NTNU – Trondheim
Norwegian University of
Science and Technology

Gold(I) Catalyzed Tandem Cyclization Reactions

Maya Rajinder Kaur

Chemical Engineering and Biotechnology
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Supervisor: Anne Fiksdahl, IKJ

Norwegian University of Science and Technology
Department of Chemistry

Declaration

I hereby declear that the presented work in this master's thesis has been conducted individually. The study has been performed in accordance with the rules and regulations for the integrated master's degree in industrial chemistry and biotechnology (Master of Science degree, 5 years) at the Norwegian University of Science and Technology (NTNU). The work has been conducted from February 2012 to July 2012.

Trondheim, July 12^{th}, 2012

Maya Rajinder Kaur

Preface

The presented work has been performed at the Department of Chemistry, Norwegian University of Science and Technology (NTNU), from February 2012 to July 2012.

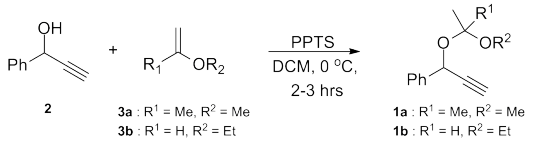
I would like to thank my supervisor, Professor Anne Fiksdahl, for accepting me as a part of her research group and giving me the opportunity to work with gold chemistry. I have truly appreciated her encouragement, guidance and help along the way.

I am grateful to post doc. Naseem Iqbal for his advice and for helping me improve my laboratory skills. I would also like to thank Ragnhild Beate Strand for interesting conversations and support. Thank you both for helpful and fun discussions at group meetings, and for creating a nice atmosphere in the lab. Much appreciation goes to Susana Villa Gonzalez and Trygve Andreassen. Susana for providing MS results, and Trygve for his help with the NMR 600.

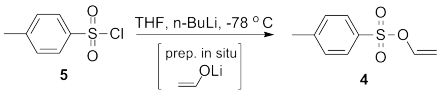
Maren Teresa Johansen, thank you for reminding me of my life outside the lab. Finally, I would like to thank Henrik Røst Breivik for solving all my troubles with LaTeX, proofreading the thesis and for always being there for me.

Abstract

The main goal of this project has been to study new gold(I) catalyzed cyclization reactions between propargyl compounds and vinyl esters. Gold catalysts have a strong affinity towards triple bonds, and alkyne-gold complexes are readily formed. These complexes exhibit a strong electrophilic character, and are activated for nucleophilic attacks. For this purpose, propargyl acetals **1a** and **1b** were prepared by an acid catalyzed reaction, and isolated in 64 - 74% yield:

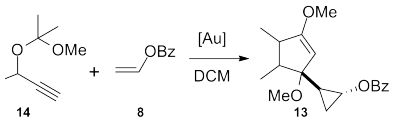


Vinyl esters are frequently used in gold(I) catalyzed cyclization reactions. Vinyl tosylate **4** has a deactivating nature such as vinyl esters, and should have similar reactivity in gold(I) catalysis. Hence, vinyl tosylate **4** was synthesized by nucleophilic substitution with a lithium enolate, and obtained in 66% yield:

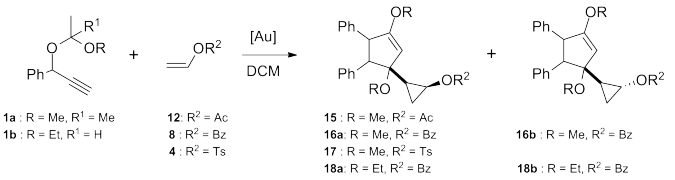


A newly discovered gold(I) catalyzed tandem reaction has been investigated in this study. In contrast to gold(I) catalyzed monocyclization reactions, this novel method generates bicyclic compounds by a cyclopropanation followed by a cyclopentenylation. The reaction forms *cis*/*trans* diastereomers, which have been separated and fully characterized.

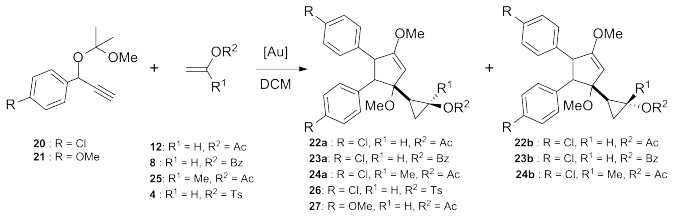
Product **13** was obtained in 5% yield from monomethyl acetal **14** and alkene **8**:



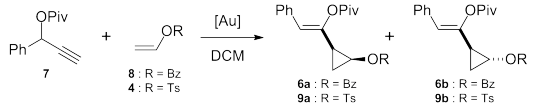
Products **15**, **16a-b**, and **17** were obtained (13 - 62%) from acetal **1a**, and alkenes **12**, **8** and **4**. Product **18a-b** was obtained (98%) from **1b** and alkene **8**:



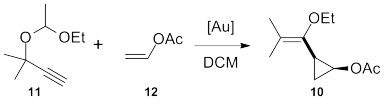
Products **22a-b**, **23a-b**, **24a-b** and **26** were prepared from propargyl acetal **20** and alkenes **12**, **8**, **25** and **4** in 14 - 56% yields. Product **27** was obtained (13%) from acetal **21** and alkene **8**:



Propargyl esters tend to favour cyclopropanation when treated with vinyl esters in gold(I) catalysis. Two new cyclopropyl compounds **6a-b** and **9a-b** were prepared (9 - 63%) from propargyl ester **7** and alkenes **8** and **4**, respectively. The *cis*/*trans* isomers generated in both reactions were separated and fully characterized:



Cyclopropyl product **10** was obtained (6%) from acetal **11** and vinyl acetate **12**:

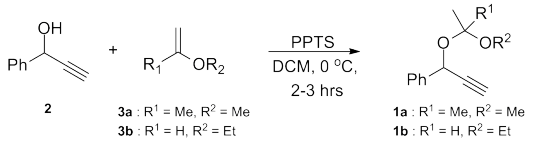


It was also attempted to study gold complexes of propargyl ester **7** and acetal **1a** by ^{1}H NMR. New ^{1}H NMR peaks of the gold-propargyl ester complex were observed. Contrarily, even at 5°C, ^{1}H NMR of the gold complex of propargyl acetal **1a** showed neither peaks of the original propargyl acetal, nor peaks of its gold complex. It was assumed that the high reactivity of the propargyl acetal caused a spontaneous polymerization.

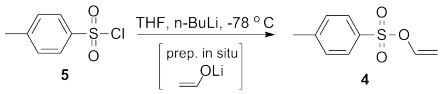
Through this study it has been observed that in contrast to propargyl esters which give cyclopropyl products, the high reactivity of propargyl acetals allows a tandem cyclization to take place, resulting in bicyclic products. It has also been found that steric effects may cause propargyl acetals to react by unexpected pathways. ^{1}H NMR confirmed a particularly high reactivity of propargyl acetal compared to propargyl ester. These results show how molecular diversity can easily be achieved by varying the substrates in gold(I) catalysis.

Sammendrag

Hovedmålet med denne masteroppgaven har vært å utforske nye gullkatalyserte reaksjoner mellom propargyl forbindelser og vinyl estere. Gullkatalysatorer har en sterk affinitet til trippelbindinger og danner lett alkyn-gull komplekser. Slike komplekser har en sterk elektrofil karakter og er aktiverte for nukleofile angrep. Propargylacetalene **1a** og **1b** ble derfor fremstilt (64 - 74%) i en syrekatalysert reaksjon:

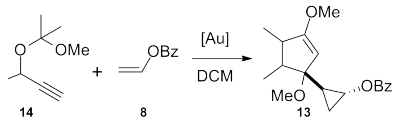


Vinyl estere er hyppig brukt i gullkatalyserte sykliseringsreaksjoner. I likhet med vinyl estere har vinyl tosylat **4** en deaktiverende karakter, og bør ha en tilsvarende reakivitet i gullkatalyse. Vinyl tosylat **4** ble derfor syntetisert ved nukleofil substitusjon med et litium enolat, i et utbytte på 66%:

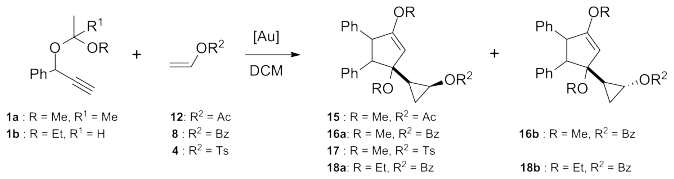


I dette studiet har en helt ny gullkatalysert tandem sykliseringsreaksjon blitt studert. I motsetning til gullkatalyserte monosykliseringsreaksjoner, kan bisykliske forbindelser bli fremstilt ved denne nye metoden. Disse blir dannet ved en syklopropanering etterfulgt av en syklopentenylering. *Cis/trans* isomerer blir dannet i reaksjonen, og disse har blitt separert og karakterisert.

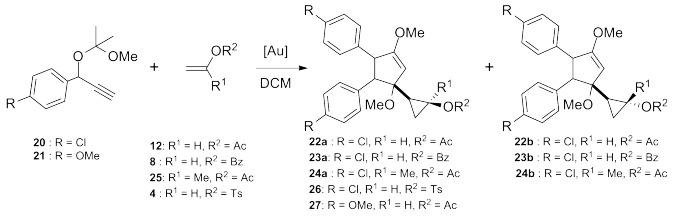
Produkt **13** ble fremstilt i et utbytte på 5%, fra propargyl acetal **14** og alken **8**:



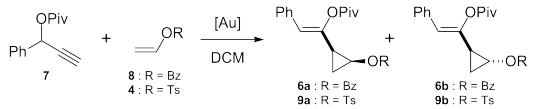
Produktene **15**, **16a-b**, og **17** ble fremstilt (13 - 62%) fra acetal **1a** og alkenene **12**, **8** og **4**. Produkt **18a-b** ble dannet (98%) fra acetal **1b** og alken **8**:



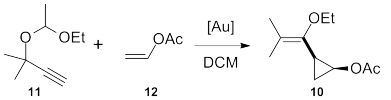
Produktene **22a-b**, **23a-b**, **24a-b** og **26** ble syntetisert (14 - 56%) fra acetal **20** og olefinene **12**, **8**, **25** og **4**. Produkt **27** ble fremstilt (13%) fra acetal **21** og alken **8**:



Propargyl estere favoriserer syklopropanering i gullkatalyserte reaksjoner med vinyl estere. To nye syklopropylforbindelser **6a-b** og **9a-b** ble fremstilt (9 - 63%) fra propargyl ester **7** og alkenene **8** og **4**. *Cis/trans* isomerene ble separert og karakterisert:



Syklopropyl forbindelse **10** ble dannet (6%) fra propargyl acetal **11** og vinyl acetat:



Det ble forsøkt å studere gullkomplekser av propargyl ester **7** og acetal **1a** med ^{1}H NMR. Det ble observert nye topper tilhørende gull-propargyl ester komplekset. Derimot det ble hverken observert topper tilhørende det originale propargyl acetalet, eller gull-propargyl acetal komplekset. Det ble antatt at den høye reaktiviteten til acetalet resulterte i en spontan polymerisering.

Dette studiet har vist at i motsetning til propargyl estere som gir syklopropyl produkter, kan det bli dannet bisykliske produkter fra propargyl acetaler på grunn av deres høye reaktivitet. Det har også blitt observert at steriske effekter kan bidra til at propargyl acetaler reagerer ved uforventede mekanismer. ^{1}H NMR bekreftet at propargyl acetaler har høyere reaktivitet enn estere. Disse resultatene viser at molekylær diversitet kan enkelt oppnås ved å variere substratene i gullkatalyse.

Symbols and abbreviations

Ac	Acetyl
ar	aromatic
as	asymmetric (IR)
br	broad
Bz	Benzoyl
calcd	calculated
CD_2Cl_2	deuterated dichloromethane
$CDCl_3$	deuterated chloroform
cm^{-1}	wave number, reciprocal centimeter
conc.	concentrated
COSY	Correlated Spectroscopy
δ	chemical shift [ppm]
δ	deformation vibration (IR)
d	doublet (NMR)
DCM	Dichloromethane
dd	doublet of doublet (NMR)
ddd	doublet of doublet of doublet (NMR)
dr	diastereomeric ratio
dt	doublet of triplet (NMR)
EE	Ethyl vinyl Ether
EI	Electron Impact (MS)
eq.	equivalent
ERG	Electron Releasing Group
ESI	Electron Spray Impact (MS)
Et	Ethyl
et al.	*et alia* (and others)
EtOAc	Ethylacetate
EWG	Electron Withdrawing Group
ϕ	dihedral angle (NMR)
γ	skeletal vibration (IR)
GLC	Gas Liquid Chromatography
HMBC	Heteronuclear Multi Bond Correlation
HR	High Resolution (MS)

HSQC	Heteronuclear Single Quantum Coherence
Hz	Hertz
IR	Infrared spectroscopy
J	coupling constant [Hz]
L	Ligand
M^+	Molecular ion
m	multiplett (NMR)
m	medium (IR)
Me	Methyl
mg	milligram
MHz	MegaHertz
min	minutes
mL	milli Litres
mmol	millimole
MOP	2-methoxypropene
mp	melting point
MS	Mass Spectroscopy
n-BuLi	*n*-Butyllithium
NEt_3	triethylamine
NHC	N-Heterocyclic Carbene
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
Nu	Nucleophile
obsd	observed
oop	out of plane vibration (IR)
Ph	Phenyl
Piv	Trimethyl acetyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
PTSA	*para*-Toulene Sulfonic acid
quint	quintet (NMR)
rf	radio frequency (NMR)
R_f	Retention factor (TLC)
rx.	reaction
s	singlet (NMR)
s	strong (IR)
st	stretch (IR)
sy	symmetric (IR)
t	triplet (NMR)
t-Bu	*tert*-Butyl
THF	Tetrahydrofuran
THP	Tetrahydropyran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
Ts	Tosylate
w	weak (IR)

Contents

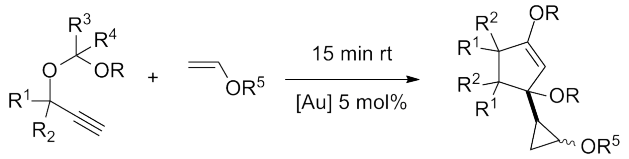
Chapter 1

Introduction

In recent few years, gold has been recognized as an efficient catalyst in organic chemistry. The field of homogeneous gold catalysis has become very active, and several new reactions are being published every week.[1] Gold(I) catalysts readily activate C-C multiple bonds, such as alkynes and alkenes, for nucleophilic attacks. Complex molecules can therefore easily be obtained by gold(I) catalysis.[2] Gold(I) has shown a stronger activation of alkynes, compared to other metals used in organic synthesis.[3] This property has previously been exploited in gold(I) catalyzed reactions with propargyl esters. Gold carbenoid complexes are readily formed in these reactions, which have shown to generate cyclic products when an alkene is present.[4–6] Propargyl acetals have also been used in gold(I) catalyzed cyclization reactions, but to a lesser extent.[7,8]

1.1 Aim of project

The Fiksdahl research group has explored several gold(I) catalyzed cyclization reactions, such as olefin cyclopropanation reactions of propargyl esters and vinyl esters.[4,9] In contrast to propargyl esters which tend to give cyclopropyl products, it has been observed that propargyl acetals treated with vinyl amides provide cyclopentenyls.[10] Recently, it was discovered in the research group that when propargyl acetals are reacted with vinyl esters instead of amides, a new tandem cyclization reaction takes place (Scheme 1.1).[11] The main goal of this project was to study gold(I) catalyzed reactions with aliphatic and aromatic acetals, and different types of vinyl esters, to see if the reaction proceed through this tandem mechanism.



Scheme 1.1: Gold(I) catalyzed tandem reaction

As mentioned, cyclopropanation reactions with propargyl esters and alkenes have previously been studied in the research group.[4] However, vinyl benzoate and tosylate had never been utilized in these reactions. Hence, a second aim was to study whether a potential cyclopropanation reaction pathway would take place with these reagents.

There is an ongoing discussion on the "true nature" of gold carbenoid intermediates.[12] A third goal was therefore to conduct low temperature NMR studies of gold complexes with a propargyl ester and a propargyl acetal.

Chapter 2

Theory

2.1 Transition metals in organic synthesis

The use of metals in organic chemistry started in 1760 when Louis Claude Cadet de Gassicourt produced cobalt based inks by using cobalt salts containing arsenic. Since then the chemistry of various metals such as magnesium, lithium, iron and nickel has been studied thoroughly.[13] It was discovered that the use of metals in organic synthesis had several advantages. Not only does all functional groups coordinate to a transition metal, the coordination also leads to increased reactivity of the functional group. The nature of organic compounds complexed to metals can be reversed in such way that nucleophilic compounds can become electrophilic and vice versa. Reactions that can be challenging under normal conditions can be facilitated by introducing a certain transition metal. In addition, transition metals can catalyze multistep cascade reactions where multiple bonds are formed in one process. A characteristic of transition metals is that they exhibit two or more stable oxidation states. They also possess different geometries and coordination numbers. Their reactivity towards organic compounds are connected to these properties. The mechanisms in organometallic chemistry are rarely straightforward, and are still not fully understood. By studying the fundamental behaviour of complexes, the reaction pathway can be deduced.[14]

In synthesis, transition metals are used in complexes with ligands (L). Metal-ligand complexes, with 18 electrons in the bonding shell, are coordinatively saturated. When transition metals form coordination complexes, the d shell becomes lower in energy than the s and p shells. Hence, the d shells are filled before the s and p shells.[14] The number of electrons in the d shell of metals increases from left to right in the periodic system. Consequently, complexes of metals in the right end have a higher tendency to become coordinatively saturated.[13]

Ligands such as R_3P, R_3N and H^- have occupied "sp^n" hybrid orbitals, which can form σ-donor bonds by overlapping with an empty "*dsp*" hybrid orbital of the metal. This type of bonding leads to augmented electron density on the metal atom. Unsaturated organic ligands such as alkenes and carbon monoxide have antibonding π^* orbitals. These orbitals are energetically and geometrically similar to the *d* orbital of the metal, as shown in Figure 2.1.[14]

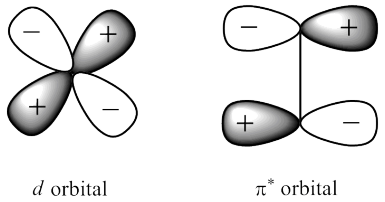
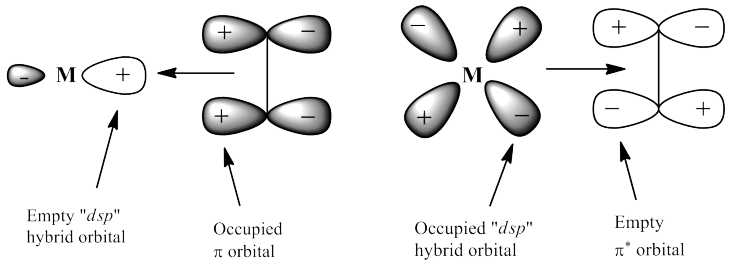


Figure 2.1: Symmetry of d-orbital and antibonding π^* orbital

As seen in Figure 2.2a, unsaturated ligands can also form σ-donor bonds with the metal by overlapping their filled bonding π orbitals with the empty "*dsp*" hybrid orbital of the metal.[14] If the transition metal has electrons in its "*dsp*" hybrid orbital, it can overlap with empty antibonding π^* orbitals of organic insaturated ligands (Figure 2.2b). In this case, electrons are donated from the metal to the ligand, which lowers the electron density on the metal and lets it exist in a low oxidation state. This type of overlap is called π back-bonding.[13] As the electron density on the metal atom is related to its reactivity, varying ligands is a method to modify the organometallic reagents.



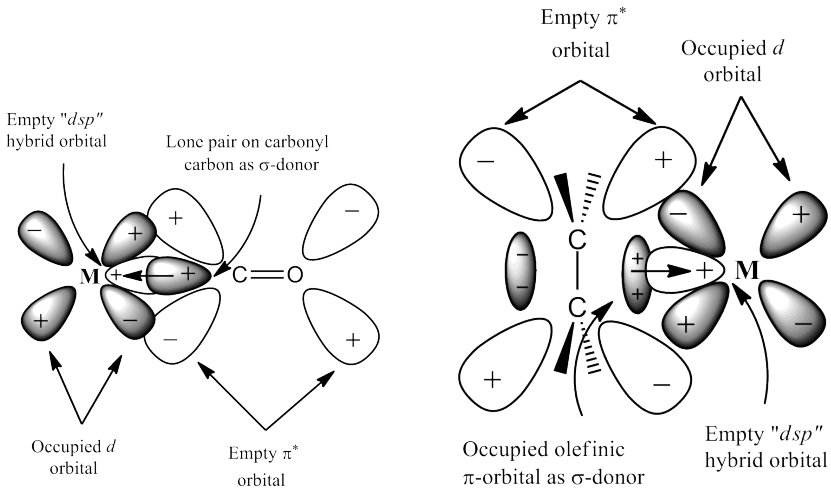
(a) π bond serving as σ-donor bond

(b) π^* orbital serving as π-acceptor

Figure 2.2: Bonding types between metal and organic unsaturated ligands

The Denwar-Chatt-Duncanson model is shown in Figure 2.3, and illustrates the two π back-bonding modes between a metal and an unsaturated organic ligand; longitudinal and perpendicular.[13, 14]

Carbon monoxide and isonitriles are examples of longitudinal acceptors, while alkenes and alkynes are examples of perpedicular acceptors.[14] X-ray experiments have demonstrated that the C-O bond of carbon monoxide and the C-C bond of ethylene are longer when coordinated to a transition metal, than when they are free. The bond length can reach that of a single bond in cases where the π back-bonding is significantly high. In this case, the system can be considered as a metalcyclopropane.[13]



(a) Longitudinal back-bonding (b) Perpendicular back-bonding

Figure 2.3: The Denwar-Chatt-Duncanson model

2.2 Gold chemistry

During the last century, the interest in gold as a catalyst has increased dramatically. In earlier times, gold was considered to be a metal with low catalytic activity. There are two major areas of gold catalysis: homogeneous and heterogeneous catalysis, where the first field is the most active area.[1]

It has been found that gold has several properties which are beneficial in organic synthesis. Gold catalysts principally exist in the oxidation states +1 and +3. Unlike many other metals used in organometallic reactions, Au(I) catalysts are not sensitive to air because of the high oxidation potential from Au(I) to Au(III). In addition, water, alcohols and oxygen are better tolerated during reactions because of the low oxophilic properties of gold, compared to most Lewis acids. The product selectivity in many reactions catalyzed by gold are found to be well controlled. This is thought to be due to gold carbenoid intermediates formed during the reaction.[3] Gold carbenoids are complexes with a double bond between carbon and gold, which can be stabilized by the presence of a heteroatom such as oxygen.[13] It is also believed that the product selectivity is well controlled because the Au-C bond prefer protodeauration over β-hydride elimination. By using gold catalysts, compounds with complex structures can easily be synthesized from simple starting materials.[3]

Coordination of a C-C multiple bond to the gold catalyst activates the bond for a nucleophilic attack.[12] The C-C multiple bond can be that of alkynes, allenes and alkenes.[15] Gold-alkyne complexes have a strong electrophilic character. This is because alkynes are good σ-donors and weaker π-acceptors towards gold. There is a large difference in bond energy between alkyne π to gold σ-donor bonding and gold to alkyne π^*-back-bonding. This may be the reason why gold(I) catalysts exhibit a stronger alkyne activation compared to other metals.[3] MS studies have shown that the alkyne-gold complexes **I** and **II**, shown in Figure 2.4, are formed easily.[12] This strong affinity towards alkynes has led to a great interest within several research groups in using propargylic substrates in gold catalysis.[4–6]

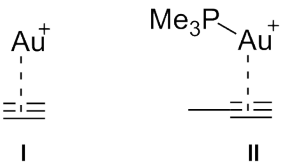
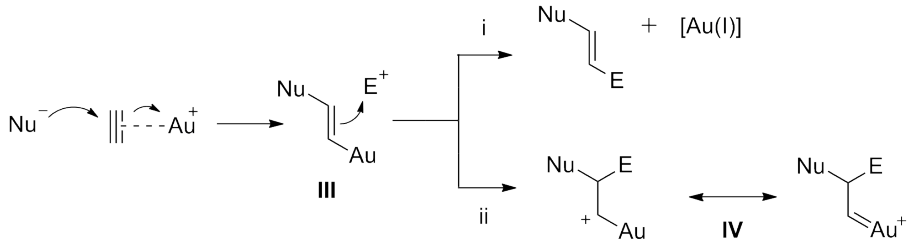


Figure 2.4: Gold(I)-alkyne complexes

The nucleophilic attack on an activated triple bond usually proceeds through an *anti* addition in cyclization reactions or when the nucleophile is weakly coordinating. The nucleophilic attack leads to formation of the vinyl-Au complex **III** shown in Scheme 2.1. *Syn* addition is more likely when the nucleophile is strongly coor-

dinating. In the presence of an electrophile E^+, the vinyl-Au complex **III** usually attacks the electrophile, resulting in regeneration of the gold catalyst as shown in Scheme 2.1, route i. If the electrophile is H^+, this step is called protodeauration.[12] It is typical for this type of reactions that the oxidation state of gold remains the same throughout the catalytic cycle.[16] A distinct path has also been suggested (Scheme 2.1, route ii), where the gold in the Au-vinyl complex makes it possible to trap the electrophile, leading to the stabilized cationic gold intermediate **IV**. In this case, it is assumed that the *5d* electrons of Au back-bond into the conjugated vacant *p* orbitals of carbon, thus stabilizing the intermediate.[17]



Scheme 2.1: Proposed pathways after a nucleophilic attack

As explained in Section 2.1, the ligands of a metal can be varied in order to fine-tune the desired outcome of a reaction. The ligands have an effect on reactivity, selectivity as well as enantioselectivity.[15] The majority of ligands are based on tertiary phosphines, such as complexes **V**-**VIII** shown in Figure 2.5. The complexes **V** and **VIII** have dialkylbiaryl ligands which are known as Buchwald type ligands.[15] Cationic complex **V** was used in this project. Complex **IX** has been used for the synthesis of a NHC-gold(I) monohydride.[12]

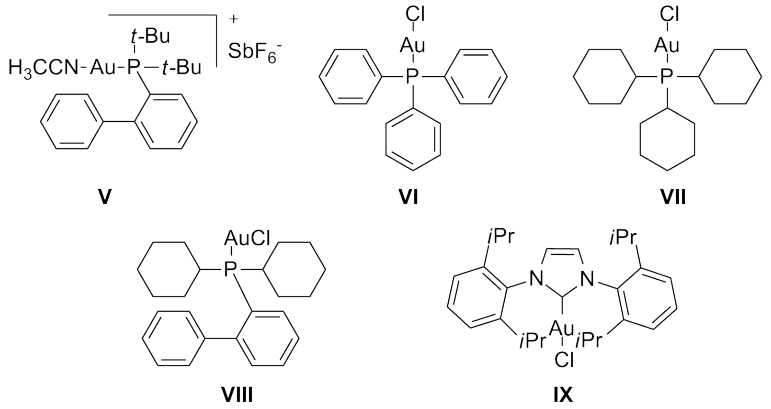
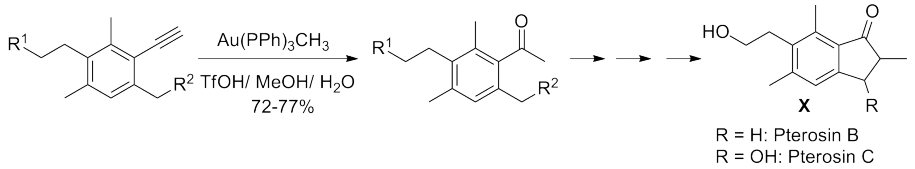


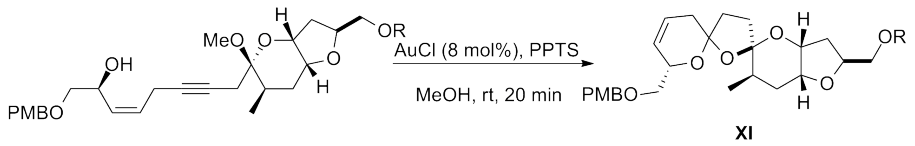
Figure 2.5: Gold catalysts

As mentioned earlier, many research groups are studying gold catalyzed reactions with alkynes as substrates. Being non-toxic, highly active and non-sensitive towards moisture or air, gold(I) catalysts are viable in organic synthesis. The synthetic utility of gold has been explored in various total syntheses where a transformation of a triple bond is desired. In the total synthesis of Pterosin B and C **X**, a gold catalyst replaced toxic mercury for the hydration step shown in Scheme 2.2.[16]



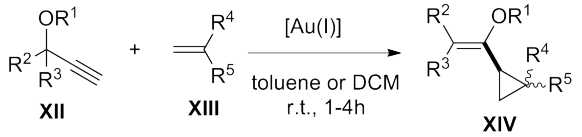
Scheme 2.2: Gold in total synthesis of Pterosin B and C

In the synthesis of the A-D rings of the toxin Azaspiracid **XI**, AuCl was used under acidic conditions to obtain the cyclic ketal moiety (Scheme 2.3). In this case the alkyne functioned as a precursor for a ketal.[16]



Scheme 2.3: Gold in total synthesis of the A-D rings of Azaspiracid

The research group of Anne Fiksdahl recently published the preparation of new highly substituted cyclopropane derivatives by treating propargyl esters **XII** with olefins bonded to heteroatoms **XIII**, in the presence of gold catalyst **V** (Fig. 2.4). Cyclopropane units are found in several natural products and are useful in pharmaceutics. This procedure led to products with a substituted cyclopropane in an allylic position **XIV**(Scheme 2.4).[4]



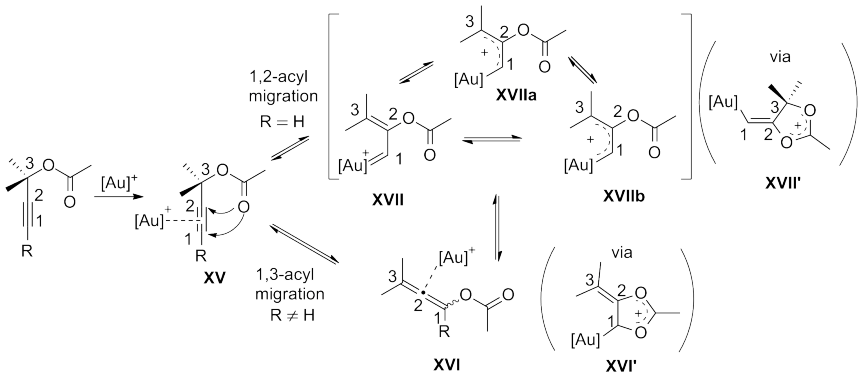
Scheme 2.4: Gold catalyzed cyclopropanation reactions

2.3 Gold(I) catalyzed cycloadditions

Cycloaddition is a traditional method for incorporation of heteroatoms into a ringstructure. The products obtained from cycloadditions usually have a defined substitution pattern which often is stereochemically controlled. The reactions proceed by forming two new ring bonds with a net reduction of bond multiplicity.[18] This type of reaction is valuable in organic synthesis because it generates two new bonds and a ring in one single process. It is an important tool when complex structures with high stereo- and regiocontrol are desired.[19]

Transition metals such as rhodium, ruthenium, cobalt, palladium and nickel have been used as catalysts for cycloaddition reactions since the 1980s. In the past few years, gold has been recognized as an excellent catalyst for this purpose. As mentioned earlier, gold has the advantage of being very carbophilic, and easily stabilize carbocationic intermediates. These properties have made it possible to run reactions that earlier have been rather challenging. Consequently, the interest in exploiting the function of gold in cycloaddition reactions has increased dramatically. Different reaction conditions and reagents can lead to different mechanistic pathways of the cyclization reaction. This opens for a variety of cyclization products. Cycloaddition reactions with gold activated alkynes proceed differently than reactions with gold activated allenes, which results in different products.[19]

Cycloaddition reactions between gold activated propargyl esters and an unsaturated reagent, are particularly interesting due to their flexibility and relevance in synthesis.[19] When coordinated to gold, propargyl esters tend to undergo 1,2- and 1,3-acyl migrations, as shown in Scheme 2.5.[19,20]

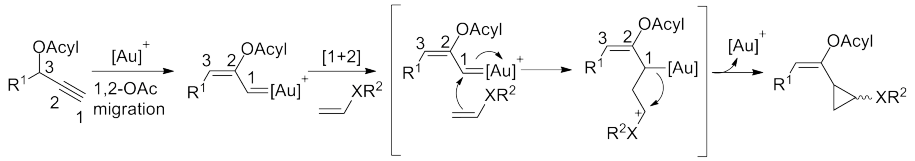


Scheme 2.5: Gold(I) catalyzed 1,2- and 1,3-acyl migration of propargyl esters

The acyl migration is initiated by an intramolecular nucleophilic attack of the acyl moiety on the gold activated alkyne **XV**. When the R group of complex **XV** is H, a 1,2-acyl migration is most likely to occur, while an 1,3-acyl migration is expected when R $\neq$ H.[19] The 1,3-acyl migration gives gold-allene species **XVI** while the 1,2 acyl migration gives gold carbenoid species **XVII**.[5] Structural studies of the gold carbenoid species **XVII** show that the bond lengths C1-C2 and C2-C3 are similar. This implies that the positive charge is not localized on Au only, but is delocalized in conjucated π-system of Au, C1, C2, C3 and O.[4,20] This is illustrated by resonance structures **XVIIa** and **XVIIb** in Figure 2.5. Both the 1,2-acyl migration and 1,3-acyl migration proceed through the formation of a 5-membered cyclic intermediates **XVI'** and **XVII'**. Studies have shown that species **XV**, **XVI** and **XVII** are in rapid equilibrium.[20] Once formed, the species **XVI** and **XVII** can be trapped in different types of cyclization reactions.[5]

2.3.1 [1+2] Cycloaddition reactions

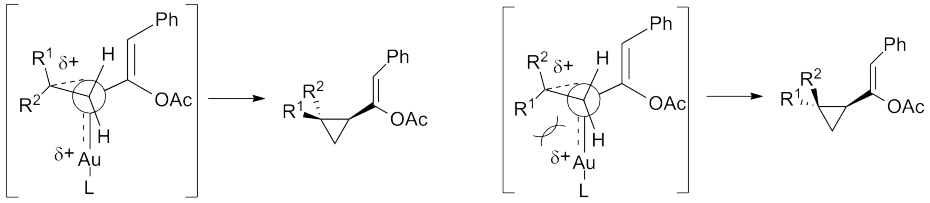
Formal [1+2] cycloaddition reactions generate cyclopropanes. This type of cycloaddition reaction can take place between a propargylic gold carbenoid complex, which was mentioned in Section 2.2 and Section 2.3, and a moderately deactivating vinylic compound. The cyclopropanation reactions studied by the research group of A. Fiksdahl, which were described in the end of Section 2.2, were gold(I) catalyzed [1+2] cycloaddition reactions.[4] The mechanism of these cycloaddition reactions has been found to proceed as illustrated in Scheme 2.6.[14] It is assumed that a vinylic gold carbenoid species of similar type as **XVII** from Scheme 2.5, acts as a carbenoid in cyclopropanation reactions of this type. It can be thought that the electron withdrawing ester stabilizes this resonance structure.[7] The cyclization is initiated by an attack of the vinyl at the carbenoid. This leads to the formation of a bond between C1 and the terminal carbon of the vinylic compound. The attack takes place at the terminal carbon due to greater stabilization of a cationic intermediate. Here, the cationic charge is located on substituted carbon. If the attack would have taken place at the non-terminal carbon, the cationic charge would have been located on a primary carbon which is less stable.[21] The deactivating ester hinders the cyclization to complete at C3, which would have lead to a cyclopentenyl ring. Instead, the cycloaddition reaction is completed by an attack of C1, closing the cyclopropane ring.[22]



Scheme 2.6: Gold(I) catalyzed [1+2] cycloaddition of propargylic ester and alkene

The products obtained from cyclopropanation reactions show high diastereoselectivity for a *cis* configuration.[4, 23] The observed *cis* selectivity has been explained by Toste *et al.* with the stereochemical models shown in Scheme 2.7.[23] The models suggests that the final configuration is dependent on steric interactions between the vinylic substituents R_1 and R_2, and the ligands of the gold complex in the transition state. A transition state, where the bulkier vinylic substituent R_1 is *trans* to the gold ligands, thereby less steric hindrance, results in *cis* configuration (Scheme 2.7a). Accordingly, a *trans* configuration is expected when the bulkier vinylic substituent R_1 is *cis* to the gold ligands in the transition state, as shown in Scheme 2.7b. Indeed, an approach where the steric effects are minimal is favoured, as *cis* selectivity has been observed experimentally.[4, 23]

When R_1 is the bulkier substituent:

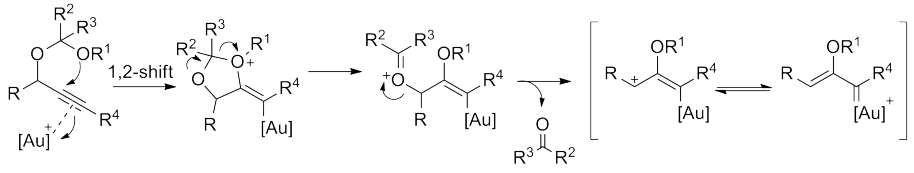


(a) Less steric effects gives *cis*-configuration (b) Steric effects gives *trans*-configuration

Scheme 2.7: Stereochemical model for cyclopropanation reactions

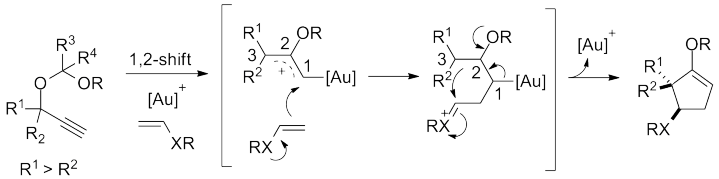
2.3.2 [2+3] Cycloaddition reactions

Cyclopentenyl products can be formed by formal [2+3] cycloaddition reactions. Previous studies in the Fiksdahl group have shown that gold activated propargyl acetals have a high tendency to produce 5-membered rings with deactivating vinylic reagents such as vinyl amides and silylenolethers.[4] It has been proposed that propargyl acetals also undergo 1,2-migration when complexed with gold, but through a slightly different pathway than for propargyl esters. A migration-fragmentation variant of the previously described 1,2-migration is illustrated in Scheme 2.8.[8]



Scheme 2.8: Migration-fragmentation sequence of a gold-acetal complex

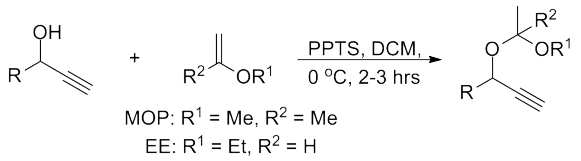
[2+3] Cycloaddition reactions may involve the gold carbenoid species **XVIIa** from Scheme 2.5, where the positive charge is delocalized over three carbons. This species may be favored due to the stabilizing effects of the electron donating alkoxy group.[8] The mechanism of a [2+3] cycloaddition reaction is shown in Scheme 2.9. The cycloaddition reaction is initiated by an nucleophilic attack by the alkene at C1. Here it can be seen that an electron donating heteroatom X, such as N or O bonded to the vinylic reagent may be capable of stabilizing a positive charged intermediate.[7,22] Due to the activating properties of the alkoxy group, carbon C3 is activated for cyclization, forming a cyclopentenyl ring. It has been demonstrated that the reaction is stereoselective for the *trans* configuration shown in Scheme 2.9.[4]



Scheme 2.9: [2+3] cycloaddition between propargyl acetal and alkene

2.4 Preparation of propargyl acetals

As explained in the previous sections, propargyl acetals are the key reagent for [2+3] cycloaddition reactions. Propargyl acetals can be synthesized from propargyl alcohols and vinyl alkyl ethers as shown in Scheme 2.10.[8] Both 2-methoxypropene (MOP) and ethyl vinyl ether (EE) are good hydroxy protecting groups. Alcohols protected with MOP and EE can easily be hydrolyzed back to alcohols under mild conditions. Hydroxy protection with EE introduces a stereogenic center, which can complicate purification and characterization.[24]

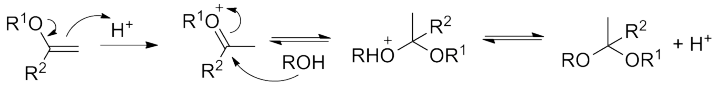


Scheme 2.10: Protection of alcohol

The reaction is acid-catalyzed and both *p*-toluenesulfonic acid (PTSA) or its pyridinium salt pyridinium *p*-toluenesulfonate (PPTS), are frequently used for this purpose. Because of the strong acidity of PTSA, this catalyst is undesired for reactions with acid-sensitive alcohols. Instead, crystalline PPTS, which is a weaker acid than acetic acid, can be used when milder conditions are desired. PPTS has

also been used to catalyze both the protection and deprotection of alcohols with tetrahydropyrans (THP).[25]

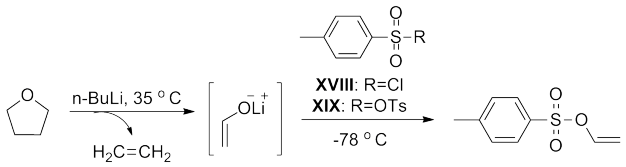
The mechanism for the reaction of vinyl alkyl ethers is shown in Scheme 2.11. The reaction is initiated by a nucleophilic addition of H^+ to the double bond, which gives an oxonium intermediate. A nucleophilic attack by the alcohol provides a protonated acetal, which is in equilibrium with the desired acetal.[24]



Scheme 2.11: Mechanism for acid catalyzed acetal formation

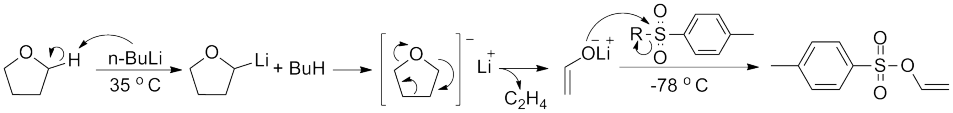
2.5 Preparation of vinyl tosylate

Sulfonates such as tosylates, mesylates and triflates are deactivating groups.[26] Reactions between propargyl esters and deactivating vinylic compounds in the presence of a gold(I) catalyst have lead to cyclopropanation reactions in various studies.[4,27] Vinyl tosylate can be produced by reacting tosyl chloride **XVIII** or anhydride **XIX** with THF treated with *n*-BuLi as shown in Scheme 2.12[28]



Scheme 2.12: Synthesis of vinyl tosylate

The mechanism for this reaction is shown in Scheme 2.13. THF is often used as a solvent for organolithium compounds. THF decomposes when treated with *n*-BuLi. The decomposition is initiated by a directed lithiation of THF, which leads to a collapse of the heterocycle. Ethylene gas and enolate are produced in this step.[29] An electrophile such as tosyl chloride or tosyl anhydride can be attacked by the nucleophilic enolate which gives vinyl tosylate.[24]



Scheme 2.13: Mechanism of the synthesis of vinyl tosylate

2.6 NMR applications

Nuclear Magnetic Resonance (NMR) is a form of absorption spectroscopy. When a sample of a chemical is placed in a magnetic field, it can absorb electromagnetic radiation in the radio frequency (rf). The frequencies that are absorbed are dependent on the chemical structure of the compound.[30] When a nucleus is surrounded by a high electron density, the nucleus is shielded from the applied magnetic field. This gives a lower NMR frequency than for nuclei that possess lower electron density. One dimensional NMR spectra such as ^{1}H and ^{13}C NMR shows the amplitude as a function of the frequency absorbed by the nuclei. Two dimensional NMR spectra such as COSY, NOESY, HSQC and HMBC have two frequency axes. Cross peaks in these spectra indicate interactions between two nuclei which are represented on their respective axis.[31]

When an unknown structure is being elucidated, a normal approach is to begin with searching for scalar coupling between nuclei. These are indirect couplings which are transmitted through chemical bonds.[32] The COSY experiment is homonuclear and shows cross peaks when protons are coupled to each other. The intensity of the cross peak is proportional to the magnitude of the coupling. Both HSQC and HMBC are heteronuclear experiments, and exhibit correlations between ^{1}H and another nuclide such as ^{13}C or ^{15}N.[31] Correlations between proton and carbon across one single bond are identified with the HSQC experiment. This means that the protons directly attached to a carbon can be determined.[32] A HMBC spectrum contains cross peaks from the correlation between proton and carbon which are separated by two or more chemical bonds. This can provide important information, as the location of quarternary carbons can be revealed.[30] By identifying the position of all bonding relationships in the molecule, the structure of a molecule can be elucidated. In many cases, also the stereochemical structure of a molecule has to be exploited. The configuration and conformation of a compound can be determined by studying spatial interactions between protons. This type of interactions are expressed in the cross peaks in a NOESY spectrum.[32] The NOESY experiment reveals how atoms in a molecule may be proximate in space to another atom in the molecule.[31] It is an exceptional tool for determining the 3D structure of a molecule.[32]

2.6.1 Determining the stereochemistry in cyclic structures

Disubstituted cyclopropanes, such as those obtained from gold(I) catalyzed cyclopropanation reactions, have two chirality centers. Thus, four stereoisomers of these products can be expected (Figure 2.6). In one pair of these stereoisomers the substituents are *cis*, while the other pair are *trans*. The pairs are enantiomers, where the pair of *cis* compounds are diastereomers of the *trans* compounds.[21] It is important to be aware of chirality when studying NMR spectra. NMR spectra of two enantiomers in an achiral solvent will be identical. Consequently, of the four possible stereoisomers of cyclopropanes that can be produced in gold(I) catalyzed reactions, only the diastereomers will be distinguishable by NMR. Diastereotopic protons, such as the methylene protons on the disubstituted cyclopropane ring, will appear at different chemical shifts because they are located in different chemical environments.[30]

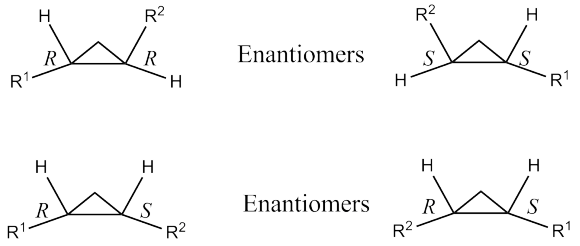


Figure 2.6: Pairs of enantiomers

The magnitude of the scalar coupling between two vicinal protons is dependent on the dihedral angle ϕ between them. The relationship between the coupling between vicinal protons and the dihedral angle can be found in the Karplus correlation plot shown in Figure 2.7.[31] Geminal protons in cyclopropanes have shown couplings around 5 Hz.[31] Vicinal *cis* protons have larger couplings (6-12 Hz) than vicinal *trans* protons (2-9 Hz) in cyclopropanes.[33]

In cyclopentanes, vicinal *cis* protons have shown a coupling of about 8 Hz, while the *trans* protons have shown a coupling of 0 Hz. According to the Karplus correlation, these couplings corresponds to dihedral angles of 0° and 90° respectively. These angles are consistent with those found between vicinal protons in cyclopentanes.[30]

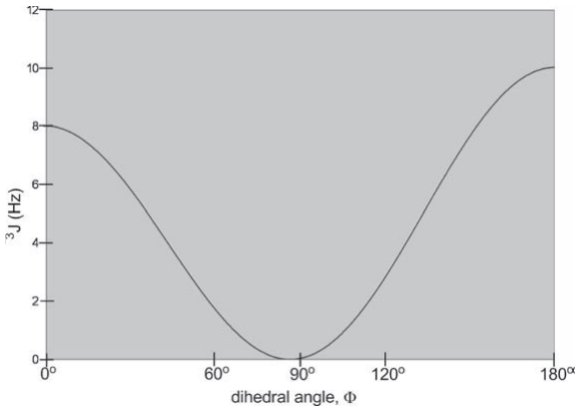
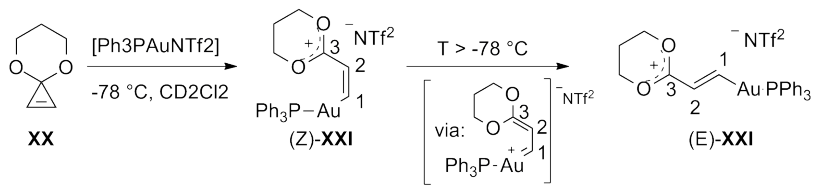


Figure 2.7: The Karplus correlation

2.6.2 NMR studies of a gold complex

As mentioned in Section 2.2, gold catalysis is a relatively new field of study.[2] Several research groups have a focus on studying the "true nature" of gold complexes.[12] The mechanisms proposed for gold catalysed reactions involve intermediates, such as the previously presented compounds **I** - **IV**. The majority of the suggested mechanisms are based on literature studies and proposed mechanisms of similar gold catalysed reactions. Established mechanisms of comparable reactions catalysed by other transition metals, have also been adapted for some gold catalysed reactions. Even though this area is expanding rapidly, the existence of many intermediates in gold catalysis is still not fully proven.[12] Different types of cyclization reactions are based on the formation of a gold carbenoid complex.[4,8,34] Research groups have therefore found it important to attain significant evidence to verify the existence of this complex.[12,35]

Organogold species (*Z*)-**XXI** can be produced by treating acetal **XX** with a gold catalyst with phosphine ligands at -78 °C (Scheme 2.14). The corresponding isomer (*E*)-**XXI** can be generated by raising the temperature slowly.[35] Studies have shown that when two methyl or phenyl groups are replaced with the acetal moiety in compound **XX**, no organogold species are detected. Instead a rapid polymerization is observed.[35]



Scheme 2.14: Organogold(I) species studied by NMR

NMR studies of species (*Z*)-**XXI** and (*E*)-**XXI** have been performed by Fürstner *et al.*[35] They found that these compounds exhibited absorptions in characteristic areas (Fig. 2.8). The chemical shifts (δ) of H1 and H2 of isomer (*Z*)-**XXI** were found to be 9.19 and 6.85 respectively. The chemical shifts of the same protons on isomer (*E*)-**XXI** were found to be 9.71 and 6.51, respectively.[35] Couplings between phosphorous and proton are usually detectable through up to five chemical bonds.[33] Indeed, a coupling between the phosphorous atom and H2 was observed for both isomers. The coupling constants were found to be 13.9 Hz and 6.5 Hz for the (*Z*) and (*E*) isomers respectively.[35]

As shown in Figure 2.8, no broadening of the H signals can be observed with both isomers present in the NMR sample. This indicates that the isomers does not interconvert readily. The slow interconversion may imply that species with double bonds between gold and C1, and C2-C3 are less favorable. Hence, these findings support formation of a gold complex with a delocalized cationic structure, instead of a gold carbenoid intermediate.[35]

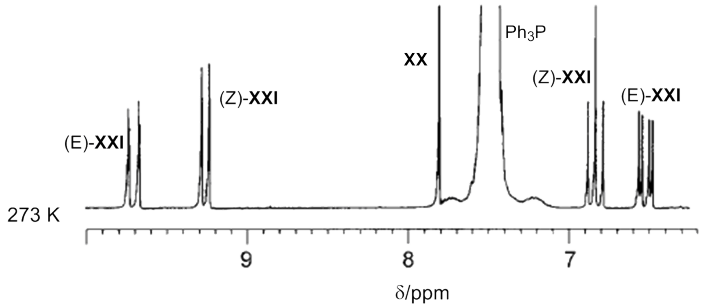
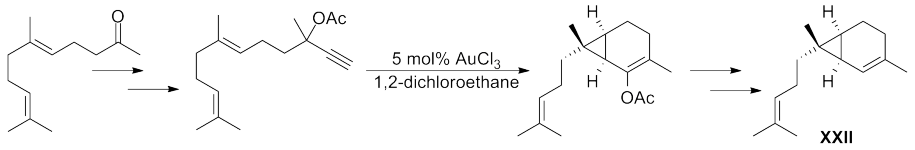


Figure 2.8: ^{1}H NMR of complexes (*Z*)-**XXI** and (*E*)-**XXI**

2.7 Utility of cyclic compounds

Gold(I) catalyzed cycloadditions are efficient and versatile reactions. Complex molecules and polycylic compounds can easily be generated by these reactions.[19] Olefin cyclopropanation reactions catalysed by gold(I) show a great stereospecific control.[4,34] Derivatives of cyclopropanes are of great value in organic synthesis. This is because different types of cyclic and acyclic compounds can be prepared from them.[36] The cyclopropane moiety can be found in several natural products, pharmaceutical drug candidates and insecticides.[37] Gold(I) has been used as a catalyst in the total synthesis of different types of carene terpenoids containing a cyclopropane ring.[16] Sesquicarene is one of the compounds in a pharmaceutical composition for increasing immune function as well as treatment and prevention of cardiovascular disease.[38] The catalyst $AuCl_3$ has been used in the total synthesis of sesquicarene **XXII** as shown in Scheme 2.15. Both the cyclopropane ring and the cyclohexene ring of compound were synthesized in an intramolecular alkene cyclopropanation reaction.[16]



Scheme 2.15: Total synthesis of sesquicarene

Phorbol esters are other cyclopropanes containing diterpenes with health benefits. These compounds are derived from plants and are tumor promoting agents. They have been used for discovering multistage carcinogenesis.[39] The general structure of a phorbol ester analogue is shown in Figure 2.9. It is not unreasonable to believe this type of compounds may be manufactured by gold catalysis in the future.

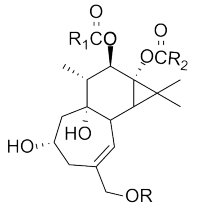


Figure 2.9: Phorbol ester analogue

Chapter 3

Results and Discussion

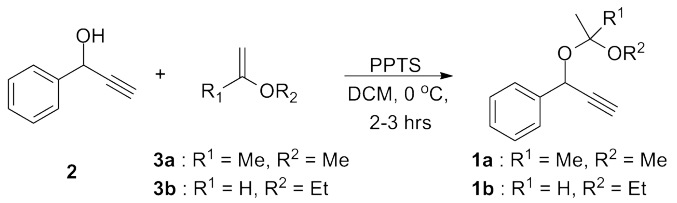
This chapter is divided in four parts. The first part covers the synthesis of starting materials, and is presented in Section 3.1. This part consists of the synthesis of propargyl acetals and vinyl tosylate. The major work is presented in Section 3.2, where details of the gold(I) catalyzed reactions are described. The gold(I) catalyzed reactions include [1+2] cycloaddition reactions and tandem reactions. In the third part, NMR studies of a gold complex are explained and discussed. Finally, suggestions for further development of the project are given in Section 3.4.

New compounds are fully characterized by NMR, MS and IR. The melting points were determined for solids. The structure of the compounds have been confirmed by 1D and 2D NMR, and is presented for all new products in this chapter. The shift values of ^{1}H and ^{13}C are given in blue and red, respectively. The configuration of the isomers were deduced by NOE correlations and J couplings. NOE correlations are shown as black and blue arrows, where blue arrows represent correlations which were essential for determining the configuration. J couplings are shown as red arrows. Literature from R. M. Silverstein[30] and E. Pretsch[33] has been used for the structure elucidation. Experimental data and characterization details of all synthesized products are given in Chapter 5.

3.1 Synthesis of starting materials

3.1.1 Synthesis of propargyl acetals 1a and 1b

Propargyl acetals **1a** and **1b** have earlier been produced and used in gold(I) catalyzed reactions in the research group of Anne Fiksdahl.[10] The acetals were prepared following a known procedure for the synthesis of non-terminal acetals.[8] As shown in Scheme 3.1, acetals **1a** and **1b** were synthesized by treating alcohol **2** with vinyl alkyl ethers **3a** and **3b**, respectively. The reaction mechanism for acid catalyzed acetal formation was explained in Section 2.4.



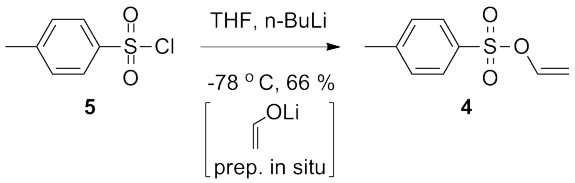
Scheme 3.1: Synthesis of propargyl acetals **1a** and **1b**

The propargyl acetals **1a** and **1b** are unstable and decompose into alcohol **2** and other unknown compounds over time, even when stored in a freezer. Consequently, the acetals had to be synthesized and purified for immediate use in gold(I) catalyzed reactions. Acetal **1a** was isolated as a colourless oil in 74% yield while acetal **1b** was isolated as a yellow oil in 64% yield. The moderate yields may be due to the rapid decomposition. The ^{1}H and ^{13}C NMR shifts and the yields are consistent with literature.[10] Full conversion of alcohol **2** was observed by TLC after 2-3 hours, even though literature suggests to leave the reaction mixture stirring over night.[8]

As explained in Section 2.6.1, diastereotopic protons can be distinguished by NMR. This was observed in the ^{1}H NMR spectrum of acetal **1b**, as the diastereotopic methylene protons appeared as splitted signals at different shift values (Appendix A.3).

3.1.2 Synthesis of vinyl tosylate 4

In Section 2.3.1 and 2.3.2, the function of vinylic compounds in gold(I) catalyzed cycloaddition reactions was explained. By reacting propargyl esters or acetals with vinyl tosylate, the heteroatom sulfur could be incorporated into complex compounds with cyclopropyl and cyclopentenyl rings. Vinyl tosylate is a known compound, and was synthesized following a procedure described by T. Skrydstup *et al.*[28] The reagent was isolated as a colourless oil in 66% yield. The yield and NMR shifts are in accordance with literature.[28]

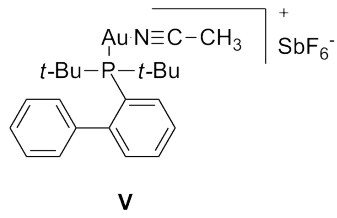


Scheme 3.2: Synthesis of vinyl tosylate **4**

The mechanism for the reaction was described in Section 2.5. An interesting step in this reaction is the *in situ* preparation of lithium enolate by the decomposition of THF with *n*-BuLi. Because of the high reactivity of *n*-BuLi, it was added to THF at 0°C. After the addition, the temperature was slowly elevated to 35°C to promote the formation of the enolate. The colour of the reaction mixture turned from bright yellow to dark red after adding *p*-toluenesunfonyl chloride (**5**). TLC showed full conversion of **5** after 1,5 hrs. The crude which was obtained after work-up had a black colour. However, when loaded on column for flash chromatography, the black material did not elute. This simplified the isolation of the desired product **4**.

3.2 Gold catalyzed reactions

The details and results of all gold(I) catalyzed reactions performed in this study, are given in Table 3.1. The *cis*/*trans* ratios were determined by GLC of the crude reaction mixture. The reactions in entry 5 to 9 were carried out with 3 equivalents of the alkene. The remaining reactions were performed with 2 equivalents of the alkene. (Acetonitrile)[(2-biphenyl)di-tert-butylphosphine]gold(I) hexafluoroantimonate (**V**) was used as a gold(I) catalyst in all the reactions (Fig. 3.1).



V

Figure 3.1: Gold catalyst **V**

Table 3.1: Details of cyclization reactions

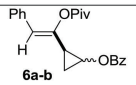
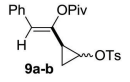
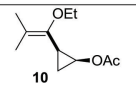
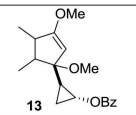
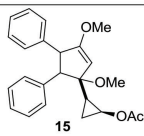
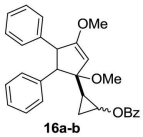
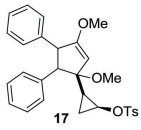
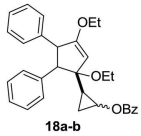
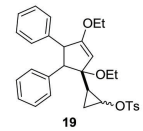
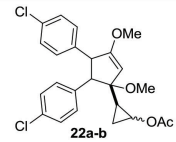
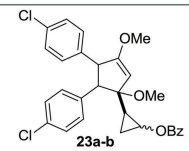
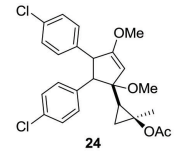
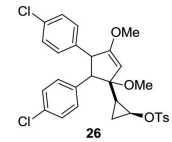
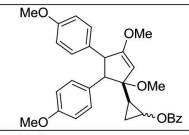
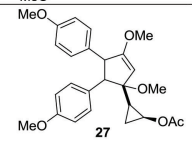
Entry	Product	Rx.	Rx. temp [ºC]	Rx. time [min]	Eluent system for flash chromatography	Ratio *cis/trans*	Yield mg [%] *cis*	*trans*
1	 **6a-b**	i	20	45	pentane, EtoAc 30:1	94:6	77.9 [59]	5.5 [4]
2	 **9a-b**	i	20	19	pentane, EtoAc (gradient) 60:1 → 5:1	63:37	9.2 [6]	4.1 [3]
3	 **10**	i	20	15	pentane, diethyl ether (gradient) 80:1 → 40:1		9.3 [6]	-
4	 **13**	i	0 → 20	30	pentane, diethyl ether 40:1		7.8 [5]	-
5	 **15**	i	15	15	pentane, EtoAc 20:1		16.0 [27]	-
6	 **16a-b**	i	20	25	pentane, EtoAc 20:1		-	-
		ii	0	25	pentane, EtoAc 30:1		8.3 [9]	18.0 [20]
		iii	-30	25	pentane, EtoAc 30:1	55:45	20.1 [24]	11.4 [14]
		iv	-40	20	pentane, DCM 1:1		22.1 [28]	26.8 [34]
7	 **17**	i	20	22	pentane, DCM 1:1		13.7 [13]	-
		ii	-35	15	pentane, EtoAc 15:1		11.7 [12]	-
		iii	-70 → -35	120	pentane, EtoAc (gradient) 50:1 → 30:1		4.5 [5]	-
8	 **18a-b**	i	20	30	pentane, EtoAc 30:1		11.6 (*cis/trans* mix) [22]	
		ii	20	50	pentane, EtoAc 32:1		9.5 (*cis/trans* mix) [11]	
		iii	- 35	120	pentane, DCM 1:1	67:33	79.3 [86]	11.1 [12]
		iv	- 35	90	pentane, DCM 1:1		25.3 [26]	4.3 [4]

Table 3.1 continuation: Details of cyclization reactions

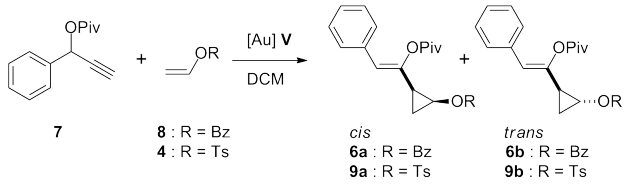
Entry	Product	Rx.	Rx. temp [ºC]	Rx. time [min]	Eluent system for flash chromatography	Ratio *cis/trans*	Yield mg [%] *cis*	*trans*
9	 **19**	i	-45→ -6	90	-		-	-
		ii	-22→ -6	60	-		-	-
10	 **22a-b**	i	20	9	pentane, EtOAc 30:1	75:25	30.1 [41]	11.4 [15]
11	 **23a-b**	i	20	18	pentane, diethyl ether 50:1	61:39	26.4 [28]	15.1 [16]
12	 **24**	i	20	11	pentane, EtOAc 40:1		26.8 (*cis/trans* mix) [34]	
		ii	20	16	pentane, diethyl ether 10:3	73:27	32.5 (*cis/trans* mix) [42] 8.1 [11]	
13	 **26**	i	20	19	pentane, diethyl ether 10:1.5		12.8 [14]	-
		ii	20	15	pentane, diethyl ether 10:0.7		9.8 [11]	-
14		i	20	1440	-		-	-
15	 **27**	i	20	12	pentane, diethyl ether (gradient) 10:1 → 5:1		7.4 [13]	-

3.2.1 Introductory studies

To acquire knowledge and experience with gold(I) catalyzed reactions, experiments were first carried out with a propargylic ester. As presented in Section 2.3.1, propargyl esters tend to provide cyclopropane products through a [1+2] cycloaddition reaction. By performing these reactions, the necessary skills for isolating and distinguishing diastereomers were gained. In addition, a propargyl acetal was tested in a gold(I) catalyzed reaction. As explained in Section 2.3.2, propargyl acetals usually give cyclopentenyl products in [2+3] cycloaddition reactions. The reactions were conducted in small scale, which resulted in a few milligrams of products (Table 3.1). This afforded demanding separations of the diastereomers. Through these introductory studies, essential practical experience and necessary background for NMR studies of complex cyclic structures was gained. Acquiring this knowledge was important for the main studies.

[1+2] cycloaddition reactions with phenyl propargyl ester 7

Gold(I) catalyzed reactions of propargyl esters with alkenes have been studied thoroughly in the research group, but have never been carried out with vinyl benzoate **8** and vinyl tosylate **4**. Pivaloate ester **7** was therefore used in gold(I) catalyzed reactions with these vinyl derivatives, as shown in Scheme 3.3.



Scheme 3.3: Synthesis of products **6a-b** and **9a-b**

The reaction between pivaloate ester **7** and vinyl benzoate **8** was clean and straightforward. The reaction was conducted at room temperature. TLC and GLC showed full conversion of the ester after 45 min. From TLC, it was apparent that only two products had been formed. The products were readily purified and isolated by flash chromatography. The *cis* and *trans* diastereomers **6a** and **6b** were obtained as yellow oils in 59% and 4% yields, respectively. By GLC, the *cis*:*trans* ratio was found to be 94:6 in favor of the *cis* isomer (Appendix E.15). (Table 3.1, entry 1 rx. i).

According to the stereochemical models suggested by Toste *et al.*,[23] which was presented in Section 2.3.1, the *cis* isomer is favored in [1+2] cycloaddition reactions. The observed results in this reaction are consistent with this model. The significant difference of the substituents of vinyl benzoate may contribute to the observed selectivity of the *cis* isomer.

The configuration of the *cis*/*trans* diastereomers was determined based on the NOESY experiment. The chemical shifts and NOE correlations are shown in Figure 3.2 for *cis* product **6a**, and in Figure 3.3 for *trans* product **6b**. The NOE correlations that were crucial for identifying the stereochemistry are shown as blue arrows. The chemical shifts are assigned by NMR spectroscopy (Appendix E).

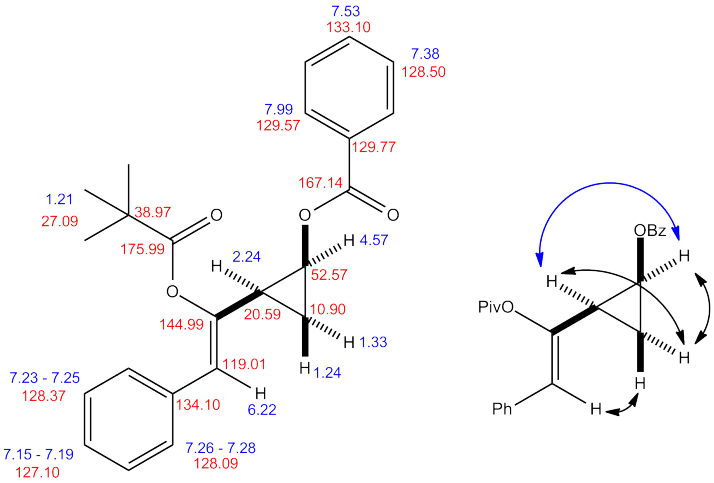


Figure 3.2: Chemical shifts and NOE correlations of *cis* compound **6a**

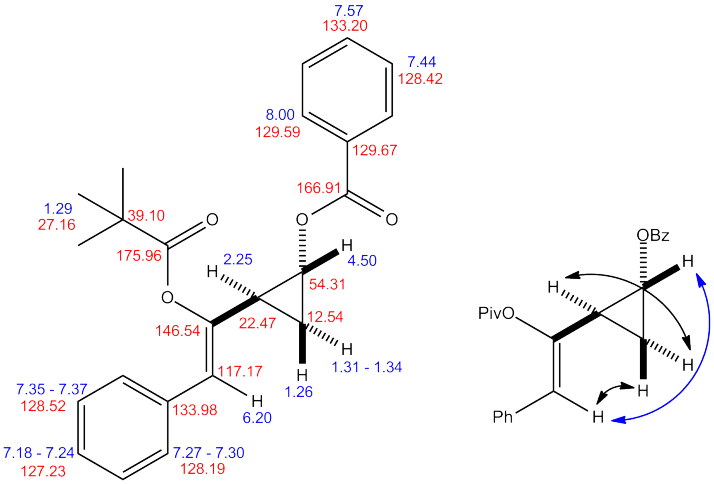


Figure 3.3: Chemical shifts and NOE correlations of *trans* compound **6b**

Replacing vinyl benzoate with vinyl tosylate led to a decrease in both isolated yields and stereoselectivity. Products **9a-b** were synthesized in a similar manner as products **6a-b**. The colour of the reaction mixture slowly changed from colourless to dark orange. TLC indicated full conversion of the starting material after 19 min. In contrast to the previously described reaction, TLC showed formation of seven products. The *cis*/*trans* diastereomers **9a** and **9b** were purified and isolated as yellow oils in 6% and 3% yields, respectively. The decrease in yield may be due to decomposition of the product during purification. GLC of the crude showed a selectivity of the *cis* isomer, and the *cis*/*trans* ratio was found to be 63:37 (Appendix F.15). (Table 3.1, entry 2, rx.i).

The chemical shifts are assigned by NMR spectroscopy (Appendix F). The *cis*/*trans* configuration of the isolated products was determined based on the NOESY experiment. Figures 3.4 and 3.5 show the chemical shifts and NOE correlations of compound **9a** and **9b** respectively. The NOE correlations that were crucial for identifying the stereochemistry are represented as blue arrows.

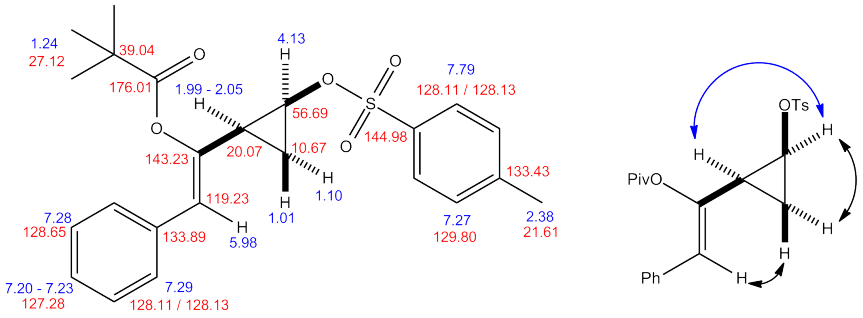


Figure 3.4: Chemical shifts and NOE correlations of *cis* compound **9a**

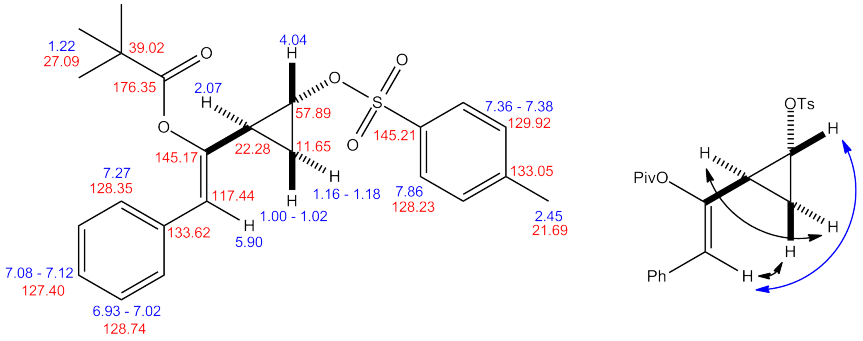
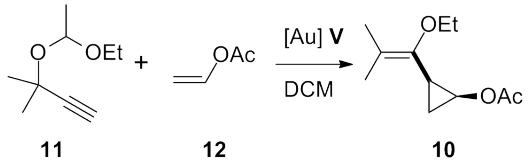


Figure 3.5: Chemical shifts and NOE correlations of *trans* compound **9b**

[1+2] cycloaddition reaction with aliphatic acetal 11

While the gold carbenoid species generated from propargyl esters have deactivating properties, the gold carbenoid species formed from propargyl acetals posses activating properties.[8] As a result, a higher reactivity of propargyl acetals was expected. To compare the two propargylic species, aliphatic propargyl acetal **11** was treated with vinyl acetate **12** in presence of gold catalyst **V** (Scheme 3.4).



Scheme 3.4: Synthesis of product **10**

As explained in Section 2.3.2, previous studies have shown that cyclopentenyl products are formed from propargyl acetals. This is due to the activating properties of the alkoxy group, which promotes a [2+3] cycloaddition reaction. An unexpected result was observed in this reaction, as no cyclopentenyl product was formed. Instead, a [1+2] cycloaddition reaction had taken place. The reaction was carried out at room temperature and the colour changed slowly from colourless to orange upon addition of the reagents. The reaction was monitored by TLC which showed full conversion of **11** after 15 min, which indeed was faster than the ester analogues. TLC indicated formation of six products during this reaction. Product **10** was purified and isolated as a colourless oil, in 6% yield. No traces of the *trans* isomer was observed. The ^{1}H and ^{13}C NMR shifts are consistent with earlier results.[11] (Table 3.1, entry 3 rx i).

Reactions with dimethyl propargyl acetal **11** and different trapping agents had previously been conducted in the research group.[11] These experiments had also generated cyclopropyl products. It can be thought that the [2+3] cycloaddition reaction is disfavoured, due to the two bulky methyl groups of acetal **11**. As shown in Figure 3.6, the steric effect caused by the methyl groups hinders the cyclization to take place at C3.

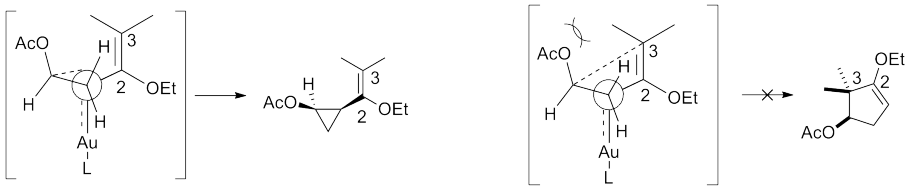
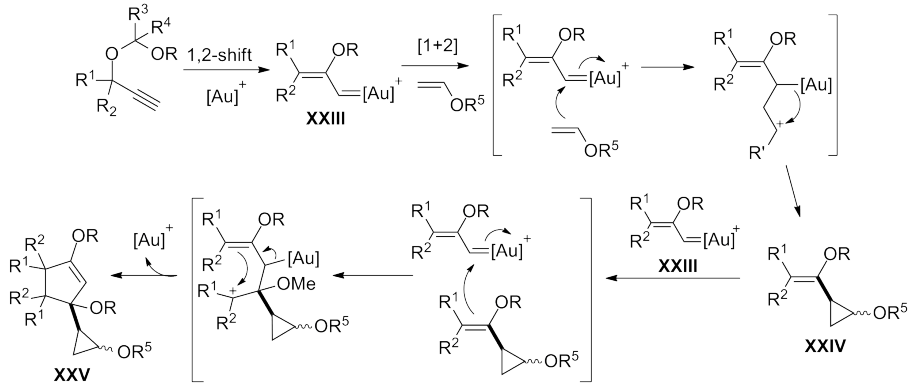


Figure 3.6: Steric effects may hinder the [2+3] cycloaddition reaction

3.2.2 Tandem cyclization reactions

Recently, a novel gold(I) catalyzed tandem cyclization reaction was discovered in the research group of Anne Fiksdahl. It was found that this reaction takes place betweeen two propargyl acetal units and one olefinic ester, in the presence of Au(I). The proposed mechanism is shown in Scheme 3.5. The first step is a 1,2-migration of the gold activated propargyl acetal, which was explained in Section 2.3 and 2.3.2. This leads to the formation of a gold carbenoid species **XXIII**, which can react with a moderately deactivating alkene. The deactivating olefinic ester promotes formation of a cyclopropane species **XXIV** instead of a cyclopentene species, which would be expected for reactions with propargyl acetals. This shows that the electronic nature of the alkene can be varied to change the outcome of gold(I) catalysed reactions. The mechanism of this step is similar to the formal [1+2] reaction which was presented in Section 2.3.1. In contrast to cyclopropyl products formed from propargyl esters, the alkoxy group of intermediate **XXIV** causes a higher reactivity of this species. Thus, instead of being a final product in the reaction, compound **XXIV** can play the role of a reactive intermediate, giving rise to a new reaction pathway. Indeed, the activating properties of both the intermediate **XXIV** and another gold carbenoid species **XXIII**, favours a [2+3] cycloaddition reaction. The mechanism of the cyclopentenylation reaction is analogous to the mechanism shown in Section 2.3.2. The tandem sequence generates a complex molecule **XXV**, which contains both a cyclopentene and a cyclopropane moiety.



Scheme 3.5: Proposed mechanism for tandem cycloaddition reaction

As explained in Section 2.3.1 and 2.3.2, formal [1+2] and [2+3] cycloaddition reactions are initiated by an attack of the terminal carbon of the alkene, at the carbenoid. The terminal carbon is situated two bonds away from the heteroatom, and the intermediate is capable of stabilizing a cationic charge. In contrast to [1+2] and [2+3] cycloaddition reactions, the second cyclization in the tandem reaction takes place between the carbon directly attached to the alkoxy group of alkene species **XXIV**, and the carbenoid (Scheme 3.5). The inversion in regioselectivity of the alkene may be due to a stabilizing contribution of substituents R^1 and R^2.

This new tandem cyclization should actually allow a third reaction pathway for the gold(I) catalyzed reaction with bulky aliphatic acetal **11** and vinyl acetate **12**, which was presented in Section 3.2.1. According to the previous discussion, these substrates are expected to favour the tandem cyclization mechanism due to the activating properties of the ethoxy group. A possible explanation of why cyclopropyl product **10** does not react in an additional [2+3] cycloaddition reaction can be the steric effects caused by both the cyclopropyl intermediate and the propargyl gold complex. It can be seen from Scheme 3.5 that the second cyclization requires that cyclopropyl intermediate **XXIV** approaches gold carbenoid species **XXIII**. Due to the bulkiness of the two methyl groups attached to both reacting species, this approach is disfavoured (Figure 3.7).

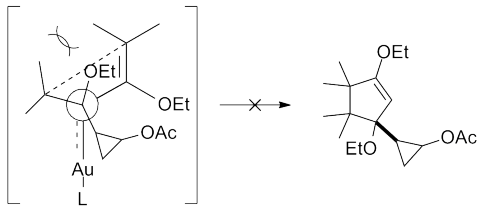


Figure 3.7: Steric effects may hinder the tandem cyclization reaction

As mentioned earlier, gold(I) catalyzed reactions with propargyl esters have been studied thoroughly. Propargyl acetals on the other hand, have been studied to a lesser extent. In order to obtain a comprehensive study of propargyl acetals in tandem reaction, experiments were conducted with different olefinic esters. In addition, the electronic nature of propargylic acetals was varied to explore its effect on the reaction.

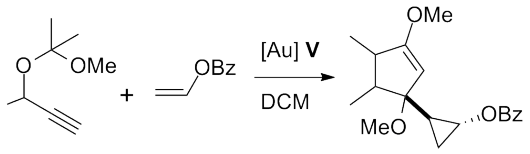
In the majority of the reactions, two diastereomers were generated due to formation of two or more chiral centres. Even though there are more than two chiral centers in the molecules, it was assumed that the stereochemistry was controlled by the substituents of the cyclopropane ring. The NOESY experiment was the main tool for determining the configuration of the diastereomers. All cyclopropyl protons in both the *cis* and *trans* diastereomers showed NOE correlations to one other. This was observed even for vicinal *trans* protons in the cyclopropyl ring. The final determination was therefore based on the presence or absence of NOE correlations between the cyclopropyl protons, and the protons in the cyclopentene ring. The NOE correlations that clearly distinguish one diastereomer from the other are shown as blue arrows. NOE correlations that support a certain configuration are shown as black arrows. The configuration of the diastereotopic cyclopropyl protons was based on NOE correlations in black colour, as well as J couplings.

A selectivity of the *cis* isomer was observed in all reactions where both isomers were isolated. The *cis* selectivity is in accordance with the stereochemical models suggested by Toste *et al.*[23] The results obtained in this research confirm previously reported *cis* selectivity in [1+2] cycloaddition reactions.[4]

As explained, coupling constants (J) and the NOESY experiment were utilized for determination of the stereochemistry of the diastereomers. In Section 2.6.1, it was explained that vicinal *trans* protons in cyclopentenyls have a coupling of 0 Hz. It was assumed that vicinal *trans* protons in a cyclopentene ring would also have small coupling constants, even though cyclopentene rings are less flexible than cyclopentenyls. The coupling constants of the vicinal protons in the cyclopentene ring of all products produced by the tandem cyclization, were less than 1.5 Hz. It was therefore assumed that the two vicinal protons in the cyclopentene ring were in a *trans* configuration for all products. As explained in Section 2.3.2, it has previously been observed stereoselective *trans* formation of cyclopentenyls by a [2+3] cycloaddition pathway. Common for all these cyclopentenyls was that they were disubstituted, having only two chiral centres. In contrast to such monocyclization reactions, the tandem pathway incorporates three chiral centres in the cyclopentene ring. Two of these chiral centres are introduced by the non-terminal alkene species **XXIV** from Scheme 3.5. Although multiple chiral centres in a compound could result in various diastereomers, only one cyclopentene configuration was observed in these studies. This supports the assumption that the stereochemistry of the two diastereomers was controlled by the the substituents of the cyclopropane ring alone. Due to the complexity of the NOESY spectra, it was not possible to determine the configuration of the cyclopentene ring. This aspect of the tandem cyclization pathway will be further studied.

Tandem cyclization reaction with aliphatic propargyl acetal 14

As a continuation of studying gold(I) catalyzed reactions with aliphatic propargylic acetals, acetal **14** was reacted with vinyl benzoate **8**, as shown in Scheme 3.6. Being comparable to the aliphatic acetal **11**, but without having a steric bulk, it was interesting to explore if acetal **14** would react by the new tandem cyclization pathway.



Scheme 3.6: Synthesis of product **13**

Indeed, a bicyclic product was formed in this reaction. This confirms that propargyl acetals generate highly reactive cyclopropyl compound of type **XXIV**, which are activated a second cyclization reaction. The substrates were added at 0°C, and the colour of the reaction mixture gradually turned from colourless to orange as the temperature reached 20°C. The reaction was monitored by TLC, which indicated full conversion of **14** after 30 min. Although the reaction was started at low temperature, several products were formed. The products had overlapping R_f values, as shown in Figure 3.8, and there was no major product. Product **13** was isolated as a gray oil in 5% yield. No traces of the *cis* isomer were detected. (Table 3.1, entry 4, rx i).

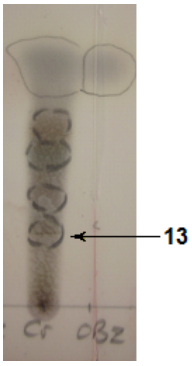


Figure 3.8: TLC in 10:3 pentane, diethyl ether

The chemical shifts are assigned by NMR spectroscopy (Appendix H). The *trans* configuration of product **13** was determined by NOE correlations. The chemical shifts and the NOE correlations of product **13**, are shown in Figure 3.9.

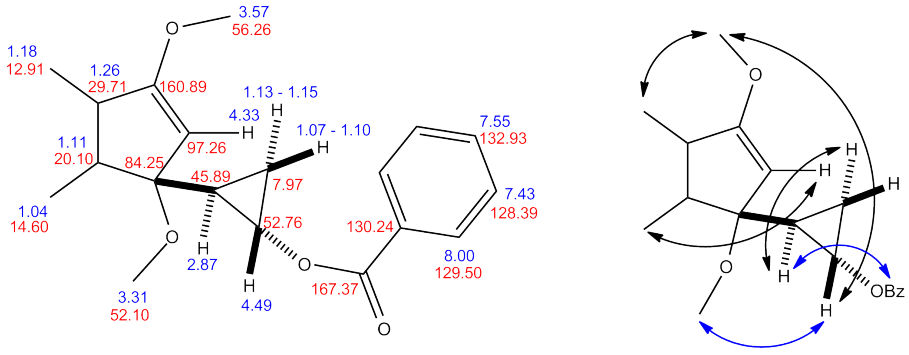
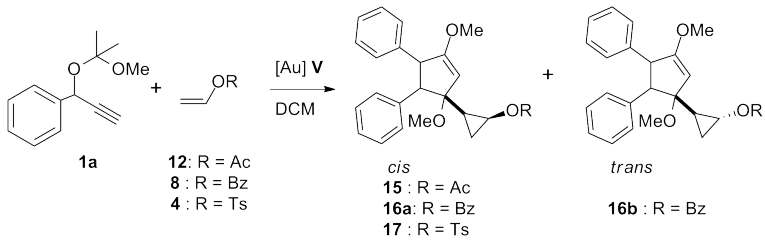


Figure 3.9: Chemical shifts and NOE correlations of *trans* compound **13**

Tandem cyclization reactions with phenyl propargyl acetal 1a and 1b

After testing gold(I) catalyzed reactions with aliphatic acetal **14**, it was desired to run the reaction with aromatic propargylic acetals. It was assumed that an aromatic group would increase the stability of the cationic intermediate formed during the second cyclization. Hence, with an alkoxy group activating cyclopropyl species **XXIV** for further cyclization, as well as increased stability of the carbocationic intermediate, the novel tandem cyclization would be promoted to a greater extent, which may lead to higher yields.

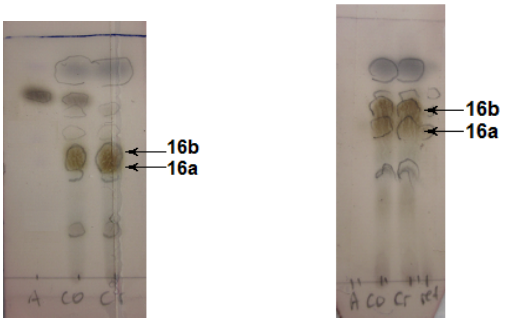
The tandem reaction with propargyl acetal **1a** was carried out with each of the alkenes **12**, **8** and **4** as shown in Scheme 3.7.



Scheme 3.7: Synthesis of products **15**, **16a-b** and **17**

As expected, the isolated yield increased when acetal **1a** was reacted with vinyl acetate **12**. The colour changed from colourless to bright yellow upon the addition of the reagents to the gold catalyst. By TLC it was found that the reaction was finished after 15 min at room temperature. Product **15** was isolated as a yellow oil in 27% yield. Product **15** has previously been synthesized in the research group, but has not been reported in literature.[11] The ^{1}H and ^{13}C NMR shifts are consistent with earlier results.[11] (Table 3.1, entry 5, rx. i).

The reaction of **1a** and vinyl benzoate **8** was conducted at room temperature, 0°C, -30°C and -40°C. The reaction at room temperature was unsuccessful (Table 3.1, entry 6, rx. i). Several products were formed, but the characteristic peaks of cyclopropane were absent in the ^{1}H spectra of these. It was believed that the reaction would proceed cleaner, with less formation of by-products, at lower temperatures. Reactions at 0°C, -30°C and -40°C were successful, but the purification of the diastereomers **16a-b** was challenging (Table 3.1, entry 6, rx. ii-iv). As seen in Figure 3.10a, the retention times of the diastereomers were very similar. During the purification on column, several fractions contained mixtures of the isomers. This resulted in moderate yields. It was found that the difference in retention times of the isomers were slightly increased with a different eluent system (Fig. 3.10b). The isomers were readily purified and isolated with the new eluent system. Product **16a** was obtained as a white solid in 28% yield. Product **16b** was obtained as a yellow oil in 34% yield. A *cis*/*trans* ratio of 55:45 was observed by GLC (Appendix J.15).



(a) TLC in 10:1 pentane, EtOAc

(b) TLC in 100% DCM

Figure 3.10: Similar retention times of the diastereomers **16a-b**

The chemical shifts of both compounds are assigned by NMR (Appendix J), and are shown in Figures 3.11 and 3.13. The stereochemistry of the *cis* and *trans* isomers were deduced by J couplings and the NOESY experiment. Scalar couplings are indicated with red arrows. The characteristic NOE correlations and J couplings are shown in figure 3.12 and 3.14. J coupling 1 in Figure 3.12 was 4.2 Hz, which is expected for vicinal *trans* protons in cyclopropanes. J coupling 2 was 10.1 Hz, which is expected for vicinal *cis* protons.

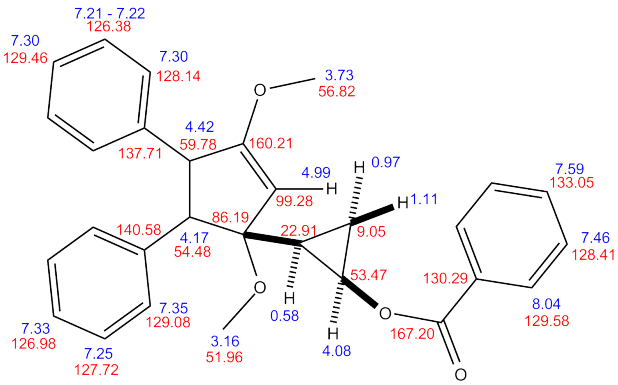


Figure 3.11: Chemical shifts of *cis* product **16a**

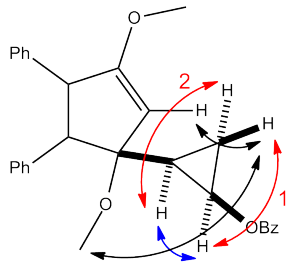


Figure 3.12: NOE correlations and J couplings for *cis* product **16a**

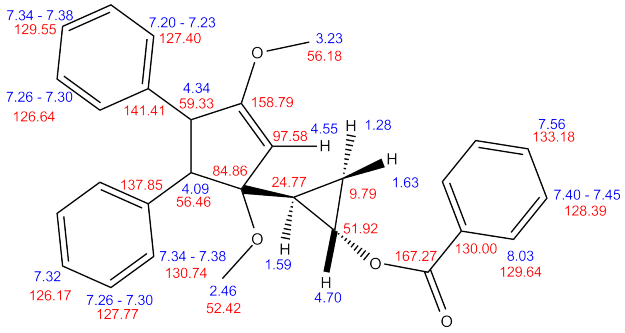


Figure 3.13: Chemical shifts of *trans* product **16b**

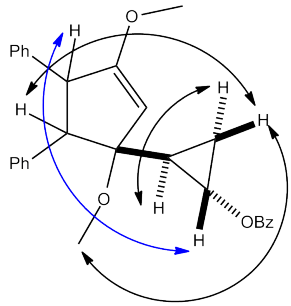


Figure 3.14: NOE correlations for *trans* product **16b**

The reaction between propargyl acetal **1a** and vinyl tosylate **4** was carried out at room temperature, -35°C and -70°C (Table 3.1, entry 7, rx i-iii). In the two first reactions, the colour changed from colourless to brown when the reagents were added to the catalyst. These reactions were finished quickly. The last reaction went rather slowly compared to the two other, and the temperature was carefully increased to -35°C. This reaction was finished after 2 hrs. The reaction at room temperature gave the highest yield of compound **17** (13%), which was isolated as a yellow oil. Due to the tailing effect of vinyl tosylate **4**, purification of the product was challenging in this experiment. This contributed to the moderate yield.

The chemical shifts of product **17** are assigned by NMR (Appendix K). The *cis* configuration of product **17** was based on the NOESY experiment. The chemical shifts, J couplings and NOE correlations are shown in Figures 3.15 and 3.16. J coupling 1 in Figure 3.16 was found to be 10.2 Hz, which corresponds to a *cis* configuration.

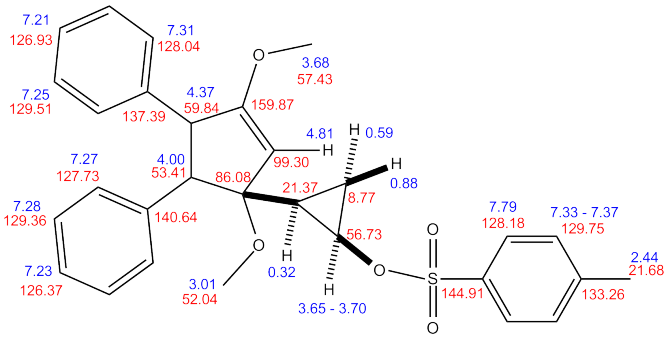


Figure 3.15: Chemical shifts of *cis* compound **17**

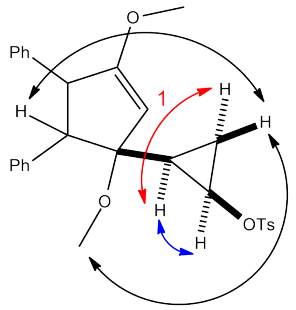
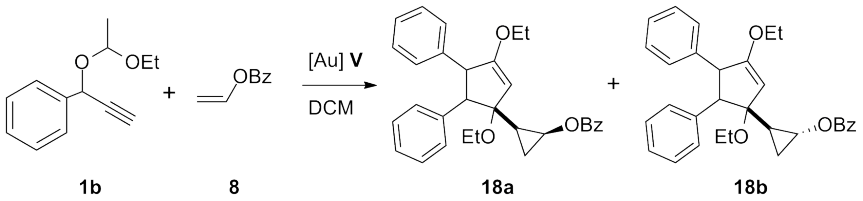


Figure 3.16: NOE correlations and J couplings of *cis* compound **17**

The tandem reaction was repeated with propargyl acetal **1b** and vinyl benzoate **8**, as shown in Scheme 3.8. The reaction was run at room temperature and -35°C (Table 3.1, entry 8, rx. i-iv).



Scheme 3.8: Synthesis of products **18a-b**

At both temperatures, the colour changed from colourless to bright yellow upon addition of the reagents. The reactions were monitored by TLC and GLC. At room temperature, the reaction was slower than the corresponding reaction with acetal **1a**. TLC indicated full conversion of **1b** after 30 and 50 min in the two attempts at room temperature. The reactions at -35°C were naturally slower, and were finished after 1.5 and 2 hrs. By TLC it was found that less by-products were formed at lower temperature. Indeed, the total yields of the two diastereomers increased when the reaction was run at -35°C. Also in this case, the purification of the two diastereomers was challenging because of close R_f values. Several purification attempts resulted in mixtures of the diastereomers. Finally, an eluent system was discovered where the two diastereomers had slightly different retention times (Figure 3.17).

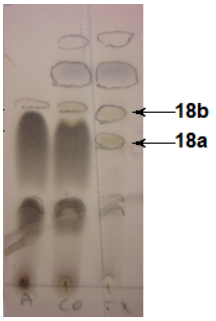


Figure 3.17: TLC in 100% DCM

Separation with the new eluent system afforded products **18a** and **18b** as yellow oils in 86% and 12% yields, respectively. A *cis*/*trans* ratio of 67:33 was observed by GLC of the crude (Appendix L.15). The configuration of the isomers was determined by J couplings and NOE correlations. The chemical shifts were assigned by NMR (Appendix L). The chemical shifts of *cis* product **18a** and *trans* product **18b** are given in Figure 3.18 and 3.20, respectively. NOE correlations and J couplings are shown in Figure 3.19 and 3.21. J coupling 1 in Figure 3.19 was 10.0 Hz, which is expected for a *cis* configuration.

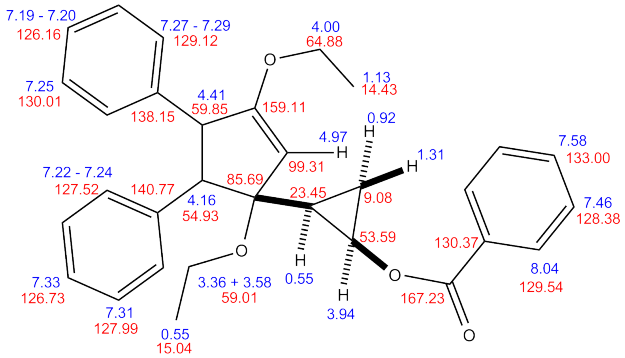


Figure 3.18: Chemical shifts of *cis* compound **18a**

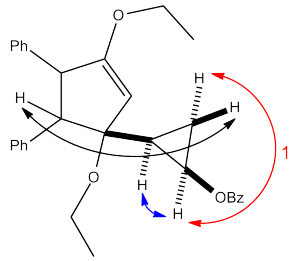


Figure 3.19: NOE correlations and J couplings of *cis* compound **18a**

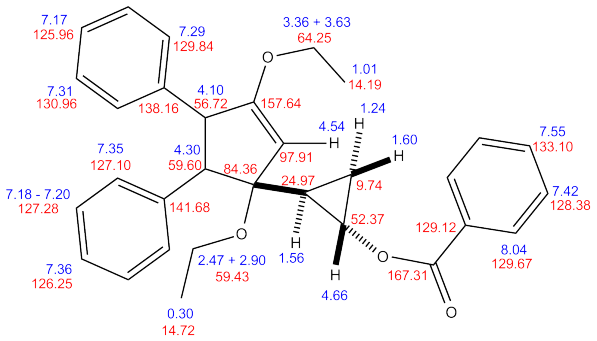
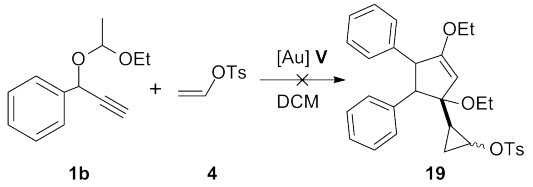


Figure 3.20: Chemical shifts of *trans* compound **18b**

Figure 3.21: NOE correlations of *trans* compound **18b**

An attempt to synthesize compound **19** from propargyl acetal **1b** and vinyl tosylate **4** failed, as shown in Scheme 3.9. (Table 3.1, entry 9, rx. i-ii).



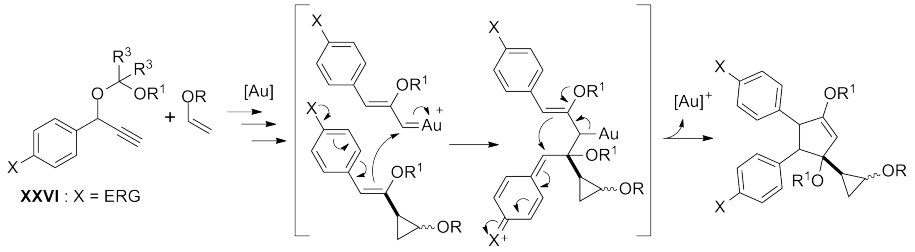
Scheme 3.9: Attempted synthesis of **19**

The reaction was carried out with starting temperatures of -45°C and -22°C. The temperature was slowly increased to -6°C. At both temperatures, a rapid colour change was observed. Two major spots appeared on the TLC plate during the reaction, and full conversion of **1b** was observed after 1 - 1.5 hrs. The crude obtained after work-up was black. Unexpectedly, the spots on TLC vanished after work-up. As this happened in both cases, the experiment was aborted. A possible explanation for this outcome may be decomposition of the products during work-up.

The successful reactions with phenyl propargyl acetals **1a** and **1b** supported the assumption that substituents capable of stabilizing cationic charge would favour the new tandem reaction pathway. This was observed by two different aspects. The first aspect is the increase in isolated yields. This shows that less by-products are formed, and the tandem cyclization pathway is favoured to a greater extent than for aliphatic acetals. The second aspect is the formation of two diastereomers. This indicates that the second cyclization is highly accessible for both isomers due to the activation caused by the alkoxy group.

Tandem cyclization reactions with phenyl propargyl acetals 20 and 21

Being aromatic, the propargyl acetals **1a** and **1b** could easily stabilize a cationic intermediate formed during the second cyclization in the tandem reaction, which was shown in Scheme 3.5. As a continuation, it was interesting to study reactions with modified aromatic propargyl acetals, with *para*-substituted electron releasing groups (ERG). It was assumed that the propargyl acetals of type **XXVI**, shown in Scheme 3.10, would give rise to an even more reactive cyclopropyl intermediate. This intermediate would not only would stabilize the cationic intermediate well, it would also promote the second step of the tandem reaction to a greater extent. This cyclopropyl intermediate would be activated by both the ERG substituent, as well as the alkoxy group. In turn, this could lead to better yields.



Scheme 3.10: Proposed mechanism of the second cyclization of the tandem reaction

The acetals **20** and **21**, shown in Figure 3.22, were therefore synthesized by students in the research group.

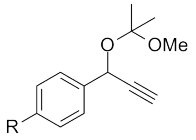


Figure 3.22: Propargyl acetals **20** and **21**

The acetals were characterized by NMR, MS and IR in this project (Appendix B and C). The chemical shifts of acetal **20** and **21** are shown in Figure 3.23.

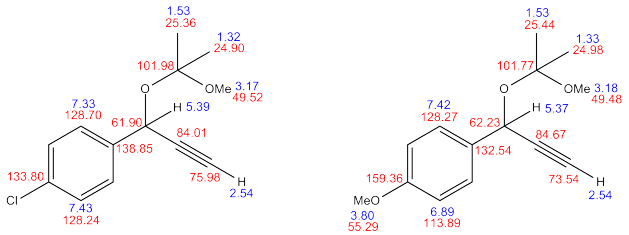
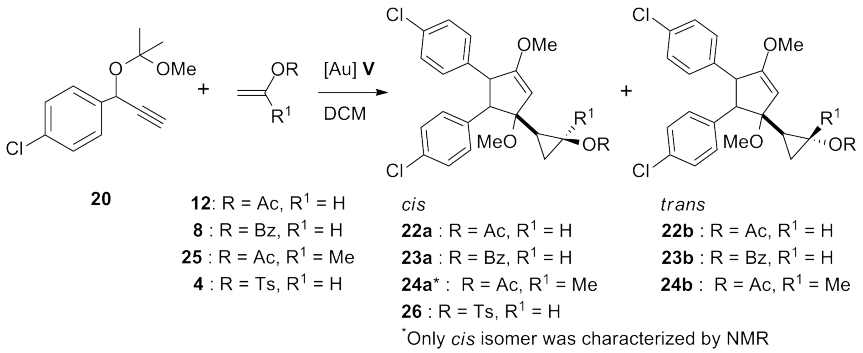


Figure 3.23: Chemical shifts of acetal **20** and **21**

The tandem cyclization reaction with propargyl acetal **20** was carried out with each of the alkenes **12**, **8**, **25** and **4**, as shown in Scheme 3.11. All reactions were run at room temperature.



Scheme 3.11: Synthesis of products **22a-b**, **23a-b**, **24a-b** and **26**

The reaction between propargyl acetal **20** and vinyl acetate **12** was fast compared to reactions with propargyl acetal **1a** and **1b** at similar conditions, which implied a higher reactivity. TLC showed full conversion of propargyl acetal **20** after 9 minutes. The colour of the reaction instantly went from colourless to yellow when the reagents were added. Two major products with comparable R_f values were formed (Figure 3.24). The two diastereomers were isolated relatively easy with flash chromatography, as yellow waxes. The yields of products **22a** and **22b** were 41% and 15% respectively. A *cis*/*trans* ratio of 75:25 was observed by GLC (Appendix M.15). (Table 3.1, entry 10, rx. i).

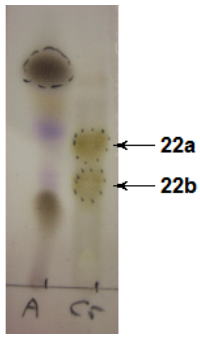


Figure 3.24: TLC in 10:2 Pentane, EtOAc

The chemical shifts of the isomers are assigned by NMR (Appendix M), and are shown in Figures 3.25 and 3.27. The stereochemistry of the diastereomeric products was determined by J couplings and the NOESY experiment. Characteristic NOE correlations and J couplings are shown in figure 3.26 and 3.28. J coupling 1 in Figure 3.26 was 10.0 Hz, which confirms a *cis* configuration between the indicated protons. J coupling 1 in Figure 3.28 was 7.3 Hz, which corresponds to a *trans* configuration.

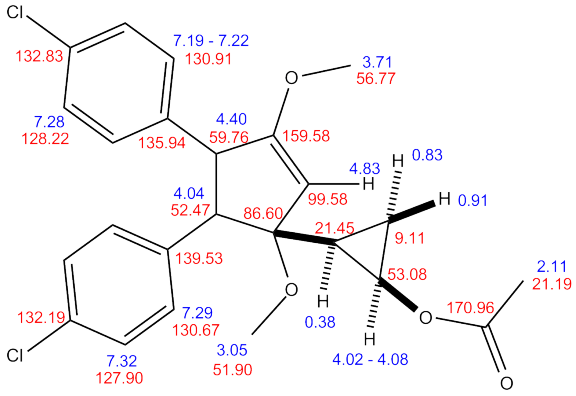


Figure 3.25: Chemical shifts of *cis* compound **22a**

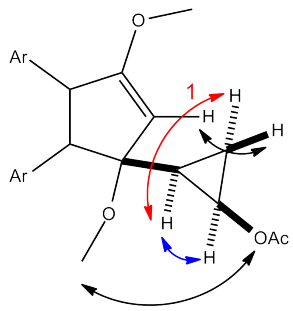


Figure 3.26: NOE correlations and J couplings for *cis* product **22a**

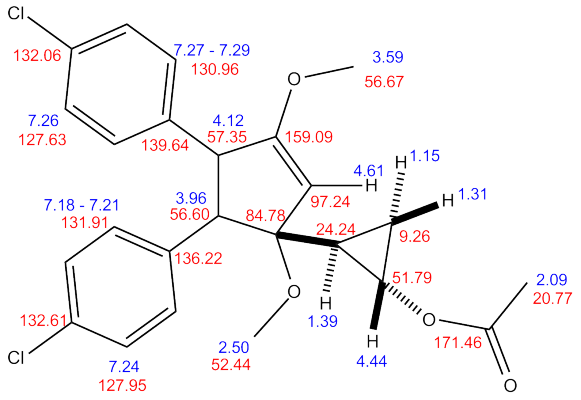


Figure 3.27: Chemical shifts of *trans* compound **22b**

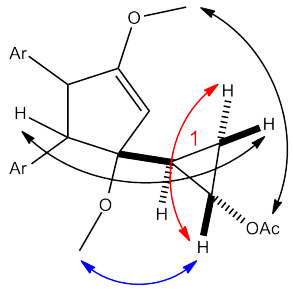


Figure 3.28: NOE correlations and J couplings for *trans* product **22b**

The isomers **23a-b** were synthesized in a similar manner as products **22a-b**. An immediate colour change from colourless to light brown was observed after adding the reagents to the gold(I) catalyst. As shown in Figure 3.29, two major products with similar R_f values were formed by the reaction. Product **23a** was isolated as a white oil in 28% yield. Product **23b** were isolated as a yellow oil in 16% yield. A *cis*/*trans* ratio of 61:39 was observed by GLC (Appendix N.15). (Table 3.1, entry 11, rx. i).

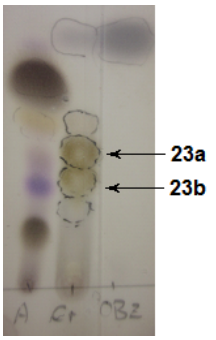


Figure 3.29: TLC in 10:2 pentane, diethyl ether

The chemical shifts of product **23a** and **23b** are assigned by NMR (Appendix N), and are shown in Figure 3.30 and 3.32. The configuration of the cyclopropyl protons in the *cis*/*trans* isomers was deduced by J couplings and the NOESY experiment. Characteristic NOE correlations and J couplings are shown in figure 3.31 and 3.33. J coupling 1 in Figure 3.31 was found to be 10.0 Hz, which supports a *cis* configuration. J coupling 2 was 4.2 Hz and indicated vicinal *trans* protons.

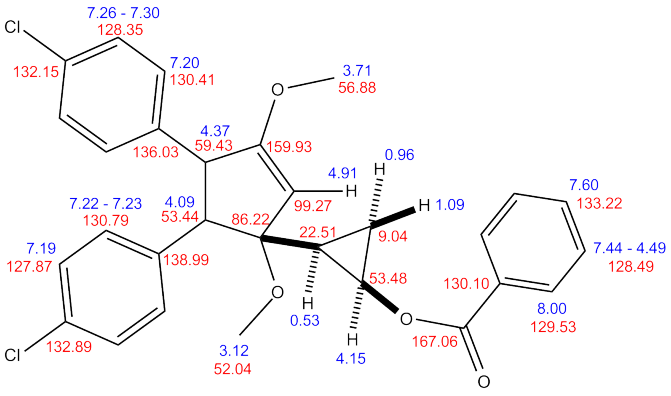


Figure 3.30: Chemical shifts of *cis* compound **23a**

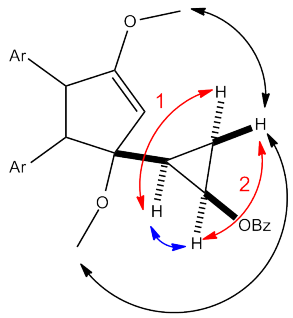


Figure 3.31: NOE correlations and J couplings for *cis* product **23a**

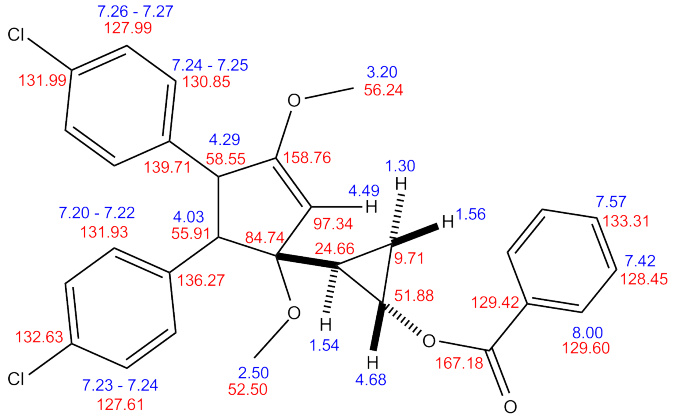


Figure 3.32: Chemical shifts of *trans* compound **23b**

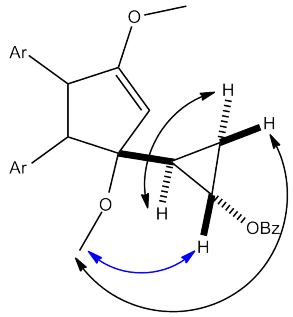


Figure 3.33: NOE correlations for *trans* product **23b**

The reaction between acetal **20** and isopentenyl acetate **25** afforded two major products with close R_f values (Figure 3.34). The colour changed immediately from colourless to light brown upon addition of the reagents to the gold(I) catalyst. Separation of the two main products was difficult as they eluted together. Different eluent systems were tried for the separation. ^{1}H and ^{13}C spectra of a purified mixture of the two products indicated that they were isomers (Appendix O.1 and O.2). The ^{13}C spectrum showed two peaks at 97.29 and 98.52 ppm, which correspond to the olefinic carbons in the cyclopentene ring of each of the isomers. Two peaks at 85.05 and 86.22 ppm belonged the quaternary carbons directly attached to the cyclopropane moiety. The peaks at 170.23 and 170.19 could be the ester carbon in each of the isomers. HRMS was obtained for the product mixture, which confirmed that they were isomers.

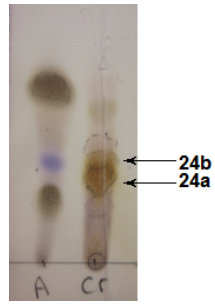


Figure 3.34: TLC in 10:3 pentane, diethyl ether

An amount of *cis* isomer **24a** was separated from a mixture of both isomers, which made it possible to characterize this product. *Cis* compound **24a** was isolated in 11% yield, and the remaining *cis*/*trans* mixture was isolated in 42% yield. The ^{1}H spectrum of the mixture was complex, and had several overlapping peaks. It was therefore not possible to assign the ^{1}H and ^{13}C NMR shifts of product **24b**. By GLC, the *cis*:*trans* ratio was found to be 73:27 (Appendix O.10). (Table 3.1, entry 12, rx. i-ii).

Based on NOE correlations, the *cis* configuration of product **24a** was determined. The chemical shifts of compound **24a** are assigned by NMR spectroscopy (Appendix O.9), and are given inn Figure 3.35. Characteristic NOE couplings are shown in Figure 3.36.

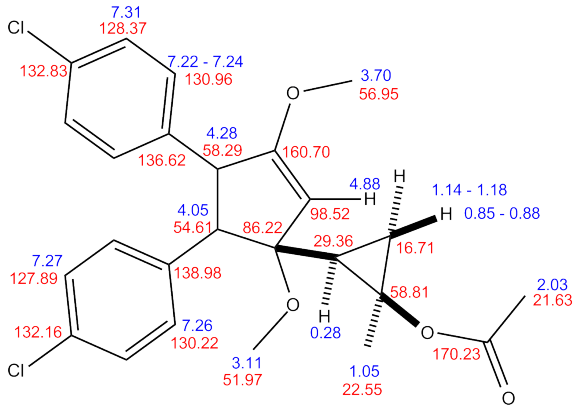


Figure 3.35: Chemical shifts of *cis* compound **24a**

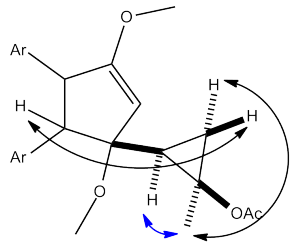


Figure 3.36: NOE correlations for *cis* product **24a**

The gold(I) catalyzed reaction between acetal **20** and vinyl tosylate **4** generated several products. The reaction immediately turned dark red when the reagents were added to the catalyst. TLC of the reaction mixture showed five weak spots. The purification and isolation of compound **26** was particularly difficult as it eluted together with other compounds. Different eluent system were tried, with the same result. Because of this problem, HRMS was not obtained for this product. A mix of compound **26** and by-products was obtained as a yellow oil, in 14% yield. (Table 3.1, entry 13, rx. i-ii).

The chemical shifts of compound **26** were assigned by NMR (Appendix P), and are shown in Figure 3.37. The *cis* configuration of product **26** was deduced by the NOESY experiment and J couplings, and are shown in Figure 3.38. J coupling 1 in Figure 3.38 is 10.2 Hz, which is consistent for a *cis* configuration.

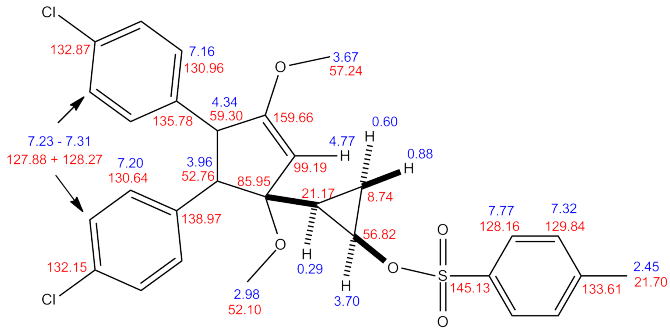


Figure 3.37: Chemical shifts of *cis* compound **26**

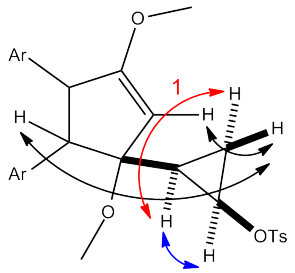
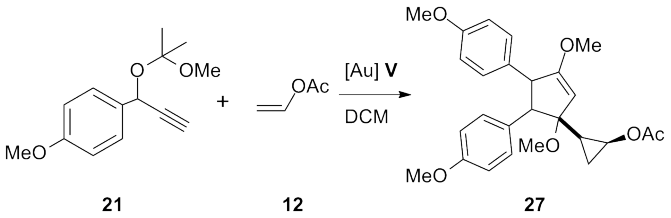


Figure 3.38: NOE correlations and J couplings for *cis* product **26**

Propargyl acetal **21** was first tested in a gold(I) catalyzed reaction with vinyl benzoate **8** (Table 3.1, entry 14, rx. i). In contrast to the previous reactions, this reaction was still not finished after 24 hrs with reflux. It was assumed that the starting material could be polluted with by-products, which hindered the reaction in taking place. Hence, the reaction was aborted and the propargyl acetal was purified on column for a second trial in gold(I) catalysis.

The gold(I) catalyzed tandem reaction of the purified acetal **21** and vinyl acetate (**12**) shown in Scheme 3.12, was finished after 12 minutes. This time, an instant colour change from colourless to red was observed. The colour gradually became dark brown. Two major products were formed, but only one of them was the desired tandem product. Product **27** was isolated in 13% yield. (Table 3.1, entry 15, rx. i).



Scheme 3.12: Synthesis of product **27**

The chemical shifts of compound **27** were assigned by NMR (Appendix Q). The NOESY experiment was used for the determination of a *cis* configuration of product **27**. The chemical shifts, NOE correlations and J couplings for product **27** are shown in Figure 3.39 and 3.40. J coupling 1 was 10.1 Hz, which is expected for vicinal *cis* protons. The ^{1}H NMR of this compound shows traces of a possible *trans* diastereomer. The cyclopentene protons and the cyclopropyl proton closest to the acetate are the most obvious ones. Their peaks are marked with red arrows in the ^{1}H spectrum (Appendix Q.1). Although the *trans* diastereomer apparently had been formed, it was not isolated.

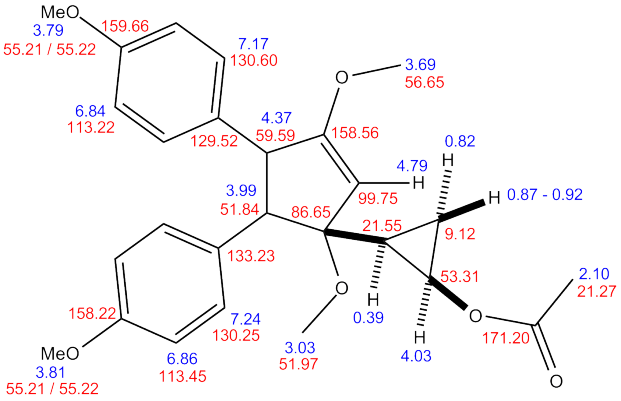


Figure 3.39: Chemical shifts of *cis* compound **27**

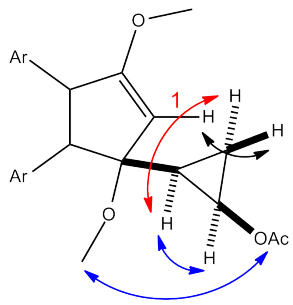


Figure 3.40: NOE correlations for *cis* product **27**

Even though a higher reactivity was expected for acetals **20** and **21**, the isolated yields did not increase noticeably. As all the gold(I) catalyzed reactions conducted at room temperature were finished quickly, it was difficult to compare the reaction times of the different propargyl acetals. It was observed that the majority of the bicyclic products were instable and decomposed at room temperature. It is possible that this affected the isolated yields, as the products might have started to decompose during work-up and purification.

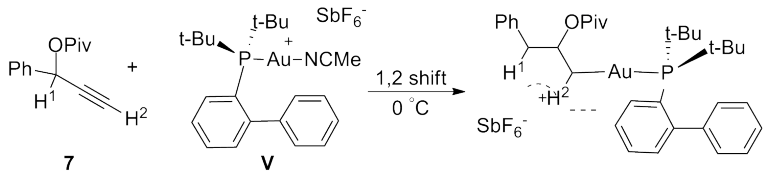
General remarks

A trend was observed in the ^{1}H NMR of the cyclization products. The cyclopropyl protons in *cis* isomers had lower shift values than the corresponding protons in *trans* isomers. This tendency has previously been detected for cyclopropyl products obtained by [1+2] cycloaddition reactions.[4] The phenomenon was most noticeable for the cyclopropyl proton attached to the same carbon as the ester substituent.

An additional trend was discovered in the ^{1}H spectra of the tandem products produced from acetals **1a**, **20** and **21**. The shift values of the protons of the methoxy groups attached to the cyclopentene ring were always higher for the *cis* isomer than the *trans* isomer. The protons of the methoxy group directly attached to the double bond had a shift value of ∼3.7 ppm in the *cis* product. For the *trans* product, the shift of the same protons had decreased to ∼3.2 ppm. The protons of the second methoxy group in the cyclopentene ring had a shift value of ∼3.1 ppm for *cis* products. The shift values of the same protons decreased to ∼2.5 ppm for the *trans* isomers. A possible explanation of this tendency could be the ring current effect caused by the aromatic substituents. The different conformations may have caused the phenyl groups to be oriented in two different positions for each of the isomers. In turn, this could have lead to the observed results.

3.3 NMR studies of gold(I) propargyl complexes

As explained in Section 2.6.2, organogold(I) species have been studied by other research groups.[35] In this project, propargyl esters and acetals had been used in gold(I) catalyzed reactions, and it was desirable to conduct NMR studies of their respective gold complexes. This study would contribute to the understanding of the "true nature" of gold complexes. To generate the gold(I) propargyl complex, stoichiometric mixtures of the propargyl ester **7** and gold(I) catalyst **V** were added simultaneously to CD_2Cl_2 at 0°C, as shown in Scheme 3.13.



Scheme 3.13: Formation of a gold complex

The addition lead to a colour change from colourless to brown. ^{1}H NMR spectra were measured at 600 MHz immediately after the addition. The experiments were run at 5°C to decrease the reactivity of the formed gold(I) complex. It was obvious that a reaction had taken place as the original ^{1}H NMR peaks of H^1 and H^2 of ester **7** were absent. These peaks were expected at 2.53 (s) and at 6.23 (s), respectively. Instead, several new doublet peaks (b-e) appeared in the region of 6.62 to 6.85 ppm, as shown in Figure 3.41. In addition, a doublet (a) was observed at 9.61 ppm. The coupling constant J of doublet a, d and e was found to be 7.7 Hz. Doublet b and c had a coupling constant of 5.5 Hz. This could be an indication of formation of two or more gold(I) propargyl intermediates.

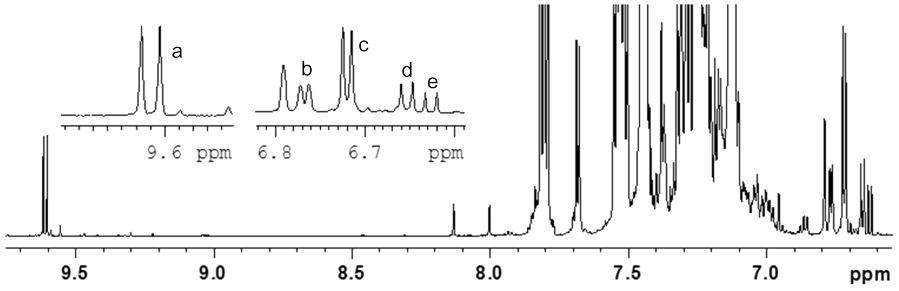


Figure 3.41: Zoom of characteristic ^{1}H peaks

These characteristic peaks had comparable shift values as the organogold(I) species studied by Fürstner *et al.*,[35] which were shown in Figure 2.8, (Section 2.6.2, page 17). Hence, it was assumed that some of these peaks might correspond to the propargyl-gold complex protons H^1 and H^2. The cationic nature of these protons causes strong deshielding of the nuclei, thus resulting in high shift values. Indeed, these results confirm a cationic gold complex instead of a gold carbenoid complex, which is in accordance with the results obtained by Fürstner *et al.*[35]
The experiment was repeated with propargyl acetal **1a**. At 5°C, the solution immediately turned black when acetal **1a** was added to the gold catalyst **V**. In contrast to the results obtained with propargyl ester **7**, no signals were detected for the propargyl gold complex protons. The phenyl and H^1-H^2 peaks of the original propargyl acetal were also absent in the spectrum. It was assumed that due to the high reactivity of acetal **1a**, a spontaneous polymerization took place. The immediate change in colour to black supports this assumption.

Actually, ^{1}H NMR studies of the gold(I) propargyl ester complex had previously been attempted in the research group. As seen in Figure 3.42, the ^{1}H NMR spectrum obtained by these studies, which were performed at room tempeature, clearly shows the propargyl-gold H^1 and H^2 peaks.[11] This indicates that the deactivating properties of propargyl ester **7** impede complex formation at low temperatures. On the other hand, when formed, the gold-propargyl ester complexes are stable enough to be treated at room temperature.

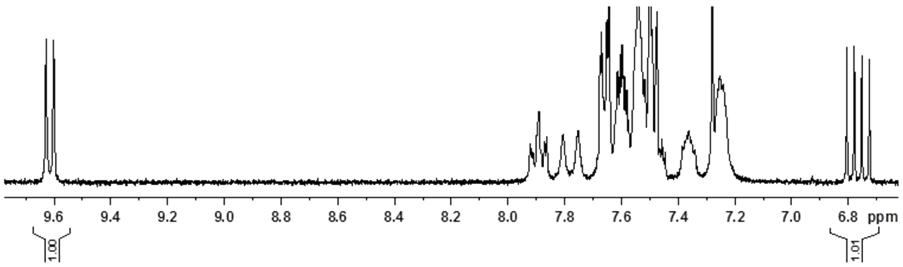


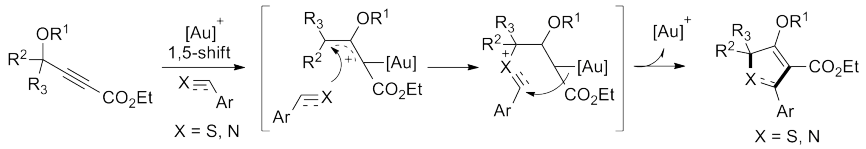
Figure 3.42: Zoom of characteristic ^{1}H peaks

The difference in reactivity of propargyl ester **7** and acetal **1a** was clearly observed by these studies. While propargyl ester **7** did not fully convert to a propargyl-gold(I) complex at 5°C, the high reactivity of acetal **1a** caused a rapid polymerization at the same temperature.

3.4 Further Work

In this project, it was confirmed that the reactivity of propargyl acetals in gold(I) catalyzed reactions is considerably higher than propargyl esters. This particular property should be further examined in experiments with different types of trapping agents. It would be interesting to produce heterocyclic compounds from propargyl acetals. Heterocyclic compounds are predominant within pharmaceutical compounds, and are found in several natural products.[18] Aldehydes have earlier been reacted with propargyl acetals in presence of a gold(I) catalyst. The reaction generated dihydrofurans in a [2+3] cycloaddition reaction.[8] A method for obtaining polycyclic compounds containing the tetrahydrofuran moiety could be to utilize cyclic ketones as trapping agents. Acyclic ketones could be used to obtain various derivatives of tetrahydrofurans. These types of products could be of commercial value, as the tetrahydrofuran subunit is found in many different natural and biologically active compounds.[40]

The incorporation of heteroatoms other than O in heterocycles should also be attempted. Similar reactions could be carried out with thioketones, thioaldehydes, imines and nitriles. This could provide an efficient route for synthesizing derivatives of thiophenes and pyrroles. Based on the method for preparing dihydrofurans,[8] a suggestion for the synthesis of S and N heterocycles is shown in Scheme 3.14. The opposite regioselectivity is caused by the EWG attached to the gold carbenoid.[8]



Scheme 3.14: Suggested synthesis of dervivatives of thiophenes and pyrroles

By using isocyanate as the trapping agent, both O and N could easily be incorporated in a complex cyclic skeletal structure. Propargyl acetals could be modified by using nitrogen or sulfur acetal derivatives instead. The reactivity of such hetero acetals should be tested in gold(I) catalysis. It would also be interesting to replace olefinic esters with thioesters, to study if the tandem cyclization reaction would take place.

Chapter 4

Conclusion

Propargyl acetal **1a** and **1b** were synthesized in acid catalyzed reactions, and isolated in 74% and 64% yields, respectively.

Vinyl tosylate **4** was prepared by fragmentation of THF upon treatment with *n*-BuLi, and trapping the formed lithium enolate with tosyl chloride **5**. Vinyl tosylate was obtained in 66% yield.

Gold catalyzed [1+2] cycloaddition reactions of pivaloate ester **7** with vinyl benzoate **8** and tosylate **4**, afforded cyclopropyl derivatives **6a-b** and **9a-b** in respective total yields of 63% and 9%. The *cis* isomer was favoured in both reactions.

Ten bicyclic compounds have been synthesized by a newly developed gold(I) catalyzed tandem reaction. This novel reaction pathway proceeds by a olefin cyclopropanation, followed by a cyclopentenylation. The second cyclization is promoted by the activating properties of highly reactive propargyl acetals. A stereoselectivity of the *cis* isomer was observed in reactions where both isomers were isolated. Bicyclic product **13** was obtained (5%), by reacting aliphatic acetal **14** with vinyl benzoate **8** in the presence of gold catalyst **V**. By changing to phenyl propargyl acetals **1a** and **1b**, reactions with vinyl acetate **12**, benzoate **8** and tosylate **4**, afforded products **15**, **16a-b**, **17** and **18a-b** in 13 - 98% yields. No tandem product was obtained by treating acetal **1b** with vinyl tosylate **4**. The gold(I) catalyzed reactions with aromatic propargyl acetals **20** and **21** and alkenes **12**, **8**, **24** and **4** provided products **22a-b**, **23a-b**, **24a-b**, **26** and **27** in 13 - 56% yields.

Low temperature NMR experiments of a stoichiometric mixture of gold catalyst **V** and propargyl ester **7** indicated the formation of a gold(I) propargyl ester complex. This finding was based on the appearance of new splitted peaks with high shift values corresponding to cationic propargyl protons. The original propargyl proton peaks were absent in the spectrum, which supported the formation of a gold complex. A similar experiment conducted with propargyl acetal **1a** showed no propargyl signals. It was assumed that a spontaneous polymerization took place, due to the particularly high reactivity of acetal **1a**, compared to ester **7**.

Chapter 5

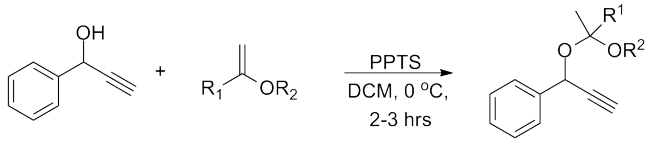
Experimental

5.1 General methods

Solvents and reagents were of synthetic grade and were used directly as supplied from the manufacturer. Dry THF and dry DCM were obtained from a MB SPS-800 Solvent Purification System (MBraun), and were used directly in the experiments. Thin layer chromatography (TLC) was performed on Merck TLC aluminium sheets, Silica gel 60 F_{254}. The TLC plates were developed by UV-light and a solution of *p*-anisaldehyde stain (5 ml conc. H_2SO_4, 1.5 ml absolute acetic acid and 3.7 ml *p*-anisaldehyde in 137 ml absolute ethanol) with heating. Gas liquid chromatography (GLC) was performed on a Varian CP-3800 with a FID detector to monitor reactions and for determining diastereomeric ratios. Supelco VersaFlash system with Versaflash cartridges with 20-45 or 45-75 μm spherical silica based on porous (70 Å) particles, was used for flash chromatography. Melting points were measured on a Stuart SMP3 melting point apparatus.
Infrared spectrometry (IR) was performed on a Nicolet 20SXC FT-IR spectrometer. The spectra were analysed using EZ OMNIC software. Mass spectrometry (MS) with electron ionization (EI) was performed on a MAT 95XL instrument (TermoQuest Finnigan). Mass spectra with electron spray ionization (ESI) were recorded by Sintef on an Agilent O-ToF instrument. All mass spectra are high resolution (HR-MS).
1D NMR spectra were recorded on Avance DPX 300 MHz and 400 MHz (Bruker) spectrometers. 2D spectra were recorded on the Avance DPX 400 (Bruker) spectrometer. All samples were dissolved in deuterated chloroform with an internal standard of TMS. Spectra were analyzed using TopSpin NMR software (Version 3.0.b.8). Chemical shifts (δ) are given as parts per million (ppm) and coupling constants (J) are given in Hertz (Hz). The peaks are given as singlets (s), doublets (d), triplets (t), quintets (quin), multiplets (m), or as a combination of these. 2D experiments were used to determine the chemical shifts and the configuration of the obtained products.

5.2 Preparation of starting materials

5.2.1 General Procedure A: Synthesis of propargyl acetals 1a-b, 20 and 21[8]



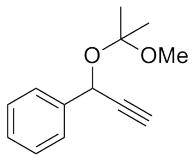
2

3a : R^1 = Me, R^2 = Me
3b : R^1 = H, R^2 = Et

1a : R^1 = Me, R^2 = Me
1b : R^1 = H, R^2 = Et

A solution of 1-phenylprop-2-yn-1-ol in DCM was cooled to 0°C before the appropriate vinyl ether and catalytic amounts of PPTS were added. The reaction mixture was stirred at room temperature for 2-3 hours until completion, and DCM (20 ml) was then added. The crude was extracted with water (3 x 20 ml). The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo*. The product was purified by flash chromatography with a suitable eluent system.

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

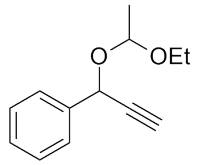


1a

Compound **1a** was synthesized following general procedure A, using 1-phenylprop-2-yn-1-ol (**2**) (208.1 mg, 1.57 mmol), 2-methoxy propene (**3a**) (10 ml, 104.42 mmol) and catalytic amounts of PPTS. An isocratic eluent of 50:1 pentane, ethyl acetate was used to isolate compound **1a** (239.1 mg, 74%), which was obtained as a clear oil.

1a: R_f = 0.78 (10:1 Pentane/EtOAc);
^{1}H-NMR (300 MHz, $CDCl_3$-TMS) (Appendix A.1) δ (ppm) 7.51 (m, 1H, H_{ar}) 7.29 - 7.38 (m, 3H, H_{ar}) 7.48 (m, 1H, H_{ar}) 5.42 (d, 1H, J = 2.2 Hz, CHC≡) 3.18 (s, 3H, OCH_3) 2.53 (d, 1H, J = 2.3 Hz, C≡CH) 1.54 (s, 3H, CCH_3) 1.33 (s, 3H, CCH_3)
^{13}C-NMR (400 MHz, $CDCl_3$-TMS) (Appendix A.2) δ (ppm) 140.25 (1C, C_{ar}) 128.53 (2C, m-CH$_{ar}$) 127.98 (1C, p-CH$_{ar}$) 126.88 (2C, o-CH$_{ar}$) 101.87 (1C, OCOCH$_3$) 84.48 (1C, CHC≡) 73.71 (1C, ≡CH) 62.60 (1C,CHC≡) 49.51 (1C, OCH$_3$) 24.42 (1C, CCH$_3$) 24.95 (1C, CCH$_3$)
^{1}H and ^{13}C NMR shifts are consistent with literature.[10]

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

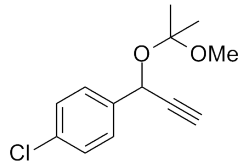


1b

Compound **1b** was synthesized following general procedure A, using 1-phenylprop-2-yn-1-ol (**2**) (232.0 mg, 1.76 mmol), ethyl vinyl ether (**3b**) (10 ml, 104.42 mmol) and catalytic amounts of PPTS. An isocratic eluent of 50:1 pentane, ethyl acetate was used to isolate compound **1b** (230.4 mg, 64%), which was obtained as a pale yellow oil.

1b: R_f = 0.78 (10:1 Pentane/EtOAc);
^{1}H-NMR (400 MHz, $CDCl_3$-TMS) (Appendix A.3) δ (ppm) 7.48-7.54 (m, 2H,H_{ar}) 7.32-7.39 (m, 3H, H_{ar}) 5.34-5.46 (d, 1H, J = 2.1 Hz, CHC≡) 4.82-5.16 (q, 1H, J = 5.36 Hz, OCHOCH_2CH_3) 3.53-3.70 (m, 2H, OCH_2CH_3) 2.59 (d, 1H, J = 2.2 Hz), ≡CH) 1.37-1.39 (dd, 3H, J = 5.3, 3.6Hz, CHCH_3) 1.18-1.24 (dt, 3H, J = 10.6, 7.04Hz, CH_2CH_3)
^{13}C-NMR (400 MHz, $CDCl_3 - TMS$) (Appendix A.4) δ (ppm) 138.93+138.72 (1C, C_{arom}) 128.81+128.73 (2C, m-CH_{arom}) 128.65+128.56 (1C, p-CH_{arom}) 127.51+127.48 (2C, o-CH_{ar}) 98.47+98.05 (1C, OCHOCH_2CH_3) 83.18+82.08 (1C, CHC≡) 75.35+74.76 (1C, ≡CH) 66.99+66.56 (1C, CHC≡) 60.82+60.18 (1C, OCH_2CH_3) 20.31+20.23 (1C, OCHCH_3) 15.58+15.38 (1C, OCH_2CH_3)
^{1}H and ^{13}C NMR shifts are consistent with literature.[10]

Purification of 1-chloro-4-(1-((2-methoxypropan-2-yl)oxy)prop-2-yn-1-yl) benzene (20)

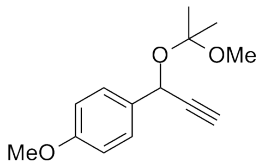


20

Compound **20** was synthesized by a student in the research group by following general procedure A. The product was used directly in gold(I) catalyzed reactions, but later had to be further purified for full characterization. An isocratic eluent of 30:1 pentane, ethyl acetate was used to isolate compound **20** (37.4 mg, 62%), which was obtained as a colourless oil.

20: R_f = 0.47 (10:2 Pentane/EtOAc);
HRMS (EI) calcd for $C_{12}H_{11}OCl$ [M-CH_4O]$^+$ 206.0493, obsd 206.0490;
^{1}H-NMR (400 MHz, $CDCl_3$-TMS) (Appendix B.1) δ (ppm) 7.43 (d, 2H, J = 8.4 Hz, CH_{ar}) 7.33 (d, 2H, J = 8.5 Hz, CH_{ar}) 5.39 (d, 1H, J = 2.2 Hz, CHC≡) 3.17 (s, 3H, OCH_3) 2.54 (d, 1H, J = 2.2 Hz, C≡CH) 1.53 (s, 3H, CCH_3) 1.32 (s, 3H, CCH_3)
^{13}C-NMR (400 MHz, $CDCl_3 - TMS$) (Appendix B.2) δ (ppm) 138.85 (1C, C_{ar}) 133.80 (1C, C_{ar}) 128.70 (2C, CH$_{ar}$) 128.24 (2C, CH$_{ar}$) 101.98 (1C, OCOCH$_3$) 84.01 (1C, CHC≡) 73.98 (1C, ≡CH) 61.90 (1C,CHC≡) 49.52 (1C, OCH$_3$) 25.36 (1C, CCH$_3$) 24.90 (1C, CCH$_3$);
IR (thin film, cm^{-1}) (Appendix B.6): 3296 (s, br, ≡C-H st) 1210 (s, CH$_3$ δ) 1146 (s, C-O-C st as) 1092 (s, C-Cl γ arom) 842 (s, ar C-H δ oop) 633 (s, br, ≡C-H δ)

Purification of 1-methoxy-4-(1-((2-methoxypropan-2-yl)oxy)prop-2-yn-1-yl)benzene (21)

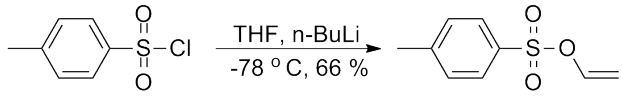


21

Compound **21** was synthesized by a student in the research group by following general procedure A. The product had to be purified and fully characterized for use in gold(I) catalyzed reactions. An isocratic eluent of 50:1 pentane, ethyl acetate was used to isolate compound **21** (125.0 mg, 29%), which was obtained as a colourless oil.

21: R_f = 0.57 (10:2 Pentane/EtOAc);
HRMS (EI) calcd for $C_{14}H_{18}O_3$ [M]$^+$ 234.1250, obsd 234.1250; ^{1}H-NMR (400 MHz, $CDCl_3$-TMS) (Appendix C.1) δ (ppm) 7.42 (d, 2H, J = 8.7 Hz, CH_{ar}) 6.89 (d, 2H, J = 8.8 Hz, CH_{ar}) 5.37 (d, 1H, J = 2.2 Hz, CHC≡) 3.80 (s, 3H, PhOCH_3) 3.18 (s, 3H, OCH_3) 2.54 (d, 1H, J = 2.2 HZ, C≡CH) 1.53 (s, 3H, CCH_3) 1.33 (s, 3H, CCH_3)
^{13}C-NMR (400 MHz, $CDCl_3 - TMS$) δ (ppm) (Appendix C.2) 159.36 (1C, C_{ar}) 132.54 (1C, C_{ar}) 128.27 (2C, CH$_{ar}$) 113,89 (2C, CH$_{ar}$) 101.77 (1C, OCOCH$_3$) 84.67 (1C, CHC≡) 73.54 (1C, ≡CH) 62.23 (1C,CHC≡) 55.29 (1C, PhOCH$_3$) 49.48 (1C, OCH$_3$) 25.44 (1C, CCH$_3$) 24.98 (1C, CCH$_3$); IR (thin film, cm^{-1}) (Appendix C.6): 3286 (s, ≡C-H st) 2991 (m, C-H st) 1463 (m, CH$_3$ δ as) 1209 (s, CH$_3$ γ) 968 (m, C-O-C st as) 826 (s, ar C-H δ oop) 637 (s, br, ≡C-H δ)

5.2.2 Synthesis of vinyl tosylate 4[28]



5 **4**

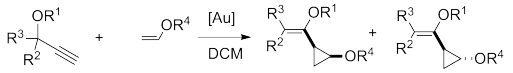
A solution of n-BuLi in hexane (2.5 M, 7.5 ml, 18.75 mmol) was added to dry THF (20 ml) at 0°C. The light yellow solution was heated to 35°C and stirred for 3 hrs. The solution was cooled to -78°C and p-toluenesulfonyl chloride **(5)** (2.80 g, 14.71 mmol) dissolved in dry THF (8.5 ml) was added dropwise during 15 min. The reaction mixture was stirred for 15 min before it was warmed to room temperature, and stirred for additional 40 min. The red-brown solution was poured into diethyl ether (80 ml), and an ice cold saturated mixture of $NaHCO_3$ was added with vigorous stirring. The aqueous phase was extracted with diethyl ether (3 x 20 ml). The organic phases were combined and washed with brine (25 ml), dried over $MgSO_4$ and concentrated in *vacuo*. The product was purified by flash chromatography using an isocratic eluent of 40:1 pentane, ethyl acetate. Compound **4** (1.9271 g, 66%) was obtained as a colourless oil.

4: R_f = 0.36 (10:1 Pentane/EtOAc);
^{1}H-NMR (400 MHz, $CDCl_3$-TMS) (Appendix D.1) δ (ppm) 7.81 (d, 2H, J = 8.0Hz, H_{ar}) 7.37 (d, 2H, J = 8.0Hz, H_{ar}) 6.62 (dd, 1H, J = 13.6, 6.0Hz, =CH) 4.90 (dd, 1H, J = 13.4, 2.4Hz, H_{trans}C=CHOTs) 4.70 (dd, 1H, J = 5.8, 2.5Hz, H_{cis}C=CHOTs) 2.45 (s, 3H, CH_3)
^{13}C-NMR (400 MHz, $CDCl_3$-TMS) (Appendix D.2) δ (ppm) 145.58 (1C, C_{ar}) 141.87 (1C, C_{ar}) 132.75 (1C, CH_2=CHOTs) 130.00 (2C, CH$_{ar}$) 128.23 (2C, CH$_{ar}$) 120.93 (1C, H_2C=CHOTs) 21.88 (1C, CH$_3$)
^{1}H and ^{13}C NMR shifts are consistent with literature.[28]

5.3 Gold(I) catalyzed cyclization reactions

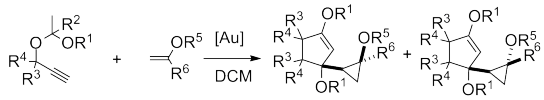
The gold(I) catalyzed reactions that provided cyclization products are summarized in Table 5.1 and 5.2.

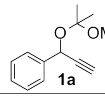
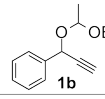
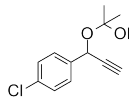
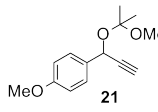
Table 5.1: [1+2] Cycloaddition reactions



Entry	Propargyl ester/acetal	Alkene	Product
1		 **8**	**6a + 6b**
2	**7**	 **4**	**9a + 9b**
3	 **11**	 **12**	**10**

Table 5.2: Tandem cyclization reactions

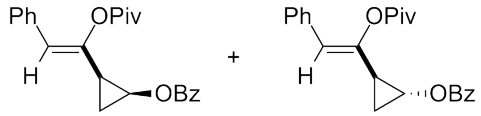


Entry	Propargyl acetal	Alkene	Product
1	 **14**	 **8**	**13**
2	 **1a**	 **12**	**15**
3		 **8**	**16a + 16b**
4		 **4**	**17**
5	 **1b**	 **8**	**18a + 18b**
6	 **20**	 **12**	**22a + 22b**
7		 **8**	**23a + 23b**
8		 **25**	**24a + 24b**
9		 **4**	**26**
10	 **21**	 **12**	**27**

5.3.1 General procedure B: Gold catalyzed reactions

The gold catalyst (0.05 eq.) was dissolved in dry DCM (1-1.5 ml) under inert conditions at the desired temperature. The appropriate propargyl acetal (1.0 eq.) or ester (1.0 eq.) and alkene (2.0-3.0 eq.) were both dissolved in dry DCM (1-1.5 ml) each, and added simultaneously to the gold catalyst. The reaction mixture was stirred until the starting material was fully converted. The catalyst was then quenched with a few drops of NEt_3. The reaction mixture was filtered through Celite™ and concentrated in *vacuo*. The product was purified by flash chromatography with a suiting eluent system.

Synthesis of (Z)-2-(2-phenyl-1-(pivaloyloxy)vinyl)cyclopropyl benzoate (6a-b)



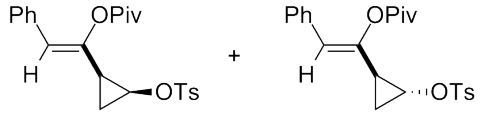
6a **6b**

Compounds **6a-b** were synthesized following general procedure B, using gold catalyst (14.0 mg, 0.02 mmol), 1-phenylprop-2-yn-1-yl pivalate **(7)** (77.8 mg, 0.36 mmol) and vinyl benzoate **8** (165.8 mg, 1.12 mmol). The reaction mixture was stirred at room temperature for 45 min. An isocratic eluent of 30:1 pentane, ethyl acetate was used to isolate compound **6a** (77.9 mg, 59%) and compound **6b** (5.5 mg, 4%) as yellow oils. (*cis*/*trans* 94:4). (Table 5.1, entry 1).

6a: R_f = 0.21 (15:1 Pentane/EtOAc);
HRMS (EI) calcd for $C_{23}H_{24}O_4$ $[M]^+$ 364.1669, obsd 364.1676;
^{1}H-NMR (400 MHz, $CDCl_3$-TMS) (Appendix E.1) δ (ppm) 7.99 (d, 2H, J = 7.2 Hz, CH_{o-OBz}) 7.53 (t, 1H, J = 7.4 Hz, CH_{p-OBz}) 7.38 (t, 2H, J = 7.7 Hz, CH_{m-OBz}) 7.26-7.28 (m, 2H, CH_{ar}) 7.23-7.25 (m, 2H, CH_{ar}) 7.15-7.19 (m, 1H, CH_{ar}) 6.22 (s, 1H, C=CH) 4.57 (td, 1H, J = 6.6, 3.7 Hz, CHOBz) 2.24 (dt, 1H, J = 8.8, 6.4 Hz, BzOCHCH) 1.33 (dt, 1H, J = 9.6, 6.7 Hz, BzOCHCH_2) 1.24 (m, 1H, BzOCHCH_2) 1.21 (s, 9H, $CO_2C(CH_3)_3$)
^{13}C-NMR (400 MHz, $CDCl_3$-TMS) (Appendix E.2) δ (ppm) 175.99 (1C, $CO_2C(CH_3)_3$) 167.14 (1C, CO_2Ph) 144.99 (1C, CH=C) 134.10 (1C, =CHC_{ar}) 133.10 (1C, CH_{p-OBz}) 129.77 (1C, CO_2C_{ar}) 129.57 (2C, CH_{o-OBz}) 128.50 (2C, CH_{m-OBz}) 128.37 (2C, CH_{ar}) 128.09 (2C, CH_{ar}) 127.10 (1C, CH_{ar}) 119.01 (1C, CH=C) 52.57 (1C, CHOBz) 38.97 (1C, $CO_2C(CH_3)_3$) 27.09 (3C, $CO_2C(CH_3)_3$) 20.59 (1C, CHCHOBz) 10.90 (1C, CH_2CHOBz);
IR (thin film, cm^{-1}) (Appendix E.7): 2947 (m, C-H st) 1724 (s, C=O st) 1265 (s, C-O st as) 1113 (s, C-O st) 711 (s, ar C-H δ oop) 694 (s, ar C-H δ oop)

6b: R_f = 0.40 (15:1 Pentane/EtOAc);
HRMS (EI) calcd for $C_{23}H_{24}O_4$ $[M]^+$ 364.1669, obsd 364.1669;
^{1}H-NMR (400 MHz, $CDCl_3$-TMS) (Appendix E.8) δ (ppm); 8.00 (d, 2H, J = 7.1 Hz, CH_{o-OBz}) 7.57 (d, 1H, J = 7.4 Hz, CH_{p-OBz}) 7.44 (m, 2H, CH_{m-OBz}) 7.35-7.37 (m, 2H, CH_{ar}) 7.27-7.30 (m, 2H, CH_{ar}) 7.18-7.24 (m, 1H, CH_{ar}) 6.20 (s, 1H, C=CH) 4.50 (m, 1H, CHOBz) 2.25 (m, 1H, BzOCHCH) 1.31-1.34 (m, 1H, BzOCHCH_2) 1.29 (s, 9H, $CO_2C(CH_3)_3$) 1.26 (m, 1H, BzOCHCH_2)
^{13}C-NMR (400 MHz, $CDCl_3$-TMS) (Appendix E.9) δ (ppm) 175.96 (1C, $CO_2C(CH_3)_3$) 166.91 (1C, CO_2Ph) 146.54 (1C, CH=C) 133.98 (1C, =CHC_{ar}) 133.20 (1C, CH_{p-OBz} 129.67 (1C, CO_2C_{ar}) 129.59 (2C, CH_{o-OBz}) 128.52 (2C, CH_{ar}) 128.42 (2C, CH_{m-OBz}) 128.19 (2C, CH_{ar}) 127.23 (1C, CH_{ar}) 117.17 (1C, CH=C) 54.31 (1C, CHOBz) 39.10 (1C, $CO_2C(CH_3)_3$) 27.16 (3C, $CO_2C(CH_3)_3$) 22.47 (1C, CHCHOBz) 12.54 (1C, CH_2CHOBz);
IR (thin film, cm^{-1}) (Appendix E.14): 2923 (m, C-H st); 1735 (s, C=O st) 1716 (s, C=O st) 1267 (s, C-O st as) 1120 (s, C-O st) 708 (s, ar C-H δ oop) 696 (s, ar C-H δ oop)

Synthesis of (Z)-2-phenyl-1-(2-(tosyloxy)cyclopropyl)vinyl pivalate (9a-b)



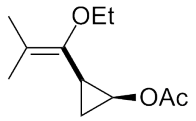
9a **9b**

Compounds **9a-b** were synthesized following general procedure B, using gold catalyst (14.8 mg, 0.02 mmol), 1-phenylprop-2-yn-1-yl pivalate **(7)** (77.1 mg, 0.36 mmol) and vinyl tosylate **4** (171.8 mg, 0.87 mmol). The reaction mixture was stirred at room temperature for 19 min. A gradient eluent of ethyl acetate in pentane was used for purification. Compound **9a** (9.3 mg, 6%) was isolated at 20:1 pentane, ethyl acetate, and compound **9b** (4.1 mg, 3%) was isolated at 10:2 pentane, ethyl acetate. Both products were yellow oils. (*cis*/*trans* 63:37). (Table 5.1, entry 2).

9a: R_f = 0.05 (10:1 Pentane/EtOAc);
HRMS (EI) calcd for $C_{23}H_{26}O_5S$ $[M]^+$ 414.1495, obsd 414.1489;
^{1}H-NMR (400 MHz, $CDCl_3$-TMS) (Appendix F.1) δ (ppm) 7.79 (d, 2H, J = 8.3 Hz, CH_{o-OTs}) 7.29 (m, 2H, CH_{ar}) 7.28 (m, 2H, CH_{ar}) 7.27 (m, 2H, CH_{m-OTs}) 7.20-7.23 (m, 1H, CH_{ar}) 5.98 (s, 1H, C=CH) 4.13 (td, 1H, J = 6.6, 3.6 Hz, CHOTs) 2.38 (s, 3H, PhCH_3) 1.99-2.05 (m, 1H, TsOCHCH) 1.24 (s, 9H, $CO_2C(CH_3)_3$) 1.10 (td, 1H, J = 7.2, 10.0 Hz, TsOCHCH_2) 1.01 (td, 1H, J = 7.7, 3.6 Hz, TsOCHCH_2)

^{13}C-NMR (400 MHz, $CDCl_3$-TMS) (Appendix F.2) δ (ppm) 176.01 (1C, $CO_2C(CH_3)_3$) 144.98 (1C, SO_3C_{ar}) 143.23 (1C, CH=C) 133.89 (1C, =CHC_{ar}) 133.43 (1C, C_{ar}Me) 129.80 (2C, CH_{m-OTs}) 128.65 (2C, CH_{ar}) 128.13 (2C, CH_{ar}) 128.11 (2C, CH_{ar}) 127.28 (1C, CH_{ar}) 119.23 (1C, CH=C) 56.69 (1C, CHOTs) 39.04 (1C, $CO_2C(CH_3)_3$) 27.12 (3C, $CO_2C(CH_3)_3$) 21.61 (1C, SO_3PhCH_3) 20.07 (1C, CHCHOTs) 10.67 (1C, CH_2CHOTs);
IR (thin film, cm^{-1}) (Appendix F.7): 2970 (m, C-H st) 1742 (s, C=O st) 1369 (s, R-SO_2-OR st as and st sy) 1190 (m, S=O st) 1177 (s, R-SO_2-OR st as and st sy) 1112 (s, C-O st) 750 (s, ar C-H δ oop) 695 (s, ar C-H δ oop)
9b: R_f = 0.14 (10:1 Pentane/EtOAc);
HRMS (EI) calcd for $C_{23}H_{26}O_5S$ $[M]^+$ 414.1495, obsd 414.1491;
^{1}H-NMR (400 MHz, $CDCl_3$-TMS) (Appendix F.8) δ (ppm); 7.86 (d, 2H, J = 8.3 Hz, CH_{o-OTs}) 7.36-7.38 (m, 2H, (m, 2H, CH_{m-OTs}) 7.27 (m, 2H, CH_{ar}) 7.08-7.12 (m, 1H, CH_{ar}) 6.93-7.02 (m, 2H, CH_{ar}) 5.90 (s, 1H, C=CH) 4.04 (ddd, 1H, J = 3.5, 2.6 Hz, CHOTs) 2.45 (s, 3H, PhCH_3) 2.07 (m, 1H, TsOCHCH) 1.22 (s, 9H, $CO_2C(CH_3)_3$) 1.16-1.18 (m, 1H, TsOCHCH_2) 1.00-1.02 (m, 1H, TsOCHCH_2) ^{13}C-NMR (400 MHz, $CDCl_3$-TMS) (Appendix F.9) δ (ppm) 176.35 (1C, $CO_2C(CH_3)_3$) 145.21 (1C, SO_3C_{ar}) 145.17 (1C, CH=C) 133.62 (1C, =CHC_{ar}) 133.05 (1C, C_{ar}Me) 129.92 (2C, CH_{m-OTs}) 128.74 (2C, CH_{ar}) 128.35 (2C, CH_{ar}) 128.23 (2C, CH_{o-OTs}) 127.40 (1C, CH_{ar}) 117.44 (1C, CH=C) 57.89 (1C, CHOTs) 39.02 (1C, $CO_2C(CH_3)_3$) 27.09 (3C, $CO_2C(CH_3)_3$) 22.28 (1C, CHCHOTs) 21.69 (1C, SO_3PhCH_3) 11.65 (1C, CH_2CHOTs);
IR (thin film, cm^{-1}) (Appendix F.14): 2971 (m, C-H st) 1739 (s, C=O st) 1369 (s, R-SO_2-OR st as and st sy) 1190 (m, S=O st) 1178 (s, R-SO_2-OR st as and st sy) 1111 (s, C-O st) 752 (s, ar C-H δ oop) 695 (s, ar C-H δ oop)

Synthesis of 2-(1-ethoxy-2-methylprop-1-en-1-yl)cyclopropyl acetate (10)

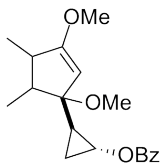


10

Compound **10** was synthesized following general procedure B, using gold catalyst (16.9 mg, 0.02 mmol), 3-(1-ethoxyethoxy)-3-methylbut-1-yne **(11)** (66.1 mg, 0.43 mmol) and vinyl acetate **12** (74.1 mg, 0.86 mmol). The reaction mixture was stirred at room temperature for 15 min. A gradient eluent of dithethyl ether in pentane was used for purification. Compound **10** (9.3 mg, 6%) was isolated at 40:1 pentane, diethyl ether as a colourless oil. (Table 5.1, entry 3).

10: R_f = 0.46 (10:3 Pentane/Diethyl ether);
^{1}H-NMR (400 MHz, $CDCl_3$-TMS) (Appendix G.1) δ (ppm) 4.35 (dt, 1H, J = 3.9, 6.6 Hz, CHOAc)) 3.72-3.80 (ddd, 1H, J = 14.2, 9.5, 7.1 Hz, CH_2CH$_3$) 3.52-3.60 (ddd, 1H, J = 14.0, 9.5, 7.0 Hz, CH_2CH$_3$) 2.00 (s, 3H, CO$_2$CH_3) 1.70 (m, 1H, AcOCHCH) 1.69 (s, 3H, C=C(CH_3)CH$_3$) 1.64 (s, 3H, C=C(CH_3)CH$_3$) 1.23 (t, 3H, J = 7.0 Hz, CH$_2$CH_3) 1.10 (dt, 1H, J = 9.5, 6.5 Hz, AcOCHCH_2) 1.00-1.05 (m, 1H, AcOCHCH_2)
^{13}C-NMR (400 MHz, $CDCl_3$-TMS) (Appendix G.2) δ (ppm) 171.87 (1C, OC=O) 141.99 (1C, (CH$_3$)$_2$C=C) 119.41 (1C, CH$_3$)$_2C$=C) 64.94 (1C, CH$_2$CH$_3$) 52.57 (1C, CHOAc) 20.97 (1C, CO$_2C_3$) 18.65 (1C, C=C(CH$_3$)CH$_3$) 17.58 (1C, C=C(CH$_3$)CH$_3$) 16.18 (1C, CHCHOAc) 15.23 (1C, CH$_2C$H$_3$) 9.70 (1C, CH$_2$CHOAc)
^{1}H and ^{13}C NMR shifts are consistent with results obtained previously in the research group.[11]

Synthesis of 2-(1,3-dimethoxy-4,5-dimethylcyclopent-2-en-1-yl) cyclopropyl benzoate (13)



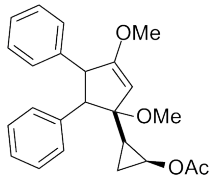
13

Compound **13** was synthesized following general procedure B, using gold catalyst (21.0 mg, 0.03 mmol) cooled to 0°C, 3-((2-methoxypropan-2-yl)oxy)but-1-yne **(14)** (77.3 mg, 0.54 mmol) and vinyl benzoate **8** (142.5 mg, 0.96 mmol). The reaction mixture was stirred at 0°C for 15 min before the icebath was removed. The reaction mixture was stirred for additional 15 min. An isocratic eluent of 40:1 pentane, dithethyl ether was used to isolate compound **13** (7.8 mg, 5%) as a gray oil. (Table 5.2, entry 1).

13: R_f = 0.44 (10:3 Pentane/Diethyl ether);
HRMS (ESI) calcd for $C_{19}H_{24}NaO_4$ $[M+Na]^+$ 339.1567, obsd 339.1572;
^{1}H-NMR (400 MHz, $CDCl_3$-TMS) (Appendix H.1) δ (ppm) 8.00 (d, 2H, J = 7.1 Hz, CH_{o-OBz}) 7.55 (t, 1H, J = 7.4 Hz, CH_{p-OBz}) 7.43 (t, 2H, J = 7.5 Hz, CH_{m-OBz}) 4.49 (m, 1H, CHOBz) 4.33 (d, 1H, J = 0.8 Hz, C=CH) 3.57 (s, 3H, =COCH_3) 3.31 (s, 3H, =CHCOCH_3) 2.87 (m, 1H, BzOCHCH) 1.26 (s, 1H, =CCHCH) 1.18 (d, 3H, J = 7.3 Hz, CH$_3$CHC=) 1.13-1.15 (m, 1H, BzOCHCH_2) 1.11 (s, 1H, =CCHCH) 1.07-1.10 (m, 1H, BzOCHCH_2) 1.04 (d, 3H, J = 7.0 Hz, CH$_3$CHCHC=)

^{13}C-NMR (400 MHz, $CDCl_3$-TMS) (Appendix H.2) δ (ppm) 167.37 (1C, O*C*=O) 160.89 (1C, CH=*C*OCH$_3$) 132.93 (1C, *C*H$_{p-OBz}$) 130.24 (1C, CO$_2$*C*$_{aromOBz}$) 129.50 (2C, *C*H$_{o-OBz}$) 128.39 (1C, *C*H$_{p-OBz}$) 97.26 (1C, C=*C*H) 84.25 (1C, =CH*C*OCH$_3$) 56.26 (1C, =CO*C*H$_3$) 52.76 (1C, *C*HOBz) 52.10 (1C, =CHCO*C*H$_3$) 45.89 (1C, *C*HCHOBz) 29.71 (1C, =C*C*HCH) 20.10 1C, =CCH*C*H) 14.60 (1C, *C*H$_3$CHCHC=) 12.91 (1C, *C*H$_3$CHC=) 7.97 (1C, *C*H$_2$CHOBz);
IR (thin film, cm^{-1}) (Appendix H.7): 2932 (w, C-H st) 1722 (m, C=O st) 1646 (m, C=C st) 1451 (m, H-C-H δ) 1269 (s, C-O st as) 1090 (s, CH$_3$ γ) 731 (s, ar C-H δ oop) 710 (s, ar C-H δ oop)

Synthesis of 2-(1,3-dimethoxy-4,5-diphenylcyclopent-2-en-1-yl)cyclo propyl acetate (15)

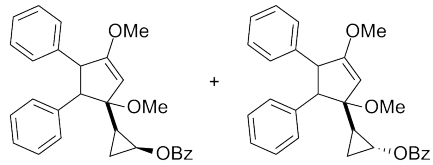


15

Compound **15** was synthesized following general procedure B, using gold catalyst (13.0 mg, 0.02 mmol), 1-((2-methoxypropan-2-yl)oxy)prop-2-yn-1-yl)benzene **1a** (63.0 mg, 0.31 mmol) and vinyl acetate **12** (77.0 mg, 0.89 mmol). The reaction mixture was stirred at room temperature for 15 min. An isocratic eluent of 20:1 pentane, ethyl acetate was used to isolate compound **15** (16.0 mg, 27%) as a yellow oil. (Table 5.2, entry 2).

15: R$_f$ = 0.43 (15:1 Pentane/EtOAc);
^{1}H-NMR (400 MHz, $CDCl_3$-TMS) (Appendix I.1) δ (ppm) 7.35-7.36 (m, 1H, *H*$_{ar}$) 7.33-7.34 (m, 2H, *H*$_{ar}$) 7.31-7.33 (2H, m, *H*$_{ar}$) 7.29 (s, 2H, *H*$_{ar}$) 7.27 (s, 2H, *H*$_{ar}$) 7.22-7.25 (m, 1H, *H*$_{ar}$) 4.85 (dd, 1H, J = 2.3, 1.5 Hz, C=C*H*) 4.44 (s, 1H, =CC*H*CH) 4.06 (d, 1H, J = 1.2 Hz, =CCHC*H*) 4.00 (dt, 1H, J = 7.1, 4.2 Hz C*H*OAc) 3.70 (s, 3H, =COC*H*$_3$) 3.04 (s, 3H, =CHCOC*H*$_3$) 2.09 (s, 3H, COOC*H*$_3$) 0.91 (ddd, 1H, J = 8.2, 6.6, 4.2 Hz, AcOCHC*H*$_2$) 0.81 (dt, 1H, J = 10.2, 6.8 Hz, AcOCHC*H*$_2$) 0.39 (ddd, 1H, J = 10.2, 8.2, 7.2 Hz, AcOCHC*H*)
^{13}C-NMR (400 MHz, $CDCl_3$-TMS) (Appendix I.2) δ (ppm) 171.20 (1C, O*C*=O) 159.74 (1C, C=*C*OCH$_3$) 141.22 (1C, *C*$_{ar}$CHCHC=) 137.58 (1C, *C*$_{ar}$CHC=) 129.66 (2C, o-*C*H$_{ar}$) 129.43 (2C, o-*C*H$_{ar}$) 127.98 (2C, m-*C*H$_{ar}$) 127.75 (2C, m-*C*H$_{ar}$) 126.91 (1C, p-*C*H$_{ar}$) 126.43 (1C, p-*C*H$_{ar}$) 99.73 (1C, C=*C*H) 86.77 (1C, =CH*C*OCH$_3$) 60.34 (1C, =C*C*HCH) 56.69 (=CO*C*H$_3$) 53.22 (1C, *C*HOAc) 53.12 (1C, =CCH*C*H) 51.84 =CHCO*C*H$_3$) 21.69 (1C, OOC*C*$_3$) 21.24 (1C, *C*HCHOAc) 9.16 (1C, *C*H$_2$CHOAc)
^{1}H and ^{13}C NMR shifts are consistent with results obtained previously in the research group.[11]

Synthesis of 2-(1,3-dimethoxy-4,5-diphenylcyclopent-2-en-1-yl)cyclo propyl benzoate (16a-b)



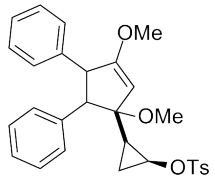
16a **16b**

Compounds **16a-b** were synthesized following general procedure B, using gold catalyst (14.5 mg, 0.02 mmol) cooled to -40°C, (1-((2-methoxypropan-2-yl)oxy)prop-2-yn-1-yl)benzene **1a** (72.5 mg, 0.35 mmol) and vinyl benzoate **8** (154.5 mg, 1.04 mmol). The reaction mixture was stirred at -40°C for 20 minutes. An isocratic eluent of 1:1 pentane, DCM was used to isolate the products. Compound **16a** was obtained as a white solid (22.1 mg, 28%) and **16b** (26.8 mg, 34%) as a yellow oil. (*cis*/*trans* 55:45). (Table 5.2, entry 3).

16a: R_f = 0.57 (DCM);
mp: 154-158°C;
HRMS (EI) calcd for $C_{29}H_{28}O_4$ $[M]^+$ 440.1982, obsd 440,1979;
^{1}H-NMR (300 MHz, $CDCl_3$-TMS) (Appendix J.1) δ (ppm) 8.04 (dd, 2H, J = 8.3, 1.3 Hz, CH_{o-OBz}) 7.59 (t, 1H, J = 7.4 Hz, CH_{p-OBz}) 7.46 (t, 2H, J = 7.7 Hz, CH_{m-OBz}) 7.23-7.35 (m, 10H, CH_{ar}) 4.99 (dd, 1H, J = 2.2, 1.3 Hz, C=CH) 4.42 (s, 1H, =CCHCH) 4.17 (s, 1H, C=CHCH) 4.08 (dt, J = 7.1, 4.2 Hz, CHOBz) 3.73 (s, 3H, =COCH_3) 3.16 (s, 3H, =CHCOCH_3) 1.11 (ddd, 1H, J = 8.1, 6.4, 4.2 Hz, BzOCHCH_2) 0.97 (dt, 1H, J = 10.1, 6.7 Hz, BzOCHCH_2) 0.58 (ddd, 1H, J = 10.1 8.2, 7.1 Hz, BzOCHCH)
^{13}C-NMR (400 MHz, $CDCl_3$-TMS) (Appendix J.2) δ (ppm) 167.20 (1C, CO_2) 160.21 (1C, C=COCH$_3$) 140.58 (1C, C_{ar}CHCHC=) 137.71 (1C, C_{ar}CHC=) 133.05 (1C, CH$_{p-OBz}$) 130.29 (1C, CO$_2C_{aromOBz}$) 129.58 (2C, CH$_{o-OBz}$) 129.46 (1C, CH$_{ar}$) 129.08 (2C, CH$_{ar}$) 128.41 (2C, CH$_{m-OBz}$) 128.14 (2C, CH$_{ar}$) 127.72 (2C, CH$_{ar}$) 126.98 (1C, C_{ar}) 126.38 (2C, CH$_{ar}$) 99.28 (1C, C=CH) 86.19 (1C, =CHCOCH$_3$) 59.78 (1C, =CCHCH) 56.82 (=COCH$_3$) 54.48 (1C, =CCHCH) 53.47 (1C, CHOBz) 51.96 (1C, =CHCOCH$_3$) 22.91 (1C, CHCHOBz) 9.05 (1C, CH$_2$CHOBz);
IR (neat, cm^{-1}) (Appendix J.7): 2927 (w, C-H st) 1722 (s, C=O st) 1644 (m, C=C st) 1452 (m, H-C-H δ) 1272 (s, C-O st as) 709 (s, ar C-H δ oop)

16b: R_f = 0.64 (DCM);
HRMS (EI) calcd for $C_{29}H_{28}O_4$ $[M]^+$ 440.1982, obsd 440.1982;
^{1}H-NMR (400 MHz, $CDCl_3$-TMS) (Appendix J.8) δ (ppm) 8.03 (d, 2H, J = 7.2 Hz, CH_{o-OBz}) 7.56 (t, 1H, J = 7.4 Hz, CH_{p-OBz}) 7.40-7.45 (m, 2H, CH_{m-OBz}) 7.34-7.23 (m, 10H, CH_{ar}) 4.70 (dt, 1H, J = 7.0, 4.6 Hz, CHOBz) 4.55 (t, 1H, J = 1.9 Hz, C=CH) 4.34 (s, 1H, =CCHCH) 4.09 (s, 1H, C=CHCH) 3.23 (s, 3H, =COCH_3) 2.46 (s, 3H, =CHCOCH_3) 1.63 (m, 1H, BzOCHCH_2) 1.59 (m, 1H, BzOCHCH) 1.28 (**m**, 1H, BzOCHCH_2)
^{13}C-NMR (400 MHz, $CDCl_3$-TMS) (Appendix J.9) δ (ppm) 167.27 (1C, CO$_2$) 158.79 (1C, C=COCH$_3$) 141.41 (1C, C_{ar}CHC=) 137.85 (1C, C_{ar}CHCHC=) 133.18 (1C, CH$_{p-OBz}$) 130.74 (2C, CH$_{ar}$) 130.00 (1C, CO$_2C_{arOBz}$) 129.64 (2C, CH$_{o-OBz}$) 129.55 (1C, CH$_{ar}$) 128.39 (2C, CH$_{m-OBz}$) 127.76 (2C, CH$_{ar}$) 127.42 (2C, CH$_{ar}$) 126.64 (2C, CH$_{ar}$) 126.17 (1C, CH$_{ar}$) 97.58 (1C, C=CH) 84.86 (1C, =CHCOCH$_3$) 59.33 (1C, =CCHCH) 56.46 (1C, =CCHCH) 56.18 (1C, =COCH$_3$) 52.42 (1C, =CHCOCH$_3$) 51.92 (1C, CHOBz) 24.77 (1C, CHCHOBz) 9.79 (1C, CH$_2$CHOBz);
IR (thin film, cm^{-1}) (Appendix J.14): 3012 (w, =CH st) 2930 (w, C-H st) 1714 (s, C=O st) 1662 (m, H-C-H δ) 1267 (s, C-O st as) 716 (s, ar C-H δ oop) 696 (s, ar C-H δ oop)

Synthesis of 2-(1,3-dimethoxy-4,5-diphenylcyclopent-2-en-1-yl) cyclopropyl tosylate (17)



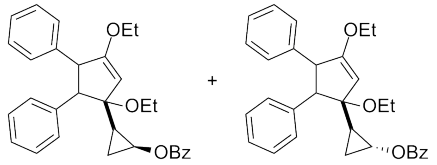
17

Compound **17** was synthesized following general procedure B, using gold catalyst (17.3 mg, 0.02 mmol), 1-((2-methoxypropan-2-yl)oxy)prop-2-yn-1-yl)benzene **1a** (87.2 mg, 0.43 mmol) and vinyl tosylate **4** (261.0 mg, 1.32 mmol). The reaction mixture was stirred at room temperature for 22 min. A gradient eluent of pentane in DCM was used for purification. Compound **17** (13.7 mg, 13%) was isolated at 100% DCM as a yellow oil. (Table 5.2, entry 4).

17: R_f = 0.28 (10:2 Pentane/EtOAc);
HRMS (EI) calcd for $C_{29}H_{30}O_5S$ $[M]^+$ 490.1808, obsd 490.1801;
^{1}H-NMR (400 MHz, $CDCl_3$-TMS) (Appendix K.1) δ (ppm) 7.79 (dd, 2H, J = 8.3, 1.8 Hz CH_{o-OTs}) 7.33-7.37 (m, 2H, CH_{m-OTs}) 7.31 (s, 2H, CH_{ar}) 7.29 (s, 2H, CH_{ar}) 7.27 (m, 2H, CH_{ar}) 7.24 (s, 2H, CH_{ar}) 7.23 (m, 1H, CH_{ar}) 7.21 (m, 1H, CH_{ar}) 4.81 (dd, 1H, J = 1.92, 1.4 Hz, C=CH) 4.37 (s, 1H, =CCHCH) 4.00 (d, 1H, J = 1.0 Hz, =CCHCH) 3.65-3.71 (m, 1H, CHOTs) 3.68 (s, 3H, =COCH_3) 3.01 (s, 3H, =CHCOCH_3) 2.45 (s, 3H, SO_3PhCH_3) 0.88 (m, 1H, TsOCHCH_2)

0.59 (dt, 1H, J = 10.3, 6.7 Hz, TsOCHCH_2) 0.32 (ddd, 1H, J = 10.2, 8.4, 7.4 Hz, TsOCHCH)
^{13}C-NMR (400 MHz, $CDCl_3$-TMS) (Appendix K.2) δ (ppm) 159.87 (1C, CH=COCH$_3$) 144.91 (1C, SO$_3C_{ar}$) 140.64 (1C, C_{ar}CHCHC=) 137.39 (1C, C_{ar}CHC=) 133.26 (1C, C_{ar}Me) 129.75 (2C, CH$_{m-OTs}$) 129.51 (2C, CH$_{ar}$) 129.36 (2C, CH$_{ar}$) 128.18 (2C, CH$_{o-OTs}$) 128.04 (2C, CH$_{ar}$) 127.73 (2C, CH$_{ar}$) 126.94 (1C, CH$_{ar}$) 126.37 (1C, CH$_{ar}$) 99.30 (1C, C=CH) 86.08 (1C, =CHCOCH$_3$) 59.84 (1C, =CCHCH) 57.43 (=COCH$_3$) 56.73 (1C, CHOTs) 53.41 (1C, =CCHCH) 52.04 (1C, =CHCOCH$_3$) 21.68 (1C, SO$_3$PhCH$_3$) 21.37 (1C, CHCHOTs) 8.77 (1C, CH$_2$CHOTs);
IR (thin film, cm^{-1}) (Appendix K.7): 2925 (w, =CH st) 1651 (w, C=C st) 1368 (m, R-SO$_2$-OR st as and st sy) 1190 (m, S=O st) 1176 (m, R-SO$_2$-OR st as and st sy) 699 (s, ar C-H δ oop)

Synthesis of 2-(1,3-diethoxy-4,5-diphenylcyclopent-2-en-1-yl)cyclo propyl benzoate (18a-b)



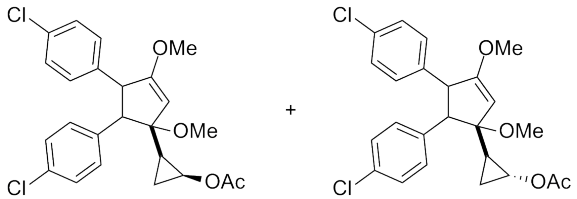
18a **18b**

Compounds **18a-b** were synthesized following general procedure B, using gold catalyst (15.2 mg, 0.02 mmol) cooled to −35°C, (1-(1-ethoxyethoxy)prop-2-yn-1-yl)benzene **1b** (80.5 mg, 0.39 mmol) and vinyl benzoate **8** (178.7 mg, 1.21 mmol). The reaction mixture was stirred at −35°C for 2 hrs. An isocratic eluent of 1:1 pentane, DCM was used to isolate compound **18a** (79.3 mg, 86%) and compound **18b** (11.1 mg, 12%) as yellow oils. (*cis*/*trans* 67:33). (Table 5.2, entry 5).

18a: R$_f$ = 0.56 (15:1 Pentane/EtOAc);
HRMS (ESI) calcd for $C_{31}H_{32}O_4Na$ [M+Na]$^+$ 491.2193, obsd 491.2183;
^{1}H-NMR (400 MHz, $CDCl_3$-TMS) (Appendix L.1) δ (ppm) 8.04 (dd, 2H, J = 8.4, 1.2 Hz, CH_{o-OBz}) 7.58 (t, 1H, J = 7.5 Hz, CH_{p-OBz}) 7.46 (m, 2H, CH_{m-OBz}) 7.19-7.33 (m, 10H, CH_{ar}) 4.97 (s, 1H, C=CH) 4.41 (s, 1H, =CCHCH) 4.16 (s, 1H, =CCHCH) 4.00 (m, 2H, =COCH_2CH$_3$) 3.93 (td, 1H, J = 9.8, 7.0 Hz CHOBz) 3.58 (quint, 1H, J = 6.9 Hz, =CHCOCH_2CH$_3$) 3.36 (quin, 1H, J = 6.9 Hz, =CHCOCH_2CH$_3$) 1.31 (t, 3H, J = 7.0 Hz, =COCH$_2$CH_3) 1.13 (ddd, 1H, J = 8.2, 6.3, 4.2 Hz, BzOCHCH_2) 0.92 (dt, 1H, J = 10.0, 6.9 Hz, BzOCHCH_2) 0.55 (t, 3H, J = 6.8 Hz, =CHCOCH$_2$CH_3) 0.52-0.58 (m, 1H, BzOCHCH)

^{13}C-NMR (400 MHz, $CDCl_3$-TMS) (Appendix L.2) δ (ppm) 167.23 (1C, O*C*=O) 159.11 (1C, CH=*C*OCH$_2$CH$_3$) 140.77 (1C, C_{ar}CHC=) 138.15 (1C, C_{ar}CHCHC=) 133.00 (1C, *C*H$_{p-OBz}$) 130.37 (1C, CO$_2$*C*$_{aromOBz}$) 130.01 (2C, *C*H$_{ar}$) 129.54 (2C, *C*H$_{o-OBz}$) 129.12 (2C, *C*H$_{ar}$) 128.38 (2C, *C*H$_{m-OBz}$) 127.99 (2C, *C*H$_{ar}$) 127.52 (2C, *C*H$_{ar}$) 126.73 (1C, *C*H$_{ar}$) 126.16 (1C, *C*H$_{ar}$) 99.31 (1C, C=*C*H) 85.69 (1C, =CH*C*OCH$_2$CH$_3$) 64.88 (1C, =CO*C*H$_2$CH$_3$) 59.85 (1C, =CCH*C*H) 59.01 (1C, =CHCO*C*H$_2$CH$_3$) 54.93 (1C, =C*C*HCH) 53.59 (1C, *C*HOBz) 23.45 (1C, *C*HCHOBz) 15.04 (1C, =CHCOCH$_2$*C*H$_3$) 14.43 (1C, =COCH$_2$*C*H$_3$) 9.08 (1C, *C*H$_2$CHOBz);
IR (thin film, cm^{-1}) (Appendix L.7): 2975 (w, C-H st) 1725 (s, C=O st) 1648 (m, C=C st) 1452 (m, H-C-H δ) 1269 (s, C-O st as) 700 (s, ar C-H δ oop)
18b: R_f = 0.61 (15:1 Pentane/EtOAc);
HRMS (EI) calcd for $C_{31}H_{32}O_4$ $[M]^+$ 468.2295, obsd 468.2295;
^{1}H-NMR (400 MHz, $CDCl_3$-TMS) (Appendix (L.8) δ (ppm) 8.04 (d, 2H, J = 7.5 Hz, C*H*$_{o-OBz}$) 7.55 (t, 1H, J = 7.4 Hz, C*H*$_{p-OBz}$) 7.42 (t, 2H, J = 7.8 Hz, C*H*$_{m-OBz}$) 7.36 (m, 1H, C*H*$_{ar}$) 7.35 (m, 2H, C*H*$_{ar}$) 7.31 (m, 2H, C*H*$_{ar}$) 7.29 (m, 2H, C*H*$_{ar}$) 7.18-7.20 (m, 2H, C*H*$_{ar}$) 7.17 (m, 1H, C*H*$_{ar}$) 4.66 (td, 1H, J = 7.3, 4.4 Hz, C*H*OBz) 4.45 (s, 1H, C=C*H*) 4.30 (s, 1H, =CCHC*H*) 4.10 (s, 1H, =CC*H*CH) 3.63 (d.quin, 1H, J = 7.0, 2.8 Hz, =COC*H*$_2$CH$_3$) 3.36 (d.quin, 1H, J = 7.0, 2.8 Hz, =COC*H*$_2$CH$_3$) 2.90 (quin, 1H, J = 6.9 Hz, =CHCOC*H*$_2$CH$_3$) 2.47 (quin, 1H, J = 6.9 Hz, =CHCOC*H*$_2$CH$_3$) 1.60 (m, 1H, BzOCHC*H*$_2$) 1.56 (m, 1H, BzOCHC*H*) 1.24 (m, 1H, BzOCHC*H*$_2$) 1.01 (t, 3H, J = 7 Hz, =COCH$_2$C*H*$_3$) 0.30 (t, 3H, J = 6.9 Hz, =CHCOCH$_2$C*H*$_3$)
^{13}C-NMR (400 MHz, $CDCl_3$-TMS) (Appendix L.9) δ (ppm) 167.31 (1C, O*C*=O) 157.64 (1C, CH=*C*OCH$_2$CCH$_3$) 141.68 (1C, C_{ar}CHCHC=) 138.16 (1C, C_{ar}CHC=) 133.10 (1C, *C*H$_{p-OBz}$) 130.96 (2C, *C*H$_{ar}$) 129.84 (2C, *C*H$_{ar}$) 129.67 (2C, *C*H$_{o-OBz}$) 129.12 (1C, CO$_2$*C*$_{aromOBz}$) 128.36 (2C, *C*H$_{m-OBz}$) 127.28 (2C, *C*H$_{ar}$) 127.10 (2C, *C*H$_{ar}$) 126.25 (1C, *C*H$_{ar}$) 125.96 (1C, *C*H$_{ar}$) 97.91 (1C, C=*C*H) 84.36 (1C, =CH*C*OCH$_2$CH$_3$) 64.25 (1C, =CO*C*H$_2$CH$_3$) 59.60 (1C, =CCH*C*H) 59.43 (1C, =CHCO*C*H$_2$CH$_3$) 56.72 (1C, =C*C*HCH) 52.37 (1C, *C*HOBz) 24.97 (1C, *C*HCHOBz) 14.72 (1C, =CHCOCH$_2$*C*H$_3$) 14.19 (1C, =COCH$_2$*C*H$_3$) 9.74 (1C, *C*H$_2$CHOBz);
IR (thin film, cm^{-1}) (Appendix L.14): 2975 (w, C-H st) 1724 (s, C=O st) 1657 (m, C=C st) 1452 (m, H-C-H δ) 1266 (s, C-O st as) 700 (s, ar C-H δ oop)

Synthesis of 2-(4,5-bis(4-chlorophenyl)-1,3-dimethoxycyclopent-2-en-1-yl)cyclopropyl acetate (22a-b)



22a **22b**

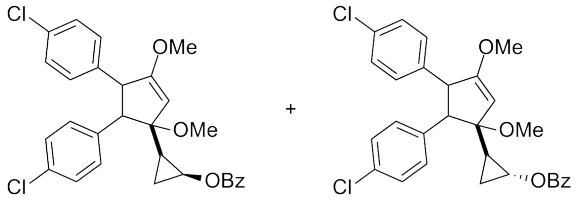
Compounds **22a-b** were synthesized following general procedure B, using gold catalyst (13.0 mg, 0.02 mmol), 1-chloro-4-(1-((2-methoxypropan-2-yl)oxy)prop-2-yn-1-yl)benzene **20** (79.1 mg, 0.33 mmol) and vinyl acetate **12** (53.6 mg, 0.62 mmol). The reaction mixture was stirred at room temperature for 9 min. An isocratic eluent of 30:1 pentane, ethyl acetate was used to isolate compound **22a** (30.1 mg, 41%) and compound **22b** (11.4 mg, 15%) as yellow waxes. (*cis*/*trans* 75:25). (Table 5.2, entry 6).

22a: R_f = 0.40 (10:2 Pentane/EtOAc);
HRMS (EI) calcd for $C_{24}H_{24}O_4Cl_2$ $[M]^+$ 446.1046, obsd 446.1043;
^{1}H-NMR (300 MHz, $CDCl_3$-TMS) (Appendix M.1) δ (ppm) 7.32 (m, 2H, CH_{ar}) 7.29 (m, 2H, CH_{ar}) 7.28 (m, 2H, CH_{ar}) 7.19-7.22 (m, 2H, CH_{ar}) 4.82 (dd, 1H, J = 2.3, 1.6 Hz, C=CH) 4.40 (s, 1H, =CCHCH) 4.02-4.08 (m, 1H, CHOAc) 4.04 (s, 1H, =CCHCH) 3.71 (s, 3H, =COCH_3) 3.05 (s, 3H, =CHCOCH_3) 2.08 (s, 3H, CO_2CH_3) 0.91 (ddd, 1H, J = 8.4, 6.7, 4.4 Hz, AcOCHCH_2) 0.83 (1H, dt, J = 10.1, 6.7 Hz, AcOCHCH_2) 0.38 (ddd, 1H, J = 10.0, 8.3, 7.3 Hz, AcOCHCH)
^{13}C-NMR (400 MHz, $CDCl_3$-TMS) (Appendix M.2) δ (ppm) 170.96 (1C, OC=O) 159.58 (1C, CH=COCH$_3$) 139.53 (1C, C_{ar}CHC=) 135.94 (1C, C_{ar}CHCHC=) 132.83 (1C, C_{ar}Cl) 132.19 (1C, C_{ar}Cl) 130.91 (2C, CH$_{ar}$) 130.67 (2C, CH$_{ar}$) 128.22 (2C, CH$_{ar}$) 127.90 (2C, CH$_{ar}$) 99.58 (1C, C=CH) 86.60 (1C, =CHCOCH$_3$) 59.76 (1C, =CCHCH) 56.77 (1C, =COCH$_3$) 53.08 (1C, CHOAc) 52.47 (1C, =CCHCH) 51.90 (1C, =CHCOCH$_3$) 21.45 (1C, CHCHOAc) 21.19 (1C, CO_2CH$_3$) 9.11 (1C, CH$_2$CHOAc);
IR (neat, cm^{-1}) (Appendix M.7): 2934 (w, C-H st) 1743 (m, C=O st) 1652 (m, C=C st) 1489 (m, H-C-H δ) 1225 (s, C-O st as) 1090 (s, arom C-Cl γ) 1014 (s, CH$_3$ γ) 907 (m, CH$_3$ γ) 730 (s, ar C-H δ oop)

22b: R_f = 0.31 (10:2 Pentane/EtOAc);
HRMS (EI) calcd for $C_{24}H_{24}O_4Cl_2$ $[M]^+$ 446.1046, obsd 446.1050;
^{1}H-NMR (300 MHz, $CDCl_3$-TMS) (Appendix M.8) δ (ppm) 7.27-7.29 (m, 2H, CH_{ar}) 7.26 (m, 2H, CH_{ar}) 7.24 (m, 2H, CH_{ar}) 7.18-7.21 (m, 2H, CH_{ar}) 4.61 (t, 1H, J = 2.0 Hz, C=CH) 4.44 (dt, 1H, J = 7.2, 4.0 Hz, CHOAc) 4.12 (dd, 1H, J = 2.1, 0.9 Hz, =CCHCH) 3.96 (s, 1H, =CCHCH) 3.59 (s, 3H, =COCH_3) 2.50 (s, 3H, =CHCOCH_3) 2.09 (s, 3H, CO_2CH_3) 1.39 (m, 1H, AcOCHCH) 1.31 (m, 1H, AcOCHCH_2) 1.15 (td, 1H, J = 9.6, 7.3 Hz, AcOCHCH_2)

^{13}C-NMR (400 MHz, $CDCl_3$-TMS) (Appendix M.9) δ (ppm) 171.47 (1C, O*C*=O) 159.09 (1C, CH=*C*OCH$_3$) 139.64 (1C, C_{ar}CHC=) 136.22 (1C, C_{ar}CHCHC=) 132.61 (1C, C_{ar}Cl) 132.06 (1C, C_{ar}Cl) 131.91 (2C, *C*H$_{ar}$) 130.96 (2C, *C*H$_{ar}$) 127.95 (2C, *C*H$_{ar}$) 127.63 (2C, *C*H$_{ar}$) 97.24 (1C, C=*C*H) 84.78 (1C, =CH*C*OCH$_3$) 57.35 (1C, =C*C*HCH) 56.67 (=CO*C*H$_3$) 56.60 (1C, =CCH*C*H) 52.44 (1C, =CHCO*C*H$_3$) 51.79 (1C, *C*HOAc) 24.24 (1C, *C*HCHOAc) 20.77 (1C, CO$_2$*C*H$_3$) 9.26 (1C, *C*H$_2$CHOAc);
IR (neat, cm^{-1}) (Appendix M.14): 2933 (w, C-H st) 1744 (m, C=O st) 1662 (w, C=C st) 1489 (m, H-C-H δ) 1223 (s, C-O st as) 1090 (s, arom C-Cl γ) 1014 (s, CH$_3$ γ) 908 (m, CH$_3$ γ) 730 (s, ar C-H δ oop)

Synthesis of 2-(4,5-bis(4-chlorophenyl)-1,3-dimethoxycyclopent-2-en-1-yl)cyclopropyl benzoate (23a-b)



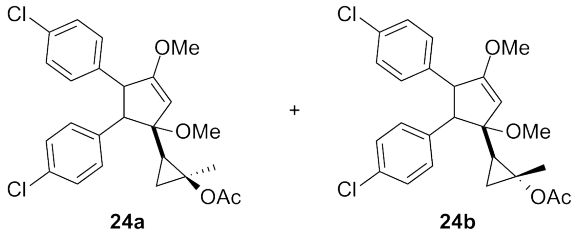
23a **23b**

Compounds **23a-b** were synthesized following general procedure B, using gold catalyst (14.4 mg, 0.02 mmol), 1-chloro-4-(1-((2-methoxypropan-2-yl)oxy)prop-2-yn-1-yl)benzene **20** (89.8 mg, 0.38 mmol) and vinyl benzoate **8** (102.5 mg, 0.69 mmol). The reaction mixture was stirred at room temperature for 18 min. An isocratic eluent of 50:1 pentane, diethyl ether was used to isolate compound **23a** (26.4 mg, 28%) as a white solid, and compound **23b** (15.1 mg, 16%) as a yellow oil. (*cis*/*trans* 61:39). (Table 5.2, entry 7).

23a: R$_f$ = 0.35 (10:2 Pentane/Diethyl ether);
mp: 174-177°C;
HRMS (EI) calcd for $C_{29}H_{26}O_4Cl_2$ $[M]^+$ 508.1203, obsd 508.1203;
^{1}H-NMR (400 MHz, $CDCl_3$-TMS) (Appendix N.1) δ (ppm) 8.00 (d, 2H, J = 7.1 Hz, CH_{o-OBz}) 7.60 (m, 1H, CH_{p-OBz}) 7.47 (t, 2H, J = 7.4 Hz, CH_{m-OBz}) 7.26-7.30 (m, 2H, CH_{ar}) 7.22-7.23 (m, 2H, CH_{ar}) 7.20 (m, 2H, CH_{ar}) 7.19 (m, 2H, CH_{ar}) 4.91 (dd, 1H, J = 2.2, 1.4 Hz, C=C*H*) 4.37 (s, 1H, =CC*H*CH) 4.15 (td, 1H, J = 7.1, 4.2 Hz, C*H*OBz) 4.09 (d, 1H, J = 1.3 Hz, =CCHC*H*) 3.71 (s, 3H, =COCH_3) 3.12 (s, 3H, =CHCOCH_3) 1.09 (ddd, 1H, J = 8.2, 6.5, 4.3 Hz, BzOCHCH$_2$) 0.96 (dt, 1H, J = 9.9, 7.0 Hz, BzOCHCH$_2$) 0.53 (ddd, 1H, J = 10.0, 8.2, 7.2 Hz, BzOCHC*H*)

^{13}C-NMR (400 MHz, $CDCl_3$-TMS) (Appendix N.2) δ (ppm) 167.06 (1C, OC=O) 159.93 (1C, CH=COCH$_3$) 138.99 (1C, C_{ar}CHCHC=) 136.03 (1C, C_{ar}CHC=) 133.22 (1C, CH$_{p-OBz}$) 132.89 (1C, C_{ar}Cl) 132.15 (1C, C_{ar}Cl) 130.79 (2C, CH$_{ar}$) 130.41 (2C, CH$_{ar}$) 130.11 (1C, CO$_2C_{aromOBz}$) 129.53 (2C, CH$_{o-OBz}$) 128.49 (2C, CH$_{m-OBz}$) 128.35 (2C, CH$_{ar}$) 127.87 (2C, CH$_{ar}$) 99.27 (1C, C=CH) 86.22 (1C, =CHCOCH$_3$) 59.43 (1C, =CCHCH) 56.88 (=COCH$_3$) 53.48 (1C, CHOBz) 53.44 (1C, =CCHCH) 52.04 (1C, =CHCOCH$_3$) 22.51 (1C, CHCHOBz) 9.04 (1C, CH$_2$CHOBz);
IR (neat, cm^{-1}) (Appendix N.7): 2934 (w, C-H st) 1721 (m, C=O st) 1651 (m, C=C st) 1489 (m, H-C-H δ) 1266 (s, C-O st as) 1090 (s, arom C-Cl γ) 1014 (s, CH$_3$ γ) 710 (s, ar C-H δ oop)
23b: R$_f$ = 0.27 (10:2 Pentane/Diethyl ether);
HRMS (EI) calcd for $C_{29}H_{26}O_4Cl_2$ [M]$^+$ 508.1203, obsd 508.1202;
^{1}H-NMR (400 MHz, $CDCl_3$-TMS) (Appendix N.8) δ (ppm) 8.00 (d, 2H J = 7.2 Hz, CH_{o-OBz}) 7.57 (t, 1H, J = 7.4 Hz, CH_{p-OBz}) 7.42 (t, 2H, J = 7.6 Hz, CH_{m-OBz}) 7.26-7.27 (m, 2H, CH_{ar}) 7.24-7.25 (m, 2H, CH_{ar}) 7.23-7.24 (m, 2H, CH_{ar}) 7.20-7.22 (m, 2H, CH_{ar}) 4.68 (dt, 1H, J = 7.2, 4.2 Hz, CHOBz) 4.49 (t, 1H, J = 1.9 Hz, C=CH) 4.29 (d, 1H, J = 1.2 Hz, =CCHCH) 4.03 (s, 1H, =CCHCH) 3.20 (s, 3H, =COCH_3) 2.50 (s, 3H, =CHCOCH_3) 1.55-1.59 (m, 1H, BzOCHCH_2) 1.53-1.55 (m, 1H, BzOCHCH) 1.27-1.32 (m, 1H, BzOCHCH)
^{13}C-NMR (400 MHz, $CDCl_3$-TMS) (Appendix N.9) δ (ppm) 167.18 (1C, OC=O) 158.76 (1C, CH=COCH$_3$) 139.71 (1C, C_{ar}CHC=) 136.27 (1C, C_{ar}CHCHC=) 133.31 (1C, CH$_{p-OBz}$) 132.63 (1C, C_{ar}Cl) 131.99 (1C, C_{ar}Cl) 131.93 (2C, CH$_{ar}$) 130.85 (2C, CH$_{ar}$) 129.60 (2C, CH$_{o-OBz}$) 129.42 (1C, CO$_2C_{aromOBz}$) 128.45 (2C, CH$_{m-OBz}$) 127.99 (2C, CH$_{ar}$) 127.61 (2C, CH$_{ar}$) 97.34 (1C, C=CH) 84.73 (1C, =CHCOCH$_3$) 58.55 (1C, =CCHCH) 56.24 (1C, =COCH$_3$) 55.91 (1C, =CCHCH) 52.50 (1C, =CHCOCH$_3$) 51.88 (1C, CHOBz) 24.66 (1C, CHCHOBz) 9.71 (1C, CH$_2$CHOBz);
IR (thin film, cm^{-1}) (Appendix N.14): 2933 (w, C-H st) 1722 (m, C=O st) 1661 (w, C=C st) 1489 (m, H-C-H δ) 1264 (s, C-O st as) 1089 (s, arom C-Cl γ) 1014 (s, CH$_3$ γ) 709 (s, ar C-H δ oop)

Synthesis of 2-(4,5-bis(4-chlorophenyl)-1,3-dimethoxycyclopent-2-en-1-yl)-1-methylcyclopropyl acetate (24a-b)

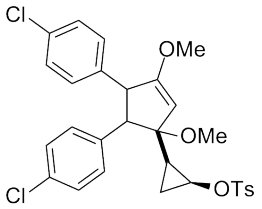


24a **24b**

Compounds **24a-b** were synthesized following general procedure B, using gold catalyst (13.4 mg, 0.02 mmol), 1-chloro-4-(1-((2-methoxypropan-2-yl)oxy)prop-2-yn-1-yl)benzene **20** (80.0 mg, 0.33 mmol) and isopropenyl acetate **25** (64.8 mg, 0.65 mmol). The reaction mixture was stirred at room temperature for 16 min. An isocratic eluent of 30:1 pentane, diethyl ether was used to isolate a mix of compound **24a** and compound **24b** as a yellow oil (32.5 mg, 42%). A small amount of compound **24a** was isolated from the isomer mixture, as a yellow oil (8.1 mg, 11%). Due to the complexity of the ^{1}H, and ^{13}C spectra of the isomer mixture (Appendix O.1 and O.2), the chemical shifts of product **24b** could not be assigned. (*cis*/*trans* 73:27). (Table 5.2, entry 8).

24a: R_f = 0.26 (10:3 Pentane/Diethyl ether);
^{1}H-NMR (400 MHz, $CDCl_3$-TMS) (Appendix O.3) δ (ppm); 7.31 (m, 2H, CH_{ar}) 7.27 (m, 2H, CH_{ar}) 7.26 (m, 2H, CH_{ar}) 7.22-7.24 (m, 2H, CH_{ar}) 4.88 (dd, 1H, J = 1.8, 1.1 Hz, C=CH) 4.28 (s, 1H, =CCHCH) 4.05 (s, 1H, =CCHCH) 3.70 (s, 3H, =COCH_3) 3.11 (s, 3H, =CHCOCH_3) 2.03 (s, 3H, CO_2CH_3) 1.14-1.18 (m, 1H, AcOCCH_2) 1.05 (s, 3H, CHCCH_3) 0.85-0.88 (m, 1H, AcOCCH_2) 0.28 (dd, 1H, J = 10.0, 7.8 Hz, AcOCCH)
^{13}C-NMR (400 MHz, $CDCl_3$-TMS) (Appendix O.4) δ (ppm) 170.23 (1C, OC=O) 160.70 (1C, CH=COCH$_3$) 138.98 (1C, C_{ar}CHCHC=) 136.62 (1C, C_{ar}CHC=) 132.83 (1C, C_{ar}Cl) 132.16 (1C, C_{ar}Cl) 130.96 (2C, CH$_{ar}$) 130.22 (2C, CH$_{ar}$) 128.37 (2C, CH$_{ar}$) 127.89 (2C, CH$_{ar}$) 98.52 (1C, C=CH) 86.22 (1C, =CHCOCH$_3$) 58.81 (1C, COAc) 58.29 (1C, =CCHCH) 56.95 (1C, =COCH$_3$) 54.61 (1C, =CCHCH) 51.97 (1C, =CHCOCH$_3$) 29.36 (1C, CHCOAc) 22.55 (1C, CHCCH$_3$) 21.63 (1C, CO_2CH_3) 16.71 (1C, CH$_2$COAc);
24b: R_f = 0.32 (10:3 Pentane/Diethyl ether);
24a-b: IR (thin film, cm^{-1}) (Appendix O.9): 2935 (w, C-H st) 1744 (m, C=O st) 1653 (m, C=C st) 1489 (m, H-C-H δ) 1207 (s, C-O st as) 1089 (s, arom C-Cl γ) 1014 (s, CH_3 γ) 908 (m, CH_3 γ) 729 (s, ar C-H δ oop);
HRMS (EI) calcd for $C_{25}H_{26}O_4Cl_2$ $[M]^+$ 460.1203, obsd 460.1205

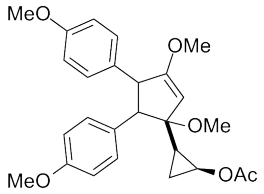
Synthesis of 2-(4,5-bis(4-chlorophenyl)-1,3-dimethoxycyclopent-2-en-1-yl)cyclopropyl tosylate (26)



26

Compound **26** was synthesized following general procedure B, using gold catalyst (13.1 mg, 0.02 mmol), 1-chloro-4-(1-((2-methoxypropan-2-yl)oxy)prop-2-yn-1-yl)benzene **20** (80.5 mg, 0.33 mmol) and vinyl tosylate **4** (112.7 mg, 0.57 mmol). The reaction mixture was stirred at room temperature for 19 min. An isocratic eluent of 10:1.5 pentane, diethyl ether was used to isolate compound **26** (12.8 mg, 14%) as a yellow oil. (Table 5.2, entry 9).
HRMS (EI) was not obtained for this compound.
26: R_f = 0.20; (10:3 Pentane/Diethyl ether);
^{1}H-NMR (400 MHz, $CDCl_3$-TMS) (Appendix P.1) δ (ppm) 7.77 (2H, d, J = 8.24 Hz, CH_{o-OTs}) 7.32 (m, 2H, CH_{m-OTs}) 7.23-7.31 (m, 4H, CH_{ar}) 7.20 (m, 2H, CH_{ar}) 7.16 (m, 2H, CH_{ar}) 4.77 (s, 1H, C=CH) 4.34 (s, 1H, =CCHCH) 3.96 (s, 1H, =CCHCH) 3.70 (m, 1H, CHOTs) 3.67 (s, 3H, =COCH_3) 2.98 (s, 3H, =CHCOCH_3) 2.45 (s, 3H, SO_3PhCH_3) 0.88 (m, 1H, TsOCHCH_2) 0.60 (dt, 1H, J = 10.3, 6.7 Hz, TsOCHCH_2) 0.29 (ddd, 1H, J = 10.2, 8.3, 7.4 Hz, TsOCHCH)
^{13}C-NMR (400 MHz, $CDCl_3$-TMS) (Appendix P.2) δ (ppm) 159.66 (1C, CH=COCH$_3$) 145.13 (1C, SO_3C_{ar}) 138.97 (1C, C_{ar}CHCHC=) 135.78 (1C, C_{ar}CHC=) 133.61 (1C, C_{ar}Me) 132.87 (1C, C_{ar}Cl) 132.15 (1C, C_{ar}Cl) 130.96 (2C, CH$_{ar}$) 130.64 (2C, CH$_{ar}$) 129.84 (2C, CH$_{m-OTs}$) 128.27 (2C, CH$_{ar}$) 128.16 (2C, CH$_{o-OTs}$) 127.88 (2C, CH$_{ar}$) 99.19 (1C, C=CH) 85.95 (1C, =CHCOCH$_3$) 59.30 (1C, =CCHCH) 57.24 (=COCH$_3$) 56.82 (1C, CHOTs) 52.76 (1C, =CCHCH) 52.10 (1C, =CHCOCH$_3$) 21.70 (1C, CHCHOTs) 21.17 (1C, CHCHOTs) 8.74 (1C, CH$_2$CHOTs);
IR (thin film, cm^{-1}) (Appendix P.7): 2935 (w, C-H st) 1653 (w, C=C st) 1489 (s, H-C-H δ) 1190 (m, S=O st) 1176 (s, R-SO_2-OR st as and st sy) 1090 (s, arom C-Cl γ) 1013 (s, CH_3 γ) 827 (s, ar C-H δ oop) 729 (s, ar C-H δ oop)

Synthesis of 2-(1,3-dimethoxy-4,5-bis(4-methoxyphenyl)cyclopent-2-en-1-yl)cyclopropyl acetate (27)



27

Compound **27** was synthesized following general procedure B, using gold catalyst (10.6 mg, 0.01 mmol), 1-methoxy-4-(1-((2-methoxypropan-2-yl)oxy)prop-2-yn-1-yl)benzene **21** (60.2 mg, 0.26 mmol) and vinyl acetate **12** (46.4 mg, 0.54 mmol). The reaction mixture was stirred at room temperature for 12 min. A gradient eluent of pentane and diethyl ether was used for purification. Compound **27** (7.4 mg, 13%) was isolated at 10:2 pentane, diethyl ether as a yellow oil. (Table 5.2, entry 10).

27: R_f = 0.20 (10:2 Pentane/EtOAc);
HRMS (EI) calcd for $C_{26}H_{30}O_6$ $[M]^+$ 438.2037, obsd 438.2033;
^{1}H-NMR (400 MHz, $CDCl_3$-TMS) (Appendix Q.1) δ (ppm) 7.24 (d, 2H, J = 8.7 Hz, CH_{ar}) 7.17 (d, 2H, J = 8.6 Hz, CH_{ar}) 6.86 (d, 2H, J = 3.9 Hz, CH_{ar}) 6.84 (d, 2H, J = 3.9 Hz, CH_{ar}) 4.79 (t, 1H, J = 1.8 Hz, C=CH) 4.37 (s, 1H, =CCHCH) 4.03 (td, 1H, J = 7.1, 4.3 Hz, CHOAc) 3.99 (s, 1H, =CCHCH) 3.81 (s, 3H, PhOCH_3) 3.79 (s, 3H, PhOCH_3) 3.69 (s, 3H, =COCH_3) 3.03 (s, 3H, =CHCOCH_3) 2.10 (s, 3H, CO_2CH_3) 0.87-0.92 (m, 1H, AcOCHCH_2) 0.82 (dt, 1H, J = 10.2, 6.7 Hz, AcOCHCH_2) 0.39 (ddd, 1H, J = 10.1, 8.1, 7.4 Hz, AcOCHCH)
^{13}C-NMR (400 MHz, $CDCl_3$-TMS) (Appendix Q.2) δ (ppm) 171.20 (1C, OC=O) 159.66 (1C, C_{ar}OMe) 158.56 (1C, CH=COCH$_3$) 158.22 (1C, C_{ar}OMe) 133.23 (1C, C_{ar}CHCHC=) 130.60 (2C, CH$_{ar}$) 130.25 (2C, CH$_{ar}$) 129.52 (1C, C_{ar}CHC=) 113.45 (2C, CH$_{ar}$) 113.22 (2C, CH$_{ar}$) 99.75 (1C, C=CH) 86.65 (1C, =CHCOCH$_3$) 59.59 (1C, =CCHCH) 56.65 (1C, =COCH$_3$) 55.22 (1C, PhCH$_3$) 55.21 (1C, PhCH$_3$) 53.31 (1C, CHOAc) 51.97 (1C, =CHCOCH$_3$) 51.84 (1C, =CCHCH) 21.55 (1C, CHCHOAc) 21.27 (1C, CO_2CH$_3$) 9.12 (1C, CH$_2$CHOAc);
IR (thin film, cm^{-1}) (Appendix Q.7): 2934 (w, C-H st) 1742 (m, C=O st) 1609 (m, C=C st) 1509 (s, ar C-C st) 1463 (m, H-C-H δ) 1227 (s, C-O st as) 1175 (s, C-O st as) 1031 (s, CH_3 γ) 830 (s, ar C-H δ oop) 729 (s, ar C-H δ oop)

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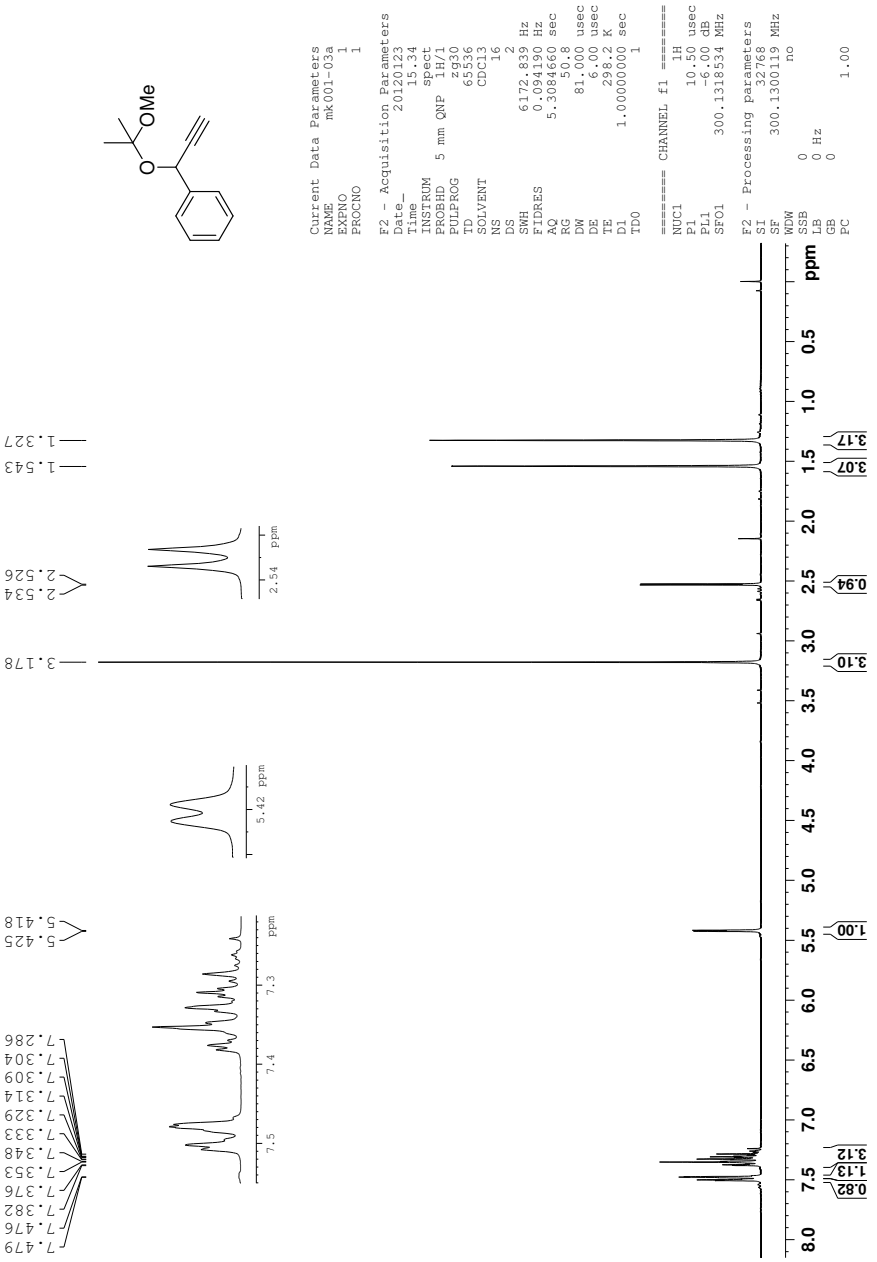
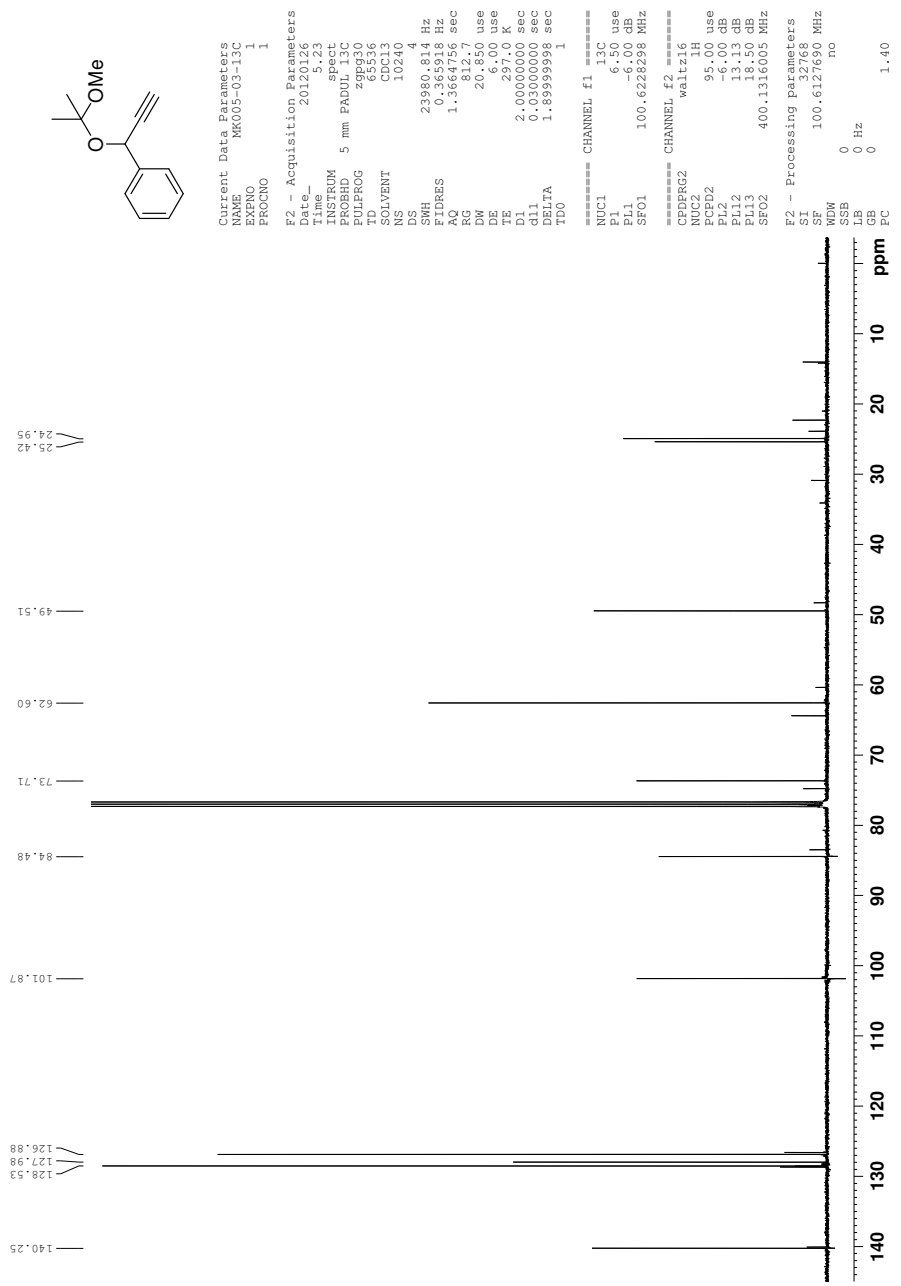
A Propargyl acetal 1a-b

A.1 ^{1}H NMR of propargyl acetal 1a



A.2 ^{13}C NMR of propargyl acetal 1a



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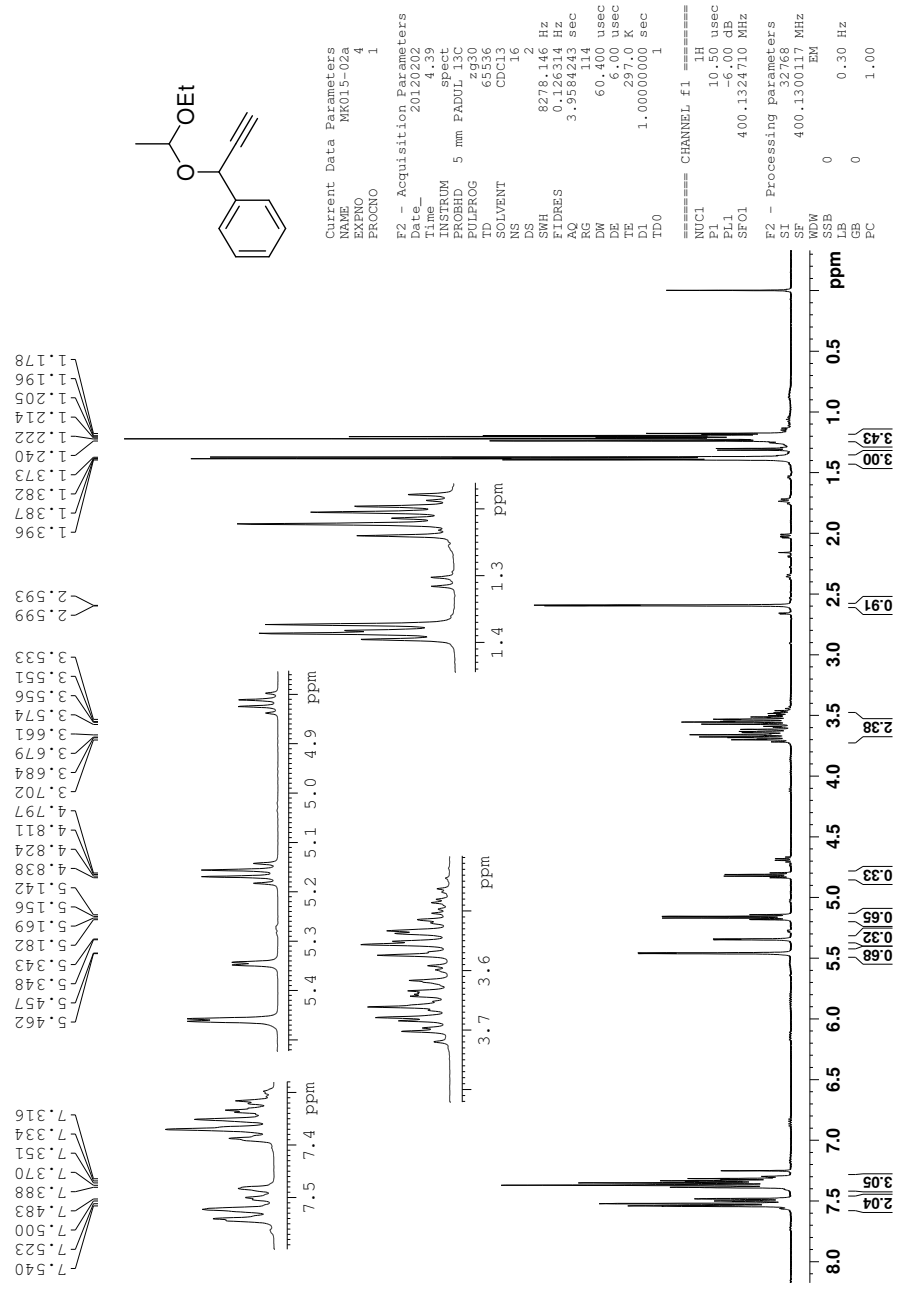

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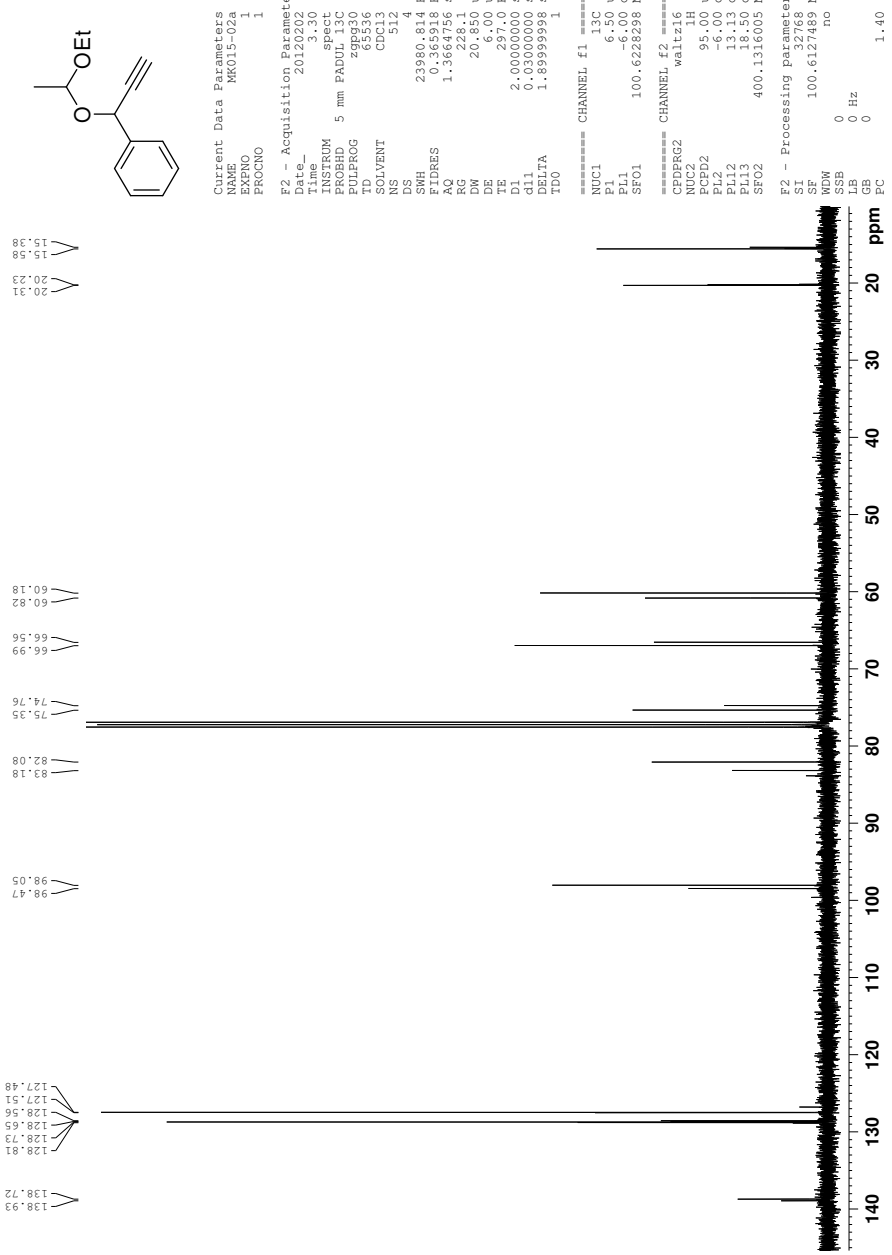

B Propargyl acetal 20

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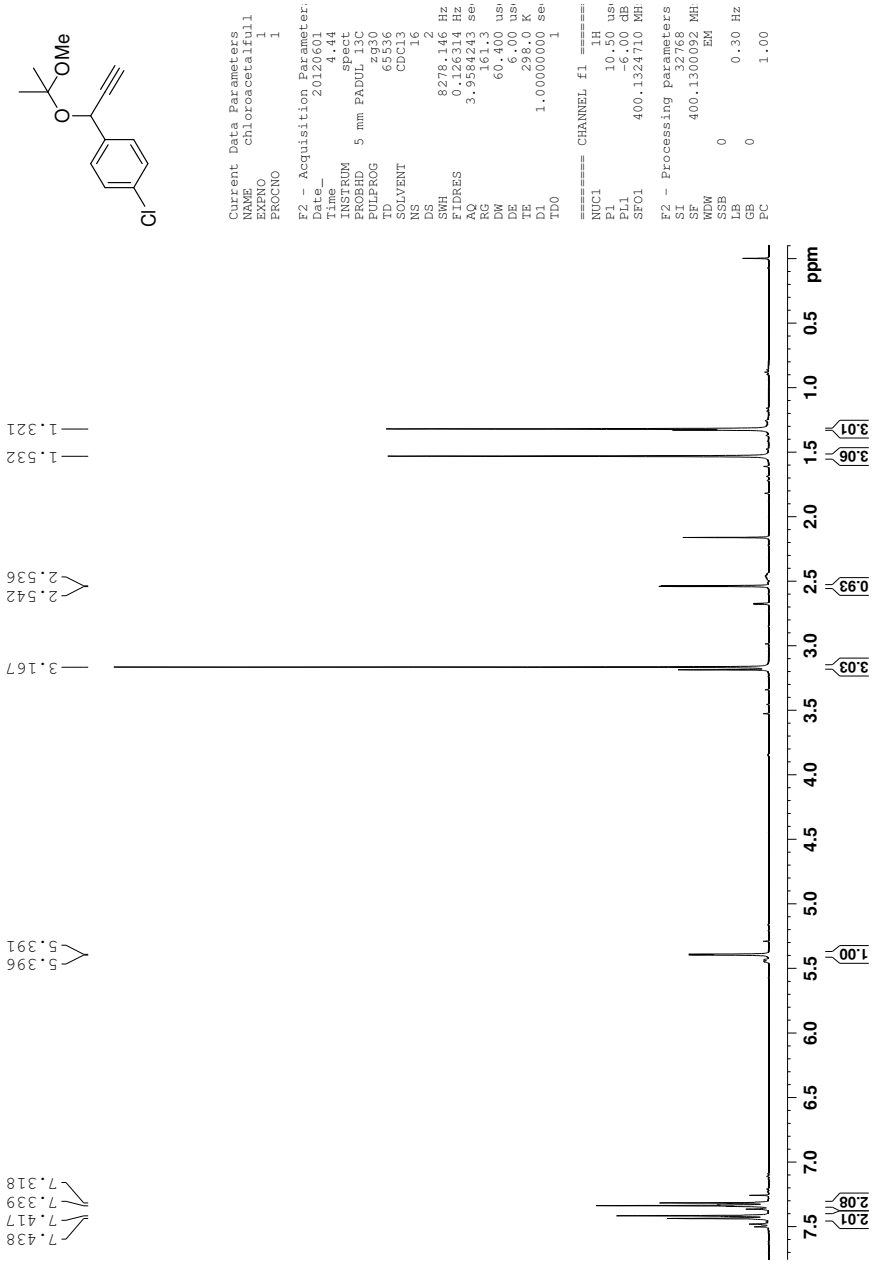

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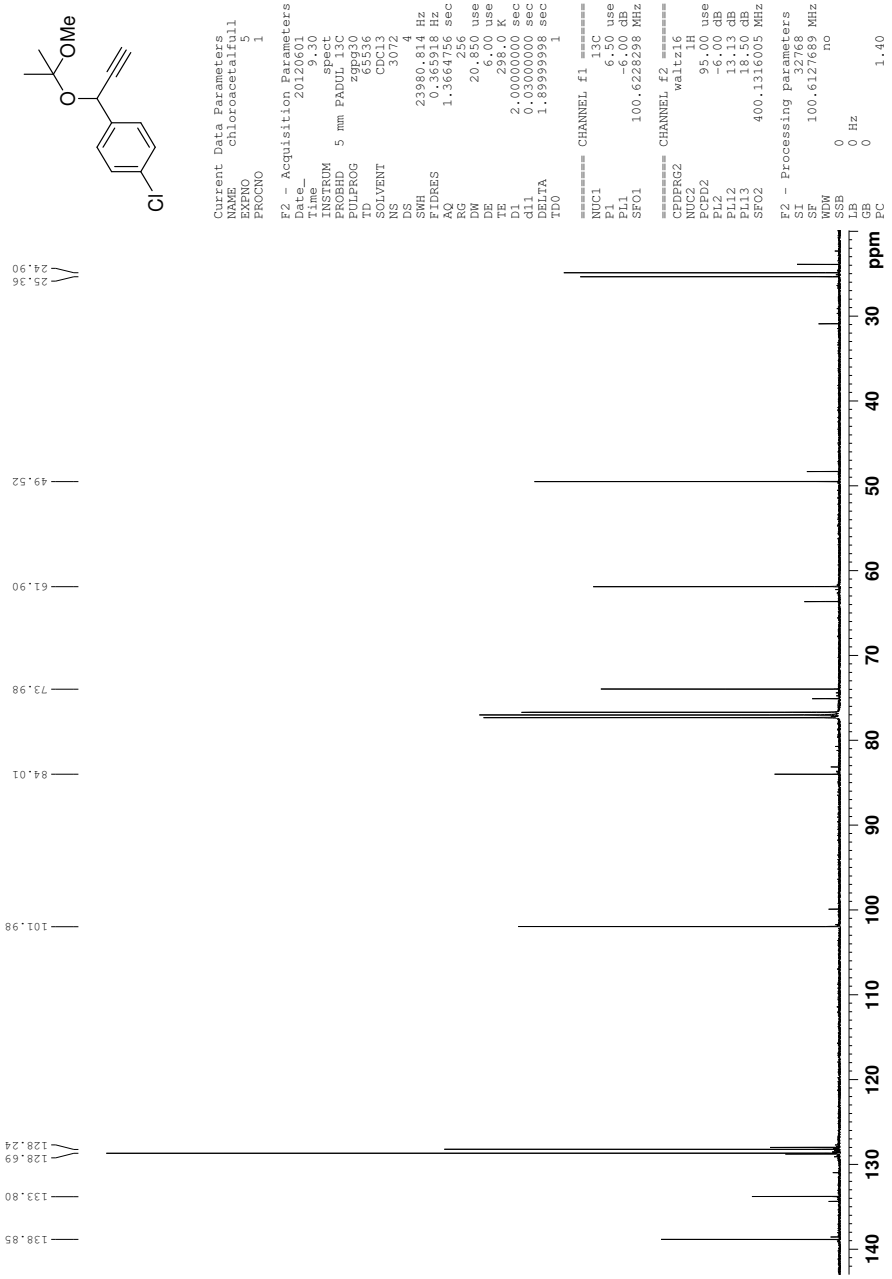

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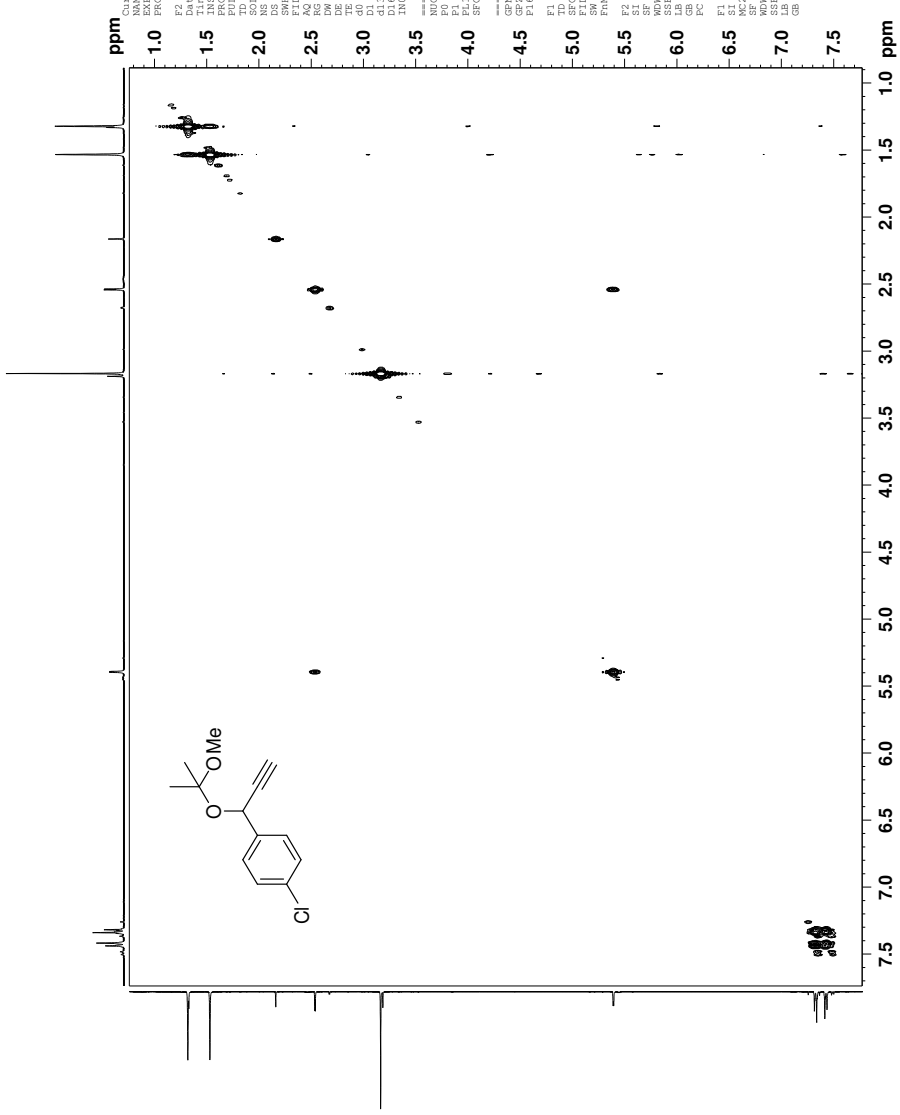

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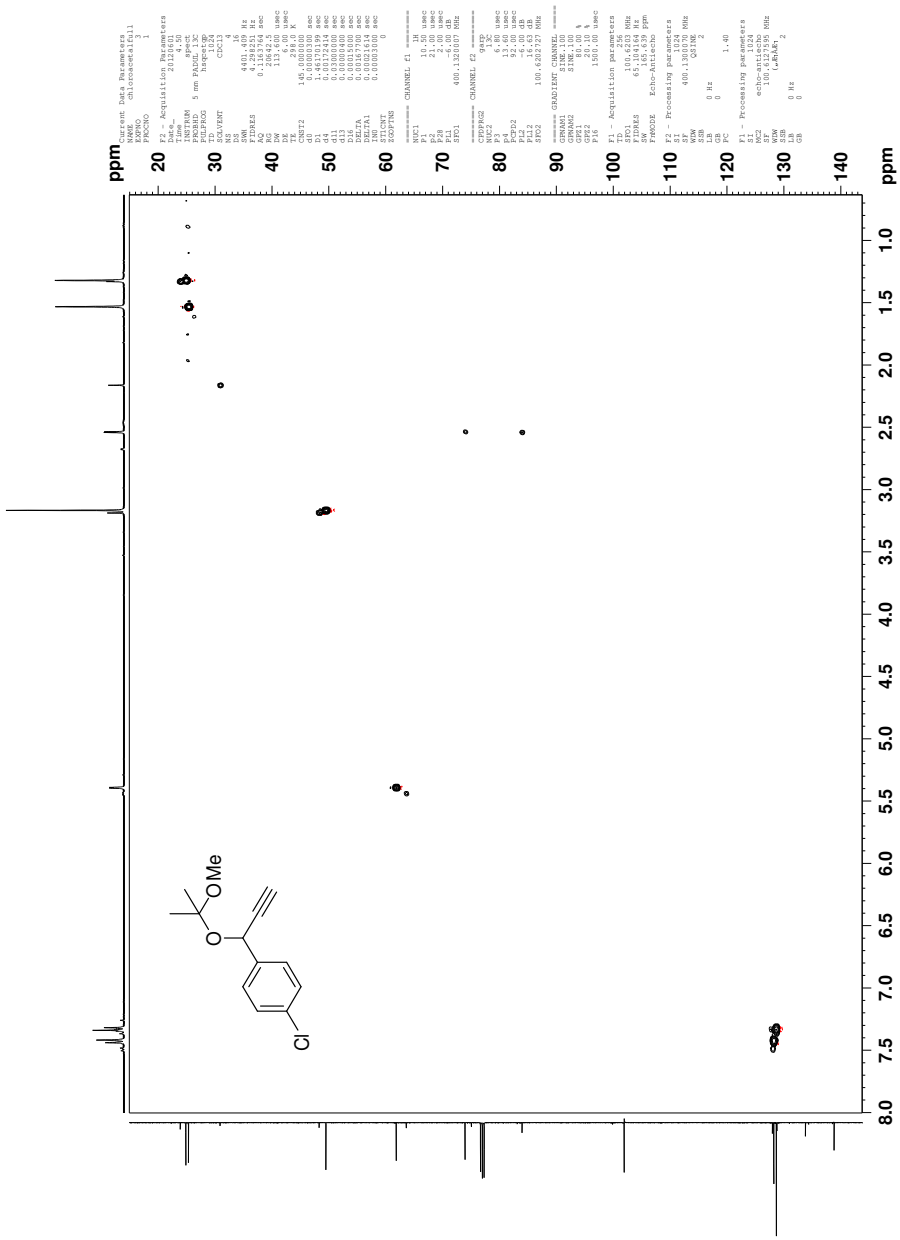

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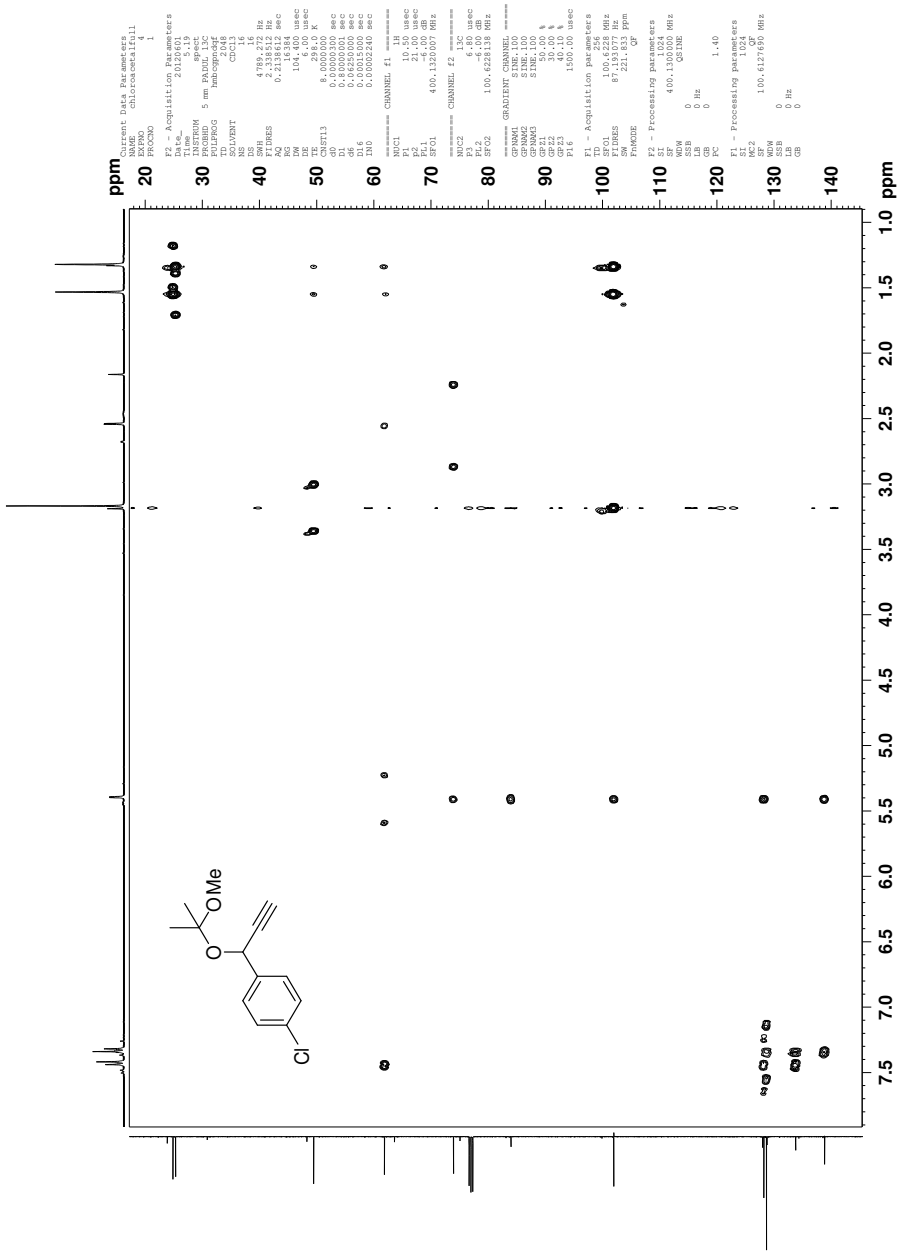

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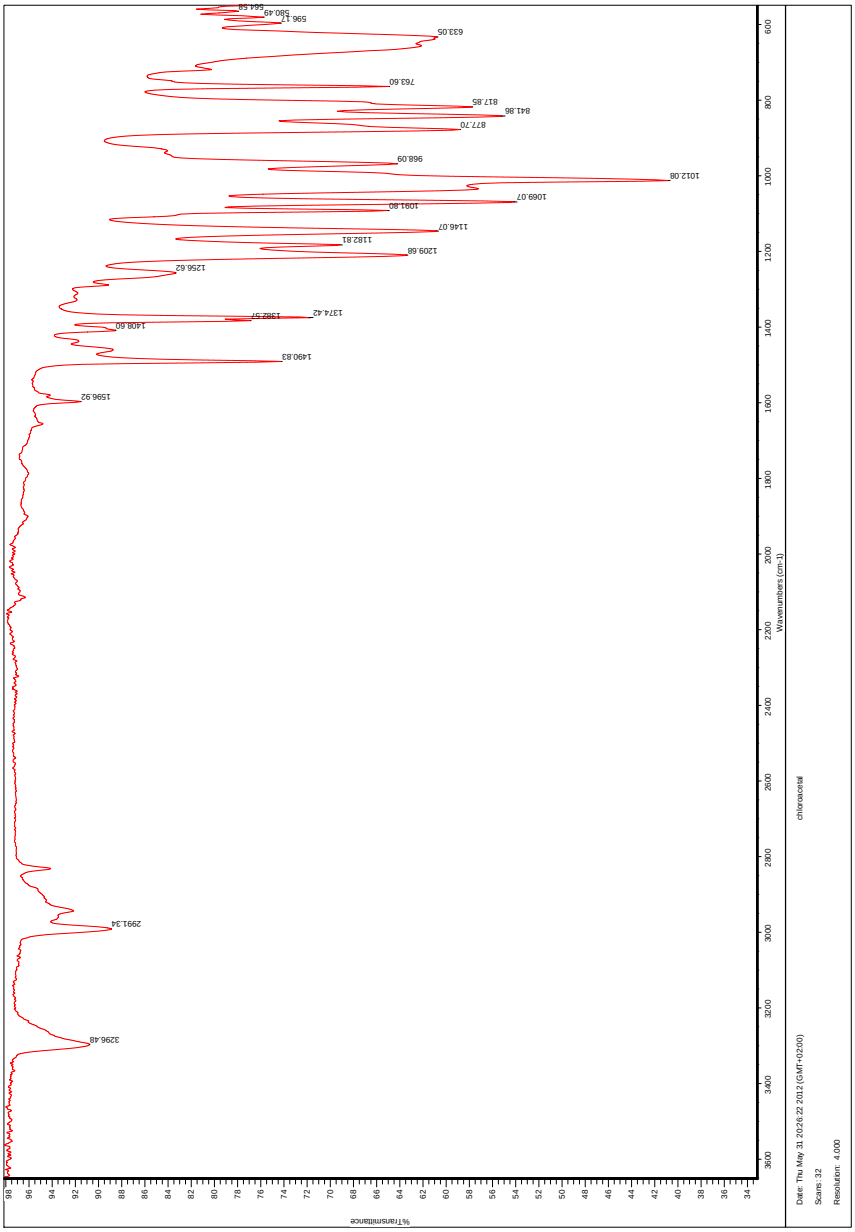
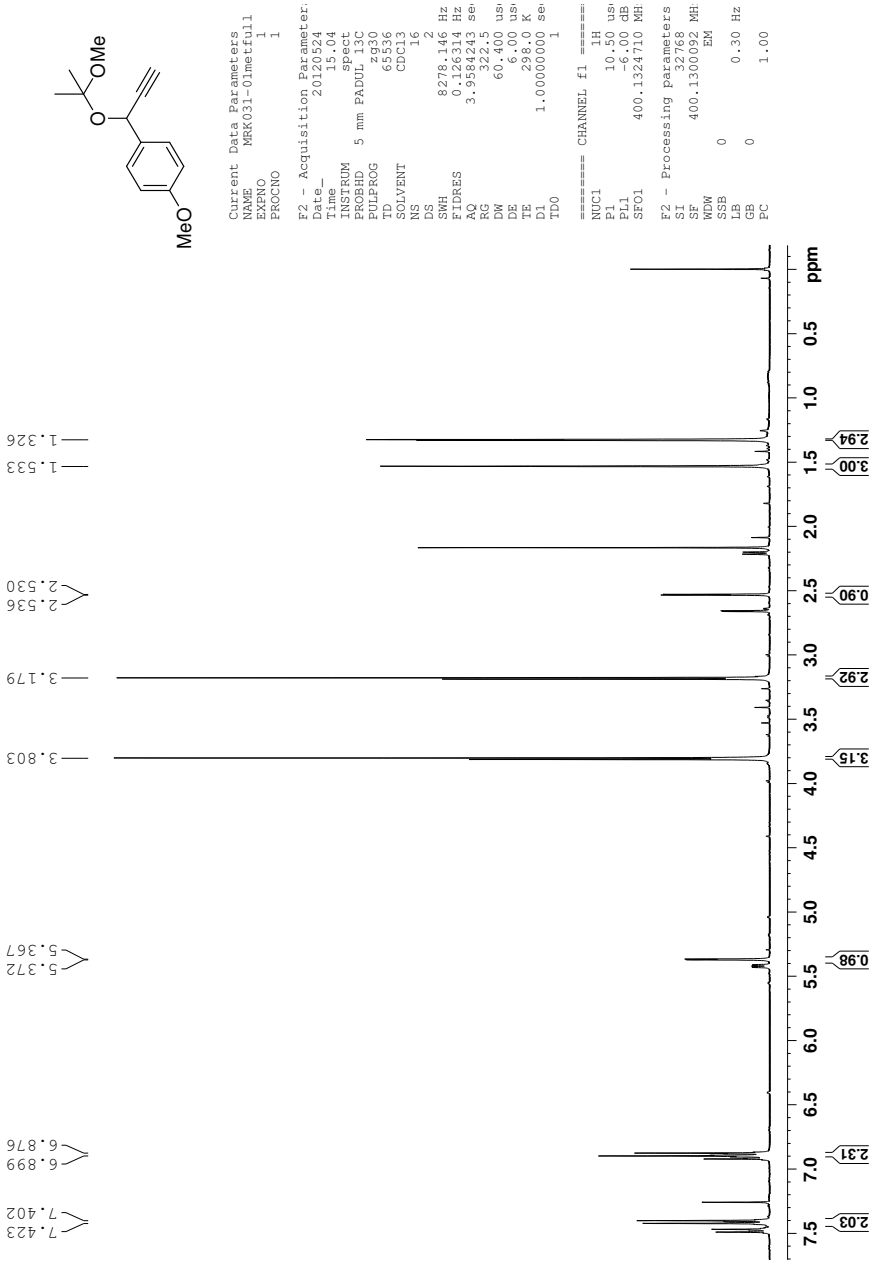


C Propargyl acetal 21

C.1 ^{1}H NMR of propargyl acetal 21



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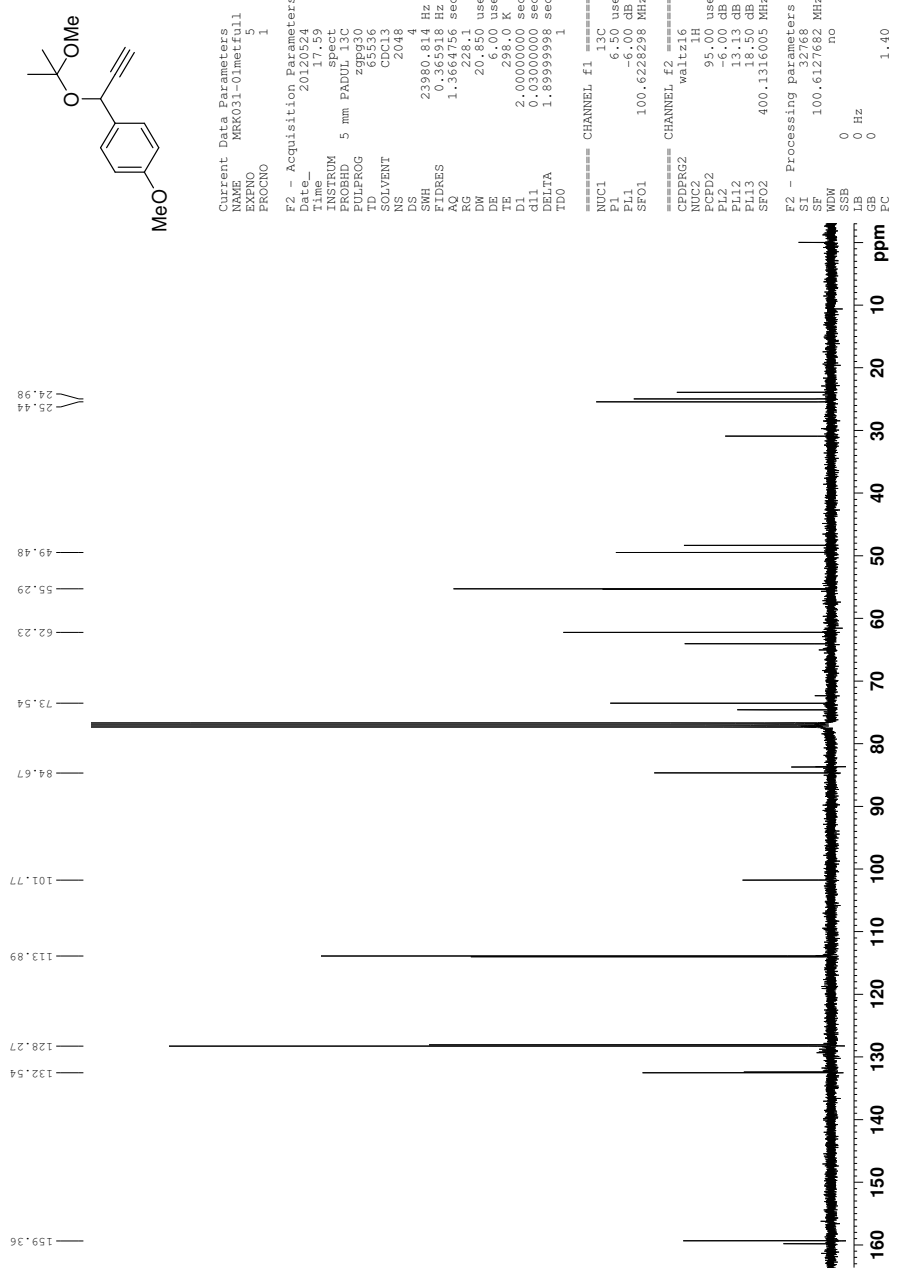

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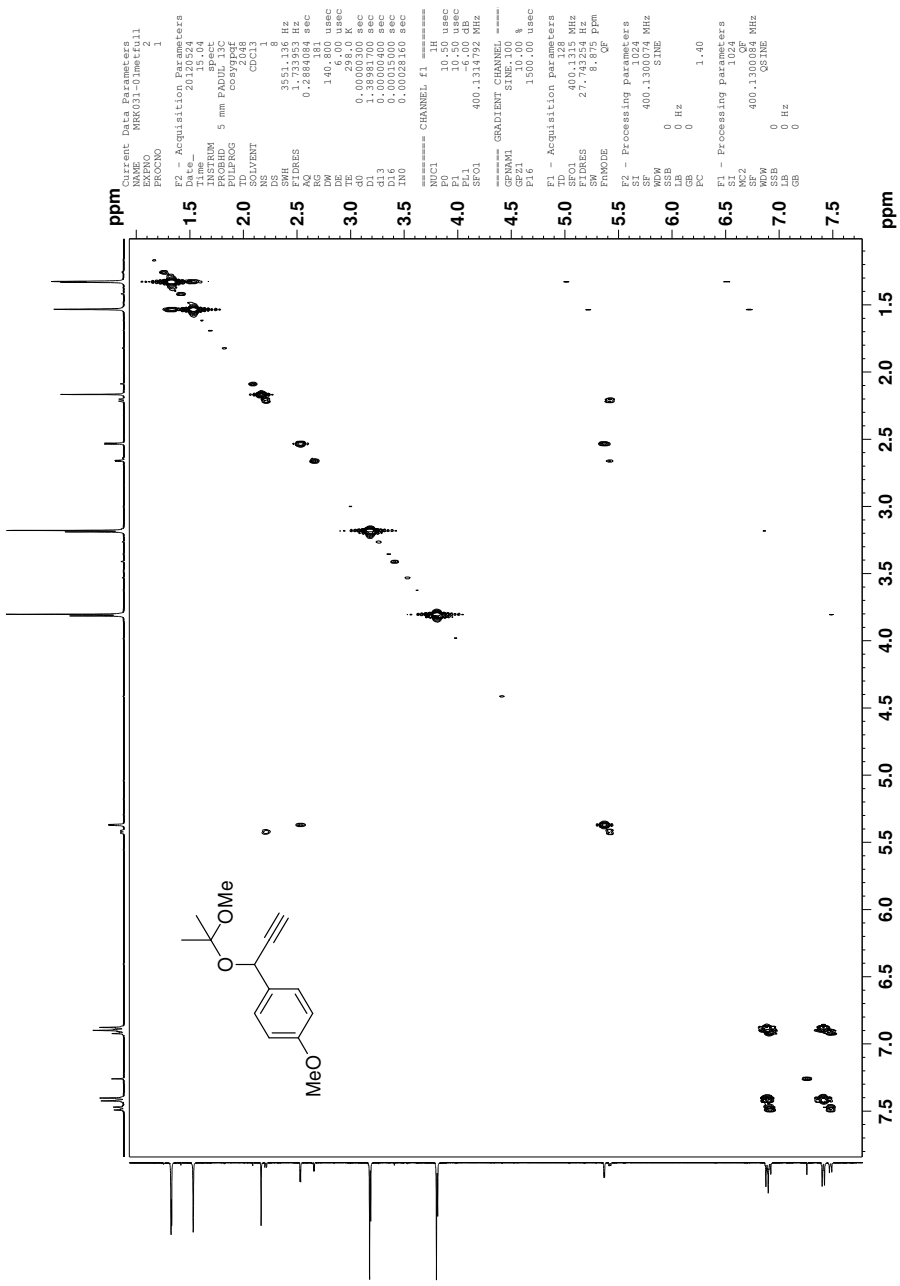

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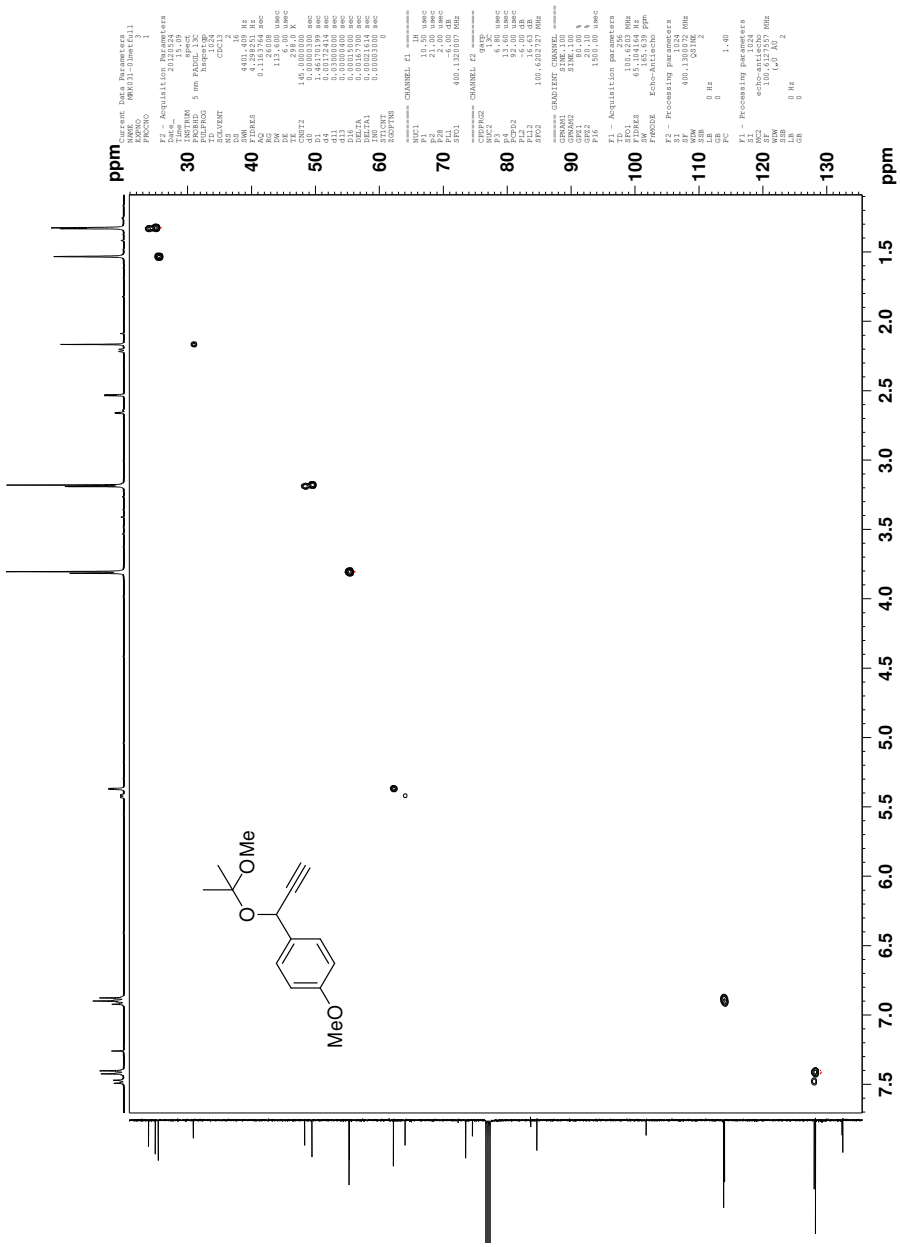

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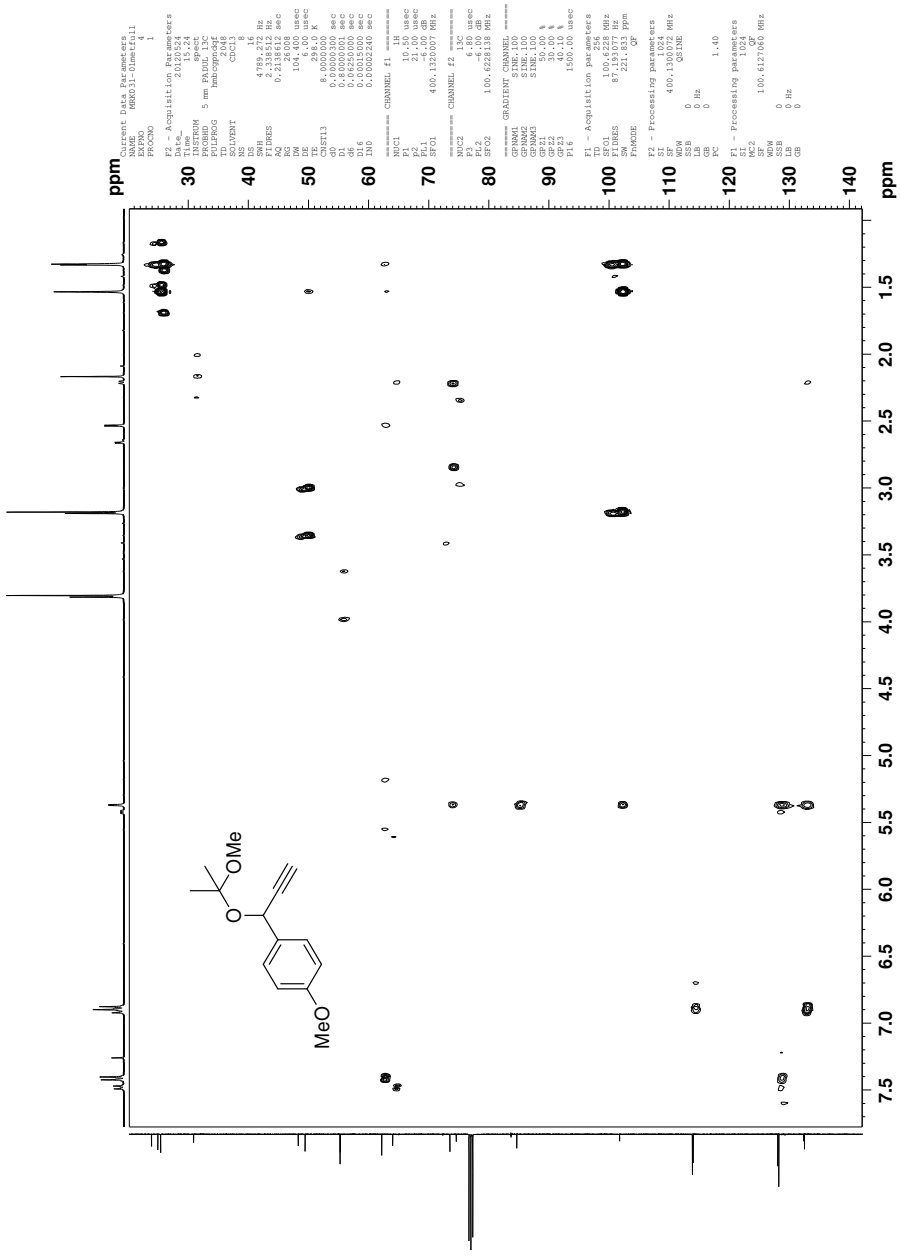

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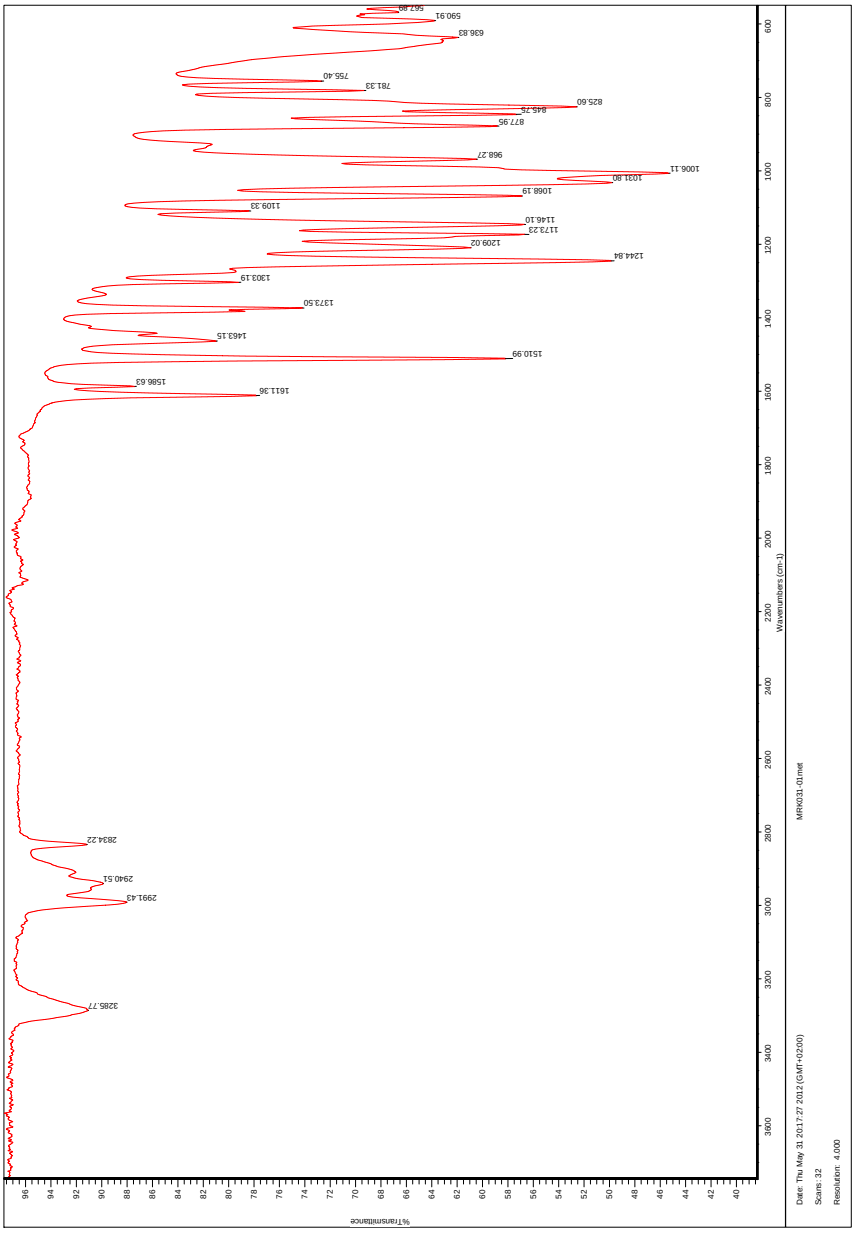
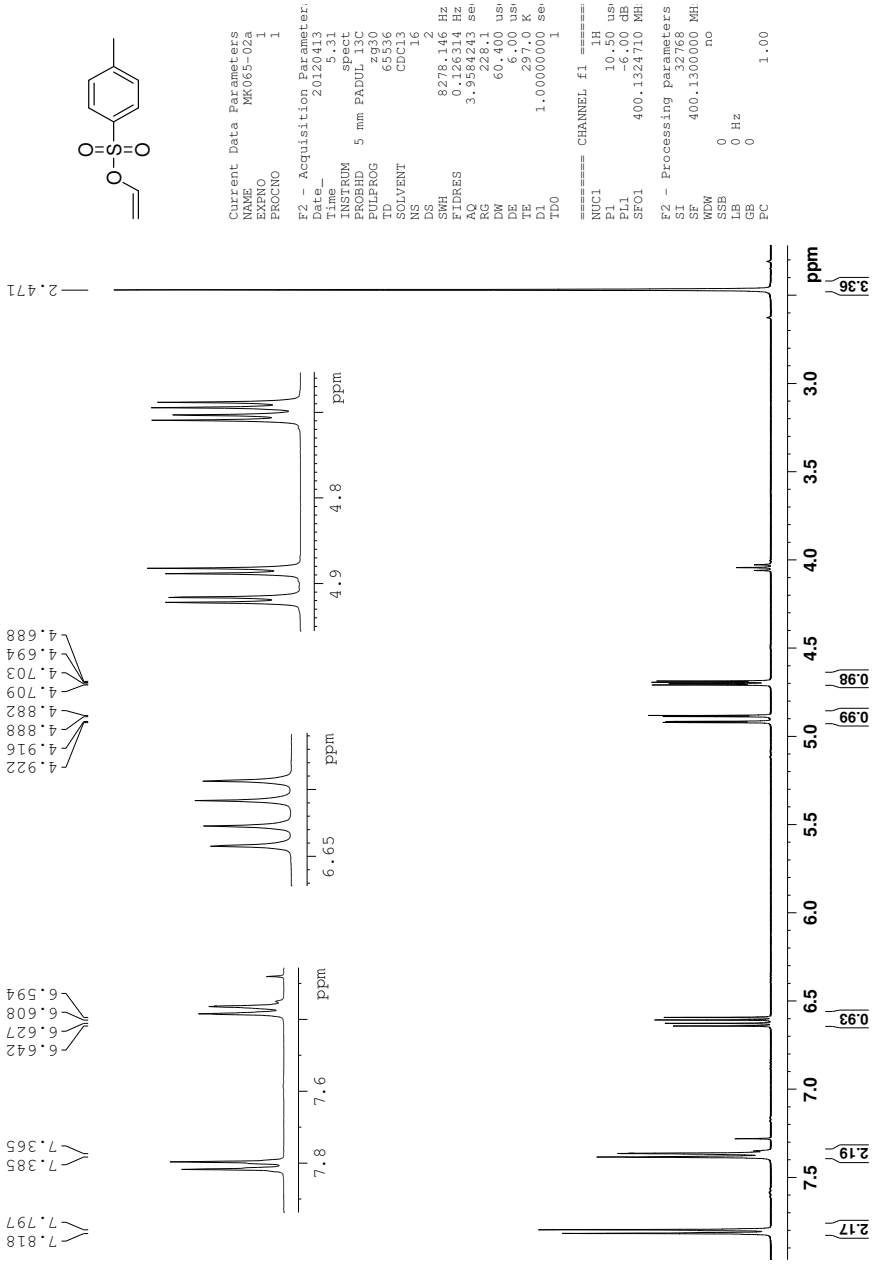


D Vinyl tosylate 4

D.1 ^{1}H NMR of vinyl tosylate 4



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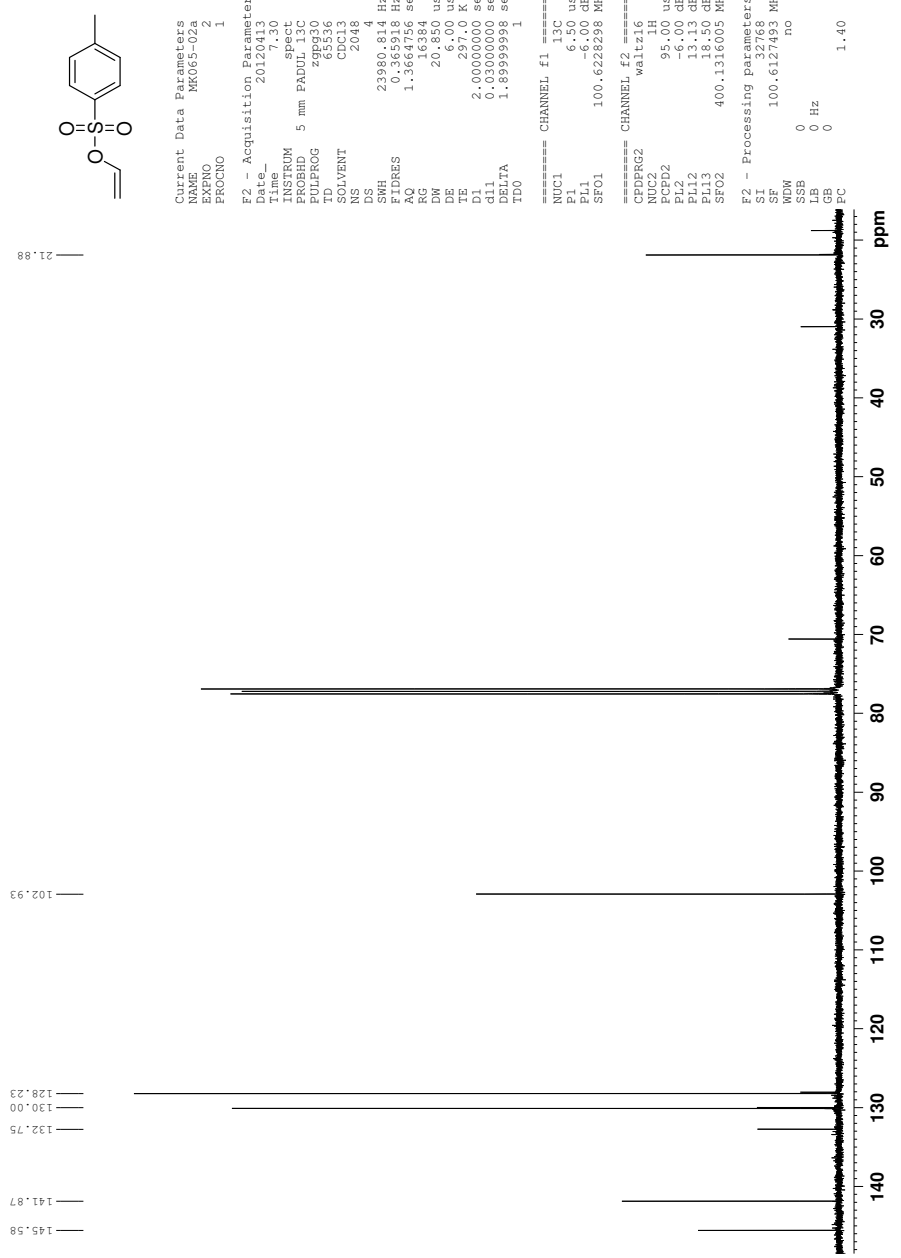
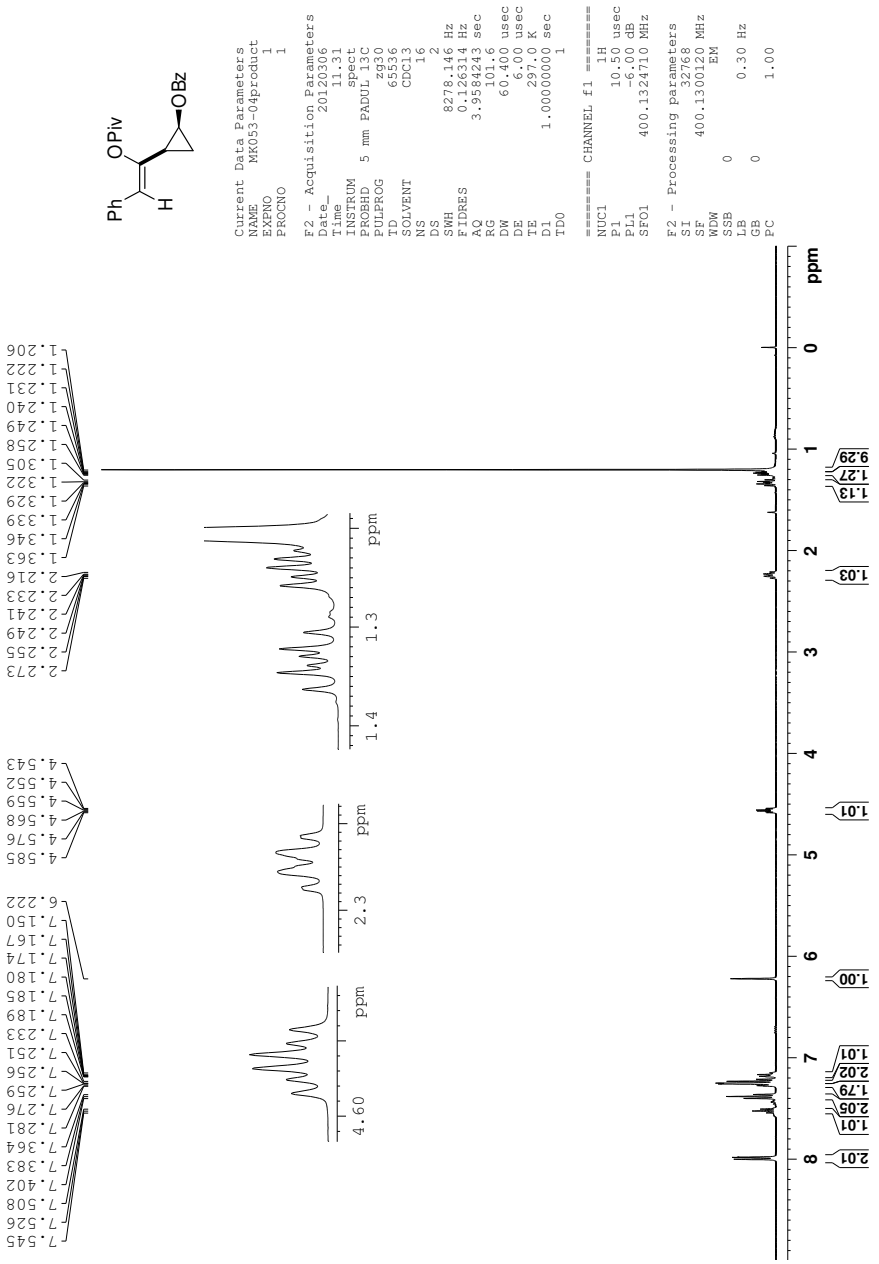


E Cyclopropyl compound 6a-b

E.1 ^{1}H NMR of cyclopropyl compound 6a



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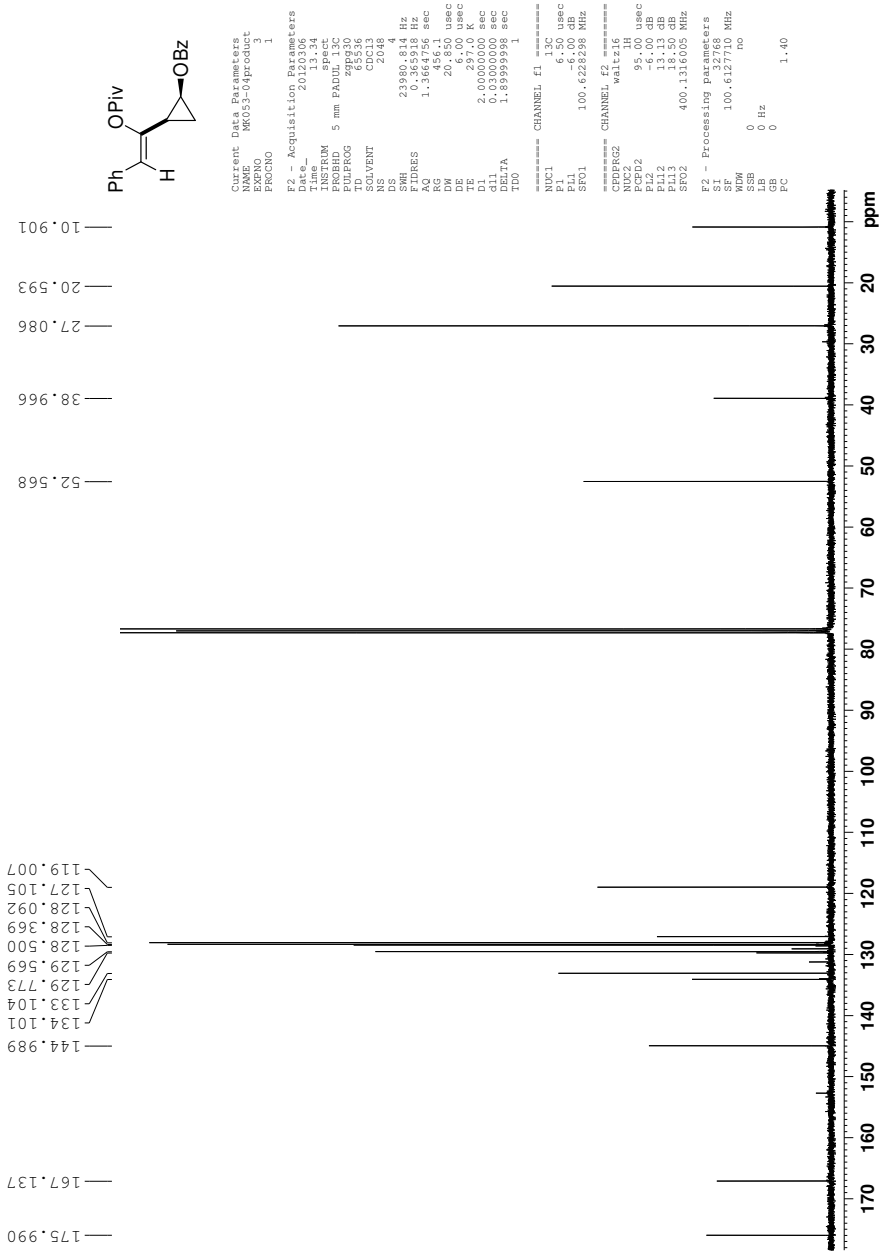

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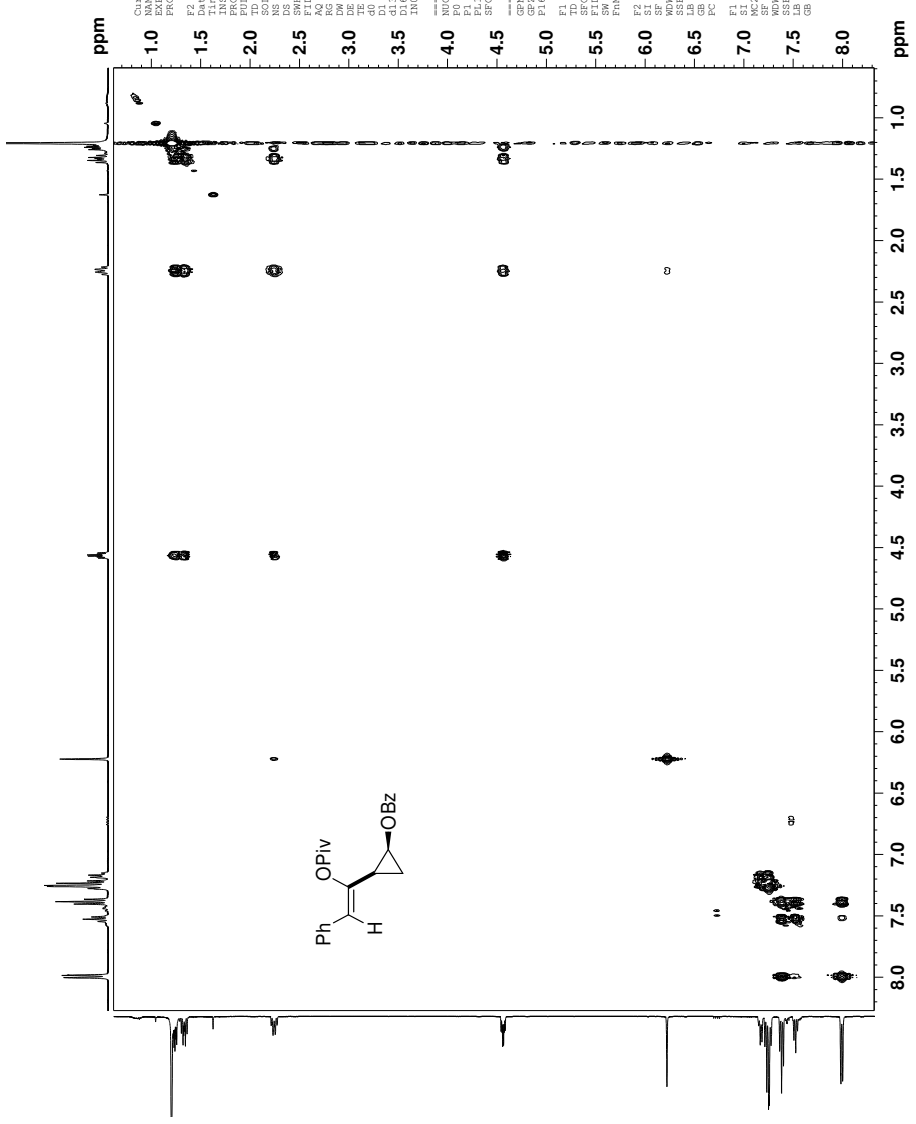

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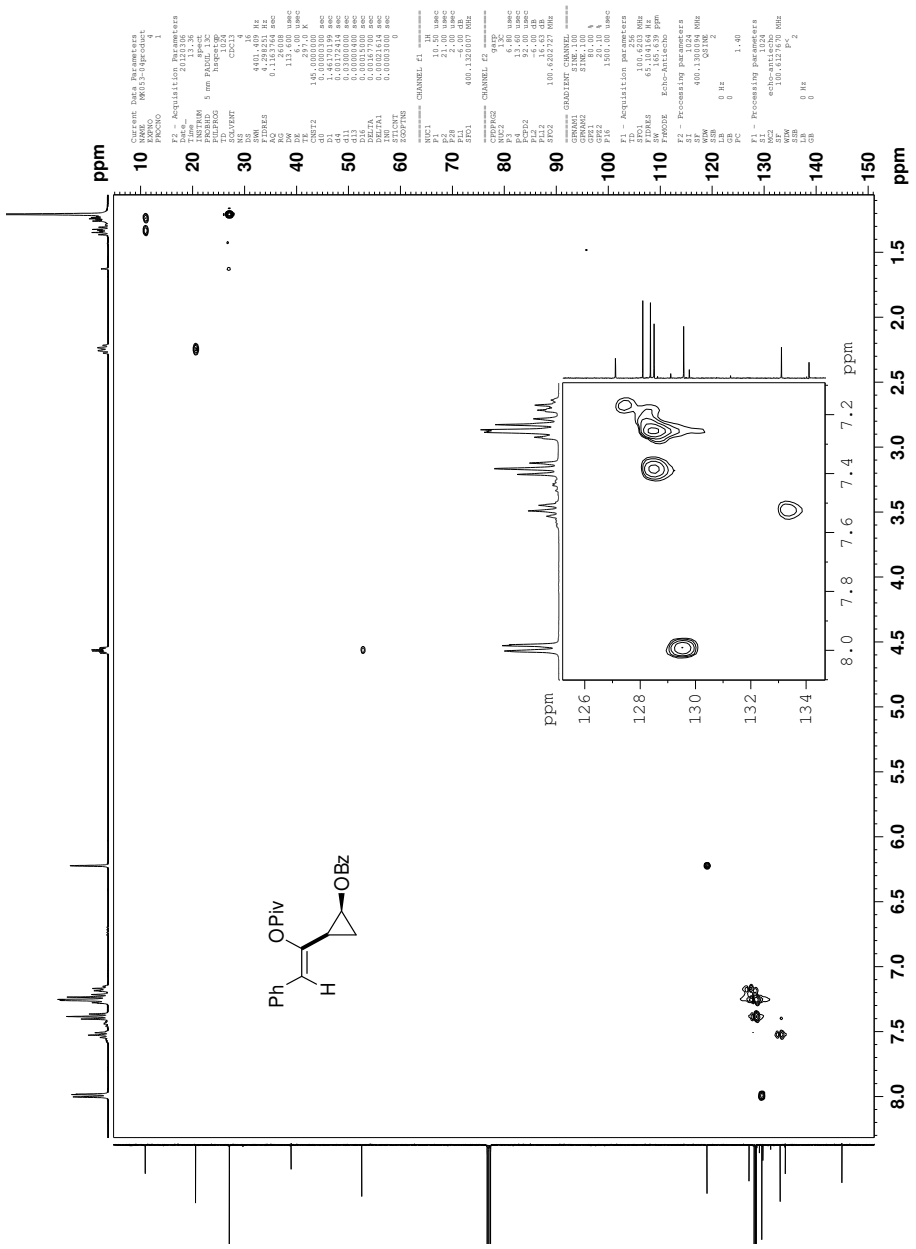

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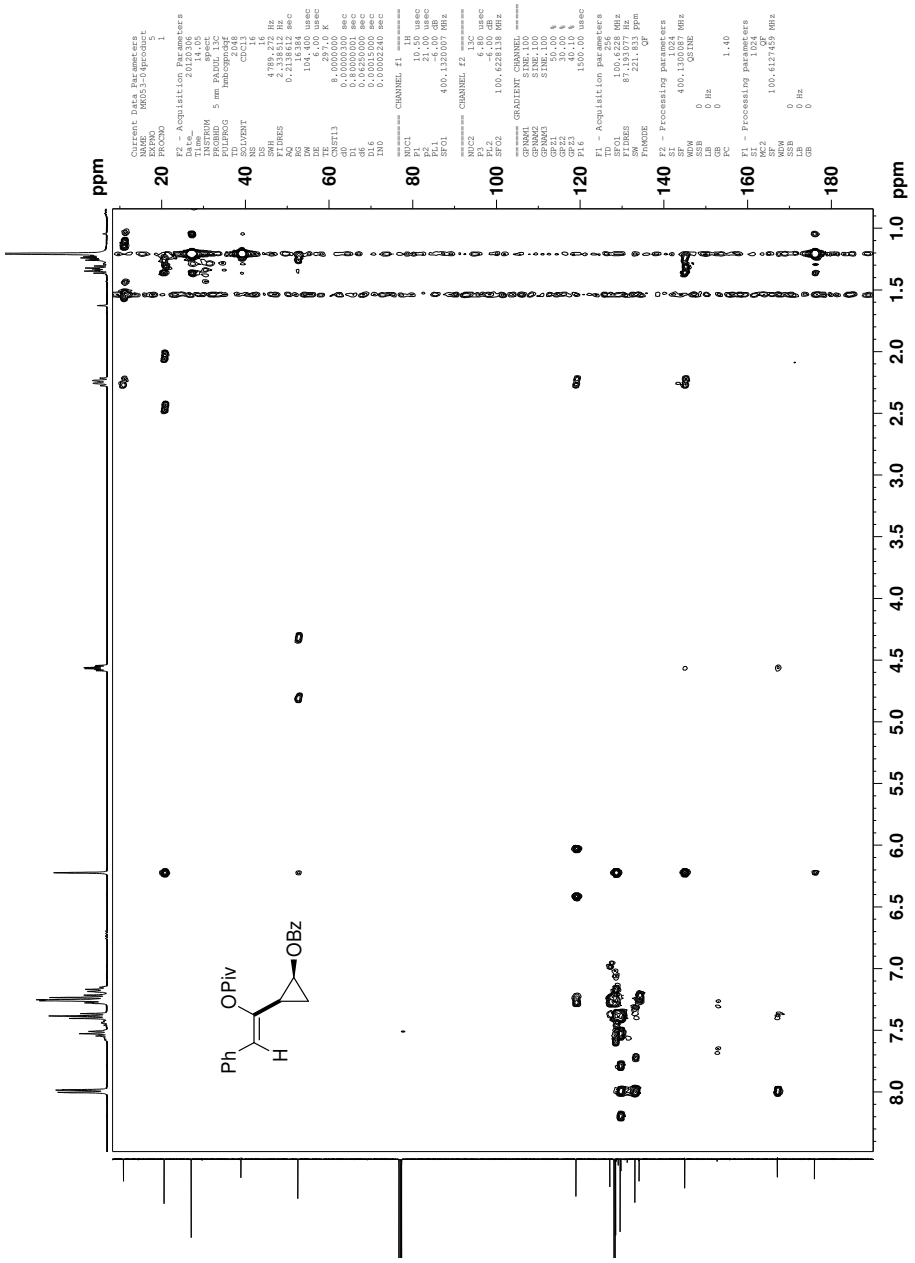

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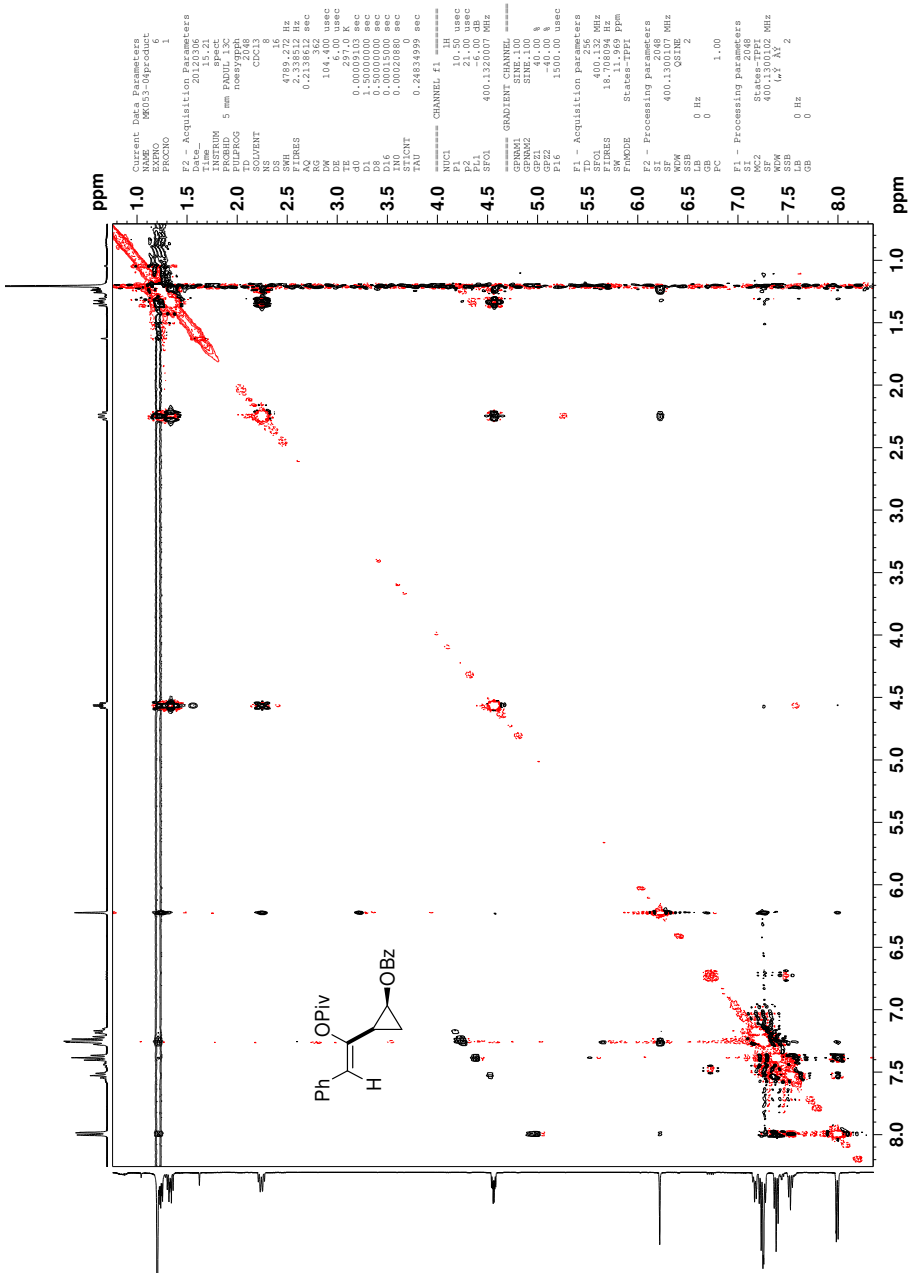
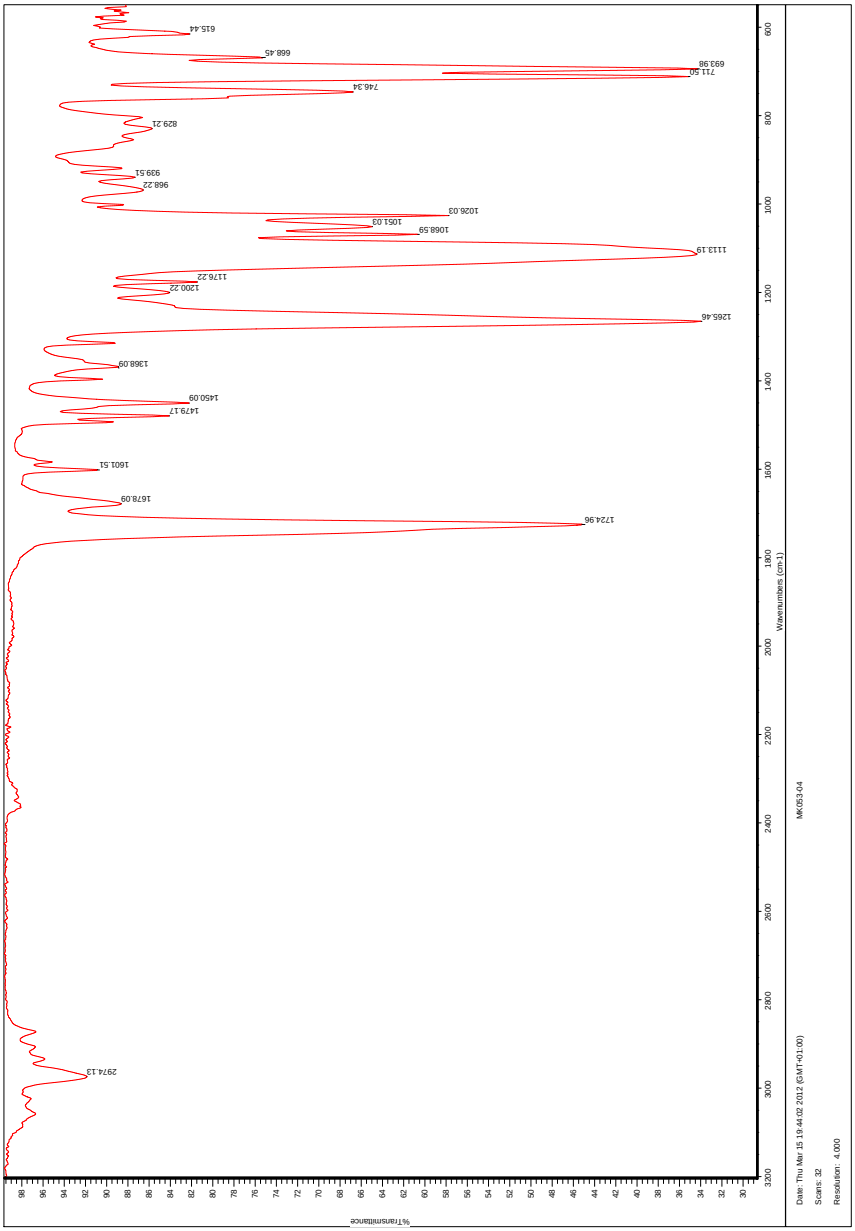


E.7 IR of cyclopropyl compound 6a



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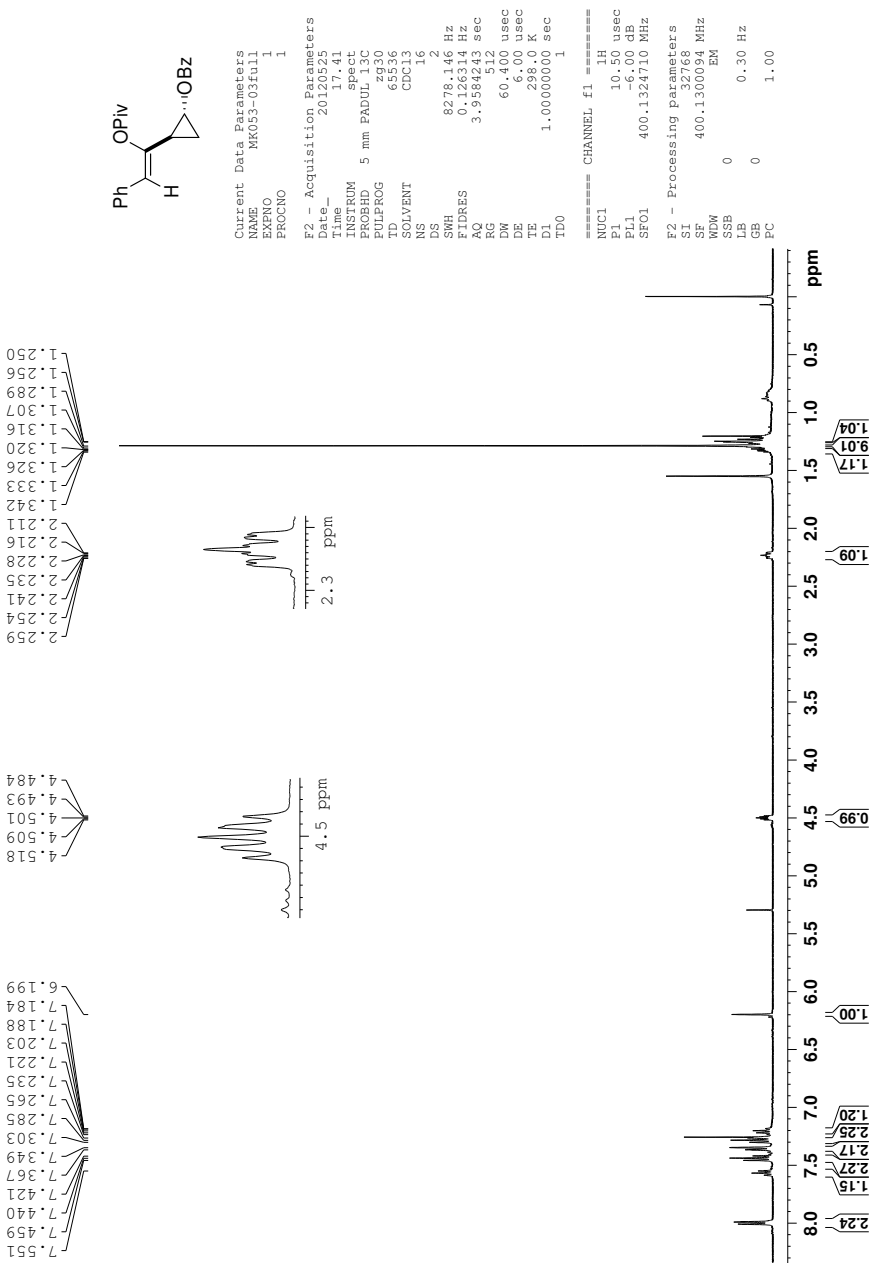

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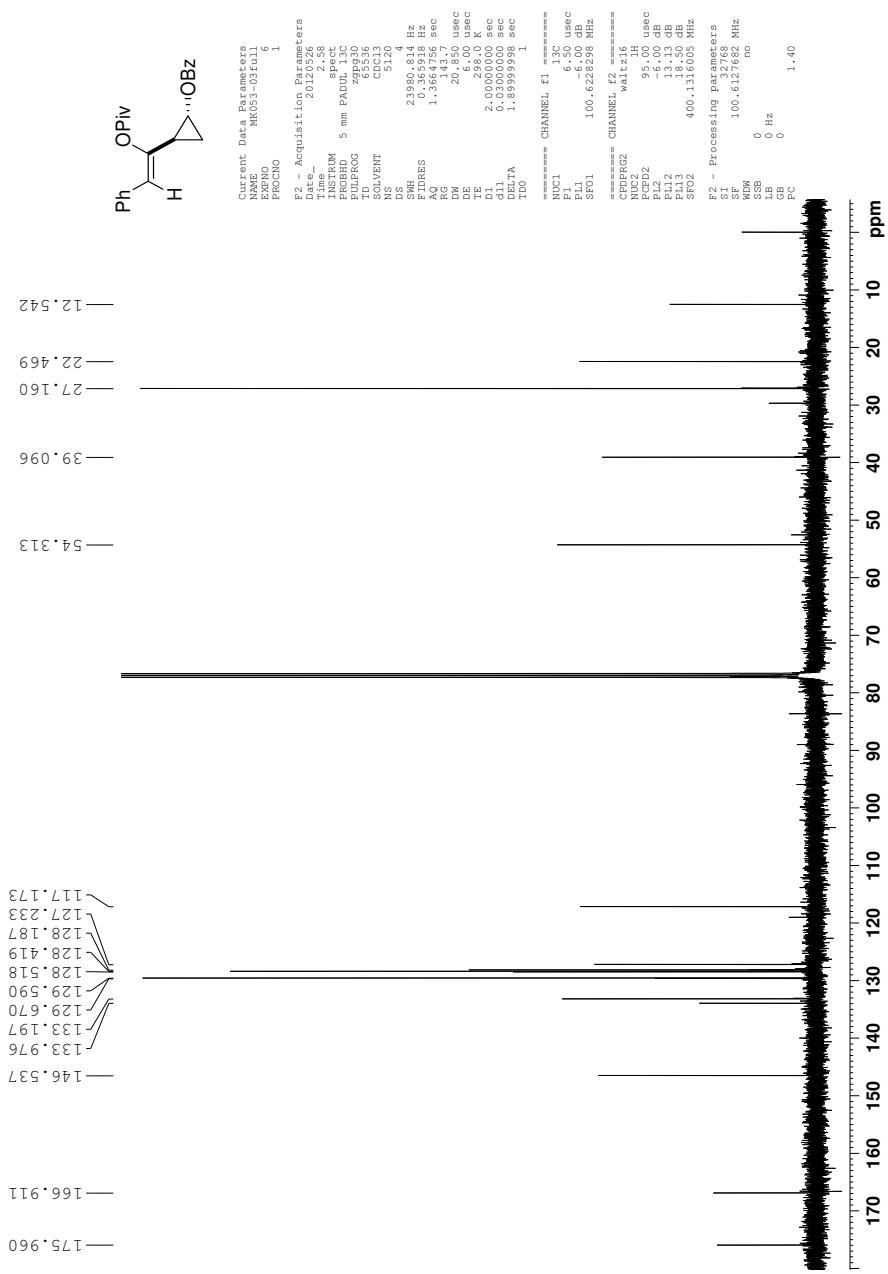

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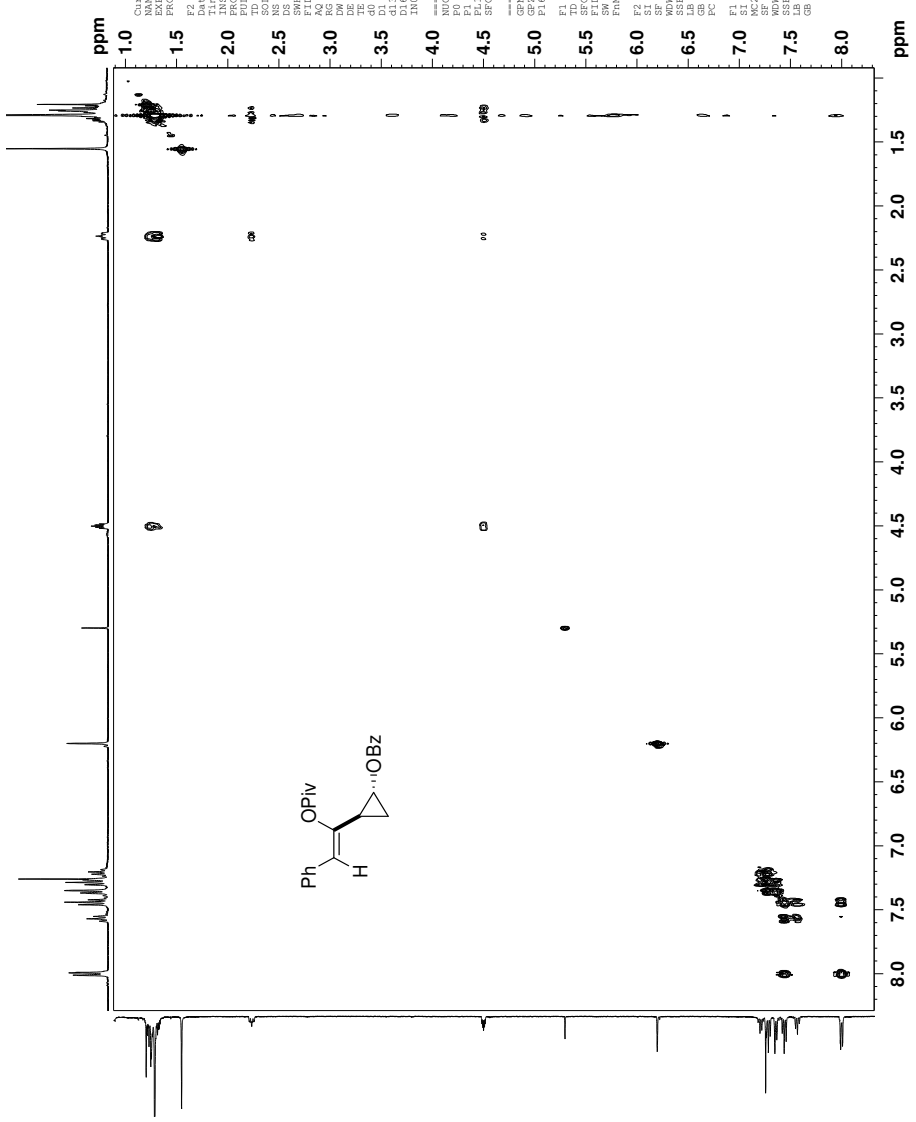

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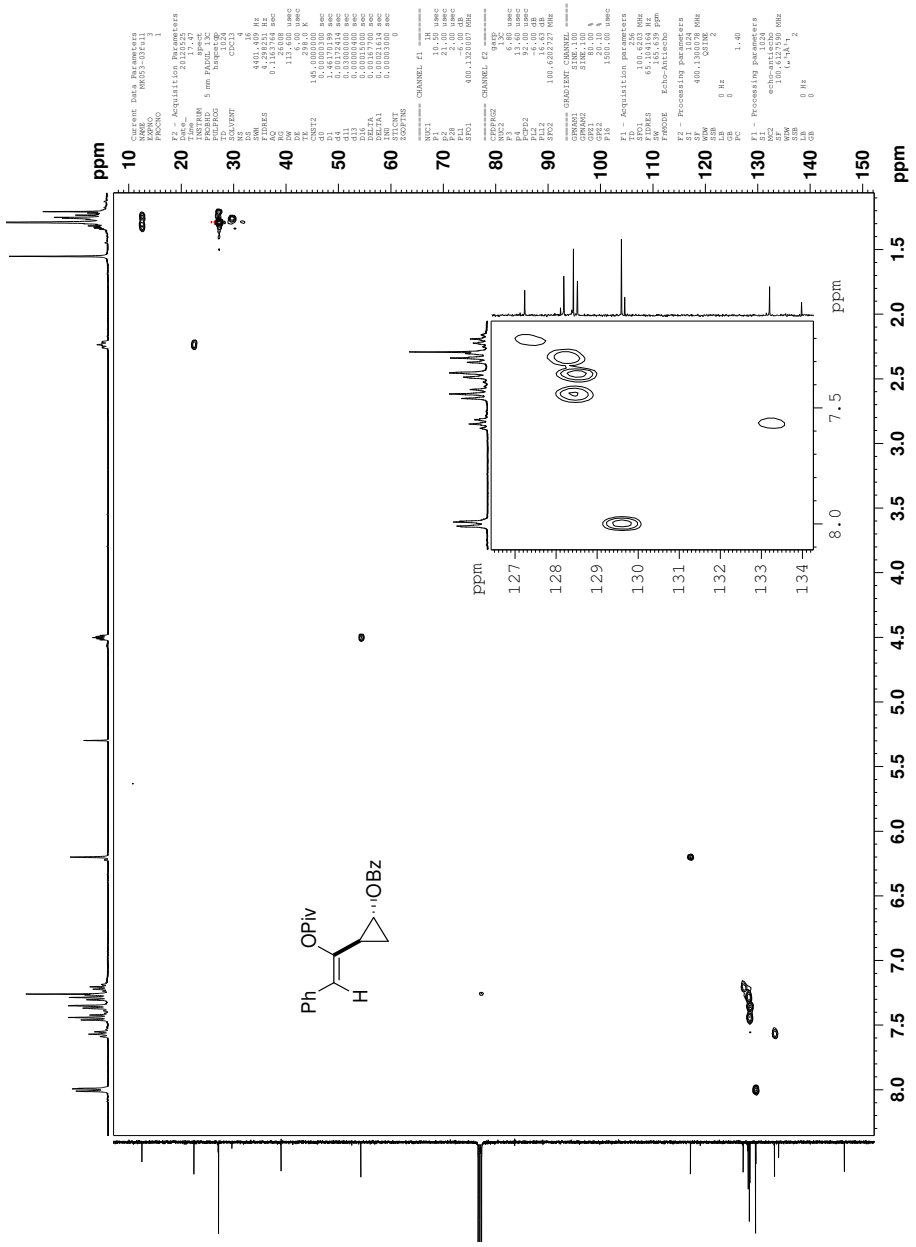
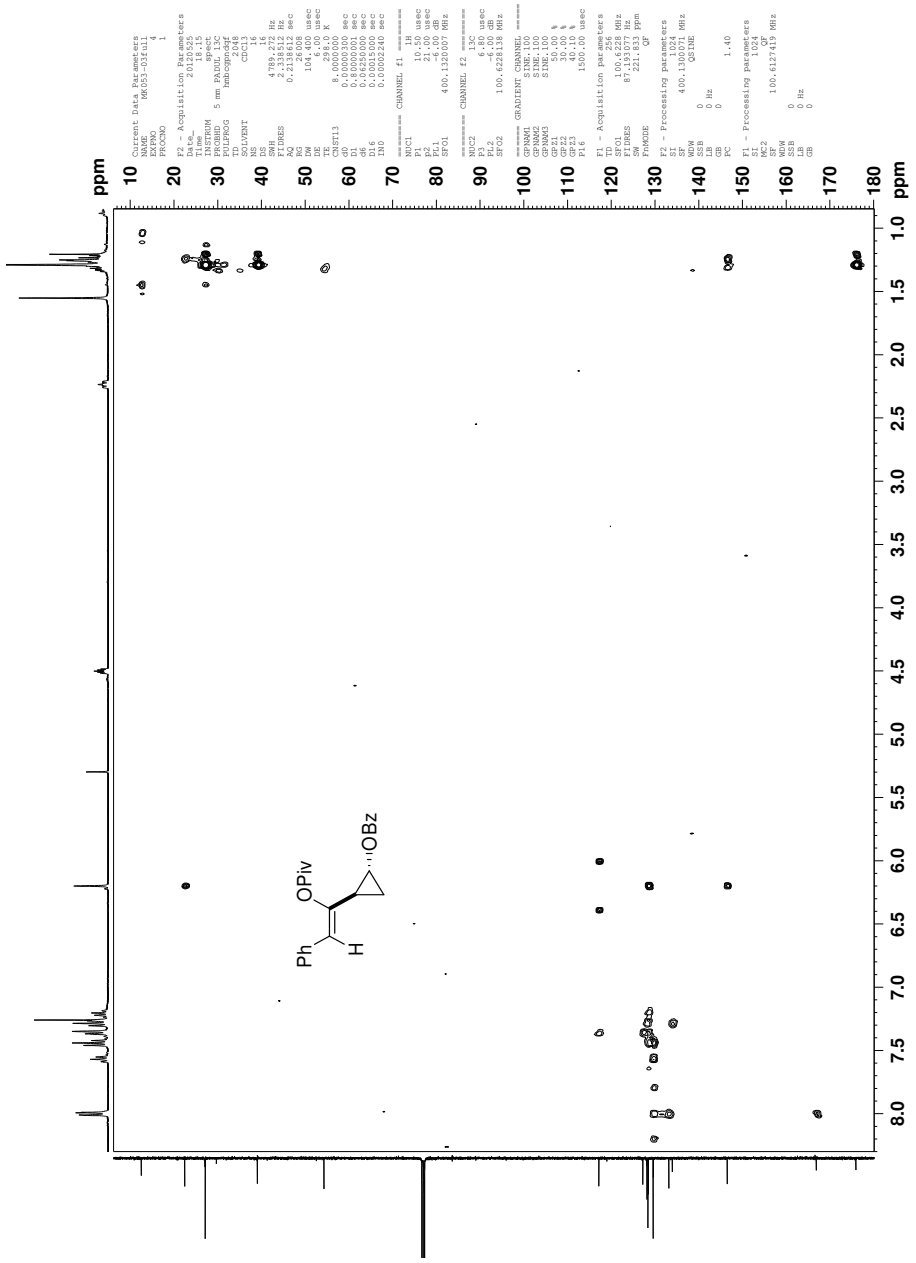


E.12 HMBC of cyclopropyl compound 6b



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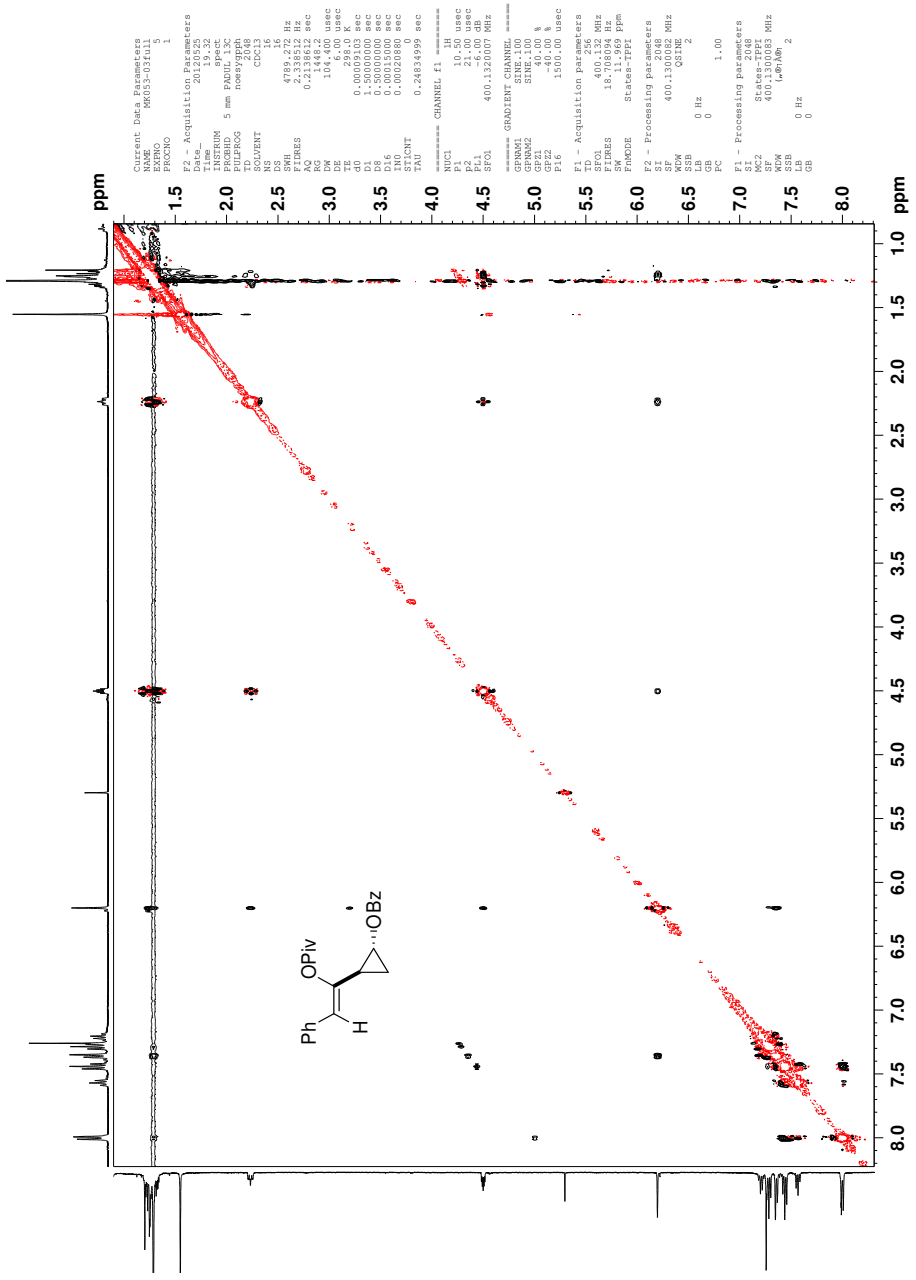

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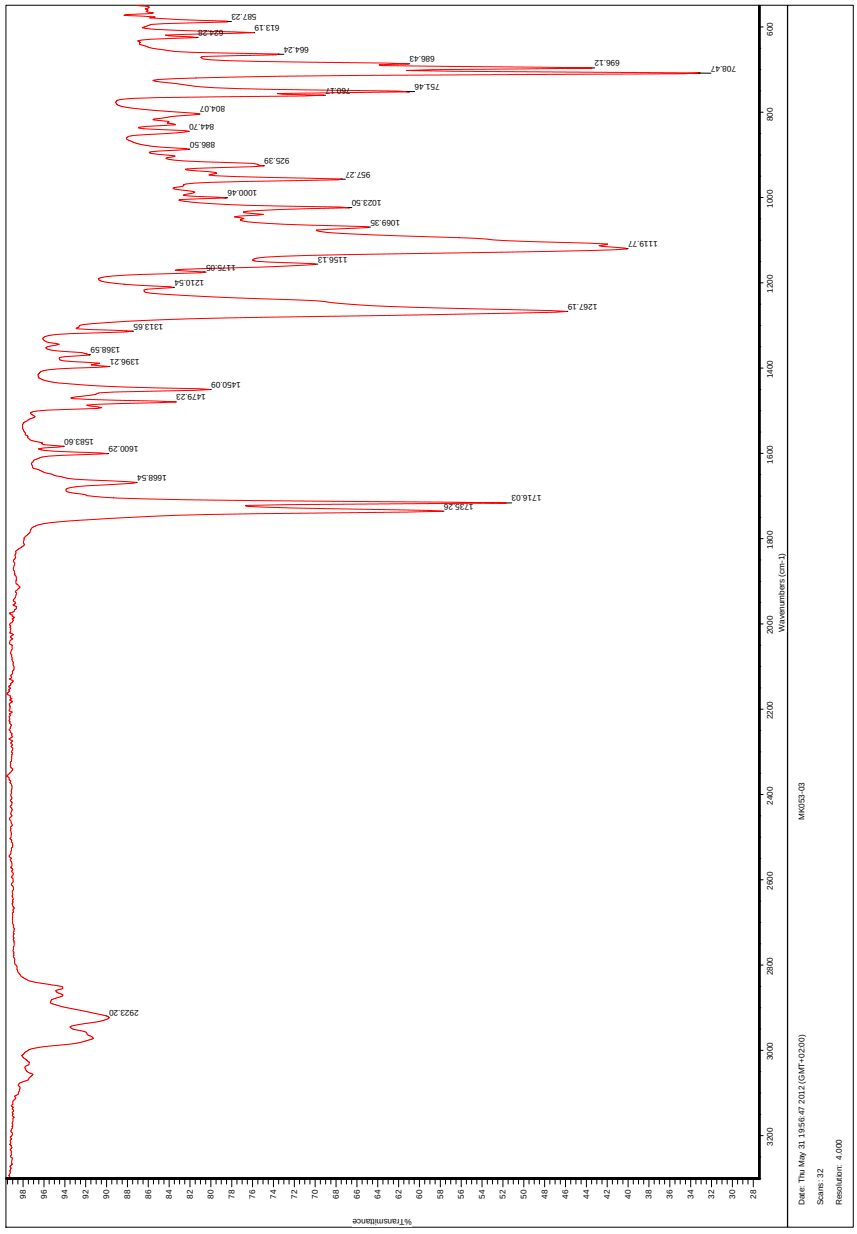
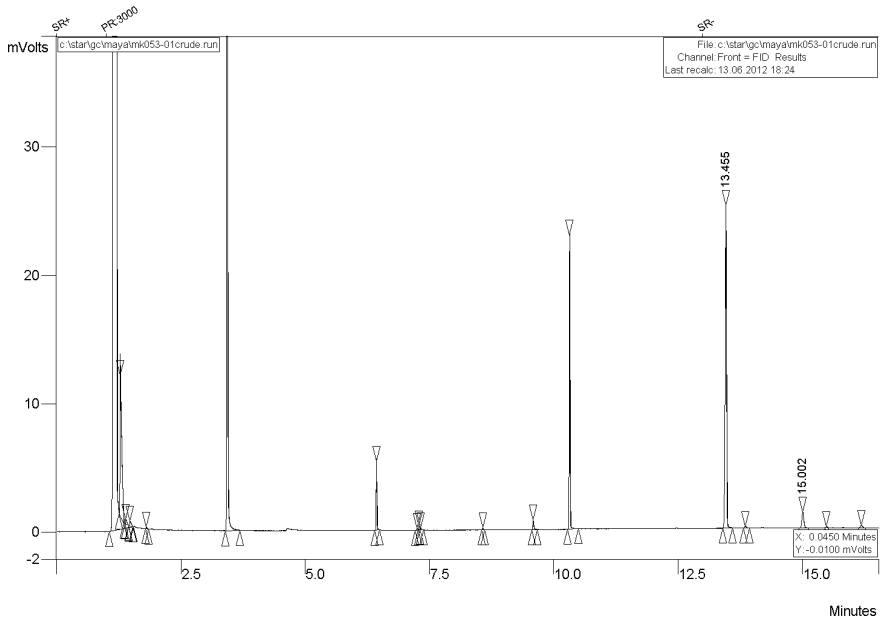


E.15 GLC chromatogram of compound product 6a-b

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Method File : c:\star\gc\maya\mrk003-01crude-front.mth
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Injection Date: 01.03.2012 18:30    Calculation Date: 13.06.2012 18:24

Operator    :                       Detector Type: 3800 (1 Volt)
Workstation: system                 Bus Address  : 44
Instrument : Varian Star #1         Sample Rate  : 10.00 Hz
Channel    : Front = FID            Run Time     : 25.805 min

** GC Workstation Multi Instrument (Demo) Version 6.41 ** 05000-30c8-d68-31e1 **

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Peak Measurement: Peak Area
Calculation Type: Percent

                                 Ret.    Time                      Width
 Peak      Peak        Result    Time   Offset      Area    Sep.   1/2   Status
  No.      Name          ()      (min)   (min)    (counts) Code  (sec)  Codes
 ---- ------------ ---------- ------- ------- ---------- ---- ------ ------
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    2                    6.49  15.002   0.000       3395   BB    2.5
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Total Unidentified Counts :      52282 counts

Detected Peaks: 5          Rejected Peaks: 3      Identified Peaks: 0

Multiplier: 1          Divisor: 1          Unidentified Peak Factor: 0

Baseline Offset: -10 microVolts          LSB:     1 microVolts

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Manual injection

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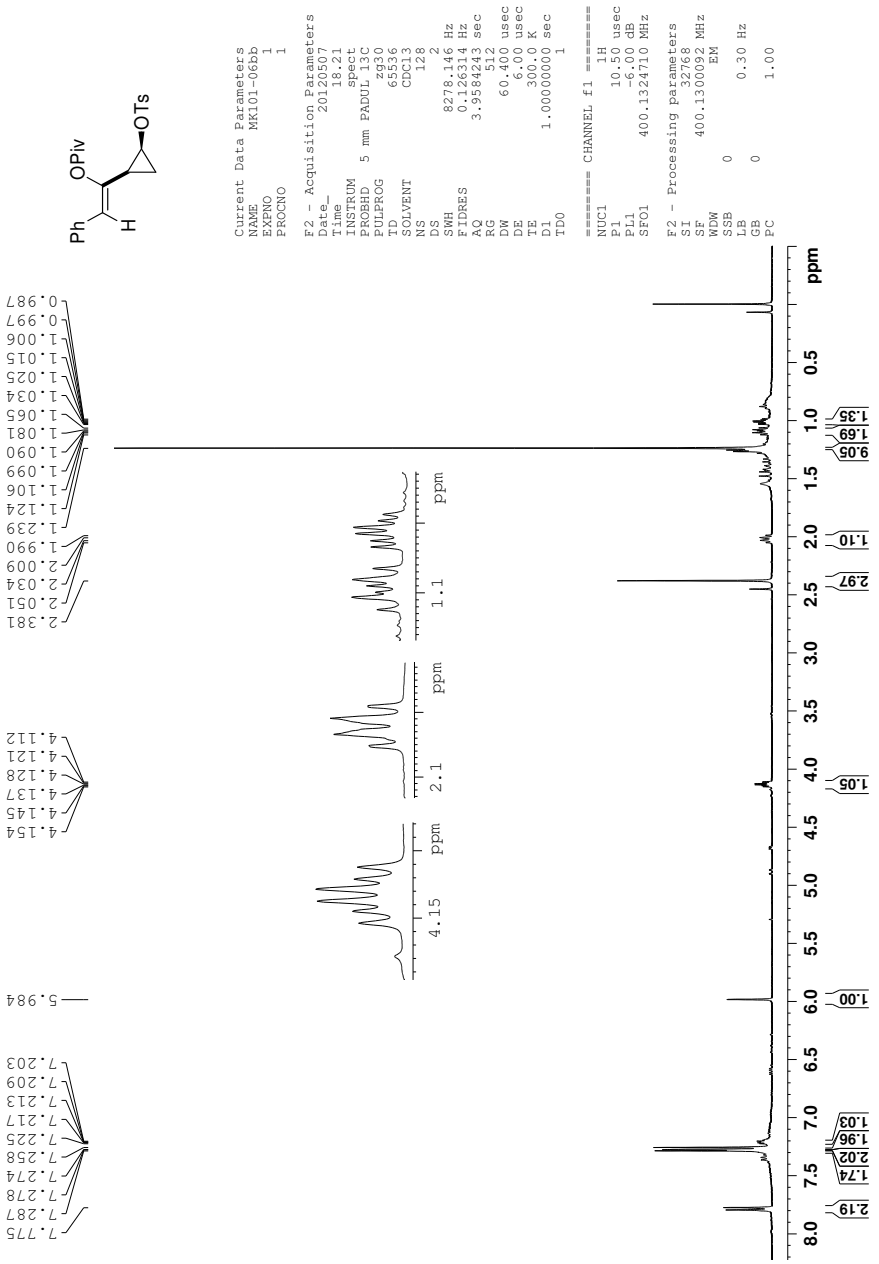
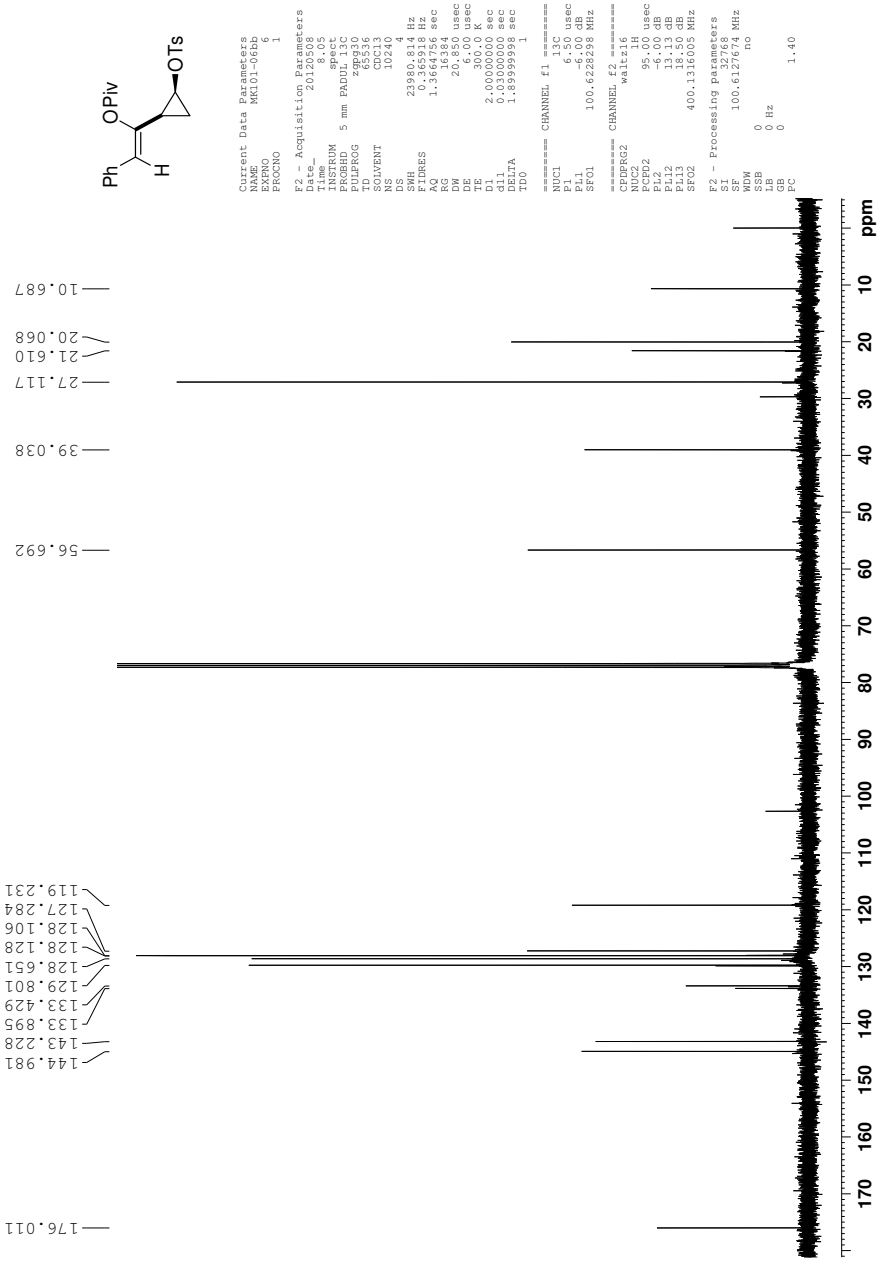
F Cyclopropyl compound 9a-b

F.1 ^{1}H NMR of cyclopropyl compound 9a



F.2 ^{13}C NMR of cyclopropyl compound 9a



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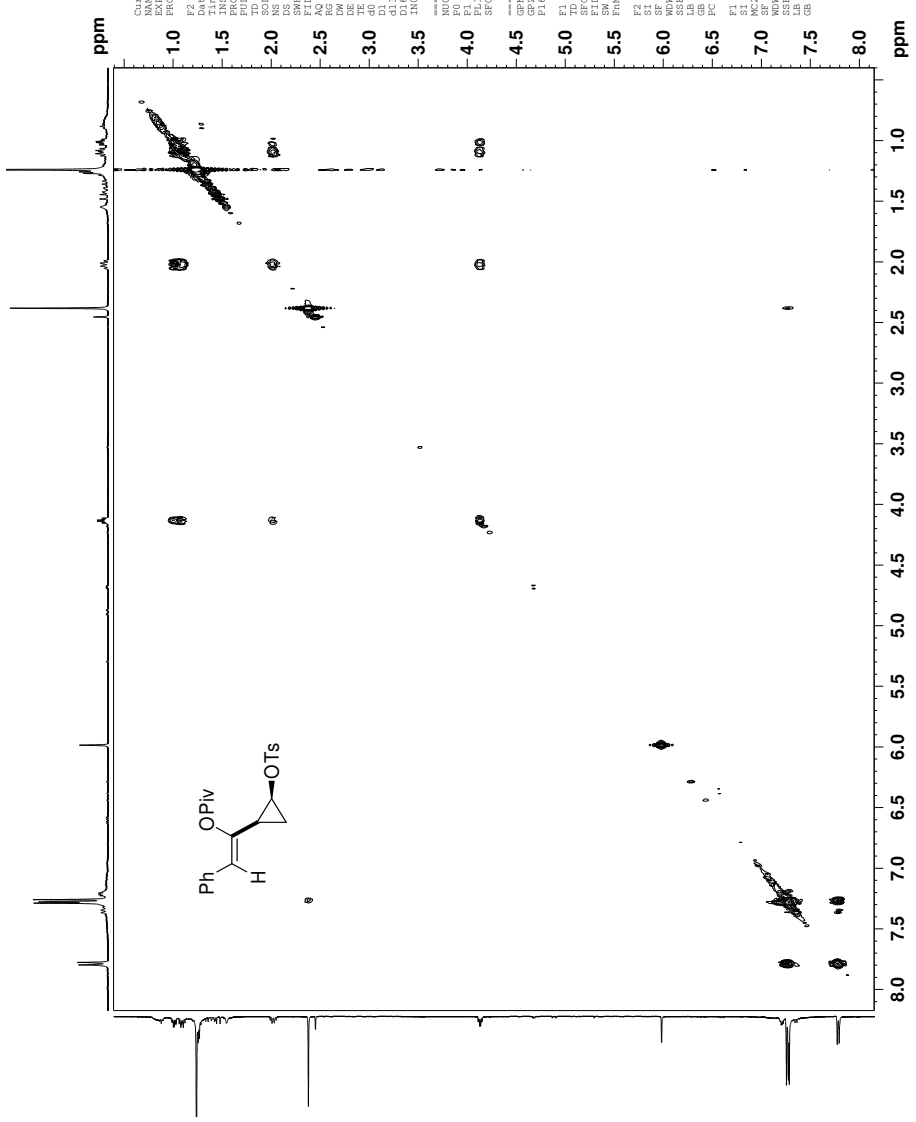
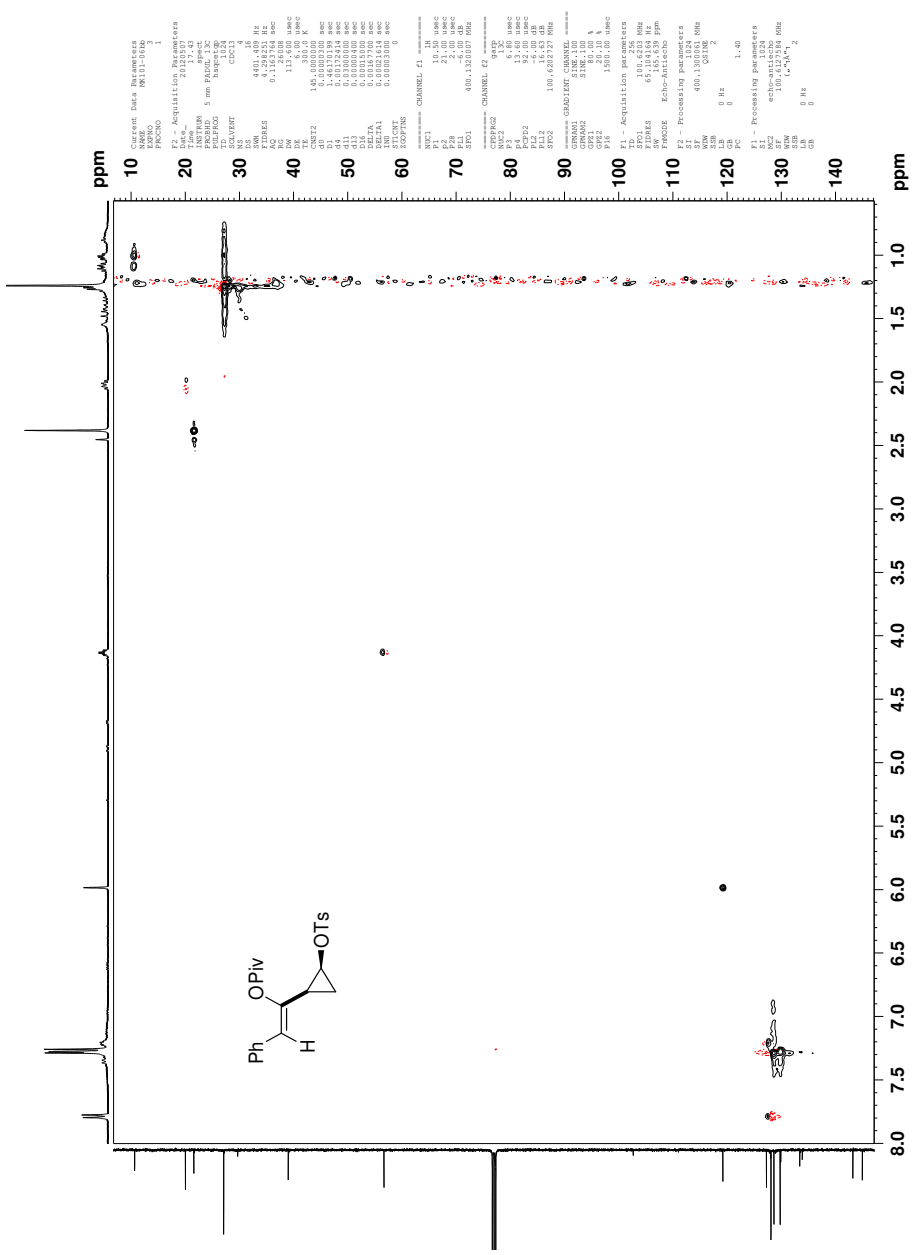


F.4 HSQC of cyclopropyl compound 9a



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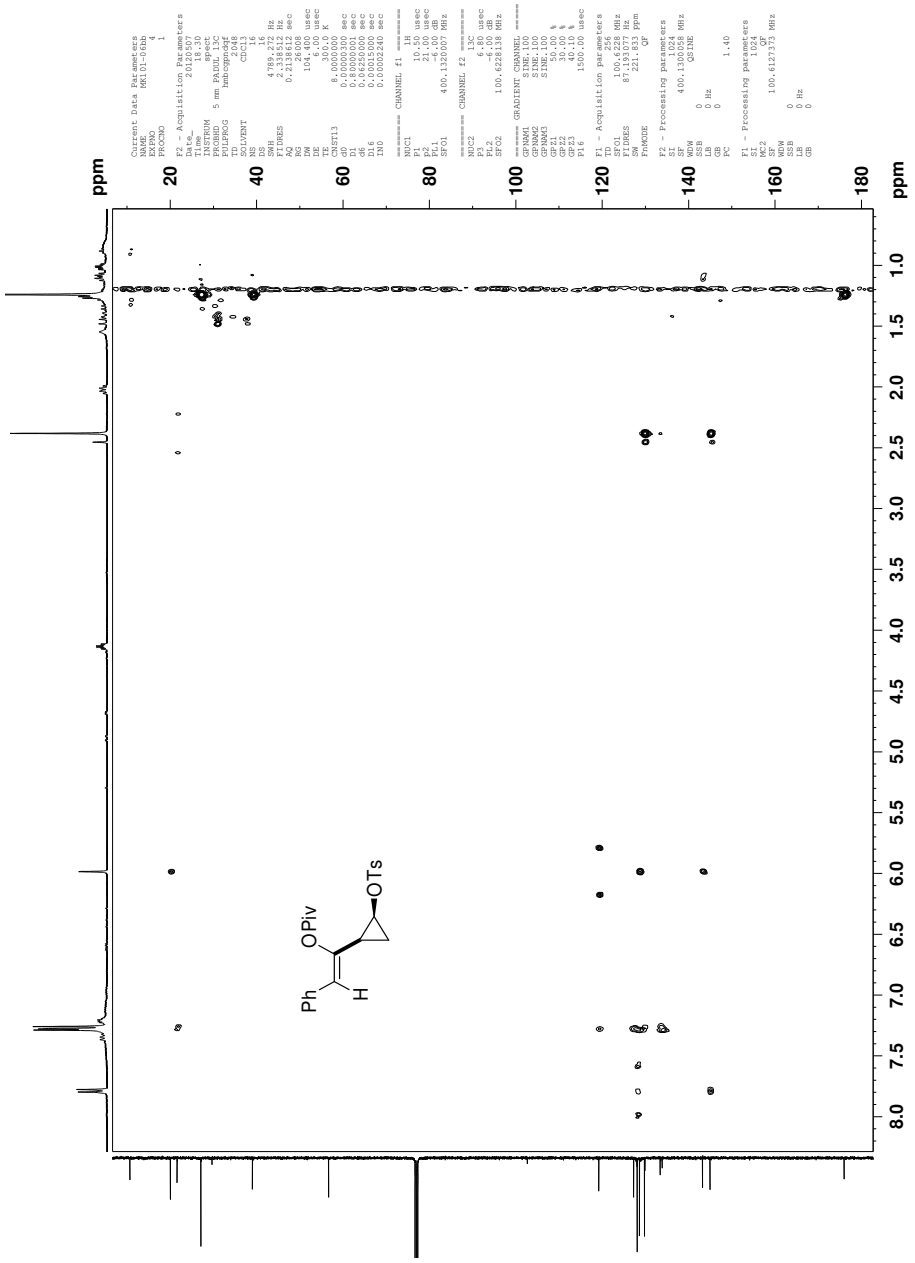

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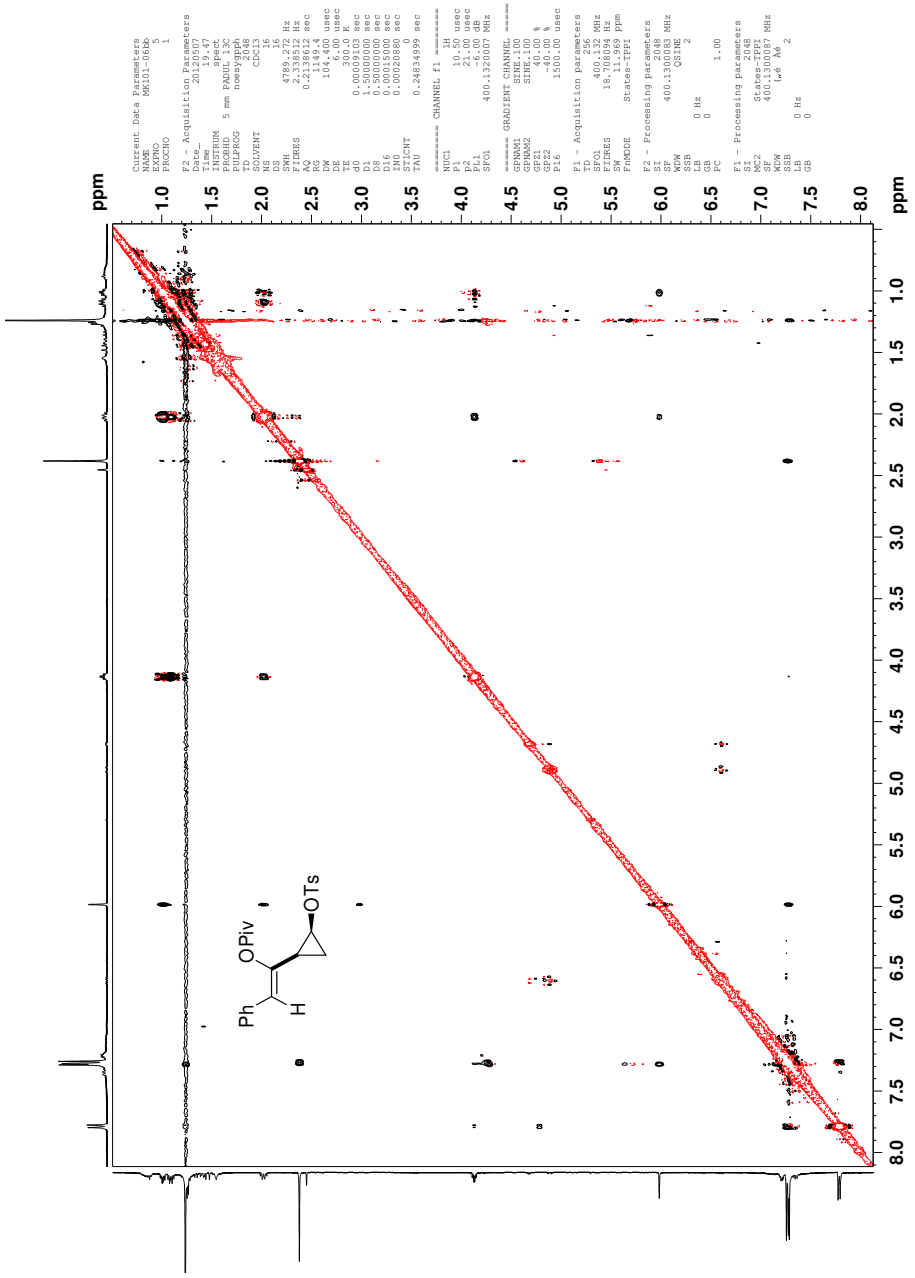
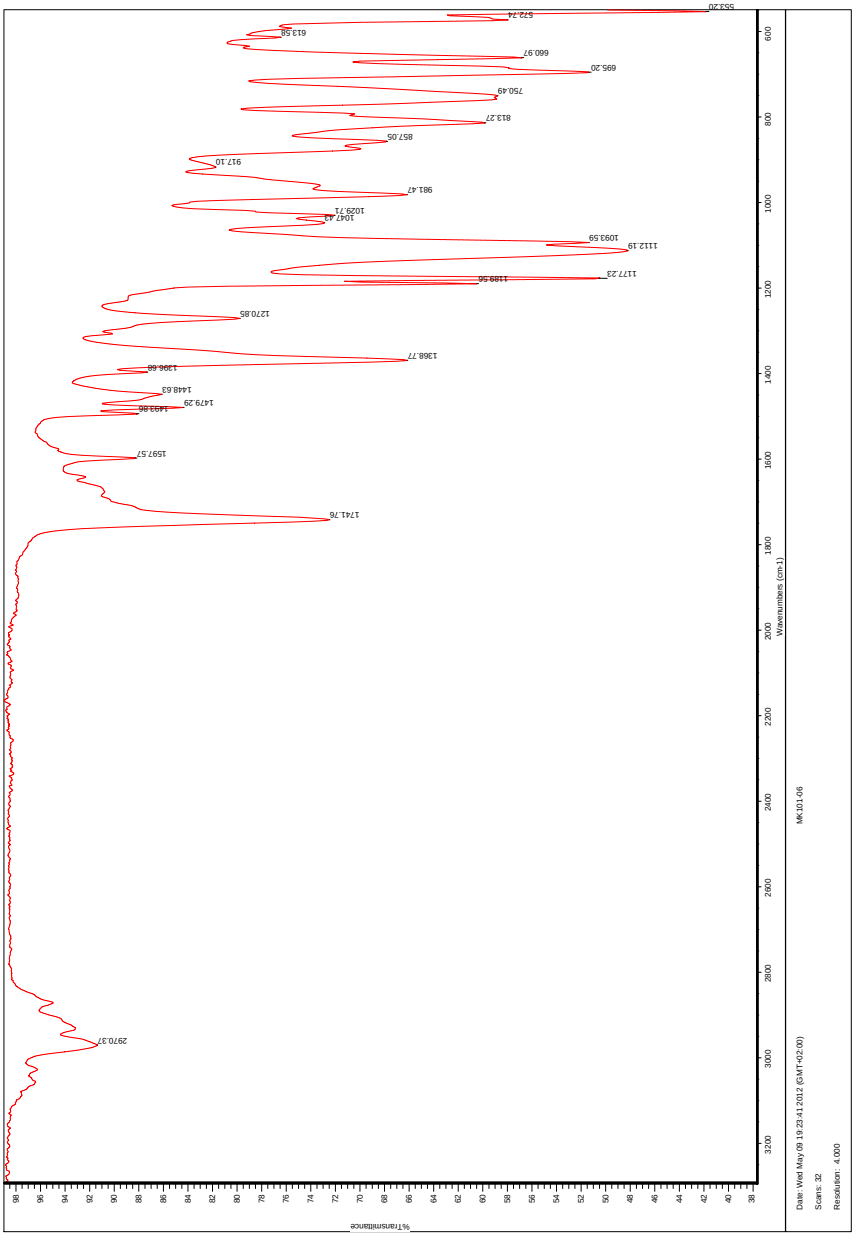


F.7 IR of cyclopropyl compound 9a



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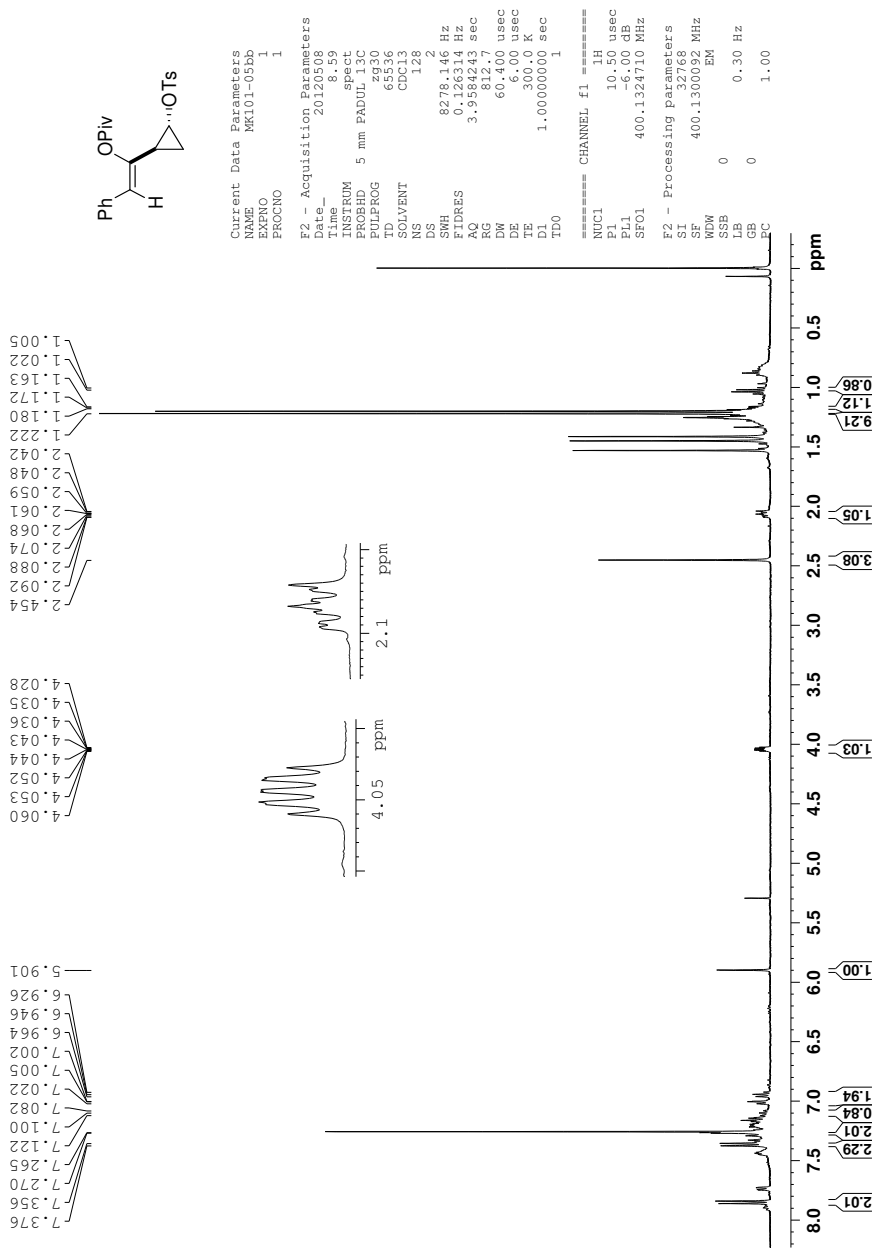

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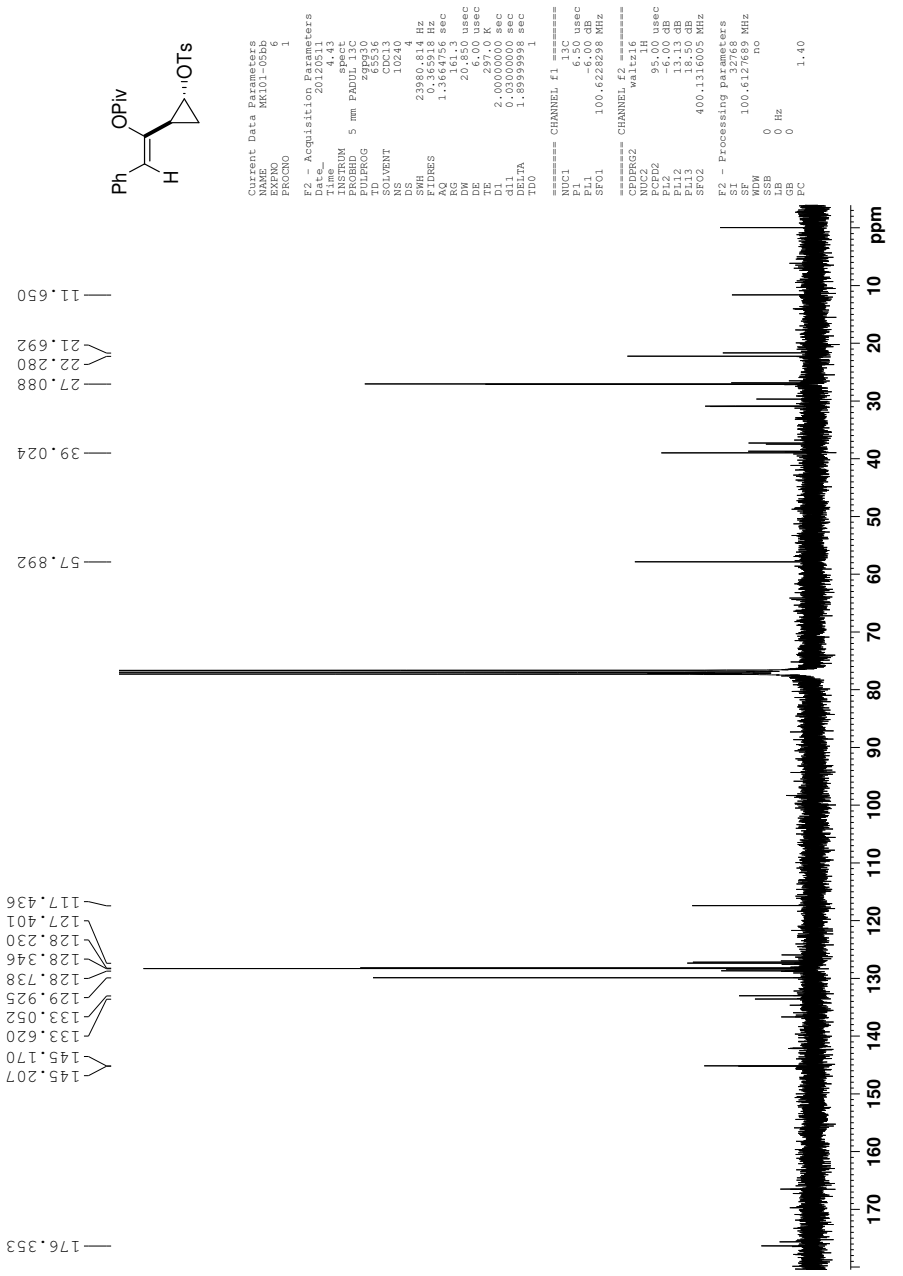

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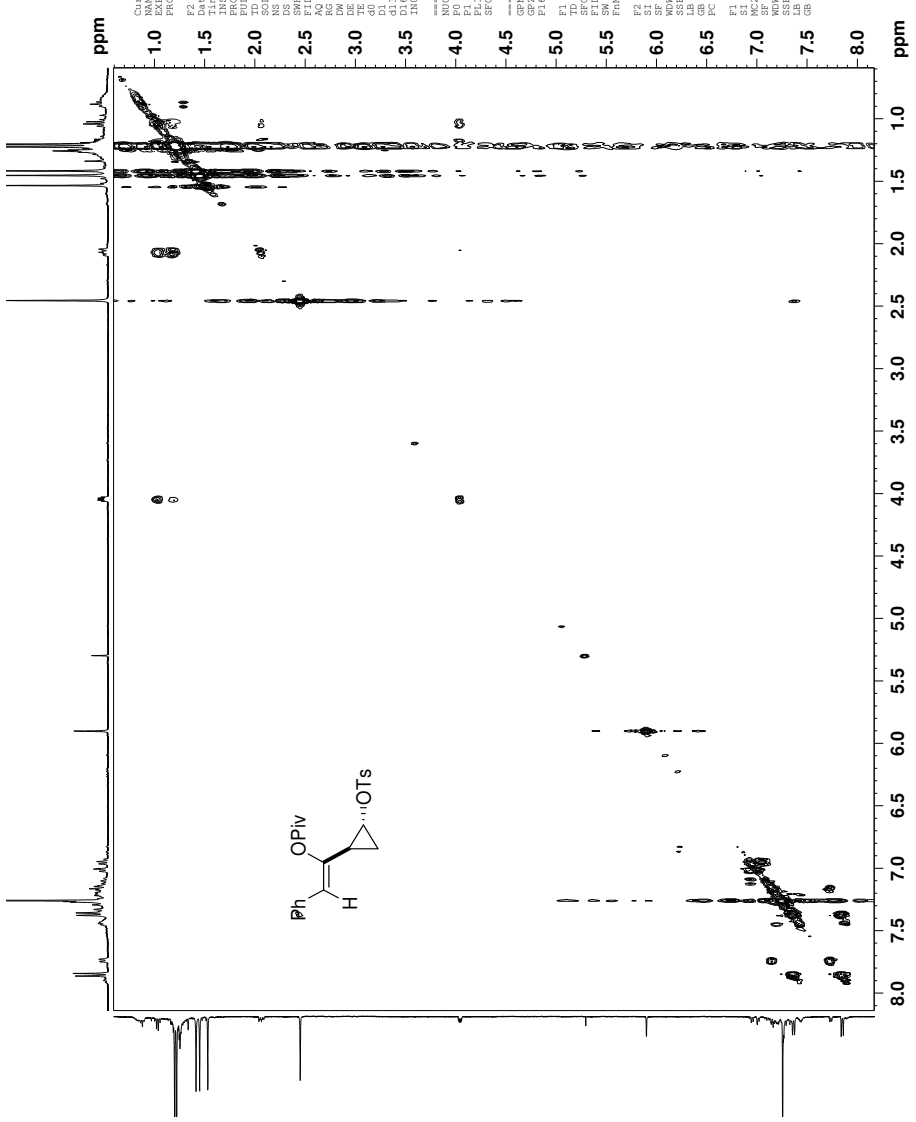

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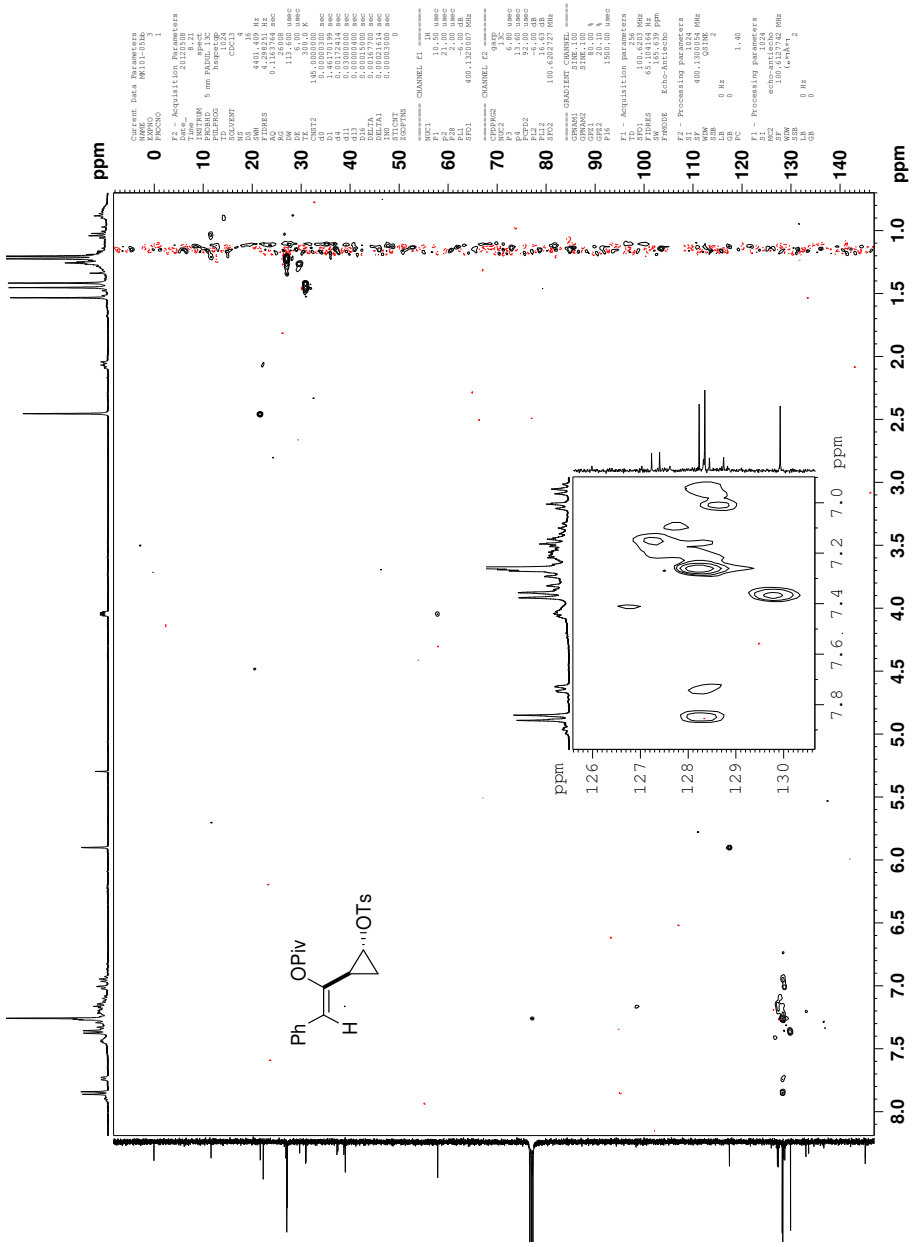

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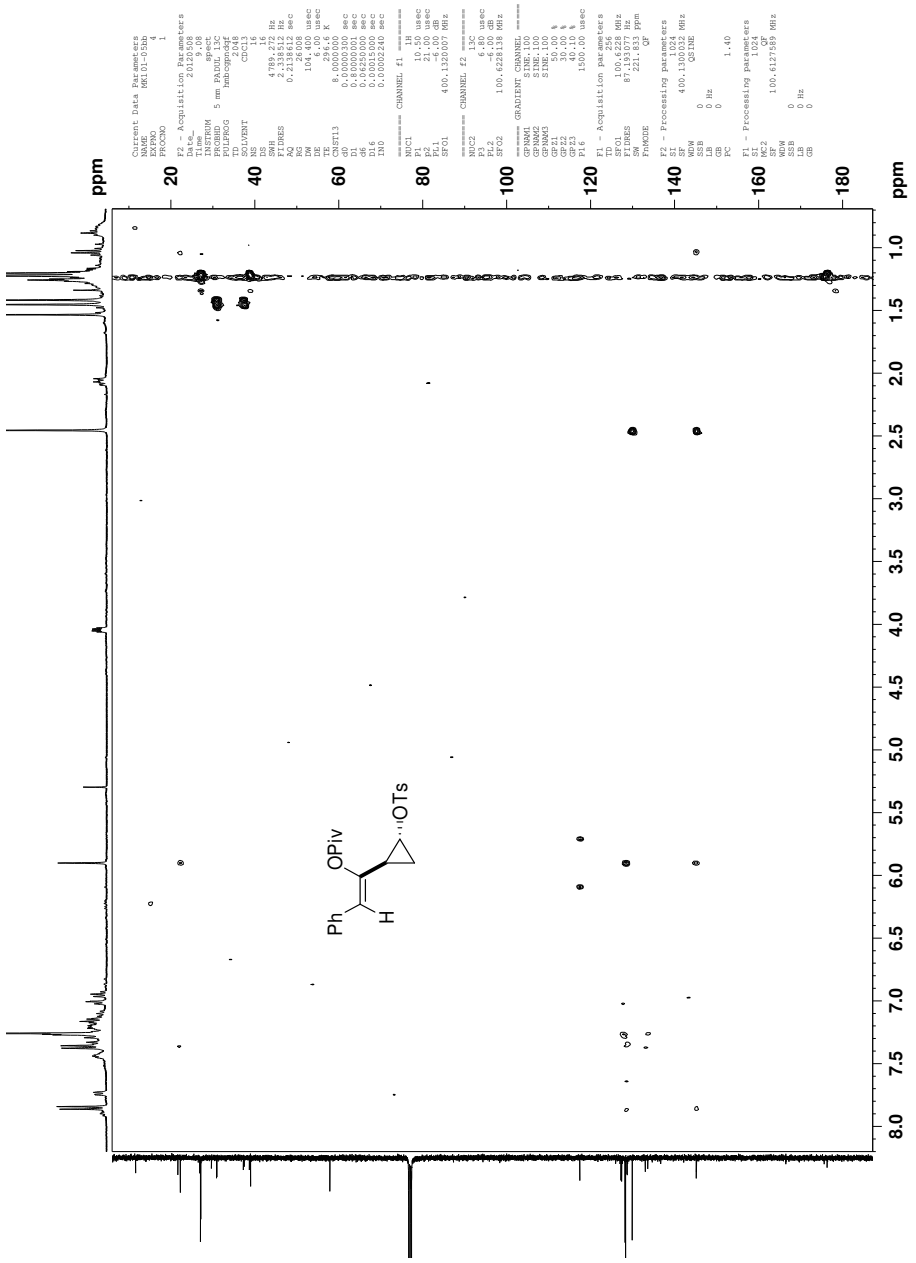

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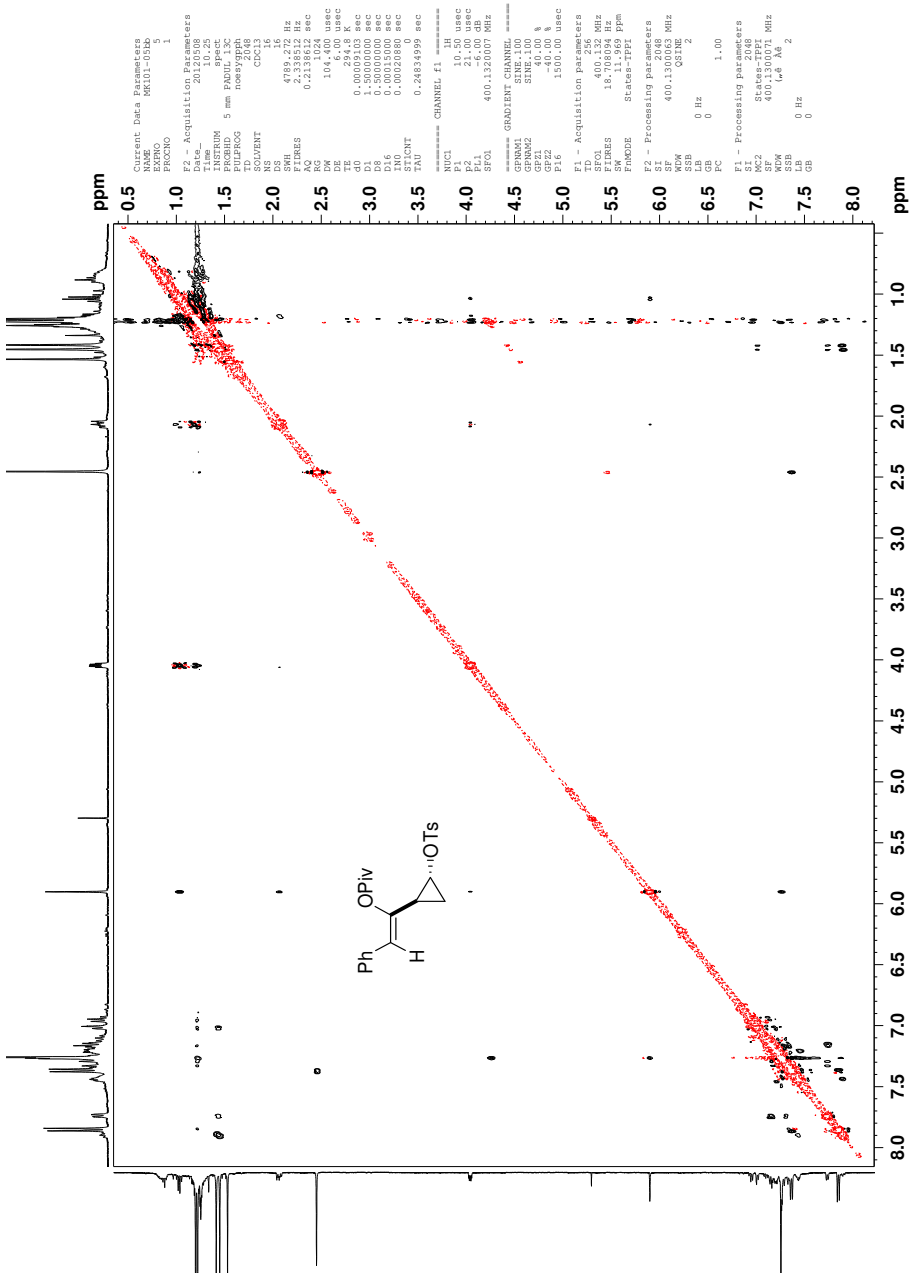
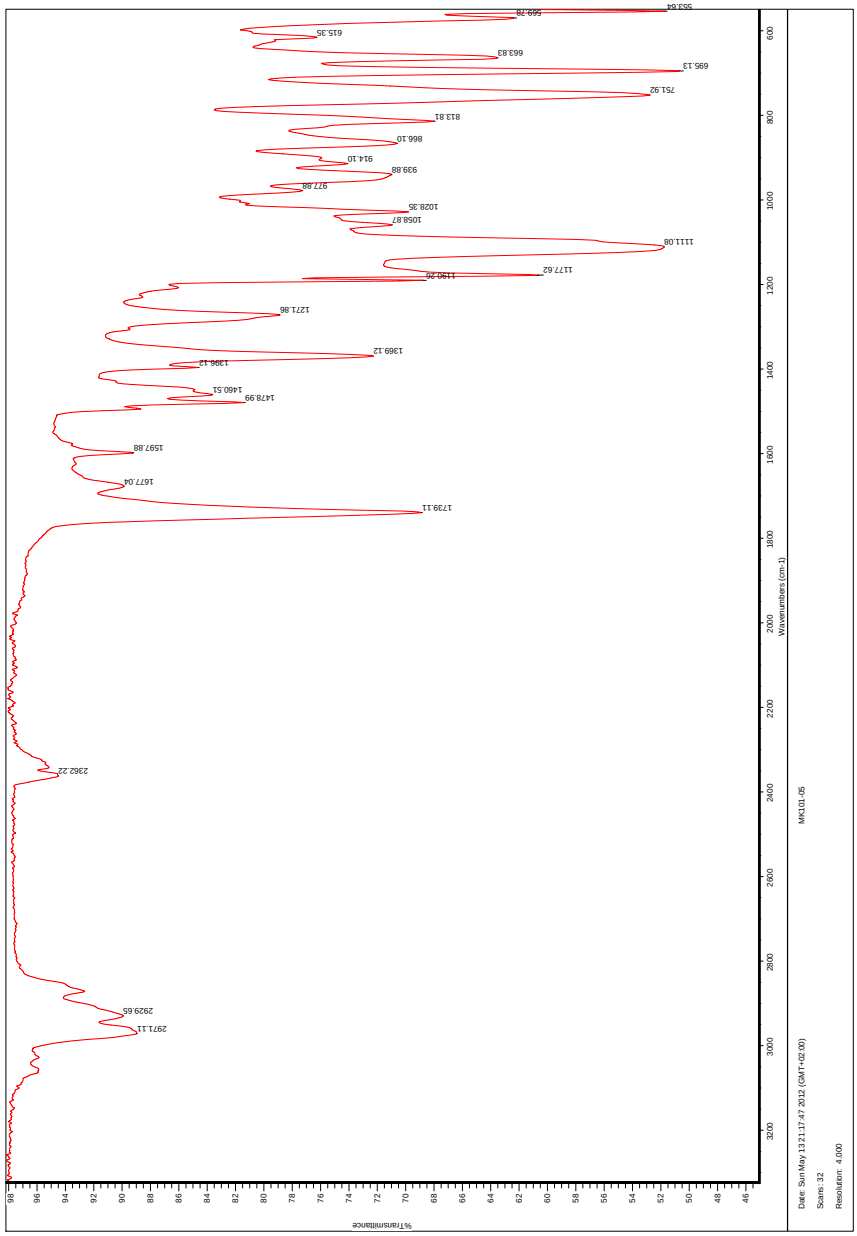
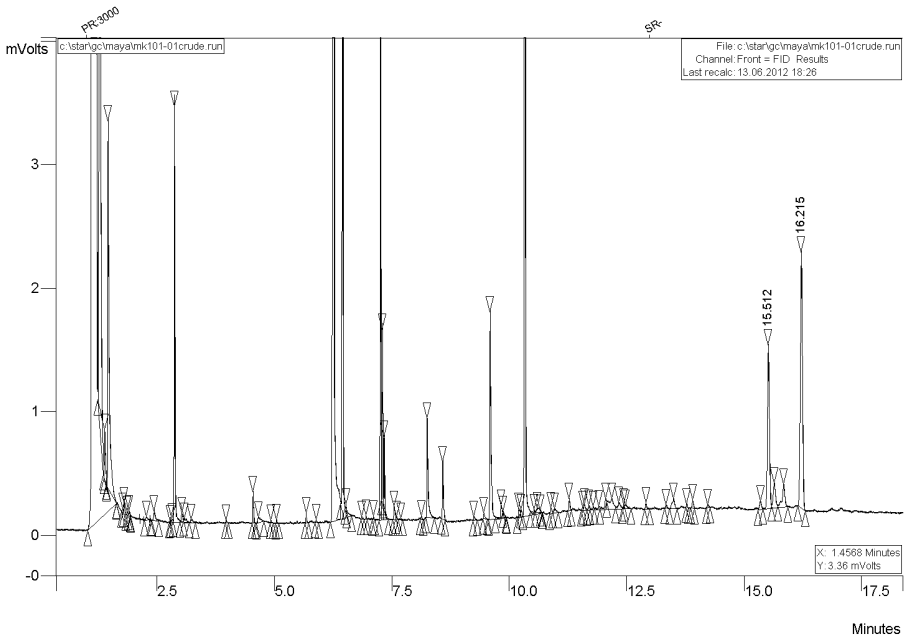


F.14 IR of cyclopropyl compound 9b



F.15 GLC chromatogram of cyclopropyl compound 9a-b



Print Date: Wed Jun 13 18:27:17 2012 Page 1 of 1

Title : Chrompack CP-Sil 5cB Low bleed/MS. 30m/0,25mmid
Run File : c:\star\gc\maya\mk101-01crude.run
Method File : c:\star\gc\maya\mrk003-01crude-front.mth
Sample ID : Manual Sample

Injection Date: 03.05.2012 16:13 Calculation Date: 13.06.2012 18:26

Operator :
Workstation: system
Instrument : Varian Star #1
Channel : Front = FID

Detector Type: 3800 (1 Volt)
Bus Address : 44
Sample Rate : 10.00 Hz
Run Time : 21.310 min

** GC Workstation Multi Instrument (Demo) Version 6.41 ** 05000-30c8-d68-31e1 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		37.25	15.512	0.000	3822	VV	2.7	
2		62.75	16.215	0.000	6439	BB	2.9	
Totals:		100.00		0.000	10261			

Total Unidentified Counts : 10261 counts

Detected Peaks: 13 Rejected Peaks: 11 Identified Peaks: 0

Multiplier: 1 Divisor: 1 Unidentified Peak Factor: 0

Baseline Offset: 32 microVolts LSB: 1 microVolts

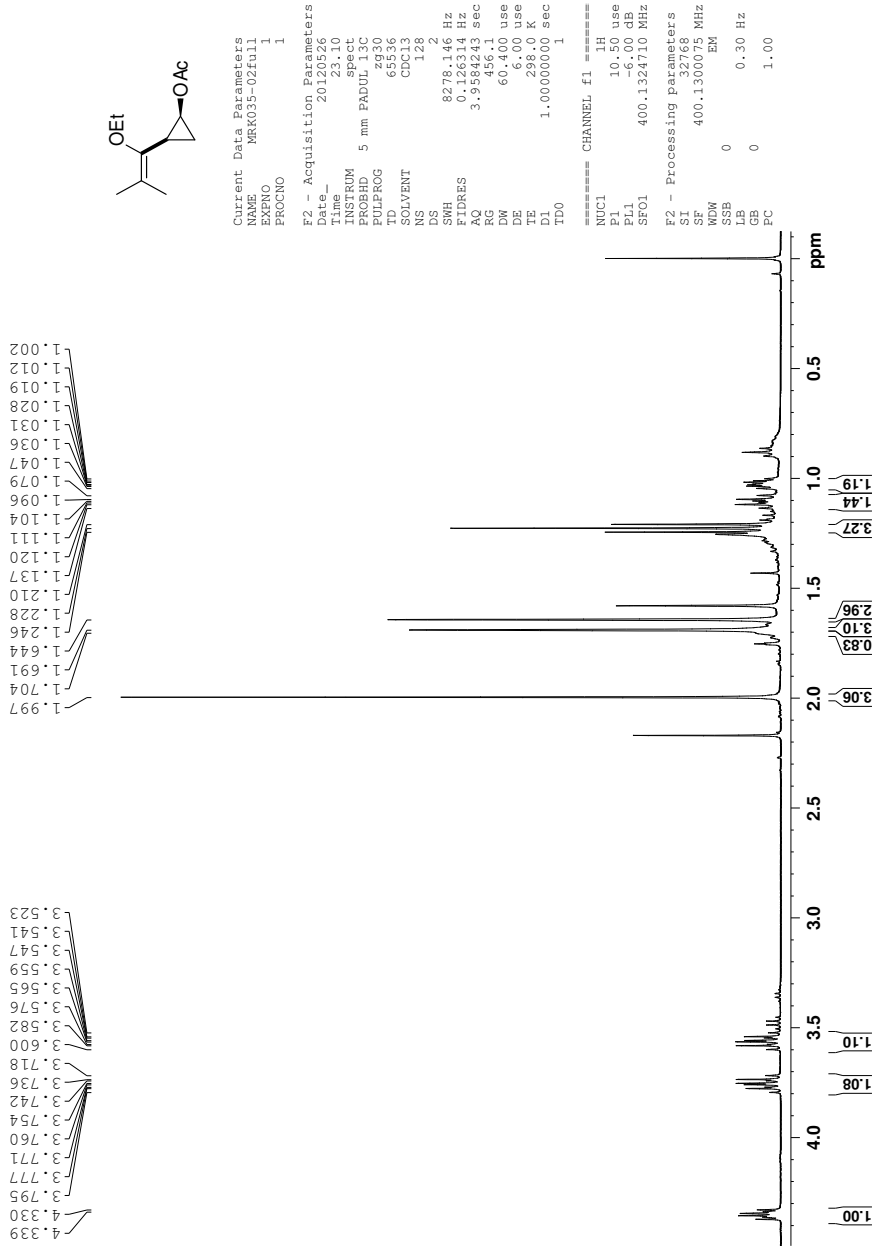
Noise (used): 16 microVolts - monitored before this run

Manual injection

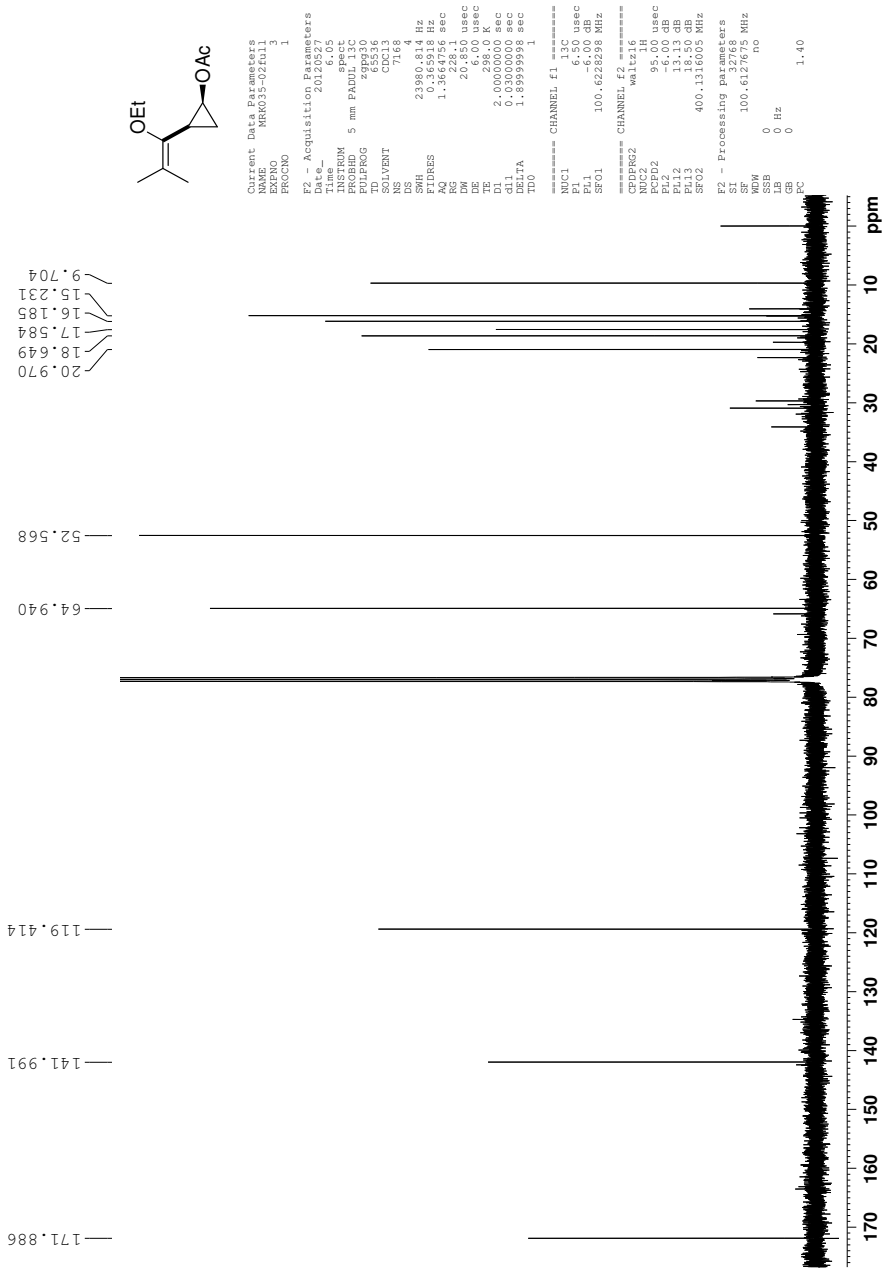
****

G Cyclopropyl compound 10

G.1 ^{1}H NMR of cyclopropyl compound 10

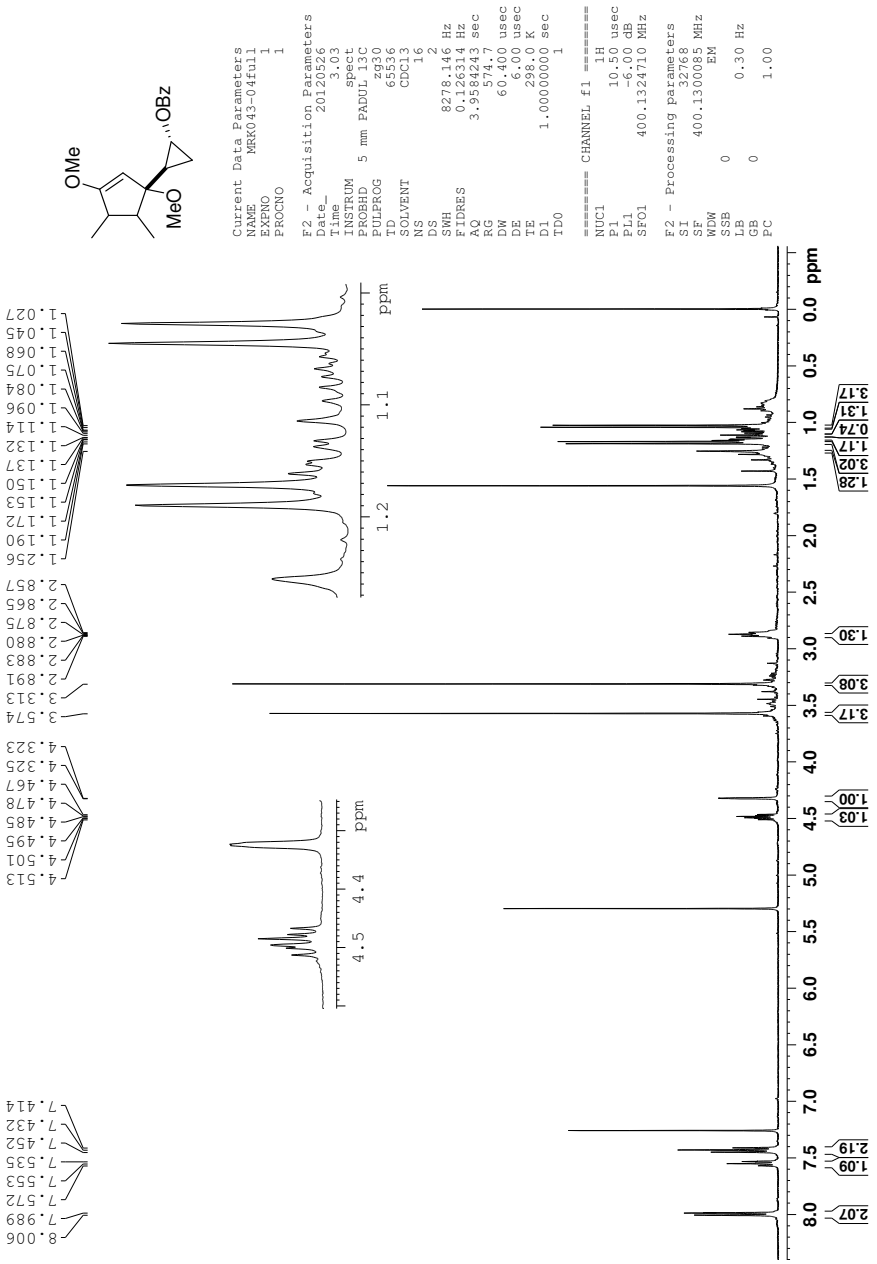


G.2 ^{13}C NMR of cyclopropyl compound 10

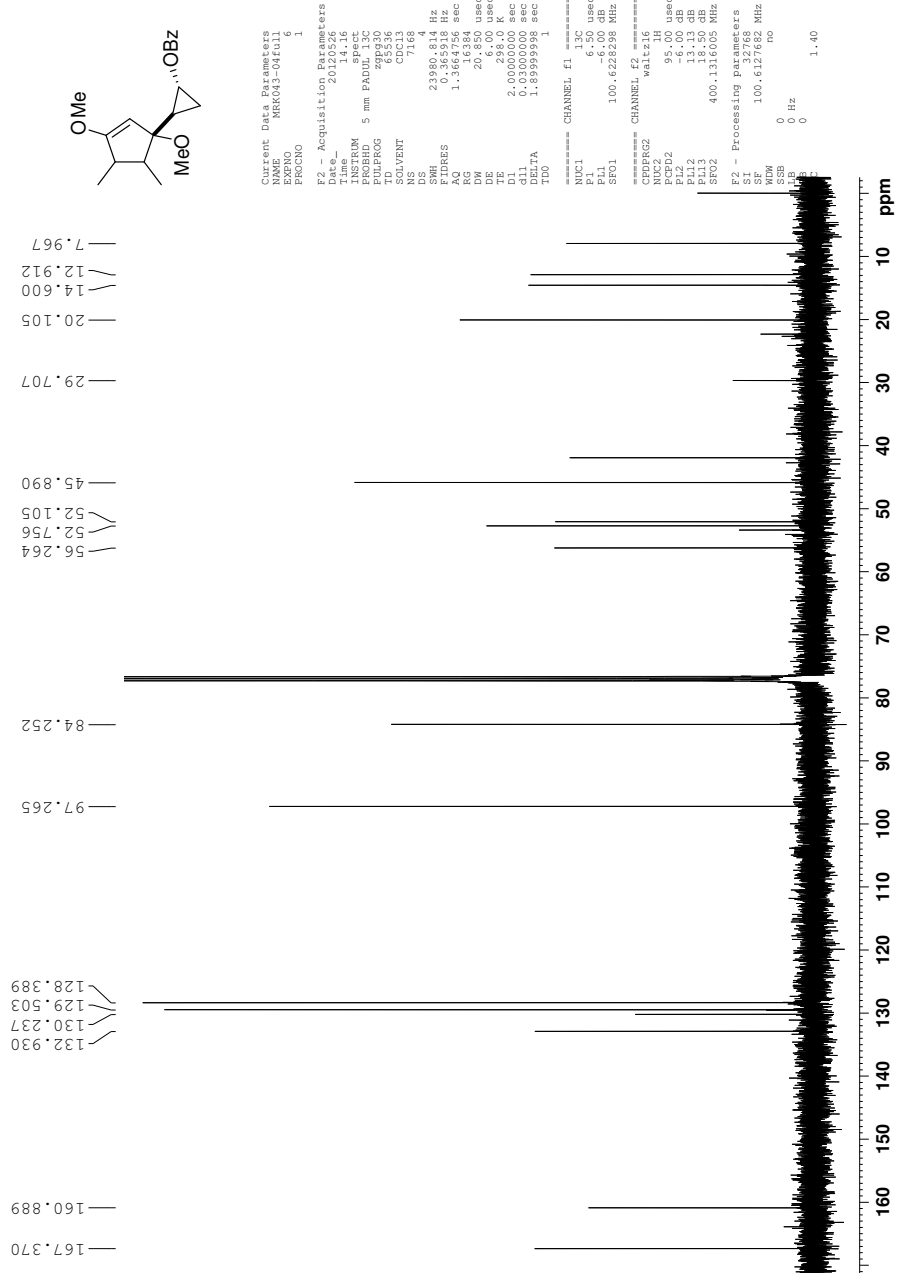


H Bicyclic compound 13

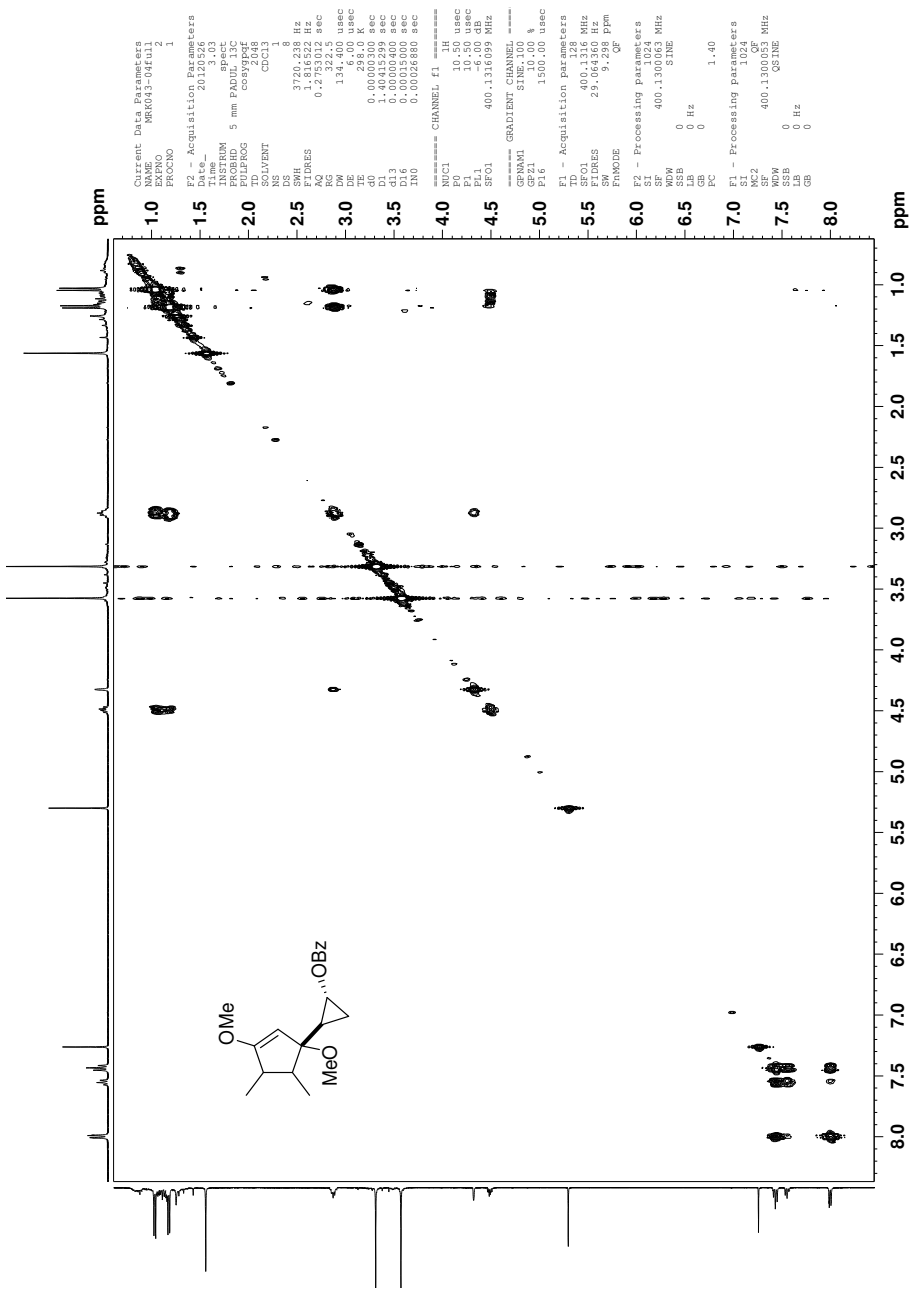
H.1 ^{1}H NMR of bicyclic compound 13



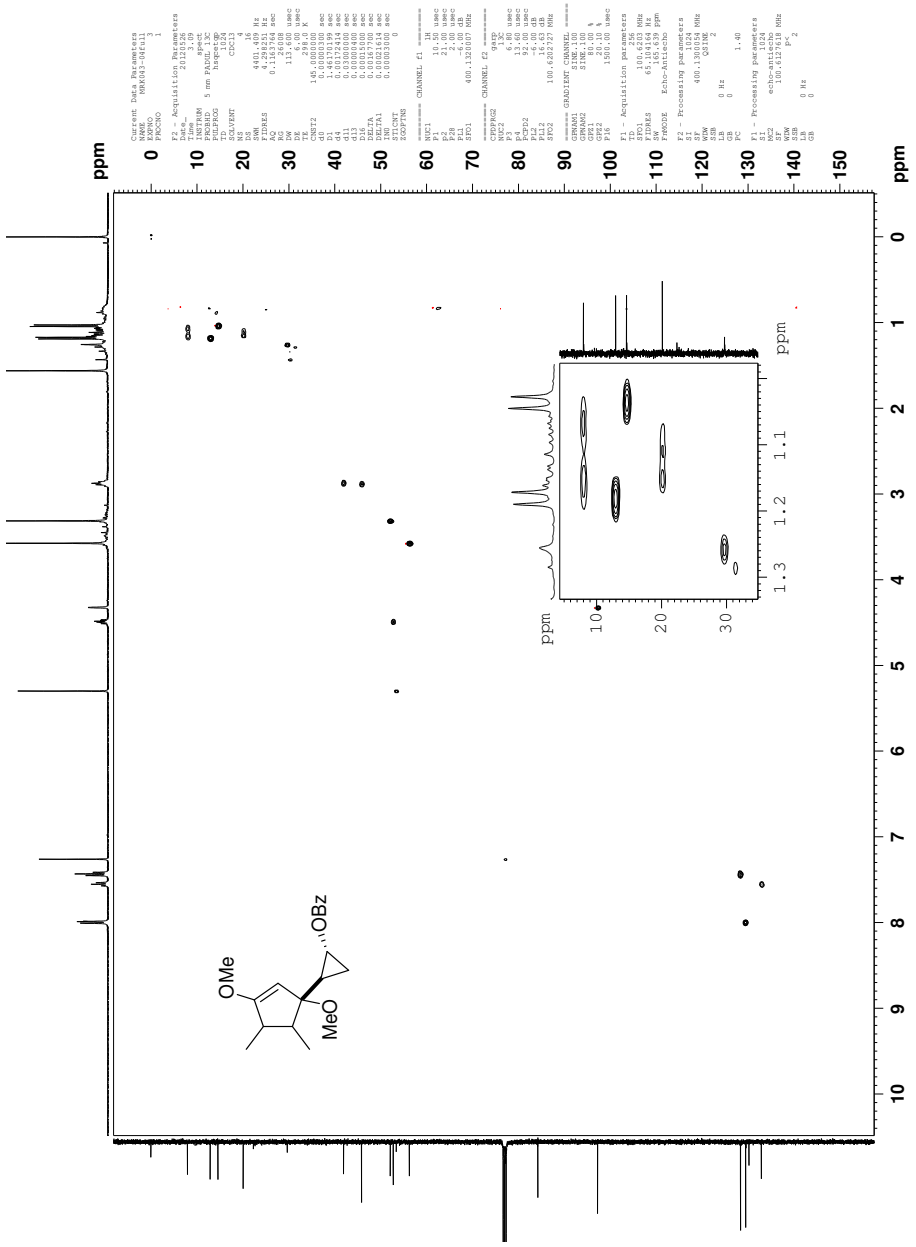
H.2 ^{13}C NMR of bicyclic compound 13



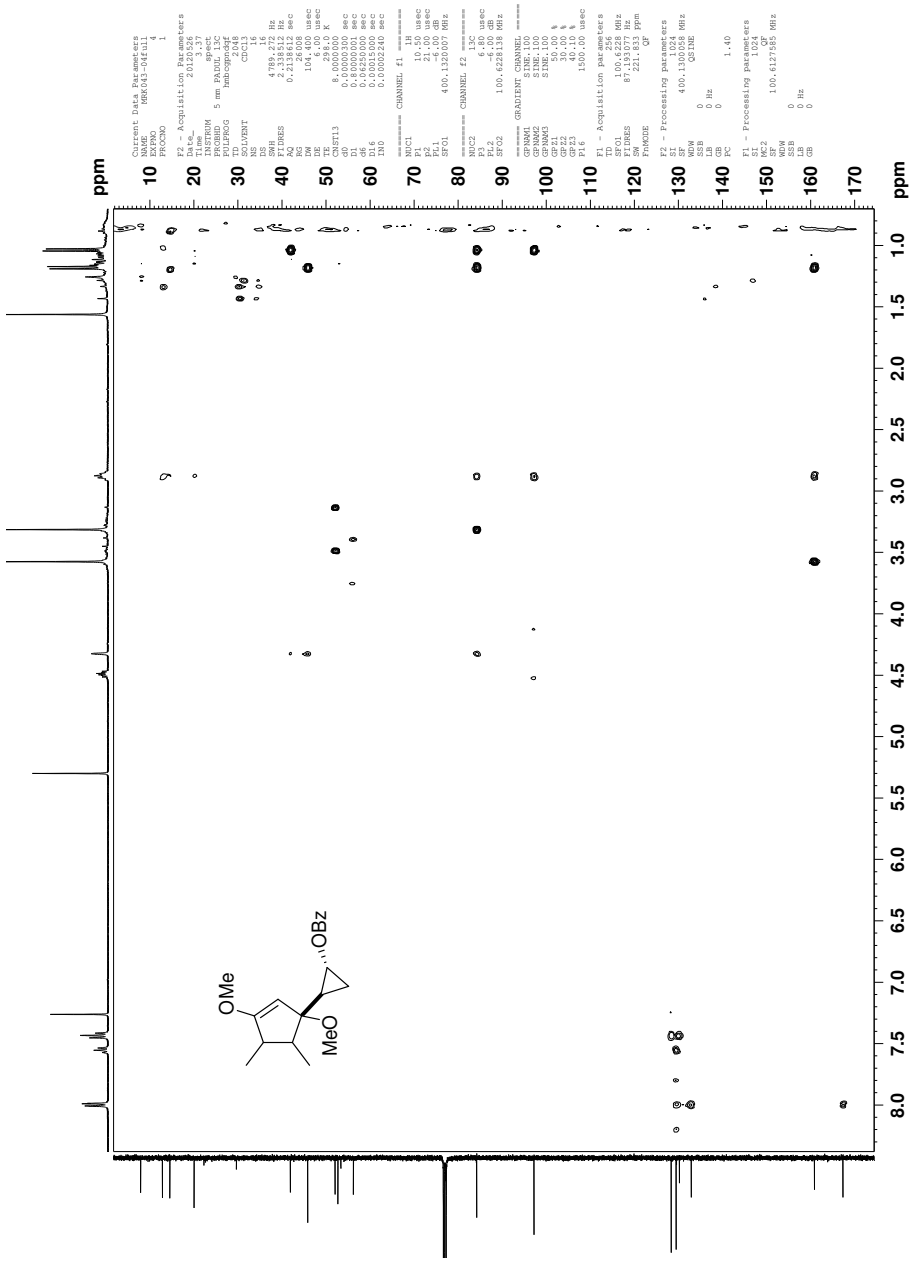
H.3 COSY of bicyclic compound 13



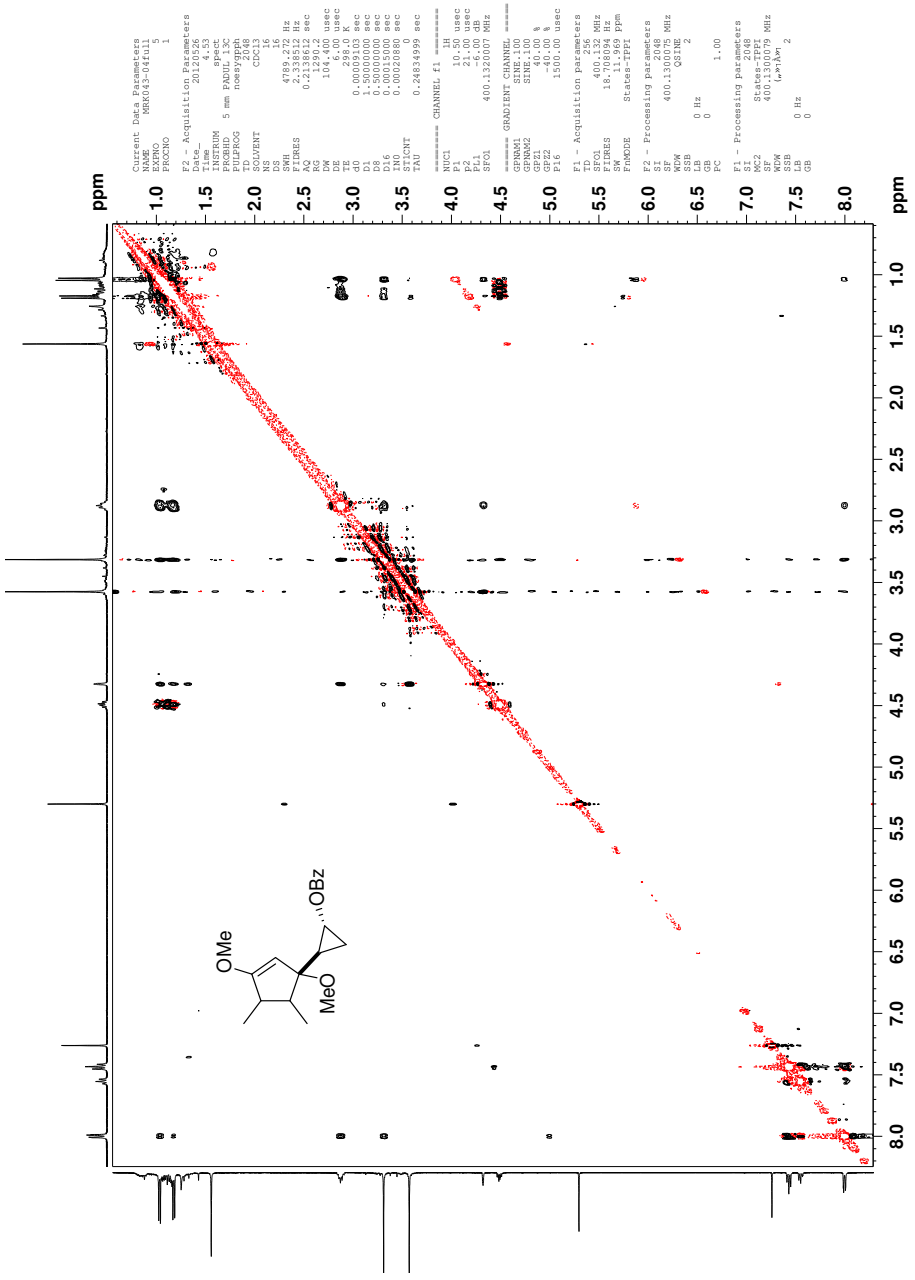
H.4 HSQC of bicyclic compound 13



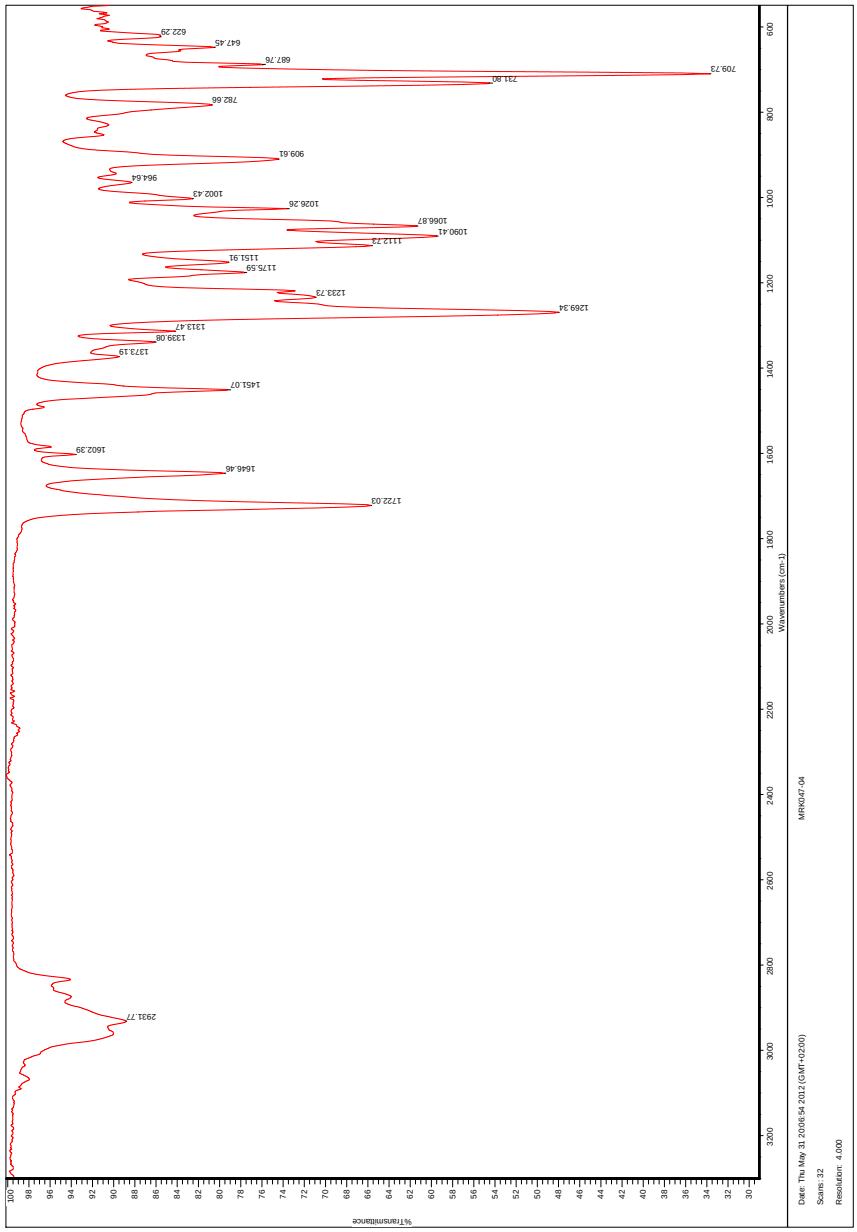
H.5 HMBC of bicyclic compound 13



H.6 NOESY of bicyclic compound 13

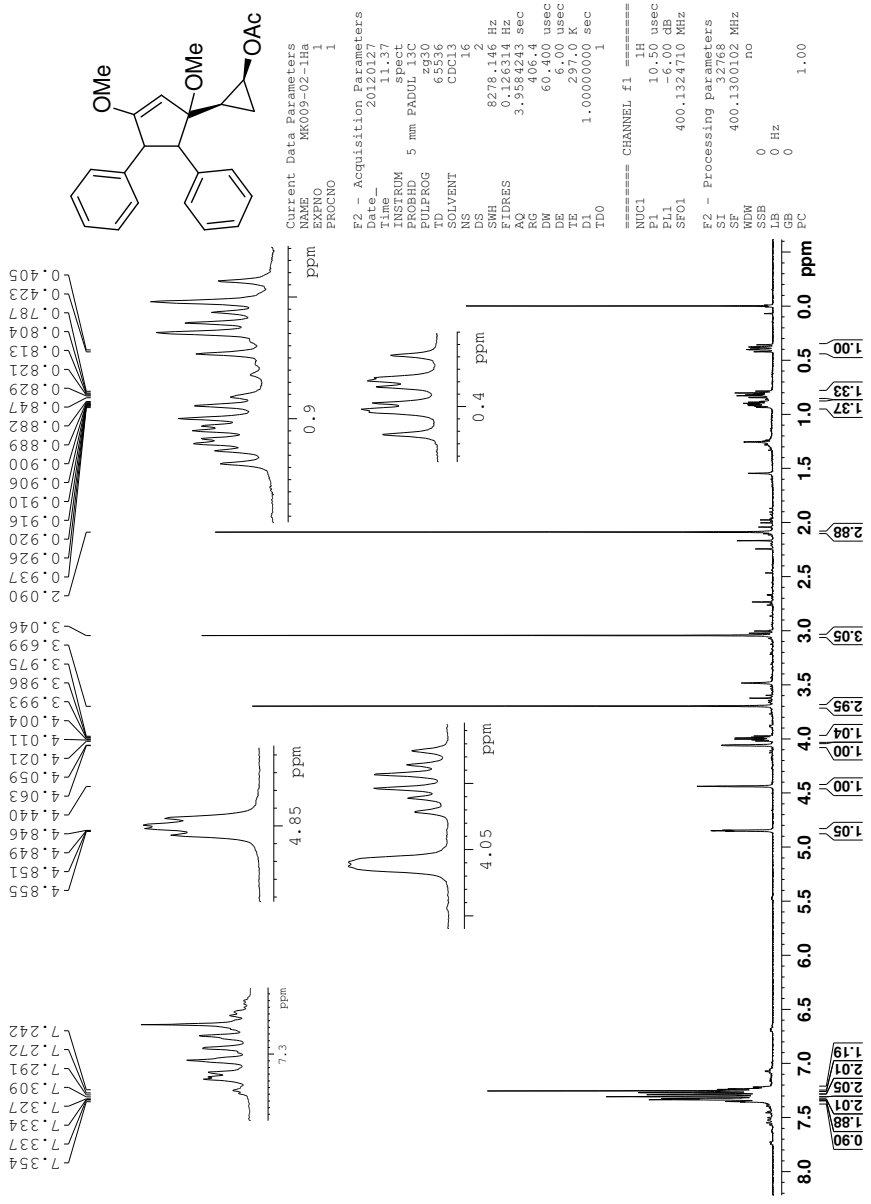


H.7 IR of bicyclic compound 13

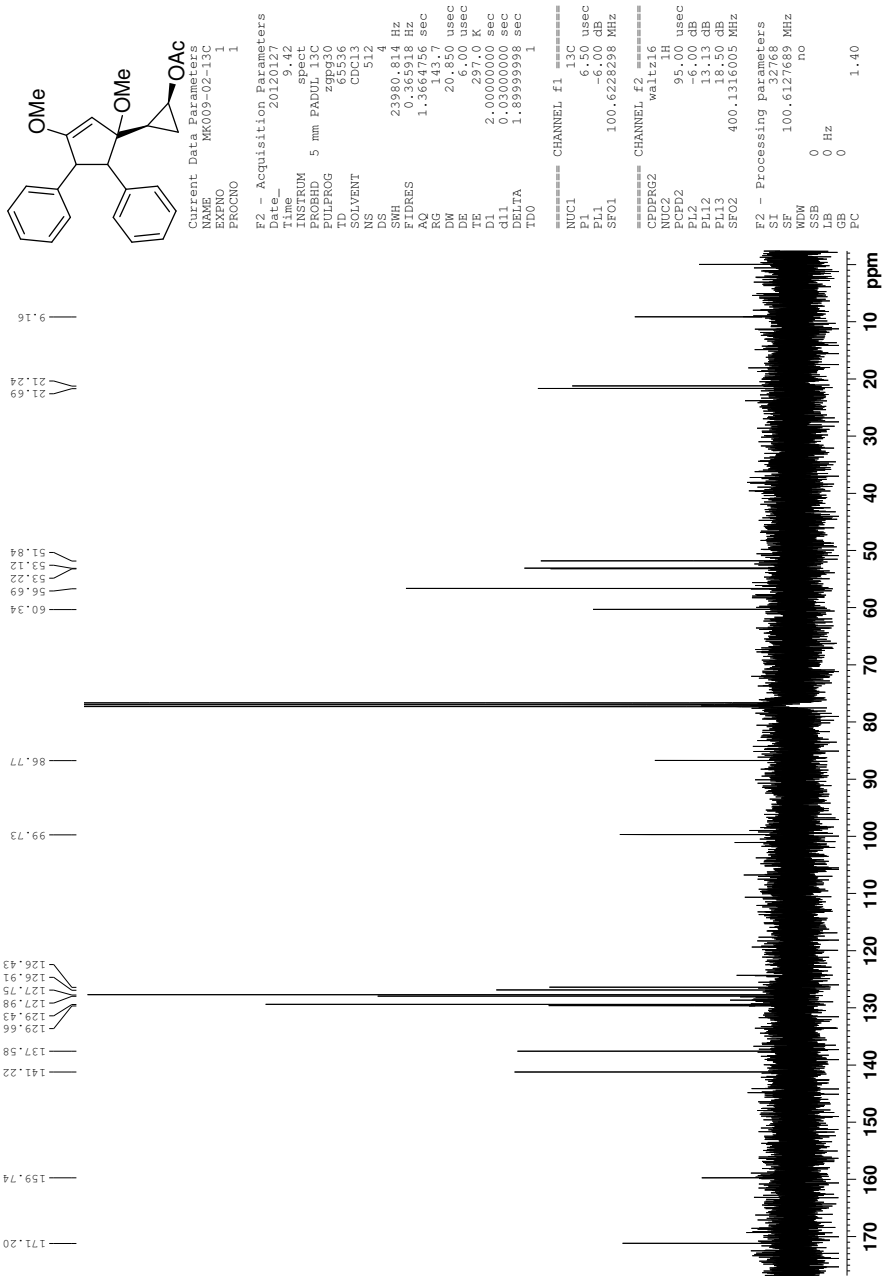


I Bicyclic compound 15

I.1 ^{1}H NMR of bicyclic compound 15

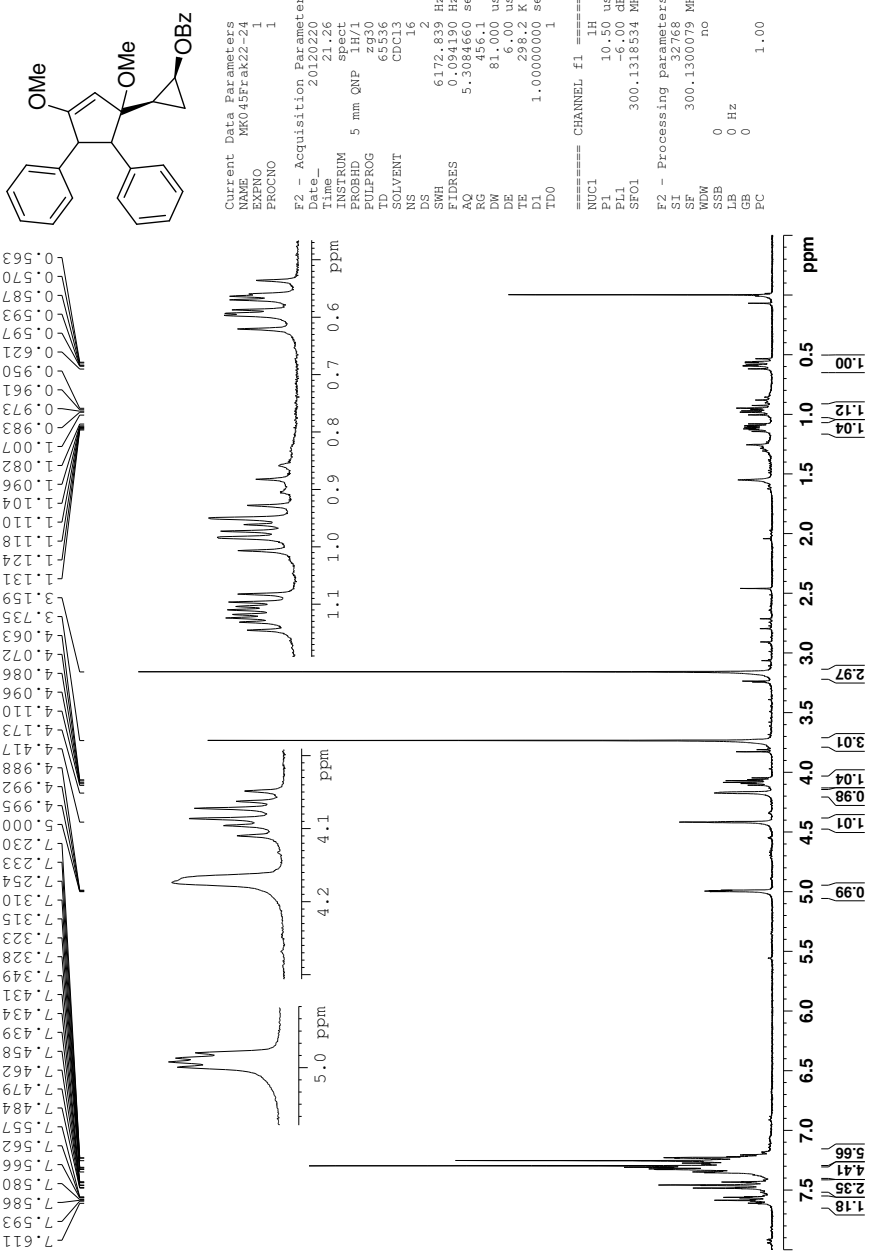


I.2 ^{13}C NMR of bicyclic compound 15

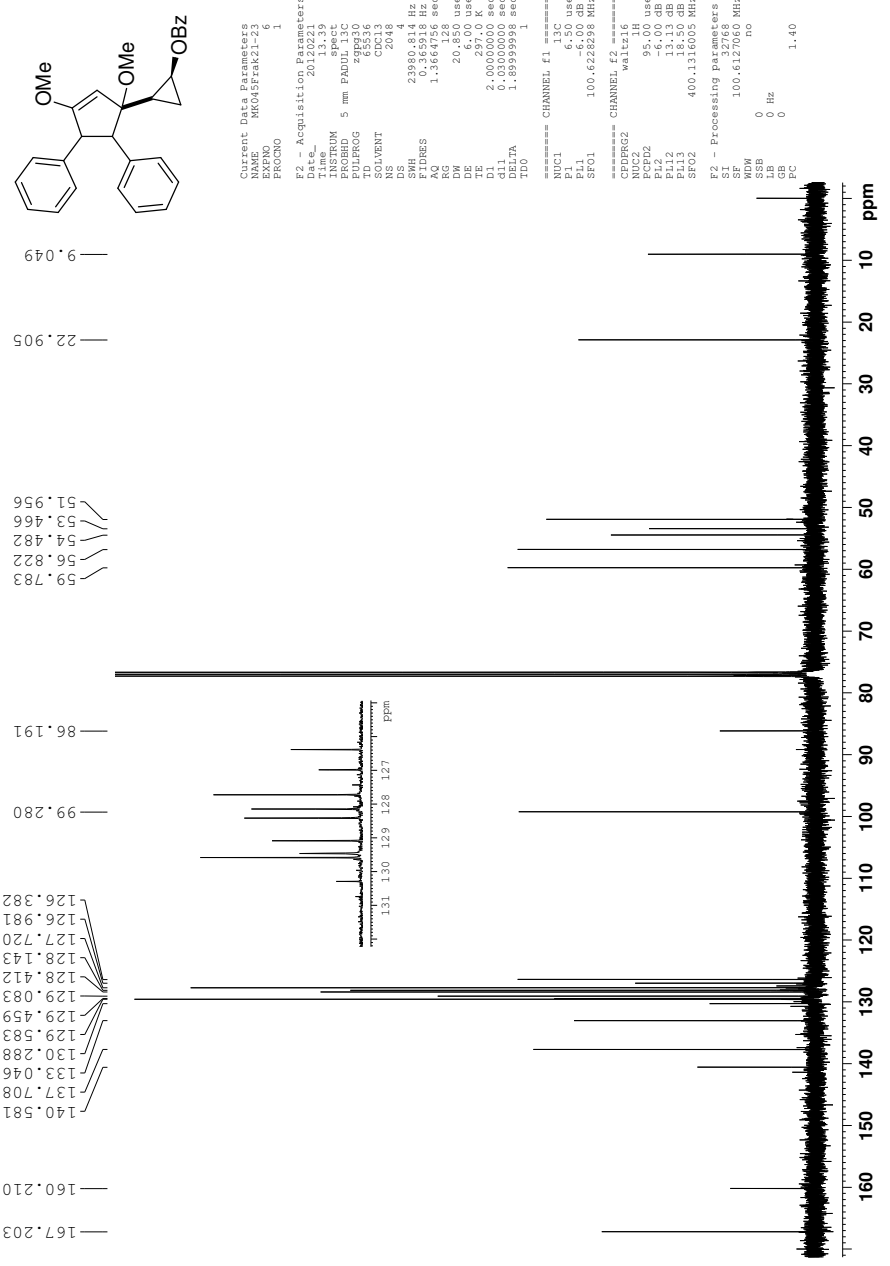


J Bicyclic compound 16a-b

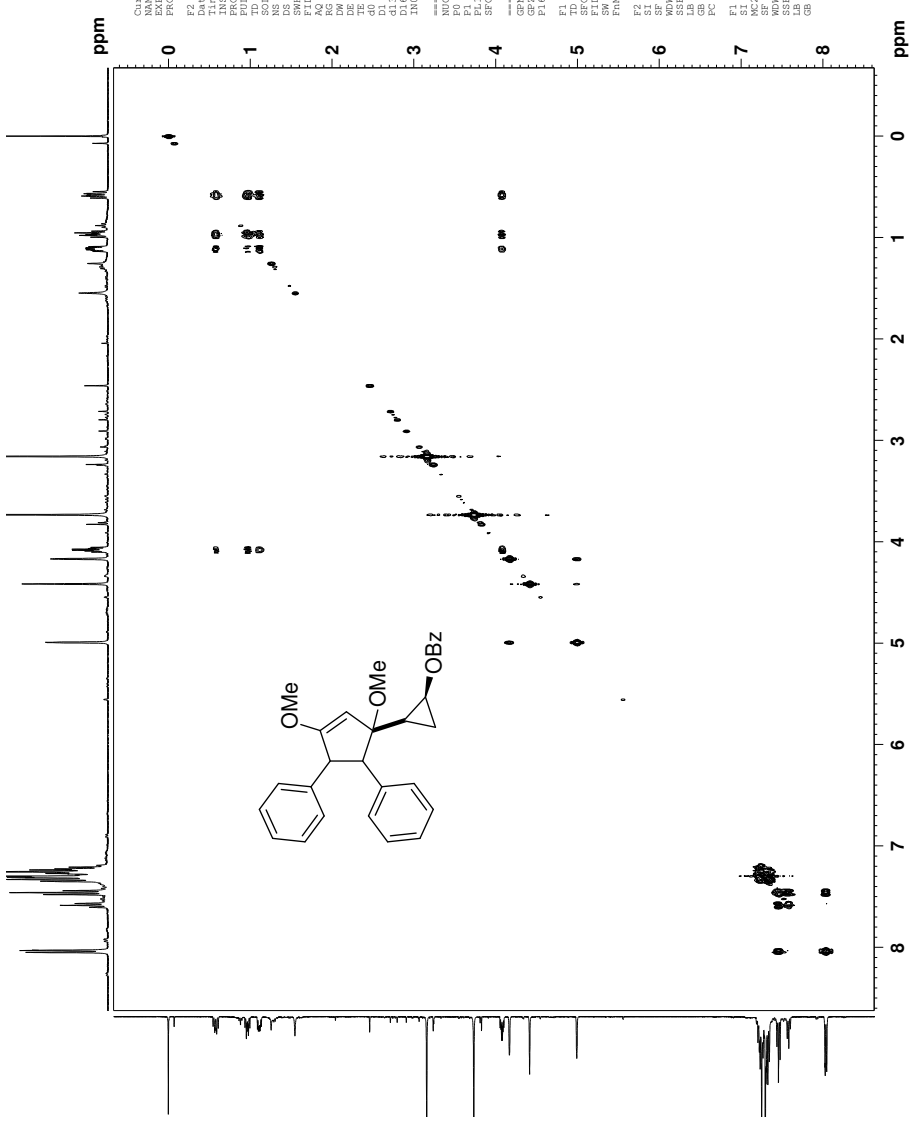
J.1 ^{1}H NMR of bicyclic compound 16a



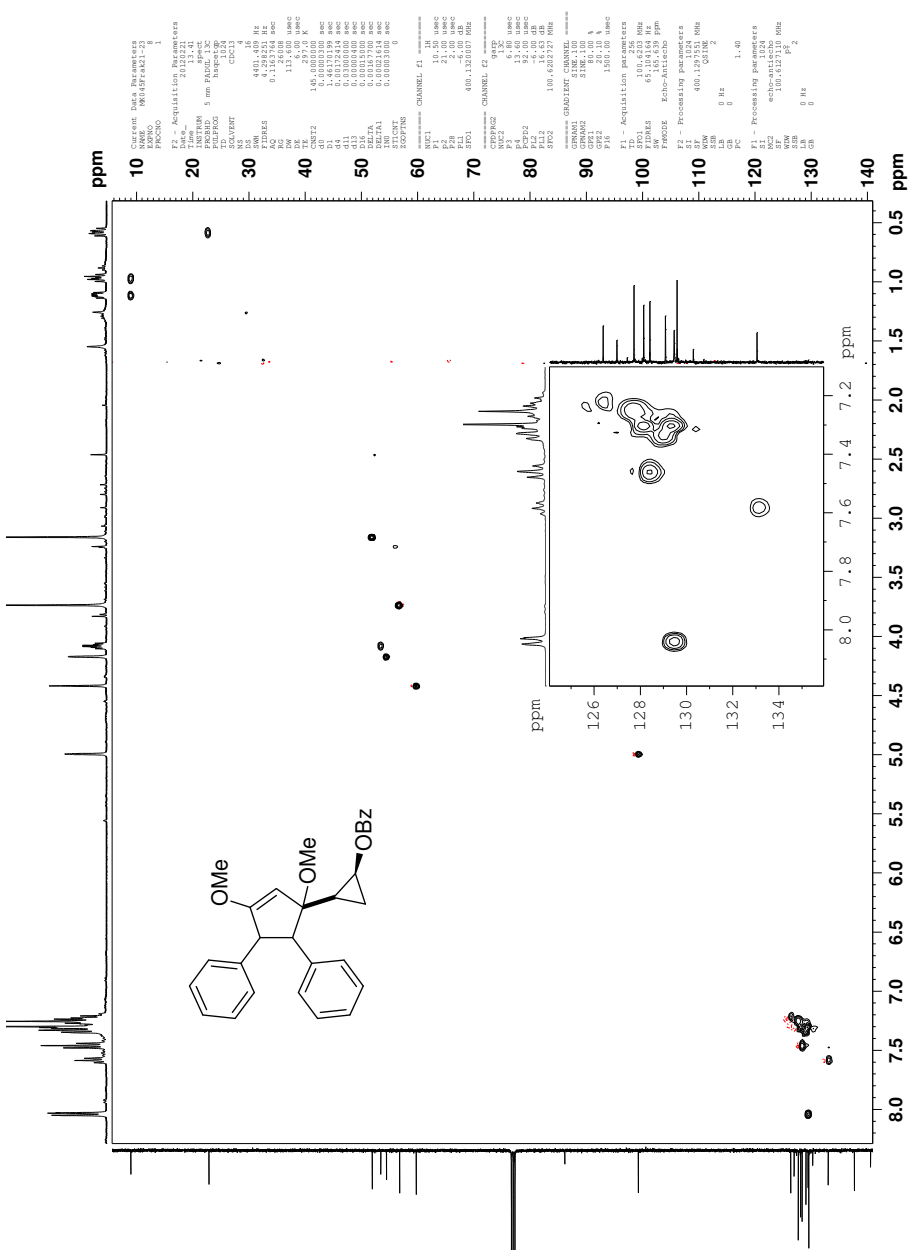
J.2 ^{13}C NMR of bicyclic compound 16a



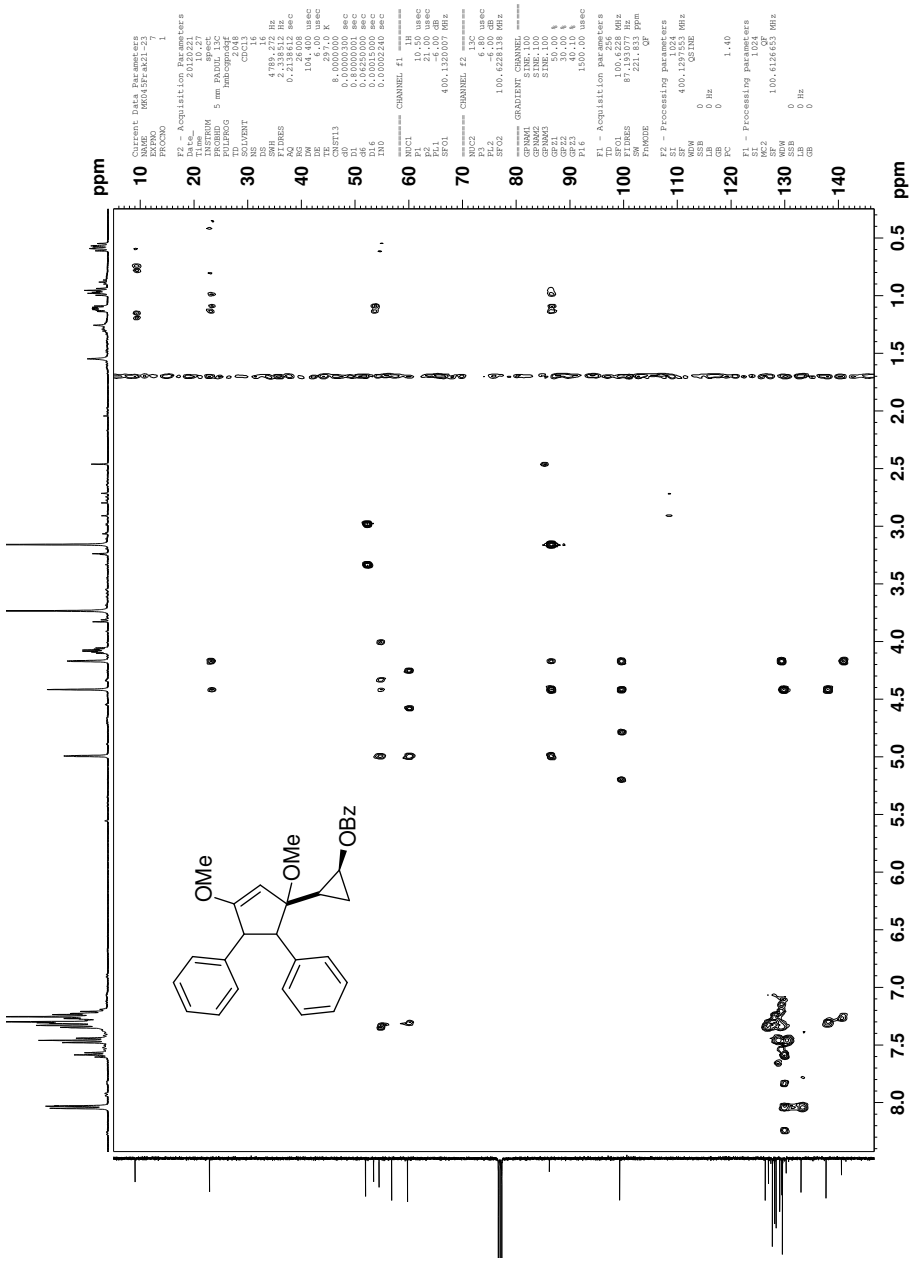
J.3 COSY of bicyclic compound 16a



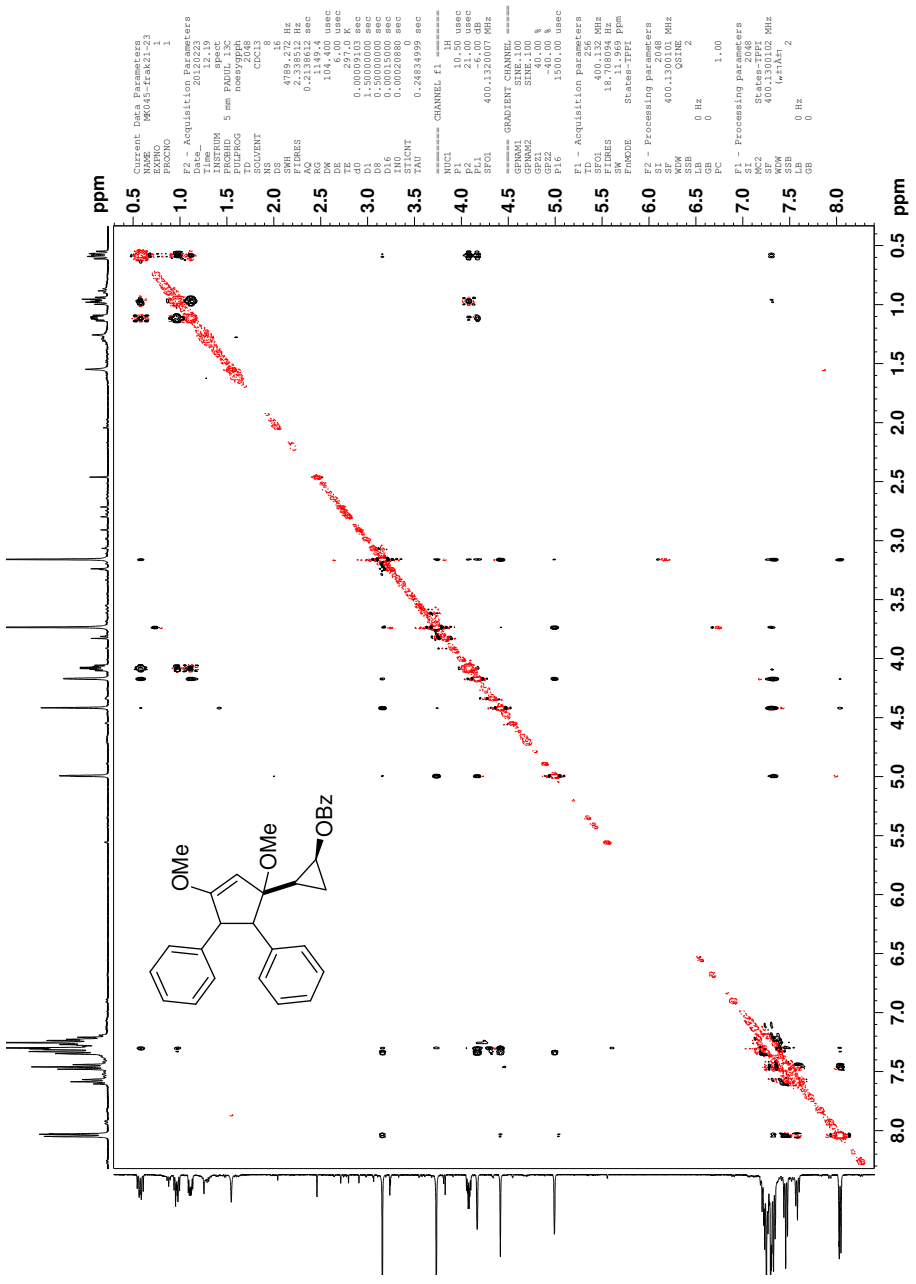
J.4 HSQC of bicyclic compound 16a



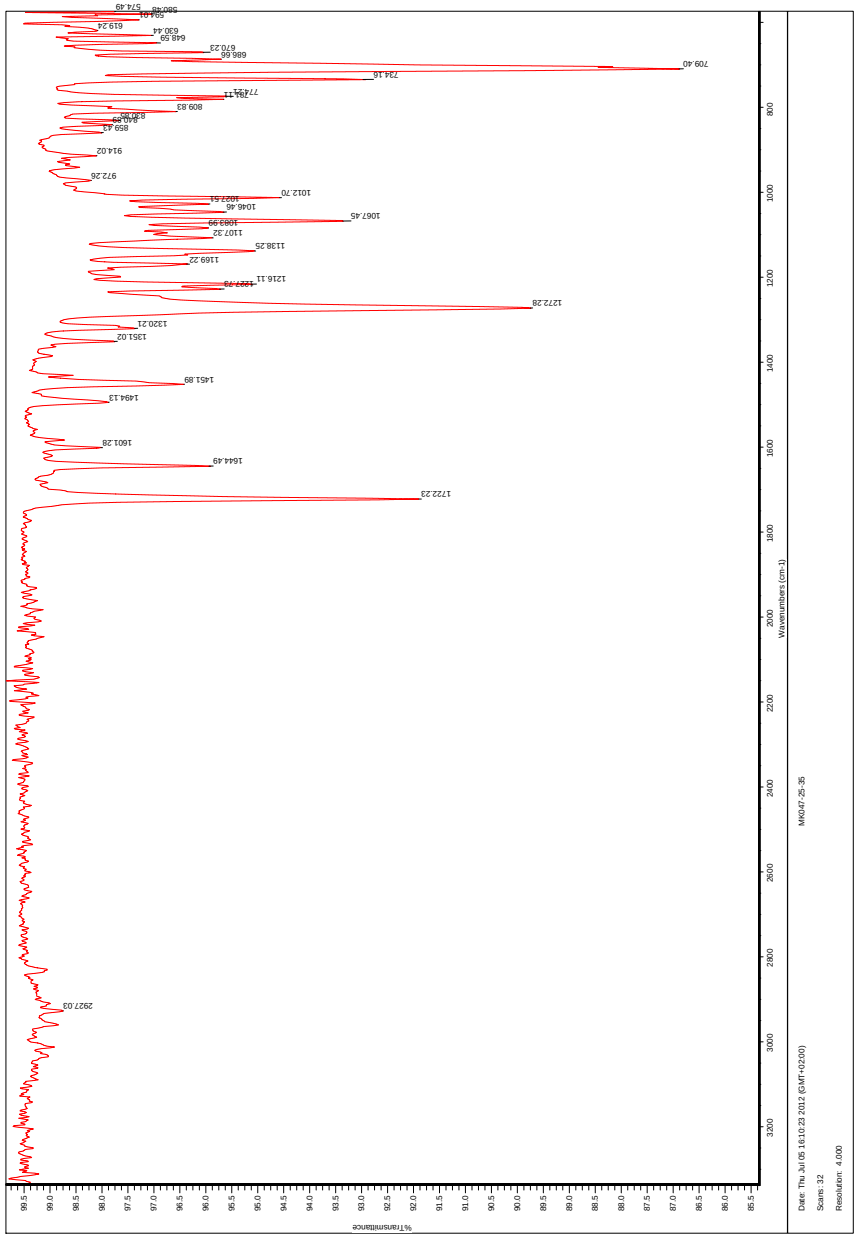
J.5 HMBC of bicyclic compound 16a



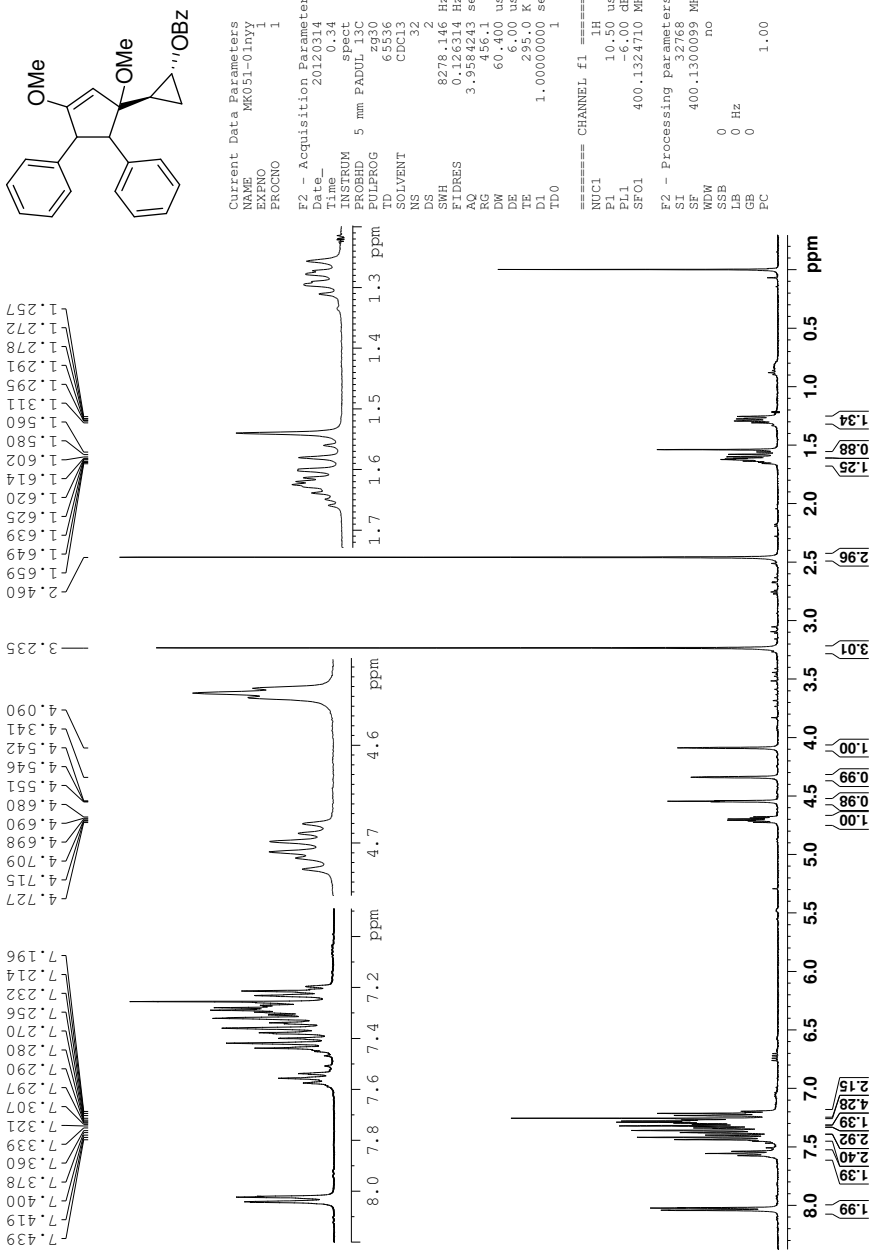
J.6 NOESY of bicyclic compound 16a



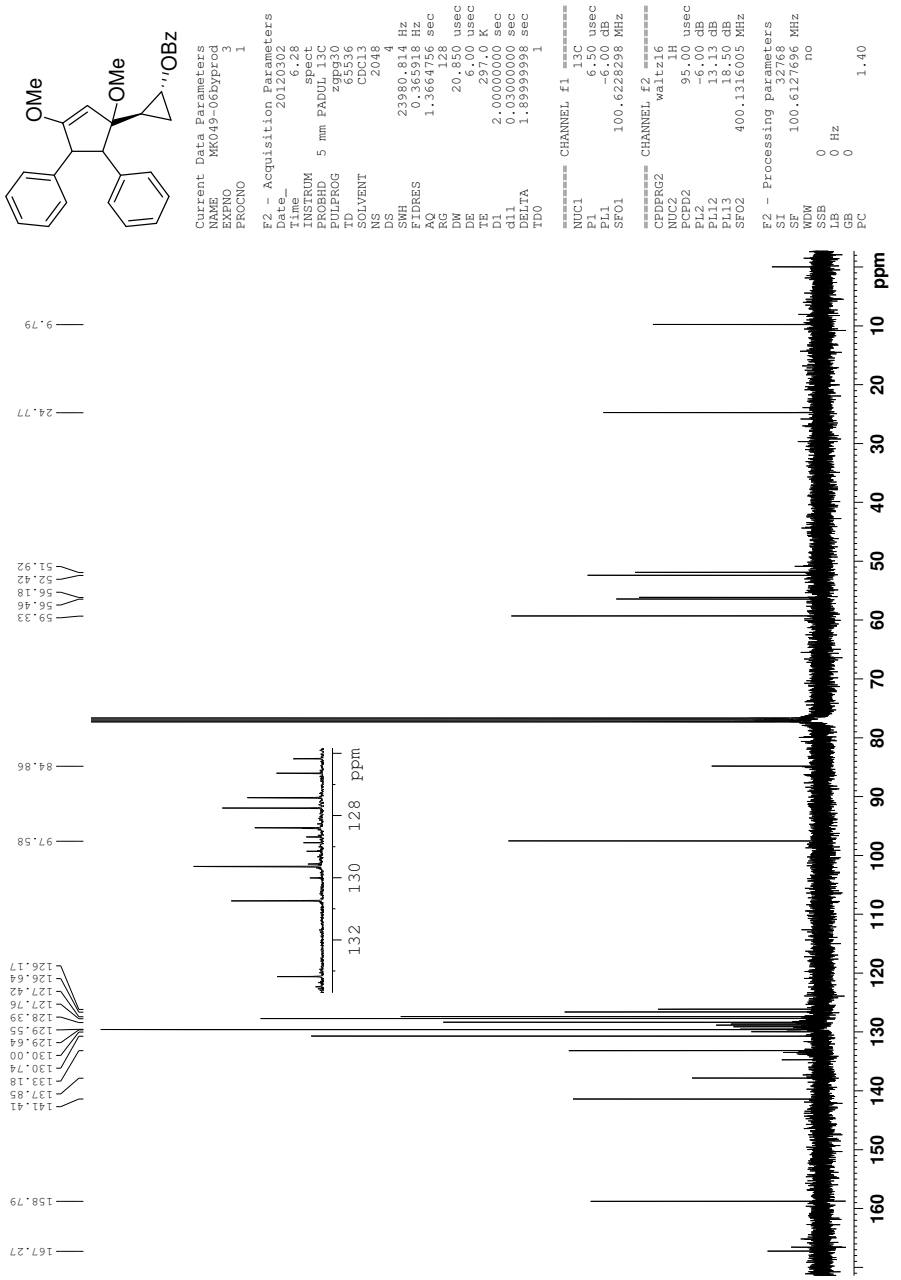
J.7 IR of bicyclic compound 16a



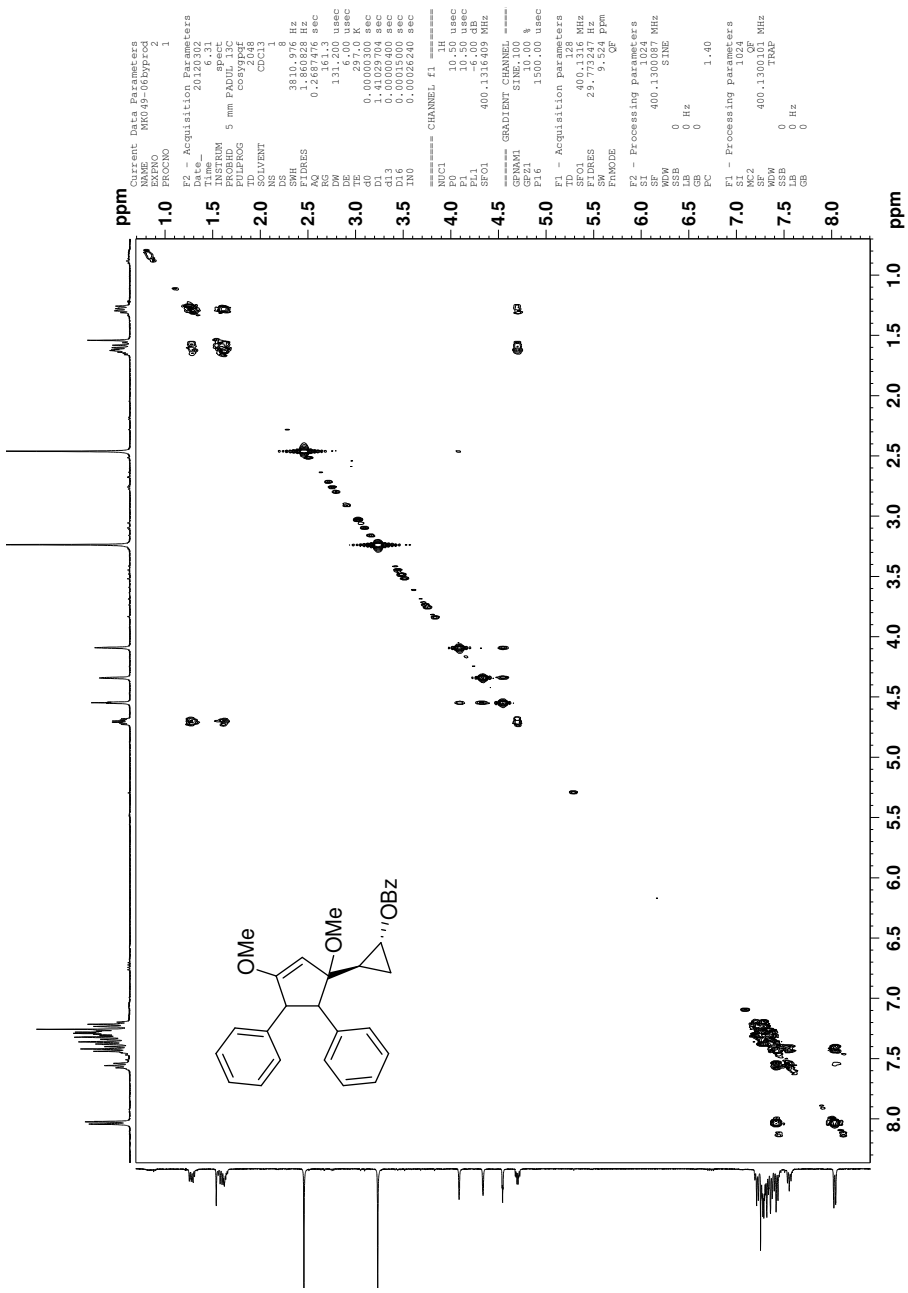
J.8 ^{1}H NMR of bicyclic compound 16b



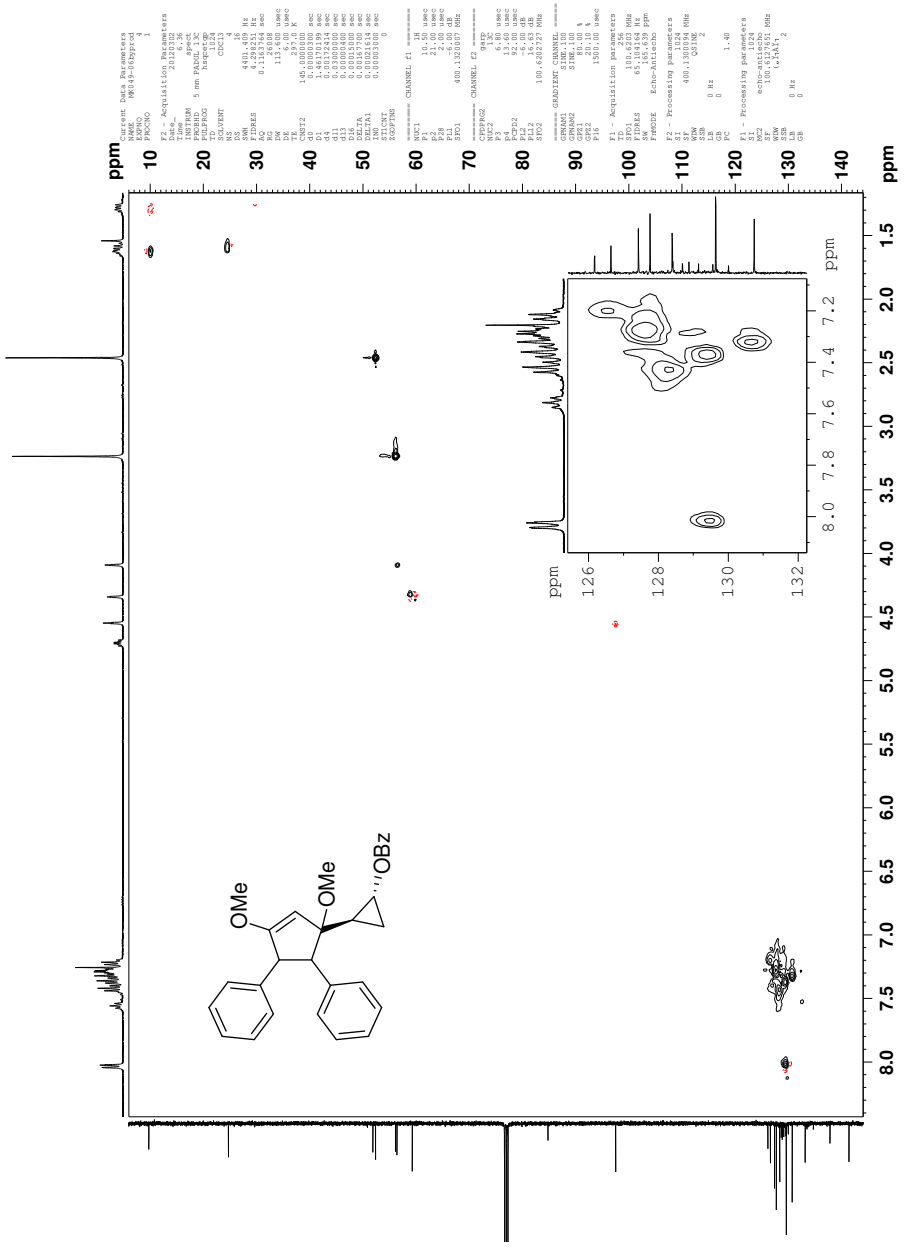
J.9 ^{13}C NMR of bicyclic compound 16b



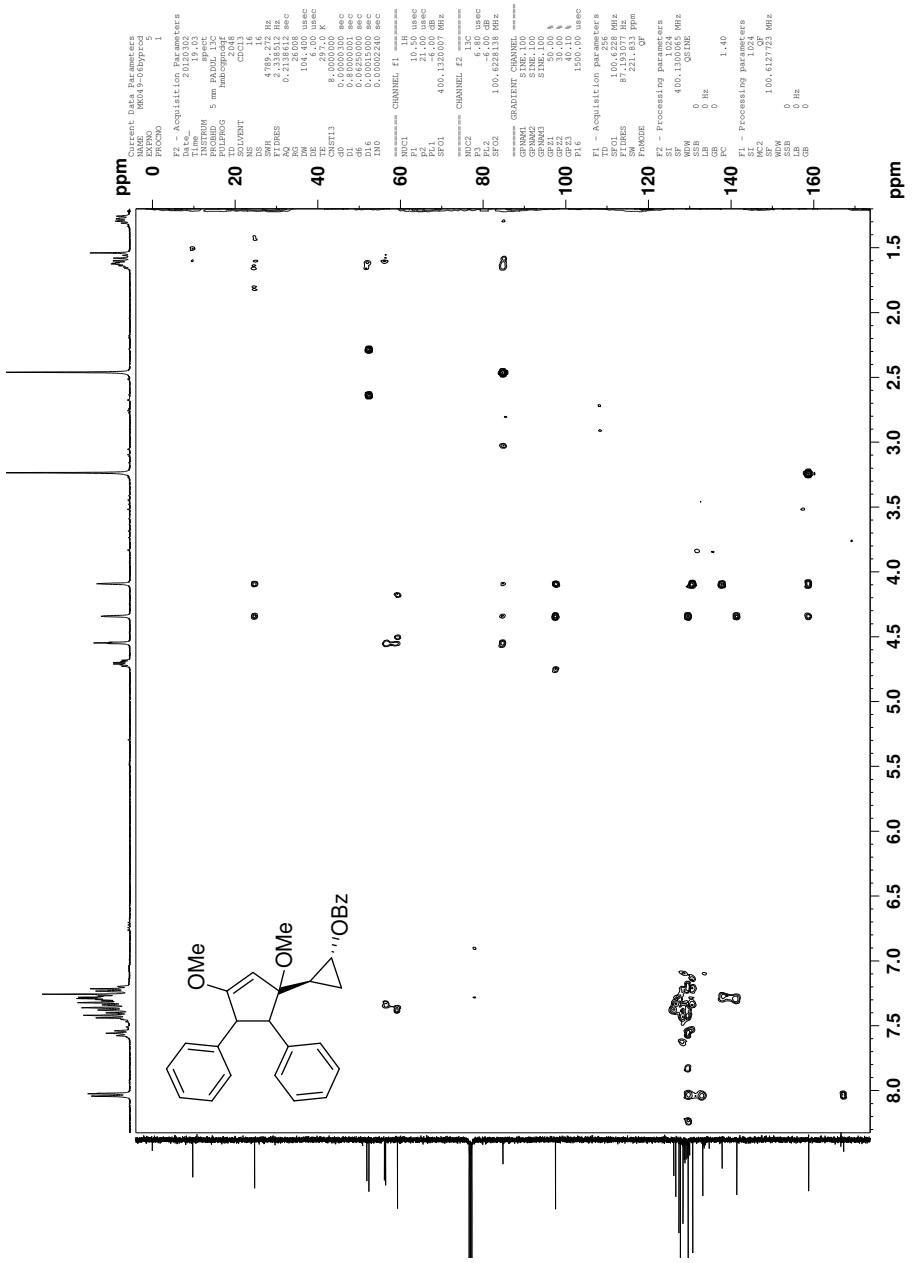
J.10 COSY of bicyclic compound 16b



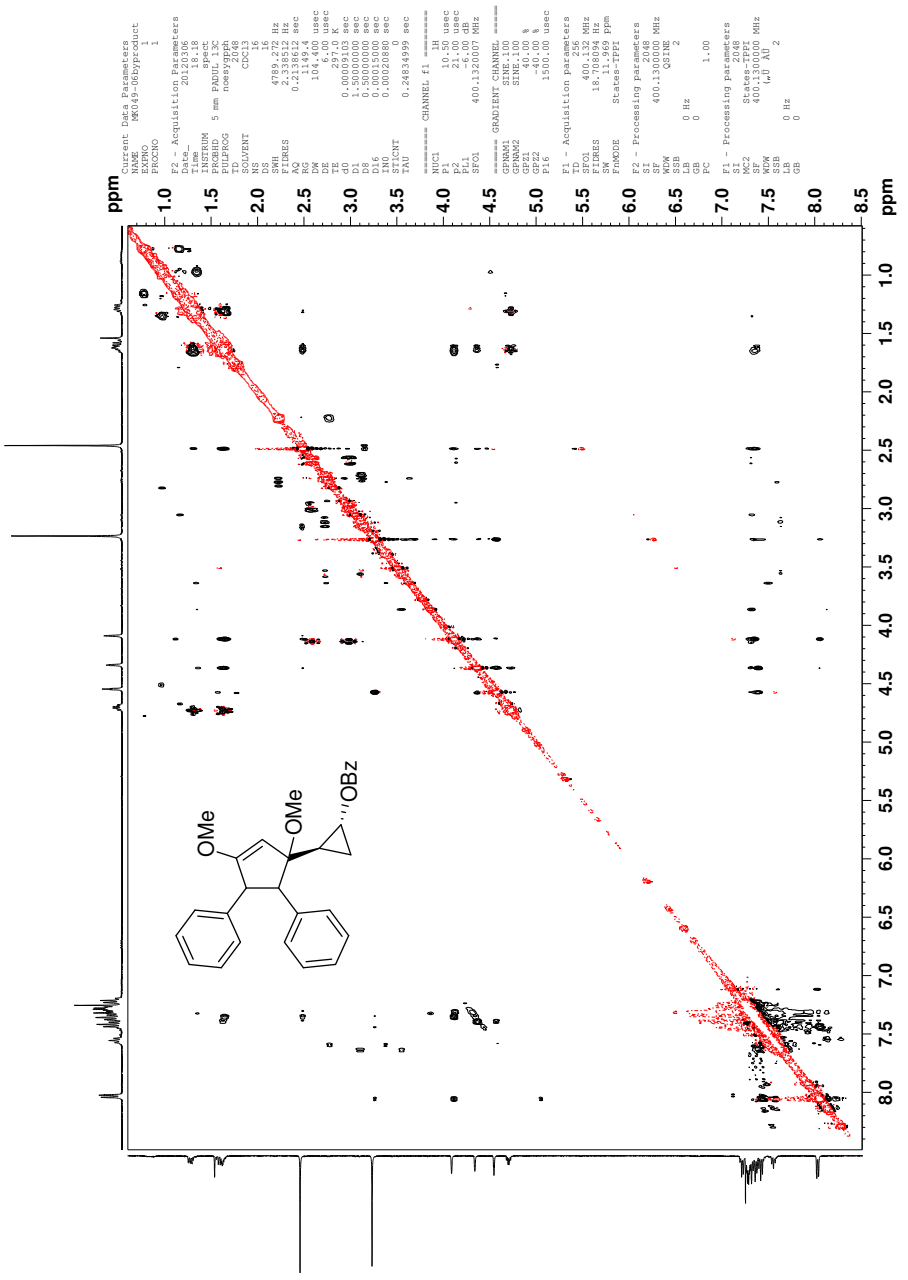
J.11 HSQC of bicyclic compound 16b



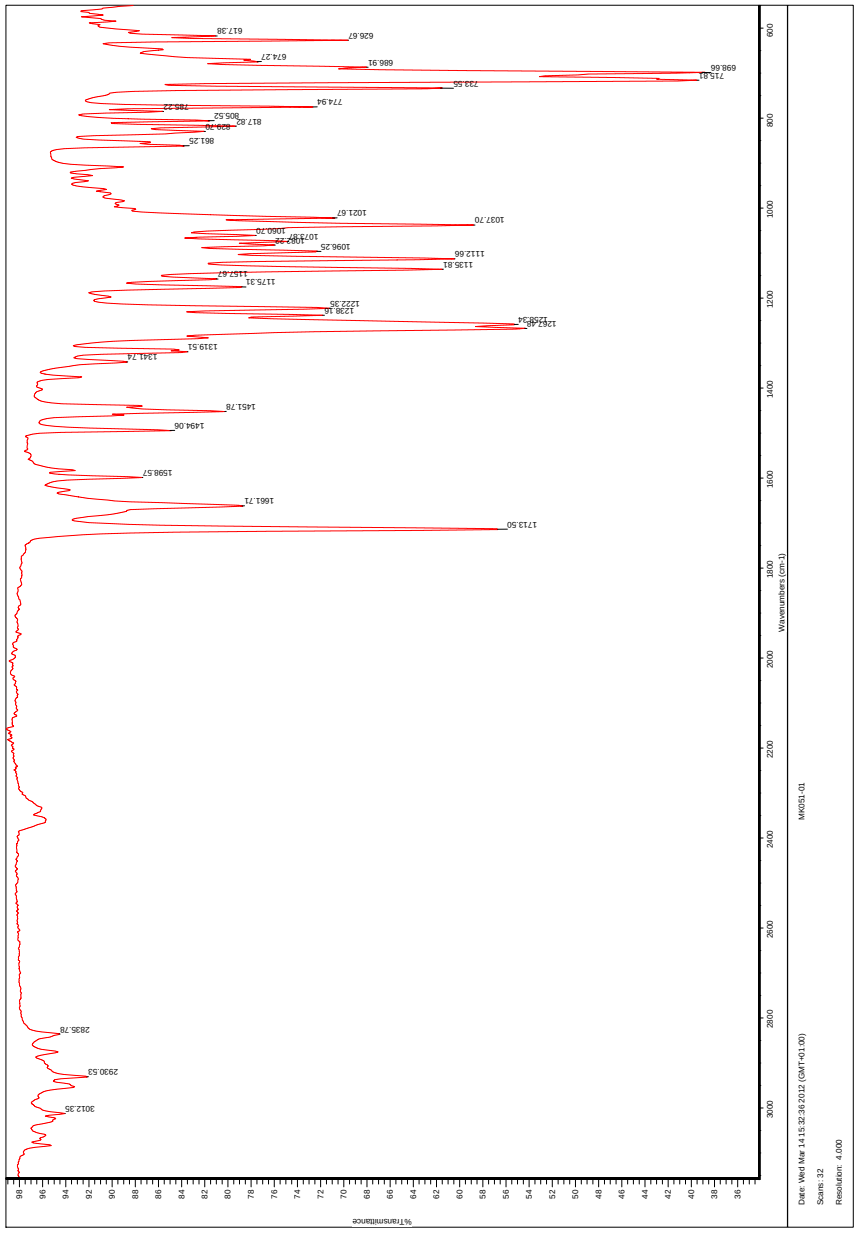
J.12 HMBC of bicyclic compound 16b



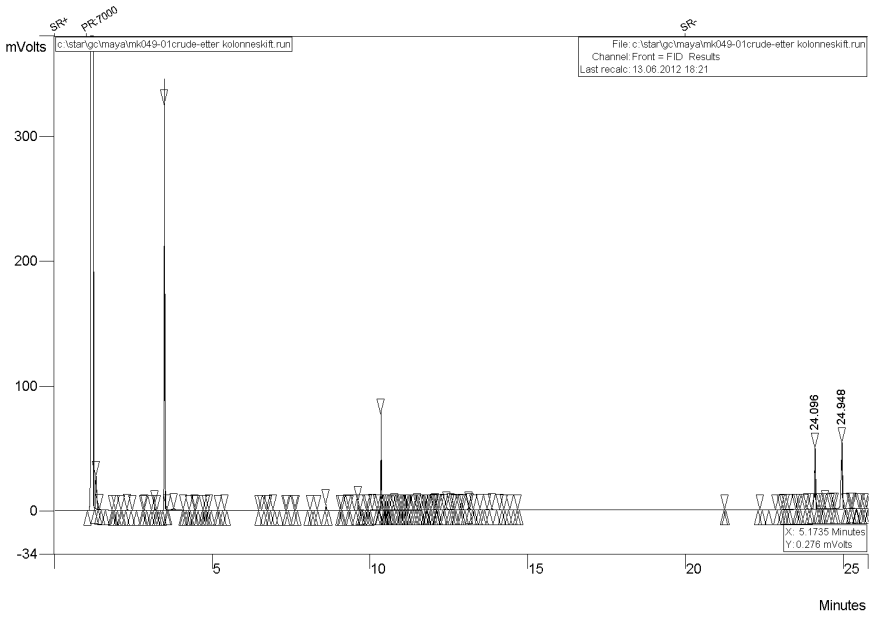
J.13 NOESY of bicyclic compound 16b



J.14 IR of bicyclic compound 16b



J.15 GLC chromatogram of bicyclic compound 16a-b

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Print Date: Wed Jun 13 18:22:11 2012            Page 1 of 1

Title       : Chrompack CP-Sil 5cB Low bleed/MS. 30m/0,25mmid
Run File    : c:\star\gc\maya\mk049-01crude-etter kolonneskift.run
Method File : c:\star\gc\maya\mrk003-01crude-front.mth
Sample ID   : Manual Sample

Injection Date: 23.02.2012 17:19    Calculation Date: 13.06.2012 18:21

Operator    :                       Detector Type: 3800 (1 Volt)
Workstation: system                 Bus Address  : 44
Instrument : Varian Star #1         Sample Rate  : 10.00 Hz
Channel    : Front = FID            Run Time     : 25.805 min

** GC Workstation Multi Instrument (Demo) Version 6.41 ** 05000-30c8-d68-31e1 **

Run Mode         : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent
```

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		44.68	24.096	0.000	130677	VV	2.3	
2		55.32	24.948	0.000	161822	VB	2.8	
	Totals:	100.00		0.000	292499			

```
Total Unidentified Counts :      292499 counts

Detected Peaks: 30           Rejected Peaks: 28      Identified Peaks: 0

Multiplier: 1           Divisor: 1           Unidentified Peak Factor: 0

Baseline Offset: 2 microVolts          LSB:      1 microVolts

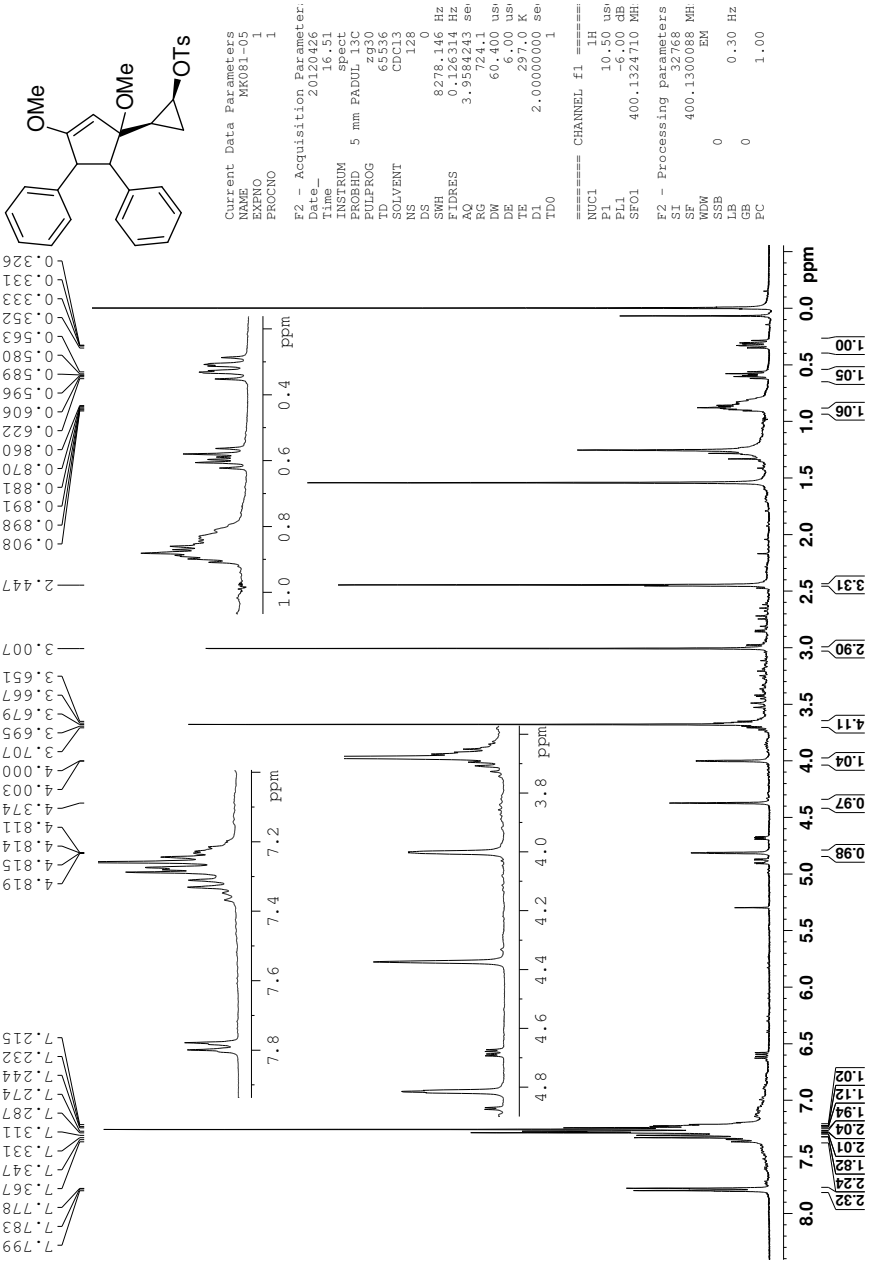
Noise (used): 16 microVolts - monitored before this run

Manual injection

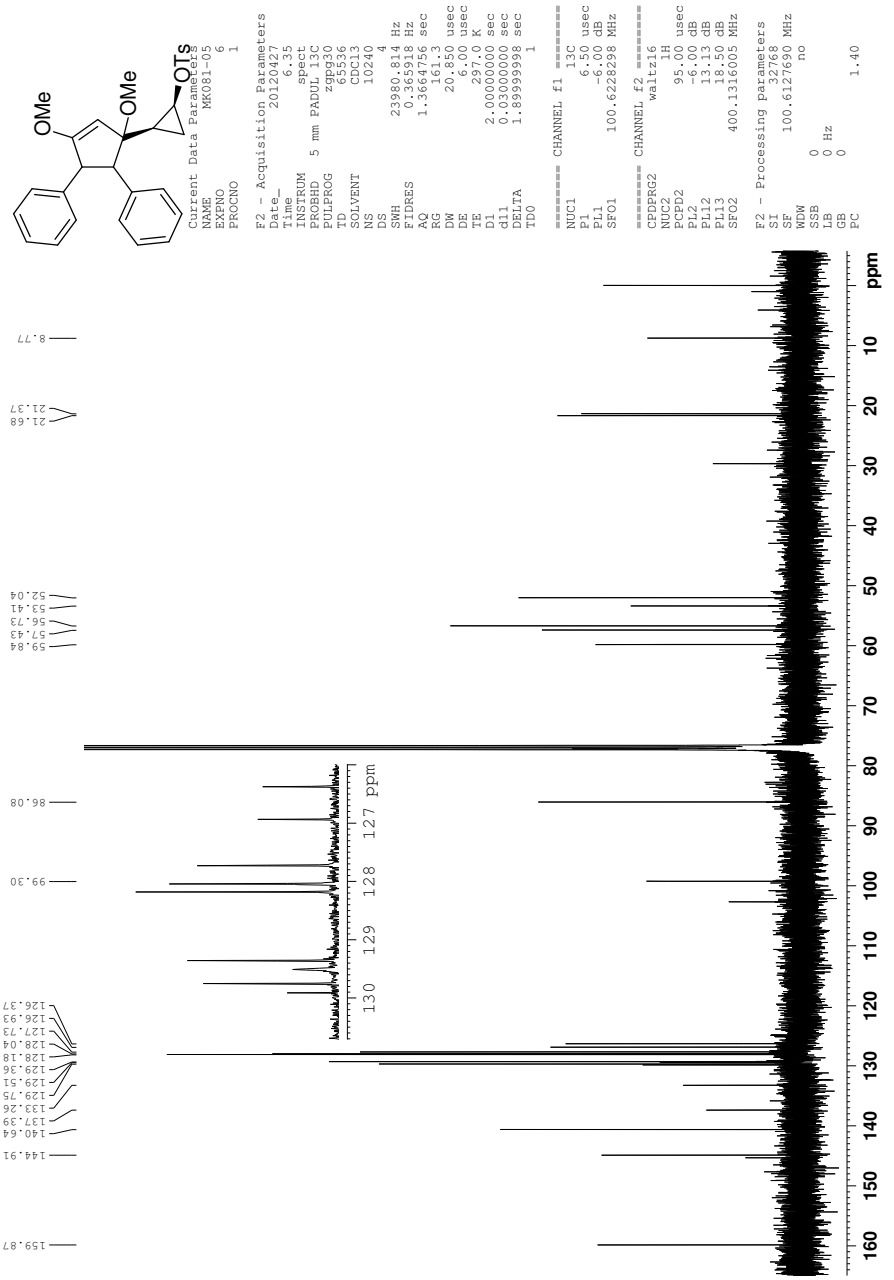
********************************************************************************
```

K Bicyclic compound 17

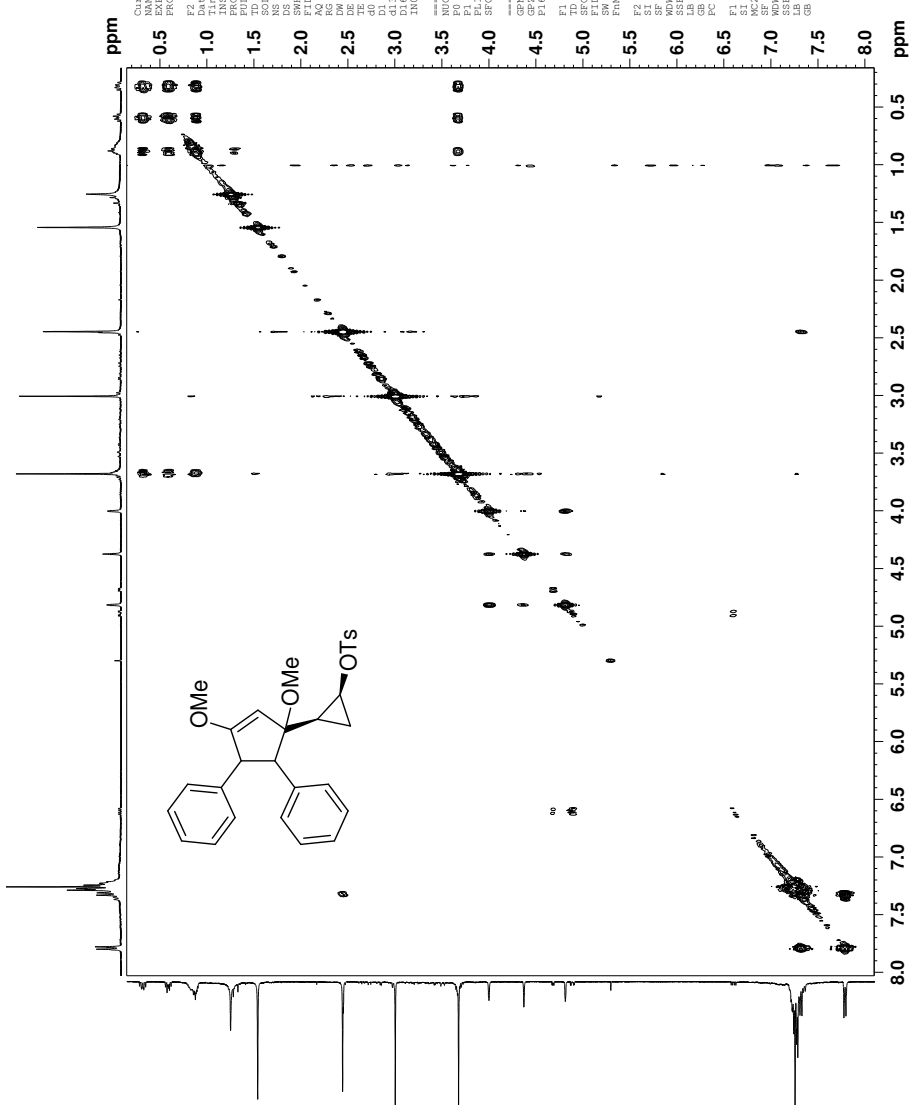
K.1 ^{1}H NMR of bicyclic compound 17



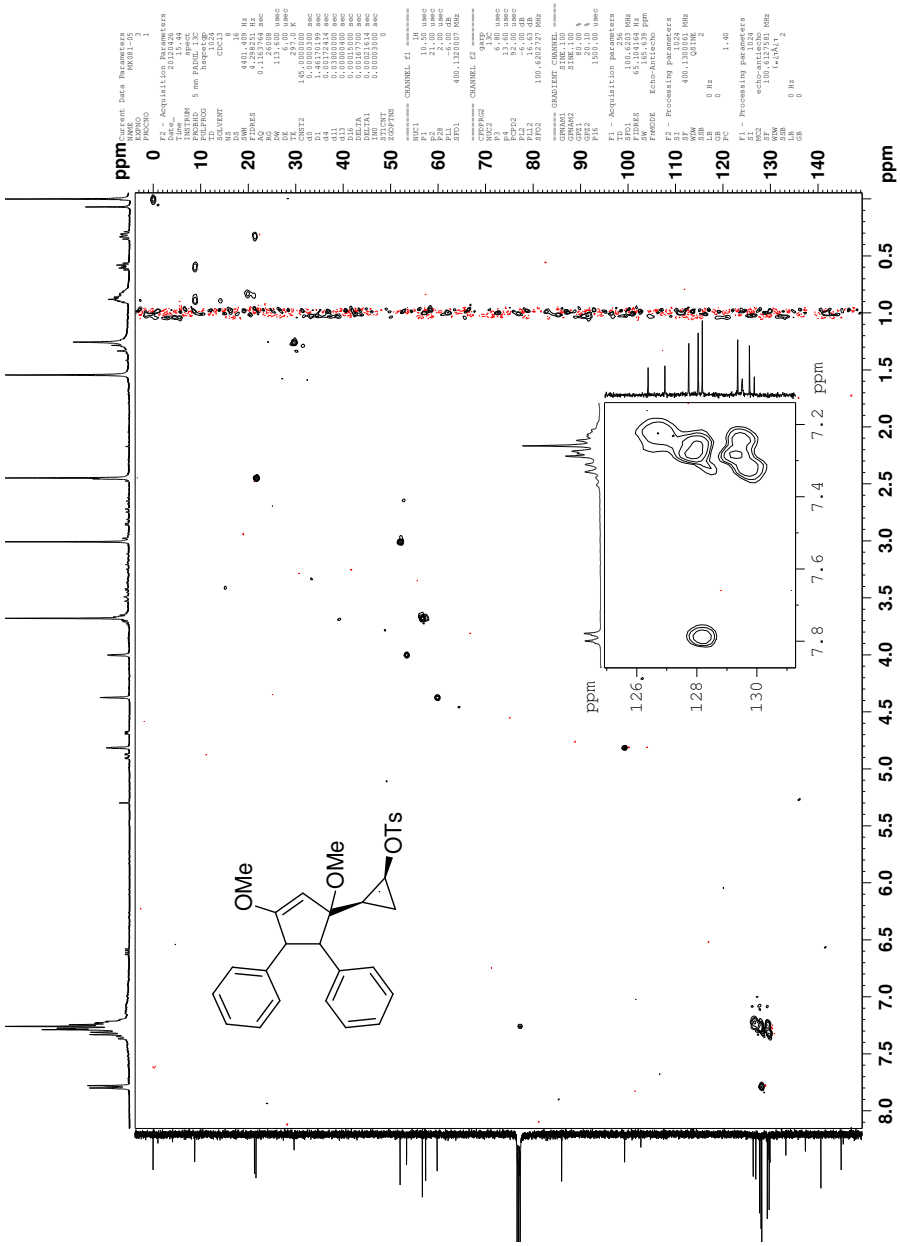
K.2 ^{13}C NMR of bicyclic compound 17



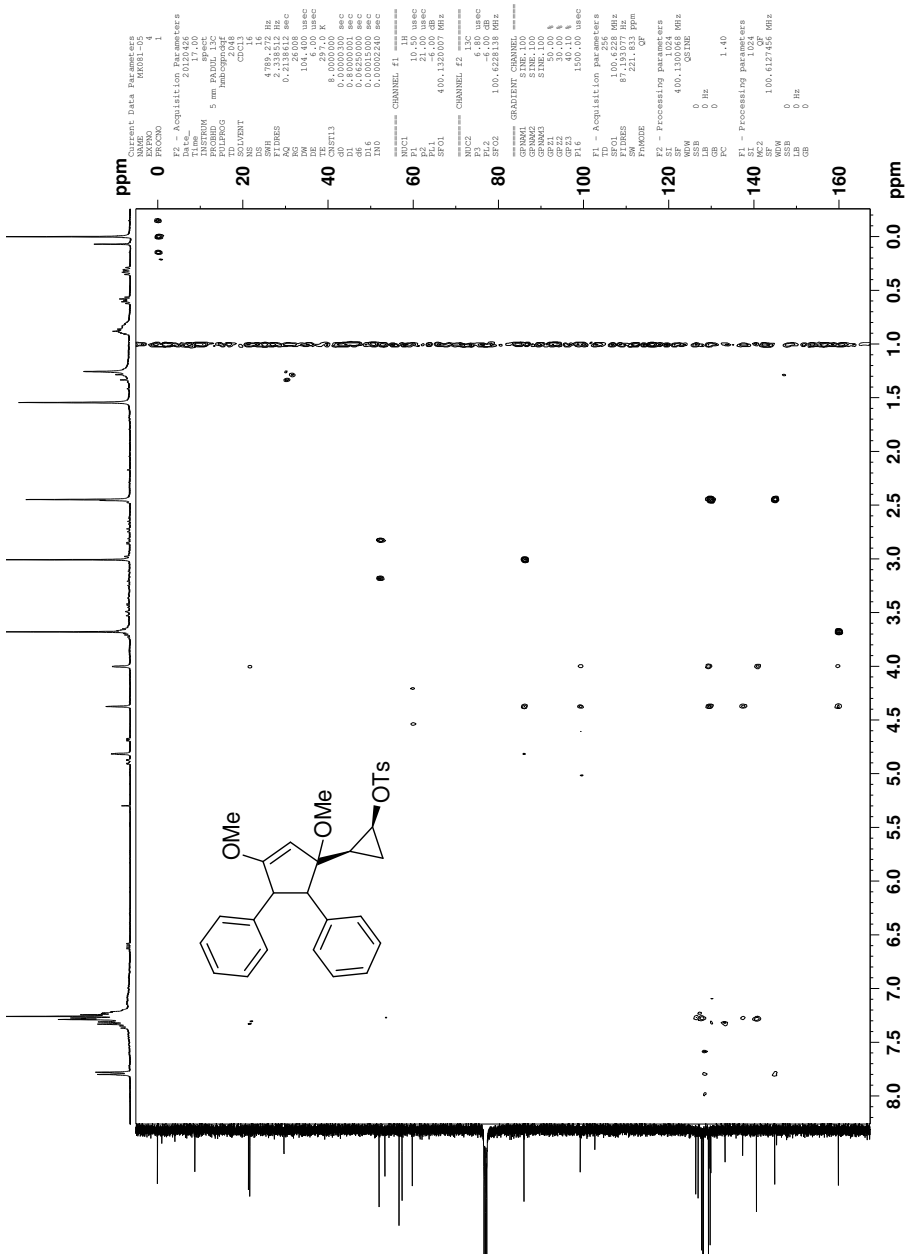
K.3 COSY of bicyclic compound 17



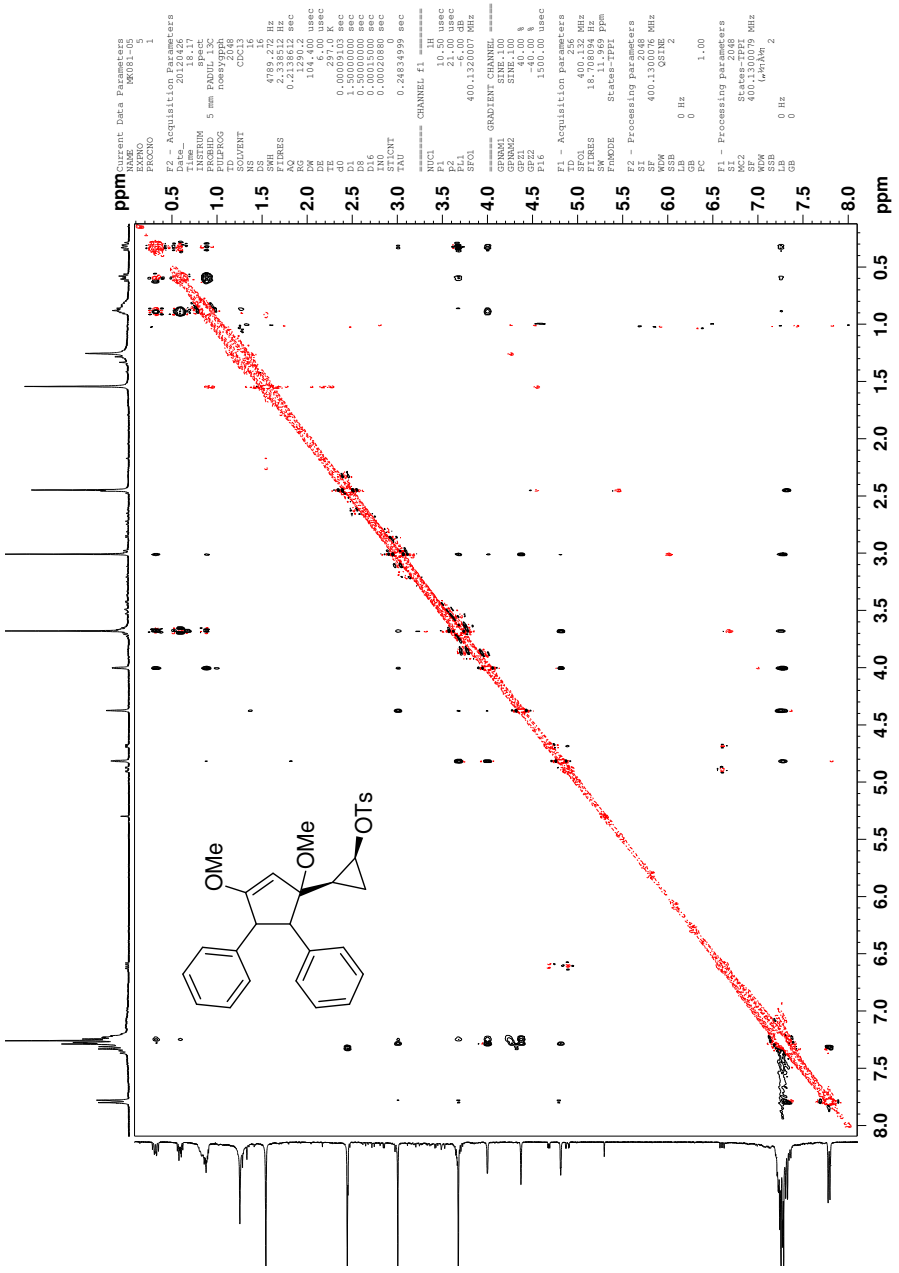
K.4 HSQC of bicyclic compound 17



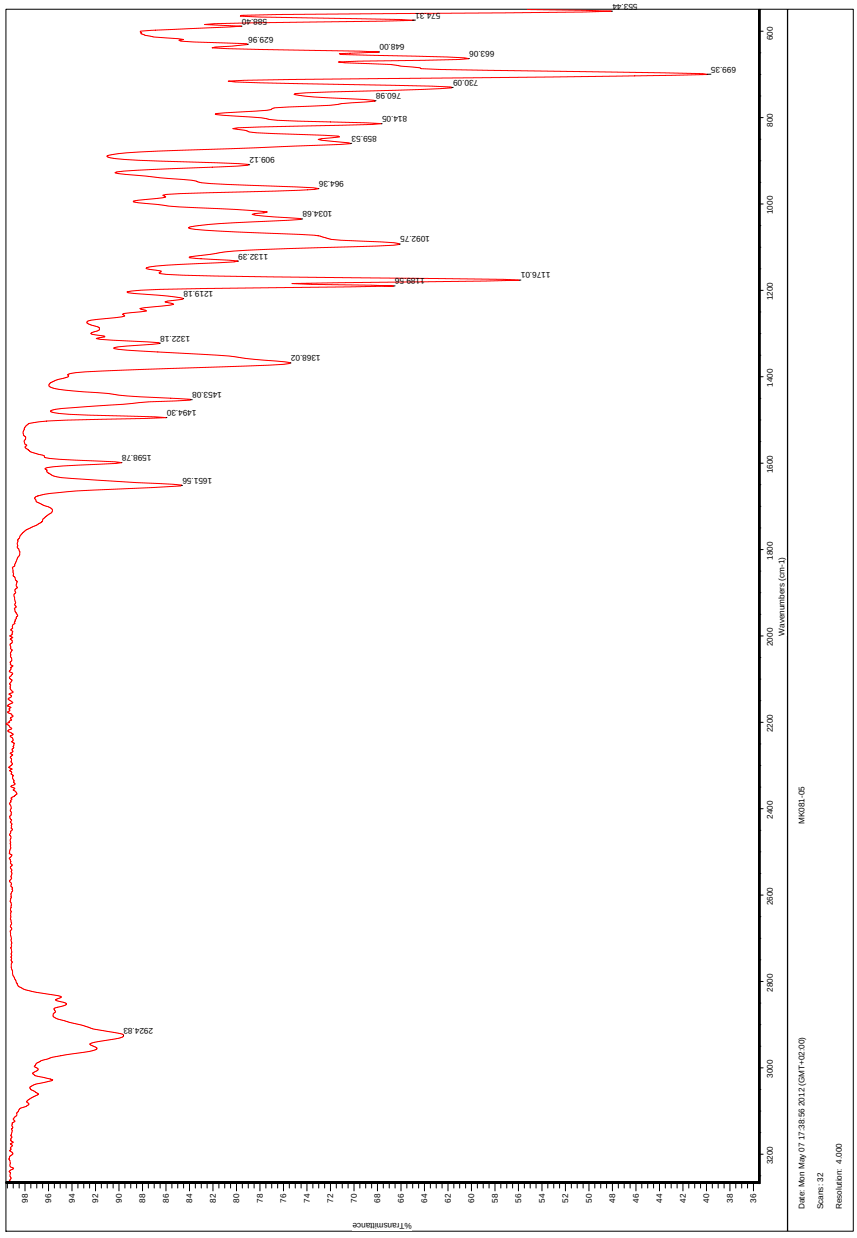
K.5 HMBC of bicyclic compound 17



K.6 NOESY of bicyclic compound 17

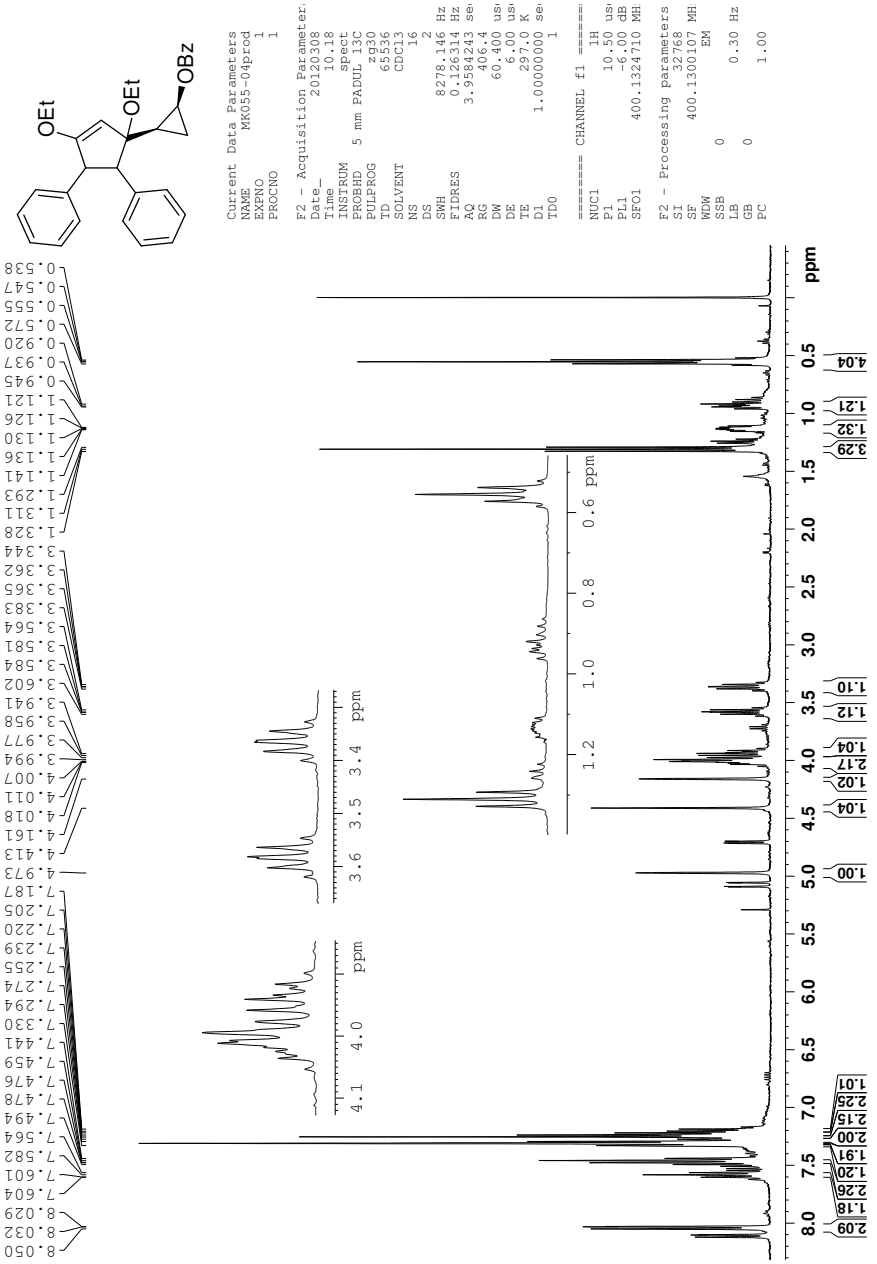


K.7 IR of bicyclic compound 17

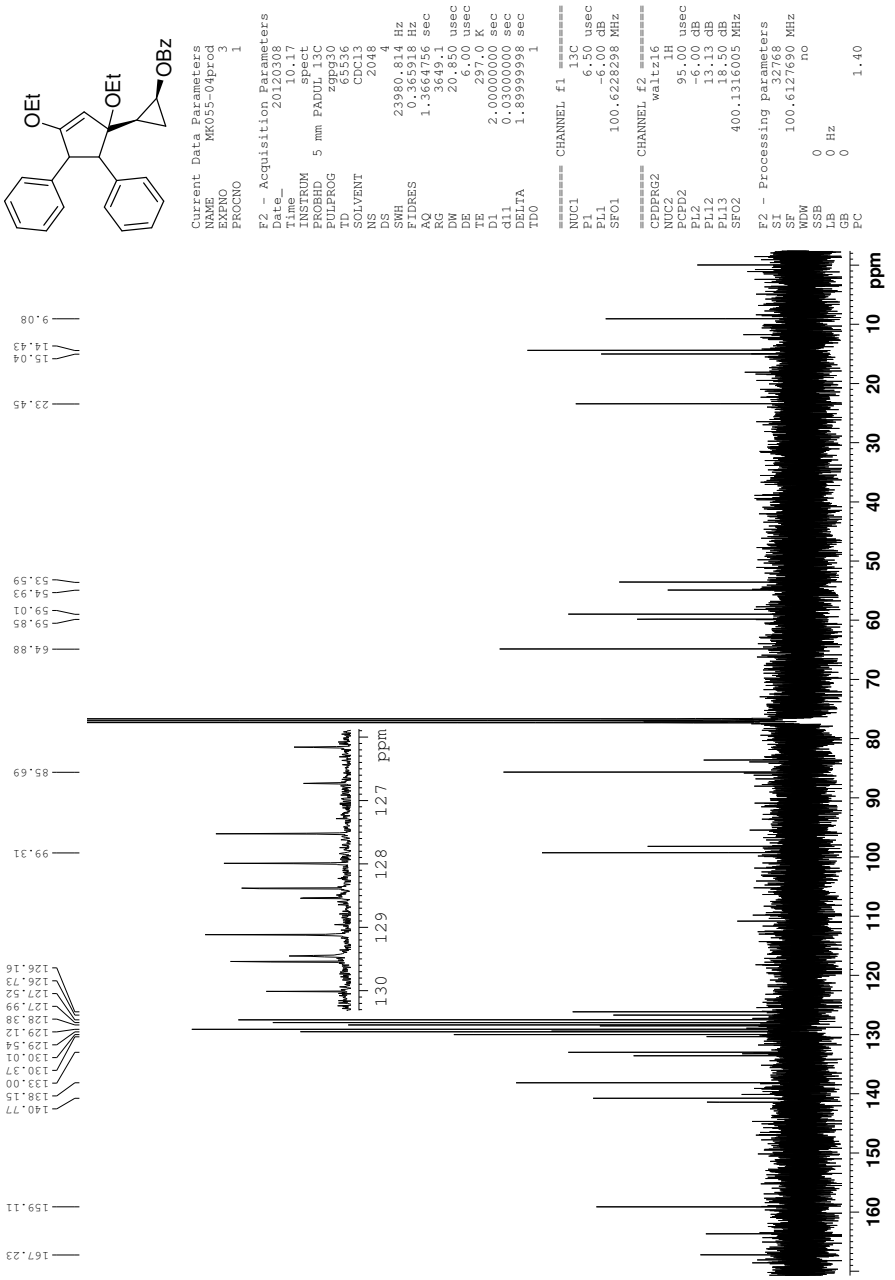


L Bicyclic compound 18a-b

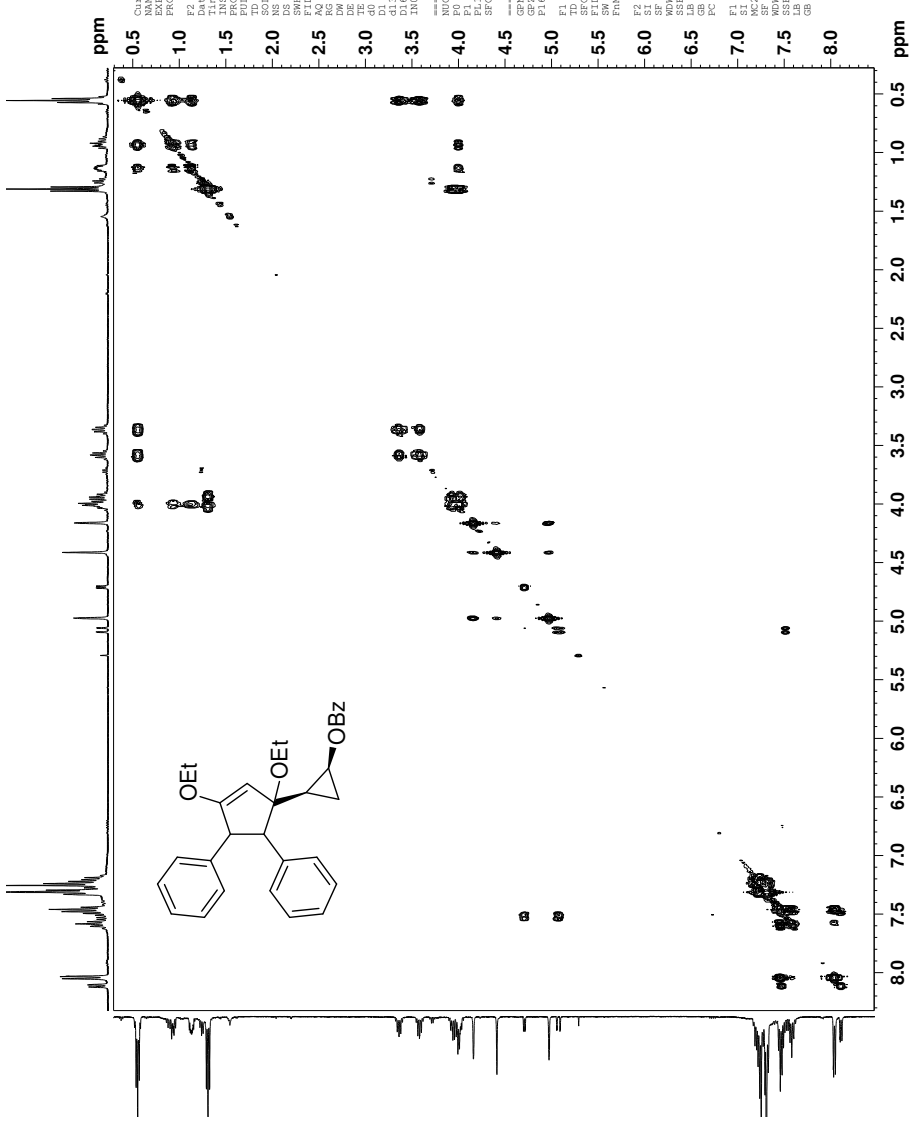
L.1 ^{1}H NMR of bicyclic compound 18a



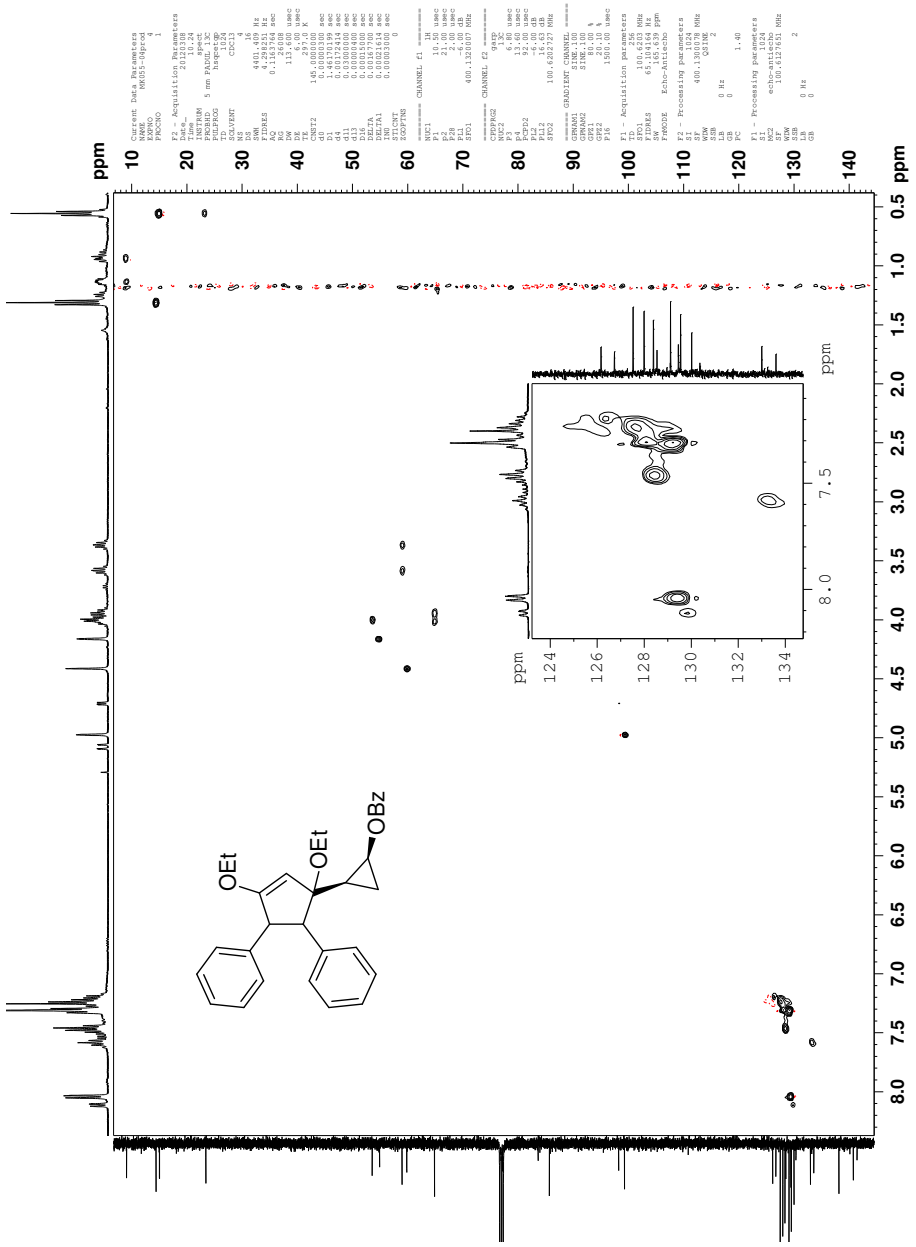
L.2 ^{13}C NMR of bicyclic compound 18a



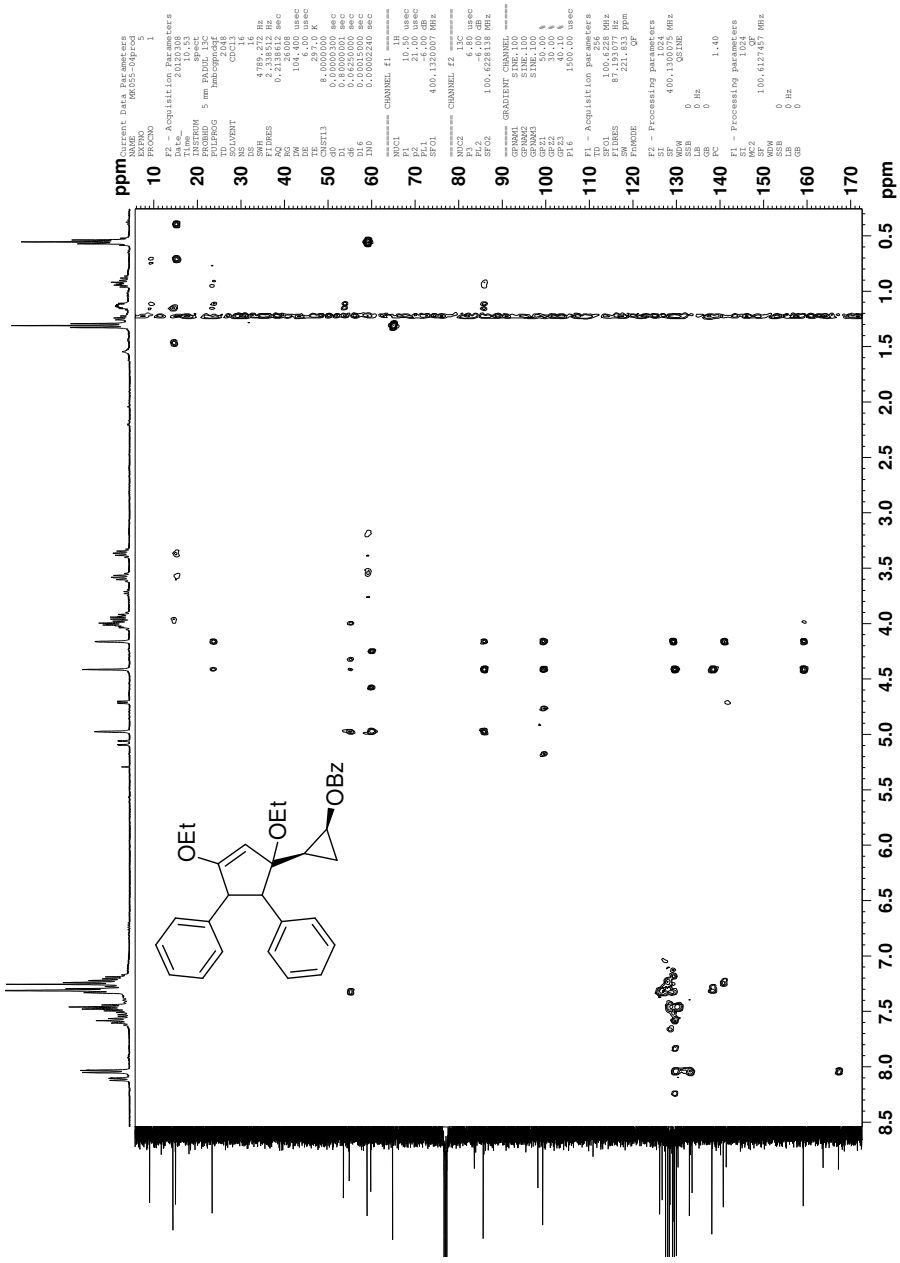
L.3 COSY of bicyclic compound 18a



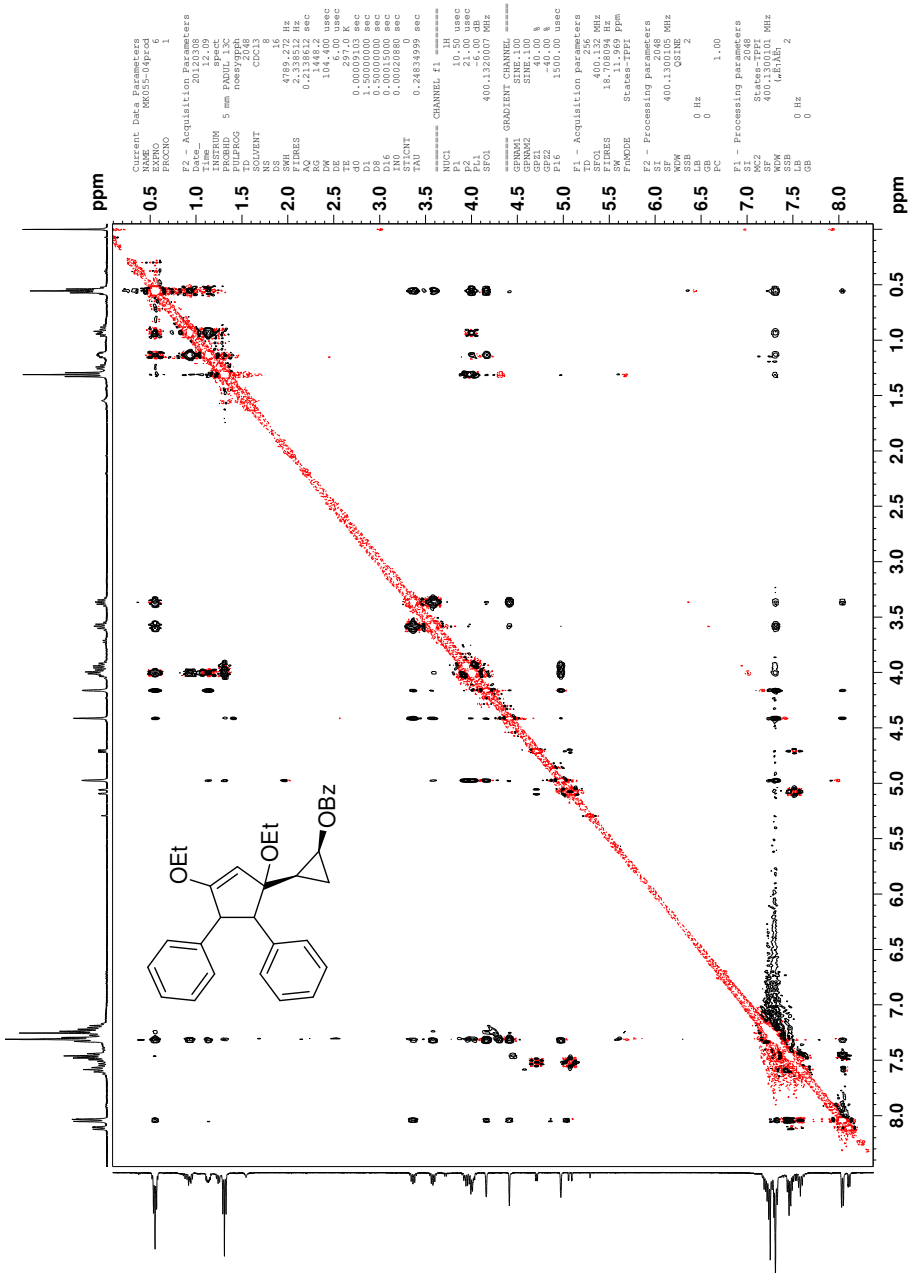
L.4 HSQC of bicyclic compound 18a



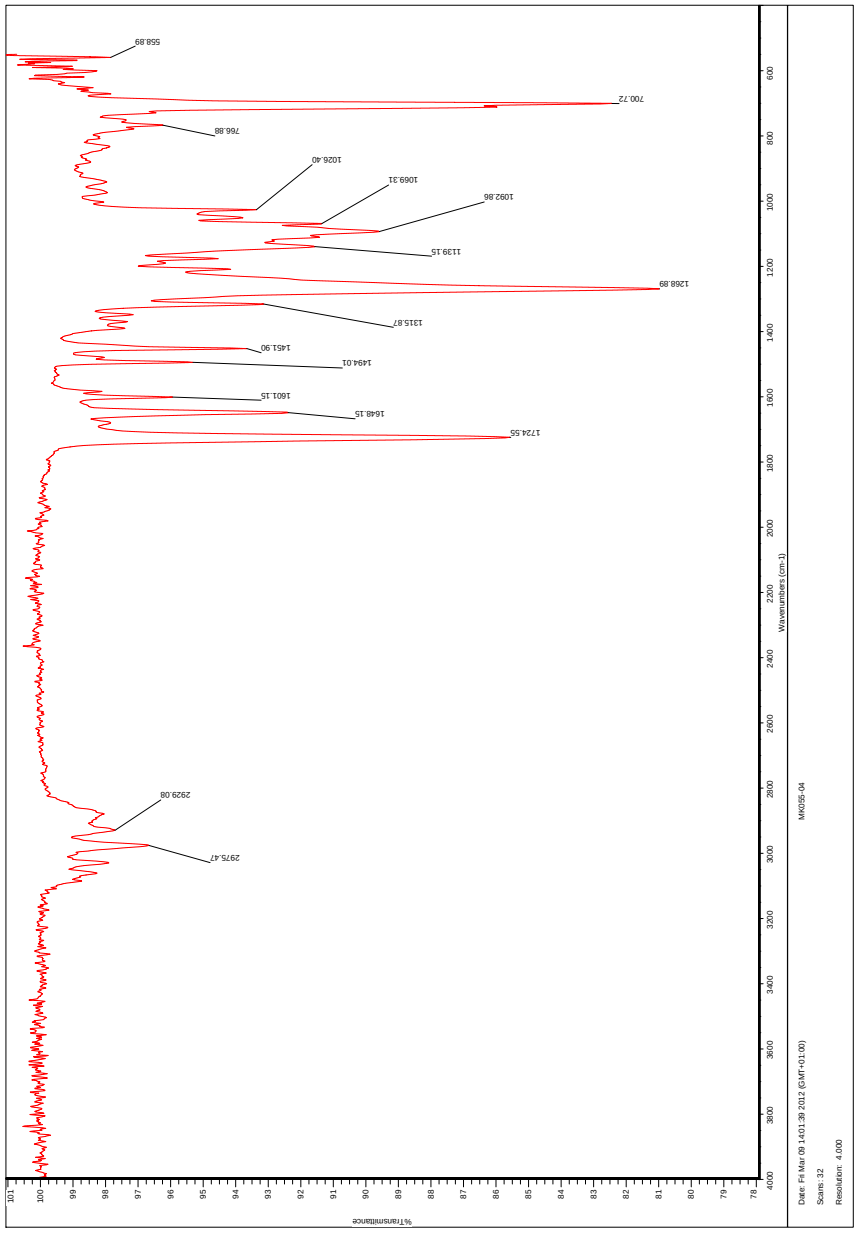
L.5 HMBC of bicyclic compound 18a



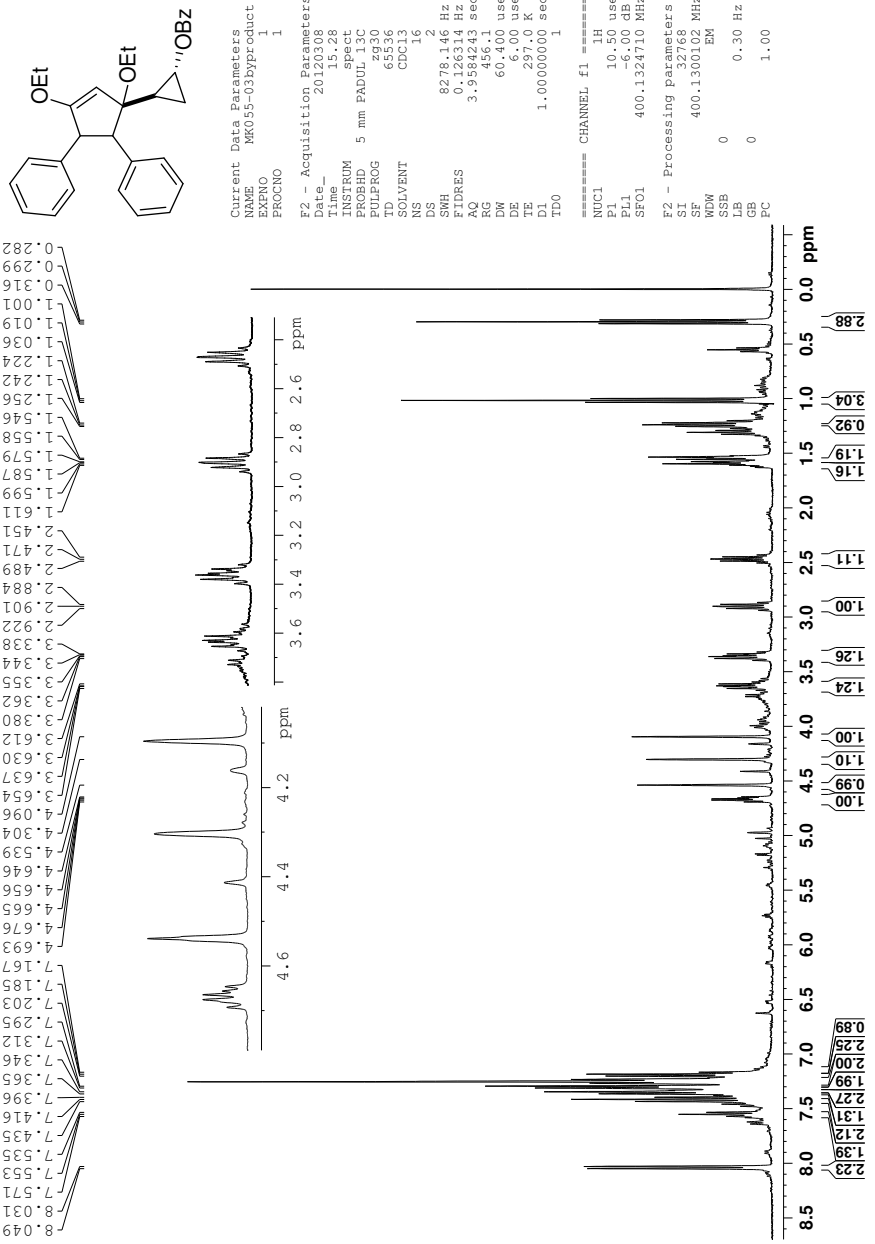
L.6 NOESY of bicyclic compound 18a



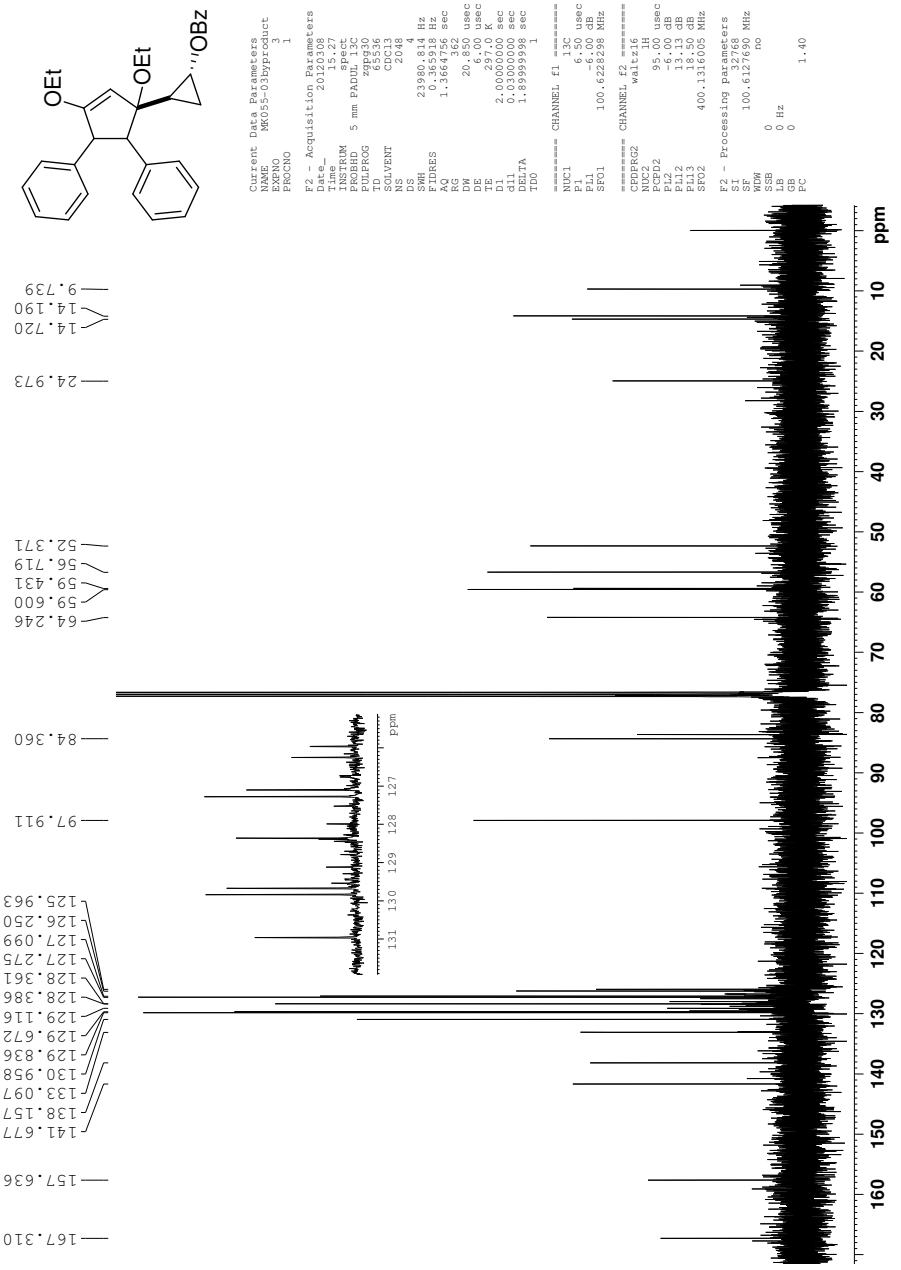
L.7 IR of bicyclic compound 18a



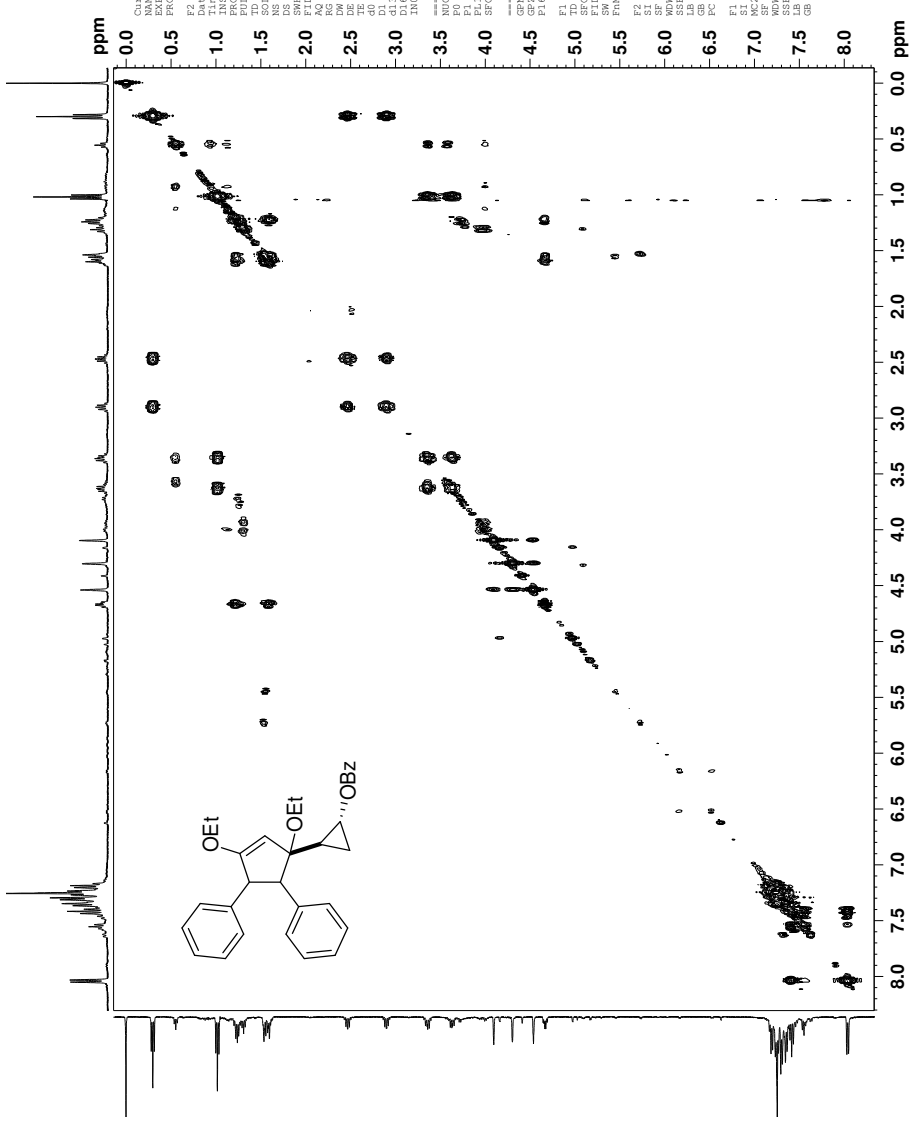
L.8 ^{1}H NMR of bicyclic compound 18b



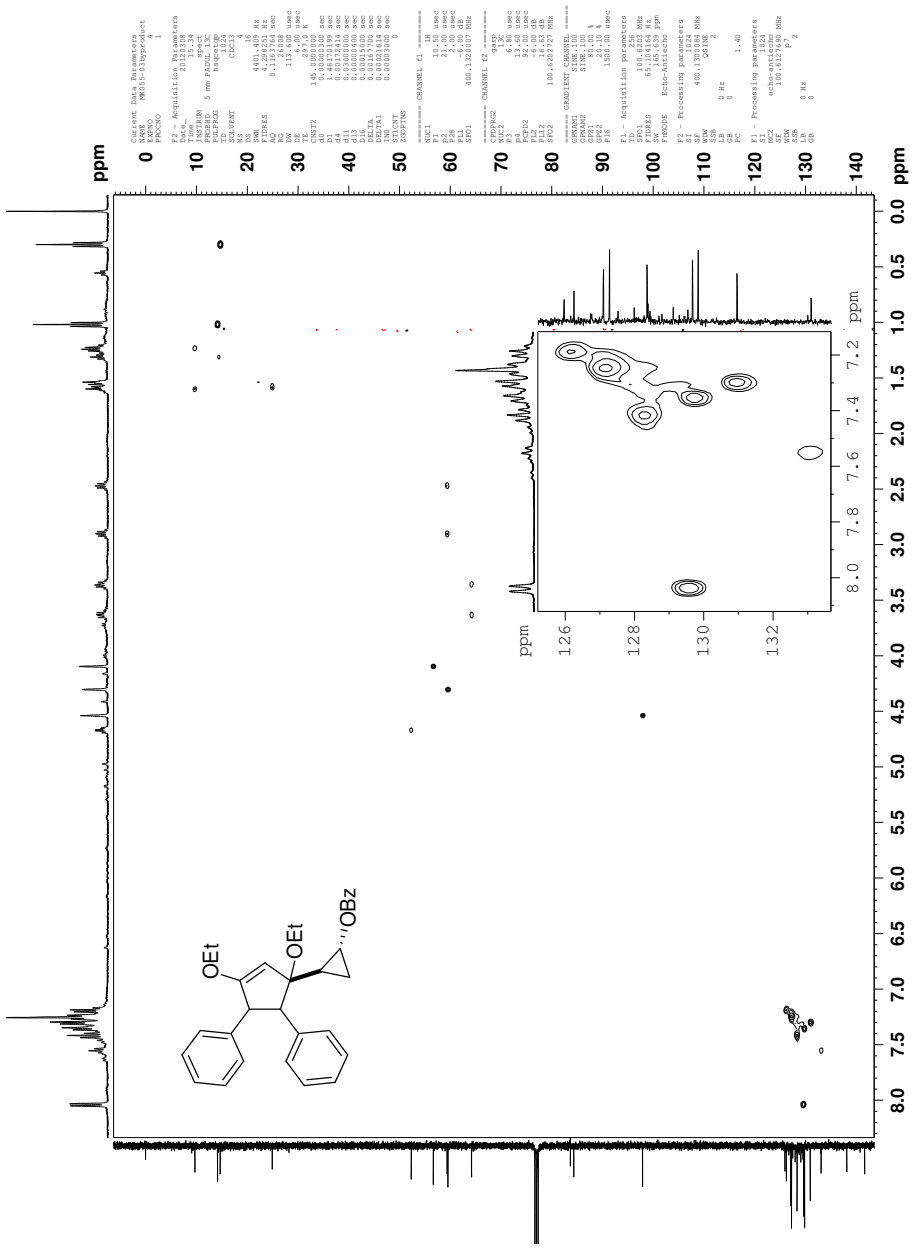
L.9 ^{13}C NMR of bicyclic compound 18b



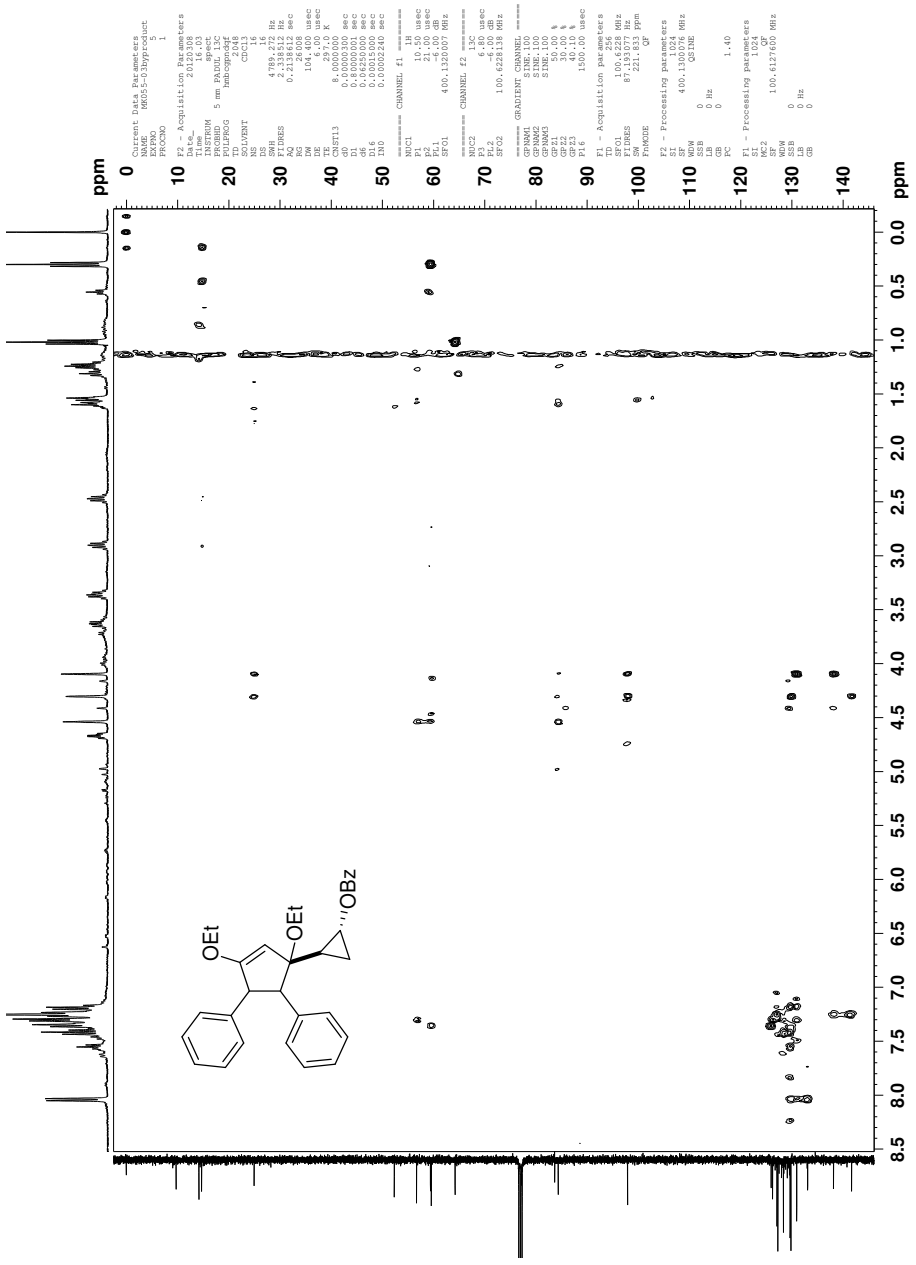
L.10 COSY of bicyclic compound 18b



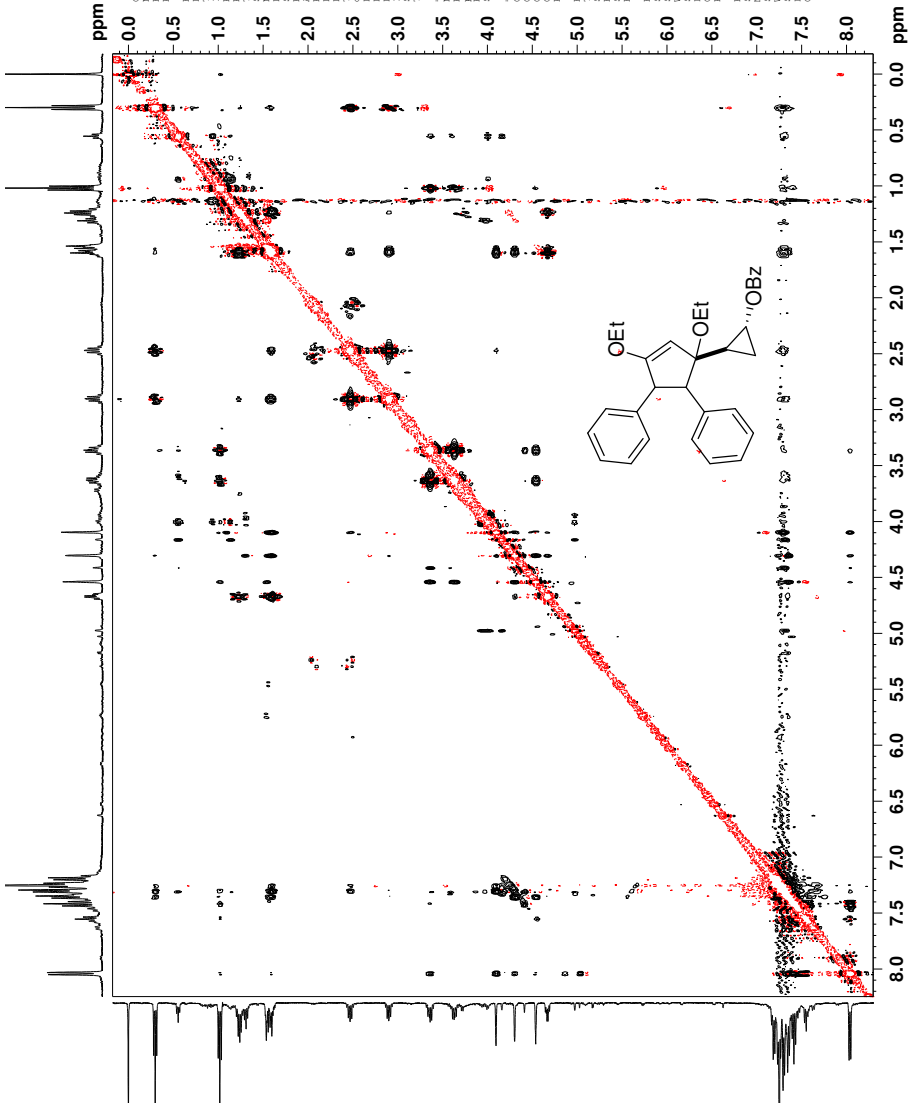
L.11 HSQC of bicyclic compound 18b



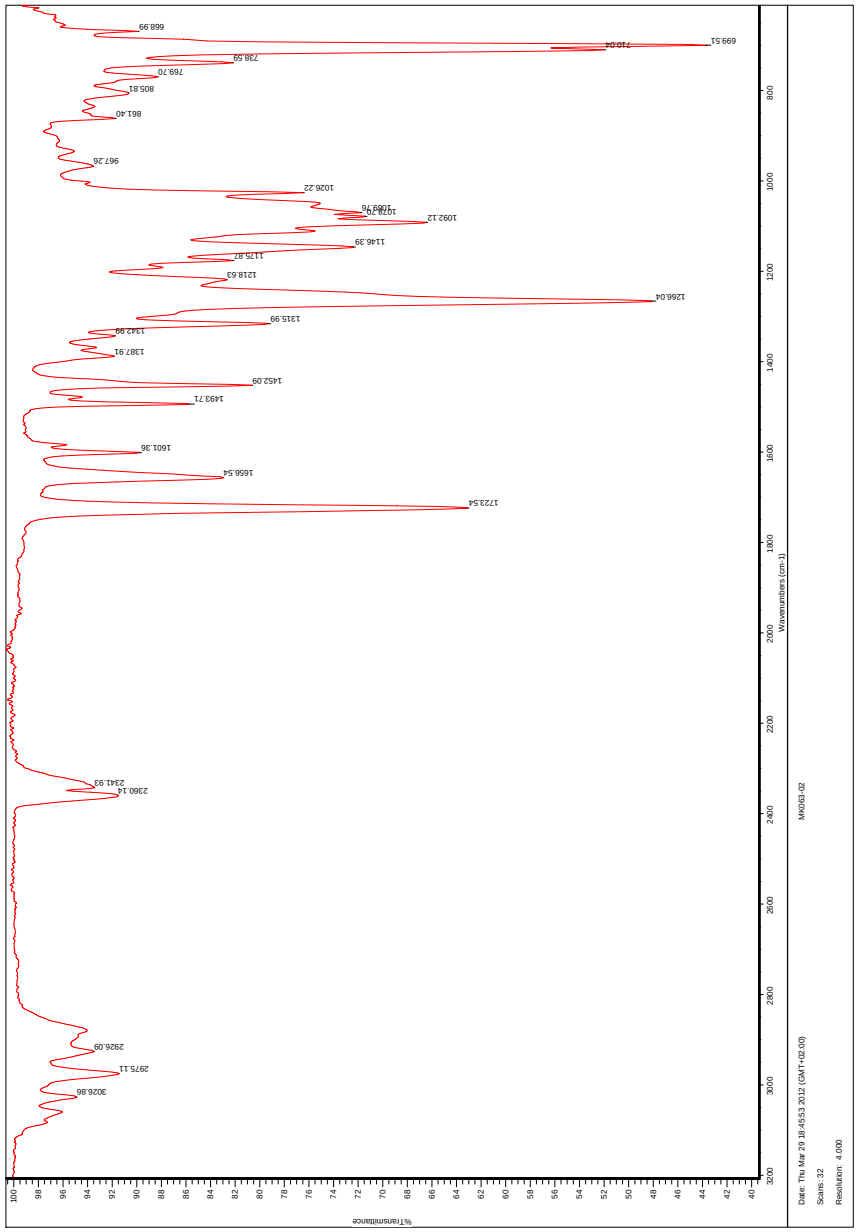
L.12 HMBC of bicyclic compound 18b



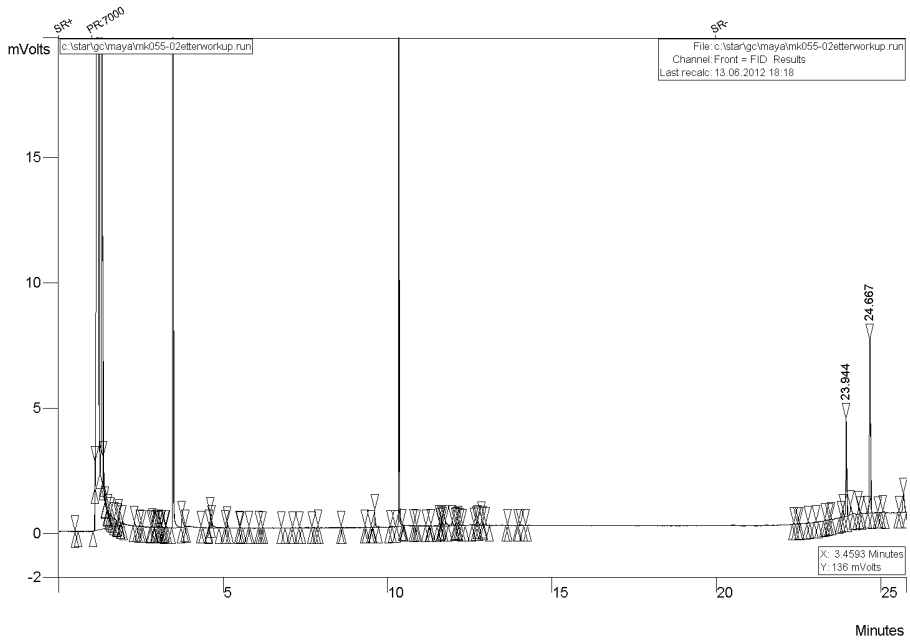
L.13 NOESY of bicyclic compound 18b



L.14 IR of bicyclic compound 18b



L.15 GLC chromatogram of bicyclic compound 18a-b



Print Date: Wed Jun 13 18:19:14 2012 Page 1 of 1

Title : Chrompack CP-Sil 5cB Low bleed/MS. 30m/0,25mmid
Run File : c:\star\gc\maya\mk055-02etterworkup.run
Method File : c:\star\gc\maya\mrk003-01crude-front.mth
Sample ID : Manual Sample

Injection Date: 07.03.2012 16:33 Calculation Date: 13.06.2012 18:18

Operator :
Workstation: system
Instrument : Varian Star #1
Channel : Front = FID

Detector Type: 3800 (1 Volt)
Bus Address : 44
Sample Rate : 10.00 Hz
Run Time : 25.805 min

** GC Workstation Multi Instrument (Demo) Version 6.41 ** 05000-30c8-d68-31e1 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		33.21	23.944	0.000	7333	VP	1.8	
2		66.79	24.667	0.000	14748	VB	2.0	
Totals:		100.00		0.000	22081			

Total Unidentified Counts : 22081 counts

Detected Peaks: 20 Rejected Peaks: 18 Identified Peaks: 0

Multiplier: 1 Divisor: 1 Unidentified Peak Factor: 0

Baseline Offset: 59 microVolts LSB: 1 microVolts

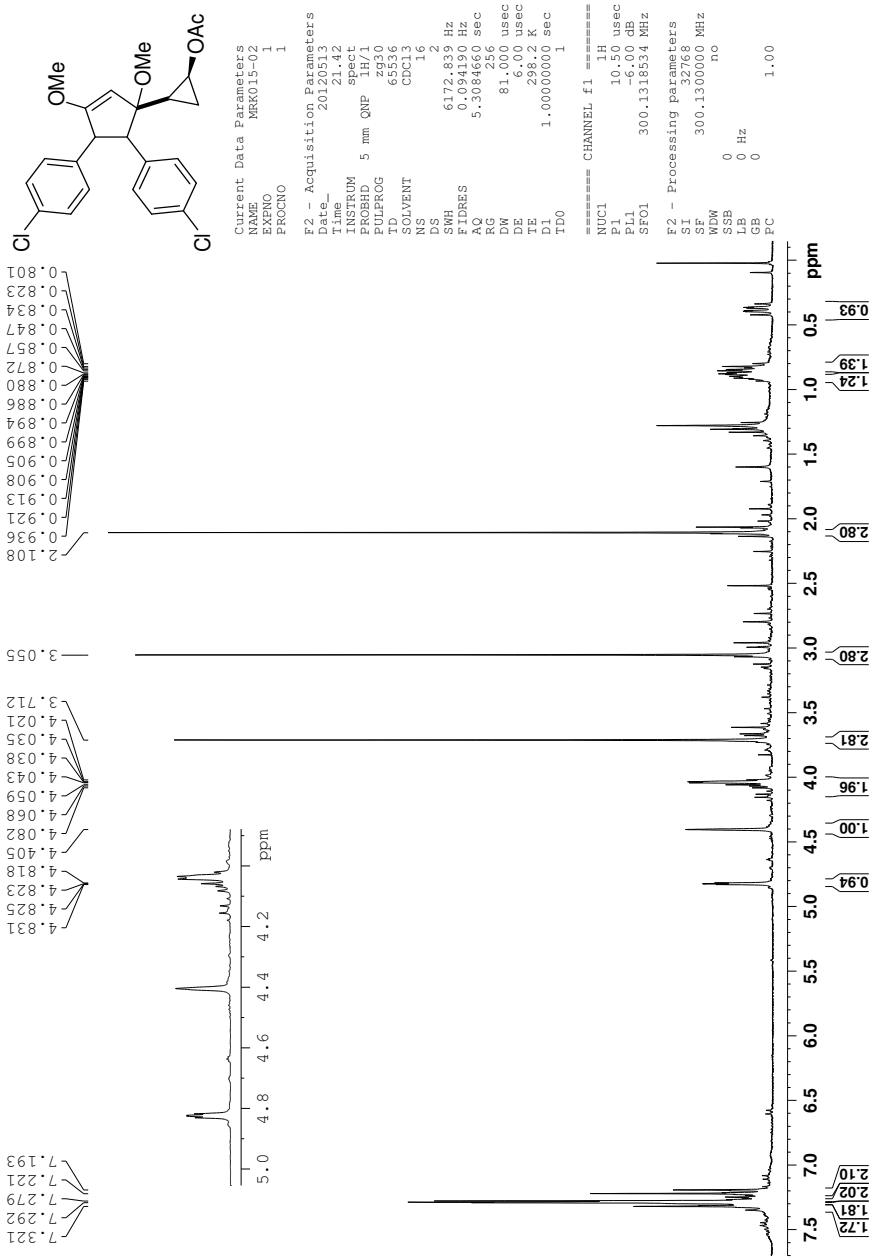
Noise (used): 17 microVolts - monitored before this run

Manual injection

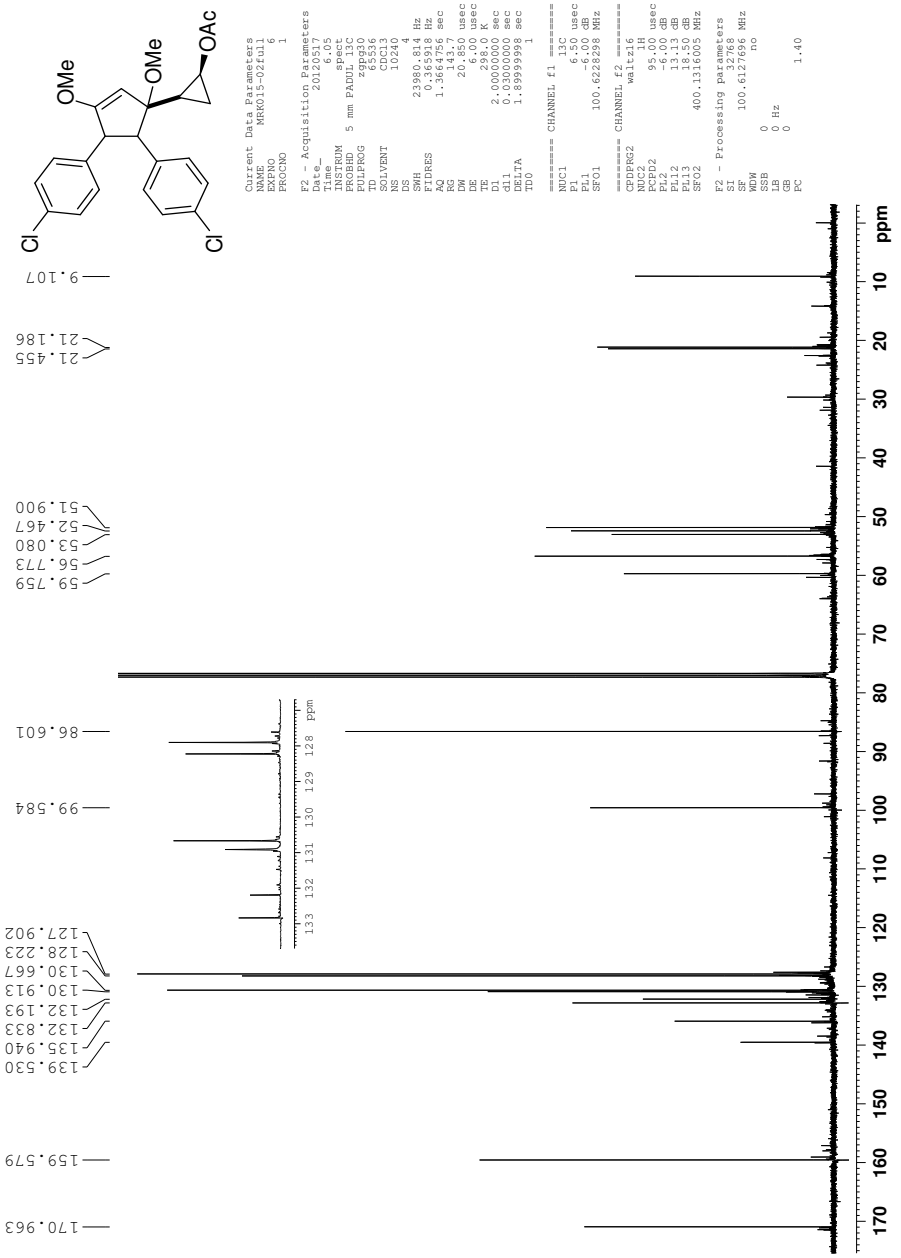
****

M Bicyclic compound 22a-b

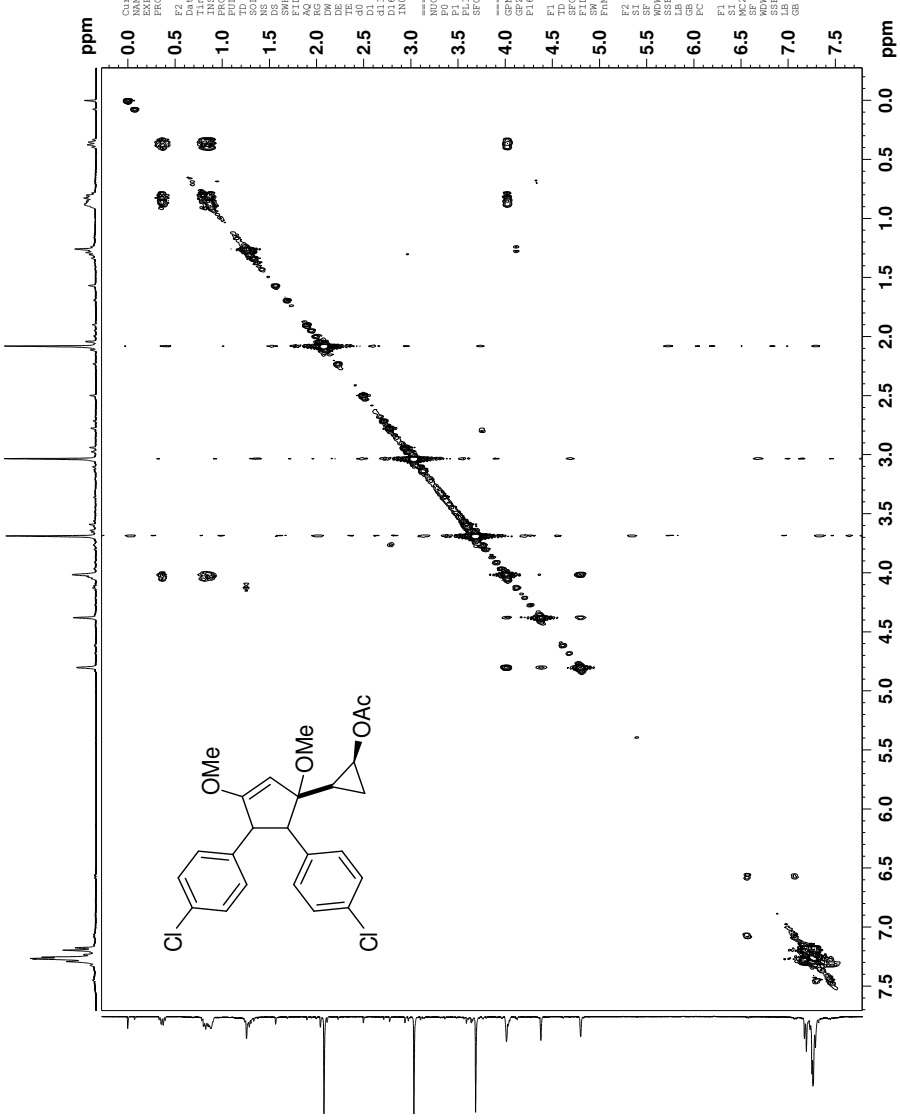
M.1 ^{1}H NMR of bicyclic compound 22a



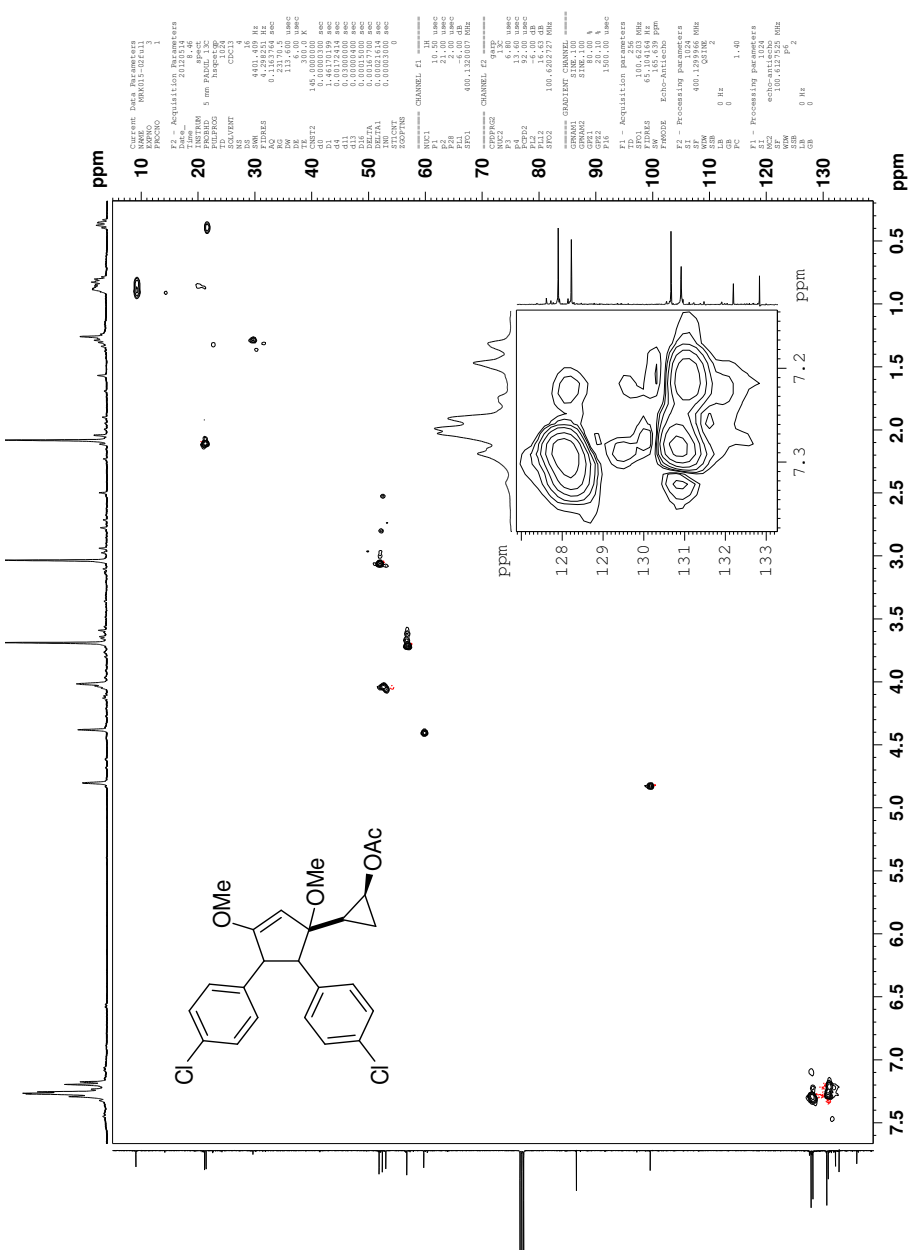
M.2 ^{13}C NMR of bicyclic compound 22a



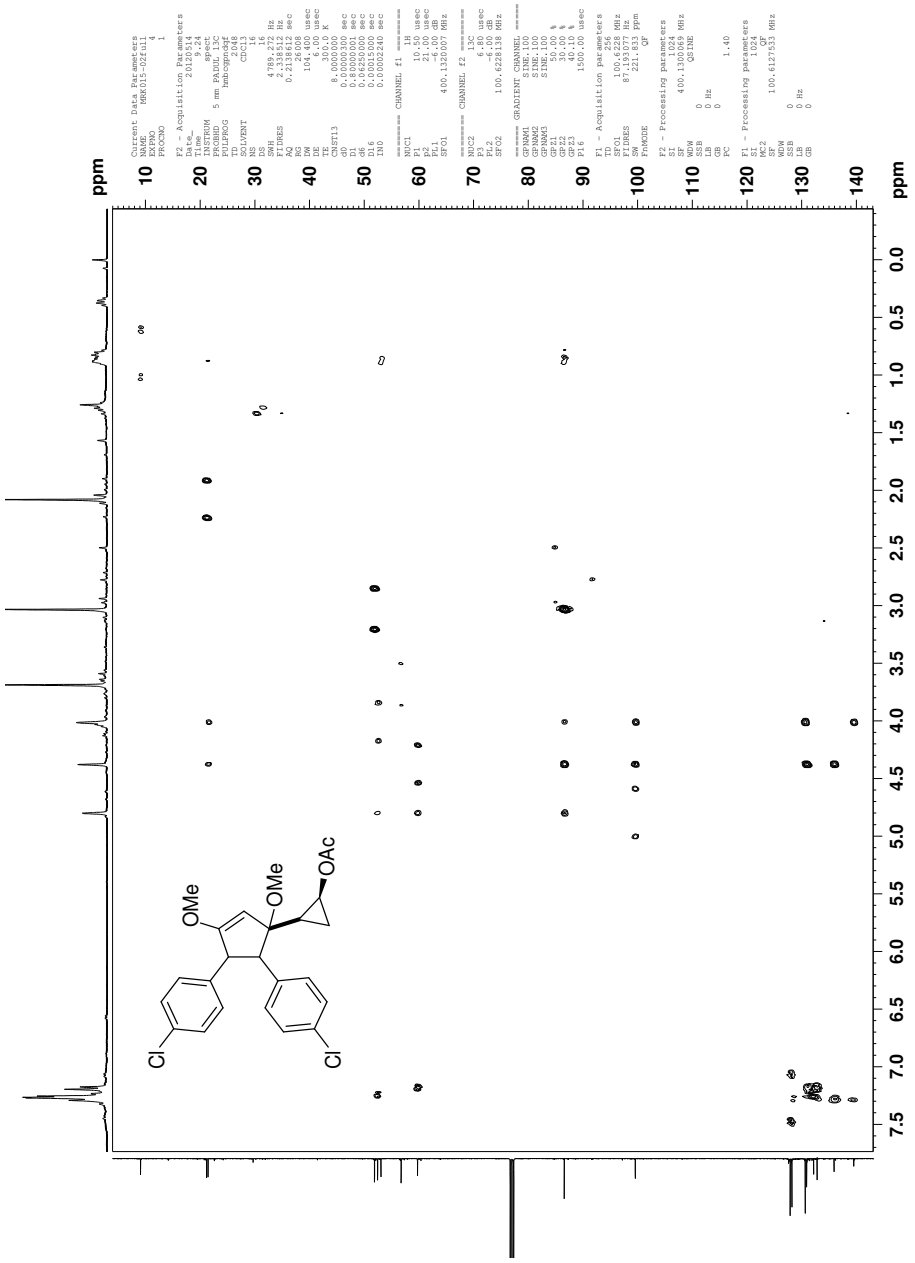
M.3 COSY of bicyclic compound 22a



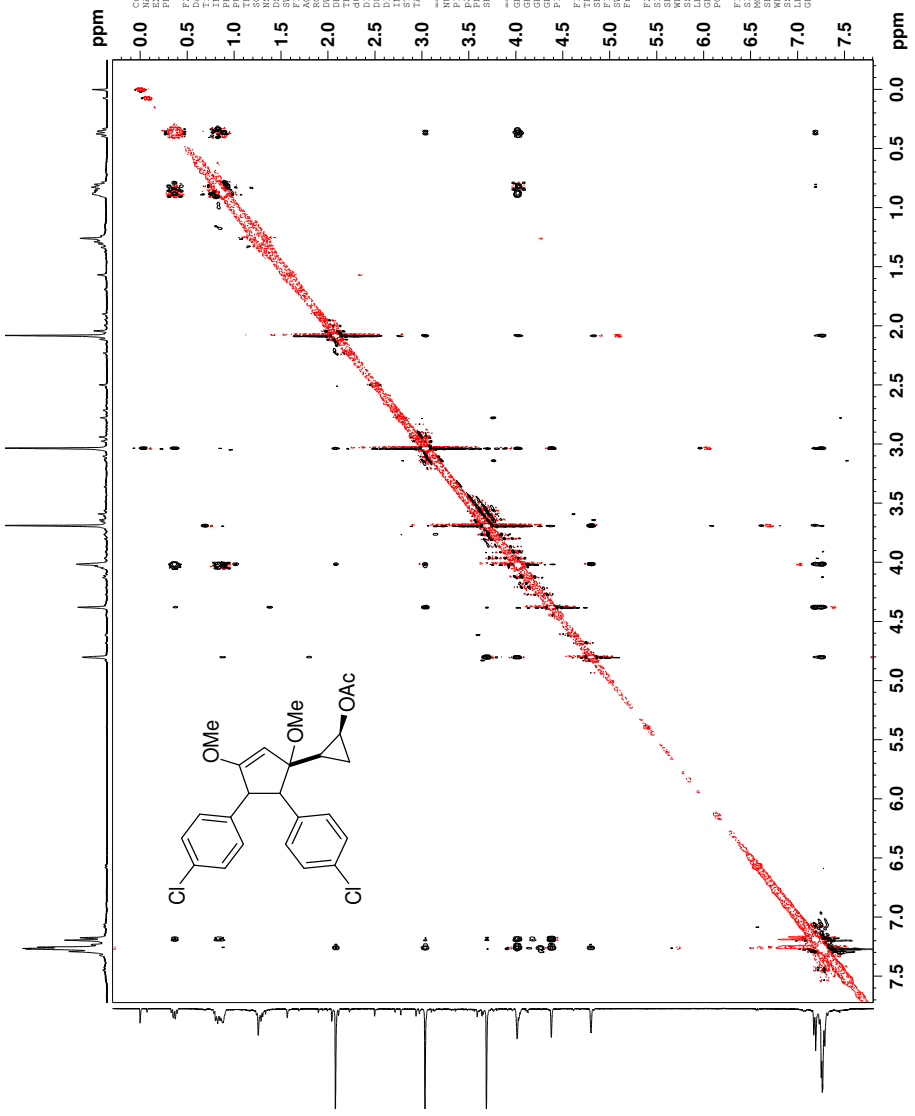
M.4 HSQC of bicyclic compound 22a



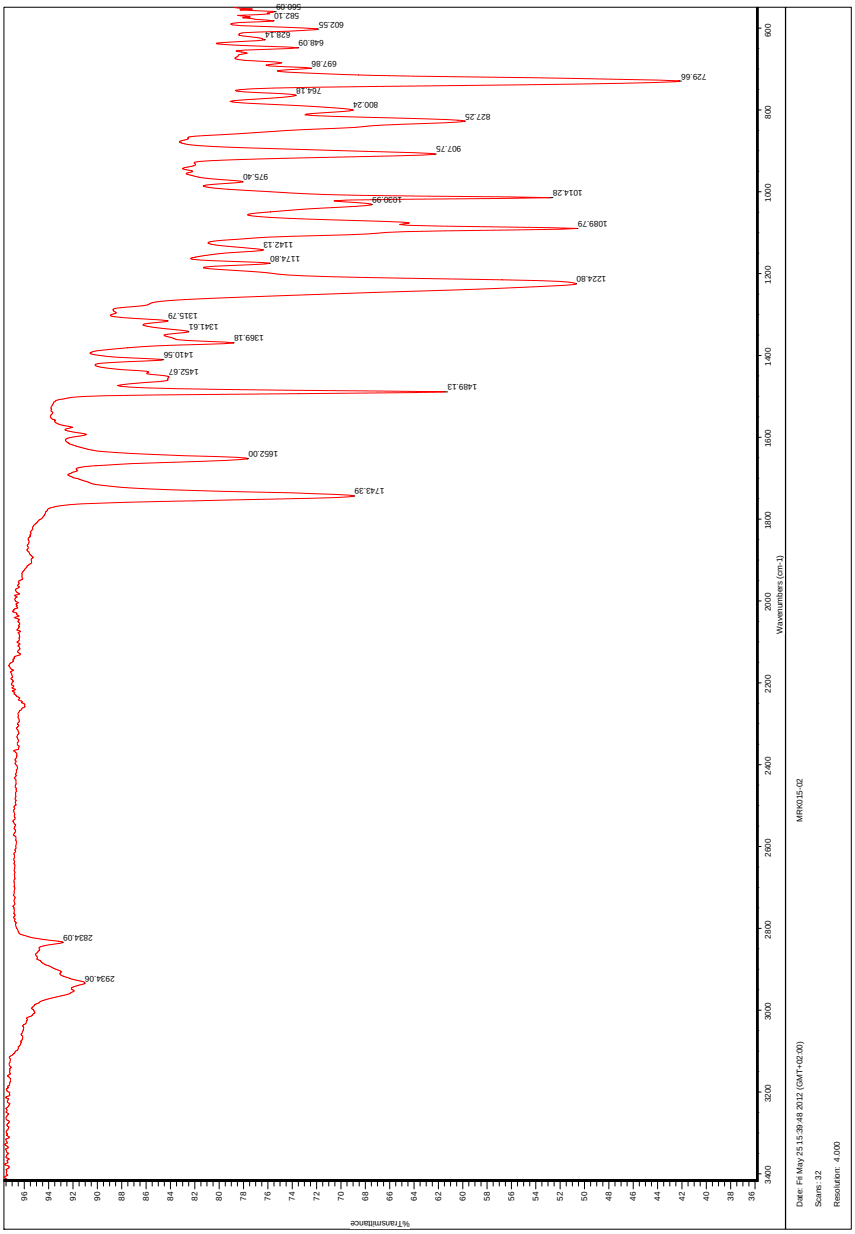
M.5 HMBC of bicyclic compound 22a



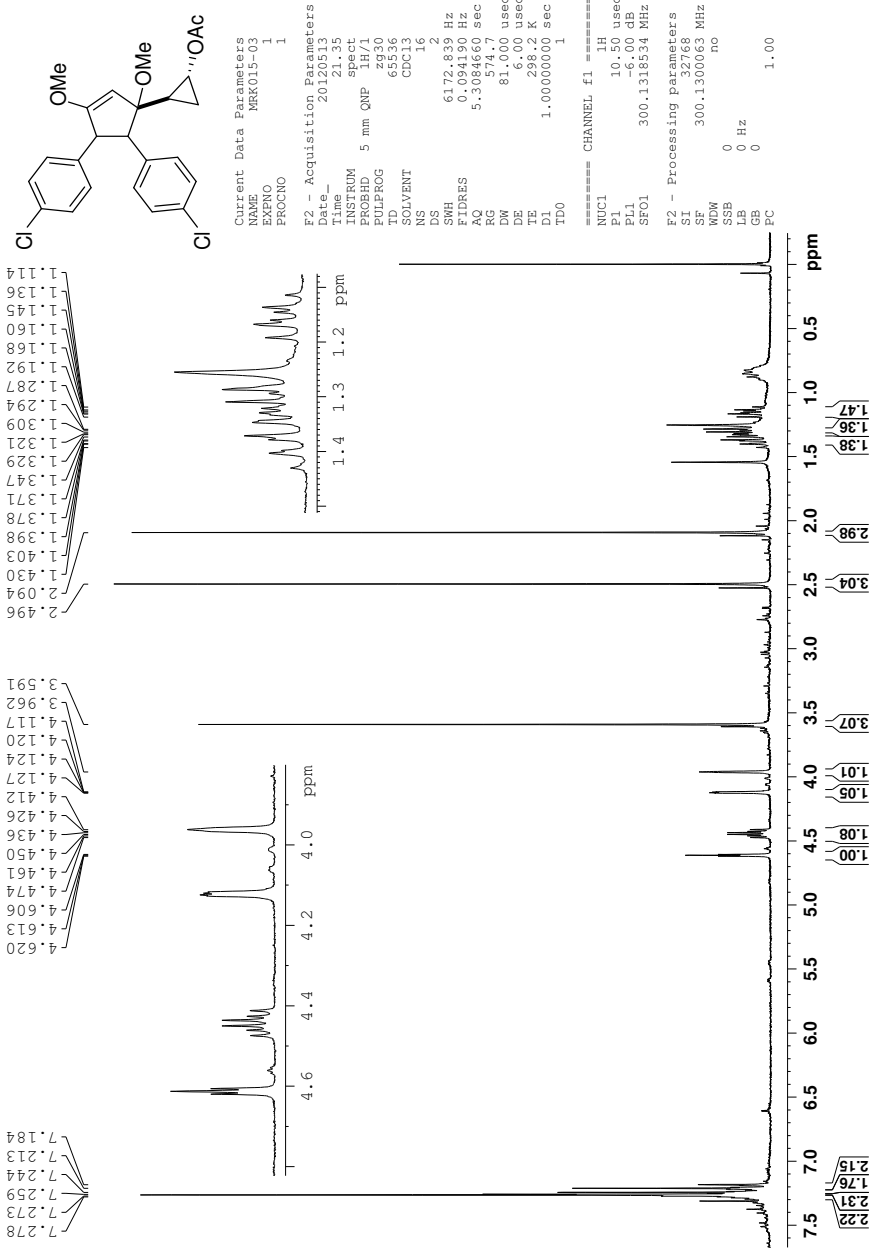
M.6 NOESY of bicyclic compound 22a



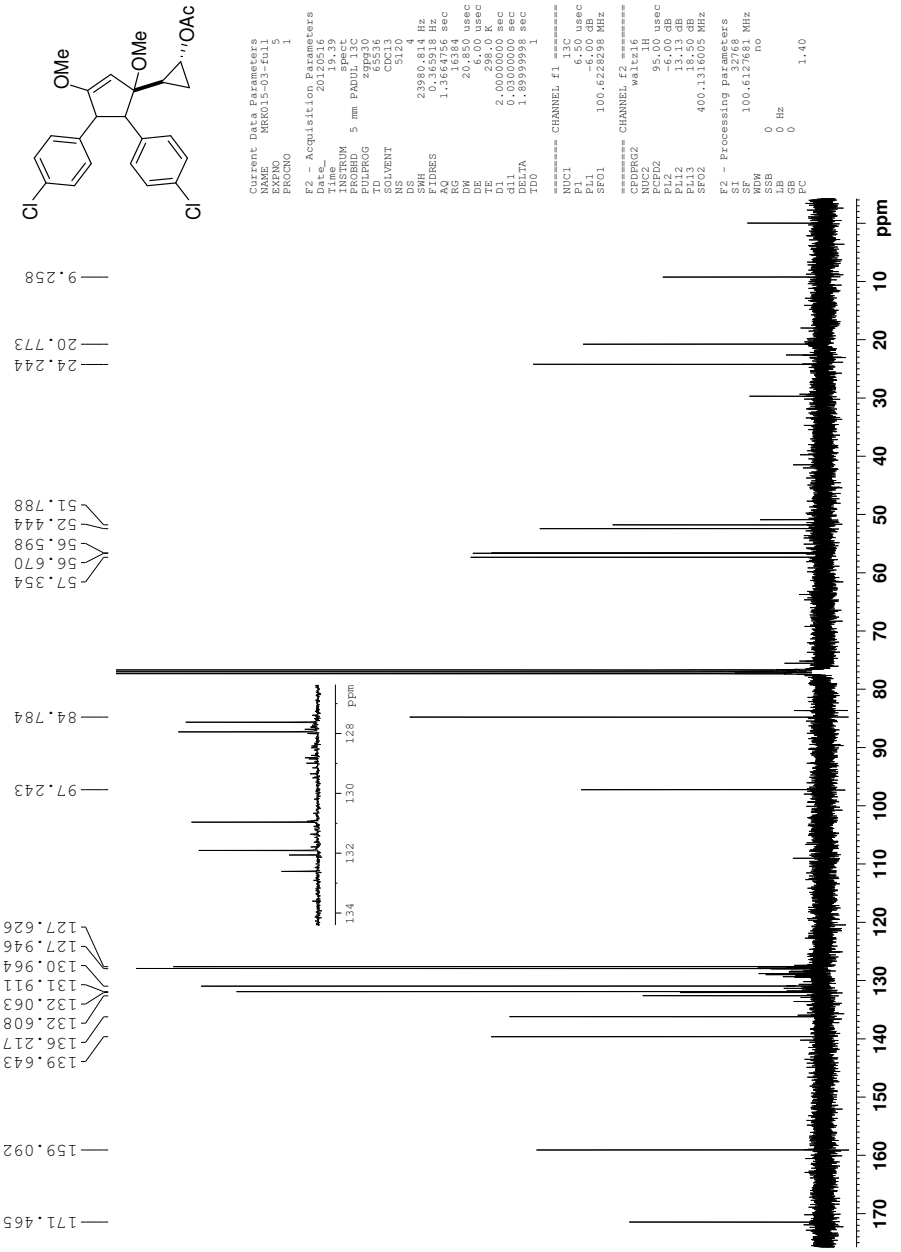
M.7 IR of bicyclic compound 22a



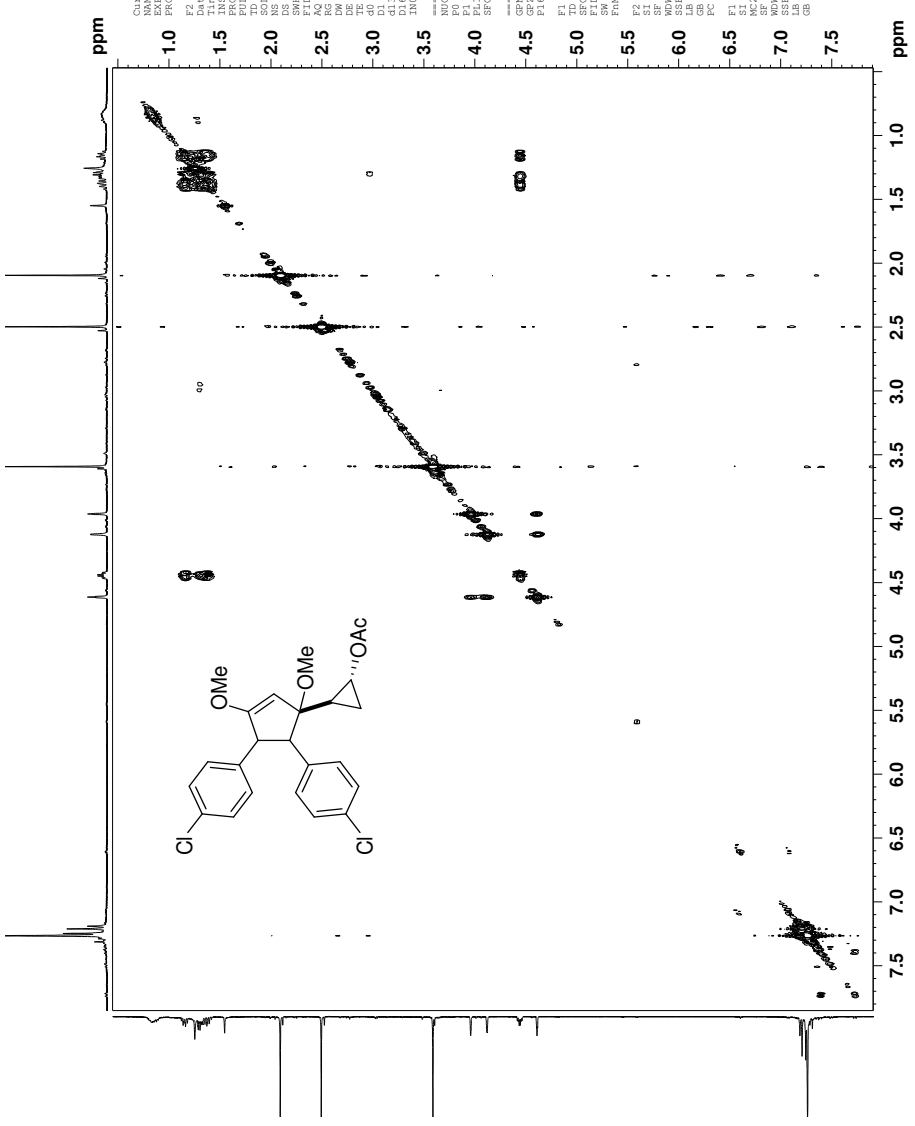
M.8 ^{1}H NMR of bicyclic compound 22b



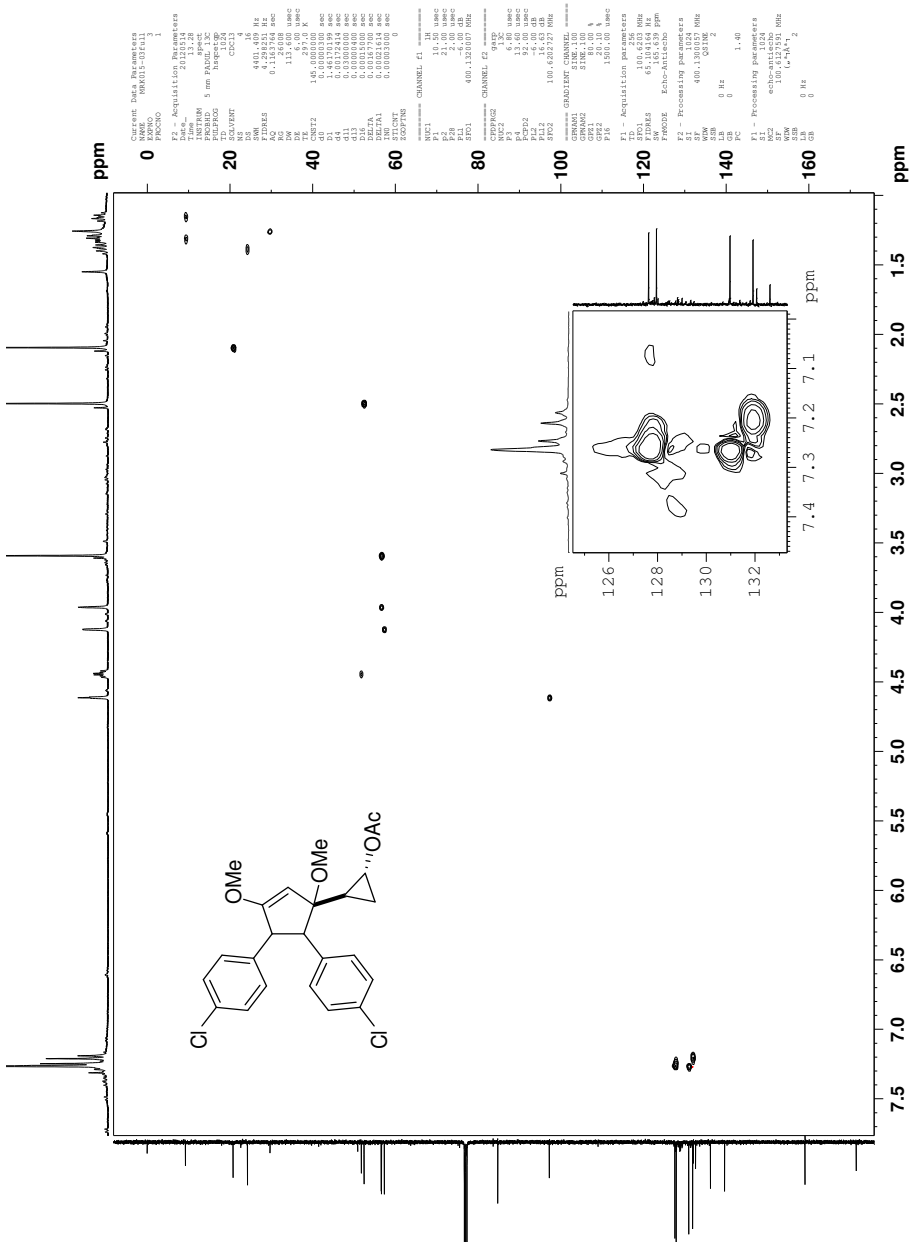
M.9 ^{13}C NMR of bicyclic compound 22b



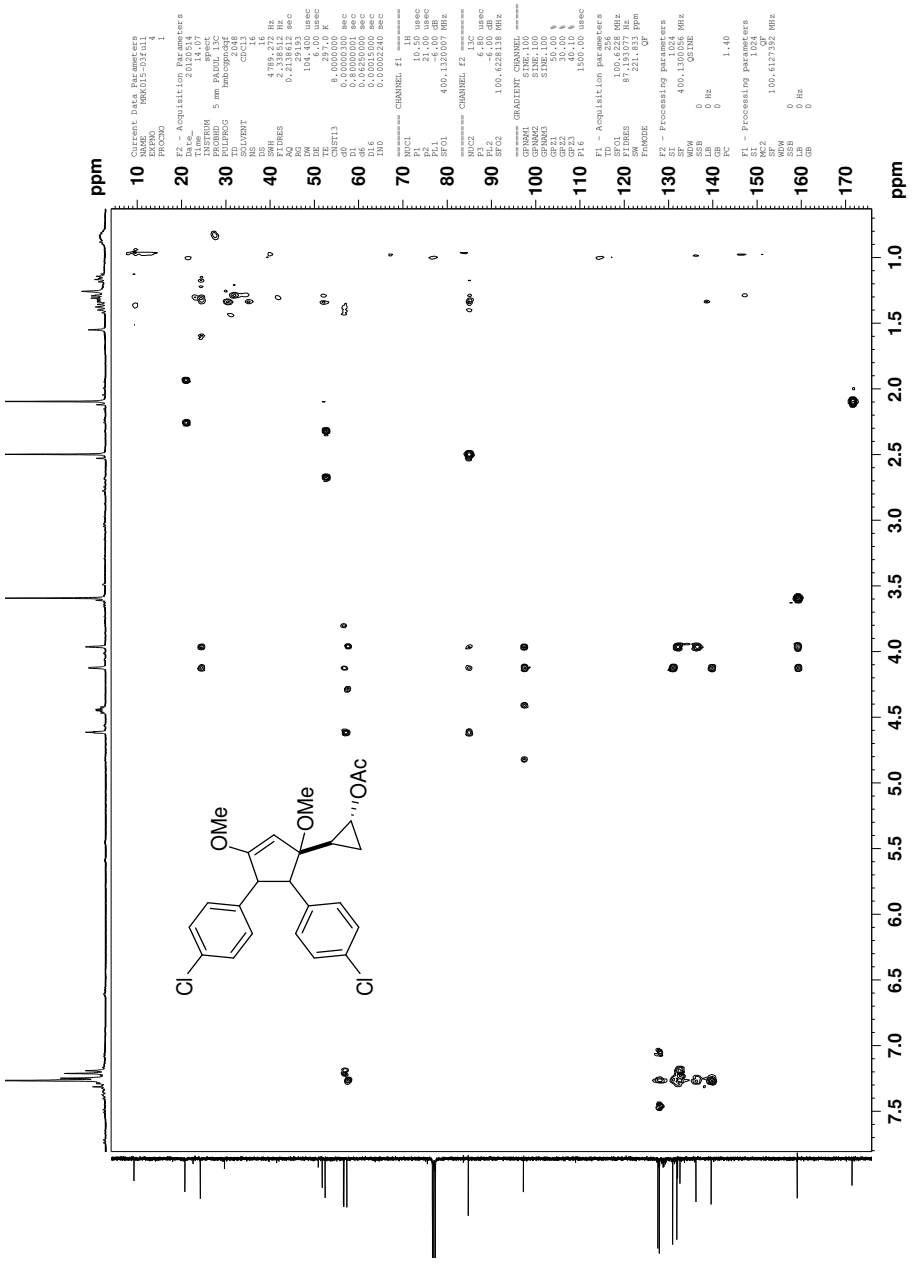
M.10 COSY of bicyclic compound 22b



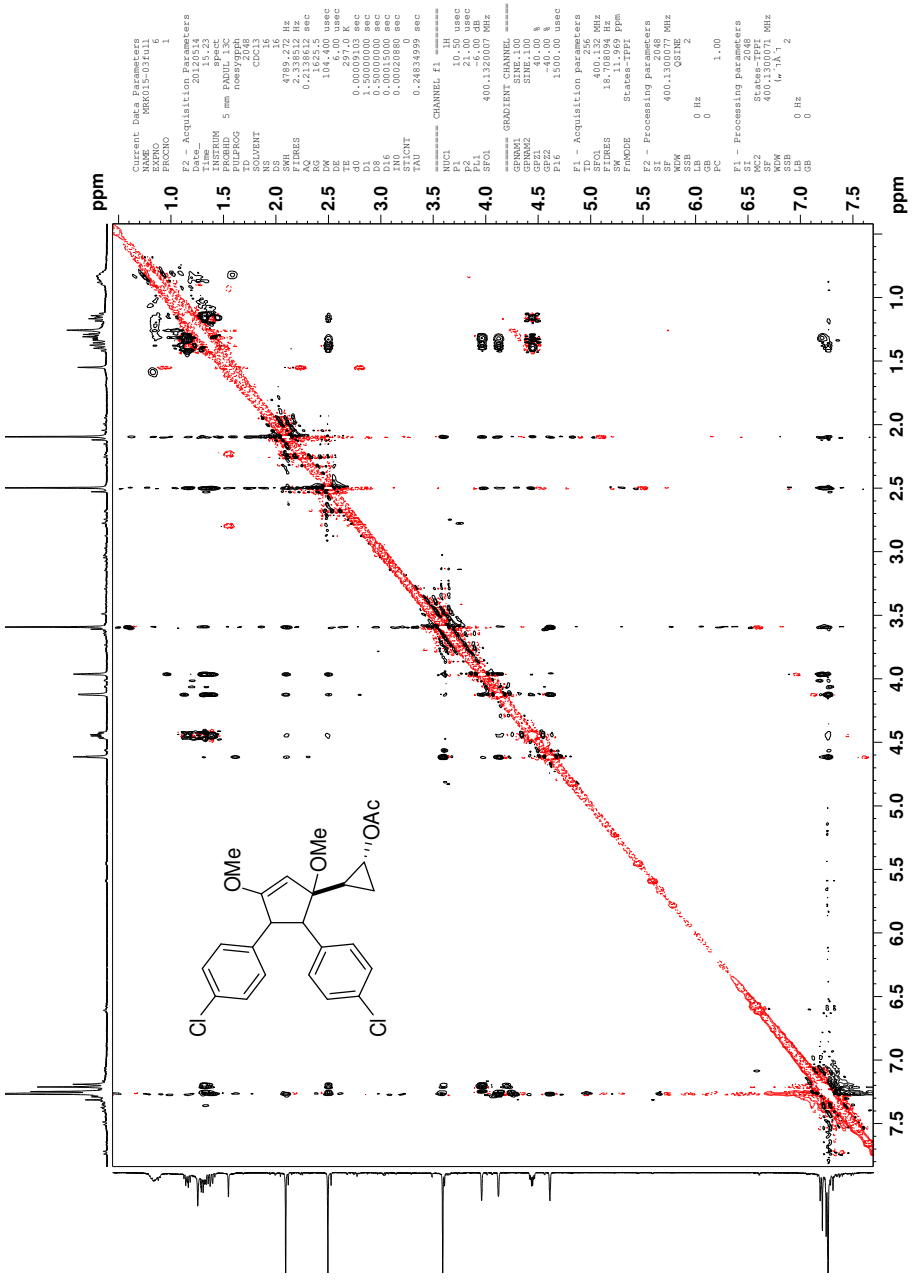
M.11 HSQC of bicyclic compound 22b



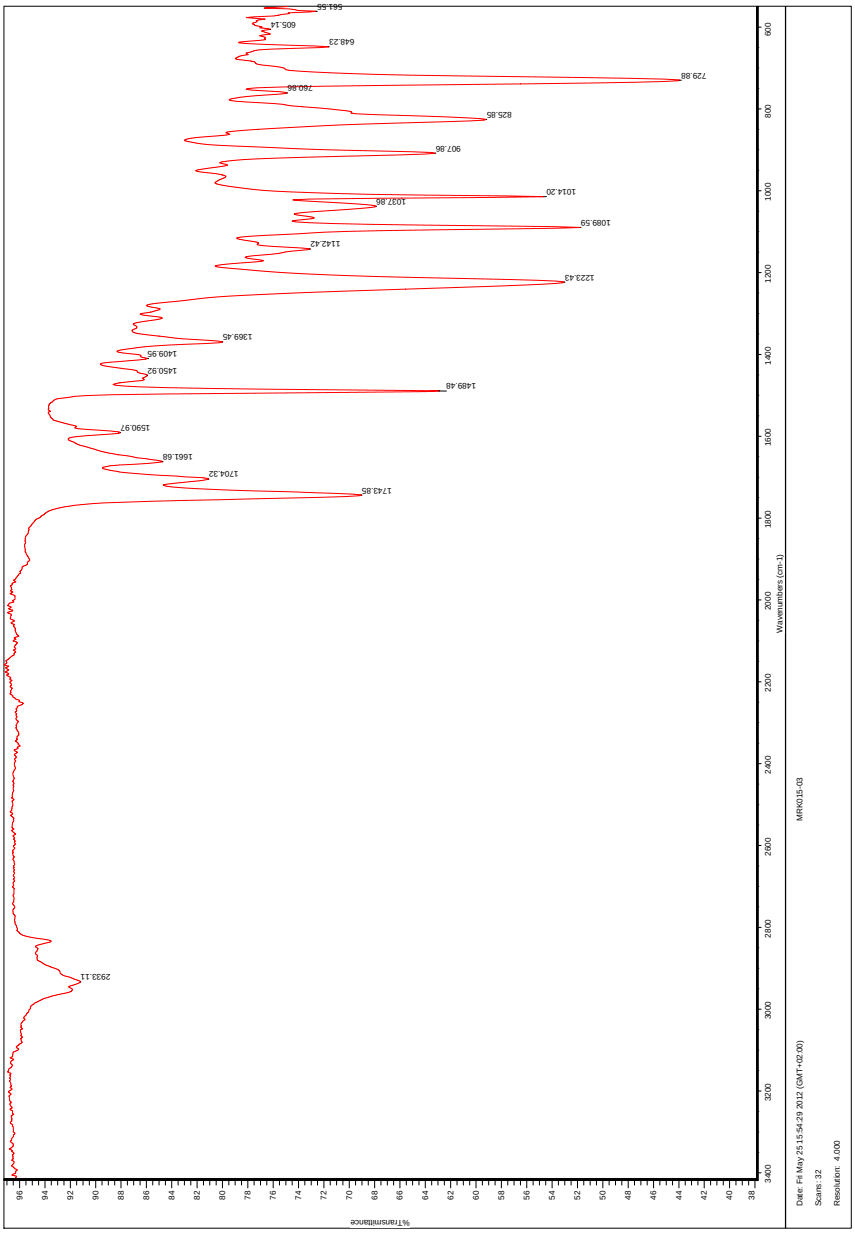
M.12 HMBC of bicyclic compound 22b



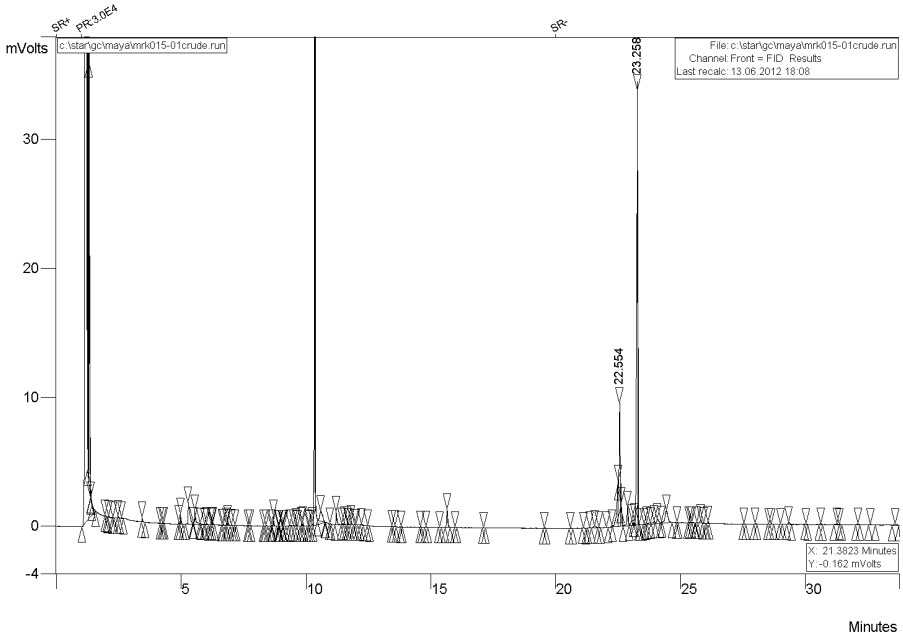
M.13 NOESY of bicyclic compound 22b



M.14 IR of bicyclic compound 22b



M.15 GLC chromatogram of bicyclic compound 22a-b

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Print Date: Wed Jun 13 18:08:48 2012            Page 1 of 1

Title        : Chrompack CP-Sil 5cB Low bleed/MS. 30m/0,25mmid
Run File     : c:\star\gc\maya\mrk015-01crude.run
Method File  : c:\star\gc\maya\mrk003-01crude-front.mth
Sample ID    : Manual Sample

Injection Date: 30.05.2012 13:39    Calculation Date: 13.06.2012 18:08

Operator    :                       Detector Type: 3800 (1 Volt)
Workstation: system                 Bus Address  : 44
Instrument : Varian Star #1         Sample Rate  : 10.00 Hz
Channel     : Front = FID           Run Time     : 33.797 min

** GC Workstation Multi Instrument (Demo) Version 6.41 ** 05000-30c8-d68-31e1 **

Run Mode         : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

                                 Ret.    Time                      Width
 Peak      Peak        Result    Time   Offset       Area    Sep.  1/2   Status
  No.      Name          ()      (min)   (min)     (counts) Code (sec)  Codes
 ---- ------------ ---------- ------- ------- ---------- ---- -----  ------
    1                   24.93  22.554   0.000      30941   VV   3.0
    2                   75.07  23.258   0.000      93145   VB   2.6
 ---- ------------ ========== ======= ======= ========== ---- -----  ------
      Totals:         100.00                    0.000     124086

Total Unidentified Counts :     124086 counts

Detected Peaks: 43          Rejected Peaks: 41     Identified Peaks: 0

Multiplier: 1          Divisor: 1          Unidentified Peak Factor: 0

Baseline Offset: -57 microVolts          LSB:     1 microVolts

Noise (used): 11 microVolts - monitored before this run

Manual injection

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```
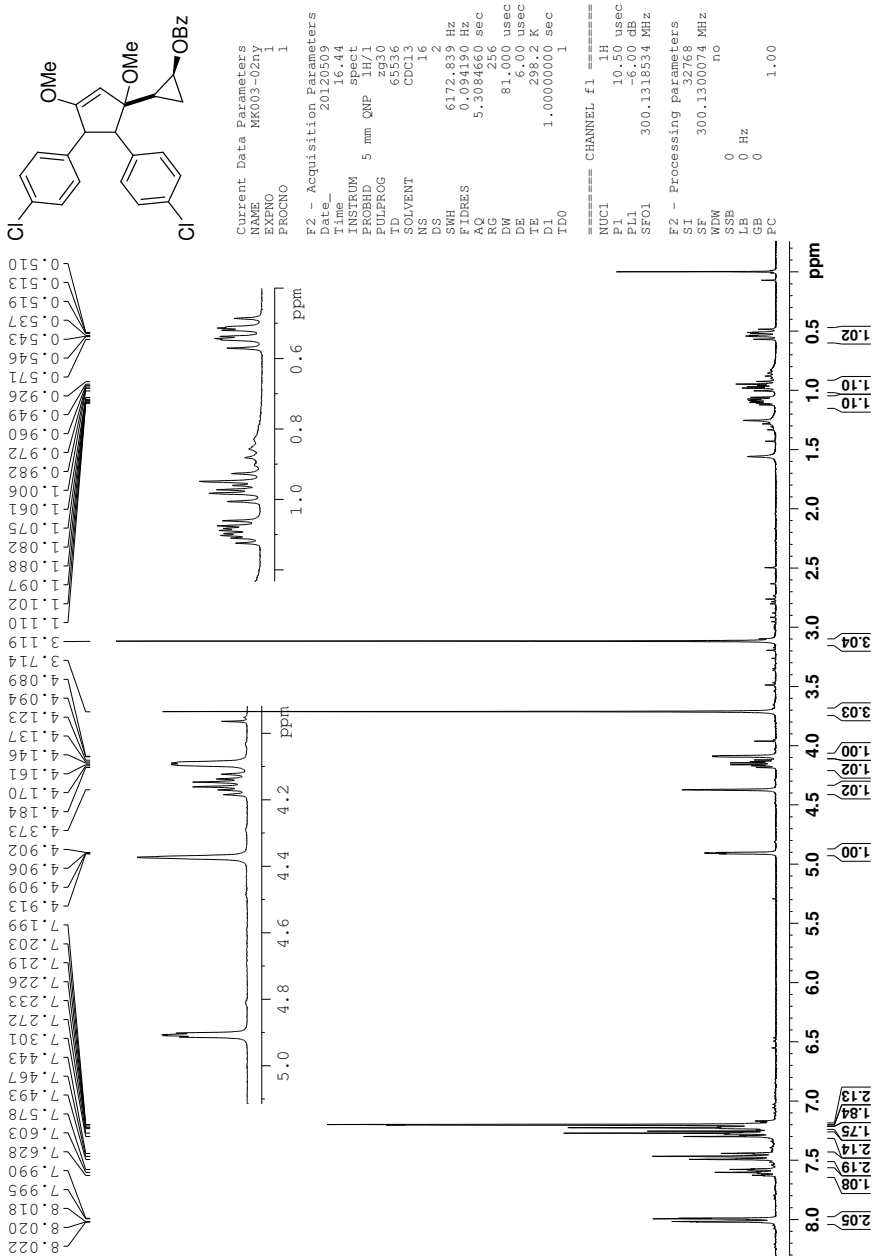
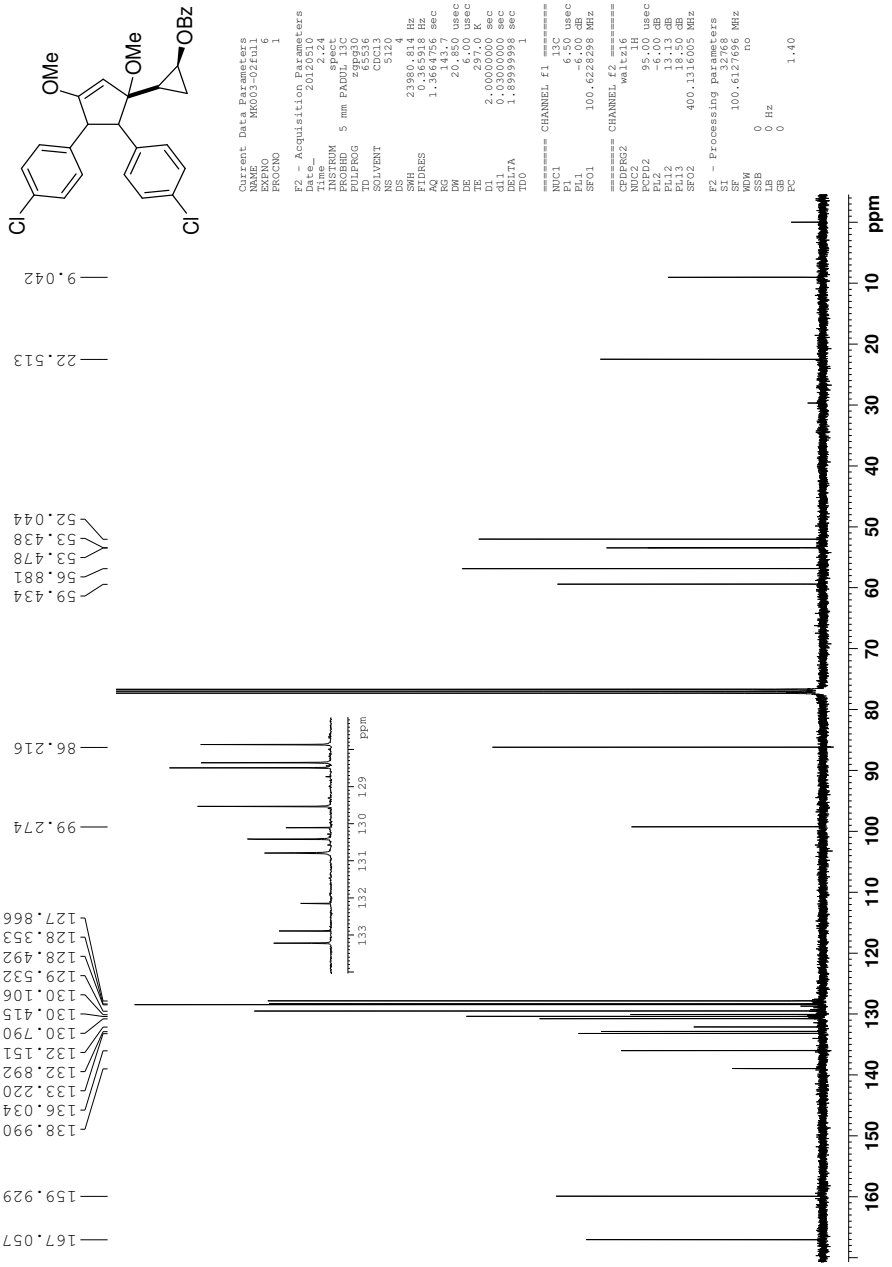

N Bicyclic compound 23a-b

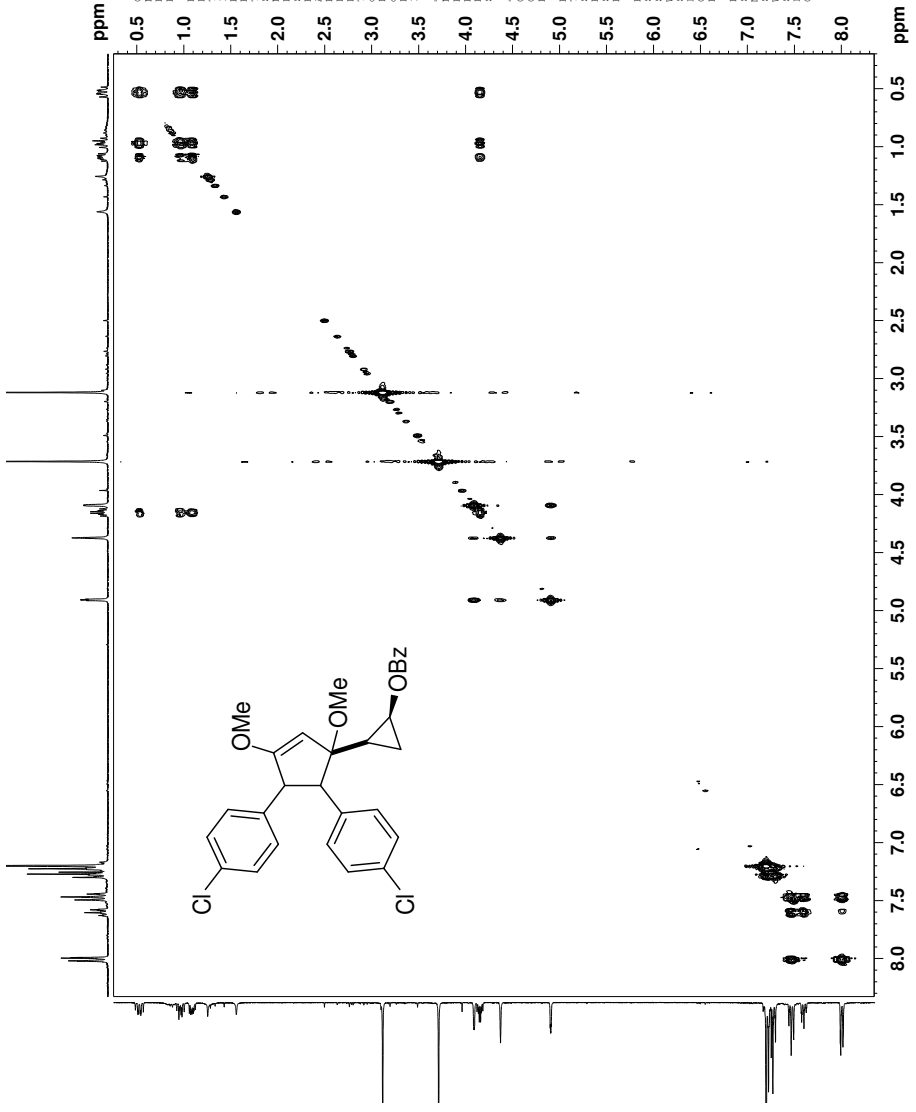
N.1 ^{1}H NMR of bicyclic compound 23a



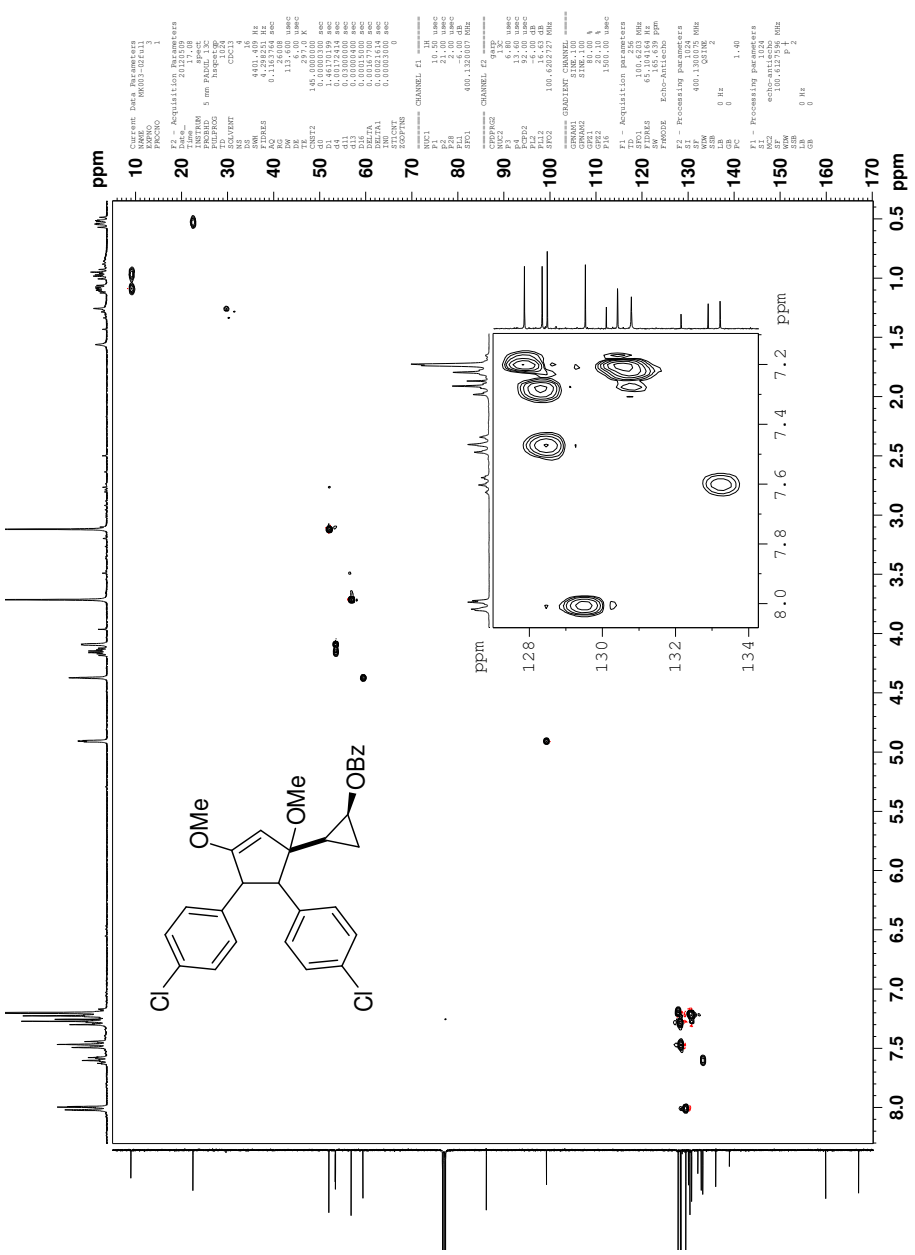
N.2 ^{13}C NMR of bicyclic compound 23a



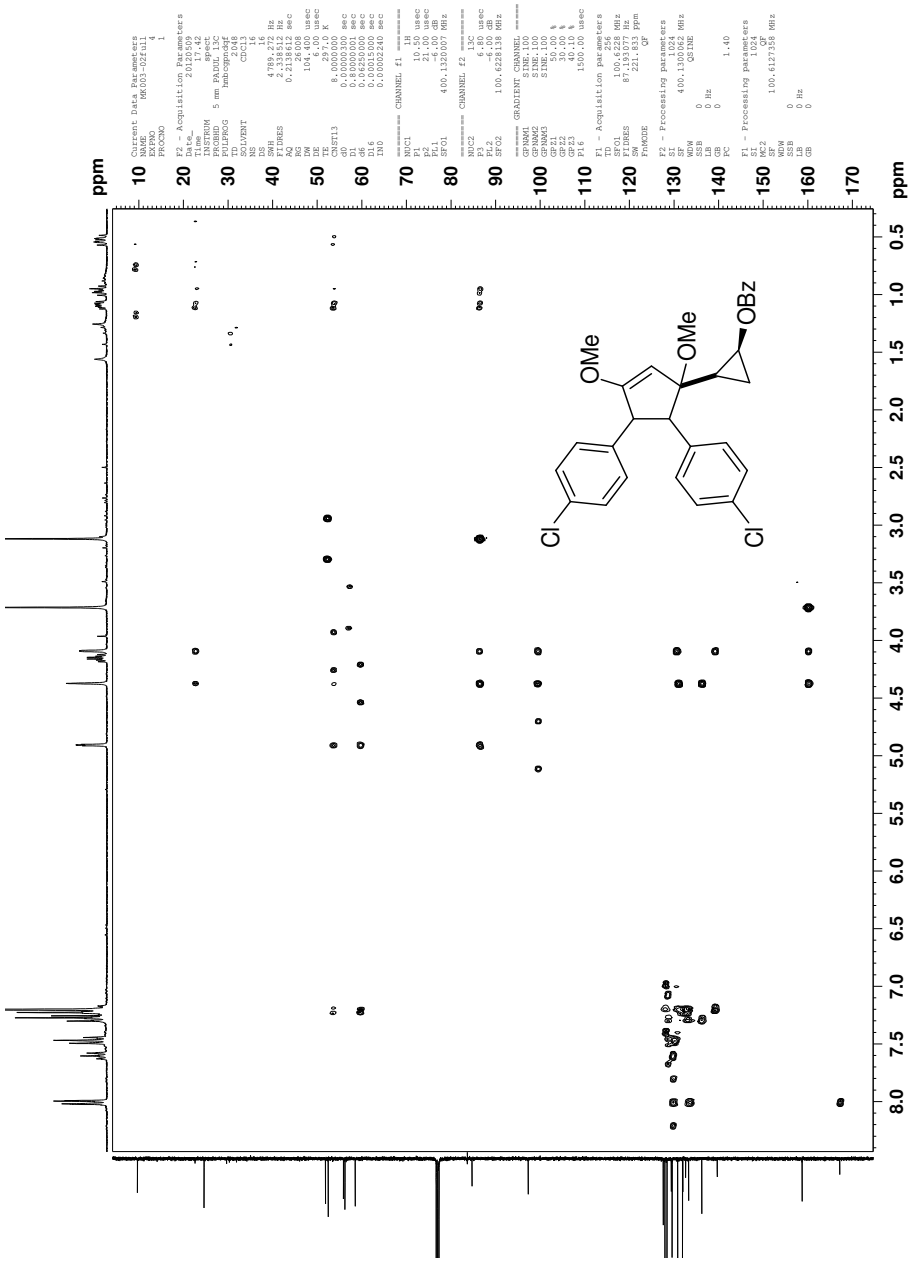
N.3 COSY of bicyclic compound 23a



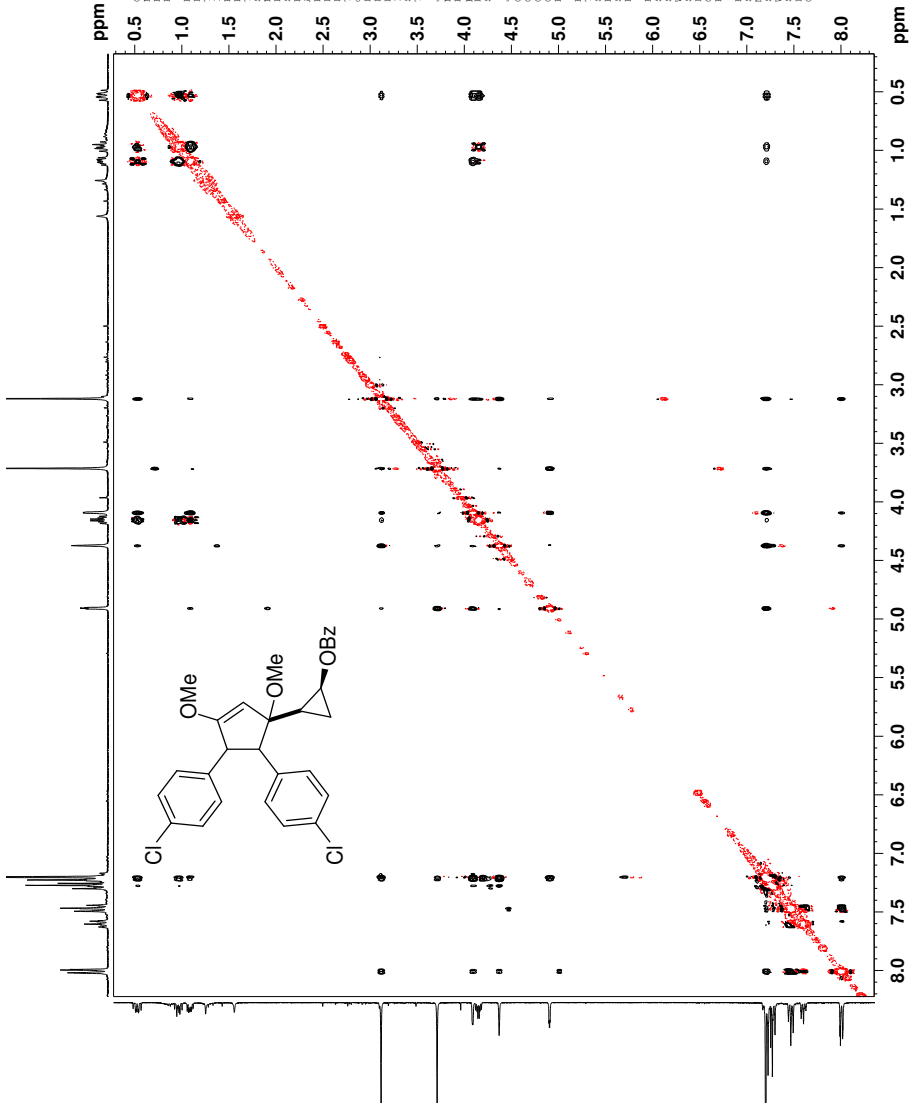
N.4 HSQC of bicyclic compound 23a



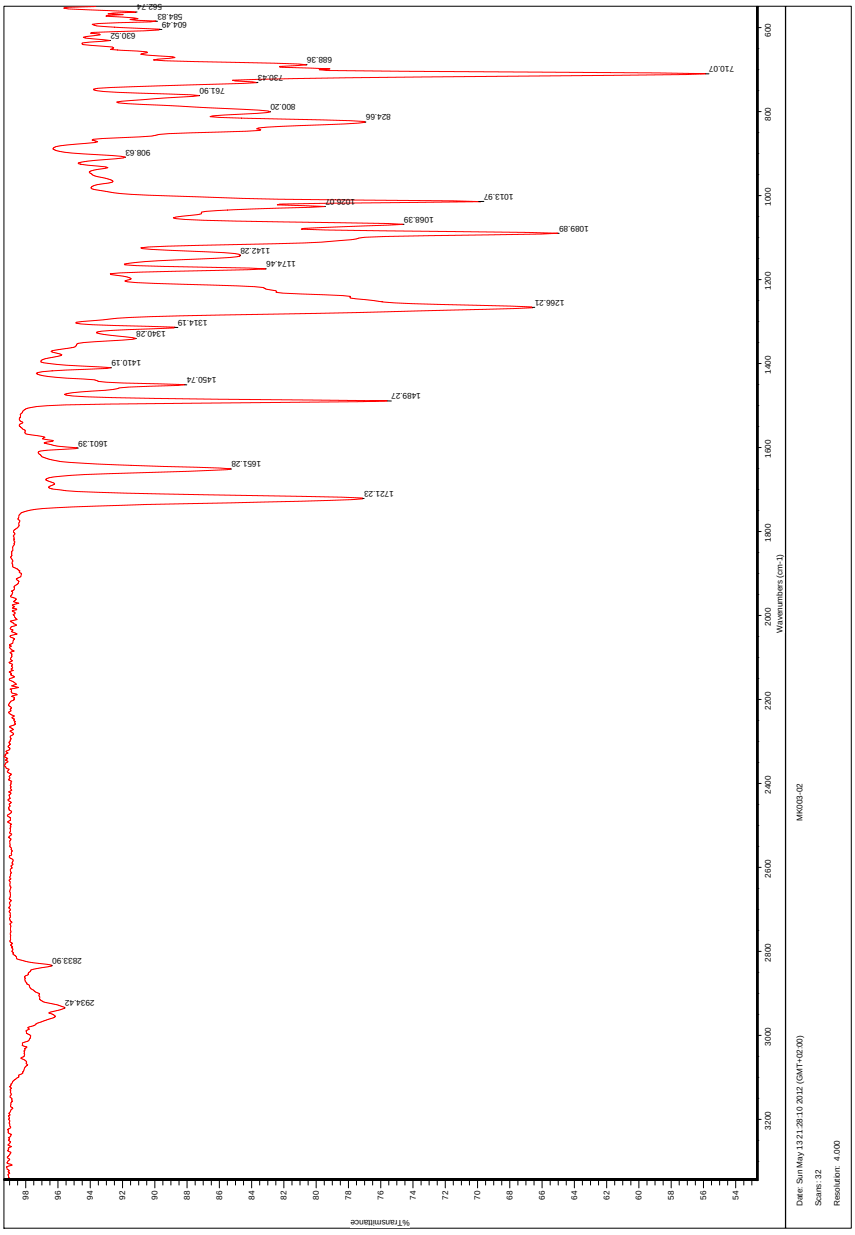
N.5 HMBC of bicyclic compound 23a



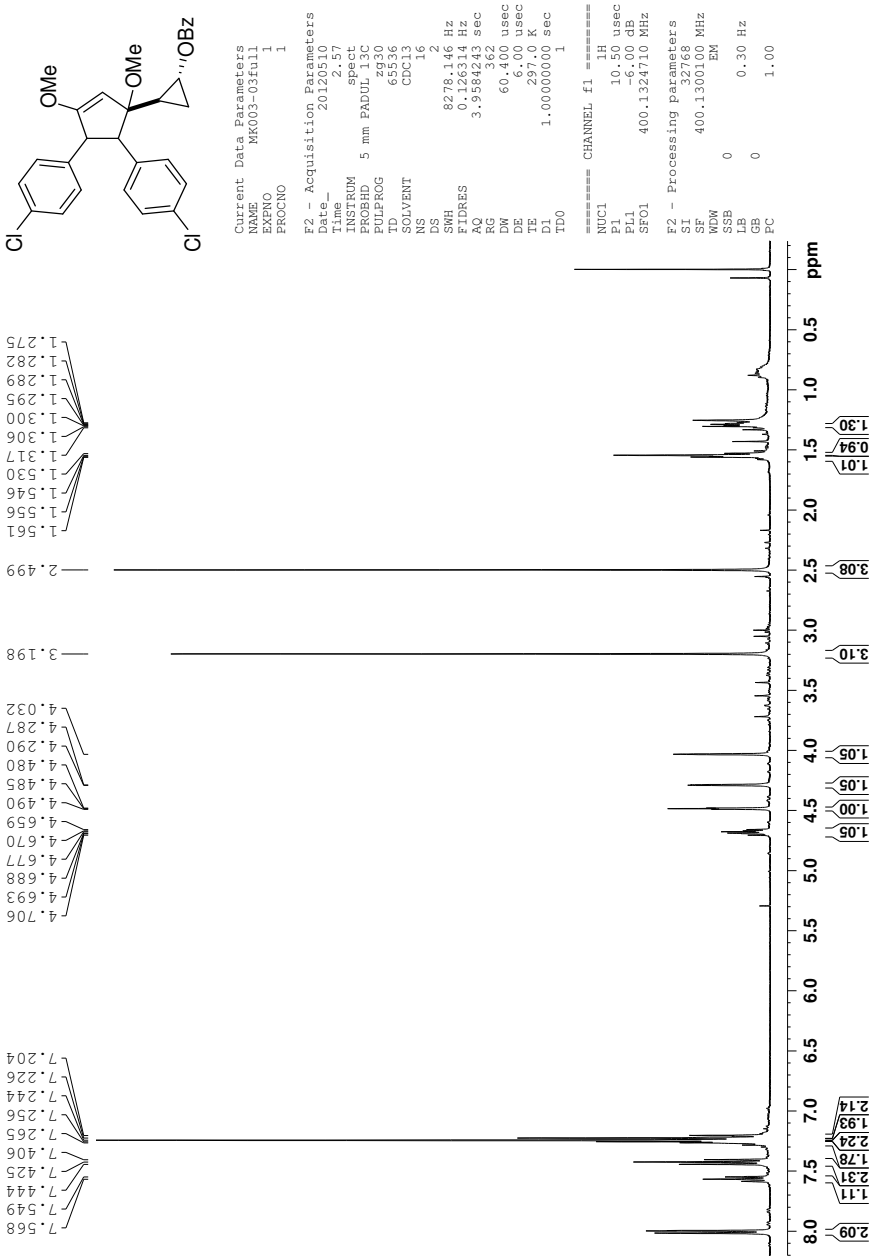
N.6 NOESY of bicyclic compound 23a



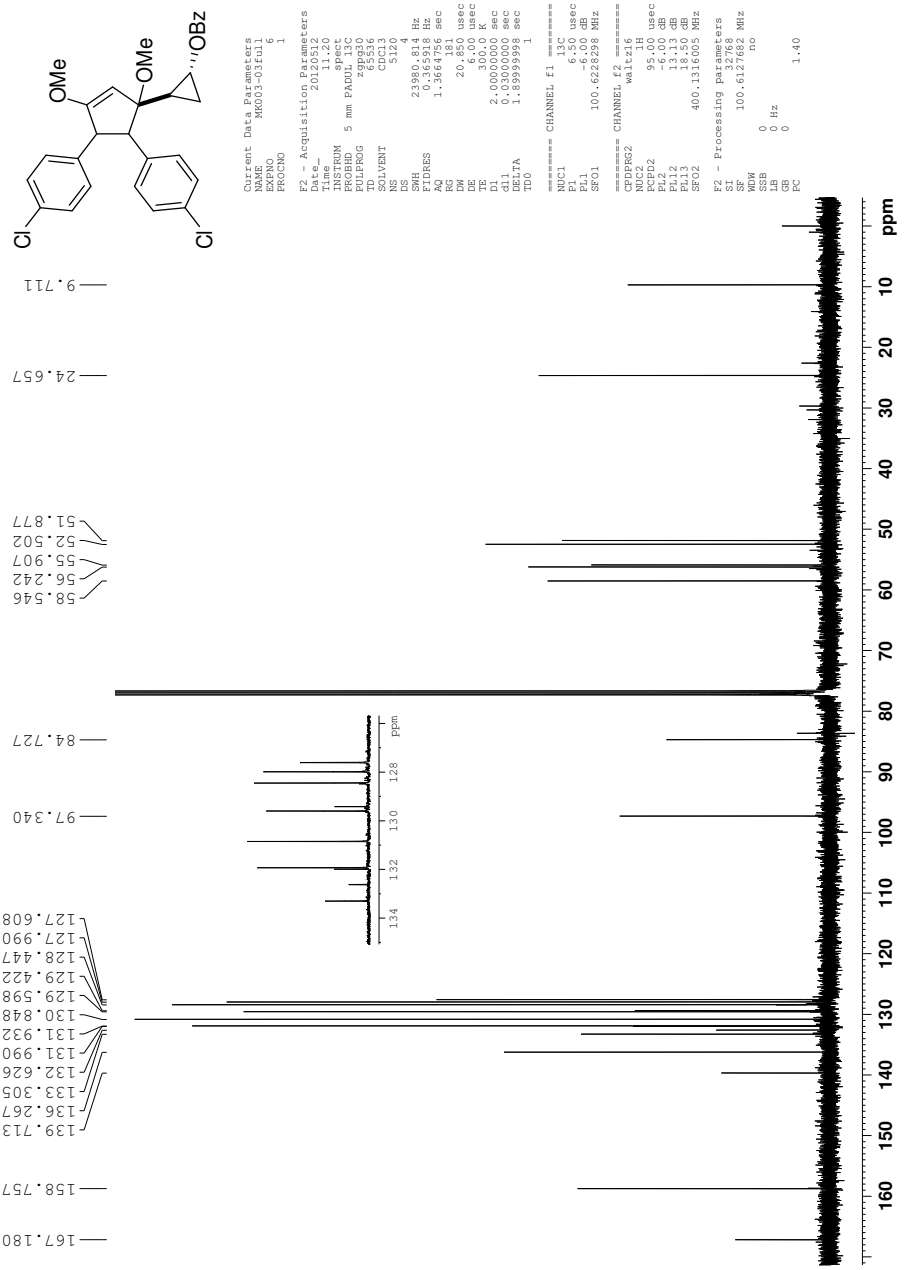
N.7 IR of bicyclic compound 23a



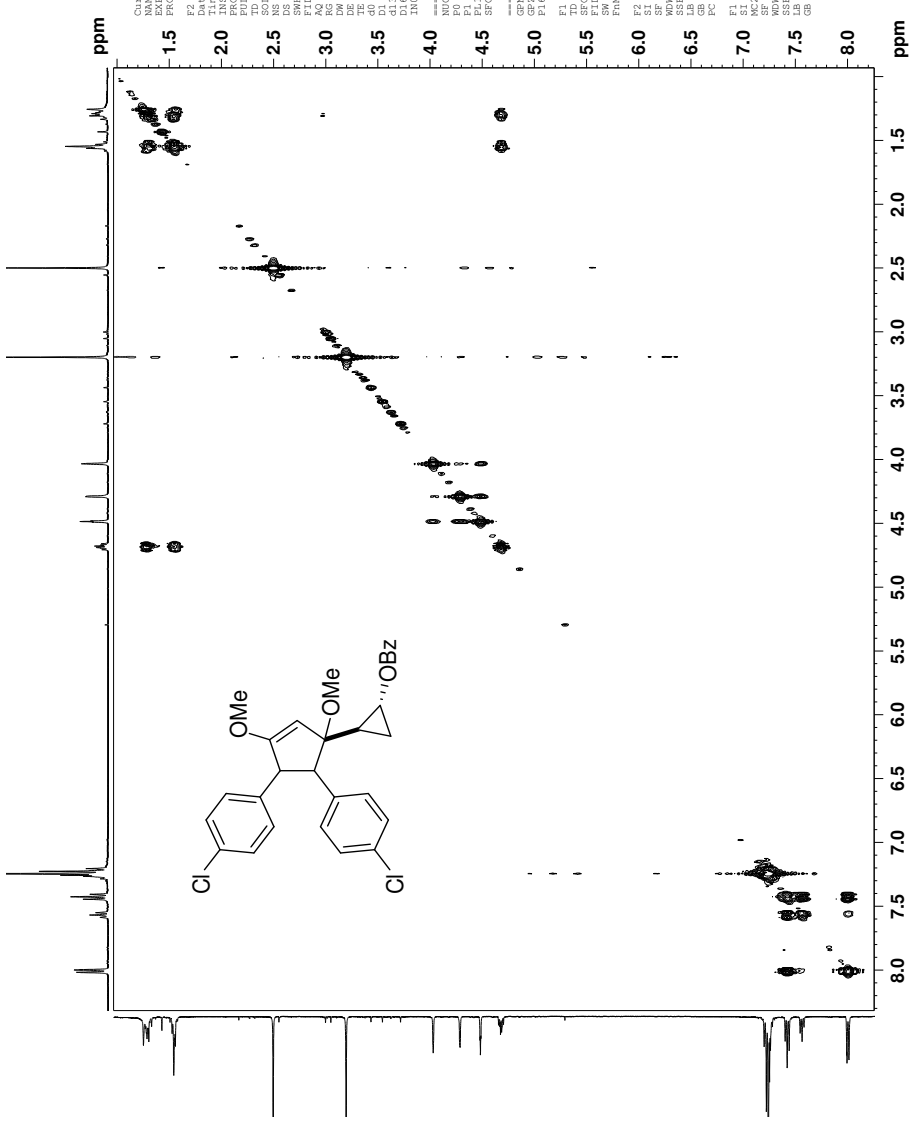
N.8 ^{1}H NMR of bicyclic compound 23b



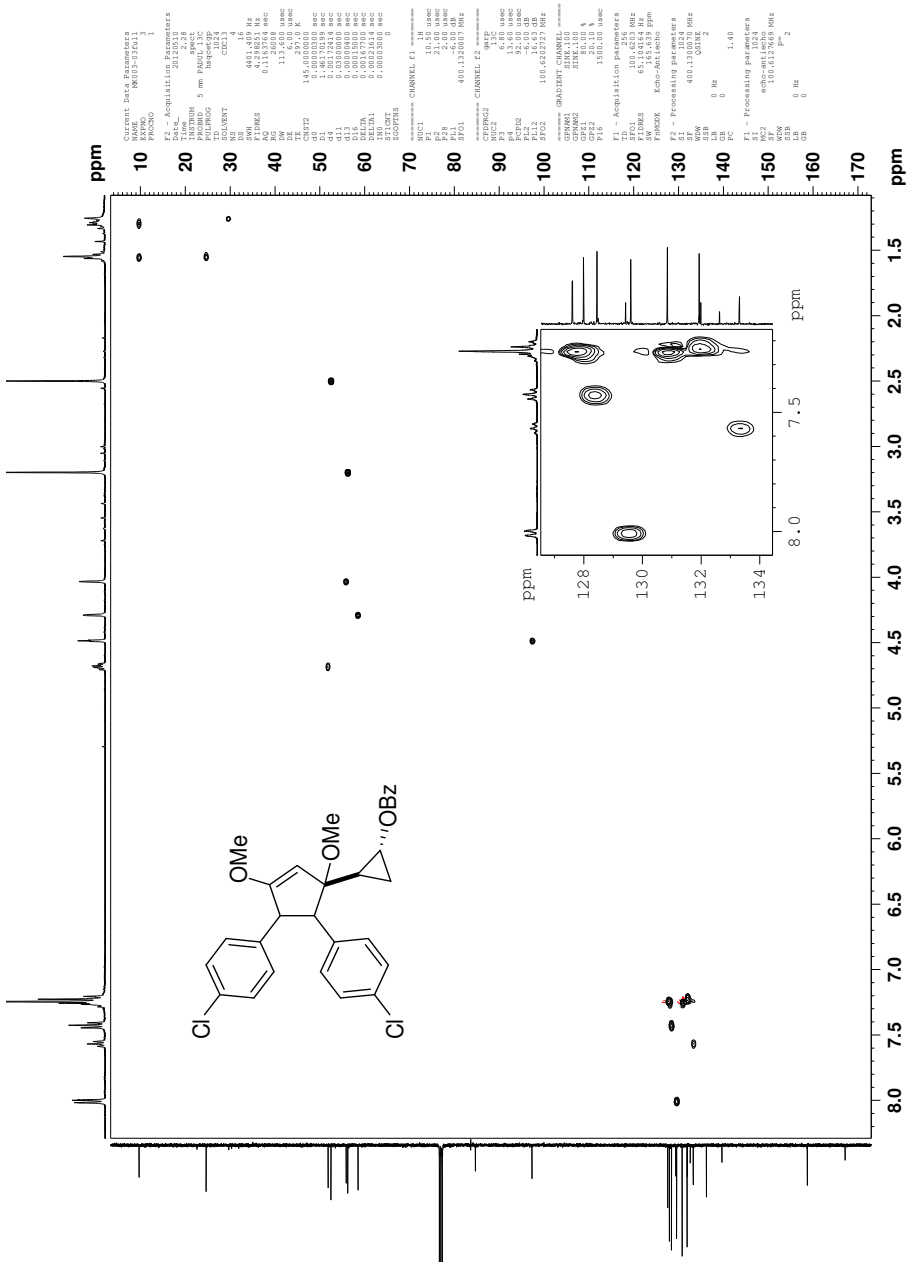
N.9 ^{13}C NMR of bicyclic compound 23b



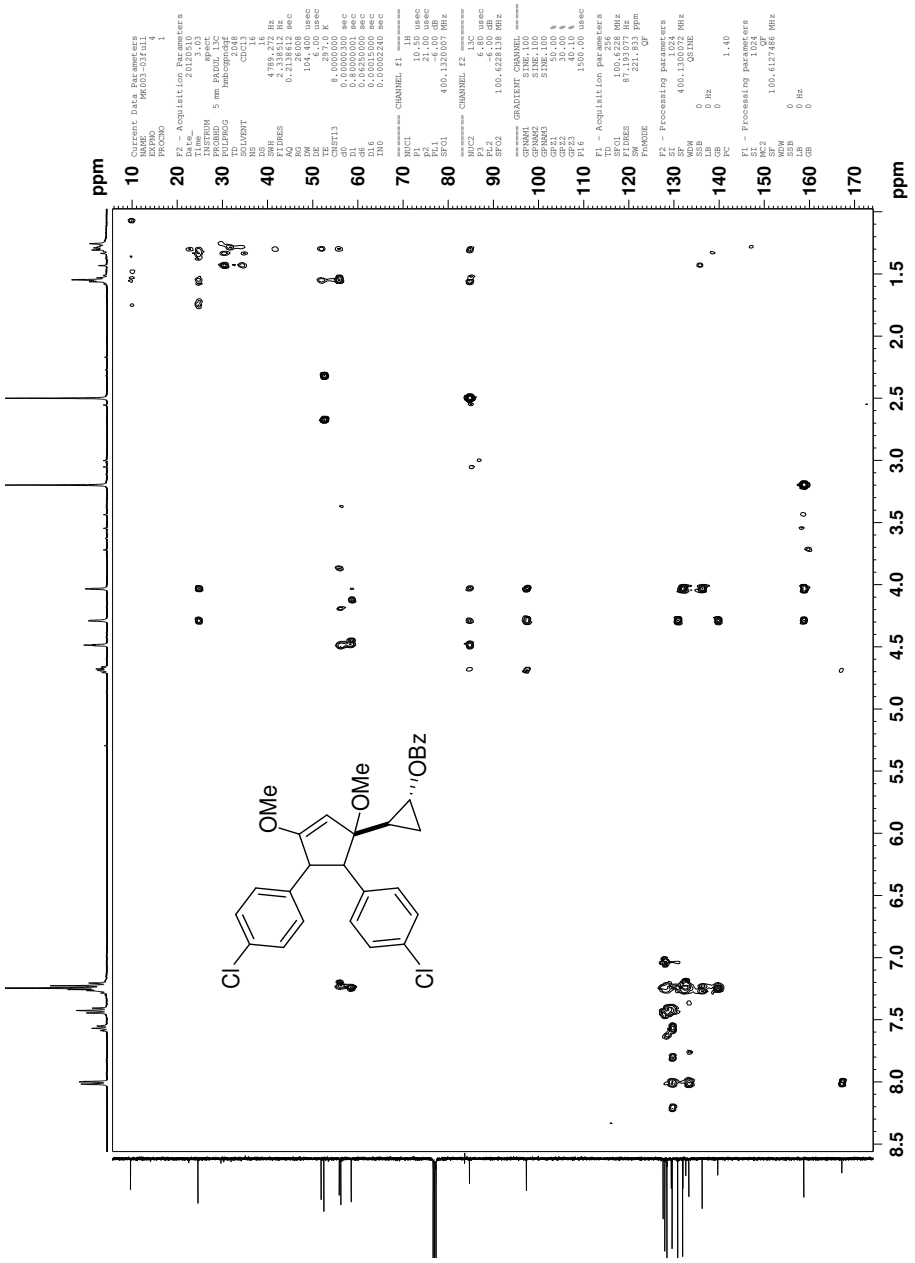
N.10 COSY of bicyclic compound 23b



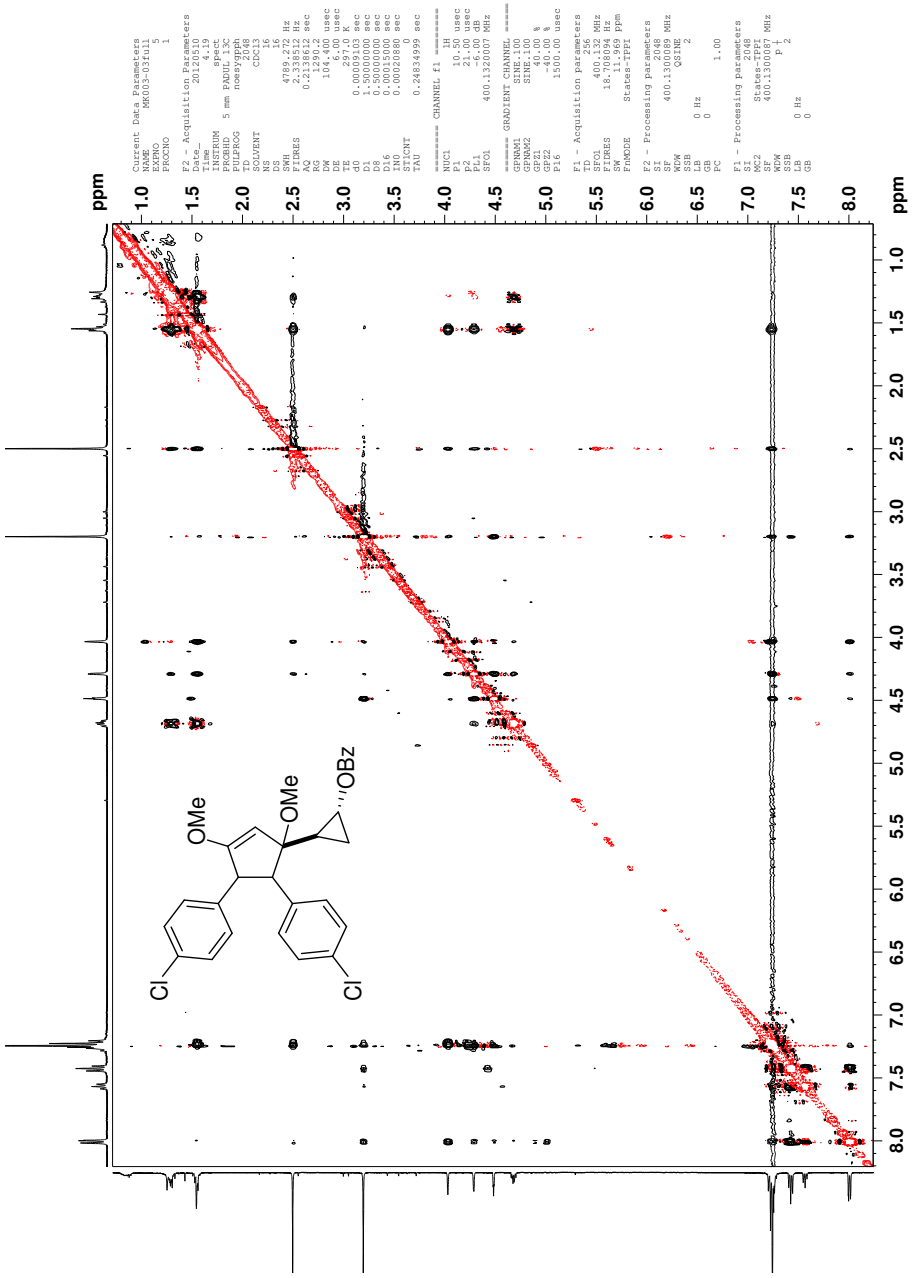
N.11 HSQC of bicyclic compound 23b



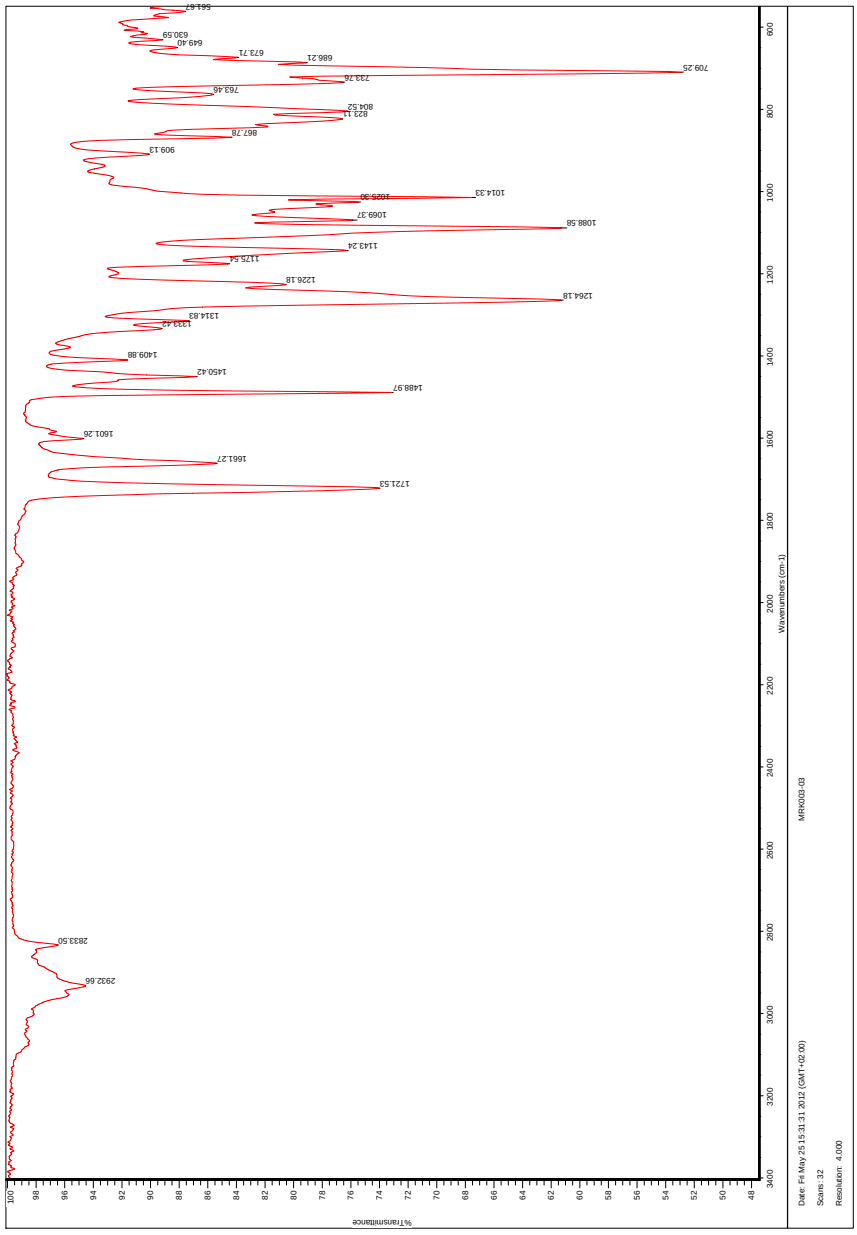
N.12 HMBC of bicyclic compound 23b



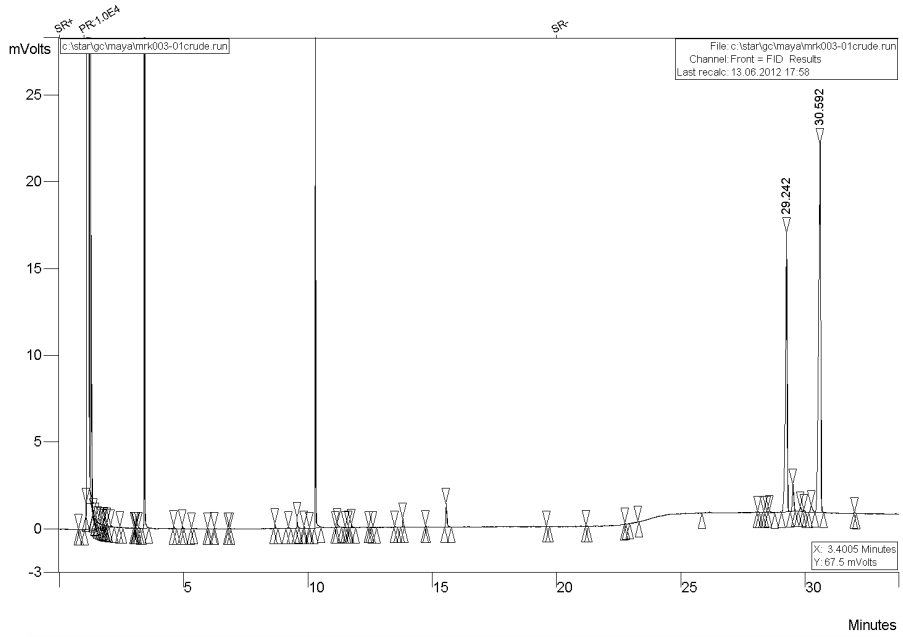
N.13 NOESY of bicyclic compound 23b



N.14 IR of bicyclic compound 23b



N.15 GLC chromatogram of bicyclic compound 23a-b

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Print Date: Wed Jun 13 17:59:49 2012            Page 1 of 1

Title       : Chrompack CP-Sil 5cB Low bleed/MS. 30m/0,25mmid
Run File    : c:\star\gc\maya\mrk003-01crude.run
Method File : c:\star\gc\maya\mrk003-01crude-front.mth
Sample ID   : Manual Sample

Injection Date: 25.05.2012 15:33    Calculation Date: 13.06.2012 17:58

Operator    :                       Detector Type: 3800 (1 Volt)
Workstation: system                 Bus Address  : 44
Instrument : Varian Star #1         Sample Rate  : 10.00 Hz
Channel     : Front = FID           Run Time     : 33.797 min

** GC Workstation Multi Instrument (Demo) Version 6.41 ** 05000-30c8-d68-31e1 **

Run Mode         : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

                                 Ret.     Time                      Width
 Peak      Peak        Result    Time    Offset       Area    Sep.  1/2   Status
  No.      Name          ()      (min)    (min)     (counts)  Code (sec)  Codes
 ---- ------------ ---------- ------- ------- ---------- ---- -----  ------
    1                   38.85  29.242   0.000      76795   BP   4.3
    2                   61.15  30.592   0.000     120883   VB   5.3
 ---- ------------ ========== ======= ======= ========== ---- -----  ------
      Totals:         100.00            0.000     197678

Total Unidentified Counts :     197678 counts

Detected Peaks: 14          Rejected Peaks: 12     Identified Peaks: 0

Multiplier: 1          Divisor: 1          Unidentified Peak Factor: 0

Baseline Offset: -66 microVolts          LSB:     1 microVolts

Noise (used): 18 microVolts - monitored before this run

Manual injection

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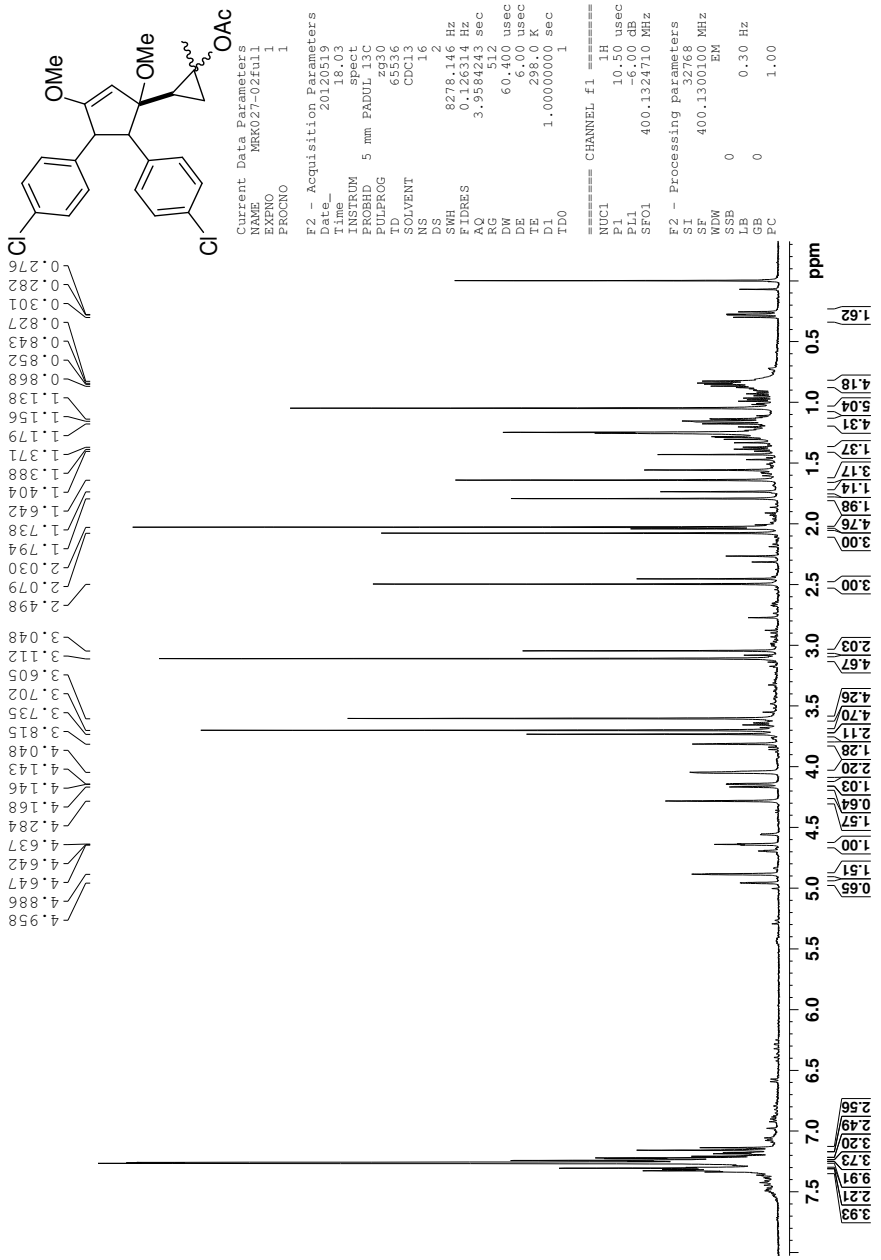
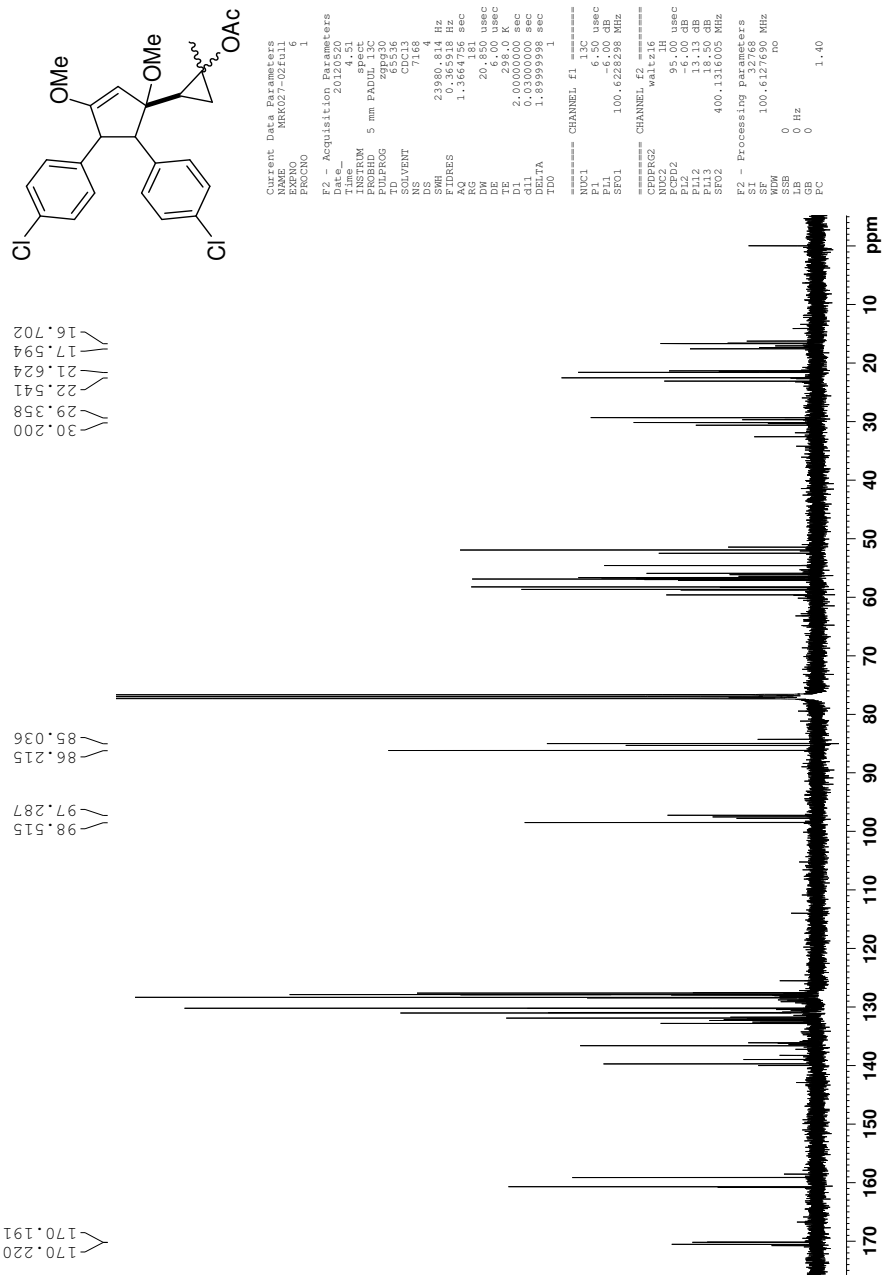
```

O Bicyclic compound 24a-b

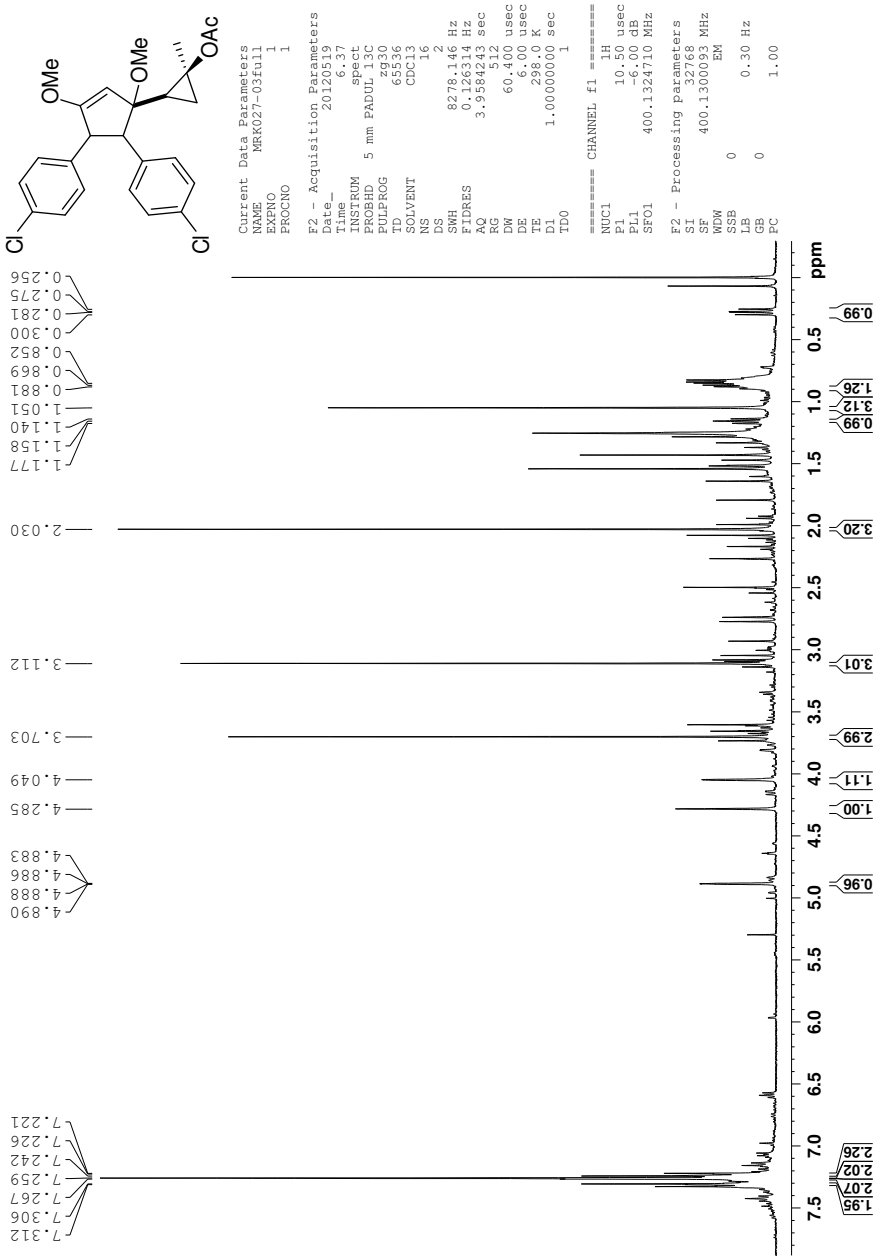
O.1 ^{1}H NMR of bicyclic compound 24a-b



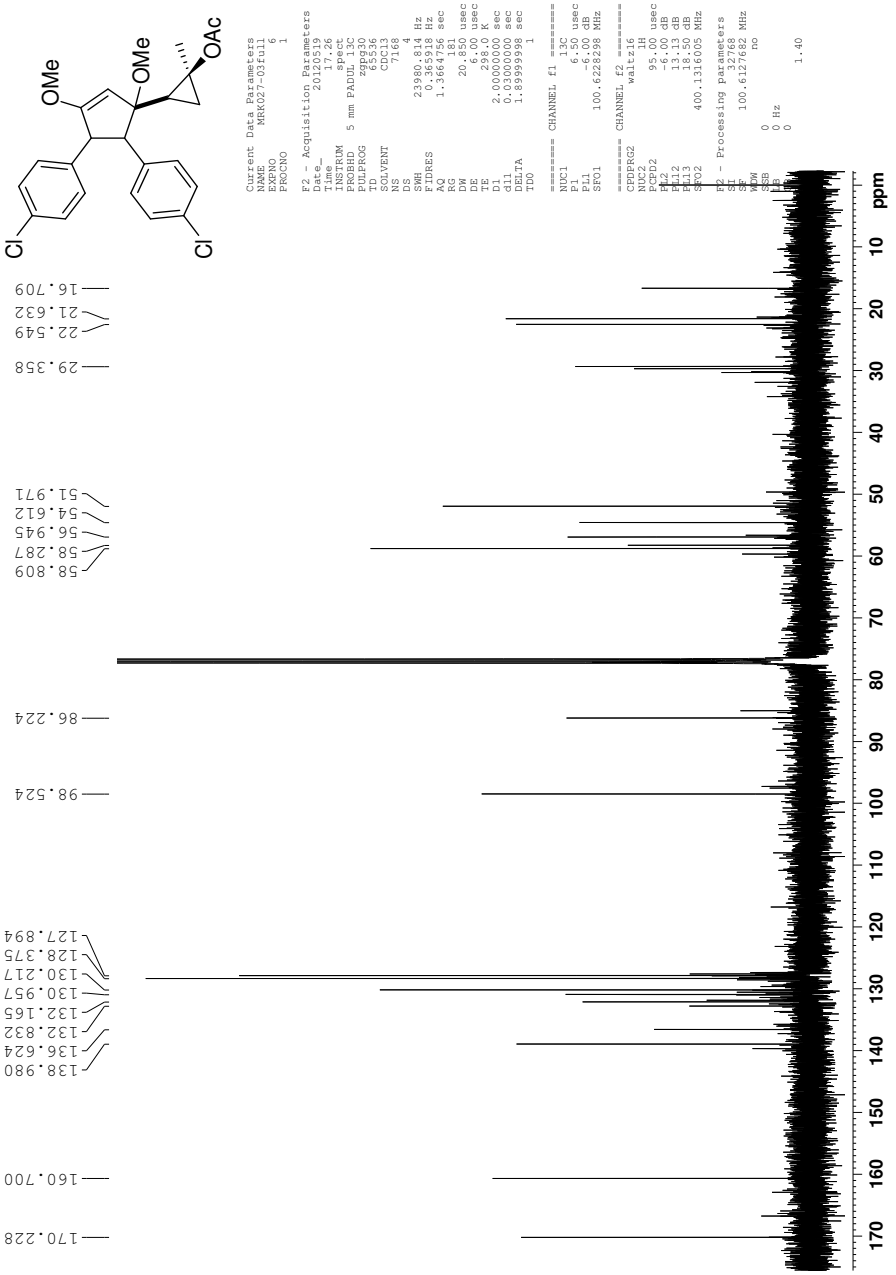
O.2 ^{13}C NMR of bicyclic compound 24a-b



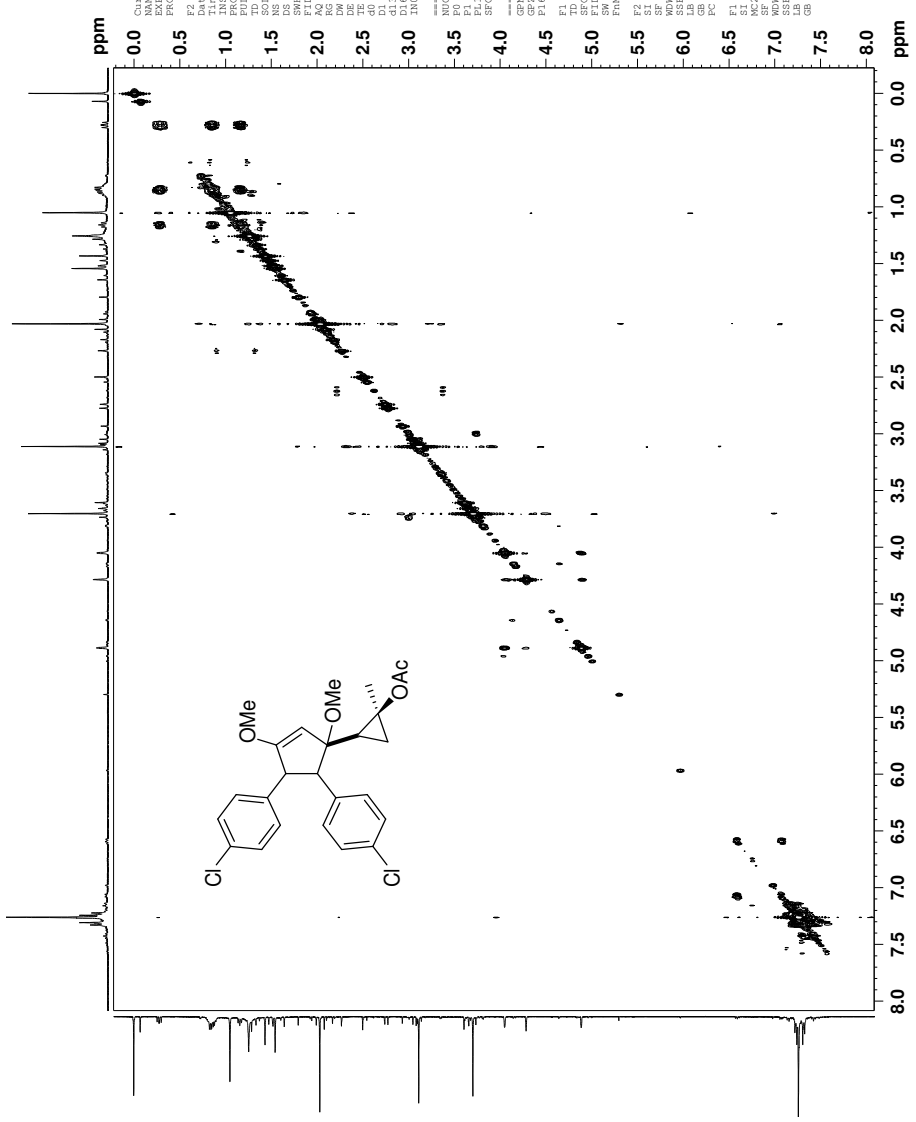
O.3 ^{1}H NMR of bicyclic compound 24a



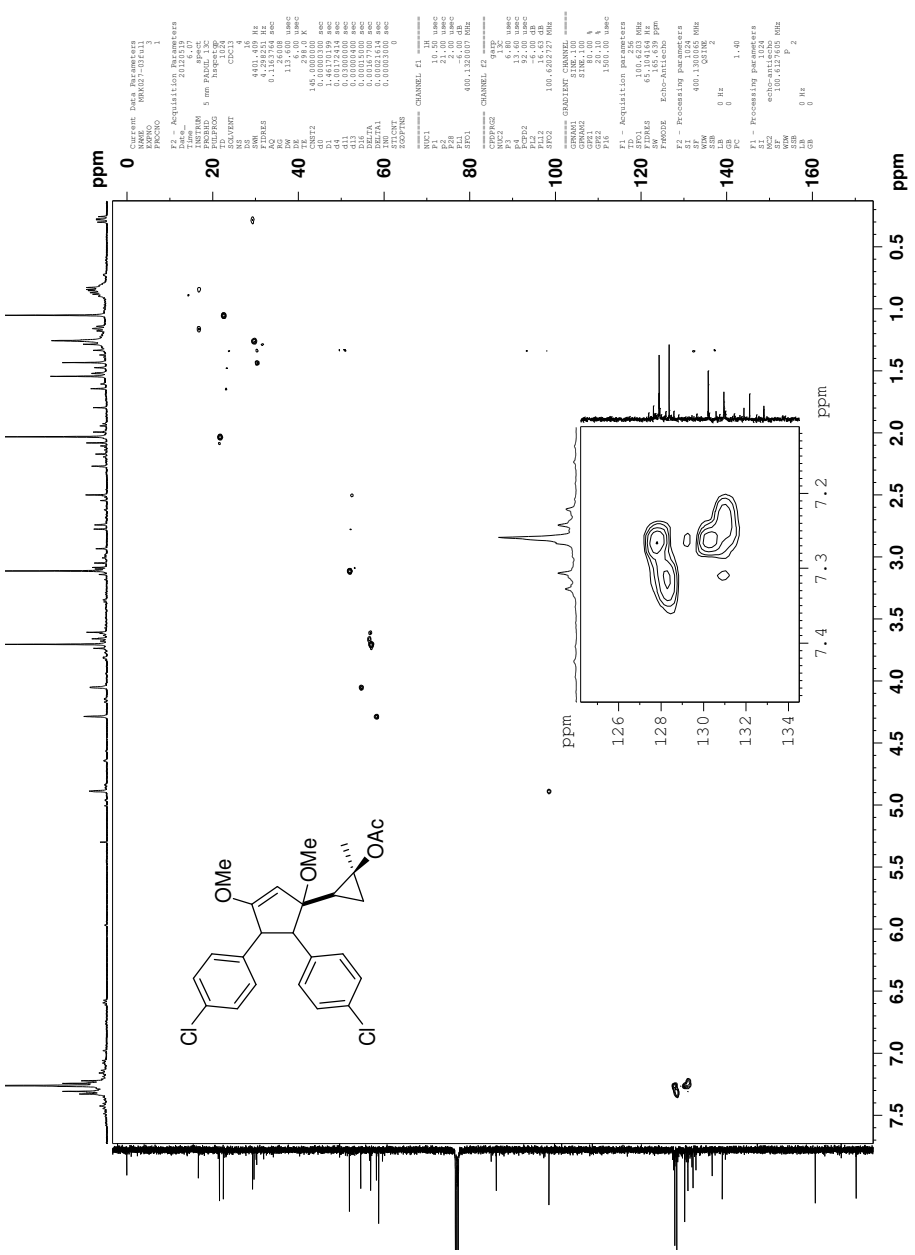
O.4 ^{13}C NMR of bicyclic compound 24a



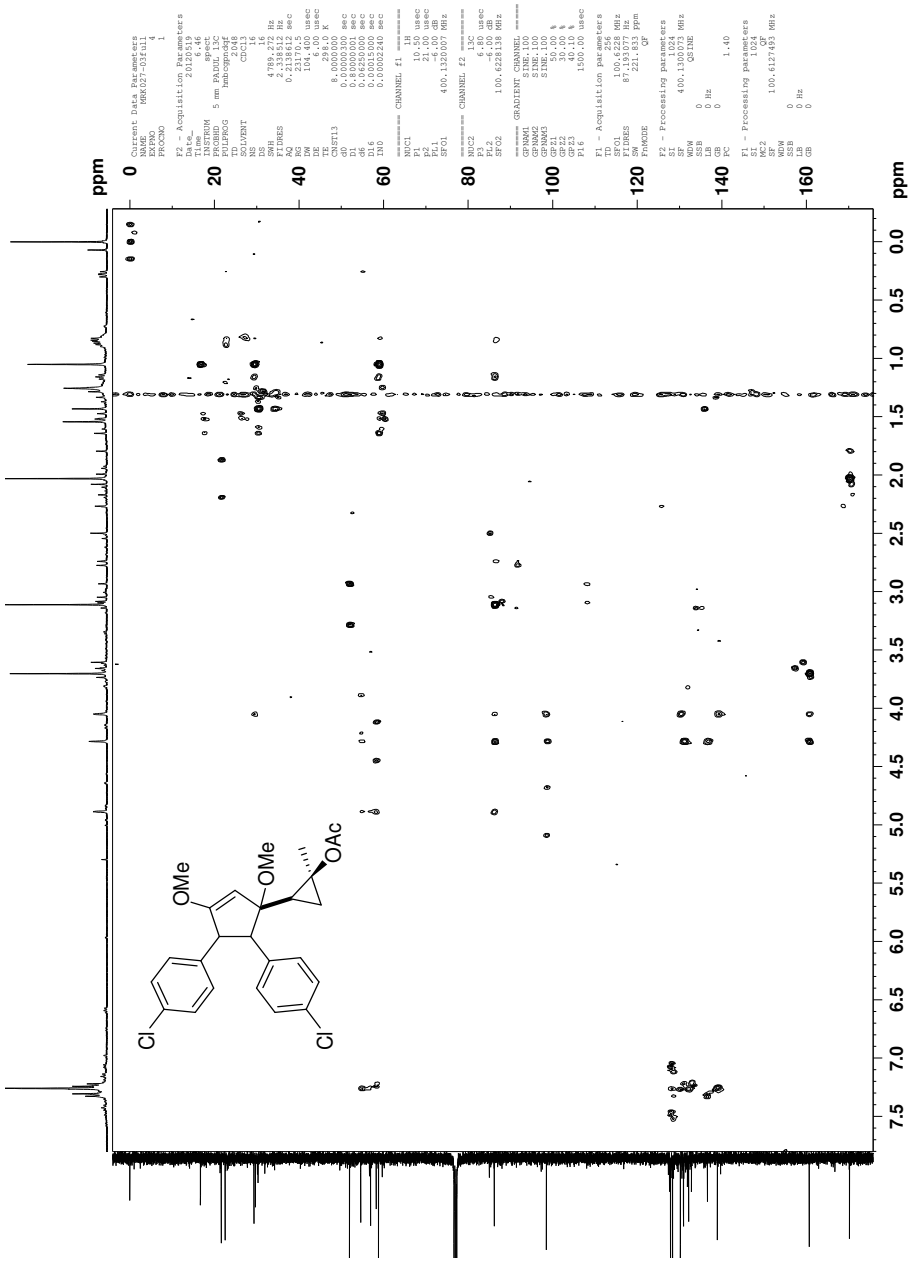
O.5 COSY of bicyclic compound 24a



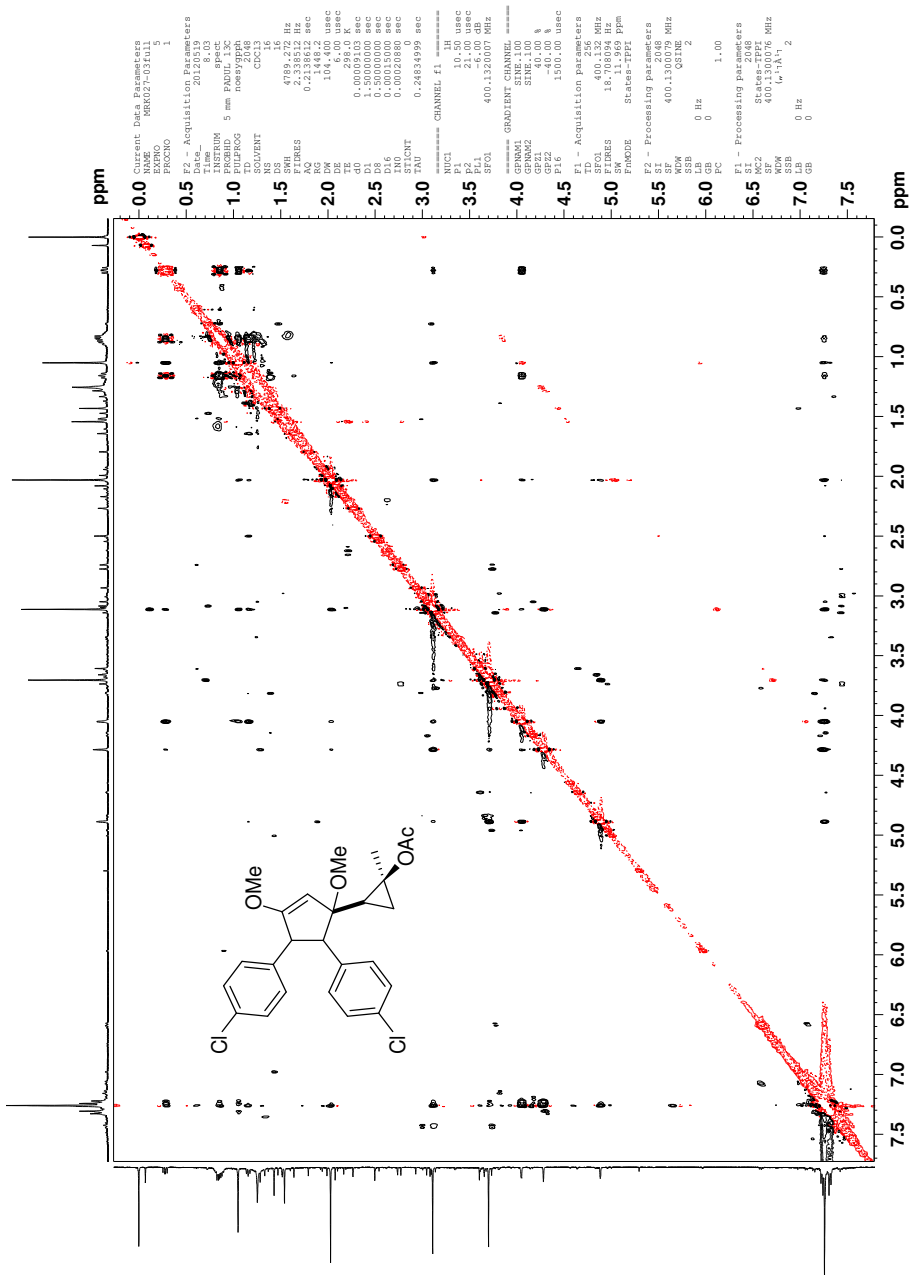
O.6 HSQC of bicyclic compound 24a



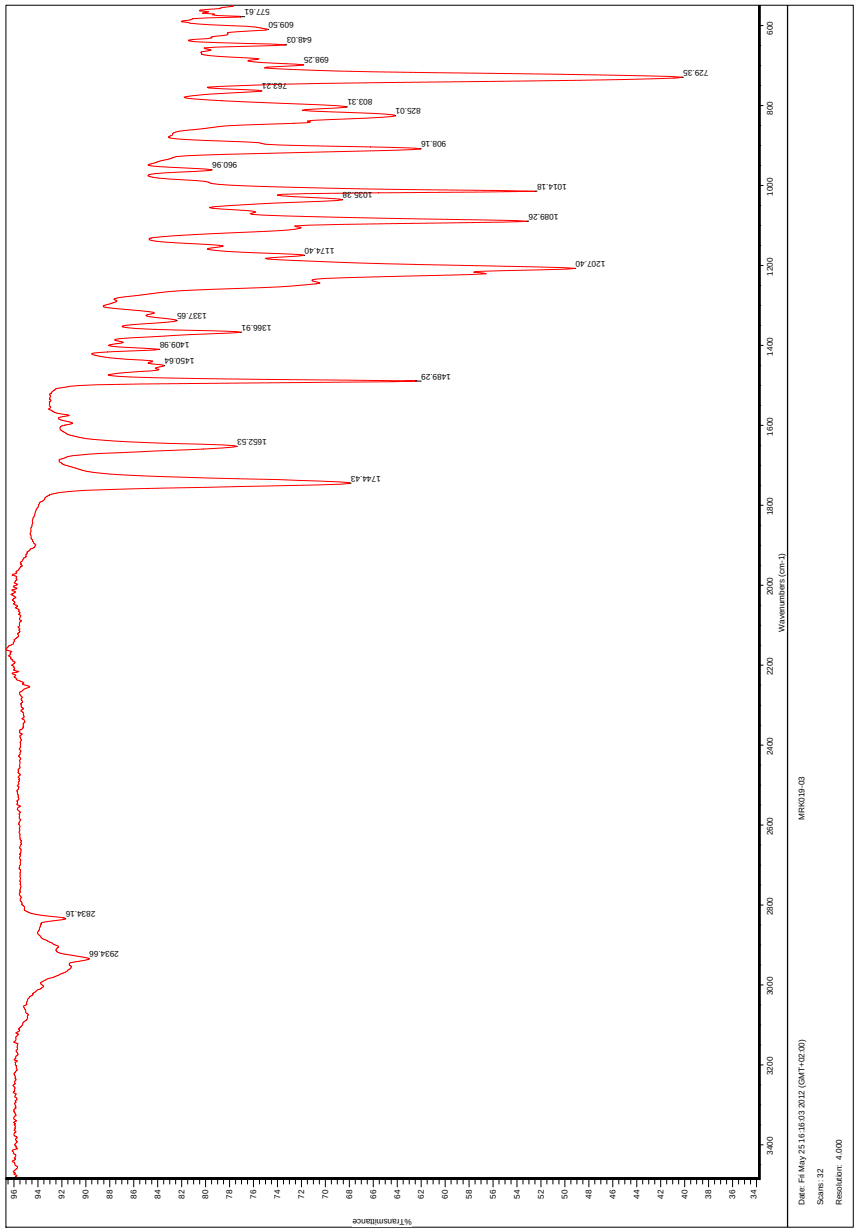
O.7 HMBC of bicyclic compound 24a



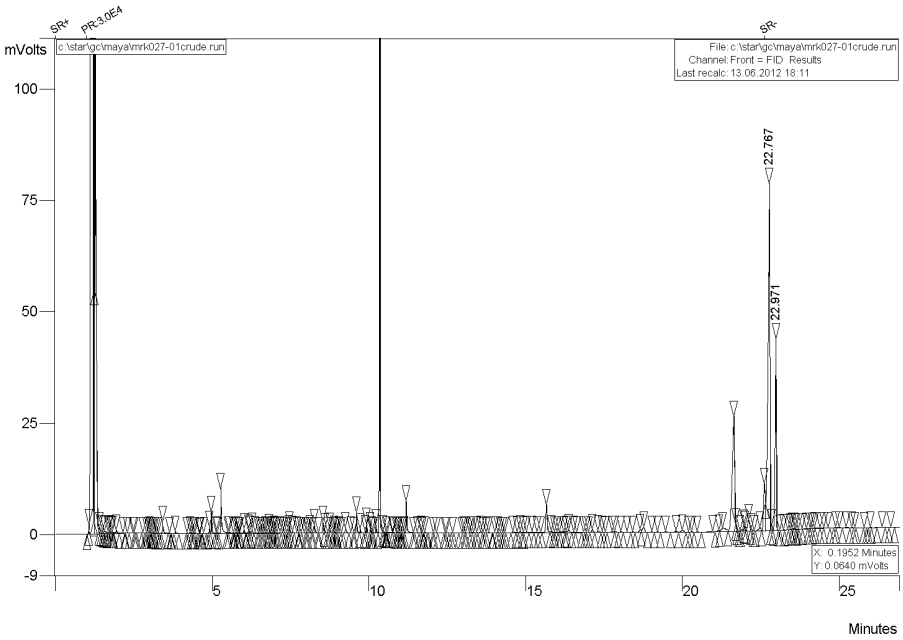
O.8 NOESY of bicyclic compound 24a



O.9 IR of bicyclic compound 24a-b



O.10 GLC chromatogram of bicyclic compound 24a-b

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Print Date: Wed Jun 13 18:12:25 2012             Page 1 of 1

Title       : Chrompack CP-Sil 5cB Low bleed/MS. 30m/0,25mmid
Run File    : c:\star\gc\maya\mrk027-01crude.run
Method File : c:\star\gc\maya\mrk003-01crude-front.mth
Sample ID   : Manual Sample

Injection Date: 16.05.2012 18:59    Calculation Date: 13.06.2012 18:11

Operator    :                       Detector Type: 3800 (1 Volt)
Workstation: system                 Bus Address  : 44
Instrument : Varian Star #1         Sample Rate  : 10.00 Hz
Channel     : Front = FID           Run Time     : 33.797 min

** GC Workstation Multi Instrument (Demo) Version 6.41 ** 05000-30c8-d68-31e1 **

Run Mode         : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

                                 Ret.    Time                          Width
 Peak      Peak        Result    Time   Offset       Area     Sep.    1/2    Status
  No.      Name          ()      (min)   (min)     (counts)  Code   (sec)   Codes
 ---- ------------ ---------- ------- ------- ---------- ---- -----  ------
    1                  73.42  22.767   0.000     312790    VV    3.7
    2                  26.58  22.971   0.000     113267    VP    2.5
 ---- ------------ ========== ======= ======= ========== ---- -----  ------
      Totals:         100.00            0.000     426057

Total Unidentified Counts :     426056 counts

Detected Peaks: 58          Rejected Peaks: 56     Identified Peaks: 0

Multiplier: 1          Divisor: 1          Unidentified Peak Factor: 0

Baseline Offset: 60 microVolts          LSB:     1 microVolts

Noise (used): 13 microVolts - monitored before this run

Manual injection

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```
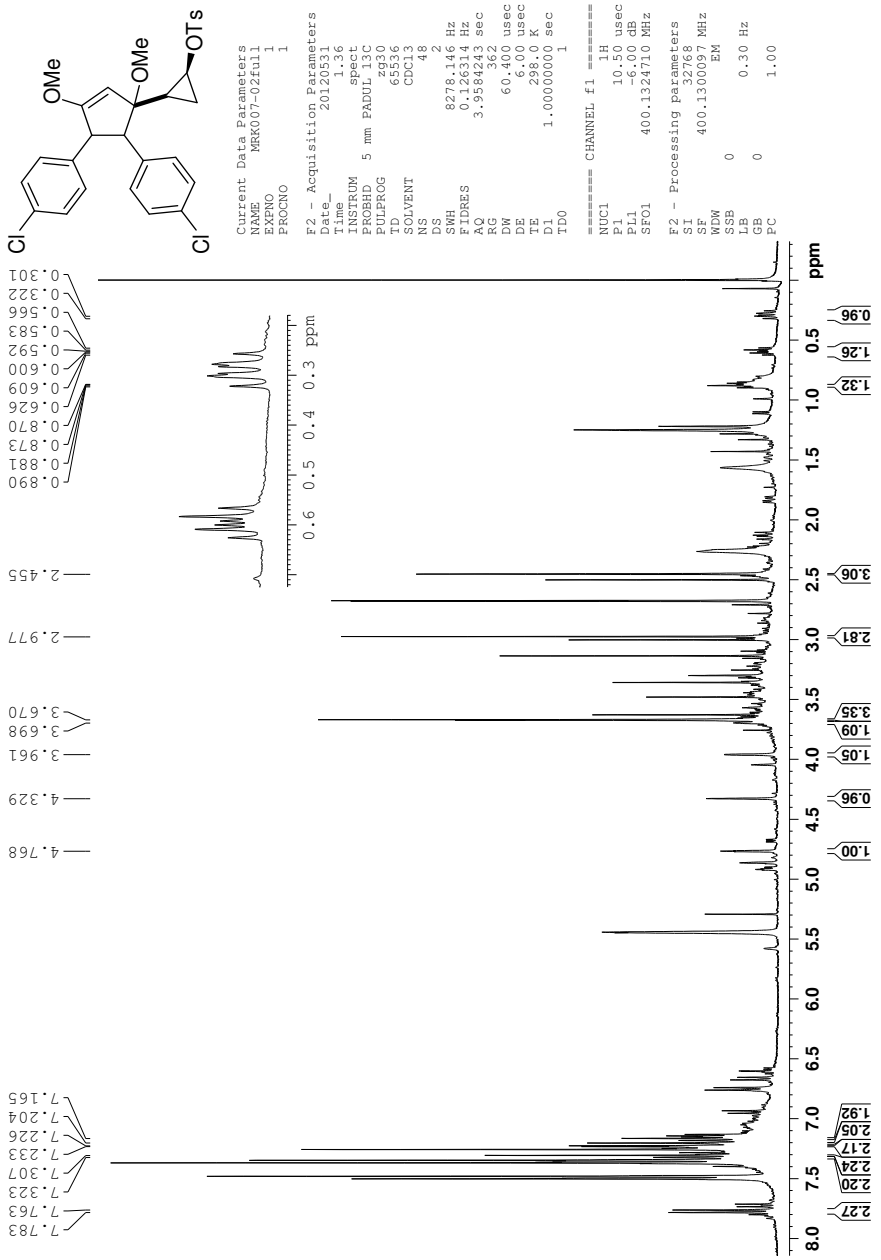
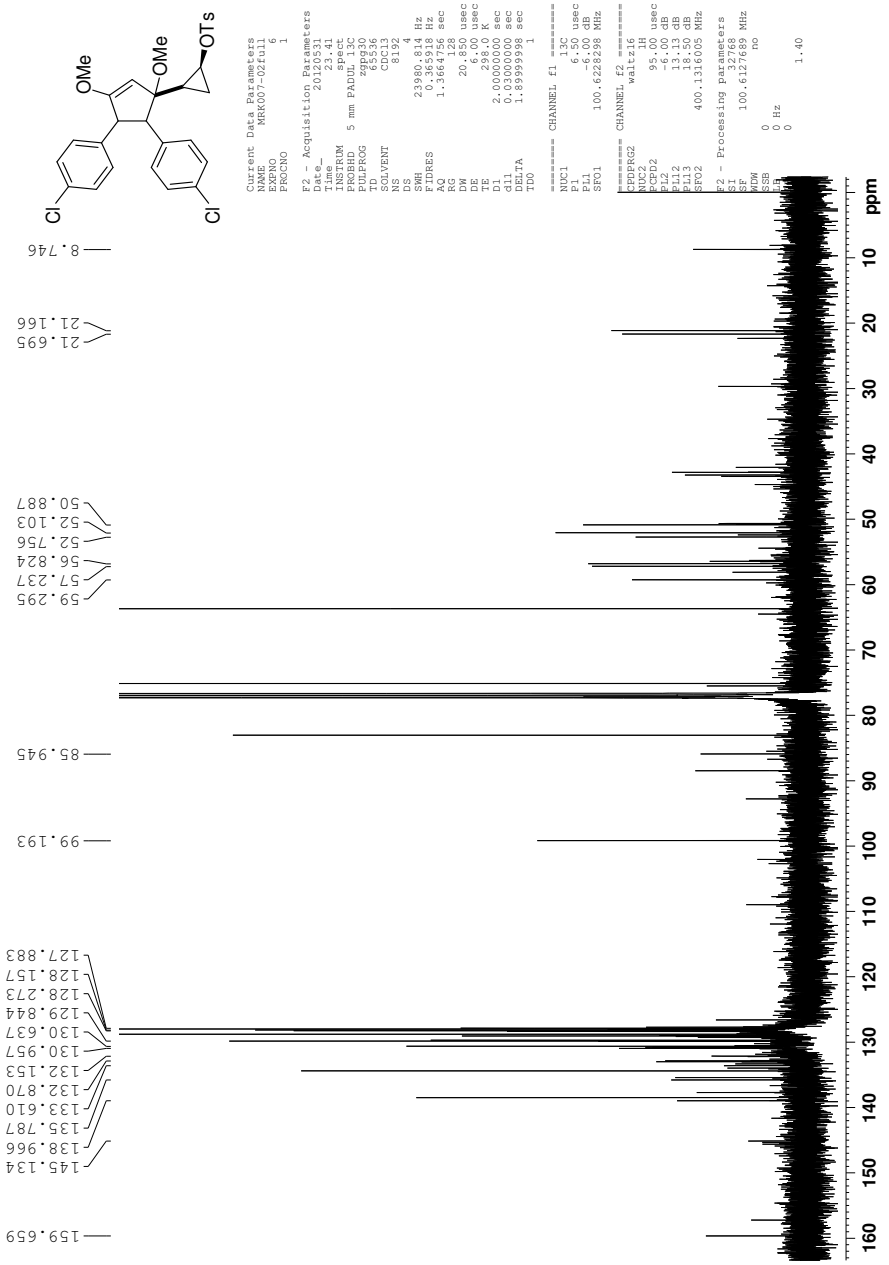

P Bicyclic compound 26

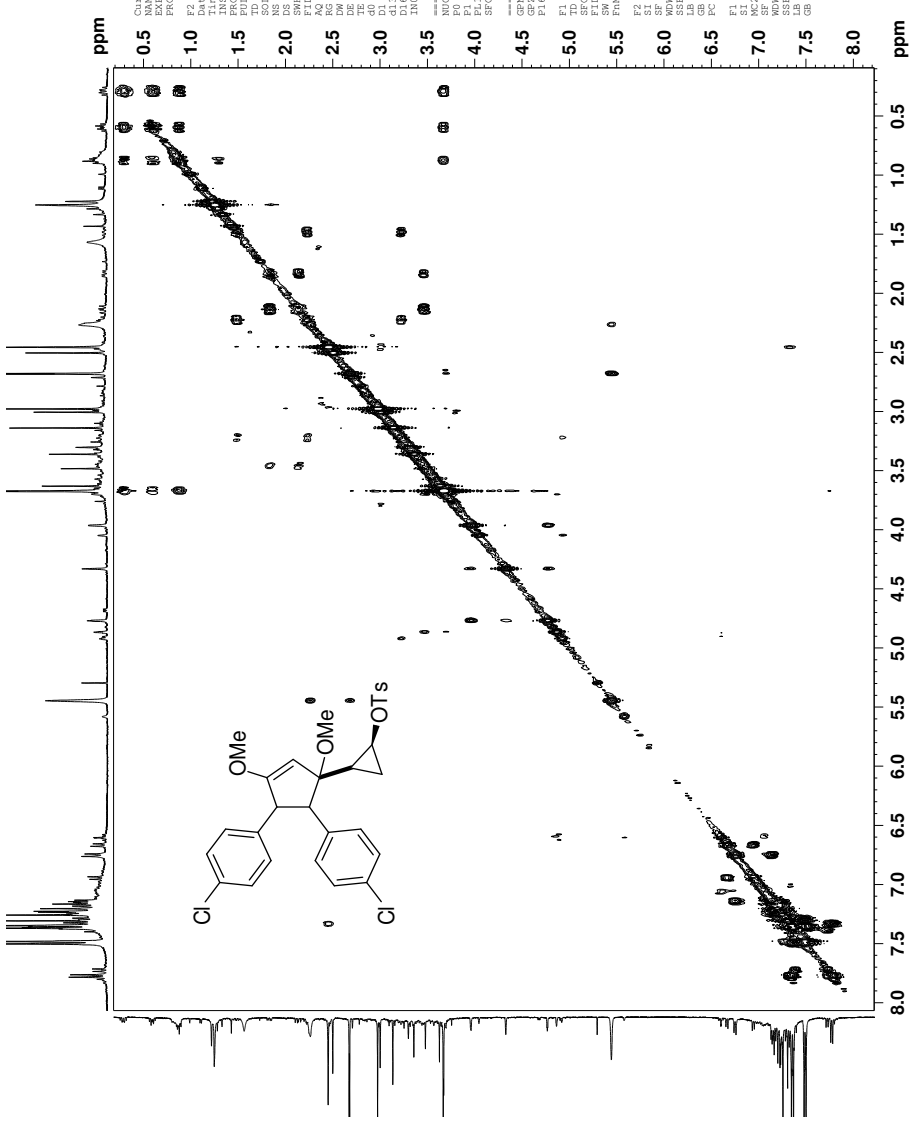
P.1 ^{1}H NMR of bicyclic compound 26



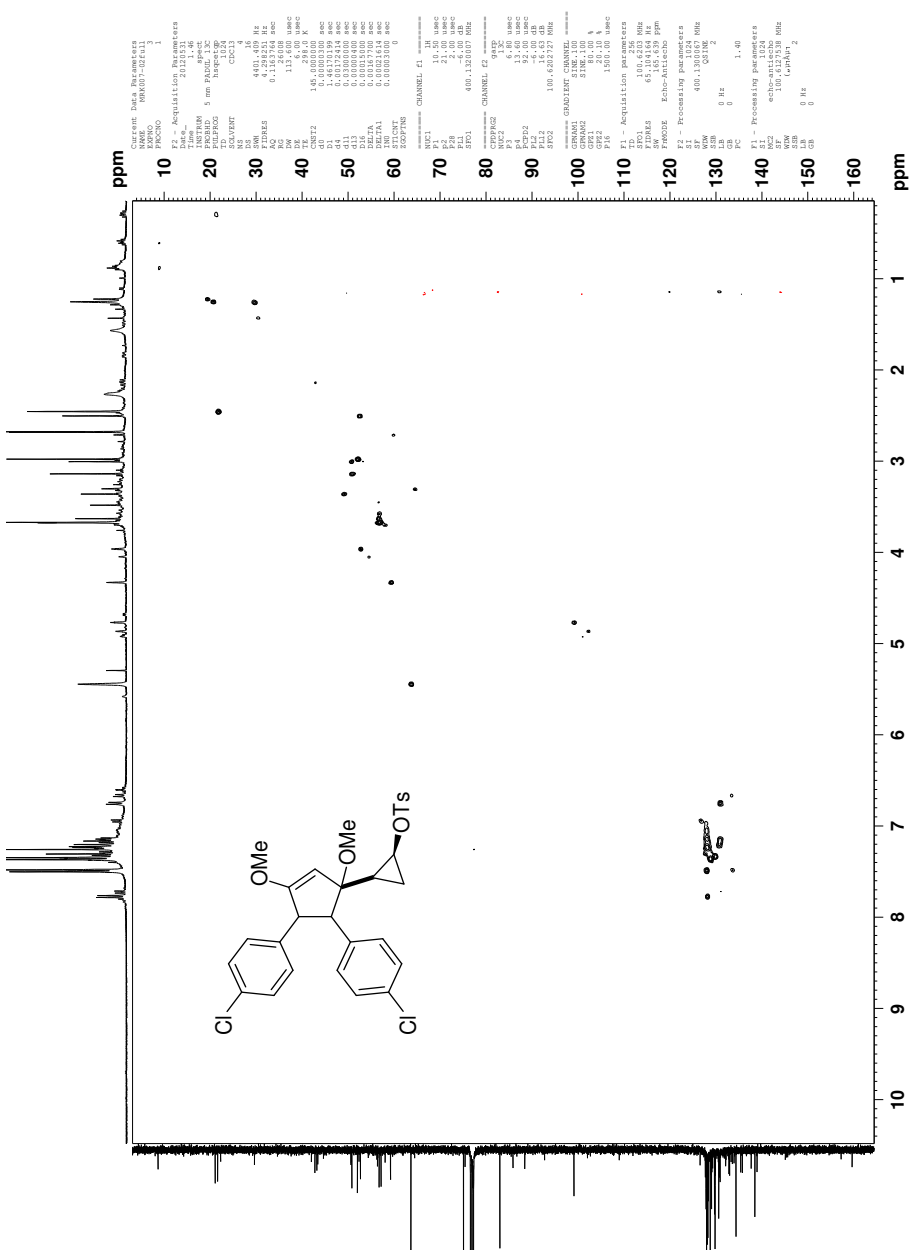
P.2 ^{13}C NMR of bicyclic compound 26



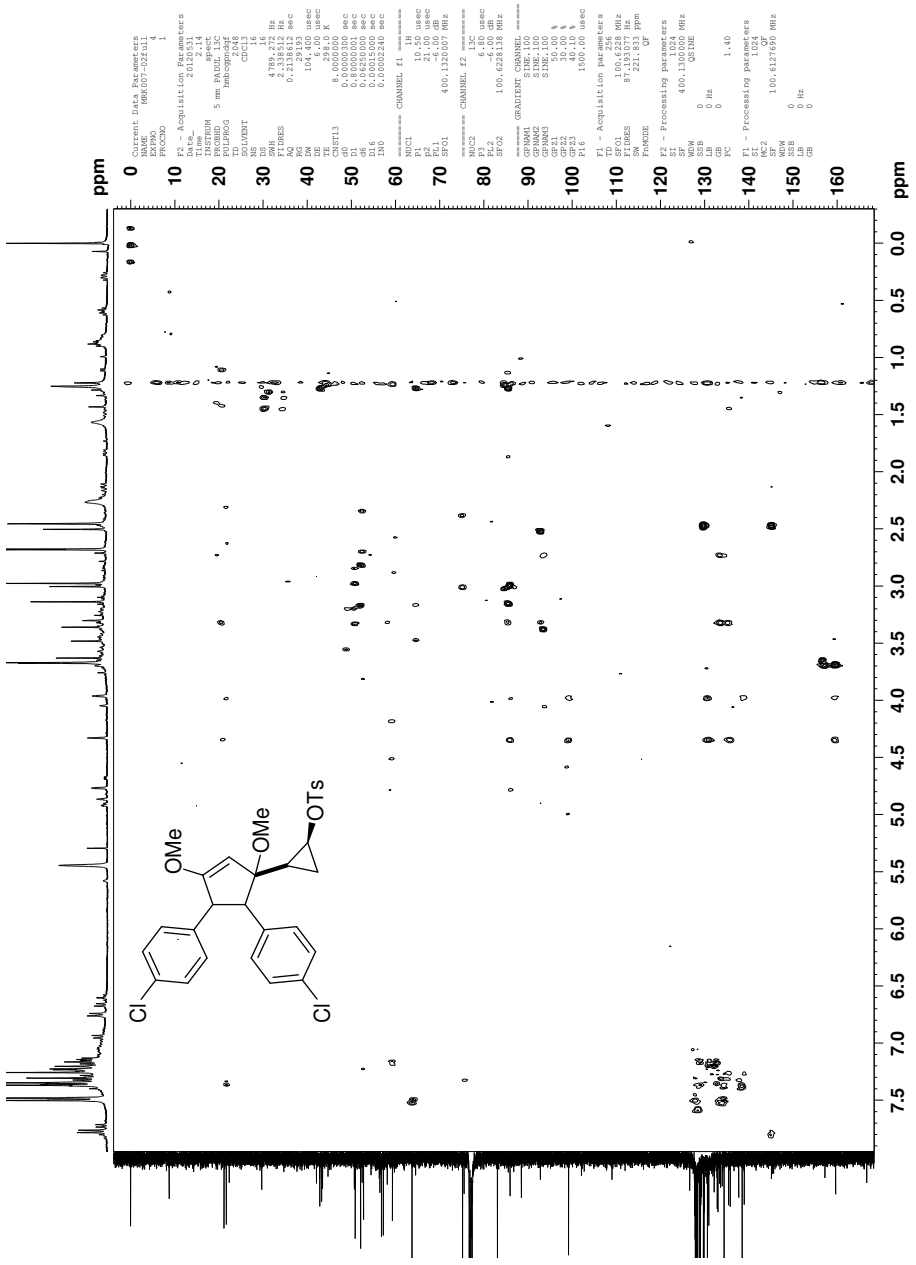
P.3 COSY of bicyclic compound 26



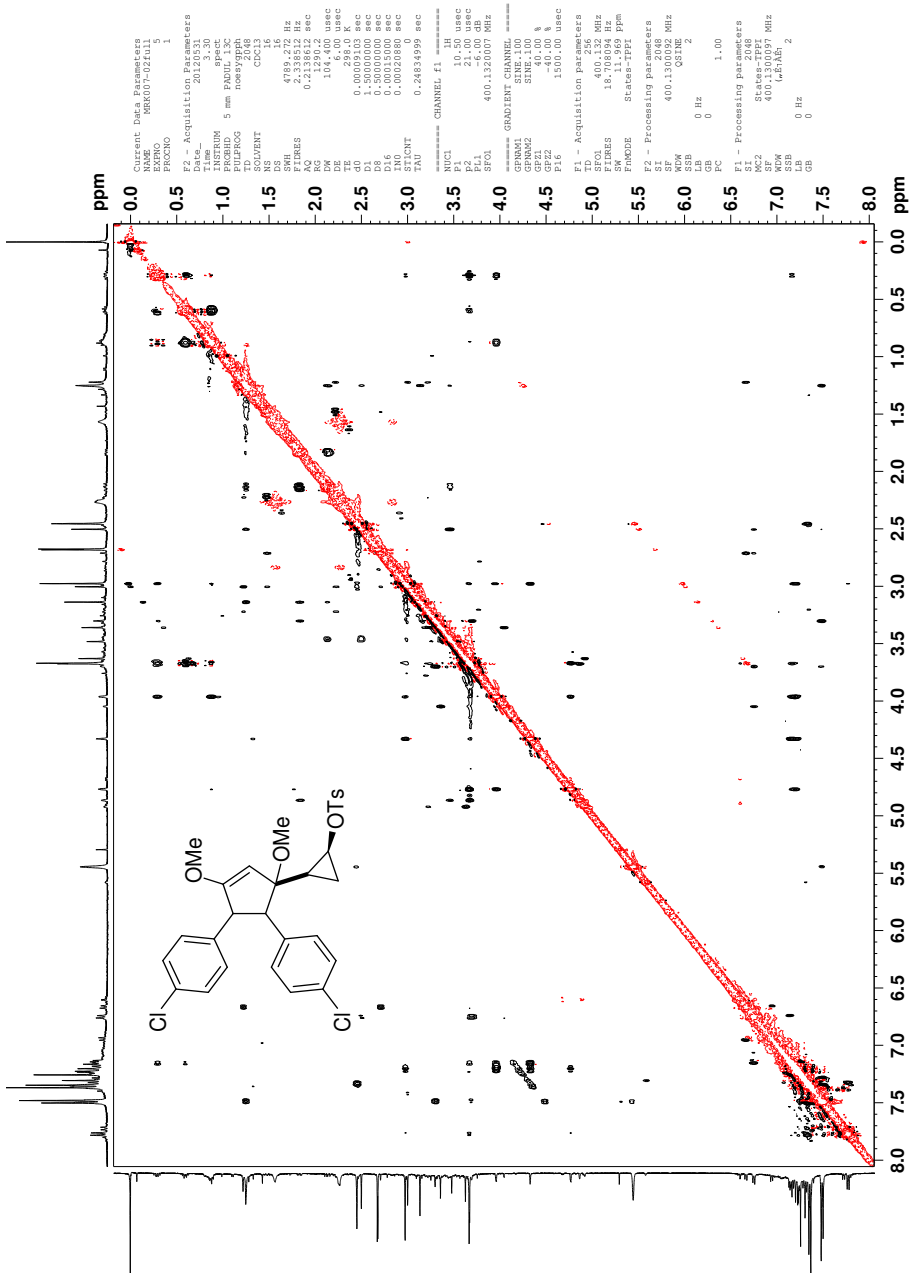
P.4 HSQC of bicyclic compound 26



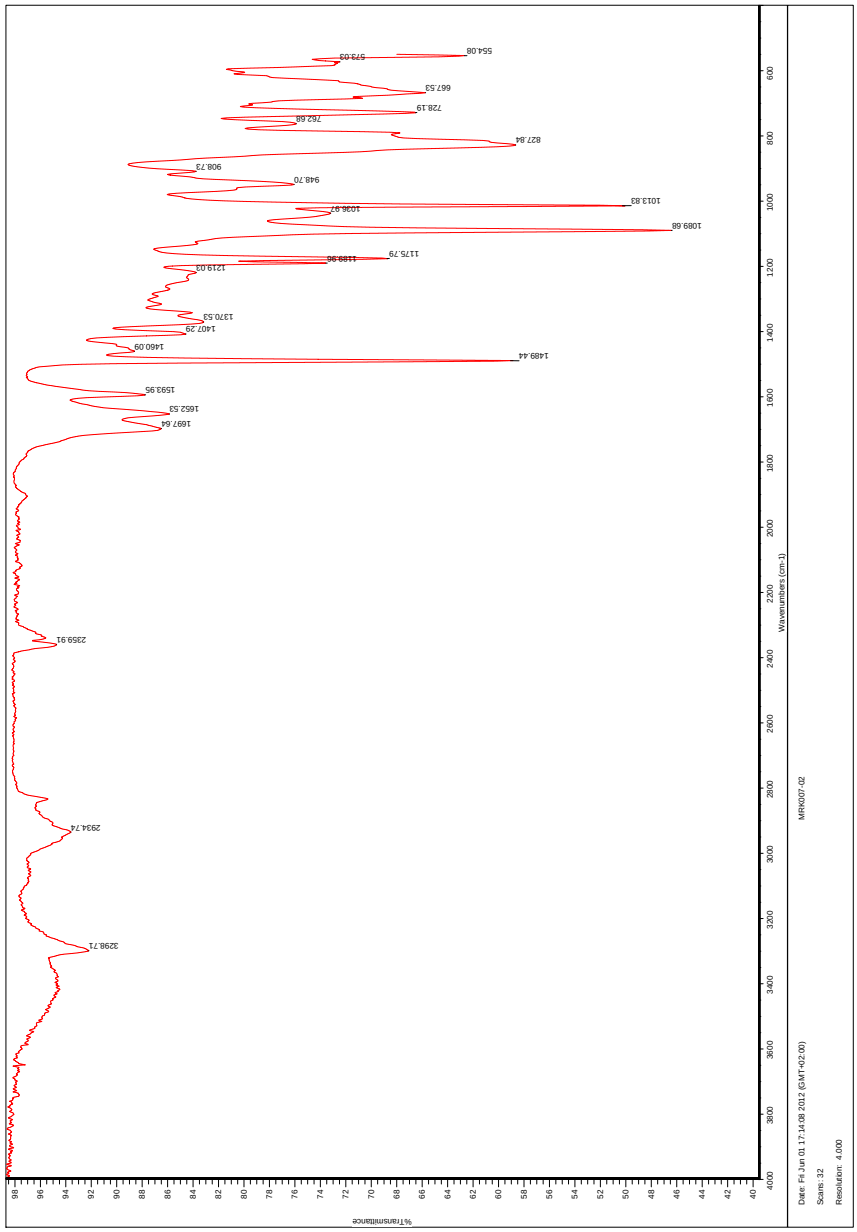
P.5 HMBC of bicyclic compound 26



P.6 NOESY of bicyclic compound 26

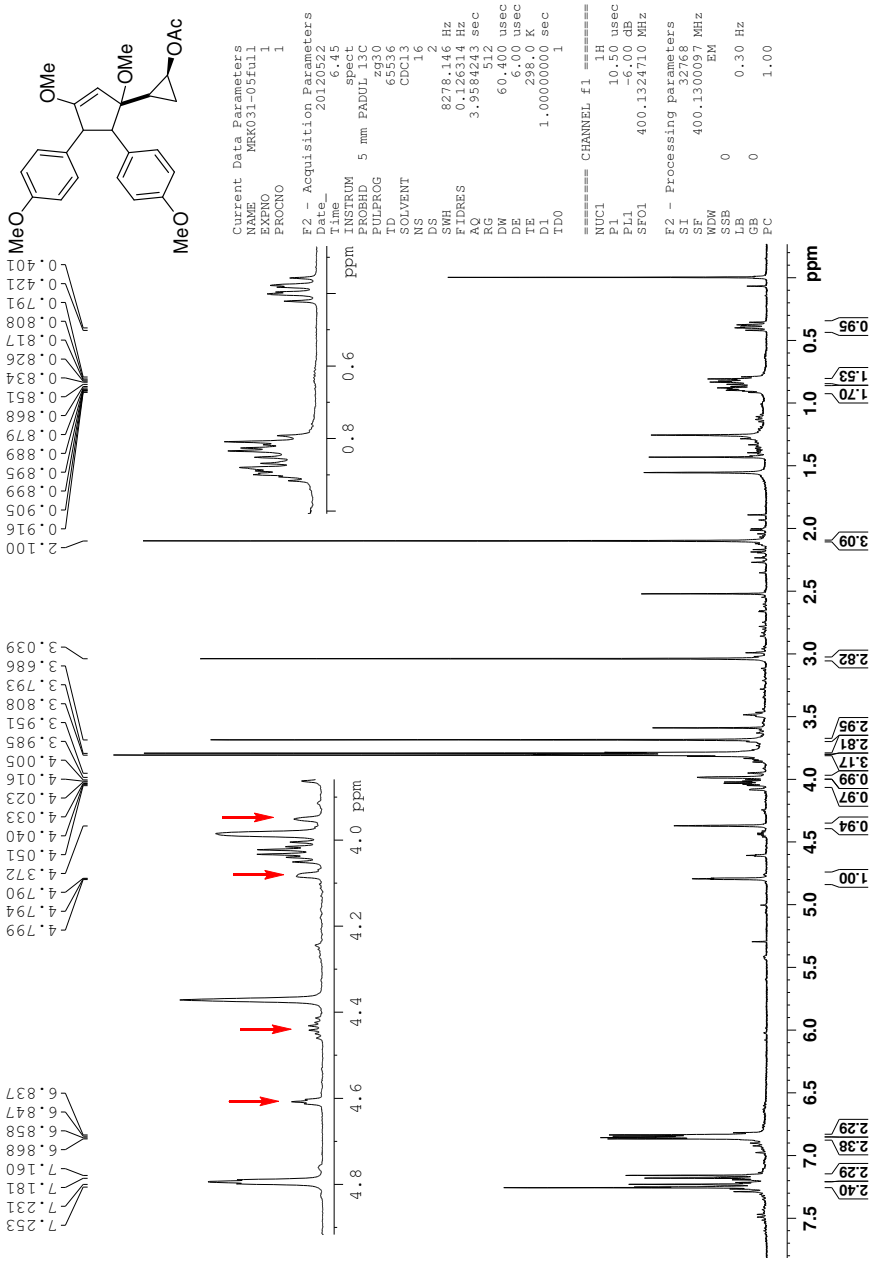


P.7 IR of bicyclic compound 26

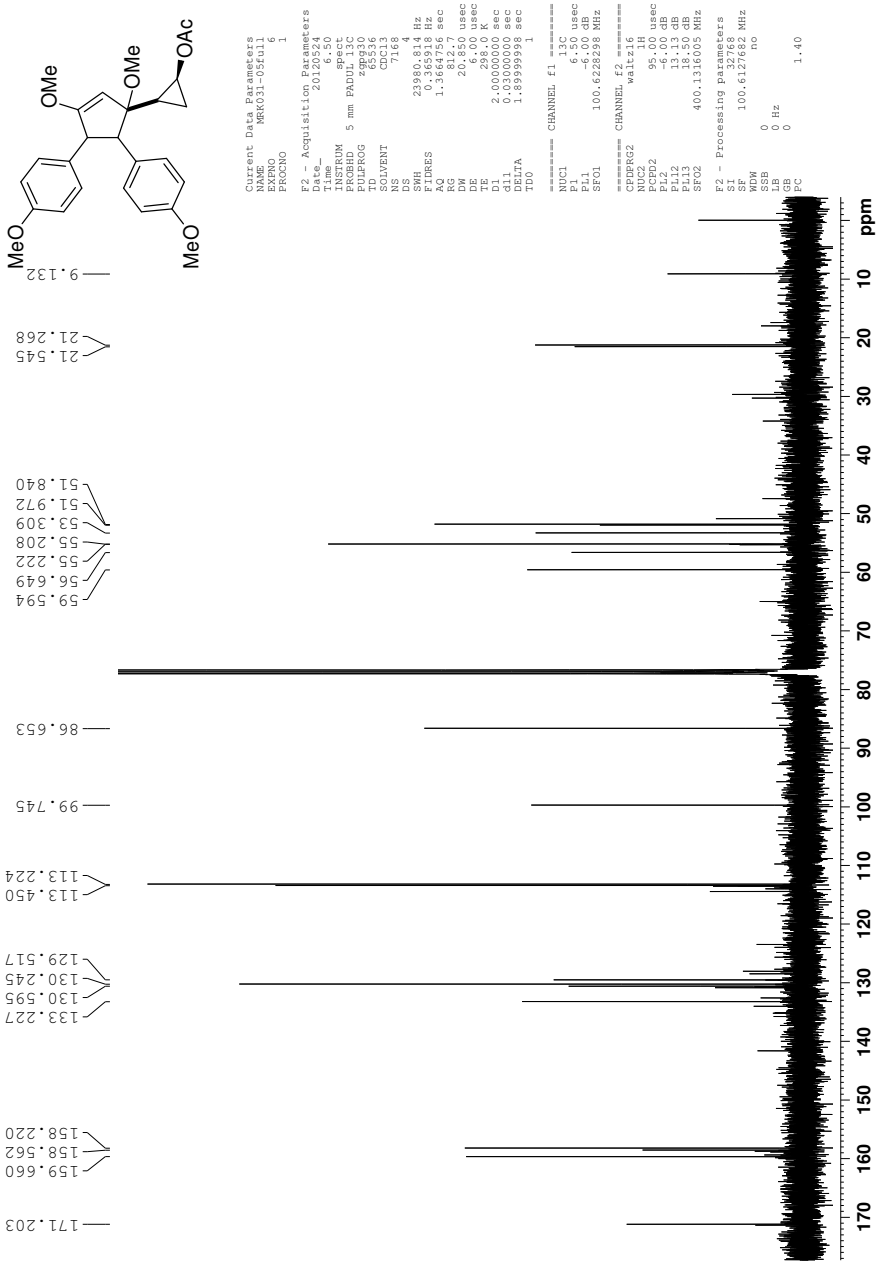


Q Bicyclic compound 27

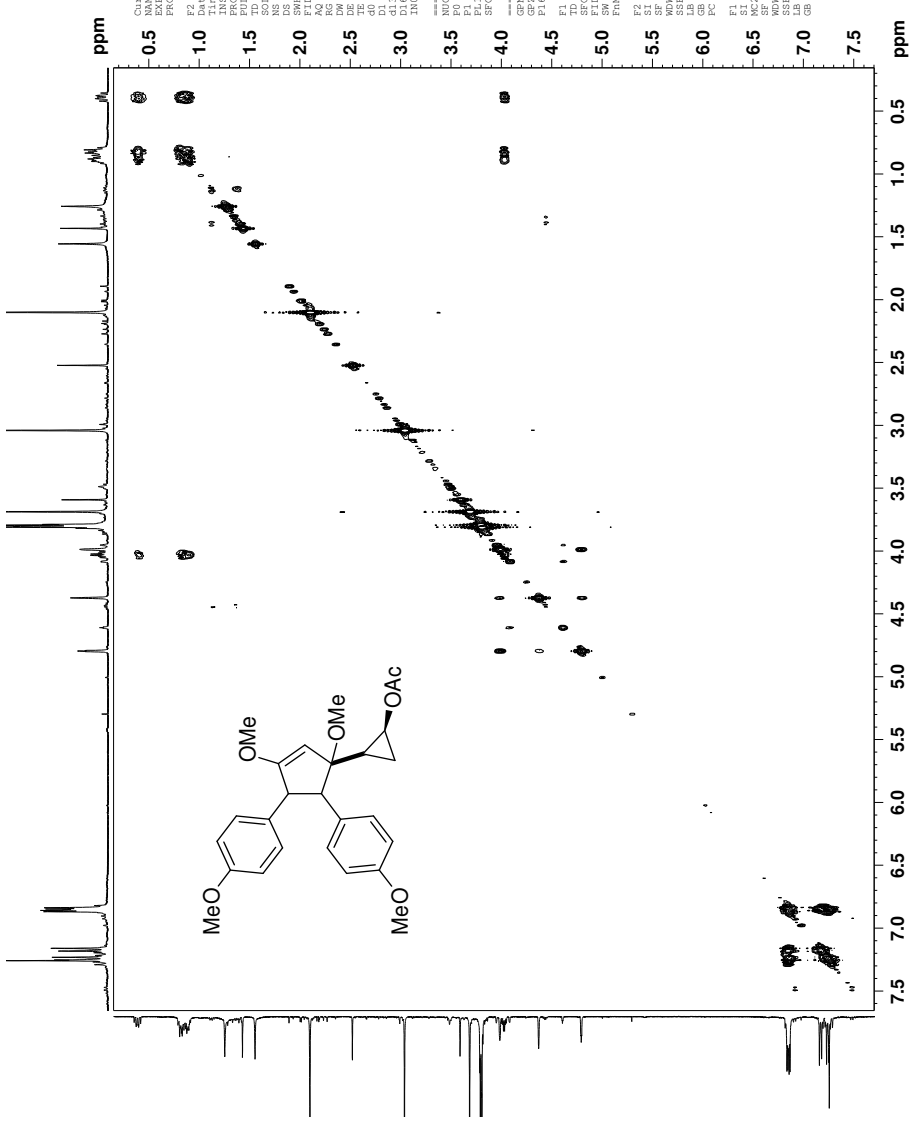
Q.1 ^{1}H NMR of bicyclic compound 27



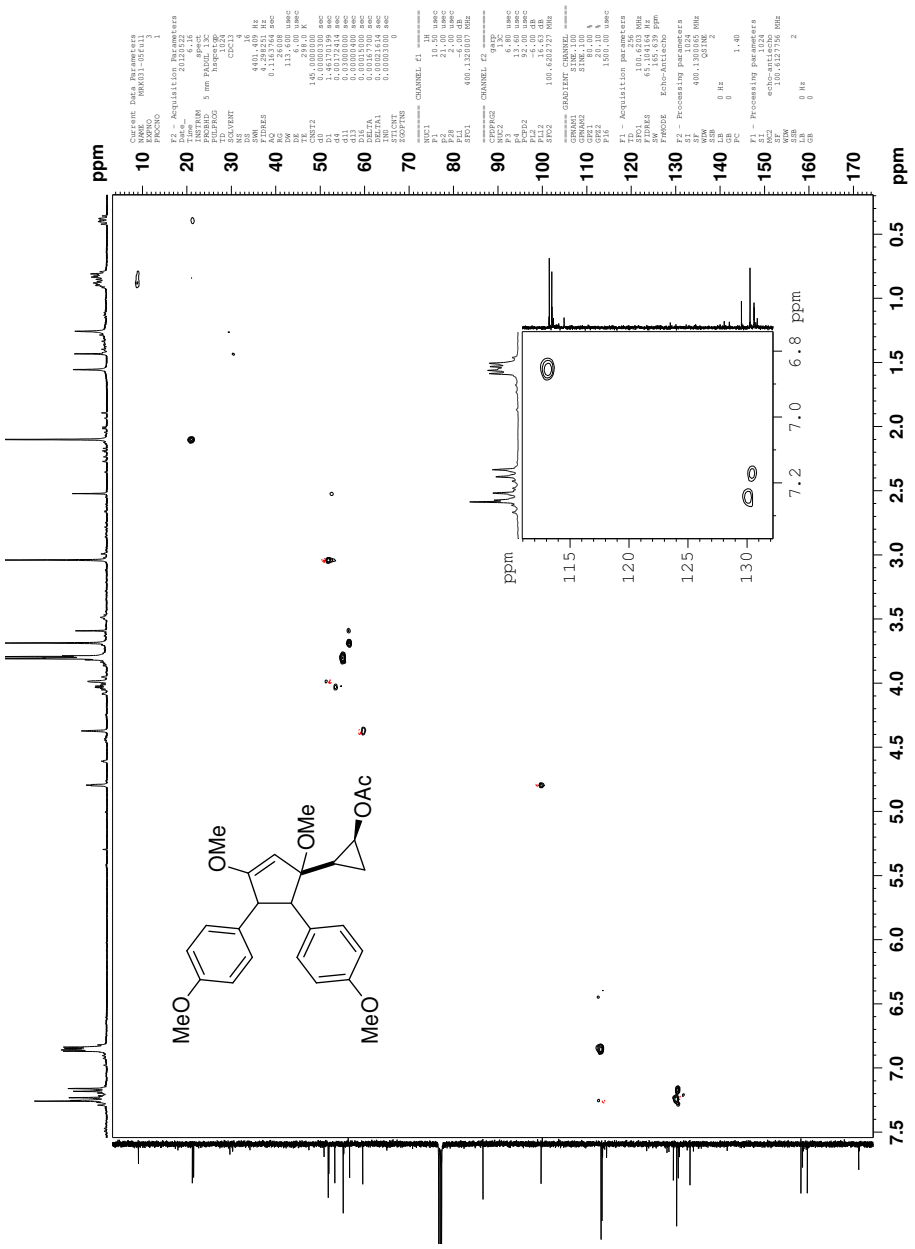
Q.2 ^{13}C NMR of bicyclic compound 27



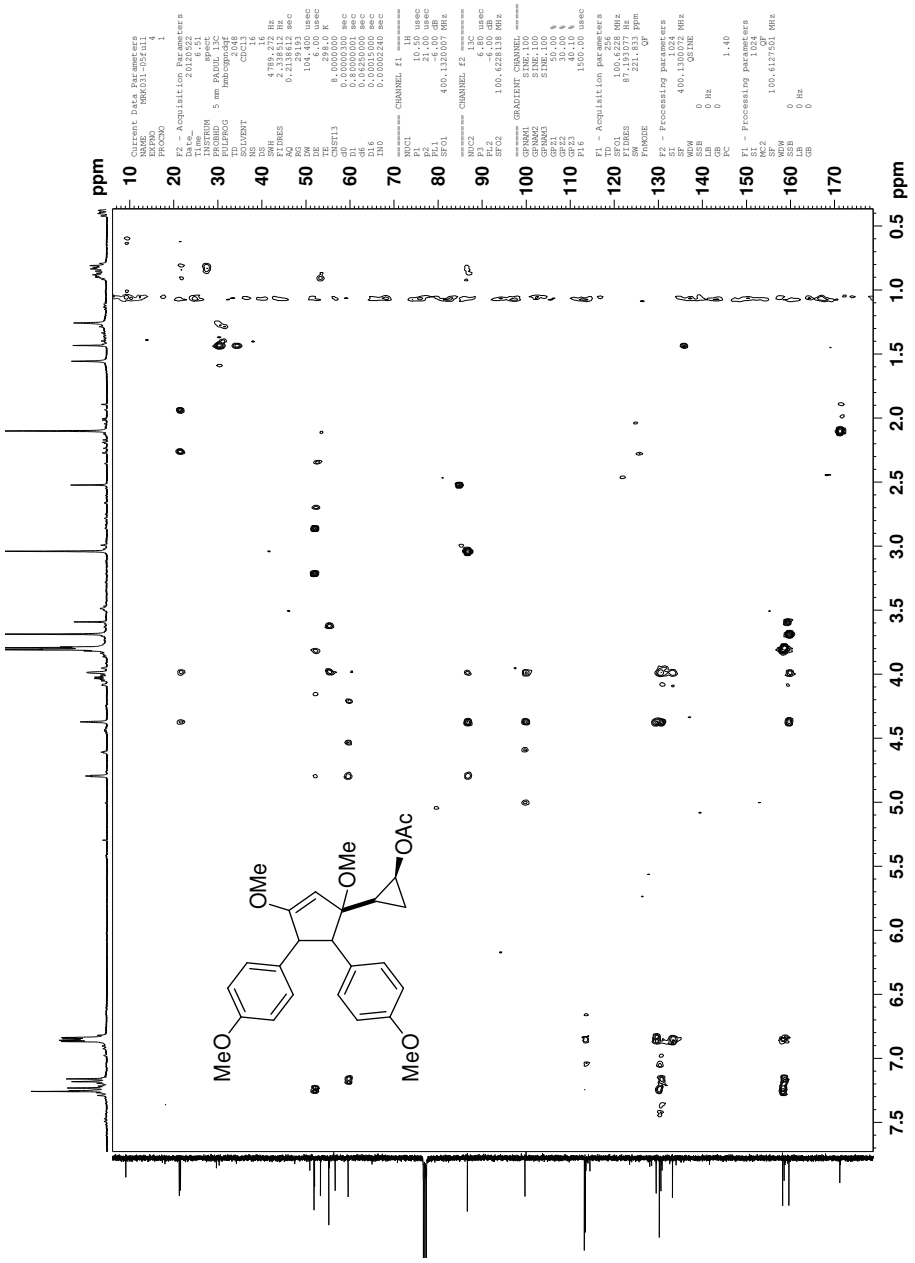
Q.3 COSY of bicyclic compound 27



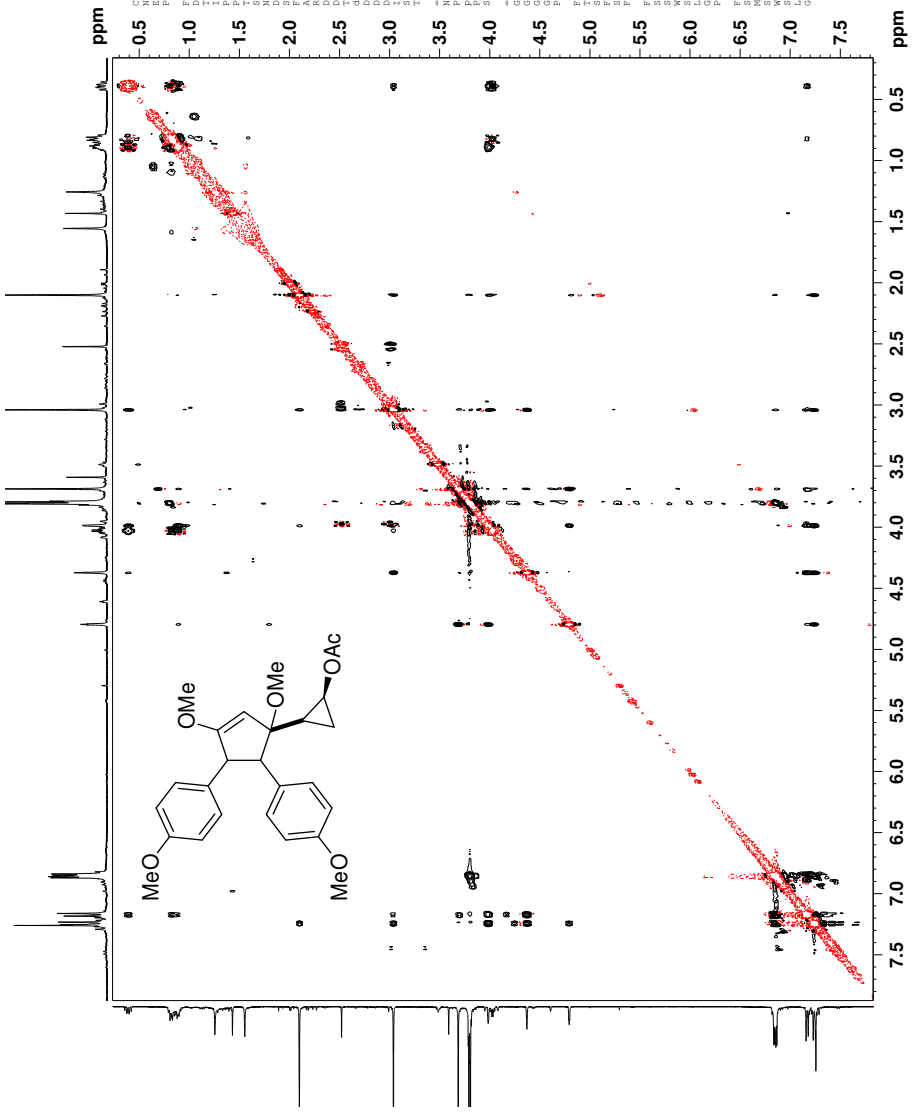
Q.4 HSQC of bicyclic compound 27



Q.5 HMBC of bicyclic compound 27



Q.6 NOESY of bicyclic compound 27



Q.7 IR of bicyclic compound 27