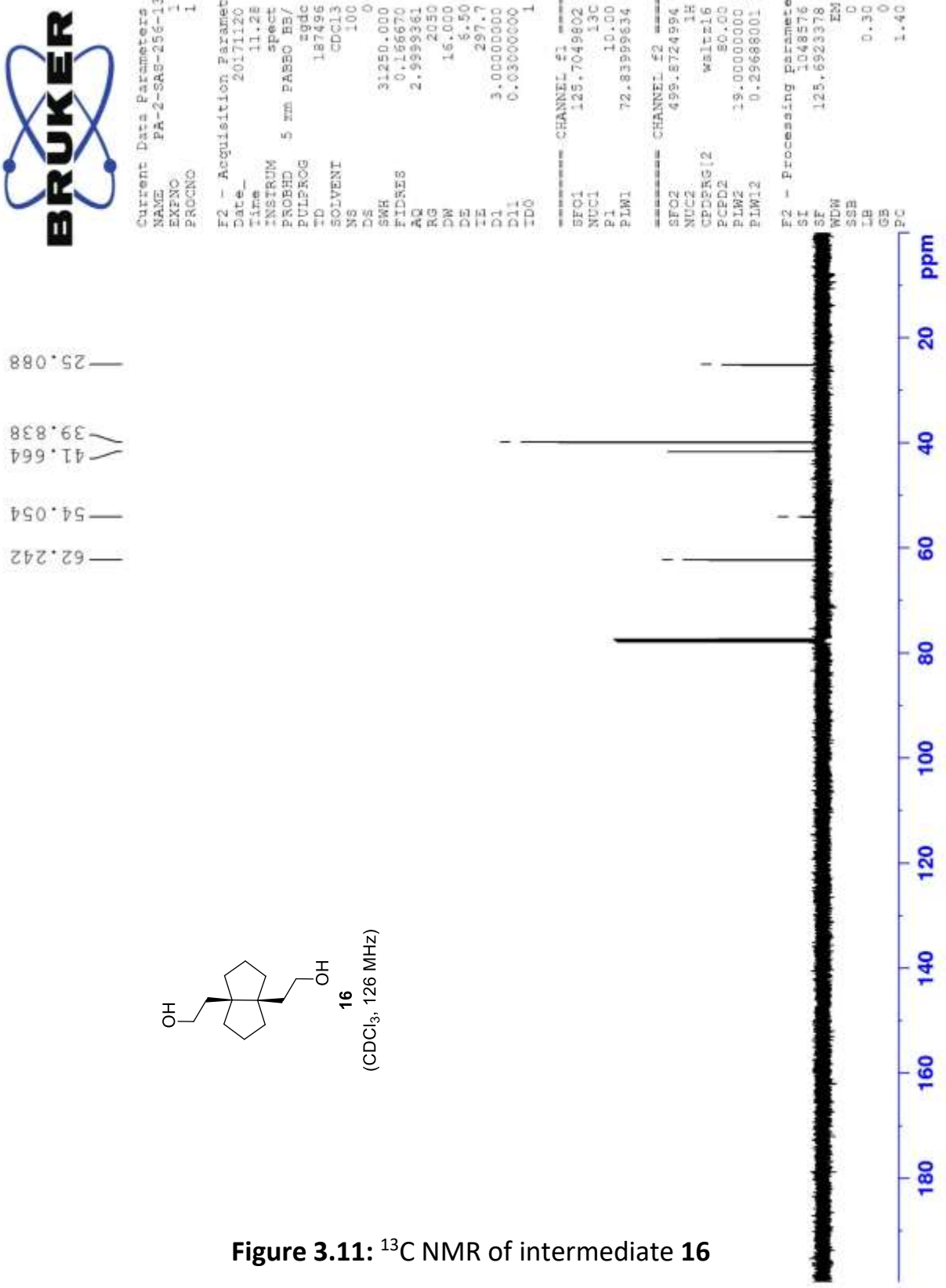


Figure 3.10: ^{1}H NMR of intermediate **16**



16

($CDCl_3$, 126 MHz)

Figure 3.11: ^{13}C NMR of intermediate **16**

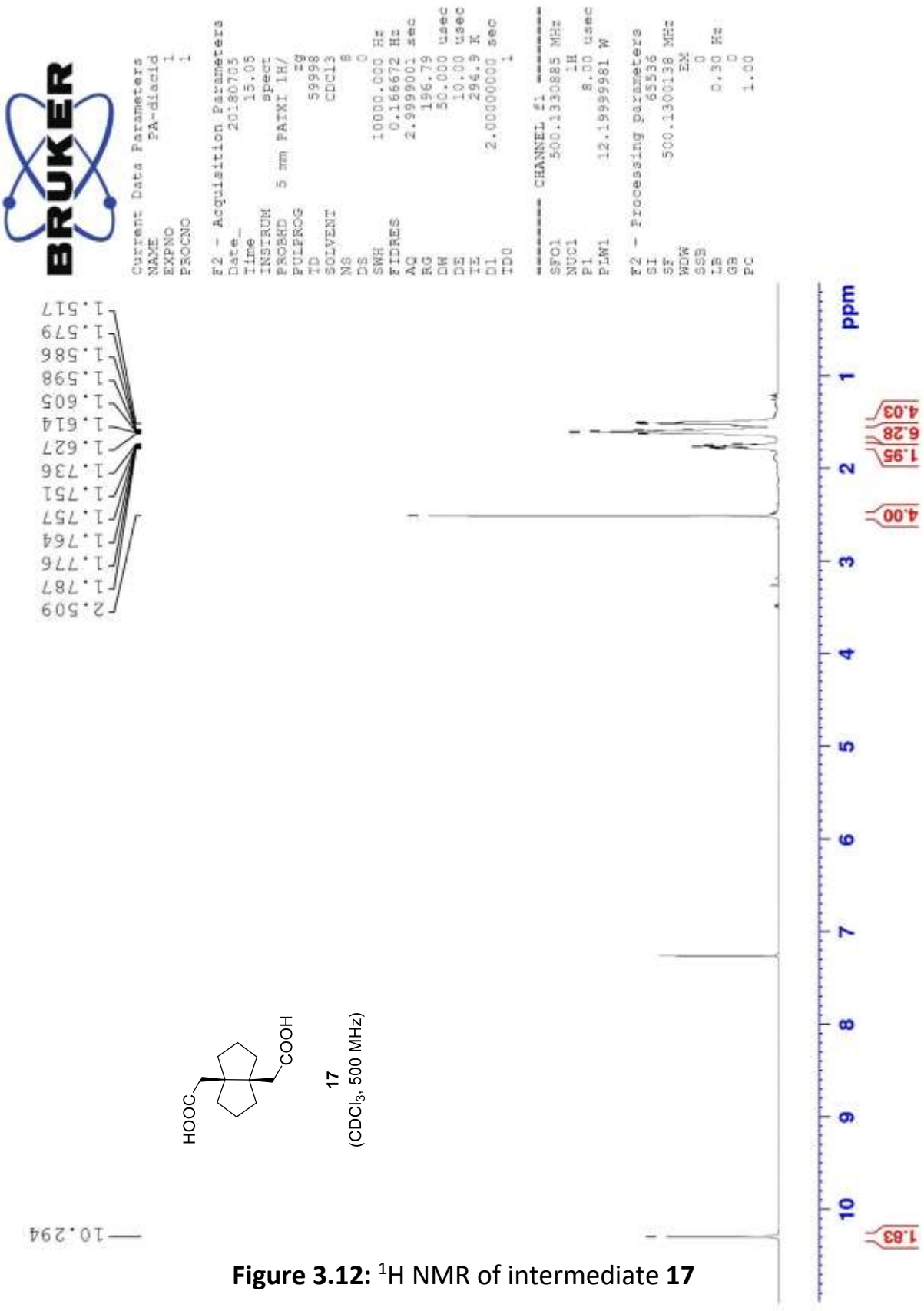


Figure 3.12: ^{1}H NMR of intermediate **17**

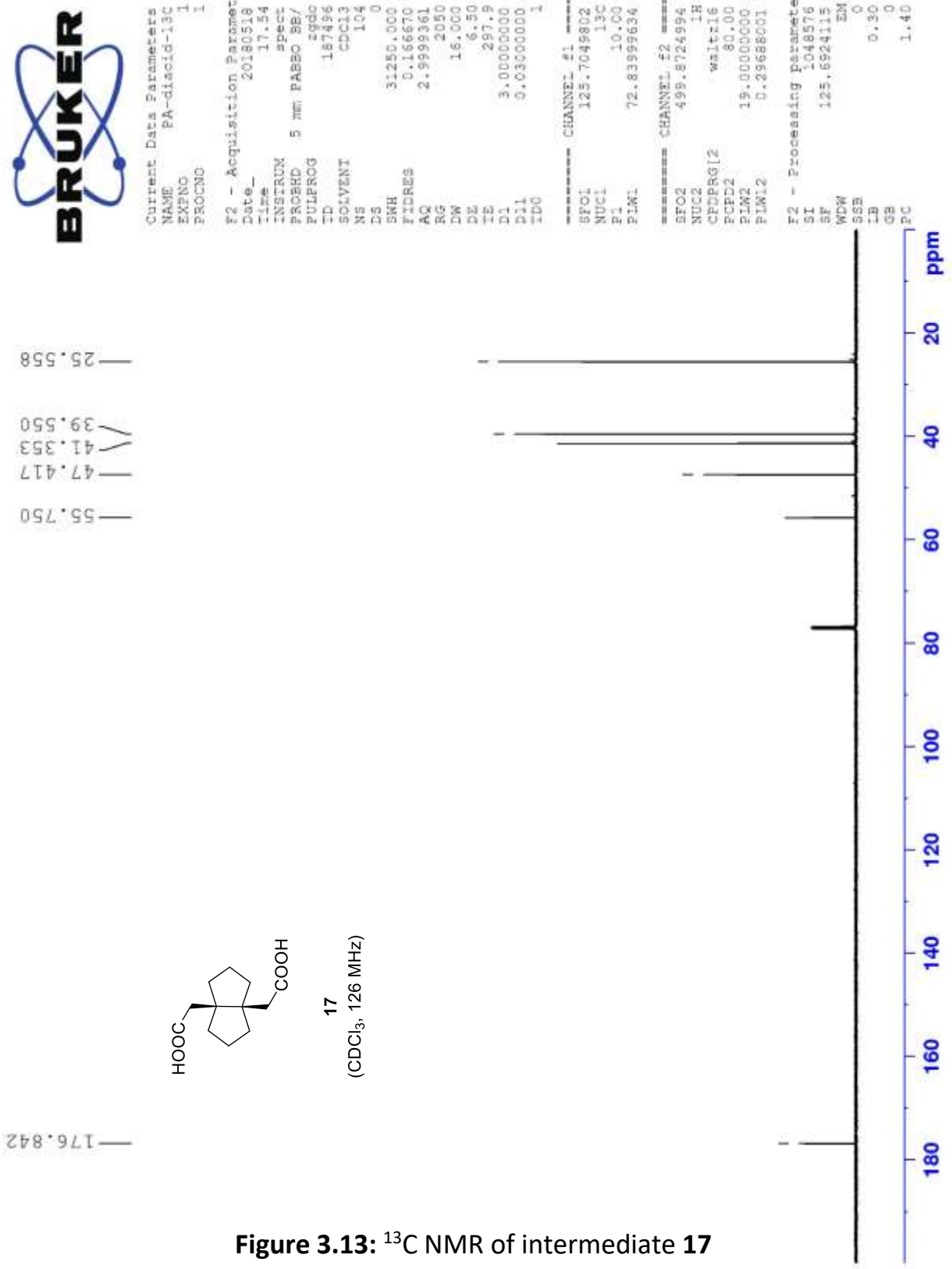
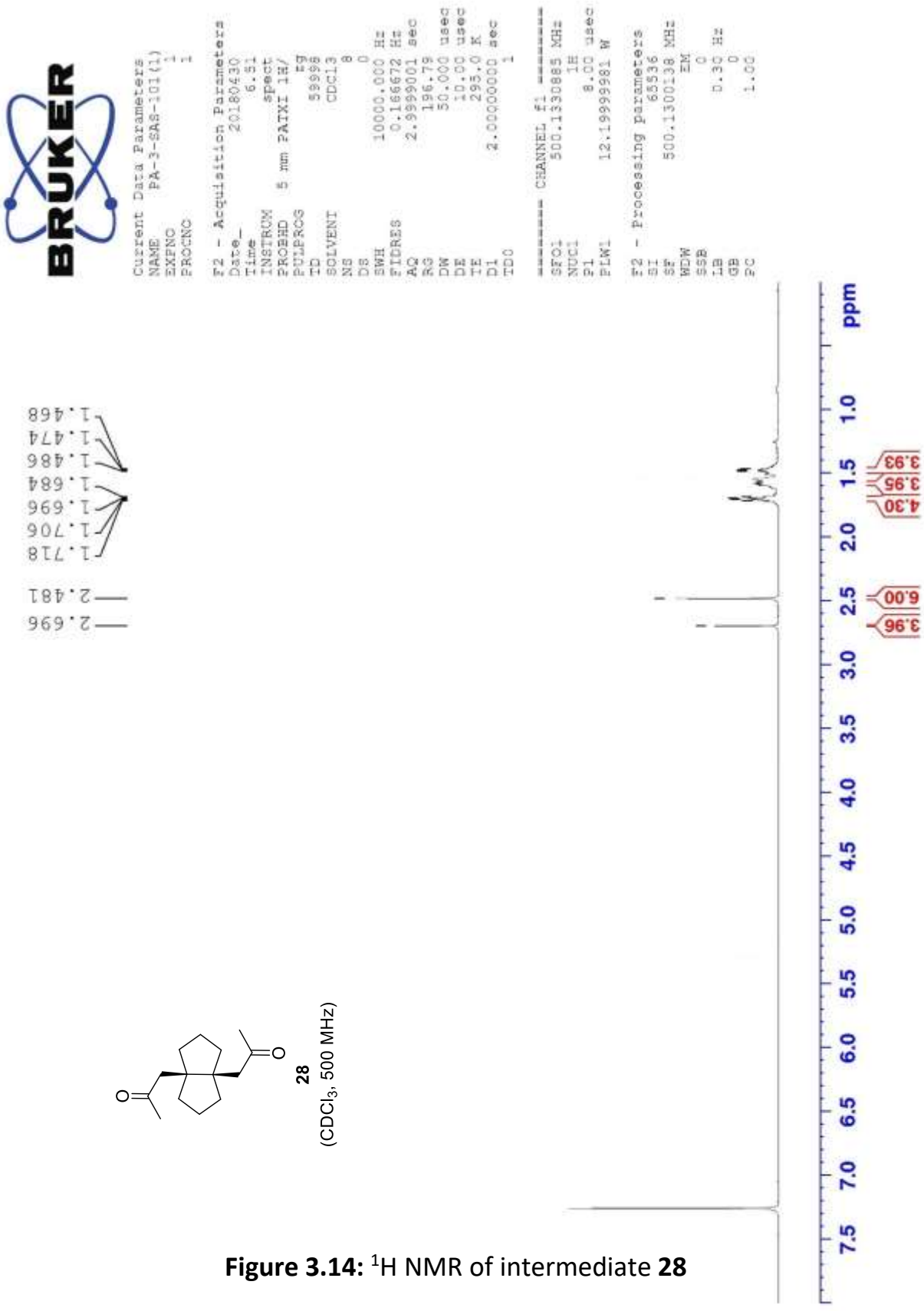


Figure 3.13: ^{13}C NMR of intermediate **17**



28

($CDCl_3$, 500 MHz)

Figure 3.14: ^{1}H NMR of intermediate **28**

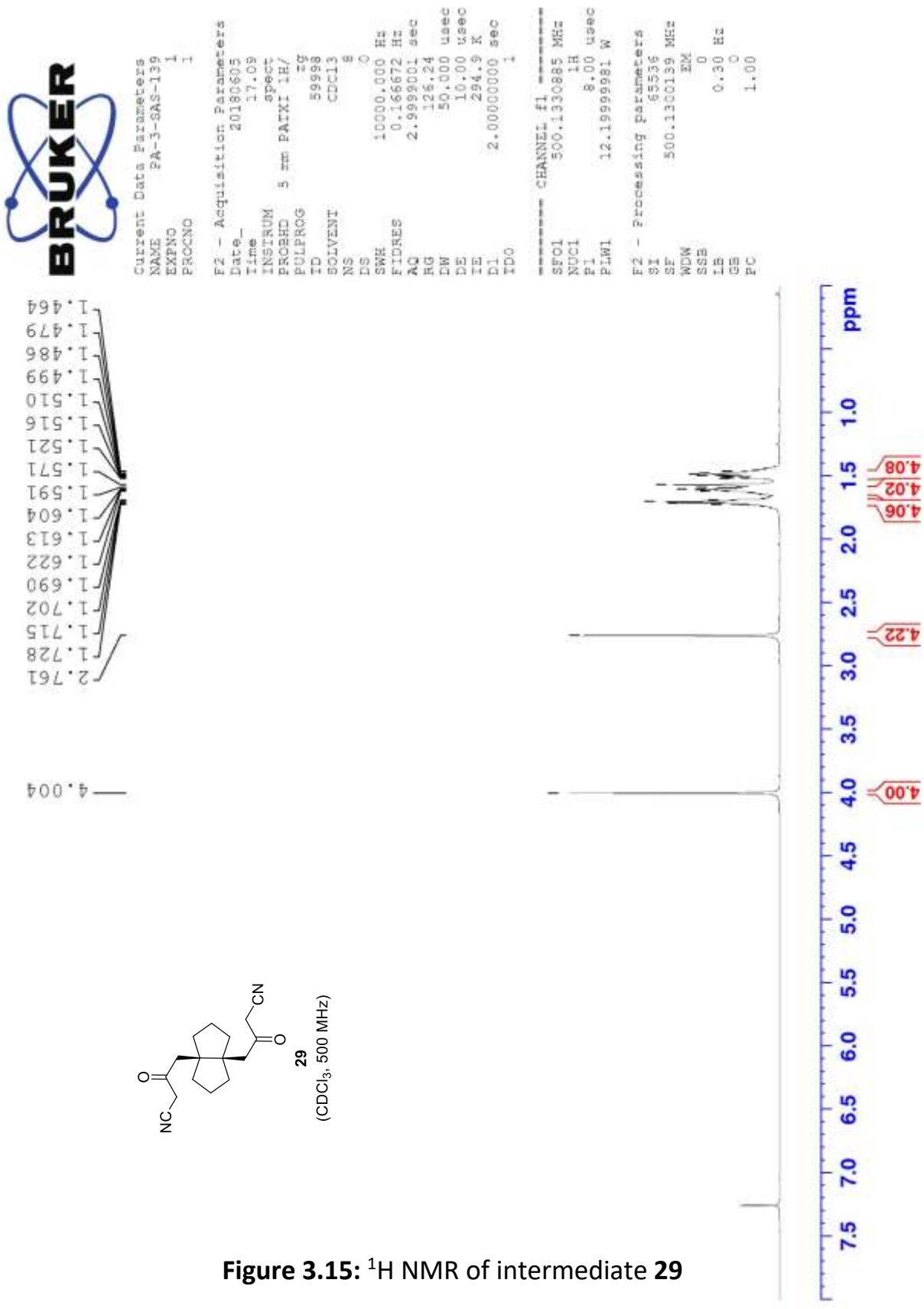


Figure 3.15: ^{1}H NMR of intermediate **29**

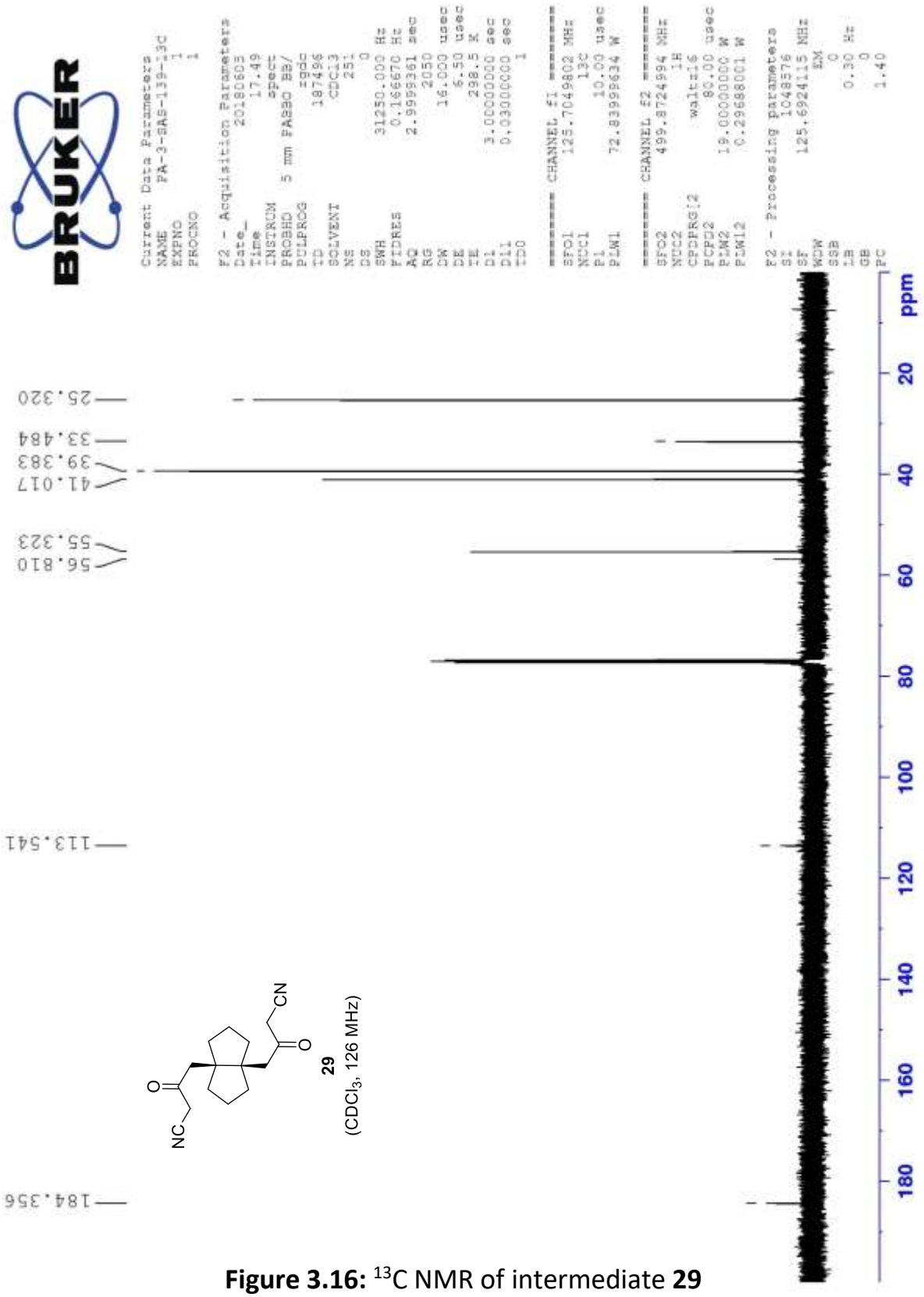


Figure 3.16: ^{13}C NMR of intermediate **29**

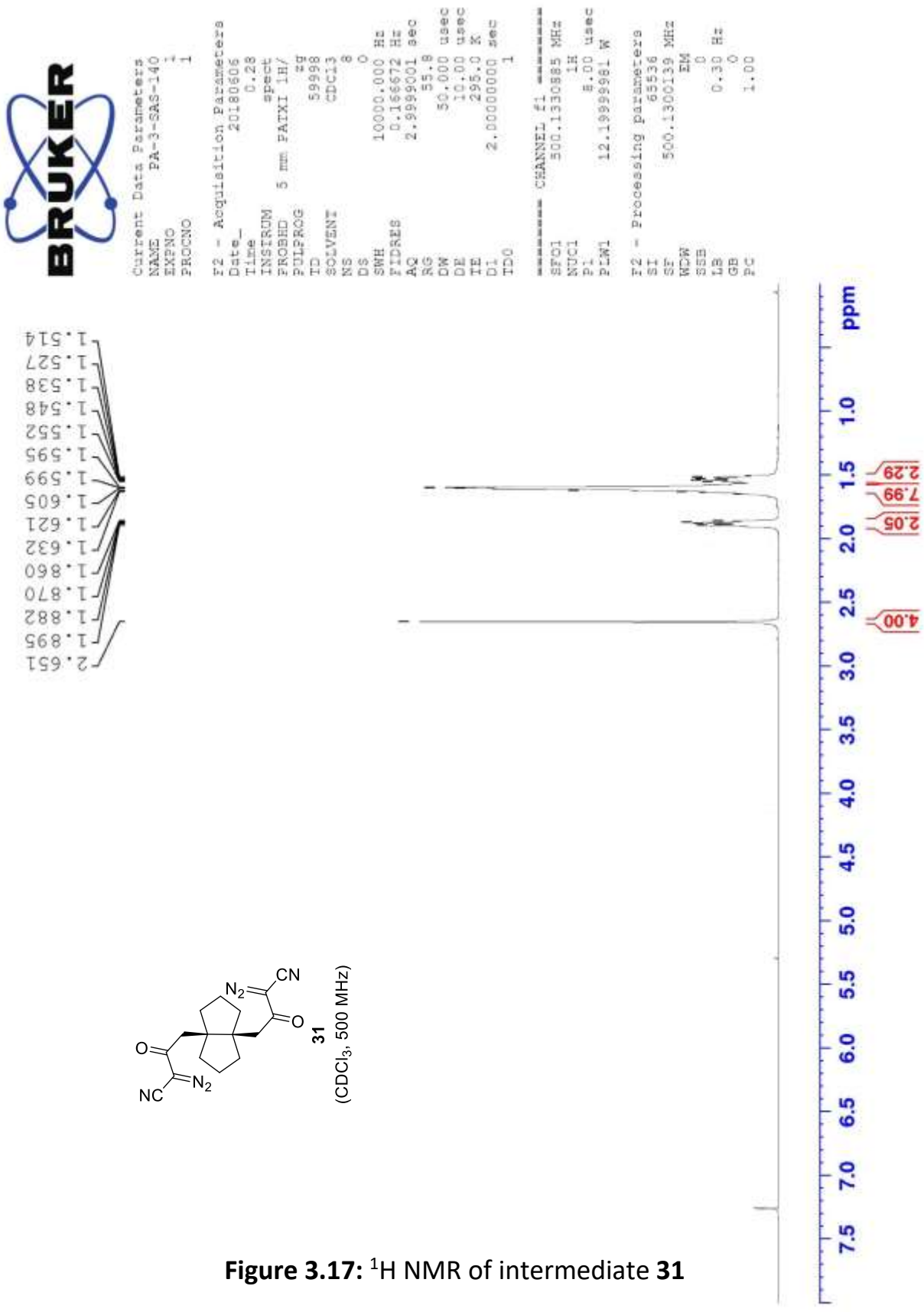


Figure 3.17: ^{1}H NMR of intermediate **31**

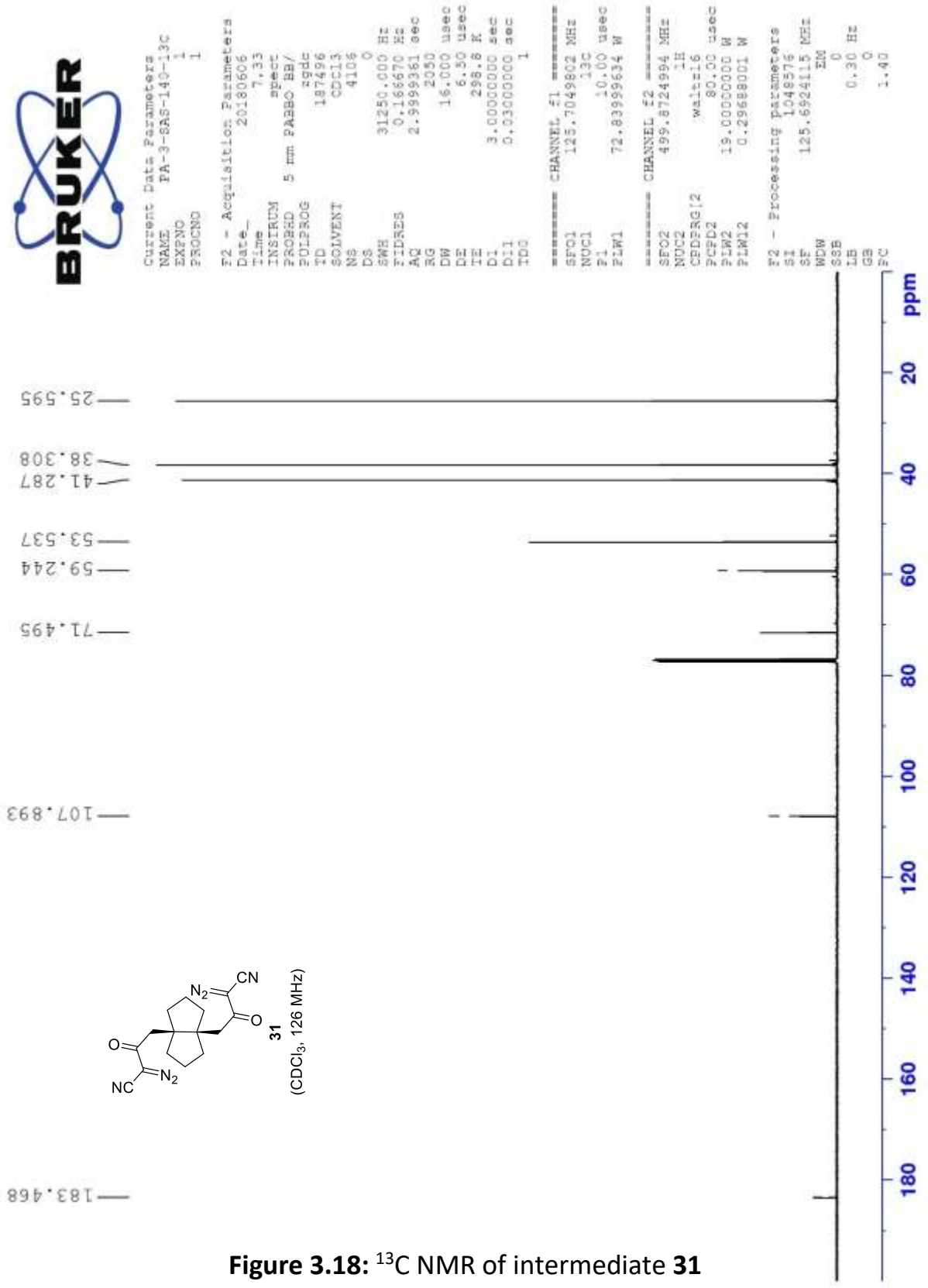


Figure 3.18: ^{13}C NMR of intermediate **31**

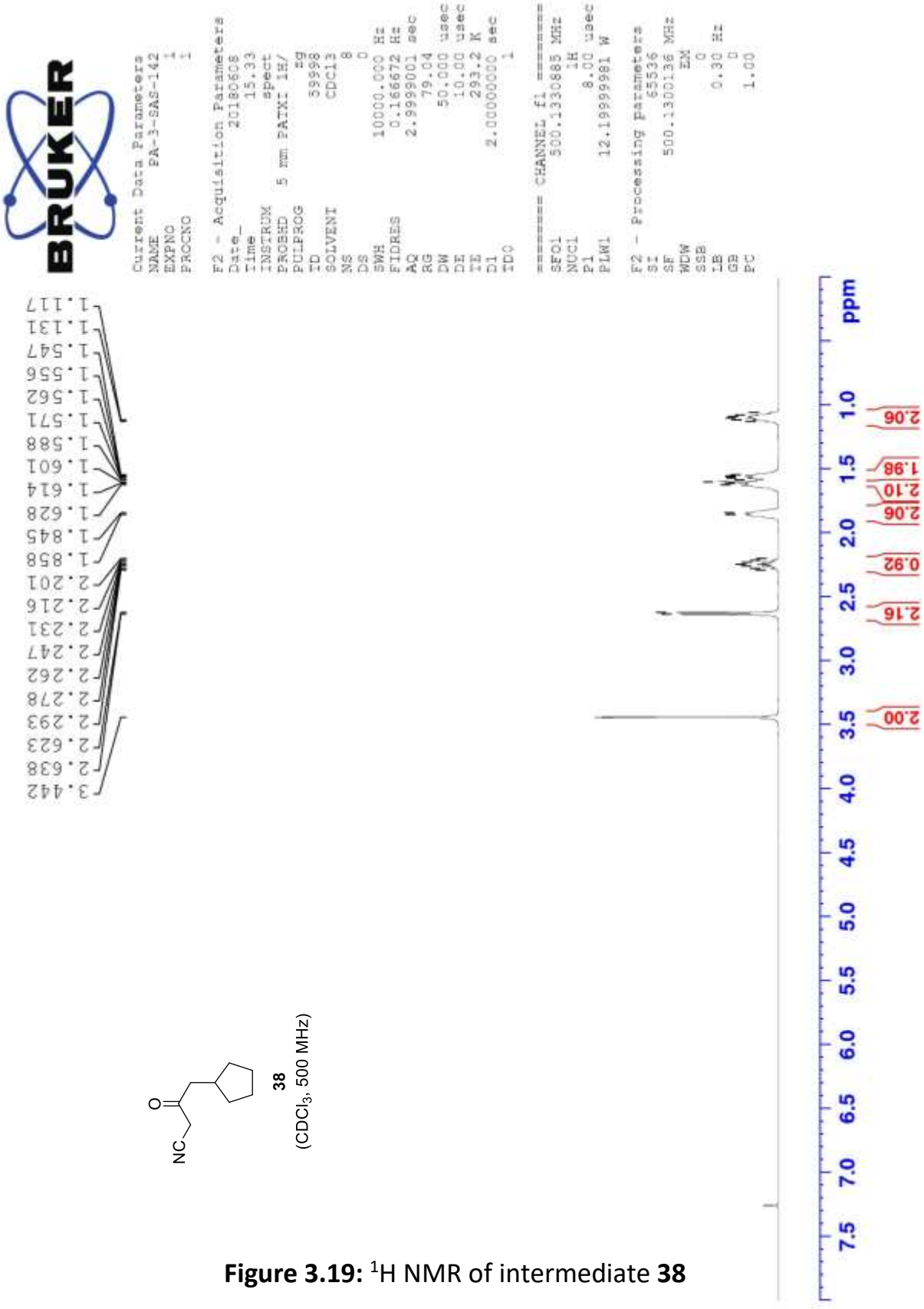


Figure 3.19: ^{1}H NMR of intermediate **38**

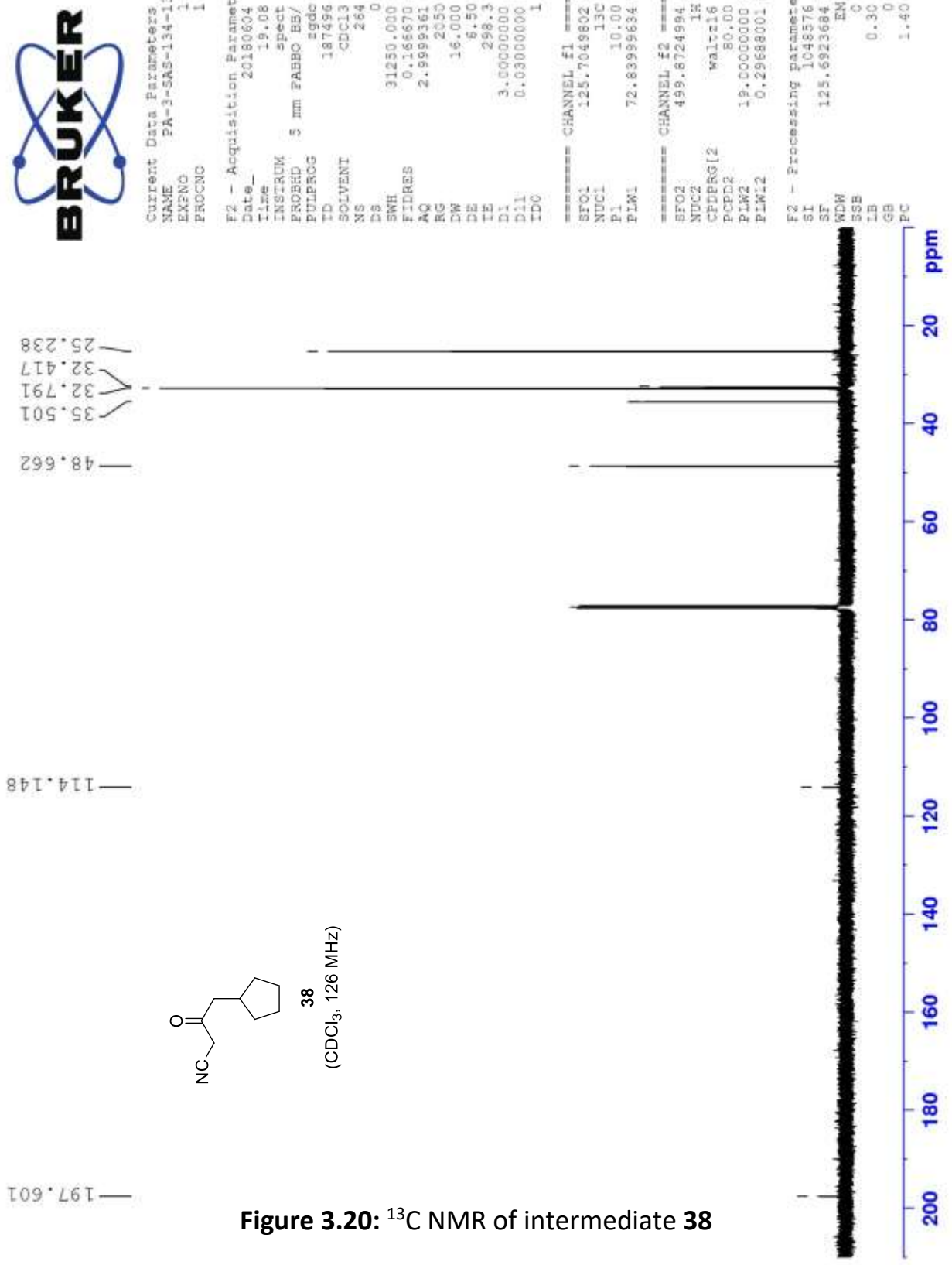


Figure 3.20: ^{13}C NMR of intermediate **38**

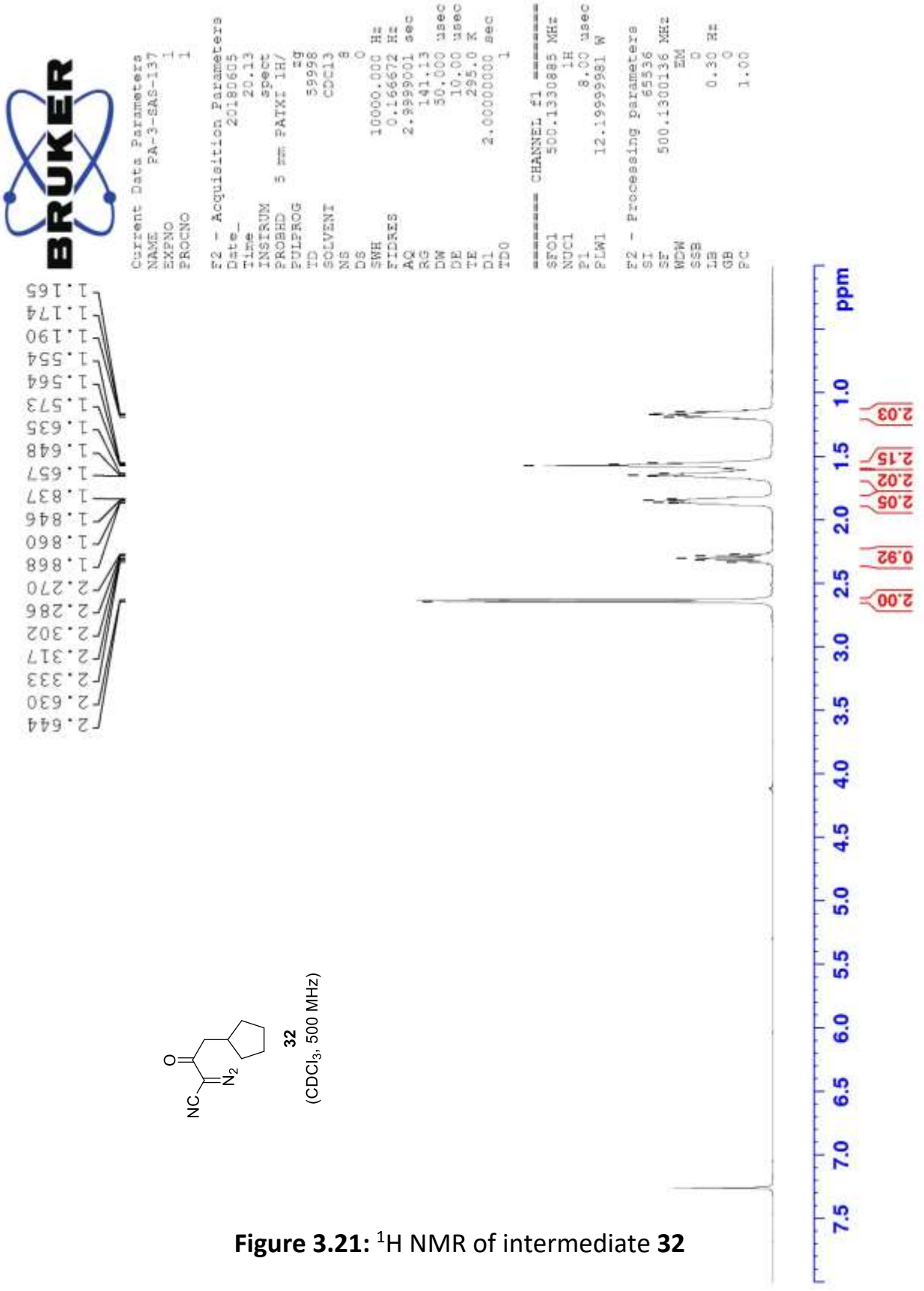
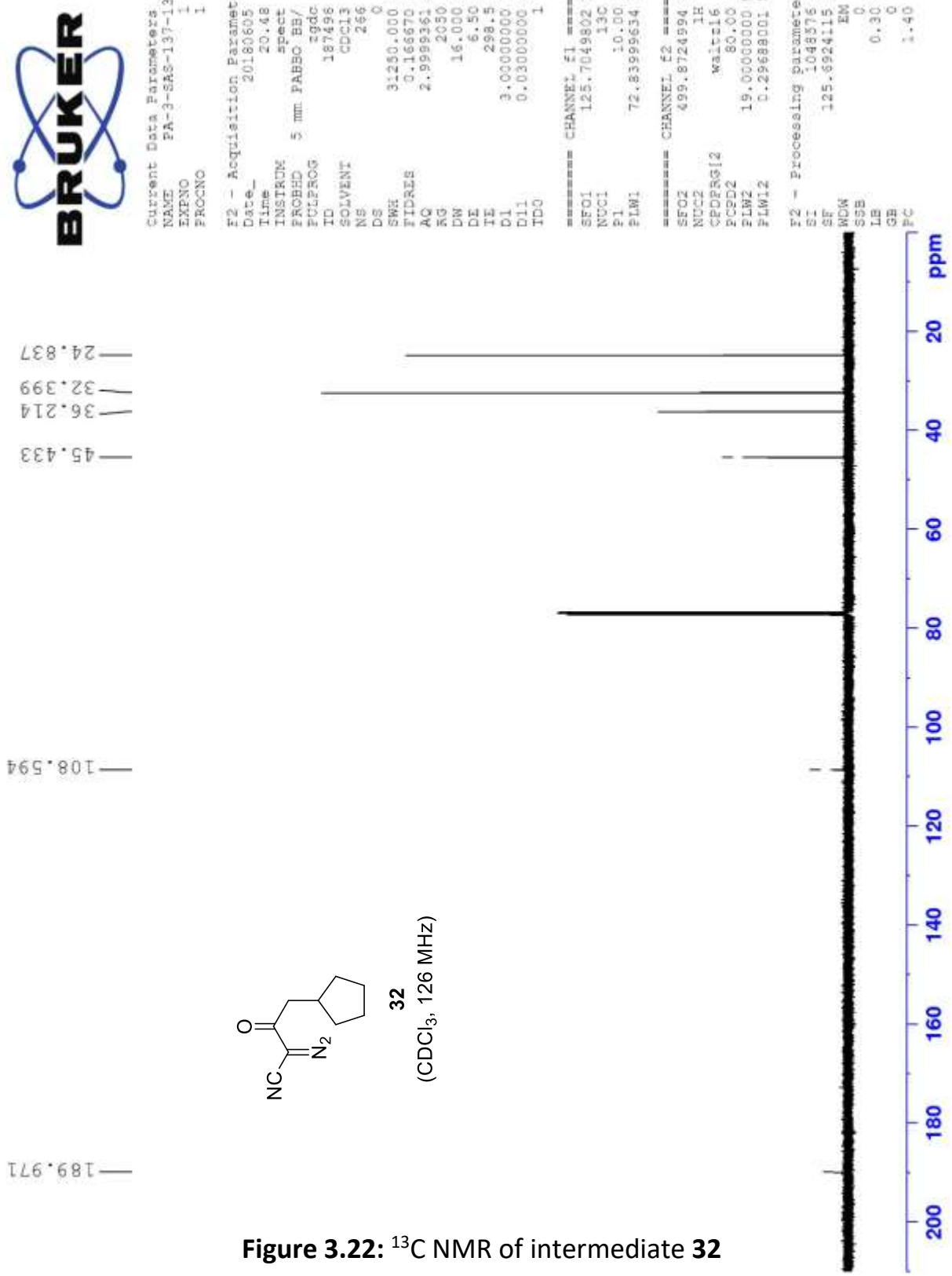


Figure 3.21: ^{1}H NMR of intermediate **32**



32

($CDCl_3$, 126 MHz)

Figure 3.22: ^{13}C NMR of intermediate **32**

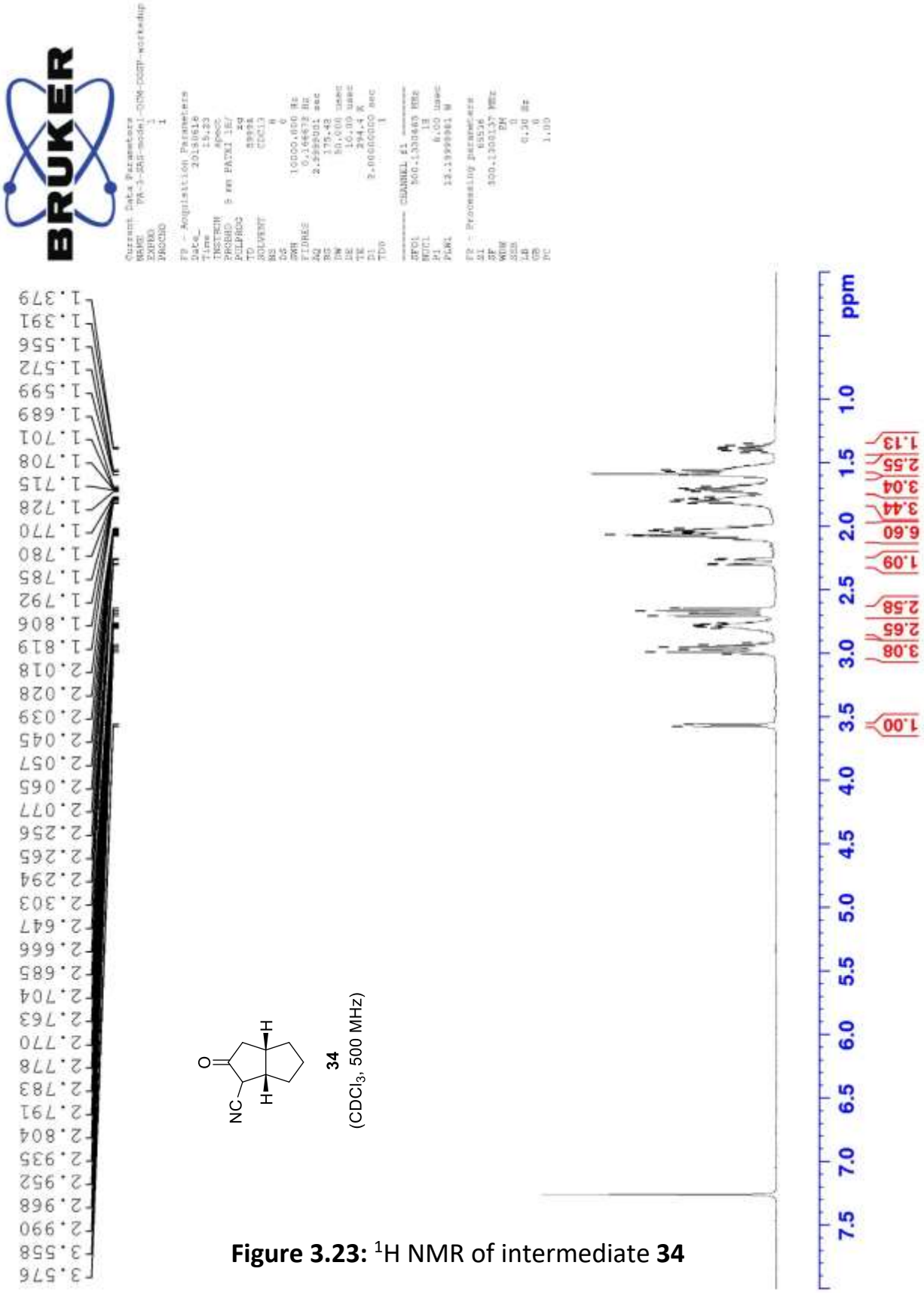


Figure 3.23: ^{1}H NMR of intermediate **34**

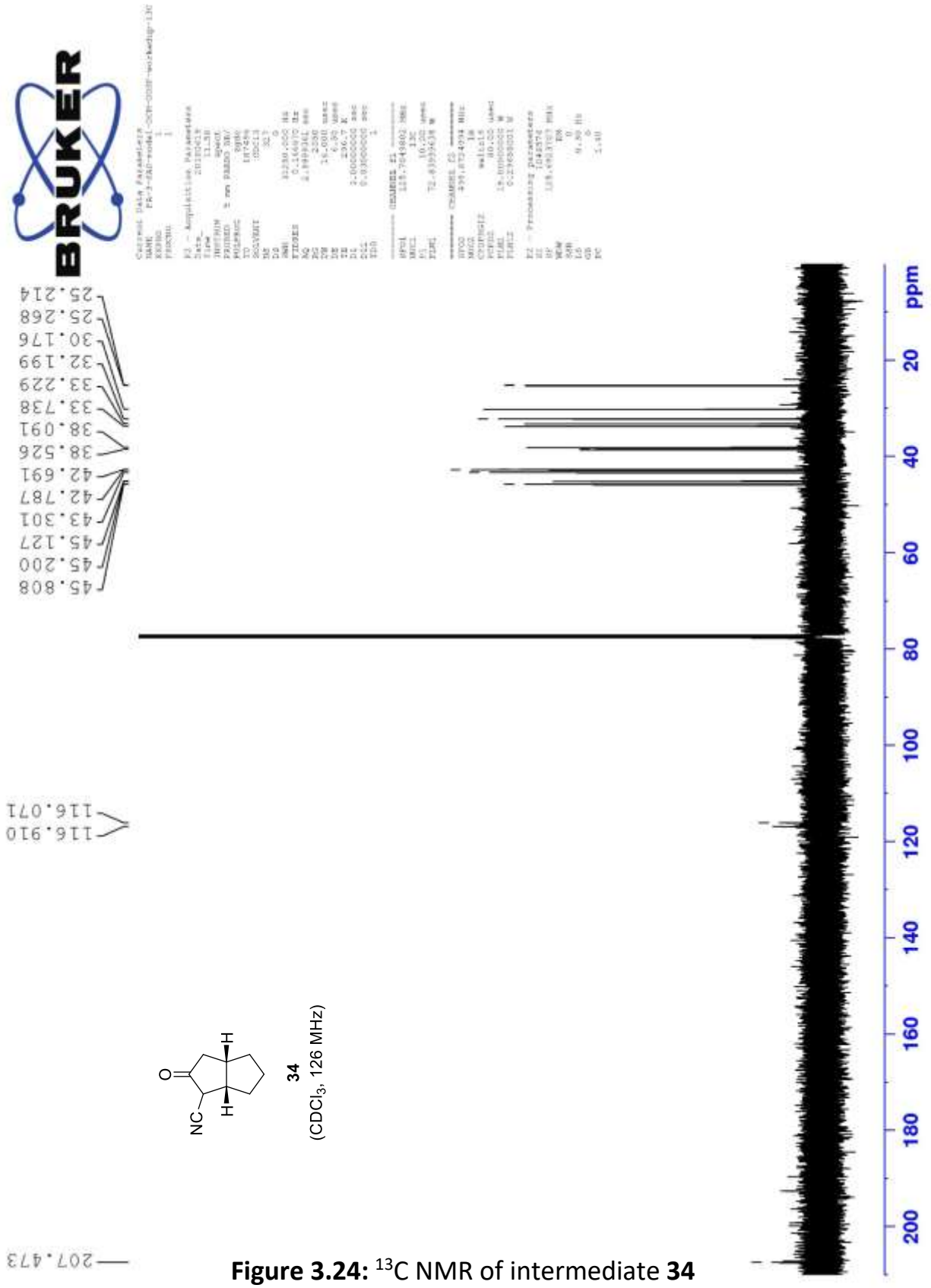


Figure 3.24: ^{13}C NMR of intermediate **34**

Chapter 4

Pauson-Khand route to waihoensene

4.1 Introduction

Since its discovery in 1973[1], the Pauson-Khand reaction has been frequently employed for the synthesis of substituted cyclopentenones. It involves a formal [2+2+1] cycloaddition between an alkene, an alkyne and carbon monoxide. This annulation process is mediated by a cobalt species.[2] Since, five-membered carbocycles are ubiquitously present in nature, the huge potential ability of this reaction was realized very fast by organic synthetic chemists around the globe.

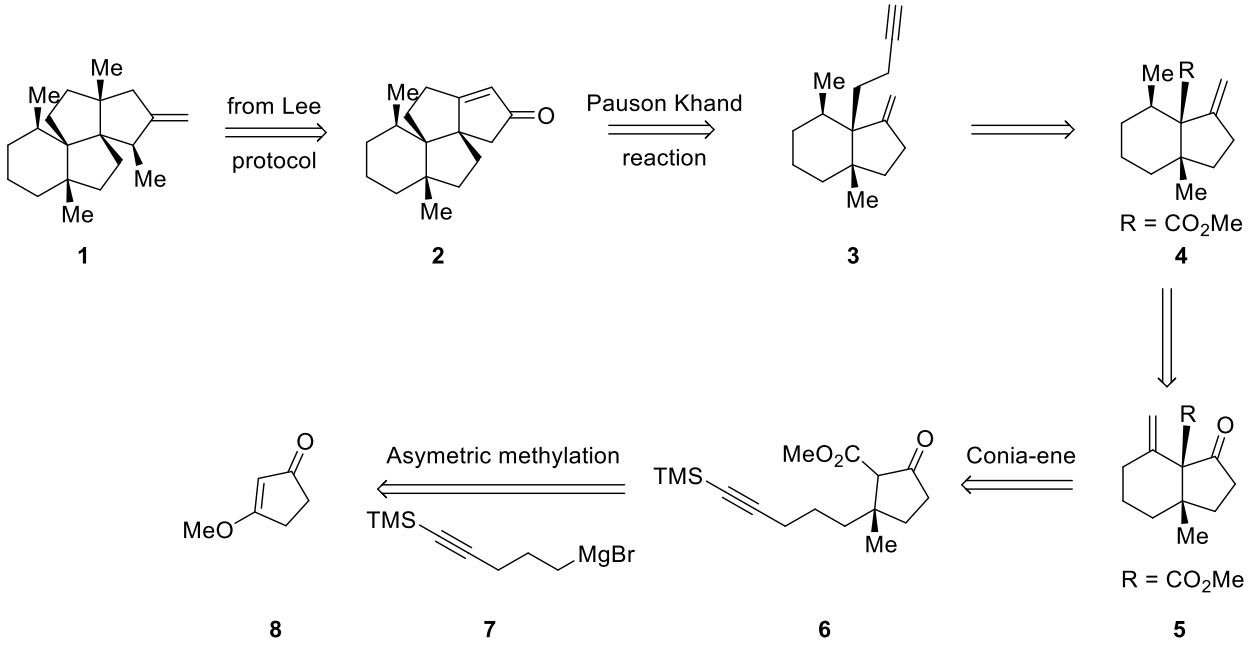
Early variants of this reaction resulted in low yields of substituted cyclopentenones, as these reactions were conducted under purely thermal conditions. In the decades since its discovery, better understanding of the reaction mechanism[3,4] has led to the development of techniques and conditions that deliver the desired cyclopentenone products in very high yields. Such is the power of this reaction, that it has been employed in the total synthesis of many complex natural products like (+)-epoxydictymene,[5] pentalenes,[6] (-)-α-kainic acid,[7] paecilomycine A,[8] (+)-achalensolide,[9] (-)-alstonerine,[10] (±)-8α-hydroxystreptazolone,[11] cedrenes,[12] (+)-ingenol,[13] (-)-retigeranic acid,[14] (+)-fusarisetin A,[15] crinipellins[16] and many more.

After the failure of the two previous routes, we had to come up with a whole new strategy for the total synthesis of the natural product waihoensene. Given that the symmetric approach to the molecule did not yield fruitful results, we had to come up with a linear route towards the natural product. Previously from our lab, quaternary center analysis strategies have been used for the synthesis of complex natural products[17] which involves setting up one chiral quaternary center with the desired stereochemistry and then using that as a handle for setting up the stereochemistry of the other chiral quaternary centers. We thought waihoensene **(1)**, that has four chiral quaternary centers could be synthesized using the same concept by planning the synthetic strategy in such a way that sets up an initial chiral quaternary center and then uses that center as a guide for setting up the correct stereochemistry at all the other centers.

4.2 Retrosynthetic Analysis

With the previous knowledge from the Lee group,[18] we knew that enone **2** can be modified further to give the natural product waihoensene **1**. For the retrosynthetic analysis, we envisioned enone **2** could arise from an intramolecular Pauson-Khand reaction between the alkene and the alkyne moieties present within the molecule **3**. The stereochemistry of the alkyne side chain in compound **3** would guide the cyclization to give the third chiral quaternary center with the desired stereochemistry. This alkyne **3**, in turn, could be generated from the β-keto-ester **4** via a number of functional group transformations. The alkene **4** could be expected to be generated from the ketone **5** via a diastereoselective hydrogenation of the olefin and the conversion of the ketone to the methylene group via the Wittig olefination of the ketone **5**. The bicyclic β-keto-ester **5** can be furnished from the monocyclic alkynyl β-keto-ester **6** via a gold-catalyzed Conia-

ene reaction.[19,20] Formation of a five-membered ring using gold-catalyzed Conia-ene reaction with alkynes and β-keto-esters are well established.[21–27] Here again, the already established chiral quaternary center should be able to guide the alkyne side chain to approach the β-keto ester from the bottom face thus setting the correct stereochemistry at the second quaternary center. Grignard reaction with the TMS alkynyl substrate **7** followed by asymmetric methylation on the starting vinyl methoxide **8** could provide the compound **6** (Scheme 4.1).

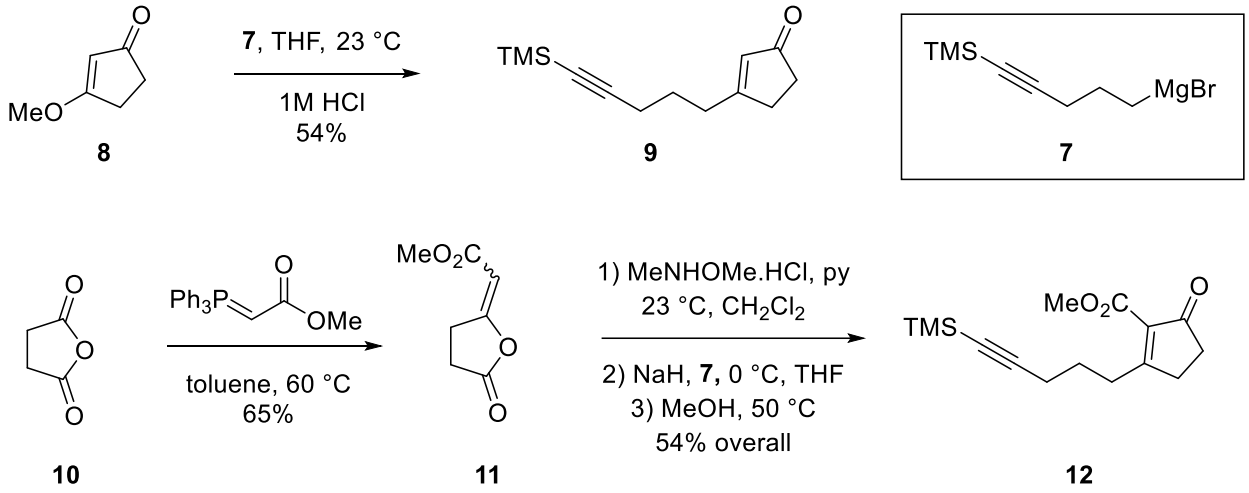


Scheme 4.1: Retrosynthesis of waihoensene

4.3 Execution of the synthetic plan

With the retrosynthetic plan in place, we ventured on our journey towards the total synthesis of the natural product. Starting from the vinyl methoxy **8**, performing a Grignard reagent with (5-bromopent-1-ynyl)trimethylsilane[28] delivered the tri-substituted enone **9** in 54%.[29] On the other hand following the procedure developed previously in our lab,[30] subjecting succinic anhydride **10**

to Wittig conditions delivered the conjugated ester **11** in 65% yield. This ester is then treated with Weinreb amide, the Grignard reagent **7** followed by dehydration to afford the tetra substituted enone **12** in 54% yield (Scheme 4.2).

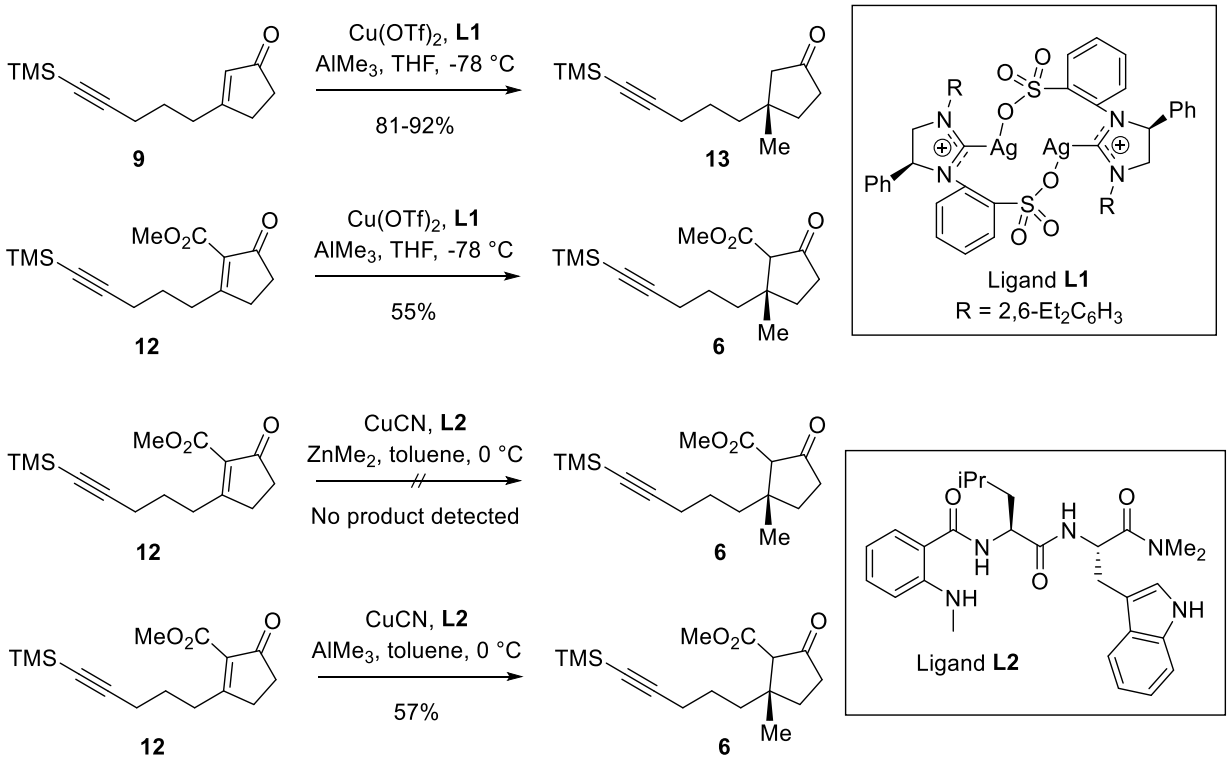


Scheme 4.2: Precursors for asymmetric methylation

4.4 Asymmetric methylation

With both the tri-substituted enone **9** and tetra-substituted enone **12** in hand, the next step was the asymmetric installation of the methyl group. To that affect, we proposed to use Hoveyda's strategy for the asymmetric conjugate addition of trimethylaluminum to five-membered ring systems in the presence of silver based chiral N-heterocyclic carbene ligands.[31,32] Using the ligand **L1**, the ketone **13** from the tri-substituted enone **9** was obtained in 82-92% yields. Using the same strategy on the tetra-substituted enone **12** however, the β-keto-ester **6** was obtained only in 55% yield. Next, in an attempt to better the yield obtained for the tetra-substituted enone **12**, we attempted to use Hoveyda's strategy for the catalytic asymmetric methylation on tetra-

substituted enones using the peptide based ligand **L2**.[33] Using the exact conditions as reported by Hoveyda with dimethylzinc as the alkylating reagent, no reaction was observed. However, switching the alkylating reagent from dimethylzinc to trimethylaluminum, delivered us the desired β-keto-ester **6** albeit still in moderate yields of 57% (Scheme 4.3).

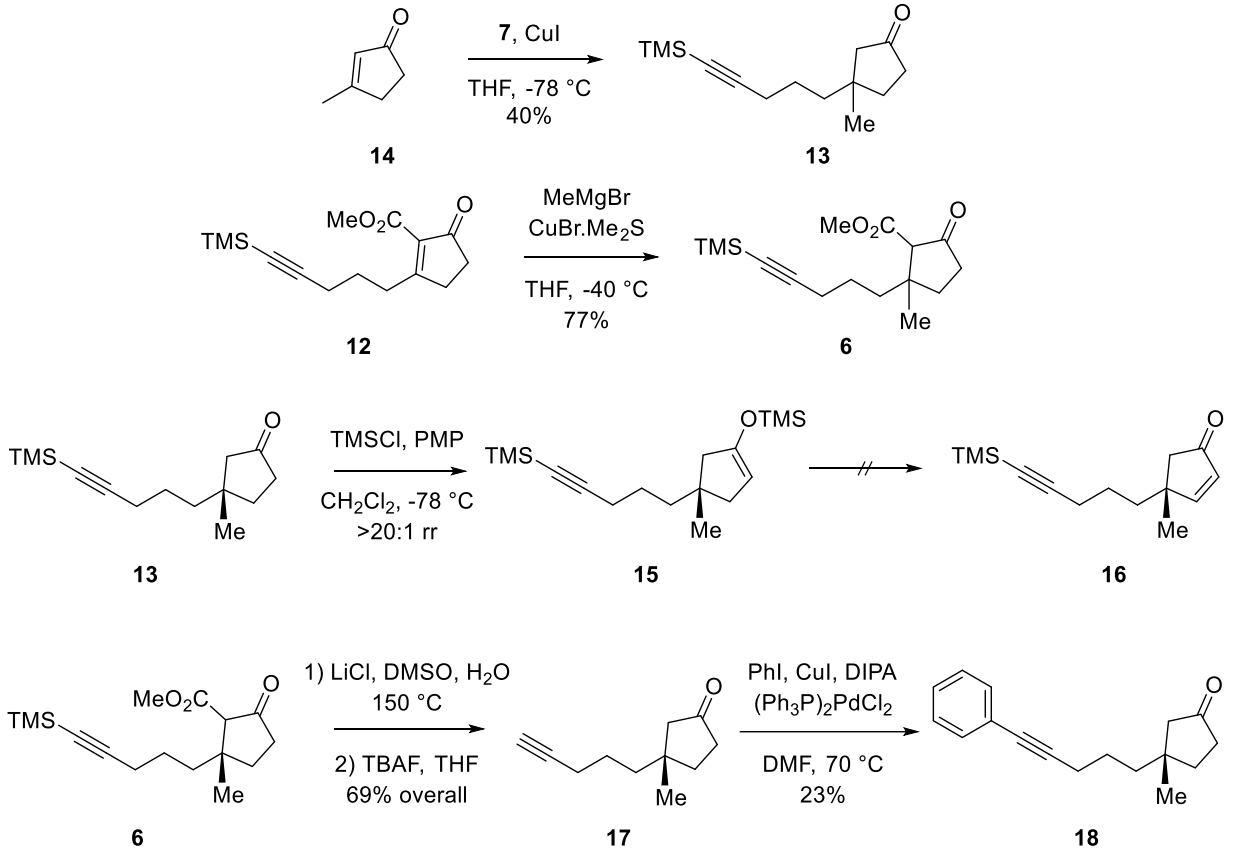


Scheme 4.3: Asymmetric methylation

4.5 Determination of ee

The next step was the determination of the ee's for the asymmetric reactions mentioned above. Racemic **13** was synthesized from ketone **14** using the Gilman reagent generated from CuI and Grignard reagent **7** in 40% yield. Racemic **6** was synthesized from β-keto-ester **12** using MeLi and CuBr.Me_2S in 77% yield. Since the above prepared compounds were not UV-active, we had to convert them into UV-active compounds. Initially, we thought to convert the ketone **13** to enone

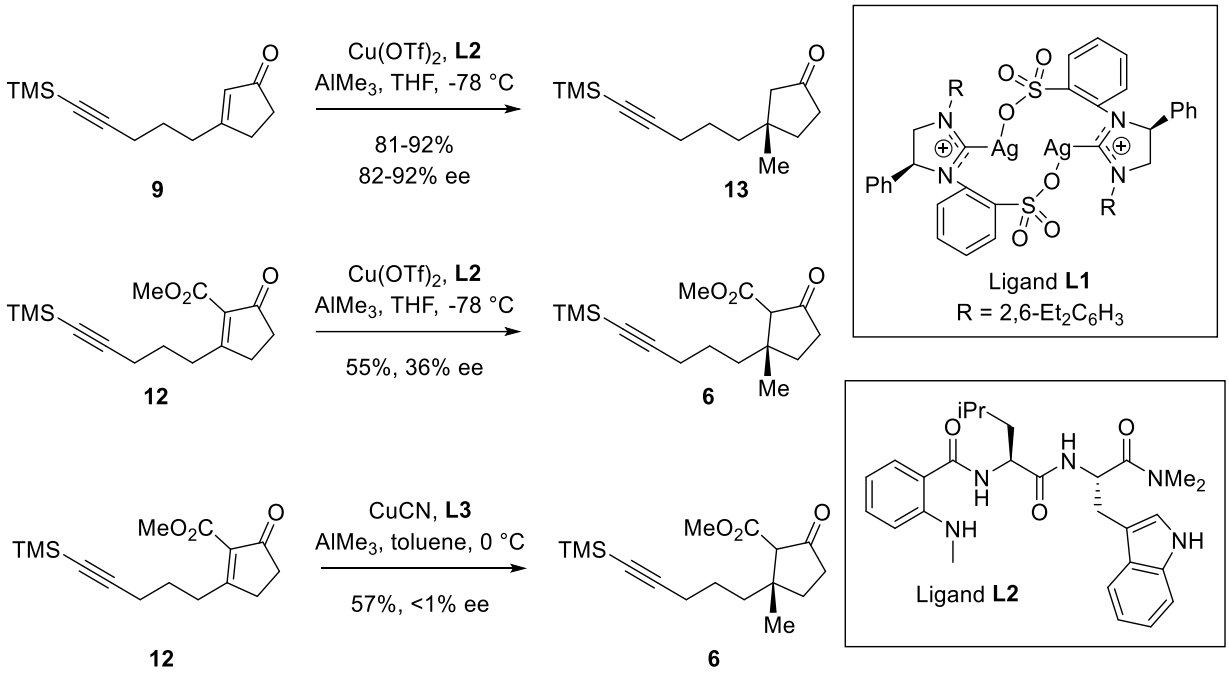
16 via an IBX mediated oxidation of the TMS enol ether of the ketone. Using a hindered base like PMP the ketone **13** was converted to the silyl enol ether **15**.[29] However, many attempts to convert **15** to enone **16** using IBX.NMO or IBX.MPO[34,35] or Saegusa-Ito[36] conditions were unsuccessful. Finally, removal of the ester from the β-keto-ester via Krapcho decarboxylation[37] to give ketone **13**, removal of the TMS and Sonogashira coupling with phenyl iodide gave the phenyl acetylene product **18** which could be analyzed by HPLC for ee determination (Scheme 4.4).



Scheme 4.4: Determination of ee

After analysis, the tri-substituted ketone **9** using Hoveyda's asymmetric conjugate addition with ligand **L1** gave 82-92% ee depending on the scale of the reaction (ee decreased with increase in

batch size), whereas the tetra-substituted ketone **12** gave only 36% ee under the same conditions. Using ligand **L2**, the tetra-substituted ketone **12** gave no ee whatsoever (Scheme 4.5). Keeping these results in mind, we stuck to using the tri-substituted ketone **9** for the total synthesis and effect a regioselective ester installation later (Scheme 4.5).

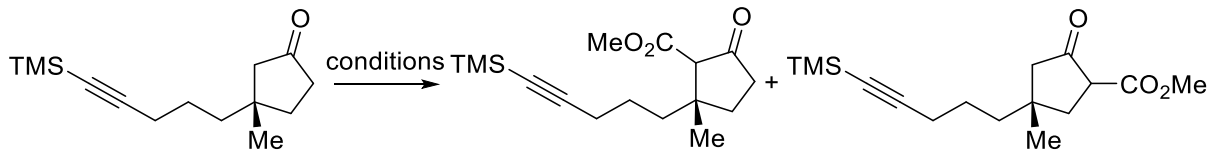


Scheme 4.5: ee's for asymmetric methylation

4.6 Regiospecific installation of ester moiety

The next step was the regiospecific installation of the ester moiety. To that end, we tried several bases that could achieve the regiospecific deprotonation of ketone **13** to deliver us the desired β-keto-ester **6** using Mander's reagent as the electrophile. Lithium diisopropylamide gave a 1:1 mixture of the desired to undesired regioisomers while bases like lithium tetramethylpiperidide, lithium diethylamine and sodium hydride gave decomposition of the starting material. Soft enolization using amine bases like triethylamine and diisopropylethylamine did not give any

reaction. Using hexamethyldisilazane bases, however gave better results and ultimately NaHMDS gave us the best ratio (1.8:1) of regioisomers with an overall yield of 88% (Table 4.1).[17,38]

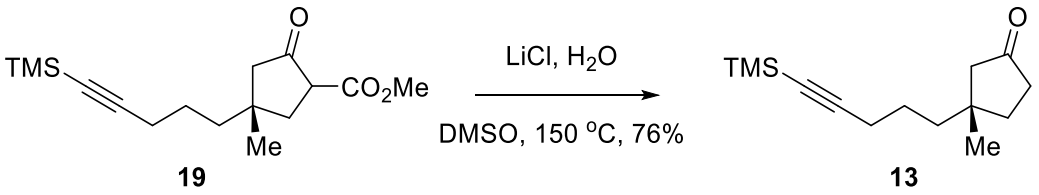


13 **6** **19**

Conditions	% yield of 6	% yield of 19
LDA, THF, 0 °C; $CNCO_2Me$, –78 °C	48%	44%
LiTMP, THF, 0 °C; $CNCO_2Me$, –78 °C	decomposition	
LEA, THF, 0 °C; $CNCO_2Me$, –78 °C	decomposition	
NaH, THF, 0 °C; $CNCO_2Me$, –78 °C	decomposition	
Et_3N, $CNCO_2Me$, CH_2Cl_2, –78 °C	N.R.	
i-Pr_2NEt, $CNCO_2Me$, CH_2Cl_2, –78 °C	N.R.	
LiHMDS, THF, 0 °C; $CNCO_2Me$, –78 °C	43%	28%
KHMDS, THF, 0 °C; $CNCO_2Me$, –78 °C	traces	
NaHMDS, THF, 0 °C; $CNCO_2Me$, –78 °C	56%	32%

Table 4.1: Regiospecific installation of ester moiety

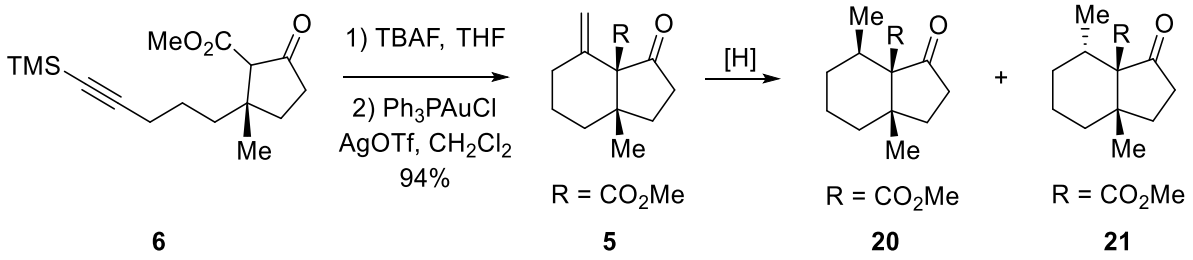
The undesired β-keto-ester **19** was recycled to give the ketone **13** back using Krapcho decarboxylation[37] in 76% yield (Scheme 4.6).



Scheme 4.6: Recovery of ketone **13**

4.7 Diastereoselective hydrogenation

With the initial chiral quaternary center set, we set out to forge the second ring and the second chiral quaternary center via a Conia-ene reaction.[24,27] Following the removal of the TMS group using TBAF, the cyclization proceeded under 1 mol% of Ag and 1 mol% of Au catalysis to deliver the bicyclic alkene **5**. With the purpose of the alkyne served, we next sought to reduce the olefin to the methyl group in a diastereoselective fashion for which the hydrogen molecule had to be formally delivered from the sterically hindered concave face. To our delight, our initial attempts using simple Pd/C catalysis delivered us the desired isomer as the major product albeit in low yields of 20%. HAT conditions (as developed by Shenvi)[39] using phenylsilane as the hydrogen donor gave us the same trend in selectivity with an increase in the yield of the desired product to 47%. This suggested that the desired product is both kinetically and thermodynamically favored over the undesired one. We observed a switch in the selectivity when homogenous catalysis using Crabtree's catalyst[40] was employed which gave us the undesired isomer as the major product, the observed trend being explained by the binding of the iridium catalyst to the neighboring ester motif thus delivering the hydrogen from the wrong face. Finally, using PtO_2, we observed the highest yields and ratio of the desired to the undesired isomer (Scheme 4.7).



6 **5** **20** **21**

Scheme 4.7: Conia-ene and hydrogenation

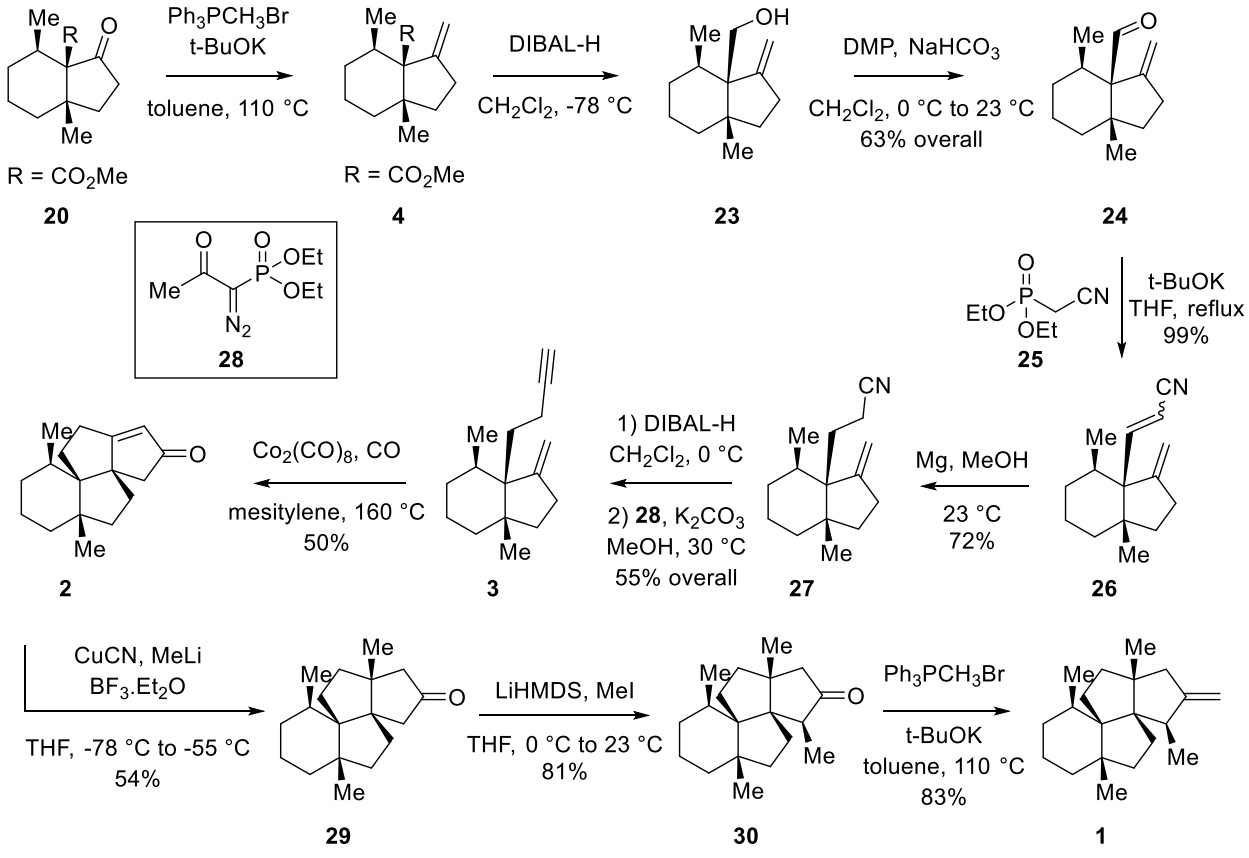
Conditions	% yield of 20	% yield of 21
H_2, Pd/C, EtOH, 23 °C	20	8
$Mn(dpm)_3$, t-BuOOH, $PhSiH_3$, i-PrOH, 23 °C	47	19
H_2, Crabtree's catalyst, CH_2Cl_2, 23 °C	11	65
H_2, PtO_2, CH_2Cl_2, 23 °C	76	24

Table 4.2: Diastereoselective hydrogenation

4.8 Final Synthesis

With the ketone **20** in hand, conversion of the ketone functionality to the alkene using excess Wittig reagent and base under reflux conditions delivered the alkene **4**. The need for huge excess of reagents was critical for the success of this step demonstrating the high steric hindrance present in the molecule.[41] The conversion of the ester moiety to the alkyne **3** for the key Pauson-Khand step was achieved in a 6-step sequence. Reduction of the ester **22** using DIBAL-H followed by DMP oxidation delivered the aldehyde **24** in 63%. Then using Horner-Wadsworth-Emmons reagent **25** the aldehyde was converted to the unsaturated nitrile **26** in 99% yield (1.7:1 ratio of double bond isomers) which was then reduced to the saturated nitrile **27** under single electron reduction conditions using Mg and MeOH in 72% yield.[42] Conversion of the nitrile **27** to the

aldehyde using DIBAL-H followed by reaction with Ohira-Bestmann reagent[43,44] **28** delivered the key Pauson-Khand precursor **3** (Scheme 4.8). With this compound in hand, performing the reaction with stoichiometric $Co_2(CO)_8$ in an atmosphere of CO in mesitylene solvent at 160 °C forged the fourth quaternary center and formed the carbon ring framework of the natural product. This molecule matched the intermediate **2** used by Lee[18] in his synthesis. Following his protocol, conjugate methyl addition using CuCN and MeLi (54% yield), followed by regioselective α-methylation using lithium hexamethylsilazane as the base delivered the ketone **30** in 81% yield. Then, using the same Wittig conditions used earlier in the synthesis, the natural product waihoensene **(1)** was achieved in 83% yield.



Scheme 4.8: Final Synthesis

This work was accomplished by the collaboration with my colleagues Mr. Cheng Peng and Mr. Zhiyao Zhou. Mr. Cheng Peng was responsible for the development of the later half of the synthesis. I was involved in the development of the early stages of the synthesis and for the development of the asymmetric version of the route.

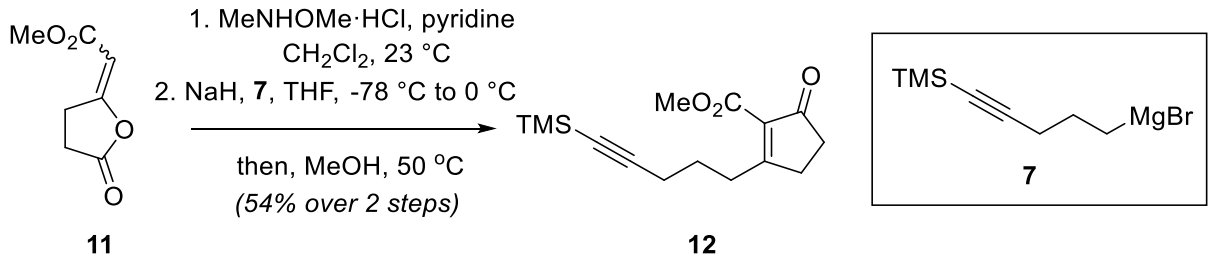
4.9 Conclusion

The natural product waihoensene was successfully synthesized in 17 steps with an overall yield of 0.8%. Key features include asymmetric conjugate addition of a methyl group to form the first quaternary center which guides the formation of the rest, Conia-ene reaction to forge the second ring and quaternary center and a Pauson-Khand reaction to construct the core ring structure of the molecule.

4.10 Experimental Procedures

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene and dichloromethane (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Anhydrous MeOH was purchased from Sigma-Aldrich and was used without further purification. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent, and an ethanolic solution of phosphomolybdic acid and cerium sulfate and a basic solution of potassium

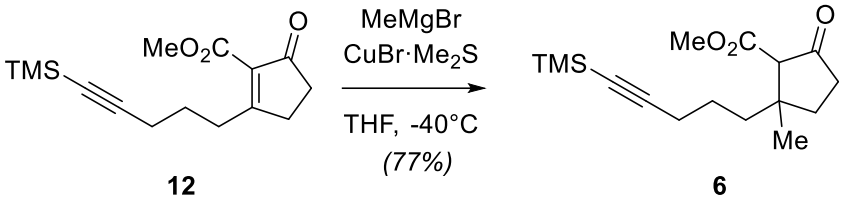
permanganate, and heat as developing agents. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker 500 MHz and 400 MHz instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet, app = apparent. IR spectra were recorded on a Perkin-Elmer 1000 series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on Agilent 6244 TOF-MS using ESI (Electrospray Ionization) at the University of Chicago Mass Spectroscopy Core Facility.



Tetra-substituted enone 12: A flame dried, 100 mL round bottom flask equipped with a magnetic stir bar at 23 °C was charged with the enol lactone **11** (6.91 g, 40.6 mmol, 1.0 equiv), CH_2Cl_2 (120 mL), pyridine (16.4 mL, 16.06 g, 203 mmol, 5.0 equiv) and *N*,*O*-dimethyl hydroxylamine hydrochloride (5.15 g, 52.8 mmol, 1.3 equiv), and the resultant solution was stirred at 23 °C for 6 h. Upon completion, the reaction contents were concentrated directly, redissolved in toluene (300 mL), filtered through a pad of Celite, and concentrated again. The resultant residue was dissolved in anhydrous THF (160 mL), the mixture was cooled to 0 °C, and NaH (60% dispersion in mineral oil, 2.11 g, 52.8 mmol, 1.3 equiv) was added in a single portion. The resultant contents were stirred for 30 min at 0 °C before being cooled down to –78 °C. In another flame dried, 250

mL 2-necked round bottom flask equipped with a magnetic stir bar and a condenser at 23 °C were added activated Mg turnings (1.98 g, 81.2 mmol, 2.0 equiv), THF (40 mL), and a crystal of I_2 under a positive argon flow. The second flask was then heated to 80 °C followed by addition of a partial amount (~5 mL) of a solution of (5-bromopent-1-ynyl)trimethylsilane (8.33 g, 40.6 mmol, 1.0 equiv) in anhydrous THF (40 mL, 1 M). After the color of I_2 dissipated, the remaining solution of (5-bromopent-1-ynyl)trimethylsilane in anhydrous THF was slowly added to the reaction mixture via syringe while maintaining the reaction contents at reflux. After stirring for 4 h, the so-formed Grignard reagent was cooled down and added to the previous reaction mixture at –78 °C. The temperature of the resultant mixture was warmed to 0 °C and stirring was continued for 1 h. Upon completion, the reaction contents were quenched by the careful addition of MeOH (60 mL), heated to 50 °C, and stirred for ~60 min with the reaction being monitored closely by TLC to avoid any deprotection of the TMS protecting group attached to the alkyne. Upon completion, the reaction contents were cooled down to 23 °C and 1 M HCl (150 mL) was added. The reaction contents were transferred to a separatory funnel. The mixture was extracted with CH_2Cl_2 (3 × 300 mL). The combined organic layers were washed with water, dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified via flash column chromatography (silica gel, hexanes/EtOAc, 1/1) to give tetra-substituted enone **12** (6.05 g, 54% yield) as a white solid. **12**: R_f = 0.45 (silica gel, hexanes/EtOAc, 1/1); IR (film) ν_{max} 2956, 2174, 1746, 1716, 1624, 1436, 1361, 1295, 1250, 1229, 1166, 1024, 843 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.83 (s, 3 H), 2.88–2.81 (m, 2 H), 2.72–2.65 (m, 2 H), 2.51–2.45 (m, 2 H), 2.31 (t, *J* = 7.0 Hz, 2 H), 1.85–1.72 (m, 2 H), 0.14 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.46, 187.46, 163.57, 132.67, 105.71, 86.82, 52.87, 35.90,

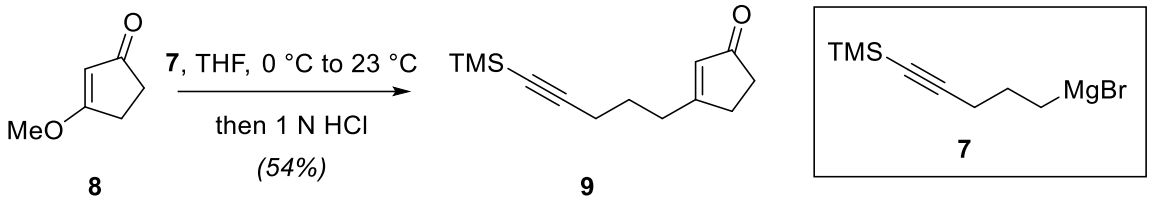
31.77, 30.48, 26.59, 19.94, 0.05; HRMS (ESI) calcd for $C_{15}H_{23}SiO_3^+$ [M + H^+] 279.1411, found 279.1415.



12 **6**

β-Keto-ester 12: A flame dried, 250 mL round bottom flask at 23 °C was charged with CuBr•Me_2S (3.55 g, 17.2 mmol, 1.2 equiv), a magnetic stir bar, and anhydrous THF (56 mL). The resultant solution was then cooled to –40 °C. MeMgBr (3.0 M in Et_2O, 11.5 mL, 34.5 mmol, 2.4 equiv) was added dropwise and the resultant solution was stirred at –40 °C for 30 min. The tetrasubstituted enone **12** (4.00 g, 14.4 mmol, 1.0 equiv) was then added dropwise as a solution in THF (56 mL) and the resultant solution was stirred at –40 °C for 2 h. Upon completion, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (50 mL) and warmed to 23 °C. The contents were then transferred to a separatory funnel and diluted with Et_2O (100 mL) and H_2O (100 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with saturated aqueous NH_4Cl solution (50 mL), H_2O and brine, dried ($MgSO_4$), filtered, and concentrated. Flash column chromatography (silica gel, hexanes/EtOAc, 9/1) of the resultant residue gave β-keto-ester **6** (3.26 g, 77% yield) as a colorless oil. **6**: R_f = 0.32 (silica gel, hexanes/EtOAc, 9/1); IR (film) ν_{max} 2956, 2361, 2338, 2174, 1757, 1751, 1734, 1718, 1700, 1684, 1653, 1636, 1616, 1576, 1559, 1540, 1507, 1457, 1249, 843, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) reported for a 4 : 2 : 1 ratio of two keto diastereomers and the enol

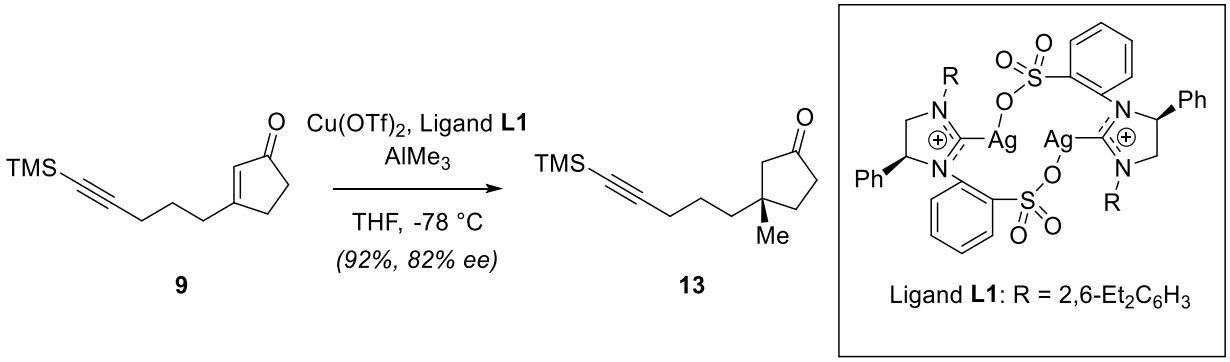
tautomer δ 10.82 (s, 1 H), 3.75 (s, 3 H), 3.71 (s, 3 H), 3.70 (s, 3 H), 2.98 (s, 1 H), 2.92 (s, 1 H), 2.56–2.29 (m, 2 H), 2.29–2.09 (m, 2 H), 1.98–1.27 (m, 6 H), 1.16 (s, 3 H), 1.11 (s, 3 H), 1.07 (s, 3 H), 0.14 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.05, 212.40, 176.74, 169.23, 168.97, 107.61, 106.85, 106.77, 85.07, 84.92, 84.36, 65.78, 64.81, 51.96, 51.92, 50.92, 44.3, 43.81, 43.70, 40.76, 39.68, 36.48, 36.19, 36.12, 33.86, 33.26, 33.23, 30.98, 27.28, 25.47, 24.52, 23.75, 23.61, 21.23, 20.44, 20.29, 0.22, 0.18, 0.17; HRMS (ESI) calcd for $C_{16}H_{27}SiO_3^+$ [M + H$^+$] 295.1724, found 295.1740.



8 9

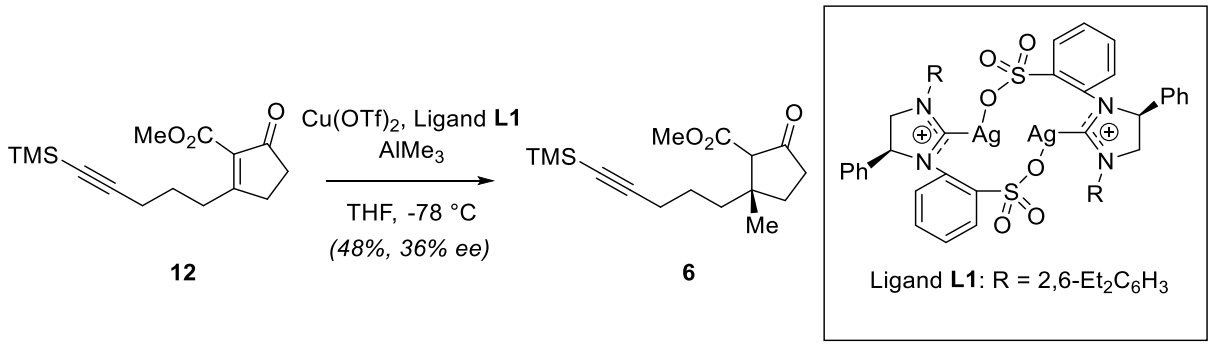
Enone 9: To a flame-dried, 500 mL 2-necked round bottom flask at 23 °C equipped with a magnetic stir bar and a condenser were added activated Mg turnings (2.10 g, 86.0 mmol, 2.0 equiv), anhydrous THF (43 mL), and a chip of I_2 under a positive argon flow. The reaction contents were then heated at 80 °C followed by addition of a partial amount (~5 mL) of a solution of (5-bromopent-1-ynyl)trimethylsilane (8.90 g, 43.0 mmol, 1.0 equiv) in anhydrous THF (43 mL, 1 M) via syringe. After the color of I_2 dissipated, the remaining solution of (5-bromopent-1-ynyl)trimethylsilane in anhydrous THF was added slowly via syringe while maintaining the reaction contents at 80 °C. After stirring for 4 h at 80 °C, the reaction contents were transferred to a solution of 3-methoxy-2-cyclopenten-1-one **8** (4.86 g, 43.0 mmol, 1.0 equiv) in anhydrous THF (86.0 mL, 0.5 M) at 0 °C via cannula over the course of ~30 min. Once the addition was complete, the mixture was gradually warmed to 23 °C and stirred at that temperature for 10 h.

Upon completion, the reaction contents were quenched by the slow addition of 1 M HCl (100 mL) and stirred for 30 min before being transferred to a separatory funnel. After separating the layers, the aqueous phase was extracted with EtOAc (3 × 100 mL) and the combined organic layers were washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated to give an orange oil. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 3/1) to give enone **9** (5.13 g, 54% yield) as a yellow oil. **9**: R_f = 0.50 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2958, 2361, 2340, 2174, 1710, 1675, 1617, 1249, 1183, 842, 760 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.00 (s, 1 H), 2.62 (dt, *J* = 4.7, 2.5 Hz, 2 H), 2.55 (t, *J* = 7.7 Hz, 2 H), 2.48–2.40 (m, 2 H), 2.33 (t, *J* = 6.9 Hz, 2 H), 1.84 (p, *J* = 7.8 Hz, 2 H), 0.18 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.93, 181.84, 129.78, 105.87, 85.73, 35.29, 32.35, 31.57, 25.99, 19.50, 0.11; HRMS (ESI) calcd for $C_{13}H_{21}SiO^+$ [M + H^+] 221.1356, found 221.1358.



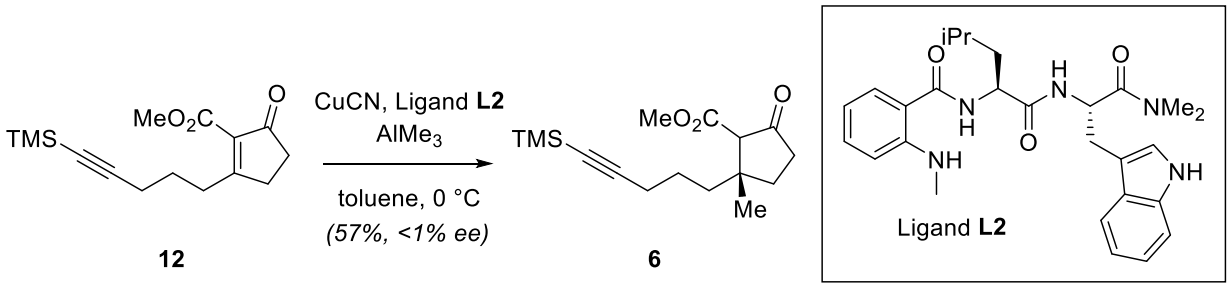
Ketone 13: To a flame-dried, 500 mL 3-necked round bottom flask at 23 °C in a glove box and equipped with a magnetic stir bar were added ligand **L1** (1.10 g, 1.01 mmol, 0.0375 equiv) and $Cu(OTf)_2$ (0.731 g, 2.02 mmol, 0.075 equiv). The reaction flask was then covered with aluminum foil, brought out of the glove box, and attached to a N_2-line via a vacuum bend. Fully degassed THF (216 mL, 3 cycles of the freeze-pump-thaw method) was then added via syringe. After stirring

the resulting turquois-blue solution at 23 °C for 10 min, the contents were cooled down to −78 °C and $AlMe_3$ (2.0 M in hexanes, 40.4 mL, 80.9 mmol, 3.0 equiv) was added dropwise via syringe over the course of 30 min. After the addition was complete, a solution of enone **9** (5.80 g, 27.0 mmol, 1.0 equiv) in fully degassed THF (54 mL) was added slowly via cannula. The resulting dark solution was stirred at –78 °C for 12 h in the absence of light. Upon completion, the reaction mixture was very slowly quenched at –78 °C by the addition of saturated aqueous Rochelle's salt (100 mL). The resulting frozen black mixture was diluted with Et_2O (100 mL) and stirred at 23 °C for 30 min until the organic layer had cleared with black precipitates forming on the bottom of the flask. The resulting biphasic mixture was filtered through a pad of Celite and the filtrate was then transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 200 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to afford a yellow oil. Purification of that residue by flash column chromatography (silica gel, hexanes/EtOAc, 9/1) gave ketone **13** (5.70 g, 92% yield, 82% *ee*) as a light yellow oil. The enantiomeric excess of the reaction was determined by analyzing the product obtained by TBAF deprotection followed by Sonogashira coupling with PhI (for details, see the HPLC section). Performing the reaction at smaller scales (~1 g of **9**) increased the *ee* up to 92% with an 81% yield. **13**: R_f = 0.30 (silica gel, hexanes/EtOAc, 9/1); $[\alpha]_D^{23}$ = –28.2° (*c* = 0.1, $CHCl_3$, 92% *ee*); IR (film) ν_{max} 2956, 2900, 2361, 2338, 2174, 1743, 1718, 1700, 1653, 1559, 1457, 1406, 1249, 1157, 843, 760, 639 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.32–2.26 (m, 2 H), 2.23 (t, *J* = 5.5 Hz, 2 H), 2.11–2.00 (m, 2 H), 1.86–1.72 (m, 2 H), 1.62–1.56 (m, 1 H), 1.55–1.46 (m, 3 H), 1.05 (s, 3 H), 0.14 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 219.72, 107.03, 84.85, 52.23, 40.87, 39.34, 36.73, 35.16, 24.96, 24.18, 20.42, 0.15; HRMS (ESI) calcd for $C_{14}H_{25}SiO^+$ [M + H^+] 237.1669, found 237.1677.



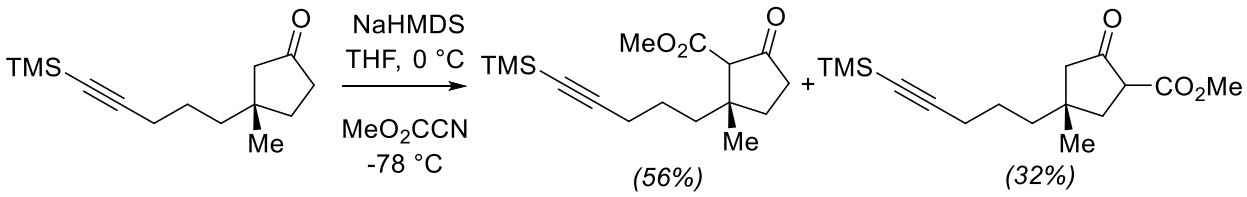
β-Keto-ester 6: To a flame-dried, 25 mL 2-necked round bottom flask at 23 °C in a glove box and equipped with a magnetic stir bar were added ligand **L1** (14.6 mg, 0.013 mmol, 0.0375 equiv) and $Cu(OTf)_2$ (9.7 mg, 0.027 mmol, 0.075 equiv). The reaction flask was then covered with aluminum foil, brought out from the glove box, and attached to a N_2-line via a vacuum bend. Fully degassed THF (2.90 mL, 3 cycles of the freeze-pump-thaw method) was then added via syringe. After stirring the resulting turquois-blue solution at 23 °C for 10 min, the contents were cooled down to −78 °C and $AlMe_3$ (2.0 M in hexanes, 0.9 mL, 1.80 mmol, 3.0 equiv) was added dropwise via a syringe. After the addition was complete, a solution of tetra-substituted enone **12** (0.100 g, 0.359 mmol, 1.0 equiv) in fully degassed THF (0.7 mL) was added slowly via a syringe. The resulting dark solution was stirred at –78 °C for 12 h in the absence of light. Upon completion, the reaction mixture was very slowly quenched at –78 °C by the addition of saturated aqueous Rochelle's salt (5 mL). The resulting frozen black mixture was diluted with Et_2O (5 mL) and stirred at 23 °C for 30 min until the organic layer had cleared with black precipitates forming on the bottom of the flask. The resulting biphasic mixture was filtered through a pad of Celite and the filtrate was then transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and

concentrated to afford a yellow oil. Purification of that residue by flash column chromatography (silica gel, hexanes/EtOAc, 9/1) gave β-keto-ester **6** (51.0 mg, 48% yield, 36% *ee*) as a colorless oil. The enantiomeric excess of the reaction was determined by analyzing the product obtained by Krapcho decarboxylation, TBAF deprotection, and Sonogashira coupling with PhI (for details, see the HPLC section).



β-Keto-ester 6: To a flame-dried, 25 mL 2-necked round bottom flask at 23 °C in a glove box and equipped with a magnetic stir bar were added CuCN (3.2 mg, 0.036 mmol, 0.1 equiv) and ligand **L2** (17.2 mg, 0.036 mmol, 0.1 equiv). The reaction flask was then brought out from the glove box and attached to a N_2-line. Fully degassed toluene (2.50 mL, 3 cycles of the freeze-pump-thaw method) was added via syringe and the reaction mixture was stirred at 23 °C for 3 h. The reaction contents were then cooled to 0 °C and $AlMe_3$ (2.0 M in hexanes, 0.54 mL, 1.08 mmol, 3.0 equiv) was added dropwise via syringe. After the addition was complete, a solution of tetra-substituted enone **12** (0.100 g, 0.359 mmol, 1.0 equiv) in fully degassed toluene (1.1 mL) was added slowly via syringe and the resultant reaction contents were stirred at 0 °C for 24 h. Upon completion, the reaction mixture was quenched very slowly at –78 °C by the addition of saturated aqueous Rochelle's salt (5 mL) and subsequently was diluted with EtOAc (5 mL). The contents were transferred to a separatory funnel and the layers were separated. The aqueous layer was

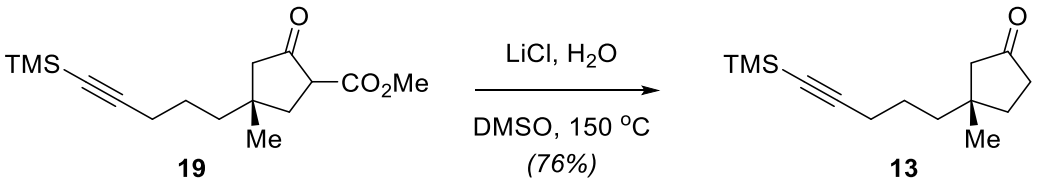
extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated to afford a dark yellow oil. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 9/1) gave β-keto-ester **6** (60.0 mg, 57% yield) as a colorless oil. [Note: using $ZnMe_2$ instead of $AlMe_3$ gave no desired product]. The enantiomeric excess of the reaction was determined by analyzing the product obtained by Krapcho decarboxylation, TBAF deprotection, and Sonogashira coupling with PhI (for details, see the HPLC section).



13 **6** **19**

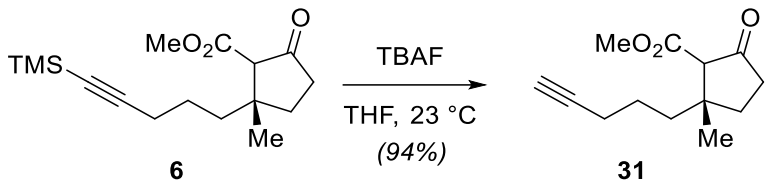
β-Keto-ester 6: To a flame dried, 500 mL round bottom flask equipped with a magnetic stir bar at 23 °C was added NaHMDS (1.0 M in THF, 55.1 mL, 55.1 mmol, 2.3 equiv) and anhydrous THF (90 mL). The solution was cooled down to 0 °C followed by the addition of ketone **13** (5.70 g, 24.1 mmol, 1.0 equiv) as a solution in anhydrous THF (10 mL). The mixture was stirred for 2 h before being cooled down to –78 °C. Mander's reagent (3.28 g, 3.06 mL, 38.5 mmol, 1.6 equiv) was then added and the resulting mixture was stirred at –78 °C for 3 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (100 mL) and diluted with EtOAc (100 mL). The reaction contents were then transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 100 mL). The combined

organic layers were dried ($MgSO_4$), filtered, and concentrated to afford a yellow oil. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 19/1) gave keto-ester **6** (3.95 g, 56% yield) as a colorless oil and the regioisomer **19** (2.30 g, 32% yield) as a colorless oil. **6**: R_f = 0.32 (silica gel, hexanes/EtOAc, 9/1); $[\alpha]_D^{23}$ = –23.0° (*c* = 0.1, $CHCl_3$, 92% *ee*); **19**: R_f = 0.28 (silica gel, hexanes/EtOAc, 9/1); $[\alpha]_D^{23}$ = –27.2° (*c* = 0.1, $CHCl_3$, 92% *ee*); IR (film) ν_{max} 2956, 2360, 2341, 2173, 1758, 1731, 1664, 1436, 1341, 1307, 1250, 1149, 1040, 843, 760, 638 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, reported for a 1.25 : 1 ratio of two keto diastereomers and a very small amount of enol tautomer) δ 3.74 (s, 3H), 3.42–3.30 (m, 1 H), 2.30–2.03 (m, 5 H), 1.66–1.32 (m, 5 H), 1.17 (s, 3 H), 1.08 (s, 3 H), 1.03 (s, 3 H), 0.15 (s, 9 H), 0.14 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.26, 211.17, 169.85, 169.80, 106.82, 106.64, 85.12, 84.96, 53.63, 53.52, 52.54, 52.53, 51.96, 51.84, 50.99, 45.71, 41.66, 40.47, 39.32, 39.28, 38.59, 37.63, 37.41, 37.39, 27.57, 25.90, 24.78, 24.14, 23.94, 20.42, 20.35, 20.26, 0.12, 0.09; HRMS (ESI) calcd for $C_{16}H_{27}SiO_3^+$ [M + H^+] 295.1724, found 295.1739.



Ketone 13: A 50 mL round bottom flask at 23 °C equipped with a magnetic stir bar was charged with β-keto-ester **19** (1.51 g, 5.13 mmol, 1.0 equiv), LiCl (0.435 g, 10.3 mmol, 2.0 equiv), H_2O (0.462 mL, 0.462 g, 25.6 mmol, 5.0 equiv) and DMSO (13 mL). The reaction contents were then heated to 150 °C and stirred at that temperature for 3 h. Upon completion, the reaction contents were cooled to 23 °C and then diluted by the addition of Et_2O (50 mL) and H_2O (25 mL). The

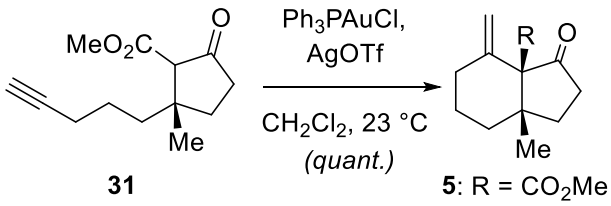
contents were then transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were then washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated to afford a yellow oil. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 9/1) gave ketone **13** (0.870 g, 76% yield) as a light yellow oil.



6 **31**

Alkyne 31: To a flame dried, 500 mL round bottom flask at 23 °C equipped with a magnetic stir bar was added a solution of β-keto-ester **6** (3.95 g, 13.4 mmol, 1.0 equiv) in anhydrous THF (150 mL). The resultant solution was then cooled to 0 °C and TBAF (1.0 M in THF, 22.0 mL, 22.0 mmol, 1.6 equiv) was then added slowly. The cooling bath was removed, and solution was allowed to warm with stirring at 23 °C for 2 h. Upon completion, the reaction contents were quenched with saturated aqueous NH_4Cl (50 mL) and diluted with Et_2O (50 mL). The reaction contents were then transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with water and brine, dried (MgSO4), filtered, and concentrated to afford a yellow oil. Purification of the residue by flash column chromatography (silica gel, hexanes/EtOAc, 8/1→ 4/1) gave alkyne **31** (2.80 g, 94% yield) as a colorless oil. **31**: R_f = 0.52 (silica gel, hexanes/Et_2O, 2/1); $[\alpha]_D^{23}$ = –21.4° (*c* = 0.1, $CHCl_3$, 92% *ee*); IR (film) ν_{max} 3289, 2953, 2874, 2360, 2342, 1756, 1727, 1653, 1615, 1436, 1408, 1348, 1279, 1221, 1160, 1110, 1033, 668, 633 cm^{-11}; ^1H NMR (500 MHz, $CDCl_3$, reported for a 1.45 : 1 :

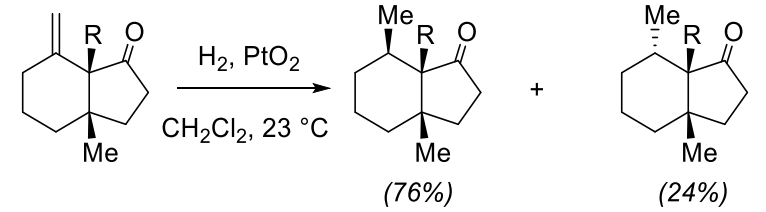
5 ratio of two keto diastereomers and the enol tautomer) δ 10.79 (s, 1 H), 3.74 (s, 3 H), 3.70 (s, 3 H), 3.69 (s, 3 H), 2.98 (s, 1 H), 2.91 (s, 1 H), 2.55–2.28 (m, 2 H), 2.23–2.09 (m, 2 H), 1.94 (dt, *J* = 11.2, 2.8 Hz, 1 H), 1.85–1.75 (m, 1 H), 1.68 (td, *J* = 12.8, 4.4 Hz, 1 H), 1.60–1.27 (m, 4 H), 1.15 (s, 3 H), 1.09 (s, 3 H), 1.06 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.25, 212.52, 176.80, 170. 80, 169.30, 169.09, 106.83, 84.74, 84.05, 83.96, 68.91, 68.79, 68.29, 65.73, 64.88, 52.08, 52.03, 50.98, 44.91, 43.89, 43.75, 40.83, 39.64, 36.66, 36.25, 36.17, 33.97, 33.49, 33.27, 31.04, 27.38, 25.52, 24.38, 23.68, 23.43, 21.27, 19.07, 19.06, 18.96; HRMS (ESI) calcd for $C_{13}H_{19}O_3^+$ [M + H^+] 223.1329, found 223.1322.



31 **5**: R = CO_2Me

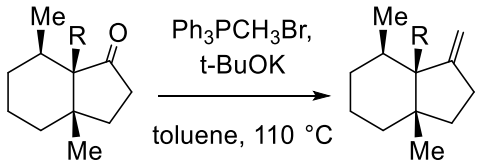
Alkene 5: To a flame dried, 250 mL round bottom flask at 23 °C equipped with a magnetic stir bar was added a solution of alkyne **31** (2.80 g, 12.6 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (100 mL) followed by Ph_3PAuCl (60.0 mg, 0.12 mmol, 0.96 mol %) and AgOTf (31.0 mg, 0.12 mmol, 0.96 mol %). The resultant cloudy mixture was stirred at 23 °C for 4 h. Upon completion, the reaction mixture was concentrated directly to a volume of ~20 mL and diluted with hexanes (~40 mL). The resultant mixture was loaded directly on a column for purification by flash column chromatography (silica gel, hexanes/Et_2O, 6/1→3/1) to afford alkene **5** (2.80 g, 100% yield) as a colorless oil. **5**: R_f = 0.49 (silica gel, hexanes/Et_2O, 2/1); $[\alpha]_D^{23}$ = +109.4° (*c* = 0.1, $CHCl_3$, 92% *ee*); IR (film) ν_{max} 3276, 3090, 2948, 2873, 2849, 1728, 1724, 1633, 1434, 1411, 1384, 1325, 1311,

1255, 1202, 1164, 1142, 1121, 1107, 1081, 1057, 1026, 994, 913, 799, 618, 582, 400 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.04 (s, 1 H), 4.74 (s, 1 H), 3.69 (d, *J* = 1.4 Hz, 3 H), 2.48 (tdd, *J* = 12.5, 5.8, 2.8 Hz, 1 H), 2.44–2.30 (m, 2 H), 2.25 (dt, *J* = 14.1, 4.3 Hz, 1 H), 2.05 (dt, *J* = 13.4, 9.1 Hz, 1 H), 1.74–1.57 (m, 3 H), 1.56–1.48 (m, 1 H), 1.40 (ddd, *J* = 12.8, 8.9, 3.7 Hz, 1 H), 1.06 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.94, 169.66, 141.03, 114.72, 69.40, 51.77, 44.72, 34.58, 33.51, 32.66, 29.80, 25.45, 21.69; HRMS (ESI) calcd for $C_{13}H_{19}O_3^+$ [M + H^+] 223.1329, found 223.1328.



Ketone 20: To a flame dried, 100 mL round bottom flask at 23 °C equipped with a magnetic stir bar was added a solution of alkene **5** (1.12 g, 5.0 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (50 mL) followed by PtO_2 (83% Pt, 53.0 mg, 0.23 mmol, 4.6 mol %). The resultant system was then degassed with H_2 using a balloon, and the resulting black suspension was stirred at 23 °C for 2 h. Upon completion, the reaction mixture was concentrated directly to a volume of ~10 mL and diluted with hexanes (~20 mL). The resultant mixture was loaded directly on a column for purification by flash column chromatography (silica gel, Et_2O/hexanes, 1/6→1/3) to afford ketone **20** (0.849 g, 76% yield) as a white crystalline solid along with the undesired diastereomer **21** (0.279 g, 24% yield) as a colorless oil. **20**: R_f = 0.48 (silica gel, hexanes/Et_2O, 2/1); $[\alpha]_D^{23}$ = +41.2 (*c* = 0.1, $CHCl_3$, 92% *ee*); IR (film) ν_{max} 2963, 2942, 2926, 2870, 1735, 1715, 1455, 1433, 1411, 1265, 1238, 1221, 1202, 1116, 1064, 1033, 1009, 972, 585 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.70

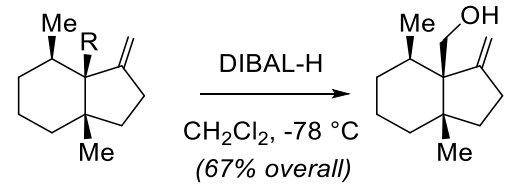
(s, 3H), 2.51–2.36 (m, 2 H), 2.24 (td, *J* = 12.0, 8.8 Hz, 1 H), 1.87–1.76 (m, 1 H), 1.72–1.62 (m, 2 H), 1.62–1.60 (m, 1 H), 1.55–1.44 (m, 3 H), 1.39 (ddd, *J* = 12.9, 8.6, 2.5 Hz, 1 H), 0.94 (d, *J* = 6.4 Hz, 3 H), 0.94 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.88, 170.33, 65.59, 51.06, 42.68, 34.91, 32.83, 31.78, 29.46, 28.48, 26.91, 20.74, 16.21; HRMS (ESI) calcd for $C_{13}H_{21}O_3^+$ [M + H$^+$] 225.1485, found 225.1485. **21**: R_f = 0.60 (silica gel, hexanes/Et_2O, 2/1); $[\alpha]_D^{23}$ = +79.8 (*c* = 0.1, $CHCl_3$, 92% *ee*); IR (film) ν_{max} 2934, 2862, 2361, 2338, 1750, 1731, 1559, 1540, 1457, 1261, 1237, 1076, 668 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.70 (s, 3H), 2.51 (ddd, *J* = 19.4, 10.1, 1.6 Hz, 1 H), 2.28 (dt, *J* = 19.1, 9.4 Hz, 1 H), 2.13 (dqd, *J* = 13.6, 6.9, 3.6 Hz, 1 H), 1.75 (dt, *J* = 13.0, 9.8 Hz, 1 H), 1.64–1.57 (m, 1 H), 1.52 (q, *J* = 3.1 Hz, 1 H), 1.47–1.37 (m, 2 H), 1.24 (dd, *J* = 13.7, 3.9 Hz, 1 H), 1.17 (d, *J* = 6.9 Hz, 3 H), 1.10 (s, 3 H), 1.07 (dd, *J* = 13.2, 9.6 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.73, 171.77, 66.28, 51.68, 43.63, 35.97, 35.95, 33.63, 32.42, 30.4, 22.47, 21.79, 17.22; HRMS (ESI) calcd for $C_{13}H_{21}O_3^+$ [M + H$^+$] 225.1485, found 225.1487.



20: R = CO_2Me **4**: R = CO_2Me

Alkene 4: To a flame dried, 500 mL round bottom flask at 23 °C in a glove box equipped with a magnetic stir bar was added KO*t*-Bu (6.80 g, 60.2 mmol, 9.0 equiv). The flask was then taken out of the glove box, charged with anhydrous toluene (100 mL) and heated to 110 °C until the solution became homogenous (typically in 10 minutes). Ph_3PCH_3Br (23.9 g, 66.9 mmol, 10 equiv) was then added in a single portion. The resulting bright yellow suspension was stirred at 110 °C for 1 h.

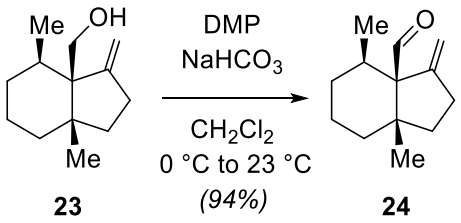
Finally, a solution of ketone **20** (1.50 g, 6.69 mmol, 1.0 equiv) in anhydrous toluene (20 mL) was added and stirring was continued for 12 h. Upon completion, the reaction contents were cooled to 23 °C and quenched by slow addition of saturated aqueous NH_4Cl (50 mL). The reaction contents were then transferred to a separatory funnel and the layers were separated. The aqueous layer was then extracted with Et_2O (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/Et_2O, 15/1→8/1) to give the desired product contaminated with Ph_3P, which was directly taken for the next step.



4: R = CO_2Me **23**

Alcohol 23: To a flame dried, 250 mL round bottom flask at 23 °C equipped with a magnetic stir bar was added the previously obtained mixture of alkene **4** and Ph_3P (6.69 mmol, 100% yield assumed) and anhydrous CH_2Cl_2 (100 mL). The reaction solution was then cooled to –78 °C and then DIBAL-H (1.0 M solution in CH_2Cl_2, 16.7 mL, 16.7 mmol, 2.5 equiv) was added. The resulting mixture was stirred at –78 °C for 1 h. Upon completion, the cold bath was removed, and the mixture was stirred at 23 °C for 5 min. The reaction mixture was quenched by slow addition of saturated aqueous Rochelle's salt (100 mL). The resultant slurry was stirred until clear (typically 1 h) and then transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$),

filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/Et_2O, 8/1→4/1) gave alcohol **23** (871 mg, 67% yield over two steps) as a white solid. **23**: R_f = 0.48 (silica gel, hexanes/EtOAc, 4/1); $[\alpha]_D^{23}$ = +11.2 (*c* = 0.1, $CHCl_3$, 92% *ee*); IR (film) ν_{max} 2932, 2361, 2337, 1685, 1653, 1643, 1559, 1457, 1372, 1070, 1044, 880 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.02 (t, *J* = 2.3 Hz, 1 H), 4.75 (t, *J* = 2.6 Hz, 1 H), 3.70 (dd, *J* = 11.3, 8.4 Hz, 1 H), 3.53–3.39 (m, 1 H), 2.55–2.35 (m, 2 H), 1.91–1.80 (m, 1 H), 1.66–1.48 (m, 3 H), 1.47–1.31 (m, 6 H), 1.04 (d, *J* = 7.2 Hz, 3 H), 1.02 (s, 3vH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.30, 106.83, 61.69, 54.13, 43.69, 36.26, 35.04, 30.17 (2 C, confirmed by DEPT 135, COSY and HSQC), 28.40, 23.73, 19.06, 15.91; HRMS (ESI) calcd for $C_{13}H_{23}O^+$ [M + H^+] 195.1743, found 195.1742.



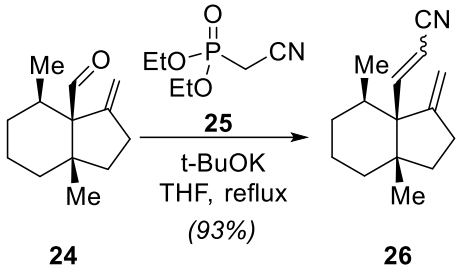
23 **24**

Aldehyde 24: To a 250 mL round bottom flask at 23 °C equipped with a magnetic stir bar was added alcohol **23** (0.871 g, 4.48 mmol, 1.0 equiv) and CH_2Cl_2 (100 mL) and then the contents were cooled down to 0 °C. Solid $NaHCO_3$ (5.00 g, 48.0 mmol, 10.7 equiv) and Dess–Martin periodinane (3.63 g, 8.60 mmol, 1.9 equiv) was then added sequentially in a single portion. The resulting white suspension was stirred at 0 °C for 5 min and then at 23 °C for 2 h. Upon completion, the reaction mixture was diluted with hexanes (50 mL) and directly loaded onto a column. Flash column chromatography (silica gel, hexanes/Et_2O, 10/1→6/1) gave aldehyde **24** (0.813 g, 94% yield) as a white solid. **24**: R_f = 0.58 (silica gel, hexanes/EtOAc, 4/1); $[\alpha]_D^{23}$ = –95.0 (*c* = 0.1, $CHCl_3$,

92% *ee*); IR (film) ν_{max} 3074, 2934, 2877, 2716, 2361, 2337, 1717, 1684, 1675, 1646, 1559, 1540, 1457, 1437, 1419, 1376, 1249, 1223, 1062, 890, 704, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.74 (d, *J* = 1.4 Hz, 1 H), 5.18 (t, *J* = 2.2 Hz, 1 H), 4.97 (t, *J* = 2.6 Hz, 1 H), 2.60–2.44 (m, 2 H), 2.09 (dt, *J* = 12.7, 9.9 Hz, 1 H), 1.72–1.65 (m, 1 H), 1.65–1.60 (m, 1 H), 1.60–1.53 (m, 2 H), 1.51 (q, *J* = 5.3, 4.8 Hz, 3 H), 1.19 (ddd, *J* = 12.4, 8.8, 3.1 Hz, 1 H), 0.95 (s, 3 H), 0.91 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.58, 152.38, 110.70, 64.14, 46.42, 33.93, 33.76, 32.76, 29.92, 28.59, 25.37, 21.03, 16.06; HRMS (ESI) calcd for $C_{13}H_{21}O^+$ [M + H^+] 193.1587, found 193.1589.

A one-pot procedure to convert alkene **4** into aldehyde **24** was also explored.[45] To a flame dried, 25 mL round bottom flask at 23 °C equipped with a magnetic stir bar under an argon atmosphere was added a solution of the mixture containing alkene **4** (obtained by Wittig reaction from 60.0 mg **20**, 0.285 mmol, 1.0 equiv) and Ph_3P in anhydrous CH_2Cl_2 (5 mL). The reaction contents were then cooled to –78 °C and DIBAL-H (1.0 M solution in CH_2Cl_2, 0.570 mL, 0.570 mmol, 2.0 equiv relative to assumed amount of **4**) was added. The reaction contents were then stirred at –78 °C for 1 h. Upon completion, the reaction contents were quenched at –78 °C by the slow addition of *t*-BuOH (1.27 g, 17.1 mmol, 30 equiv) and then warmed to 23 °C and stirred at that temperature for 1 h. Then, solid $NaHCO_3$ (0.300 g, 2.85 mmol, 10 equiv) was added followed by Dess–Martin periodinane (0.970 g, 2.28 mmol, 8.0 equiv). The mixture was then stirred at 23 °C for 1 h. Upon completion, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous $Na_2S_2O_3$ (10 mL). The reaction contents were transferred to a separatory funnel and diluted with Et_2O (15 mL) and H_2O (15 mL). The layers were separated, and the aqueous layer was then extracted with Et_2O (3 × 15 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. The resultant

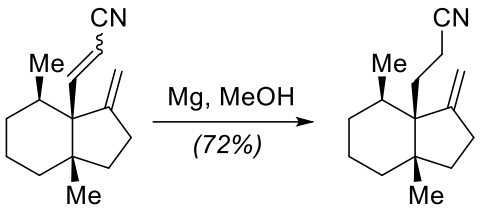
residue was purified by flash column chromatography (silica gel, hexanes/Et_2O, 10/1→6/1) to afford aldehyde **24** (30.1 mg, 55% yield overall) as a white solid.



24 **26**

Unsaturated nitrile 26: To a flame dried, 100 mL round bottom flask at 23 °C inside a glove box and equipped with a magnetic stir bar was added *t*-BuOK (2.36 g, 21.0 mmol, 5.0 equiv). The reaction flask was then taken out of the glove box, charged with anhydrous THF (80 mL) and stirred until the solution became homogenous. Diethyl cyanomethylphosphonate **25** (3.80 mL, 3.45 g, 19.5 mmol, 4.6 equiv) was then added slowly, and the resulting pale yellow solution was stirred at 23 °C for 1 h. Finally, a solution of aldehyde **24** (0.813 g, 4.21 mmol, 1.0 equiv) in anhydrous THF (20 mL) was added and the resulting solution was heated to 65 °C and stirring was continued for 18 h. Upon completion, the reaction contents were cooled to 23 °C and quenched by slow addition of saturated aqueous NH_4Cl (50 mL). The reaction contents were then transferred to a separatory funnel and the layers were separated. The aqueous layer was then extracted with Et_2O (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/Et_2O, 10/1→6/1) to afford **26** (0.844 g, 93% yield, mixture of both diastereomers) as a colorless oil. **26**: R_f = 0.66 and 0.54 (silica gel, hexanes/Et_2O, 4/1); ^1H NMR (500 MHz, $CDCl_3$,

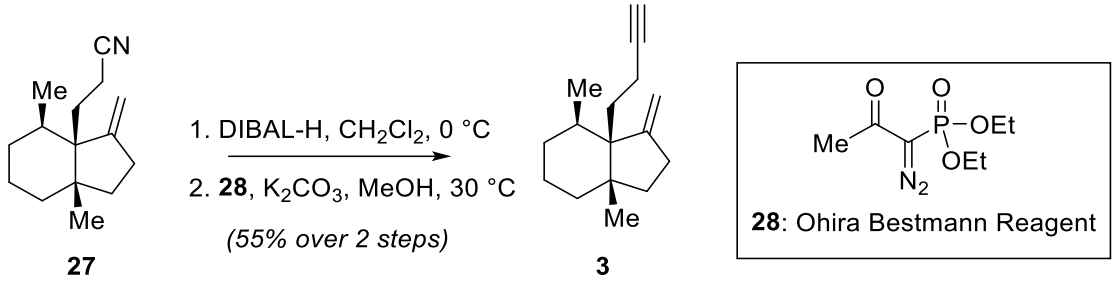
diagnostic peaks of crude material as a 1.7 : 1 mixture of *cis* : *trans* disposed diastereomers) *cis*: δ 6.34 (d, *J* = 12.9 Hz, 1 H); *trans*: δ 6.78 (d, *J* = 17.0 Hz, 1 H).



26 **27**

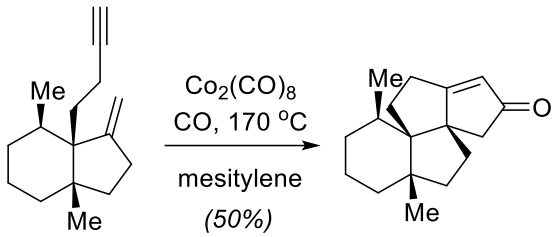
Nitrile 27: To a flame dried, 500 mL round bottom flask at 23 °C equipped with a magnetic stir bar was added unsaturated nitrile **26** (0.820 g, 3.80 mmol, 1.0 equiv) and anhydrous MeOH (240 mL). The mixture was then cooled down to 0 °C and Mg turnings (activated with HCl washings, 2.90 g, 119 mmol, 31.4 equiv) were added. Stirring was continued at 0 °C for 15 min, at which point the cooling bath was removed and stirring was continued for another 3 h at 23 °C, during which time the Mg turnings disappeared and a cloudy precipitate was formed. [CAUTION: The reaction was exothermic and required close monitoring.] Upon completion, the reaction mixture was cooled to 0 °C and quenched by slow addition of a 6 M aqueous solution of HCl (50 mL). The reaction mixture was diluted with Et_2O (100 mL) and H_2O (200 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/Et_2O, 8/1→6/1) afforded nitrile **27** (0.602 g, 72% yield) as a crystalline solid. **27**: R_f = 0.54 (silica gel, hexanes/Et_2OAc, 4/1); $[\alpha]_D^{23}$ = –12.6 (*c* = 0.1, $CHCl_3$, 92% *ee*); IR (film) ν_{max} 2913, 2361, 2338, 2246,

1734, 1717, 1700, 1684, 1653, 1645, 1576, 1559, 1540, 1473, 1457, 1447, 886, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.02 (s, 1 H), 4.66 (s, 1 H), 2.47–2.34 (m, 2 H), 2.33–2.23 (m, 1 H), 2.15 (ddd, *J* = 16.9, 12.3, 4.8 Hz, 1 H), 1.95 (tdd, *J* = 12.0, 5.0, 2.5 Hz, 1 H), 1.82 (tq, *J* = 7.5, 3.9 Hz, 1 H), 1.65 (tt, *J* = 12.5, 4.2 Hz, 1 H), 1.56–1.45 (m, 3 H), 1.36–1.30 (m, 3 H), 1.27–1.20 (m, 2 H), 1.06 (s, 3 H), 1.05–1.01 (m, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.70, 120.93, 107.47, 51.62, 44.31, 36.60, 35.87, 29.01, 28.64, 27.87, 26.75, 22.24, 17.64, 15.50, 11.82; HRMS (ESI) calcd for $C_{15}H_{24}N^+$ [M + H^+] 218.1903, found 218.1904.



Alkyne 3: To a flame dried, 250 mL round bottom flask at 23 °C equipped with a magnetic stir bar was added nitrile **27** (0.602 g, 2.76 mmol, 1.0 equiv) and anhydrous CH_2Cl_2 (50 mL). After cooling the resultant solution to 0 °C, DIBAL-H (1.0 M in CH_2Cl_2, 5.00 mL, 5.00 mmol, 1.8 equiv) was added and stirring was continued for 1 h at 0 °C. Upon completion, the mixture was quenched by the dropwise addition of saturated aqueous Rochelle's salt (50 mL). The slurry was stirred at 23 °C until clear (typically 1 h) before being transferred to a separatory funnel. The layers were then separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resulting crude product was dissolved in Et_2O (20 mL) and filtered through a short column of silica gel. The resultant crude product was directly used in the next step without further purification.

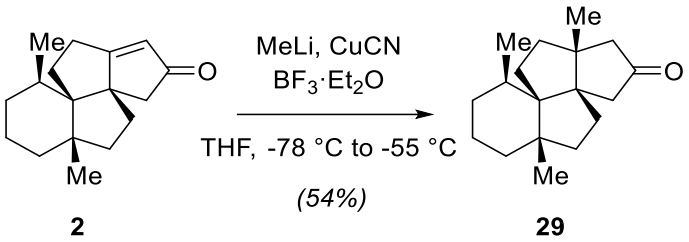
Next, to a 250 mL round bottom flask at 23 °C equipped with a magnetic stir bar, crude aldehyde (2.76 mmol, 100% yield assumed) and anhydrous MeOH (35 mL) were added under argon atmosphere. K_2CO_3 (0.95 g, 6.87 mmol, 2.5 equiv) and diethyl 1-diazo-2-oxopropylphosphonate **28** (0.80 g, 4.16 mmol, 1.5 equiv) were then added sequentially at 23 °C. The resulting yellow solution was then warmed to 30 °C and stirred at that temperature for 12 h. Upon completion, the reaction contents were quenched by the dropwise addition of saturated aqueous $NaHCO_3$ (30 mL). The mixture was then diluted with Et_2O (30 mL) and H_2O (30 mL) and the contents were transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/Et_2O, 1/0→30/1→10/1) afforded alkyne **3** (0.347 g, 58% yield) as a light yellow oil. **3**: R_f = 0.50 (silica gel, hexanes); $[\alpha]_D^{23}$ = –12.4 (*c* = 0.1, $CDCl_3$, 92% *ee*); IR (film) ν_{max} 3311, 3071, 2937, 2361, 2337, 2118, 1646, 1559, 1540, 1458, 1448, 1385, 1374, 884, 668, 625 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.96 (t, *J* = 2.2 Hz, 1 H), 4.64 (t, *J* = 2.5 Hz, 1 H), 2.37 (ddt, *J* = 9.9, 5.0, 2.4 Hz, 2 H), 2.20–2.00 (m, 2 H), 1.93 (t, *J* = 2.6 Hz, 1 H), 1.87–1.77 (m, 2 H), 1.66 (tt, *J* = 12.6, 4.1 Hz, 1 H), 1.58–1.49 (m, 2 H), 1.45–1.37 (m, 1 H), 1.38–1.27 (m, 3 H), 1.21 (dtd, *J* = 12.9, 9.1, 8.1, 4.0 Hz, 2 H), 1.05 (s, 3 H), 1.03 (d, *J* = 7.3 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.62, 106.65, 85.83, 67.61, 51.79, 44.28, 36.71, 35.89, 30.08, 29.31, 29.12, 28.06, 22.48, 17.99, 15.61, 13.04; HRMS (ESI) calcd for $C_{16}H_{25}^+$ [M + H^+] 217.1951, found 217.1954.



3 **2**

Tetracyclic enone 2: To a flame dried, 100 mL round bottom flask at 23 °C equipped with a magnetic stir bar was added alkyne **3** (0.203 g, 0.94 mmol, 1.0 equiv). Fully degassed mesitylene (20 mL, 3 cycles of the freeze-pump-thaw method) was then added under an argon atmosphere. $Co_2(CO)_8$ (0.370 g, 1.07 mmol, 1.1 equiv, weighed out in a glove box and placed in a plastic micro centrifuge tube) was added to the reaction flask in a single portion at 23 °C. The resulting dark brown solution turned wine red after stirring for 2 h, at which point TLC analysis indicated full consumption of the starting material and the formation of a red complex. The reaction system was then degassed with CO and heated to 160 °C using a pre-heated oil bath. The solution was stirred at this temperature for an additional 24 h during which time a cobalt mirror formed along the walls. Upon completion, the reaction mixture was directly loaded onto a column (silica gel) and eluted with hexanes to remove mesitylene. Subsequent flash column chromatography (silica gel, EtOAc/hexanes, 1/6→4/1) yielded tetracyclic enone **2** (0.115 g, 50% yield) as a brown oil. **2**: R_f = 0.34 (silica gel, hexanes/Et_2O, 3/1); $[\alpha]_D^{23}$ = –15.6 (*c* = 0.1, $CHCl_3$, 92% *ee*); IR (film) ν_{max} 2942, 2868, 1712, 1636, 1463, 1412, 1386, 1196, 1168, 833 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 5.55 (t, *J* = 1.6 Hz, 1 H), 2.50 (d, *J* = 16.7 Hz, 1 H), 2.14 (d, *J* = 16.8 Hz, 1 H), 2.00–1.89 (m, 2 H), 1.68 (ddd, *J* = 13.9, 9.2, 4.7 Hz, 1H), 1.52–1.43 (m, 1 H), 1.35 (ddd, *J* = 13.4, 8.7, 4.3 Hz, 2 H), 1.26–1.14 (m, 4 H), 1.13–1.06 (m, 2 H), 1.06–0.99 (m, 3 H), 0.88 (s, 3 H), 0.70 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (126 MHz, C_6D_6) δ 208.72, 191.91, 120.54, 64.17, 56.55, 50.73, 45.04, 41.49, 38.72, 37.64, 33.41,

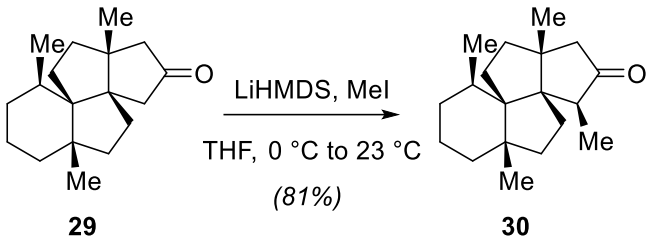
32.81, 30.38, 27.58, 24.59, 17.55, 17.08; HRMS (ESI) calcd for $C_{17}H_{25}O^+$ [M + H^+] 245.1900, found 245.1904.



2 **29**

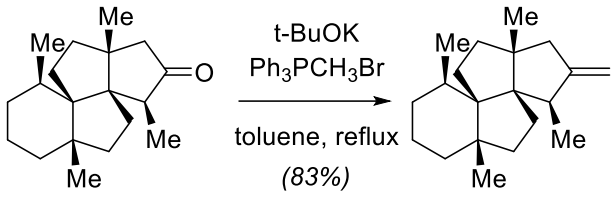
Ketone 29: 29 was synthesized via a slightly modified procedure used by the Lee group.[18] To a flame dried, 25 mL round bottom flask at 23 °C under an argon atmosphere and equipped with a magnetic stir bar was added CuCN (0.104 g, 1.16 mmol, 3.0 equiv) followed by anhydrous THF (5 mL). The solution was cooled to –78 °C and MeLi (1.6 M solution in Et_2O, 1.45 mL, 2.32 mmol, 6.0 equiv) was added. The cooling bath was removed and the reaction mixture was warmed to 23 °C and stirred for 10 min. The resultant colorless solution was then cooled to –78 °C and BF_3•Et_2O (100 µL, 132 mg, 0.93 mmol, 2.4 equiv) was added. A solution of tetracyclic enone **2** (94.7 mg, 0.387 mmol, 1.0 equiv) was then added slowly and the reaction system was moved to a –55 °C cooling bath and stirred for 2 h. The reaction contents were quenched by dropwise addition of a saturated aqueous solution of NH_4Cl (5 mL). The reaction contents were then transferred to a separatory funnel and diluted with H_2O (10 mL) and Et_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, Et_2O/hexanes, 1/8→1/6) yielded ketone **29** (54.8 mg, 54% yield) as a

white crystalline solid. **29**: R_f = 0.53 (silica gel, hexanes/Et_2O, 3/1); $[\alpha]_D^{23}$ = +80.2 (*c* = 0.1, $CHCl_3$, 82% *ee*); ^1H NMR and ^{13}C NMR spectra match those reported by the Lee group.[18]



29 **30**

Ketone 30: 30 was synthesized using a slightly modified procedure from the Lee group.[18] To a flame dried, 25 mL round bottom flask at 23 °C inside a glove box and equipped with a magnetic stir bar was added solid LiHMDS (70.4 mg, 0.420 mmol, 2.0 equiv). The flask was then taken out of the glove box and anhydrous THF (2 mL) was added. The reaction contents were then cooled to 0 °C and a solution of ketone **29** (54.8 mg, 0.210 mmol, 1.0 equiv) in anhydrous THF (2 mL) was added slowly. Stirring was continued at 0 °C for 2 h before MeI (65.0 µL, 0.149 g, 1.05 mmol, 5.0 equiv) was added. The reaction contents were then warmed to 23 °C and stirred at that temperature for another 12 h. Upon completion, the reaction was quenched by slow addition of saturated aqueous NH_4Cl (5 mL). The contents were transferred to a separatory funnel and diluted with Et_2O (10 mL) and H_2O (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification of the resulting residue by flash column chromatography (silica gel, Et_2O/hexanes, 1/10→1/6) yielded ketone **30** (46.5 mg, 81% yield) as a yellow oil. **30**: R_f = 0.59 (silica gel, hexanes/Et_2O, 3/1); $[\alpha]_D^{23}$ = +22.8 (*c* = 0.1, $CHCl_3$, 82% *ee*); ^1H NMR and ^{13}C NMR spectra match those reported by the Lee group.[18]



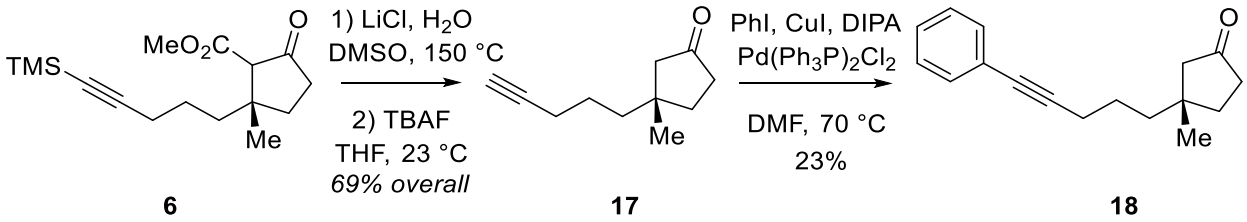
30 waihoensene **(1)**

Waihoensene (1): To a flame dried, 10 mL round bottom flask at 23 °C inside a glove box and equipped with a magnetic stir bar was added KO*t*-Bu (0.172 g, 1.53 mmol, 9.0 equiv). The flask was then taken out of the glove box, charged with anhydrous toluene (3 mL), and heated at 110 °C until the solution became homogenous (typically in 5 minutes). Ph_3PCH_3Br (0.607 g, 1.70 mmol, 10 equiv) was then added in a single portion. The resulting bright yellow suspension was stirred at 110 °C for 1 h. Finally, a solution of ketone **30** (46.5 mg, 0.170 mmol, 1.0 equiv) in anhydrous toluene (2 mL) was added and stirring was continued at 110 °C for another 1 h. Upon completion, the reaction contents were cooled to 23 °C and quenched by slow addition of saturated aqueous NH_4Cl (5 mL). The reaction contents were then transferred to a separatory funnel and diluted with Et_2O (10 mL) and H_2O (10 mL). The layers were separated, and the aqueous layer was then extracted with Et_2O (3 $\times$ 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by flash chromatography (silica gel, pentane) to give waihoensene (**1**, 38.4 mg, 83% yield) as a colorless oil. An analytical sample was prepared by reverse phase preparative TLC (Partisil® KC18, Whatman®, methanol, 91% recovery). **1**: R_f = 0.59 (silica gel, pentane); $[\alpha]_D^{23}$ = +40.6 (*c* = 0.1, $CHCl_3$, 82% *ee*); lit: $[\alpha]_D^{22}$ = +43.9 (*c* = 0.09, $CHCl_3$);[6] IR (film) ν_{max} 3068, 2931, 2867, 2361, 2338, 1734, 1717, 1700, 1684, 1653, 1559, 1540, 1521, 1507, 1472, 1457, 1375, 876, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.68 (q, *J* = 1.9 Hz, 2 H), 2.71 (q, *J* = 7.4 Hz, 1 H), 2.22 (q, *J* = 2.1 Hz, 2 H), 1.78 (pd, *J* = 7.0, 3.6 Hz, 1 H),

1.64 (td, *J* = 13.7, 6.6 Hz, 1 H), 1.59–1.56 (m, 1 H), 1.56–1.54 (m, 1 H), 1.53–1.46 (m, 2 H), 1.46–1.42 (m, 1 H), 1.42–1.40 (m, 1 H), 1.40–1.36 (m, 1 H), 1.36–1.28 (m, 2 H), 1.28–1.25 (m, 1 H), 1.25–1.22 (m, 1 H), 1.18–1.14 (m, 1 H), 1.14–1.10 (m, 1 H), 1.04 (d, *J* = 7.3 Hz, 3 H), 1.02 (s, 3 H), 1.01 (s, 3 H), 0.91 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.64, 102.87, 68.18, 60.33, 52.45, 47.98, 44.62, 43.80, 41.95, 40.85, 35.88, 31.79, 30.41, 30.19, 28.65, 25.31, 24.95, 19.81, 19.14, 17.50; HRMS (ESI) calcd for $C_{20}H_{33}^+$ [M + H^+] 273.2577, found 273.2575.

4.11 HPLC Analysis

4.11.1 Preparation of compound 18 for HPLC analysis



6 **17** **18**

Ketone 18. To a 10 mL round bottom flask equipped with a magnetic stir bar was added β-keto-ester **6** (60.0 mg, 0.203 mmol, 1.0 equiv), DMSO (0.5 mL), LiCl (18.0 mg, 0.406 mmol, 2.0 equiv) and H_2O (20.0 mg, 20.0 µL, 1.015 mmol, 5.0 equiv) at 23 °C. The resultant mixture was then heated to 150 °C and stirred for 3 h. Upon completion, the reaction was cooled to 23 °C and diluted by the addition of Et_2O (3 mL) and H_2O (3 mL). The contents were transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated to afford crude ketone **13** as a yellow oil (36.0 mg) which was directly used for the next step.

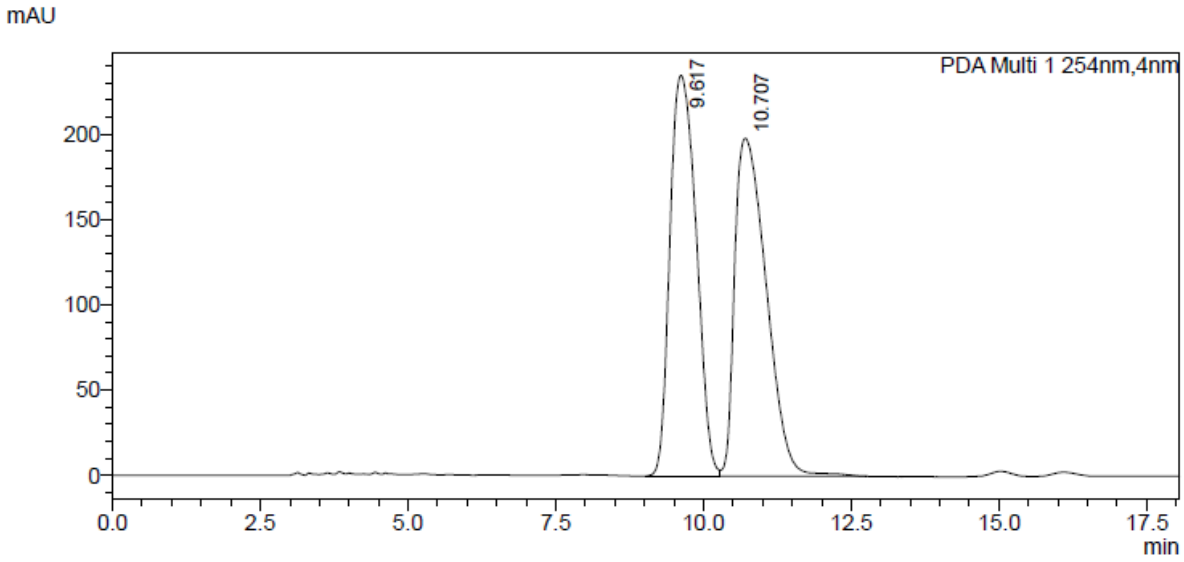
Next, to a flame dried, 10 mL round bottom flask equipped with a magnetic stir bar was added ketone **13** (36.0 mg, 0.154 mmol, 1.0 equiv) and anhydrous THF (0.75 mL) at 23 °C. TBAF (1.0 M in THF, 190 µL, 0.190 mmol, 1.2 equiv) was then added slowly and the solution was allowed to stir at 23 °C for 2 h. Upon completion, the reaction contents were quenched with H_2O (3 mL) and diluted with EtOAc (3 mL). The reaction contents were transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated to afford a yellow oil. Purification of the residue by flash column chromatography (silica gel, hexanes/EtOAc, 9/1) gave alkyne **17** (23.0 mg, 69% overall yield) as a colorless oil. **17**: R_f = 0.28 (silica gel, hexanes/EtOAc, 9/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.32–2.26 (m, 2 H), 2.20 (ddt, *J* = 6.7, 4.0, 1.9 Hz, 2 H), 2.11–2.00 (m, 2 H), 1.96 (t, *J* = 2.6 Hz, 1 H), 1.85–1.73 (m, 2 H), 1.65–1.45 (m, 4 H), 1.05 (s, 3 H).

Finally, to a flame dried, 10 mL round bottom flask at 23 °C and equipped with a magnetic stir bar was added $Pd(Ph_3P)_2Cl_2$ (6.6 mg, 9.12 mmol, 0.1 equiv), CuI (1.8 mg, 9.12 mmol, 0.1 eq), *i*-Pr_2NH (37.0 mg, 51.6 µL, 365.3 mmol, 4 equiv) and a solution of alkyne **17** (15.0 mg, 91.3 mmol, 1.0 equiv) in DMF (0.7 mL). The resultant mixture was then heated to 70 °C and stirred for 4 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl solution (5 mL) and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with NH_4Cl (5 mL), H_2O (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. Purification of the resultant residue by preparative TLC (silica gel, hexanes/EtOAc, 9/1, 2 runs) gave alkyne **18** (5.1 mg, 23% yield) as a colorless oil. **18**: R_f = 0.20 (silica gel, hexanes/EtOAc, 9/1); ^{1}H NMR (500

MHz, $CDCl_3$) δ 7.43–7.39 (m, 2 H), 7.34–7.29 (m, 3 H), 2.48–2.42 (m, 2 H), 2.36–2.30 (m, 2 H), 2.17–2.05 (m, 2 H), 1.91–1.78 (m, 2 H), 1.74–1.56 (m, 4 H), 1.11 (s, 3 H).

4.11.2 HPLC Traces of 18 (ChiralPak AD-H column, 99:1 hexanes/i-PrOH, 1mL/min, 254 nm)

Racemate:



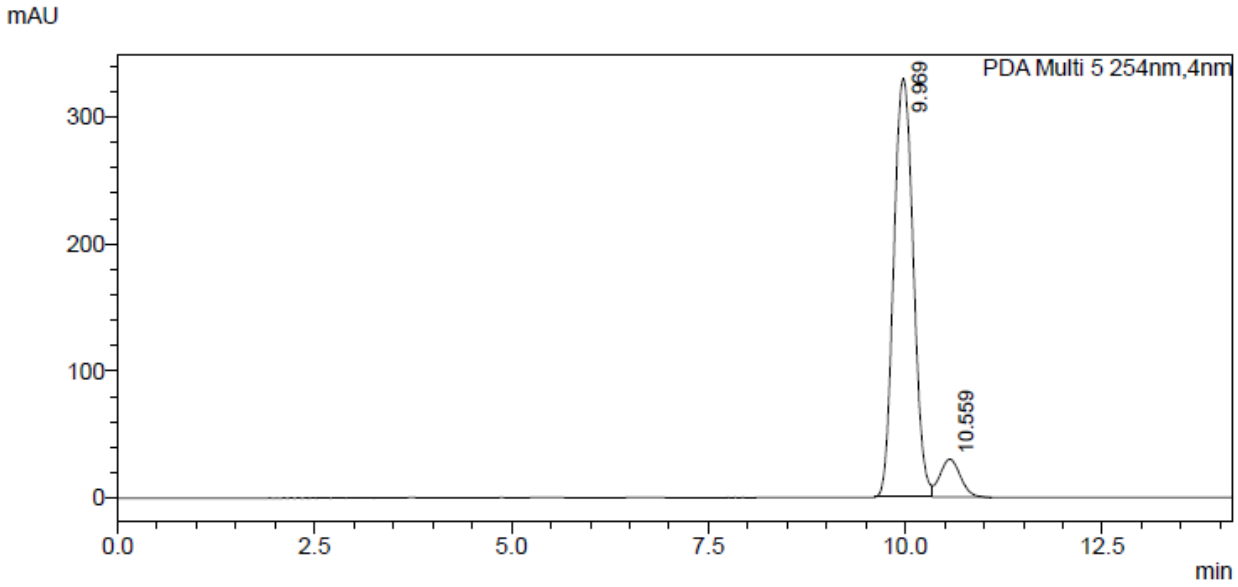
<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%	Height%
1	9.617	7269275	234895	49.632	54.251
2	10.707	7376963	198082	50.368	45.749
Total		14646238	432977	100.000	100.000

Figure 4.1: HPLC traces of racemate

82% ee



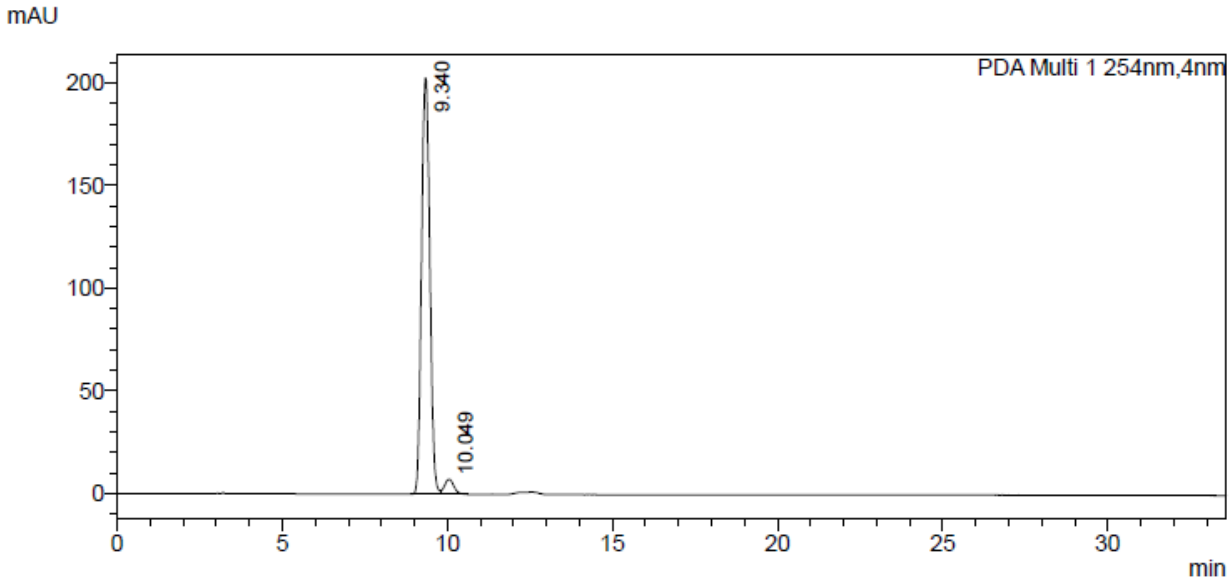
<Peak Table>

PDA Ch5 254nm

Peak#	Ret. Time	Area	Height	Unit	Area%	Height%
1	9.969	5702433	329405		91.388	91.698
2	10.559	537369	29824		8.612	8.302
Total		6239801	359229		100.000	100.000

Figure 4.2: HPLC traces of 82% ee

92% ee



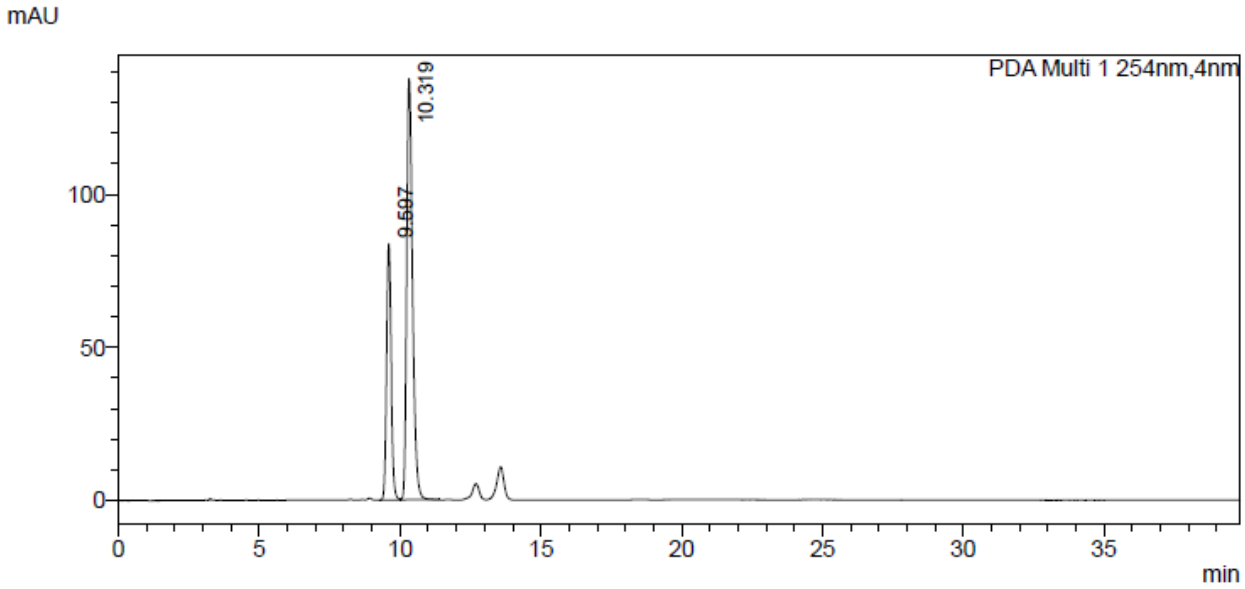
<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%	Height%
1	9.340	3540995	202876	96.102	96.533
2	10.049	143620	7287	3.898	3.467
Total		3684615	210163	100.000	100.000

Figure 4.3: HPLC traces of 92% ee

36% *ee*



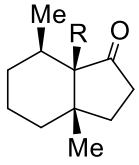
<Peak Table>

PDA Ch1 254nm

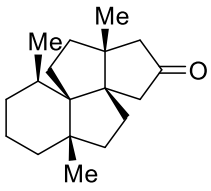
Peak#	Ret. Time	Area	Height	Area%	Height%
1	9.597	946105	83640	32.197	37.825
2	10.319	1992389	137485	67.803	62.175
Total		2938495	221125	100.000	100.000

Figure 4.4: HPLC traces of 36% ee

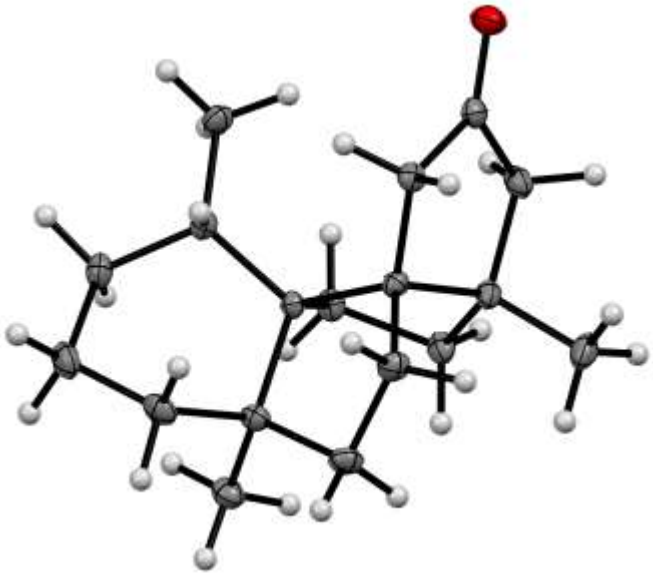
4.12 ORTEP structures of (±)-20 and (±)-29



20: R = CO_2Me



29



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4.14 NMR's of selected intermediates

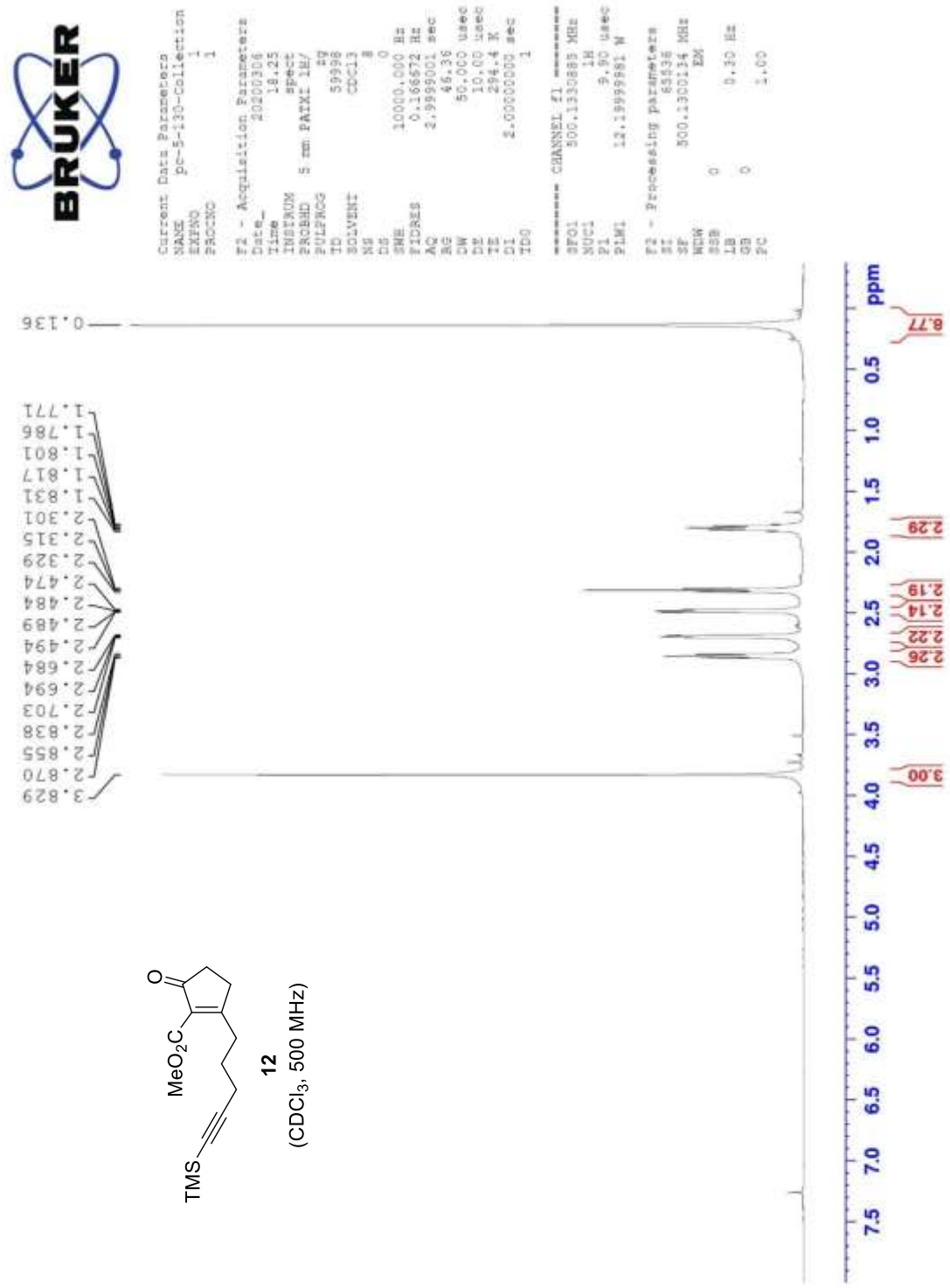


Figure 4.5: ^{1}H NMR of intermediate **12**

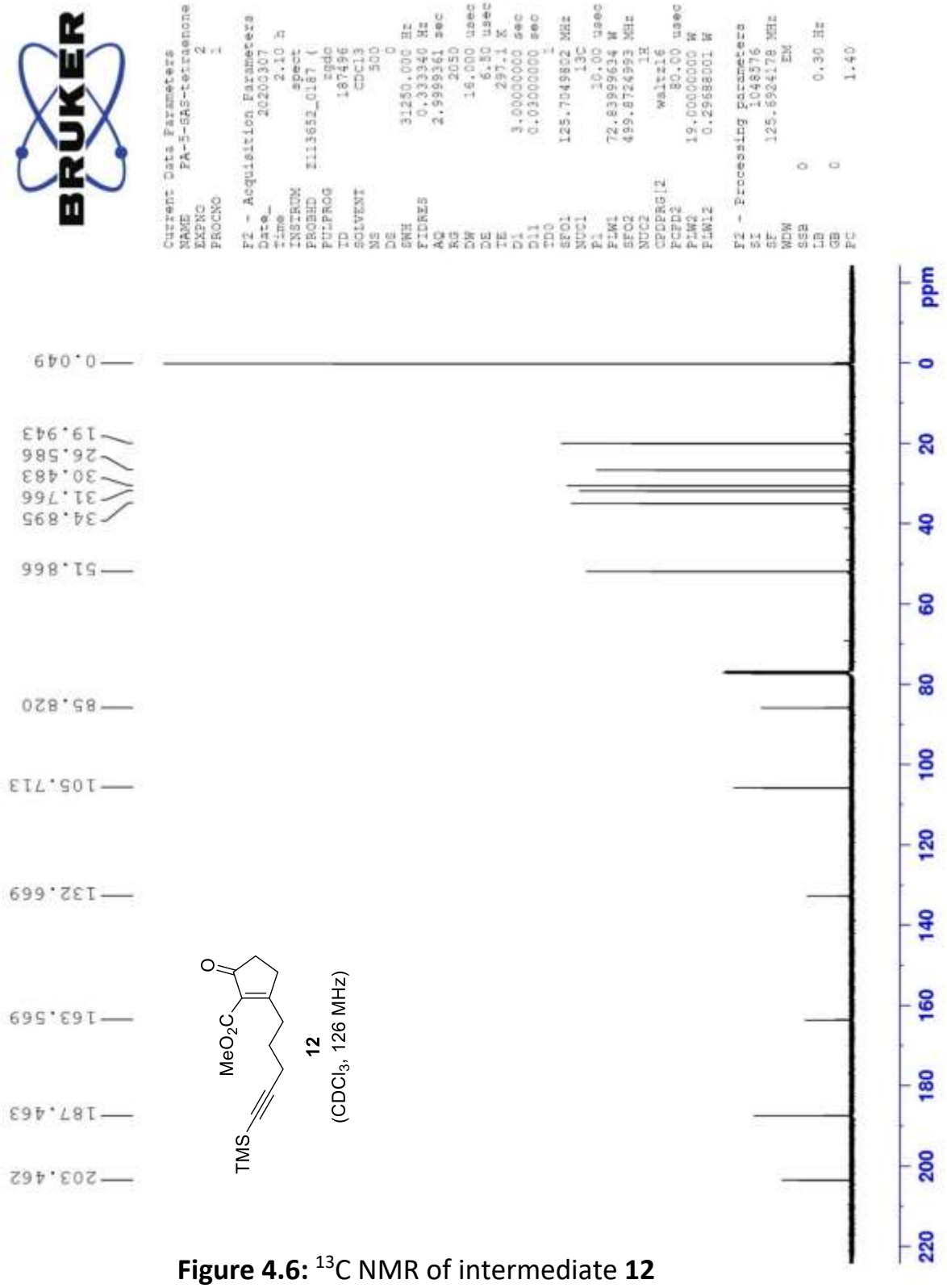


Figure 4.6: ^{13}C NMR of intermediate **12**

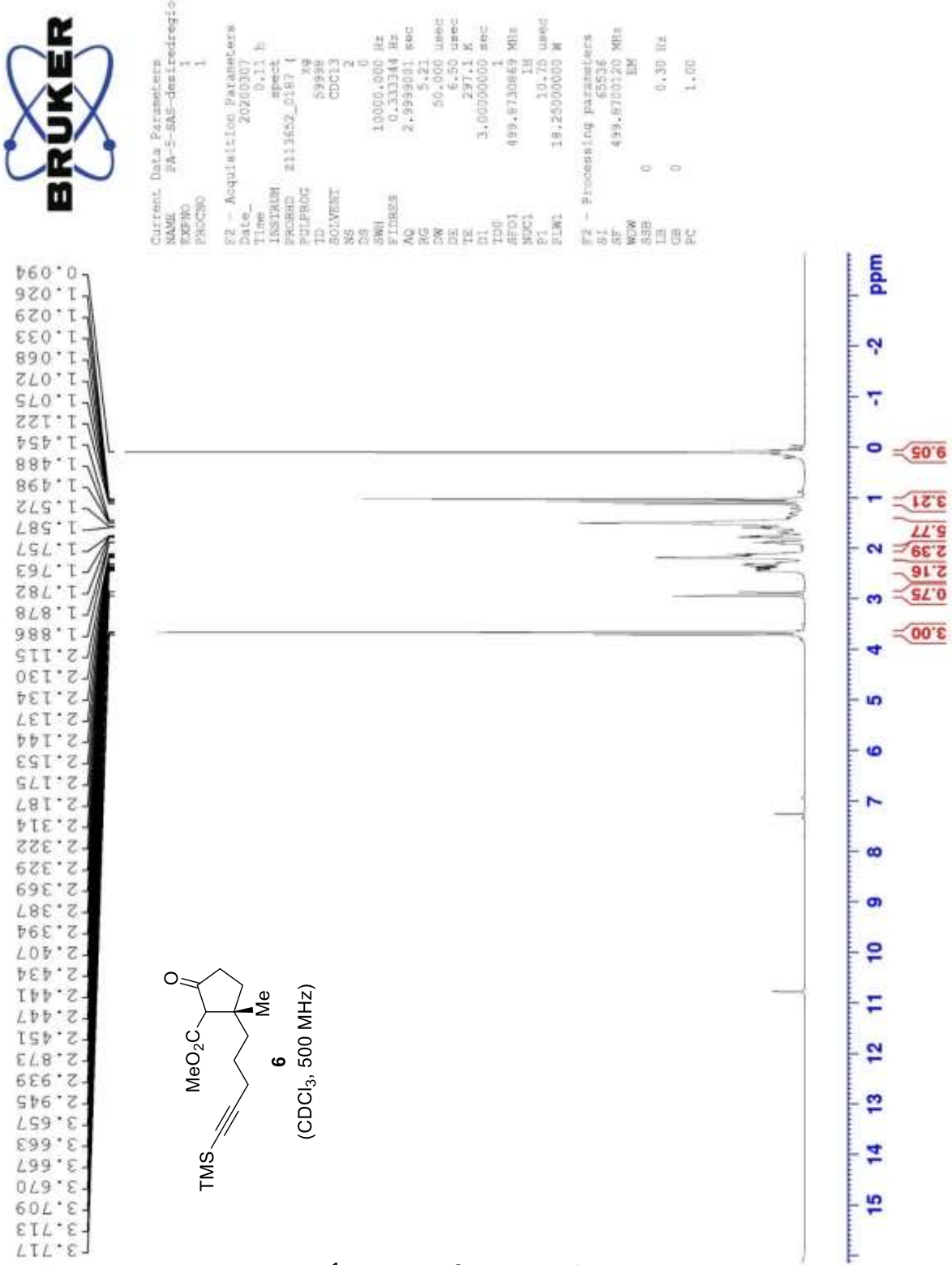


Figure 4.7: ^{1}H NMR of intermediate **6**

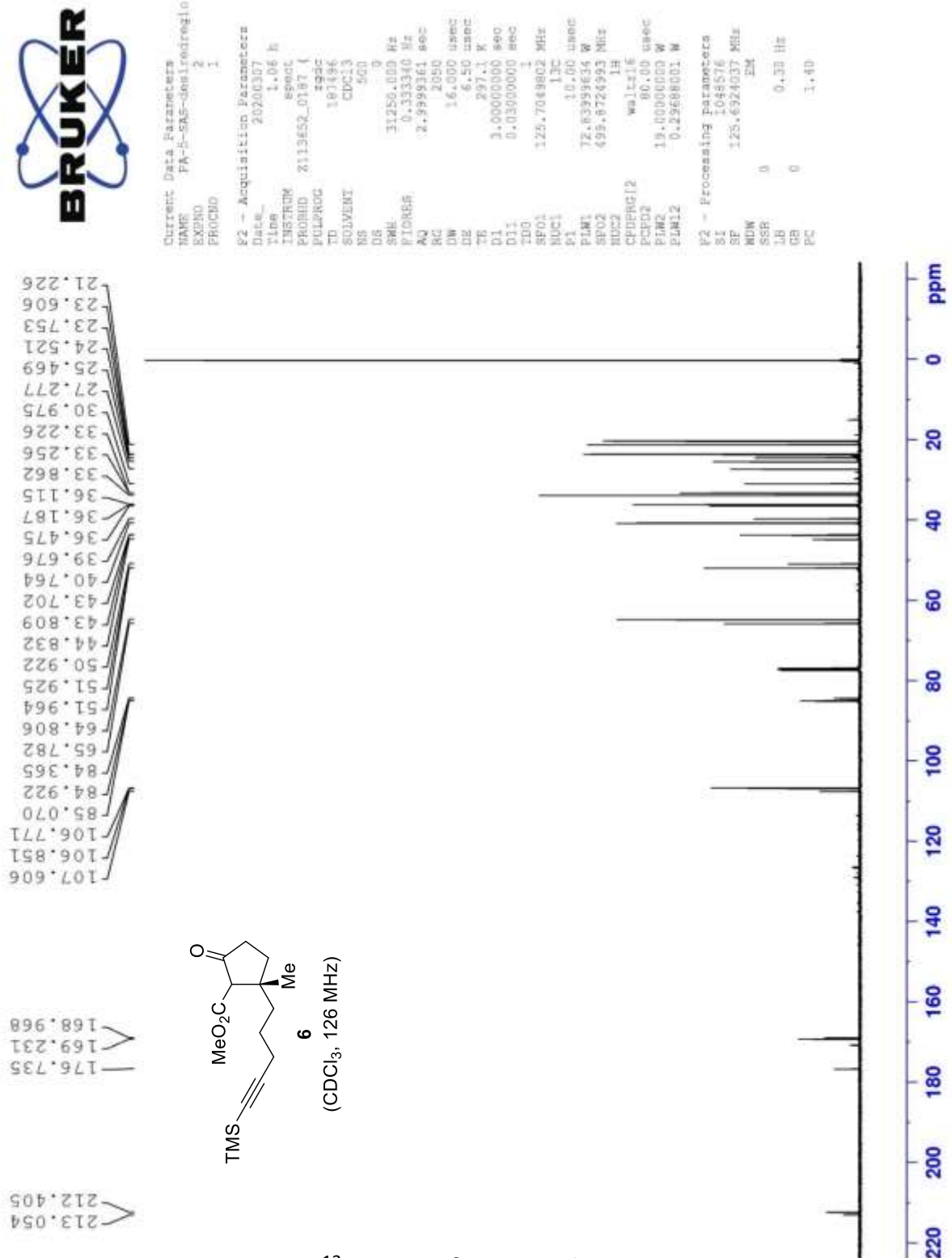


Figure 4.8: ^{13}C NMR of intermediate **6**

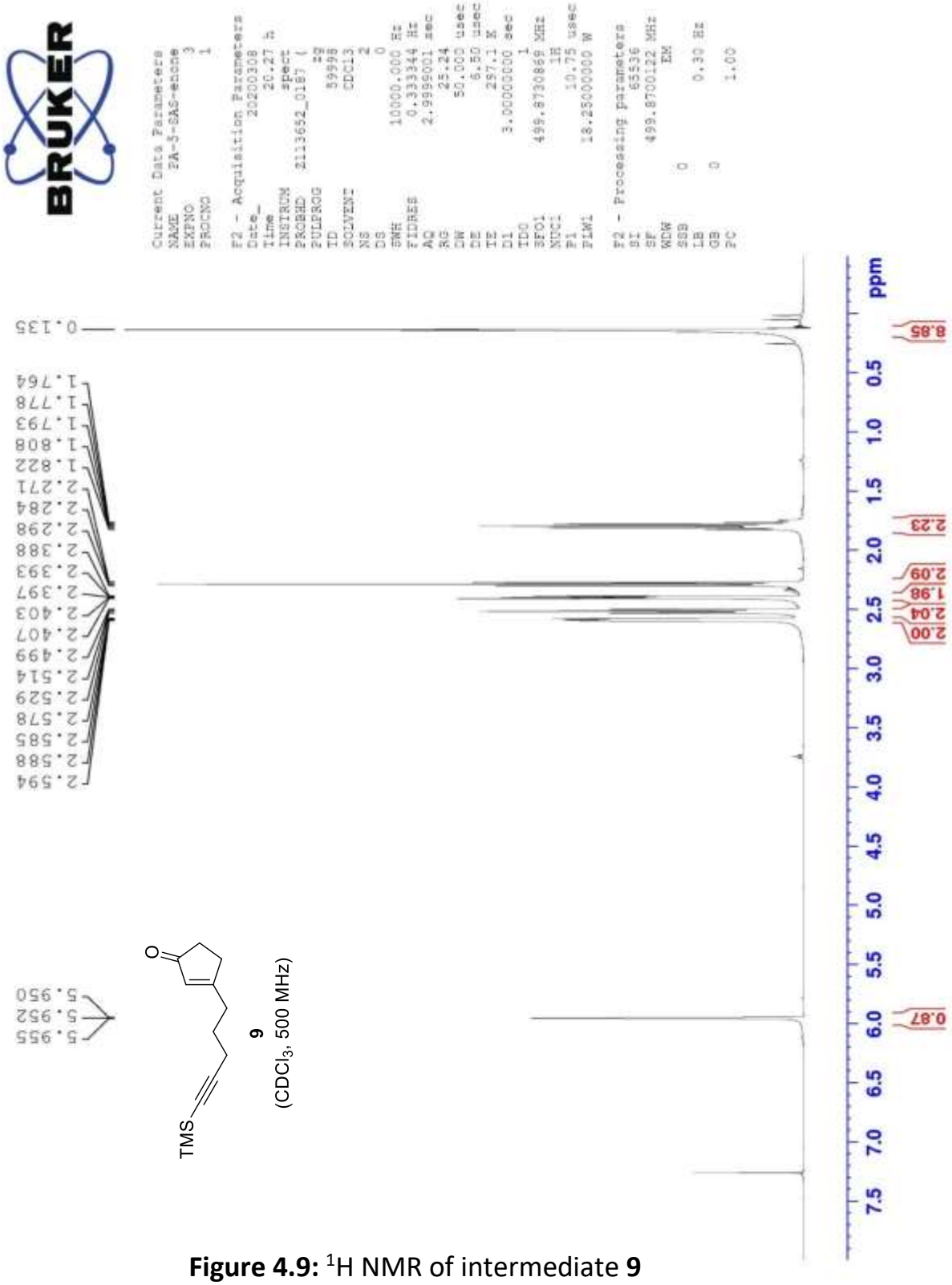


Figure 4.9: ^{1}H NMR of intermediate **9**

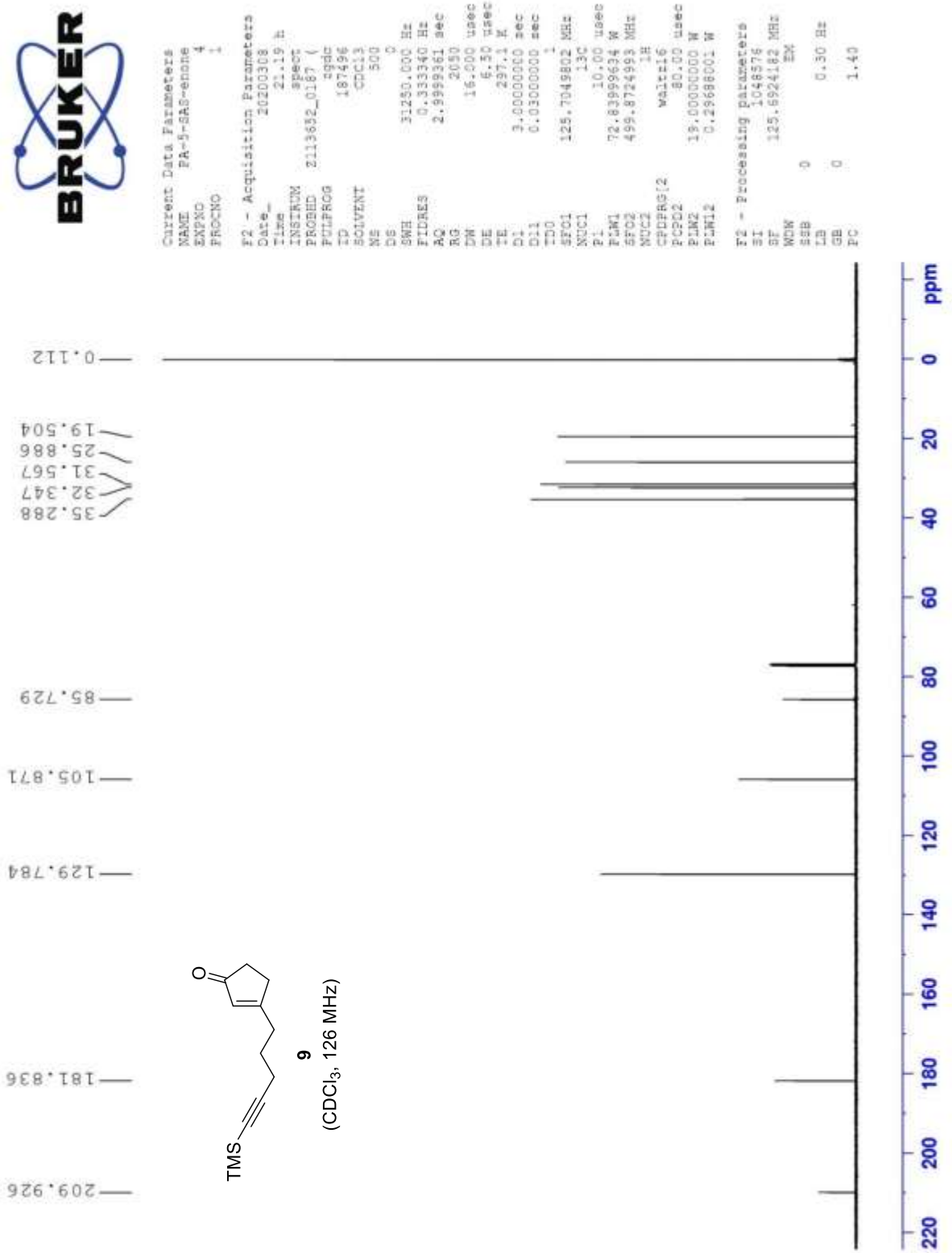


Figure 4.10: ^{13}C NMR of intermediate **9**

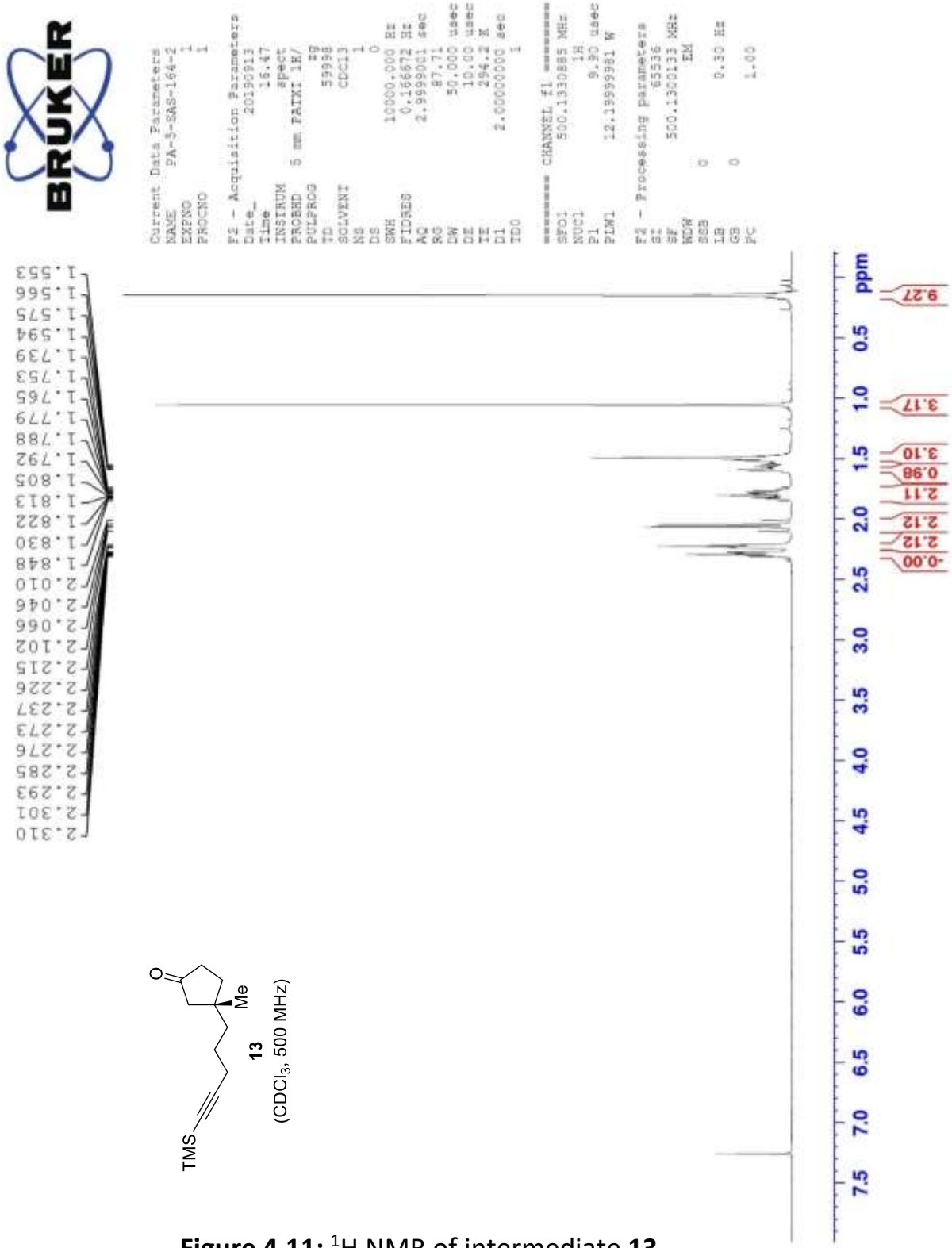


Figure 4.11: ^{1}H NMR of intermediate **13**

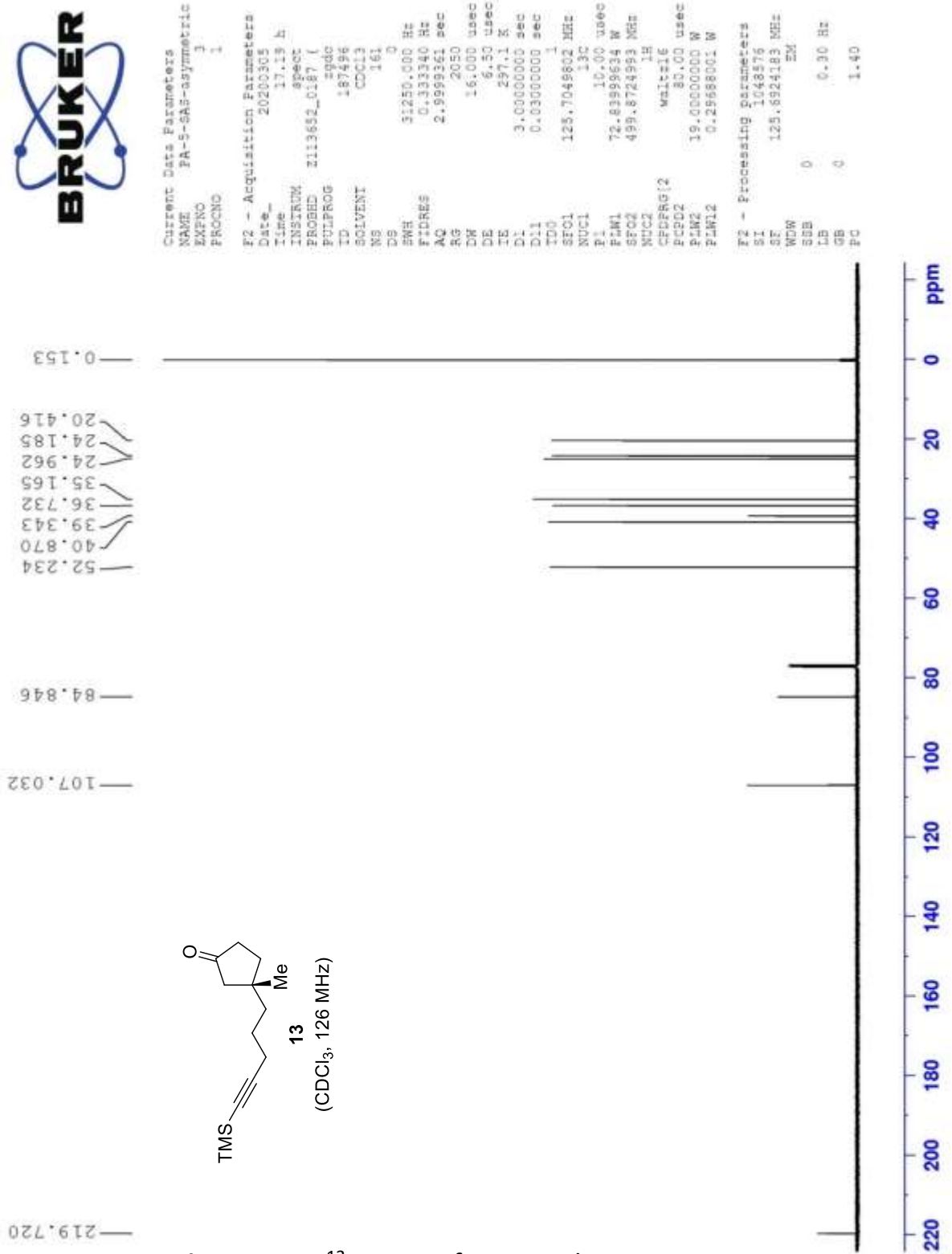
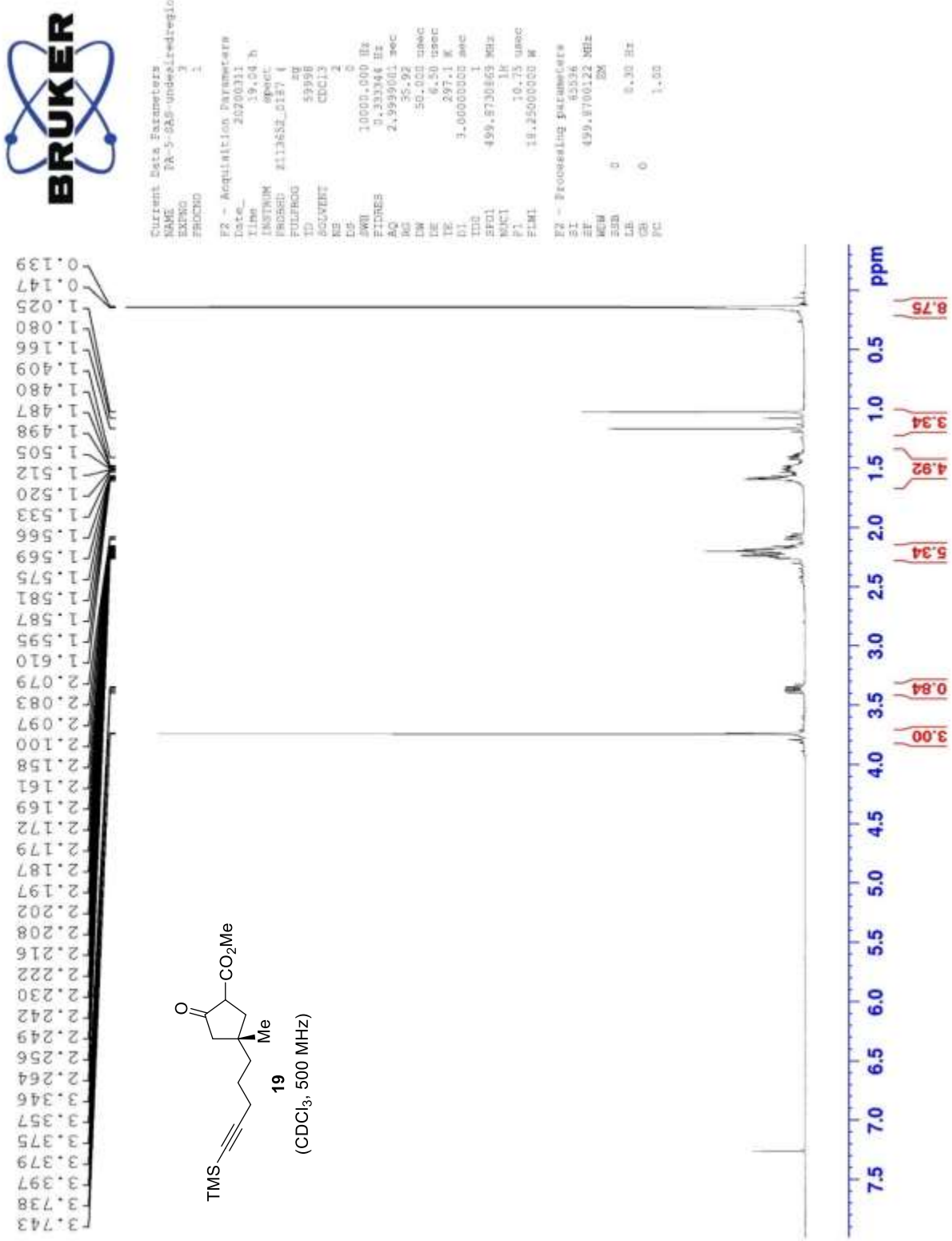


Figure 4.12: ^{13}C NMR of intermediate **13**



19

($CDCl_3$, 500 MHz)

Figure 4.13: ^{1}H NMR of intermediate **19**

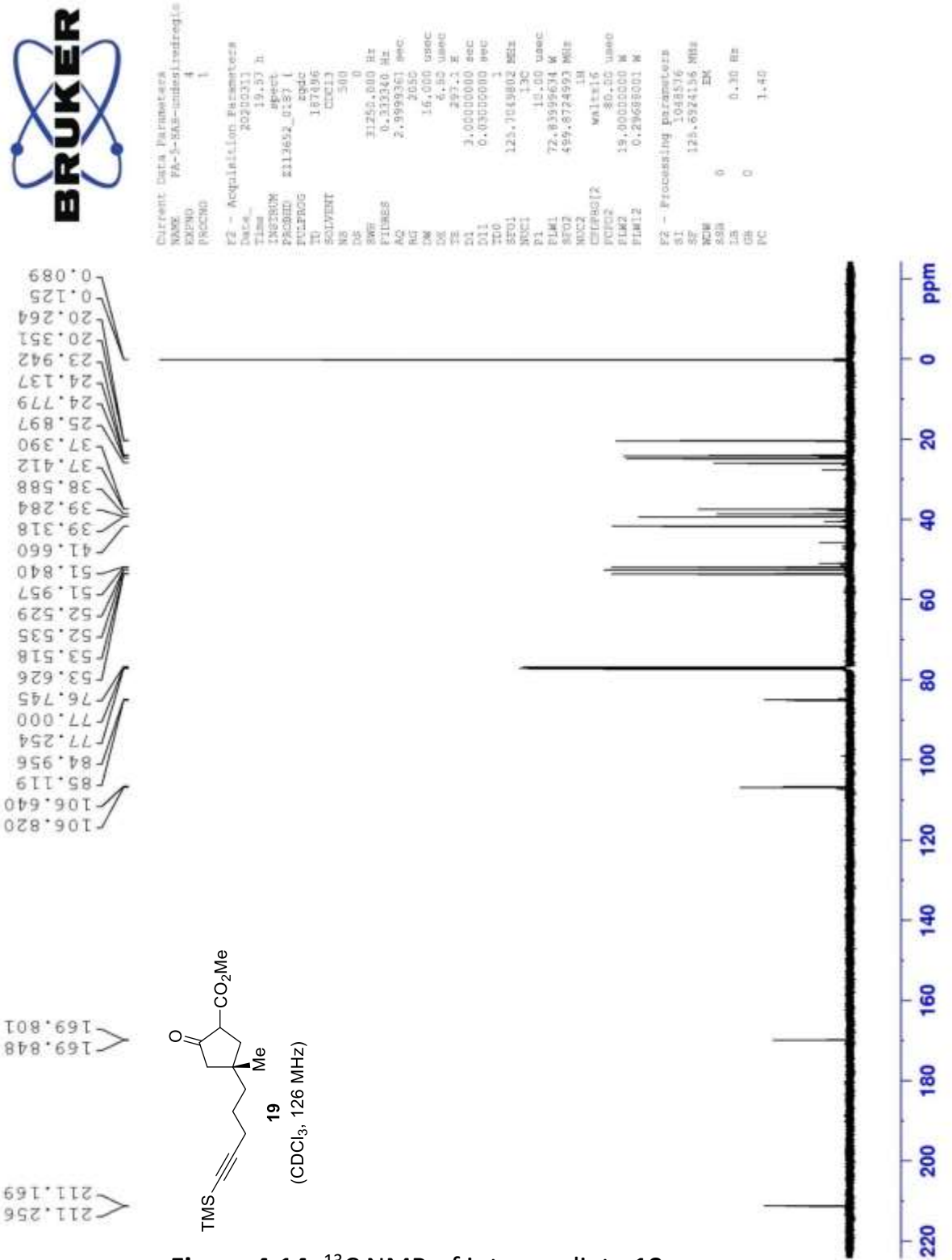


Figure 4.14: ^{13}C NMR of intermediate **19**

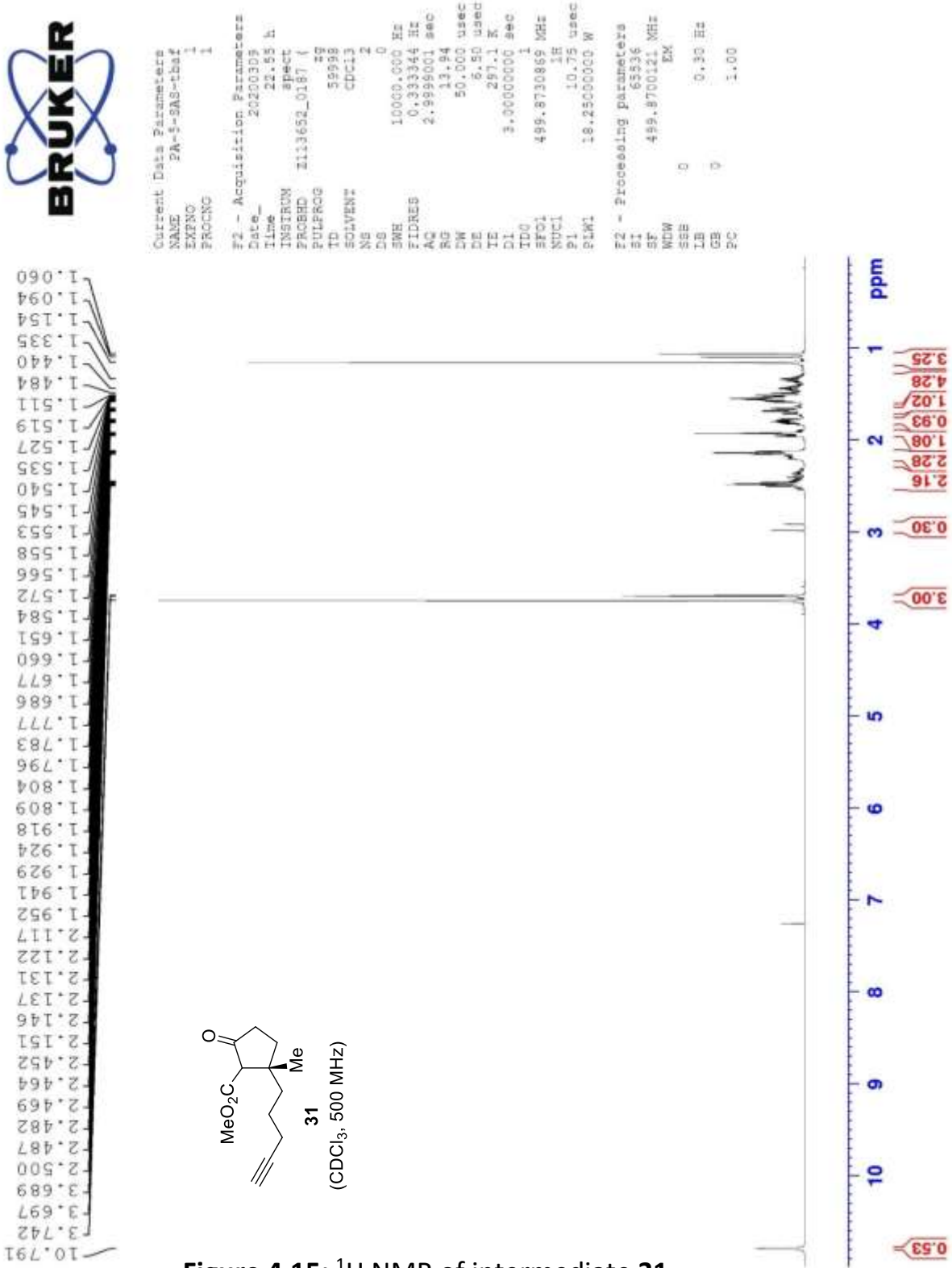


Figure 4.15: ^{1}H NMR of intermediate **31**

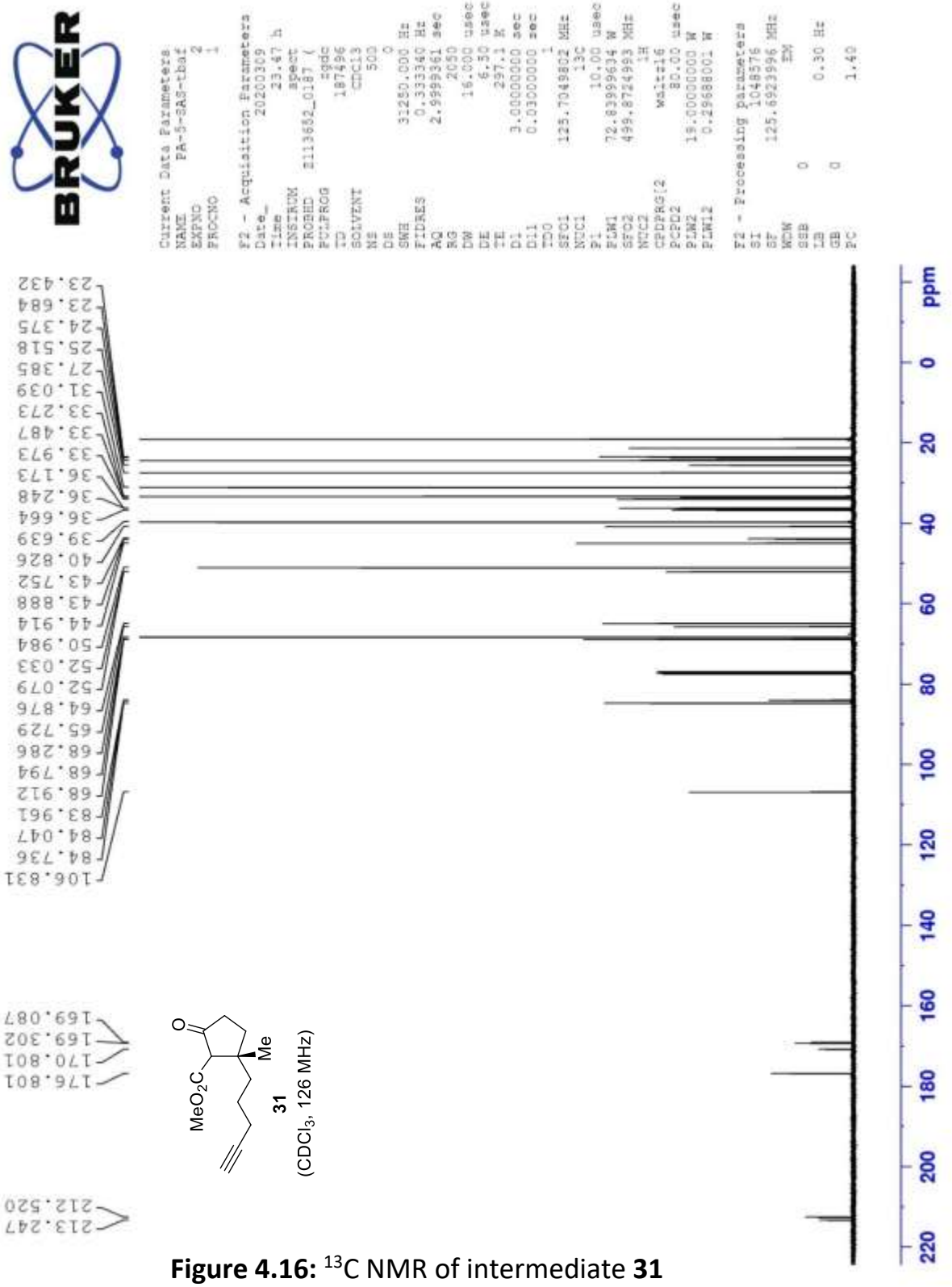


Figure 4.16: ^{13}C NMR of intermediate **31**

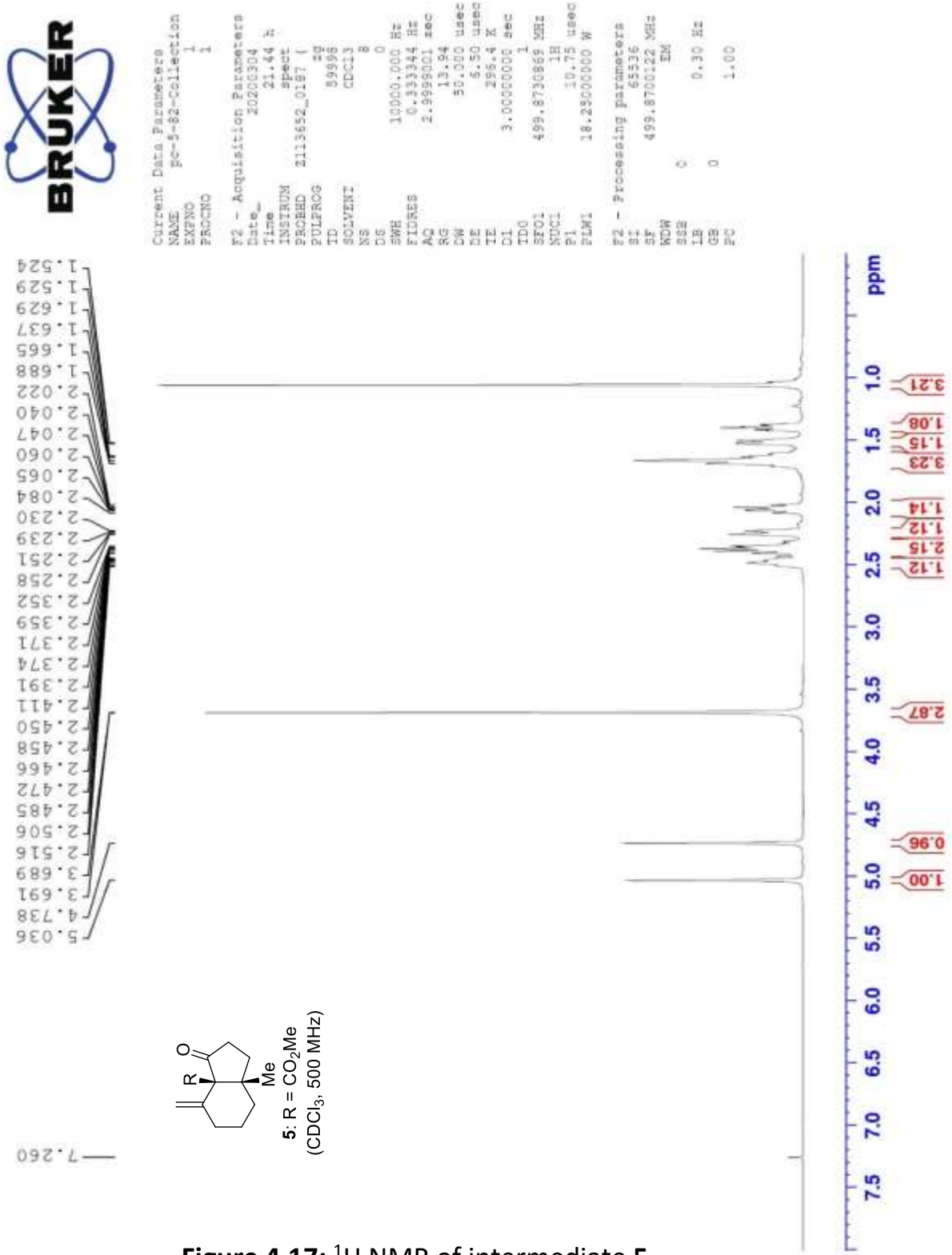


Figure 4.17: ^{1}H NMR of intermediate **5**

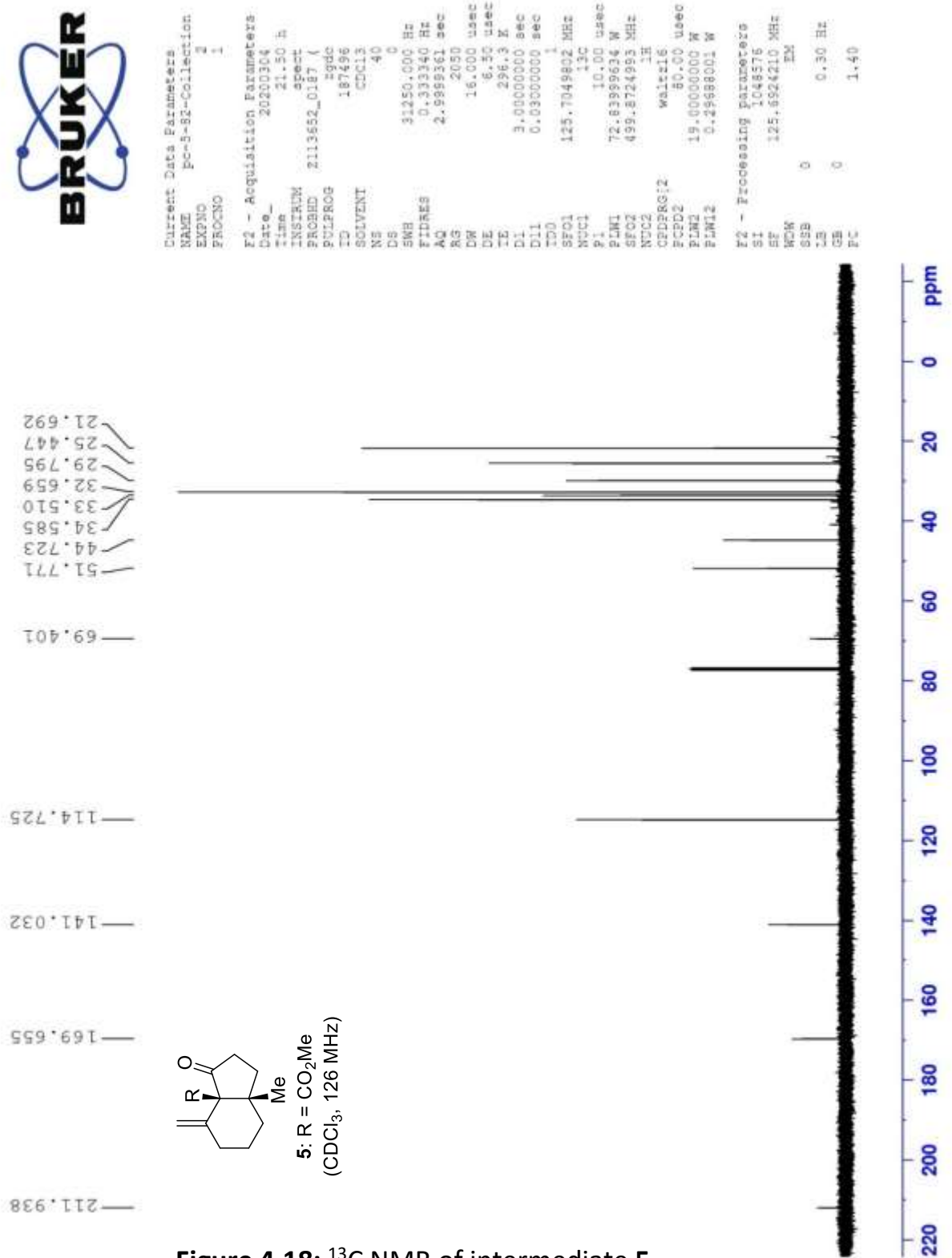


Figure 4.18: ^{13}C NMR of intermediate **5**

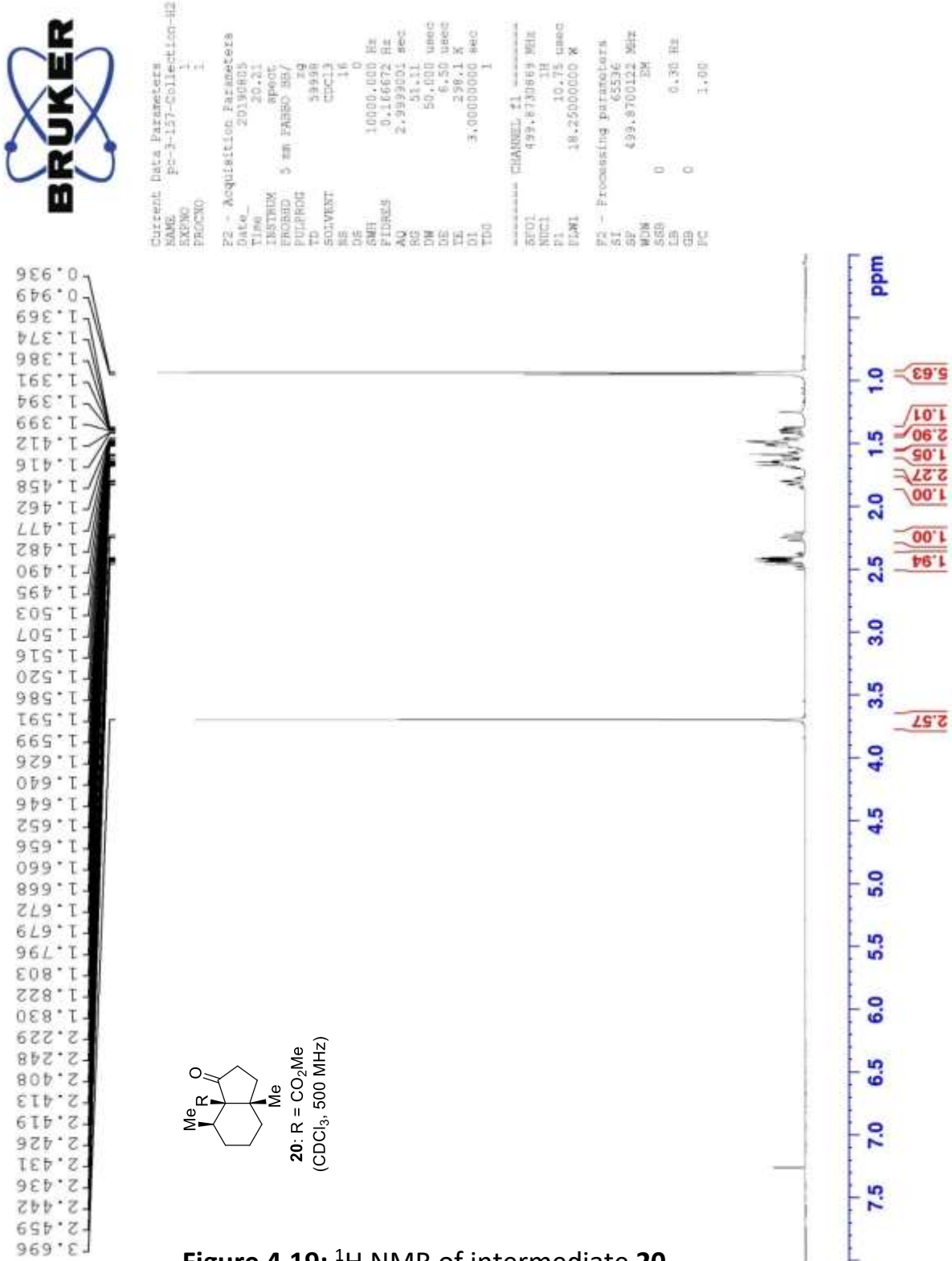


Figure 4.19: ^{1}H NMR of intermediate **20**

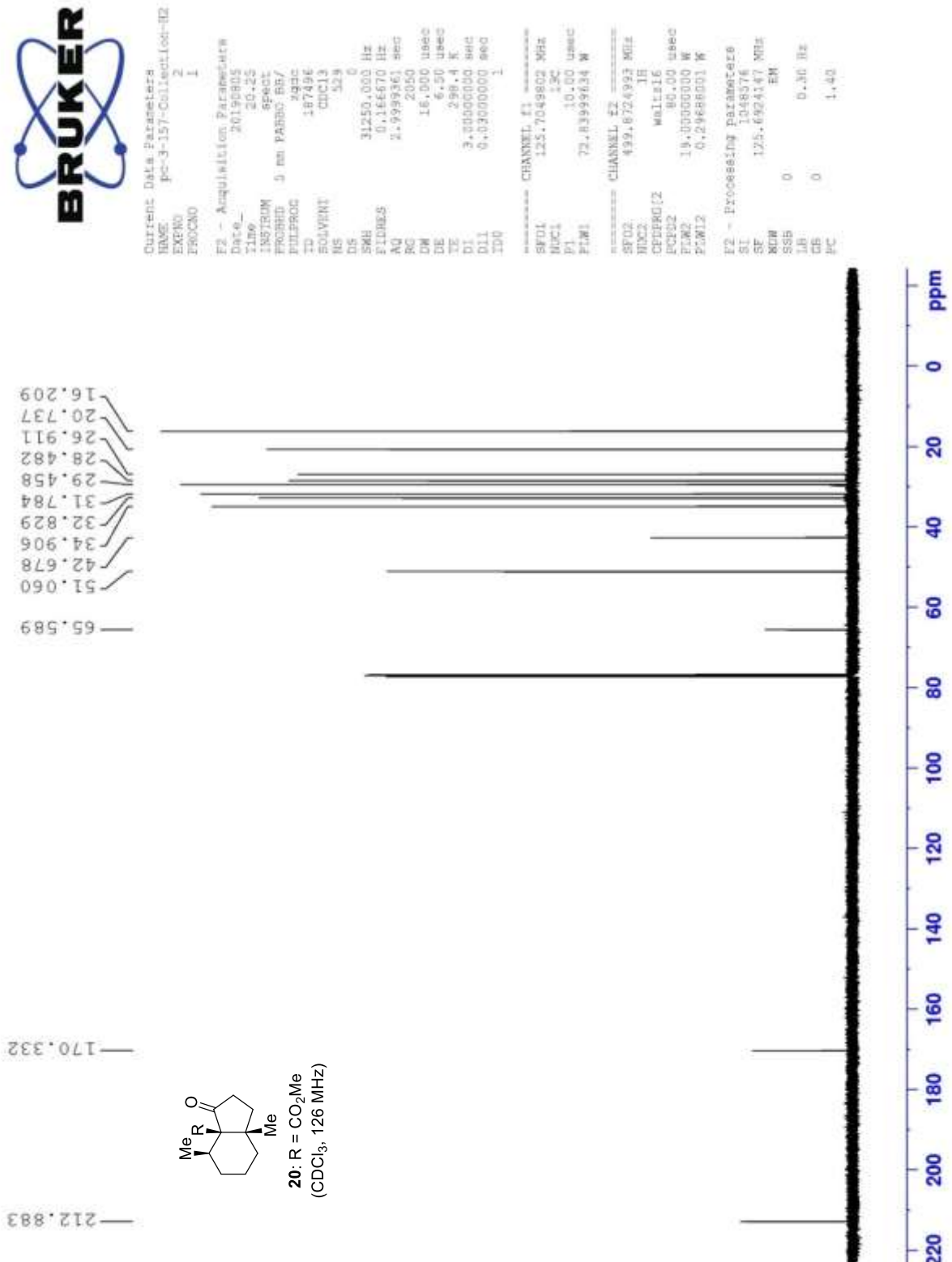


Figure 4.20: ^{13}C NMR of intermediate **20**

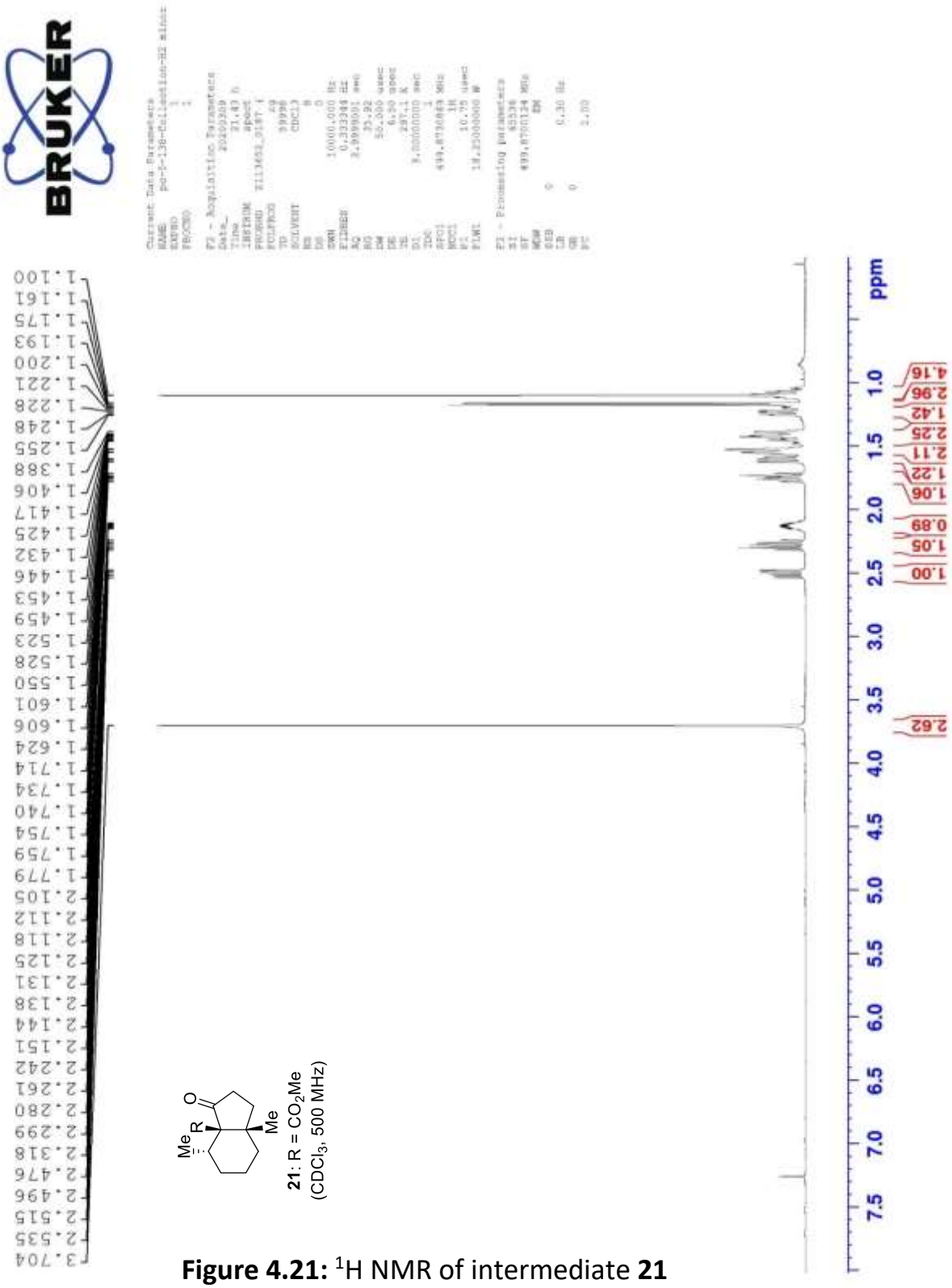


Figure 4.21: ^{1}H NMR of intermediate **21**

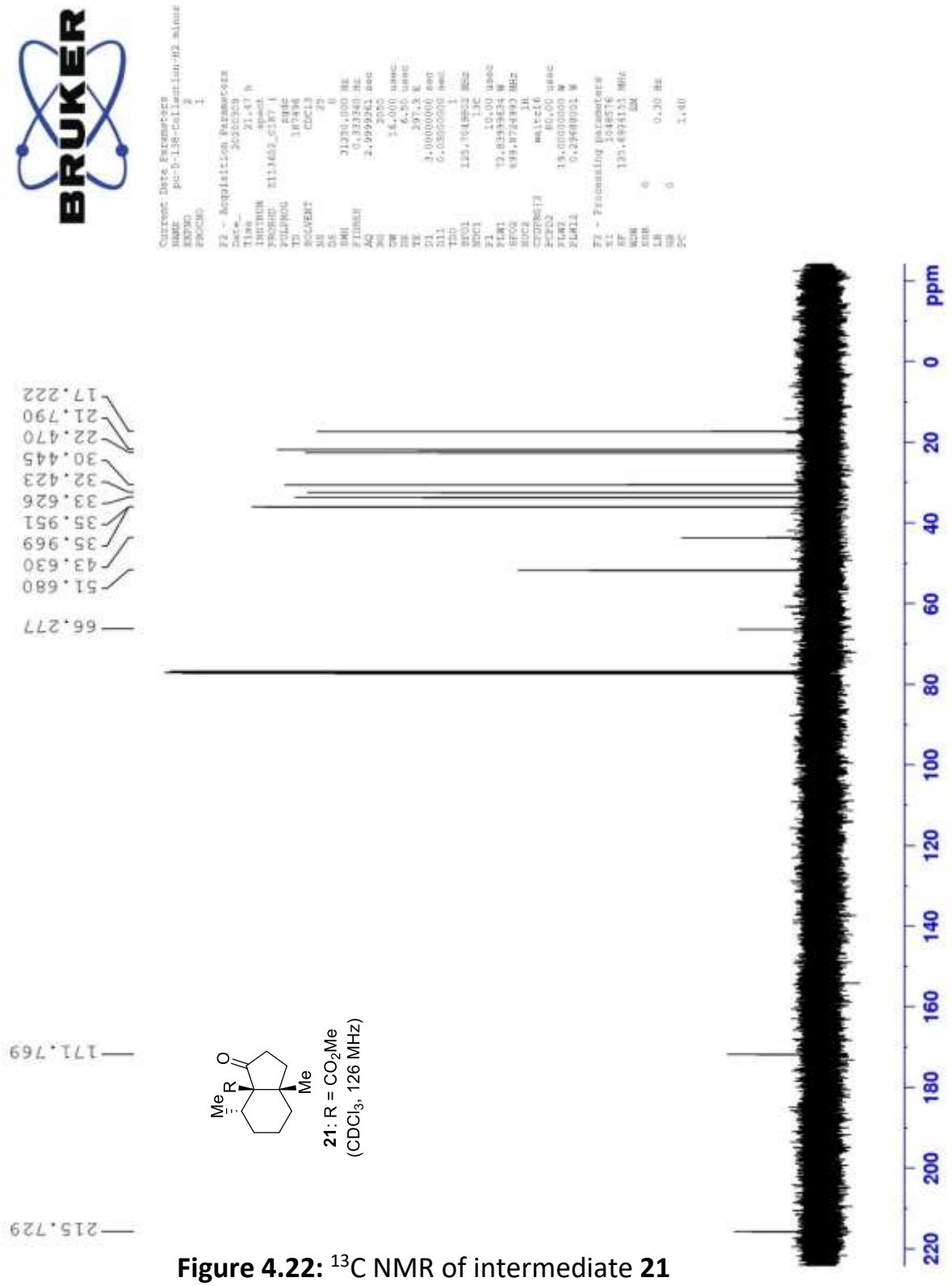


Figure 4.22: ^{13}C NMR of intermediate **21**

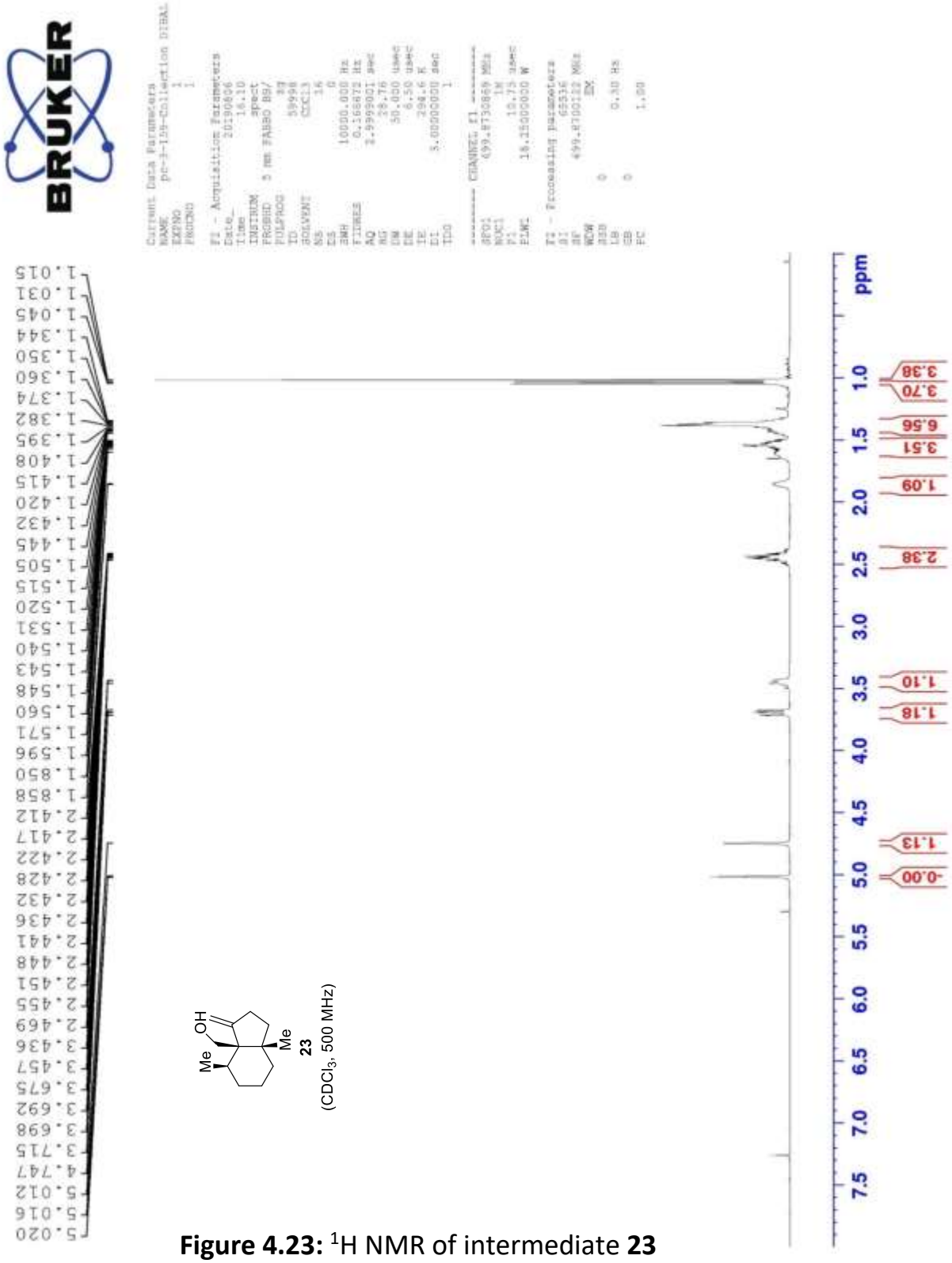


Figure 4.23: ^{1}H NMR of intermediate **23**

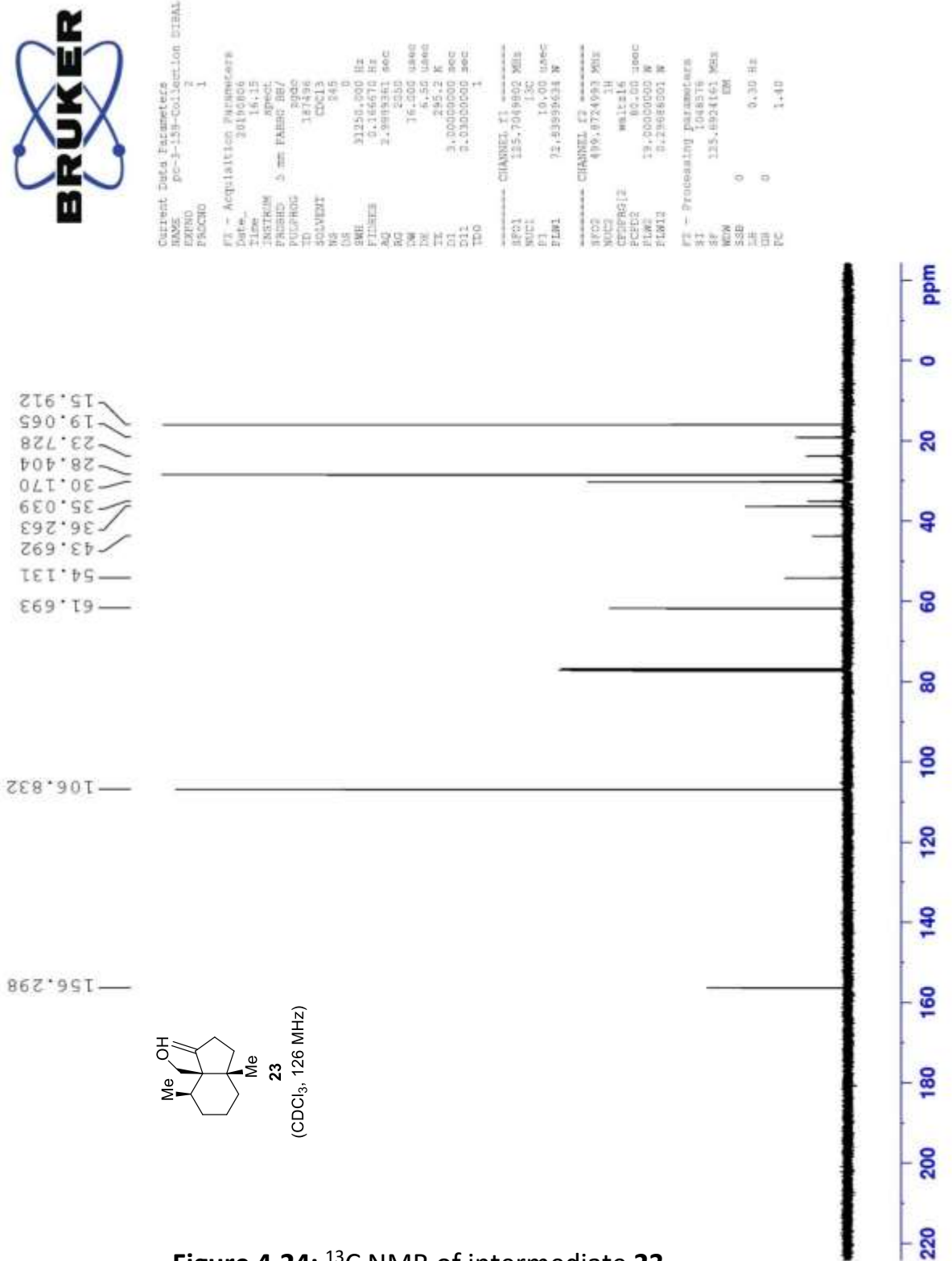


Figure 4.24: ^{13}C NMR of intermediate **23**

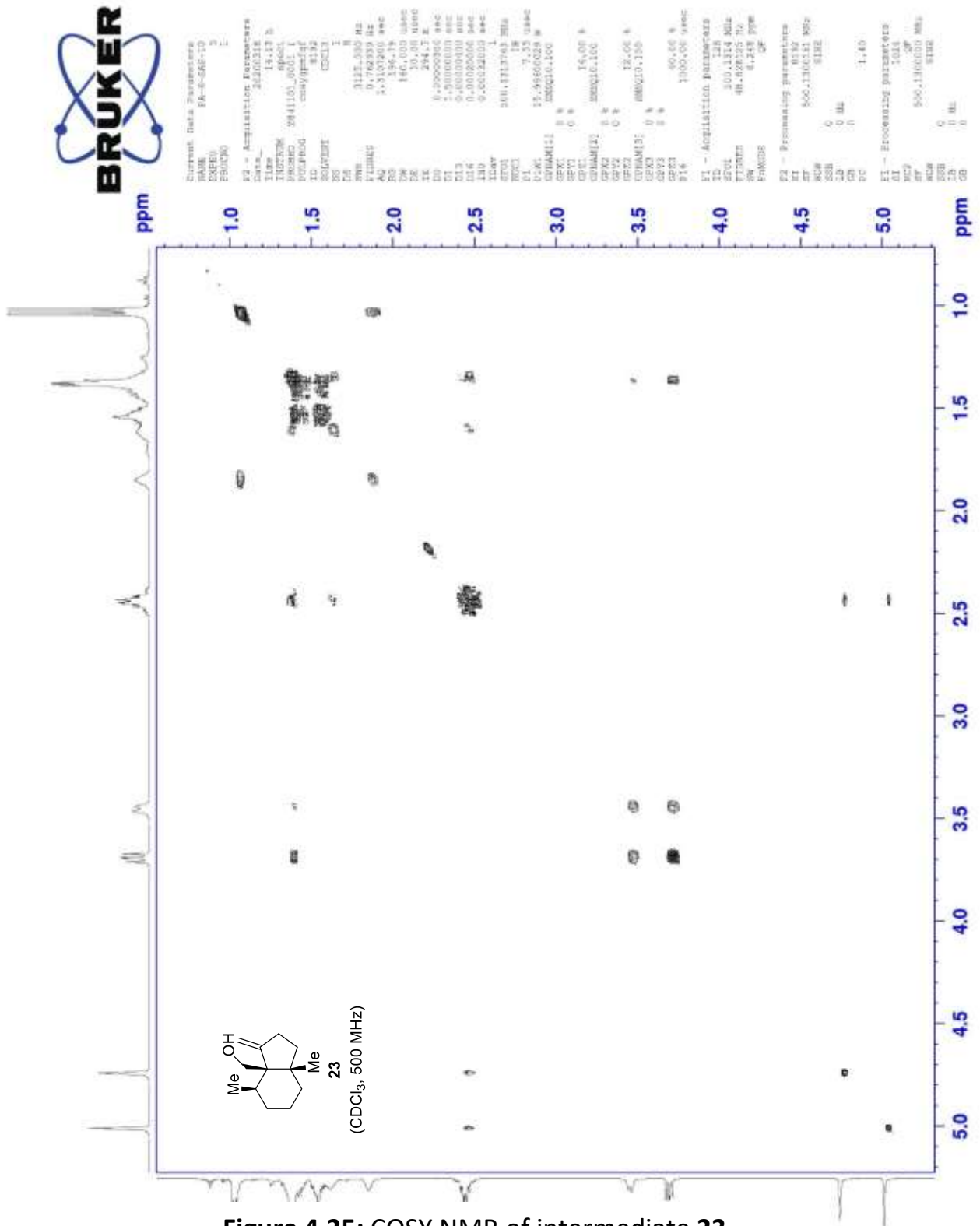


Figure 4.25: COSY NMR of intermediate **23**

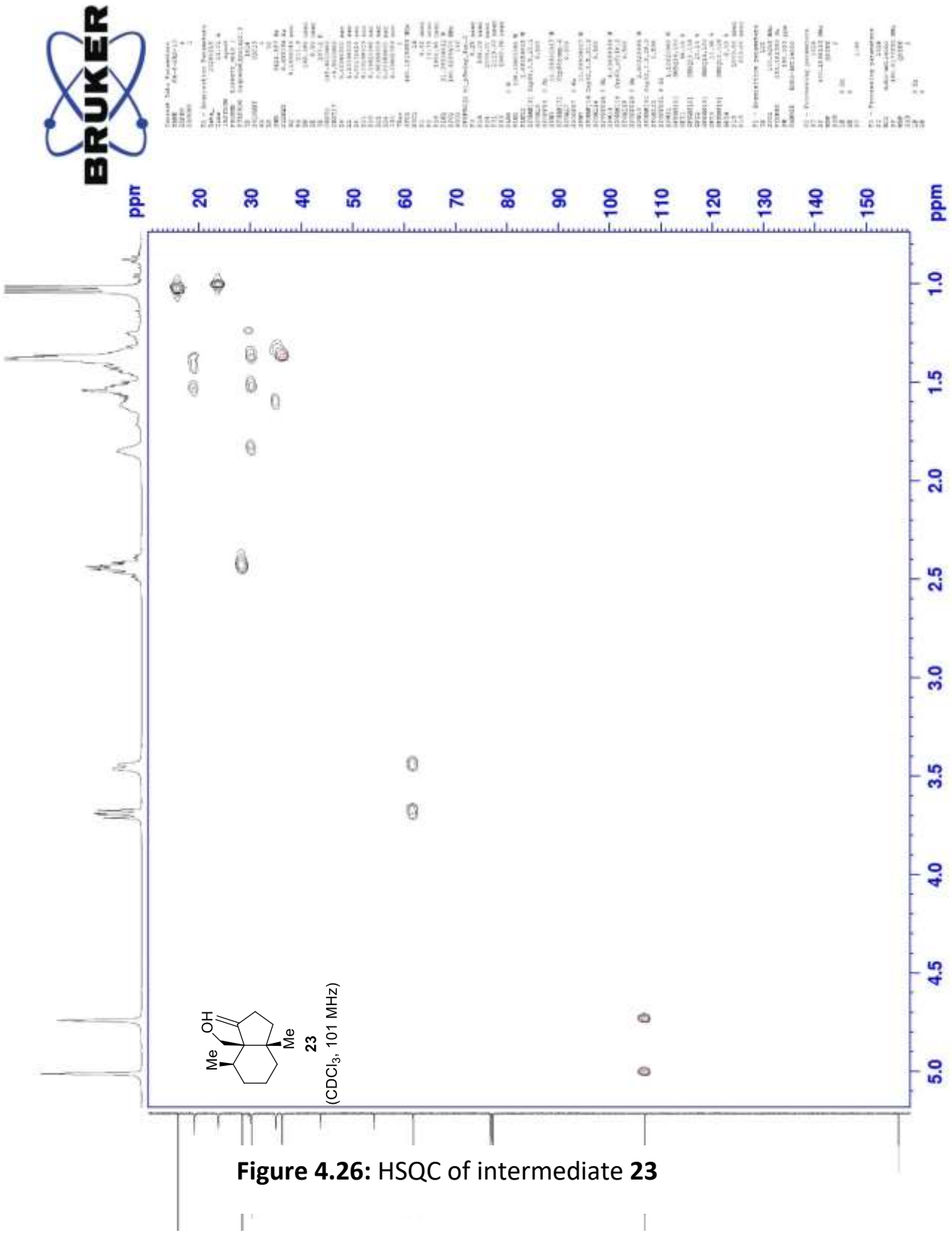


Figure 4.26: HSQC of intermediate **23**

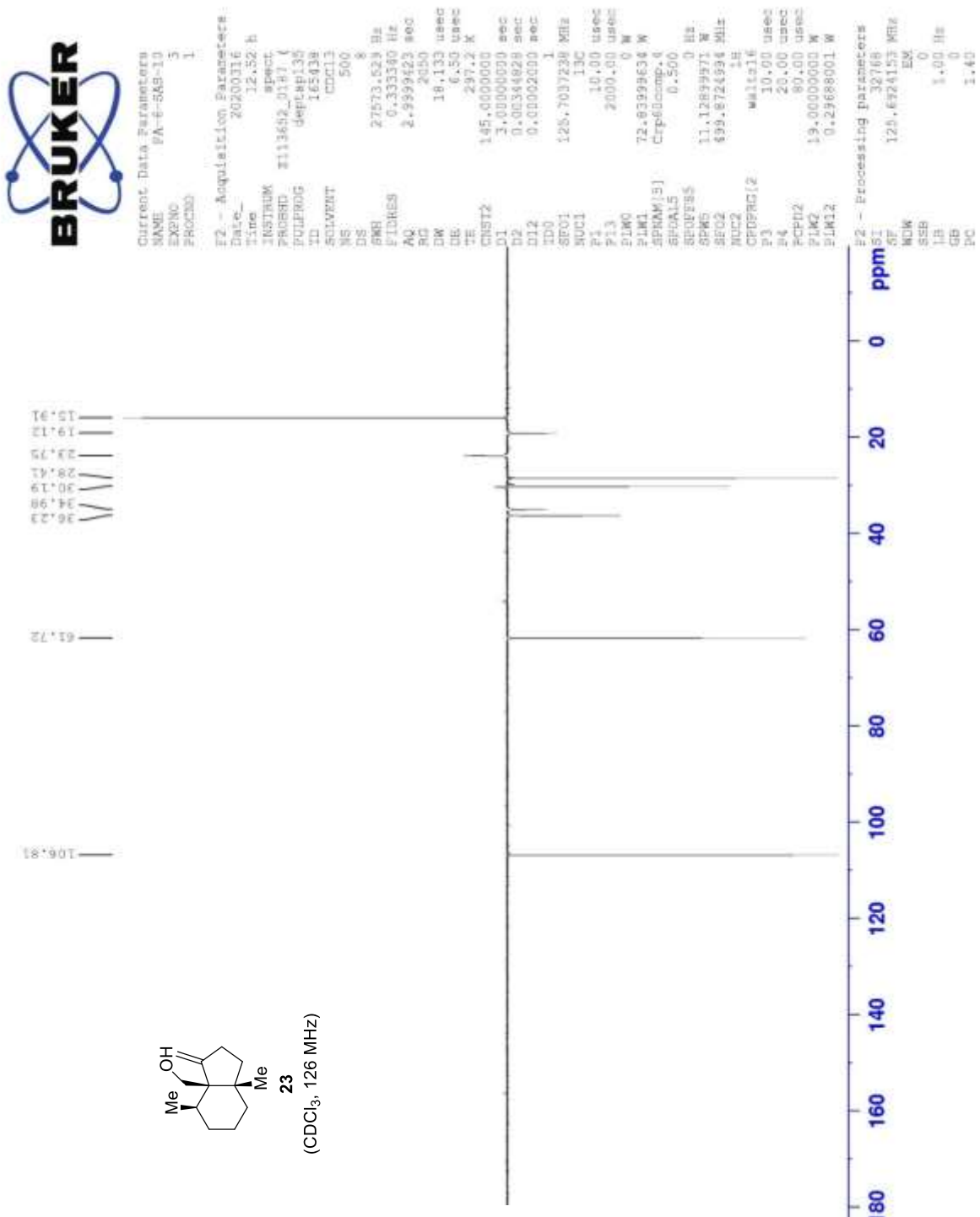


Figure 4.27: DEPT135 of intermediate **23**

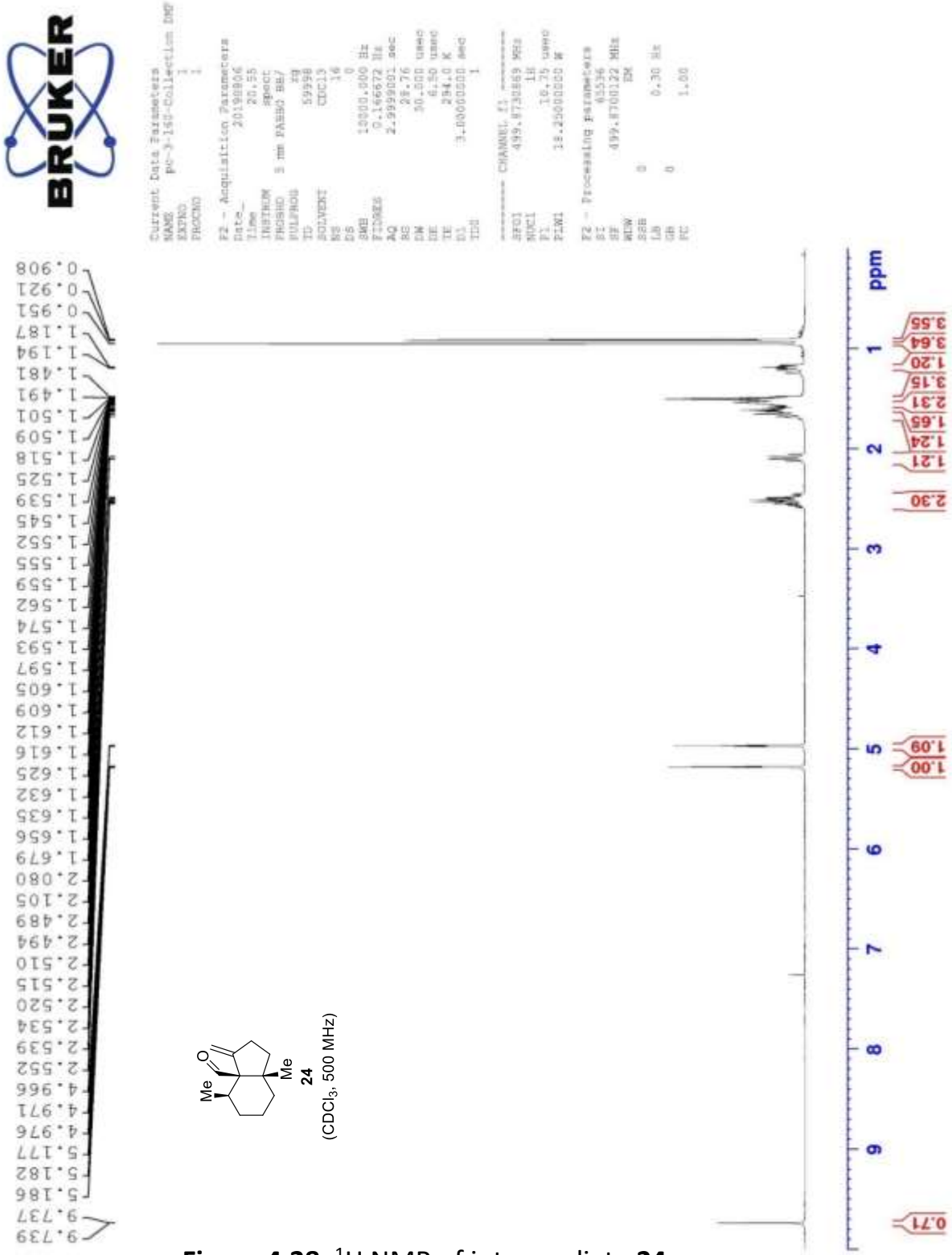


Figure 4.28: ^{1}H NMR of intermediate **24**

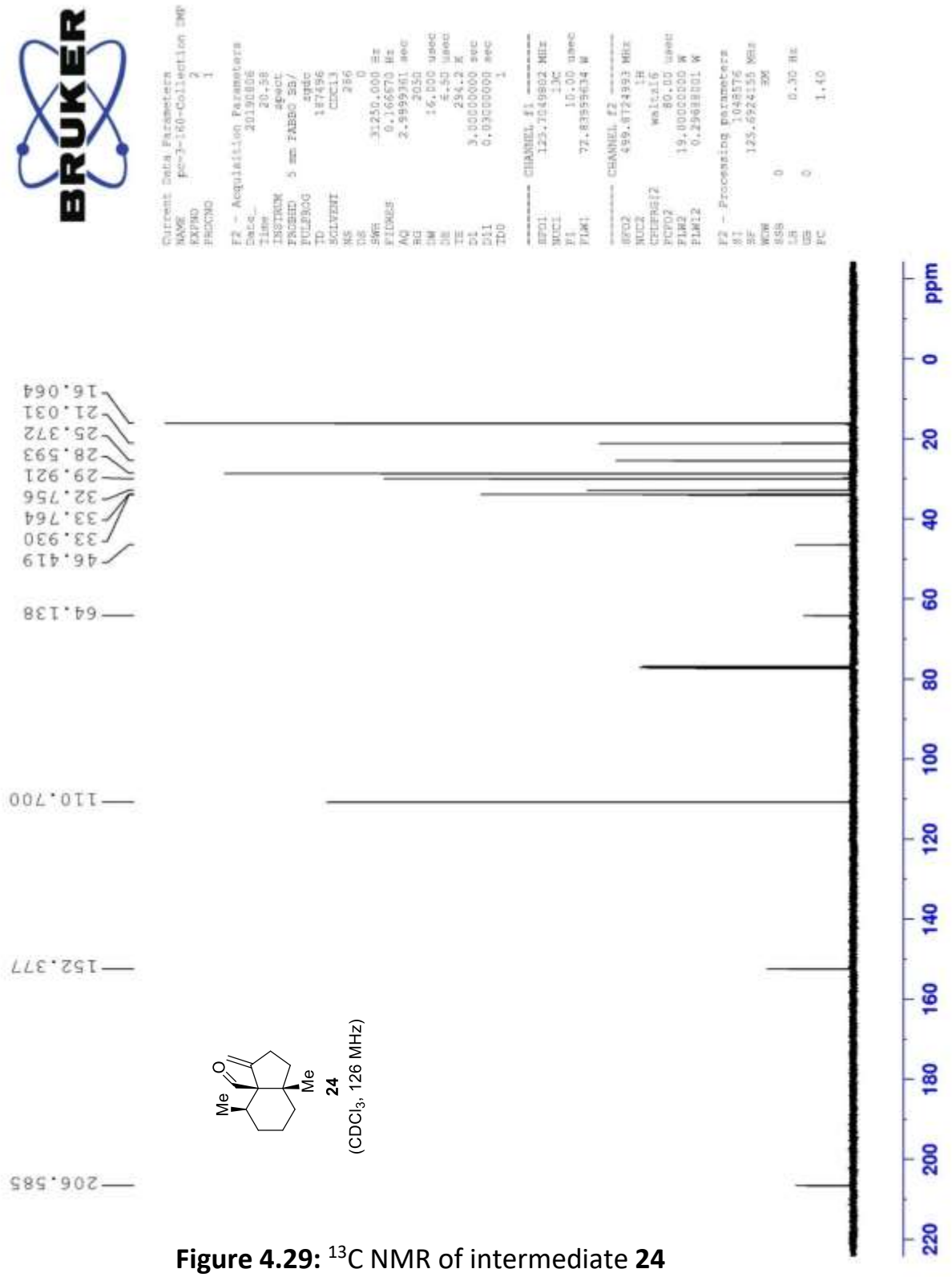


Figure 4.29: ^{13}C NMR of intermediate **24**

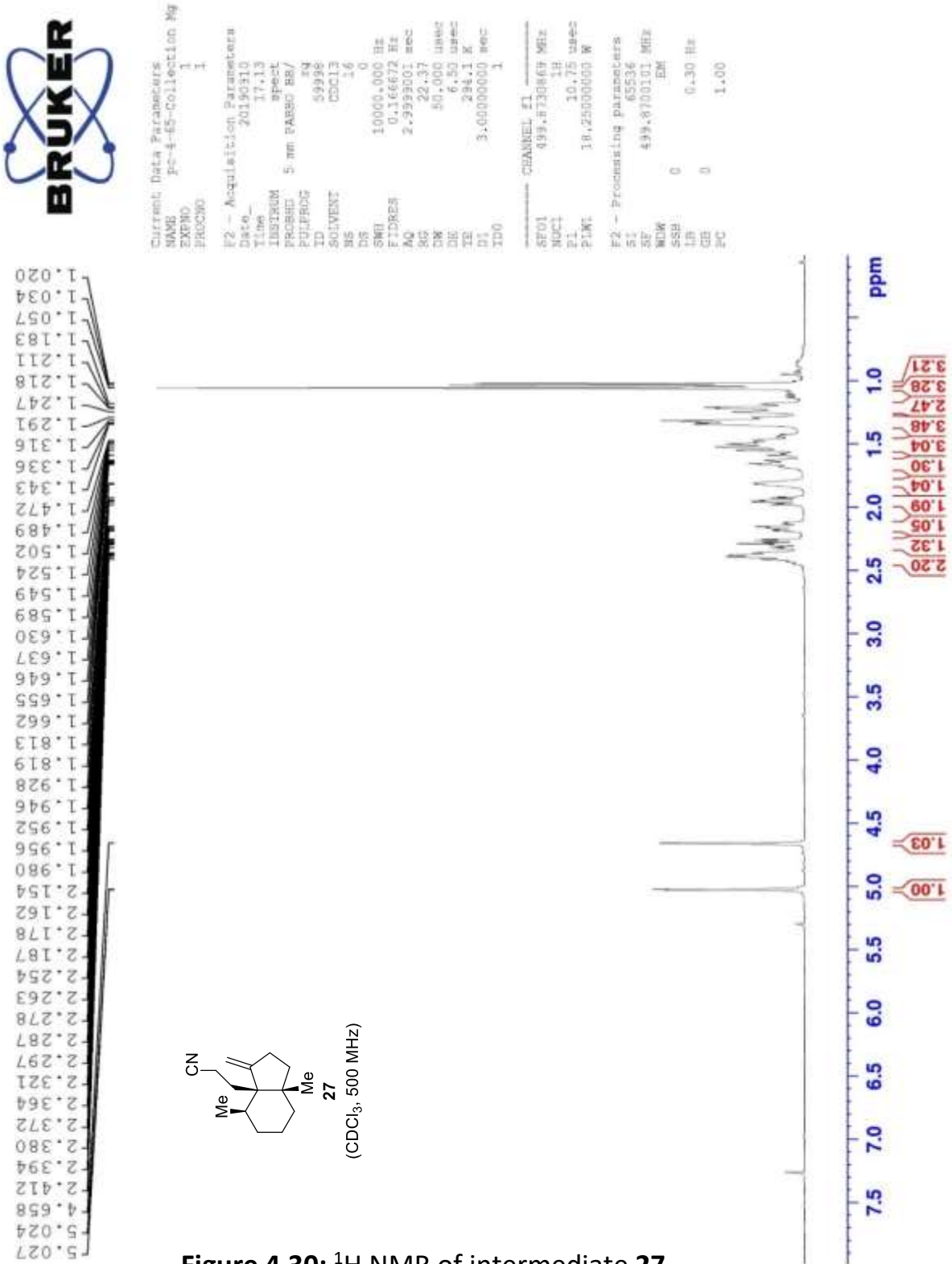


Figure 4.30: ^{1}H NMR of intermediate **27**

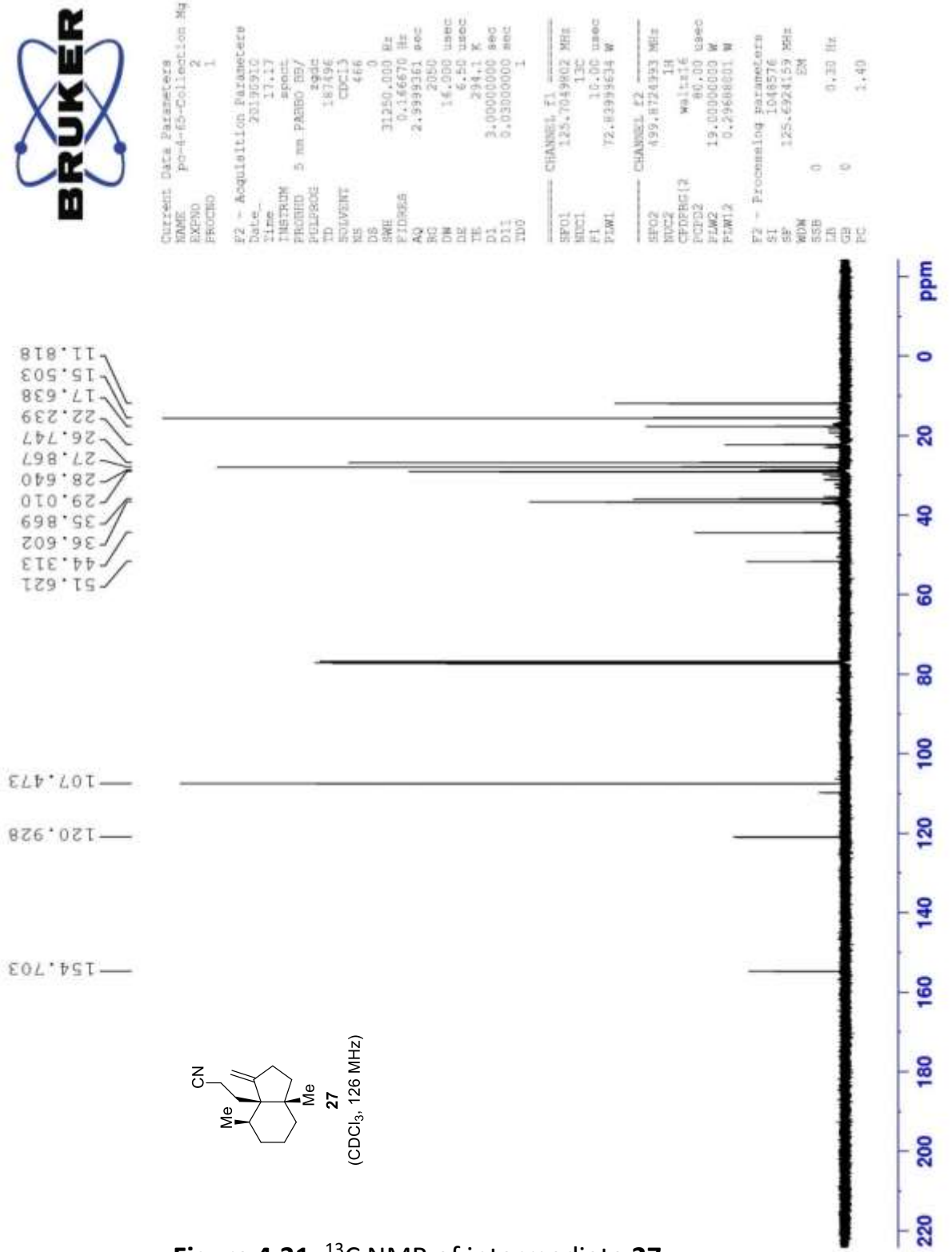


Figure 4.31: ^{13}C NMR of intermediate **27**

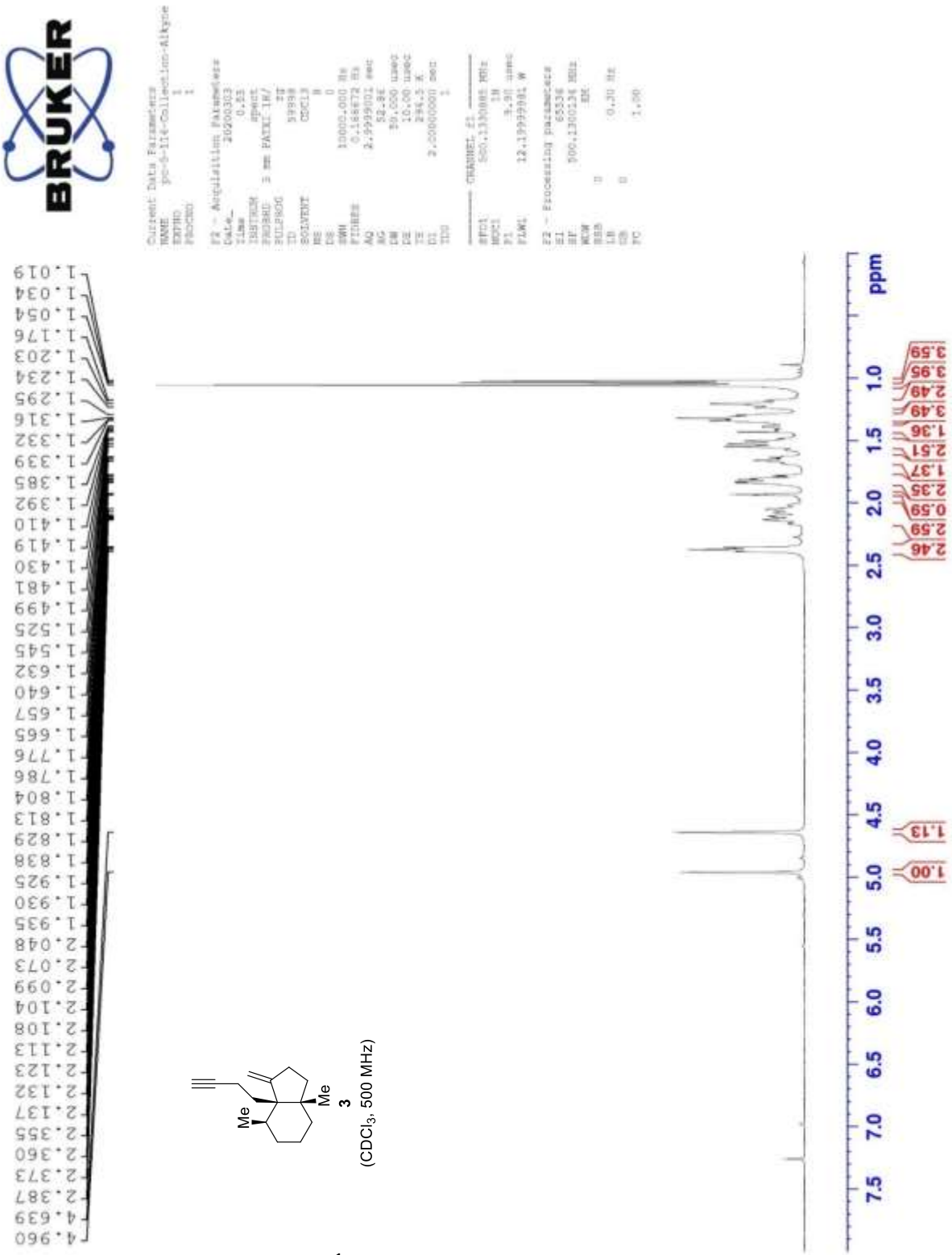


Figure 4.32: ^{1}H NMR of intermediate **3**

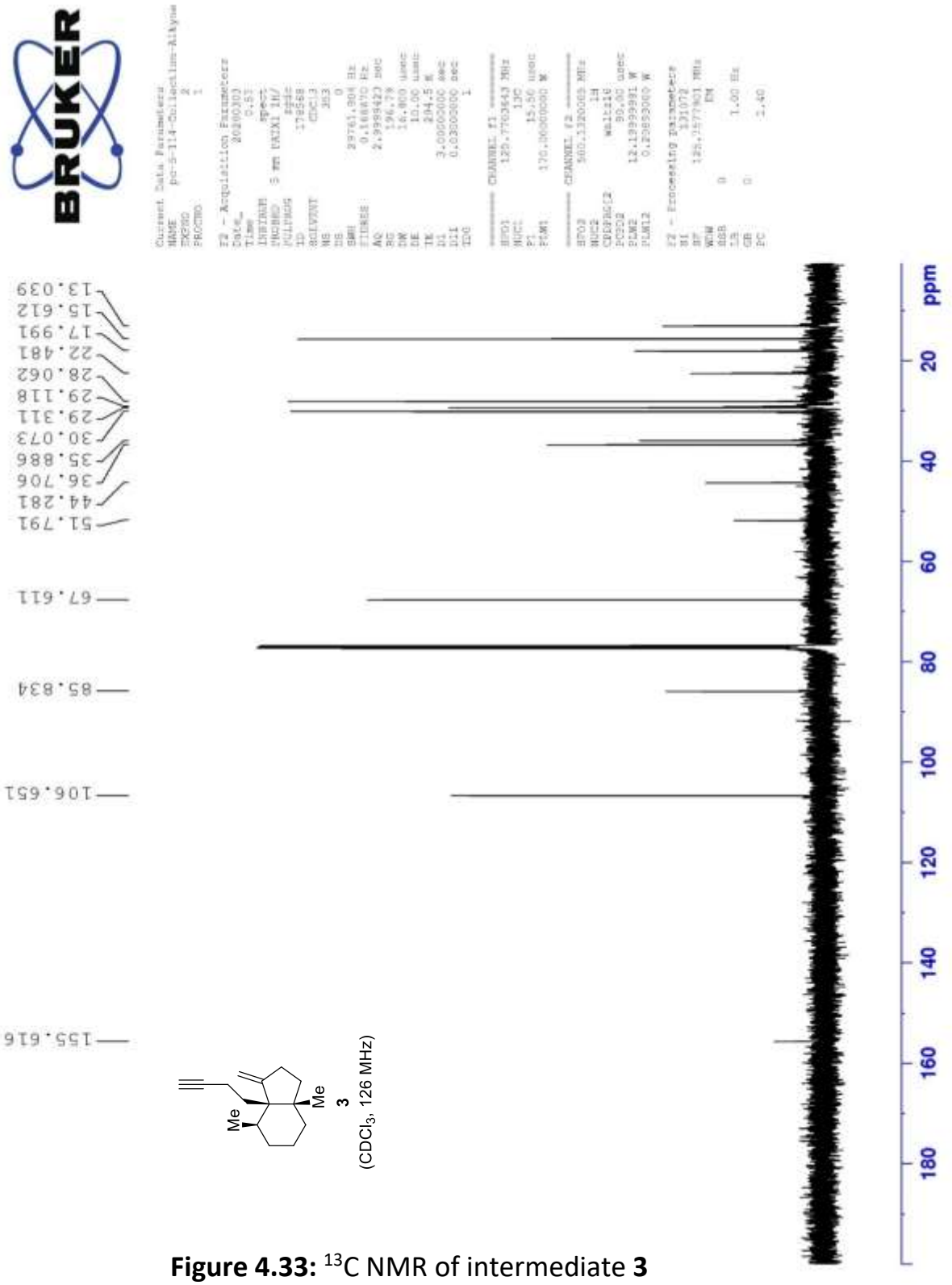


Figure 4.33: ^{13}C NMR of intermediate **3**

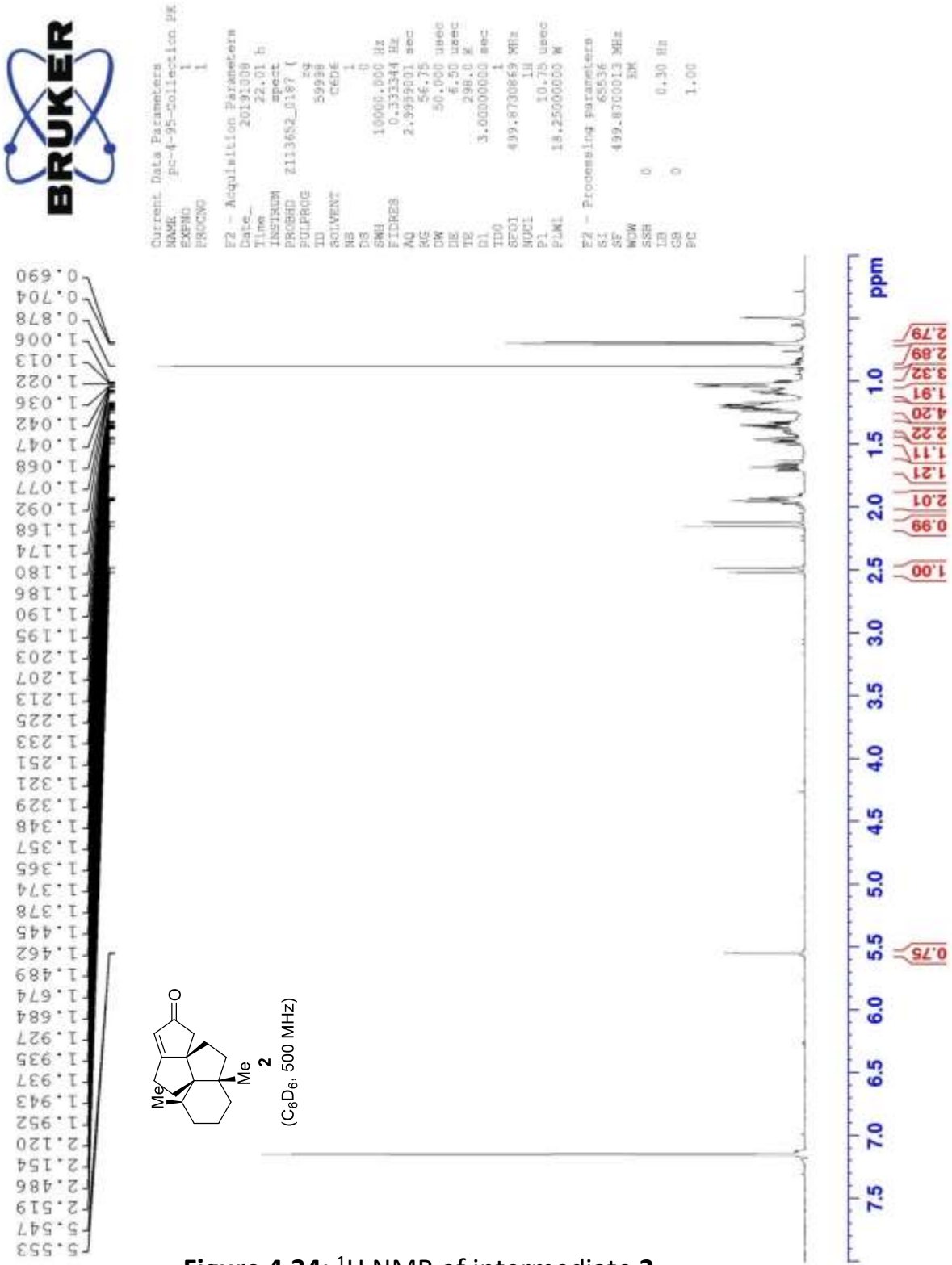


Figure 4.34: ^{1}H NMR of intermediate **2**

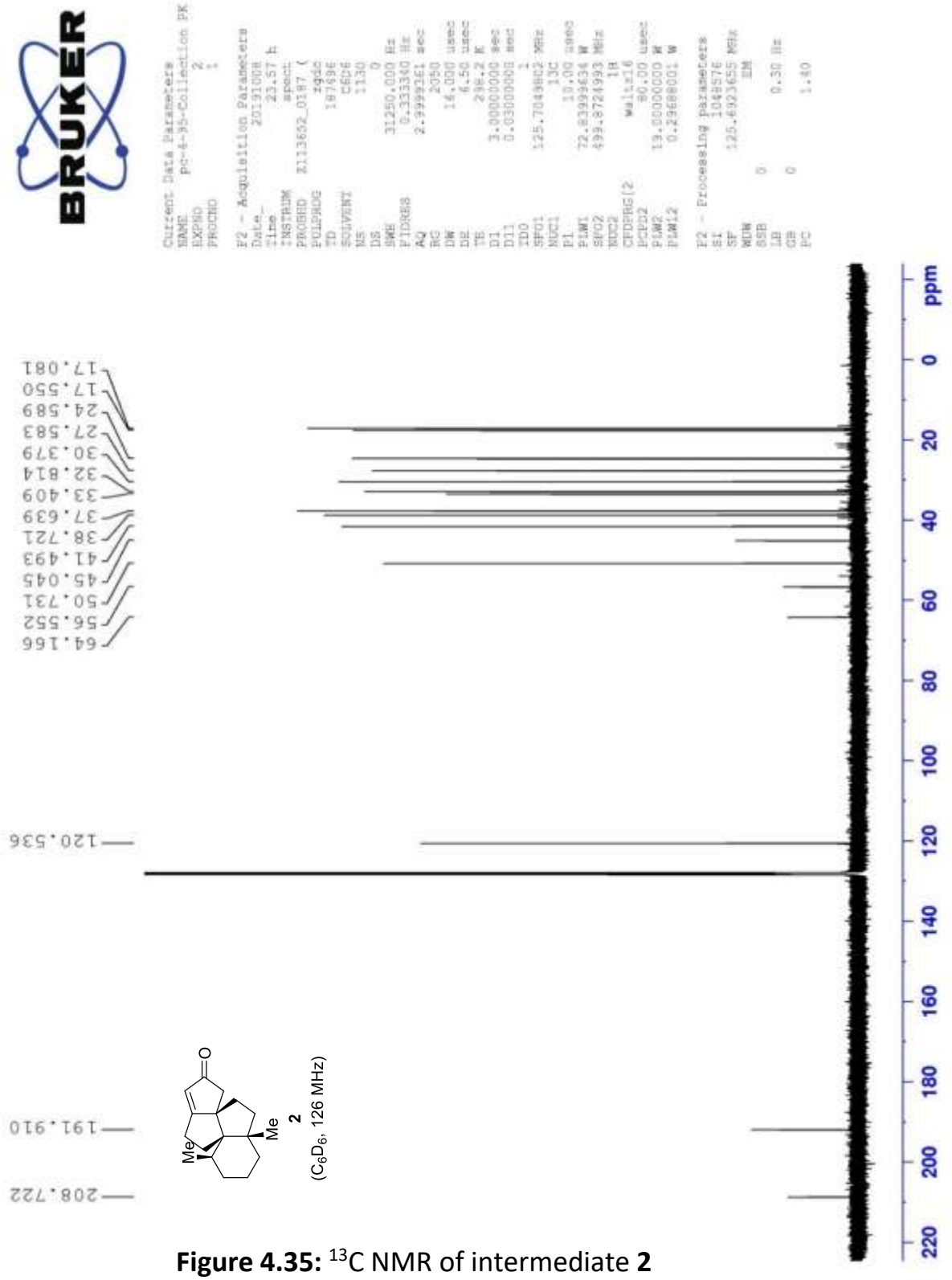


Figure 4.35: ^{13}C NMR of intermediate **2**

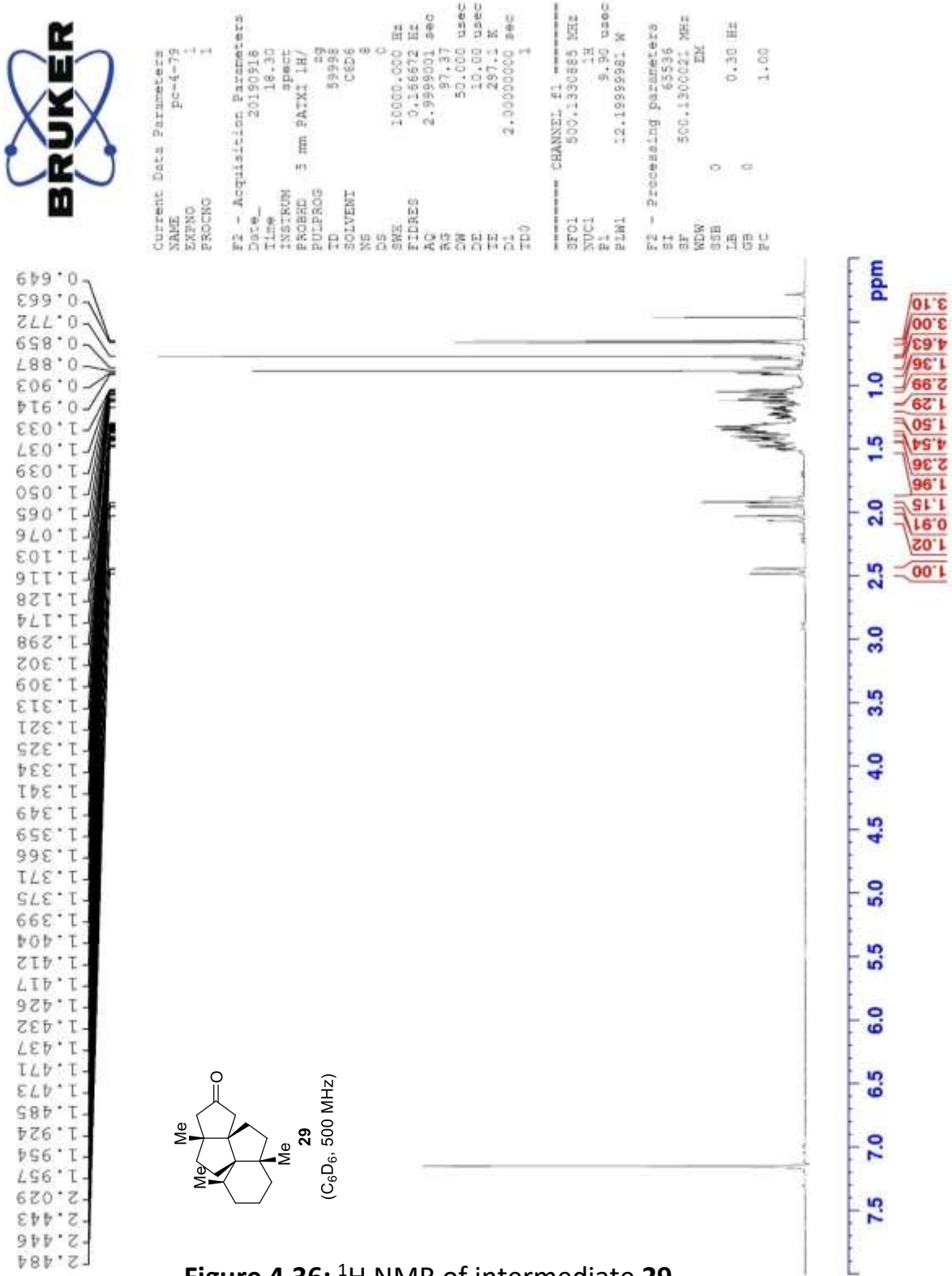


Figure 4.36: ^{1}H NMR of intermediate **29**

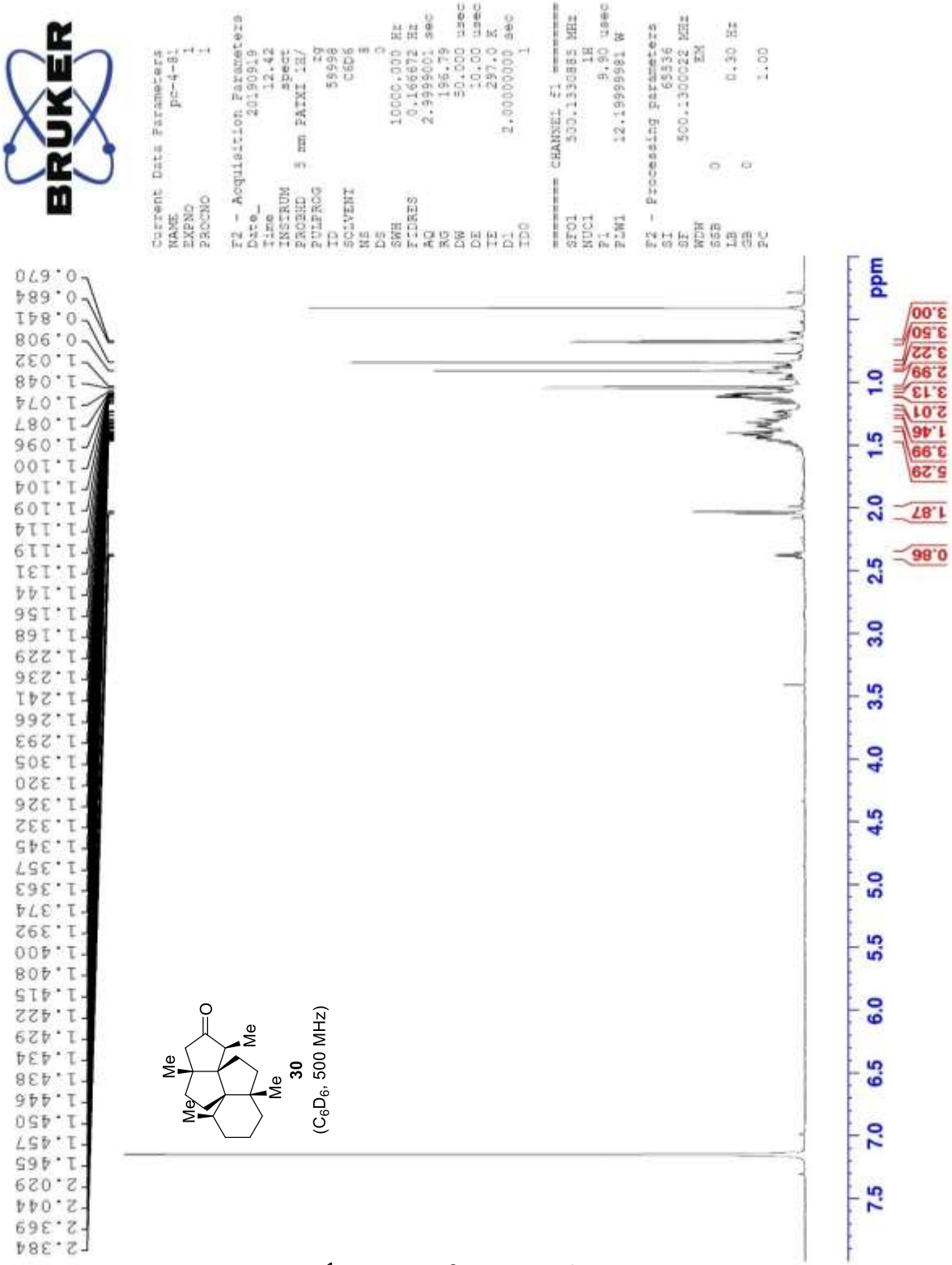


Figure 4.37: ^{1}H NMR of intermediate **30**

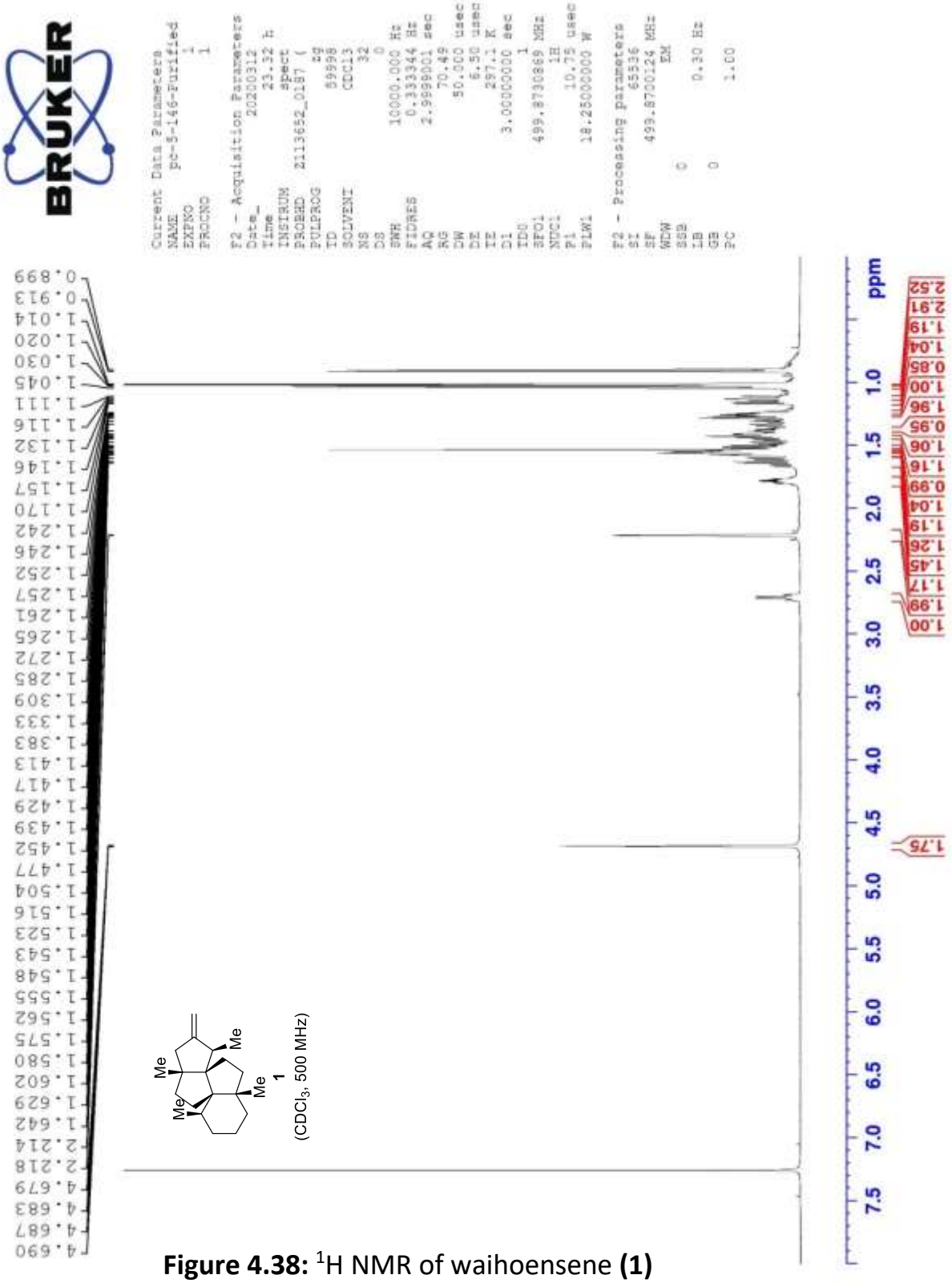


Figure 4.38: ^{1}H NMR of waihoensene **(1)**

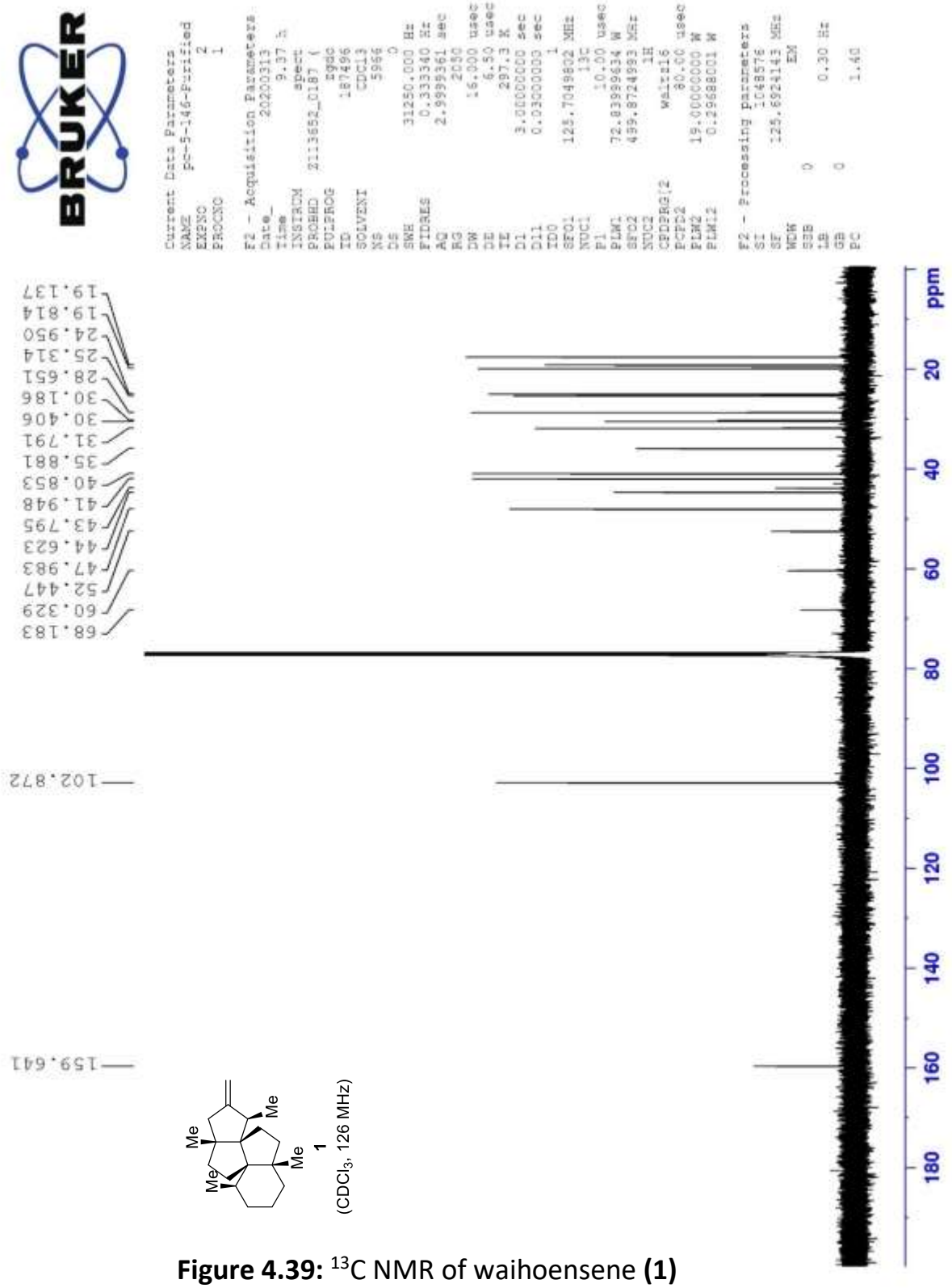


Figure 4.39: ^{13}C NMR of waihoensene **(1)**