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Vinyl Amide Reactions in the Presence of Gold(I) Catalyst

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Declaration

I hereby declear that the work presented in this thesis has been conducted independently and in accordance with the rules and regulations for the integrated Master's degree in Industrial chemistry and biotechnology (sivilingeniør/masters programme, 5 years) at the Norwegian University of Science and Technology (NTNU). The work has been conducted from October 2011 to March 2012

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Guro Blakstad

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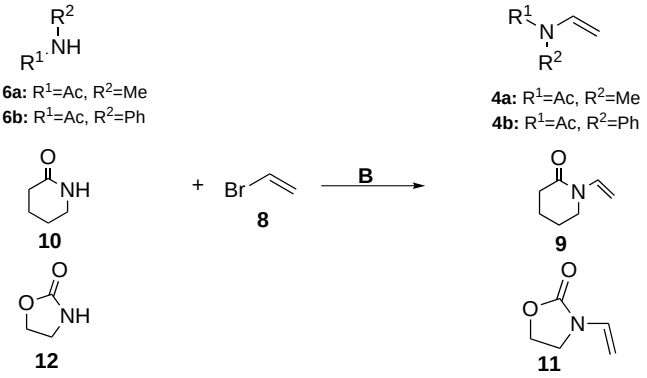
To my friends, thank you for taking me out of my bubble for coffee and food.

A special thanks to Maren Bøe for correcting my chemical english. And finally, to my dear friend, Astrid Lydersen, thank you for being my personal assistant, driver, chef, technical support and mental punching bag. You are worth your weight in gold.

Summary

The purpose of this project has been to investigate reactions with vinyl amides in the presence of gold(I) catalyst. Vinyl amides are good nucleophiles, and four vinyl amides were synthesized in a copper catalyzed cross-coupling reaction (Scheme 1). Reactions of **6a-b**, **10** and **12** afforded acyclic vinyl amides **4a-b** (33-43%) and heterocyclic vinyl amides N-vinyl valerolactam **9** (43%) and 3-vinyloxazolidin-2-one **11** (89%).



Scheme 1 Preparation of vinyl amides **4a-b**, **9** and **11** substrates

Terminal triple bond systems are useful in gold(I) catalyzed reactions since gold(I) activates the π-cloud for nucleophilic attack. Propargyl acetals are suitable substrates for such gold(I) catalyzed reactions. Thus, two new propargyl acetals, methoxy acetal **1a** and ethoxy acetal **1b**, were synthesized from alcohol **2** and vinyl ethers **3a-b** in acid catalyzed reactions (40-60% yields) (Scheme 2).

Scheme 2 Preparation of propargyl acetals **1a-b** substrates

The first part of this project has been to investigate gold(I) catalyzed reactions of propargyl acetals with vinyl amides. Gold catalysts are known to be alkynophilic, activating π-systems such as propargylic substrates for nucleophilic attack, by e.g vinyl amides. This makes propargyl acetals **1a-b** and the vinyl amides suitable subtrates in gold(I) catalyzed reactions.

Gold catalyst **I** has been used in this project (Figure 1).

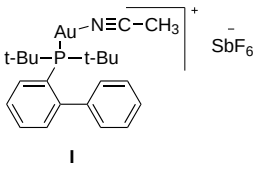


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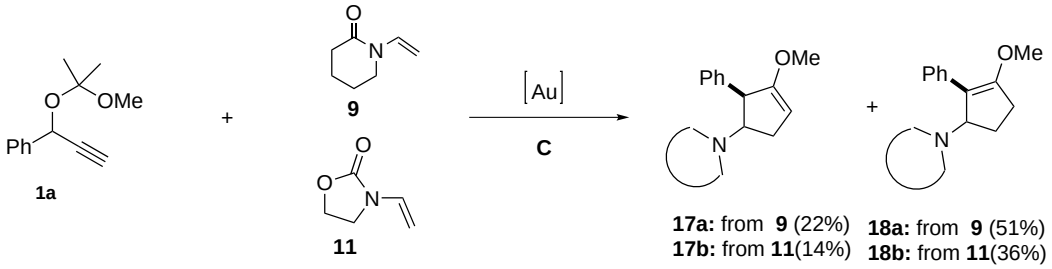
Figure 1 Gold(I) catalysts used in the project

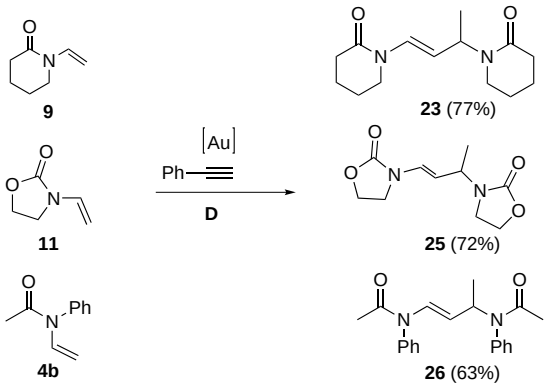
The cyclopentenyl products **17a** and **18a** (22-51%) were obtained in a gold(I) catalyzed [3+2] cycloaddition reaction of methoxy acetal **1a** and vinyl amides **9** and **11**, as two vinyl ether isomers. The corresponding products **17b** and **18b** (14-36%) were obtained in a similar reaction (Scheme 3).



Scheme 3 Gold(I) catalyzed reactions between acetal **1a** and heterocyclic vinyl amides **9** and **11**

Formation of the cyclopentenyl products **17-18** indicates that electron releasing substrates would rather undergo cyclopentenylation than cyclopropanation.

The second part of this project was the investigation of vinyl amide dimerization reactions. A variety of catalytic conditions are known to promote selective homo-and heterodimerization of vinyl compounds. We wanted to investigate dimerization reactions of acyclic vinyl amides **4a-b** and the heterocyclic vinyl amides **9** and **11** in the presence of phenylacetylene and gold(I) catalyst. The vinyl amides **4b**, **9** and **11** successfully afforded homodimerization products **23**, **25** and **26** in 63-77% yield (Scheme 4).

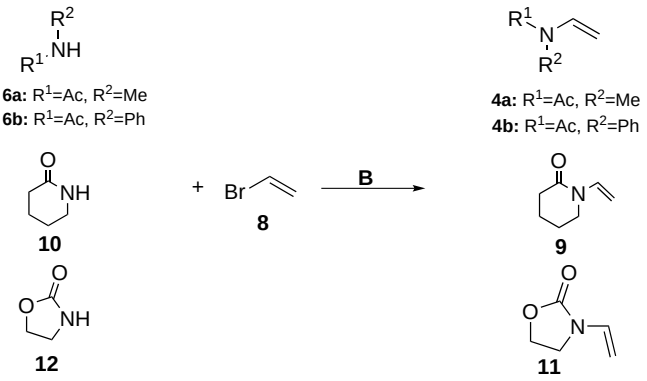


Scheme 4 Dimerization reactions of vinyl amides **4b**, **9** and **11**

The effect of the gold(I) catalyst in the new dimerization reactions is discussed in this project.

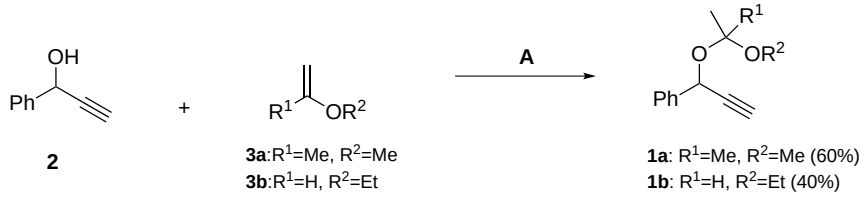
Sammendrag

Hovedmålet med denne masteroppgaven har vært å utforske reaksjoner med vinyl amider i nærvær av gull(I)katalysator. Vinylamider er gode nukleofiler i gullkatalyserte reaksjoner, og fire vinyl amider ble syntetisert i kobberkatalyserte cross-koblingsreaksjoner (Skjema 1). Asykliske vinylamider **4a-b** (33%), og heterosykliske vinylamider N-vinylvalerolactam **9** (43%) og 3-vinyloxazolidin-2-one **11** (89%) ble syntetisert fra vinylbromid og hhv **6a-b**, δ-valerolactam **10** og oxazolidin-2-one **12**.



Skjema 1 Fremstilling av vinylamider **4a-b**, **9** og **11**

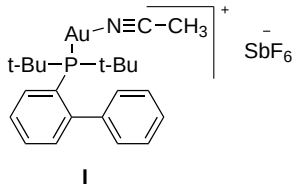
Terminale trippelbond-systemer er nyttige i gull(I)katalyserte reaksjoner. Gull(I) er kjent for å aktivere π-systemer for nukleofilt angrep. To nye propargylacetaler, metoksyacetal **1a** og etoksyacetal **1b**, ble derfor fremstilt i en syrekatalysert reaksjon (40-60% utbytte) (Skjema 2).



Skjema 2 Fremstilling av propargylacetaler **1a-b**

Første del av dette prosjektet har vært å undersøke gull(I)katalyserte reaksjoner av propargylacetaler med vinylamider. Gull(I)katalysatorer er alkynofile, og aktiverer π-systemer som f.eks propargylsubstrater for nukleofilt angrep fra f.eks vinylamider. Dette gjør propargylacetaler **1a-b** og vinylamider **4a-b**, **9** og **11** til egnede substrater i gull(I)katalyserte reaksjoner.

I dette prosjektet har gullkatalysator **I** blitt benyttet (Figur 1).



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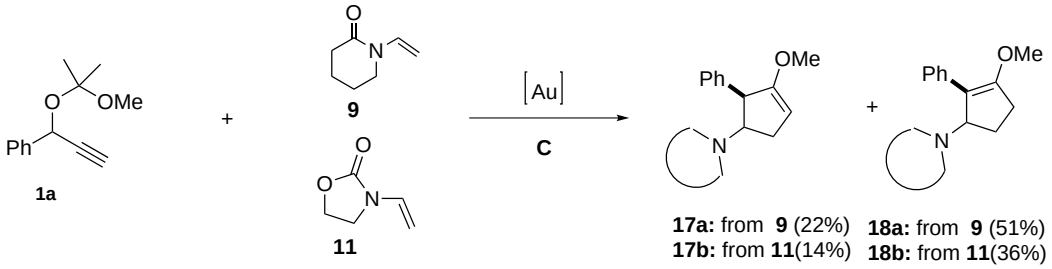
Figur 1 Gull(I)katalysator benyttet i prosjektet

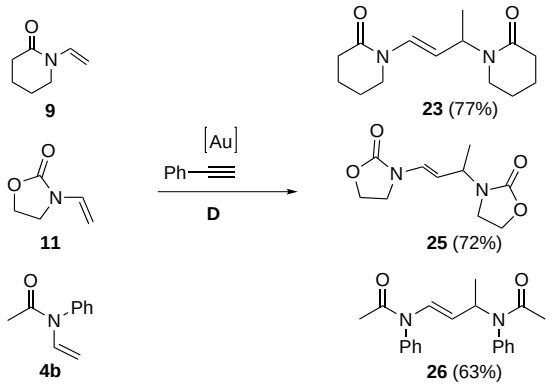
Syklopentenylproduktene **17a** og **18a** (22-51%) ble fremstilt i en gull(I)katalysert [3+2] sykloaddisjonsreaksjon fra metoksyacetal **1a** og vinylamid **9**. Produktene ble isolert som to isomere vinyletere. I en korresponederende reaksjon ble syklopentenylprodukter **17b** og **18b** (14-36%) fremstilt (Skjema 3).



Skjema 3 Gull(I)katalysert reaksjon med acetal **1a** og heterosyklisk vinylamider **9** og **11**

Dannelsen av produkt **17-18** indikerer at [3+2] sykloaddisjon er foretrukket fremfor syklopropanering dersom man har en gull(I)katalysert reaksjon med et elektrontiltrekkende substrat, slik som propargylacetaler, og elektrondonerende substrat, slik som vinylamider.

Andre del av dette prosjektet har vært å undersøke dimeriseringsreaksjoner av vinylamider. Ulike katalytiske betingelser er kjent for å gi selektiv homo-og heterodimerisering av vinylforbindelser. Vi ønsket å undersøke dimerisering av asykliske vinylamider (**4a-b**) og heterosykliske vinylamider (**9** og **11**) i reaksjoner med fenylacetylen og gull(I)katalysator. Dimeriseringsprodukter **23**, **25** og **26** ble fremstilt fra hhv vinylamider **4b**, **9** og **11** (72-85% utbytte) (Skjema 4).



Skjema 4 Dimeriseringsreaksjoner av vinylamider **4b**, **9** og **11**

Effekten av gull(I)katalysatoren i disse nye dimeriseringsreaksjonen er diskutert i dette prosjektet.

Abbreviatons

Ac	Acetal
arom	aromatic
br	broadened
calc	calculated
$CDCl_3$	deuterated chloroform
cm^{-1}	wave number, reciprocal centimeter
conc	concentrated
COSY	Correlated Spectroscopy
δ	chemical shift [ppm]
d	doublet (NMR)
D_2O	deuterated water
DCM	Dichloromethane
dd	doublet of doublet (NMR)
ddt	doublet of doublet of triplet(NMR)
dt	doublet of triplet (NMR)
dm	doublet of multiplet (NMR)
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
EE	1-Ethoxyl-Ethyl ether
e.g	exempli gratia (for example)
EI	Electron Impact (MS)
equiv	equivalent
ERG	Electron Releasing Groups
ESI	Electron Spray Impact (MS)

Et	Ethyl
et al.	*et alia* (and others)
EWG	Electron Withdrawing Groups
GC	Gas Chromatography
h	hour
HMBC	Heteronuclear Multi Bond Coherence
HR	High Resolution (MS)
HSQC	Heteronulclear Single Quantum Coherence
Hz	Hertz
IR	Infrared spectroscopy
J	coupling constant [Hz]
L	Ligand
m	multiplet (NMR)
M	Molar [mol/litre]
Me	Methyl
MeOH	Methanol
mg	milligram
MHz	MegaHertz
μmol	micromol
min	minutes
mL	millilitres
mmol	millimol
MOP	2-MethOxy-2-Propyl ethers
mp	melting point
MS	Mass spectroscopy
NHC	N-Heterocyclic Carbene
nm	nanometer
NMR	Nuclear Magnetic Resonance spectroscopy
NOESY	Nuclear Overhauser Effect spectroscopy
Nu	Nucleophile
obsd	observed

π	pi
Ph	Phenyl
obsd	observed
Piv	Trimethyl acetyl
ppm	parts per million
PPTS	*para*-Toluene Sulfonic acid
quin	quintett (NMR)
R_f	Retention factor (TLC)
rt	room temperature
σ	sigma
s	singlet (NMR)
t	triplet (NMR)
t-Bu	*tert*-Butyl
TFA	Trifluoro acetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyranyl ether
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
Ts	Tosyl
UV	Ultraviolet
Å	Ångstrøm

Contents

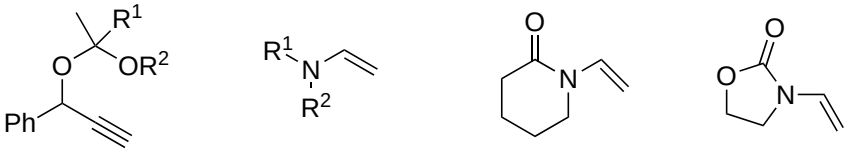
Chapter 1

Introduction

It is well known that gold(I) complexes are versatile and efficient catalysts to promote a variety of organic transformations. In particular, gold(I) catalysts have an exeptional ability to activate C-C multiple bonds towards nucleophilic attack.[1] They have an affinity towards π- systems, such as triple bond systems.[2] This makes gold catalysts useful in reactions with propargyl esters and propargyl acetals.

1.1 Aim of project

In a recent study of cyclopropanation by Fiksdahl *et al*, [3+2] cycloadditions of propargyl esters and vinyl amides have been observed.[3]
This master project is a continuation of the previous project carried out by Jørn E. Tungen and Christian Sperger in the group of prof. Anne Fiksdahl. Their aim was to study the cyclopropanation pathway in reactions involving propargyl esters and vinylic compunds in the presence of gold(I)catalyst. They discovered that [3+2] cycloaddition took place for some compounds.[3] The main goal for the present project was to study gold(I) catalyzed [3+2] cycloaddition of propargyl acetals **1** and vinyl amides **4**, **9** and **11** (Figure 1.1).



1 **4** **9** **11**

Figure 1.1 Propargylacetals **1** and vinyl amides **4**, **9** and **11**

However, during these studies, a homodimerization of some vinyl amides occured. Thus, a second aim was to study dimerization reactions involving gold(I) catalyst, phenylacetylene and different vinyl amides. Homodimerization was investigated, but some studies on heterodimerization between cyclic and acyclic vinyl amides were also included.

Chapter 2

Theory

2.1 General principles of organometallic chemistry

Gold(I) catalyzed reactions and reactions with other organometallic compounds is a field in organometallic chemistry that is less explored. Organometallic compounds are in general both air- and -moisture sensitive, and this has made chemists careful to use organometallic chemistry in their syntheses.[4] Well known compounds such as alkyl lithiums or Grignard reagents are known to hydrolyze vigorously in solution, and organoaluminiums even react with air.[5]

Organometallic compounds are compunds containing at least one metal-carbon bond.[5] The presence of electrons in the *d*-orbitals separates the transition metals from the main group metals. The transition metals have free *d*-orbitals and are also called d-block metals. The *d*-orbitals are filled for the tranistion metals as we move to the right in the Periodic Table. But as these orbitals often are lower in energy than the next *s*- or *p*-orbital, the transition metals have filled *d*-orbitals with free *s*-and *p*-orbitals.[5] This enables transition metal ions to bind to ligands (L) and form complexes of type ML_n.[4] Metal-carbon bond of elements to the right in the Periodic Table are of a more covalent character than of those to the left.[5] This makes compounds such as alkyl lithium, Grignard reagents, and alkyl aluminiums reactive towards hydrolysis, while organosilicon compounds are more stable.[5]
If a complex obey the 18-electron rule for a stable metal complex, the centre metal atom has noble gas configuration of 18 electrons in the valence shells.[6]

Transition metals can have a number of ligands attached to them and each ligand can be attached with more than one site.[6] Unlike the transition metals, the ligands usually have full sp^n-hybridized orbitals that can overlap with the empty 'dsp' orbital of the metal, thus leading to an increase in electron density on the central metal atom.[6] As for Grignard reagents, R-Mg, the ligands are attached to the metal through σ- bonds, as σ-complexes [6], as seen in Figure 2.1. R_3P, R_3N and H^- are examples of such σ-donors.

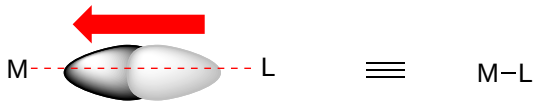


Figure 2.1 σ-bond between vacant 'dps' orbital of metal and filled lone pair on ligand

A σ-bond interaction is also possible with any filled d orbital of the metal and vacant ligand orbital with appropriate symmetry such as π^* orbitals, as shown in Figure 2.2. This decrease in electron density on the central metal atom is called back-bonding.[6] An example of this type of bond is a complex with CO as a ligand.

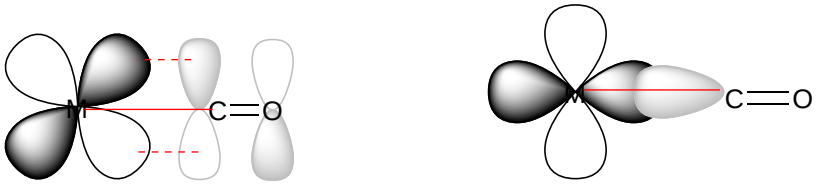


Figure 2.2 a) Filled d orbital, emptyπ^* b) Empty d orbital, filled sp

In alkene bonding there are no σ-bonds to the metal. The metal-alkene bond is located in the middle of the π- bond in between two p-orbitals. These types of complexes are called π-complexes and the metal-ligand bond has both σ- and π character, as shown in Figure 2.3.

Figure 2.3 a) Vacant d orbital, filledπ on ligand acting as σ-donor b) Filled d orbital, empty olefin π^* orbitals

The stereoselectivity of these reactions is usually *trans*, as the incoming reagents usually approach from the side opposite of the metal.[6]

2.2 Gold catalysis

Gold catalysis has been neglected by organic chemists for a long time. However, homogenous gold catalysis of organic reactions have expanded rapidly in recent years.[7]
Gold can exist in two oxidation states; Au(I) and Au(III).[2] Although Au complexes can undergo oxidative addition/reductive elimination, these are rare. The lack of change in oxidation state makes coupling chemistry difficult.[2] Unlike alkyl lithium, Grignard and organoaluminium mentioned earlier, gold catalysts are not sensitive to air or moisture due to their high oxidation potential.[8] Gold complexes are less oxophilic than common Lewis acids, but slightly more reactive as "soft" carbon Lewis acids (e.g double and triple bonds).[2] This allows reactions to take place in the presence of oxygen, water and alcohols.[9] In addition, gold catalysts show high tolerance towards different functional groups, thus it is possible to avoid protecting groups. In this way gold catalysts are more effective towards "step-economy".[10] The mentioned properties of the gold complexes makes them useful in organic synthesis, where it is possible to reach complex molecules in a few reaction steps.[10]

There are many commercially available gold(I)catalysts, as shown in Figure 2.4. Typical ligands are tertiary phosphine ligands (**I-III**).[11] Other ligands such as NHC is also used (**IV**).

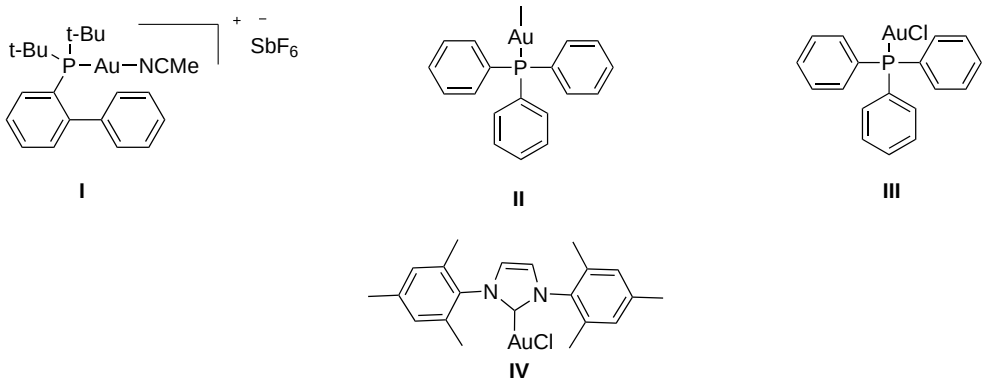
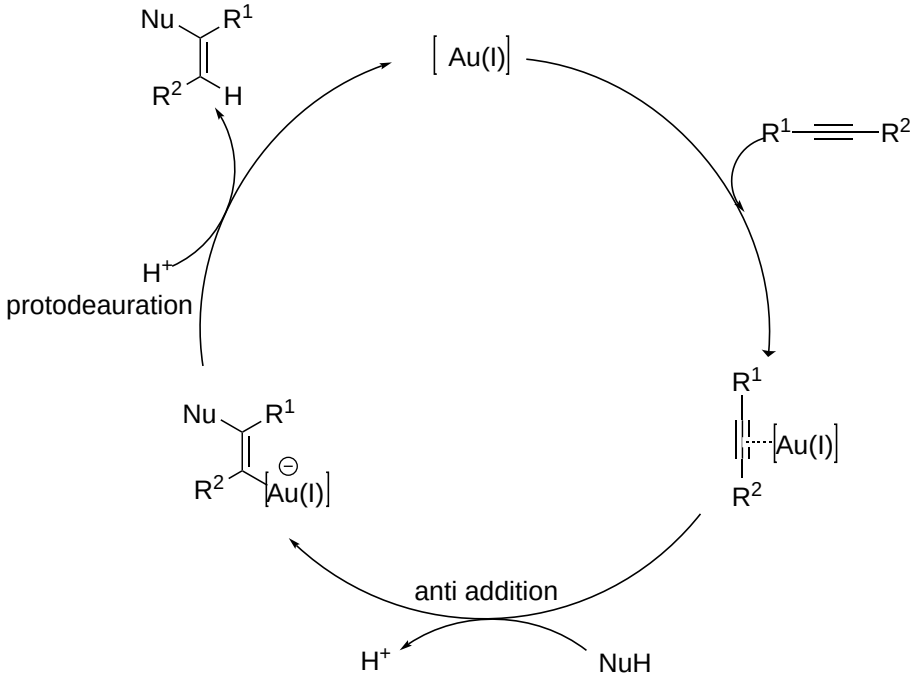


Figure 2.4 Different gold(I) catalysts

In our studies, we have used catalyst **I**. This is a cationic catalyst, which activates π-systems, including alkenes, alkynes and allenes.[12]

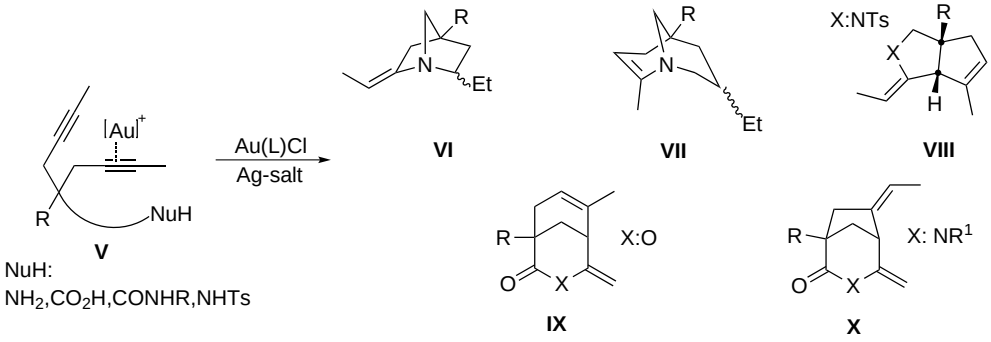
In case of reactions with alkynes, the catalyst activates the triple bond for nucleophilic attack in a catalytic cycle, shown in Scheme 2.1.



Scheme 2.1 Nucleophilic attack of triple bonds by gold(I) catalyst

The gold catalyst activates the triple bond, which is then attacked by a nucleophile in an anti fashion. Gold is further replaced by a proton through protodeauration to obtain the alkene and regenerate the catalyst.

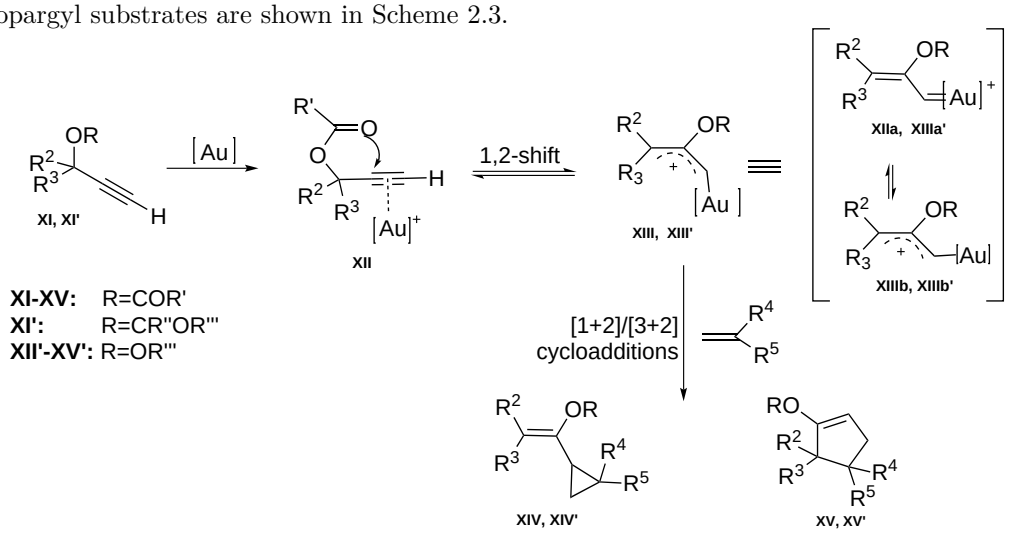
By varying the nature of the nucleophile, many different complex structures can be obtained. The incorporation of an internal nucleophile in 1,6-diyne substrates(**V**) has enabled tandem cyclization. This method has previously been developed in the Fiksdahl research group, where a number of new bicyclic heterocycles (**VI-X**) were formed.[9]



Scheme 2.2 Gold(I) catalyzed tandem cyclizations

2.3 Gold(I) catalyzed [3+2] cycloaddition of propargyl substrates with vinylamides

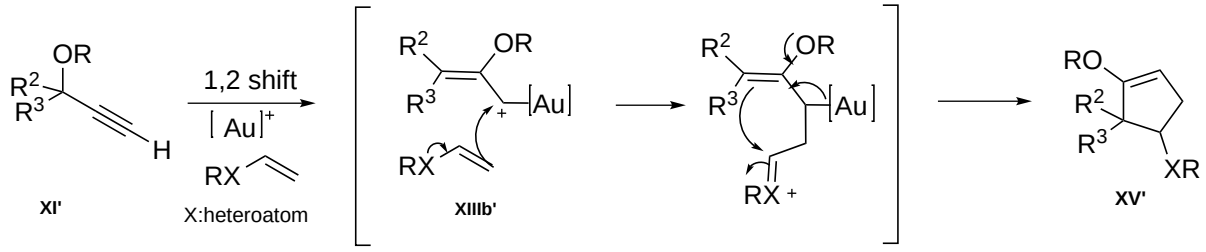
A number of cyclization and cycloaddition reactions have been shown to take place in the presence of Au(I) catalysts, mainly with phosphine ligands.[11] In our research group, [1+2] cycloaddition of propargyl esters have been studied previously.[3] The proposed pathway involves an attack of the acyl group on the inner carbon of the activated triple bond. This is known as 1,2-acyloxy shift.[8] The intermediate, a gold carbenoid, acts as a carbene to give [1+2] cycloaddition with a double bond and gives a cyclopropane-product. During these studies, it was discovered that some compounds, in particular propargyl acetals, would rather undergo [3+2] cycloaddition, giving a cyclopentenyl product.[3] The proposed reaction pathways for the [1+2] and [3+2] cycloaddition of propargyl substrates are shown in Scheme 2.3.



Scheme 2.3 Gold promoted activation of propargylic substrates

The mechanism proposes an equilibrium between the gold carbenoid and the allylic cation. Fiksdahl *et al* recently investigated propargylic esters (**XI**) as precursors for the formation of gold carbenoids (**XIII**). These carbenoids are proposed to be reactive intermediates in a variety of reactions, olefin cyclopropanations in particular.[13][14][15]

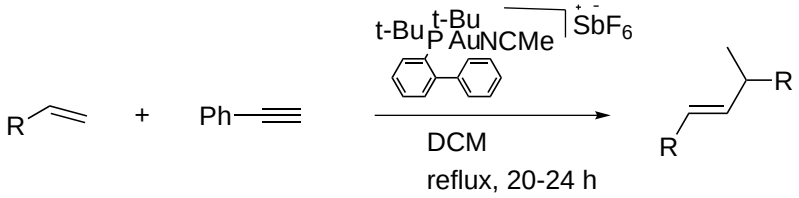
Propargyl acetals (**XI'**) are also known to undergo rearrangement to provide gold carbenoids.[16] The reaction is a modified 1,2-/1,4-alkoxy shift method, including cleavage of a ketone or an aldehyde leaving group (Scheme 2.4). Such reactions may involve an active gold species with a more delocalized positive charge, represented as **XIIIb'** in Scheme 2.3.[17]



Scheme 2.4 Gold(I) catalyzed [3+2] cycloaddition of propargyl acetals with vinyl derivatives

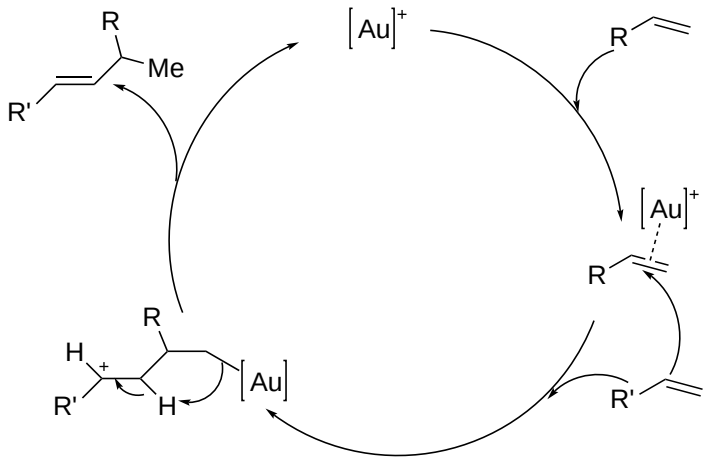
2.4 Dimerization of vinylamides

In contrast to the reductive coupling products obtained by certain transition metal catalyzed tail-to-tail dimerization of alkenes, homodimerization may take place by a head-to-tail or head-to-head coupling (Scheme 2.5).[18]
A variety of catalytic conditions, based on e.g. Lewis acids; In, Pd, Fe, Ni, Ru, Co and Rh complexes are known to promote selective head-to-tail homo- and hetero-dimerizations.[19]



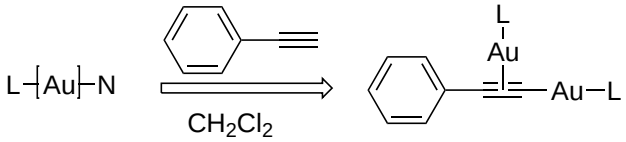
Scheme 2.5 Dimerization of vinyl amides

The alkene head-to-tail homo-and hetero-dimerization may take place by an initial gold(I) activation of the alkene, followed by an attack of the second alkene-unit at the vinylic gold(I)-complex. By a cationic mechanism and through C-C double-bond activation, the reaction proceeds. A protodeauration by a 1,3-proton shift would enable regeneration of the vinylic C=C double bond together with the gold(I) catalyst, see Scheme 2.6. Due to the bulkyness of the substituents, the *trans* isomer would be the expected product from this mechanism.



Scheme 2.6 Proposed mechanism for dimerization of vinyl amides

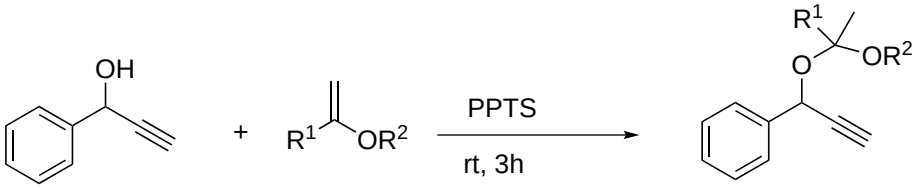
However, recent publications suggest a different mechanism through an acid-catalyzed reaction.[20] These studies indicates the formation of superacid $HSbF_6$ when phenylacetylene is reacted with gold(I) catalyst **I**, see Scheme 2.7, forming a digold complex. In this complex, gold replaces the terminal proton of phenylacetylene, generating the superacid $HSbF_6$. This superacid may be the active catalyst in the dimerization reactions.



Scheme 2.7 Formation of digold complex from gold(I) catalyst and phenylacetylene

2.5 Preparation of acetals

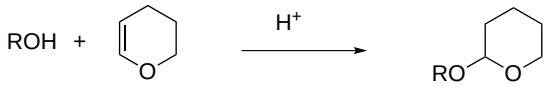
We wanted to study the gold(I) catalyzed cyclization reactions of vinylic enamides with propargyl acetals. These acetals could be synthesized from propargyl alcohol and vinyl ethers, as shown in Scheme 2.8.



Scheme 2.8 Preparation of propargyl acetals

A number of acetal protecting groups are used to avoid unwanted reactions of alcohols.[21] If the alcohol is chiral, like the propargyl alcohol, the result may be a mixture of two diastereomers of the acetal. Two diastereomers may complicate purification and/or characterization.

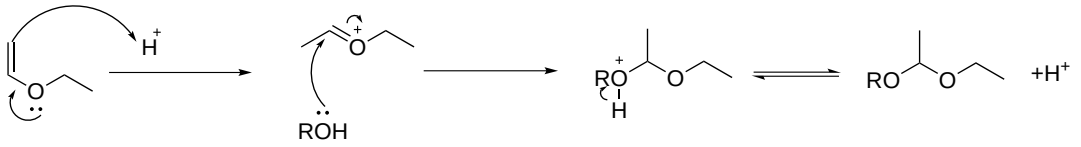
The most utilized protecting acetal is tetrahydropyranyl ether (THP), see Scheme 2.9.



Scheme 2.9 Preparation of THP group

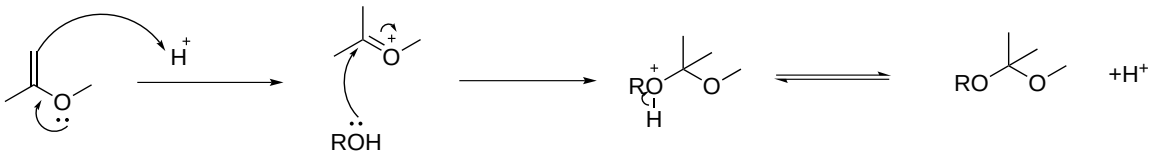
THP is inert to basic and nucleophilic reagents and is does not change under conditions such as hydride reduction, organometallic reactions, or base-catalyzed reactions in aqueous solution.[21]

Ethyl vinyl ethers (EE) are another choice of hydroxy group protection.[21] As for THP ethers, the derivative, 1-ethoxyethyl ether also introduces an additional stereogenic center. A mechanism for the reaction is shown in Scheme 2.10.



Scheme 2.10 Mechanism for preparing 1-ethoxy-1-ethyl ethers

The oxonium intermediate is similar to the oxonium ion in normal acetal-formation of carbonyl compunds.[6] By utilizing 2-methoxy-2-propyl ethers (MOP ethers) the problem of diastereomers will be avoided. MOP ethers can be prepared by treating the alcohol with 2-methoxypropene in the presence of an acid, similar to hte preparation of 1-ethoxyethyl ether, see Scheme 2.11.



Scheme 2.11 Mechanism for preparing MOP ethers

As shown in Scheme 2.10 and Scheme 2.11 , these reactions are acid catalyzed. *para*-Toluene sulfonic acid (PPTS) is commonly used as catalyst in these reactions. It is stable as a solid, and as strong an acid as sulfuric acid.[6] In addition it is cheap and readily available, as it is a byproduct in the synthesis of saccharin.[6]

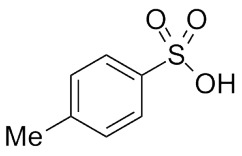
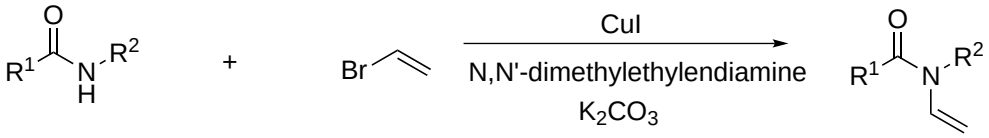


Figure 2.5 Structure of catalyst, PPTS

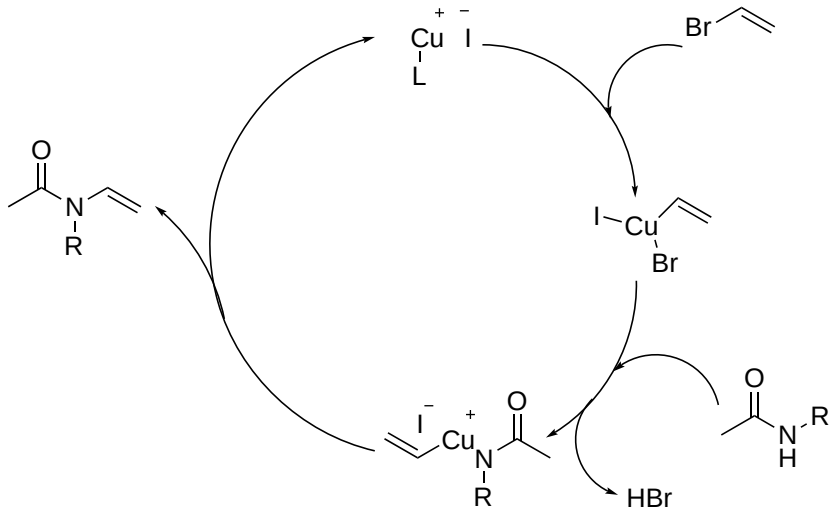
2.6 Preparation of vinyl amides

Functionalized aromatic and heteroaromatic amines are key building blocks for the syntheses of pharmaceuticals, polymers, or materials. To recognize their vast importance, many synthetic methods for the formation of C-N bonds have emerged.[22] Enamides are important synthetic intermediates and there are a number of protocols for preparing them.[22] However, they suffer from either low yields or a lack of stereocontrol in the double bond geometry.[23] Due to their synthetic utility, the preparation of enamides has received considerable attention over the past decade. The introduction of chelating ligands resulted in major improvements and dramatic softening of the reaction conditions compared with the original Goldberg's procedure.[22] Buchwald and co-workers studied this reaction extensively and developed an experimentally simple and inexpensive catalytic system based on the use of 1,2-diamine ligands and K_2CO_3 as base, as shown in Scheme 2.12. This system is highly effective also for secondary amides. The reactions tolerates a variety of functional groups, including many that are not compatible with palladium catalysis.[22]



Scheme 2.12 Copper mediated cross-coupling of vinyl halide and amide

The copper catalyst coordinates to the vinyl halide, activating it for nucleophillic attack by the amide. This produces acid, neutralized by the base in the reaction mixture, here K_2CO_3. A cross-coupling between the amide and vinyl halide gives vinyl amide as the product (Scheme 2.13).



Scheme 2.13 Suggested mechamism for copper catalyzed coupling of vinyl halide and amide

2.7 Use of product and results

Gold catalysis is an expanding field. Complex molecules are synthesized in few steps with high selectivity. Compounds synthesized in gold catalyzed reactions may be used as building blocks in further syntheses of complex molecules. Studies on gold(I) complexes will give further information on how to improve selectivity of different reactions.

By gold(I) catalyzed [3+2] cycloadditions of propargyl acetals and vinyl amides, cyclopentene derivatives are easily obtained. Reaction conditions are mild, and the reactions are selective. Different homo- and heterodimers of vinyl amides may be obtained in few step by reactions of vinyl amide, gold(I) catalyst and phenylacetylene.

Chapter 3

Results and Discussion

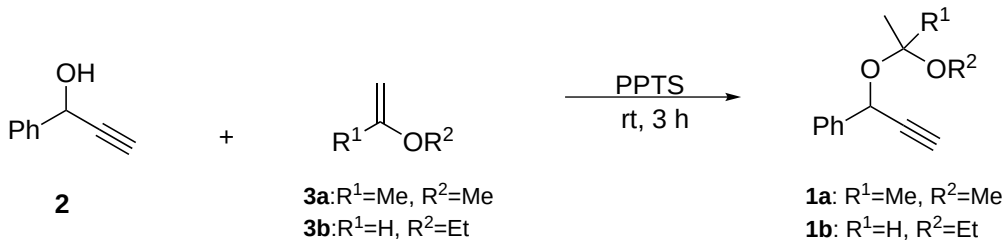
This chapter is divided into five sections. Preparation of starting materials, including new propargyl acetals and vinyl amides are presented in section 3.1. The results from gold catalyzed cyclopentenylation are presented in section 3.2. This includes cyclopentenylderivatives from reactions between the different propargyl acetals and vinyl amides. Gold catalyzed dimerization of vinyl amides are further presented in section 3.3; including homodimerization (section 3.3.1) of cyclic and acyclic vinyl amides and heterodimerization (section 3.3.2) of two different vinyl amides. An unexpected development occured during these studies. As a result the behaviour of the gold(I) catalyst is discussed in section 3.4. Outlook and perspectives are discussed in section 3.5.

New products are characterized by NMR, MS and IR, as far as there was sufficient amount. The respective melting points have been measured for solids. New compounds have been structure elucidated by NMR. ^{1}H- and ^{13}C-shift values are presented in Figure 3.2-3.11, in blue and red respectively. Litterature from Silverstein *et al* have been used to determine and characterize the structures.[24] The experimental details and the characterization data are reported in Chapter 5.

3.1 Synthesis of starting materials

3.1.1 Syntheses of acetals

Propargyl acetal **1a** and **1b** was synthesized by reacting propargyl alcohol **2** with the appropriate vinyl ether, as shown in Scheme 3.1. The mechanism and theory for preparation of propargyl acetals EE and MOP are discussed in Chapter 2.5.



Scheme 3.1 Preparation of propargyl acetals **1a-b**

The procedure for the preparation of acetals from non-terminal propargylic alcohol is known[25],

but methoxy acetal **1a** and ethoxy acetal **1b** have not previously been reported. The acetals were isolated as clear (**1a**) and yellow (**1b**) oils with respective yields of 60% and 40%. Both compounds are highly unstable at room temperature and immediately decompose into the alcohol and to other unidentified biproducts. Some of the decomposed material has similar retention on flash column as the desired product. This made purification on silica column difficult and ultimately resulting in moderate isolated yields. The ethoxy acetal **1b** was less stable than the methoxy analouge, acetal **1a**, and might also decompose on the column, affording low isolated yield. NMR-shift values for acetal **1b** are complex, indicating the formation of diastereomers (Figure 3.1).

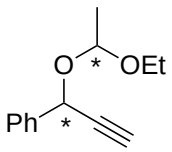


Figure 3.1 Diastereotopic protons of **1b**

The diastereotopic protons are not a problem for acetal **1a**. As discussed in Chapter 2.3, this compound has no acetal stereogenic centre. The solution to the decomposition problem was to use the acetal in further synthesis immidiately after preparation and isolation. Another solution was to store the compound at low temperature to slow down the decomposition. It is evident from TLC and GC that conversion of alcohol **2** was complete after 3 h.

Characterizations of propargyl acetals **1a** and **1b** are based on NMR spectroscopy, MS and IR. Chemichal shifts are assigned from NMR (Appendix A-B), see Figure 3.2 and Figure 3.3.

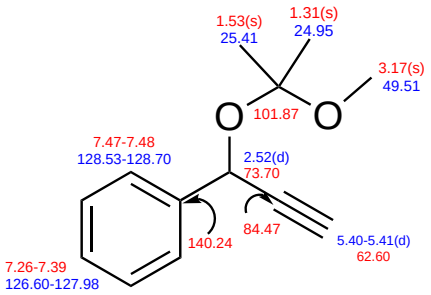


Figure 3.2 Structure and chemical shifts for methoxy acetal **1a**

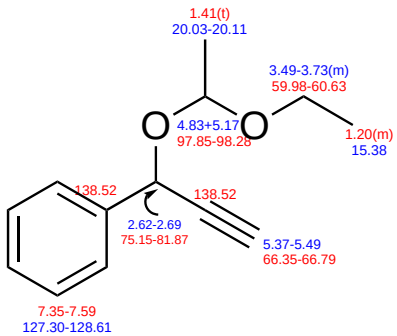
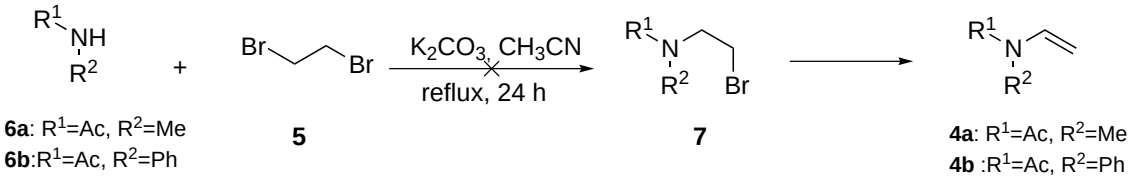


Figure 3.3 Structure and chemical shifts for ethoxy acetal **1b**

3.1.2 Syntheses of vinyl amides

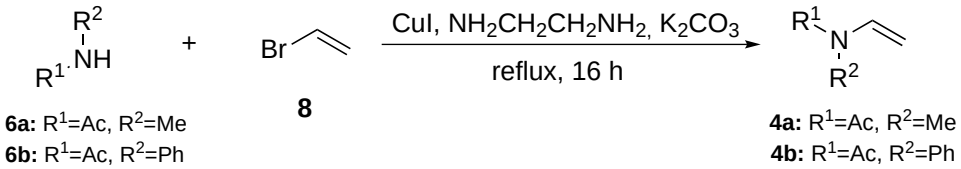
Attempts to synthesize vinyl amide **4a-b** through the known addition-elimination method were performed , shown in Scheme 3.2.[26]



Scheme 3.2 Attempt to synthesize vinylamide **4a-b**

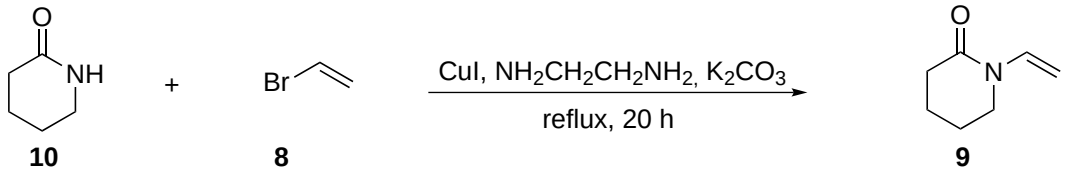
TLC and GC showed no evidence of conversion of the starting material. The reaction time was increased from 24 hours to 48 hours, and the base altered between K_2CO_3, $LiCO_3$ or $CeCO_3$, had no effect on the reaction.

A different procedure through copper catalyzed cross-coupling reaction improved the results. Vinyl amides **4a-b** were synthesized from amides **6a-b** and vinylbromide **8** (Scheme 3.3), as described in *General procedure B*. These compunds were isolated as white solids, and respective yields were 43% and 33%. Both compounds were synthesized from by a known procedure.[23] Compound **4a** is also commercially available from Sigma-Aldrich. For further use in the gold catalyzed reactions, the commercial compound was utilized.

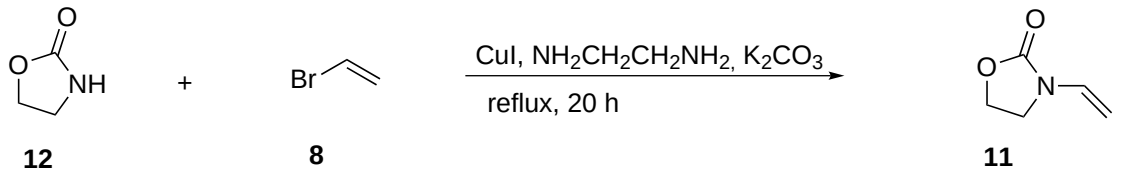


Scheme 3.3 Synthesis of vinyl amides **4a-b**

N-vinyl valerolactam **9** and 3-vinyloxazolidin-2-one **11** are previously reported, and they were synthesized from δ-valerolactam (**10**) and oxazolidin-2-one (**12**), as described for vinyl amides **4a-b**. The only difference being reaction time, as shown in Scheme 3.4 and Scheme 3.5.



Scheme 3.4 Synthesis of vinyl amide **9**



Scheme 3.5 Synthesis of vinyl amide **11**

N-vinyl valerolactam **9** was isolated as a bright yellow solid in 43% yield after purification with flash chromatography. Pure 3-vinyloxazolidin-2-on **11** was isolated as a brown liquid in 89% yield. The crude product was not further purified. Yields and ^{1}H-NMR shifts for the prepared vinyl amides are in accordance with litterature.[27]

3.2 Gold(I) catalyzed [3+2] cycloaddition

Gold(I) catalyst **I** has been used in all gold(I) catalyzed reactions.

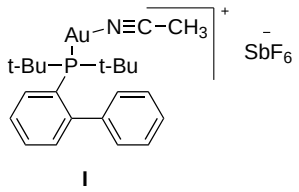
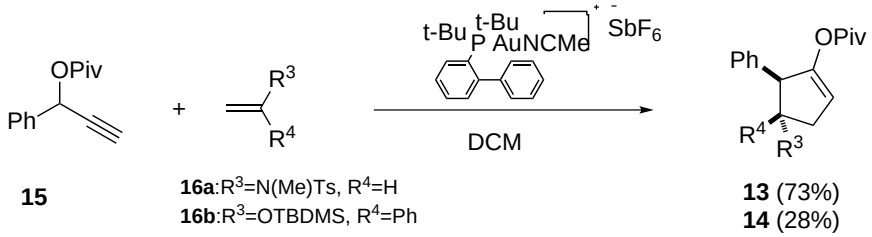


Figure 3.4 (Acetonitrile)[(2-biphenyl)di-tert-butylphosphine]gold(I) hexafluoroantimonate

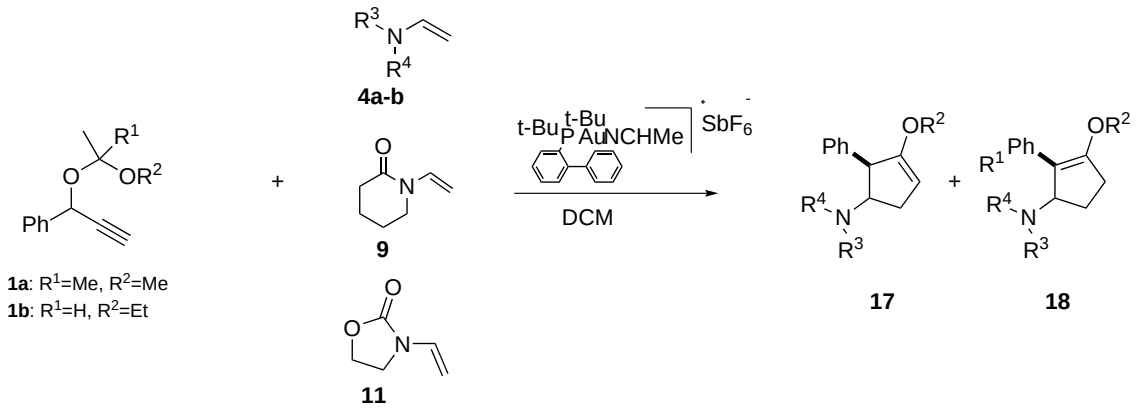
During the studies of gold(I) catalyzed olefin cyclopropanation reactions of different propargyl esters, gold(I) catalyzed [3+2] cycloaddition of the terminal propargyl ester (**15**) with electron-rich vinyl compounds (**16a-b**) were reported , as shown in Scheme 3.6.[3]



Scheme 3.6 Formation of cyclopentenyl esters

The mechanism for these types of reactions are discussed in Chapter 2.3.

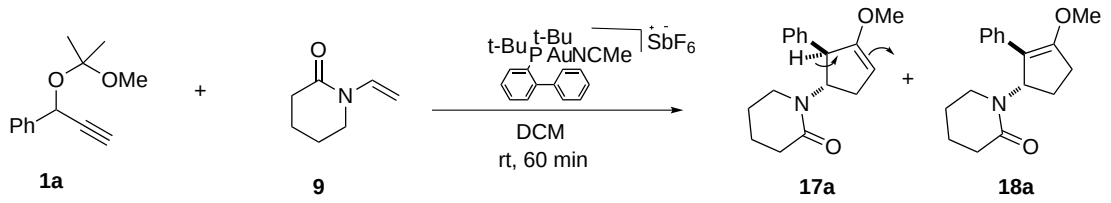
To further investigate the possible gold(I) catalyzed [3+2]-cycloaddition pathway, the electronic and steric nature reactants were varied. Propargylic (**1a-b**) and vinylic (**4a-b**, **9** and **11**) species were used. Different combinations of the propargyl acetals and vinyl amides were added to the gold catalyst, then stirred at room temperature for 15-60 minutes, see Scheme 3.7.



Scheme 3.7 Gold(I) catalyzed [3+2] cycloaddition

3.2.1 Gold(I) catalyzed [3+2] cycloaddition with acetal 1a

Reactions with methoxy acetal **1a** and the heterocyclic vinyl amide **9** gave to major products, **17a** and **18a**. These products were relatively easy to separate from the minor products with flash chromatography. The products were isolated as brown oils, in respective yields of 22% and 51%. The reaction time was increased compared to reactions with less steric hindered vinyl group (e.g heterocyclic vinyl amide **11**). GC and TLC indicated full conversion of substrate **1a** in 60 minutes. The suggested mechanism for the formation of products **17a** and **18a** by [3+2] cycloaddition is presented in Chapter 2.3.



Scheme 3.8 Synthesis of cycloaddition-products **17a** and **18a**

Expected to be the initially formed product, as suggested in Scheme 2.4, Chapter 2.3, compound **17a** is the minor product. Isomerization of the double bond of the cyclopentene ring takes place during the reaction, giving the additional product **18a**. Compound **18a** is the major product because the double bond is conjugated to the phenyl group and the effect of the EWG on the amide. The two isomers are characterized by NMR, IR and MS (Appendix F-G). Figure 3.5 and Figure 3.6 show chemical shifts for compound **17a** and **18a**. Stereochemistry for compound **17a** have been determined by H-H NOE-experiments (Appendix F.6).

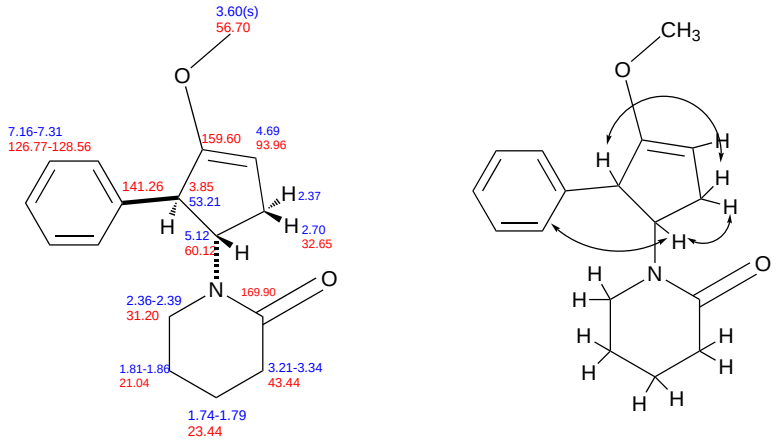


Figure 3.5 Structure, chemical shifts and NOE-connections for **17a**

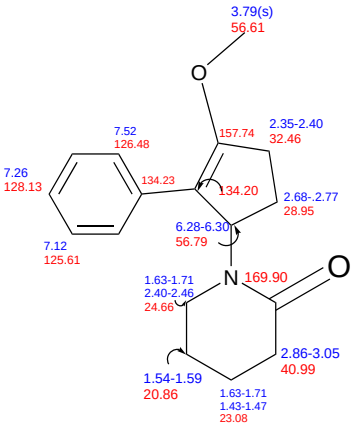
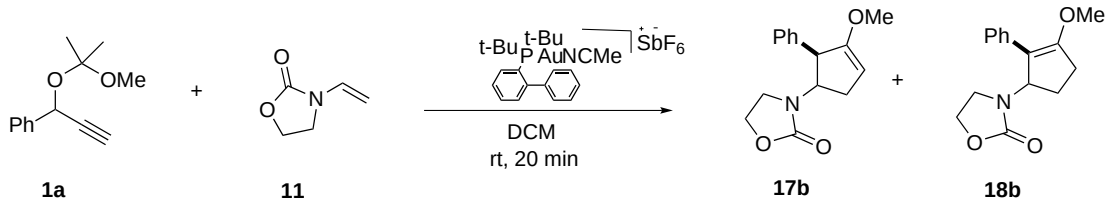


Figure 3.6 Structure, chemical shifts for **18a**

Reaction of methoxy acetal **1a** and the heterocyclic vinyl amide **11** also gave two major products, compound **17b** and **18b** (Scheme 3.9). They were isolated as colorless (**17b**) and brown (**18b**) oils, with respective yields of 14% and 36%. The reaction was similar to the synthesis of products **17a** and **18a**.



Scheme 3.9 Synthesis of cycloaddition-products **17b** and **18b**

The colour of the reaction mixture rapidly changed from yellow to dark brown after adding the reactants to the gold(I) catalyst. GC and TLC indicated full conversion of acetal **1a** in 20 minutes

at room temperature. The reaction was fast compared to the synthesis of compounds **17a** and **18a**. The two isomers were characterized by NMR, IR and MS (Appendix H-I). Figure 3.7 and Figure 3.8 show chemical shifts for products **17b** and **18b**. Stereochemistry for compound **17b** have been determined by H-H NOE-experiments (Appendix H.6)

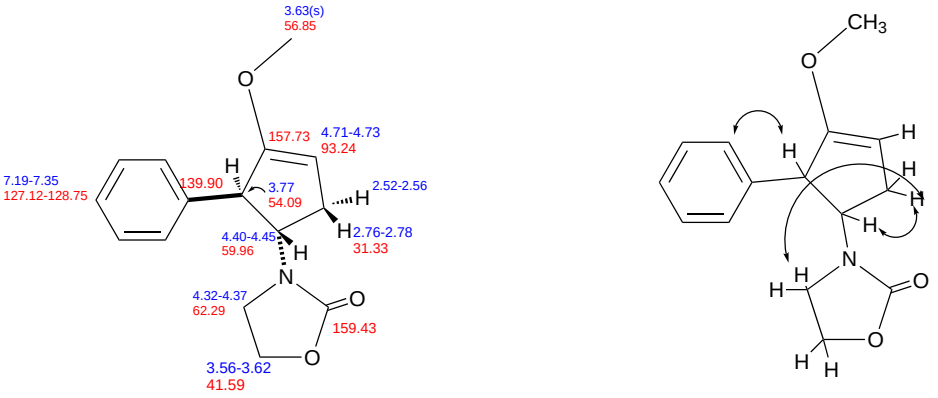


Figure 3.7 Structure, chemical shifts and NOE-connections for **17b**

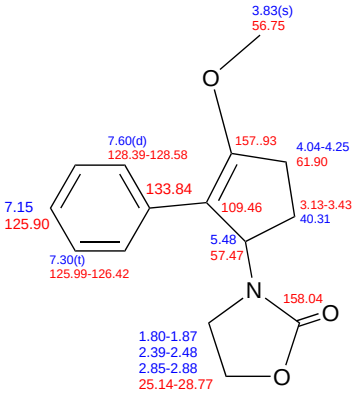
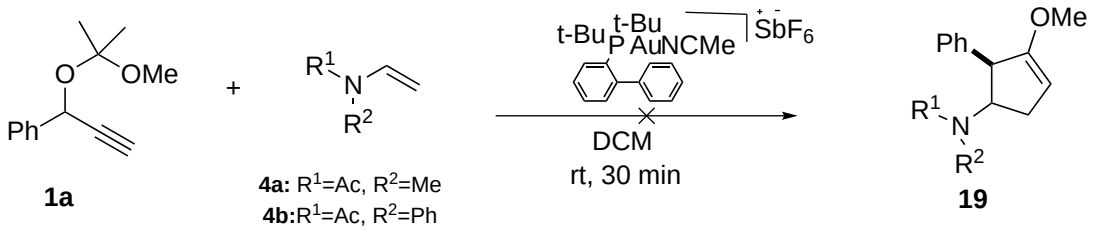


Figure 3.8 Structure, chemical shifts and NOE-connections for **18b**

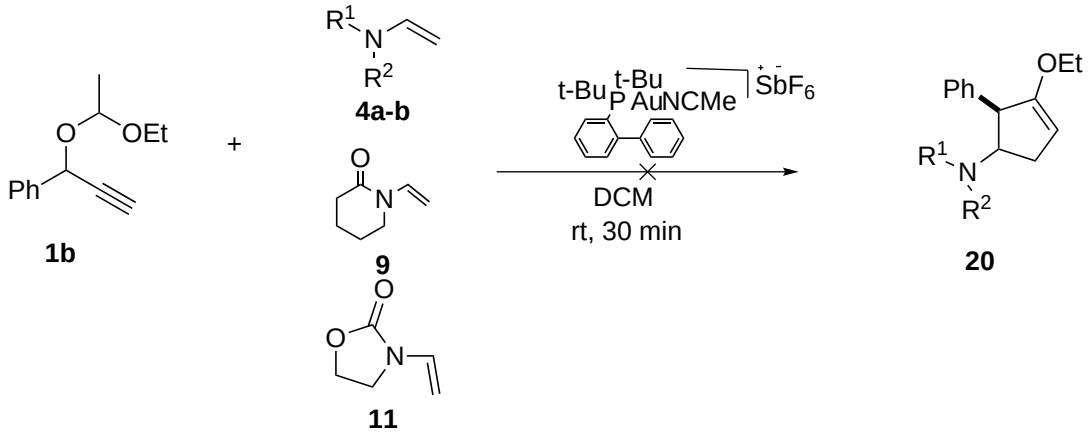
The gold(I) catalyzed reactions between heterocyclic vinyl amides **9**,**11** and methoxy acetal **1a** gave the expected cyclopentenyl products. They were easily isolated and characterized. However, replacing the heterocyclic vinyl amides with the acyclic vinyl amides **4a** and **4b**, different results were obtained (Scheme 3.10). TLC indicated many spots, and GC gave no indication of formation of a cyclopentenylation product formed. There were no major products in the reaction, all products had similar retention on flash chromatography. ^{1}H-NMR of the crude product and isolated fractions after the flash chromatography revealed none of the characteristic peaks for the cyclopentenyl ring.



Scheme 3.10 Attempt to synthesize **19**

3.2.2 Gold(I) catalyzed [3+2] cycloaddition with acetal 1b

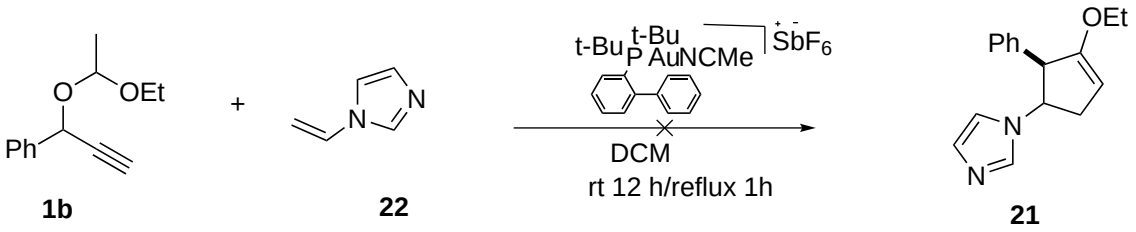
As discussed in section 3.1, acetal **1b** was highly unstable and decomposed readily. Reactions with ethoxy acetal **1b** and vinyl amides in gold(I) catalyzed [3+2] cycloadditions were unsuccessful (Scheme 3.11).



Scheme 3.11 Attempt to synthesize compound **20**

All reactions were monitored by TLC and GC and these showed a rapid and full conversion of acetal **1b**. However, based on GC, there were no sign of conversion into cyclopentenyl products. Each reaction gave indications of 6-7 close spots on TLC, difficult to separate by flash chromatography. Acetal **1b** has one methyl group while acetal **1a** has two methyl groups. The different pathway for the two acetals may be due to this decreased bulkyness of ethoxy acetal **1b**.

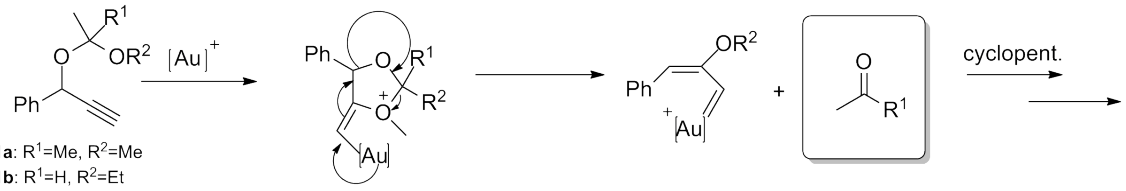
In addition to react acetal **1b** with vinyl amides **4a-b**, **9** and **11**, an attempt to react acetal **1b** with the commercially available cyclic vinyl amine **22** failed, Scheme 3.12. Both TLC and GC indicated no conversion of acetal **1b** after stirring overnight at room temperature, nor after 1 hour reflux. It seems as if carbonyl moiety is essential for such reactions to take place.



Scheme 3.12 Attempt to synthesize compound **21**

A study of gold-catalyzed cyclizations of 1,6-diynes investigates the difference of methyl-and ethyl-substituents on the diynes.[8] The studies showed lower reactivity towards cyclization of the ethyl-substituted diynes compared to methyl-substituted. These studies involves a di-substituted alkyne, where steric hindrance from substituents may play a greater role than from our mono-substituted acetals. However the sterical hindrance should be taken into consideration for the decreased reactivity for our reactions. Another factor for the difference in reactivity between methoxy acetal **1a** and ethoxy acetal **1b** may be the different leaving group ability for the two acetals. Acetone will be leaving group for acetal **1a**. This is a better leaving group than the acetaldehyde produced in

reactions with acetal **1b**, thus increases the reactivity for acetal **1a**, as can be seen from the first step of the reaction (Scheme 3.13).

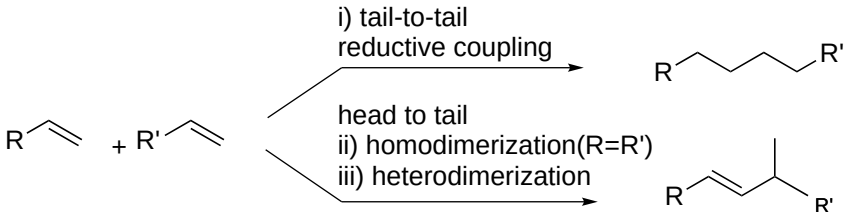


Scheme 3.13 First step of proposed cyclopentenylation mechanism

The formation of cyclopentenyl products **17-18** may indicate that the electron releasing alkoxy group of the propargyl acetals are important for stabilizing the allylic gold(I) species, as discussed in Scheme 2.3, Chapter 2.3, to favour the [3+2] cycloaddition reactions. This is in contrast to the electron withdrawing substrates, such as propargyl esters, who would rather undergo cyclopropanation.

3.3 Dimerization of vinyl amides

During our studies of the gold(I) catalyzed cyclization reactions of propargyl esters, it was discovered that some of the vinyl amides would rather undergo a head-to-tail dimerization instead of cyclization. Tail-to-tail coupled products of alkenes from reductive coupling through metallacycle have been reported, as discussed in Chapter 2.4.[19] However, there were no reports on gold(I) catalyzed head-to-tail coupling. It was desirable to investigate further the coupling pathways of different vinyl amides (Scheme 3.14), and the possible role of the gold(I) catalyst in these reactions.



Scheme 3.14 Dimerization processes

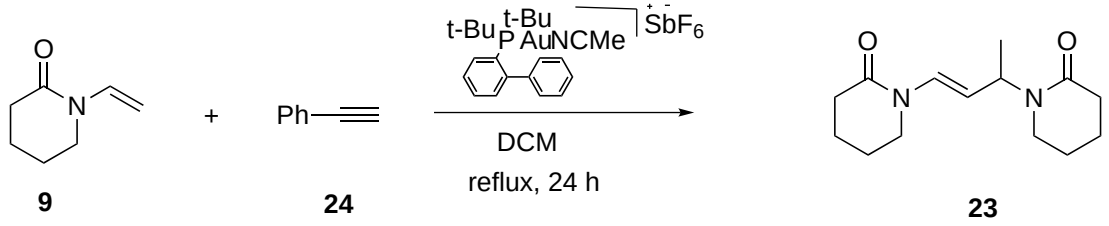
Experiments conducted with propargylic substrates and vinyl amides, but without gold(I) catalyst, gave no dimerization. Nor did reactions with gold(I) catalyst and vinyl amide, without propargylic substrate. This indicates that the propargyl compound is necessary for the reaction. Further investigation indicated that the triple bond system needed to be terminal in order for a reaction to take place. Phenylacetylene is readily available and doesn't require special reaction conditions, so this was our choice of triple bond system in the dimerization reactions. Our studies of the possible pathways for dimerization reactions are discussed in this section.

3.3.1 Homodimerization of vinylamides

Experiments on homodimerization of acyclic vinyl amides **4a-b** and heterocyclic vinyl amides **9** and **11** were conducted as described in *General Method D*, Chapter 5. Phenylacetylene, **24**, equivalent to the vinyl amide was used. Phenylacetylene and vinyl amide were added to the gold(I) catalyst

in DCM and refluxed until complete conversion of the vinyl amide. Reactions were monitored by TLC and GC.

Dimer product **23** was obtained in 79% yield, by reacting vinyl amide N-vinyl valerolactam **9** in the presence of phenylacetylene and gold(I) catalyst under reflux for 24 hours (Scheme 3.15).



Scheme 3.15 Synthesis of dimerization product **23**

The dimer product **23** was isolated as the only major product by flash chromatography. The white solid was characterized by NMR and MS. The chemical shifts are assigned by NMR-spectroscopy (Appendix J). The high characteristic *trans* coupling-constant (J=15) confirms that the *trans*-isomer is selectively formed. Figure 3.9 show chemical shift for product **23** determined by NMR.

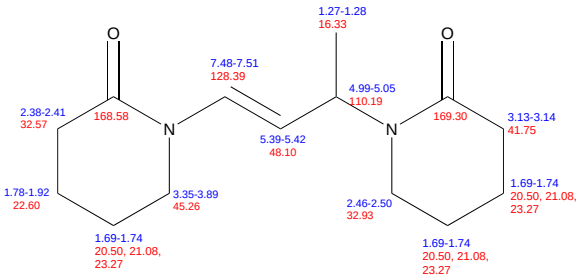
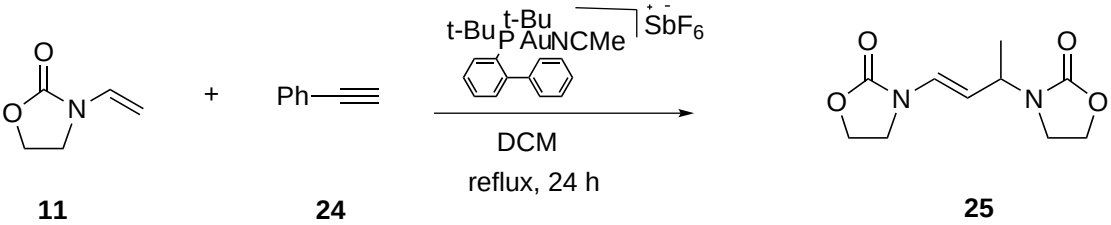


Figure 3.9 Structure and chemical shifts for dimer **23**

The gold(I) catalyzed reaction of the second cyclic amide, 3-vinyloxazolidin-2-one **11**, was similar to dimerization of vinyl amide **9**, and gave a 72% yield of dimer **25**. The reaction was monitored by GC and TLC and indicated complete conversion of vinyl amide **11** after 20 hours reflux, as shown in Scheme 3.16.



Scheme 3.16 Synthesis of dimerization product **25**

There was only one major product from the reaction. This was readily purified and isolated by flash chromatography, as decribed in Chapter 5.4. The chemical shifts are assigned by NMR-spectroscopy (Appendix K). Figure 3.10 shows chemical shifts for dimer product **25**.

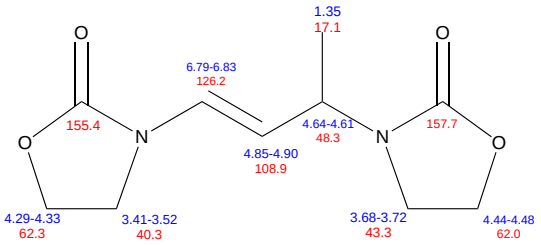
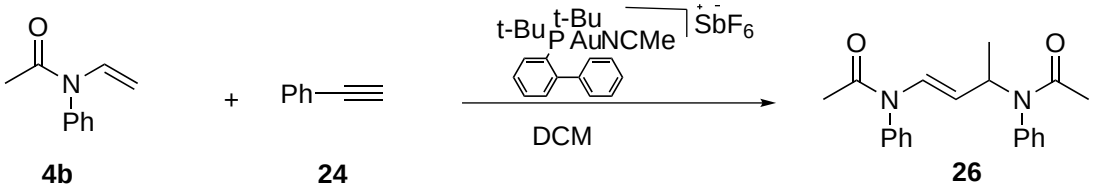


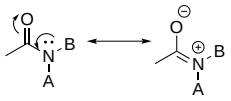
Figure 3.10 Structure and chemical shifts for dimer **25**

Acyclic vinyl amide **4b** reacted similar as heterocyclic vinyl amides **9** and **11** and yielded 63% dimer product **26**, as shown in Scheme 3.17.

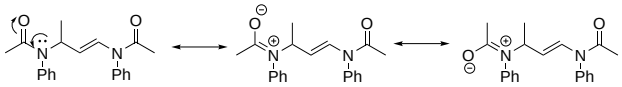


Scheme 3.17 Synthesis of dimerization product **26**

There was one major product from the reaction, and product **26** was isolated as a brown oil (63% yield). Spectroscopic data (NMR) of dimer **26** was different than that of dimer **23** and **25**. It is appearant from ^{1}H-NMR (Appendix L.1) and HSQC (Appendix L.3) that one methyl group gives rise to two signals at δ=1.82 (br) and δ=2.17 (s). It is known that for compounds of similar character, such as dimethylformamide (DMF), the two N-methyl groups gives two different signals in ^{1}H-NMR.[28] These two peaks coalesce into one broad peak at 100°C and one sharp peak at higher temperature. From this it is appearant that the two methyl groups are differently shielded at room temperature, whereas in higher temperature they become equivalent. The reason for this is well known and is due to a double bond character of the C-N bond, which results in a hindered rotation. Thus, the two methyl bonds are in different magnetic environment at room temperature. The barrier of rotation is overcome at higher temperature, of which the two methyl groups exchange places so rapidly, they are no longer distinguished by NMR. If we look at this effect for compound **26**, we can explain the two peaks corresponding to two different environments of one methyl group in ^{1}H-NMR, see Scheme 3.18.



Scheme 3.18 a) Hindered free rotation for DMF



b) Hindered free rotation for product **26**

The reason why this effect is only appearant for one of the methyl groups in dimer **26** may be because the double bond in the bridge between the two monomers is electron donating. Thus destabilizing a positive charge on the nitrogen clostest, and therefore there will be no double bond character between this nitrogen and carbon.

Figure 3.11 shows the structure and chemical shifts for compound **26**. The chemical shifts are assigned by NMR-spectroscopy of dimer **26** in $CDCl_3$ (Appendix L.1-L.5).

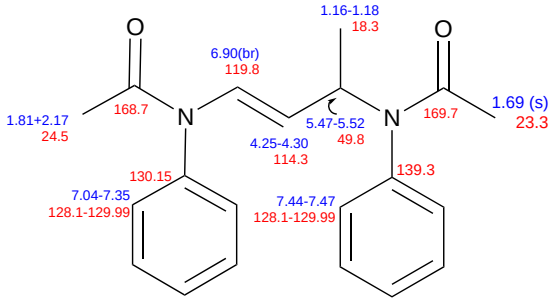
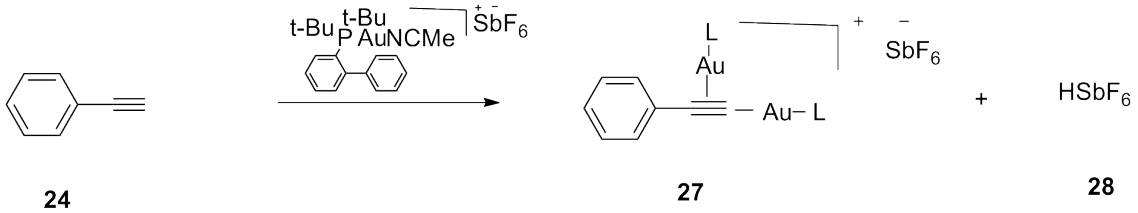


Figure 3.11 Structure, chemical shifts for **26**

In general, the addition of D_2O to ^{1}H-NMR samples enables the identification of -OH and -NH protons. In D_2O these protons are exchanged by deuterated proton and they disappear from the spectra.
^{1}H-NMR of dimer **26** in $CDCl_3/D_2O$ revealed no proton exchange (Appendix L.8), confirming that the broad peaks at δ=1.82 and δ=6.90 are not exchangable protons, such as -OH or -NH protons. However, ^{1}H-NMR of dimer **26** in DMSO lead to a change in shift values for the methyl groups (Appendix L.7). This result is comparable to the change in shift values for DMF in $CDCl_3$ and DMSO, further indicating similar properties of the C-N bond for product **26**.[29] The broad peak at δ=6.90 in $CDCl_3$ appeared in DMSO as a splitted multiplet.

In contrast to reactions of acetyl phenyl substrate **4b**, the acetyl methyl analouge **4a** afforded more complex product mixtures. Vinyl amide **4a** seems to be highly reactive in all reactions. In an attempt to synthesize a dimer of vinyl amide **4a**, there were no major products. TLC and GC indicated several products, with similar retention on flash column.

At the end of this work, it was discovered by a Valencia research group, that phenylacetylene coordinates double to the gold(I) catalyst, where a σ-interaction between phenylacetylene and gold replaces the terminal proton, generating the superacid $HSbF_6$ of the counterion, as shown in Scheme 3.19.[20]



Scheme 3.19 Suggestion for synthesis and structure of cationic digold complex[20]

This acid formed *in situ* may be the active catalyst for the dimerization-reactions.

The total results of homodimerization obtained by this project and others are presented in Table 3.1.[30]

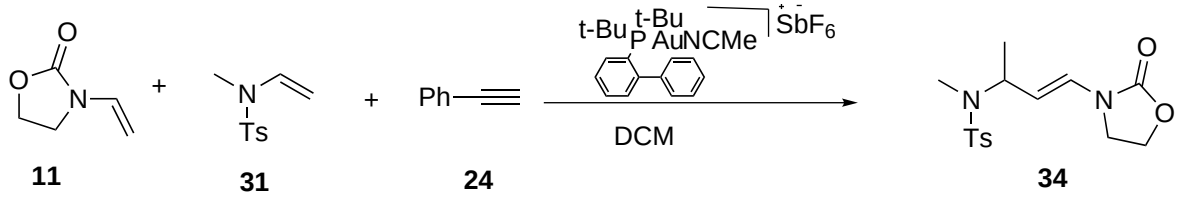
Table 3.1: Summary dimerization.

Amide	Amide number	Dimer formation	Dimer yields(%)
	**11**	Yes	79
	**13**	Yes	72
	**29***	Yes	85
	**30***	Yes	89
	**4a**	No	
	**4b**	Yes	85
	**31***	No	
	**32***	No	
	**33***	No	

*Work done by Post.Doc Naseem Iqbal[30]

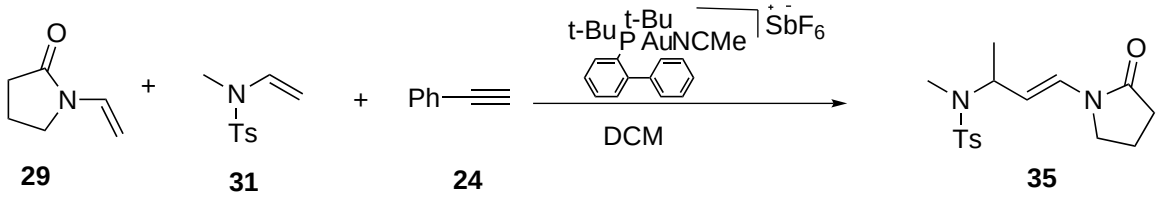
3.3.2 Heterodimerization of vinylamides

To continue the studies of dimerization, we wanted to investigate the potential for chemoselective heterodimerization between to different vinyl amides in the presence of gold(I) catalyst and phenylacetylene. Two vinyl amides with respectively electron withdrawing and electron releasing amide groups were chosen in order to obtain high selectivity of mixed dimer, see Scheme 3.20.



Scheme 3.20 Attempt to synthesize heterodimer **34** from **11** and **31**

The reaction between heterocyclic vinyl amide **11** and acyclic vinyl amide **31** gave only homodimer **25** (Scheme 3.16). However, corresponding reactions conducted by post.doc Naseem Iqbal yielded heterodimer **35** in 43% yield between electron deficient heterocyclic amide **29** and electron rich vinyl amide **31**, see Scheme 3.21. This indicates that mixed dimerizations of vinyl amides are possible and should be investigated further.



Scheme 3.21 Heterodimerization of **29** and **31**

3.4 Catalyst-studies

As decribed in section 3.3, a recently published article reports *in situ* formation of super acid $HSbF_6$ in the reactions with our gold(I) catalyst and phenylacetylene. The gold(I) catalyst coordinates to phenylacetylene to form an equilibrium, as described in Scheme 3.19, generating the superacid $HSbF_6$ (**28**) and a digold complex (**27**).

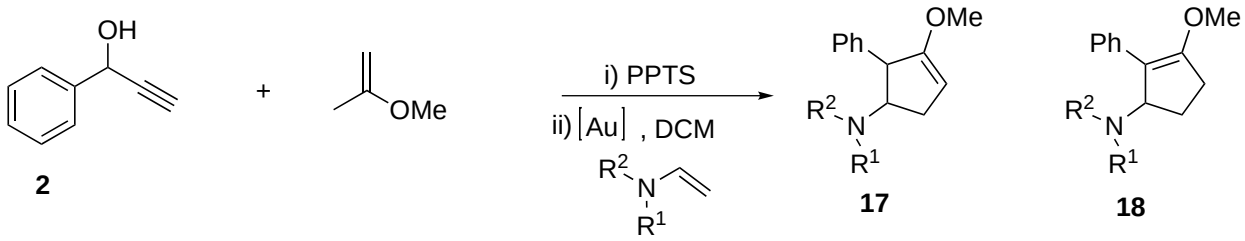
The generation of the super acid is the result of replacement of the terminal alkyne proton by a σ- interaction beween carbon and gold. This is in contrast to previous assumptions that gold interacts with the π-cloud of the triple-bond systems. Reasearch related to this work, using TFA as an acid catalyst, yielded a dimer without gold catalyst involved.[30], but in poor yield and without complete conversion. This indicates that the acid may be the active catalyst in the dimerization reactions. $HSbF_6$ is a commercial available acid. Further studies will indicate if *in situ* generation of the super acid would be more convinient than adding the highly reactive super acid reactant. This would utlimately allow less harsh conditions.

3.5 Outlook and Perspectives

As a natural outlook for this work, further studies involving the gold catalyst and phenylacetylene should be conducted. The dimerization of vinyl amides were first discovered in gold(I) catalyzed reactions with propargyl acetals. It would be interesting to investigate if the propargyl acetals coordinate to gold, generating a digold complex similar to the one reported, and to seeif it would be possible to isolate this complex. NMR and x-ray images of the complex would give information on this matter.

Further testing on reaction conditions regarding dimerization should also be conducted. It will be interesting to see if it would be possible to separatly add the super acid as a reactant, or if it is better to generate this *in situ* from the gold catalyst and phenylacetylene. It will also be interesting to see the difference in reactiontime, temperature, conversion, selectivity etc.

Regarding cycloaddition reactions, positive results are obtained from studies on other one-pot reactions being conducted in the research group. A suggestion on a one-pot reaction from alcohol **2** to cyclopentenyl products **17-18** is shown in Scheme 3.22.



Scheme 3.22 One-pot reaction from alcohol **2** to cyclic products **17-18**

Chapter 4

Conclusion

In acid catalyzed reactions, two new propargyl acetals **1a-b** (60% and 40% yield), has been synthesized from propargyl alcohol **2** and vinyl ethers **3a-b**.

Four different vinyl amides were synthesized by copper catalyzed cross-coupling reactions. Vinyl amides **4a-b** (33-43%) were obtained from amides **6a-b**. N-vinyl valerolactam **9** was synthesized from δ-valerolactam **10** in 43 % yield and N-vinyloxazolidin-2-one **11** was synthesized from oxazolidin-2-one **12** in 89% yield.

Gold(I) catalyst **I** was added to methoxy acetal **1a** and heterocyclic vinyl amide **9** in DCM. The reaction gave [3+2] cycloaddition products **17a** and **18a** in 22% and 51% yield. Similarly, reaction between methoxy acetal **1a** and N-vinyloxazolidin-2-one **11** gave cyclopentenyl products **17b** and **18b** in 14% and 36% yield. No [3+2] cycloaddition took place in reactions between methoxy acetal **1a** and acyclic vinyl amides **4a-b**, nor between ethoxy acetal **1b** and the vinyl amides.

In the presence of gold(I) catalyst and phenylacetylene, vinyl amides **4b**, **9** and **11** gave the corresponding homodimerization *trans* products **23** (79%), **25** (72%) and **26** (63%). Acyclic vinyl amide **4a** yielded no dimer.

Heterodimerization reaction of electron withdrawing vinyl amide **11** and electron releasing vinyl amide **31** was unsuccessful. However, heterodimerization reaction of comparable compound **29** and **31** has been performed in the research group, and gave heterodimer **35** (43%).

Chapter 5

Experimental section

5.1 General

^{1}H-, ^{13}C-, COSY-, HMBC-, -NOESY and HSQC-spektra were recorded on Bruker Avance DPX 300 MHz or 400 MHz spectrometer. All chemical shifts are reported in ppm (parts per million, δ) referenced downfield to TMS (δ=0.0). Coupling constants (J) are reported in Hertz (Hz) and all multiplicities are indicated as br (broadened), s (singlet), d (doublet), dd (doublet of doublets) t (triplet) , dt (doublet of triplets), ddt (doublet of doublet of triplets), quin (quintett), m (multiplet) and dm (doublet of multiplets). COSY, HMBC, HSQC and NOESY experiments have been used to determine chemical shifts and structures (Appendix A-L).

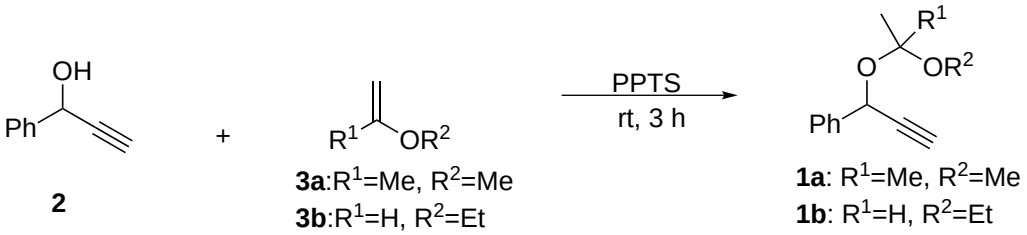
Infrared spectra (IR) were recorded on Nicolet 20SXC FT-IR spectrometer.

Accurate mass determination, EI and ESI, was performed on MAT95XL ThermoFinnigan and Agilent G1969 TOF MS instruments respectively. For ESI analyses, samples were injected into the instrument using an Agilent 1100 series HPLC. A direct injection analysis without any chromatography was performed for the EI analyses.

Reactions were monitored by gas chromatography (GC) performed on a Varian CP-3800. Thin layer chromatography (TLC) were performed on Merck TLC aluminum sheets, Silica gel 60 F_{254}. The TLC plates were visualized in either UV-lys (254 nm) or stained with p-anis aldehyde stain solution (5 mL conc. H_2SO_4, 1.5 mL absolute acetic acid and 3.7 mL *p*-anisaldehyde in 137 mL absolute ethanol) followed by heating. Flash column chromatography was performed using Supelco VersaFlash system with VersaFlash cartridges packed with 20-45 or 45-75 μm spherical silica based porous (70 Å) particles. All chemicals and solvents were of synthetic grade and were not further purified before use. All dry dichloromethane (DCM) was collected from a Braun MB SPS-800 purification system and stored over 4 Å molecular sieve nitrogen. All reactions were performed under a static atmosphere of nitrogen in dried glasware.

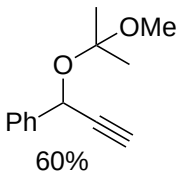
5.2 Preparation of starting materials

5.2.1 General procedure A: Preparation of acetal 1a-b



To a solution of 1-phenyl-2-propyn-1-ol in desired vinyl ether cooled to 0°C, a catalytic amount of PPTS was added. The reaction mixture was stirred at room temperature for 3 hours, until reaction was complete. The mixture was diluted with dichloromethane (120 mL) and washed with water (3*120 mL) and brine (120 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo* to obtain the crude product. The residue was purified by silica gel VersaFlash in suitable eluent system to obtain the desired acetal.

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



60%
1a

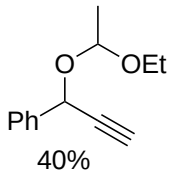
Methoxy acetal **1a** was synthesized according to *General Procedure A* from alcohol **2** (300.1 mg, 2.28 mmol) mixed with methoxypropene (18 mL) and PPTS (3 mg, catalytic amount) for 3 hr. Flash chromatography (n-pentane/EtOAc 50:1) yielded compound **1a** (278.6 mg, 59.9%) as a clear liquid.
1a: R_f=0.78 (n-Pentane/EtOAc 4:1); ^{1}H-NMR (400 MHz, $CDCl_3$-TMS)(Appendix A.1):δ 7.47 (d, 2H$_{arom}$), 7.26-7.39 (m, 3H$_{arom}$), 5.40 (d, J=2.3 Hz, 1H, PhCH), 3.17 (s, 3H, OCH_3), 2.51 (d, J=2.3 Hz, 1 H, CCH), 1.53 (s, 3H, CCH_3);

^{13}C-NMR (400 MHz, $CDCl_3$-TMS)(Appendix A.2):δ 140.24 (1C, C_{arom}), 128.70 (1C, CH$_{arom}$), 128.53 (1C, CH$_{arom}$), 127.98 (1C, CH$_{arom}$), 126.86 (1C, CH$_{arom}$), 126.60 (1C, CH$_{arom}$), 101.87 (1C, CH$_3C$), 84.47 (1C, CHC), 73.70 (1C, CCH), 62.60 (1C, CO), 49.51 (1C, OCH$_3$), 25.41 (1C, CCH$_3$), 24.95 (1C, CCH$_3$);

IR(thin film, cm^{-1})(Appendix A.3): 3286, 2990, 2831, 1256, 1146, 1067, 697;

HRMS (ESI) was performed for $C_{13}H_{16}O_2$ [M-Na]$^+$ but results were inconclusive due to decomposition.

Synthesis of (1-(1-Ethoxyethoxy)prop-2-yn-1-yl)benzene(1b)



40%
1b

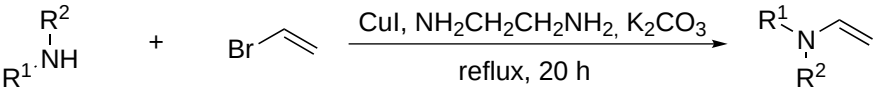
Ethoxy acetal **1b** was syntesized according to *General Procedure A* from alcohol **2** (500.2 mg, 3.79 mmol) mixed with ethylvinyl ether(24 mL) and PPTS (11 mg, catalytic amount). Compound **1b** was isolated as a bright yellow liquid in 40.0% yield by flash chromatography (n-pentane/EtOAc 50:1).
1b: R_f= 0.78 (n-Pentane/EtOAc 4:1); ^{1}H-NMR(400 MHz, $CDCl_3$-TMS)(Appendix B.1): 7.51-7.59 (m, 2H$_{arom}$), 7.34-7.40 (m, 3H$_{arom}$), 5.45-5.46 (d, J=2.2 Hz, 0.5H, CHCCH), 5.34-5.35 (d, J=2.2 Hz, 0.5H, CHCCH), 5.14-5.18 (q, J=5.4 Hz, 0.5H, OCH), 4.79-4.83 (q, J=5.4 Hz, 0.5H, OCH), 3.49-3.73 (m, 2H, CH_2), 2,.62-2.69 (dd, J=2.24 Hz, 1H, CCHC), 1.40-1.42 (t, 3H, CHCH_3), 1.21-1.27 (m, 3H, CH_2CH_3);

^{13}C-NMR(400 MHz, $CDCl_3$-TMS)(Appendix B.2): 138.73 (1C, C_{arom}), 138.52 (1C, CCHC), 128.61 (1C, CH$_{arom}$), 128.53 (2C, CH$_{arom}$), 128.40 (1C, CH$_{arom}$), 127.30 (1C, CH$_{arom}$), 98.28+97.85 (1C, OCH), 81.87+75.15 (1C, C$_{arom}$$C$H), 66.79+66.35 (1C, CHC$C$H), 59.97+60.63 (1C, CH$_2$), 20.11+20.03 (1C, OCH$_3$), 15.38 (1C, CH_2CH_3);

IR(thin film, cm^{-1})(Appendix B.6): 3288, 2977, 2934, 1450, 1273, 1078, 1067, 697;

HRMS (ESI) was performed for $C_{13}H_{16}O_2$ [M-Na]$^+$ but results were inconclusive due to decomposition.

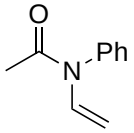
5.2.2 General procedure B: Preparation of vinyl amides 4b, 9 and 11



6a-b **8** **4a-b**
10 **9**
12 **11**

Under complete inert conditions, the amide, vinyl bromide (1.0 M soln in THF, 2.0 equiv), CuI (0.05 equiv), *N,N'*-dimethylethylenediamine (0.10 equiv) and K_2CO_3 (2.0 equiv) was added to a schlenk flask, fitted with magnetic stir bar and reflux condenser. The vial was sealed tightly using parafilm, and the reaction mixture was heated to 110°C and let stir overnight. Upon completion of the reaction, the mixture was filtered through Celite^{TM}, rinsed with EtOAc and the solvent was removed *in vacuo* to obtain the crude product. The crude product was purified with silica gel Versa Flash, using suitable eluent system of EtOAc in n-pentane, to obtain the desired enamide.

Synthesis of *N*-phenyl-*N*-metyl acetamide (4b)

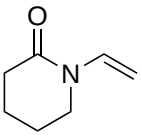


33%
4b

Enamide **4b** was synthesized according to *General Procedure B* from amide **6b** (300.2 mg, 2.22 mmol) mixed with vinylbromide (4.43 mL 1M solution in THF, 4.43 mmol, 2 equiv), *N,N'*-dimethylethylenediamine (23.2 mg, 0.263 mmol, 0.10 equiv), CuI (21.13 mg, 0.1109 mmol, 0.05 equiv) and K_2CO_3 (615 mg, 4.44 mmol, 2.0 equiv). Reaction was stirred at 110°C overnight and enamide **4b** was isolated as white solid in 32.5% yield by flash chromatography (n-pentane/EtOAc 20:1).
4b: R_f=0.61(n-Pentane/EtOAc 4:1); ^{1}H-NMR(400 MHz, $CDCl_3$-TMS)(Appendix C.1):δ 7.70 (m, 1H, NC*H*), 7.43-7.52 (m, 3H, H_{arom}), 7.18-7.20 (d, 1H, CH_2), 4.38-4.40 (d, 1H, J=9, CH_2), 3.84-3.88 (d, 1H, J=16, CH_2), 1.88 (s, 3H, CH_3);

^{13}C-NMR(400 MHz, $CDCl_3$-TMS)(Appendix C.2):δ 166.80 (1C, *C*=O), 139.20 (1C, N*C*H), 133.73 (1C, C_{arom}), 129.99 (2C, *C*H$_{arom}$), 128.92 (2C, *C*H$_{arom}$), 127.69 (1C, *C*H$_{arom}$), 96.27 (1C, CH*C*H$_2$), 23.27 (1C, *C*H$_3$);
^{1}H-NMR shifts and yields are according to litterature.[27]

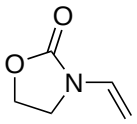
Synthesis of *N*-Vinyl valerolactam (9)



43%
9

Enamide **9** was synthesized according to *General Procedure B* from amide **10** (217.1 mg, 2.19 mmol) mixed with vinylbromide (4.43 mL 1M solution in THF, 4.43 mmol, 2 equiv), *N,N'*-dimethylethylenediamine (34.1 mg, 0.386 mmol, 0.10 equiv), CuI (21.3 mg, 0.1118 mmol, 0.05 equiv) and K_2CO_3 (613 mg, 4.43 mmol, 2.0 equiv). The reaction was stirred at 110°C overnight and enamide **9** was isolated as bright yellow solid (117.7 mg, 43.0%) by flash chromatography (n-pentane/EtOAc 20:1).
9:R_f= 0.42 (4:1 n-Pentane/EtOAc); ^{1}H-NMR(400 MHz,$CDCl_3$-TMS)(Appendix D.1):δ 7.60-7.68 (dd, J_1=9.1 Hz, J_2=14.2 Hz, 1H, NC*H*), 4.42-4.49 (dd, J_1=16.3 Hz, J_2=20.1 Hz, 2H, CHCH_2), 3.40-3.43 (t, 2H, NCH_2), 2.50-2.53 (t, 2H, C=OCH_2), 1.82-1.94 (dm, 4H, *C*H_2*C*H_2);
^{13}C-NMR(400 MHz,$CDCl_3$-TMS)(Appendix D.2): δ 168.66 (1C, *C*=O), 132.44 (1C, N*C*H), 93.44 (1C, CH*C*H$_2$), 44.28 (1C, N*C*H$_2$), 32.94 (1C, C=O*C*H$_2$), 22.52 (1C, *C*H$_2$*C*H$_2$), 20.57 (1C, *C*H$_2$*C*H$_2$);
^{1}H-NMR shifts and yields are according to litterature.[27]

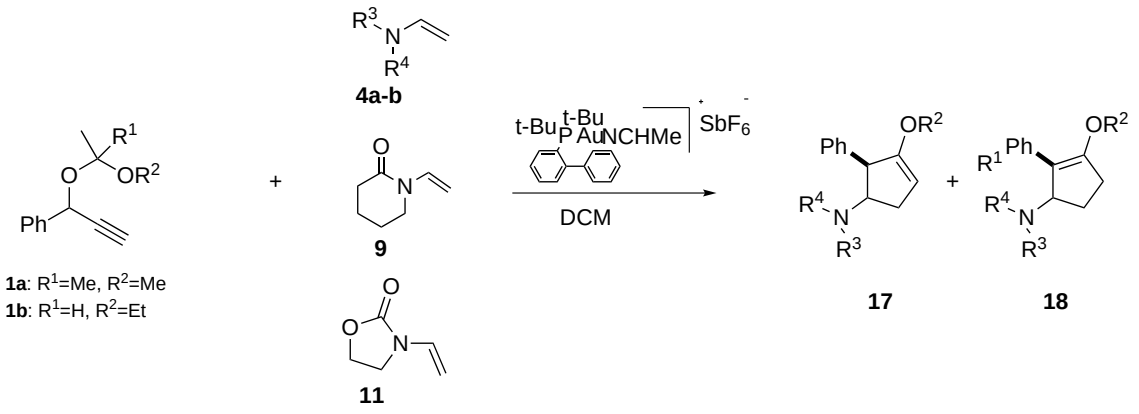
Synthesis of 3-Vinyloxazolidin-2-one (11)



89%
11

Enamide **11** was synthesized according to *General Procedure B* from amide **12** (221.2 mg, 2.54 mmol), vinylbromide (4.58 mL 1M solution in THF, 4.58 mmol, 2 equiv), *N,N'*-dimethylethylenediamine (32.5 mg, 0.368 mmol, 0.10 equiv), CuI (21.8 mg, 0.1145 mmol, 0.05 equiv) and K_2CO_3 (677 mg, 4.89 mmol, 2.0 equiv). Reaction was stirred at 110°C overnight and compound **11** was obtained as dark oil (254.7 mg, 89.0%).
11: ^{1}H-NMR(400 MHz, $CDCl_3$-TMS)(Appendix E.1):δ 6.84-6.90 (dd, J_1=8.9 Hz J_2=15.8 Hz, 1H, NC*H*), 4.43-4.47 (t, J=7.9 Hz, 2H, OCH_3), 4.42-4.44 (d, J=15.8 Hz, 1H, CHCH_2), 4.28-4.32 (d, J=15.8 Hz, 1H, CHCH_2), 3.70-3.74 (t, J=8.2 Hz, 2H, NCH_2);
^{1}H-NMR shifts and yields are according to litterature.[27]

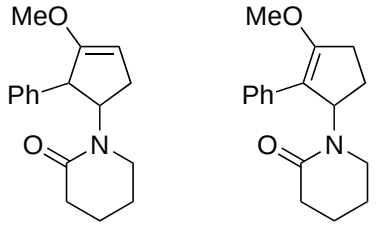
5.3 Gold(I) catalyzed [2+3] cycloadditon



5.3.1 General procedure C: Gold(I) catalyzed cyclization between acetal and vinyl amide

To a schlenk flask, the gold catalyst was added (0.05 equiv) and solved in DCM. The acetal (1.0 equiv) and enamide (3.0 equiv) was diluted with DCM and added simultanously to the gold catalyst. The reaction mixture was stirred at room temperature for 15-60 min. Upon completion, the reaction mixture was quenched with NEt_3, filtered through Celite^{TM}, rinsed with DCM and the solvent was removed *in vacuo* to obtain the crude product. The crude product was purified with silica gel Versa Flash, using suitable eluent system of MeOH in DCM.

Synthesis of 1-(3-methoxy-2-phenylcyclopent-3-en-1-yl)piperidin-2-one (17a) and 1-(3-methoxy-2-phenylcyclopent-2-en-1-yl)piperidin-2-one (18a)



22% **17a** 51% **18a**

According to *General Procedure C*, methoxy acetal **1a** (31.5 mg, 0.150 mmol) and vinyl amide **9** (65.2 mg, 0.520 mmol) were added to the gold catalyst (7.1 mg, 9.1 μmol) in DCM and stirred at room temperature for 60 minutes. Flash chromatography (DCM/MeOH 50:1) yielded compound **17a** (8.91 mg, 22.0%) and **18a** (21.4 mg, 51.0%) as dark yellow oils.
17a: R_f= 0.31 (50:1 DCM/MeOH); ^{1}H-NMR(400 MHz, $CDCl_3$-TMS)(Appendix F.1):δ 7.31-7.40 (m, 5H_{arom}), 5.14 (dt, J=5.5 Hz, 1H, CHN), 4.69 (m, 1H, C=CH), 3.85-3.86 (d, J=4.6 Hz, 1H, CCHCH), 3.60 (s, 3H, OCH_3), 3.21-3.34 (dm, 2H, C=OCH_2), 2.67-2.74 (ddt, J_1=2.0 Hz, J_2=8.5 Hz, J_3=4.8 Hz, J_4=6.2 Hz, 1H, CHCH_2), 2.36-2.39 (t, J=6.5 Hz, 2H, NCH_2), 1.81-1.86 (m, 2H, NCH_2CH_2), 1.74-1.79 (m, 2H, CH_2CH_2);

^{13}C-NMR(400 MHz, $CDCl_3$-TMS)(Appendix F.2):δ 169.5 (1C, C=O), 159.6 (1C, CO), 141.3 (1C, C_{arom}), 128.6 (2C, CH_{arom}), 127.7 (2C, CH_{arom}), 126.7 (1C, CH_{arom}), 94.0 (1C, C=CH), 60.1 (1C, CHN), 56.7 (1C, OCH$_3$), 53.2 (1C, PhCH), 43.4 (1C, O=CCH$_2$), 32.7 (1C, C=CHCH$_2$), 31.2 (1C, NCH$_2$), 23.4 (1C, O=CH$_2$$CH_2$), 21.0 (1C, NCH$_2$$CH_2$);

IR(thin film, cm^{-1})(Appendix F.7): 2942, 2361, 1631, 1241, 1172, 696;

HRMS (EI) calcd for $C_{17}H_{21}NO_2$ [M-H]$^+$ 272.1645, obsd 272.1645;

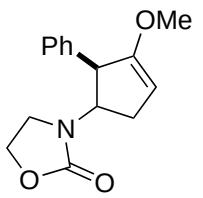
18a: R_f= 0.23 (50:1 DCM/MeOH); ^{1}H-NMR(400 MHz,$CDCl_3$-TMS)(Appendix G.1):δ 7.53 (d, J=7.4 Hz, 2H_{arom}), 7.28 (t, J=5.4 Hz, 2H_{arom}), 7.12 (t, J=7.4 Hz, 1H_{arom}), 6.28-6.30 (m, 1H, CHN), 3.79 (s, 3H, OCH_3), 2.86-3.05 (dm, 2H, C=OCH_2), 2.68-2.77 (m, 2H, CHCH_2), 2.40-2.46 (m, 1H, NCH_2), 2.35-2.40 (t, J_1=7.2 Hz, J_2=6.7 Hz, 2H, $CHCH_2CH_2$), 1.63-1.71 (m, 3H, NCH_2, C=OCH_2CH_2), 1.54-1.59 (m, 2H, NCH_2CH_2), 1.43-1.47 (m, 1H, NCH_2CH_2);

^{13}C-NMR(400 MHz,$CDCl_3$-TMS)(Appendix G.2):δ 169.9 (1C, C=O), 157.7 (1C, CO), 134.2 (1C, C_{arom}), 128.1 (2C, CH_{arom}), 126.4 (2C, CH_{arom}), 125.6 (1C, CH_{arom}), 110.4 (1C, C=CH), 56.8 (1C, CHN), 56.6 (1C, OCH$_3$), 41.0 (1C, C=OCH$_2$), 32.5 (1C, $CHCH_2CH_2$), 28.9 (1C, CHCH$_2$), 24.7 (1C, NCH$_2$), 23.1 (1C, O=CH$_2$$CH_2$), 20.9 (1C, NCH$_2$$CH_2$);

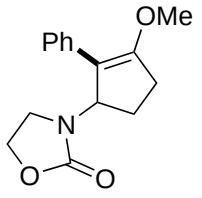
IR(thin film, cm^{-1})(Appendix G.7): 2942, 2362, 1622, 1442, 1165, 696;

HRMS (EI) calcd for $C_{17}H_{21}NO_2$ [M-H]$^+$ 272.1645, obsd 272.1645;

Synthesis of 3-(3-methoxy-2-phenylcyclopent-3-en-1-yl)oxazolidin-2-one (17b) and 3-(3-methoxy-2-phenylcyclopent-2-en-1-yl)oxazolidin-2-one (18b)



14%
17b



36%
18b

According to *General Procedure C*, methoxy acetal **1a** (106.2 mg, 0.520 mmol) and vinyl amide **11** (171.3 mg, 1.51 mmol) were added to the gold catalyst (22.0 mg, 28.5 μmol) in DCM and stirred at room temperature for 20 minutes. Flash chromatography (DCM/MeOH 50:1) yielded compound **17b** (19.3 mg, 14.0%) as a colourless oil and **18b** (48.1 mg, 35.0%) as yellow oil.

17b: R_f= 0.65 (20:1 DCM/MeOH); ^{1}H-NMR(400 MHz, $CDCl_3$-TMS)(Appendix H.1):δ 7.19-7.35 (m, 5H_{arom}), 4.72 (d, J=1.4 Hz, 1H, C=CH), 4.40-4.45 (m, 1H, CHN), 4.32-4.37 (m, 2H, NCH$_2$CH_2O), 3.77-3.78 (d, 1H, PhCH), 3.63 (s, 3H, OCH_3), 3.56-3.62 (m, 2H, NCH$_2$CH_2O), 2.76-2.83 (ddt, J_1=2.2 Hz, J_2=5.6 Hz, 1H, CHCH_2), 2.32-2.38 (dm, J=15.6 Hz, 1H, CHCH_2), 1.74-1.79 (m, 2H, CH$_2$CH_2);

^{13}C-NMR(400 MHz, $CDCl_3$-TMS)(Appendix H.2):δ 159.6 (1C, C=O), 159.4 (1C, CO), 139.9 (1C, C_{arom}), 128.7 (2C, CH$_{arom}$), 127.6 (2C, CH$_{arom}$), 127.1 (1C, CH$_{arom}$), 93.2 (1C, C=CH), 61.9 (1C, NCH$_2$), 59.9 (1C, NCH), 56.8 (1C, OCH$_3$), 54.1 (1C, PhC), 41.6 (1C, OCH$_2$), 31.3 (1C, CHCH$_2$);

IR(thin film, cm^{-1})(Appendix H.7): 2934, 1736, 1251, 1229, 700;

HRMS (ESI) (Appendix H.8) calcd for $C_{15}H_{17}NO_3$ [M-Na]$^+$ 259.1208, obsd 259.1213;

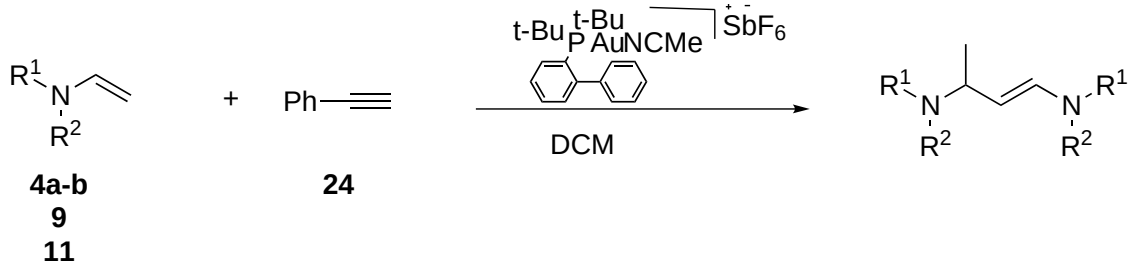
18b: R_f= 0.33 (20:1 DCM/MeOH); ^{1}H-NMR(400 MHz, $CDCl_3$-TMS)(Appendix I.1):δ 7.60 (d, J=7.4 Hz, 2H_{arom}), 7.22 (t, J=7.8 Hz, 2H_{arom}), 7.16 (t, J=7.4 Hz, 1H_{arom}), 5.47-5.49 (t, J_1=2.5 Hz, J_2=6.1 Hz, 1H, CHN), 4.05-4.26 (dm, 2H, CCH$_2$CH_2), 3.35 (s, 3H, OCH_3), 3.37-3.43 (q, 1H, CHCH$_2$CH_2), 3.14-3.19 (q, 1H, CHCH$_2$CH_2), 2.68-2.85 (m, 2H, NCH$_2$CH_2), 2.39-2.48 (dq, 1H, NCH_2CH_2O), 1.80-1.88 (dq, 1H, NCH_2CH_2O);

^{13}C-NMR(400 MHz, $CDCl_3$-TMS)(Appendix I.2):δ 158.0 (1C, C=O), 157.9 (1C, CO), 133.8 (1C, C_{arom}), 128.4 (2C, CH$_{arom}$), 126.4 (2C, CH$_{arom}$), 125.9 (1C, CH$_{arom}$), 109.5 (1C, C=CH), 61.9 (1C, CCH$_2$), 57.5 (1C, CHN), 56.8 (1C, OCH$_3$), 40.3 (1C, CHCH$_2$), 28.7 (1C, NCH_2CH_2O), 25.1 (1C, NCH_2CH_2O);

IR(thin film, cm^{-1})(Appendix I.3): 2944, 2355, 1731, 1240, 1164, 697;

HRMS (ESI) (Appendix I.8) calcd for $C_{15}H_{17}NO_3$ [M-Na]$^+$ 259.1208, obsd 259.1212;

5.4 Dimerization



4a-b
9
11

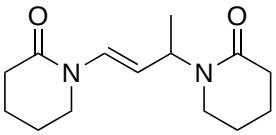
24

Scheme 5.4 Homodimerization

5.4.1 General procedure D: Dimerization of vinyl amide in presence of triplebond system

To a schlenk flask, the gold catalyst was added (0.05 equiv) and solved in DCM. Phenylacetylene (1.0 equiv) and enamide (1.0 equiv) was diluted with DCM and added simultanously to the gold catalyst. The reaction mixture was stirred under reflux for 20-24 hours. Upon completion, the reaction mixture was quenched with NEt_3, filtered through Celite^{TM}, rinsed with DCM and the solvent was removed *in vacuo* to obtain the crude product. The crude product was purified with silica gel Versa Flash, using suitable eluent system of MeOH in DCM.

Synthesis of *(E)*-1,1'-(but-1-ene-1,3-diyl)bis(piperidin-2-one (23)



77%
23

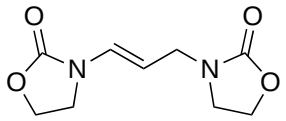
Dimer **23** was synthesized according to *General Procedure D* from vinyl amide **9** (54.6 mg, 0.436 mmol), phenylacetylene (51.6 mg, 0.506 mmol) and gold(I) catalyst (17.7 mg, 22.9 μmol) in DCM. Reaction mixture was stirred under reflux for 24 hours. Flash chromatography (DCM/MeOH 40:1) yielded dimer **23** (86.3 mg, 77.0%) as a white solid.

23: R_f= 0.24 (DCM/MeOH 20:1); ^{1}H-NMR(400 MHz, $CDCl_3$-TMS)(Appendix J.1):δ 7.48.7.52 (dd, J_1=1.44 Hz, J_2=15.0, 1H, NC*H*), 5.39-5.42 (m, 1H, CH=C*H*), 4.99-5.05 (dd, J_1=5.6 Hz, J_2=14.9 Hz, 1H, CH_3C*H*), 3.36-3.39 (t, 2H, NCH_2), 3.12-3.14 (m, 2H, C=OCH_2), 2.46-2.50 (t, 2H, NCH_2), 2.38-2.41 (m, 2H, C=OCH_2), 1.78-1.92 (m, 2H, C=OCH_2CH_2), 1.69-1.74 (m, 6H, $CH_2CH_2CH_2$, $CH_2CH_2CH_2$), 1.27-1.29 (d, 3H, CH_3);

^{13}C-NMR(400 MHz, $CDCl_3$-TMS)(Appendix J.2): 169.30 (1C, *C*=O), 168.58 (1C, *C*=O), 128.39 (1C, N*C*H=C), 110.19 (1C, CH=CH*C*H), 48.10 (1C, CH=*C*H), 45.26 (1C, N*C*H_2), 41.75 (1C, C=O*C*H_2), 32.93 (1C, N*C*H_2), 32.57 (1C, C=O*C*H_2), 23.27 (1C, $CH_2CH_2CH_2$), 22.60 (1C, C=OCH_2*C*H_2), 21.08 (1C, *C*$H_2CH_2CH_2$), 20.50 (1C, $CH_2CH_2CH_2$), 16.33 (1C, *C*H_3);

HRMS (EI) calcd for $C_{14}H_{22}N_2O_2$ $[M\text{-}H]^+$ 250.1676, obsd 250.1676.

Synthesis of *(E)*-3,3'-(but-1-ene-1,3-diyl)bis(oxazolidin-2-one (25)



72%
25

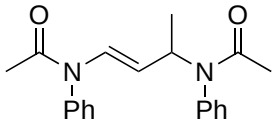
Dimer **25** was synthesized according to *General Procedure D* from vinyl amide **11** (113.4 mg, 1.00 mmol), phenylacetylene (92.8 mg, 0.909 mmol) and gold(I) catalyst (33.1 mg, 42.9 μmol) in DCM. Reaction mixture was stirred under reflux for 20 hours. Flash chromatography (DCM/MeOH 30:1) yielded dimer **25** (162.9 mg, 72.0%) as a light yellow solid.

25: R_f= 0.65 (DCM/MeOH 20:1); ^{1}H-NMR(400 MHz, $CDCl_3$-TMS)(Appendix K.1):δ 6.80-6.83 (d, J=14.8 Hz, 1H, NCH), 4.85-4.90 (dd, J_1=5.9 Hz, J_2=8.6 Hz, 1H, CH_3CHCH), 4.54-4.61 (quint, J=6.6, 1H, NCH), 4.44-4.48 (t, J=7.8 Hz, 2H, OCH_2), 4.29-4.33 (t, J=7.9 Hz, 2H, OH_2), 3.68-3.72 (t, J=8.2 Hz, 2H, NCH_2), 3.41-3.52 (sekstett, J=8.2 Hz, 2H, NCH_2), 1.35-1.36 (d, J= 7.0 Hz, 3H, CH_3);

^{13}C-NMR(400 MHz, $CDCl_3$-TMS)(Appendix K.2): 157.71 (1C, C=O), 157.37 (1C, C=O), 126.21 (1C, NCH), 108.91 (1C, CHCHCH), 62.30 (1C, OCH$_2$), 62.03 (1C, OCH$_2$), 48.26 (1C, CH_3CH), 43.26 (NCH$_2$), 40.3 (1C, NCH$_2$), 17.05 (1C, CH$_3$) ;

IR(neat, cm^{-1})(Appendix K.7): 3293, 2923, 1731, 1480, 1230, 697;
HRMS (EI) calcd for $C_{10}H_{14}N_2O_4$ [M-H]$^+$ 226.0948, obsd 226.0949.

Synthesis of *(E)-N,N'*-(but-1-ene-1,3-diyl)bis(N-phenylacetamide) (26)



63%
26

Compound **26** was synthesized according to *General Procedure D* from vinyl amide **4b** (77.1 mg, 0.480 mmol), phenylacetylene (51.3 mg, 0.503 mmol) and gold(I) catalyst (19.2 mg, 24.8 μmol) in DCM. Reaction mixture was stirred under reflux for 2 hours. Flash chromatography (DCM/MeOH 30:1) yielded compound **26** (108.8 mg, 63.7%) as a yellow oil.

26: R_f= 0.13 (DCM/MeOH 20:1); ^{1}H-NMR(400 MHz, $CDCl_3$-TMS)(Appendix L.1):δ 7.45-7.54 (m, 4H$_{arom}$), 7.28-7.35 (m, 4H$_{arom}$), 7.04 (d, J=5.8 Hz, 2H$_{arom}$), 6.90 (br, 1H, CH=CHN), 5.47-5.52 (quin, J=6.8 Hz, 1H, NCH), 4.25-4.30 (dd, J_1=6.7 Hz, J_2=14.5 Hz, 1H, NCH=CH), 2.17 (s, 1H, O=CCH_3), 1.82 (br, 3H, O=CCH_3), 1.69 (s, 3H, C=OCH_3), 1.16-1.18 (d, J=6.8 Hz, 3H, NCHCH_3);

^{1}H-NMR(400 MHz, DMSO)(Appendix L.7):δ 7.35-7.56 (m, 8H$_{arom}$), 7.20-7.27 (m, 2H$_{arom}$), 6.99-7.02 (m, 1H, CH=CHN), 5.21-5.34 (quin, J=7.1 Hz, 1H, NCH), 4.03-4.08 (dd, J_1=7.6 Hz, J_2=14.4

Hz, 1H, NCH=CH), 2.03 (s, 1H, O=CCH_3), 1.74 (br, 3H, O=CCH_3), 1.60 (s, 3H, C=OCH_3), 1.00-1.02 (d, J=6.8 Hz, 3H, NCHCH_3);

^{13}C-NMR(400 MHz, $CDCl_3$-TMS)(Appendix L.2): 169.65 (1C, C=O), 168.68 (1C, C=O), 139.34 (1C, C_{arom}), 130.15 (1C, C_{arom}), 129.99 (1C, CH$_{arom}$), 129.01 (2C, CH$_{arom}$), 128.91 (2C, CH$_{arom}$), 128.73 (2C, CH$_{arom}$), 128.13 (2C, CH$_{arom}$), 124.06 (1C, CH$_{arom}$) 119.81 (1C, NCH), 114.31 (1C, NCH=CH), 49.80 (1C, CH_3CH), 24.54 (1C, C=OCH$_3$), 23.30 (1C, C=OCH$_3$), 18.25 (1C, CHCH$_3$);

IR(thin film, cm^{-1})(Appendix L.6): 3293, 3064, 2973, 2359, 1656, 1260, 957;
Due to technical problems HRMS could not be performed for compound **26**.

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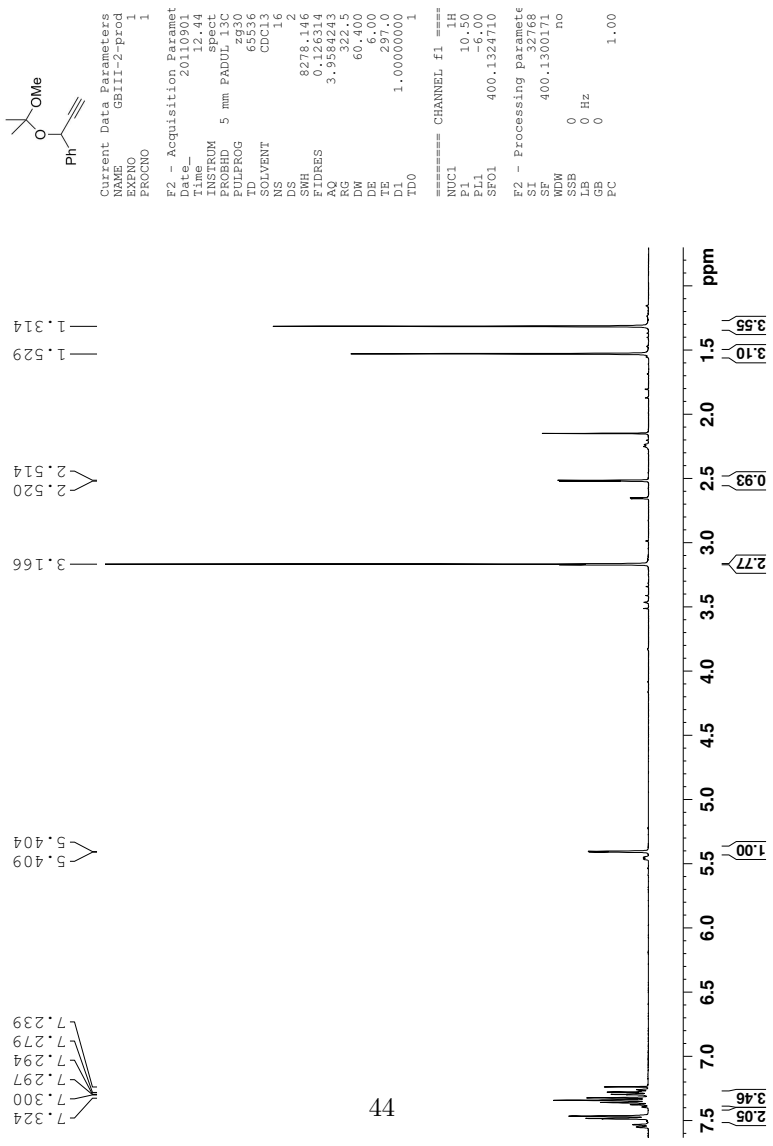
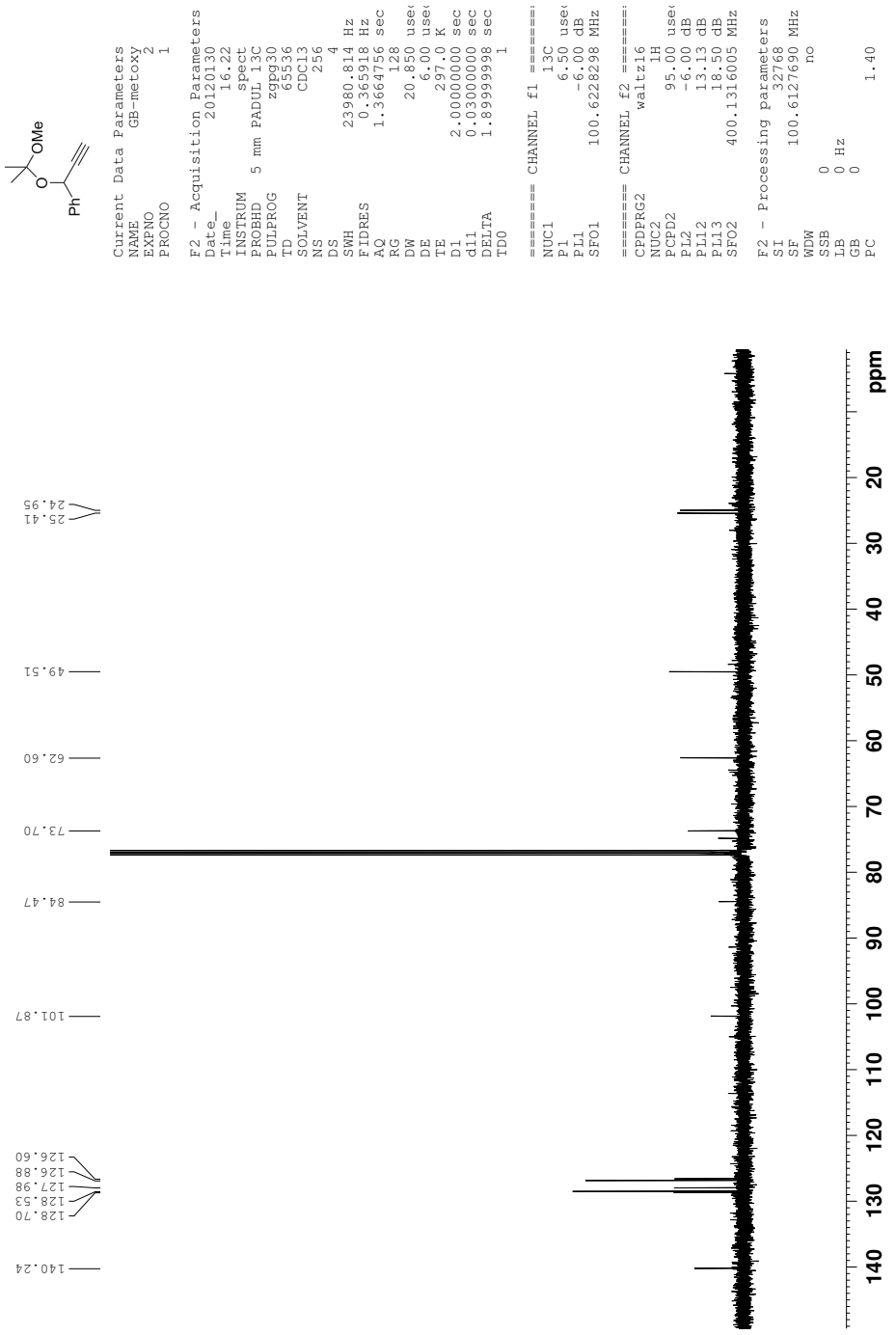
Appendix A

Methoxy acetal 1a

A.1 ^{1}H-NMR Methoxy acetal 1a



A.2 ^{13}C-NMR Methoxy acetal 1a



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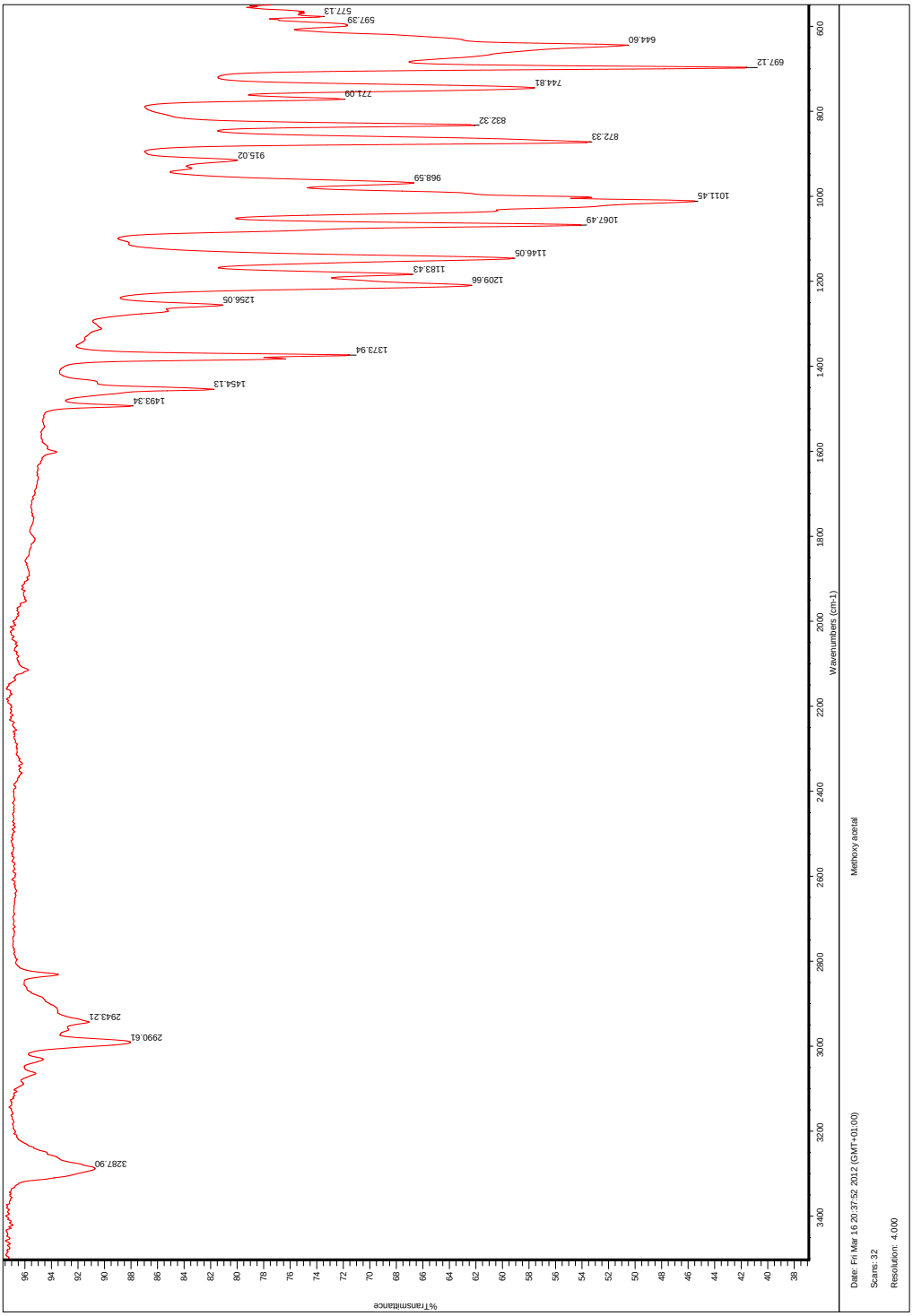
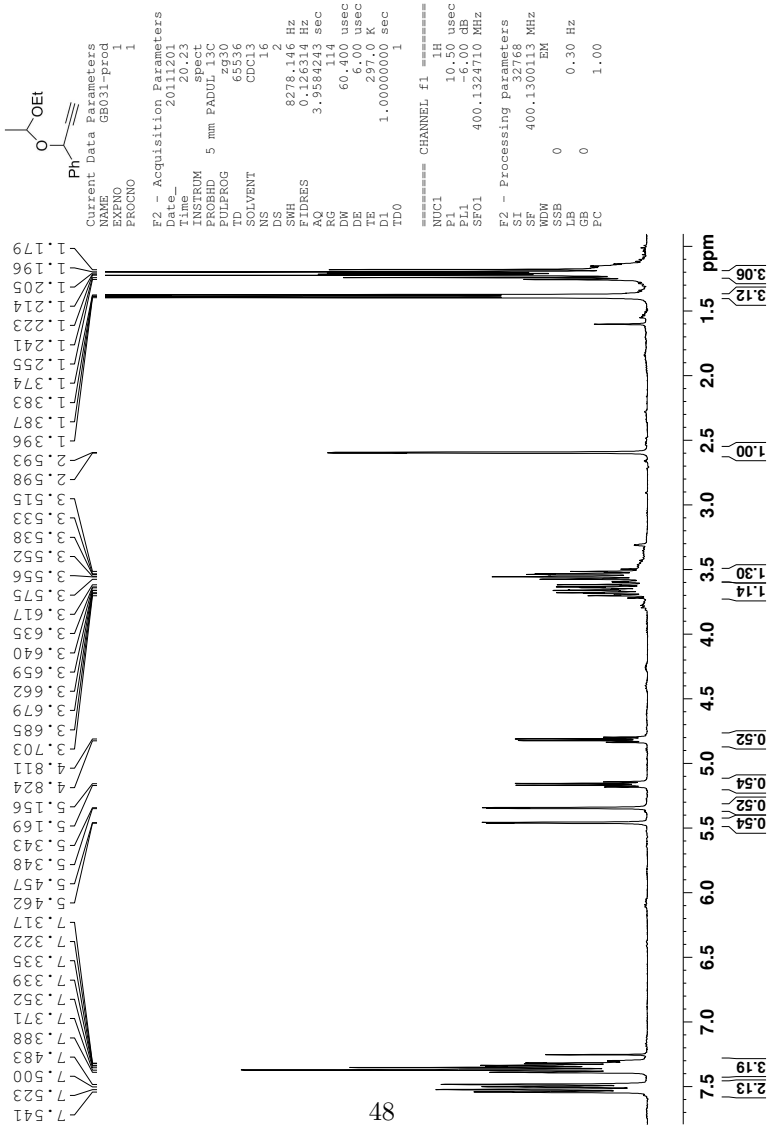


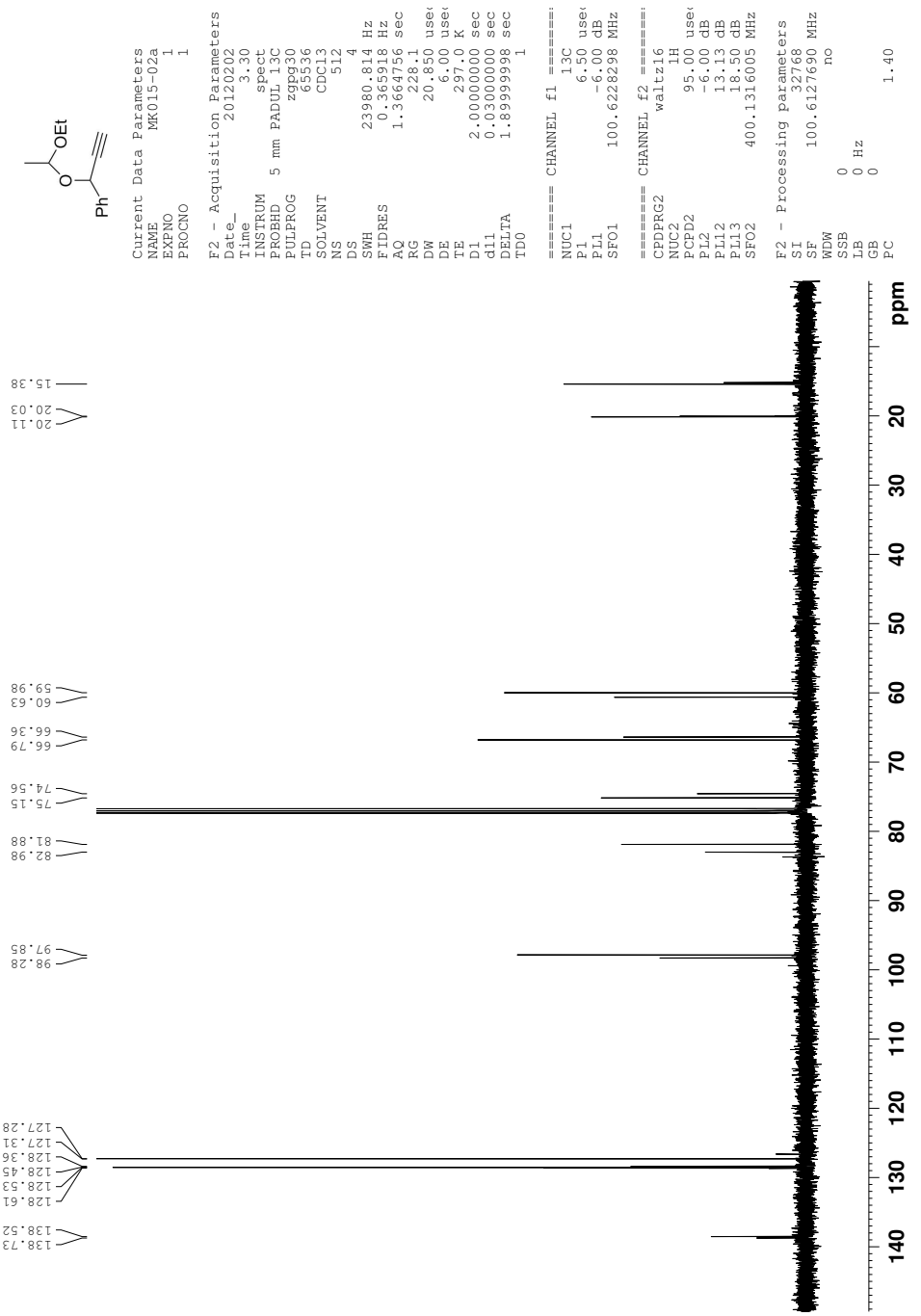
Appendix B

Ethoxy acetal 1b

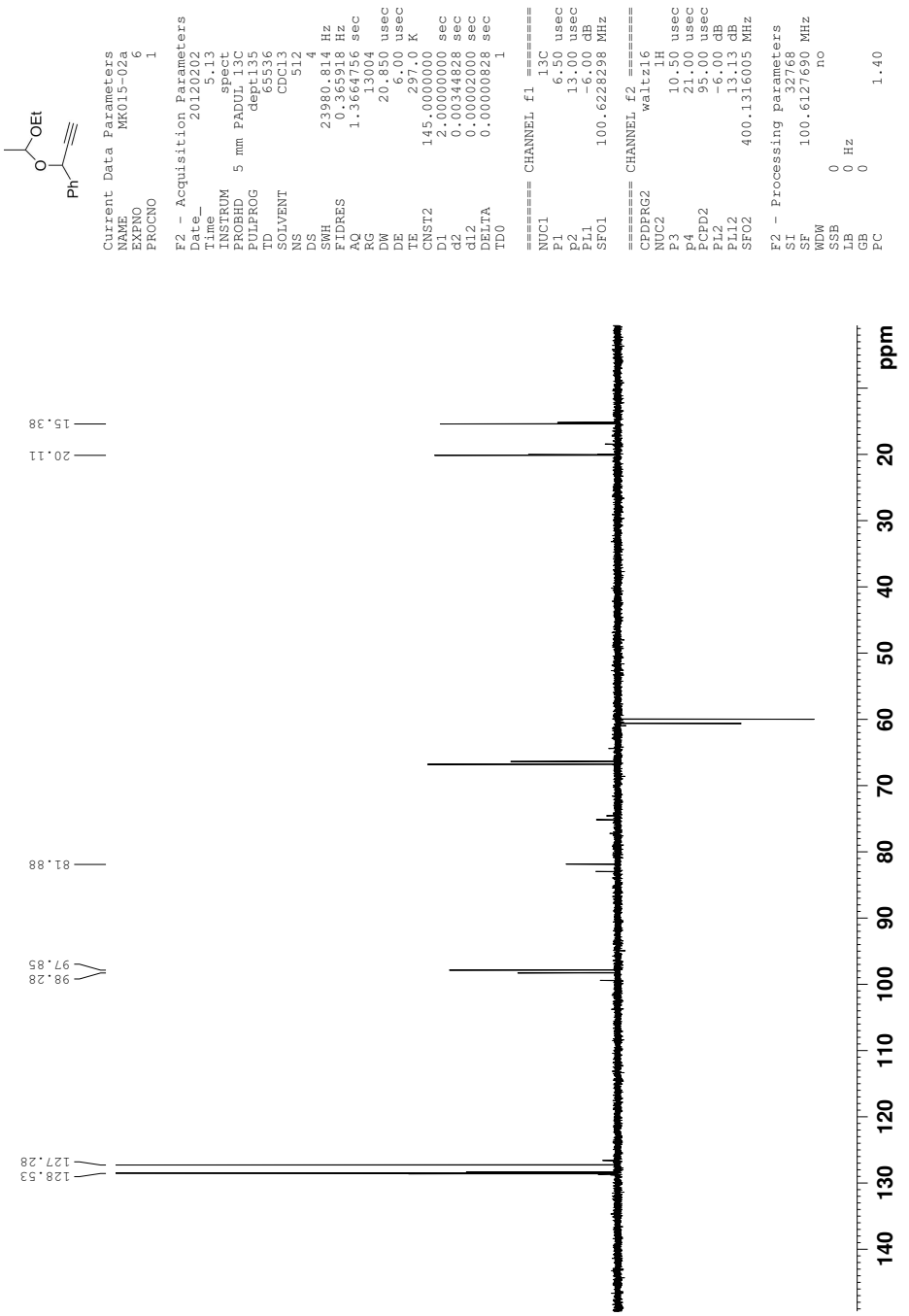
^{1}H-NMR Ethoxy acetal 1b



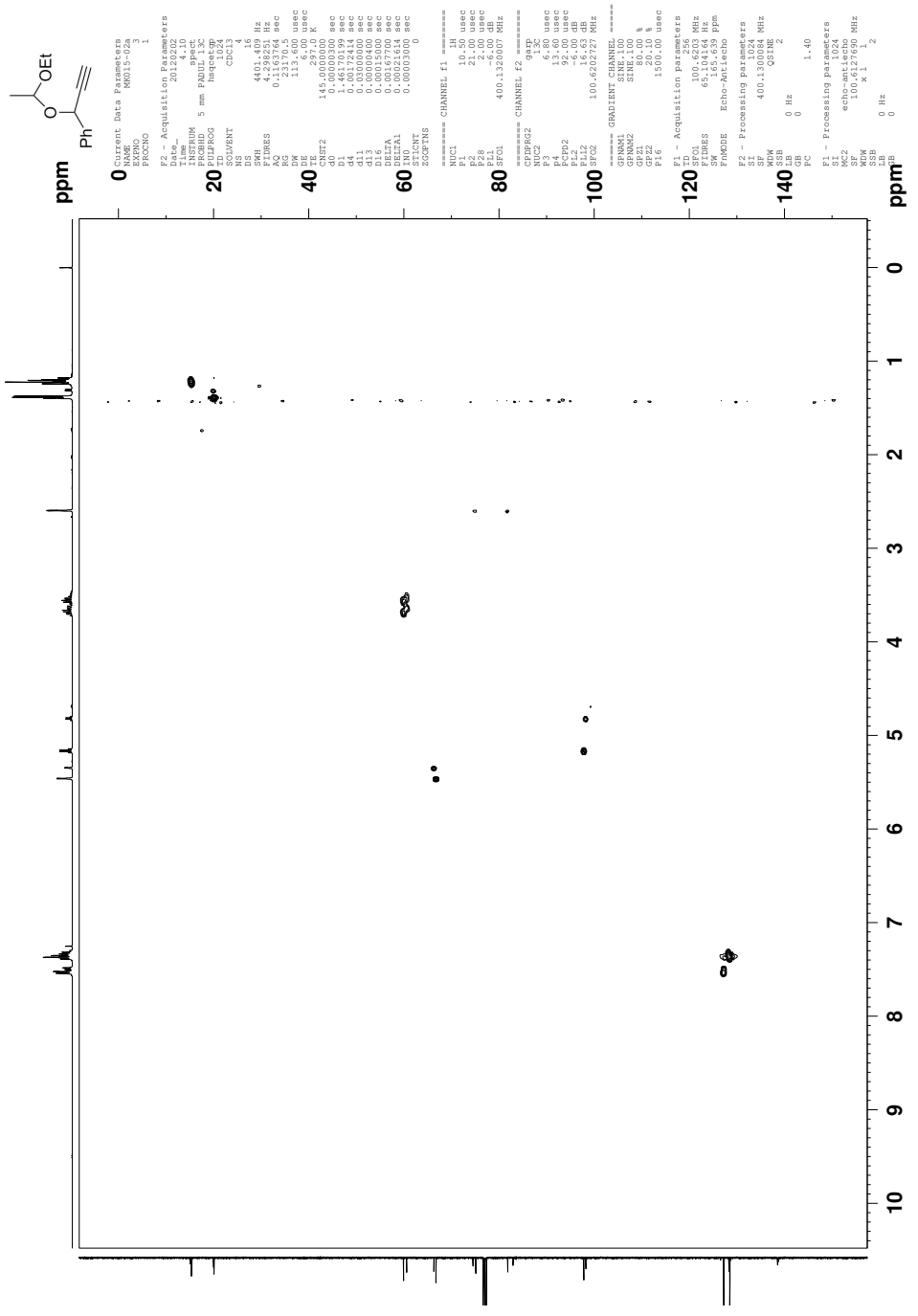
B.1 ^{13}C-NMR Ethoxy acetal 1b



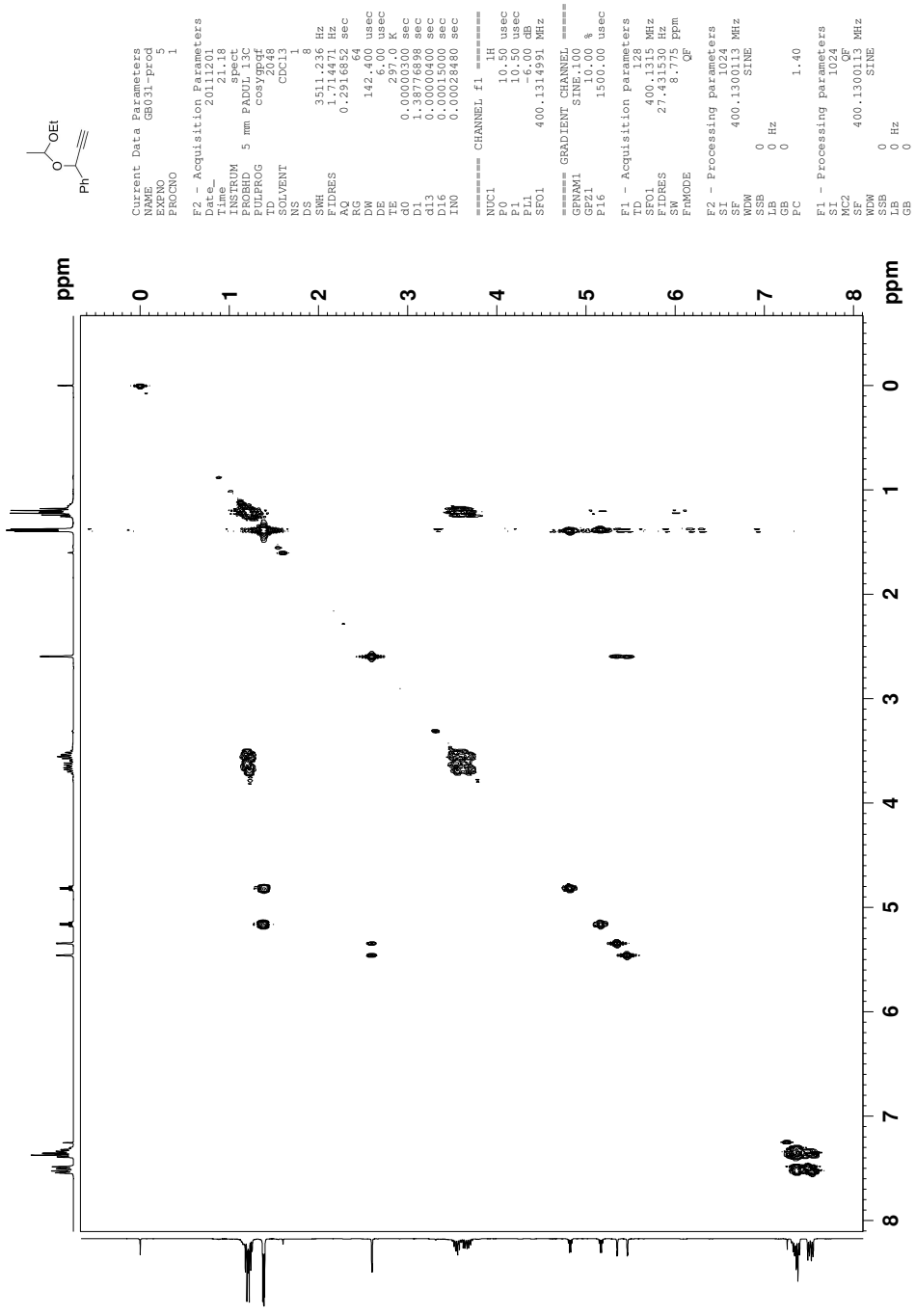
B.2 Dept-NMR Ethoxy acetal 1b



B.3 HSQC-NMR Ethoxy acetal 1b



B.4 COSY-NMR Ethoxy acetal 1b



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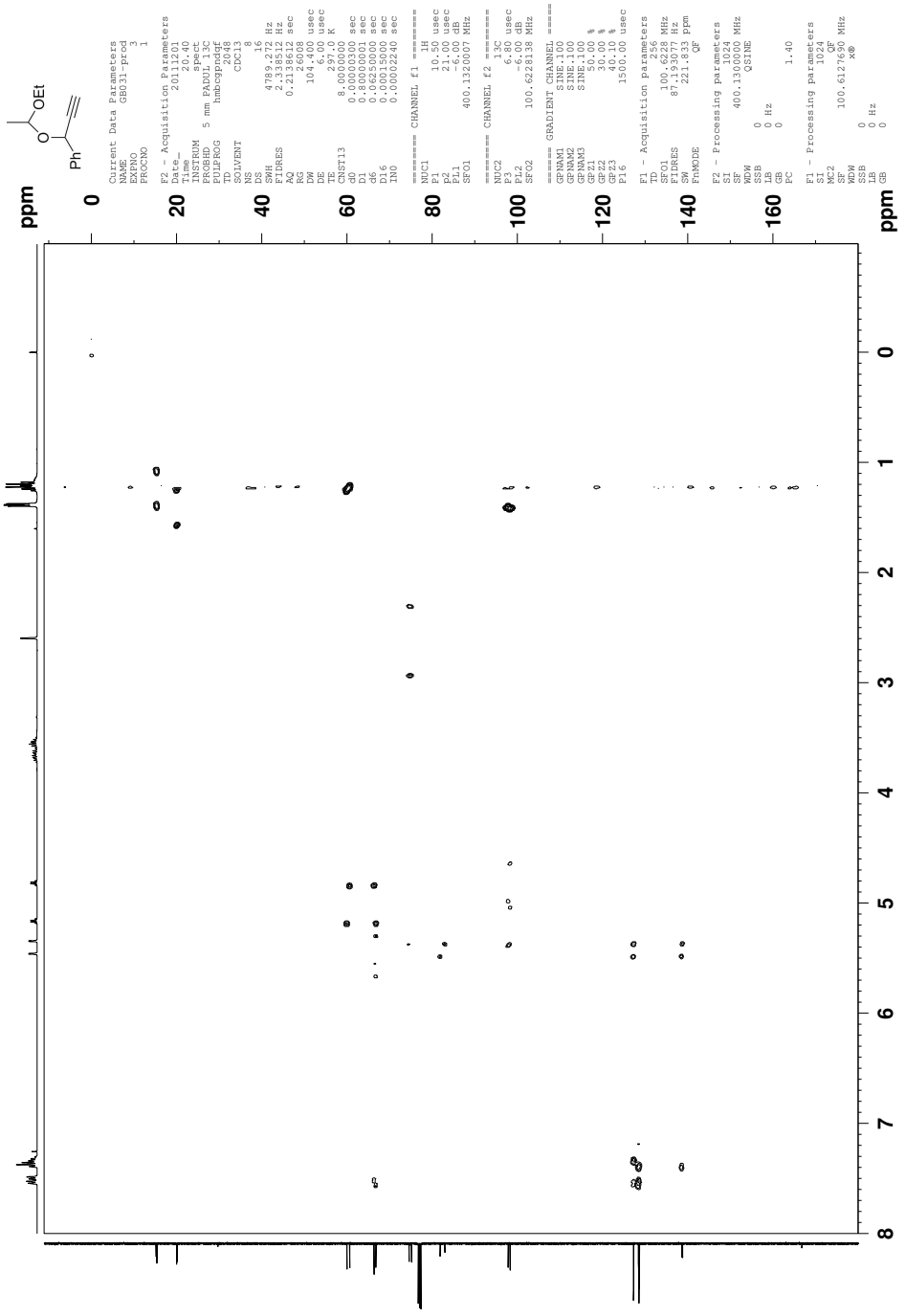
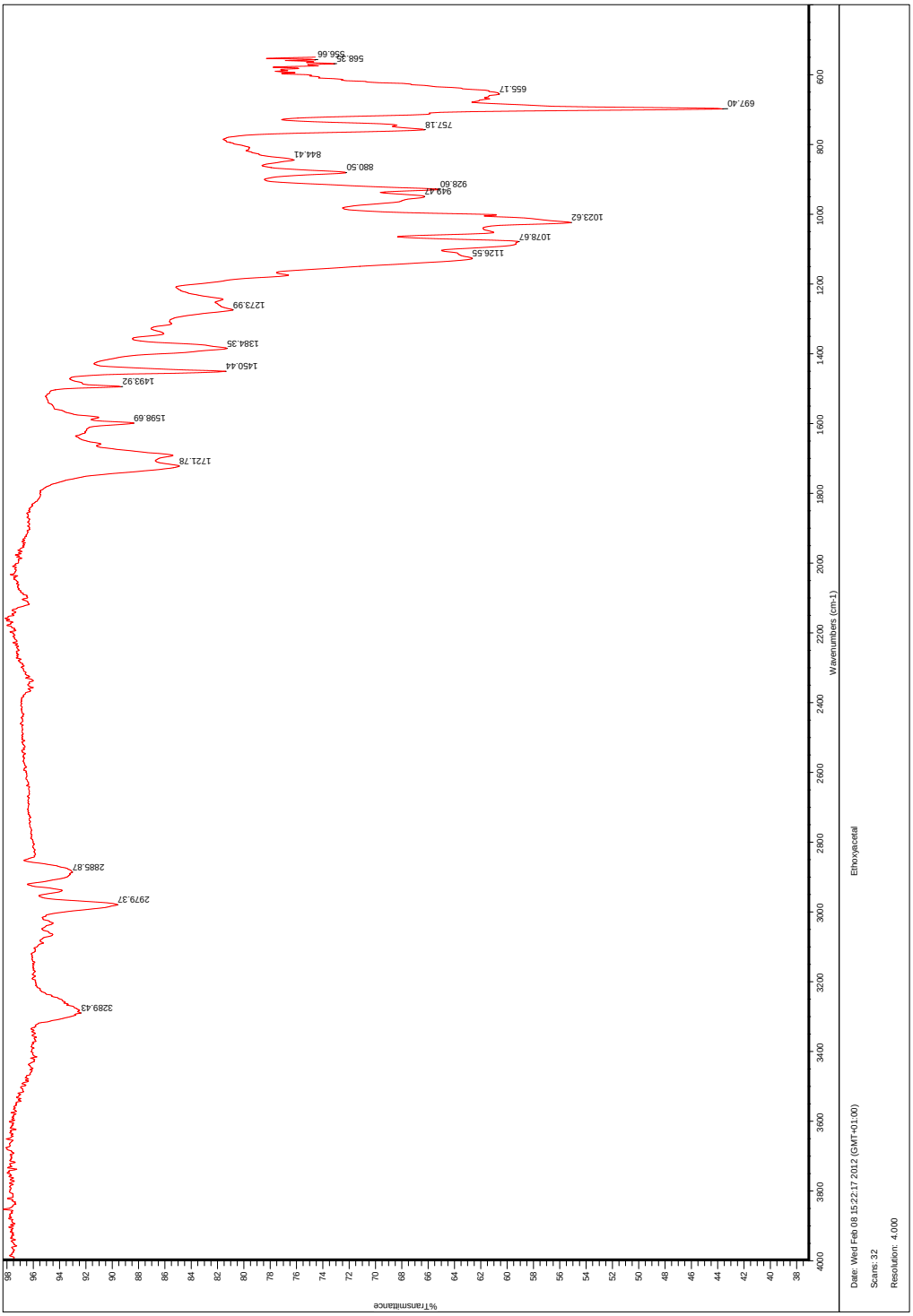


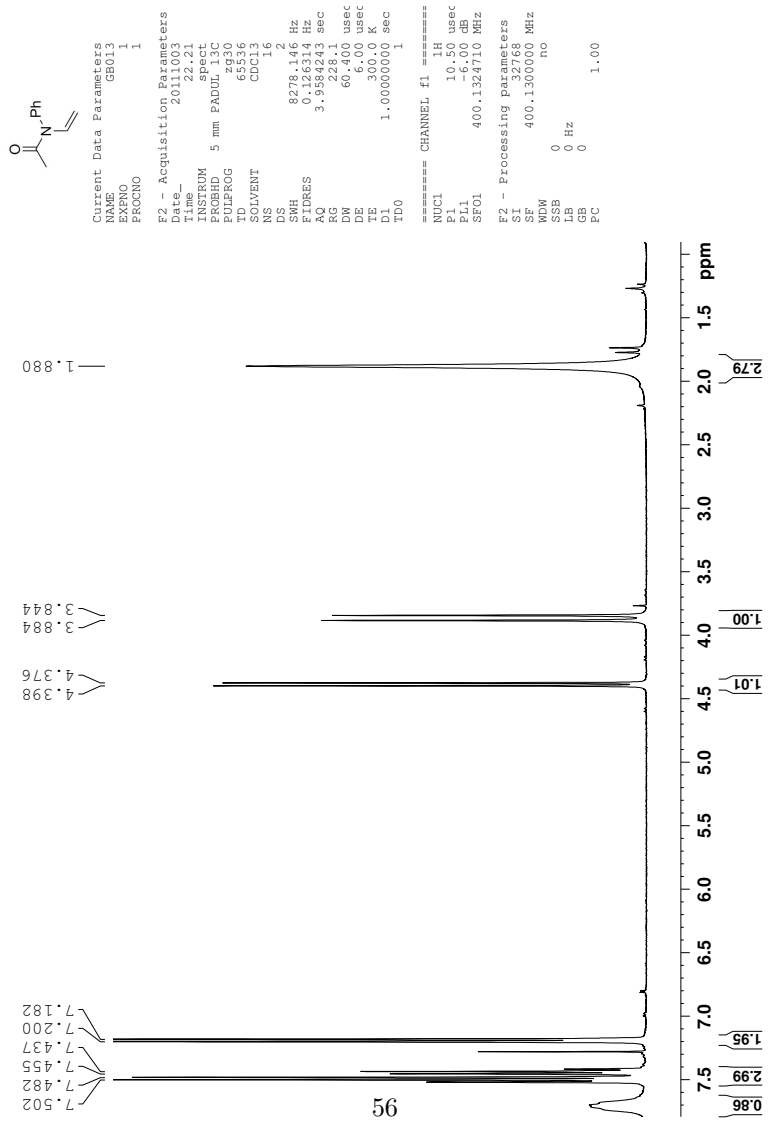
B.6 IR Ethoxy acetal 1b



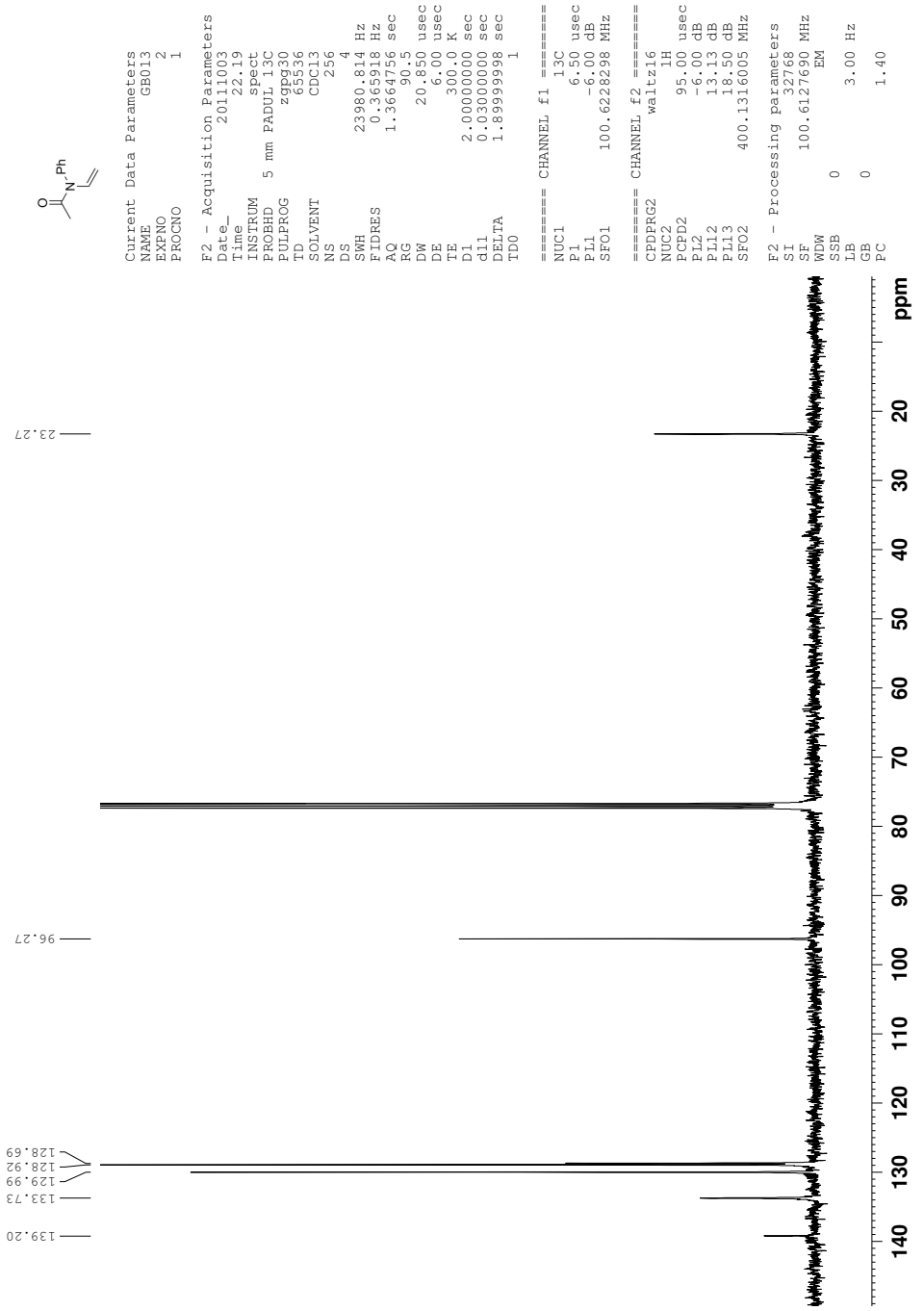
Appendix C

Vinyl amide 4b

C.1 ^{1}H-NMR Vinyl amide 4b



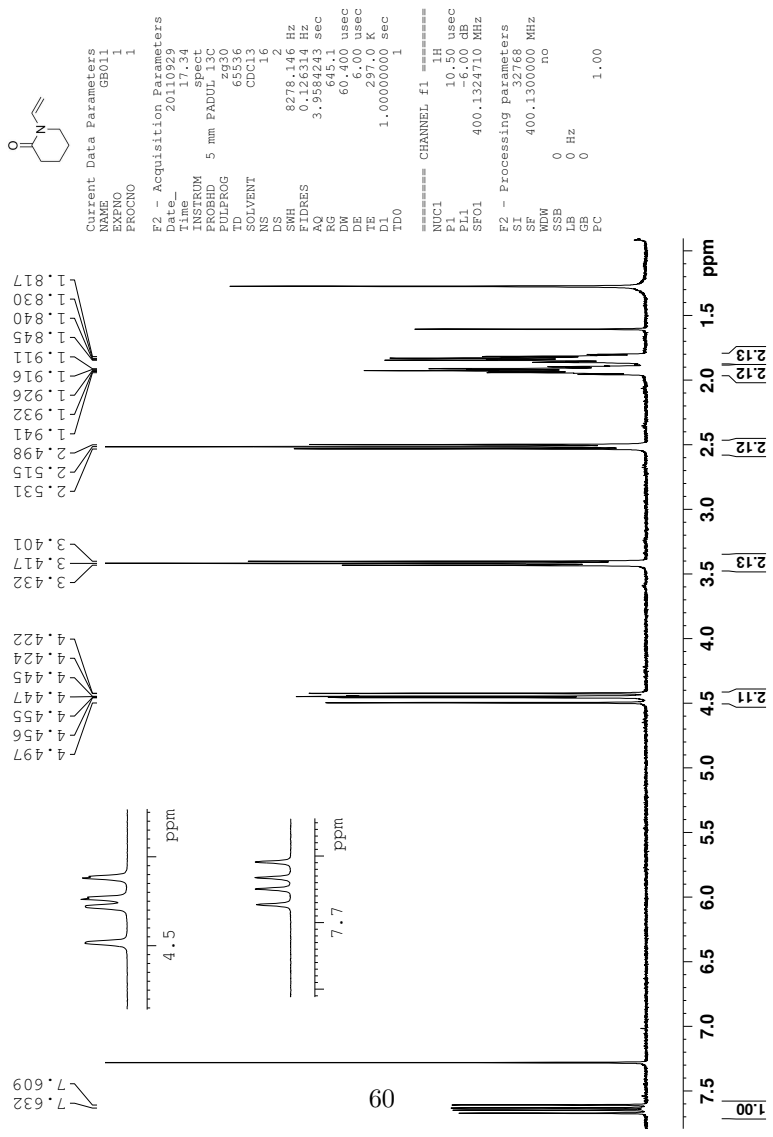
C.2 ^{13}C-NMR Vinyl amide 4b



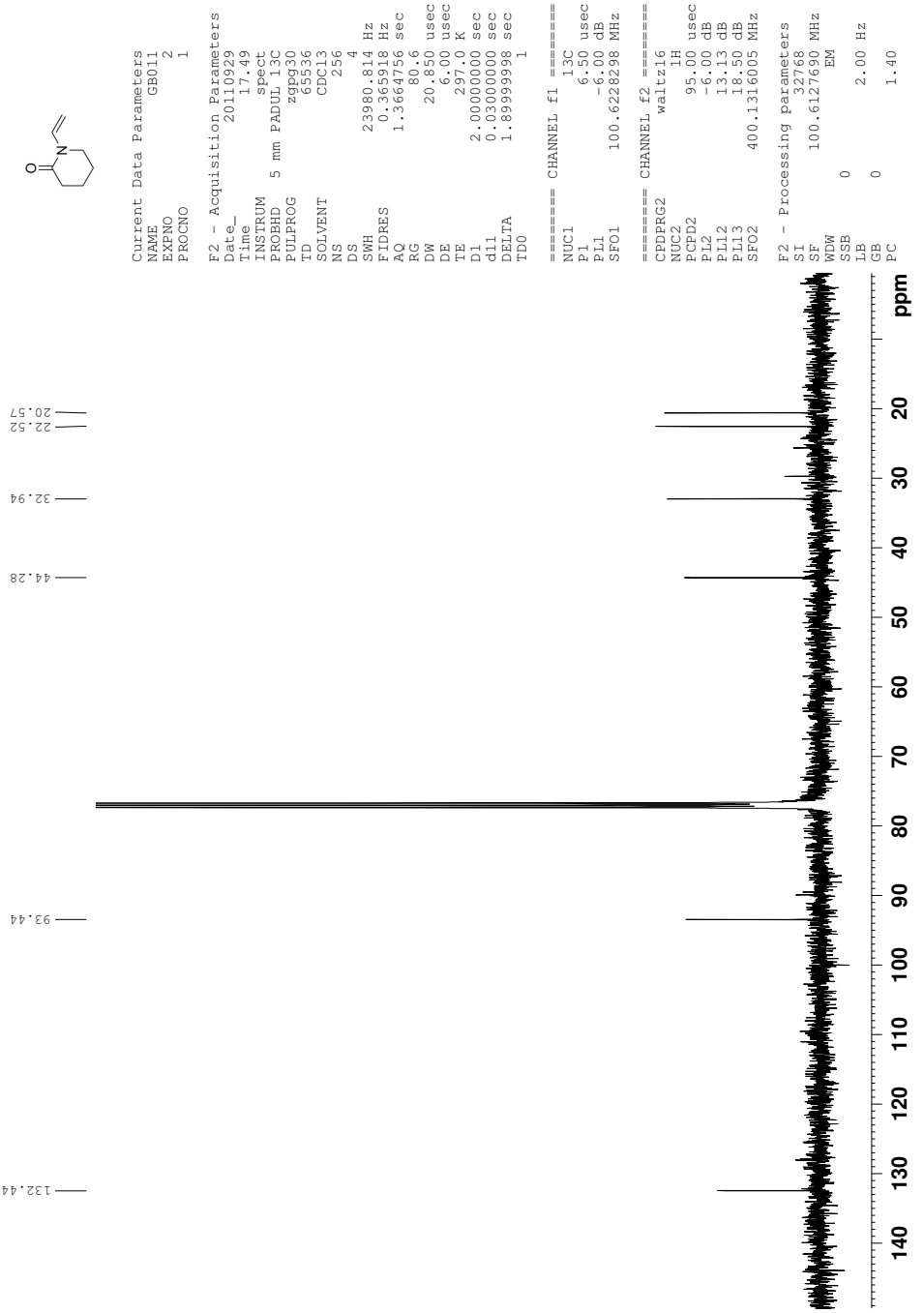
Appendix D

N-vinyl valerolactam 9

D.1 ^{1}H-NMR N-vinyl valerolactam 9



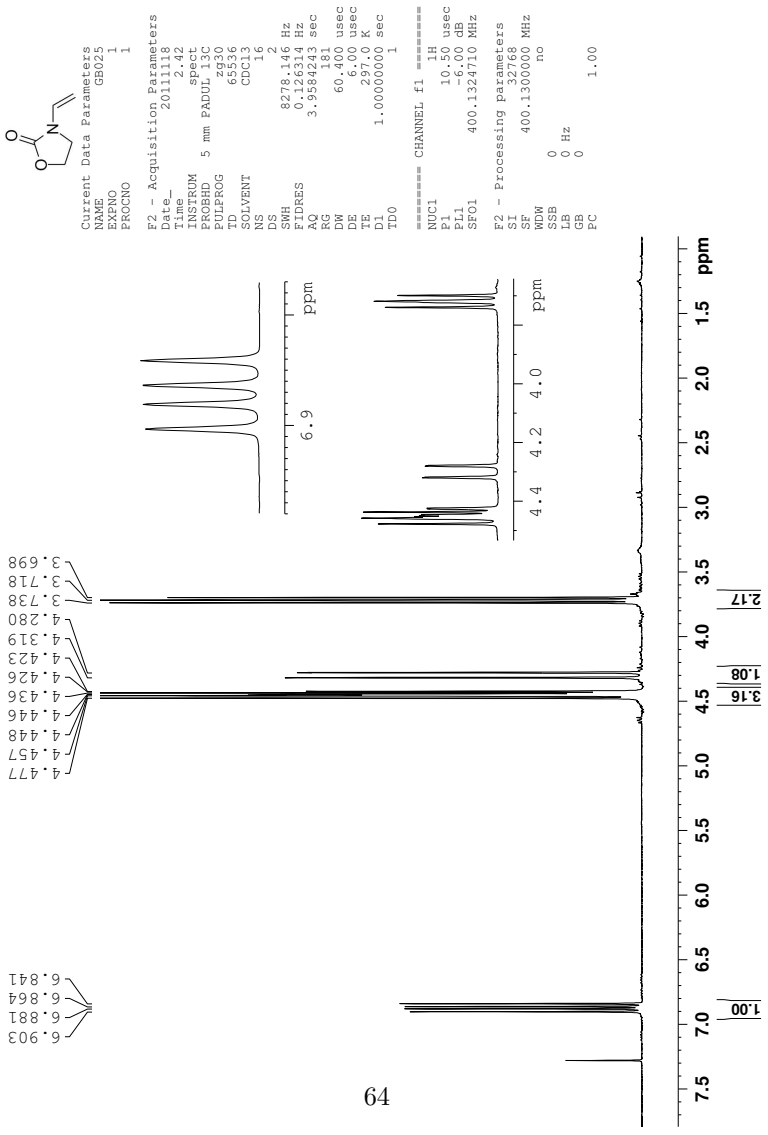
^{13}C-NMR N-vinyl valerolactam 9



Appendix E

3-vinyloxazolidin-2-on 11

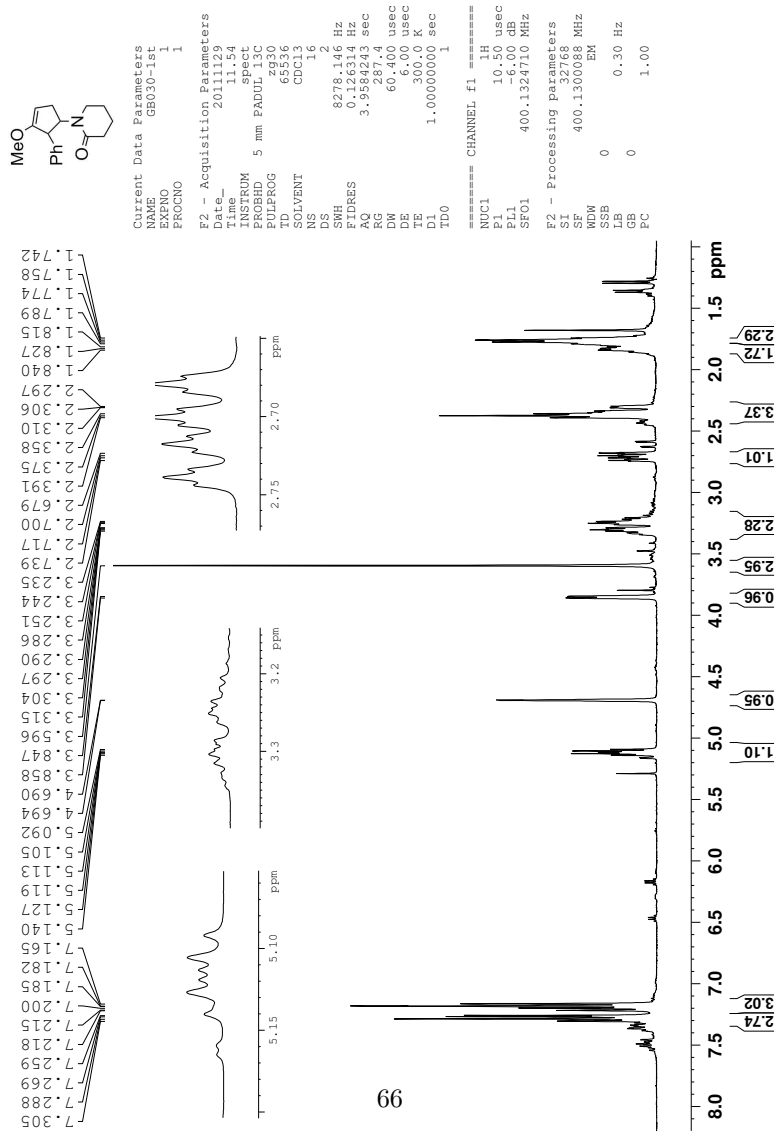
E.1 ^{1}H-NMR 3-vinyloxazolidin-2-on 11



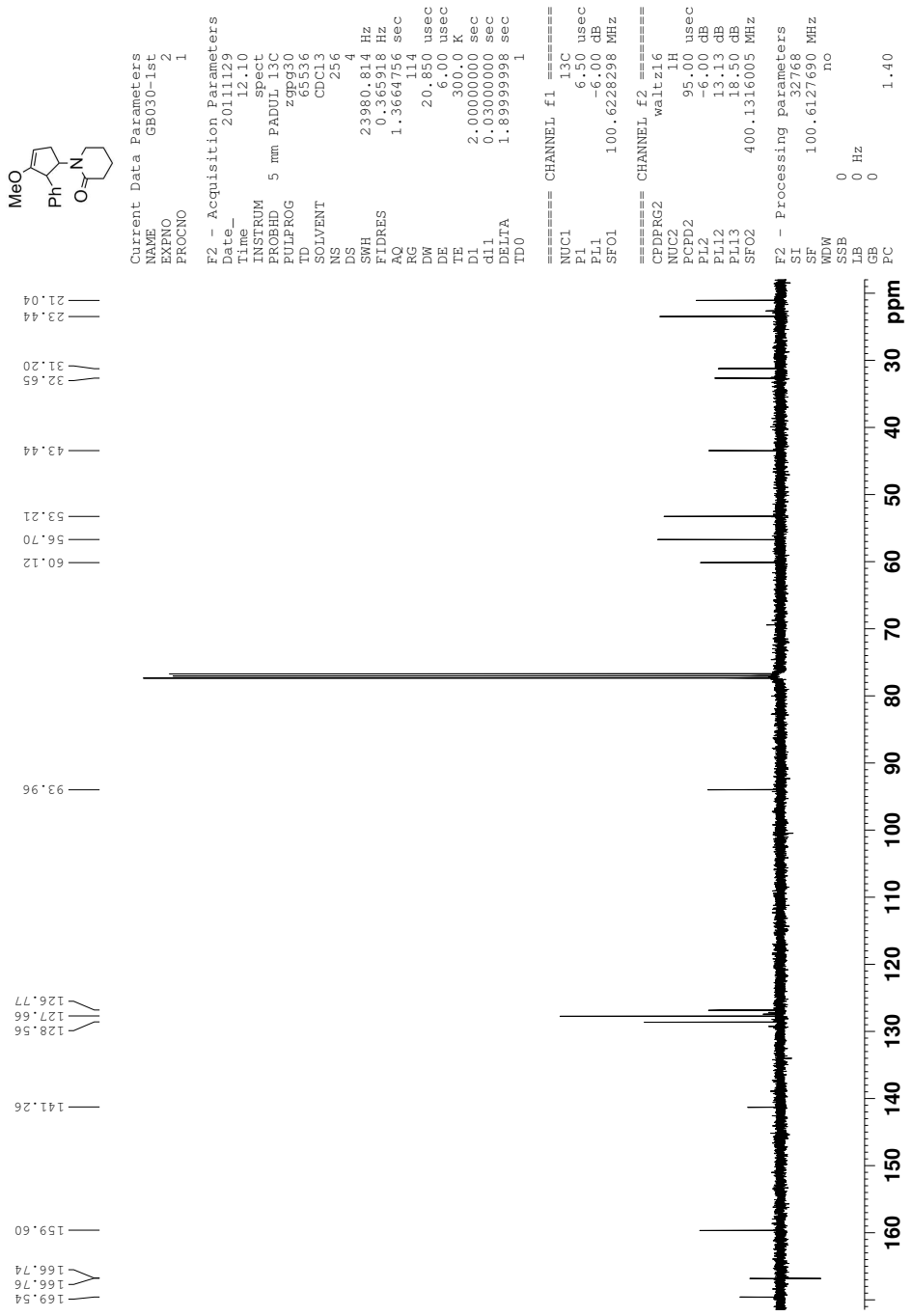
Appendix F

[3+2] cycloaddition product 17a

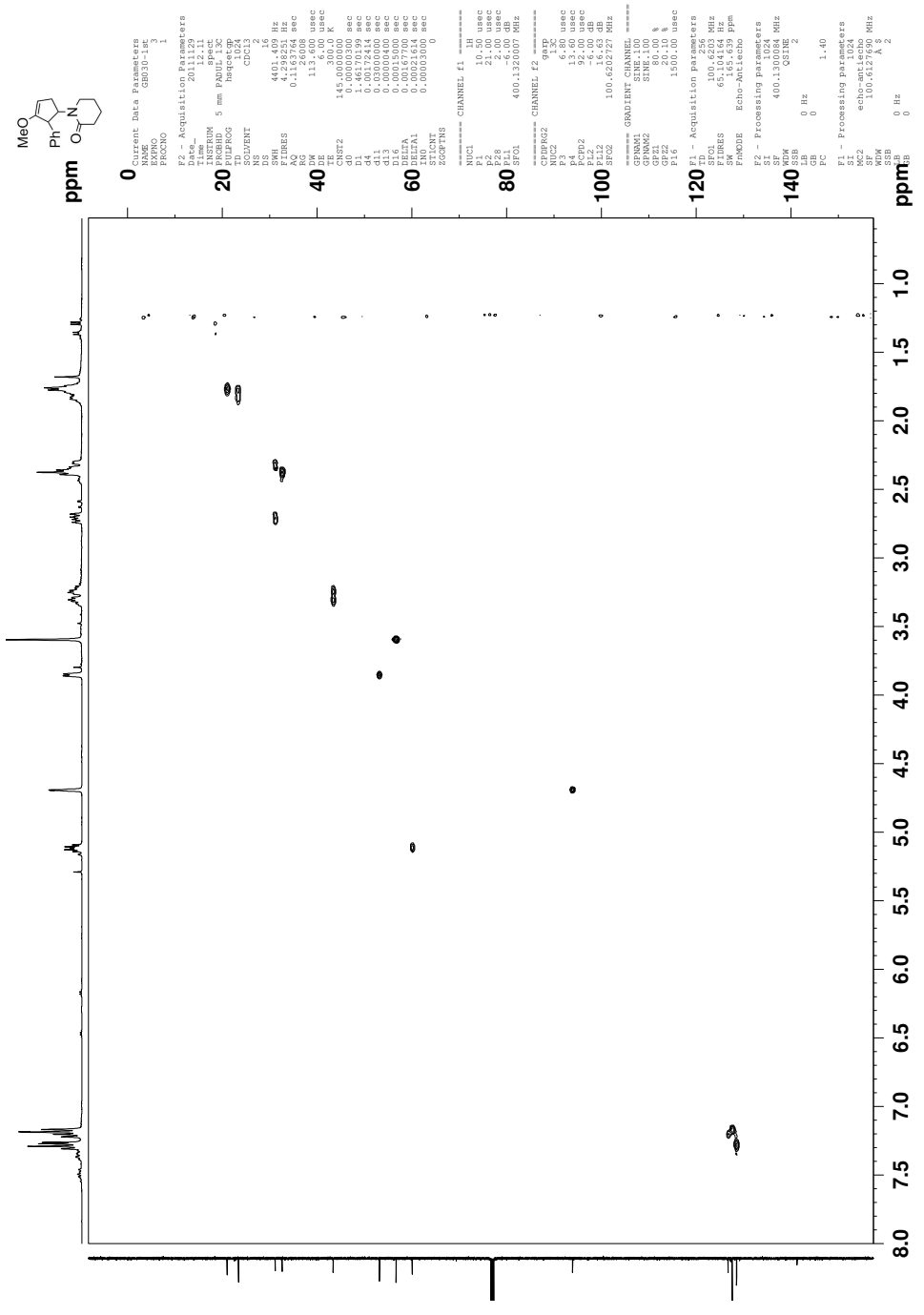
F.1 ^{1}H-NMR [3+2] cycloaddition product 17a



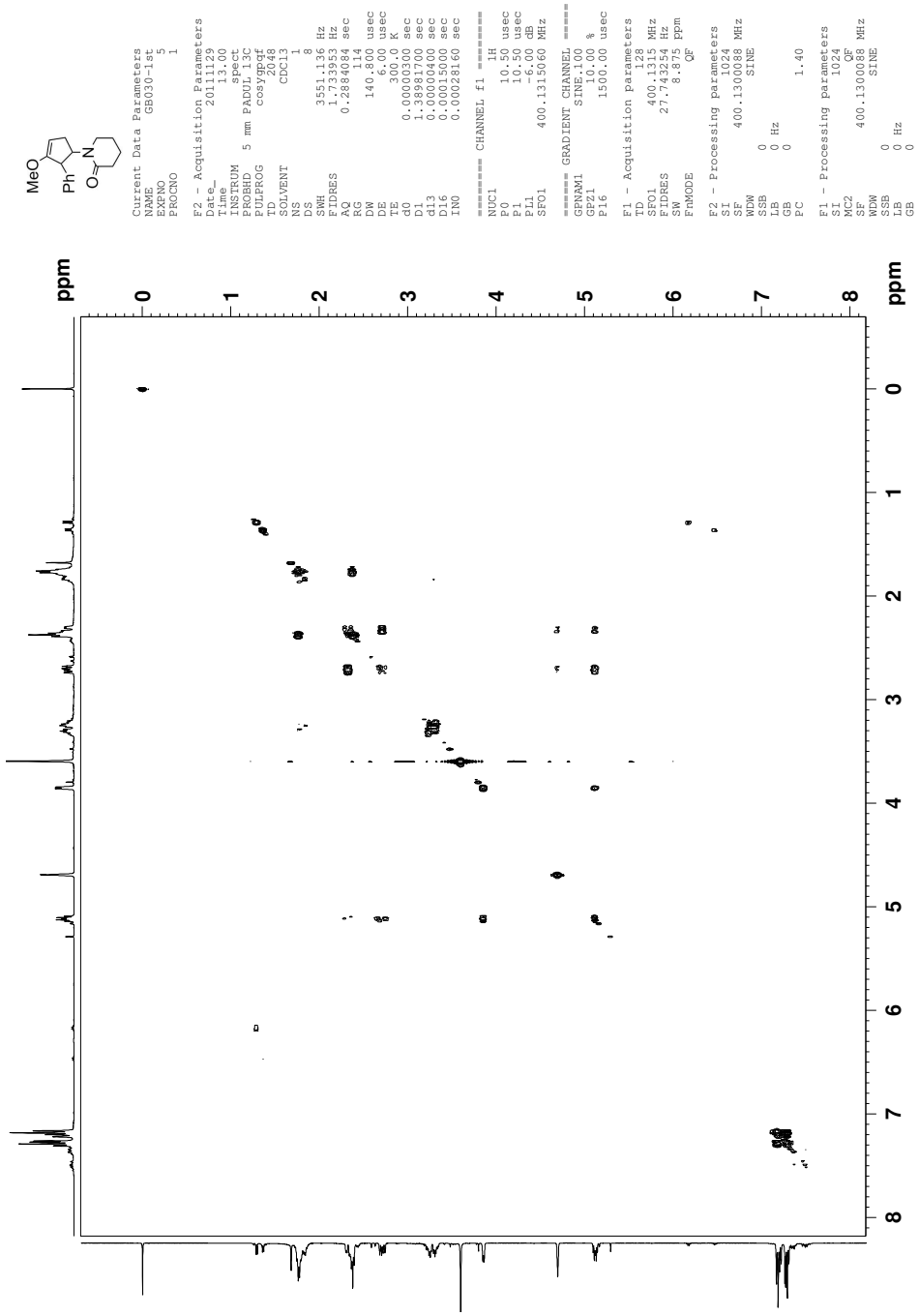
F.2 ^{13}C-NMR [3+2] cycloaddition product 17a



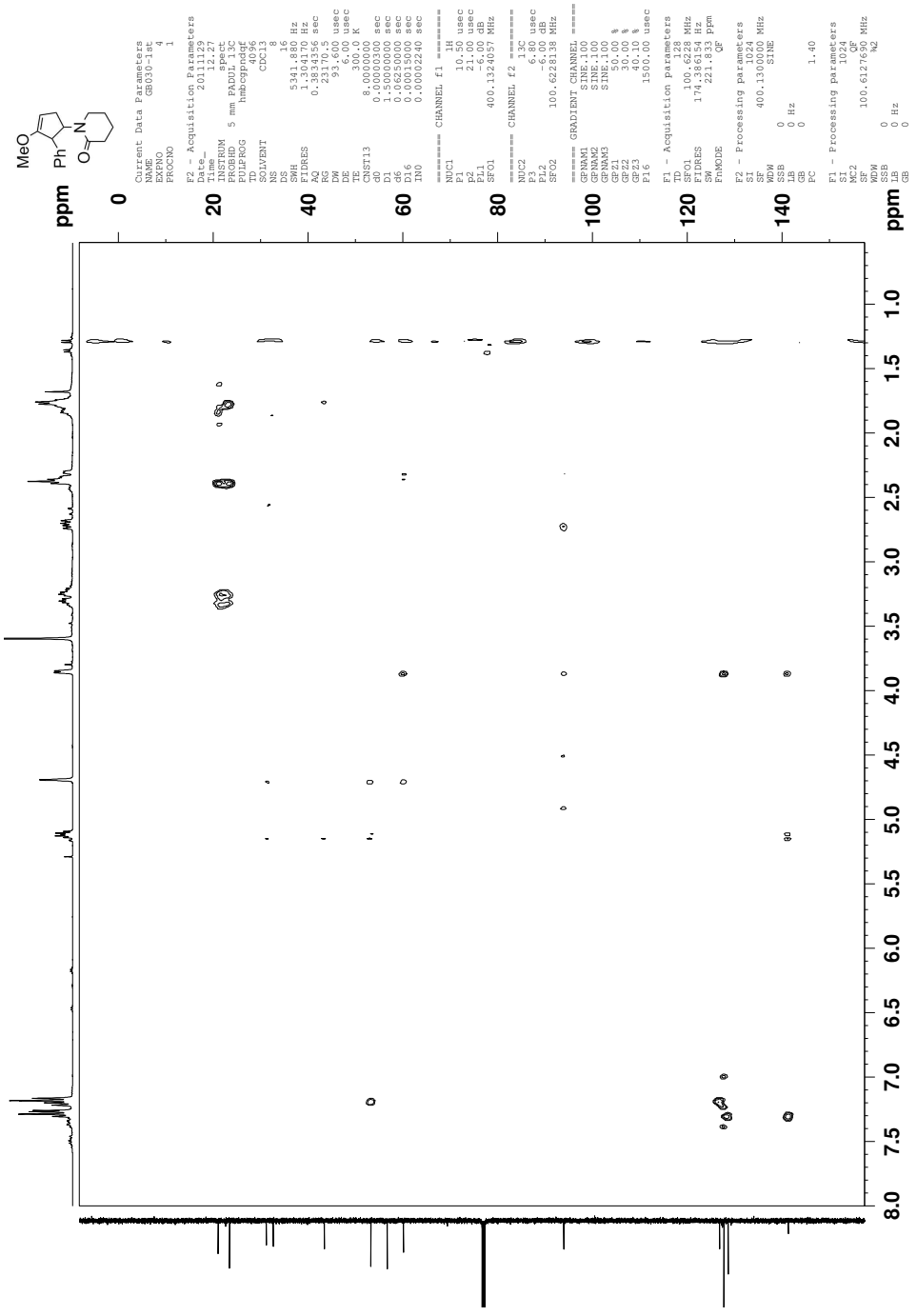
F.3 HSQC-NMR [3+2] cycloaddition product 17a



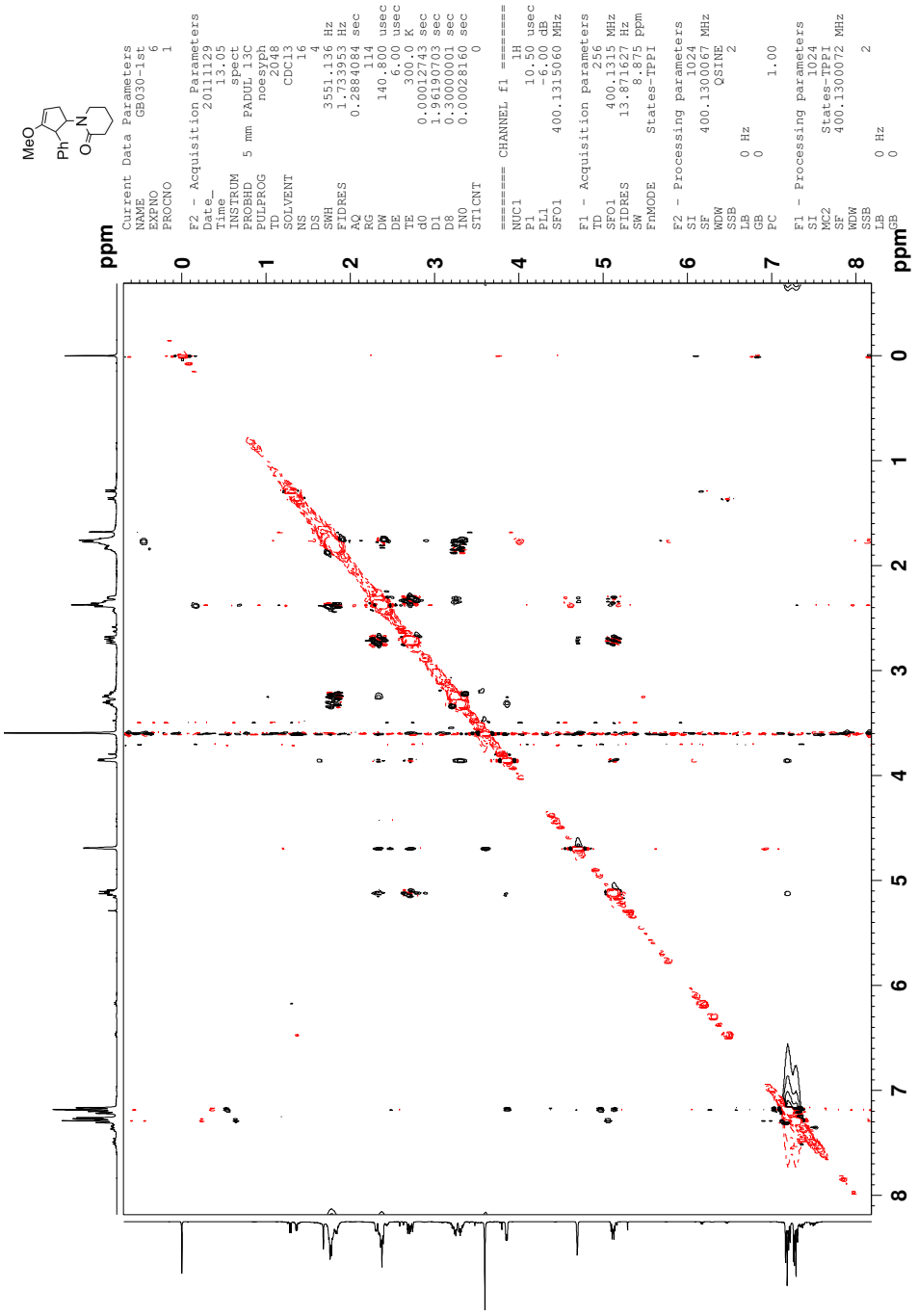
F.4 COSY-NMR [3+2] cycloaddition product 17a



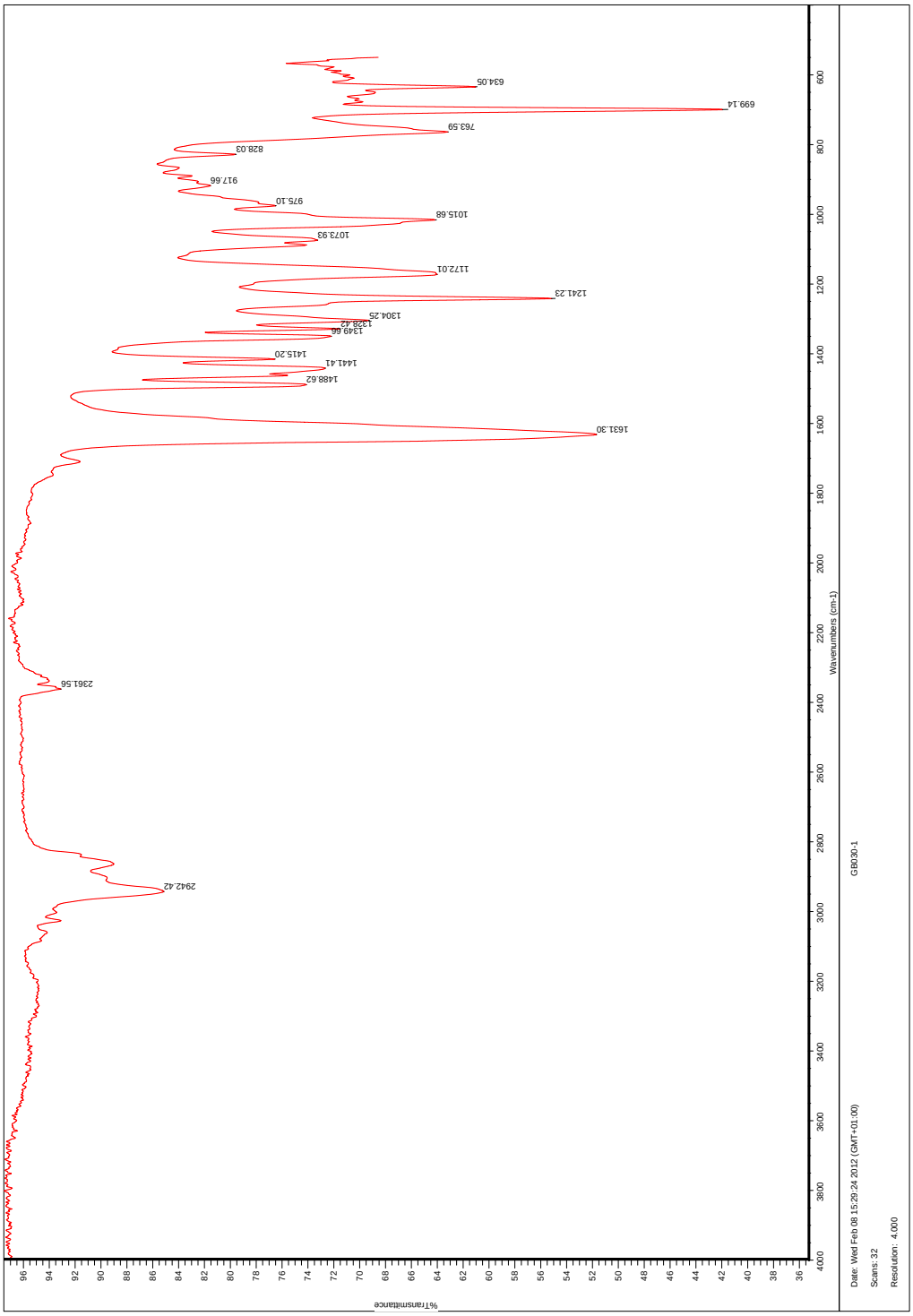
F.5 HMBC-NMR [3+2] cycloaddition product 17a



F.6 NOESY-NMR [3+2] cycloaddition product 17a



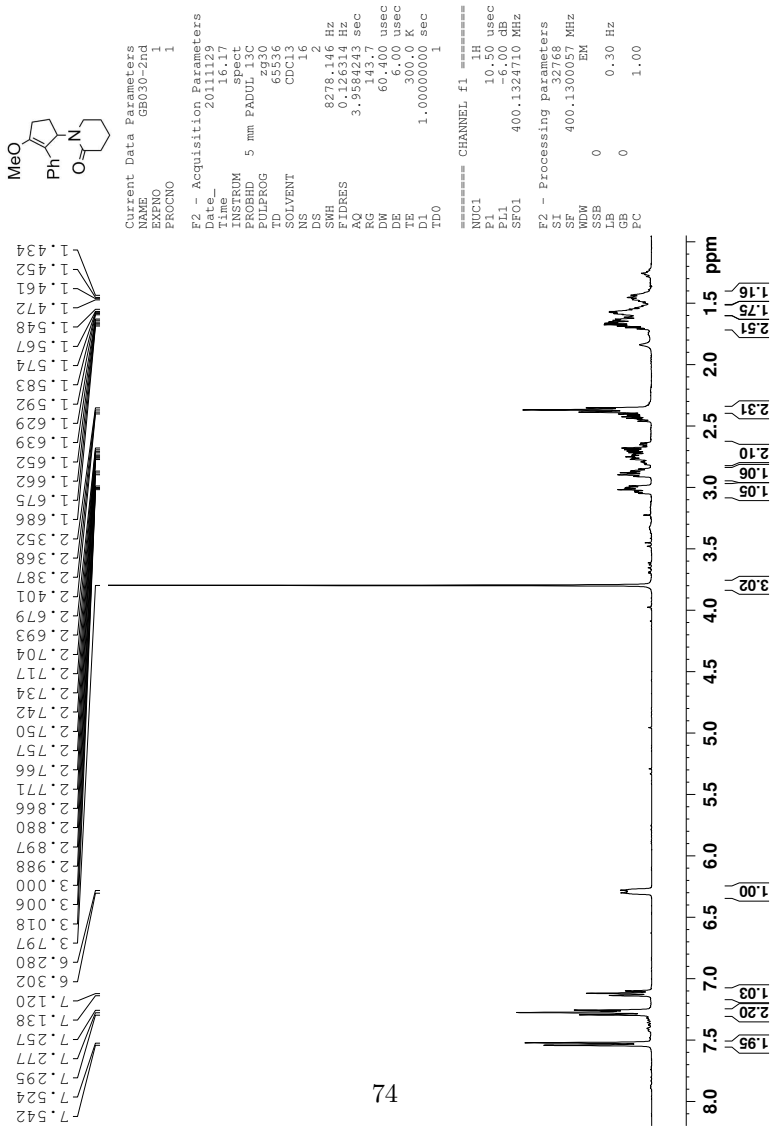
F.7 IR [3+2] cycloaddition product 17a



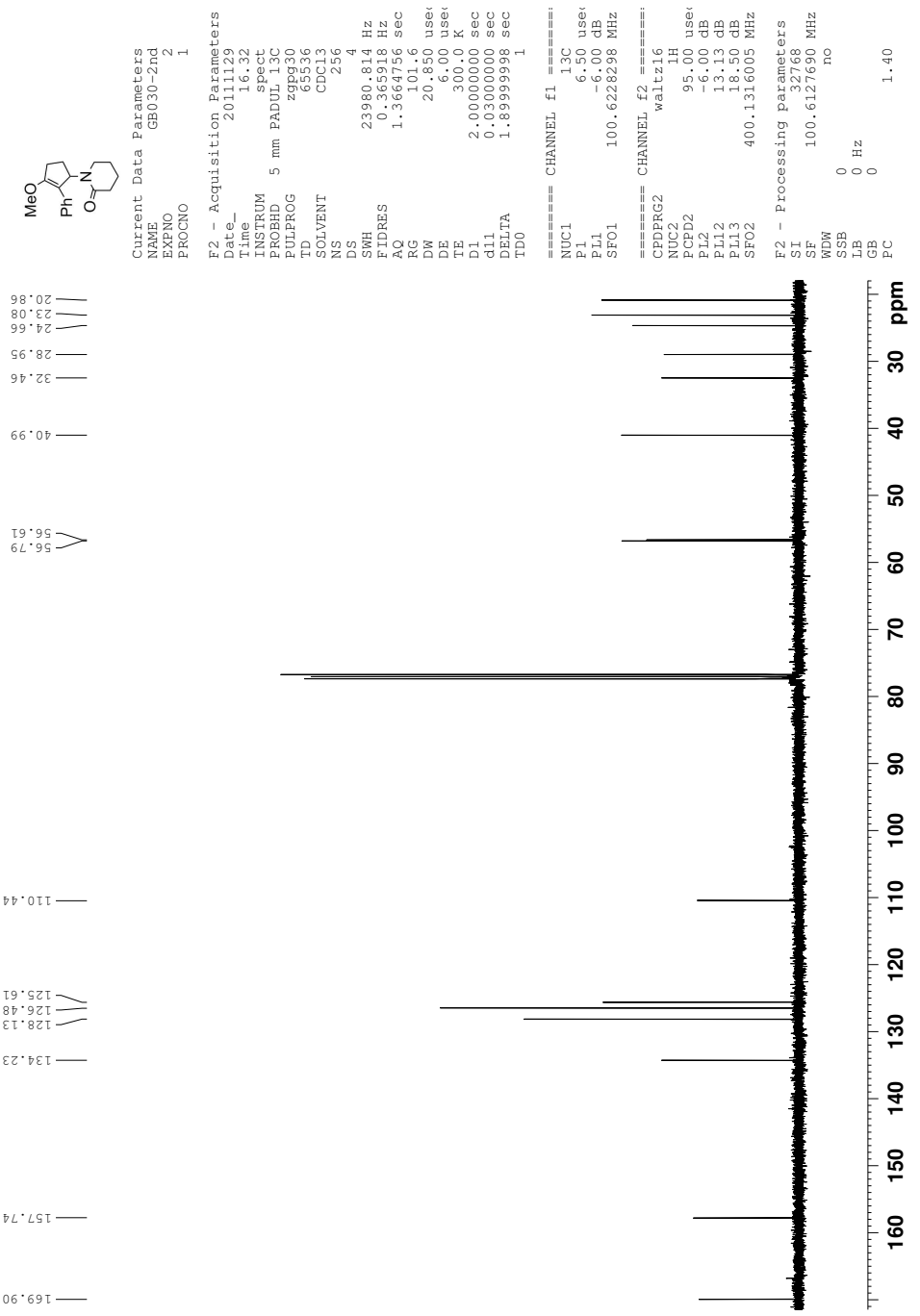
Appendix G

[3+2] cycloaddition product 18a

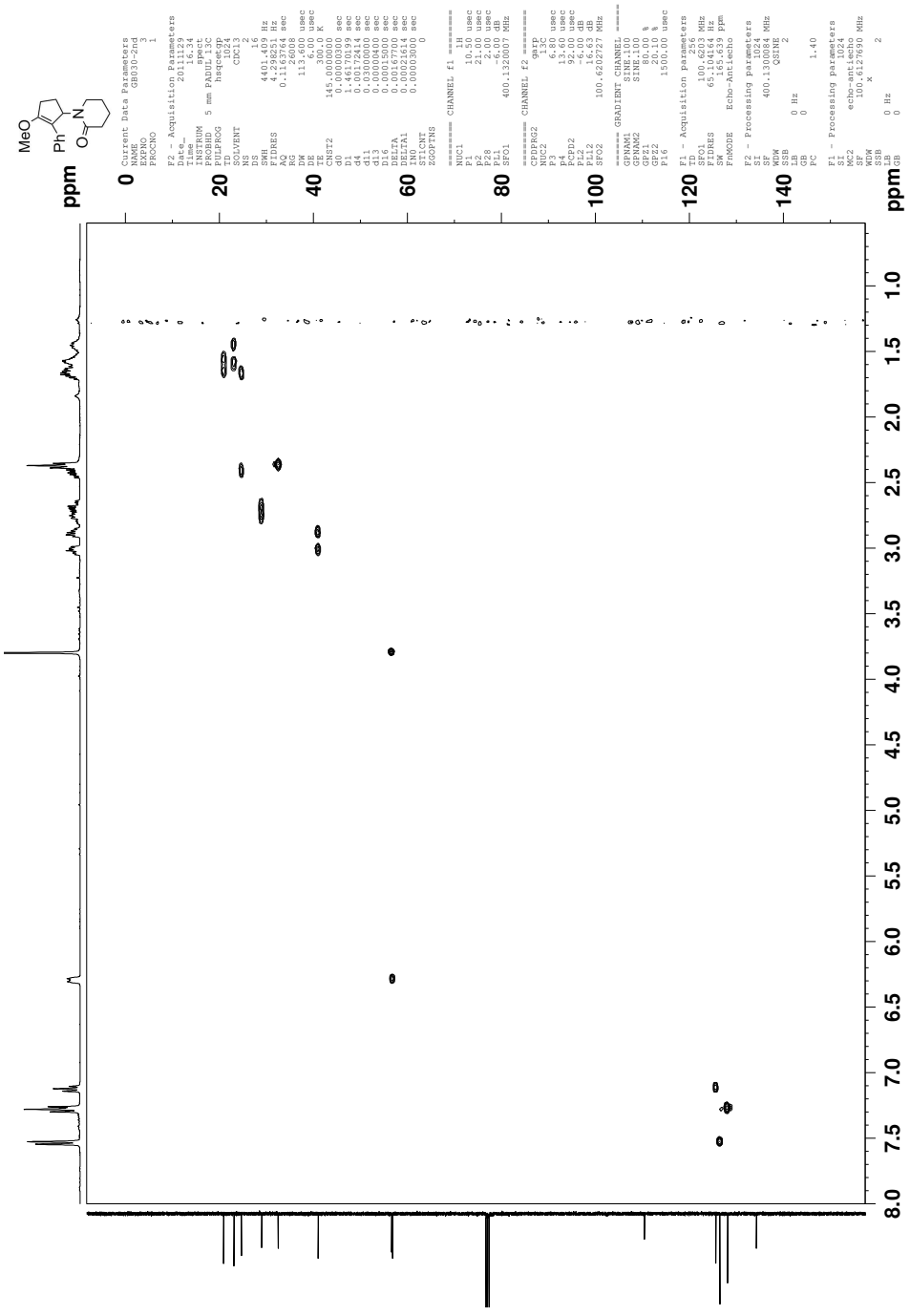
G.1 ^{1}H-NMR [3+2] cycloaddition product 18a



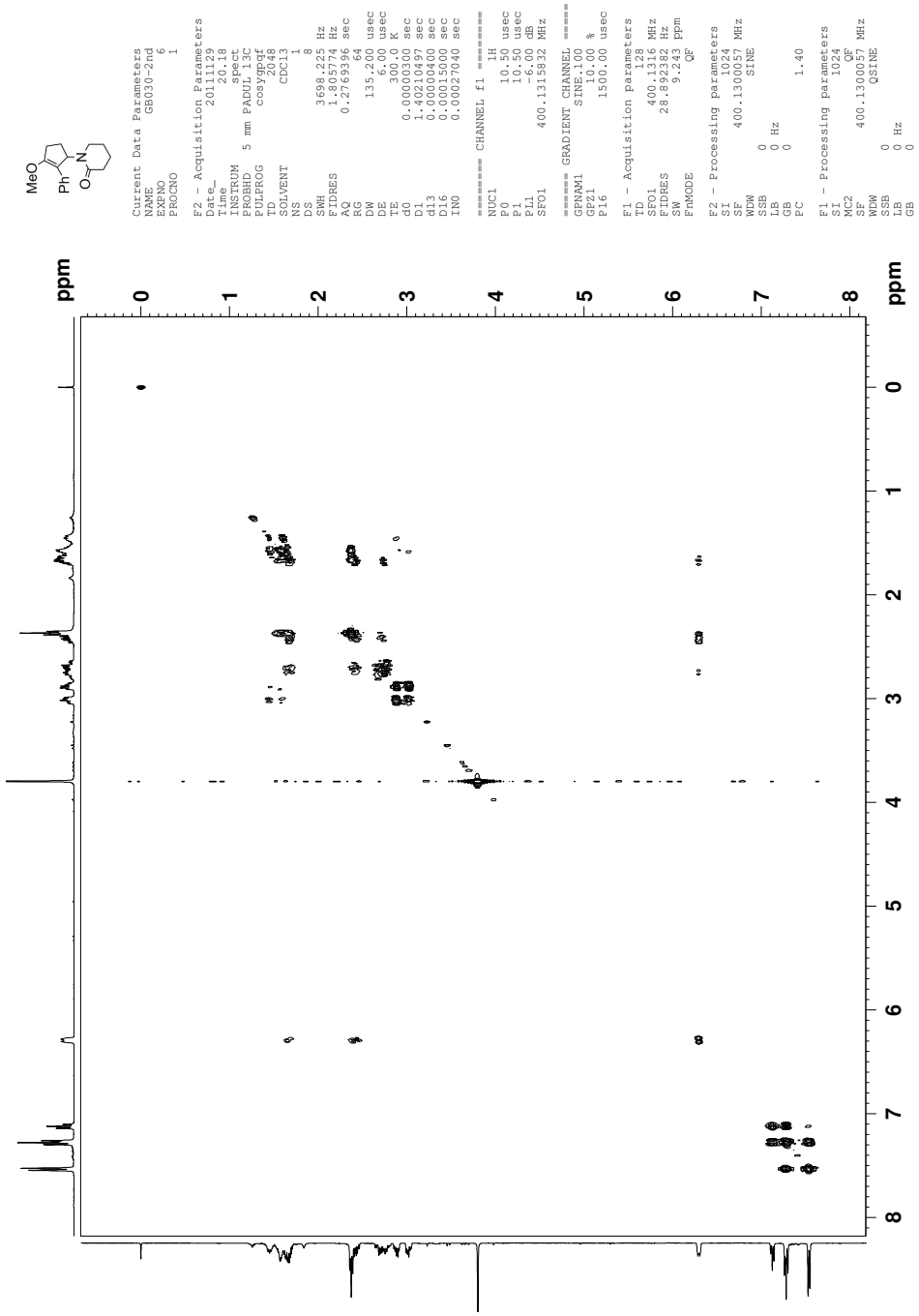
G.2 ^{13}C-NMR [3+2] cycloaddition product 18a



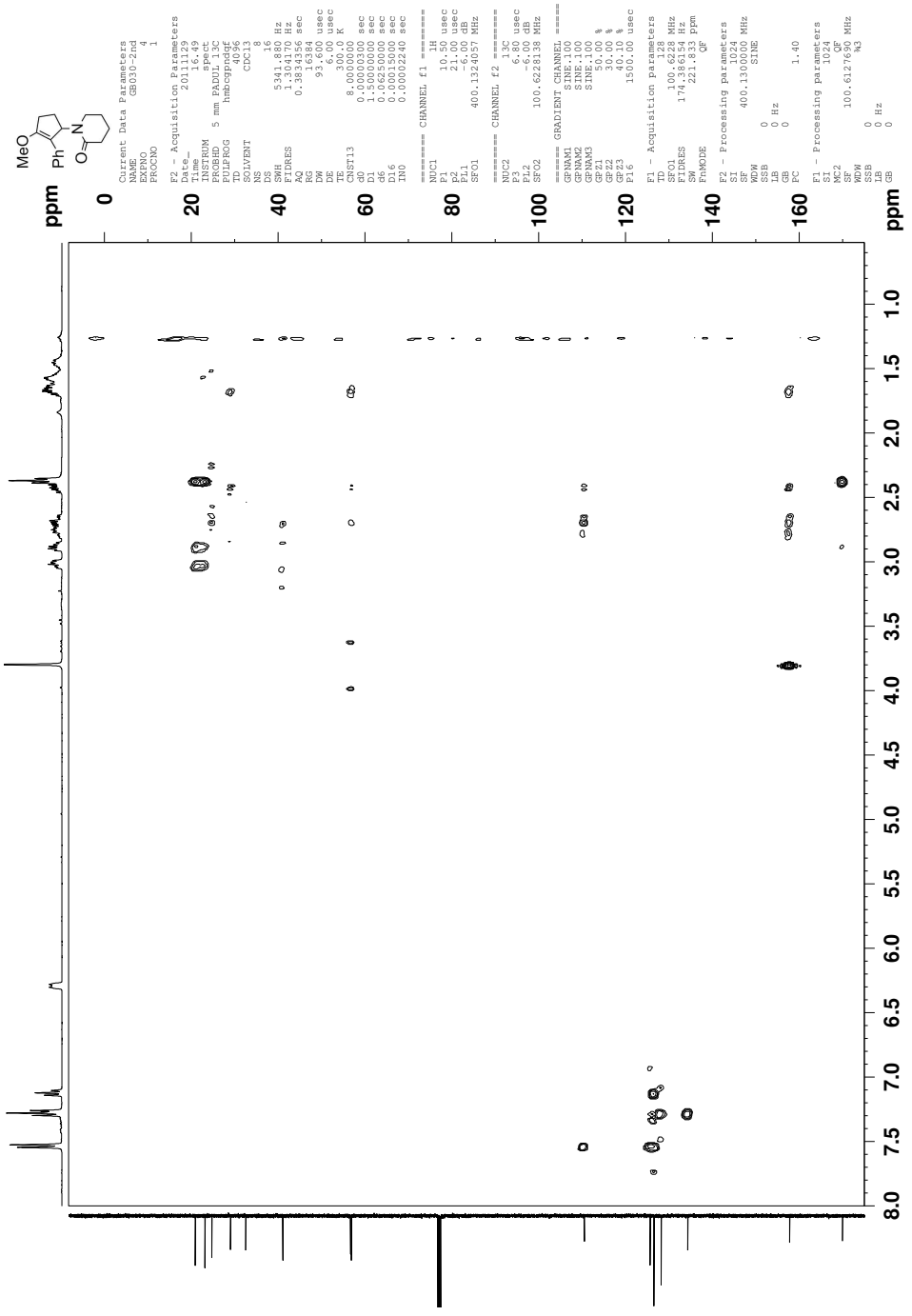
G.3 HSQC-NMR [3+2] cycloaddition product 18a



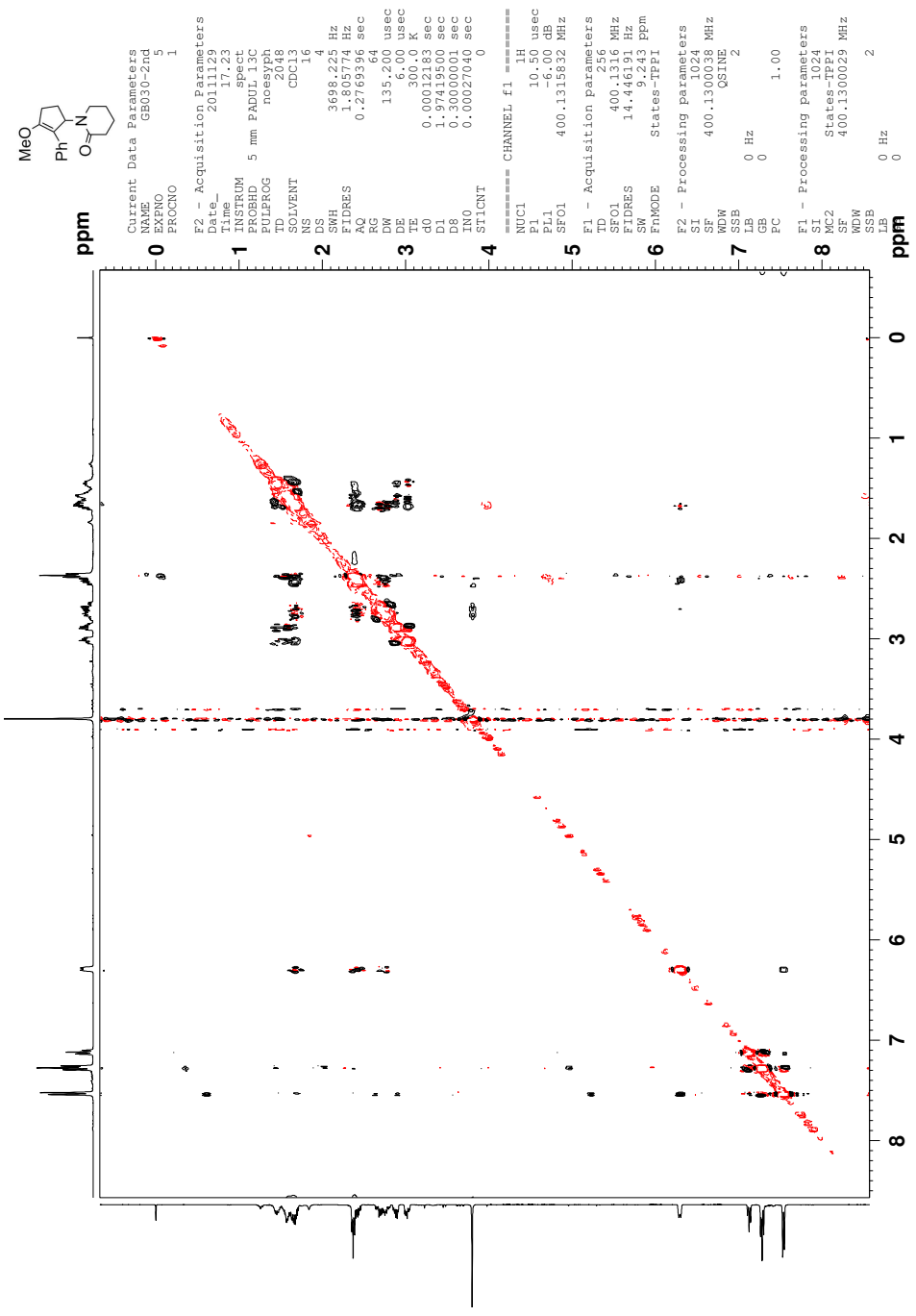
G.4 COSY-NMR [3+2] cycloaddition product 18a



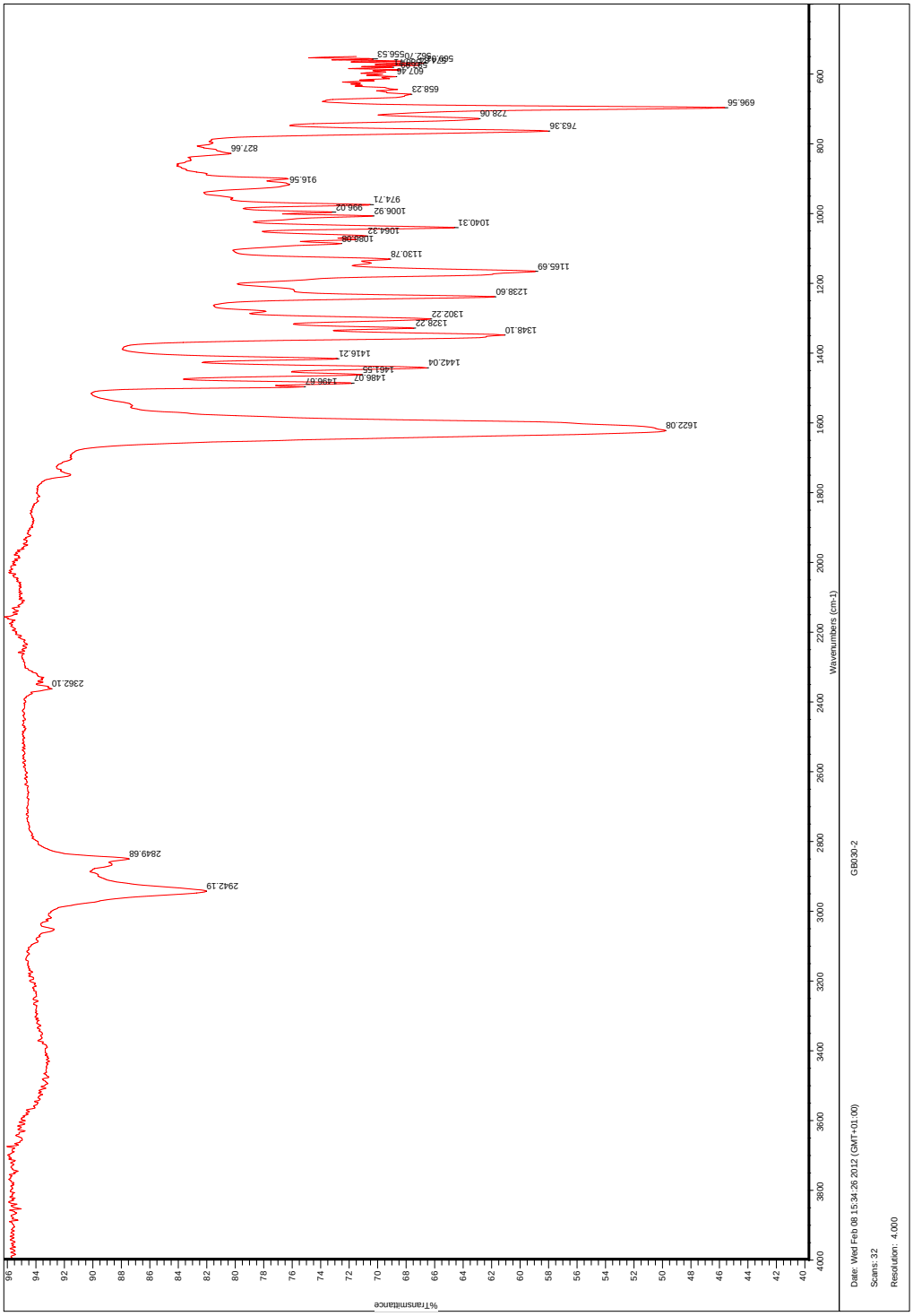
G.5 HMBC-NMR [3+2] cycloaddition product 18a



G.6 NOESY-NMR [3+2] cycloaddition product 18a



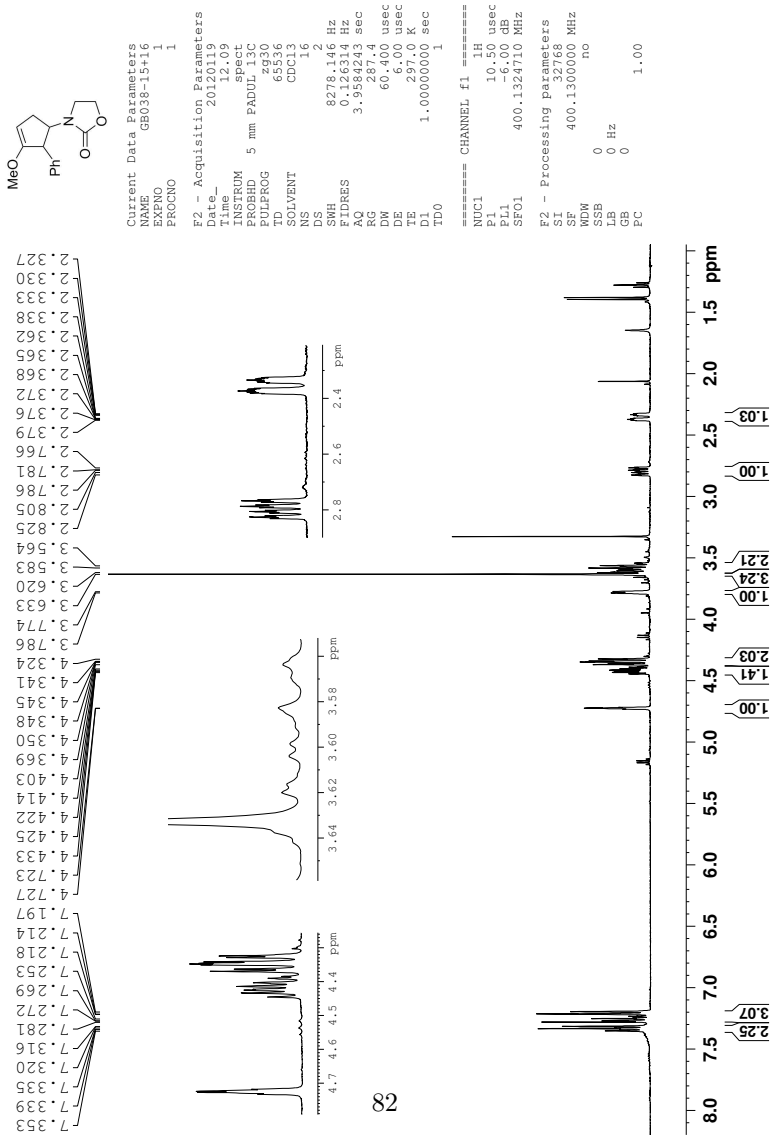
G.7 IR [3+2] cycloaddition product 18a



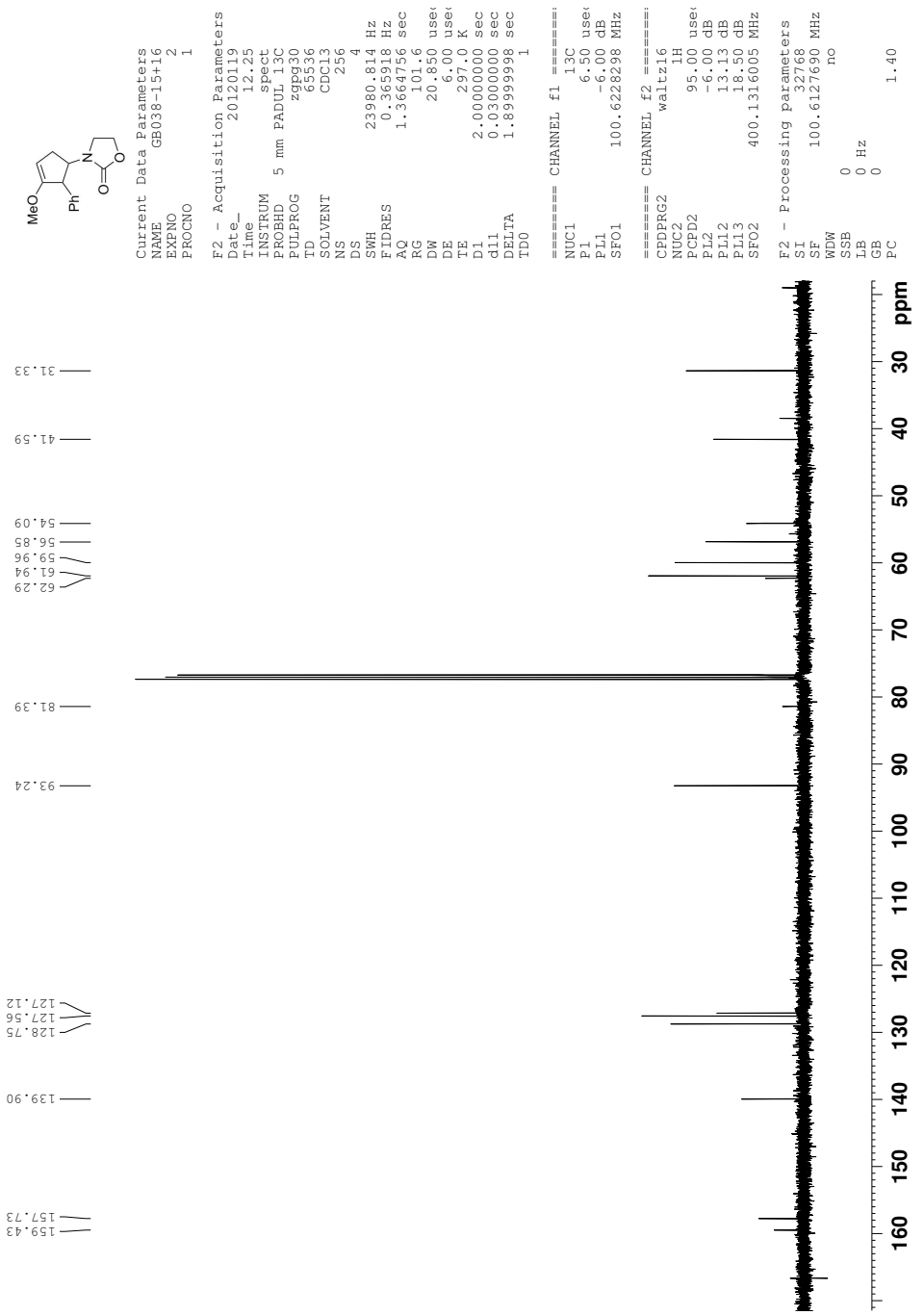
Appendix H

[3+2] cycloaddition product 17b

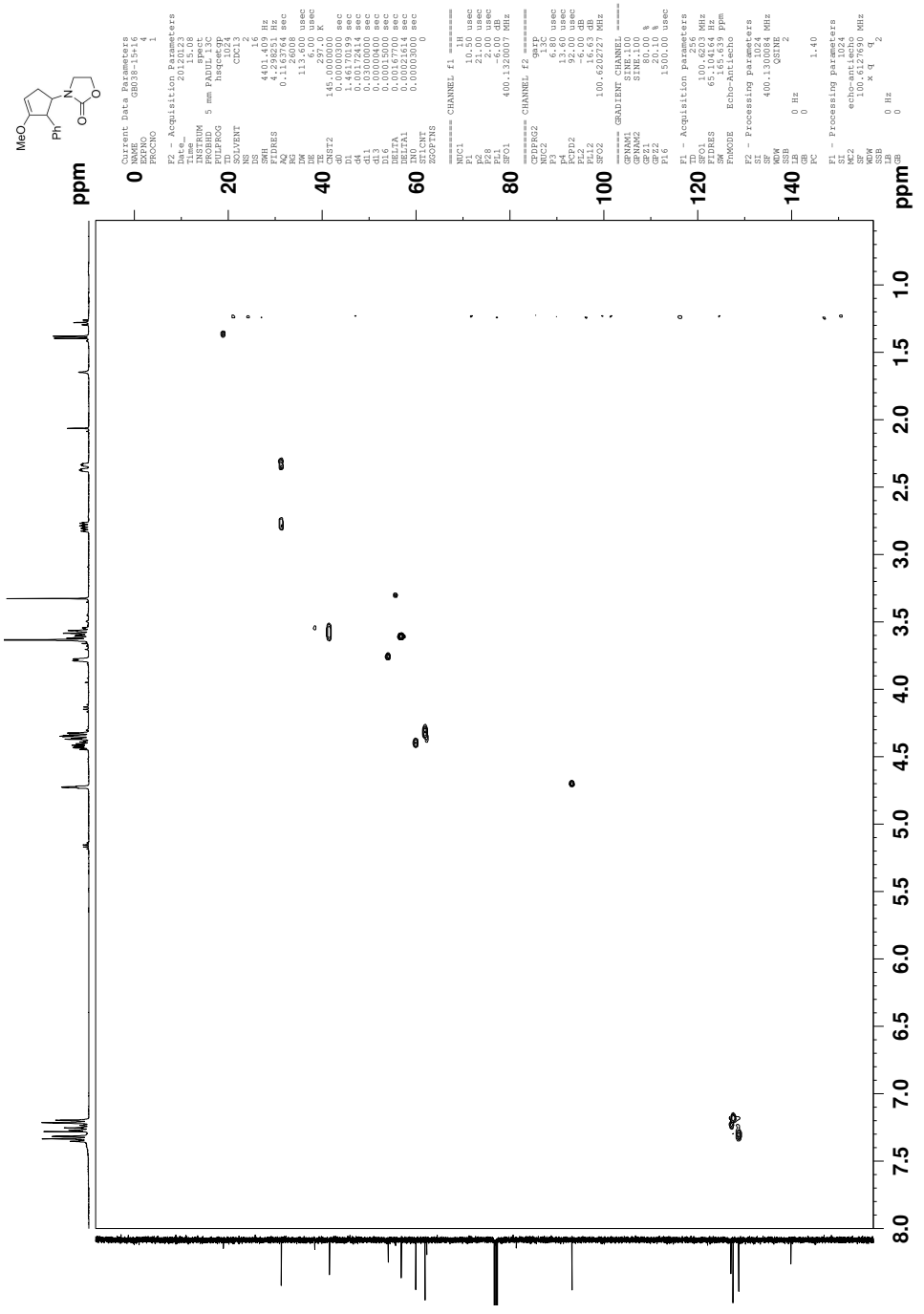
H.1 ^{1}H-NMR [3+2] cycloaddition product 17b



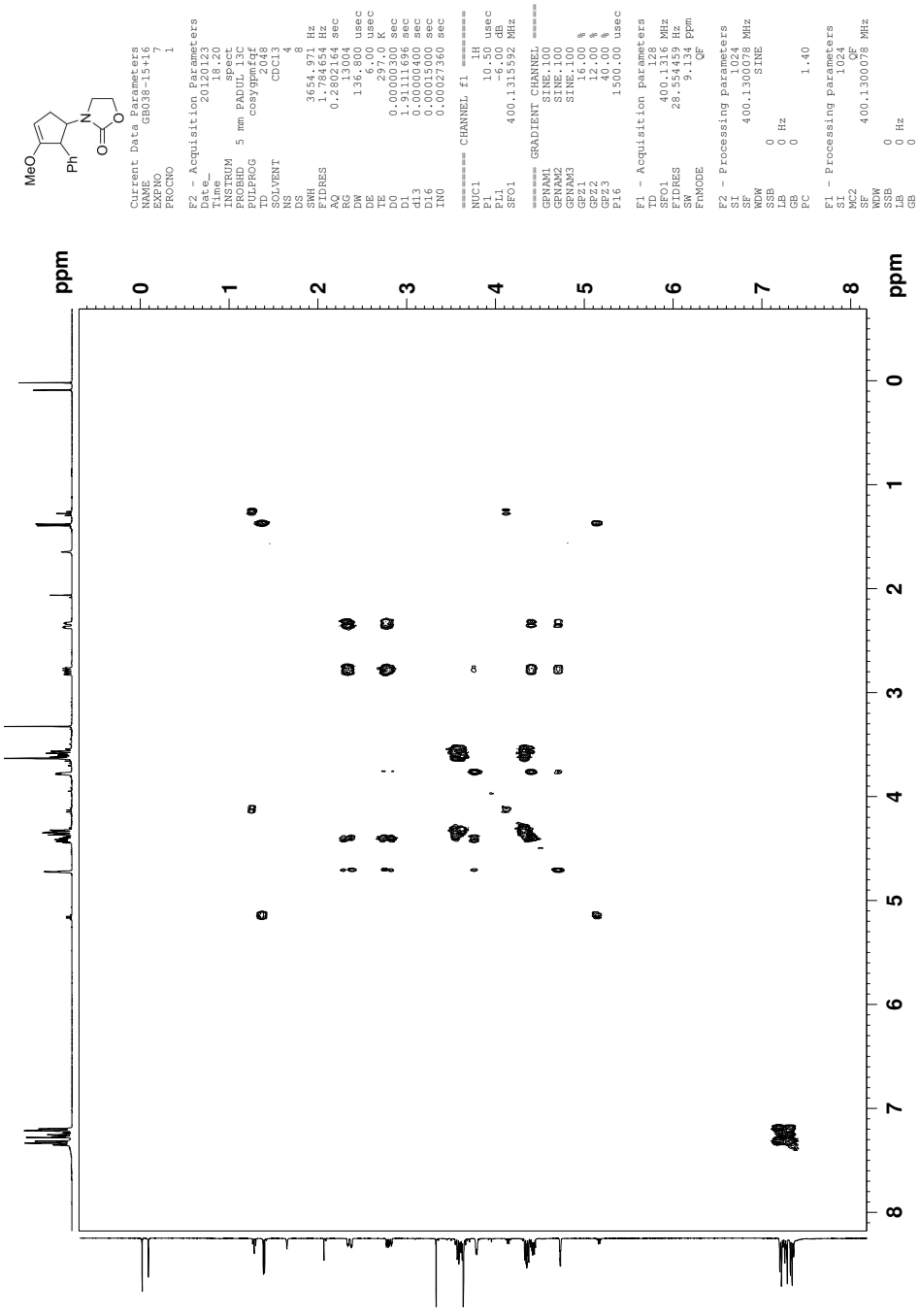
H.2 ^{13}C-NMR [3+2] cycloaddition product 17b



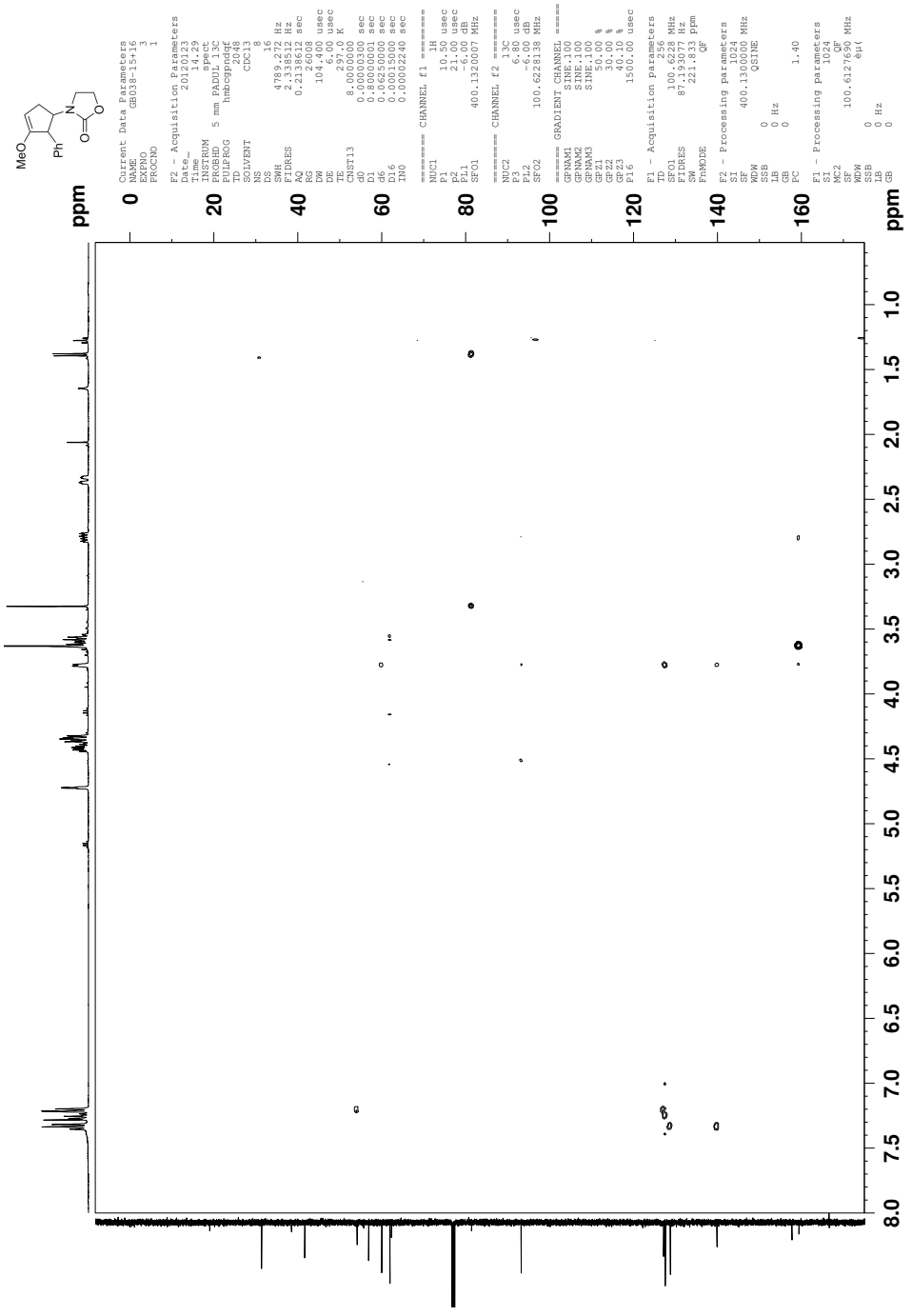
H.3 HSQC-NMR [3+2] cycloaddition product 17b



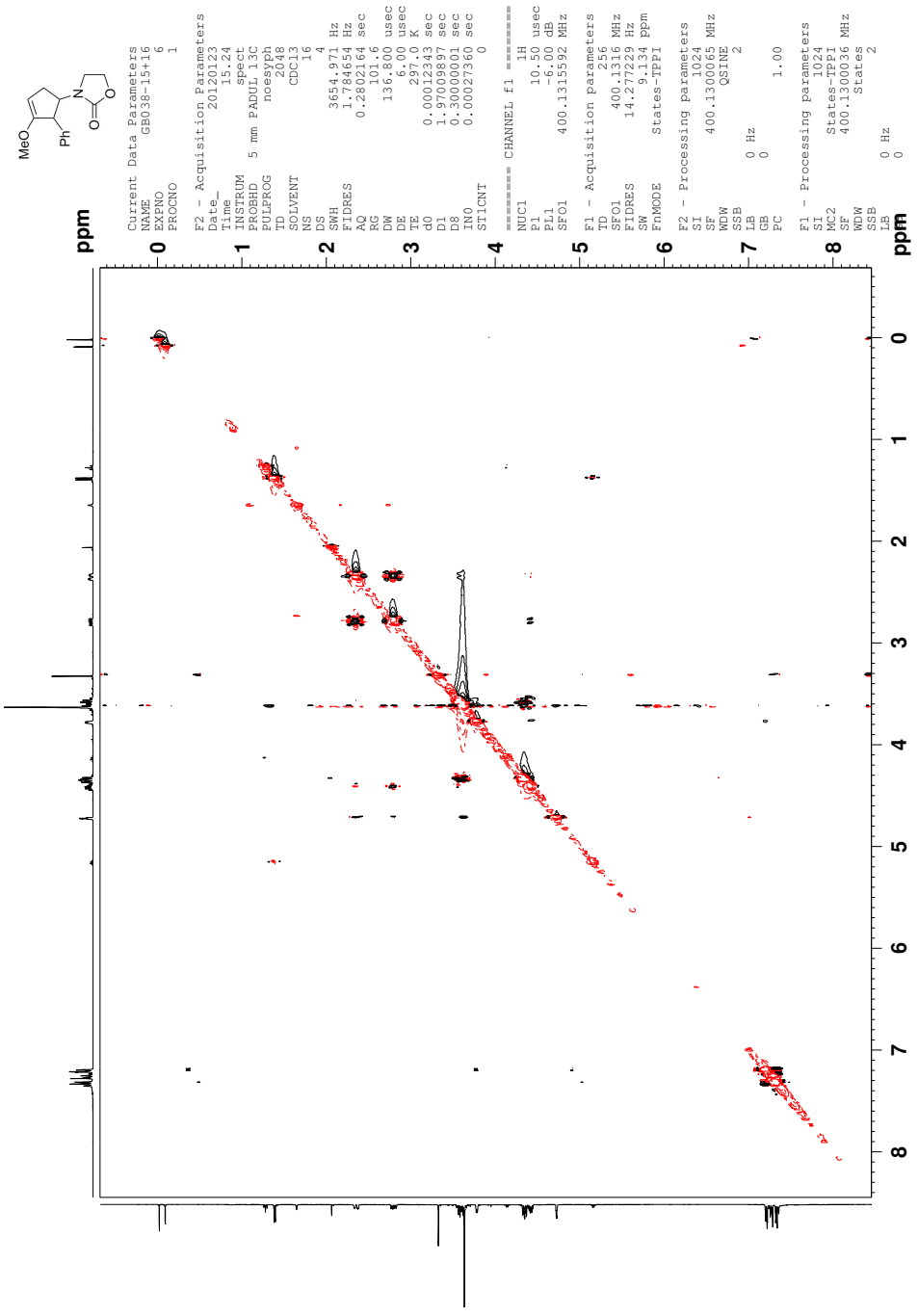
H.4 COSY-NMR [3+2] cycloaddition product 17b



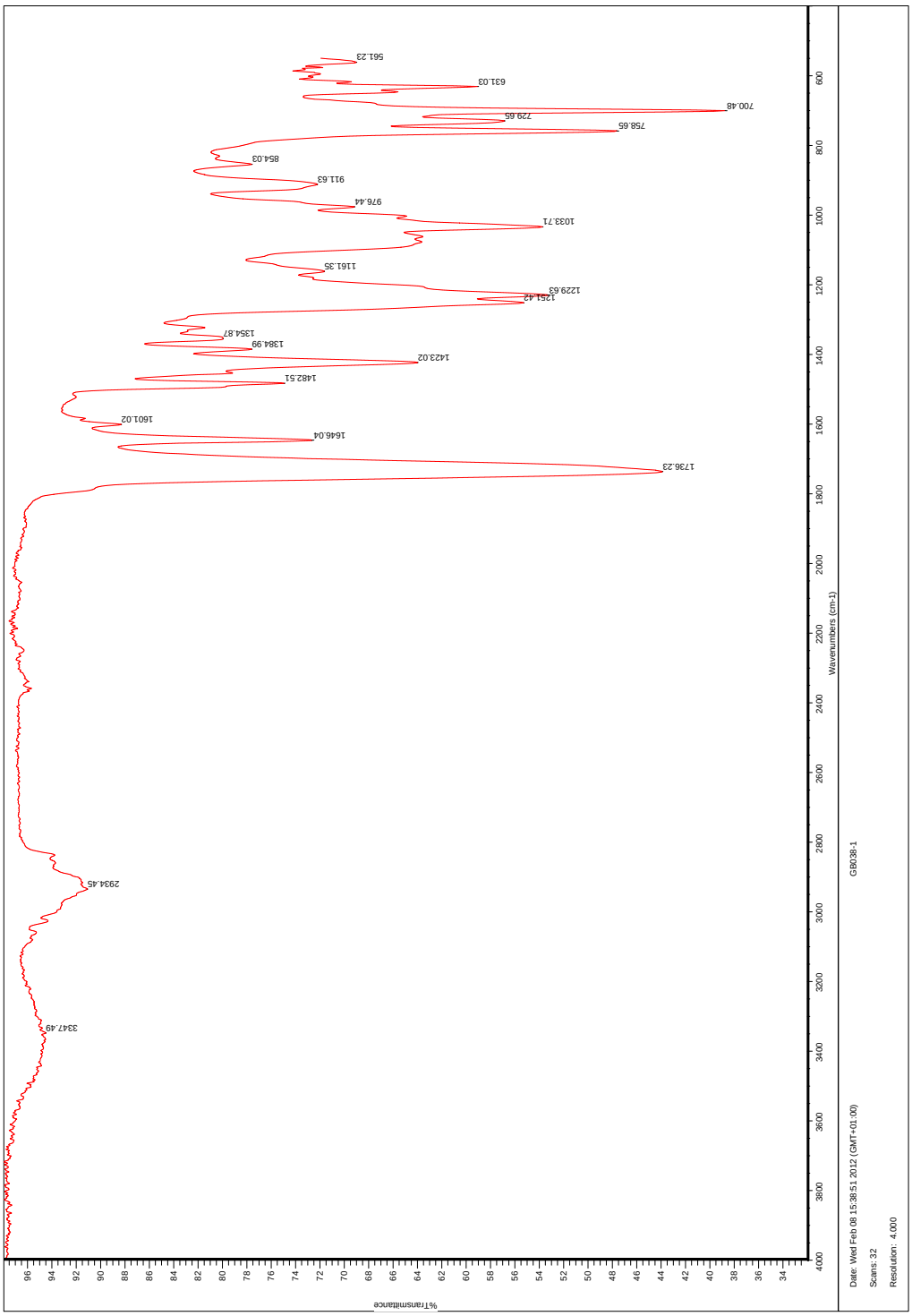
H.5 HMBC-NMR [3+2] cycloaddition product 17b



H.6 NOESY-NMR [3+2] cycloaddition product 17b



H.7 IR [3+2] cycloaddition product 17b



H.8 MS [3+2] cycloaddition product 17b

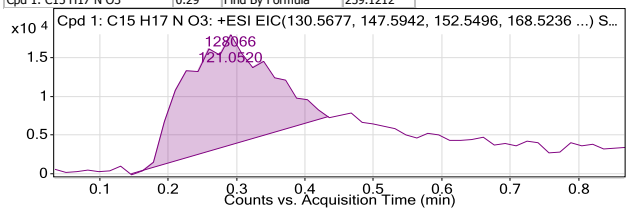
Qualitative Compound Report

Data File	2012-39_028.d	**Sample Name**	2012-39
Sample Type	Sample	**Position**	Vial 91
Instrument Name	Instrument 1	**User Name**	
Acq Method		**IRM Calibration Status**	Success
DA Method	ExtractForMPP_KFD.m	**Comment**	

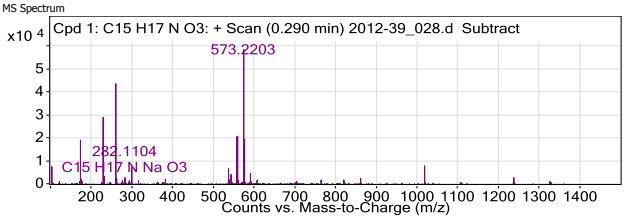
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C15 H17 N O3	0.29	259.1212	2996	C15 H17 N O3	259.1208	1.51

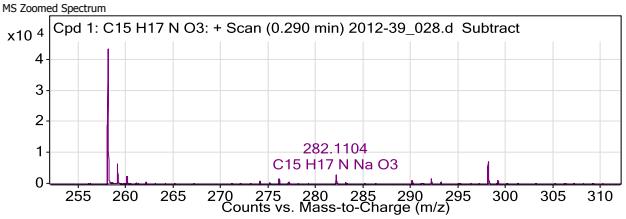
Compound Label	RT	Algorithm	Mass
Cpd 1: C15 H17 N O3	0.29	Find By Formula	259.1212



MS Spectrum



MS Zoomed Spectrum



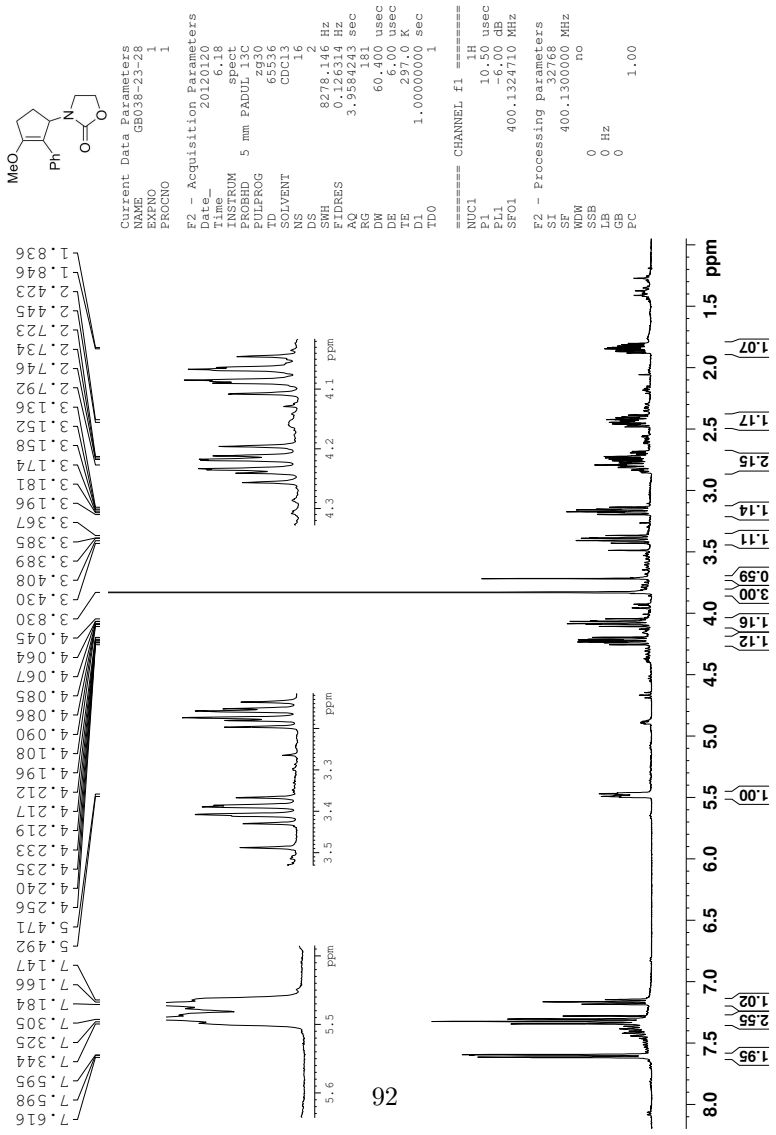
MS Spectrum Peak List

m/z	*Calc m/z*	Diff(ppm)	z	Abund	Formula	Ion
282.1104	282.1101	1.3	1	3016	C15 H17 N Na O3	(M+Na)+
568.2641				1072		

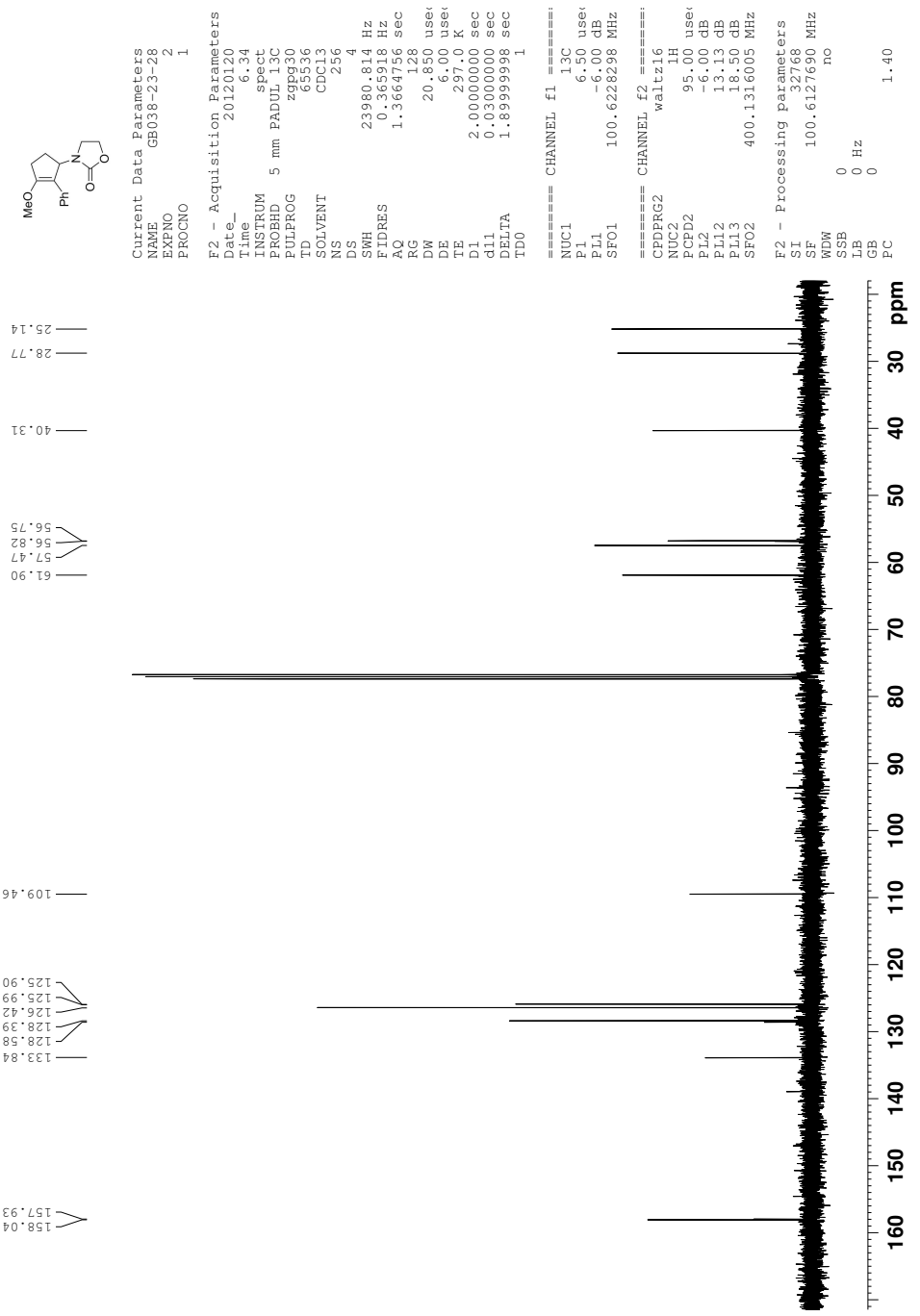
Appendix I

[3+2] cycloaddition product 18b

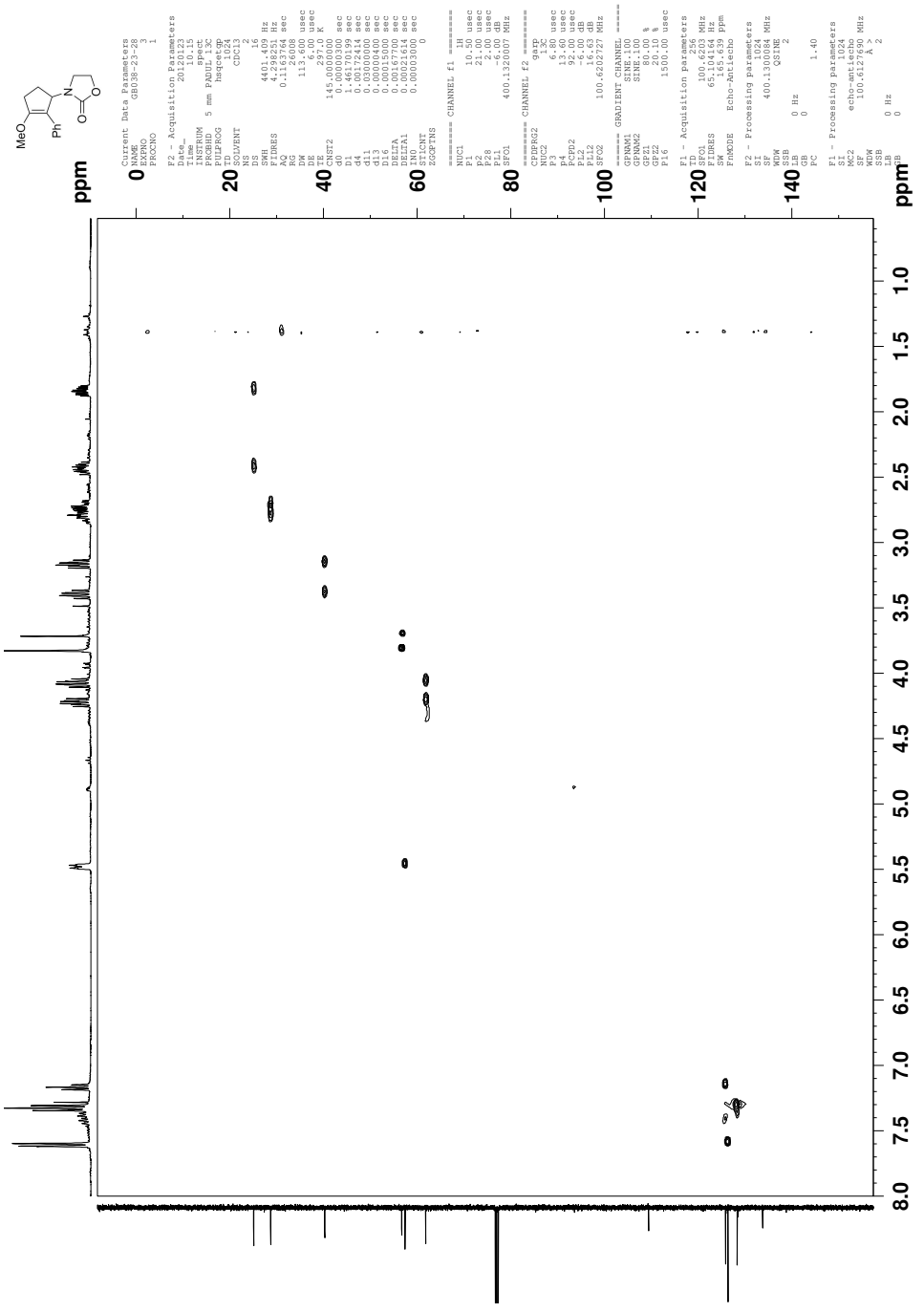
I.1 ^{1}H-NMR [3+2] cycloaddition product 18b



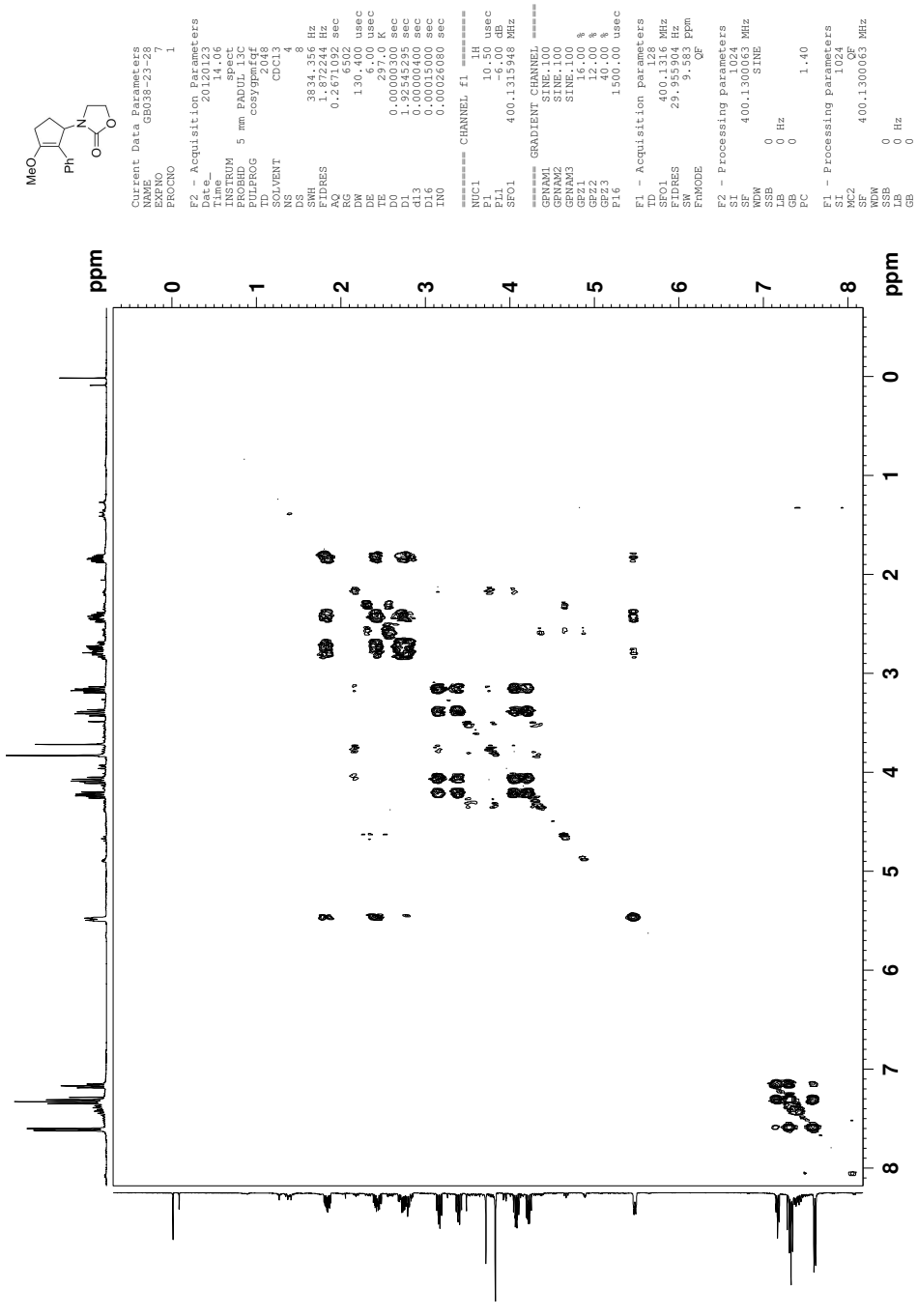
I.2 ^{13}C-NMR [3+2] cycloaddition product 18b



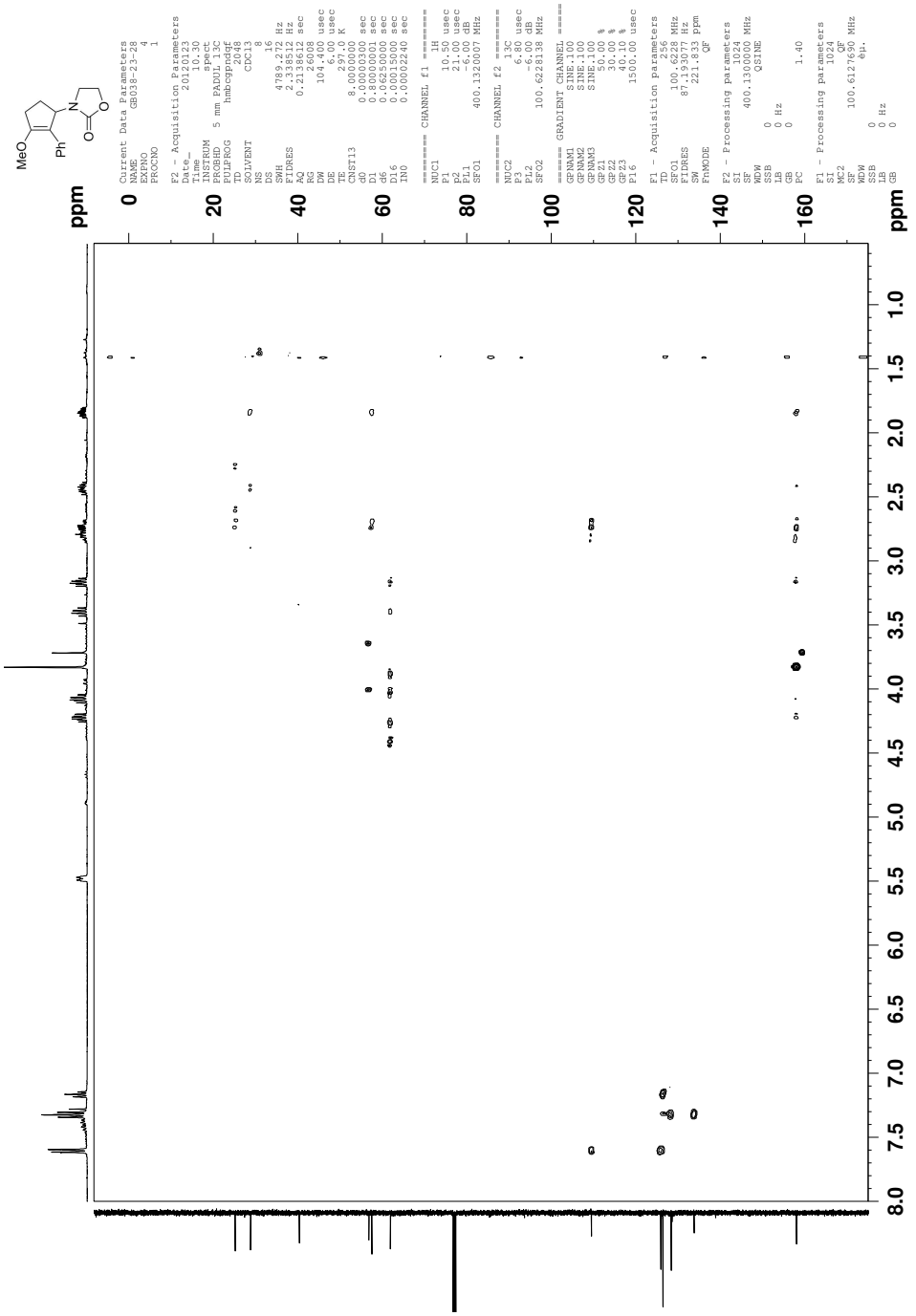
I.3 HSQC-NMR [3+2] cycloaddition product 18b



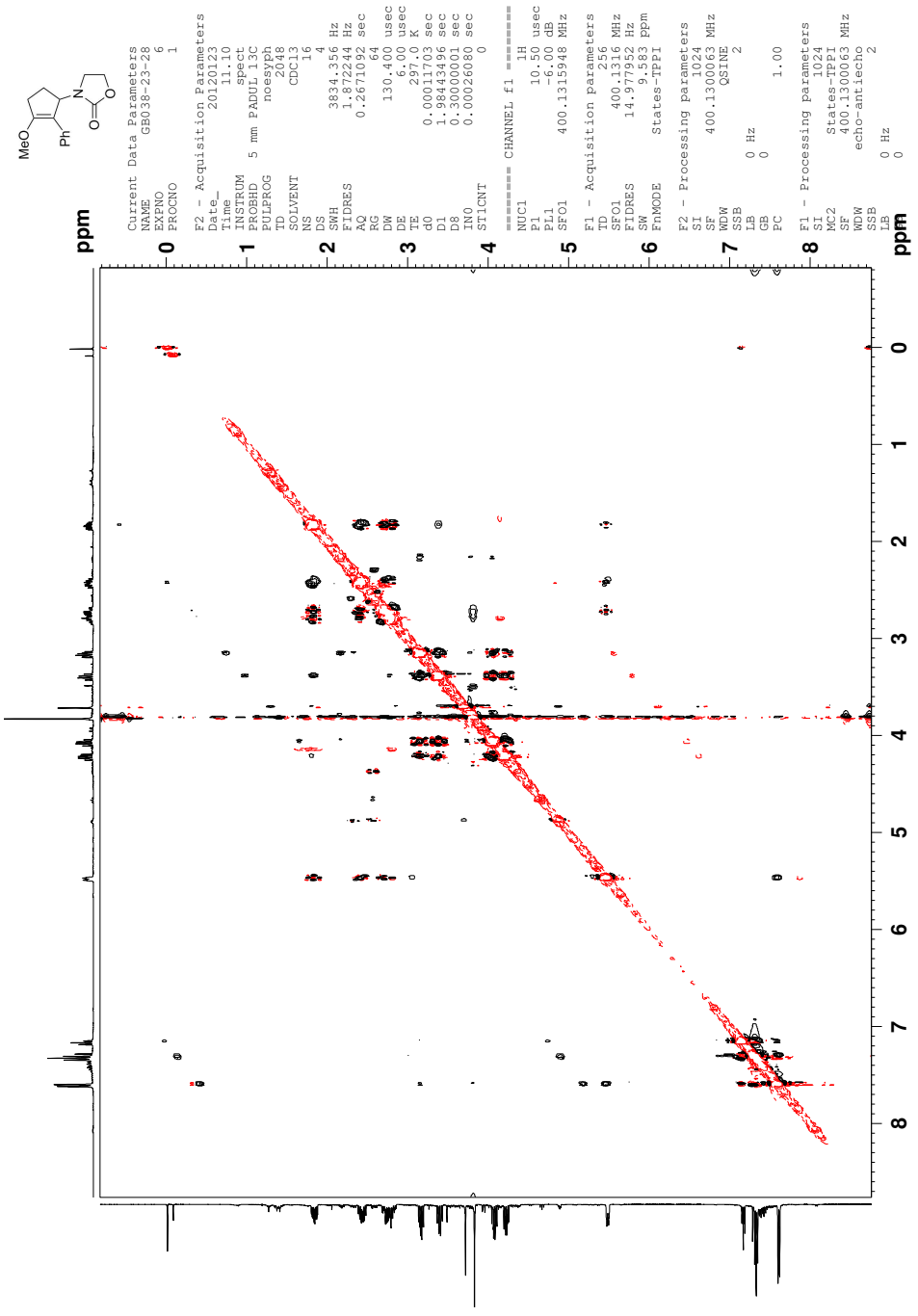
I.4 COSY-NMR [3+2] cycloaddition product 18b



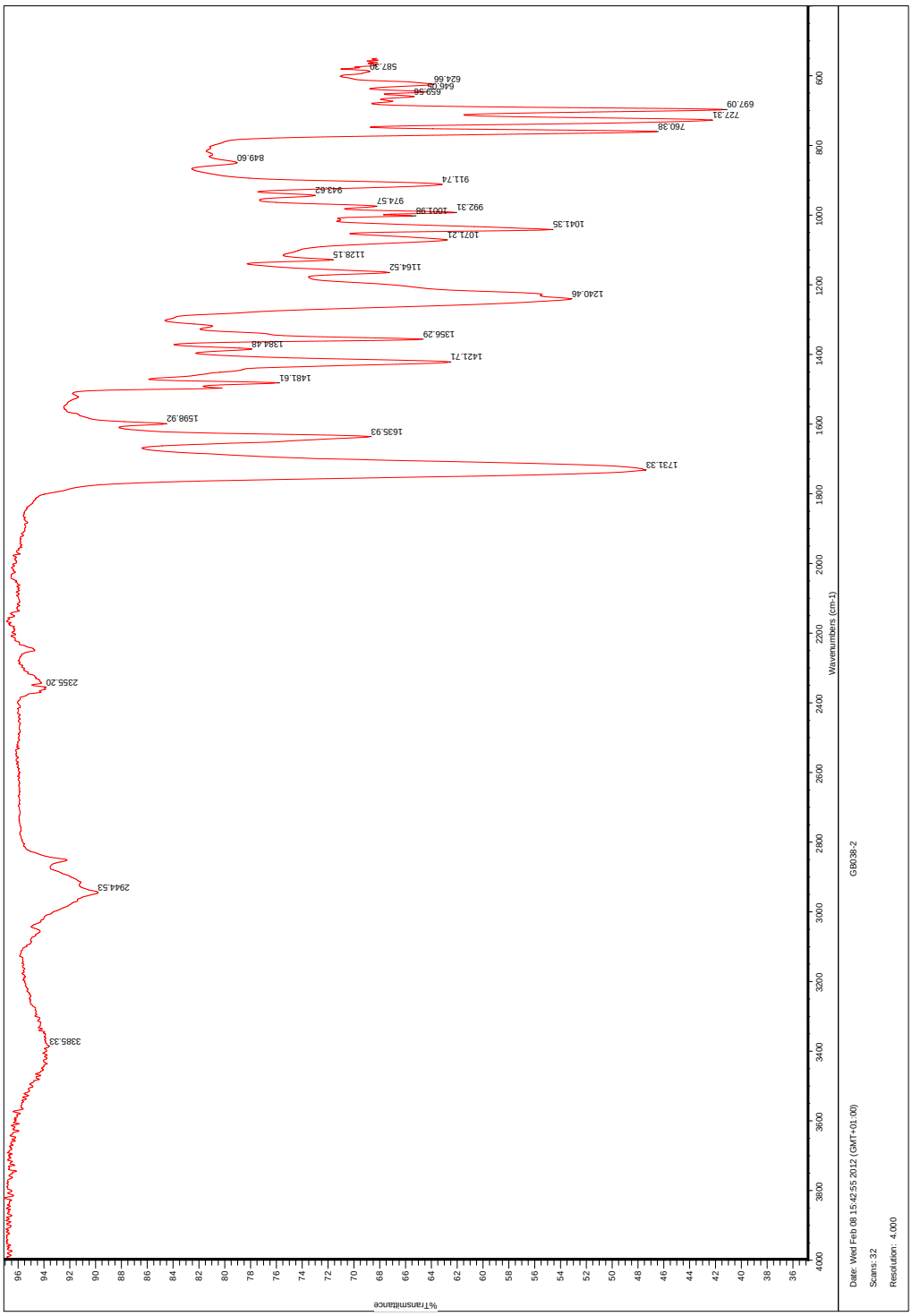
I.5 HMBC-NMR [3+2] cycloaddition product 18b



I.6 NOESY-NMR [3+2] cycloaddition product 18b



I.7 IR [3+2] cycloaddition product 18b



I.8 MS [3+2] cycloaddition product 18b

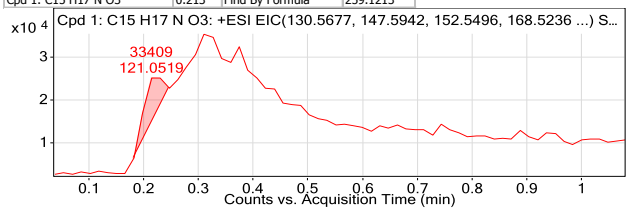
Qualitative Compound Report

Data File	2012-38_024.d	**Sample Name**	Unavailable
Sample Type	Unavailable	**Position**	Unavailable
Instrument Name	Unavailable	**User Name**	Unavailable
Acq Method		**IRM Calibration Status**	Success
DA Method	ExtractForMPP_KFD.m	**Comment**	Sample information is unavailable

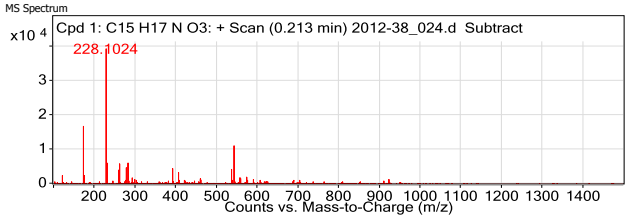
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C15 H17 N O3	0.213	259.1213	4826	C15 H17 N O3	259.1208	1.73

Compound Label	RT	Algorithm	Mass
Cpd 1: C15 H17 N O3	0.213	Find By Formula	259.1213



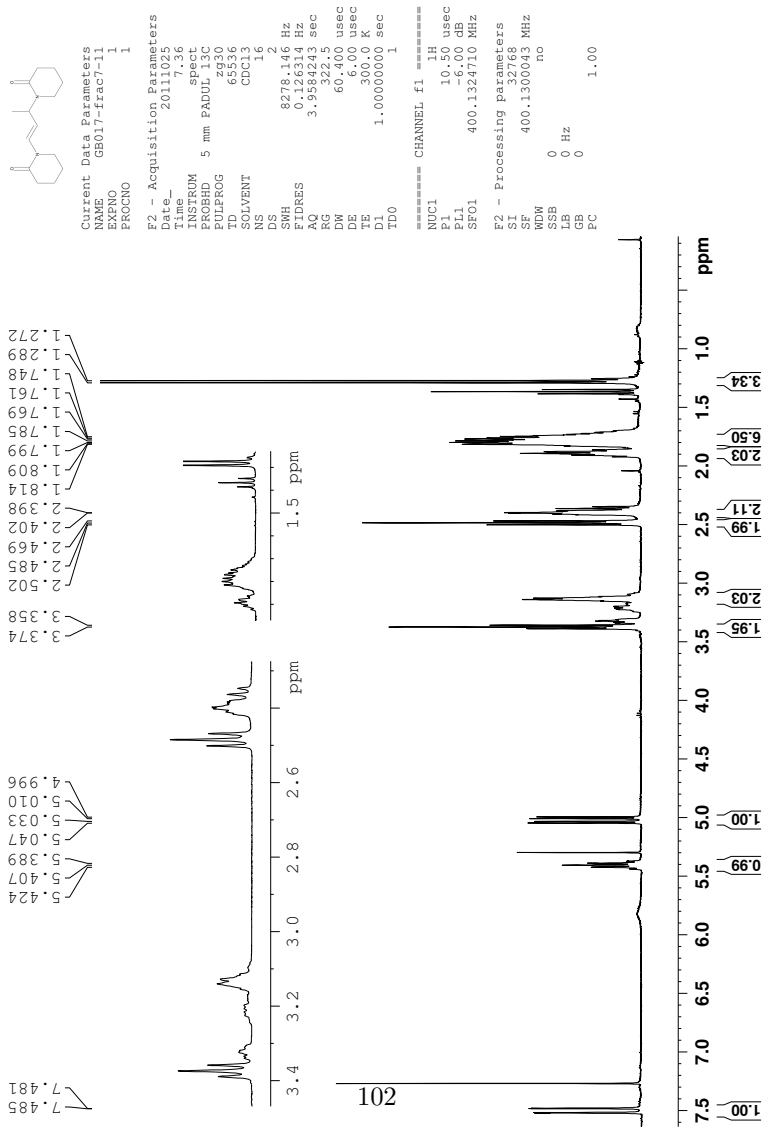
MS Spectrum



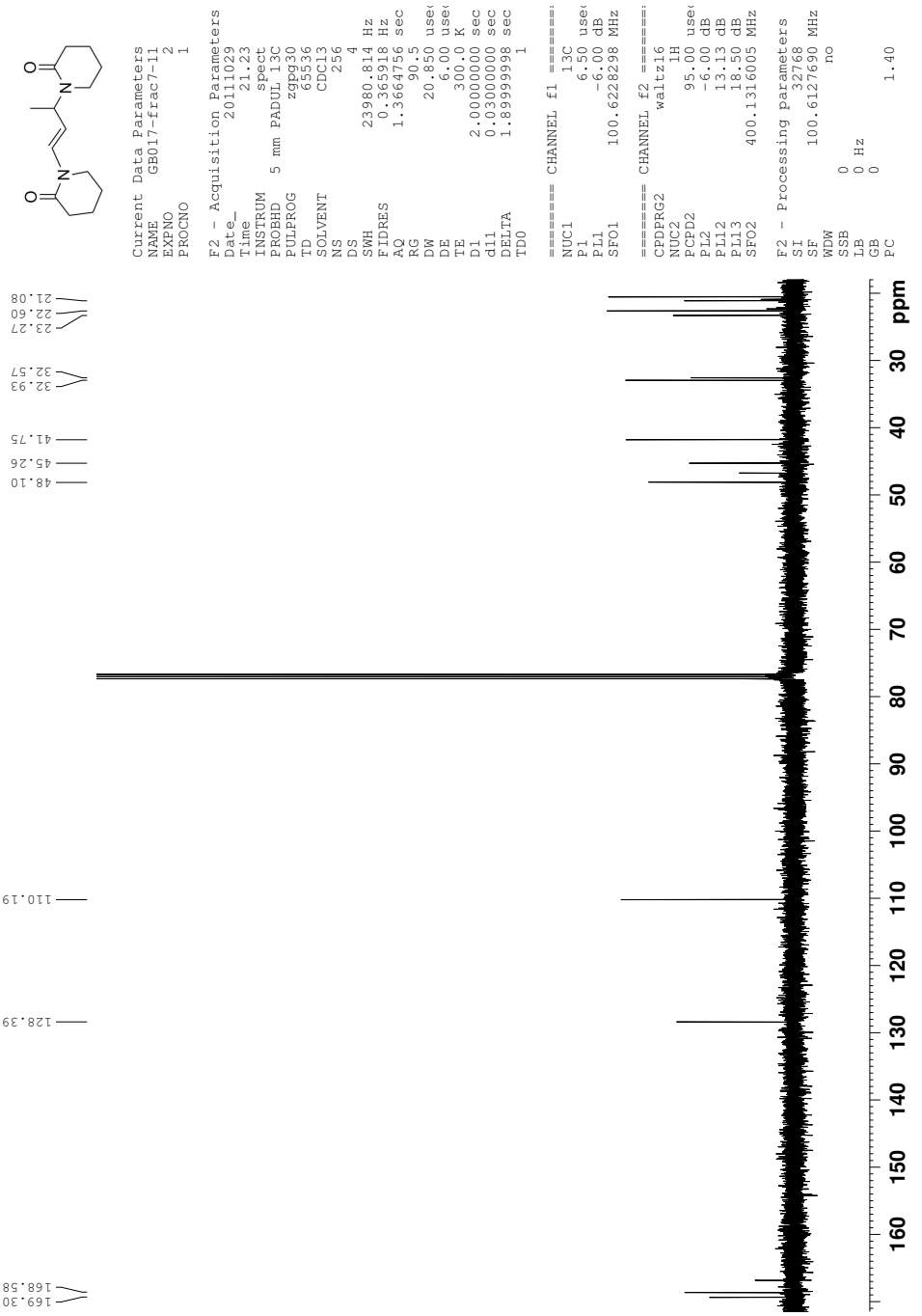
Appendix J

Dimerization product 23

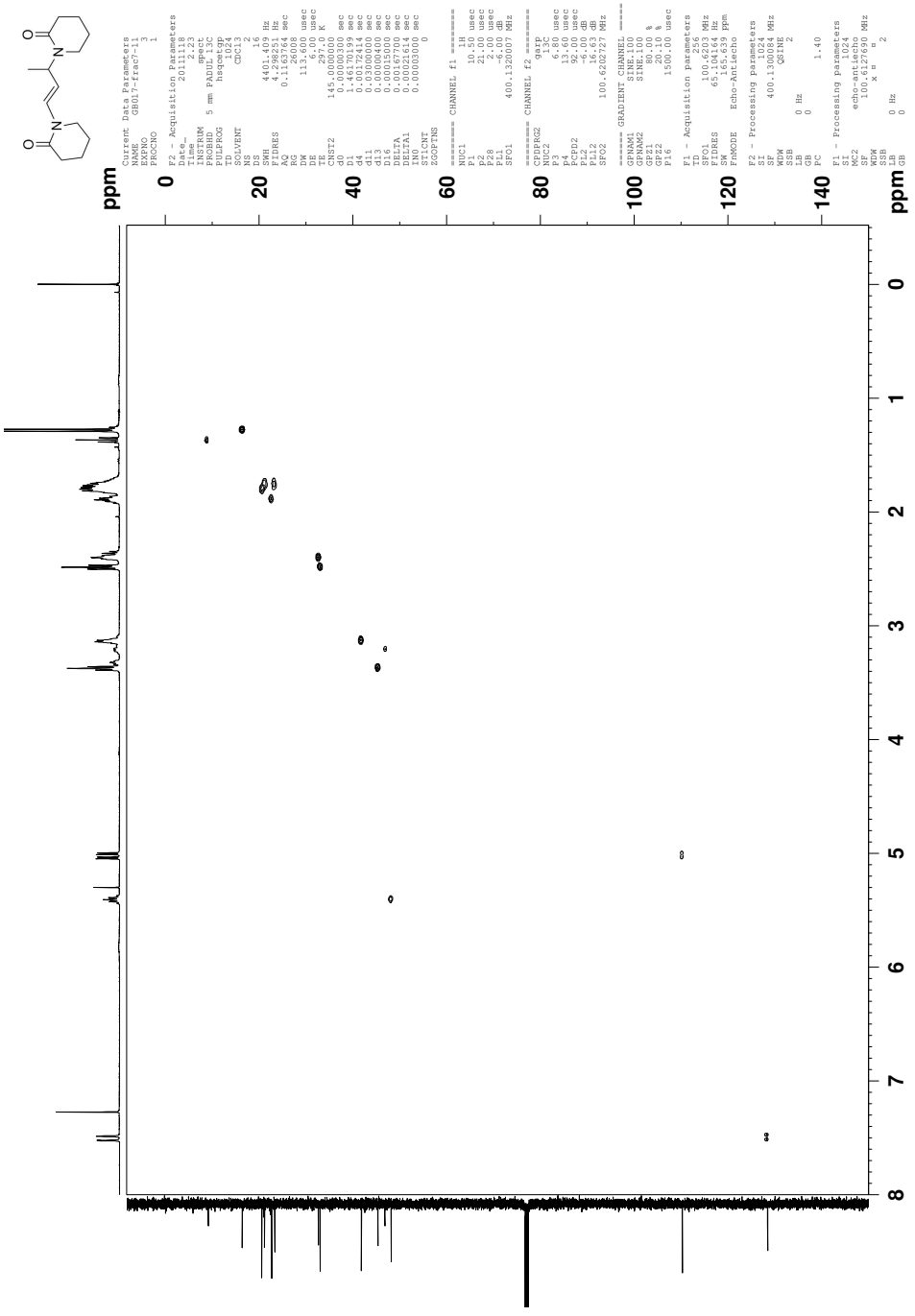
J.1 ^{1}H-NMR Dimerization product 23



J.2 ^{13}C-NMR Dimerization product 23



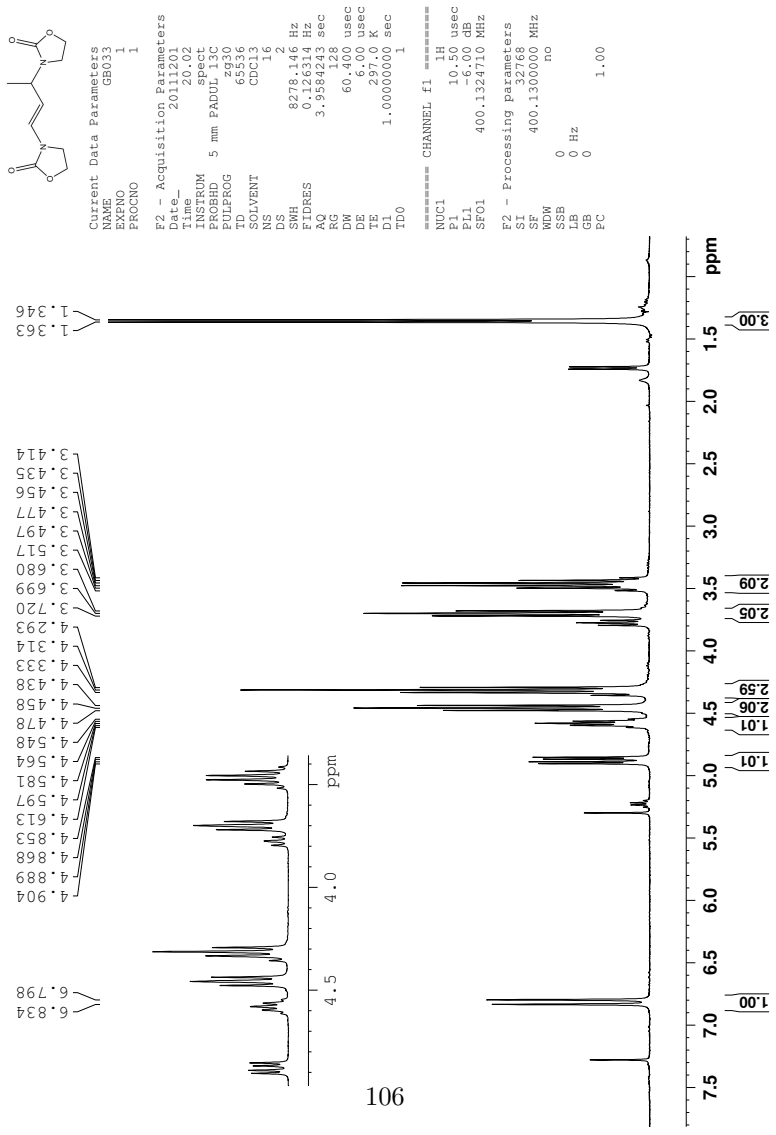
J.3 HSQC-NMR Dimerization product 23



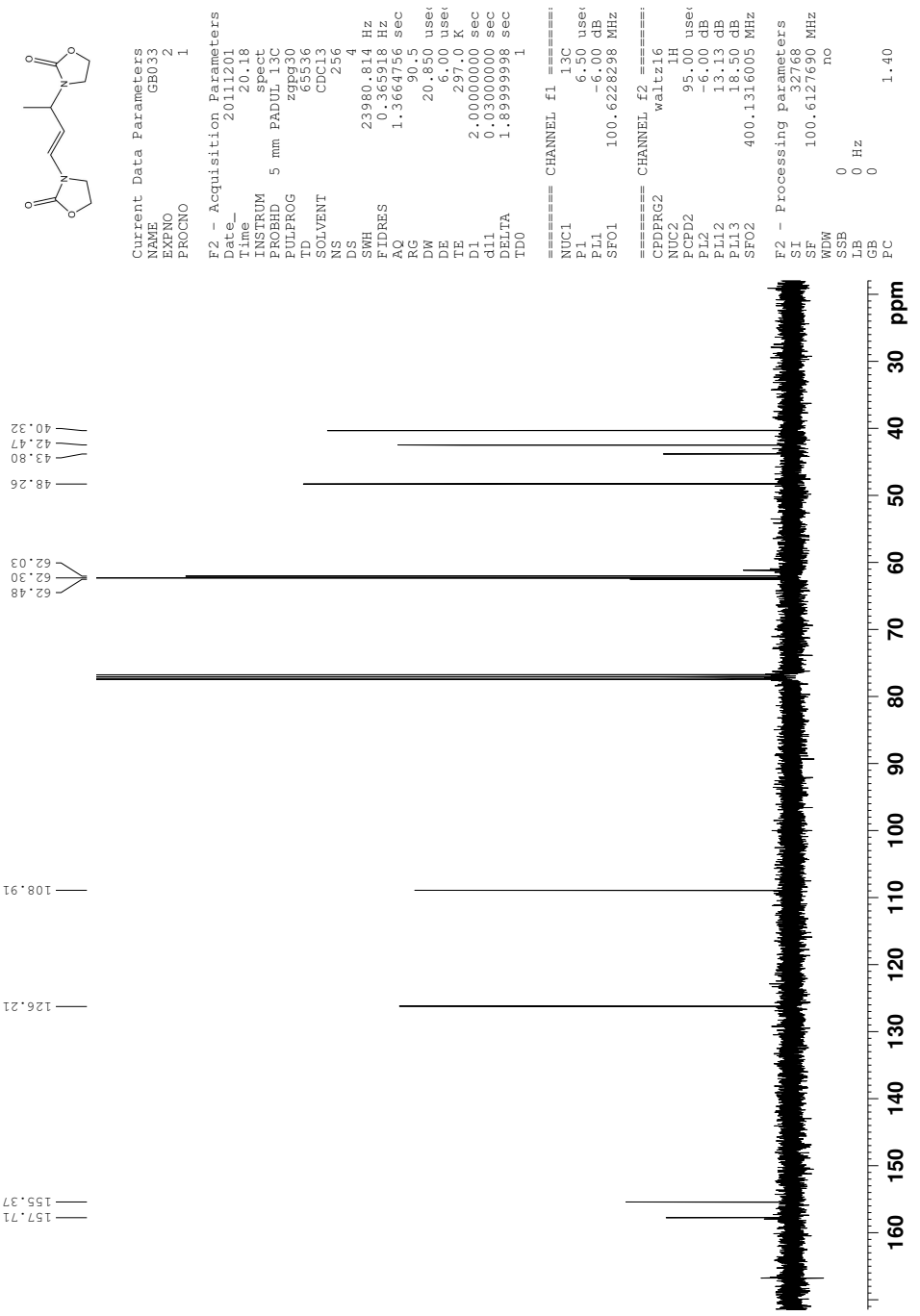
Appendix K

Dimerization product 25

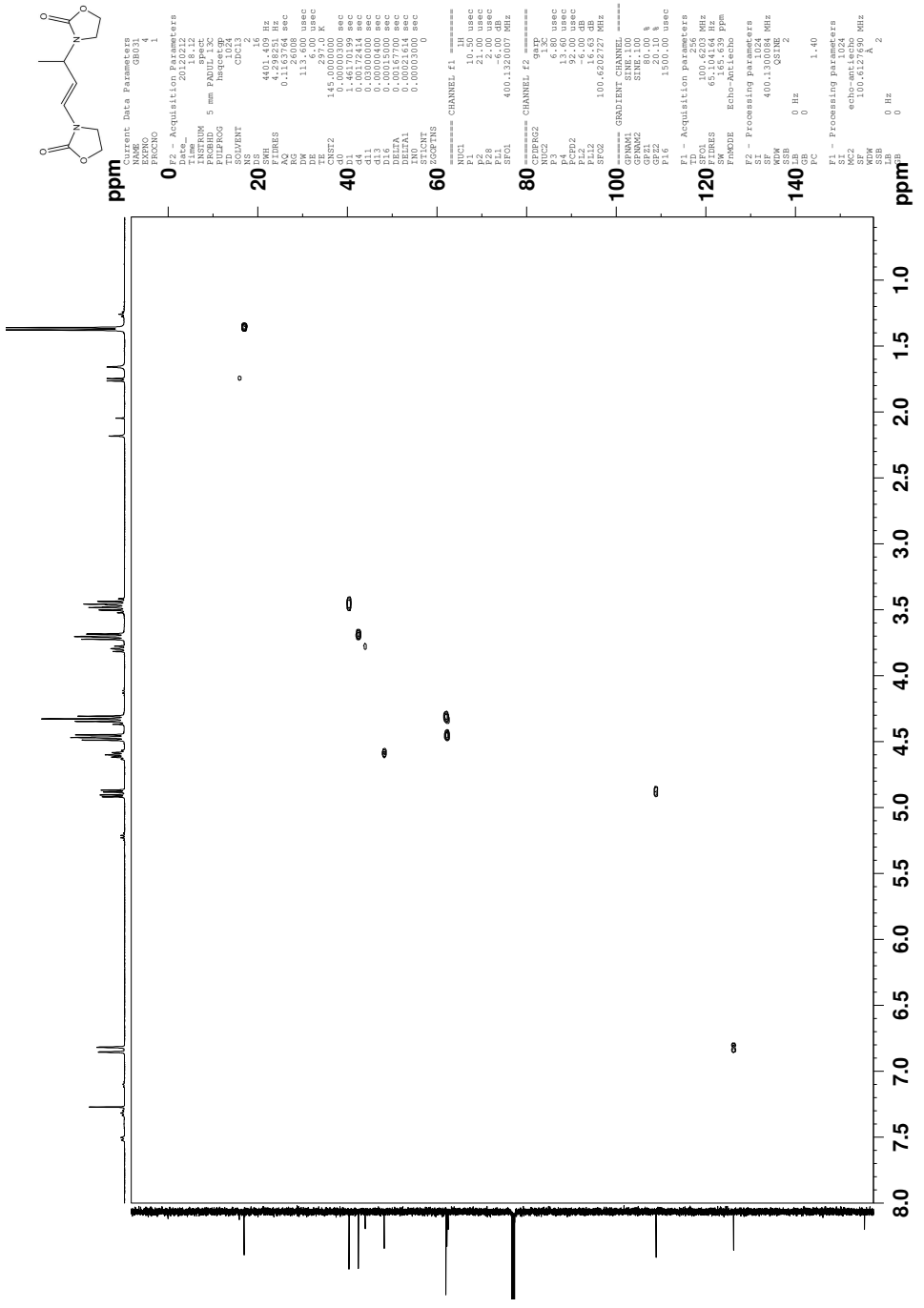
K.1 ^{1}H-NMR Dimerization product 25



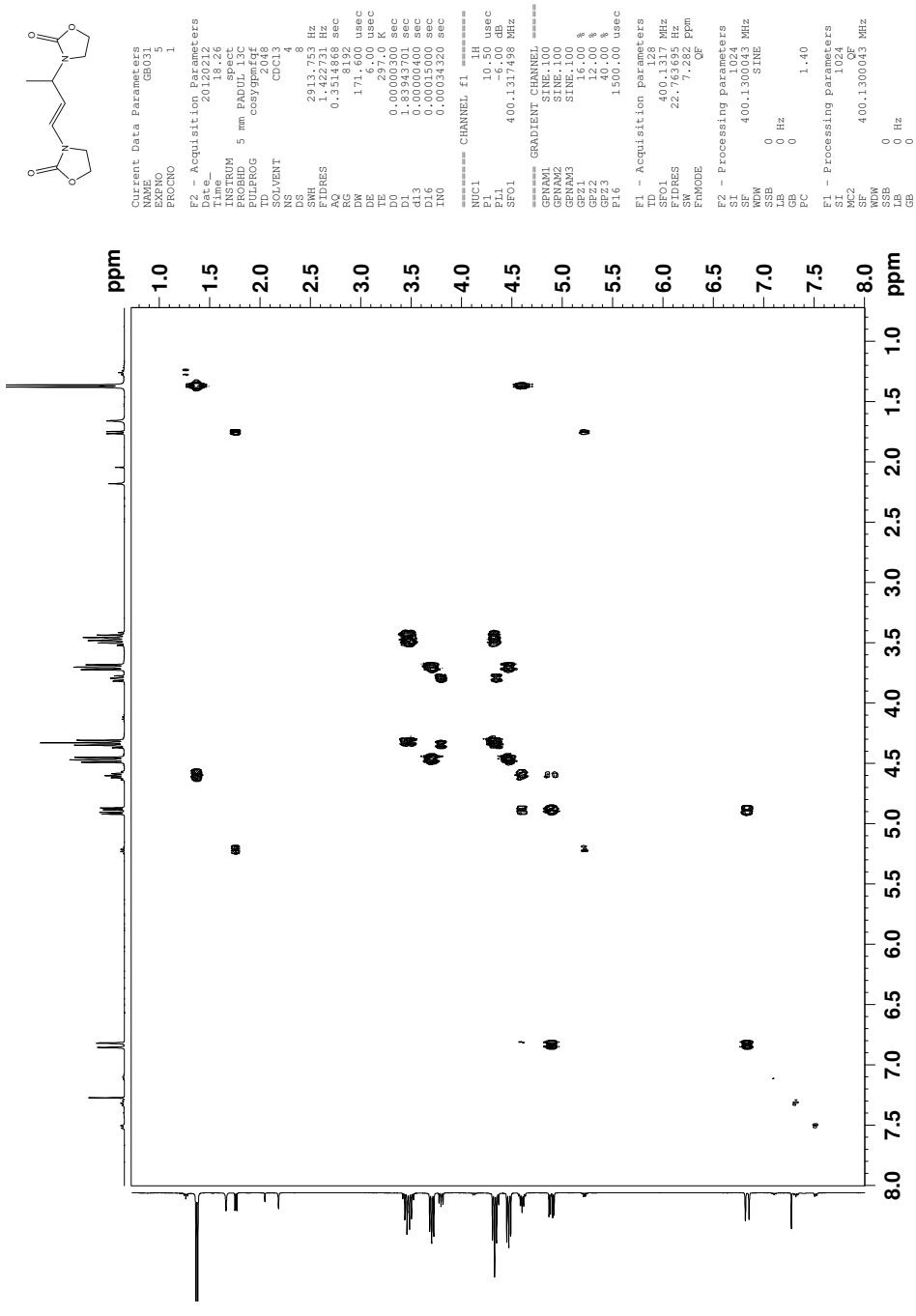
K.2 ^{13}C-NMR Dimerization product 25



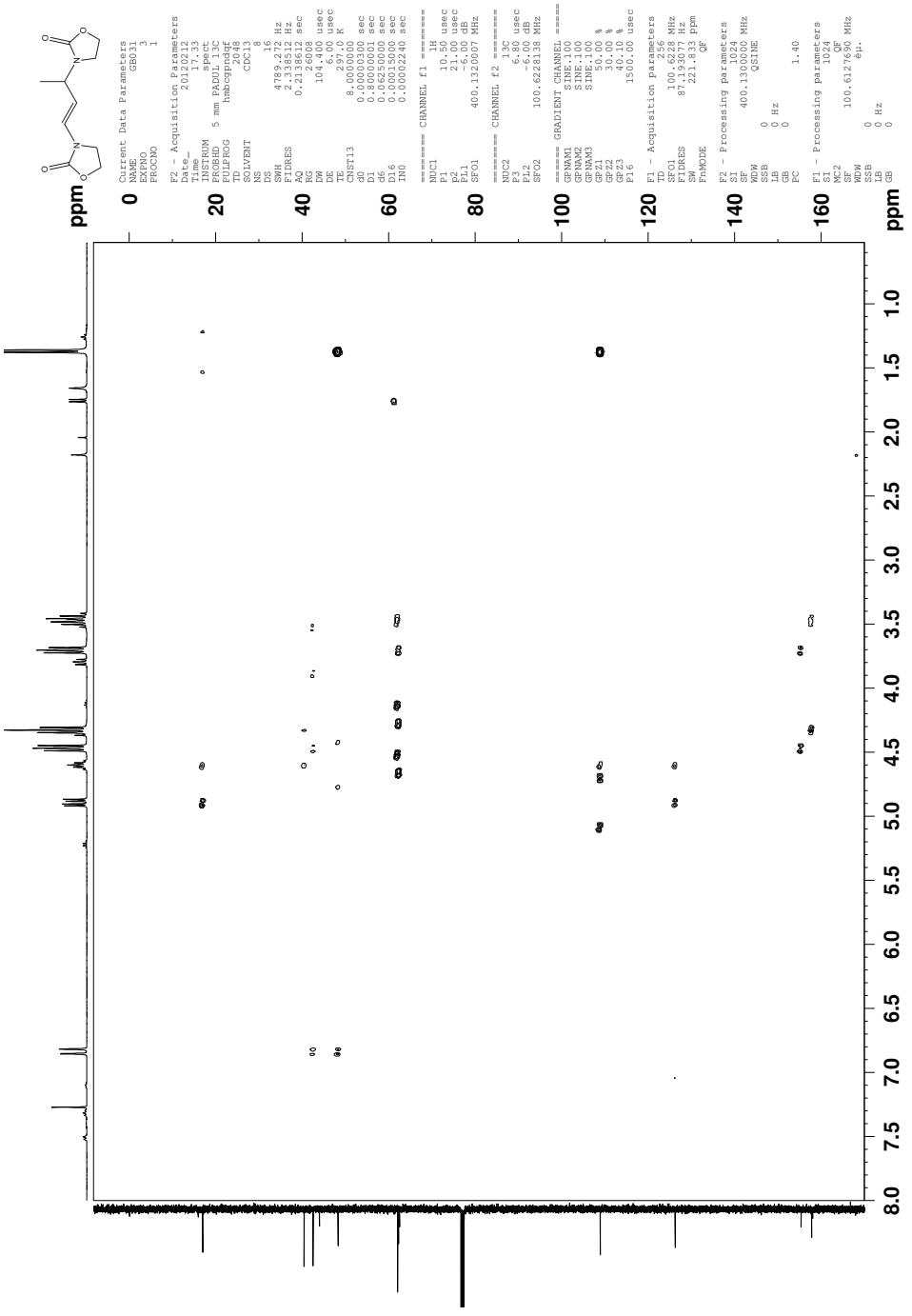
K.3 HSQC-NMR Dimerization product 25



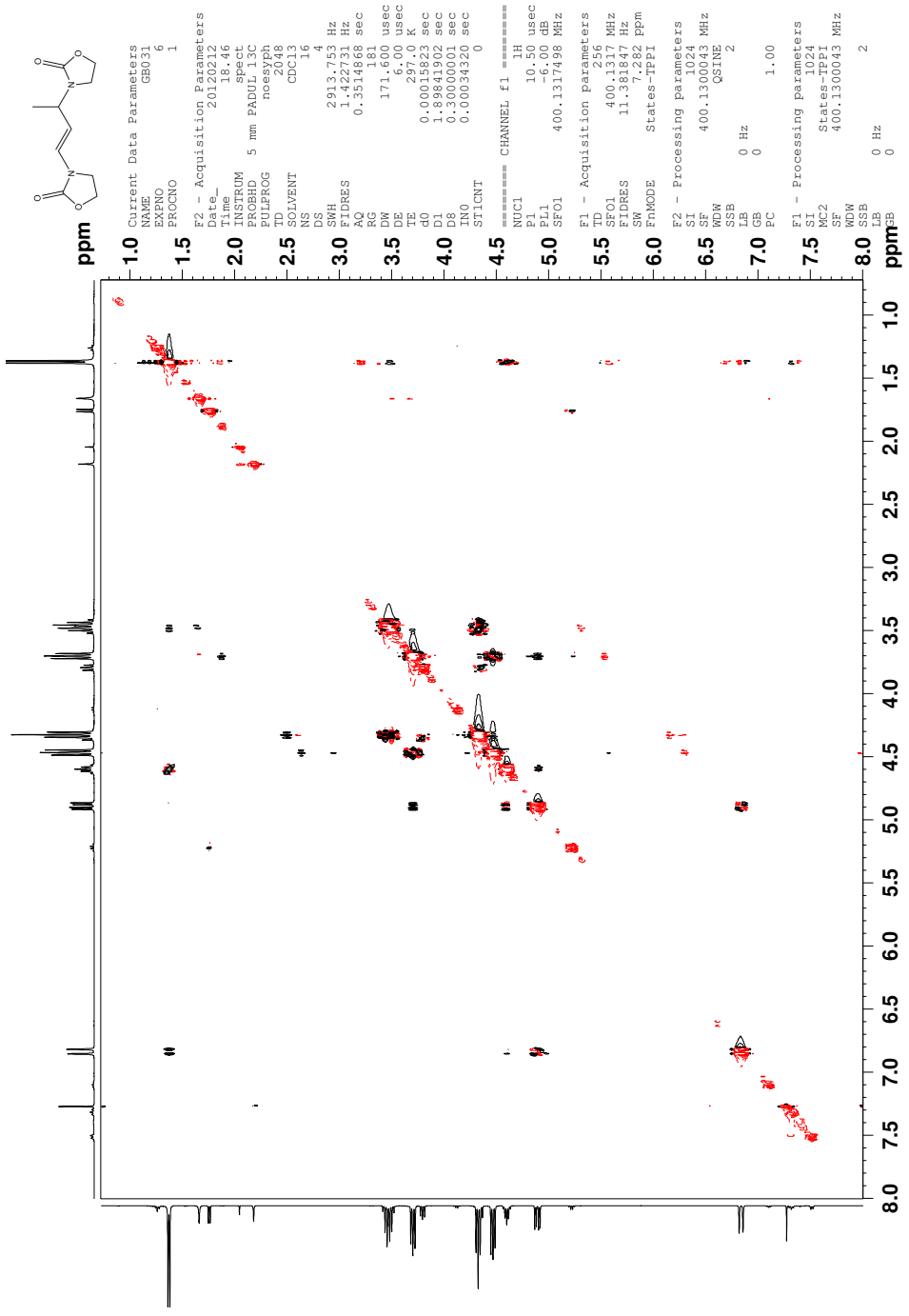
K.4 COSY-NMR Dimerization product 25



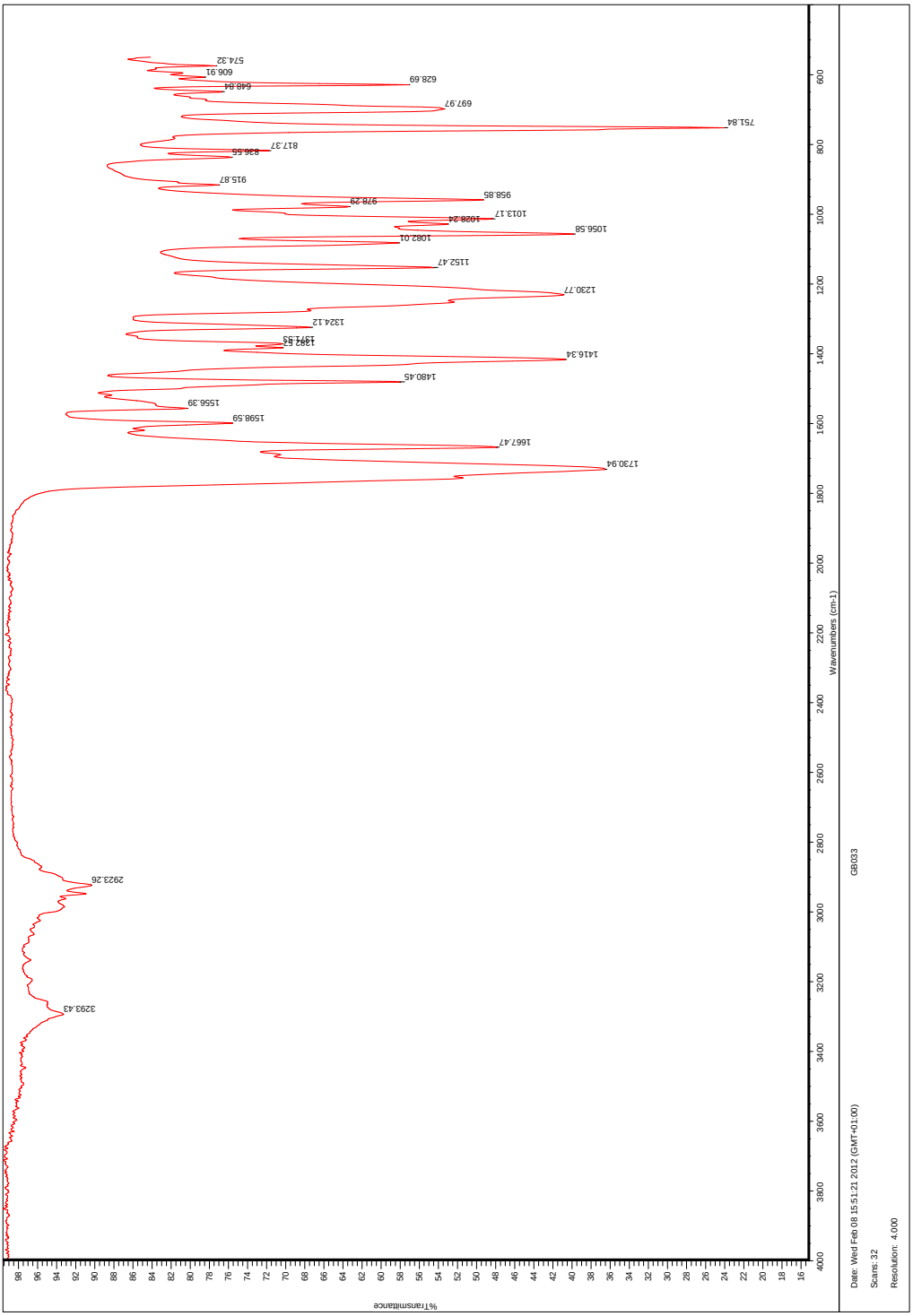
K.5 HMBC-NMR Dimerization product 25



K.6 NOESY-NMR Dimerization product 25



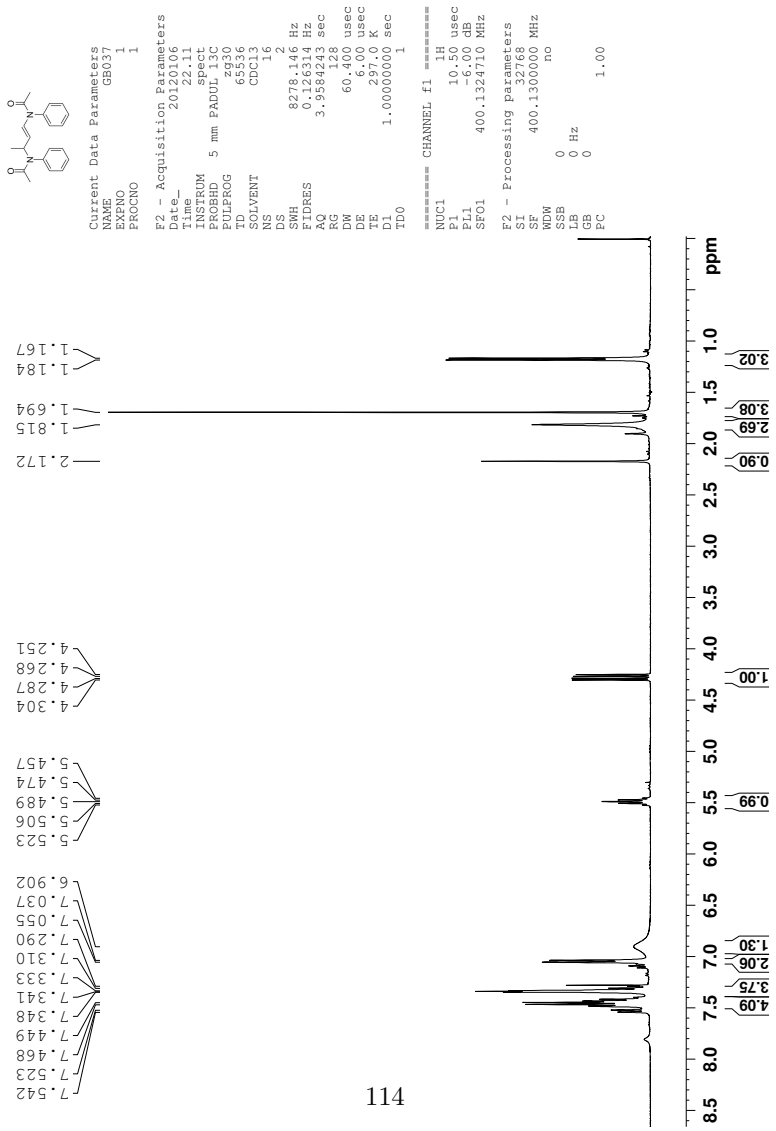
K.7 IR Dimerization product 25



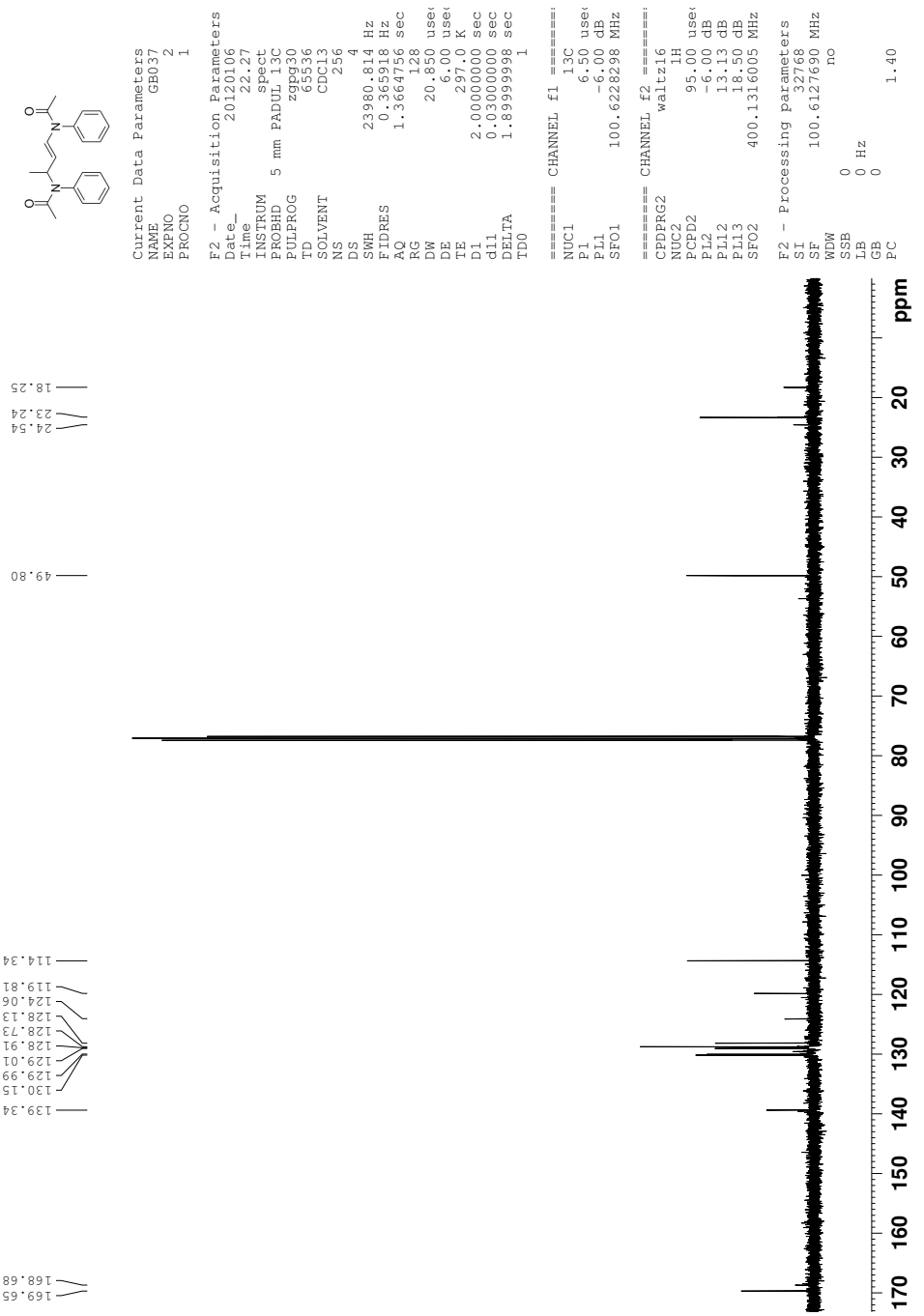
Appendix L

Dimerization product 26

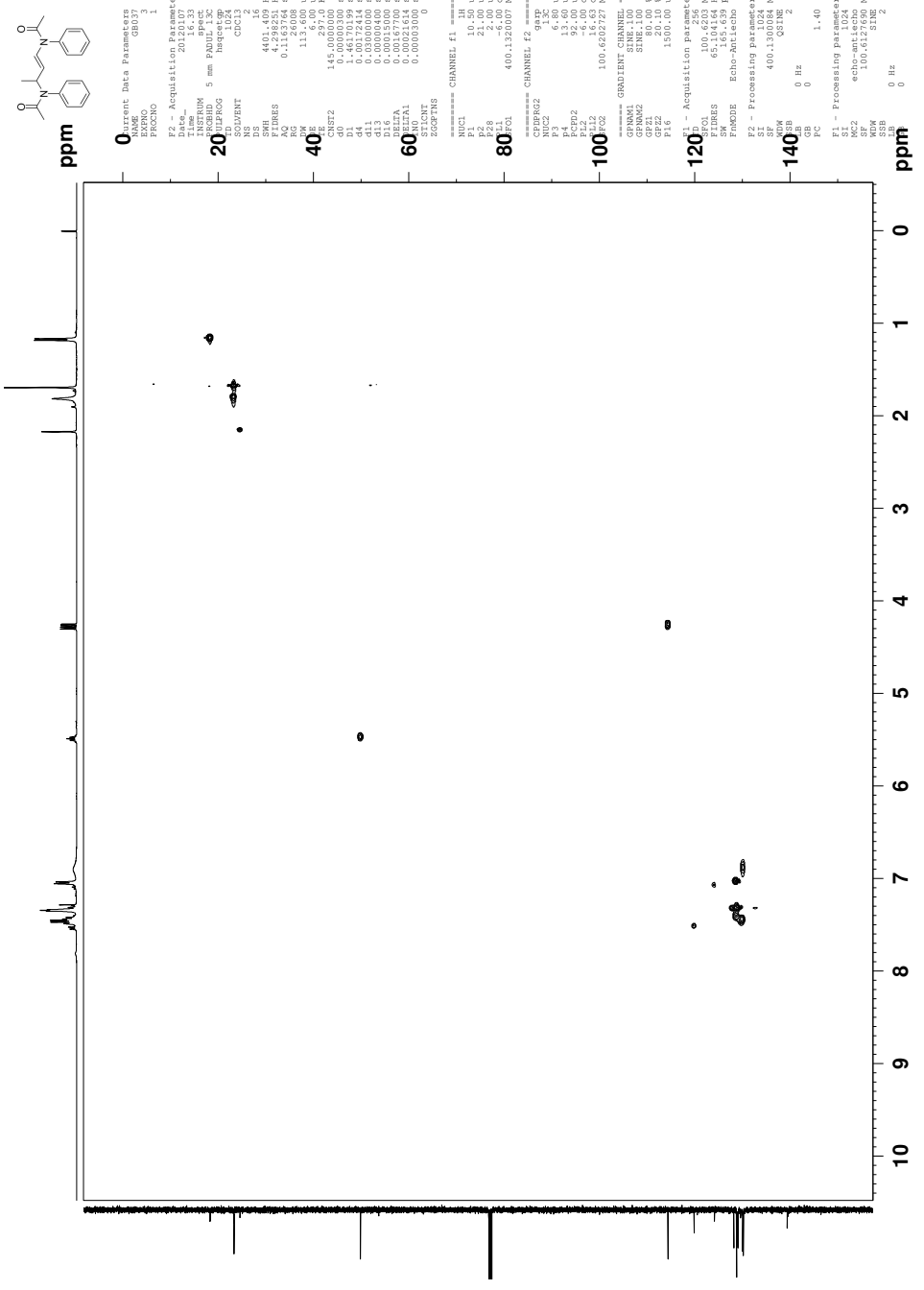
L.1 ^{1}H-NMR Dimerization product 26



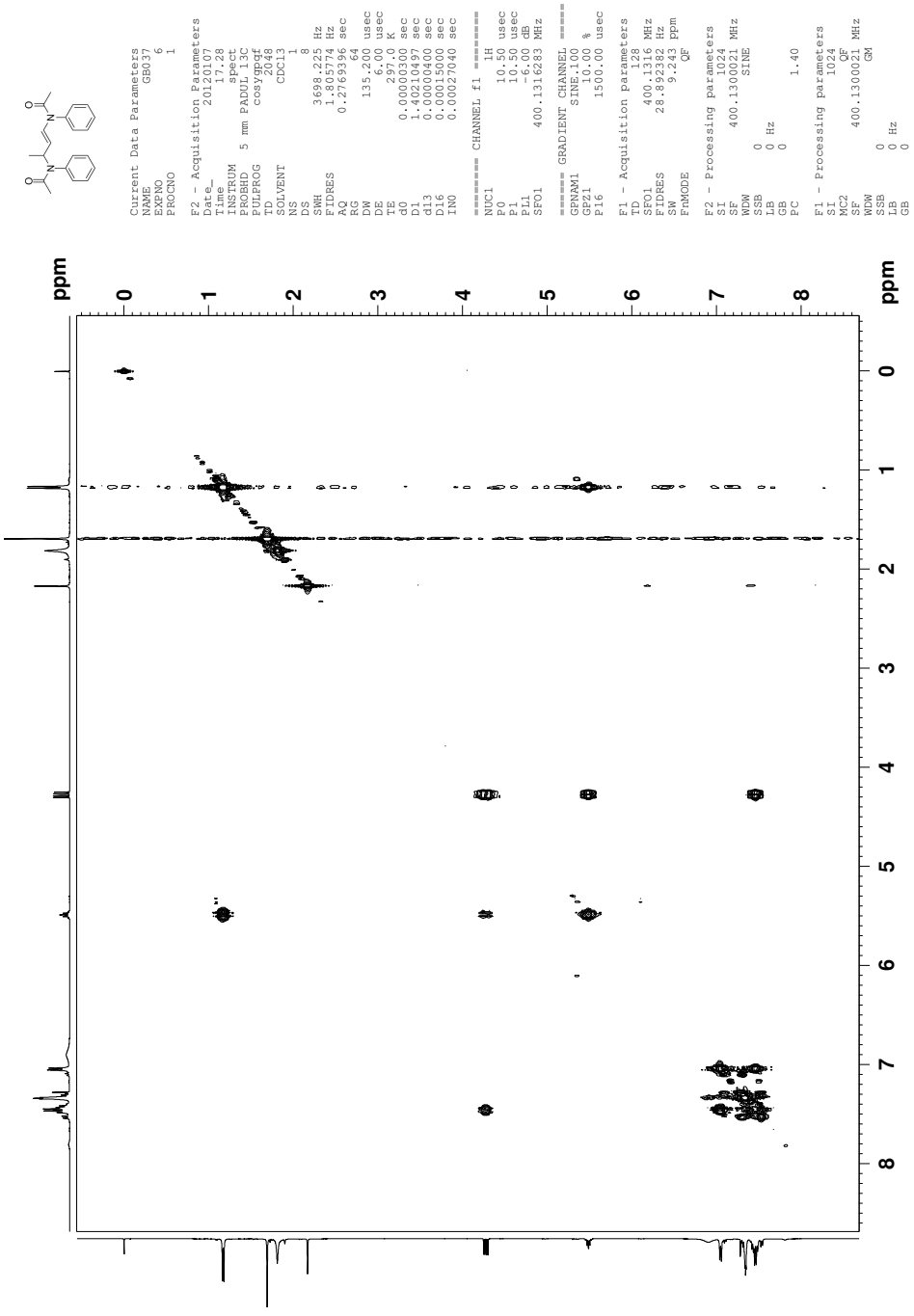
L.2 ^{13}C-NMR Dimerization product 26



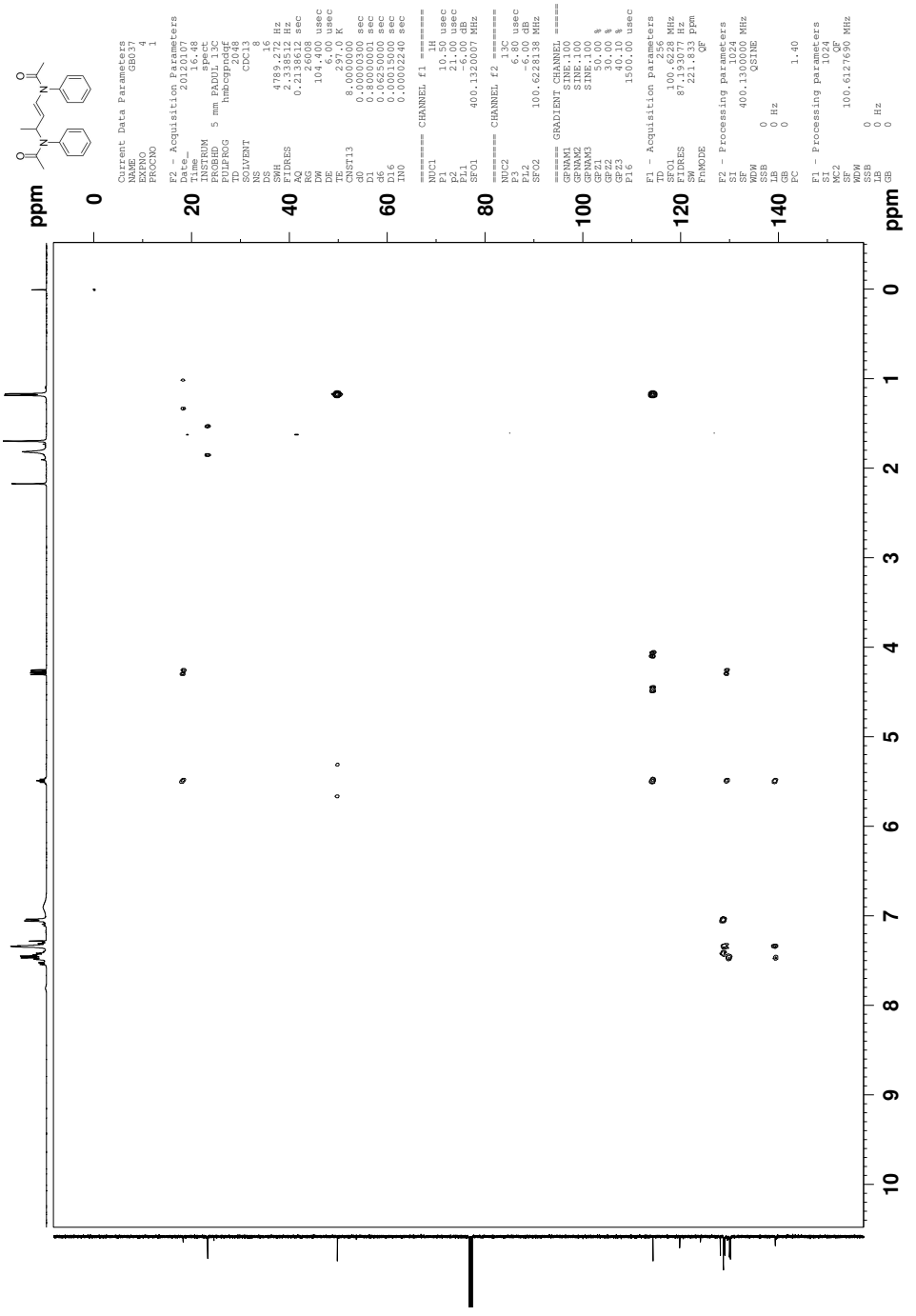
L.3 HSQC-NMR Dimerization product 26



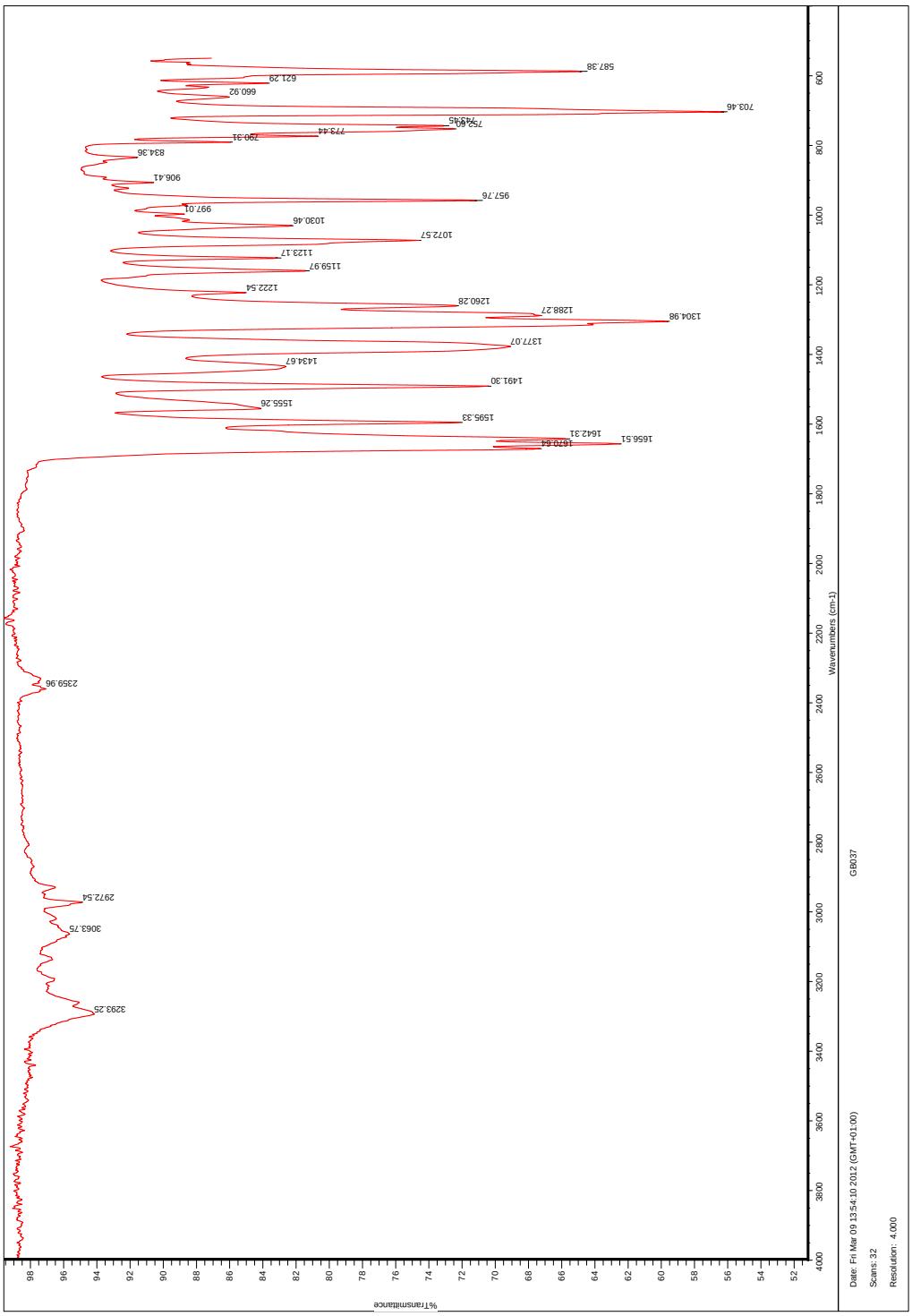
L.4 COSY-NMR Dimerization product 26



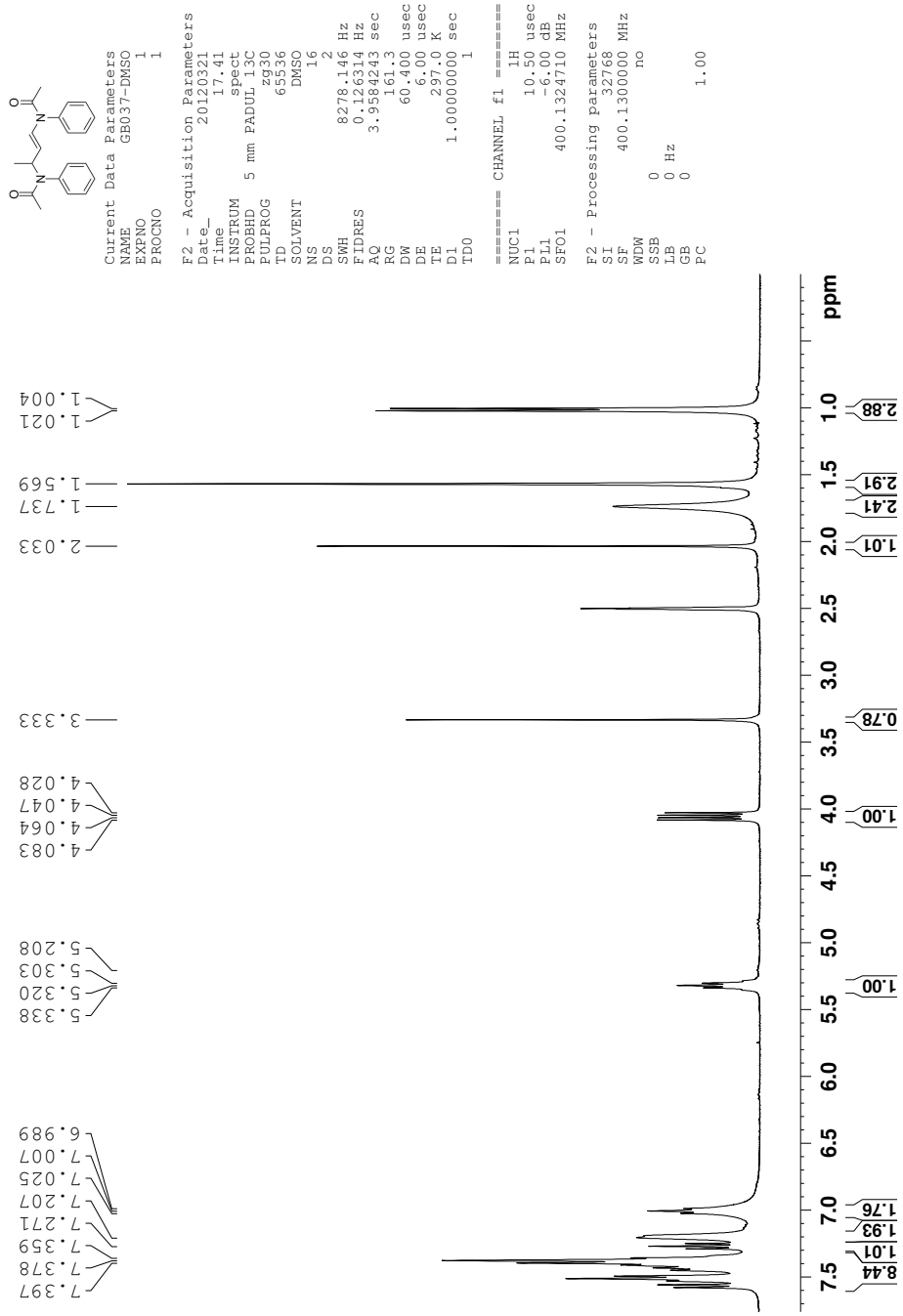
L.5 HMBC-NMR Dimerization product 26



L.6 IR Dimerization product 26



L.7 ^{1}H-NMR Dimerization product 26 in DMSO



L.8 ^{1}H-NMR Dimerization product 26 in $CDCl_3/D_2O$