NTNU – Trondheim
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Novel Au(I) Catalyzed Cycloaddition Reactions of Propargyl Acetals

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Declaration

I hereby declare that the presented work in this master's thesis has been conducted individually. The study has been conducted in accordance with the rules and regulation for the integrated master's degree in Industrial Chemistry and Biotechnology (Master of Science degree, 5 years) at the Norwegian University of Science and Technology. The work has been performed from January 2015 to June 2015.

Trondheim, June 18th, 2015

Sigvart Evjen

Preface

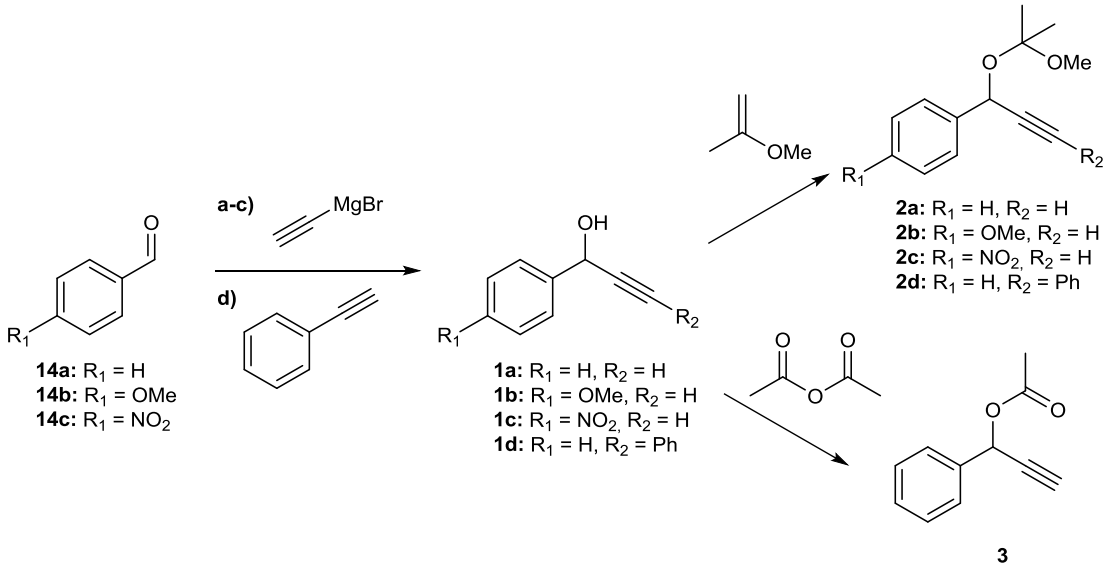
The presented work has been performed at the Department of Chemistry, Norwegian University of Science and Technology (NTNU) from January 2015 to June 2015.

I am grateful to thank my supervisor, Professor Anne Fiksdahl, for accepting me as part of her research group and giving me the opportunity to work under her tutelage. The encouragement, enthusiast and guidance along the way have truly been appreciated.

I would like to thank Alexander Asplin and Melanie Huey-Siah for the fun time spent together in the lab. Thanks go to Susana Villa Gonzalez for providing MS results. Much appreciation goes to Anton Brondz and Torun Margareta Melø for taking the time to run NMR 600 samples at St. Olavs Hospital.

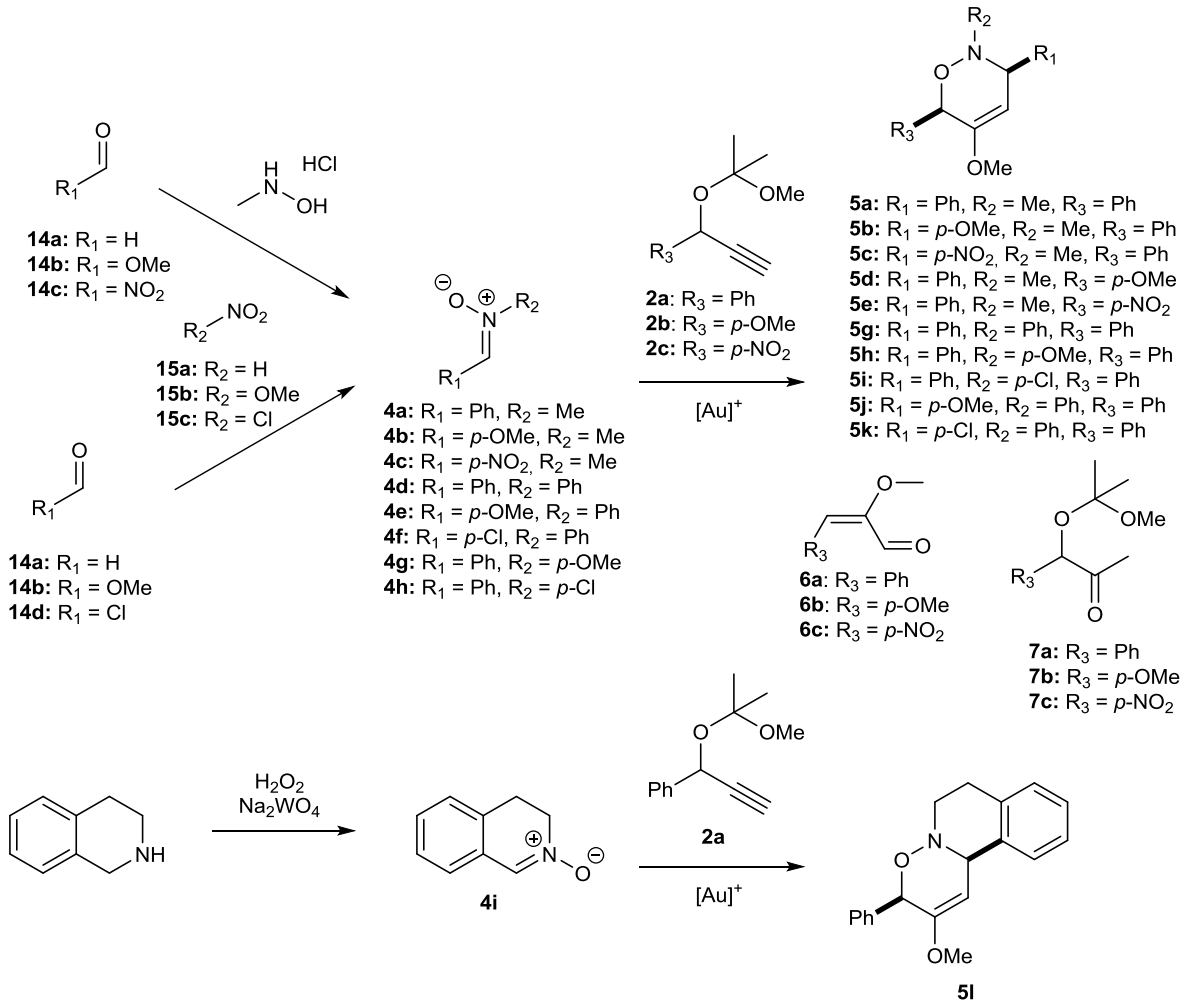
Abstract

The goal of this master's thesis was to investigate novel gold(I) catalyzed cycloaddition reactions of nitrones and azides with propargyl acetals. Screening of the reactions was performed by testing reagents with electron withdrawing and electron donating substituents. A variety of propargyl substrates were synthesized from corresponding aldehyde and alkyne building blocks. The propargyl alcohols **1a-c** (72-99 %) were afforded from benzalhydes **13a-c** through Grignard reactions, while the propargyl alcohol **1d** (92 %) was prepared from benzaldehyde **14a** and acetylide. The propargyl acetals **2a-d** (79-95 %) were obtained by a subsequent acid catalyzed reaction with methoxypropene. The corresponding propargyl ester **3** (84 %) was prepared from alcohol **1a** and acetic anhydride.

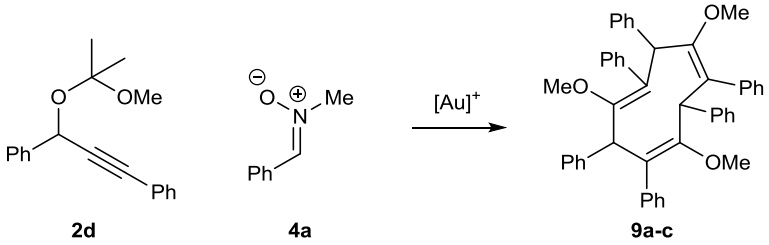


A series of relevant nitrones were prepared by different approaches. *N*-Methyl nitrones **4a-c** (65-94 %) were synthesized by condensation of benzaldehydes **14a-c** and hydroxylamine. The diarylnitrones **4d-h** (19-30 %) were prepared by one-pot synthesis from benzaldehydes **14a,b,d** and nitroaryls **15a-c**. The bicyclic nitrone **4i** (45 %) was obtained by tungsten-catalyzed oxidation of isoquinoline.

One of the novel gold(I) catalyzed [3+3] cycloaddition reactions investigated in this study gave 1,2-oxazines from propargyl acetals and nitrones with high diasteroselectivity. The oxazines **5a**,**c-d**,**g**,**i-k** (6-54 %) were obtained from propargyl acetals **2a-c** and nitrones **4a-i**. Undesired by-products **6a-c** (0.4 – 39 %) and **7a-c** (19 – 36 %) formed by oxidation and hydration, respectively, were worked up.

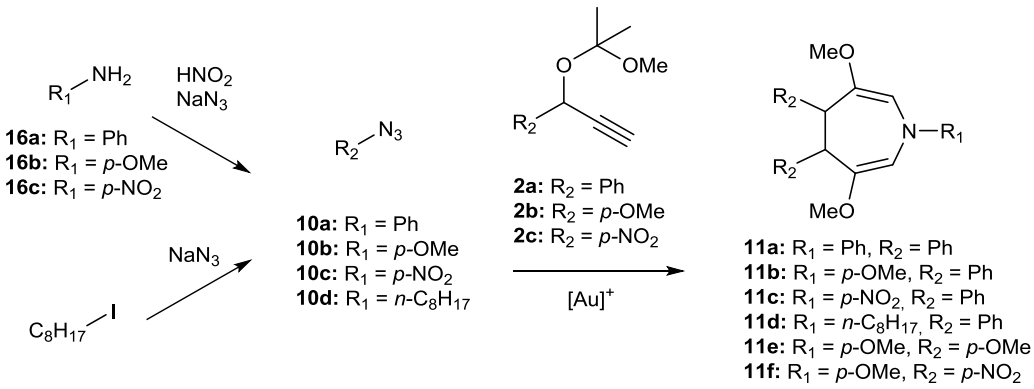


A novel 9-member ring structure **9a-c** (26 %) was obtained by gold(I) catalysis of propargyl acetal **2d** and nitrone **4a** as a trimer of acetal **2d**.

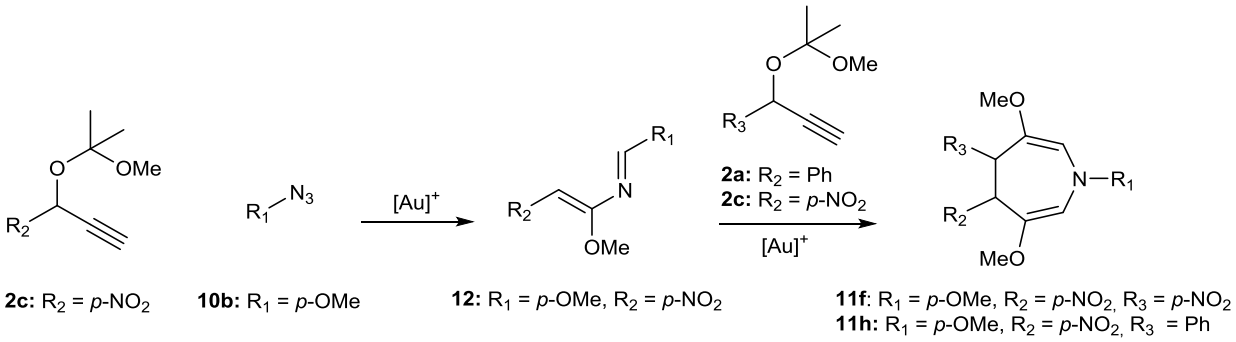


Selected azides necessary for studying cycloaddition reactions of propargyl acetals and azides were prepared. Arylazides **10a-c** (63-82 %) were prepared by forming diazonium salts from arylamines **16a-c** and reacting these with sodium azide. Alkylazide **10d** (54 %) was prepared by S_N2 reaction from iodooctane.

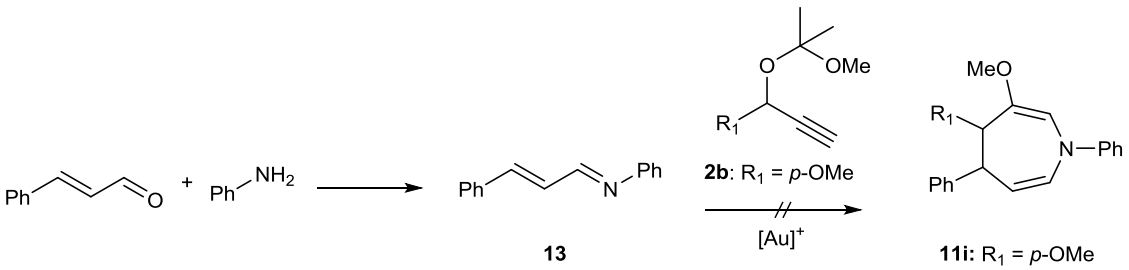
Propargyl acetals **2a-c** and azides **10a-c** were found to generate azepines **11a-c**, **e-f** (42-94 %) by gold(I) catalysis through a tandem reaction. The azepine is proposed to be formed via oxidation of propargyl acetal to imine followed by a [4+3] cycloaddition of acetal and imine. High diastereoselectivity was obtained in these reactions, but the *cis*/*trans*-configuration could not be determined.



In the reaction of propargyl acetal **2c** and azide **10b**, an intermediate imine **12** (31 %) was isolated. Reacting imine **12** with acetals **2a** and **2c** afforded azepine **11f** (52 %) and **11h** (45 %), respectively. This approach allows the synthesis of non-symmetrically substituted azepines.



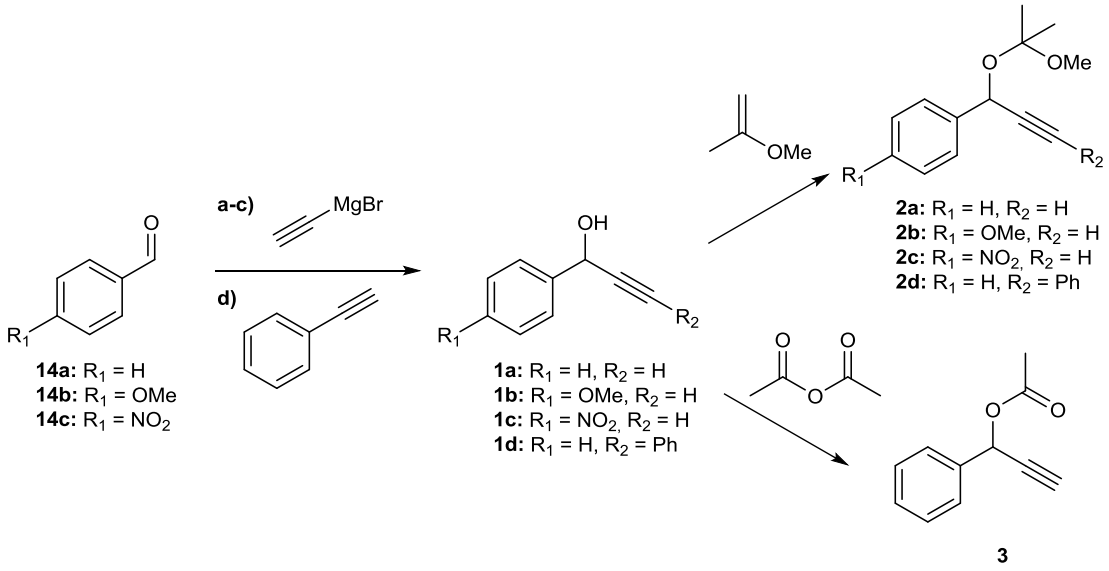
The imine **13** (69 %) was prepared in order to test gold(I) catalyzed [4+3] cycloaddition with propargyl acetal **2b**. Conversion was obtained, but no specific product was isolated.



In summary, two new methods for diastereoselective preparation of interesting oxazine and azepine heterocycles with potential biological activity were developed. Furthermore, a novel 9-membered ring synthesis by trimerization of propargyl acetal was discovered.

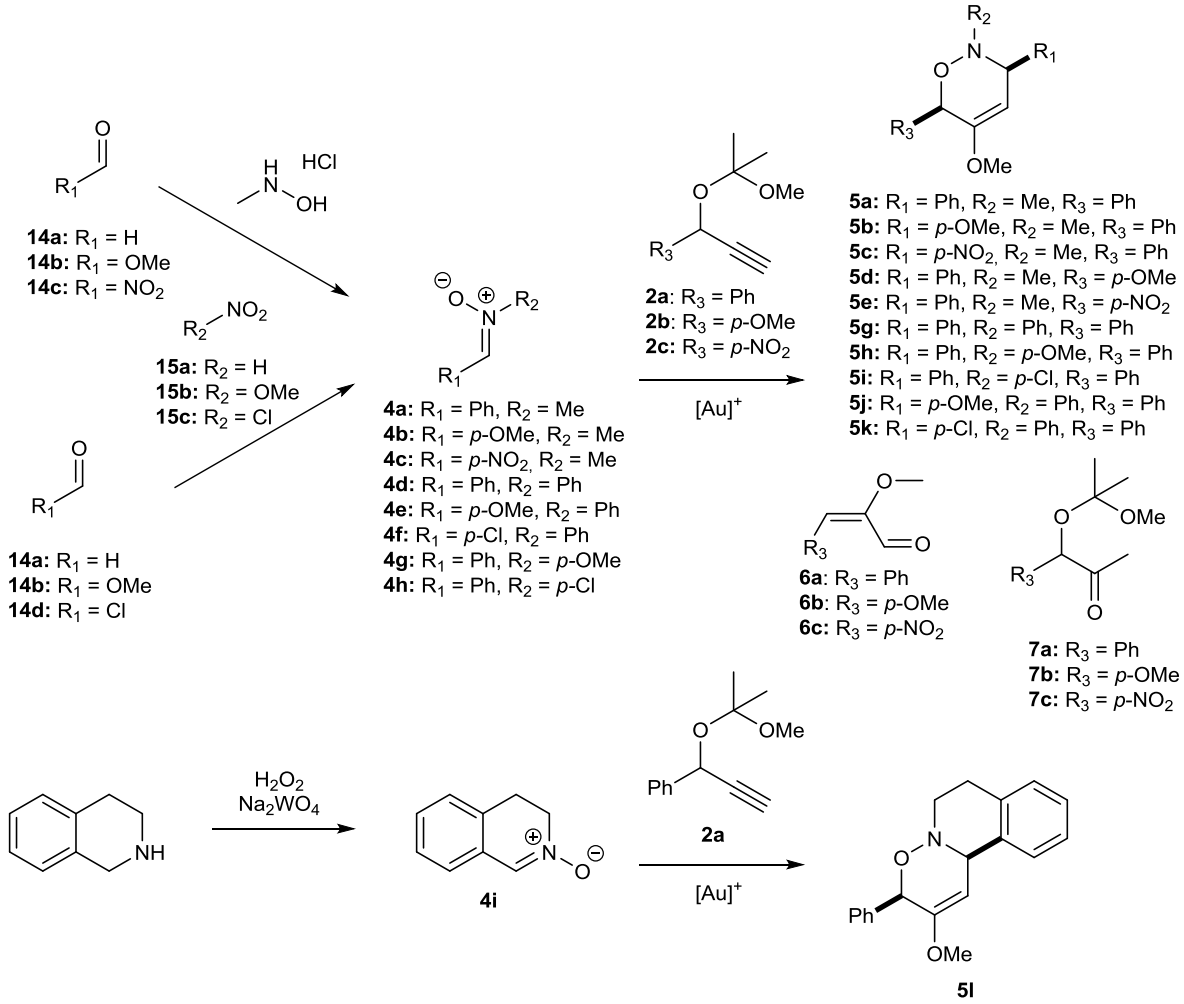
Sammendrag

Målet med denne masteroppgaven var å studere nye gull(I) katalyserte sykloaddisjonsreaksjoner mellom propargylacetaler og nitroner, samt mellom propargylacetaler og azider. En screening av reaksjonene ble utført ved å teste reagensene med elektrontiltrekkende og elektrondonnerende substituenter. Ulike propargylsubstrater ble syntetisert fra aldehyder og alkyner. Propargylalkoholene **1a-c** (72-99 %) ble lagd fra benzaldehyder **14a-c** ved Grignard reaksjoner, mens propargylalkoholen (92 %) **1d** ble framstilt fra benzaldehyd **14a** og acetylid. Propargylacetalene **2a-d** (79-95 %) ble oppnådd ved en påfølgende syrekatalysert reaksjon med metoksypropen. Den tilsvarende propargylesteren **3** (84 %) ble dannet fra alkohol **1a** og eddiksyre anhydrid.

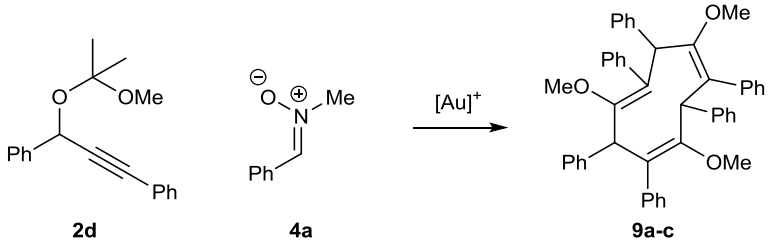


En serie av relevante nitroner ble fremstilt gjennom ulike metoder. *N*-Metylnitroner **4a-c** (64-94 %) ble fremstilt ved kondensasjon av benzaldehyder **14a-c** og hydroksylamin. Diarylnitronene **4d-h** (19-30 %) ble syntetisert ved en alt-i-ett reaksjon fra benzaldehydener **14a,b,d** og nitroaryler **15a-c**. Det bisykliske nitronet **4i** (45 %) ble lagd ved wolframkatalysert oksidasjon fra isoquinolin.

Den nye gull(I)katalyserte [3+3] sykloaddisjonreaksjonen studert i dette forsøket dannet 1,2-oksaziner fra propargylacetaler og nitroner med høy diastereoselektivitet. Oksazinene **5a**,**c-d**,**g**,**i-k** (6-54 %) ble oppnådd fra propargylacetalene **2a-c** og nitronene **4a-i**. De uønskede biproduktene **6a-c** (0.4 – 39 %) og **7a-c** (19 – 36 %), som ble dannet ved henholdsvis oksidasjon og hydratisering, ble opparbeidet.

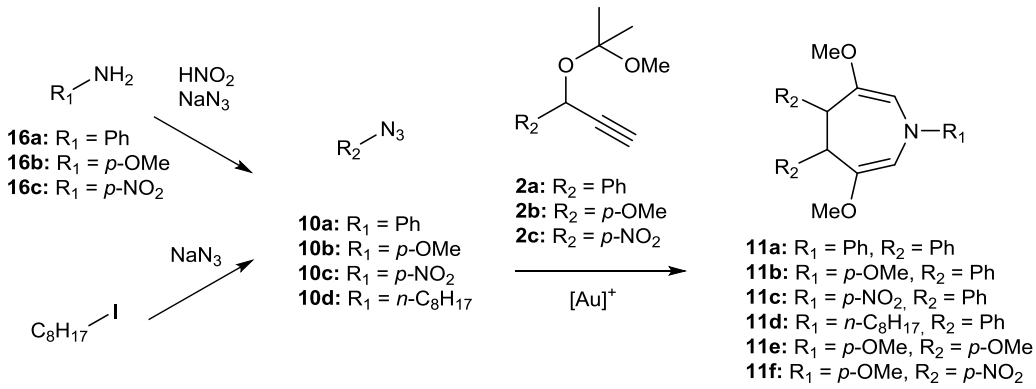


En ny 9-ringstruktur **9a-c** (26 %) ble oppnådd ved gull(I)katalyse av propargyl acetal **2d** og nitron **4a** som en trimer av acetal **2d**.

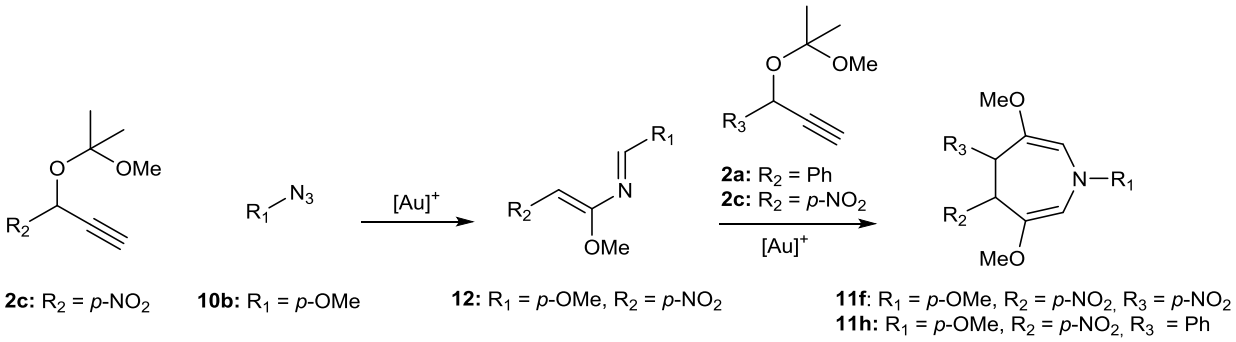


Utvalgte azides nødvendig for å studere sykloaddisjonsreaksjoner av propargylacetaler og azider ble fremstilt. Arylazider **10a-c** (63 – 82 %) ble syntetisert ved dannelse av diazoniumsalter fra arylaminene **16a-c** og reaksjon av disse med natriumazid. Alkylazid **10d** (54 %) ble dannet via S_N2 reaksjon av jodoktan.

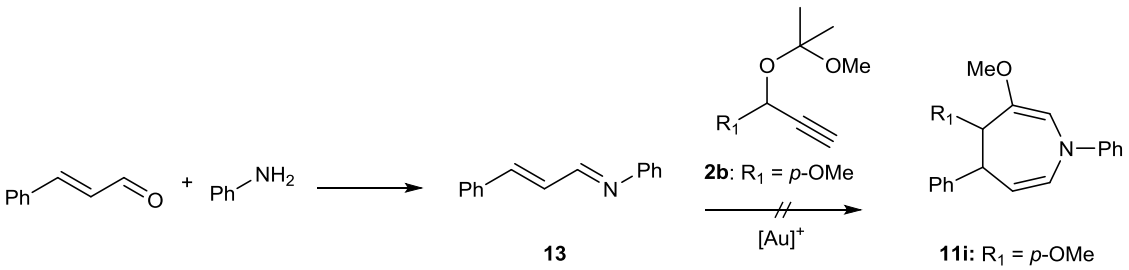
Propargylacetalene **2a-c** og azidene **10a-c** ble funnet å danne azepinene **11a-c**, **e-f** (42 – 94 %) ved gull(I)katalyse gjennom en tandemreaksjon. Azepinene ble antatt oppnådd via oksidasjon av propargyl acetal til imine, fulgt av en [4+3] sykloaddsjon av acetal og imine. Høy diasteroselektivitet ble oppnådd for reaksjonen, men *cis*/*trans*-konfigurasjonen kunne ikke bli bestemt.



I reaksjonen mellom propargylacetal **2c** og azid **11b**, ble et imin**intermediat** **12** (31 %) isolert. Ved å reagere imine **12** med acetalene **2a** og **2c** ble henholdsvis azepin **11f** (52 %) og **11h** (45 %) fremstilt. Denne metoden muliggjør framstillingen av ikke-symmetriske azepiner.



Iminet **13** (69 %) ble dannet for å teste gull(I)katalysert sykloaddisjon med propargylacetal **2b**. Omsetning ble oppnådd, men produkt ble ikke isolert.



Oppsummert ble nye diastereoselektive fremstillingsmetoder av interresante oksazin- og azepinheterosykler med potensiell biologisk aktivitet utviklet. I tillegg ble det oppdaget en ny 9-ringssyntese via trimerisering av propargyl acetal.

Symbols and Abbreviations

Ac	Acetyl
Ar	aromatic
as	asymmetric (IR)
br	broad
$CDCl_3$	deuterated chloroform
cm^{-1}	wave number, reciprocal centimeter
conc.	concentrated
COSY	Correlated Spectroscopy
δ	chemical shift [ppm]
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
DCM	Dichloromethane
d	doublet (NMR)
dd	doublet of doublets (NMR)
ddd	doublet of doublet of doublet (NMR)
DMAP	4-Dimethylaminopyridine
dr	diastereomeric ratio
dt	doublet of triplet (NMR)
eq.	equivalent
et al.	et alia (and others)
Et_3N	Triethylamine
EtOAc	Ethyl acetate
EVE	ethyl vinyl ether
HMBC	Heteronuclear Multi Bond Correlation
HR	High Resolution (MS)
HSQC	Heteronuclear Single Quantum Coherence
Hz	Hertz
IR	Infrared Spectroscopy
J	coupling constant [Hz]
L	Ligand
M^+	Molecular ion
m	multiplett (NMR)
m	medium (IR)
Me	Methyl
MHz	megahertz
min	minutes
mL	millilitre
mmol	millimol
MOP	2-Methoxypropene
MS	Mass Spectroscopy
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Effect Spectroscopy
Nu	Nucleophile
obsd	observed
oop	out of plane vibration (IR)
o.n.	overnight
p	*para*
Ph	Phenyl

ppm	parts per million
PPTS	pyridium *p*-toluenesulfonate
quint	quintet (NMR)
R_f	Retention factor (TLC)
rx.	reaction
s	singlet (NMR)
s	strong (IR)
st	stretch (IR)
sy	symmetric (IR)
t	triplet (NMR)
t-Bu	*tert*-Butyl
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TsOH	*p*-Toluenesulfonic acid
vs	very strong (IR)
w	weak (IR)

Contents

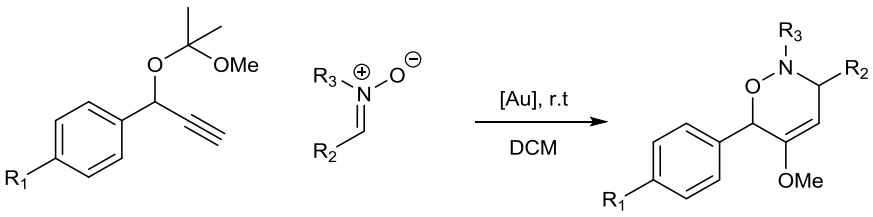
1. Introduction

Organometallic chemistry is the study of chemical compounds containing one or more bonds between a metal and a carbon.[1] In 1760, Louis Claude Cadet de Gassicourt used cobalt salts containing arsenic to produce cobalt based ink, presenting the first documented application of metals in organic chemistry.[2] Since then the a variety of metals in organometallic chemistry has been studied.[3]

Over the course of the last couple of decades gold catalysis has gone from obscurity to fame through the discovery of novel gold catalyzed reactions. The major fields of gold catalysis are homogeneous and heterogeneous catalysis, where the former is the currently most active area.[4] The research group of Anne Fiksdahl has over the last few years been active in the field of homogeneous gold catalysis. At present there is no commercial use of gold catalysis, but homogeneous gold catalysis is used in an increasing number of total syntheses.[5] The study of gold(I) catalyzed reactions is the main target of the present research. Gold catalysts readily activate C-C multiple bonds, such as alkynes and alkenes, for nucleophilic attack,[6] whereupon most gold catalysis is based, whether it is hydrogenation,[7] heterofunctionalization[8] or cycloaddition reaction.[9] The Fiksdahl group has performed comparative studies of the reactivity of propargyl esters and propargyl acetals with unsaturated compounds through gold(I) catalysis.[10] Propargyl esters treated with vinylic compounds undergo [2+1] cycloaddition reactions to form cyclopropane units,[10a] whereas acetals react with vinylic substrates through a [3+2] cycloaddition mechanism.[10b] Propargyl acetals have proven to be highly reactive compared to their ester counterparts and exhibit high potential for the development of new cycloaddition reactions.[10] Thus far the Fiksdahl group has reported tandem cyclization reactions between two propargyl acetal units and olefinic esters.[11] The reaction between propargyl acetals and diarylic imines gives a [5+2] cycloaddition to 7-membered benzazepines products.[12]

1.1 Aim of project

The main target of the present work has been to investigate novel gold(I) catalyzed [3+3] cycloaddition reactions occurring between propargyl acetal and nitrones, which were shown to afford 1,2-oxazines in the project leading up this master's thesis, Scheme 1.1.[13] Nitrones are 1,3-dipolar compounds, where the electrons are delocalized over three atoms. Oxazines have been the object of interest for the past three decades as they constitute an important class of natural and non-natural products and show useful biological activity.[14] The current approach represents a novel reaction pathway for the synthesis of 1,2-oxazines, presented in Scheme 1.1.



Scheme 1.1: Gold(I) catalyzed [3+3] cycloadditon to oxazine

The second goal of the project was to study the scope of reactivity between propargyl acetals and azides. The hypothesis was that acetals and azides could afford triazines by gold(I) catalysis because azides are 1,3-dipoles.

2. Theory

In the following section, a brief background of relevant topics for this thesis is presented. First, an overview of theory regarding gold catalysis is provided, followed by a presentation of selected gold(I) catalyzed reactions. Next the different functional groups relevant for the present study are described. Preparation of propargyl acetals, propargyl esters and imines are presented. A brief introduction of the NMR-methods used for structural elucidation is given and finally X-ray powder diffraction is introduced.

2.1 Organometallic catalysis

Transition metals facilitate many reactions that are not possible under mild conditions because transition metals can change the electrophilic nature of compounds. They are able to coordinate to almost all functional groups and have a strong effect on reaction rates. Transition metals are generally characterized by having two or more stable oxidation states and this ability plays an important role in catalysis. To allow the metals to readily switch between these states during reactions, organometallic complexes are used in organic synthesis.[1]

Organometallic complexes consist of a metal surrounded by ligands (L). In metal-ligand complexes, the energy of the metal-d shell is lower than the s- and p-shells. As a result, the d-shells are filled before the s- and p- shells.[1] Saturated ligands have saturated "sp^n"-hybrid orbitals and act as σ-donors to the empty "*dsp*"-hybrid orbital of the metal. Typical ligands with this nature are R_3P, R_3N and H, and these ligands increase the electron density of the metal. Unsaturated ligands, such as alkynes and alkenes, have anti-bonding π*-orbitals. They form σ-donor bonds through overlapping between their filled π-orbital and the empty "*dsp*"-hybrid orbital of the metal as illustrated in Figure 2.1a. In addition, the occupied metal *d*-orbitals can overlap with the anti-bonding π*-orbitals of the ligand shown in Figure 2.1b.[1]

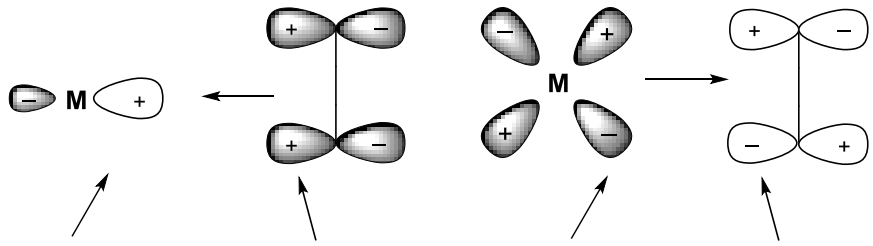


Figure 2.1: Orbitals forming σ-donor bonds between ligands and transition metals

The reasons for the bond strength observed between transition metals and unsaturated ligands are the small gap in energy between the d-orbitals and the anti-bonding π*-orbitals as well as their symmetry, illustrated in Figure 2.2.[1]

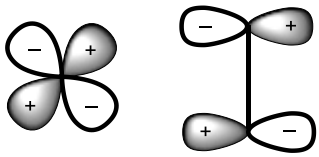


Figure 2.2: Symmetry of *d*-orbitals (left) and π*-orbitals (right)

The two types of π back-bonding modes between a metal and an unsaturated organic ligand are illustrated in Figure 2.3. These modes are longitudinal and perpendicular, where carbon monoxide and isonitriles are examples of the former and alkenes are examples of the latter. For electrophilic metals, alkenes act primarily as σ-donor ligands and the C=C bond length remains practically unaltered compared to free alkenes. Electron rich metals increase the C=C bond length to such an extent through back-bonding that the alkene hybridization and bond length replicate alkanes. In this case, the system can be considered to act as a metalocyclopropane.[3]

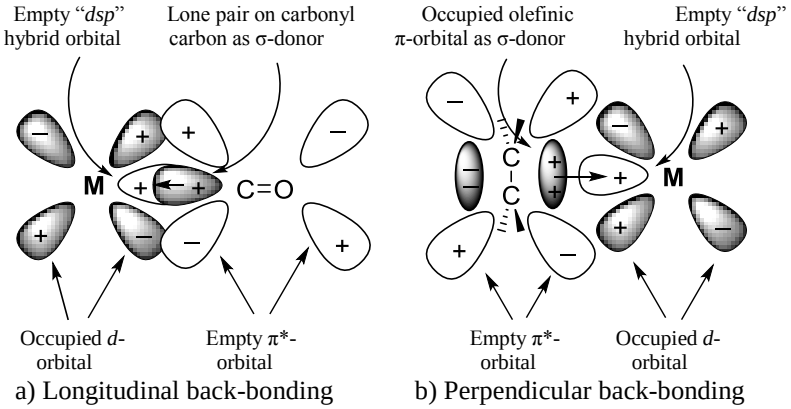
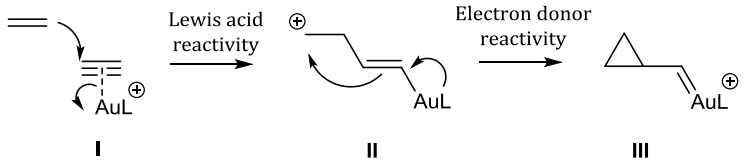


Figure 2.3 The Denwar-Chatt-Duncanson model

2.2 Gold chemistry

Gold has been discovered to possess several properties beneficial in organic synthesis. The oxidation states of gold catalysts are primarily +1 and +3. Unlike many other metals utilized in organometallic catalysis, Au(I) catalysts are insensitive to air due to the high oxidation potential from Au(I) to Au(III). Au(I) expresses an atypical reaction mechanism by manipulation of oxidation states throughout the catalytic cycle, where Au(I) does not change oxidation state as is common in transition metal catalysis. As an example the reaction of a Au(I)-alkyne complex with an alkene, **I**, proceeds through the Lewis acid reactivity of Au(I) to vinyl-Au complex **II**, followed by electron donor reactivity to gold carbenoid **III** as illustrated in Scheme 2.1. This Lewis acid/electron donor dual behavior has been highlighted in various transformations in which gold carbene intermediates have been invoked.[15]



Scheme 2.1: Lewis acid/electron donor dual behavior of gold(I)

Because gold has low oxophilic properties, it tolerates water, alcohols and oxygen better than most Lewis acids. Many reactions catalyzed by gold are found to have well controlled product selectivity. This is considered to be because of gold carbenoid intermediates formed during the reactions.[16] Gold carbenoids are double bond complexes between carbon and gold, which can be stabilized through resonance in the presence of a heteroatom such as oxygen.[3] The product selectivity is believed to be well controlled because the Au-C bond prefers protodeauration over *β*-hydride elimination. As the result of these abilities, gold catalysts can be used to form complex molecules from simple starting materials.[16]

The gold catalyst coordinates with C-C multiple bonds of alkynes, alkenes and allenes,[17] activating the bond for a nucleophilic attack.[18] Alkynes are good σ-donors and weaker π-acceptors towards gold, giving gold-alkyne complexes a strong electrophilic character. Studies have shown that there is a large difference in bond energy between alkyne π to gold σ-donor bonding and gold to alkyne π*-back-bonding, and this could be the reason why Au(I) catalysts exhibit a stronger alkyne activation compared to other metals.[16] This strong affinity towards alkynes combined with the dual behavior of Au(I) has led to great interest in using propargylic substrates in gold catalysis.[10a, 19]

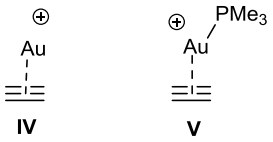


Figure 2.4: Au(I)-alkyne complexes

Studies report that the Au(I)-alkyne complexes **IV** and **V** shown in Figure 2.4 are readily formed.[18] These complexes are activated towards a nucleophilic attack through an *anti*-addition to give the vinyl-Au complex analogous to **II**, Scheme 2.1, in cases where the nucleophile is weakly coordinating towards gold. Nucleophiles experiencing strong coordination towards gold prior to nucleophilic attack prefer *syn*-addition.[18]

Based on the reaction, various gold-ligands can be used in order to tune the reaction towards desired products and to control enantioselectivity.[17] The most common ligands are tertiary phosphines, **VI** and **VII** presented in Figure 2.5 are two such complexes.[17] NHC type ligands such as **VIII** and **IX** are also commonly utilized as ligands in gold catalysis.[18]

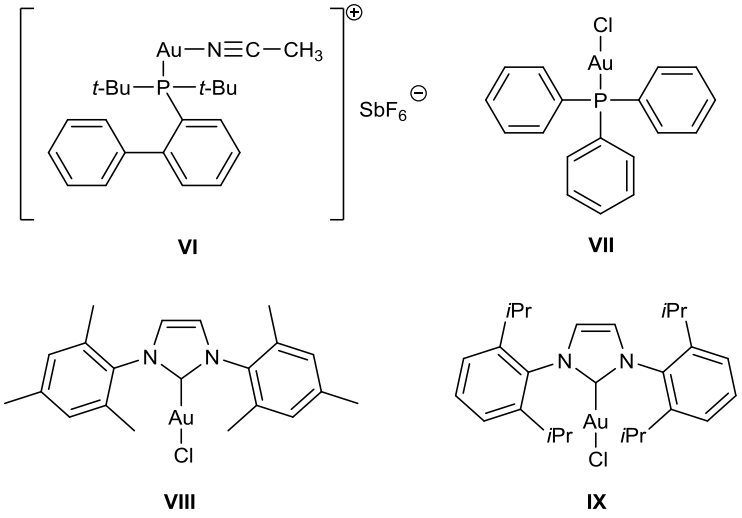
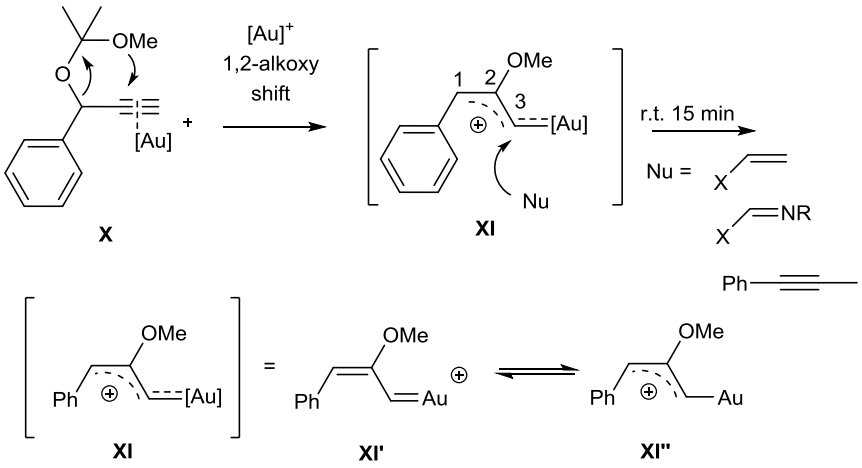


Figure 2.5: Gold(I) catalysts

2.3 Gold(I) catalyzed cycloadditions of propargyl acetals

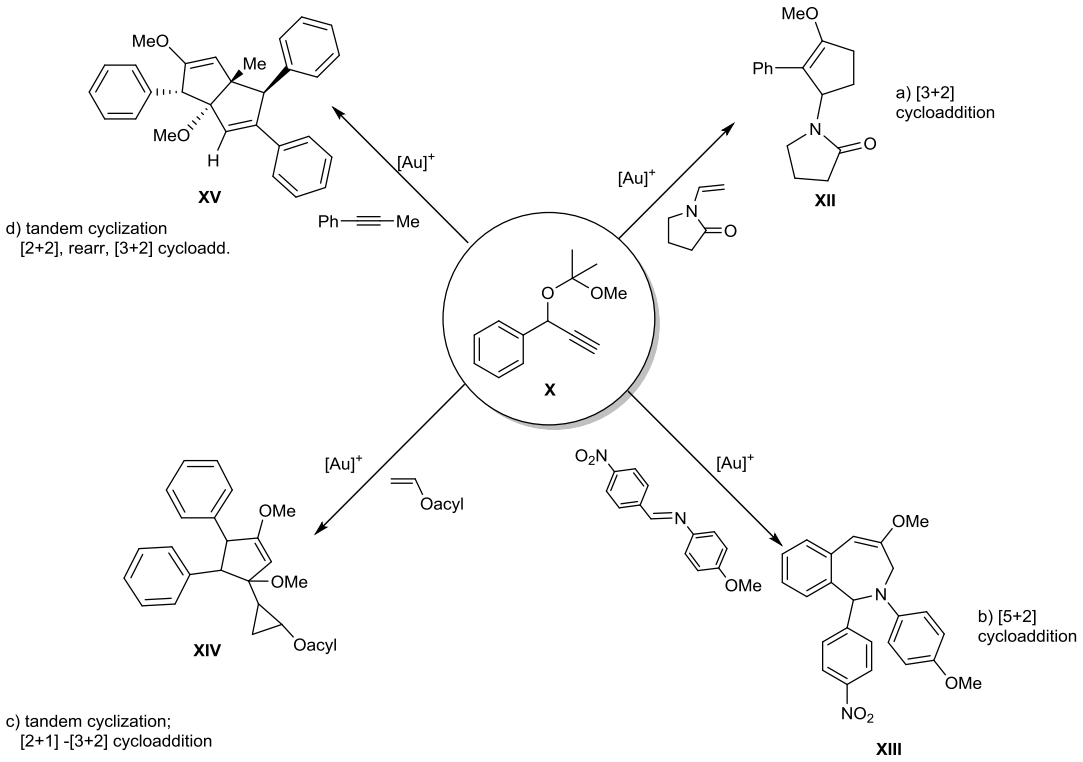
The Fiksdahl group has carried out a comparative study on chemoselective gold(I) catalyzed cycloadditions of propargyl acetals and multiple bond substrates.[10] These investigations have demonstrated that propargyl acetals, relative to propargyl esters, form highly reactive propargyl-gold(I) carbenoid intermediates, followed by different novel cyclization pathways through reaction with multiple bond reactants. The mechanism generally observed for these reactions is presented in Scheme 2.2.[10b]



Scheme 2.2: General mechanism for gold(I) catalysis of propargyl acetals

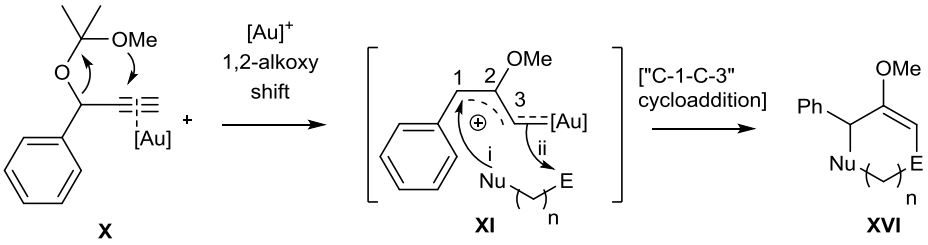
Analogue to general gold(I) catalysis, the gold(I) catalyst coordinates to alkyne **X**. An intramolecular nucleophilic attack, giving a 1,2-alkoxy shift, yields a gold(I) carbenoid intermediate **XI**. This intermediate contains a highly delocalized positive charge, represented by the resonance structure between an allylic cation-Au **XI'** and Au(I) carbenoid **XI''**, as the result of the Au(I) dual behavior. The intermediate **XI** is readily accessible to nucleophilic attack by unsaturated electrophiles at the C-3 position. Subsequent ring closure at the "C-1" position through the gold carbenoid

electron donating ability, Scheme 2.1, affords a variety of cycloaddition products.[10b, 11-12, 20] Novel cyclization reactions studied by the Fiksdahl group are presented in Scheme 2.3.[10b, 11-12, 20]



Scheme 2.3: Reactions studied by the Fiksdahl group

As shown in Scheme 2.3 propargyl acetal **X** undergoes [3+2] cycloaddition with *N*-vinyl lactams to afford cyclopentene **XII**.[10b] Propargyl acetal **IX** and benzaldimines give [5+2] cycloaddition to yield benz[c]azepine **XIII**,[12] while vinylic O-acyls and alkynes give tandem cyclization through, respectively, [2+1]-[3+2] cycloadditions to cyclopropylcyclopentene **XIV**[11] and a [2+2] cycloaddition followed by rearrangement and a [3+2] cycloaddition to yield the dicyclopentene **XV**[20]. These reactions are proposed to pass through the propargyl-gold(I) carbenoid intermediate **XI** with nucleophilic attack on C-3 as shown in Scheme 2.2.



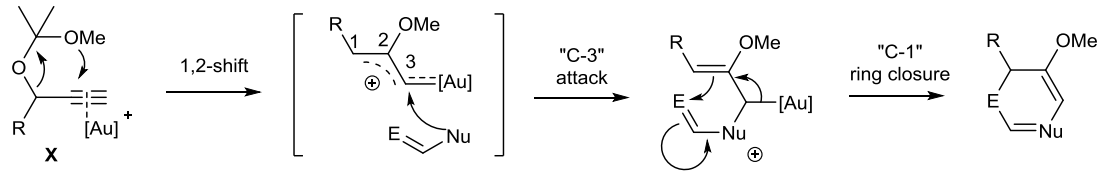
Scheme 2.4: General mechanism for gold(I) catalyzed "C-1-C-3" cycloaddition

Nucleophilic attack on "C-1" has also been observed as in the reaction to **XIV**, Scheme 2.3, giving "C-1-C-3" cycloaddition products **XVI** as shown in Scheme 2.4.[11] The nucleophilic part of the dipolarophile performs a "C-1" attack, step i, followed by C-3 attack of the gold(I) carbenoid on the electrophilic pole, step ii. In

contrast to the "C-3-C-1" reaction in Scheme 2.2, the opposite regioselectivity was observed due to the nucleophile attacking at the electrophilic "C-3" position of the gold carbenoid complex **X**. This is illustrated by the opposite regioselectivity of **XII**, Scheme 2.3, formed through a "C-3-C-1" cyclization,[10b] and **XIV**, Scheme 2.3, obtained through a "C-1-C-3" mechanism.[11] In the reaction to **XIV**, this is believed to be the result of steric hindrance. A similar "C-1-C-3" reaction order was reported for [3+2] cycloaddition reactions of non-terminal propargyl acetals connected to electron-withdrawing group, with aldehydes.[21]

2.4 [3+3] Cycloaddition reactions

Formal [3+3] cycloadditions reactions form 6-membered cyclic structures. Such reactions are possible by combining two 1,3-dipoles. 1,3-Dipoles are organic molecules with delocalized electrons over three atoms, which can be represented by either allyl-type or propargyl/allenyl-type zwitterionic octet/sextet structures. The allyl-type has a bent geometry whereas the propargyl/allenyl-type is linear. In both types four electrons are shared in a π-system covering three atoms.[22] Nitrones are allyl-type 1,3-dipoles and dimerize through [3+3] cycloaddition at elevated temperatures.[23] The Au(I) carbenoid complex **XI**, Scheme 2.2, has the ability to act as an all-carbon 1,3-dipole to give formal cyclization reactions.[10b, 11-12, 20-21, 24] Propargyl acetals might therefore react with other 1,3-dipoles through a formal [3+3] cycloaddition reaction. [3+3] Cycloadditions are uncommon reactions and have currently a very limited application. Transition metal catalysis is required for most [3+3] cycloaddition reactions to occur.[25] Propargyl esters have been reported to undergo gold(III) catalyzed [3+3] cycloaddition reactions with azomethine ylides.[26] A mechanism used to predict the regioselectivity of a "C-3-C-1" formal Au(I) catalyzed [3+3] cycloaddition of propargyl acetal **X** with an 1,3-dipole is presented in Scheme 2.6. The reaction follows the standard "C-3-C-1" cycloaddition mechanism in Scheme 2.2.



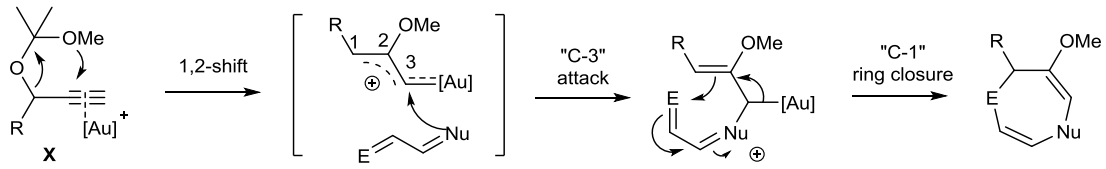
Scheme 2.6: [3+3] cycloaddition following the "C-3-C-1" cycloaddition mechanism

2.5 [4+3] Cycloaddition reactions

Unlike the less addressed [3+3] cycloaddition reactions, [4+3] cycloaddition reactions have been studied to a much larger extent. Electronically, the [4+3] cycloaddition is related to the [4+2] Diels-Alder reaction and instead of an alkene, a dienophile allyl cation participates as the reactive dienophile for the formation of a seven member ring.[27] For this purpose, oxallyl cations have shown to be reactive dienophiles in the synthesis of seven member rings and are often used in natural compound synthesis.[28]

Toste et al.[29] have reported a gold(III) catalyzed formal [4+3] cycloaddition reaction to azepine from propargyl ester with conjugated imines which was proposed

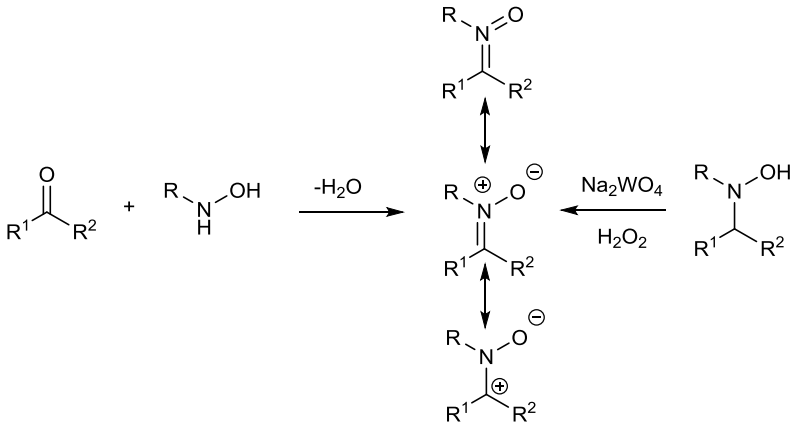
to pass through a step-wise mechanism analogue to the mechanism presented in Scheme 2.7. This is one of few cases where dienophilic 1,3-dipoles have been reported. By comparison, reacting nitrones with dienes by heating affords [3+2] cycloaddition reactions,[30] whereas azides form pyrrolines in intramolecular reaction with dienes.[31] Dienes and imine analogues have been shown to be reactive towards carbenes, as both vinylcarbenoids[32] and alkyne Fischer type vinyl carbenes[33] have been reported to form [4+3] cycloaddition reactions with dienes and imines, respectively. The suggested reaction mechanism of a formal [4+3] cycloaddition reaction between propargyl acetal **X** and a diene following "C-3-C-1" cycloaddition pathway is illustrated in Scheme 2.8.



Scheme 2.7: [4+3] cycloaddition following "C-3-C-1" cycloaddition mechanism

2.6 Nitrones

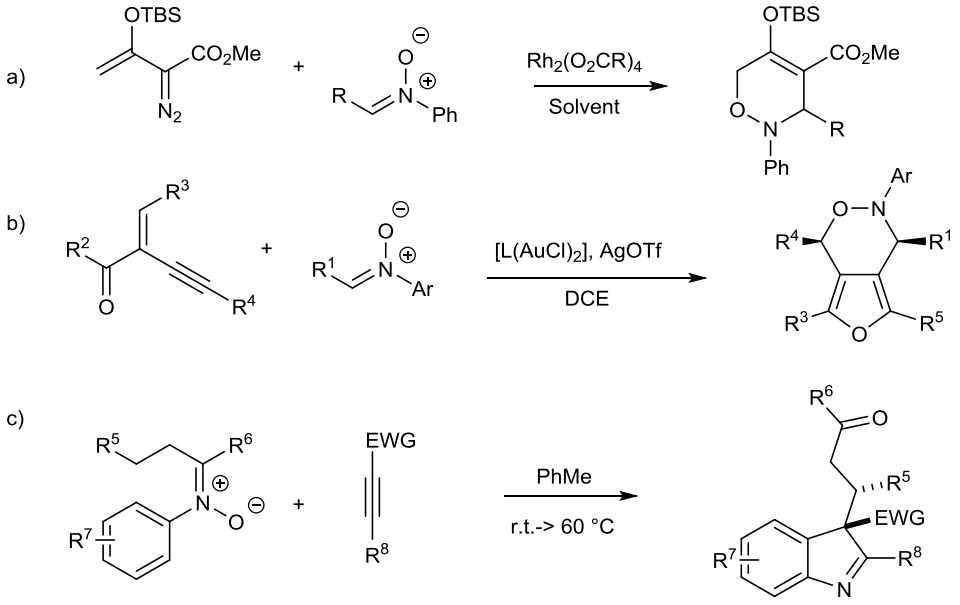
Nitrones are *N*-oxides of imines and were discovered more than a century ago.[34] They are commonly utilized for synthesizing heterocycles containing both oxygen and nitrogen. Nitrones express a strong affinity towards cycloadditions because of the nucleophilic nature of the oxide and electrophilicity of the imine. Preparation of nitrones is usually conducted by the oxidation of hydroxylamines[35] or condensation of carbonyl compounds with monosubstituted hydroxylamines.[36] Scheme 2.8 shows nitrone preparation by condensation of carbonyls and hydroxylamines and by oxidation of hydroxylamines, with proposed resonance structures of nitrones.



Scheme 2.8: Formation of nitrones and nitrone resonances

The most studied reactions of nitrones are [3+2] cycloadditions with alkenes and alkynes to form 5-member heterocycles.[34, 37] Nitrone acts as the 1,3-dipole and the alkene or alkyne as the dipolarophile. Due to the electrophilicity of the C=N bonds. nitrones has been used in reactions with nucleophilic reagents such as metal hydrides and organometallic reagents.[38] Other transformations involving nitrones have been

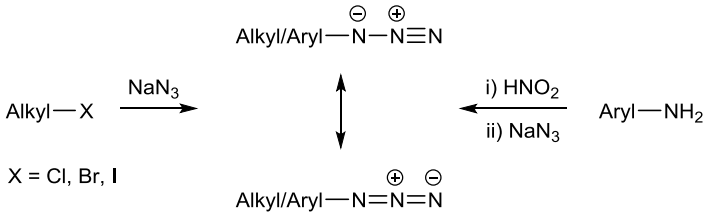
reported.[39] Recent discoveries include [3+3] cycloaddition with vinylcarbenes to give 3,6-dihydro-1,2-oxazines, seen in Scheme 2.9a,[25b] tandem [3+3] cycloaddition to give furo[3,4-*d*]-[1,2]-oxazine, shown in Scheme 2.9b,[40] and reaction of α,β-unsaturated *N*-aryl ketonitrones and activated alkynes to afford C3-quaternary indolenines, illustrated in Scheme 2.9c.[41]



Scheme 2.9: Recently discovered nitrone transformations

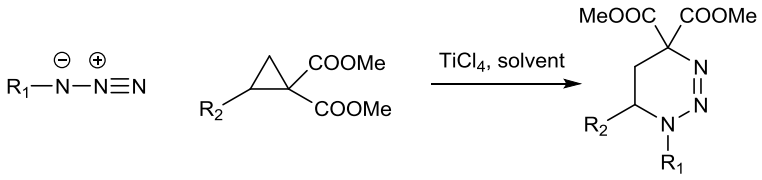
2.7 Azides

Azides are allenyl-type zwitterions and are notorious for their explosive character. Alkyl azides are usually prepared by S_N2 reactions of alkyl halides with inorganic azide. Aryl azides are prepared by displacement of the appropriate diazonoium salt with sodium azide.[42] Scheme 2.10 illustrates the preparation of organic azides as well as their resonance structures.



Scheme 2.10: Formation of azide and azide resonances

Despite their sometimes unfavourable stability, azides have proven to be important in Click Chemistry, as the Huisgen [3+2] cycloaddition reaction of azides and alkynes is one of the most famous Click reactions.[43] When not the target of a cycloaddition reaction, azides can be used for rearrangement reactions such as the Curtius rearrangement[44] and Schmidt reaction[45]. One [3+3] cycloaddition reaction of azides has been reported, by a titanium chloride catalyzed reaction with cyclopropane diesters, shown in Scheme 2.11.[46]



Scheme 2.11: Titanium chloride catalyzed [3+3] cycloaddition of azide and cyclopropane diester

2.8 Oxazines

Unsaturated heterocyclic 6-member rings containing oxygen and nitrogen are called oxazines.[47] Three isomers exist depending on the relative positions of the heteroatoms, giving the 1,2-, 1,3- and 1,4 oxazines illustrated in Figure 2.4, which are the O-analogues of the corresponding isomeric diazines.[48]

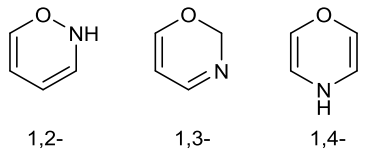
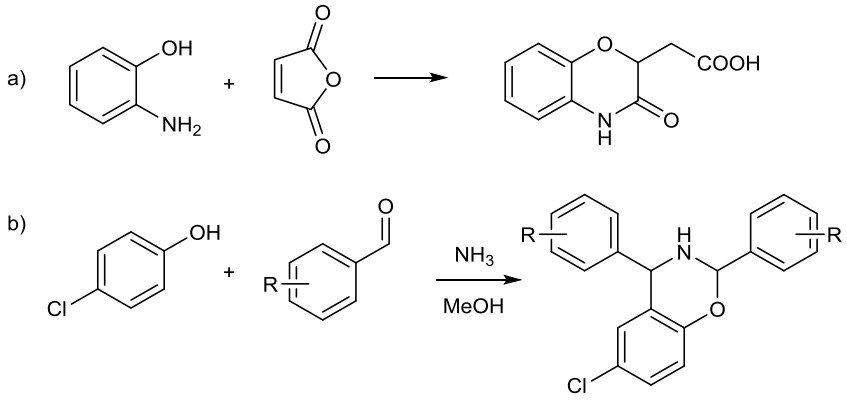


Figure 2.4: 1,2-,1,3- and 1,4-oxazines

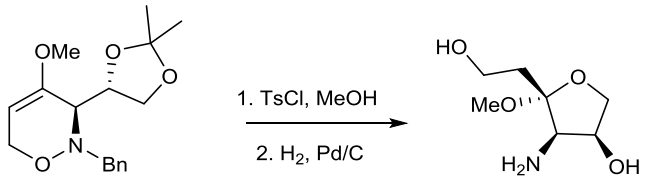
The term oxazine is derived from the oxygen (oxa-) and nitrogen (aza-) present in the unsaturated 6-member ring (-ine) and the relative positions of the atoms are indicated by numbers.[48] Depending on the positions of the heteroatoms and number of double bonds, a variety of synthesis pathways have been found to form oxazines.[48] A couple of preparations for 1,2-oxazines were illustrated in Scheme 2.9a and 2.9b. Preparation of 1,3-oxazine[49] and 1,4-oxazine[50] are shown in respectively Scheme 2.12a and 2.12b, respectively.



Scheme 2.12: Preparation of 1,3-oxazine and 1,4-oxazine applied in biological studies

Studies suggest that 1,4-oxazines have potential use as antitubercular, antibacterial and antifungal agents,[49] while 1,3-oxazines have already been proven to exhibit these properties in several studies of different compounds.[51] 1,2-Oxazines derivatives are

reported as good mglur1 antagonists.[52] Reductive ring opening of 1,2-oxazines have been used in the synthesis of amino sugar mimetics.[53] One such application is the synthesis of dideoxyamino sugar derivatives, illustrated in Scheme 2.13.[53]



Scheme 2.13: Synthesis of dideoxyamino derivative from 1,2-oxazine

2.9 Triazines

As the case for oxazines, triazines are six member heteroaromatic rings, but instead of containing one oxygen and nitrogen, they contain three nitrogens. Depending on the positions of the nitrogens, three different isomers are possible, as depicted in Figure 2.5.

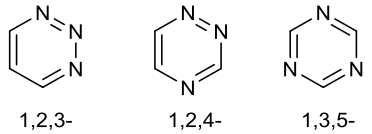


Figure 2.5: 1,2,3-, 1,2,4- and 1,3,5-triazines

The term triazine is derived from the three (tri-) nitrogens (aza-) in the six member ring (-ine) and as for the oxazine their relative positions are represented by numbers. The different triazines are prepared by different procedures. The 1,3,5-isomere is readily prepared by Pinner triazine synethesis,[54] whereas the Bamberger triazine synthesis affords 1,2,4-triazines.[55] Formation of 1,2,3-triazines often require more specialized methods, such as reacting a diazonium salt with an amine and achieving ring closure by intramolecular cyclization with a neighboring ester moiety.[56] Various synthetic analogues of 1,2,3-triazines have been synthesized, some of which have shown excellent pharmacological activity.[57] One such pharmacological active compound is the 1,2,3-triazine microbial agent presented in Figure 2.6.[58]

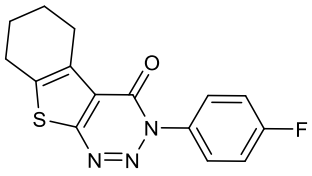


Figure 2.6: A 1,2,3-triazine microbial agent

2.10 Azepines

Azepines are seven member rings containing a single nitrogen atom. The most used azepine is caprolactam, which is used to produce Nylon 6. Caprolactam is mainly synthesized by Beckmann rearrangement from cyclohexanone.[59] Other azepine preparation methods include intramolecular cyclization reactions through nucleophilic addition,[60] radical addition,[61] condensation reaction,[62] olefin metathesis[63] and pyrolysis.[64] There are, however, few examples of azepine synthesis via intermolecular cycloaddition reactions.[29, 65]

Many azepines, especially benzazepines express pharmacological activity. Several benzazepine prescription drugs are in use, such as benazepril,[66] fenoldopam,[67] locaserin[68] and varenicline.[69] A couple of monocyclic azepine drugs are meptazinol[70], shown in Figure 2.7, and proheptazine[71], both of which are opioid analgesics.

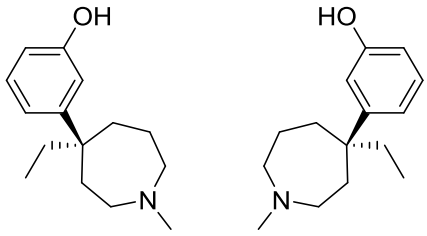
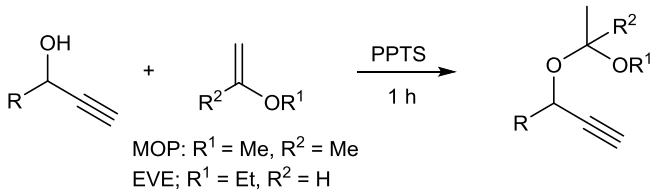


Figure 2.7: Meptazinol

2.11 Preparation of propargyl acetals

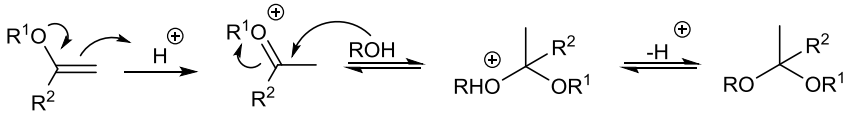
Because of their reactivity towards cyclization described in previous sections, propargyl acetals are the key reagents for several novel cycloaddition reactions. Propargyl acetals are prepared from propargyl alcohols and vinyl alkyl ethers by acid catalysis, Scheme 2.14.[21] Acetals formed from 2-methoxypropene (MOP) are readily hydrolyzed back to alcohols under mild condition. Ethyl vinyl ether (EVE) is also used to prepare acetals, but this introduces an extra stereogenic center to the molecules, which is undesirable for this study as it complicates work-up and characterization.[72]



Scheme 2.14: Formation of acetal from alcohol

As both formation and cleavage of acetals easily occur under mild conditions, weaker acids are desirable in order to avoid unnecessary by-products. Strong acids run the risk of removing the acetal following its formation. The weak acid pyridinium *p*-toluenesulfonate (PPTS) was chosen as catalyst based on this requirement.

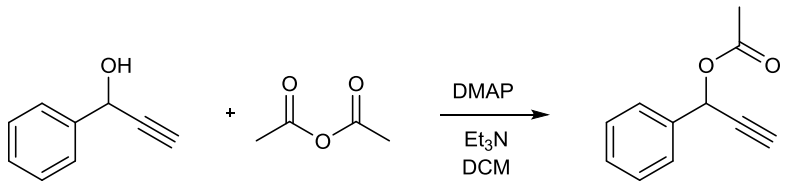
The acid catalyzed mechanism for the formation of acetal from alcohol and vinyl alkyl ether is shown in Scheme 2.15. Initiation of the reactions occurs by an addition of H^+ to the vinyl, affording an oxonium intermediate. Nucleophilic attack by the alcohol yields the desired acetal following deprotonation.[72]



Scheme 2.15: Mechanism for acid catalyzed acetal formation

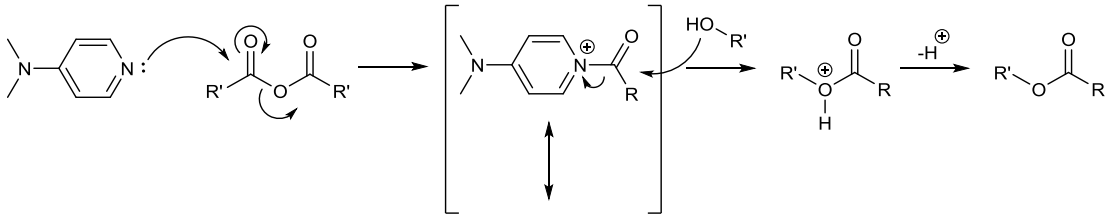
2.12 Preparation of propargyl ester

Propargyl esters are standard moieties in gold catalysis when performing both intramolecular and intermolecular cyclizations. The propargyl ester was prepared from propargyl alcohol and acetic anhydride through catalysis with DMAP, Scheme 2.16.[73] These conditions are similar to the conditions in the Steglich esterification of carboxylic acids, but differ as anhydrides do not need to be activated by a coupling reagent, such as DCC.[73b]



Scheme 2.16: Formation of ester from alcohol

By utilizing DMAP as a catalyst, the reaction is mild and can be performed at room temperature. The mechanism for the catalyzed reaction is presented in Scheme 2.17. The reaction is initiated by nucleophilic attack of DMAP on the anhydride and formation of pyridinium amide. Nucleophilic attack by the alcohol affords the target ester after deprotonation.[73b]

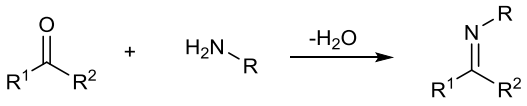


Scheme 2.17: Mechanism for esterification from anhydrides with DMAP

2.13 Preparation of imines

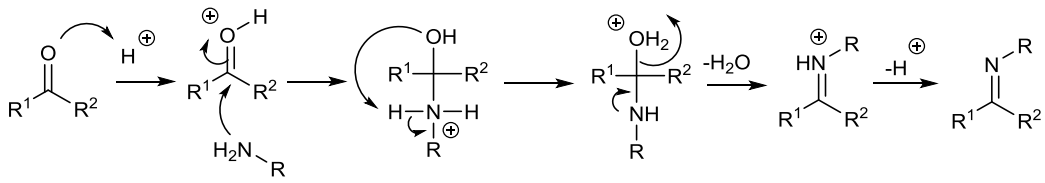
Imines are *N*-derivatives of aldehydes and ketones, where O has been exchanged with NR. In cases where the R group is not H, the imine is called a Schiff base.[74] The

most common preparation method for imines is by condensation of the corresponding aldehyde or ketone with a primary amine, as shown in Scheme 2.15. This equilibrium favors the carbonyl and dehydration agents such as molecular sieve and magnesium sulfate are added in order to shift the equilibrium towards the imine by removal of water.[72]



Scheme 2.15: Preparation of imine from carbonyl and primary amine

The acid catalyzed mechanism for this reaction is shown in Scheme 2.16. The reaction is initiated by protonation of the carbonyl forming an oxonium intermediate. Nucleophilic attack by the primary amine to the carbonyl position, gives an ammonium ion. A proton shift followed by elimination of water affords an iminium ion. Deprotonation yields the corresponding imine.[72]



Scheme 2.16: Mechanism for acid catalyzed imine formation

2.14 Structure elucidation

NMR was the selected methods for structure eleucidation of novel products. The NMR methods are based on the alignment of nuclei in magnetic fields according to their spin quantum numbers. Their alignment can be perturbed by employing a radio frequency pulse. The required perturbation frequency dependents on the external magnetic field and the electron density surrounding the different nuclei in the sample, serving as a fingerprint of the structural moieties of the nuclei.[75] One dimensional NMR spectra of magnetically active nuclei, such as ^{1}H, ^{13}C and ^{19}F, show amplitudes as a function of absorption at a given frequency. In two dimensional NMR, such as COSY, NOESY, HSQC and HMBC, the spectra have two frequency axes. Interactions between two nuclei are represented by cross peaks in the spectra. The nuclei are represented on their respective axis.[76]

Correlation spectroscopy (COSY) exhibits cross peaks emerging from coupling between protons. Heteronuclear single-quantum correlation spectroscopy (HSQC) shows correlation between ^{1}H and another nuclide, usually ^{13}C, through a single bond, while Heteronuclear multiple-bond correlation spectroscopy (HMBC) shows long range correlations spanning two or more bonds. The Nuclear Overhauser effect spectroscopy (NOESY) identifies homonuclear atoms in proximity of one-another.[77]

2.15 Powder X-ray diffraction

Powder X-ray diffraction is a method for identifying the molecular structure of a crystal. The method applies X-rays to a powder or microcrystalline sample and measures the diffraction bands which appear as a result of repeating layers within the crystalline structures scattering the X-rays.[78] Scattering is caused by the electrons in the atoms. When the X-rays strike the electrons a secondary spherical wave is emanated from the electron. These waves cancel in most directions as a result of destructive interference, but are found to add constructively in certain specific directions. Bragg's law is used to determine these directions:[79]

$$2dsin\theta = n\lambda$$

Here d is the distance between diffracting layers of atoms or molecules, θ is the incident angle, n is an integer representing the number of layers, and λ is the wavelength of the applied beam. The equation above can be simplified to:

$$2d_1 sin\theta = \lambda$$

This gives the length d_1 between two neighboring layers.

In single crystal X-ray diffraction these directions d appear as spots on the diffraction pattern called reflections. In powder X-ray diffraction the directions appear as smooth diffraction rings instead. The different rings represent the distance between repeating layers within the crystal. Because similar lengths will give constructive interference, stronger signals represent lengths which are more frequent and therefore more ordered in the analyzed sample.[78] The data of the distances within the crystal can then be analyzed by software to determine the molecular structure and positions of the atoms in the crystal.

3. Results and Discussion

This chapter is divided into three parts. Section 3.1 covers the preparation of starting materials propargyl acetals and esters. The other two cover the reactions of nitrones and azides with propargyl acetals, respectively, and the preparation of starting nitrones and azides.

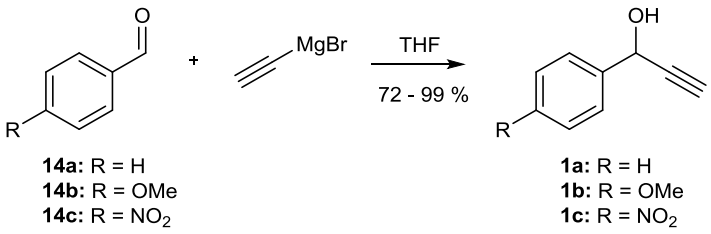
All new compounds have been fully characterized by NMR, IR and MS where possible, see Chapter 6 and Appendices. The shifts of new compounds were designated by 2D NMR and are presented in this section. All reactions were monitored by TLC.

3.1 Preparation of propargyl starting materials

In this section, the preparation of propargyl acetals and propargyl ester for the Au(I) catalyzed reactions are presented. As mentioned in Section 2.3, the reactions of propargyl acetals have previously been studied by the Fiksdahl group.[10b, 11-12, 20]

3.1.1 Synthesis of propargyl alcohols

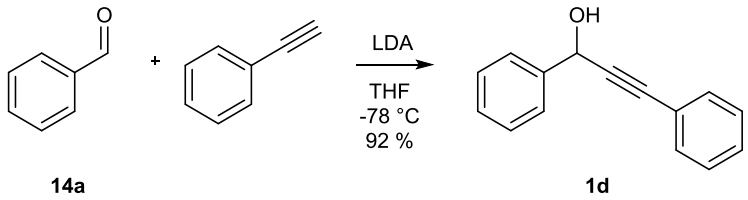
Before propargyl acetals could be prepared, the preceding propargyl alcohols **1a-d** had to be synthesized. The propargyl alcohols **1a-c** were prepared, shown in Scheme 3.1, by Grignard reactions following a reported procedure from the corresponding aldehydes **14a-c** and commercial ethynylmagnesium bromide.[80]



Scheme 3.1: Synthesis of propargyl alcohols **1a-c**

The alcohol **1a** was readily obtained by the standard procedure[80] without any purification after work-up as a yellow solid in 99 % yield. Alcohol **1b** was isolated by a silica flash column as a colorless oil in 92 % yield. For some unknown reason, extraction and washing of alcohol **1c** following the reaction proved surprisingly difficult, with DCM and water being miscible, but silica flash chromatography afforded the alcohol **2c** as a yellow solid in 72 % yield. The ^{1}H- and ^{13}C-NMR shifts and yields were consistent with results reported in literature.[81] The reactions were initially stopped after 2 h as reported in literature,[81-82] but were later worked up after an hour when full conversion was observed after about half an hour.

Propargyl alcohol **1d** was synthesized following a different procedure from phenylacetylene **15** and benzaldehyde **13a** according to literature.[83]

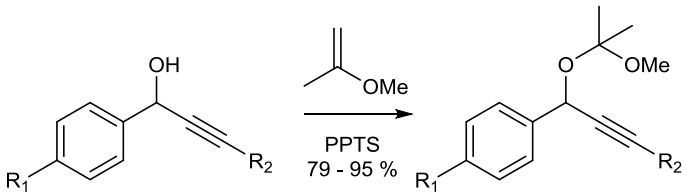


Scheme 3.2: Synthesis of propargyl alcohol **1d**

Phenylacetylene was deprotonated by LDA to perform a nucleophilic attack on the aldehyde **14a**, see Scheme 3.2. Work-up afforded the product **2d** as a yellow solid in 92 % yield. The ^{1}H- and ^{13}C-NMR shifts and yield were in accordance with literature.[84]

3.1.2 Synthesis of propargyl acetals

From the alcohols **1a-d** presented above, the propargyl acetals **2a-d** of interest for this study were synthesized. The applied procedure was based on a literature synthesis of terminal propargyl acetals by treating alcohol with methoxypropene,[24] presented in Scheme 3.3. Here PPTS acts as an acid catalyst and the acid catalyzed reaction mechanism is presented in Section 2.11.



Scheme 3.3: Synthesis of propargyl alcohols **3a-d**

All the propargyl acetals **2a-d** are unstable and decompose back to their corresponding alcohols as well as other unknown compounds even when stored in a freezer. Therefore, they need to be prepared and isolated just ahead of the gold(I) catalyzed reactions. The acetals **2a** and **2b** were isolated as colorless oils in respective yields of 95 % and 91 %, whereas acetal **2c** was obtained as a yellow oil in 91 % yield. Despite being reported as a procedure for terminal acetals,[24] the reaction gave the phenyl-substituted acetal **2d** with full conversion and isolated in 79 % yield following purification by flash chromatography. In the reported procedure the reactions were left to stir overnight,[24] but because full conversion was obtained in under an hour for all four acetals in the present work, they were worked up after an hour. Furthermore it was discovered that some decomposition occurred during flash chromatography, as the acidic positions in silica catalyze the reverse reaction back to alcohol. To prevent this, a small amount, 0.5 %, of triethylamine was added to the eluent, which improved the yields compared to previously obtained yields in the research group.[10b, 11-12]

^{1}H- and ^{13}C-NMR shifts of **2a-c** were in agreement with literature.[10b, 11] The chemical shifts of acetal **2d** which could be determined from 2D NMR (Appendix B) are presented in Figure 3.1. HRMS of the product could not be obtained due to decomposition.

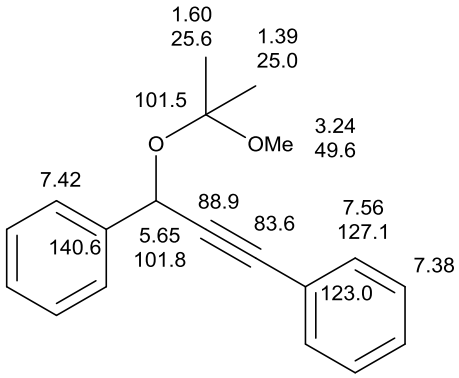
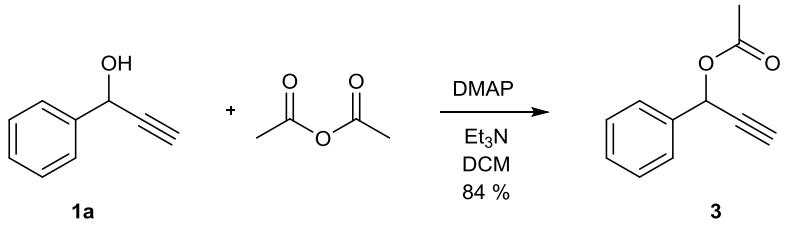


Figure 3.1: Chemical shifts of acetal **2d**

3.1.3 Synthesis of propargyl ester

Propargyl acetals were derived from the more studied propargyl esters,[10b] which have been thoroughly investigated and undergo a variety of gold(III) catalyzed reactions.[4, 7, 29, 85] The propargyl esters are less reactive than their acetal counterparts, but it is of interest to investigate if the reactions studied with propargyl acetals are possible with propargyl esters as well. The propargyl ester **3** was synthesized following a literature procedure.[73a] As illustrated in Scheme 3.4, propargyl ester **3** was prepared from alcohol **1a** and acetic anhydride by using DMAP as catalyst. The mechanism for the reaction is presented in Scheme 2.17, Section 2.12.



Scheme 3.4: Synthesis of propargyl ester **3**

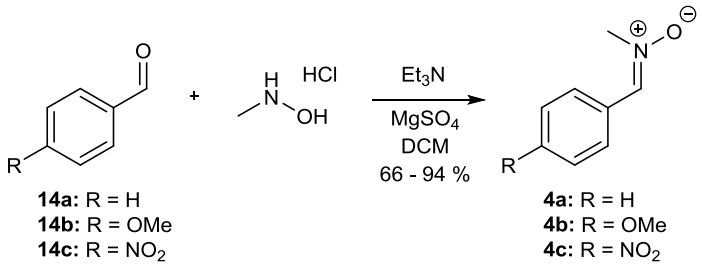
Following the standard procedure[73a] the propargyl ester **3** was afforded in a yield of 84 % as a colorless oil. The ^{1}H-shifts correspond with literature.[73a]

3.2 Au(I) catalyzed reaction of propargyl acetals and nitrones

In this section, preparation of nitrones and gold(I) catalyzed reactions between propargyl acetal **2a-d**, propargyl ester **3** and nitrones **4a-i** are presented.

3.2.1 Preparation of nitrones

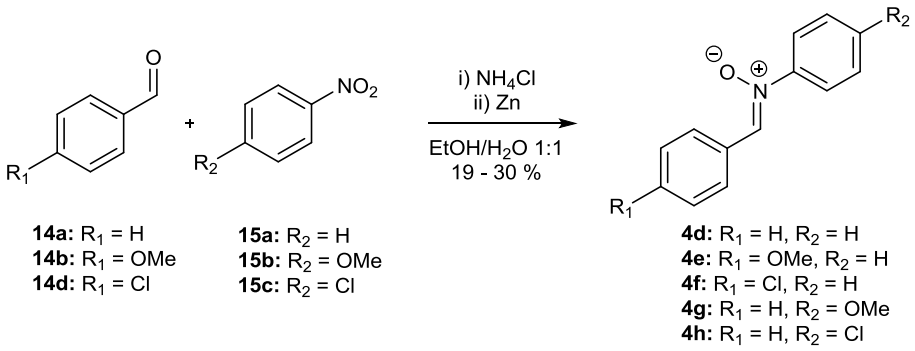
As presented in Section 2.4, [3+3] cycloaddition requires two 1,3-dipolar compounds. To prepare the nitrone component for these [3+3] cycloaddition reactions, different preparation methods were required depending on the substituents. The nitrones **4a-c** were prepared by a condensation reaction between aldehydes **14a-c** and *N*-methylhydroxylamine following a reported procedure.[86] The mechanism for the reaction to nitrone **4a-c** in Scheme 3.1 is analogue to the acid catalyzed reaction to imine shown in Scheme 2.16, Section 2.12.



Scheme 3.5: Synthesis of nitrones **4a-c**

By following the literature procedure,[86] nitrone **4a** was isolated in 92 % yield as a white solid, whereas nitrone **4b** was isolated as a white solid in 66 % yield. Nitrones **4c** was afforded as a yellow solid in 94 % yield. All the products were isolated by silica flash chromography, eluent EtOAc. ^{1}H-NMR spectra correspond to previously reported data.[86-87]

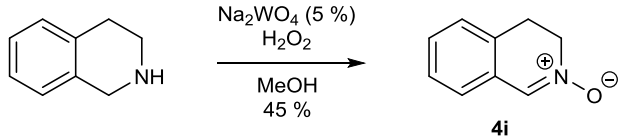
To synthesize diarylnitrones, a condensation reaction between aromatic hydroxylamines and benzaldehydes is possible, but the hydroxylamines have to be prepared, often by reduction of their respective nitroaryles. Fortunately, the nitrones **4d-h** could be prepared directly by a one-pot reaction from the corresponding aldehydes **14a-b**,**d** and nitroaryles **15a-c** according to a reported procedure.[88] Zinc powder reduces the nitroaryls to *N*-phenylhydroxylamines which subsequently condensate to the corresponding nitrones **4d-h** in the presence of a weak acid and aldehydes. Because *p*-nitro-substituents would be reduced by zinc in the preparation of the diarylnitrones, Scheme 3.6, *p*-chloro nitrones **4f** and **4h** were prepared instead.



Scheme 3.6: Synthesis of nitrones **4d-h**

In accordance with the reported procedure,[88] diarylnitrone **4d** was obtained in 30 % yield, the same as for **4e**. Nitrone **4f** was isolated in 19 % yield, while the nitrones **4g** and **4h** were afforded in respective yields of 29 % and 20 %. All nitrones **4d-h** were obtained as white solids after purification. The products were either purified by flash chromatography or recrystallized from EtOAc. The reactions were not optimized, neither in this work nor the reported procedure,[88] and over-reduction due to excess of zinc as well as incomplete condensation in the aqueous media were considered to be the main reasons for the low yields. Low yields were not an issue in the present work as all reactants and reagents were inexpensive and the goal was to prepare reactants for the gold catalyst reactions. ^{1}H-NMR shifts were in accordance with literature.[88-89]

A condensation reaction to generate nitrone **4i** is not as suited as for the nitrones presented above. Instead, oxidation of a secondary amine by hydrogen peroxide with tungsten catalysis, see Scheme 3.7, is a well suited method for preparation.[90]



Scheme 3.7: Synthesis of nitone **4i**

Nitrone **4i** was prepared by tungsten catalyzed oxidation from isoquinoline **20** as previously reported.[90] TLC of the starting compound indicated that it was not pure, but the different retention times observed could be the result of tautomerism as only a single main product was observed. Full conversion was not obtained, due to the use of old H_2O_2 in the reaction, which meant the added amount of H_2O_2 was lower than calculated. Instead of performing a distillation as was done in the reported procedure,[90] the nitrones was purified by silica flash column chromatography, eluent EtOAc/Et_3N 20:1, to afford the nitrone in 45 % yield. ^{1}H-NMR corresponded with reported data.[90]

3.2.2 Gold catalyzed reactions of propargyl acetal and nitrone

The details and results of gold(I) catalyzed reaction related reactions between different acetals and nitrones are presented in Table 3.1. All reactions were performed with one equivalent of nitrone and with (acetonitrile)[(2-biphenyl)di-*tert*-butylphospine]gold(I) hexafluoroantimonate (**VI**) as gold(I) catalyst. A solvent screening was not performed, as previous studies within the research group always reported DCM as the best solvent.[10b, 11-12] Acetonitrile has been reported as a viable alternative, but DCM was preferred due to its lower boiling point. All reactions were performed at room temperature, 20 °C. In the following section these reactions will be discussed in more detail.

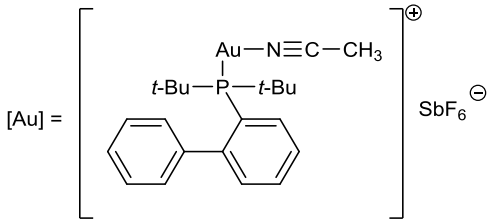
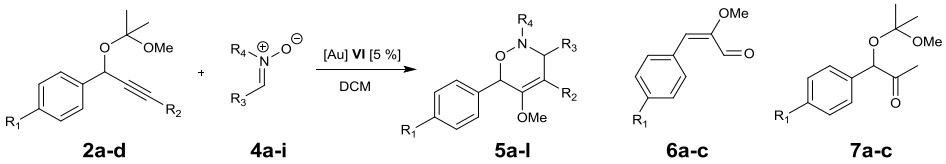
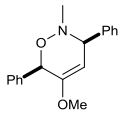
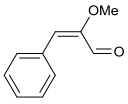
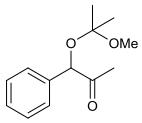
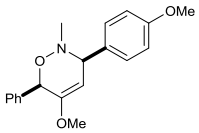
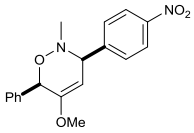
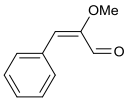
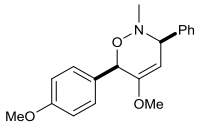
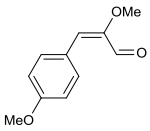
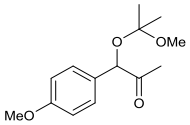
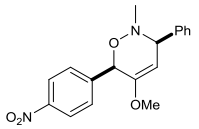
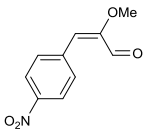
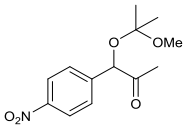
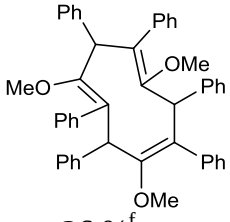
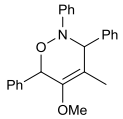


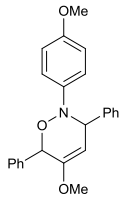
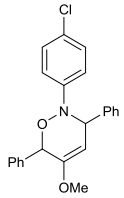
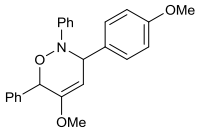
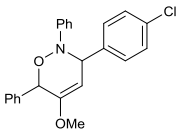
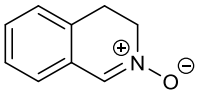
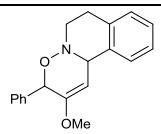
Figure 3.2: Gold catalyst **VI**

Table 3.1: Details for reactions of propargyl acetals and nitrones



2a-d **4a-i** **5a-l** **6a-c** **7a-c**

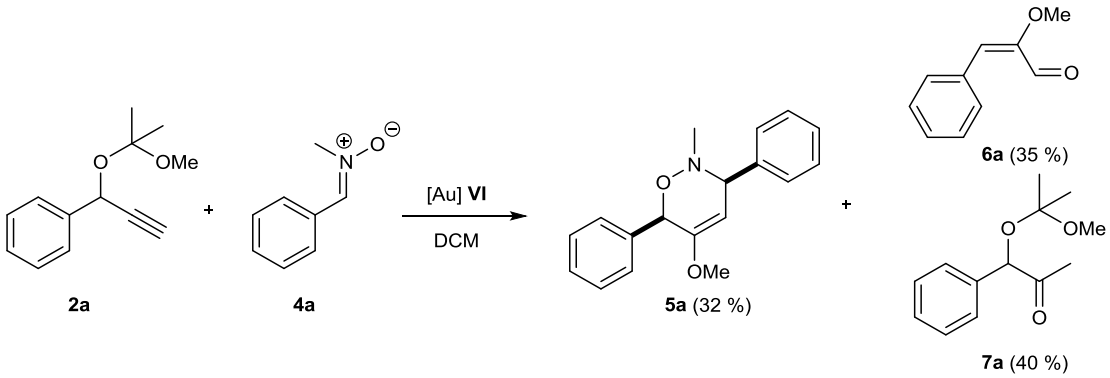
Entry	Acetal	Nitrone	Rx.time [min]	Products and yields		
				5	**6**	**7**
1	**2a** R_1 = Ph R_2 = H	**4a** R_3 = Ph R_4 = Me	120	 **5a** 32 %	 **6a** 35 %	 **7a** 40 %[a]
2	**2a** R_1 = Ph R_2 = H	**4b** R_3 = *p*-OMe R_4 = Me	30	 **5b** < 1 %[b]	-[d]	-[d]
3	**2a** R_1 = Ph R_2 = H	**4c** R_3 = *p*-NO_2 R_4 = Me	1440	 **5c** 36 %	 **6a** 36 %	-[d]
4	**2b** R_1 = *p*-OMe R_2 = H	**4a** R_3 = Ph R_4 = Me	30	 **5d** 21 %[e]	 **6b** 22 %	 **7b** 21 %[e]
5	**2c** R_1 = *p*-NO_2 R_2 = H	**4a** R_3 = Ph R_4 = Me	1440	 **5e** -[c]	 **6c** <1 %[b]	 **7c** 19 %
6	**2d** R_1 = Ph R_2 = Ph	**4a** R_3 = Ph R_4 = Me	1440	 26 %[f]		
7	**2a** R_1 = Ph R_2 = H	**4d** R_3 = Ph R_4 = Ph	30	 **5g** 11 %	-[d]	-[d]

8	**2a** R_1 = Ph R_2 = H	**4e** R_3 = Ph R_4 = *p*-OMe	30	 **5h** <1 %[b]	-[d]	-[d]
9	**2a** R_1 = Ph R_2 = H	**4f** R_3 = Ph R_4 = *p*-Cl	30	 **5i** 54 %	-[d]	-[d]
10	**2a** R_1 = Ph R_2 = H	**4g** R_3 = *p*-OMe R_4 = Ph	30	 **5j** 6 %[e]	-[d]	-[d]
11	**2a** R_1 = Ph R_2 = H	**4h** R_3 = *p*-Cl R_4 = Ph	30	 **5k** 23 %	-[d]	-[d]
12	**2a** R_1 = Ph R_2 = H	**4i** 	120	 **5l** -[b]	-[d]	-d

a) Yields from reaction using 3 equivalents of nitrones.[13]
b) Trace amounts as impurity.
c) No product observed.
d) Not worked up.
e) Obtained as a mixture
f) Oxazine product not observed

Synthesis of oxazine 5a and initial studies

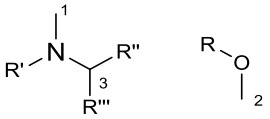
The reactivity of propargyl acetals with unsaturated compounds have been thoroughly studied within the Fiksdahl group.[10b, 11-12, 20] Some of the resulting products were presented in Section 2.3. During the research project leading up to this master's thesis the gold(I) catalysed reaction between propargyl acetal **2a** and nitrone **4a** with catalyst **VI** was studied, Scheme 3.8. Under the initial conditions three equivalents of nitrones were used.[13]



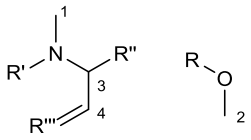
Scheme 3.8: Synthesis of oxazine **5a**

The reaction afforded three products, oxazine **5a**, aldehyde **6a** and ketone **7a**. NMR of the crude mixture under the initial conditions showed a selectivity of 80 % for ketone **7a** and 10 % for both oxazine **5a** and aldehyde **6a**. Under these conditions oxazine **5a** was isolated as a colorless oil in 8 % yield, while the ketone was obtained in a yield of 40 % as a colorless oil, following two silica flash columns. Because the acetal group was determined to still be present in the ketone **7a**, it was assumed to be the product of an attack by the nitrone **4a** on the propargyl acetal **2a** before formation of the gold carbenoid intermediate **XI**, Scheme 3.9. By reducing the amount of nitrone to one equivalent, the selectivity was increased to roughly 45 % for the oxazine at the expense of ketone.[13] The relative selectivity between oxazine and aldehyde had not been altered. These new conditions gave the oxazine **5a** in 32 % yield as a colorless liquid. Aldehyde **6a** was obtained as a colorless oil in 35 % yield. Both isolated after a silica flash column chromatography with an eluent of *n*-pentane/EtOAc 20:1.

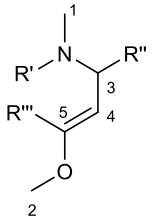
The structure elucidations of the three products **5a**, **6a** and **7a** are given below. First a step-wise approach in the elucidation of the structure of the cycloaddition product **5a** is presented, spectra are available in Appendix E. Numbers in the figures indicate the position of H and C in the molecule. The characteristic peaks of the N-CH_3 (1) and O-CH_3 (2) were identified by ^{1}H- and ^{13}C-NMR. Through COSY and HMBC correlations, the methine (3) connected with the nitrogen was found, corresponding to the same position as in the nitrone **4a**, see above.



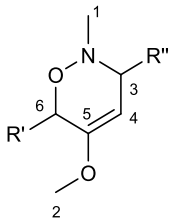
Through COSY, the methine (3) was observed to couple to a neighboring vinylic methine (4).



HMBC results for the methine (4) and methoxy (2) showed a connection of these groups through a quaternary vinyl C (5).



Coupling between the vinyl C (5) and H belonging to a CH group (6) was observed in HMBC. Based on the shift values of this CH group, the starting materials and the "C-1-C-3" cycloaddition mechanism presented in Section 2.3 the ring was closed with an oxygen to afford a 6-membered heterocycle.



HMBC showed connection of the methines (3) & (6) to phenyls as expected from the starting compounds. From these observations the structure of the compound **5a** shown in Figure 3.1 was determined. Chemical shifts that could be designated to their respective nuclei are presented in Figure 3.3. Analysis by HRMS gave a peak of (M+H), in agreement with the determined structure.

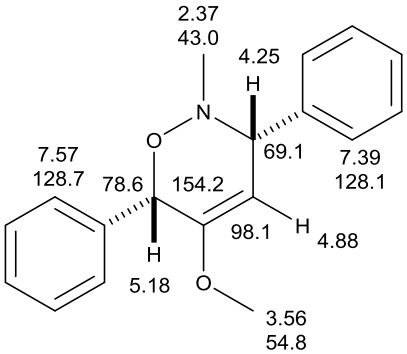


Figure 3.3: Compound **5a** with determined chemical shifts

The configuration of **5a** was determined to be *cis* based on a NOESY experiment. No other diastereomer was observed in crude mixture nor isolated. The NOE correlations of oxazine **5a** are shown in Figure 3.4. Bold double headed arrow represents the NOE

correlation decisive for determining the configuration. In the NOESY spectra a weak correlation between the H3 and H6 protons were observed, which can only be observed in the *cis* configuration.

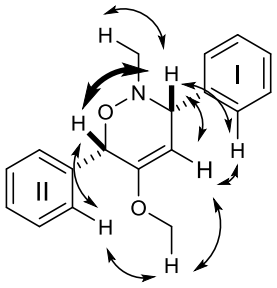
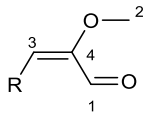


Figure 3.4: NOE correlations of compound **5a**.

Later oxazine compounds were assumed to have the *cis* configuration as the major isomer.

The structure of product **6a** was resolved through data collected by NMR. The spectra are presented in Appendix L. Numbers indicate the position of H and C in the molecule. An aldehyde (1), a methoxy (2) and a methine (3) group were identified through ^{1}H, ^{13}C and HSQC spectra. HMBC showed that all three groups were connected to the same quaternary vinylic C (4).



Further interpretation of the HMBC spectrum gave a phenyl group attached to the methine (3) affording the structure presented in Figure 3.5. Chemical shifts were identified following deeper analysis of the spectra. A peak of (M+H) was observed by HRMS, in agreement with the determined structure. IR gave a strong peak at 1683 cm^{-1}, characteristic for carbonyl C=O stretch.

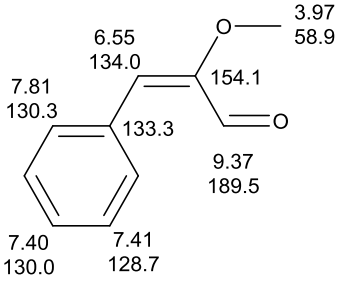
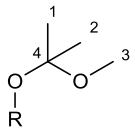
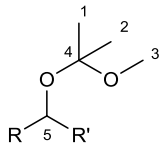


Figure 3.5: Compound **6a** with chemical shifts

The last observed product **7a** in the reaction was elucidated by NMR-data given in Appendix N. Two methyls (1 and 2) and a methoxy group with similar shifts to the propargyl acetal **3a** were identified by ^{1}H and ^{13}C spectra. These were connected with a quaternary C (4) to yield the acetal structure of the propargyl **2a**.



By using the similarity to starting propargyl **2a**, methine (5) was found by comparing the ^{1}H and ^{13}C shifts with the propargyl **2a**.



From the remaining NMR shifts, the structure of ketone **7a** was elucidated and is presented in Figure 3.6, inclurding the observed chemical shifts. HRMS of the sample did not give the molecular peak or any peaks deriving from possible fragmentations of the compound. The IR spectra, when taken showed that the compound had decomposed. As NMR was the only measurements recorded directly following purification, these measurements are considered to contain the most reliable data. HRMS could not be obtained as product **7a** decomposed in the pre-heater.

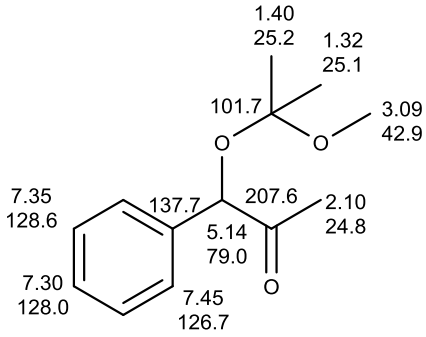
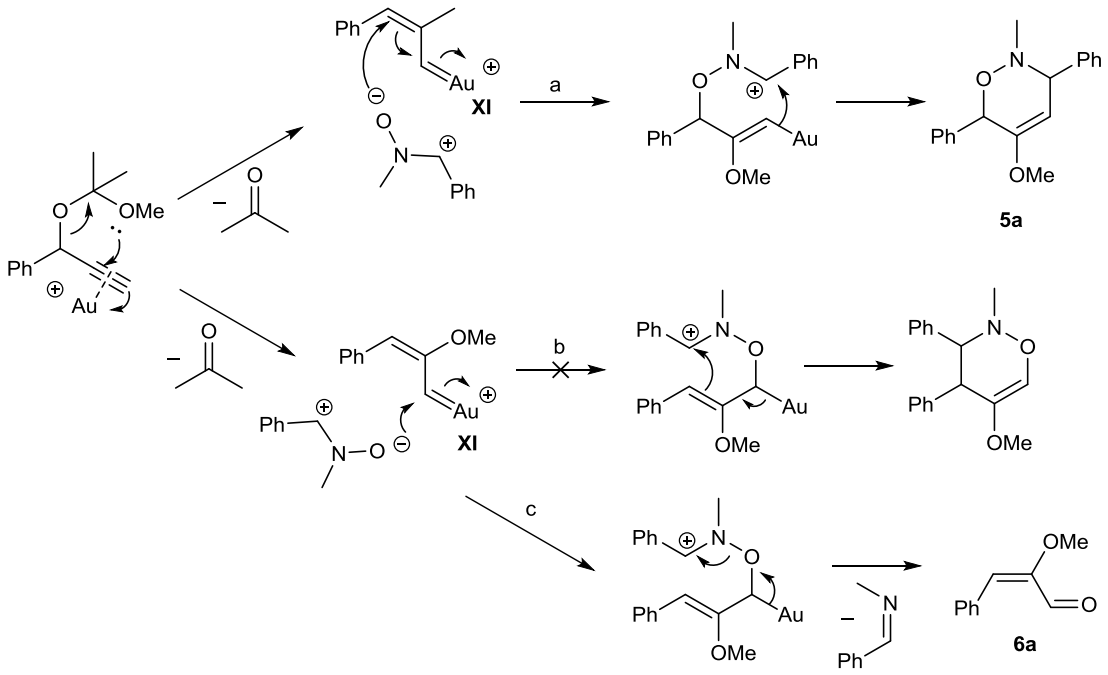


Figure 3.6: Compound **7a** with chemical shifts

In summary three compounds were identified for the gold(I) catalyzed reaction between propargyl acetal **2a** and nitrone **4a**; 1,2-oxazine **5a**, an aldehyde **6a** and a ketone **7a**.

The structure of the oxazine cycloaddition product **5a** corresponds to the product of a "C-1-C-3" cycloaddition mechanism as described in Section 2.3. A suggested mechanism through a "C-1-C-3" cycloaddition of the gold carbenoid **XI** is presented in Scheme 3.9a. The expected cycloaddition product afforded from a "C-3-C-1" cycloaddition reaction, as discussed in Section 2.4, would be a 3,4-diphenyl substituted 1,2-oxazine as shown in Scheme 3.9c. However, this compound was not observed in any of the reactions performed. The hypothesis is that instead of ring closure along mechanism b, Scheme 3.9b, an oxidation to aldehyde **6a** occurs and proceeds according to mechanism c, Scheme 3.9c.

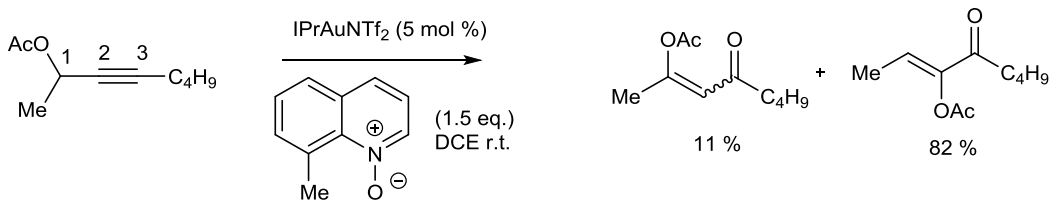


Scheme 3.9: Proposed mechanisms for gold-activated reaction to oxazine **5a** and aldehyde **6a**

The first proposed mechanism 3.9a follows the standard "C-1-C-3" cycloaddition, presented in Section 2.3, to yield the oxazine **5a**. Reaction to aldehyde is suggested to proceed along a "C-3" nucleophilic attack, but instead of ring closure, the nitrone is reduced to imine by regeneration of the catalyst.

As illustrated in Scheme 2.10a, Section 2.3, Doyle et al.[25b] have reported that nitrones and vinylcarbenes undergo a [3+3] cycloaddition Rh(II) catalyzed reaction. 3-Methyl vinylcarbenes show high conversion with rhodium catalysis, while 3-aryl vinyl carbenes were unsuccessful. Silver and copper catalysts gave conversion of 3-aryl vinyl carbenes, suggested to be the result of the Lewis acid nature of these catalysts, giving a Lewis acid catalysis.[91] The gold catalytic reaction of propargyl acetals is supposed to follow a gold carbenoid reaction pathway, and to give successful reactions with phenyl propargyl acetal. Our reaction to 1,2-oxazine **5a** with gold catalysis was successful with an aryl substituent without using Lewis acid catalysis.

The oxidation of the acetal to aldehyde **6a** can be related to the observations of an article by Ji et al.[92] where they have reported a Au(I) catalyzed oxidation of propargylic carboxylates by nitrones, Scheme 3.10.



Scheme 3.10: Oxidation of propargyl ester with nitrone

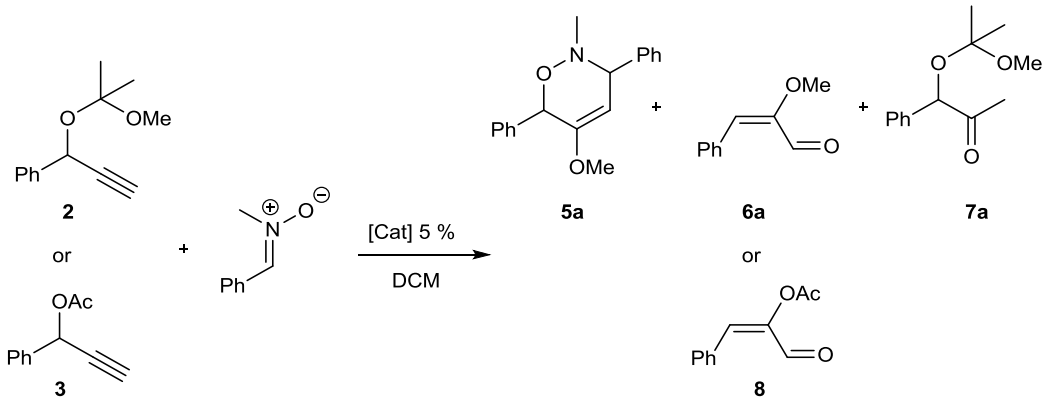
In this work, the preferred nucleophilic attack was observed on the "C-3" position relative to the acetate group, with no "C-2" attack. In our study, attack on the "C-2" position of the propargyl acetal **3a** was the main product for higher concentrations of nitrone **4a**, yielding the ketone **7a**, while "C-3" position was favored with lower nitrone **4a** concentrations, giving aldehyde **6a**. This suggests that "C-3" addition of nitrone **4a** follows metoxy/acetate migration. Ketone **7a** is formally obtained through a hydration of alkyne. During the student project, it was determined that hydration did not occur in absence of nitrones. Furthermore, hydration was less favored in presence of water.[13] Therefore, hydration is promoted through the nitrone, but mechanism has not been determined.

Neither in previous studies,[13] improvement of the selectivity of "C-1" attack relative to "C-3" for the reaction to oxazine **5a**, also with different reaction temperatures has not been successful. Changing the substituents to more electron withdrawing or donating groups is expected to alter the product selectivity, as will be presented below.

Catalyst testing

In previous studies carried out in the research group, the gold catalyst **VI**, shown in Figure 3.2, was observed to be the best catalyst commercially available.[10b] To certify this, some common gold catalysts were tested in order to compare (Table 3.2). Both gold catalyst **VI** and Ph_3PAuCl **VII** are gold(I) catalysts, whereas $PicAuCl_2$ and Ph_3PAuCl_3 are gold(III) catalysts. Both propargyl acetal **2a** and propargyl ester **3** were examined to investigate if [3+3] reaction with propargyl ester was possible as well. All reactions were performed in DCM at 20 °C with one equivalent of nitrone. Conversion and yield of products were determined by ^{1}H-NMR of the crude reaction mixture.

Table 3.2: Details for catalyst testing of reactions between propargyl acetals **2a** and propargyl esters **3** with nitrone **4a**.



Catalyst	Reactant	Conversion	Time	Product in crude mixture [%]		
VI	**2a**	99 %	2 h	**5a** (32[a])	**6a** (35[a])	**7a** (8)
Ph_3PAuCl	**2a**	24 %	24 h	**5a (**15)	**6a** (9)	-[b]
$PicAuCl_2$	**2a**	37 %	24 h	**5a** (15)	**6a** (22)	-[b]
Ph_3PAuCl_3	**2a**	<5 %	24 h	-[b]	**6a** (< 5)	-[b]
VI	**3**	<5 %	24 h		**8** (< 5)	
Ph_3PAuCl	**3**	<5 %	24 h		**8** (< 5)	
$PicAuCl_2$	**3**	25 %	24 h		**8** (19[a])	
Ph_3PAuCl_3	**3**	7 %	24 h		**8** (7)	

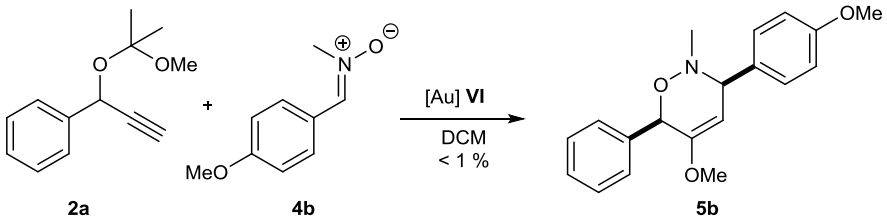
a) Isolated yield
b) Not observed in NMR of crude mixture

Ph_3PAuCl, **VII**, has been reported to be a less active gold(I) catalyst than **VI**,[10b] and this was the case here, with 24 % conversion obtained after 24 h. A slightly improved selectivity towards [3+3] cycloaddition was obtained, but with a lower total yield. The two gold(III) catalysts tested, $PicAuCl_2$ and Ph_3PAuCl_3, were not expected to exhibit the same catalytic effect as **VI** and this was also found to be the case. Interestingly, $PicAuCl_2$, favored the oxidation product **6a** to a larger extent than what was observed for **VI**, but the lower conversion still makes it a worse catalyst to **6a** overall.

The initial results proved that nitrones afford [3+3] cycloaddition with propargyl acetals. Acetals are more reactive species compared to the more frequently studied propargyl esters. The reactivity of the propargyl ester **3** with nitrone **4a** was attempted to investigate if this would also give a [3+3] cycloaddition or oxidation as reported for nitrones used by Ji et al.[92] The reaction between ester **3** and nitrone **4a** was performed with the four different gold catalysts to investigate if any of these would yield cycloaddition. The standard gold(I) catalyst **VI** used for propargyl acetals afforded a conversion of < 5 % with the product being the oxidation product. The less active gold(I) catalyst barely gave any conversion. The two common gold(III) catalysts $PicAuCl_2$ and $Au(PPh_3)Cl_3$ gave conversions of 25 % and 7 %, respectively. In both cases only oxidation was observed. These results were as expected, as [3+3] cycloaddition reactions of propargyl esters and nitrones have not been reported. The oxidation product **8** was isolated from reaction with $PicAuCl_2$ in 19 % yield as a colorless oil. ^{1}H- and ^{13}C-NMR correspond with literature, (Appendix P).[93]

Attempted synthesis of oxazine 5b

Having confirmed that gold(I) catalysis of propargyl acetals and nitrones afford cycloaddition, the scope of the reaction was to be determined by modifying the substituents of nitrone and acetal. First the acetal **2a** was reacted with nitrone **4b** in an attempt to prepare oxazine **5b**, Scheme 3.11. Methoxy substituents are strongly electron donating and the nitrone **5b** was expected to be a stronger nucleophile than **5a**.

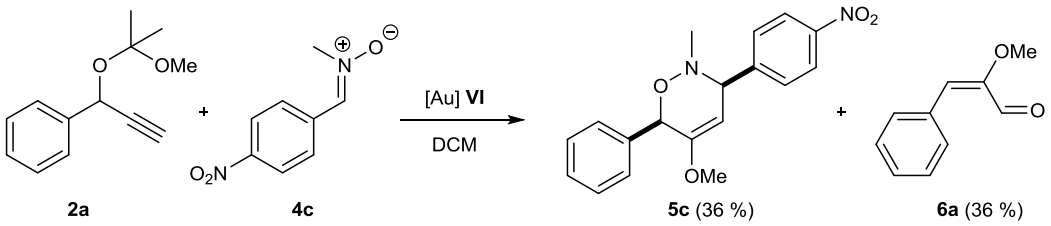


Scheme 3.11: Synthesis of oxazine **5b**

The reaction was complete after 30 min, shorter time than entry **1**. Three products were formed in the reaction, the target oxazine **5b** as well as the aldehyde **6a** and ketone **7a**. However, NMR of the crude mixture showed low selectivity towards the desired product **5b**, with oxidation to **6a** being favored. The oxazine **5b** was not isolated by flash chromatography, and was only observed in trace amounts. ^{1}H-NMR data from the trace amounts suggested that only one diasteromer was formed.

Synthesis of oxazine 5c

While the methoxy group used for preparation of **5b** is strongly electron donating, nitro groups are strongly electron withdrawing. By having testing the reactivity with both a nitro and methoxy substituent, a wide reaction scope has been assessed. The nitro group was expected to yield a less reactive nitrone than for **5a**. The reaction to oxazine **5c** from acetal **2a** and nitrone **4c** is presented in Scheme 3.12.



Scheme 3.12: Synthesis of oxazine **5c**

The reaction between propargyl acetal **2a** and nitrone **4c** was complete after 24 h. NMR of the crude mixture showed an apparently equal selectivity for [3+3] cycloaddition and oxidation, with negligible amount of hydrolysis. Following silica flash chromatography, eluent *n*-pentane/EtOAc 10:1, oxazine **5c** and aldehyde **6a** were isolated, respectively, as a yellow oil and a colorless oil, both in a yield of 36 %. A single diastereomer of product **5c** was observed.

The chemical shifts of product **5c** were assigned by NMR (Appendix F). The *cis* configuration of product **5c** was determined based on NOESY experiment. The chemical shifts are presented in Figure 3.8 and the NOE correlations are presented in Figure 3.9. The bold arrow indicates the NOE correlation determining the configuration.

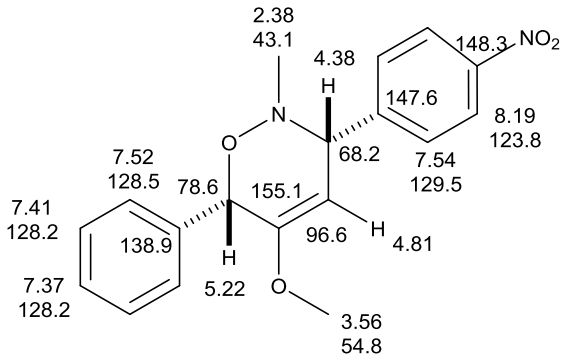


Figure 3.8: Chemical shifts of product **5c**

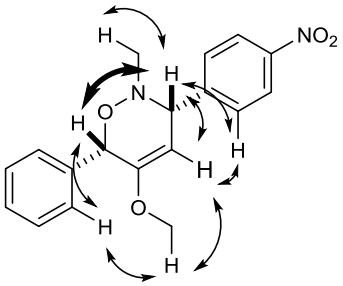
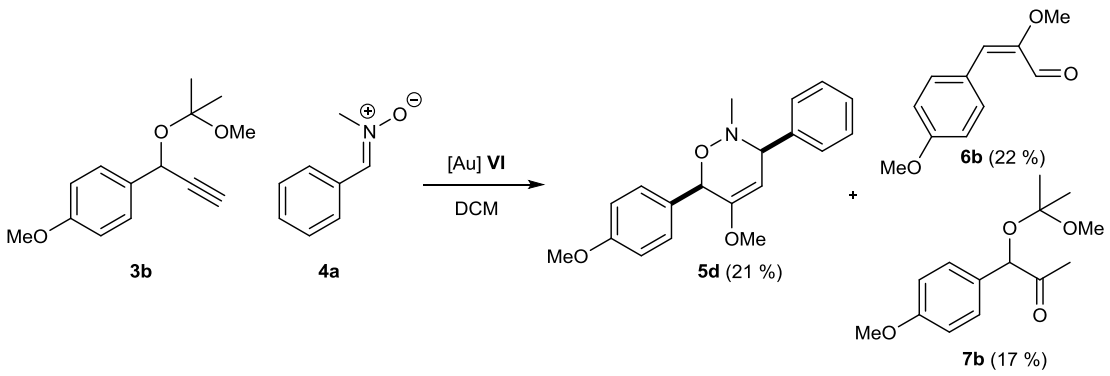


Figure 3.9: NOE correlations of product **5c**

Synthesis of oxazine 5d

Having investigated that changing the electronegativity of the nitrone substituent affected the reaction rate slightly and partly affected the selectivity, modification of the acetal was thereafter studied. In a next step, the effects of modifying the aryl substituent of the propargyl acetal were studied. The acetal **2b**, containing an electron donating methoxy group, was reacted with nitrone **4a**, Scheme 3.13.

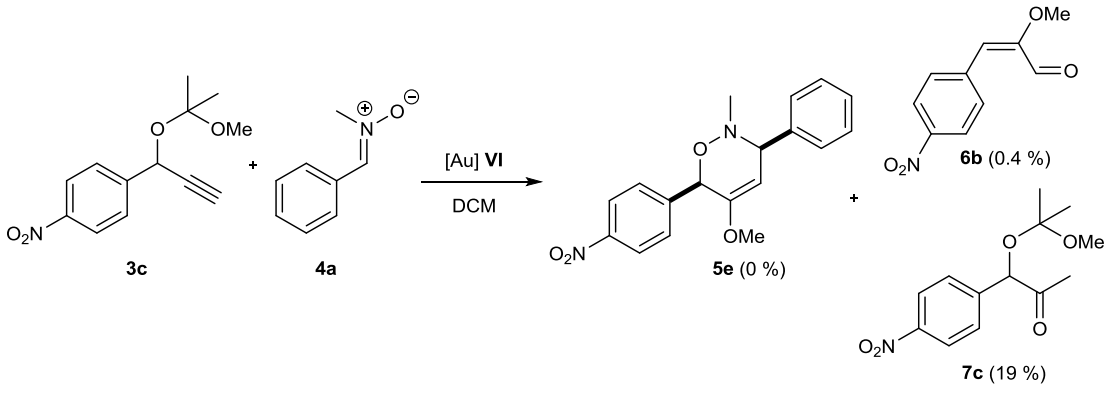


Scheme 3.13: Synthesis of oxazine **5d**

The rate of the reaction was significantly faster than for acetal **2a** with nitrone **4a**, due to the methoxy substituent's electron donating effect stabilizing the gold carbenoid intermediate, and was complete in less than 30 min. Once again poor selectivity between cycloaddition and oxidation was observed with NMR of the crude mixture showing an almost 1:1:1 ratio between the three products **5d**, **6b** and **7b**. A single product spot was observed on TLC and after a silica column chromatography of the sample, it was discovered that the three products experience the same retention in a *n*-pentane/EtOAc eluent system. Oxazine **5d**, aldehyde **6b** and ketone **7b** were obtained as a mixture in respective yields, 23 %, 25 % and 21 %. Purifications by a second silica flash column, eluent *n*-pentane/DCM 3:1 → DCM, only afforded aldehyde **6b** as an isolated product 21 %. Oxazine **5d** and ketone **7b** were not obtained. ^{1}H-NMR shifts of **6b** corresponded with literature.[94]

Attempted synthesis of oxazine 5e

To test how a less reactive propargyl acetal reacts with nitrones, the propargyl acetal **2c** was reacted with nitrone **4a**, Scheme 3.14.



Scheme 3.14: Attempted synthesis of oxazine **5e**

For this reaction, only a low conversion, ca. 25 %, was observed after 24 h. Formation of the [3+3] cycloaddition product was not observed. Instead the hydration product **7c** was observed as the main product and isolated in a yield of 21 %. Small amounts (2 %) of aldehyde **6c** impurities could be observed in this isolated sample. No aldehyde

was found in other fractions, which meant it was obtained in a yield of 0.4 %. Compound **7c** was observed to readily decompose at room temperature when exposed to air and even at -20 °C if stored for a week under nitrogen atmosphere.

The chemical shifts of **7c** were assigned by 2D-NMR (Appendix O) and are presented in Figure 3.11. HRMS of **7c** could not be obtained due to decomposition. ^{1}H-NMR data of aldehyde **6c** corresponded with literature data.

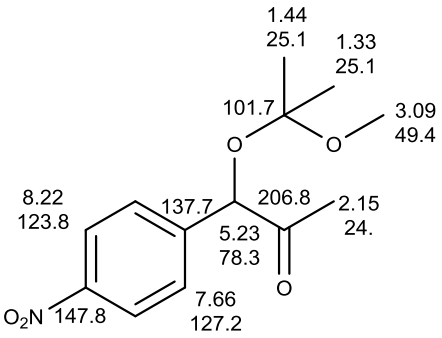
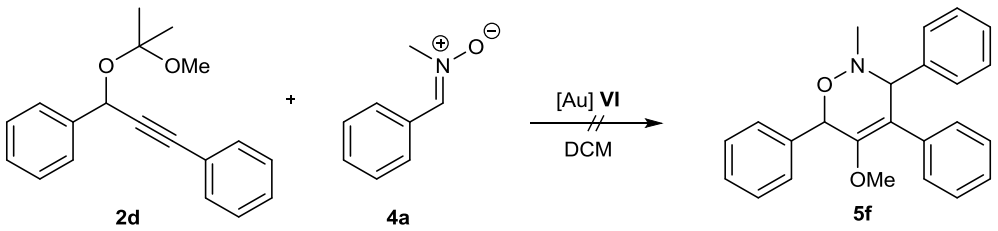


Figure 3.11: Chemical shifts of **7c**

Attempted synthesis of oxazine 5f and successful synthesis of trimers 9a-c

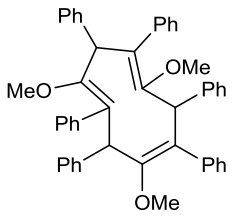
So far only terminal propargyl acetals have been tested and reported in the Fiksdahl group.[10b, 11-12] Au(I) catalysis is not limited to terminal alkynes because gold(I) coordinates to the alkyne instead of performing an oxidative additions as often observed in copper catalysis.[95] To investigate if using a substituted alkyne would afford the same reaction pattern, acetal **2d** and nitrone **4a** were attempted reacted to oxazine **5f**, Scheme 3.15.



Scheme 3.15: Attempted synthesis of oxazine **5f**

The reaction was completed after 30 min and TLC indicated that two major products had been formed. However, the product was not worked up before after 24 h. Silica flash chromatography of the sample gave two products samples, one containing a single pure compound **9a** as a white crystalline solid and another which appeared to be a white solid mixture of two diastereomers of the single isolated compound **9b-c**. The NMRs of these products suggested that a much more complex reaction than that of a single [3+3] cycloaddition, oxidation or hydration had occurred and that the major products were different diastereomers of a single compound.

The reaction initially proposed was that the target oxazine **5f** was formed, followed by a tandem cycloaddition reaction of the oxazine with a second acetal. However, the NMR shifts (Appendix Q) did not correspond with any possible structural combinations. HRMS (Appendix Q.8) gave a mass of 666.3132, which corresponds with $[M^+] = C_{48}H_{42}O_3$ and from this the product was suggested to be a trimer formed by cycloaddition of three propargyl units. To solve the structure, focus was paid to the HMBC spectrum, which showed that the three methoxy groups only coupled with vinylic ethers. Furthermore only three non-aromatic protons were observed in the molecules, all of which were assumed to be the benzylic protons of **2d** and have remained benzylic. A total of six aromatic rings were observed which was in accordance with the HRMS result. The double bond equivalent was calculated to be 28. The six phenyls were responsible for 24 of these and the vinyls for three. Consequently, the product had to be a monocyclic compound and proposed to be a 9-member ring. Only one 9-member ring was found to afford the benzylic protons as singlets observed in ^{1}H-NMR and without coupling in COSY. The suggested structure was that of **9a-c** and is depicted in Figure 3.12. The total yield for **9a-c** was 26 %. Configuration could not be determined as NOE correlations between the benzylic protons could not be observed and aryl protons were indistinguishable. Chemical shifts of compounds **9a-c** could not be assigned. Melting point was not measured because there was not sufficient compound after other analyses were performed.



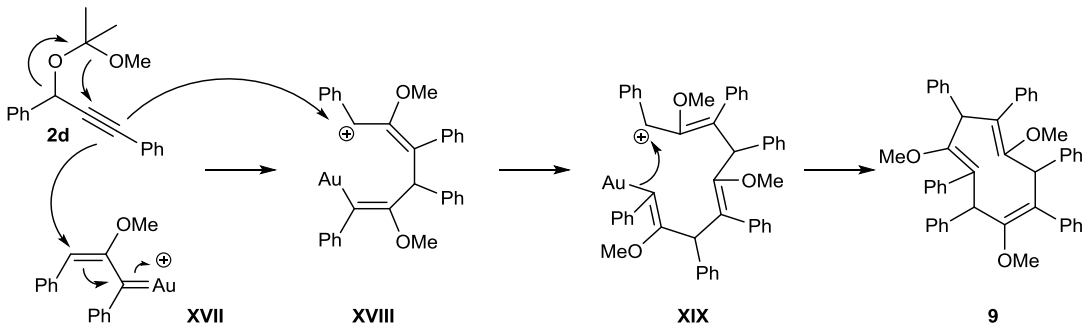
9a-c

Figure 3.12: Proposed structure of the trimer product **9a-c** of acetal **2d**

This is a highly symmetric structure and depending on the diastereomer, it would be expected that the protons would be equivalent in NMR if the product was an all *syn* diasteromer. In fact, only two diasteromers are possible for this compound, because of symmetry. However, three diasteromers or conformational structured were obtained. It was suggested that the crowded structure allows very limited mobility of the substituents and these may be "locked" in a certain conformation after the ring formation. This locking would then give rise to different shifts of the nuclei in the molecule, and is indeed observed. The methoxy shifts range from 2.5 to 3.2 ppm downfield of TMS, while benzylic protons have shifts of 4.5-5.5 ppm. Aromatic shifts as low as 5.8 were observed. These variations suggest a strong anisotropic effect in the structure, caused by the six phenyl substituents. The nuclei's position relative to the phenyls would either give strong shielding or de-shielding of the nuclei. This effect has previously been observed within the Fiksdahl group with other highly substituted ring systems.[20]

This reaction was hypothesized to be possible because of the diphenyl substituents on the propargyl acetal **2d**. These phenyl substituents stabilize the gold carbenoid**, XVII** in Scheme 3.16, than the terminal acetals **2a-c** and a longer lifetime of the intermediate is to be expected. A gold carbenoid can react with a propargyl acetal to

form a dimer, before reaction with a third unit of carbenoid or acetal closes the ring. This suggested mechanism is a tandem reaction and is presented in Scheme 3.16.



Scheme 3.16: Proposed mechanism for trimerization of acetal **2d** to compound **9**

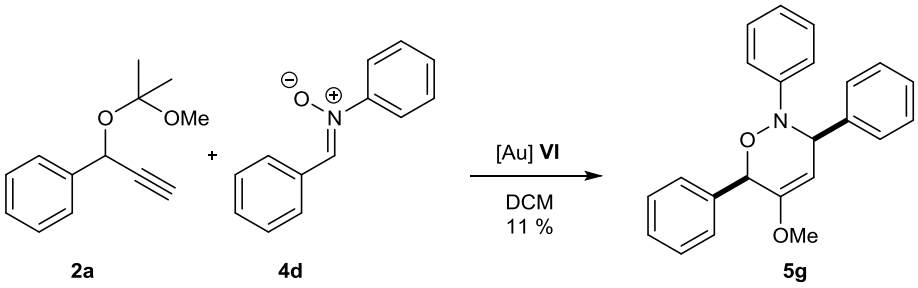
The reaction is proposed to proceed through nucleophilic attack of propargyl acetal **2d** on the gold carbenoid formed from acetal **2d**, **XVII**. The resulting intermediate, **XVIII**, is a highly stabilized allylic cation, which is attacked by a second acetal to afford intermediate **XIX**. Product **9** is obtained by ring closing and regeneration of the catalyst. Whether or not the propargyl acetal **2d** forms carbenoid with gold or coordinates with gold prior to the reaction is unknown. The effect of nitrone in the reaction was not investigated, but the initial assumption was that nitrones do not partake in the reaction and instead decreased the yield.

The question regarding the argument for the tandem mechanism in Scheme 3.16 is that ring closing to 6-membered rings takes place with reaction rates several magnitudes faster than 7-membered rings. Larger rings are expected to have even slower reaction rates. However, the dimer was not isolated nor observed for the reaction. An explanation is that the 6-membered dimer ring would be too sterically hindered to be formed, which allows the formation of the 9-membered trimer ring.

The reaction was only performed once, because the structure of the product was not solved until a week before submission deadline and there was not time to redo the reaction. Because the product had to be purified by two silica flash columns, higher yields are expected. To determine the nature of the reaction, further investigations need to be performed. Similar 9-membered ring synthesis methods were not found and this appears to be a novel preparation method for this ring structure.

Synthesis of oxazine 5g

So far, *N*-methyl nitrones have been observed to afford [3+3] cycloaddition, albeit at low yields. It was decided to investigate if *N*-aryl nitrones, Table 3.1 entry **7**-**11**, would be more reactive and selective towards [3+3] cycloaddition. The *N*-aryl substituents have a greater ability to stabilize the carbocation intermediate, because of resonance within the aromatic ring, in the reaction mechanism suggested in Scheme 3.9a, thus a faster reaction rate could be observed if formation of the carbocation was the rate-determining step. Acetal **2a** was reacted with nitrone **4d**, as shown in Scheme 3.17.



Scheme 3.17: Synthesis of oxazine **5g**

A higher reaction rate was observed for the reaction of acetal **2a** and nitrone **4d** compared to the reaction between acetal **2a** and nitrone **4a**. Acetal **2a** was fully converted in less than 30 min. Unfortunately, a very complex mixture of products were obtained according to TLC, even more complex than what was observed for the *N*-methyl nitrones. Increased complexity of the product mixture was proposed to be caused by reduction of nitrone to imine. The diaryl imine is an unsaturated compound which can react with propargyl acetal to form benzazepines. This reaction has previously been studied within the Fiksdahl group.[12] To isolate the desired oxazine **5g**, three column flash silica columns were performed in the order of *n*-pentane/EtOAc 100:1, *n*-pentane/DCM 10:1 and *n*-pentane/DCM/EtOAc 100:2:1. This choice was a result of the products not being soluble in the *n*-pentane/EtOAc eluent and limited separation in the *n*-pentane/DCM eluent. This afforded the product **5g** in a very modest yield of 11 %. Higher yields are expected if the isolation is successful after the first column. The oxidation product **5a** was observed by TLC for the reaction. The chemical shifts of product **5g** were assigned by 2D NMR (Appendix I) and are presented in Figure 3.13.

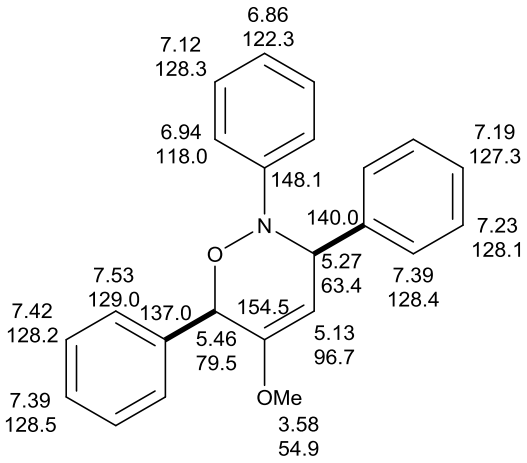
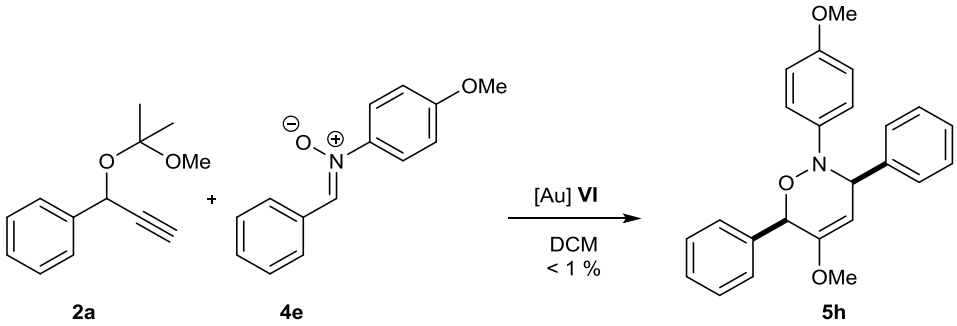


Figure 3.13: Chemical shifts of product **5g**

Attempted synthesis of oxazine 5h

Having observed that diarylnitrones afford oxazines with acetals, diarylnitrones containing substituents were investigated. The effect of using an *N*-aryl containing an electron-donating methoxy substituent was studied by reaction of acetal **2a** with nitrone **4e**, Scheme 3.18.

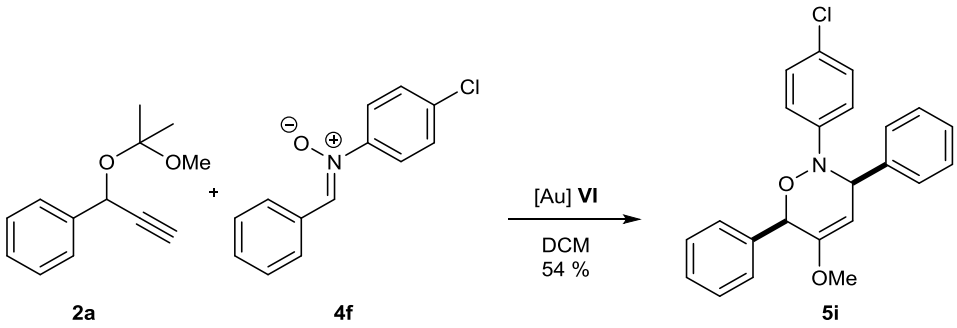


Scheme 3.18: Synthesis of oxazine **5h**

The reaction once more formed a multitude of compounds, according to TLC, and acetal was fully converted in 7 minutes. Aldehyde **6a** was observed as the major product in the reaction. The product **5h** was attempted purified, but could not be isolated. Small amounts of product with characteristic ^{1}H-NMR shifts were as impurities. Electron rich *N*-aryls appeared to favor oxidation by "C-3" attack instead of the desired "C-1" attack.

Synthesis of oxazine 5i

As an electron-rich *N*-aryl primarily afforded oxidation, nitrone **4f**, containing an electron poor *N*-aryl, was tested to investigate if this would reverse the selectivity and favor cycloaddition. The reaction of acetal **2a** and nitrone **4f** to oxazine **5i** is presented in Scheme 3.19.



Scheme 3.19: Synthesis of oxazine **5i**

The reagents were fully converted after 23 minutes and a major product was formed according to TLC. The product **5i** was isolated by silica flash chromatography, EtOAc:*n*-pentane 1:100, as a colorless wax in 54 % yield. This is the best yield afforded thus far and an increased selectivity towards cycloaddition at the expense of oxidation was observed. Electron poor *N*-aryl substituents give a higher regioselectivity towards "C-1" attack. The chemical shifts of product **5i** were assigned by 2D NMR (Appendix I).

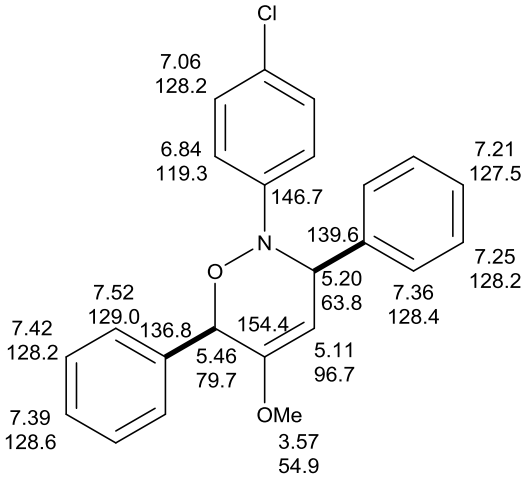
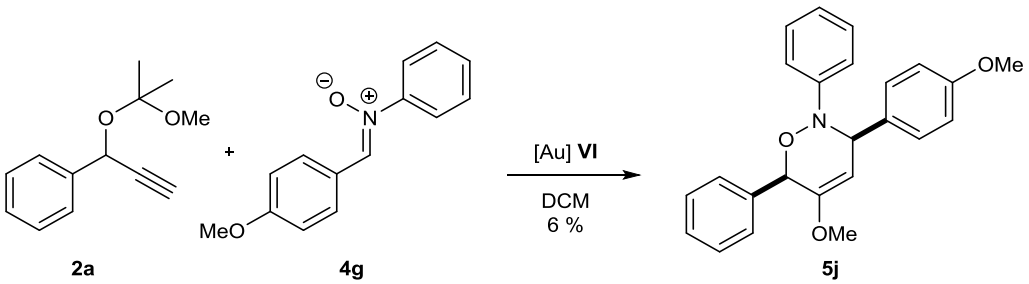


Figure 3.14: Chemical shifts of oxazine **5i**

Synthesis of oxazine 5j

The electron-rich diarylnitrone **4g** analogue of **4b** was reacted with acetal **2a** to synthesize oxazine **5j**, Scheme 3.20.



Scheme 3.20: Synthesis of oxazine **5j**

Acetal **2a** and nitrone **4g** were fully converted after 12 min. As observed for the previous methoxy substituted nitrones. **4b** and **4e**, oxidation to **6a** was the major product. A complex mixture of products was obtained. The oxazine **5j** was attempted purified by silica flash chromatography, eluent *n*-pentane/EtOAc 20:1. Product **5j** was obtained, but in a low yield of 6 % and with impurities of *p*-anisaldehyde **14b**. Aldehyde **14b** was formed by hydrolysis of the imine by-product afforded by nitrone oxidation of acetal. There was no time to purify the product further. The chemical shifts of product **5j** were assigned by 2D NMR (Appendix J) and are presented in Figure 3.15.

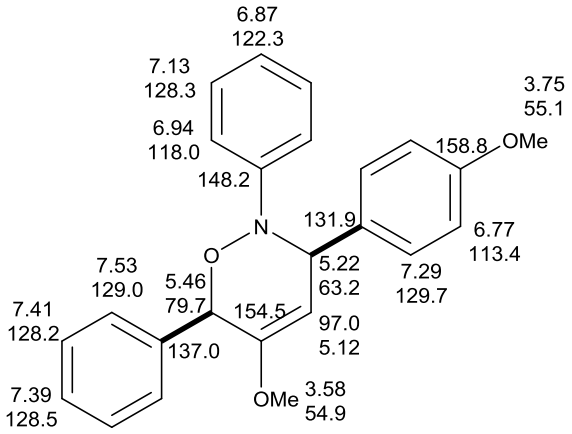
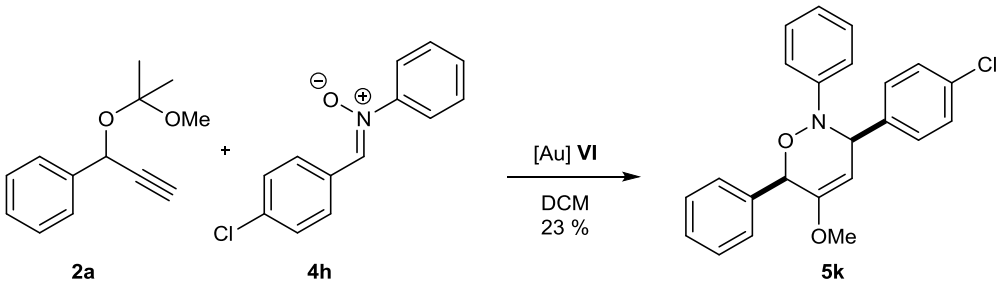


Figure 3.15: Chemical shifts of oxazine **5j**

Synthesis of oxazine 5k

To compare the effects of an electron withdrawing substituent on the non-*N*-aryl of the nitrone with the reaction to oxazines **5g** and **5j**, acetal **2a** and nitrone **4h** were reacted to **5k** as illustrated in Scheme 3.21.



Scheme 3.21: Synthesis of oxazine **5k**

The reaction was complete after 30 min. Several products were formed and product **5k** was isolated by silica flash chromatography, eluent *n*-pentane/EtoAc 100:1. Following the general trend observed for the reaction to oxazines, a higher yield was obtained for the reaction with electron withdrawing substituents on the nitrone. An initial preparation of compound **5k** had afforded 15-20 % yield, but because of decomposition the reaction had to be repeated. Due to errors with the NMR acquisition, COSY, HSQC and NOESY spectra were not obtained. Chemical shifts of product **5k** were assigned by HMBC (Appendix K) and shifts of previous compounds.

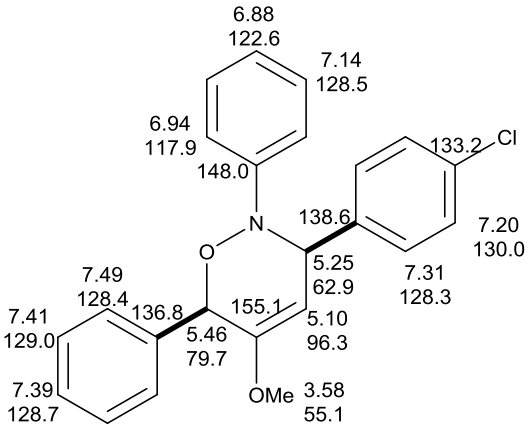
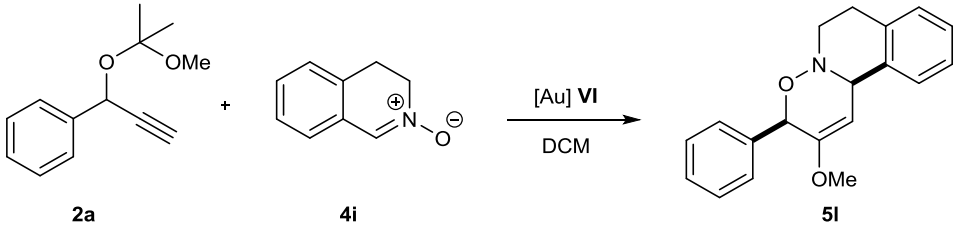


Figure 3.16: Chemical shifts of oxazine **5k**

Attempted synthesis of oxazine 5l

All the nitrones investigated, **4a-h**, have been non-cyclic nitrones, and therefore the cyclic nitrone **4i** was reacted with acetal **2a**, Scheme 3.22.



Scheme 3.22: Synthesis of oxazine **5i**

Full conversion of acetal was obtained within 2 h. Several products were worked up, but the product **5l** could not be identified. HRMS suggested formation of the tricyclic product. The oxidation product **6a** was observed. Other products than usually observed for the reaction to oxazine appeared to have been obtained, but these were not isolated and there was no time to investigate the reaction further.

General remarks

In this section the novel [3+3] cycloaddition reaction between propargyl acetals and nitrones was investigated. In all successful reactions, high diastereoselectivity was obtained. Higher yields were obtained with nitrones containing electron withdrawing groups. Strongly electron donating methoxy substituents on the nitrones primarily afforded oxidation. Higher reaction rates were obtained for diaryl nitrones than for *N*-methyl nitrones, but an increased number of background reactions were observed. Increasing the electron donating character of the substituents on the propargyl acetal increased the reaction rate. A novel 9-membered ring synthesis was obtained by trimerization of propargyl acetal **2d**.

The ^{1}H-NMR shifts of the oxazine ring were found to be characteristically broad and found in the region 4.2-5.3 ppm downfield from TMS. Splitting of the signals within

the oxazines **5a-d** as result of coupling between neighboring protons was not observed. The suggestion for this is that the dihedral angle between the two protons is approximately 90°. From the Karplus equation this would give a coupling close to 0 Hz.[96] For the oxazines **5g-k** splitting of the signals was observed, with J = 3.4-4.5 Hz. These results suggest that *N*-methyl and *N*-phenyl oxazines rings have different bond angles.

NOESY spectra were taken to validate the isomerism of the compounds. However, because of incorrect acquisition parameters in experiments conducted at St. Olavs Hospital, the signal to noise ratio was too poor to provide useful data. All product oxazines were assumed to have *cis* isomerism as the major product. This could be assumed because the reaction mechanism would be the same and the similar steric factors would be determining in the transition state in all cases.

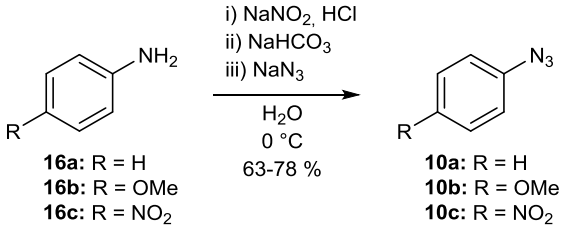
Because of the number of products formed in the reactions to oxazines, the reactions were monitored by NMR or IR when possible. Reactions were initially performed in small scale in order to identify the retention of the product and improve yield.

3.3 Au(I) catalyzed reactions of propargyl acetals with azides and imines

In this section, preparation of azides and imines are presented. Gold(I) catalyzed reactions of propargyl acetal **2a-d** with azides **10a-d** and imines **12-13** are presented.

3.3.1 Preparation of azides

Azides are allenyl 1,3-dipoles and can react with propargyl acetals through a [3+3] cycloaddition reaction as was observed for nitrones. Arylazides **10a-c** were prepared from their respective arylamines **16a-c** following a reported procedure, Scheme 3.23.[97]

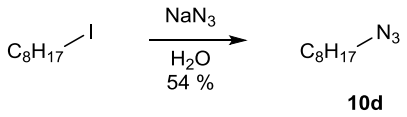


Scheme 3.23: Synthesis of azides **10a-c**

By the reported procedure, azide **10a** was isolated as a yellow solid in 78 % yield. Azides **10b** and **10c** were isolated in 68 % and 63 % yield, respectively. All three azides were isolated by silica flash chromatography. Azides should not be stored pure, even in small amounts if containing a C/N ratio below 3, because of their instability.[98] Therefore, azides **10a** and **10c** were prepared just ahead of their reactions. Azidobenzene **10a** was attempted stored by dissolving in THF, but decomposed even at -20 °C. Interestingly, azide **10c** proved to be stable when stored dissolved in THF at -20 °C, despite a C/N ratio of 2. This indicates that the nitro

group actually stabilizes the compound relative to hydrogen. As a result of this metoxyazide **10b** was used as the main azide in this study, as its C/N ratio of 2.67 is the same as for azidooctane **10d**, which can be stored safely in the freezer when dissolved in THF. ^{1}H-NMR corresponds with literature.[99]

To investigate if alkylazides reacted differently from arylazides, alkylazide **10d** was prepared by a S_N2 reaction from 1-iodooctane according to a reported procedure, illustrated in Scheme 3.24.[100]



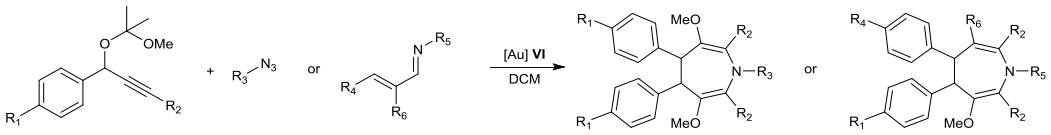
Scheme 3.24: Synthesis of azide **10d**

For the reaction, sodium azide was added in excess to avoid back-substitution of iodide. The reaction could not be monitored by TLC as neither the reactant nor product **10d** were visible. The reaction was assumed to have gone to completion and worked-up. The azide, **10d** was obtained in 54 % yield. Because the ^{1}H-NMR spectra of azide **10d** and iodooctane **22** were so similar, ^{13}C-NMR was used to confirm full conversion to pure azide **10d** after work-up.[101]

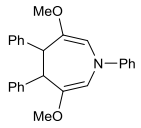
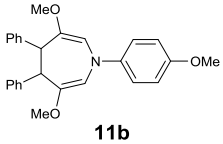
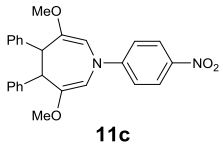
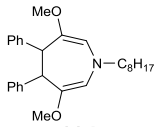
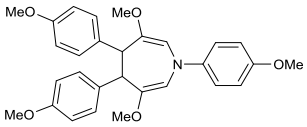
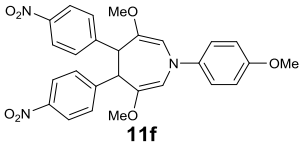
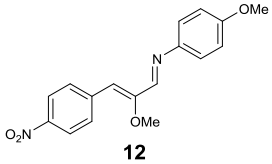
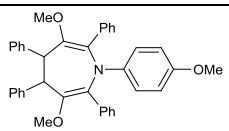
3.3.2 Gold catalyzed reactions of propargyl acetals with azides and imines

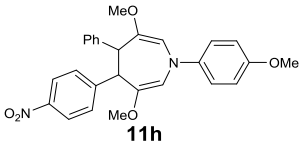
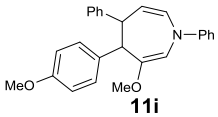
The reaction and conditions of all gold(I) catalyzed reactions relevant to the formation of the azepines are presented in Table 3.3. Unless noted otherwise, the reactions were carried out in equimolar amounts of acetal and azide. Catalyst **VI** was used as catalyst (2.5 % relative to the amount of acetal). All reactions were performed in DCM.

Table 3.3: Details for reactions of propargyl acetals with azides and imines



2a-d **10a-d** **12, 13** **11a-g** **11h, i**

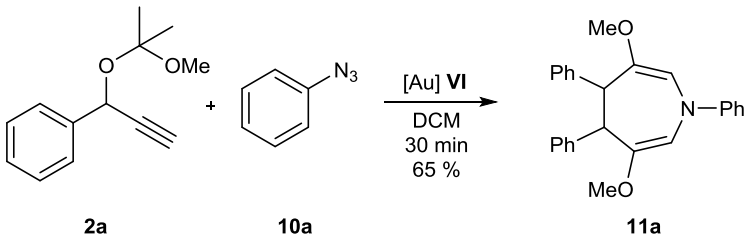
Entry	Acetal	Azide/ Imine	Product	Rx.	Rx. temp [°C]	Rx.time [min]	Yield [%]
1	**2a** R_1 = Ph R_2 = H	**10a** R_3 = Ph	 **11a**	i	-20	120	75
				ii	0	30	84
				iii[a]	20	30	65
				iv	20	30	78
2	**2a** R_1 = Ph R_2 = H	**10b** R_3 = *p*-OMe	 **11b**	i	-78	480	-[b]
				ii	-40	240	72
				iii	-20	120	54
				iv	0	30	82
				v[c]	20	30	67
3	**2a** R_1 = Ph R_2 = H	**10c** R_3 = *p*-NO_2	 **11c**	i	20	1440	78
4	**2a** R_1 = Ph R_2 = H	**10d** R_3 = *n*-C_8H_{17}	 **11d**	i	20	1440	-[d]
5	**2b** R_1 = *p*-OMe R_2 = H	**10b** R_3 = *p*-OMe	 **11e**	i	20	15	94
6	**2c** R_1 = *p*-NO_2 R_2 = H	**10b** R_3 = *p*-OMe	 **11f**	i	20	1440	42
6	**2c** R_1 = *p*-NO_2 R_2 = H	**10b** R_3 = *p*-OMe	 **12**	i	20	1440	31
7	**2d** R_1 = Ph R_2 = Ph	**10b** R_3 = *p*-OMe	 **11g**	i	20	30	-[d]

8	**2a** R_1 = Ph R_2 = H	**12** R_4 = *p*-NO_2 R_5 = *p*-OMe R_6 = OMe	 **11h**	i	20	60	54
9	**2b** R_1 = *p*-OMe R_2 = H	**13** R_4 = Ph R_5 = Ph R_6 = H	 **11i**	i	20	120	-[d]

a) 5 % Catalyst **VI** and 3 eq. azide was used.
b) No reaction.
c) 0.5 eq. azide was used.
d) Product could not be isolated.

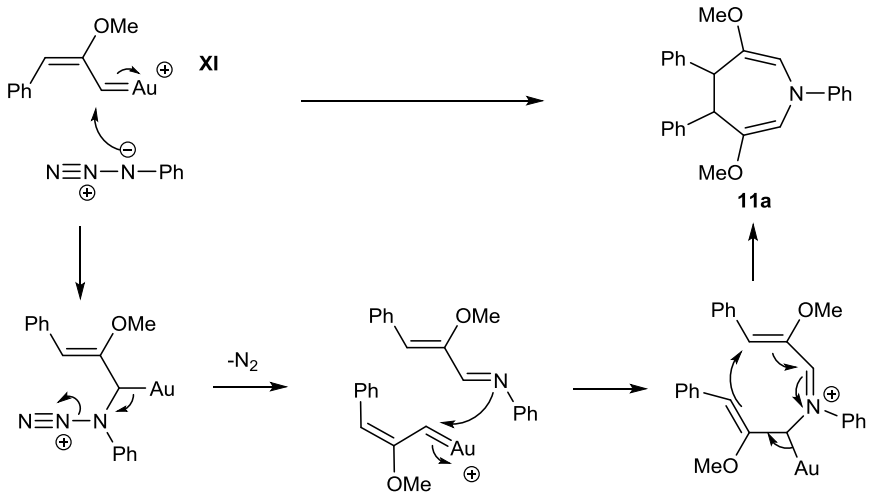
Synthesis of azepine 11a and initial studies

Based on the discovery of the cycloaddition reaction between propargyl acetals and nitrones, it was suggested that propargyl acetals and azides could afford a similar [3+3] cycloaddition reaction to novel 1,2,3-triazines structures. Both nitrones and azides are 1,3-dipoles. However, azides were believed not to possess the oxidative nature inherent to nitrones and were proposed to be able to selectively react through a [3+3] cycloaddition reaction without the byproducts observed for nitrones. Hence, propargyl acetal **2a** was reacted with three equivalents of azide **10a**, as illustrated in Scheme 3.25.



Scheme 3.25: Synthesis of azepine **10a**

The reaction was complete after 25 min and the reaction mixture turned red upon full conversion. A major product was obtained, which afforded a blue color on the TLC plate upon staining with *p*-anisaldehyde stain, without heating. Heating discolored the stain yellow. No intermediates could be observed from by NMR of the crude mixture, conversion >99 %, and only one diastereomer of the product was observed. The azepine **11a** was isolated in 65 % yield by silica flash chromatography, eluent *n*-pentane/EtOAc 40:1. No triazine was observed for the reaction. From the structure of the azepine **11a** and an article found during the writing process covering the reaction between propargyl esters and azides,[65] a reaction mechanism was proposed, presented in Scheme 3.26.



Scheme 3.26: Proposed reaction mechanism for formation of azepine **11a** by Au(I) catalysis of propargyl acetal **2a** and azide **10a**

It was suggested that the reaction takes place by an initial addition of azide to the "C-3" position of the gold carbenoid **XI**. A conjugated imine is formed by elimination of N_2 and regeneration of the catalyst. This imine may then undergo a [4+3] cycloaddition reaction with another acetal carbenoid to afford the azepine.

To improve the possibility of a reaction, the first attempted reaction to **11a** was performed with three equivalents of azide. Upon discovering the rapid reaction rate, the amount of azide was reduced to equimolar amounts as stated at the start of this section. Also, the amount of catalyst was reduced to 2.5 % for the remaining reactions. These conditions increased the yield to 78 % and only a minor reduction of the reaction rate was observed. The conditions from entry 1, rx. iv, were therefore kept as part of the standard conditions. Decreasing the temperature from 20 °C to 0 °C and then -20 °C did not alter the product selectivity with yields of 84 % and 75 %.

In the initial phases, before HRMS was measured, a second improbable structure of the product was suggested in compound **11a'**, Figure 3.17, by a tandem [3+3], [3+3] cycloaddition reaction.

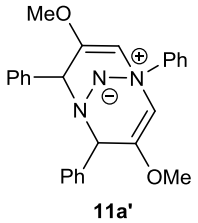


Figure 3.17: Suggested structure of a tandem [3+3], [3+3] cycloaddition reaction product

The compound **11a'** was believed to be unstable. To differentiate between the two possibilities, **11a** and **11a'**, the product was dissolved in styrene and heated to reflux in 2 h to observe if any reaction occurred. If present, compound **11a'** could act as a trapped nitrene and could afford a [2+1] cycloaddition reaction with styrene at

elevated temperatures, while **11a** would hopefully remain unreactive and not decompose. After purification of the reaction mixture by silica flash chromatography, the starting compound was regenerated and proven stable up to 145 °C, which strongly indicating the structure not being that of **11a'**. This was later confirmed by HRMS, Appendix S.8.

The chemical shifts of the product were assigned by 2D NMR (Appendix S) and are shown in Figure 3.18. Because of the symmetry of the molecule, the stereochemistry could not be determined by NOESY. The reaction mechanism would suggest *anti*-configuration of the product, because of less interaction between the neighboring phenyls in the transition state. High selectivity towards the *anti* diastereomer was obtained in previous studies of gold(III) catalyzed reactions to azepines from propargyl esters.[29, 65]

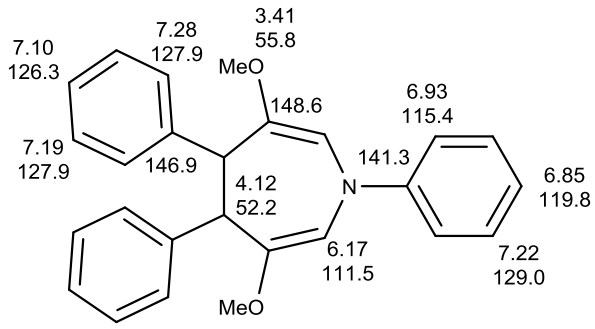
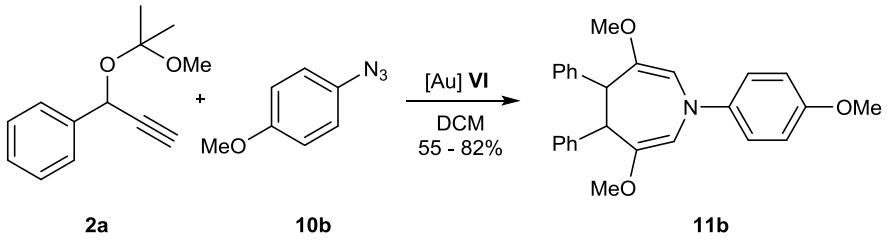


Figure 3.18: Chemical shifts of product **11a**

Synthesis of azepine 11b and attempts at functionalization of azepine

In same manner as performed for the oxazines, different substituents of the reactants were tested in order to observe their effect on the product selectivity and yields. Using the reaction conditions determined for the reaction to azepine **11a**, azepine **11b** was prepared from acetal **2a** and azide **10b**, illustrated in Scheme 3.27.



Scheme 3.27: Synthesis of azepine 11b

Similarly to azepine **11a**, product **11b** was reacted at different temperatures, at -78 °C, -40 °C, -20 °C, 0 °C and 20 °C. The only observable effect was increasing reaction rate with increasing temperature. As for **11a**, all reaction mixtures turned red upon full conversion (15 min at 20 °C) and a blue/green color was produced upon *p*-anisaldehyde staining of the TLC-plate. Again heating discolored the stain yellow. Only one diastereomer was observed for the reaction and the product **11b** was isolated by silica flash chromatography, eluent *n*-pentane/EtOAc 20:1, as a white solid 55-82

% yield. The temperature of the reaction was decreased to -78 °C in order to investigate if the triazine could be isolated or observed. However, at -78 °C there was no reaction. At -40 °C, the azepine was afforded, albeit at a slow rate, 4 h. Stoichiometric amounts of acetal and azide were used in entry **v** for **11b**, in order to investigate if this had any effect on yield and selecivity, but apart from a slight retardation of the reaction rate, no other effects were evident. Stoichiometric amounts were not used for the remaining reactions, as it was decided to keep the acetal as limiting reactant, since it allowed the isolation of the proposed intermediate imine, Scheme 3.23. Isolation of imine would be possible if the reaction rate to imine exceeds the reaction rate of [4+3] cycloaddition to azepine.

The *syn*/*anti* configuration of product **11b** was attempted determined by Chiral HPLC, where a single peak would indicate *syn* configuration (meso-stereomer) and two peaks would indicate *anti* configuration (enantiomers). Only one peak was observed, which was inconclusive as it could merely mean no separation of the enantiomers. A powder X-ray crystallography measurement of the azepine **11b** was performed to determine the configuration, Appendix V.9. At the time of writing, the data had not been analyzed. If left at room temperature in chloroform, the product started decomposing $t_{1/2}$ = 5-6 days, affording a dark green mixture. If stored isolated in the fridge, no decomposition was observed after two months. This suggested that the compound was liable in the presence of acids. The chemical shifts of the product were assigned by 2D NMR (Appendix T) and are shown in Figure 3.19.

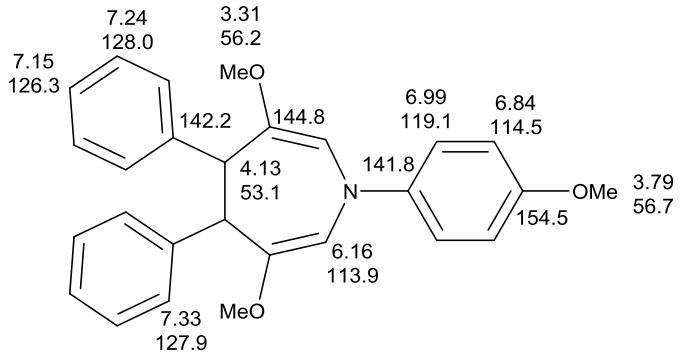
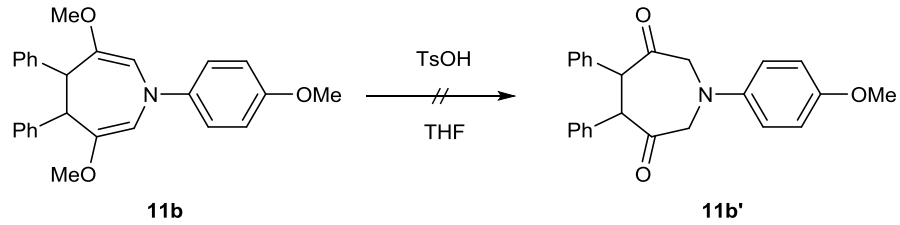


Figure 3.19: Chemical shifts of product **11b**

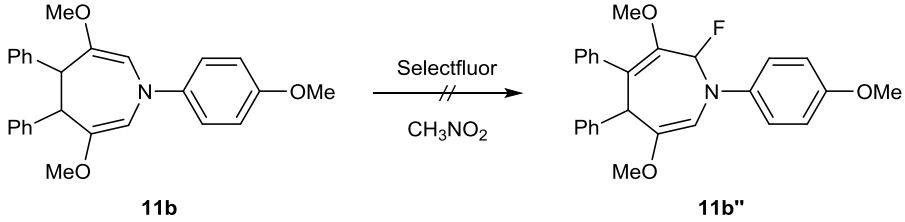
Vinyl ethers are precursors for ketones, and the ketone **11b'** was attempted prepared from azepine **11b**. Analysis of the ketone **11b'** could determine the *cis*/*anti*-configuration of compound **11b** because characteristic NOE correlations would be expected to be observed between the α-carbonyl and benzyl protons. Hence, the *cis*- and *trans*-configurations would give rise to different NOE correlations. This was attempted by treating azepine **11b** with *p*-tosylic acid (30 mol %) in THF, Scheme 3.28.[102]



Scheme 3.28: Attempted synthesis of product **11b'**

The reaction mixture turned dark green before turning brown as the reaction went on. NMR of the crude mixture indicated that the azepine had completely decomposed within 1 hour, without the formation of any apparent main compounds and the target ketone could not be isolated. What appeared to be smaller fragment molecules were observed. Decreasing the temperature to 0 °C and reducing the amount of acid to 10 % also failed to afford the ketone, with the reaction proceeding in similar fashion.

As an alternative to the hydrolysis, Selectfluor was attempted reacted with one of the vinyl ethers of azepine **11b** to afford a fluorinated azepine **11b''**, to investigating if the azepine was suitable to electrophilic fluorination, Scheme 3.29.[102]



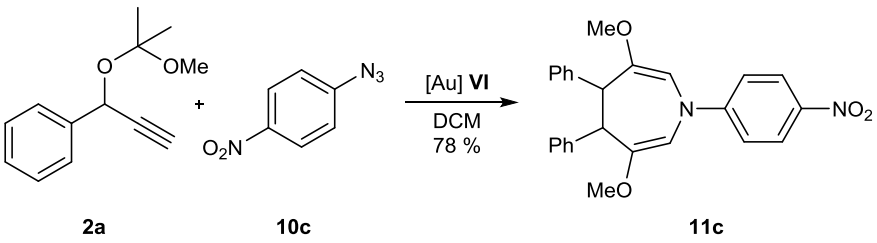
Scheme 3.29: Attempted synthesis of product **11b''**

Here the reaction mixture spontaneously turned dark blue before shading to brown after 30 min. NMR of the crude mixture showed decomposition of the product to numerous products and no specific products were isolated.

These two observations could suggest that the vinyl ether is too electron rich, at least in the case of **11b**, as both acid and electrophiles lead to decomposition. In the reaction with electrophile to **11b''**, there was a possibility of polymerization of the vinyl ether by living cationic polymerization. Vinyl ethers have been reported to afford polymerization by addition of electron acceptors.[103] Hence, Selectfluor could act as an initiator for polymerization in the presence of this electron rich azepine.

Synthesis of azepine 11c

Having tested azide containing an electron rich aryl substituent, the azide **10c** with an electron poor aryl substituent was reacted with acetal. In Scheme 3.30, the preparation of azepine **11c** from acetal **2a** and azide **10c** is illustrated.



Scheme 3.30: Synthesis of azepine **11c**

Following the general procedure, azepine **11c** was reacted at 20 °C until full conversion was observed by TLC, 24 h. Again the reaction mixture turned red upon full conversion. Slight heating of *p*-anisaldehyde stain on TLC afforded a green color which turned yellow upon further heating. Two diastereomere were isolated as a yellow mixture in a combined yield of 78 %. A diastereomeric ration of 3:1 was observed by NMR.

The chemical shifts of the isomers were based on 2D NMR (Appendix U) and are shown in Figures 3.20 and 3.21.

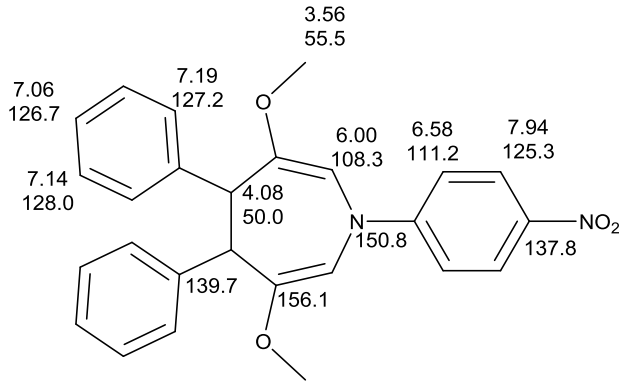


Figure 3.20: Chemical shifts of product **11c**

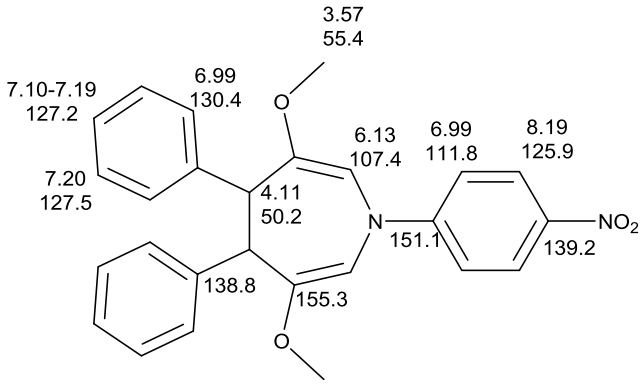
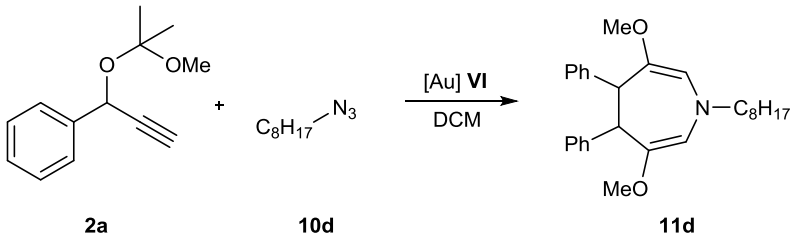


Figure 3.21: Chemical shifts of product **11c'**

Attempted synthesis of azepine 11d

After preparing azepine **11c** with good yields, the question was if using a presumably less reactive substituent would yield a reaction. Azepine **11d** was attempted synthesized from alkyl azide **10d**, Scheme 3.31, despite the alkyl chain's poor ability to stabilize the charged transition state in the suggested mechanism, Scheme 3.26.

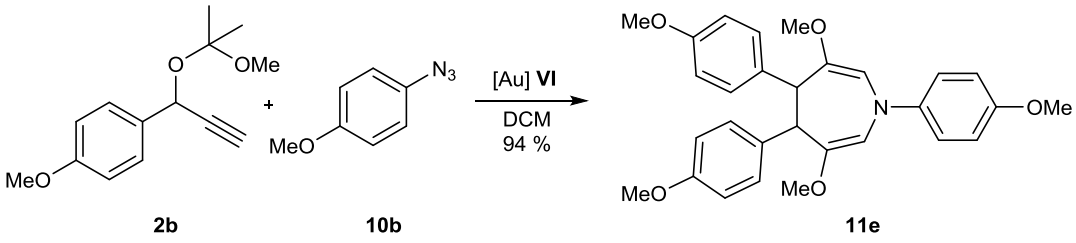


Scheme 3.31: Attempted synthesis of azepine **11d**

TLC suggested that **11d** was formed after 24 h, but only low conversion was obtained. The product turned blue without application of *p*-anisaldehyde stain on TLC and upon purification with silica flash chromatography, the product readily decomposed on the column as a blue ring was formed on the column before disappearing completely. This instability could be caused by an increase in the electron density of the vinyl ether bond, as the alkyl chain is even more electron donating than the *p*-methoxyphenyl in **11b**. Toste et al.[29] did not report any *N*-alkyl imine reactants, which could suggest that they experienced similar problems with reactivity. The silica used in flash chromatography contains Lewis acid sites, which can act as electron acceptors. This was proposed as the reason for the reaction on the column. Liu et al.[65] countered the problem with low reactivity of alkyl azides by adding five equivalents of propargyl ester.

Synthesis of azepine 11e

Having investigated the effects of changing the substituents on the azide, the influence of electron donating groups was acetal **2b** was reacted with azide **10b** to afford azepine **11e**, according to Scheme 3.32.



Scheme 3.32: Synthesis of azepine **10e**

In the reaction, full conversion to azepine **11e** was obtained after 5 min, when the reaction mixture turned red. Upon staining with *p*-anisaldehyde stain on TLC, a blue color was observed. Further heating changed the color of the stain to yellow. The product was purified by silica flash chromatography, eluent *n*-pentane/EtOAc, and

was afforded as a colorless viscous oil in 94 % yield as a single diastereomer. In the same manner as the compounds described above, **11b** and **11d**, instability was observed for product **11e**, with a $t_{1/2}$ < 2 h in chloroform at 20 °C.

The chemical shifts of the product **11e** were assigned by comparing with shifts of the other azepine products and are presented in Figure 3.22. The product decomposed before 2D NMR experiments were performed. ^{1}H- and ^{13}C-NMR spectra were obtained (Appendix V).

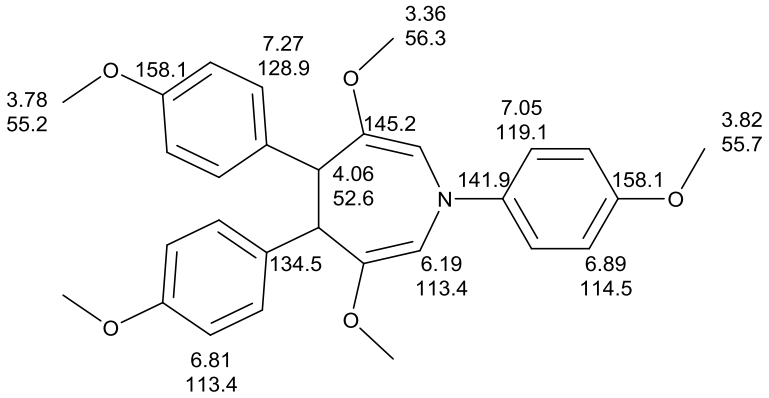
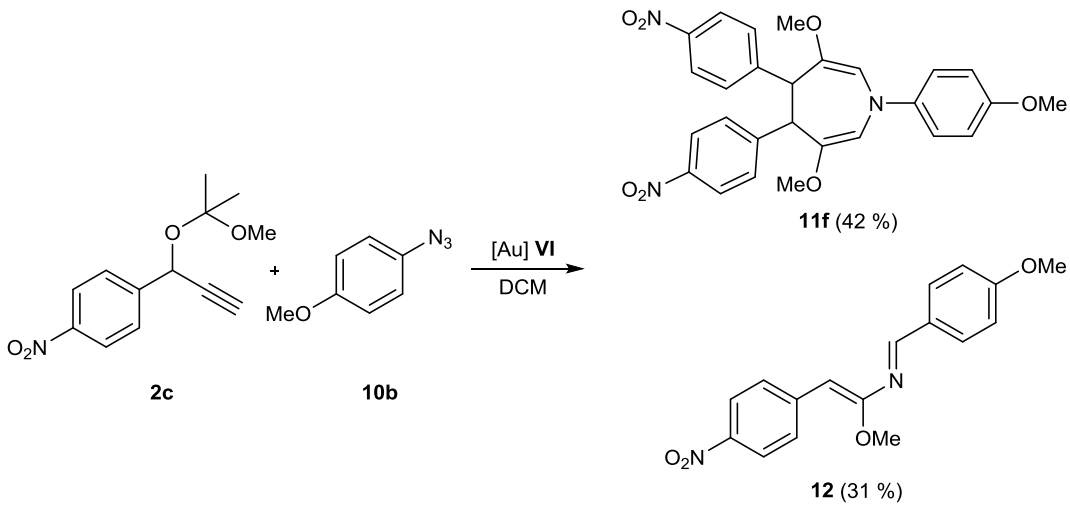


Figure 3.22: Chemical shifts of product **11e**

Synthesis of azepine 11f and imine 12

To test the final aryl substituent of the reaction between propargyl acetals and azides the acetal **2c** containing an electron-withdrawing nitro group was reacted with azide **10b** to azepine **11f**, illustrated in Scheme 3.33.



Scheme 3.33: Synthesis of azepine **11f** and imine **12**

In this case, azepine **11f** was prepared from acetal **2c** and azide **10b**, but unlike the previous reactions an imine **12** was isolated despite full conversion of acetal, in 24 h. The reaction mixture changed color to red when the reaction was complete. Staining

the TLC-plate with *p*-anisaldehyde stain did not produce a blue/green color upon heating the product even when heated, but a yellow stain for both products with R_f values of 0.42 for product **11f** and 0.45 for imine **12**, eluent *n*-pentane/EtOAc 4:1. The two compounds were isolated by silica flash chromatography, in an eluent of EtOAc:pentane 1:5, to afford product **11f** and **12** in respective yields of 42 % and 31 %. Only one diastereomer of **11f** was observed.

The isolation of the imine **12** supports the suggested mechanism illustrated in Scheme 3.23, as it is analogue to the intermediate imine. Isolation of the intermediate imine **12** in this reaction is believed to be due to comparable reaction rates of acetal **2c** with imine **12** and with azide **10b**, therefore expending the acetal **3c** on the formation of both azepine and triazine. This observation suggests that for other reported reactions **11a-e**, the imine intermediates have a higher reaction rate than the starting azide which is the reason imine intermediates have not been observed. To confirm that the imine **12** is an intermediate of the product **11f**, imine **12** was added more acetal **2c**, affording the azepine **11f** in a yield of 52 %, thus confirming this hypothesis. The low yield obtained in this reaction is believed to be caused by the small amount of substrate reacted.

The chemical shifts of product **11f** and **12** were assigned by 2D NMR (Appendix W and Y) and are presented in Figure 3.23 and Figure 3.24, respectively.

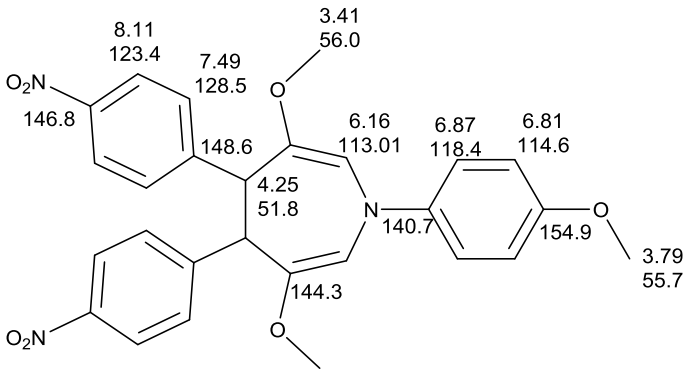


Figure 3.23: Chemical shifts of product **11f**

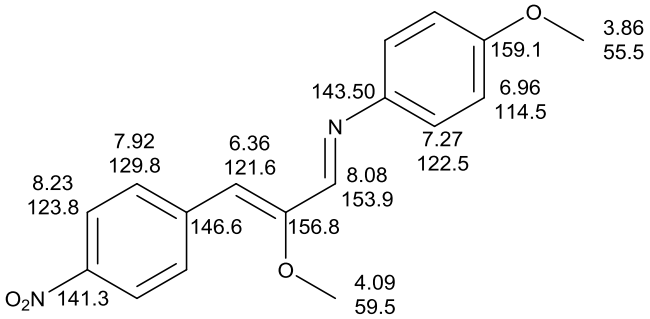
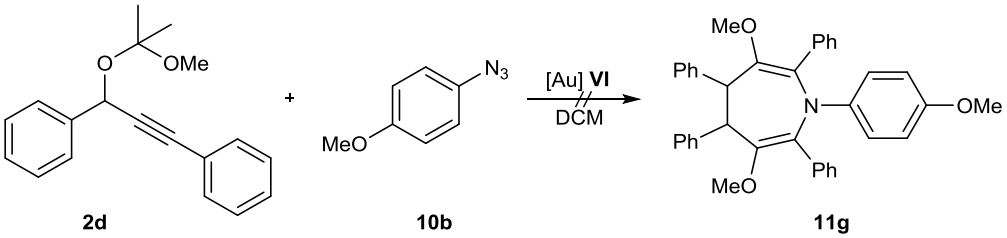


Figure 3.24: Chemical shifts of product **12**

The lack of NOE correlation between the methoxy and vinyl protons, indicates a (*Z*)-configuration of the imine **12**.

Attempted synthesis of azepine 11g

Although the reaction of acetal **2d** and nitrone **4a** did not appear to give a [3+3] cycloaddition reaction as intended, acetal **2d** and azide **10b** were reacted to see if this would produce a different result and afford azepine **11g**, Scheme 3.34.

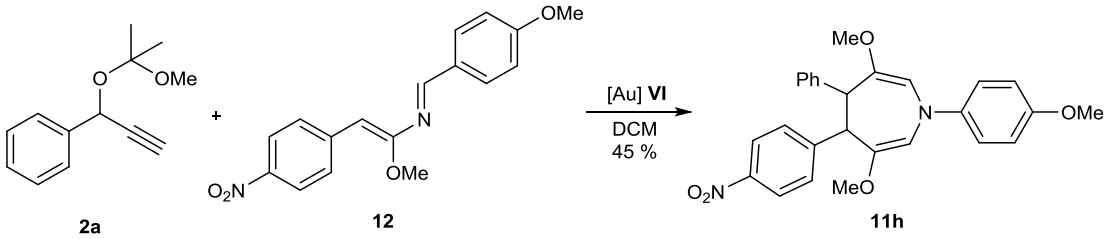


Scheme 3.34: Attempted synthesis of azepine **11g**

The acetal was fully converted within 30 min, and a complex mixture of products was observed by TLC. Staining with *p*-anisaldehyde stain and heating did not produce any colored stains, but weak spots on TLC with similar retention as product **9** was observed. Isolation by a gradient column *n*-pentane/EtOAc 40:1 → 5:1 was attempted, but no specific product was isolated. The higher reaction rate of azide **10b** with propargyl acetals compared to the reaction rate of nitrone **4a** with propargyl acetals could be the reason for why compound **9** was not formed.

Synthesis of azepine 10h

All the azepines produced this far have been symmetrical in structure and NOE correlations of the stereochemistry did not provided satisfactory insight. Therefore, reacting acetal **2a** with imine **12** was performed in order to prepare azepine **11h** containing three distinct aryl substituents, Scheme 3.35. This would give rise to different shifts for the benzylic positions as well as coupling between these. These couplings were indeed observed, as shown in Figure 3.25. The NOE correlation between the two benzylic protons was observed, but because of possible bond rotations, it was not possible to determine if product **11h** has a *trans* or *anti* configuration of the neighboring aryls.



Scheme 3.35: Synthesis of azepine **11h**

For the reaction, the mixture turned red upon completion of the reaction and staining with *p*-anisaldehyde stain on TLC afforded a blue color, which turned yellow upon heating. Silica flash chromatography gave the product as a yellow oil in a yield of 45

%. As an excess of acetal **2a** was applied, the alcohol **1a** was obtained as a major impurity in the product, but assignment of NMR shifts was still possible from 2D spectra (Appendix X), Figure 3.25.

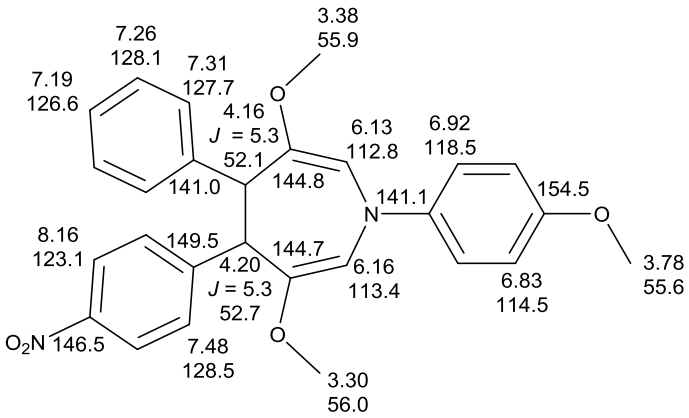
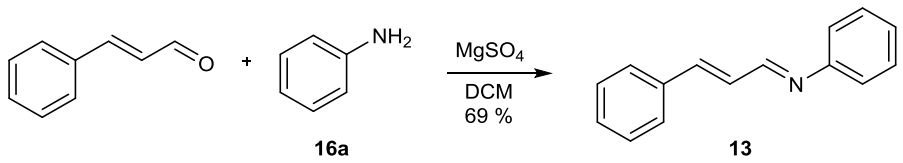


Figure 3.25: Chemical shifts of product **11h**

Azepine formation by [4+3] cycloaddition of propargyl acetal 2a and conjugated imine 13

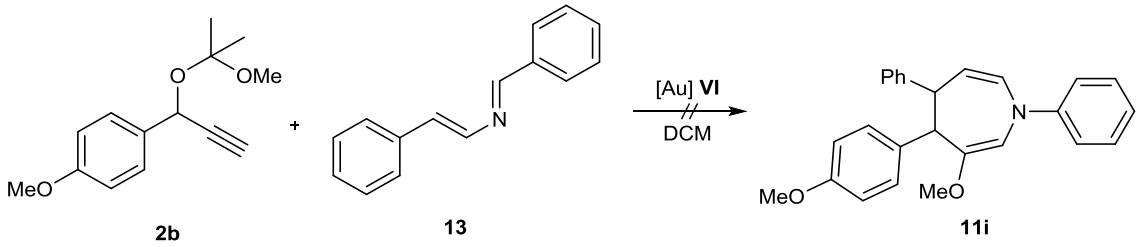
From the previously observed reactivity of imine **12** and other imine intermediates formed during the tandem reaction as well as results from Toste et al.[29], a simple conjugated imine, **13**, was prepared in order to investigate if [4+3]-cycloaddition with propargyl acetals was possible. This imine differs from what was used in the work by Toste,[29] by not having a substituent in the β-position of the imine.



Scheme 3.33: Synthesis of imine **13**

The imine **13** was prepared by a standard condensation reaction from cinnamaldehyde and amine **16a** following a reported procedure.[104] The product **13** readily crystallized upon removal of solvent and was washed with ethyl acetate to afford a yellow solid in 69 % yield. ^{1}H-NMR corresponded with literature.[105]

Acetal **2b** was reacted with imine **13** in the presence of gold catalyst **VI**, Scheme 3.34 To improve the possibility of reaction, 3 equivalents of imine was added. The acetal **2b** was used in order to distinguish between NMR shifts of aryl substituents of the target azepine **11i**.



Scheme 3.34: Attempted synthesis of azepine **11i**

The reaction was completed after 2 h at 20 °C, but it appeared that more than a single product had been formed. Purification by silica column chromatography afforded mixtures of compounds, with similar patterns to what has been observed for degradation of azepine **11b** and **11e**. NMR-peaks in the area 3.3-4.0 ppm downfield from TMS, corresponding to azepine structures, could be observed. This suggests that the azepine **11i** is initially formed, but that the vinyl ether/amine present in the molecule is too electron rich and thusly readily decomposes. Consequently, a less electron rich acetal, such as **2a** should be tested with **13** to investigate if this yields a more stable product. The synthetic approach to azepine **11h** and **11i** allows synthesis of non-symmetrical azepines.

General remarks

In the present study, the novel synthesis of azepines through a tandem reaction from propargyl acetals and azides was presented. This procedure allows highly diasteroselective synthesis of azepines through gold(I) catalysis in high yields. Compared to the previously reported procedure with propargyl esters and azides, only one equivalent of acetal was required to obtain full conversion, instead of five.[65] The reaction could also be performed with stoichiometric amounts of acetal and azide. The reaction rate was found to increase when propargyl acetals and azides contained electron donating substituents. The azepines were found to be stable when heated, but susceptible to electrophiles and acid. The stability of the azepines appeared to decrease with increasing electron density within the azepine ring.

Notification

The NMR situation during the period of this master's thesis was very difficult. In the initial period, from January until March there was full access to NMR facilities locally at NTNU. NMR measurements could be performed personally and there was no delay between delivery of the sample, measurement and results. In the period April to June, NMR measurements were performed at St. Olavs Hospital due to renovation. During this period the shortest time it took from delivery to retrieval of results were two days. However, the service was at times marred by failure, breaks in the running of samples of up to three weeks and incorrect acquisition parameters, which led to products having to be remade as a result of decomposition and need to re-measure. This brought the work to almost a stand-still in this period. Because of an error with the NMR equipment, some compounds lack 2D NMR spectra.

4. Conclusion

In this master's thesis, new Au(I) catalyzed cycloaddition reactions of propargyl acetals have been performed and three novel reactions have been developed. Oxazine and azepine heterocycles were obtained by novel gold(I) catalyzed methods. The new approach allows for highly diasteroselective preparation of these compounds at high reaction rates. Furthermore, a novel 9-membered ring synthesis was discovered by trimerization of propargyl acetal.

1,2-Oxazines containing a variety of substituents were formed by [3+3] cycloaddition reactions between acetals. The oxazines **5a**,**c-d**,**g**,**i-k** were obtained in 6 – 54 % yield. High diastereoselectivity towards the *cis* isomer was obtained, with no *trans* observed in the reactions. Two major by-products were formed in the reactions to oxazines, aldehydes **6a-c** and ketones **7a-c**, in respective yields of 0.4 - 39 % and 17 - 36 %. These products are formed by attack of the nucleophile on different positions of the propargyl acetals.

Azepines were prepared by a novel tandem reaction between propargyl acetal and azide. The reaction is proposed to pass through an oxidation of acetal to imine and a [4+3]-cycloaddition between propargyl acetal and imine. Azepines **11a-c, 11e-f**, were synthesized and isolated in yields of 42 – 94 %. An intermediate imine **12** was isolated in a yield of 31 % and used to prepare the azepines **11f** and **11h** in respective yields of 52 and 45 %, allowing preparation of non-symmetric azepines.

Imine **13** was prepared by a condensation reaction in a yield of 69 %. An attempt to perform a [4+3]-cycloaddition reaction with propargyl acetal to azepine did not afford an isolated product, but indicated that a cycloaddition had occurred.

The 9-membered ring **9a-c** was obtained in 26 % by Au(I) catalyzed trimerization of propargyl acetal **2d**. A high selectivity towards the 9-membered ring formation was observed and provides a novel preparation method for highly substituted cyclononyl rings.

Propargyl alcohol **1a**-c were prepared by Grignard reactions in yields of 72 – 99 %, while alcohol **1d** was synthesized in 92 % yield by reaction of benzaldehyde **13a** and deprotonated phenylacetylene.

Propargyl acetals **2a-d** were synthesized by acid catalyzed reactions and isolated in yields of 79-95 %. Propargyl ester **3** was obtained in 84 % yield by esterification of alcohol **1a**.

Nitrones **4a-c** were prepared by condensation of corresponding aldehydes **13a-c** with *N*-methylhydroxylamine in yields of 66-94 %. The nitrones **4d-h** were synthesized in 19-30 % yields by one-pot reactions from nitrobenzenes and benzaldehydes by Zn reduction followed by condensation. Oxidation of isoquinoline afforded oxazine **4i** in 45 % yield.

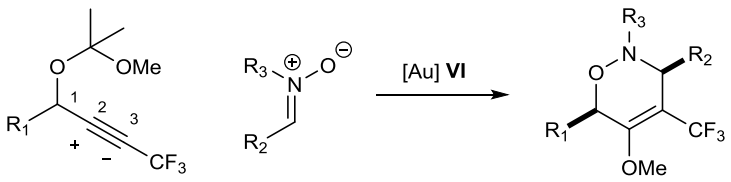
Azides **10a-c** were prepared via diazonium displacement in yields of 56-87 %. Azide **10d** was synthesized by S_N2 reaction from 1-iodooctane in 54 % yield.

5. Outlook

The present project provides an interesting insight into the possibility of gold(I) catalyzed [3+3] cycloaddition between propargyl acetals and 1,3-dipoles. Of interest would be to investigate if other 1,3-dipoles would react similarly to nitrones and azides. In this spirit, azomethine imine, another 1,3-dipole, has been reported to afford gold(III) catalyzed [3+3] cycloaddition reactions with propargyl esters,[26] as presented in Section 2.4. A study on how different 1,3-dipoles react with gold(I) catalysis is therefore expected to afford a variety of novel [3+3] cycloaddition reactions with propargyl acetals as well as with propargyl esters. The challenge often associated with 1,3-dipoles is their stability and they are often prepared in situ under rigorous conditions. Strong alkaline conditions are often required, which could deactivate the gold catalyst. However, several reliable methods of preparation are available for 1,3-dipoles such as diazo compounds. Ozone and nitrous oxide are readily available, but the stability of any resulting [3+3] cycloaddition products is questionable. Isocyanates and isothiocyanates are other possible substrates for [3+3] cycloaddition reactions.[106] Several other oxides, imines and ylides apart from those already mentioned above are 1,3-dipoles, some of which are now possible to generate in situ following recent development within rhodium catalysis.[107] In this respect, the present work serves as an initial investigation with several routes for further work.

As part of the present work, conjugated imines were observed to react with propargyl acetals and form azepines through [4+3] cycloaddition reactions. Initial results suggest high reactivity towards cycloaddition. Further investigation of this reaction could afford the synthesis of several interesting biological precursors.

Successful studies within the Fiksdahl group have recently been conducted with trifluoromethylation of homopropargyl acetals.[108] By trifluoromethylating the propargyl acetals used in the present study, the electrophilic nature of the alkyne would be strongly affected and could give rise to a different or improved regioselectivity especially for the [3+3] cycloaddition to oxazines. Trifluoromethyl would induce a negative charge on the "C-3" position of the acetal (Figure 5.1) and oxidation through attack of the nitrone at this position would be less likely. This may decrease the amount of by-product and provide a new route for trifluoromethylation of oxazines, Figure 5.1.



Figur 5.1: Synthesis of trifluoromethylated oxazines

6. Experimental section

6.1 General methods

Commercial grade reagents were used as supplied by the manufacturer. Dry solvents were collected from a solvent purification system MB SPS-800 Solvent Purification System (MBraun). All reactions were monitored by the use of NMR and thin-layer chromatography (TLC) using silica gel 60 F254 (0.25 mm thickness). The TLC plates were developed by UV-light and a solution of *p*-anisaldehyde stain (5 mL conc. H_2SO_4, 1.5 mL absolute acetic acid and 3.7 mL *p*-anisaldehyde in 137 mL absolute EtOH) with heating. Flash chromatography was carried out using silica Merck silica gel 60 (0.040−0.063 mm) in glass columns. Yields are reported corrected for solvent and impurities.

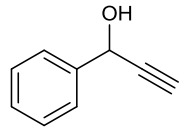
Infrared spectrometry (IR) was performed on a Nicolet 20SXC FT-IR spectrometer. The spectra were analyzed with EZ OMNIC software. Accurate mass determination (HRMS) in positive and negative mode was performed on a "Synapt G2-S" Q-TOF instrument from Waters. Samples were ionized by the use of ASAP probe (APCI), no chromatography separation was used previous to the mass analysis.

^{1}H- and ^{13}C-NMR spectra were recorded using either a Bruker Avance DPX 400 MHz or Bruker Avance III 600Mhz spectrometer. Spectra are presented with acquisition parameters. ^{1}H chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane (TMS δ = 0.0) as the internal standard. Peaks are characterized as s (singlets), d (doublets), t (triplets) or m (multiplets). Coupling constants (J) are given in Hertz (Hz). The values of the chemical shifts were determined by means of COSY, HMQC, HMBC and NOESY NMR experiments.

General procedure 1

To a pre-dried reaction flask under nitrogen atmosphere, aldehyde **14a-c** and Grignard reagent in 0.5 M THF was added and stirred. The mixture was neutralized with sat. NH_4Cl, diluted with DCM and washed with sat. $NaHCO_3$ and brine. The organic phase was dried over anhydrous $MgSO_4$ and solvent removed in vacou. If required, the product was purified by silica flash chromatography (*n*-pentane/EtOAc), to afford the corresponding propargyl alcohols.

1-Phenylprop-2-yn-1-ol (1a)



1a

Following general procedure 1, aldehyde **14a** (1.06 g, 10 mmol, 1 eq.) and ethynylmagnesium bromide (30 mL, 15 mmol, 1.5 eq.) were reacted to yield the corresponding propargyl alcohol **1a** as a yellow oil (1.30 g, 99 %).

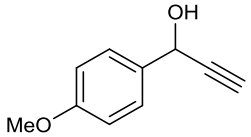
R_f = 0.19 (*n*-pentane/EtOAc 10:1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix A.1) 7.56 (m, 2H, Ar), 7.40 (m, 2H, Ar), 7.35 (m, 1H, Ar), 5.48 (dd, 1H, *J* = 1.7 Hz, 6.2 Hz, CH-O), 2.67 (d, 1H, *J* = 1.9 Hz, C≡CH), 2.20 (d, 1H, *J* = 6.3 Hz, OH).

^{13}C-NMR (400 MHz, CDCl3) δ (ppm) (Appendix A.2) 140.1 (1C, C), 128.7 (2C, CH), 128.5 (1C, CH), 126.6 (2C, CH), 83.6 (1C, C), 74.8 (1C, CH), 64.4 (1C, CH).

^{1}H- and ^{13}C-NMR correspond with previously reported data.[81]

1-(4-Methoxyphenyl)prop-2-yn-1-ol (1b)



1b

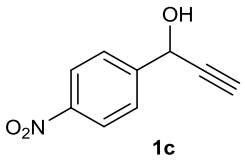
Following general procedure 1, aldehyde **14b** (1.12 g, 8.2 mmol, 1 eq.) and ethynylmagnesium bromide (20 mL, 10 mmol, 1.2 eq.) were reacted. After purification by flash chromatography (*n*-pentane/EtOAc 4:1) the corresponding propargyl alcohol **1b** was obtained as a white solid (1.23 g, 92 %).

R_f = 0.14 (*n*-pentane/EtOAc 10:1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix A.3) 7.50 (m, 2H, Ar), 6.94 (m, 2H, Ar), 5.45 (dd, 1H, *J* = 2.2 Hz, 6.1 Hz, CH-O), 3.84 (s, 3H, O-CH_3), 2.68 (d, 1H, *J* = 2.2 Hz, C≡CH), 2.11 (d, 1H, *J* = 6.1 Hz, OH).

^{1}H-NMR corresponds with previously reported data.[82a]

1-(4-Nitrophenyl)-prop-2-yn-1-ol (1c)



1c

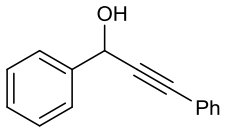
Following general procedure 1, aldehyde **13c** (1.51 g, 10 mmol, 1 eq.) and ethynylmagnesium bromide (20 mL, 10 mmol, 1 eq.) were reacted. After purification by flash chromatography (*n*-pentane/EtoAc 4:1) the corresponding propargyl alcohol **1c** was afforded as a yellow solid (1.92 g, 72%).

R_f = 0.22 (*n*-pentane/EtOAc 4:1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix A.4) 8.28 (m, 2H, Ar), 7.76 (m, 2H, Ar), 5.60 (dd, 1H, *J* = 2.2 Hz, 5.9 Hz, CH-OH), 2.76 (d, 1H, *J* = 2.3 Hz, C≡CH), 2.38 (d, 1H, *J* = 5.9, OH).

^{1}H-NMR corresponds with previously reported data.[82b]

1,3-Diphenylprop-2-yn-1-ol (1d)



1d

Phenylacetylene (530 mg, 5 mmol, 1 eq.) was dissolved in dry THF (10 mL) and cooled to -78°C. 2M LDA in THF (2.7 mL, 5.4 mmol, 1.2 eq.) was slowly added and the mixture was stirred at -78°C for 30 min. Aldehyde **14a** (540 mg, 5.1 mmol, 1.05 eq.) was added dropwise and the reaction was stirred for 1 h. The solution was neutralized by sat. NH_4Cl (10 mL) and EtOAc (10 mL) was added before washing with sat. $NaHCO_3$ (20 mL) and brine (20 mL), and drying over $MgSO_4$. The solvent was evacuated to give the propargyl alcohol **1d** as a colorless oil (958 mg, 92 %).

R_f = 0.20 (*n*-pentane/EtOAc 10:1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix A.5) 7.65 (m, 2H, Ar), 7.50 (m, 2H, Ar), 7.44 (m, 2H, Ar), 7.38 (m, 1H, Ar), 7.35 (m, 2H, Ar), 7.34 (m, 1H, Ar), 5.72 (s, 1H, CH-O).

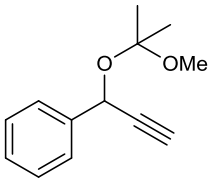
^{13}C-NMR (400 MHz, CDCl3) δ (ppm) (Appendix A.6) 140.6 (1C, C), 131.8 (2C, CH), 128.7 (2C, CH), 128.6 (1C, CH), 128.5 (1C, CH), 128.4 (2C, CH), 126.7 (2C, CH), 122.4 (1C, C), 88.6 (1C, C), 86.7 (1C, C), 65.2 (1C, CH).

^{1}H- and ^{13}C-NMR correspond with previously reported data.[84]

General procedure 2

To a cooled solution of propargyl alcohol **1a-d** (1 eq.) in 2-methoxypropene (1 mL per 100 mg alcohol), PPTS was added in catalytic amounts and stirred for 1 h. The product was purified by flash silica chromatography (*n*-pentane/EtOAc/Et_3N).

(1-((2-Methoxypropan-2-yl)oxy)prop-2-yn-1-yl)benzene (2a)



2a

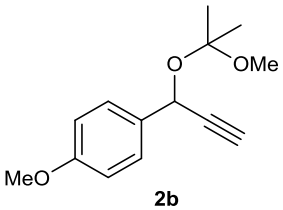
Following general procedure 2, alcohol **1a** (106 mg, 0.80 mmol) afforded acetal **2a** (156 mg, 95 %) as a colorless oil after purification by flash chromatography (*n*-pentane/EtOAc/Et_3N 200:5:1).

R_f = 0.74 (*n*-pentane/EtOAc, 10:1).

^{1}H-NMR (400 MHz, CDCl3) δ (ppm) (Appendix B.1) 7.49 (m, 2H, Ar), 7.36 (m, 2H, Ar), 7.30 (m, 1H, Ar), 5.43 (d, 1H, J = 2.2 Hz, CH-O), 3.19 (s, 3H, OCH_3), 2.53 (d, 1H, J = 2.2 Hz, C≡CH), 1.55 (s, 3H, CCH_3), 1.33 (s, 3H, CCH_3).

^{1}H-NMR corresponds with previously reported data.[10b]

1-Methoxy-4-(1-((2-methoxypropan-2-yl)oxy)prop-2-yn-1-yl)benzene (2b)



2b

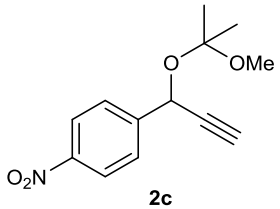
Following general procedure 2, alcohol **1b** (530 mg, 3.3 mmol) gave acetal **2b** (697 mg, 91 %) as a colorless oil after purification by flash chromatography (*n*-pentane/EtOAc/Et_3N 200:10:1).

R_f = 0.37 (*n*-pentane/EtOAc 10:1).

^{1}H-NMR (400 MHz, CDCl3) δ (ppm) (Appendix B.2) 7.43 (m, 2H, Ar), 6.91 (m, 2H, Ar), 5.39 (d, 1H, J = 2.2 Hz, CH-O), 3.83 (s, 3H, O-CH_3), 3.20 (s, 3H, O-CH_3), 2.55 (d, 1H, J = 2.2 Hz. C≡CH), 1.55 (s, 3H, CH_3), 1.35 (s, 3H, CH_3).

^{1}H-NMR corresponds with previously reported data.[11]

1-(1-((2-Methoxypropan-2-yl)oxy)prop-2-yn-1-yl)-4-nitrobenzene (2c)



2c

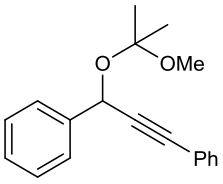
Following general procedure 2, alcohol **1c** (223 mg, 1.25 mmol) afforded acetal **2c** (285 mg, 91 %) as a yellow oil after purification by flash chromatography (*n*-pentane/EtOAc/Et_3N 200:20:1).

R_f = 0.35 (*n*-pentane/EtOAc 10:1).

^{1}H-NMR (400 MHz, CDCl3) δ (ppm) (Appendix B.3) 8.25 (m, 2H, Ar), 7.69 (m, 2H, Ar), 5.54 (d, 1H, *J* = 2.2 Hz, CH-O), 3.20 (s, 3H, O-CH_3), 2.60 (d, 1H, *J* = 2.2 Hz. C≡CH), 1.58 (s, 3H, CH_3), 1.36 (s, 3H, CH_3).

^{1}H-NMR corresponds with previously reported data.[11]

(3-((2-Methoxypropan-2-yl)oxy)prop-1-yne-1,3-diyl)dibenzene (2d)



2d

Following general procedure 2, alcohol **1d** (202 mg, 0.97 mmol) afforded acetal **2d** (222 mg, 79 %) as a colorless oil following purification by flash chromatography (*n*-pentane/EtOAc/Et_3N 200:5:1).

R_f = 0.53 (*n*-pentane/EtOAc 10:1).

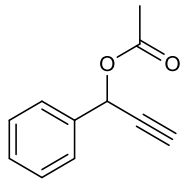
HRMS: Molecular peak not found.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix B.4) 7.56 (m, 2H, Ar), 7.41 (m, 2H, Ar), 7.37 (m, 2H, Ar), 7.31 (m, 1H, Ar), 7.29 (m, 2H, Ar), 7.28 (m, 1H, Ar), 5.65 (s, 1H, CH-O), 3.24 (s, 3H, O-CH_3), 1.60 (s, 3H, CH_3), 1.39 (s, 3H, CH_3).

^{13}C-NMR (400 MHz, CDCl3) δ (ppm) (Appendix B.5) 140.6 (1C, C), 131.6 (2C, CH), 128.5 (2C, CH), 128.2 (1C, CH), 128.2 (2C, CH), 127.9 (1C, CH), 127.1 (2C, CH), 123.0 (1C, C), 101. 8 (1C, C), 89.9 (1C, C), 83.7 (1C, C), 63.4 (1C, CH), 49.5 (1C, CH_3), 25.6 (1C, CH_3), 25.0 (1C, CH_3).

IR (thin film, cm^{-1}) (Appendix B.9) 2997 (w, C-H st), 1488 (w, C-C Ar. bend), 1376 (w, C-H rock), 1216 (m, C-O st), 1150 (s, C-O st), 1065 (s, C-O, st), 1008 (s, C-O st), 944 (s, C-O st), 871 (s, C-H oop), 755 (vs, C-H oop), 688 (vs, C-H oop).

1-Phenylprop-2-yn-1-yl acetate (3)



3

The propargyl ester **3** was prepared by treating the corresponding propargyl alcohol **1a** (138 mg, 1.0 mmol, 1 eq.) dissolved in DCM at 0 °C with DMAP (17.9 mg, 14 mol %), Et_3N (0.21 ml, 1.5 mmol, 1.5 eq.) and acetic anhydride (0.2 ml, 1.5 mol, 1.5 eq.) for 3 h. The ester **3** (150 mg, 84 %) was obtained after silica flash chromatography (*n*-pentane/EtOAc 6:1) as a white oil.

R_f = 0.57 (*n*-pentane/EtOAc 10:1).

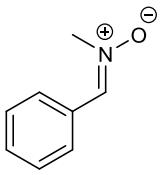
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix C.1) 7.56 (m, 2H, Ar), 7.39-7.44 (m, 3H, Ar), 6.47 (d, 1H, J = 2.3, CH-O), 2.67 (d, 1H, J = 2.3, C≡CH), 2.14 (s, 3H, CH_3).

^{1}H-NMR corresponds with previously reported data.[73a]

General procedure 3

Aldehyde **14a-c** (1 eq.), hydroxylamine hydrochloride (1.5 eq.), triethylamine (1.5 eq.) and $MgSO_4$ were added to DCM (1 mL per mmol aldehyde) and stirred for 24 h. The reaction mixture was filtrated, washed with 1M HCl (1 mL per mmol aldehyde), sat. $NaHCO_3$ (1 mL per mmol aldehyde) and brine (1 mL per mmol aldehyde) followed by drying over $MgSO_4$, filtration and evaporation of the solvent.

N-Methyl-1-phenylmethanimine oxide (4a)



4a

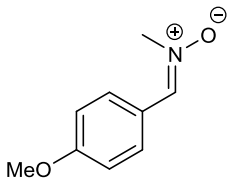
Following general procedure 3, benzaldehyde **14a** (1.06 g, 10 mmol, 1 eq.) and *N*-methylhydroxylamine hydrochloride (1.25 g, 15 mmol, 1.5 eq.) were reacted to afford nitrone **4a** (1.24 g, 92 %) as a white solid.

R_f = 0.21 (EtOAc).

^{1}H-NMR (400 MHz, CDCl3) δ (ppm) (Appendix D.1) 8.21 (m, 2H, Ar), 7.42 (m, 3H, Ar), 7.37 (s, 1H, CH=N), 3.89 (s, 3H, N-CH_3).

^{1}H-NMR corresponds with previously reported data.[86]

1-(4-Methoxyphenyl)-N-methylmethanimine oxide (4b)



4b

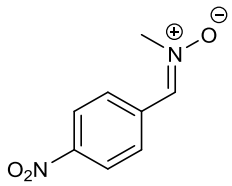
Following general procedure 3, aldehyde **14b** (542 mg, 4.0 mmol, 1 eq.) and *N*-methylhydroxylamine hydrochloride (467 mg, 5.6 mmol, 1.4 eq.) were reacted to yield nitrone **4b** (432 mg, 66 %) as a white solid.

R_f = 0.25 (EtOAc).

^{1}H-NMR (400 MHz, CDCl3) δ (ppm) (Appendix D.2) 8.23 (m, 2H, Ar), 7.31 (s, 1H, CH=N), 6.96 (m, 2H, Ar), 3.87 (s, 6H).

^{1}H-NMR corresponds with previously reported data.[86]

N-Methyl-1-(4-nitrophenyl)methanimine oxide (4c)



4c

Following general procedure 3, aldehyde **14c** (1.02 g, 6.8 mmol, 1 eq.) and *N*-methylhydroxylamine hydrochloride (864 mg, 10.2 mmol. 1.5 eq.) were reacted to give nitrone **4c** (1.15 g, 94 %) as a yellow solid.

R_f = 0.12 (EtOAc).

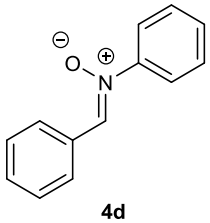
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix D.3) 8.40 (m, 2H, Ar), 8.28 (m, 2H, Ar), 7.55 (s, 1H, CH=N), 3.98 (s, 1H, N-CH_3).

^{1}H-NMR corresponds with previously reported data.[87]

General procedure 4

Aldehyde **14a,b,d** (1 eq.), nitroaryl **15a-c** (1 eq.) and ammonium chloride (3 eq.) were dissolved in EtOH/H_2O 1:1 (3 mL per mmol aldehyde) at 0 °C. Zinc powder (2 eq.) was added slowly over 4 h, while maintaining the temperature at 0 °C. After addition of zinc, the reaction was let stand to room temperature and stirred for another 16 h. The product was extracted by DCM (3 x 2 mL per mmol aldehyde), washed with brine (2 mL per mmol aldehyde) and dried over $MgSO_4$. The solvent was evacuated and the product was purified either by recrystallization in EtOAc or by silica flash column chromatography (*n*-pentane/EtOAc).

(Z)-N,1-Diphenylmethanimine oxide (4d)



4d

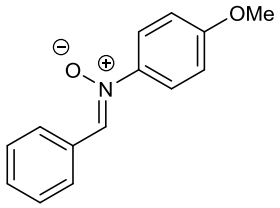
Following general procedure 4, nitrone **4d** was obtained as a white solid (1.19 g, 30 %) from aldehyde **14a** (2.12 g, 20 mmol) and nitroaryl **15a** (2.46 g, 20 mmol) after silica flash column chromatography (EtOAc).

R_f = 0.04 (*n*-pentane/EtOAc 10:1).

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) (Appendix D.4) 8.40 (m, 2H, Ar), 7.93 (s, 1H, CH=N), 7.78 (m, 2H, Ar), 7.46-7.51 (6H, Ar).

^{1}H-NMR corresponds with previously reported data.[89a]

(Z)-N-(4-Methoxyphenyl)-1-phenylmethanimine oxide (4e)



4e

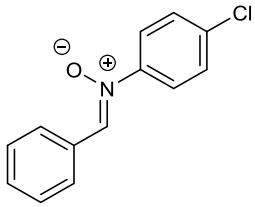
Following general procedure 4, nitrone **4e** was obtained as a white solid (1.36 g, 30 %) from aldehyde **14a** (2.12 g, 20 mmol) and nitroaryl **15b** (3.06 g, 20 mmol) after recrystallization from EtOAc.

R_f = 0.03 (*n*-pentane/EtOAc 10:1).

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) (Appendix D.5) 8.38 (m, 2H, Ar), 7.87 (s, 1H, CH=N), 7.74 (m, 2H, Ar), 7.45-7.49 (m, 3H, Ar), 6.97 (m, 2H, Ar).

^{1}H-NMR corresponds with previously reported data.[88]

(Z)-N-(4-Chlorophenyl)-1-phenylmethanimine oxide (4f)



4f

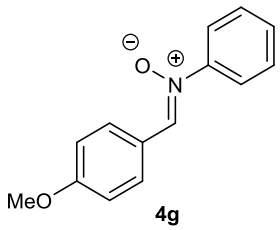
Following general procedure 4, nitrone **4f** was obtained as a white solid (0.87 g, 19 %) from aldehyde **14a** (2.12 g, 20 mmol) and nitroaryl **15c** (3.15 g, 20 mmol) after recrystallization from EtOAc.

R_f = 0.07 (*n*-pentane/EtOAc 10:1).

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) (Appendix D.6) 8.39 (m, 2H, Ar), 7.90 (1H, CH=N), 7.75 (m, 2H, Ar), 7.48-7.50 (m, 3H, Ar), 7.46 (m, 2H, Ar).

^{1}H-NMR corresponds with previously reported data.[89b]

(Z)-1-(4-Methoxyphenyl)-N-phenylmethanimine oxide (4g)



4g

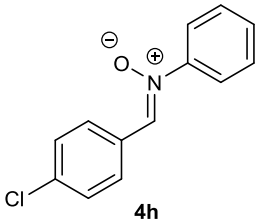
Following general procedure 4, nitrone **4g** was obtained as a white solid (0.91 g, 20 %) from aldehyde **14b** (2.72 g, 20 mmol) and aryl **15a** (2.46 g, 20 mmol) after recrystallization from EtOAc.

R_f = 0.15 (*n*-pentane/EtOAc 1:1).

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) (Appendix D.7) 8.41 (m, 2H, Ar), 7.86 (s, 1H, CH=N), 7.78 (m, 2H, Ar), 7.45-7.49 (m, 3H, Ar), 7.00 (m, 2H, Ar).

^{1}H-NMR corresponds with previously reported data.[89c]

(Z)-1-(4-Chlorophenyl)-N-phenylmethanimine oxide (4h)



4h

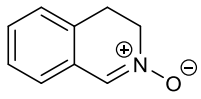
Following general procedure 4, nitrone **4h** was obtained as a white solid (1.39 g, 29 %) from aldehyde **14d** (2.81 g, 20 mmol) and nitroaryl **15a** (2.46 g, 20 mmol) after silica flash column chromatography (EtOAc).

R_f = 0.05 (*n*-pentane/EtOAc 10:1).

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) (Appendix D.8) 8.36 (m, 2H, Ar), 7.91 (s, 1H, CH=N), 7.77 (m, 2H, Ar), 7.48-7.50 (m, 3H, Ar), 7.45 (m, 2H, Ar).

^{1}H-NMR corresponds with previously reported data.[89b]

3,4-Dihydroisoquinoline 2-oxide (4i)



4i

Isoquinoline (1.33 g, 10 mmol, 1 eq.) and $Na_2WO_2 \cdot 2H_2O$ (0.165 g, 0.40 mmol, 0.05 eq.) were added to methanol (20 mL). To the solution was added 50 % aqueous hydrogen peroxide (1.56 g, 30 mmol, 3 eq.) dropwise with ice cooling. After the addition was complete, the reaction mixture was stirred at room temperature for 3 h. Methanol was removed in vacou. Dichloromethane (100 mL) and sat. NaCl solution (40 mL) were added to the residue. The organic layer was separated, washed with sat. NaCl solution (40 mL), dried over $MgSO_4$ and filtered. Purification by silica flash chromatography, EtOAc/Et_3N 20:1, gave the nitrone **4i** (661 mg, 45 %) as a pale yellow oil.

R_f = 0.06 (EtOAc/Et_3N 20:1).

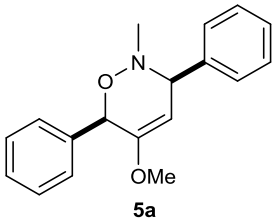
^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) (Appendix D.9) 7.76 (s, 1H, CH=N), 7.27-7.28 (m, 2H, Ar), 7.21-7.22 (m, 2H, Ar), 4.12 (t, 2H, J = 7.8 Hz, CH_2-N), 3.19 (t, 2H, J = 7.8 Hz, CH_2).

^{1}H-NMR corresponds with previously reported data.[90]

General procedure 5

Propargyl acetal **2a-d** (1 eq.) and nitrone **4a-i** (1 eq.) were dissolved in dry DCM (c = 250 mM propargyl acetal). Gold catalyst **VI** (5 mol%) was subsequently added. The reaction mixture was stirred, and the reaction was monitored by the use of TLC and NMR. After full conversion the reaction mixture was either used for product isolation by flash chromatography, filtered through a small pad of Celite for subsequent ^{1}H-NMR analysis of the crude reaction mixture after evaporation of the solvent or analyzed directly as a crude sample.

5-Methoxy-2-methyl-3,6-diphenyl-3,6-dihydro-2H-1,2-oxazine (5a)



5a

Compound **5a** was prepared according to general procedure 5, using propargyl acetal **2a** (54 mg, 0.26 mmol), nitrone **4a** (36 mg, 0.26 mmol) and catalyst (10 mg, 13 μmol). After a flash chromatography (*n*-pentane/EtOAc 100:1), re-purification by a second flash silica gel column (*n*-pentane/EtOAc 20:1) afforded 26 mg (35 %) of oxazine **5a** as a colorless liquid.

R_f = 0.35 (*n*-pentane/EtOAc 10:1).

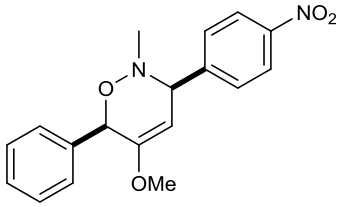
HRMS (ASAP) (Appendix E.8) calcd for $C_{18}H_{20}NO_2$ $[M+H]^+$ 282.1494, obsd 282.1496.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix E.1) 7.57 (m, 2H, Ar), 7.27-7.39 (m, 8H, Ar), 5.18 (s, 1H, CH-O), 4.88 (s, 1H, CH=C), 4.25 (s, 1H, CH-N), 3.56 (s, 3H, O-CH_3), 2.37 (s, 3H, N-CH_3).

^{13}C-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix E.2) 154.2 (1C, C), 140 (1 or 2 C, C), 128.6-8 (3 or 4C, CH), 128.5 (2C, CH), 128.1 (2C, CH), 127.9 (2 or 3C, CH), 98.1 (1C, CH), 78.6 (1C, CH), 69.1 (1C, CH), 54.8 (1C, CH_3), 43.0 (1C, CH_3).

IR (thin film, cm^{-1}) (Appendix E.7): 2961 (w, C-H st), 1670 (m, C=C st), 1213 (s, C-O st), 714 (s, C-H oop), 695 (s, C-H oop).

5-Methoxy-2-methyl-3-(4-nitrophenyl)-6-phenyl-3,6-dihydro-2H-1,2-oxazine (5c)



5c

Compound **5c** was prepared according to general procedure 5, using propargyl acetal **2a** (118 mg, 0.58 mmol), nitrone **4c** (110 mg, 0.61 mmol) and catalyst (23 mg, 30 μmol). Purification by silica flash chromatography (*n*-pentane/EtOAc 5:1) afforded 68 mg (36 %) of oxazine **5c** as a yellow liquid.

R_f = 0.13 (*n*-pentane/EtOAc 10:1).

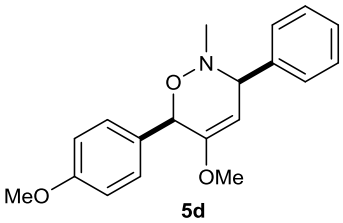
HRMS (ASAP) (Appendix F.8) calcd for $C_{18}H_{19}N_2O_4$ $[M+H]^+$ 327.1345, obsd 327.1346.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix F.1) 8.19 (m, 2H, Ar), 7.51-7.56 (m, 4H, Ar), 7.36-7.43 (m, 3H, Ar), 5.22 (s, 1H, CH-O), 4.81 (s, 1H, CH=C), 4.38 (s, 1H, CH-N), 3.58 (s, 3H, O-CH_3), 2.38 (s, 3H, N-CH_3).

^{13}C-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix F.2) 155.1 (1C, C), 148.6 (1C, C) 147.6 (1C, C), 138.9 (1C, C), 129.5 (2C, CH), 128.5 (2C, CH), 128.2 (3C, CH) 124.3 (1C, C), 123.8 (2C, CH), 96.6 (1C, CH), 78.6 (1C, CH), 58.2 (1C, CH), 55.9 (1C, CH_3), 43.1 (1C, CH_3).

IR (thin film, cm^{-1}) (Appendix F.7) 2966 (vw, C-H st), 1662 (w, C=C st), 1517 (vs, N-O as st), 1345 (vs, N-O sy st), 1210 (s, C-O st), 1070 (m, C-O st), 838 (s, C-H oop), 727 (vs, C-H oop), 696 (vs, C-H oop).

5-Methoxy-6-(4-methoxyphenyl)-2-methyl-3-phenyl-3,6-dihydro-2H-1,2-oxazine (5d)



5d

Compound **5d** was prepared according to general procedure 5, using propargyl acetal **2b** (102 mg, 0.44 mmol), nitrone **4a** (59 mg, 0.44 mmol) and catalyst (17.8 mg, 23 μmol). Attempted purification by silica flash column chromatography afforded oxazine **5d** (32 mg, 23 %) in an oily yellow mixture with aldehyde **6b** (25 %) and ketone **7b** (21 %).

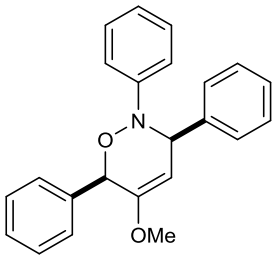
R_f = 0.13 (*n*-pentane/EtOAc 10:1).

HRMS (ASAP) (Appendix G.3) calcd for $C_{19}H_{22}NO_3$ $[M+H]^+$ 312.1600, obsd 312.1600.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix G.1) 9.33 (s, 1H, CH=O), 7.81 (m, 2H, Ar), 7.51 (m, 2H, Ar), 7.36-7.40 (m, 7H, Ar), 6.95-6.97 (m, 4H, Ar), 6.90 (m, 2H, Ar), 5.16 (s, 1H, CH-O), 5.12 (s, 1H, CH-O), 4.90 (s, 1H, CH=C), 4.28 (s, 1H, CH-N), 3.96 (s, 3H, O-CH_3), 3.88 (s, 3H, O-CH_3), 3.85 (s, 3H, O-CH_3), 3.82 (s, 3H, O-CH_3), 3.58 (s, 3H, O-CH_3), 3.11 (s, 3H, O-CH_3), 2.38 (s, 3H, N-CH_3), 2.11 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.34 (s, 3H, CH_3). Compound **5d**, **6b** and **7b** were approximated to be equimolar for the sake of counting.

IR (thin film, cm^{-1}) (Appendix G.2) 1681 (m, C=O st), 1600 (s, C-C Ar st), 1509 (s, C-C Ar st), 1250 (vs, C-O st), 1213 (s, C-O st), 1174 (s, C-O st), 1151 (s, C-O st), 1030 (vs, C-O st), 829 (s, C-H oop), 760 (m, C-H oop), 700 (m, C-H oop).

5-Methoxy-2,3,6-triphenyl-3,6-dihydro-2H-1,2-oxazine (5g)



5g

Compound **5g** was prepared according to general procedure 5, using propargyl acetal **2a** (207 mg, 1.01 mmol), nitrone **4d** (203 mg, 1.03 mmol) and catalyst (36.6 mg, 47 μmol. After a flash chromatography (*n*-pentane/EtOAc 100:1), re-purification by two more silica columns (*n*-pentane/DCM 10:1 and *n*-pentane/DCM/EtOAc 100:2:1) afforded 38 mg (11 %) of oxazine **5g** as a colorless liquid.

R_f = 0.46 (*n*-pentane/EtOAc 10:1).

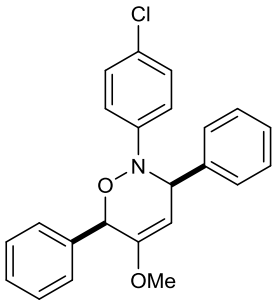
HRMS (ASAP) (Appendix H.8) calcd for $C_{23}H_{22}NO_2$ $[M+H]^+$ 344.1651, obsd 344.1647.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) (Appendix H.1) 7.53 (m, 2H, Ar), 7.37-7.24 (m, 5H, Ar), 7.23 (m, 2H, Ar), 7.19 (m, 1H, Ar), 7.12 (m, 2H Ar), 6.94 (m, 2H, Ar), 6.86 (m, 1H, Ar), 5.46 (s, 1H, CH-O), 5.27 (d, 1H, *J* = 3.5 Hz, CH-N), 5.13 (d, 1H, *J* = 4.3 Hz, CH=C), 3.58 (s, 3H, O-CH_3).

^{13}C-NMR (600 MHz, $CDCl_3$) δ (ppm) (Appendix H.2) 154.5 (1C, C), 148.1 (1C, C), 140.0 (1C, C), 137.0 (1C, C), 129.0 (2C, CH), 128.5 (1C, CH), 128.4 (2C, CH), 128.3 (2C, CH), 128.2 (2C, CH), 128.1 (2C, CH), 127.3 (1C, CH), 122.3 (1C, CH), 118.0 (2C, CH), 96.7 (1C, CH), 79.5 (1C, CH), 63.4 (1C, CH), 54.9 (1C, CH_3).

IR (thin film, cm^{-1}) (Appendix H.7) 2925 (w, C-H st), 1599 (m, C-C Ar st), 1492 (s, C-C Ar st), 1453 (m, C-C Ar st), 1225 (s, C-O st), 1174 (m, C-O st), 1054 (m, C-O st), 753 (s, C-H oop), 696 (C-H oop).

2-(4-Chlorophenyl)-5-methoxy-3,6-diphenyl-3,6-dihydro-2H-1,2-oxazine (5i)



5i

Compound **5i** was prepared according to general procedure 5, using propargyl acetal **2a** (116 mg, 0.57 mmol), nitrone **4f** (133 mg, 0.58 mmol) and catalyst (21 mg, 27 µmol). Purification by silica flash chromatography (*n*-pentane/EtOAc 100:1) afforded 116 mg (54 %) of oxazine **5i** as a colorless wax.

R_f = 0.54 (*n*-pentane/EtOAc 10:1).

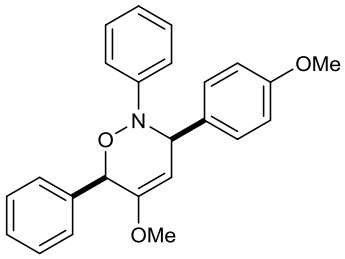
HRMS (ASAP) (Appendix I.8) calcd for $C_{23}H_{21}NO_2Cl$ $[M+H]^+$ 378.1261, obsd 378.1255.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) (Appendix I.1) 7.52 (m, 2H, Ar), 7.41 (m, 2H, Ar), 7.39 (m, 1H, Ar), 7.36 (m, 2H, Ar), 7.25 (m, 2H, Ar), 7.21 (m, 1H, Ar), 7.06 (m, 2H, Ar), 6.84 (m, 2H, Ar), 5.45 (s, 1H, CH-O), 5.20 (d, 1H, *J* = 3.4 Hz, CH-N), 5.11 (d, 1H, *J* = 4.3, CH=C), 3.57 (s, 3H, O-CH_3).

^{13}C-NMR (600 MHz, $CDCl_3$) δ (ppm) (Appendix I.2) 154.4 (1C, C), 146.7 (1C, C), 139.6 (1C, C), 136.8 (1C, C), 129.0 (2C, CH), 128.6 (2C, 1C + 1CH), 128.4 (2C, CH), 128.2 (6C, CH), 127.5 (1C, CH), 119.3 (2C, CH), 96.7 (1C, CH), 79.8 (1C, CH), 63.8 (1C, CH), 54.9 (1C, CH_3).

IR (thin film, cm^{-1}) (Appendix I.7) 1670 (m, C=C st), 1488 (vs, C-C Ar st), 1453 (m, C-C Ar st), 1225 (s, C-O st), 1174 (m, C-O st), 1058 (m, C-O st), 828 (m, C-H oop), 760 (m, C-H oop), 731 (m, C-H oop), 698 (vs, C-H oop).

5-Methoxy-3-(4-methoxyphenyl)-2,6-diphenyl-3,6-dihydro-2H-1,2-oxazine (5j)



5j

Compound **5j** was prepared according to general procedure 5, using propargyl acetal **2a** (100 mg, 0.49 mmol), nitrone **4g** (113 mg, 0.50 mmol) and catalyst (19 mg, 25 μmol). Purification by silica flash chromatography (*n*-pentane/EtOAc 20:1) afforded 11 mg (6 %) of oxazine **5j** in a mixture with *p*-anisaldehyde **14b** as a colorless oil.

R_f = 0.29 (*n*-pentane/EtOAc 10:1).

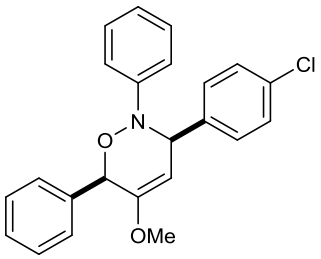
HRMS (ASAP) (Appendix J.8) calcd for $C_{24}H_{24}NO_3$ $[M+H]^+$ 374.1756, obsd 374.1754.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) (Appendix J.1) 7.53 (m, 2H, Ar), 7.41 (m, 2H, Ar), 7.39 (m, 1H, Ar), 7.29 (m, 2H, Ar), 7.13 (m, 2H, Ar), 6.94 (m, 2H, Ar), 6.87 (m, 1H, Ar), 6.77 (m, 2H, Ar), 5.46 (s, 1H, CH-O), 5.22 (d, 1H, J = 6.4, CH-N), 5.12 (d, 1H, J = 4.3, CH=C), 3.75 (s, 3H, O-CH_3), 3.58 (s, 3H, O-CH_3).

^{13}C-NMR (600 MHz, $CDCl_3$) δ (ppm) (Appendix J.2) 158.8 (1C, C), 154.5 (1C, C), 148.2 (1C, C), 137.0 (1C, C), 131.9 (1C, C), 129.3 (2C, CH), 129.0 (2C, CH), 128.5 (1C, CH), 128.3 (2C, CH), 128.2 (2C, CH), 122.3 (1C, CH), 118.0 (2C, CH), 113.4 (2C, CH), 97.0 (1C, CH), 79.7 (1C, CH), 63.2 (1C, CH), 55.1 (1C, CH_3), 54.9 (1C, CH_3).

IR (thin film, cm^{-1}) (Appendix J.7) 1601 (s, C-C Ar st), 1512 (s, C-C Ar st), 1454 (m, C-C Ar st), 1251 (vs, C-O st), 1161 (s, C-O st), 1024 (s, C-O st), 832 (m, C-H oop), 744 (m, C-H oop), 697 (m, C-H oop).

3-(4-Chlorophenyl)-5-methoxy-2,6-diphenyl-3,6-dihydro-2H-1,2-oxazine (5k)



5k

Compound **5k** was prepared according to general procedure 5, using propargyl acetal **2a** (98 mg, 0.48 mmol), nitrone **4h** (115 mg, 0.50 mmol) and catalyst (18.4 mg, 23 μmol). Purification by silica flash chromatography (*n*-pentane/EtOAc 100:1) afforded 42 mg (23 %) of oxazine **5k** as a colorless wax.

R_f = 0.56 (*n*-pentane/EtOAc 10:1).

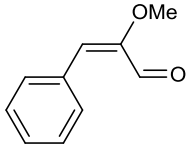
HRMS (ASAP) (Appendix K.5) calcd for $C_{23}H_{21}NO_2Cl$ $[M+H]^+$ 378.1261, obsd 378.1254.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) (Appendix K.1) 7.49 (m, 2H, Ar), 7.41 (m, 2H, Ar), 7.39 (m, 1H, Ar), 7.31 (m, 2H, Ar), 7.20 (m, 2H, Ar), 7.14 (m, 2H, Ar), 6.94 (m, 2H, Ar), 6.88 (m, 1H, Ar), 5.46 (s, 1H, CH-O), 5.25 (d, 1H, *J* = 4.0, CH-N), 5.10 (d, 1H, *J* = 4.5, CH=C), 3.58 (s, 3H, O-CH_3).

^{13}C-NMR (600 MHz, $CDCl_3$) δ (ppm) (Appendix K.2) 155.1 (1C, C), 148.0 (1C, C), 138.6 (1C, C), 136.8 (1C, C), 133.2 (1C, C), 130.0 (2C, CH), 129.0 (2C, CH), 128.7 (1C, CH), 128.5 (2C, CH), 128.4 (2C, CH), 128.3 (2C, CH),122.6 (1C, CH), 117.9 (2C, CH), 96.3 (1C, CH), 79.7 (1C, CH), 62.9 (1C, CH), 55.1 (1C, CH_3).

IR (thin film, cm^{-1}) (Appendix K.4) 1686 (m, C=C st), 1598 (m, C-C Ar st), 1492 (s, C-C Ar st), 1454 (m, C-C Ar st), 1210 (m, C-O st), 1148 (m, C-N st), 1091 (s, C-O st), 1025 (m, C-O st), 1013 (s, C-O st), 833 (m, C-H oop), 760 (m, C-H oop), 745 (m, C-H oop), 698 (m, C-H oop).

2-Methoxy-3-phenylacrylaldehyde (6a)



6a

Compound **6a** was prepared according to general procedure 5, using propargyl acetal **2a** (118 mg, 0.58 mmol), nitrone **4c** (110 mg, 0.61 mmol) and catalyst (23 mg, 30 μmol). Purification by silica flash chromatography (*n*-pentane/EtOAc 5:1) gave 34

mg (36 %) of aldehyde **6a** as a colorless liquid.

R_f = 0.60 (*n*-pentane/EtOAc 10:1).

HRMS (ASAP) (Appendix L.7) calcd for $C_{10}H_{11}O_2$ $[M+H]^+$ 163.0759, obsd 163.0758.

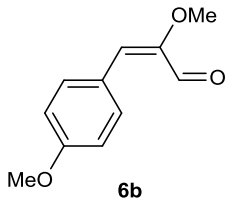
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix L.1) 9.37 (s, 1H, CH=O), 7.81 (m, 2H, Ar), 7.41 (m, 3H, Ar), 6.55 (s, 1H, CH=C), 3.97 (s, 3H, O-CH_3).

^{13}C-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix L.2) 189.5 (1C, C), 154.1 (1C, C), 135.0 (1C, CH), 133.3 (1C, C), 130.2 (2C, CH), 130.0 (1C, CH), 128.7 (2C, CH) 58.8 (1C, CH_3).

IR (thin film, cm^{-1}) (Appendix L.6): 2940 (w, C-H st), 1683 (vs, C=O st), 1455 (m, H-C-H δ), 1359 (m, CH_3 bend), 1150 (m, C-O st), 1032 (m, C-O st), 692 (m, C-H oop).

^{1}H- and ^{13}C-NMR correspond with previously reported data.[94]

2-Methoxy-3-(4-methoxyphenyl)acrylaldehyde (6b)



6b

Compound **6b** was prepared according to general procedure 5, using propargyl acetal **2b** (102 mg, 0.44 mmol), nitrone **4a** (59 mg, 0.44 mmol) and catalyst (17.8 mg, 23 μmol). After silica flash chromatography (*n*-pentane/EtOAc 10:1), re-purification by a second silica column afforded the aldehyde **6b** (19 mg, 22 %) as a colorless oil.

R_f = 0.13 (*n*-pentane/EtOAc 10:1).

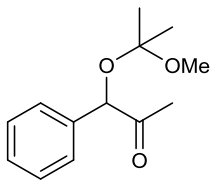
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix M.1) 9.31 (s, 1H, CH=O), 7.79 (m, 2H, Ar), 6.93 (m, 2H, Ar), 6.52 (s, 1H, CH=C), 3.94 (s, 3H, O-CH_3), 3.87 (s, 3H, O-CH_3).

^{13}C-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix M.2) 181.3 (1C, CH=O), 161.1 (1C, C), 152.9 (1C, C), 134.6 (1C, CH), 132.2 (2C, CH), 126.1 (1C, C), 114.2 (2C, CH), 58.7 (1C, CH_3), 55.4 (1C, CH).

IR (thin film, cm^{-1}) (Appendix M.4): 1681 (s, C=O st), 1601 (vs, C-C Ar st), 1510 (m, C-C Ar st), 1256 (s, C-O st), 1176 (m, C-O st), 1154 (m, C-O st), 1032 (m, C-O st).

^{1}H- and ^{13}C-NMR correspond with previously reported data.[94]

1-((2-Methoxypropan-2-yl)oxy)-1-phenylpropan-2-one (7a)



7a

Compound **7a** was prepared according to the general procedure for gold(I) catalyzed cycloaddition, using propargyl acetal **2a** (51 mg, 0.25 mmol), nitrone **4a** (103 mg, 0.76 mmol) and catalyst (10 mg, 13 μmol). Purification by flash chromatography (*n*-pentane/EtOAc 20:1) afforded 22 mg (40 %) of ketone **9a** as a colorless oil.

R_f = 0.19 (*n*-pentane/EtOAc 10:1).

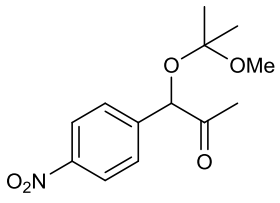
HRMS: Molecular peak not found.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix N.1) 7.45 (m, 2H, Ar), 7.35 (m, 2H, Ar), 7.30 (m, 1H, Ar), 5.14 (s, 1H, C<u>H</u>-O), 3.09 (s, 3H, O-CH_3), 2.10 (s, 3H, C-CH_3), 1.40 (s, 3H, C-CH_3), 1.32 (s, 3H, C-CH_3).

^{13}C-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix N.2) 207.6 (1C, C=O), 137.7 (1C, C), 128.6 (2C, CH), 128.0 (2C, CH), 126.7 (1C, CH), 101.7 (1C, C), 79.0 (1C, C), 42.9 (1C, CH_3) 25.1 (2C, CH_3), 24.8 (1C, CH_3).

IR (thin film, cm^{-1}) Decomposed.

1-((2-methoxypropan-2-yl)oxy)-1-(4-nitrophenyl)propan-2-one (7c)



7c

Compound **7c** was prepared according to general procedure 5, using propargyl acetal **3c** (130 mg, 0.52 mmol), nitrone **4a** (71 mg, 0.53 mmol) and catalyst (19.2 mg, 25 μmol). Purification by silica flash chromatography, *n*-pentane/EtOAc 10:1 → 1:1, out at 5:1, gave ketone **7c** (26 mg, 19 %) as a yellow oil.

R_f = 0.16 (*n*-pentane/EtOAc 10:1).

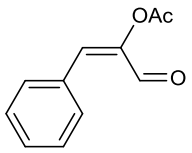
HRMS: Molecular peak not found.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix O.1) 8.22 (m, 2H, Ar), 7.66 (m, 2H, Ar), 5.23 (s, 1H, CH-O), 3.09 (s, 3H, O-CH_3), 2.15 (s, 3H, C-CH_3), 1.44 (s, 3H, C-CH_3), 1.33 (s, 3H, C-CH_3).

^{13}C-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix O.2) 206.8 (1C, C=O), 147.8 (1C, C), 145.0 (1C, C), 127.2 (2C, CH), 123.8 (2C, CH), 102.2 (1C, C), 78.3 (1C, C), 49.4 (1C, CH_3), 25.1 (12C, CH_3), 24.7 (1C, CH_3).

IR (thin film, cm^{-1}) Decomposed.

3-Oxo-1-phenylprop-1-en-2-yl acetate (8)



8

Propargyl ester (46 mg, 0.26 mmol, 1 eq.) and nitrone (38 mg, 28 mmol, 1 eq.) were dissolved in DCM (1 mL). Gold catalyst $PicAuCl_2$ (5.3 mg, 14 µmol, 0.05 eq.) was subsequently added. The reaction mixture was stirred for 24 h and the product **8** (9 mg, 19 %) was isolated as colorless oil by silica flash chromatography (*n*-pentane/EtOAc 20:1).

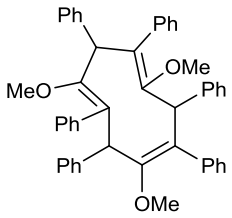
R_f = 0.54 (*n*-pentane/EtOAc 10:1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix P.1) 9.43 (s, 1H, CH=O), 7.79 (m, 2H, Ar), 7.46 (m, 3H, Ar), 7.03 (s, 1H, C=CH), 2.40 (s, 3H, CH_3).

^{13}C-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix P.2) 185.5 (1C, CH=O), 167.6 (1C, COO), 146.1 (1C, C), 136.5 (1C, CH), 131.0 (1C, CH), 130.5 (1C, C) 130.4 (2C, CH), 128.7 (2C, CH), 20.6 (1C, CH_3).

^{1}H- and ^{13}C-NMR correspond with previously reported data.[93]

(1Z,4Z,7Z)-1,4,7-trimethoxy-2,3,5,6,8,9-hexaphenylcyclonona-1,4,7-triene (9a-c)



9a-c

Compound **9a-c** was prepared according to general procedure 5, using propargyl acetal **2d** (98 mg, 0.35 mmol), nitrone **4a** (50 mg, 0.37 mmol) and catalyst (14.6 mg, 19 μmol). After flash silica column chromatography (*n*-pentane/EtOAc, 40:1), re-purification by a second flash column afforded a pure diastereomer/conformation of **9a** (9 mg, 13 %) as a white solid and a mixture of two diastereomers/conformations of **9b-c** (9 mg, 13 %) as a white solid.

9a: R_f = 0.43 (*n*-pentane/EtOAc 10:1).

HRMS (ASAP) (Appendix Q.8) calcd for $C_{48}H_{42}O_3$ $[M]^+$ 666.3134, obsd 666.3132.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix Q.1) 7.06-7.61 (m, 23 H, Ar), 6.73 (m, 1H, Ar), 6.61 (m, 2H, Ar), 6.47 (m, 2H, Ar), 5.86 (m, 2H, Ar), 5.53(s, 1H, CH), 5.51 (s, 1H, CH), 4.54 (s, 1H, CH), 3.19 (s, 3H, O-CH_3), 3.03 (s, 3H, O-CH_3), 2.46 (s, 3H, O-CH_3).

^{13}C-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix Q.2) 151.94 (1C, C), 151.83 (1C, C), 151.33 (1C, C), 144.48 (3C, C), 135.55 (1C, C), 134.89 (1C, C), 134.60 (1C,C) 129.92 (2C, CH), 129.71 (2C, CH), 129.12 (2C, CH), 128.38 (2C, CH), 128.18 (2C, CH), 128.06 (2C, CH), 128.01 (2C, CH), 127.87 (2C, CH), 127.81 (2C, CH), 127.68 (2C, CH), 127.57 (2C, CH), 126.35 (2C, CH), 125.71 (1C, CH), 125.35 (1C, CH), 123.96 (1C, CH), 123.28 (1C, CH), 121.43 (1C, CH) , 120.98 (1C, CH), 57.08 (1C, CH_3), 55.78 (1C, CH_3), 55.34 (1C, CH_3), 44.22 (1C, CH), 43.26 (1C, CH), 40.84 (1C, CH). Shifts were reported with two decimals to differentiate between signals.

IR (thin film, cm^{-1}) (Appendix Q.7): 1594 (w, C-C Ar st), 1496 (m, C-C Ar st), 1439 (w, C-H bend), 1231 (w, C-O st), 1091 (s, C-O st), 1070 (m, C-O st), 909 (s, C-H oop), 779 (m, C-H oop), 727 (vs, C-H oop), 696 (vs, C-H oop).

9b-c: R_f = 0.37 (*n*-pentane/EtOAc, 10:1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix Q.9) 6.70-7.60 (m, 56H, Ar), 6.50 (m, 2H, Ar), 6.25 (m, 2H, Ar), 5.72(s, 1H, CH), 5.37 (s, 1H, CH), 5.21 (s, 1H, CH), 4.66-4.67 (s, 3H, CH), 3.06 (s, 3H, O-CH_3), 3.03 (s, 3H, O-CH_3), 2.99 (s, 3H, O-CH_3), 2.91 (s, 3H, O-CH_3), 2.60 (s, 3H, O-CH_3), 2.53 (s, 3H, O-CH_3). Compound **9b** and **9c** were approximated to be equimolar for the sake of counting.

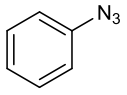
^{13}C-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix Q.10) 152.09 (1C, C), 152.02 (1C, C), 151.93 (1C, C), 151.56 (1C, C), 151.22 (1C, C), 150.97 (1C, C), 145.52 (2C, C), 144.59 (1C, C), 144.15 (1C, C), 143.94 (1C, C), 142.95 (1C, C), 135.66 (1C, C),

134.91 (1C, C), 134.74 (1C, C), 134.70 (1C, C), 134.65 (1C, C) 134.26 (1C, C), 130.03 (2C, CH), 129.95 (2C, CH), 129.32 (2C, CH), 129.24 (2C, CH), 129.18 (2C, CH), 128.99 (2C, CH), 128.85 (2C, CH), 128.39 (2C, CH), 128.21 (2C, CH), 128.11 (2C, CH), 128.07 (2C, CH), 128.02 (2C, CH), 128.00 (2C, CH), 127.97 (2C, CH), 127.81 (2C, CH), 127.75 (2C, CH), 127.66 (2C, CH), 127.45 (2C, CH), 127.20 (2C, CH), 126.59 (2C, CH), 126.55 (2C, CH), 125.80 (1C, CH), 125.54 (1C, CH), 125,31 (1C, CH), 124.74 (1C, CH), 124.25 (1C, CH), 123.98 (1C, CH), 123.84 (1C, CH), 123.10 (1C, CH), 121.57 (1C, CH), 121.36 (1C, CH), 120.27 (1C, CH), 119.21 (1C, CH), 60.39 (1C, CH_3), 56.30 (1C, CH_3), 56.04 (1C, CH_3), 55.75 (1C, CH_3), 55.65 (1C, CH_3), 55.09 (1C, CH_3), 44.38 (1C, CH), 43.88 (1C, CH), 43.47 (1C, CH), 43.14 (1C, CH), 42.76 (1C, CH), 40.81 (1C, CH). Shifts were reported with two decimals to differentiate between signals. Compound **9b** and **9c** were approximated to be equimolar for the sake of counting.

General procedure 6

To water (12 mL), conc. HCl (2 mL) was added and cooled to 0°C. Amine **16a-c** (1 eq.) was added dropwise, maintaining a temperature of 0°C in the solution. A cooled $NaNO_2$ solution (2 eq. in 4 mL water) was added dropwise while keeping the reaction temperature below 5 °C. The mixture was stirred for 30 min. Sat. HCO_3 was added until pH = 7. A cooled solution of NaN_3 (2 eq. in 4 mL water) was added dropwise without letting the reaction temperature surpass 5 °C. The product was extracted with ether (3 x 20 mL) and dried over anhydrous $MgSO_4$. The solvent was evacuated to afford the product. If required the product was further purified by silica flash chromatography (*n*-pentane).

Phenylazide (10a)



10a

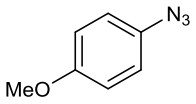
Following general procedure 6, aniline **16a** (1 g, 10.7 mmol) afforded 1.13 g (88 %) of azide **10a** as a yellow viscous oil.

R_f = 0.80 (*n*-pentane/EtOAc 10:1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix R.1) 7.35 (m, 2H, Ar), 7.14 (m, 1H, Ar), 7.03 (m, 2H, Ar).

^{1}H-NMR corresponds with previously reported data.[99a]

1-Azido-4-methoxybenzene (10b)



10b

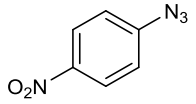
Following general procedure 6, *p*-anisidine **16b** (1.02 g, 8.1 mmol) afforded 0.82 g (68 %) of azide **10b** as a yellow solid after flash chromatography.

R_f = 0.75 (*n*-pentane/EtOAc 10:1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix R.2) 6.98 (m, 2H, Ar), 6.91 (m, 2H, Ar), 3.82 (s, 3H, O-CH_3).

^{1}H-NMR corresponds with previously reported data.[99b]

1-Azido-4-nitrobenzene (10c)



10c

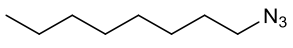
Following general procedure 6, 4-nitroaniline **16c** (1.00 g, 6.1 mmol) afforded 0.75 g (63 %) of azide **10c** as a yellow solid after flash chromatography.

R_f = 0.51 (*n*-pentane/EtOAc 10:1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix R.3) 8.27 (m, 2H, Ar), 7.16 (m, 2H, Ar).

^{1}H-NMR corresponds with previously reported data.[99b]

1-Azidooctane (10d)



10d

To an aceton/H_2O mixture (3:1, 20 mL), 1-iodooctane (660 mg, 2.8 mmol, 1 eq.) and sodium azide (0.536 mg, 8.3 mmol, 3 eq.) were added and heated to 50 °C for 12 h. Acetone was removed, product was extracted with pentane (3 x 10 mL) and tried over $MgSO_4$. Solvent was evacuated and azide **10d** was obtained as a colorless liquid (155 mg, 54 %).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix R.4) 3.28 (t, 2H, J = 7.0 Hz, CH_2-N), 1.62 (quint, 2H, J = 7.5 Hz, CH_2), 1.3-1.4 (m, 10 H, 5 x CH_2), 0.92 (t, 3H, J = 7.8 Hz, CH_3).

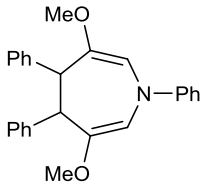
^{13}C-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix R.5) 51.5 (1C, CH_2), 31.8 (1C, CH_2), 29.2 (1C, CH_2), 29.1 (1C, CH_2), 28.8 (1C, CH_2), 26.7 (1C, CH_2), 22.6 (1C, CH_2), 14.1 (1C, CH_3).

^{1}H- and ^{13}C-NMR correspond with previously reported data.[101]

General procedure 7

Propargyl acetal **2a-d** (1 eq.) and azide **10a-d** (1 eq.) or amine **12-13** (1 eq.) were dissolved in dry DCM (c = 250 mM propargyl acetal). Gold catalyst **VI** (2.5 mol%) was subsequently added. The reaction mixture was stirred, and the reaction was monitored by the use of TLC and NMR. After full conversion the reaction mixture was either used for product isolation by flash chromatography, filtered through a small pad of Celite for subsequent ^{1}H-NMR analysis of the crude reaction mixture after evaporation of the solvent or analyzed directly as a crude sample.

3,6-Dimethoxy-1,4,5-triphenyl-4,5-dihydro-1H-azepine (11a)



11a

Compound **11a** was prepared according to general procedure 7, using acetal **2a** (95 mg, 0.47 mmol), azide **10a** (59 mg, 49 mmol) and catalyst (9.1 mg, 12 μmol) at 0 °C. Purification by silica flash chromatography (*n*-pentane/EtOAc 40:1) afforded azepine **11a** (70 mg, 78 %) as a viscous colorless oil.

R_f = 0.62 (*n*-pentane/EtOAc 10:1).

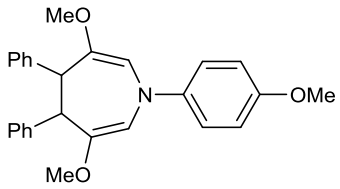
HRMS (ASAP) (Appendix S.8) calcd for $C_{26}H_{26}NO_2$ $[M+H]^+$ 384.1958, obsd 384.1956.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix S.1) 7.28 (m, 4H, Ar), 7.22 (m, 2H, Ar), 7.19 (m, 4H, Ar), 7.10 (m, 2H, Ar), 6.95 (m, 2H, Ar), 6.85 (m, 1H, Ar), 6.17 (s, 2H, C=C<u>H</u>-N), 4.12 (s, 2H, CH), 3.41 (s, 6H, O-CH_3).

^{13}C-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix S.2) 148.6 (2C, C), 146.9 (2C, C), 141.3 (1C, C), 129.0 (2C, CH), 127.9 (4C, CH), 127.9 (4C, CH), 126.3 (2C, CH), 119.8 (1C, CH), 115.4 (2C, CH), 111.5 (2C, CH), 55.8 (2C, CH_3), 52.2 (2C, CH).

IR (thin film, cm^{-1}) (Appendix S.7) 3028 (vw, C-H Ar st), 1594 (m, C-C st), 1491 (m, C-C st), 1304 (m, C-N st), 1278 (m, C-O st), 1205 (s, C-O st), 1158 (m, C-O st), 1012 (m, C-O st), 753 (vs, C-H oop), 701 (s, C-H oop).

3,6-Dimethoxy-1-(4-methoxyphenyl)-4,5-diphenyl-4,5-dihydro-1H-azepine (11b)



11b

Compound **11b** was prepared according to general procedure 7, using acetal **2a** (114 mg, 0.56 mmol), azide **10b** (75 mg, 0.50 mmol) and catalyst (10.4 mg, 13 μmol). Purification by silica flash chromatography (*n*-pentane/EtOAc 10:1) afforded azepine **11b** (98 mg, 85 %) as a white solid.

R_f = 0.27 (*n*-pentane/EtOAc 10:1).

Mp: 108-109 °C.

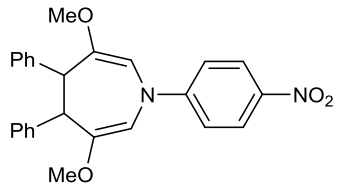
HRMS (ASAP) (Appendix T.8) calcd for $C_{27}H_{28}NO_3$ $[M+H]^+$ 414.2069, obsd 414.2065.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix T.1) 7.33 (m, 4H, Ar), 7.24 (m, 4H, Ar), 7.15 (m, 2H, Ar), 6.99 (m, 2H, Ar), 6.84 (m, 2H, Ar), 6.16 (s, 2H, C=C<u>H</u>-N), 4.13 (s, 2H, CH), 3.79 (s, 3H, O-CH_3), 3.31 (s, 6H, O-CH_3).

^{13}C-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix T.2) 154.5 (1C, C), 144.8 (2C, C), 142.2 (2C, C), 141.8 (1C, C), 128.0 (4C, CH), 127.9 (4C, CH), 126.3 (2C, CH), 119.1 (2C, CH), 114.5 (2C, CH), 113.6 (2C, CH), 56.7 (1C, CH_3), 56.2 (2C, CH_3), 53.1 (2C, CH).

IR (thin film, cm^{-1}) (Appendix T.7) 1506 (vs, C-C st), 1242 (vs, C-O st), 1200 (s, C-O st), 1132 (s, C-O st), 1033 (s, C-O st), 810 (m, C-H oop), 696 (vs, C-H oop).

3,6-Dimethoxy-1-(4-nitrophenyl)-4,5-diphenyl-4,5-dihydro-1H-azepine (11c)



11c

Compound **11c** was prepared according to general procedure 7, using acetal **2a** (101 mg, 0.50 mmol), azide **10c** (79 mg, 0.48 mmol) and catalyst (10.4 mg, 13 μmol). Purification by silica flash chromatography (*n*-pentane/EtOAc 10:1) afforded a mixture of azepines **11c** and **11c'** (83 mg, 78 %, dr 3:1) as a pale yellow wax.

11c: R_f = 0.16 (*n*-pentane/EtOAc 10:1).

HRMS (ASAP) (Appendix U.7) calcd for $C_{26}H_{25}N_2O_4$ $[M+H]^+$ 429.1814, obsd 429.1810.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix U.1) 7.94 (m, 2H, Ar), 7.19 (m, 4H, Ar), 7.14 (m, 4H, Ar), 7.06 (m, 2H, Ar), 6.58 (m, 2H, Ar), 6.00 (s, 2H, C=CH-N), 4.08 (s, 2H, CH), 3.56 (s, 6H, O-CH_3).

^{13}C-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix U.2) 156.0 (2C, C), 150.8 (1C, C), 139.7 (2C, C), 137.8 (1C, C), 128.0 (4C, CH), 127.1 (4C, CH), 126.7 (2C, CH), 125.3 (2C, CH), 111.2 (2C, CH), 108.3 (2C, CH), 55.5 (2C, CH_3), 50.0 (2C, CH).

IR (thin film, cm^{-1}) (Appendix U.6): 1590 (s, C-C Ar st), 1511 (m, N-O as st), 1490 (m, N-O as st), 1335 (s, C-O st), 1304 (vs, C-O/N st), 1283 (s, C-O/N st), 1117 (m, C-O st), 701 (m, C-H oop).

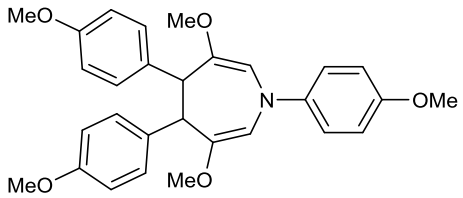
11c': R_f = 0.16 (*n*-pentane/EtOAc 10:1).

HRMS (ASAP) (Appendix U.7) calcd for $C_{26}H_{25}N_2O_4$ $[M+H]^+$ 429.1814, obsd 429.1810.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix U.1) 8.19 (m, 2H, Ar), 7.20 (m, 4H, Ar), 7.10-7.19 (m, 2H, Ar), 6.99 (m, 6H, Ar) 6.13 (s, 2H, C=CH-N), 4.11 (s, 2H, CH), 3.57 (s, 6H, O-CH_3).

^{13}C-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix U.2) 155.3 (2C, C), 151.1 (1C, C), 138.8 (2C, C), 139.2 (1C, C), 130.4 (4C, CH), 127.5 (4C, CH), 127.2 (2C, CH), 125.9 (2C, CH), 111.8 (2C, CH), 107.4 (2C, CH), 55.4 (2C, CH_3), 50.2 (2C, CH).

3,6-Dimethoxy-1,4,5-tris(4-methoxyphenyl)-4,5-dihydro-1H-azepine (11e)



11e

Compound **11e** was prepared according to general procedure 7, using acetal **2b** (102 mg, 0.44 mmol), azide **10b** (66 mg, 0.45 mmol) and catalyst (10.6 mg, 14 μmol). Purification by silica flash chromatography (*n*-pentane/EtOAc 5:1) afforded azepine **11e** (99 mg, 94 %) as a colorless wax.

R_f = 0.09 (*n*-pentane/EtOAc 10:1).

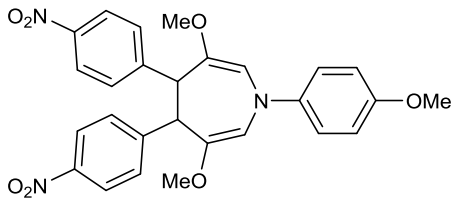
HRMS (ASAP) (Appendix V.4) calcd for $C_{29}H_{41}NO_5$ $[M+H]^+$ 473.2202, obsd 473.2201.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix V.1) 7.27 (m, 4H, Ar), 7.05 (m, 2H, Ar), 6.89 (m, 2H, Ar), 6.81 (m, 4H, Ar), 6.19 (s, 2H, C=CH-N), 4.06 (s, 2H, CH), 3.82 (s, 3H, O-CH_3), 3.78 (s, 6H, O-CH_3), 3.36 (s, 6H, O-CH_3).

^{13}C-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix V.2) 158.1 (3C, C), 145.2 (2C, C), 141.9 (1C, C), 134.5 (2C, C), 128.9 (4C, CH), 119.1 (2C, CH), 114.5 (2C, CH), 113.4 (4C, CH), 113.4 (2C, CH), 56.3 (2C, CH_3), 55.7 (1C, CH_3), 55.2 (2C, CH_3), 52.6 (2C, CH).

IR (thin film, cm^{-1}) (Appendix V.3): 1506 (vs, C-C Ar st), 1460 (m, C-C Ar st), 1242 (s, C-O st), 1200 (m, C-O st), 1179 (m, C-O st), 1132 (m, C-O st), 1034 (m, C-O st), 853 (m, C-H oop).

3,6-Dimethoxy-1-(4-methoxyphenyl)-4,5-bis(4-nitrophenyl)-4,5-dihydro-1H-azepine (11f)



11f

Compound **11f** was prepared according to general procedure 7, using acetal **2c** (130 mg, 0.52 mmol), azide **10b** (8.2 mg, 0.55 mmol) and catalyst (9.6 mg, 12 μmol). Purification by silica flash chromatography (*n*-pentane/EtOAc 4:1) afforded azepine **11f** (55 mg, 42 %) as a yellow wax.

R_f = 0.42 (*n*-pentane/EtOAc 3:1).

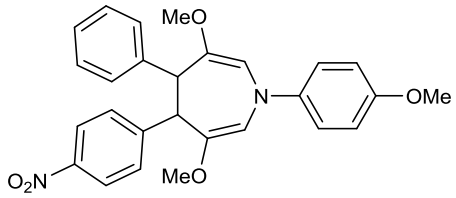
HRMS (ASAP) (Apppendix W.7) calcd for $C_{27}H_{25}N_3O_7$ $[M+H]^+$ 503.1693, obsd 503.1689.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) (Appendix W.1) 8.11 (m, 4H, Ar), 7.49 (m, 4H, Ar), 6.87 (m, 2H, Ar), 6.81 (m, 2H, Ar), 6.16 (s, 2H, C=CH-N), 4.25 (s, 2H, CH), 3.79 (s, 3H, CH_3), 3.41 (s, 6H, CH_3).

^{13}C-NMR (600 MHz, $CDCl_3$) δ (ppm) (Appendix W.2) 154.9 (1C, C), 148.6 (2C, C), 146.8 (2C, C), 144.3 (2C, C), 140.7 (1C, C), 128.5 (4C, CH), 123.4 (4C, CH), 118.4 (2C, CH), 114.6 (2C, CH), 113.1 (2C, CH), 56.0 (2C, CH_3), 55.7 (1C, CH_3), 51.6 (2C, CH).

IR (thin film, cm^{-1}) (Appendix W.6): 1512 (vs, N-O as st), 1340 (vs, C-N st), 1242 (s, C-O st), 1200 (s, C-O st), 1138 (m, C-O st), 1034 (m, C-N st), 857 (m, C-H oop), 815 (m, C-H oop), 727 (m, C-H oop).

3,6-Dimethoxy-1-(4-methoxyphenyl)-4-(4-nitrophenyl)-5-phenyl-4,5-dihydro-1H-azepine (11h)



11h

Following general procedure 7, acetal **2a** (24 mg, 117 μmol), imine **12** (21 mg, 67 μmol) and catalyst (1.5 mg, 2 μmol) were reacted to yield imine **11h** (14 mg, 45 %) as a viscous yellow oil after flash chromatography (*n*-pentane/EtOAc 10:1).

R_f = 0.23 (*n*-pentane/EtOAc 10:1).

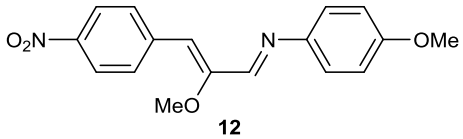
HRMS (ASAP) (Appendix X.8) calcd for $C_{27}H_{26}N_2O_5$ $[M+H]^+$ 458.1842, obsd 458.1843.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) (Appendix X.1) 8.08 (m, 2H, Ar), 7.48 (m, 2H, Ar), 7.31 (m, 2H, Ar), 7.26 (m, 2H, Ar), 7.19 (m, 1H, Ar), 6.92 (m, 2H, Ar), 6.83 (m, 2H, Ar) 6.16 (s, 1H, C=CH-N), 6.13 (s, 1H, C=CH-N), 4.20 (d, 1H, *J* = 5.3 Hz, CH), 4.16 (d, 1H, *J* = 5.3 Hz, CH), 3.78 (s, 3H, O-CH_3), 3.38 (s, 3H, O-CH_3), 3.30 (s, 3H, O-CH_3).

^{13}C-NMR (600 MHz, $CDCl_3$) δ (ppm) (Appendix X.2) 154.54 (1C, C), 149.54 (1C, C), 146.45 (1C, C), 144.77 (1C, C), 144.69 (1C, C), 141.09 (1C, C), 141.03 (1C, C), 128.53 (2C, CH), 128.08 (2C, CH), 127.70 (2C, CH), 126.63 (1C, CH), 123.14 (2C, CH), 118.45 (2C, CH), 114.47 (2C, CH), 113.42 (1C, CH), 112.80 (1C, CH), 56.02 (1C, CH_3), 55.92 (1C, CH_3), 55.59 (1C, CH_3), 52.66 (1C, CH), 52.09 (1C, CH).

IR (thin film, cm^{-1}) (Appendix X.7): 1506 (s, N-O as st), 1444 (m, C-C Ar st), 1340 (s, N-O sy st), 1246 (s, C-O st), 1038 (m, C-O st), 696 (vs, C-H oop).

(2Z)-2-Methoxy-N-(4-methoxyphenyl)-3-(4-nitrophenyl)prop-2-en-1-imine 12



12

Compound **11f** was prepared according to general procedure 7, using acetal **2c** (130 mg, 0.52 mmol), azide **10b** (8.2 mg, 0.55 mmol) and catalyst (9.6 mg, 12 μmol). Purification by silica flash chromatography (*n*-pentane/EtOAc 4:1) afforded azepine **11f** (50 mg, 31 %) as a yellow oil.

R_f = 0.45 (*n*-pentane/EtOAc 3:1).

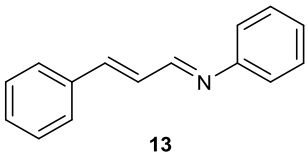
HRMS (ASAP) (Appendix Y.8) calcd for $C_{17}H_{17}N_2O_4$ $[M+H]^+$ 313.1188, obsd 313.1192.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) (Appendix Y.1) 8.23 (m, 2H, Ar), 8.08 (s, 1H, CH=N), 7.92 (m, 2H, Ar), 7.27 (m, 2H, Ar), 6.96 (m, 2H, Ar), 6.36 (s, 1H, C=CH), 4.09 (s, 3H, O-CH_3), 3.86 (s, 3H, O-CH_3).

^{13}C-NMR (600 MHz, $CDCl_3$) δ (ppm) (Appendix Y.2) 159.05 (1C, C), 156.87 (1C, C), 153.92 (1C, CH=N) 146.60 (1C, C), 143.50 (1C, C), 141.25 (1C, C), 129.78 (2C, CH), 123.81 (2C, CH), 122.47 (2C, CH), 121.60 (1C, CH), 114.50 (2C, CH), 59.45 (1C, CH_3), 55.53 (1C, CH_3).

IR (thin film, cm^{-1}) (Appendix Y.7): 1610 (m, C-C st), 2590 (m, C-C st), 1506 (s, C-C st), 1340 (vs, C-O st), 1241 (s, C-O st), 1039 (m, C-O st), 873 (m, C-H oop), 831 (m, C-H oop).

(2E)-N,3-Diphenylprop-2-en-1-imine (13)



13

Cinnamaldehyde (1.33 g, 10 mmol, 1 eq.) and aniline (0.94 g, 10 mmol, 1 eq.) were dissolved in DCM (10 mL). Anhydrous $MgSO_4$ (2 g) was added and the reaction was stirred for 24 h. The reaction mixture was filtered and the solvent removed in vacou. The product was washed with EtOAc to afford the imine **13** (1.43 g, 69 %) as a yellow solid.

R_f = 0.57 (*n*-pentane/EtOAc 10:1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Appendix Z.1) 8.30 (dd, 1H, J = 0.7 Hz, 7.4 Hz, CH=N), 7.57 (m, 2H, Ar), 7.37-7.44 (m, 5H), 7.16-7.26 (m, 5H).

^{1}H-NMR corresponds with previously reported data.[105]

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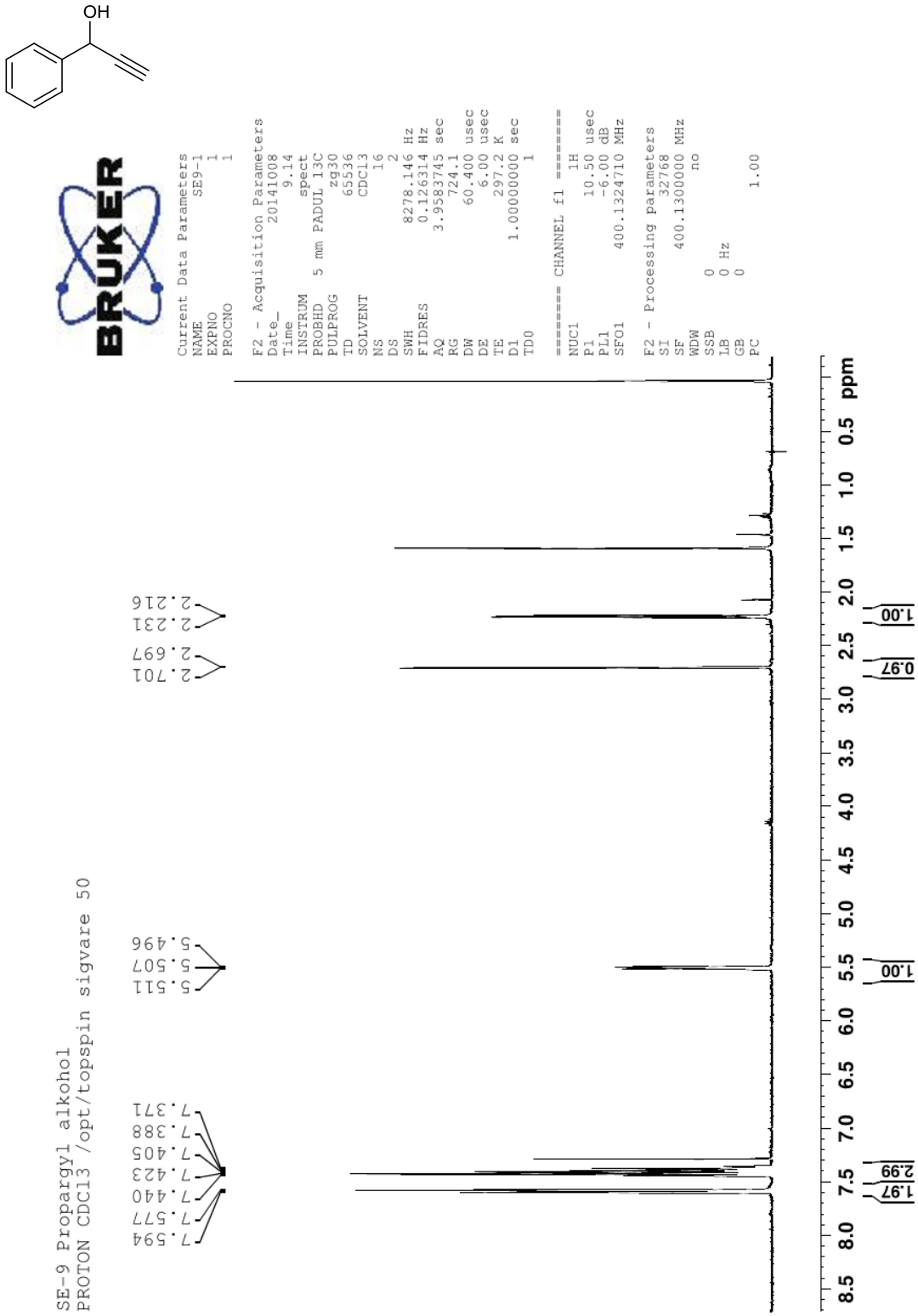
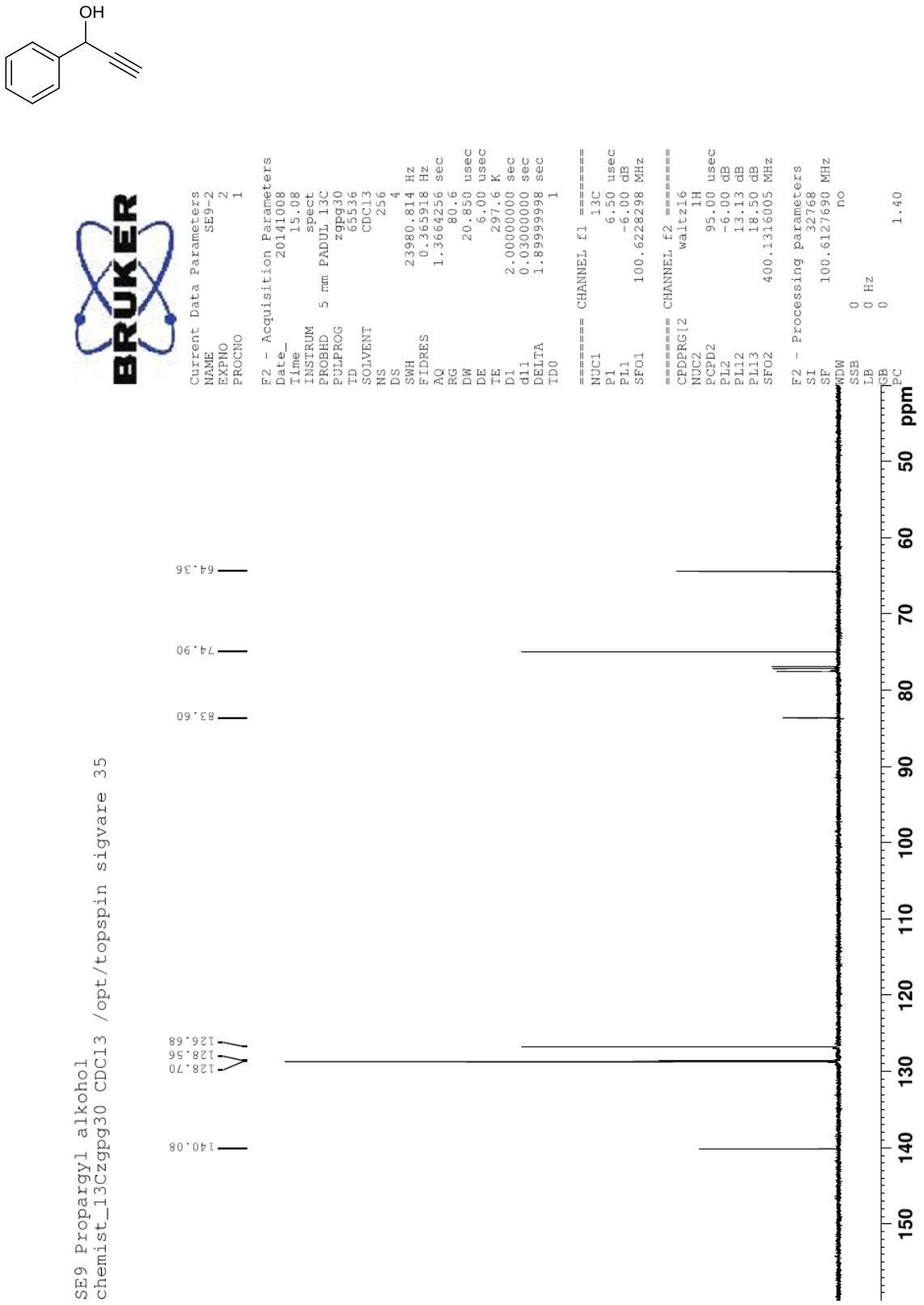
Appendix A Spectra of alcohols 1a-d

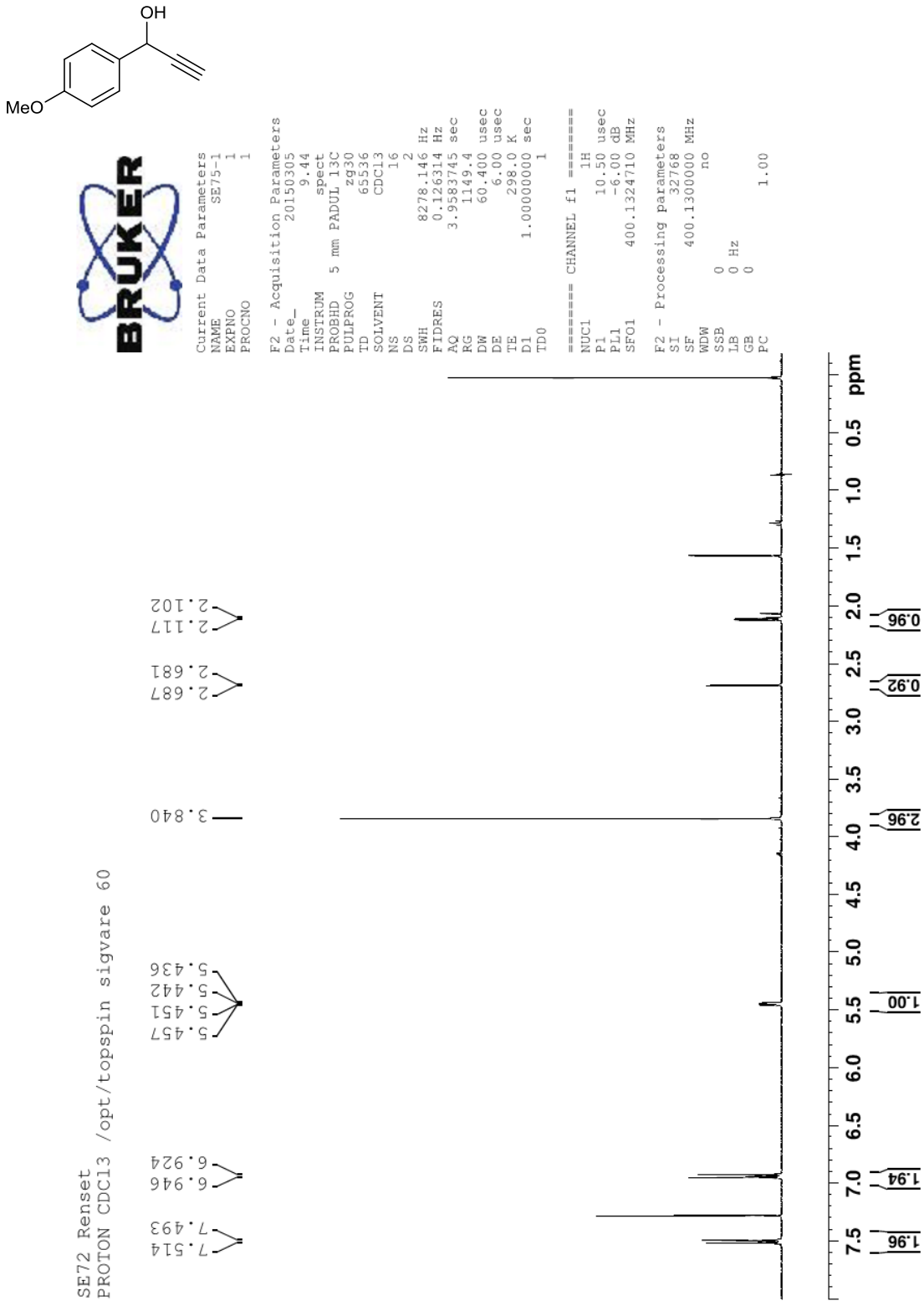
Appendix A.1 ^{1}H-NMR spectrum of propargyl alcohol 1a



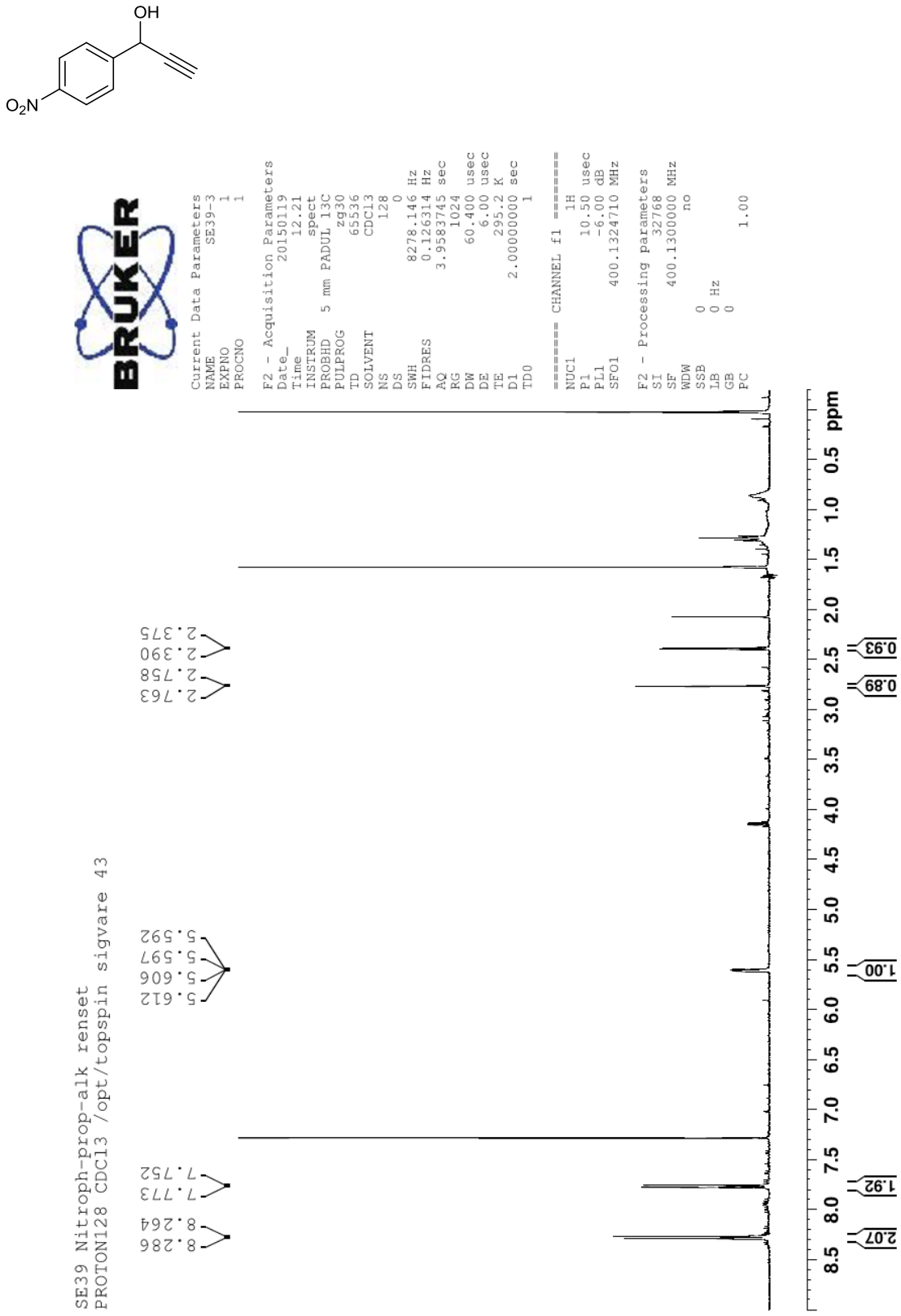
Appendix A.2 ^{13}C-NMR spectrum of propargyl alcohol 1a



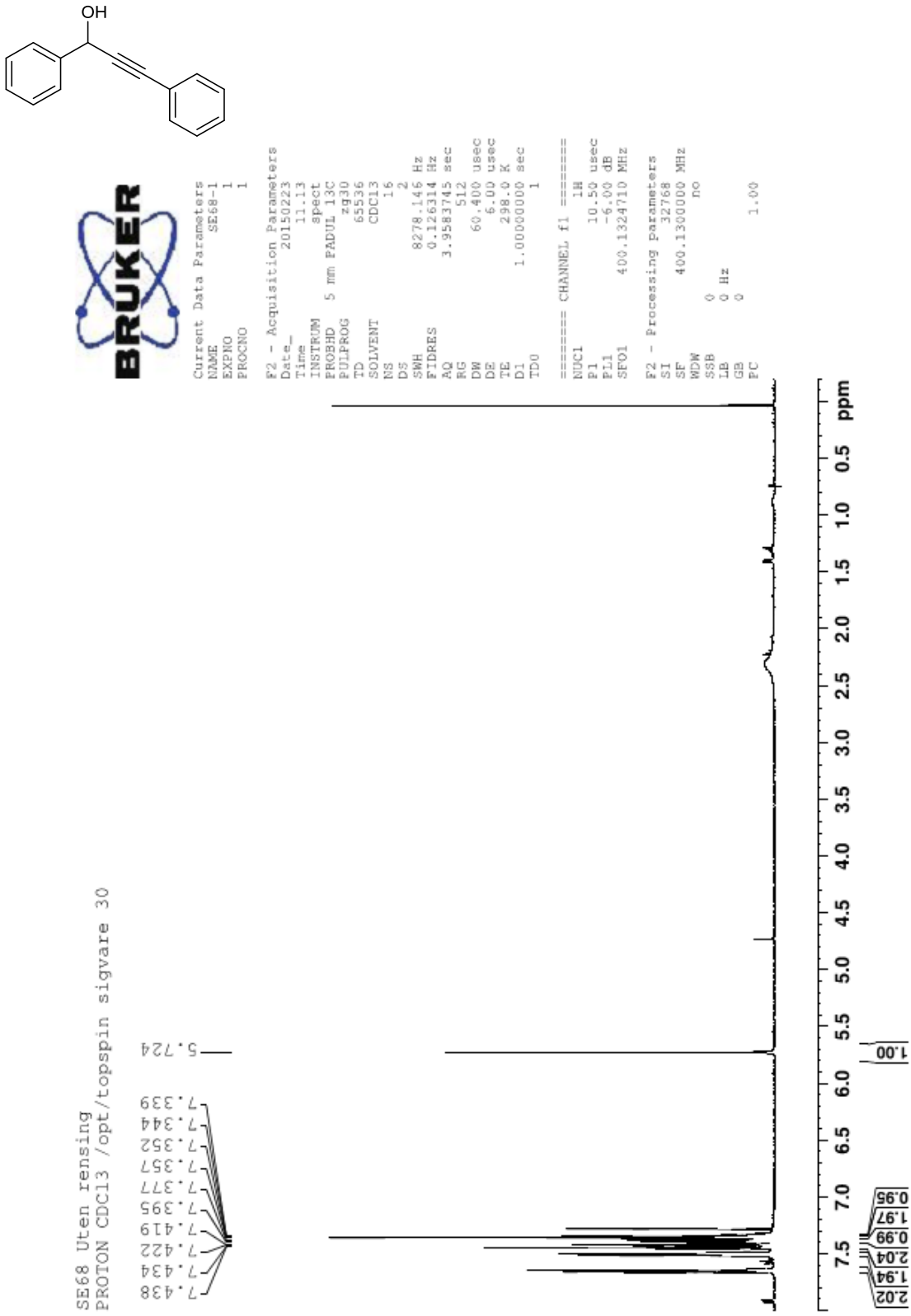
Appendix A.3 ^{1}H-NMR spectrum of propargyl alcohol 1b



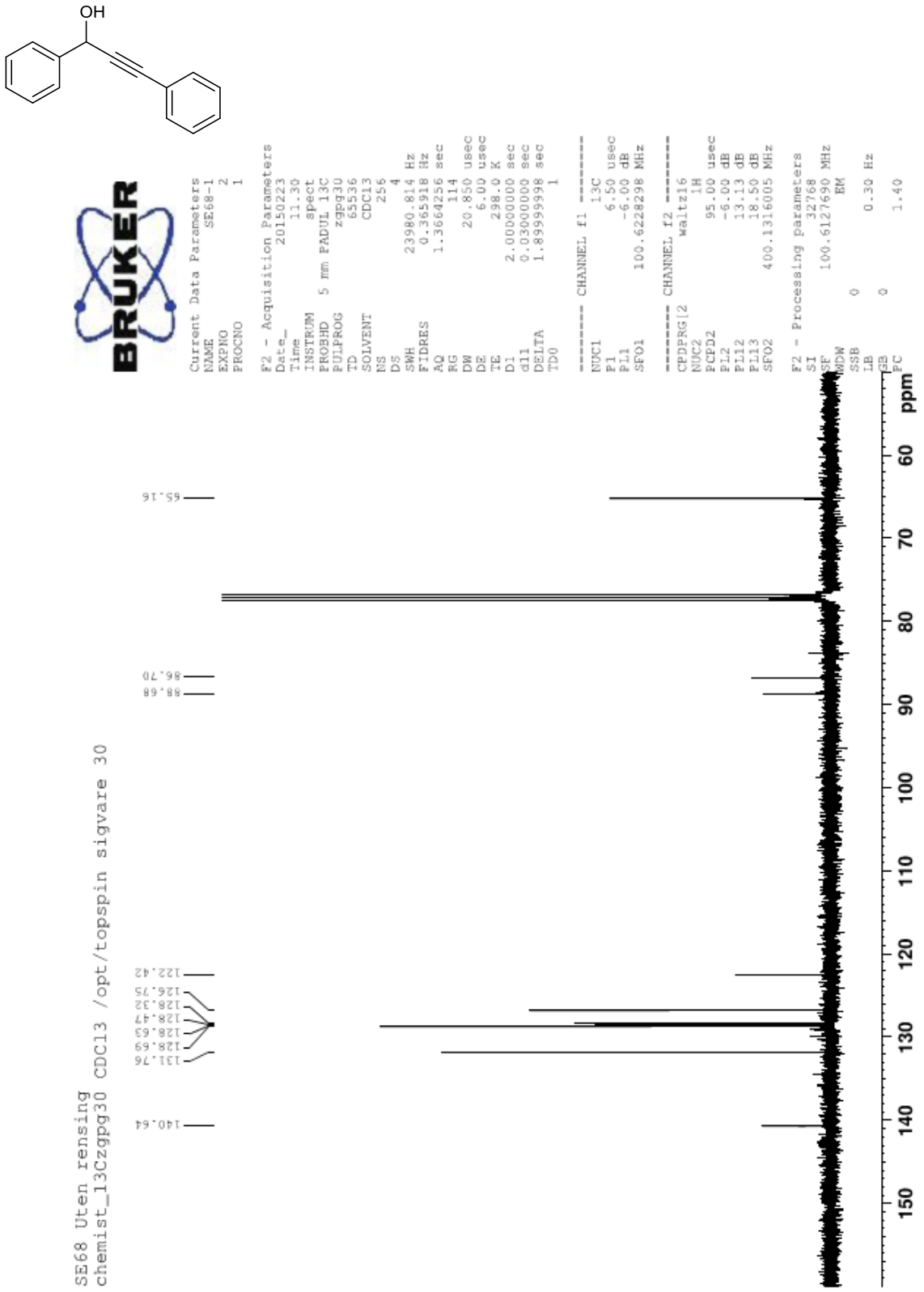
Appendix A.4 ^{1}H-NMR spectrum of propargyl alcohol 1c



Appendix A.5 ^{1}H-NMR spectrum of proparyl alcohol 1d

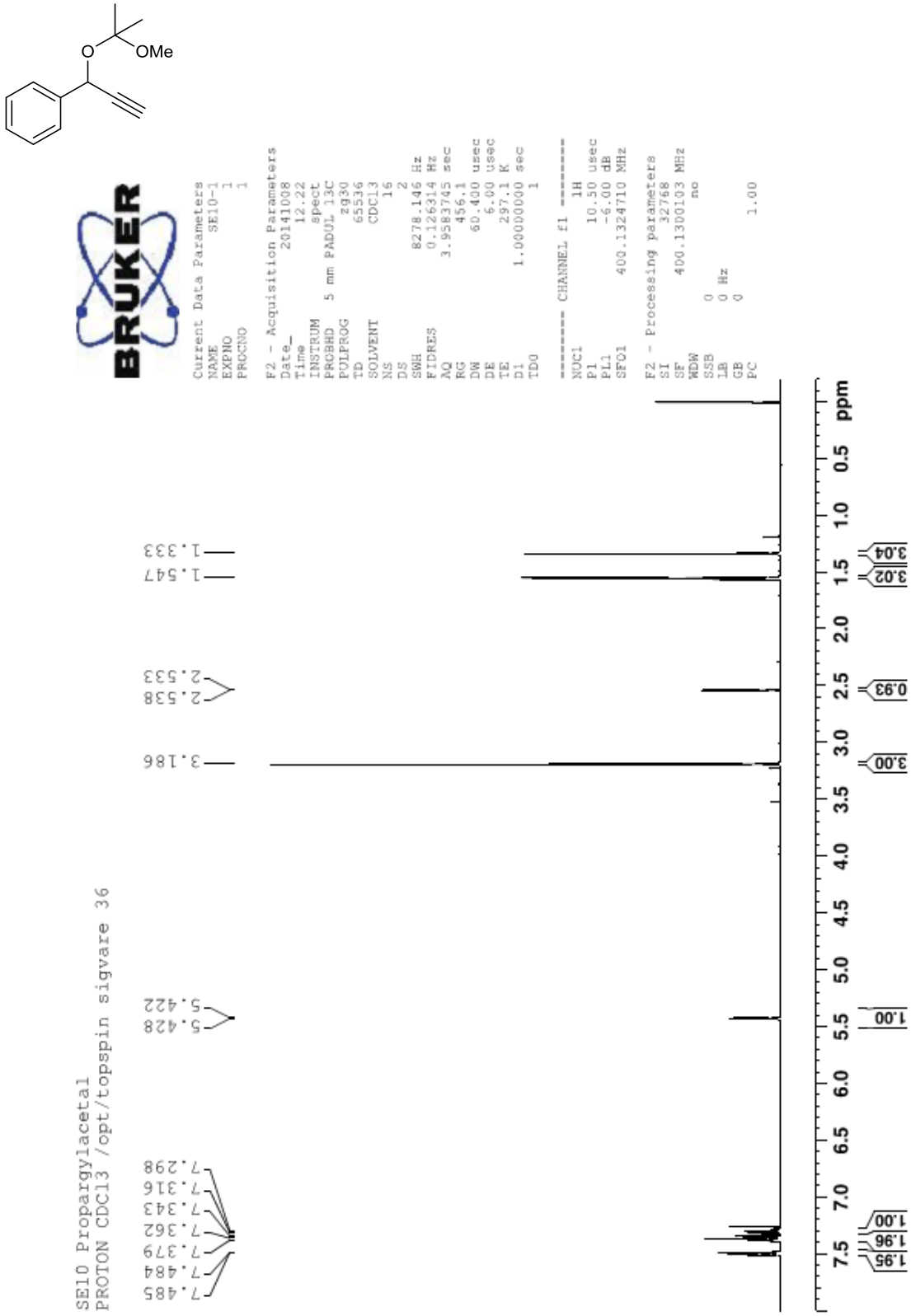


Appendix A.6 ^{13}C-NMR spectrum of propargyl alcohol 1d

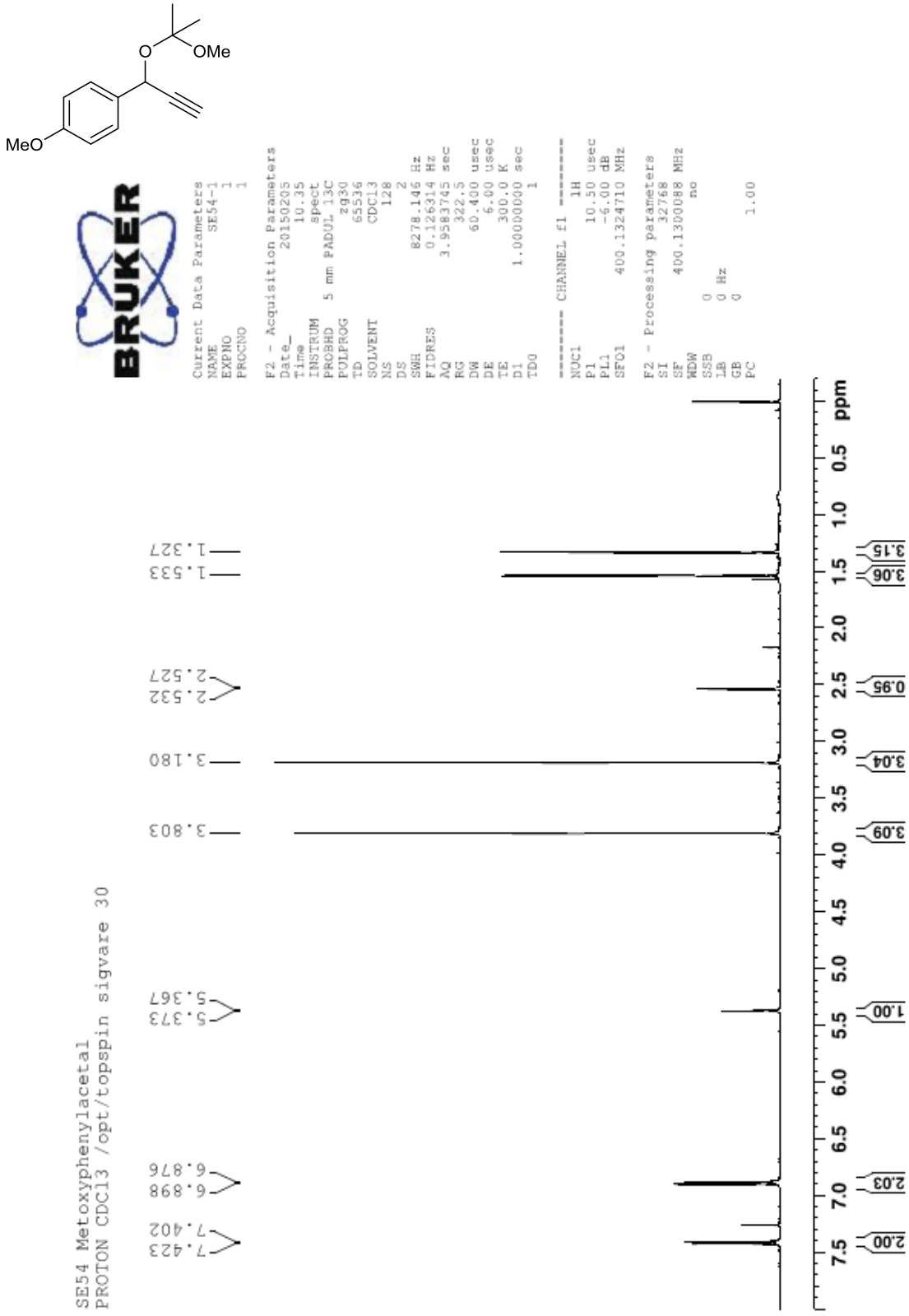


Appendix B Spectra of acetals 2a-d

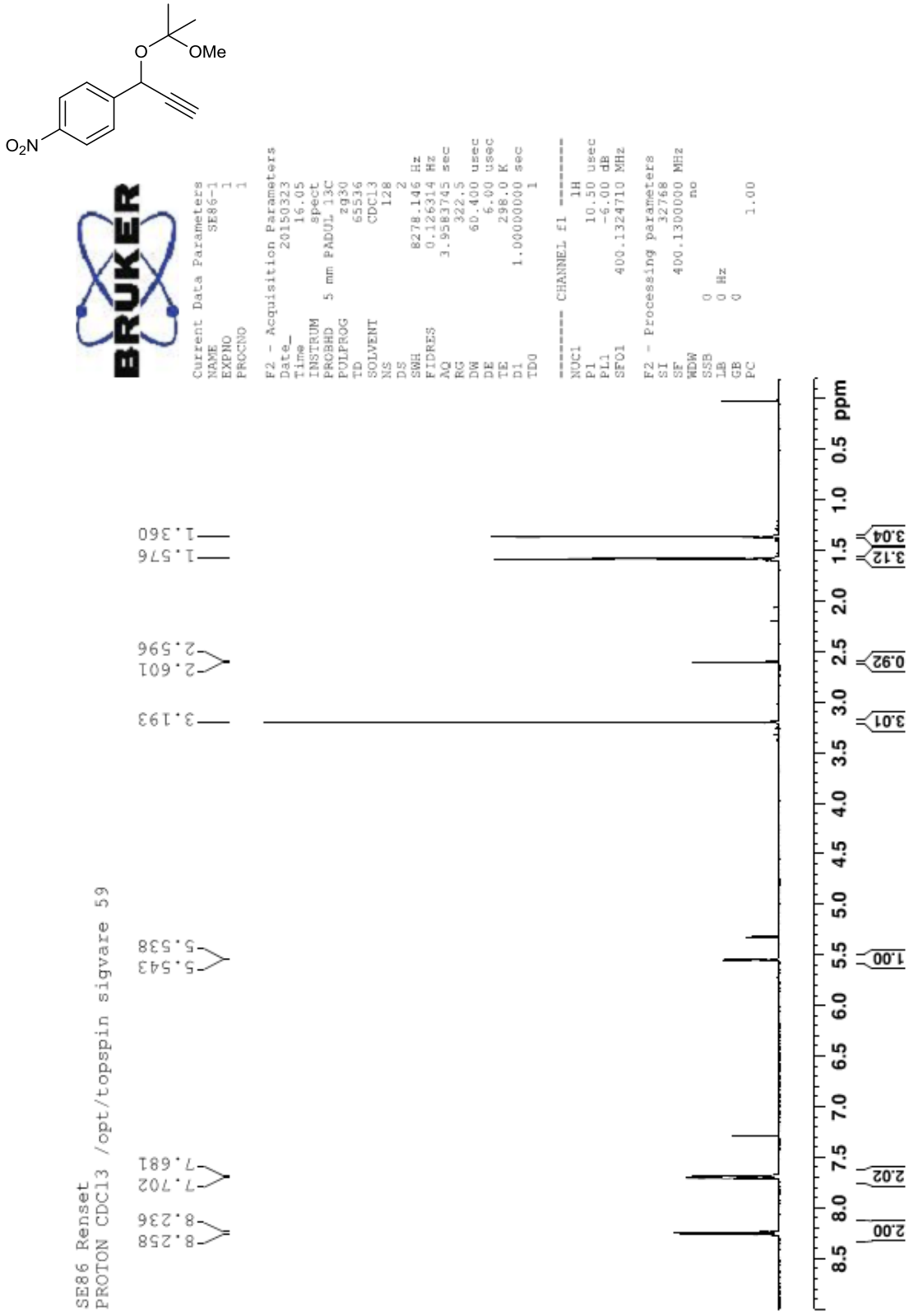
Appendix B.1 ^{1}H-NMR spectrum of propargyl acetal 2a



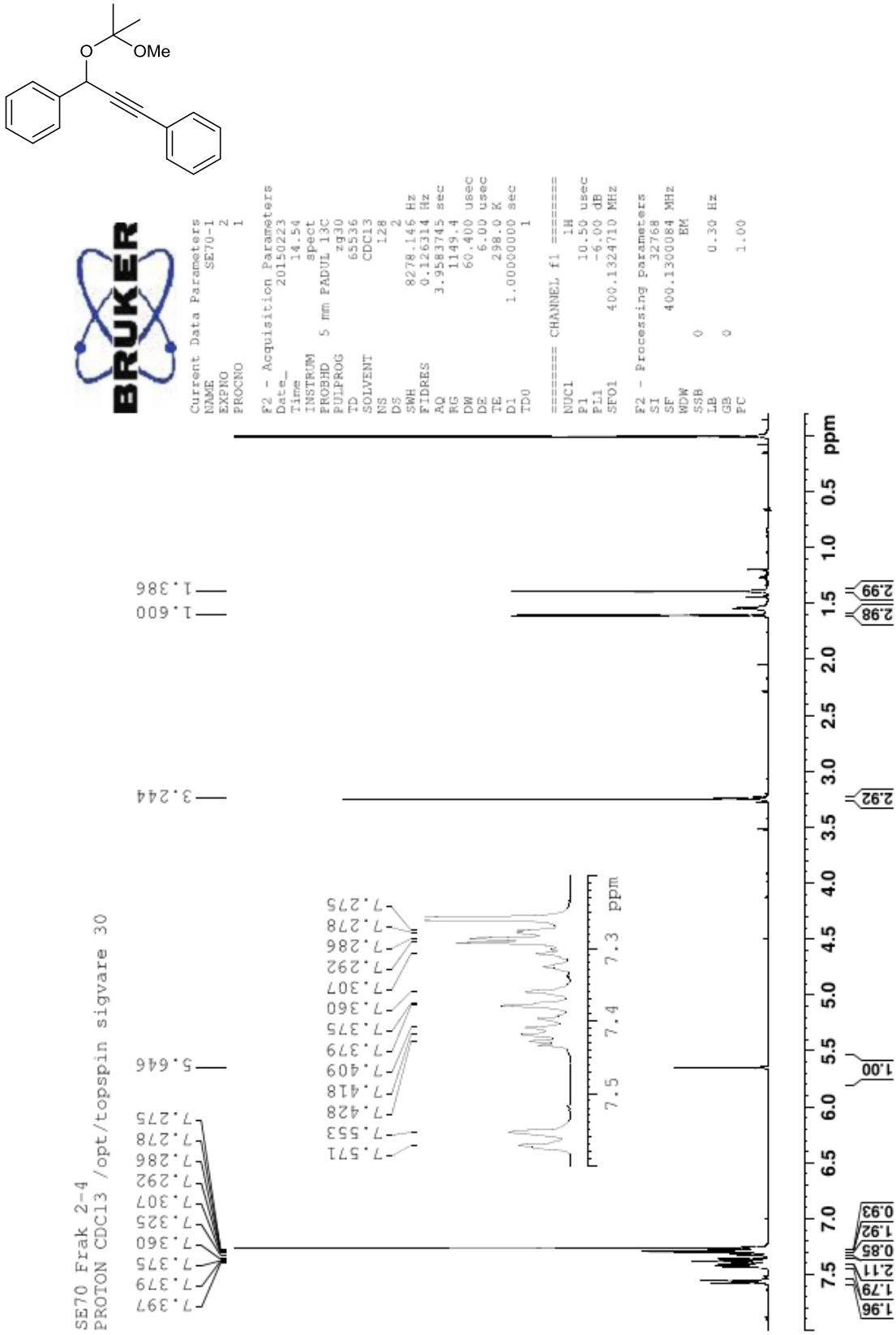
Appendix B.2 ^{1}H-NMR spectrum of propargyl acetal 2b



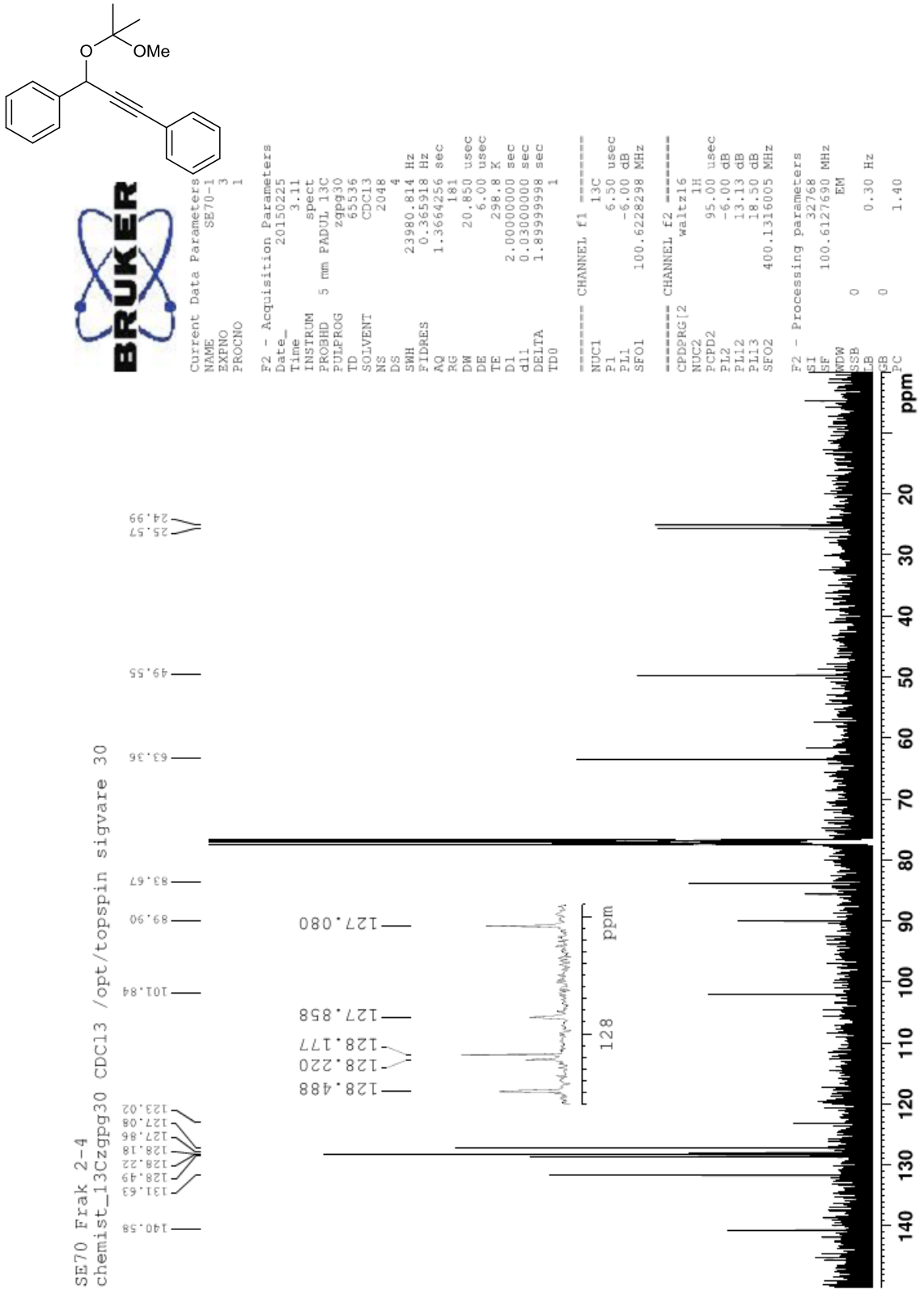
Appendix B.3 ^{1}H-NMR spectrum of propargyl acetal 2c



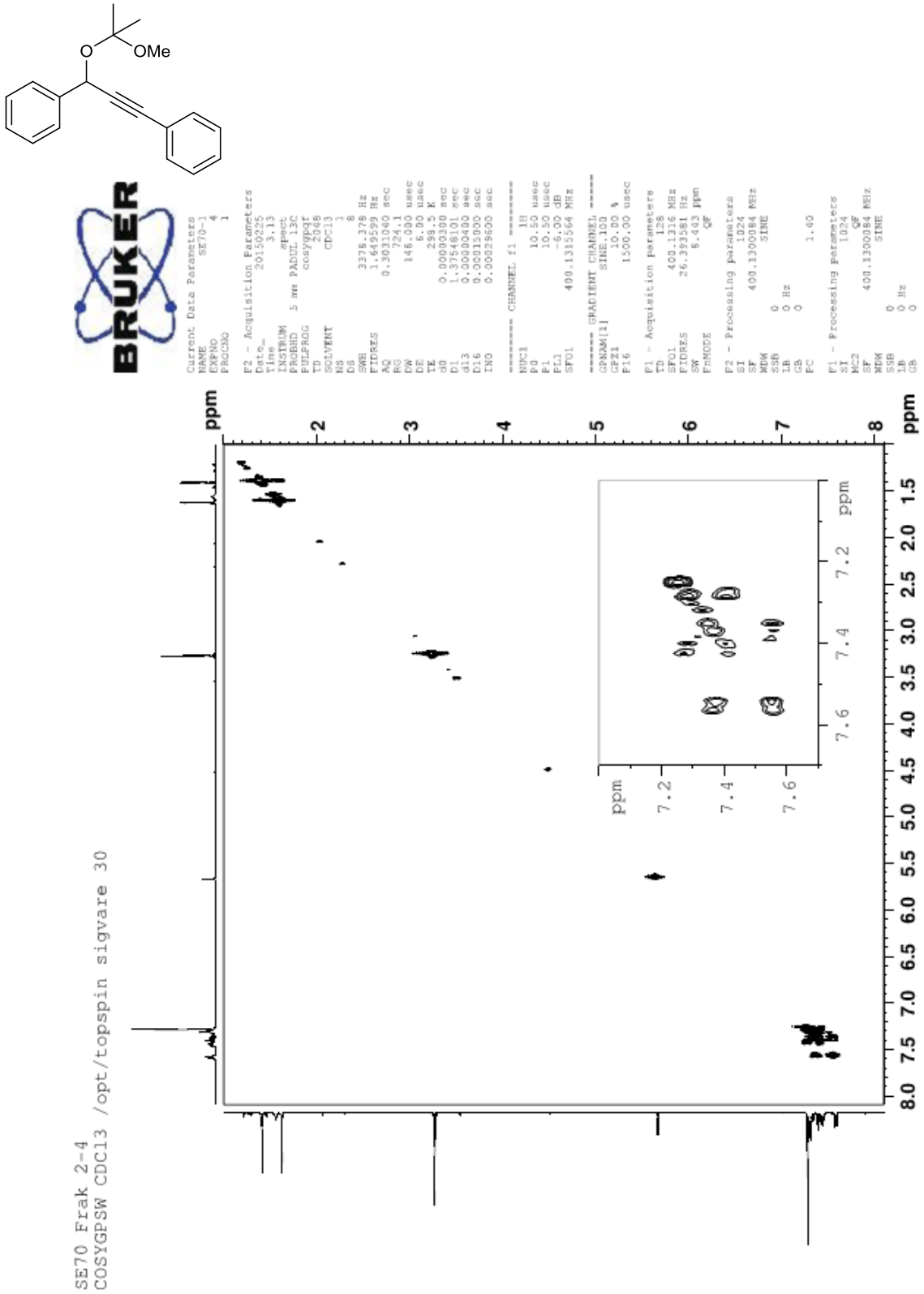
Appendix B.4.1 ^{1}H-NMR spectrum of propargyl acetal 2d



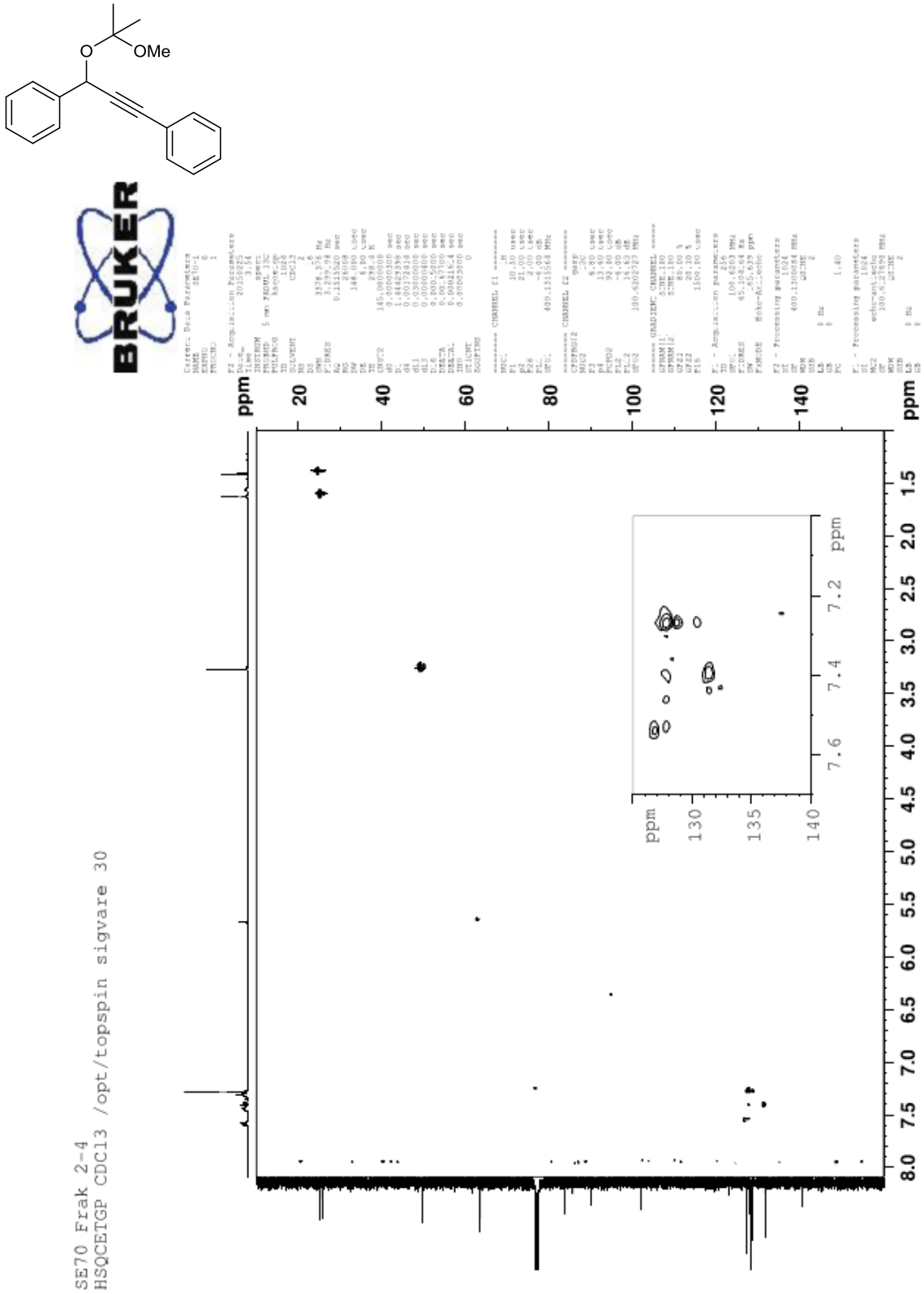
Appendix B.5 ^{13}C-NMR spectrum of propargyl acetal 2d



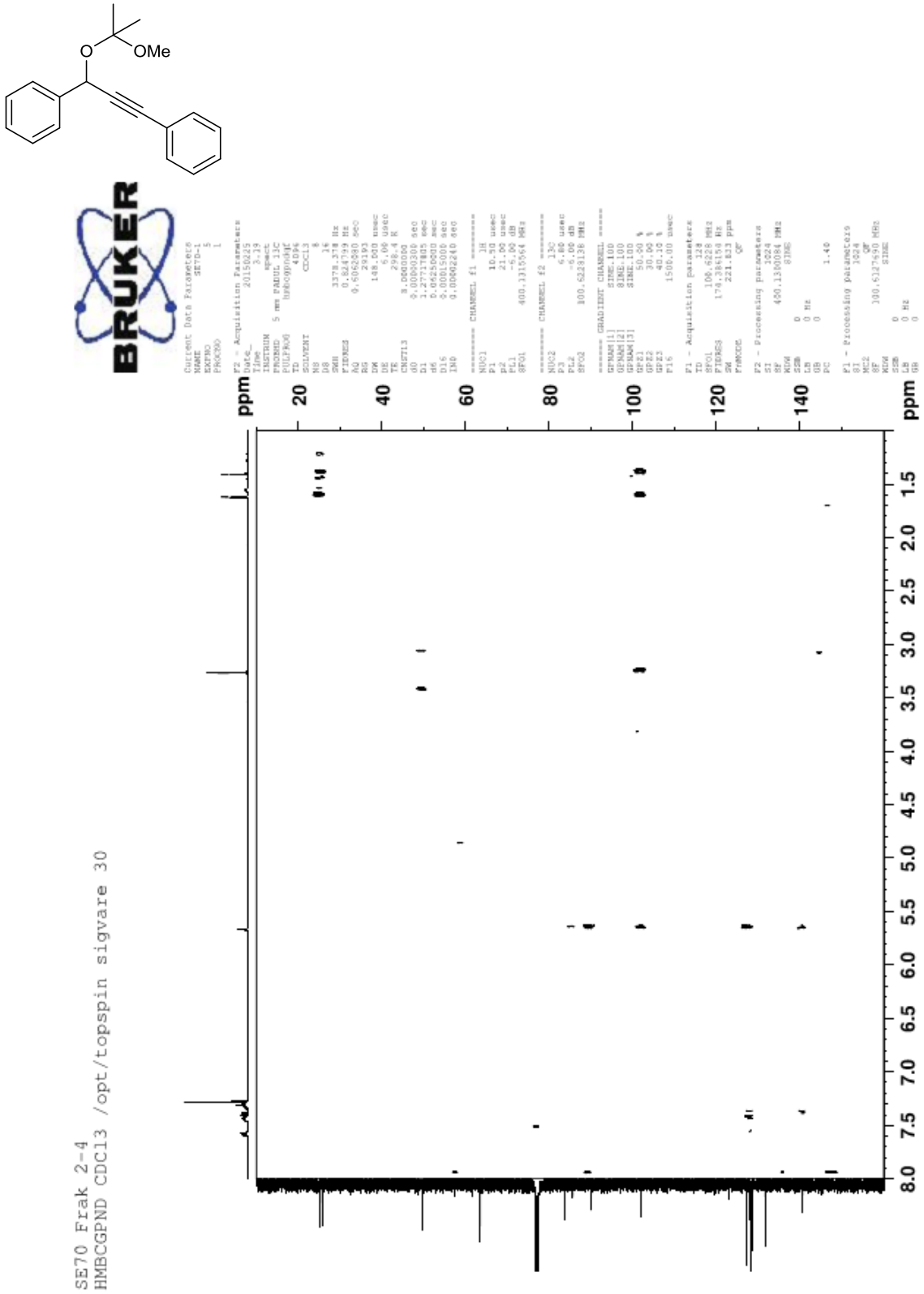
Appendix B.6 COSY spectrum of propargyl acetal 2d



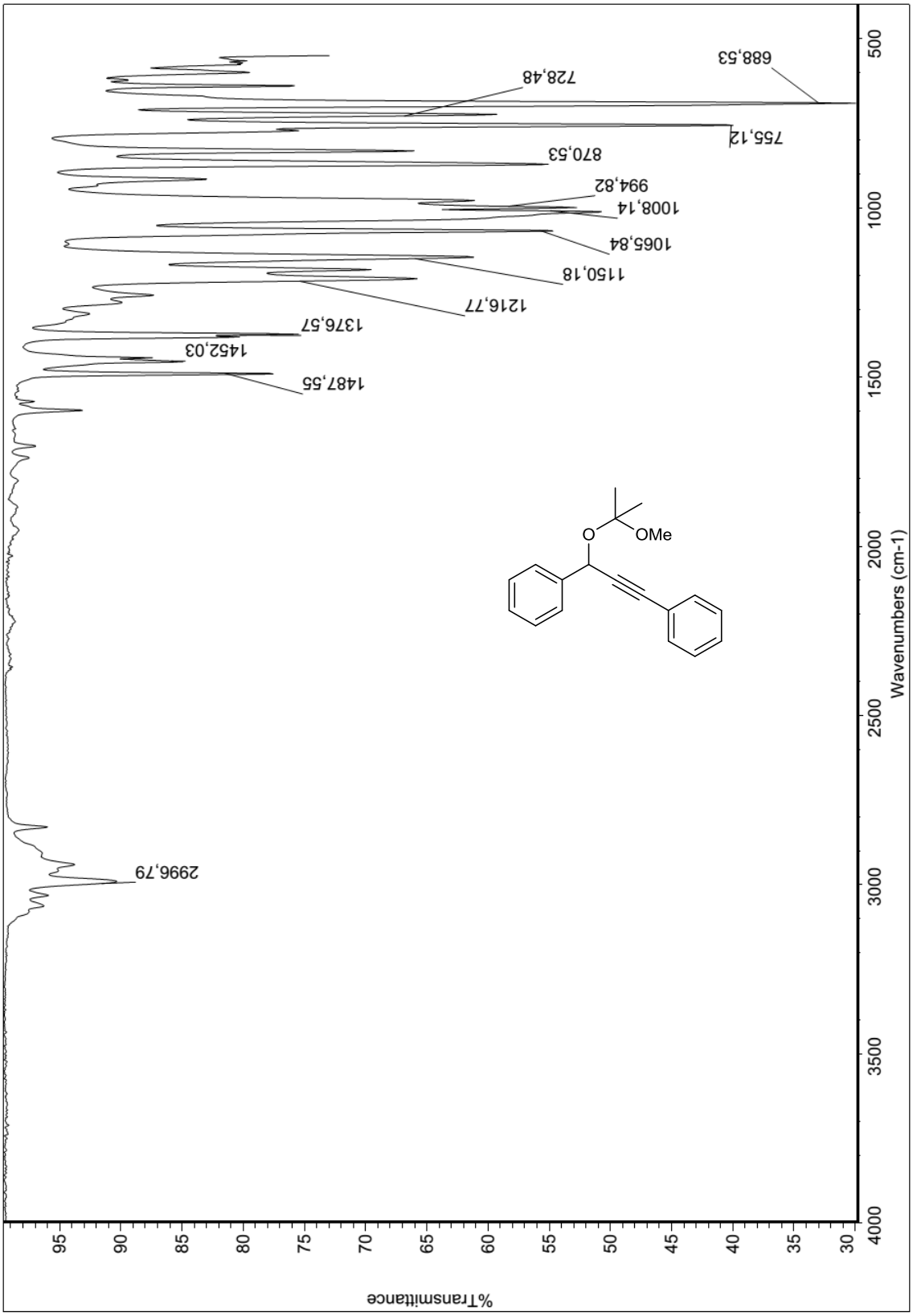
Appendix B.7 HSQC spectrum of propargyl acetal 2d



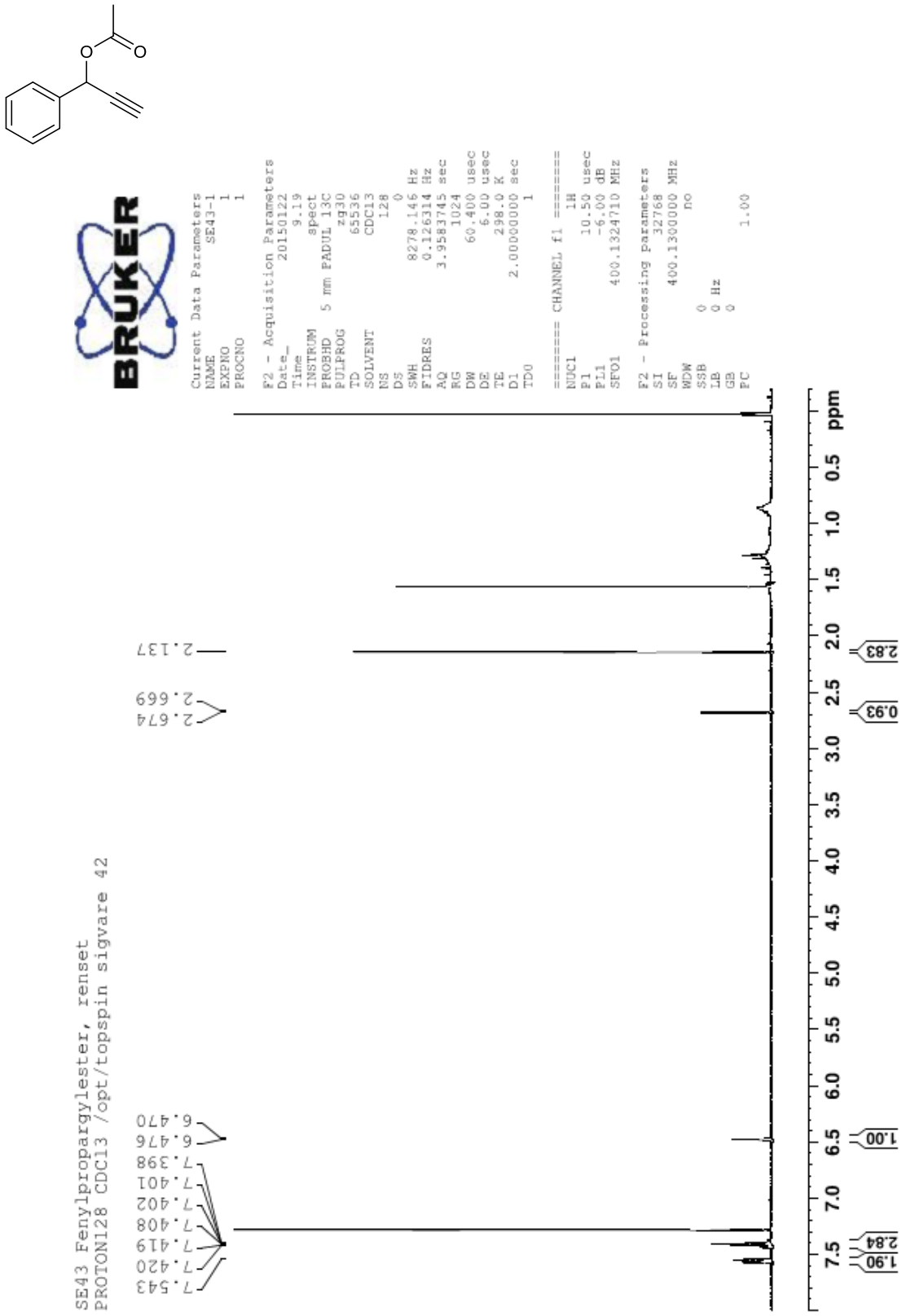
Appendix B.8 HMBC spectrum of propargyl acetal 2d



Appendix B.9 IR-spetrum of propargyl acetal 2d

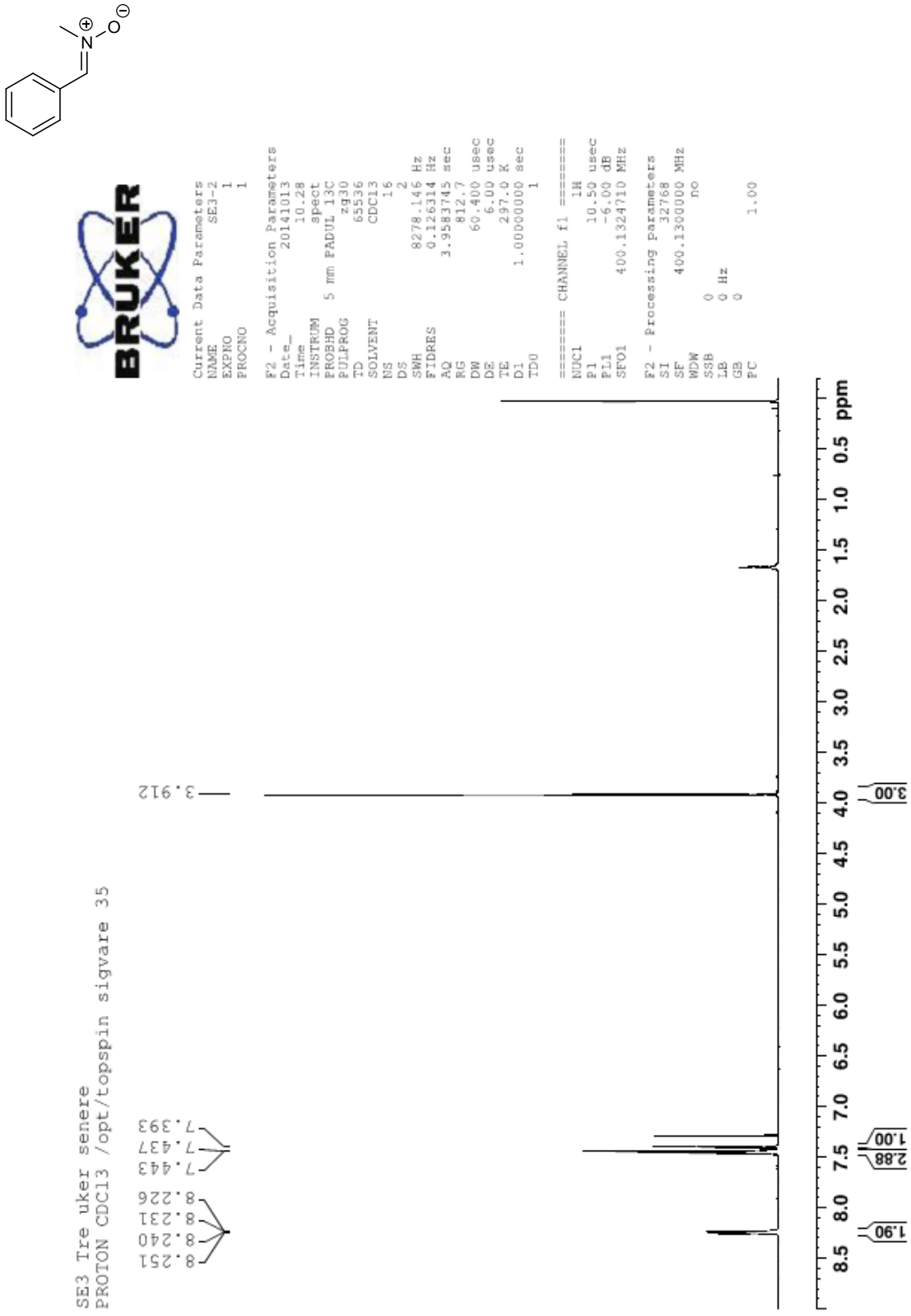


Appendix C ^{1}H-NMR spectrum of propargyl ester 3

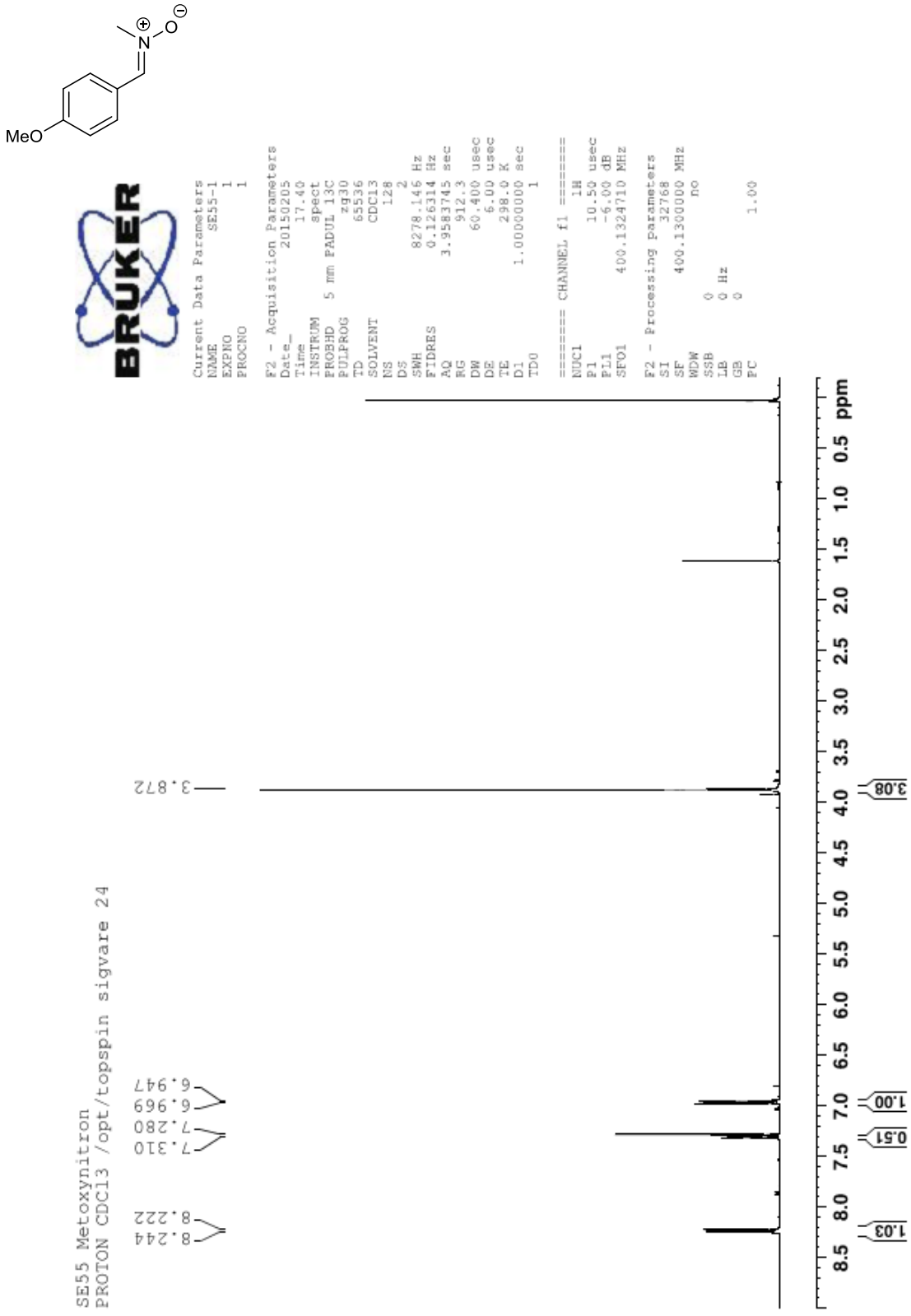


Appendix D Spectra of nitrones 4a-i

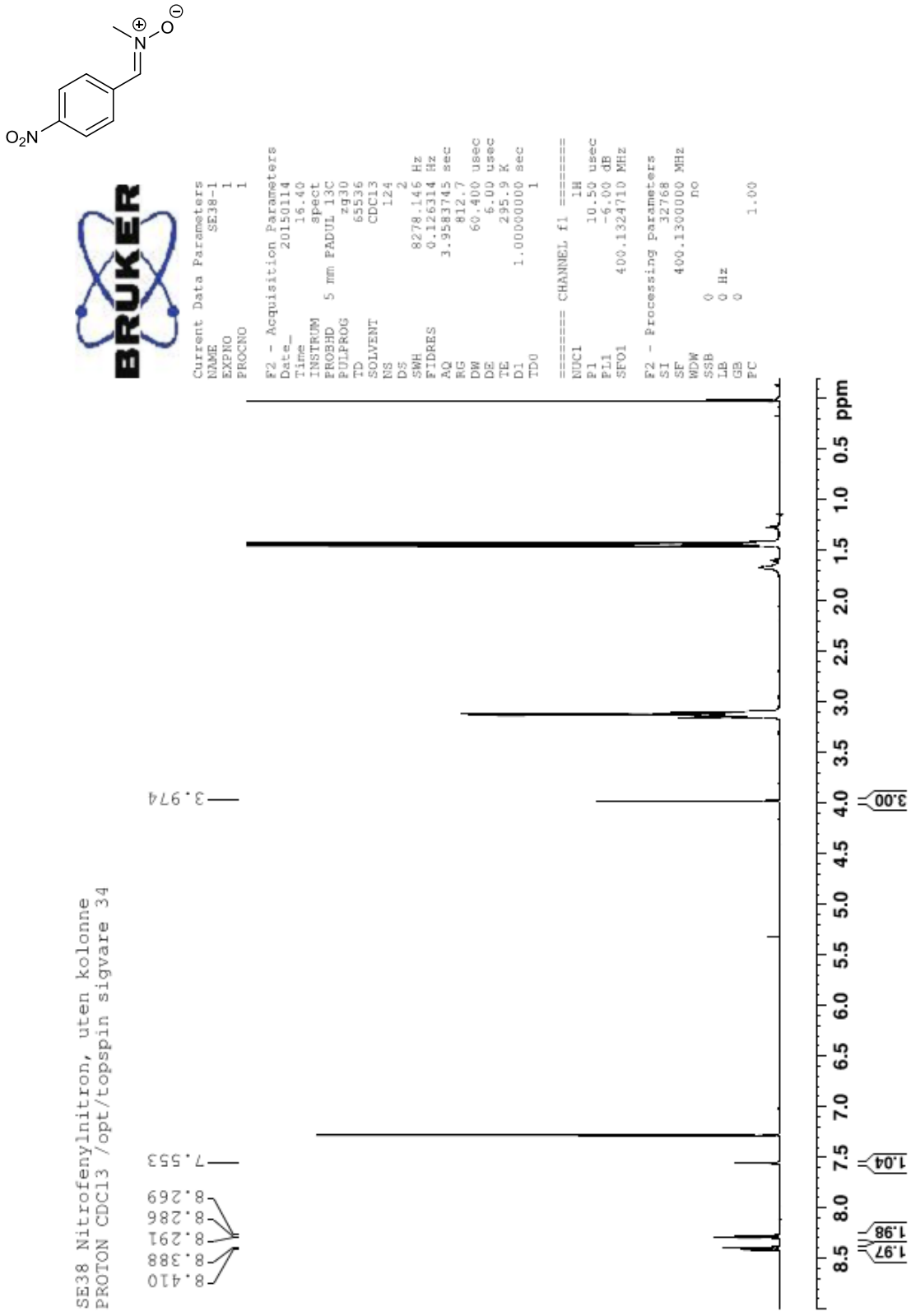
Appendix D.1 ^{1}H-NMR spectrum of nitrone 4a



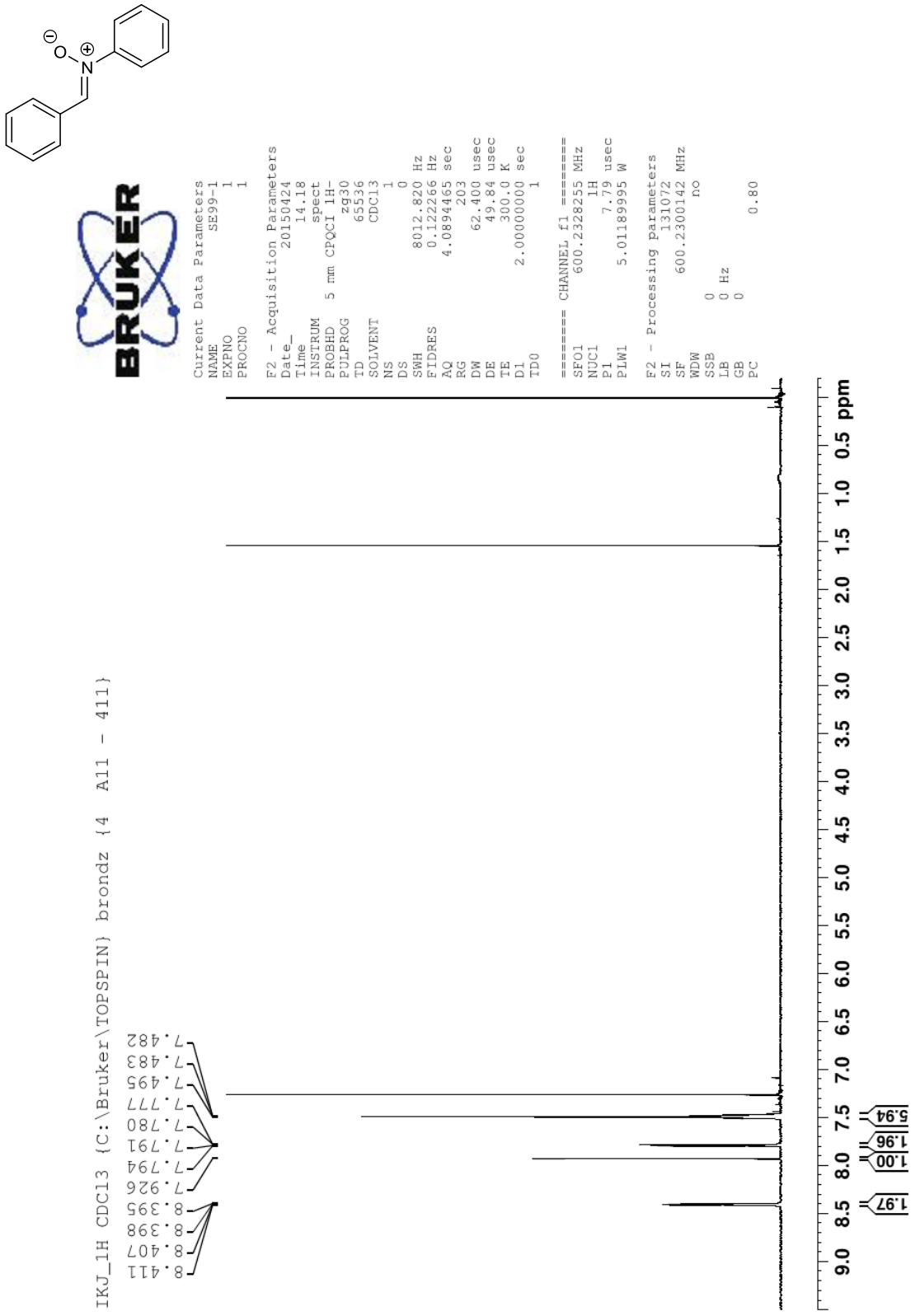
Appendix D.2 ^{1}H-NMR spectrum of nitrone 4b



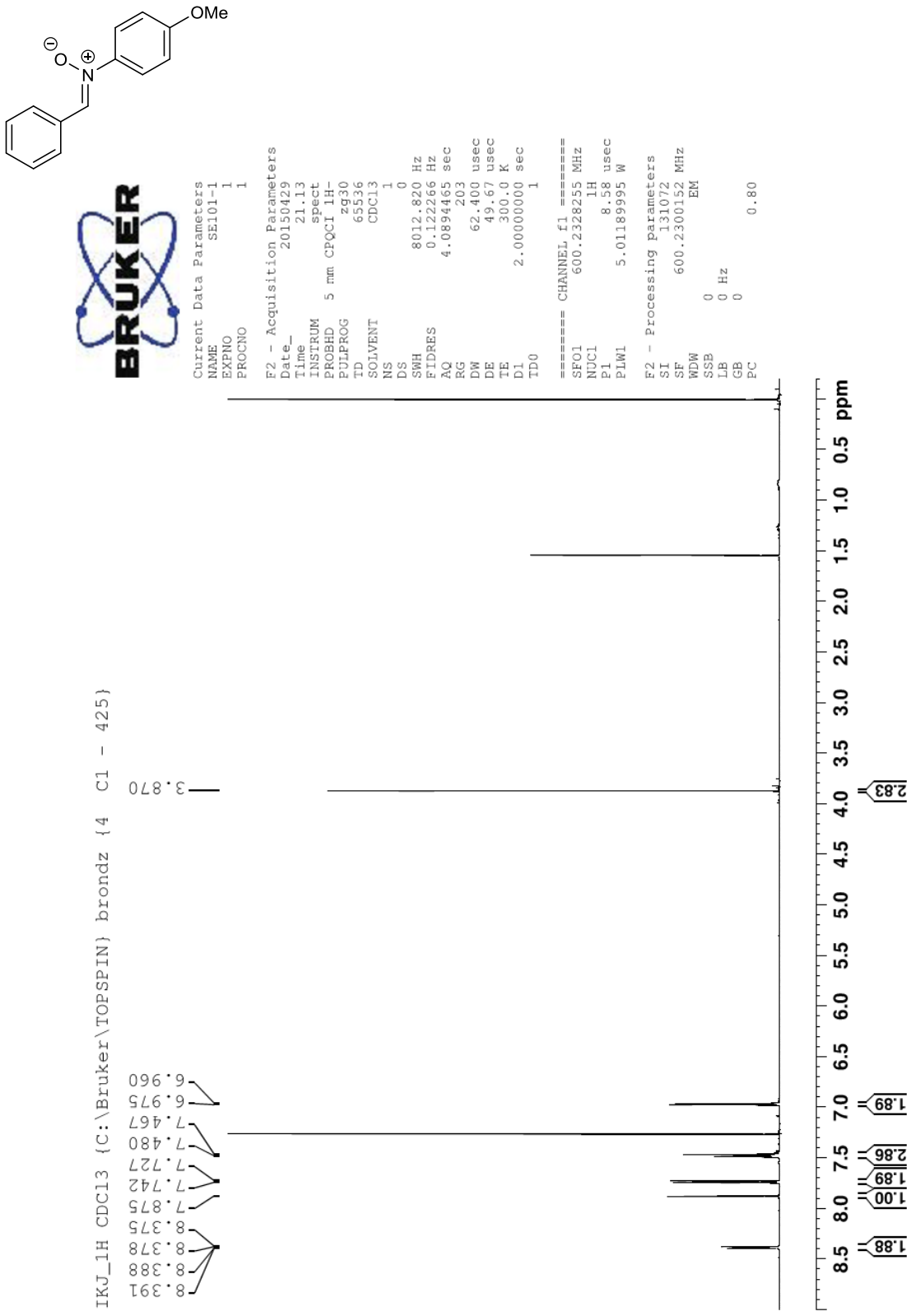
Appendix D.3 ^{1}H-NMR spectrum of nitrone 4c



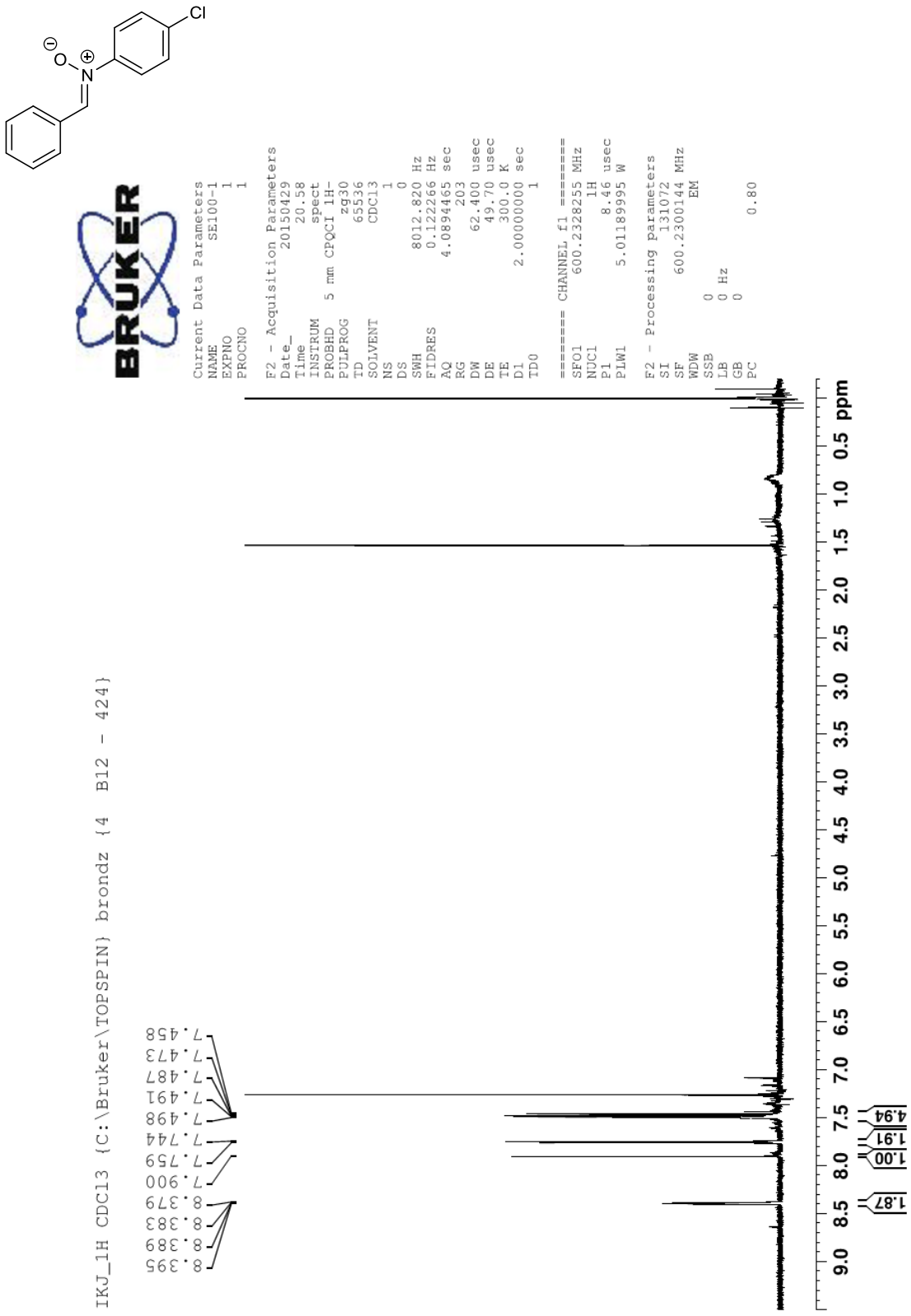
Appendix D.4 ^{1}H-NMR spectrum of nitrone 4d



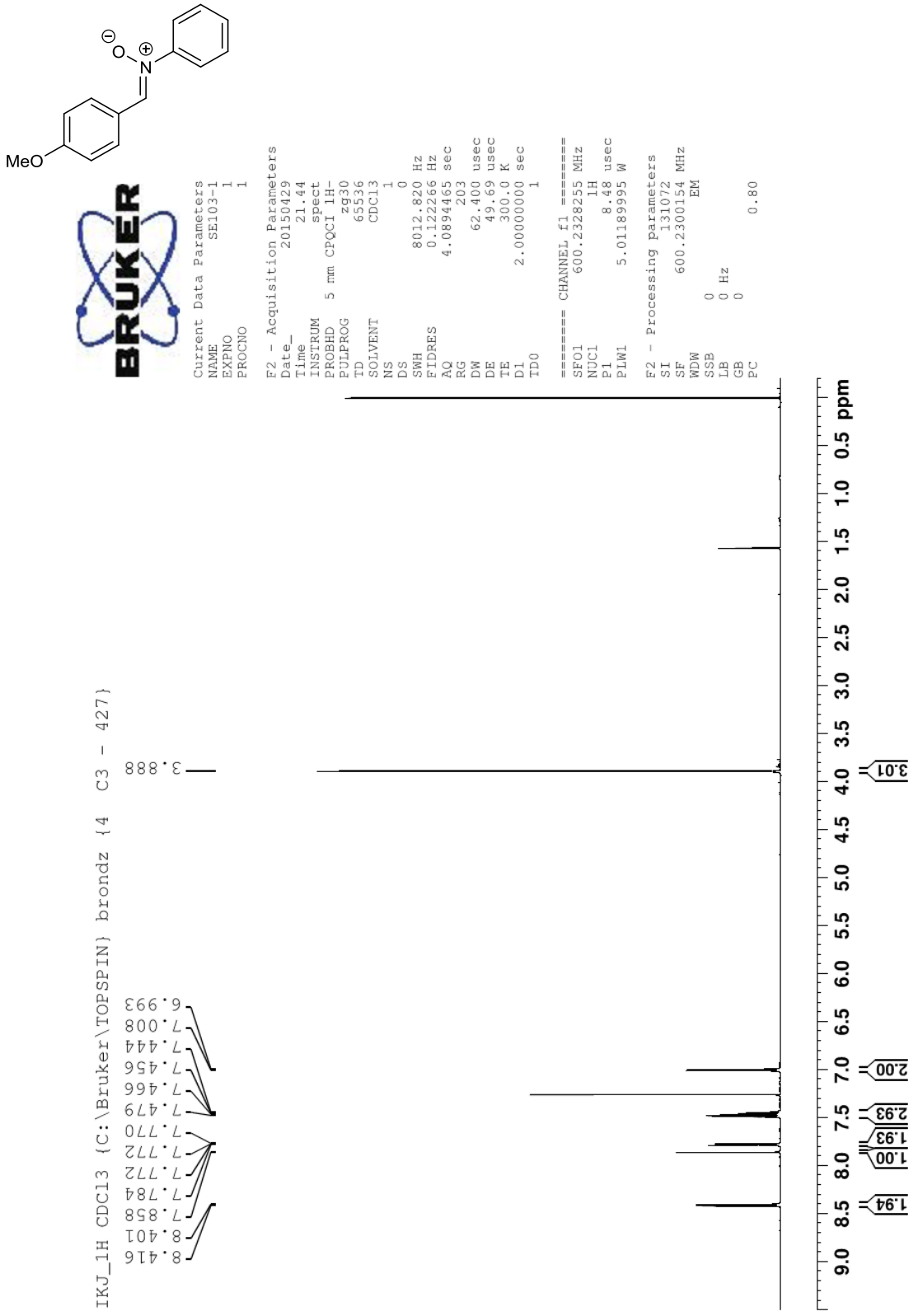
Appendix D.5 ^{1}H-NMR spectrum of nitrone 4e



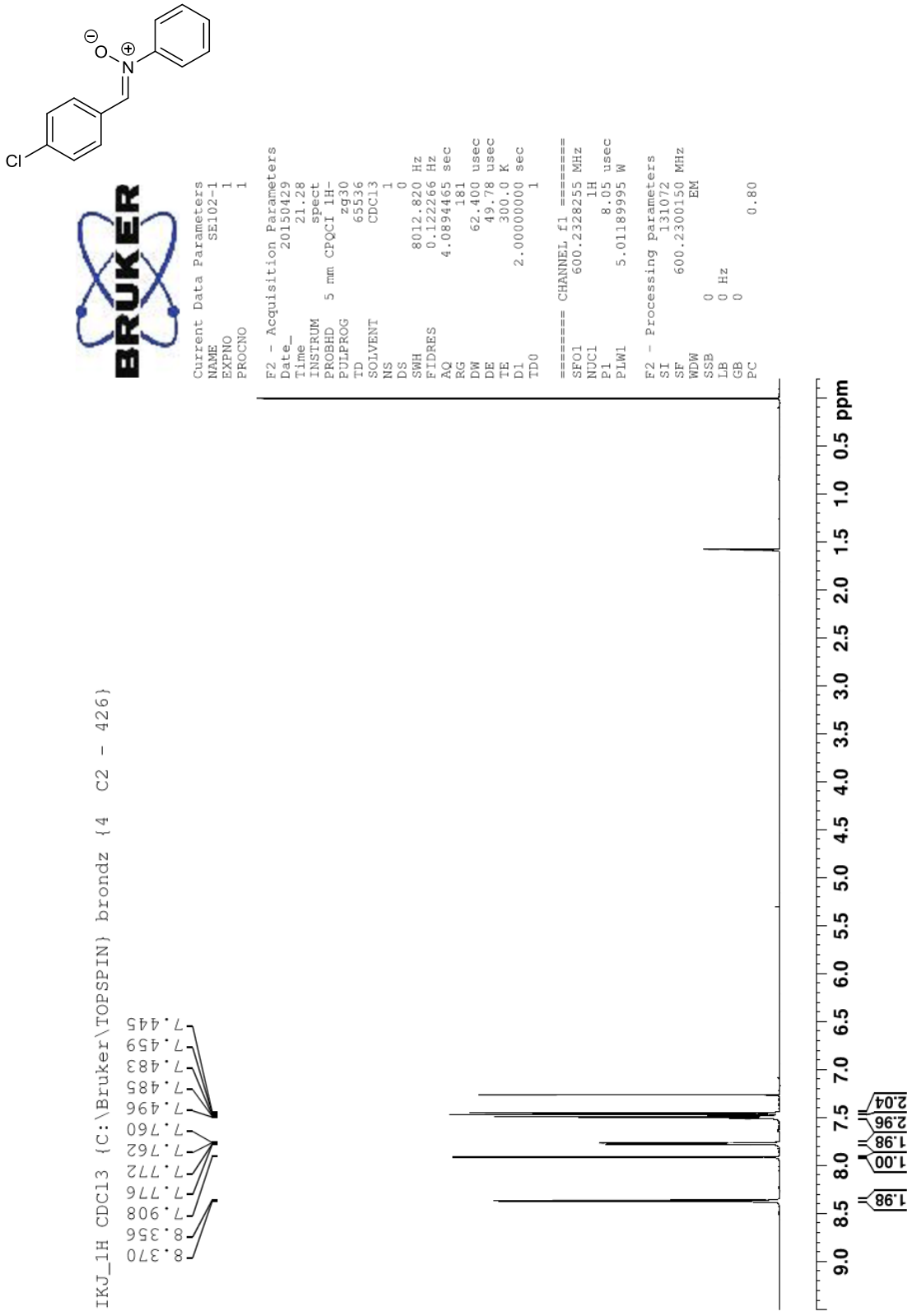
Appendix D.6 ^{1}H-NMR spectrum of nitrone 4f



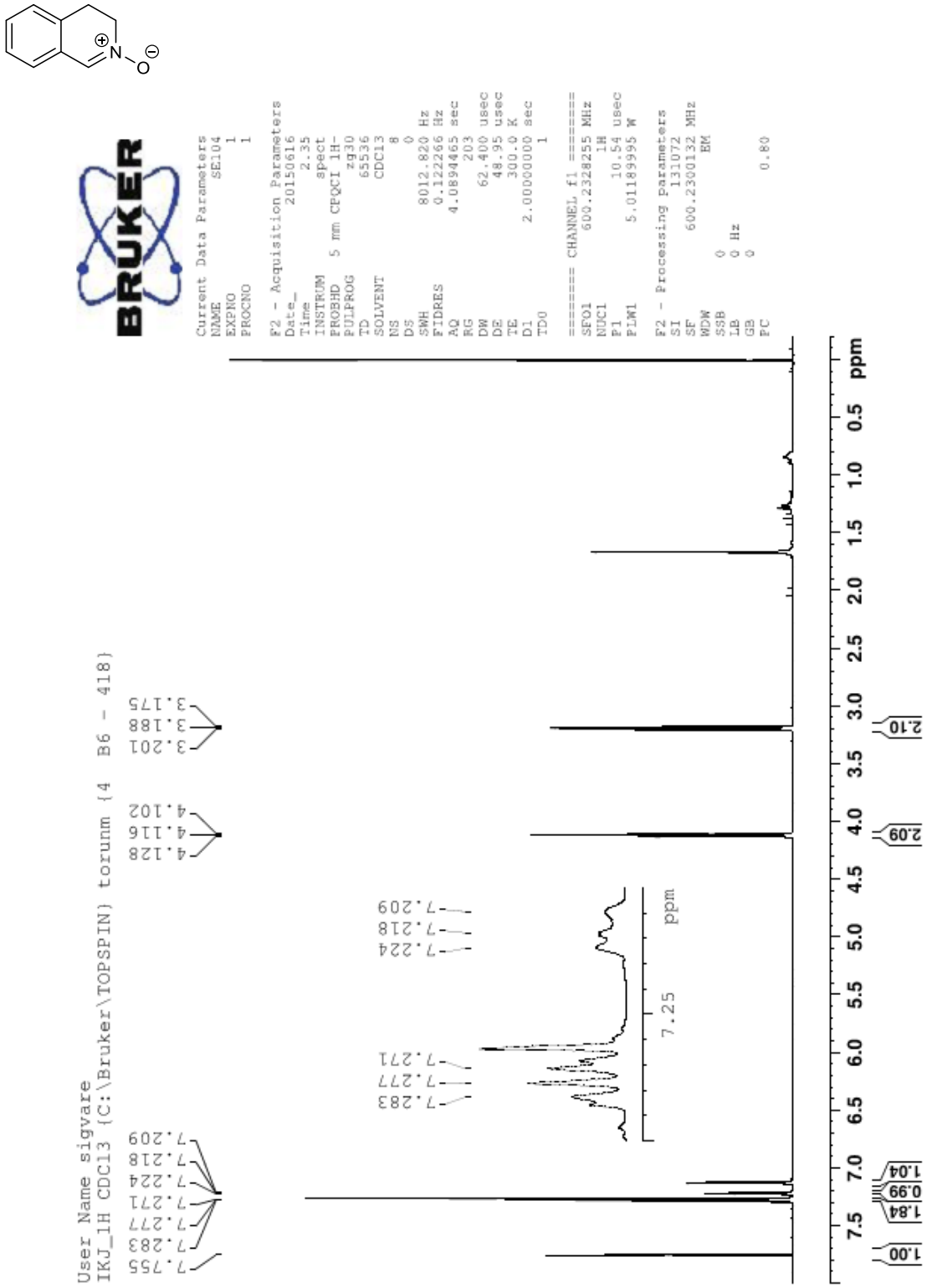
Appendix D.7 ^{1}H-NMR spectrum of nitrone 4g



Appendix D.8 ^{1}H-NMR spectrum of nitrone 4h

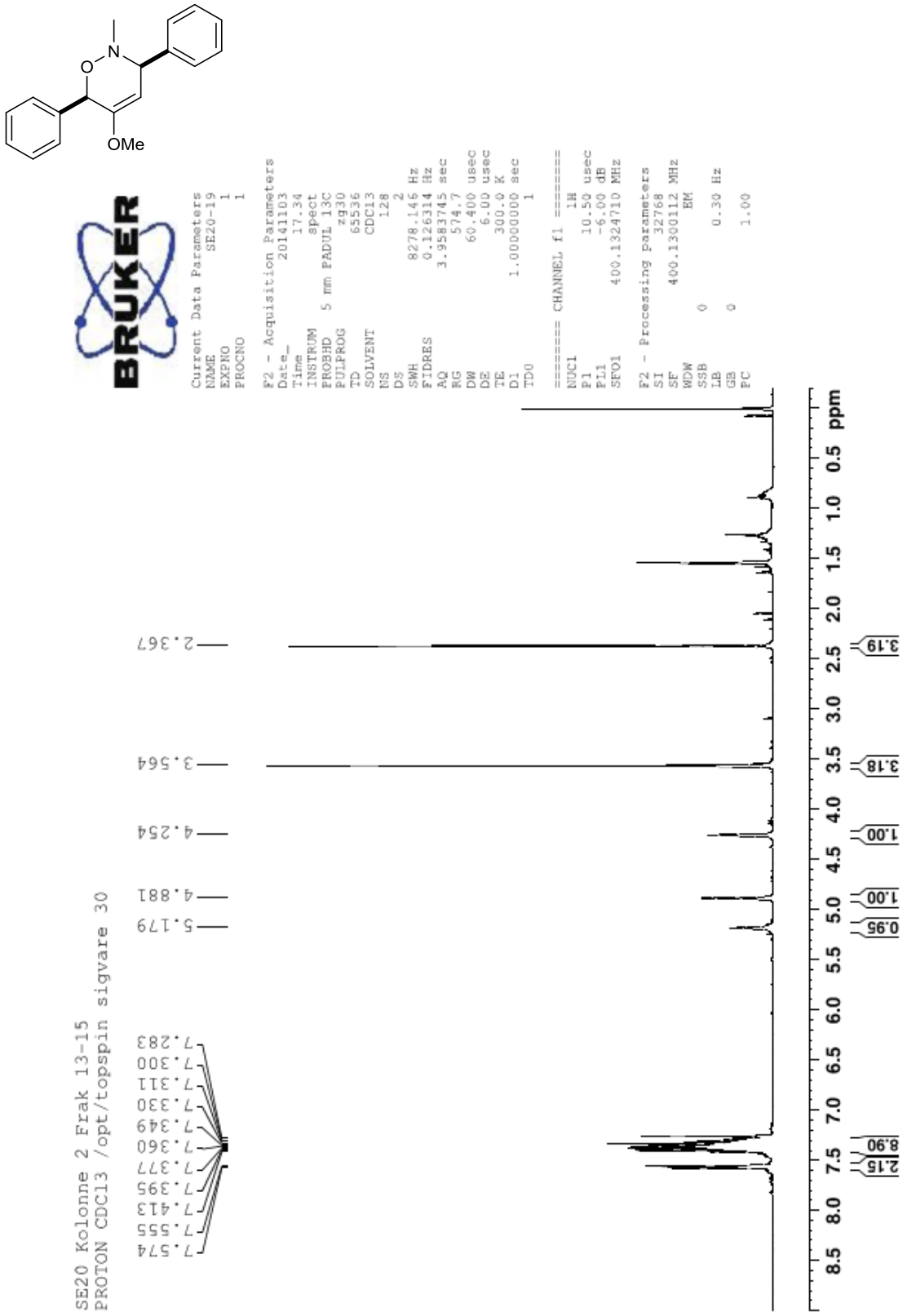


Appendix D.9 ^{1}H-NMR spectrum of nitrone 4i

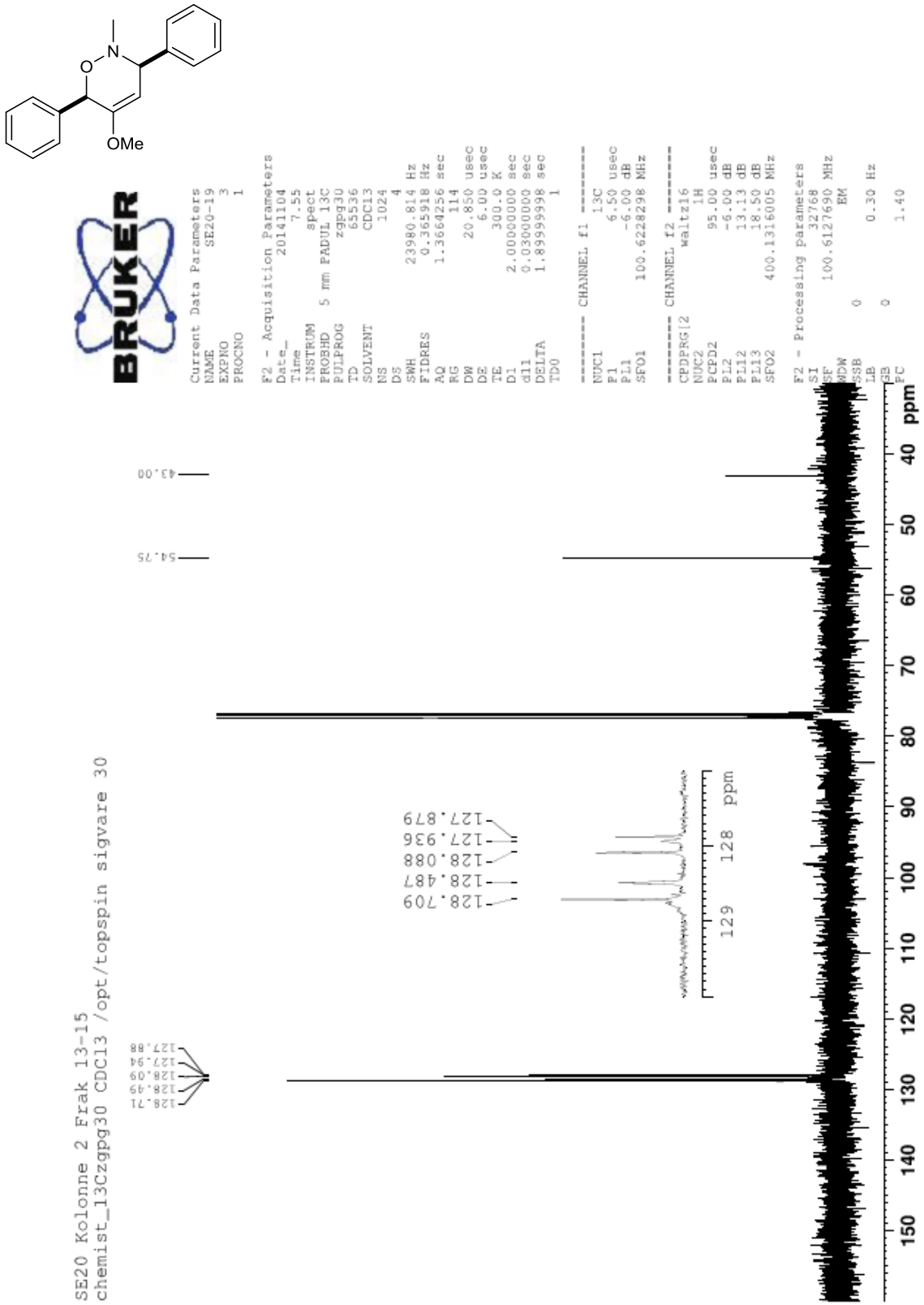


Appendix E Spectra of oxazine 5a

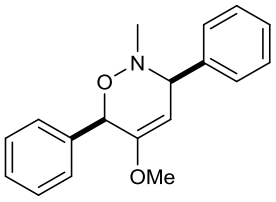
Appendix E.1 ^{1}H-NMR spectrum of oxazine 5a

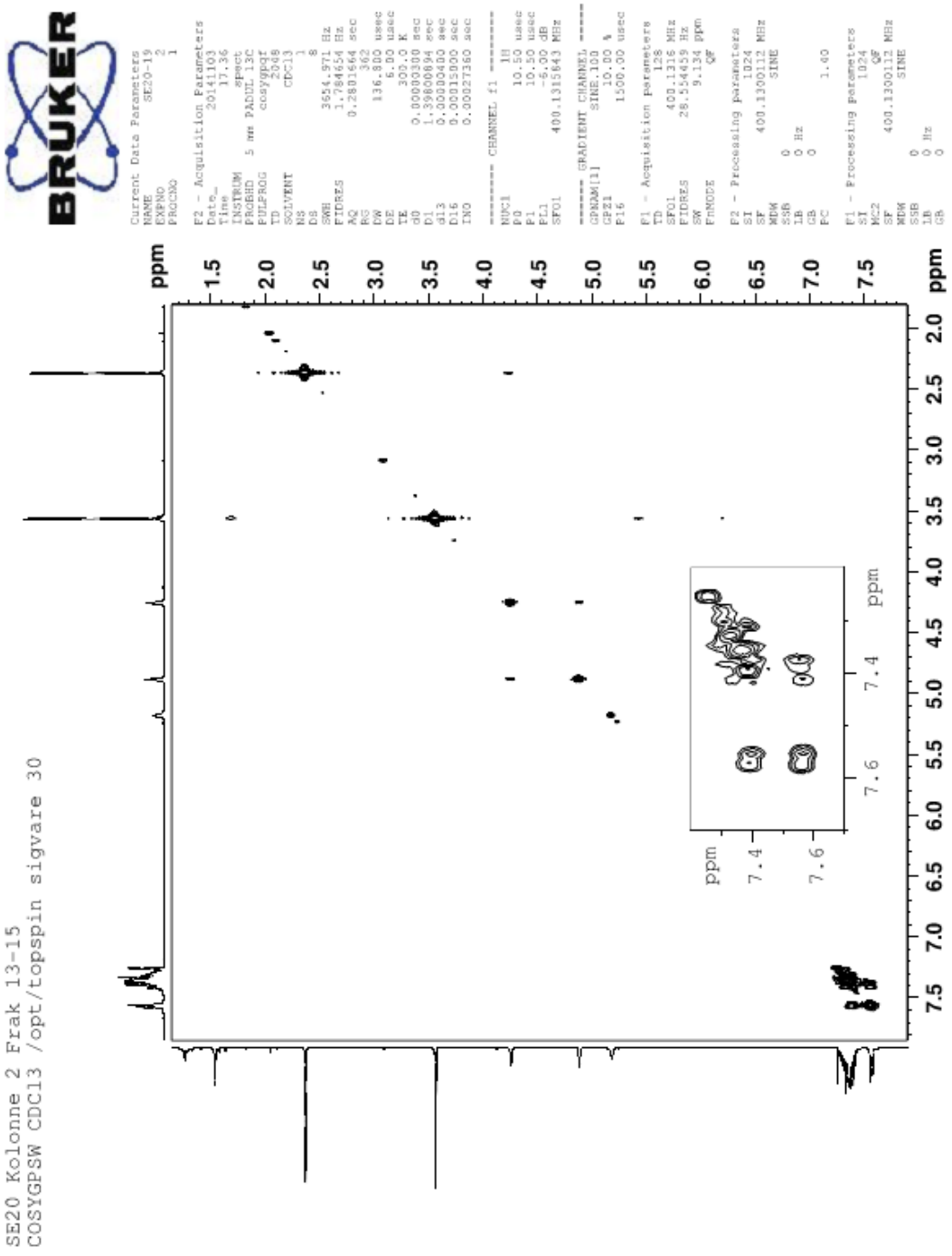


Appendix E.2 ^{13}C-NMR spectrum of oxazine 5a

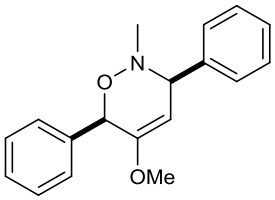


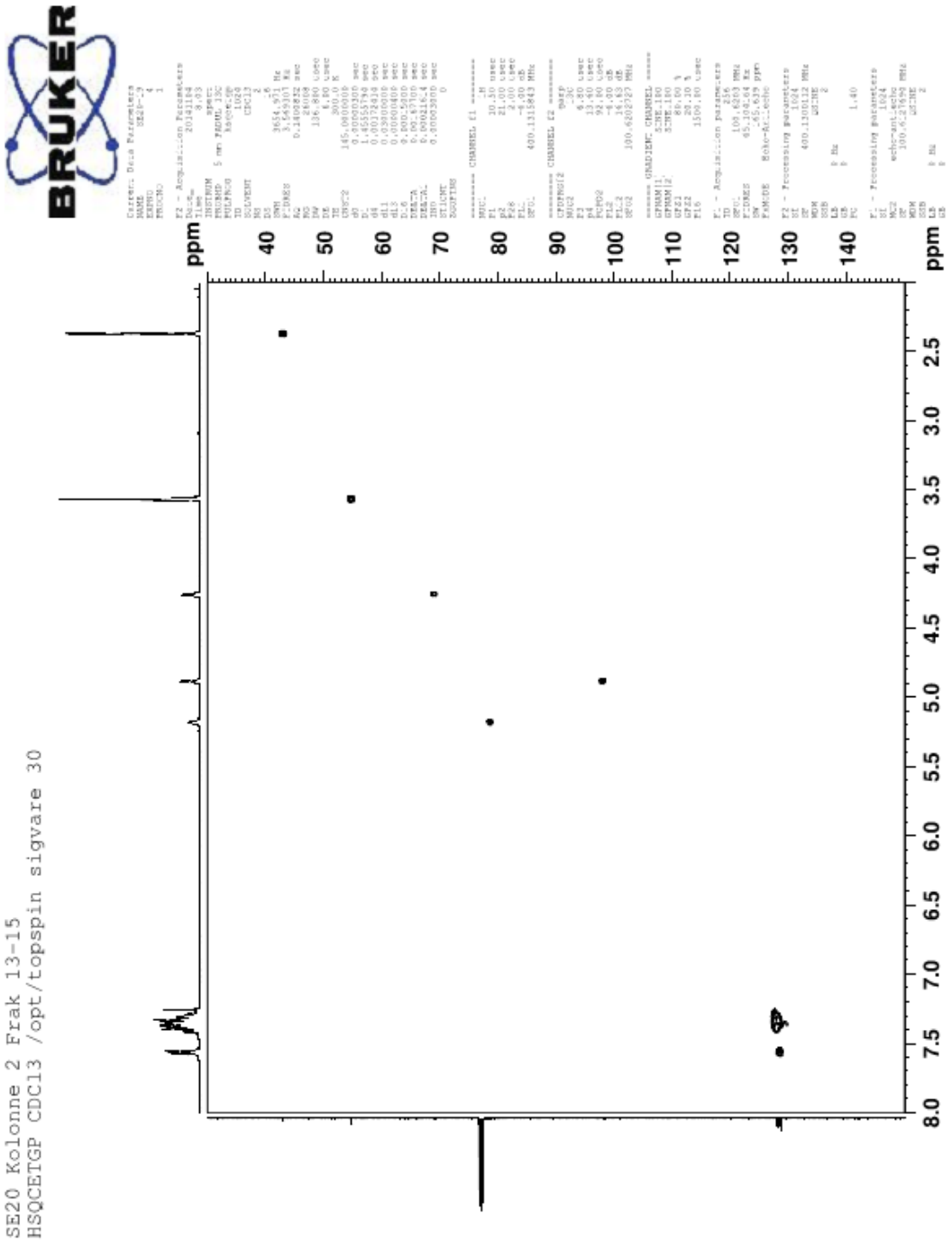
Appendix E.3 COSY spectrum of oxazine 5a



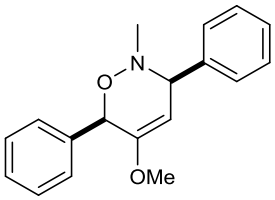


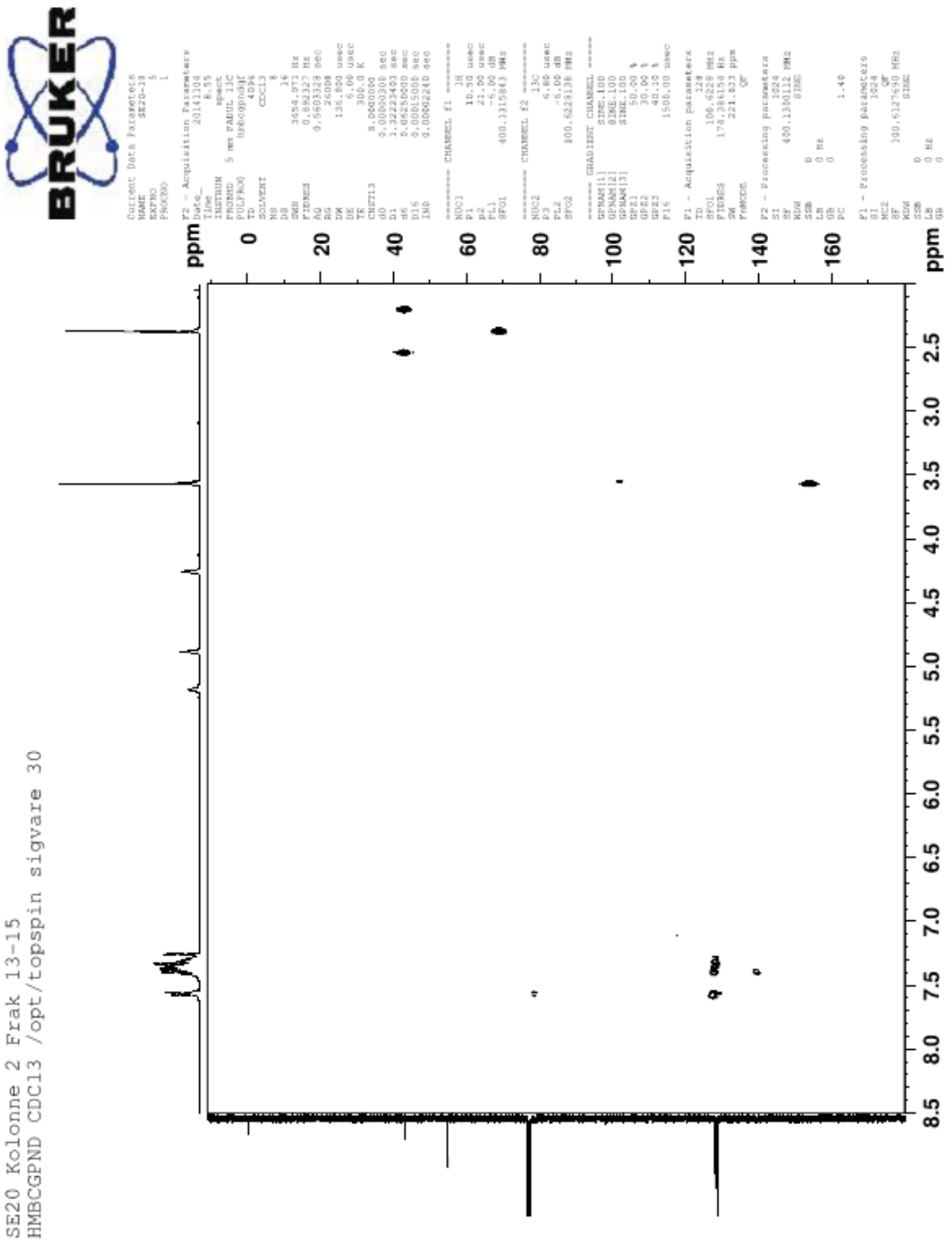
Appendix E.4 HSQC spectrum of oxazine 5a



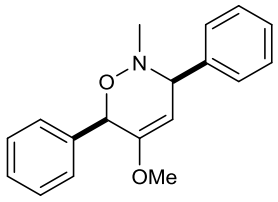


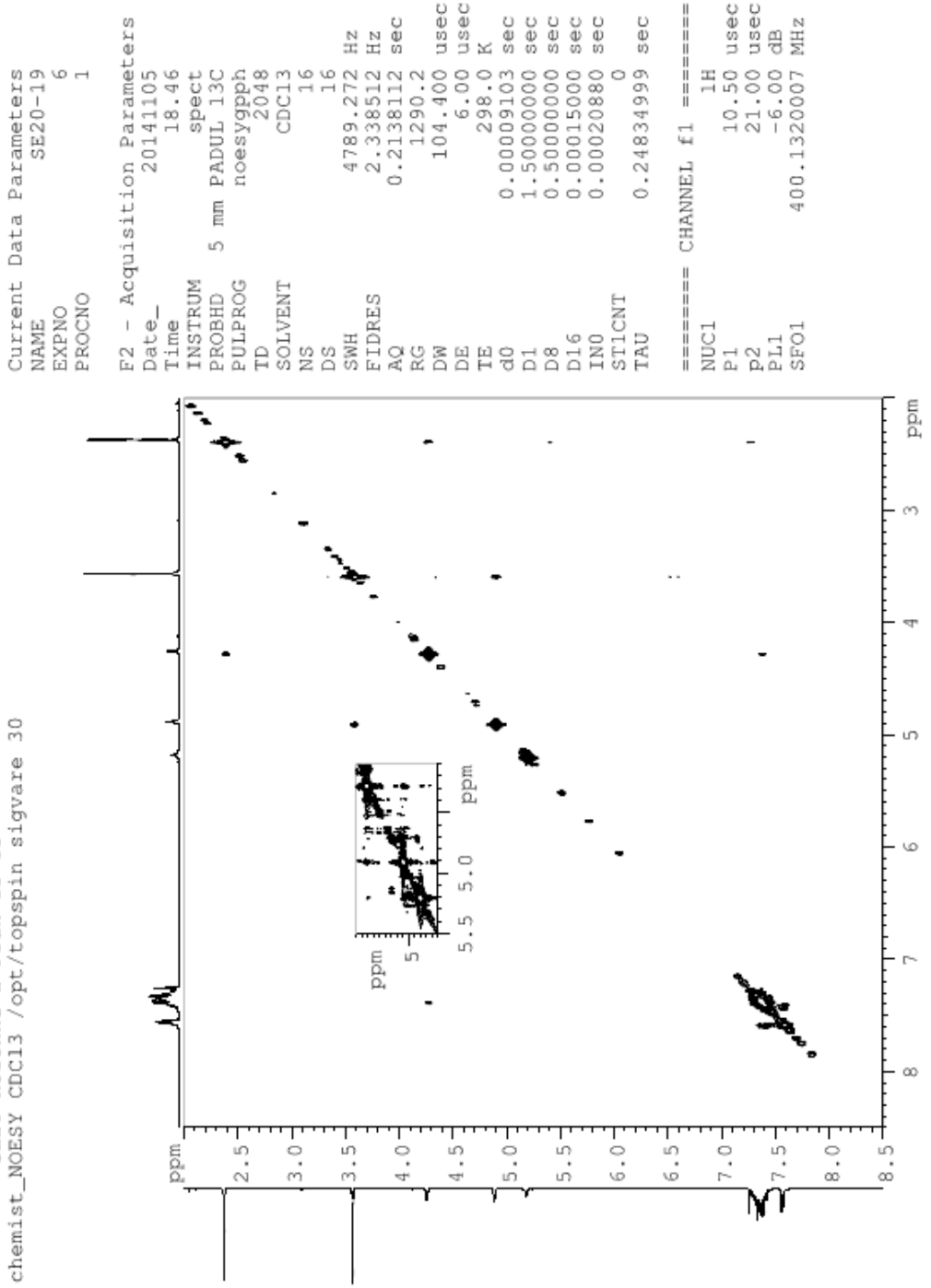
Appendix E.5 HMBC spectrum of oxazine 5a



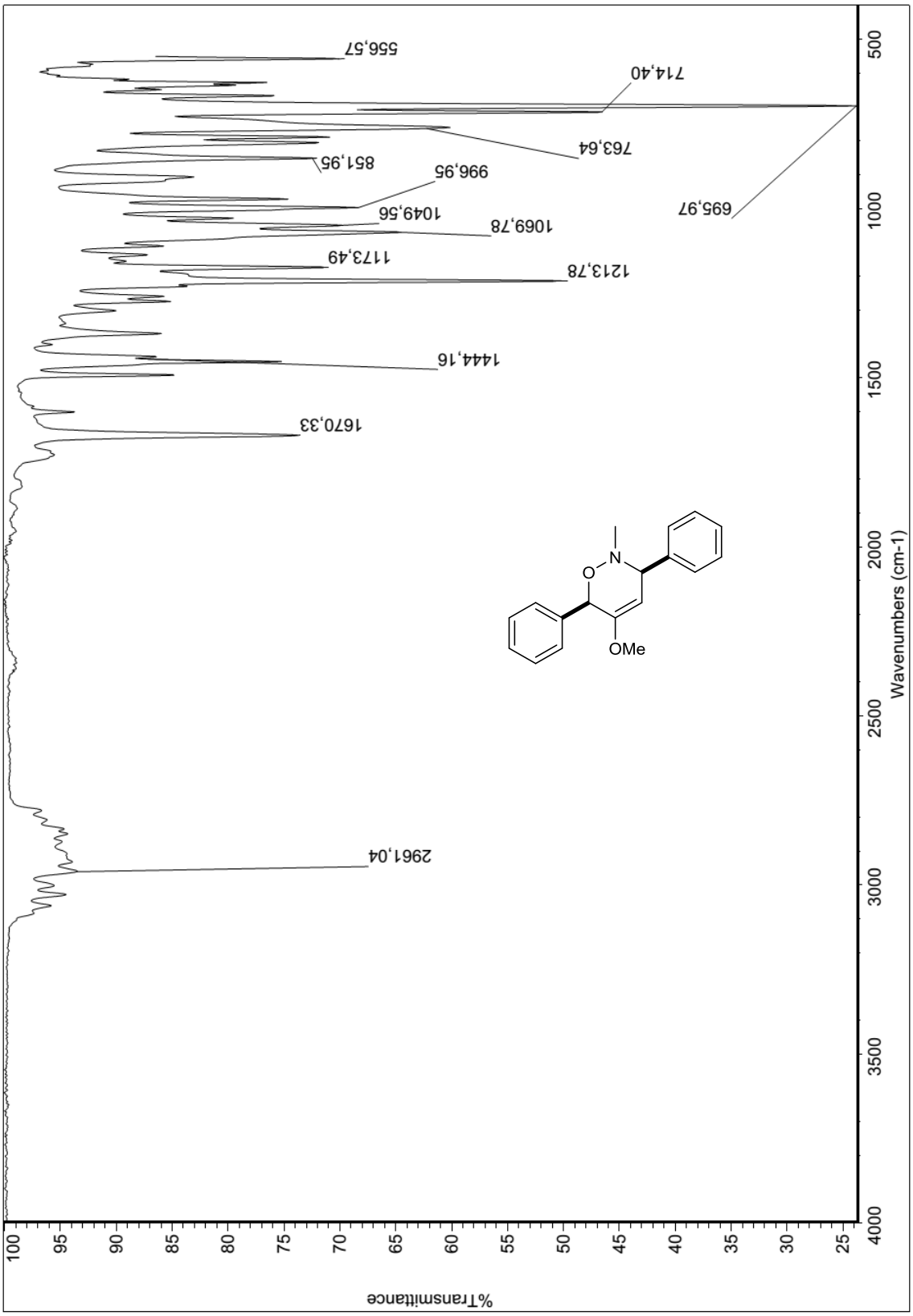


Appendix E.6 NOESY spectrum of oxazine 5a





Appendix E.7 IR spectrum of oxazine 5a

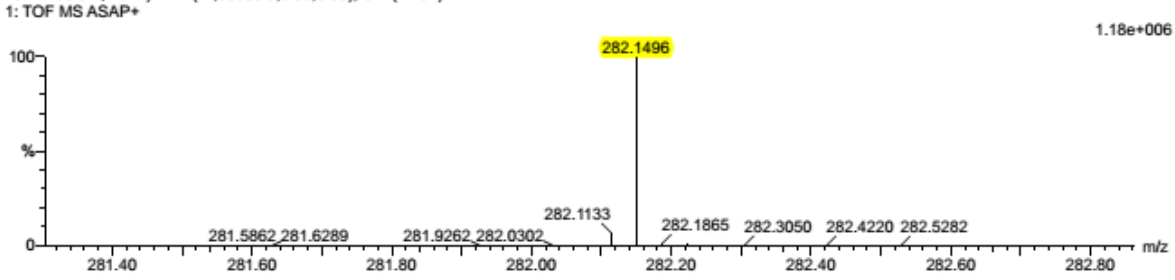


Appendix E.8 MS of oxazine 5a

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 2.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

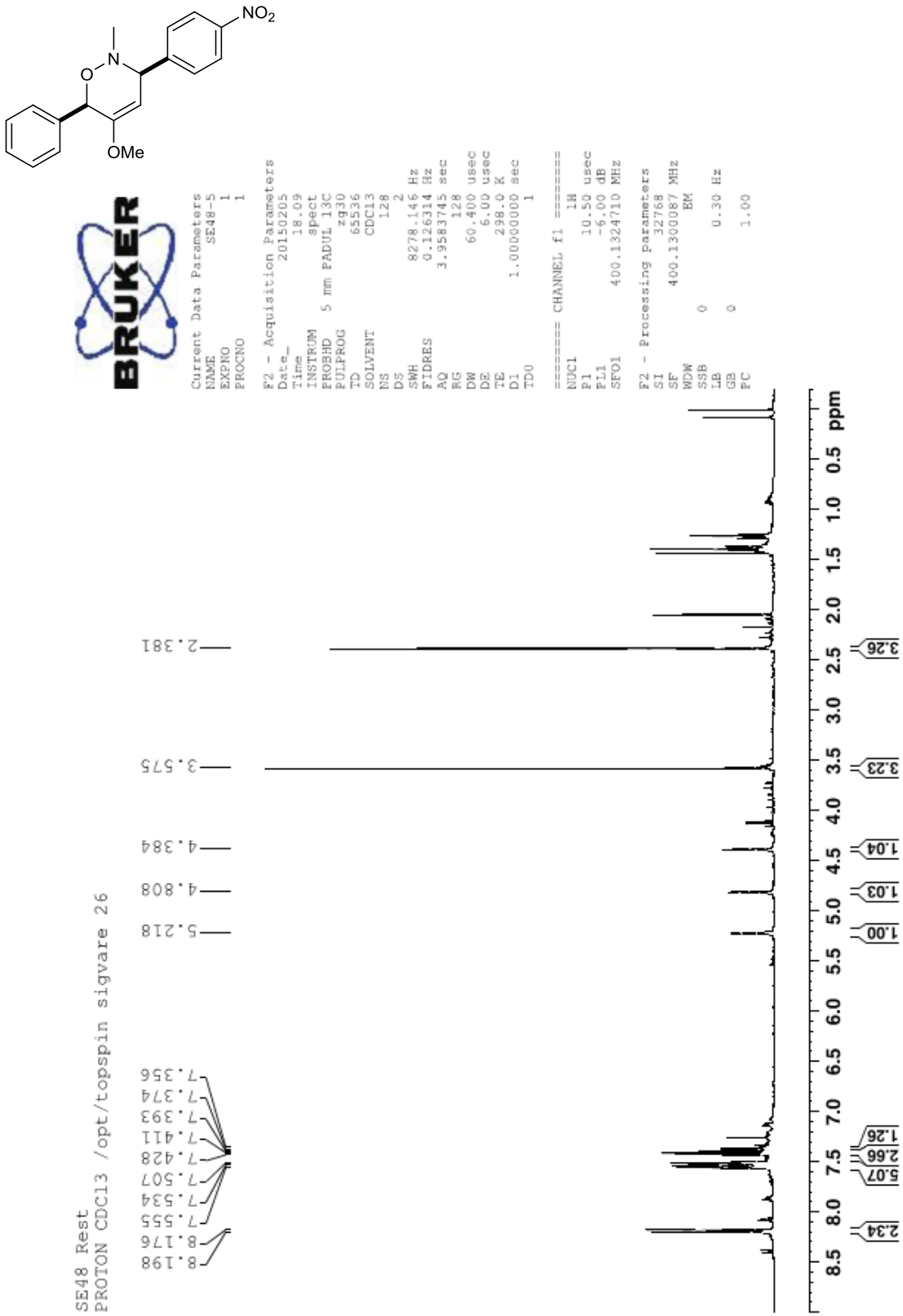
Monoisotopic Mass, Odd and Even Electron Ions
504 formula(e) evaluated with 2 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-200 O: 0-200
2014-168 82 (1.621) AM2 (Ar,35000.0,0.00,0.00); Cm (77:82)
1: TOF MS ASAP+



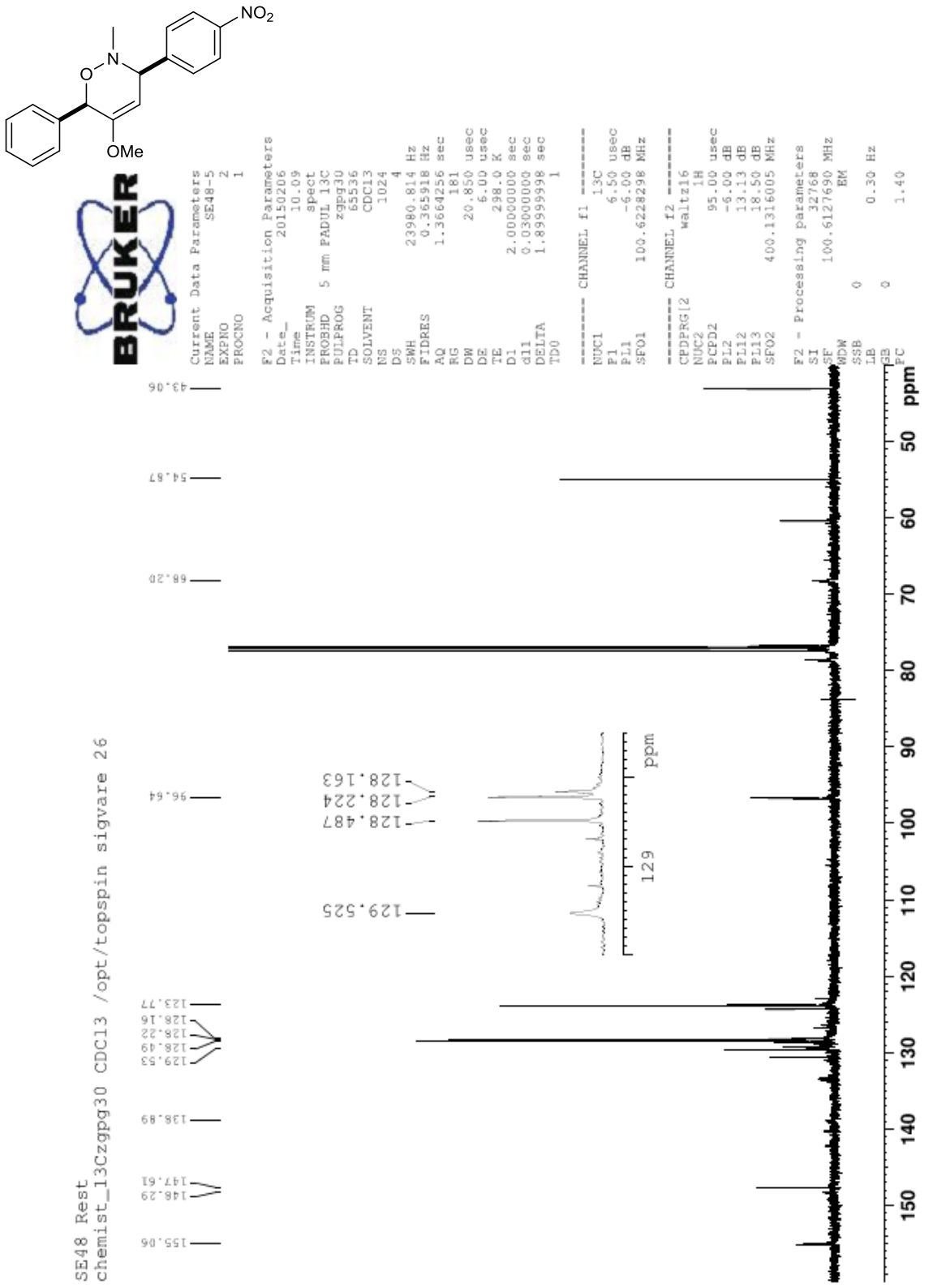
Minimum:				-1.5					
Maximum:		5.0	2.0	50.0					
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula	
282.1496	282.1494	0.2	0.7	9.5	323.0	1.018	36.13	C18 H20 N O2	[M+H]+ ion observed
	282.1499	-0.3	-1.1	2.5	322.4	0.448	63.87	C3 H16 N13 O3	

Appendix F Spectra of oxazine 5c

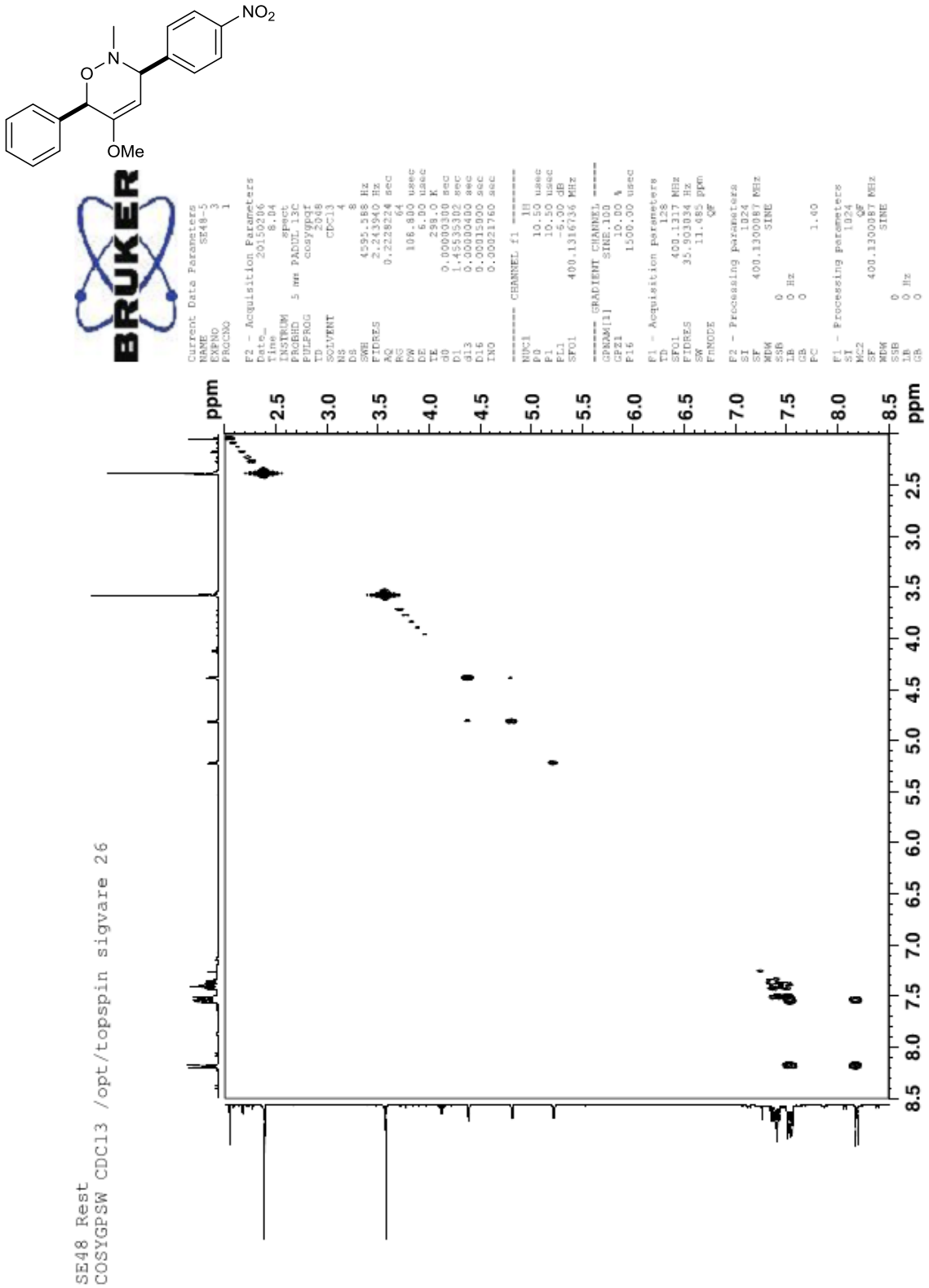
Appendix F.1 ^{1}H-NMR spectrum of oxazine 5c



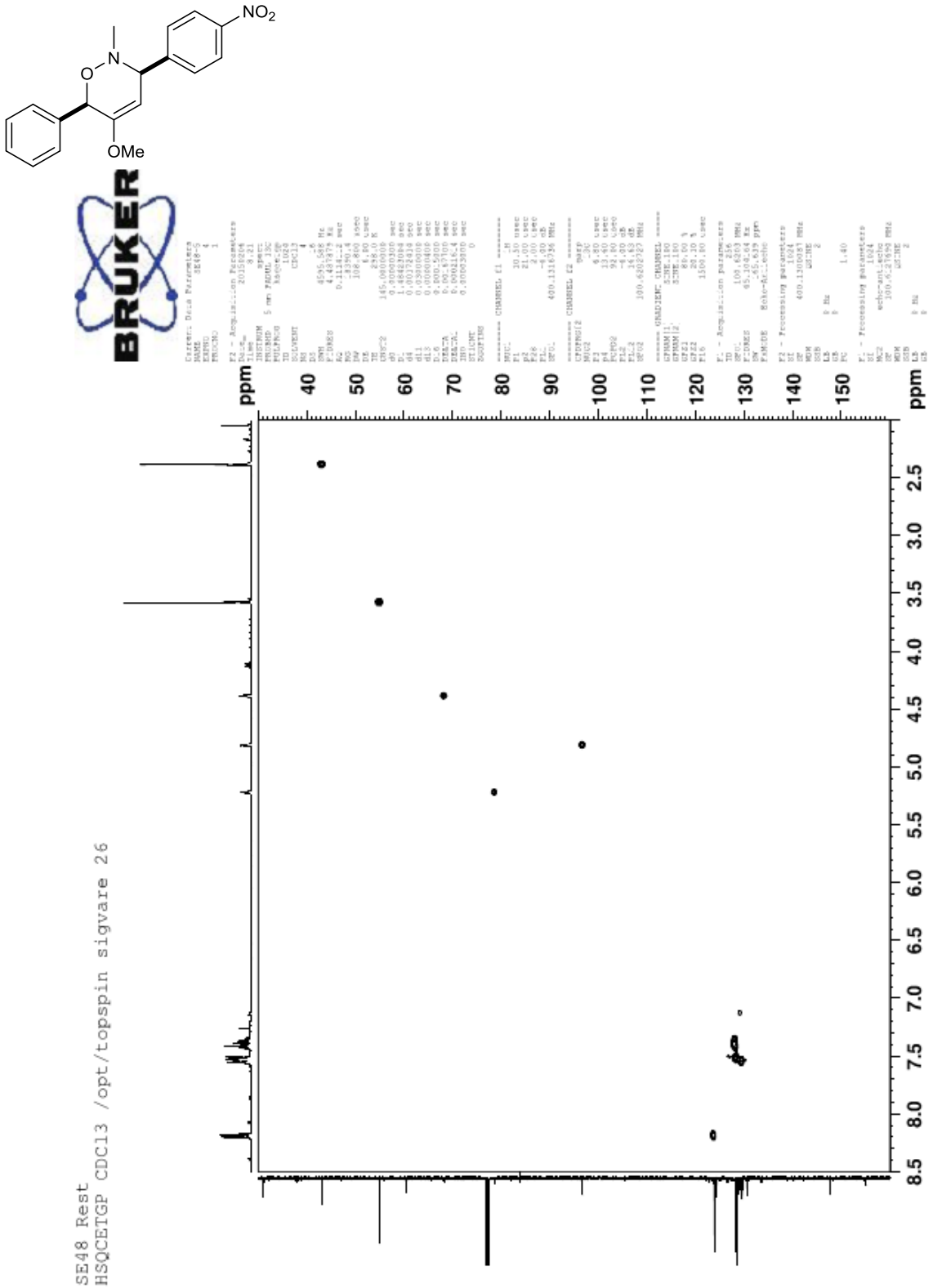
Appendix F.2 ^{13}C-NMR spectrum of oxazine 5c



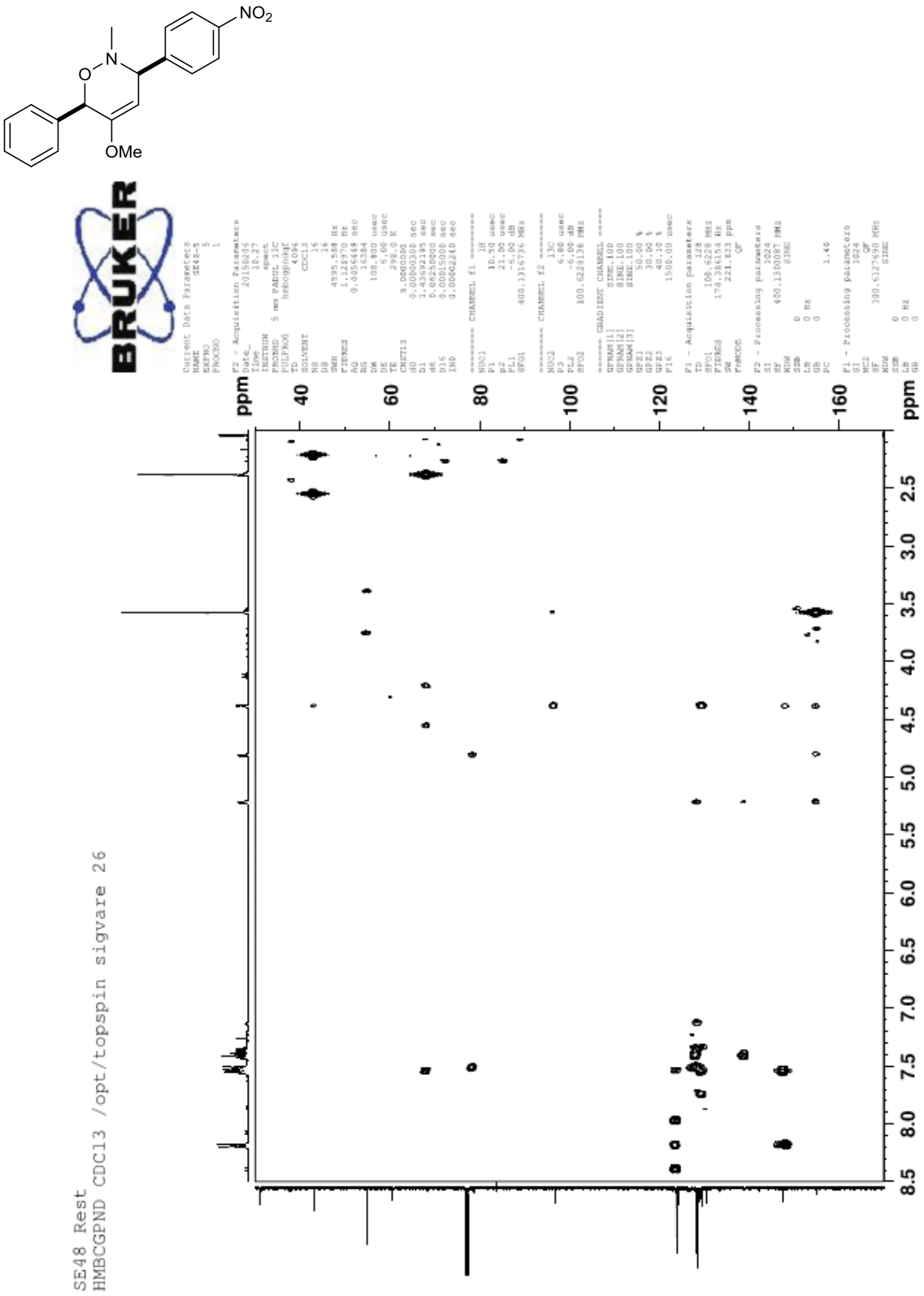
Appendix F.3 COSY spectrum of oxazine 5c



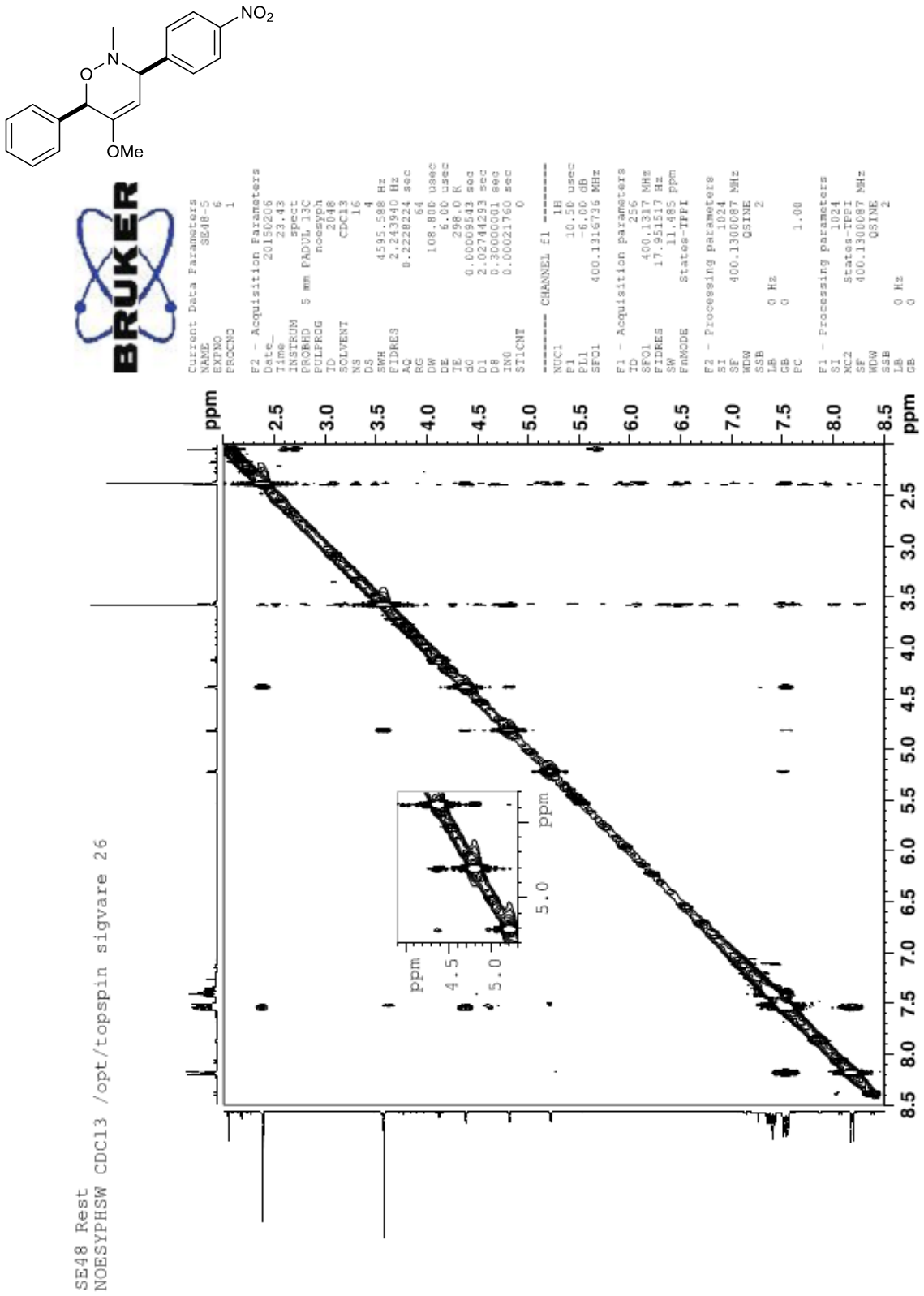
Appendix F.4 HSQC spectrum of oxazine 6c



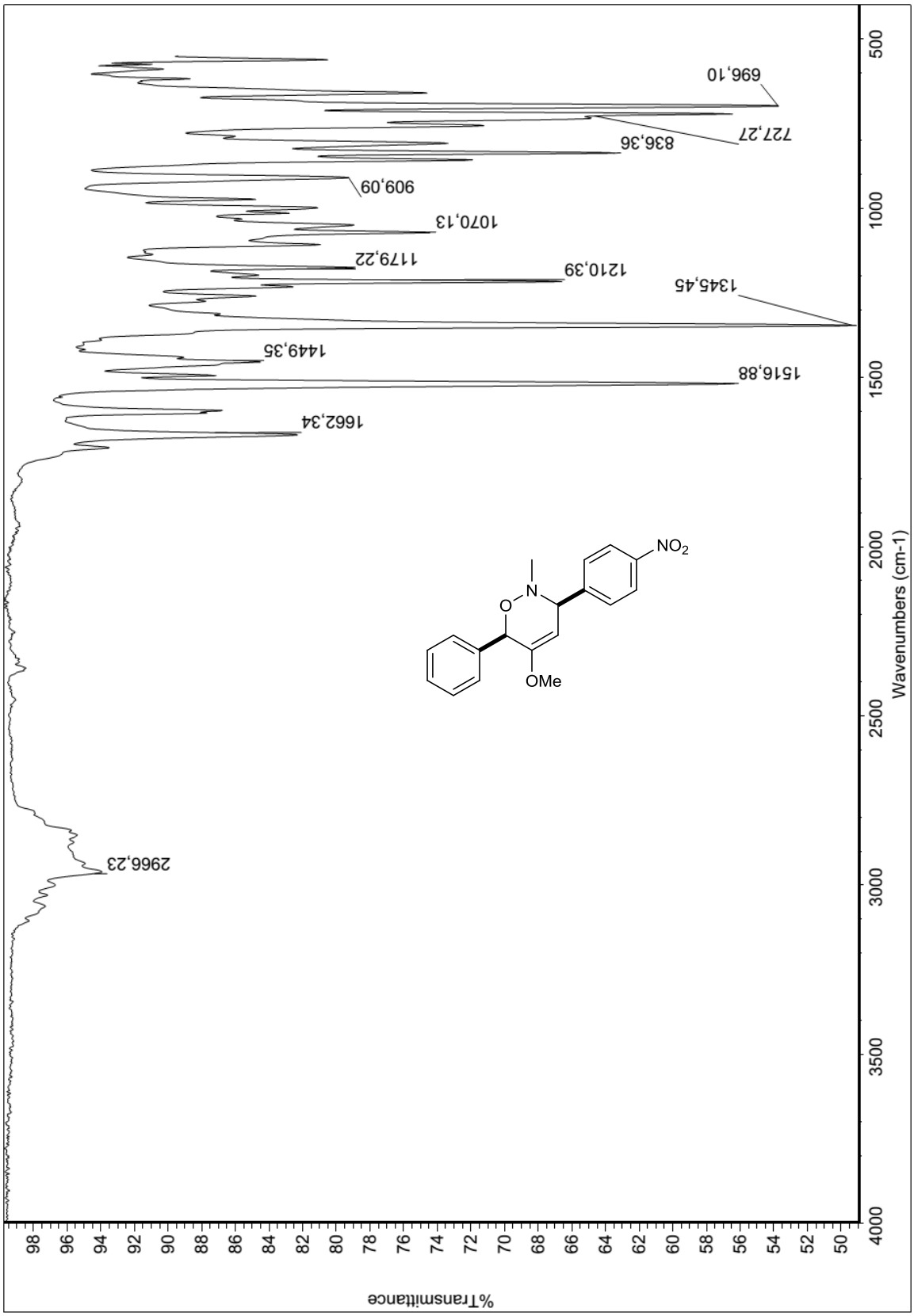
Appendix F.5 HMBC spectrum of oxazine 5c



Appendix F.6 NOESY spectrum of oxazine 5c



Appendix F.7 IR spectrum of oxazine 5c



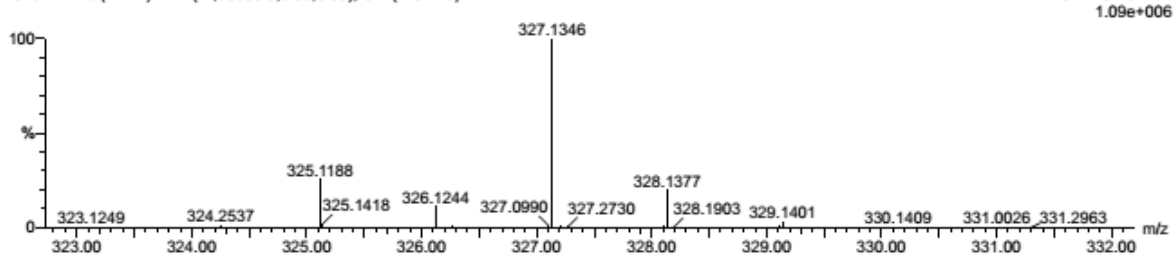
Appendix F.8 MS of oxazine 5c

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 2.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
1674 formula(e) evaluated with 3 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-15 O: 0-200 P: 0-2
NT-MSLAB-Operator-SVG
2015-14 125 (2.447) AM2 (Ar,35000.0,0.00,0.00); Cm (118:125)

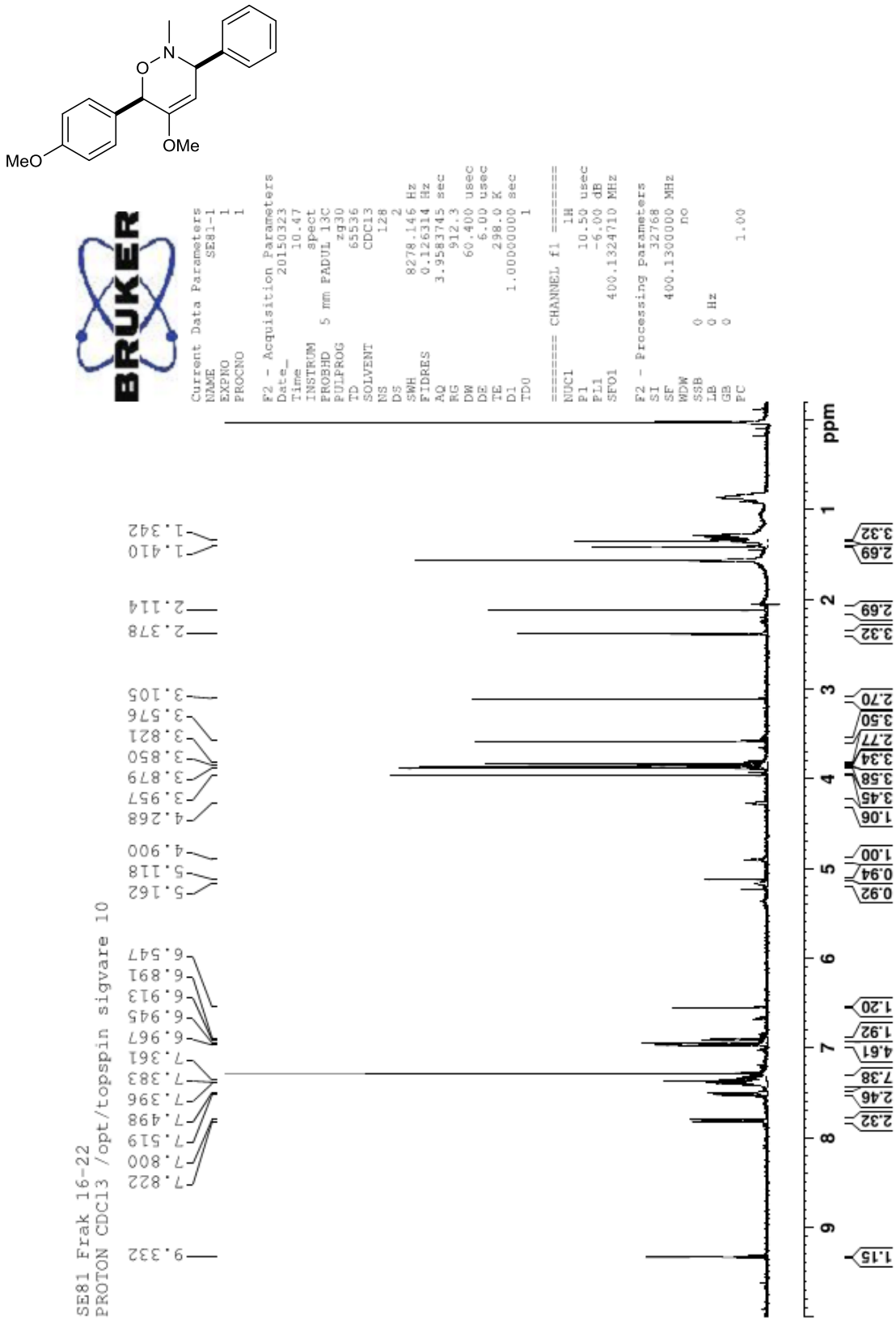
1: TOF MS ASAP+
1.09e+006



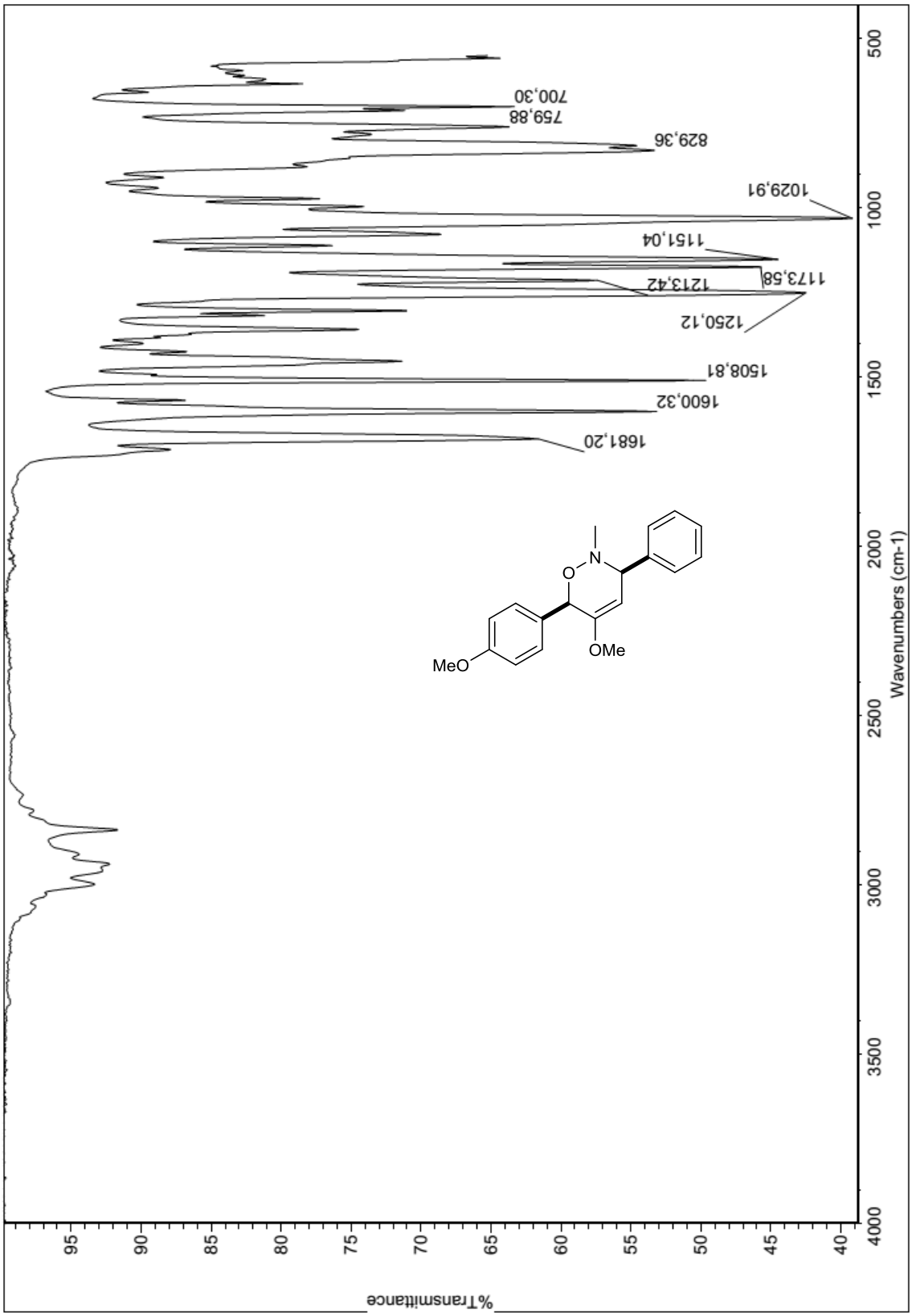
Minimum:				-1.5					
Maximum:		5.0	2.0	50.0					
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula	ION OBSERVED
327.1346	327.1345	0.1	0.3	10.5	1347.2	0.000	100.00	C18 H19 N2 O4	[M+H]+
	327.1350	-0.4	-1.2	3.5	1365.9	18.696	0.00	C3 H15 N14 O5	
	327.1351	-0.5	-1.5	1.5	1357.6	10.468	0.00	C10 H25 N4 O4 P2	

Appendix G Spectra of oxazine 5d, aldehyde 6b and ketone 7b mixture

Appendix G.1 ^{1}H-NMR spectrum of oxazine 5d in mixture



Appendix G.2 IR spectra of oxazine 5d in mixture



Appendix G.3 MS of oxazine 5d

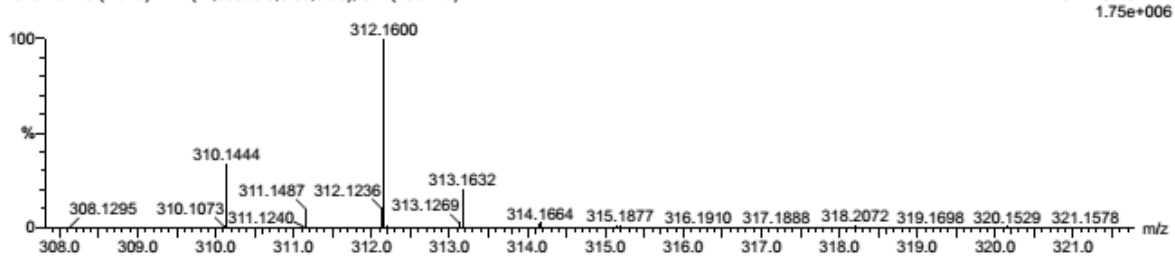
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 3.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
1677 formula(e) evaluated with 5 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-15 O: 0-200 S: 0-3

NT-MSLAB-Operator-SVG
2015-15 119 (2.325) AM2 (Ar,35000.0,0.00,0.00); Cm (105:119)

1: TOF MS ASAP+
1.75e+006

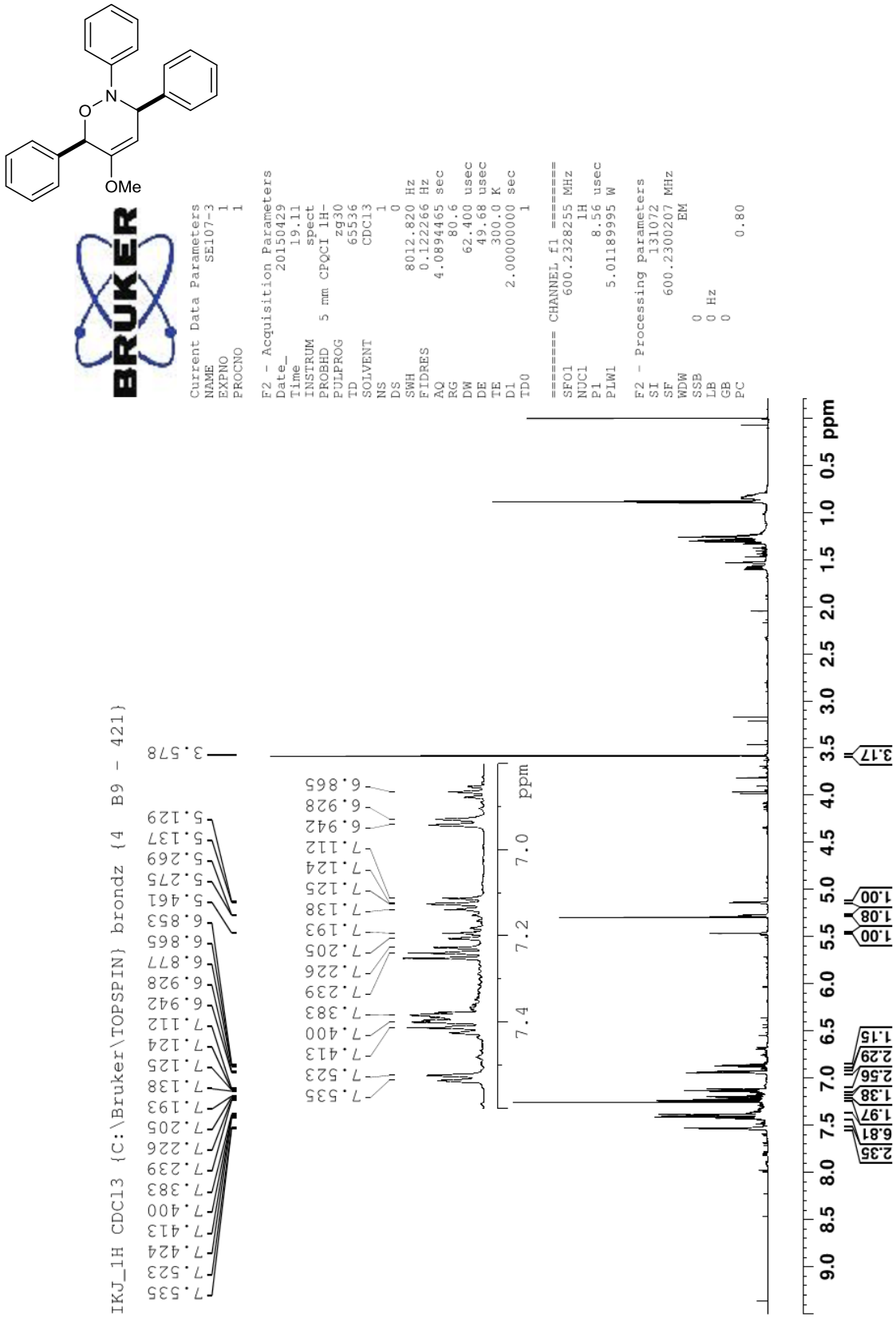


Minimum:				-1.5				
Maximum:		5.0	3.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
312.1600	312.1600	0.0	0.0	9.5	1381.1	0.000	100.00	C19 H22 N O3
	312.1602	-0.2	-0.6	-0.5	1406.3	25.213	0.00	C12 H30 N3 S3
	312.1605	-0.5	-1.6	2.5	1398.8	17.713	0.00	C4 H18 N13 O4
	312.1593	0.7	2.2	0.5	1402.2	21.108	0.00	C11 H26 N3 O5 S
	312.1607	-0.7	-2.2	5.5	1401.4	20.269	0.00	C12 H22 N7 O S

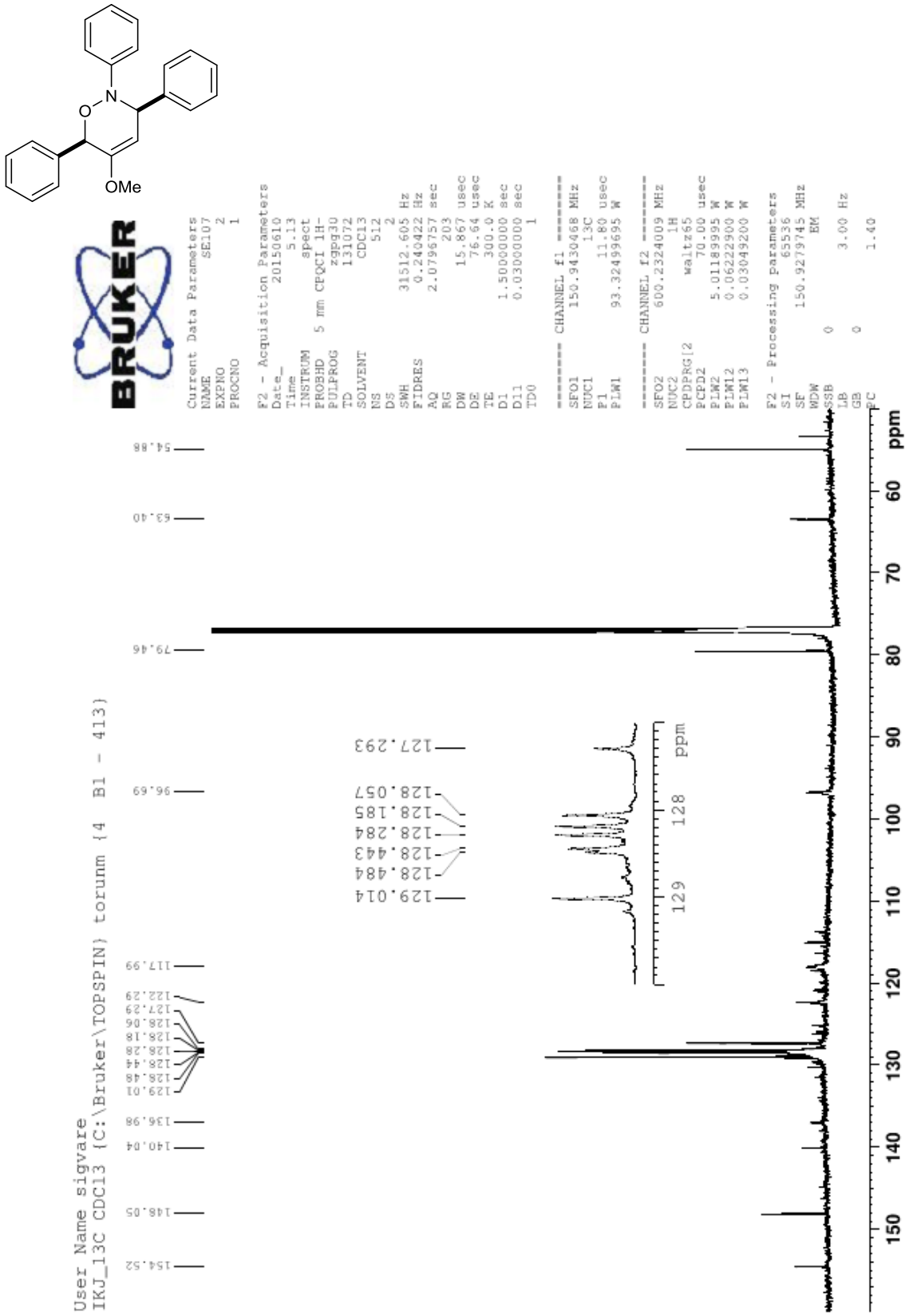
ion observed [M+H]+

Appendix H Spectra of oxazine 5g

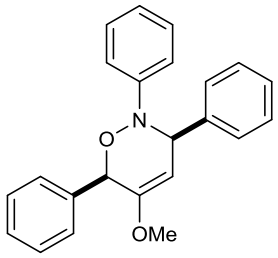
Appendix H.1 ^{1}H-NMR spectrum of oxazine 5g

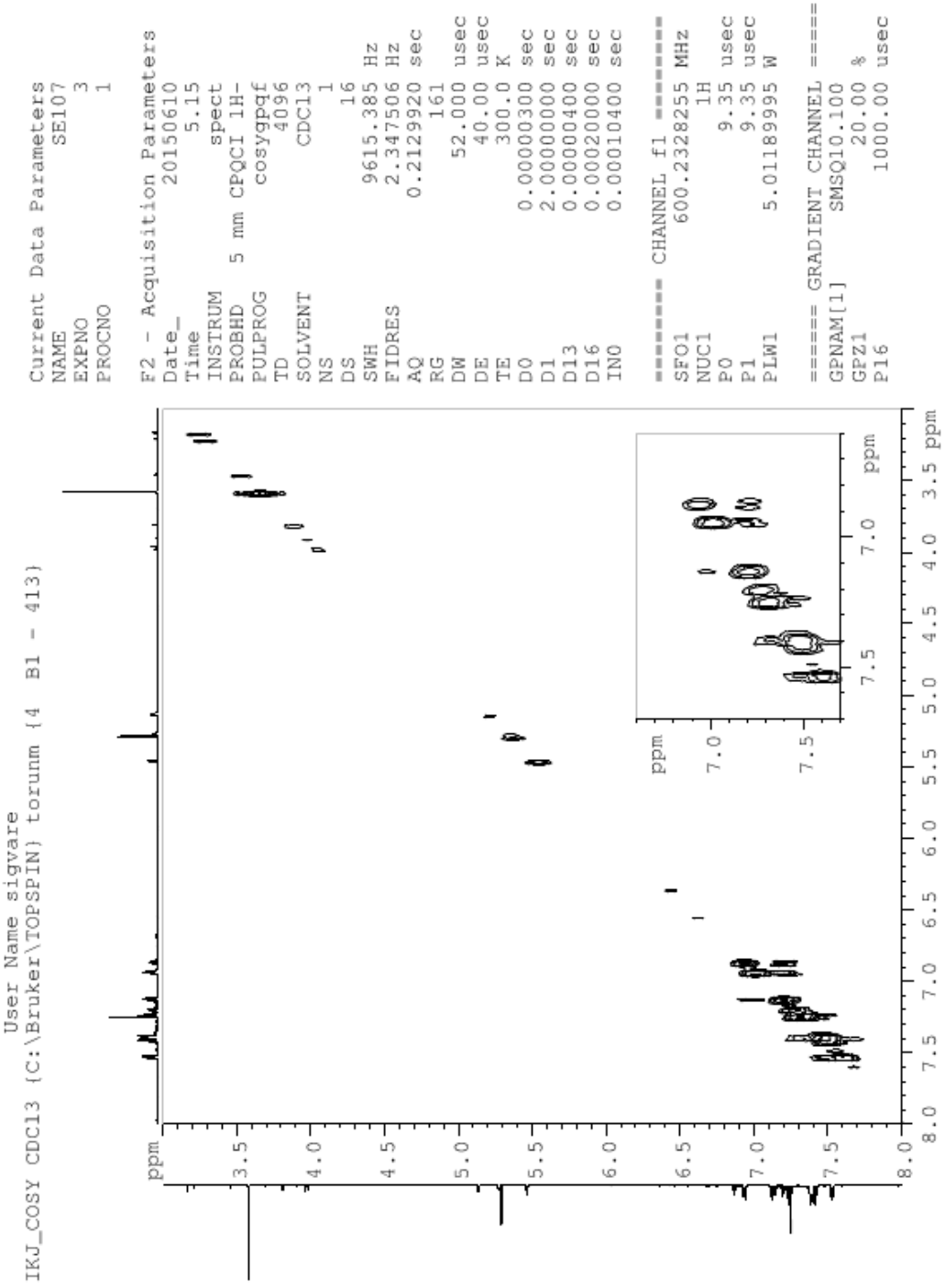


Appendix H.2 ^{13}C-NMR spectrum of oxazine 5g

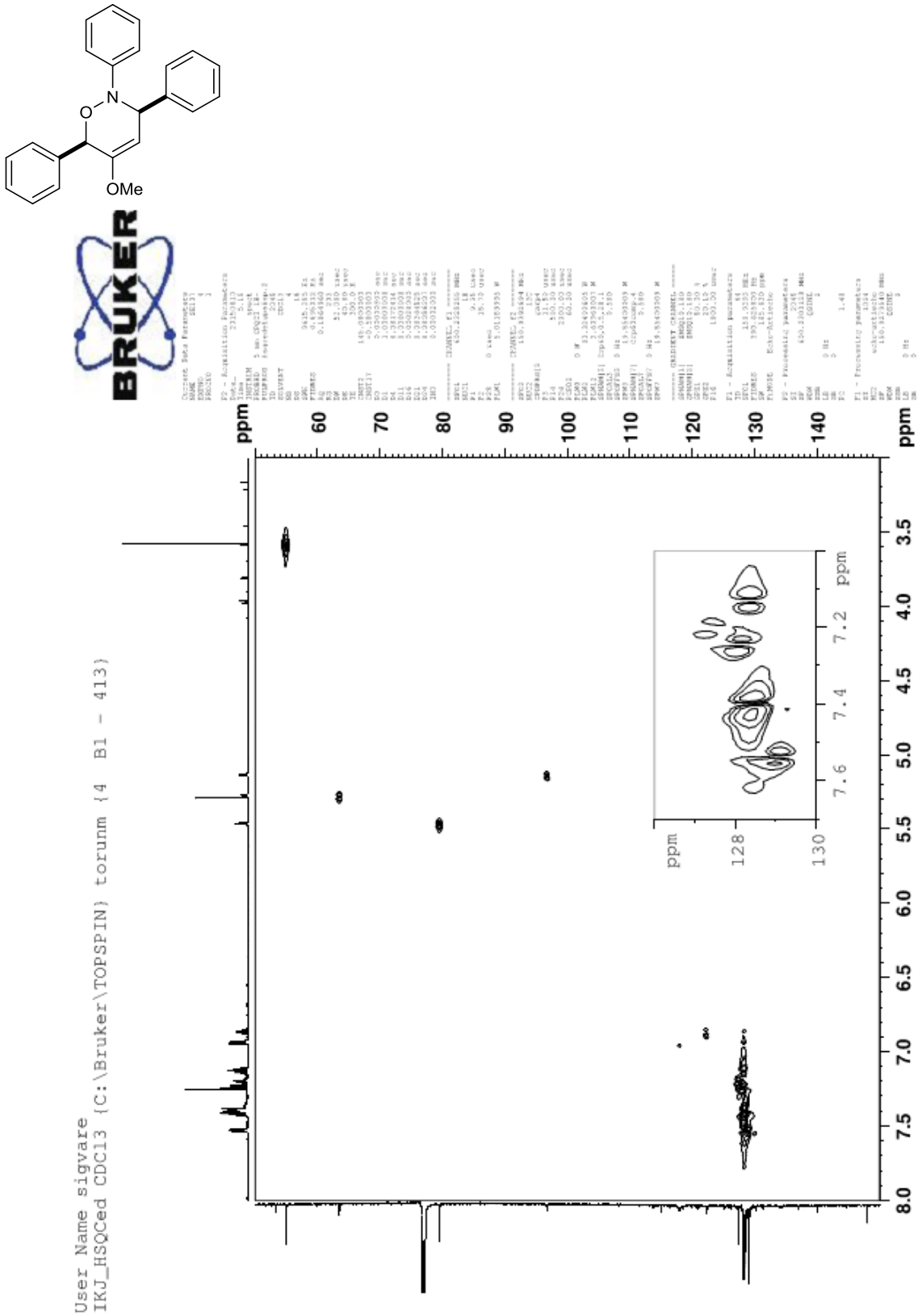


Appendix H.3 COSY spectrum of oxazine 5g

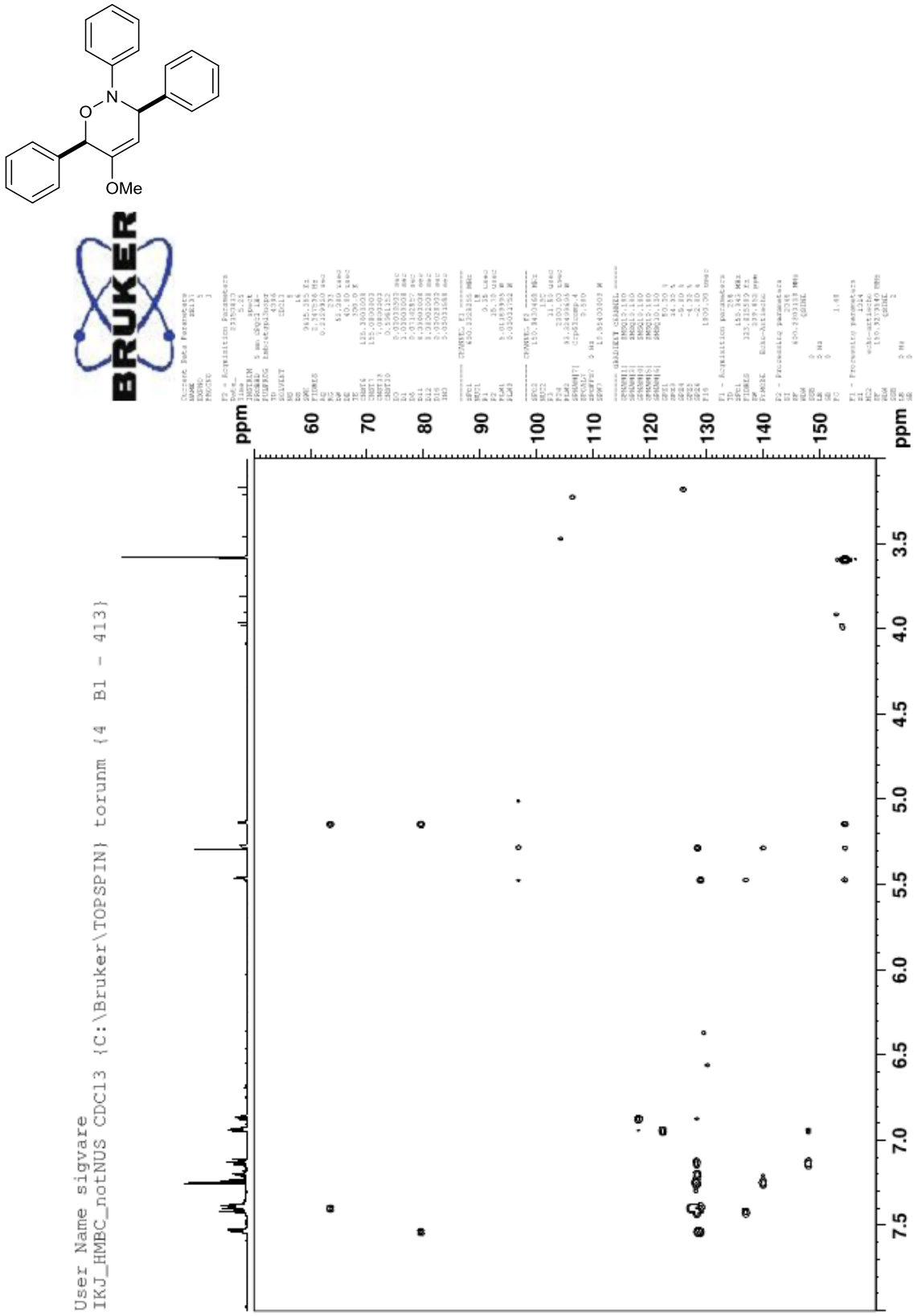




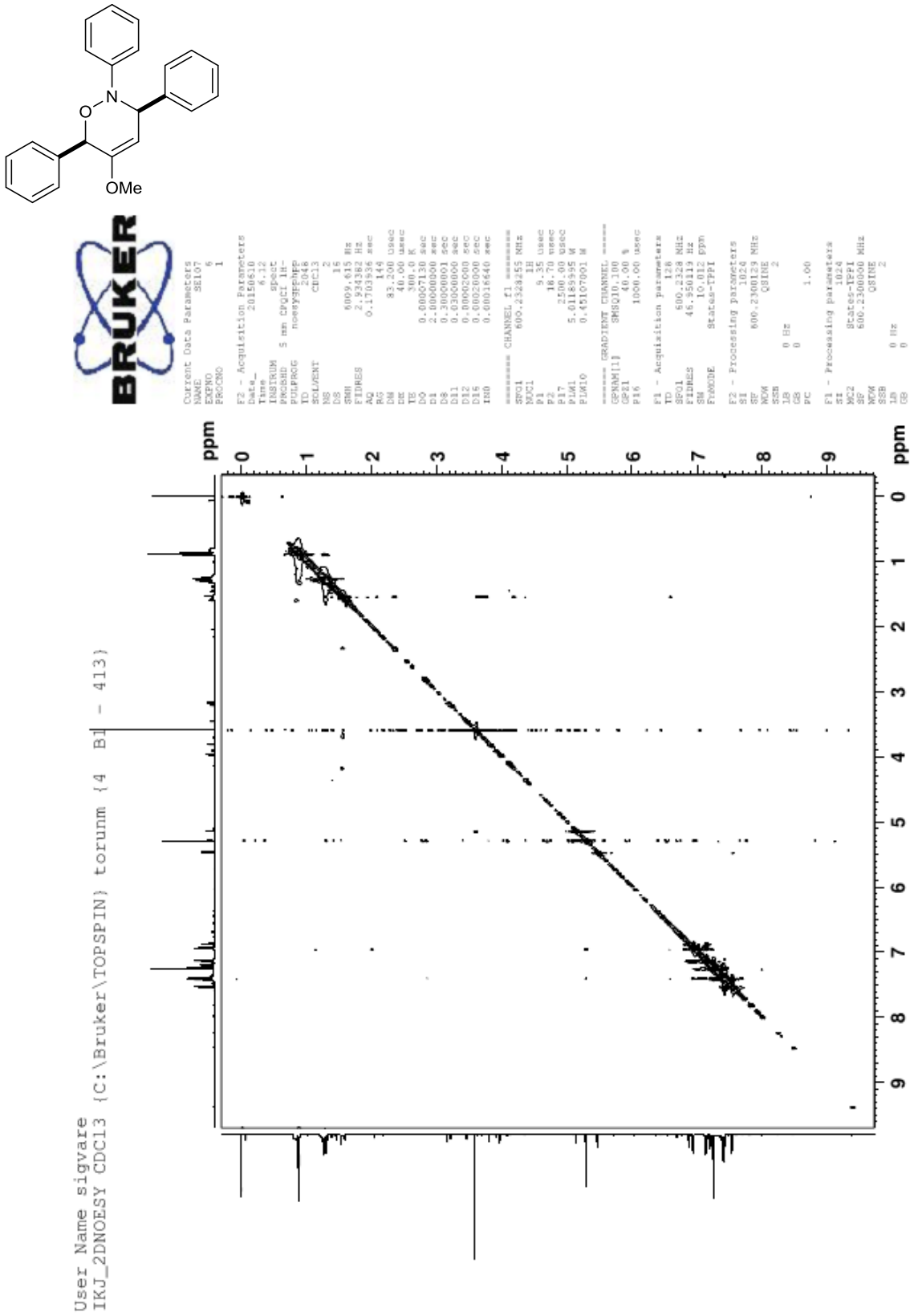
Appendix H.4 HSQC spectum of oxazine 5g



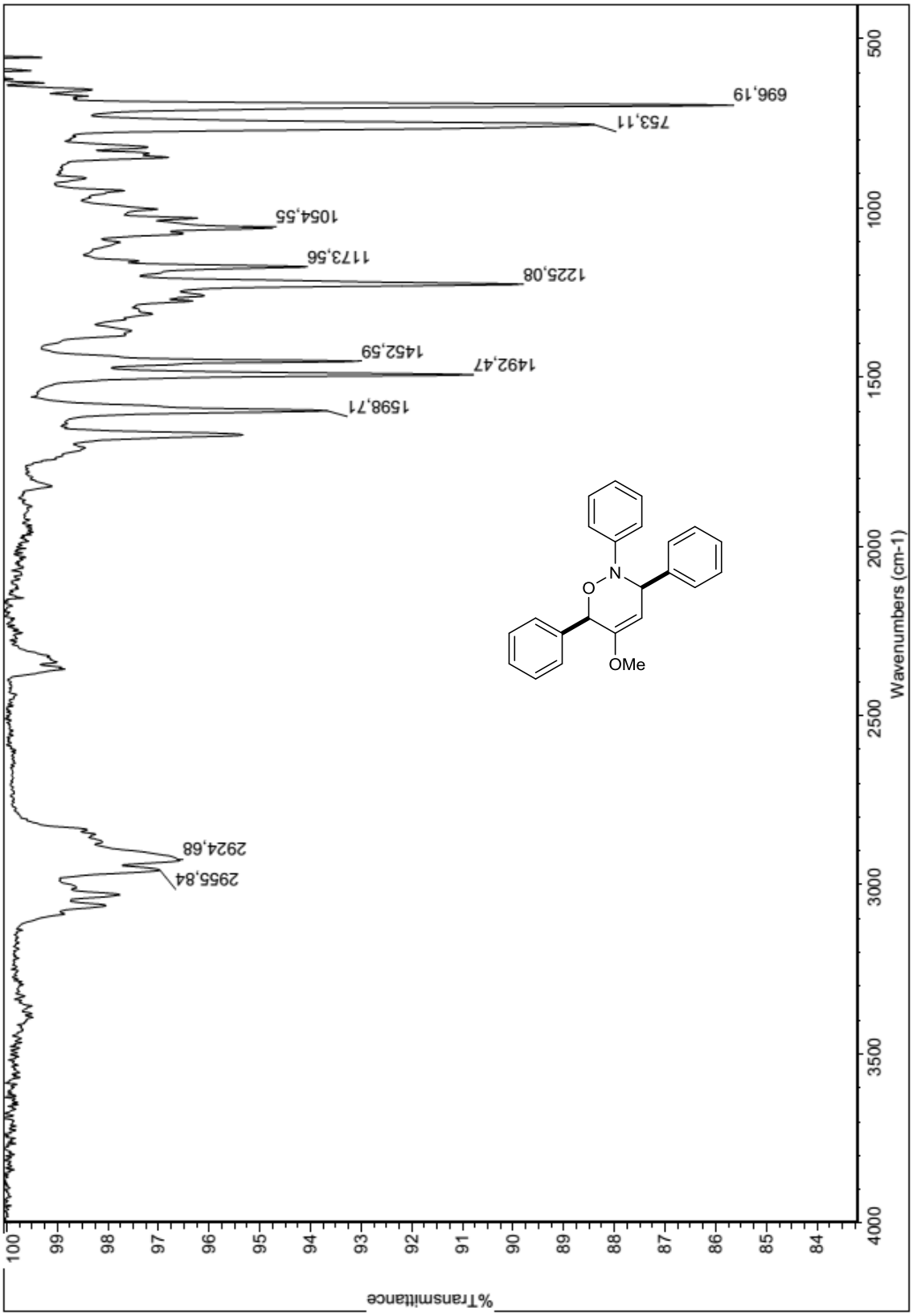
Appendix H.5 HMBC spectrum of oxazine 5g



Appendix H.6 NOESY spectrum of oxazine 5g



Appendix H.7 IR spectrum of oxazine 5g



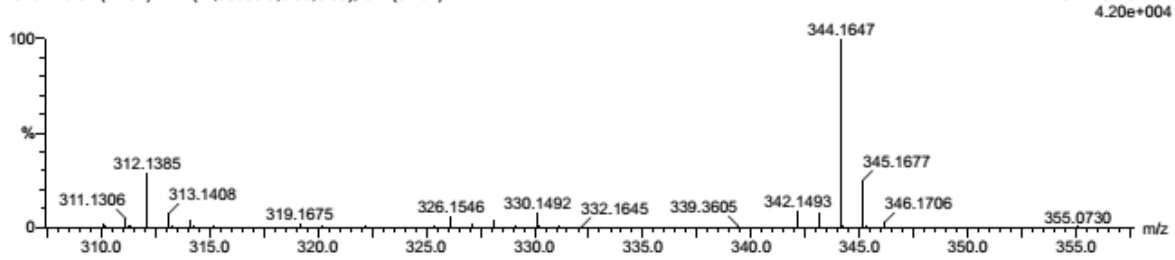
Appendix H.8 MS of oxazine 5g

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 3.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
803 formula(e) evaluated with 3 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-500 H: 0-1000 N: 0-50 O: 0-100
NT-MSLAB-Operator-SVG
2015-219 61 (1.207) AM2 (Ar,35000.0,0.00,0.00); Cm (61:67)

1: TOF MS ASAP+
4.20e+004

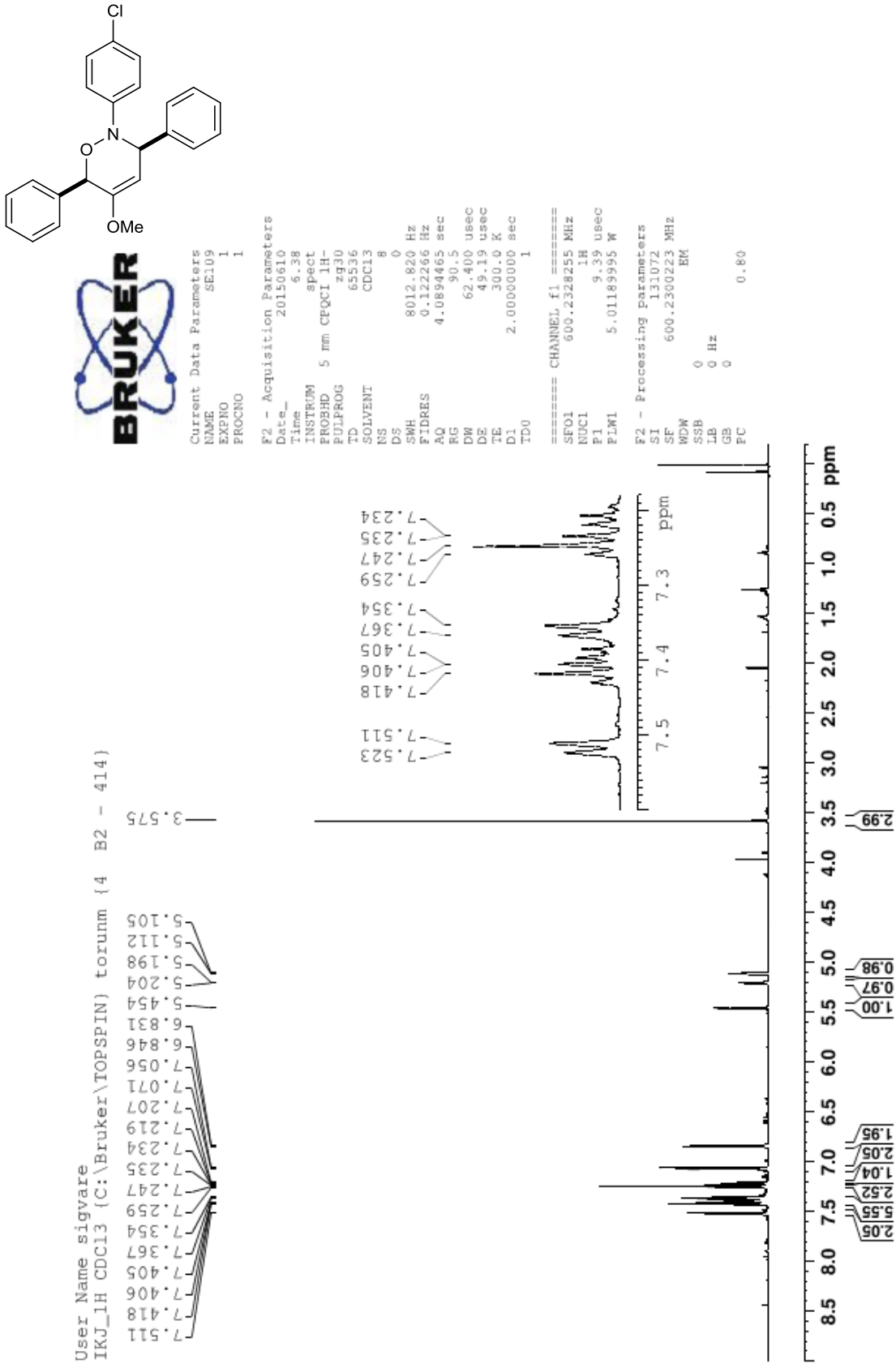


Minimum:				-1.5				
Maximum:		5.0	3.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
344.1647	344.1651	-0.4	-1.2	13.5	174.3	0.000	100.00	C23 H22 N O2
	344.1642	0.5	1.5	1.5	188.8	14.511	0.00	C7 H22 N9 O7
	344.1656	-0.9	-2.6	6.5	188.6	14.243	0.00	C8 H18 N13 O3

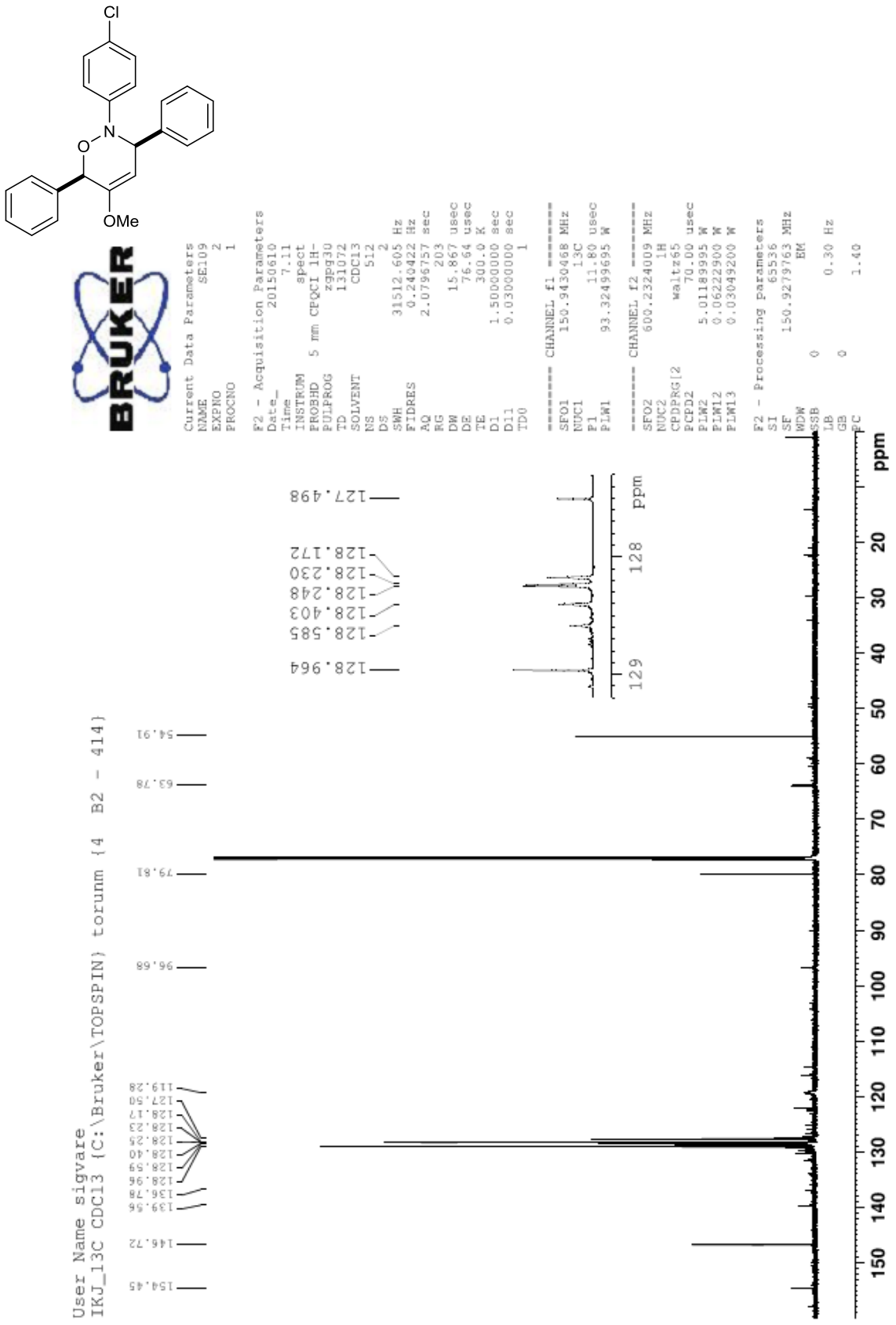
Ion observed [M+H]

Appendix I Spectra of oxazine 5i

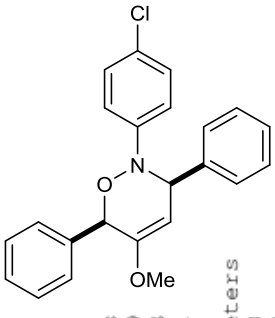
Appendix I.1 ^{1}H-NMR spectrum of oxazine 5i

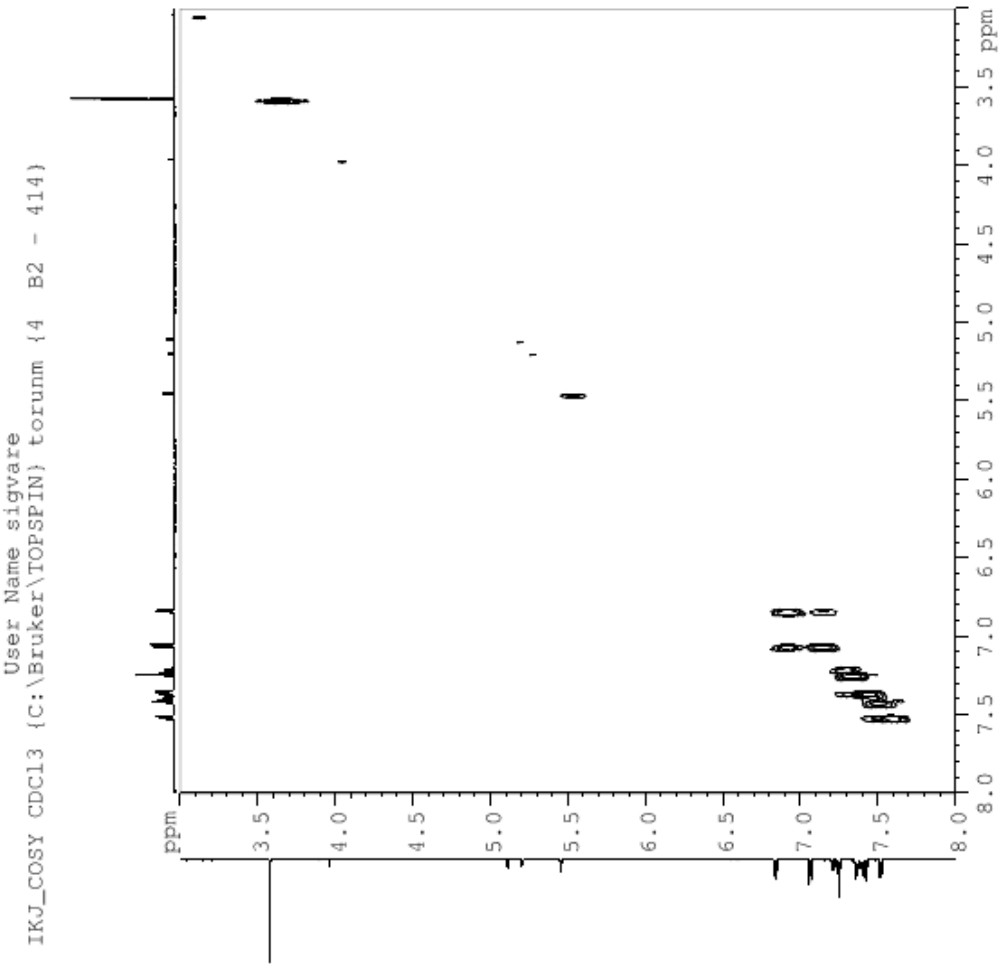


Appendix I.2 ^{13}C-NMR spectrum of oxazine 5i

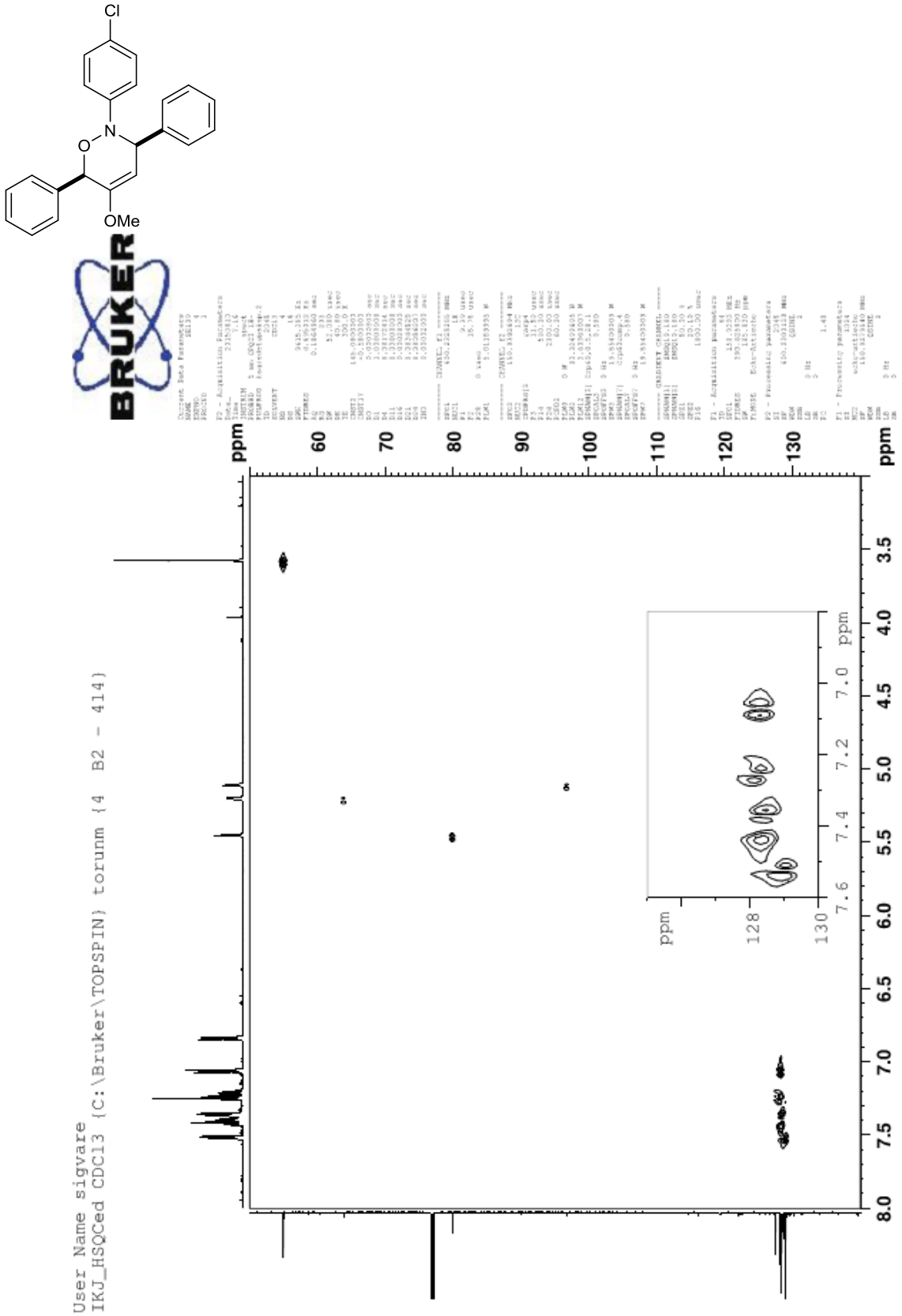


Appendix I.3 COSY spectrum of oxazine 5i

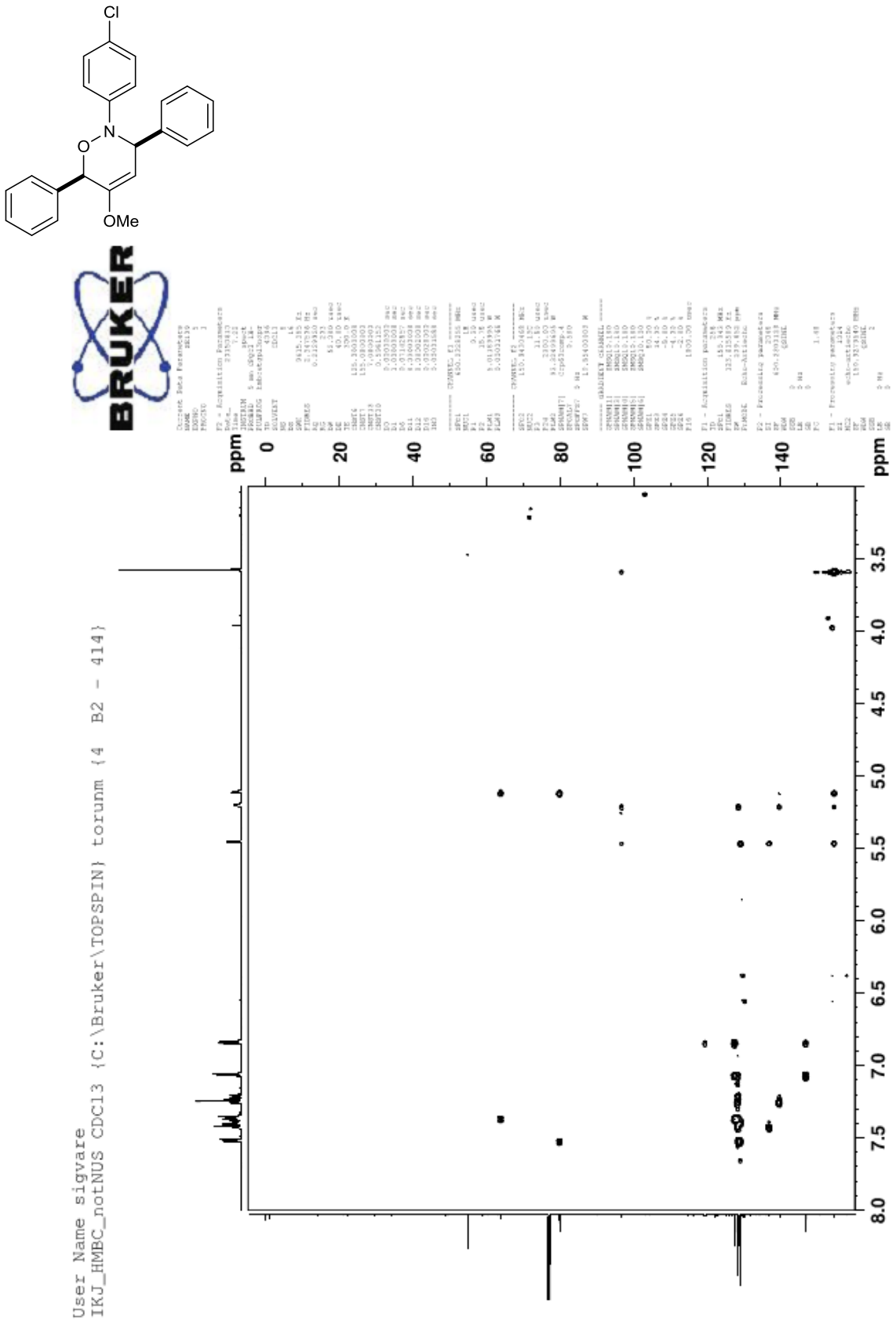




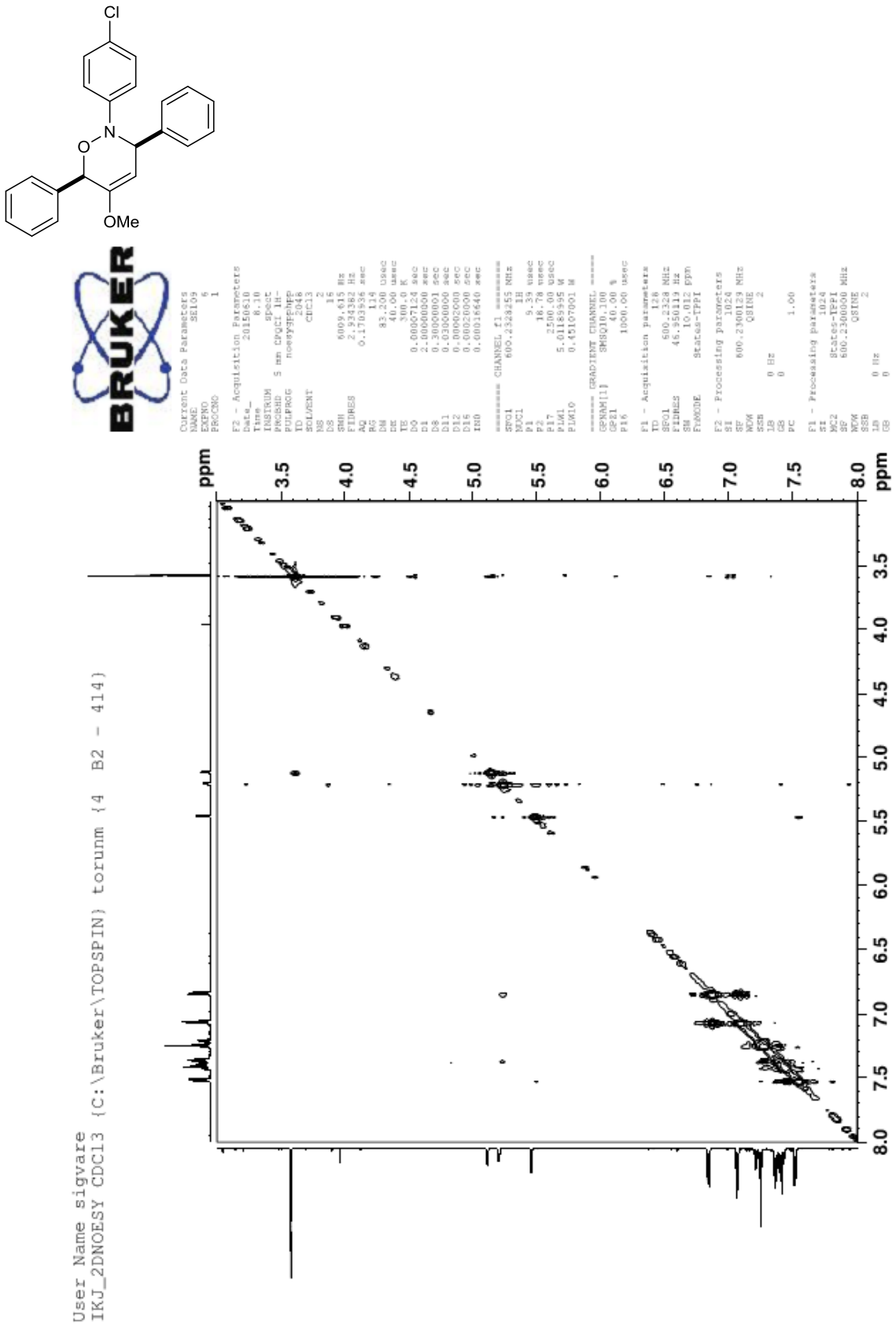
Appendix I.4 HSQC spectrum of oxazine 5i



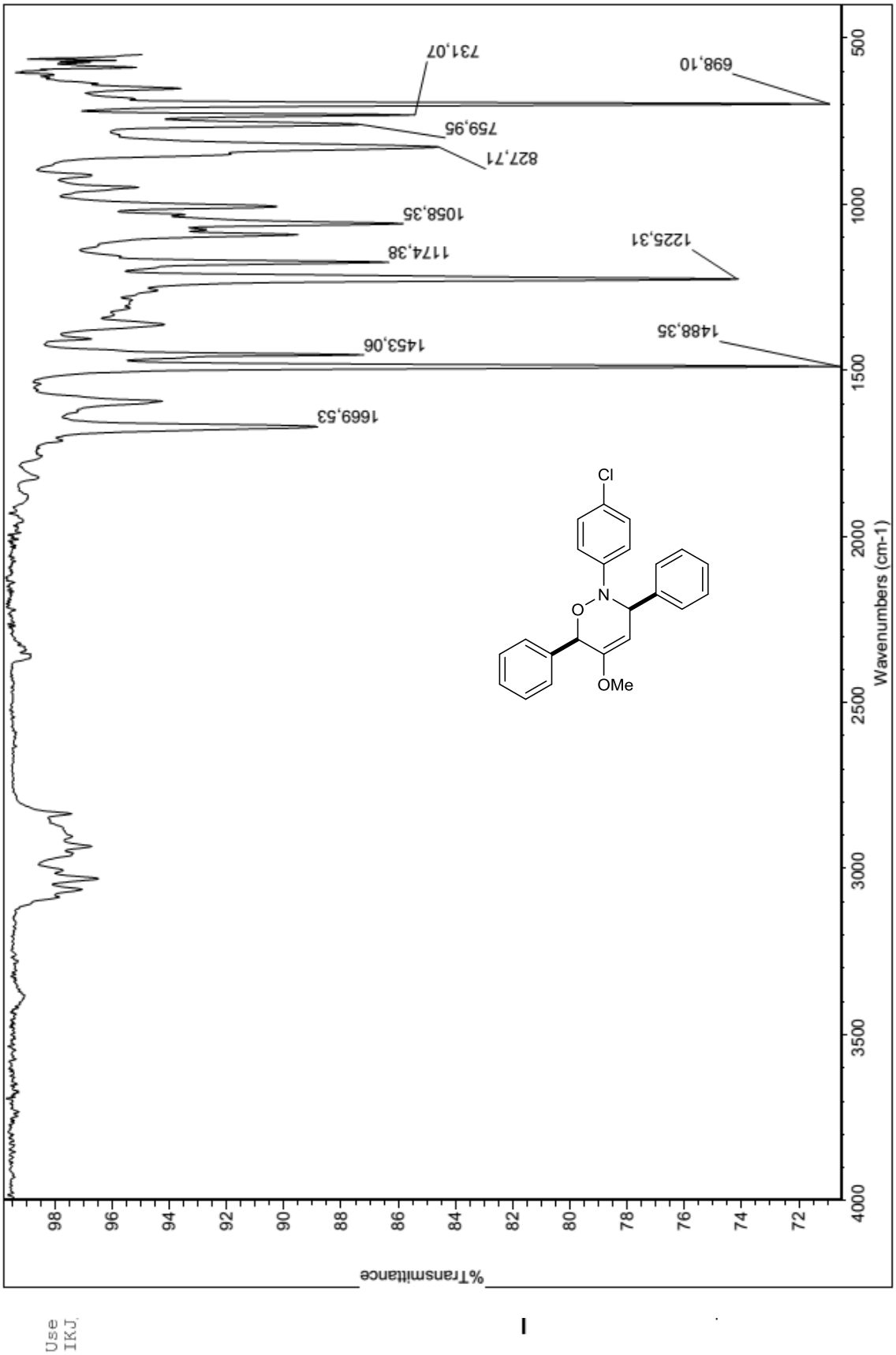
Appendix I.5 HMBC spectrum of oxazine 5i



Appendix I.6 NOESY spectrum of oxazine 5i



Appendix I.7 IR spectrum of oxazine 5i



Appendix I.8 MS of oxazine 5i

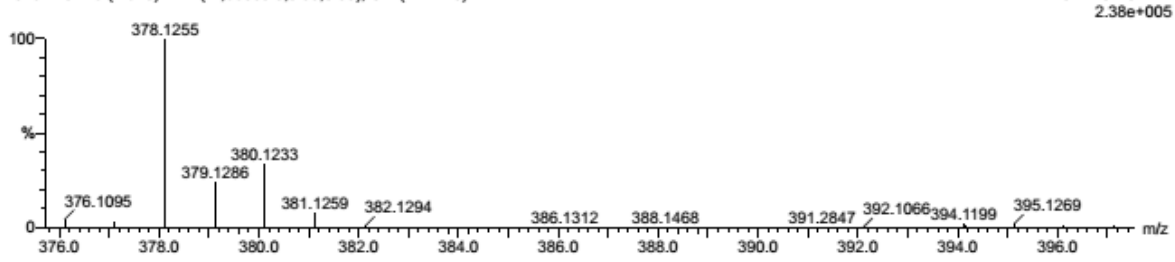
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 3.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
1380 formula(e) evaluated with 5 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-500 H: 0-1000 N: 0-50 O: 0-100 Cl: 1-2

NT-MSLAB-Operator-SVG
2015-220 119 (2.326) AM2 (Ar,35000.0,0.00,0.00); Cm (117:120)

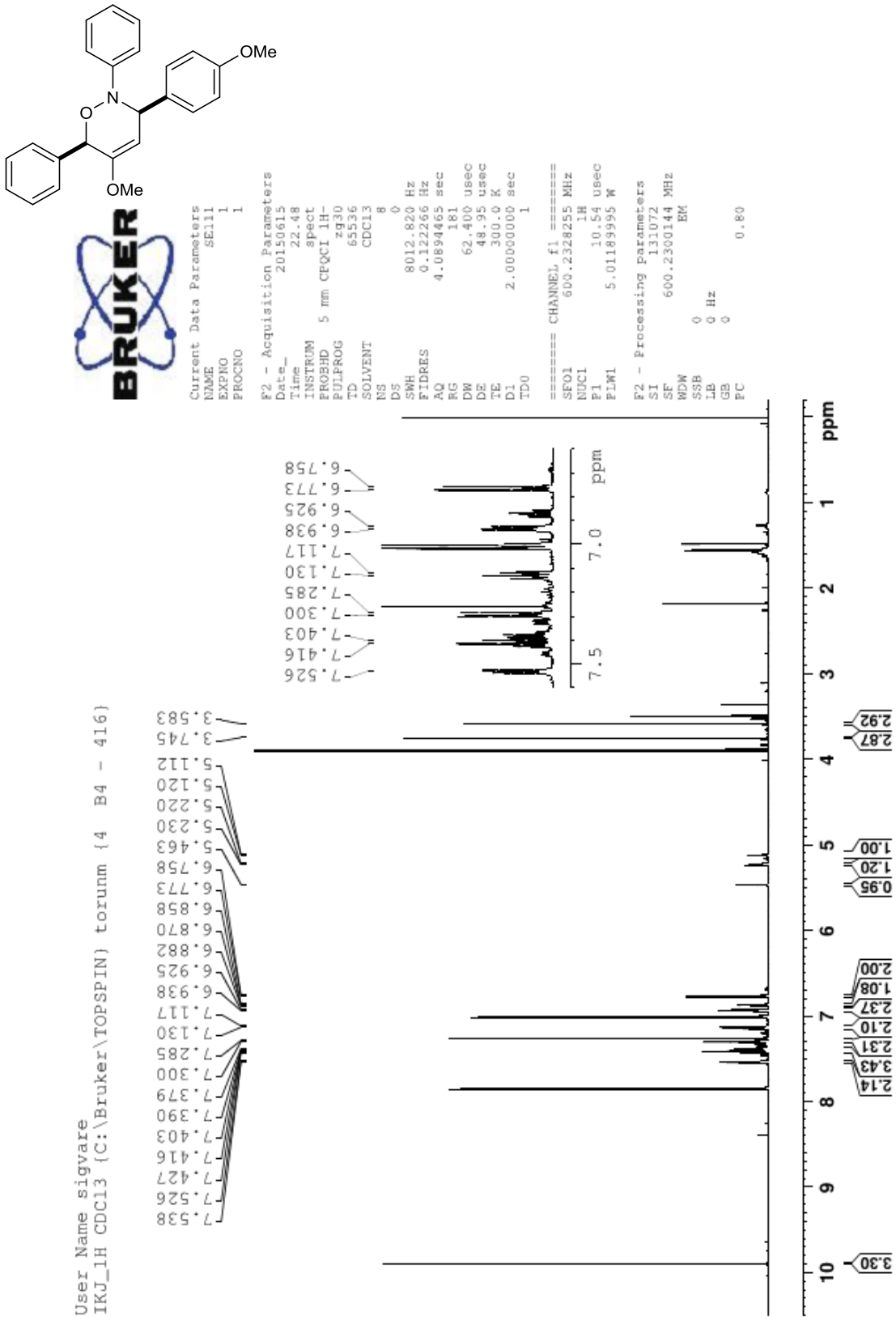
1: TOF MS ASAP+
2.38e+005



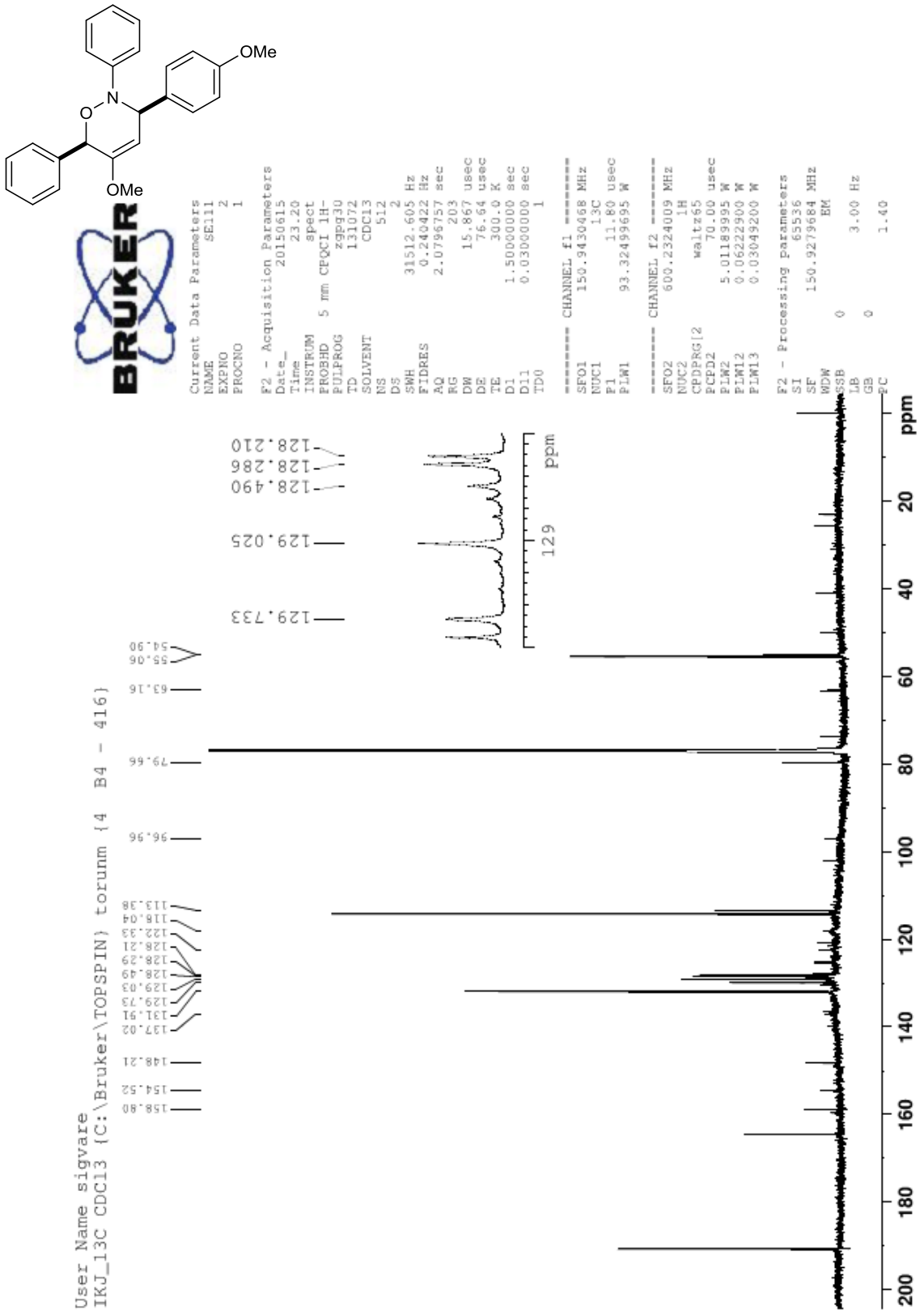
Minimum:				-1.5				
Maximum:		5.0	3.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
378.1255	378.1261	-0.6	-1.6	13.5	189.3	0.000	100.00	C23 H21 N O2 Cl Ion observed [M+H]
	378.1252	0.3	0.8	9.5	200.0	10.690	0.00	C18 H22 N5 Cl2
	378.1266	-1.1	-2.9	6.5	200.9	11.657	0.00	C8 H17 N13 O3 Cl
	378.1252	0.3	0.8	1.5	201.4	12.165	0.00	C7 H21 N9 O7 Cl
	378.1257	-0.2	-0.5	2.5	207.4	18.138	0.00	C3 H18 N17 O Cl2

Appendix J Spectra of oxazine 5j

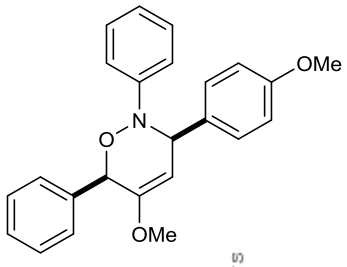
Appendix J.1 ^{1}H-NMR spectrum of oxazine 5j



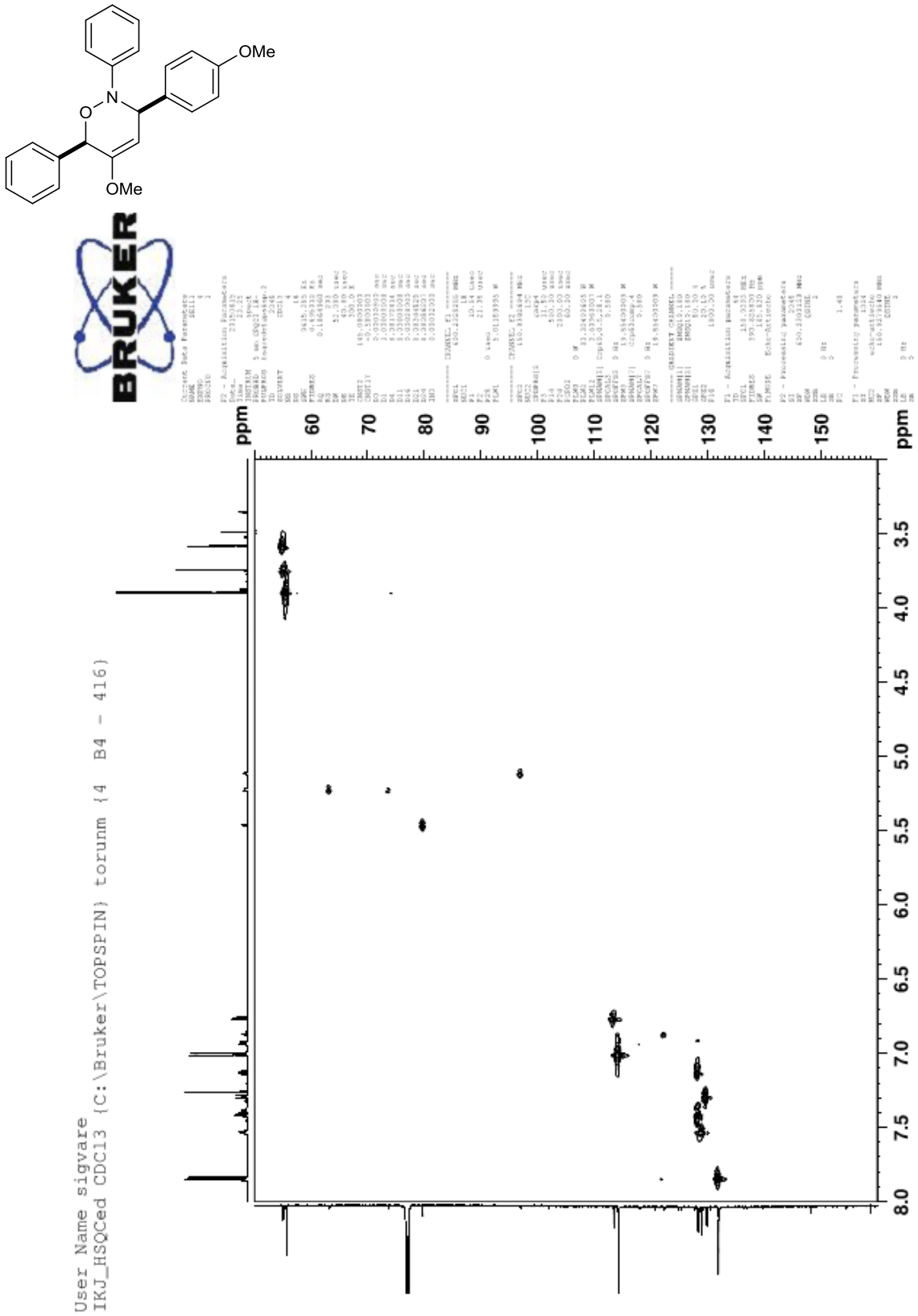
Appendix J.2 ^{13}C-NMR spectrum of oxazine 5j



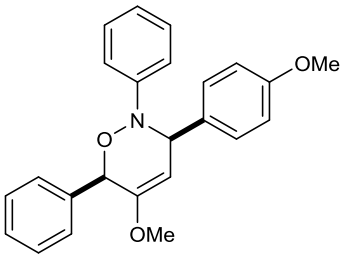
Appendix J.3 COSY spectrum of oxazine 5j

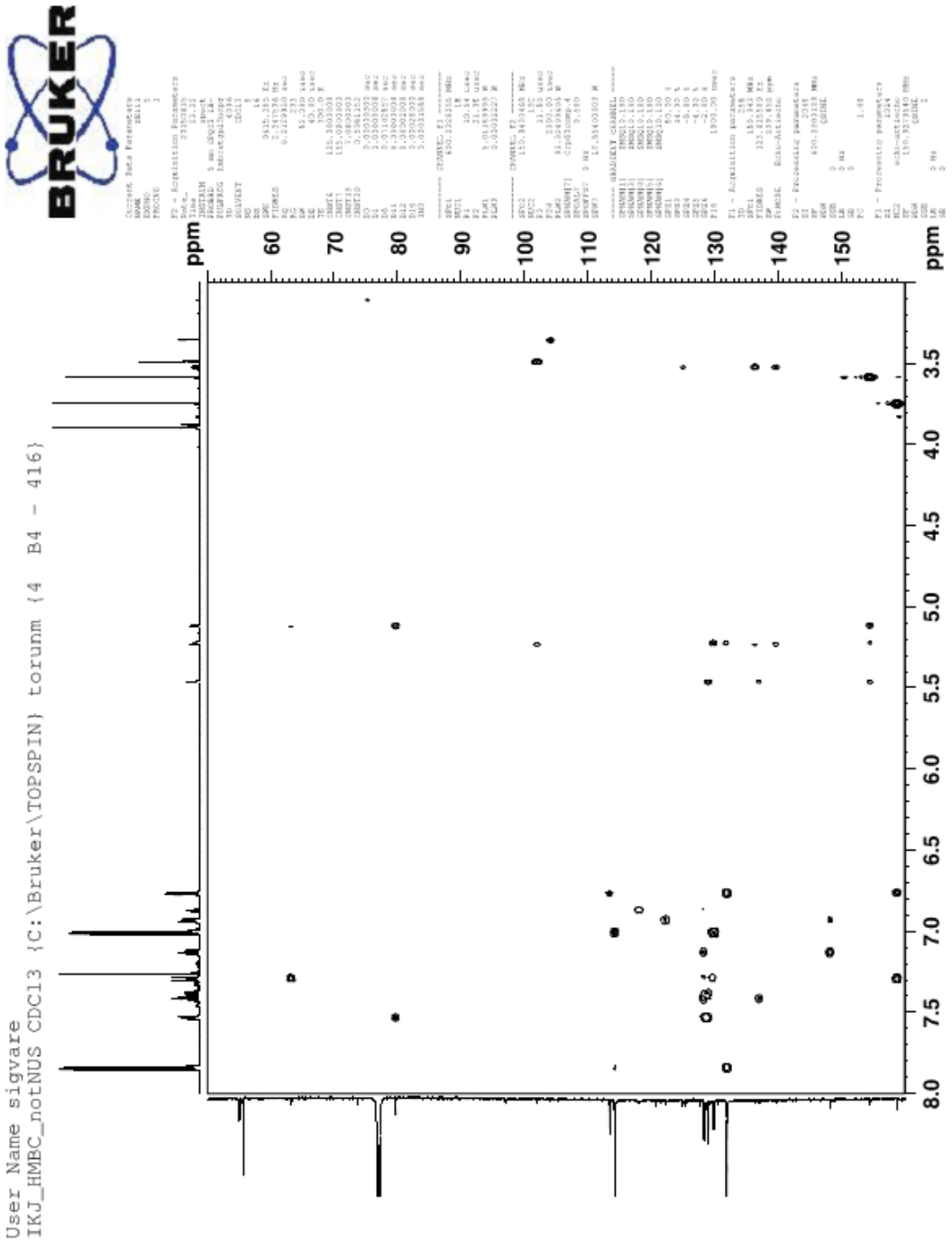


Appendix J.4 HSQC spectrum of oxazine 5j

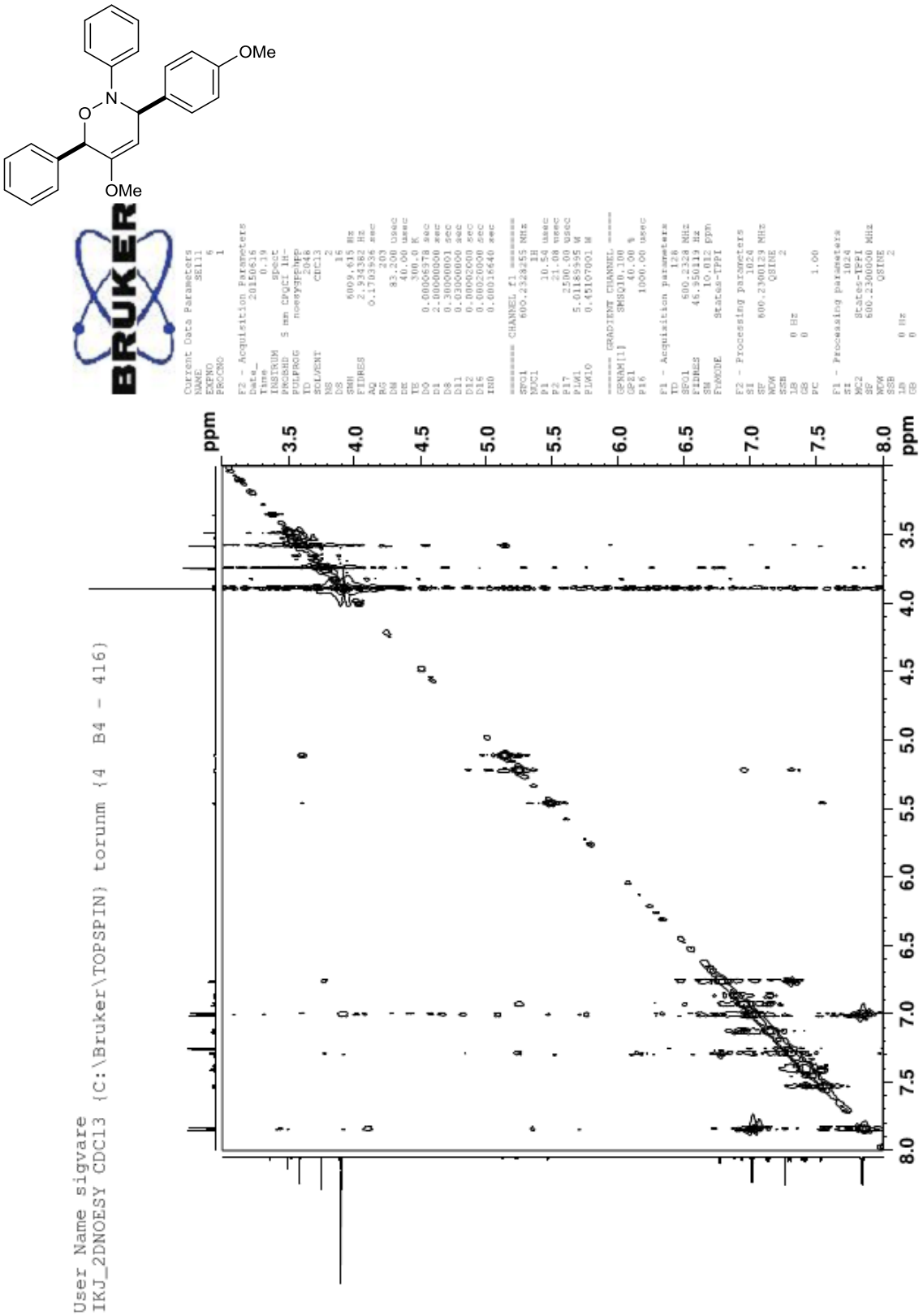


Appendix J.5 HMBC spectrum of oxazine 5j

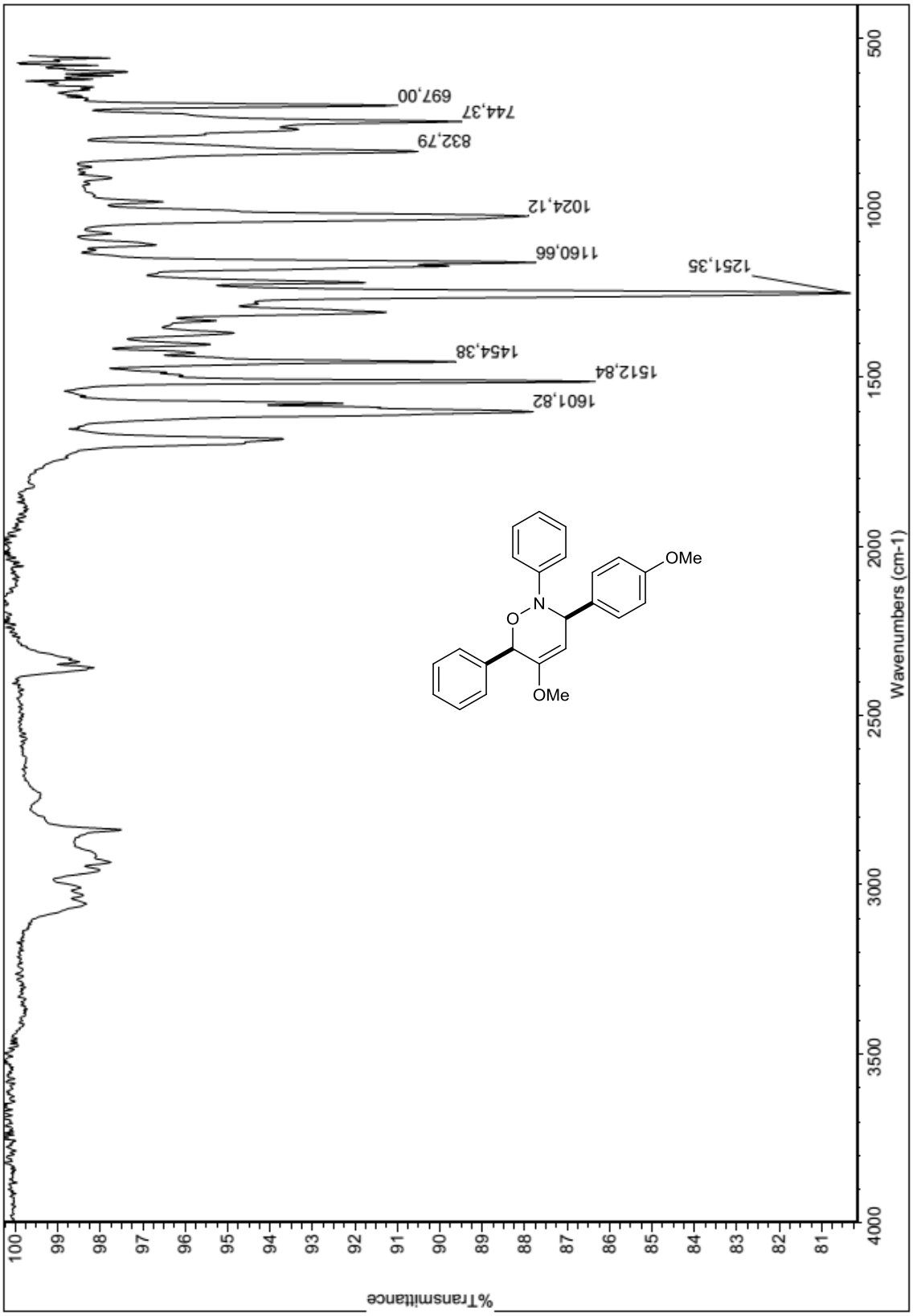




Appendix J.6 NOESY spectrum of oxazine 5j



Appendix J.7 IR spectrum of oxazine 5j



Appendix J.8 MS of oxazine 5j

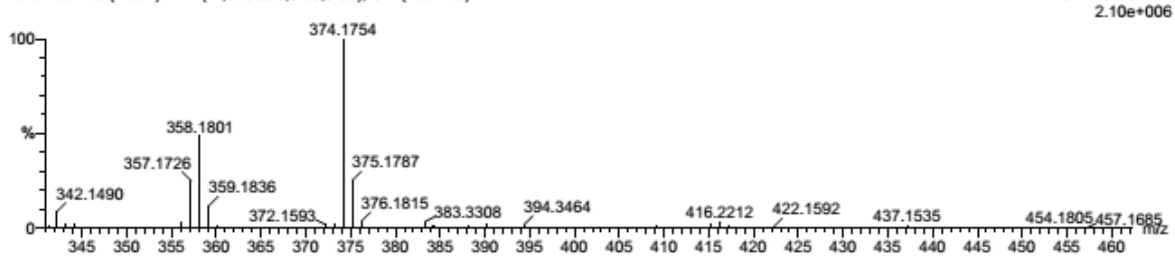
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 2.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
5018 formula(e) evaluated with 6 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-50 O: 0-100 S: 0-3 Br: 0-2

NT-MSLAB-Operator-SVG
2015-156 130 (2.551) AM2 (Ar,35000.0,0.00,0.00); Cm (130:138)

1: TOF MS ASAP+
2.10e+006

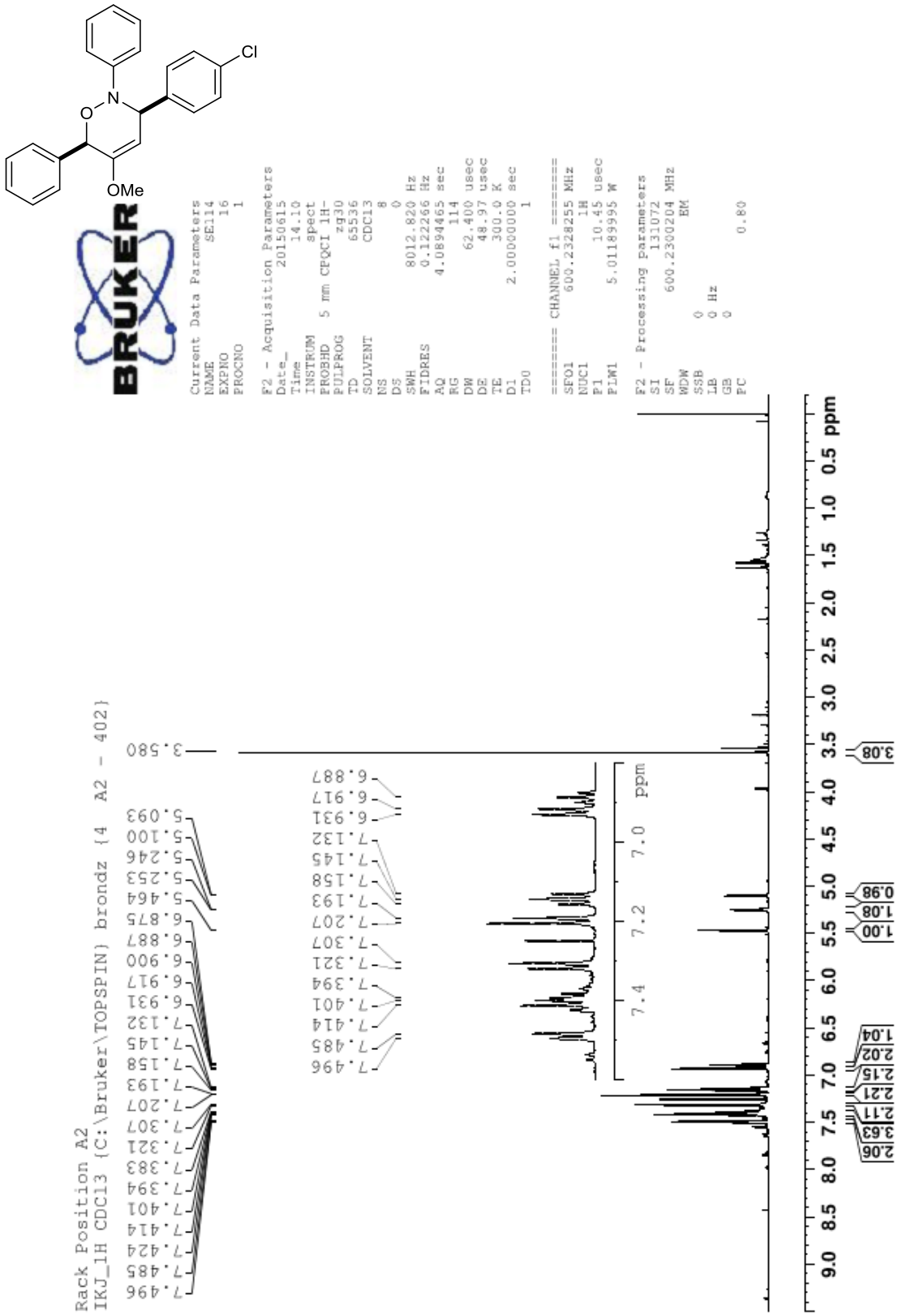


Minimum:				-1.5				
Maximum:		5.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
374.1754	374.1756	-0.2	-0.5	13.5	1288.4	0.000	100.00	C24 H24 N O3
	374.1757	-0.3	-0.8	0.5	1309.8	21.381	0.00	C9 H28 N9 O3 S2
	374.1758	-0.4	-1.1	3.5	1310.9	22.498	0.00	C17 H32 N3 S3
	374.1750	0.4	1.1	4.5	1306.4	17.936	0.00	C16 H28 N3 O5 S
	374.1748	0.6	1.6	1.5	1303.1	14.643	0.00	C8 H24 N9 O8
	374.1761	-0.7	-1.9	6.5	1302.3	13.847	0.00	C9 H20 N13 O4

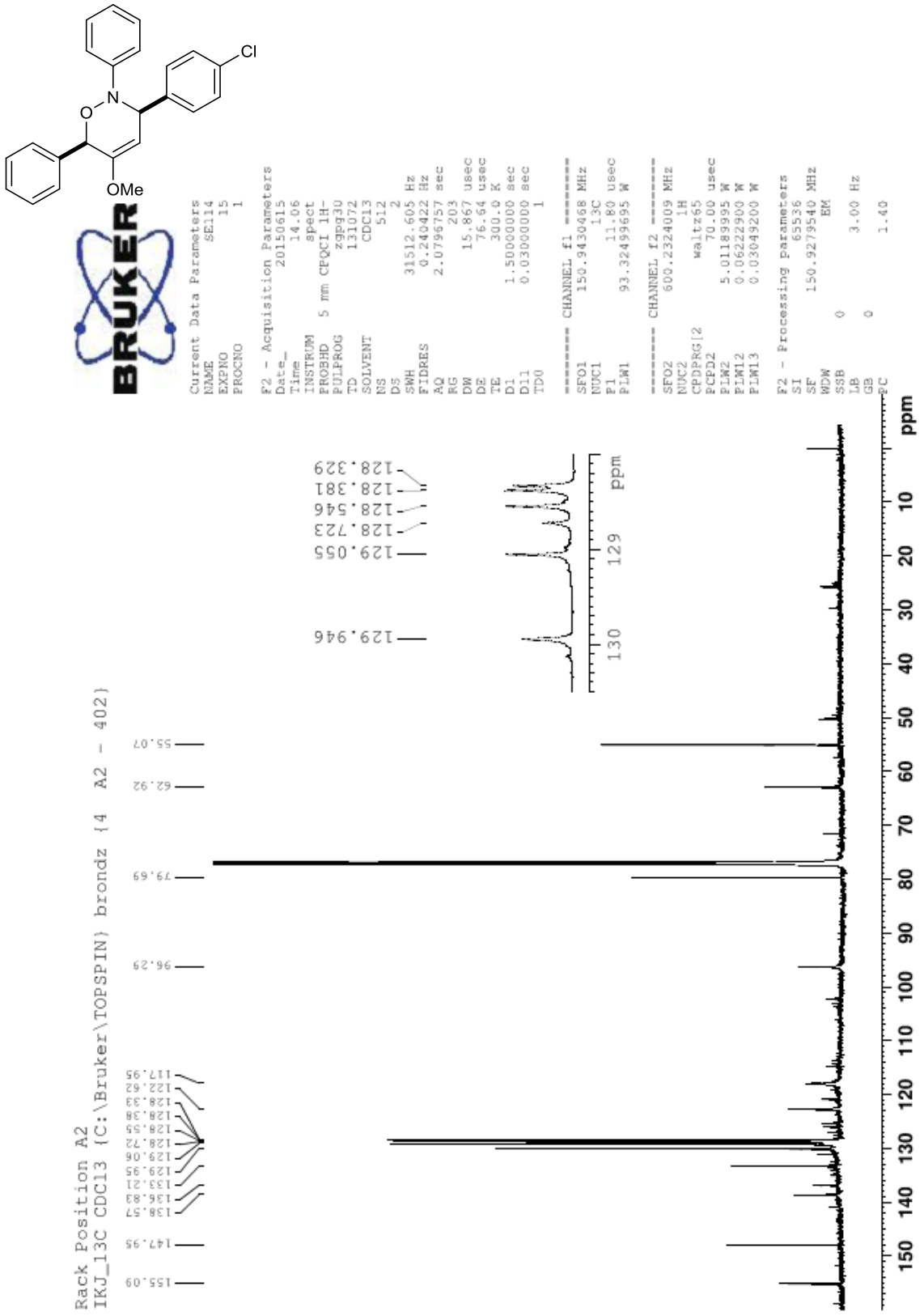
Ion observed [M+H]+

Appendix K Spectra of oxazine 5k

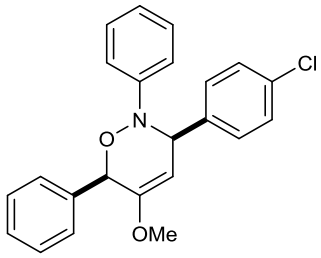
Appendix K.1 ^{1}H-NMR spectrum oxazine 5k

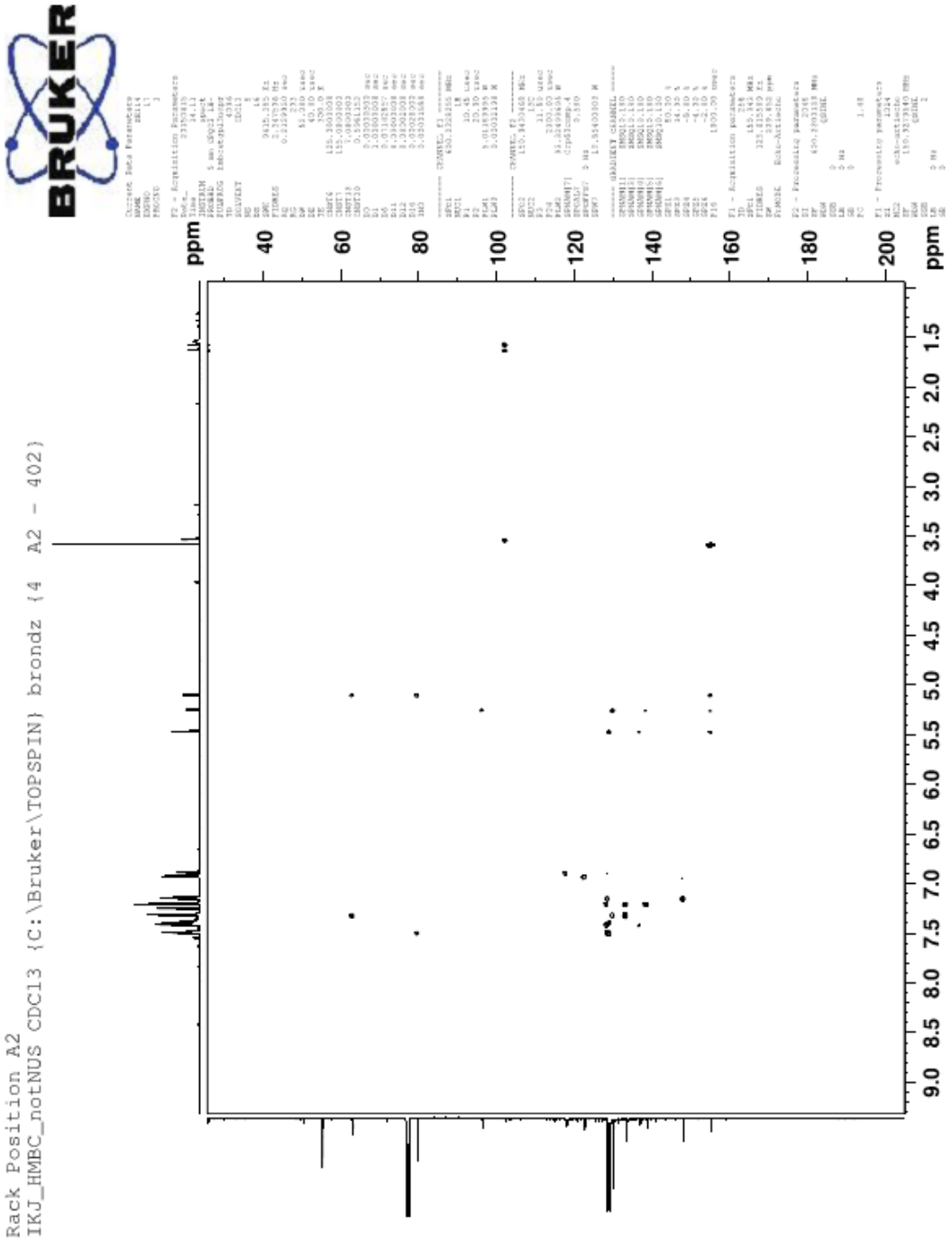


Appendix K.2 ^{13}C-NMR spectrum of oxazine 5k

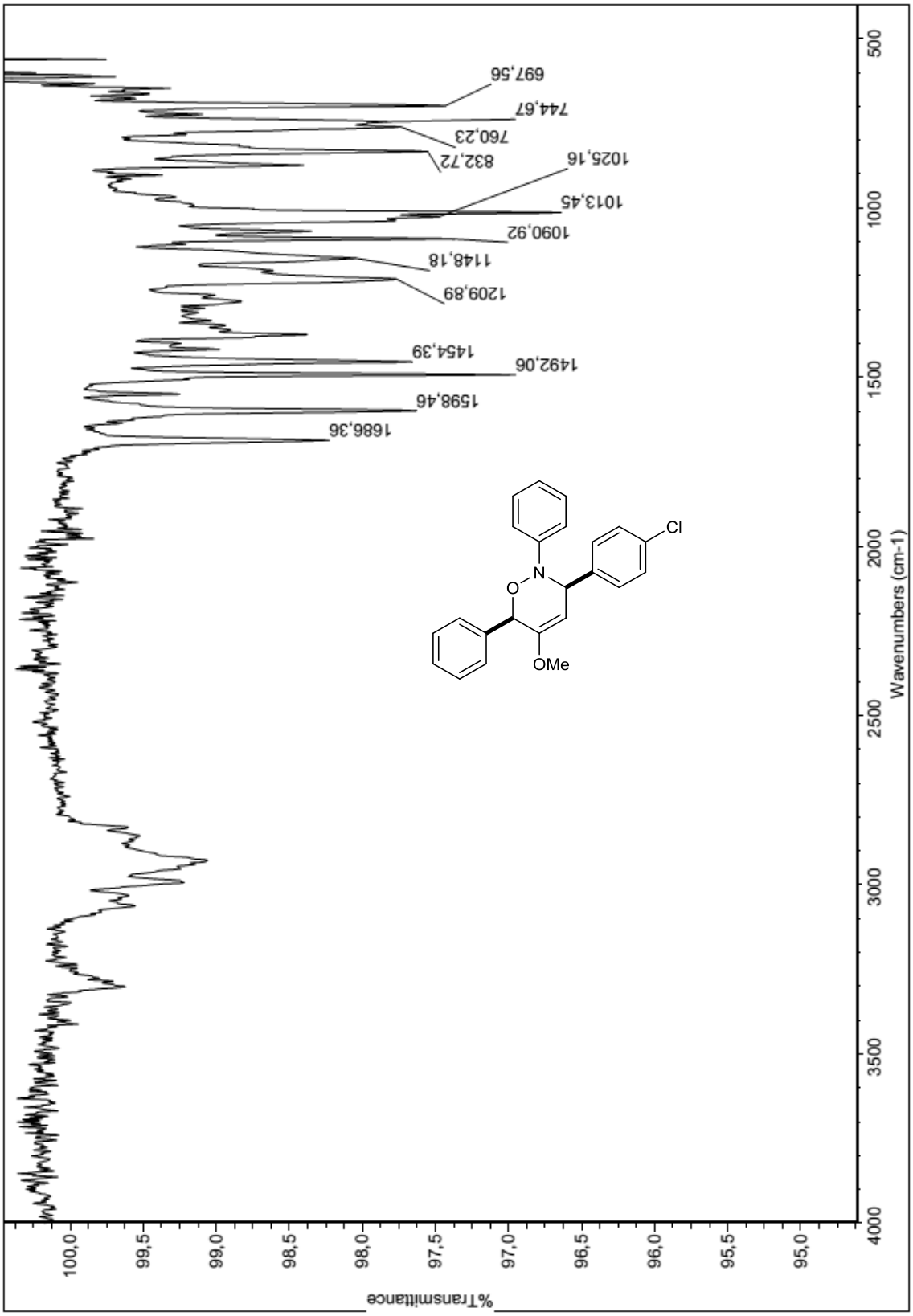


Appendix K.3 HMBC spectrum of oxazine 5k





Appendix K.4 IR spectrum of oxazine 5k



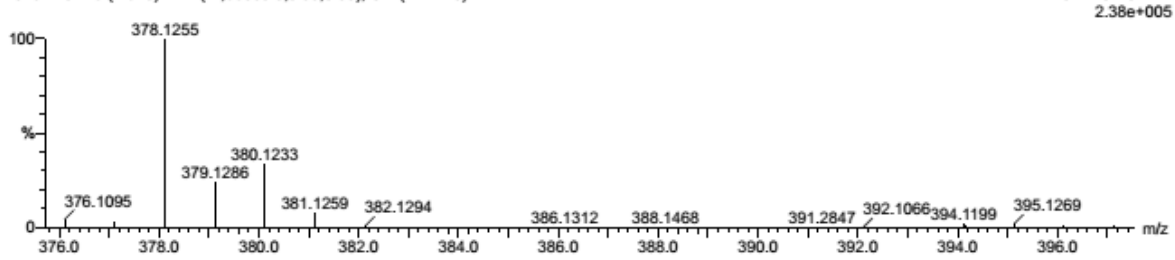
Appendix K.5 MS of oxazine 5k

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 3.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
1380 formula(e) evaluated with 5 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-500 H: 0-1000 N: 0-50 O: 0-100 Cl: 1-2
NT-MSLAB-Operator-SVG
2015-220 119 (2.326) AM2 (Ar,35000.0,0.00,0.00); Cm (117:120)

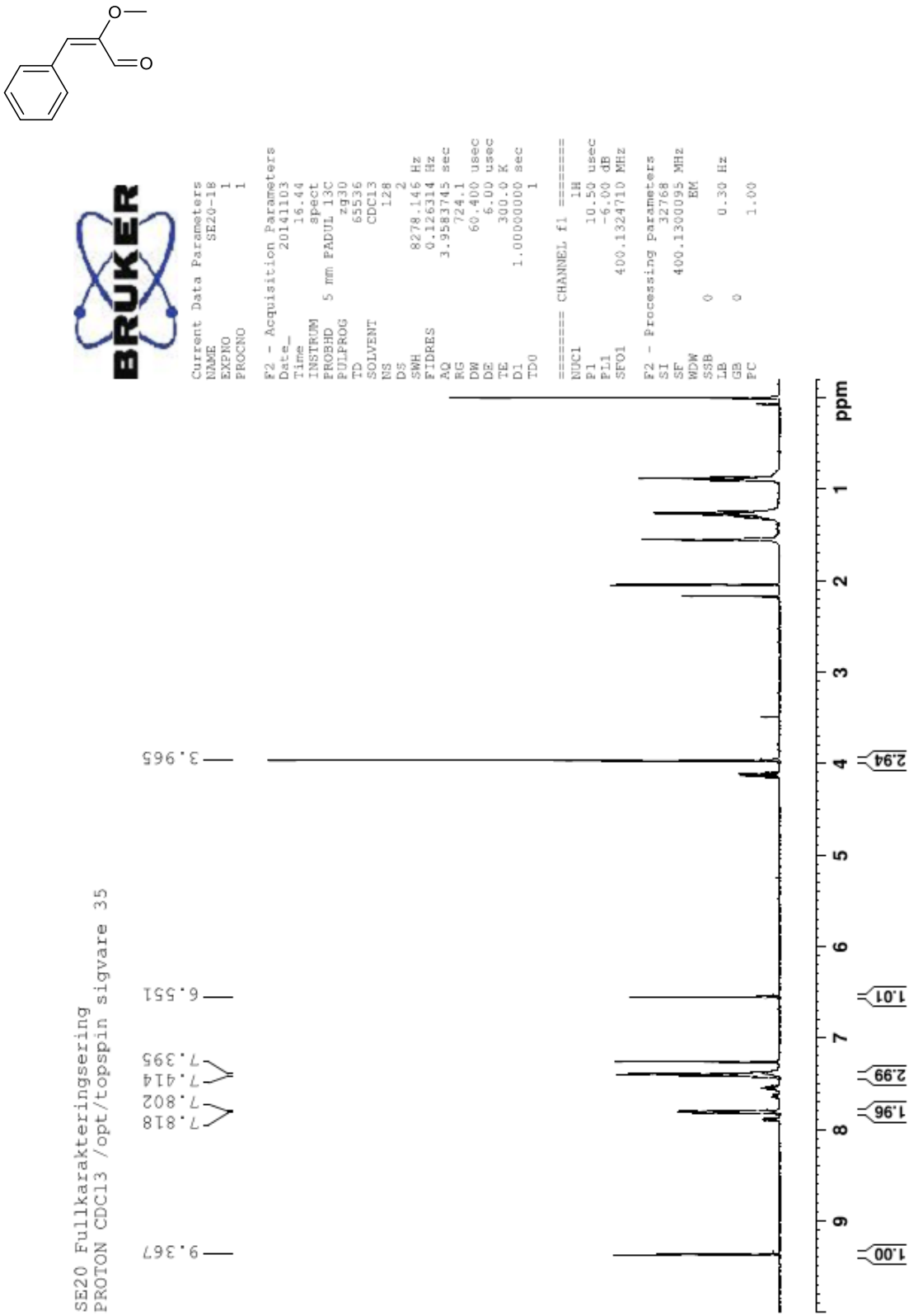
1: TOF MS ASAP+
2.38e+005



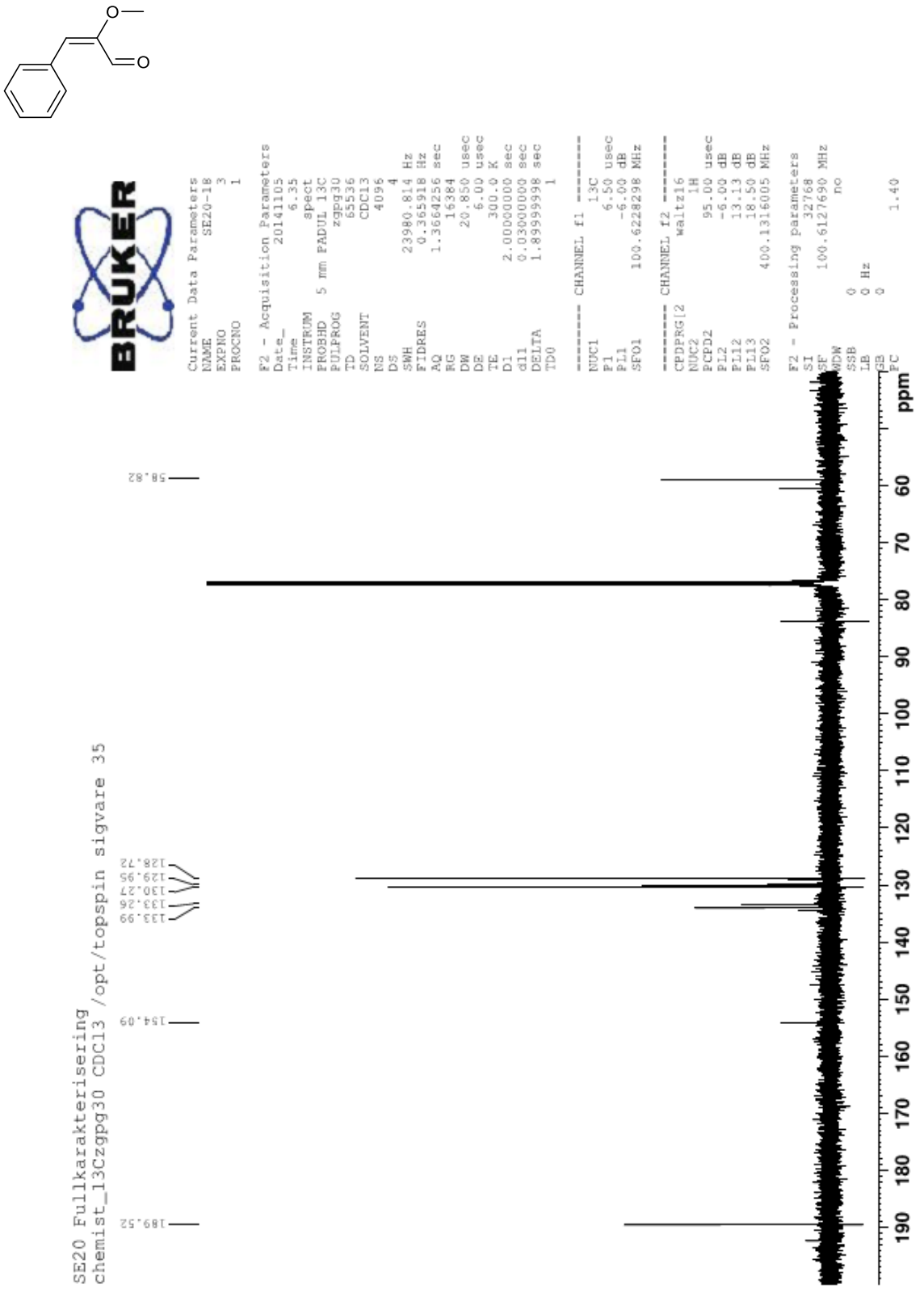
Minimum:				-1.5				
Maximum:		5.0	3.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
378.1255	378.1261	-0.6	-1.6	13.5	189.3	0.000	100.00	C23 H21 N O2 Cl Ion observed [M+H]
	378.1252	0.3	0.8	9.5	200.0	10.690	0.00	C18 H22 N5 Cl2
	378.1266	-1.1	-2.9	6.5	200.9	11.657	0.00	C8 H17 N13 O3 Cl
	378.1252	0.3	0.8	1.5	201.4	12.165	0.00	C7 H21 N9 O7 Cl
	378.1257	-0.2	-0.5	2.5	207.4	18.138	0.00	C3 H18 N17 O Cl2

Appendix L Spectra of aldehyde 6a

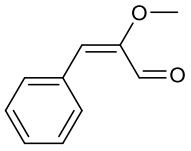
Appendix L.1 ^{1}H-NMR spectrum of aldehyde 6a

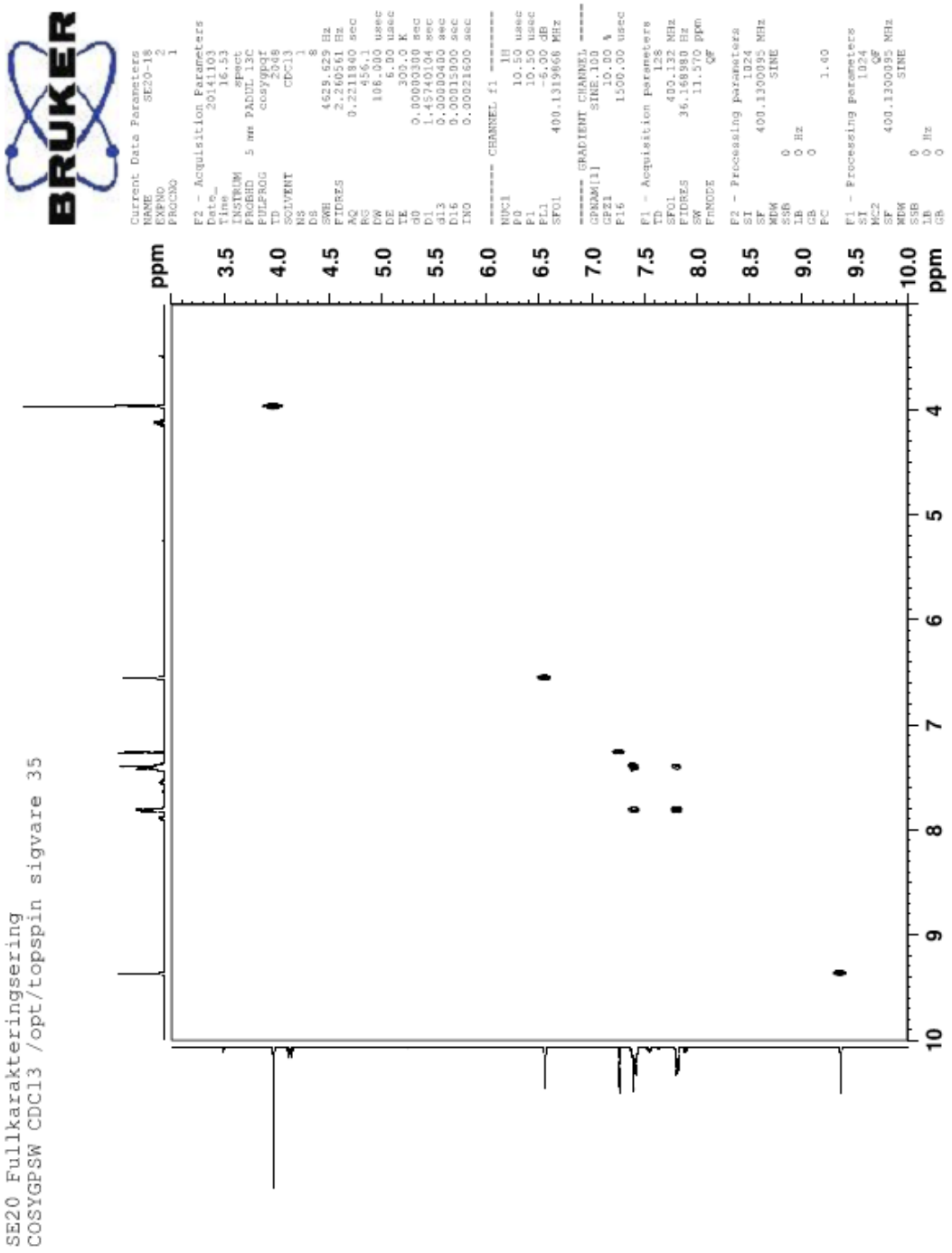


Appendix L.2 ^{13}C-NMR spectrum of aldehyde 6a

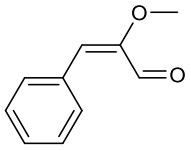


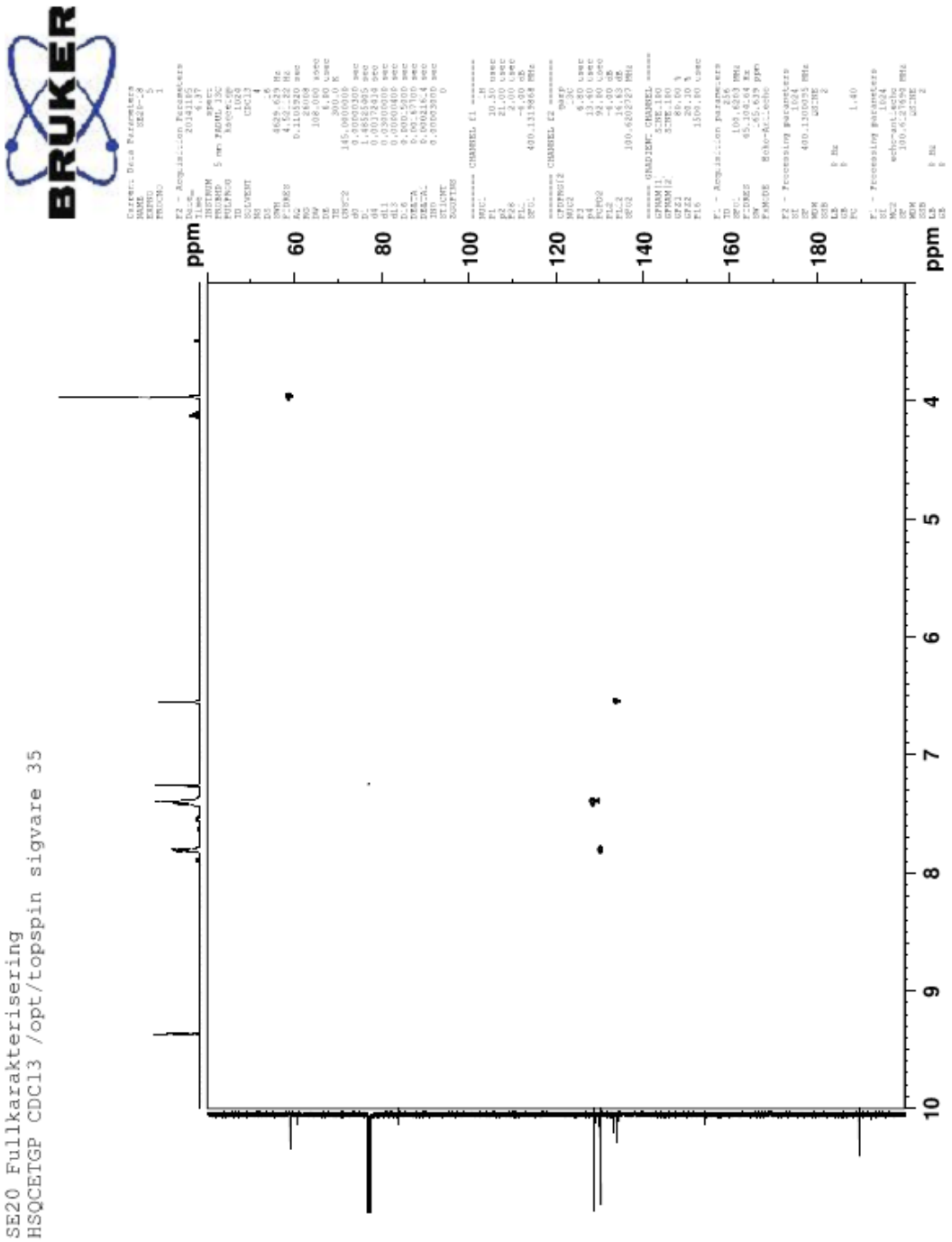
Appendix L.3 COSY spectrum of aldehyde 6a



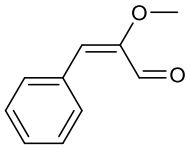


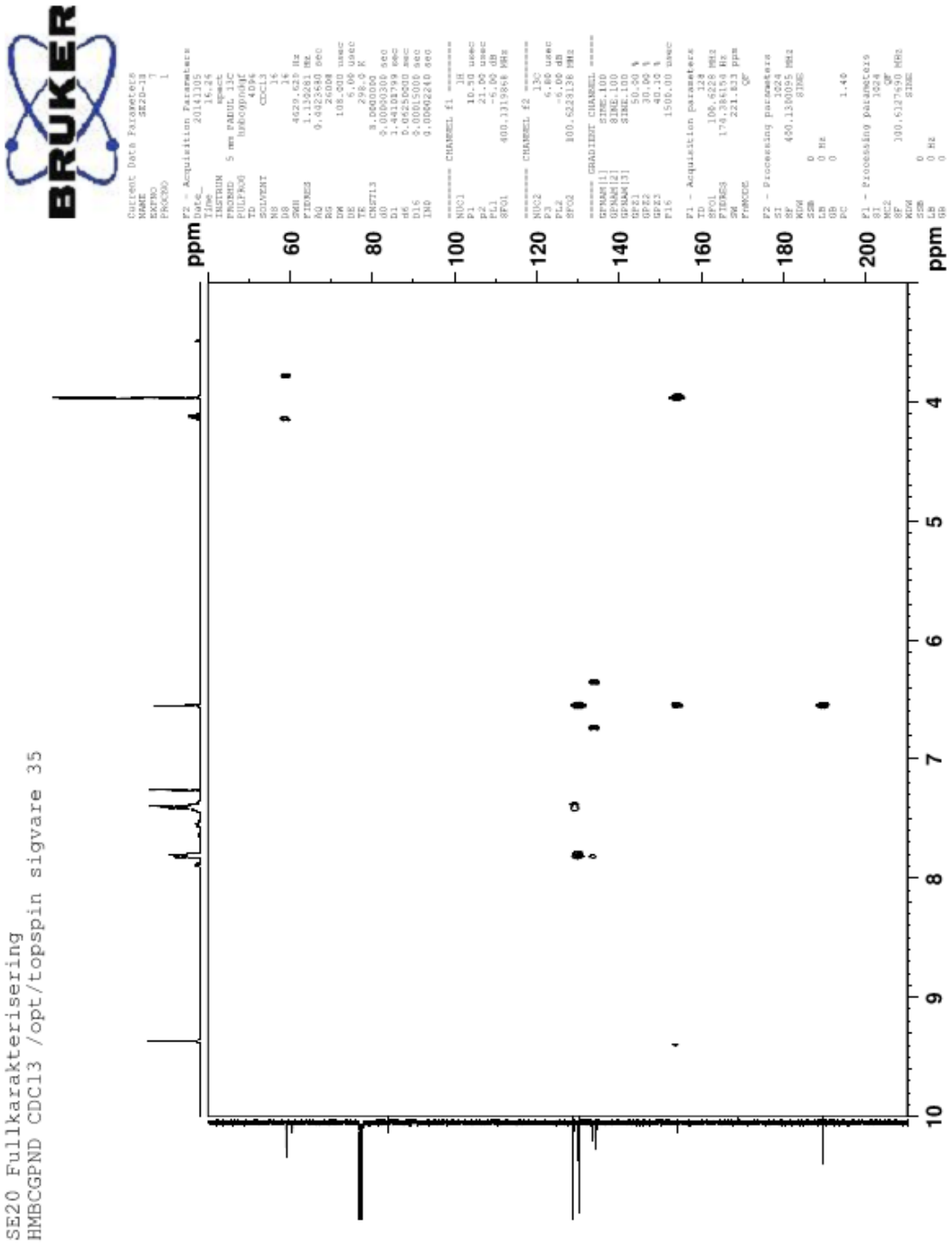
Appendix L.4 HSQC spectrum of aldehyde 6a



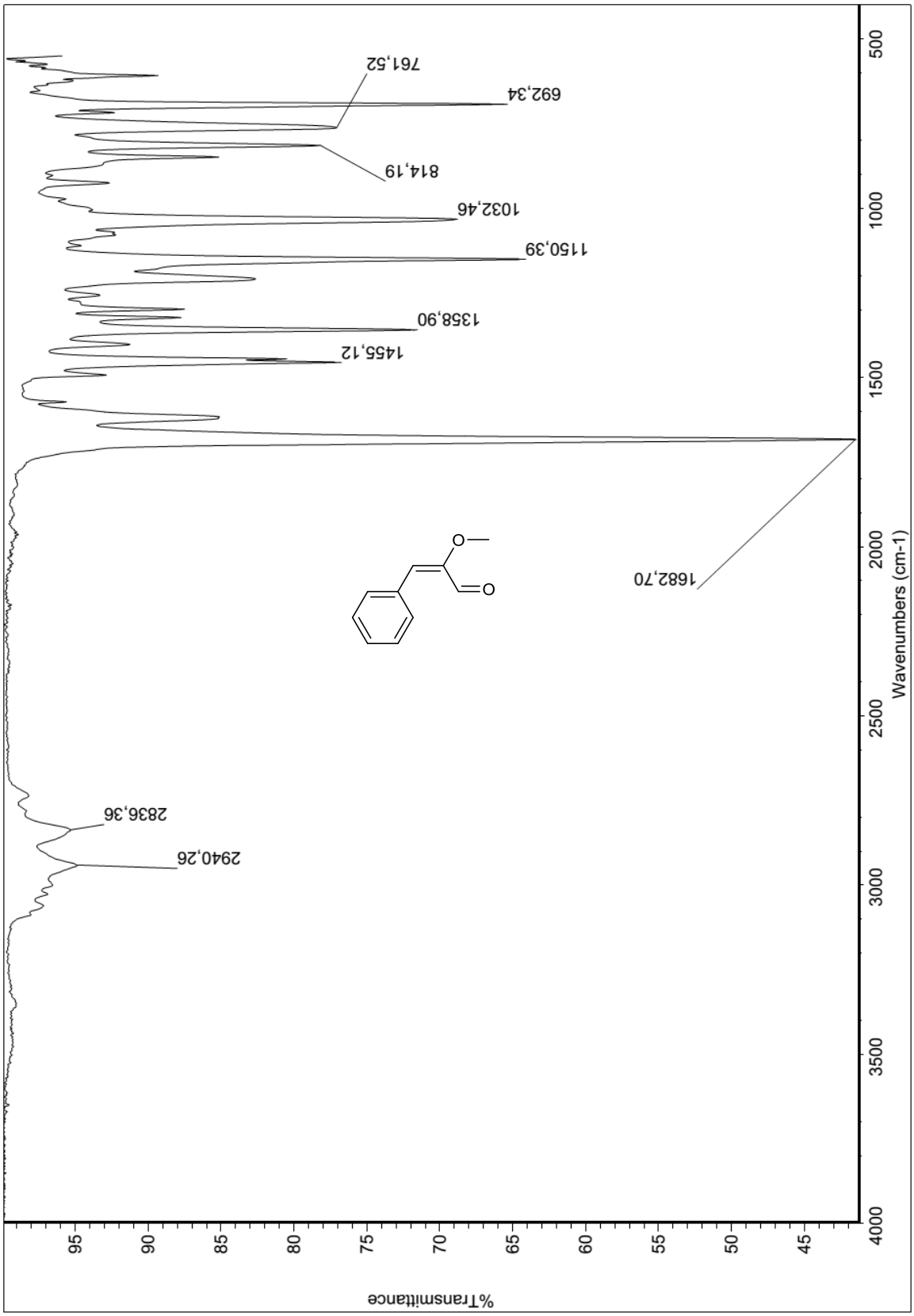


Appendix L.5 HMBC spectrum of aldehyde 6a





Appendix L.6 IR spectrum of aldehyde 6a



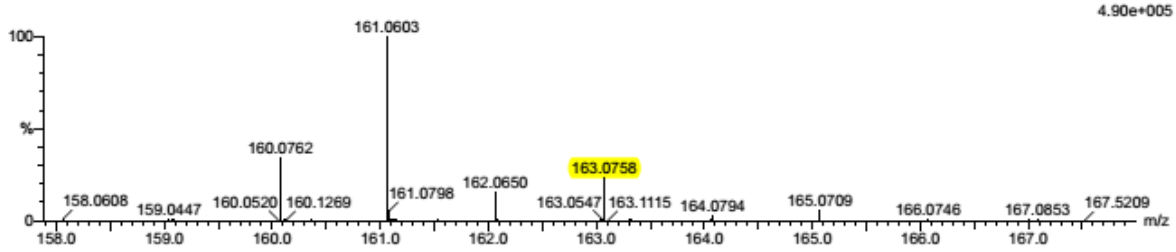
Appendix L.7 MS of aldehyde 6a

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 2.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
309 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-200 O: 0-200 S: 0-6
2014-183 34 (0.691) AM2 (Ar,35000.0,0.00,0.00); Cm (34)
1: TOF MS ASAP+

4.90e+005

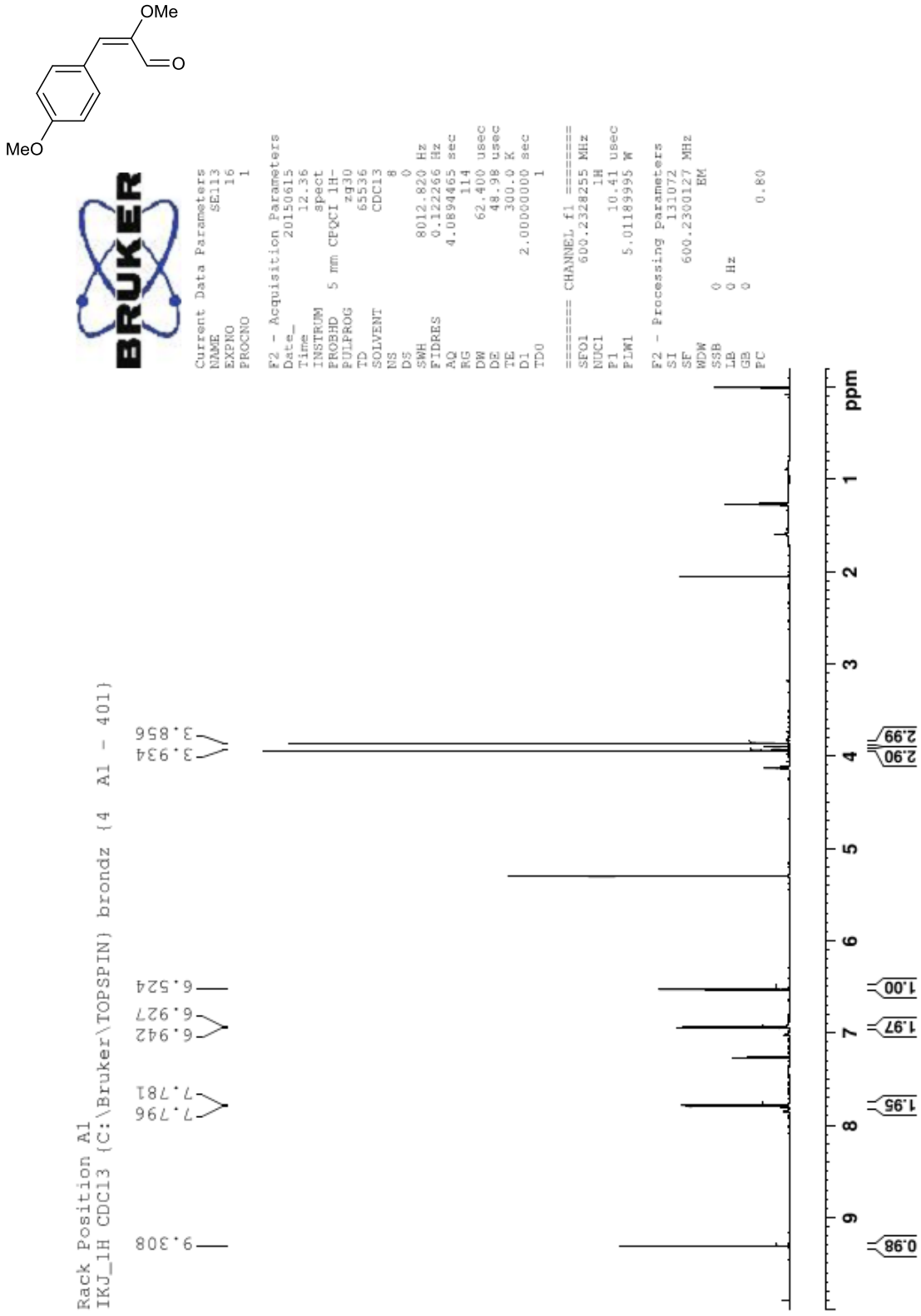


Minimum:				-1.5				
Maximum:		5.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
163.0758	163.0759	-0.1	-0.6	5.5	1392.2	n/a	n/a	C10 H11 O2

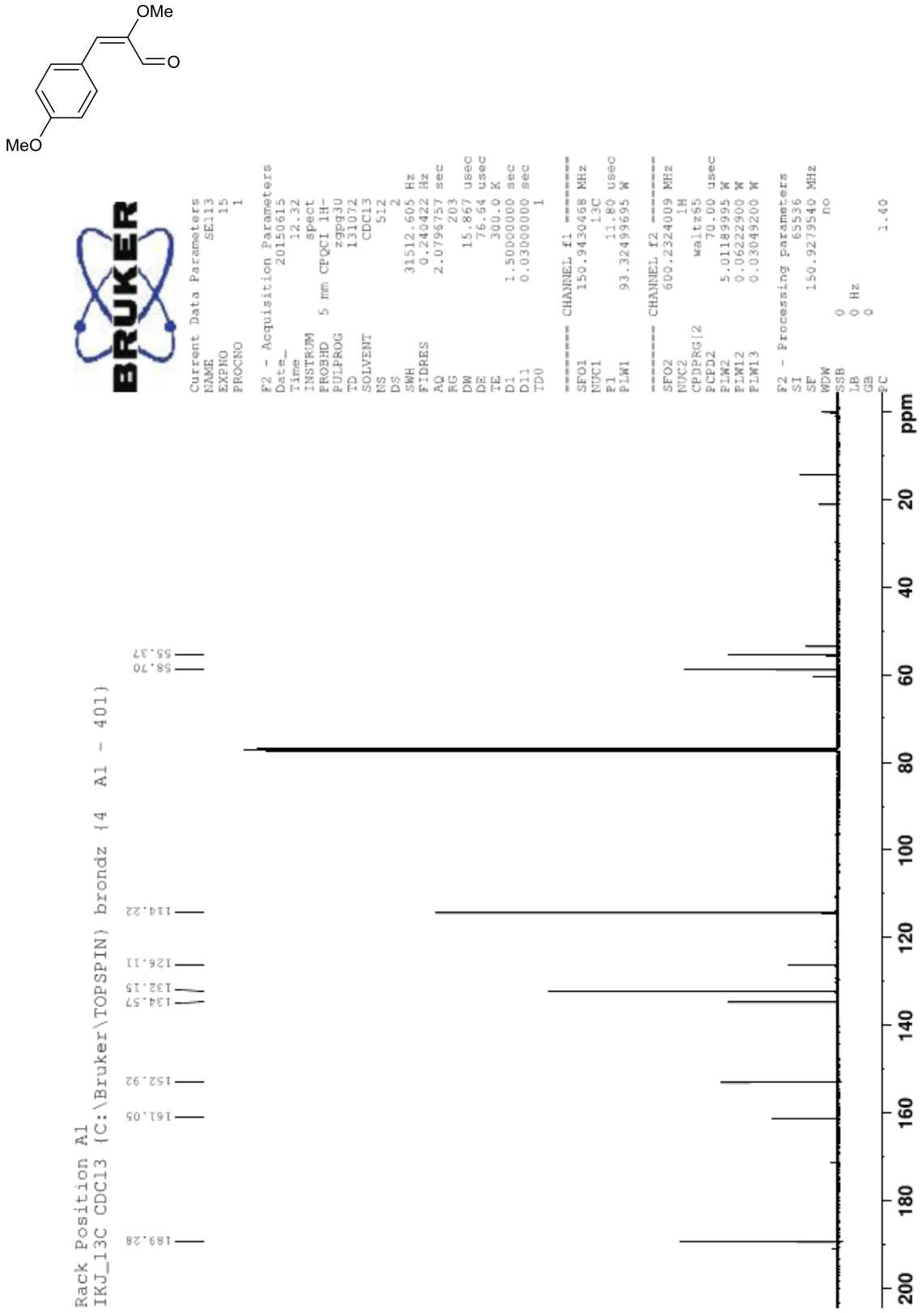
[M+H]+ ion observed

Appendix M spectra of aldehyde 6b

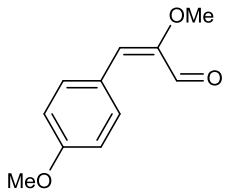
Appendix M.1 ^{1}H-NMR spectra of aldehyde 6b

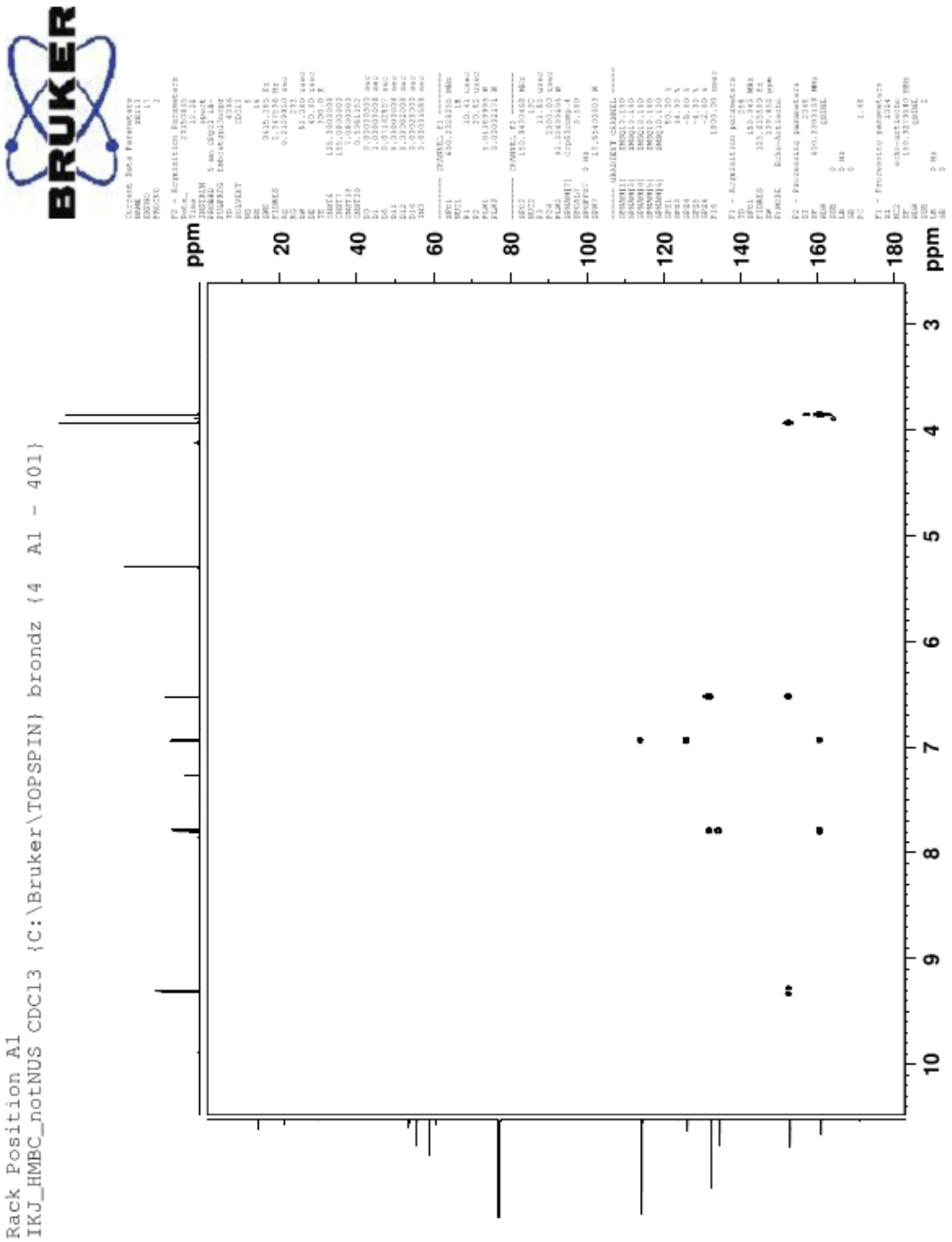


Appendix M.2 ^{13}C-NMR spectrum of aldehyde 6b

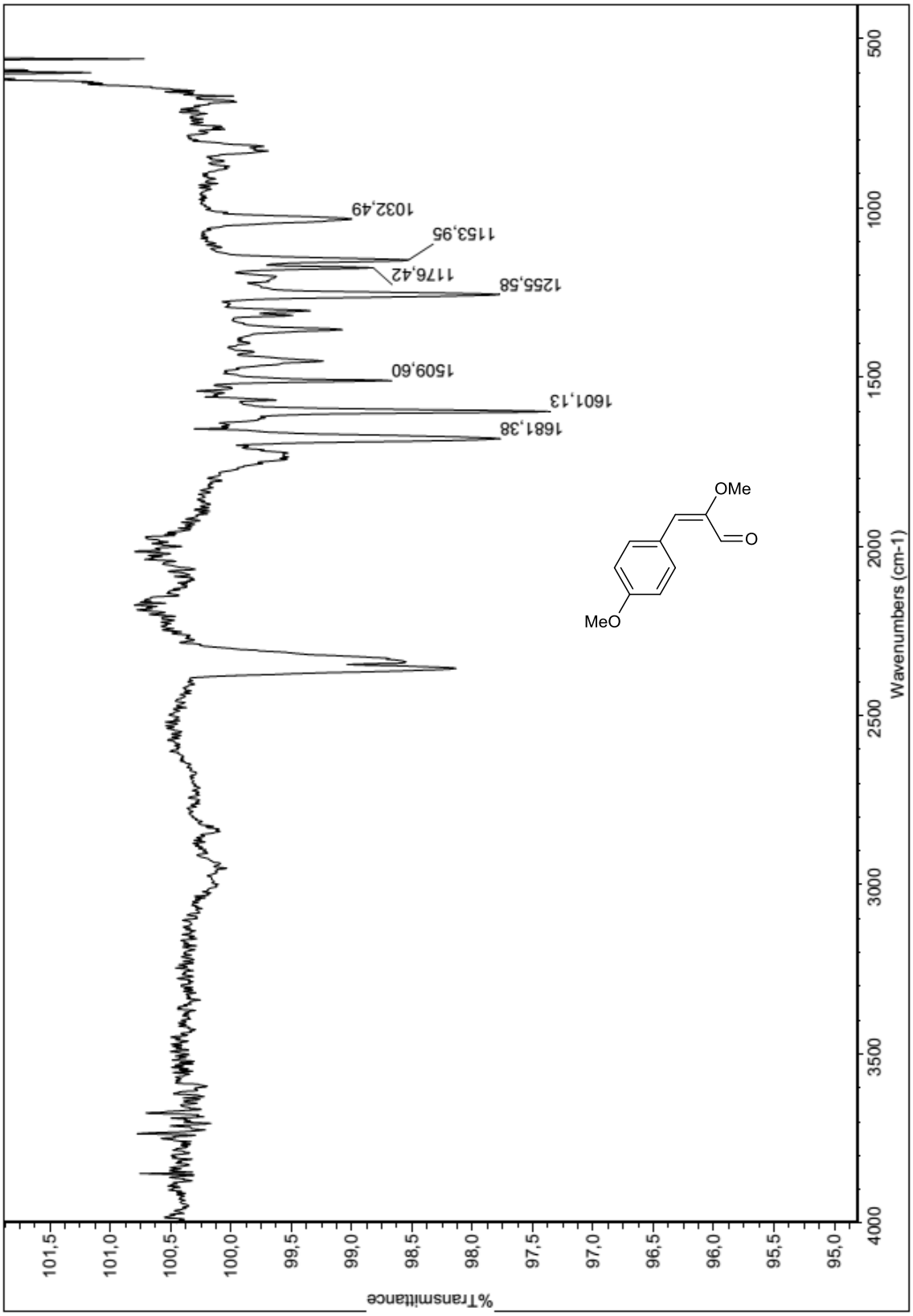


Appendix M.3 HMBC spectrum of aldehyde 6b



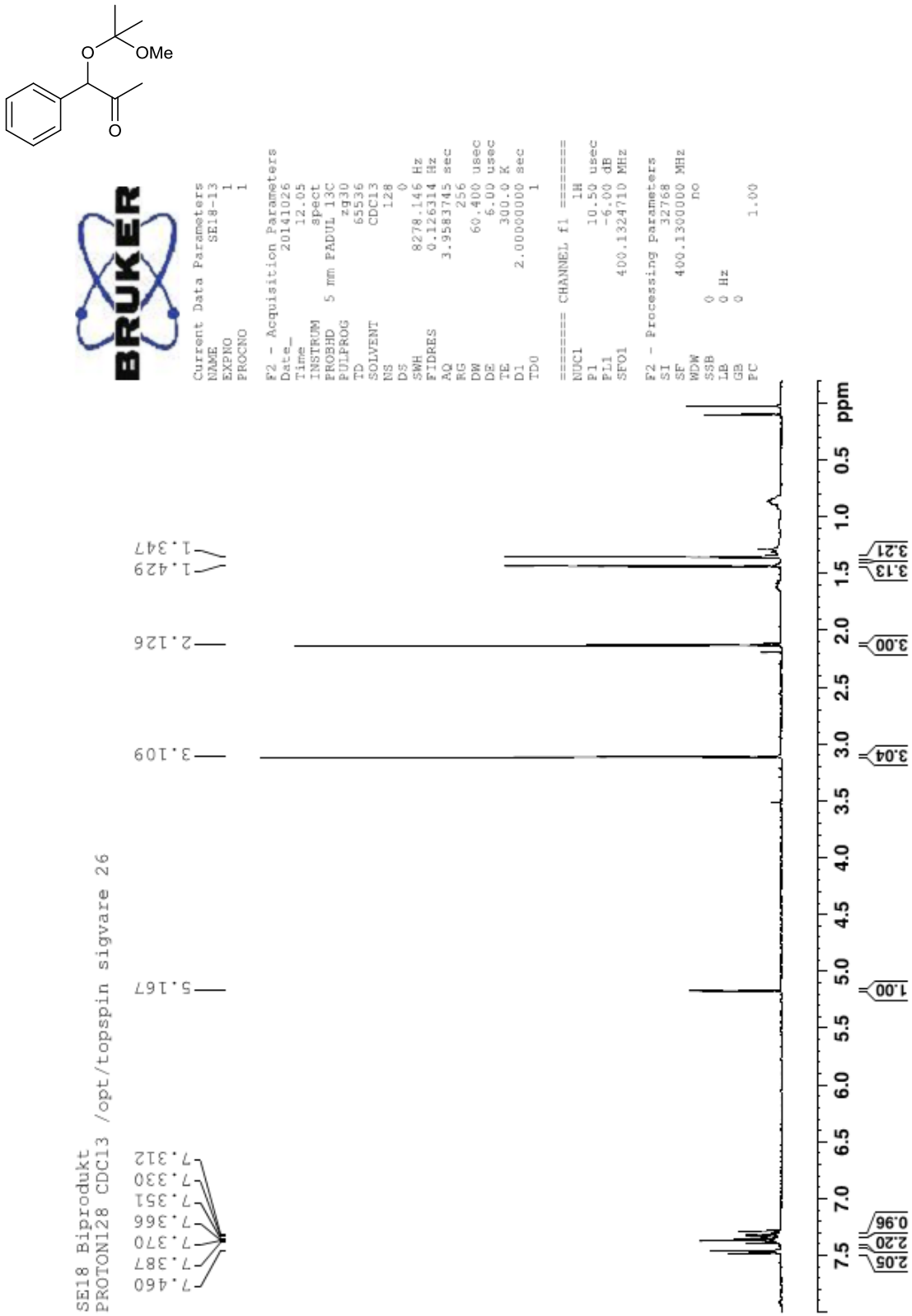


Appendix M.4 IR spectrum of aldehyde 6b

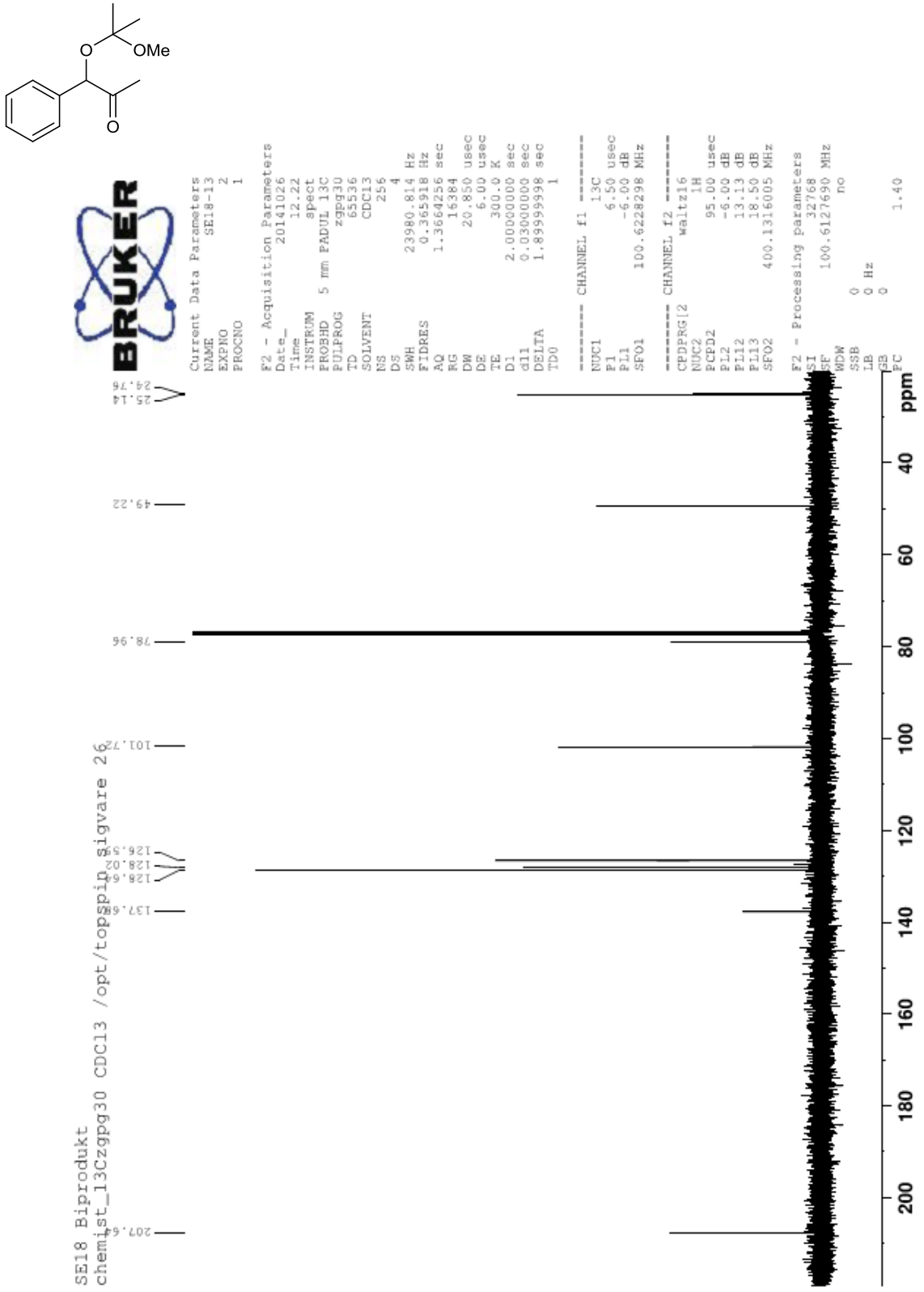


Appendix N Spectra of ketone 7a

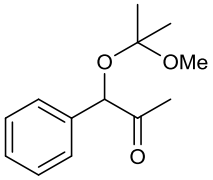
Appendix N.1 ^{1}H-NMR spectrum of ketone 7a

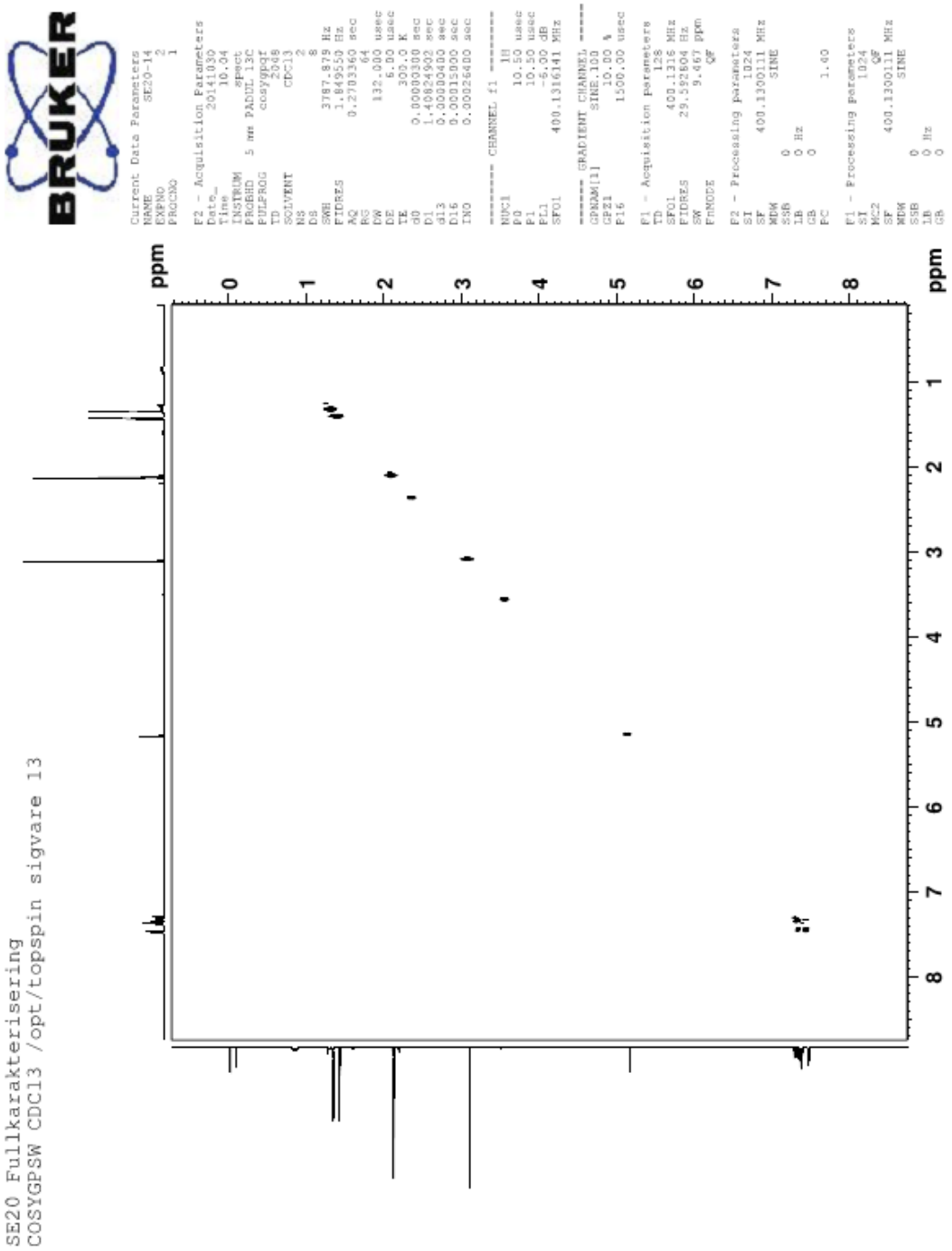


Appendix N.2 ^{13}C-NMR spectrum of ketone 7a

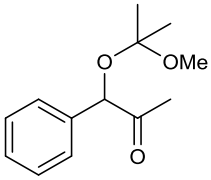


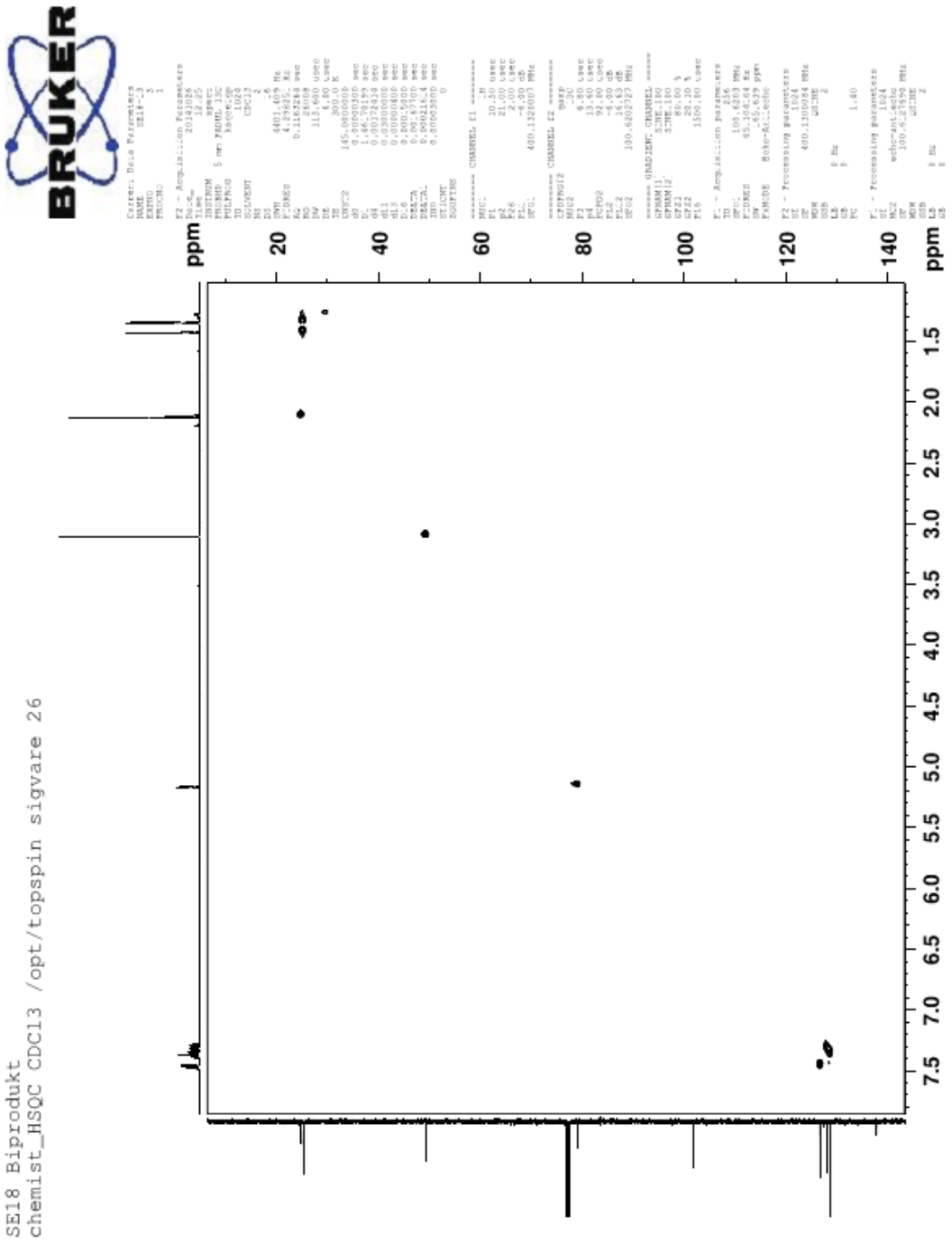
Appendix N.3 COSY spectrum of ketone 7a



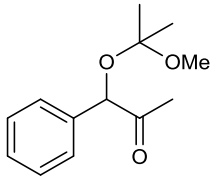


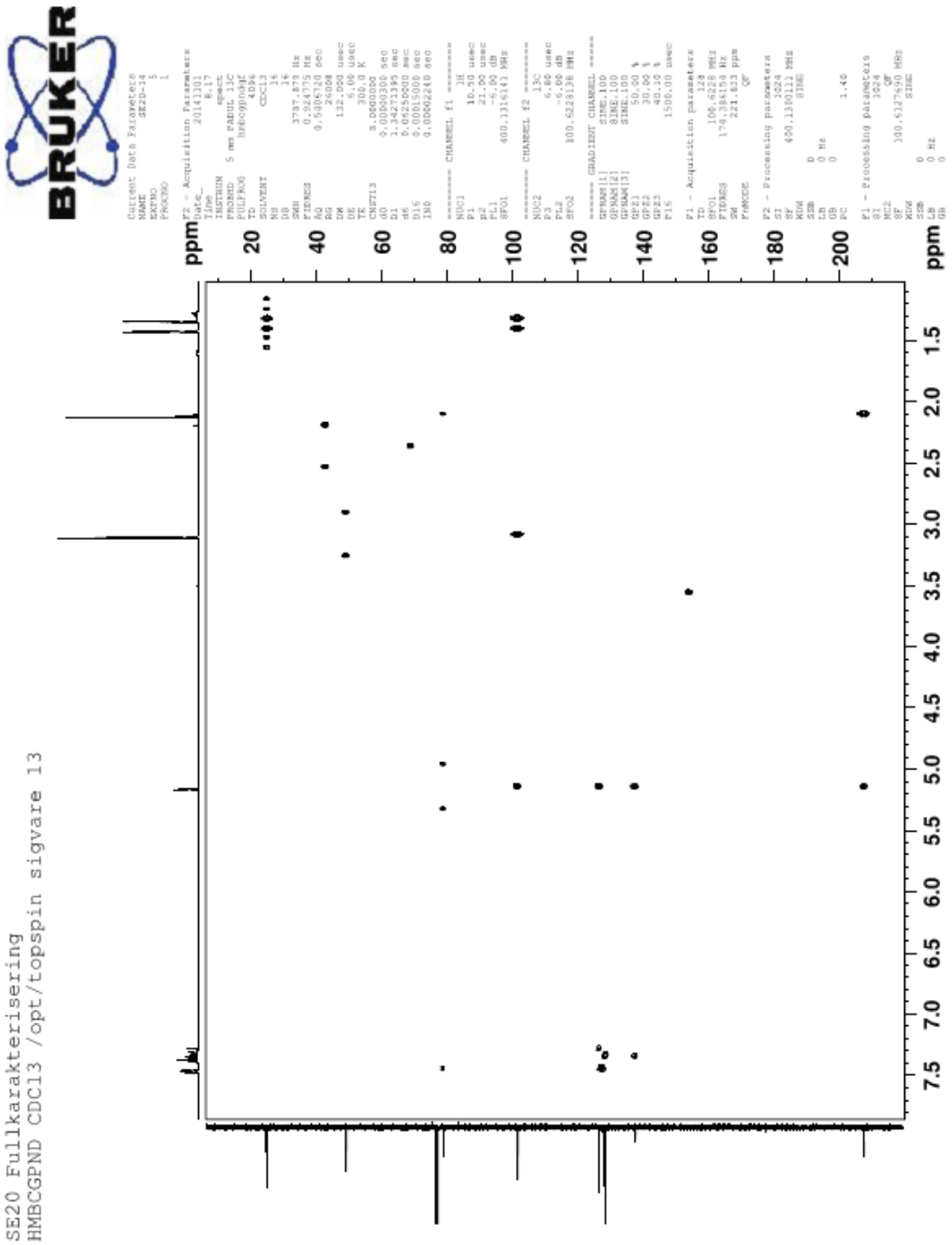
Appendix N.4 HSQC spectrum of ketone 7a





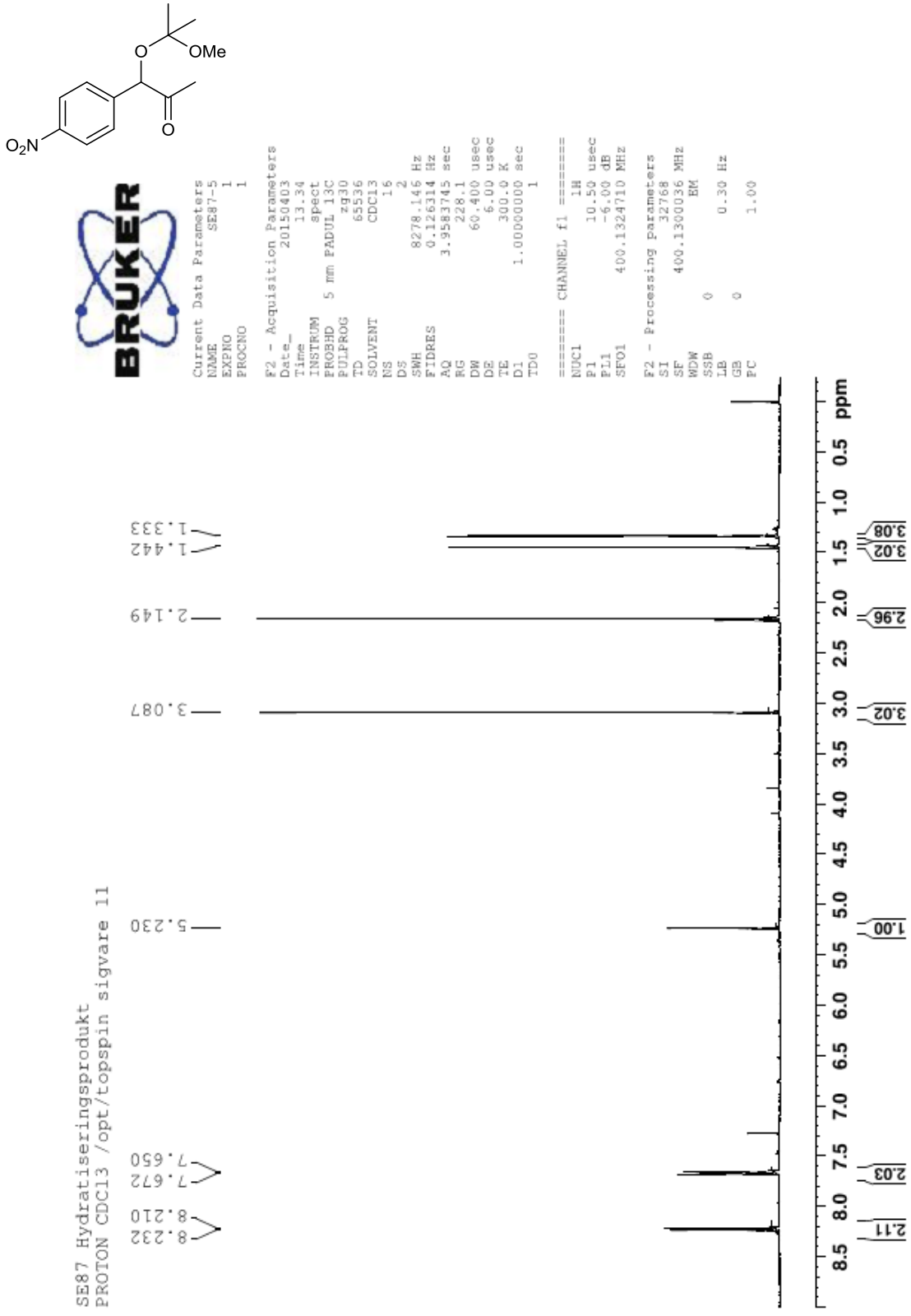
Appendix N.5 HMBC spectrum of ketone 7a



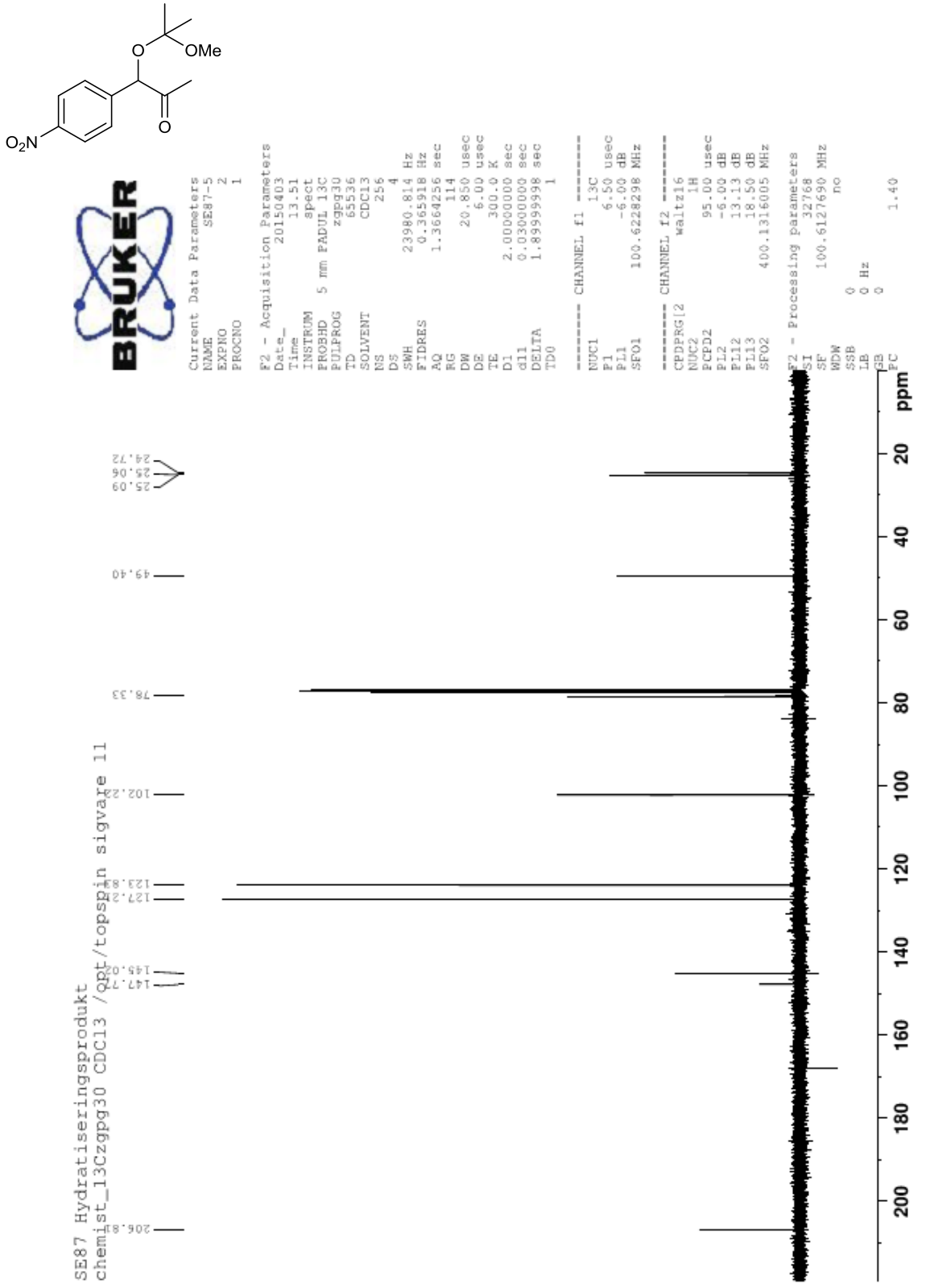


Appendix O Spectra of ketone 7c

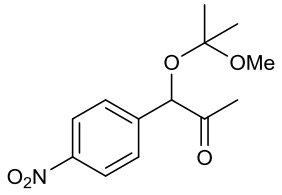
Appendix O.1 ^{1}H-NMR spectrum of ketone 7c

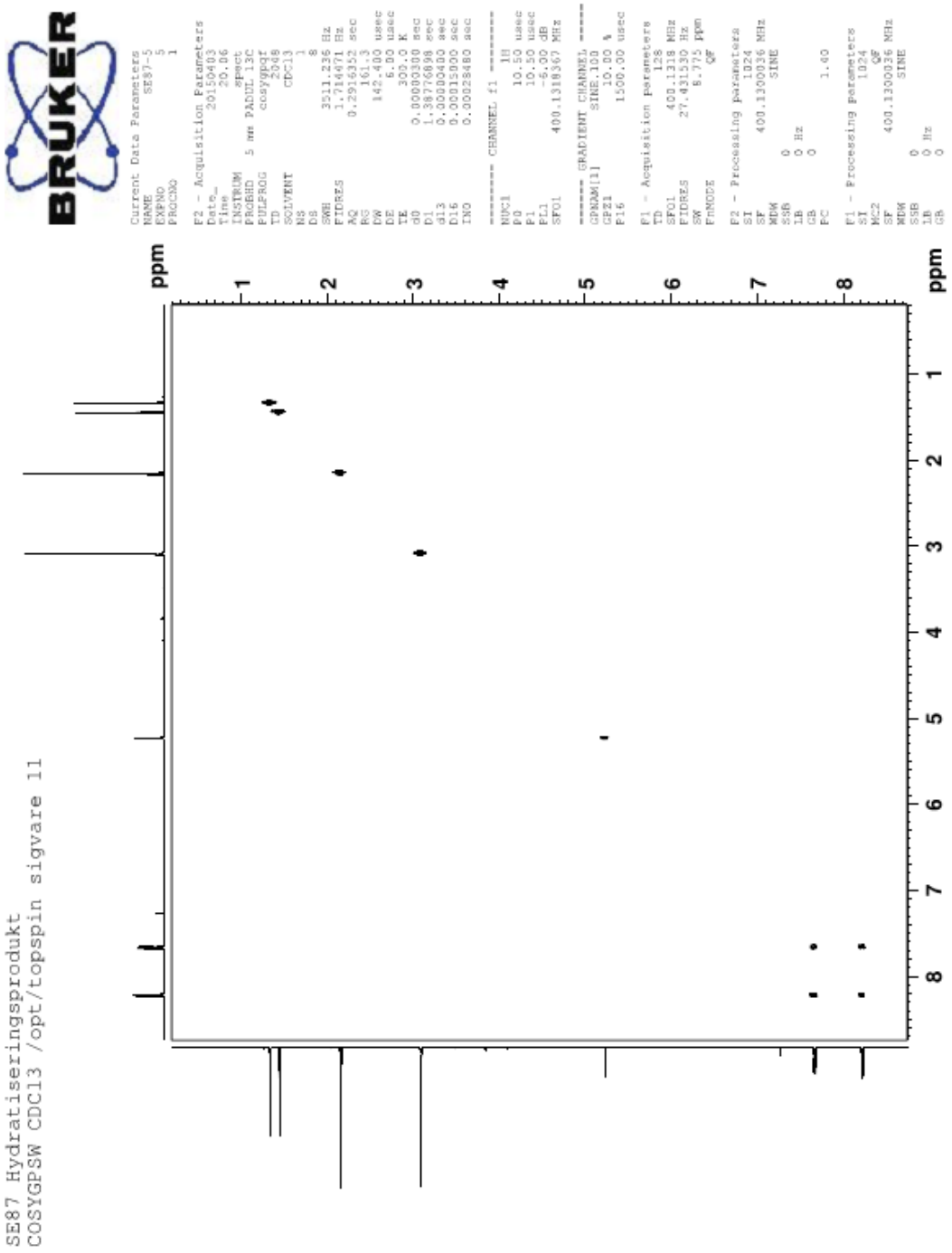


Appendix O.2 ^{13}C-NMR spectrum of ketone 7c

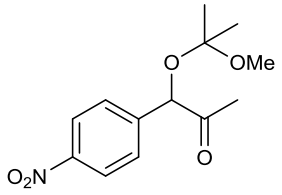


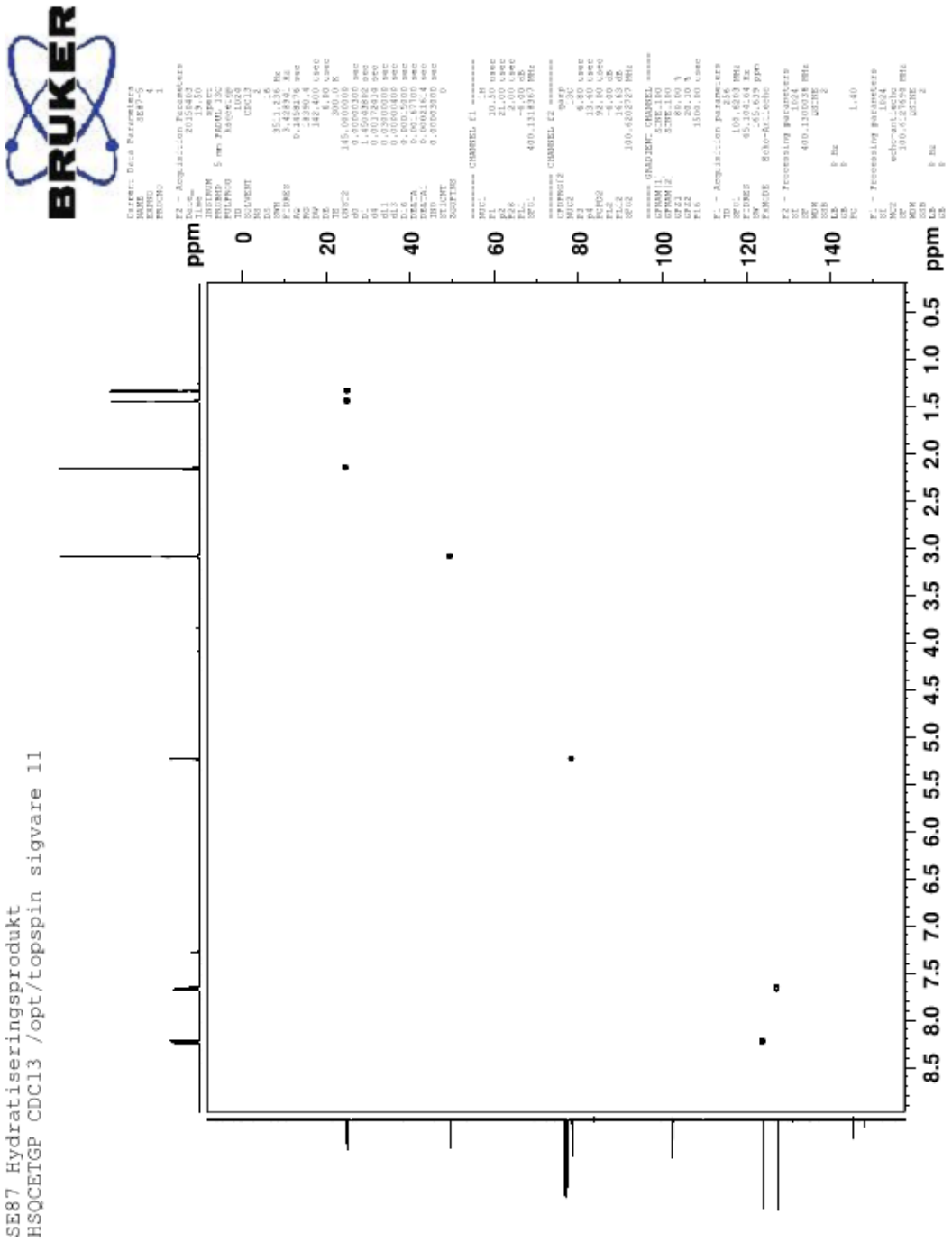
Appendix O.3 COSY spectrum of ketone 7c



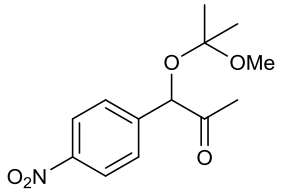


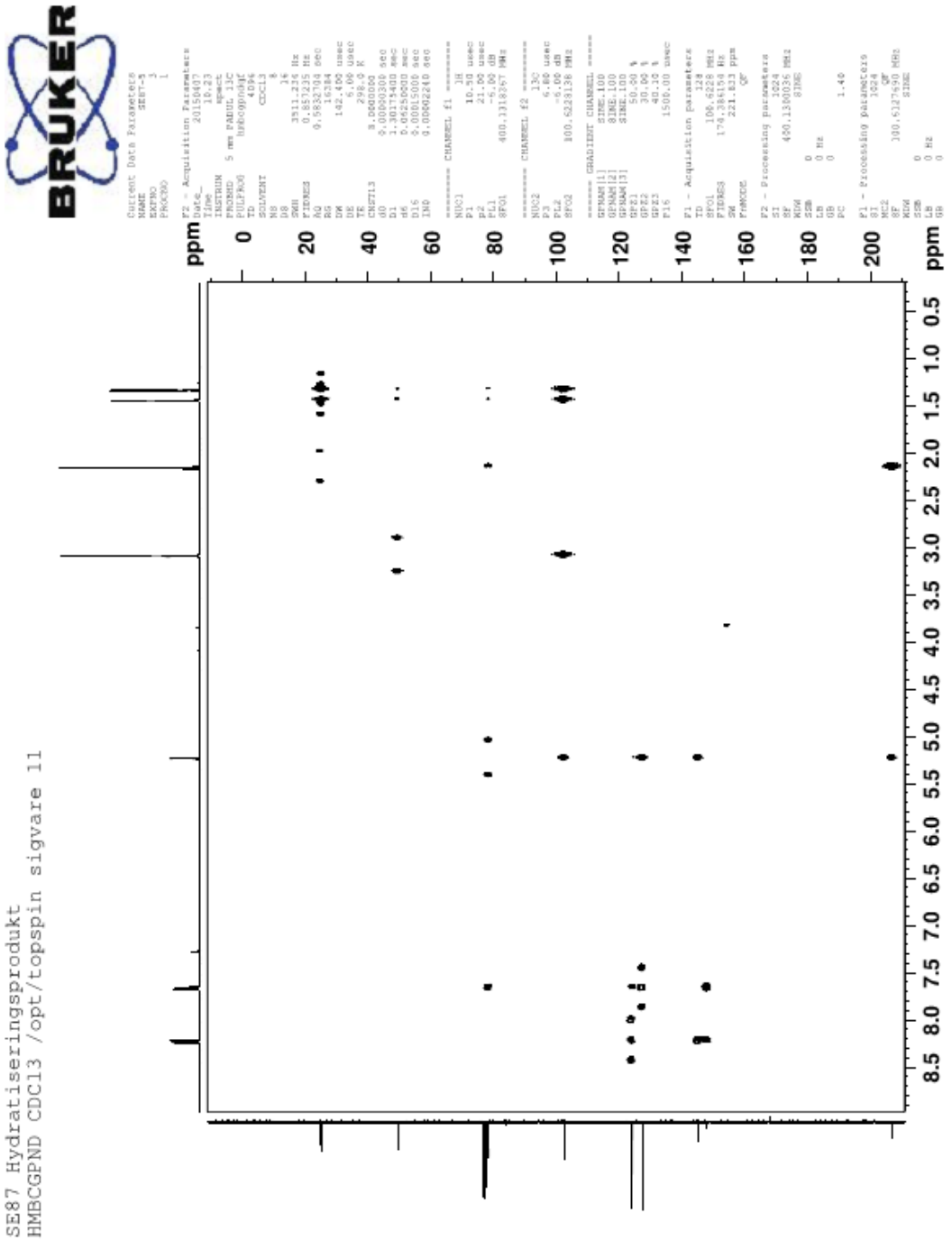
Appendix O.4 HSQC spectrum of ketone 7c





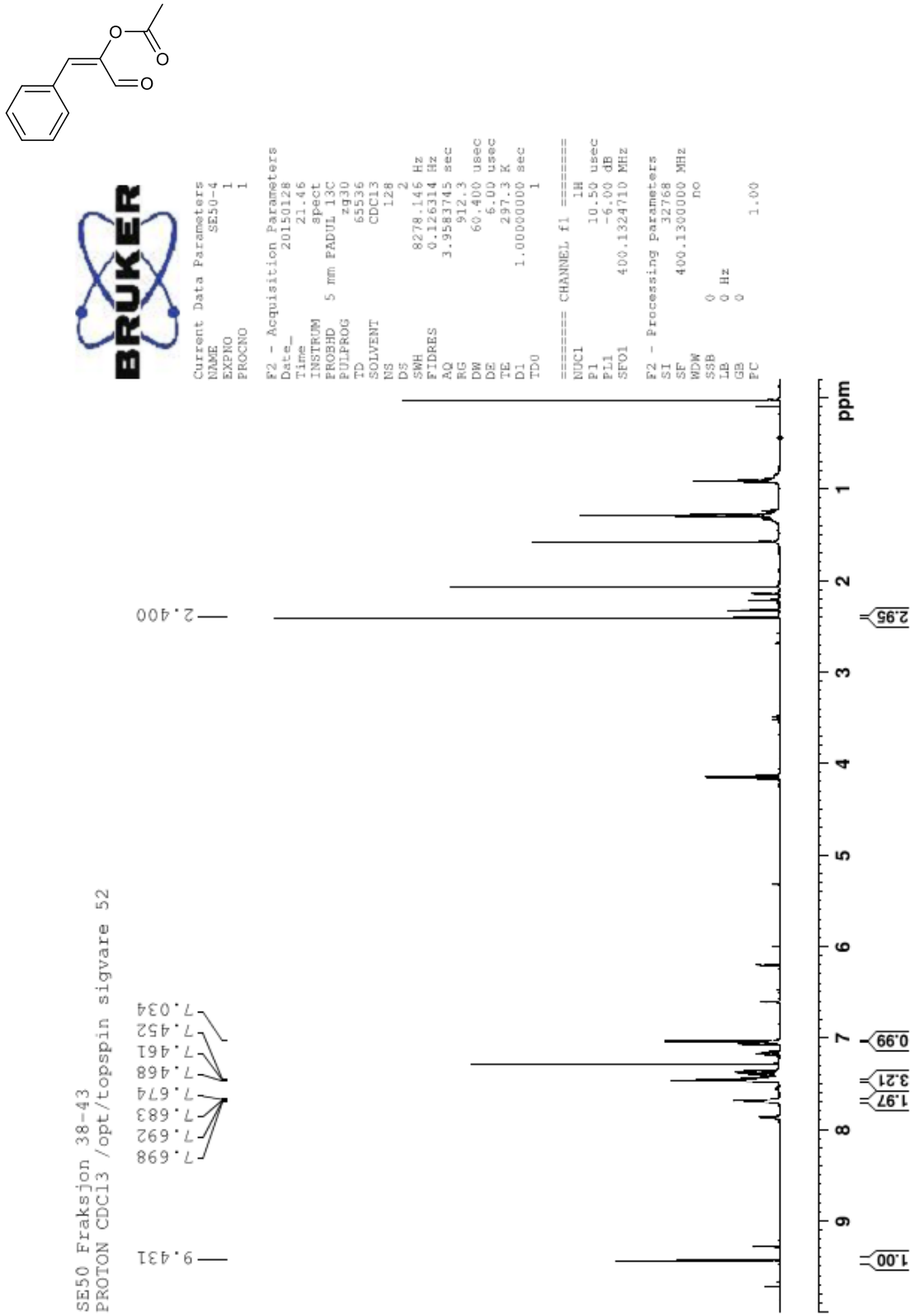
Appendix O.5 HMBC spectrum of ketone 7c



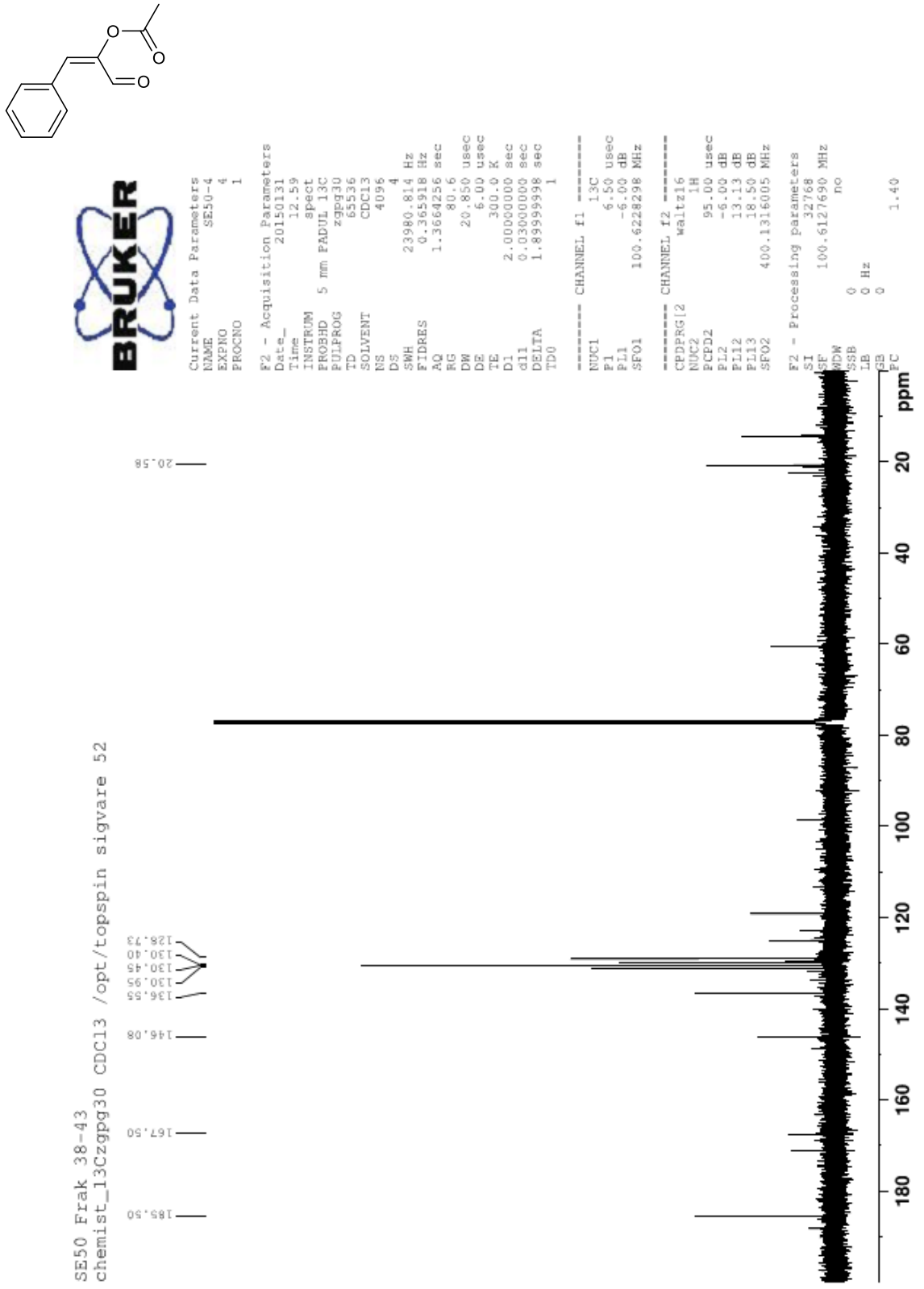


Appendix P Spectra of aldehyde 8

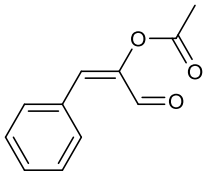
Appendix P.1 ^{1}H-NMR spectrum of aldehyde 8

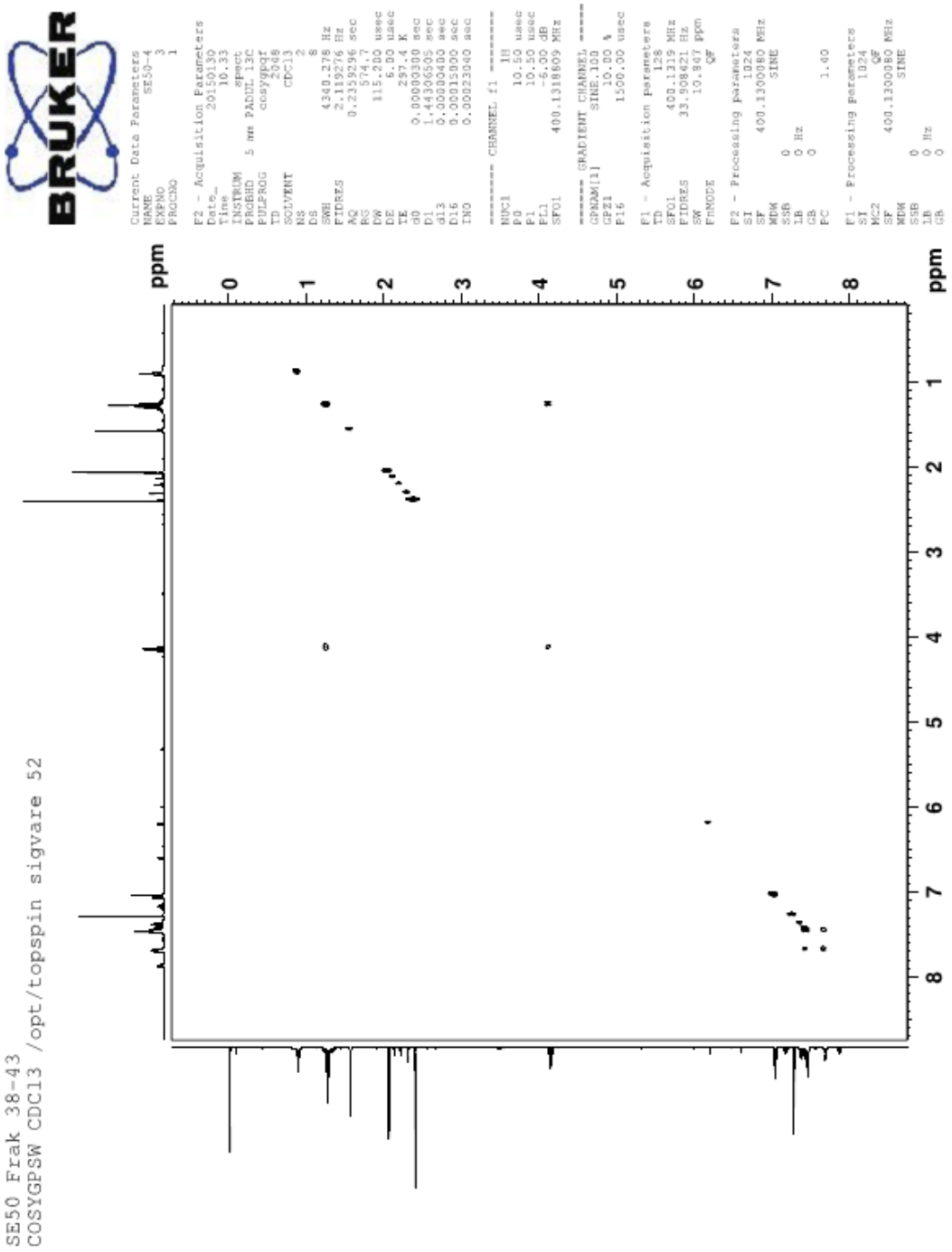


Appendix P.2 ^{13}C-NMR spectrum of aldehyde 8

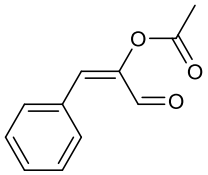


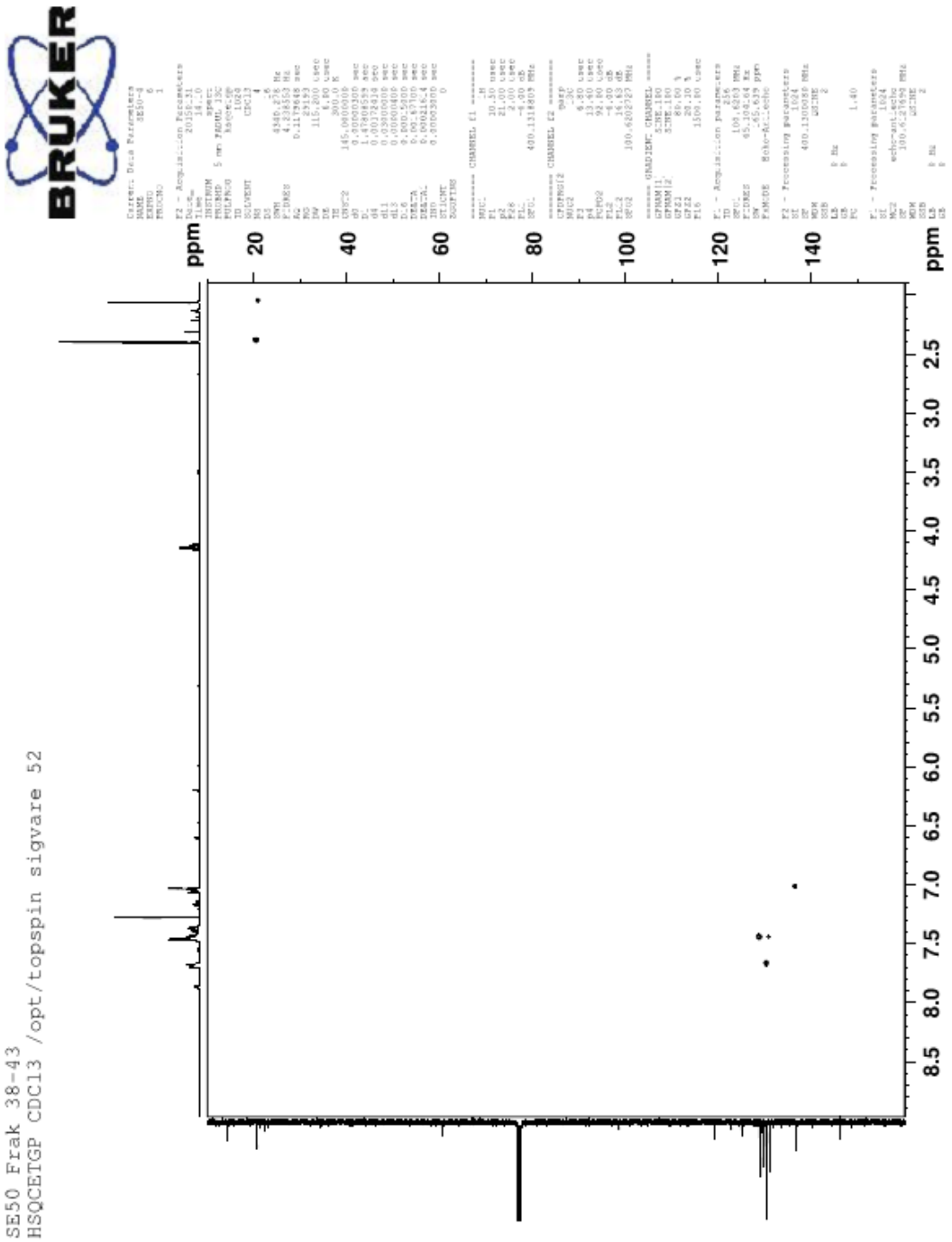
Appendix P.3 COSY spectrum of aldehyde 8



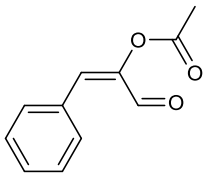


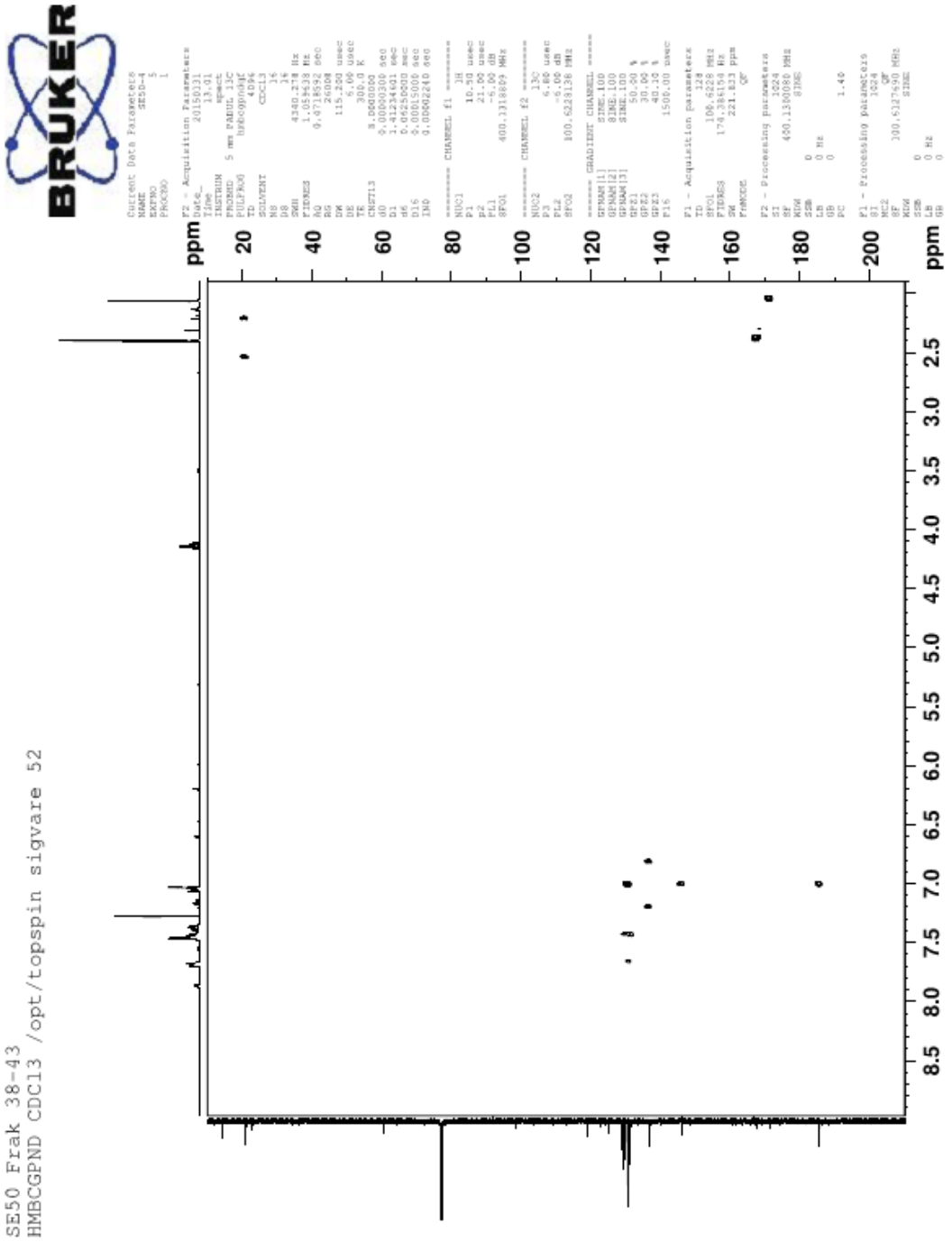
Appendix P.4 HSQC spectrum of aldehyde 8





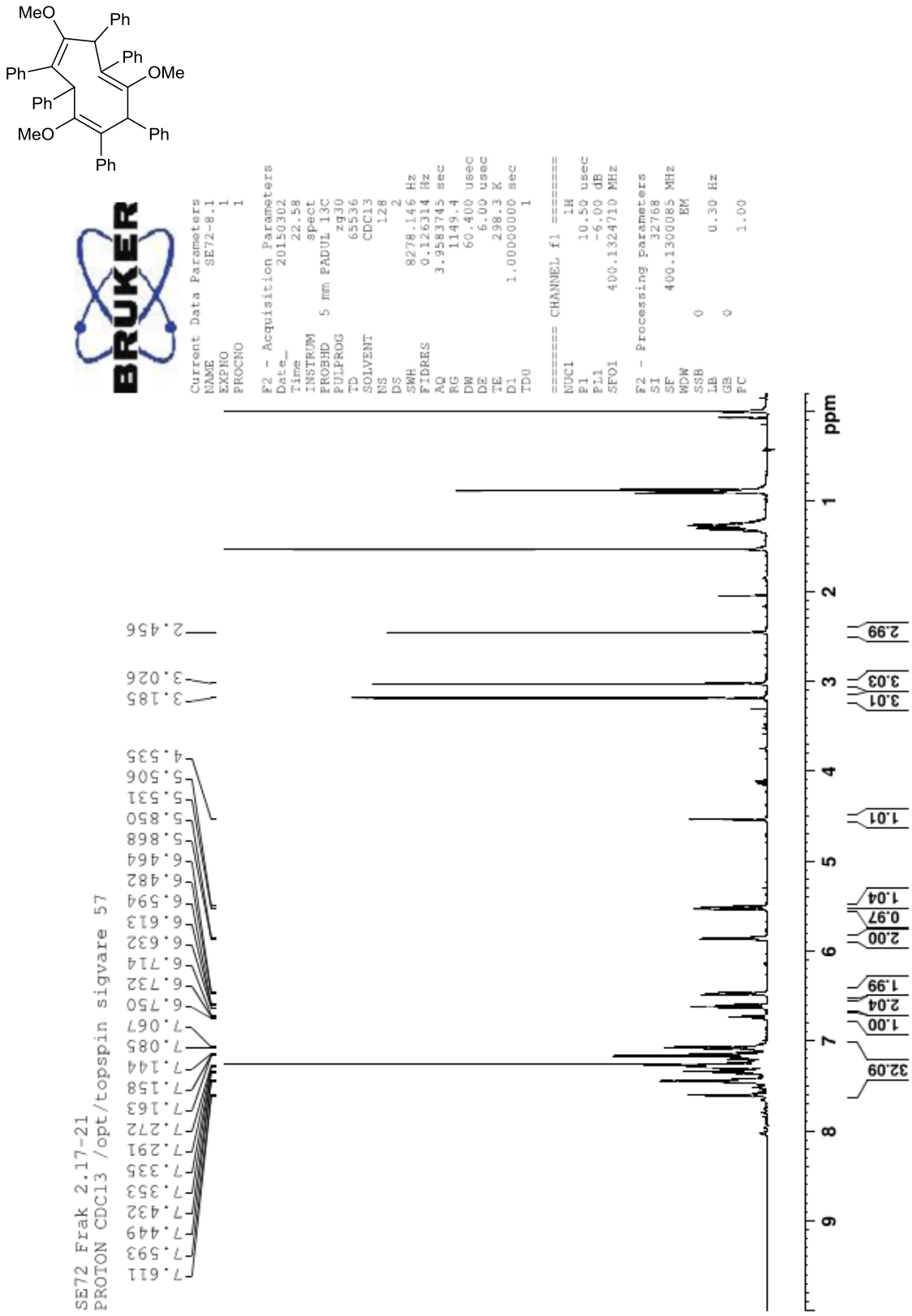
Appendix P.5 HMBC spectrum of aldehyde 8



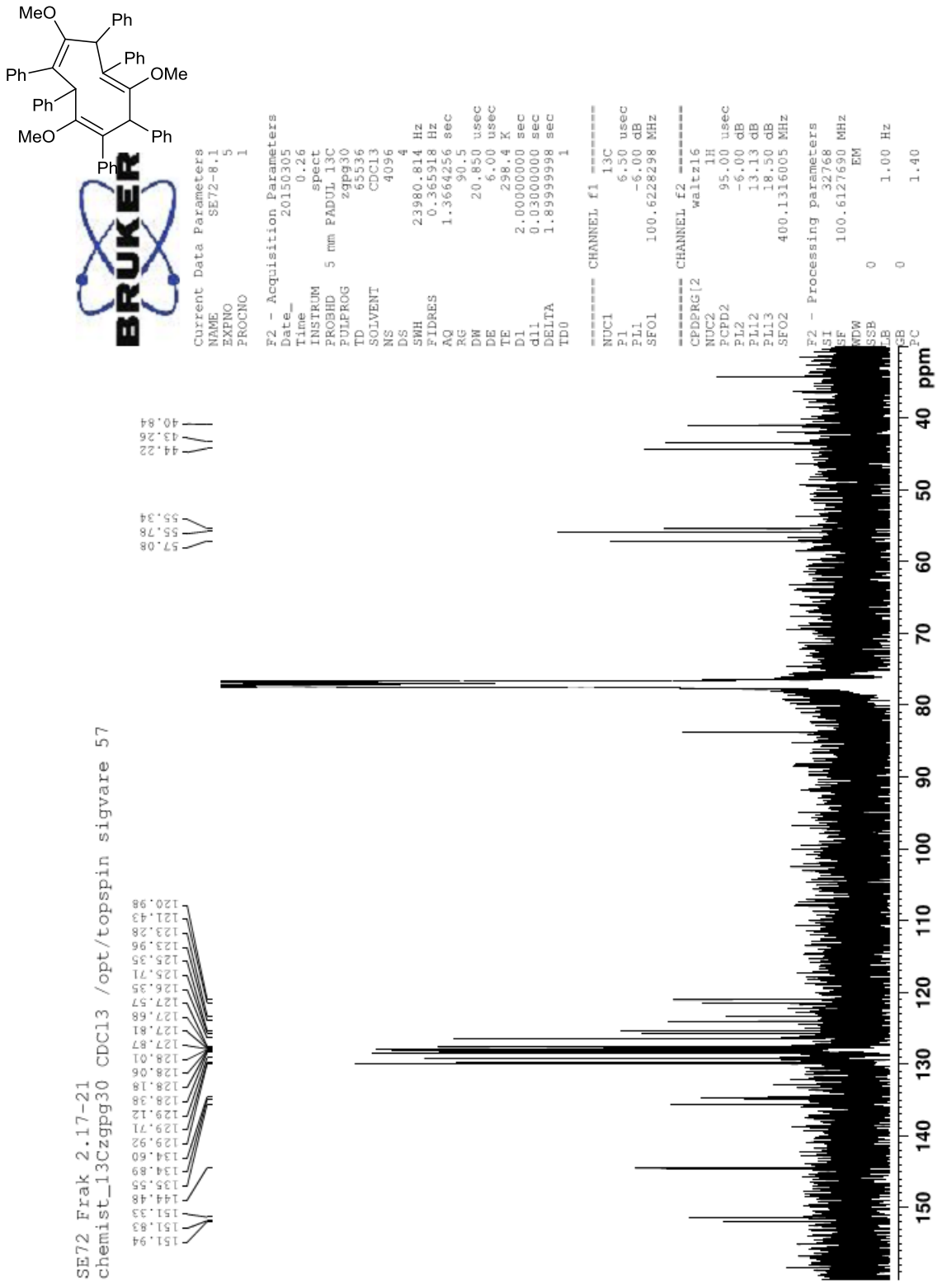


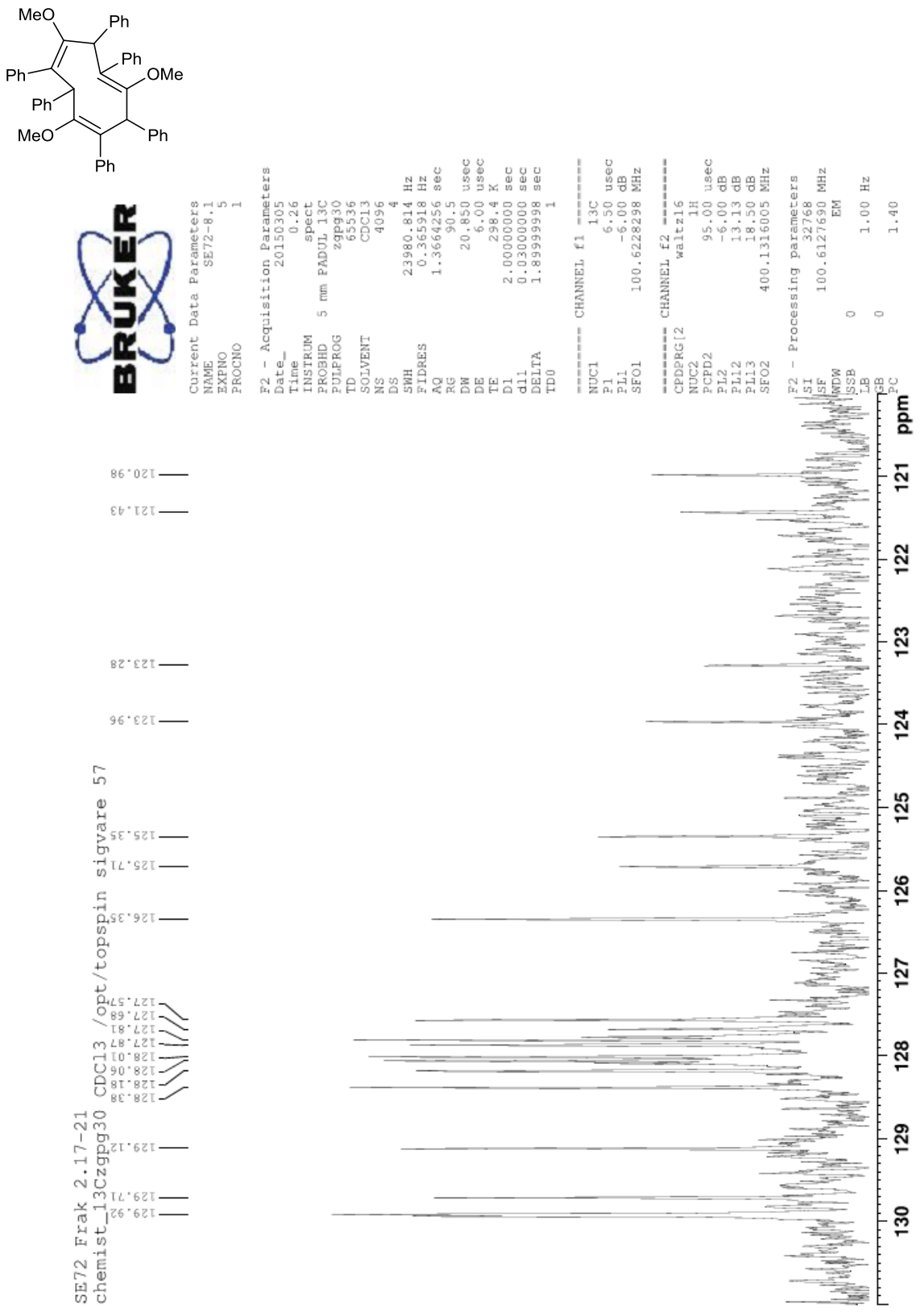
Appendix Q Spectra of trimers 9a-c

Appendix Q.1 ^{1}H-NMR spectrum of trimer 9a



Appendix Q.2 ^{13}C-NMR spectra of trimer 9a

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OMe
Ph
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Ph
Ph
BRUKER
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PROCNO 1
F2 - Acquisition Parameters
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Time 0.26
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NS 4096
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SWH 23980.814 Hz
FIDRES 0.365918 Hz
AQ 1.3664256 sec
RG 90.5
DW 20.850 usec
DE 6.00 usec
TE 298.4 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
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P1 6.50 usec
PL1 -6.00 dB
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 95.00 usec
PL2 -6.00 dB
PL12 13.13 dB
PL13 18.50 dB
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SSB 0
LB 1.00 Hz
GB 0
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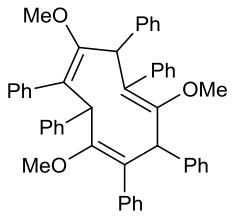
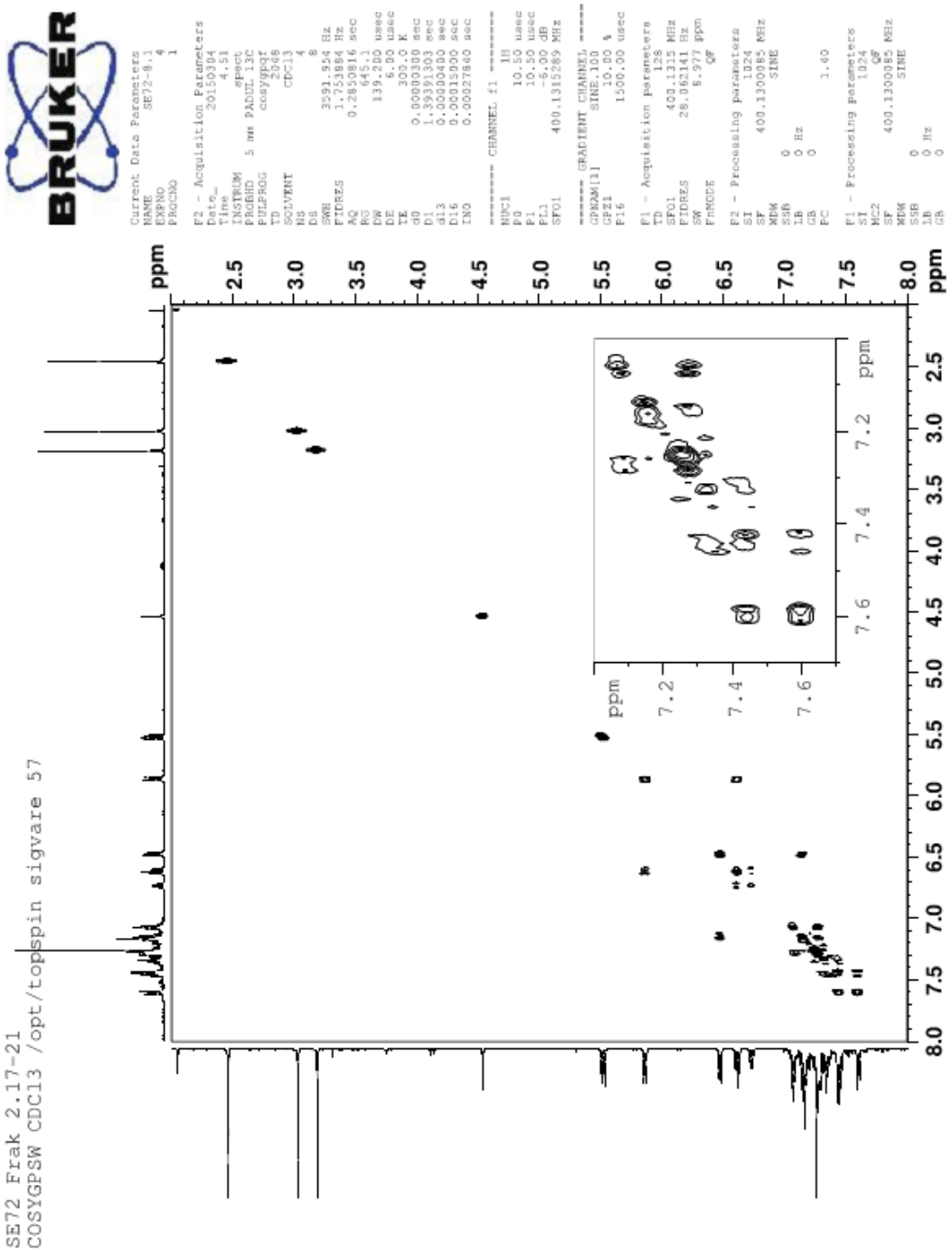
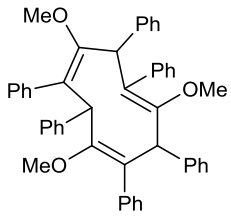
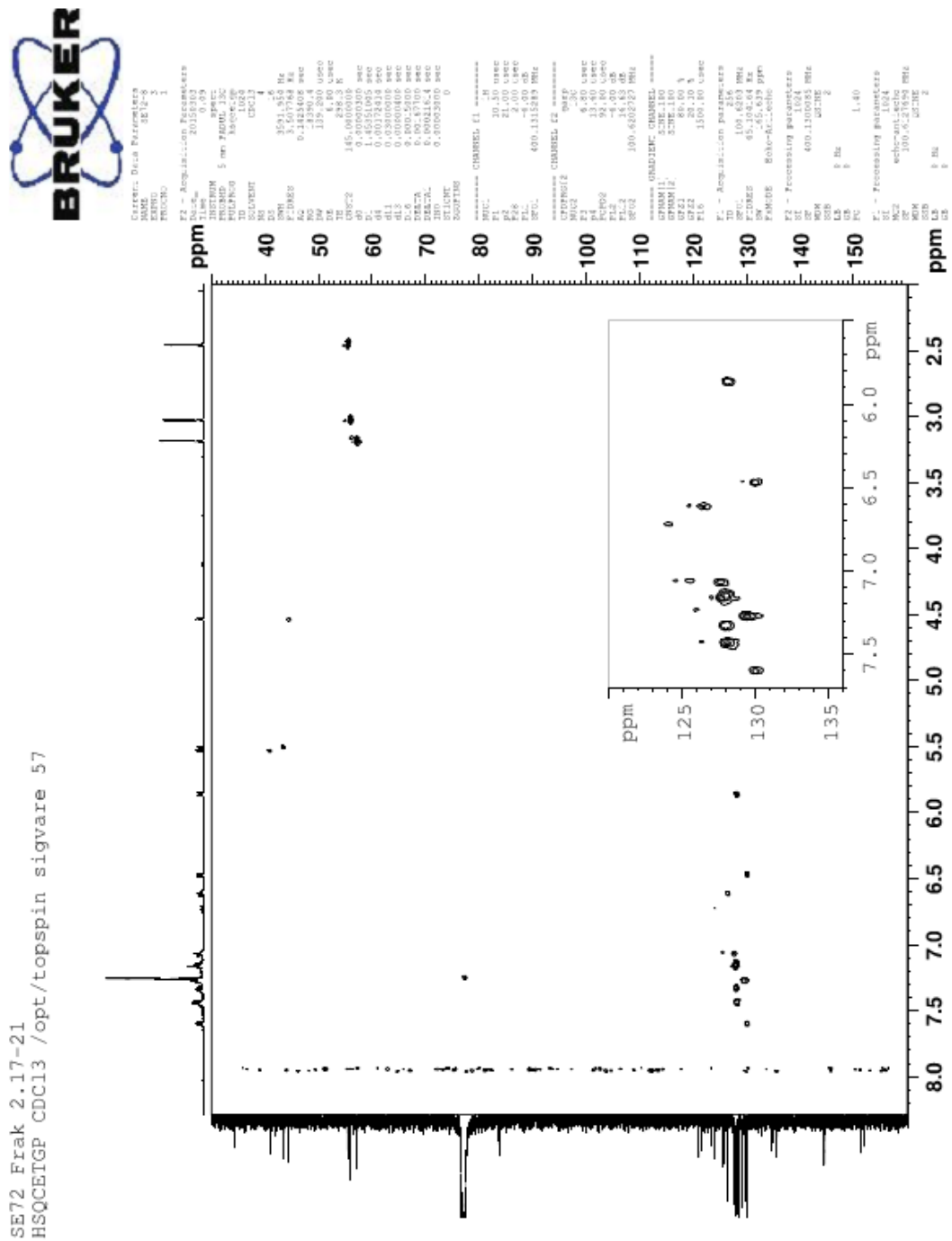
Appendix Q.3 COSY spectrum of trimer 9a



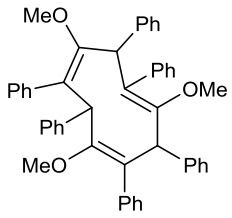


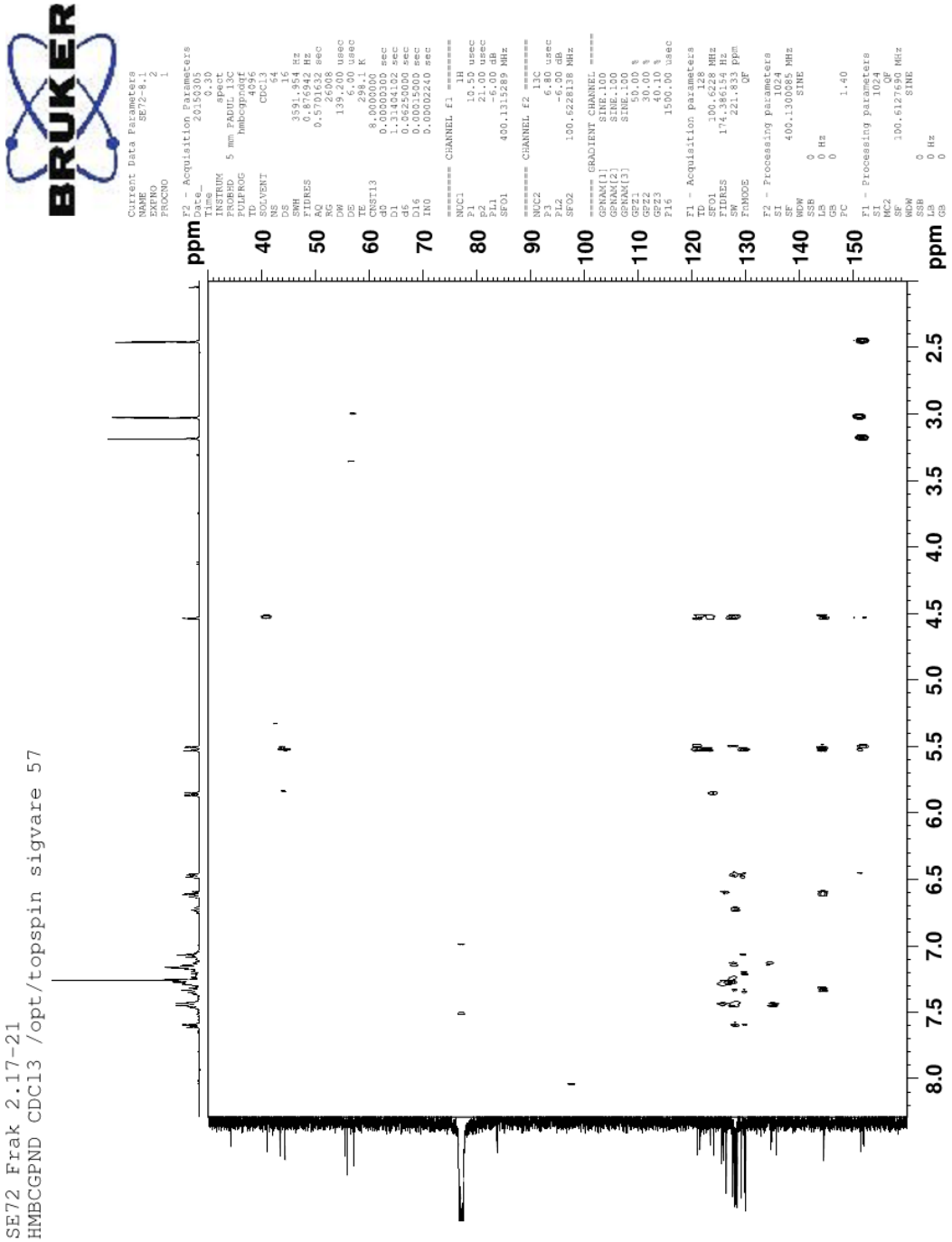
Appendix Q.4 HSQC spectrum of trimer 9a



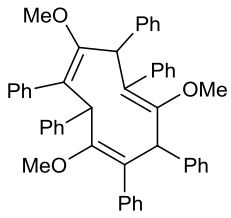


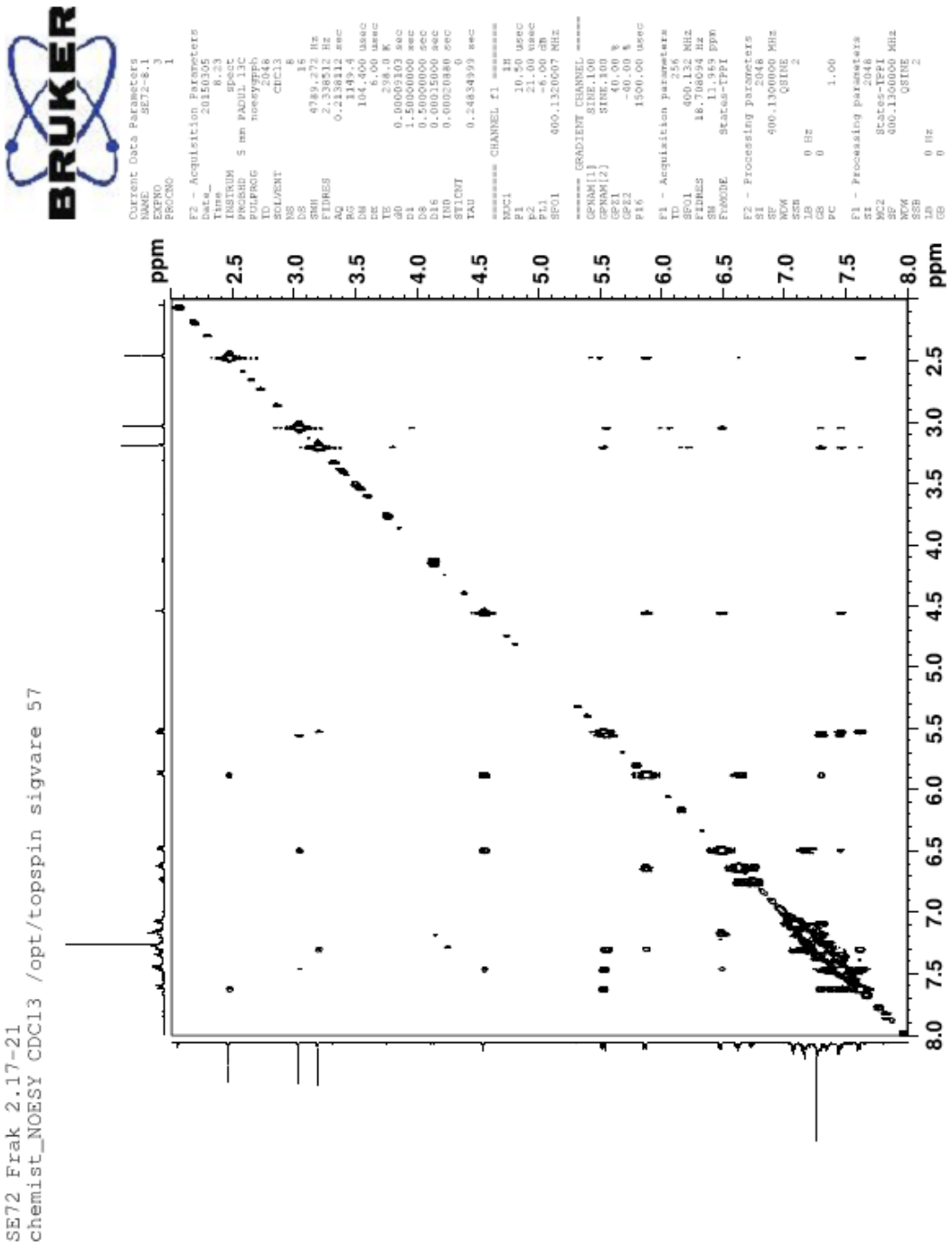
Appendix Q.5 HMBC spectrum of trimer 9a



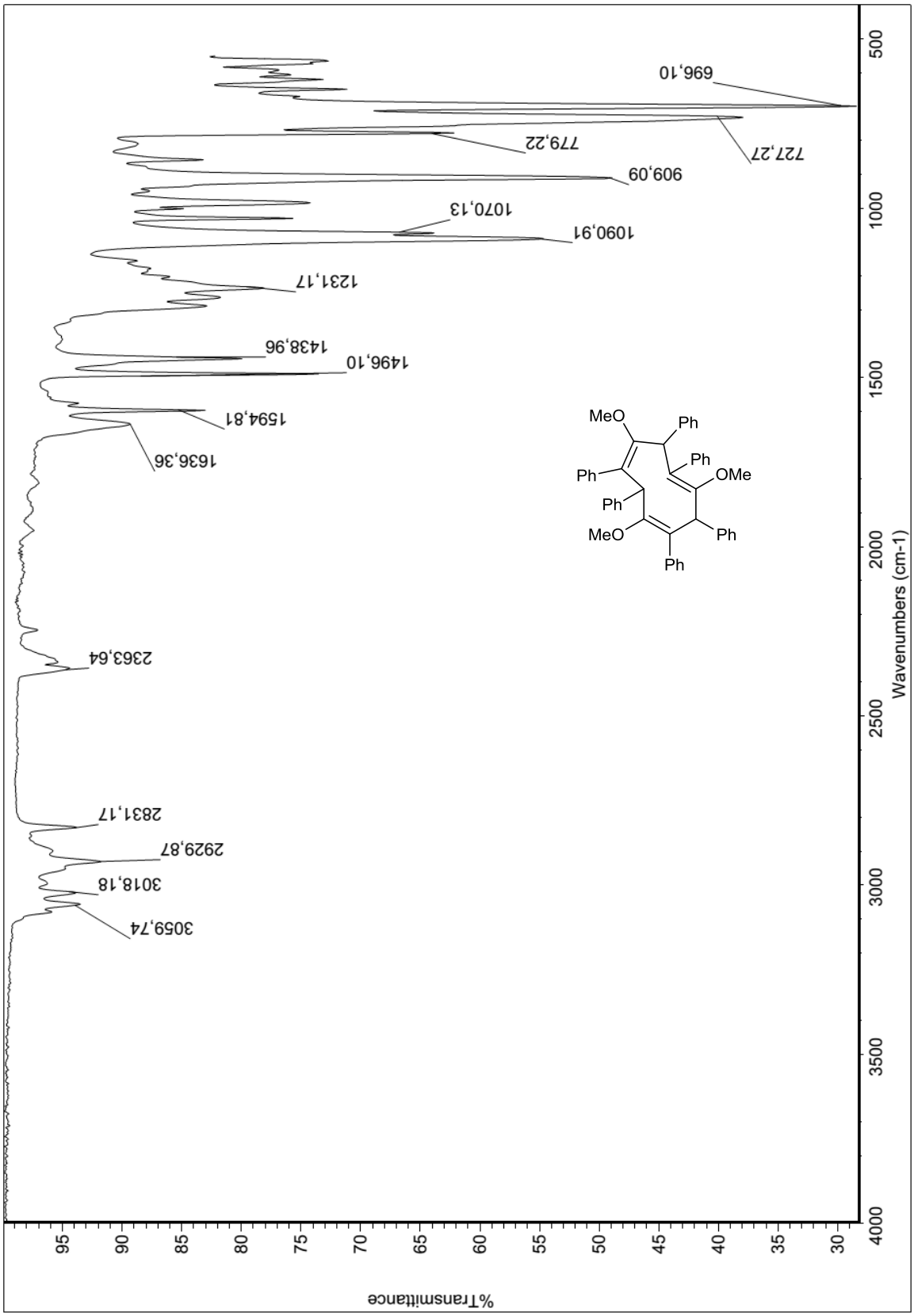


Appendix Q.6 NOESY spectrum of trimer 9a





Appendix Q.7 IR spectrum of trimer 9a



Appendix Q.8 MS spectrum of trimer 9a

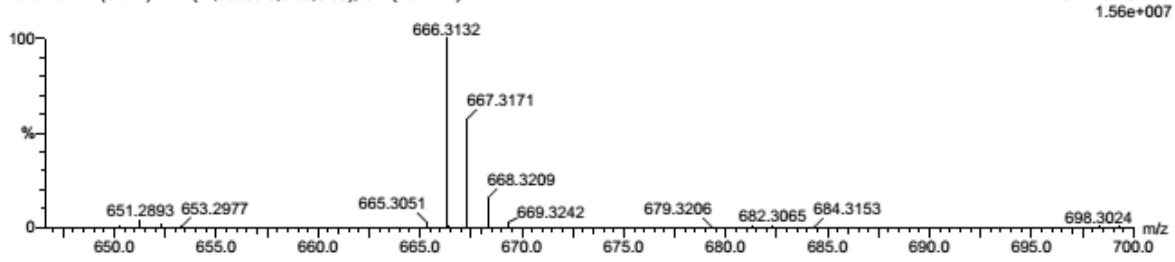
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 3.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd Electron Ions
206 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-500 H: 0-1000 O: 0-100

NT-MSLAB-Operator-SVG
2015-40 274 (5.342) AM2 (Ar,35000.0,0.00,0.00); Cm (257:274)

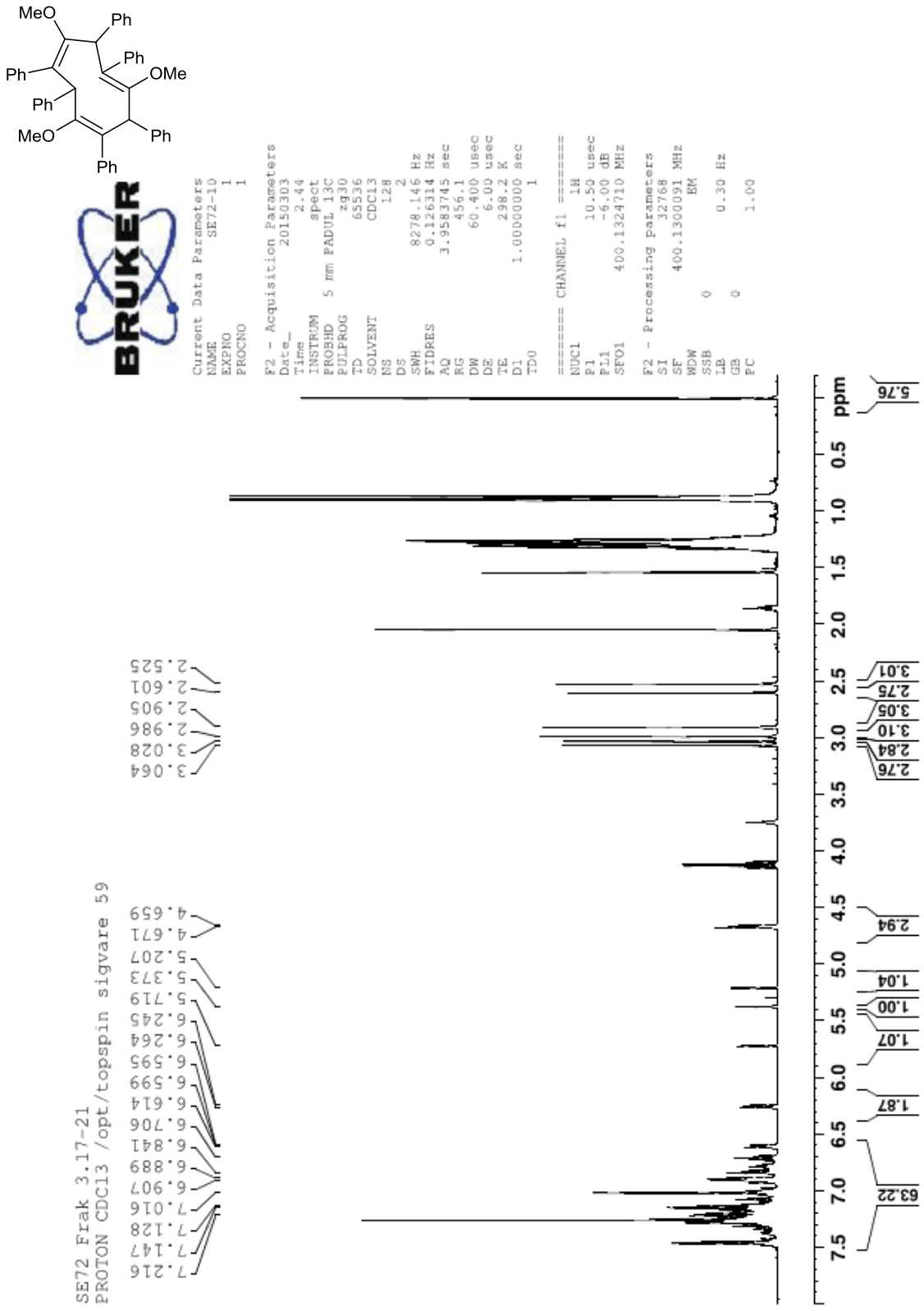
1: TOF MS ASAP+
1.56e+007



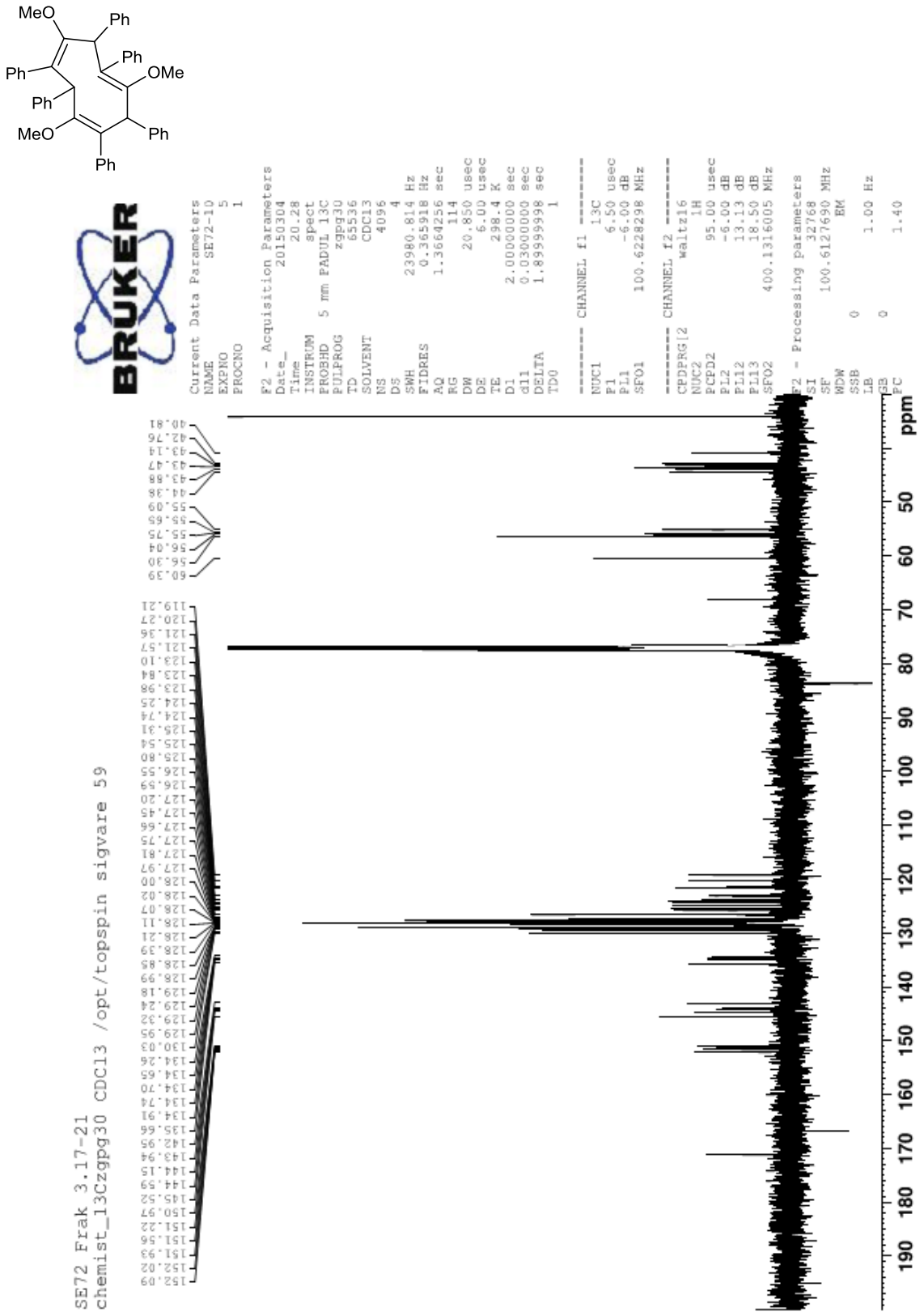
Minimum:				-1.5				
Maximum:		5.0	3.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
666.3132	666.3134	-0.2	-0.3	28.0	315.9	n/a	n/a	C48 H42 O3

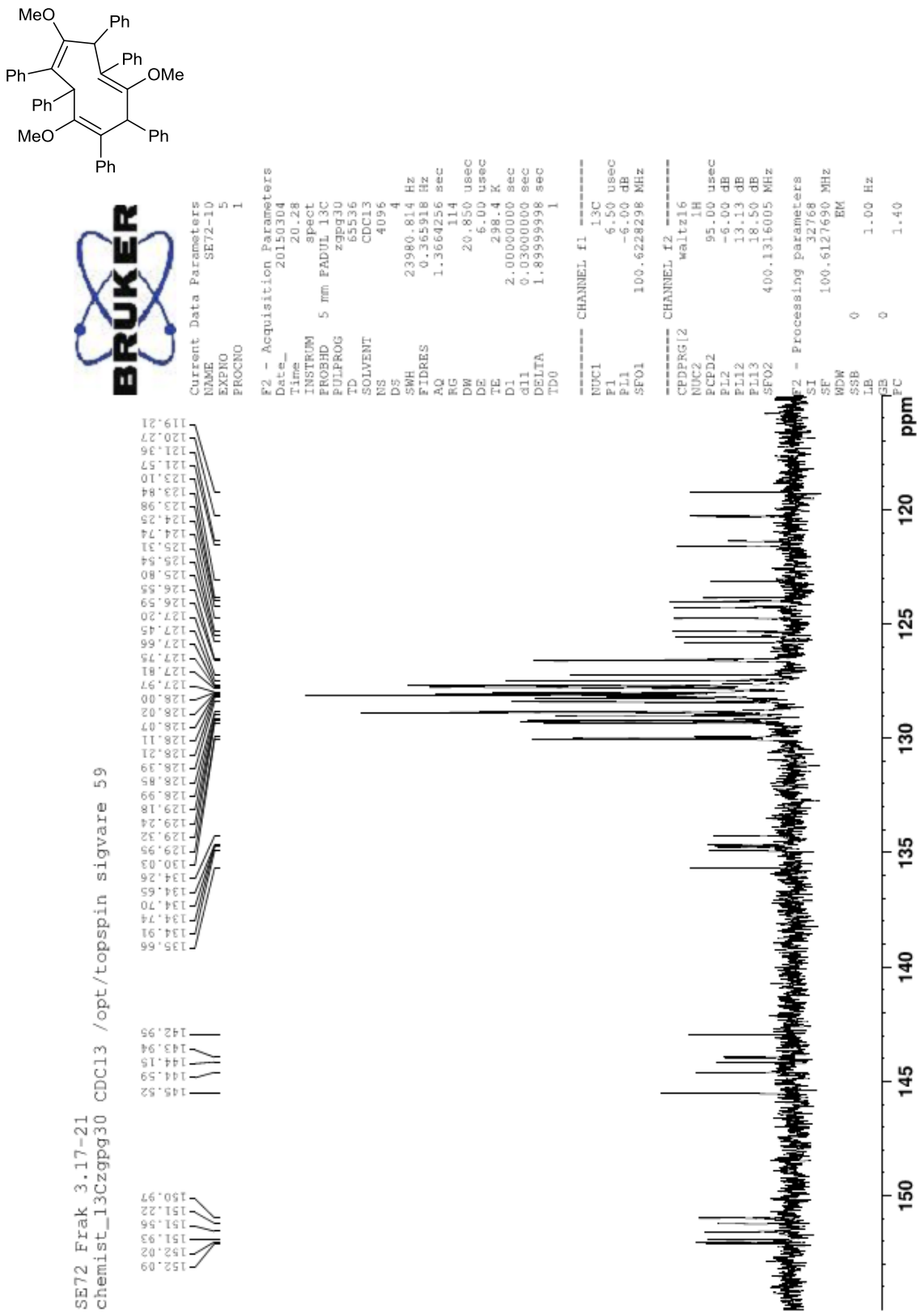
Ion observed [M]*+

Appendix Q.9 ^{1}H-NMR spectrum of trimers 9b-c

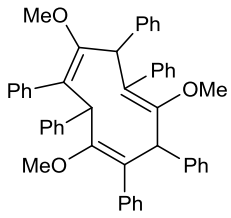


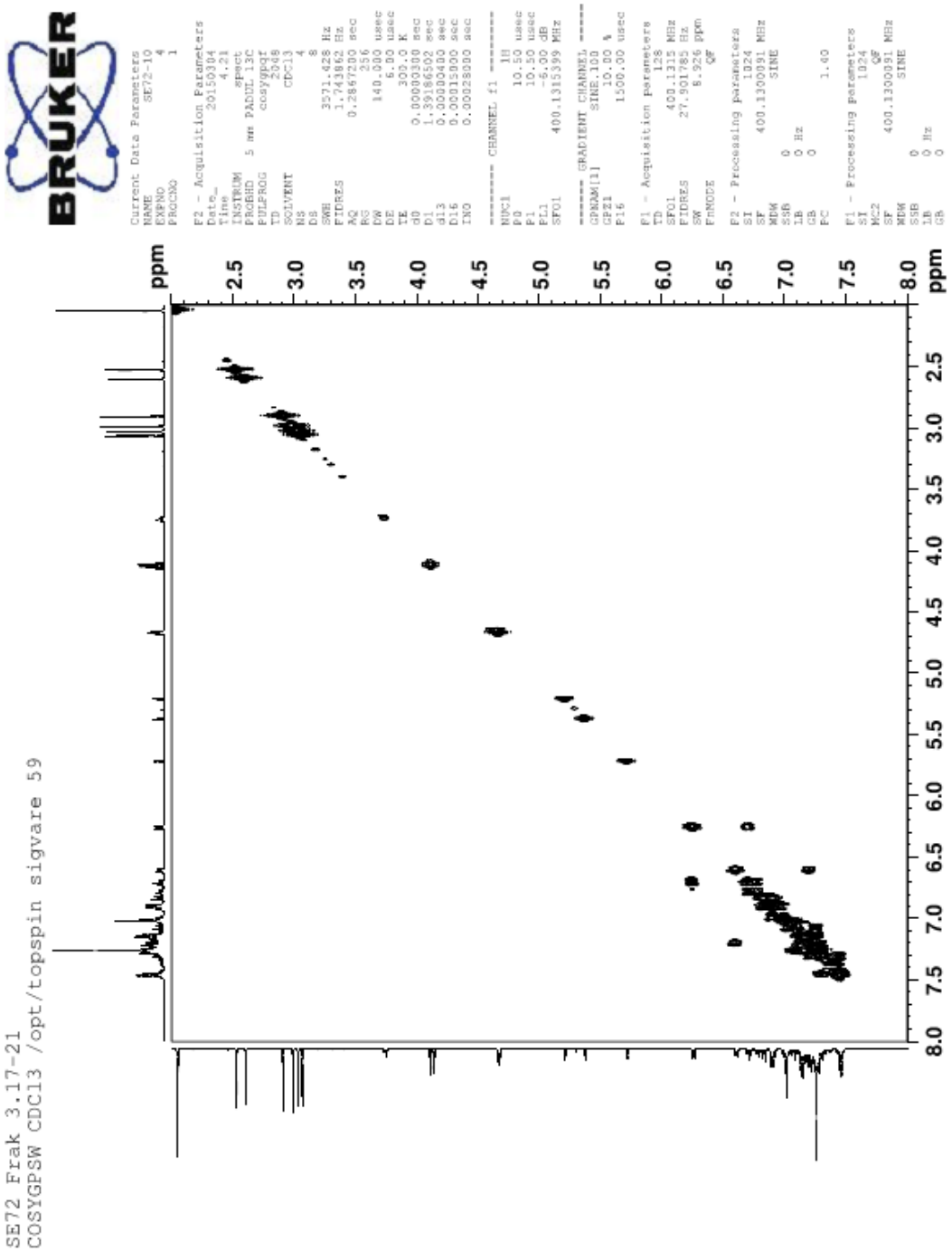
Appendix Q.10 ^{13}C-NMR spectra of trimers 9b-c



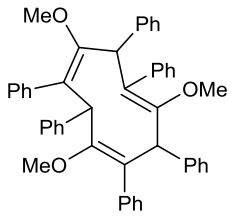

MeO
Ph
Ph
Ph
OMe
Ph
Ph
MeO
Ph
Ph
BRUKER
SE72 Frak 3.17-21
chemist_13Czgpg30 CDC13 /opt/topspin sigvare 59
Current Data Parameters
NAME SE72-10
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150304
Time 20.28
INSTRUM spect
PROBHD 5 mm PADUL 13C
PULPROG zgpg30
TD 65536
SOLVENT CDC13
NS 4096
DS 4
SWH 23980.814 Hz
FIDRES 0.365918 Hz
AQ 1.3664256 sec
RG 114
DW 20.850 usec
DE 6.00 usec
TE 298.4 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 6.50 usec
PL1 -6.00 dB
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 95.00 usec
PL2 -6.00 dB
PL12 13.13 dB
PL13 18.50 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
ppm

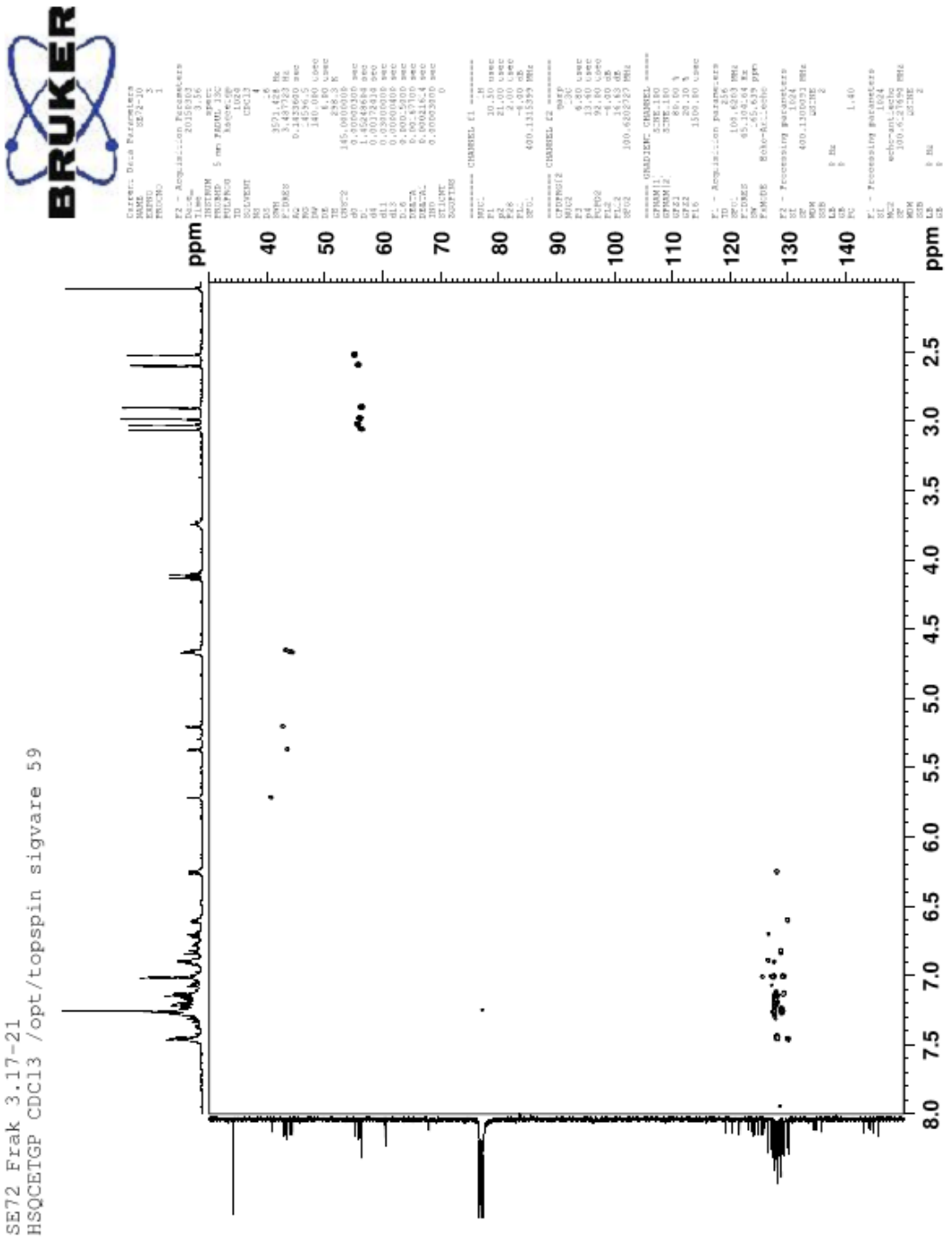
Appendix Q.11 COSY spectrum of trimers 9b-c



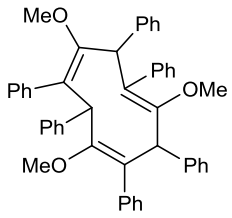


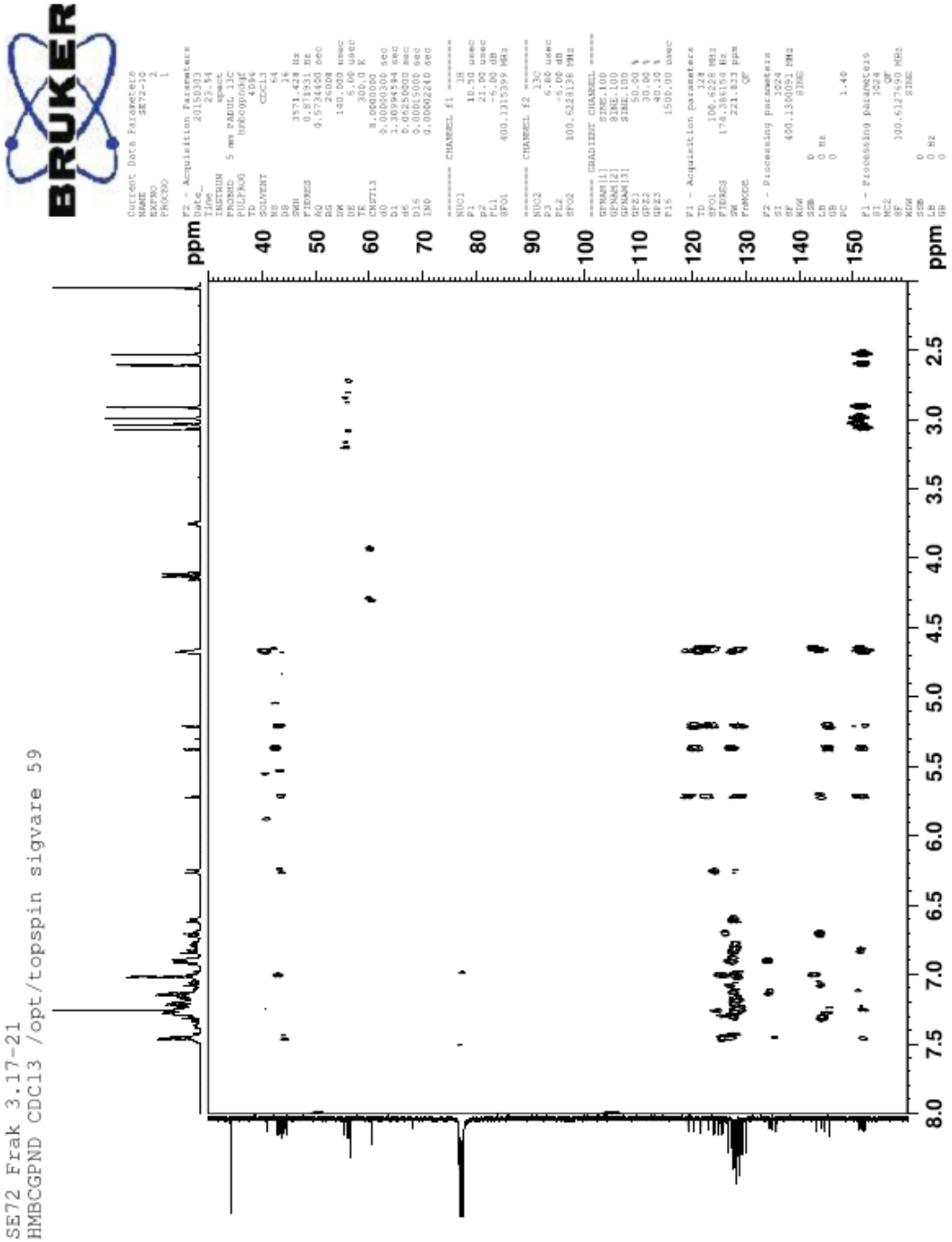
Appendix Q.12 HSQC spectrum of trimers 9b-c





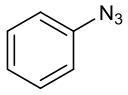
Appendix Q.13 HMBC spectrum of trimers 9b-c

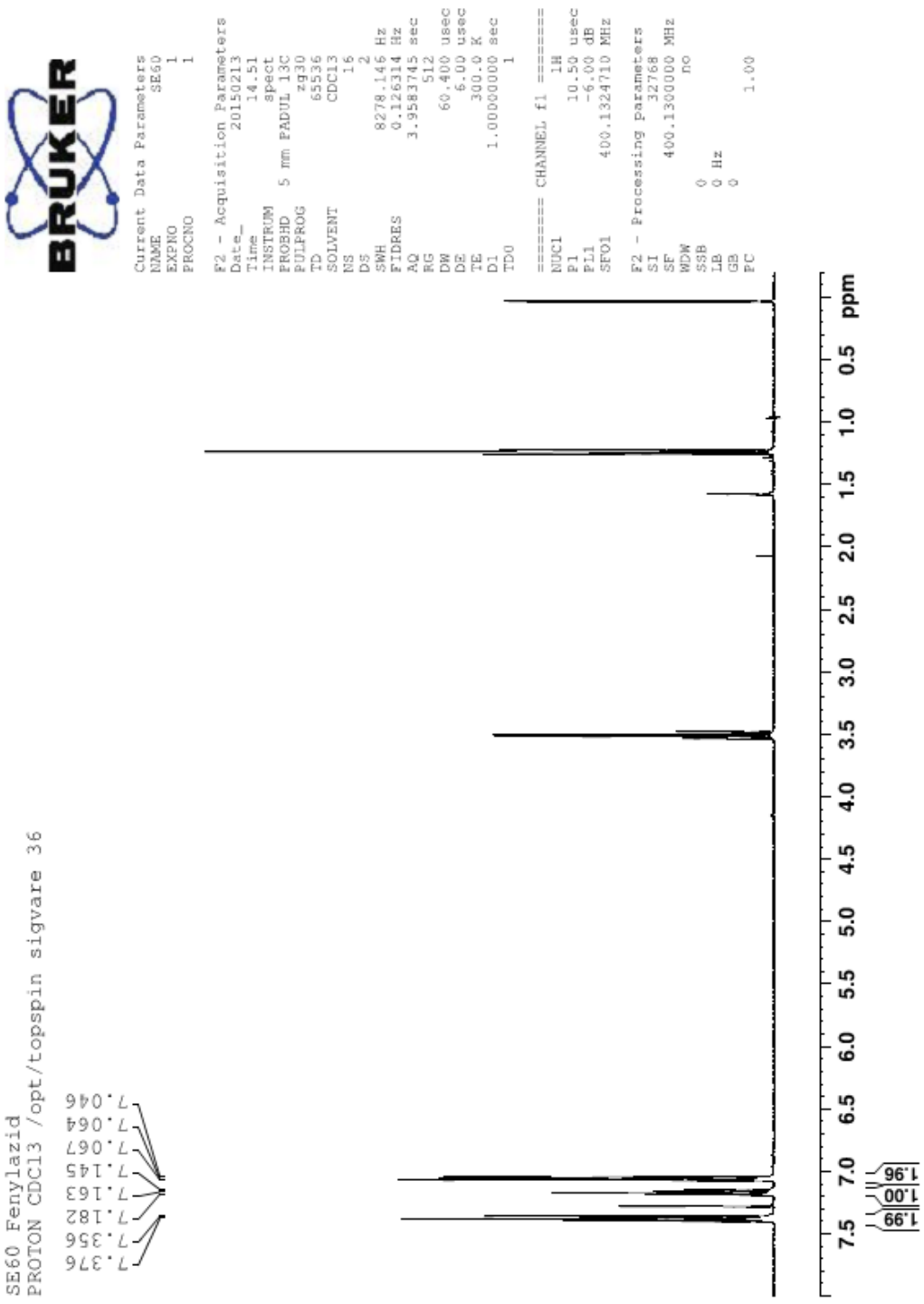




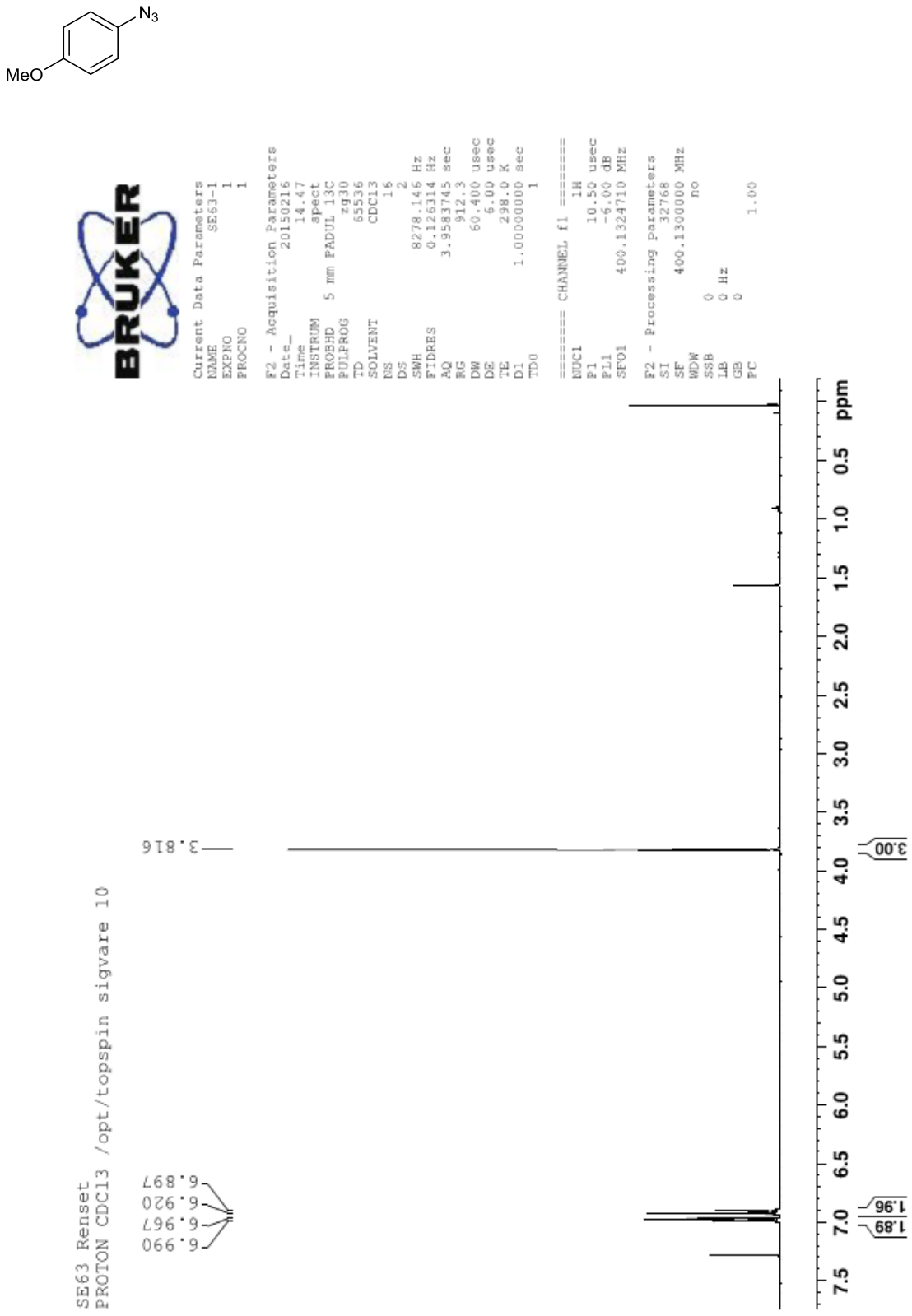
Appendix R Spectra of azides 10a-d

Appendix R.1 ^{1}H-NMR spectrum of azide 10a

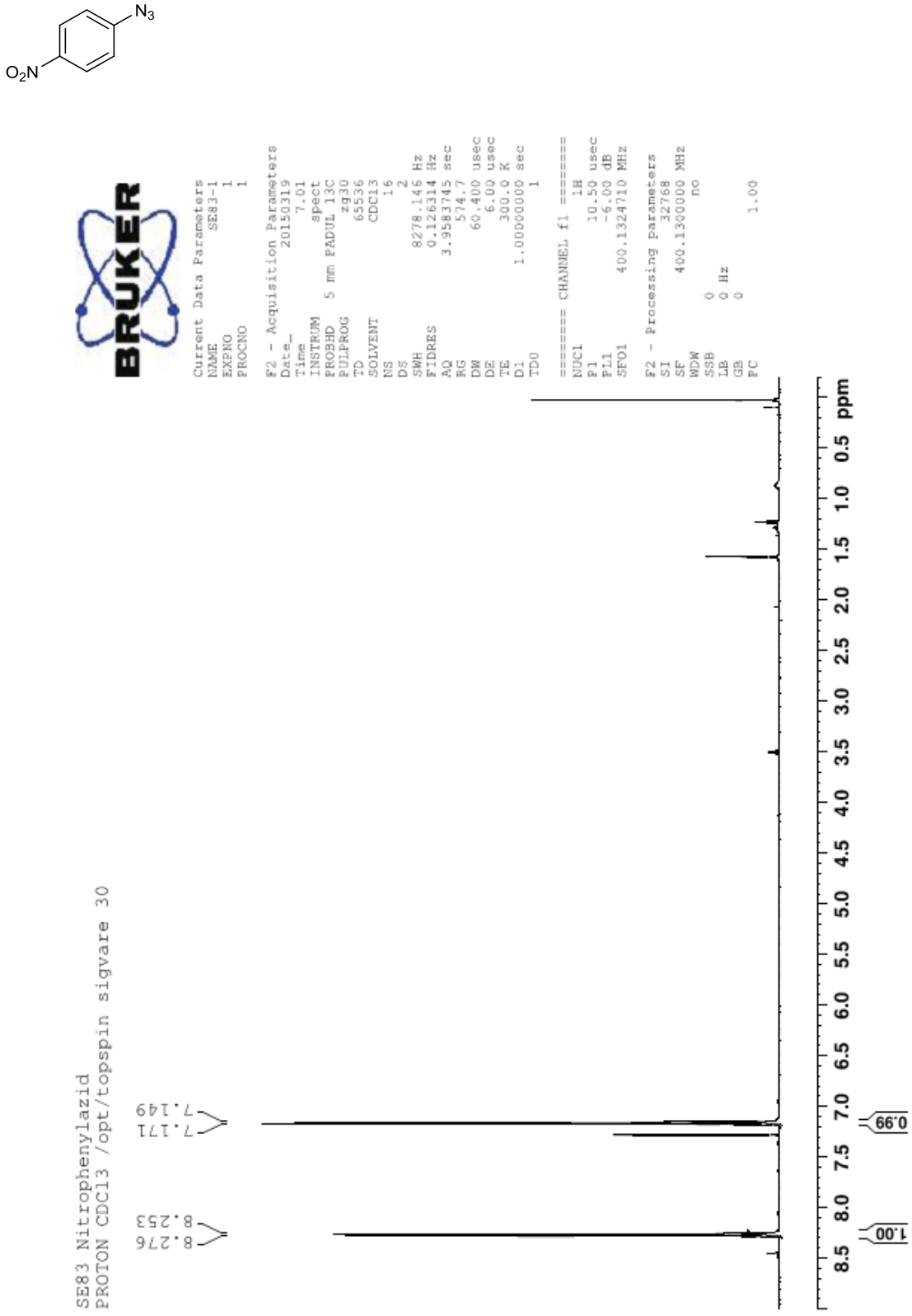




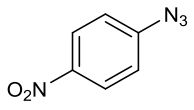
Appendix R.2 ^{1}H-NMR spectrum of azide 10b

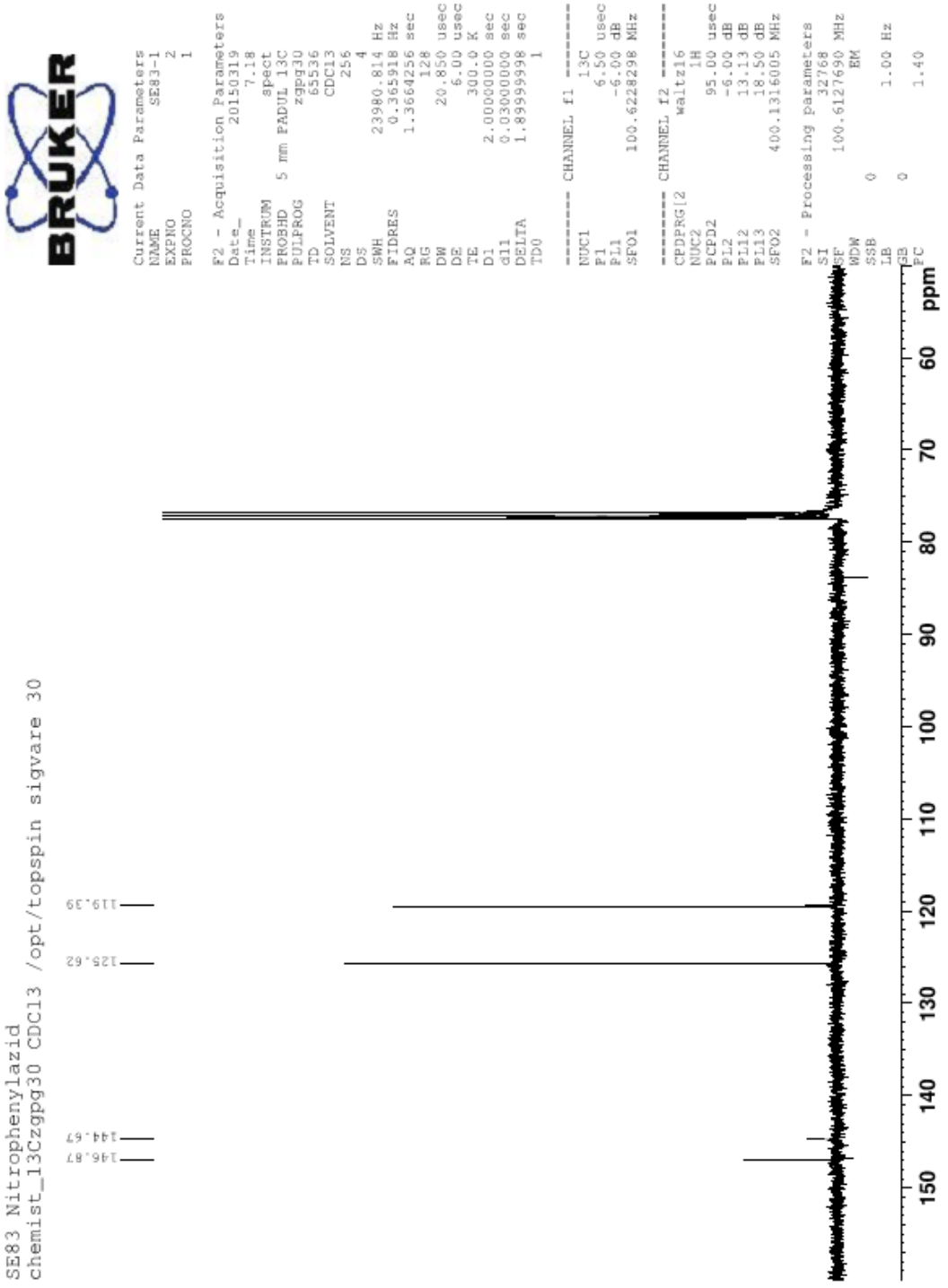


Appendix R.3 ^{1}H-NMR spectrum of azide 10c

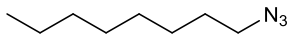


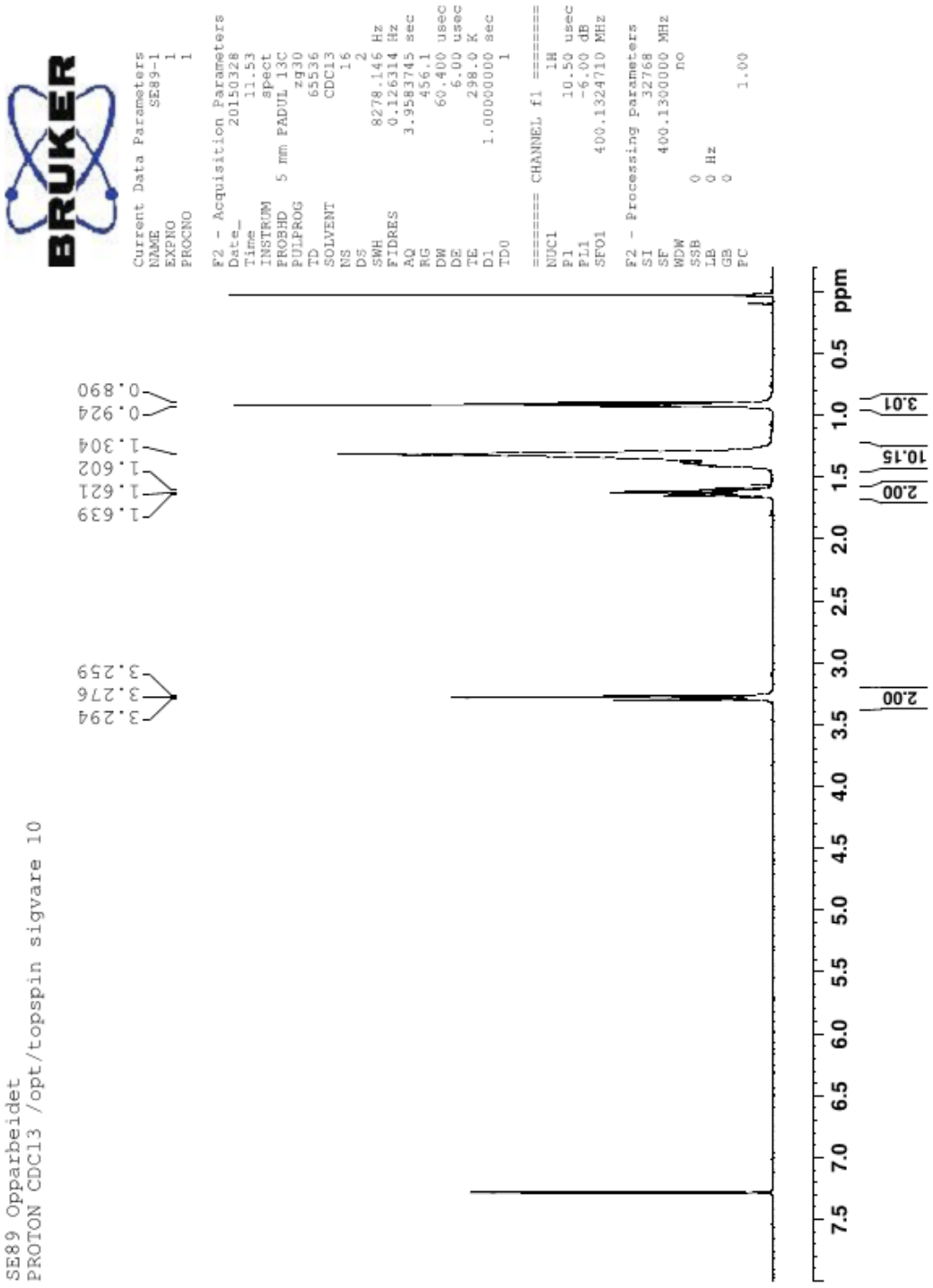
Appendix R.4 ^{13}C-NMR spectrum of azide 10c



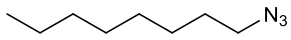


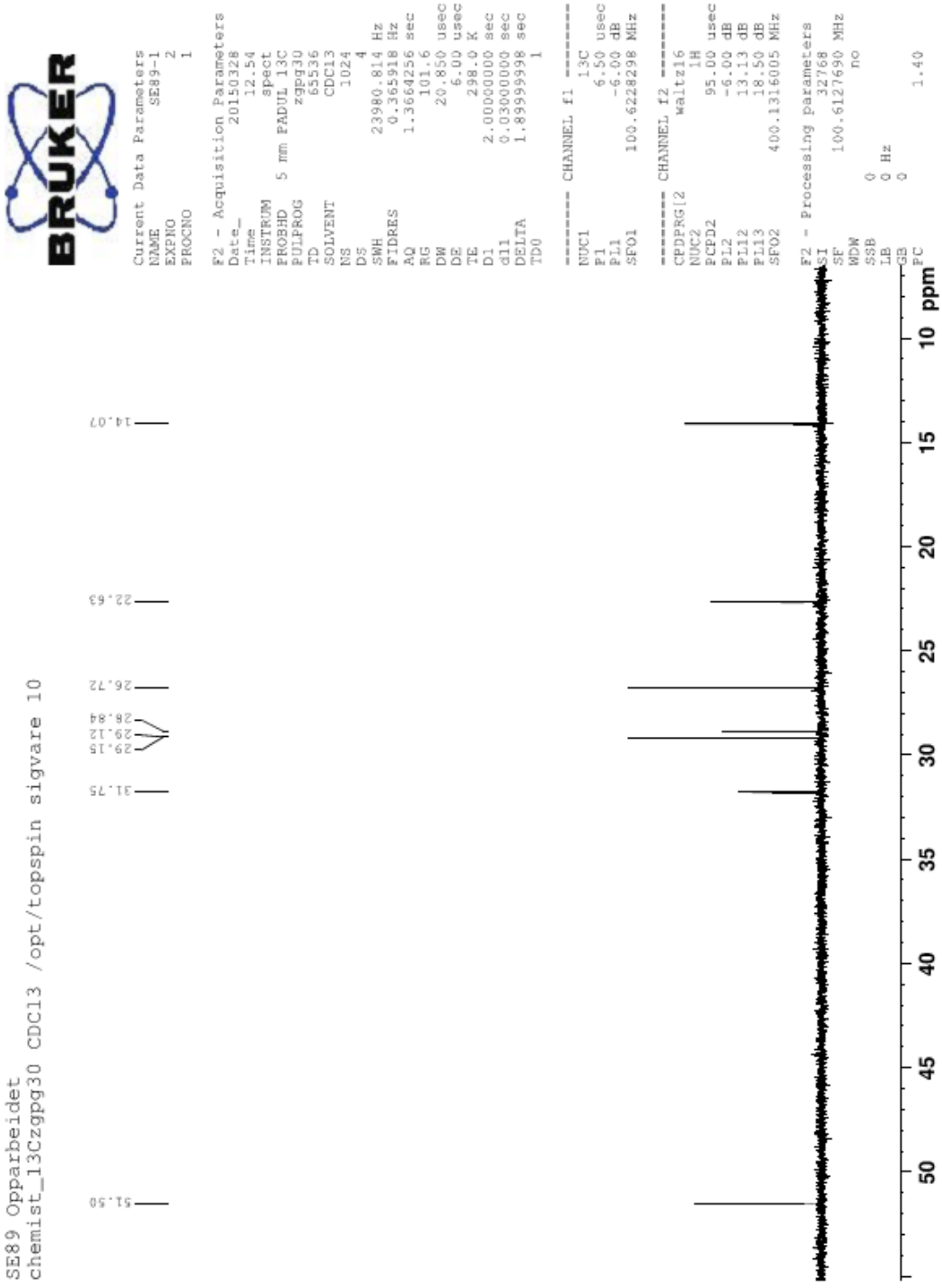
Appendix R.5 ^{1}H-NMR spectrum of azide 10d





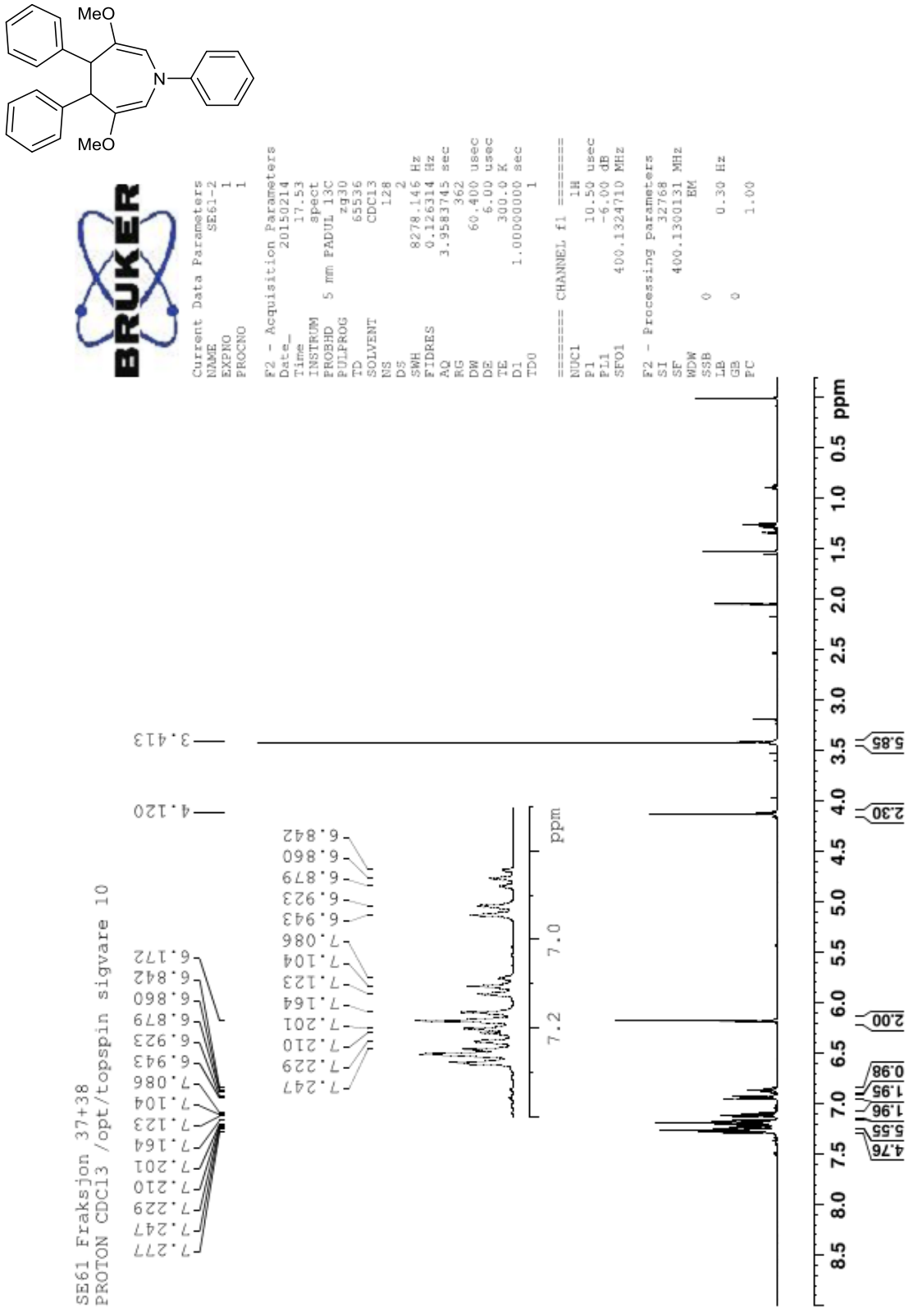
Appendix R.6 ^{13}C-NMR spectrum of azide 10d



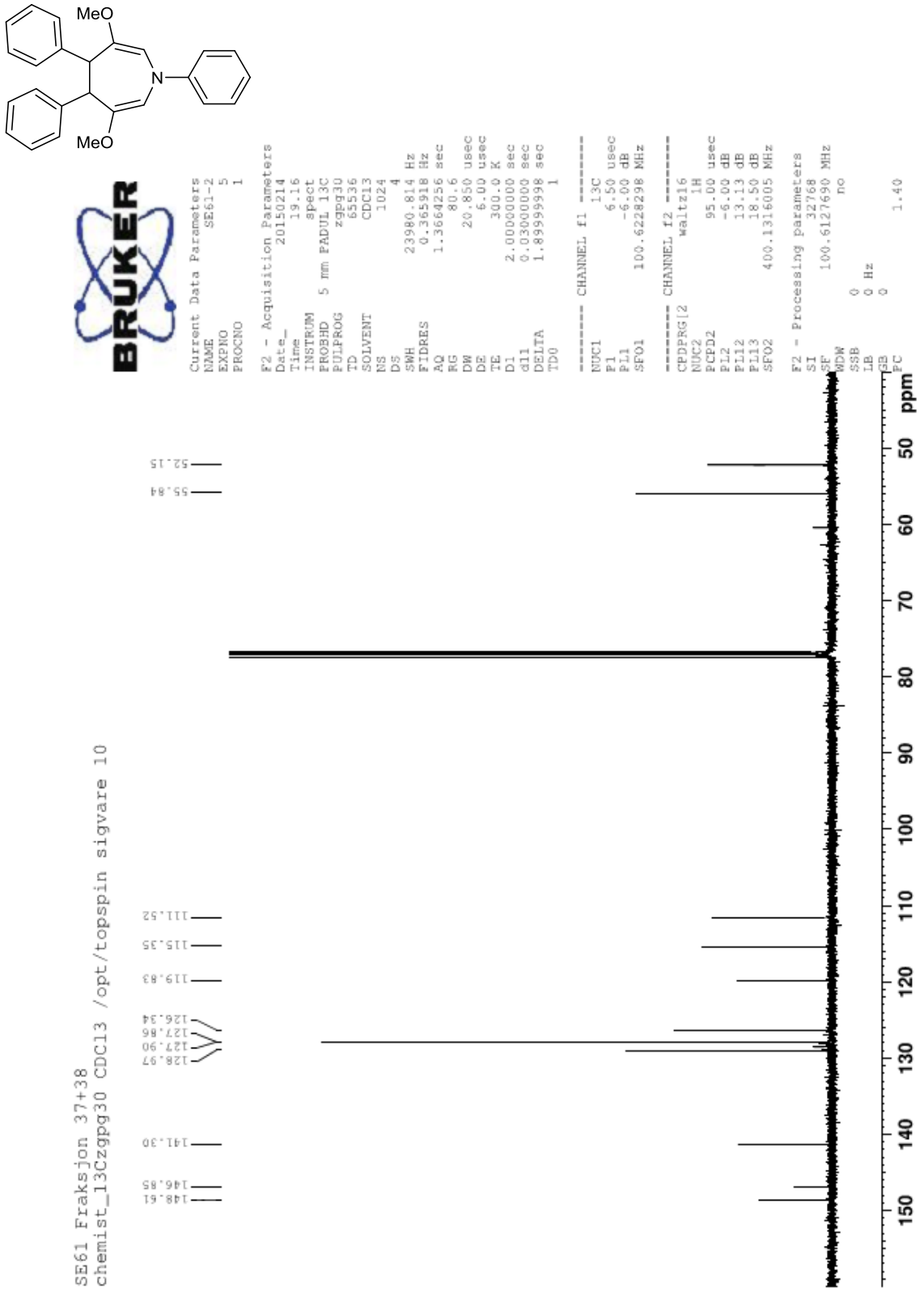


Appendix S Spectra of azepine 11a

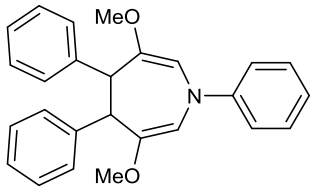
Appendix S.1 ^{1}H-NMR spectrum of azepine 11a

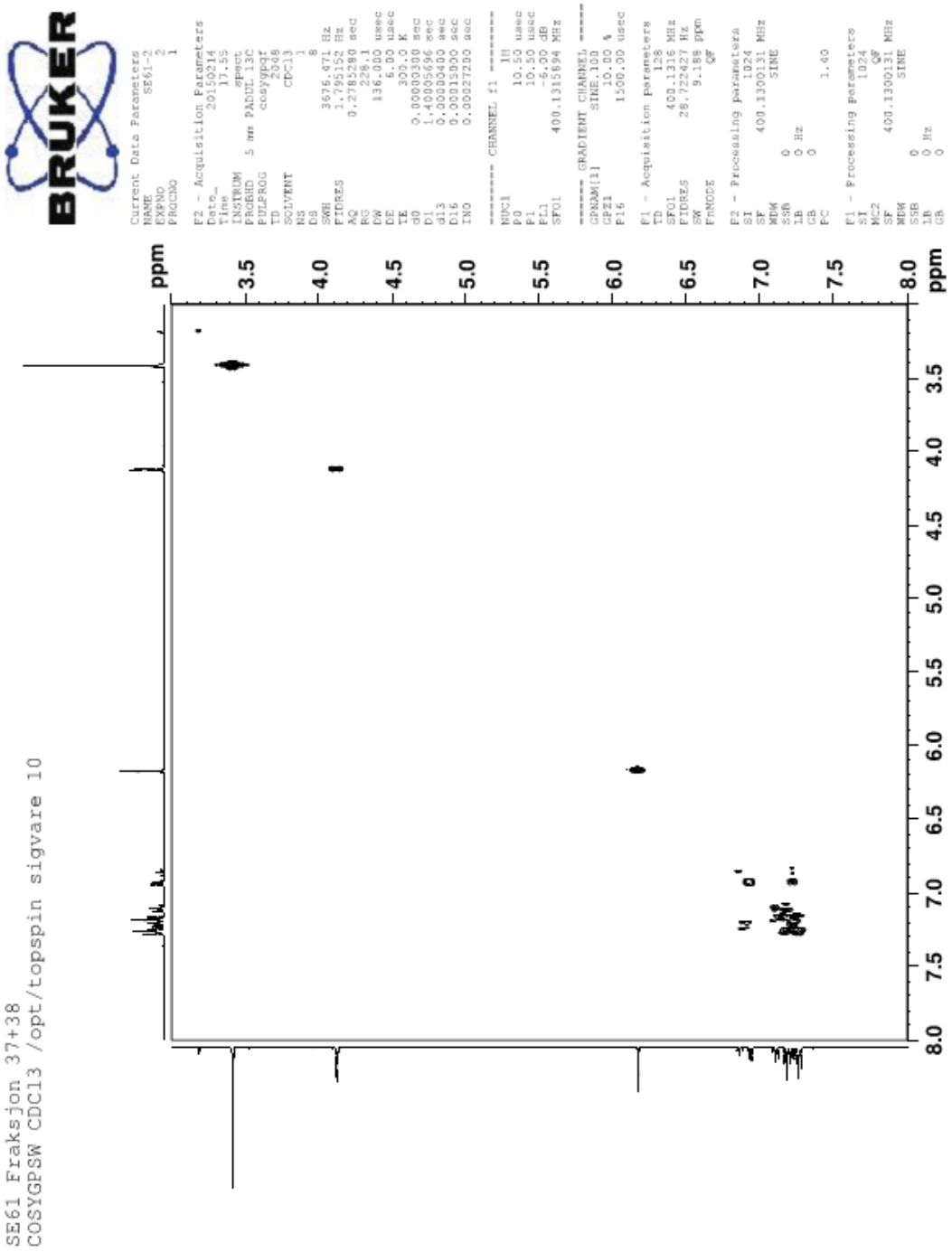


Appendix S.2 ^{13}C-NMR spectrum of azepine 11a

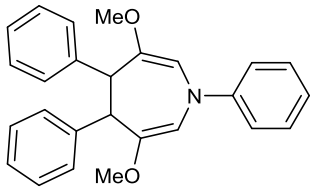


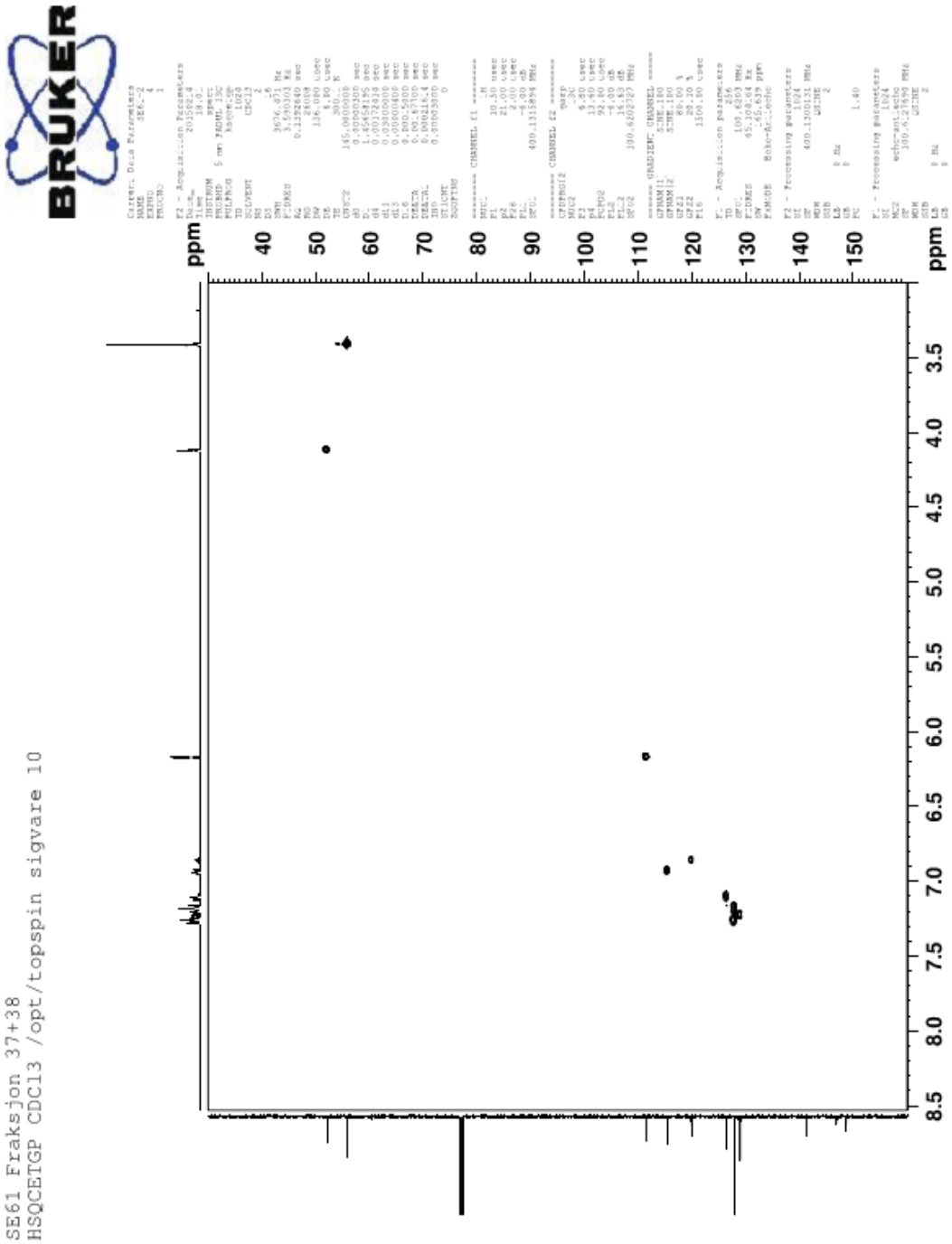
Appendix S.3 COSY spectrum of azepine 11a



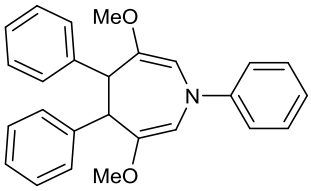


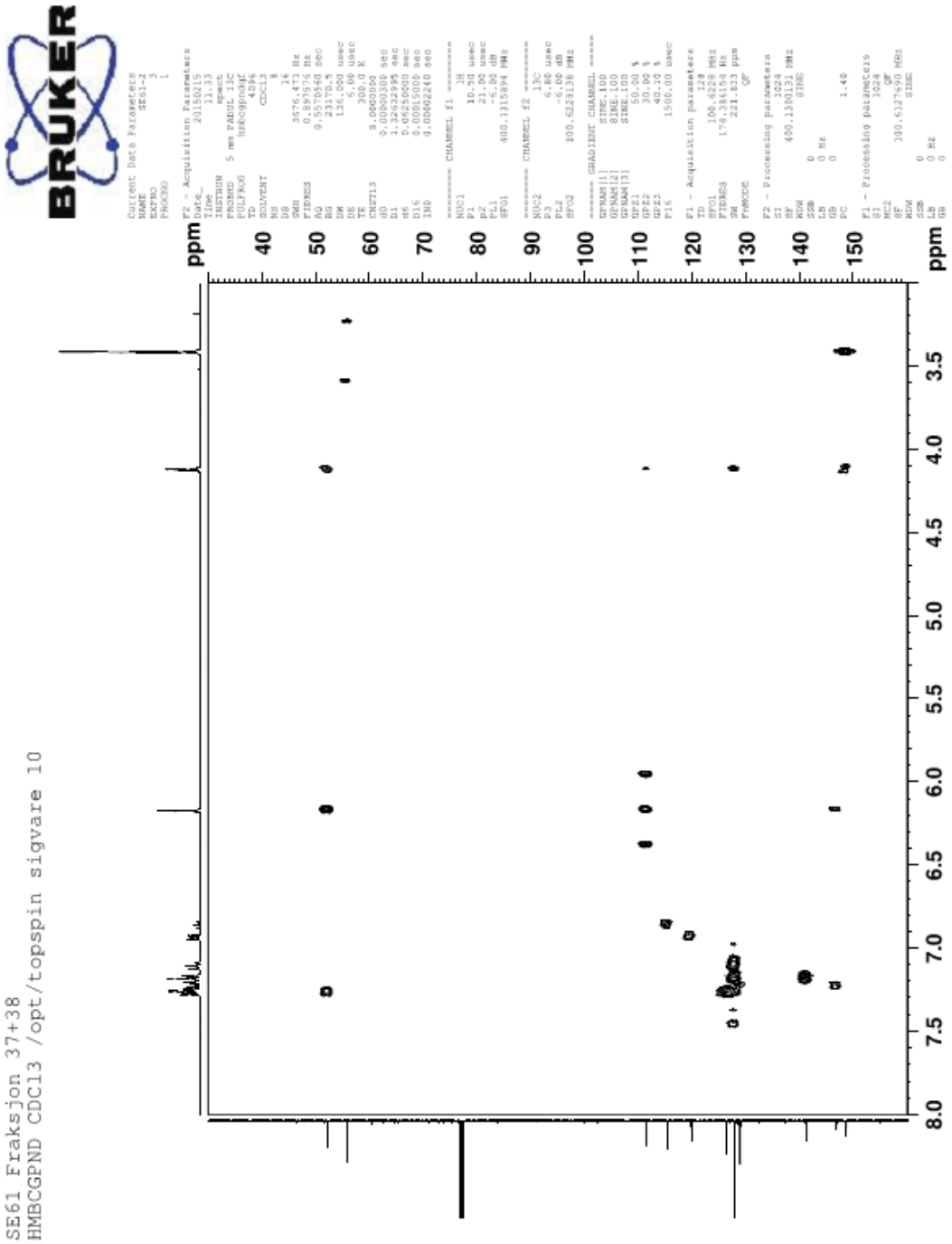
Appendix S.4 HSQC spectrum of azepine 11a



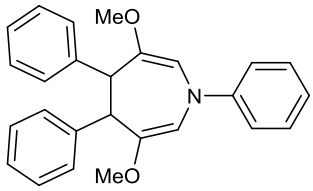


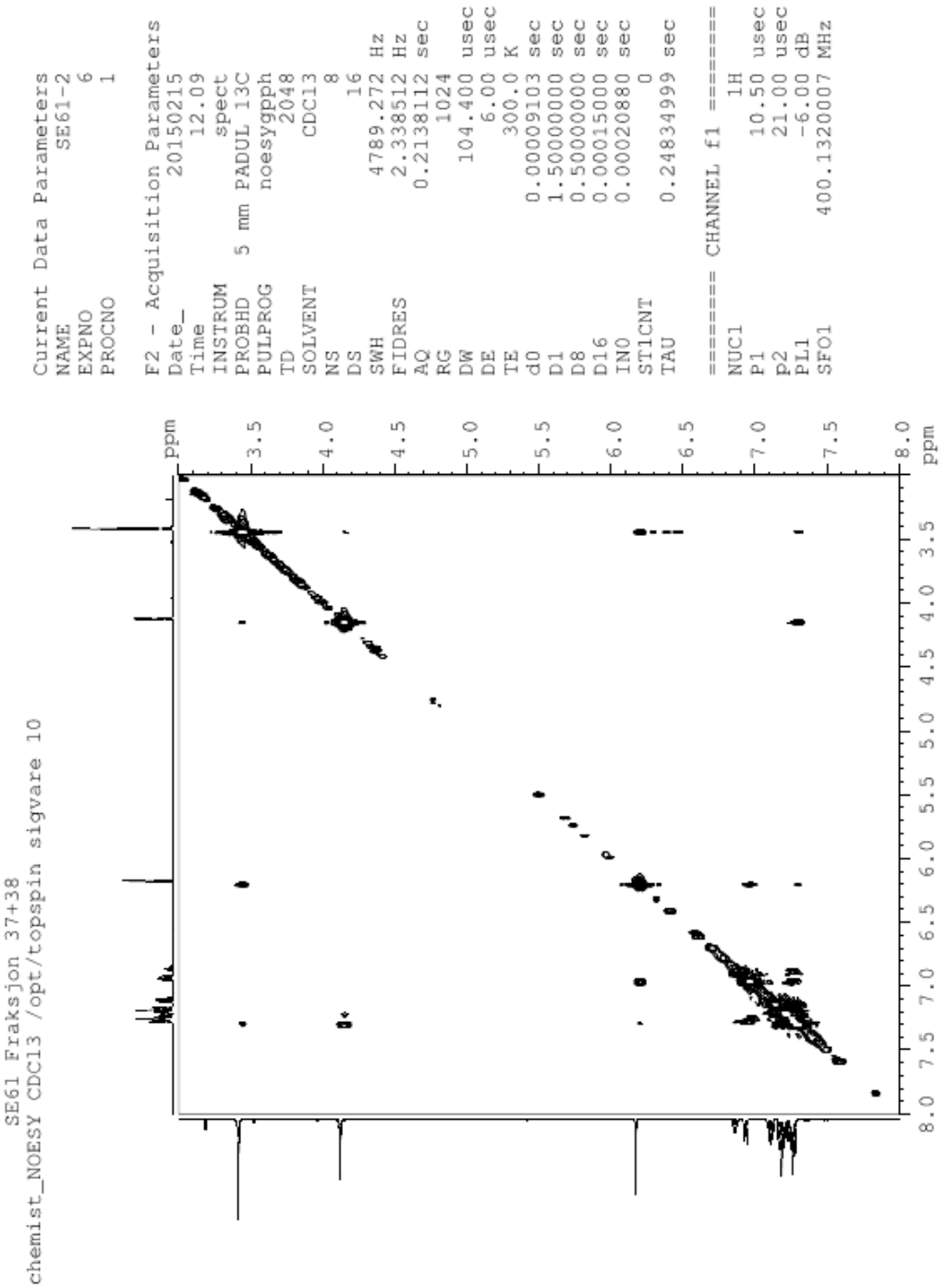
Appendix S.5 HMBC spectrum of azepine 11a



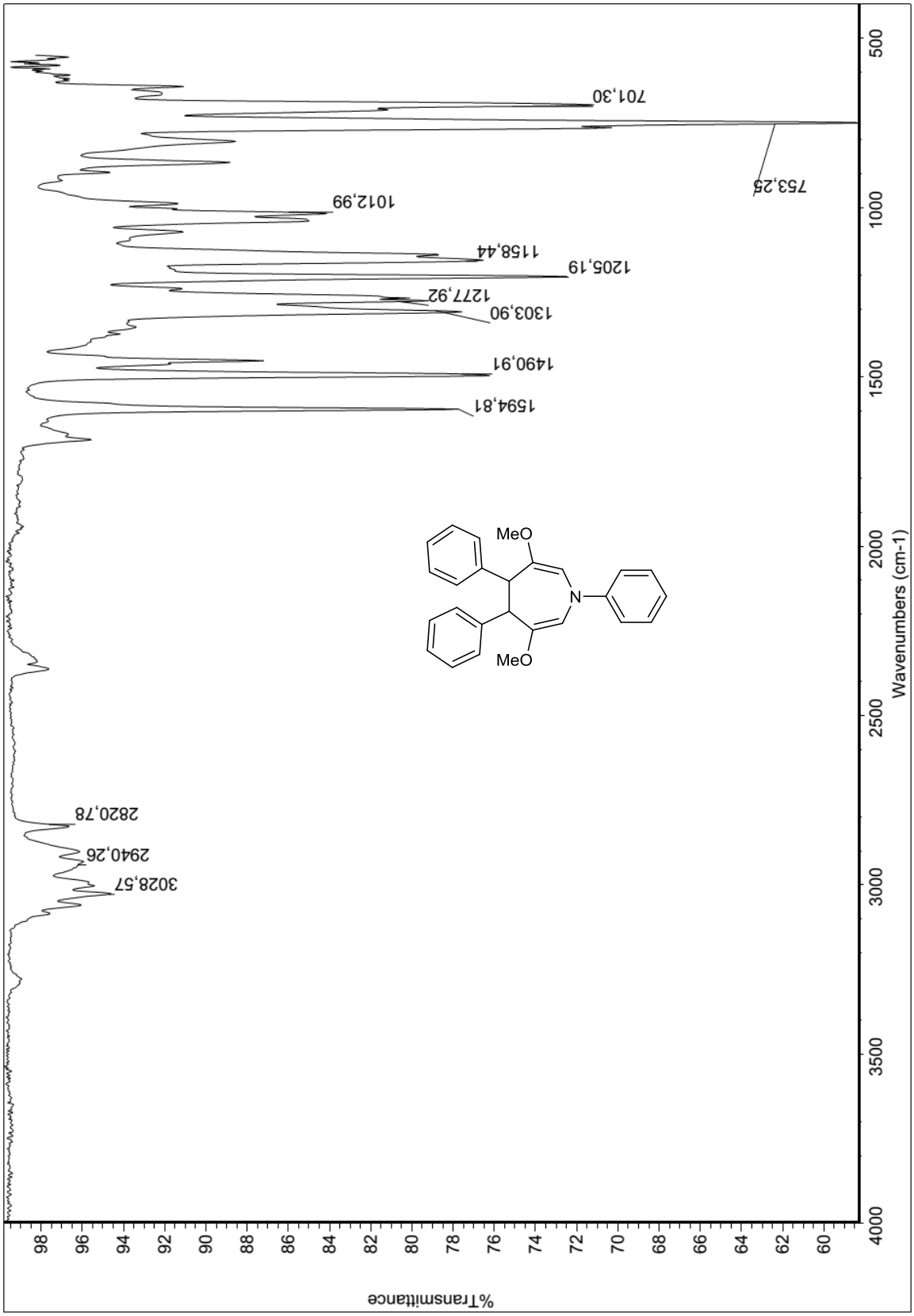


Appendix S.6 NOESY spectrum of azepine 11a





Appendix S.7 IR spectrum of azepine 11a



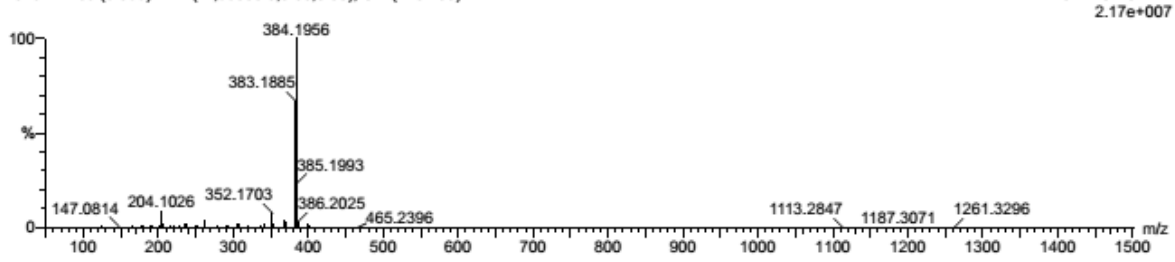
Appendix U.8 MS azepine 11a

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 3.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
1112 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-100 O: 0-200
NT-MSLAB-Operator-SVG
2015-21 155 (3.033) AM2 (Ar,35000.0,0.00,0.00); Cm (148:155)

1: TOF MS ASAP+
2.17e+007

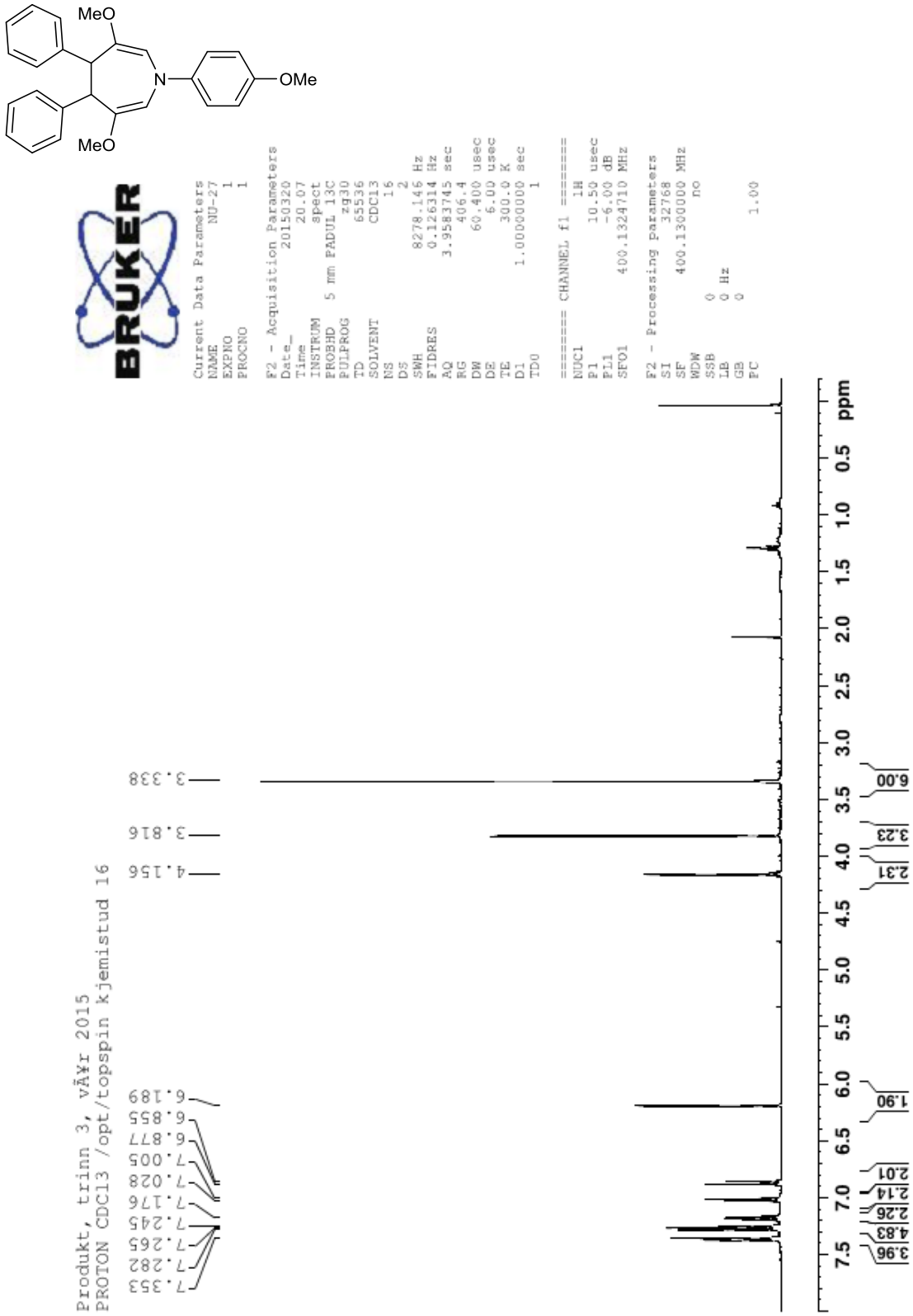


Minimum:				-1.5				
Maximum:		5.0	3.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
384.1956	384.1955	0.1	0.3	2.5	1533.7	7.585	0.05	C10 H26 N9 O7
	384.1964	-0.8	-2.1	14.5	1526.2	0.001	99.95	C26 H26 N O2

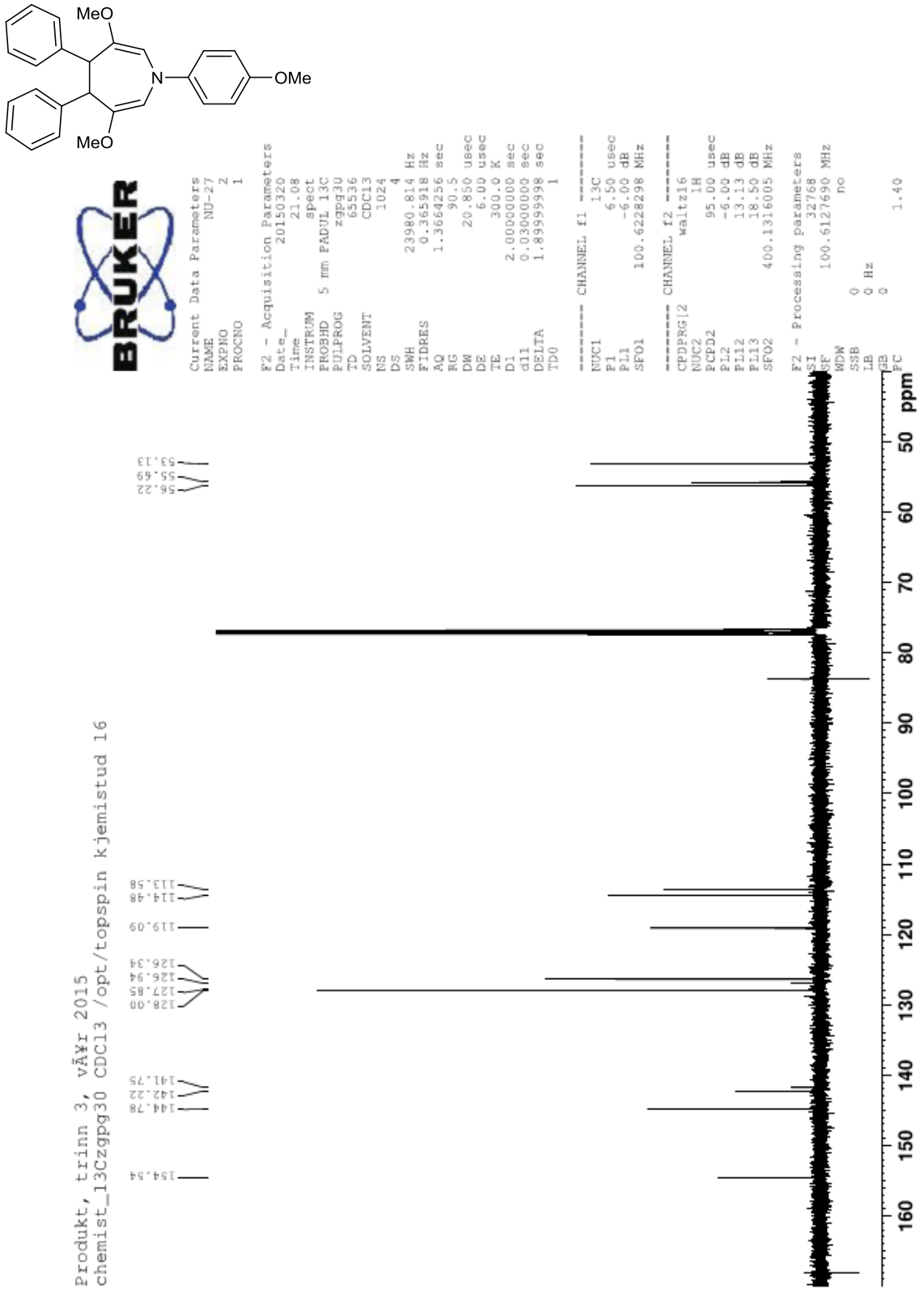
IOn observed [M+H]+

Appendix T Spectra of azepine 11b

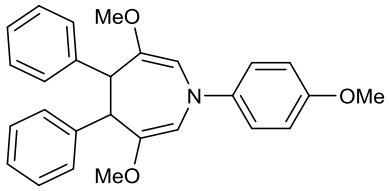
Appendix T.1 ^{1}H-NMR spectrum of azepine 11b

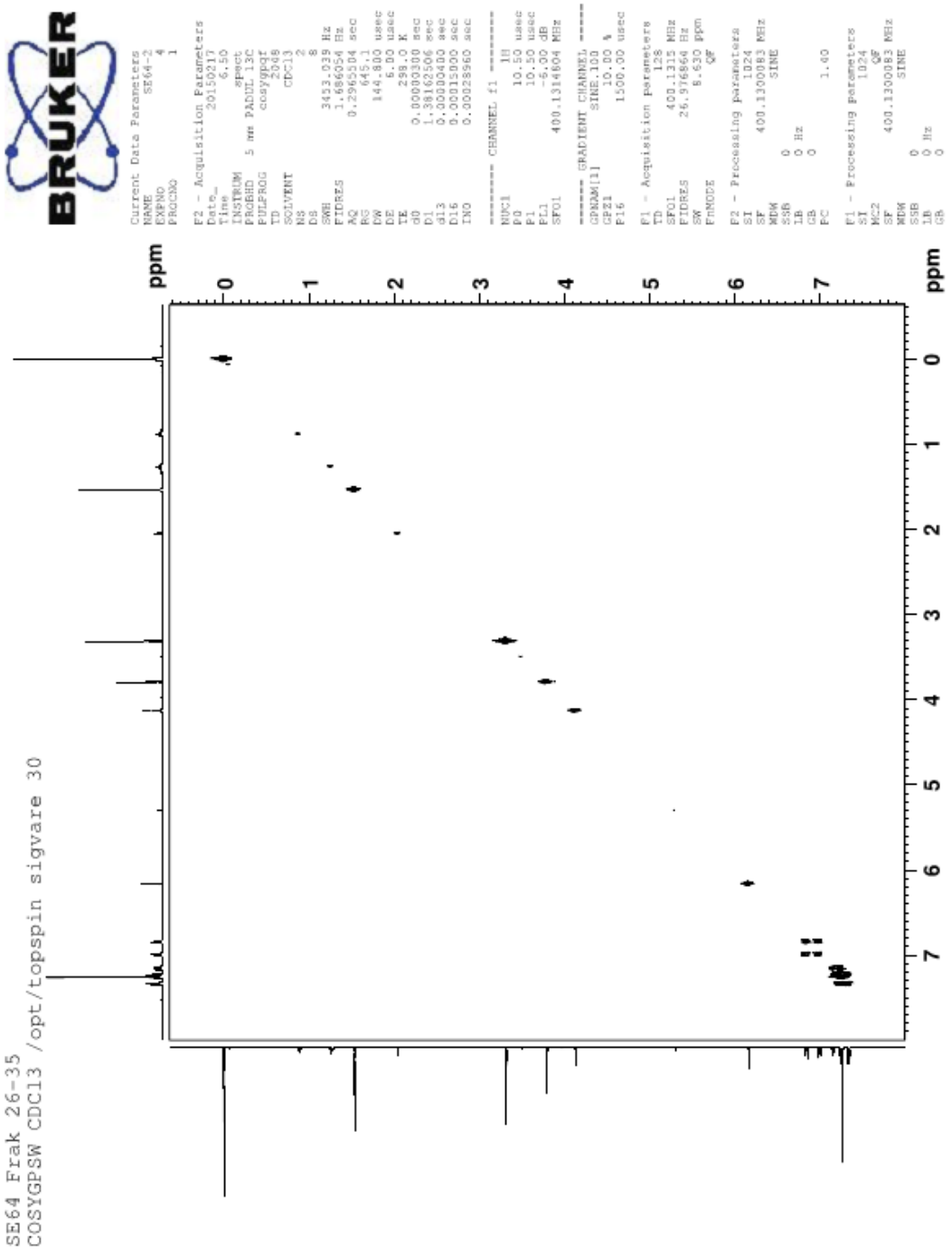


Appendix T.2 ^{13}C-NMR spectrum of azepine 11b

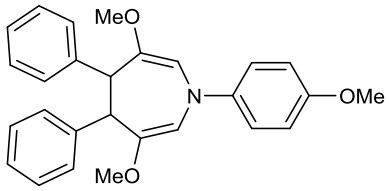


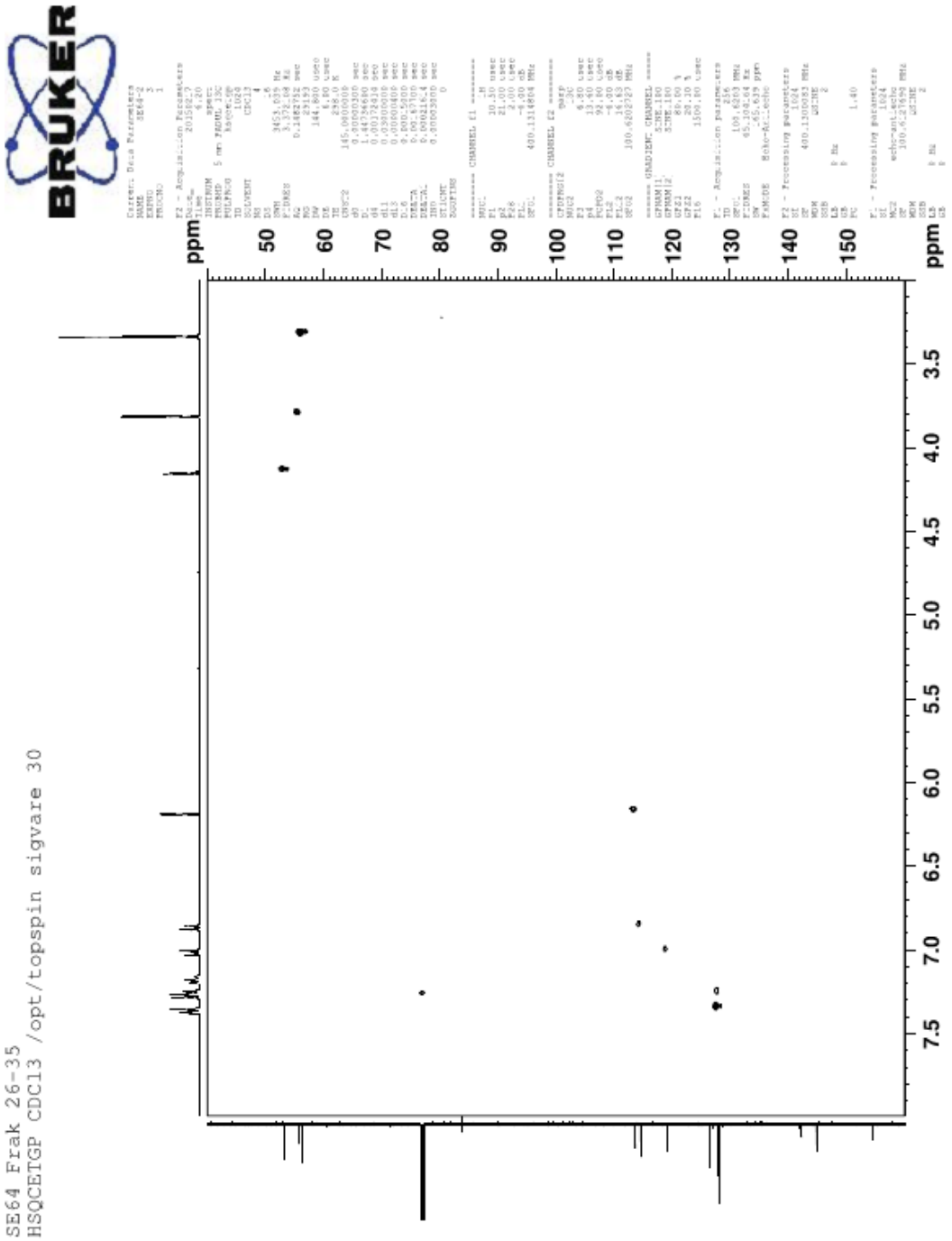
Appendix T.3 COSY spectrum of azepine 11b



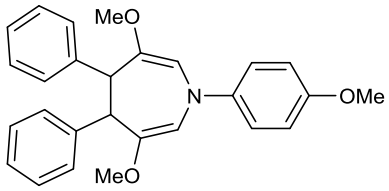


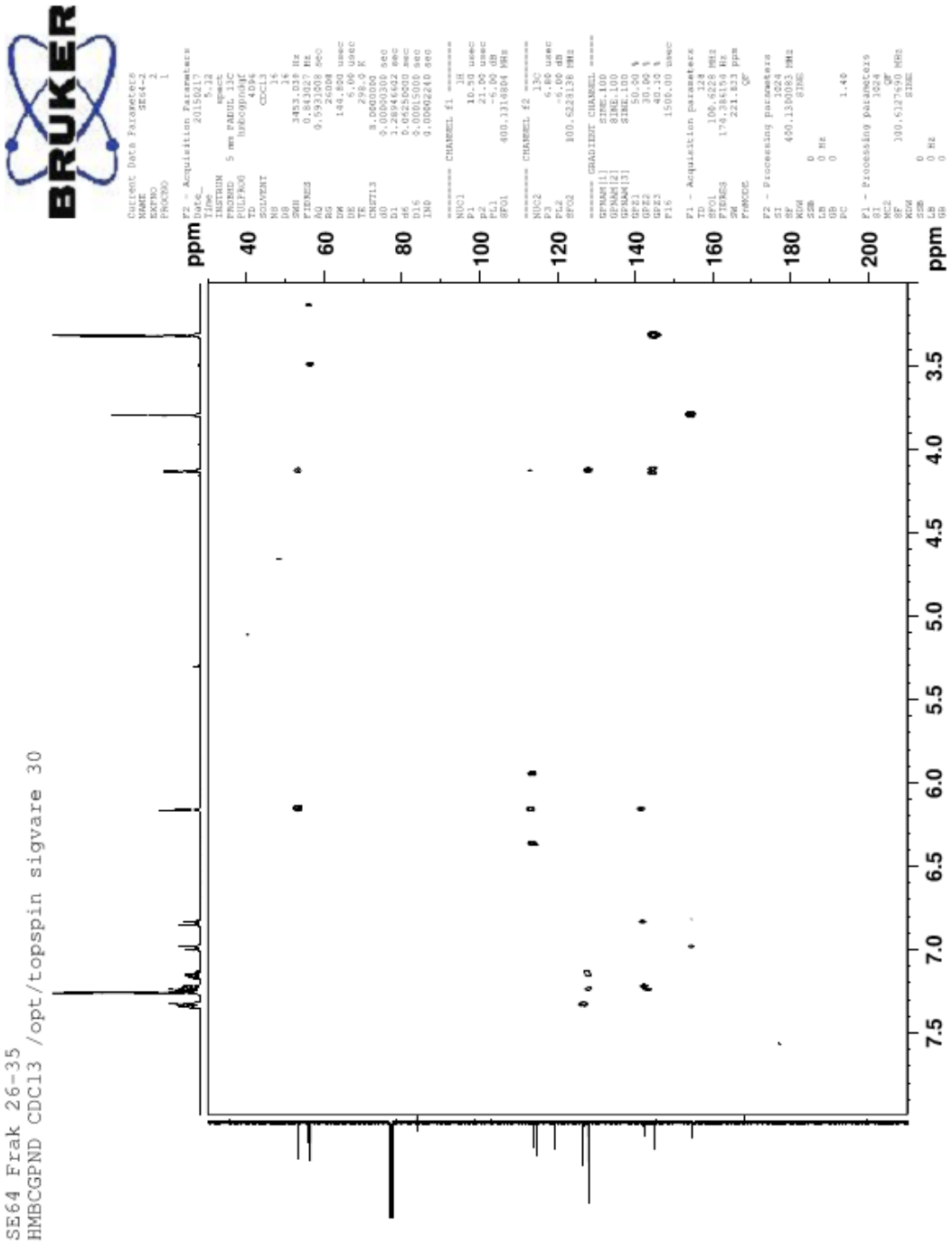
Appendix T.4 HSQC spectrum of azepine 11b



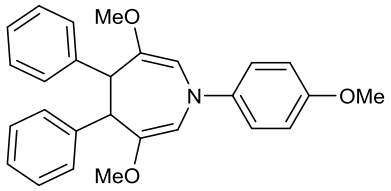


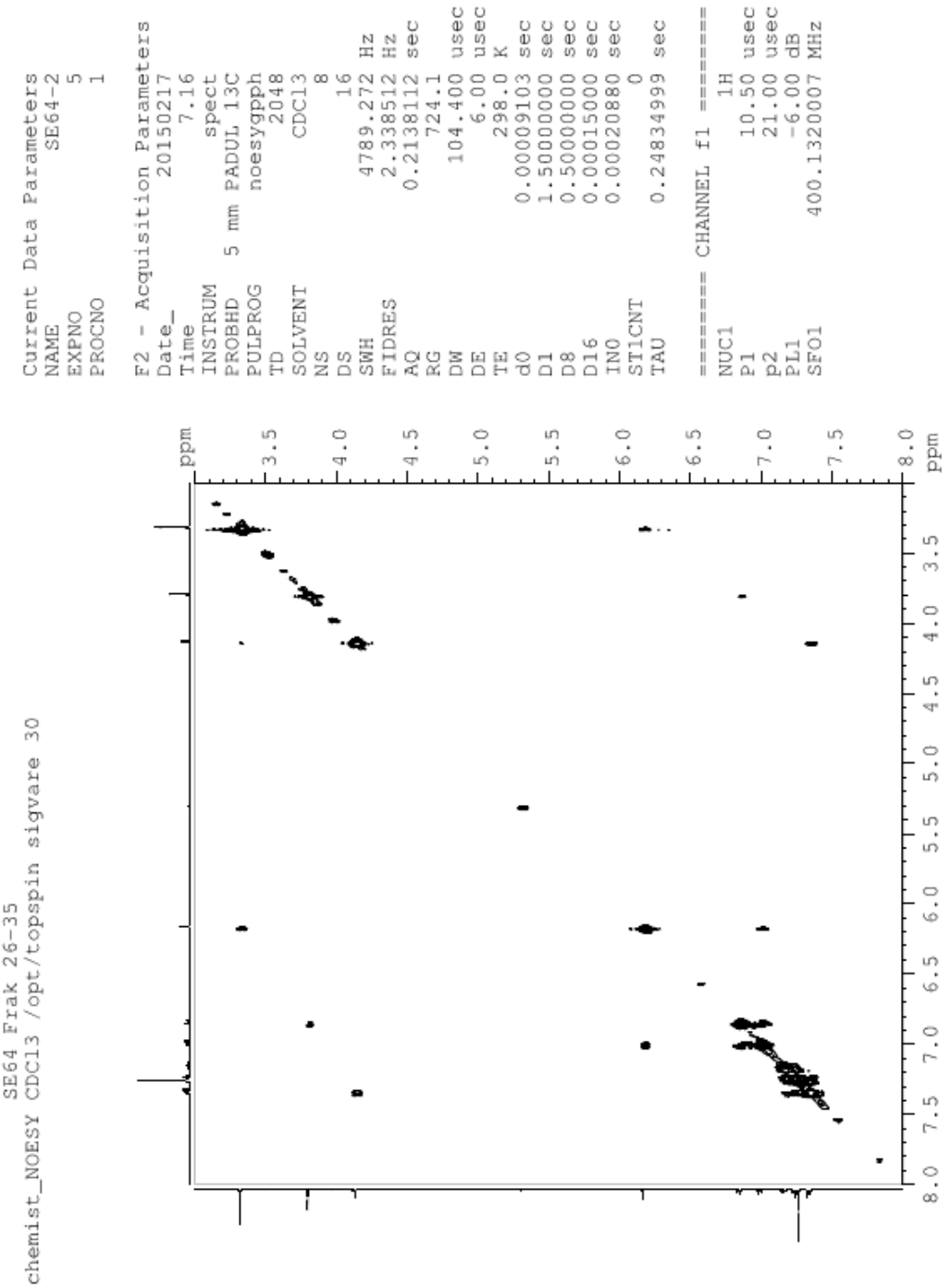
Appendix T.5 HMBC spectrum of azepine 11b



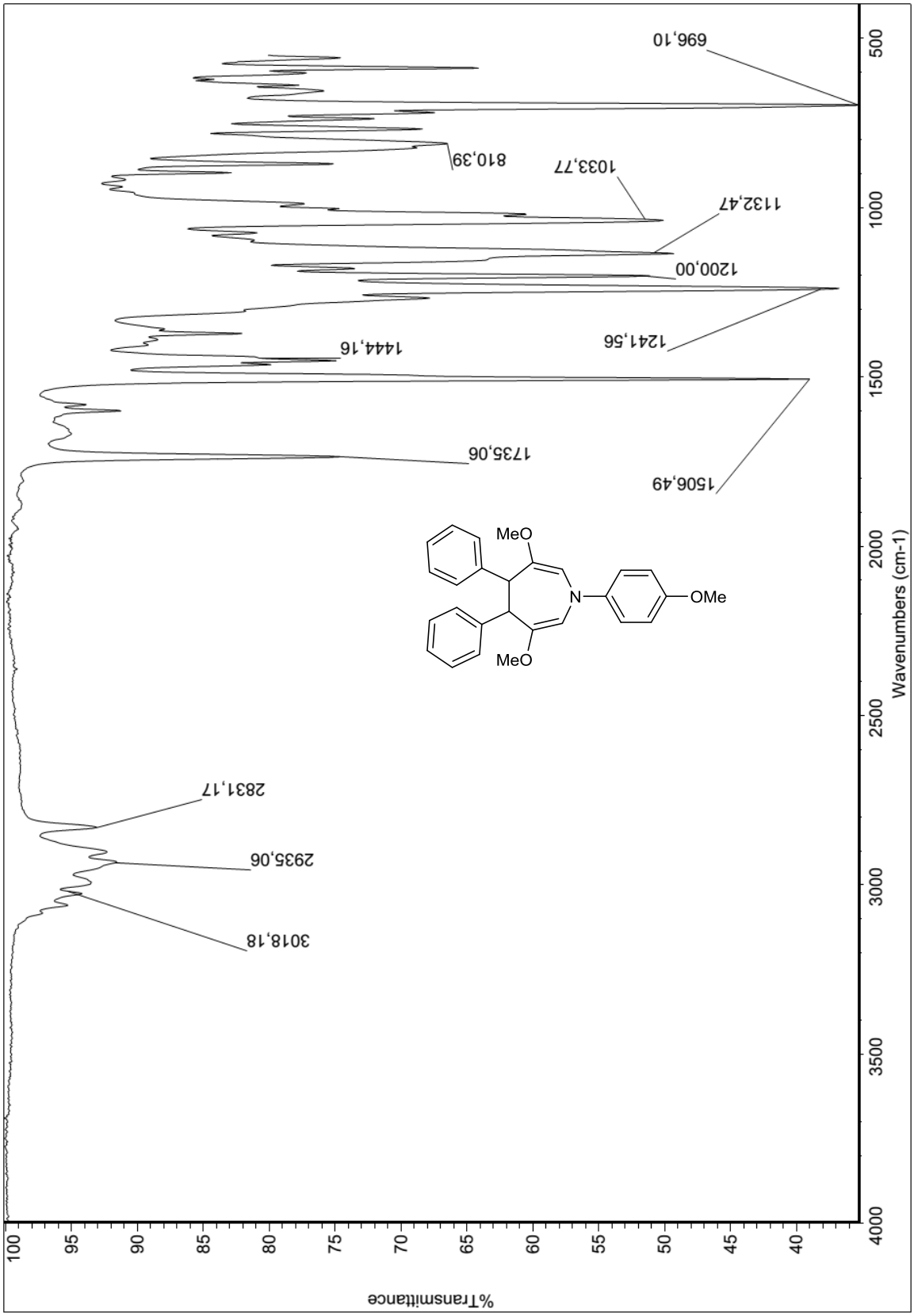


Appendix T.6 NOESY spectrum of azepine 11b





Appendix T.7 IR spectrum of azepine 11b

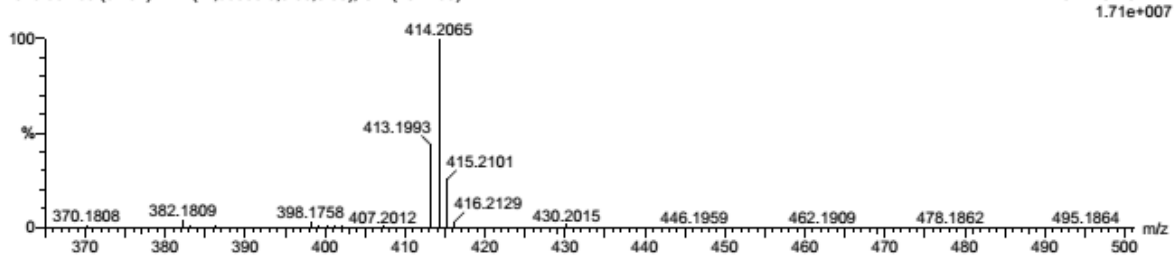


Appendix T.8 MS of azepine 11b

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

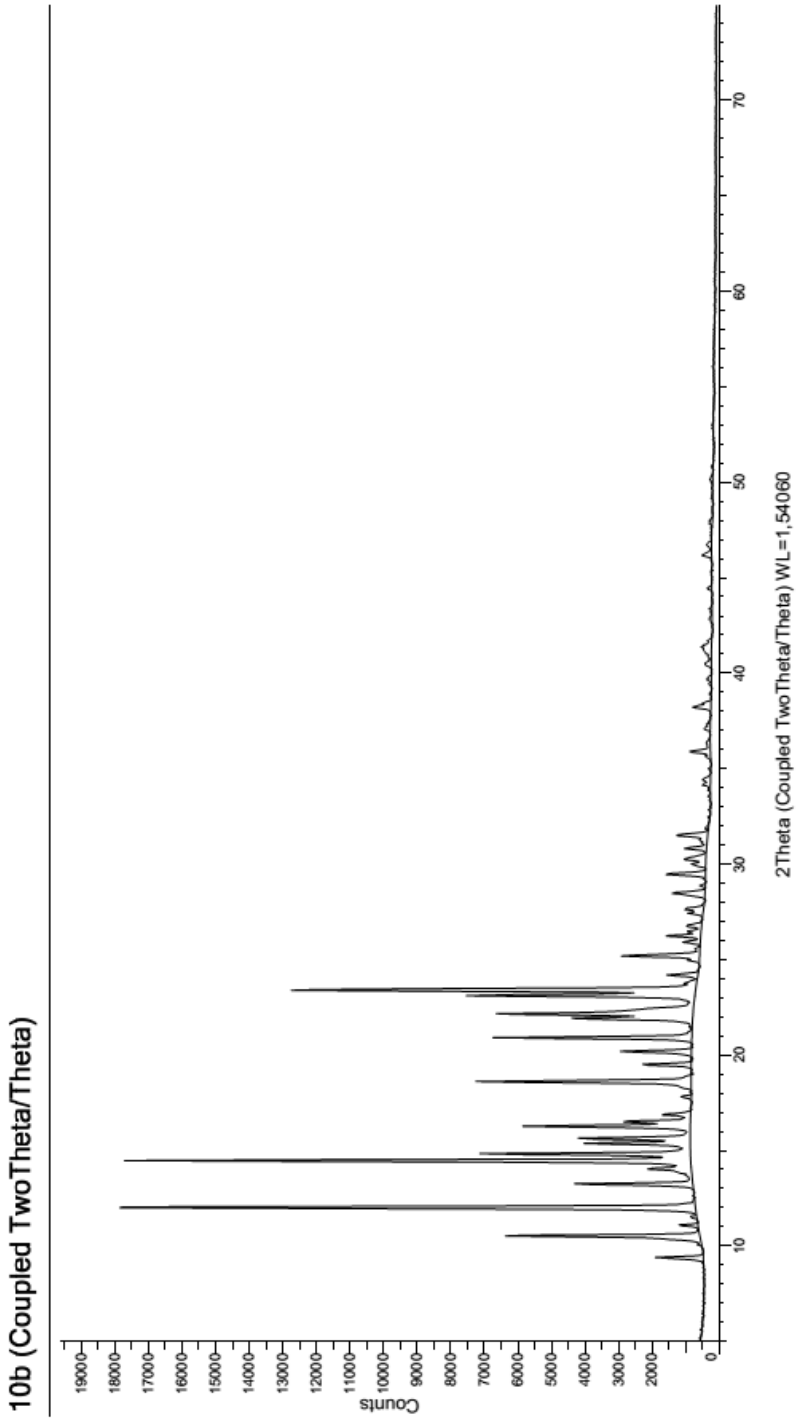
Monoisotopic Mass, Even Electron Ions
823 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-10 O: 0-200
NT-MSLAB-Operator-SVG
2015-96 190 (3.704) AM2 (Ar,35000.0,0.00,0.00); Cm (182:190) 1: TOF MS ASAP+
1.71e+007



Minimum:				-1.5				
Maximum:		5.0	5.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
414.2065	414.2069	-0.4	-1.0	14.5	1448.8	0.001	99.92	C27 H28 N O3
	414.2061	0.4	1.0	2.5	1456.0	7.194	0.08	C11 H28 N9 O8

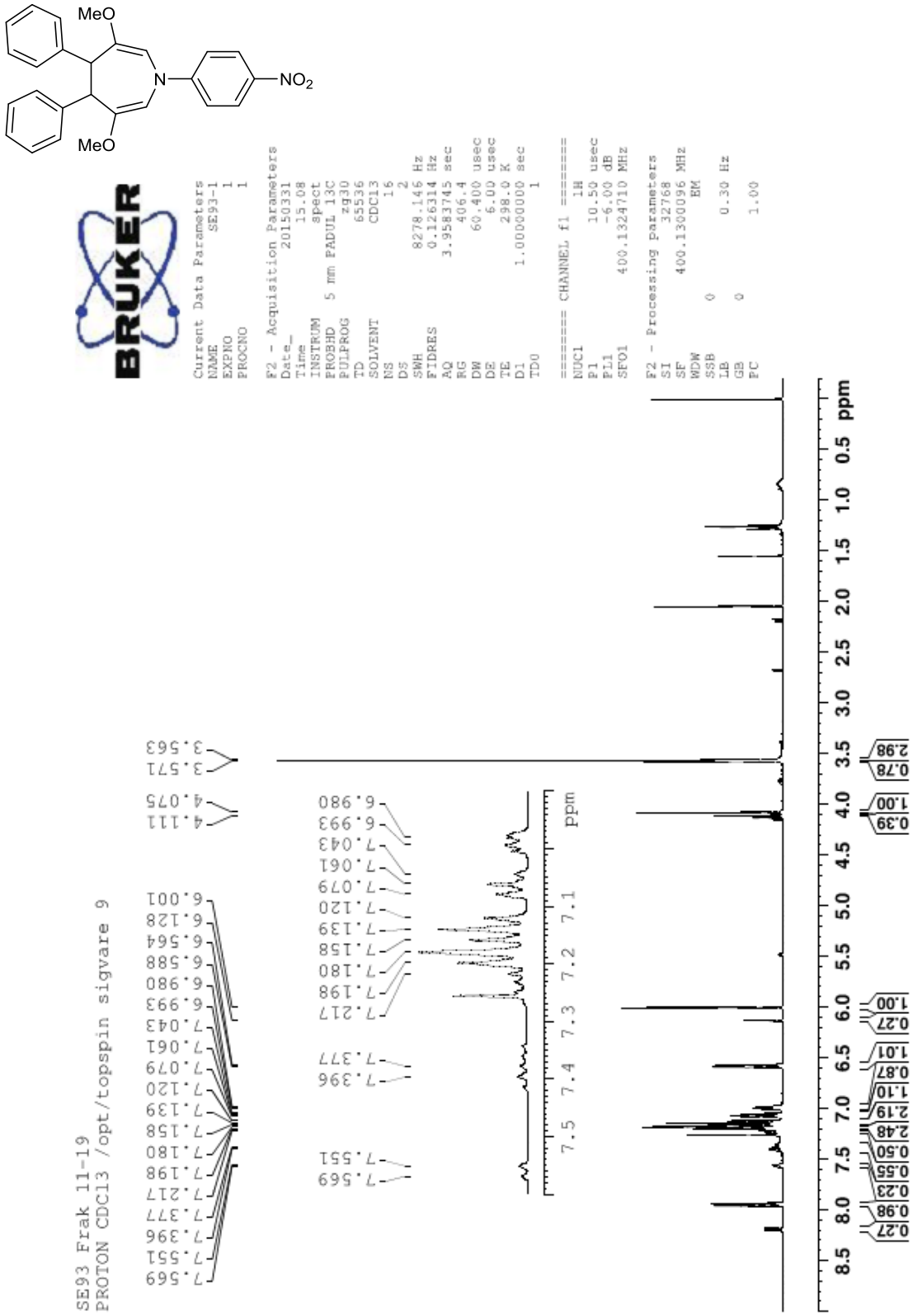
Ion observed [M+H]+

Appendix T.9 X-ray powder diffraction spectrum of azepine 11b

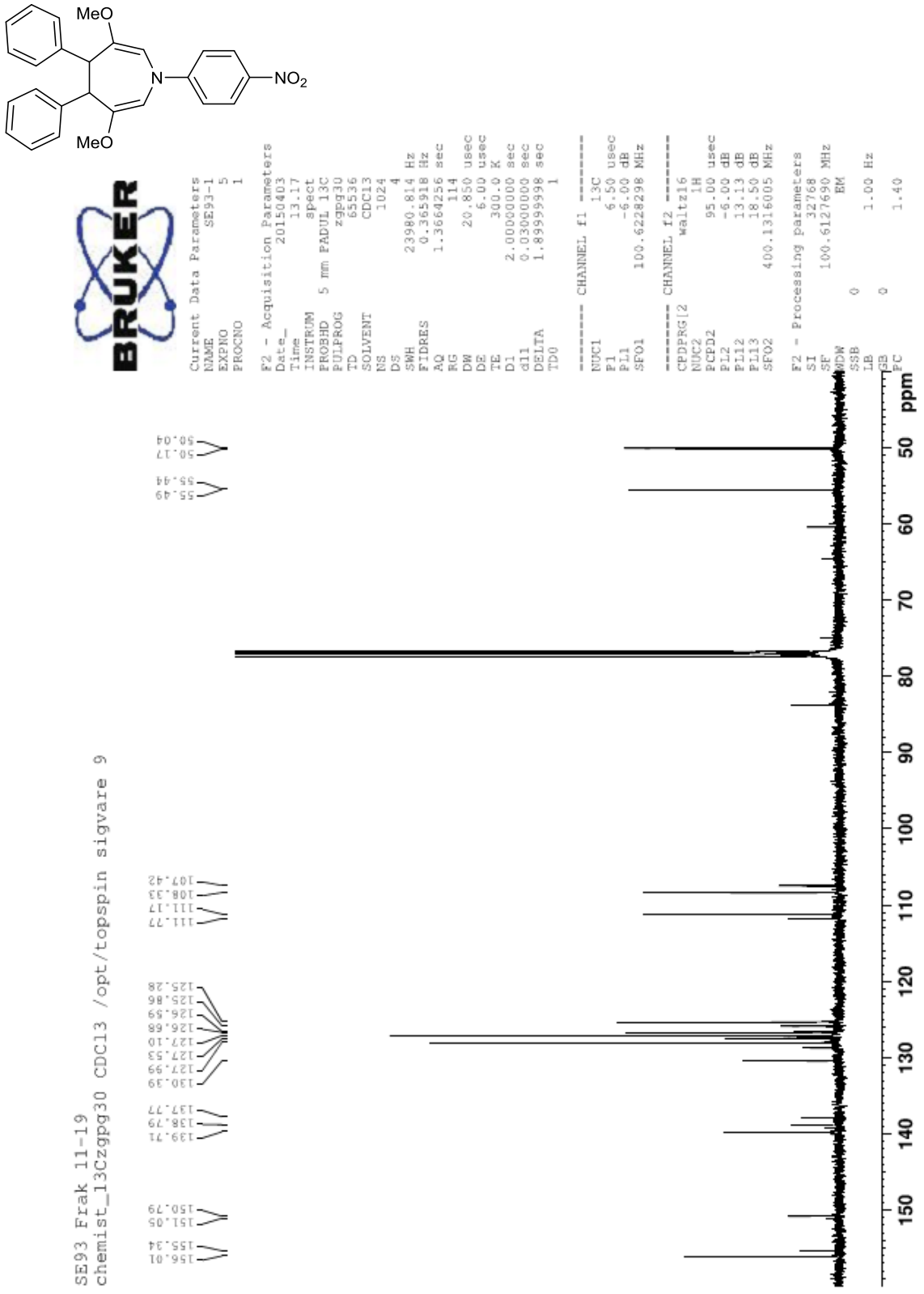


Appendix U Spectra of azepine 11c and 11c'

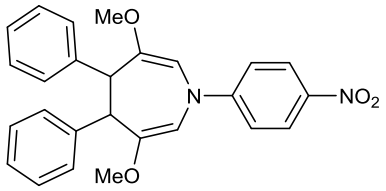
Appendix U.1 ^{1}H-NMR spectrum of azepine 11c and 11c'

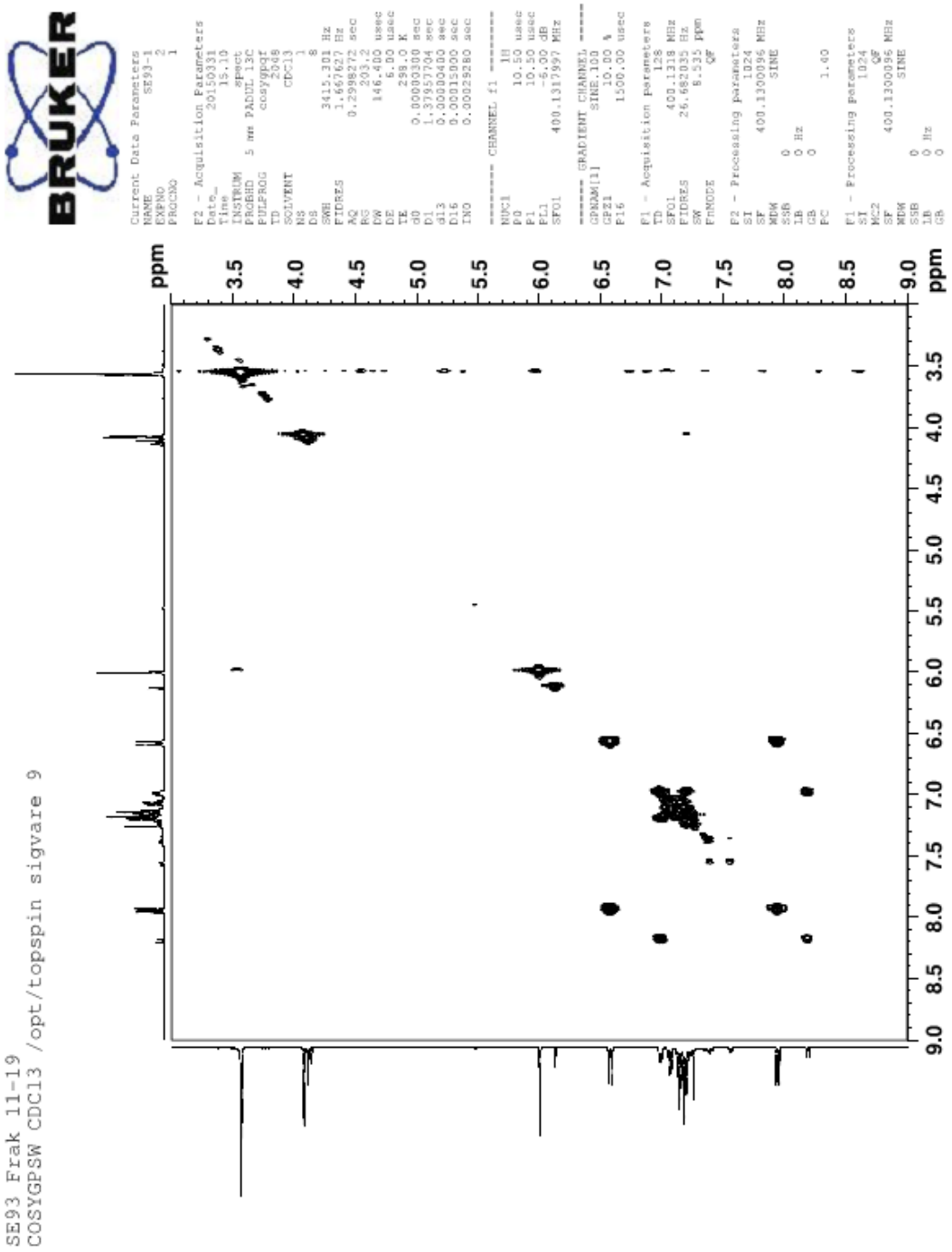


Appendix U.2 ^{13}C-NMR spectrum of azepine 11c and 11c'

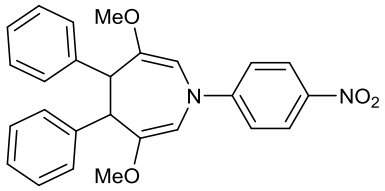


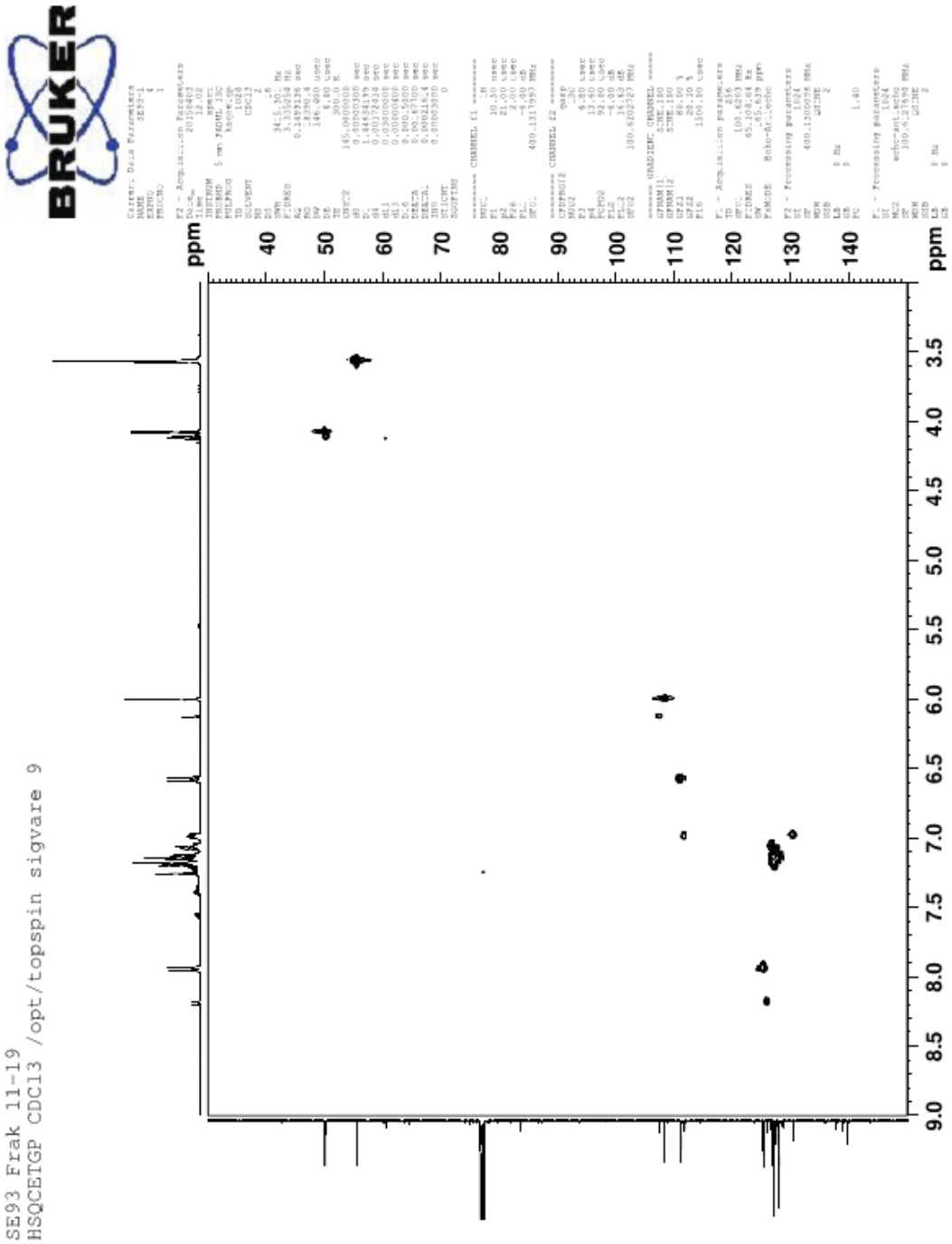
Appendix U.3 COSY spectrum of azepine 11c and azepine 11c'



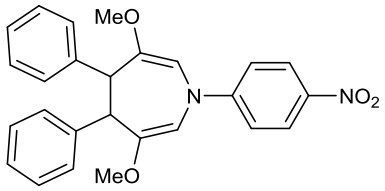


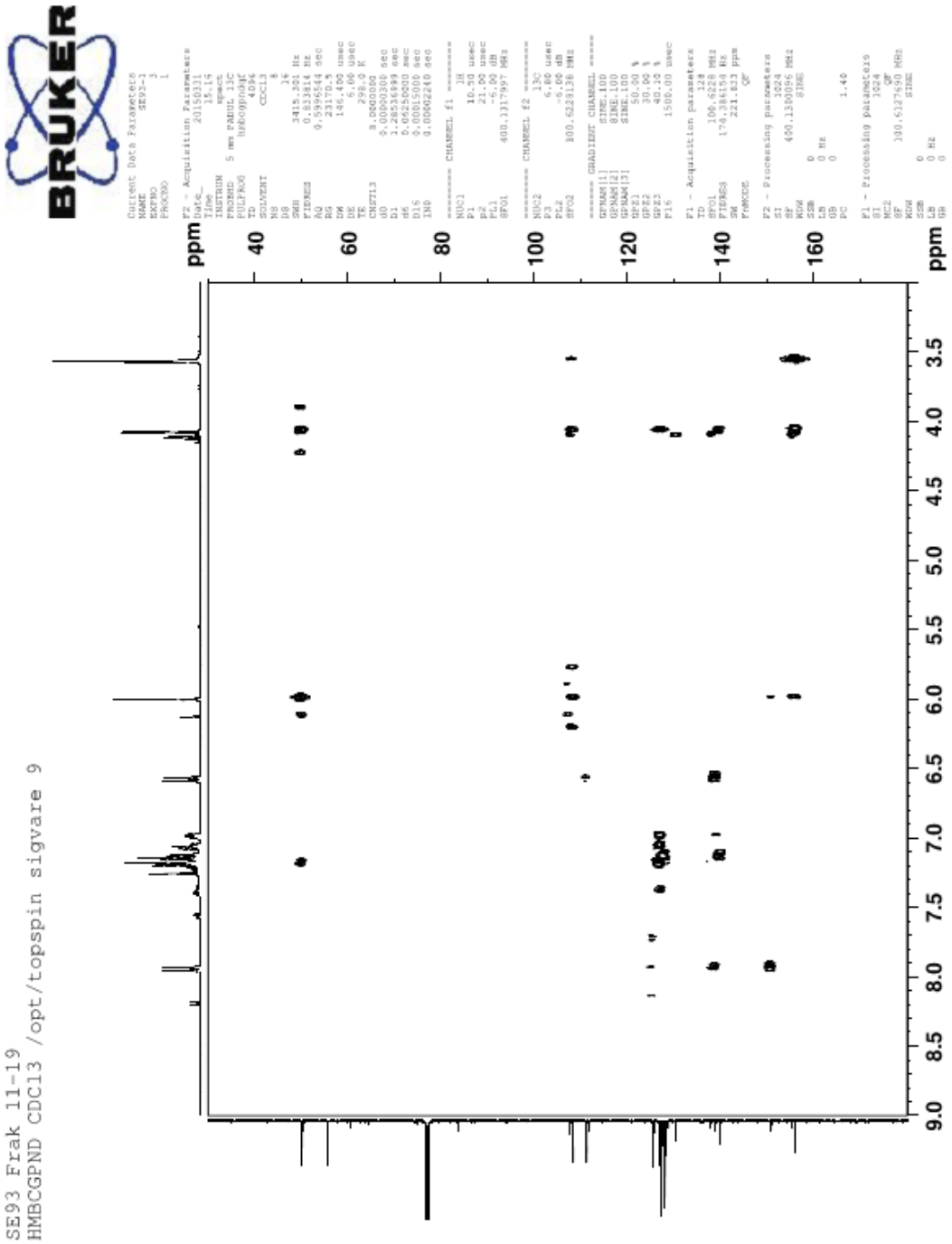
Appendix U.4 HSQC spectrum of azepine 11c and 11c'



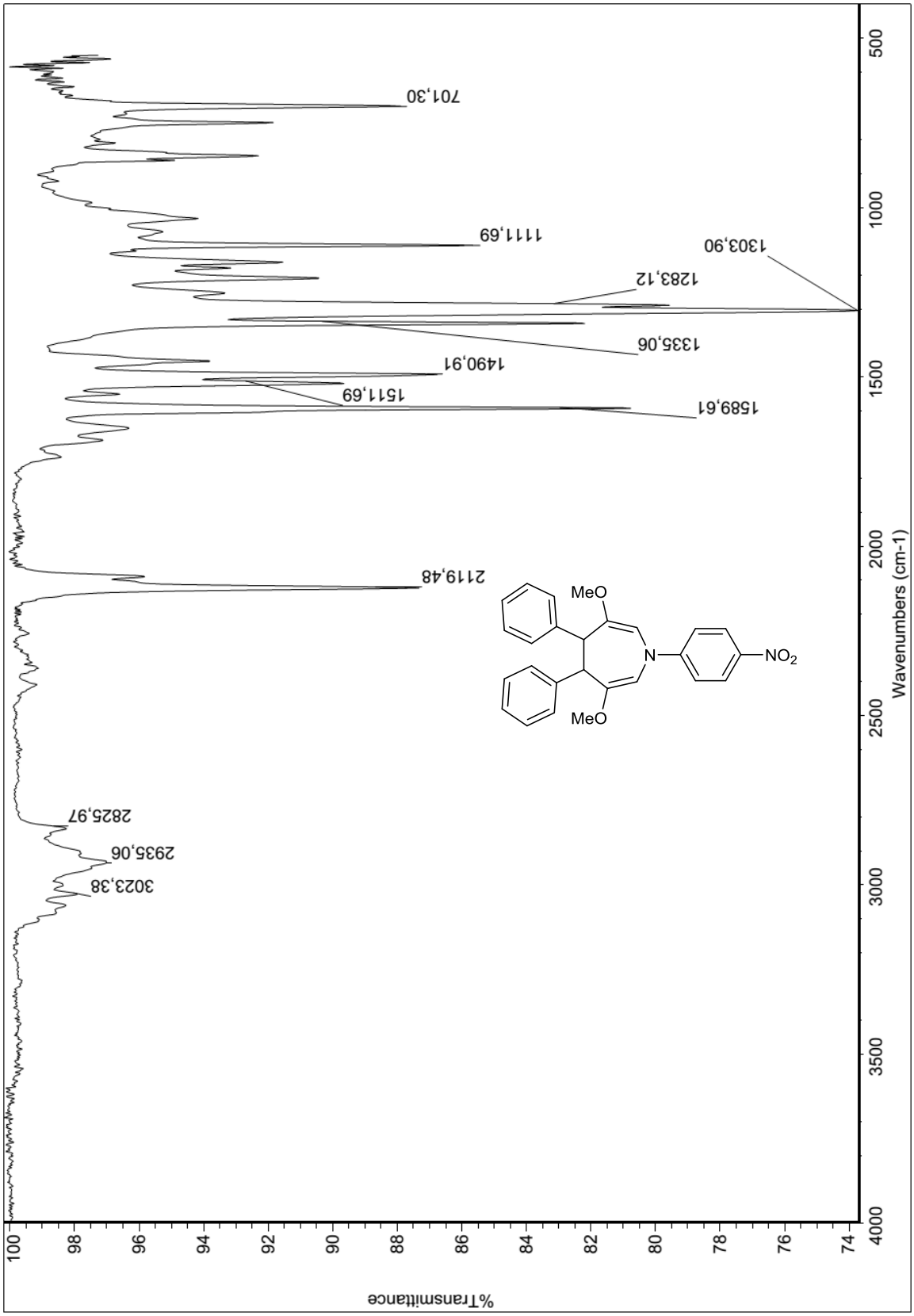


Appendix U.5 HMBC spectrum of azepine 11c and 11c'





Appendix U.6 IR spectrum of azepine 11c and 11c'



Appendix U.7 MS of azepine 11c and 11c'

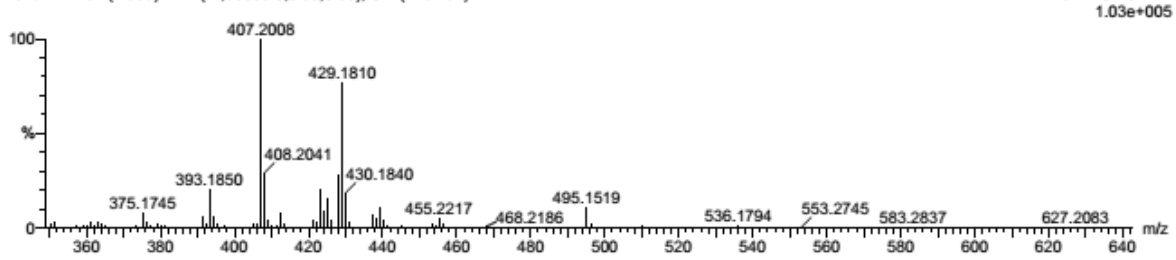
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 2.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
2240 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-50 O: 0-200 I: 0-2

NT-MSLAB-Operator-SVG
2015-117 152 (2.963) AM2 (Ar,35000.0,0.00,0.00); Cm (149:152)

1: TOF MS ASAP+
1.03e+005

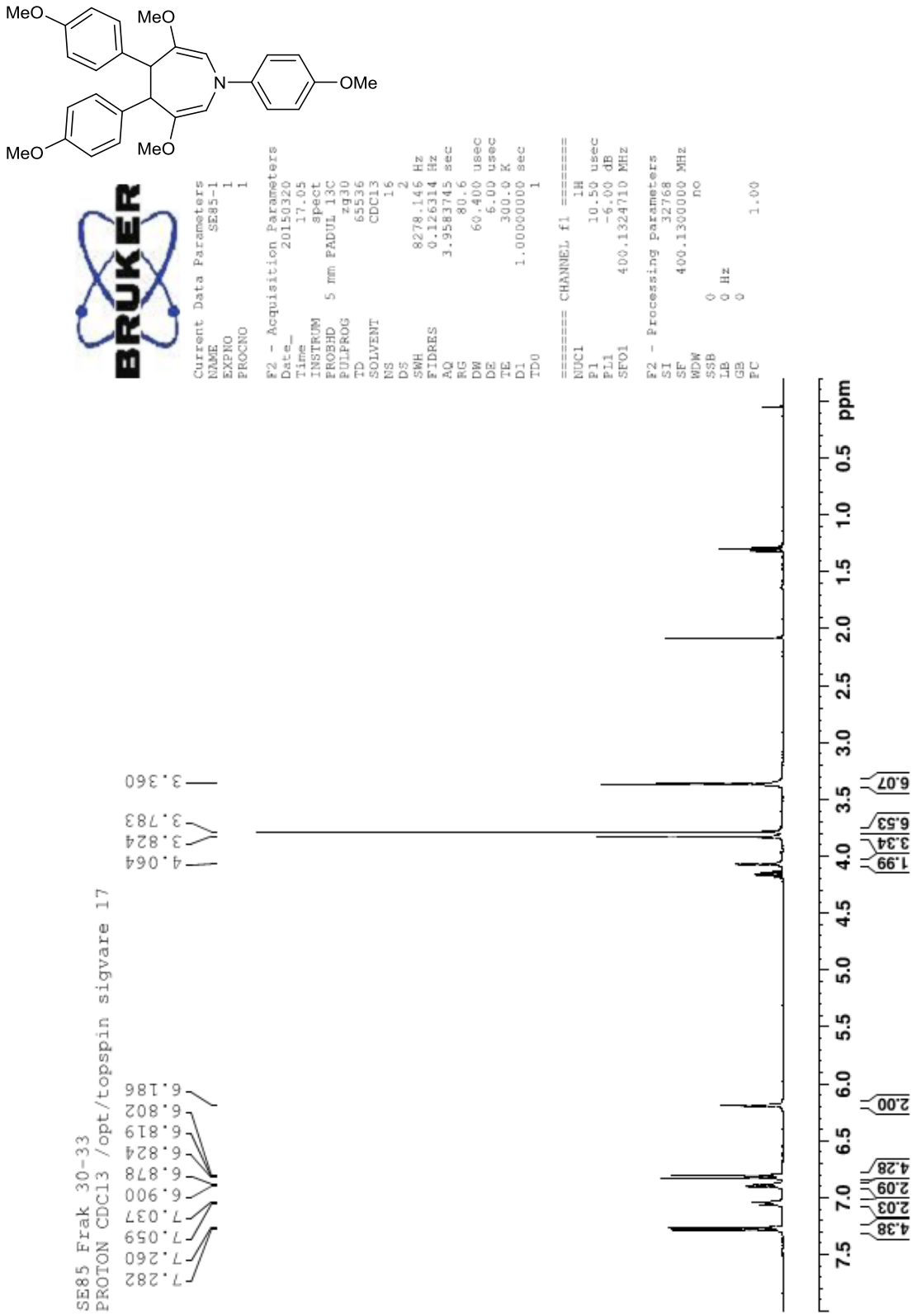


Minimum:				-1.5				
Maximum:		5.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
429.1810	429.1814	-0.4	-0.9	15.5	669.4	0.000	99.96	C26 H25 N2 O4
	429.1806	0.4	0.9	3.5	677.1	7.738	0.04	C10 H25 N10 O9

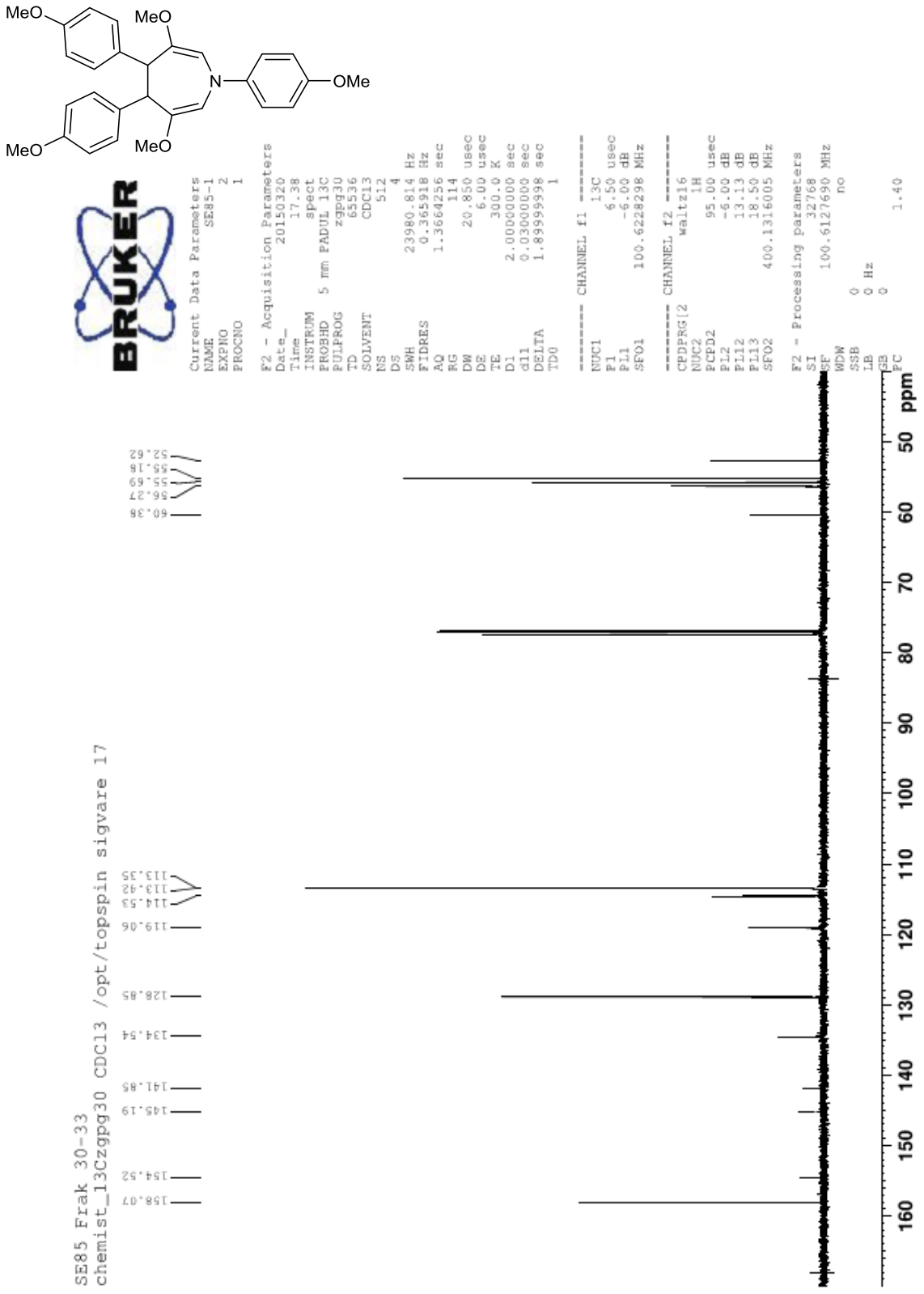
Ion observed [M+H]+

Appendix V Spectra of azepine 11e

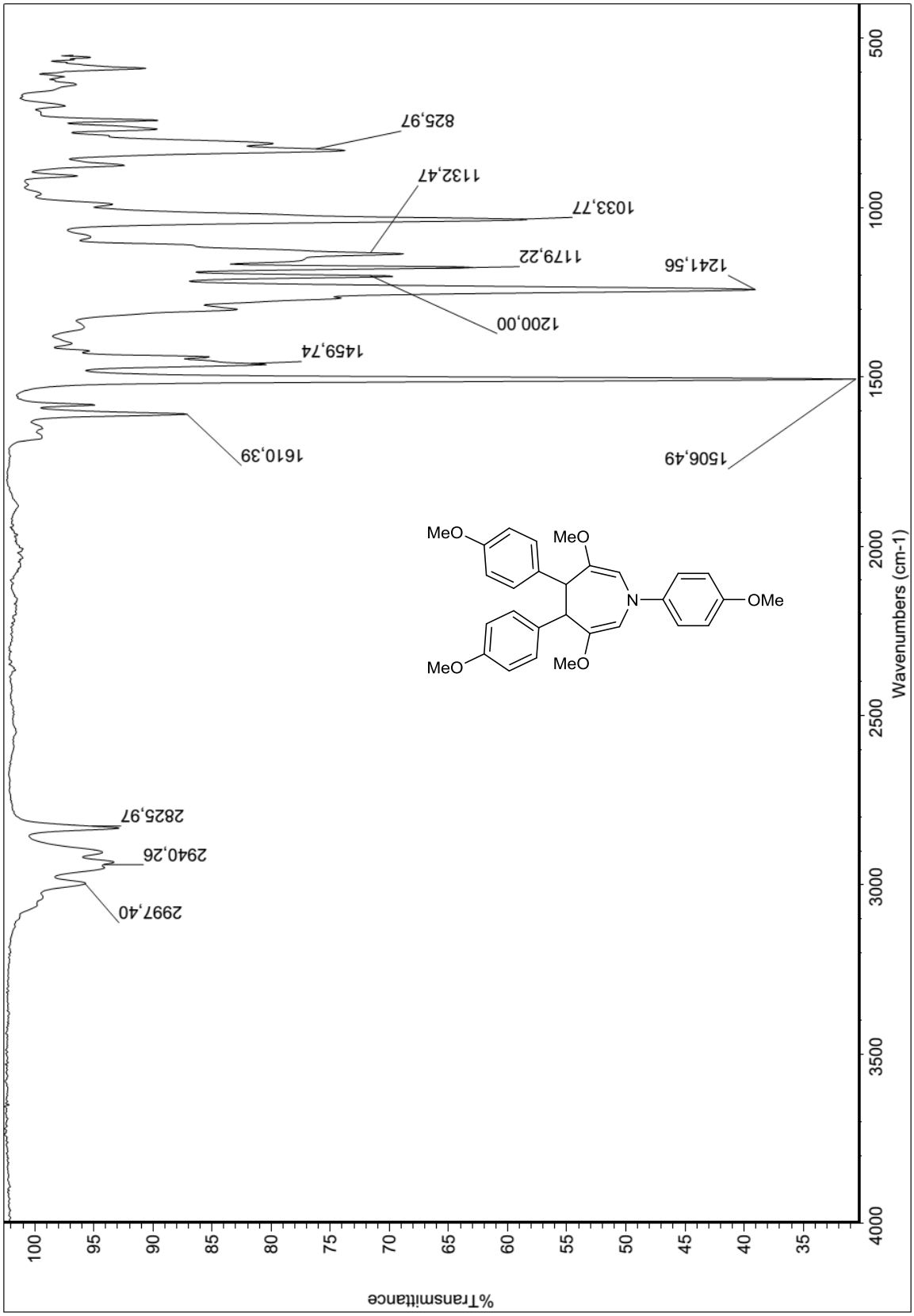
Appendix V.1 ^{1}H-NMR spectrum of azepine 11e



Appendix V.2 ^{13}C-NMR spectrum of azepine 11e



Appendix V.3 IR spectrum of azepine 11e



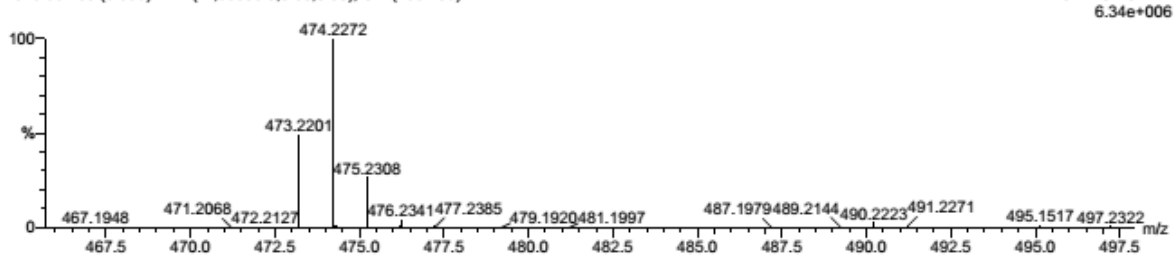
Appendix V.4 MS of azepine 11e

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 2.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd Electron Ions
1078 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-10 O: 0-200
NT-MSLAB-Operator-SVG
2015-95 200 (3.893) AM2 (Ar,35000.0,0.00,0.00); Cm (190:203)

1: TOF MS ASAP+
6.34e+006

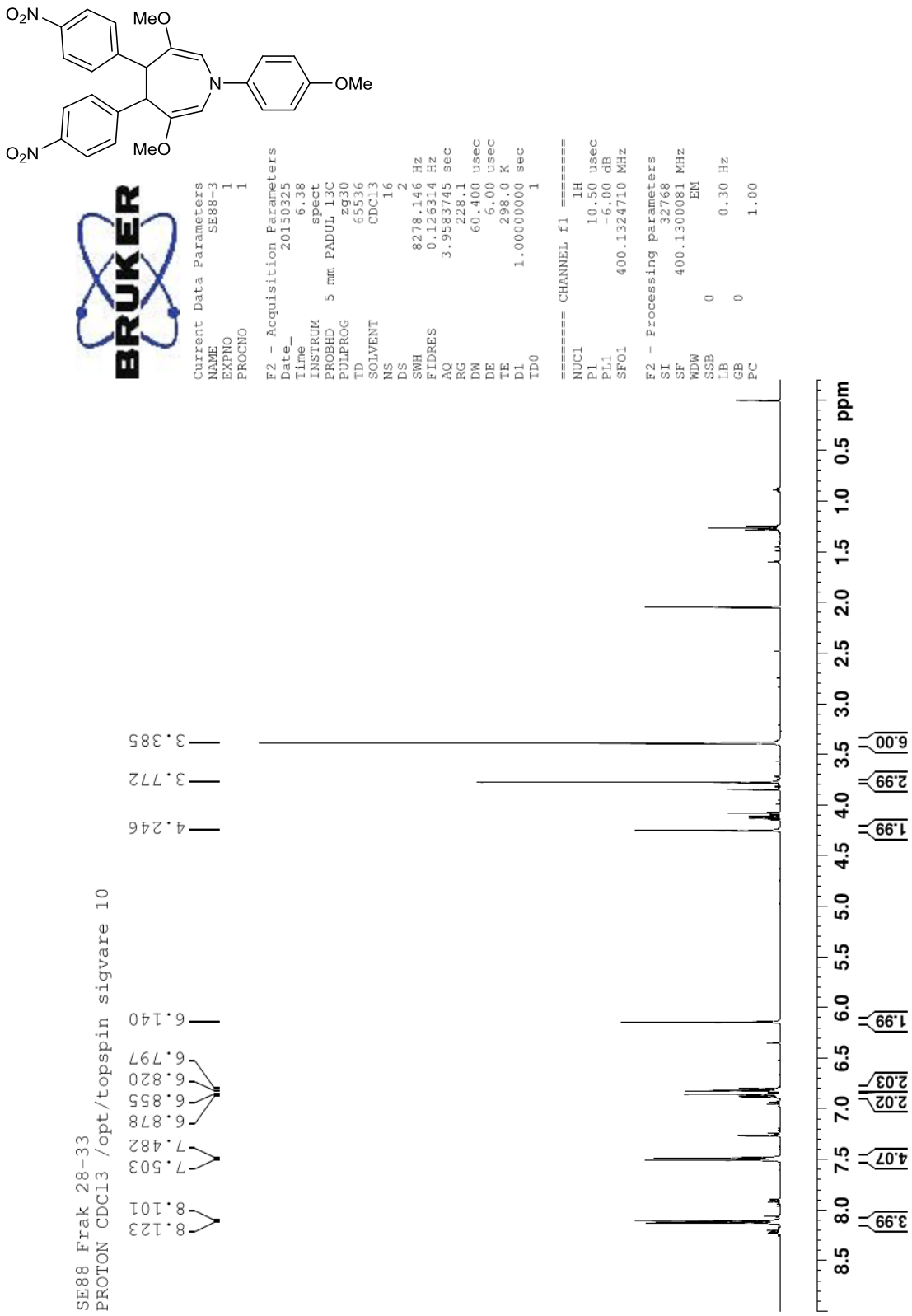


Minimum:				-1.5				
Maximum:		5.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
473.2201	473.2202	-0.1	-0.2	15.0	1272.0	0.122	88.55	C29 H31 N O5
	473.2194	0.7	1.5	3.0	1274.0	2.167	11.45	C13 H31 N9 O10

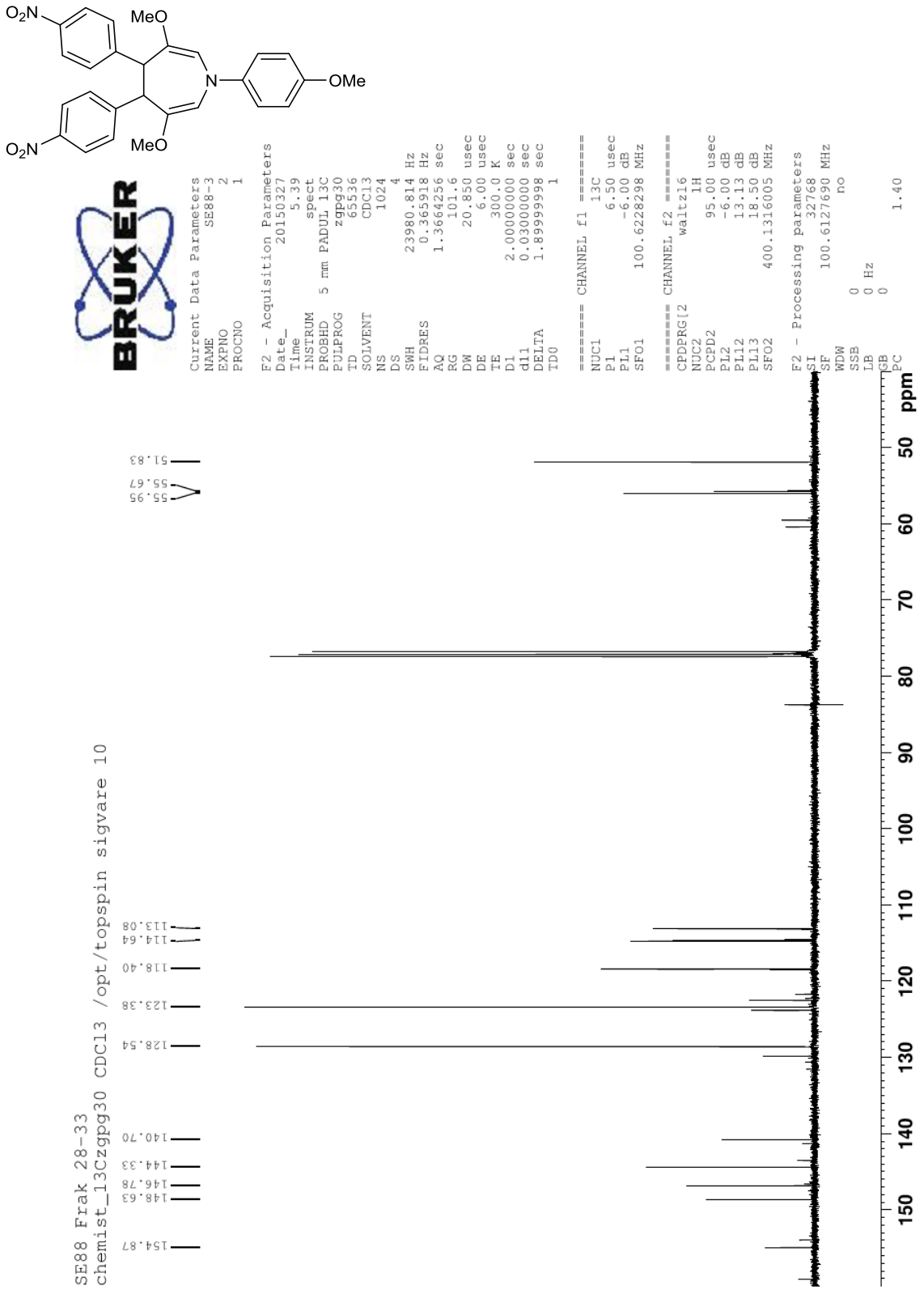
Ion observed [M]*+

Appendix W Spectra of azepine 11f

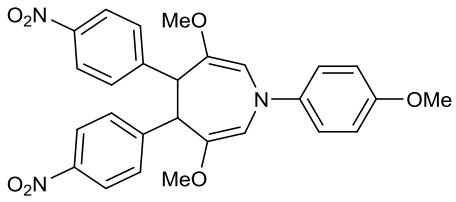
Appendix W.1 ^{1}H-NMR spectrum of azepine 11f

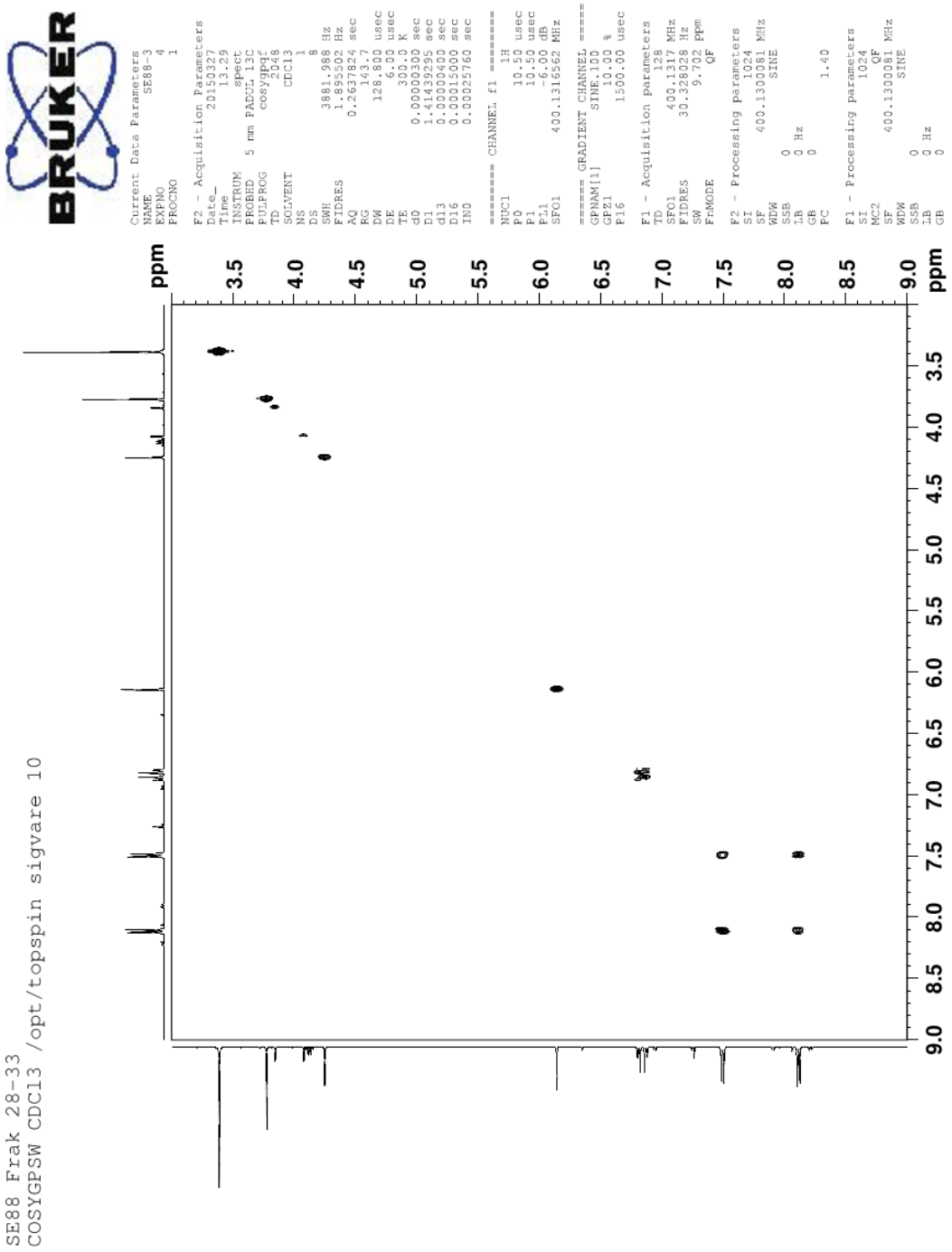


Appendix W.2 ^{13}C-NMR spectrum of azepine 11f

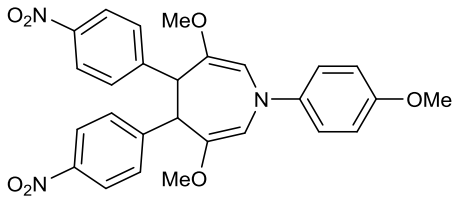


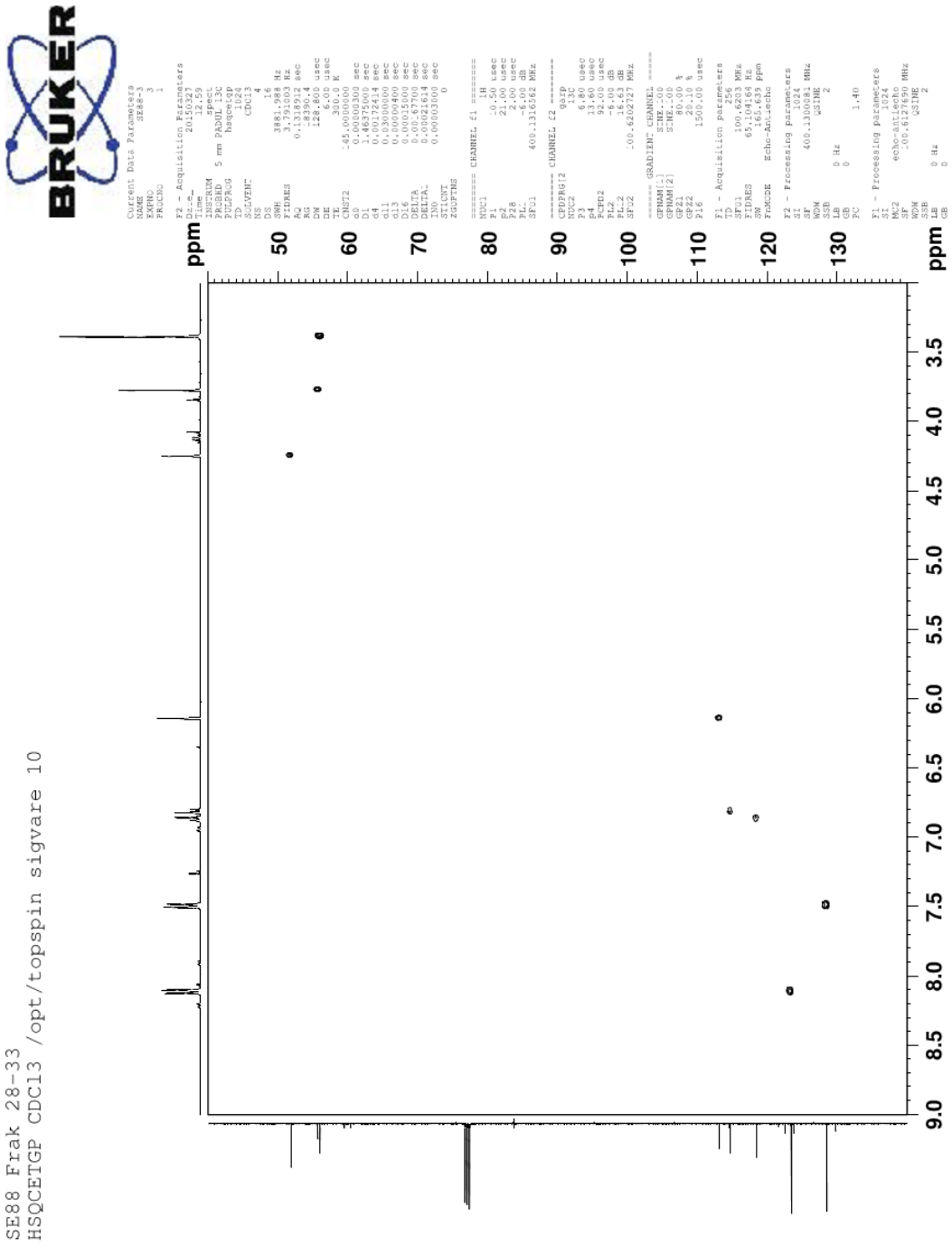
Appendix W.3 COSY spectrum of azepine 11f



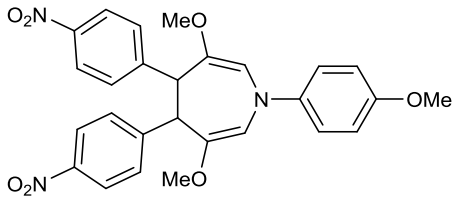


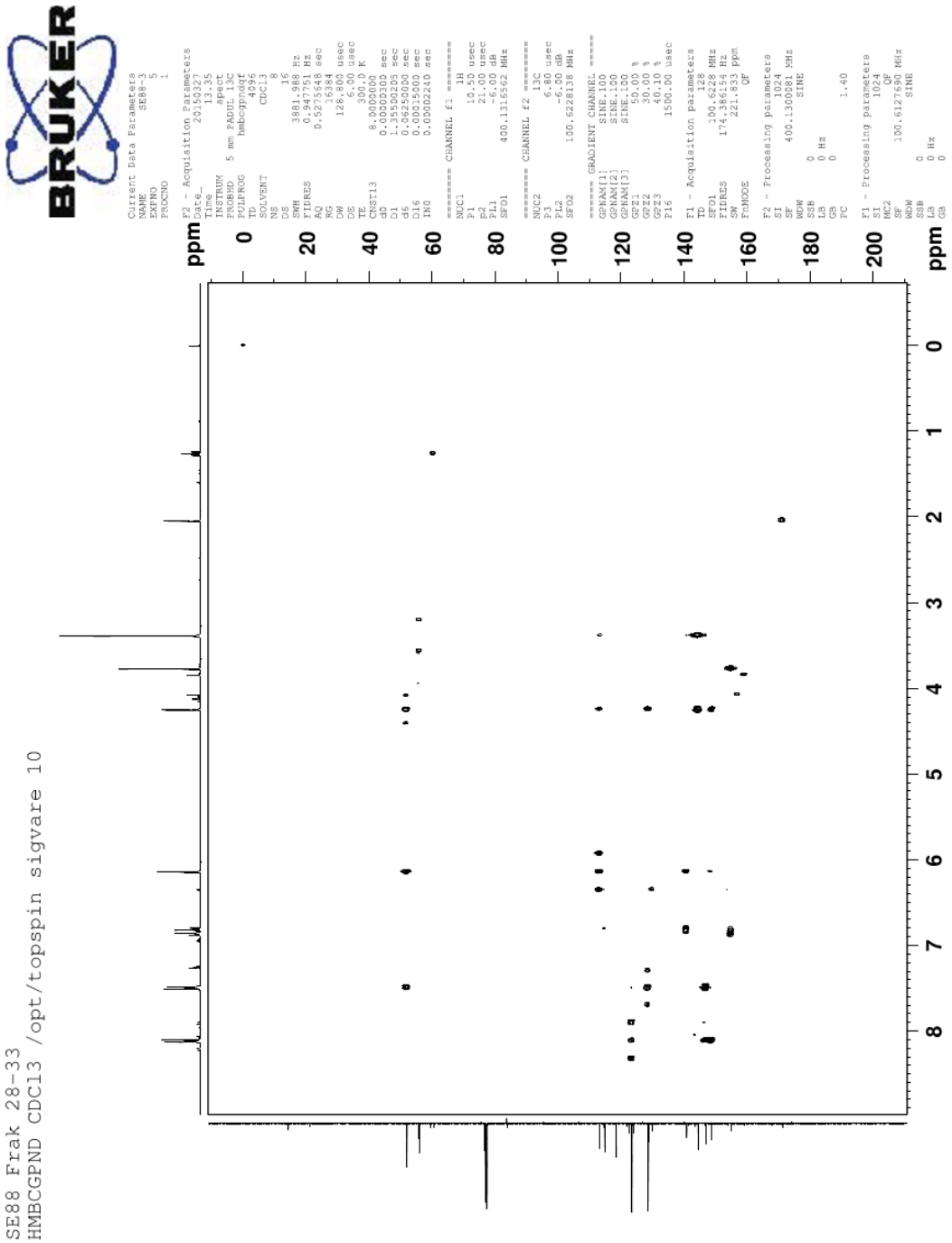
Appendix W.4 HSQC spectrum of azepine 11f



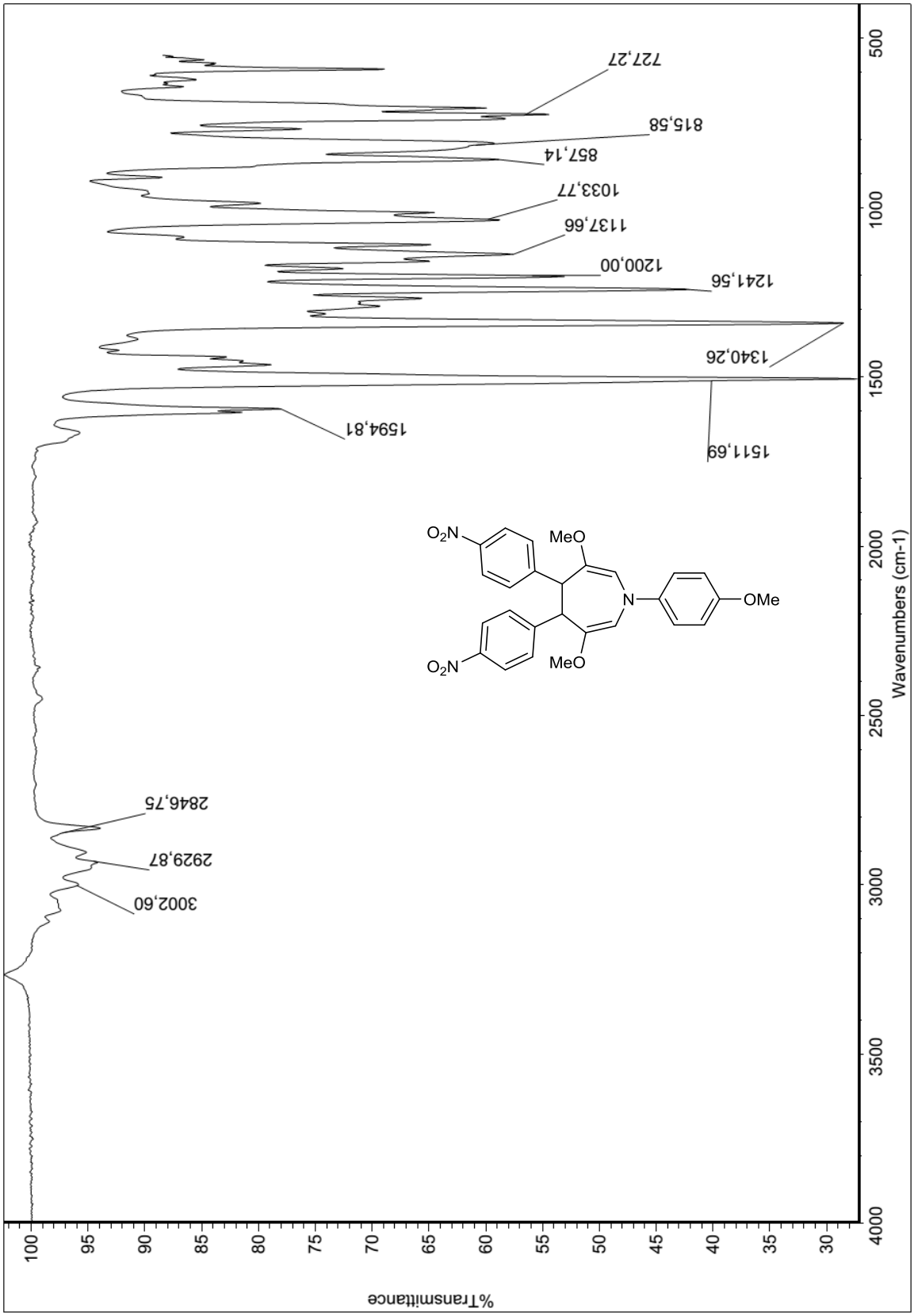


Appendix W.5 HMBC spectrum of azepine 11f





Appendix W.6 IR spectrum of azepine 11f



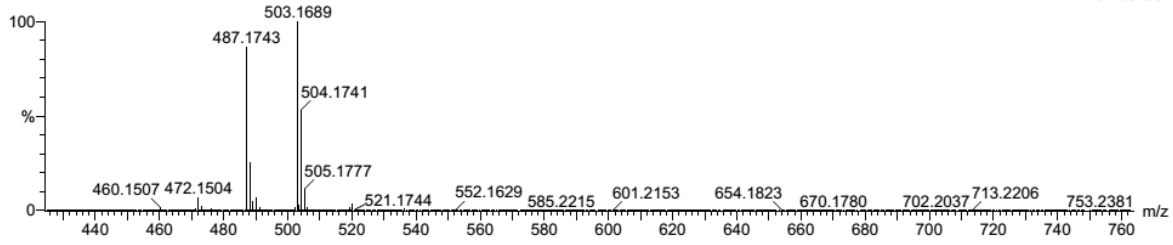
Appendix W.7 MS of azepine 11f

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 2.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd Electron Ions
2315 formula(e) evaluated with 6 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-50 O: 0-200
NT-MSLAB-Operator-SVG
2015-115 310 (6.030) AM2 (Ar,35000.0,0.00,0.00); Cm (297:316)

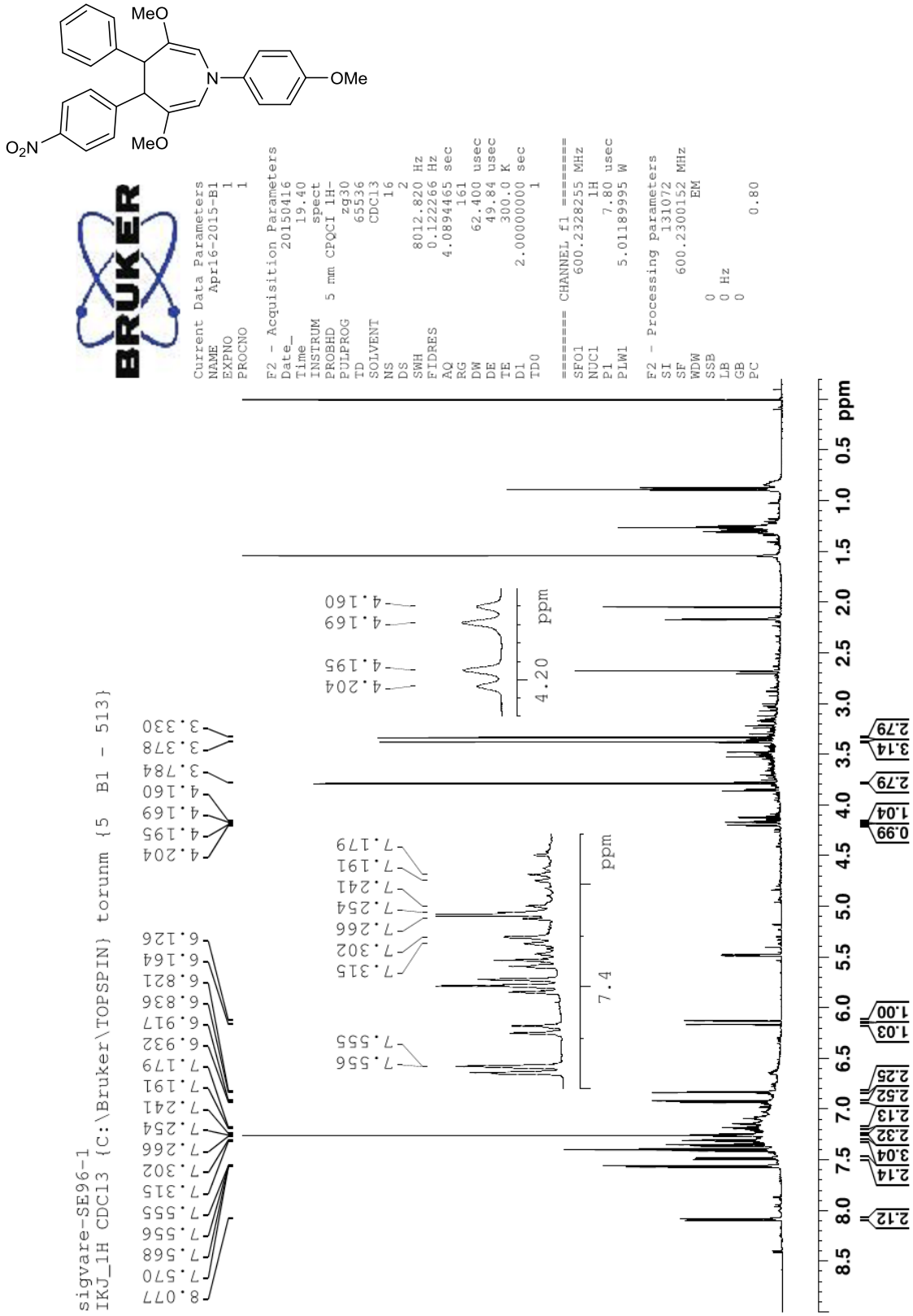
1: TOF MS ASAP+
6.46e+007



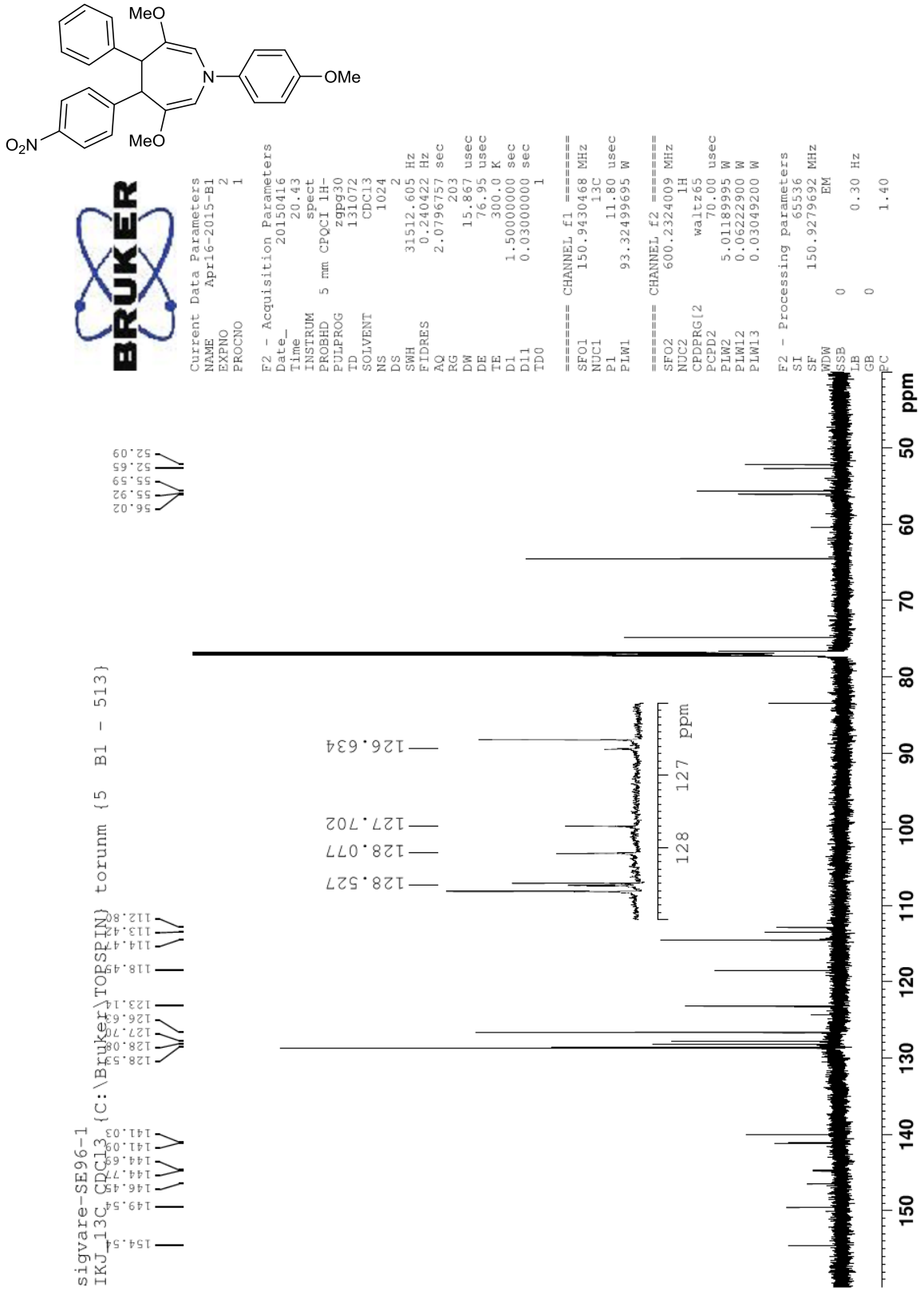
Minimum:				-1.5				
Maximum:		5.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
503.1689	503.1693	-0.4	-0.8	17.0	1352.0	0.172	84.20	C27 H25 N3 O7 Ion observed [M]*+
	503.1684	0.5	1.0	16.0	1358.1	6.331	0.18	C9 H13 N25 O2
	503.1684	0.5	1.0	5.0	1356.5	4.709	0.90	C11 H25 N11 O12
	503.1698	-0.9	-1.8	-1.0	1354.8	2.995	5.00	C14 H33 N O18
	503.1698	-0.9	-1.8	10.0	1356.1	4.266	1.40	C12 H21 N15 O8
	503.1679	1.0	2.0	23.0	1354.3	2.487	8.31	C24 H17 N13 O

Appendix X Spectra of azepine 11h

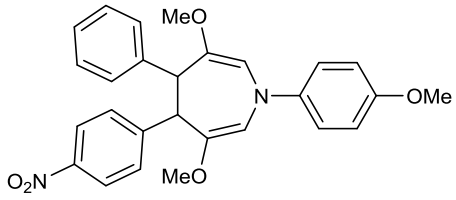
Appendix X.1 ^{1}H-NMR spectrum of azepine 11h

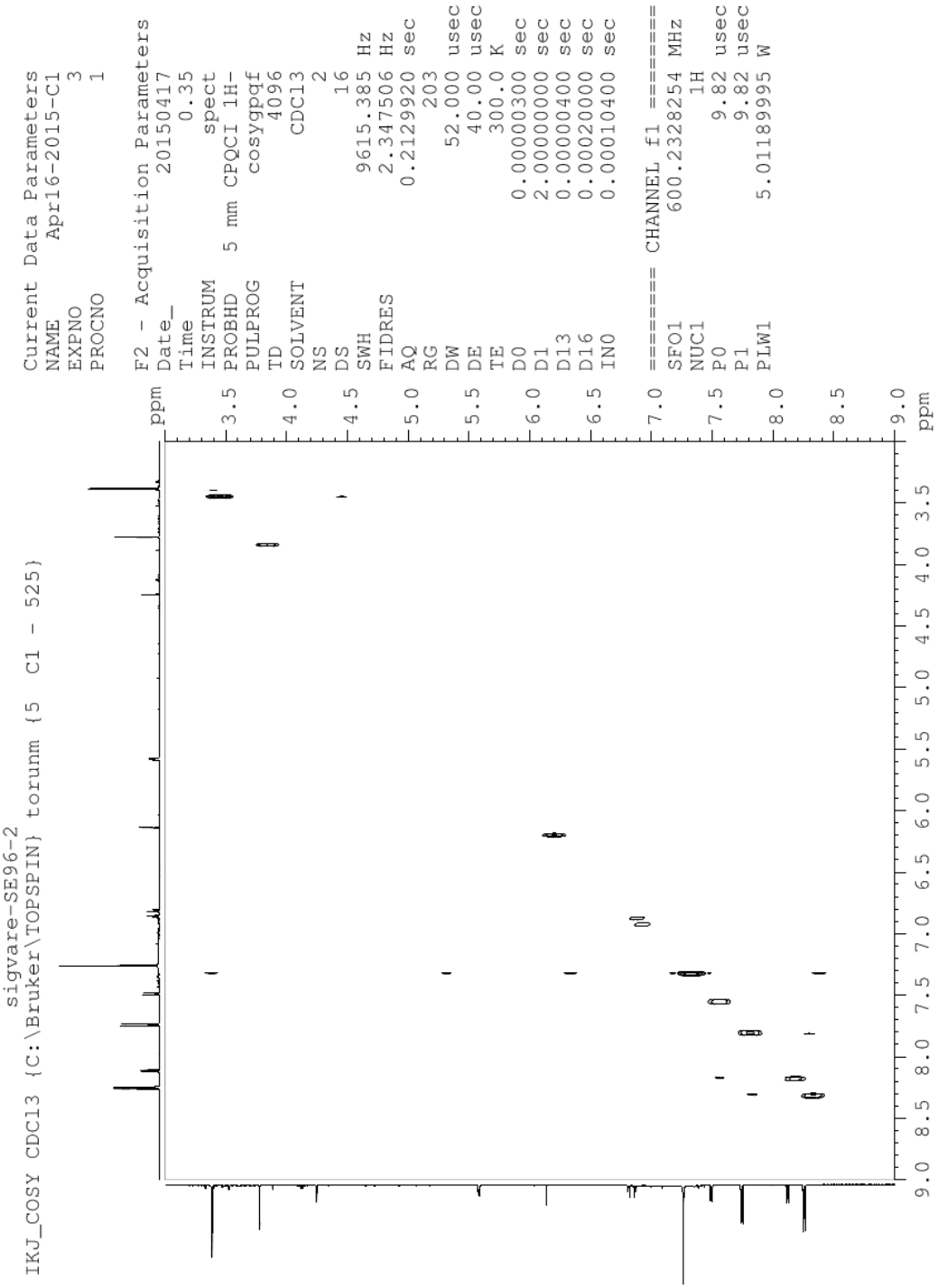


Appendix X.2 ^{13}C-NMR spectrum of azepine 11h

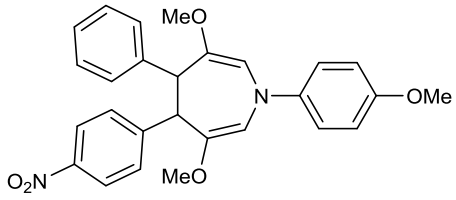


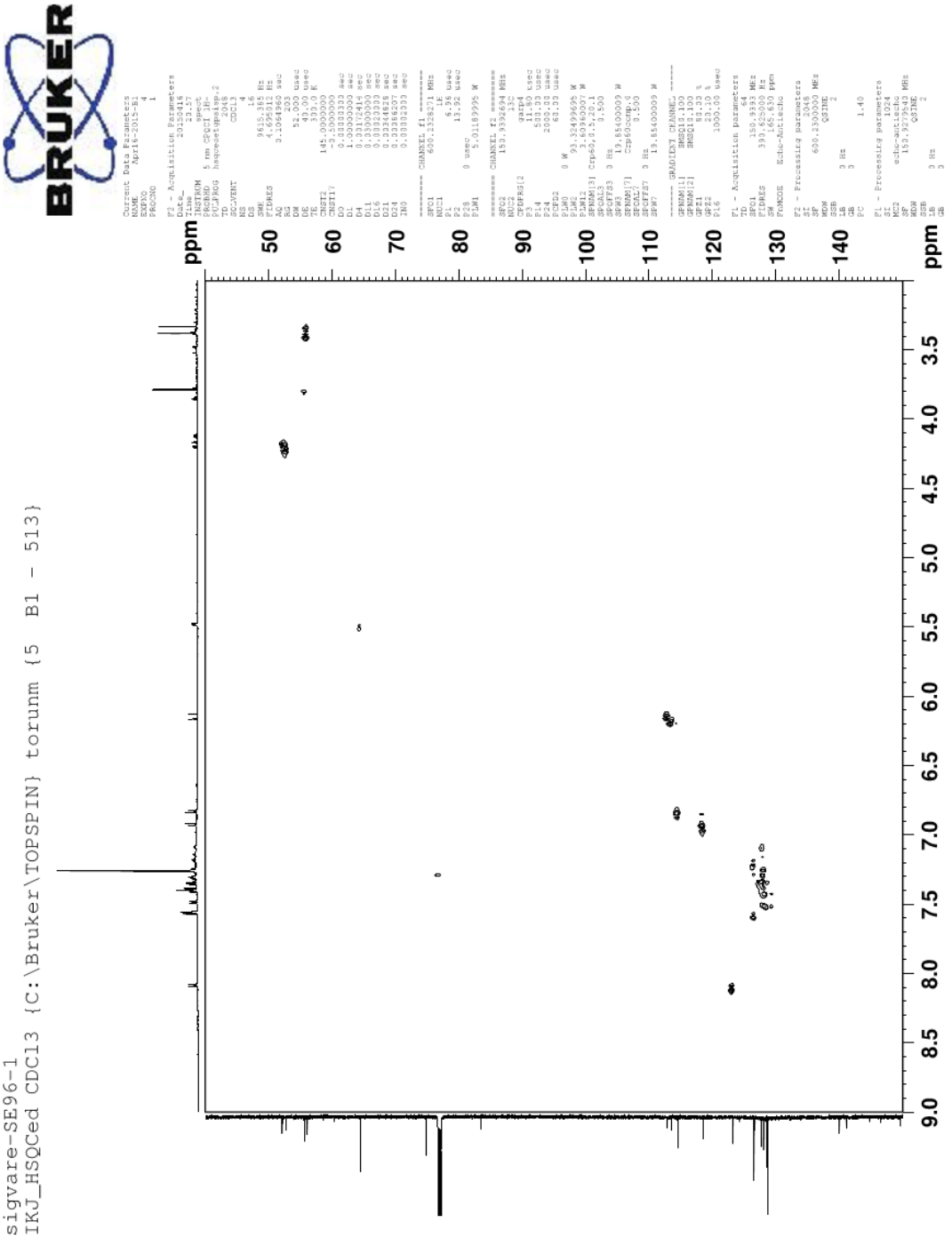
Appendix X.3 COSY spectrum of azepine 11h



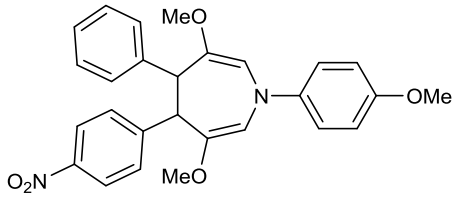


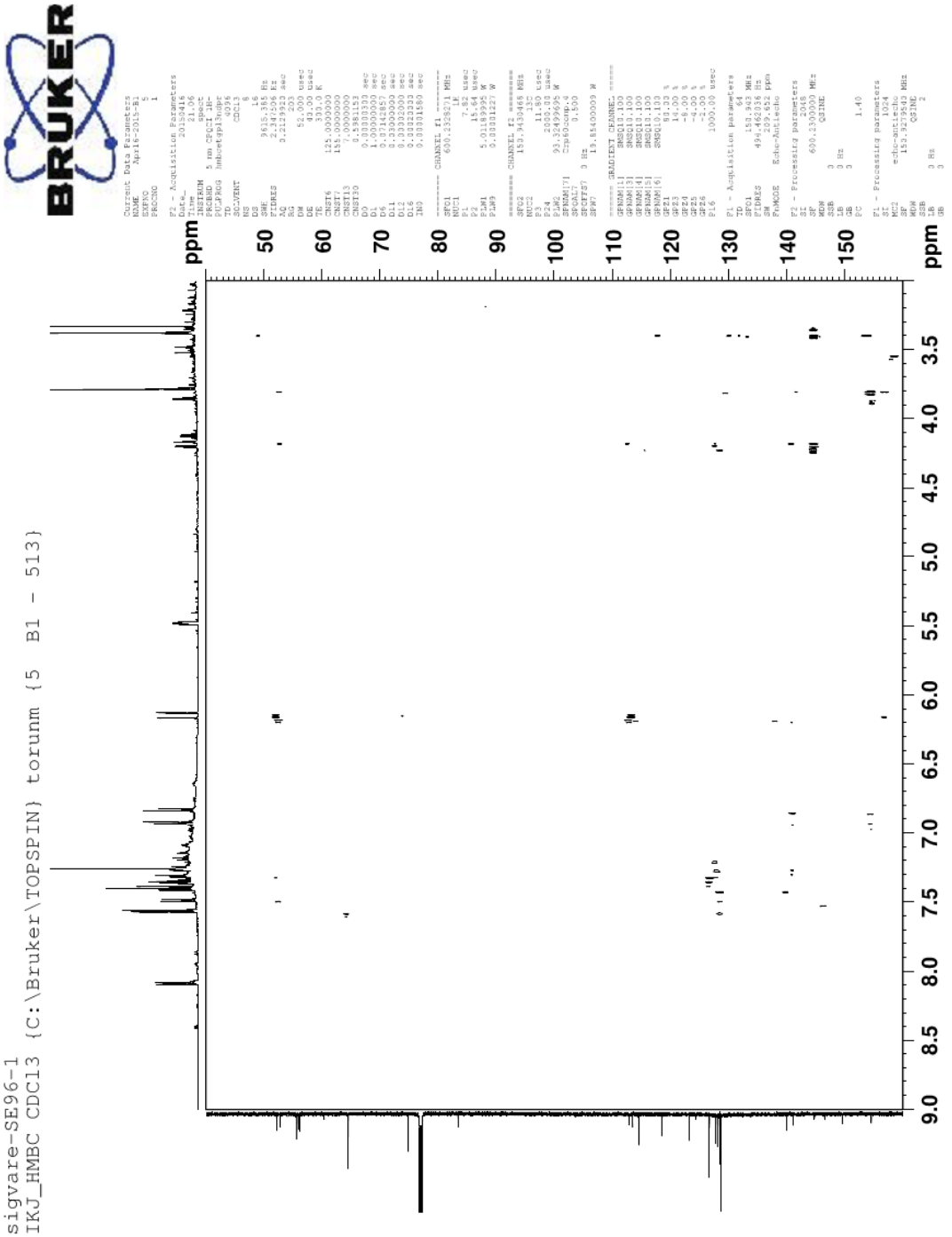
Appendix X.4 HSQC spectrum of azepine 11h



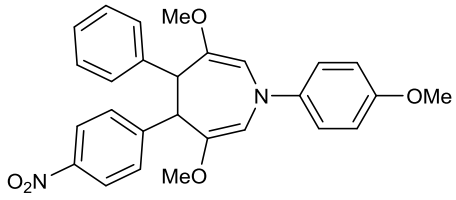


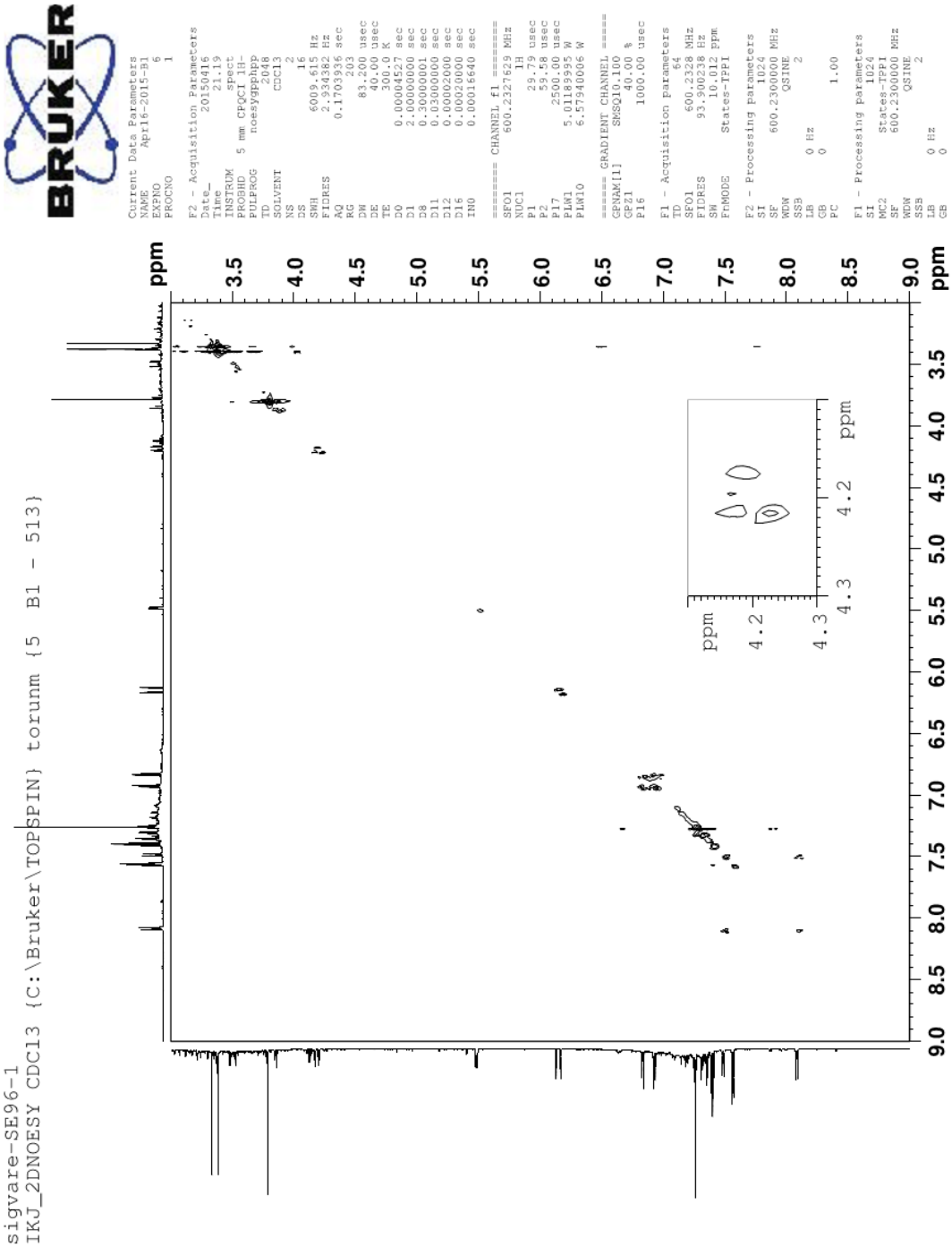
Appendix X.5 HMBC spectrum of azepine 11h



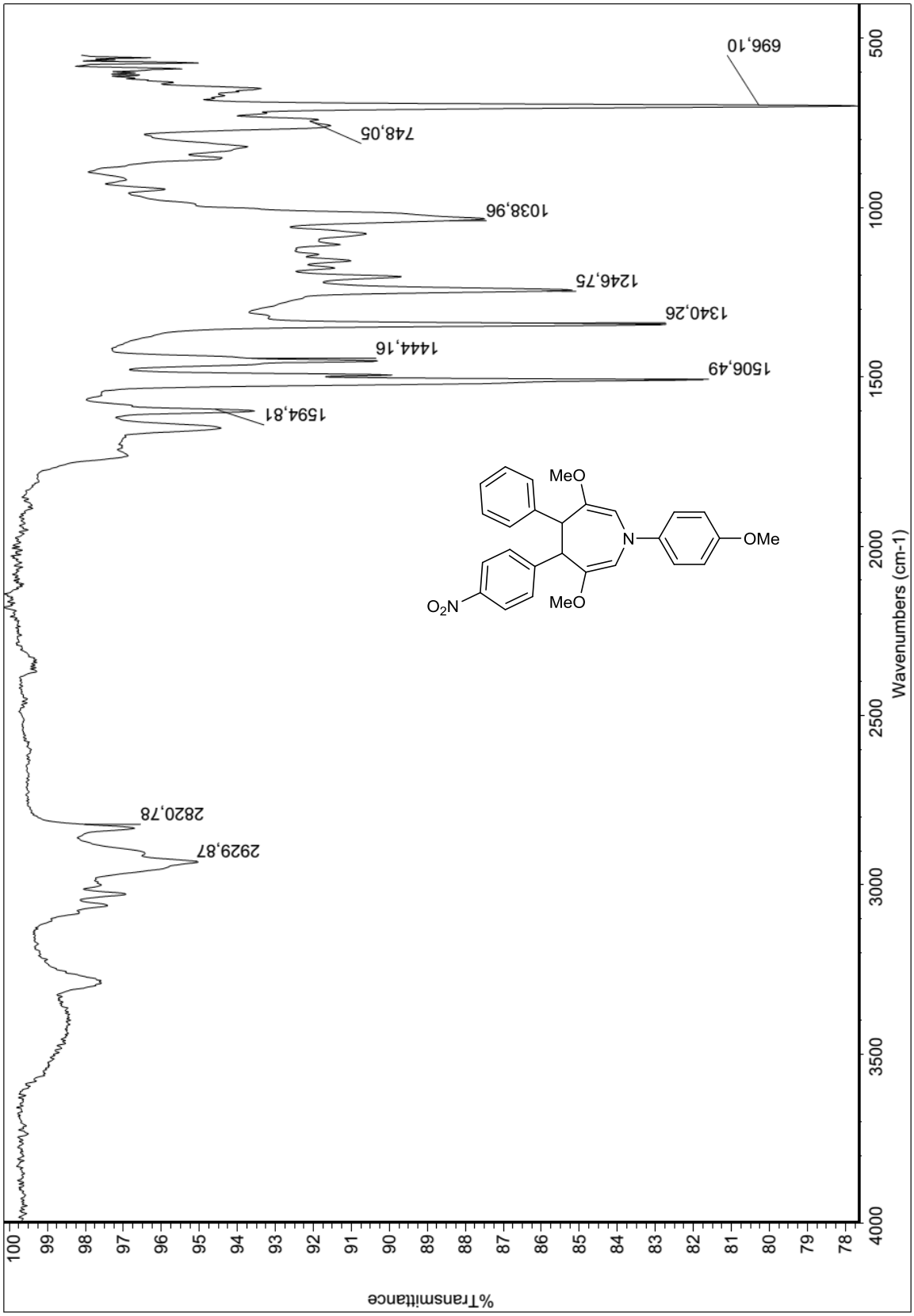


Appendix X.6 NOESY spectrum of azepine 11h





Appendix X.7 IR spectrum of azepine 11h



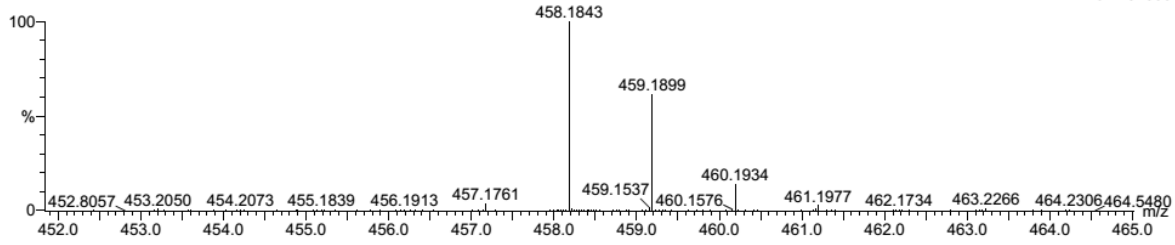
Appendix X.8 MS of azepine 11h

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 2.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd Electron Ions
1760 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-50 O: 0-100
NT-MSLAB-Operator-SVG
2015-158 229 (4.462) AM2 (Ar,35000.0,0.00,0.00); Cm (214:229)

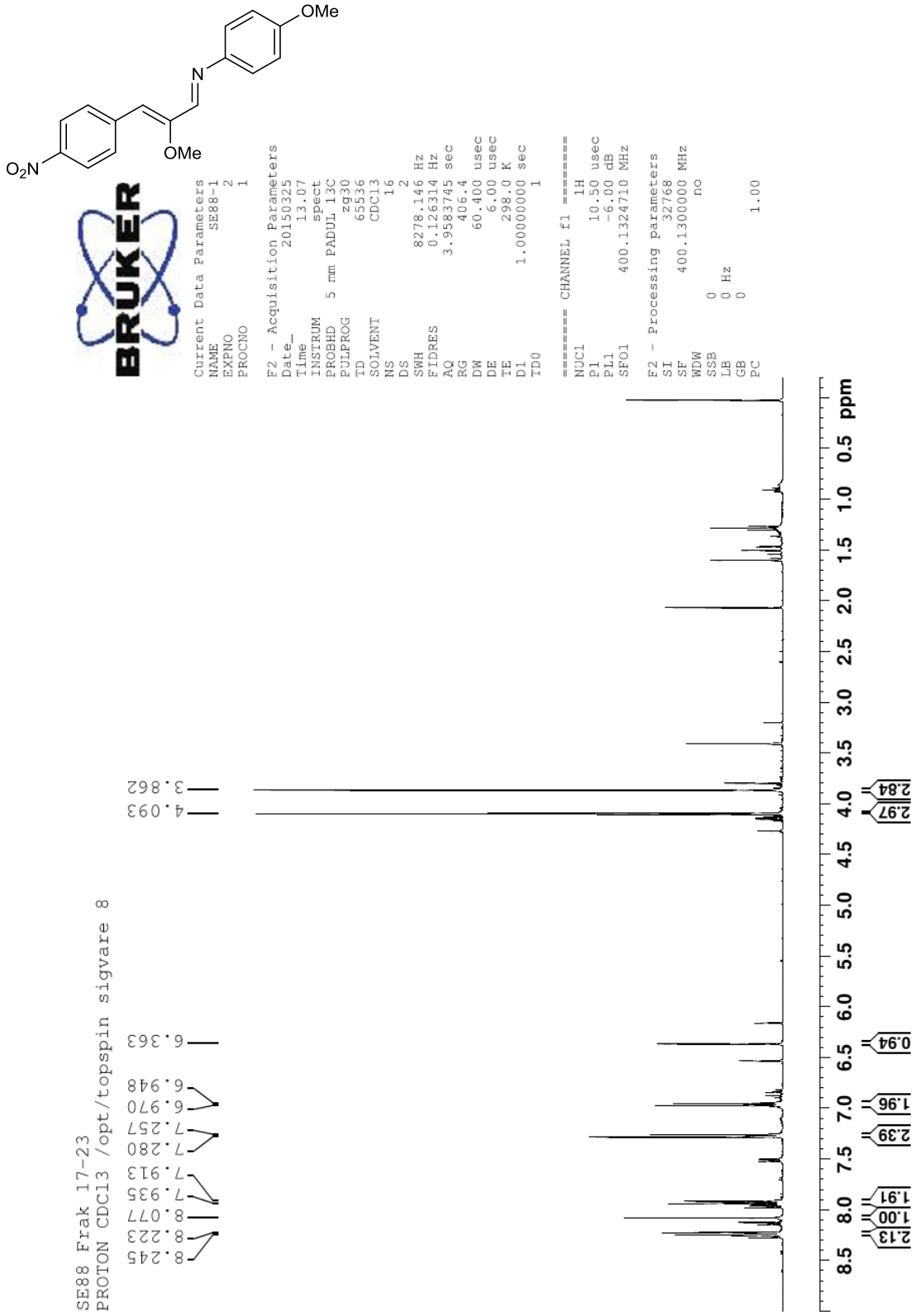
1: TOF MS ASAP+
6.44e+006



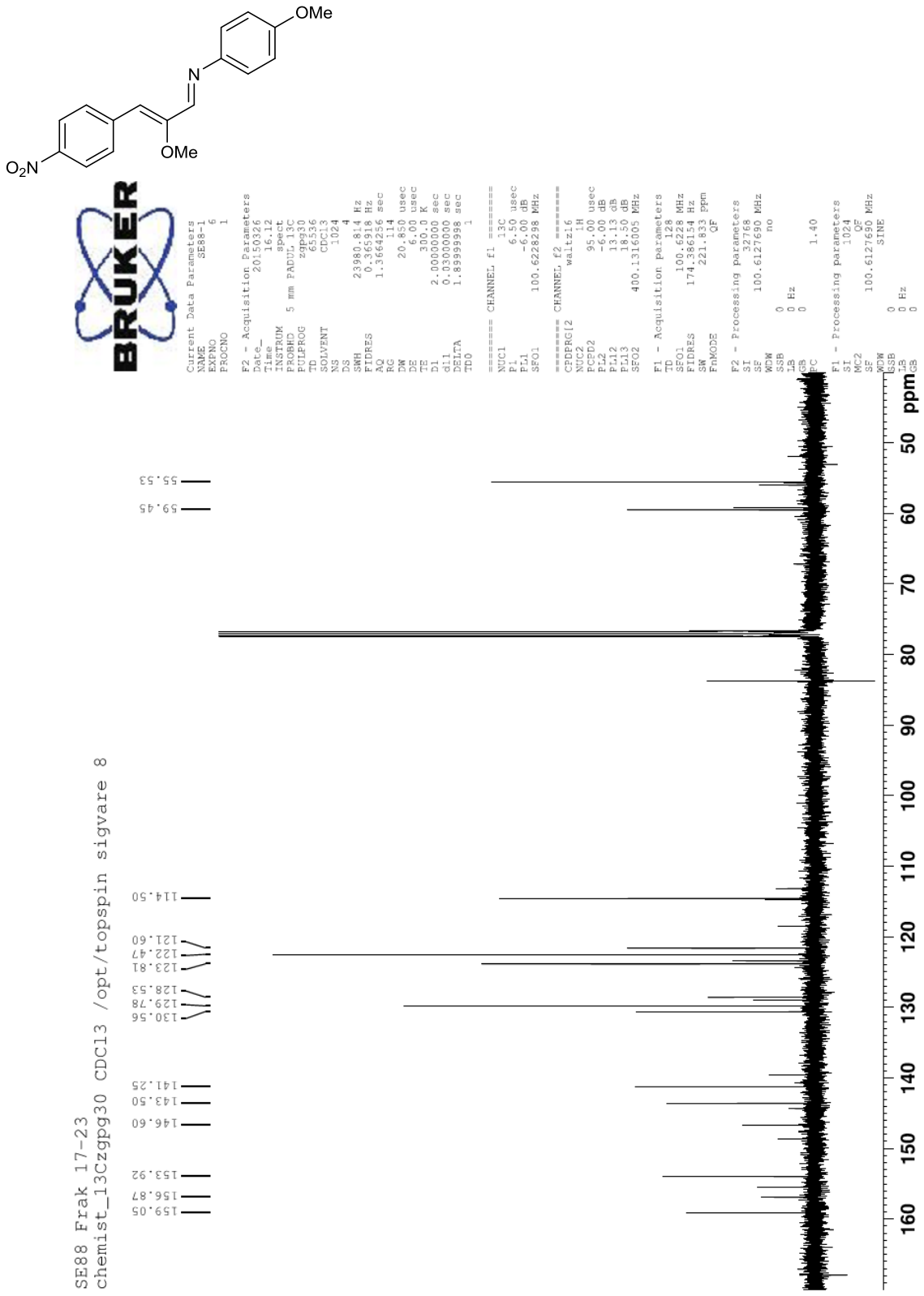
Minimum:				-1.5				
Maximum:		5.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
458.1843	458.1842	0.1	0.2	16.0	1314.6	0.031	96.98	C27 H26 N2 O5 Ion observed [M]*+
	458.1847	-0.4	-0.9	9.0	1318.1	3.501	3.02	C12 H22 N14 O6

Appendix Y Spectra of imine 12

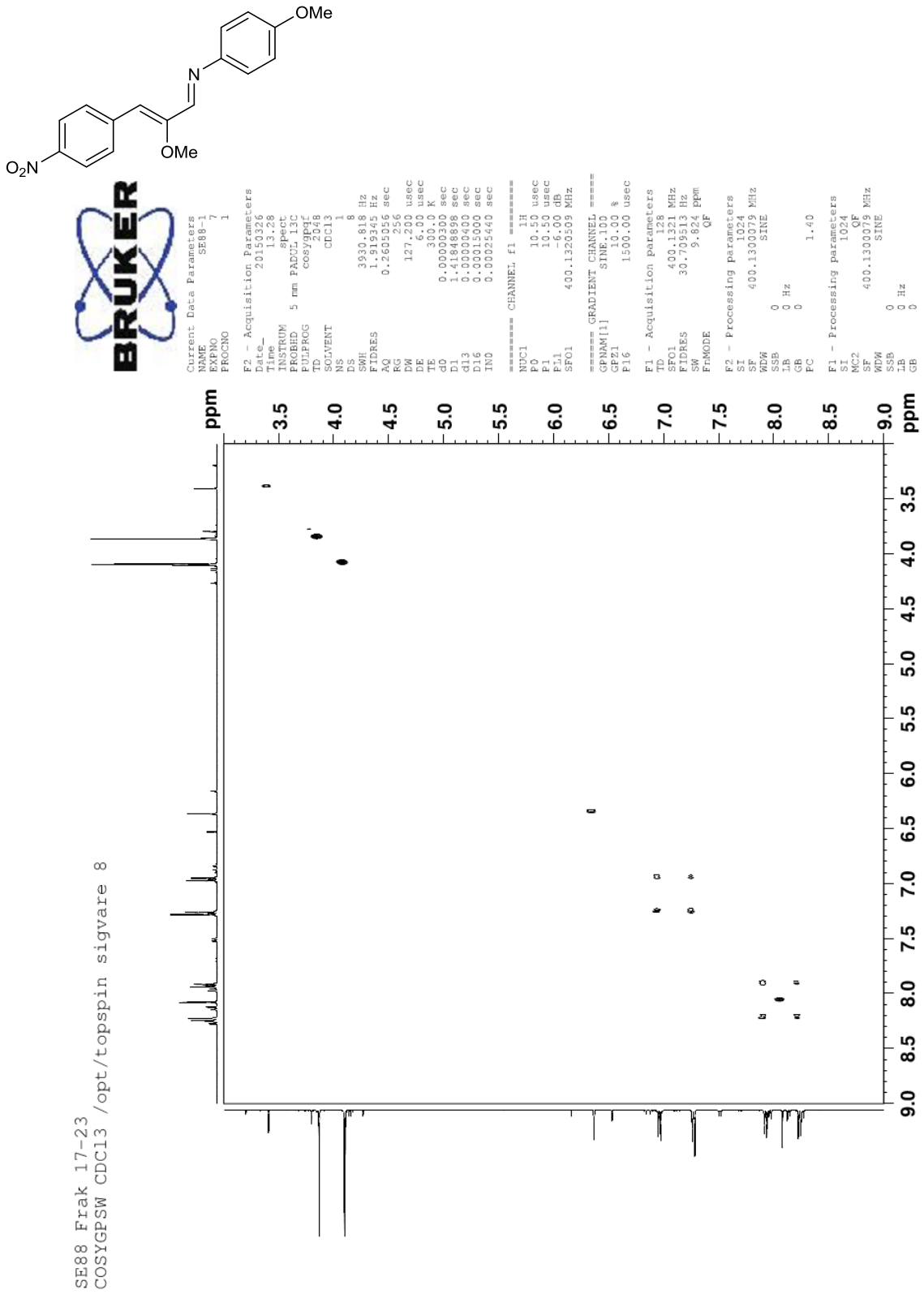
Appendix Y.1 ^{1}H-NMR spectrum of imine 12



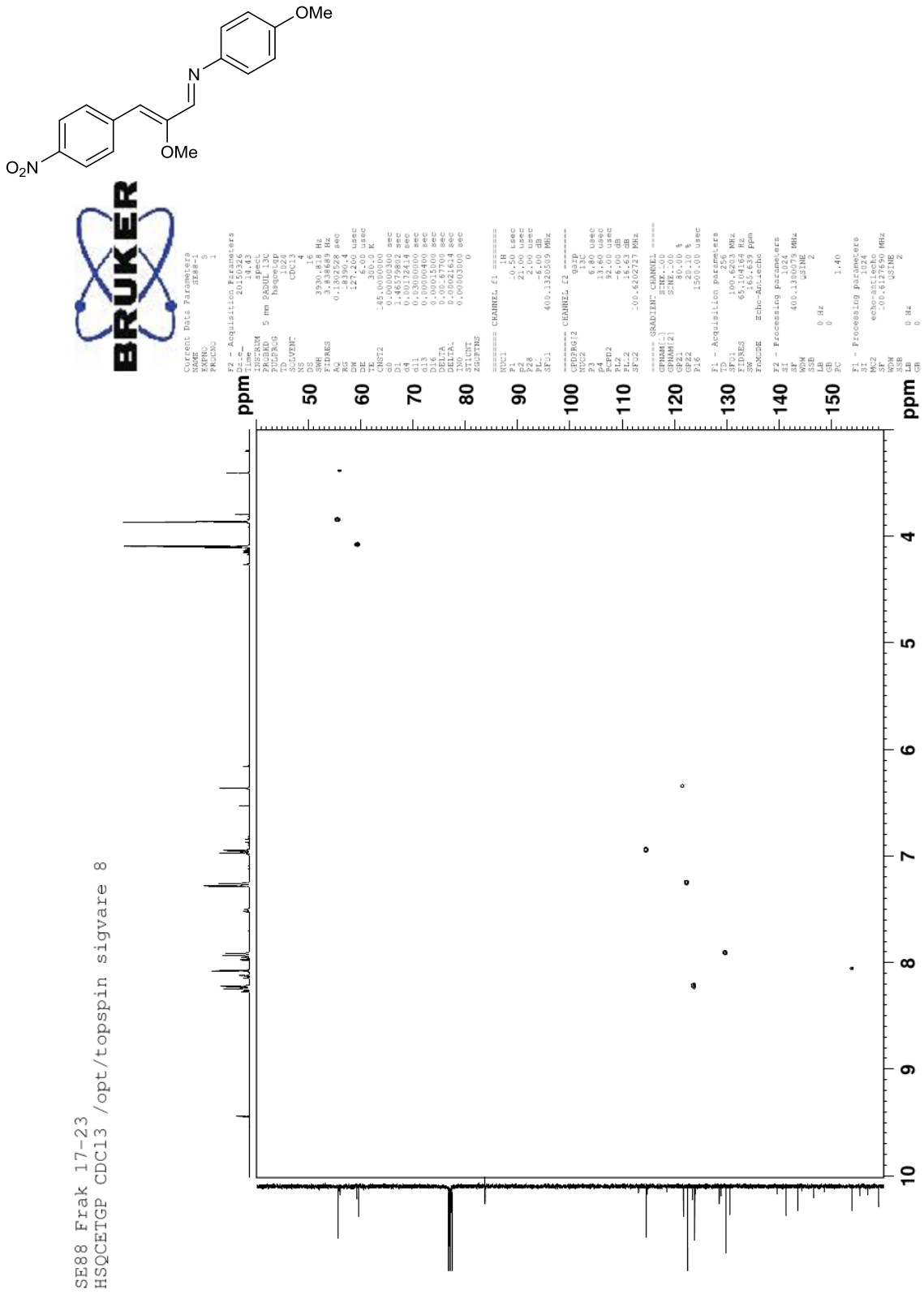
Appendix Y.2 ^{13}C-NMR spectrum of imine 12



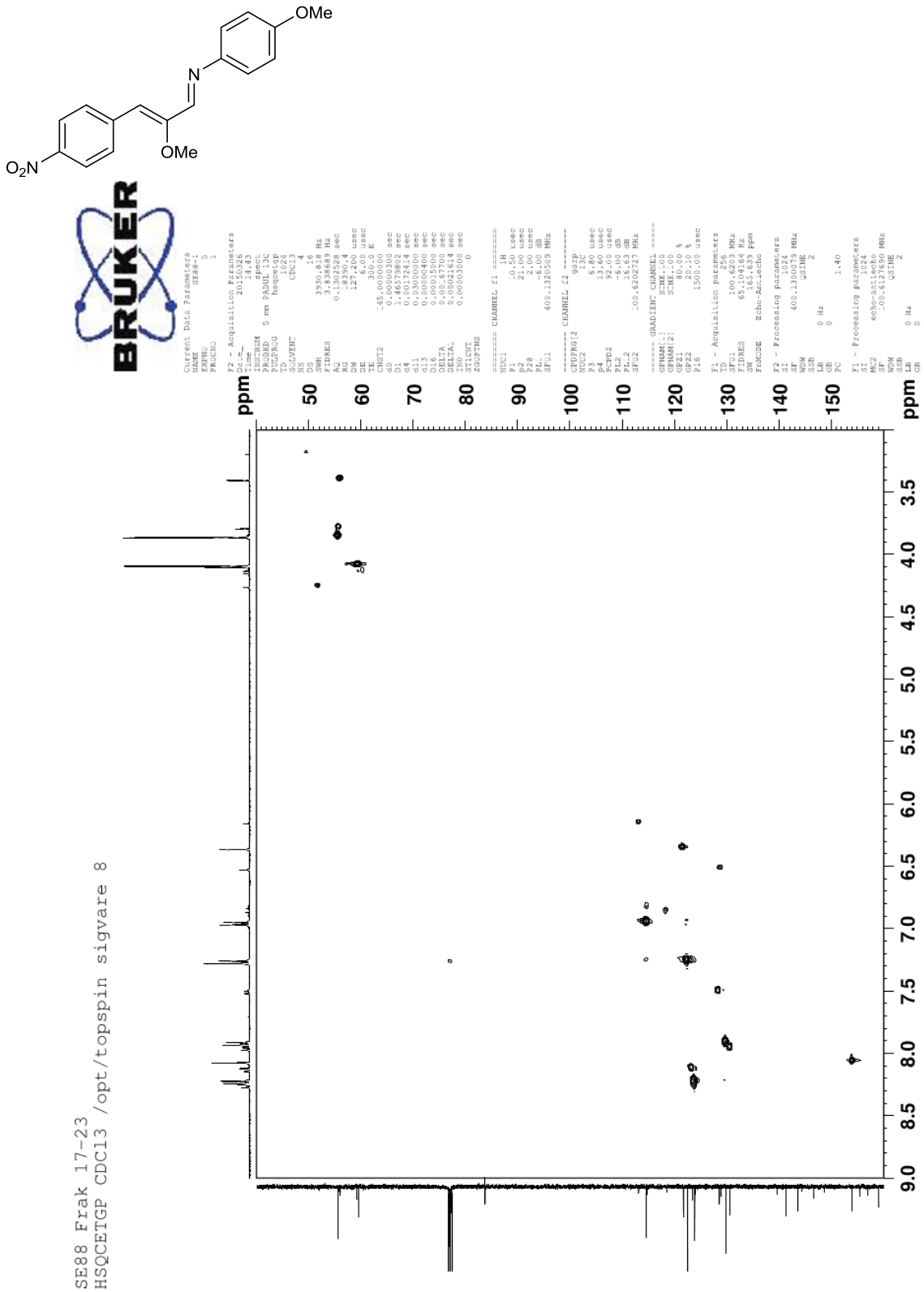
Appendix Y.3 COSY spectrum of imine 12



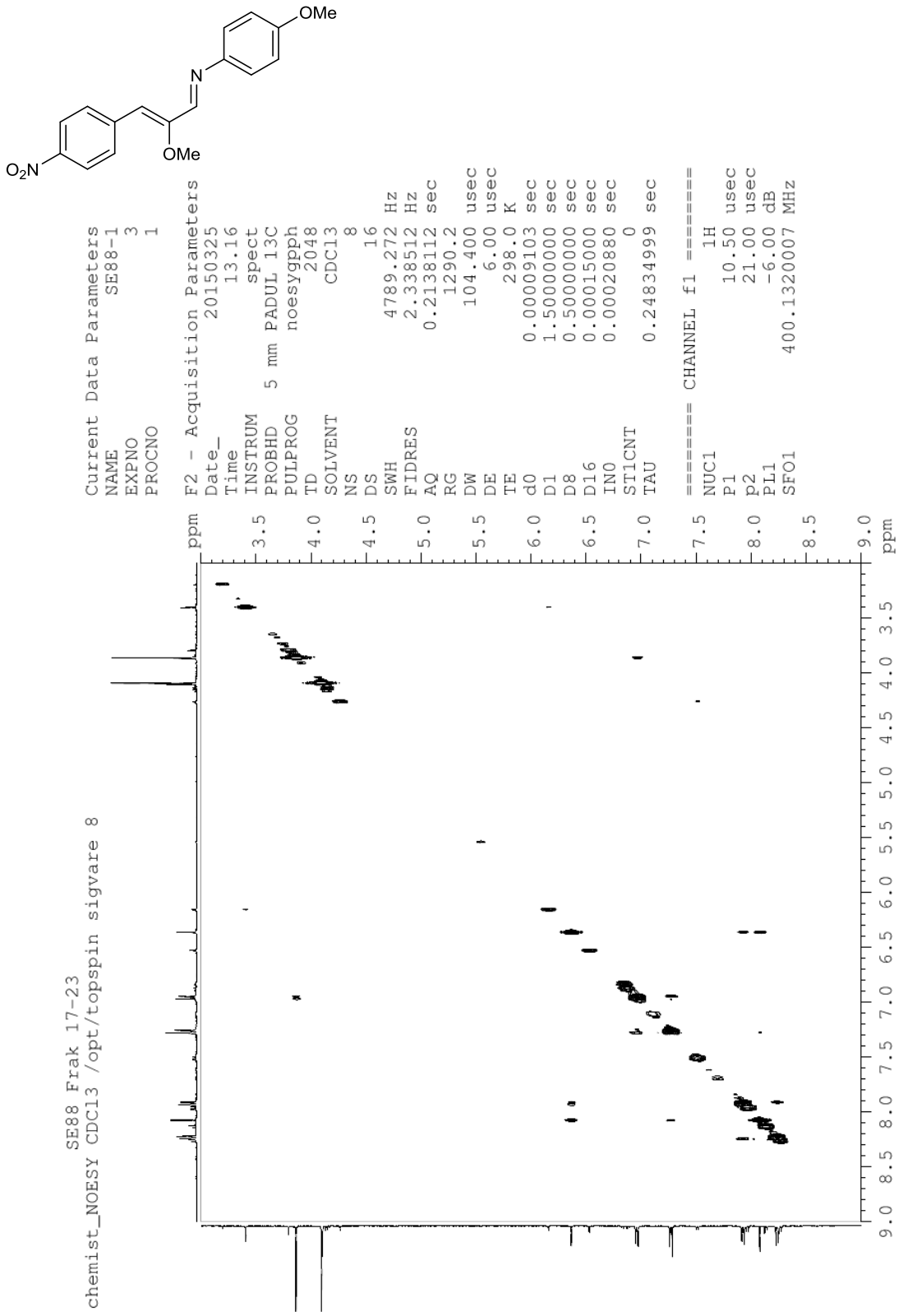
Appendix Y.4 HSQC spectrum of imine 12



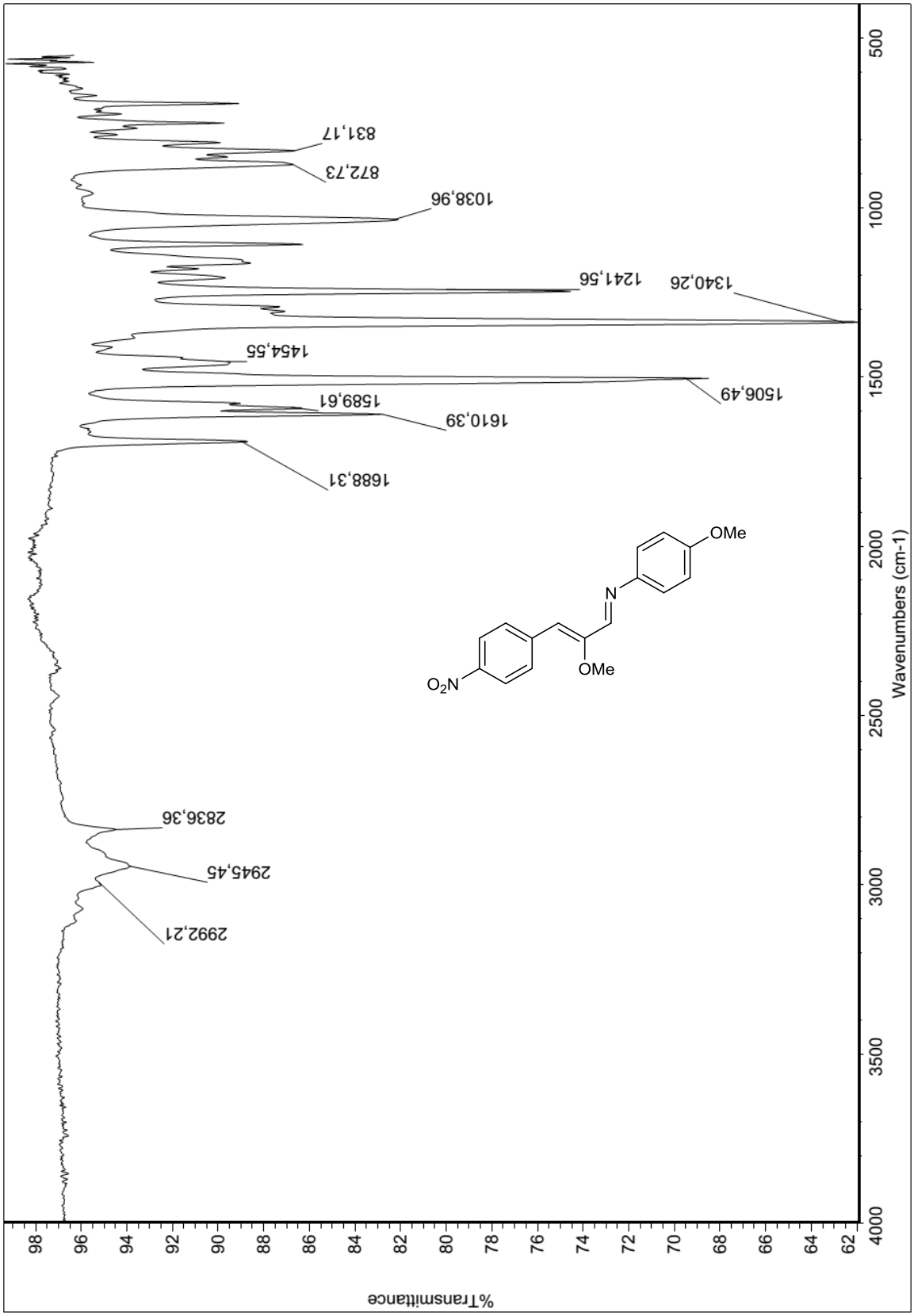
Appendix Y.5 HMBC spectrum of imine 12



Appendix Y.6 NOESY spectrum of imine 12



Appendix Y.7 IR spectrum of imine 12



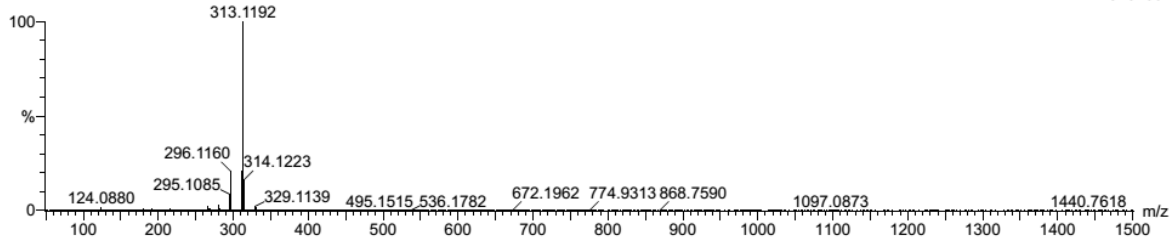
Appendix Y.8 MS of imine 12

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 2.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
672 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-50 O: 0-200
NT-MSLAB-Operator-SVG
2015-114 168 (3.273) AM2 (Ar,35000.0,0.00,0.00); Cm (166:178)

1: TOF MS ASAP+
1.31e+007



Minimum:				-1.5				
Maximum:		5.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
313.1192	313.1193	-0.1	-0.3	3.5	1707.6	11.790	0.00	C2 H13 N14 O5
	313.1188	0.4	1.3	10.5	1695.8	0.000	100.00	C17 H17 N2 O4 Ion observed [M+H]+

Appendix Z ^{1}H-NMR spectrum of imine 13