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New Synthetic Methodologies Directed toward Pharmacologically Active Compounds as well as Silole Based Chromophores for Analytical and Optoelectronic Applications

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Graduate Program in Chemistry
A thesis submitted in partial fulfillment of the requirements for the degree in Doctor of Philosophy

New Synthetic Methodologies Directed toward Pharmacologically Active Compounds as well as Silole Based Chromophores for Analytical and Optoelectronic Applications

(Spine title: Synthesis of Siloles, Azaindoles, Piperidines, and Tetrahydropyrans)

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by

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New Synthetic Methodologies Directed toward Pharmacologically Active Compounds as well as Silole Based Chromophores for Analytical and Optoelectronic Applications

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Abstract and Keywords

Abstract - The development of new and efficient synthetic methodologies to prepare heterocyclic compounds has received great attention over the years due to their importance in the pharmaceuticals and fine chemicals industries. Described herein are several novel syntheses of a variety of heterocycles including siloles, azaindoles, piperideines, piperidines and tetrahydropyrans.

A one-pot, two-step methodology involving Tamao's reductive cyclization followed by Negishi cross coupling was utilized to synthesize several new series of silole-based chromophores. The property studies revealed new electropolymerized poly(thienyl-silole)s with enhanced photoefficiency for all-polymer solar cells. In addition, a new procedure is developed for the synthesis of the first dissymmetric silole tethered to amine functionality. The synthesized compounds hold great promise in the arena of biosensors and solar cell applications.

Furthermore, a novel and practical two step sequence for the preparation of C2 substituted 5-azaindoles has been reported. The synthetic sequence features a [3+2] dipolar cycloaddition between nitriles and a 3,4-cyclopropanopiperidine followed by SeO_2 oxidation.

Finally, the annulation reaction between 2-alkoxy-1,1-cyclobutane diesters and imines or aldehydes gave access to highly functionalized piperidines and tetrahydropyrans, respectively. Both the synthesis of those donor-acceptor cyclobutanes and their subsequent annulations are catalyzed by catalytic $Yb(OTf)_3$. Although known for more than two decades, this is the first use of 2-alkoxy-1,1-cyclobutane diesters in

dipolar cycloadditions.

The new reactions are done under mild conditions providing the target compounds in high yields and excellent selectivity. The divergent nature and cost effectiveness of these methods make them very suitable for combinatorial applications in the pharmaceutical industry.

Keywords: Heterocyclic Compounds, Siloles, Azaindoles, Piperidines, Piperideines, Tetrahydropyrans, Cyclopropanes, Cyclobutanes, Electrochemiluminescence, Solar Cells, Dipolar Cycloaddition, Lewis Acid Catalysis, New Synthetic Methodologies

I kneel humbly to ALLAH thanking HIM for showing me the right path, without HIS help my efforts would have gone astray.

"My Lord! Grant me the power and ability that I may be grateful for Your Favours which You have bestowed on me and on my parents, and that I may do righteous good deeds that will please You, and admit me by Your Mercy among Your righteous slaves."

[The Holy Quran 27:19]

This work is dedicated to the 2011 Egyptian revolution (Revolution of 25th January): To the people who sacrificed their souls for dignity, freedom and justice for all Egyptians!

Acknowledgements

It has been a difficult road and I would not have been able to reach this current stage of life without the love and the continuous support from my wife, family and friends. First of all, I would like to thank my loving wife. It is your wisdom, encouragement and support that helped me tremendously in all of my life struggles. I am truly fortunate to have a partner like you. Special thanks also to my mother, my brothers and my sons: You have always stood behind me and for that I am truly grateful. I would also dedicate this thesis to the memory of my father and my mother-in-law.

I owe special thanks to my advisor Prof. Brian L. Pagenkopf for allowing me to join his group and giving me the chance to work on many interesting research projects. Brian, we barely had time to talk about anything but my thesis work and I am really indebted to your guidance and support.

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I could not leave UWO without mentioning the support staff. What would the department of chemistry be like without your ironical remarks? Special thanks to: Dr. Mathew Willans (NMR), Dr. Guerman Popov (X-Ray), Mr. Warren Lindsay (Departmental Manager), Mr. Barakat Misk (Electronics Shop), Mr. Doug Hairsine (Mass Spec) and Mrs. Darlene McDonald (Graduate Secretary).

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List of Abbreviations

Å	Ångstrom
A	acceptor
ann.	annulation
Bn	benzyl
br.	broad
BT	bithiophene
PBT	polybithiophene
*t*Bu	*tert*-butyl
CVs	cyclic voltammograms
Cp	cyclopentadienyl
$Cu(TBS)_2$	bis(*N*-tertbutylsalicylamidinato)copper(II)
D	donor
d	doublet
dd	doublet of a doublet
DA	donor-acceptor
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DHP	dihydropyran
DMSO	dimethylsulfoxide
DPA	9,10-Diphenylanthracene
ECL	electrochemiluminescence
eV	electron volt
E	unspecified electrophile
ET	electron-transporting
EtOAc	ethyl acetate
*n*Hex	*n*-hexyl
HMDS	hexamethyldisilazane
HOMO	Highest Occupied Molecular Orbital
HRMS	high resolution mass spectrometry
Hz.	Hertz
kcal/mol	kilocalorie / mole
LA	Lewis Acid
LiNaph	lithium naphthalene
LUMO	Lowest Unoccupied Molecular Orbital
λ_{max}	wave length maxima
m	multiplet
MS	molecular sieves
NBS	*N*-bromosuccinimide
NCP	*N*-chlorophthalimide
nm	nanometer
NMR	nuclear magnetic resonance
NOE	*Nuclear Overhauser enhancement*
Nu	unspecified nucleophile
Ox.	oxidation

PL	photoluminescence
ppm	parts per million
*i*Pr	isopropyl
q	quartet
QE	Quantum Efficiency
R_f	retention factor
rt	room temperature
ss-DNA	single strand- deoxyribonucleic acid
s	singlet
t	triplet
temp	temprature
Tf, triflate	trifluoromethanesulfonate
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSOTf	trimethylsilyl trifluoromethanesulfonate
Ts	*p*-toluenesulfonyl (tosyl)
TsOH	*p*-toluenesulfonic acid monohydrate
UV-Vis	Ultraviolet-Visible

Chapter 1: Structural Tuning of Siloles: Synthesis and Electrochemiluminescence of New Silole Based Chromophores for Analytical and Optoelectronic Application

This chapter describes the work done in our research group towards the development of silole-based materials for applications in biological sensors and photoelectronic devices. In addition to a short introduction on the fundamentals of electrochemiluminescence (ECL), a brief literature review on the chemistry and properties of siloles will be discussed. I acknowledge Mrs. Barbora Morra for synthesizing silole **1.16b**. Otherwise, in addition to proposing a modified synthesis of the dissymmetric siloles **1.36**, the whole synthetic work presented in this chapter was done by me. Since fully investigating these new materials is highly interdisciplinary in nature, the Pagenkopf group has been collaborating with several research groups at the University of Western Ontario. The ECL and photoluminescence (PL) of the synthesized compounds have been investigated by the research group of Prof. Zhifeng Ding. The electro polymerization behavior for solar cell applications was studied by Prof. Oleg A. Semenikhin's research group. While not intended to be exhaustive, a section summarizing the results obtained by our collaborators will be included. Some of these results have been published in *J. Phys. Chem. B*.[1]

1.1. Introduction

1.1.1. Basics of Electrochemiluminescence (ECL)

Electrochemiluminescence (ECL) or electrogenerated chemiluminescence as the word implies is the light emission from an exited state molecule that is produced due to a high-energy electron transfer (ET) reaction between electrogenerated radical anions and cations. According to the method involved, ECL could be annihilation or a co-reactant

process.[2] A schematic representation of annihilation ECL is given in **Figure 1.1**. In a typical process, the radical anions ($R^{-\bullet}$) and radical cations ($R^{+\bullet}$) of the luminophore (R) are produced during a sequential reduction and oxidation at the surface of an electrode by scanning (scanning ECL) or pulsing (pulsing ECL) the potential within a short time interval. The annihilation reaction between these ions provides the excited state (R^*) as well as a ground state molecule. The energy is then released in the form of light when R^* returns to the ground state (R).[2] An alternative way to obtain intense ECL is through a co-reactant process where another substance is used to produce strong reducing or oxidizing intermediates that can interact with the radical ions of the emitter ($R^{-\bullet}$ or $R^{+\bullet}$) to generate its excited state (R^*). Commonly used co-reactants are tri-*n*-propylamine and benzoyl peroxide.[2]

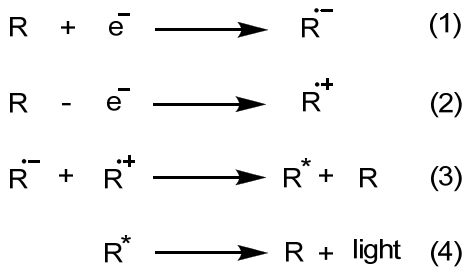


Figure 1.1 – General mechanism of annihilation ECL

Over the last decade, ECL has been extensively investigated and has found a variety of commercial applications in biomedical diagnostics (e.g. immunoassays), pharmaceutical and environmental analyses.[3] The development of ECL-based systems with high sensitivity, selectivity and quantum efficiency has expanded the research interest in designing new luminophores. The new material should be cheap and/or easily prepared. In addition, the radical ions should be easily produced under the ECL

conditions and are of sufficient stability to allow for the inter diffusion process.[2] The first attempt to study the ECL properties of siloles was reported by Pagenkopf and Bard in 2006.[4]

1.1.2. Siloles as Novel Materials for Optoelectronic Applications

The chemistry of siloles has continued to receive much attention with respect to their syntheses and properties.[5] Of special note is the recent and remarkable progress of siloles containing π-conjugated systems due to their potential as conducting materials for novel applications such as light-emitting devices,[6] nitroaromatic sensors[7] and biosensors.[8] The unique electronic features of the silole ring arise from its low-lying LUMO, which is substantially different from cyclopentadiene and other heterocycles (**Figure 1.2)**.[9]

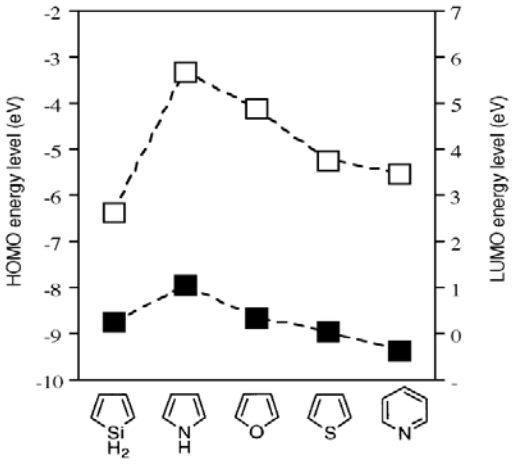


Figure 1.2 – Relative energy levels of HOMOs (white squares) and LUMOs (black squares) for silole vs. other heterocycles (from ref. 9)

Over the last decade, siloles have set themselves aside as fascinating electronic materials. However, in comparison to other related π-conjugated systems such as pyrroles and thiophenes, siloles remain relatively unexplored, partly because of their difficult

synthesis.[10] In addition to the meticulous exploration of silole properties, the pioneering efforts by the groups of Tamao and West to construct the silole ring have provided a solid foundation for others to build upon leading to the recent advancement of silole chemistry.[11]

In 1997, Barton's group utilized a dibromo silole **1.1**,[11] to synthesize the silole-acetylene polymers **1.2** (**Figure 1.3**).[12] When compared to the corresponding poly(phenyleneethynylene)s (λ_{max} = 425 nm),[13] and poly (thiopheneethynylene)s (λ_{max} = 438 nm,[14] the silole-containing polymers significantly showed red-shifted absorptions (λ_{max} = 494 nm) implicating the importance of the silole ring in the properties of these substances.

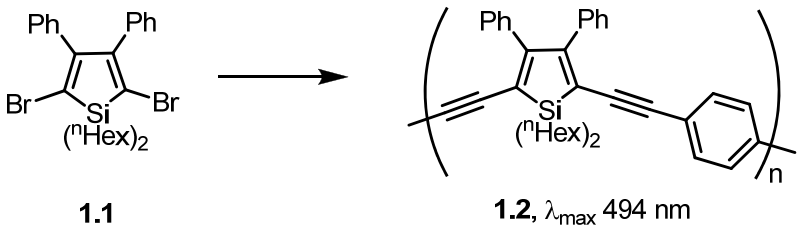


Figure 1.3 – Absorption data for polymer **1.2** in THF

In 1998, Tamao and co-workers reported a series of 2,5-diethynylsilole monomers and their polymerized products (e.g. **1.3** and **1.4**, **Figure 1.4**).[15] The synthesized polymers significantly showed narrow bandgaps (up to 1.8 eV). Moreover, a bathochromic shift in the absorption spectrum was observed when a diethynylthiophene moiety was incorporated. Despite the unique electronic features of these novel materials, the conductivities of the synthesized polymers were found to be moderate.

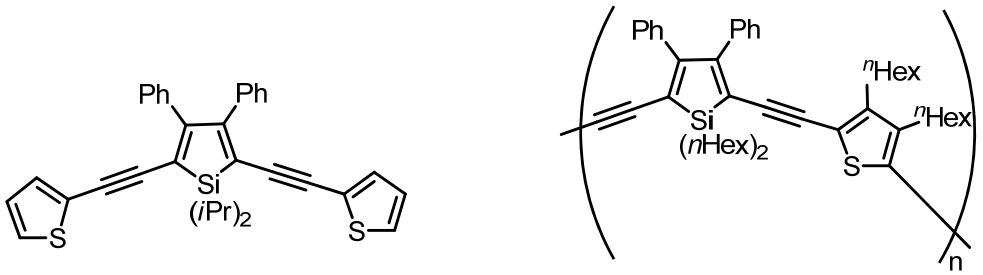


Figure 1.4 – Absorption data for polymers **1.4** in chloroform

In a subsequent study towards the development of efficient electron-transporting (ET) materials for organic devices, the Tamao's research group has prepared a symmetrically substituted series of 2,5-diaryl siloles **1.5-1.7** (**Figure 1.5**).[6d] In order to optimize the physical properties of the synthesized siloles, different substitution patterns have been investigated including; various mono-subtituted phenyl rings, extended π-conjugated and heteroaryl groups. Whereas compound **1.7** emerged as highly efficient fluorophores with potential application as emissive material, compound **1.6** showed high performance as a new ET material.

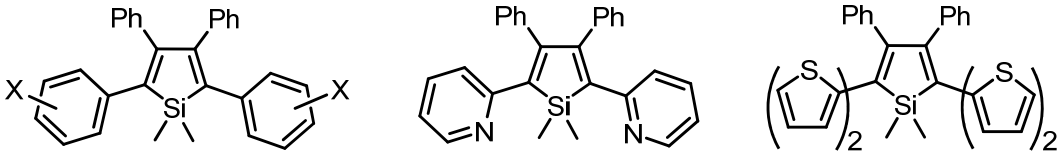


Figure 1.5 – Symmetric siloles **1.5-1.7**.

The ability to fine tune the electronic properties of siloles have been impeded by the challenges of synthesizing dissymmetric siloles and hence varying the functional groups at the silole termini.[16] In addition, the iterative and length-specific synthesis of

oligomeric silole requires a dissymmetric silole that can serve either as a starting point or an end cap.[17] In this regard, the dissymmetric silole **1.8** reported by the Pagenkopf research group in 2004 was used to synthesize the first silole-containing extended chromophores bearing electronically dissimilar functional groups at C(2) and C(5) **1.9** as well as oligomeric siloles of precise composition **1.10** (**Figure 1.6**).[16,17]

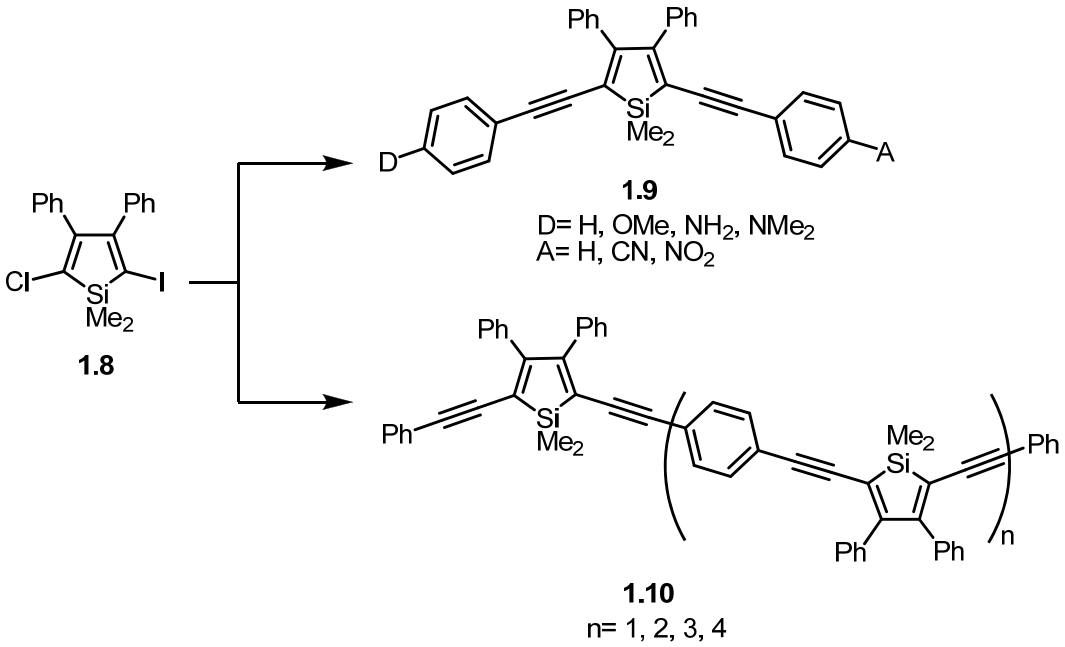
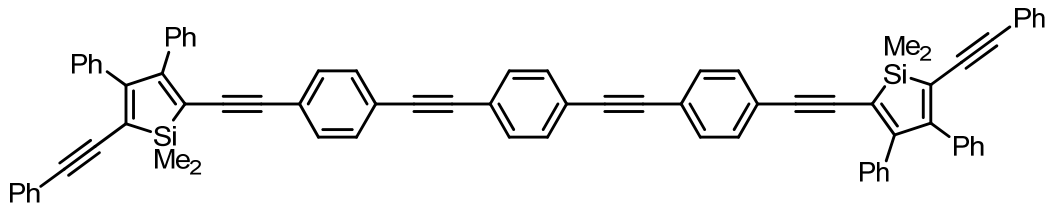


Figure 1.6 – Donor- acceptor dissymmetric siloles **1.9** and oligomeric siloles **1.10**

The electronic spectra of donor-aceptor (DA) siloles **1.9** showed a stepwise bathochromic shift ranging from 429 nm (parent silole; D = A = H) to 496 nm (the most polar silole; D = NMe_2 & A = NO_2) (**Figure 1.6**).[16] This study indicated the important role of electron delocalization in these substances which can be fine tuned by manipulation of peripheral push-pull substituents at the C(2) and C(5) positions. The consequences of varying the nature of the DA groups were also observed in the PL spectra. The silole having OCH_3 as a donor group and NO_2 as an acceptor group

displayed the longest wavelength emission, at 649 nm (**Figure 1.6**). To the best of our knowledge, this is the longest wavelength emission for a compound possessing only a single silole in the chromophore.[16] On the other hand, the relatively low molecular weight oligomers **1.10** (**Figure 1.6**) displayed a similar absorption maximum (492 nm) to the analogous high molecular weight silole-containing polymers **1.2** (494 nm). From these observations, the effective conjugation length within the corresponding silole polymers was established for the first time and it is approximately equal to that of the tetramer **1.10** (**Figure 1.6,** n = 3). Unfortunately, the quantum efficiencies were modest with the monomer being the most efficient.[17]

In order to examine the influence of a single silole ring on the properties of an extended chromophore, the Pagenkopf group synthesized silole **1.11** (**Figure 1.7**) for direct comparison the trimer silole **1.10** (**Figure 1.6**, n = 2). The absorption and emission maxima of **1.11** were blue-shifted relative to trimer **1.10**, but interestingly the quantum efficiency was 20.11×10^{-2} in the case of **1.11** versus 0.37×10^{-2} for trimer **1.10**.[17]

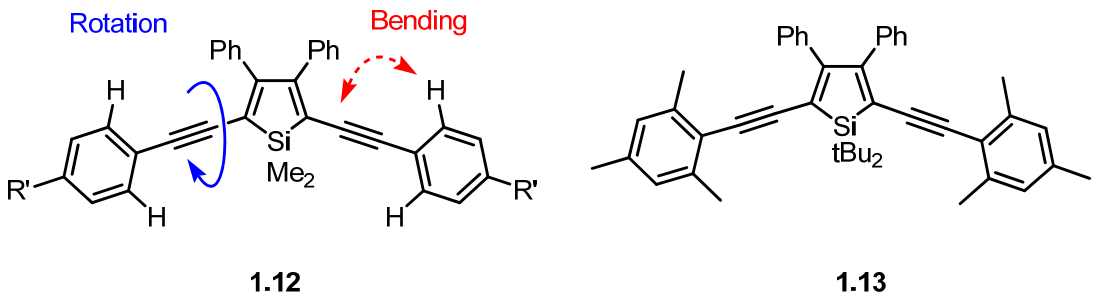


1.11

Figure 1.7 – Extended chromophore **1.11**

In addition to C2 and C5 functionalization, manipulating the steric requirements of the silole ring substituents would increase the energy barriers for non-emissive decay

processes and ultimately result in increased PL efficiency. Thus, our group also investigated some silole modifications intended to impart "rigidity" or restricted rotation compared to the parent chromophore **1.12** (**Figure 1.8)**.[18] The outcome of this effort was the preparation of the first highly efficient 3,4-diphenylsilole fluorophore **1.13**, having a quantum efficiency of 63% (determined with reference to fluorescein).[18] When compared to **1.12 (**quantum efficiency is 9%),[16] this pioneering discovery welcomed siloles as promising structurally tunable fluorophores and unambiguously refuted the notion that all 3,4-disubstituted siloles will possess intrinsically low quantum efficiencies. Therefore, the electrogenerated chemiluminescence (ECL) properties were examined. However, moderate ECL quantum yields were obtained.[4] This might be attributed to instability of their radical cations needed for ECL generation.[2]

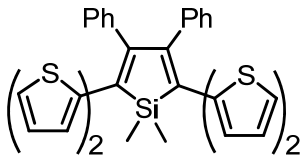


1.12 **1.13**

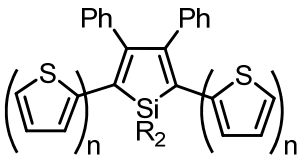
Figure 1.8 – Sterically rigid, highly fluorescent silole **1.13**. I acknowledge Dr. Pagenkopf for generating graphic **1.12**

Considering that siloles **1.7** are efficient electron transporting materials, we expected that replacement of the methyl substituents with larger *i*Pr, *t*Bu and *n*Hex groups would increase the energy barriers for non-emissive decay, stabilize the radical anions, and thus result in enhanced PL and ECL. Therefore the target chromophores **1.14** were prepared and the electronic properties (UV-Vis, PL, and ECL) of these new hybrids

were investigated (**Figure 1.9**).[19] In general, easier and reversible oxidation was observed with extended conjugation (n = 2) and branched substituents on the silicon (R = *i*Pr or *t*Bu). In addition, cyclic voltammograms (CVs) showed that the radical cations are more stable than the anions. This was translated into enhanced ECL efficiency highlighting the potential applications of these siloles.[19]



1.7

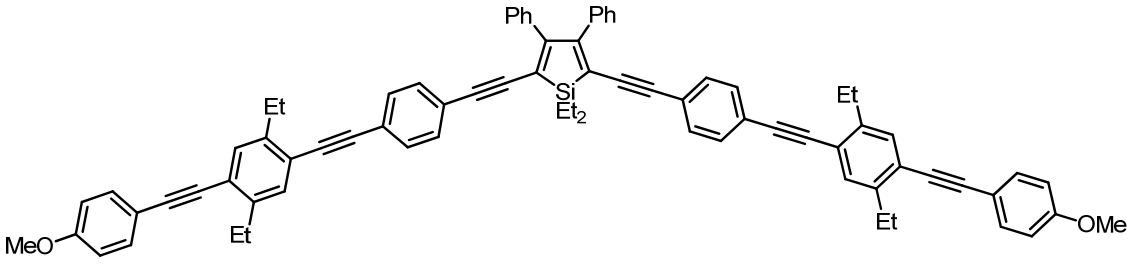


1.14

n = 1, 2
R = *t*Bu, *i*Pr, *n*Hex

Figure 1.9 – Thiophene-silole hybrids

Finally, a new series of 3,4-diphenylsiloles incorporating arylene ethynylene strands at the 2,5-positions (e.g. **1.15**, **Figure 1.10**) have been reported by Ding *et al*. in 2007.[20] The respective photoluminescence properties were investigated as a function of chain length. When compared to our silole **1.13** (quantum efficiency is 20%), double incorporation of arylene ethynylene strands in **1.15** (quantum efficiency is 50%) was found to be effective for enhancing the photoluminescence.[20]



1.15

Figure 1.10 – Arylene ethynylene/ silole hybrid

1.1.3. Research Objectives

Development of silole chromophores bearing fine-tuned properties depends on the ability to control the electronic nature of the molecule by varying the silole at the 2 and 5-termini, substitution on the silicon atom as well as the conjugated system. Considering the unique features of siloles **1.5 – 1.6**,[6d] including narrow energy gap, high conductivity, long emissive life time and high thermal stability, the objective of this study is to fine-tune the properties of those siloles for ECL-based biomedical applications and optoelectronic industries.

It was anticipated that enhanced PL and ECL could be obtained if the methyl substituents on the silicon atom of **1.5** and **1.6** are replaced by *n*-hexyl groups (**1.16** and **1.17**, **Figure 1.11**)**.** In addition to possible improved solubility, the bulky *n*-hexyl groups might increase the energy barriers for the non-emissive decay and hence stabilize the radical anions required for ECL annihilation. Furthermore, the effect of different electron donating and withdrawing groups on the one-electron transfer process involved and hence the electronic properties of those siloles will be examined.

In collaboration with Prof. Zhifeng Ding's research group, we previously discovered that bithiophene-silole hybrid (**1.14**, n = 2) is a more efficient fluorophore than thiophene-silole hybrid (**1.14**, n = 1).[19] Therefore, it was envisioned that siloles **1.18** with a more extended conjugation (terthiophene) will have lower redox potentials and hence the radical ions will be easily generated. Ultimately, better ECL efficiency is anticipated for **1.18**.

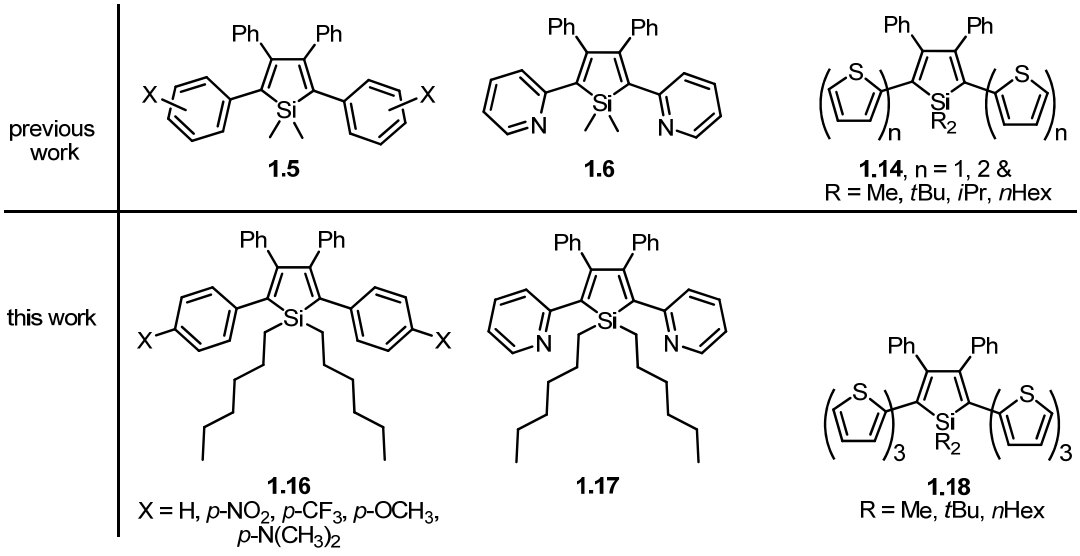


Figure 1.11 – Target Siloles **1.16**, **1.17** and **1.18**

The ultimate objective of this research project is to develop an efficient fluorophore for analytical applications in clinical and biomedical diagnostics. An essential requirement for ECL-based analytical methods is that these siloles should have one binding-site through which the important biological molecules, such as single stranded DNA (ss-DNA), antibody and/or oligonucleotide, could be conjugated via efficient and practical routes, such as a click reaction (**Figure 1.12,** A),[21] or amide formation (**Figure 1.12,** B).[22]

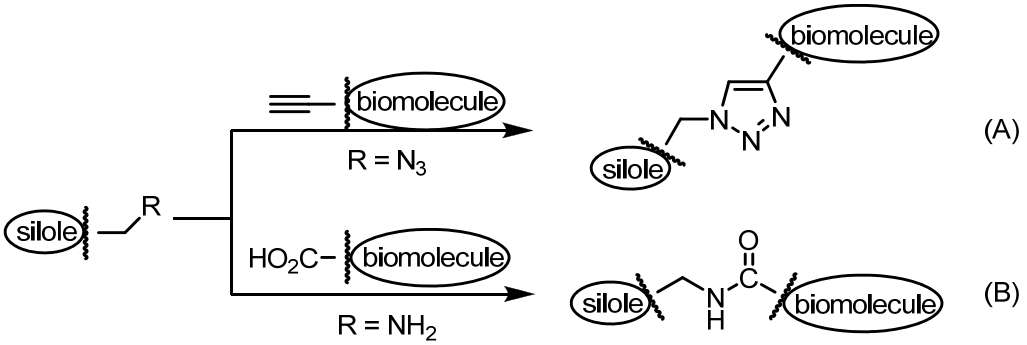


Figure 1.12 – Silole-labeled biosensors

This study will pursue an efficient methodology to prepare dissymmetric siloles by installing NH_2 and/or N_3 on one side of the ring (**Figure 1.13**).

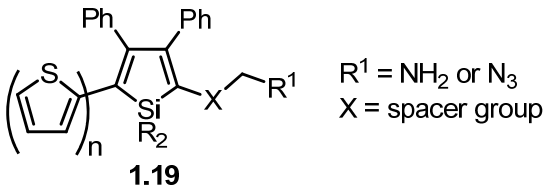


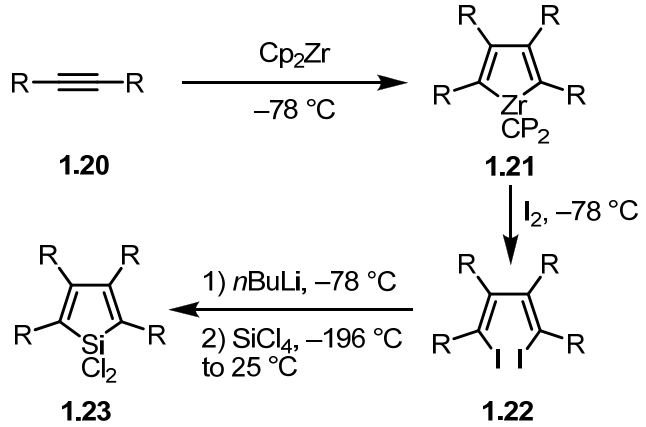
Figure 1.13 – Target dissymmetric siloles

It is believed that these new silole-based materials will find a wide variety of applications in biomedical and optoelectronic industries (e.g. biosensors and solar cells). The synthetic effort toward these silole targets will be discussed in the following section.

1.2. Results and Discussions

1.2.1. Synthesis of Symmetric Siloles 1.16 – 1.18

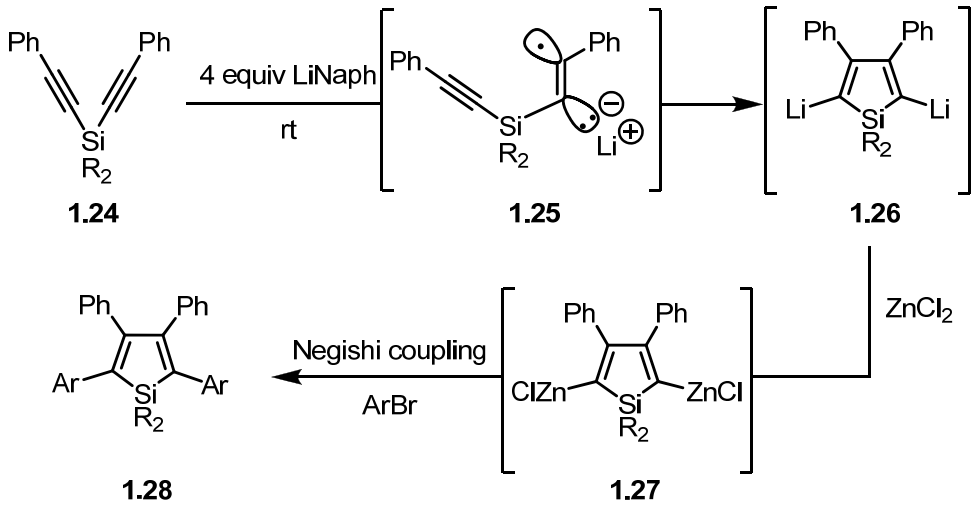
The silole ring can be obtained via a zirconocene mediated reductive cyclization of acetylenes (**Scheme 1.1**).[23]



Scheme 1.1 – Zirconocene mediated reductive cyclization of acetylenes.

However direct transmetallation from zirconium to silicon is generally ineffective and therefore a series of steps involving iodination, lithiation and electrophilic trapping sequences have been developed (**Scheme 1.1**).[23]

Developed by Tamao in 1994, the intramolecular reductive cyclization of diethynylsilanes utilizing lithium naphthalene (LiNaph) enables a one pot, practical and cost effective synthesis of siloles (**Scheme 1.2**).[11]

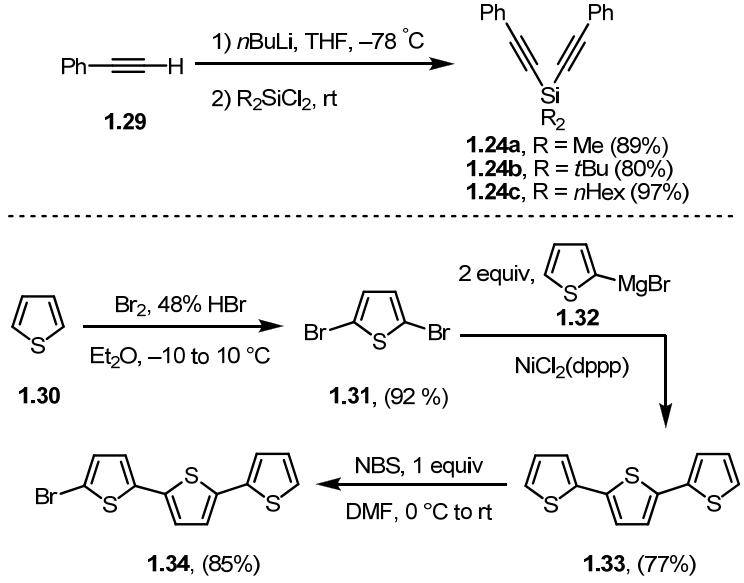


Scheme 1.2 – Tamao's reductive cyclization/transmetallation/Negishi coupling one pot synthesis of siloles

The key point to attain high yield is the dropwise addition of the diethynylsilane **1.24** into an electron-pool consisting of an excess amount (4 equiv) of the reductant LiNaph, and thereby both acetylene moieties are reduced simultaneously to form an anion radical intermediate **1.25** that undergoes radical coupling to form the 3,4-carbon–carbon bond, leaving anions at the 2,5-positions. The resulting 2,5-dilithiosiloles **1.26** can be transmetallated using excess $ZnCl_2$. In addition to serving as an oxidizing agent for residual LiNaph,[16] the use of $ZnCl_2$ at this step allows for *in situ* generation of the

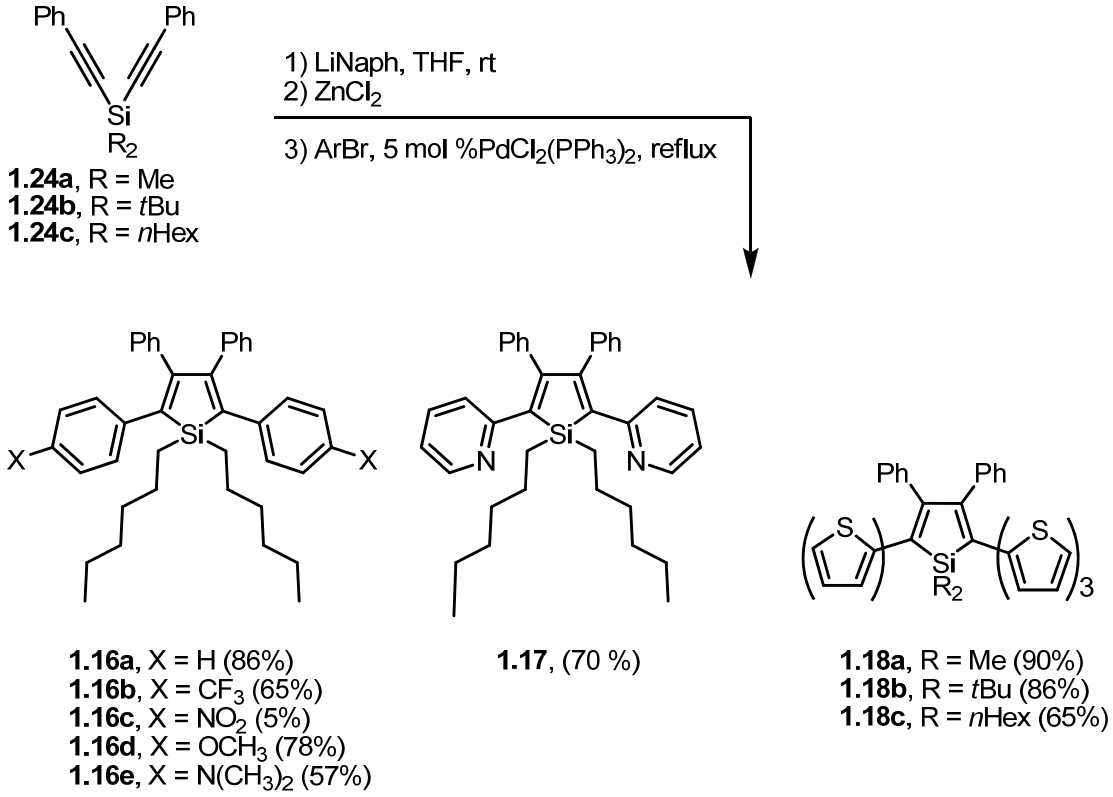
versatile chlorozinc intermediate that can be used directly for a Negishi cross coupling reaction with different aryl halides.[24] Furthermore, when compared to the dilithio-silole, the chlorozinc intermediate **1.27** is considerably less basic and less nucleophilic.[16] Therefore, a one pot, two step methodology involving Tamao's reductive cyclization followed by Negishi cross-coupling strategy was utilized to achieve the target compounds **1.16** – **1.18**.

Starting from the commercially available phenylacetylene **1.29** and thiophene **1.30**, the synthetic intermediates; bis(phenylethynyl)dialkylsilanes **1.24a-c** and bromoterthiophene **1.34** were prepared according to the published procedures and obtained in good to excellent yields (**Scheme 1.3**).[25] Extra care should be followed during the preparation of terthiophene due its high vapour pressure and phototoxicity.[25c]



Scheme 1.3 – Synthesis of the starting materials. **1.24c** was kindly provided by Mr. Xin (Kevin) Wang, a previous student in our group.

The intramolecular reductive cyclization of bis(phenylethynyl)dialkylsilane **1.24a-c** using an excess amount (4 equiv) of LiNaph, followed by transmetallation with $ZnCl_2$ and treatment with different aryl halides in presence of $PdCl_2(PPh_3)_2$ catalyst provided compounds **1.16a-e**, **1.17** and **1.18a-c**, in moderate to good yields (**Scheme 1.4**). Since all intermediates involved in this methodology are sensitive to moisture, air and light, the whole reaction sequence was carried out under an inert atmosphere of dry argon, and protected from light using aluminum foil. Single crystals of silole **1.18b** were grown from a concentrated CH_2Cl_2 solution by slow diffusion of pentane. The x-ray structure was solved and the ORTEP is presented in **Figure 1.14**.



Scheme 1.4 – Synthesis of the target siloles **1.16** – **1.18**. **1.16b** was prepared by Mrs. Barbora Morra

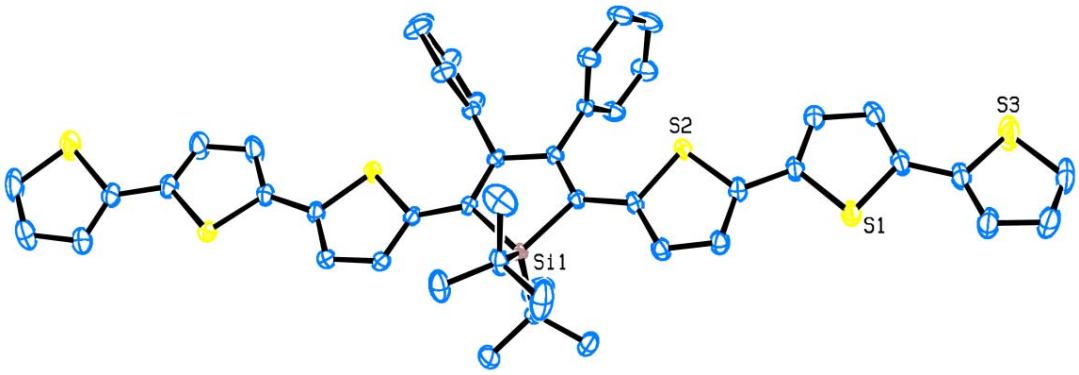
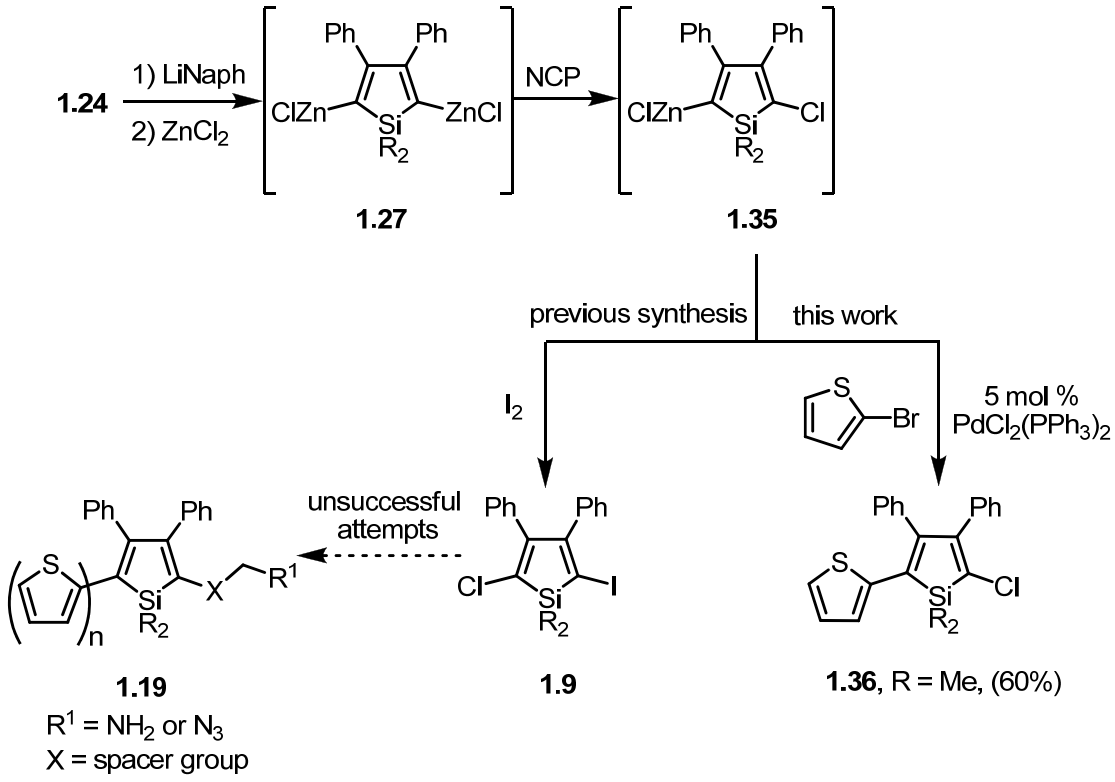


Figure 1.14 – X-ray crystal structure of **1.18b**

1.2.2. Synthesis of Dissymmetric Siloles 1.36 – 1.41

Considering the attenuated nucleophilicity of the chlorozinc intermediate **1.27** (**Scheme 1.5**), our group previously reported an efficient methodology to prepare the first dissymmetric silole series.[16] The methodology involved a two step halogenation where a slow monochlorination using *N*-chlorophthalimide (NCP) followed by iodination with I_2 afforded the chloroiodosilole **1.9** (**Scheme 1.5**).[16] Although the synthesis of the intermediate **1.9** was a milestone step for us, working with this silole is complicated by its high light sensitivity and instability. Because it decomposes within minutes from isolation, it should be used directly for the successive cross coupling reactions.

Much of experimental effort has been dedicated over the years by our group to synthesize the target silole **1.19** utilizing the synthetic intermediate **1.9** however with no success (**Scheme 1.5**). In fact it was quite a challenging task.



Scheme 1.5 – Synthesis of dissymmetric silole **1.36**

To simplify the reaction sequence and to isolate a stable product; instead of treating with iodine, the chlorozinc intermediate **1.35** was subjected directly to the cross coupling reaction conditions with bromothiophene. By following this modified procedure, the versatile monochloro thiophene-silole hybrid **1.36** was isolated in 60% yield (**Scheme 1.5**). When compared to the iodochlorosilole **1.9**, the monochlorosilole **1.36** is very stable and crystalline solid that can be stored for extended periods of time without any decomposition. Single crystals of silole **1.36** were grown from a concentrated CH_2Cl_2 solution by slow diffusion of pentane. The x-ray structure was solved and the ORTEP is presented in **Figure 1.15**.

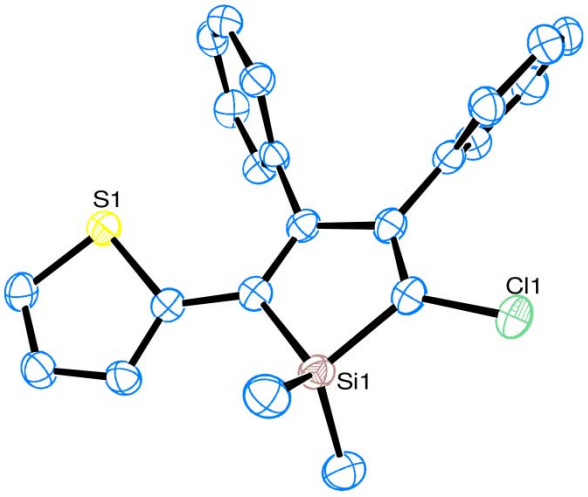
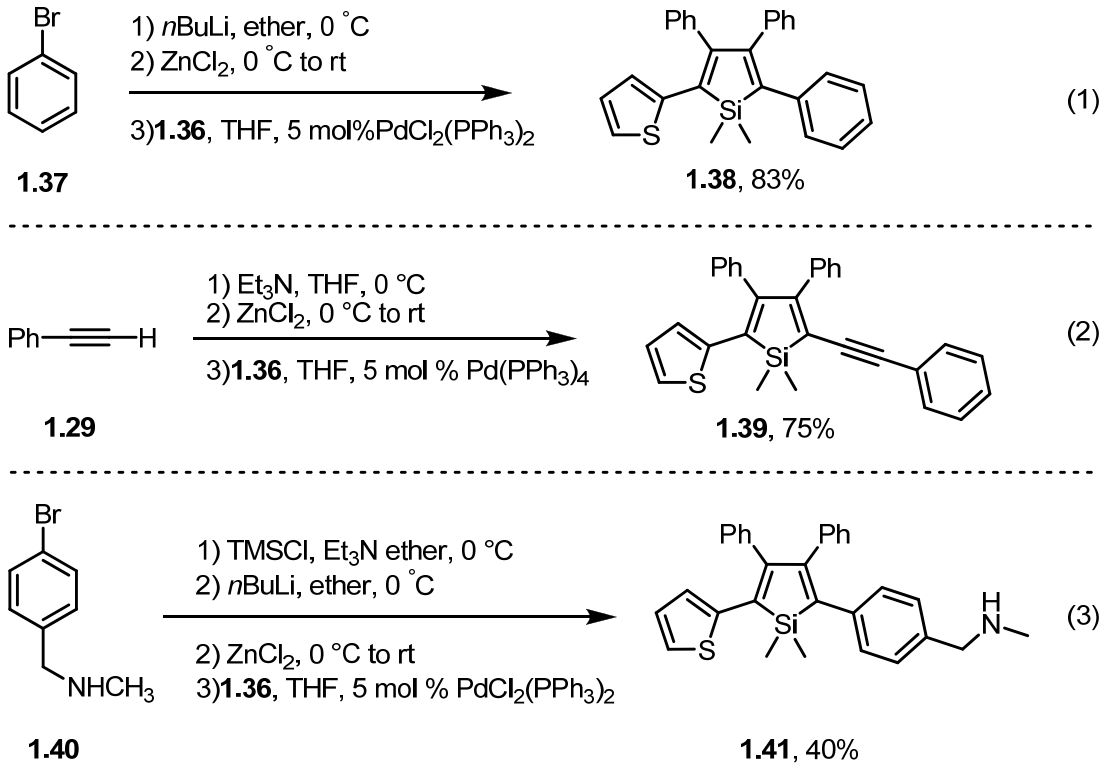


Figure 1.15 – X-ray structure of dissymmetric silole **1.36**

Having the chlorosilole **1.36** in hand, it was treated with the chlorozinc intermediates generated from bromobenzene **1.37** (**Scheme 1.6**, equation 1), phenyl acetylene **1.29** (**Scheme 1.6**, equation 2) and 1-(4-bromophenyl)-*N*-methylmethanamine **1.40** (**Scheme 1.6**, equation 3). The expected novel dissymmetric siloles **1.38**, **1.39** and **1.41** were obtained in moderate to excellent yields (**Scheme 1.6**). To avoid any harsh deprotection condition that might destroy the silole ring, a very labile protecting group trimethylsilyl (TMS) was selected to protect amine **1.40** during cross coupling reaction.[26] It was easily removed during the aqueous work-up to provide the free amine **1.41** required for conjugation with biomolecules.



Scheme 1.6 – Synthesis of dissymmetric siloles **1.38**, **1.39** and **1.41**

In summary, a one pot reaction sequence featuring Tamao's reductive cyclization, transmetallation and Negishi cross coupling reaction has been used to prepare a new series of structurally modified siloles with anticipated fine tuned properties. In addition, a new synthesis of dissymmetric siloles has been developed and applied efficiently to prepare the first dissymmetric silole tethered to amine functionality. Current synthetic efforts in our group are directed toward structural modification of the conjugated system, the substitution pattern on the silicon atom, the spacer group and the binding functionality. Due to the unique electronic properties of the silole ring, the synthesized compounds hold great promise in the arena of biosensors and optoelectronic industries. While not intended to be comprehensive, the following section summarizes the results obtained by our collaborative research groups.

1.3. Electronic Properties of Siloles 1.16 – 1.18

Studying the electronic properties of these synthetic siloles is one of the most important components in this project. It indicates not only the potential of these siloles for future applications, but also where the subsequent synthetic effort should go. Our group acknowledges the immense effort made by our collaborators. The UV-Vis absorption, photoluminescence (PL) and electrochemiluminescence (ECL) properties of siloles **1.16 – 1.17** were investigated by Prof. Zhifeng Ding's research group. The electro polymerization behavior of siloles **1.18a** for solar cell applications was studied by Prof. Oleg A. Semenikhin's research group. Some of these results are summarized in the following sections.

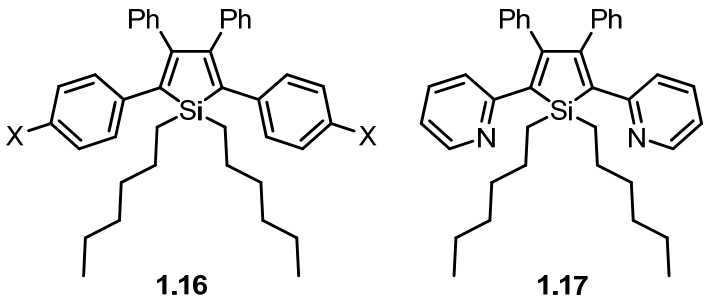
1.3.1. UV-Vis Absorption, PL and ECL Properties of Siloles 1.16 – 1.17

The UV-Vis absorption, PL and ECL properties for siloles **1.16 - 1.17** were investigated. **Table 1.1** summarizes the data obtained from absorption, PL and ECL spectra. The absorption and PL spectra are presented in **Figure 1.16**.

The conjugative groups e.g. **1.16c** and **1.16e** showed the lowest energy absorption and emission. The observed excimer peaks are due to the enhanced dimerization facilitated by the long hexyl chain. Unlike the thiophene-silole hybrids (data is not presented here), low quantum yields were observed in the scanning ECL. On the other hand, the pulsing technique was able to improve the quantum yields noticeably. The remarkable difference in the efficiency between the scanning and pulsing ECL can be attributed to the instability of the radical ions produced by these siloles. Because both the radical anions and cations are generated simultaneously within a very short time interval

in the pulsing ECL, the chance to generate the excited state is higher and hence the efficiency. Because the initial data obtained from the cyclic voltamograms (CVs) is not conclusive, additional information is required. Detailed computational and experimental work is underway to further investigate the redox properties of these siloles

Table 1.1 – Spectroscopic data of siloles **1.16** – **1.17**[a]



silole	Abs. λ_{max} (nm)	PL		ECL	
		λ_{max} (nm)	QE (%)[b]	λ_{max} (nm) monomer/excimer	QE (%)[c] scanning/pulsling
1.16a, X = H	355	398/470	1.21	418/615	0.56/54.68
1.16b, X = CF_3	355	401/460	1.98	NA[d]	0.70/10.46
1.16c, X = NO_2	395	430/520	4.11	463/654	0.22/33.93
1.16d, X = OCH_3	375	493/541	1.60	485/574	0.19/76.99
1.16e, X = $N(CH_3)_2$	425	332/634	48.93	NA[d]	0.17/20.63
1.17	355	400/467	0.72	410/630	0.18/214

[a]determined in benzene/acetonitrile solvent mixture at room temperature.[b]With respect to DPA.[c]Annihilation mechanism, relative to DPA.[d]Produced flat spectra

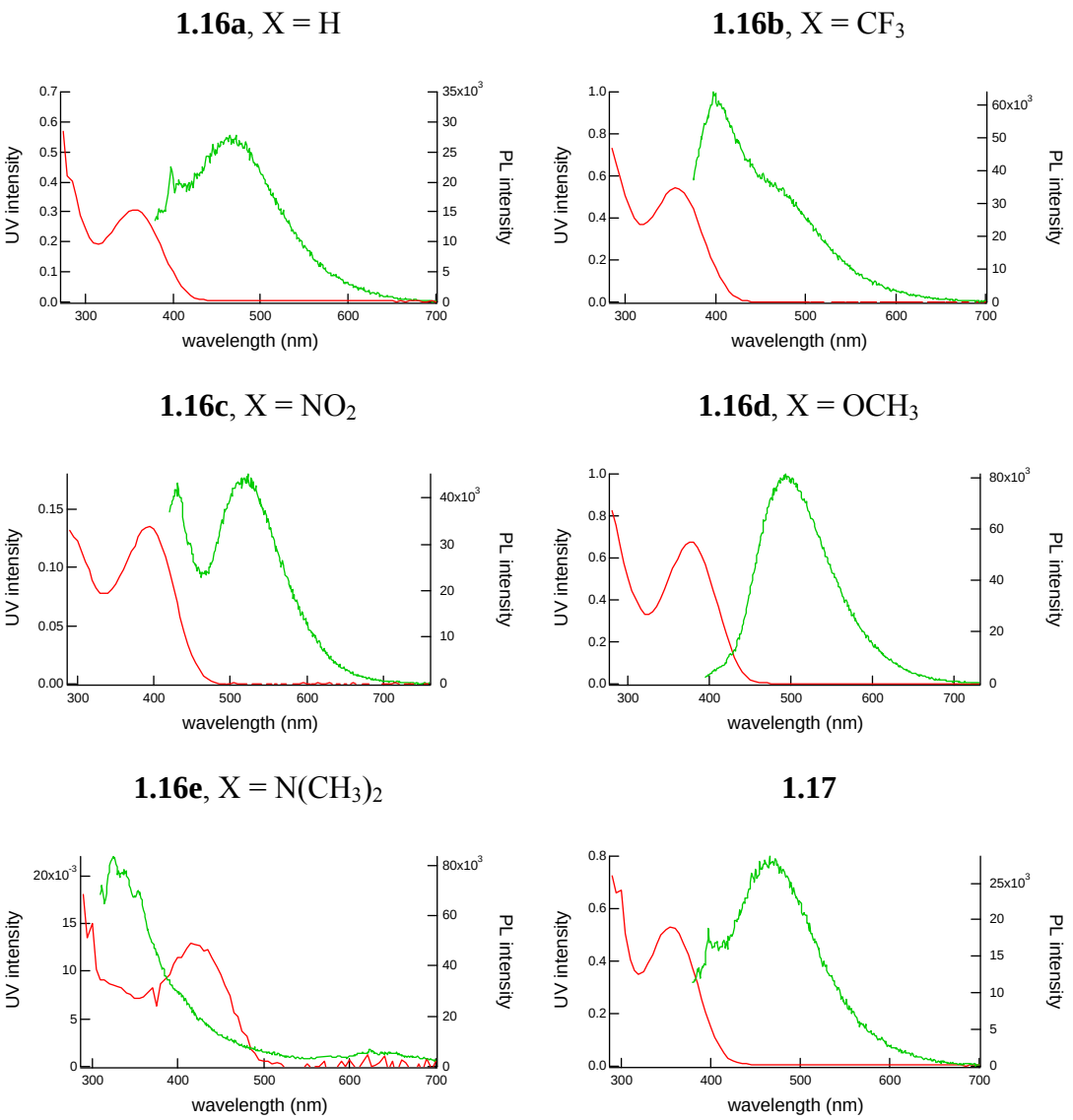
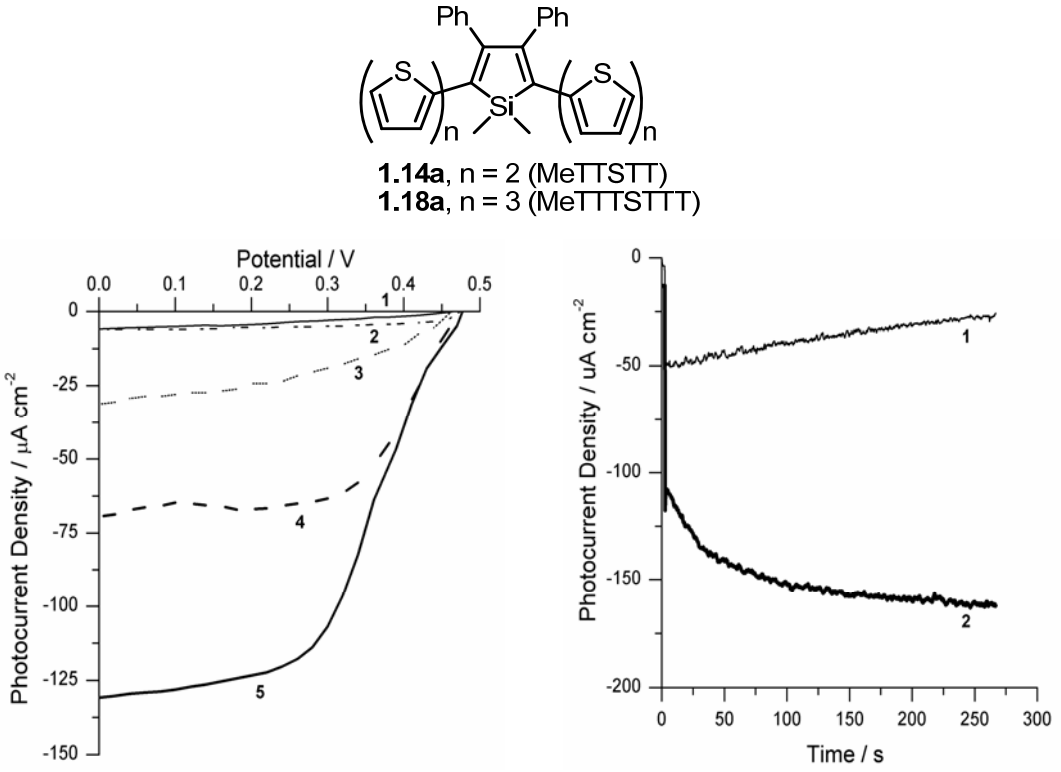


Figure 1.16 – UV-visible absorption (red) and normalized PL emission (green) spectra of the silole series **1.16** – **1.17** in 1.5:1 benzene/acetonitrile solvent.

1.3.2. Poly(thienyl-silole)s for All-polymer Solar Cells

To examine the utility of these materials for all-polymer solar cells application, the electrochemical and photoelectrochemical properties of electropolymerized poly(thienyl-silole)s were investigated by Prof. Semenikhin's research group. The materials were

prepared by electrochemical anodic polymerization of silole **1.14a** (MeTTSTT) and **1.18a** (MeTTTSTTT, as well as co-polymerization of these monomers with 2,2'-bithiophene (BT) (**Figure 1.17**).[1]



(A) (B)

Figure 1.17 – Photocurrent-potential dependencies and photocurrent decay against time of poly(thienyl-silole)s (A) Photocurrent-potential dependencies for films of MeTTTSTTT (1), MeTTSTT (2), PBT (3), 1:1 copolymer of MeTTTSTTT-BT (4) and 1:1 copolymer of MeTTSTT-BT (5) measured in oxygen-saturated acetonitrile solution. (B) Photocurrent decay against time of PBT (1) and 1:1 copolymer of MeTTSTT-BT (2).

As shown in **Figure 1.17**A, the photocurrent measurements showed that the introduction of siloles gave rise to a remarkable enhancement in the photocurrent of the copolymer material (**Figure 1.17**A, curve 5 and 4) as compared to non-modified parent

polybithiophene (PBT) (**Figure 1.17**A, curve 3). Copolymerization of BT with silole **1.14a** (MeTTSTT) gave the highest photocurrent (**Figure 1.17**A, curve 5).

A major drawback of the use of organic materials in solar cells is their tendency to rapid photodegradation resulting in photocurrent decay. As shown in (**Figure 1.17**B, curve 1), the photocurrent magnitude of polybithiophene (PBT) rapidly decreased with time. In contrast, the magnitude of the photocurrents of Me-TTTSTTT-BT and Me-TTSTT-BT copolymers grows with time to reach a stable plateau (**Figure 1.17**B, curve 2). These results indicate the superior stability of these materials and their great promise as electron-acceptor for all-organic solar cells.

1.4. Conclusion and Future Work

In summary, several new series of symmetric and dissymmetric silole-based chromophores were prepared by a one pot reaction sequence featuring Tamao's reductive cyclization, transmetallation and Negishi cross coupling. In addition, a new methodology was developed for the synthesis of the first dissymmetric silole containing a secondary amine functionality that can be used for conjugation with various biomolecules. This methodology provides a new way for structural modification of siloles and hence novel materials for biological sensors and optoelectronic applications. The electronic properties (UV-Vis, PL, ECL) and the electropolymerization behavior of these siloles were investigated. This has lead to the discovery of new electropolymerized poly(thienyl-silole)s for all-polymer organic solar cells, displaying enhanced photoefficiency when compared to the non-modified polybithiophene. Through extensive collaborations among physicists, biologists, synthetic and analytical chemists, future efforts are directed toward

structural modification of these siloles. Due to the unique properties of these materials, the synthesized compounds hold great promise for biosensors, solar cells and optoelectronic applications.

1.5. Experimental

1.5.1. General

All reactions were carried out under an inert atmosphere of dry argon unless otherwise indicated. Flasks were oven or flame dried and allowed to cool in a desiccator prior to use. All reagents and chemicals were of reagent quality, obtained from common commercial sources and used without further purification unless otherwise noted. All reactions were protected from light using aluminum foil. All solvents for the reactions were obtained from an Innovative Technology SPS-400-5 solvent dispensing system. For reactions involving lithium naphthalenide (LiNaph), THF was degassed with argon prior to use. LiNaph solutions were titrated using a literature method.[27] $ZnCl_2$ was flame-dried under vacuum and stored in glovebox. Progress of reactions was monitored by thin layer chromatography (TLC) performed on F254 silica gel plates. Column chromatography was performed with Silica Flash P60 60 Å silica gel from Silicycle according to the Still method.[28]

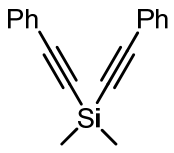
The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were obtained on a Varian Mercury 400 MHz NMR spectrometer. Chemical shifts (δ) were expressed in parts per million (ppm) downfield from tetramethylsilane using the residual protonated solvent as an internal standard (chloroform-*d*, ^{1}H 7.25 ppm, ^{13}C 77.0 ppm).When peak multiplicities are given, the following abbreviations are used: s, singlet; d, doublet; t,

triplet; dd, doublet of a doublet; m, multiplet. Coupling constants for all spectra are expressed in Hertz (Hz). HRMS (CI, FAB) were obtained with a Finnigan MAT 8200 instrument. For known intermediates, only NMR was performed for characterization.

1.5.2. Detailed Experimental Procedures

1.5.2.1. General Procedure for the Synthesis of Bis(Phenylethynyl)dialkylsilane

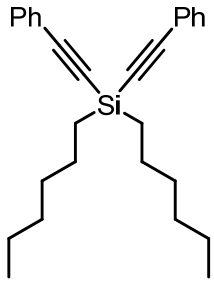
A solution of phenylacetylene (2.5 equiv) in THF (1 mL/ 1 mmol) was cooled to –78 °C (internal temperature). *n*BuLi (2.1 equiv) was added dropwise into the flask such that the internal temperature did not exceed –50 °C. It was allowed to warm to 0 ºC, and dichlorodialkylsilane (1.0 equiv) was charged into the pale yellow solution dropwise such that the internal temperature did not exceed 10 ºC. Then it was allowed to react at rt and monitored by TLC. Upon completion (ca 30 min), the reaction mixture was poured into a half saturated ammonium chloride aqueous solution, followed by extraction with ethyl acetate. The combined organic layers were washed with H_2O, brine, dried ($MgSO_4$), and concentrated in vacuum.



Dimethylbis(phenylethynyl)silane (1.24a)[19]

The reaction was done at 23 mmol scale to yield the product as white powder. Recrystallization from hexanes yielded 5.34 g (89%) of the desired product as white

crystals. R_f 0.56 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.49 (m, 4H), 7.34-7.28 (m, 6H), 0.48 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.1, 128.8, 128.2, 122.6, 105.9, 90.6, 0.5.



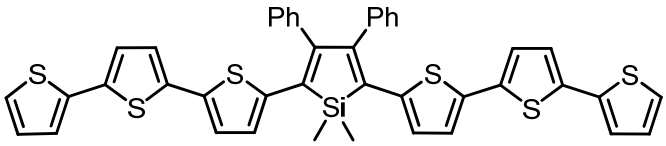
Dihexylbis(phenylethynyl)silane (1.24c)[19]

The reaction was done at 23 mmol scale to yield the product yellow oil (97% yield, 9.00 g). R_f 0.35 (10% CH_2Cl_2/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.46 (m, 4H), 7.30-7.24 (m, 6H), 1.64-1.55 (m, 4H), 1.44 (dt, *J* = 14.1, 7.0 Hz, 4 H), 1.35-1.29 (m, 8H), 0.92-0.85 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.0, 128.7, 128.1, 122.8, 106.6, 89.4, 32.7, 31.5, 23.7, 22.6, 14.8, 14.1.

1.5.2.2. General Procedure for the One-pot Reductive Cyclization/ Negishi Cross-coupling Reaction

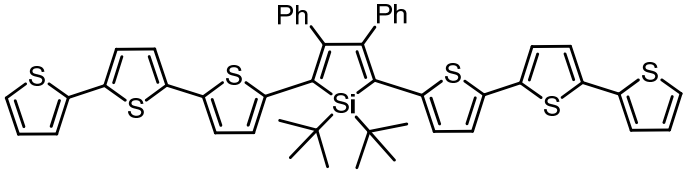
A solution of bis(phenylethynyl) dialkylsilane **1.24** (1.5 mmol, 1.0 equiv) was added dropwise into a solution of LiNaph (16 mL, 0.38 M, 6.1 mmol, 4.0 equiv) at rt. The solution was cooled to –10 °C (internal reaction temperature) and $ZnCl_2$ dissolved in THF (25 mL, 0.30 M, 7.5 mmol, 5.0 equiv) was added via syringe in one portion. The fine black suspension was allowed to react for 20 min. To this solution was added

$PdCl_2(PPh_3)_2$ (52 mg, 0.075 mmol, 5 mol %) and aryl halide (3.3 mmol, 2.2 equiv). The reaction mixture was set to reflux and monitored by TLC. Upon completion (ca 12 h), the reaction mixture was allowed to cool to rt, added an aqueous solution of HCl (0.1N, 10 mL) and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (20 mL), brine (2 x 20 mL), dried ($MgSO_4$), and concentrated in vacuum. The product was then purified by flash chromatography on silica gel (hexanes → 30% CH_2Cl_2/hexanes gradient).



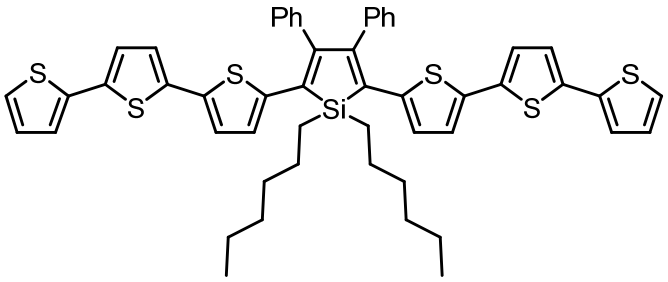
2,5-Di(2,2'-terthiophen-5-yl)-1,1-dimethyl-3,4-diphenyl-1*H*-silole (1.18a)

The reaction was done at 1.5 mmol scale to yield the product as reddish black solid (90% yield, 1.0 g). R_f 0.27 (30% CH_2Cl_2/hexanes); mp: 350 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-7.17 (m, 8H), 7.12-7.10 (m, 2H), 7.02-6.98 (m, 6H), 6.97(d, *J* = 3.7 Hz, 2H), 6.94 (d, *J* = 3.9 Hz, 2H), 6.81(d, *J* = 3.7 Hz, 2H), 6.77(d, *J* = 3.9 Hz, 2H) 0.72 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 142.4, 138.7, 137.2, 136.7, 136.5, 136.0, 131.7, 129.4, 128.6, 128.0, 127.8, 127.4, 124.4, 124.3, 123.9, 123.6, 123.1, -1.7; HRMS m/z 754.0443 (calcd for $C_{42}H_{30}SiS_6$, 754.0441).



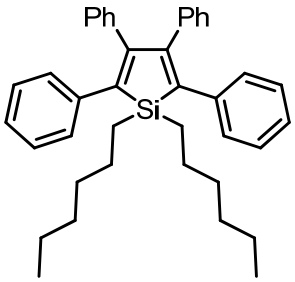
2,5-Di(2,2'-terthiophen-5-yl)-1,1-di-*tert*-butyl-3,4-diphenyl-1*H*-silole (1.18b)

The reaction was done at 1 mmol scale to yield the product as a reddish brown solid (86% yield, 0.763 g). R_f 0.37 (20% CH_2Cl_2/hexanes); mp: 58-60 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (dd, *J* = 5.1, 1.0 Hz, 2H), 7.12 - 7.10 (m, 2 H), 7.07-7.04 (m, 6H), 7.0-6.95 (m, 4H), 6.88-6.84 (m, 8H), 6.65 (d, *J* = 3.9 Hz, 2H), 1.27 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 144.0, 139.3, 137.5, 136.8, 136.6, 135.8, 133.3, 130.2, 129.3, 128.1, 128.0, 127.0, 124.5, 124.5, 123.8, 123.7, 123.0, 77.6, 77.2, 76.9, 29.6, 20.8; HRMS m/z 838.1381 (calcd for $C_{48}H_{42}SiS_6$, 838.1380).



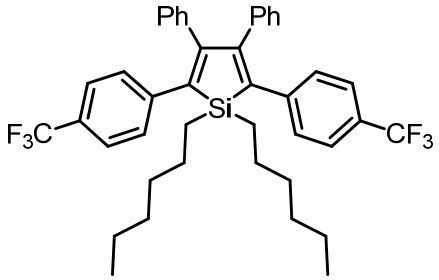
2,5-Di(2,2'-terthiophen-5-yl)-1,1-dihexyl-3,4-diphenyl-1*H*-silole (1.18c)

The reaction was done at 1 mmol scale to yield the product as a reddish brown solid (65% yield, 0.572 g). R_f 0.29 (hexanes); mp: 140-142 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.17 (m, 8H), 7.12 (dd, *J* = 3.7, 1.2 Hz, 2H), 7.01-6.96 (m, 8H), 6.95 (d, *J* = 3.9 Hz, 2H), 6.81 (d, *J* = 3.7 Hz, 2H), 6.76 (d, *J* = 3.91 Hz, 2H), 1.53-1.45 (m, 4H), 1.36 (dd, *J* = 7.8, 6.8 Hz, 4 H), 1.27-1.17 (m, 12H), 0.86-0.80 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 142.7, 139.0, 137.2, 136.6, 136.6, 135.8, 130.6, 129.5, 128.6, 128.0, 127.8, 127.4, 124.3, 124.3, 123.8, 123.5, 123.1, 32.5, 31.5, 23.6, 22.6, 14.1; HRMS m/z 894.2004 (calcd for $C_{51}H_{48}SiS_6$, 894.2006).



1,1-Dihexyl-2,3,4,5-tetraphenyl-1*H*-silole (1.16a)

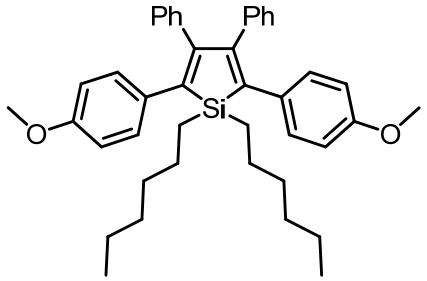
The reaction was done at 1 mmol scale to yield the product as yellow oil (86% yield, 0.476 g). R_f 0.27 (hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 - 7.09 (m, 4 H), 7.05 (d, *J* = 7.2 Hz, 2 H), 7.03 - 6.97 (m, 6 H), 6.92 (d, *J* = 7.0 Hz, 4 H), 6.82 - 6.77 (m, 4 H), 1.44 -1.36 (m, 4 H), 1.30 (dt, *J* = 14.3, 6.9 Hz, 4 H), 1.24 - 1.16 (m, 8 H), 1.04 - 0.98 (m, 4 H), 0.84 (t, *J* = 6.8 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 140.7, 140.4, 139.0, 130.0, 128.9, 127.8, 127.3, 126.1, 125.3, 32.7, 31.4, 23.5, 22.5, 14.1, 12.0; HRMS m/z 554.3373 (calcd for $C_{40}H_{46}Si$, 554.3369).



1,1-Dihexyl-3,4-diphenyl-2,5-bis(4-(trifluoromethyl)phenyl)-1*H*-silole (1.16b)

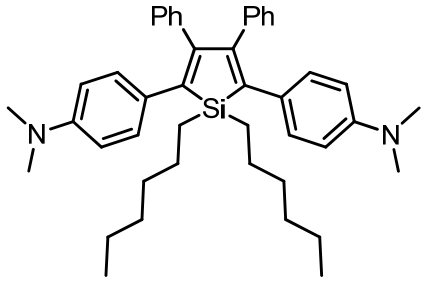
The reaction was done at 1 mmol scale to yield the product as yellow oil (65% yield, 0.448 g). R_f 0.22 (hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.0 Hz, 4H), 7.01 (t, *J* = 8.3 Hz, 10 H), 6.75 (d, *J* = 6.4Hz, 4H), 1.38-1.26 (m, 8H), 1.21-1.12 (m, 8H),

1.04-0.98 (m,4H), 0.83 (t, J = 6.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 144.1, 140.3, 138.0, 129.8, 128.8, 127.6, 126.7, 125.7, 124.9, 124.9, 32.7, 31.4, 23.4, 22.4, 14.0, 11.8; HRMS m/z 690.3123 (calcd for $C_{42}H_{44}SiF_6$, 690.3116).



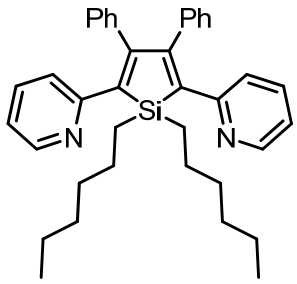
1,1-Dihexyl-2,5-bis(4-methoxyphenyl)-3,4-diphenyl-1*H*-silole (1.16d)

The reaction was done at 1 mmol scale to yield the product as yellow oil (78% yield, 0.480 g). R_f 0.13 (hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02-6.97(m, 6H), 6.82 (d, J = 8.6 Hz, 4 H), 6.78 (dt, J = 3.7, 2.8 Hz, 4 H), 6.65 (d, J = 8.8 Hz, 4 H), 3.73 (s, 6 H), 1.40 - 1.32 (m, 4 H), 1.29 - 1.25 (m, 4 H), 1.21 - 1.14 (m, 8 H), 1.0 - 0.95 (m, 4 H), 0.82 (t, J = 6.8 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 154.2, 139.5, 139.0, 132.7, 130.1, 130.0, 127.4, 125.9, 113.3, 55.0, 32.7, 31.5, 23.5, 22.5, 14.1, 12.3; HRMS m/z 614.3565 (calcd for $C_{42}H_{44}SiF_6$, 614.3580).



4,4'-(1,1-Dihexyl-3,4-diphenyl-1*H*-silole-2,5-diyl)bis(*N*,*N*-dimethylaniline) (1.16e)

The reaction was done at 1 mmol scale to yield the product as yellow oil (57% yield, 0.36 g). R_f 0.16 (5% ethylacetate-hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 – 6.99 (m, 6 H), 6.85 - 6.80 (m, 6 H), 6.79 (s, 2 H), 6.48 (d, *J* = 8.8 Hz, 4 H), 2.87 (s, 12 H), 1.42 - 1.36 (m, 4 H), 1.30 - 1.25 (m, 6 H), 1.20 - 1.16 (m, 6 H), 1.02 – 0.98 (m, 4 H), 0.82 (t, *J* = 6.7 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 148.1, 140.6, 138.0, 130.1, 130.1, 128.5, 127.5, 125.6, 111.9, 40.4, 32.7, 31.6, 23.6, 22.6, 14.2, 13.0; HRMS m/z 640.4240 (calcd for $C_{44}H_{56}N_2Si$, 640.4213).

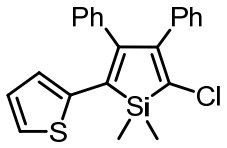


2,2'-(1,1-Dihexyl-3,4-diphenyl-1*H*-silole-2,5-diyl)dipyridine (1.17)

The reaction was done at 1 mmol scale to yield the product as yellow oil (70% yield, 0.389 g). R_f 0.6 (5% ethylacetate-hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (dt, *J* = 4.9, 0.8 Hz, 2 H), 7.22 - 7.16 (m, 2 H), 7.12- 7.07 (m, 6 H), 6.92 - 6.86 (m, 6 H), 6.50 (dd, *J* = 8.1, 0.5 Hz, 2 H), 1.44 - 1.39 (m, 4 H), 1.29 - 1.25 (m, 4 H), 1.23 - 1.15 (m, 12 H), 0.81 (t, *J* = 6.8 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 155.8, 149.1, 144.0, 139.6, 134.8, 129.3, 127.9, 126.5, 122.5, 120.0, 32.7, 31.5, 23.8, 22.6, 14.1, 12.6; HRMS m/z 556.3250 (calcd for $C_{38}H_{44}N_2Si$, 556.3274).

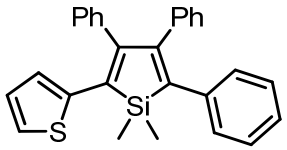
1.5.2.3. General Procedure for the Synthesis of Dissymmetric Siloles

A solution of bis(phenylethynyl) dialkylsilane **1.24a** (1.0 equiv) was added dropwise into a solution of LiNaph in THF (4.0 equiv) at rt. The solution was cooled to –10 °C (internal reaction temperature) and ZnCl2 dissolved in THF (5.0 equiv) was added via syringe in one portion. The fine black suspension was allowed to react for 20 min. After cooling the reaction then cooled to –78 °C, *N*-chlorophthalimide solution in THF (1.0 equiv) was added dropwise. The reaction then allowed to stir at –78 °C for 30 min. To this solution was added $PdCl_2(PPh_3)_2$ (5 mol %) and aryl halide (1.3 equiv). Then the reaction mixture was set to reflux and monitored by TLC. Upon completion (ca 12 h), the reaction mixture was allowed to cool to rt and concentrated. The crude product dissolved in minimum amount of CH_2Cl_2 was applied on silica gel and purified by flash chromatography (hexanes → 30% CH_2Cl_2/hexanes gradient).



2-Chloro-1,1-dimethyl-3,4-diphenyl-5-(thiophen-2-yl)-1*H*-silole (1.36)

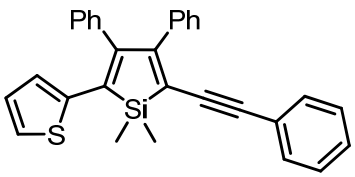
The reaction was done at 5 mmol scale to yield the product as yellow powder. Recrystallization from CH_2Cl_2/hexanes yielded 1.1 g (60%) of the desired product as yellow crystals. R_f 0.3 (hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 - 7.19 (m, 3 H), 7.18 - 7.13 (m, 3 H), 7.05 - 6.99 (m, 5 H), 6.90 - 6.87 (m, 1 H), 6.84 - 6.81 (m, 1 H), 0.60 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 150.1, 142.4, 138.3, 135.9, 133.1, 131.0, 129.6, 129.1, 128.5, 127.5, 127.4, 127.1, 127.0, 126.2, 125.7, -4.3; HRMS m/z 378.0657 (calcd for $C_{22}H_{19}ClSSi$, 378.0665).



1,1-Dimethyl-2,3,4-triphenyl-5-(thiophen-2-yl)-1*H*-silole (1.38)

To a solution of bromobenzene (1.5 equiv) in ether cooled to 0 °C, *n*BuLi (1.5 equiv) was added dropwise. The reaction then allowed to stir at 0 °C. After completion (ca 1 h), the reaction mixture was carefully transferred via cannula to a solution of $ZnCl_2$ (1.8 equiv) in THF at 0 °C. The reaction then allowed to stir at rt. After completion (ca 30 min), MeTSiCl **1.36** (1.0 equiv) and $Pd(PPh_3)_4$ (5 mol %) were added. The reaction then was set to reflux. After completion (ca 16 h), the reaction was cooled to rt, diluted with hexanes, filtered through silica plug and concentrated. The product was purified by flash chromatography (hexanes → 10% CH_2Cl_2/hexanes gradient).

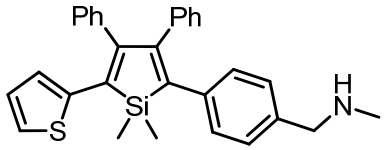
The reaction was done at 0.2 mmol scale to yield the product as yellow powder (83% yield, 0.07 g). R_f 0.16 (hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 - 7.16 (m, 3 H), 7.11 (br. s., 2 H), 7.04 - 6.94 (m, 10 H), 6.88 - 6.84 (m, 3 H), 0.59 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 152.2, 142.9, 139.9, 139.5, 139.2, 138.9, 133.0, 129.8, 128.8, 128.8, 128.4, 127.9, 127.4, 127.1, 126.2, 126.1, 125.6, 125.6, -2.8; HRMS m/z 420.1367 (calcd for $C_{28}H_{24}SSi$, 420.1368).



1,1-Dimethyl-3,4-diphenyl-2-(phenylethynyl)-5-(thiophen-2-yl)-1*H*-silole (1.39)

To a solution of $ZnCl_2$ (1.5 equiv) in THF, Et_3N (3 equiv) and phenylacetylene (1.2 equiv) were added. After stirring the reaction mixture at rt for 30 min, silole **1.36** (1.0 equiv) and $Pd(PPh_3)_4$ (5 mol %) were added. The reaction then was set to reflux. After completion (ca 16 h), the reaction was cooled to rt, diluted with hexanes, filtered through silica plug and concentrated. The product was purified by flash chromatography (hexanes → 10% CH_2Cl_2/hexanes gradient.

The reaction was done at 0.2 mmol scale to yield the product as yellow powder (75% yield, 0.07 g). R_f 0.33 (10% CH_2Cl_2/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.250 - 7.20 (m, 8 H), 7.15 - 7.11 (m, 5 H), 7.06 - 7.02 (m, 3 H), 6.89 - 6.84 (m, 2 H), 0.61 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 151.0, 142.7, 138.6, 138.0, 134.1, 131.4, 129.8, 129.2, 128.6, 128.1, 127.8, 127.5, 127.0, 126.2, 126.1, 124.6, 121.1, 98.8, 89.8, -3.7; HRMS m/z 444.1365 (calcd for $C_{30}H_{24}SSi$, 444.1368).



1-(4-(1,1-Dimethyl-3,4-diphenyl-5-(thiophen-2-yl)-1*H*-silol-2-yl)phenyl)-*N*-methylmethanamine (1.41)

To a solution of 1-(4-bromophenyl)-*N*-methylmethanamine (3.0 equiv) in ether cooled to 0 °C, TMSCl (3.3 equiv) and Et_3N (3.5 equiv) were added. The reaction then allowed to stirr at rt. After completion (ca 16 h), the heterogeneous reaction mixture was allowed to

separate and the ether layer was carefully decanted via a syringe into another flask. Then the solution was cooled to 0 °C and *n*BuLi (3.0 equiv) was added dropwise. The reaction then allowed to stirr at 0 °C. After completion (ca 2 h), the reaction mixture was carefully transferred via cannula to a solution of $ZnCl_2$ (3.3 equiv) in THF at 0 °C. The reaction then allowed to stir at rt. After completion (ca 30 min), silole **1.36** (1.0 equiv) and $Pd(PPh_3)_4$ (5 mol %) were added. The reaction then was set to reflux. After completion (ca 16 h), the reaction was cooled to rt, diluted with hexanes, filtered through silica plug and concentrated. The crude product was then dissolved in ethyl acetate and poured into water, followed by extraction with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuum. The product was purified by flash chromatography (ethyl acetate → 5% MeOH/CH_2Cl_2 gradient).

The reaction was done at 0.2 mmol scale to yield the product as yellow oil (40% yield, 0.04 g). R_f 0.16 (ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 - 7.16 (m, 3 H), 7.05 - 7.02 (m, 2 H), 7.02 - 6.96 (m, 6 H), 6.90 (d, *J* = 8.4 Hz, 2 H), 6.88 - 6.81 (m, 4 H), 3.62 (s, 2 H), 2.41 (s, 3 H), 0.87 (br. s., 1 H), 0.58 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 152.3, 142.9, 139.5, 139.2, 139.1, 138.1, 137.5, 132.8, 129.8, 128.8, 128.4, 127.8, 127.5, 127.1, 126.2, 126.1, 125.5, 55.8, 36.1, -2.7; HRMS m/z 463.1796 (calcd for $C_{30}H_{29}NSSi$, 463.1790).

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Chapter 2: Cyclopropane Activation for Dipolar Cycloaddition: Synthesis of 5-Azaindoles via a Cycloaddition Reaction between Nitriles and Donor−Acceptor Cyclopropanes

This chapter describes the expansion of current group methodology, namely nitriles/donor−acceptor (DA) cyclopropanes formal [3+2] cycloaddition, to include a highly efficient synthesis of 5-azaindoles. In addition to a brief introduction on the bonding and general reactivity of small membered cycloalkanes (cyclopropane and cyclobutane), the utility of cyclopropane rings in dipolar cycloaddition will be discussed. The whole synthetic work presented in this chapter was done by me and the results have been published in *Organic Letters*.[1] Some portions of the text and schemes have been reproduced in part with permission from Moustafa, M. M. A. R.; Pagenkopf, B. L. *Org. Lett*. **2010**, *12*, 3168. Copyright **2010** American Chemical Society.

2.1. Introduction

2.1.1. Bonding and General Reactivity of Small Membered Cycloalkanes

Due to their biological activity, high chemical reactivity, and their relative stability at room temperature, cyclopropane[2] and cyclobutane[3] derivatives have been emerged as important pharmacophores in many drugs and as versatile building blocks in modern organic synthesis. Because of the inherent ring strain, both cyclopropanes and cyclobutanes can undergo a facile C−C bond cleavage. In contrast, it is difficult to cleave this bond of cyclopentanes and the higher cycloalkanes.[4] On the other hand, cyclopropane shows a reactivity profile similar to olefins by reacting readily with bromine,[5] and

sulfuric acid.[6] However cyclobutanes donot react with either of these reagents. This can be explained by differences of structures and energies of these compounds.[4]

Despite the large difference in C−C−C bond angles, cyclobutane has a ring strain (26.3 kcal/mol) similar to that of cyclopropane (27.5 kcal/mol).[4] This may be explained by invoking a 1,3 (nonbonded) carbon/carbon interactions.[7] Cyclobutane has two interactions with a relative small distance between the carbons. Because all of the carbons are bonded to each other, cyclopropane does not have such interaction. This cross-ring repulsion can also explain why cyclobutanes have markedly longer C−C bond lengths. The C−C bond lengths of cyclobutanes cover a range of 1.521–1.606 Å depending on the substitution pattern, with an average value of 1.554 Å. In contrast, cyclopropane has shorter C−C bond lengths and cyclopentane is only 0.013 Å greater.[4]

The C−C−C bond angle of cyclobutane is 88°, with a puckered conformation, to minimize the torsional interaction between the two adjacent methylene groups (**Figure 2.1**).[4] However this leads to increased bond angle strain. The balance between these two strains controls the equilibrium geometry. The properties of the C−H bonds in cyclobutane are much closer to those of the other cycloalkanes.[4] In contrast, The C−C−C bond angle of cyclopropane is 60° which is a large deviation from the 109.5° expected for sp^3−hybridized carbons. As explained by Förster-Coulson-Moffitt model, the high *p* character in the C−C bonds of cyclopropane (ring bonds) must lead to high *s* character in its C−H bonds (peripheral bonds). Therefore the C−H bonds of cyclopropane are shorter and stronger.[4] In addition, the electron density is thought to lie on the outside of the ring

because of the geometric constraints of the cyclopropane ring.[8] As a result, reactivity of cyclopropane is closer to that of alkenes rather than alkanes.[9]

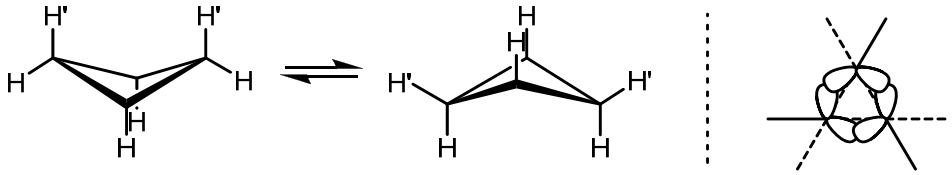


Figure 2.1 – Puckered conformation of cyclobutane and Förster-Coulson-Moffitt model of cyclopropane bonding

The inherent reactivity of cyclopropanes and cyclobutanes can be further enhanced through the use of activating substituents. In general, there are three classes of activated cyclopropanes. The first class is activated with electron-withdrawing groups and those cyclopropanes can react as homo Michael acceptors with a variety of nucleophiles (**Figure 2.2**, Equation i). In the second class, the cyclopropane ring is substituted with electron-donating groups and those cyclopropanes can be cleaved by different electrophiles (**Figure 2.2**, Equation ii). In each case an ionic intermediate will be generated that can be used in the subsequent transformations. The third class is donor−acceptor (DA) cyclopropane where both donor and acceptor groups are utilized in a synergistic fashion (**Figure 2.2**, Equation iii). Under mild conditions, usually LA catalysis, those cyclopropanes undergo ring opening to form 1,3-zwitterionic intermediates that can be used as dipole equivalents in many useful transformations. Dipolar cycloaddition involving activated cyclopropanes (DA cyclopropanes) is extensively studied and has been demonstrated by the preparation of highly substituted carbo- and heterocyclic natural and unnatural targets.[10] In contrast, reports that extend these methodologies to cyclobutanes are rare. This was surprising because both rings

have very similar ring strain suggesting a facile heterolytic ring opening of the cyclobutanes and potential homologous applications (**Figure 2.2**, Equation iv). The utility of doubly activated cyclopropanes will be discussed in this chapter while the use of cyclobutanes in dipolar cycloaddition will be covered in chapter 3.

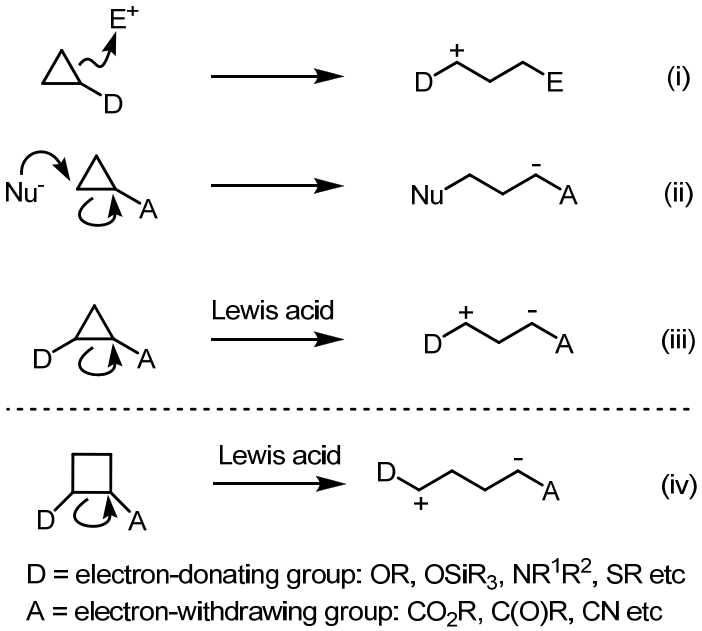


Figure 2.2 – Activated cyclopropane and cyclobutane

2.1.2. Formal [3+2] Cycloaddition of DA Cyclopropanes

While there are a wide variety of annulation reactions involving DA cyclopropanes, this section will deal only with the formal intermolecular [3+2] cycloaddition reactions of 1,1-cyclopropanediesters **2.1** (**Figure 2.3**, Equation i) and/or 2-alkoxy cyclopropane carboxylic ester **2.3** (**Figure 2.3**, Equation ii). A particular emphasis will be placed on aldehydes, imines and nitriles. Other dipolarophiles for example; isocyanates,[11] isothiocyanates,[12] azodicarbonyl derivatives,[13] acetylenes,[14] alkenes,[15] silyl enol ethers,[16] silyl ketene acetals,[17] allenylsilanes,[18] nitrones,[19] and diazenes[20] will not be covered.

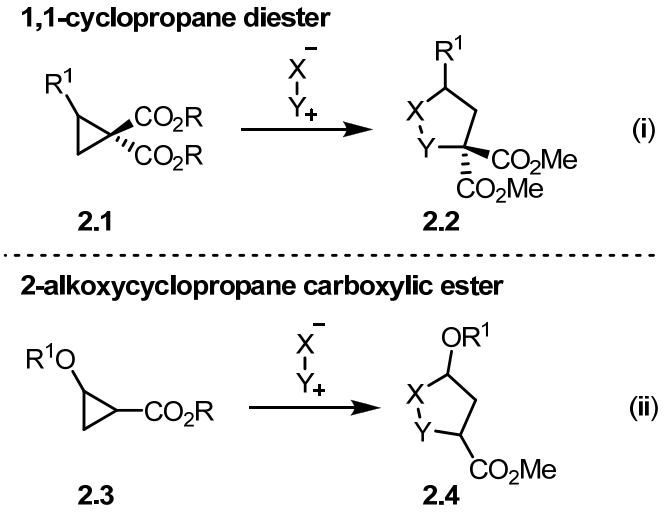
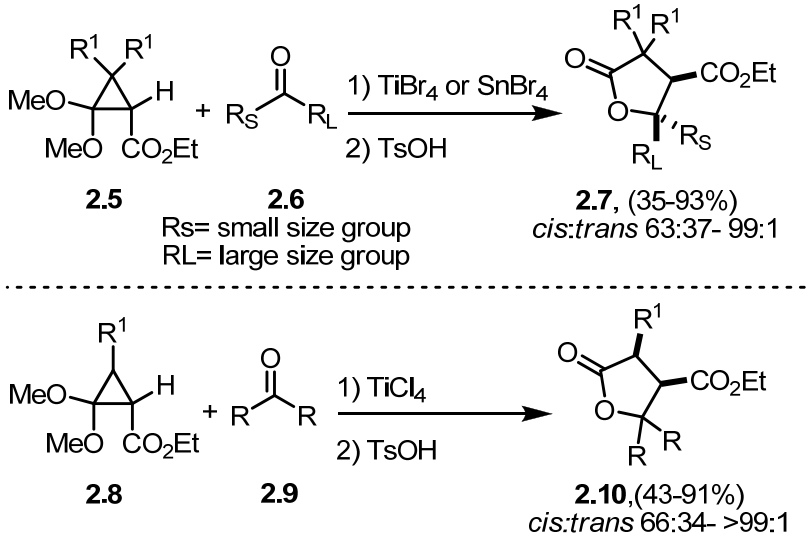


Figure 2.3 – The formal [3+2] cycloaddition of 1,2-dipoles with DA cyclopropane

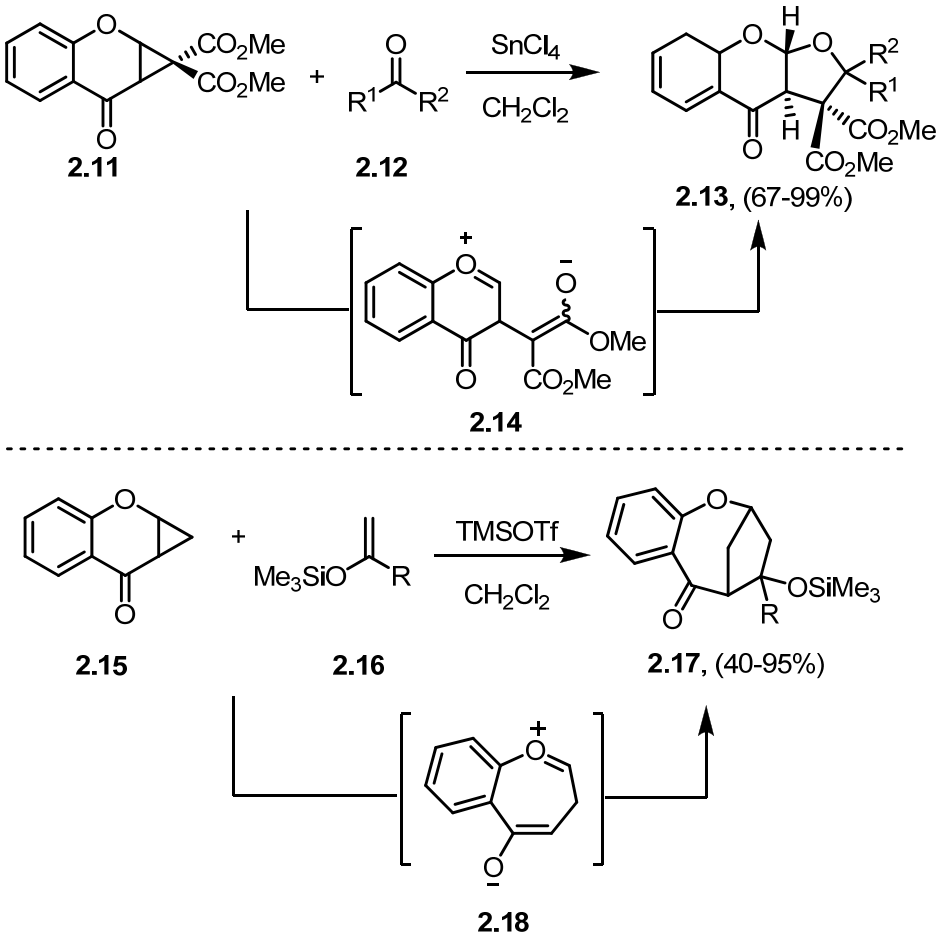
Among different dipolarophiles examined, aldehydes and ketones have been studied extensively. For instance, Saigo and co-workers have reported a highly diastereoselective synthesis of γ-lactones **2.7** and **2.10** by a LA catalyzed reaction of carbonyl compounds with cyclopropane **2.5** and **2.8**, respectively (**Scheme 2.1**).[21]



Scheme 2.1 – Cycloaddition between 2,2-dialkoxycyclopropane carboxylic ester and aldehydes or ketones

The diastereoselectivity of the reaction varies according to LA utilized and the substitution pattern of the substrates. In general, a high *cis*-selectivity was obtained with $TiBr_4$, $SnBr_4$ and $TiCl_4$ whereas $ZrCl_4$ was moderately *trans*-selective (**Scheme 2.1)**.

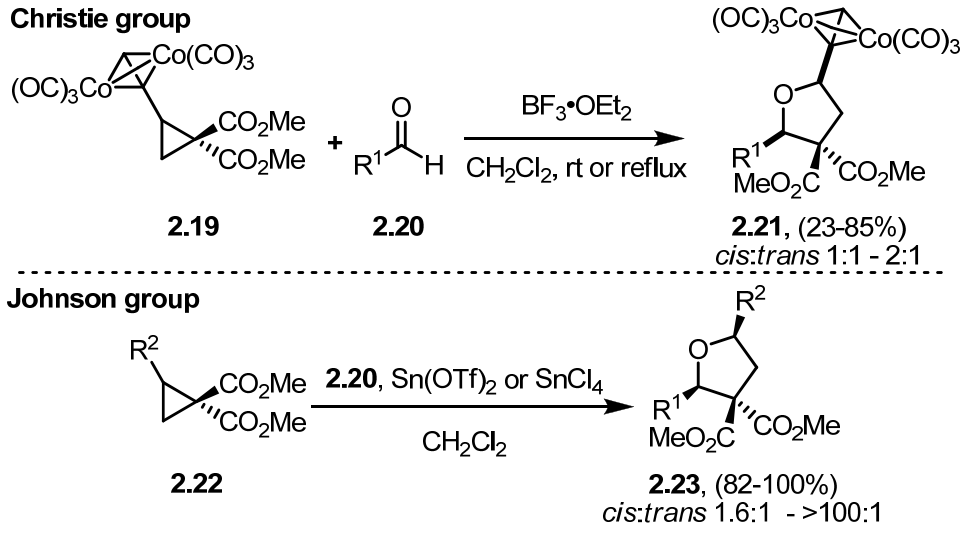
In 2000, Sugita et al reported a related reaction with a chromatene-derived 1,1-cyclopropanediesters **2.11** where the *trans*-fused tetrahydrofuro[2,3-b][1]benzopyranones **2.13** were obtained in good yields and high diastereoselectivities (**Scheme 2.2**).[22]



Scheme 2.2 – Cycloaddition reactions with chromatene derived cyclopropanes

In absence of the diester functionality, an *endo* ring cleavage occurs giving rise to a different zwitterion intermediate **2.18**, that can be trapped with silyl enol ethers **2.17** to afford the oxepanone derivatives **2.17** in 40-95% yield (**Scheme 2.2**).[22]

A few years later the same annulation was extended to other 1,1-cyclopropanediesters activated with different types of donating groups. For example, a cobalt-complexed 2-ethynyl group (**2.19**) reported by Christie and co-workers,[23] and aromatic substituents (**2.22**) reported by the Johnson group (**Scheme 2.3**).[24] The reaction conditions, scope and product diastereoselectivity vary according to cyclopropane nature.

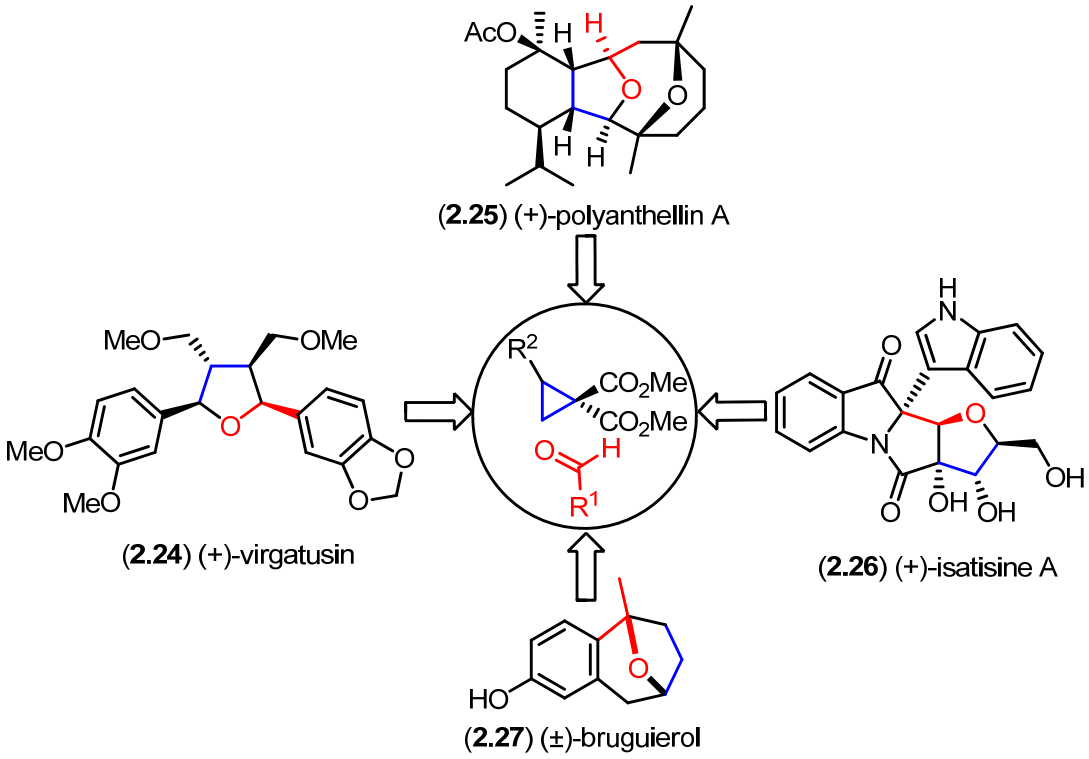


Scheme 2.3 – The reaction of aldehydes and 1,1-cyclopropanediester

In Christie's work, three equivalents of BF_3•OEt_2 was optimal for the cycloaddition to occur where aliphatic, electron-deficient or neutral aryl aldehydes undergo the reaction to provide the target tetrahydrofurans **2.21** however in moderate yield and diastereoselectivity. Unfortunately, electron-rich aromatic aldehydes were incompatible to the reaction conditions.[23] In contrast, the Johnson's $Sn(OTf)_2$-catalyzed

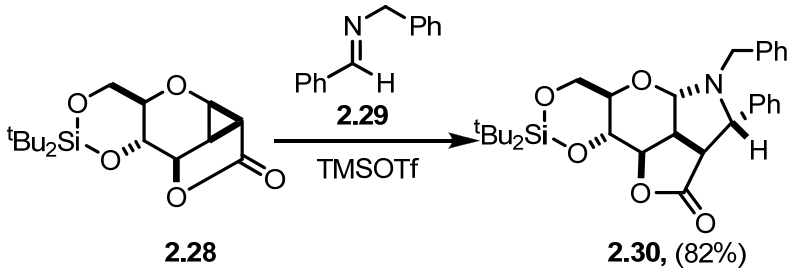
approach provided the desired tetrahydrofurans **2.23** in excellent diastereoselectivities and yields.[24] While $Sn(OTf)_2$ promoted the reaction with aromatic, alkenyl, and alkynyl aldehydes, $SnCl_4$ effectively catalyzed the reaction with aliphatic ones (**Scheme 2.3**).[25] More recently, Johnson reported an asymmetric variant where enantioenriched tetrahydrofurans were obtained via a dynamic kinetic resolution of racemic cyclopropanes and aldehydes.[26]

The cycloaddition reaction between DA cyclopropanes and aldehydes has been applied in the synthesis of many natural products including (+)-virgatusin **2.24**,[27] (+)-polyanthellin A **2.25**,[28] (+)-isatisine A **2.26**,[29] and (±)-bruguierol **2.27** (intramolecular annulation) (**Scheme 2.4**).[30]



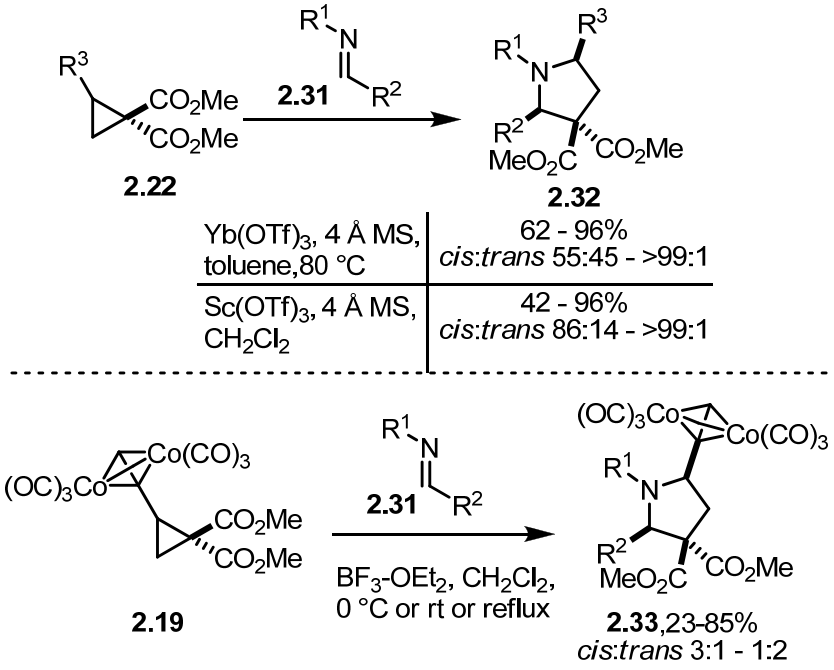
Scheme 2.4 – Applications of DA cyclopropane-aldehyde cycloaddition

DA cyclopropanes have also been reported to undergo cyclization with imines to furnish pyrrolidine derivatives in a stereoselective manner.[31] The Pagenkopf group has shown that TMSOTf can mediate the cycloaddition of imine **2.29** with glucal–derived DA cyclopropane **2.28**. The reaction displayed excellent stereoselectivity and furnished the aminal product **2.30** in 82% yield (**Scheme 2.5**).[10e]



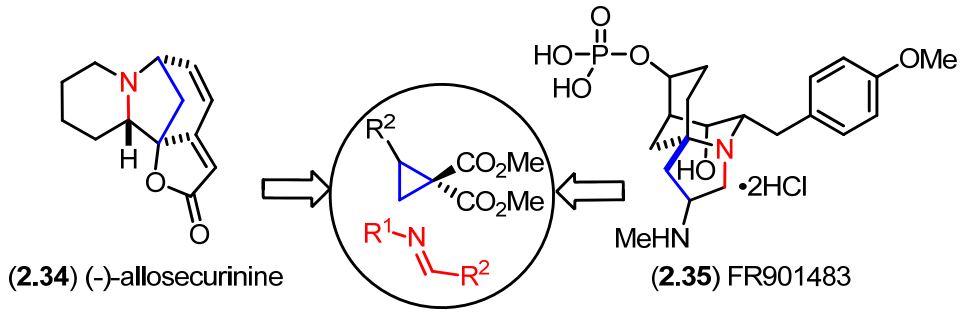
Scheme 2.5 – Annulation reactions of glucal–derived DA and iminies

In addition, the annulation reaction between 1,1-cyclopropanediesters and imines has been examined by several research groups including the Kerr,[32] the Tang,[33] the Christie[34] and the Johnson groups.[35] When the reaction of cyclopropane **2.22** and *in situ* generated aromatic imines **2.31** is catalyzed by $Yb(OTf)_3$, refluxing toluene was required to give 2,5-*cis*-pyrrolidines **2.32** (**Scheme 2.6**) as the major product.[32] Interestingly, when the more reactive $Sc(OTf)_3$ was used, better diastereocontrol can be achieved and the reaction can be done at milder conditions.[33] On the other hand, the annulation of cobalt-complexed 2-ethynyl-1,1-cyclopropanediester **2.19** with imines **2.31** is catalyzed by BF_3•OEt_2 to produce pyrrolidines **2.33** in moderate diastereoselectivity and yield (**Scheme 2.6**).[34] More recently, the Johnson group has reported an asymmetric variant where enantioenriched pyrrolidines were obtained via a dynamic kinetic resolution of racemic cyclopropanes and imines.[35]



Scheme 2.6 – The reaction of imines and 1,1-cyclopropanediesters

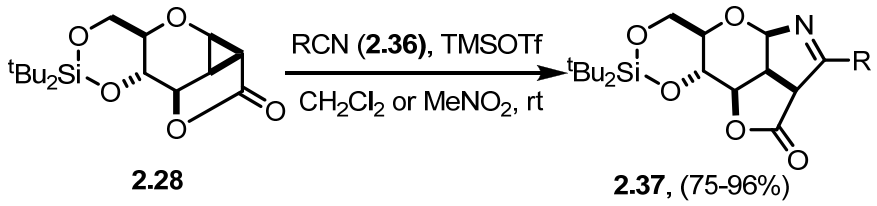
The cycloaddition reaction between 1,1-cyclopropanediesters and imines has been applied in the synthesis of (-)-allosecurinine **2.34**,[36] and FR901483 **2.35** (**Scheme 2.7**).[37]



Scheme 2.7 – Applications of DA cyclopropane-imine cycloaddition

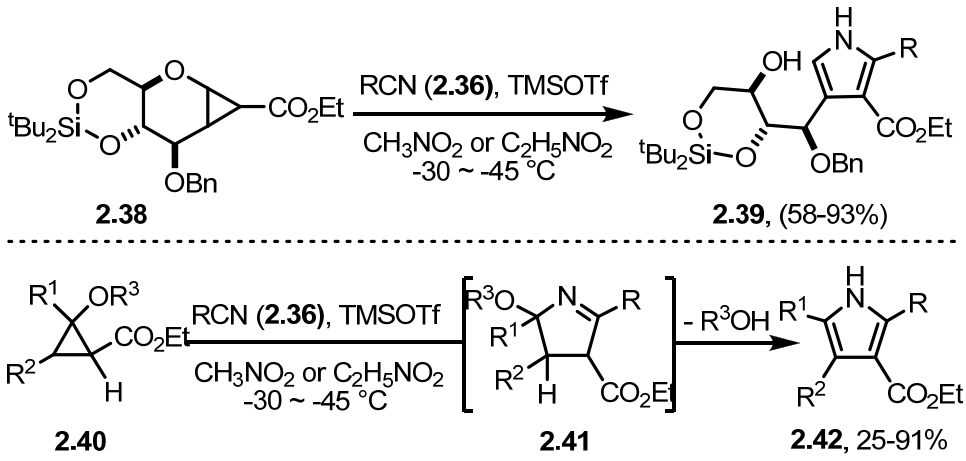
The annulation reaction between nitriles and DA cyclopropanes was first reported by the Pagenkopf group in 2003,[38] where a highly stereoselective formal [3+2] cycloaddition reaction between glycal-derived cyclopropane **2.28** and nitriles **2.36**

afforded 3,4-dihydro-2*H*-pyrroles **2.37** (**Scheme 2.8)**. The reaction is mediated efficiently with TMSOTf at room temperature affording only one diastereomeric product **2.37**. The cycloaddition demonstrated a broad scope where α,*β*-unsaturated, aliphatic and aromatic nitriles participated in the reaction. In addition, the di-*tert*-butylsilylene protective group is not a necessary structural feature. Unfortunately, electron deficient nitriles failed to participate.



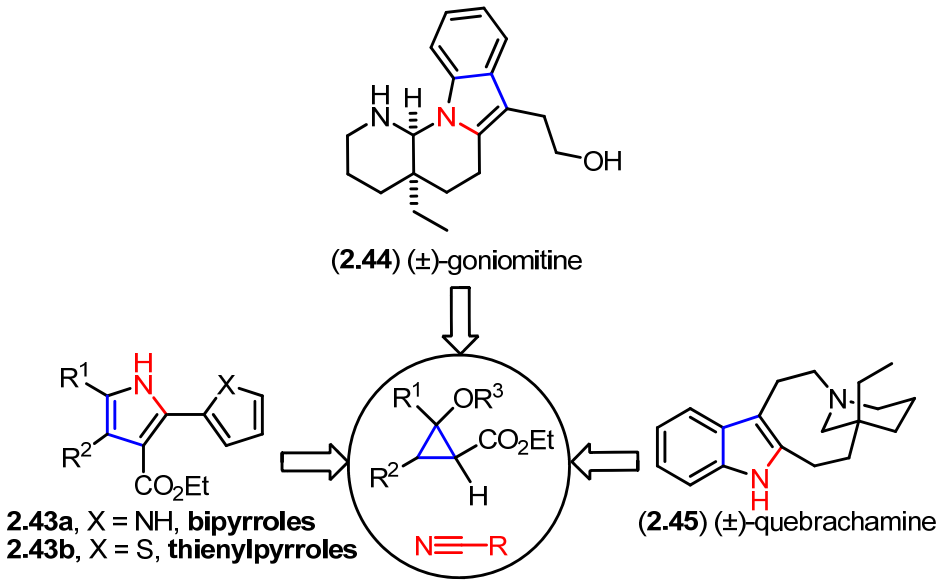
Scheme 2.8 – Nitriles/glycal-derived DA cyclopropane cycloaddition

Under these conditions the internal lactone linkage in **2.28** is important for the cycloaddition to occur. Therefore, attempted reaction between nitriles and cyclopropane **2.38** gave multiple products.[38] Interestingly, when the cycloaddition was done at lower temperature, the pyrrole derivatives **2.39** were obtained in excellent yields.[39] This observation prompted extending the reaction to general non-carbohydrate-derived DA cyclopropane substrates **2.40** and a highly efficient pyrrole synthesis was reported.[39] The reaction is highly regiospecific permitting the synthesis of multi substituted pyrroles **2.42** in moderate to excellent yields with a precise control on the substitution pattern (**Scheme 2.9**).



Scheme 2.9 – Pyrrole synthesis through nitrile/DA cyclopropane cycloaddition

Shortly afterward, this reaction was applied to the synthesis of many natural and unnatural targets including bipyrroles **2.43a** and thienylpyrroles **2.43b**,[40] (±)-goniomitine **2.44**,[41] and (±)-quebrachamin **2.45** (**Scheme 2.10**).[42] The effectiveness, cost efficiency and regioselectivity of this powerful annulation encouraged our group to apply it for the synthesis of 5-azaindoles. This work will be covered in the following section.



Scheme 2.10 – Applications of DA cyclopropane/nitrile cycloaddition

2.2. Synthesis of 5-Azaindoles via a Cycloaddition Reaction between Nitriles and DA Cyclopropanes

2.2.1. Research Objectives

Due to enhanced solubility and perhaps superior bioavailability and activity, the development of azaindoles as indole isosteres has received considerable attention over the past decade.[43] These efforts have resulted in the discovery of many active drug candidates (see **Figure 2.4** for representative examples).[44] Despite the promising potential of these heterocycles, they remain largely underexplored, in part due to the limited synthetic methods to prepare and functionalize the azaindole nucleus.

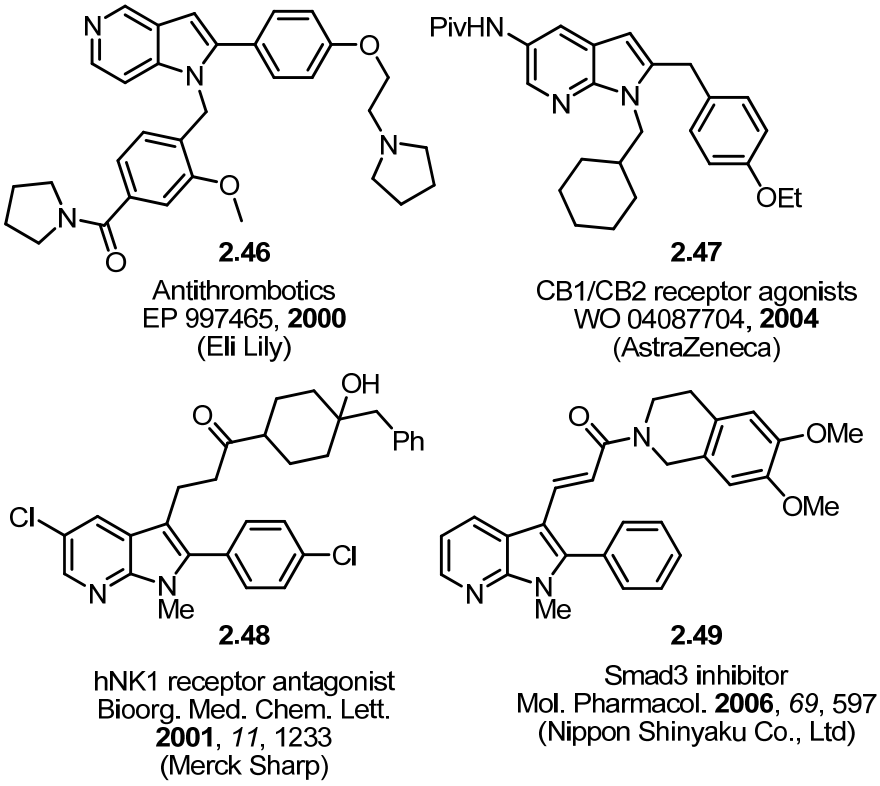
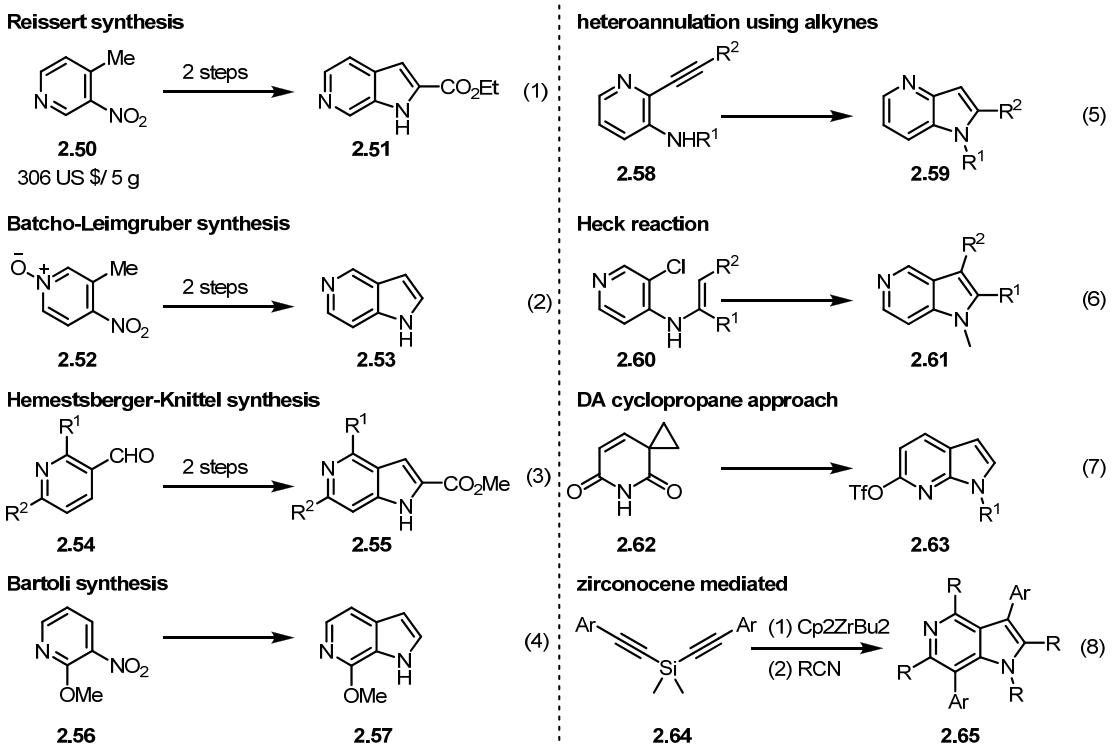


Figure 2.4 – Examples of pharmacologically active azaindoles

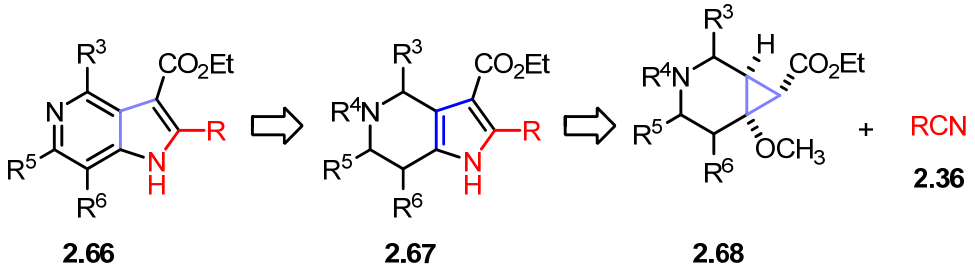
While there are many synthetic methods available for the preparation of substituted indoles,[45] only a few have been developed for the preparation of azaindoles. Some of the classic methods either do not work or are inefficient. The alternative methods generally rely on highly functionalized pyridine substrates, which are expensive or require multistep syntheses to prepare.[46] Some recent examples are summarized in **Scheme 2.11**.[46, 47] Additionally, C2 and C3 substituted 5-azaindoles are notoriously difficult to access as they often depend on multistep approaches involving highly functionalized pyridines, or strong bases to lithiate the 5-azaindole itself followed by electrophile trapping.[47]



Scheme 2.11 – Synthetic approaches to azaindoles

The goal of my research was to expand the formal [3+2] cycloaddition reaction between DA cyclopropanes and nitriles developed by our group in order to gain a

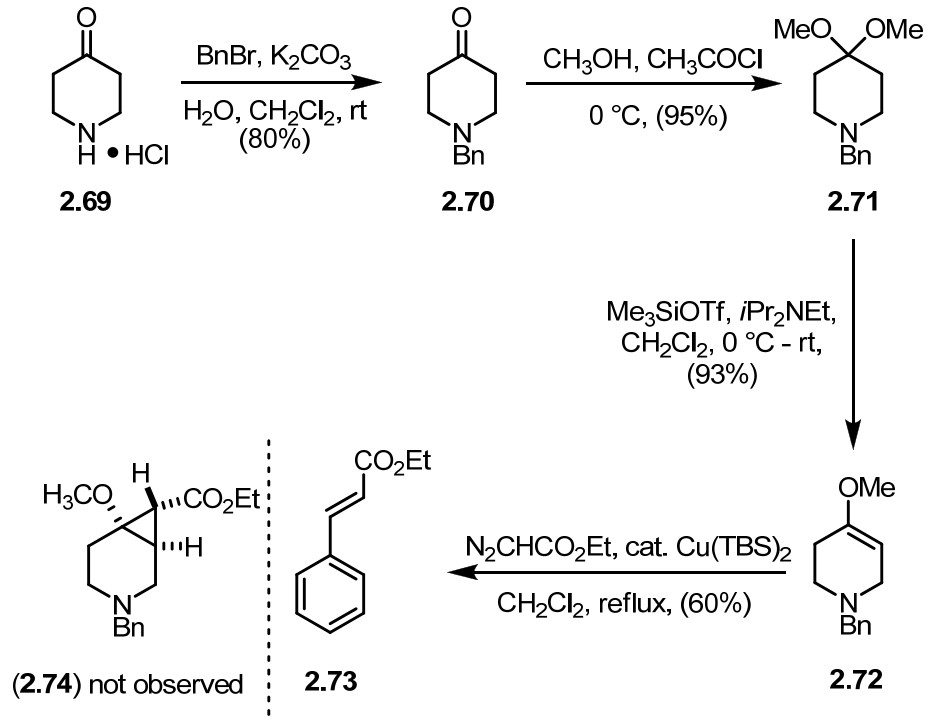
versatile access to azaindole heterocycles. The new approach envisioned a two step sequence for the synthesis of 5-azaindoles **2.66** by oxidation of a tetrahydro-1*H*-pyrrolo[3,2-c]pyridine intermediate **2.67** obtained through a cycloaddition reaction between nitriles **2.36** and a 3,4-cyclopropanopiperidine **2.68** (**Scheme 2.12**). This strategy allows for an easy access to a wide variety of C2 functionalized azaindoles simply by varying the starting nitrile.



Scheme 2.12 – Retrosynthetic analysis of azaindoles

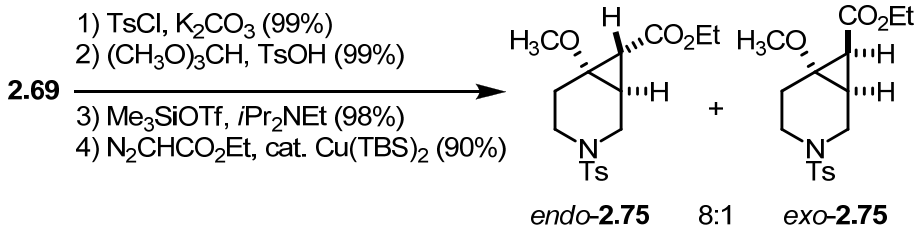
2.2.2. Results and Discussions

The synthesis of the cyclopropanopiperidine began with benzyl protection of 4-piperidone **2.69** followed by acetalization in acidic methanol (**Scheme 2.13**).[48] Then the resulting acetal **2.71** was converted to enol ether **2.72** under Gassman's conditions;[49] however, when **2.72** was subjected to cyclopropanation with ethyl diazoacetate in presence of $Cu(TBS)_2$,[50] the ethyl cinnamate **2.73** was obtained in 60% yield and none of the desired cyclopropane **2.74** was observed. The cinnamate is likely formed by nucleophilic attack of the piperidine nitrogen at the carbene followed by nucleophilic attack of the formed carbanion at the benzylic position followed by elimination.



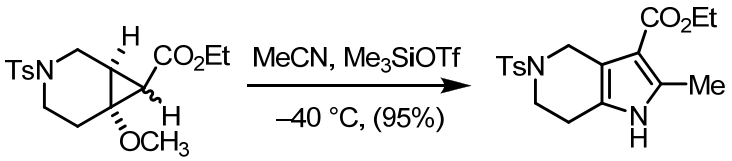
Scheme 2.13 – Attempted synthesis of the cyclopropanopiperidine

To avoid this undesired reaction a tosyl protecting group was employed (**Scheme 2.14**),[51] and cyclopropanation under the same conditions afforded the desired cyclopropane **2.75** in 90% yield as an inconsequential 8 : 1 mixture of *endo* to *exo* diastereomers (**Scheme 2.14**).



Scheme 2.14 – Access to cyclopropanopiperidines

With cyclopropane **2.75** in hand it was allowed to react with acetonitrile under the standard annulation conditions (1.0 equiv. Me_3SiOTf, –40 °C).[39] Both diastereomers worked equally well to give the tetrahydropyrrolopyridine **2.76a** as a white solid in 95% isolated yield (**Scheme 2.15**). This material was easily and economically prepared on gram scale, and was selected as a model substrate for screening oxidation conditions to provide the desired azaindole nucleus.

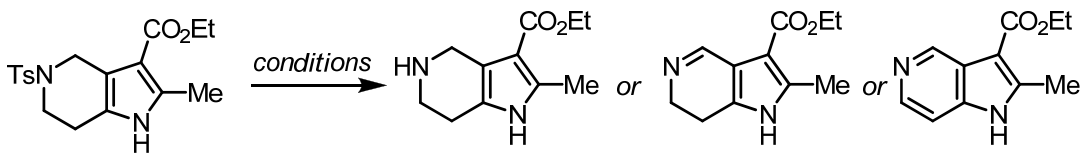


2.75 **2.76a**

Scheme 2.15 – Nitrile annulation

It was thought that either a two step sequence involving elimination or deprotection of the tosylate followed by oxidation would be acceptable, as well as a one step process to give the azaindole directly. Various strategies were explored, including strong bases,[52] Na-naphthalenide,[53] DDQ,[54] Pd/C, and MnO_2.[55] In each case, either decomposition or no reaction was observed (**Table 2.1**, entries 1– 6). Ultimately it was found that SeO_2 executed the desired oxidation extraordinarily well and afforded the azaindole in 92% isolated yield (**Table 2.1**, entry 7).[56] A control experiment was done where the product after SeO_2 was isolated directly without basic work up. In this case the fully oxidized product was obtained as sulfonyl salt with the pyridine nitrogen. Therefore a basic workup is only necessary to neutralize this salt. It is noteworthy that both oxidation and deprotection of the tosylate group was done in a single step utilizing SeO_2.

Table 2.1 – Deprotection and oxidation

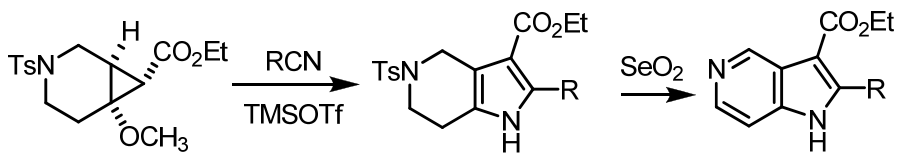


2.76a **2.77** **2.78** **2.79a**

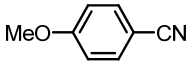
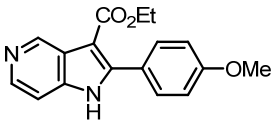
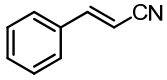
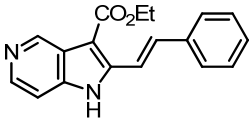
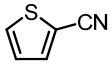
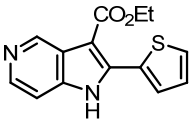
entry	conditions	yield (%)
1	MeONa/MeOH	decomposition
2	*t*BuOK/*t*BuOH	decomposition
3	Na-naphthalenide/THF	decomposition
4	DDQ/toluene	decomposition
5	5% Pd/C, mesitylene	no reaction
6	MnO_2,CH_2Cl_2	no reaction
7	SeO_2, dioxane	92% azaindole (**2.79a**)

With reaction conditions established for both the nitrile annulation and subsequent oxidation the reaction scope was explored, and the results are summarized in **Table 2.2**. The reaction works well with other aliphatic nitriles (**Table 2.2**, entry b) as well as aromatic and electron rich aromatic nitriles (**Table 2.2**, entries c and d). Unsaturated nitriles are effective (**Table 2.2**, entry e) as are those containing heteroatoms, such as 2-thiophenecarbonitrile (**Table 2.2**, entry f). The annulation reaction is conveniently run with a large excess of nitrile as solvent, but where this is impractical, nitromethane was employed. Unfortunately, sterically hindered (e.g., pivalonitrile and isobutyronitrile) or electron deficient nitriles (e.g., 4-bromobenzonitrile) did not engage in the reaction.

Table 2.2 – Scope of azaindole synthesis[a]



2.75 **2.76** **2.79**

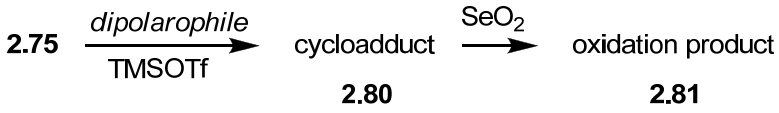
entry	nitrile	azaindole (**2.79**)	ann. yield	ox. yield
a	MeCN	R = Me	95%	92%
b	EtCN	R = Et	62%	94%
c	PhCN	R = Ph	92%	97%
d			86%	81%
e			69%	61%
f			87%	61%

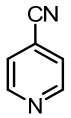
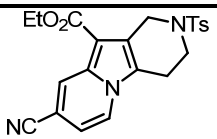
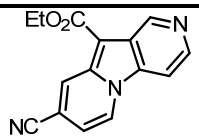
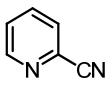
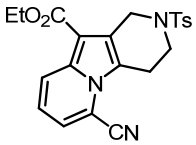
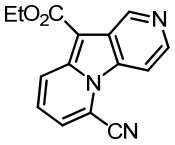
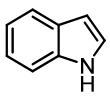
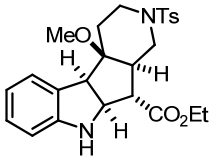
[a]Cycloaddition reactions were run at –40 °C using 1.0 equiv of cyclopropane, 2.0 equiv nitrile, 1.0 equiv Me_3SiOTf in nitromethane solvent. In the case of acetonitrile (entry a), excess nitrile was used as solvent. Oxidation conditions: 5 equiv of SeO_2 in refluxing dioxane.

The Pagenkopf group had shown previously that other functional groups can react in formal dipolar cycloadditions with DA cyclopropanes, including electron deficient pyridines[57] and indoles.[58] While not intended to be exhaustive, **Table 2.3** shows that the 3,4-cyclopropanopiperidine **2.75** reacts analogously to afford fused azaindoles very efficiently. The reactions with both 4-cyanopyridine and 2-cyanopyridine gave their

respective tetrahydro-pyridoindolizines (**Table 2.3**), and both underwent oxidation with SeO_2 to the pyridoindolizine. The single crystal x-ray structure of **2.81b** was solved and the ORTEP is presented in (**Figure 2.5**). The cycloaddition with indole provided the cycloadduct **2.80c** in 57% yield, but the standard SeO_2 oxidation conditions were ineffective in this case.

Table 2.3 – [3+2] Cycloannulation between pyridines and indole with cyclopropane **2.59**



entry	dipolarophile	annulation product (**2.80**)	yield	oxidation product (**2.81**)	yield
a			**2.80a** (71%)		**2.81a** (99%)
b			**2.80b** (53%)		**2.81b** (64%)
c[a]			**2.80c** (57%)	decomposition	N/A

[a] Relative stereochemistry was not determined but was assigned by analogy only. For a relevant discussion with similar systems, see reference 58.

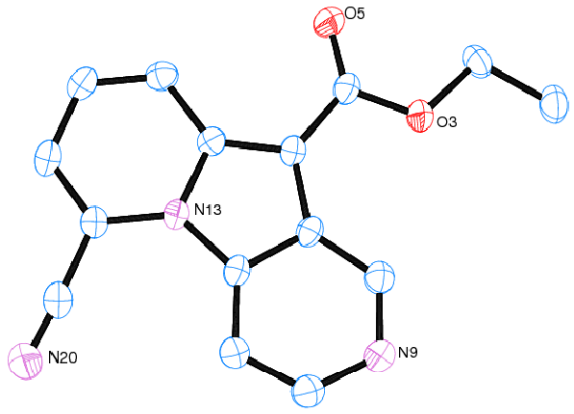


Figure 2.5 – X-ray crystal structure of **2.81b**

2.2.3. Summary

A novel and practical two step sequence for the preparation of C2 substituted 5-azaindoles and fused azaindoles has been reported. The target compounds were obtained in 34-87% overall yield. The synthetic sequence starts with an easily prepared and inexpensive piperidine based DA cyclopropane, which is then allowed to react with nitriles, pyridines and indoles. A subsequent SeO_2 mediated oxidation cleaves the tosyl protecting group and oxidizes the substrates to provide the aromatic azaindoles.

2.3. Experimental

2.3.1. General

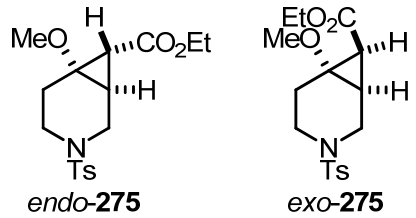
All reactions were run under an argon atmosphere unless otherwise indicated. Flasks were oven dried and cooled in a dessicator prior to use. Solvents and reagents were purified by standard methods.[59] Dichloromethane, dioxane were purified by passing the

solvents through activated alumina columns. $MeNO_2$ was dried by refluxing under CaH_2 for one hour prior to distillation. Synthetic intermediates including enol ethers,[51] bis(N-tertbutylsalicylamidinato)copper(II) ($Cu(TBS)_2$),[50] and ethyl diazoacetate were prepared according to the published procedures. All other chemicals were of reagent quality and used as obtained from commercial sources unless otherwise noted. The progress of reactions were monitored by thin layer chromatography (TLC) performed on F254 silica gel plates. The plates were visualized by staining with ceric ammonium molybdate,[60] or p-anisaldehyde. Column chromatography was performed with Silica Flash P60 60 Å silica gel from Silicycle according to the Still method.[61]

The ^1H and ^{13}C NMR data were obtained on 400 or 600 MHz spectrometers. All spectra were obtained in deuterated chloroform and/or DMSO-d_6. The spectra were referenced to residual chloroform (at δ 7.25 ppm for ^1H spectra and the center peak of the triplet at δ 77.0 (t) for ^{13}C spectra) and DMSO-d_6 (at δ 2.49 ppm for ^1H spectra and the center peak of the multiplet at δ 39.50 (m) for ^{13}C spectra). When peak multiplicities are given, the following abbreviations are used: s, singlet; d, doublet; dd, doublet of doublets; td, triplet of doublets; t, triplet; q, quartet; m, multiplet; br, broad; EI mass spectra were obtained spectrometer at an ionizing voltage of 70 eV. Melting points are uncorrected.

2.3.2. Detailed Experimental Procedures

2.3.2.1. Cyclopropane Synthesis



endo-**275** *exo*-**275**

***endo* - Ethyl 6-methoxy-3-tosyl-3-azabicyclo[4.1.0]heptane-7-carboxylate (*endo*-2.75) and *exo*- ethyl 6-methoxy-3-tosyl-3-azabicyclo[4.1.0]heptane-7-carboxylate (*exo*-2.75)**

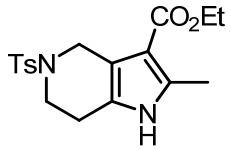
To a refluxing solution of the corresponding enol ether,[51] (1.33g, 5 mmol) and $Cu(TBS)_2$,[50] (0.014 g, 0.25 mmol) in 15 mL CH_2Cl_2, diazoacetate (1.09 mL, 10.4 mmol) was added drop wise over 3 hrs. After refluxing for 8 h at room temperature, the solvent evaporated and the crude reaction mixture was flashed on silica gel using EtOAc/hexanes (10–30%) for elution to provide the *endo* diastereomer as yellow oil (80% yield, 1.4 g). R_f 0.16 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.49 (d, *J* = 8.4, 2H), 7.22 (d, *J* = 8.01, 2H), 4.07–3.99 (m, 2H), 3.28 (d, *J* = 11.72, 1H), 3.09 (s, 3H), 3.06-2.97(m, 2H), 2.58-2.55 (m, 1H), 2.32 (s, 3H), 2.18-2.10 (m, 3H), 1.67 (d, *J* = 6.25, 1H), 1.15 (t, *J* = 7.13, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 143.5, 132.8, 129.5, 127.1, 64.6, 60.4, 54.1, 43.6, 42.4, 30.6, 27.9, 25.3, 21.1, 13.9; HRMS *m/z* 353.12970 (calcd for $C_{17}H_{23}NO_5S$, 353.1297).

The *exo* diastereomer was obtained as yellow oil (10% yield, 0.17 g). R_f 0.2 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.54 (d, *J* = 8.4, 2H), 7.23 (d, *J* = 8.01, 2H), 4.11-4.03 (m, 3H), 3.40-3.33 (m, 1H), 3.20 (dd, *J* = 12.31, 7.03 Hz, 1H), 3.16 (s, 3H), 2.78-2.71(m, 1H), 2.48-2.42 (m, 1H), 2.34 (s, 3H), 2.10-2.03 (m, 1H), 1.84 (d, *J* =

10.75, 1H), 1.72-1.67(m, 1H), 1.18 (t, J = 7.23, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 143.3, 133.3, 129.4, 127.3, 61.5, 60.5, 53.7, 42.1, 40.6, 28.5, 23.9, 23.5, 21.3, 13.8; HRMS *m/z* 353.1293 (calcd for $C_{17}H_{23}NO_5S$, 353.1297).

2.3.2.2. General Procedure for the Cycloaddition Reaction

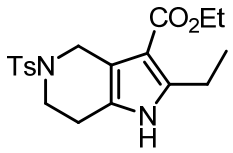
To a solution of cyclopropane **275** (0.17 g, 0.5 mmol) and nitrile (1.0 mmol, 2 eq) in $MeNO_2$ (3.0 mL) at –40 °C, TMSOTf (0.1 ml, 0.5 mmol) was added dropwise. After completion (14-18 h, TLC), 5.0 mL of EtOAc was added and the mixture was poured into a saturated solution of $NaHCO_3$ (15 mL). The heterogeneous mixture was separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered through Celite and concentrated under reduced pressure. Purification by flash chromatography on silica gel using EtOAc-hexanes for elution provided the title compounds.



Ethyl 2-methyl-5-tosyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-c]pyridine-3-carboxylate (2.76a)

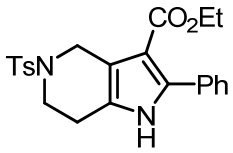
White powder (95% yield, 0.17 g). R_f 0.5 (50% EtOAc/hexanes); mp 158–160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ8.10 (s, 1H), 7.67 (d, J = 8.21, 2H), 7.27 (d, J = 8.01, 2H), 4.25 (s, 2H), 4.21(q, J = 7.52, 2H), 3.37 (t, J = 5.67, 2H), 2.63 (t, J = 5.37, 2H), 2.43 (s, 3H), 2.40 (s, 3H), 1.33 (t, J = 7.03, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 143.3,

135.0, 134.2, 129.5, 127.4, 122.3, 114.6, 108.4, 59.2, 44.7, 43.2, 22.9, 21.4, 14.45, 13.2; HRMS *m/z* 362.1310 (calcd for $C_{18}H_{22}N_2O_4S$, 362.1300).



Ethyl 2-ethyl-5-tosyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-c]pyridine-3-carboxylate (2.76b)

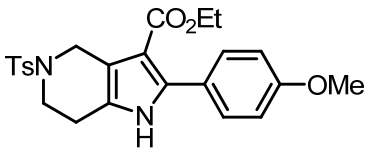
White powder (62% yield, 0.10 g). R_f 0.18 (30% EtOAc/hexanes); mp 50–52 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ8.47 (s, 1H), 7.64 (d, *J* = 8.21, 2H), 7.25 (d, *J* = 8.01, 1H), 4.23–4.17 (m, 4H), 3.34 (t, *J* = 5.47, 2H), 2.85 (q, *J* = 7.42, 2H), 2.62 (s, 2H), 2.37 (s, 3H), 1.31 (t, *J* = 7.03, 3H), 1.14 (t, *J* = 7.52, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 143.3, 141.1, 133.9, 129.54, 127.3, 122.3, 114.4, 107.3, 59.1, 44.7, 43.3, 22.8, 21.4, 20.5, 14.3, 13.6; HRMS *m/z* 376.1467 (calcd for $C_{19}H_{24}N_2O_4S$, 376.1457).



Ethyl 2-phenyl-5-tosyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-c]pyridine-3-carboxylate (2.76c)

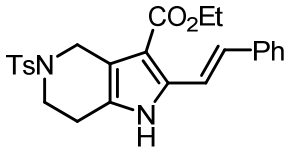
White powder (92% yield, 0.15 g). R_f 0.16 (30% EtOAc/hexanes); mp 54-56 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ8.10 (s, 1H), 7.71 (d, *J* = 8.21, 2H), 7.47 (d, *J* = 7.82, 2H), 7.38–7.29 (m, 5H), 4.34 (s, 2H), 4.15(q, *J* = 7.23, 2H), 3.34 (t, *J* = 5.67, 2H), 2.73 (t, *J* =

5.57, 2H), 2.41 (s, 3H), 1.23 (t, *J* = 7.13, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 143.4, 136.8, 134.2, 132.0, 129.6, 128.9, 128.2, 128.0, 127.5, 124.6, 116.2, 108.7, 59.5, 44.8, 43.1, 23.0, 21.4, 14.1; HRMS *m/z* 424.1462 (calcd for $C_{23}H_{24}N_2O_4S$, 424.1457).



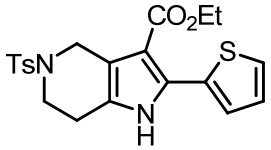
Ethyl 2-(4-methoxyphenyl)-5-tosyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridine-3-carboxylate (2.76d)

Yellow oil (86% yield, 0.39 g). R_f 0.16 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.54 (s, 1H), 7.66 (d, *J* = 8.21, 2H), 7.38 (d, *J* = 8.79, 2H), 7.27 (d, *J* = 8.01, 2H), 6.82 (d, *J* = 8.79, 2H), 4.29 (s, 2H), 4.09 (q, *J* = 7.03, 2H), 3.76 (s, 3H), 3.37 (t, *J* = 7.03, 2H), 2.66 (t, *J* = 5.47, 2H), 2.39 (s, 3H), 1.22 (t, *J* = 7.13, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 159.4, 143.4, 137.0, 133.9, 130.2, 129.5, 127.4, 124.3, 124.2, 115.6, 113.3, 107.9, 59.4, 55.2, 44.8, 43.1, 22.9, 21.4,14.2; HRMS *m/z* 454.1572 (calcd for $C_{24}H_{26}N_2O_5S$, 454.1562).



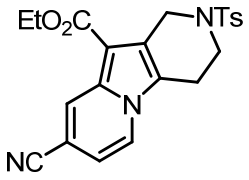
(E)-Ethyl 2-styryl-5-tosyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridine-3-carboxylate (2.76e)

White powder (69% yield, 0.12 g). R_f 0.15 (30% EtOAc/hexanes); mp 63-65 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ8.73 (s, 1H), 7.75 (d, *J* = 16.80, 1H), 7.68 (d, *J* = 7.21, 2H), 7.40 (d, *J* = 7.62, 2H), 7.30-7.27 (m, 4H), 7.20 (t, *J* = 7.33, 1H), 6.72 (d, *J* = 17.00, 1H), 4.29-4.24 (m, 4H), 3.39 (t, *J* = 5.67, 2H), 2.71 (t, *J* = 5.67, 2H), 2.40 (s, 3H), 1.36 (t, *J* = 7.13, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 143.5, 136.7, 134.5, 134.0, 129.6, 128.6, 127.7, 127.4, 126.8, 126.3, 125.7, 117.6, 116.6, 110.2, 59.7, 44.7, 43.1, 23.1, 21.4, 14.4; HRMS *m/z* 450.1602 (calcd for $C_{25}H_{26}N_2O_4S$, 450.1613).



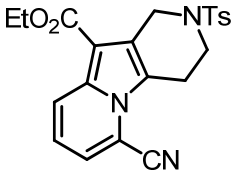
Ethyl 2-(thiophen-2-yl)-5-tosyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridine-3-carboxylate (2.76f)

White powder (87% yield, 0.37 g). R_f 0.14 (40% EtOAc/hexanes); mp 45-48 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.68 (d, *J* = 8.21, 2H), 7.40 (dd, *J* = 3.66, 1.17 Hz, 1H), 7.30–7.28 (m, 3H), 7.01 (dd, *J* = 5.13, 3.66 Hz, 1H), 4.31 (s, 2H), 4.21 (q, *J* = 7.18, 2H), 3.41 (t, *J* = 5.72, 2H), 2.70 (t, *J* = 5.72, 2H), 2.40 (s, 3H), 1.30 (t, *J* = 7.11, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 143.4, 134.1, 132.9, 129.8, 129.6, 127.4, 127.3, 127.0, 125.9, 124.9, 116.3, 109.1, 59.8, 44.8, 43.0, 22.9, 21.4, 14.2; HRMS *m/z* 430.1010 (calcd for $C_{21}H_{22}N_2O_4S_2$, 430.1021).



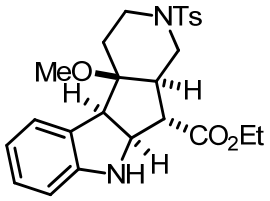
Ethyl 8-cyano-2-tosyl-1,2,3,4-tetrahydropyrido[3,4-*b*]indolizine-10-carboxylate (2.80a)

Light brown powder (71%, 0.15 g). R_f 0.8 (10% MeOH/DCM); mp 183–185 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.75 (s, 1H), 7.71 (d, *J* = 8.06, 2H), 7.30 (d, *J* = 8.06, 2H), 6.83 (dd, *J* = 7.11, 1.69 Hz, 1H), 4.56 (s, 2H), 4.36 (q, *J* = 7.08, 2H), 3.57 (t, *J* = 5.72, 2H), 2.91 (t, *J* = 5.64, 2H), 2.40 (s, 3H), 1.42 (t, *J* = 7.18, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 143.8, 133.9, 132.5, 129.7, 127.4, 126.1, 124.8, 122.2, 121.8, 118.2, 112.1, 104.1, 103.6, 60.2, 44.6, 42.6, 21.9, 21.5, 14.5; HRMS *m/z* 423.1253 (calcd for $C_{22}H_{21}N_3O_4S$, 423.1253).



Ethyl 6-cyano-2-tosyl-1,2,3,4-tetrahydropyrido[3,4-*b*]indolizine-10-carboxylate (2.80b)

Yellow crystals (53% yield, 0.22 g). R_f 0.28 (40% EtOAc/hexanes); mp 158–160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 9.04, 1H), 7.72 (d, *J* = 8.06, 2H), 7.30 (d, *J* = 8.06, 2H), 7.26 (d, *J* = 6.84, 1H), 6.97 (dd, *J* = 8.07, 7.45 Hz, 1H), 4.53 (s, 2H), 4.34 (q, *J* = 7.08, 2H), 3.50 (t, *J* = 5.62, 2H), 3.43 (t, *J* = 5.62, 2H), 2.40 (s, 3H), 1.42 (t, *J* = 6.96, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 143.7, 135.3, 133.8, 129.7, 127.5, 124.9, 124.3, 121.8, 119.3, 114.7, 107.3, 103.2, 60.0, 44.8, 42.9, 24.0, 21.4, 14.4; HRMS *m/z* 423.1261 (calcd for $C_{22}H_{21}N_3O_4S$, 423.1253).



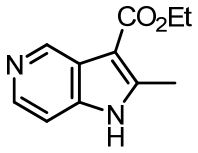
10a-Methoxy-5,5a,6,6a,7,8,9,10,10a,10b decahydrocyclopentadiene[*c*]pyridine[5,6-*b*]indole-6-carboxylic acid ethyl ester (2.80c)

White powder (57% yield, 0.8 g). R_f 0.17 (30% EtOAc/hexanes); mp 45–47 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.21, 2H), 7.27 (d, *J* = 8.01, 2H), 7.09 (d, *J* = 7.42, 1H), 7.01 (t, *J* = 7.33, 1H), 6.61 (t, *J* = 7.33, 1H), 6.54 (d, *J* = 7.82, 1H), 4.59 (dd, *J* = 10.36, 5.28 Hz, 1H), 4.32 (brs, 1H), 4.18 (q, *J* = 7.23, 2H), 3.82 (dd, *J* = 10.94, 3.91 Hz, 1H), 3.71 (d, *J* = 11.72, 1H), 3.41 (d, *J* = 10.55, 1H), 3.09 (s, 1H), 2.95 (dd, *J* = 12.70, 5.28 Hz, 1H), 2.69 (t, *J* = 11.14, 1H), 2.52 (s, 3H), 2.38 (s, 3H), 2.08 (td, *J* = 4.10, 1H), 1.69 (td, *J* = 4.49, 1H), 1.28 (t, *J* = 7.13, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 152.5, 143.1, 134.0, 129.5, 128.5, 127.2, 125.3, 118.0, 109.9, 81.1, 66.7, 60.6, 56.8, 52.7, 50.7, 50.6, 50.5, 44.3, 41.48, 29.5, 21.3, 14.1.; HRMS *m/z* 470.1889 (calcd for $C_{25}H_{30}N_2O_5S$, 470.1875).

2.3.2.3. General Procedure for SeO_2 Oxidation

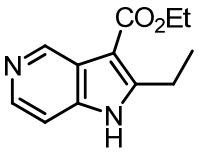
To a solution of pyrrole (1.0 mmol) in dioxane (5.0 mL), SeO_2 (5.0 mmol, 5 eq) was added. The heterogeneous reaction mixture was heated at reflux for 24-40 h. After completion, the reaction was allowed to cool to rt and $NaHCO_3$ (2 g) and anhydrous $MgSO_4$ (1 g) were added. After stirring for 30 min the heterogeneous mixture was filtered and the solids were washed with EtOAc (3 x 5 mL). The collected filtrate was

washed with 10% NaOH (3 x 10 mL) and the organic layer was separated. The organic layer was extracted with HCl 10% (3 x 10 mL). The combined acidic extracts were collected and neutralized with 10% NaOH and back extracted with EtOAc (3 x 10 mL). The organic layer then washed with brine, dried ($MgSO_4$), filtered through celite and concentrated under reduced pressure to provide the title compounds.



Ethyl 2-methyl-1*H*-pyrrolo[3,2-*c*]pyridine-3-carboxylate (2.79a)

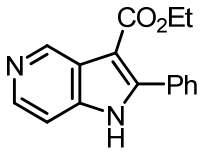
White powder (92% yield, 0.18 g). R_f 0.24 (10% MeOH/DCM); mp 145–150 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.10 (s, 1H), 8.21 (d, *J* = 5.27, 1H), 7.34 (d, *J* = 5.27, 1H), 4.29 (q, *J* = 6.83, 2H), 2.66 (s, 3H), 1.35 (t, *J* = 7.03, 3H); ^{13}C NMR (600 MHz, DMSO-d_6) δ 164.3, 145.8, 142.7, 140.9, 138.6, 123.3, 106.4, 102.2, 59.1, 14.3, 13.3; HRMS *m/z* 204.0892 (calcd for $C_{16}H_{14}N_2O_2$, $C_{11}H_{12}N_2O_2$, 204.0899).



Ethyl 2-ethyl-1*H*-pyrrolo[3,2-*c*]pyridine-3-carboxylate (2.79b)

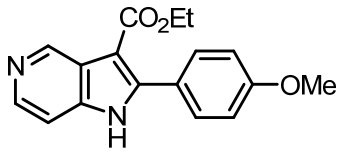
White powder (94% yield, 0.20 g). R_f 0.14 (10% MeOH/DCM); mp 135–137 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.12 (brs, 1H), 8.24 (brs, 1H), 7.39 (s, 1H), 4.29 (q, *J* = 6.94, 2H), 3.10 (q, *J* = 7.48, 2H), 1.35 (t, *J* = 7.04, 3H), 1.26 (t, *J* = 7.55, 3H); ^{13}C NMR

(100 MHz, DMSO-d_6) δ 172.0, 164.2, 151.4, 142.9, 140.9, 138.7, 106.7, 101.4, 59.2, 20.3, 14.36, 13.4; HRMS *m/z* 218.1058 (calcd for $C_{12}H_{14}N_2O_2$, 218.1055).



Ethyl 2-phenyl-1*H*-pyrrolo[3,2-c]pyridine-3-carboxylate (2.79c)

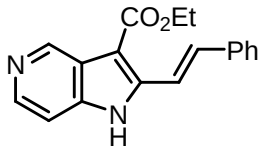
Off-white powder (97% yield, 0.25 g). R_f 0.17 (10% MeOH/DCM); mp 210-213 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.29 (d, *J* = 5.28, 1H), 7.73–7.71 (m, 2H), 7.51–7.49 (m, 3H), 7.42 (d, *J* = 5.42, 1H), 4.22 (q, *J* = 7.04, 2H), 1.25 (t, *J* = 7.11, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.7, 145.5, 143.9, 141.4, 139.2, 130.9, 130.02, 129.3, 127.8, 123.9, 106.9, 102.4, 59.4, 14.1; HRMS *m/z* 266.1047 (calcd for $C_{16}H_{14}N_2O_2$, 266.1055).



Ethyl 2-(4-methoxyphenyl)-1*H*-pyrrolo[3,2-*c*]pyridine-3-carboxylate (2.79d)

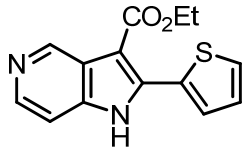
White powder (81% yield, 0.23 g). R_f 0.11 (10% MeOH/DCM); mp 198-200 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (brs, 1H), 8.29 (brs, 1H), 7.68 (d, *J* = 8.50, 2H), 7.42(s, 1H), 7.05 (d, *J* = 8.50, 2H), 3.23 (q, *J* = 7.04, 2H), 3.83 (s, 3H), 1.27 (t, *J* = 7.04, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.8,160.2, 145.7, 143.7, 141.2, 139.2, 131.5,

122.9, 113.4, 101.8, 100.2, 94.3, 59.4, 55.3, 14.2; HRMS *m/z* 296.1156 (calcd for $C_{17}H_{16}N_2O_3$, 296.1161).



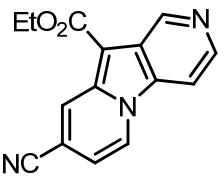
(*E*)-Ethyl 2-styryl-1*H*-pyrrolo[3,2-*c*]pyridine-3-carboxylate (2.79e)

Yellow powder (61% yield, 0.18 g). R_f 0.20 (10% MeOH/DCM); mp 258-260 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.17 (brs, 1H), 9.30 (brs, 1H), 8.00 (d, *J* = 16.40, 1H), 7.60–7.56 (m, 3H), 7.46 (t, *J* = 7.61, 2H), 7.42 (d, *J* = 5.72, 1H), 7.38 (t, *J* = 7.32, 1H), 4.37 (q, *J* = 7.03, 2H), 1.41 (t, *J* = 7.03, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.0, 143.4, 142.9, 141.8, 140.0, 135.8, 134.0, 129.0, 128.9, 126.8, 116.7, 106.6, 103.6, 59.6, 14.2.; HRMS *m/z* 292.1205 (calcd for $C_{18}H_{16}N_2O_2$, 292.1212).



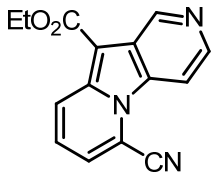
Ethyl 2-(thiophen-2-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-3-carboxylate (2.79f)

Yellow powder (61% yield, 0.8 g). R_f 0.2 (10% MeOH/DCM); mp 170-175 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (brs, 1H), 8.29 (brs, 1H), 7.94 (s, 1H), 7.81 (d, *J* = 4.69, 1H), 7.42 (d, *J* = 5.27, 1H), 7.24–7.23(m, 1H), 4.34 (q, *J* = 7.03, 2H), 1.37 (t, *J* = 7.32, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.7, 143.30, 141.1,139.8, 139.1, 131.8, 130.3, 129.8, 127.1, 124.1, 106.9, 101.9, 59.6, 14.2; HRMS *m/z* 272.0612 (calcd for $C_{14}H_{12}N_2O_2S$, 272.0619).



Ethyl 8-cyanopyrido[3,4-*b*]indolizine-10-carboxylate (2.81a)

Yellow powder (73% yield, 0.19 g). R_f 0.17 (10% MeOH/DCM); mp 168–171 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.42 (brs, 1H), 9.17 (d, *J* = 7.23, 1H), 8.52 (brs, 1H), 8.50 (s, 1H), 8.26 (d, *J* = 5.47, 1H), 7.23 (d, *J* = 6.84, 1H), 4.36 (q, *J* = 7.03, 2H), 1.42 (t, *J* = 7.03, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.1, 144.9, 141.09, 136.6, 134.0, 128.4, 126.1, 122.9, 117.4, 111.2, 110.6, 106.9, 96.8, 59.9, 14.3; HRMS *m/z* 265.0856 (calcd for $C_{15}H_{11}N_3O_2$, 265.0851).



Ethyl 6-cyanopyrido[3,4-*b*]indolizine-10-carboxylate (2.81b)

Yellow crystals (64% yield, 0.16 g). R_f 0.30 (10% MeOH/DCM); mp 183-186 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.61 (s, 1H), 8.61 (dd, *J* = 9.38, 1.17 Hz, 1H), 8.58 (d, *J* = 6.06, 1H), 8.46 (dd, *J* = 6.15, 1.07 Hz, 1H), 7.90 (dd, *J* = 7.03, 1.17 Hz, 1H), 7.60 (dd, *J* = 9.38, 6.84 Hz, 1H),4.41 (q, *J* = 7.10, 2H), 1.43 (t, *J* = 7.13, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.4, 145.4, 139.5, 133.8, 127.5, 125.0, 124.8, 123.2, 114.5, 111.1, 107.4, 107.2, 96.2, 59.9, 14.4; HRMS *m/z* 265.0846 (calcd for $C_{15}H_{11}N_3O_2$, 265.0851).

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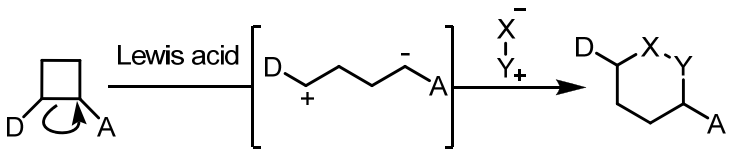
Chapter 3: Cyclobutane Activation for Dipolar Cycloaddition: New Synthesis of Alkoxy Substituted Donor−Acceptor (DA) Cyclobutanes and their First Use in Dipolar Cycloaddition with 1,2-Dipoles

This chapter describes the development of a new synthesis of alkoxy substituted 1,1-cyclobutane diesters (DA cyclobutanes) and their utility for the first time in dipolar cycloaddition to prepare highly substituted piperidines, piperideines and tetrahydropyrans. A brief summary of the reactivity and utility of cyclobutane rings in dipolar cycloaddition will be covered. The cyclobutane chemistry presented in this chapter was proposed, proofed and optimized by me. Part of the synthetic work was carried out in collaboration with colleagues Mr. Andrew C. Stevens and Mr. Benjamin P. Machin; namely the tetrahydropyran methodology; and the results have been published in *Organic Letters*.[1] The individual contributions for the tetrahydropyran methodology are as follows: the reaction concept was designed, proofed and firstly optimized by me. I made the cyclobutane starting materials and cycloadducts derived from 1-methoxycyclohex-1-ene. The rest of substrate scope and examining different reaction conditions was carried by Mr. Andrew C. Stevens and Mr. Benjamin P. Machin. Some portions of the text and schemes have been reproduced in part with permission from Moustafa, M. M. A. R.; Pagenkopf, B. L. *Org. Lett*. DOI: 10.1021/ol102062t and Moustafa, M. M. A. R.; Stevens, A. C.; Machin, B. P.; Pagenkopf, B. L. *Org. Lett*. DOI: 10.1021/ol102063f.

3.1. Introduction

3.1.1. Formal [4+2] Cycloaddition of DA Cyclobutanes

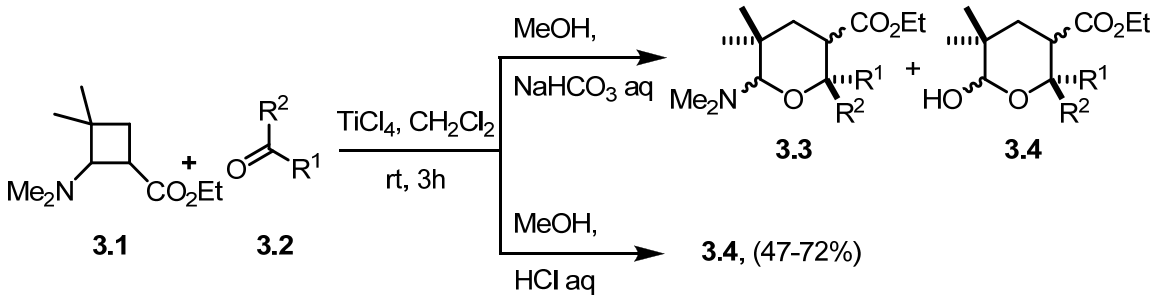
The introduction of cyclobutane derivatives, as molecular building blocks in the synthesis of highly complex compounds has gained increasing importance in the last decades. This is mainly because cyclobutane derivatives are easily obtained by many reliable methods. In addition, activated cyclobutanes can undergo a facile and selective bond cleavage under a variety of conditions due to an inherent ring strain. The cleavage point and rate are dependent on the reaction mechanism, conditions, reagents and the ring substituents.[2] While there are numerous reactions involving C−C bond cleavage of cyclobutanes, this section will include an extensive review of the cycloaddition examples where cyclobutane ring is being used as 1,4–dipole equivalent (**Scheme 3.1**).



Scheme 3.1 – Dipolar cycloadditions with cyclobutanes

Saigo and coworkers at the University of Tokyo were the first to utilize activated cyclobutanes in cycloaddition reactions in a similar fashion to cyclopropanes.[3] In the presence of titanium(IV) chloride, a novel [4+2] annulation reaction between 2-(dimethylamino)cyclobutanecarboxylic esters **3.1** and carbonyl compounds **3.2** proceeds easily to give the pyran derivatives **3.4** in moderate to good yields (**Scheme 3.2**). When a basic work up was involved a mixture of unhydrolyzed dimethylamino derivative **3.3** and δ-lactol **3.4** were obtained. In order to hydrolyze **3.3** into **3.4**, acidic treatment was

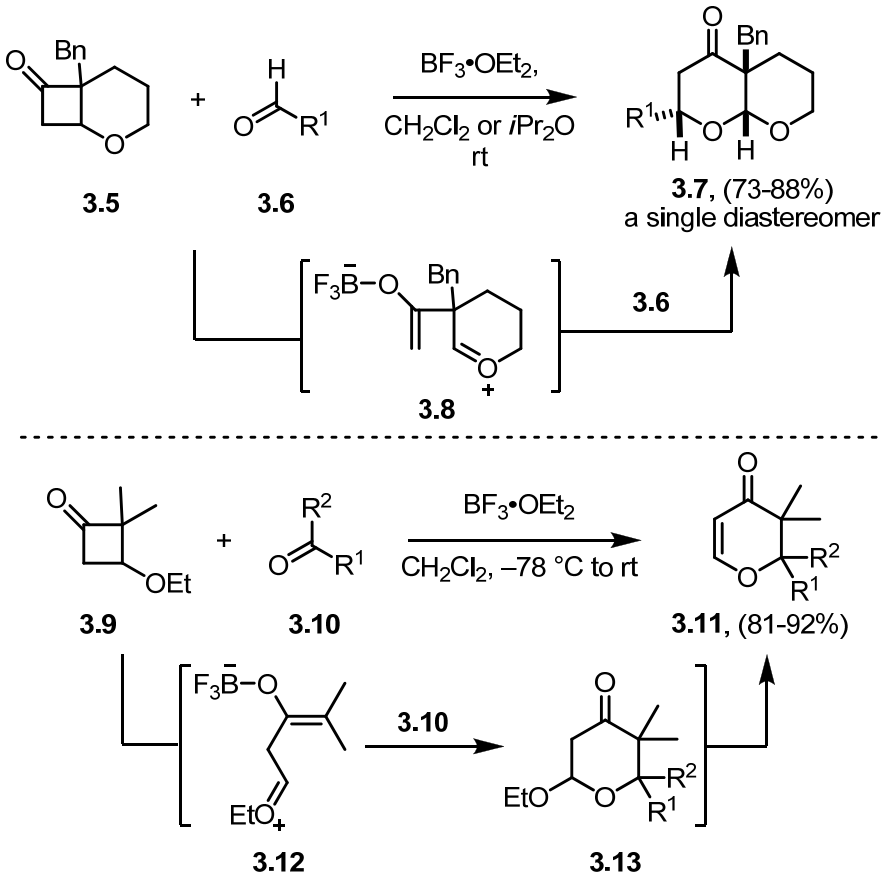
required. Although Saigo obtained a mixture of stereoisomers with his amine activated cyclobutanes, moderate to excellent diastereoselectivities were obtained when other activating groups were utilized (*vide infra*).



Scheme 3.2 – The reaction of dimethylamino cyclobutanecarboxylic esters and carbonyl compounds

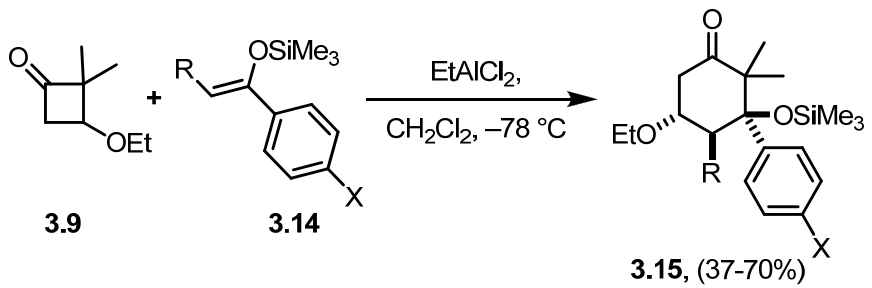
Since Saigo's first communication in 1991, surprisingly no other reports appeared until very recently where the Matsuo group has extended the previous reaction to alkoxy-activated cyclobutanones rings.[4] They have shown that aldehydes or ketones undergo a BF_3•OEt_2-catalyzed [4+2] annulation reaction with 3-alkoxycyclobutanones **3.5** and **3.9** to give substituted δ-pyrones **3.7** and **3.11** respectively (**Scheme 3.3**). Compared to Saigo's cycloaddition, a single diastereomer was obtained in case of aldehydes cycloadducts. On the other hand cycloadducts of ketones were obtained in moderate diastereoselectivity when the reaction done in CH_2Cl_2. Interestingly, the diastereomeric ratio of these cycloadducts dramatically increased when diisopropyl ether was employed as a solvent. In addition to this marked diastereoselectivity, a regioselective ring opening was also observed. While the bicyclic cyclobutanone **3.5** gave rise to less substituted enolate intermediates **3.8**, more substituted enolates **3.12** were generated from the monocyclic cyclobutanone **3.9** (**Scheme 3.3**). The new methodology was utilized

efficiently to prepare various multisubstituted dihydro-δ-pyrones, which might be difficult to be accessed by hetero Diels-Alder chemistry.[5] Shortly thereafter, Matsuo has extended the annulation reactions of these 3-alkoxycyclobutanones to include silyl enol ethers,[6] allyl silanes,[7] and imines.[8]



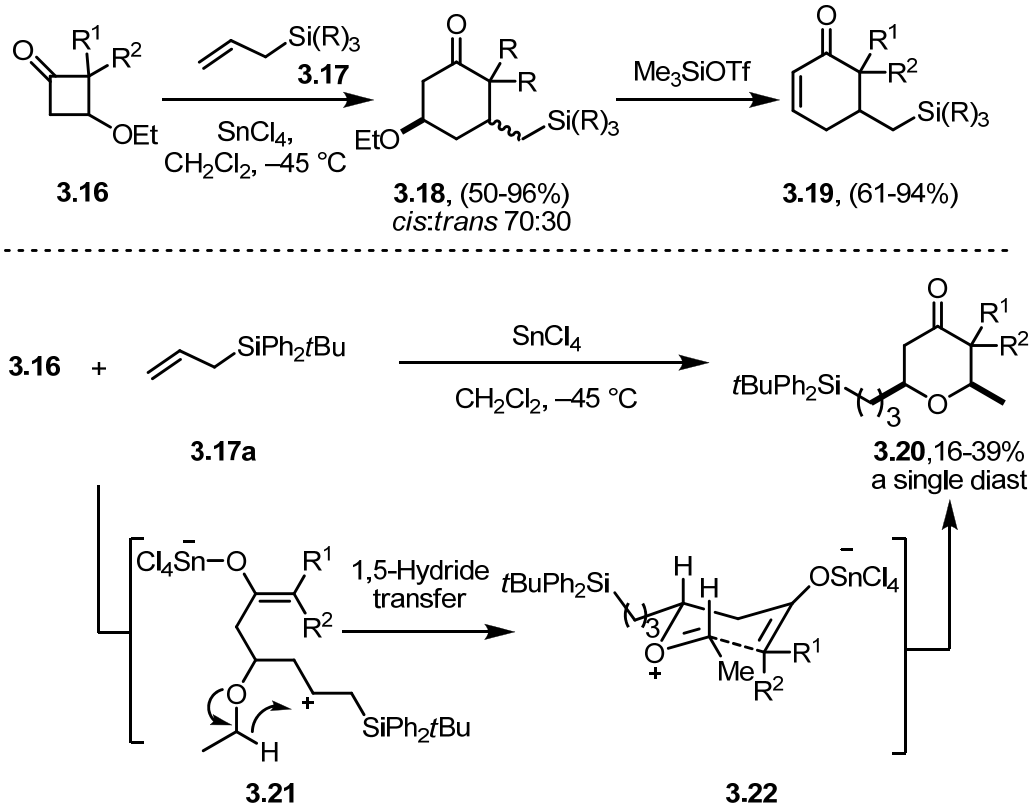
Scheme 3.3 – The reaction of 3-alkoxycyclobutanones with carbonyl compounds.

From various Lewis acids screened, $EtAlCl_2$ catalyzed the desired annulation of silyl enol ether **3.14** with different 3-alkoxycyclobutanone (e.g. **3.9)** to yield highly oxygenated cyclohexanone derivatives **3.15** in moderate yield and good selectivity (**Scheme 3.4**).[6]



Scheme 3.4 – The reaction of silyl enol ether and 3-alkoxycyclobutanone

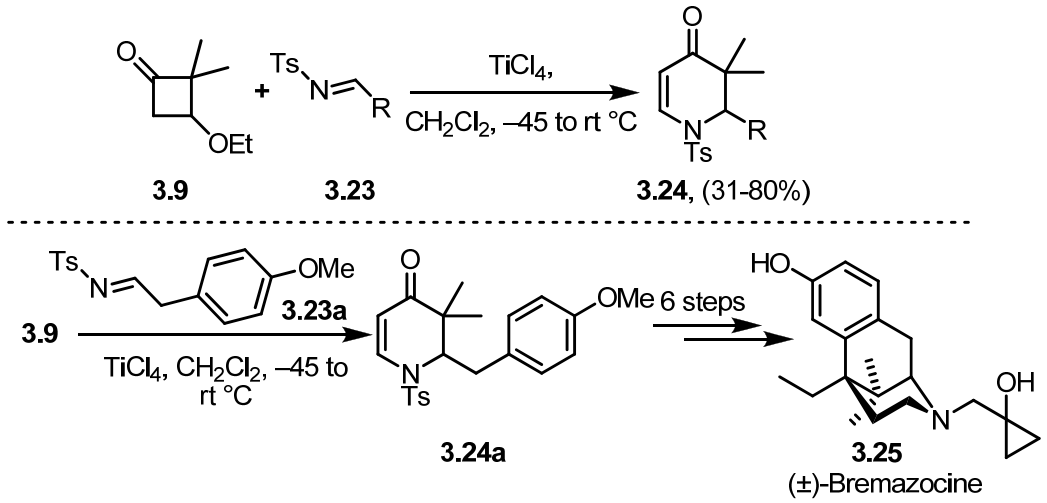
On the other hand, tin(IV) chloride was the best catalyst for the formal [4+2] cycloaddition between allysilanes **3.17** and 3-alkoxycyclobutanones **3.16** (**Scheme 3.5**).[7] The cyclohexanone cycloadducts **3.18** were obtained in good yield however in moderate diastereoselectivity. Furthermore, when these cycloadducts were treated with Me_3SiOTf, the versatile cyclohexenone derivatives **3.19** were synthesized in good to excellent yields over two steps. Interestingly, when a sterically none demanding silyl group was employed (e.g. allyl trimethylsilane), the desired cycloaddition occurred rather than elimination of the silyl group. These results are in contrast to the usual tendency of LA catalyzed reactions of allyltrimethylsilane with carbonyl compound to give the allylation products. When the bulky $SiPh_2tBu$ group was employed, the unexpected pyrones **3.20** were obtained in moderate yields (**Scheme 3.5**). This pyrone product is believed to arise from the more stable zwitterionic intermediate **3.22** generated through a 1,5-hydride transfer of the *β*–silyl cation **3.21**. The tendency toward the hydride shift and hence the pyrone formation improved by increasing the steric demand of the R substituent of the cyclobutane **3.16**.



Scheme 3.5 – The reaction of allysilane and 3-alkoxycyclobutanone

Finally, the Matsuo group has very recently extended the cycloaddition reactions of the alkoxycyclobutanones to include imine based dipolarophiles.[8] A formal [4+2] cycloaddition reaction was achieved when **3.9** was treated with different *N-p*-toluenesulfomyl imines **3.22** in the presence of catalytic $TiCl_4$ to yield different dihydropyridone derivatives **3.24** after elimination of ethanol from the expected cycloadducts (**Scheme 3.6**). Cleverly, this cycloaddition has been applied to the synthesis of bremazocine **3.25** in six steps starting from the cycloadduct **3.24a**. When compared to the many natural products that have been prepared through DA cyclopropane based methodologies, the synthesis of bremazocine **3.25**, published in

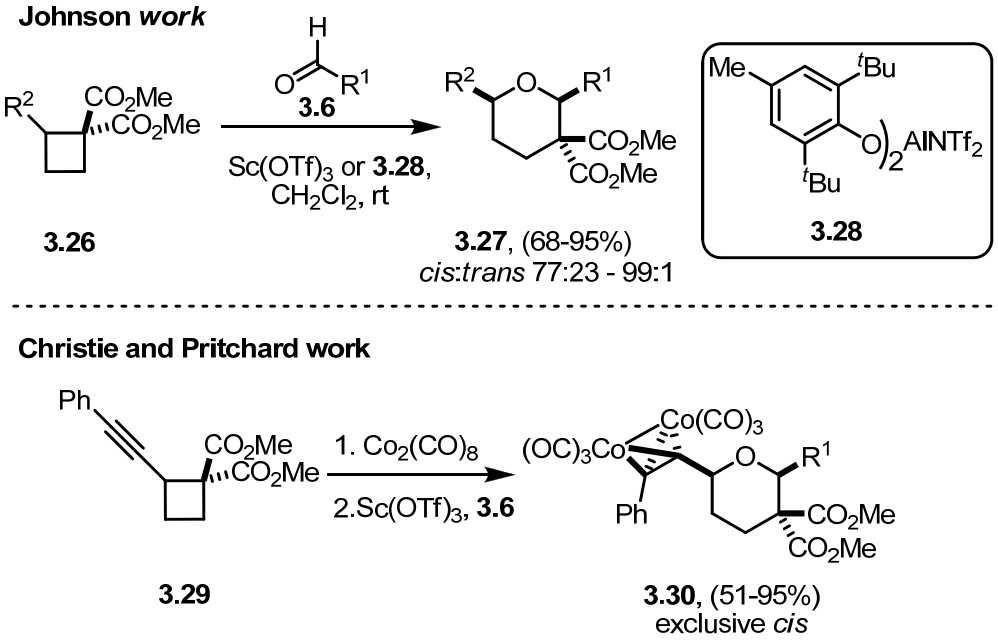
2010,[8] is the first natural product to be synthesized based on DA cyclobutane cycloadditions.



Scheme 3.6 – The reaction of imines and 3-alkoxycyclobutanone

In the previous examples either the cyclobutane or the cyclobutanone is activated by dimethylamino, or alkoxy substituents, respectively. However the first reports regarding the annulation of 1,1-cyclobutanediesters **3.26** and **3.29**, activated by carbon-based activating groups were published in 2009 simultaneously by Christie and Pritchard,[9] and the Johnson groups (**Scheme 3.7**).[10] In Johnson's work, the reaction with different electron deficient and/or electron rich aromatic aldehydes was efficiently catalyzed by $Sc(OTf)_3$. However, a more bulky LA **3.28** was required to activate the cyclobutane ring toward aliphatic aldehydes. In both cases, the *cis*-2,6-disubstituted tetrahydropyrans **3.27** were obtained in excellent yields and diastereoselectivities (**Scheme 3.7**).[10] When compared to Johnson's work, the cycloaddition reported by Christie and Pritchard is limited to cyclobutanes activated by a dicobalt-alkyne complex. In addition, shorter reaction time, high diastereoselectivity and yield were observed only

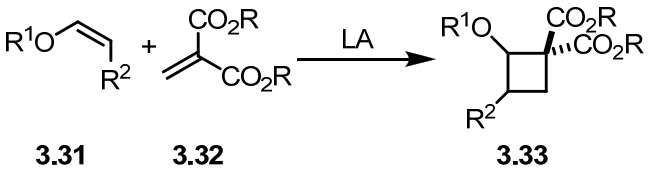
with electron rich aromatic aldehydes. When aliphatic and/or electron deficient aldehydes were utilized, either a poor yield, diastereoselectivity or a limited scope was observed (**Scheme 3.7**).[9] This is in contrast to the homologues reaction with DA cyclopropanes where the electron deficient aldehydes react faster.



Scheme 3.7 – The reaction of aldehydes and 1,1-cyclobutane diesters

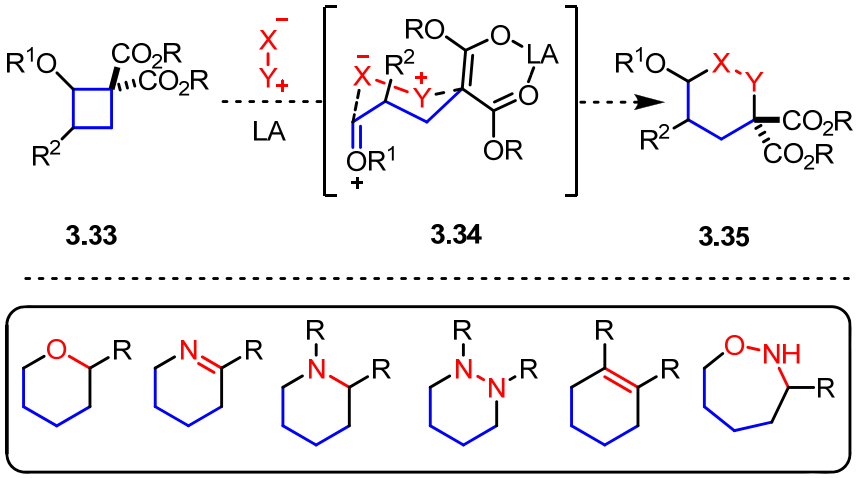
3.1.2. Research Objectives

Doubly activated 2-alkoxy-1,1-cyclobutane diesters **3.33** are interesting 1,4-dipole equivalents because they can be prepared in a single step from the corresponding enol ether and methylidene malonate by LA catalysis (**Scheme 3.8**). Although they are known compounds, the use of these DA cyclobutanes in dipolar cycloadditions had not been realized prior to the work presented in this thesis.



Scheme 3.8 – Lewis acid catalyzed synthesis of 2-alkoxy-1,1-cyclobutane diesters

The objective of my research was to synthesize these cyclobutanes and to utilize them in dipolar cycloadditions. Under LA catalysis these cyclobutanes are expected to undergo a facile heterolytic bond cleavage to form 1,4-zwitterion intermediates **3.34** that can be trapped with different 1,2- and 1,3-dipoles including aldehydes, nitriles, imines, diazines, acetylenes, nitrones, etc (**Scheme 3.9**).



Scheme 3.9 – Targeted formal [4+2] cycloadditon with 1,2 and 1,3 dipoles e.g. aldehydes, nitriles, imines, diazines, acetylenes, nitrones, etc.

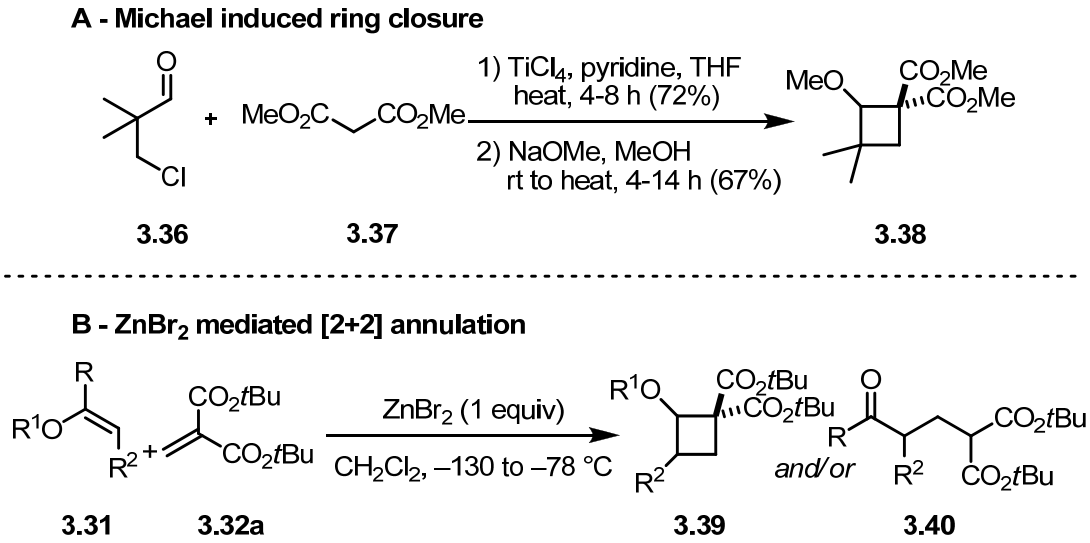
The expected six and/or seven membered carbo and heterocycles are important cores of many natural and unnatural products. The introduction of the formal [4+2] cycloaddition of 2-alkoxy-1,1-cyclobutane diesters as a new way to achieve these rings is expected to have a great impact on the scope, versatility and utility of DA cyclobutane

based methodologies. The following sections will discuss the synthesis of these DA cyclobutanes and their use for the first time to prepare piperidine, piperideines and tetrahydropyrans.

3.2. Results and Discussions

3.2.1. Synthesis of 2-Alkoxy-1,1-Cyclobutane Diesters

Although there are many recent highly efficient and stereoselective syntheses of cyclobutanes activated by silyl ether groups,[11] the syntheses of cyclobutanes activated by alkyl ethers are very limited.[12] Two methods have been reported that allow access to alkoxy substituted DA cyclobutanes with geminal electron withdrawing groups in good yields (**Scheme 3.10**).



Scheme 3.10 – Synthesis of 2-alkoxy-1,1-cyclobutane diesters

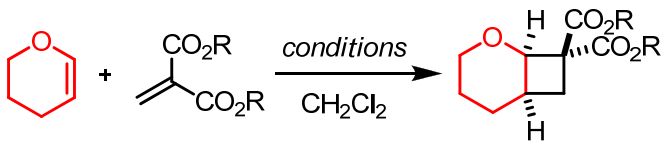
The use of a Michael induced ring closure of acyclic substrates (e.g **3.36**) was not selected as a preparative route as it offers limited control over the stereochemistry and

required multiple steps. On the other hand, the $ZnBr_2$ mediated [2+2] annulation reaction reported by Roberts in 1986 appeared much more promising since the same LA ($ZnBr_2$) can be used in the subsequent [4+2] reaction allowing for a one-pot tandem process (**Scheme 3.10**).

Based on this earlier precedence, $ZnBr_2$ was taken as the Lewis acid for the cycloaddition of dihydropyran **3.31a** and di-*t*-butyl methylidene malonate **3.32a**. Unfortunately, duplication of the conditions reported by Roberts, in our hands, gave a poor yield (39% **Table 3.1**, entry 1), and isolation of the cyclobutane was complicated by both considerable byproducts and the stoichiometric $ZnBr_2$. More problematic, however, was our inability to extend this methodology to the more readily available and cheaper diethyl methylidene malonate **3.32b** (depending on their synthesis from the corresponding malonates, they cost approximately 150$/5g for **3.32a** and 120$/kg for **3.32b**). Only trace amounts of the desired cyclobutane **2.39b** was isolated along with a complex mixture of polymerization and ring opened byproducts (**Table 3.1**, entry 2). This may be attributed to the higher reactivity of diethyl methylidene malonate **3.32b** and its tendency to rapid polymerization when compared to **3.32a**. To improve the outcome of the reaction, other Lewis acids were screened, including TMSOTf, $ZnCl_2$, $Sc(OTf)_3$, and $Yb(OTf_3$ (**Table 3.1**). Although TMSOTf and $ZnCl_2$ were completely ineffective, $Sc(OTf)_3$, and $Yb(OTf_3)$ emerged as highly effective catalysts, with $Yb(OTf)_3$ being the catalyst of choice due to slightly higher yields and lower catalyst cost (**Table 3.1**, entries 5 and 6). The use of catalytic $Yb(OTf)_3$ rather than stoichiometric $ZnBr_2$ made the reactions operationally much simpler to perform, requiring only a simple filtration through silica plug to provide the cyclobutane in high purity and yield. In addition,

comparable yields were obtained with catalyst loadings as low as 2 mol % however longer reaction times are required.

Table 3.1 – Optimization of the 2-alkoxy-1,1-cyclobutane diesters synthesis



3.31a **3.32a,** R = *t*Bu **3.32b,** R = Et **3.39a,** R = *t*Bu **3.39b,** R = Et

entry	R	catalyst	temperature	yield (%)[a]
1	*t*Bu	1 equiv $ZnBr_2$	–130 °C to –78 °C	39[b]
2	Et	1 equiv $ZnBr_2$	–130 °C to –78 °C	17[b]
3	Et	1 equiv $ZnCl_2$	–130 °C to –78 °C	0[c]
4	Et	1 equiv TMSOTf	–78 °C	0[c]
5	Et	10 mol % $Sc(OTf)_3$	–78 °C	78
6	Et	10 mol % $Yb(OTf)_3$	–78 °C	84

[a] Isolated yield. [b] Product contaminated by ring opened and polymeric substance. [c] Polymeric substances observed.

The crude cyclobutane obtained from the reaction catalyzed by $Yb(OTf)_3$ (**Figure 3.1**, C) is sufficiently pure and even cleaner than the purified material obtained when $ZnBr_2$ is used (**Figure 3.1**, A).

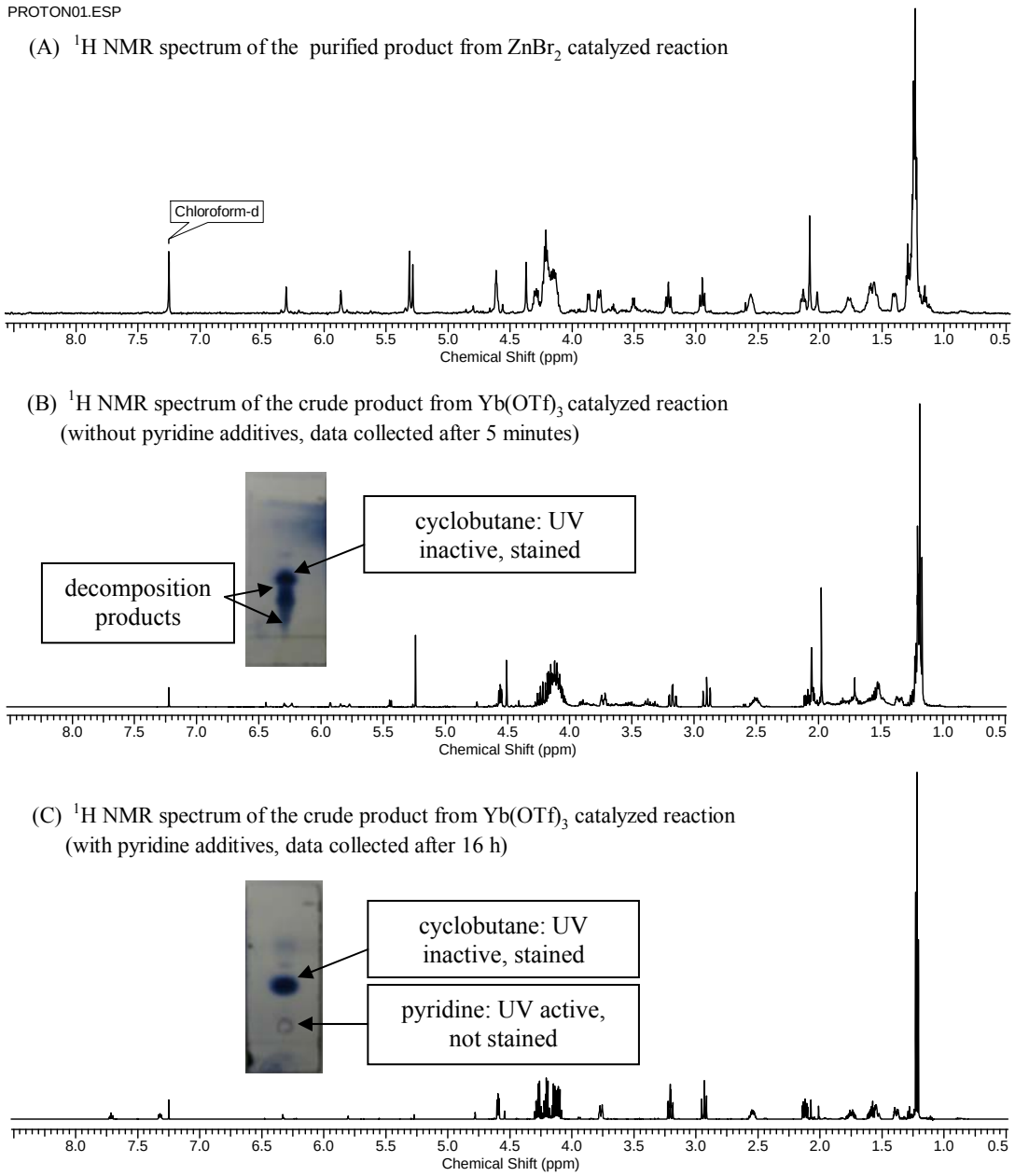


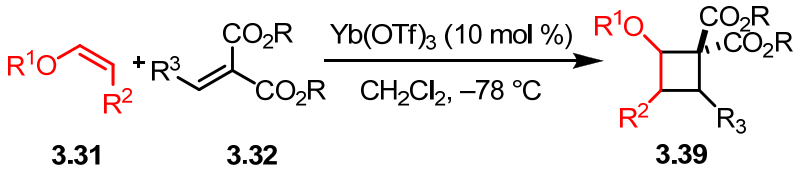
Figure 3.1 – ^{1}H NMR spectra of **3.39b** isolated from $ZnBr_2$ and $Yb(OTf)_3$ (with and without pyridine additive) catalyzed reactions as well as the TLC images.

On the other hand, it was observed that the cyclobutane ring is very sensitive to $Yb(OTf)_3$ and it decomposes within minutes after isolation if there are any traces of the catalyst left (**Figure 3.1**, b). Therefore, the cyclobutane should be purified once collected to avoid any decomposition. For large scale applications, few drops of pyridine

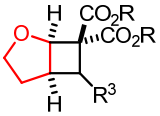
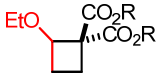
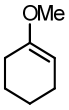
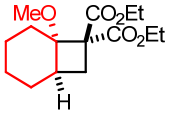
(equivalent amount to LA) can be added to the reaction at –78 °C before filtration. The pyridine additive chelates $Yb(OTf)_3$ and prevents cyclobutane ring opening (**Figure 3.1,** c).

With a promising catalyst identified for the desired [2+2] annulation, the reaction scope was explored, and the results are summarized in **Table 3.2**.

Table 3.2 – Scope of the cyclobutane synthesis



3.31 **3.32** **3.39**

Entry	Enol Ether	Cyclobutane	yields[a]
1			**3.39c**, R^3= H, R = Et (93%) **3.39d**, R^3= H, R = *t*Bu (72%) **3.39e**, R^3= R = Me (NR)[b]
2			**3.39f**, R = Me (56%) **3.39g**, R = Et (80%)
3			**3.39h**, (70%)

[a] Isolated yield. When possible, only one diastereomer was isolated. [b] No reaction was observed. When the reaction warmed up to rt, polymerization takes place.

The range of compatible methylidene malonates has been expanded from the most stable *t*-butyl, to now encompass ethyl and the very reactive methyl derivatives. All methylidene malonates gave the target DA cyclobutanes in good to excellent yields

(entries 1-3). Unfortunately, the more substituted and stable 2-ethylidenemalonate was an ineffective reactant partner under these conditions (entry 1, **3.39e**). The range of enol ethers that participated in the cycloaddition was quite broad with cyclic, acyclic and higher-substitution patterns being tolerated (entries 1-3). All cyclobutanes were obtained in good to excellent yields and as single diastereomers. Some of the cyclobutanes were prepared on large scale in a single pot, with reactions providing the cyclobutane in up to 12 grams. The relative stereochemistry of the *cis*-products was assigned on the basis of NOE interactions. A representative spectrum (for cyclobutane **3.39b**) is presented in **Figure 3.2**.

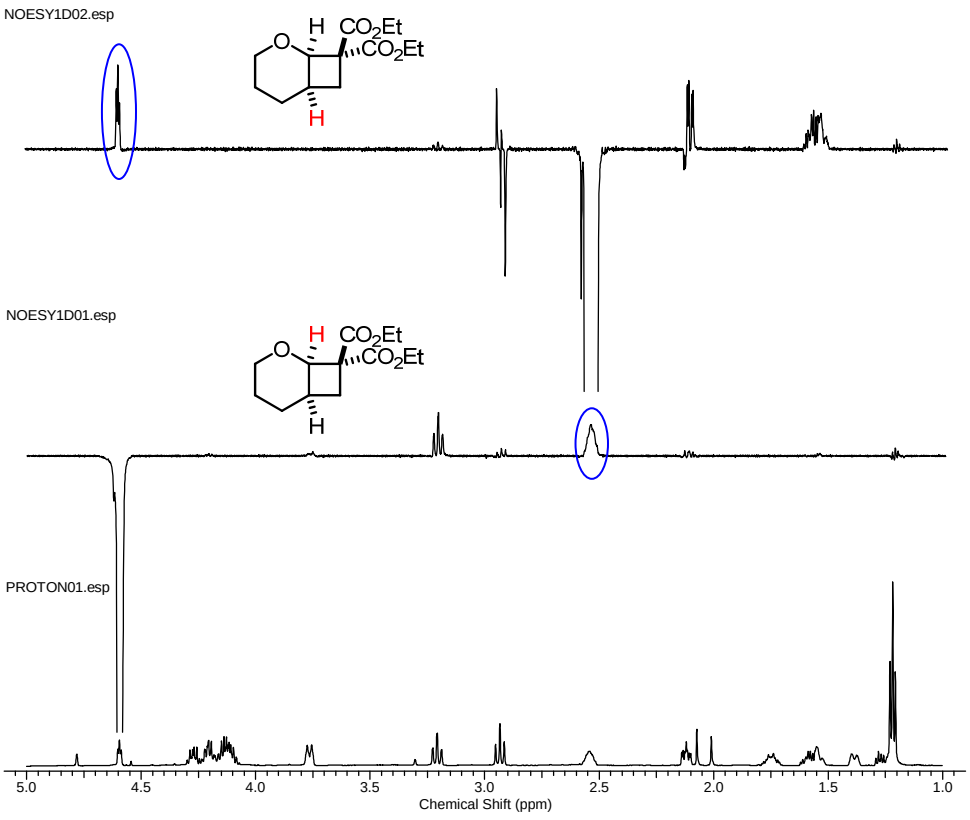
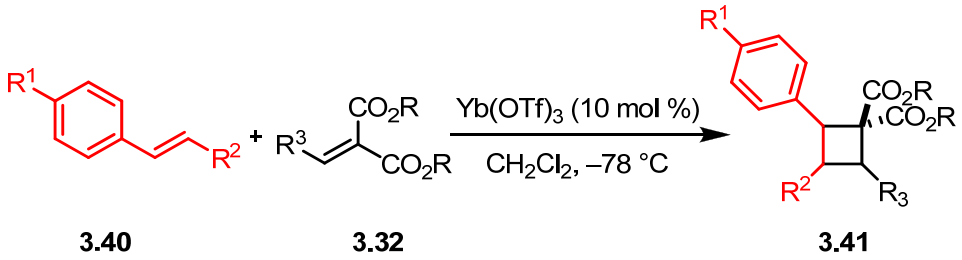


Figure 3.2 – 1D NOESY of cyclobutane **3.39b**

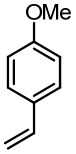
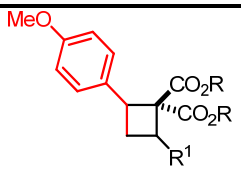
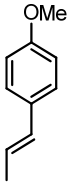
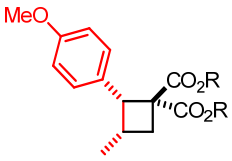
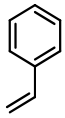
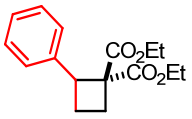
The 1D NOESY spectrum showed a strong interaction in the positive direction of the spectrum (highlighted in a blue circle) between the ring junction protons when either of them is irradiated (the irradiated proton colored red appears in the negative direction of the spectrum) (**Figure 3.2**).

Next, the ability of $Yb(OTf)_3$ to catalyze the same annulation reaction between methylidene malonates **3.32** and other electron rich alkenes was explored (**Table 3.3**).

Table 3.3 – Annulation reaction between styrene derivatives and methylidene malonates



3.40 **3.32** **3.41**

entry	styrene derivatives	cyclobutane	yields[a]
1			**3.41a**, R^3 = H, R = Et (81%) **3.41b**, R^3 = Ph, R = Me (NR)[b]
2			**3.41c**, R = Me (51%) **3.41d**, R = Et (71%) **3.41e**, R= *t*Bu (59%)
3			**3.41f**, (NR)[b]

[a]Isolated yield. When possible, only one diastereomer was isolated. [b]No reaction was observed. When the reaction warmed up to rt, polymerization takes place.

The [2+2] reaction of methylidene malonates **3.32** with *p*-vinyl anisole (**Table 3.3**, entry 1) and anethole (**Table 3.3**, entry 2) gave cyclobutanes **3.41a-e** as a single diastereomeric product. Similarly to 2-ethylidenemalonate, no reaction was observed with the more substituted 2-benzylidenemalonate (**Table 3.3**, entry 1, **3.41b**). Unfortunately, no reaction was observed with styrene and only polymerization products were observed (**Table 3.3**, entry 3, **3.41f**).

In summary, ytterbium triflate has been shown to be an excellent catalyst for the [2+2] annulation reaction between a wide variety of electron rich alkenes and methylidene malonates. The use of ytterbium triflate makes the reactions operationally much simpler to perform, and gives single diastereomeric products that are obtained cleaner and in higher yield. The use of these synthetically useful cyclobutanes in dipolar cycloaddition reactions will be covered in the following sections.

3.2.2. Formal [4+2] Cycloaddition of Alkoxy-substituted DA Cyclobutanes and Imines: Stereoselective Synthesis of Piperidines

Functionalized piperidine rings are among the most common heterocyclic cores in many natural compounds and unnatural synthetic analogues. **Figure 3.3** shows several representative examples.[13,14]Due to their broad pharmacological effects, the development of new synthetic methodologies to prepare piperidine heterocycles has received enormous attention over the years.[14] While a comprehensive review is beyond the scope of this thesis, some of the commonly used methods to prepare piperidines are summarized in **Figure 3.4**. In general, piperidines can be easily accessed by nucleophilic substitution, reductive amination, hydroamination, Michael addition, ring-closing metathesis, ene

reaction, radical cyclization, reduction of pyridine (**Figure 3.4**) and/or cycloaddition reactions (**Scheme 3.11**).[14]

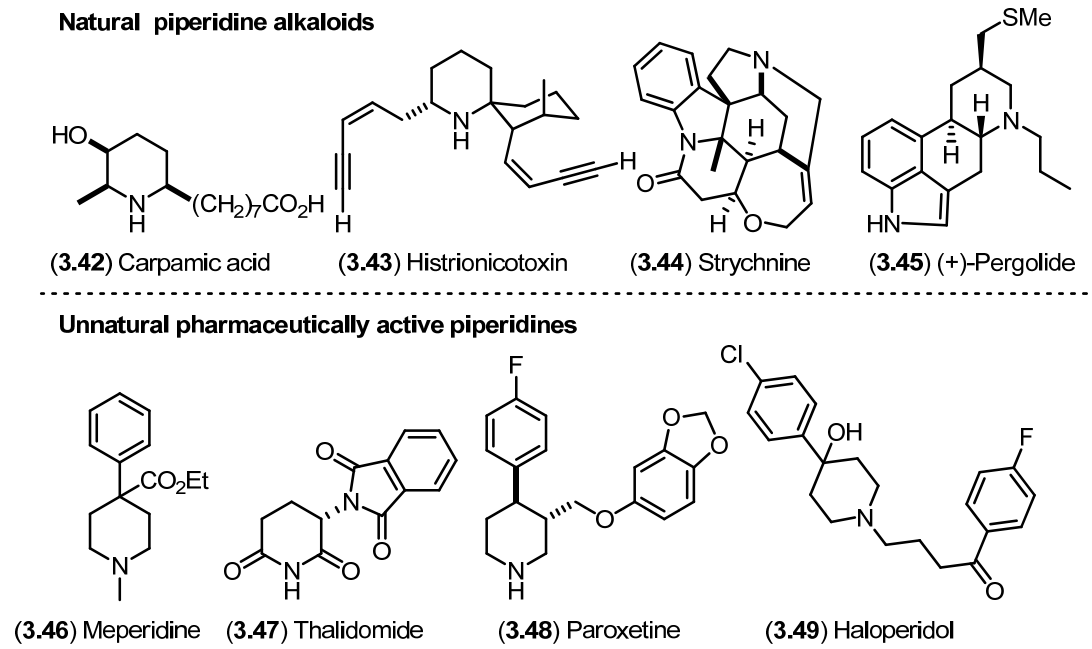


Figure 3.3 – Biologically active piperidines

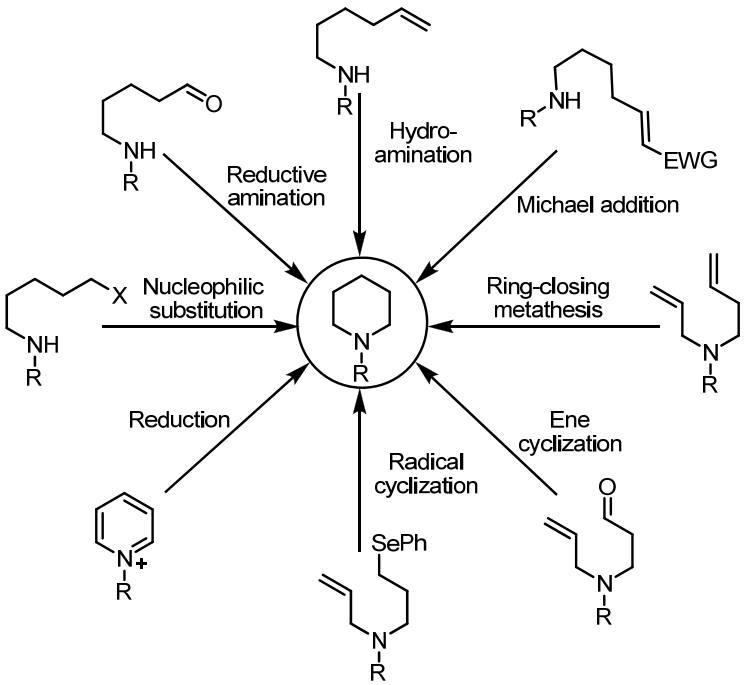
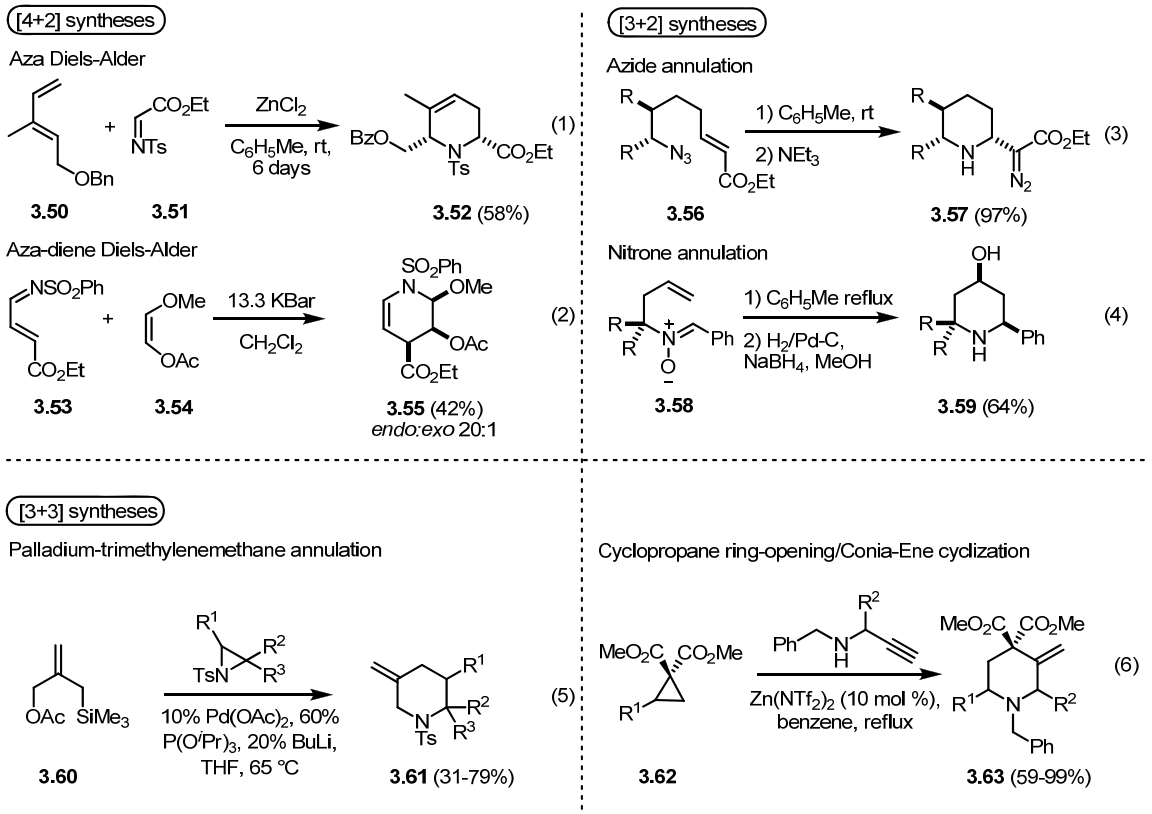


Figure 3.4 – Synthetic approaches toward piperidines

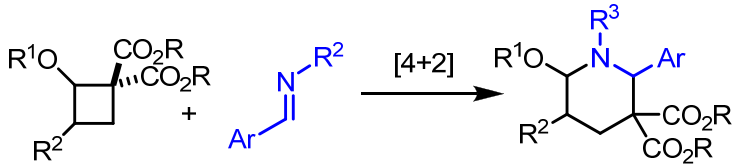
Although, many of these methods have been applied successfully in the synthesis of different piperidine derivatives, the stereoselective synthesis of multisubsituted piperidines and those containing quaternary carbons remains a known synthetic challenge.[14e] Cycloaddition reactions and related syntheses are among the most important methods that have been developed to solve this problem. **Scheme 3.11** shows some recent examples including Diels-Alder approach (equation 1&2),[15] dipolar cycloaddition with azides (equation 3)[16] and/or nitrones (equation 4),[17] palladium-trimethylenemethane mediated annulation (equation 5)[14f,18] and cyclopropane ring-opening/Conia-Ene cyclization (equation 6).[19]



Scheme 3.11– Cycloaddition routes and related syntheses toward multisubsituted piperidines

Indeed, these methods provide a reliable and efficient solution however with a variety of limitations..[14e] As such, the development of concise, versatile, efficient and stereocontrolled routes to multisubstituted piperidines stands to be of great importance to synthetic and medicinal chemists.

Imines have been utilized by us[20] and others[21] as dipolarophiles in Lewis acid-catalyzed [3+2] cycloadditions with DA cyclopropanes to furnish pyrrolidine derivatives in a stereoselective manner. At the onset of this project, analogous reactions with DA cyclobutanes were not known,[22] thus we sought to access the piperidine nucleus **3.65** through a Lewis acid-catalyzed formal [4+2] cycloaddition of appropriately substituted DA cyclobutanes **3.39** and imines **3.64** (**Scheme 3.12**). Given our ongoing interest in alkoxy substituted DA cyclopropanes,[23] the analogous cyclobutanes were chosen as substrates for the exploration of this chemistry.

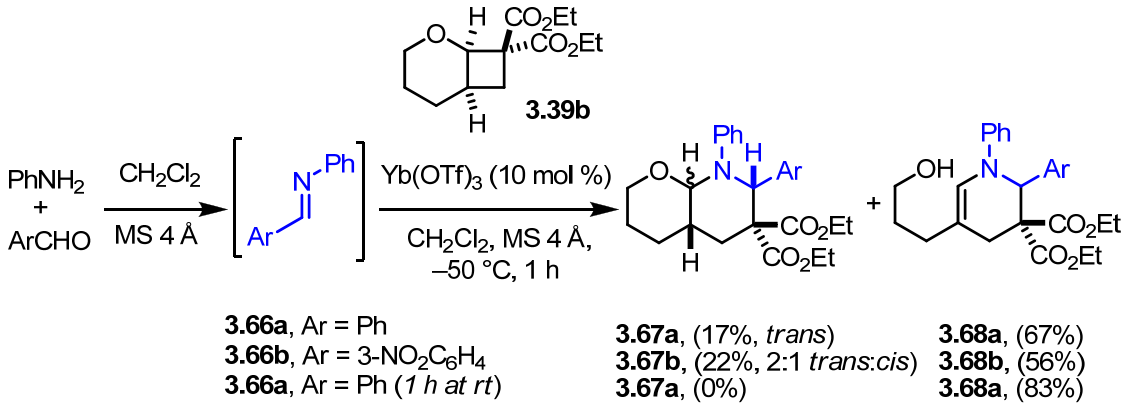


3.39 **3.64** **3.65**

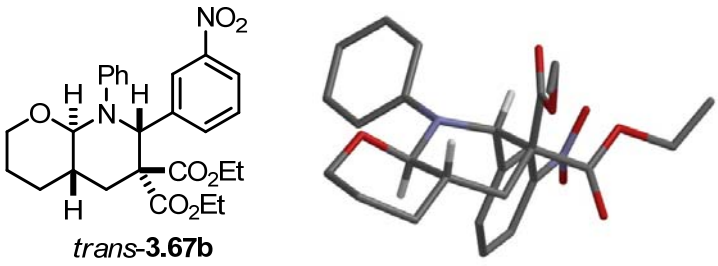
Scheme 3.12 – Formal [4+2] cycloaddition of DA cyclobutanes and imines

Since $Yb(OTf)_3$ has been identified as a superior catalyst for the synthesis of alkoxy substituted DA cyclobutanes (**Table 3.1**), the feasibility of using it to catalyze the [4+2] cycloaddition of these cyclobutanes with imines was explored to allow for a

possible one-pot synthesis of piperidine.[24] To our delight, upon exposure of cyclobutane **3.39b** and imine **3.66a** (prepared *in situ*) to catalytic $Yb(OTf)_3$ at –50 °C, the *trans* fused bicyclic piperidine *trans*-**3.67a** as a single diastereomer and piperideine **3.68a** were observed (**Scheme 3.13**). On the other hand, reaction of imine **3.66b** gave cycloadduct **3.67b** as a 2:1 mixture of diastereomers as well as the piperideine **3.68b**. The relative stereochemistry of *trans*-**3.67b** and *cis*-**3.67b** was assigned on the basis of NOE interactions, and ultimately confirmed by single-crystal X-ray analysis (**Figure 3.5** and **Figure 3.6**). It is likely that the piperideine **3.68** is produced from cycloadduct **3.67** by tetrahydropyran ring opening followed by a proton transfer. In order to isolate a single product, the reaction was warmed to room temperature for an hour after consumption of the cyclobutane to drive the product from the piperidine **3.67a** to the piperideine **3.68a**.

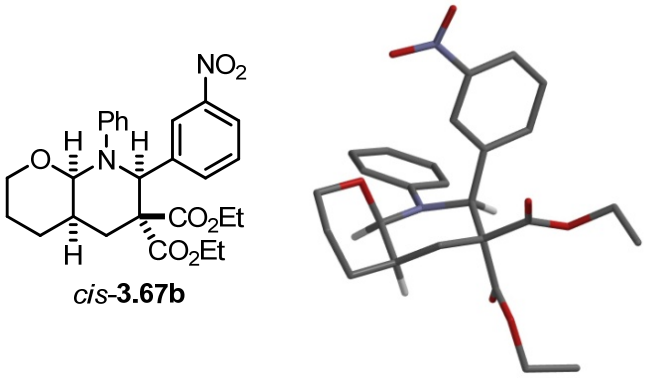


Scheme 3.13 – Formal [4+2] cycloaddition of 2-alkoxy-1,1-cyclobutane diesters and imines



trans-**3.67b**

Figure 3.5 – Single crystal X-ray structure of *trans*-**3.67b**

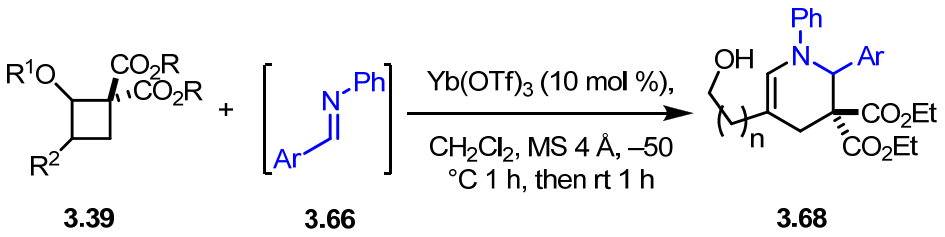


cis-**3.67b**

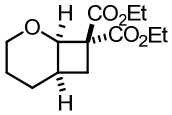
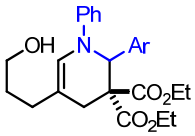
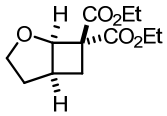
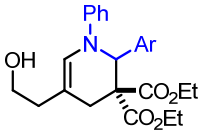
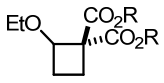
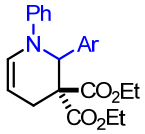
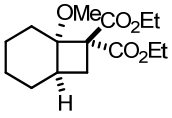
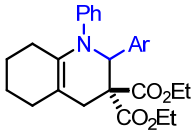
Figure 3.6 – Single crystal X-ray structure of *cis*-**3.67b**

Having demonstrated that the piperdeine synthesis was successful, the scope for the reaction was explored and the results are summarized in **Table 3.4**. Unfortunately, the scope for the formal [4+2] reaction is quite limited. While aniline-derived imines were effective substrates, no reaction was observed with imines bearing aliphatic substituents on the nitrogen. The reaction tolerated various substituents at C2 including cinnamyl, naphthyl, electron rich or deficient aromatic and heteroaromatic (**Table 3.4, 3.68a-3.68g**). On the other hand, the more reactive cyclobutanes **3.39g** and **3.39h** gave complex mixtures when subjected to the same reaction conditions.

Table 3.4 – Ytterbium triflate catalyzed synthesis of piperdeines



3.39 **3.66** **3.68**

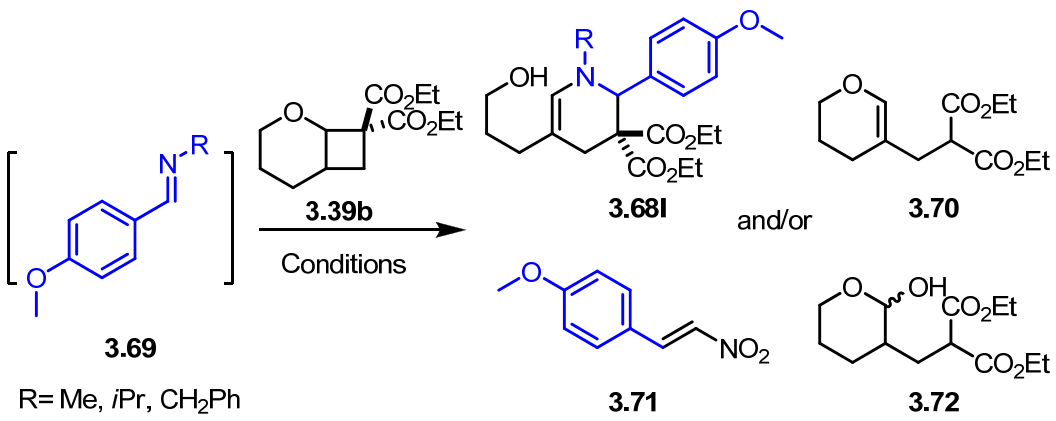
entry	cyclobutane **3.39**	piperideine **3.68**	yield[a]
1	 **3.39b**		**3.68a**, Ar = C_6H_5 (83%) **3.68b**, Ar = 3-$NO_2C_6H_4$ (73%) **3.68c**, Ar = 4-$MeOC_6H_4$ (77%) **3.68d**, Ar = 2-thienyl (42%) **3.68e**, Ar = 1-naphthyl (84%)
2	 **3.39c**		**3.68f**, Ar = Ph (86%) **3.68g**, Ar = 3-$NO_2C_6H_4$ (81%)
3	 **3.39g**		**3.68h**, Ar = C_6H_5 (NR)[b] **3.68i**, Ar = 3-$NO_2C_6H_4$ (NR)[b] **3.68j**, Ar = 4-$MeOC_6H_4$ (NR)[b]
4	 **3.39h**		**3.68k**, Ar = C_6H_5 (NR)[b]

[a]Isolated yield. [b]Complex reaction mixture was observed.

In regard to the nitrogen functionalization, extensive optimization has been done to install a variety of aliphatic groups including methyl, *iso* propyl and/or benzyl however with no success and the results are summarized in **Table 3.5** (entries 1-11). A wide variety of reaction conditions have been examined including different LAs (Et_2ALCl_2, $MgCl_2$, $MgBr_2$, $SnCl_2$, $ZnCl_2$, $ZnBr_2$, $Zn(OTf)_2$, $Yb(OTf)_3$, $Sc(OTf)_3$, $TiCl_4$), different

solvents (sulfolane, CH_2Cl_2, toluene) and/or different reaction temperatures (–50 °C, 0 °C or ambient).

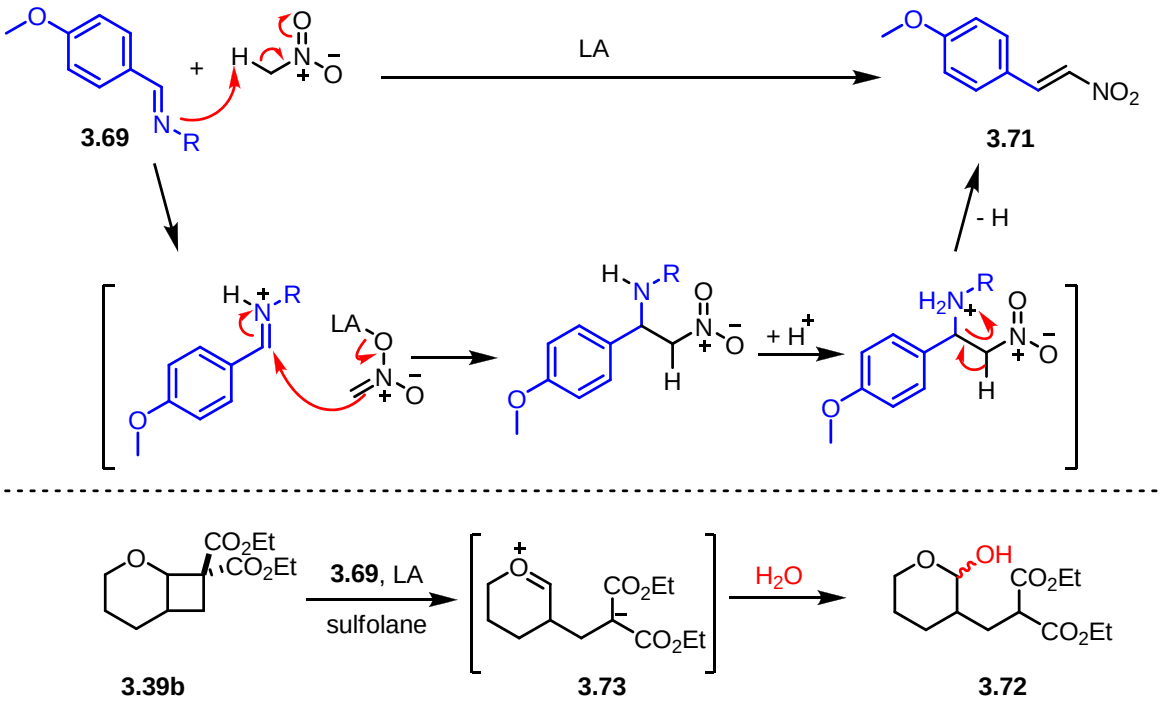
Table 3.5 – Optimizing the reaction conditions with aliphatic imines[a]



entry	LA (10 mol %)	CH_2Cl_2 –50 °C, 12 h	CH_2Cl_2 0 °C, 12 h	CH_2Cl_2 rt, 12 h	toluene, rt	CH_3NO_2 –50 °C- rt	sulfol-ane, rt
1	Et_2ALCl_2	NR[b]	**3.70**	--	--	--	--
2	$MgCl_2$	NR	NR	**3.70**	--	--	--
3	$MgBr_2$	NR	**3.70**	--	--	--	--
4	$SnCl_2$	NR	decomp.	--	--	--	--
5	$ZnCl_2$	NR	decomp.	--	--	--	--
6	$ZnBr_2$	NR	NR+decomp.	--	--	--	--
7	$Zn(OTf)_2$	NR	NR	**3.68l**[c]	--	--	--
8	$Yb(OTf)_3$	NR	NR	**3.68l**[c]	**3.68l**[c]	**3.71**	**3.72**
9	$Sc(OTf)_3$	**3.68l**[c]	--	--	--	--	--
10	$TiCl_4$	decomp.[d]	--	--	--	--	--
11	TMSOTf	**3.70**	--	--	--	--	--

[a] reaction monitored by NMR.[b]NR= no reaction and only cyclobutane observed. [c] traces of the product and decomposition.[d]decomp.= decomposition.

In general, either cyclobutane ring opening product **3.70** and/or decomposition were obtained. Traces of the expected cycloadduct **3.68l** as well as decomposition products were observed when the reaction catalyzed by $Zn(OTf)_2$, or $Sc(OTf)_3$ or $Yb(OTf)_3$ (**Table 3.5**, entries 7-9). In order to stabilize the oxocarbenium ion intermediate and hence to avoid cyclobutane decomposition, more polar solvents were examined including CH_3NO_2 and sulfolane.[23a,25] When CH_3NO_2 was used, it underwent enolization under the reaction condition following by addition to the imine and elimination providing the nitro alkene **3.71** (**Scheme 3.14**). Therefore sulfolane as a polar and inert solvent was examined.[25] However, lactol **3.72** was isolated due to addition of water to the zwitterion intermediate **3.73**. Since sulfolane is a very hygroscopic solvent, the attempts to make it dry were met with failure.[25]

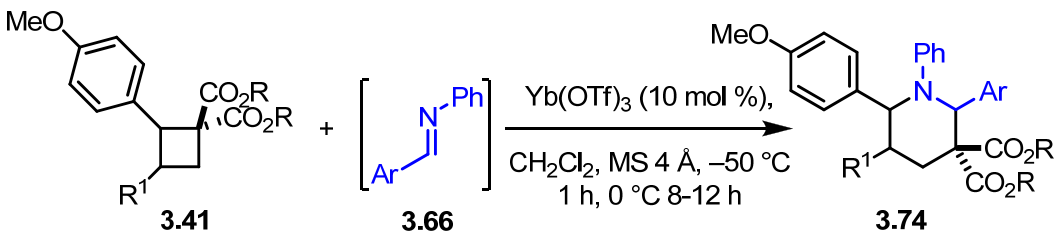


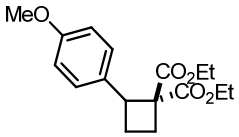
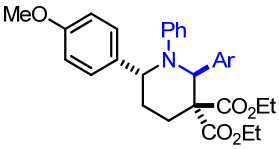
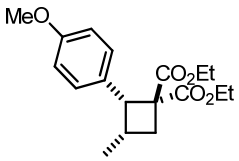
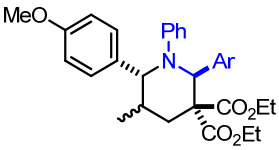
Scheme 3.14 – Plausible mechanism for **3.71** and **3.72** formation

Despite the limited scope of the new methodology, the substitution pattern of the piperideines **3.68a-g** on the N1, C2 and C3 positions as well as the C5-C6 alkene functionality and the aliphatic alcohol side chain on C5 can provide a valuable handle for further synthetic manipulation. In addition, the milder reaction condition and cost effectiveness associated with this one pot approach compete to other related reaction for example Diels-Alder cycloaddition. In fact, targeting those piperideines using aza-diene Diels-Alder reaction could be a difficult task to realise since the aza-dienes can suffer from competitive imine addition and/or tautomerisation.[14e]

Since only aldehydes have been reported to undergo dipolar cycloaddition with cyclobutanes activated with carbon based donating groups, the ability of $Yb(OTf)_3$ to catalyze the same annulation with cyclobutanes **3.41** was then explored (**Table 3.6**). In contrast to the cyclobutanes activated by alkoxy group, the cycloaddition of imines with cyclobutane **3.41a** required higher temperatures and longer reaction times (0 °C for 10 h vs. –50 °C for 1 h). Nonetheless, the cycloaddition proceeded smoothly to provide pentasubstituted piperidines **3.74**. All the cycloadducts **3.74a-f** were obtained in moderate to good yields and exclusively as the *trans*-diastereomer. Similar to cyclobutanes activated by alkoxy group **3.39**, electron-rich or deficient aromatic, conjugated aromatic, and heteroaromatic imines participated in the reaction providing the piperidines **3.74a-3.74f**. Unfortunately, cyclobutane **3.41d** failed to react productively with imines, and only decomposition was observed along with traces of the piperidine **3.74g**.

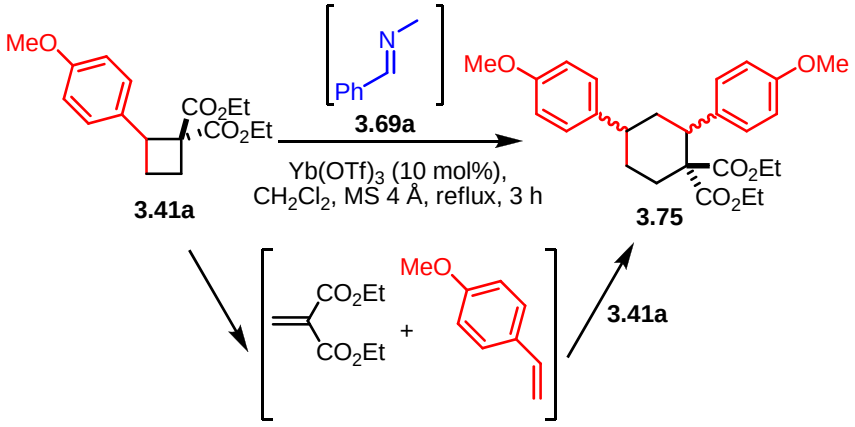
Table 3.6 – Synthesis of pentasubstituted piperidines



entry	cyclobutane **3.41**	piperidine **3.74**	yield[a]
1	 **3.41a**		**3.74a**, Ar = Ph (62%) **3.74b**, Ar = 3-NO_2 C_6H_4 (86%) **3.74c**, Ar = 4-MeO C_6H_4 (73%) **3.74d**, Ar = 2-thienyl (59%) **3.74e**, Ar = 1-naphthyl (68%) **3.74f**, Ar = $CHCPh_2$ (61%)
2	 **3.41d**		**3.74g**, Ar = Ph (traces)

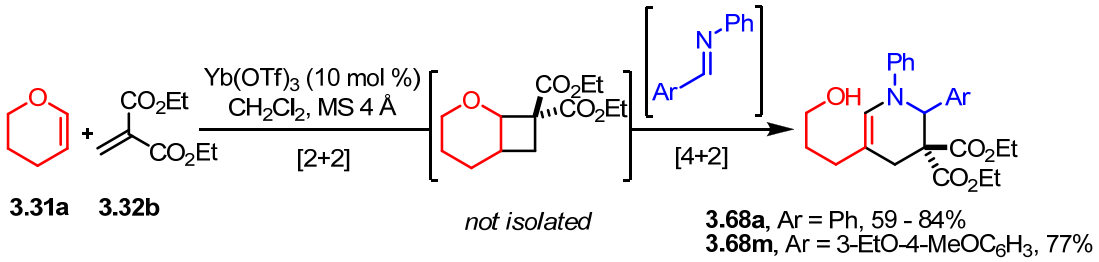
[a] Isolated yield

Again this cycloaddition does not tolerate aliphatic substituent on the imine nitrogen (**Scheme 3.15**). When the reaction was heated in CH_2Cl_2, interestingly a retro [2+2] followed by [4+2] annulation between styrene and the cyclobutane starting material **3.41a** was observed and the cyclohexane derivative **3.75** was isolated. This observation suggests that these DA cyclobutanes can undergo formal [4+2] cycloaddition reaction with other electron rich olefin to form multi substituted cyclohexanes.



Scheme 3.15 – Annulation of cyclobutane **3.41a** and aliphatic imines

Finally, the possibility of carrying out the cyclobutane formation/imine annulation sequence in one pot was examined. When a CH_2Cl_2 solution of imine was added to a concentrated solution of the *in situ* formed cyclobutane, the expected cycloadducts were obtained in yields ranging from (59 – 84%). The variation in yield is attributed to the purity of methylidene malonate, as higher yields were observed with freshly prepared methylidene malonate.



Scheme 3.16 – One pot, multi-step synthesis of piperideines

In summary, the use of 2-alkoxy-1,1-cyclobutane diesters for the first time in dipolar cycloadditions have been reported. They undergo a formal [4+2] cycloaddition with imines to afford highly substituted piperidines and piperideines. Although there are

some limitations, this new piperidine synthesis has some advantages when compared to other related [4+2] cycloaddition for example aza-diene Diels-Alder reaction. It starts with readily available and cheap DA cyclobutanes. In addition, the reaction can be done under milder conditions and with a broader scope. Finally, a one pot procedure for cyclobutane synthesis and subsequent imine cycloaddition can be achieved easily. Future efforts include applying this methodology in the total synthesis of piperidine natural products and developing an asymmetric variant.

3.2.3. Formal [4+2] Cycloaddition of Alkoxy-substituted DA Cyclobutanes and Aldehydes Catalyzed by $Yb(OTf)_3$

Six-membered oxygenated heterocycles are a common structural feature in a plethora of bioactive compounds including naturally occurring carbohydrates and non carbohydrates products as well as synthetic analogues. **Figure 3.7** shows some representative examples. These compounds can vary from simple tetrahydropyrans, spiroketals, chromanes and flavanones to more elaborate architectures present in marine natural products such as palytoxin and maitotoxin.[26]

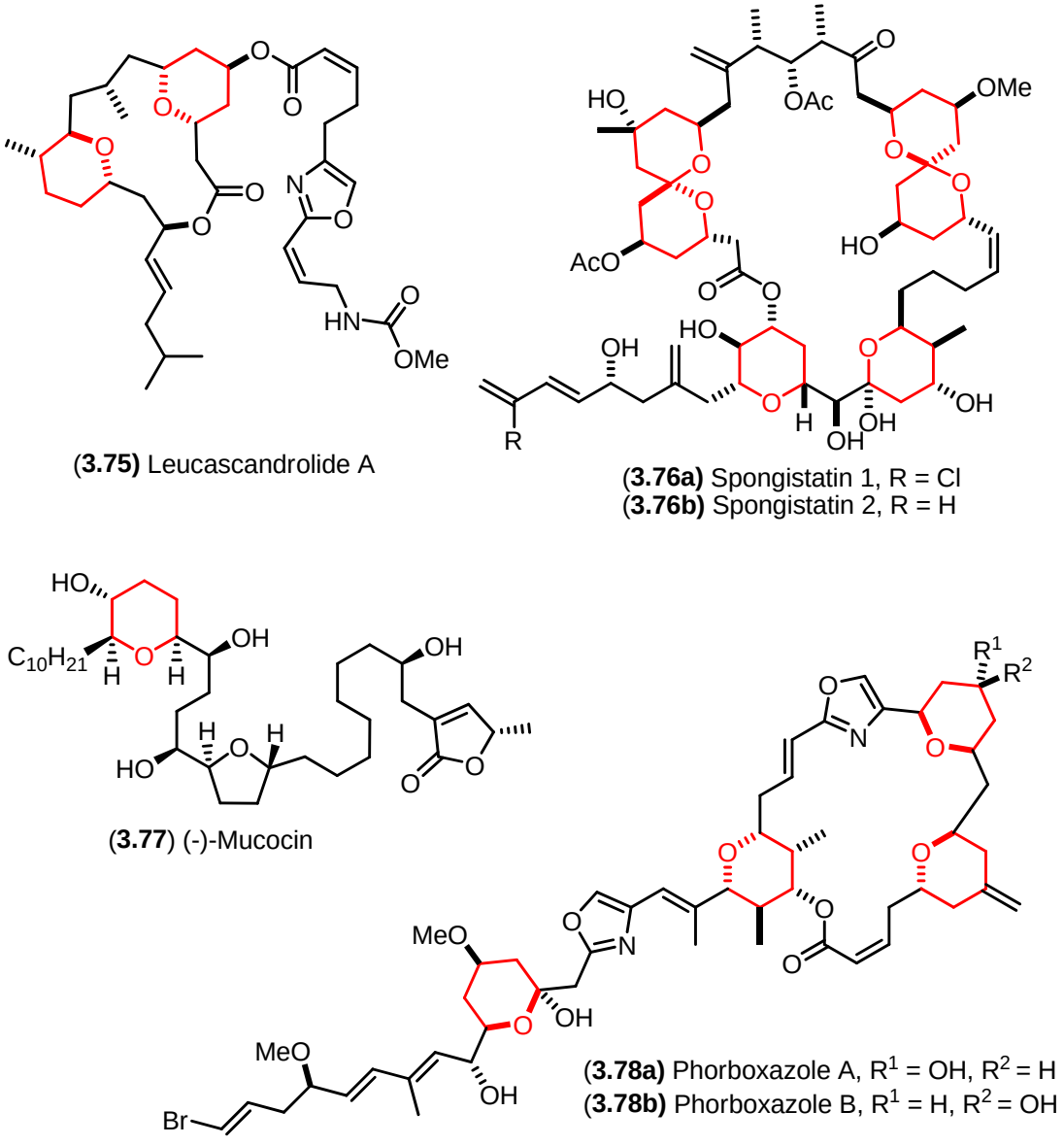
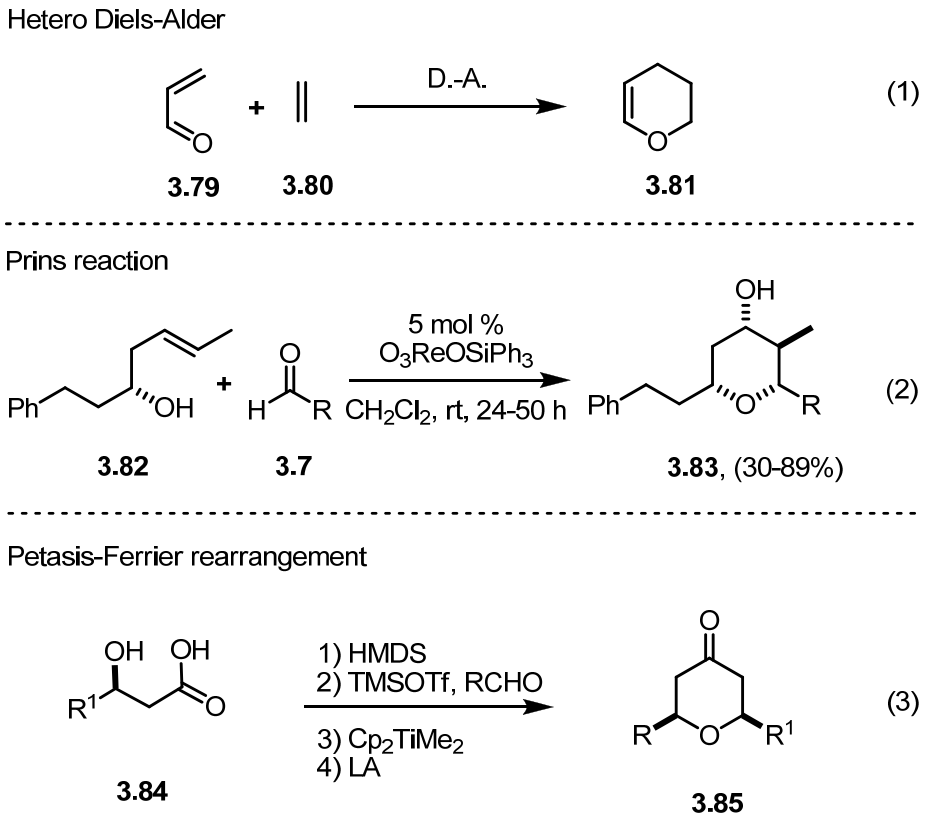


Figure 3.7 – Biologically active tetrahydropyrans

Due to their wide range of functionalities and biological activities, the development of new syntheses of these heterocycles has continued to be of major importance. In general, the tetrahydropyran ring can be prepared by numerous intramolecular cyclizations of an oxygenated precursor for example nucleophilic substitution, ring-closing metathesis, Michael additions as well as alkyne, alkene, allene

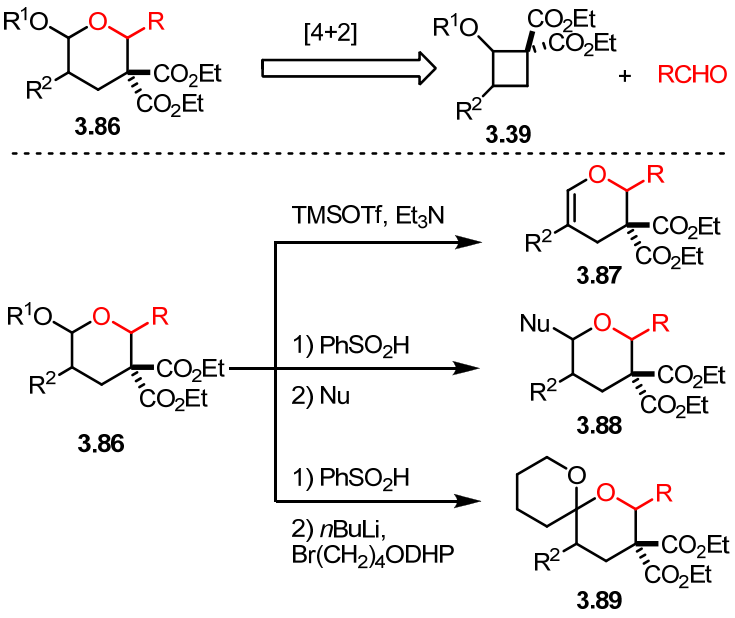
and/or epoxide mediated cyclization.[26] These methods are widely used and provide the target structures in a highly efficient and simple way. On the other hand, a variety of intermolecular syntheses of tetrahydropyrans have also been reported (**Scheme 3.17**). Classical and extensively used examples are the [4+2] Hetero Diels-Alder (**Scheme 3.17**, equation 1**)**,[27] the Prins cyclization (**Scheme 3.17**, equation 2**)**,[28] the Petasis-Ferrier rearrangement (**Scheme 3.17**, equation 3**)**.[29]



Scheme 3.17 – Intermolecular syntheses of tetrahydropyrans

Having demonstrated the utility of 2-alkoxy-1,1-cyclobutane diesters in the synthesis of piperidines and piperideines, it was envisioned that the tetrahydropyran rings could also be formed by the formal [4+2] dipolar cycloaddition of these DA cyclobutanes

with aldehydes (**Scheme 3.18**). When compared to the related [4+2] annulation reaction (**Scheme 3.7**),[9,10] the unique feature of this approach is that the expected cycloadduct will have an anomeric carbon bearing an alkoxy substituent that can be easily modified (e.g., C-glycosidation reactions and elimination)[30] providing important pyran derivatives **3.87** – **3.89** that can be further elaborated into many natural products (**Scheme 3.18**).

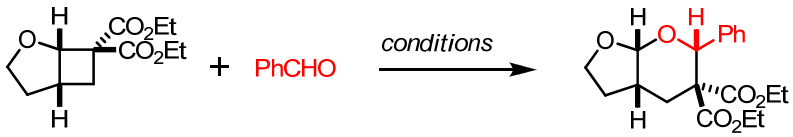


Scheme 3.18 – Formal [4+2] approach to tetrahydropyrans and the potential utility of the expected cycloadduct.

Therefore cyclobutane **3.39c** was allowed to react with benzaldehyde **3.90** (**Table 3.7**). As expected, $Yb(OTf)_3$ catalyzed the annulation reaction very efficiently to afford the fused acetal **3.91** which was obtained in moderate to excellent yield and as a single diastereomer under a variety of reaction conditions. The optimization studies revealed that temperature had little effect on the yield or diastereoselectivity (**Table 3.7**, entries 1 – 3). In addition, the reaction could be effected with catalyst loadings as low as 0.5 mol % (**Table 3.7**, entry 8). Furthermore, the reactions were complete in 2 min when done in

the microwave reactor (**Table 3.7**, entry 9). Finally, we noticed that the aldehyde equivalency had very little effect on the yield (**Table 3.7**, entries 5 and 6). It is important to note that only a single diastereomer was observed by NMR. The relative stereochemistry of the *cis*-product was assigned on the basis of NOE interactions.

Table 3.7 – Optimization of the [4+2] cycloaddition between DA cyclobutanes and benzaldehyde[a]



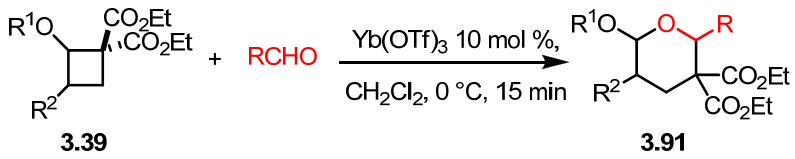
3.39c **3.90** **3.91a**

entry	conditions[b]				yield[b] (%)
	$Yb(OTf)_3$ (mol %)	PhCHO (equiv)	temp (°C)	time (min)	
1	10	3.0	-40	120	70
2	10	3.0	0	15	84
3	10	3.0	20	15	78
5	10	1.1	0	15	78
6	10	0.9	0	15	68
7	2	1.1	0	45	74
8[d]	0.5	1.1	25	18 h	79
9[e]	2	1.1	60	2	76

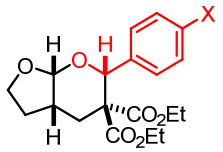
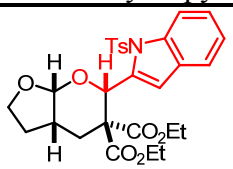
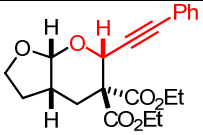
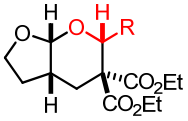
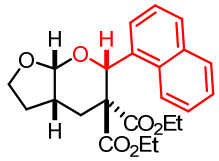
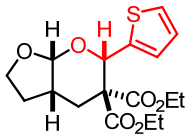
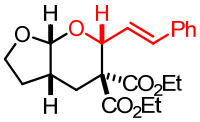
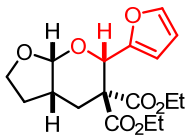
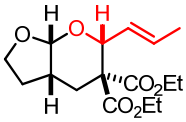
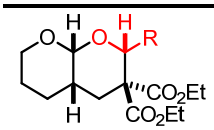
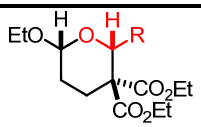
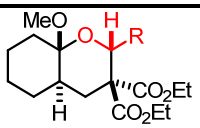
[a]The proof of concept reaction was done by me. The extensive optimization presented in this table was done by Mr. Andrew C. Stevens and Mr. Benjamin P. Machin. [b]Reactions were conducted on 0.4 mmol scale.[c] Isolated yield.[d]No reaction was observed at 0 °C. [e]Reaction was conducted in a microwave reactor.

After the reaction conditions were optimized, the scope was explored and the results are summarized in **Table 3.8**.

Table 3.8 – Scope of the formal [4+2] cycloaddition of DA cyclobutanes and aldehydes[a]



3.39 **3.91**

tetrahydropyrans **3.91**/ yield[b]			
 **3.91a**, X = H, 84% **3.91b**, X = OMe, 80% **3.91c**, X = Cl, 89% **3.91d**, X = CN, 88% **3.91e**, X = NO_2, 75%	 **3.91g**, 80%	 **3.91j**, 62%	 **3.91m**, R = $(CH_2)_2Ph$, 68% **3.91n**, R = $(CH_2)_4CH_3$, 56% **3.91o**, R = CH_3, 51% **3.91p**, R = *i*Pr, 58% **3.91q**, R= cyclopropyl, 72%
 **3.91f**, 80%	 **3.91h**, 69%	 **3.91k**, 87%	
	 **3.91i**, 71%	 **3.91l**, 51%	
 **3.91r**, R = Ph, 60% **3.91s**, R = $(CH_2)_2Ph$, 62%	 **3.91t**, R = Ph, 72% **3.91u**, R = $(CH_2)_2Ph$, 70%	 **3.91v**, R = *p*-C_6H_4OMe, 76% **3.91w**, R = *p*-C_6H_4Cl, 69% **3.91x**, R = *m*-$C_6H_4NO_2$, 60% **3.91y**, R = *trans*-C_2H_2Ph,71% **3.91z**, R = 2- thienyl, 56%	

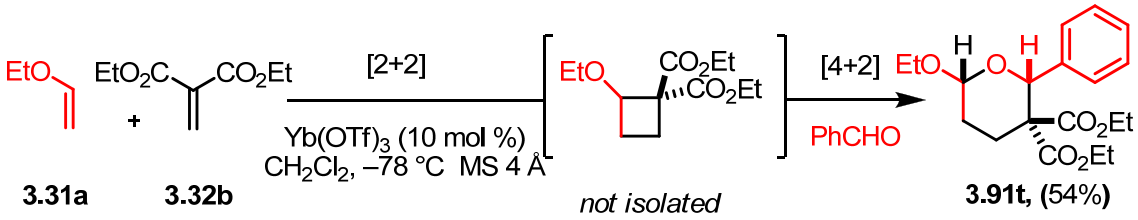
[a]cyclobutane starting materials and cycloadducts **3.91v** – **3.91z** were prepared by me. The rest of the scope was done by Mr. Andrew C. Stevens and Mr. Benjamin P. Machin. [b]Isolated yield. For cycloadducts **3.91v** – **3.91z**, reagents were added –50 °C then the reactions warmed gradually to 0 °C.

Aromatic aldehydes were found to be excellent reaction partners regardless of whether they were electron rich (**3.91b**), halogenated (**3.91c**), or electron poor (**3.91d, 3.91e**). In addition, heteroaromatic (2-furfural, 2-thiofurfural, and indole-2-carboxaldehyde, entries **3.91g–3.91i**) as well as conjugated aldehydes (**3.91j–3.91l**) underwent the cycloaddition. All tetrahydropyrans **3.91a-3.91l** were obtained as a single diastereomer in moderate to excellent yields ranging from 51% to 89% (**Table 3.8**).

In Johnson's previous work, a stronger Lewis acid was required for aliphatic aldehydes to react with aryl-substituted cyclobutanes.[10] Interestingly, we discovered that the same mild Lewis acid, $Yb(OTf)_3$, effectively catalyzed the [4+2] cycloaddition between the alkoxy-substituted cyclobutanes and aliphatic aldehydes (**Table 3.8**). Examining the reaction scope revealed that linear (dihydrocinnamaldehyde, **3.91m**, and hexanal, **3.91n**), acetaldehyde (**3.91o**), branched (isobutyraldehyde, **3.91p**), and cyclopropyl aldehydes (**3.91q**) all underwent the cycloaddition to provide exclusively the cis bicyclic acetals (**Table 3.8**, **3.91m-3.91q**).

Several additional DA cyclobutanes were investigated (**Table 3.8**). Tetrahydropyran-fused cyclobutane **3.39b** underwent successful cycloaddition with both aromatic and aliphatic aldehydes to afford the all *cis*-products (**3.91r, 3.91s**). The unsubstituted cyclobutane **3.39c** also participated in the cycloaddition with aliphatic and aromatic aldehydes (**3.91t, 3.91u**). Furthermore, the cyclohexyl-fused cyclobutane **3.39d** underwent cycloaddition with aromatic aldehydes to afford the fused ring systems **3.91v–3.91z**, each as a single diastereomer. Unfortunately, when aliphatic aldehydes were allowed to react with **3.39d**, decomposition was observed.

Next, the possibility of carrying out the cyclobutane formation/aldehyde annulation sequence in a one pot was examined (**Scheme 3.19**). When benzaldehyde was added to a solution of the *in situ* formed cyclobutane **3.39g** at –78 °C and the reaction then was allowed to warm to 0 °C, the tetrahydropyran **3.91t** was obtained in 54% yield. Although, it provides a lower yield than the two-step sequence, the one-pot reaction allowed for the efficient synthesis of this tetrahydropyrans **3.91t** in eight gram scale for further synthetic manipulations.[30]



Scheme 3.19 – One pot, multi-step synthesis of tetrahydropyan

When compared to imines, aldehydes are more efficient dipolarophiles in the annulation reaction with 2-alkoxy 1,1-cyclobutane diesters. In addition to the broader scope and the shorter reaction times, the tetrahydropyran cyloadducts were obtained in moderate to excellent yields and as single diastereomers.

In summary, by utilizing the formal [4+2] annulation between aldehydes and DA cyclobutanes, a novel synthesis of tetrahydropyran derivatives is reported. The reaction was efficiently catalyzed by $Yb(OTf)_3$ with a wide variety of aldehydes. The new method highly selective for the *cis*-diastereomer and provide the product in moderate to excellent yields. Developing an asymmetric variant of this methodogly and further applying it in the total synthesis of pyran-based natural products are future projects in our group.

3.3. Chapter Summary

Although known for more than two decades, the first use of 2-alkoxy-1,1-cyclobutane diesters in dipolar cycloaddition was reported. Both the synthesis of those donor-acceptor cyclobutanes and their subsequent annulation with imines (*in situ* formed) as well as aldehydes are catalyzed by catalytic $Yb(OTf)_3$. In addition, novel syntheses of several bilogicaly important heterocycles including piperidine, piperideine and tetrahydropyrans were also reported. The reactions are done under very mild conditions providing the products in high yields and excellent selectivity. Future efforts are to target different heterocycles by identify new dipolarophile partners, to develop an asymmetric variant of the current methodologies and to apply them in the total synthesis of biologically active natural compounds as well as synthetic analogues.

3.4. Experimental

3.4.1. General

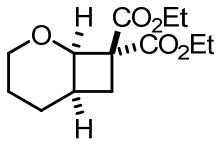
^{1}H and ^{13}C NMR spectra were recorded using a Varian Mercury 400 or 600 MHz spectrometers. Chemical shifts (δ) were expressed in parts per million (ppm) downfield from tetramethylsilane using the residual protonated solvent as an internal standard (chloroform-*d*, ^{1}H 7.25 ppm and ^{13}C 77.00 ppm). Coupling constants were expressed in Hertz (Hz). When peak multiplicities are given, the following abbreviations are used: s, singlet; d, doublet; dd, doublet of doublets; td, triplet of doublets; t, triplet; q, quartet; m, multiplet; br, broad. HRMS (CI, FAB) were obtained with a Finnigan MAT 8200 instrument. Melting points are uncorrected. X-ray analysis were carried out at low temperature (–123 °C) on a Nonius Kappa-CCD diffractometer. The progress of reactions

were monitored by thin layer chromatography (TLC) performed on F254 silica gel plates. The plates were visualized by staining with ceric ammonium molybdate (CAM),[31] or potassium permanganate. Column chromatography was performed with Silica Flash P60 60 Å silica gel from Silicycle according to the Still method. [32] All solvents were obtained from an Innovative Technology SPS-400-5 solvent purification system. All chemicals were of reagent quality and used as obtained from commercial sources unless otherwise noted. Flasks were oven dried and cooled in a desiccator prior to use. Reactions were carried out under an inert atmosphere (dry argon) unless otherwise indicated.

3.4.2. General Procedure A for the [2+2] Synthesis of Cyclobutanes 3.39b-h and 3.41a-e

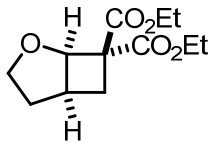
To a solution of $Yb(OTf)_3$ (0.01 eq) in CH_2Cl_2 (0.5 mmol/ 10.0 mL) maintained at –78 °C was added simultaneously by syringe pump over 45 minutes a solution of enol ether (1.2 equiv) in CH_2Cl_2 (5 mmol/ 10.0 mL) and a second solution of methylidene malonate[33] (1.0 equiv) in CH_2Cl_2 (5 mmol/ 10.0 mL) (both at rt). To avoid any polymerizations and side reactions, methylidene malonate solution should be dilute and have roughly the same molar concentration of the enol ether. Alternatively, alkenes (6 mmol of enol ether and 5 mmol of methylidene malonate) can be dissolved in CH_2Cl_2 (20.0 mL), cooled down to approximately –78 °C, then this solution was added through a cannula to CH_2Cl_2 solution of $Yb(OTf)_3$ maintained at –78 °C. After the reaction appeared complete (tlc, 1-3 h), pyridine (0.01 eq) was added at –78 °C and the reaction was filtered while still cold through a silica gel (2 cm) and celite (1 cm) bilayer pad open to the atmosphere. The filtrate was concentrated under reduced pressure. Purification of

the residue by flash column chromatography on silica gel using EtOAc-hexanes for elution (buffered with 1% Et_3N) provided the title compounds. The procedure was effectively run at up to 50 mmol scale for some cyclobutanes.



Diethyl 2-oxabicyclo[4.2.0]octane-8,8-dicarboxylate (3.39b):[34]

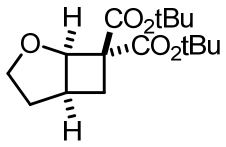
The synthesis was done at 50 mmol scale to yield cyclobutane as colorless oil (87% yield, 11.14 g). R_f 0.40 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.62 (t, *J* = 4.1 Hz, 1H), 4.32-4.27 (m, 1H), 4.25-4.20 (m, 1H), 4.18-4.11 (m, 2H), 3.78 (d, *J* = 11.7 Hz, 1H), 3.23 (t, *J* = 10.5 Hz, 1H), 2.95 (t, *J* = 11.1 Hz, 1H), 2.56 (apparent s, 1H), 2.14 (ddd, *J* = 11.4, 8.4, 3.5, 1H), 1.81-1.73 (m, 1H), 1.64-1.55 (m, 2H), 1.39 (d, *J* = 14.0, 1H), 1.24 (t, *J* = 7.0, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 168.0, 75.4, 64.5, 61.3, 61.2, 55.9, 29.6, 28.2, 22.7, 20.8, 14.1, 14.0; HRMS *m/z* 256.1315 (calcd for $C_{13}H_{20}O_5$, 256.1311).



Diethyl 2-oxabicyclo[3.2.0]heptane-7,7-dicarboxylate (3.39c):

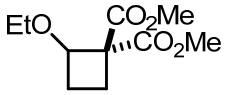
The synthesis was done at 40 mmol scale to yield cyclobutane as colorless oil (93% yield, 9.00 g). R_f 0.48 (30% EtOAc/hexanes); ^{1}H NMR (400MHz , $CDCl_3$) δ 4.96 (dd, *J* = 5.5, 2.7 Hz, 1 H), 4.29- 4.12 (m, 4 H), 4.11- 4.04 (m, 1 H), 3.99- 3.92 (m, 1 H), 3.14- 3.06 (m,

1 H), 2.48 (dd, *J* = 13.5, 6.8 Hz, 1 H), 2.28 (ddd, *J* = 13.3, 9.0, 2.7 Hz, 1 H), 1.79- 1.73 (m, 2 H), 1.23 (td, J = 7.0, 3.5 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 168.0, 81.7, 69.5, 61.3, 56.3, 35.9, 31.1, 29.3, 14.09, 13.98; HRMS *m/z* 242.1150 (calcd for $C_{12}H_{18}O_5$, 242.1154).



Di-*tert*-butyl 2-oxabicyclo[3.2.0]heptane-7,7-dicarboxylate (3.39d):

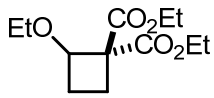
The synthesis was done at 5 mmol scale to yield cyclobutane as colorless oil (72% yield, 1.00 g). R_f 0.50 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.91 (dd, *J* = 5.5, 2.0 Hz, 1H), 4.05 (t, *J* = 7.6 Hz, 1H), 3.95 (td, *J* = 9.5, 6.1 Hz, 1H), 3.06-3.02 (m, 1H), 2.39 (dd, *J* = 13.1, 6.7 Hz, 1H), 2.16 (ddd, *J* = 12.8, 9.3, 2.3 Hz, 1H),1.80-1.71 (m, 2H), 1.46 (s, 9H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 167.4, 81.5, 81.2, 81.1, 69.3, 57.6, 35.5, 31.2, 29.1, 27.9, 27.8; HRMS *m/z* 299.1857 (calcd for $C_{16}H_{26}O_5$, 298.1780).



Dimethyl 2-ethoxycyclobutane-1,1-dicarboxylate (3.39f):

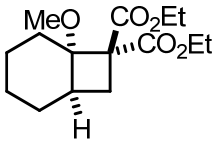
The synthesis was done at 35 mmol scale to yield cyclobutane as colorless oil (56% yield, 4.2 g). R_f 0.33 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.45 (t, *J* = 8.3 Hz, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 3.54-3.46(m, 1H), 2.49 (quin, *J* = 5.8 Hz, 1H), 2.16 (td, *J*

= 9.0, 6.8 Hz, 2H), 1.70 (apparent q, *J* = 9.0 Hz, 1H), 1.12 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.42 , 169.5, 75.5, 65.1, 61.0, 52.5, 52.4, 26.0, 21.0, 15.0; HRMS *m/z* 216.0992 (calcd for $C_{10}H_{16}O_5$, 216.0998).



Diethyl 2-ethoxycyclobutane-1,1-dicarboxylate (3.39g):

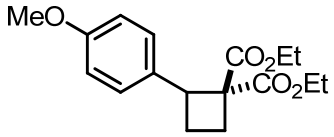
The synthesis was done at 1 mmol scale to yield cyclobutane as colorless oil (80% yield, 0.19 g). R_f 0.40 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.45 (t, *J* = 8.5 Hz, 1H), 4.30-4.10 (m, 4H), 3.74-3.66 (m, 1H), 3.54-3.47 (m, 1H), 2.49 (quin, *J* = 6.2 Hz, 1H), 2.16 (td, *J* = 8.8, 6.4 Hz, 2H), 1.68 (apparent q, *J* = 9.3, 1H), 1.25 (dt, *J* = 10.2, 7.1 Hz, 6H), 1.13 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 168.6, 75.4, 65.1, 61.3, 61.2, 61.1, 25.9, 20.9, 14.9, 14.1, 14.0; HRMS *m/z* 244.1310 (calcd for $C_{12}H_{20}O_5$, 244.1311).



Diethyl 6-methoxybicyclo[4.2.0]octane-7,7-dicarboxylate (3.39h):

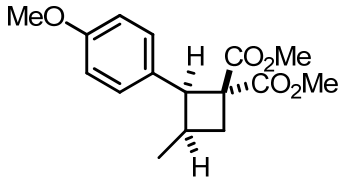
The synthesis was done at 85 mmol scale to yield cyclobutane as colorless oil (70% yield, 16 g). R_f 0.33 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23-4.18 (m, 4H), 3.35 (s, 3H), 2.79-2.75 (m, 1H), 2.42 (d, *J* = 13.1 Hz, 1H), 2.31 (t, *J* = 10.2 Hz, 1H), 1.78 (t, *J* = 11.3 Hz, 1H), 1.58-1.53 (m, 2H), 1.50-1.48 (m, 1H), 1.41 (d, *J* = 14.6 Hz, 1H),

1.30 (t, *J* = 7.5 Hz, 1H), 1.26 (t, *J* = 6.9 Hz, 6H), 1.20 (d, *J* = 12.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 168.8, 81.3, 62.8, 61.3, 60.8, 51.6, 36.5, 27.4, 25.0, 23.2, 21.1, 20.1, 14.0,13.9; HRMS *m/z* 284.1631 (calcd for $C_{15}H_{24}O_5$, 284.1624).



Diethyl 2-(4-methoxyphenyl)cyclobutane-1,1-dicarboxylate (3.41a):

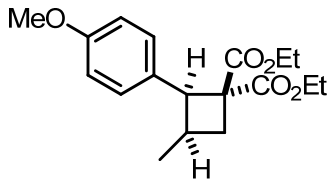
The synthesis was done at 15 mmol scale to yield cyclobutane as colorless oil (81% yield, 3.7 g). R_f 0.35 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 4.30 (t, *J* = 9.6 Hz, 1H), 4.27-4.23 (m, 1H), 4.21-4.16(m, 1H), 3.81-3.78 (m, 1H), 3.76 (s, 3H), 3.70-3.65 (m, 1H), 2.66 (dt, *J* = 9.3 Hz, 2.34 Hz, 1H), 2.55 (quin, *J* = 9.8 Hz, 1H), 2.20 (apparent q, *J* = 9.3 Hz, 1H), 2.13 (dq, *J* = 8.7, 2.93 Hz, 1H), 1.26 (t, *J* = 7.0 Hz, 3H), 0.80 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 169.4, 158.5, 131.3, 128.8, 113.3, 61.1, 60.8, 59.6, 55.2, 44.3, 25.4, 20.8, 14.0, 13.6; HRMS *m/z* 306.1474 (calcd for $C_{17}H_{22}O_5$, 306.1467).



Dimethyl 2-(4-methoxyphenyl)-3-methylcyclobutane-1,1-dicarboxylate (3.41c):

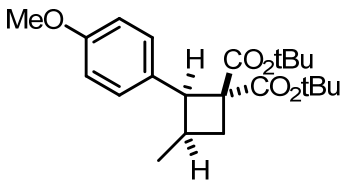
The synthesis was done at 35 mmol scale to yield cyclobutane as colorless oil (51% yield, 5.20 g). R_f 0.45 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.5

Hz, 2H), 6.80 (d, *J* = 8.5 Hz, 2H), 3.78 (d, *J* = 7.0 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.27 (s, 3H), 2.96-2.86 (m, 1H), 2.80 (dd, *J* = 11.3, 8.3 Hz, 1H), 1.77 (dd, *J* = 11.1, 9.1 Hz, 1H), 1.11 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.15, 169.9, 158.5, 130.3, 128.6, 113.4, 57.0, 55.1, 52.3, 51.9, 33.6, 29.1, 20.3; HRMS *m/z* 292.1311 (calcd for $C_{16}H_{20}O_5$, 292.1311).



Diethyl 2-(4-methoxyphenyl)-3-methylcyclobutane-1,1-dicarboxylate (3.41d):

The synthesis was done at 1 mmole scale to yield cyclobutane as colorless syrup (71% yield, 0.22 g). R_f 0.28 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.5 Hz, 2H), 6.79 (d, *J* = 8.5 Hz, 2H), 4.29-4.13 (m, 2H), 3.84-3.8 (m, 1H), 3.78 (d, *J* = 3.9 Hz, 1H), 3.76 (s, 3H), 3.72-3.64 (m, 1H), 2.97-2.86 (m, 1H), 2.97 (dd, *J* = 11.3, 8.5 Hz, 1H), 1.76 (dd, *J* = 10.9, 8.9 Hz, 1H), 1.25 (t, *J* = 7.0 Hz, 3H), 1.12 (d, *J* = 6.6 Hz, 3H), 0.79 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 169.6, 158.5, 130.5, 128.8, 113.4, 61.1, 60.8, 56.9, 55.2, 52.0, 33.6, 28.9, 20.4, 14.0, 13.6; HRMS *m/z* 320.1633 (calcd for $C_{18}H_{24}O_5$, 320.1624).

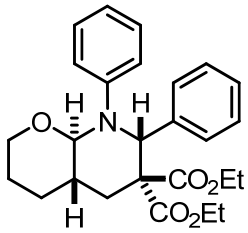


Di-*tert*-butyl 2-(4-methoxyphenyl)-3-methylcyclobutane-1,1-dicarboxylate (3.41e):

The synthesis was done at 5 mmol scale to yield cyclobutane as white solid (59% yield, 1.00 g). R_f 0.32(30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.9 Hz, 2H), 3.76 (s, 3H), 3.74 (d, *J* = 10.1 Hz, 1H), 2.88-2.78 (m, 1H), 2.70 (dd, *J* = 10.9, 8.2 Hz, 1H), 1.64 (dd, *J* = 10.9, 8.9 Hz, 1H), 1.46 (s, 9H), 1.11 (d, *J* = 6.6 Hz, 3H), 1.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 168.8, 158.4, 130.8, 129.2, 113.3, 80.89, 80.73, 68.1, 57.9, 55.3, 51.3, 33.6, 28.2, 27.9, 27.4, 20.3; HRMS *m/z* 376.2291 (calcd for $C_{22}H_{32}O_5$, 376.2250).

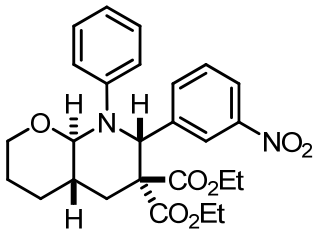
3.4.3. General Procedure B for the Formal [4+2] Cycloaddition of Imine and Cyclobutanes 3.39b and 3.39c: Synthesis of Piperideine 3.68a-g

A solution of aldehyde (1 eq, 3 mmol) and amine (1 eq, 3 mmol) dissolved in dry CH_2Cl_2 (2 mL) was stirred at rt over activated 4 Å MS (ca. 2 g) under Ar for 1 h. Without isolation the *in situ* generated imine was added via cannula to a solution of $Yb(OTf)_3$ (0.01 eq) in CH_2Cl_2 (0.5 mL) over activated 4 Å MS (ca. 1 g) in a –50 °C cold bath, followed immediately by neat cyclobutane (1.0 eq, 1 mmol). The reaction was maintained at –50 °C until complete (tlc, 30 – 60 min), and then allowed to warm to rt. After an hour the reaction mixture was treated with solid $NaHCO_3$ (ca. 0.5 g) and filtered through a silica gel (2 cm) and celite (1 cm) bilayer pad open to the atmosphere. The filtrate was concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel using EtOAc-hexanes for elution (buffered with 1% Et_3N) provided the title compounds.

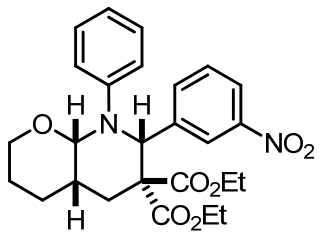


Diethyl 7,8-diphenylhexahydro-2*H*-pyrano[2,3-*b*]pyridine-6,6(7*H*)-dicarboxylate (3.67a):

This piperidine was obtianed as a minor product when the reaction (according to general procedure A) was stoped at –50 °C after ca. 30 min. Colorless syrup (17% yield, 0.02 g) as a single diasteriomer. R_f 0.26 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11-7.06 (m, 5H), 7.02 (d, *J* = 6.4, 2H), 6.91 (d, *J* = 8.2, 2H), 6.83 (t, *J* = 7.3, 1H), 5.61 (s, 1H), 4.68 (d, *J* = 8.2, 1H), 4.40-4.34 (m, 2H), 3.93 (dd, *J* = 11.7, 4.7, 1H), 3.79-3.75 (m, 1H), 3.72-3.67 (m, 1H), 3.56-3.52 (m, 1H), 2.5-2.44 (m, 2H), 1.91 (d, *J* = 12.9, 1H), 1.76-1.74 (m, 1H), 1.68-1.65(m, 1H), 1.61-1.57 (m, 2H), 1.36 (t, *J* = 7.0, 3H), 0.86 (t, *J* = 7.0, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 168.4, 146.6, 136.7, 129.9, 127.9, 127.6,127.5, 124.2, 122.6, 87.4, 68.7, 67.1, 62.1, 61.4, 58.7, 38.0, 30.4, 29.3, 26.0, 14.1, 13.4; HRMS *m/z* 437.2206 (calcd for $C_{26}H_{31}NO_5$, 437.2202).



trans-**3.67b**



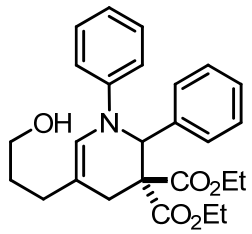
cis-**3.67b**

Diethyl 7-(3-nitrophenyl)-8 phenylhexahydro-2*H*-pyrano[2,3-*b*]pyridine-6,6(7*H*)-dicarboxylate (3.67b):

This piperidine was obtianed as a minor product when the reaction (according to general procedure A) was stoped at –50 °C after ca. 30 min. Yellow powder (22% yield, 0.03 g) as two diasteriomers (2:1 *trans*:*cis*); *trans*-**3.67b**: recrystallization from CH_2Cl_2/hexanes yielded yellow crystals. R_f 0.25 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.2, 1H), 7.95 (s, 1H), 7.36 (d, *J* = 7.6, 1H), 7.29 (t, *J* = 7.6, 1H), 7.08 (t, *J* = 7.6, 2H), 6.9 (d, *J* = 7.6, 2H), 6.85 (t, *J* = 7.0, 1H), 5.78 (s, 1H), 4.64 (d, *J* = 8.2, 1H), 4.42-4.35 (m, 2H), 3.94 (dd, *J* = 11.7, 4.7, 1H), 3.84-3.80 (m, 1H), 3.75-3.71 (m, 1H), 3.57 (t, *J* = 11.1, 1H), 2.52 (dd, *J* = 14.6, 3.5, 1H), 2.37 (t, *J* = 14.0, 1H), 1.94 (d, *J* = 11.7, 1H), 1.78-1.74 (m, 1H), 1.64-1.59 (m, 3H), 1.37 (t, *J* = 7.0, 3H), 0.91 (t, *J* = 7.0, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 168.0, 147.4, 145.9, 139.2, 135.6, 128.6, 128.3, 124.2, 123.8, 123.1, 122.5, 87.4, 67.9, 67.2, 62.4, 61.8, 58.5, 37.8, 30.3, 29.2, 25.9, 14.1, 13.5; HRMS *m/z* 482.2043 (calcd for $C_{26}H_{30}N_2O_7$, 482.2053).

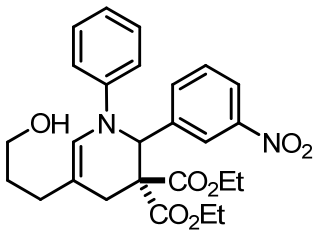
cis-**3.67b**: recrystallization from CH_2Cl_2/hexanes yielded yellow crystals. R_f 0.31 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (t, *J* = 2.0, 1H), 8.04 (d, *J* = 7.6, 1H), 7.97 (d, *J* = 9.3, 1H), 7.32 (t, *J* = 7.9, 1H), 7.21-7.19 (m, 2H), 7.17-7.14 (m, 2H), 6.81-6.79 (m, 1H), 6.04 (s, 1H), 4.77 (d, *J* = 2.3, 1H), 4.34-4.30 (m, 1H), 4.28-4.24 (m, 1H), 4.18 (d, *J* = 11.1, 1H), 3.89-3.86 (m, 1H), 3.73-3.70 (m, 1H), 3.62-3.58 (m, 1H), 2.82 (t, *J* = 14.0, 1H), 2.08 (dd, *J* = 14.0, 2.9, 1H), 1.95-1.91 (m, 1H), 1.75 (d, *J* = 13.5, 1H), 1.45 (d, *J* = 12.3, 1H), 1.29 (t, *J* = 7.0, 3H), 1.04 (t, *J* = 7.0, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 168.3, 148.1, 147.7, 140.5, 136.4, 129.0, 128.5, 125.6, 122.5,

120.8, 118.0, 85.3, 66.3, 62.2, 61.7, 59.9, 59.7, 31.8, 29.0, 24.1, 20.8, 14.0, 13.64; HRMS *m/z* 482.2043 (calcd for $C_{26}H_{30}N_2O_7$, 482.2053).



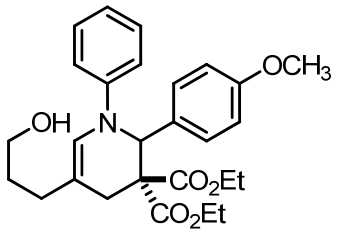
Diethyl-(3-hydroxypropyl)-1,2-diphenyl-1,2-dihydropyridine-3,3(4*H*)-dicarboxylate (3.68a):

The synthesis was done at 0.3 mmole scale to yield the tiltled compound as colorless oil (81% yield, 0.10 g). R_f 0.13 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.26 (m, 5H), 7.19-7.15 (m, 2H), 6.84-6.80 (m, 3H), 6.59 (s, 1H), 5.51 (s, 1H), 4.16-4.04 (m, 4H), 3.69 (t, *J* = 6.4, 2H), 2.58 (d, *J* = 17.2, 1H), 2.50 (d, *J* = 17.2, 1H), 2.71 (t, *J* = 7.4, 2H), 1.78-1.71 (m, 2H), 1.60 (brs, 1H), 1.19 (t, *J* = 7.2, 3H), 1.06 (t, *J* = 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 168.6, 147.0, 139.8, 129.0, 128.5, 127.9, 127.1, 124.4, 120.3, 115.9, 107.9, 62.5, 61.9, 61.7, 57.6, 31.1, 26.5, 13.9, 13.8; HRMS *m/z* 437.2194 (calcd for $C_{26}H_{31}NO_5$, 437.2202).



Diethyl 5-(3-hydroxypropyl)-2-(3-nitrophenyl)-1-phenyl-1,2-dihydropyridine-3,3(4*H*)-dicarboxylate (3.68b):

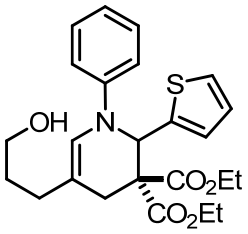
The synthesis was done at 0.3 mmole scale to yield the tiltled compound as colorless oil (73% yield, 0.10 g). R_f 0.12 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (t, *J* = 1.76, 1H), 8.13 (d, *J* = 8.2, 1H), 7.63 (d, *J* = 7.8, 1H), 7.48 (t, *J* = 7.2, 1H), 7.20 (t, *J* = 8.0, 2H), 6.87 (t, *J* = 7.4, 1H), 6.80 (d, *J* = 7.8, 2H), 6.61 (s, 1H), 5.65 (s, 1H), 4.20-4.02 (m, 4H), 3.70 (t, *J* = 6.4, 2H), 2.64 (d, *J* = 17.5, 1H), 2.45 (d, *J* = 17.5, 1H), 2.24 (t, *J* = 7.8, 2H), 1.75 (quin, *J* = 6.9, 2H), 1.53 (brs, 1H), 1.24 (t, *J* = 7.0, 3H), 1.06 (t, *J* = 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 168.2, 148.3, 146.5, 142.0, 133.4, 129.6, 129.2, 124.3, 123.0, 122.2, 120.9, 116.1, 108.5, 62.26, 62.20, 62.0, 61.3, 57.3, 31.0, 30.9, 26.4, 13.9, 13.7; HRMS *m/z* 482.2026 (calcd for $C_{26}H_{30}N_2O_7$, 482.2053).



Diethyl 5-(3-hydroxypropyl)-2-(4-methoxyphenyl)-1-phenyl-1,2-dihydropyridine-3,3(4*H*)-dicarboxylate (3.68c):

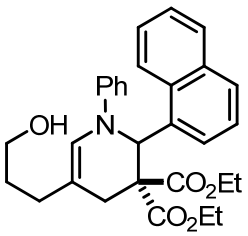
The synthesis was done at 0.3 mmole scale to yield the tiltled compound as colorless oil (77% yield, 0.10 g). R_f 0.14 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.6, 2H), 7.15 (d, *J* = 7.4, 2H), 6.83 (d, *J* = 8.2, 2H), 6.79 (d, *J* = 8.6, 3H), 6.57 (s, 1H), 5.47 (s, 1H), 4.17-4.03 (m, 4H), 3.76 (s, 3H), 3.69 (t, *J* = 6.2, 2H), 2.58 (d, *J* = 17.8, 1H), 2.50 (d, *J* = 17.9, 1H), 2.21 (t, *J* = 7.4, 2H), 1.75 (quin, *J* = 6.6, 2H), 1.35 (brs, 1H),

1.20 (t, *J* = 7.0, 3H), 1.05 (t, *J* = 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 168.7, 159.1, 147.0, 131.8, 129.0, 128.3, 124.3, 120.2, 115.8, 113.8, 107.7, 77.3, 62.5, 61.67, 61.65, 61.3, 57.7, 55.1, 31.1, 26.5, 13.9, 13.80; HRMS *m/z* 467.2297 (calcd for $C_{27}H_{33}NO_6$, 467.2308).



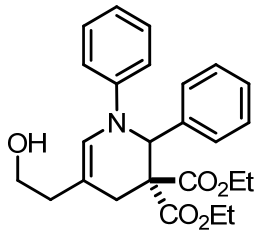
Diethyl 5-(3-hydroxypropyl)-1-phenyl-2-(thiophen-2-yl)-1,2-dihydropyridine-3,3(4*H*)-dicarboxylate (3.68d):

The synthesis was done at 0.3 mmole scale to yield the tiltled compound as colorless oil (42% yield, 0.05 g). R_f 0.16 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.17 (m, 3H), 6.95 (d, *J* = 3.5, 1H), 6.91-6.83(m, 4H), 6.39 (s, 1H), 5.89 (s, 1H), 4.26-4.09 (m, 2H), 4.02 (q, *J* = 7.0, 2H), 3.69 (t, *J* = 6.4, 2H), 2.69 (d, *J* = 17.6, 1H), 2.58 (d, *J* = 17.6, 1H), 2.21 (t, *J* = 7.4, 2H), 1.77 (quin, *J* = 7.0, 2H), 1.59 (brs, 1H), 1.24 (t, *J* = 7.2, 3H), 0.98 (t, *J* = 7.0, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ168.5, 168.3, 146.6, 141.5, 129.1, 126.3, 126.0, 125.2, 123.2, 120.4, 115.8, 109.5, 62.5, 61.95, 61.87, 58.22, 58.1, 31.1, 30.9, 27.0, 13.9, 13.6; HRMS *m/z* 443.1753 (calcd for $C_{24}H_{29}NO_5S$, 443.1766).



Diethyl 5-(3-hydroxypropyl)-2-(naphthalen-1-yl)-1-phenyl-1,2-dihydropyridine-3,3(4*H*)-dicarboxylate (3.68e):

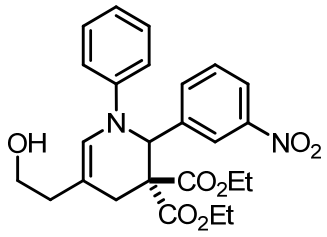
The synthesis was done at 0.3 mmole scale to yield the tiltled compound as colorless oil (84% yield, 0.12 g). R_f 0.12 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.8, 1H), 7.87 (d, *J* = 8.2, 1H), 7.97 (d, *J* = 8.2, 1H), 7.65 (d, *J* = 7.6, 1H), 7.53 (t, *J* = 7.6, 1H), 7.48 (t, *J* = 7.0, 1H), 7.42 (t, *J* = 7.9, 1H), 7.12 (t, *J* = 7.0, 2H), 6.81-6.78 (m, 3H), 6.72 (s, 1H), 6.43 (s, 1H), 4.21-4.11 (m, 2H), 3.73 (t, *J* = 6.4, 2H), 3.51-3.43 (m, 2H), 2.75 (d, *J* = 16.7, 1H), 2.64 (d, *J* = 16.7, 1H), 2.28 (t, *J* = 7.3, 2H), 1.80 (quin, *J* = 6.8, 2H), 1.58 (brs, 1H), 1.13 (t, *J* = 7.0, 3H), 0.83 (t, *J* = 7.0, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ169.6, 168.8, 147.0, 136.3, 133.3, 130.2, 129.18, 129.07, 128.52, 125.97, 125.84, 125.75, 125.4, 124.7, 122.2, 120.3, 115.9, 107.5, 62.4, 61.66, 61.51, 57.1, 56.4, 31.0, 27.1, 13.8, 13.17; HRMS *m/z* 487.2343 (calcd for $C_{30}H_{33}NO_5$, 487.2359).



Diethyl 5-(2-hydroxyethyl)-1,2-diphenyl-1,2-dihydropyridine-3,3(4*H*)-dicarboxylate (3.68f):

The synthesis was done at 0.3 mmole scale to yield the tiltled compound as colorless oil (86% yield, 0.10 g). R_f 0.15 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.25 (m, 5H), 7.20-7.16 (m, 2H), 6.86-6.82 (m, 3H), 6.65 (s, 1H), 5.59 (s, 1H), 4.16-4.04 (m, 4H), 3.81-3.75 (m, 1H), 3.71-3.65 (m, 1H), 2.66 (d, *J* = 17.2, 1H), 2.45 (d, *J* = 17.6,

1H), 2.39-2.35 (m, 2H), 1.89 (brs, 1H), 1.18 (t, *J* = 7.2, 3H), 1.02 (t, *J* = 7.0, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 168.3, 146.7, 139.5, 129.0, 128.5, 128.0, 127.2, 126.6, 120.6, 116.1, 104.7, 62.3, 62.0, 61.8, 60.2, 58.0, 37.7, 25.7, 13.8, 13.70; HRMS *m/z* 423.2045 (calcd for $C_{25}H_{29}NO_5$, 423.2046).

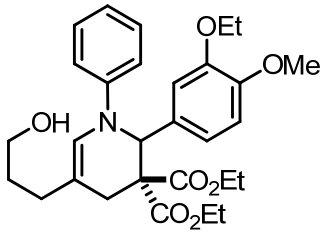


Diethyl 5-(2-hydroxyethyl)-2-(3-nitrophenyl)-1-phenyl-1,2-dihydropyridine-3,3(4*H*)-dicarboxylate (3.68g):

The synthesis was done at 0.3 mmole scale to yield the tiltled compound as colorless oil (81% yield, 0.11 g). R_f 0.14 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (t, *J* = 1.9, 1H), 8.13 (dd, *J* = 8.2, 1.5, 1H), 7.69 (d, *J* = 7.8, 1H), 7.49 (t, *J* = 8.2, 1H), 7.20 (t, *J* = 7.4, 2H), 6.89 (t, *J* = 7.0, 1H), 6.81 (d, *J* = 7.8, 2H), 6.66 (s, 1H), 5.71 (s, 1H), 4.20-4.06 (m, 4H), 3.84-3.78 (m, 1H), 3.75-3.69 (m, 1H), 2.72 (d, *J* = 17.5, 1H), 2.41-2.36 (m, 3H), 1.88 (brs, 1H), 1.24 (t, *J* = 7.0, 3H), 1.02 (t, *J* = 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ168.9, 168.0, 148.3, 146.3, 141.8, 133.5, 129.69, 129.29, 126.4, 123.1, 122.4, 121.3, 116.2, 105.7, 62.37, 62.31, 61.7, 60.3, 57.7, 37.7, 25.8, 13.9, 13.6; HRMS *m/z* 468.1898 (calcd for $C_{25}H_{28}N_2O_7$, 468.1897).

3.4.4. General Procedure C for the One-pot [2+2]/ [4+2] Synthesis of Piperideines 3.68a and 3.68m

A solution of cyclobutane was prepared according to General Procedure A (1:1 equiv of enol ether and freshly prepared methylidene malonate is employed), and without isolation a solution of imine prepared according to General Procedure B was added. The reaction mixture was then concentrated while still cold to a total volume of ca. 2 mL. The reaction was then maintained at –50 °C until complete (tlc, 30 – 60 min), and then allowed to warm to rt and processed as described under General Procedure B to afford the title compounds.



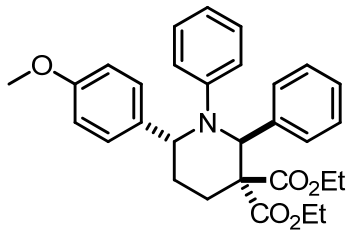
Diethyl 2-(3-ethoxy-4-methoxyphenyl)-5-(3-hydroxypropyl)-1-phenyl-1,2-dihydropyridine-3,3(4*H*)-dicarboxylate (3.68m):

The synthesis was done at 0.5 mmole scale to yield the tiltled compound as colorless oil (84% yield, 0.21 g). R_f 0.11 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 - 7.15 (m, 2 H), 6.86 - 6.82 (m, 4 H), 6.81 (dd, *J* = 8.2, 1.8 Hz, 1 H), 6.76 - 6.74 (m, 1 H), 6.57 (s, 1 H), 5.44 (s, 1 H), 4.14 (dq, *J* = 11.0, 7.1 Hz, 1 H), 4.10 - 4.02 (m, 5 H), 3.78 (s, 3 H), 3.68 (t, *J* = 6.4 Hz, 2 H), 2.61 (d, *J* = 17.6 Hz, 1 H), 2.56 (d, *J* = 17.6 Hz, 1 H), 2.20 (t, *J* = 7.3 Hz, 2 H), 1.78 - 1.70 (m, 2 H), 1.68 (s, 1 H), 1.43 (t, *J* = 7.0 Hz, 3 H), 1.19 (t, *J* = 7.3 Hz, 3 H), 1.04 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 168.7, 149.1, 147.9, 147.1, 132.2, 129.0, 124.3, 120.3, 119.5, 116.0, 112.2, 110.6, 107.8, 77.3,

76.7, 64.1, 62.5, 61.7, 57.8, 55.8, 31.3, 31.1, 26.6, 14.8, 13.9, 13.8; HRMS *m/z* 511.2550 (calcd for $C_{29}H_{37}NO_7$, 511.2570).

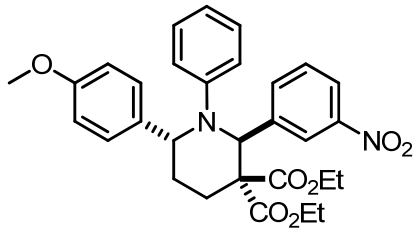
3.4.5. General Procedure D for the Formal [4+2] Cycloaddition of Imine and Cyclobutanes 3.41a: Synthesis of Piperidine 3.74a-f

The general procedure B was employed, except that after addition of cyclobutane the cold bath temperature was set to 0 °C and maintained at this temperature until complete (tlc, 8 – 12 h). Workup and purification as described in general procedure B provided the title compounds.



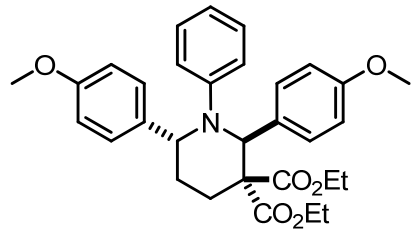
Diethyl 6-(4-methoxyphenyl)-1, 2-diphenylpiperidine-3,3-dicarboxylate (3.74a):

The synthesis was done at 0.3 mmole scale to yield the tiltled compound as colorless oil (62% yield, 0.90 g). R_f 0.22 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-7.19 (m, 2H), 7.13-7.09 (m, 5H), 6.90-6.81 (m, 4H), 6.64-6.61 (m, 3H), 5.66 (s, 1H), 4.73 (dd, *J* = 11.5, 3.7, 1H), 4.39 (q, *J* = 7.1, 2H), 3.87-3.75 (m, 2H), 3.65 (s, 3H), 2.75 (td, *J* = 14.5, 4.1, 1H), 2.56-2.52 (m, 1H), 2.14 (dq, *J* = 13.9, 3.4, 1H), 1.68-1.57 (m, 1H), 1.37 (t, *J* = 7.0, 3H), 0.92 (t, *J* = 7.0, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 168.9, 157.8, 149.6, 137.68, 137.07, 129.85, 128.1, 127.65, 127.61, 127.3, 125.1, 121.7, 113.4, 67.7, 61.81, 61.36, 59.0, 56.6, 54.9, 34.2, 24.5, 14.2, 13.5; HRMS *m/z* 487.2357 (calcd for $C_{30}H_{33}NO_5$, 487.2359).



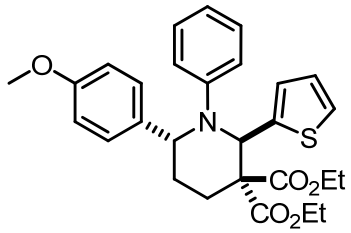
Diethyl 6-(4-methoxyphenyl)-2-(3-nitrophenyl)-1-phenylpiperidine-3,3-dicarboxylate (3.74b):

The synthesis was done at 0.3 mmole scale to yield the tiltled compound as colorless oil (86% yield, 0.13 g). R_f 0.16 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (t, *J* = 1.9, 1H), 8.0 (dd, *J* = 8.2, 1.5, 1H), 7.51 (d, *J* = 7.8, 1H), 7.31 (t, *J* = 8.2, 1H), 7.09 (d, *J* = 8.9, 2H), 6.89 (t, *J* = 7.4, 2H), 6.81 (d, *J* = 7.4, 2H), 6.66-6.62 (m, 3H), 5.83 (s, 1H), 4.71 (dd, *J* = 11.5, 3.7, 1H), 4.41 (qd, *J* = 7.1, 2.5, 2H), 3.92-3.79 (m, 2H), 3.66 (s, 3H), 2.68-2.55 (m, 2H), 2.2 (dq, *J* = 14.0, 3.5, 1H), 1.70-1.63 (m, 1H), 1.38 (t, *J* = 7.2, 3H), 0.98 (t, *J* = 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 168.5, 158.0, 148.8, 147.5, 140.2, 136.2, 135.7, 128.6, 128.0, 124.7, 124.1, 122.4, 122.2, 119.9, 113.5, 67.0, 62.1, 61.7, 58.8, 56.8, 55.0, 33.9, 24.4, 14.2, 13.6; HRMS *m/z* 532.2195 (calcd for $C_{30}H_{32}N_2O_7$, 532.2210).



Diethyl 2,6-bis(4-methoxyphenyl)-1-phenylpiperidine-3,3-dicarboxylate (3.74c):

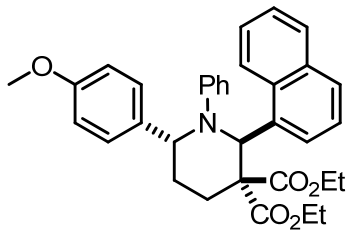
The synthesis was done at 0.3 mmole scale to yield the tiltled compound as colorless oil (73% yield, 0.11 g). R_f 0.14 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (t, *J* = 8.9, 4H), 6.88 (t, *J* = 7.4, 2H), 6.80 (d, *J* = 7.8, 2H), 6.63 (t, *J* = 8.6, 5H), 5.60 (s, 1H), 4.67 (dd, *J* = 11.5, 3.3, 1H), 4.38 (q, *J* = 7.0, 2H), 3.89-3.75 (m, 2H), 3.69 (s, 3H), 3.65 (s, 3H), 2.72 (td, *J* = 14.6, 3.9, 1H), 2.50 (d, *J* = 14.8, 1H), 2.12 (dq, *J* = 13.8, 3.3, 1H), 1.67-1.59 (m, 1H), 1.37 (t, *J* = 7.2, 3H), 0.95 (t, *J* = 7.0, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 168.9, 158.6, 157.7, 149.7, 137.1, 130.9, 129.7, 128.1, 127.6, 125.2, 121.7, 113.3, 112.8, 67.2, 61.7, 61.3, 59.1, 56.4, 54.9, 34.3, 24.4, 14.2, 13.7; HRMS *m/z* 517.2452 (calcd for $C_{31}H_{35}NO_6$, 517.2464).



Diethyl 6-(4-methoxyphenyl)-1-phenyl-2-(thiophen-2-yl)piperidine-3,3-dicarboxylate (3.74d):

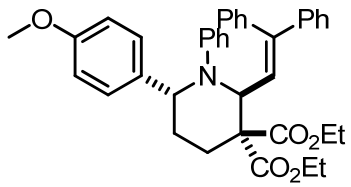
The synthesis was done at 0.3 mmole scale to yield the tiltled compound as colorless oil (59% yield, 0.10 g). R_f 0.25 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, *J* = 5.0, 1H), 7.0 (d, *J* = 8.6, 2H), 6.92 (t, *J* = 7.4, 2H), 6.81 (d, *J* = 7.4, 2H), 6.78-6.69(m, 2H), 6.60 (d, *J* = 8.6, 2H), 6.53 (d, *J* = 3.5, 1H), 5.93 (s, 1H), 4.47 (dd, *J* = 11.3, 3.1, 1H), 4.40 (q, *J* = 7.0, 2H), 3.96-3.87 (m, 2H), 3.65 (s, 3H), 3.65 (s, 3H), 2.71-2.56 (m, 2H), 2.06-2.02 (m, 1H), 1.66-1.55 (m, 1H), 1.39 (t, *J* = 7.2, 3H), 0.98 (t, *J* = 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 168.5, 157.8, 149.5, 136.9, 136.5, 128.6, 128.3,

127.7, 125.5, 125.0, 122.4, 113.4, 65.0, 61.9, 61.5, 59.0, 56.7, 54.9, 34.2, 24.9, 14.3, 13.6; HRMS *m/z* 493.1915 (calcd for $C_{28}H_{31}NO_5S$, 493.1923).



Diethyl 6-(4-methoxyphenyl)-2-(naphthalen-1-yl)-1-phenylpiperidine-3,3-dicarboxylate (3.74e):

The synthesis was done at 0.3 mmole scale to yield the tiltled compound as colorless oil (68% yield, 0.10 g). R_f 0.30 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.9, 1H), 7.64 (d, *J* = 7.4, 1H), 7.27 (d, *J* = 8.2, 1H), 7.24 (dd, *J* = 7.0, 2.3, 1H), 7.08 (t, *J* = 7.4, 1H), 6.94-6.88(m, 2H), 6.79 (d, *J* = 8.6, 2H), 6.57 (s, 1H), 6.52 (d, *J* = 7.8, 2H), 6.35 (t, *J* = 7.8, 2H), 6.27 (d, *J* = 8.6, 2H), 6.06 (t, *J* = 7.4, 1H), 4.65 (dd, *J* = 11.3, 3.9, 1H), 4.12-4.04(m, 2H), 3.27 (s, 3H), 3.11-3.03 (m, 1H), 2.80-2.72 (m, 1H), 2.54 (td, *J* = 14.6, 4.3, 1H), 2.20-2.15(m, 1H), 1.89 (dq, *J* = 14.0, 3.5, 1H), 1.39-1.28(m, 1H), 1.03 (t, *J* = 7.0, 3H), 0.16 (t, *J* = 7.0, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 168.7, 157.8, 149.1, 137.2, 135.0, 133.4, 132.6, 128.19, 128.1, 128.06, 127.4, 126.5, 125.3, 124.8, 124.3, 123.8, 121.5, 113.3, 61.8, 61.0, 59.2, 58.0, 56.7, 54.9, 34.1, 24.2, 14.2, 12.96; HRMS *m/z* 537.2510 (calcd for $C_{34}H_{35}NO_5$, 537.2515).

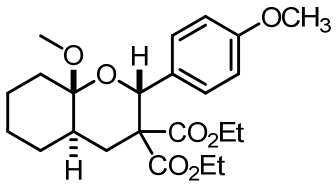


Diethyl 2-(2,2-diphenylvinyl)-6-(4-methoxyphenyl)-1-phenylpiperidine-3,3-dicarboxylate (3.74f):

The synthesis was done at 0.3 mmole scale to yield the tiltled compound as colorless oil (61% yield, 0.10 g). R_f 0.21 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.23(m, 2H), 7.13-7.10(m, 3H), 7.05-6.99(m, 4H), 6.96-6.92(m, 2H), 6.84-6.77(m, 3H), 6.60 (d, *J* = 8.6, 2H), 6.43 (d, *J* = 11.3, 1H), 6.16 (d, *J* = 7.0, 2H), 4.96 (d, *J* = 11.3, 1H), 4.57 (dd, *J* = 11.3, 3.1, 1H), 4.32 (q, *J* = 7.0, 2H), 4.25-4.17(m, 1H), 3.94-3.86(m, 1H), 3.65 (s, 3H), 2.64-2.47 (m, 2H), 1.99 (dd, *J* = 13.6, 3.1, 1H), 1.65-1.54(m, 1H), 1.32 (t, *J* = 7.2, 3H), 1.11 (t, *J* = 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 169.4, 157.7, 149.6, 146.5, 143.3, 138.5, 136.5, 129.1, 128.3, 128.0, 127.8, 127.47, 127.4, 126.8, 126.6, 122.6, 120.2, 113.3, 61.7, 61.5, 61.3, 59.0, 56.1,54.9, 34.6, 25.0, 14.2, 13.7; HRMS *m/z* 589.2827 (calcd for $C_{38}H_{39}NO_5$, 589.2828).

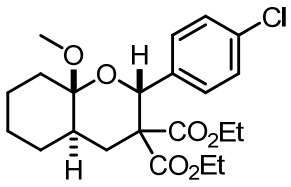
3.4.6. General Procedure E for the Annulation Reaction Between Aldehydes and Cyclobutane 3.39h:[35]

To a solution of $Yb(OTf)_3$ (0.01 equiv, 0.004 mmol) in CH_2Cl_2 (2.0 mL) at -50 °C, aldehyde (3.0 equiv, 1.2 mmol) and cyclobutane (1.0 equiv, 0.4 mmol) dissolved in CH_2CL_2 (2.0 mL) were added. The reaction mixture then warmed gradually to 0 °C (ca 1-2 h). After completion, it was filtered through silica gel pad (2 cm). The filtrate was concentrated under reduced pressure. Purification by flash column chromatography on silica gel using EtOAc-hexanes for elution provided the title compounds. TEA (1%) was added to the eluent to buffer silica gel.



Diethyl 8a-methoxy-2-(4-methoxyphenyl)hexahydro-2*H*-chromene-3,3(4*H*)-dicarboxylate (3.91v)

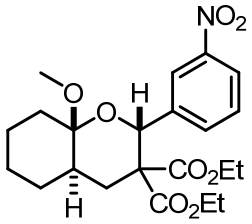
Colourless oil (76% yield, 0.09 g). R_f 0.3 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.7 Hz, 2 H), 6.78 (m, *J* = 8.7 Hz, 2 H), 5.25 (s, 1 H), 4.09 (q, *J* = 7.3 Hz, 2 H), 4.01 (dq, *J* = 10.7, 7.2 Hz, 1 H), 3.82-3.78 (m, 1 H), 3.77 (s, 3 H), 3.11 (s, 3 H), 2.19-2.14 (m, 1 H), 2.11 (t, *J* = 12.4 Hz, 1 H), 2.08-2.03 (m, 1 H), 2.02 (d, *J* = 12.8 Hz, 1 H), 1.71 (d, *J* = 8.4 Hz, 1 H), 1.61 (d, *J* = 9.9 Hz, 1 H), 1.44-1.31 (m, 5 H), 1.14 (t, *J* = 7.1 Hz, 3 H), 0.94 ppm (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 169.6, 158.8, 131.8, 129.1, 112.5, 99.0, 72.5, 61.0, 60.4, 58.9, 55.2, 47.1, 39.4, 33.2, 31.2, 28.6, 25.6, 22.6, 13.9, 13.5; HRMS *m/z* 420.2159 (calcd for $C_{23}H_{32}O_7$, 420.2148).



Diethyl 2-(4-chlorophenyl)-8a-methoxyhexahydro-2*H*-chromene-3,3(4*H*)-dicarboxylate (3.91w)

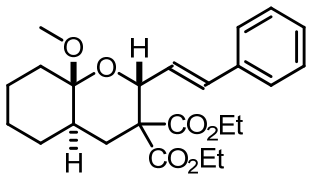
Colourless oil (69% yield, 0.08 g). R_f 0.5 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.6 Hz, 2 H), 7.21 (d, *J* = 8.6 Hz, 2 H), 5.29 (s, 1 H), 4.10 (q, *J* = 7.0 Hz, 2 H), 3.99 (dq, *J* = 10.7, 7.1 Hz, 1 H), 3.77 (dq, *J* = 10.8, 7.1 Hz, 1 H), 3.10 (s, 3

H), 2.13-2.09 (m, 2 H), 2.08-2.05 (m, 1 H), 2.04-2.00 (m, 1 H), 1.71-1.70 (m, 1 H), 1.62-1.60 (m, 1 H), 1.44-1.1.32 (m, 5 H), 1.15 (t, *J* = 7.0 Hz, 3 H), 0.92 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 169.3, 138.2, 133.0, 129.3, 127.3, 99.1, 72.2, 61.2, 60.6, 58.9, 47.1, 39.4, 33.2, 31.2, 28.5, 25.6, 22.6, 13.9, 13.5; HRMS *m/z* 425.1283 (calcd for $C_{22}H_{29}ClO_6$, 424.1653).



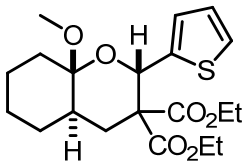
Diethyl 8a-methoxy-2-(3-nitrophenyl)hexahydro-2H-chromene-3,3(4*H*) dicarboxylate (3.91x)

Colourless oil (60% yield, 0.104 g). R_f 0.4 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 5.41 (s, 1H), 4.15 (q, *J* = 7.0 Hz, 2H), 4.02-3.97 (m, 1H), 3.86-3.80 (m, 1H), 3.11 (s, 3H), 2.21-2.13 (m, 2H), 2.11-2.07 (m, 1H), 2.03 (d, *J* = 10.6 Hz, 1H), 1.71 (d, *J* = 9.1 Hz, 1H), 1.64 (d, *J* = 8.4 Hz, 1H), 1.46-1.42 (m, 1H), 1.40-1.34(m, 4H), 1.17 (t, *J* = 7.1 Hz, 3H), 0.90 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 168.8, 147.5, 141.9, 134.1, 127.9, 123.1, 122.2, 99.5, 71.9, 61.5, 60.7, 59.2, 47.1, 39.6, 33.1, 31.1, 28.4, 25.5, 22.5, 13.8, 13.5; HRMS *m/z* 435.1882 (calcd for $C_{22}H_{29}NO_8$, 435.1893).



Diethyl 8a-methoxy-2-styrylhexahydro-2*H*-chromene-3,3(4*H*)-dicarboxylate (3.91y)

Colourless oil (71% yield, 0.08 g). R_f 0.25 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.3 Hz, 2 H), 7.27 (t, *J* = 7.7 Hz, 2 H), 7.21 - 7.18 (m, 1 H), 6.65 (dd, *J* = 16.1, 6.6 Hz, 1 H), 6.58 (d, *J* = 16.1 Hz, 1 H), 4.74 (d, *J* = 7.0 Hz, 1 H), 4.19 (q, *J* = 7.0 Hz, 2 H), 4.14 - 4.08 (m, 2 H), 3.17 (s, 3 H), 2.15 - 2.02 (m, 3 H), 1.85 - 1.80 (m, 1 H), 1.70 (d, *J* = 12.1 Hz, 1 H), 1.61 (d, *J* = 12.4 Hz, 1 H), 1.41 - 1.38 (m, 3 H), 1.29-1.24 (m, 2 H), 1.21 (t, *J* = 7.1 Hz, 3 H), 1.15 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 169.4, 137.0, 131.1, 128.4, 127.4, 127.3, 126.5, 99.0, 77.3, 76.7, 72.9, 61.3, 60.9, 59.0, 47.0, 40.1, 32.5, 31.3, 28.5, 25.6, 22.5, 14.03, 14.0; HRMS *m/z* 416.2202 (calcd for $C_{24}H_{32}O_6$, 416.2199).



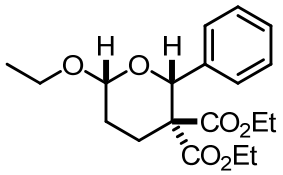
Diethyl 8a-methoxy-2-(thiophen-2-yl)hexahydro-2*H*-chromene-3,3(4*H*)-dicarboxylate (3.91z)

Colourless oil (56% yield, 0.06 g). R_f 0.3 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (dd, *J* = 5.1, 1.2 Hz, 1 H), 7.03 (d, *J* = 3.5 Hz, 1 H), 6.89 (dd, *J* = 5.1, 3.9 Hz, 1 H), 5.56 (s, 1 H), 4.20-4.10 (m, 2 H), 4.02 (dq, *J* = 10.7, 7.1 Hz, 1 H), 3.88 (dq, *J* = 10.7, 7.1 Hz, 1 H), 3.15 (s, 3 H), 2.11-2.03 (m, 4 H), 1.70-1.68 (m, 1 H), 1.62-1.60 (m, 1 H), 1.42-1.33 (m, 5 H), 1.17 (t, *J* = 7.0 Hz, 3 H), 0.96 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 169.1, 142.7, 125.7, 125.3, 124.3, 99.4, 70.1, 61.3, 60.8, 59.3,

47.2, 39.5, 33.0, 31.1, 28.5, 25.6, 22.6, 13.9, 13.5; HRMS *m/z* 396.1595 (calcd for $C_{20}H_{28}O_6S$, 396.1607).

3.4.7. General Procedure F for the One-pot [2+2] / [4+2] Synthesis of Tetrahydropyran.

To a solution of $Yb(OTf)_3$ (0.01 eq) in CH_2Cl_2 (10.0 mL/ 0.25 mmol) at –78 °C, the enol ether (1.1 equiv) was dissolved in CH_2Cl_2 (10.0 mL/ 5 mmol) and methylidene malonate (1.0 equiv) dissolved in CH_2Cl_2 (10.0 mL/ 5 mmol) were added by syringe pump over 30 minutes. Both solutions were added simultaneously. After 1h, aldehyde (3.0 equiv) was added. The reaction mixture warmed gradually to 0 °C. After completion (25 min), the reaction was filtered through silica gel pad (2 cm). The filtrate was concentrated under reduced pressure. Purification by flash column chromatography on silica gel using EtOAc-hexanes for elution provided the title compounds. TEA (1%) was added to the eluent to buffer silica gel.



Diethyl 6-ethoxy-2-phenyldihydro-2*H*-pyran-3,3(4*H*)-dicarboxylate (3.91t):

The reaction was done at 45 mmol scale to yield the titled product as colourless oil (54% yield, 8.50 g). R_f 0.40 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.43 (m, 2 H), 7.28-7.22 (m, 3 H), 5.08 (s, 1 H), 4.67 (dd, *J* = 9.4, 2.7 Hz, 1 H), 4.12 (qd, *J* = 7.2, 2.3 Hz, 2 H), 3.05-3.97 (m, 1 H), 3.95-3.84 (m, 2 H), 3.51 (dq, *J* = 9.6, 7.1 Hz, 1 H),

2.63-2.57 (m, 1 H), 2.12 (td, *J* = 13.3, 4.7 Hz, 1 H), 2.00-1.90 (m, 1 H), 1.87 - 1.81 (m, 1 H), 1.20 (t, *J* = 7.0 Hz, 3 H), 1.14 (t, *J* = 7.2 Hz, 3 H), 0.94 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 168.3, 139.2, 127.4, 127.1, 102.5, 79.4, 64.3, 61.4, 60.6, 58.5, 31.1, 27.8, 15.1, 13.8, 13.5; HRMS *m/z* 350.1711 (calcd for $C_{19}H_{26}O_6$, 350.1729).

3.5. References

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[34] Structures assignments were confirmed by 2D NMR (refer to the spectral data section).

[35] For genral procedure for the synthesis and characterization of tetrahydropyrans **3.91**, see refrence 1b.

Appendix 1

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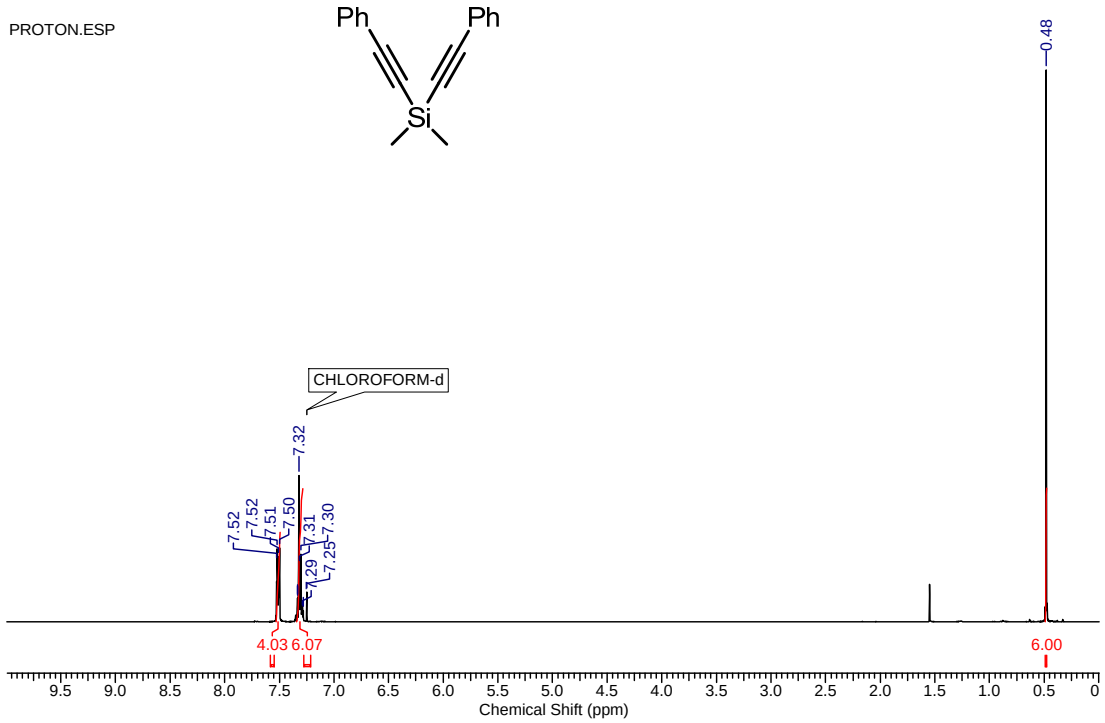
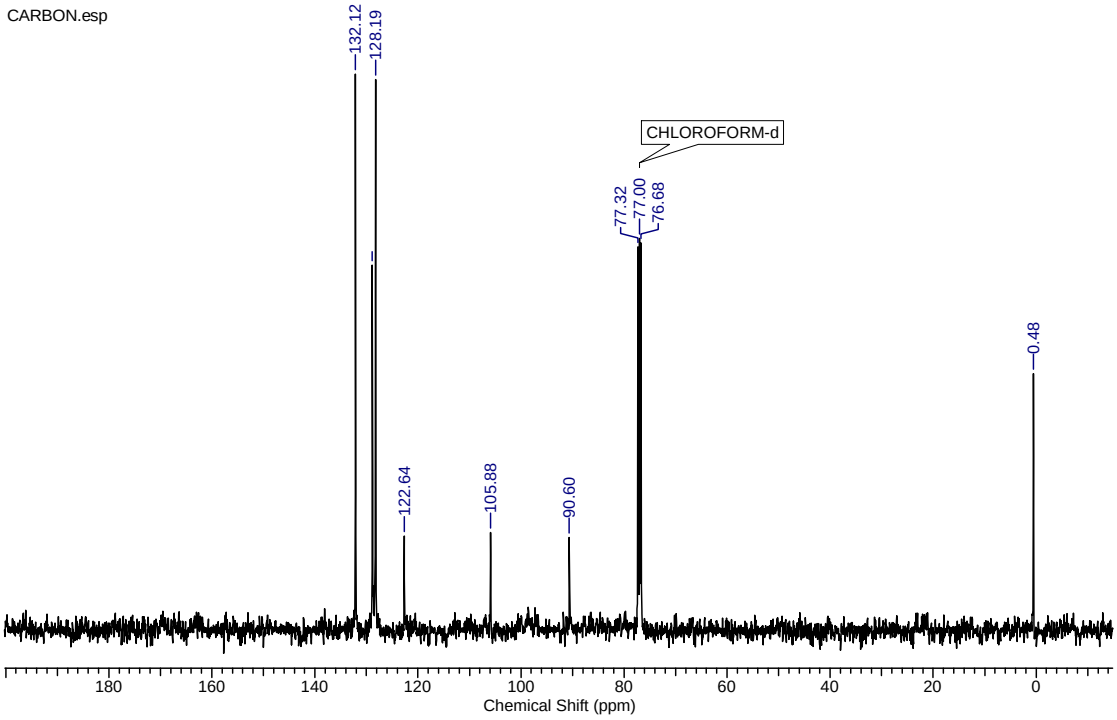
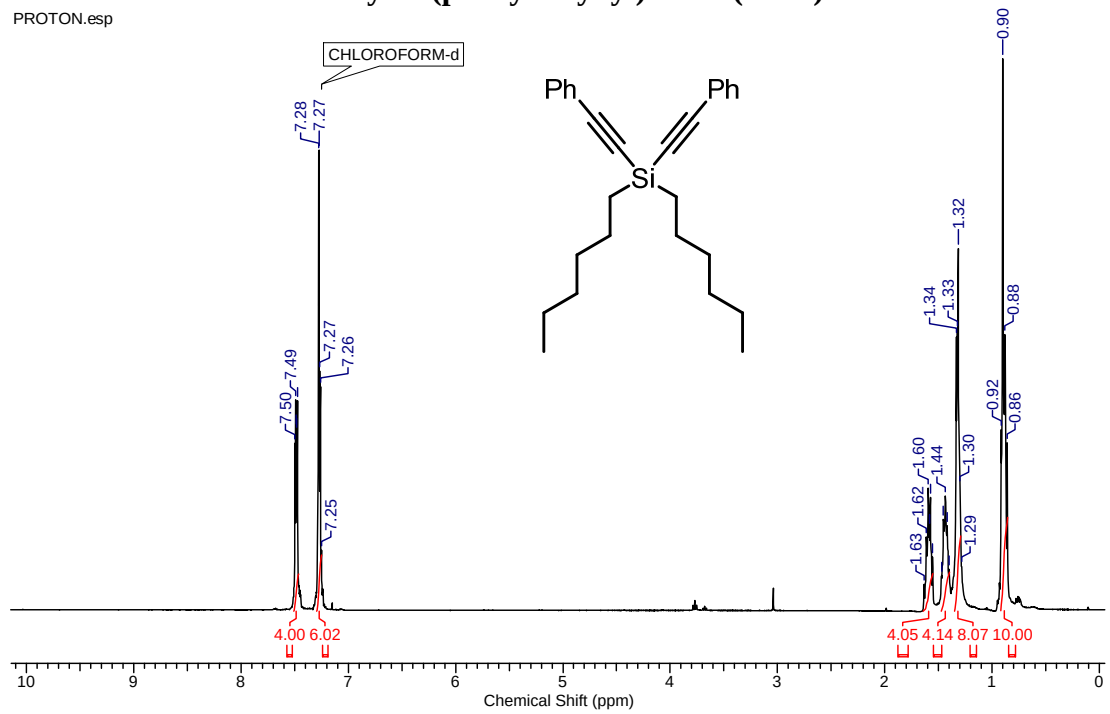
Appendix 2 – NMR Spectra for Compounds Presented in Chapter 1

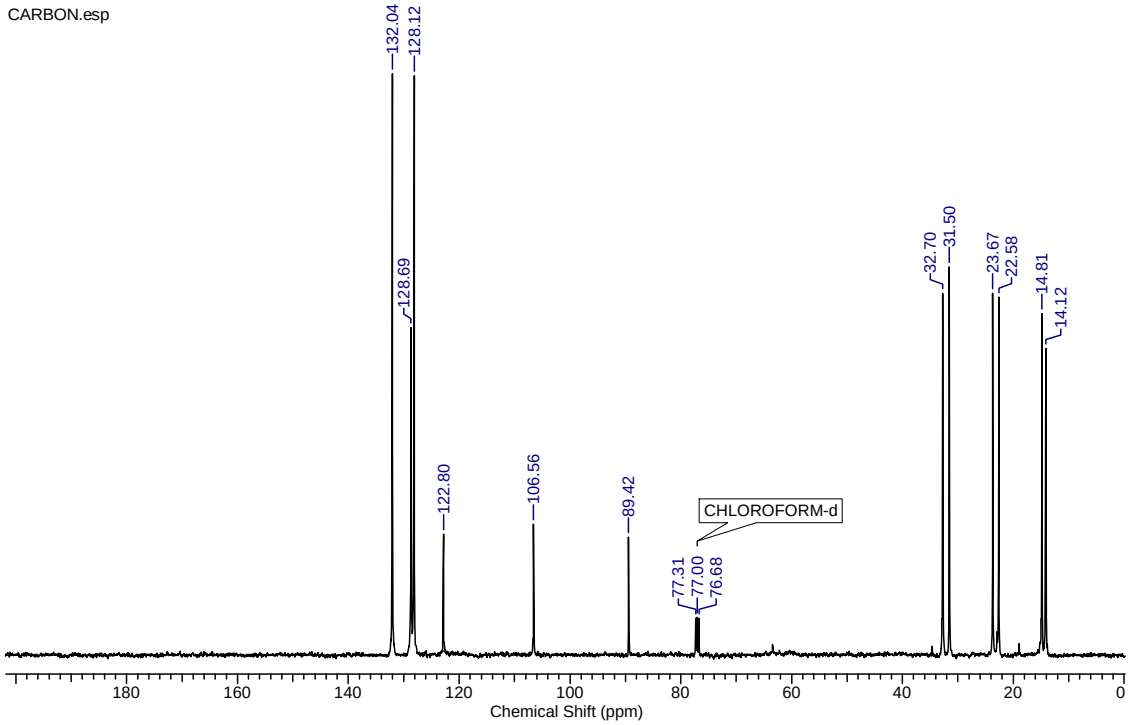
Dimethylbis(phenylethynyl)silane (1.24a)





Dihexylbis(phenylethynyl)silane (1.24c)





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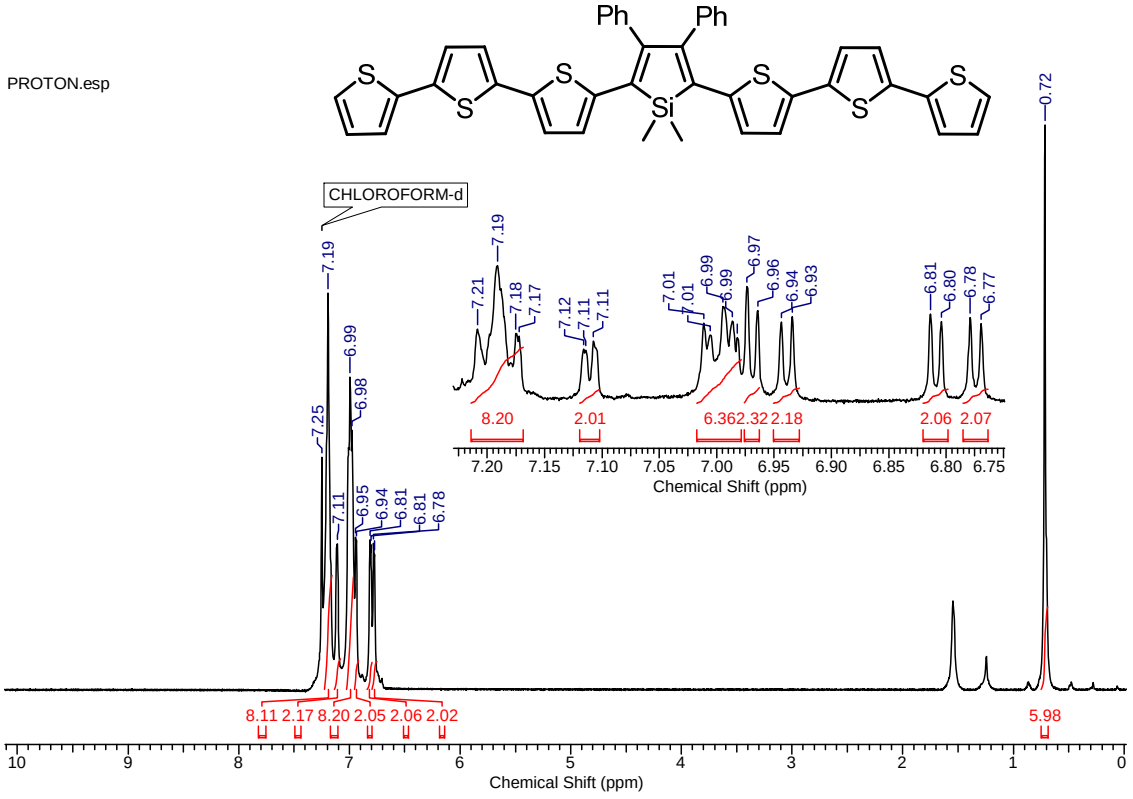
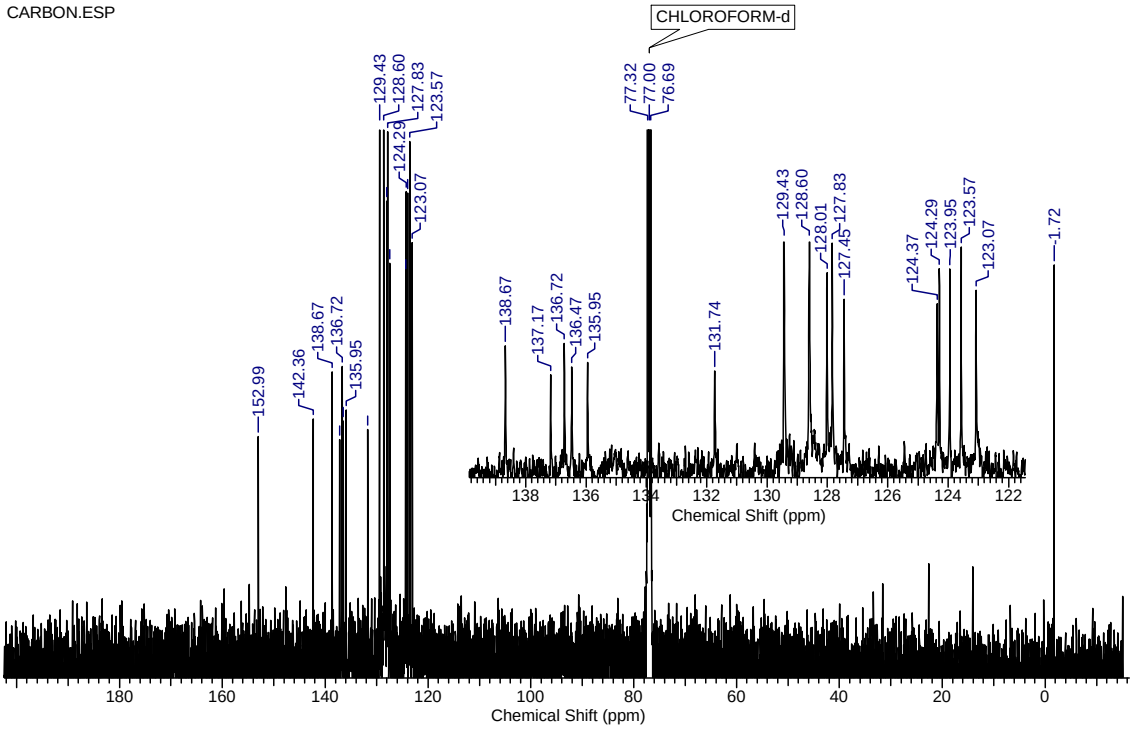
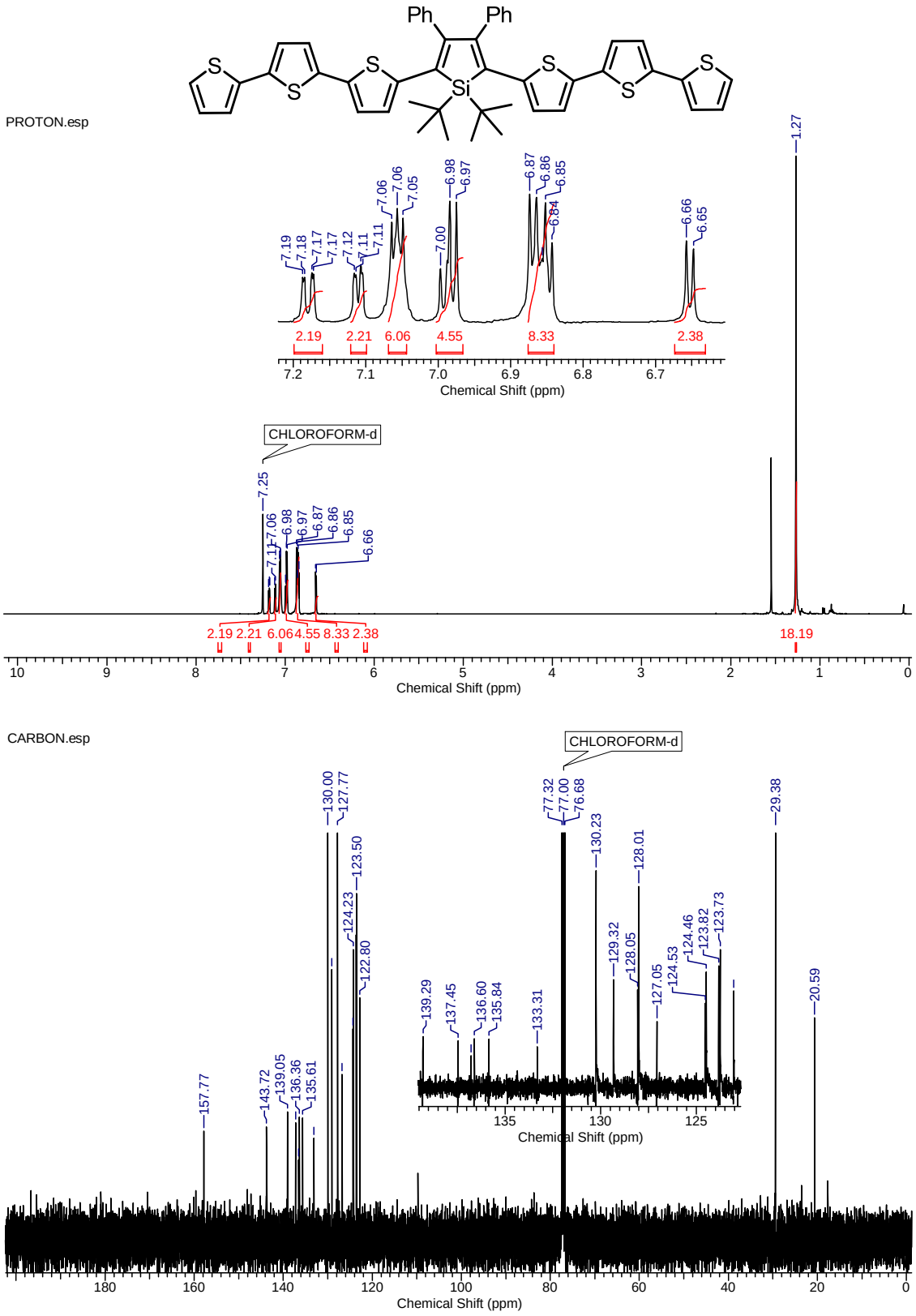
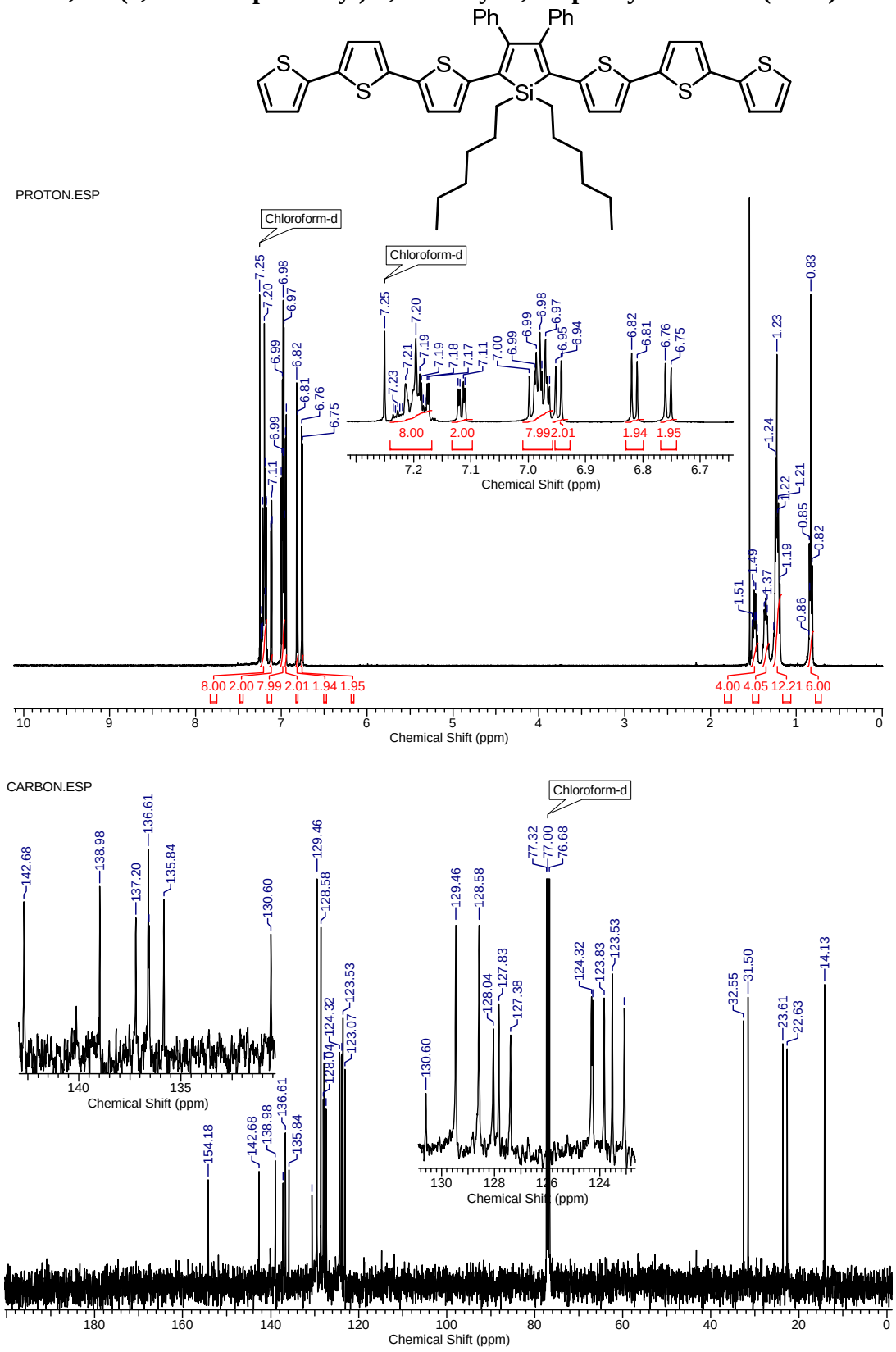




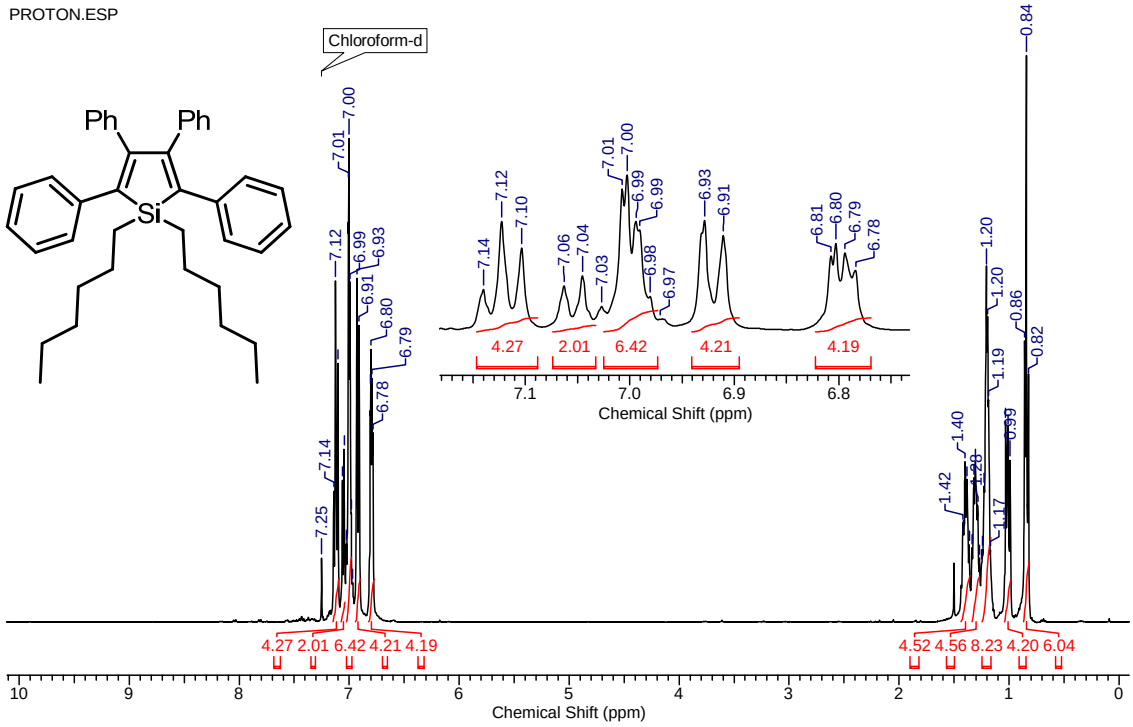
2,5-di(2,2'-terthiophen-5-yl)-1,1-di-*tert*-butyl-3,4-diphenyl-1*H*-silole (1.18b)

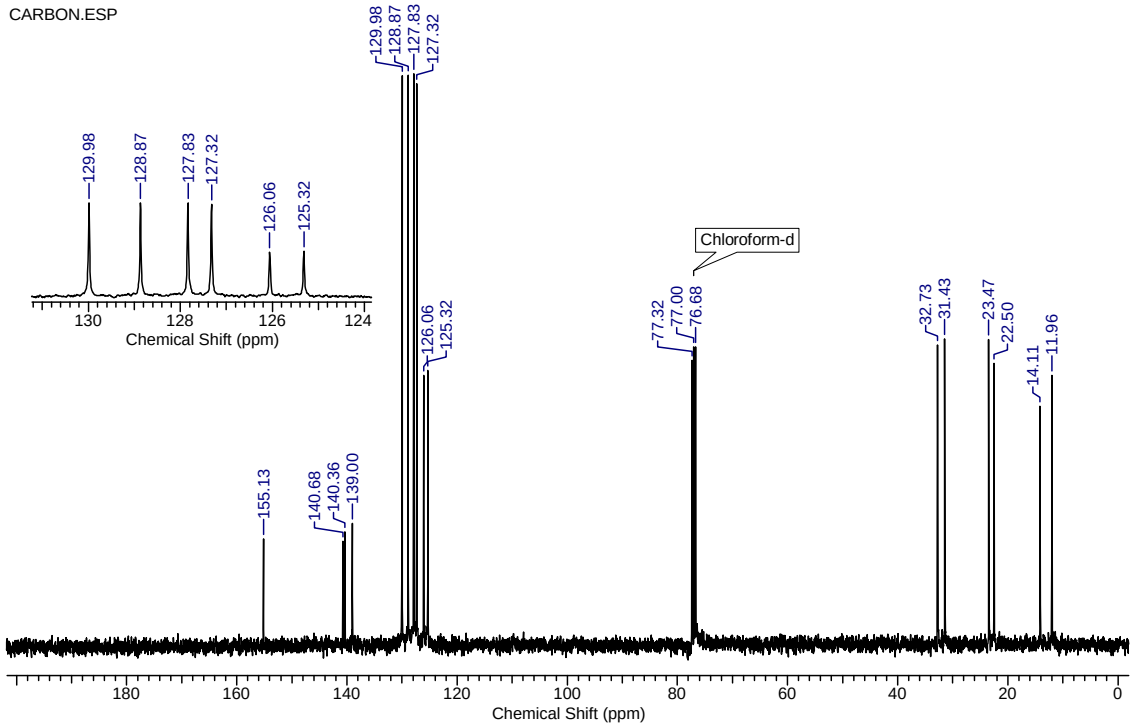


2,5-di(2,2'-terthiophen-5-yl)-1,1-dihexyl-3,4-diphenyl-1*H*-silole (1.18c)



1,1-dihexyl-2,3,4,5-tetraphenyl-1*H*-silole (1.16a)





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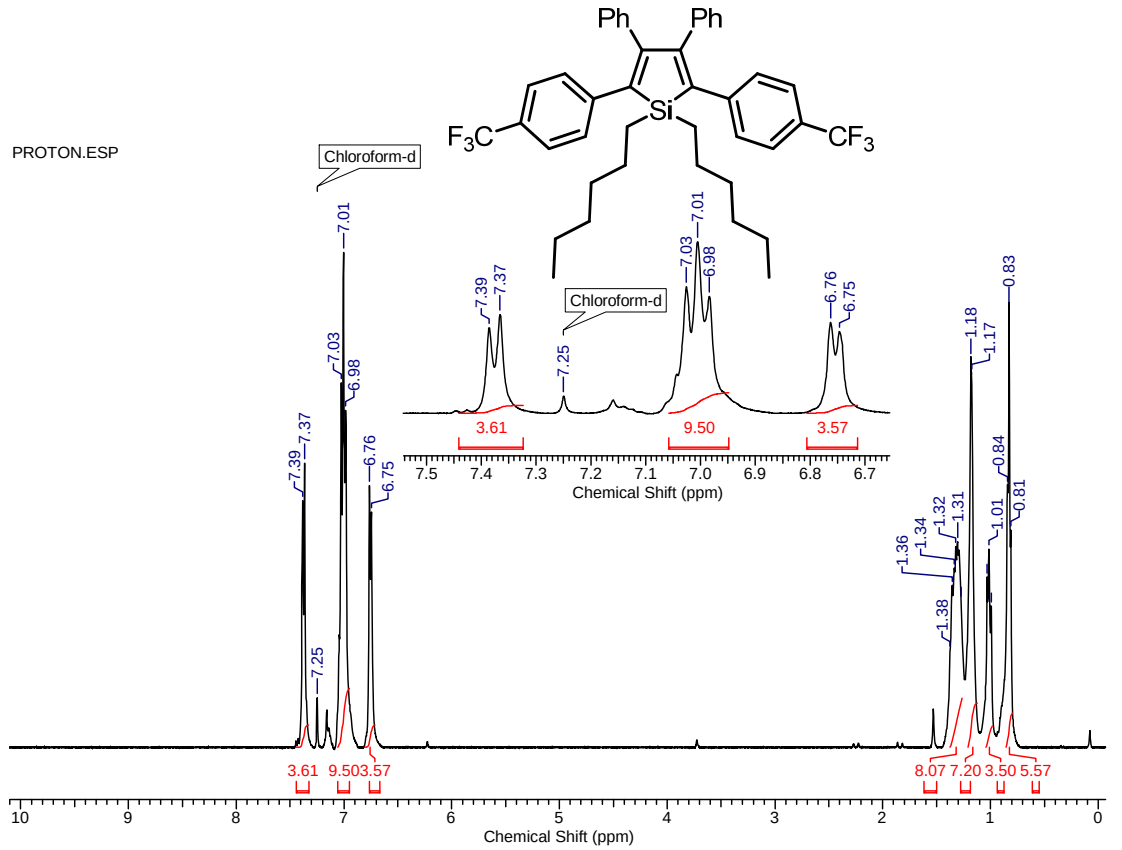
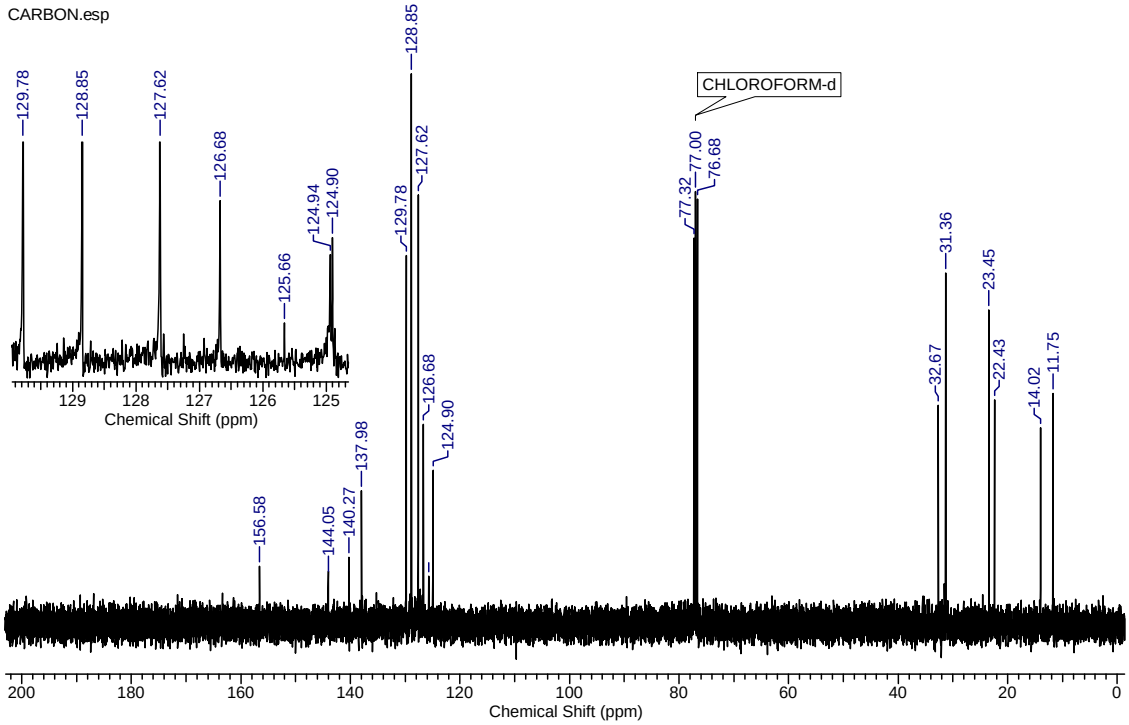
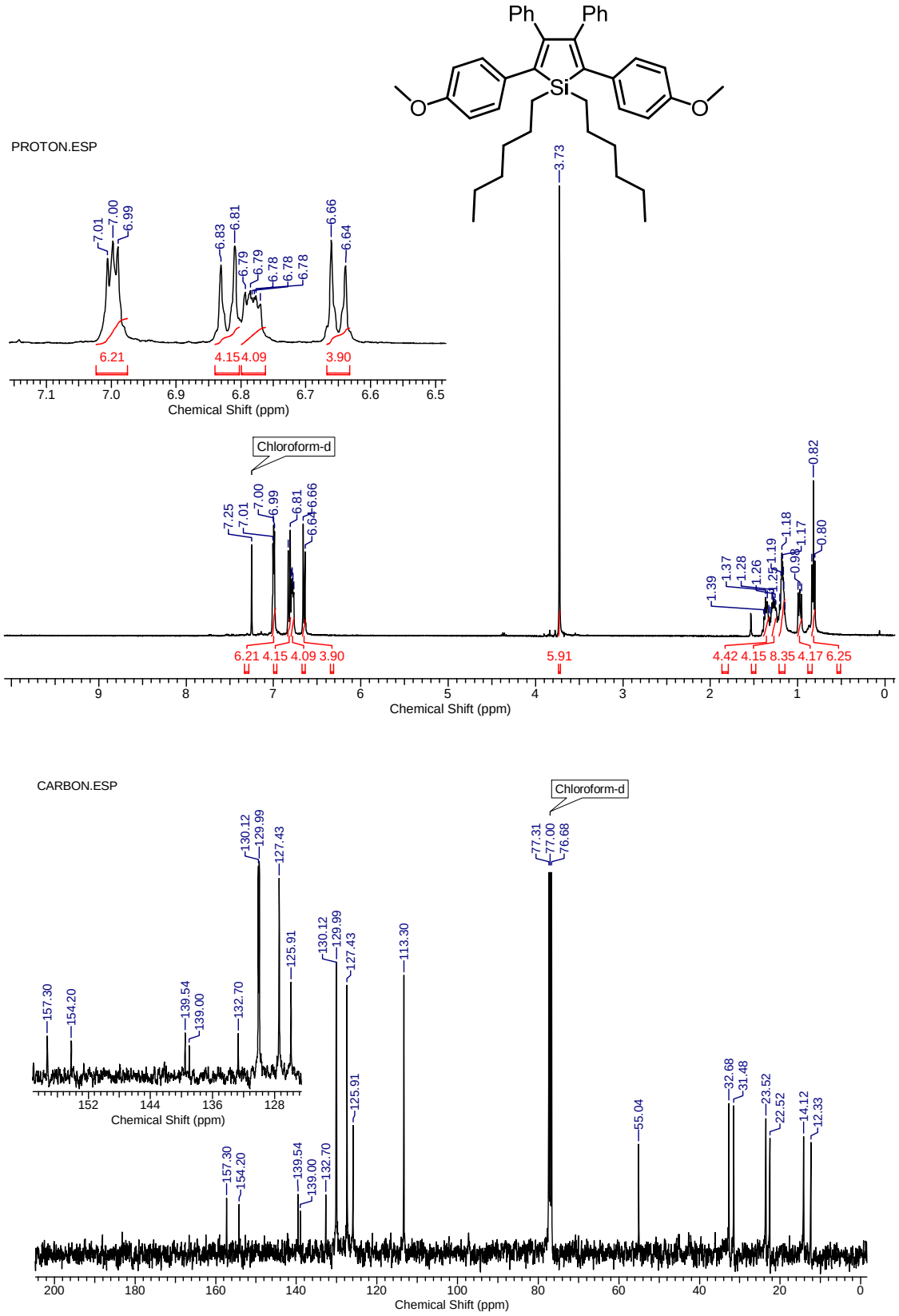
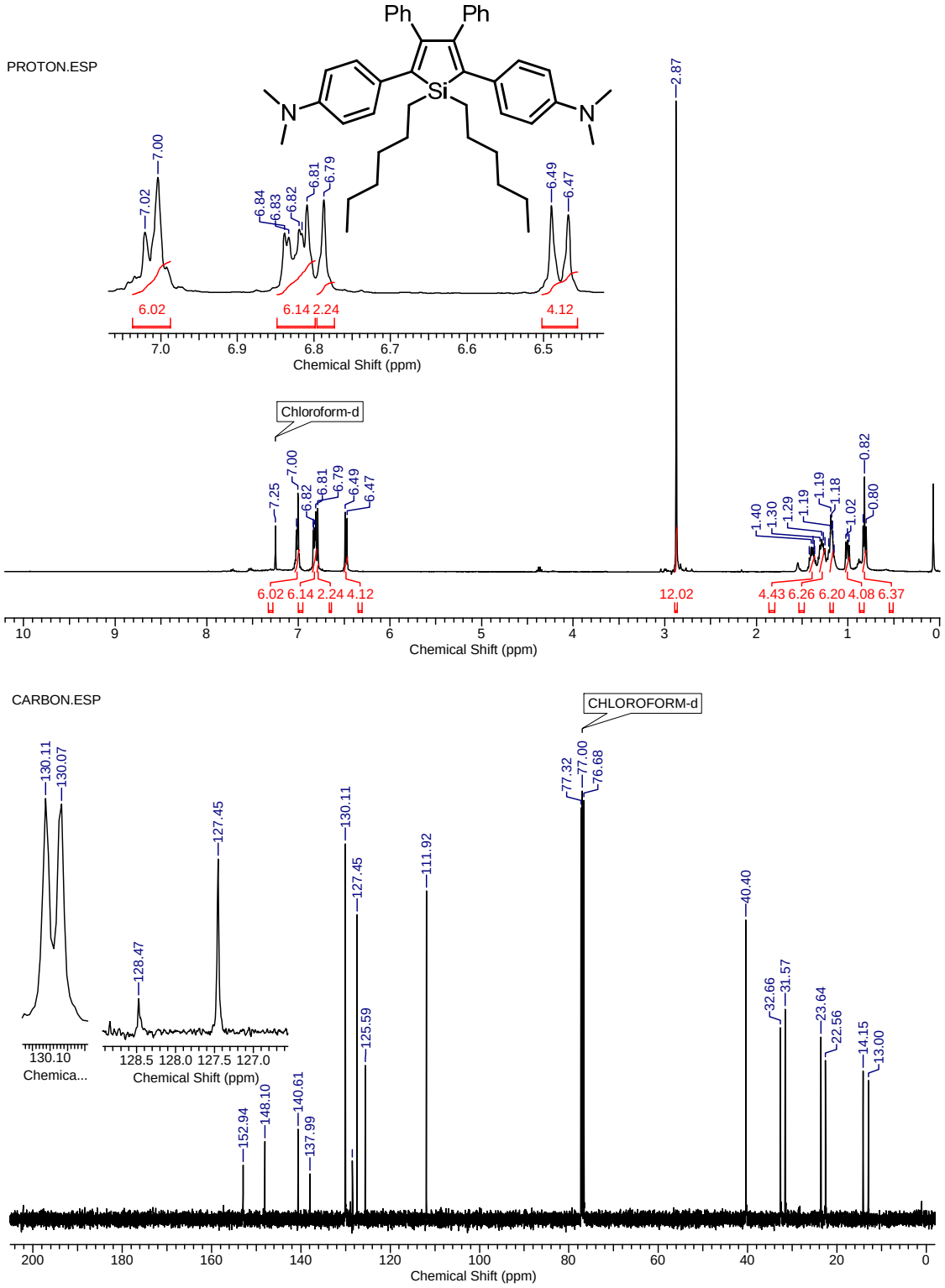




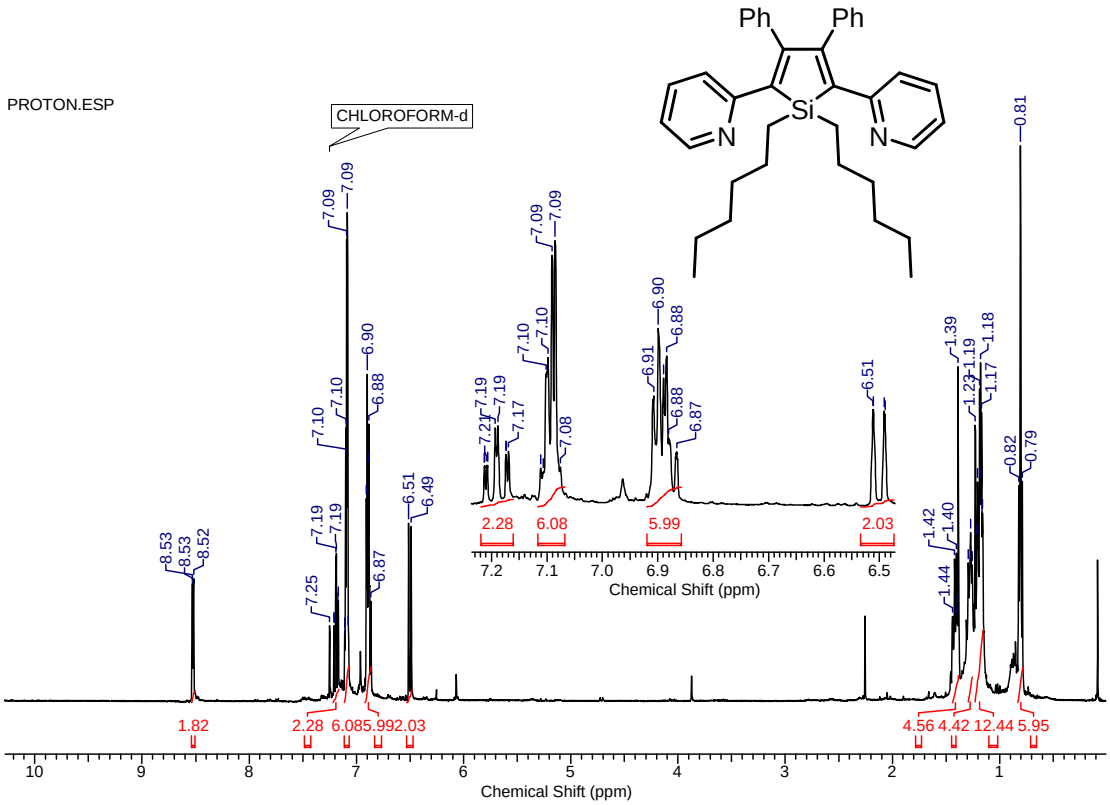
1,1-dihexyl-2,5-bis(4-methoxyphenyl)-3,4-diphenyl-1*H*-silole (1.16d)

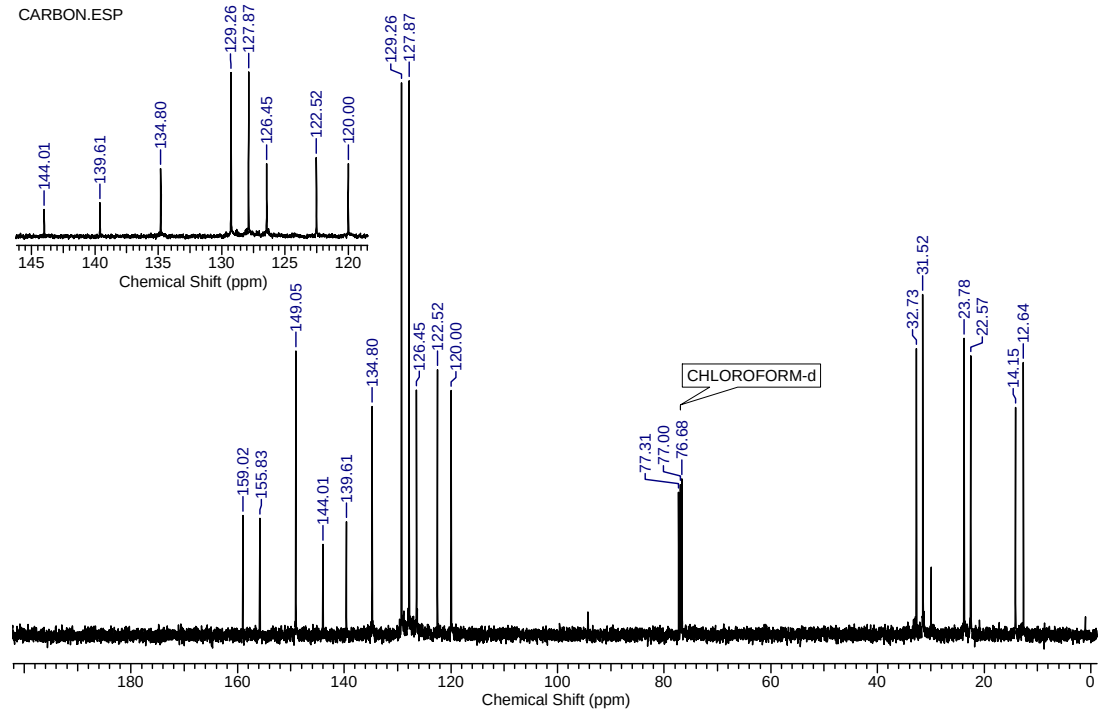


4,4'-(1,1-dihexyl-3,4-diphenyl-1*H*-silole-2,5-diyl)bis(*N*,*N*-dimethylaniline) (1.16e)

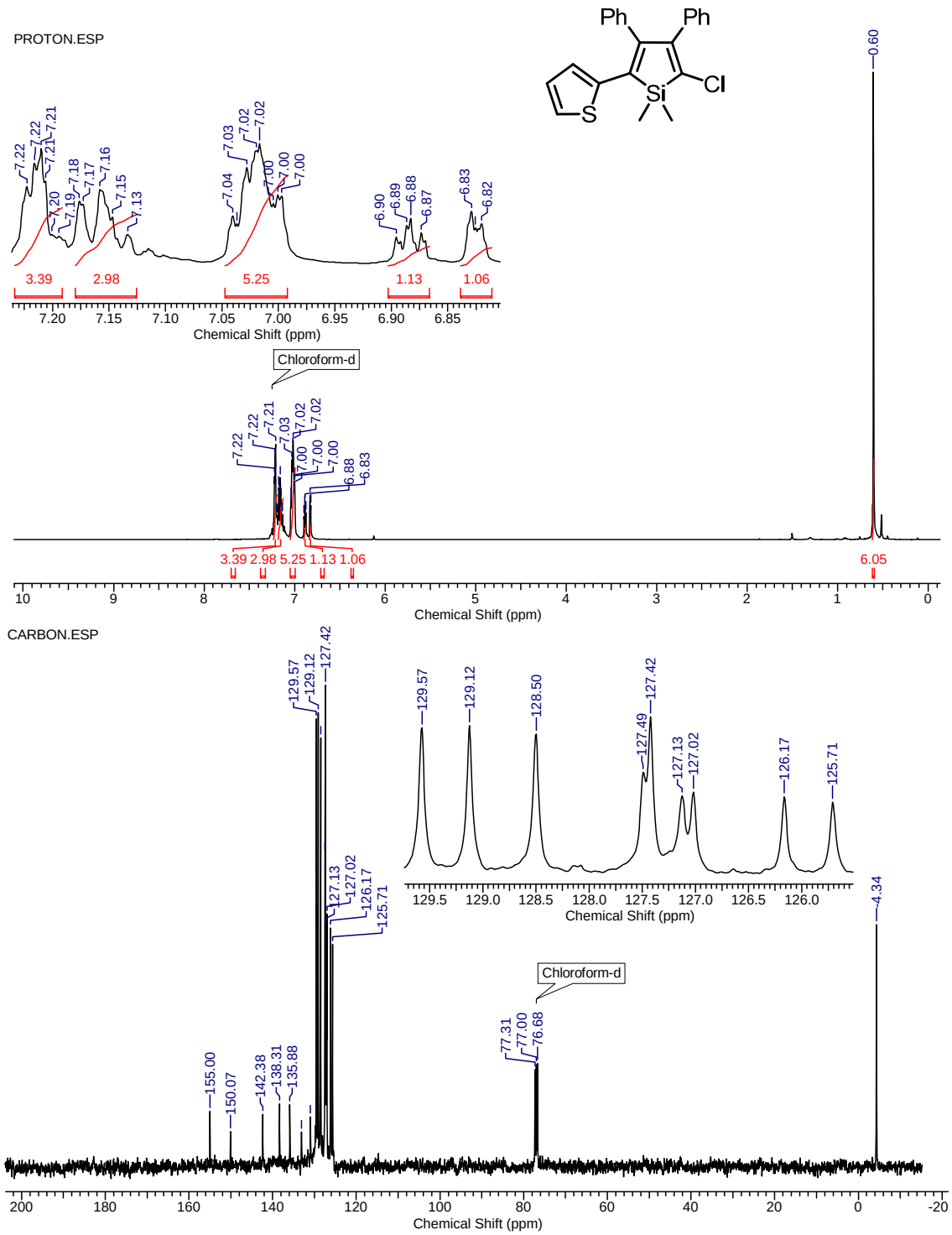


2,2'-(1,1-dihexyl-3,4-diphenyl-1*H*-silole-2,5-diyl)dipyridine (1.17)

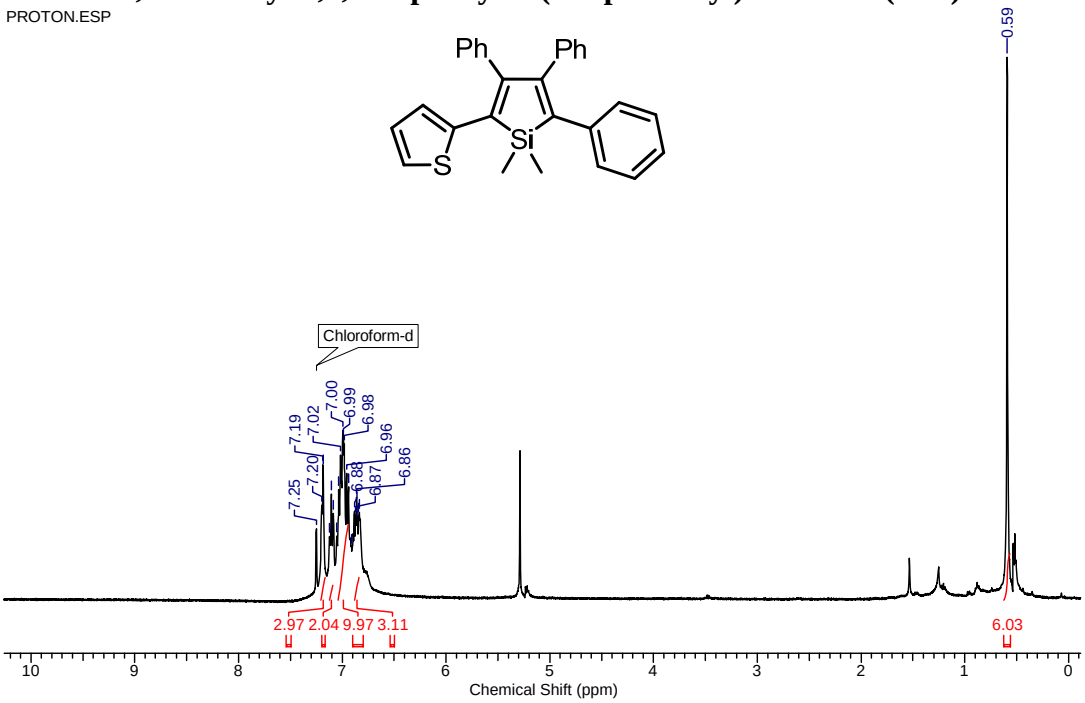


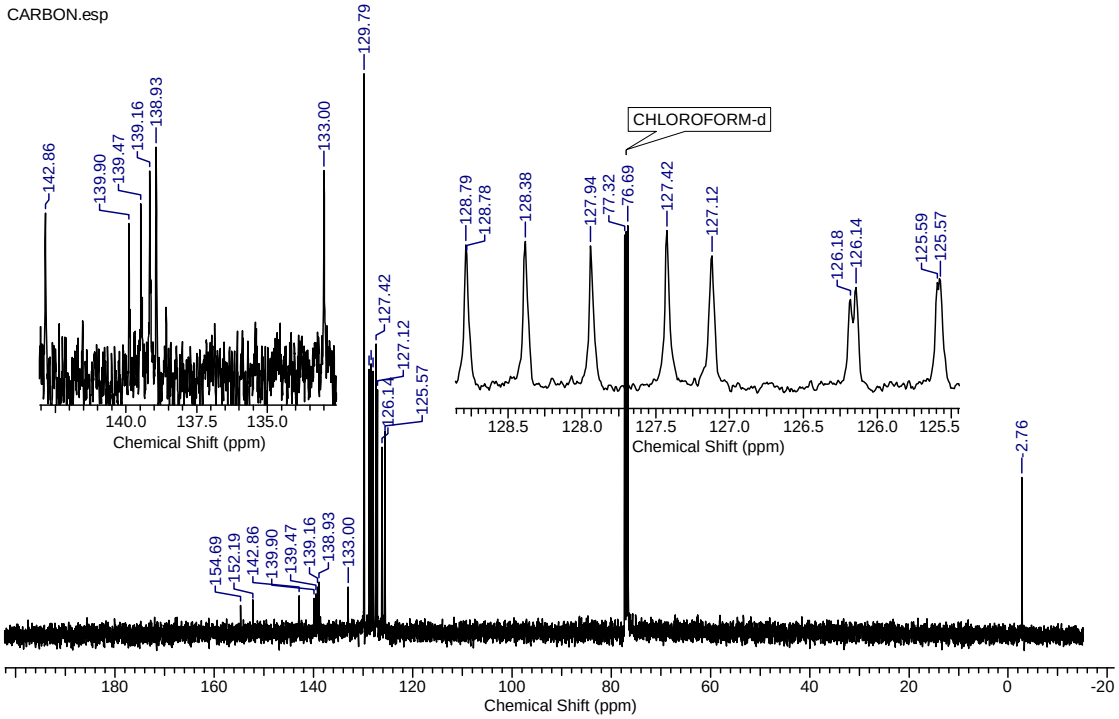


2-chloro-1,1-dimethyl-3,4-diphenyl-5-(thiophen-2-yl)-1*H*-silole (1.36)

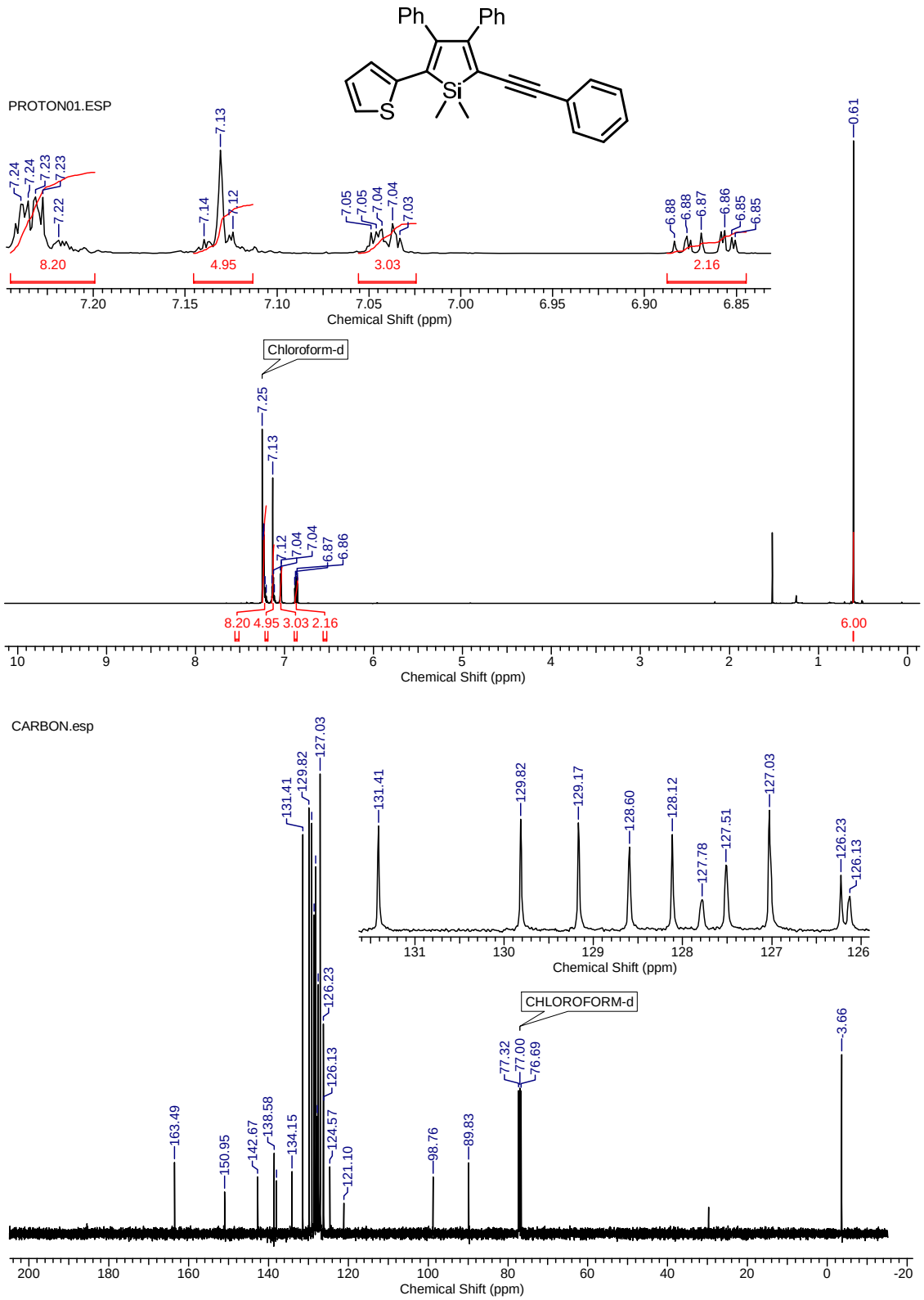


1,1-dimethyl-2,3,4-triphenyl-5-(thiophen-2-yl)-1*H*-silole (1.38)

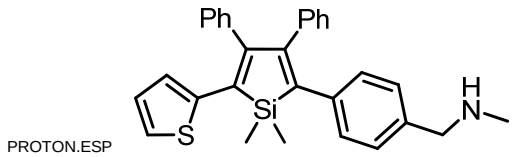


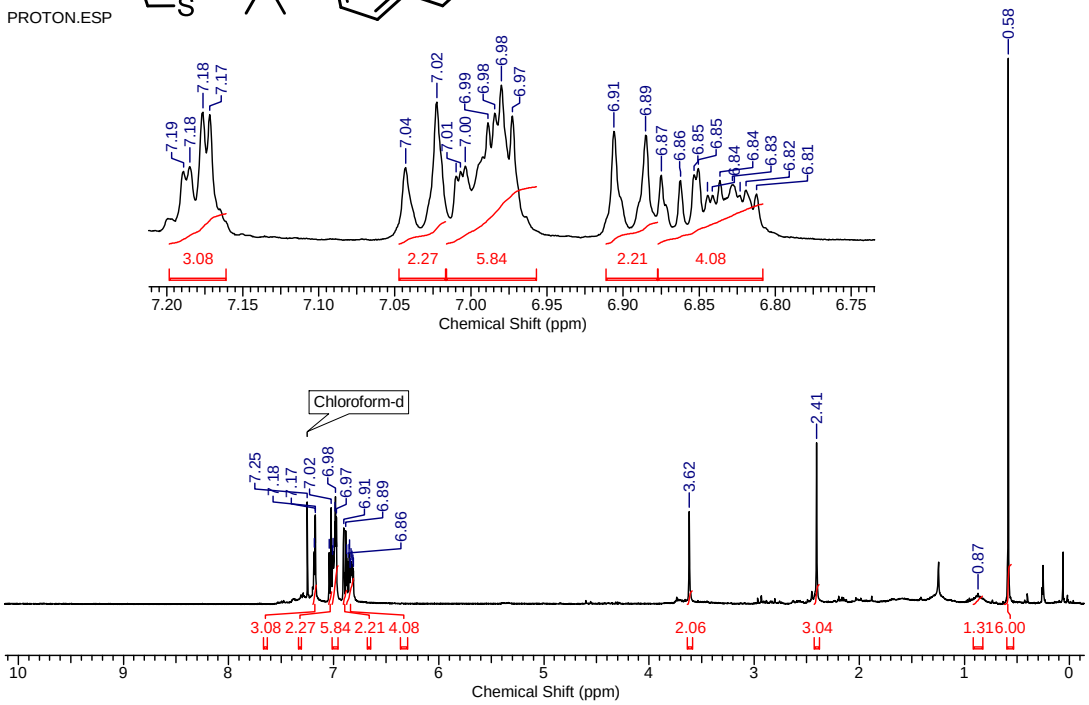


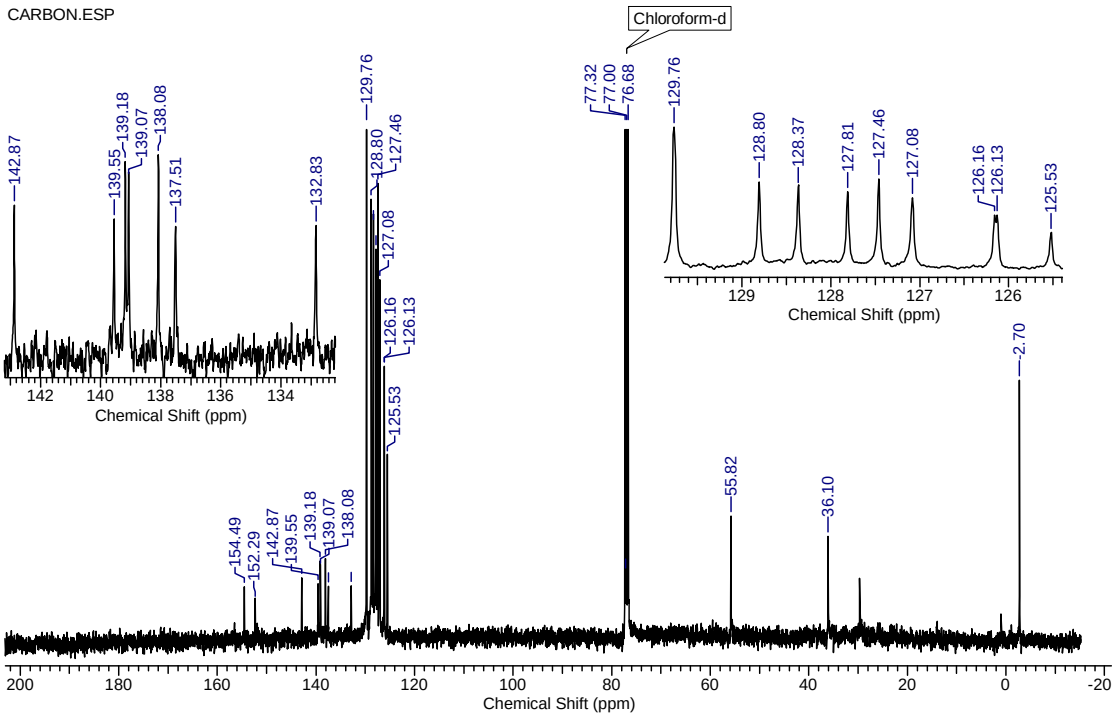
1,1-dimethyl-3,4-diphenyl-2-(phenylethynyl)-5-(thiophen-2-yl)-1*H*-silole (1.39)



1-(4-(1,1-dimethyl-3,4-diphenyl-5-(thiophen-2-yl)-1*H*-silol-2-yl)phenyl)-*N*-methylmethanamine (1.41)

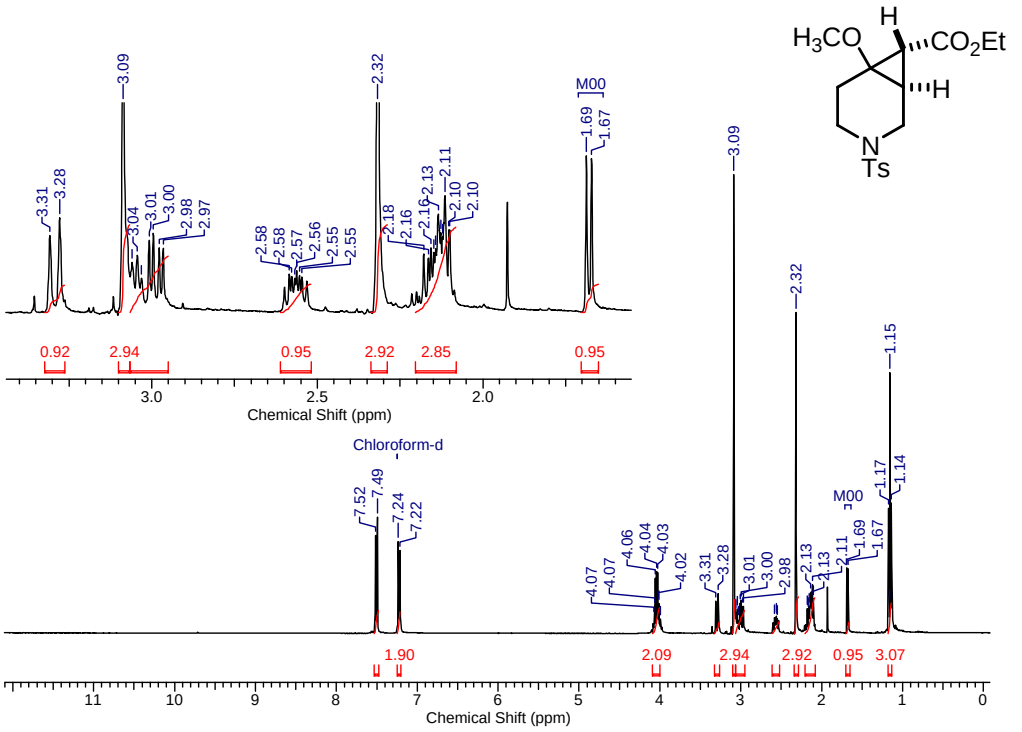


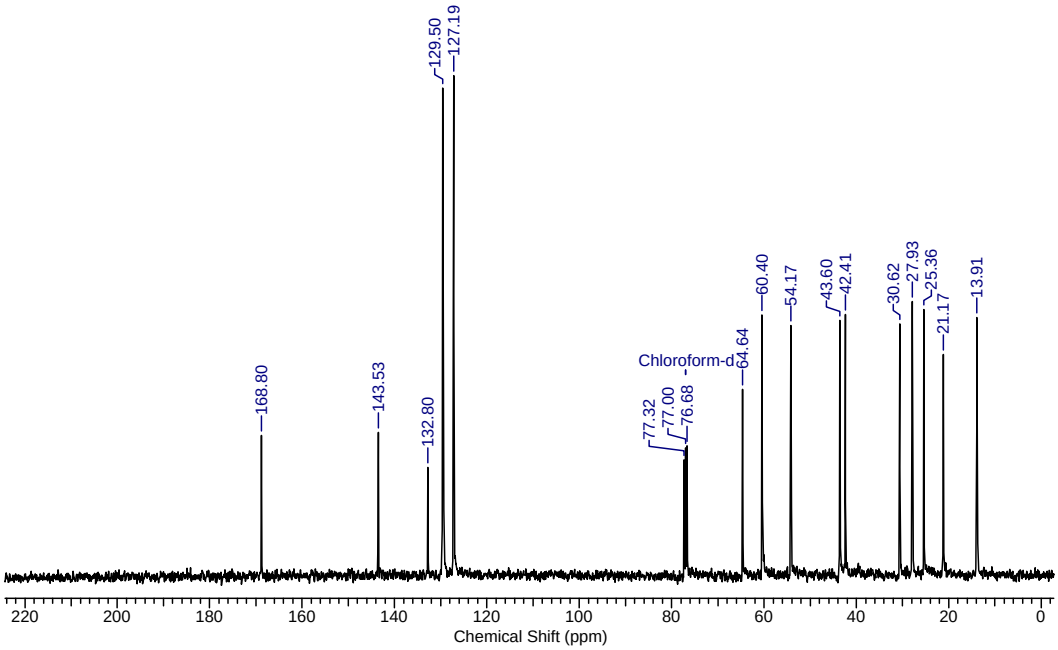




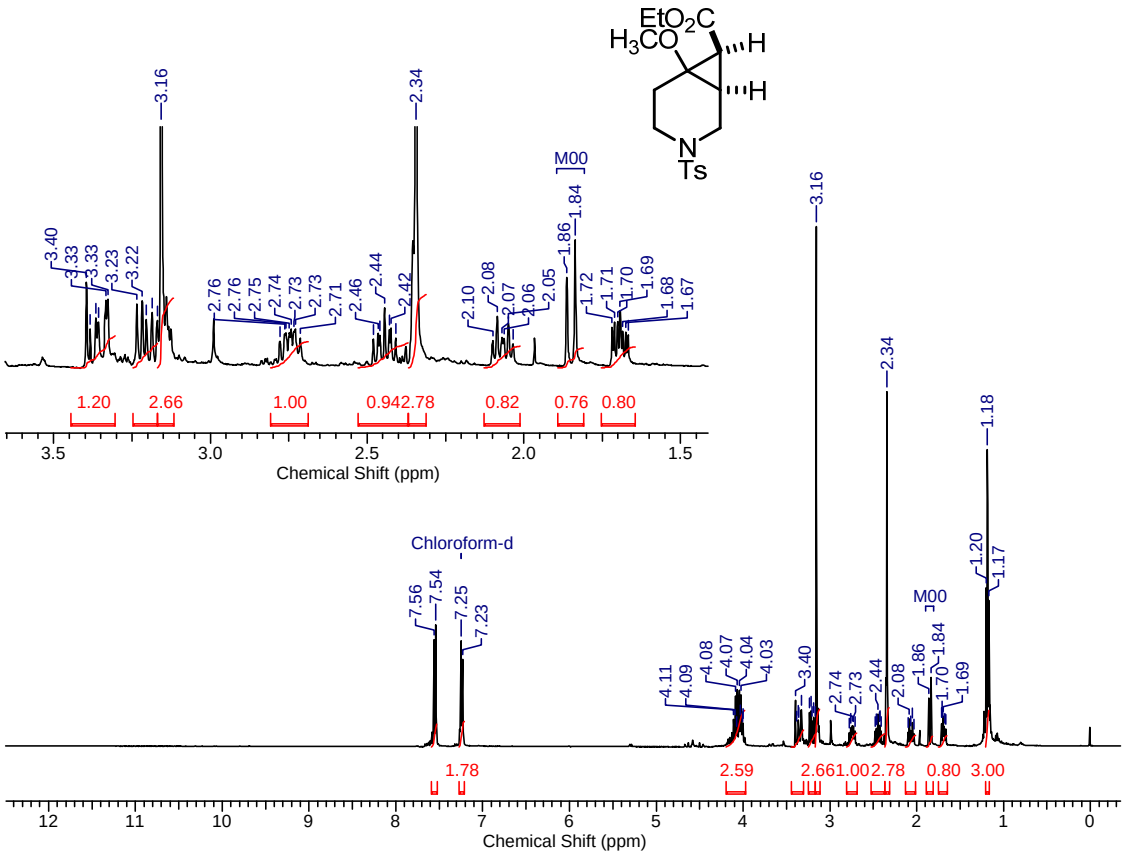
Appendix 3 – NMR Spectra for Compounds Presented in Chapter 2

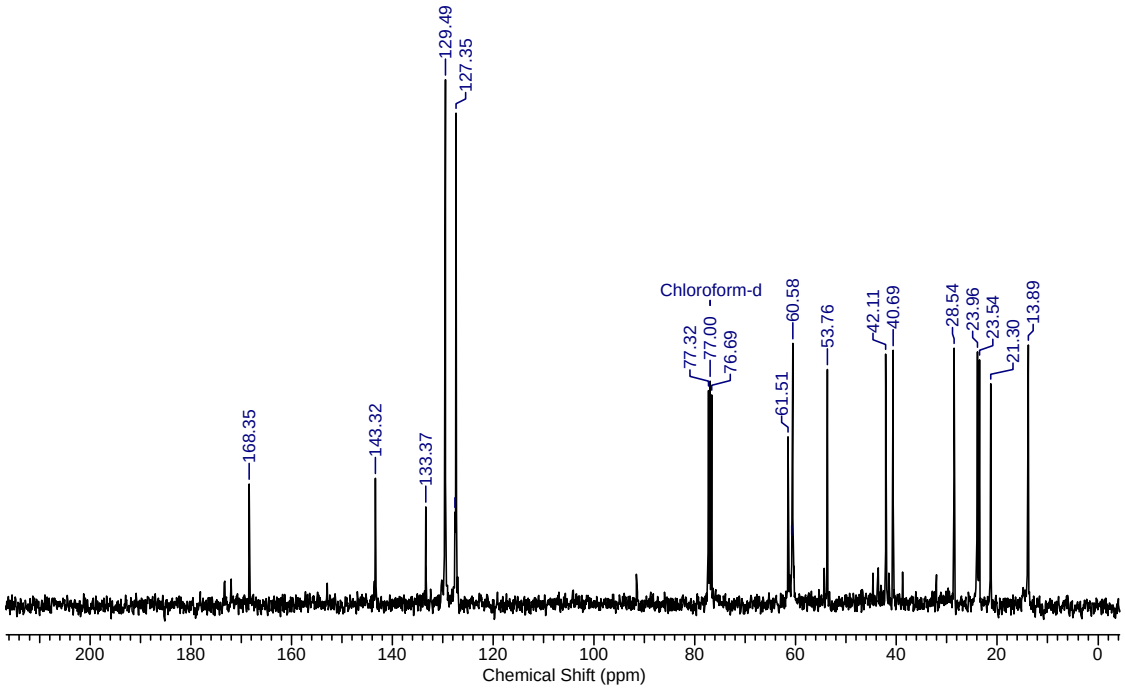
endo- Ethyl-6-methoxy-3-tosyl-3-azabicyclo[4.1.0]heptane-7-carboxylate (*endo*-2.75)





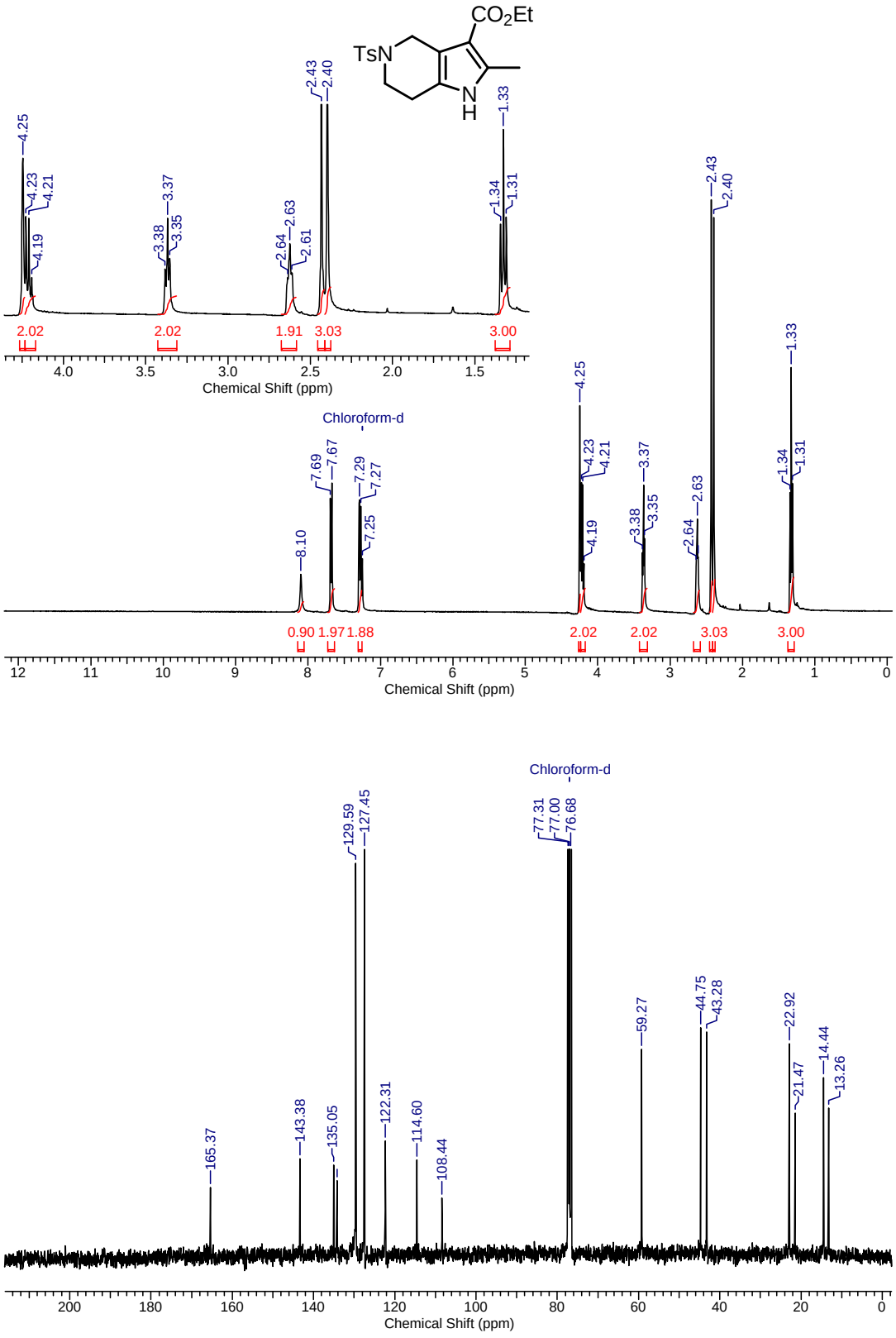
exo-Ethyl 6-methoxy-3-tosyl-3-azabicyclo[4.1.0]heptane-7-carboxylate (_exo_-2.75)



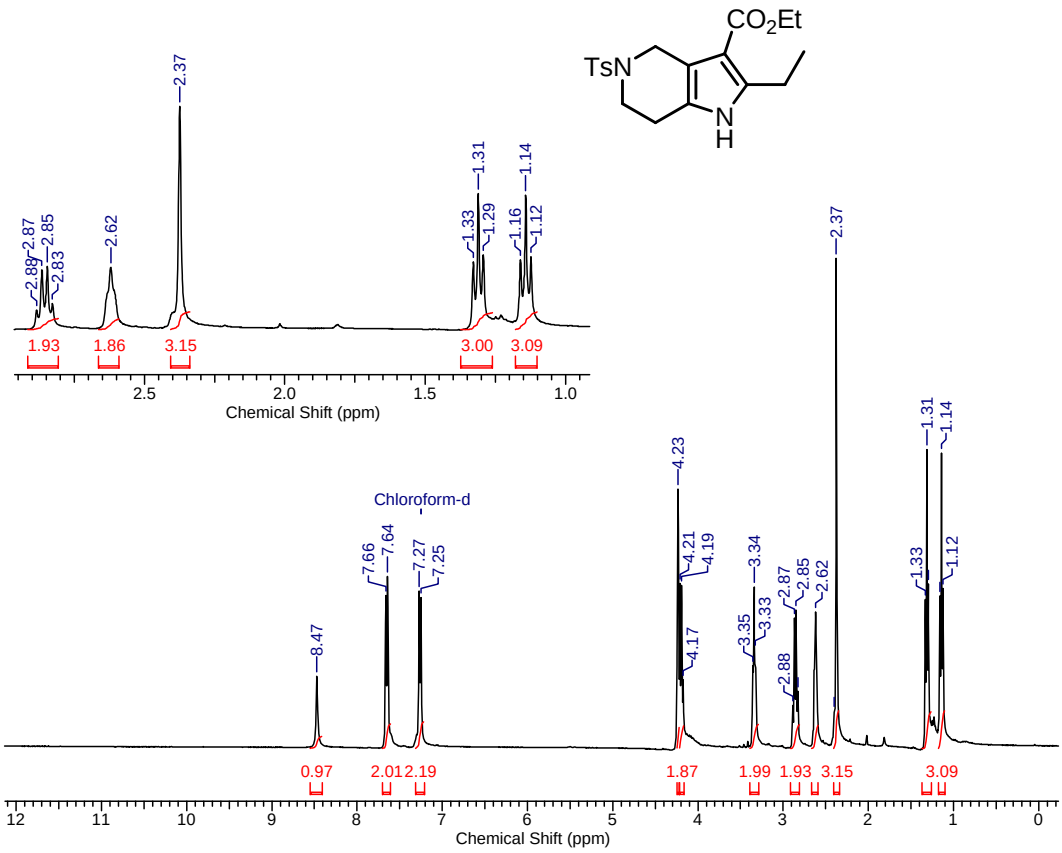


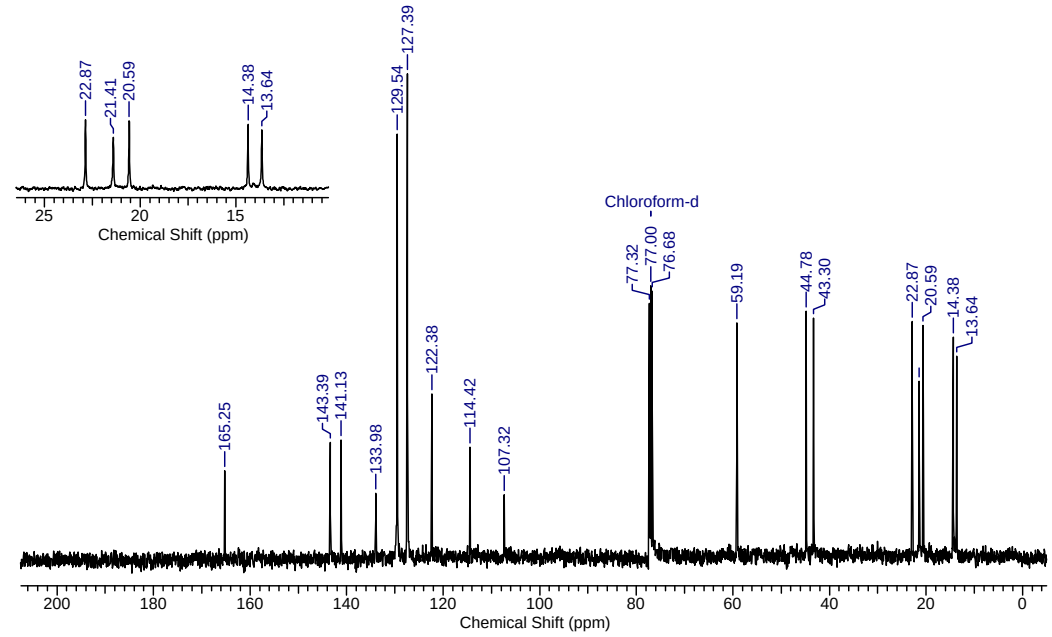
Ethyl 2-methyl-5-tosyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridine-3-carboxylate

(2.76a)

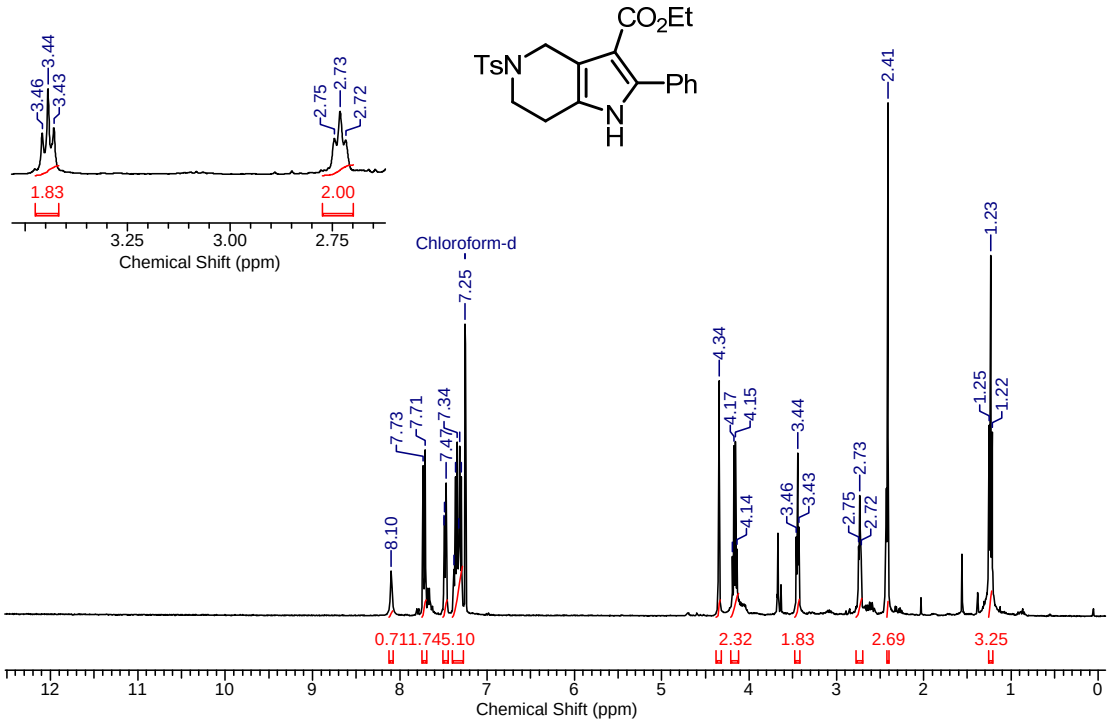


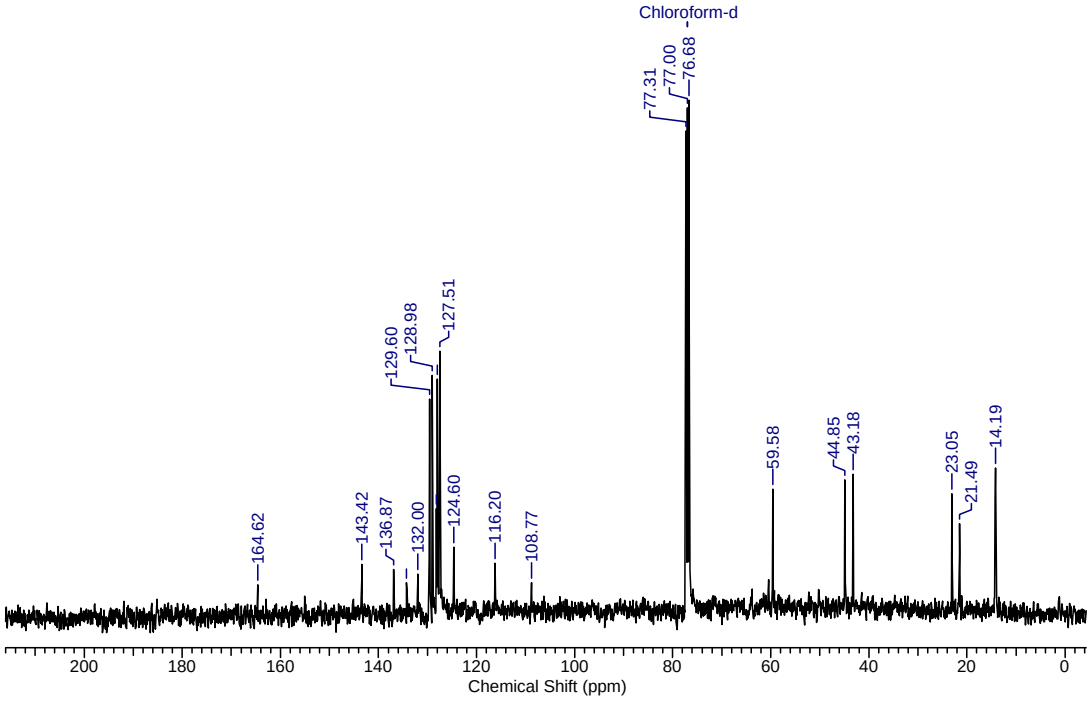
Ethyl 2-ethyl-5-tosyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridine-3-carboxylate (2.76b)



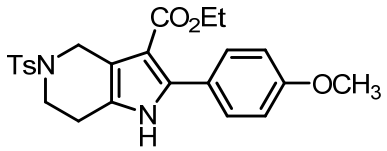


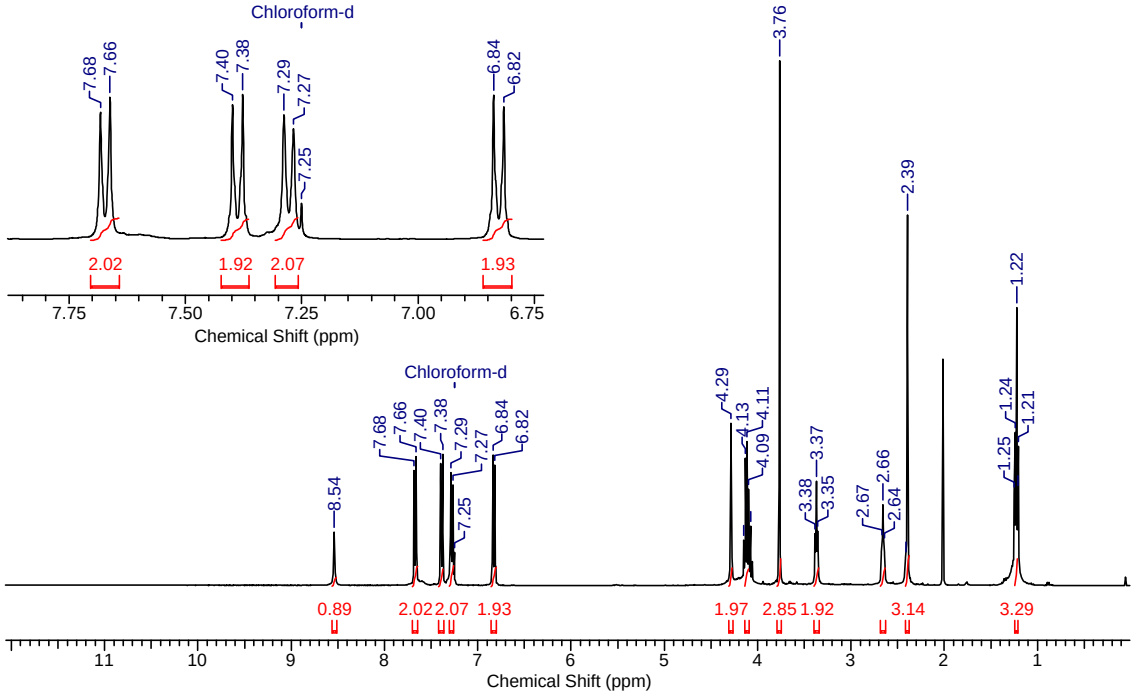
Ethyl 2-phenyl-5-tosyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridine-3-carboxylate (2.76c)

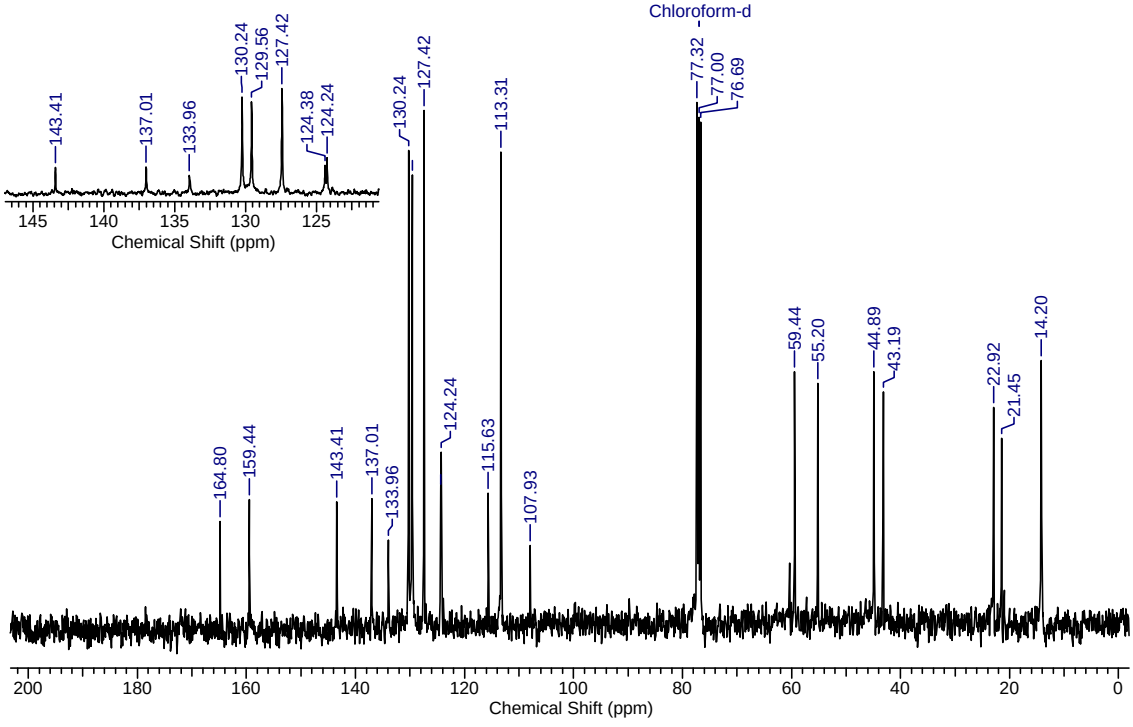




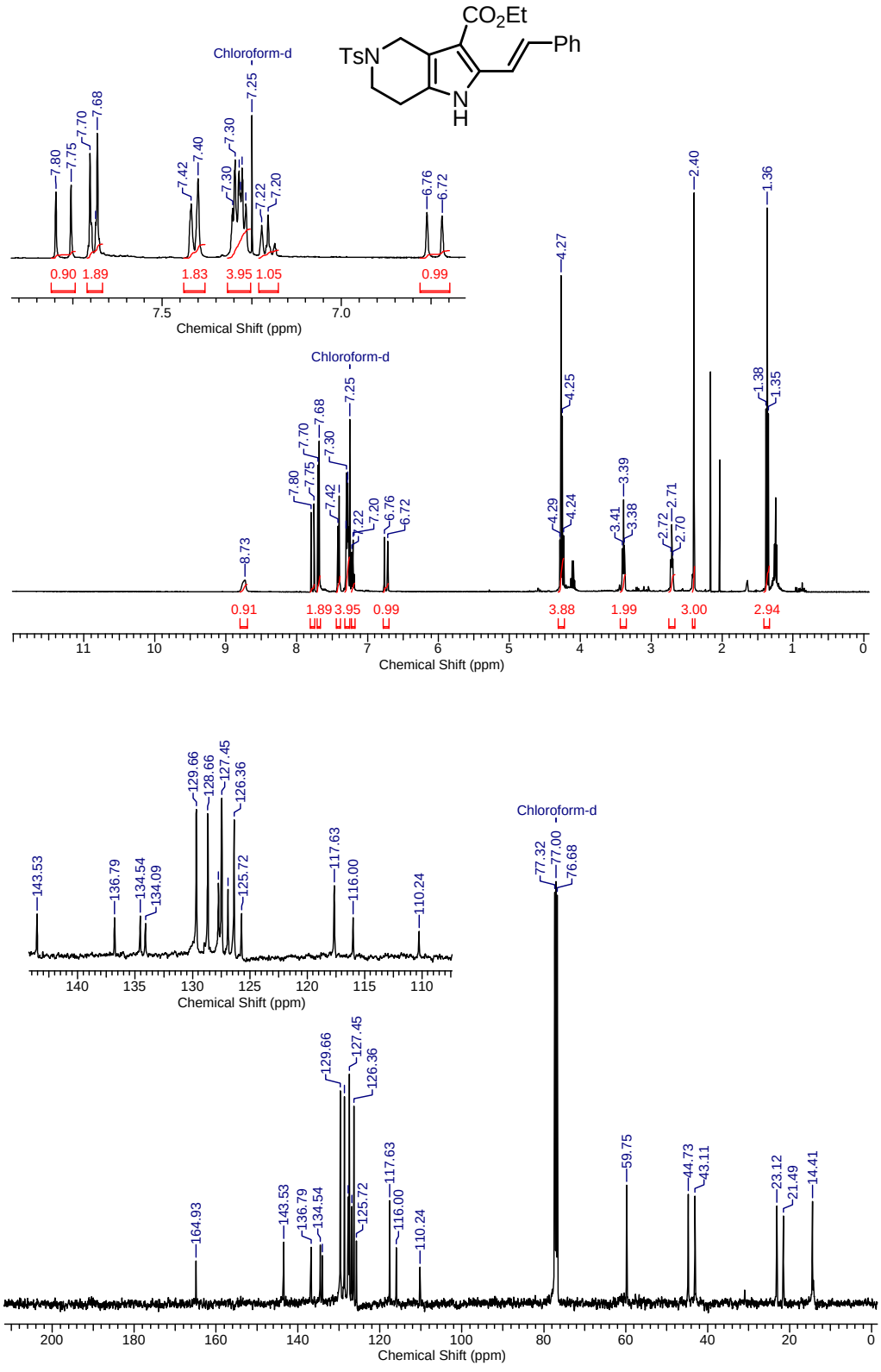
Ethyl 2-(4-methoxyphenyl)-5-tosyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridine-3-carboxylate (2.76d)



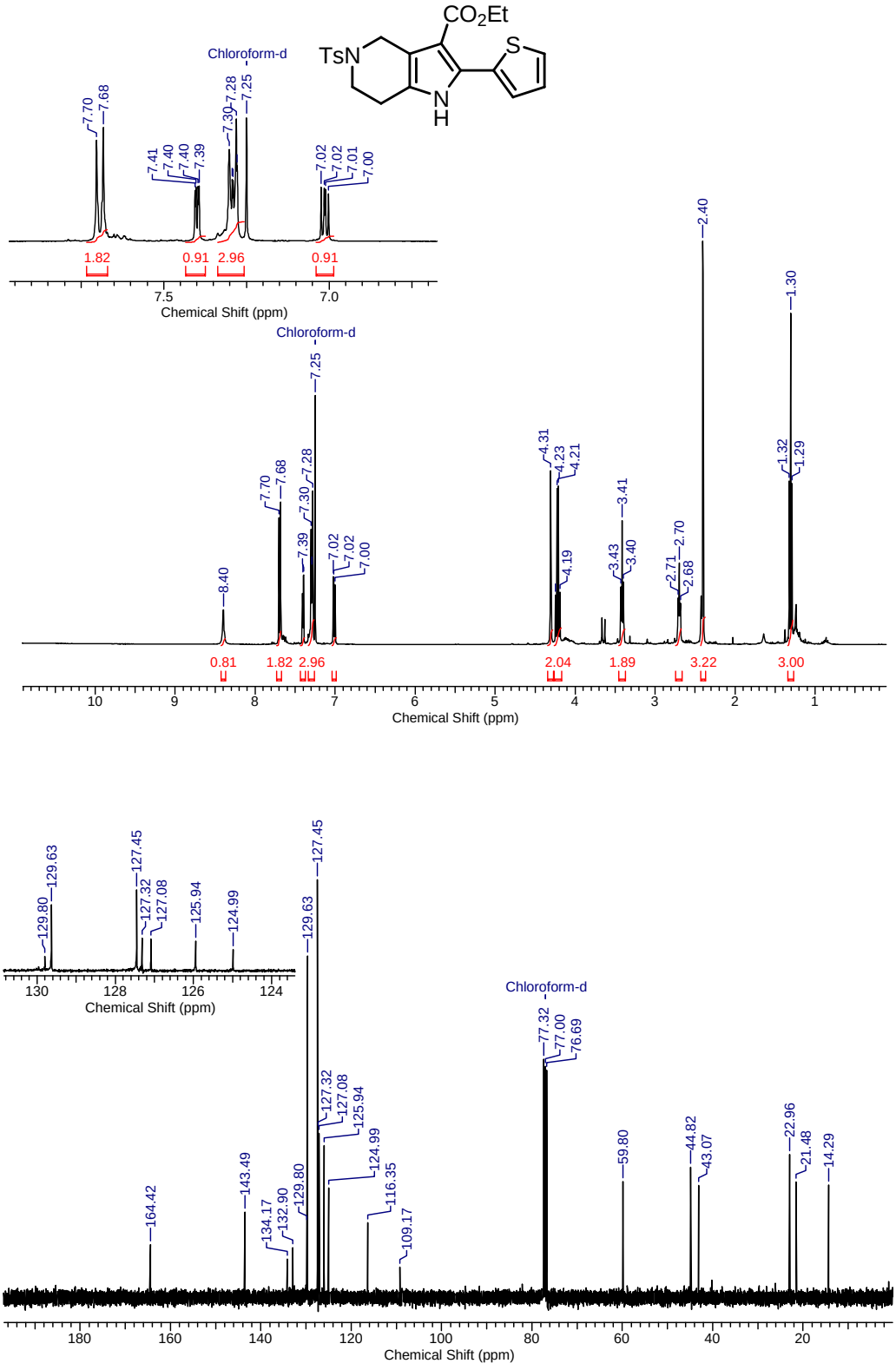




Ethyl 2-styryl-5-tosyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridine-3-carboxylate (2.76e)

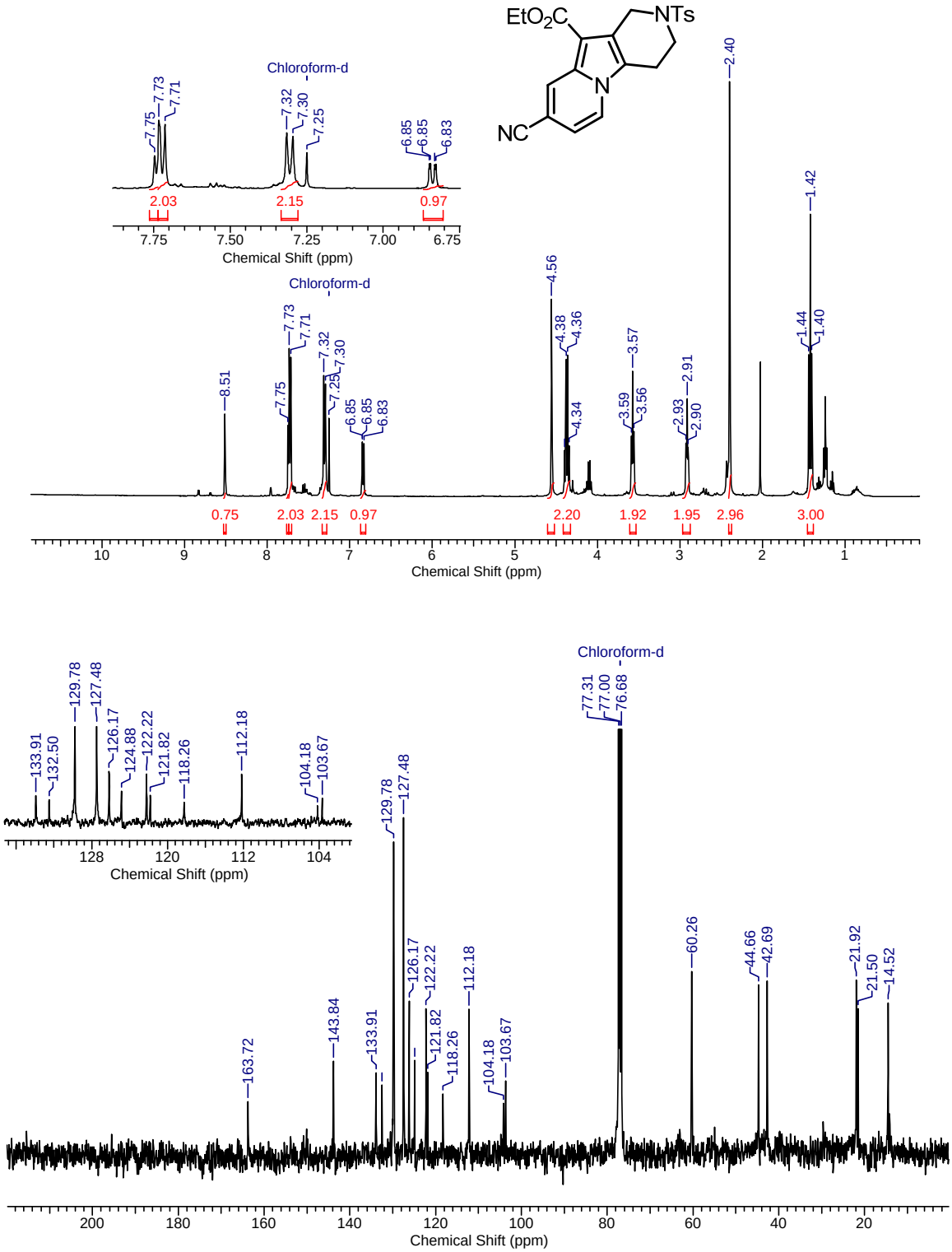


Ethyl 2-(thiophen-2-yl)-5-tosyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridine-3-carboxylate (2.76f)



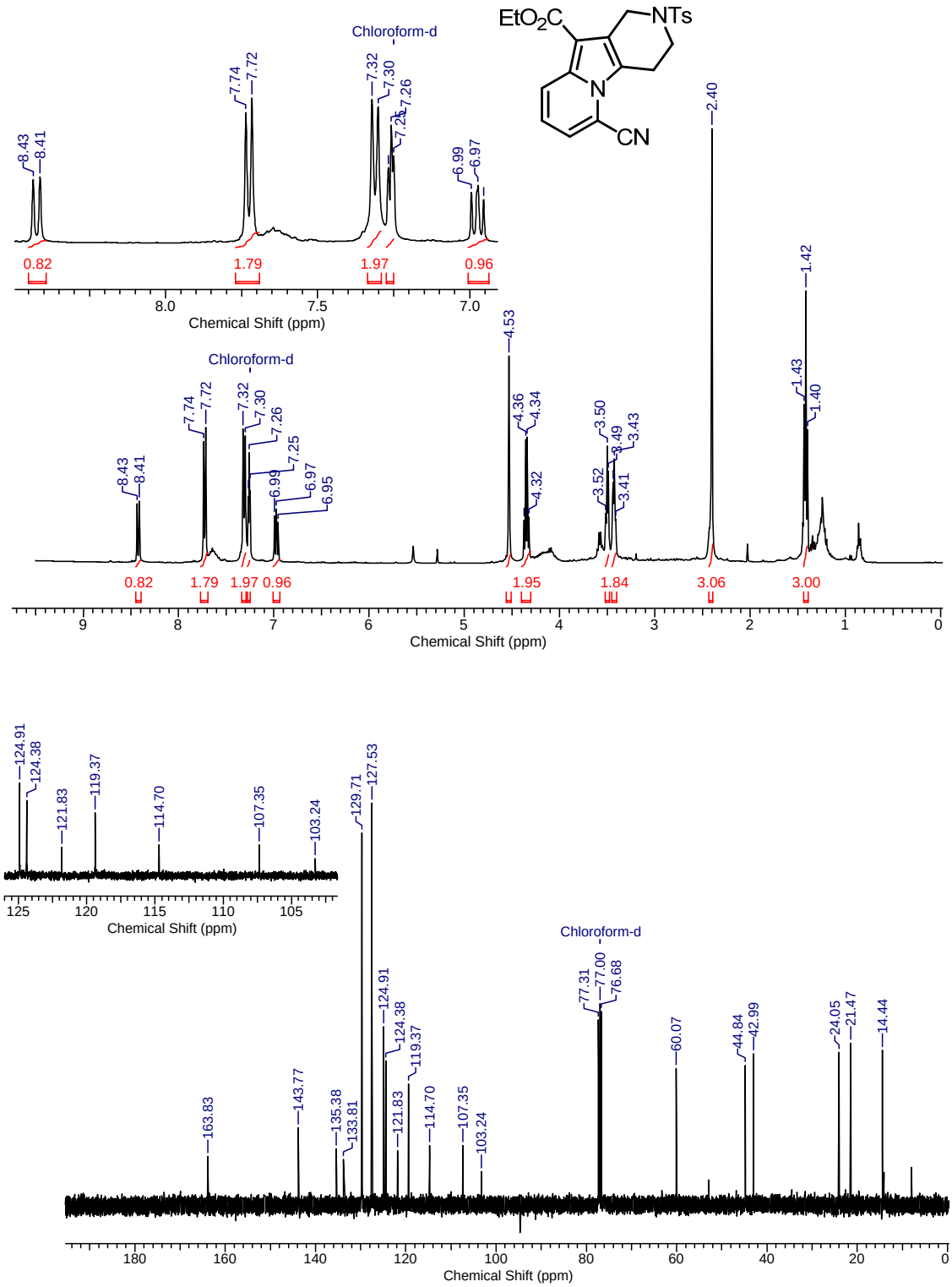
Ethyl 8-cyano-2-tosyl-1,2,3,4-tetrahydropyrido[3,4-*b*]indolizine-10-carboxylate

(2.80a)

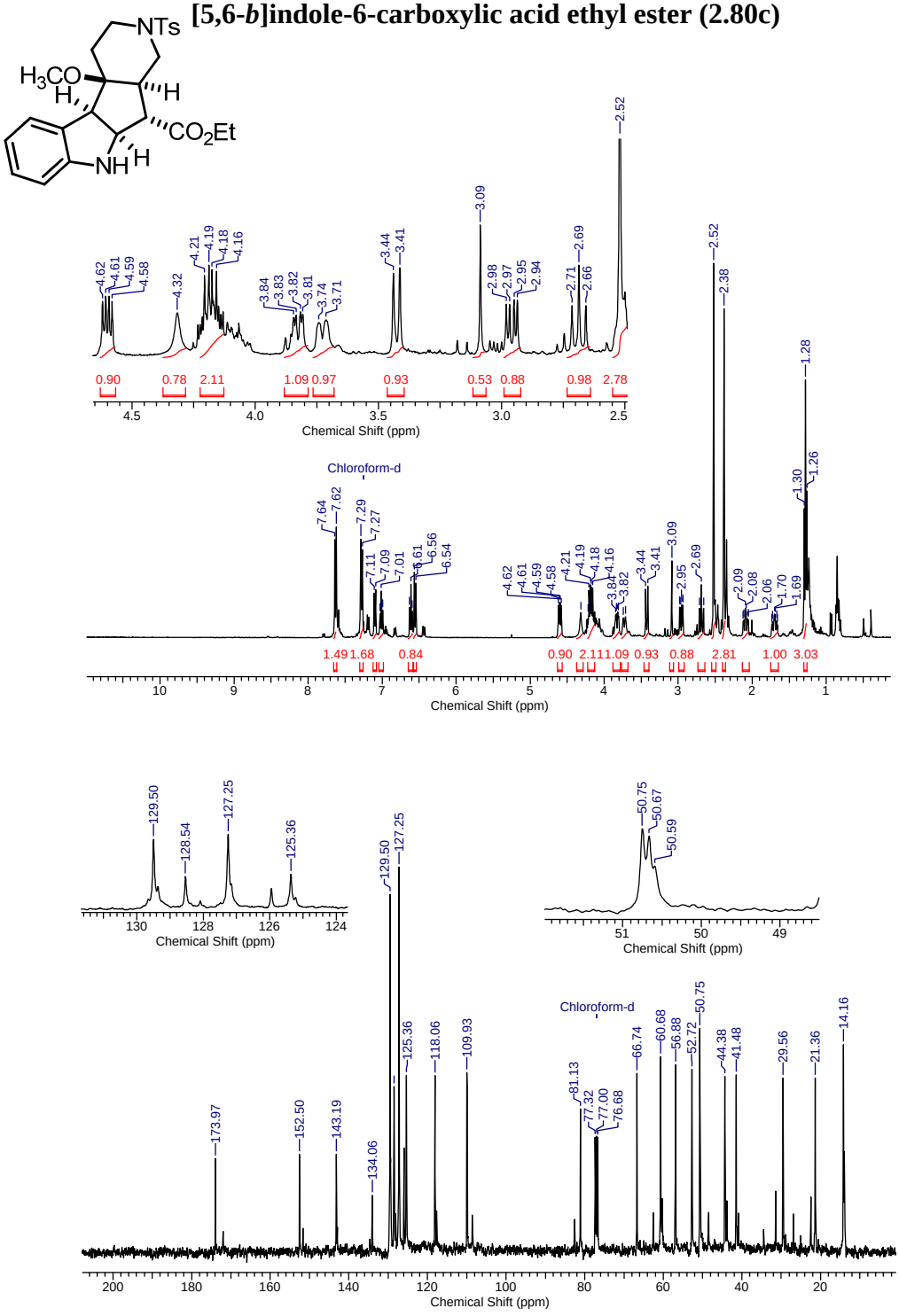


Ethyl 6-cyano-2-tosyl-1,2,3,4-tetrahydropyrido[3,4-*b*]indolizine-10-carboxylate

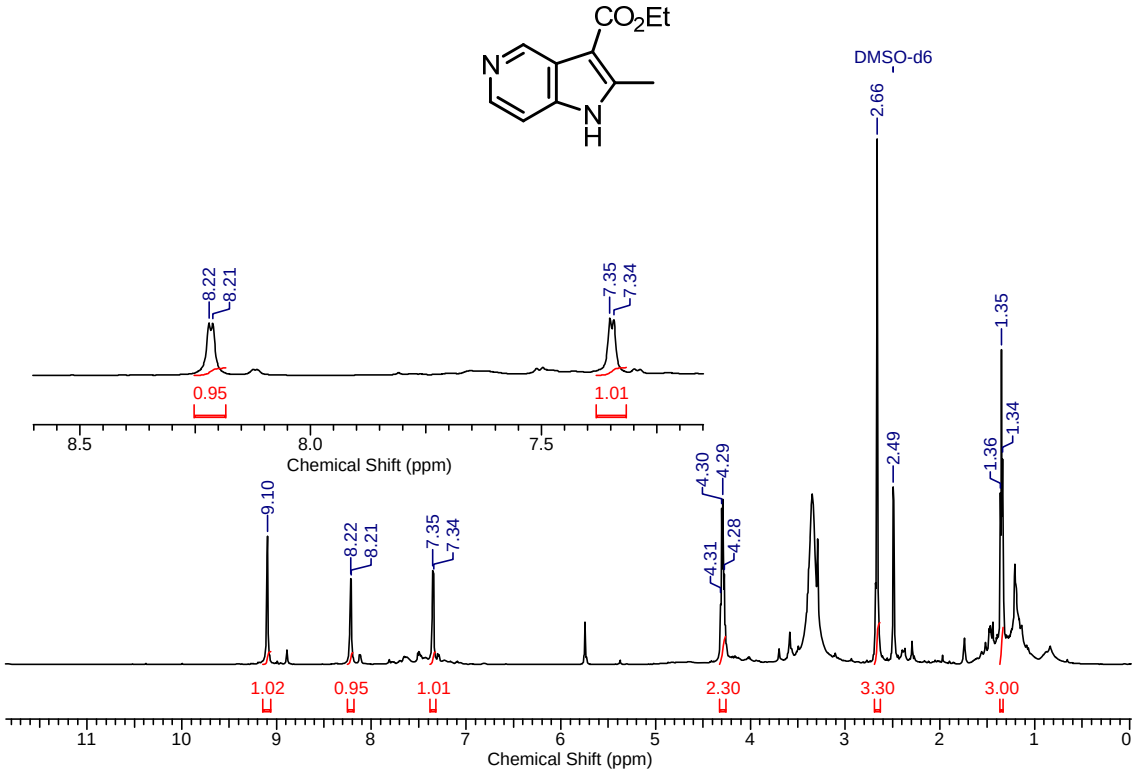
(2.80b)

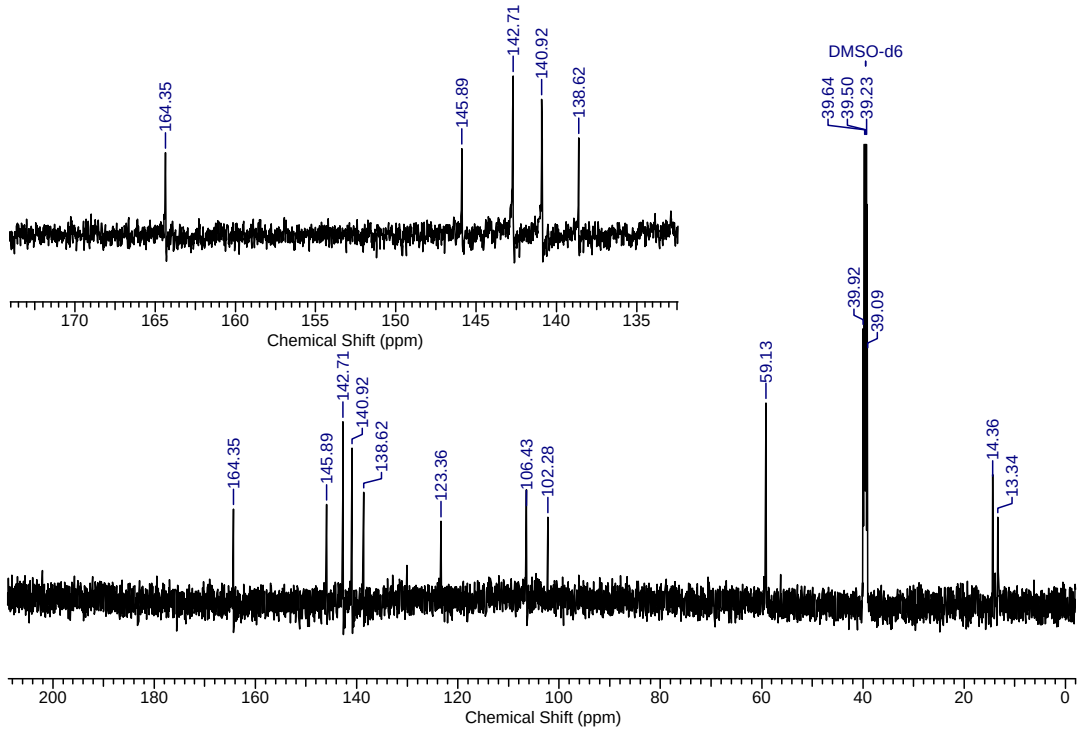


10a-Methoxy-5,5a,6,6a,7,8,9,10,10a,10b-decahydrocyclopentadiene[*c*]pyridine [5,6-*b*]indole-6-carboxylic acid ethyl ester (2.80c)

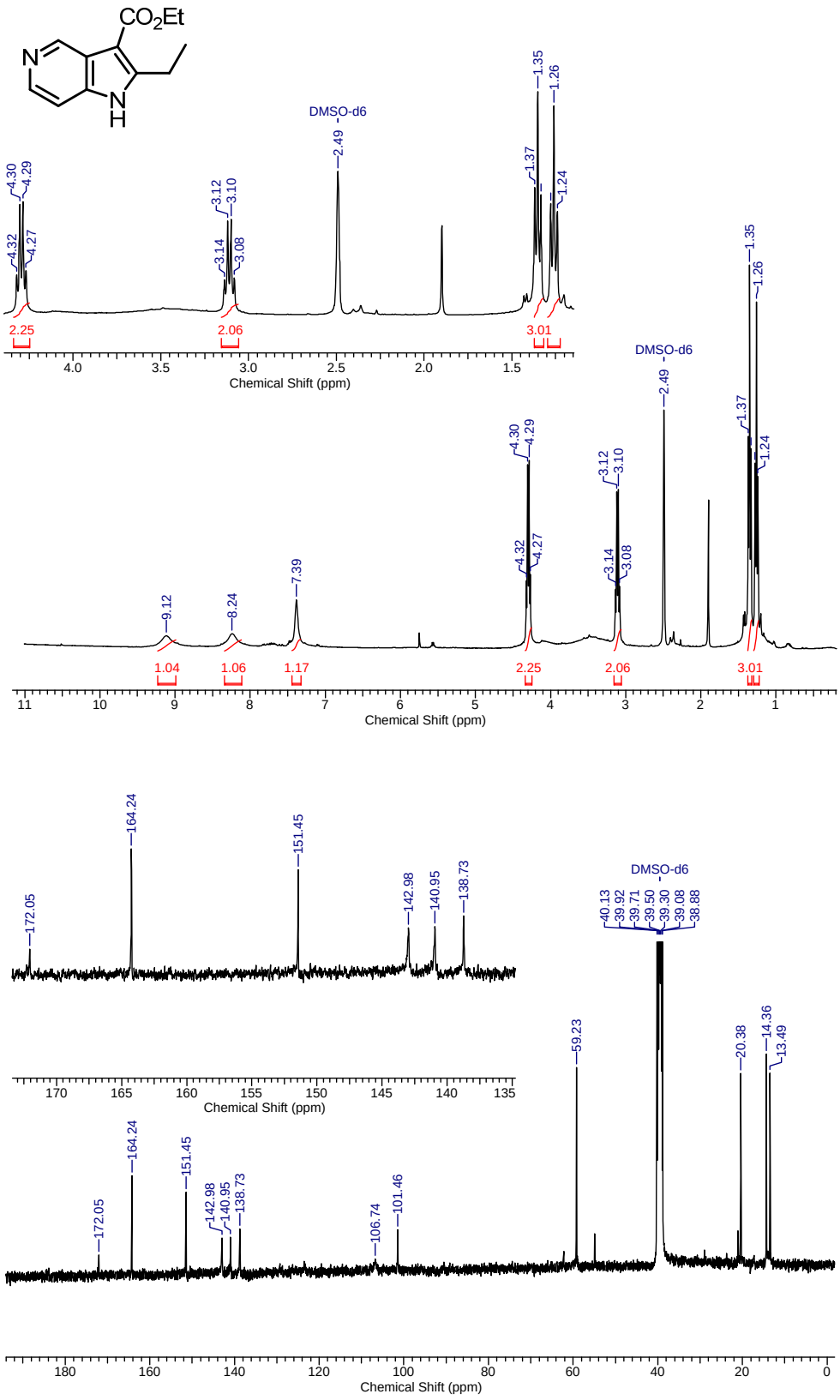


Ethyl 2-methyl-1*H*-pyrrolo[3,2-*c*]pyridine-3-carboxylate (2.79a)

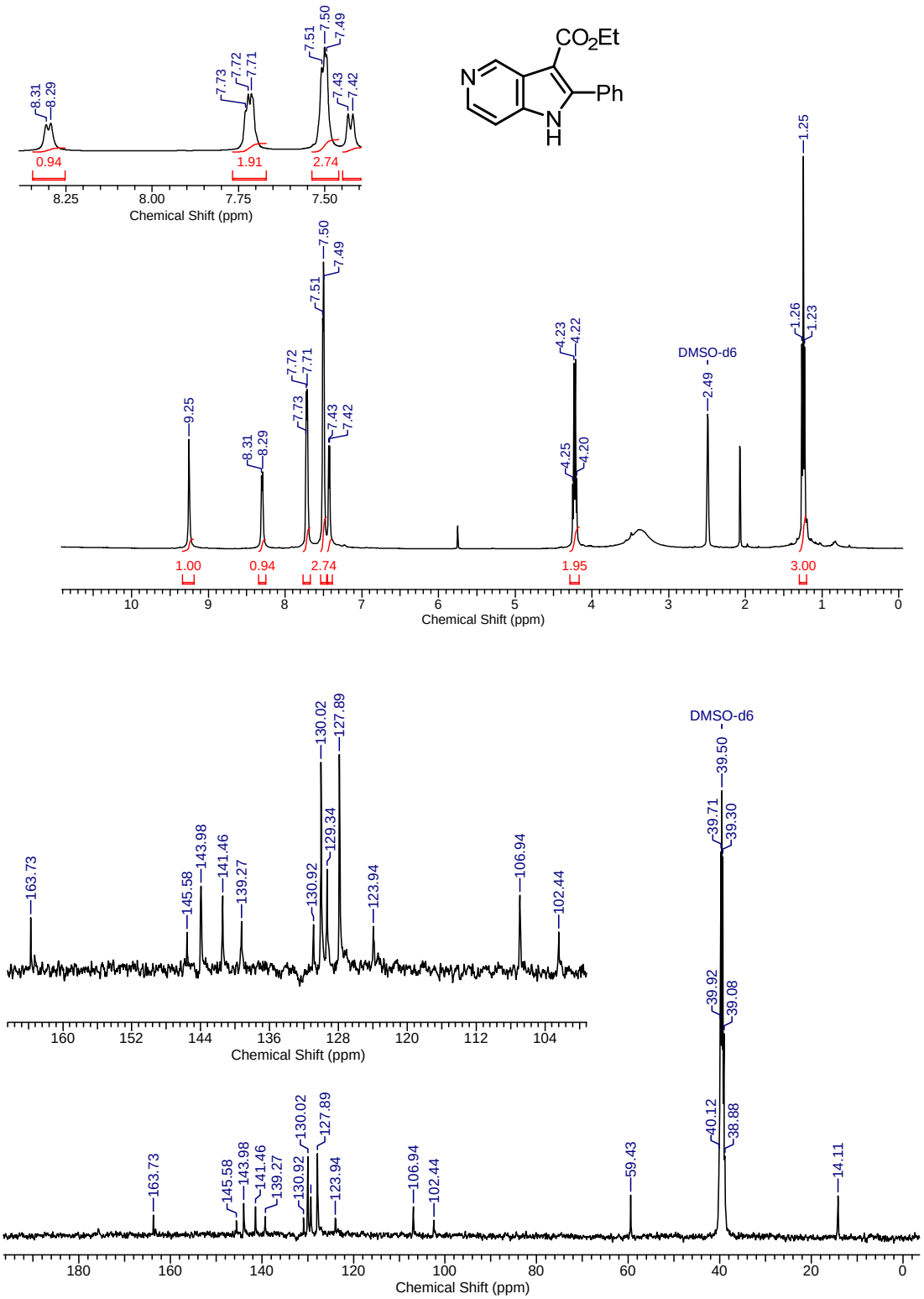




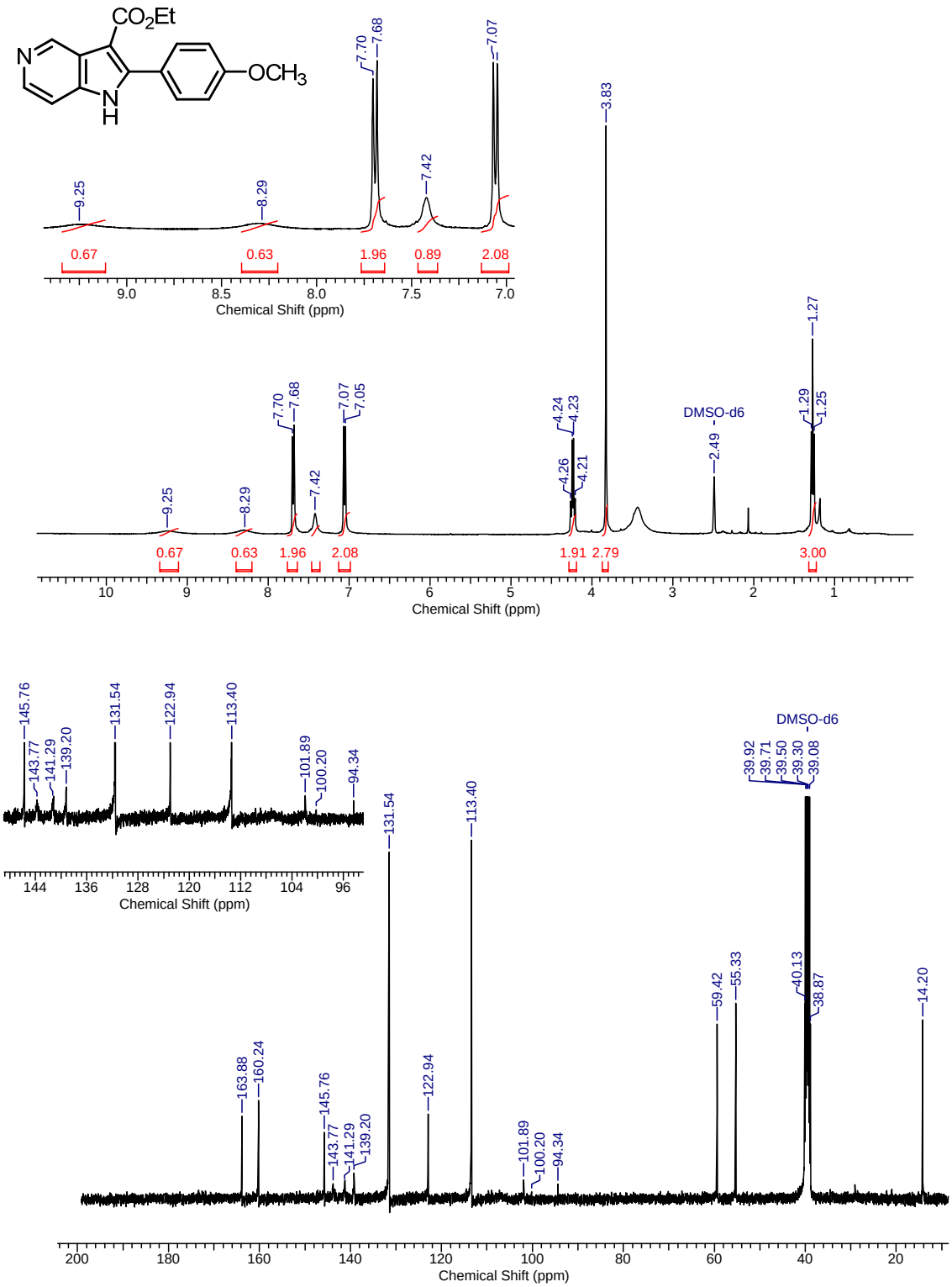
Ethyl 2-ethyl-1*H*-pyrrolo[3,2-*c*]pyridine-3-carboxylate (2.79b)



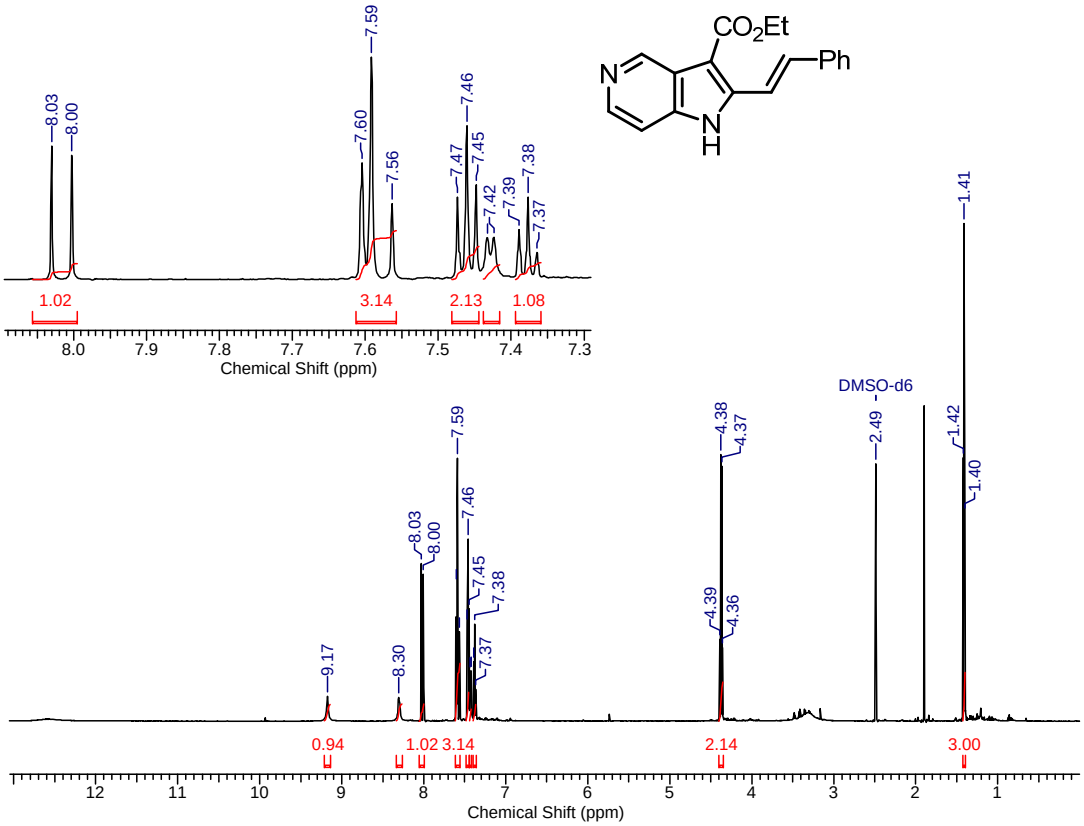
Ethyl 2-phenyl-1*H*-pyrrolo[3,2-*c*]pyridine-3-carboxylate (2.79c)

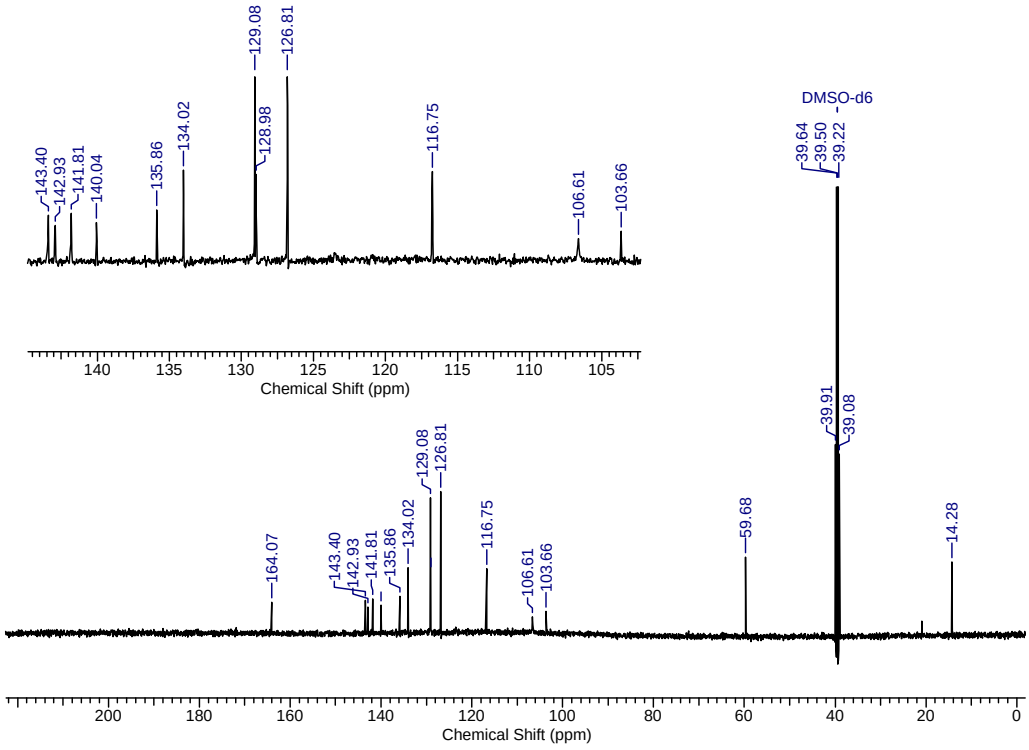


Ethyl 2-(4-methoxyphenyl)-1*H*-pyrrolo[3,2-*c*]pyridine-3-carboxylate (2.79d)

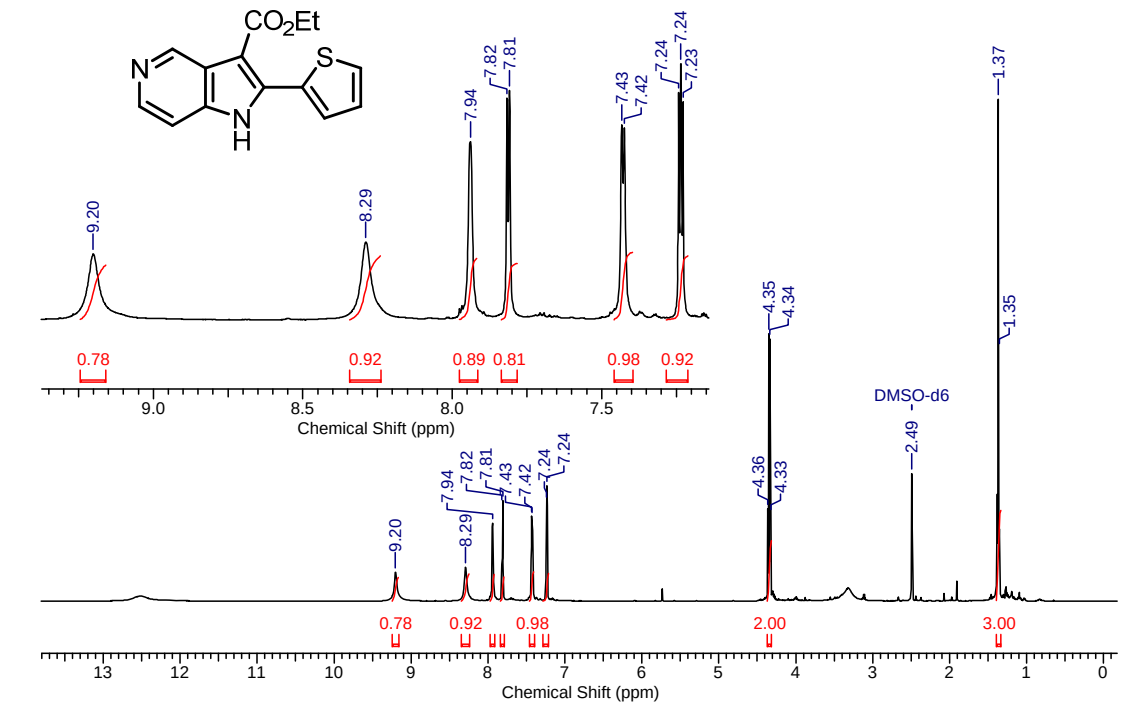


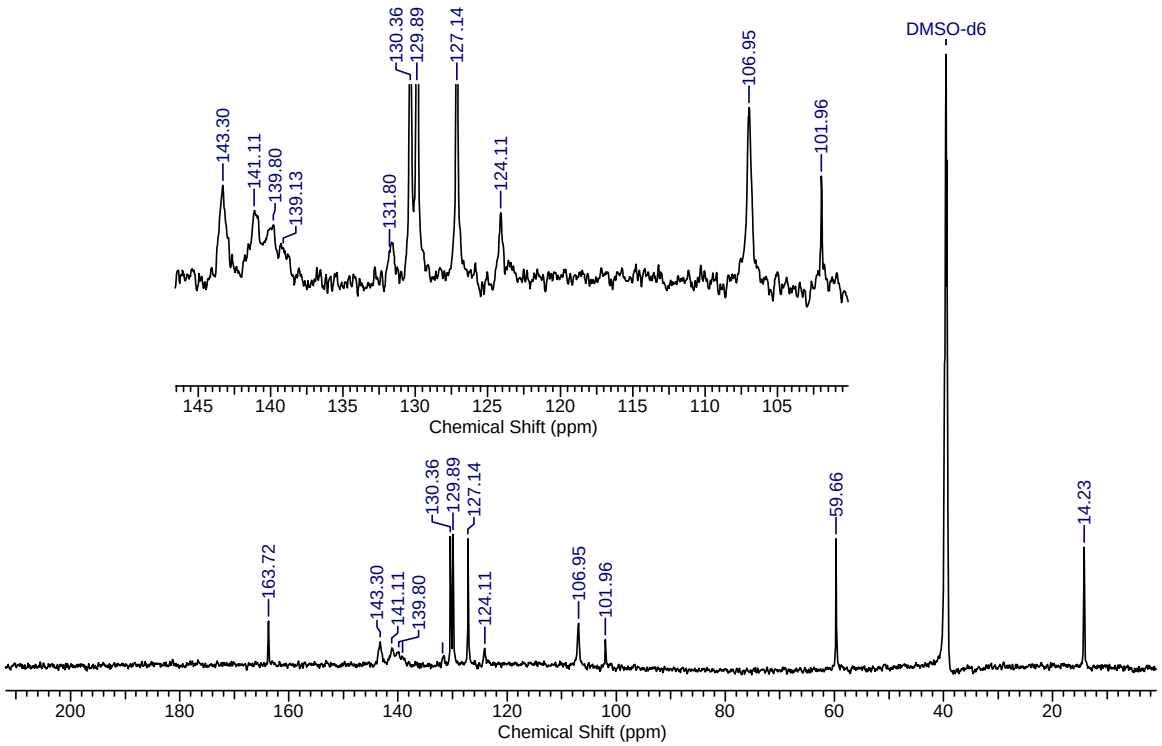
Ethyl 2-styryl-1*H*-pyrrolo[3,2-*c*]pyridine-3-carboxylate (2.79e)



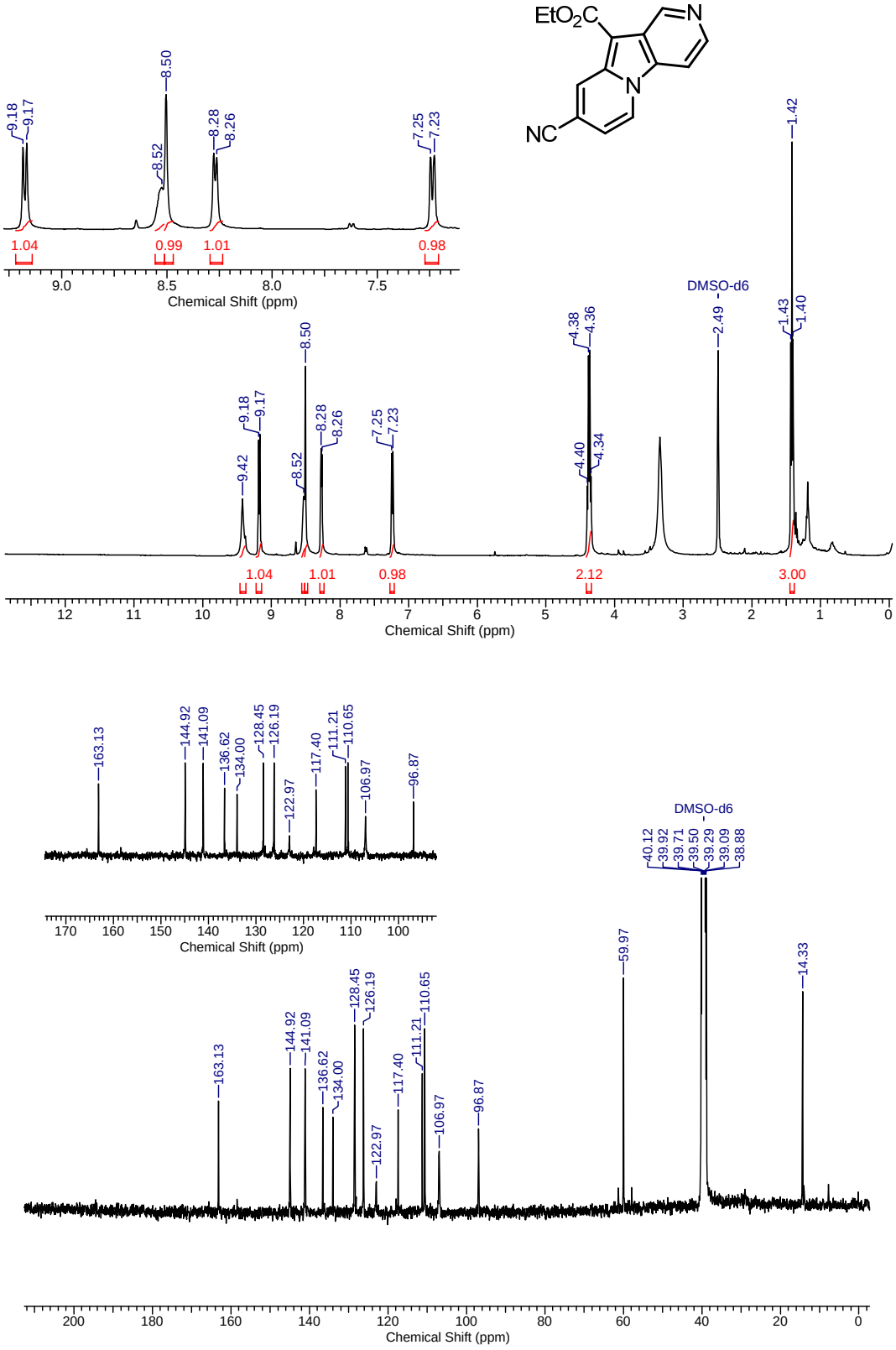


Ethyl 2-(thiophen-2-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-3-carboxylate (2.79f)

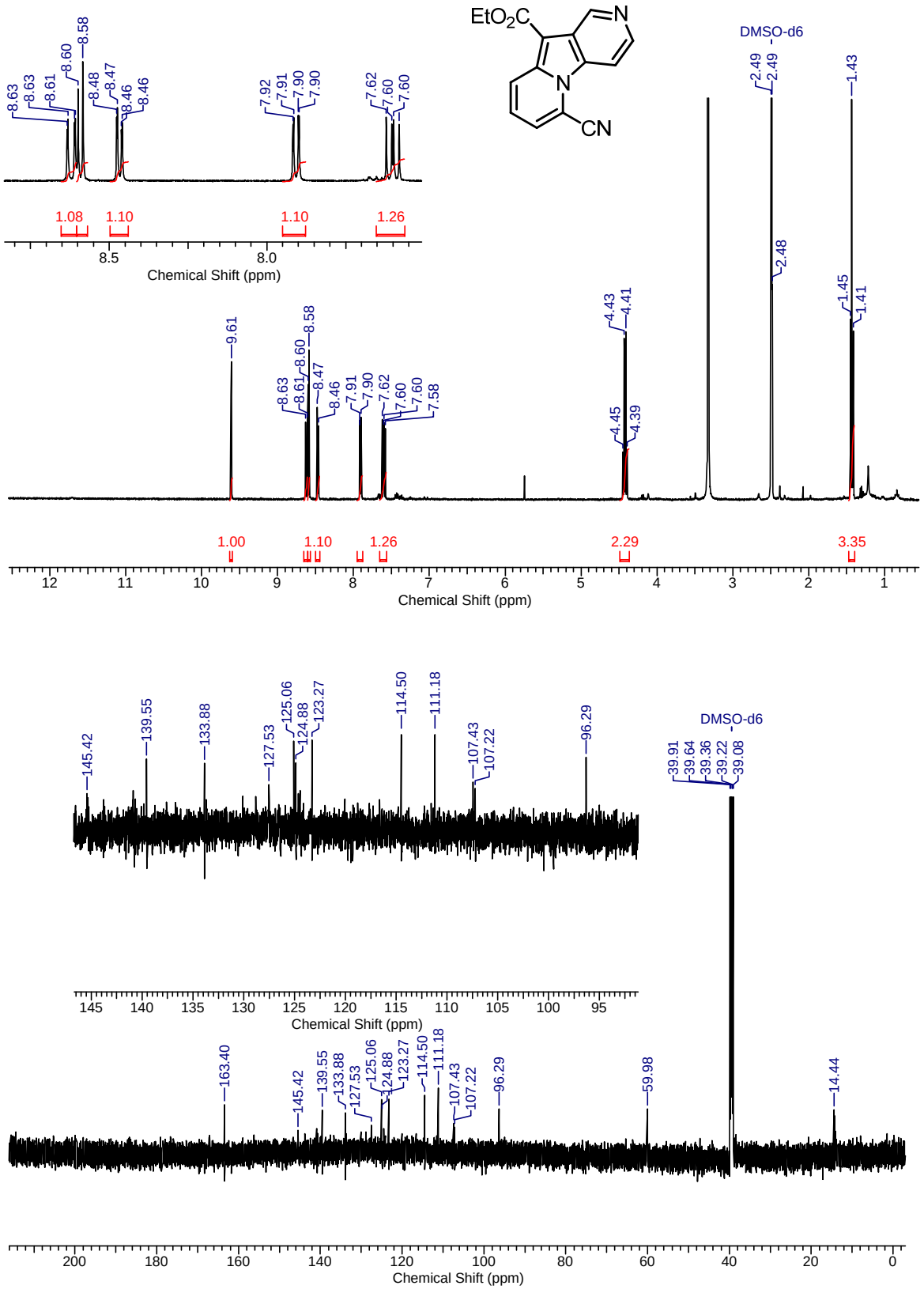




Ethyl 8-cyanopyrido[3,4-*b*]indolizine-10-carboxylate (2.81a)

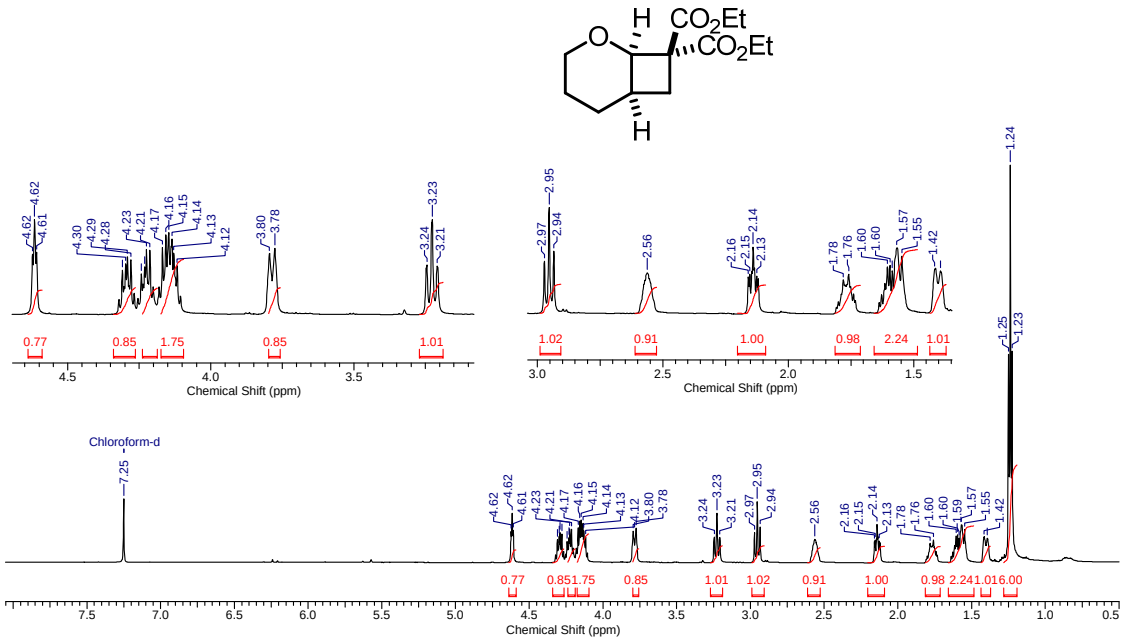


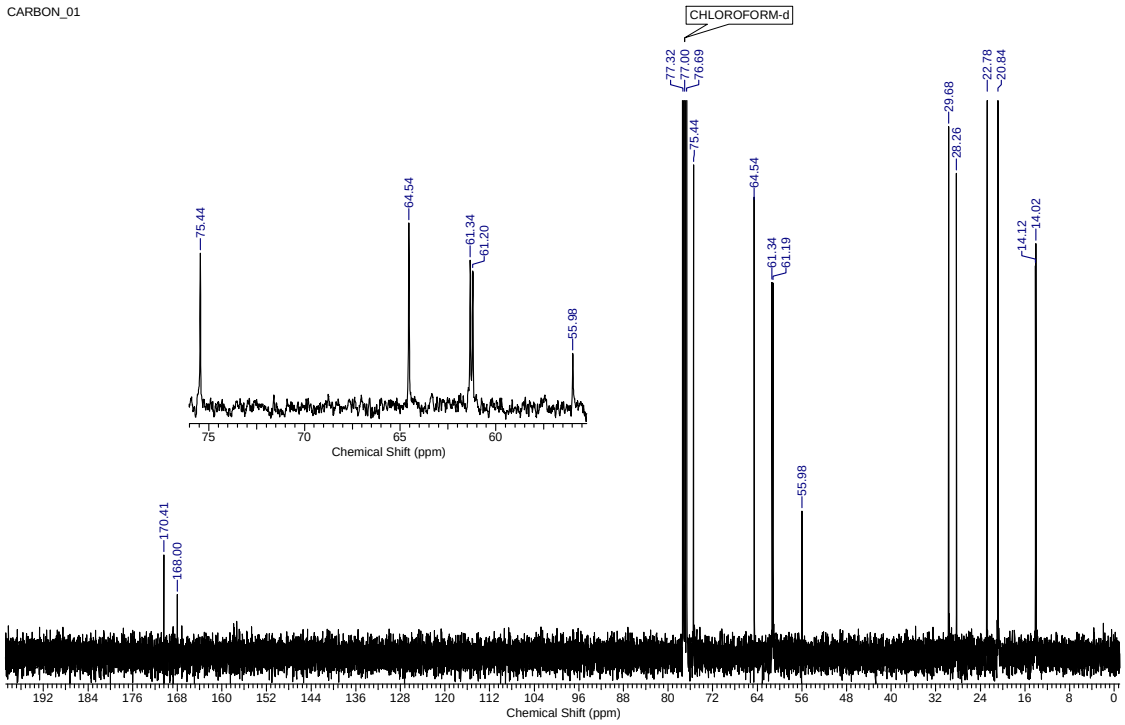
Ethyl 6-cyanopyrido[3,4-*b*]indolizine-10-carboxylate (2.81b)

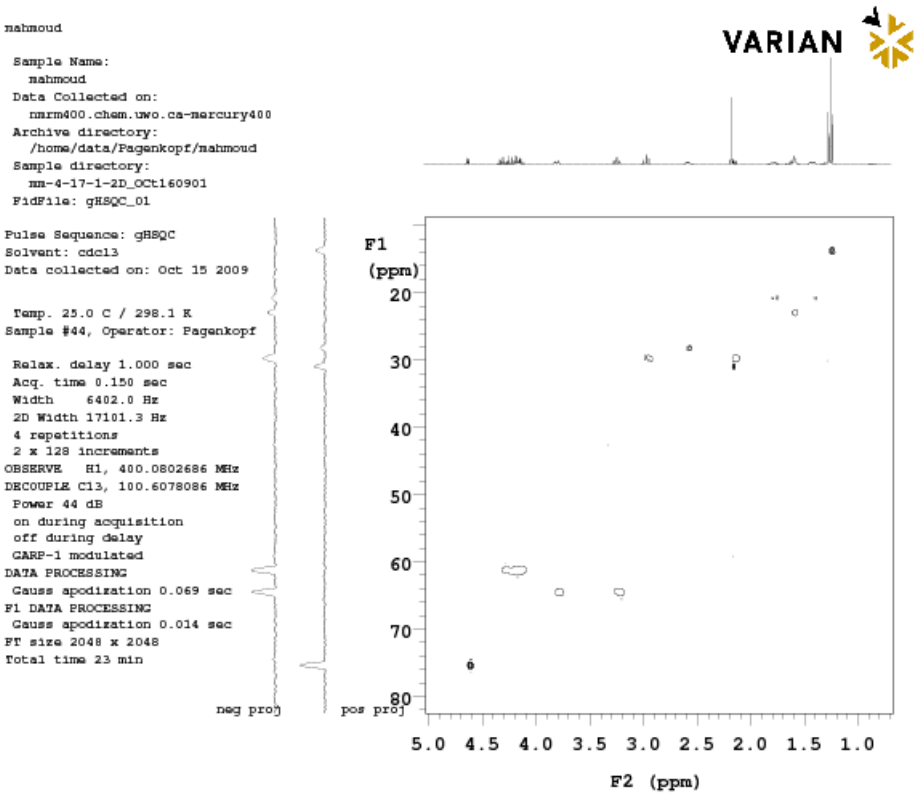


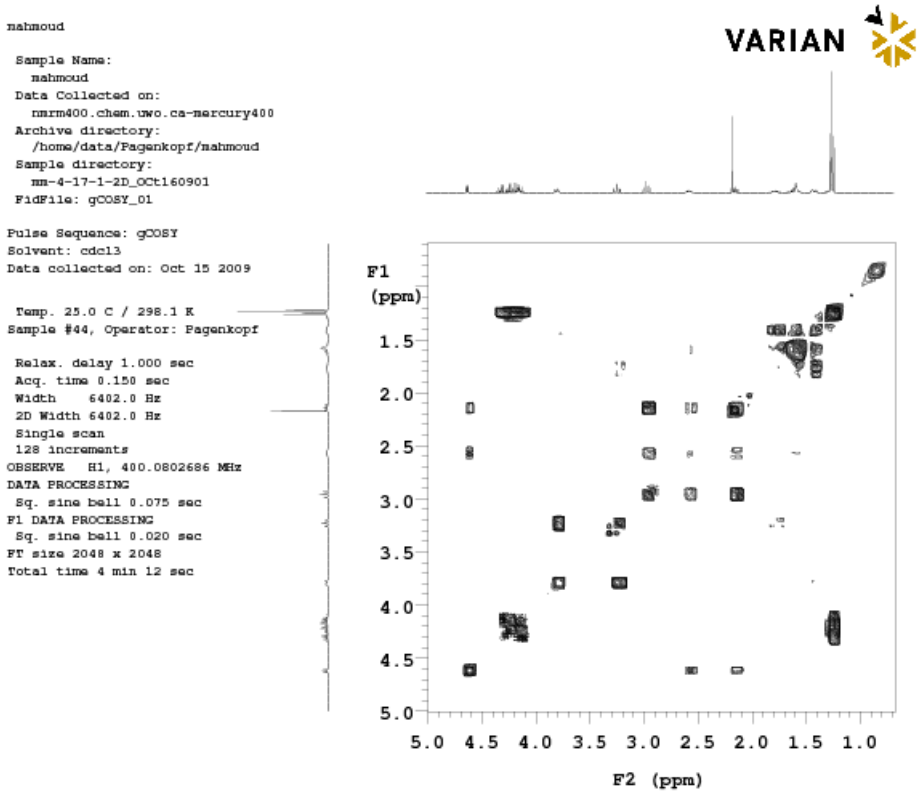
Appendix 4 – NMR Spectra for Compounds Presented in Chapter 3

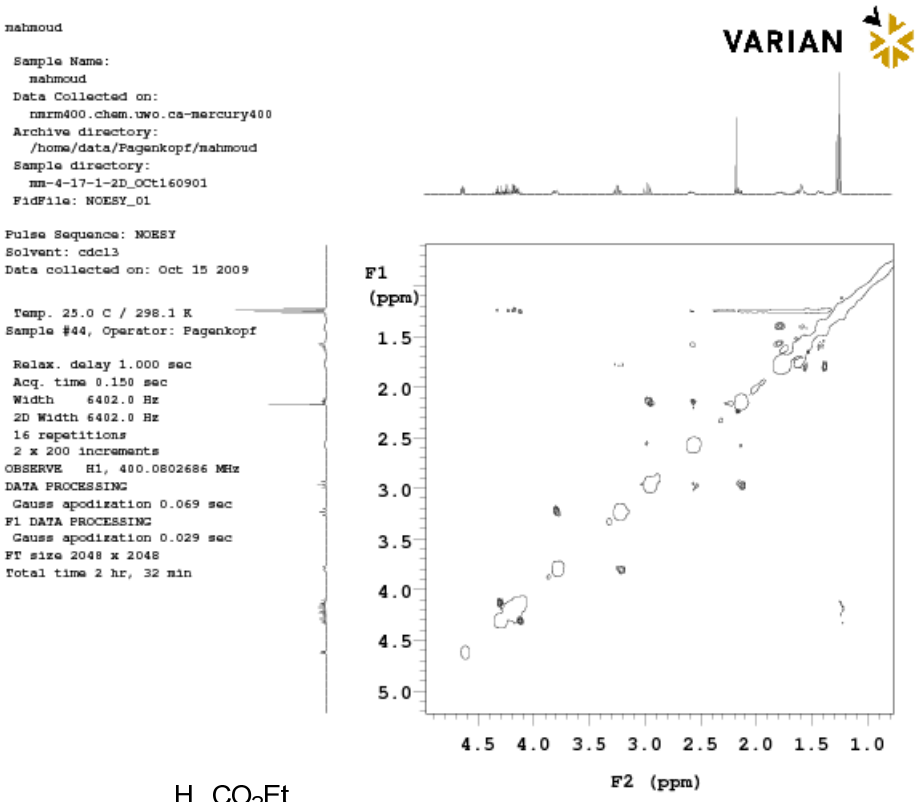
Diethyl 2-oxabicyclo[4.2.0]octane-8,8-dicarboxylate (3.39b)

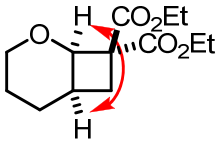


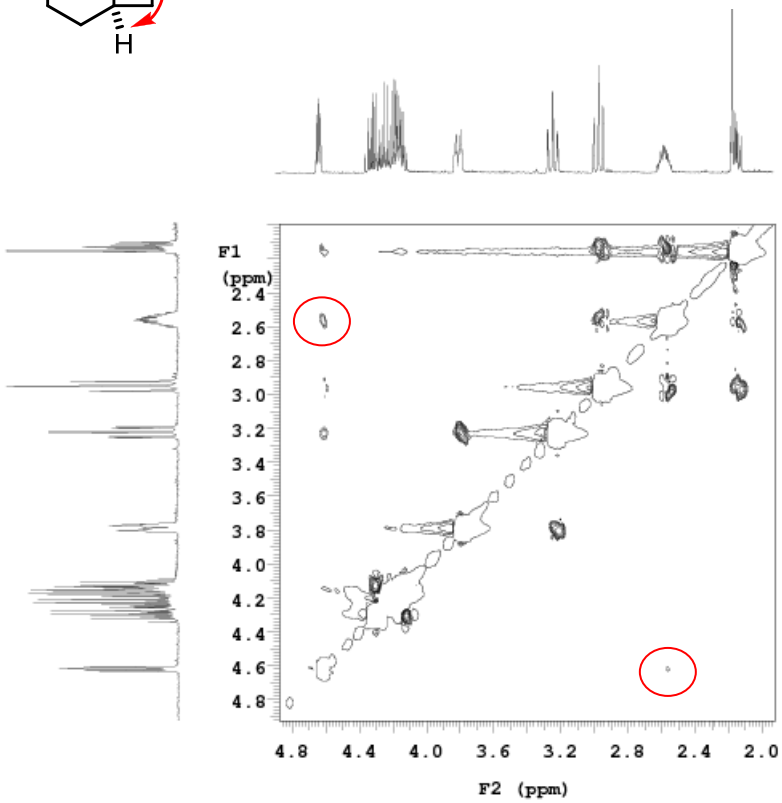



nahmoud
Sample Name:
nahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/nahmoud
Sample directory:
nm-4-17-1-2D_OCt160901
FidFile: gHSQC_01
Pulse Sequence: gHSQC
Solvent: cdcl3
Data collected on: Oct 15 2009
Temp. 25.0 C / 298.1 K
Sample #44, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 17101.3 Hz
4 repetitions
2 x 128 increments
OBSERVE H1, 400.0802686 MHz
DECOUPLE C13, 100.6078086 MHz
Power 44 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.014 sec
FT size 2048 x 2048
Total time 23 min
VARIAN
F1
(ppm)
20
30
40
50
60
70
80
neg proj
pos proj
5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
F2 (ppm)

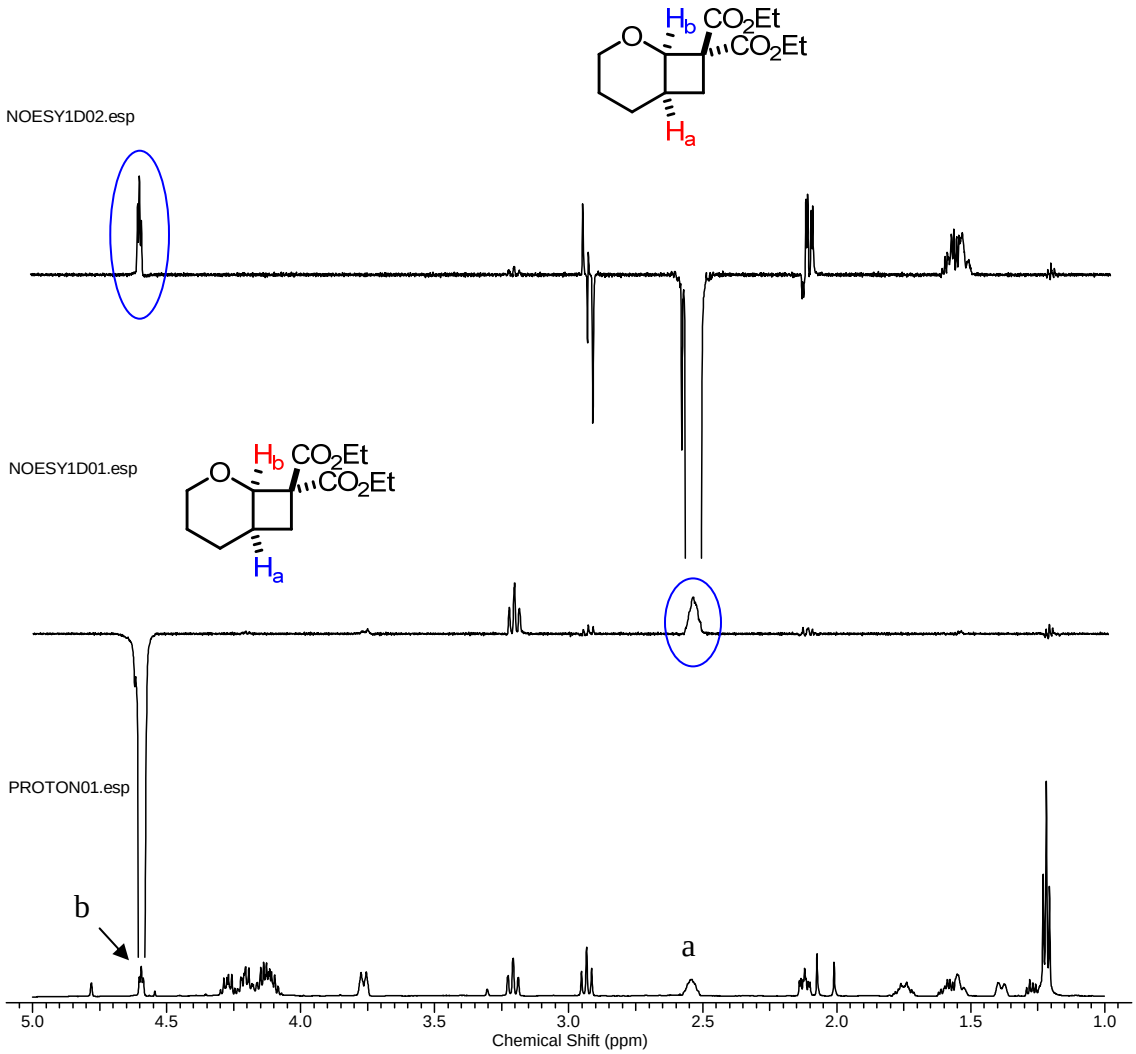

nahmoud
Sample Name:
nahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/nahmoud
Sample directory:
nm-4-17-1-2D_OCt160901
FidFile: gCOSY_01
Pulse Sequence: gCOSY
Solvent: cdcl3
Data collected on: Oct 15 2009
Temp. 25.0 C / 298.1 K
Sample #44, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
Single scan
128 increments
OBSERVE H1, 400.0802686 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sq. sine bell 0.020 sec
FT size 2048 x 2048
Total time 4 min 12 sec
VARIAN
F1
(ppm)
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
F2 (ppm)


nahmoud
Sample Name:
nahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/nahmoud
Sample directory:
nm-4-17-1-2D_OCt160901
FidFile: NOESY_01
Pulse Sequence: NOESY
Solvent: cdcl3
Data collected on: Oct 15 2009
Temp. 25.0 C / 298.1 K
Sample #44, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
16 repetitions
2 x 200 increments
OBSERVE H1, 400.0802686 MHz
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.029 sec
FT size 2048 x 2048
Total time 2 hr, 32 min
VARIAN
F1 (ppm)
F2 (ppm)


H
CO2Et
O
CO2Et
H

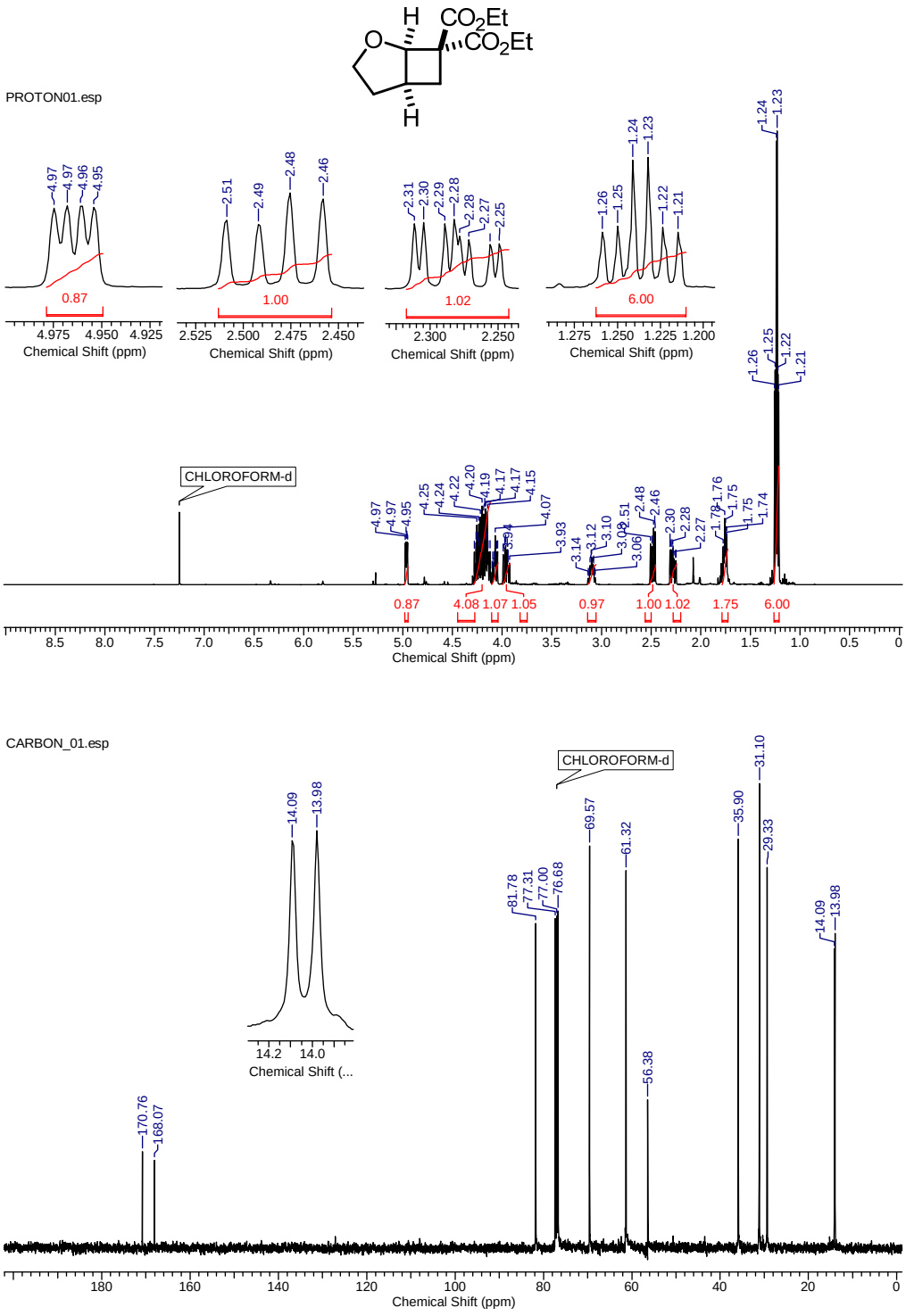

F1 (ppm)
F2 (ppm)

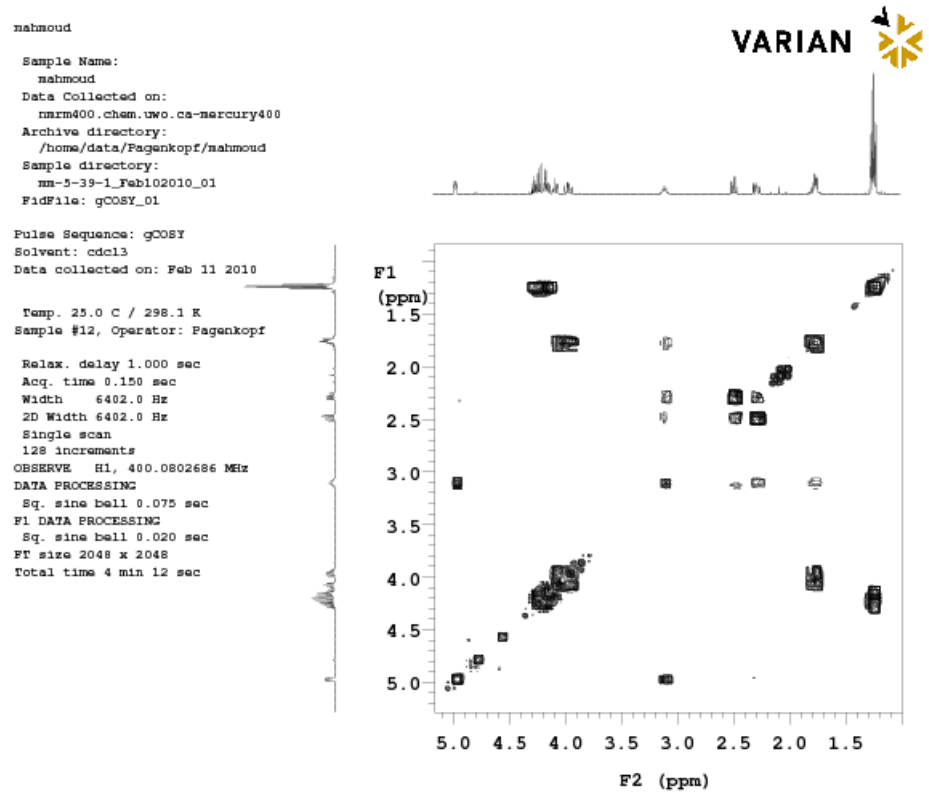
1D NOESY[1]

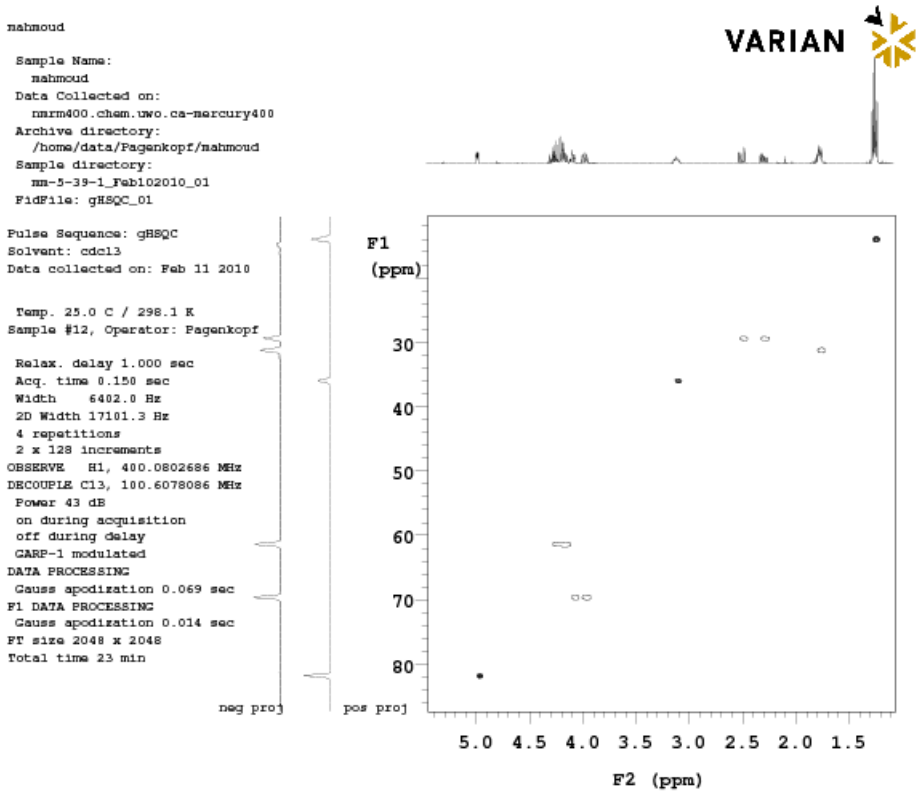


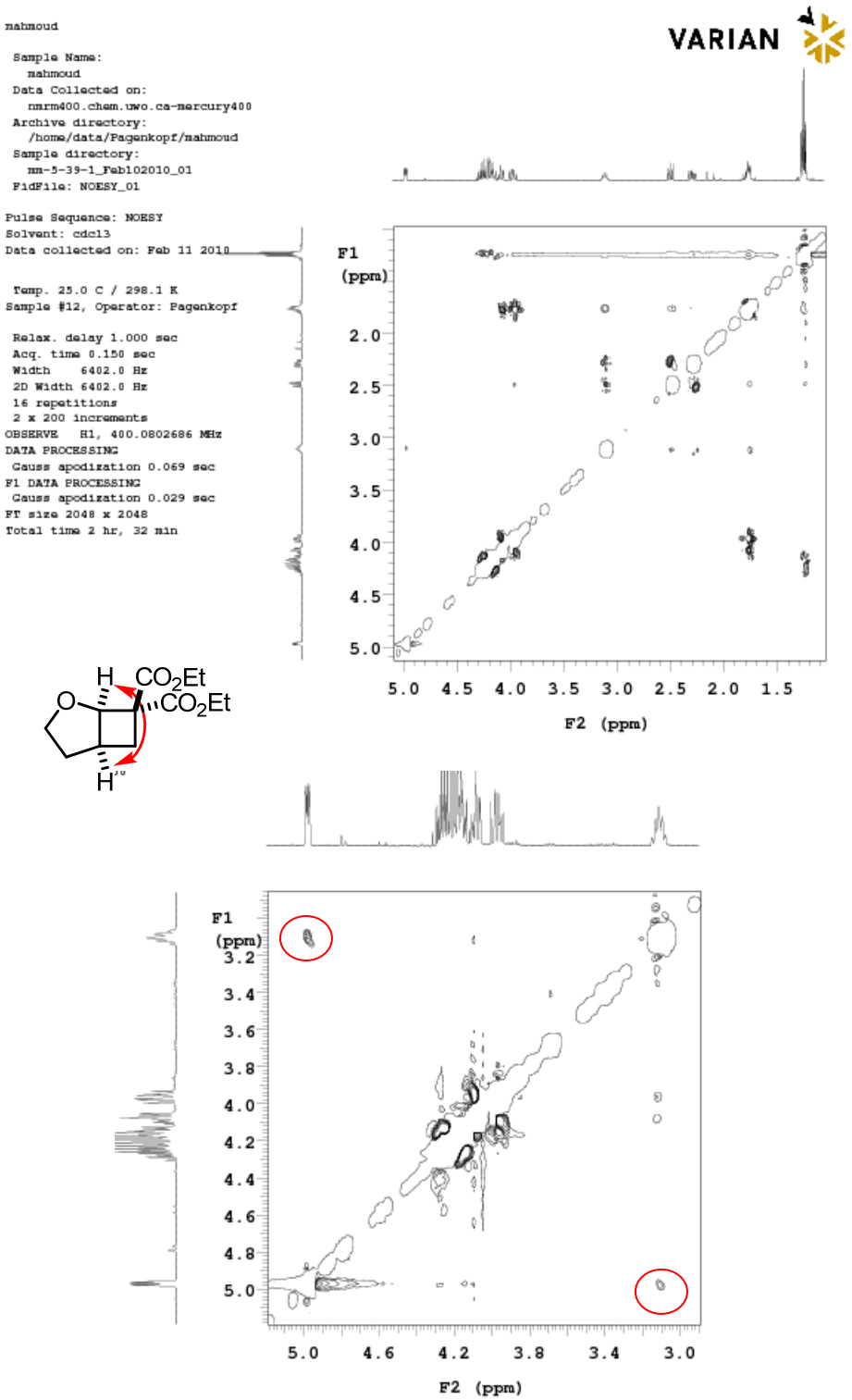
[1] The irradiated proton is colored red and the important nOe interaction is highlighted in blue colors

Diethyl 2-oxabicyclo[3.2.0]heptane-7,7-dicarboxylate (3.39c)

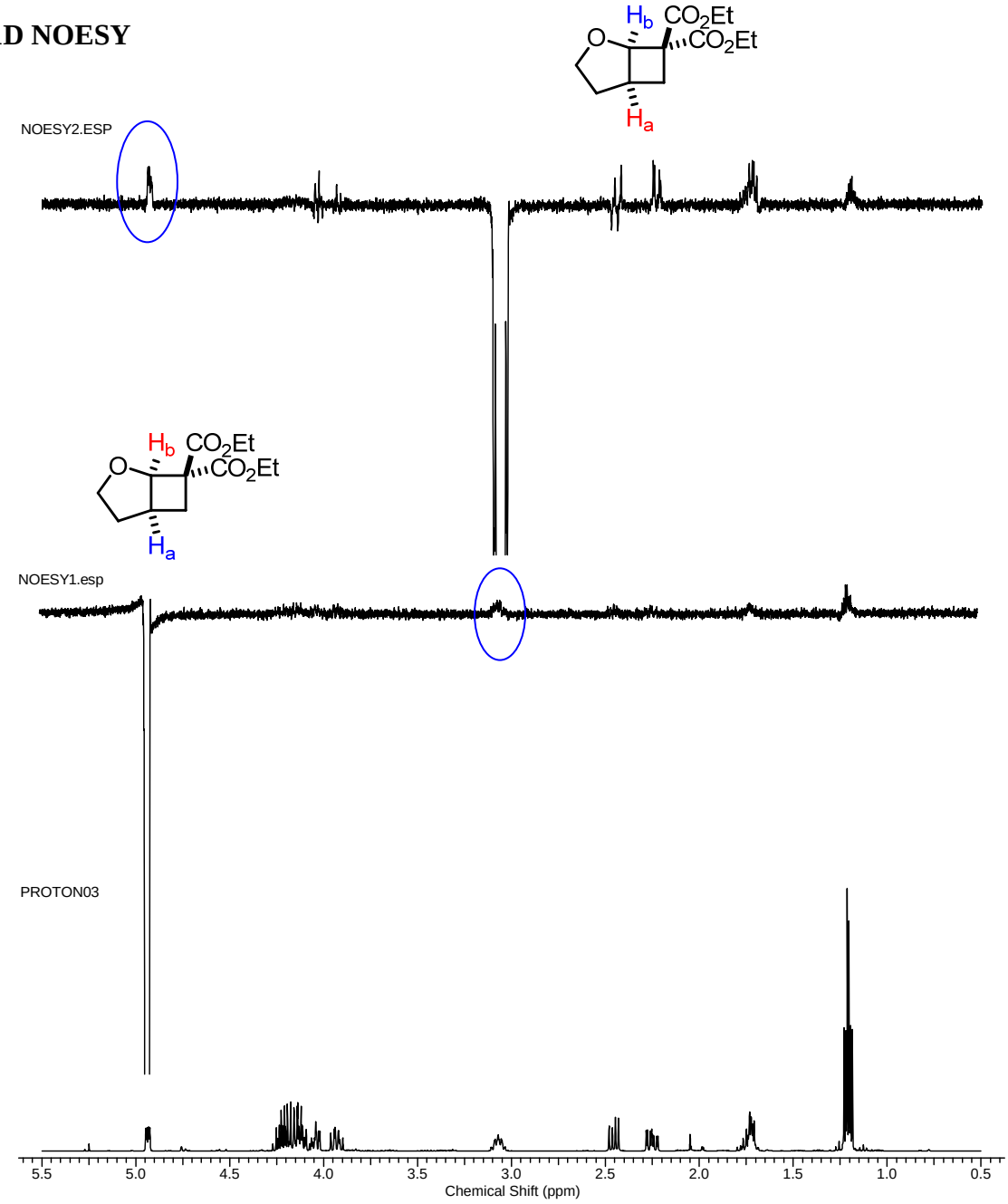



mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-5-39-1_Feb102010_01
FidFile: gCOSY_01
Pulse Sequence: gCOSY
Solvent: cdcl3
Data collected on: Feb 11 2010
Temp. 25.0 C / 298.1 K
Sample #12, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
Single scan
128 increments
OBSERVE H1, 400.0802686 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sq. sine bell 0.020 sec
FT size 2048 x 2048
Total time 4 min 12 sec
VARIAN
F1
(ppm)
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5
F2 (ppm)

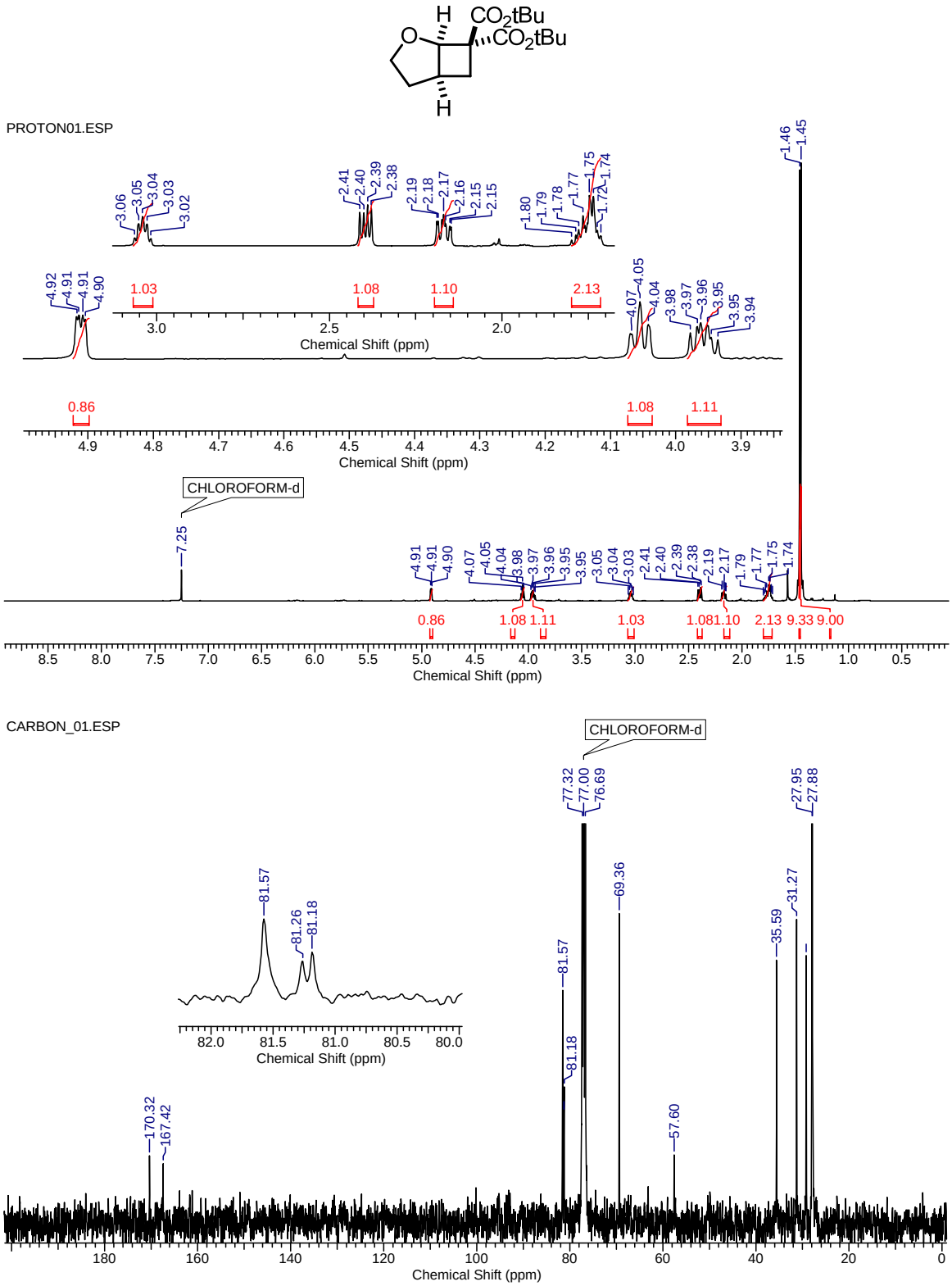

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-5-39-1_Feb102010_01
FidFile: gHSQC_01
Pulse Sequence: gHSQC
Solvent: cdcl3
Data collected on: Feb 11 2010
Temp. 25.0 C / 298.1 K
Sample #12, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 17101.3 Hz
4 repetitions
2 x 128 increments
OBSERVE H1, 400.0802686 MHz
DECOUPLE C13, 100.6078086 MHz
Power 43 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.014 sec
FT size 2048 x 2048
Total time 23 min
neg proj
pos proj
VARIAN
F1
(ppm)
30
40
50
60
70
80
5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5
F2 (ppm)


mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-5-39-1_Feb102010_01
FidFile: NOESY_01
Pulse Sequence: NOESY
Solvent: cdcl3
Data collected on: Feb 11 2010
Temp. 25.0 C / 298.1 K
Sample #12, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
16 repetitions
2 x 200 increments
OBSERVE H1, 400.0802686 MHz
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.029 sec
FT size 2048 x 2048
Total time 2 hr, 32 min
VARIAN
F1 (ppm)
F2 (ppm)
H
CO2Et
CO2Et
O
H
F1 (ppm)
F2 (ppm)

1D NOESY


Hb CO2Et
O
CO2Et
Ha
NOESY2.ESP
Hb CO2Et
O
CO2Et
Ha
NOESY1.esp
PROTON03
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical Shift (ppm)

Di-tert-butyl 2-oxabicyclo[3.2.0]heptane-7,7-dicarboxylate (3.39d)



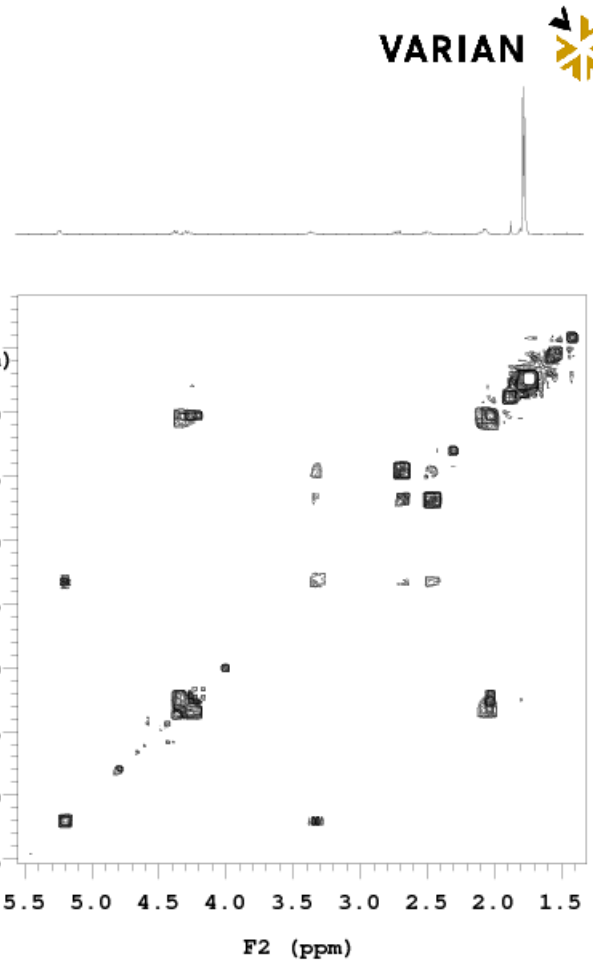
mahmoud

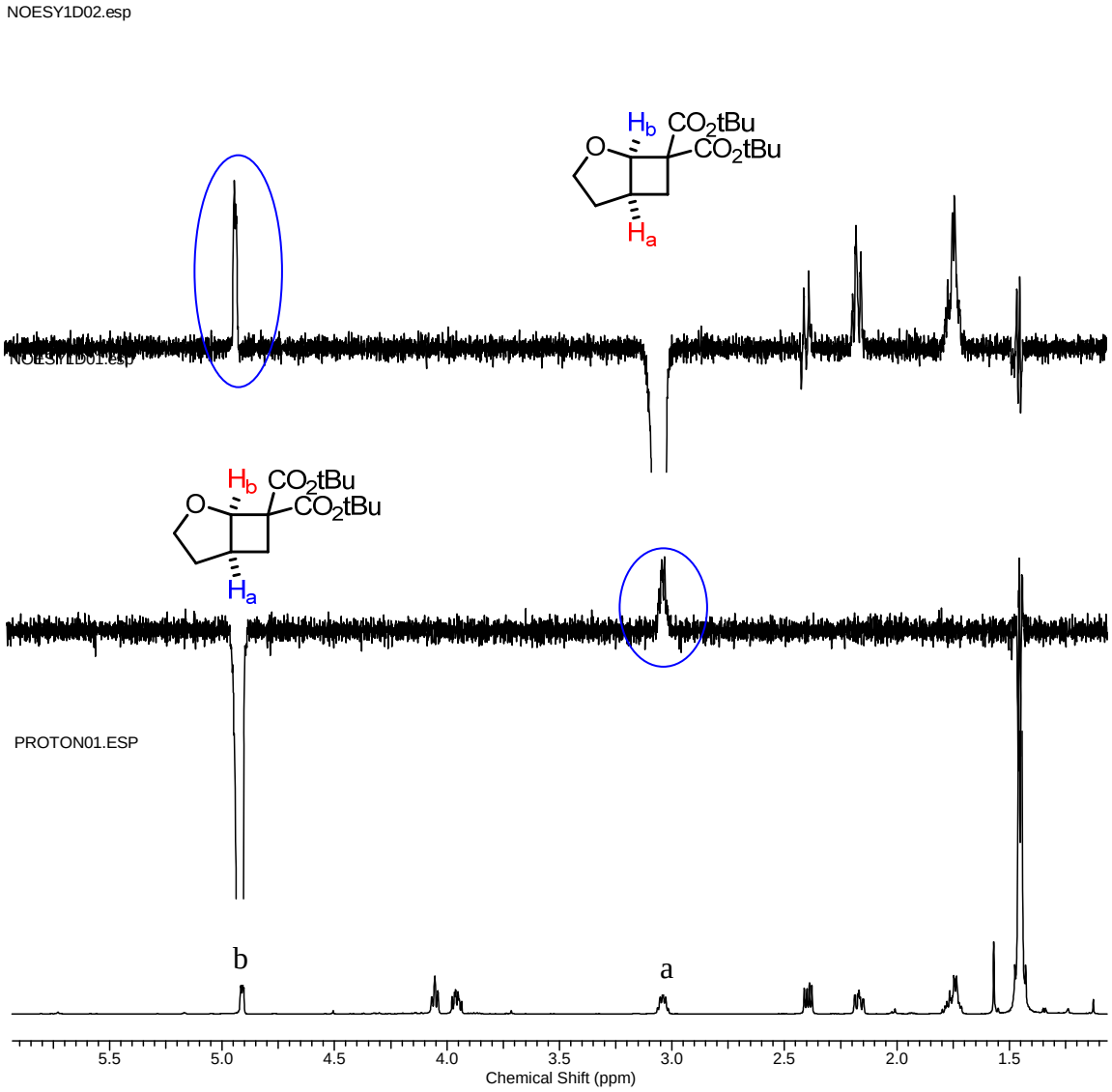
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-5-31-1_Jan262010_01
FidFile: gCOSY_01

Pulse Sequence: gCOSY
Solvent: cdcl3
Data collected on: Jan 26 2010

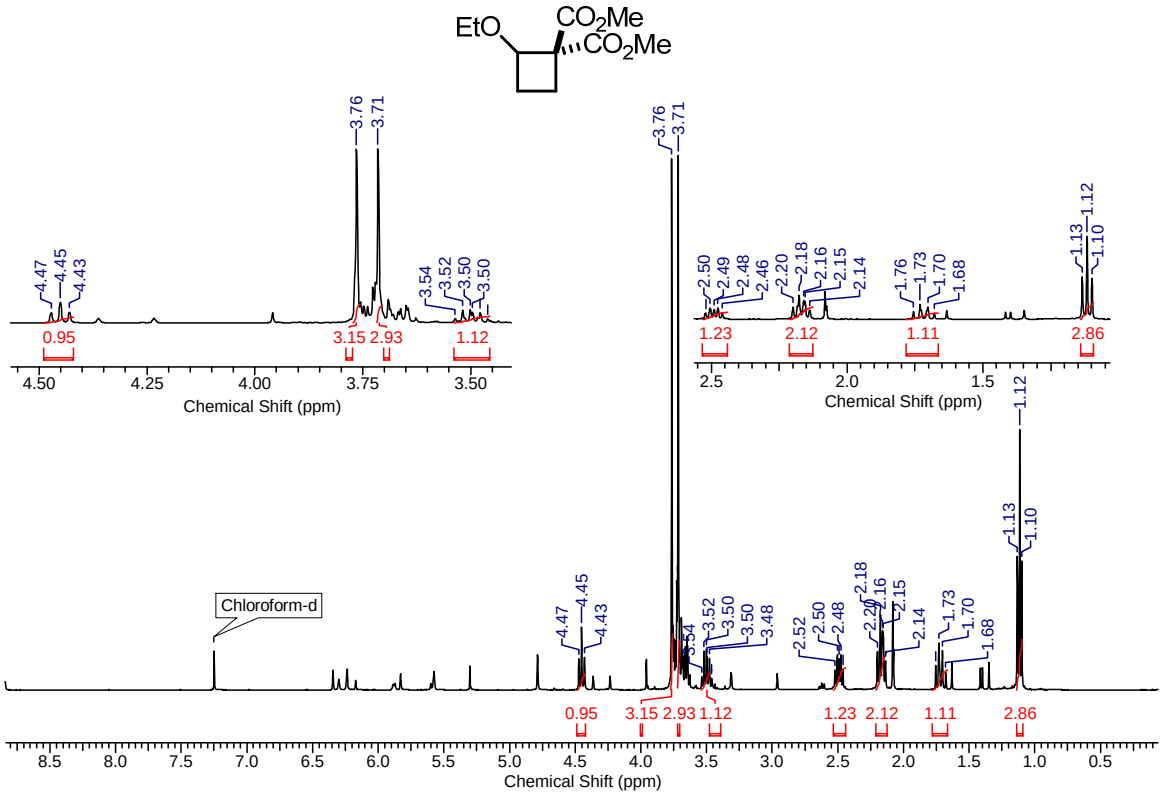
Temp. 25.0 C / 298.1 K
Sample #3, Operator: Pagenkopf

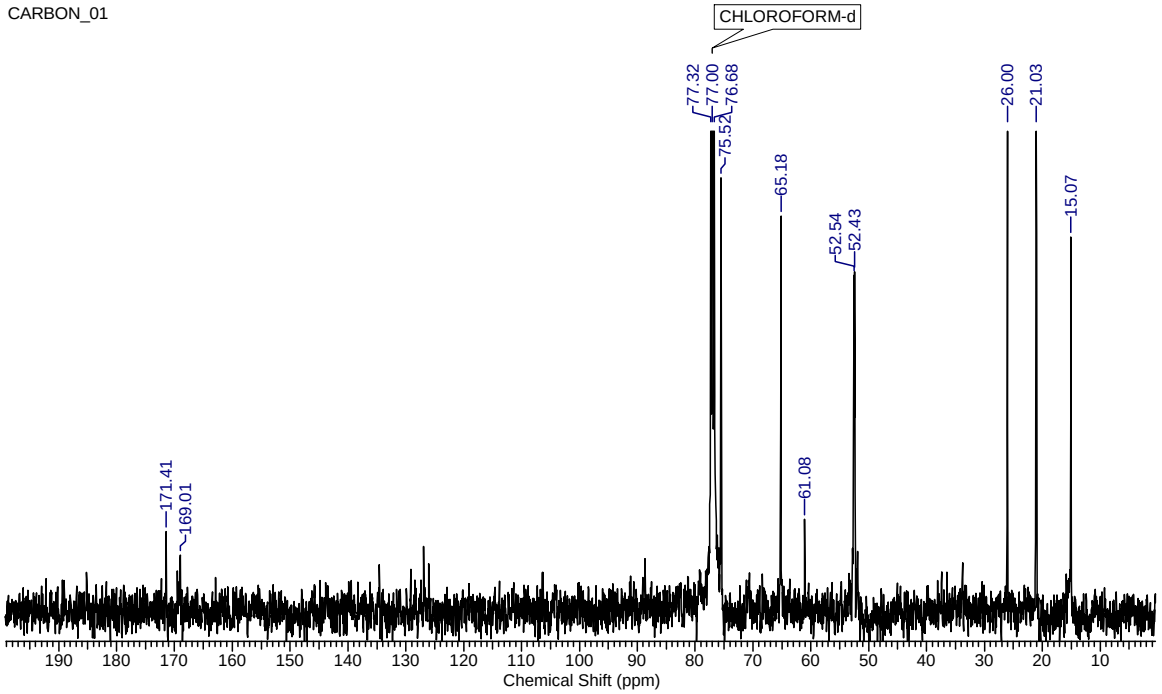
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
Single scan
128 increments
OBSERVE H1, 400.0802686 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sq. sine bell 0.020 sec
FT size 2048 x 2048
Total time 4 min 12 sec



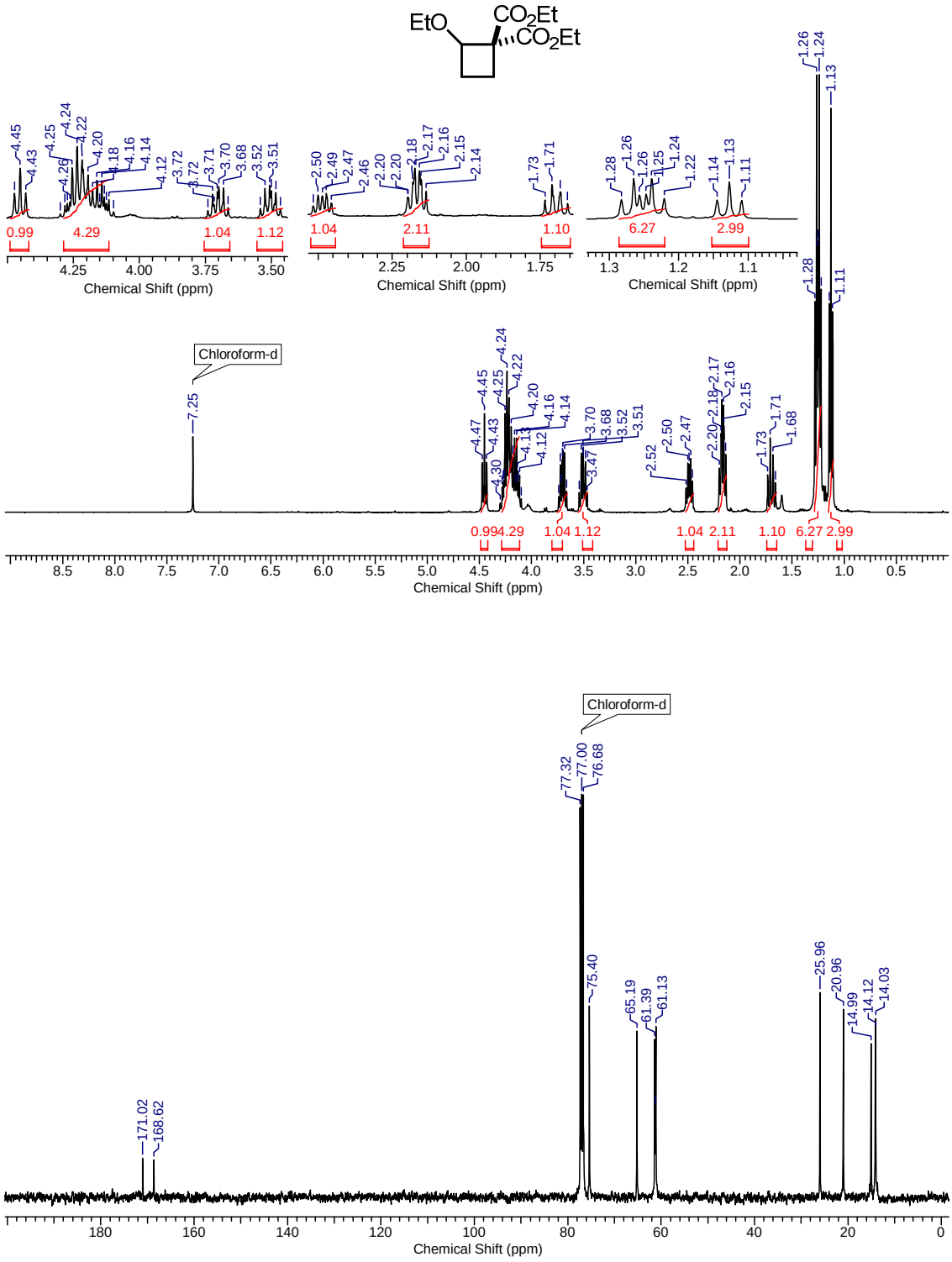

NOESY1D02.esp
Hb CO2tBu
O
CO2tBu
Ha
NOESY1D01.esp
Hb CO2tBu
O
CO2tBu
Ha
PROTON01.ESP
b
a
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

Dimethyl 2-ethoxycyclobutane-1,1-dicarboxylate (3.39f)

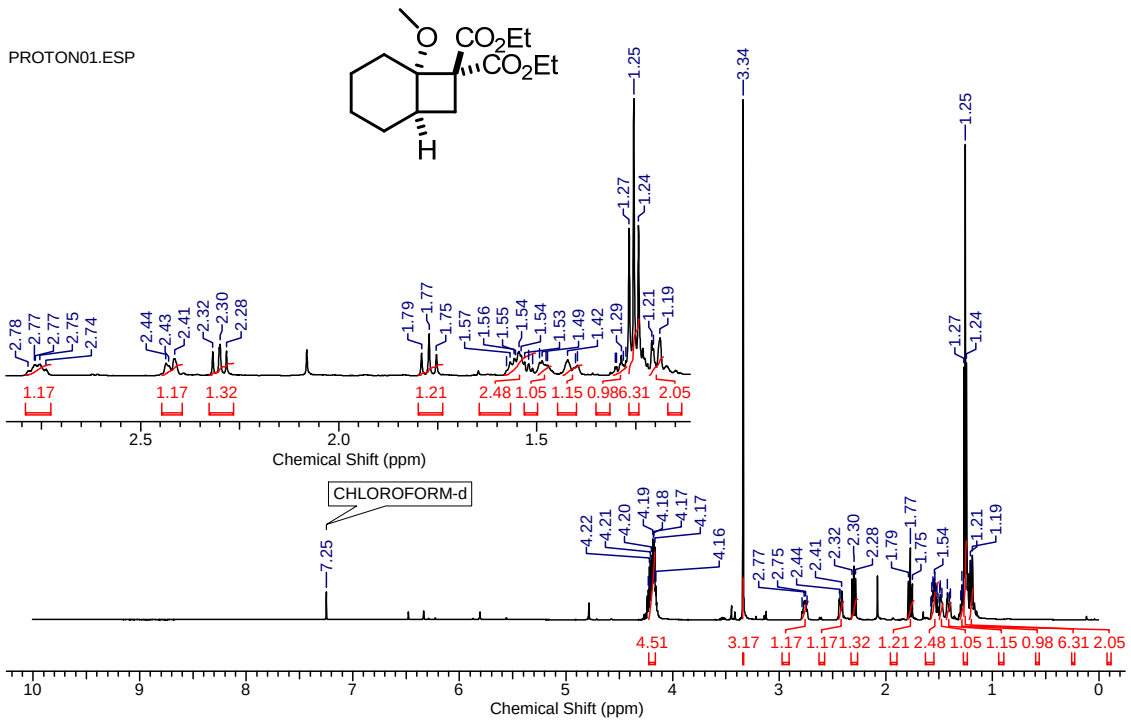


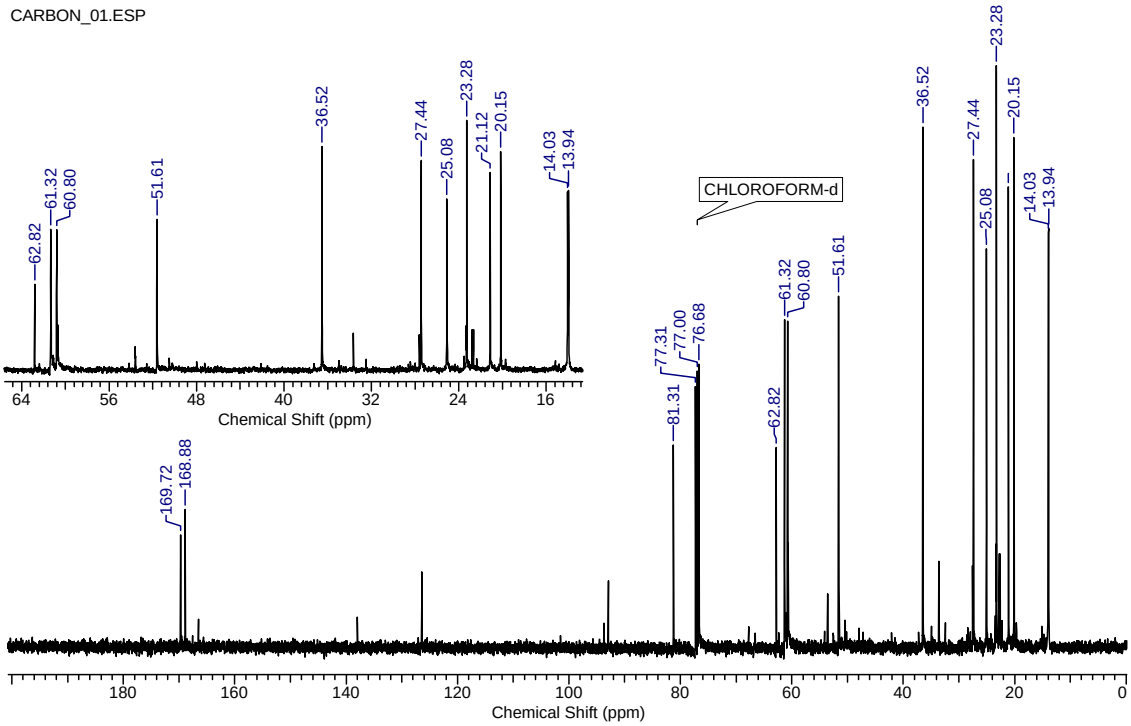


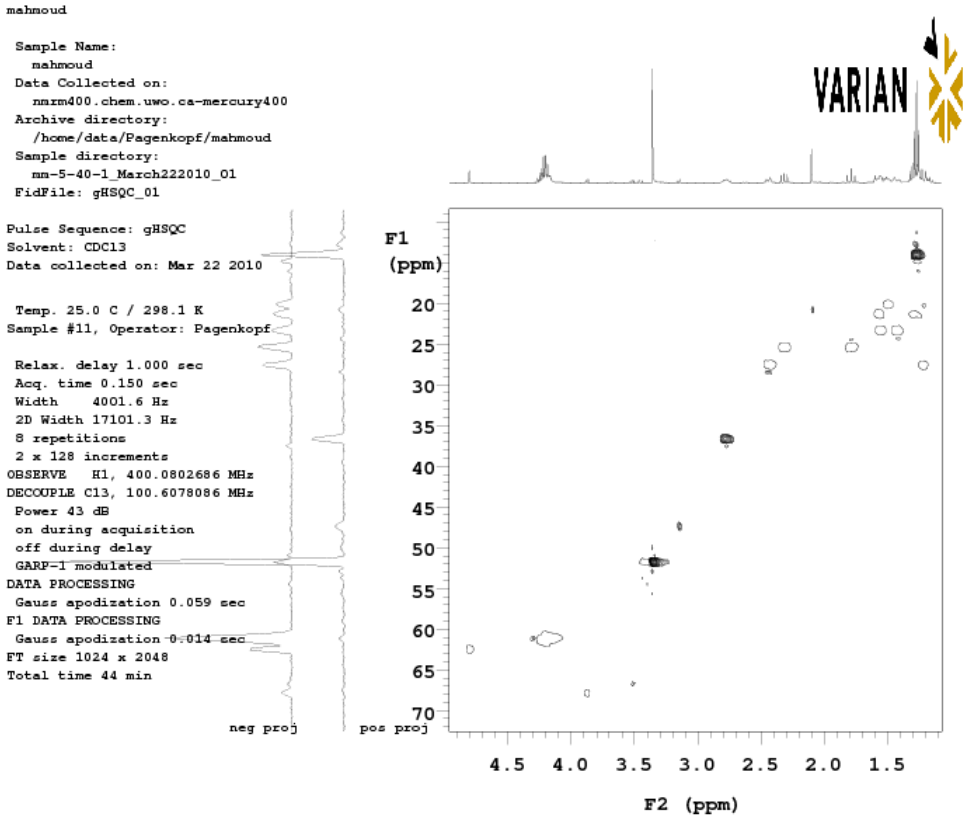
Diethyl 2-ethoxycyclobutane-1,1-dicarboxylate (3.39g)

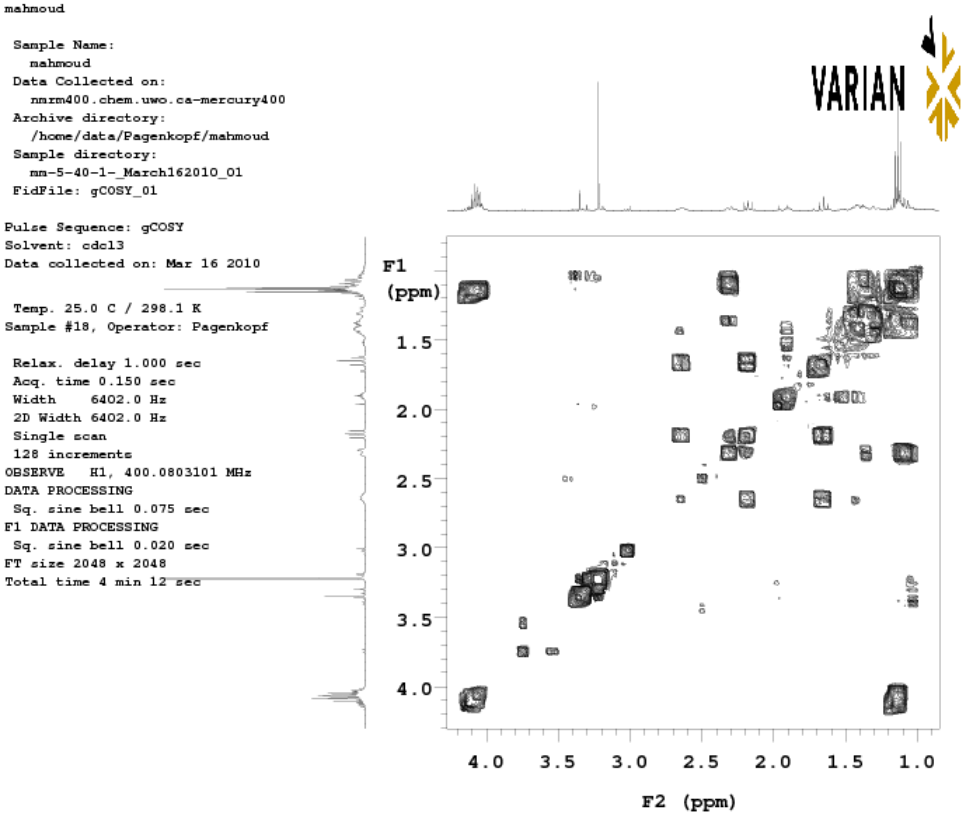


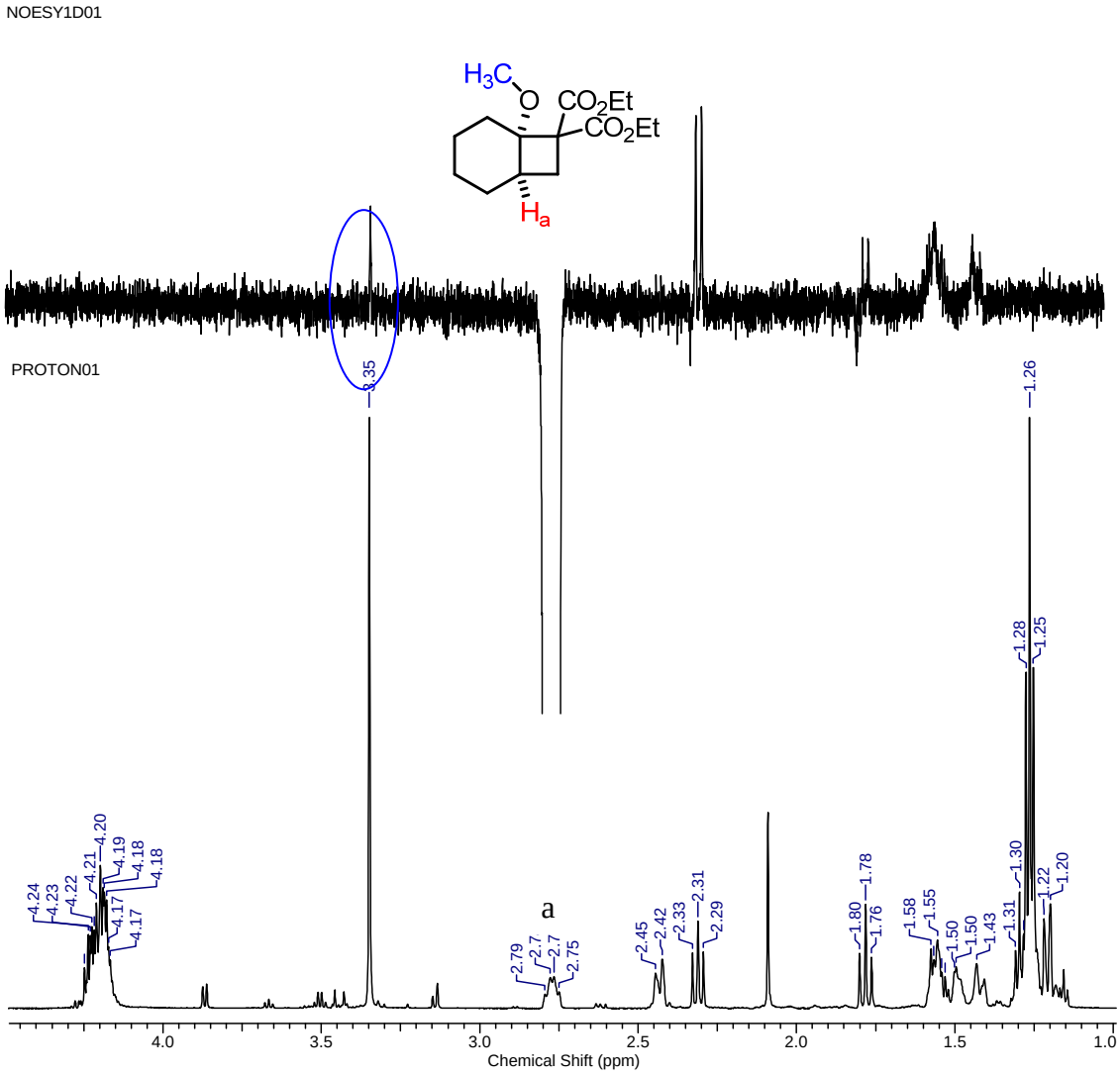
Diethyl 6-methoxybicyclo[4.2.0]octane-7,7-dicarboxylate (3.39h)



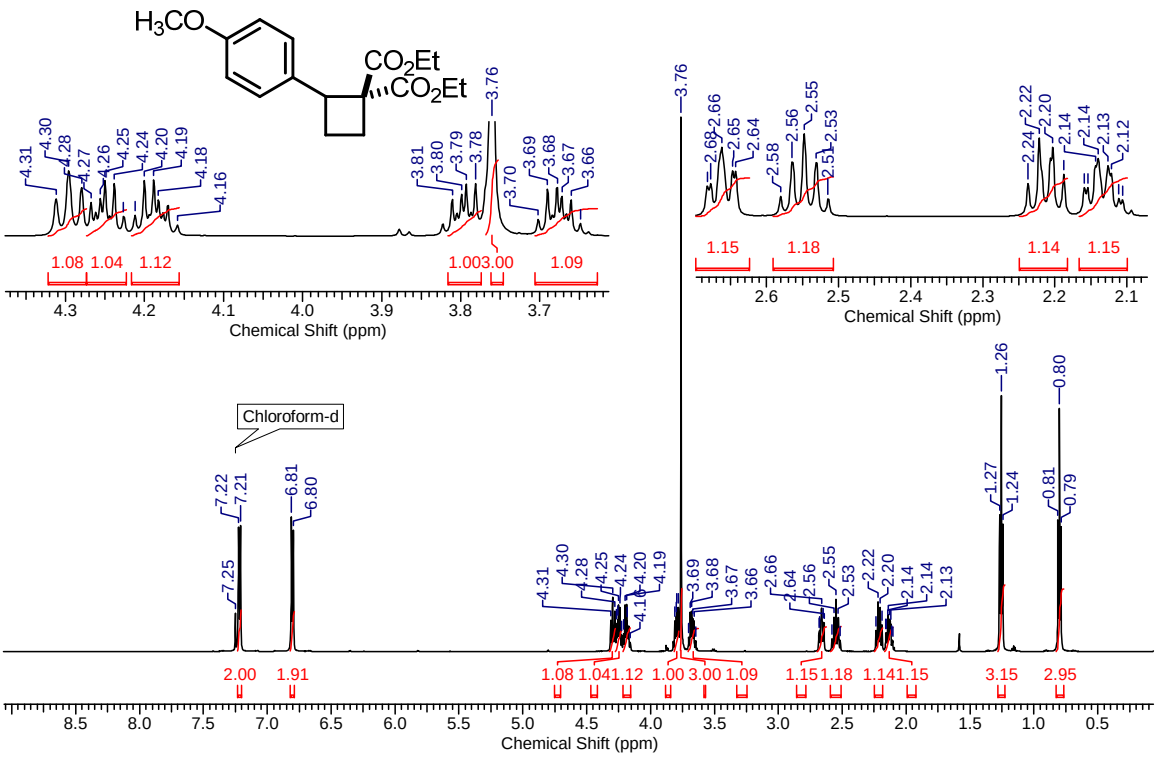


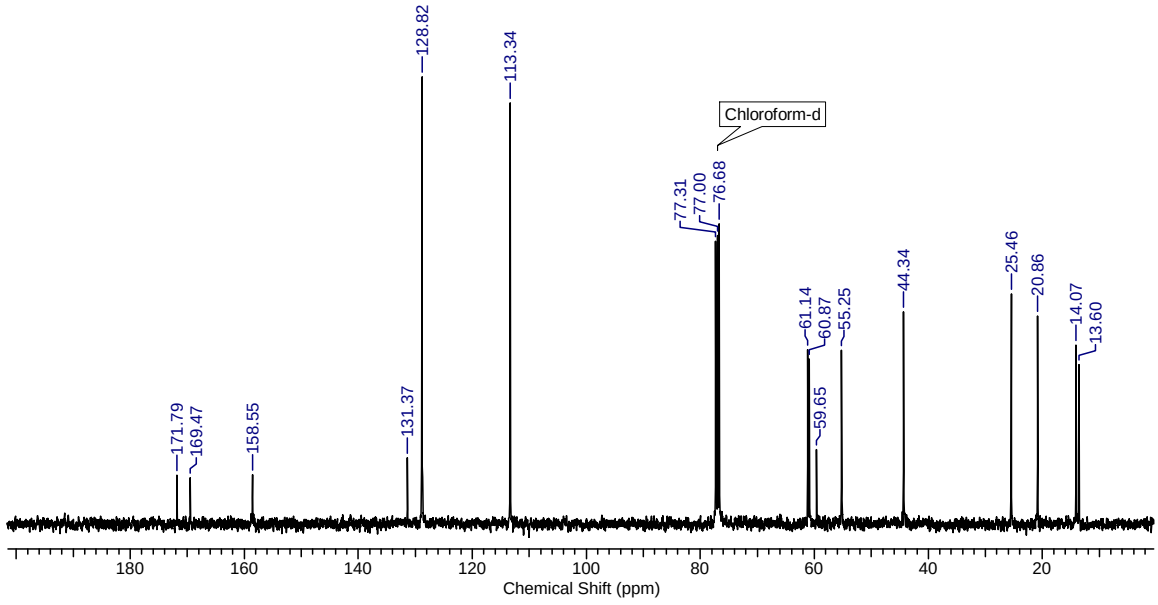

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-5-40-1_March222010_01
FidFile: gHSQC_01
Pulse Sequence: gHSQC
Solvent: CDCl3
Data collected on: Mar 22 2010
Temp. 25.0 C / 298.1 K
Sample #11, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 4001.6 Hz
2D Width 17101.3 Hz
8 repetitions
2 x 128 increments
OBSERVE H1, 400.0802686 MHz
DECOUPLE C13, 100.6078086 MHz
Power 43 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Gauss apodization 0.059 sec
F1 DATA PROCESSING
Gauss apodization 0.014 sec
FT size 1024 x 2048
Total time 44 min
neg proj
pos proj
F1 (ppm)
20
25
30
35
40
45
50
55
60
65
70
4.5 4.0 3.5 3.0 2.5 2.0 1.5
F2 (ppm)


mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-5-40-1-_March162010_01
FidFile: gCOSY_01
Pulse Sequence: gCOSY
Solvent: cdcl3
Data collected on: Mar 16 2010
Temp. 25.0 C / 298.1 K
Sample #18, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
Single scan
128 increments
OBSERVE H1, 400.0803101 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sq. sine bell 0.020 sec
FT size 2048 x 2048
Total time 4 min 12 sec
F1 (ppm)
1.5
2.0
2.5
3.0
3.5
4.0
4.0 3.5 3.0 2.5 2.0 1.5 1.0
F2 (ppm)

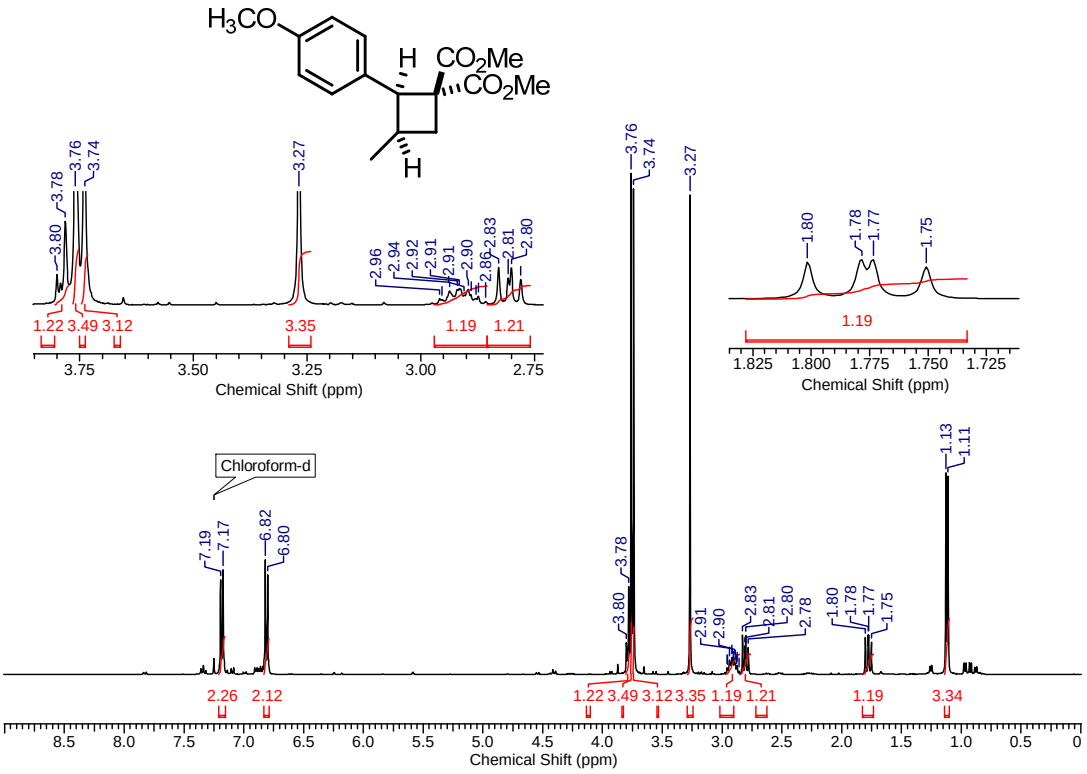

NOESY1D01
H3C
O
CO2Et
CO2Et
Ha
PROTON01
3.35
1.26
1.28
1.25
4.24
4.23
4.22
4.21
4.20
4.19
4.18
4.18
4.17
4.17
a
2.79
2.7
2.7
2.75
2.45
2.42
2.33
2.31
2.29
1.80
1.78
1.76
1.58
1.55
1.50
1.50
1.43
1.31
1.30
1.22
1.20
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)

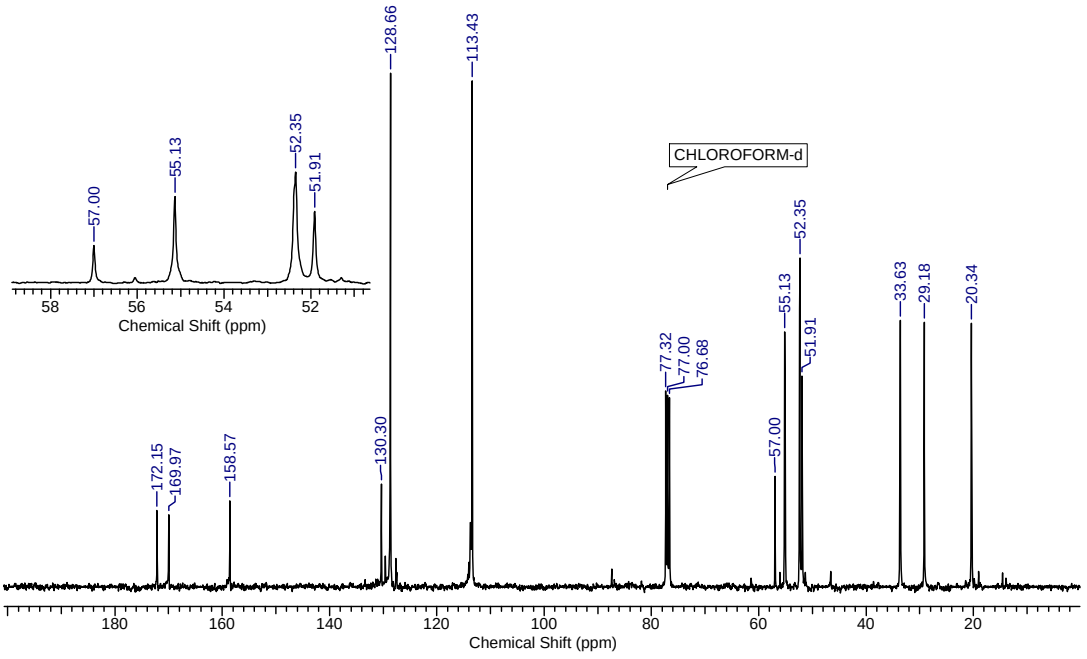
Diethyl 2-(4-methoxyphenyl)cyclobutane-1,1-dicarboxylate (3.41a)

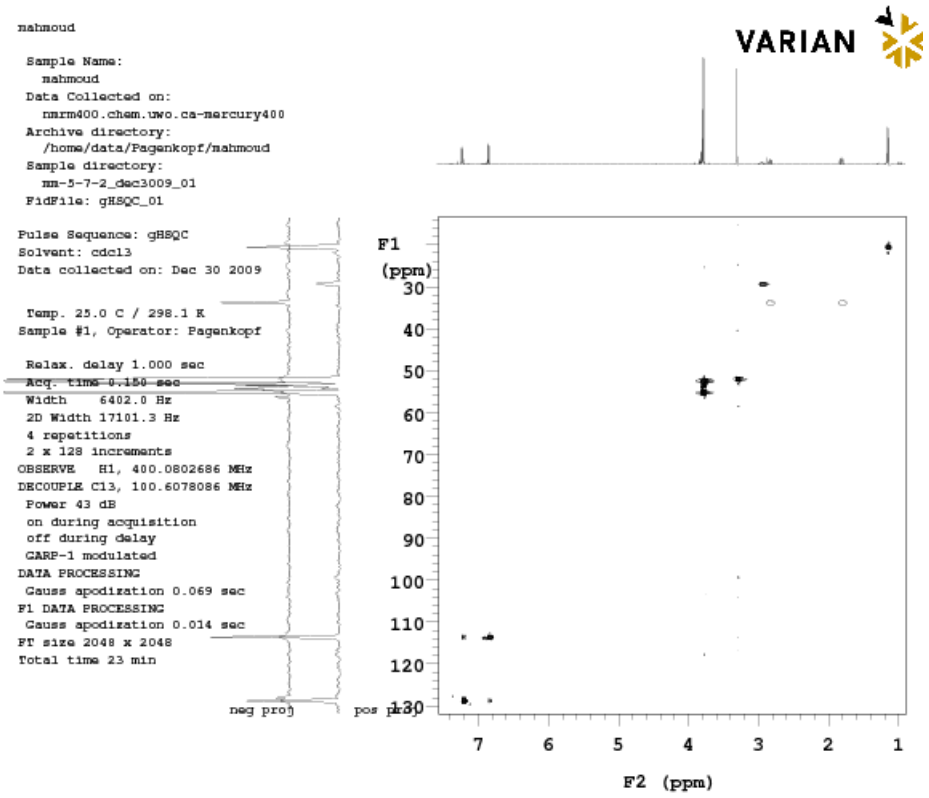


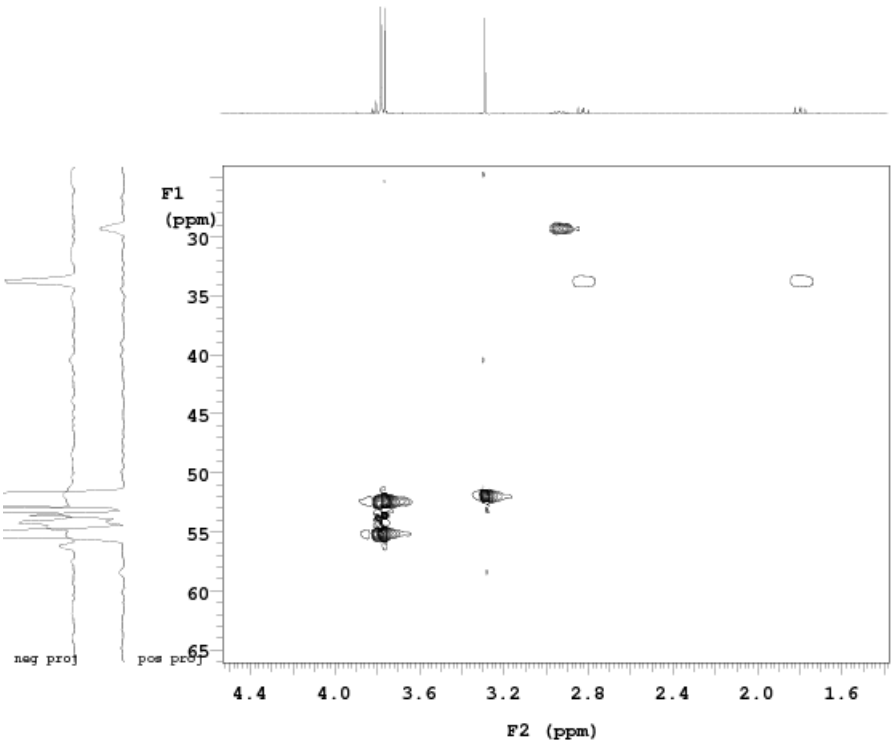


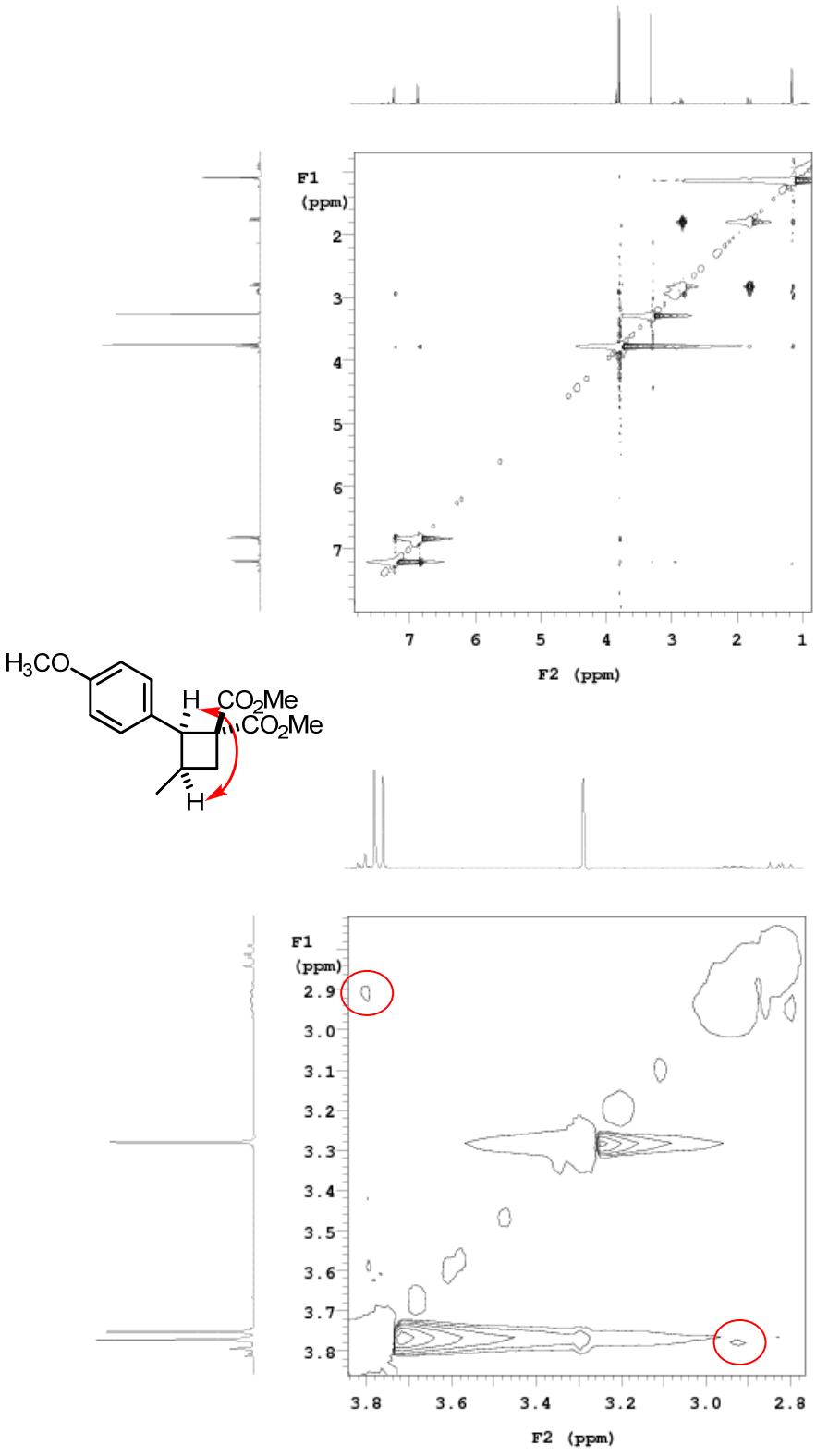
Dimethyl 2-(4-methoxyphenyl)-3-methylcyclobutane-1,1-dicarboxylate (3.41c)



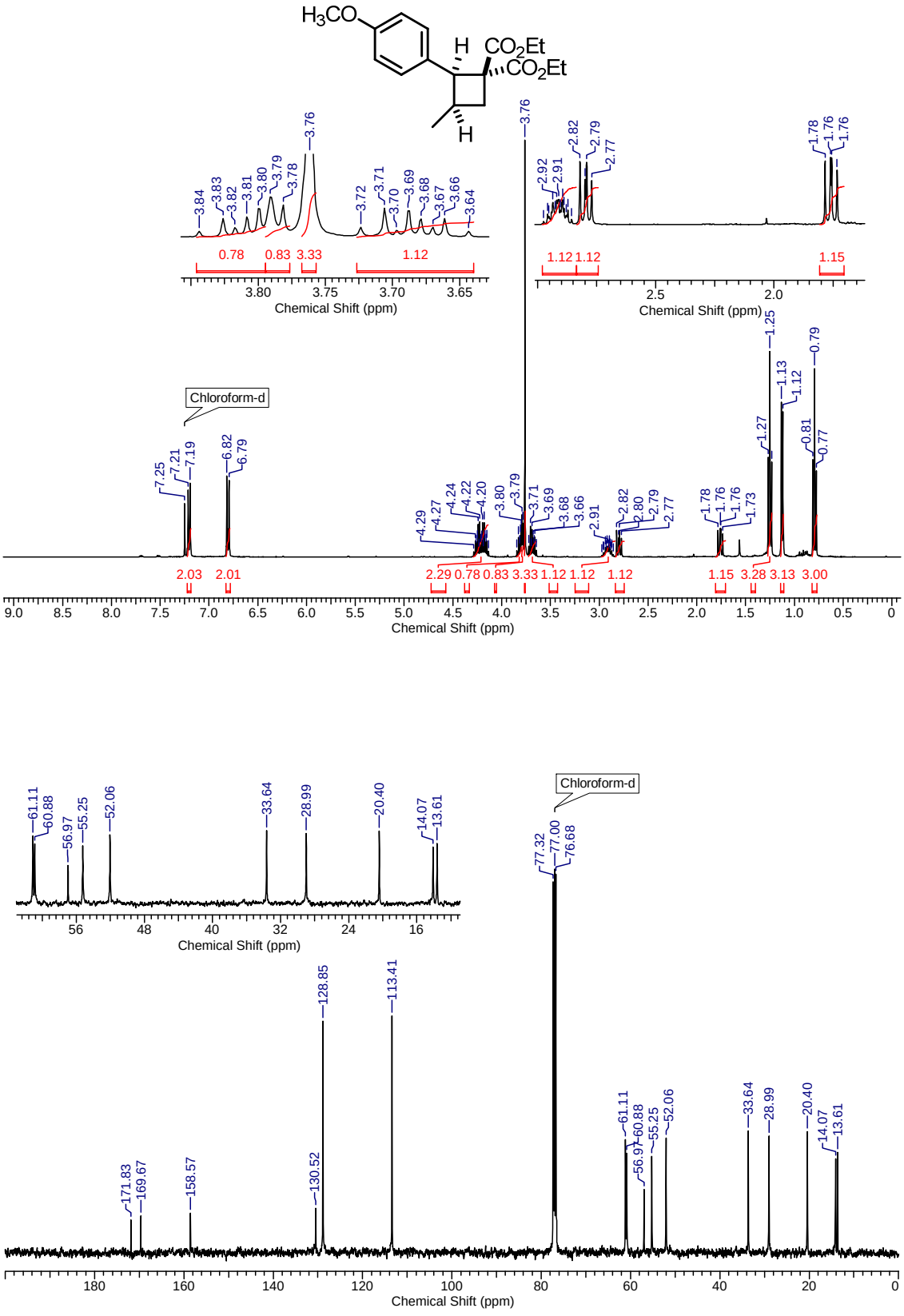


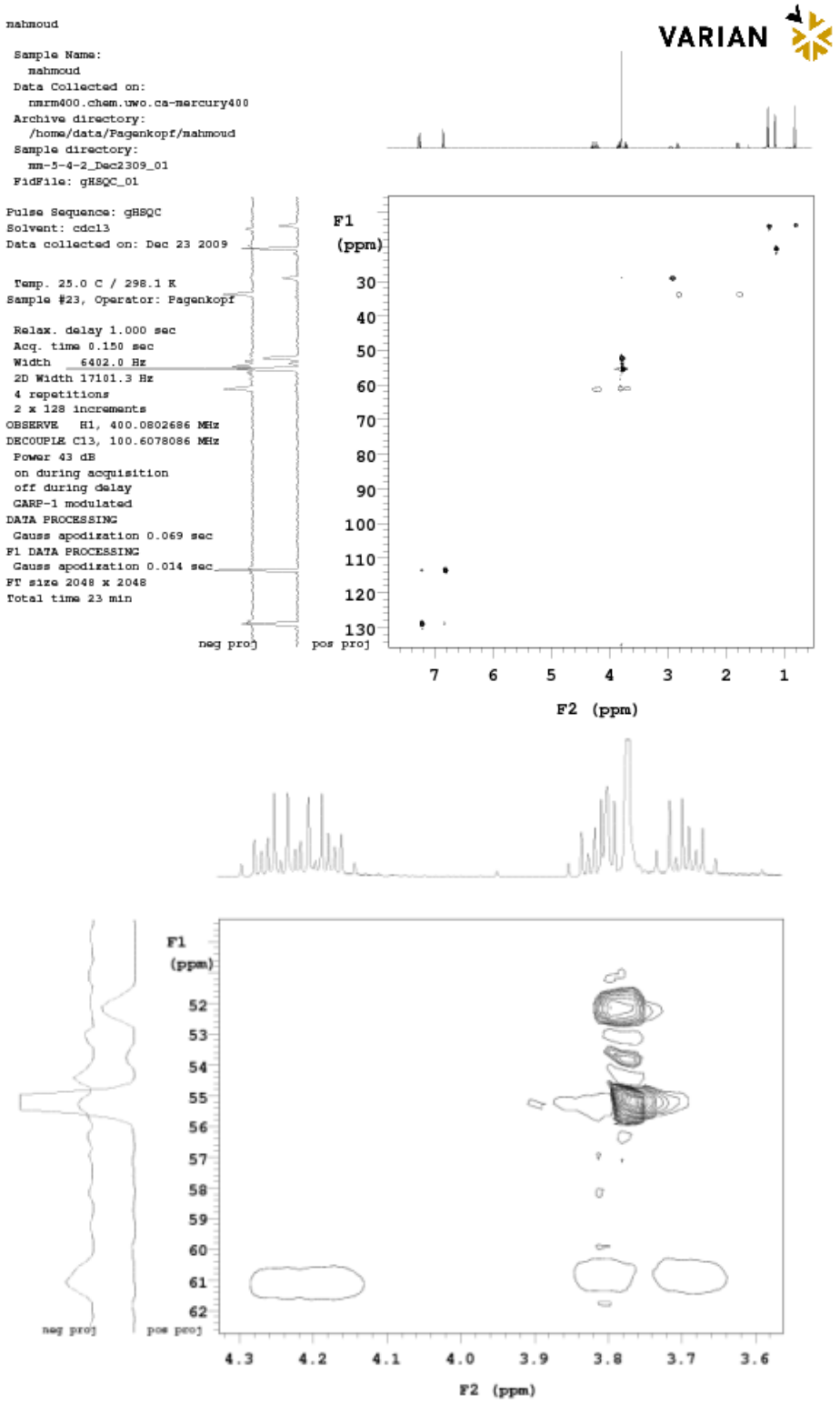

nahmoud
Sample Name:
nahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/nahmoud
Sample directory:
nm-5-7-2_dec3009_01
FidFile: gHSQC_01
Pulse Sequence: gHSQC
Solvent: cdcl3
Data collected on: Dec 30 2009
Temp. 25.0 C / 298.1 K
Sample #1, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 17101.3 Hz
4 repetitions
2 x 128 increments
OBSERVE H1, 400.0802686 MHz
DECOUPLE C13, 100.6078086 MHz
Power 43 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.014 sec
FT size 2048 x 2048
Total time 23 min
VARIAN
F1
(ppm)
F2 (ppm)

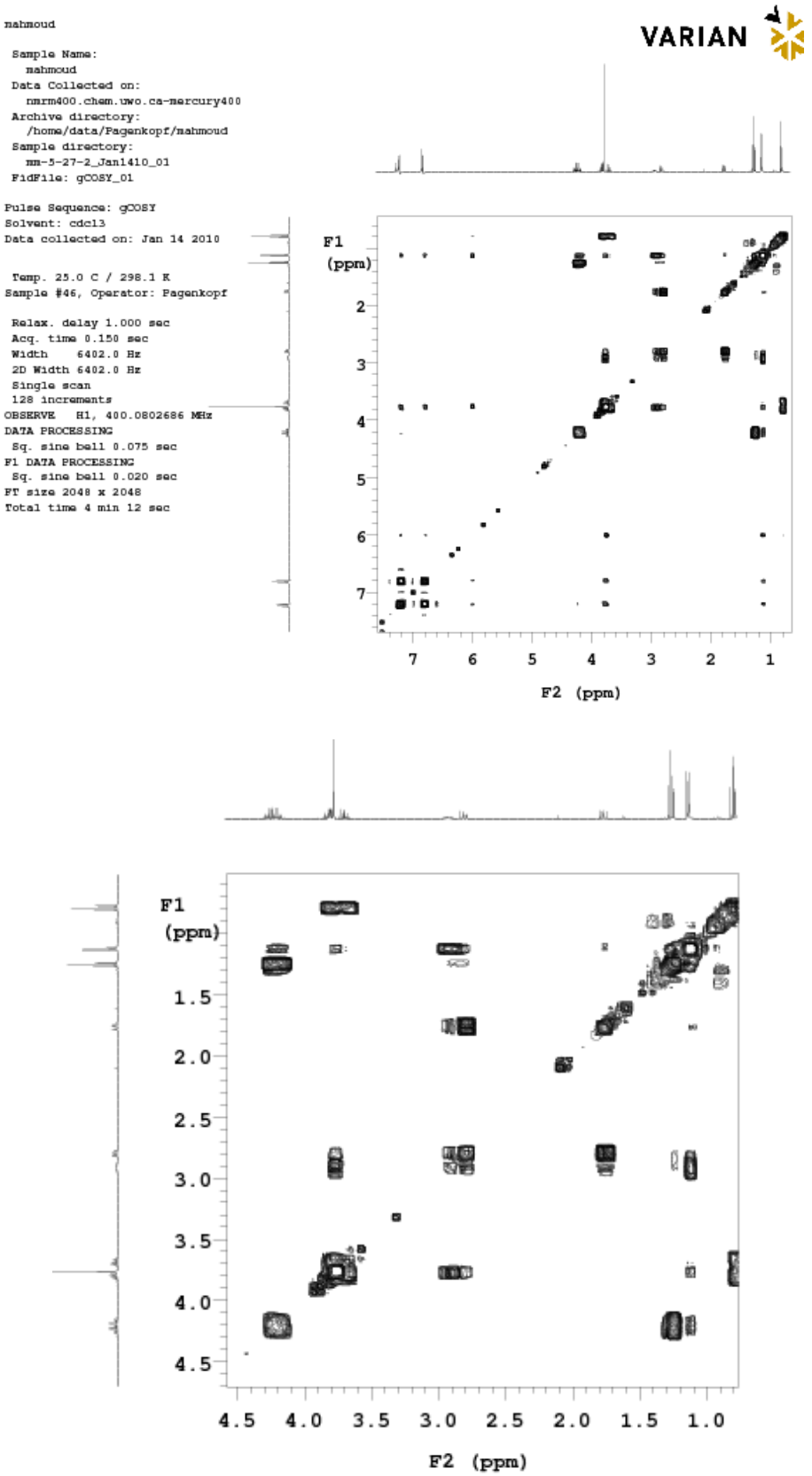

F1
(ppm)
F2 (ppm)

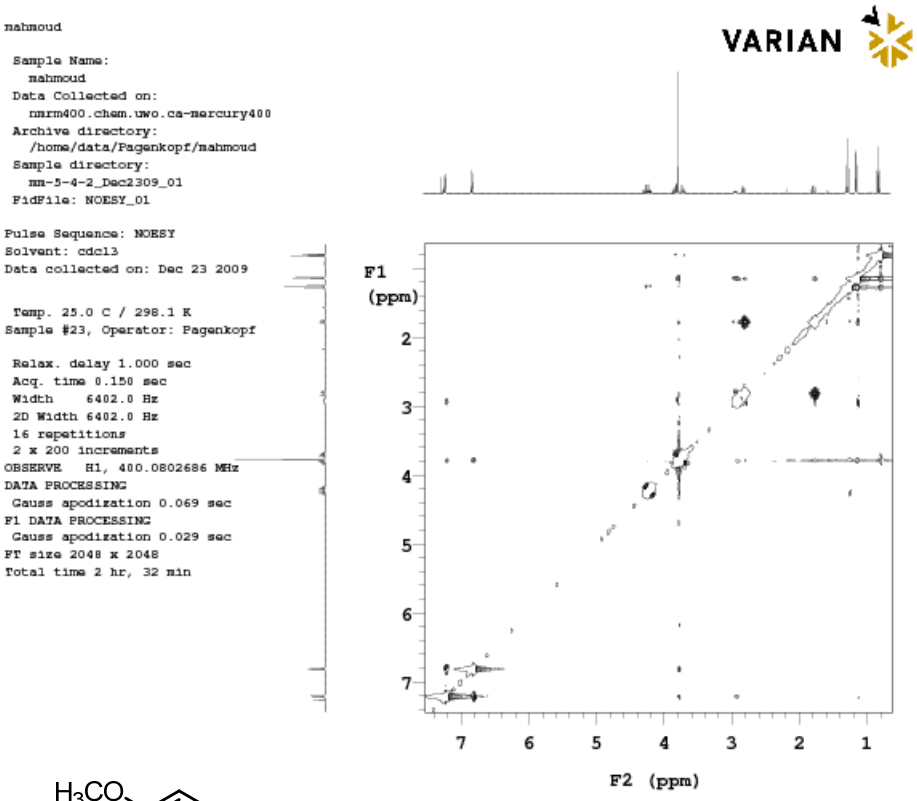

F1
(ppm)
2
3
4
5
6
7
7
6
5
4
3
2
1
F2 (ppm)
H3CO
H
CO2Me
CO2Me
H
F1
(ppm)
2.9
3.0
3.1
3.2
3.3
3.4
3.5
3.6
3.7
3.8
3.8
3.6
3.4
3.2
3.0
2.8
F2 (ppm)

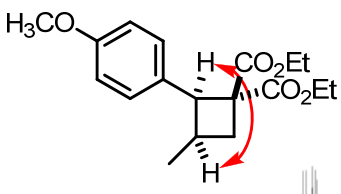
Diethyl 2-(4-methoxyphenyl)-3-methylcyclobutane-1,1-dicarboxylate (3.41d)

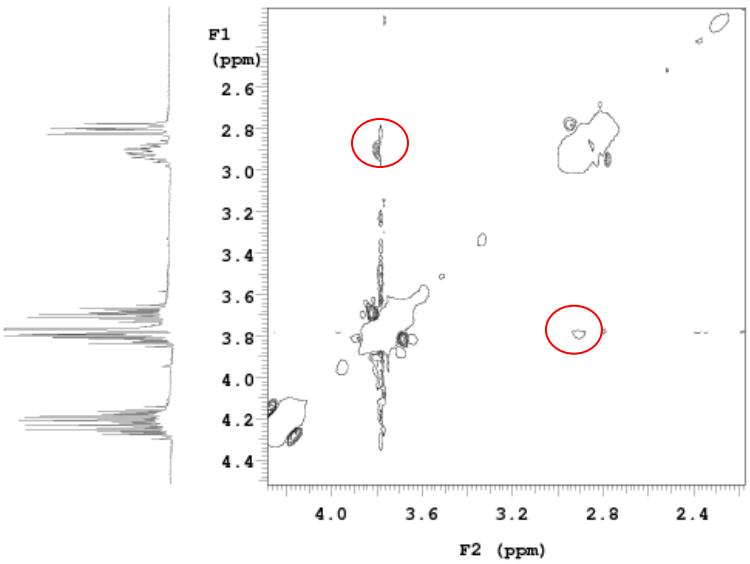



nahmoud
Sample Name:
nahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/nahmoud
Sample directory:
nm-5-4-2_Dec2309_01
FidFile: gHSQC_01
Pulse Sequence: gHSQC
Solvent: cdcl3
Data collected on: Dec 23 2009
Temp. 25.0 C / 298.1 K
Sample #23, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 17101.3 Hz
4 repetitions
2 x 128 increments
OBSERVE H1, 400.0802686 MHz
DECOUPLE C13, 100.6078086 MHz
Power 43 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.014 sec
FT size 2048 x 2048
Total time 23 min
VARIAN
F1
(ppm)
30
40
50
60
70
80
90
100
110
120
130
neg proj
pos proj
7
6
5
4
3
2
1
F2 (ppm)
F1
(ppm)
52
53
54
55
56
57
58
59
60
61
62
neg proj
pos proj
4.3
4.2
4.1
4.0
3.9
3.8
3.7
3.6
F2 (ppm)

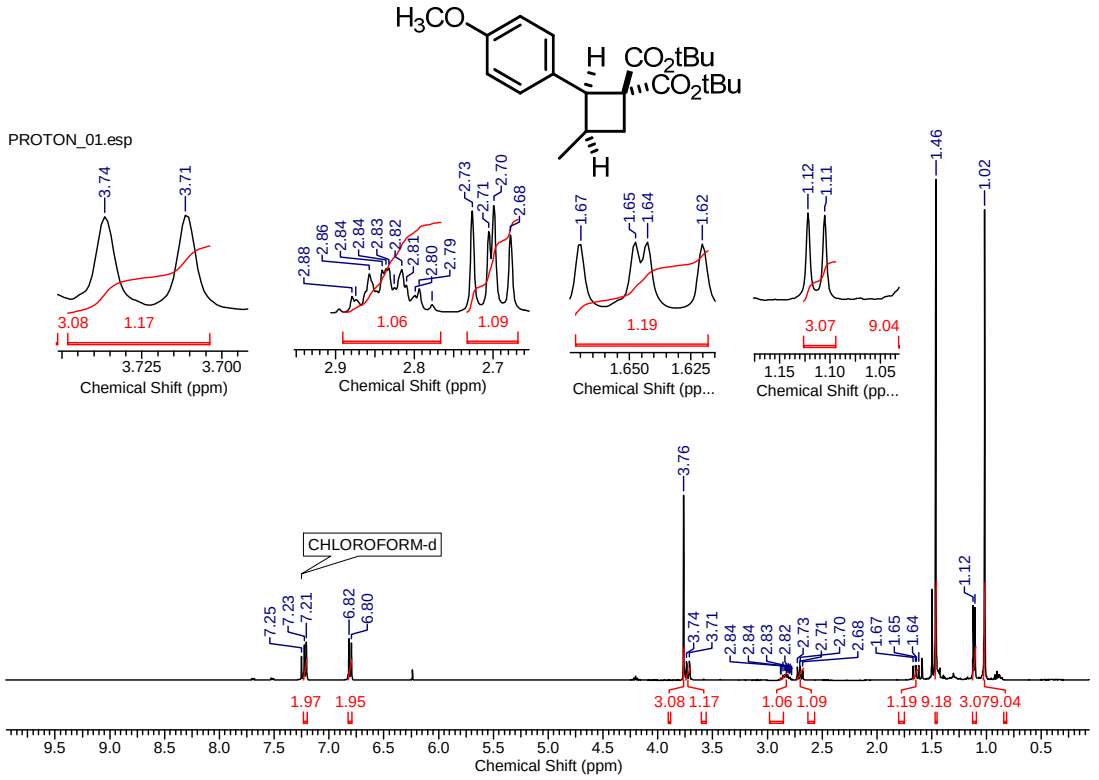

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-5-27-2_Jan1410_01
FidFile: gCOSY_01
Pulse Sequence: gCOSY
Solvent: cdcl3
Data collected on: Jan 14 2010
Temp. 25.0 C / 298.1 K
Sample #46, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
Single scan
128 increments
OBSERVE H1, 400.0802686 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sq. sine bell 0.020 sec
FT size 2048 x 2048
Total time 4 min 12 sec
VARIAN
F1 (ppm)
F2 (ppm)
F1 (ppm)
F2 (ppm)

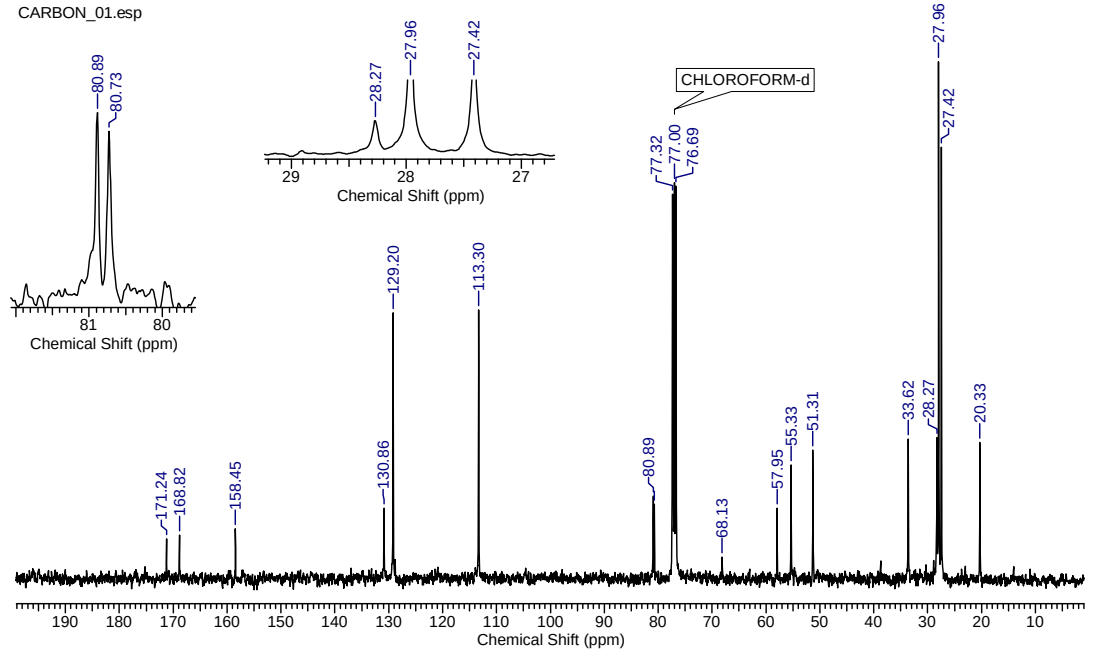

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-5-4-2_Dec2309_01
FidFile: NOESY_01
Pulse Sequence: NOESY
Solvent: cdcl3
Data collected on: Dec 23 2009
Temp. 25.0 C / 298.1 K
Sample #23, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
16 repetitions
2 x 200 increments
OBSERVE H1, 400.0802686 MHz
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.029 sec
FT size 2048 x 2048
Total time 2 hr, 32 min
VARIAN
F1 (ppm)
F2 (ppm)

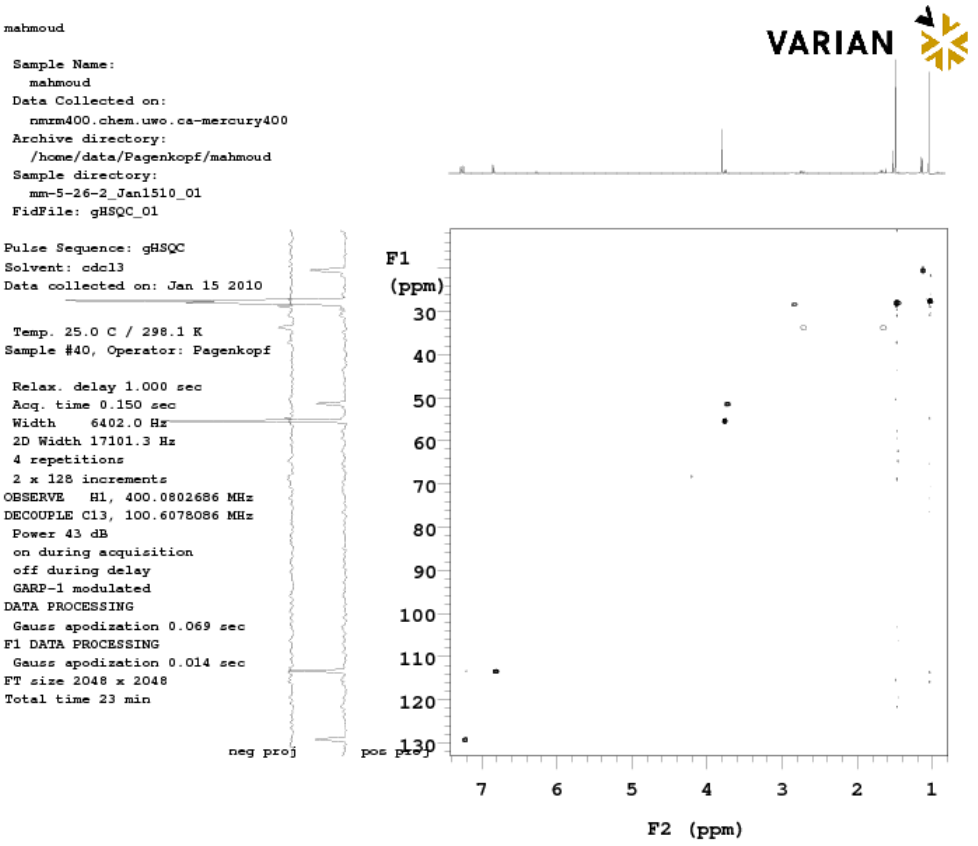

H3CO
H
CO2Et
CO2Et
H

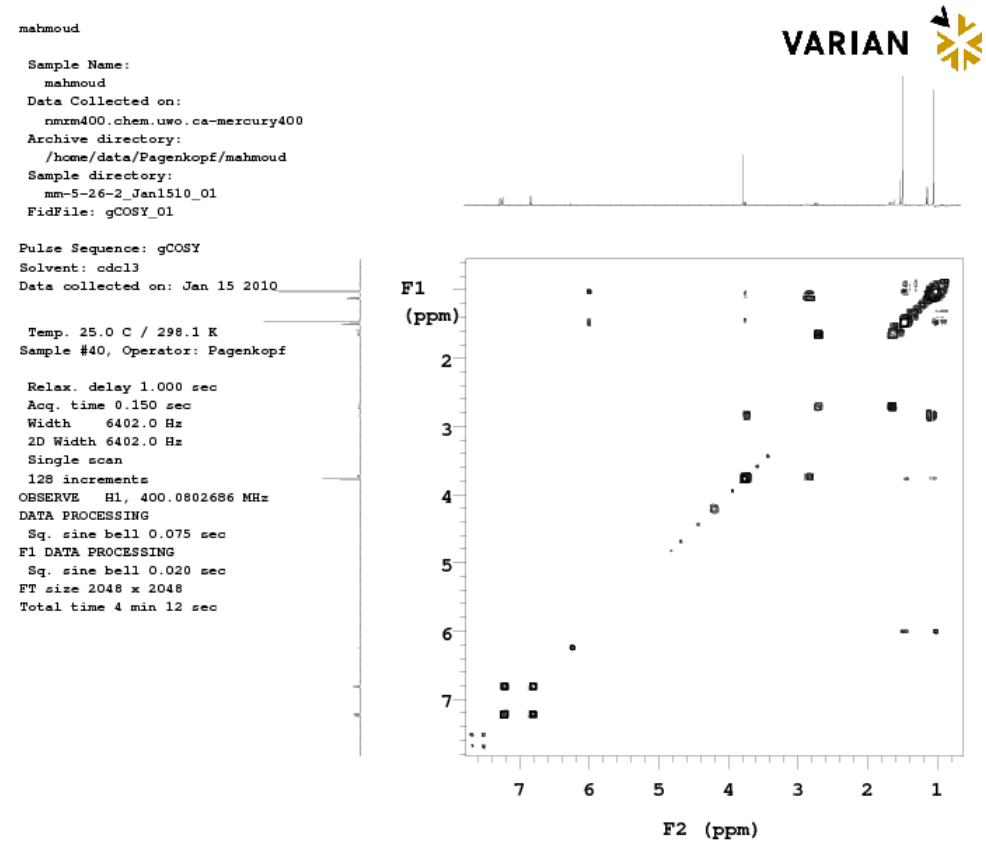

F1 (ppm)
F2 (ppm)

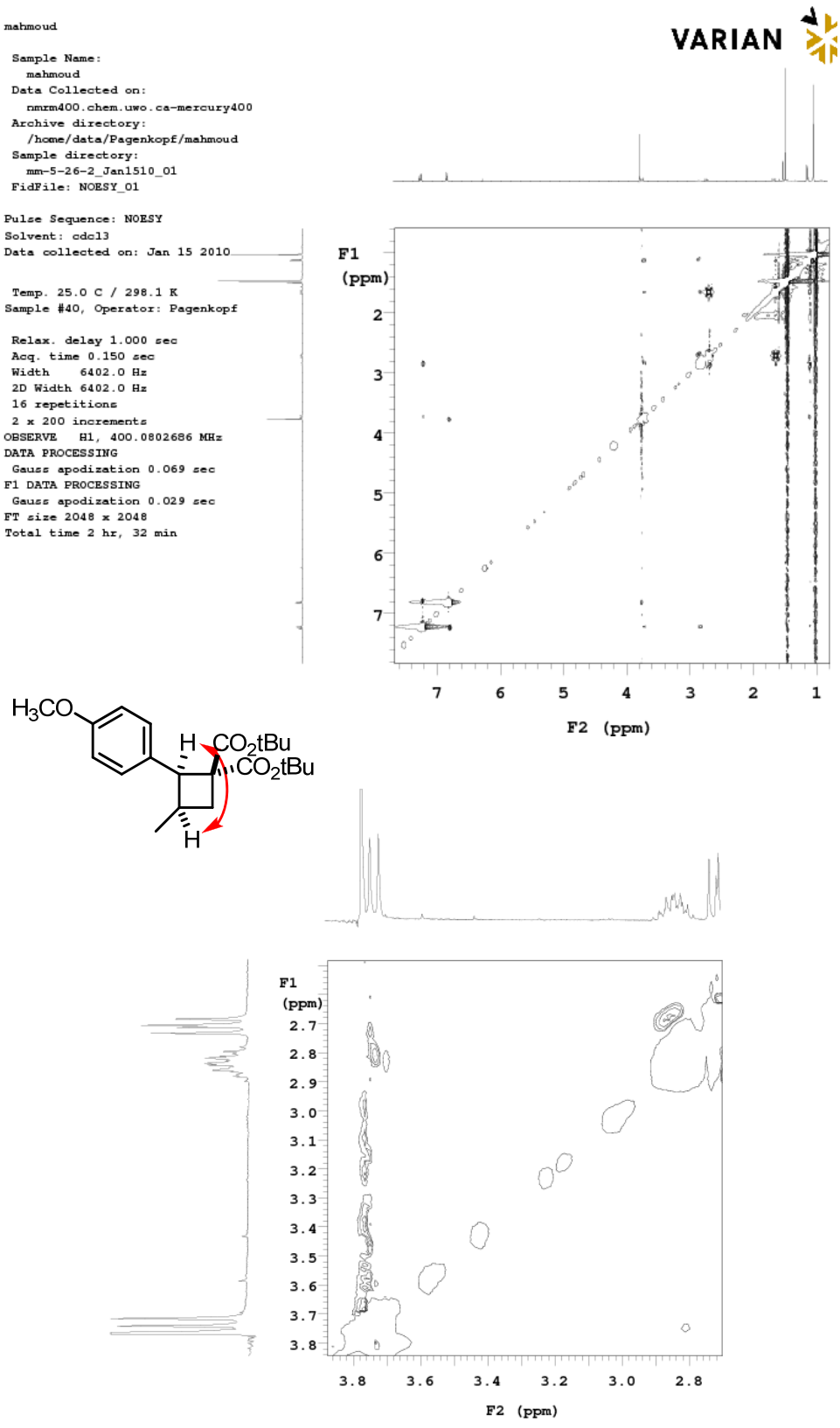
Di-tert-butyl 2-(4-methoxyphenyl)-3-methylcyclobutane-1,1-dicarboxylate(3.41e)



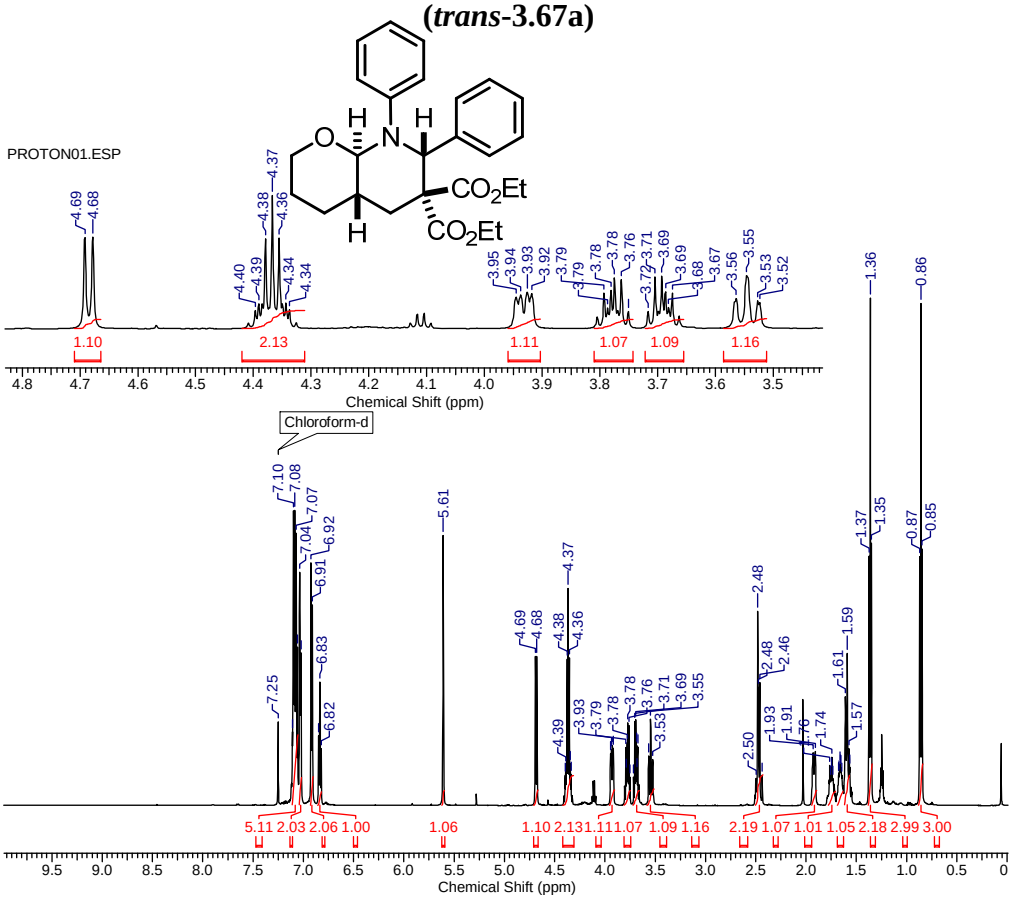


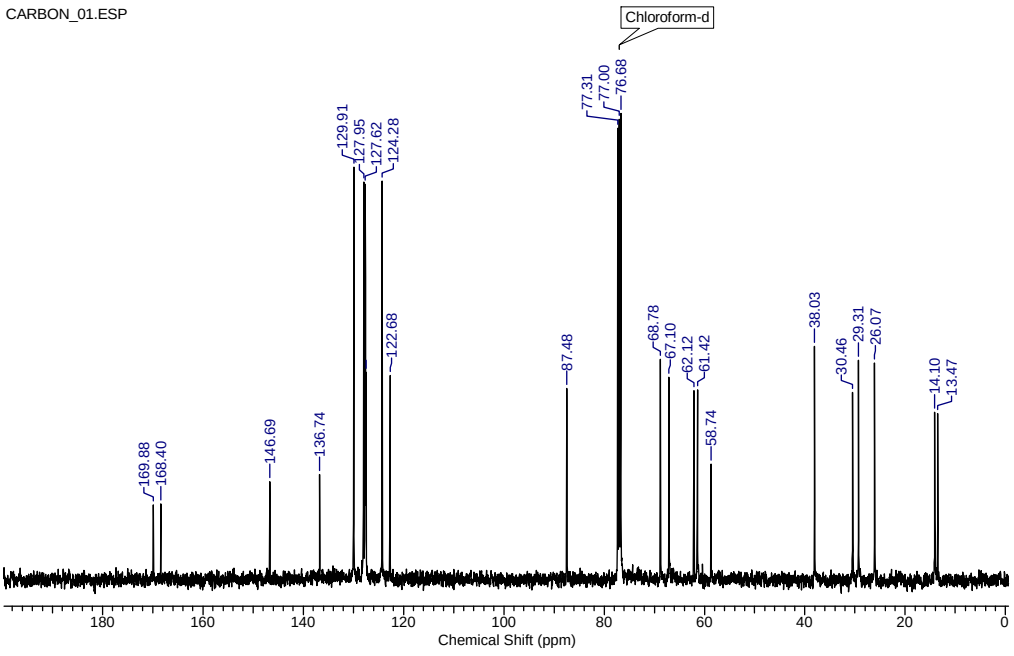

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-5-26-2_Jan1510_01
FidFile: gHSQC_01
Pulse Sequence: gHSQC
Solvent: cdcl3
Data collected on: Jan 15 2010
Temp. 25.0 C / 298.1 K
Sample #40, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 17101.3 Hz
4 repetitions
2 x 128 increments
OBSERVE H1, 400.0802686 MHz
DECOUPLE C13, 100.6078086 MHz
Power 43 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.014 sec
FT size 2048 x 2048
Total time 23 min
neg proj
pos proj
VARIAN
F1
(ppm)
30
40
50
60
70
80
90
100
110
120
130
7
6
5
4
3
2
1
F2 (ppm)

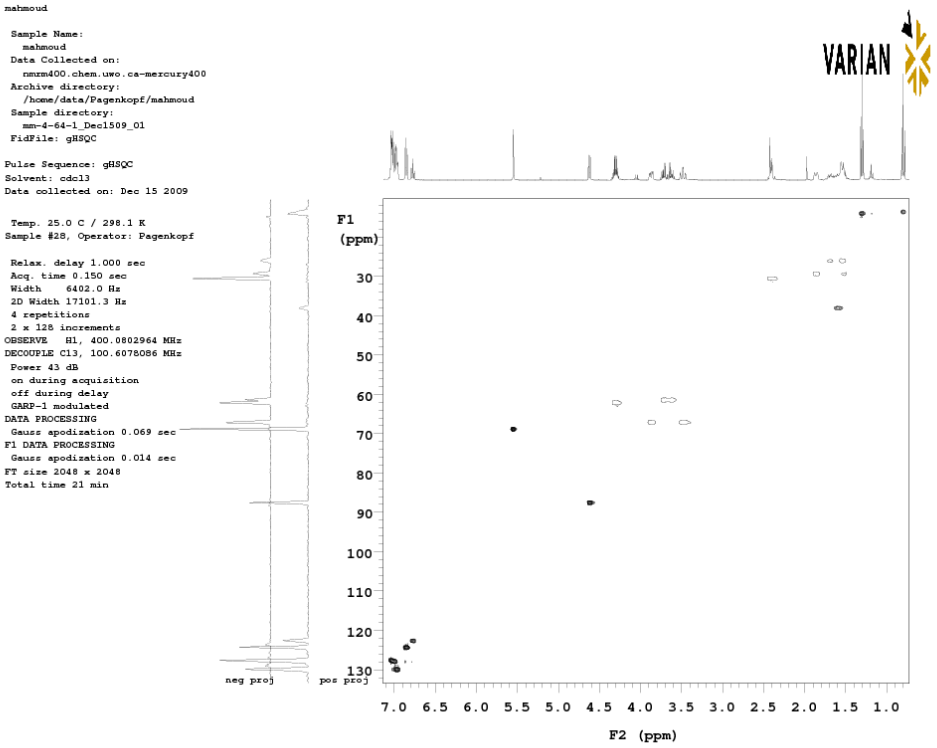

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-5-26-2_Jan1510_01
FidFile: gCOSY_01
Pulse Sequence: gCOSY
Solvent: cdcl3
Data collected on: Jan 15 2010
Temp. 25.0 C / 298.1 K
Sample #40, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
Single scan
128 increments
OBSERVE H1, 400.0802686 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sq. sine bell 0.020 sec
FT size 2048 x 2048
Total time 4 min 12 sec
VARIAN
F1
(ppm)
2
3
4
5
6
7
7
6
5
4
3
2
1
F2 (ppm)

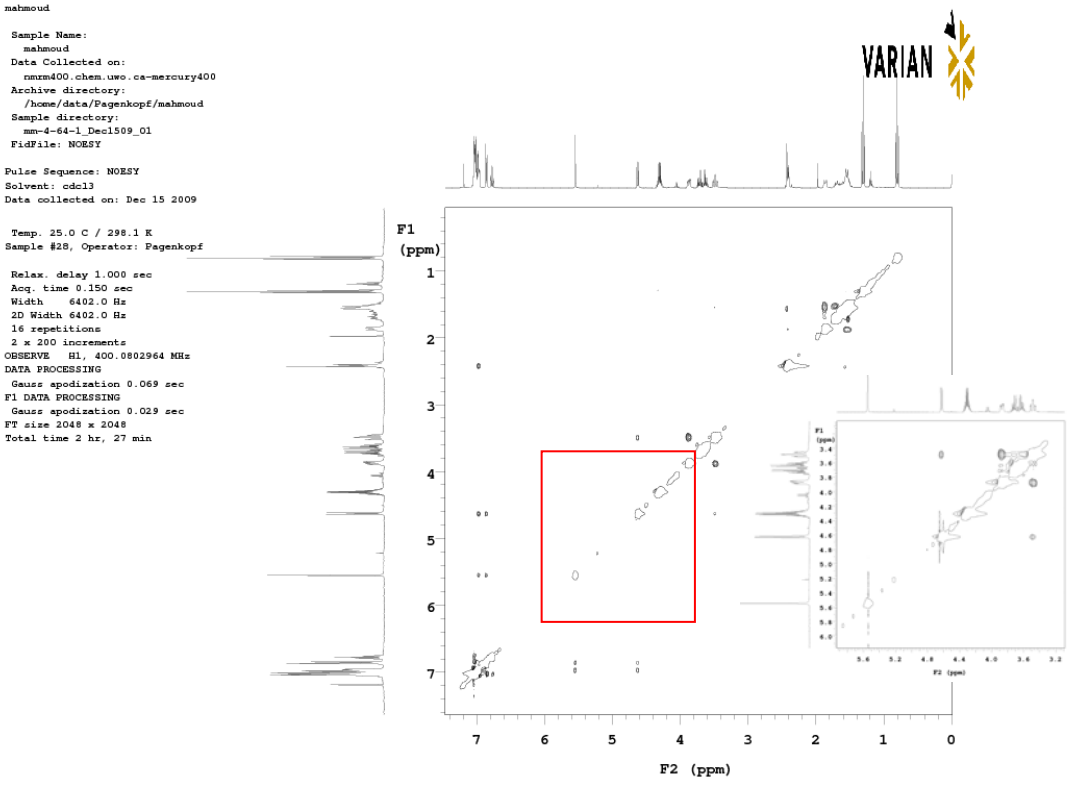

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-5-26-2_Jan1510_01
FidFile: NOESY_01
Pulse Sequence: NOESY
Solvent: cdcl3
Data collected on: Jan 15 2010
Temp. 25.0 C / 298.1 K
Sample #40, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
16 repetitions
2 x 200 increments
OBSERVE H1, 400.0802686 MHz
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.029 sec
FT size 2048 x 2048
Total time 2 hr, 32 min
VARIAN
F1 (ppm)
F2 (ppm)
H3CO
H
CO2tBu
CO2tBu
H

Diethyl 7,8-diphenylhexahydro-2*H*-pyrano[2,3-*b*]pyridine-6,6(7*H*)-dicarboxylate (*trans*-3.67a)

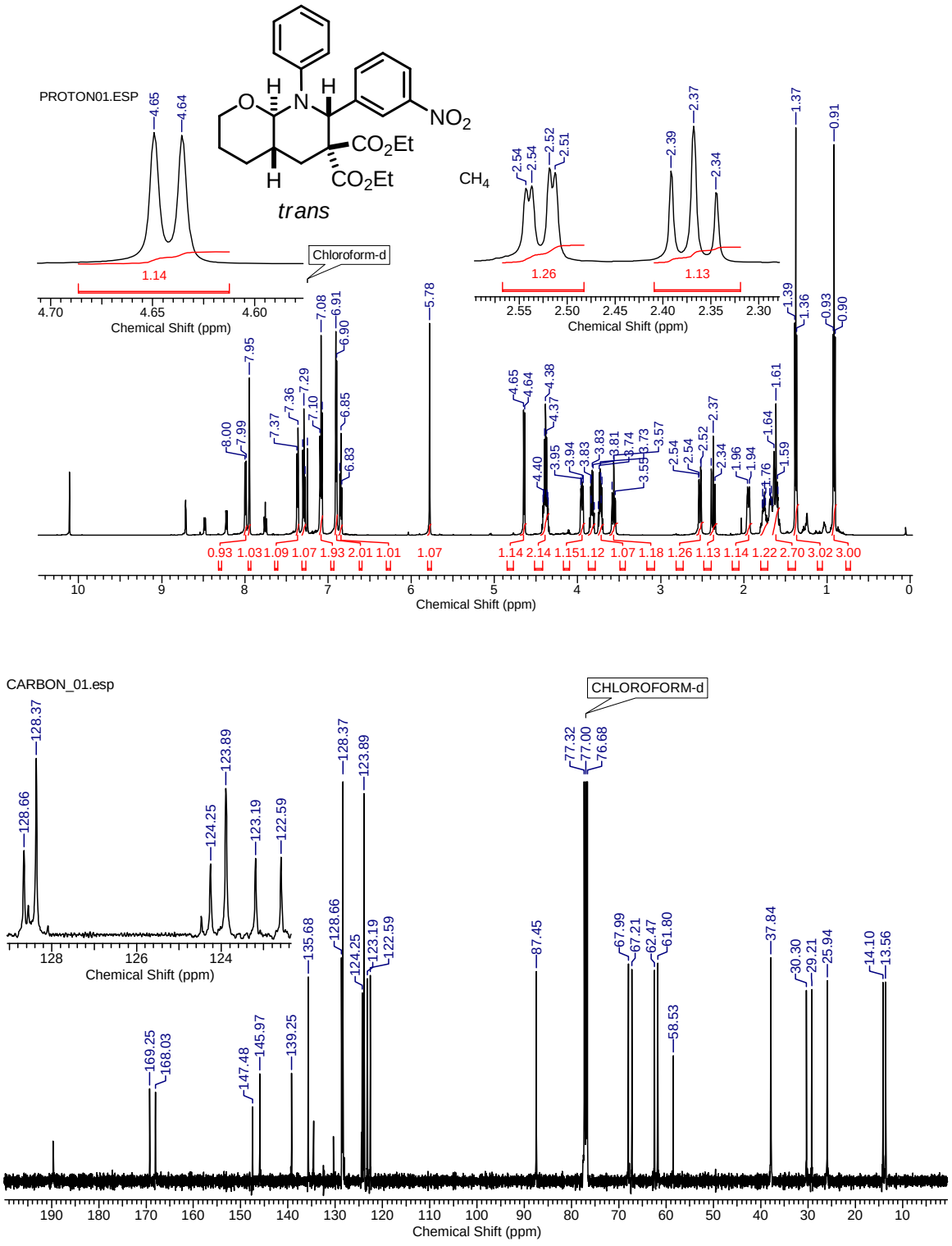





mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-4-64-1_Dec1509_01
FidFile: gHSQC
Pulse Sequence: gHSQC
Solvent: cdcl3
Data collected on: Dec 15 2009
Temp. 25.0 C / 298.1 K
Sample #28, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 17101.3 Hz
4 repetitions
2 x 128 increments
OBSERVE H1, 400.0802964 MHz
DECOUPLE C13, 100.6078086 MHz
Power 43 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.014 sec
FT size 2048 x 2048
Total time 21 min
VARIAN
F1 (ppm)
neg proj
pos proj
F2 (ppm)


mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-4-64-1_Dec1509_01
FidFile: NOESY
Pulse Sequence: NOESY
Solvent: cdcl3
Data collected on: Dec 15 2009
Temp. 25.0 C / 298.1 K
Sample #28, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
16 repetitions
2 x 200 increments
OBSERVE H1, 400.0802964 MHz
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.029 sec
FT size 2048 x 2048
Total time 2 hr, 27 min
VARIAN
F1 (ppm)
F2 (ppm)

Diethyl 7-(3-nitrophenyl)-8 phenylhexahydro-2*H*-pyrano[2,3-*b*]pyridine-6,6(7*H*)-dicarboxylate (*trans*-3.67b)[2]



[2] Product contaminated with 20% 3-nitrobenzaldehyde arising from aldimine hydrolysis during flash chromatography.

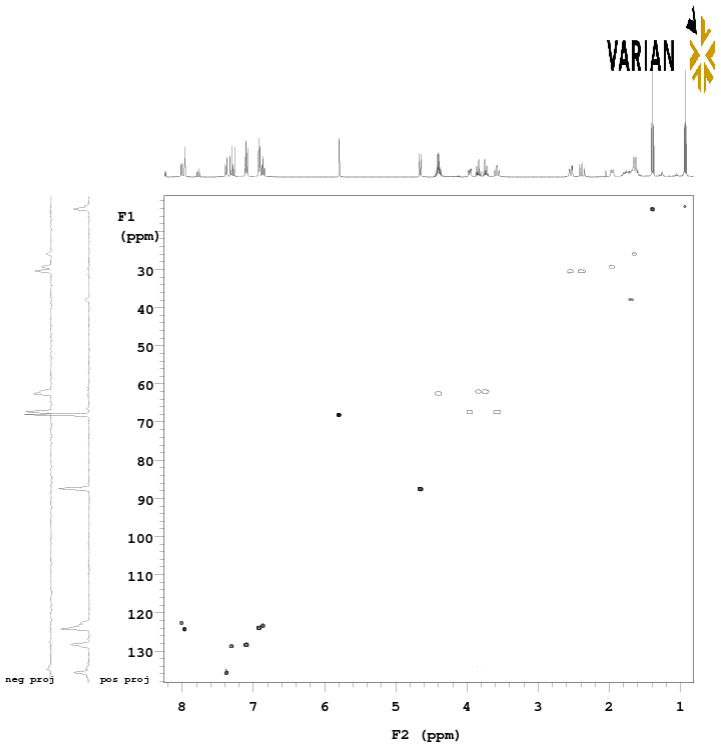
mahmoud

Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-5-1B-3_Dec2009_02
FidFile: gHSQC

Pulse Sequence: gHSQC
Solvent: cdcl3
Data collected on: Dec 20 2009

Temp. 25.0 C / 298.1 K
Sample #14, Operator: Pagenkopf

Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 17101.3 Hz
4 repetitions
2 x 128 increments
OBSERVE H1, 400.0802686 MHz
DECOUPLE C13, 100.6078086 MHz
Power 43 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.014 sec
FT size 2048 x 2048
Total time 21 min



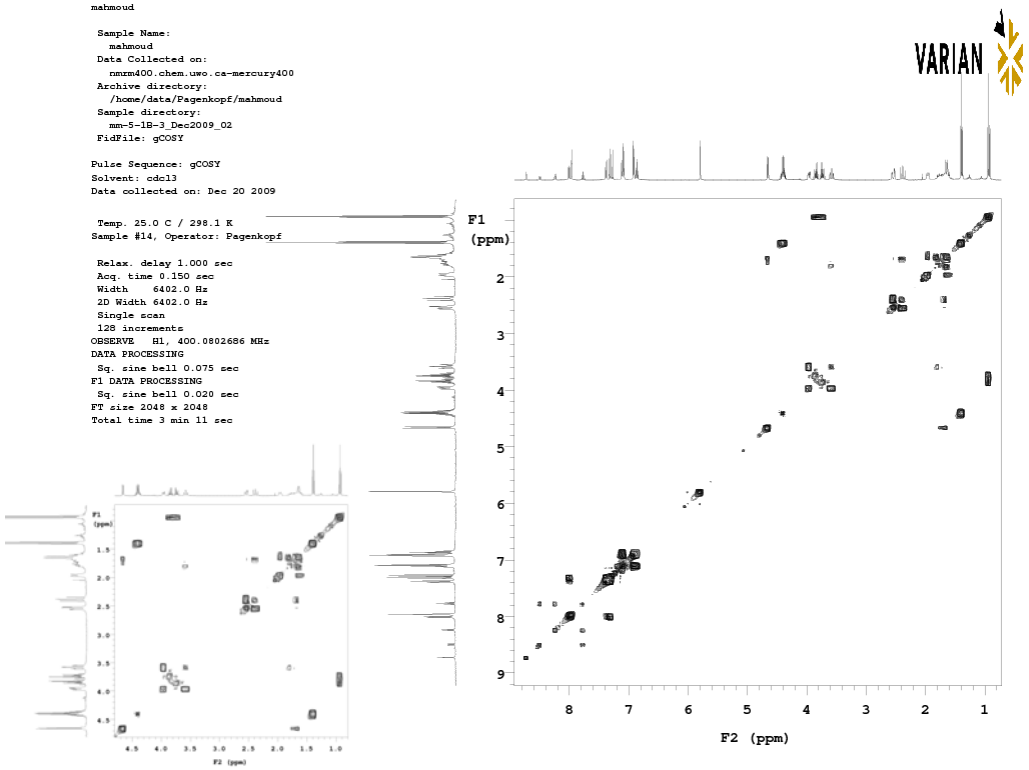
mahmoud

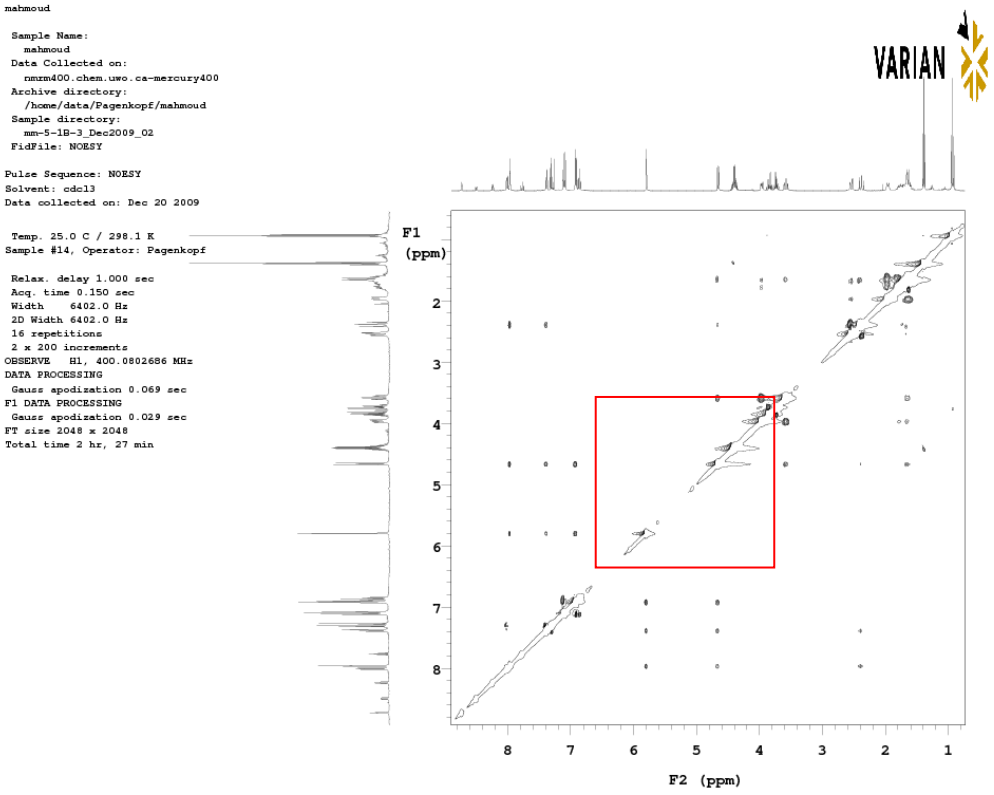
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-5-1B-3_Dec2009_02
FidFile: gCOSY

Pulse Sequence: gCOSY
Solvent: cdcl3
Data collected on: Dec 20 2009

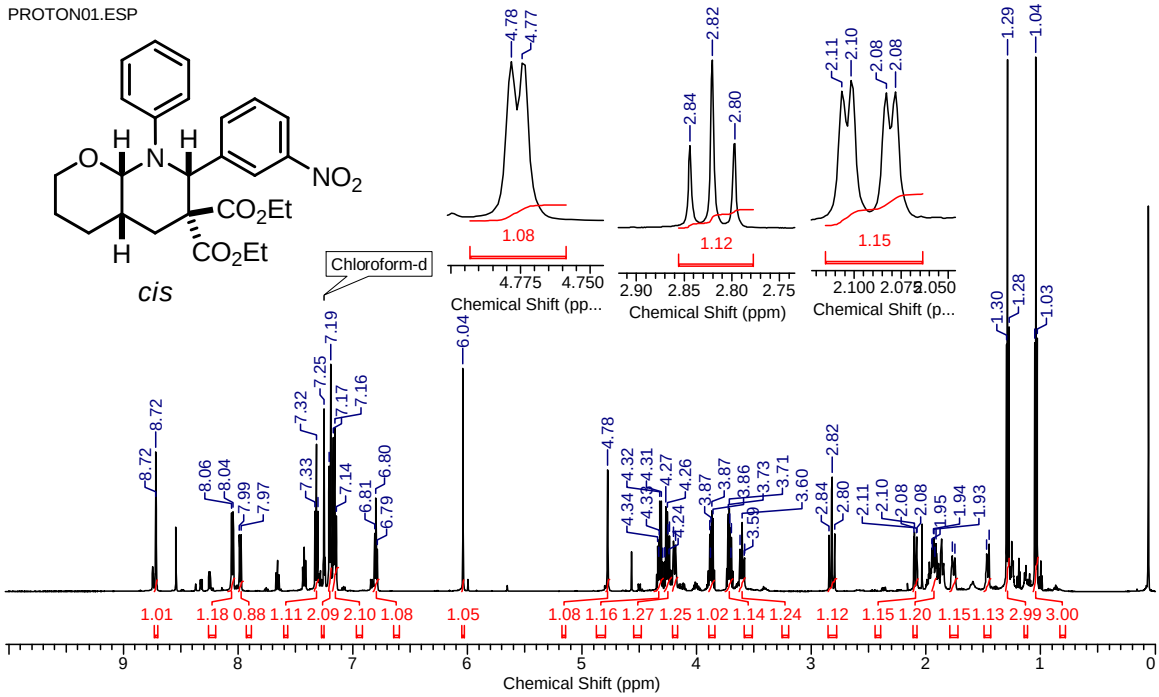
Temp. 25.0 C / 298.1 K
Sample #14, Operator: Pagenkopf

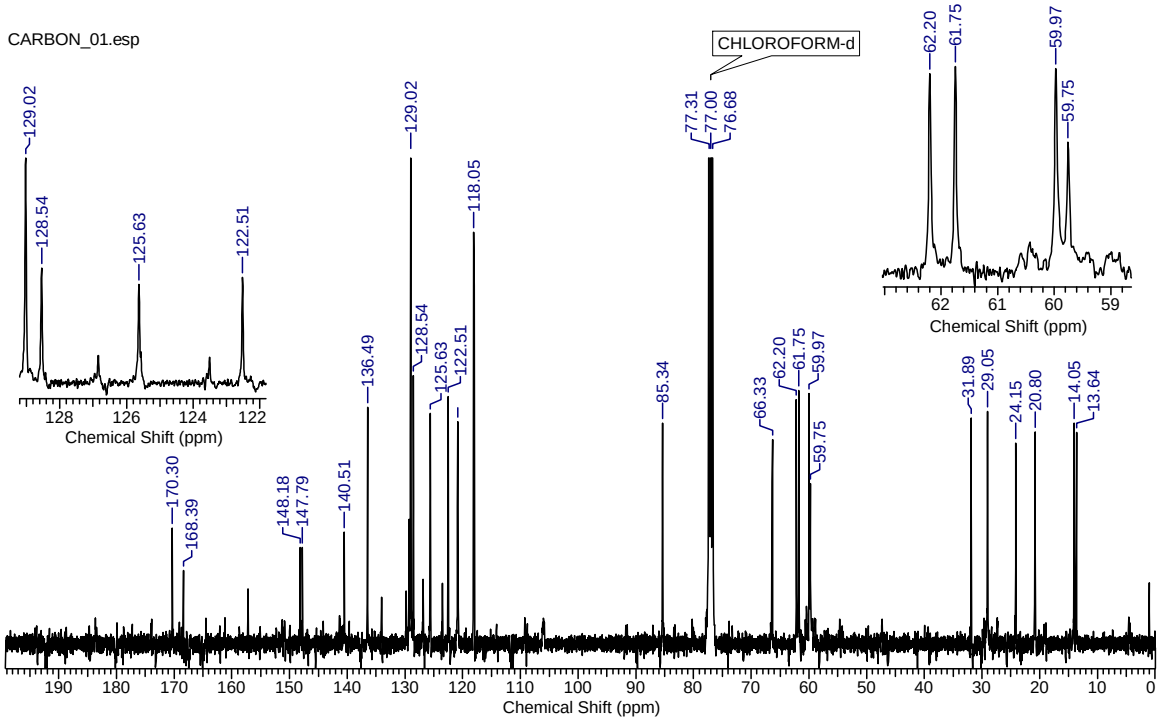
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
Single scan
128 increments
OBSERVE H1, 400.0802686 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sq. sine bell 0.020 sec
FT size 2048 x 2048
Total time 3 min 11 sec



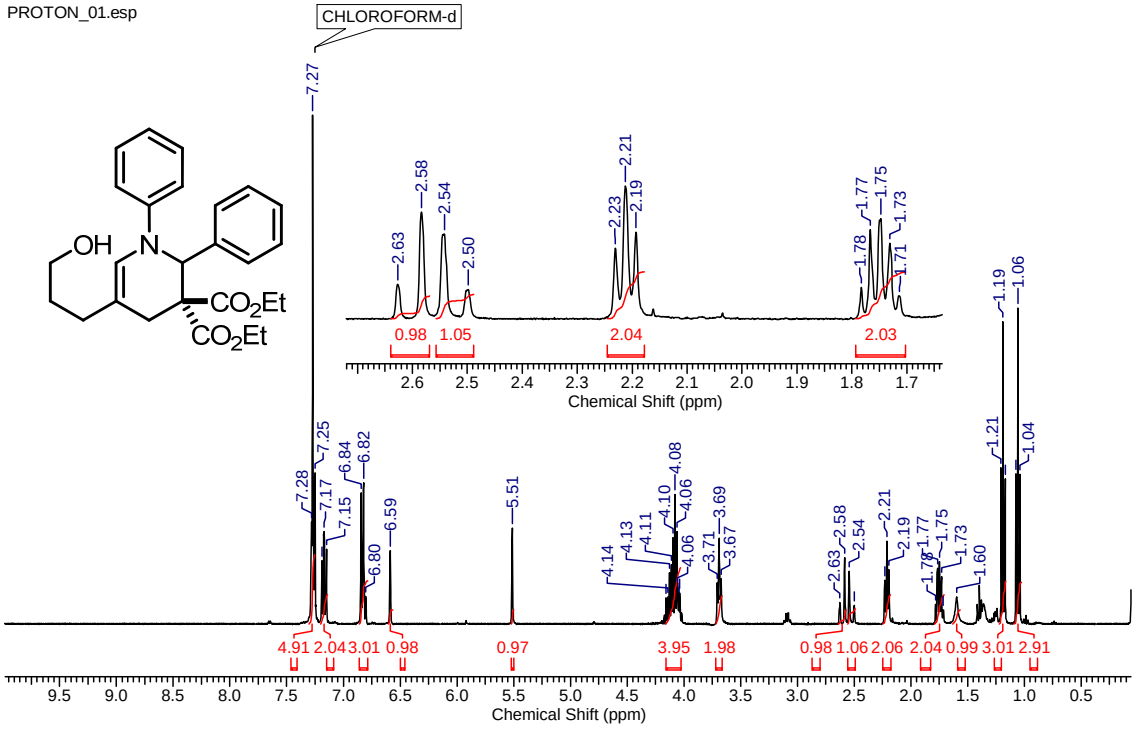

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-5-1B-3_Dec2009_02
FidFile: NOESY
Pulse Sequence: NOESY
Solvent: cdcl3
Data collected on: Dec 20 2009
Temp. 25.0 C / 298.1 K
Sample #14, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
16 repetitions
2 x 200 increments
OBSERVE H1, 400.0802686 MHz
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.029 sec
FT size 2048 x 2048
Total time 2 hr, 27 min
VARIAN
F1 (ppm)
F2 (ppm)

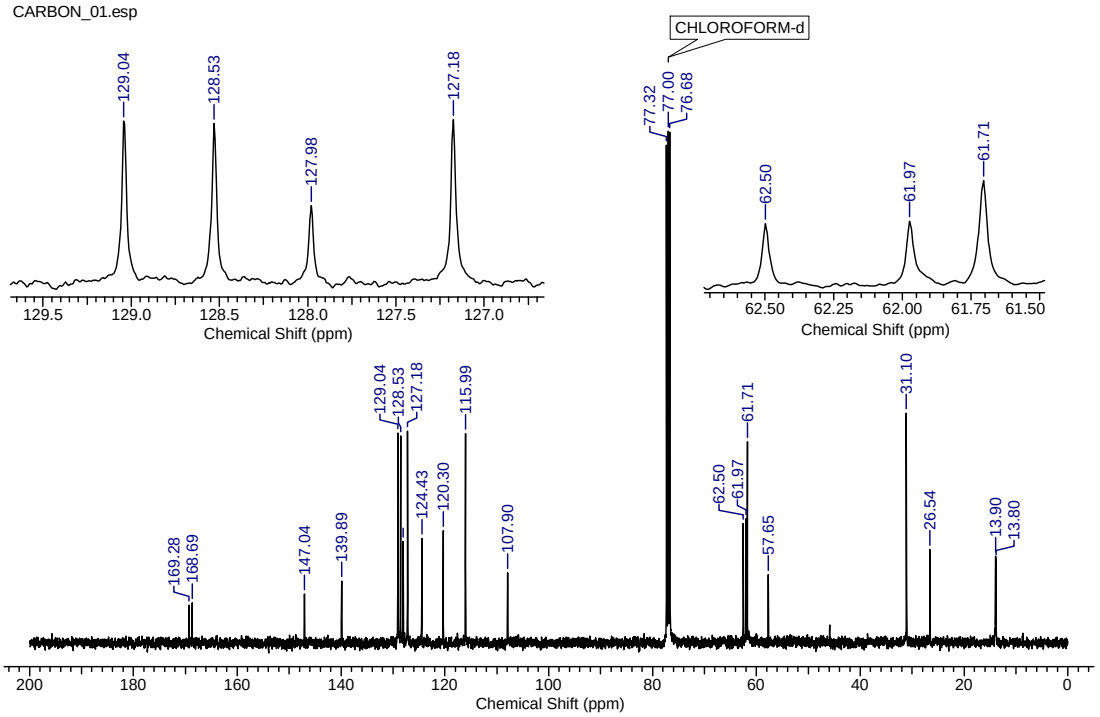
Diethyl 7-(3-nitrophenyl)-8 phenylhexahydro-2*H*-pyrano[2,3-*b*]pyridine-6,6(7*H*)-dicarboxylate (*cis*-3.67b)

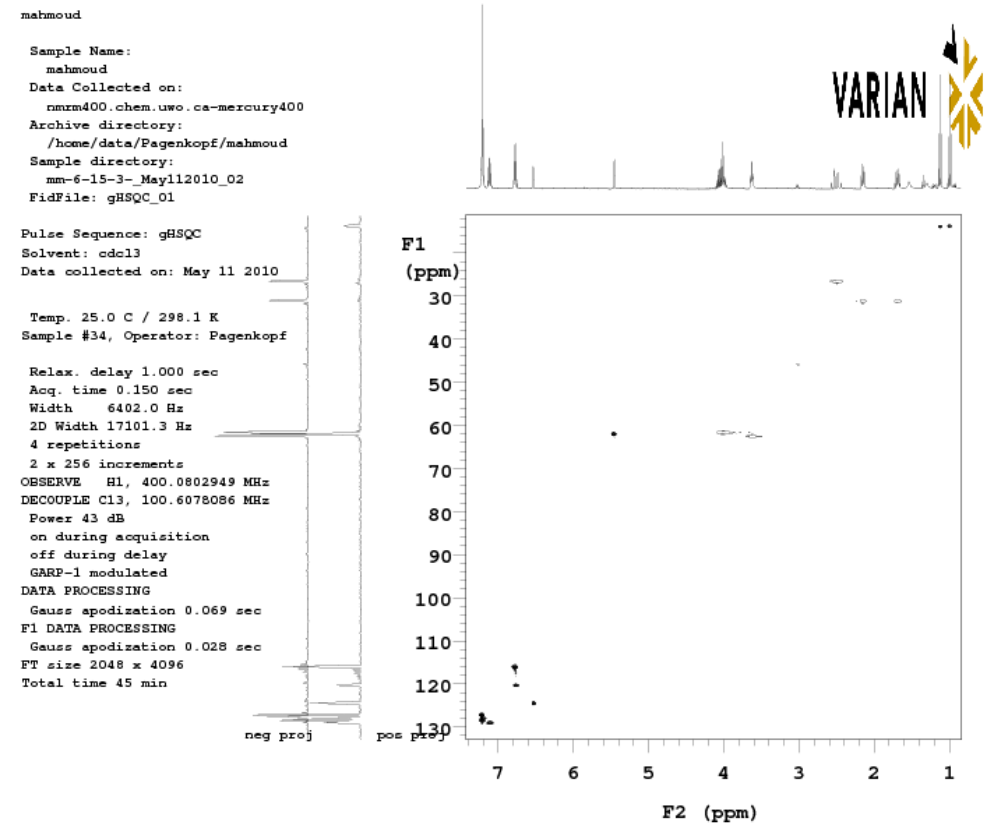


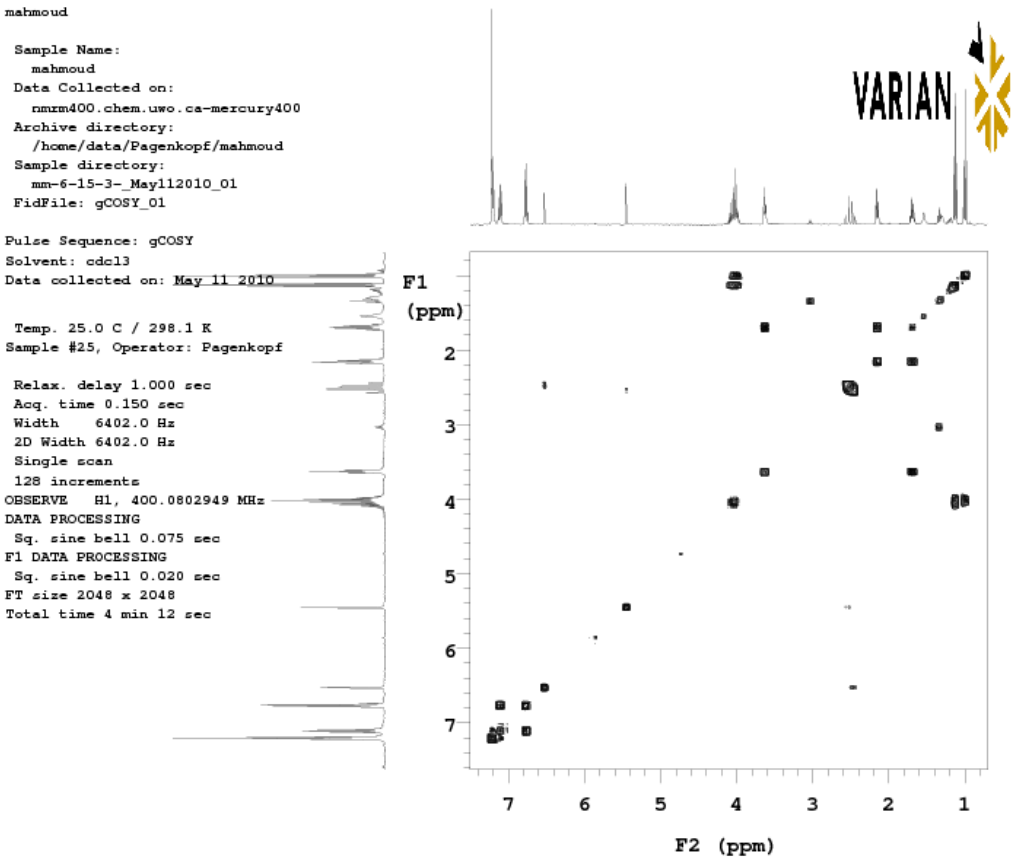


Diethyl 5-(3-hydroxypropyl)-1,2-diphenyl-1,2-dihydropyridine-3,3(4*H*)-dicarboxylate (3.68a)

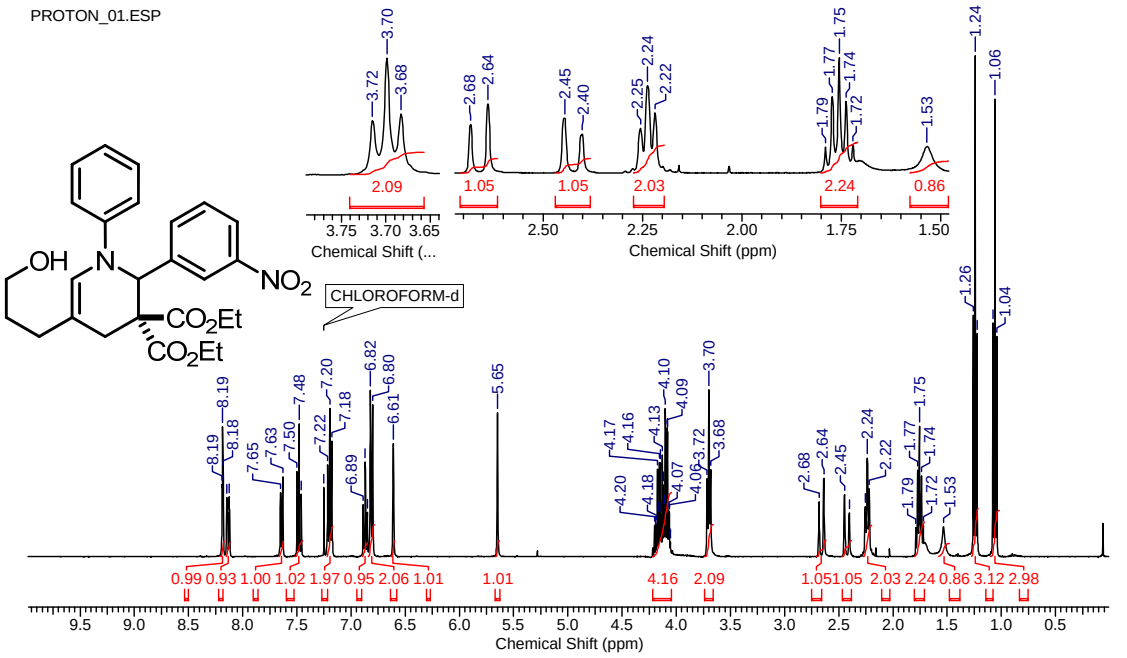


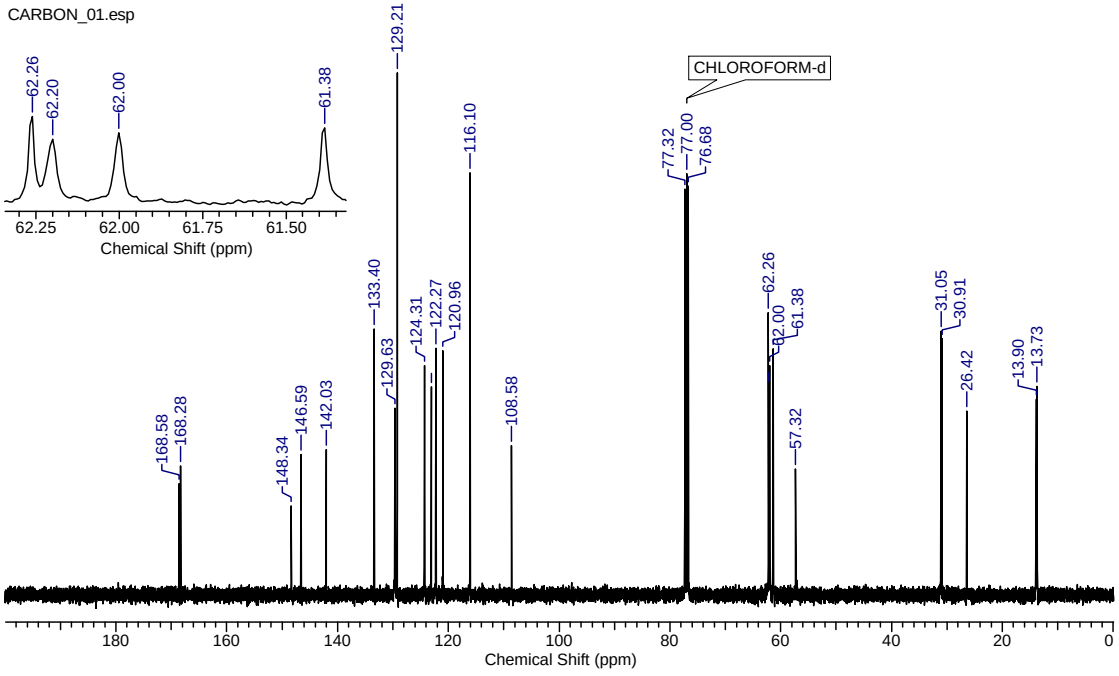


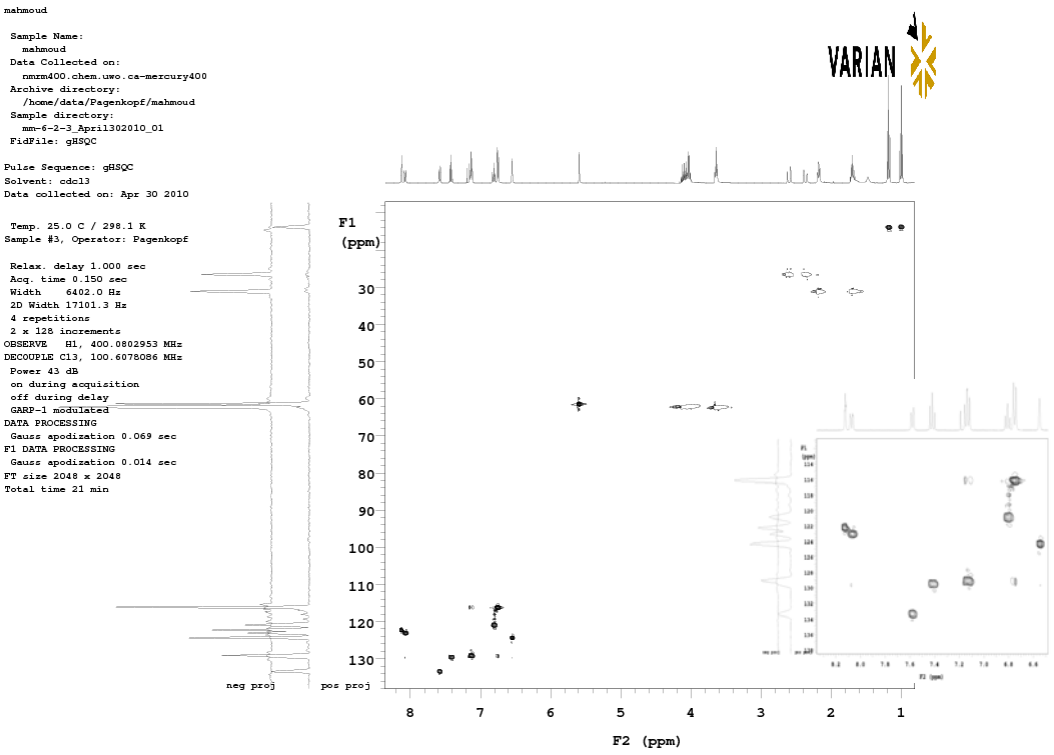

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-6-15-3-_May112010_02
FidFile: gHSQC_01
Pulse Sequence: gHSQC
Solvent: cdcl3
Data collected on: May 11 2010
Temp. 25.0 C / 298.1 K
Sample #34, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 17101.3 Hz
4 repetitions
2 x 256 increments
OBSERVE H1, 400.0802949 MHz
DECOUPLE C13, 100.6078086 MHz
Power 43 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.028 sec
FT size 2048 x 4096
Total time 45 min
VARIAN
F1
(ppm)
30
40
50
60
70
80
90
100
110
120
130
neg proj
pos proj
7
6
5
4
3
2
1
F2 (ppm)

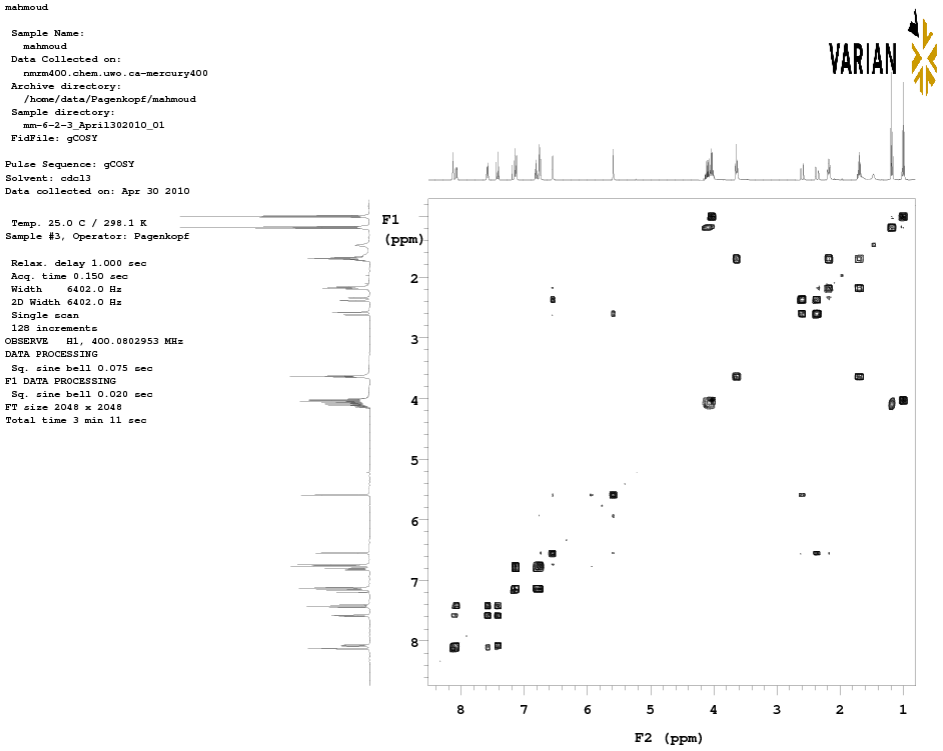

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-6-15-3-_May112010_01
FidFile: gCOSY_01
Pulse Sequence: gCOSY
Solvent: cdcl3
Data collected on: May 11 2010
Temp. 25.0 C / 298.1 K
Sample #25, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
Single scan
128 increments
OBSERVE H1, 400.0802949 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sq. sine bell 0.020 sec
FT size 2048 x 2048
Total time 4 min 12 sec
VARIAN
F1
(ppm)
2
3
4
5
6
7
7
6
5
4
3
2
1
F2 (ppm)

Diethyl 5-(3-hydroxypropyl)-2-(3-nitrophenyl)-1-phenyl-1,2-dihydropyridine-3,3(4*H*)-dicarboxylate (3.68b):

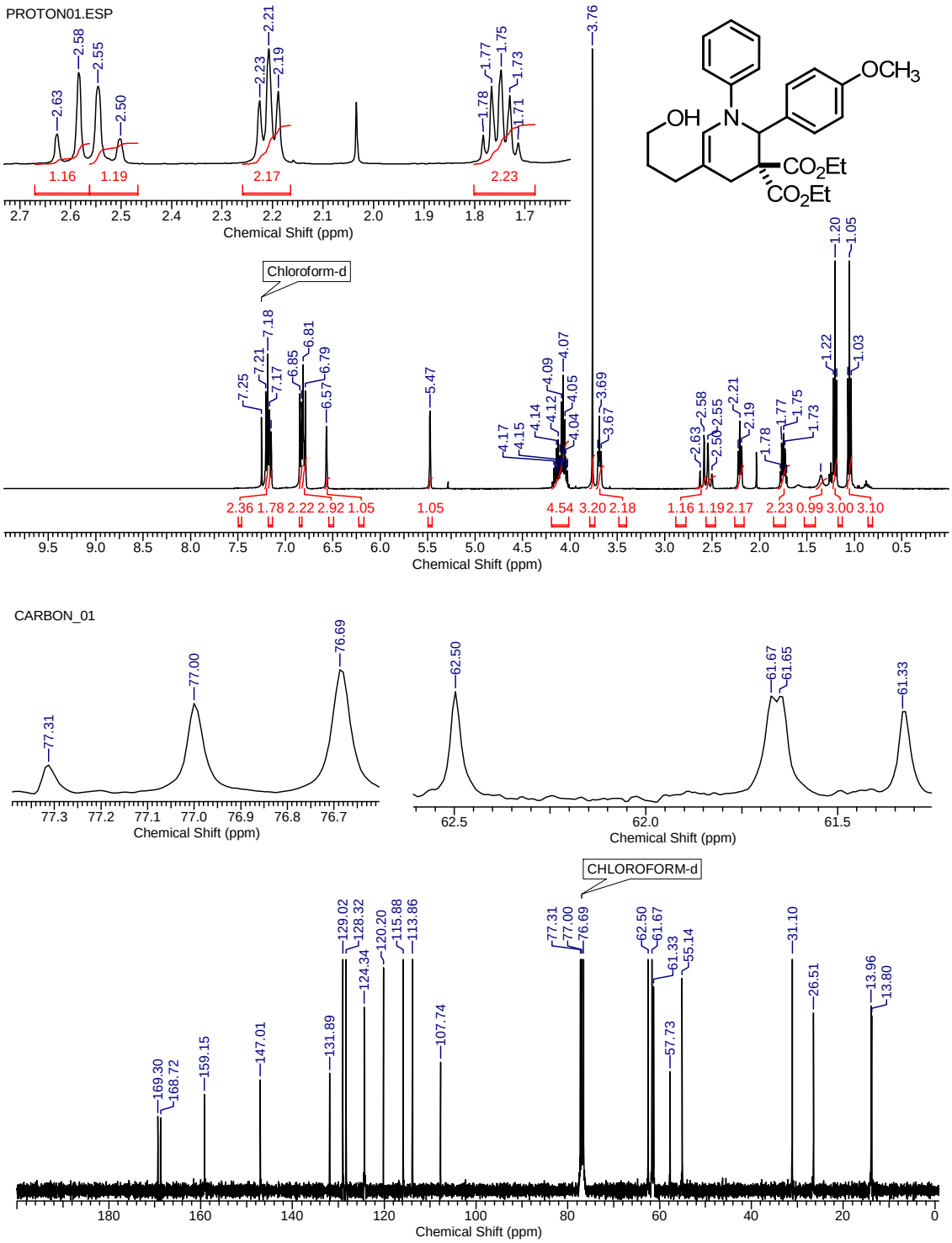


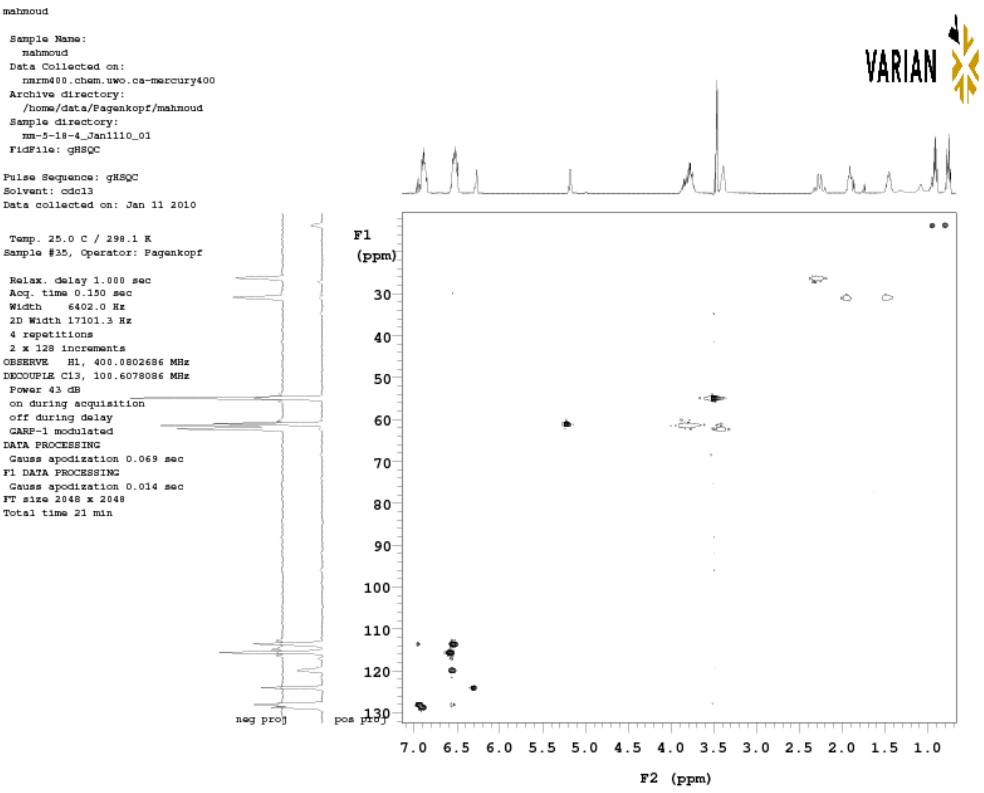


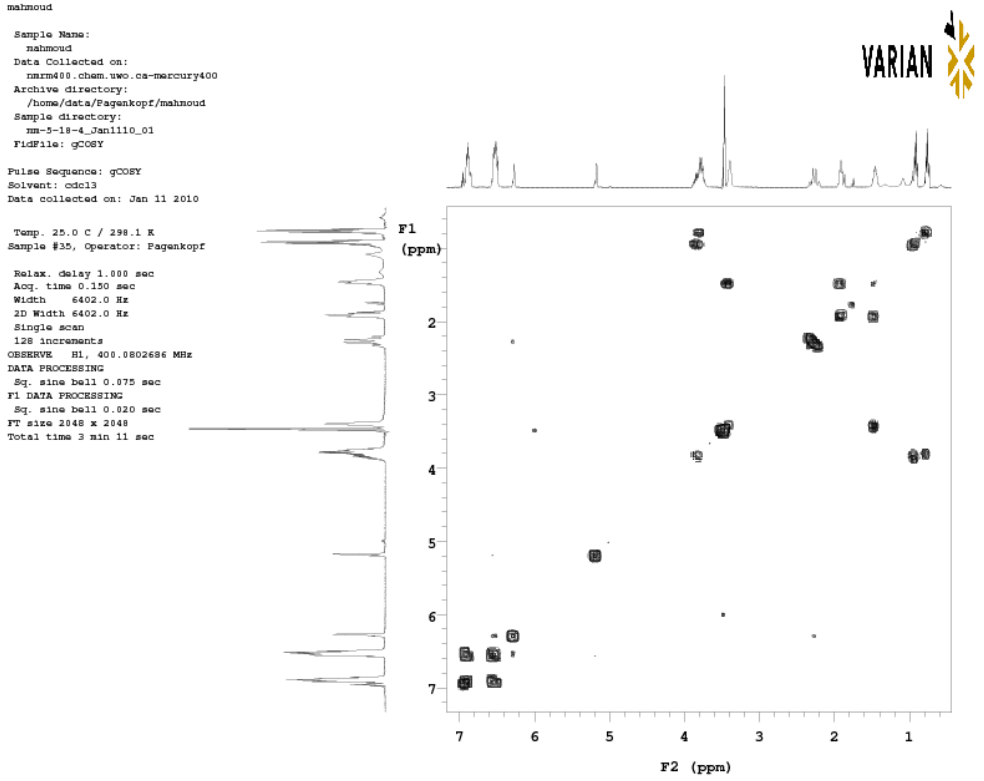

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-6-2-3_April302010_01
FidFile: gHSQC
Pulse Sequence: gHSQC
Solvent: cdcl3
Data collected on: Apr 30 2010
Temp. 25.0 C / 298.1 K
Sample #3, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 17101.3 Hz
4 repetitions
2 x 128 increments
OBSERVE H1, 400.0802953 MHz
DECOUPLE C13, 100.6078086 MHz
Power 43 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.014 sec
FT size 2048 x 2048
Total time 21 min
VARIAN
F1
(ppm)
neg proj
pos proj
F2 (ppm)


mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-6-2-3_April302010_01
FidFile: gCOSY
Pulse Sequence: gCOSY
Solvent: cdcl3
Data collected on: Apr 30 2010
Temp. 25.0 C / 298.1 K
Sample #3, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
Single scan
128 increments
OBSERVE H1, 400.0802953 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sq. sine bell 0.020 sec
FT size 2048 x 2048
Total time 3 min 11 sec
VARIAN
F1
(ppm)
F2 (ppm)

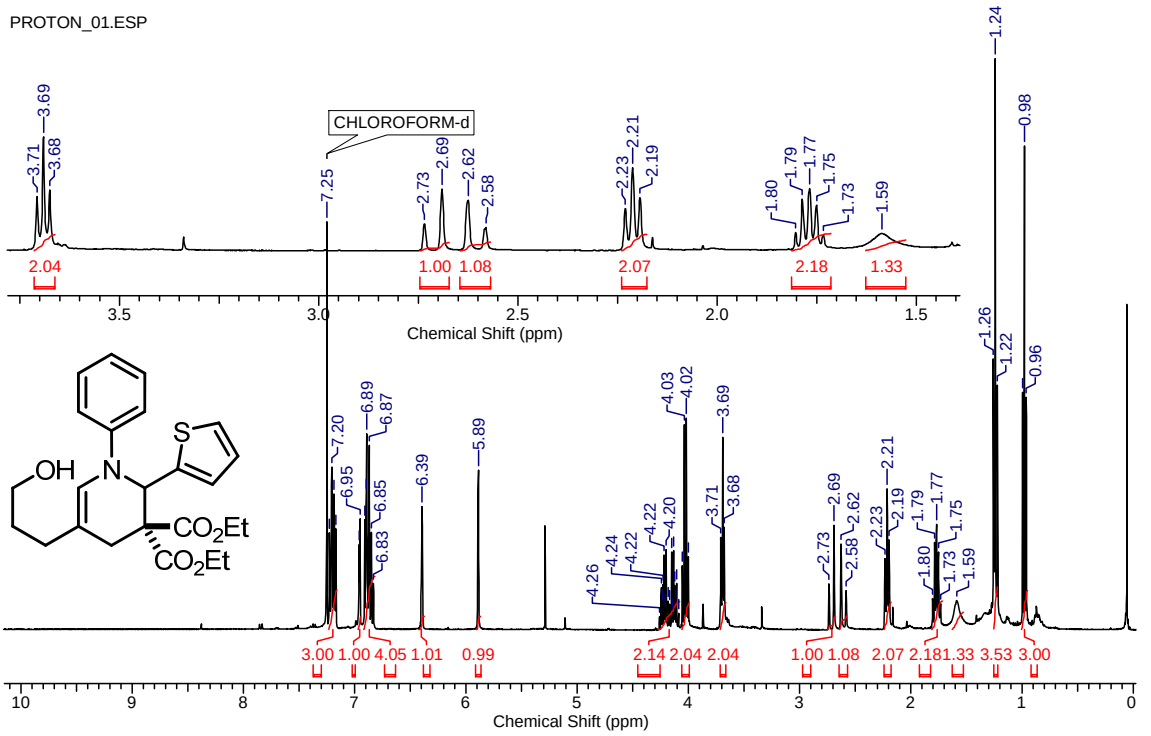
Diethyl 5-(3-hydroxypropyl)-2-(4-methoxyphenyl)-1-phenyl-1,2-dihydropyridine-3,3(4*H*)-dicarboxylate (3.68c)

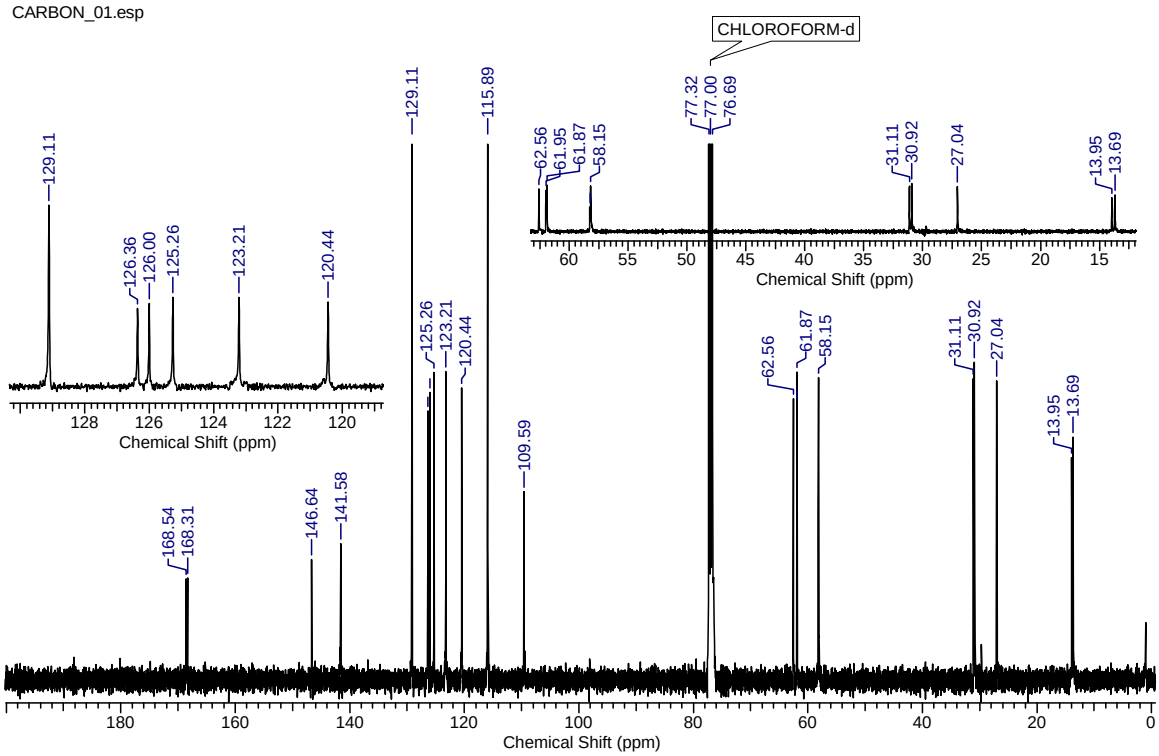


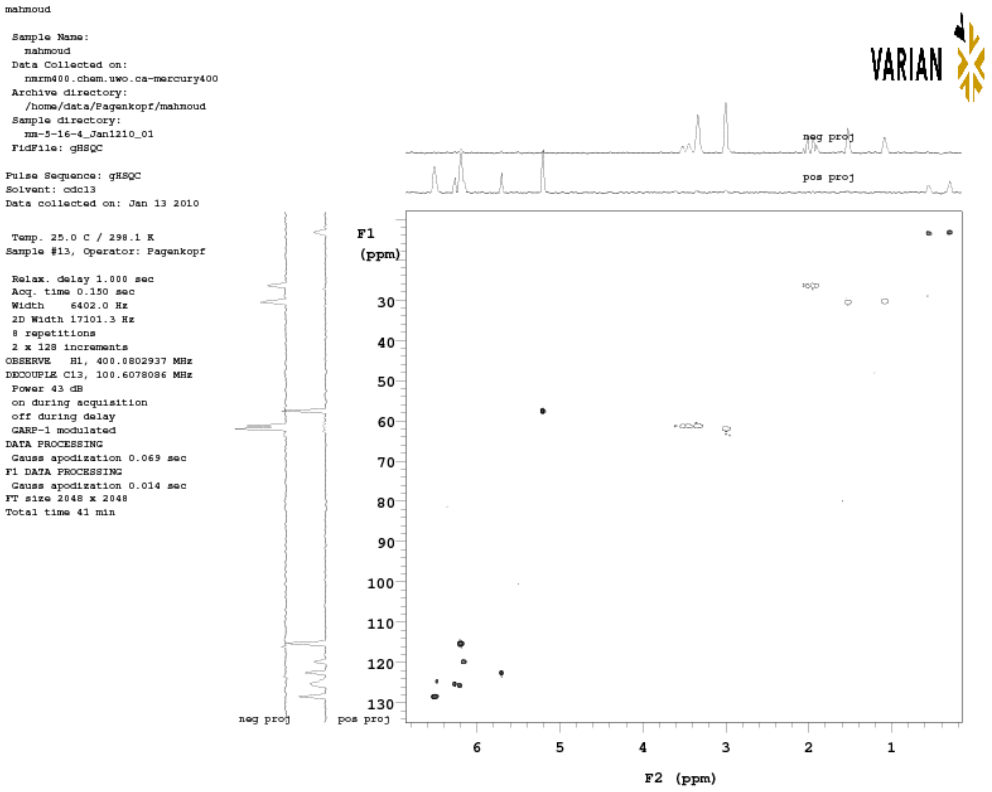

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
nm-5-18-4_Jan1110_01
FidFile: gHSQC
Pulse Sequence: gHSQC
Solvent: cdcl3
Data collected on: Jan 11 2010
Temp. 25.0 C / 298.1 K
Sample #35, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 17101.3 Hz
4 repetitions
2 x 128 increments
OBSERVE H1, 400.0802686 MHz
DECOUPLE C13, 100.6078086 MHz
Power 43 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.014 sec
FT size 2048 x 2048
Total time 21 min
VARIAN
F1
(ppm)
neg proj
pos proj
F2 (ppm)


mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
nm-5-18-4_Jan1110_01
FidFile: gCOSY
Pulse Sequence: gCOSY
Solvent: cdcl3
Data collected on: Jan 11 2010
Temp. 25.0 C / 298.1 K
Sample #35, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
Single scan
128 increments
OBSERVE H1, 400.0802686 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sq. sine bell 0.020 sec
FT size 2048 x 2048
Total time 3 min 11 sec
VARIAN
F1
(ppm)
F2 (ppm)

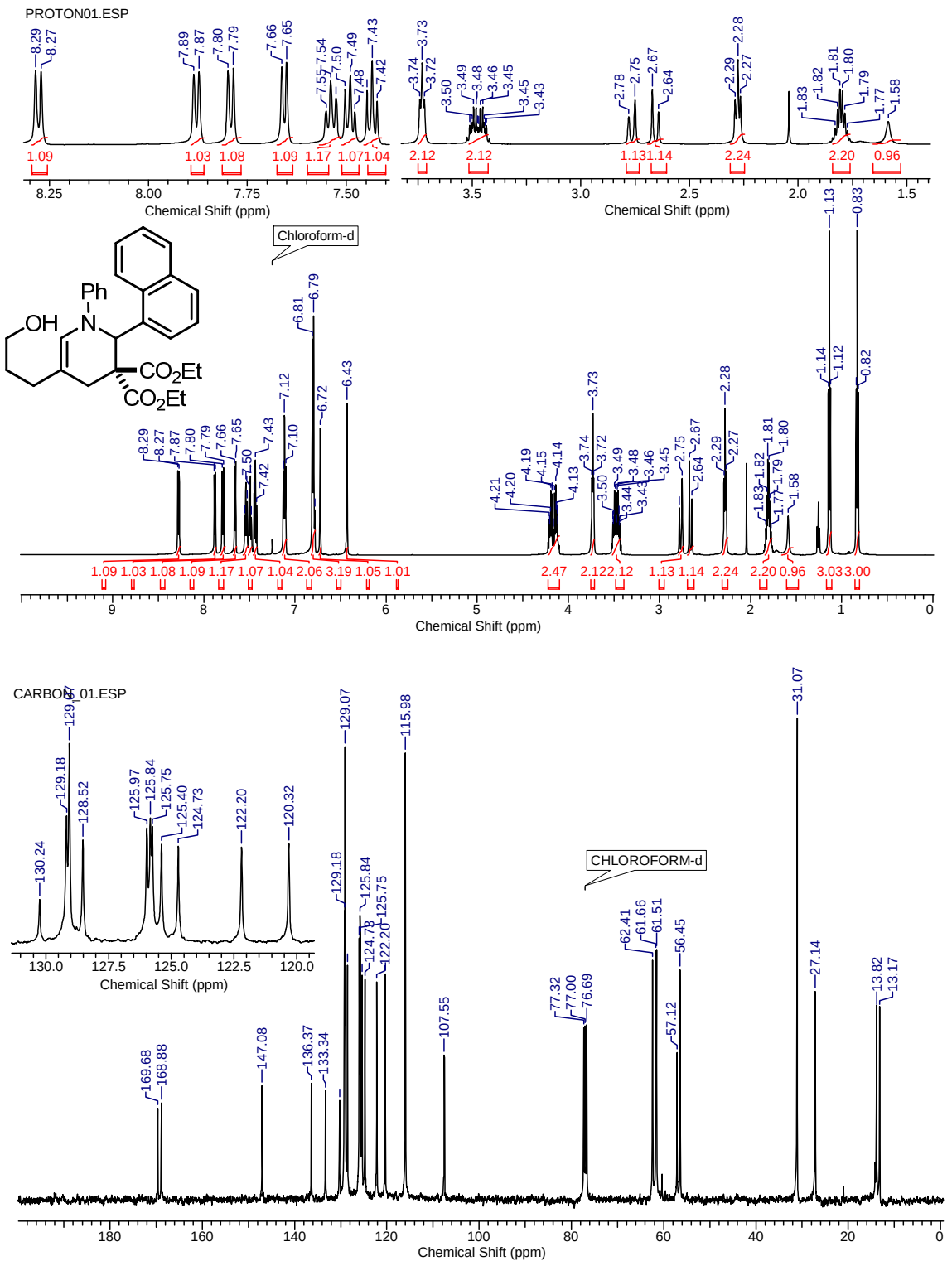
Diethyl 5-(3-hydroxypropyl)-1-phenyl-2-(thiophen-2-yl)-1,2-dihydropyridine-3,3(4*H*)-dicarboxylate (3.68d):

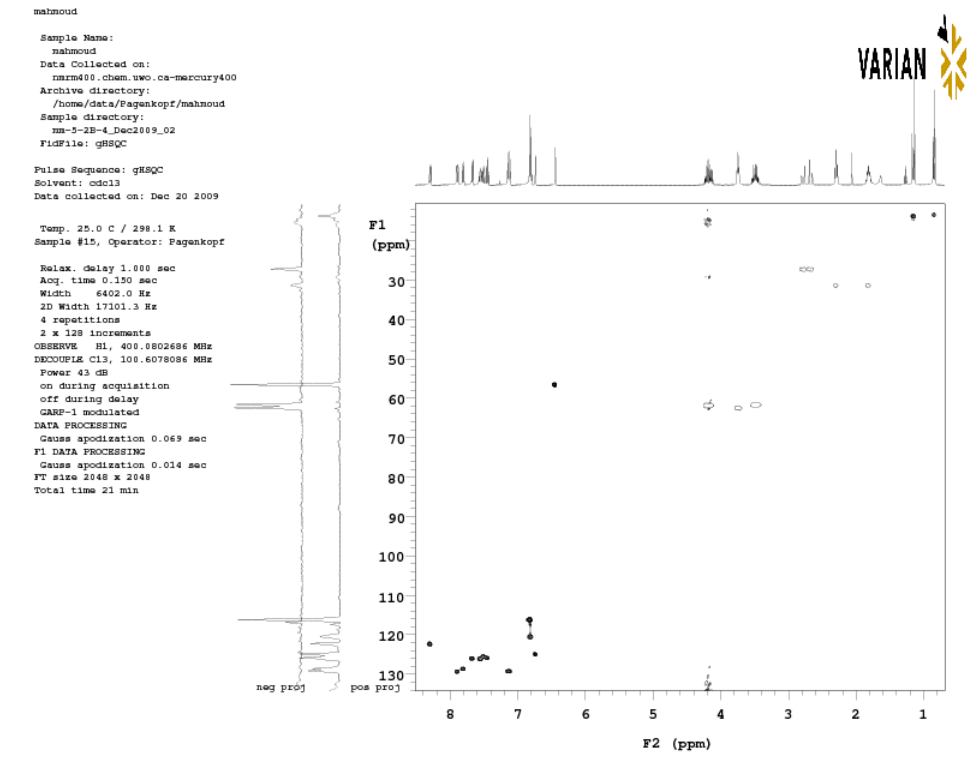


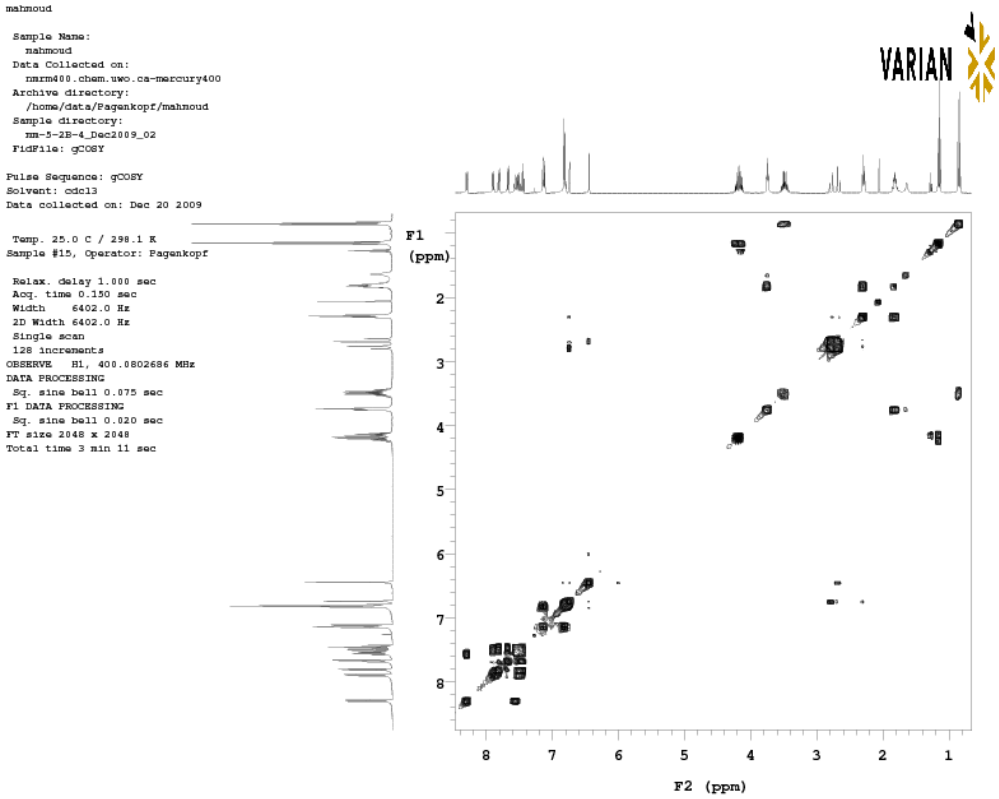



mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-5-16-4_Jan1210_01
FidFile: gHSQC
Pulse Sequence: gHSQC
Solvent: cdcl3
Data collected on: Jan 13 2010
Temp. 25.0 C / 298.1 K
Sample #13, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 17101.3 Hz
8 repetitions
2 x 128 increments
OBSERVE H1, 400.0802937 MHz
DECOUPLE C13, 100.6078086 MHz
Power 43 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.014 sec
FT size 2048 x 2048
Total time 41 min
VARIAN
neg proj
pos proj
F1
(ppm)
30
40
50
60
70
80
90
100
110
120
130
neg proj
pos proj
6
5
4
3
2
1
F2 (ppm)

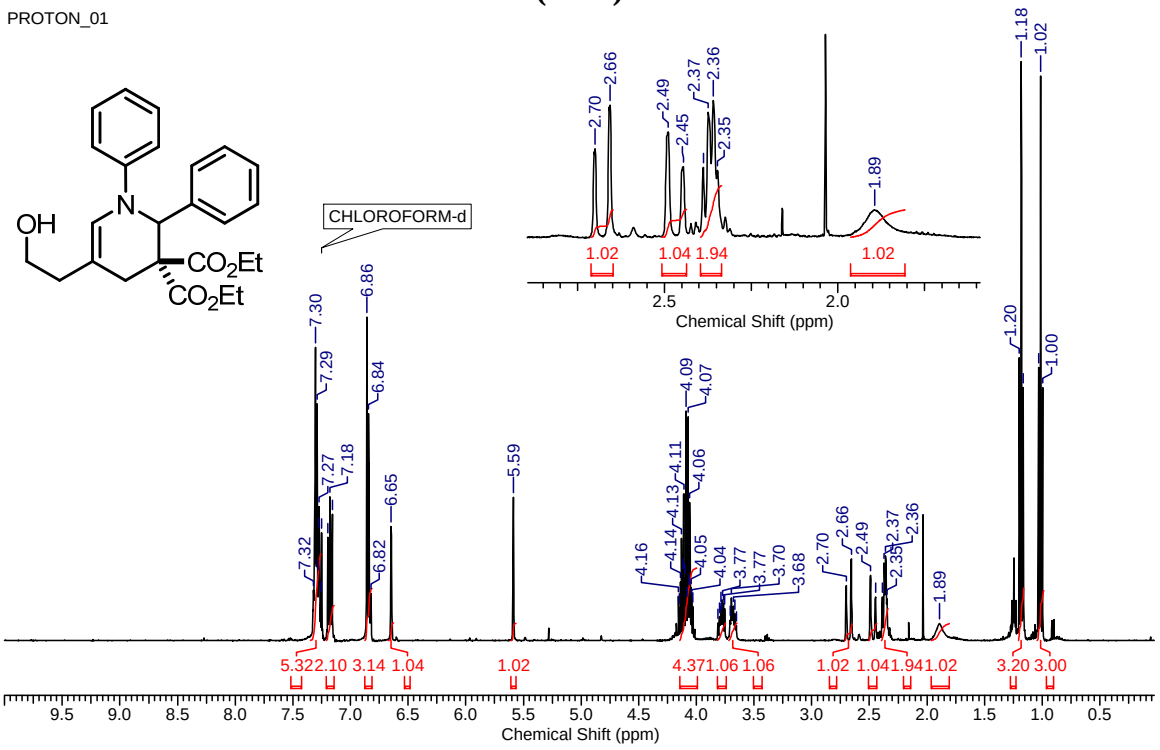
Diethyl 5-(3-hydroxypropyl)-2-(naphthalen-1-yl)-1-phenyl-1,2-dihydropyridine-3,3(4*H*)-dicarboxylate (3.68e):

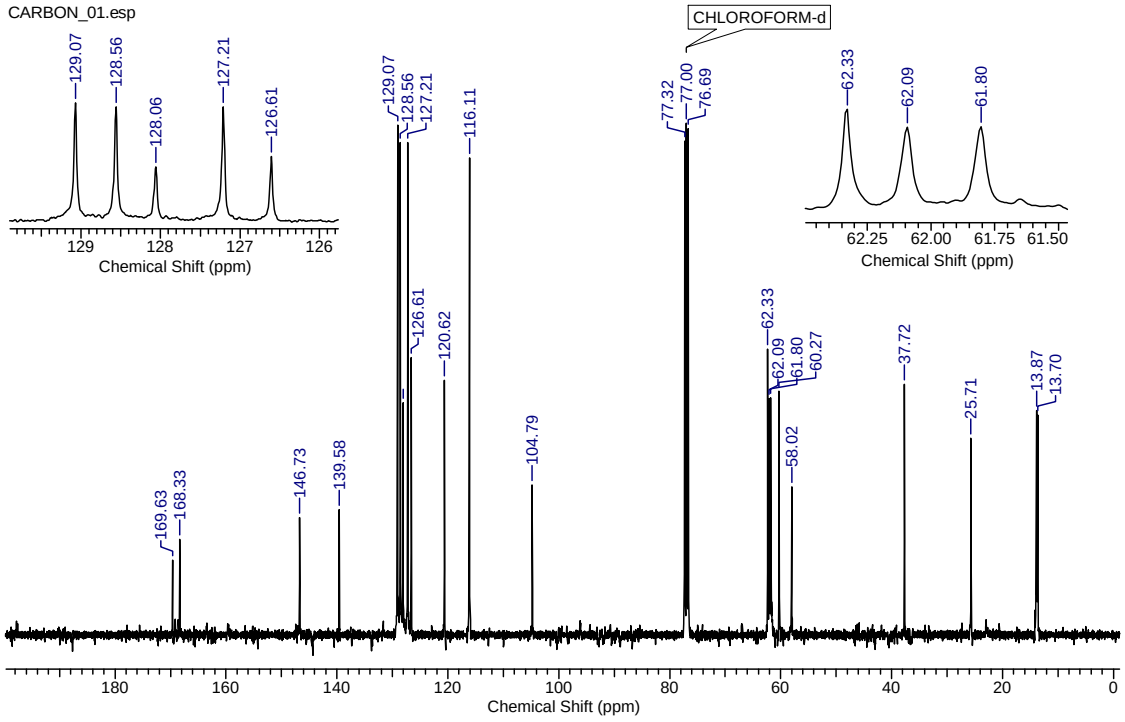


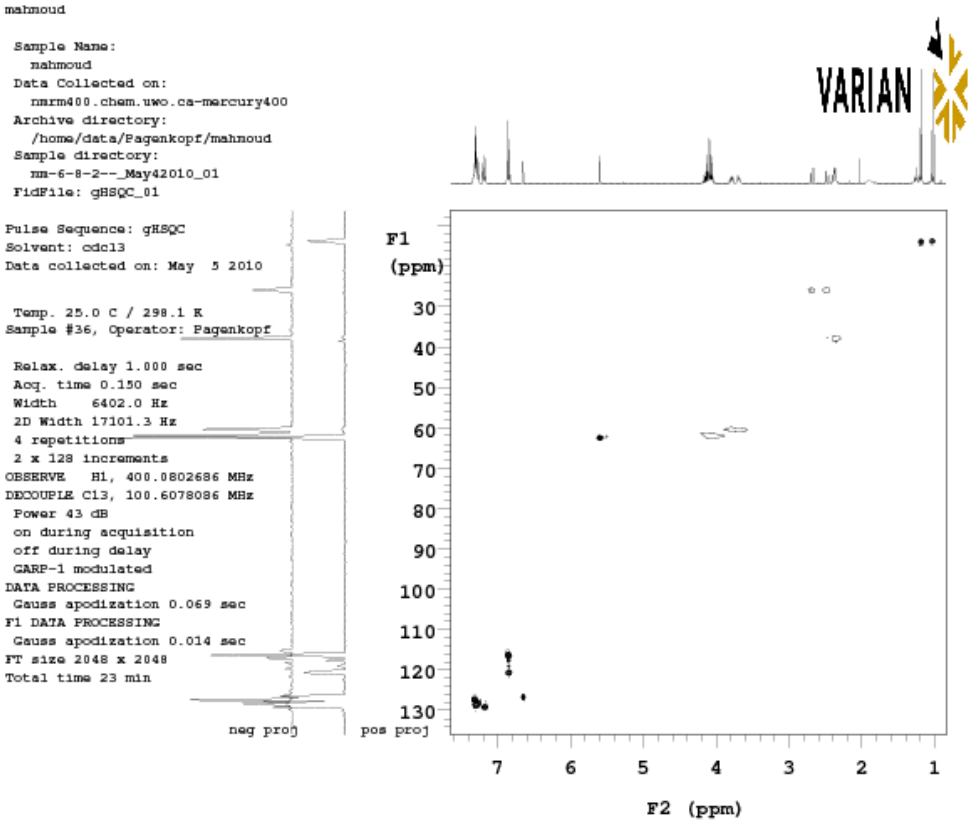

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
nm-5-2B-4_Dec2009_02
FidFile: gHSQC
Pulse Sequence: gHSQC
Solvent: cdcl3
Data collected on: Dec 20 2009
Temp. 25.0 C / 298.1 K
Sample #15, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 17101.3 Hz
4 repetitions
2 x 128 increments
OBSERVE H1, 400.0802686 MHz
DECOUPLE C13, 100.6078086 MHz
Power 43 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.014 sec
FT size 2048 x 2048
Total time 21 min
VARIAN
F1
(ppm)
neg proj
pos proj
F2 (ppm)

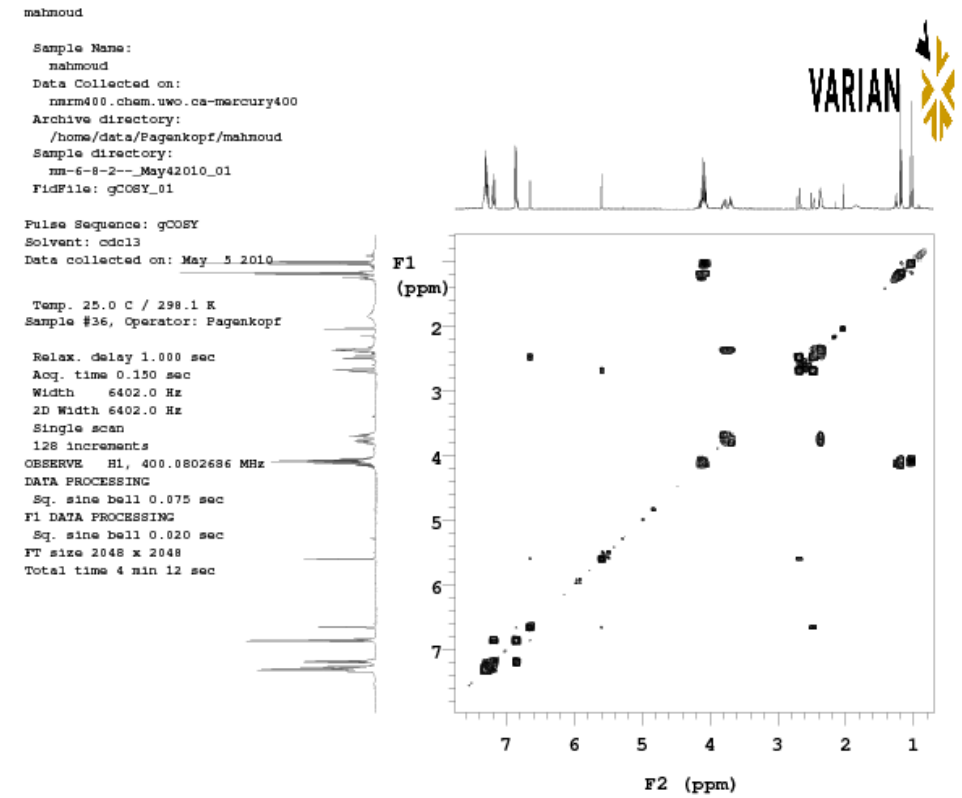

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
nm-5-2B-4_Dec2009_02
FidFile: gCOSY
Pulse Sequence: gCOSY
Solvent: cdcl3
Data collected on: Dec 20 2009
Temp. 25.0 C / 298.1 K
Sample #15, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
Single scan
128 increments
OBSERVE H1, 400.0802686 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sq. sine bell 0.020 sec
FT size 2048 x 2048
Total time 3 min 11 sec
VARIAN
F1
(ppm)
F2 (ppm)

Diethyl 5-(2-hydroxyethyl)-1,2-diphenyl-1,2-dihydropyridine-3,3(4*H*)-dicarboxylate (3.68f)

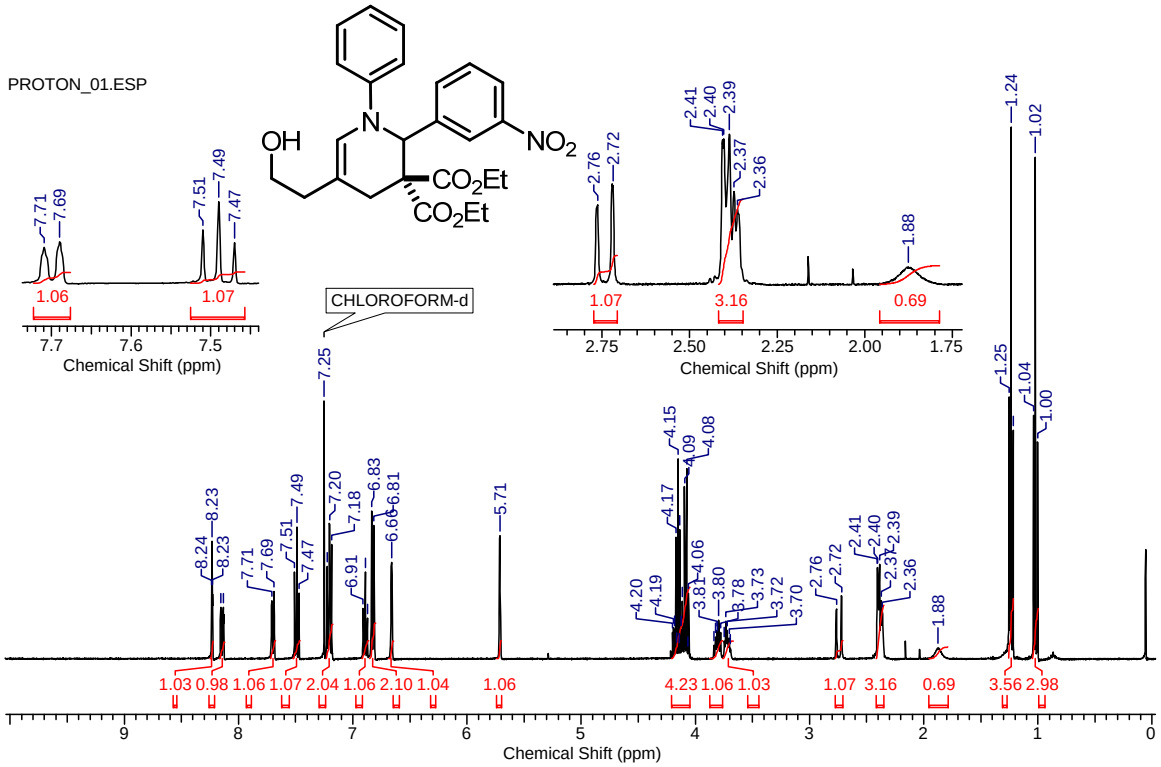


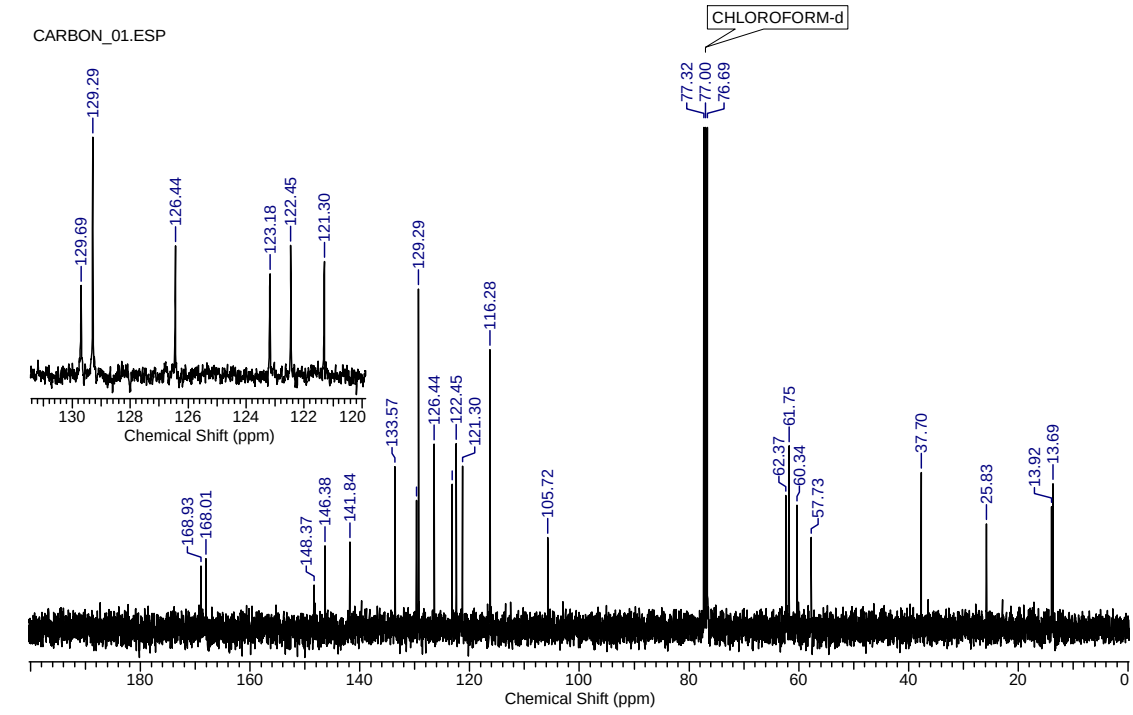


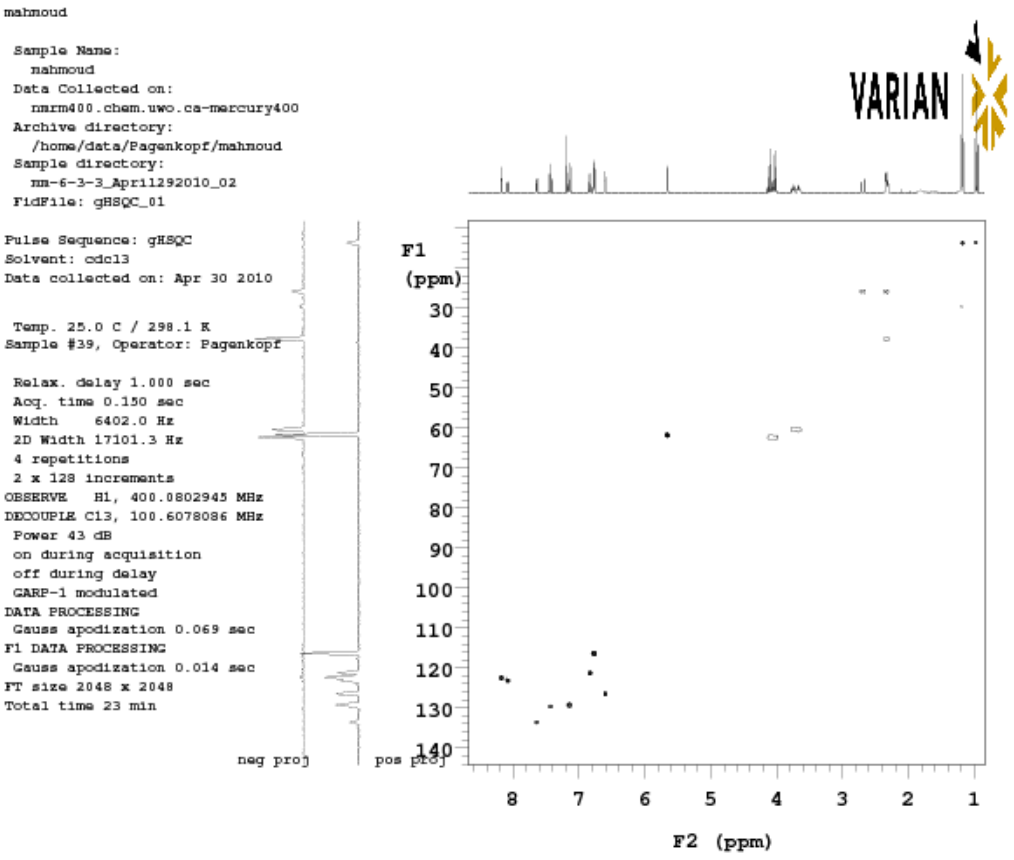

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
nm-6-8-2--_May42010_01
FidFile: gHSQC_01
Pulse Sequence: gHSQC
Solvent: cdcl3
Data collected on: May 5 2010
Temp. 25.0 C / 298.1 K
Sample #36, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 17101.3 Hz
4 repetitions
2 x 128 increments
OBSERVE H1, 400.0802686 MHz
DECOUPLE C13, 100.6078086 MHz
Power 43 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.014 sec
FT size 2048 x 2048
Total time 23 min
neg proj
pos proj
F1
(ppm)
30
40
50
60
70
80
90
100
110
120
130
7
6
5
4
3
2
1
F2 (ppm)

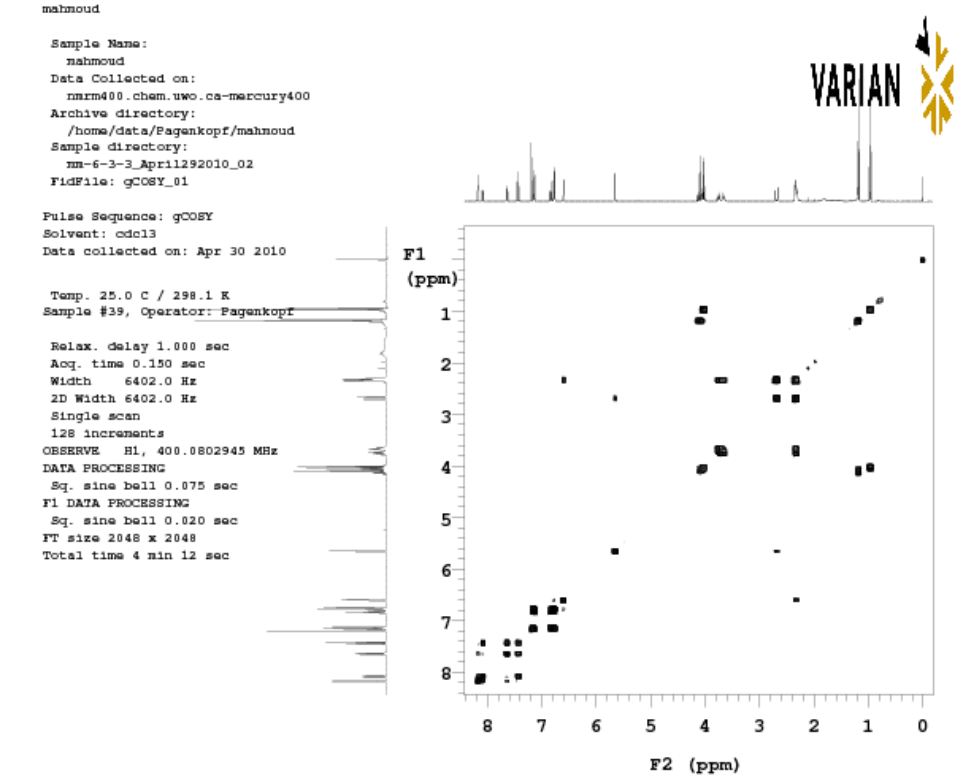

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
nm-6-8-2--_May42010_01
FidFile: gCOSY_01
Pulse Sequence: gCOSY
Solvent: cdcl3
Data collected on: May 5 2010
Temp. 25.0 C / 298.1 K
Sample #36, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
Single scan
128 increments
OBSERVE H1, 400.0802686 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sq. sine bell 0.020 sec
FT size 2048 x 2048
Total time 4 min 12 sec
F1
(ppm)
2
3
4
5
6
7
7
6
5
4
3
2
1
F2 (ppm)

Diethyl 5-(2-hydroxyethyl)-2-(3-nitrophenyl)-1-phenyl-1,2-dihydropyridine-3,3(4*H*)-dicarboxylate (3.68g):

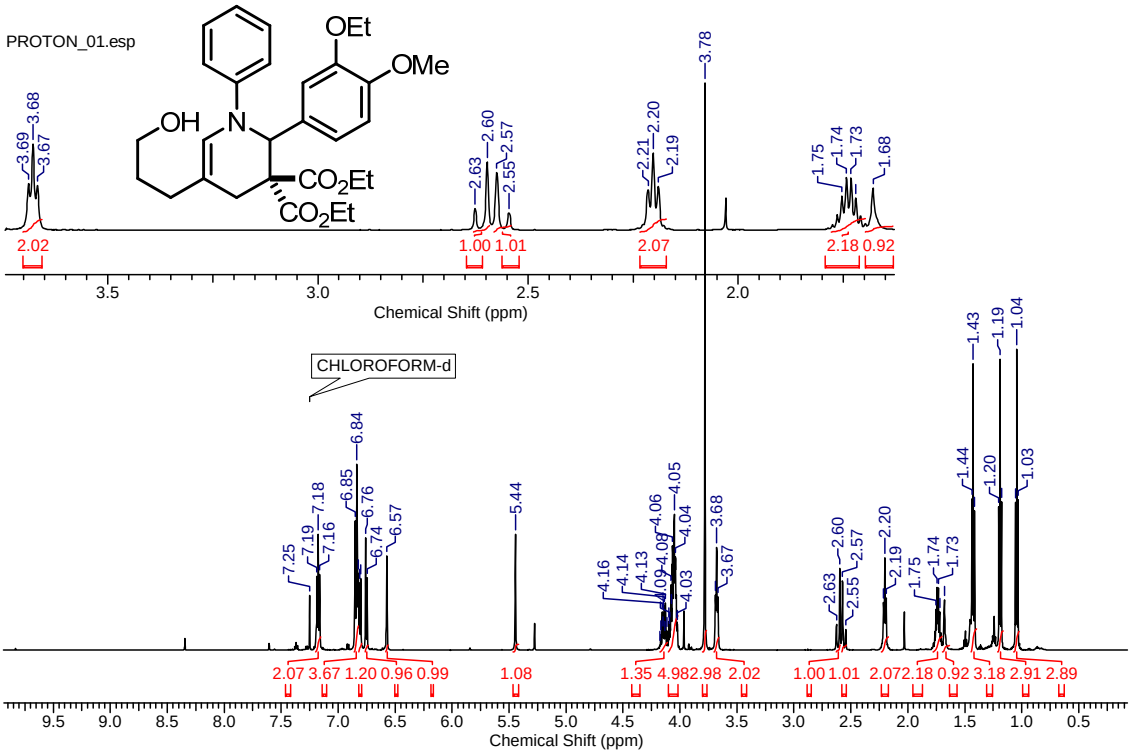


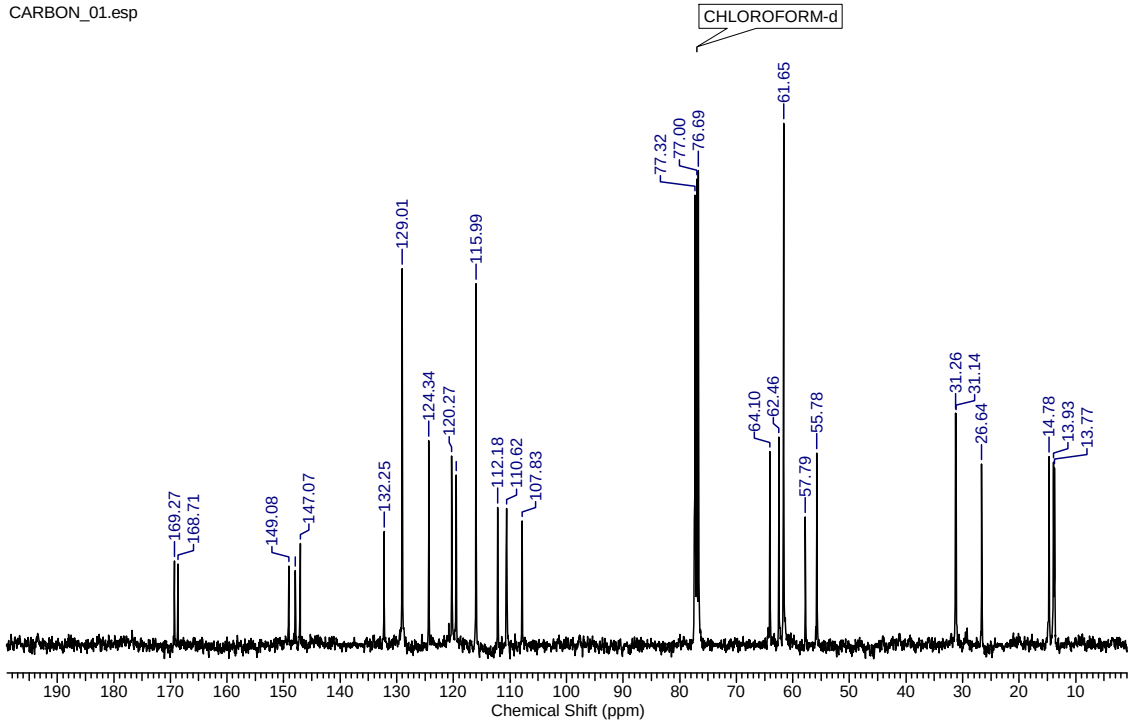


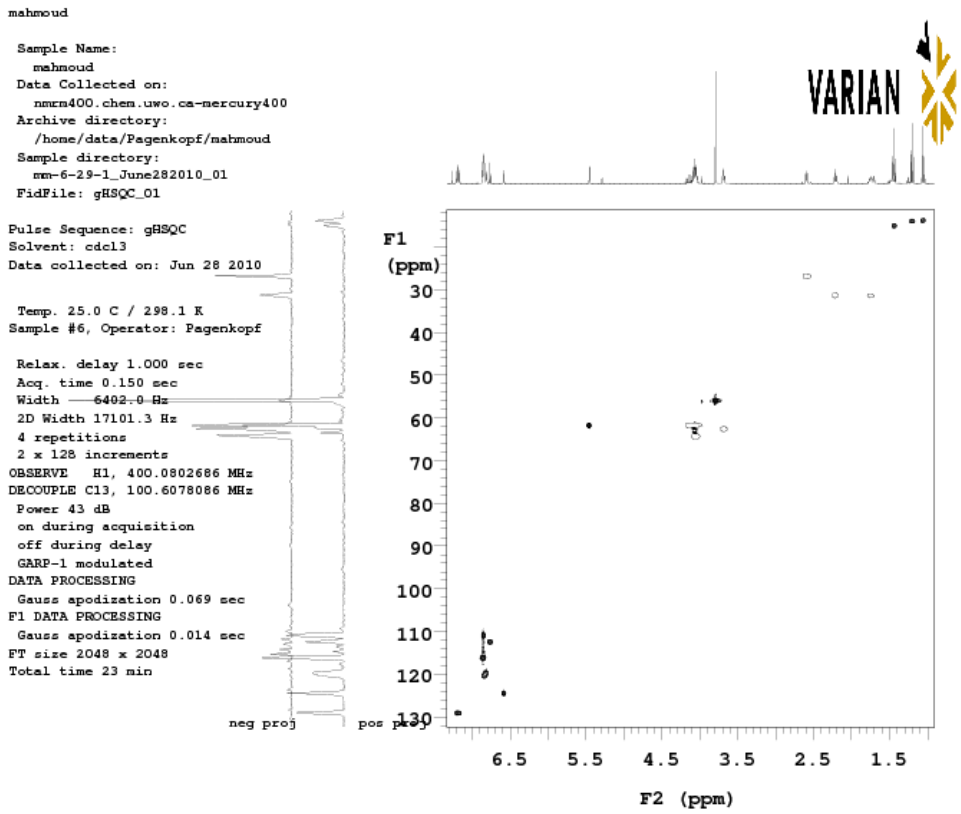

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
nm-6-3-3_April292010_02
FidFile: gHSQC_01
Pulse Sequence: gHSQC
Solvent: cdcl3
Data collected on: Apr 30 2010
Temp. 25.0 C / 298.1 K
Sample #39, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 17101.3 Hz
4 repetitions
2 x 128 increments
OBSERVE H1, 400.0802945 MHz
DECOUPLE C13, 100.6078086 MHz
Power 43 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.014 sec
FT size 2048 x 2048
Total time 23 min
VARIAN
F1
(ppm)
30
40
50
60
70
80
90
100
110
120
130
140
neg proj
pos proj
8
7
6
5
4
3
2
1
F2 (ppm)

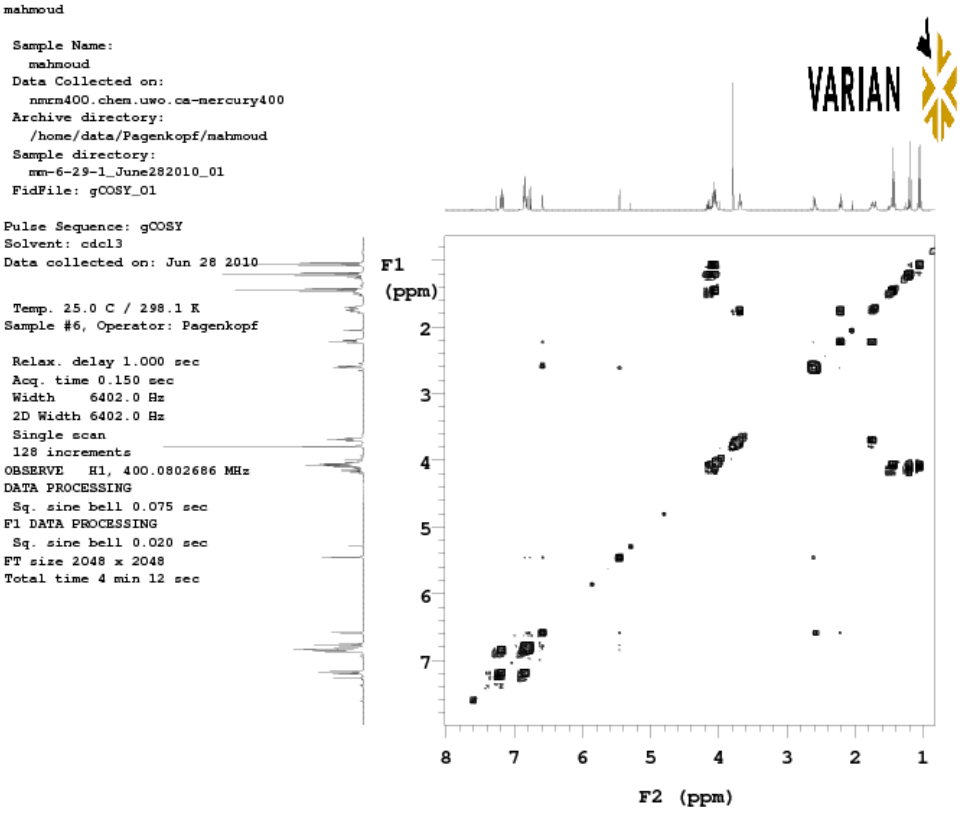

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
nm-6-3-3_April292010_02
FidFile: gCOSY_01
Pulse Sequence: gCOSY
Solvent: cdcl3
Data collected on: Apr 30 2010
Temp. 25.0 C / 298.1 K
Sample #39, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
Single scan
128 increments
OBSERVE H1, 400.0802945 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sq. sine bell 0.020 sec
FT size 2048 x 2048
Total time 4 min 12 sec
VARIAN
F1
(ppm)
1
2
3
4
5
6
7
8
8
7
6
5
4
3
2
1
0
F2 (ppm)

Diethyl 2-(3-ethoxy-4-methoxyphenyl)-5-(3-hydroxypropyl)-1-phenyl-1,2-dihydropyridine-3,3(4*H*)-dicarboxylate (3.68m)

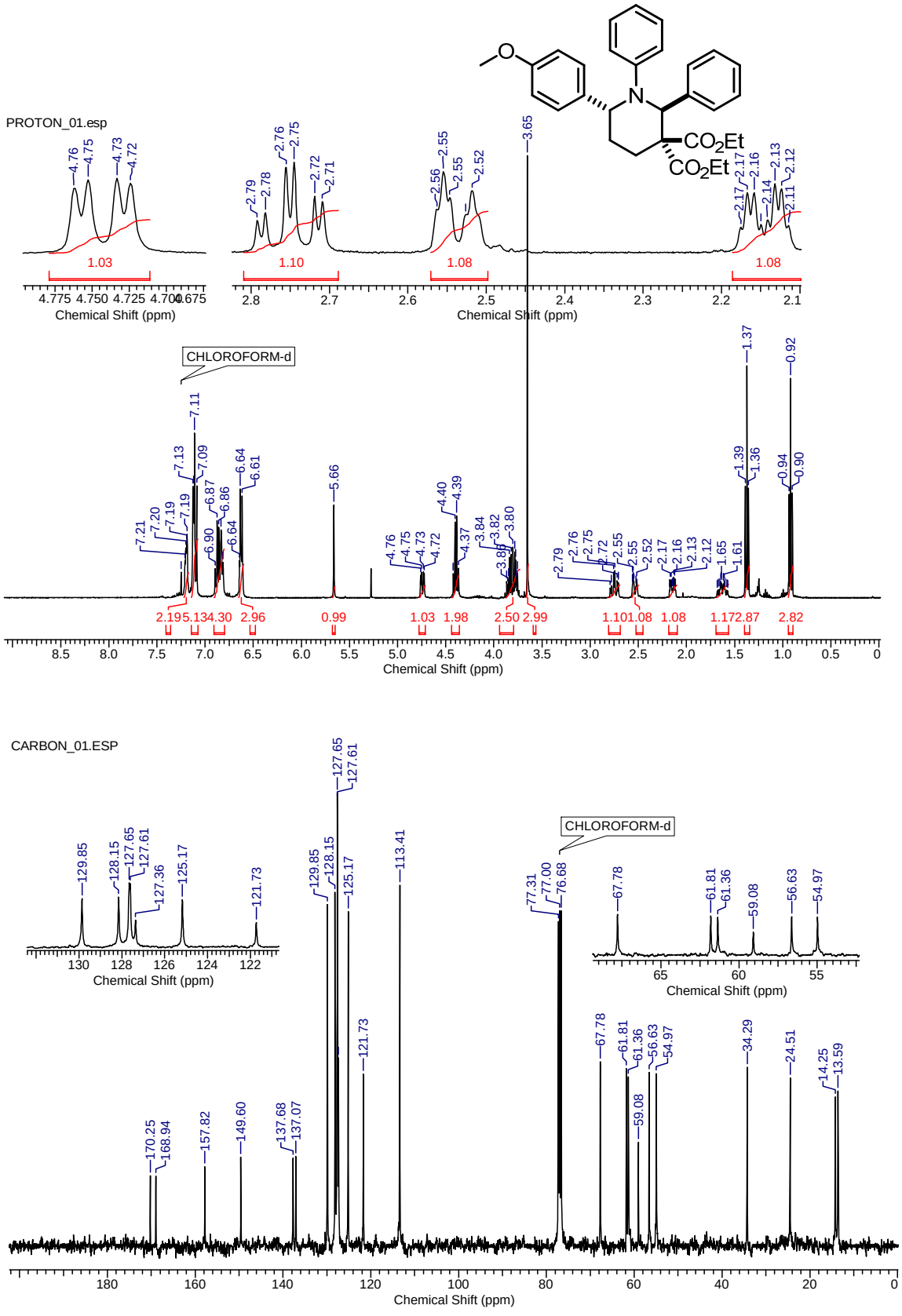


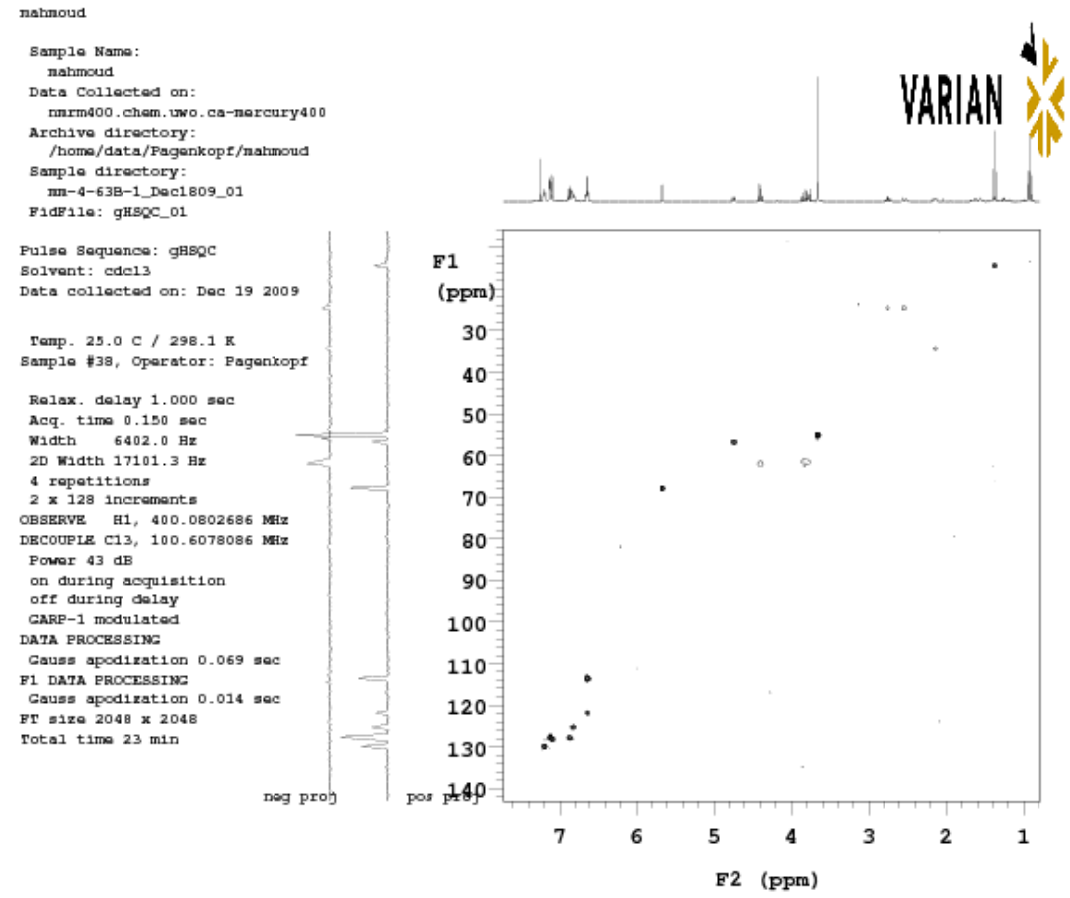


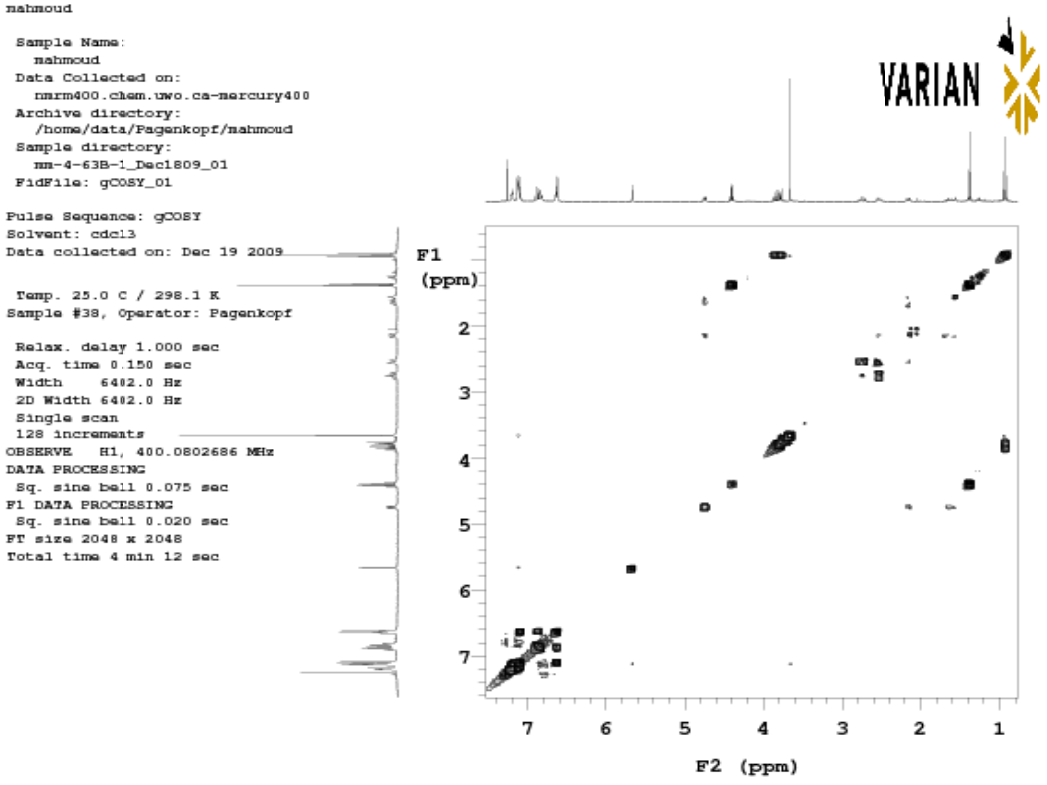

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-6-29-1_June282010_01
FidFile: gHSQC_01
Pulse Sequence: gHSQC
Solvent: cdcl3
Data collected on: Jun 28 2010
Temp. 25.0 C / 298.1 K
Sample #6, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 17101.3 Hz
4 repetitions
2 x 128 increments
OBSERVE H1, 400.0802686 MHz
DECOUPLE C13, 100.6078086 MHz
Power 43 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.014 sec
FT size 2048 x 2048
Total time 23 min
VARIAN
F1 (ppm)
30
40
50
60
70
80
90
100
110
120
130
neg proj
pos proj
6.5
5.5
4.5
3.5
2.5
1.5
F2 (ppm)

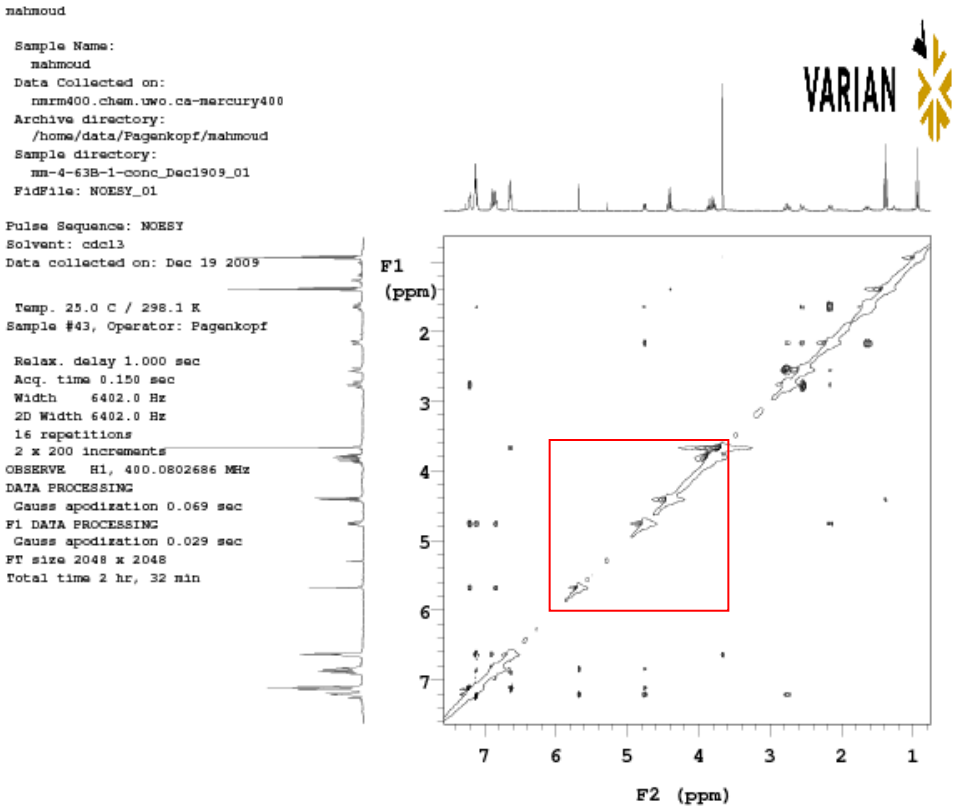

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-6-29-1_June282010_01
FidFile: gCOSY_01
Pulse Sequence: gCOSY
Solvent: cdcl3
Data collected on: Jun 28 2010
Temp. 25.0 C / 298.1 K
Sample #6, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
Single scan
128 increments
OBSERVE H1, 400.0802686 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sq. sine bell 0.020 sec
FT size 2048 x 2048
Total time 4 min 12 sec
VARIAN
F1 (ppm)
2
3
4
5
6
7
8
7
6
5
4
3
2
1
F2 (ppm)

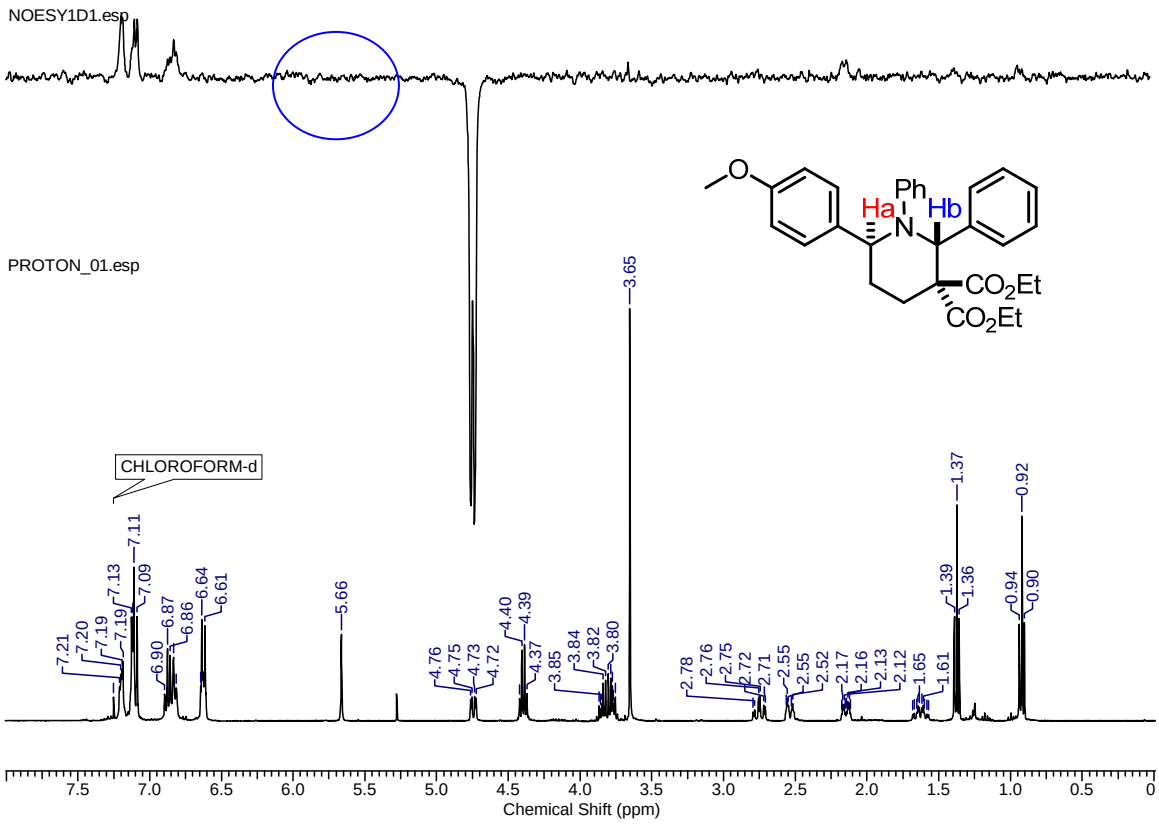
Diethyl 6-(4-methoxyphenyl)-1,2-diphenylpiperidine-3,3-dicarboxylate (3.74a)



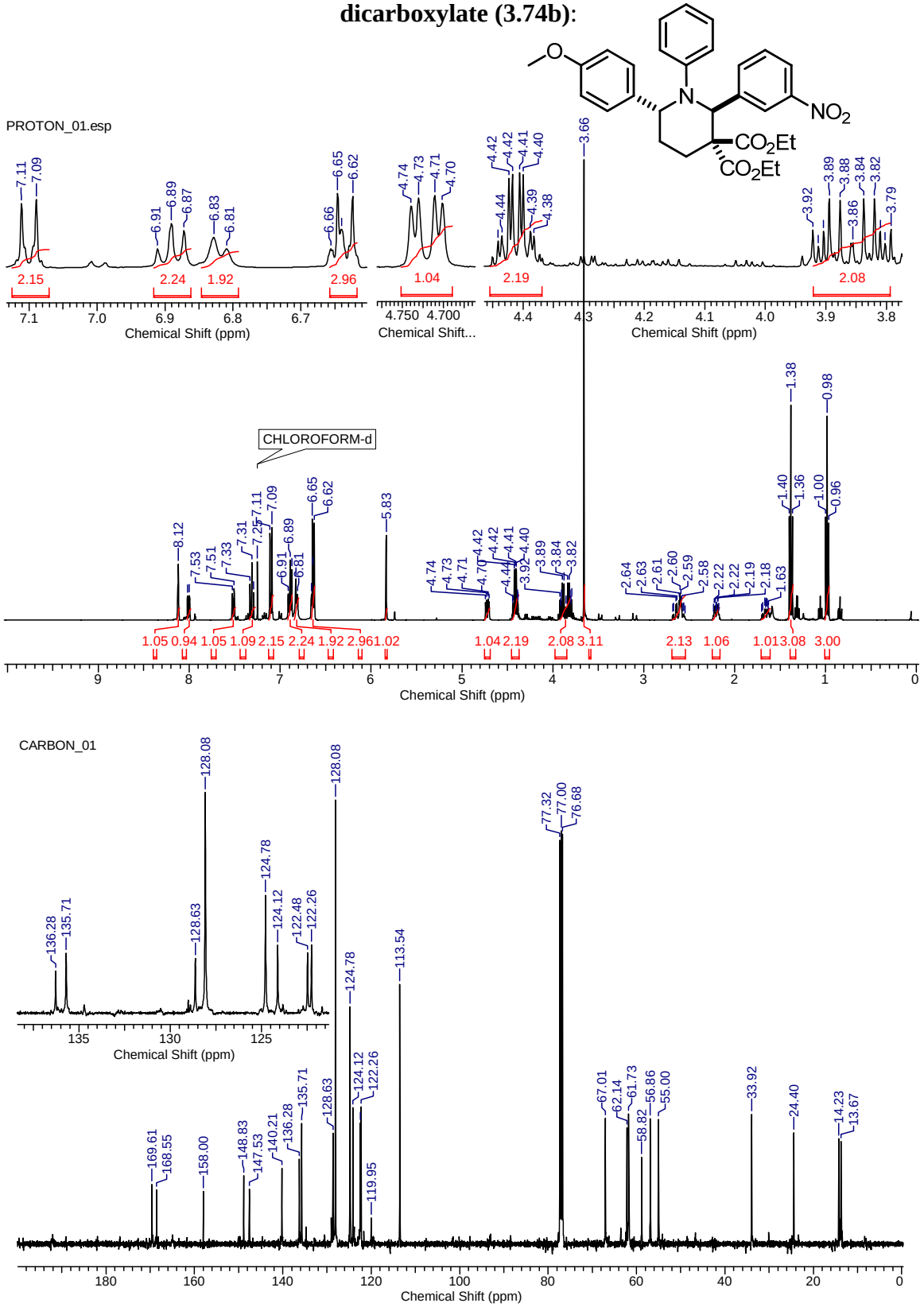

nahmoud
Sample Name:
nahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/nahmoud
Sample directory:
nm-4-63B-1_Dec1809_01
FidFile: gHSQC_01
Pulse Sequence: gHSQC
Solvent: cdcl3
Data collected on: Dec 19 2009
Temp. 25.0 C / 298.1 K
Sample #38, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 17101.3 Hz
4 repetitions
2 x 128 increments
OBSERVE H1, 400.0802686 MHz
DECOUPLE C13, 100.6078086 MHz
Power 43 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.014 sec
FT size 2048 x 2048
Total time 23 min
VARIAN
F1
(ppm)
30
40
50
60
70
80
90
100
110
120
130
140
7
6
5
4
3
2
1
F2 (ppm)

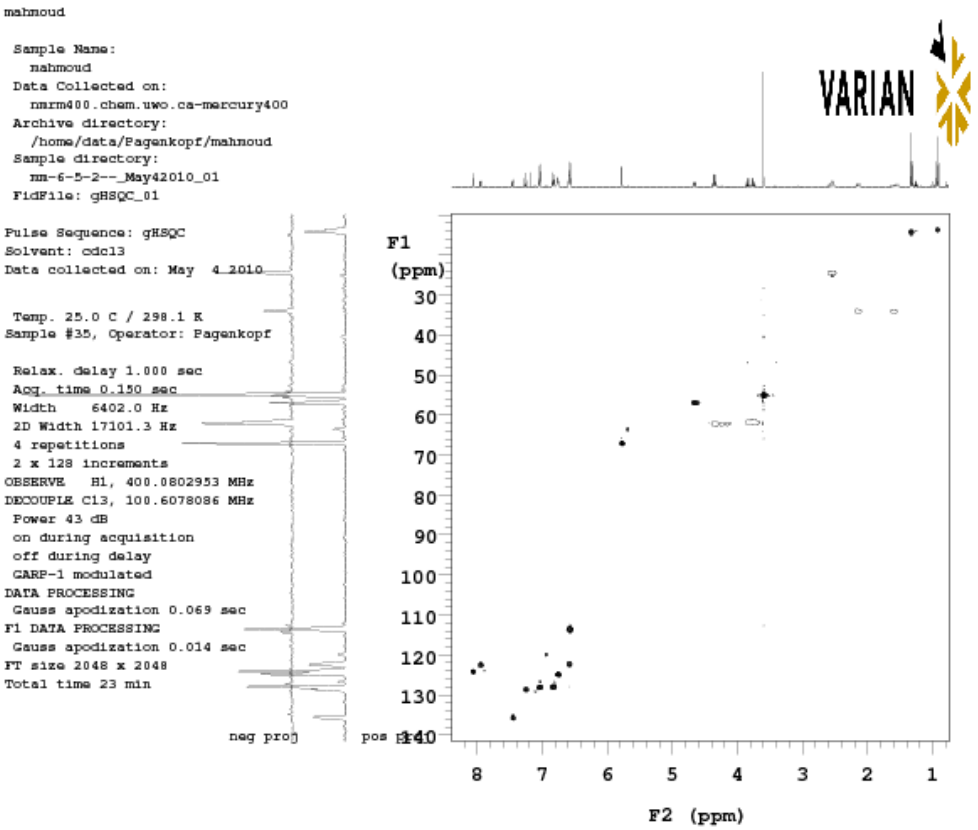

nahmoud
Sample Name:
nahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/nahmoud
Sample directory:
nm-4-63B-1_Dec1809_01
FidFile: gCOSY_01
Pulse Sequence: gCOSY
Solvent: cdcl3
Data collected on: Dec 19 2009
Temp. 25.0 C / 298.1 K
Sample #38, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
Single scan
128 increments
OBSERVE H1, 400.0802686 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sq. sine bell 0.020 sec
FT size 2048 x 2048
Total time 4 min 12 sec
VARIAN
F1
(ppm)
2
3
4
5
6
7
7
6
5
4
3
2
1
F2 (ppm)

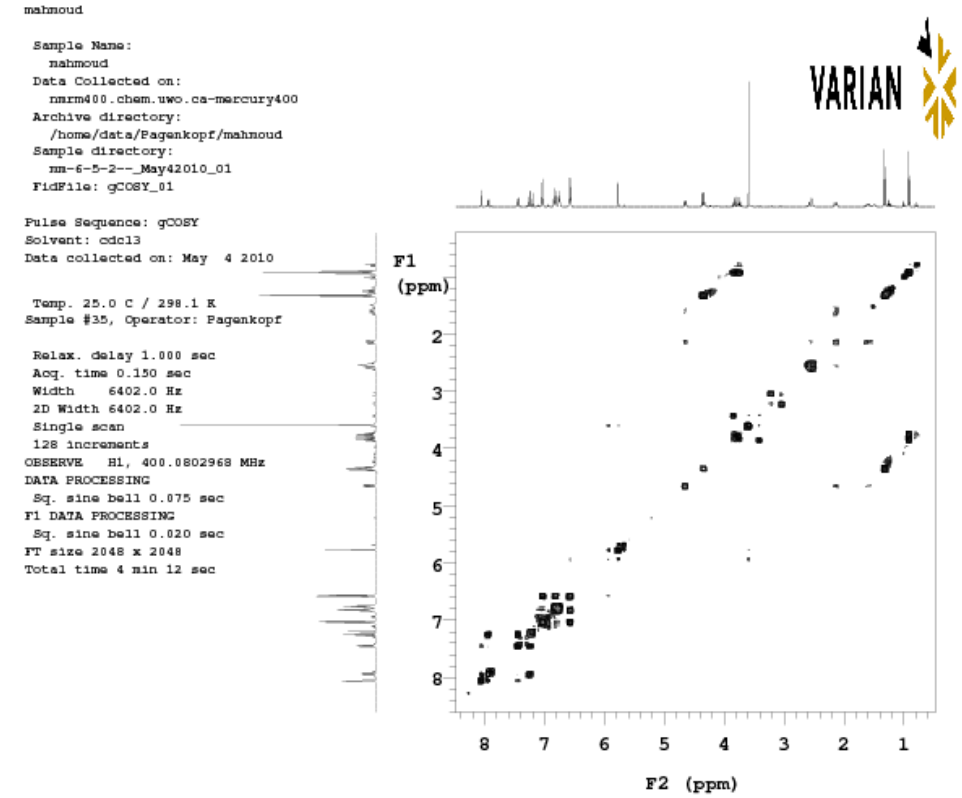

nahmoud
Sample Name:
nahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/nahmoud
Sample directory:
nm-4-63B-1-conc_Dec1909_01
FidFile: NOESY_01
Pulse Sequence: NOESY
Solvent: cdcl3
Data collected on: Dec 19 2009
Temp. 25.0 C / 298.1 K
Sample #43, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
16 repetitions
2 x 200 increments
OBSERVE H1, 400.0802686 MHz
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.029 sec
FT size 2048 x 2048
Total time 2 hr, 32 min
VARIAN
F1 (ppm)
F2 (ppm)

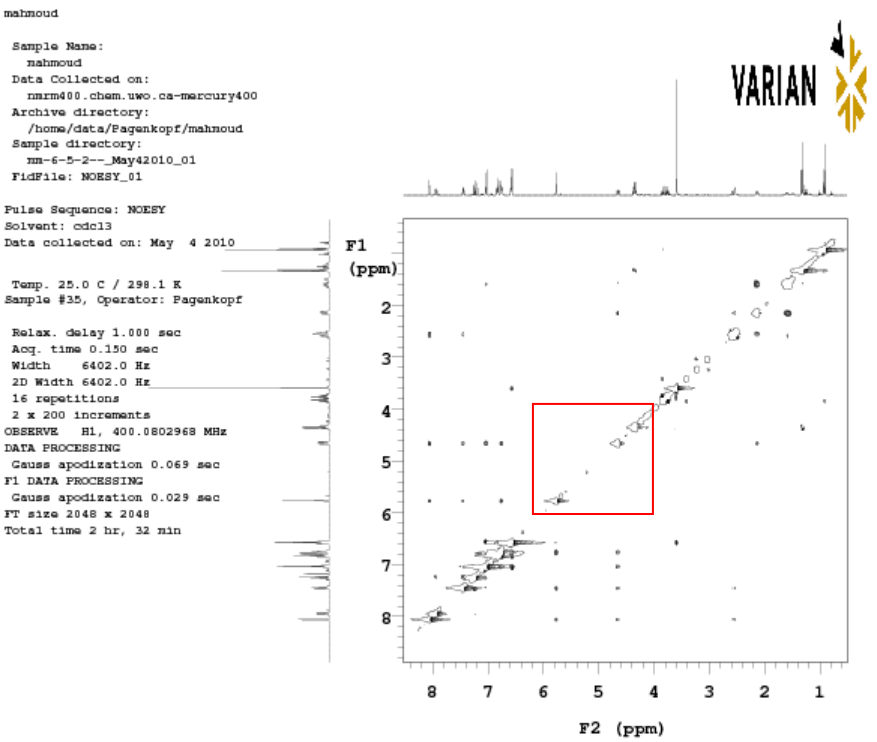

NOESY1D1.esp
PROTON_01.esp
Ha
Hb
Ph
N
O
CO2Et
CO2Et
CHLOROFORM-d
Chemical Shift (ppm)

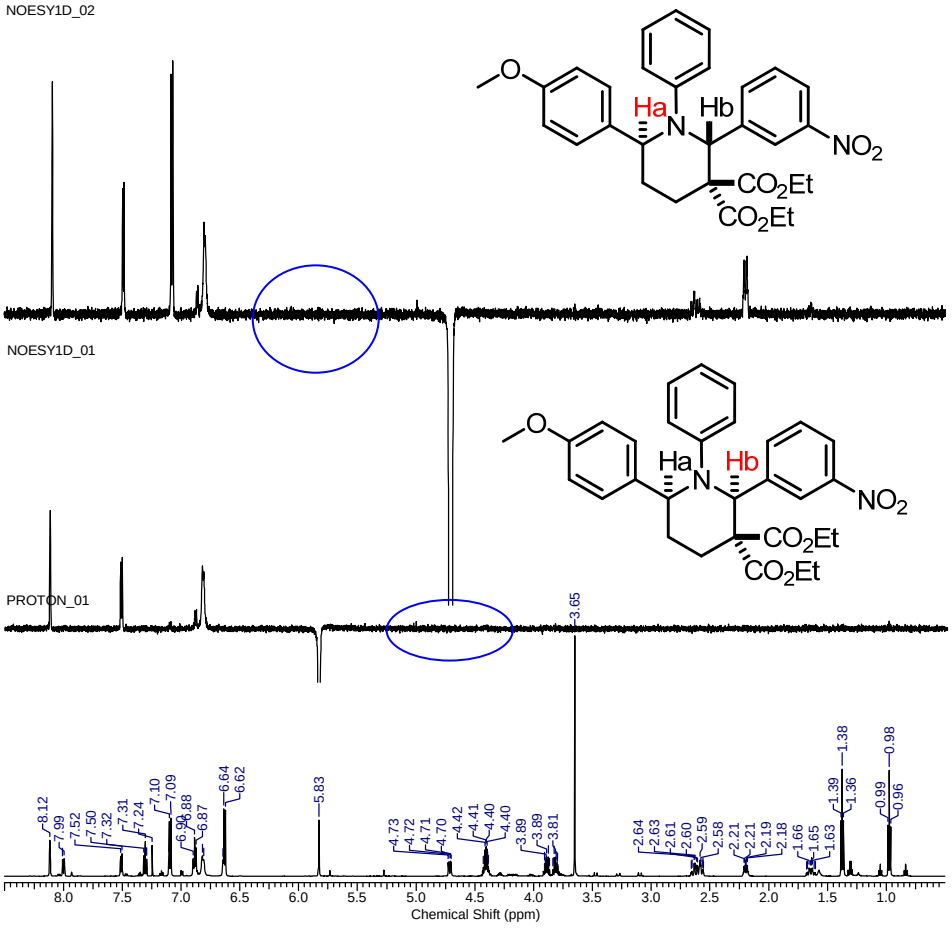
Diethyl 6-(4-methoxyphenyl)-2-(3-nitrophenyl)-1-phenylpiperidine-3,3-dicarboxylate (3.74b):



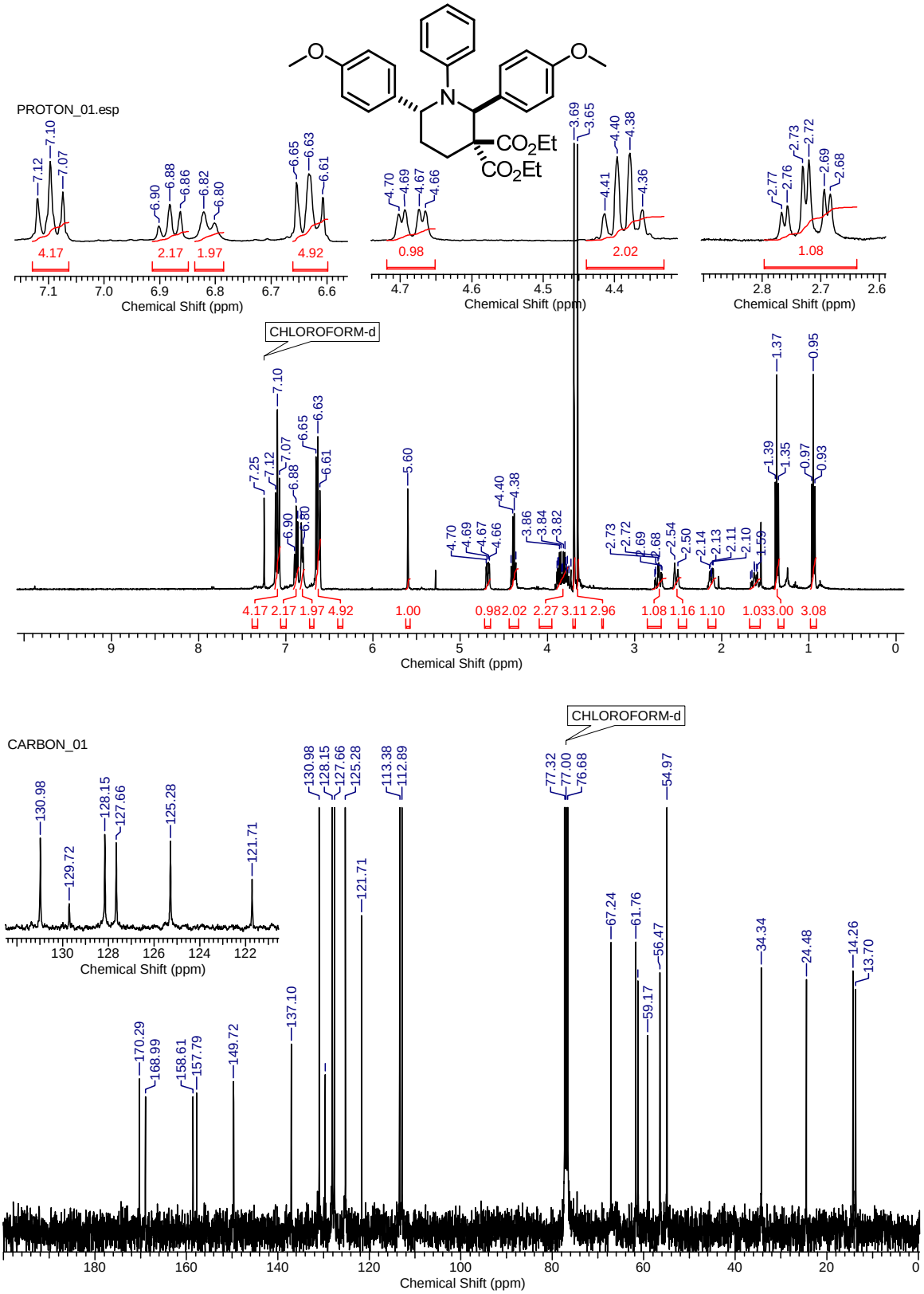

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-6-5-2--_May42010_01
FidFile: gHSQC_01
Pulse Sequence: gHSQC
Solvent: cdcl3
Data collected on: May 4 2010
Temp. 25.0 C / 298.1 K
Sample #35, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 17101.3 Hz
4 repetitions
2 x 128 increments
OBSERVE H1, 400.0802953 MHz
DECOUPLE C13, 100.6078086 MHz
Power 43 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.014 sec
FT size 2048 x 2048
Total time 23 min
VARIAN
F1
(ppm)
F2 (ppm)

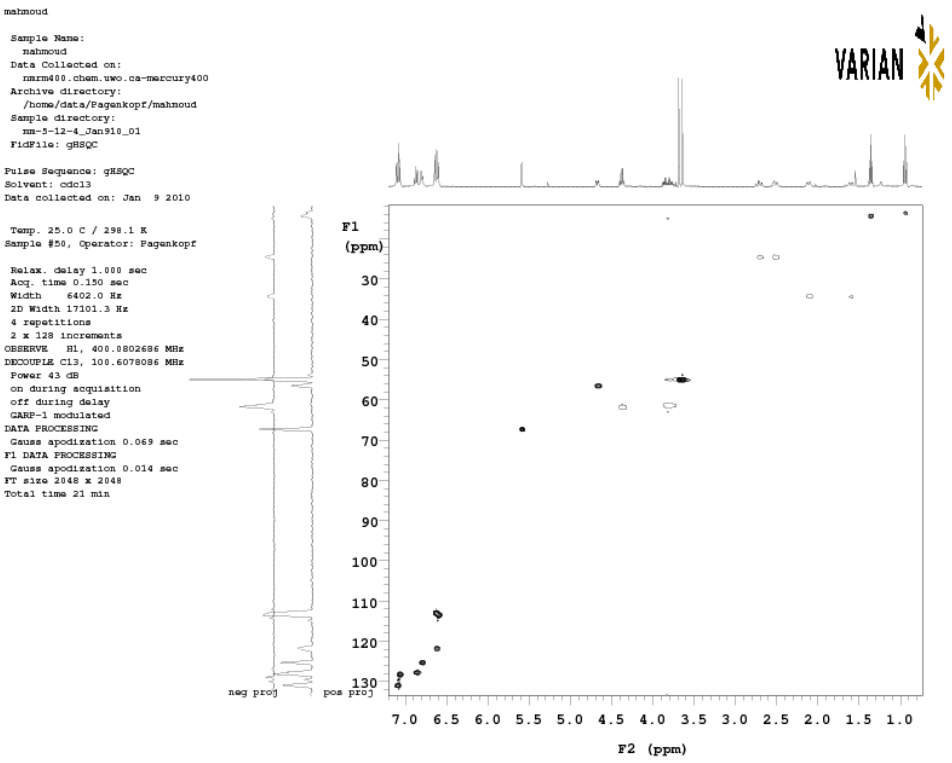

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-6-5-2--_May42010_01
FidFile: gCOSY_01
Pulse Sequence: gCOSY
Solvent: cdcl3
Data collected on: May 4 2010
Temp. 25.0 C / 298.1 K
Sample #35, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
Single scan
128 increments
OBSERVE H1, 400.0802968 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sq. sine bell 0.020 sec
FT size 2048 x 2048
Total time 4 min 12 sec
VARIAN
F1
(ppm)
F2 (ppm)

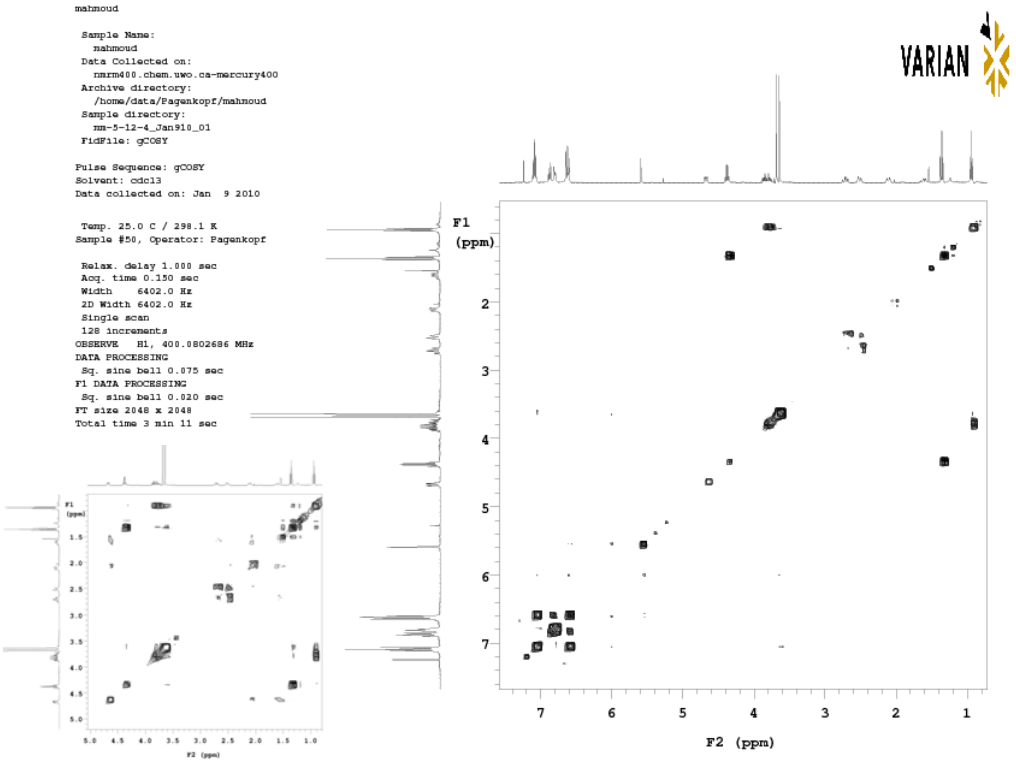

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-6-5-2--_May42010_01
FidFile: NOESY_01
Pulse Sequence: NOESY
Solvent: cdcl3
Data collected on: May 4 2010
Temp. 25.0 C / 298.1 K
Sample #35, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
16 repetitions
2 x 200 increments
OBSERVE H1, 400.0802968 MHz
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.029 sec
FT size 2048 x 2048
Total time 2 hr, 32 min
VARIAN
F1 (ppm)
F2 (ppm)

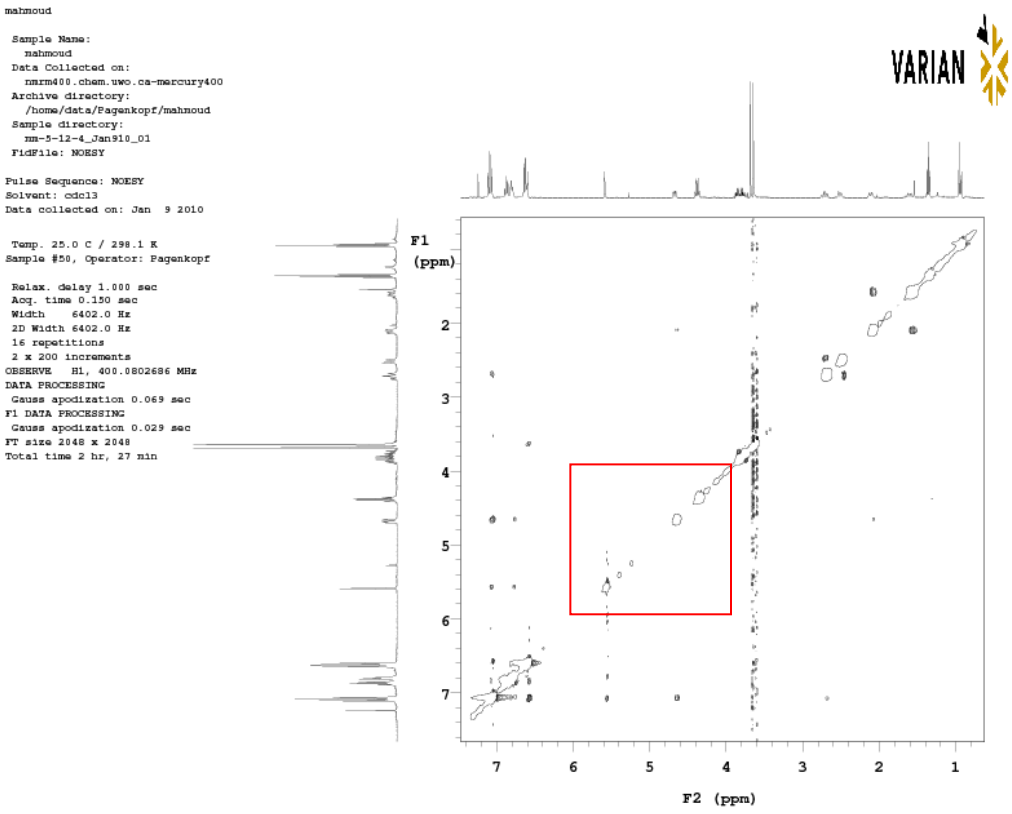

NOESY1D_02
Ha
Hb
NO2
CO2Et
CO2Et
NOESY1D_01
PROTON_01
3.65
Chemical Shift (ppm)

Diethyl 2,6-bis(4-methoxyphenyl)-1-phenylpiperidine-3,3-dicarboxylate (3.74c):

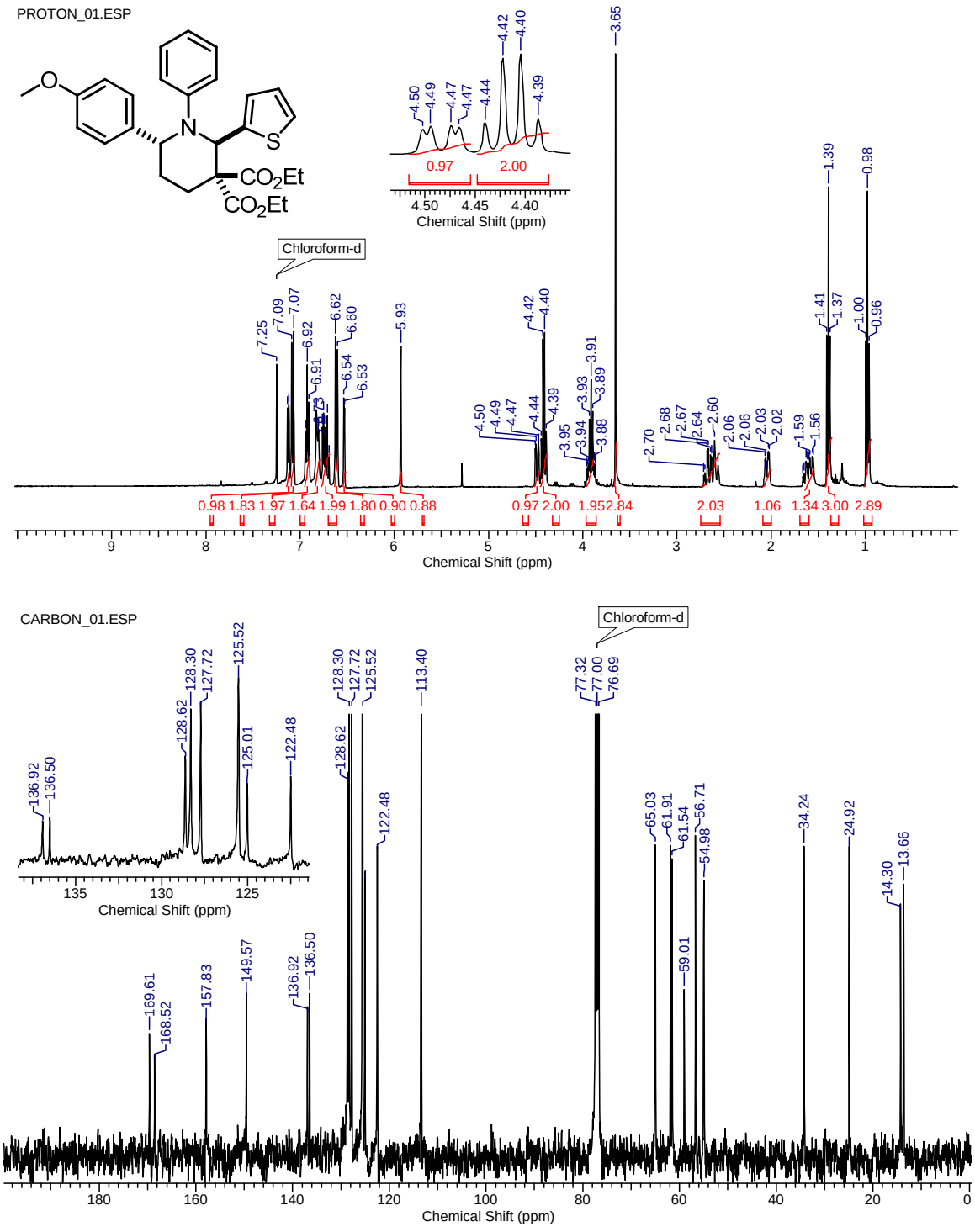


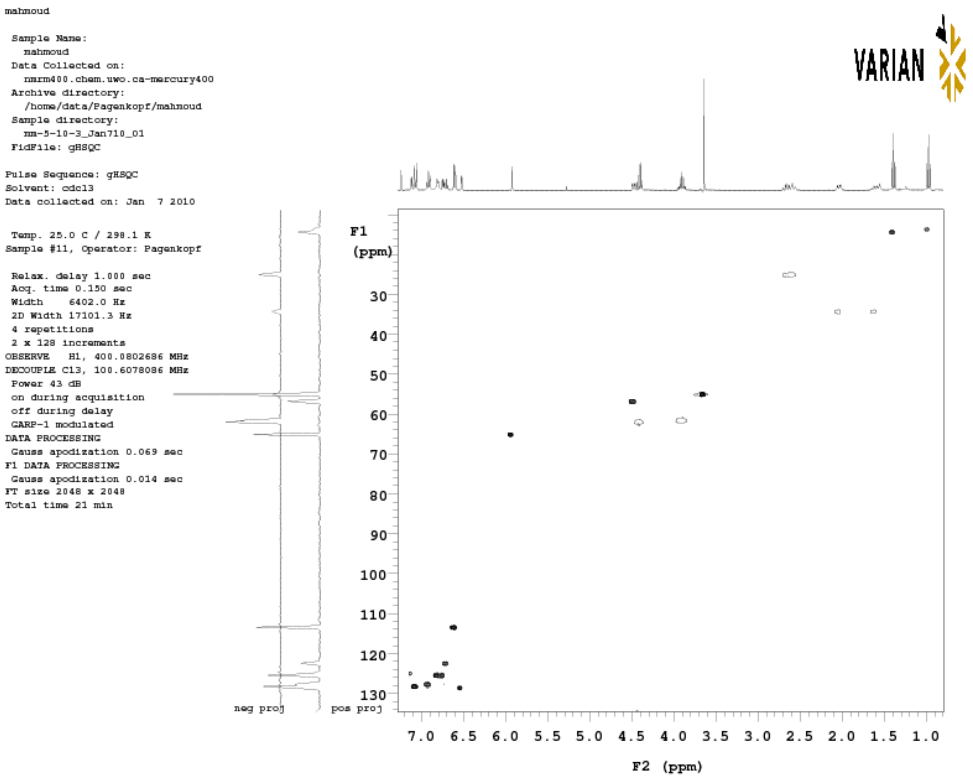

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-5-12-4_Jan910_01
FidFile: gHSQC
Pulse Sequence: gHSQC
Solvent: cdcl3
Data collected on: Jan 9 2010
Temp. 25.0 C / 298.1 K
Sample #50, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 17101.3 Hz
4 repetitions
2 x 128 increments
OBSERVE H1, 400.0802686 MHz
DECOUPLE C13, 100.6078086 MHz
Power 43 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.014 sec
FT size 2048 x 2048
Total time 21 min
VARIAN
F1 (ppm)
neg proj
pos proj
F2 (ppm)

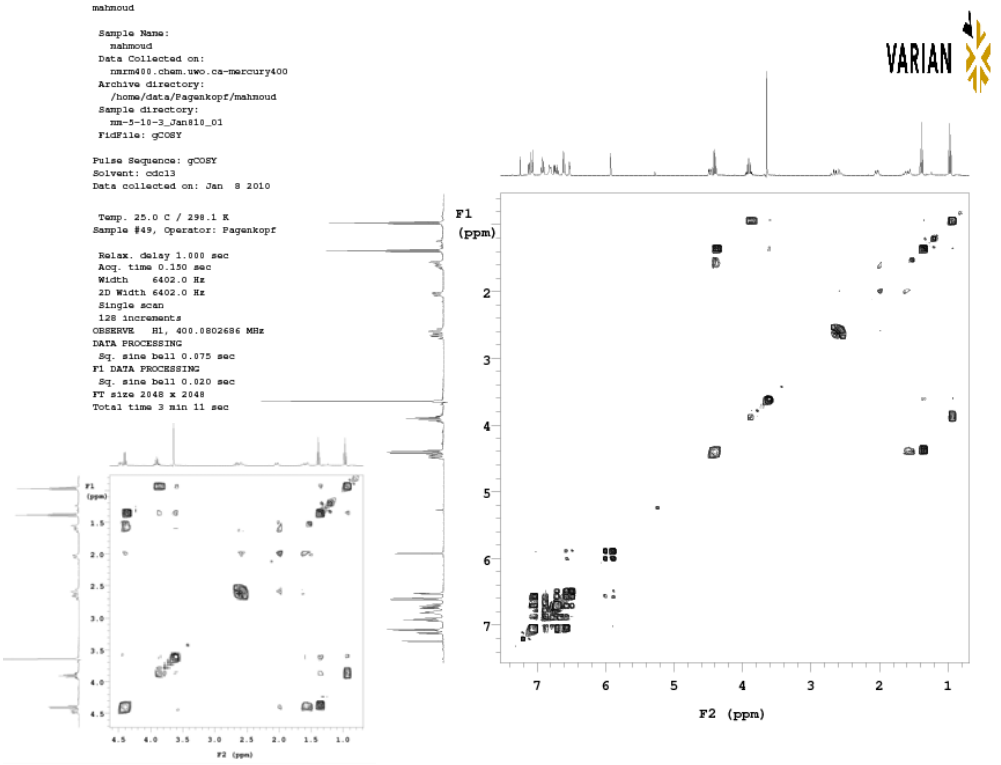

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-5-12-4_Jan910_01
FidFile: gCOSY
Pulse Sequence: gCOSY
Solvent: cdcl3
Data collected on: Jan 9 2010
Temp. 25.0 C / 298.1 K
Sample #50, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
Single scan
128 increments
OBSERVE H1, 400.0802686 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sq. sine bell 0.020 sec
FT size 2048 x 2048
Total time 3 min 11 sec
VARIAN
F1 (ppm)
F2 (ppm)

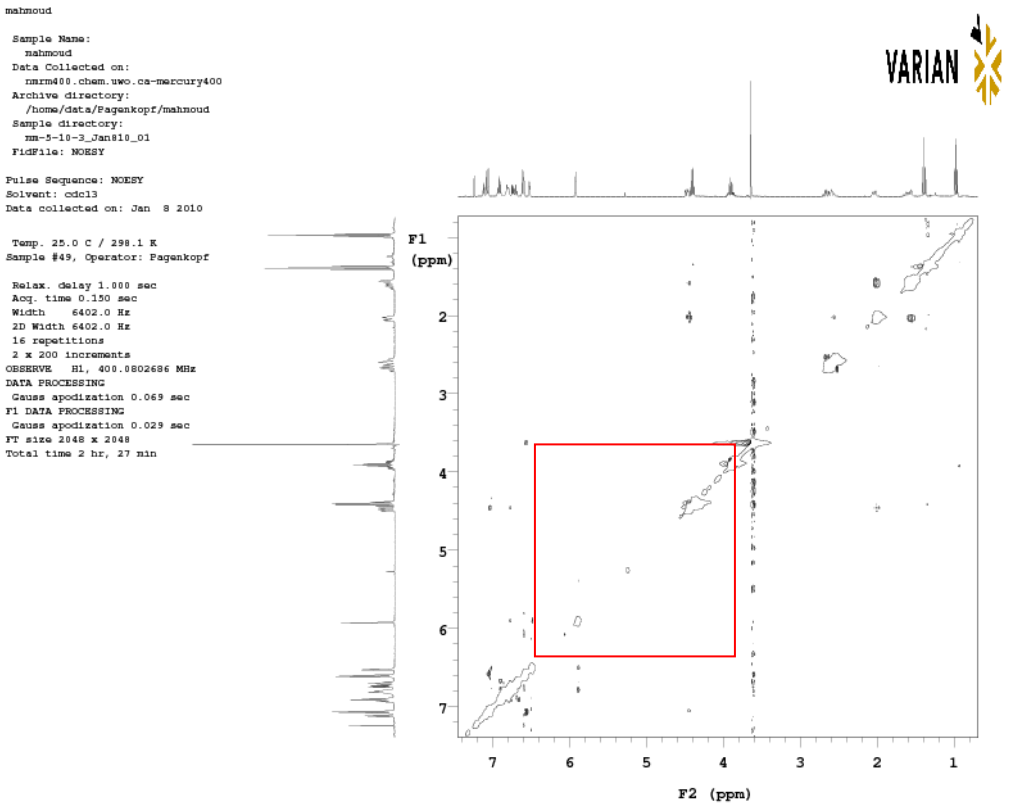

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
nm-5-12-4_Jan910_01
FidFile: NOESY
Pulse Sequence: NOESY
Solvent: cdcl3
Data collected on: Jan 9 2010
Temp. 25.0 C / 298.1 K
Sample #50, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
16 repetitions
2 x 200 increments
OBSERVE H1, 400.0802686 MHz
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.029 sec
FT size 2048 x 2048
Total time 2 hr, 27 min
VARIAN
F1 (ppm)
F2 (ppm)

Diethyl 6-(4-methoxyphenyl)-1-phenyl-2-(thiophen-2-yl)piperidine-3,3-dicarboxylate (3.74d):

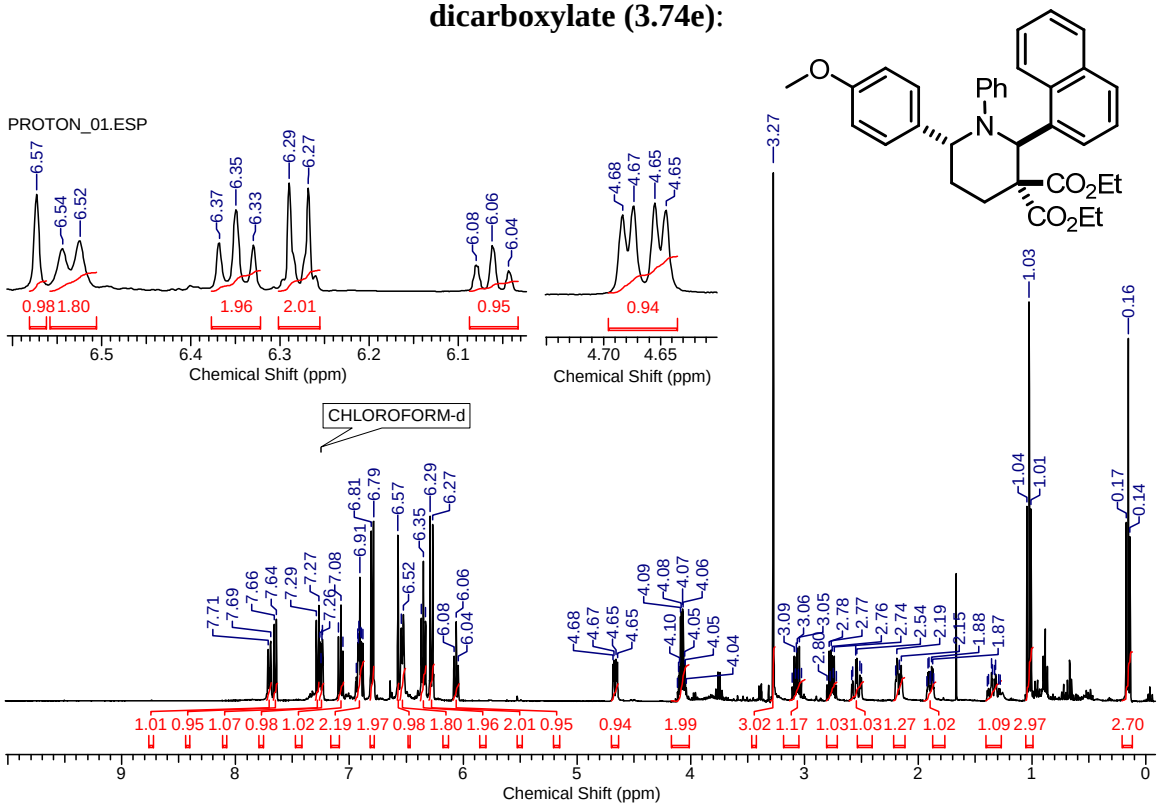


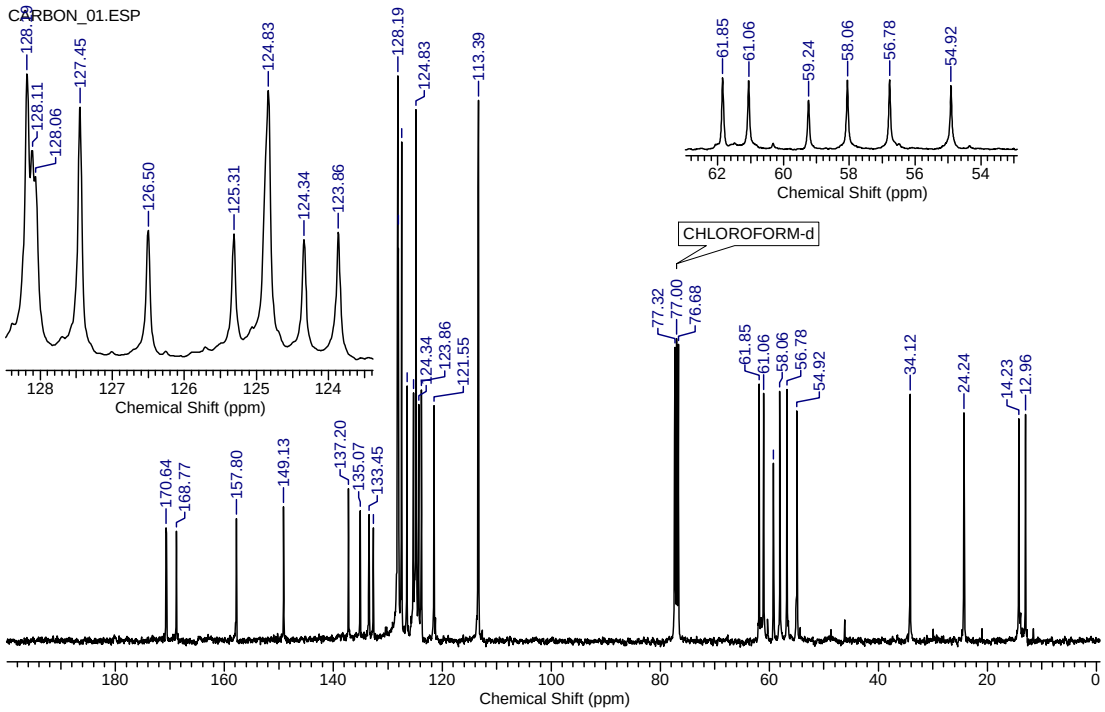

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
nm-5-10-3_Jan710_01
FidFile: gHSQC
Pulse Sequence: gHSQC
Solvent: cdcl3
Data collected on: Jan 7 2010
Temp. 25.0 C / 298.1 K
Sample #11, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 17101.3 Hz
4 repetitions
2 x 128 increments
OBSERVE H1, 400.0802686 MHz
DECOUPLE C13, 100.6078086 MHz
Power 43 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.014 sec
FT size 2048 x 2048
Total time 21 min
VARIAN
F1 (ppm)
neg proj
pos proj
F2 (ppm)

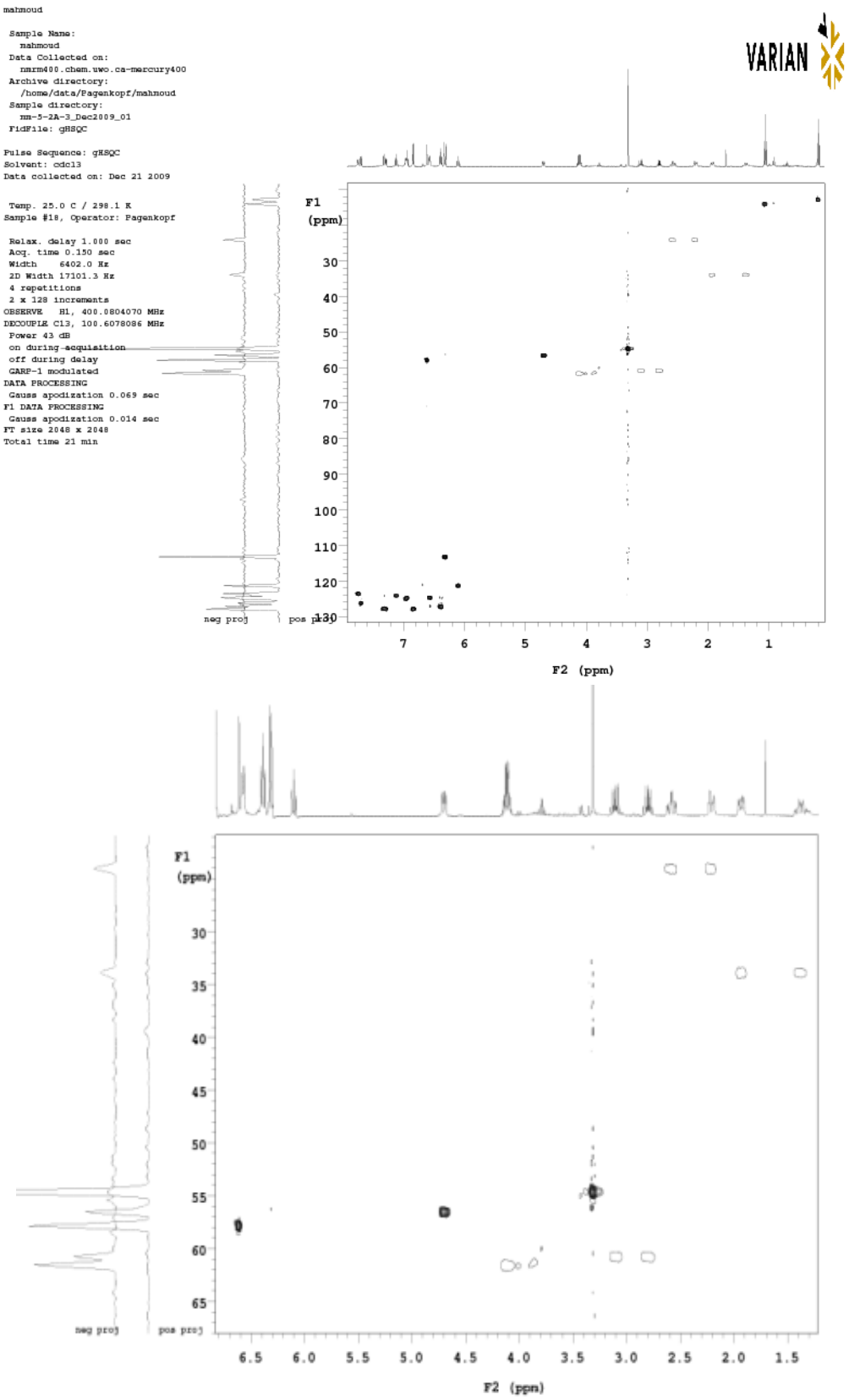

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
nm-5-10-3_Jan810_01
FidFile: gCOSY
Pulse Sequence: gCOSY
Solvent: cdcl3
Data collected on: Jan 8 2010
Temp. 25.0 C / 298.1 K
Sample #49, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
Single scan
128 increments
OBSERVE H1, 400.0802686 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sq. sine bell 0.020 sec
FT size 2048 x 2048
Total time 3 min 11 sec
VARIAN
F1 (ppm)
F2 (ppm)


mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-5-10-3_Jan810_01
FidFile: NOESY
Pulse Sequence: NOESY
Solvent: cdcl3
Data collected on: Jan 8 2010
Temp. 25.0 C / 298.1 K
Sample #49, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
16 repetitions
2 x 200 increments
OBSERVE H1, 400.0802686 MHz
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.029 sec
FT size 2048 x 2048
Total time 2 hr, 27 min
VARIAN
F1 (ppm)
F2 (ppm)
1
2
3
4
5
6
7

Diethyl 6-(4-methoxyphenyl)-2-(naphthalen-1-yl)-1-phenylpiperidine-3,3-dicarboxylate (3.74e):






mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
nm-5-2A-3_Dec2009_01
FidFile: gHSQC
Pulse Sequence: gHSQC
Solvent: cdcl3
Data collected on: Dec 21 2009
Temp. 25.0 C / 298.1 K
Sample #18, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 17101.3 Hz
4 repetitions
2 x 128 increments
OBSERVE H1, 400.0804070 MHz
DECOUPLE C13, 100.6078086 MHz
Power 43 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.014 sec
FT size 2048 x 2048
Total time 21 min
VARIAN
F1 (ppm)
F2 (ppm)
neg proj
pos proj

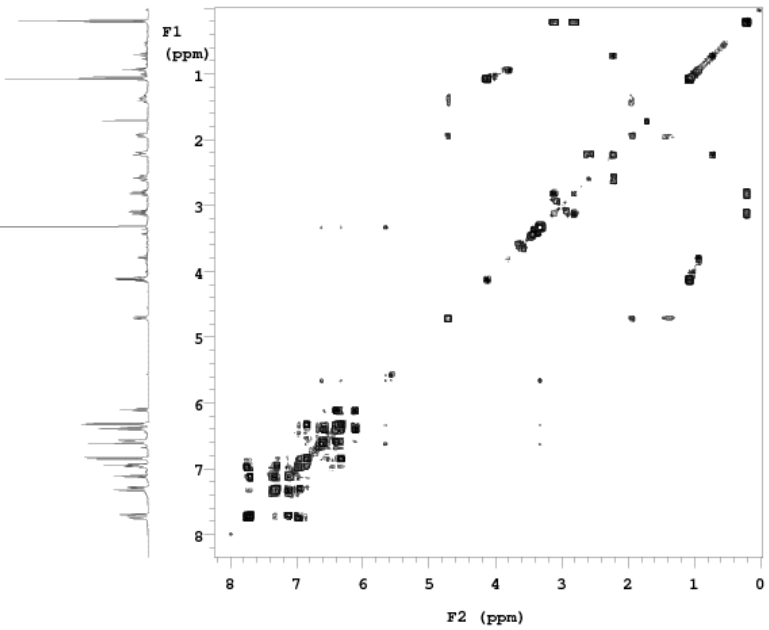
mahmoud

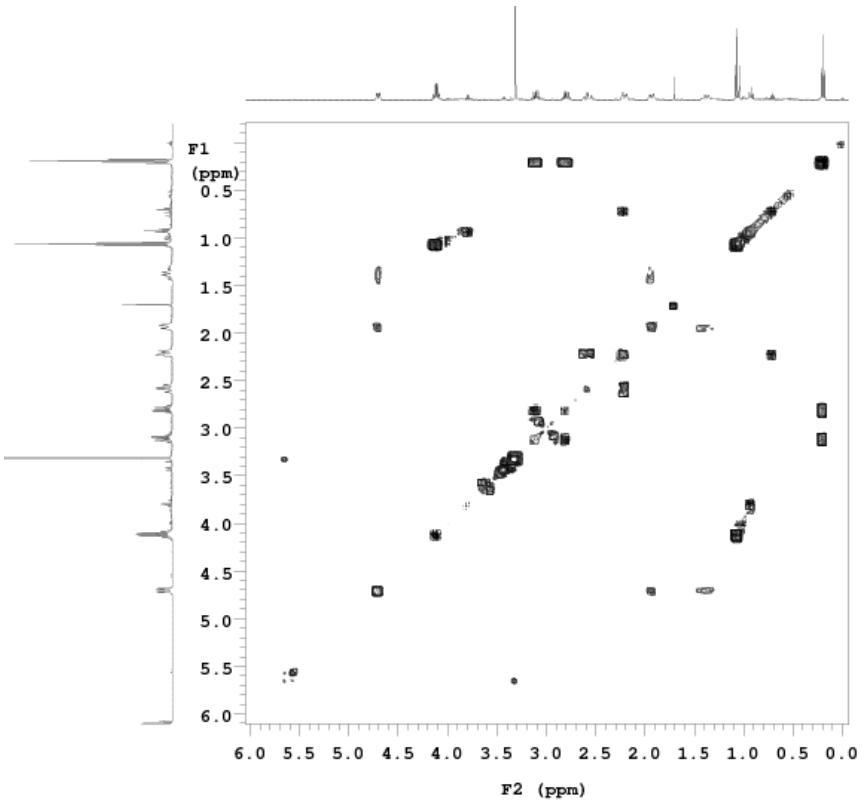
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
nm-5-2A-3_Dec2009_01
FidFile: gCOSY

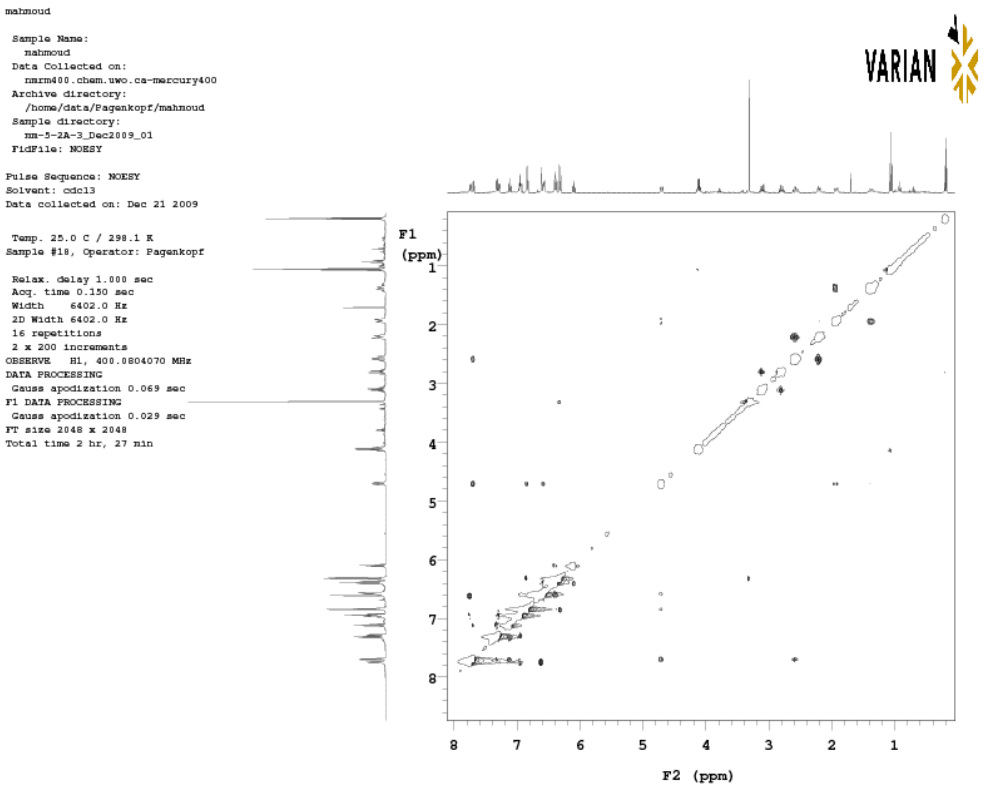
Pulse Sequence: gCOSY
Solvent: cdcl3
Data collected on: Dec 21 2009

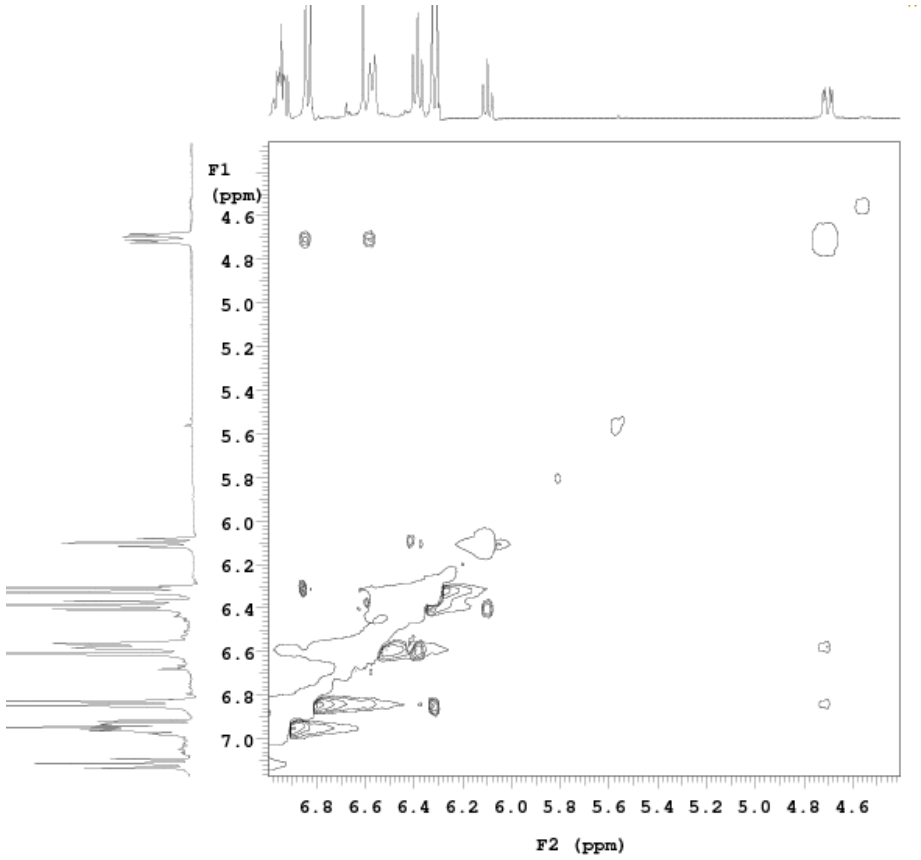
Temp. 25.0 C / 298.1 K
Sample #18, Operator: Pagenkopf

Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
Single scan
128 increments
OBSERVE H1, 400.0804070 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sq. sine bell 0.020 sec
FT size 2048 x 2048
Total time 3 min 11 sec

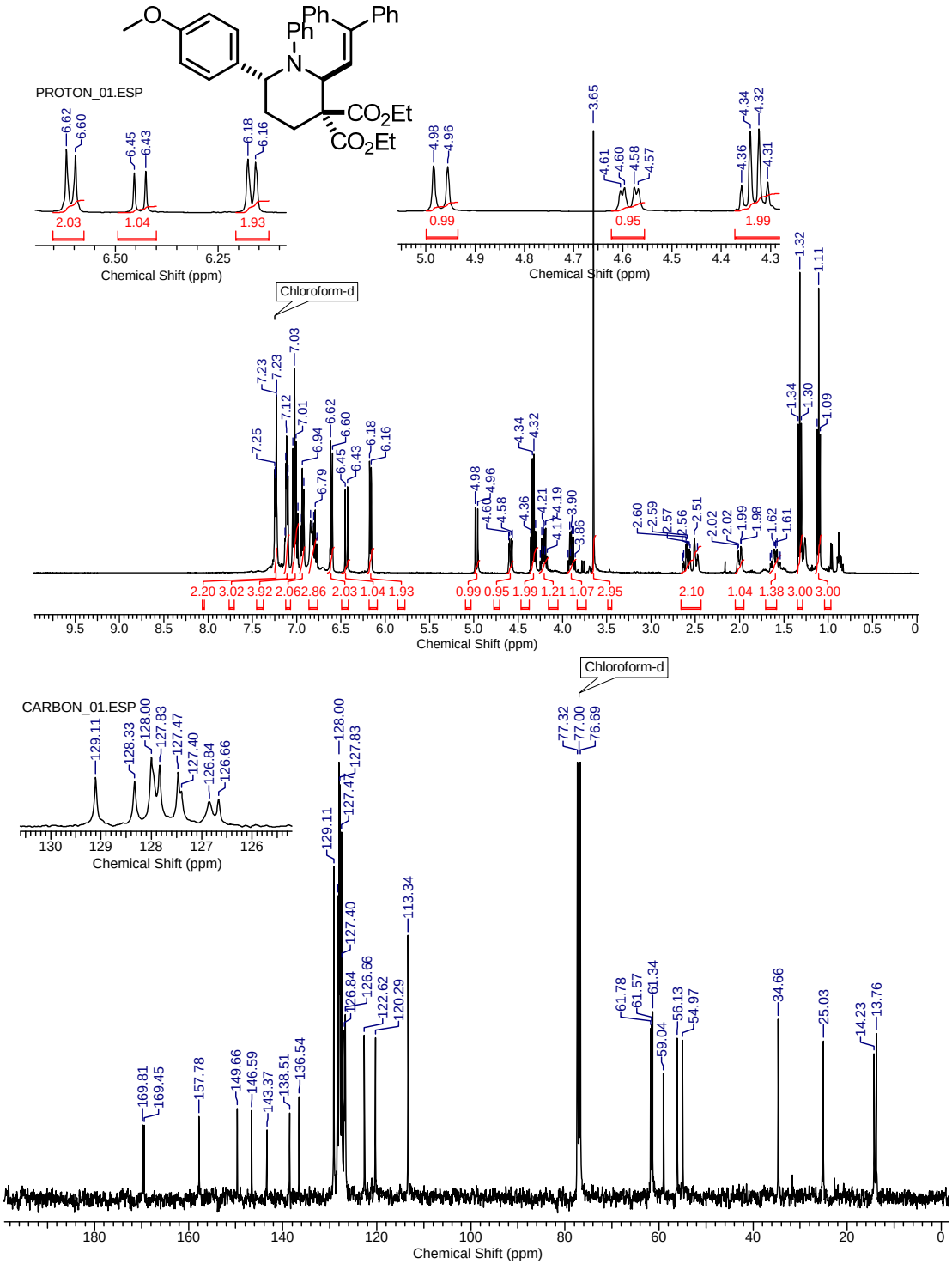


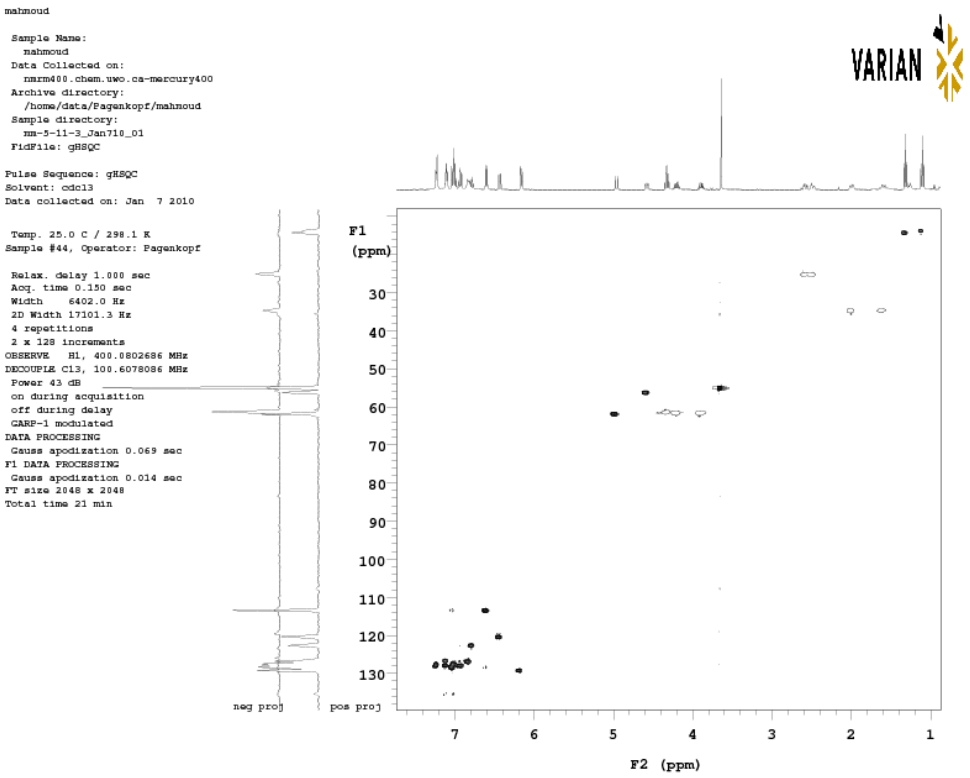


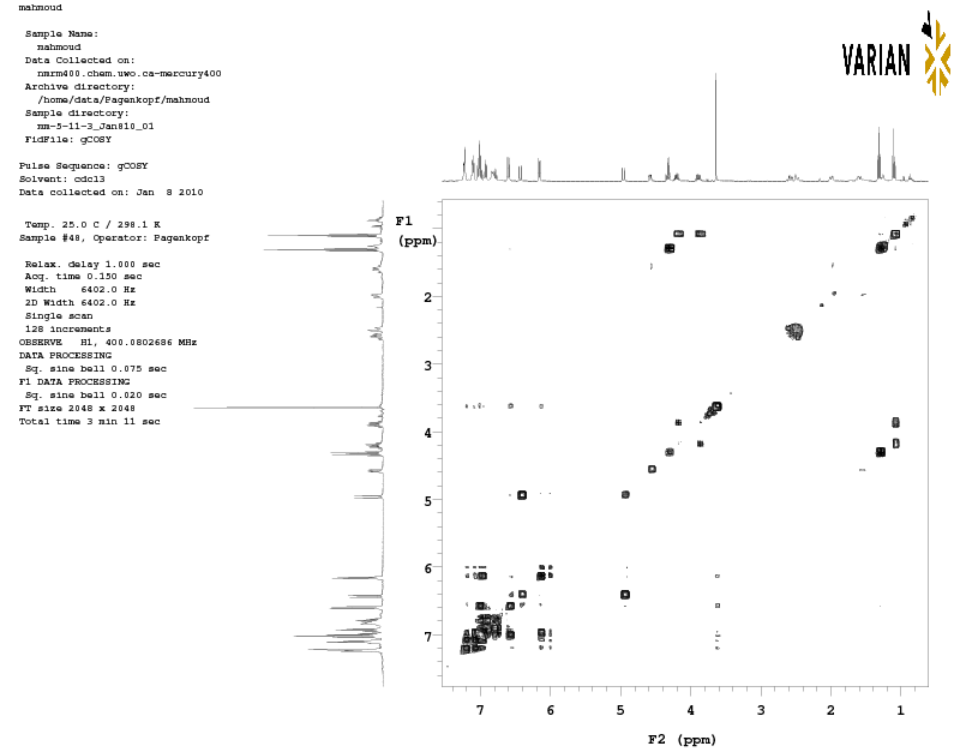

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
nm-5-2A-3_Dec2009_01
FidFile: NOESY
Pulse Sequence: NOESY
Solvent: cdcl3
Data collected on: Dec 21 2009
Temp. 25.0 C / 298.1 K
Sample #18, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
16 repetitions
2 x 200 increments
OBSERVE H1, 400.0804070 MHz
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.029 sec
FT size 2048 x 2048
Total time 2 hr, 27 min
VARIAN
F1 (ppm)
F2 (ppm)

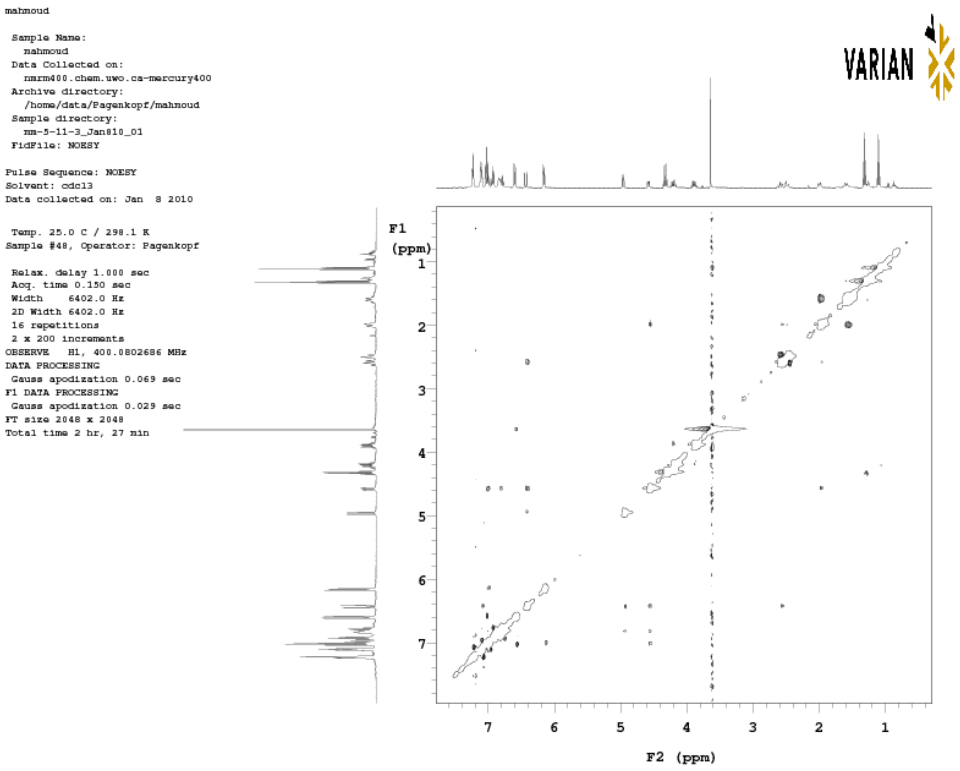

F1 (ppm)
F2 (ppm)

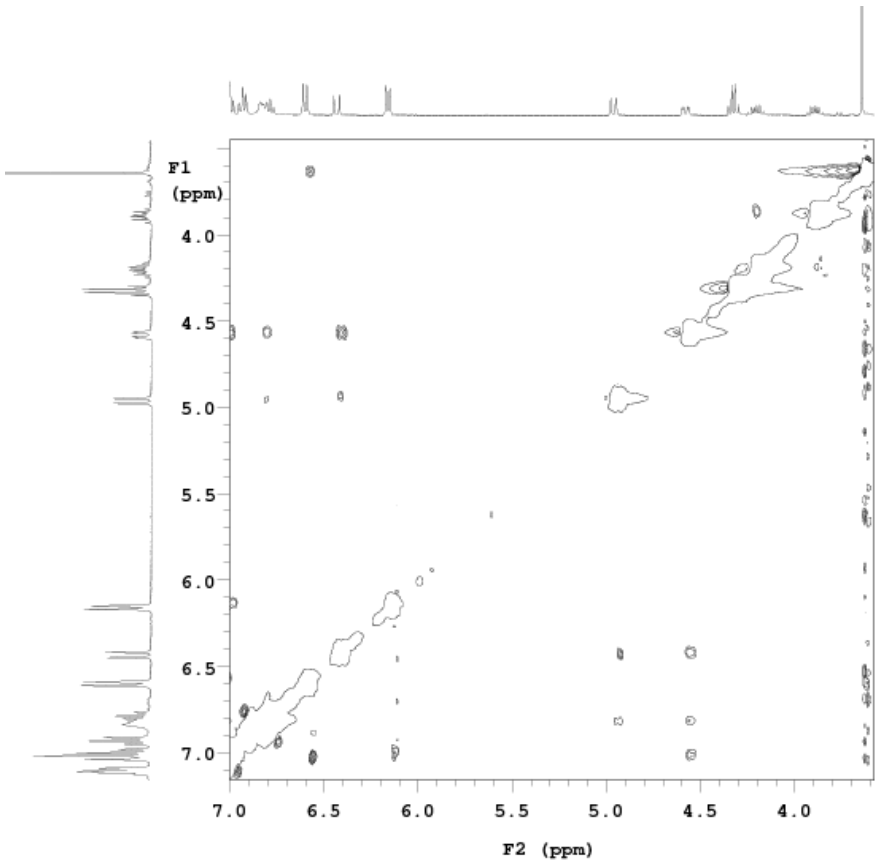
Diethyl 2-(2,2-diphenylvinyl)-6-(4-methoxyphenyl)-1-phenylpiperidine-3,3-dicarboxylate (3.74f):



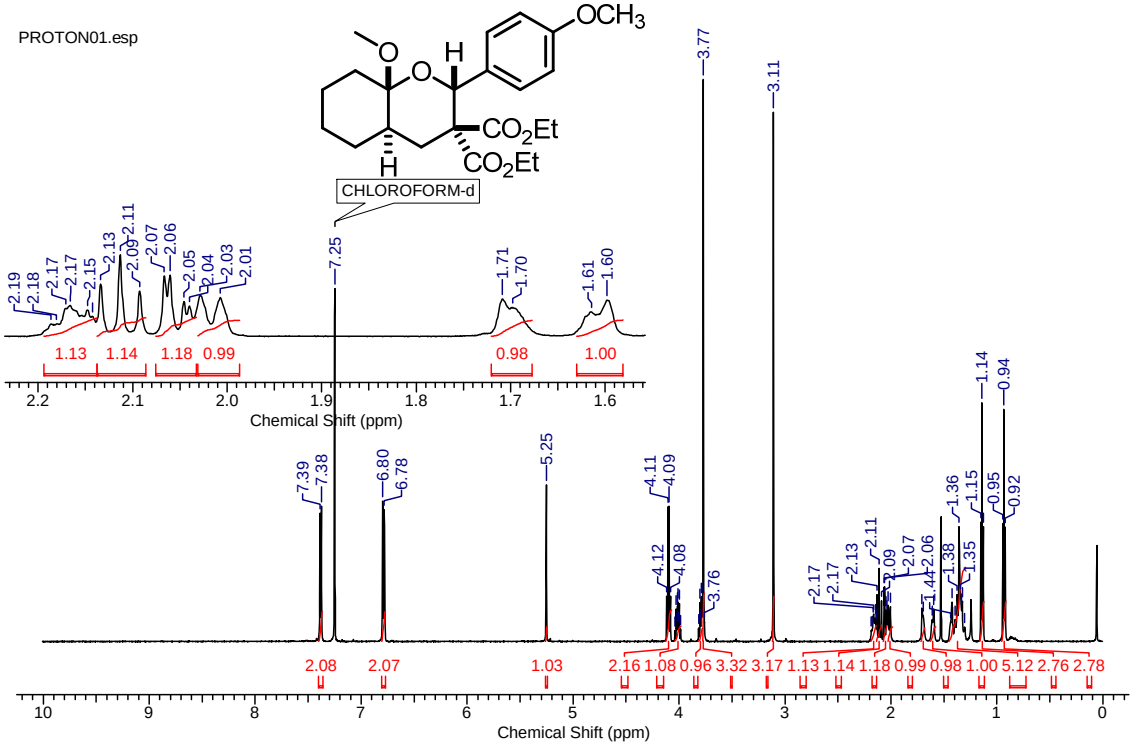

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
nm-5-11-3_Jan710_01
FidFile: gHSQC
Pulse Sequence: gHSQC
Solvent: cdcl3
Data collected on: Jan 7 2010
Temp. 25.0 C / 298.1 K
Sample #44, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 17101.3 Hz
4 repetitions
2 x 128 increments
OBSERVE H1, 400.0802686 MHz
DECOUPLE C13, 100.6078086 MHz
Power 43 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.014 sec
FT size 2048 x 2048
Total time 21 min
VARIAN
F1 (ppm)
neg proj
pos proj
F2 (ppm)

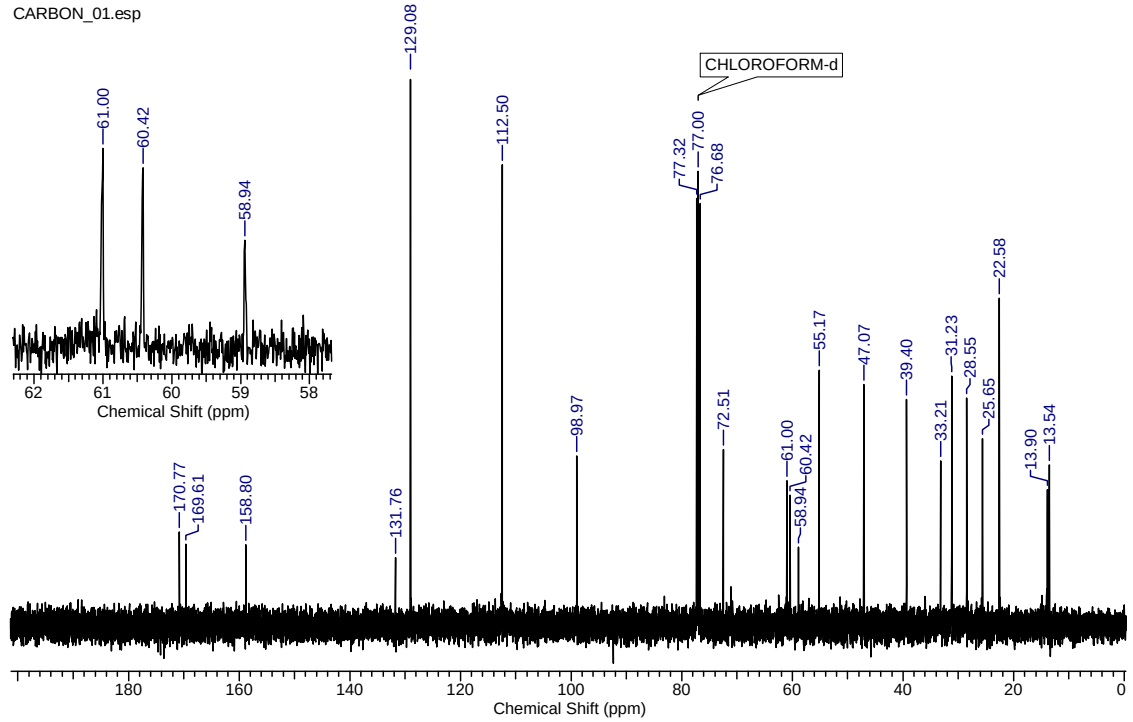

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
nm-5-11-3_Jan810_01
FidFile: gCOSY
Pulse Sequence: gCOSY
Solvent: cdcl3
Data collected on: Jan 8 2010
Temp. 25.0 C / 298.1 K
Sample #48, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
Single scan
128 increments
OBSERVE H1, 400.0802686 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sq. sine bell 0.020 sec
FT size 2048 x 2048
Total time 3 min 11 sec
VARIAN
F1 (ppm)
F2 (ppm)

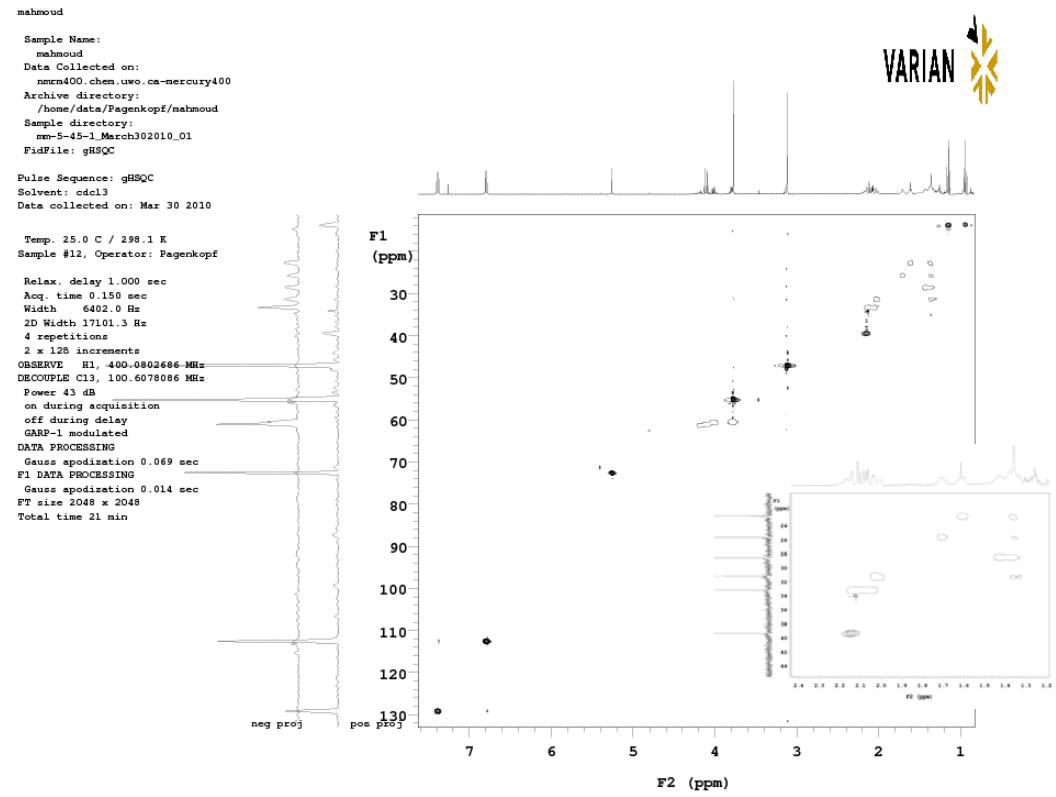

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
nm-5-11-3_Jan810_01
FidFile: NOESY
Pulse Sequence: NOESY
Solvent: cdcl3
Data collected on: Jan 8 2010
Temp. 25.0 C / 298.1 K
Sample #48, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
16 repetitions
2 x 200 increments
OBSERVE H1, 400.0802686 MHz
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.029 sec
FT size 2048 x 2048
Total time 2 hr, 27 min
VARIAN
F1 (ppm)
F2 (ppm)

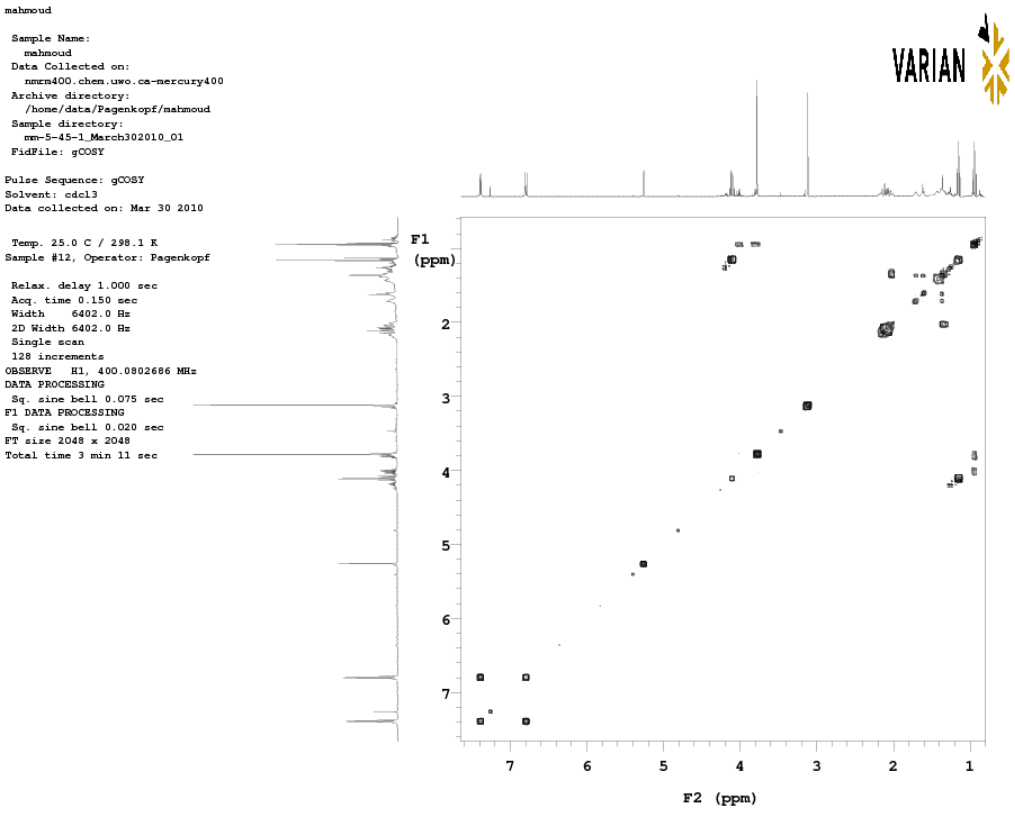

F1 (ppm)
F2 (ppm)

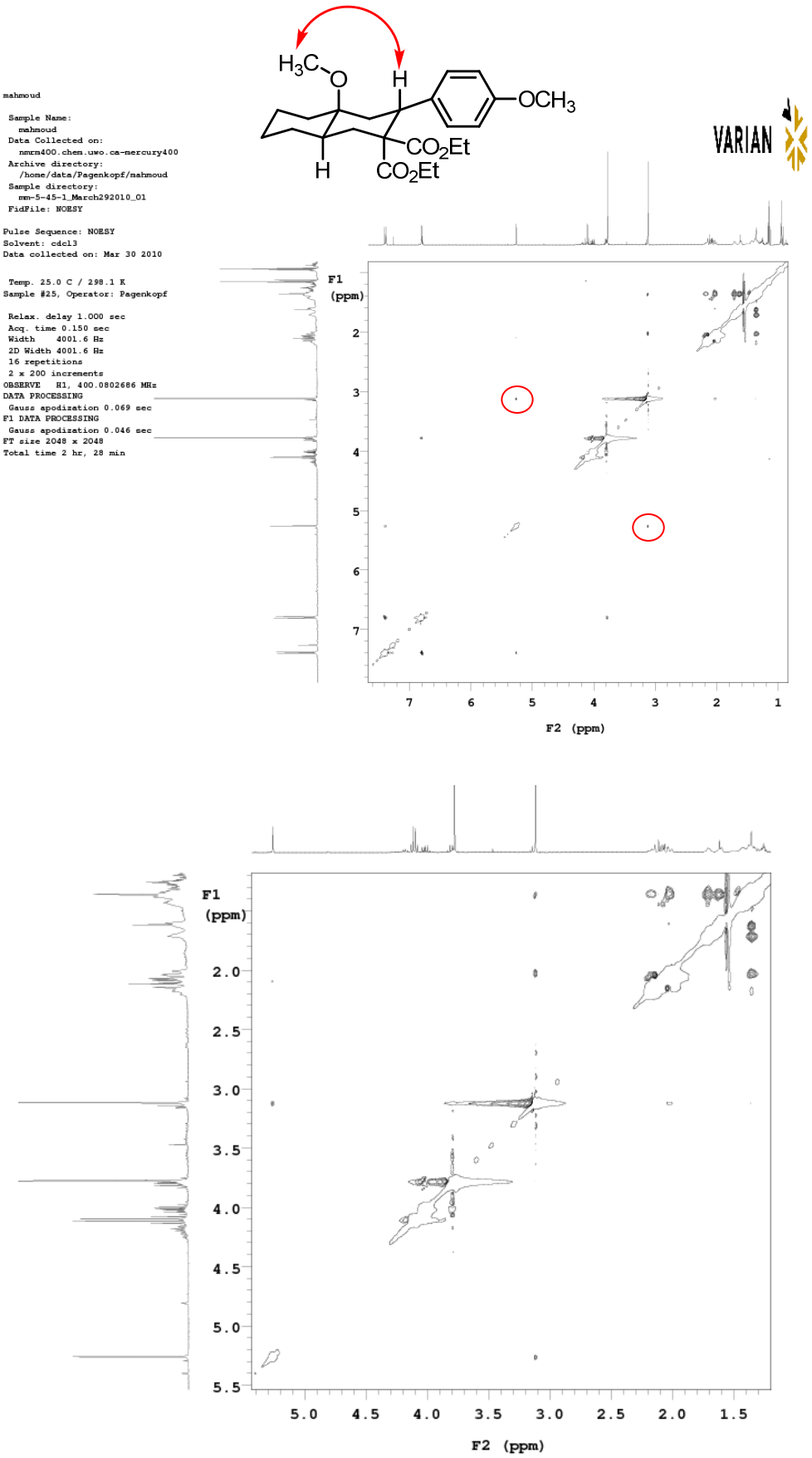
Diethyl 8a-methoxy-2-(4-methoxyphenyl)hexahydro-2*H*-chromene-3,3(4*H*)-dicarboxylate (3.91v)

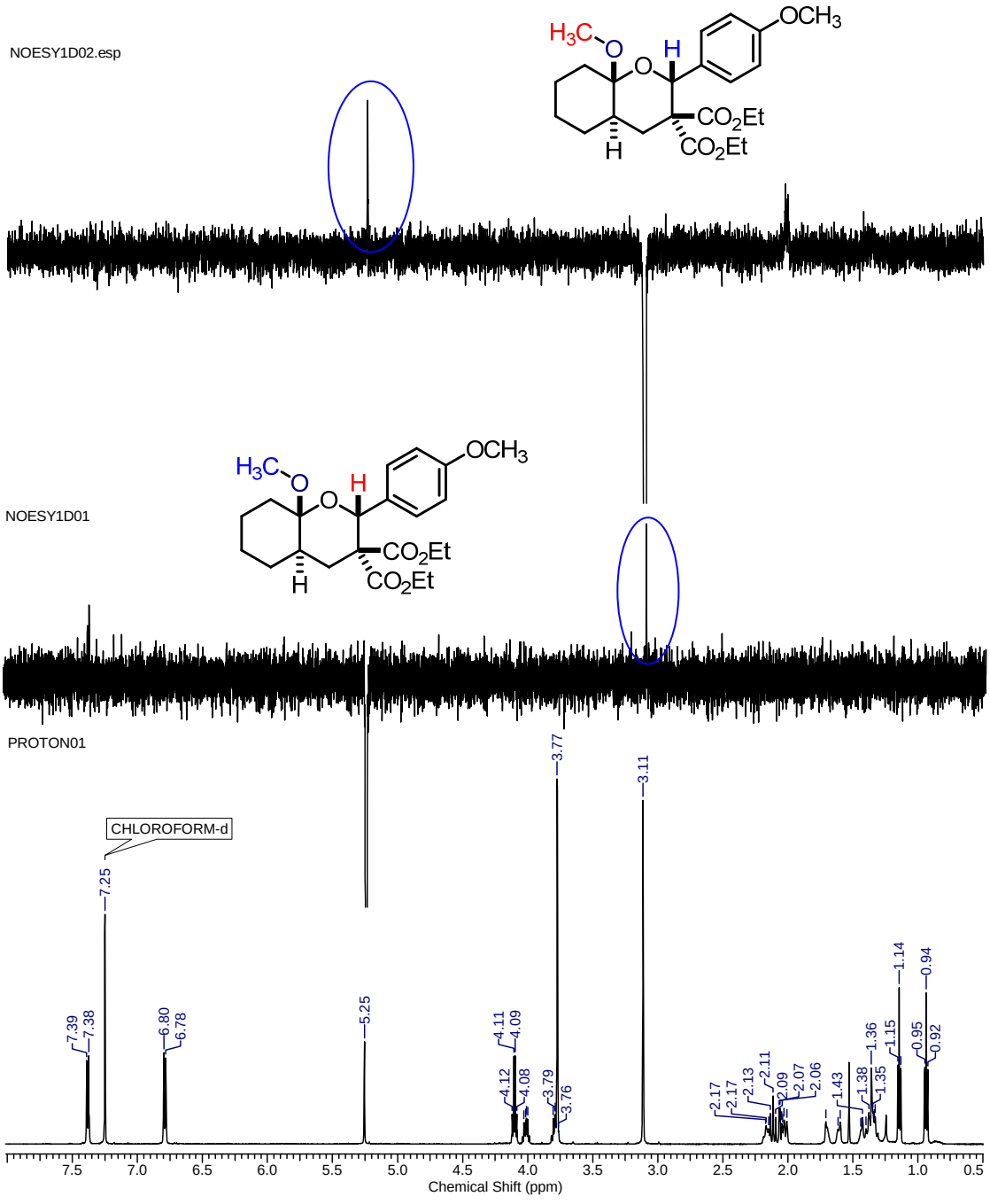




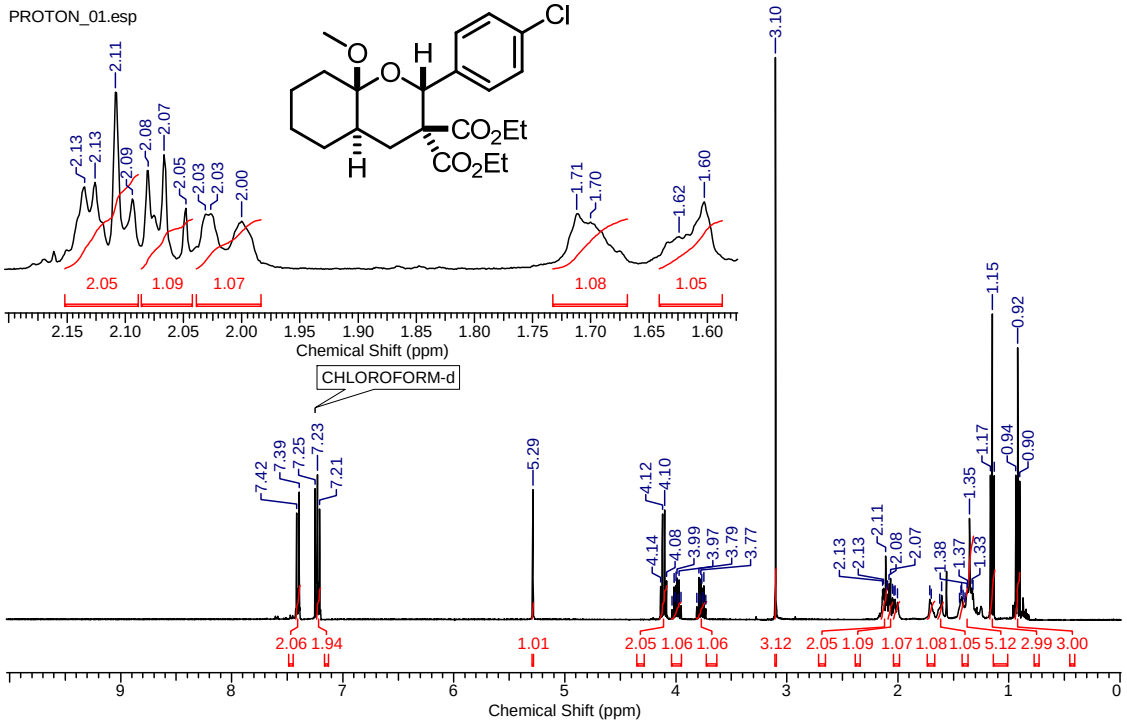

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-5-45-1_March302010_01
FidFile: gHSQC
Pulse Sequence: gHSQC
Solvent: cdcl3
Data collected on: Mar 30 2010
Temp. 25.0 C / 298.1 K
Sample #12, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 17101.3 Hz
4 repetitions
2 x 128 increments
OBSERVE H1, 400.0802686 MHz
DECOUPLE C13, 100.6078086 MHz
Power 43 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.014 sec
FT size 2048 x 2048
Total time 21 min
VARIAN
F1 (ppm)
neg proj
pos proj
F2 (ppm)

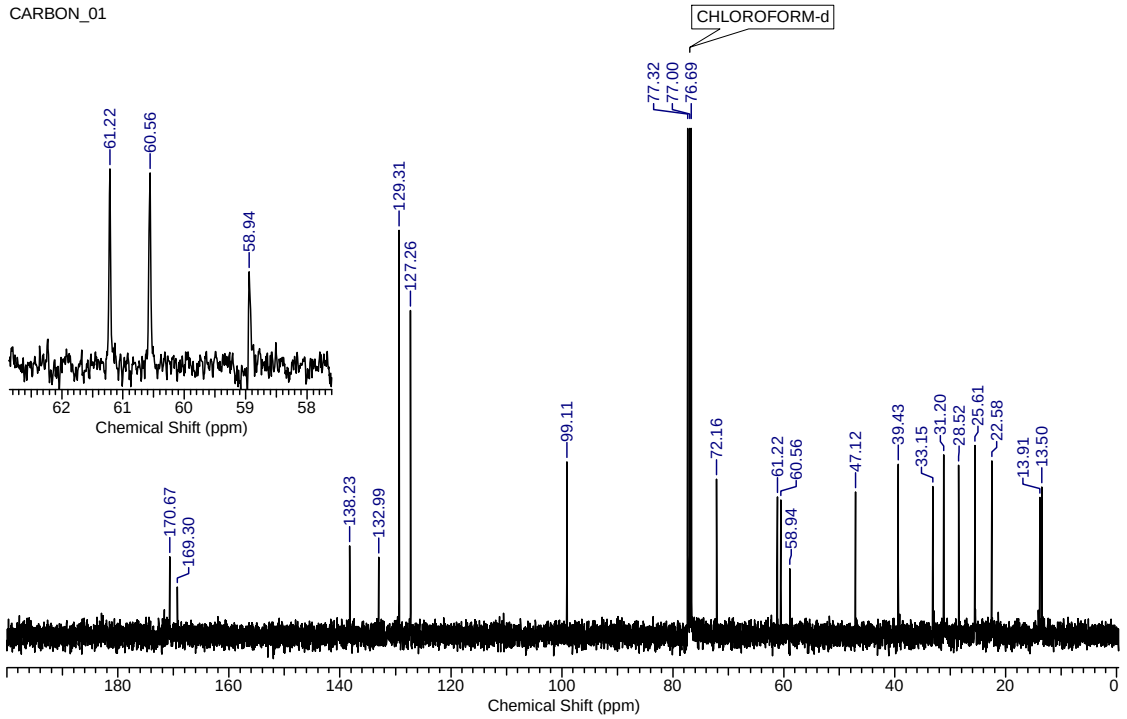

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-5-45-1_March302010_01
FidFile: gCOSY
Pulse Sequence: gCOSY
Solvent: cdcl3
Data collected on: Mar 30 2010
Temp. 25.0 C / 298.1 K
Sample #12, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
Single scan
128 increments
OBSERVE H1, 400.0802686 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sq. sine bell 0.020 sec
FT size 2048 x 2048
Total time 3 min 11 sec
VARIAN
F1 (ppm)
F2 (ppm)

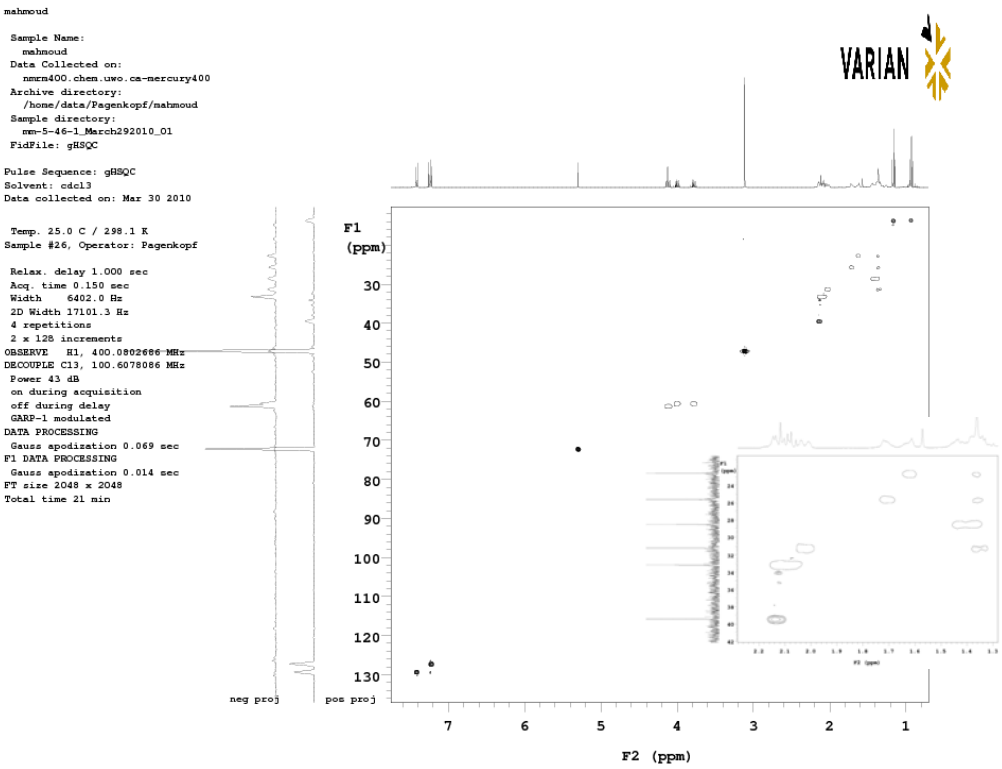

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-5-45-1_March292010_01
FidFile: NOESY
Pulse Sequence: NOESY
Solvent: cdcl3
Data collected on: Mar 30 2010
Temp. 25.0 C / 298.1 K
Sample #25, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 4001.6 Hz
2D Width 4001.6 Hz
16 repetitions
2 x 200 increments
OBSERVE H1, 400.0802686 MHz
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.046 sec
FT size 2048 x 2048
Total time 2 hr, 28 min
H3C
O
H
OCH3
CO2Et
H
CO2Et
VARIAN
F1 (ppm)
F2 (ppm)
F1 (ppm)
F2 (ppm)

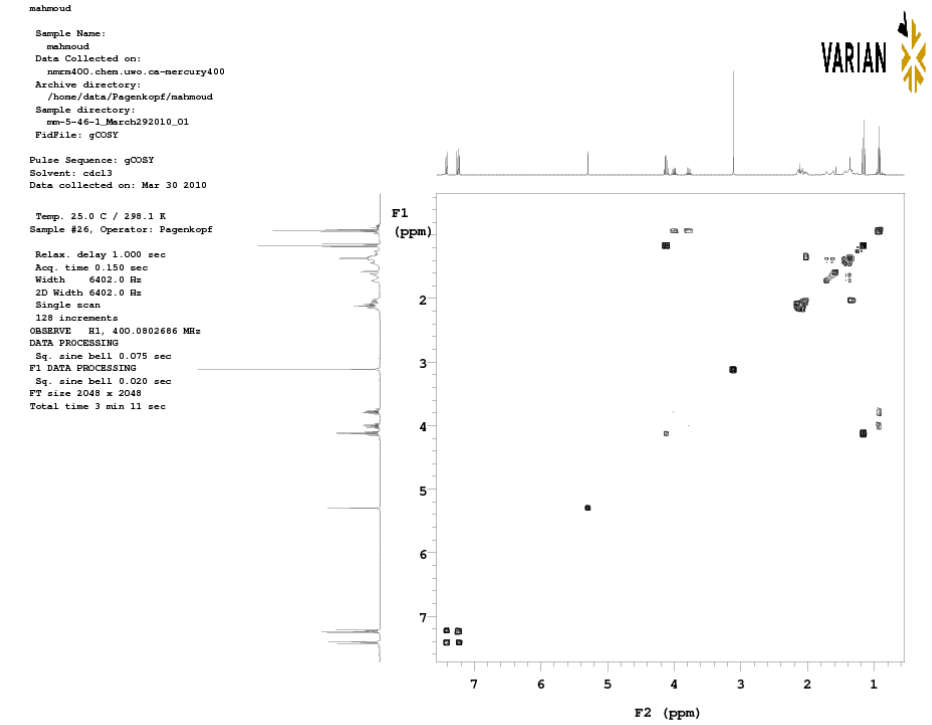

NOESY1D02.esp
NOESY1D01
PROTON01
CHLOROFORM-d
7.25
7.39
7.38
6.80
6.78
5.25
4.11
4.09
4.12
4.08
3.79
3.76
3.77
3.11
2.17
2.17
2.13
2.11
2.09
2.07
2.06
1.43
1.38
1.36
1.35
1.15
1.14
0.95
0.94
0.92
Chemical Shift (ppm)

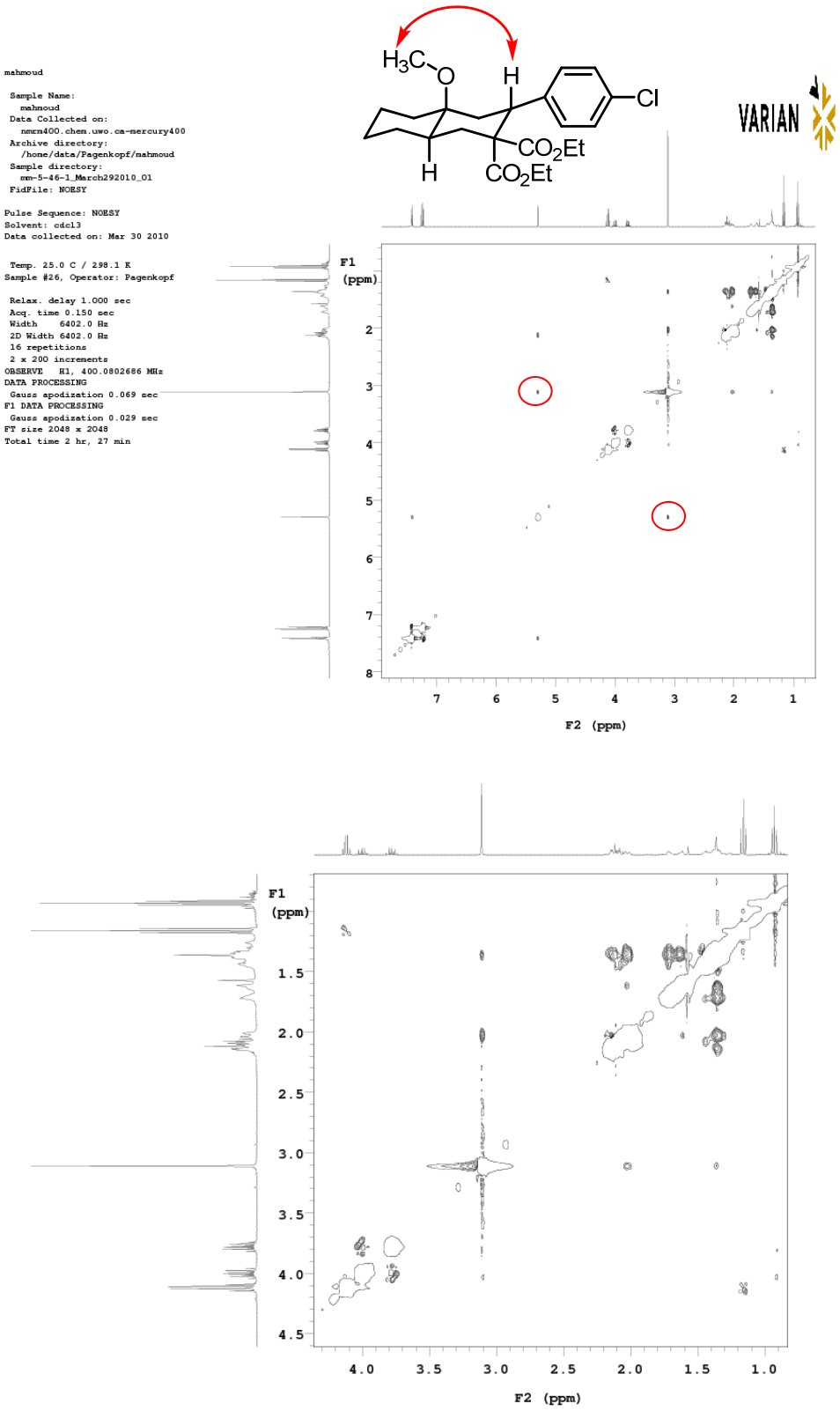
Diethyl 2-(4-chlorophenyl)-8a-methoxyhexahydro-2*H*-chromene-3,3(4*H*)-dicarboxylate (3.91w)

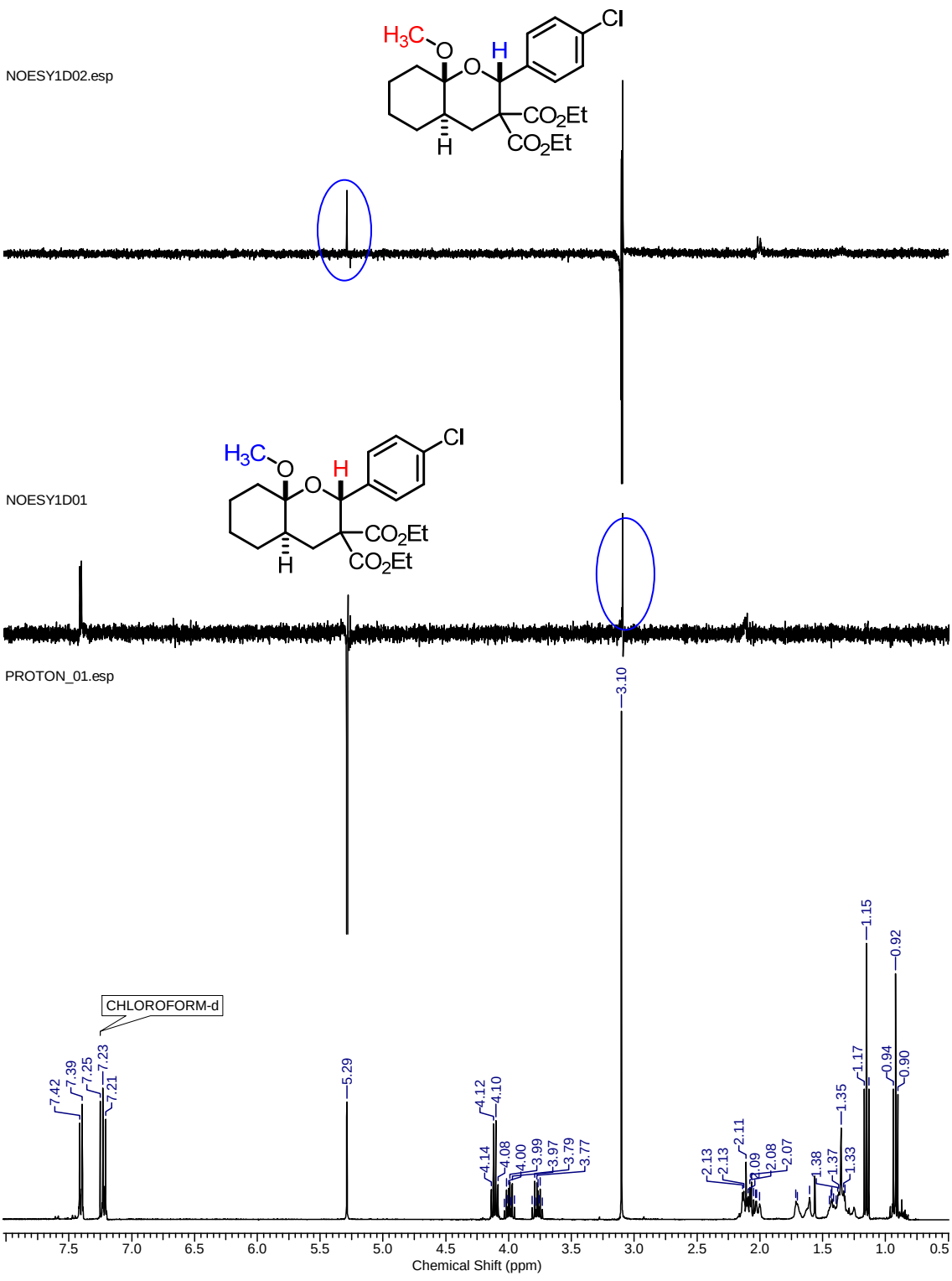




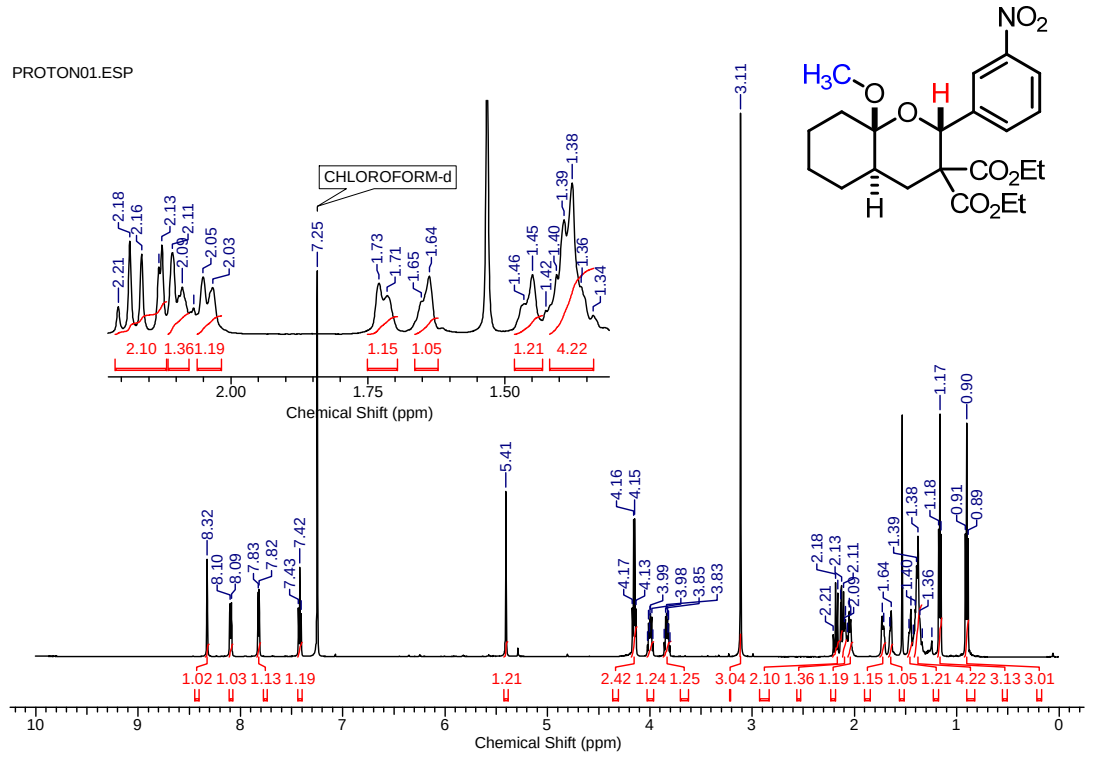

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-5-46-1_March292010_01
FidFile: gHSQC
Pulse Sequence: gHSQC
Solvent: cdcl3
Data collected on: Mar 30 2010
Temp. 25.0 C / 298.1 K
Sample #26, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 17101.3 Hz
4 repetitions
2 x 128 increments
OBSERVE H1, 400.0802686 MHz
DECOUPLE C13, 100.6078086 MHz
Power 43 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.014 sec
FT size 2048 x 2048
Total time 21 min
VARIAN
F1 (ppm)
neg proj
pos proj
F2 (ppm)

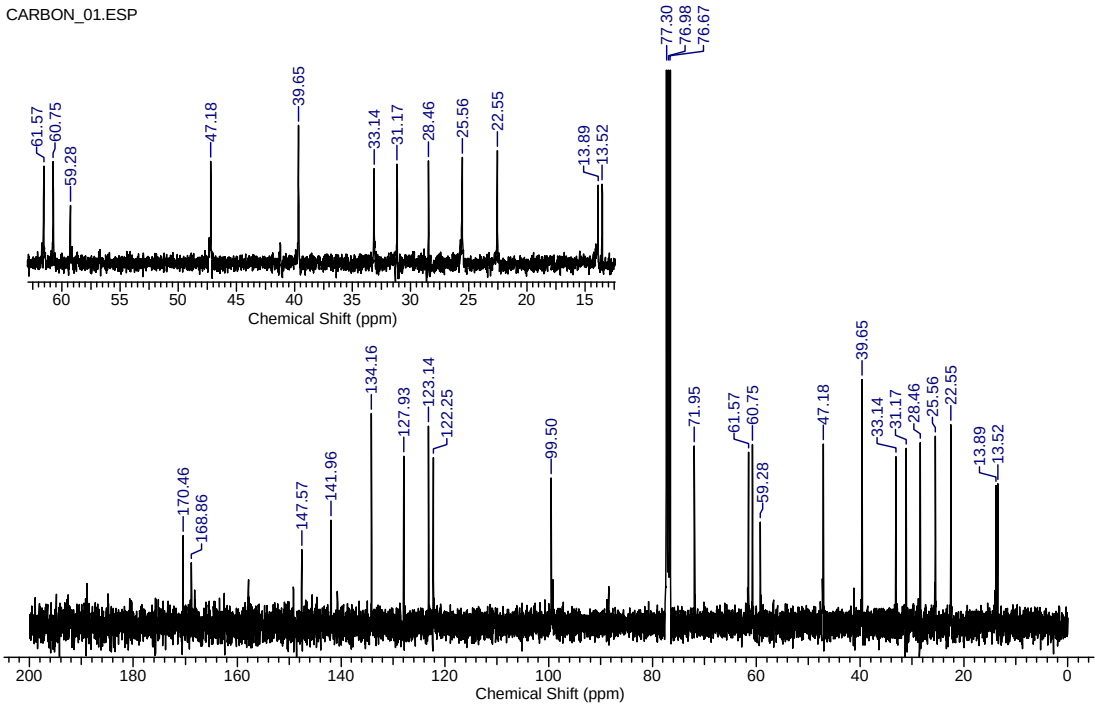

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-5-46-1_March292010_01
FidFile: gCOSY
Pulse Sequence: gCOSY
Solvent: cdcl3
Data collected on: Mar 30 2010
Temp. 25.0 C / 298.1 K
Sample #26, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
Single scan
128 increments
OBSERVE H1, 400.0802686 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sq. sine bell 0.020 sec
FT size 2048 x 2048
Total time 3 min 11 sec
VARIAN
F1 (ppm)
F2 (ppm)

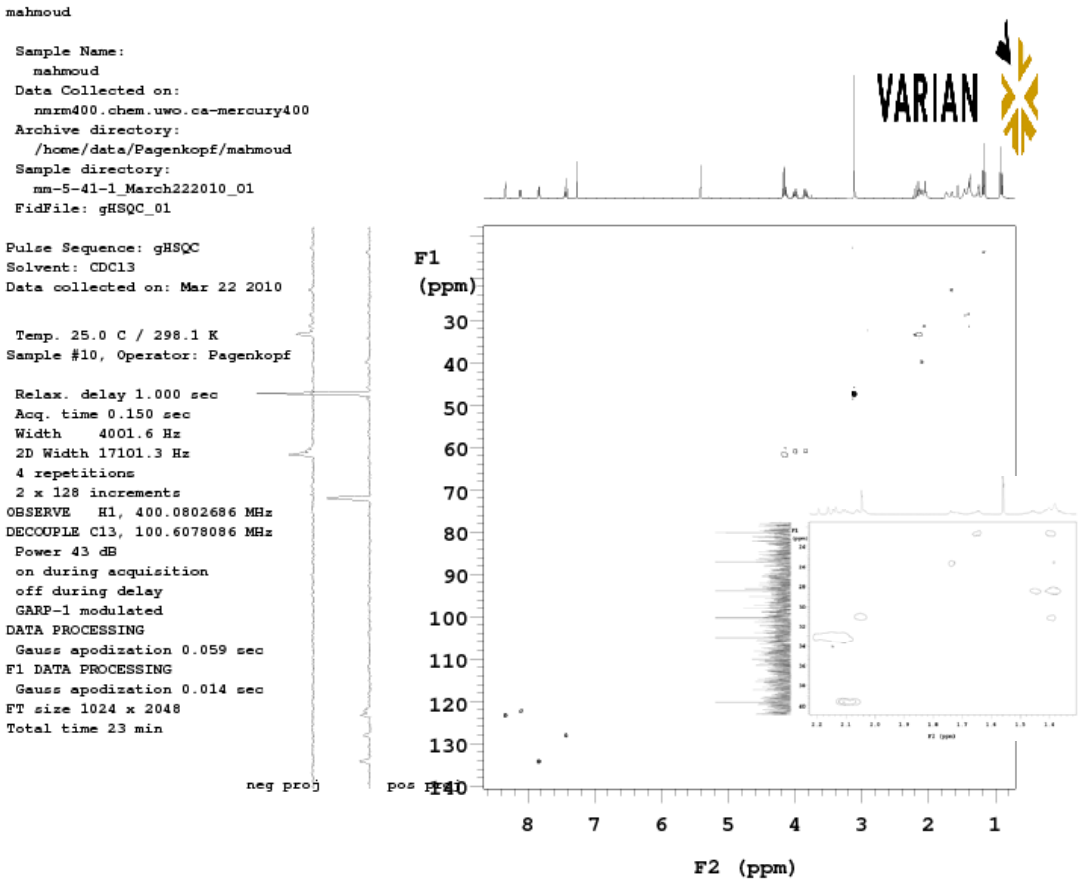

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrn400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-5-46-1_March292010_01
FidFile: NOESY
Pulse Sequence: NOESY
Solvent: cdcl3
Data collected on: Mar 30 2010
Temp. 25.0 C / 298.1 K
Sample #26, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
16 repetitions
2 x 200 increments
OBSERVE H1, 400.0802686 MHz
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.029 sec
FT size 2048 x 2048
Total time 2 hr, 27 min
H3C
O
H
Cl
CO2Et
H
CO2Et
VARIAN
F1 (ppm)
F2 (ppm)
F1 (ppm)
F2 (ppm)

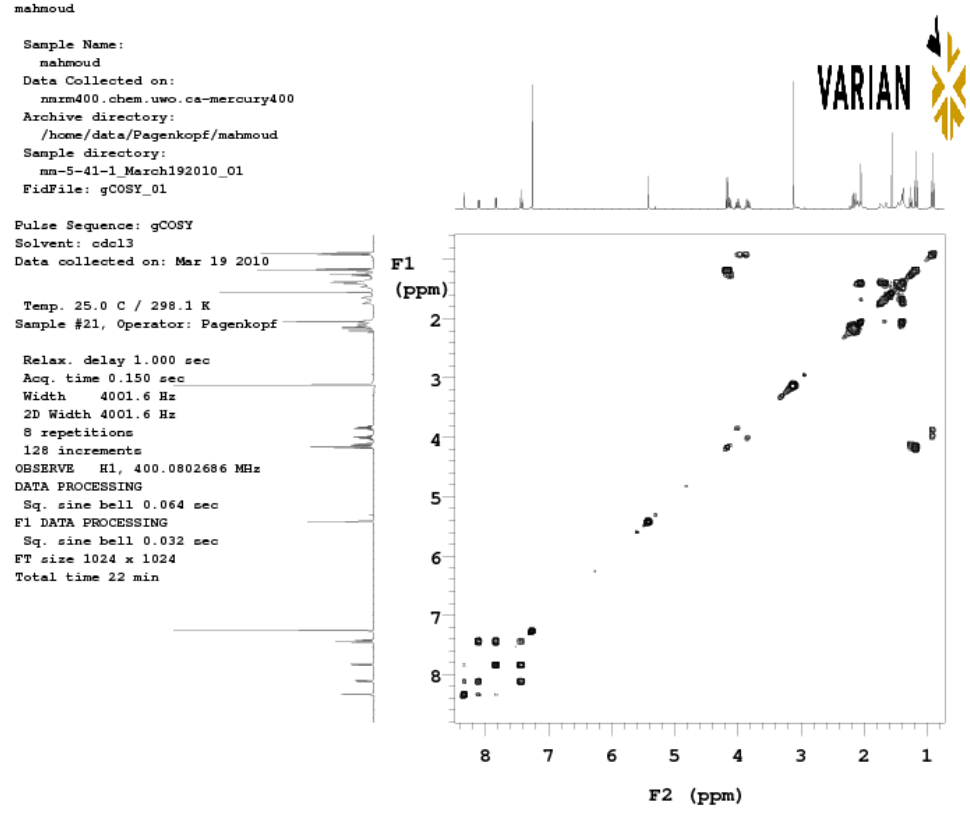

NOESY1D02.esp
NOESY1D01
PROTON_01.esp
H3C
O
O
H
Cl
CO2Et
CO2Et
H
CHLOROFORM-d
7.42
7.39
7.25
7.23
7.21
5.29
4.12
4.10
4.14
4.08
4.00
3.99
3.97
3.79
3.77
3.10
2.13
2.13
2.11
2.09
2.08
2.07
1.38
1.37
1.35
1.33
1.17
1.15
0.94
0.92
0.90
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical Shift (ppm)

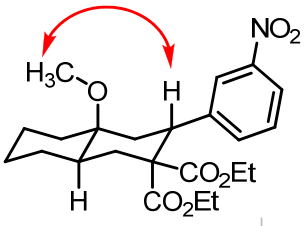
Diethyl 8a-methoxy-2-(3-nitrophenyl)hexahydro-2*H*-chromene-3,3(4H)-dicarboxylate (3.91x)



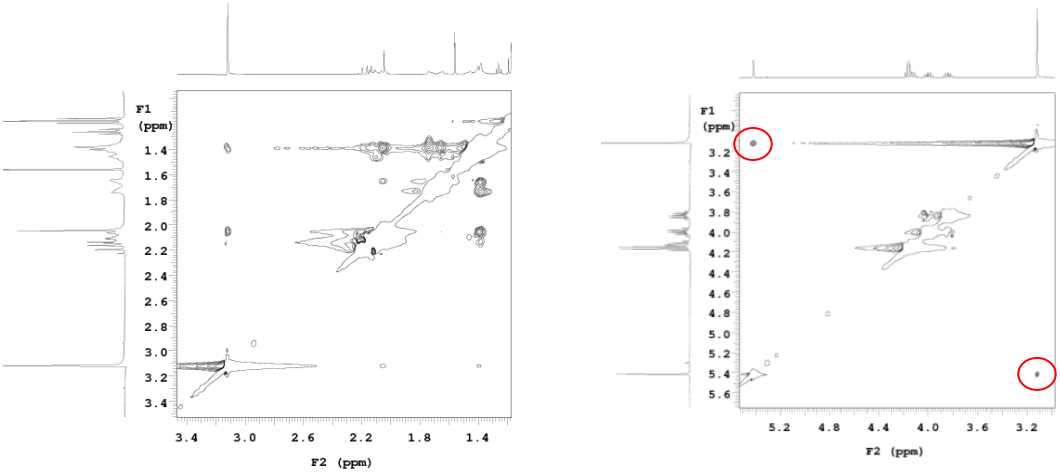


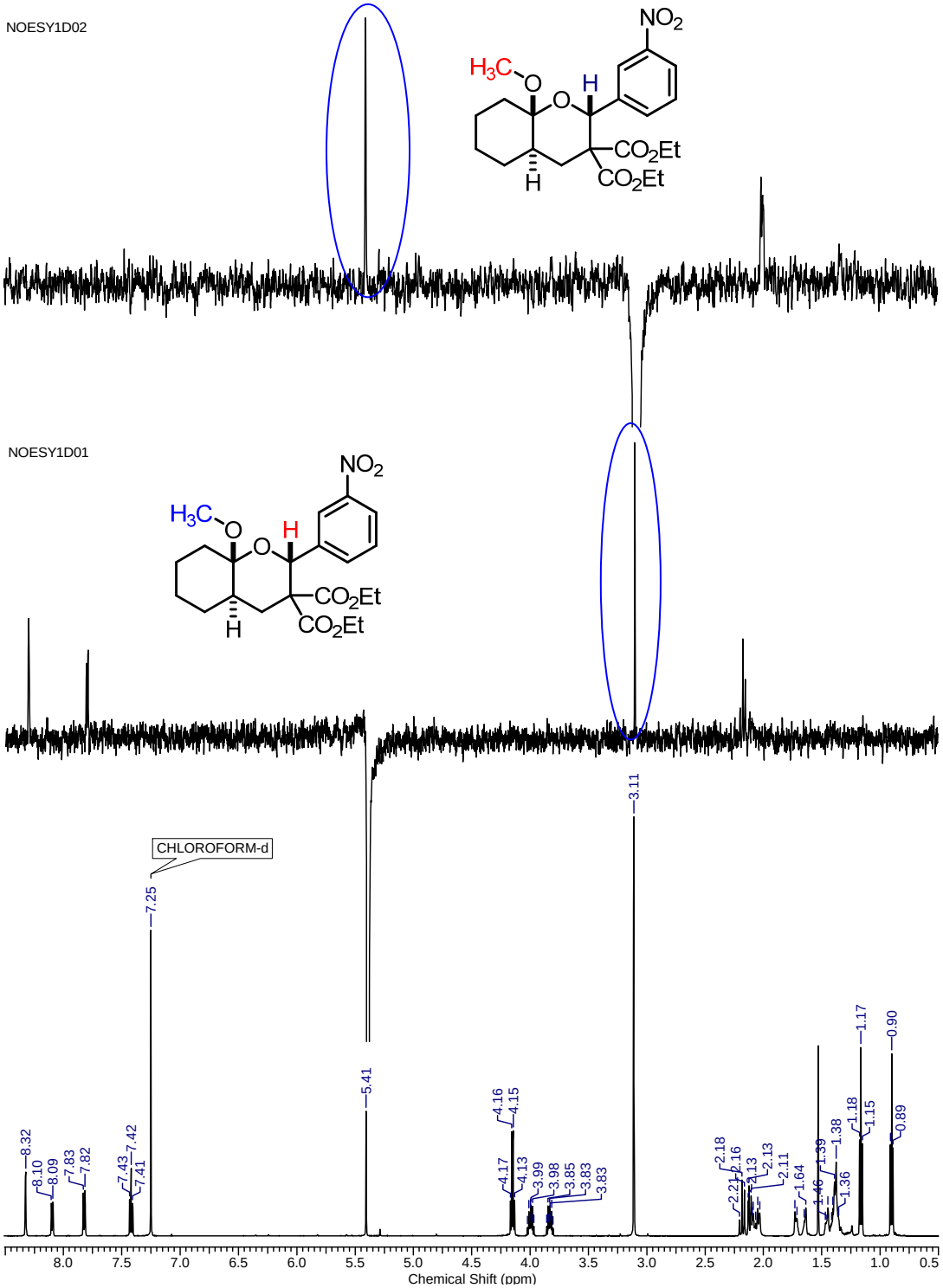

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
nm-5-41-1_March222010_01
FidFile: gHSQC_01
Pulse Sequence: gHSQC
Solvent: CDCl3
Data collected on: Mar 22 2010
Temp. 25.0 C / 298.1 K
Sample #10, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 4001.6 Hz
2D Width 17101.3 Hz
4 repetitions
2 x 128 increments
OBSERVE H1, 400.0802686 MHz
DECOUPLE C13, 100.6078086 MHz
Power 43 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Gauss apodization 0.059 sec
F1 DATA PROCESSING
Gauss apodization 0.014 sec
FT size 1024 x 2048
Total time 23 min
VARIAN
F1
(ppm)
30
40
50
60
70
80
90
100
110
120
130
140
neg proj
pos proj
8
7
6
5
4
3
2
1
F2 (ppm)


mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
nm-5-41-1_March192010_01
FidFile: gCOSY_01
Pulse Sequence: gCOSY
Solvent: cdcl3
Data collected on: Mar 19 2010
Temp. 25.0 C / 298.1 K
Sample #21, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 4001.6 Hz
2D Width 4001.6 Hz
8 repetitions
128 increments
OBSERVE H1, 400.0802686 MHz
DATA PROCESSING
Sq. sine bell 0.064 sec
F1 DATA PROCESSING
Sq. sine bell 0.032 sec
FT size 1024 x 1024
Total time 22 min
VARIAN
F1
(ppm)
2
3
4
5
6
7
8
8
7
6
5
4
3
2
1
F2 (ppm)

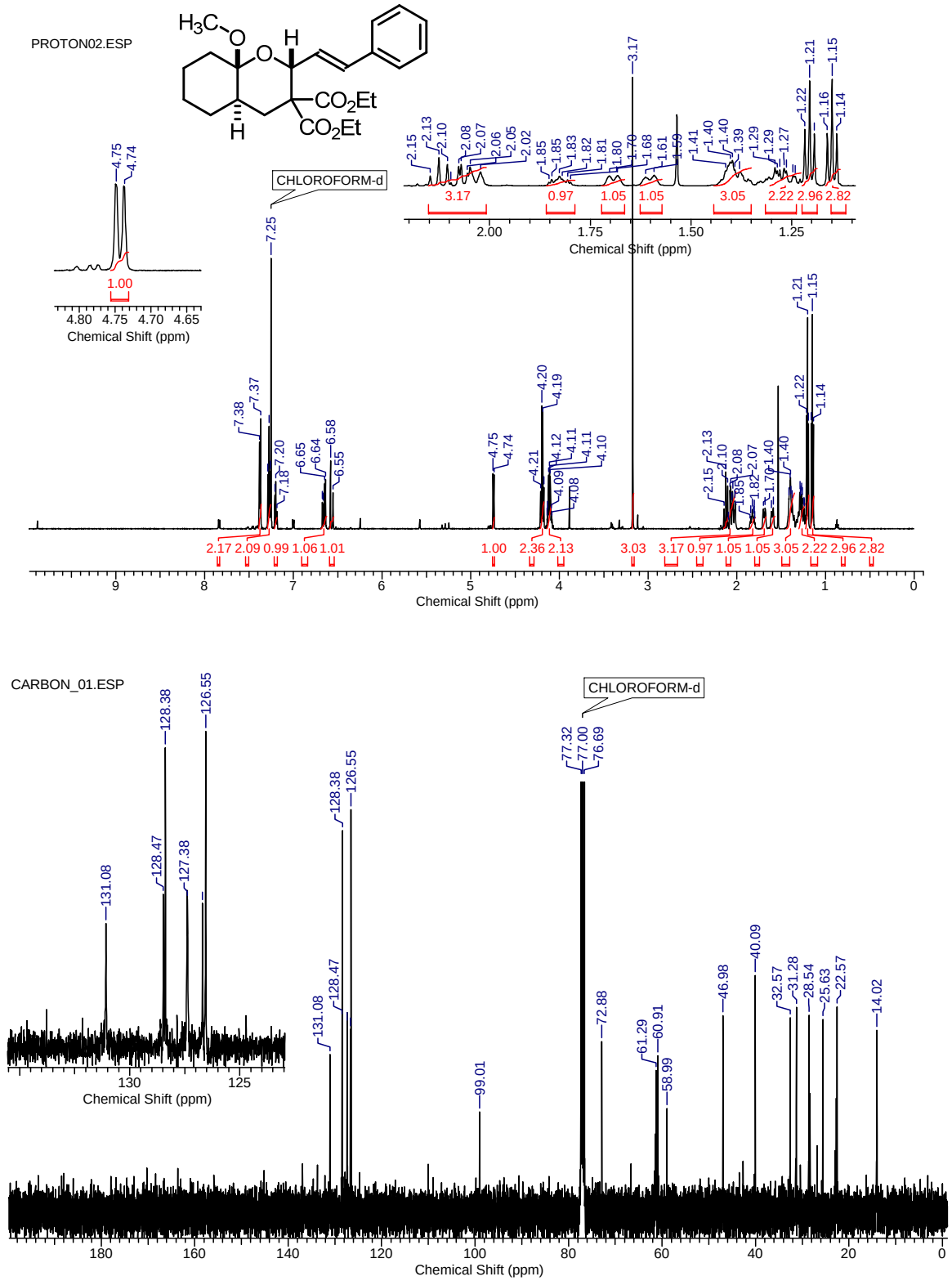


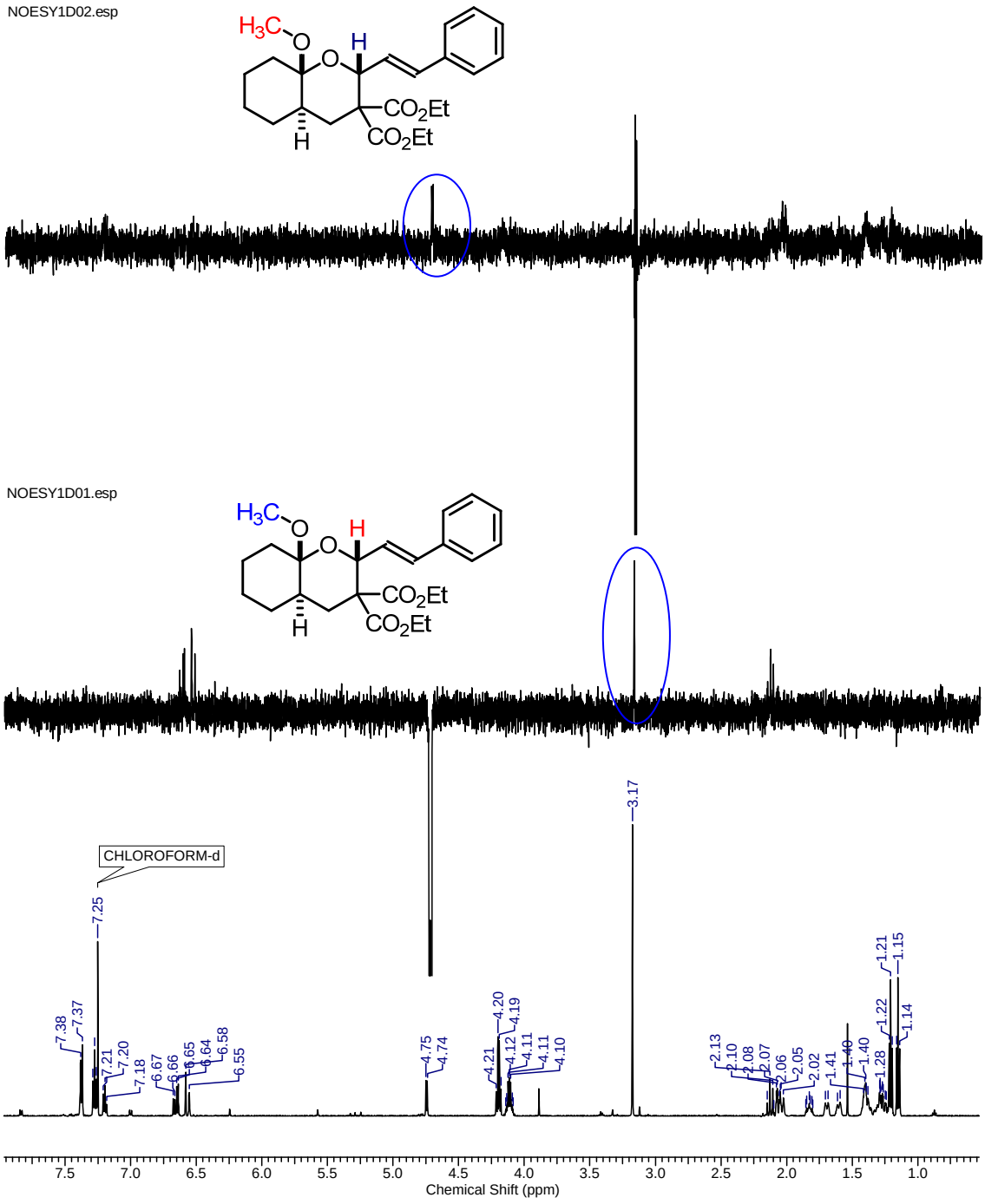

```
mahmoud

 Sample Name:
   mahmoud
 Data Collected on:
   nmrm400.chem.uwo.ca-mercury400
 Archive directory:
   /home/data/Pagenkopf/mahmoud
 Sample directory:
   mm-5-41-1_March192010_01
 FidFile: NOESY_01

Pulse Sequence: NOESY
Solvent: cdcl3
Data collected on: Mar 19 2010

 Temp. 25.0 C / 298.1 K
Sample #21, Operator: Pagenkopf

 Relax. delay 1.000 sec
 Acq. time 0.150 sec
 Width     4001.6 Hz
 2D Width 4001.6 Hz
 16 repetitions
 2 x 200 increments
OBSERVE   H1, 400.0802686 MHz
DATA PROCESSING
 Gauss apodization 0.069 sec
F1 DATA PROCESSING
 Gauss apodization 0.046 sec
FT size 2048 x 2048
Total time 2 hr, 33 min
```



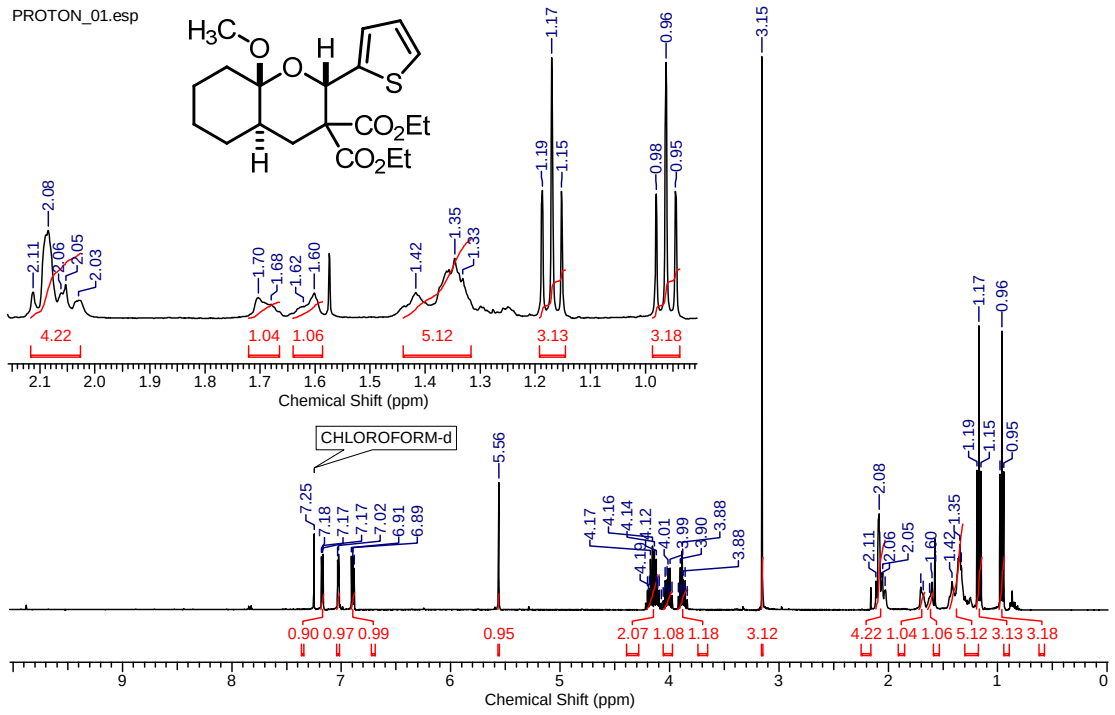

NOESY1D02
NO2
H3C
O
O
H
CO2Et
CO2Et
H
NOESY1D01
NO2
H3C
O
O
H
CO2Et
CO2Et
H
CHLOROFORM-d
7.25
5.41
3.11
8.32
8.10
8.09
7.83
7.82
7.43
7.42
7.41
4.17
4.16
4.15
4.13
3.99
3.98
3.85
3.83
3.83
2.18
2.16
2.13
2.11
1.64
1.46
1.39
1.38
1.36
1.18
1.17
1.15
0.90
0.89
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical Shift (ppm)

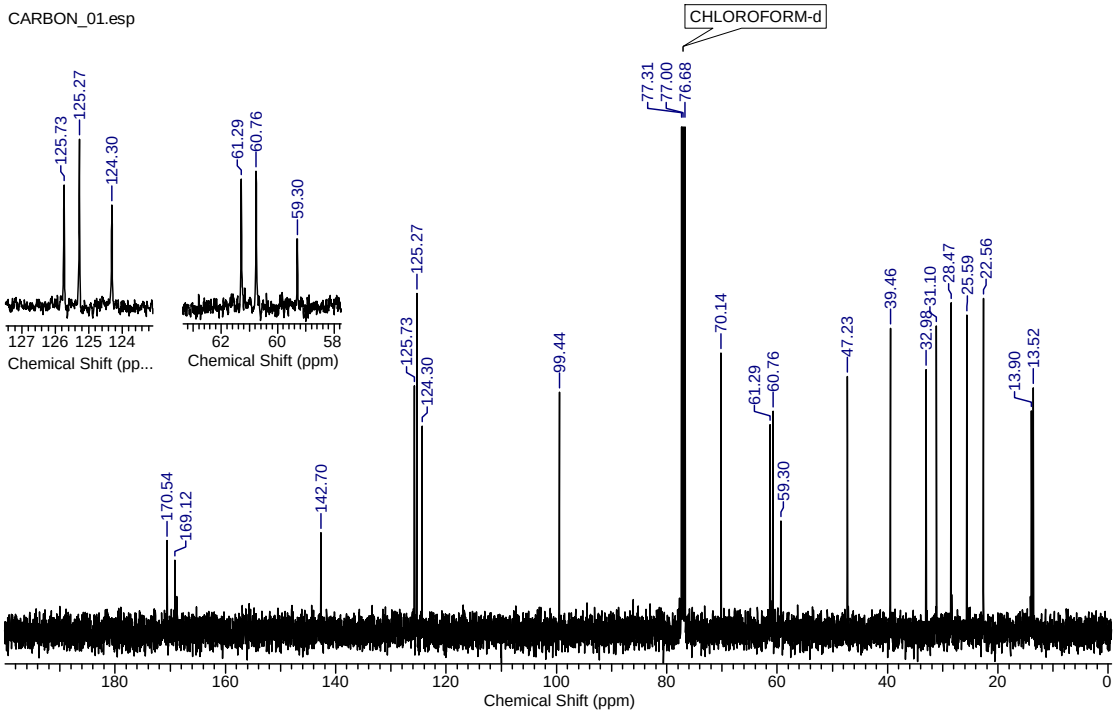
Diethyl 8a-methoxy-2-styrylhexahydro-2*H*-chromene-3,3(4*H*)-dicarboxylate (3.91y)

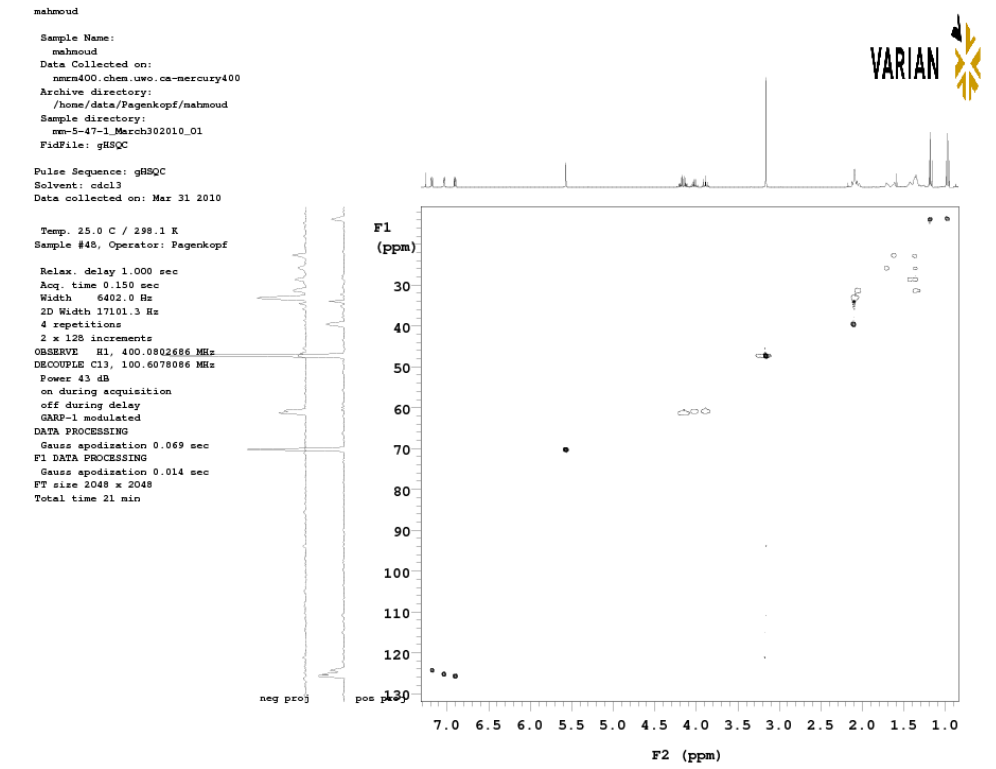


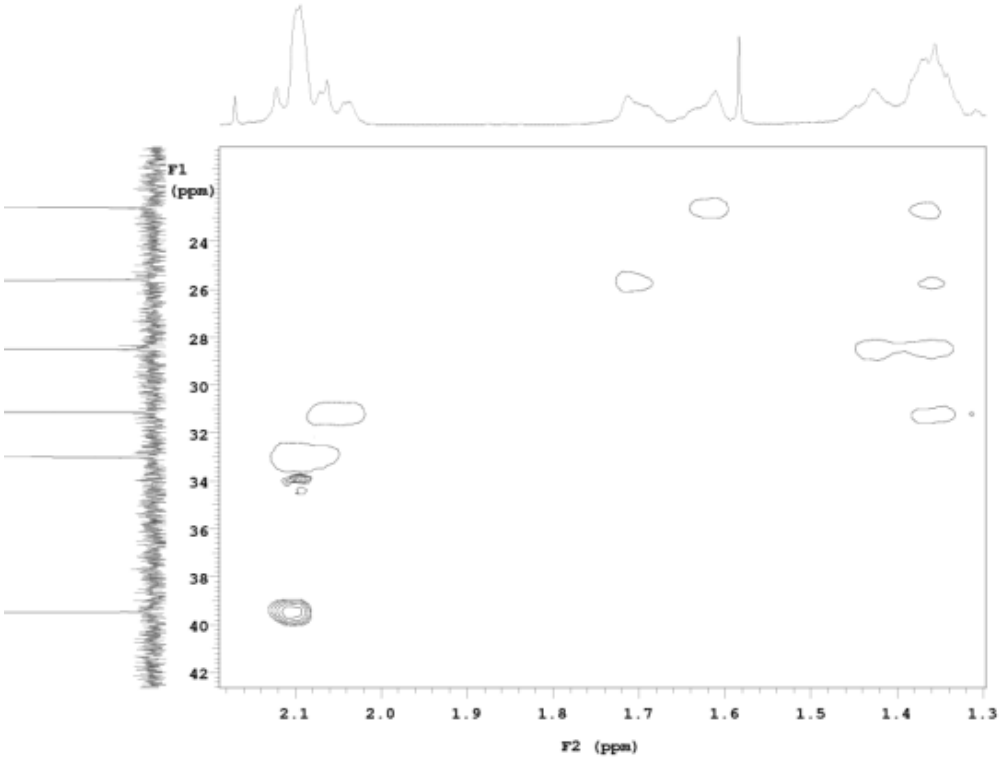

NOESY1D02.esp
H3C
O
O
H
CO2Et
CO2Et
H
NOESY1D01.esp
H3C
O
O
H
CO2Et
CO2Et
H
CHLOROFORM-d
7.25
7.38
7.37
7.21
7.20
7.18
6.67
6.66
6.65
6.64
6.58
6.55
4.75
4.74
4.21
4.20
4.19
4.12
4.11
4.11
4.10
3.17
2.13
2.10
2.08
2.07
2.06
2.05
2.02
1.41
1.40
1.40
1.28
1.22
1.21
1.15
1.14
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)

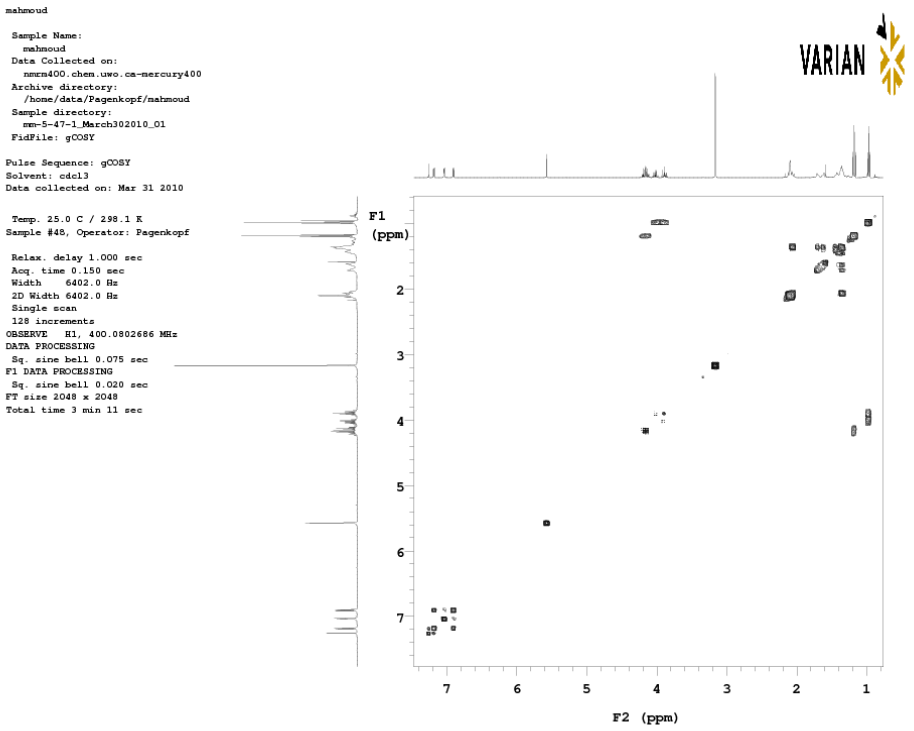
Diethyl 8a-methoxy-2-(thiophen-2-yl)hexahydro-2*H*-chromene-3,3(4*H*)-dicarboxylate (3.91z)

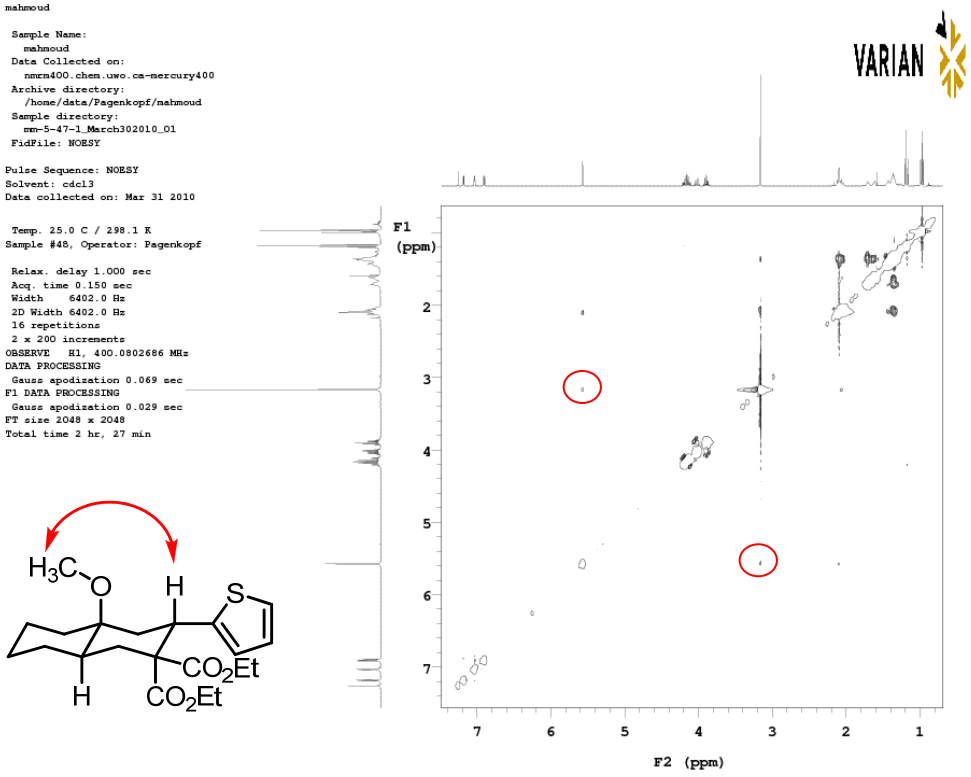


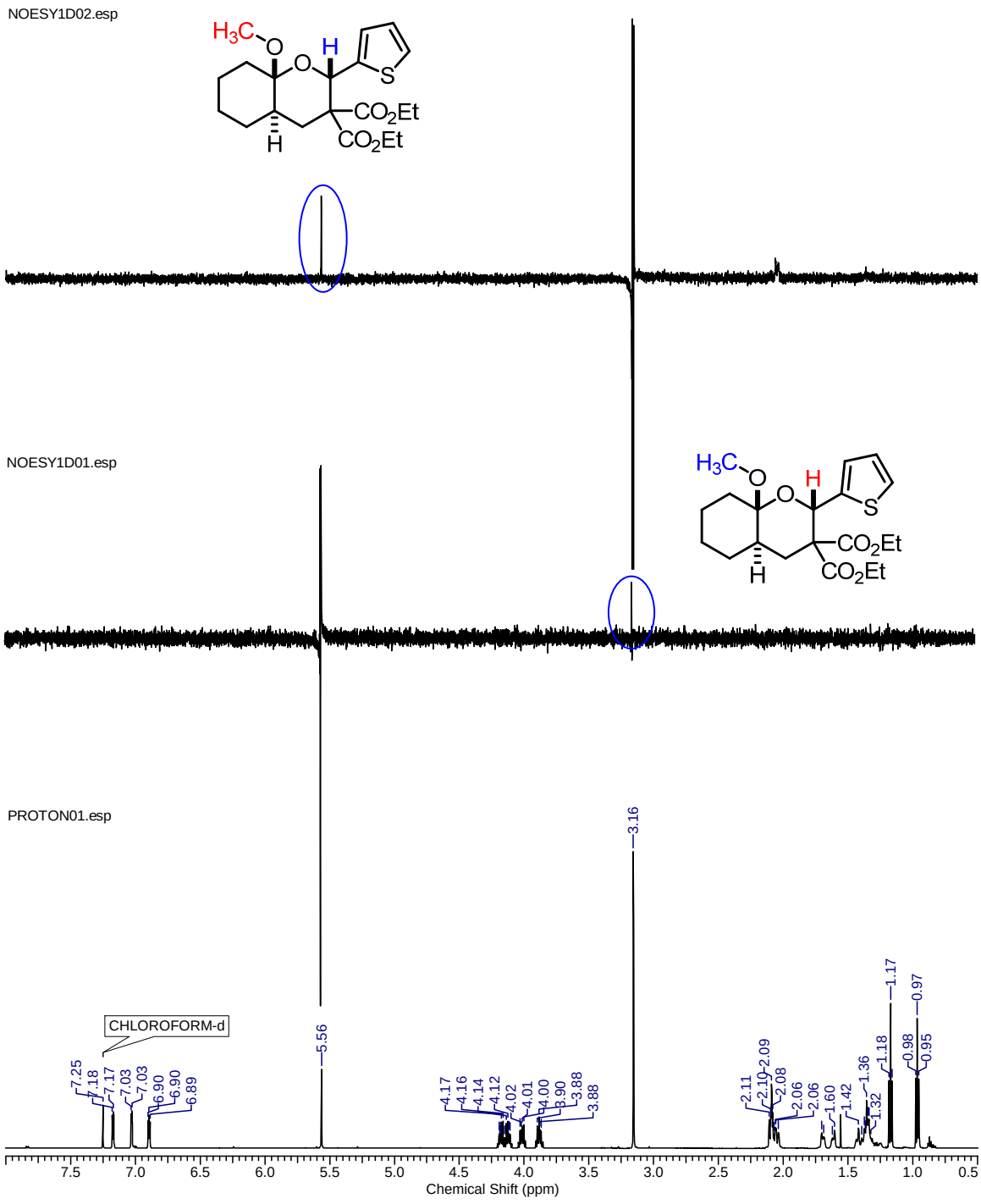



mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrn400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mn-5-47-1_March302010_01
FidFile: gHSQC
Pulse Sequence: gHSQC
Solvent: cdcl3
Data collected on: Mar 31 2010
Temp. 25.0 C / 298.1 K
Sample #48, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 17101.3 Hz
4 repetitions
2 x 128 increments
OBSERVE H1, 400.0802686 MHz
DECOUPLE C13, 100.6078086 MHz
Power 43 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.014 sec
FT size 2048 x 2048
Total time 21 min
VARIAN
F1 (ppm)
F2 (ppm)
neg proj
pos proj

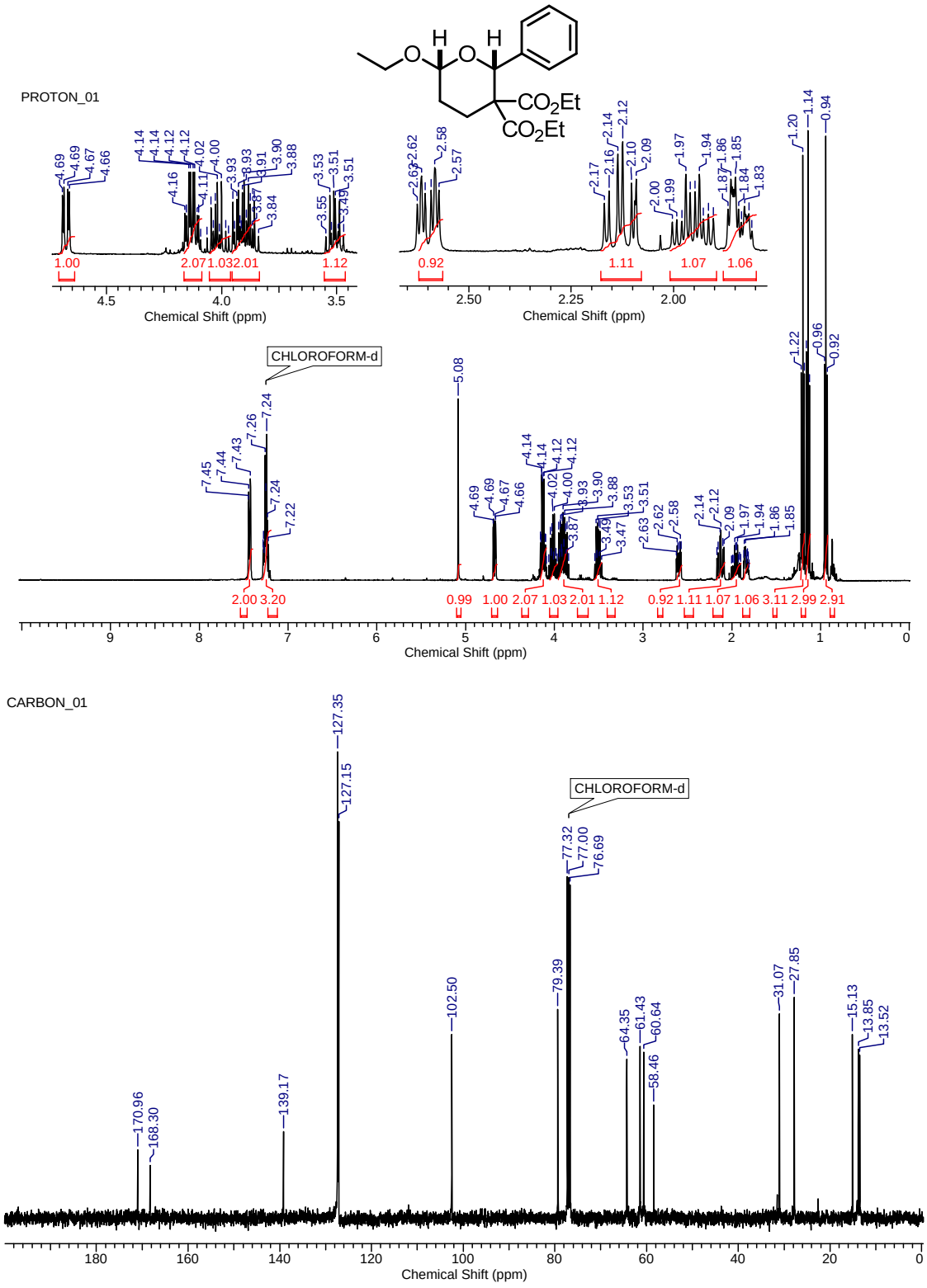

F1 (ppm)
F2 (ppm)

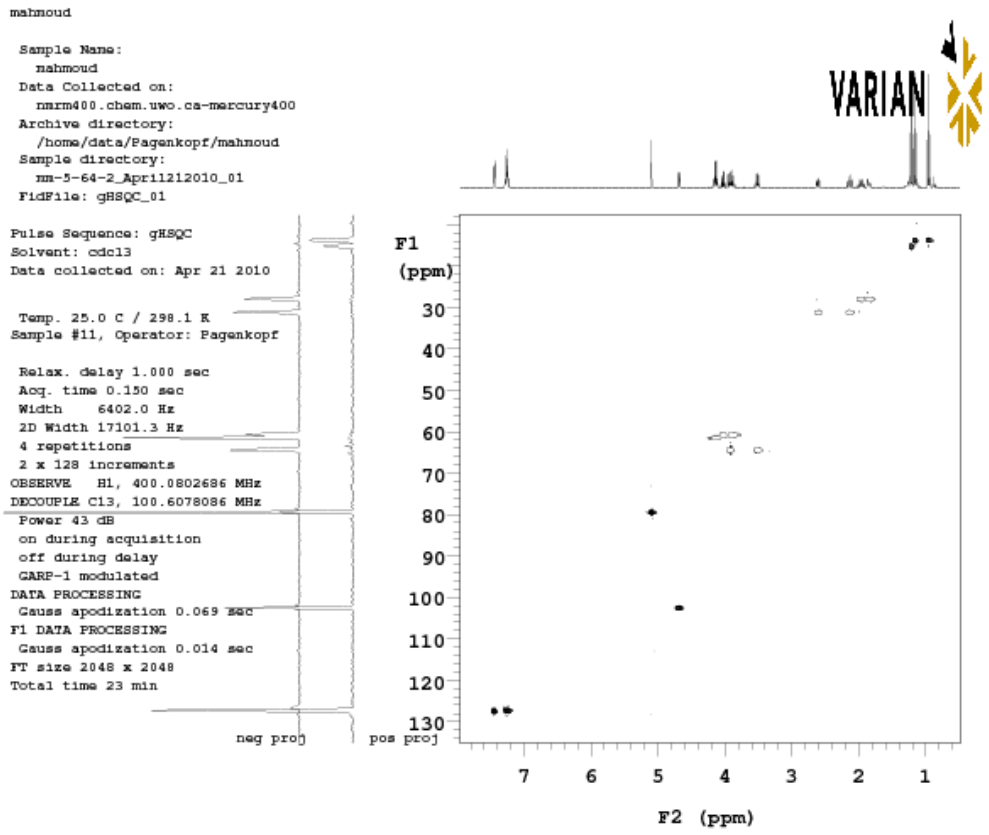

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-5-47-1_March302010_01
FidFile: gCOSY
Pulse Sequence: gCOSY
Solvent: cdcl3
Data collected on: Mar 31 2010
Temp. 25.0 C / 298.1 K
Sample #48, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
Single scan
128 increments
OBSERVE H1, 400.0802686 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sq. sine bell 0.020 sec
FT size 2048 x 2048
Total time 3 min 11 sec
VARIAN
F1 (ppm)
F2 (ppm)

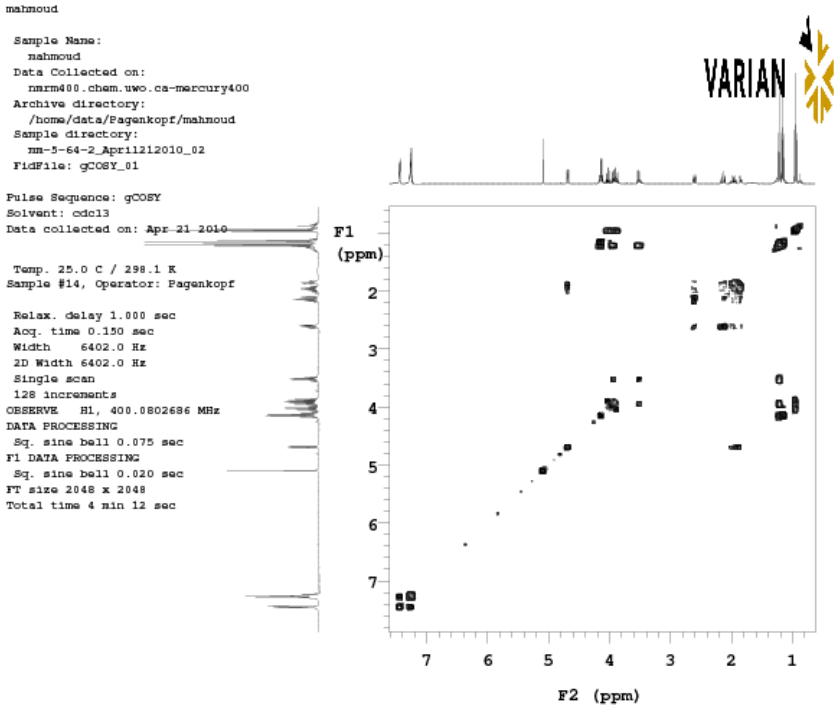

mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
mm-5-47-1_March302010_01
FidFile: NOESY
Pulse Sequence: NOESY
Solvent: cdcl3
Data collected on: Mar 31 2010
Temp. 25.0 C / 298.1 K
Sample #48, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
16 repetitions
2 x 200 increments
OBSERVE H1, 400.0802686 MHz
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.029 sec
FT size 2048 x 2048
Total time 2 hr, 27 min
VARIAN
F1 (ppm)
F2 (ppm)
H3C
O
H
S
CO2Et
H
CO2Et

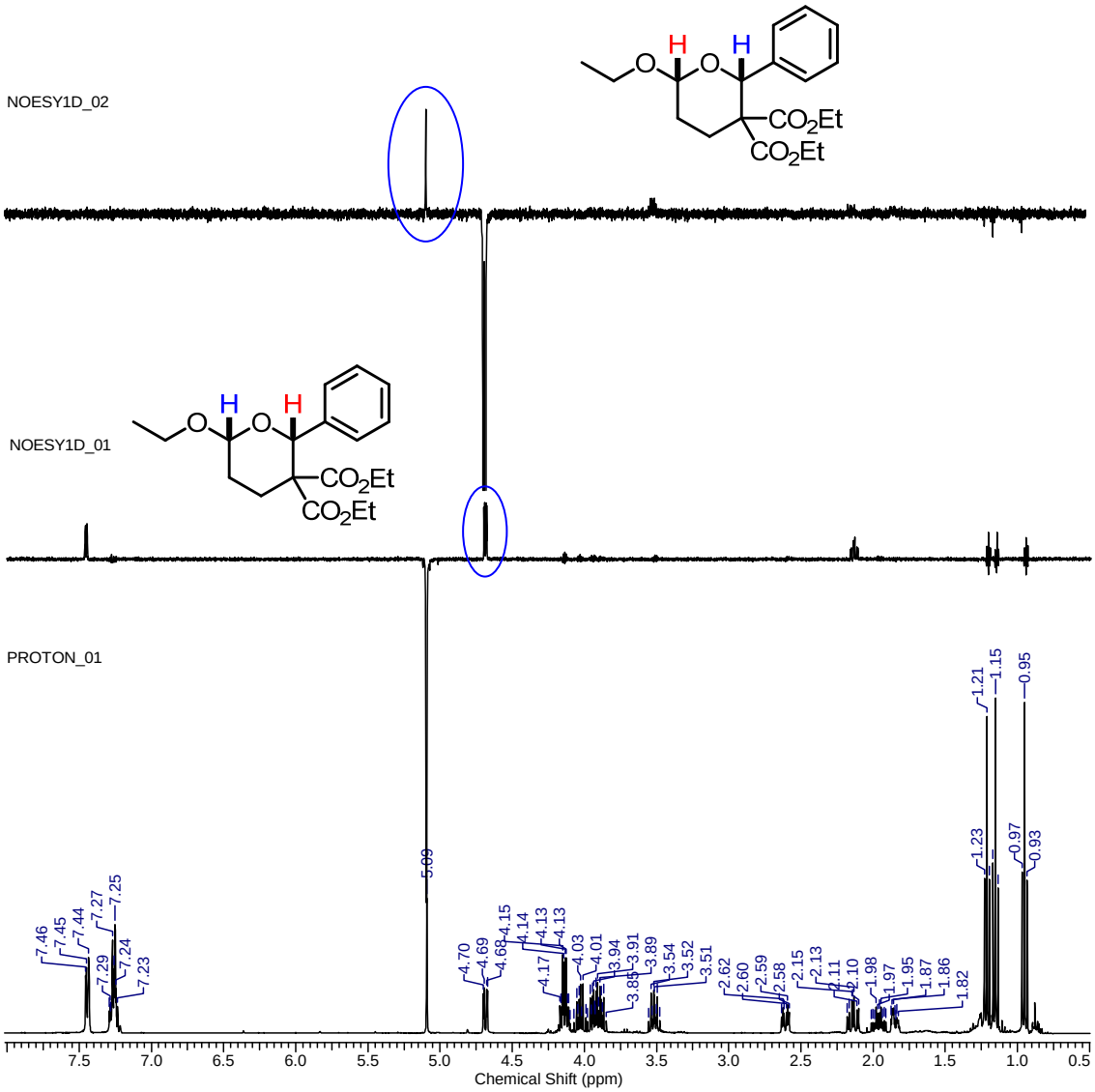

NOESY1D02.esp
H3C
O
O
H
S
CO2Et
CO2Et
H
NOESY1D01.esp
H3C
O
O
H
S
CO2Et
CO2Et
H
PROTON01.esp
CHLOROFORM-d
7.25
7.18
7.17
7.03
7.03
6.90
6.90
6.89
5.56
4.17
4.16
4.14
4.12
4.02
4.01
4.00
3.90
3.88
3.88
3.16
2.11
2.10
2.09
2.08
2.06
2.06
1.60
1.42
1.36
1.32
1.18
1.17
0.98
0.97
0.95
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical Shift (ppm)

Diethyl 6-ethoxy-2-phenyldihydro-2*H*-pyran-3,3(4*H*)-dicarboxylate (3.91t)




mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
nm-5-64-2_Apr11212010_01
FidFile: gHSQC_01
Pulse Sequence: gHSQC
Solvent: cdcl3
Data collected on: Apr 21 2010
Temp. 25.0 C / 298.1 K
Sample #11, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 17101.3 Hz
4 repetitions
2 x 128 increments
OBSERVE H1, 400.0802686 MHz
DECOUPLE C13, 100.6078086 MHz
Power 43 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.014 sec
FT size 2048 x 2048
Total time 23 min
neg proj
pos proj
F1 (ppm)
F2 (ppm)
VARIAN


mahmoud
Sample Name:
mahmoud
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/mahmoud
Sample directory:
nm-5-64-2_Apr11212010_02
FidFile: gCOSY_01
Pulse Sequence: gCOSY
Solvent: cdcl3
Data collected on: Apr 21 2010
Temp. 25.0 C / 298.1 K
Sample #14, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
Single scan
128 increments
OBSERVE H1, 400.0802686 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sq. sine bell 0.020 sec
FT size 2048 x 2048
Total time 4 min 12 sec
F1 (ppm)
F2 (ppm)
VARIAN


NOESY1D_02
NOESY1D_01
PROTON_01
H
H
O
O
CO2Et
CO2Et
7.46
7.45
7.44
7.27
7.25
7.29
7.24
7.23
5.09
4.70
4.69
4.68
4.15
4.14
4.13
4.13
4.17
4.03
4.01
3.94
3.91
3.89
3.85
3.54
3.52
3.51
2.62
2.60
2.59
2.58
2.15
2.13
2.11
2.10
1.98
1.97
1.95
1.87
1.86
1.82
1.23
1.21
1.15
0.97
0.93
0.95
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical Shift (ppm)

Curriculum Vitae

Mahmoud M. Abd Rabo Moustafa

Education

- **Ph.D. (Organic chemistry) University of Western Ontario, Canada** — 2011
- **The Pharmacy Examining Board of Canada**
  Evaluating exam (Successfully passed) — 2009
- **M.Sc. (Pharmaceutical chemistry) Al-Azhar University, Egypt** — 2006
- **B. Pharmacy, Al-Azhar University, Egypt** — 2000

Research and Relevant Work Experience

- **Teaching assistant** (University of Western Ontario, Canada) — 2007-2010
- **Research assistant** (University of Western Ontario, Canada) — 2007-2010
- **Assistant lecturer:** (Al-Azhar University, Faculty of Pharmacy, Egypt) — 2003-2006
- **Research assistant** (Al-Azhar University, Faculty of Pharmacy, Egypt) — 2003-2006
- **Research assistant** (National Center for Radiation Research and Technology, Egypt) — 2000-2003
- **Pharmacist** (Hosam pharmacy, Cairo, Egypt)
  Senior pharmacist (part time) — 2001-2006
  Junior pharmacist (part time) — 2000-2001

Workshops and Training

- Future professors workshop series (UWO) — 2010
- Accessibility in teaching training sessions (UWO) — 2010
- The American Chemical Society summer school on green chemistry and sustainability (ACS) — 2009
- Teaching assistant training program (UWO) — Jan 2007
- Communication in the Canadian classroom (UWO) — Jan 2007

Awards and Scholarships

- Graduate thesis research award (UWO) — 2010
- Dissertation year award (UWO) — 2010
- The Egyptian academy of scientific research and technology scholarship — 2007-2010
- The faculty of pharmacy dean's award, Al-Azhar University — 2000
- The Egyptian ministry of education award for high school students — 1995

Publications

8) Filing a patent/writing three articles is underway.

7) "Formal [4+2] Cycloaddition of Alkoxy-Substituted Donor-Acceptor Cyclobutanes and Aldehydes Catalyzed by $Yb(OTf)_3$" **Moustafa, M. M. Abd Rabo**; Stevens, A. C; Machin, B. P.; Pagenkopf, B. L. *Org. Lett*. **2010**, *12*, 4736–4738.

6) "Ytterbium Triflate Catalyzed Synthesis of Alkoxy-Substituted Donor–Acceptor Cyclobutanes and their Formal [4+2] Cycloaddition with Imines: Stereoselective Synthesis of Piperidines" **Moustafa, M. M. Abd Rabo**; Pagenkopf, B. L. *Org. Lett*. **2010**, *12*, 4732–4735.

5) "Synthesis of 5-Azaindoles via a Cycloaddition Reaction between Nitriles and Donor-Acceptor Cyclopropanes" **Moustafa, M. M. Abd Rabo**; Pagenkopf, B. L. *Org. Lett*. **2010**, *12*, 3168–3171.

4) "Electrochemical and Photovoltaic Properties of Electropolymerized Poly(thienyl-silole)s" Byers, J.C.; DiCarmine, P. M.; **Moustafa, M. M. Abd Rabo**; Wang, X.; Pagenkopf, B. L.; Semenikhin, O.A. *J. Phys. Chem. B* **2009**,*113*, 15715–15723.

3) "Silole Based Acetylenes as Advanced π-conjugated Systems for Optoelectronic Applications" Moustafa, M. M. Abd rabo; Pagenkopf, B. L. *Comptes rendus Chimie* **2009**, *12*, 359–365.

2) "Novel Quinazolinone Derivatives As Possible Antitumor Agents" Barakat, S. E; Ghorab, M. M.; Saker, H. M.; **Abd Rabo, M. M.** Phosphorus, *Sulfur and Silicon and the Related Elements*, **2007**, *182,* 1–13.

1) "Synthesis and Antitumor Activity of Some Novel Quinazoline Derivatives Bearing the Biologically Active Thione Moiety" Ghorab, M. M.; Barakat, S. E.; Saker, H. M.; **Abd Rabo, M. M.** *Arzneim.Forsch./Drug Res*., **2006**, *56*, 665–670.

Presentations (***** denotes oral presentation, presenting author is underlined)

10) *****"Annulation reactions of strained cycloalkanes: Novel syntheses of heterocycles and biologically active natural products" **Moustafa, M. M. Abd Rabo**; Pagenkopf, B. L.; ACS national meeting (2011, Anaheim, CA)

9) "Structural tuning of siloles: Synthesis and property studies of new silole based chromophores for analytical and optoelectronic applications" **Moustafa, M. M. Abd Rabo**; Pagenkopf, B. L.; ACS national meeting (2011, Anaheim, CA)

8) "Formal [4+2] Cycloaddition of Donor-Acceptor Cyclobutanes and Aldimines: Stereoselective Synthesis of Piperidine" **Moustafa, M. M. Abd Rabo;** Pagenkopf, B. L.; *The 14th Symposium on the Latest Trends in Organic Synthesis* (**2010**, St. Catharines, ON)

7) "Formal [4+2] Cycloaddition of Alkoxy-Substituted Donor-Acceptor Cyclobutanes and Aldehydes Catalyzed by $Yb(OTf)_3$" **Moustafa, M. M. Abd Rabo**; Stevens, A. C; Machin, B. P.; Pagenkopf, B. L.; *The 14th Symposium on the Latest Trends in Organic Synthesis* (**2010**, St. Catharines, ON)

6) "Synthesis of 5-Azaindoles via a Cycloaddition Reaction between Nitriles and Donor-Acceptor Cyclopropanes" **Moustafa, M. M. Abd Rabo**; Pagenkopf, B. L.; *the 93rd CSC Conference* (**2010**, Toronto, ON)

5) "[4+2] Cycloaddition of Donor-Acceptor Cyclobutanes and Aldimines:

Stereoselective Synthesis of Piperidine" **Moustafa, M. M. Abd Rabo**; Pagenkopf, B. L.; *The 93rd CSC Conference* (**2010**, Toronto, ON)

4) "Synthesis and Electrochemical Properties of New Silole Based Luminophores" **Moustafa, M. M. Abd Rabo**; *ACS Green Chemistry Summer School* **2009**, Golden, Colorado

3) "Silole Chemistry Lights Our Life: Synthesis and Electrochemical Properties of New Silole Based Luminophores" **Moustafa, M. M. Abd Rabo**; Pagenkopf, B. L.; The 22nd Annual Western Research Forum (**2009**, UWO, London, ON)

2)*"Silole Chemistry Lights Our Life: Synthesis and Electrogenerated Chemiluminescence (ECL) of New Silole Based Materials" **Moustafa, M. M. Abd Rabo**; *The 92nd CSC Conference* (**2009**, Hamilton, ON)

1) "Silole Chemistry Lights Our Life: Synthesis and Electrochemical Properties of New Silole Based Luminophores" **Moustafa, M. M. Abd Rabo**; Na, C.; Pagenkopf, B. L.; Ding, Z.; The *19th Quebec-Ontario Mini Symposium of Bioorganic and Organic Chemistry* (**2008**, Toronto, ON)