# SYNTHESIS OF QUINOLINES AS NEURAL PROTECTIVE REAGENTS AND PROGRESS TOWARDS TOTAL SYNTHESIS OF (+) - MYRICERIC ACID A

by

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B.S., East China University of Science and Technology
2005

AN ABSTRACT OF A DISSERTATION

submitted in partial fulfillment of the requirements for the degree

DOCTOR OF PHILOSOPHY

Department of Chemistry
College of Arts and Sciences

KANSAS STATE UNIVERSITY
Manhattan, Kansas

2014

# Abstract

The first chapter of this dissertation introduces and discusses the synthesis of a series of substituted quinolines as glycogen synthase kinase-3β (GSK-3β) inhibitors. GSK-3β is highly associated with Alzheimer's disease (AD), and it is suggested that inhibition of this enzyme could alleviate the symptoms of AD. Total 16 novel substituted quinolines were designed and synthesized, and their bio-activities were evaluated on MC65 cell protection assay. Four of the most active compounds were selected to test their enzyme inhibitory activities on GSK-3β and protein kinase C assays. Among these compounds, 4-{[6-methoxy-4-methyl-5-(3-(trifluoromethyl)phenoxy)quinolin-8-ylamino]methyl} phenol (**1.5**) shows the highest MC65 cell protection and GSK-3β enzyme inhibitory activities and potential enzyme specificity. Structure-activity relationship (SAR) was built as well, and the binding mode was simulated via computational method to interpret the observed SAR. Although additional bio-evaluation is needed, compound **1.5** is a promising lead compound for the development of more active and less toxic drug for the counteraction of AD.

The second chapter introduces the progress on the total synthesis of myriceric acid A. Myriceric acid A is a triterpene-type natural product which was isolated from the young twigs of *Myrica cerifera.* It is a non-peptide endotheline-1 (ET-1) receptor antagonist. The total synthesis of this natural product started from the stereoselective synthesis of bicyclic intermediate (*R*)-5,8a-dimethyl-3,4,8,8a-tetrahydronaphthalene-1,6(2*H*,7*H*)-dione [**(-)-2.28**]. Then a new method was developed to enatioselectively synthesize the tricyclic intermediate (4a*R*,8*R*,8a*R*)-8-(*tert*-butyldimethylsilyloxy)-1,4a,8a-trimethyl-4,4a,4b,5,6,7,8,8a,9,10-decahydro phenanthren-2(3H)-one [**(+)-2.72**] which used the synthesized optically-pure (4a*R*,5*R*)-5-(*tert*-butyldimethylsilyloxy)-1,4a-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one [**(-)-2.53**] derived from **(-)-2.28** and α-trimethylsilylvinyl ethyl ketone via a cascade reductive Michael addition – aldol condensation reaction. After functional group inter-conversion, the desired tricyclic intermediate (4a'*S*,8a'*R*)-1',1',4a',8a'-tetramethyldecahydro-1'H-spiro[[1,3]dioxolane-2,2'-phenanthren]-8'(3'H)-one [**(-)-2.33**] was synthesized. An intramolecular cascade Michael addition-aldol condensation reaction was designed to construct the triterpene-skeleton of myriceric acid A, and the desired starting material for this reaction was prepared with the trimethyl{(4a'*R*,8a'*R*)-1',1',4a',8a'-tetramethyl-3',4',4a',4b',5',6',8a',9',10',10a'-decahydro-1'H-

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Approved by:

Major Professor
Dr. Duy H.Hua

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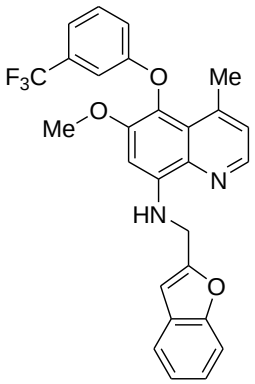
# List of Abbreviations

| | |
|---|---|
| Aβ | Amyloid beta peptide |
| Ac | Acetate |
| AD | Alzheimer's disease |
| AIBN | Azobisisobutyronitrile |
| AMP-PNP | Adenylyl imidodiphosphate |
| APP | Amyloid precursor protein |
| ATP | Adenosine triphosphate |
| BBB | Blood brain barrier |
| $BBr_3$ | Boron tribromide |
| $BF_3$.ether | Boron triflouride etherate |
| CDI | Carbonyldiimidazole |
| CNS | Central nervous system |
| D-CSA | D-Camphorsulfonic acid |
| DCM | Dichloromethane |
| DBU | 1,8-Diazabicyclo[5.4.0]undec-7-ene |
| DIBAL-H | Diisopropylaluminum hydride |
| DMSO | Dimethyl sulfoxide |
| EC | Endothelial cell |
| ET-1 | Endothelin-1 |
| EtOH | Ethanol |
| FGI | Functional group interconversion |
| HCl | Hydrochloric acid |
| IBX | 2-Iodoxybenzoic acid |
| $IP_3$ | Inositol triphosphate-3 |
| GPCR | G-protein coupled receptors |
| GSK-3α | Glycogen synthase kinase-3 alpha |
| GSK-3β | Glycogen synthase kinase-3 beta |
| HMPA | Hexamethylphosphoramide |

| | |
|---|---|
| HPLC | High performance liquid chromatography |
| LDA | Lithium diisopropylamide |
| LPNM | Lithium perchlorate/Nitromethane |
| $NaIO_4$ | Sodium periodate |
| $OsO_4$ | Osmium tetraoxide |
| PKC | Protein kinase C |
| PPTS | Pyridinium *p*-toluenesulfonate |
| PTSA | *p*-Toluenesulfonic acid |
| SAR | Structure activity relationship |
| SR | Sarcoplasmic reticulum |
| $SOCl_2$ | Thionyl chloride |
| TBAF | Tetrabutylammonium fluoride |
| TBSCl | *t*-Butyldimethylsilyl chloride |
| TBS-OTf | *t*-Butyldimethylsilyl triflate |
| TC | Tetracycline |
| THF | Tetrahydrofuran |
| TMS | Trimethylsilyl |
| TMSCl | Trimethylsilylchloride |

# Structure-number correlation list



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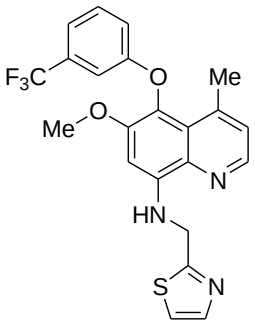

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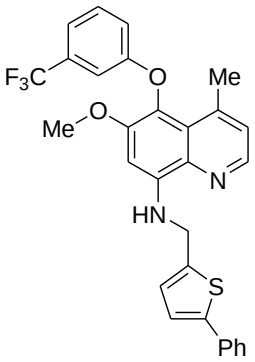

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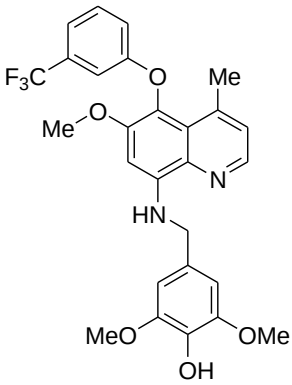

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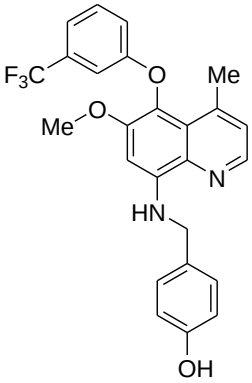

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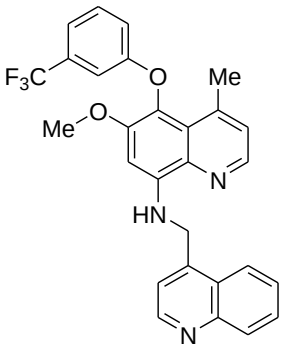

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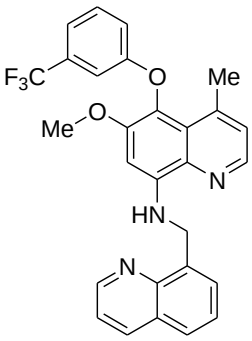

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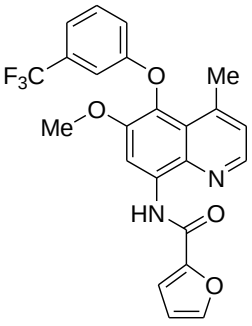

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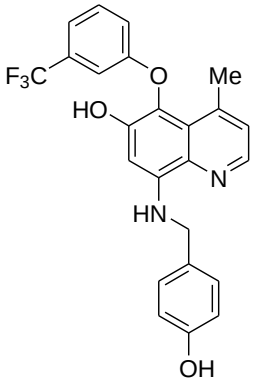

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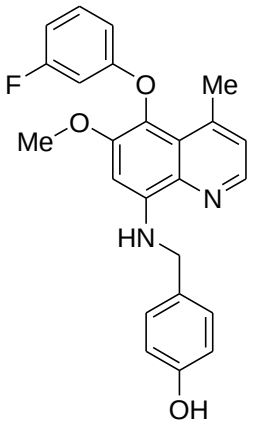


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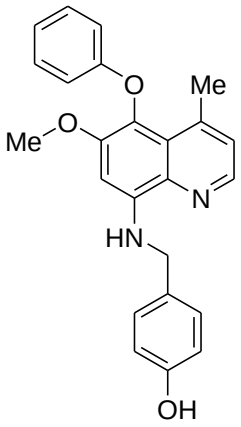


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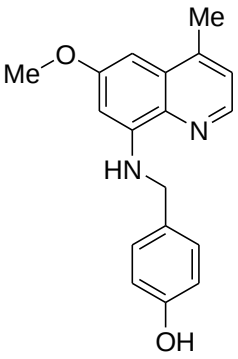


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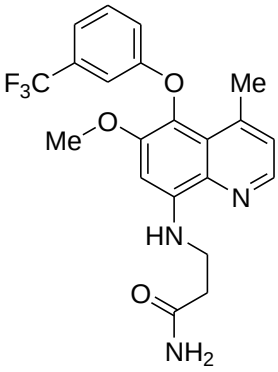


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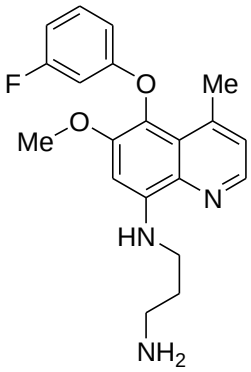


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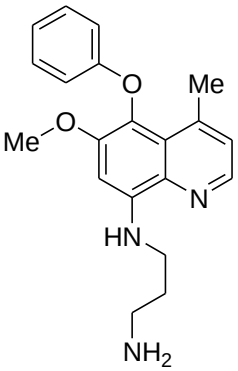


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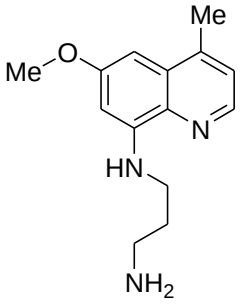


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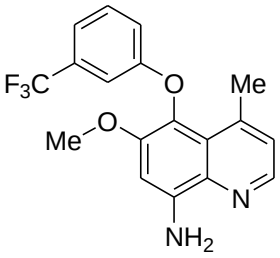


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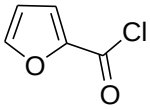


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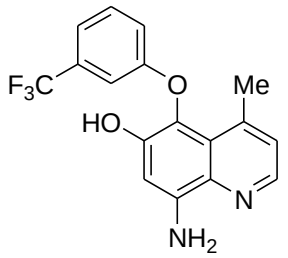


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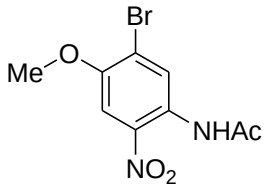


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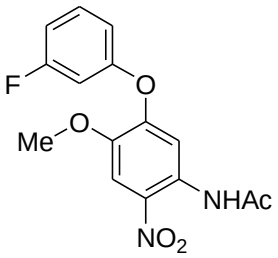


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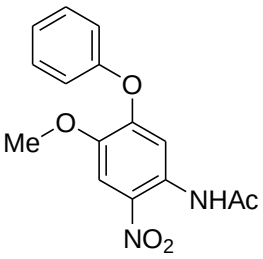


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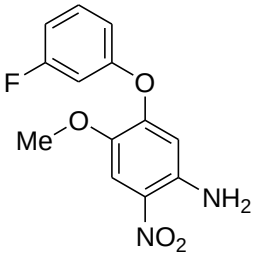


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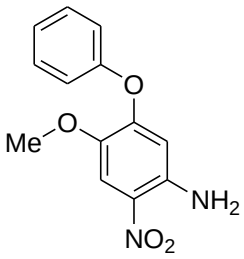


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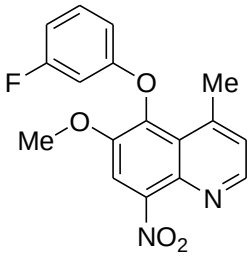


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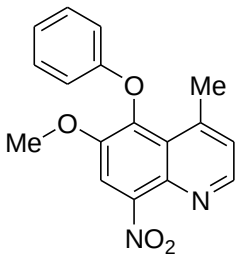


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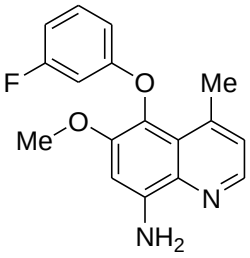


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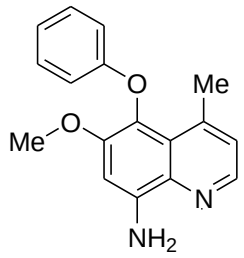

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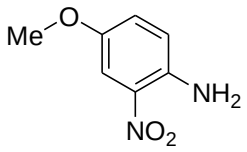

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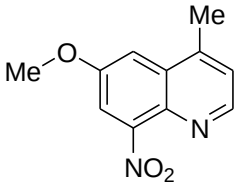

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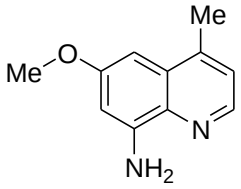

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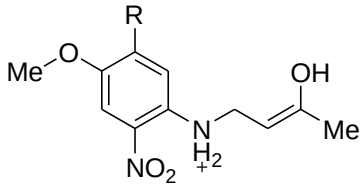

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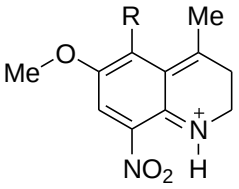

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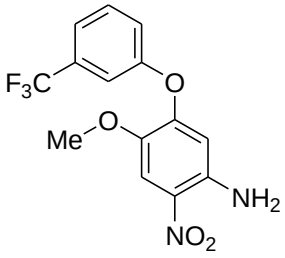

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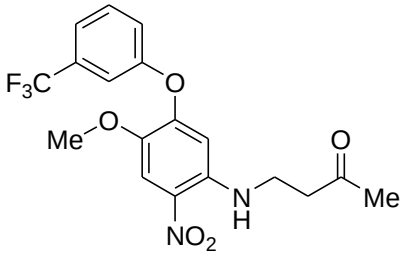

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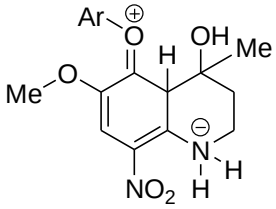

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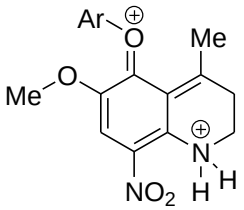


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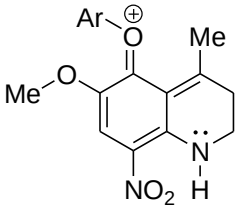


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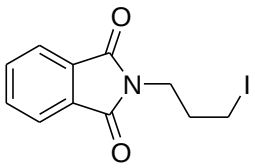


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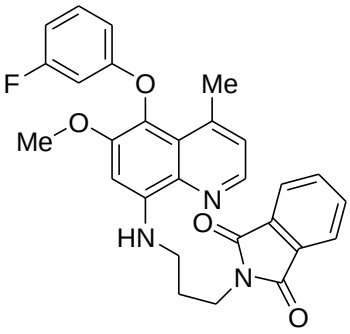


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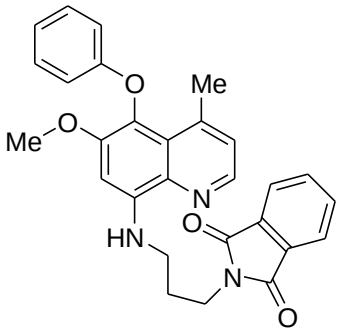


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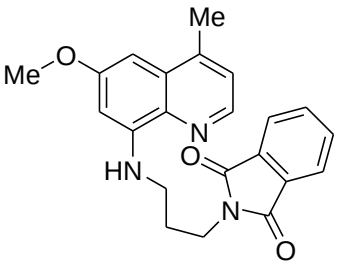


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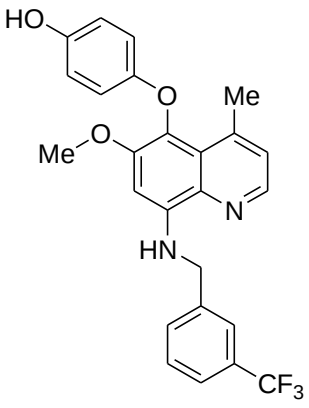


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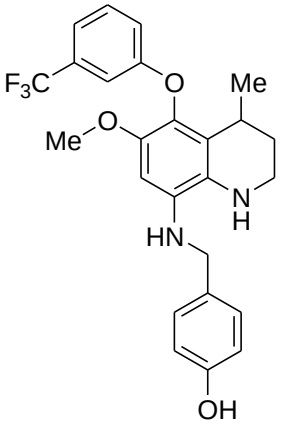


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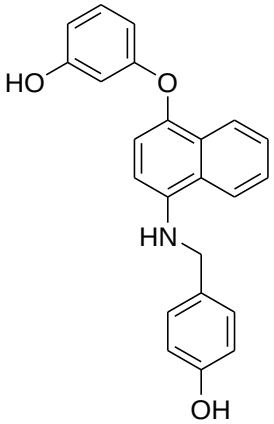


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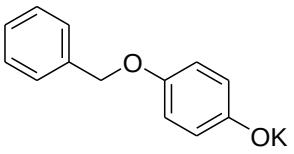


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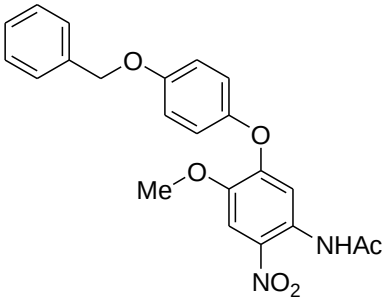


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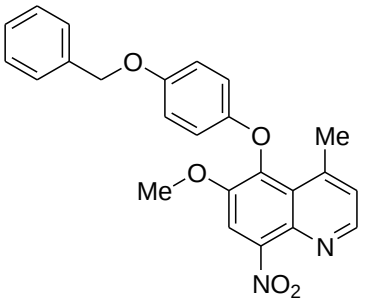


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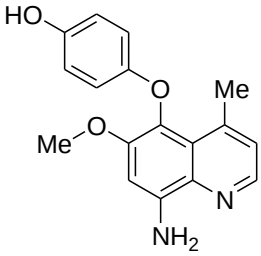


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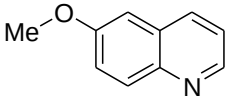


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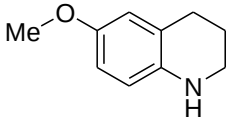


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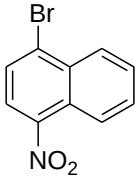


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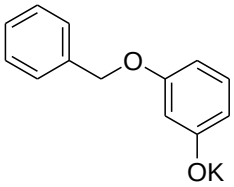


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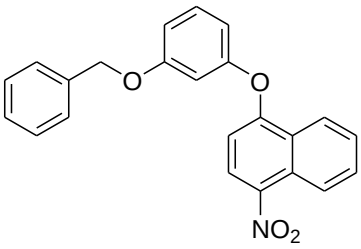


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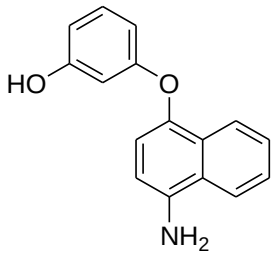


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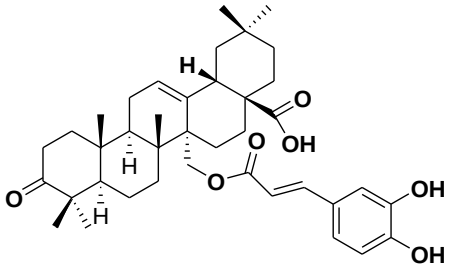
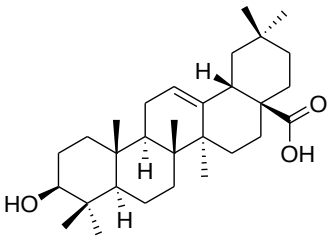
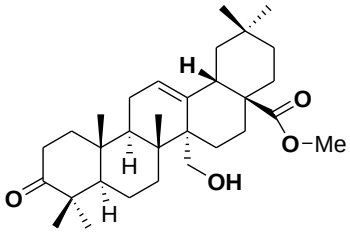


**Myriceric acid A**



**Oleanolic acid**



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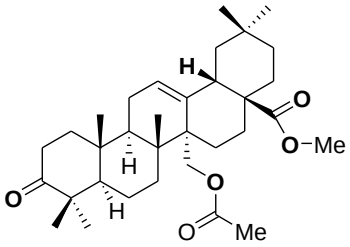

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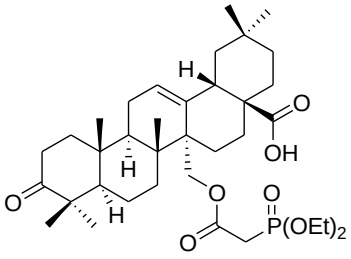

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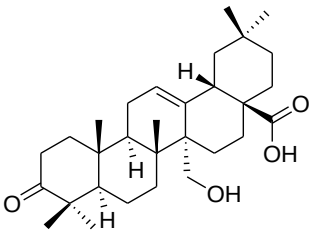

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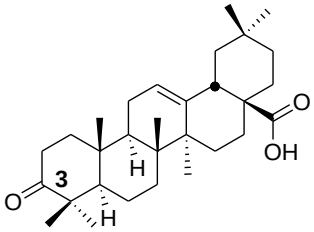

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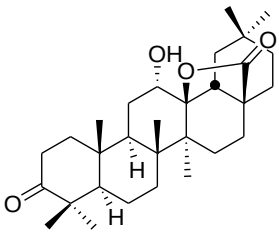

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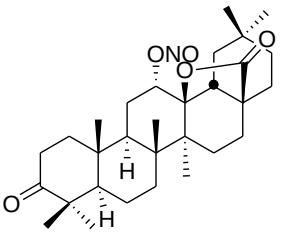

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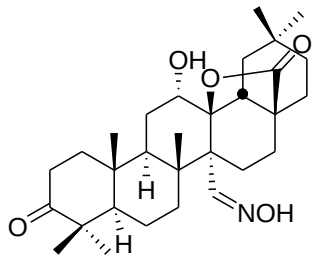


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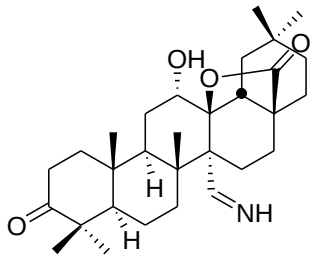


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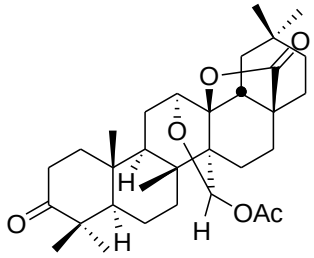


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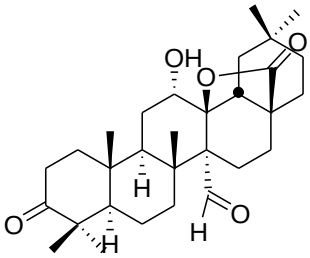


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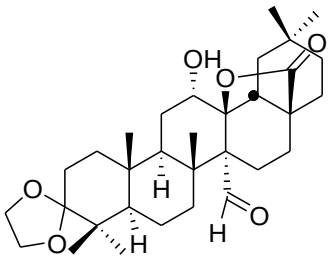


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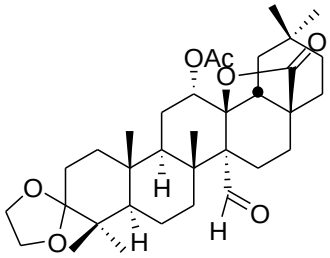


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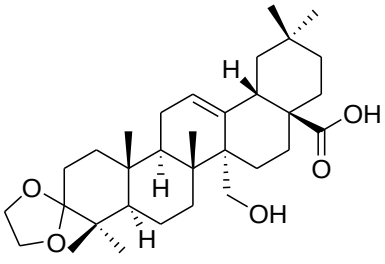


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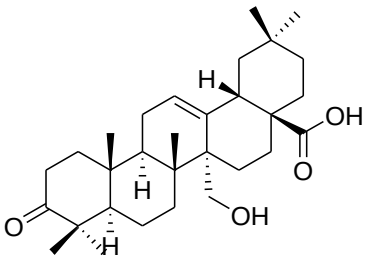


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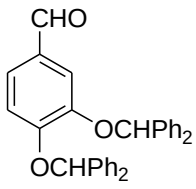


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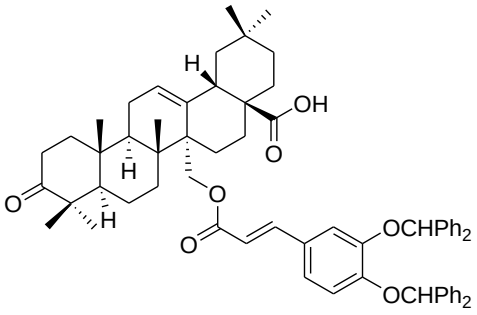


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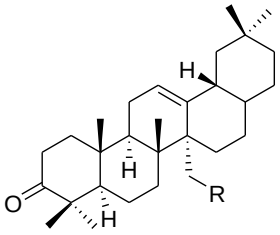
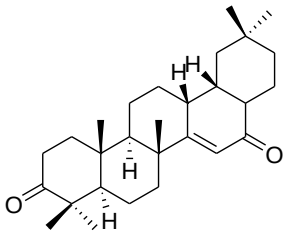



**R = OH, or any carboxlic acid ester**

**2.18**

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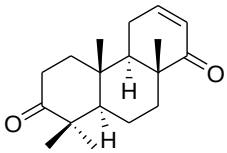


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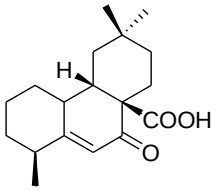


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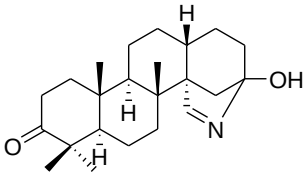


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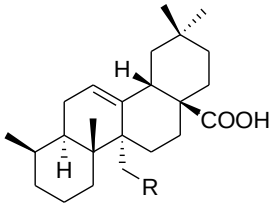
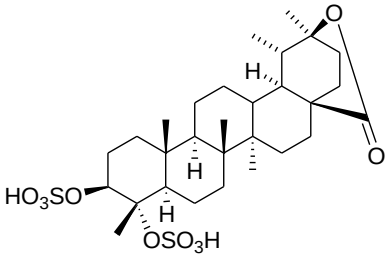



**R = OH, or any carboxlic acid ester**

**2.23**

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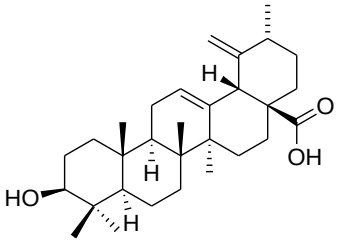


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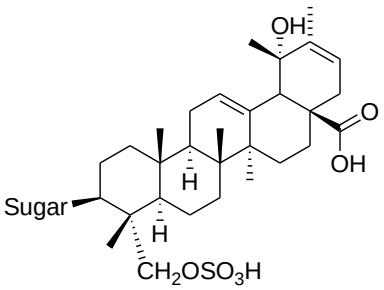


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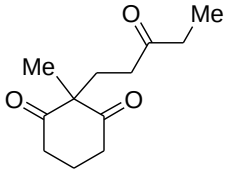


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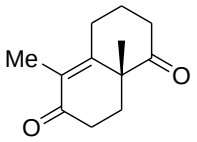
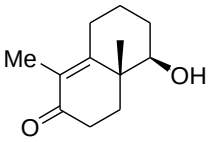
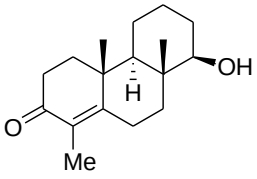



**(-)-2.28**




**(-)-2.29**

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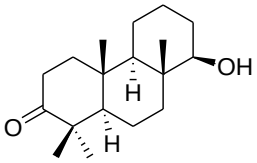


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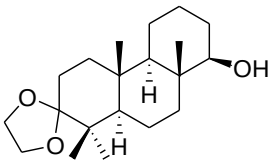
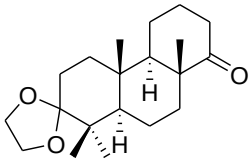



**(-)-2.32**

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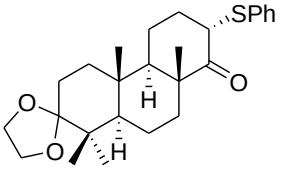


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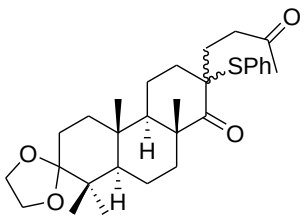


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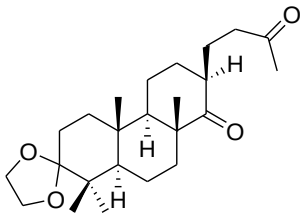


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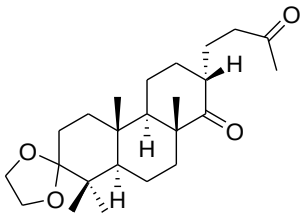


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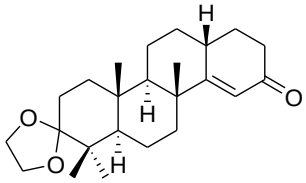


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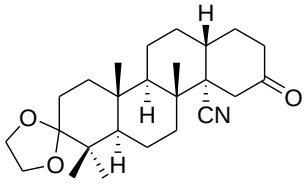


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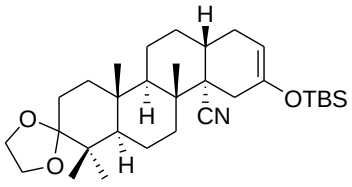


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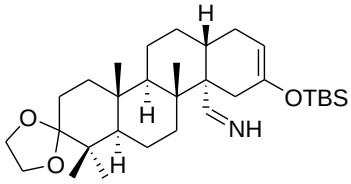


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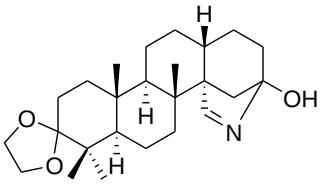


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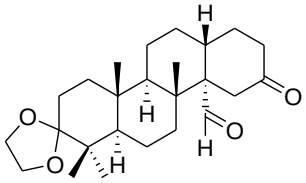


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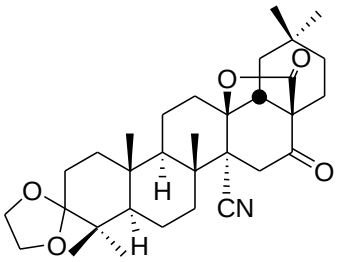


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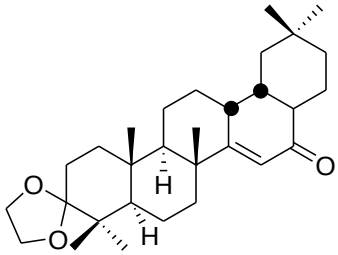
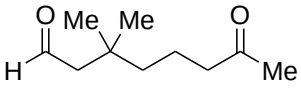



**(+)-2.45**

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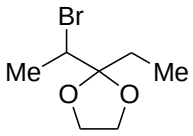


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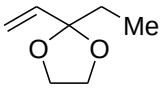


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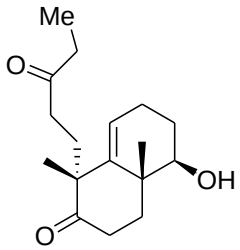


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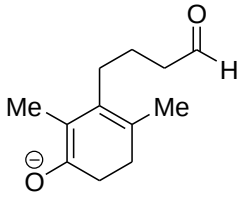


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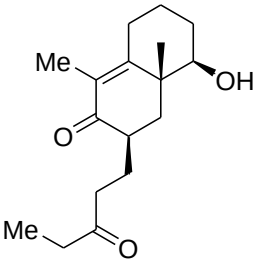


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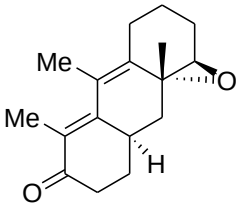


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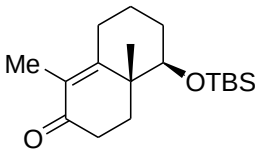
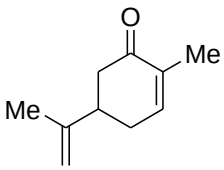



**(-)-2.53**

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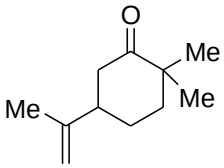
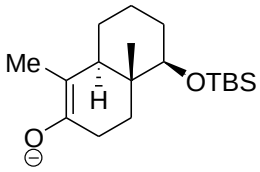



**2.55**

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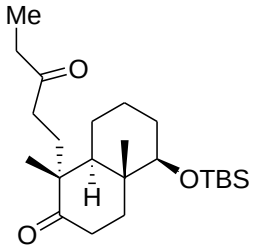


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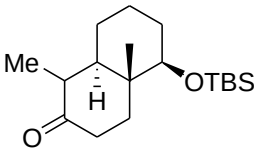
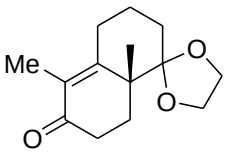



**(-)-2.58**

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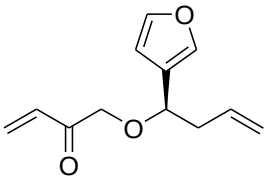


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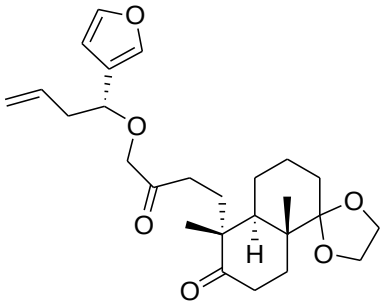


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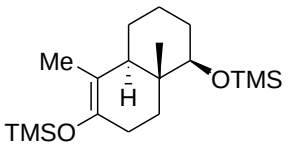


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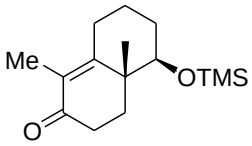


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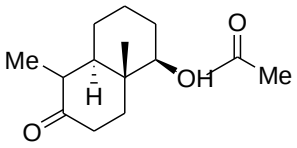


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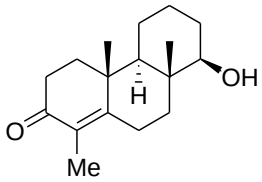


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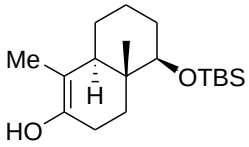


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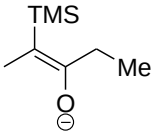


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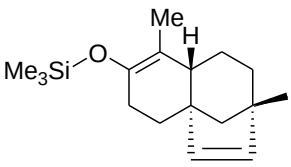


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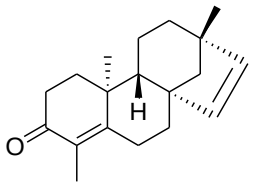


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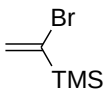


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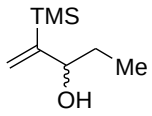


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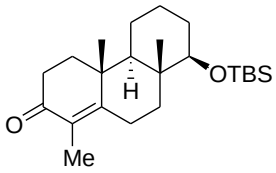


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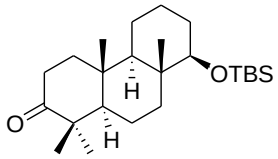


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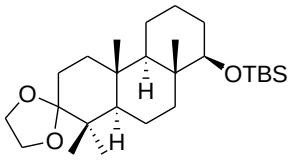


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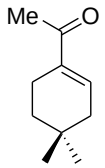


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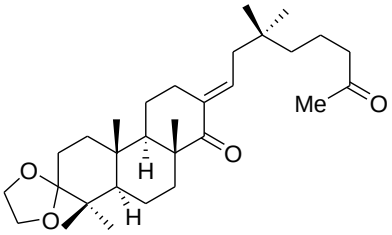
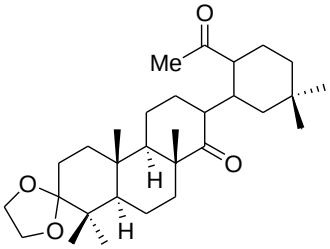



**(-)-2.76**

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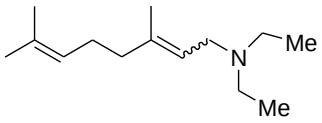


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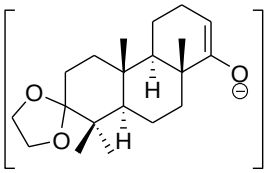


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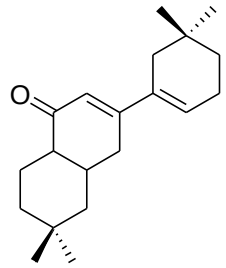


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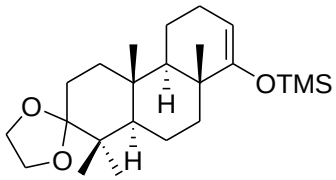


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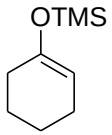
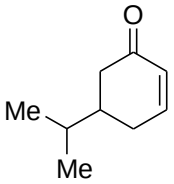



**2.82**

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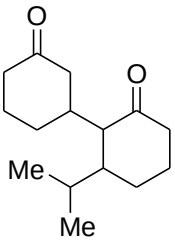


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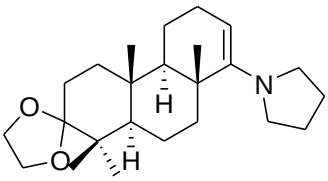


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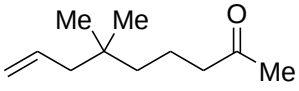


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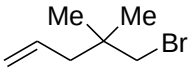


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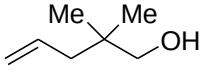


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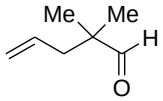


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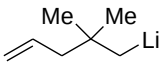


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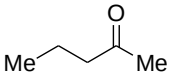


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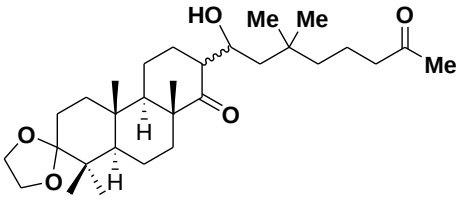


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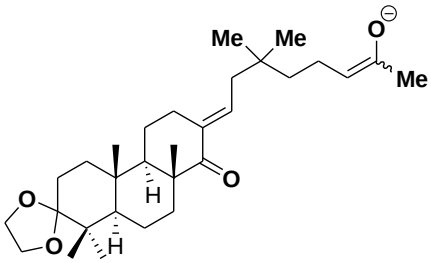


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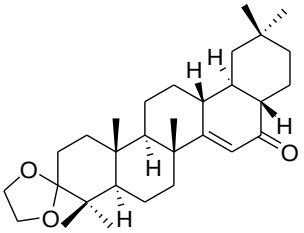


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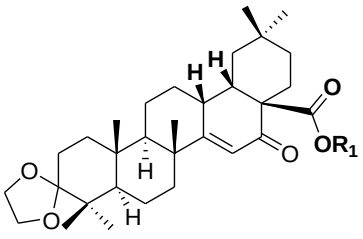


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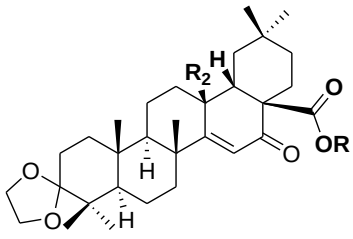


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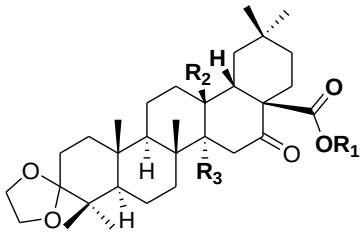


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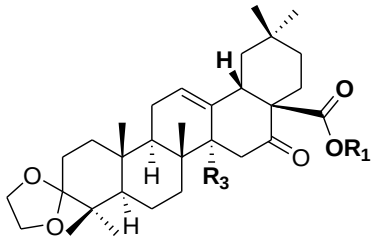

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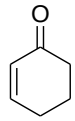

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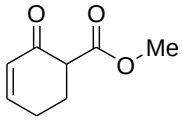

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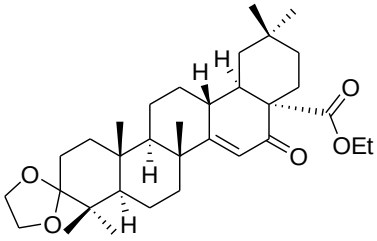

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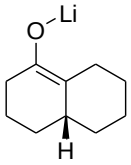

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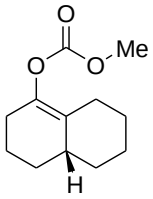

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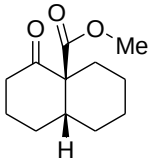

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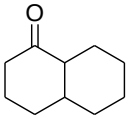

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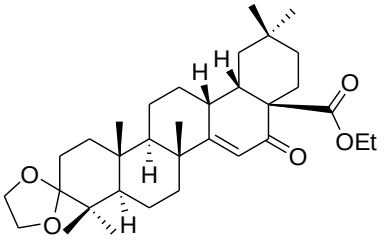

**(-)-2.106**

# Acknowledgements

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# Chapter 1 - Synthesis of quinolines as glycogen synthase kinase 3-beta (GSK 3-β) inhibitors possessing neural protective activities

## 1.1 Introduction – GSK-3β and its relationship with Alzheimer's disease (AD)

Glycogen synthase kinase-3 are the thirdly discovered kinases for controlling the activity of glycogen synthase enzyme, and, in human body, two isoforms of glycogen synthase kinase-3 exist, which are named as glycogen synthase kinase-3 alpha (GSK-3α) and glycogen synthase kinase-3 beta (GSK-3β).[1] GSK-3β is found having a high level of concentration in central nervous system (CNS) tissue and playing an important role in many neuronal cellular activities.[2] The imbalanced activity of GSK-3β is associated with many CNS degenerative diseases, such as Alzheimer's disease (AD).[3]

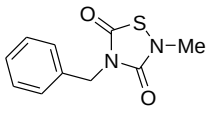
AD now is the most common type of dementia, and about 50 - 80 % of dementia patients are diagnosed as AD patients.[4a] Development of this disease is highly associated with the increase of age, and most of AD patients are 65 or older. This disease is aggravated over time. At the early stage, AD only induces a short-term memory loss; but the advanced-stage AD causes cognitive impairment, long term memory loss, and loss of motor functions as well.[4b] Most AD patients die in about 9 years after the diagnose of the disease. Till now, there is still no cure for the AD because the detailed pathological mechanism is still not known. However, considering that most of AD patients are elderly and slowing down the AD development could reduce their suffer and prolong their life presently, all of the available therapies are aiming alleviate the symptoms.[4]

AD shows two main pathological characters: extracellular toxic amyloid beta (Aβ) oligomer deposits and intracellular fibrillary tangles.[4] Toxic Aβ oligomer is composed of the toxic Aβ peptide which is cleaved from the amyloid precursor protein (APP), and the intracellular tangles are made of the hyper-phosphorylated tau proteins.[4b] These toxic Aβ oligomer and fibrillary tangles induce the neuronal cell death.[4b] GSK-3β is indirectly or directly associates with the formations of Aβ oligomer and fibrillary tangles.[3] In AD's brain, GSK-3β is highly expressed and deregulated.[3] Highly expressed GSK-3β hyper-phosphorylates tau protein to produces fibrillary tangles.[4b] Inhibition of GSK-3β by lithium chloride shows protection effect on neural cells.[5] In AD mice model, lithium chloride treatment reduces the Aβ oligomer

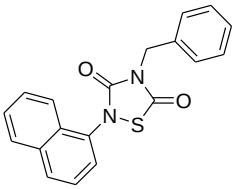
production.[8] In clinical trial, combination of lithium with drug Divalporex which has been shown to inhibit GSK-3β is used to reduce the hyper-phosphorylation of tau.[8] Therefore, GSK-3β is a potential target for alleviation of the AD symptoms.

There are only 2 types of FDA approved drugs for AD in the market now;[6] however, these drugs either have strong side-effects or show less therapeutic effect than expected after long-term study.[7] Research on discovering new drug with better therapeutic effect and less side-reactions for AD are highly demanded and carrying out by scientists. Drug candidates for AD which are targeting GSK-3β have been reported as well.[3,8,9] Among these reported inhibitors, only two candidates are currently in the clinical trial for AD, which are Np-12 (phase I)[8] and tideglusib (phase II)[9]; however, there is still no conclusive result is reported yet. The rest of the GSK-3β inhibitors are still in the different stages of drug discovery.[9]

**Figure 1.1 : Structure of Np-12 and tideglusib**



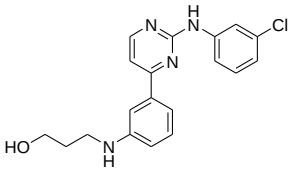
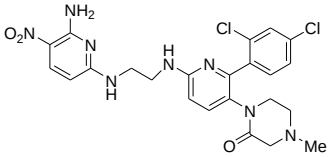
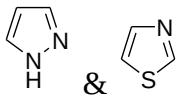
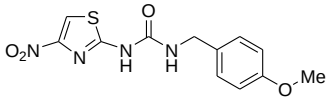

**Np-12 (Phase I)**




**tideglusib (Phase II)**

It is worthy to note that most of these reported GSK-3 inhibitors are pyrimidine analog, pyridine analog, pryarzole and thiazole analog compounds (Table 1.1).[3,8] To expand the structural diversity of drug candidates and enhance the possibility to develop more effictive medicine for AD, novel GSK-3β inhibitors as AD drug candidates possessing different structural characters a.

**Table 1.1 : First three of the largest groups of reported GSK-3 inhibitors [3,8]**

| | Numbers of compounds reported | Example |
|---|---|---|
| Pyrimidine analog  | Around 1500, about 160 of them have $IC_{50}$ under 100 nM; |  **CGP60474, $IC_{50}$: 10 nM.** |
| Pyridine analog  | Around 1400, about 120 of them have $IC_{50}$ under 100 nM; |  **CT20026, $IC_{50}$: 4 nM.** |
| Pryarzole analog  | Around 700, about 80 of them have $IC_{50}$ under 100 nM; |  **ARA014418, $IC_{50}$: 101 nM.** |

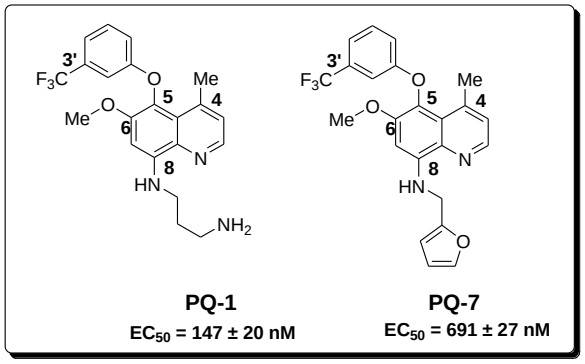
In this study, a focus library of quinoline compounds were designed and synthesized as the novel type of GSK-3β inhibitors possessing neural cell protection activities.

## 1.2 Design and syntheses of quinoline compounds

In this section, the design and syntheses of quinolines are described and discussed.

Initially, reported compounds **PQ-1**[10] and **PQ-7**[10] which were firstly prepared by Dr. Aibin Shi in Dr. Duy H. Hua's laboratory were tested their activities on MC65 cell protection assay, and the $EC_{50}$ is 147 ± 20 nM for **PQ-1** and 691 ± 27 nM for **PQ-7,** respectively (Details about the MC65 cell assay will be introduced in the section 1.3). Structures of **PQ-1** and **PQ-7** are depicted in Figure 1.2. Total four substituents are attached on their quinoline core, and they are 4-methyl group, 5-(3-triflouromethylphenoxyl) group, 6-methoxyl and 8-amino group. For **PQ-1** and **PQ-7**, the structural difference is the substituent connected at the 8-amino group. **PQ-1** has an alkyl amino group, and **PQ-7** contains furan moiety in the 8-amino substituent. With these positive feedbacks from neuronal cell protection assay, **PQ-1** and **PQ-7** were selected as the lead compounds to develop a library of novel quinolines with higher neuronal cell protection activities.

**Figure 1.2 : Structure of PQ-1 and PQ-7[10]**

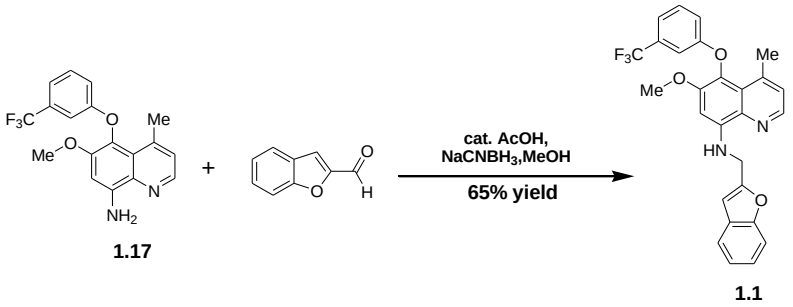



Decided by the lead compounds, two categories of compounds, **PQ-1** derivatives and **PQ-7** derivatives, were designed and synthesized. **PQ-7** derivative compounds are introduced firstly.

By altering the furan moiety with other heterocycles or aromatic structures, compounds **1.1** – **1.8** were initially designed and synthesized.

Amino quinolone **1.17**[10] was coupled with benzofuran-2-carboxylaldehyde to form compound **1.1** via reductive amination reaction (Scheme 1.1).

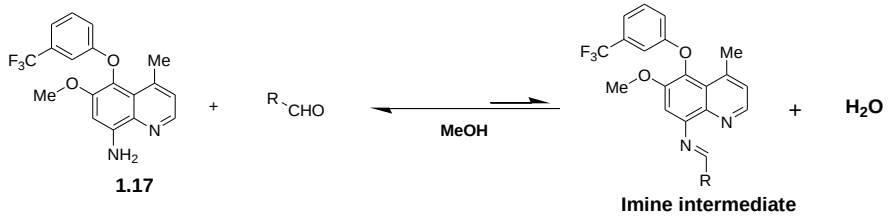
**Scheme 1.1 : Synthesis of compound 1.1**




The optimal procedure for this reductive amination reaction was explored.

Initially, acetic acid and sodium cyanoborohydride were planned to be added only after compound **1.17** and the aldehyde were completely transferred into the imine intermediate. However, after stirring at 25 $^{o}$C over 14 hours, less than 10% of the starting materials were transferred into the desired imine, and the rest stayed unchanged. The imine formation is an equilibrium process. Since amino group (–$NH_2$) of compound **1.17** is not a strong nucleophile, the attack to the aldehyde carbonyl is demoted. Therefore, the reaction reaches equilibrium after forming little amount of imine and stop (Scheme 1.2).

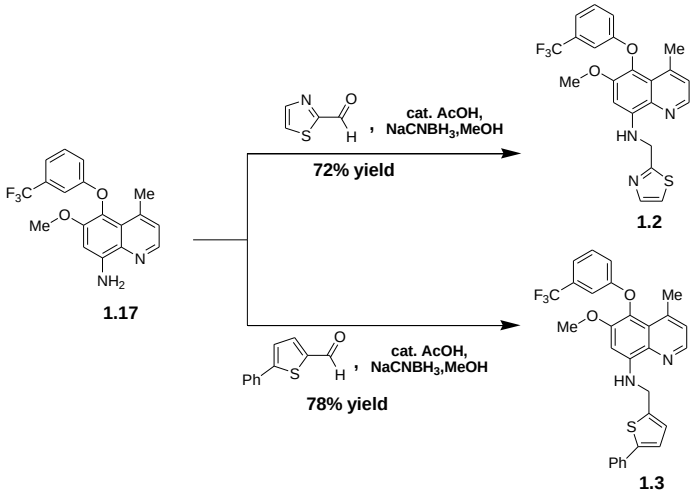
**Scheme 1.2: Incomplete formation of imine intermediate**




The alternative strategy was to add acetic acid and sodium cyanoborohydride after compound **1.17** and aldehyde were stirred at 25 $^{o}$C for 30 minutes; then, this mixture was stirred at 25 $^{o}$C for 14 hours. Sodium cyanoborohydride could reduce the imine intermediate to generate desired product, and the disappearing of imine intermediate in the reaction mixture drives reaction equilibrium going forward to the right to complete the reaction. The problem of this method is that sodium caynoborohydride could also slowly reduce the aldehyde during long reaction period, and this process consumes both the aldehyde and reducing reagent. To solve this problem, excess amount of aldehyde (1.2 eq.) and sodium cyanoborohyride (3.0 eq.) are used in the reaction. This method is proven to be effective for synthesizing designed compounds, but the drawback is the yields are moderate. It might because the formed secondary amine could also undergo reductive amination reaction with the aldehyde to yield a dialkylated byproduct, which could consume the desired product.

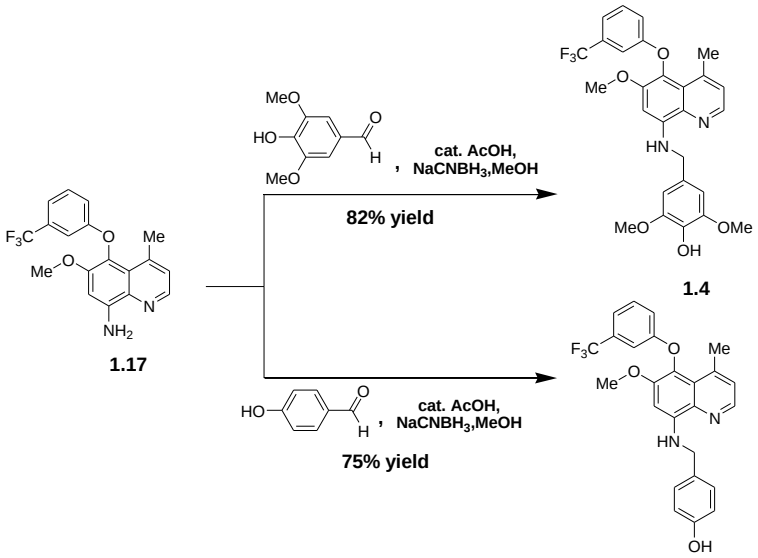
Besides furans, sulfur-containing heterocyclic aldehydes were coupled with compound **1.17** as well. With thiazole-2-carboxylaldehyde and 5-phenyl thiophene-2-carboxylaldehyde, compound **1.2** and **1.3** were synthesized via the reductive amination reaction under the optimized condition, respectively (Scheme 1.3).

**Scheme 1.3 : Syntheses compound 1.2 and 1.3**



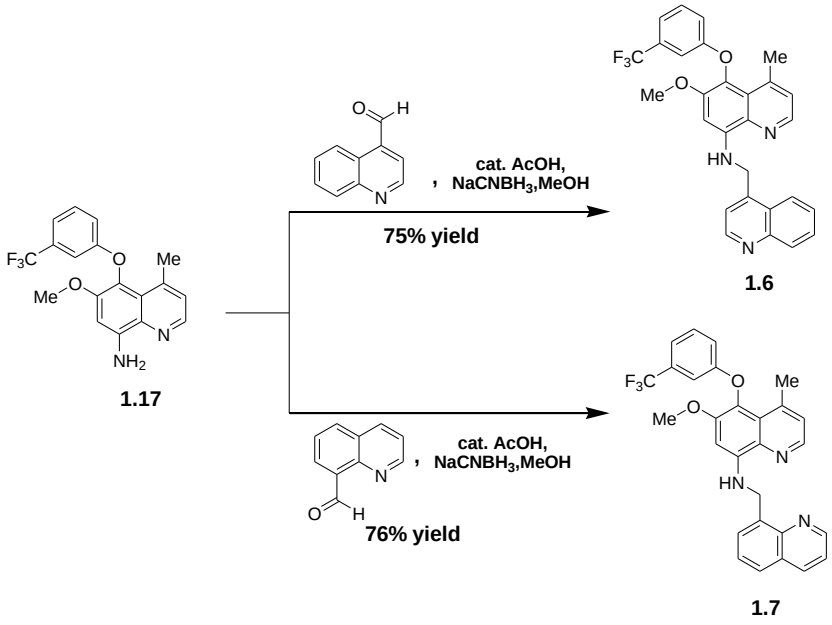
3,5-Dimethoxy-4-hydroxyl benzaldehyde, 4-hydroxyl benzaldehyde, were also coupled with compound **1.17** to give compounds **1.4** and **1.5** (Scheme 1.4).

**Scheme 1.4 : Syntheses of compound 1.4 and 1.5**



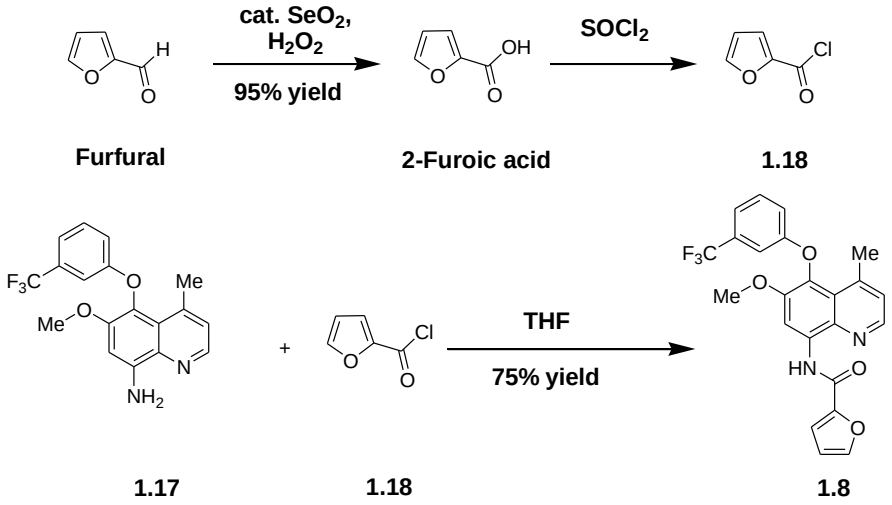

Bi-quinoline structures were designed as well. Amino quinoline **1.17** was treated with carboxylaldehyde substituted quinoines[11] to give compound **1.6** and **1.7**, respectively (Scheme 1.5).

**Scheme 1.5 : Syntheses of compound 1.6 and 1.7**



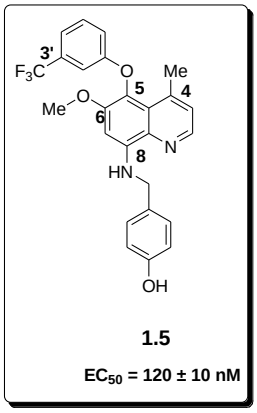
Till then, all of the designed compounds were the *N*-alkylated derivatives of **1.17**. To explore the potential of other functionality, an *N*-amidation product **1.8** was therefore designed and synthesized. To prepare compound **1.8**, furfural was oxidized by hydrogen peroxide with selenium dioxide as a catalyst to yield 2-furoic acid.[12] This carboxylic acid was treated with thionyl chloride ($SOCl_2$) to give compound **1.18** which was directly introduced into compound **1.17** in dry tetrahydrofuran (THF) solution at 0 $^oC$ to give compound **1.8** (Scheme 1.6).[13]

**Scheme 1.6 : Synthesis of compound 1.8**



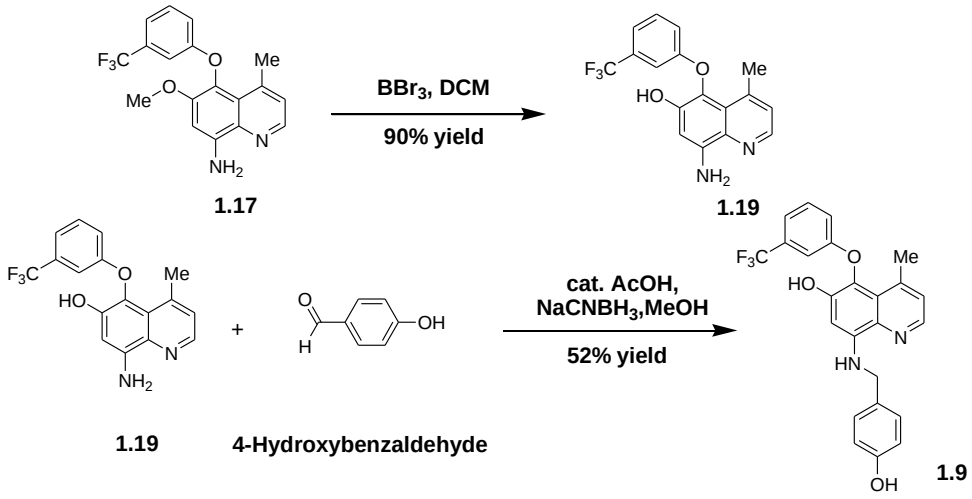

Prepared compounds **1.1** – **1.8** were tested their cell protection activities on MC65 cell protection assay, and compound **1.5** is turned out to be the most active one with $EC_{50}$ = 120 ± 10 nM (Testing results are summarized in section 1.3). This compound is six times more active than **PQ-7**, which indicates the success of structure modification. From this stage, compound **1.5** was selected as lead compound for the further structure modification (Figure 1.3). Compounds **1.9** – **1.12** are all derived from compound **1.5**.

**Figure 1.3 : Structure of compound 1.5**



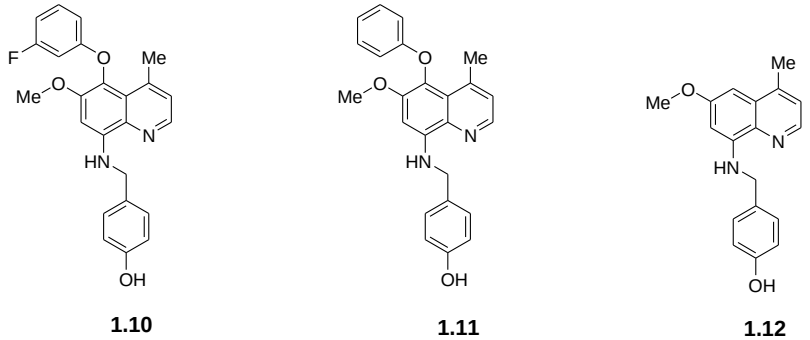
By keeping the 8-(4-hydroxylbenzyl) amino group unchanged, 6-methoxy group of compound **1.5** was modified into 6-hydroxyl group to generate structure of compound **1.9**. To prepare **1.9**, compound **1.17** was treated with boron tribromide ($BBr_3$) in dry dichloromethane (DCM) over 14 hours to generated intermediate **1.19** which was coupled with 4-hydroxy benzaldehye by the same method as that for the synthesis of compound **1.5** to yield compound **1.9** (Scheme 1.7). However, the desired product **1.9** could not dissolve well in most of the common solvents. Various solvents combinations were tried for column chromatographic purification, but pure product could not be obtained. Finally, to remove the impurities, a recrystallization procedure was carried out after the column chromatography. Therefore, the overall yield of this reaction was lower than compound **1.5**.

**Scheme 1.7 : Synthesis of compound 1.9**




5-(3-Trifluoromethylphenoxyl) group of compound **1.5** was also modified into 5-(3-fluorophenoxyl), 5-phenoxyl and hydrogen to generate the structures of compounds **1.10**, **1.11**, **1.12**, respectively (Figure 1.3).

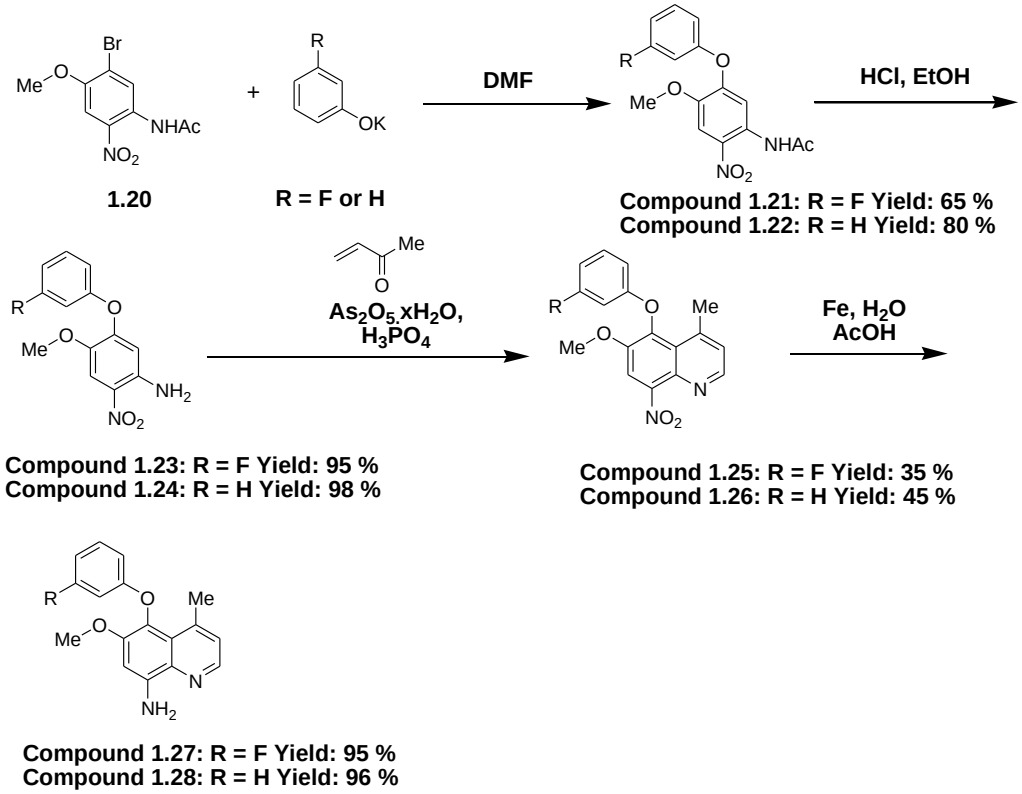
**Figure 1.4 : Structures of designed 1.10, 1.11 and 1.12**



To synthesize these designed compounds, amino quinolines **1.27**, **1.28** and **1.31** were needed to be prepared.

Amino quinolines **1.27** and **1.28** were prepared in the same method as that of compound **1.17**.[10] Bromide **1.20** was treated with potassium 3-fluorophenolate and potassium phenolate respectively to give $S_NAr$ products **1.21** and **1.22**. 3-Fluoro, an electron-withdrawing group, decreased the reactivity of the phenolate, and, therefore, the reaction yield was lower than that of **1.22**. Removals of the acetate groups of **1.21** and **1.22** were furnished by refluxing in hydrochloric acid (HCl) and ethanol (EtOH) solution to give anilines **1.23** and **1.24** respectively in quantitative yields. Methyl vinyl ketone was added dropwisely into a mixture of compound **1.23**, arsenic pentoxide hydrate in phosphoric acid at 120 $^oC$ to give nitro quinoline **1.25**. Nitro quinoline **1.26** was synthesized in the same way by using compound **1.24** as the starting material. The nitro group in compounds **1.25** and **1.26** was reduced by iron powder and acetic acid to give amino quinolines **1.27** and **1.28** (Scheme 1.8).

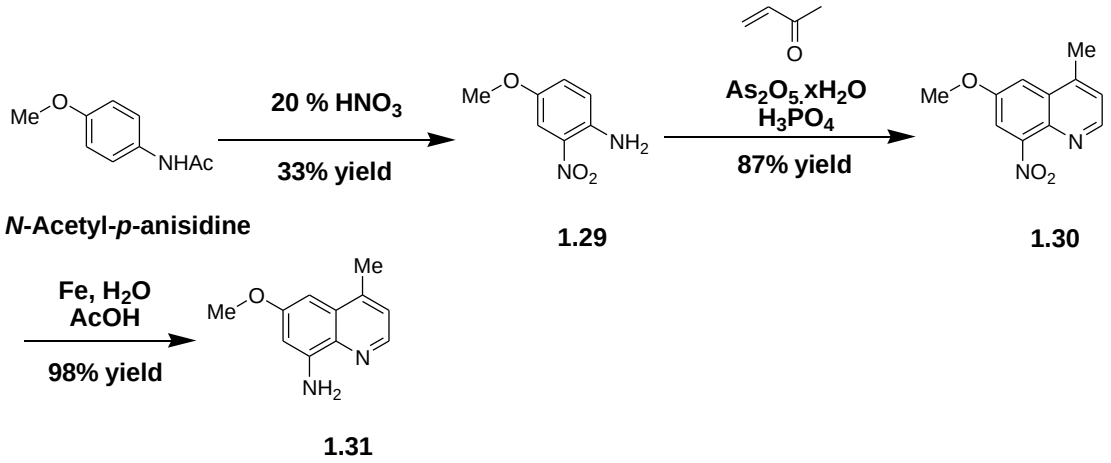
**Scheme 1.8 : Syntheses of compounds 1.27 and 1.28**




*N*-Acetyl-*p*-anisidine was treated with 20 % nitric acid to yield nitration–deacetylation product **1.29** in one pot. Aniline **1.29** reacted with methyl vinyl ketone, arsenic pentoxide hydrate

in phosphoric acid to furnish the synthesis of nitro quinoline **1.30**. Reduction of **1.30** with iron powder in acetic acid gave quinoline **1.31** (Scheme 1.9).

**Scheme 1.9 : Synthesis of compound 1.31**




*N*-Acetyl-*p*-anisidine

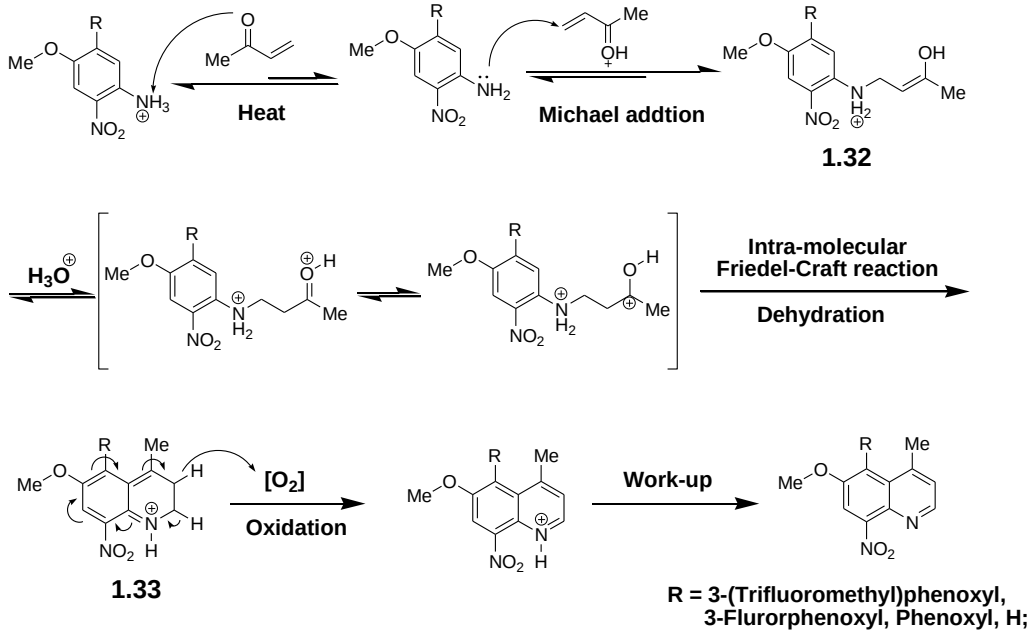
**1.29**

**1.30**

**1.31**

Quinoline synthesis is the key step in the syntheses of designed quinolines, and a possible mechanism is proposed herein (Scheme 1.10).

**Scheme 1.10 : Proposed mechanism for quinoline synthesis reaction**



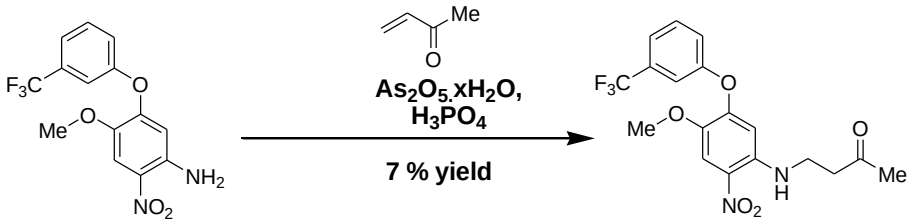

**1.32**

**1.33**

**R = 3-(Trifluoromethyl)phenoxyl, 3-Flurorphenoxyl, Phenoxyl, H;**

This quinoline synthesis reaction starts with Michael addition of the aniline $-NH_2$ to methyl vinyl ketone. This is proven by the isolation of the Michael-addition intermediate **1.35** from the synthesis of compound **1.17** (R = 3-trifluoromethylphenoxyl) (Scheme 1.11).[10] Intra-molecular Friedel-Craft reaction followed by dehydration are carried out to furnish the cyclic structure construction.

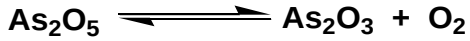
**Scheme 1.11 : Isolation of the Michael addition product from the synthesis of 1.17[10]**




**1.34** **1.35**

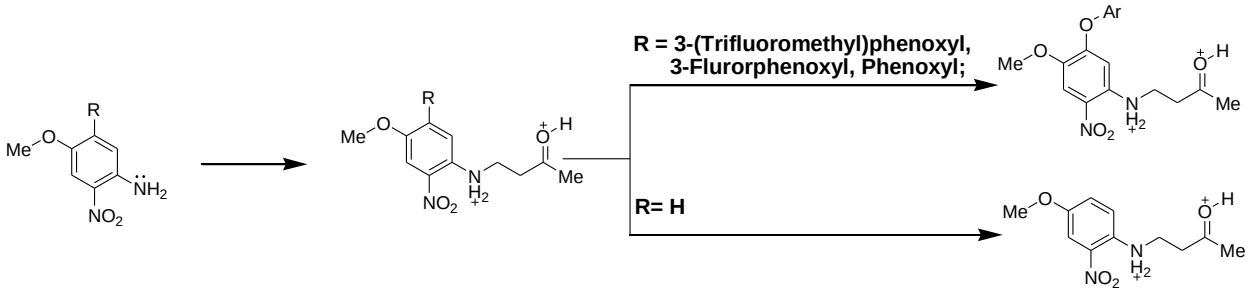
An oxidation step is needed to finish the synthesis of aromatic quinoline structure. This reaction was carried out with and without argon protection, and the reaction yields did not show significant difference. This indicates that the oxidizing reagent is not the oxygen in the air. Under heating, $As_2O_5$ decomposes to give $As_2O_3$ and oxygen (Scheme 1.12);[14] hence, $As_2O_5$ probably is the oxygen source to provide the oxygen *in situ* to furnish the oxidation. Work-up of the reaction with sodium hydroxide gave free quinoline compounds.

**Scheme 1.12 : Oxygen from $As_2O_5$[14]**




In the proposed mechanism above, the intramolecular Friedel-Craft reaction is the key step for quinoline structure construction. A detailed mechanism of this step is proposed as well to interpret the reaction outcomes. Firstly, the Michael addition products are divided into 2 groups: (1) with aryloxyl at 6-position (compound **1.32**, **1.23**, **1.24**); (2) without aryloxyl at 6-position (compound **1.30**) (Scheme 1.13).

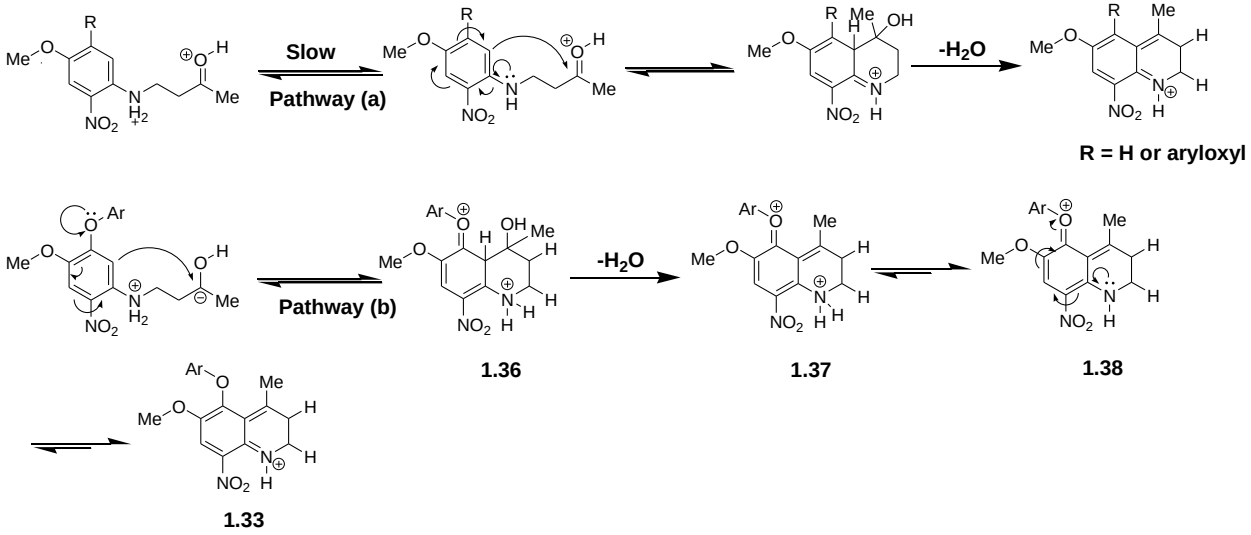
**Scheme 1.13 : Two groups of compounds for mechanism proposal**




For group (1) compounds, there are two possible mechanisms for the intramolecular Friedel-Craft reaction (Scheme 1.14). Pathway (a) is the aniline nitrogen undergoes deprotonation firstly to free the long pair electrons and then donates this long pair of electrons to initiate the Friedel-Craft process; pathway (b) is the 6-oxygen donates one long pair of electrons to initiate the Friedel-Craft reaction. Considering the reaction is carried out in the highly acidic

environment, the deprotonation of the aniline nitrogen could be slow. Hence, it is more reasonable that pathway (b) is the predominate route for the Friedel-Craft reaction. A di-cation intermediate **1.37** was formed after the dehydration. To stabilize the structure, the nitrogen could be easily deprotonated to yield a free amine intermediate **1.38** which is the resonance structure of compound **1.33**.

**Scheme 1.14 : Possible mechanisms for the intramolecular Friedel-Craft reaction**

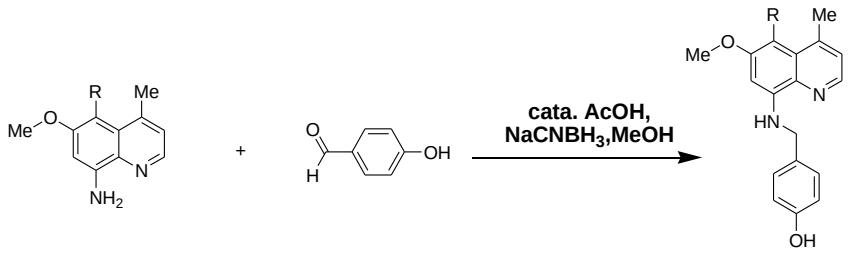



Mechanism (b) could perfectly interpret the observed reaction outcomes. For different quinolines, the yield changes from 25 % of **1.17** [R = 3-(trifluoromethyl) phenoxyl], 35 % of **1.25** (R = 3-fluoropehnxoyl) to 45 % of **1.26** (R = phenoxyl). With stronger electron withdrawing groups attached, the reaction yield is lower. It might because that the electron withdrawing group destabilized the quinone cation intermediate **1.36**. The electron withdrawing abilities comparison is: $-CF_3$ > -F > -H; hence, the yield is **1.17** < **1.25** < **1.26**.

For the group (2) compound **1.31**, since no aryloxyl group is available at 6-position, pathway (a) is the only possible mechanism to give the desired product. Meanwhile, the disappearing of 6-aryloxyl significantly reduces the steric hindrance in the Friedel-Craft reaction step; hence, a higher yield (87 %) is achieved.

Compounds **1.10**, **1.11** and **1.12** were prepared from quinolines **1.27**, **1.28** and **1.31** respectively by using the same method as that of synthesis of compound **1.5** (Scheme 1.15).

**Scheme 1.15 : Syntheses of compounds 1.10, 1.11, 1.12**




**1.27: R = 3-Fluorphenoxyl**
**1.28: R = Phenoxyl**
**1.31: R = H**

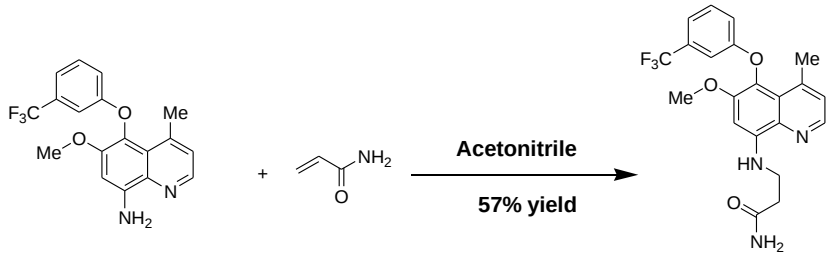
**4-Hydroxybenzaldehyde**

**1.10: R = 3-Fluorphenoxyl Yield:65 %**
**1.11: R = Phenoxyl Yield: 84 %**
**1.12: R = H Yield: 73%**

Till now, syntheses of **PQ-7** derivative compounds are all described and discussed. The syntheses of **PQ-1** derivative compounds will be introduced.

First **PQ-1** derivative compound, compound **1.13**, was synthesized by a Michael addition reaction of compound **1.17** with acrylamide in acetonitrile (Scheme 1.16).

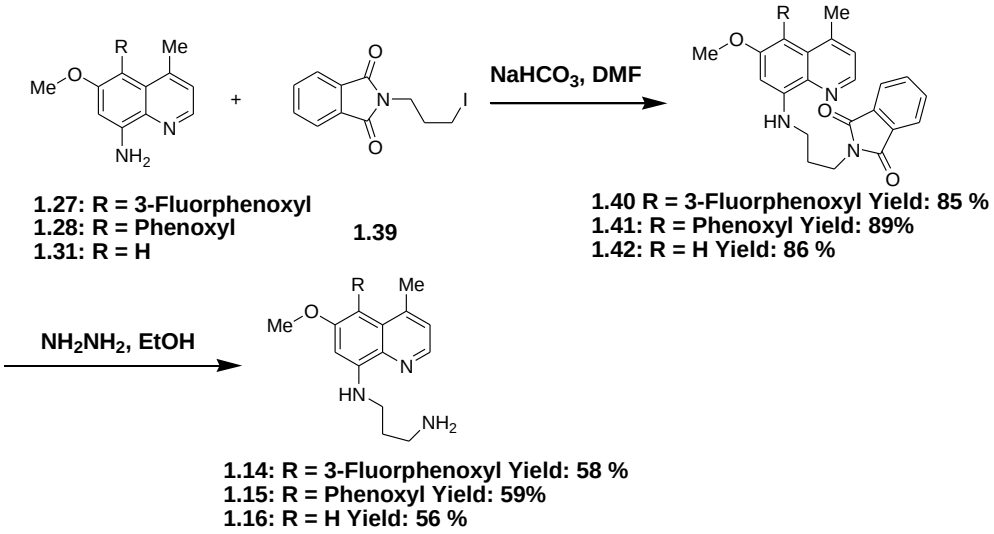
**Scheme 1.16 : Synthesis of compound 1.13**




**1.17** **1.13**

With the synthesized amino quinolins **1.27**, **1.28** and **1.30** in hand, three new **PQ-1** derivative compounds were prepared. Compounds **1.27**, **1.28** and **1.30** were treated with iodide **1.39** and sodium bicarbonate as the base in DMF to yield *N*-substituted compounds **1.40**, **1.41**, **1.42**, respectively. The imido groups were deprotected by refluxing in hydrazine ethanol solution to give compounds **1.14**, **1.15** and **1.16** (Scheme 1.16).

**Scheme 1.17 : Syntheses of compounds 1.14, 1.15, 1.16**




**1.27: R = 3-Fluorphenoxyl**
**1.28: R = Phenoxyl**
**1.31: R = H**

**1.39**

**1.40 R = 3-Fluorphenoxyl Yield: 85 %**
**1.41: R = Phenoxyl Yield: 89%**
**1.42: R = H Yield: 86 %**

**1.14: R = 3-Fluorphenoxyl Yield: 58 %**
**1.15: R = Phenoxyl Yield: 59%**
**1.16: R = H Yield: 56 %**

All the designed quinoline compounds were synthesized and discussed, and, in the next section, bio-evaluation results of these novel quinoline compounds are summarized.

## 1.3 Bio-evaluation results for synthesized quinoline compounds

The synthesized quinoline compounds **1.1** – **1.16** were firstly treated with succinic acid to generate the corresponding succinic salt. These prepared salts were used to screen their bio-activity on MC65 cell protection assay.

MC65 cell possesses a S$\beta$C gene which could produce C99 fragment APP.[15] This APP eventually could be cleaved to generate toxic Aβ peptide which induces cell death.[15] Tetracycline (TC) is introduced to MC65 cells to suppress S$\beta$C gene's expression.[15] Designed quinoline compounds were incubated with MC65 cells in the absence of TC to test their cell protection activity against the Aβ peptide induced cyto-toxicity.[15] This work was carried out by Dr. Izumi Maezawa and Dr. Lee-Way Jin. The cell protection activity results of compounds **1.1** – **1.16** are summarized in Table 1.2.

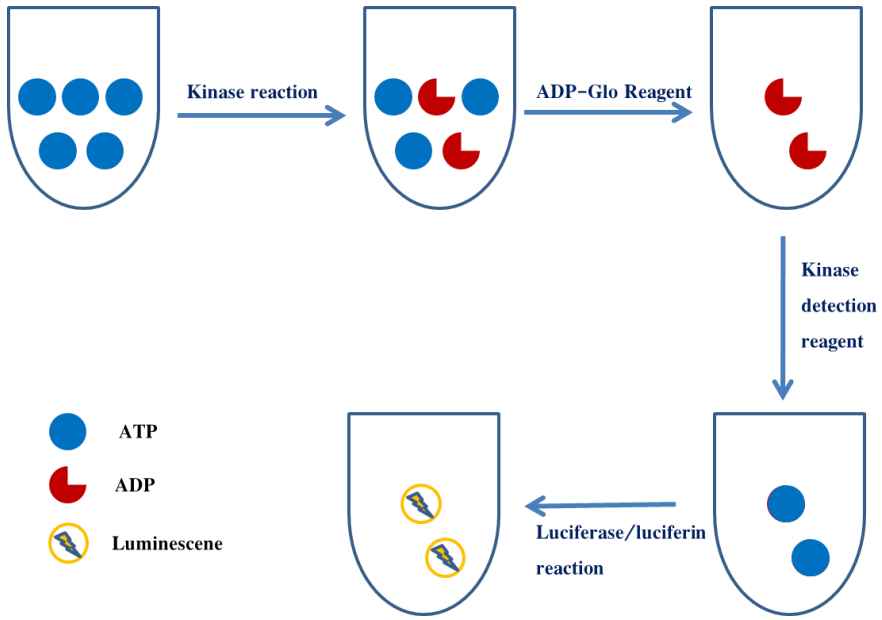
**Table 1.2 : $EC_{50}$ (μM) and $TD_{50}$ (μM) Values of quinoline compounds on MC65 protection assay**

| | $EC_{50}$ | $TD_{50}$ | | $EC_{50}$ | $TD_{50}$ | | $EC_{50}$ | $TD_{50}$ |
|---|---|---|---|---|---|---|---|---|
| **1.1** | 0.46 ± 0.10 | > 50 | **1.2** | 2.39 ± 0.06 | 20.32 ± 1.22 | **1.3** | 0.39 ± 0.02 | 14.50 ± 1.68 |
| **1.4** | 0.48 ± 0.03 | 2.91 ± 0.15 | **1.5** | 0.12 ± 0.01 | 1.38 ± 0.08 | **1.6** | 0.13 ± 0.01 | 3.35 ± 0.36 |
| **1.7** | 0.19 ± 0.02 | > 50 | **1.8** | 3.47 ± 0.32 | > 50 | **1.9** | 0.30 ± 0.01 | 3.31 ± 0.30 |
| **1.10** | 0.70 ± 0.01 | 2.60 ± 0.20 | **1.11** | 0.53 ± 0.01 | 4.00 ± 0.38 | **1.12** | 2.62 ± 0.15 | 20.54 ± 0.21 |
| **1.13** | 0.50 ± 0.02 | > 50 | **1.14** | 0.60 ± 0.02 | 7.28 ± 0.25 | **1.15** | 0.42 ± 0.01 | 8.16 ± 0.01 |
| **1.16** | 17.62 ± 0.37 | > 50 | **PQ-1** | 0.15 ± 0.20 | 2.09 ± 0.02 | **PQ-7** | 0.69 ± 0.03 | 42.82 ± 2.43 |

To explore the mechanism, four of the most active compounds **1.5** ($EC_{50}$ = 0.12 ± 0.01 μM), **1.6** ($EC_{50}$ = 0.13 ± 0.01 μM), **1.7** ($EC_{50}$ = 0.19 ± 0.02 μM) and **1.9** ($EC_{50}$ = 0.30 ± 0.01 μM) were selected to test their enzyme inhibitory activities on GSK-3β ADP-Glo™ kinase assay[16] and protein kinase C (PKC)-PepTag™ kinase assay[17]. These works were done by Sahani Weerasekara and Dr. Keshar Prasain in Dr. Duy Hua's lab.

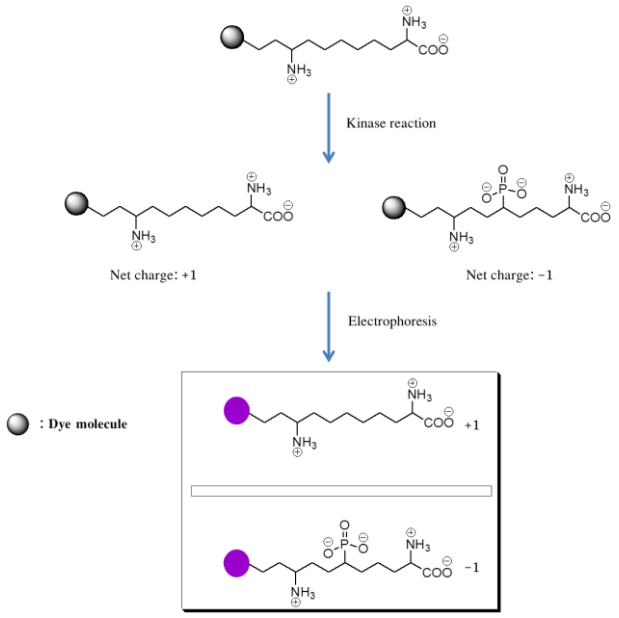
On GSK-3β ADP-Glo™ kinase assay, there are four steps to test the enzyme inhibitory activities of designed quinolines (Figure 1.5).[16] Firstly, the compound, enzyme, ATP and substrate are incubated at 25 °C for 1 hour; then, ADP-Glo™ reagent is introduced to stop the enzyme reaction and deplete the unreacted ATP. Thirdly, the remaining ADP is converted into ATP by the kinase detection reagent. At last, via a luciferase/luciferin reaction, the newly synthesized ATP is used to generate a light signal which is measured by luminometer. The measure luminescence is correlated with the concentration of ADP which is generated from the kinase reaction and therefore reflects the enzyme activity.

**Figure 1.5 : Procedure for operating GSK-3β ADP-Glo$^{TM}$ kinase assay[16]**




On PKC PepTag$^{TM}$ kinase assay, a dye molecule attached eleven amino acids residue is used as the substrate, and, at pH = 7.4, this substrate held +1 net charge. There are three steps to test the enzyme inhibitory activities of designed quinolines (Figure 1.5).[17] Firstly, the kinase reaction is carried out by the incubation of compound with the substrate, ATP and enzyme at pH = 7.4 and 31 $^{o}$C for 45 minutes. After the kinase reaction, the phosphorylated substrate would held -1 net charge at the reaction pH while the unphosphorylated substrate stays unchanged. Secondly, the enzyme is destroyed to stop the reaction, and the phosphorylated substrate and the unphosphorylated substrate are separated by electrophoresis. At last, the fluorescence intensities of the bands from the electrophoresis experiment are measured, and these intensities are correlated with the enzyme activity.

**Figure 1.6 : Procedure for operating PKC PepTag™ kinase assay[17]**




Results on the enzyme inhibitory assays are summarized in Table 1.3.

**Table 1.3 : Enzyme inhibition activities of 1.5, 1.6, 1.7 and 1.9 on GSK-3β and PKC assays**

| Quinoline | GSK-3β | PKC |
|---|---|---|
| **PQ-1** | > 1 mM | 35 ± 8 nM |
| **PQ-7** | > 1 μM | 42.3 nM |
| **1.5** | 35 ± 6.36 nM | 240 ± 21.2 μM |
| **1.6** | > 1 mM | 216.3 nM |
| **1.7** | > 1mM | 400 ± 13.7 μM |
| **1.9** | 158 ± 19.1 nM | 750 ± 9.3 μM |

## 1.4 Discussion

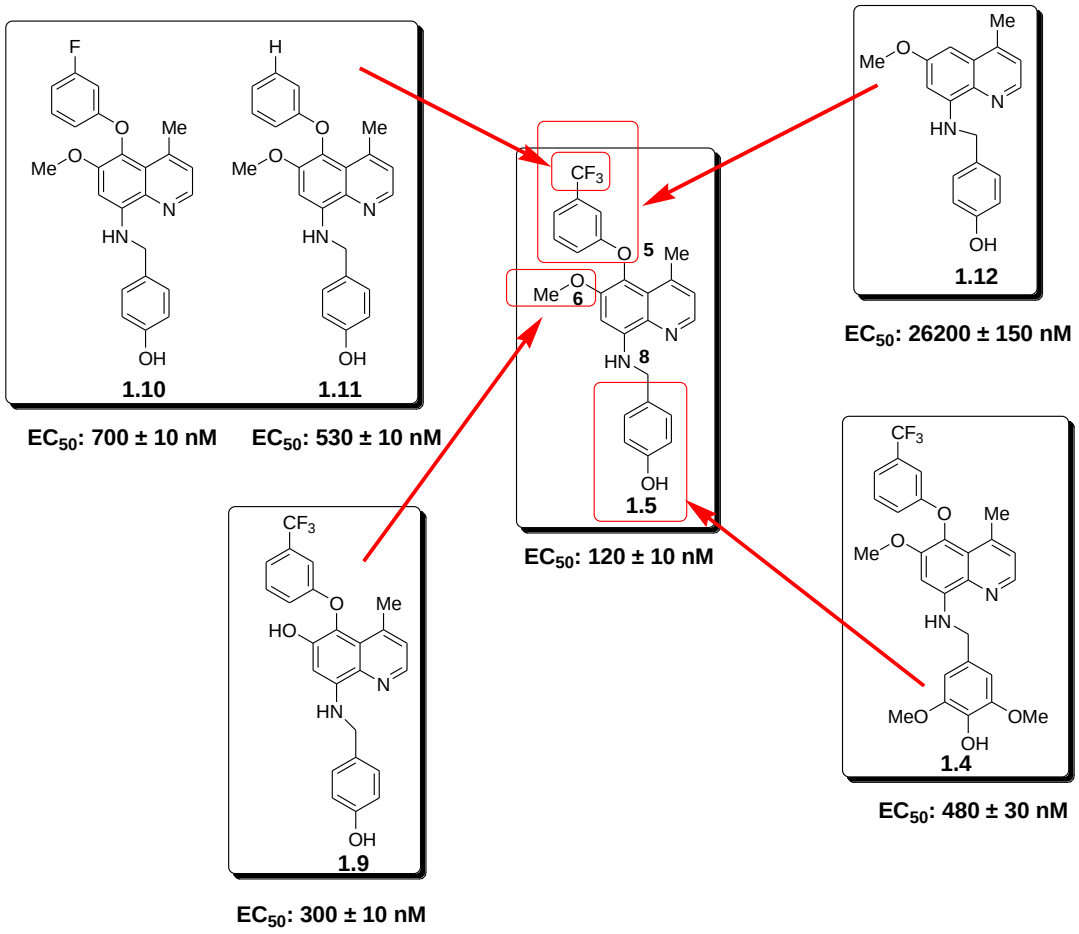
Designed quinoline compounds were synthesized and evaluated their bio-activities on both cell and enzymes assays. From these bio-evaluation results, a structure-activity relationship (SAR) could be derived, which may help to the development of a higher efficient and lower toxic drug candidate for AD therapy in future. Moreover, to explore the mechanism, a computational

experiment was also carried out to simulate the binding mode of the designed quinolines with GSK-3β. All of these works are discussed in this section.

### *1.4.1 Structure-activity relationship of the synthesized quinoline compounds*

From results of MC65 cell protection assay, a SAR could be derived (Figure 1.7).

**Figure 1.7 : Structures activity relationship of synthesized quinoline compounds**




Structural modifications of **PQ-1** do not give a positive feedback. The new synthesized **PQ-1** analog compounds do not show better cell protection activities, and changes made on the **PQ-1**'s structure impair the bio-activity. From the result of the enzyme inhibitory assays, **PQ-1** is PKC inhibitor instead of GSK-3β inhibitor which indicates **PQ-1** protects the neuronal cell through different mechanism. Since this research is aiming to discover a GSK-3β inhibitor, **PQ-1** derivatives are not considered for deriving the SAR.

Among the **PQ-7** derivatives, compound **1.5** shows the highest cell protection activity and GSK-3β inhibitory activity. Some **PQ-7** derivative compounds (compound **1.6** and **1.7**) were

also examined their GSK-3β inhibitory activities; but the results indicate they are not the GSK-3β inhibitors. Hence, only the compounds derived from **1.5** are used to derive the SAR.

Compound **1.5** possesses the highest cell protection activity ($EC_{50}$ = 120 ± 10 nM). Comparing with quinoline **1.5**, compounds **1.4** shares the same substitution groups on the 4-, 5- and 6- positions of quinoline core, and the difference is the functionality which is connected to 8-amino group. The cell protection results suggest the importance of 4-hydroxybenzyl group to the activity of designed compounds. Any changes on this portion of the molecule cause the decrease of the activity. Structure of compound **1.4** is very similar to compound **1.5**; however, the addition of two methoxyl groups on the phenyl ring decreases quinoline **1.4** 's activity ($EC_{50}$ = 480 ± 30 nM) four times comparing to compound **1.5**. 5-Aryloxy group is also very important. Removal of the 5-aryloxy group in compound **1.5** gives compound **1.12**, and compound **1.12** ($EC_{50}$ = 26.20 ± 0.15 μM) almost lose the cell protection activity. Trifluoro group on the 5-aryloxy is also proven to be unsubstitutable for the activity, and the replacements of it with fluoro [compound **1.10** ($EC_{50}$ = 700 ± 10 nM)] or hydrogen [compound **1.11** ($EC_{50}$ = 530 ± 10 nM)] decrease the activity. Replacement of the methoxy group with hydroxyl group at 6- position [compound **1.9 (**$EC_{50}$ = 300 ± 10 nM)] did not improve the activity neither.

In summary, 3-trifluoromethylphenoxyl at 5- position, methoxyl at 6- position and 4-hydroxybenzyl at 8-amino position are all important to the designed quinoline compound activity. To modify **1.5**'s structure to get more effective GSK-3β inhibitors, the functions of these substitutions in inhibiting GSK-3β should be learned. The best way to acquire these information is from the co-crystal structure of GSK-3β with compound **1.5**. However, this experiment dose not have to chance to be carried out yet. Hence, a computational docking experiment was carried out to simulate the binding mode of **1.5** to GSK-3β. The design of the docking experiment and the results are summarized in the next section.

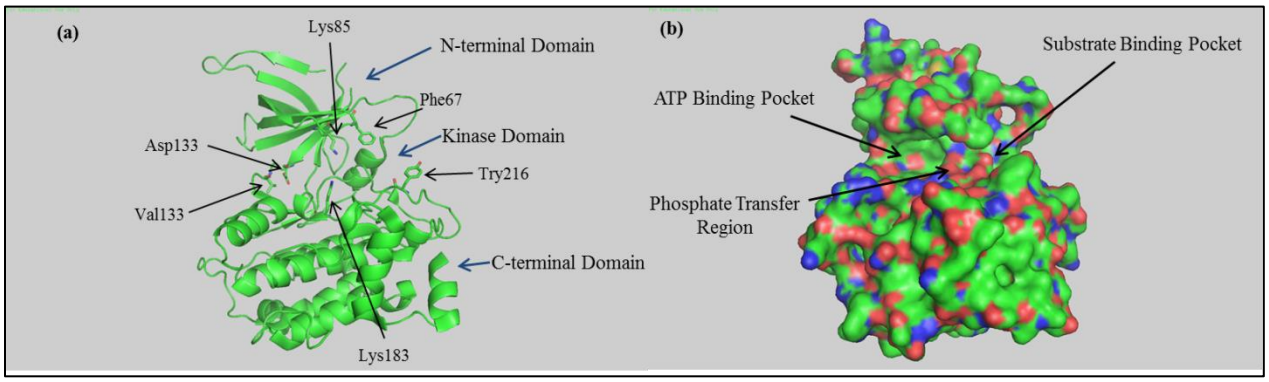
### *1.4.2 Computational experiment and the result*

To understand the mechanism of **1.5**'s inhibitory activity on GSK-3β, a computer-docking experiment was carried out, and the result is introduced and discussed in this section.

To begin with, the structural properties of GSK-3β is briefly introduced herein. Figure 1.8 shows one of the reported GSK-3β crystal structures in both cartoon and surface representations.[18] GSK-3β has a small N-terminal domain and large C-terminal domain. The

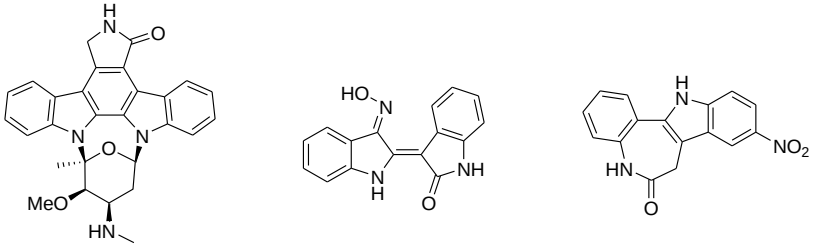
kinase domain lies in the space between these two domains and is responsible for the kinase reaction.[18] This domain is divided into three regions by their functions: ATP-binding pocket, phosphate transfer region and substrate binding groove.[18]

**Figure 1.8 : Cartoon and surface representations of GSK-3β[18]: (a) Cartoon representation; (b) Surface representation (Green: carbon; Red: oxygen; Blue: nitrogen; Yellow: sulfur)**




Studies indicate that some residues in the kinase domain are extremely important to the enzyme's activity.[18,19] In the ATP-binding pocket, residues Asp133 and Val135 are suggested to be vital for the binding the ATP molecule to enzyme. Adenylyl imidodiphosphate (AMP-PNP) which has similar structure as the ATP was co-crystalized with GSK-3β to mimic the binding mode of ATP molecule with the enzyme.[19] From the structure of the co-crystal, hydrogen-bonding interactions are detected between residues Asp133 and Val135 with the adenylyl group of the AMP-PNP.[19] Moreover, these hydrogen-bonding interactions are conserved in the co-crystal structures of GSK-3β with some of its ATP-competitive inhibitors, such as staurosporine, indirubin-3'-monoxime and alsterpaullone (Figure 1.9).[19] In the phosphate transfer region, Lys85 and Lys183 are responsible for the enzyme's binding to the phosphates in AMP-PNP molecule.[19] In the substrate binding groove, two residues, Phe67 and Try216, are suggested to control the enzyme's activity.[3,20] F67A mutant GSK-3β lose its activity on the phosphorylation of substrate peptide, which indicates that Phe67 is vital for GSK-3β's substrate recognition.[20] Residue Try216 could be self-phosphorylated to be the pTry216 by GSK-3β, and pTry216 has a conformational change comparing with Try216. The enzyme is activated to hyperphosphorylate the substrate, such as tau, after Try216 is phosphoryated.[2]

**Figure 1.9 : Structures of staurosporine, indirubin-3'-monoxime and alsterpaullone[19]**




**Staurosporine** **Indirubin-3'-monoxime** **Alsterpaullone**

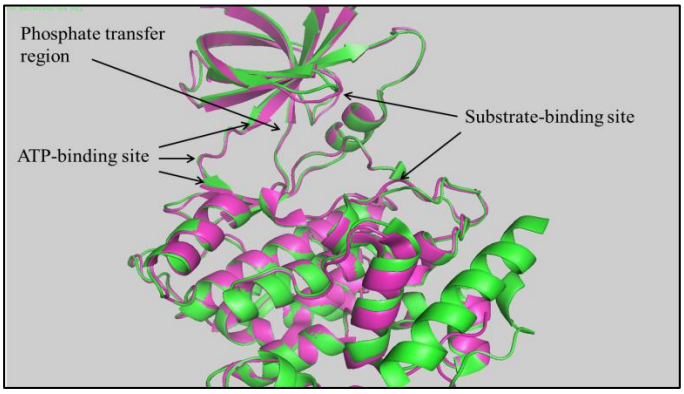
Autodock Vina was used as the computer docking program.[21] The 3D structure of compound **1.5** was constructed via Chem3D 11.0. The exact binding site of compound **1.5** to GSK-3β was unknown; therefore, compound **1.5** was docked in whole kinase domain. Docking conformation of **1.5** with the lowest binding energy was supposed to simulate the real binding mode of compound **1.5**.

The crucial step for the computer docking is to choose the right crystal structure of GSK-3β, and the criterions are rationally investigated. Since computer docking by Autodock Vina is a rigid docking process,[21] the 3D structure of GSK-3β for docking should mimic the real structure of the enzyme in the enzyme and inhibitor (compound **1.5**) complex. For GSK-3β, it has different structural characters for different types of inhibitors. If compound **1.5** is an ATP-competitive inhibitor and binds into the ATP-binding pocket, it would block ATP molecule bind to the enzyme. Hence, the Try216 would not have chance to be phosphorylated, and the enzyme would be in an inactive state. Moreover, it is highly possible that the compound conserved some similar interactions as other ATP-competitive inhibitors do. To resemble the similar interactions, the key residues in the ATP binding pocket should have the similar conformations as those of the same residues in other known GSK-3β-inhibitor co-crystals. If compound **1.5** is a substrate competitive inhibitor and binds to the substrate binding groove of GSK-3β, the enzyme is highly possible in its activated state. Since residue Try216 phosphorylation is self-phosphorylation process (in other words, intramolecular process), this phosphorylation process is fast in the presence of ATP (the enzyme assay environment). When the inhibitor binds into the substrate binding groove, it is highly possible that the Try216 is phosphorylated and the enzyme is in active state. Unfortunately, the exact binding site of compound **1.5** with GSK-3β is not clear. In other words, whether compound **1.5** is an ATP-competitive inhibitor or substrate competitive

inhibitor was not known. Hence, the protein structures for both possible cases should be considered.

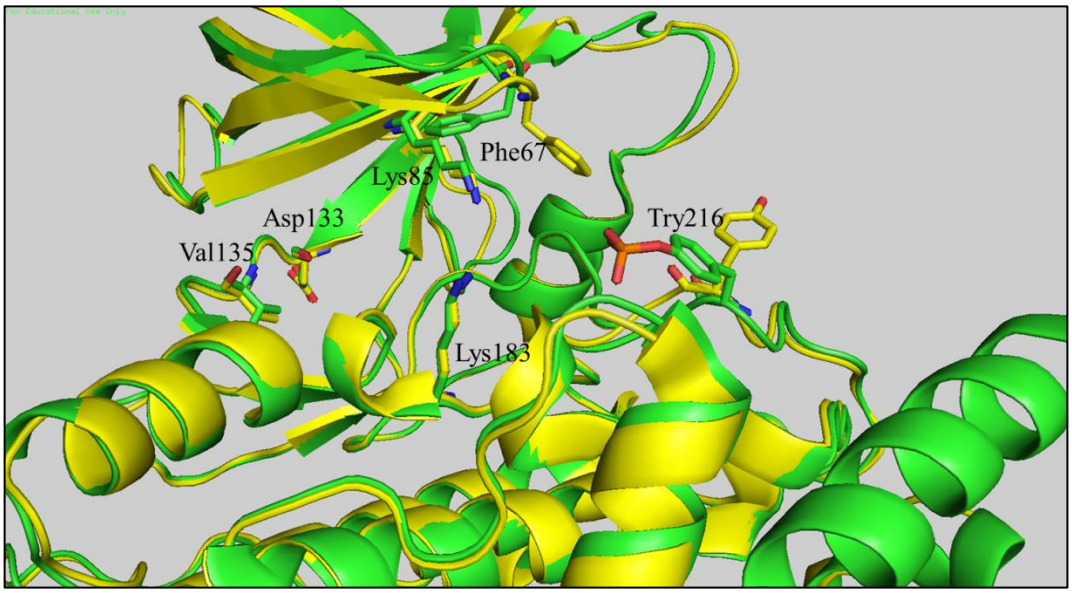
Considering the ideal docking would probe the ATP binding pocket and substrate binding groove with equal chance in one experiment, the ideal protein structure should be able to perfectly mimic the real protein for each case. In other words, the ideal protein crystal structure used for docking should possess the ATP binding pocket which should be the same as the one in the inactive enzyme, and a substrate binding pocket which should be the same as the one in the active enzyme! This seemed impossible. However, after screening the available crystal structures of GSK-3β,[22] fortunately, file 1O9U[23] is finally found to satisfy this criterion. It had the same ATP binding pocket as the inactive enzyme, and the phosphorylation of residue Try216 caused the conformational change in the substrate binding pocket compares with the inactive enzyme.[23] This enzyme is overlaid with inactive enzyme[18] to show the difference in the substrate binding pocket (Figure 1.10) .

**Figure 1.10 : Overlay of crystal structure 1O9U (Green) with inactive enzyme (pdb: 1I09) (Pink)**



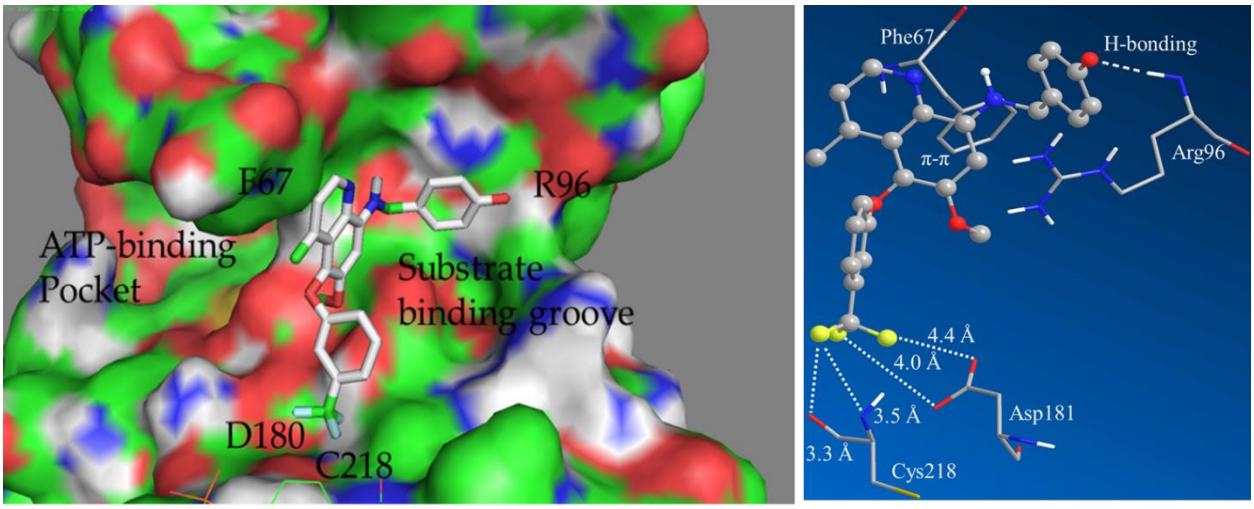

Meanwhile, crystal structure 1O9U is also overlaid with the crystal structure of GSK-3β which was complex with the known ATP-competitive inhibitor (alsterpaullone, pdb: 1Q3W)[19] to compare the conformations of key residues in the ATP binding pocket. From the overlay, it is obvious that the key residues (Asp133, Val135, Lys85, Lys183) in the ATP-binding pocket and phosphate transfer region share very similar conformations. Therefore, it is highly possible that the docking environment in the ATP-binding pocket is well mimicked the "real" case if compound **1.5** is an ATP-competitive inhibitor (Figure 1.11).

**Figure 1.11 : Overlay of crystal structure 1O9U (Green) with enzyme complex with ATP-competitive inhibitor (pdb: 1Q3W) (Yellow)**




Crystal structure for docking (file: 1O9U) was added hydrogens by MOL Probity program[24] before docking experiment, and the results are displayed in Figure 1.12.

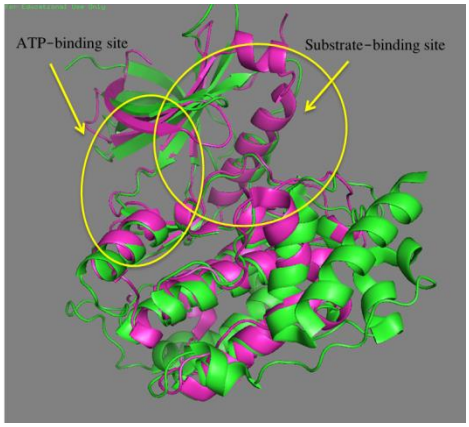
**Figure 1.12 : Docking result of compound 1.5 with GSK-3β**




From the docking result, the conformation with lowest binding energy is displayed in Figure 1.12. Compound **1.5** binds into the substrate binding groove of GSK-3β, instead of ATP-binding pocket. A hydrogen bonding interaction between hydroxyl group on the benzyl ring and residue Arg96 is discovered in the result. π-π Interaction is also found between the quinoline core of compound **1.5** and residue Phe67 in the computer simulation. Trifluoromethyl group is found having close contacts with residues Asp181 and Cys218.

Docking result suggests that compound **1.5** is a substrate-competitive inhibitor; hence, this could explain high enzyme inhibitory selectivity. Since GSK-3β and PKC have distinct substrate binding areas, the substrate-competitive inhibitors "fit" for the GSK-3β would not "fit" in PKC.

**Figure 1.13 : Overlay of crystal structure of GSK-3β 1O9U (Green) with PKC-θ 1XJD (Yellow)**




The observed SAR could also be interpreted by the docking result. In docked conformation, compound **1.5** opens its structure to support itself binds in the substrate binding groove; therefore, the "length" of the molecule is important. A shorter molecule (compound **1.16**) has less possibility to conserve this type of binding to GSK-3β. Meanwhile, the trifluoromethyl group and 4-hydroxyl group on the benzyl ring are two terminals of the structure and have important interactions with residues of GSK-3β to secure the binding of **1.5**. As discussed above, residue Phe67 is important for substrate recognition of the enzyme[20]; hence, the detected π-π interaction might responsible for the deactivation of the enzyme.

To sum up, via the computational experiment, the binding mode of compound **1.5** to GSK-3β is simulated. The importance of the required substitutions and quinoline core are demonstrated and explained. The information acquired from the SAR and computational experiment provides clues for designing more effective GSK-3β inhibitors, and this work will be discussed in the next section.

### *1.4.3 Future work*

The novel quinoline analog compounds with higher bio-activities and less toxicities are being expected to be developed in future. Since the most active quinoline compound till now is

**1.5**, this compound is used as the lead compound. Aiding by the information obtained from the SAR analysis and computational experiment, some novel GSK-3β inhibitors derived from **1.5** is proposed herein.

The criterions for designing new **1.5**-derived inhibitors are discussed firstly. From the derived SAR, the threefold molecular structure is required for the inhibitor's activity; 4-hydoxybenzyl group, 5-(3-trifluoromethylphenoxyl) group and 6-methoxyl group are also important to the quinoline **1.5**'s activity. Roles of the threefold structure and these substituents are interpreted by computer simulation. The threefold structure is essential for binding to the wide substrate binding groove of GSK-3β; 4-hydroxyl group acts as the hydrogen bond donor; trifluoromethyl group has polar-polar interactions with residues in the substrate binding groove, and quinoline core is proposed to be responsible for the deactivation of enzyme via π-π interaction with Phe67. According to these information, the new designed inhibitors should maintain the threefold structure to ensure secure binding to wide-opened area; at the two terminals of the molecule, functional groups should be carefully designed to ensure an interaction with residues in the substrate binding groove. From the rigid docking result, it is worthy to note that the quinoline core of **1.5** is not in the perfectly parallel position of the phenyl ring of Phe67, which indicates this π-π interaction may not be well-established. Since this π-π interaction is proposed to be important for enzyme's deactivation, enhancement on this π-π interaction is supposed to increase the designed inhibitor's activity. Hence, modifications made on the structure of **1.5** are aiming to improve this π-π interaction. To achieve this purpose, the stereo-position of the quinoline core could adjusted by modify the whole structure; or other aromatic moieties could be used to instead of quinoline.

Moreover, to assist design new inhibitors, two parameters, log $P_{Octanol/Water}$ and log S, are predicted by computer simulation method for each proposed molecules. log $P_{Octanol/Water}$ Value is used to estimate the lipophilicity of the drug candidates.[25] The definition is, in the mixture of octanol and water at the equilibrium, the log value of the solute concentration in octanol minus the log value of the solute concentration in water (Equation 1.1).[25] log P Value is important parameter for CNS drugs: with higher log P value, the drug candidate has higher chance to pass the blood-brain barrier (BBB) by diffusion, which has better bio-availability.

**Equation 1.1 : Definition of log $P_{Octanol/Water}$**

$$\log P_{Octanol/Water} = \log c_{solute\ in\ octanol} - \log c_{solute\ in\ water} = \log [c_{solute\ in\ octanol} / c_{solute\ in\ water}]$$

log S Value is also very important for the bio-availability of drug candidates. It is defined as the log value of the drug's solubility in water (Equation 1.2).[26] The higher of log S, the better solubility of the drug in water, and the better the drug distribution in body.[26] For CNS drugs, the higher log S indicates a better diffusion to penetrate the BBB to reach the brain.[26]

**Equation 1.2 : Definition of log S**

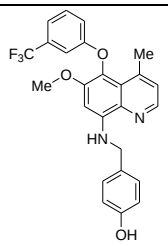
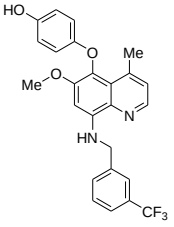
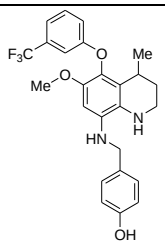
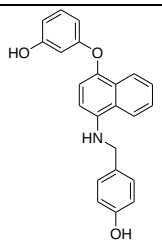
$$\log S = \log \text{solubility}_{\text{water}}$$

The log P and log S Values could be predicated by the computer program: ALOGPS 2.1.[27]

Meanwhile, Lipinski's the rules-of-five for designing more drug-like molecules are also utilized to evaluate the proposed inhibitors.[28] The rules-of-five are including: log P should be in the range of -0.4 – +5.6; molecular weight should be in the range of 180 – 500; number of atoms should be in the range of 20 – 70; rotatable bonds should be less than 10; hydrogen bond donors should less than 5; hydrogen bonding acceptors less than or equal to 10; for CNS drugs, total nitrogen and oxygen atoms' number [$n_{(N+O)}$] should less than or equal to 5, and the other rule is $\log P - n_{(N+O)} > 0$.[28]

According to the discussed, three compounds are designed, and their properties are predicted and summarized in Table 1.4

**Table 1.4 : Structure and predicted properties of the newly designed quinolines**

| | **1.5** | **1.43** | **1.44** | **1.45** |
|---|---|---|---|---|
| Structure |  |  |  |  |
| log $P_{Octanol/Water}$ | 5.50 | 5.62 | 5.44 | 4.93 |
| log $S_{Water}$ | -6.25 | -5.63 | -6.20 | -5.35 |
| Molecular weight | 454.15 | 454.15 | 458.18 | 357.14 |
| Number of atoms | 54 | 54 | 58 | 46 |
| Rotatable bonds | 8 | 8 | 8 | 7 |
| Hydrogen bond donors | 2 | 2 | 2 | 3 |
| Hydrogen bond acceptors | 3 | 3 | 3 | 1 |
| $n_{(N+O)}$ | 5 | 5 | 5 | 4 |
| log P - $n_{(N+O)}$ | + 0.50 | + 0.62 | + 0.44 | +0.93 |

By exchanging position of the terminal substituents (3-trifluoromethylphenoxyl group and 4-hydroxybenzyl group), compound **1.43** is designed. If the hydroxyl group and trifluoromethyl group of the compound **1.43** could assumable the similar binding mode as that of **1.5**, the quinoline core of **1.43** will have a chance to adjust its position towards Phe67, which may strengthen the π-π interaction. By reducing quinoline core of **1.5** into benzopiperidine, the compound **1.44** is designed. From the docking result of **1.5**, only the non-nitrogen containing aromatic ring of the quinoline has the π-π interaction with Phe67, and nitrogen containing portion of quinoline sits apart from Phe67. The piperidine of the **1.44** will have chair conformation; therefore, with the π-π interaction unchanged, this chair-conformation piperidine is expected to have a new hydrophobic-hydrophobic interaction with benzyl's methylene group of Phe67, which also could strengthen the binding of inhibitor to Phe67 of GSK-3β. By replacing the quinoline core of **1.5** in to naphthalene, compound **1.45** is designed. The trifluoromethyl

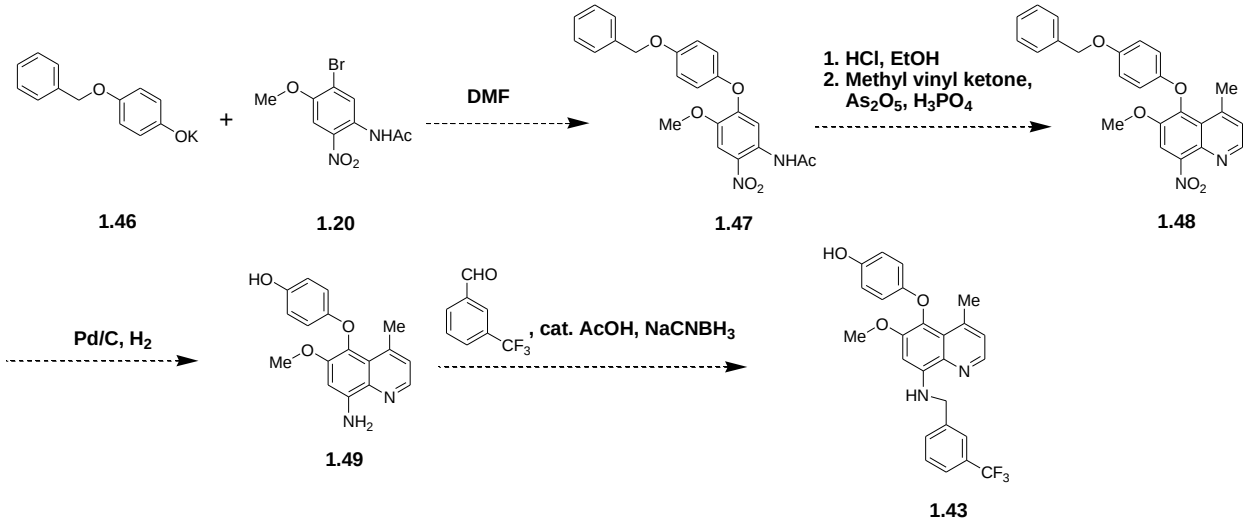
group is changed into hydroxyl group to reduce the log P value. The naphthalene core of **1.45** is expected to improve π-π interaction with Phe67.

The log P and log S values of these designed inhibitors are predicted and summarized in Table 1.4. From the results, all of these newly designed GSK-3β inhibitors are satisfying the rules-of-five and expected to be the qualified CNS drug candidates.

Syntheses of these designed GSK-3β inhibitors are proposed herein as well.

Compound **1.43** could be synthesized via the same synthetic route as compound **1.5**. Phenolate **1.46** will be treated with bromide **1.20** to give compound **1.47**. Following the same quinoline synthesis procedure, **1.48** will be prepared. Hydrogenantion with Pd/C as catalyst could remove the benzyl group and reduce the nitro group in one-pot to give **1.49**.[29] Amino quinoline **1.49** will be coupled with 3-trifluoromethyl benzaldehyde to give desired **1.43** (Scheme 1.18).

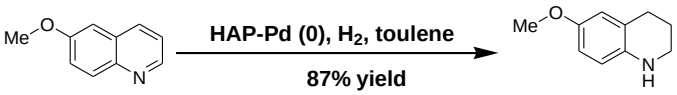
**Scheme 1.18 : Synthesis of compound 1.43**




**1.46** **1.20** **1.47** **1.48** **1.49** **1.43**

Compound **1.44** could be directly generated by reduction of the quinoline of compound **1.5.** In 2010, a hydroxyapatite (HAP) supported Pd nanoparticle is reported to be used to regio-selectively reduce the quinoline in good yield (Scheme 1.19).[30]

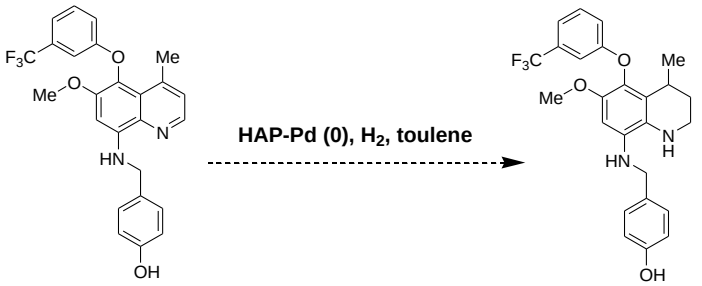
**Scheme 1.19 : Quinoline reduction with HAP supported Pd nanoparticle[30]**




**1.50** **1.51**

Hence, compound **1.44** could be prepared under this reduction condition with compound **1.5** as the starting material (Scheme 1.20).

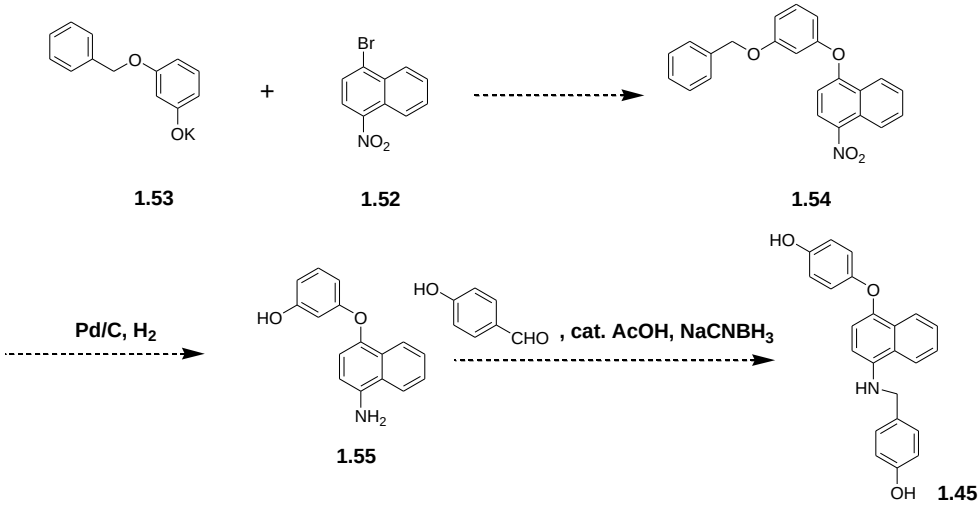
**Scheme 1.20 : Synthesis of compound 1.44**




**1.5** **1.44**

The synthesis of compound **1.45** could be start with the commercial available compound **1.52**. Similar as the synthesis of **1.43**, bromide **1.52** will be treated with phenolate **1.53** to generate compound **1.54**. Hydrogenantion with Pd/C as catalyst could remove the benzyl group and reduce the nitro group in **1.54** in one-pot to give **1.55**.[29] Compound **1.53** will coupled with 4-hydroxyl benzaldehyde to give desired **1.45** (Scheme 1.21).

**Scheme 1.21 : Synthesis of compound 1.45**




**1.53** **1.52** **1.54**

**1.55** **1.45**

In summary, with the information from the SAR study and computational docking of compound **1.5**, three new GSK-3β inhibitors are designed which will provide a direction for further investigation on discovering more effective GSK-3β inhibitor. log P and log S Values of these proposed compounds are predicted as well, and these inhibitors are also evaluated by the rules-of-five. The designing ideas for these new inhibitors is described, and the syntheses of these compounds are also proposed.

### *1.4.4 Concerns*

Although the bio-evaluation experiments gave very promising results, a few issues are still needed to be taken into account. Firstly, it still lacks of convincing evidence that designed quinolines could inhibit the GSK-3β in cell system. The difficulty in solving this problem is the GSK-3β-overexpressed cell system is difficult to obtain. Therefore, at this stage, this experiment cannot carried out. Also, whether the designed quinoline compound could reduce the hyper-phosphorylation of tau level and/or Aβ oligomer production in an AD mice model is needed to be determined. This experiment is crucial to predict the designed inhibitor's therapeutic effect and should be performed if the requirements for this experiment, such as funding, mice model, could be satisfied.

## 1.5 Conclusion

A focus library of quinoline compounds was designed, synthesized, and their bio-activities evaluated on cell and enzymes assays. Compound **1.1** - **1.7** were synthesized from **1.17** with various aldehydes via reductive amination reactions. Amide **1.8** was synthesized from **1.17** with **1.18**, and compound **1.18** was prepared from furfural. A deprotection of methoxyl of **1.17** with $BBr_3$ was performed to give **1.19**, and compound **1.19** reacted with 4-hydoxybenzaldehyde to give compound **1.9**. Compound **1.27**, **1.28** and **1.31** were prepared in similar reaction sequences as that of compound **1.17** from the same starting material **1.20**. From **1.27**, **1.28**, **1.31**, similar reductive amination reactions were performed with 4-hydoxybenzaldehyde to yield compound **1.10**, **1.11** and **1.12**. Compound **1.13** was prepared from **1.17** with acrylamide via Michael addition reaction. **1.14**, **1.15** and **1.16** were synthesized via a $S_N2$ reaction and deprotection reaction from **1.27**, **1.28** and **1.31**, respectively.

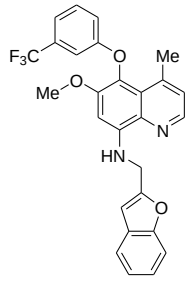
Bio-activities of compounds **1.1** – **1.16** were evaluated on MC65 cell protection assay. Most of quinoline compounds were found to have cell protection activities in nanomolar ranges. Four of the most active compounds were selected to test their enzyme inhibitory activities on GSK-3β and PKC enzyme assays. Compound **1.5** is found to be the most active compound in the synthesized quinoline compounds. A structure activity relationship of designed quinolines is derived. The binding mode of **1.5** with GSK-3β was simulated by the computational method, and several important interactions are shown in the result. The information acquired from the SAR

study and docking experiment gives clues for designing more effective GSK-3β inhibitors, and three novel GSK-3β inhibitors are proposed. Meanwhile, synthetic routes of these proposed inhibitors are suggested. In future, inhibition of GSK-3β in cell system and the level of phosphorylated tau in *in vivo* AD model by quinolines' need to be performed.

## 1.6 Experimental Section

**General procedure:** Melting points were tested on Thomas Hoover capillary melting point apparatus. Nuclear magnetic resonance spectra were obtained at 400 MHz for $^{1}H$ and 100 MHz for $^{13}C$ in deuteriochloroform and reported in ppm, unless otherwise indicated. Low-resolution mass spectra were taken from an API 2000-triple quadrupole ESI-MS/MS mass spectrometer (from Applied Biosystems). Benzofuran-2-carboxylaldehyde, thiazole-2-carboxylaldehyde, 5-phenyl thiophene-2-carboxylaldehyde, 3,5-dimethoxy-4-hydroxyl benzaldehyde, 4-hydroxyl benzaldehyde and furfural, and aldehydes for synthesizing compounds **1.1**, **1.2**, **1.3**, **1.4**, **1.5** and **1.8** were purchased from Aldrich chemical Co.. Arcylamide was purchase from Fisher Scientific Co. Quinoline-4-carboxylaldehyde and quinoline-8-carboxylaldehyde for synthesizing **1.6** and **1.7** were prepared by Dr. Laxman Pokerhel in Dr. Duy Hua's laboratory[11].

***N-(Benzofuran-2-ylmethyl)-6-methoxy-4-methyl-5-(3-trifluoromethylphenoxy) quinolin-8-amine (1.1).***

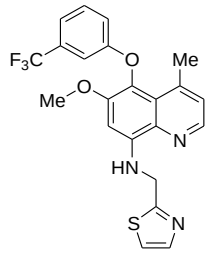



**1.1**

A solution of 25.0 mg (0.071 mmol) of 6-methoxy-4-methyl-5-(3-(trifluoromethyl) phenoxy)quinolin-8-amine (**1.17**) and 11.3 mg (0.078 mmol) 2-benzofurancaboxaldehyde in 1 mL of dried methanol (distilled over magnesium) was stirred under argon at 25$^{o}$C for 30 minutes.

To it, 2 drops of acetic acid was added. The mixture was stirred at 25 $^{o}$C for 30 minutes. Then, 3.4 mg (0.213 mmol) of sodium cyanoborohydride were added, the solution was stirred 12 hours, diluted with 30 mL of aqueous ammonium chloride solution, and extracted three times with ethyl acetate. The combined extract was washed with water, brine, dried ($MgSO_4$), concentrated, and column chromatographed using a mixture of hexane and diethyl ether (1:1) as an eluent to 22.1 mg (65% yield) of compound **1.1** as a yellow oil. $^{1}$H NMR δ 8.44 (d, *J* = 4.4 Hz, 1H), 7.52 (d, *J* = 5.6 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.27 (td, *J* = 7.6, 1.6 Hz, 1H), 7.25 – 7.20 (m, 2H), 7.11 (dd, *J* = 4.4, 0.8 Hz, 1H), 7.08 (s, 1H), 6.91 (dd, *J* = 8.0, 2.0 Hz, 2H, overlap with NH), 6.71 (d, *J* = 0.8 Hz, 1H), 6.64 (s, 1H), 4.74 (s, 2H, $CH_2N$), 3.79 (s, 3H, OMe), 2.63 (s, 3H, Me); $^{13}$C NMR δ 159.8, 155.5, 155.2, 150.9, 145.3, 143.9, 143.0, 133.9, 132.1 (q, $^{2}J_{CF}$ = 32 Hz, C-$CF_3$), 130.2, 128.6, 126.5, 125.3, 124.5, 124.2, 123.6 (q, $^{1}J_{CF}$ = 239 Hz, $CF_3$), 123.0, 121.1, 118.3, 118.2 (q, $^{3}J_{CF}$ = 4 Hz), 112.3 (q, $^{3}J_{CF}$ = 4 Hz), 111.4, 104.1, 93.9, 56.8, 41.8, 23.4; MS (electrospray), m/z 501.3 $(M+Na)^{+}$. The succinic salt of **1.1** was generated by dissolving 20 mg (0.042 mmol) of **1.1** with 5 mg (0.042 mmol) of succinic acid in 4 mL of methanol. Then the methanol was concentrated off, the residue was dissolved in 1 mL acetonitrile, diluted with 10 mL deionized water and lyophilized to give a quantitative yield of the succinic salt of **1.1**.

***6-Methoxy-4-methyl-N-(thiazol-2-ylmethyl)-5-(3-trifluoromethylphenoxy)quinolin-8-amine (1.2).***

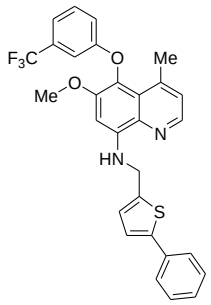



**1.2**

Prepared via the same procedure as compound **1.1**. Starting from 25.0 mg (0.071 mmol) of compound **1.17** and 8.8 mg (0.078 mmol) 2-thiazolecarboxaldehyde gave 22.7 mg (72% yield) of compound **1.2** as a light yellow oil. $^{1}$H NMR δ 8.46 (d, *J* = 4.4 Hz, 1H), 7.77 (d, *J* = 3.6 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 3.6 Hz, 1H), 7.25 – 7.20 (m, 2H), 7.11 (d, *J* = 3.6 Hz, 1H), 7.07 (s, 1H, NH), 6.91 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.57 (s, 1H), 4.94 (d, *J* = 5.6 Hz, 2H,

$CH_2N$), 3.71 (s, 3H, OMe), 2.62 (s, 3H, Me); $^{13}C$ NMR δ 171.2, 159.7, 150.8, 145.4, 143.6, 143.0, 142.9, 134.0, 132.1 (q, $^2J_{CF}$ = 33 Hz, C-$CF_3$), 130.2, 126.8, 125.3, 124.5, 124.1 (q, $^1J_{CF}$ = 271 Hz, -$CF_3$), 119.6, 118.3, 118.2 (q, $^3J_{CF}$ = 4 Hz), 112.3 (q, $^3J_{CF}$ = 4 Hz), 94.5, 56.7, 46.3, 23.4; MS (electrospray ionization), m/z 468.2 $(M+Na)^+$. Succinic salt of **1.2** was prepared in the same way as compound **1.1** by dissolving 20 mg (0.045 mmol) of **1.2** and 5.3 mg (0.045 mmol) of succinic acid in 4 mL methanol.

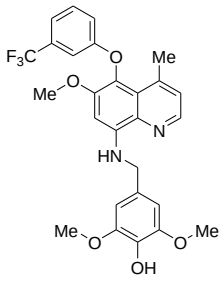
***6-Methoxy-4-methyl-N-[(5-phenylthiophen-2-yl) methyl]-5-(3-trifluoromethyl phenoxy) quinolin -8 - amine (1.3).***




**1.3**

Prepared via the same procedure as compound **1.1**. Starting from 25.0 mg (0.071 mmol) of compound **1.17** and 12.6 mg (0.078 mmol) of 5-phenyl thiophene-2-carboxaldehyde gave 27.1 mg (78% yield) of compound **1.3** as a green oil. $^1H$ NMR δ 8.44 (d, *J* = 4.4 Hz, 1H), 7.57 (d, *J* = 7.4 Hz, 2H), 7.38 – 7.19 (m, 6H), 7.11 – 7.08 (m, 2H), 6.93 – 6.86 (m, 2H), 6.62 (s, 1H), 4.75 (d, *J* = 5.2 Hz, 2H, $CH_2N$), 3.78 (s, 3H, OMe), 2.62 (s, 3H, Me); $^{13}C$ NMR δ 159.8, 150.9, 145.3, 144.0, 143.9, 142.9, 142.2, 134.6, 134.0, 132.1 (q, $^2J_{CF}$ = 32 Hz, C-$CF_3$), 130.2, 129.1, 127.6, 126.5, 126.4, 125.9, 125.3, 124.5, 124.1 (q, $^1J_{CF}$ = 270 Hz, $CF_3$), 123.0, 118.3, 118.2 (q, $^3J_{CF}$ = 4 Hz), 112.3 (q, $^3J_{CF}$ = 4 Hz), 94.1, 56.8, 43.6, 23.3; MS (electrospray), m/z 521.0 $(M+H)^+$. Succinic salt of **1.3** was prepared in the same way as compound **1.1** by starting with 20 mg (0.040 mmol) of **1.3** and 4.8 mg (0.040 mmol) of succinic acid.

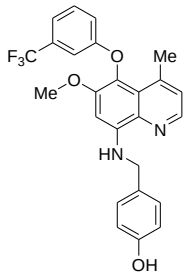
***2,6-Dimethoxy-4-{[6-methoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinolin-8-ylamino]methyl}phenol (1.4).***



**1.4**

Prepared via the same procedure as compound **1.1**. Starting from 25.0 mg (0.071 mmol) of compound **1.17** and 14.2 mg (0.078 mmol) of 3, 5-dimethoxy-4-hydroxybenzaldehyde gave 27.3 mg (75% yield) of compound **1.4** as a yellow solid. Melting point: 173 - 175 $^{o}$C; $^{1}$H NMR δ 8.41 (d, *J* = 4.4 Hz, 1H), 7.34 (t, *J* = 8.4 Hz, 1H), 7.22 (d, *J* = 7.1 Hz, 1H), 7.10 (d, *J* = 4.0 Hz, 1H), 7.03 (s, 1H), 6.94 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.72 (bs, 1H, OH), 6.71 (s, 2 H), 6.49 (s, 1H), 5.55 (s, 1H, NH), 4.48 (d, *J* = 4.0 Hz, 2H), 3.88 (s, 6H, 2 OMe), 3.75 (s, 3H, OMe), 2.62 (s, 3H, Me); $^{13}$C NMR δ 159.9, 151.0, 147.5, 145.1, 144.6, 142.9, 134.2, 134.0, 132.1 (q, $^{2}J_{CF}$ = 33 Hz, C-$CF_3$), 130.2, 130.1, 126.2, 125.3, 124.5, 124.1 (q, $^{1}J_{CF}$ = 271 Hz, $CF_3$), 118.4, 118.2 (q, $^{3}J_{CF}$ = 4 Hz), 112.1 (q, $^{3}J_{CF}$ = 4 Hz), 104.5, 93.8, 56.7 (OMe), 56.6 (2 OMe), 48.7, 23.4; MS (electrospray), m/z 537.5 $(M+Na)^{+}$, 515.2 $(M+H)^{+}$. Succinic salt of **1.4** was prepared in the same way as compound **1.1** by starting with 20 mg (0.039 mmol) of **1.4** and 4.5 mg (0.039 mmol) of succinic acid.

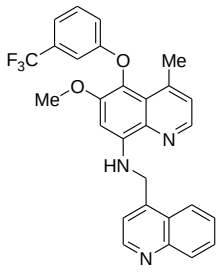
***4-{[6-Methoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinolin-8-ylamino]methyl} phenol (1.5).***



**1.5**

A solution of 25.0 mg (0.071 mmol) of 6-methoxy-4-methyl-5-(3-(trifluoromethyl)phenoxy)quinolin-8-amine (**1.17**) and 9.5 mg (0.078 mmol) *p*-hydoxybenzaldehyde in 1 mL of dried methanol (distilled over magnesium) was stirred under argon at 25$^{o}$C for 30 minutes. To it, 2 drops of acetic acid was added. The mixture was stirred at 25 $^{o}$C for 1 hour. Then, 13.4 mg (0.213 mmol) of sodium cyanoborohydride were added, the solution was stirred 12 hours, diluted with 30 mL of aqueous ammonium chloride solution, and extracted three times with ethyl acetate. The combined extract was washed with water, brine, dried ($MgSO_4$), concentrated, and column chromatographed using a mixture of hexane and diethyl ether (1:1). The column purified product was washed with 3 mL hexane and diethyl ether (1:1) to give pure **1.5** 26.4 mg (82 %) as yellow solid. Melting point: 170 - 171$^{o}$C; $^{1}$H NMR δ 8.41 (d, *J* = 4.0 Hz, 1H), 7.35 - 7.32 (m, 3H), 7.25 - 7.21 (m, 1H), 7.11 - 7.06 (m, 2H), 6.93 (dd, *J* = 8.0, 2.4 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 2H), 6.71 (s, 1H, OH), 6.47 (s, 1H), 4.80 (s, 1H, -NH,), 4.48 (d, *J* = 4.4 Hz, 2H, $CH_2N$), 3.74 (s, 3H, OMe), 2.61 (s, 3H, Me); $^{13}$C NMR δ 159.9, 155.3, 151.1, 145.1, 144.5, 143.1, 133.9, 132.2 (q, $^{2}J_{CF}$ = 33 Hz, C-$CF_3$), 130.9, 130.2, 129.3, 126.1, 125.2, 124.6, 124.2 (q, $^{1}J_{CF}$ = 271 Hz, $CF_3$), 118.4, 118.2 (q, $^{3}J_{CF}$ = 4 Hz), 115.8, 112.3 (q, $^{3}J_{CF}$ = 4 Hz), 93.8, 56.7, 47.8, 23.4; MS (electrospray), m/z 477.0 $(M+Na)^{+}$, 455.1 $(M+H)^{+}$. Succinic salt of **1.5** was prepared in the same way as compound **1.1** by starting with 20 mg (0.044 mmol) of **1.5** and 5.2 mg (0.044 mmol) of succinic acid.

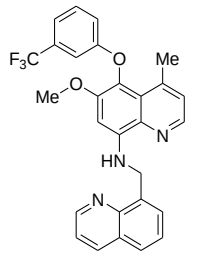
***6-Methoxy-4-methyl-N-(quinolin-4-ylmethyl)-5-(3-trifluoromethylphenoxy)quinolin-8-amine (1.6).***




**1.6**

A solution of 25.0 mg (0.071 mmol) of 6-methoxy-4-methyl-5-(3-(trifluoromethyl)phenoxy)quinolin-8-amine (**1.17**) and 12.5 mg (0.078 mmol) quinoline-4-caboxaldehyde in 1 mL of dried methanol (distilled over magnesium) was stirred under argon at 25$^{o}$C for 30 minutes. To it, 4 drops of acetic acid was added. The mixture was stirred at 25 $^{o}$C for 1 hour. Then, 3.4 mg (0.213 mmol) of sodium cyanoborohydride were added, the solution was stirred 12 hours, diluted with 30 mL of aqueous ammonium chloride solution, and extracted three times with ethyl acetate. The combined extract was washed with water, brine, dried ($MgSO_4$), concentrated, and column chromatographed using a mixture of hexane and diethyl ether (1:1). The column purified product was washed with 3 mL hexane and diethyl ether (1:1) to give pure **1.6** 28.3 mg (75 %) as yellow solid. Melting point: 155 $^{o}$C – 159 $^{o}$C. $^{1}$H NMR: δ 8.88 (d, *J* = 4.4 Hz, 1H), 8.44 (d, *J* = 4.4 Hz, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 8.15 (d, *J* = 8.8 Hz, 1H), 7.79 (t, *J* = 3.2 Hz, 1H), 7.64 (t, *J* = 6.4 Hz, 1H), 7.55 (d, *J* = 3.6 Hz, 1H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.07 (s, 1H), 7.00 (t, *J* = 6.0 Hz, 1H), 6.95 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.40 (s, 1H), 5.09 (d, *J* = 5.6 Hz, 2H), 3.65 (s, 3H), 2.65 (s, 3H); $^{13}$C NMR: δ 159.8, 151.0, 150.8, 148.6, 145.4, 144.1, 144.0, 143.1, 134.0, 132.2 (q, $^{2}J_{CF}$ = 33 Hz, C-$CF_3$), 130.7, 130.2, 129.6, 127.1, 126.8, 126.7, 125.4, 124.7, 124.2 (q, $^{1}J_{CF}$ = 271 Hz, $CF_3$), 123.0, 119.5, 118.4, 118.2 (q, $^{3}J_{CF}$ = 4 Hz), 112.3 (q, $^{3}J_{CF}$ = 4 Hz), 93.9, 56.8, 44.9, 23.3; MS, m/z 490.2 $(M+H)^{+}$. Succinic salt of **1.6** was prepared in the same way as compound **1.1** by starting with 20 mg (0.041 mmol) of **1.6** and 4.8 mg (0.040 mmol) of succinic acid.

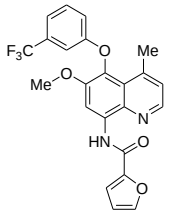
***6-Methoxy-4-methyl-N-(quinolin-8-ylmethyl)-5-(3-trifluoromethylphenoxy) quinolin -8-amine (1.7).***



**1.7**

Prepared via the same as compound **1.4**. Starting from 25.0 mg (0.071 mmol) of compound **1.17** and 12.2 mg (0.078 mmol) of quinoline-8-caboxaldehyde gave 26.5 mg (76% yield) of compound **1.7** as yellow solid. Melting point: 158 - 160 $^{o}$C; $^{1}$H NMR δ 9.05 (m, 1H), 8.42 (d, *J* = 4.4 Hz, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 6.8 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.47 (dd, *J* = 7.2, 4.4 Hz, 1H), 7.32 (t, *J* = 8.4 Hz, 1H), 7.20 (d, 8.4 Hz, 1H), 7.09 – 7.07 (m, 3H), 6.91 (d, *J* = 7.2 Hz, 1H), 6.61 (s, 1H), 5.31 (d, *J* = 6 Hz, 2H, $CH_2N$), 3.65 (s, 3H, -OMe), 2.61 (s, 3H, Me); $^{13}$C NMR δ 160.0, 151.2, 149.8, 146.8, 145.0, 144.8, 142.7, 137.0, 136.7, 134.1, 132.1 (q, $^{2}J_{CF}$ = 32 Hz, C-$CF_3$), 130.2, 128.6, 128.1, 127.4, 126.7, 125.9, 125.2, 124.5, 124.2 (q, $^{1}J_{CF}$ = 270 Hz, $CF_3$), 121.4, 118.3, 118.1 (q, $^{3}J_{CF}$ = 3 Hz), 112.3 (q, $^{3}J_{CF}$ = 3 Hz), 93.8, 56.7 (OMe), 43.8 ($CH_2N$), 23.4 (Me); MS (electrospray), m/z 512.2 $(M+Na)^{+}$, 490.2 $(M+H)^{+}$. Succinic salt of **1.7** was prepared in the same way as compound **1.1** by starting with 20 mg (0.041 mmol) of **1.7** and 4.8 mg (0.040 mmol) of succinic acid.

***N-[6-Methoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinolin-8-yl]furan-2-carboxamide (1.8).***



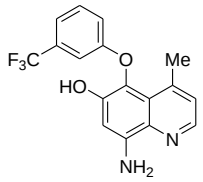
**1.8**

Furfural (200 mg, 2.1 mmol), selenium dioxide (9 mg, 0.08 mmol) and 280 mg (4.2 mmol) of 50 % hydrogen peroxide were mixed with 10 mL THF. This mixture was heated to reflux for 3 hours and cooled to room temperature, diluted with 10 mL ethyl acetate. This mixture was washed with

5 % aq. sodium hydroxide. Obtained aqueous solution was acidified with 2N HCl to pH = 3 ~ 4 and extracted with ethyl acetate 3 times. The combined organic layer was washed with water, brine, dried with $MgSO_4$ and concentrated to give 2-furoic acid 200 mg (98 % yield) which is pure enough to do next step.

12 mg of 2-Furoic acid (0.11 mmol) was refluxed in 2 mL thionyl chloride under argon. The excess thionyl chloride was distilled off under vacuum to give compound **1.18** with quantitative yield. Compound **1.18** was dissolved in 1 mL dry THF, and this solution was cooled to -78$^{o}$C. To this solution was added compound **1.17** (35 mg, 0.11 mmol) in 1 mL THF. The mixture was stirred at -78 $^{o}$C until all the **1.17** was dissolved. Then this solution was warmed to 25 $^{o}$C and stirred overnight. . The reaction solution was diluted with aqueous sodium bicarbonate solution, and extracted three times with ethyl acetate. The combined extract was washed with water, brine, dried ($MgSO_4$), concentrated, and column chromatographed using a mixture of hexane and ethyl acetate (1:1) as an eluent to give 30.5 mg (75% yield) of compound **1.8** as a white solid. Melting point: 201 - 204$^{o}$C; $^{1}$H NMR δ 11.0 (s, 1H, -NH), 9.0 (s, 1H), 8.60 (d, $J$ = 4.0 Hz, 1H), 7.65 (s, 1H), 7.33 (t, $J$ = 7.6 Hz, 1H), 7.28 (d, $J$ = 4.0 Hz, 1H), 7.25 (d, $J$ = 8.9 Hz, 1H), 7.20 (d, $J$ = 3.5 Hz, 1 H), 7.11 (s, 1H), 6.94 (d, $J$ = 7.4 Hz, 1H), 6.62 (d, $J$ = 3.5 Hz, 1H), 3.91 (s, 3H, OMe), 2.70 (s, 3H, Me); $^{13}$C NMR δ 169.3, 159.1, 156.8, 153.4, 150.0, 148.4, 146.6, 145.0, 143.6, 134.3 (q, $^{2}J_{CF}$ = 96 Hz, C-$CF_3$), 131.5, 130.4, 125.4, 125.1, 122.7 (q, $^{1}J_{CF}$ = 278 Hz, $CF_3$), 118.7, 118.3 (q, $^{3}J_{CF}$ = 4 Hz), 115.5, 112.8, 112.4 (q, $^{3}J_{CF}$ = 4 Hz), 105.3, 56.8 (OMe), 23.4 (Me); MS (electrospray), m/z 465 $(M+Na)^{+}$, 443.3 $(M+H)^{+}$. Succinic salt of **1.8** was prepared in the same way as compound **1.1** by starting with 30 mg (0.068 mmol) of **1.8** and 8.1 mg (0.068 mmol) of succinic acid.

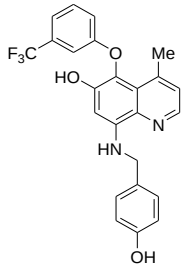
***8-Amino-4-methyl-5-(3-trifluoromethylphenoxy)quinolin-6-ol (1.19).***




**1.19**

To compound **1.17** (98.2 mg, 0.282 mmol) in 2 ml dried dichloromethane (distilled over calcium hydride) at 0 $^{o}$C was added 1 ml 1.0 M $BBr_3$'s dichloromethane solution (4.0 eq); then this mixture was warmed to 25$^{o}$C and stirred overnight. The reaction solution was diluted with aqueous sodium bicarbonate solution, and extracted three times with dichloromethane. The combined extract was washed with water, brine, dried ($MgSO_4$), and concentrated to give 78.2 mg of compound **1.19** as brown solid which is pure enough for next step. Melting point: 133 - 135$^{o}$C; $^{1}$H NMR δ 8.46 (d, *J* = 4.4 Hz, 1H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 7.2 Hz, 1H), 7.14 (s, 1H), 7.08 (d, *J* = 3.6 Hz, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.73 (s, 1H), 5.40 (bs, 1H, OH), 5.30 – 5.10 (bs, 2H, $NH_2$), 2.55 (s, 3H); $^{13}$C NMR δ 159.1, 147.8, 145.4, 144.2, 141.8, 134.9, 133.1 (q, $^{2}J_{CF}$ = 37 Hz, C-$CF_3$) 130.9, 125.1, 124.5, 124.2, 123.0 (q, $^{1}J_{CF}$ = 270 Hz, $CF_3$), 119.5, 118.2 (q, $^{3}J_{CF}$ = 4 Hz), 112.5 (q, $^{3}J_{CF}$ = 4 Hz), 100.5, 22.7 (Me); MS (electrospray), m/z 335.1 $(M+H)^{+}$.

***8-(4-Hydroxybenzylamino)-4-methyl-5-(3-trifluoromethylphenoxy)quinolin-6-ol (1.9).***

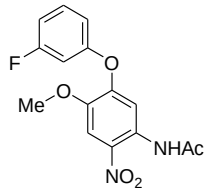



**1.9**

50.0 mg (0.149 mmol) of compound **1.19** was stirred with 20.0 mg (0.163 mmol) of *p*-hydroxybenzaldehyde in 2 mL dry methanol for 30 minutes until the solid dissolved. Then 3 drops of acetic acid was injected, and this brown mixture was stirred for 30 minutes at 25 $^{o}$C. To it 28.5 mg (0.450 mmol) of sodium cyanoborohydride were added, the solution was stirred 12 hours. Yellow solid participated out from the solution. This mixture was diluted with 30 mL of aqueous ammonium chloride solution, and extracted three times with ethyl acetate. The

combined extract was washed with water, brine, dried ($MgSO_4$), concentrated, and column chromatographed using a mixture of hexane and diethyl ether (1:1) as an eluent; the obtained product was recrystallized with 2 mL of hexane and diethyl ether (1:1) to give 34.2 mg (52% yield) of compound **1.10** as yellow solid; mp: 194 - 195$^{o}$C; $^{1}$H NMR (DMSO-*d*6) δ 9.64 (bs, 1H, NH), 9.28 (s, 1H, OH), 8.37 (d, *J* = 4.0 Hz, 1H), 7.47 (t, *J* = 8.4 Hz, 1H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 4.4 Hz, 1H), 7.01 (s, 1H), 6.97 – 6.93 (m, 2H), 6.72 (d, *J* = 8.4 Hz, 2H), 6.36 (s, 1H), 4.32 (d, *J* = 6 Hz, 2H), 2.51 (s, 3H, Ar-Me; overlap with DMSO-*d*6 signal); $^{13}$C NMR (DMSO-*d*6) δ 160.2, 157.1, 149.5, 144.4, 144.37, 141.3, 133.6, 131.6, 130.9 (q, $^{2}J_{CF}$ = 31 Hz, -C-$CF_3$), 130.1, 129.1 125.5, 124.6, 124.5 (q, $^{1}J_{CF}$ = 270 Hz, $CF_3$), 123.1, 119.5, 118.3 (q, $^{3}J_{CF}$ = 4 Hz), 115.9, 112.0 (q, $^{3}J_{CF}$ = 4 Hz), 97.2, 46.7 ($CH_2N$), 23.1 (Me); MS (electrospray), m/z 441.5 $(M+H)^{+}$. Succinic salt of **1.9** was prepared in the same way as compound **1.1** by starting with 30 mg (0.068 mmol) of **1.9** and 8.1 mg (0.068 mmol) of succinic acid.

### *4-Acetamino-5-nitro-2-(3-fluorophenyloxy) anisole (1.21).*

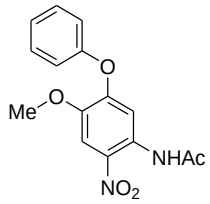



**1.21**

Mixture of 3-fluorophenol (300.0 mg, 2.678 mmol) and potassium *t*-butoxide (300.5 mg, 2.678 mmol) in 10 mL dried *t*-butanol (distilled over sodium) was stirred at 25 $^{o}$C for 12 hours under argon. Then, *t*-butanol was concentrated off under vacuum to yield the potassium 3-fluorophenolate as a yellow solid. The yielded 3-fluorophenolate in 4 mL dry DMF (distilled over calcium hydride) was added into *N*-(5-bromo-4-methoxy-2-nitrophenyl)acetamide **1.20** (722.5 mg, 2.500 mmol) in 4 mL dry DMF at 60 $^{o}$C under argon. Then this solution was stirred at 120$^{o}$C for 24 hours. The cooled solution was poured onto ice-water with vigorous stirring. The participated solid was collected by filtration and recrystallized with ethanol to give 520.5 mg (65% yield) of compound **1.21** as a light yellow solid. Melting point: 125 - 126$^{o}$C; $^{1}$H NMR δ 10.46 (s, 1H, NH), 8.37 (s, 1H), 7.78 (s, 1H), 7.37 (td, *J* = 8.4, 6.4 Hz, 1H), 6.94 (td, *J* = 7.6, 2.4 Hz, 1H), 6.89 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.81 (dt, *J* = 9.6, 2.4 Hz, 1H), 3.95 (s, 3H, OMe), 2.23 (s, 3H, Me);

$^{13}$C NMR δ 169.2 (C=O), 164.7 (d, $^{1}J_{CF}$ = 247 Hz, CF), 156.2 (d, $^{3}J_{CF}$ = 11 Hz), 152.9, 145.7, 131.141 (d, $^{3}J_{CF}$ = 10 Hz), 131.137, 115.4 (d, $^{4}J_{CF}$ = 3.6 Hz), 112.3 (d, $^{2}J_{CF}$ = 21 Hz), 110.7, 108.7, 107.8, 107.5, 56.7 (OMe), 25.8 (Me); MS (electrospray), m/z 343.3 $(M+Na)^{+}$.

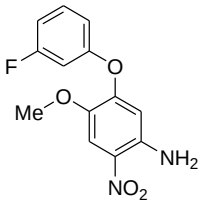
***4-Acetamino-5-nitro-2-phenyloxyanisole (1.22).***




**1.22**

Prepared via the same procedure as compound **1.21**. Potassium phenolate was made from 360 mg (3.825 mmol) of phenol and 429.3 mg (3.825 mmol) of potassium *t*-butoxide. Starting from the obtained phenolate and compound **1.20** (982 mg, 3.400 mmol) gave 821.0 mg (yield 80%) of compound **1.22** as yellow solid. Melting point: 124 - 126$^{o}$C; $^{1}$H NMR δ 10.46 (s, 1H, NH), 8.25 (s, 1H), 7.80 (s, 1H), 7.49 - 7.39 (m, 2H), 7.29 - 7.22 (m, 1H), 7.12 - 7.09 (m, 2H), 3.96 (s, 3H, OMe), 2.23 (s, 3H, Me); $^{13}$C NMR δ 169.2, 154.7, 154.3, 145.4, 131.4, 130.4, 125.8, 120.4, 109.20, 109.18, 108.48, 108.47, 56.7 (OMe), 25.7 (Me); MS (electrospray), m/z 325.3 $(M+Na)^{+}$.

***4-Amino-5-nitro-2-(3-fluorophenyloxy) anisole (1.23).***

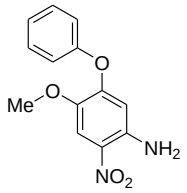



**1.23**

Compound **1.21** (310.0 mg, 0.968 mmol) was stirred with 35 mL conc. HCl and ethanol (1:7)'s solution at reflux for 2 hours. This solution was poured onto ice-water mixture, stirred for 30 minutes. The resulted solid was collected by filtration, washed with water, vacuum dried to give 240.3 mg of **1.23** (95 %, yield) as organge solid which is pure enough for next step. Melting point: 120 - 121$^{o}$C; $^{1}$H NMR δ 7.70 (s, 1 H), 7.34 (td, *J* = 8.4, 6.4 Hz, 1H), 6.92 (td, *J* = 7.6, 2.4 Hz, 1H), 6.87 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.81 (dt, *J* = 9.6, 2.4 Hz, 1H), 6.13 (s, 1H), 5.96 (s, 2H,

$NH_2$), 3.90 (s, 3H, OMe); $^{13}$C NMR δ 163.6 (d, $^1J_{CF}$ = 247 Hz, CF), 156.2 (d, $^3J_{CF}$ = 10 Hz), 154.4, 142.2, 141.9, 131.1 (d, $^3J_{CF}$ = 10 Hz), 126.7, 115.7 (d, $^4J_{CF}$ = 3 Hz), 112.2 (d, $^2J_{CF}$ = 20.6 Hz), 108.3, 107.9 (d, $^2J_{CF}$ = 24 Hz), 106.1, 56.6 (OMe); MS (electrospray), m/z 279.2 $(M+H)^+$.

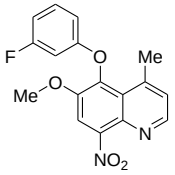
***4-Amino-5-nitro-2-phenyloxyanisole (1.24).***




**1.24**

Prepared via the same procedure as compound **1.23**. Deprotection of compound **1.22** (260.0 mg, 0.839 mmol) gave 213.7 mg (98% yield) of **1.24** as yellow solid. Melting point: 162 - 163°C; $^1$H NMR δ 7.65 (s, 1H), 7.44 - 7.40 (m, 2H), 7.27 - 7.23 (m, 1H), 7.12 - 7.09 (m, 2H), 6.01 (s, 1H), 6.10 – 5.3 (bs, 2 H, $NH_2$), 3.92 (s, 3H, OMe); $^{13}$C NMR δ 155.8, 154.7, 142.1, 142.0, 130.4, 125.6, 120.8, 108.0, 104.6, 56.6 (OMe); MS (electrospray), m/z 261.2 $(M+H)^+$.

***6-Methoxy-4-methyl-8-nitro-5-(3-fluorophenyloxy)quinoline (1.25).***

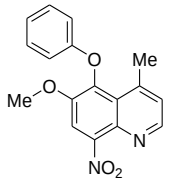



**1.25**

A mixture of compound **1.23** (240.0 mg, 0.863 mmol) and $H_3AsO_4$ (395.2 mg, 1.736 mmol) in 3 mL 85 % $H_3PO_4$ was heated to 120 °C. Methyl vinyl ketone (90.8 mg, 1.290 mmol) was added dropwise into this mixture. After stirring for 30 minutes, this dark solution was quickly poured onto ice-water mixture. This mixture was basified to pH = ~ 10 with 2N NaOH, and extracted with dichloromethane 3 times. The combined extract was washed with water, brine, dried ($MgSO_4$), concentrated, and column chromatographed using a mixture of hexane and ethyl acetate (2:1) as an eluent to give 99.0 mg (35% yield) of compound **1.25** as brown solid. Melting point: 167 - 169°C; $^1$H NMR δ 8.76 (d, *J* = 4.3 Hz, 1H), 7.88 (s, 1H), 7.28 - 7.21, (m, 2H), 6.78 (td, *J* = 2.4, 0.16 Hz, 1H), 6.76 - 6.56 (m, 2H), 3.89 (s, 3H, OMe), 2.73 (s, 3H, Me); $^{13}$C NMR δ 163.9 (d, $^1J_{CF}$ = 246 Hz, CF), 159.1 (d, $^3J_{CF}$ =10 Hz), 150.9, 148.4, 146.9, 143.9, 140.1, 136.2,

130.8 (d, $^{3}J_{CF}$ = 10 Hz), 125.9, 125.3, 111.9, 110.9 (d, $^{4}J_{CF}$ = 3 Hz), 109.7 (d, $^{2}J_{CF}$ = 21 Hz), 103.3 (d, $^{2}J_{CF}$ = 25 Hz), 57.4 (OMe), 23.4 (Me); MS (electrospray), m/z 329.3 $(M+H)^{+}$.

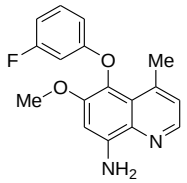
***6-Methoxy-4-methyl-8-nitro-5-phenyloxyquinoline (1.26).***




**1.26**

Prepared via the same procedure as compound **1.25**. Starting from methyl vinyl ketone (89.8 mg, 1.275 mmol), **1.24** (220.0 mg, 0.846 mmol), $H_3AsO_4$ (387.0 mg, 1.689 mmol) and 3 mL 85% $H_3PO_4$ gave 118.0 mg (45 % yield) of compound **1.26** as brown solid. Melting point: 170 - 172$^{o}$C; $^{1}$H NMR δ 8.76 (d, *J* = 4.3 Hz, 1H), 7.88 (s, 1H), 7.28 - 7.21 (m, 2H), 7.22 (d, *J* = 2.0 Hz, 1H), 7.05 (t, *J* = 6.0 Hz, 1H), 6.81 - 6.78 (m, 2H), 3.89 (s, 3H, OMe), 2.73 (s, 3H, Me); $^{13}$C NMR δ 158.0, 150.9, 148.6, 146.5, 144.3, 140.8, 136.4, 130.4, 130.0, 125.8, 125.5, 122.7, 120.8, 115.2, 112.2, 57.4 (OMe), 23.5 (Me); MS (electrospray), m/z 311.2 $(M+H)^{+}$.

***8-Amino-6-methoxy-4-methyl-5-(3-fluorophenyloxy)quinoline (1.27).***

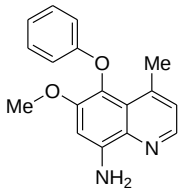



**1.27**

Compound **1.25** (35.0 mg, 0.106 mmol) and iron powder (33.6 mg, 0.636 mmol) was mixed with 5 mL aqueous 10 % AcOH solution and heated to reflux for 2 hours. The mixture was cooled to 25 $^{o}$C and diluted with water. This mixture was firstly extracted with 20 mL THF, then, followed by diethyl ether 2 times. The combined organic solution was washed with water and brine, dried ($MgSO_4$), concentrated, and column chromatographed using a mixture of hexane and diethyl ether (1:1) as an eluent to give 29.0 mg (92% yield) of compound **1.27** as yellow solid. Melting point: 146 - 147 $^{o}$C; $^{1}$H NMR δ 8.45 (d, *J* = 4.3 Hz, 1H), 7.19 (dd, *J* = 8.2, 6.6 Hz, 1H), 7.08 (d, *J* = 4 Hz, 1H), 6.8 (s, 1H), 6.67 (td, *J* = 8.2, 2.3 Hz, 1H), 6.60 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.48 (dt, *J*

= 10.9, 2.0 Hz, 1H), 5.15 (bs, 2H, $NH_2$), 3.85 (s, 3H, OMe), 2.62 (s, 3H, Me); $^{13}$C NMR δ 164.0 (d, $^{1}J_{CF}$ = 244 Hz), 161.0 (d, $^{3}J_{CF}$ = 10 Hz), 150.7, 145.6, 143.6, 143.0, 134.0, 130.4 (d, $^{3}J_{CF}$ = 9 Hz), 127.6, 125.1, 124.7, 111.0 (d, $^{4}J_{CF}$ = 3 Hz), 108.4 (d, $^{2}J_{CF}$ = 21 Hz), 102.9 (d, $^{2}J_{CF}$ = 25 Hz), 98.0, 56.4 (OMe), 22.9 (Me); MS (electrospray), m/z 299.3 $(M+H)^{+}$.

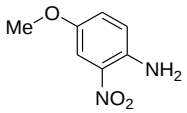
### *8-Amino-6-methoxy-4-methyl-5-phenyloxyquinoline (1.28).*




**1.28**

Prepared via the same procedure as compound **1.27**. Starting from compound **1.26** (57 mg, 0.184 mmol), iron (62.0 mg, 1.100 mmol) and 10 mL aqueous 10% AcOH solution gave 47.4 mg (92% yield) of compound **1.28** as brown solid. Melting point: 145 - 146 $^{o}$C; $^{1}$H NMR δ 8.44 (d, *J* = 4.3 Hz, 1H), 7.26 - 7.20 (m, 2H), 7.03 (dd, *J* = 4.4, 0.8 Hz, 1H), 6.97 (t, *J* = 3.6 Hz, 1H), 6.79 - 6.76 (m, 3H), 5.15 (bs, 2H, $NH_2$), 3.78 (s, 3H, OMe), 2.63 (s, 3H, $CH_3$); $^{13}$C NMR δ 159.7, 150.8, 145.5, 143.3, 143.26, 134.1, 129.7, 128.0, 125.0, 124.9, 121.5, 115.0, 98.4, 56.8 (OMe), 23.4 (Me); MS (electrospray), m/z 281.4 $(M+H)^{+}$.

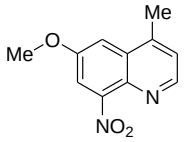
### *4-Methoxy-2-nitrobenzenamine (1.29)*




**1.29**

*N*-Acetyl-*p*-anisidine (2.0 g, 12.0 mmol) was mixed with 20 % nitric acid, and this mixture was heated to reflux for 1 h and poured onto the ice-water mixture. After vigorous stirring for 10 minutes, the solid was collected by filtration to give crude product. The crude product was purified by recrystallization in ethanol to give 413 mg (33 % yield) of compound **1.29** as brown solid. $^{1}$H NMR δ 7.54 (d, *J* = 3.2 Hz, 1H), 7.08 (dd, *J* = 9.3, 4.3 Hz, 1H), 6.76 (d, *J* = 9.3 Hz, 1H), 3.79 (s, 3H); MS, m/z 169.0 $(M+H)^{+}$.

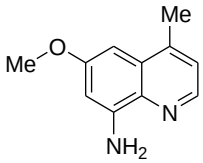
***6-methoxy-4-methyl-8-nitroquinoline (1.30).***




**1.30**

Prepared via the same procedure as compound **1.25**. Starting from methyl vinyl ketone (275 mg, 3.93 mmol), **1.29** (440.0 mg, 2.62 mmol), $H_3AsO_4$ (1.20 g, 5.24 mmol) and 12 mL 85% $H_3PO_4$ gave 500.0 mg (87 % yield) of compound **1.30** as brown solid. Melting point: 159 - 162 $^oC$; $^1H$ NMR ($CDCl_3$) δ 8.77 (d, *J* = 4 Hz, 1H), 7.67 (d, *J* = 2.8 Hz, 1H), 7.40 (d, *J* = 2.8 Hz, 1H), 7.33 - 7.34 (m, 1H), 4.00 (s, 3H, OMe), 2.70 (s, 3H, $CH_3$). $^{13}C$ NMR δ 156.1, 149.9, 143.4, 135.3, 130.3, 123.8, 115.6, 106.2, 56.4 (OMe), 19.4 (Me); MS (electrospray), m/z 241.0 $[M+Na]^+$, 219.1 [M+H].

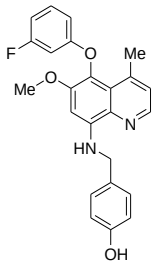
***8-Amino-6-methoxy-4-methylquinoline (1.31).***




**1.31**

Prepared via the same procedure as compound **1.27**. Starting from compound **1.30** (250 mg, 1.15 mmol), iron (385.0 mg, 6.88 mmol) and 60 mL aqueous 10% AcOH solution gave 212 mg (98% yield) of compound **1.31** as brown solid. Melting point: 88 - 91 $^oC$; $^1H$ NMR δ 8.48 (d, *J* = 4.4 Hz, 1H), 7.17 (dd, *J* = 4.4, 0.8 Hz, 1H), 6.59 (d, *J* = 2.4 Hz, 1H), 6.55 (d, *J* = 2.4 Hz, 1H), 5.13 (bs, 2H, $NH_2$), 3.80 (s, 3H, OMe), 2.61 (s, 3H, $CH_3$); $^{13}C$ NMR δ 158.8, 145.8, 144.8, 142.9, 135.1, 129.9, 122.8, 101.2, 91.5, 55.4 (OMe), 19.4 (Me);. MS (electrospray), m/z 189.3 [M+H].

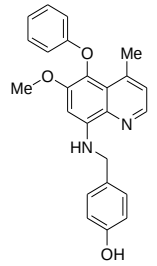
***4-{[5-(3-Fluorophenoxy)-6-methoxy-4-methylquinolin-8-ylamino]methyl}phenol (1.10).***




**1.10**

Prepared via the same procedure same as compound **1.5**. Starting from compound **1.27** (34.0 mg, 0.114 mmol) and *p*-hydroxbenzaldehyde (15.3 mg, 0.125 mmol) gave 29.2 mg (65 %) of compound **1.12** as yellow solid. Melting point: 168 - 169 $^{o}$C; $^{1}$H NMR δ 8.41 (d, *J* = 4.8 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.19 (dt, *J* = 8.4, 6.8 Hz, 1H), 7.10 (dd, *J* = 4.4, 0.8 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 2H), 6.66 (td, *J* = 6, 0.4 Hz, 1H), 6.62 (dd, *J* = 8.4, 0.4 Hz, 1H), 6.51 - 6.49 (m, 3H), 5.02 (s, 1H, OH), 4.44 (s, 2H, $CH_2N$), 3.79 (s, 3H, OMe), 2.65 (s, 3H, Me); $^{13}$C NMR δ 164.0 (d, $^{1}J_{CF}$ = 247 Hz), 161.2 (d, $^{3}J_{CF}$ = 10 Hz), 155.4, 151.2, 145.0, 144.3, 143.4, 133.7, 130.7, 130.4 (d, $^{3}J_{CF}$ = 10 Hz), 129.4, 126.4, 125.2, 124.7, 115.8, 111.0 (d, $^{4}J_{CF}$ = 3 Hz), 108.3 (d, $^{2}J_{CF}$ = 21 Hz), 103.0 (d, $^{2}J_{CF}$ = 21 Hz), 93.9, 56.8 (OMe), 47.8 ($CH_2N$), 23.4 (Me); MS (electrospray), m/z 427.1 $(M+Na)^{+}$. Succinic salt of **1.10** was prepared in the same way as compound **1.1** by starting with 20 mg (0.047 mmol) of **1.10** and 5.5 mg (0.047 mmol) of succinic acid.

***4-[(6-methoxy-4-methyl-5-phenoxyquinolin-8-ylamino)methyl]phenol (1.11).***

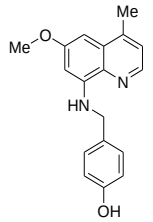



**1.11**

Prepared via the same procedure same as compound **1.5**. Starting from compound **1.28** (58.0 mg, 0.207 mmol) and *p*-hydroxbenzaldehyde (27.8 mg, 0.228 mmol) gave 73.9 mg (84 %) of compound **1.11** as yellow solid. Melting point: 181 - 182 $^{o}$C; $^{1}$H NMR δ 8.41 (d, *J* = 4.0 Hz, 1H), 7.31 – 7.23 (m, 4H), 7.08 (d, *J* = 4.4 Hz, 1H), 6.95 (t, *J* =7.2 Hz, 1H), 6.81 - 6.79 (m, 4H), 6.54

(s , 1H), 6.53 (bs, 1H, OH), 6.08 (bs, 1H, NH), 4.45 (s, 2H, $CH_2N$), 3.79 (s, 3H, OMe), 2.67 (s, 3H, Me); $^{13}C$ NMR δ 159.8, 155.4, 151.3, 144.9, 144.0, 143.7, 133.8, 130.7, 129.7, 129.4, 126.8, 125.04, 125.0, 121.4, 115.7, 115.1, 94.32, 94.30, 56.9 (OMe), 47.8 ($CH_2N$), 23.5 (Me); MS (electrospray), m/z 409.2 $(M+Na)^+$, 387.1 $(M+H)^+$. Succinic salt of **1.11** was prepared in the same way as compound **1.1** by starting with 20 mg (0.052 mmol) of **1.11** and 6.1 mg (0.052 mmol) of succinic acid.

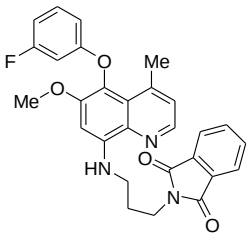
### *8-Amino-6-methoxy-4-methylquinoline (1.12).*




**1.12**

Prepared via the same procedure same as compound **1.5**. Starting from compound **1.31** (100.0 mg, 0.532 mmol) and *p*-hydroxbenzaldehyde (71.4 mg, 0.585 mmol) gave 114.2 mg (73%) of compound **1.12** as yellow solid. Melting point: 164 $^oC$; $^1H$ NMR δ 8.43 (d, *J* = 4.4 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 4.0 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 2H), 6.46 (d, *J* = 2.8 Hz, 1H), 6.43 (bs, 1H, -OH), 6.34 (d, *J* = 1.6 Hz, 1H), 6.07 (bs, 1H, -NH), 4.38 (d, *J* = 4.8 Hz, 2H), 3.90 (s, 3H, -OMe), 2.62 (s, 3H, Ar-Me); $^{13}C$ NMR δ 159.4, 155.4, 146.2, 144.2, 143.4, 134.8, 130.8, 129.9, 129.3, 122.9, 115.6, 97.2, 89.3, 55.4, 47.5, 19.5 ; MS, m/z 295.2 $(M+H)^+$. Succinic salt of **1.12** was prepared in the same way as compound **1.1** by starting with 20 mg (0.068 mmol) of **1.12** and 8.1 mg (0.068 mmol) of succinic acid.

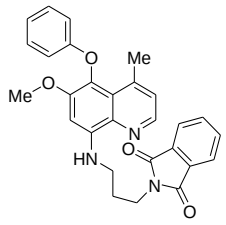
### *6-Methoxy-8- (3-phtalimidopropylamino)-4-methyl-5-(3-fluorophenyloxy)quinoline (1.33).*




**1.33**

The solution of compound **1.27** (25.0 mg, 0.084 mmol), 3-iodopropylphthalimide (26.0 mg, 0.084 mmol) and $NaHCO_3$ (7.0 mg, 0.084 mmol) mixed with 0.5 mL dry DMF (distilled over calcium hydride) under argon. This mixture was heated to 80 $^oC$ for 48 hours. After cooling to 25 $^oC$, this mixture was diluted with water, extracted with ethyl acetate 3 times, washed with water, brine, dried ($MgSO_4$), concentrated, and column chromatographed using a mixture of hexane and diethyl ether (1:1) as an eluent to recover 13.5 mg of compound **1.27** and give 17.0 mg (85% yield, basing on recovered compound **1.27**) of compound **1.33** as yellow solid. Melting point: 146 - 147 $^oC$; $^1H$ NMR δ 8.36 (d, *J* = 4.3 Hz, 1H), 7.86 - 7.82 (m, 2H), 7.73 - 7.69 (m, 2H), 7.18 (dt, *J* = 7.2, 6.4 Hz, 1H), 7.04 (d, *J* = 4 Hz, 1H), 6.65 (td, *J* = 8.2, 2.3 Hz, 1H), 6.60 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.52 (bs, 1H, -NH), 6.50 - 6.42 (m, 2H), 3.91 (t, *J* = 6.7 Hz, 2H, $CH_2N$), 3.83 (s, 3H, OMe), 3.43 (q, *J* = 5.4 Hz, 2H, $CH_2N$), 2.60 (s, 3H, Ar-Me), 2.19 (pent, *J* = 7.0 Hz, 2H, $CH_2$); $^{13}C$ NMR δ 168.7 (C=O), 163.9 (d, $^1J_{CF}$ = 244 Hz), 161.2 (d, $^3J_{CF}$ = 10 Hz), 151.1, 144.9, 144.3, 142.8, 134.2, 132.3, 130.4 (d, $^3J_{CF}$ = 10 Hz), 126.1, 125.1, 124.5, 123.5, 111.0 (d, $^4J_{CF}$ = 3 Hz), 108.3 (d, $^2J_{CF}$ = 21 Hz), 102.9 (d, $^2J_{CF}$ = 25 Hz), 93.1, 56.9 (OMe), 41.2 ($CH_2N$), 36.2 ($CH_2N$), 28.2 ($CH_2$), 23.3 (Me); MS (electrospray), m/z 508.2 $(M+Na)^+$, 486.2 $(M+H)^+$.

### *6-Methoxy-8- (3-phtalimidopropylamino)-4-methyl-5-phenyloxyquinoline (1.34).*

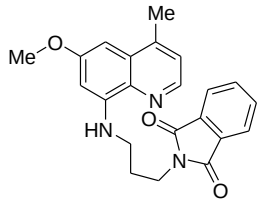



**1.34**

Prepared via the same procedure as compound **1.33**. Starting from compound **1.28** (37.0 mg, 0.133 mmol), 3-iodopropylphthalimide (41.0 mg, 0.133 mmol) and $NaHCO_3$ (12.0 mg, 0.133 mmol) gave 17.3 mg (89 % yield, basing on the recovered compound **1.28** ) of compound **1.34** and recovered compound **1.28** 27.1 mg. Melting point: 164 - 165 $^oC$; $^1H$ NMR δ 8.36 (d, *J* = 4.3 Hz, 1H), 7.85 - 7.82 (m, 2H), 7.72 - 7.69 (m, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.01 (d, *J* = 4.3 Hz, 1H), 6.93 (t, *J* = 7.4 Hz, 1H), 6.77 (d, *J* = 8.6 Hz, 2H), 6.49 - 6.46 (m, 2H), 3.91 (t, *J* = 6.6 Hz, 2H, $CH_2N$), 3.83 (s, 1H, OMe), 3.43 (q, *J* = 7.0 Hz, 2H, $CH_2N$), 2.61 (s, 3H, Ar-Me), 2.20 (pent, *J* = 7.0 Hz, 2H, $CH_2$); $^{13}C$ NMR δ 168.7, 159.8, 151.2, 144.9, 144.0, 143.0, 134.2, 134.0, 132.3,

129.7, 126.5, 125.0, 124.8, 123.5, 121.4, 115.1, 93.4, 57.0 (OMe), 41.2 ($CH_2N$), 36.2 ($CH_2N$), 28.2 ($CH_2$), 23.3 (Me); MS (electrospray), m/z 468.3 $(M+H)^+$.

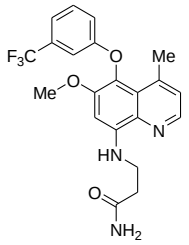
***2-[3-(6-Methoxy-4-methylquinolin-8-ylamino)propyl]isoindoline-1,3-dione (1.35).***



**1.35**

Prepared via the same procedure as compound **1.33**. Starting from compound **1.31** (70.0 mg, 0.372 mmol), 3-iodopropylphthalimide (115.0 mg, 0.372 mmol) and $NaHCO_3$ (31.0 mg, 0.372 mmol) gave 57.3 mg (86 % yield, basing on the recovered compound **1.31** ) of compound **1.35** and recovered compound **1.31** 35.5 mg. $^1$H NMR δ 8.40 (d, *J* = 4.3 Hz, 1H), 7.88 - 7.80 (m, 2H), 7.72 – 7.65 (m, 2H), 7.14 (d, *J* = 3.8 Hz, 1H), 6.41 - 6.40 (m, 2H, ArH & NH), 6.28 (d, *J* = 2.3 Hz, 1H), 3.91 (s, 3H, OMe), 3.87 (t, *J* = 6.6 Hz, 2H, $CH_2N$), 3.36 (q, *J* = 6.6 Hz, 2H, $CH_2N$), 2.59 (s, 3H, $CH_3$), 2.13 (pent, *J* = 7.0 Hz, 2H, $CH_2$); $^{13}$C NMR δ 168.7 (CO), 159.3, 146.3, 144.3, 142.8, 135.0, 134.2, 132.3, 129.7, 123.5, 122.9, 96.4, 89.0, 55.4 (OMe), 40.9 ($CH_2N$), 36.2 ($CH_2N$), 28.1 ($CH_2$), 19.5 (Me); MS (electrospray), m/z 398.0 $[M+Na]^+$, 376.3 $[M+H]^+$.

***3-[6-Methoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinolin-8-ylamino]propanamide (1.13).***

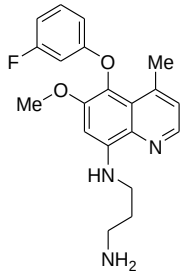


**1.13**

Compound **1.17** (70.0 mg, 0.201 mmol) and acrylamide (14.3 mg, 0.201 mmol) was dissolved in 3 mL acetonitrile in a sealed tube. The system was degased with argon and heated to 120 $^o$C for 30 hours. The solvent was concentrated off, and residue was directly column chromatographed using a mixture of hexane and diethyl ether (1:1) as an eluent to give 48.2 mg (57% yield) of compound **1.13** as a light brown solid. Melting point: 170 - 172$^o$C; $^1$H NMR δ 8.40 (d, *J* = 4.4

Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.08 – 7.05 (m, 2H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.58 – 6.49 (m, 2 H), 5.75 (broad s, 1H, NH), 5.56 (broad s, 1H, NH), 3.83 (s, 3H, OMe), 3.71 (t, *J* = 6.4 Hz, 2H, $CH_2N$), 2.72 (t, *J* = 6.4 Hz, 2H. $CH_2CO$), 2.61 (s, 3H, Me); $^{13}C$ NMR δ 173.6, 159.8, 151.0, 145.2, 144.2, 142.8, 134.0, 132.1 (q, $^2J_{CF}$ = 32 Hz, C-$CF_3$), 130.2, 126.3, 125.4, 124.6 124.1 (q, $^1J_{CF}$ = 268 Hz, $CF_3$), 118.4, 118.2 (q, $^3J_{CF}$ = 4 Hz), 112.2 (q, $^3J_{CF}$ = 4 Hz), 93.7, 56.9 (OMe), 39.9 ($CH_2$), 35.7 ($CH_2$), 23.3 (Me); MS (electrospray), m/z 442.6 $(M+Na)^+$, 420.4 $(M+H)^+$. Succinic salt of **1.13** was prepared in the same way as compound **1.1** by starting with 40 mg (0.095 mmol) of **1.13** and 11.2 mg (0.095 mmol) of succinic acid.

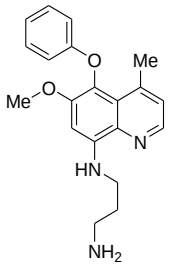
### *6-Methoxy-8-[(3-aminopropyl)amino]-4-methyl-5-(3-fluorophenyloxy)quinoline (1.14).*




**1.14**

Compound **1.33** (17.0 mg, 0.035 mmol) in 6 mL 20 % hydrazine in ethanol's solution was heated to reflux overnight. After concentrating ethanol off, the residue was diluted with 10 % aqueous $K_2CO_3$ solution, extracted with dichloromethane 3 times, dried over $K_2CO_3$, concentrated and column chromatographed using a mixture of dichloromethane and methanol (4:1) as an eluent to give 7.5 mg (58% yield) of compound **1.14** as yellow solid. Melting point: 96 - 97 $^oC$; $^1H$ NMR δ 8.38 (d, *J* = 4.4 Hz, 1H), 7.18 (dt, *J* =8.0, 7.6 Hz, 1H), 7.05 (d, *J* = 4.3 Hz, 1H), 6.66 (td, *J* = 8.2, 2.3 Hz, 1H), 6.61 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.58 - 6.46 (m, 2H), 6.41 (bs, 1H), 3.85 (s, 3H, OMe), 3.42 (t, *J* = 6.6 Hz, 2H, $CH_2N$), 3.00 (t, *J* = 7.0 Hz, 2H, $CH_2N$), 2.66 (bs, 2H, $NH_2$), 2.60 (s, 3H, Ar-Me), 2.17 (pent, *J* = 6.6 Hz, 2H); $^{13}C$ NMR δ 164.0 (d, $^1J_{CF}$ = 243 Hz), 161.3 (d, $^3J_{CF}$ = 10 Hz), 151.2, 144.9, 144.6, 142.9, 133.9, 130.5 (d, $^3J_{CF}$ = 10 Hz), 126.1, 125.2, 124.6, 111.0 (d, $^4J_{CF}$ = 3 Hz), 108.3 (d, $^2J_{CF}$ = 22 Hz), 102.8 (d, $^2J_{CF}$ = 25 Hz), 93.2, 56.9 (OMe), 41.4 ($CH_2N$), 40.5 ($CH_2N$), 32.2 ($CH_2$), 23.1 (Me); MS (electrospray), m/z 356.2 $(M+H)^+$. Succinic salt of **1.14** was prepared in the same way as compound **1.1** by starting with 5 mg (0.014 mmol) of **1.14** and 1.6 mg (0.014 mmol) of succinic acid.

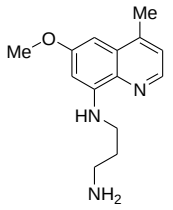
***6-Methoxy-8-[(3-aminopropyl)amino]-4-methyl-5-phenyloxyquinoline (1.15).***



**1.15**

Prepared via the same procedure same as compound **1.11**. Starting from compound **1.34** (17.3 mg, 0.036 mmol) gave 7.2 mg (59% yield) of compound **1.15** as yellow solid. Melting point: 130 - 131 $^{o}$C; $^{1}$H NMR δ 8.33 (d, *J* = 4.3 Hz, 1H), 7.21 (t, *J* = 8.6 Hz, 2H), 6.98 (d, *J* =4.4 Hz, 1H), 6.92 (t, *J* = 8.6 Hz, 1H), 6.75 (d, *J* = 8.6 Hz, 2H), 6.49 (s, 1H), 6.30 (bs, 1H, NH), 4.35 (bs, 2H, $NH_2$), 3.81 (s, 3H, OMe), 3.42 (t, *J* = 6.2 Hz, 2H, $CH_2N$), 3.10 (t, *J* = 6.6 Hz, 2H, $CH_2N$), 2.60 (s, Ar-Me), 2.11 (pent, *J* = 6.2 Hz, 2H, $CH_2$); $^{13}$C NMR δ 159.8, 151.3, 144.9, 144.1, 143.3, 133.9, 129.7, 126.7, 125.0, 124.9, 121.4, 115.0, 93.9, 57.1 (OMe), 41.2 ($CH_2N$), 39.4 ($CH_2N$), 29.9 ($CH_2$), 23.4 (Me); MS (electrospray), m/z 338.1 $(M+H)^+$. Succinic salt of **1.15** was prepared in the same way as compound **1.1** by starting with 5 mg (0.015 mmol) of **1.15** and 1.8 mg (0.015 mmol) of succinic acid.

***6-Methoxy-8-[(3-aminopropyl)amino]-4-methylquinoline (1.16).***



**1.16**

Prepared via the same procedure same as compound **1.11**. Starting with compound **1.35** (20 mg, 0.093 mmol) gave compound **1.16** 12.1 mg (56 %, yield) as yellow oil. $^{1}$H NMR δ 8.41 (d, *J* = 4.3 Hz, 1H), 7.16 (d, *J* = 4.6 Hz, 1H), 6.42 (d, *J* = 2.3 Hz, 1H), 6.32 (d, *J* = 2.3 Hz, 1H), 6.27 (bs, 1H, NH), 3.92 (s, 3H, OMe), 3.35 (t, *J* = 6.3 Hz, 2H, $CH_2N$), 2.90 (t, *J* =7.0 Hz, 2H, $CH_2N$), 2.59 (s, 3H, Me), 1.92 (pent, *J* = 6.6 Hz, 2H, $CH_2$); $^{13}$C NMR δ 159.2, 146.6, 144.2, 142.9, 135.0, 129.7, 122.9, 96.3, 88.8, 55.4 (OMe), 41.3 ($CH_2N$), 40.4 ($CH_2N$), 33.0 ($CH_2$), 19.5 (Me); MS (electrospray), m/z 245.2 $(M+H)^+$. Succinic salt of **1.16** was prepared in the same way as

compound **1.1** by starting with 10 mg (0.041 mmol) of **1.16** and 4.8 mg (0.040 mmol) of succinic acid.

***Procedure for enzyme inhibition assays***

**PKC assays**: Enzyme (PKC) was incubated with substrate (P-L-S-R-T-L-S-V-A-A-K, c = 0.4 μg/μl in $H_2O$), the activator solution (1 mg/ml phosphatidylserine in water), substrate protection solution, and the test compounds (inhibitors) in the buffer solution (100 mM HEPES, 6.5 mM $CaCl_2$, 5 mM DTT, 50 mM $MgCl_2$, and 5 mM ATP) at 30 $^oC$ for 45 minutes. The system was warmed to 100 $^oC$ for 10 minutes to stop the enzyme reaction, and the reaction was loaded into the agarose gel placed in a horizontal gel electrophoresis chamber. The electrophoresis was carried out for 30 minutes at 100 V. The photograph of the gel was taken under UV by Kodak Gel Logic 1500 Digital Imaging System, and quantification of both phosphorylated and nonphosphorylated substrates were carried out by Imagequant 5.2 software (Molecular Dynamics/Amersham Biosciences).

**GSK-3β assays**. Enzyme (GSK-3β) was incubated with substrate, ATP, and the test compound for 40 minutes at room temperature. Then, an equal amount of ADP-Glo™ Reagent was introduced into the reaction mixture and incubated at room temperature for 40 minutes. 10 μL of kinase detection reagent was added and incubated at room temperature for further 30 minutes. The luminescence of the mixture was measured using a Glo Max multi detection luminometer.

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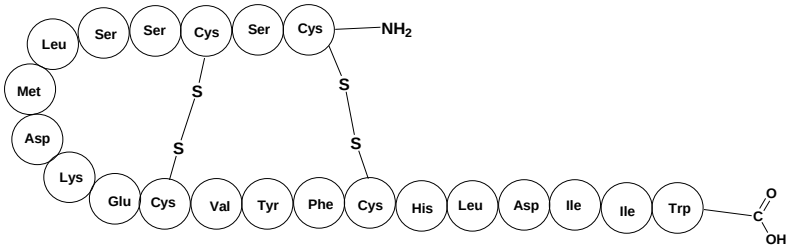
# Chapter 2 - Progress on total synthesis of (+)-Myriceric acid (A)

## 2.1 Introduction

### *2.1.1 Endotheline-1 peptide and bio-activity, isolation and structure characterization of (+)-myriceric acid A*

In 1988, a vasoconstrictor peptide was isolated from the culture supernatant of porcine endothelial cell (EC) by Yanasigawa *et al*., which is now known as endothelin-1 (ET-1).[1] The structure of ET-1 was determined by the same group and shown in Figure 2.1.[1] ET-1 is 21-residue peptide which contains four cysteines. It has a fused bicyclic structure which is built up by two disulfide bridges (Cys1-Cys15 and Cys3-Cys11) and essential for ET-1's activity. Destruction of this bicyclic structure led the ET-1 to be inactive.[2]

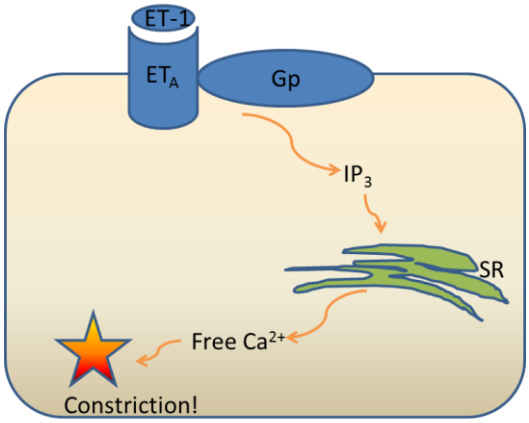
**Figure 2.1 : Structures of ET-1[1]**




The ET-1 preferring vasoconstrictory receptor, which is termed as $ET_A$ receptor, was firstly identified by DNA-cloning and expression methodology from bovine lung.[3] Bovine's $ET_A$ receptor is found in vascular smooth muscle cells and contains 427 amino acids, and its molecular mass is about 48.5 kilodaltons.[3] It is considered as the member of the superfamily of G-protein coupled receptors (GPCR) because of their high homology in the transmembrane domains.[2] Till now, no crystal structure of human $ET_A$ receptor is reported.

Signal transduction for vascular constriction starts from the binding of ET-1 to $ET_A$ on the membrane of vascular muscle cell.[4] This binding could increase the formation of inositol triphosphate ($IP_3$) in the vascular muscle cell, and the elevated level of $IP_3$ could stimulate the sarcoplasmic reticulum (SR) to release calcium into cytoplasm. The increased cytosolic concentration of free calcium eventually induces the vasoconstriction (Figure 2.2). [4,5]

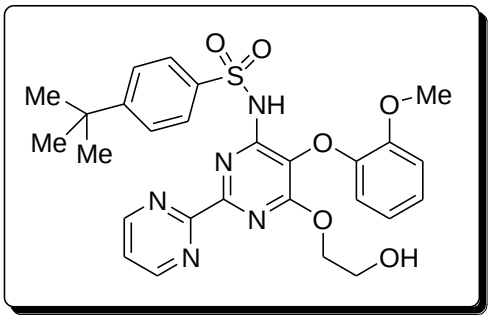
**Figure 2.2 : Vascular signal transduction for constriction[4]**




ET-1 is known as the most potent mammalian vasoconstrictor peptide ($EC_{50}$ = 4.0 ± 2.2 × $10^{-1}$ nM in porcine right proximal coronary artery assay) and characterized by its long lasting vasoconstriction effect and high difficulty in rinsing out from the system. ET-1 induced vasoconstriction is closely associated with calcium ion concentration; vasoconstriction could not occur in calcium-free environment or significantly reduced in the presence of calcium channel blocker. [1]

Studies indicates that ET-1 and/or its receptors are involved in many cardiovascular diseases such as: heart failure, coronary vasospasm and hypertension.[4] Applications of ET-1 receptor antagonists gave promising therapeutic effects on these diseases.[2,4] For example, Bosentan, a non-selective ET-1 receptor antagonist, is in market for pulmonary hypertension (Figure 2.3).[4] However, because of the strong side effects of these drugs, for example, the hepatotoxicity from Bosentan, the discovery of new ET-1 receptor antagonist with less toxicity and higher efficiency have been continued.

**Figure 2.3 : Structure of Bosentan[4]**

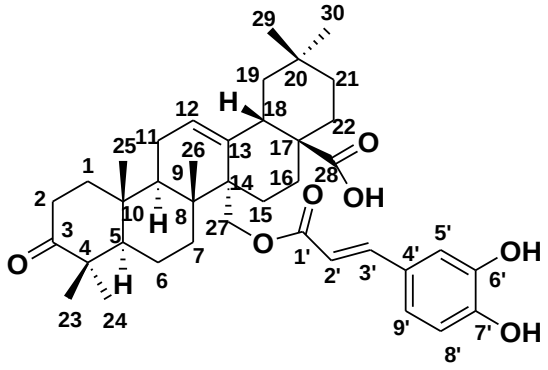



In 1996, Sakurawi, K. *et al*. found that the methanol extract of fresh *Myrica cerifera*'s twigs could prevent the ET-1-induced cytosolic free calcium concentration increase in rat aortic

smooth muscle A7r5 cells with $IC_{50}$ of 35 μg/mL.[6] Further purification gave a more active fraction ($IC_{50}$ = 0.11 μg/mL).[6] At last, a pure compound was obtained by semi-preparative reverse phase high performance liquid chromatography (HPLC).[6] This compound inhibits not only on ET-1 induced cytosolic calcium concentration increase ($IC_{50}$ = 0.0075 μg/mL) but also specifically antagonized ET-1's binding to $ET_A$ ($IC_{50}$ = 0.04 μg/mL).[6] This compound is now known as myriceric acid A.

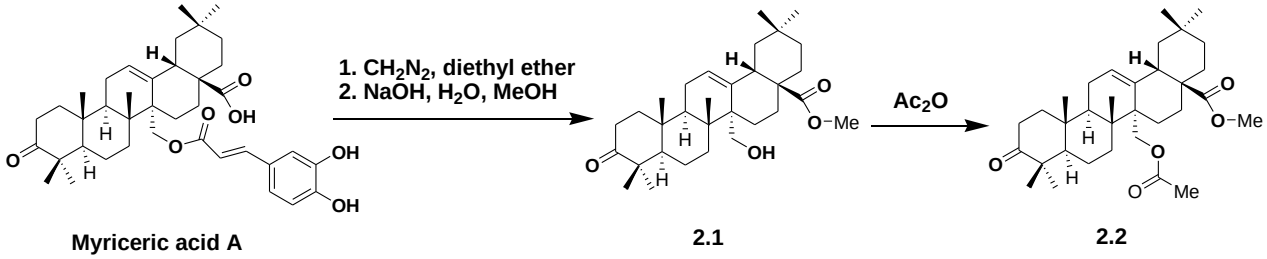
The structure of myriceric acid A was proposed on the results from high resolution mass spectrometry, $^{1}H$ NMR and $^{13}C$ NMR.[6] Myriceric acid A showes a mass of 632.3715, and its molecular formula is calculated as $C_{39}H_{52}O_7$. Results of NMR experiments indicates the existing of a trans-caffeoyl group and a triterpene moiety (Figure 2.4).

**Figure 2.4 : Structure of myriceric acid A[6]**




Isolated myriceric acid A was methylated by diazomethane, and the caffeoyl acid ester was hydrolyzed off by sodium hydroxide to give ester alcohol **2.1.** Compound **2.1** was acetylated by acetic anhydride to form the diester **2.2** which is crystalline solid (Scheme 2.1).[6]

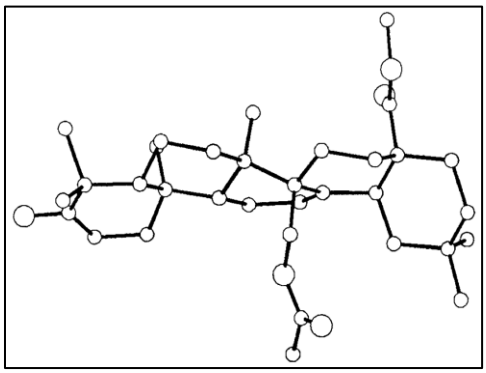
**Scheme 2.1 : Synthesis of compound 2.2[6]**




The crystal structure of **2.2** is resolved by X-ray analysis and shown in Figure 2.5. The absolute configuration of compound **2.2** was assigned according to the positive Cotton effect in

the circular dichroism (CD) experiment.[6,7] This X-ray structure plus NMR experiments results confirmed the structure of myriceric acid A.

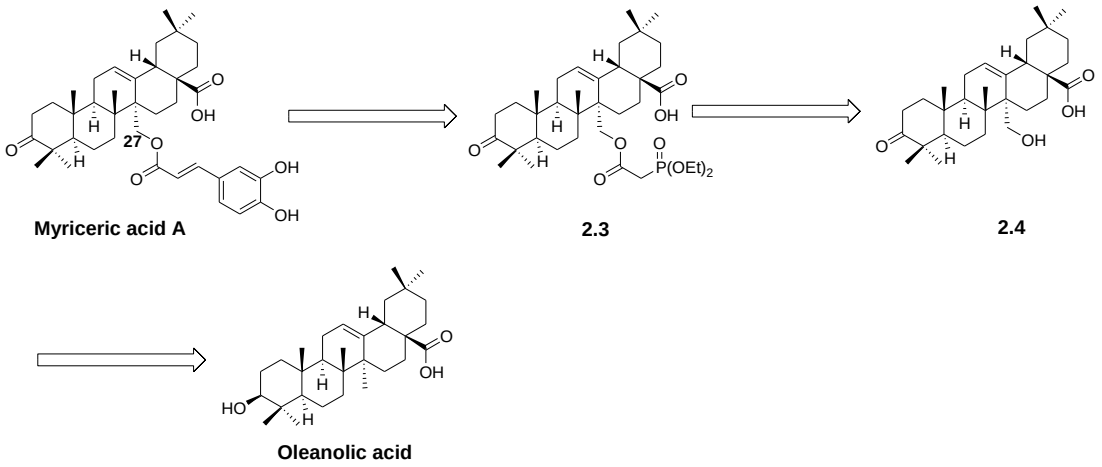
**Figure 2.5 : Crystal structure of compound 2.5[6]**



### *2.1.2 Semi-synthesis of myriceric acid A*

The semi-synthesis of myriceric acid A was accomplished in 1997 by Konoike, T. *et al*..[8] This partial synthesis used oleanolic acid as the starting material via 14 steps to give final product myriceric acid A. The retro-synthetic analysis is shown in Scheme 2.2.[8] As the authors mentioned in the article, direct acylation of 27-hydroxy group with caffeic acid could not be achieved with an acceptable yield; hence, final product myriceric acid A was prepared from compound **2.3** in alternative strategy. Compound **2.3** could be converted from compound **2.4**, and compound **2.4** was derived from oleanolic acid.

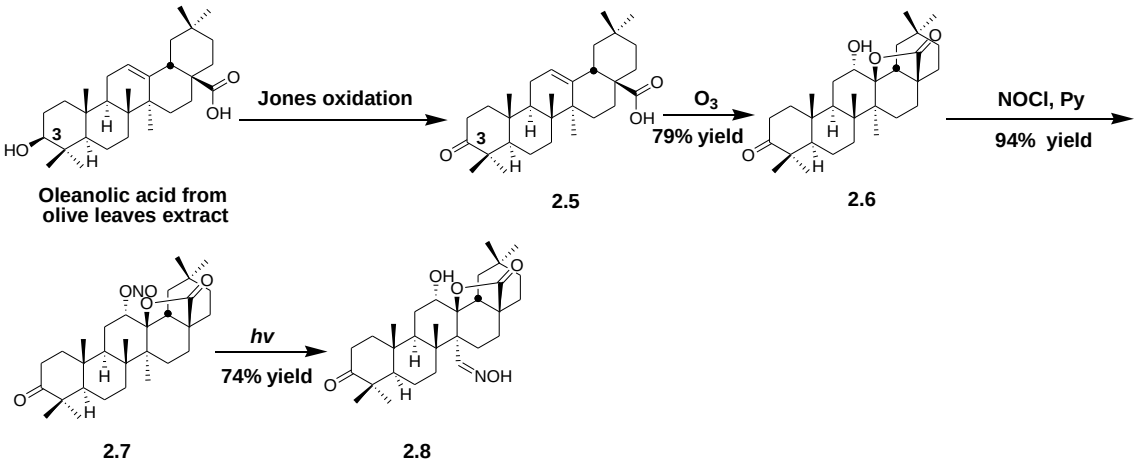
**Scheme 2.2 : Retro-synthetic analysis of partial synthesis of myriceric acid A[8]**




The semi-synthesis of myriceric acid started with the oxidation of the 3-hydroxy group in oleanolic acid (500 mg, $309.00 form Sigma-Aldrich). Jones oxidation of oleanolic acid gave

compound **2.5**. Olefin functionality in **2.5** was epoxidized by ozone, and the epoxide ring was opened by the attack of carboxylate nearby to give lactone **2.6** in one pot. Compound **2.6** was treated with nitrosyl chloride to form the unstable nitrite **2.7**. Light irradiation of **2.7** gave desired product compound **2.8** via Barton reaction[9] (Scheme 2.3).

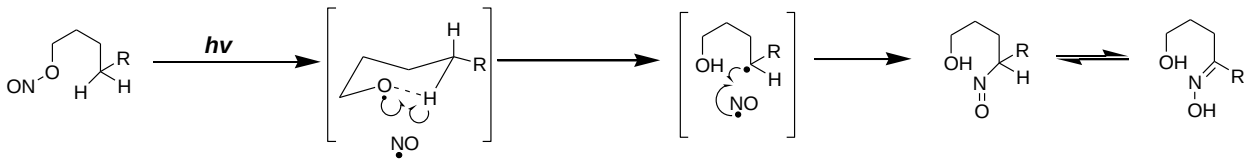
**Scheme 2.3 : Partial synthesis of myriceric acid A (Part 1)[8]**




Ozone is a strong oxidizing reagent, and, in most cases, ozone reacts with olefin to form the trioxolane. The dissect of O-O bond in trioxolane yields the carbonyl compound to furnish the olefin cleavage. However, for olefin with strong steric hindrance, the epoxidation to the double bonds by ozone is preferred, and this is called "partial cleavage" of the olefin.[10]

The mechanism of Barton's reaction is described herein to explain the transformation from compound **2.7** into **2.8**.[9] Under the light irrigation, nitrosol moiety could be decomposed to give oxygen radical and nitric oxide radical. The formed oxygen radical abstract the hydrogen to give the hydroxyl group and hydrocarbon radical. This hydrocarbon radical reacts with the nitrc oxide radical nearby to form new nitroso compound which could be epimerized to oxime.

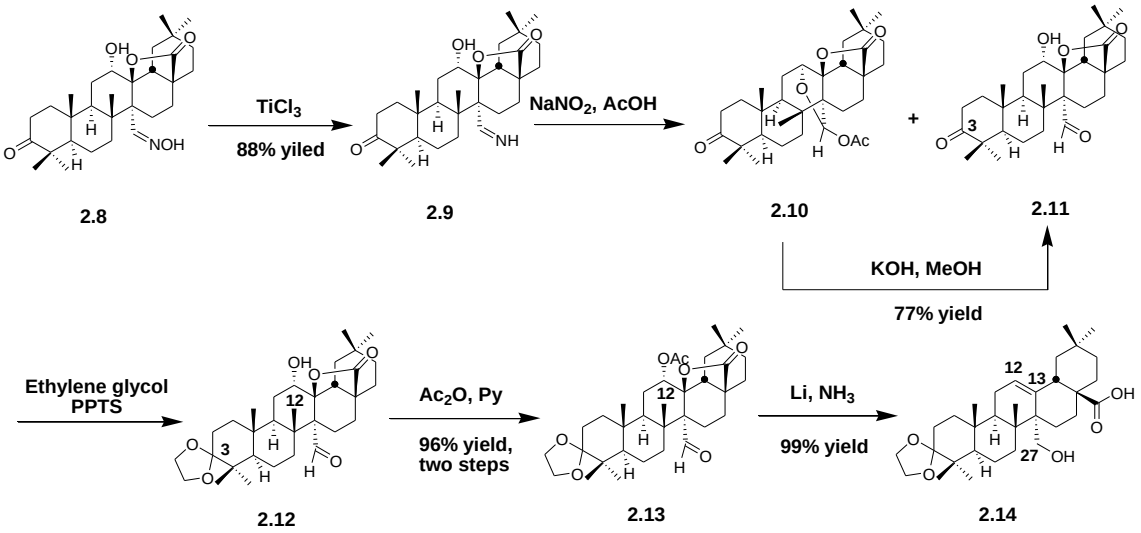
**Scheme 2.4 : Barton's reaction mechanism**




Reduction of oxime **2.8** with titanium trichloride gave imine **2.9**. This imine was highly stable because of the "shielding" effect given by the pentacyclic structure, and the hydrolyzation of this imine was furnished by sodium nitrite in acetic acid. The mechanism was probably via an hydroxyl-azoimine intermediate (-C=N=N-OH), and this azoimine hydrolyzed readily to give

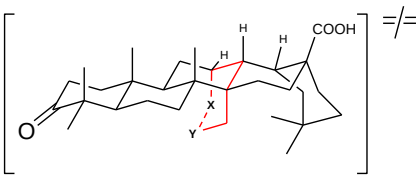
aldehyde **2.11**. However, partial of the formed aldehyde **2.11** reacted with nearby hydoxy group to give acetal **2.10**. This acetal **2.10** was hydrolyzed under basic condition to regenerate aldehyde **2.11**. C3-carbonyl group in **2.11** was then protected with ethylene glycol to give acetal **2.12**, and acetylation of C12-hydroxy group in **2.12** was carried out with acetic anhydride in pyridine to give **2.13**. 12-13 Olefin regeneration and aldehyde reduction in **2.14** was achieved by lithium ammonia reductive elimination. The mechanism of this step was discussed in the paper. Authors indicated that the aldehyde functionality acted as "electron transporter" in this process. It initially obtained electrons from lithium and, then, transferred them to the 12-carbon to reduce the acetate off. The formed anion underwent elimination of the lactone, and the aldehyde was reduced then to give desired **2.14** (Scheme 2.5).[8]

**Scheme 2.5 : Partial synthesis of myriceric acid A (Part 2)[8]**




It's worthy to note that the reactivity relationships between 27- position C-H and 12-position C-H. The intramolecular reactions between these two positions are much easier to proceed because a six-member ring transition state is readily achieved to facilitate the reaction (Figure 2.6). Examples are Barton's reaction[9] and the transformation of **2.14** from **2.13**. This interesting discovery could be applied into the total synthesis of myriceric acid A.

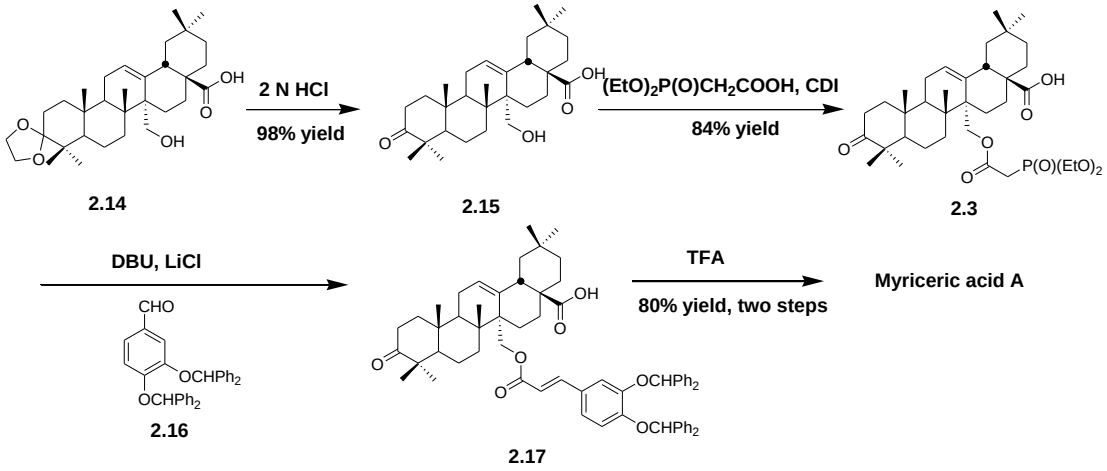
**Figure 2.6 : Intramolecular six-member ring transition state**




**X, Y = H or substitute**

Compound **2.14** was treated with 2 N HCl to give ketone **2.15**. The installation of 27-position caffeic acid ester was furnished in three steps by starting with **2.15** via Horner-Wadsworth-Emmons (HWE) olefination reaction. Alcohol **2.15** was firstly treated with diethylphosphonoacetic acid and carbonyldiimidazole (CDI) to give the ester **2.3**. Ester **2.3** reacted with benzaldehyde **2.16** to give **2.17** readily. Deprotection of **2.17** with trifluoroacetic acid finally gave desired product myriceric acid A (Scheme 2.6).[8]

**Scheme 2.6 : Partial synthesis of myriceric acid A (Part 3)[8]**



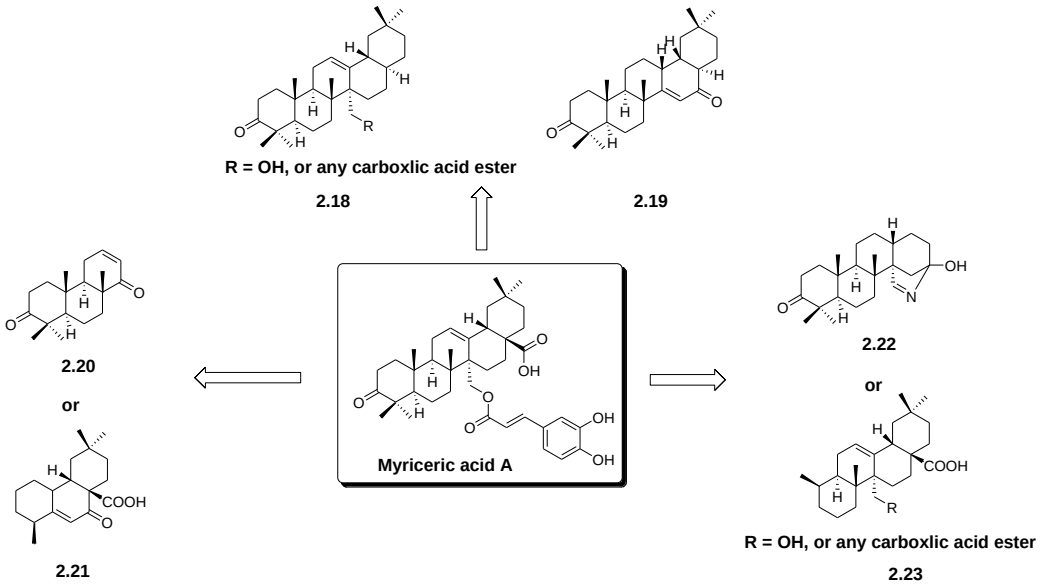

### *2.1.3 Importance of total synthesis of myriceric acid A*

The semi-synthesis of myriceric acid A was accomplished;[8] however, so far, no total synthesis of myriceric acid A has been reported, and this work is still highly needed for the following reasons.

Firstly, total synthesis of myriceric acid A will led to the intermediates and/or compounds derived from it to assist the study of its structure-activity relationship (SAR). As mentioned above, myriceric acid A is a non-peptide ET-1-specific antagonist in the reported natural products, and it has great potential in the treatment of ET-1 and/or ET-1 receptor related diseases,

such as: heart failure and pulmonary hypertension[3]. Hence, the study of its SAR will not only provide information to disclose the therapeutic mechanism but also lead to the development of more potent drug candidates. Unlike total synthesis, the partial synthesis of myriceric acid A only gave compounds with very limited numbers and structural varieties which is not enough for SAR study; however, as depicted in Figure 2.7 below, many useful and interesting intermediates and novel compounds could be synthesized via the methodology for the total synthesis of myriceric acid A and used for the SAR study.

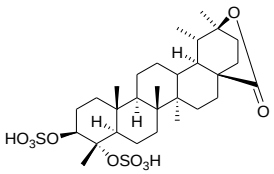
**Figure 2.7 : Intermediates could be synthesized in total synthesis of myriceric acid A**




Secondly, total synthesis of myriceric acid A may provide a protocol to synthesize other triterpene-type natural products. As the largest group of the isolated compounds in the natural products, triterpene-type natural products are reported to have various novel biological properties, such as antioxidant, antibiotic, anticancer activities, *etc.*.[11] However, the applications of these compounds are limited because of their low availability from natural sources. Therefore, obtaining triterpene-type natural products via chemical method is one of possible solutions to solve this problem. The methods developed to construct the triterpene skeleton and modify the functionalities in the total synthesis of myriceric acid A could also be used to synthesis of other triterpene compounds directly or after modification. Hence, the protocol for synthesis of similar type of triterpene compounds can be developed based on the achievement of the total synthesis of myriceric acid A. The semi-synthesis method for myriceric acid A which started from

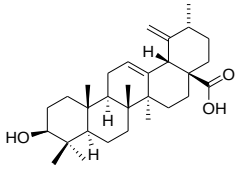
oleanolic acid could only be used to synthesize myriceric acid and only suitable for a limited number of triterpene compounds (Figure 2.8).[11]

**Figure 2.8 : Few examples of the reported triterpene-type natural products[11]**



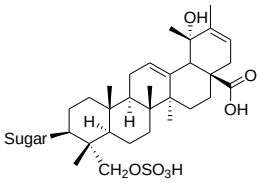

**Isolated from extract of *Fagonia arabica*, anticancer activity [11a]**

**2.24**




**Isolated from extract of *Baeckea gunniana*, DNA Polymerase beta Inhibitors [11b]**

**2.25**




**Isolated from extract of *Melissa officinalis*, potential antimicrobial activity [11c]**

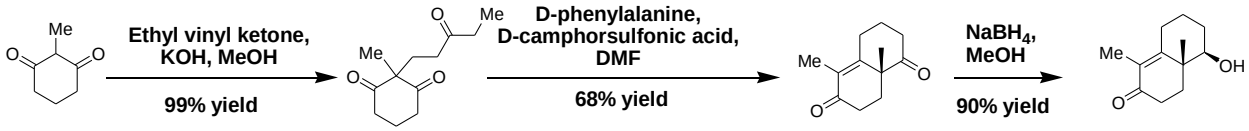
**2.26**

### *2.1.4 Progress made by Angelo Aguilar[12]*

This project was initially carried out by a former graduate student, Dr. Angelo Aguilar, in Hua's laboratory.[12] His work will be briefly introduced in this section.

Initially, 2-methyl-1,3-cyclohexanedione was treated with ethyl vinyl ketone to give a Michael addition product **2.27** in a quantitative yield. Then enantio-selective intramolecular aldol condensation was carried out with ketone **2.27**, D-phenylalanine and D-camphorsulfonic acid (D-CSA) to give two ring enone-ketone **(-)-2.28** with 95%ee. Selective reduction of **(-)-2.28** with 0.25 eq. sodium borohydride gave alcohol **(-)-2.29** in high yield (Scheme 2.7).

**Scheme 2.7 : Progress made by Aguilar (Part 1)[12]**




**2-Methyl-1,3-cyclohexanedione**

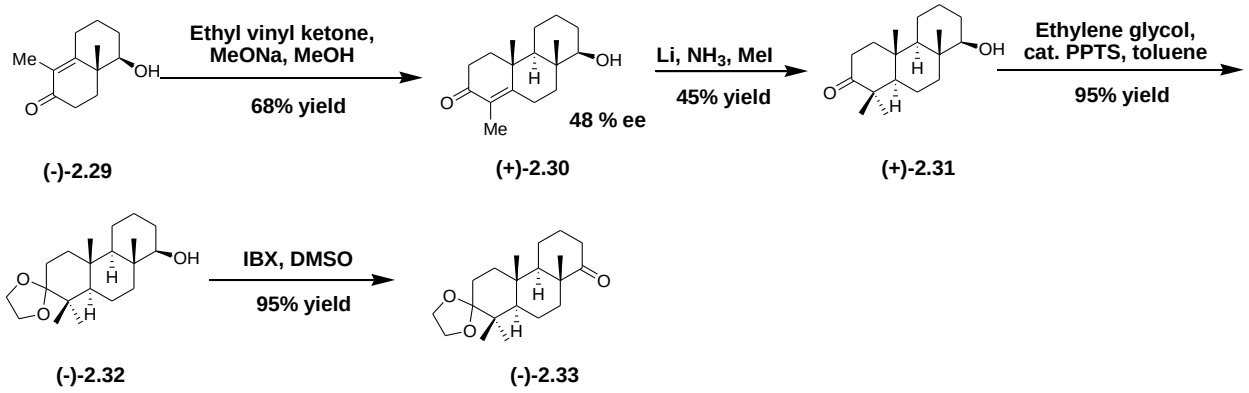
**2.27**

**(-)-2.28**

**(-)-2.29**

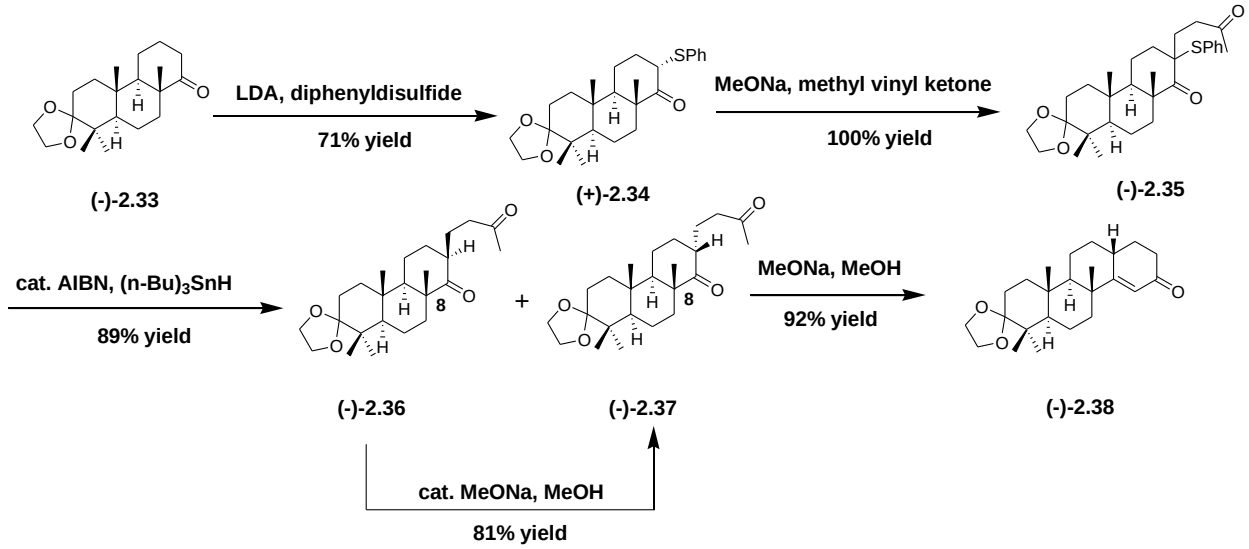
Robinson annulation of alcohol **(-)-2.29** with ethyl vinyl ketone was carried out by using sodium methoxide as base to give three ring compound **(+)-2.30** in 68% yield. Optical rotation of the obtained **(+)-2.30** was taken and compared with the value of enantiomerically pure compound, which indicated 48%ee of optical purity. Optically impure enone **(+)-2.30** was reduced by lithium-liquid ammonia, the generated enolate was trapped by methyl iodide to give ketone **(+)-2.31**. Ketone **(+)-2.31** was treated with ethylene glycol and pyridinium *p*-toluenesulfonate (PPTS) to give the protected compound **(-)-2.32**. Alcohol **(-)-2.32** was oxidized by 2-iodoxybenzoic acid (IBX) to give three ring ketone **(-)-2.33** (Scheme 2.8).

**Scheme 2.8 : Progress made by Aguilar (Part 2)**[12]



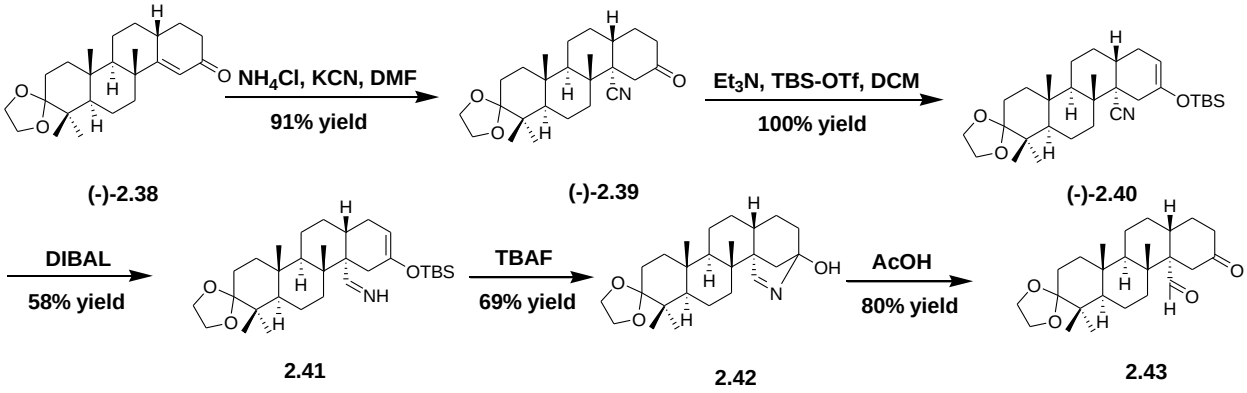

To activate the carbonyl's α-H, ketone **(-)-2.33** was treated lithium diisopropylamide (LDA) and diphenyldisulfide to yield sulfide **(+)-2.34**. Compound **(+)-2.34** then underwent Michael addition reaction with methyl vinyl ketone to give **(-)-2.35**. Removal of the phenylsulfide in **(-)-2.35** was achieved by the radical reduction reaction with azobisisobutyronitile (AIBN) and tributyltin hydride to form a mixture of **(-)-2.36** and **(-)-2.37**. Intramolecular aldol condensation of **(-)-2.37** furnished the ring formation to yield four ring compound **2.38**. However, compound **(-)-2.36** could not undergo the same aldol condensation to give tetracyclic compound. The reason might be the C8-methyl group blocks the enolate of methyl ketone attacking the carbonyl from the top face. Stirred with sodium methoxide in methanol, compound **(-)-2.36** could be transferred into compound **(-)-2.37** and finally gave to same cyclized compound **(-)-2.38** (Scheme 2.9).

**Scheme 2.9 : Progress made by Aguilar (Part 3)**[12]



Sodium nitrile was introduced to enone **(-)-2.38** to give a Michael addition product **(-)-2.39**, then, enol silyl ether **(-)-2.40** was obtained by treating ketone **(-)-2.39** with *t*-butyldimethylsilyl triflate (TBS-OTf) and triethyl amine. The nitrile in **(-)-2.40** was reduced to imine **2.41** with diisopropyl aluminum hydride (DIBAL-H). Removal of *t*-butyldimethylsilyl group in **2.41** with tetrabutylammonium fluoride (TBAF) gave hemiaminal **2.42**. Under acidic condition, hemiaminal **2.42** was hydrolyzed to give aldehyde ketone **2.43** (Scheme 2.10).

**Scheme 2.10 : Progress made by Aguilar (Part 4)**[12]




No further progress was made by Dr. Angelo Aguilar because of the available time, and this project was continued by me during my Ph.D period research. The progress I made will be introduced and discussed in the following sections.

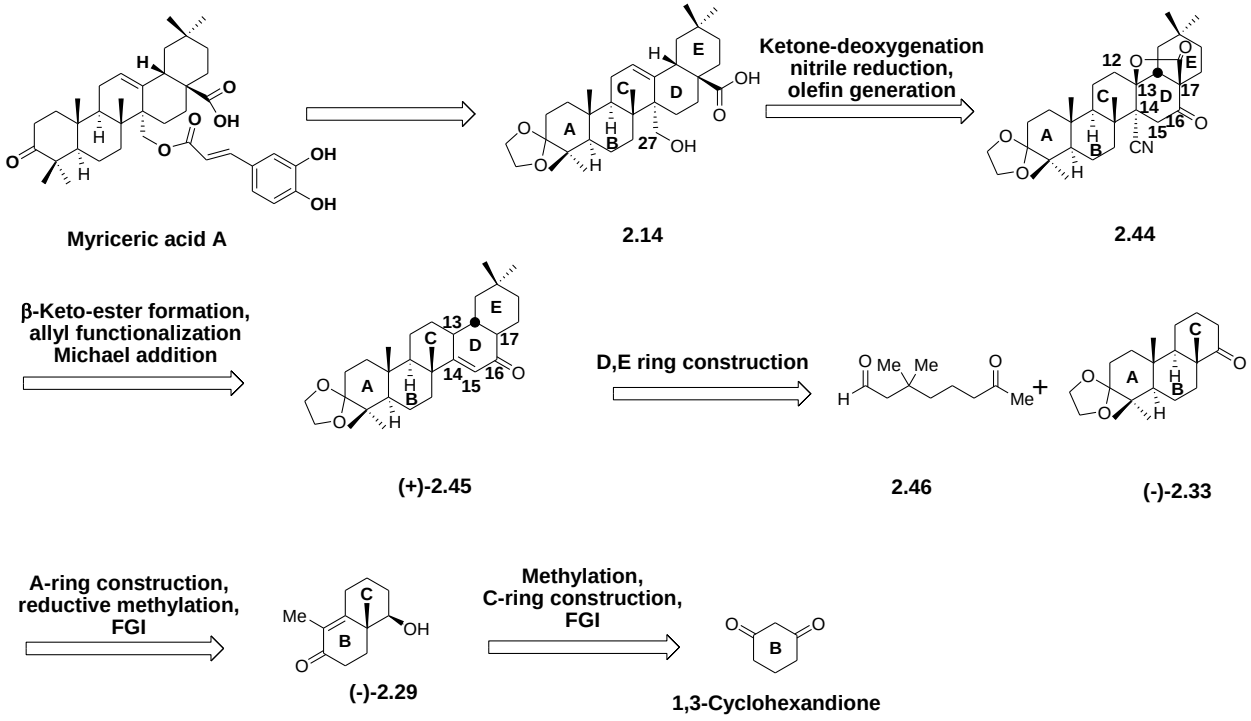
## 2.2 Retro-synthetic analysis of myriceric acid A

To get a better understanding and more rational design of this project, retro-synthetic analysis was conducted and is descripted in this section.

Since the synthetic route from compound **2.14** to myriceric acid A have already been reported in the partial synthesis of myriceric acid A (Scheme 2.6)[8], the target molecule of this project could be compound **2.14**. Compound **2.14** could be synthesized from compound **2.44** via several steps: deoxygenantion of the C16-carbonyl group to methylene, reduction of the C14-nitrile into alcohol, and the elimination to give 12-13 olefin. Compound **2.44** could be obtained from **(+)-2.45** after the 17-position β-keto-ester formation, 13-position allylic functionalization and Michael addition of enone. D, E rings in **(+)-2.45** could be constructed via an aldol condensation-Michael addition-aldol condensation sequence by using three ring compound **(-)-2.33** and novel keto-aldehyde **2.46** as the starting materials. Compound **(-)-2.33** could be formed

from (-)-**2.29** via A-ring formation, reductive methylation and functional group interconversion (FGI) steps. A new method was developed to solve the problem of getting low enantio-excess of the **(-)-2.33**, and this method will be discussed in the following section. Two ring compound **(-)-2.29** could be synthesized form 1,3-cyclohexanedione.

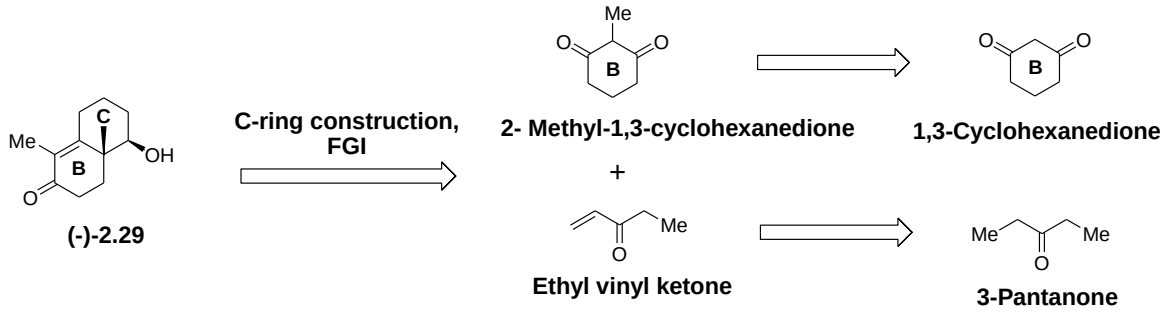
**Figure 2.9 : Retro-synthesis of 2.14**




## 2.3 Preparation of starting materials for asymmetric synthesis of B, C-ring

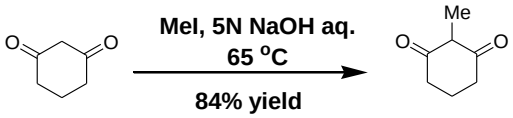
Transformation from 2-methyl-1,3-cyclohexanedione to keto-alcohol **(-)-2.29** was accomplished by following the Aguilar's procedure,[12] and this section introduces the preparation of the starting materials for synthesis of compound **(-)-2.29** (Figure 2.10).

**Figure 2.10 : Transformation from 1,3-cyclohexanedione to (-)-2.29**



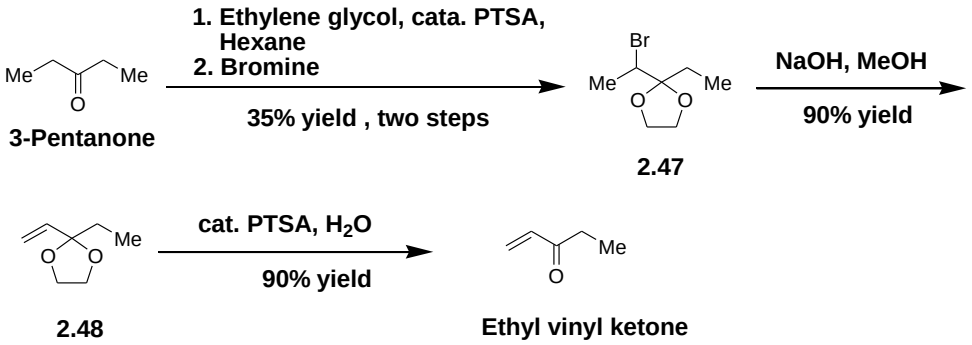
According to the literature,[13] 1,3-cyclohexanedione was treated with iodomethane in aqueous NaOH solution at 65 $^{o}$C for 1 day to yield the 2-methyl-1,3-cyclohexanedione in high yield (Scheme 2.11).

**Scheme 2.11 : Synthesis of 2-methyl-1,3-cyclohexanedione**




Another required starting material for synthesizing C ring, ethyl vinyl ketone, was prepared in 3 steps. This synthesis started with the protection of 3-pentanone with ethylene glycol, and the generated acetal was treated with bromine in one pot to give bromide **2.47**.[14] The elimination of bromide in **2.47** with sodium hydroxide in methanol generated alkene **2.48**.[15] Removal of the acetal group in **2.48** with catalytic amount of *p*-toluenesulfonic acid (PTSA) gave pure ethyl vinyl ketone (Scheme 2.12).

**Scheme 2.12 : Synthesis of ethyl vinyl ketone**




With ethyl vinyl ketone and 2-methyl-1,3-cyclohexandione, the two ring enone alcohol **(-)-2.29** was prepared utilizing the same method as Aguilar[12] did (Scheme 2.7). Mechanism for the asymmetric intramolecular cyclization to construct C-ring was discussed in Aguilar's dissertation as well.[12]

## 2.4 Asymmetric synthesis of A-ring and functionalization of A-B-C ring structure

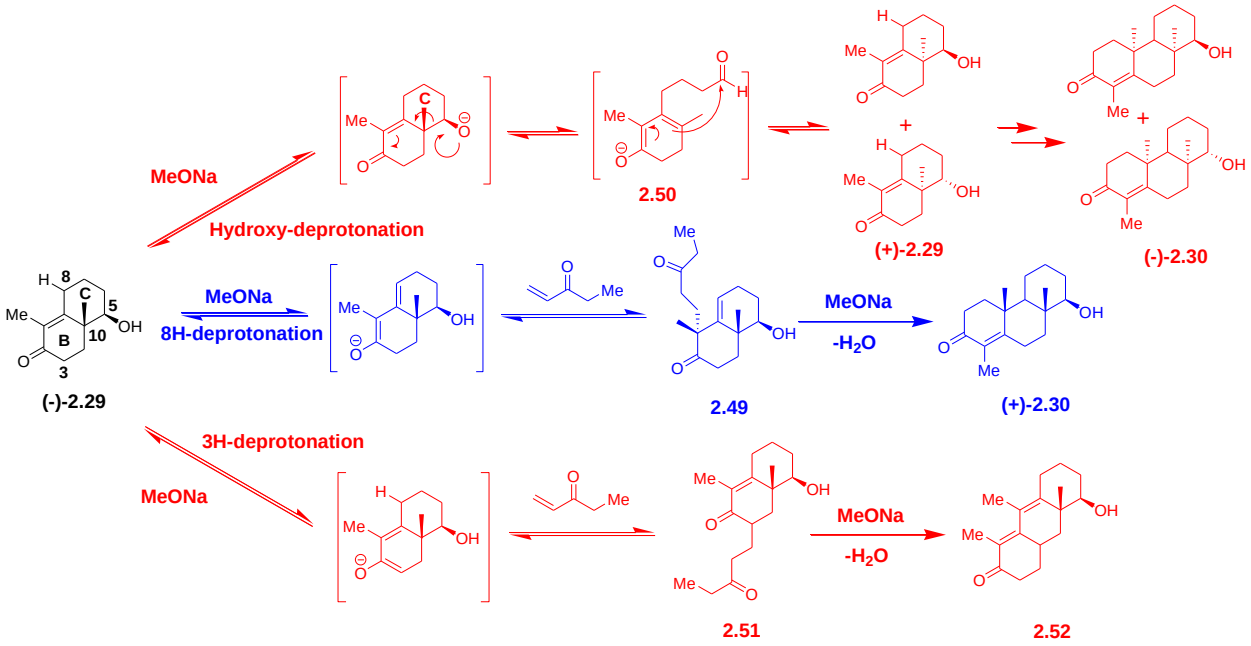
A novel method for the asymmetric transformation from **(-)-2.29** to **(-)-2.33** was discovered and is discussed in this section (Figure 2.11).

**Figure 2.11 : Transformation from (-)-2.29 to (-)-2.33**

(-)-2.33 (-)-2.29

The traditional method for the synthesis of A ring from **(-)-2.29** was originally reported by Honda, T. *et al.* in 1981[16] and further investigated[17] in 2003 by Honda, T, *et al.*. Starting with optically-pure **(-)-2.29** could only afford an enantio-rich product **(+)-2.30** (48%ee) with moderate yield (68%). To obtain the enantio-pure product, an enzyme resolution procedure is required.[17] As the only reported method, it has been used by many chemist to prepare three-ring compound **(+)-2.30** in their synthesis till now. A mechanism was proposed explain the difficulty in the formation of enantio-pure product (Scheme 2.13).[17]

**Scheme 2.13 : Mechanistic explanation for the difficulty in preparation of enantiomerically pure (+)-2.30 by traditional method**



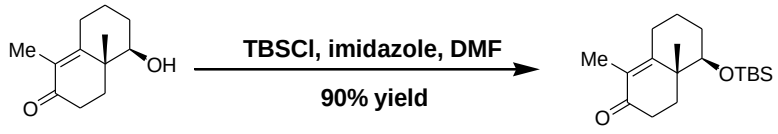

Deprotonation of C8-H by sodium methoxide gave the thermodynamic enolate. Because of the steric effect of the C10-methyl group, ethyl vinyl ketone could only approach the enolate from its α-face to generate Michael addition product **2.49**. Intramolecular aldol condensation of **2.49** catalyzed by sodium methoxide formed desired product **(+)-2.30** (blue route in Scheme 2.13). However, the deprotonation of 5-hydroxy group led to C-ring opening and gave the

enolate-aldehyde intermediate **2.50**. Intramolecular aldol reaction of intermediate **2.50** could generate the opposite enantiomer **(+)-2.29** which followed the same reaction sequence to give **(-)-2.30**, the undesired enantio-isomer of **(+)-2.30**, which decreased the optical purity of the final product. Meanwhile, the kinetic deprotonation of C3-H in **(-)-2.29** gave the kinetic enolate, and this enolate could undergo Michael addition with ethyl vinyl ketone as well to give intermediate **2.51**. Cyclization and dehydration of **2.51** formed compound **2.52**, the structure isomer of **(+)-2.30**, which decreased the yield of desired product.

Considering the complexity of following steps of myriceric acid A's total synthesis, an enantio-pure tricyclic intermediate is desperately needed. With the traditional synthetic method, only enantio-rich tricyclic compound was obtained, and enzyme-resolution step was required to get the enantio-pure compound. However, to obtain large quantity of enantio-pure tricyclic compound, using enzyme resolution method become impossible if the cost, time, work inputs and the lose of the unwanted enantiomer were taken into account. Hence, an enantio-selective A-ring synthesis reaction is highly demanded. To develop such reaction, many attempts were made.

One way to prevent the C-ring opening is to block the formation of 5-alkoxide intermediate. Hence**,** the 5-hydroxy group in **(-)-2.29** was protected by TBSCl in DMF with imidazole as base to give **(-)-2.53** (Scheme 2.14). However, Honda, T.[17] mentioned that the TBS group in **(-)-2.53** was readily cleaved under sodium methoxide/methanol reflux condition. Consequently, other reaction pathways and conditions, instead of traditional Robinson annulation condition, should be considered.

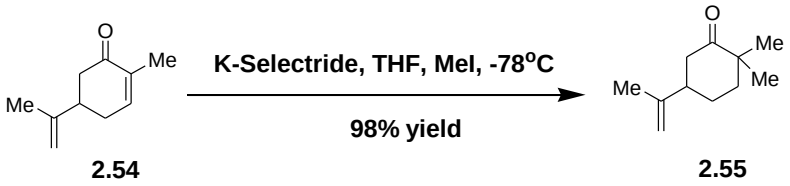
**Scheme 2.14 : Preparation of (-)-2.53**




**(-)-2.29** **(-)-2.53**

In 1976, Fortunato and Ganem reported a cascade enone reductive-alkylation reaction. The enone was reduced by K-selectride firstly, and the formed enolate was trapped by alkyl halides to give the alkylated ketone (Scheme 2.15).[18]

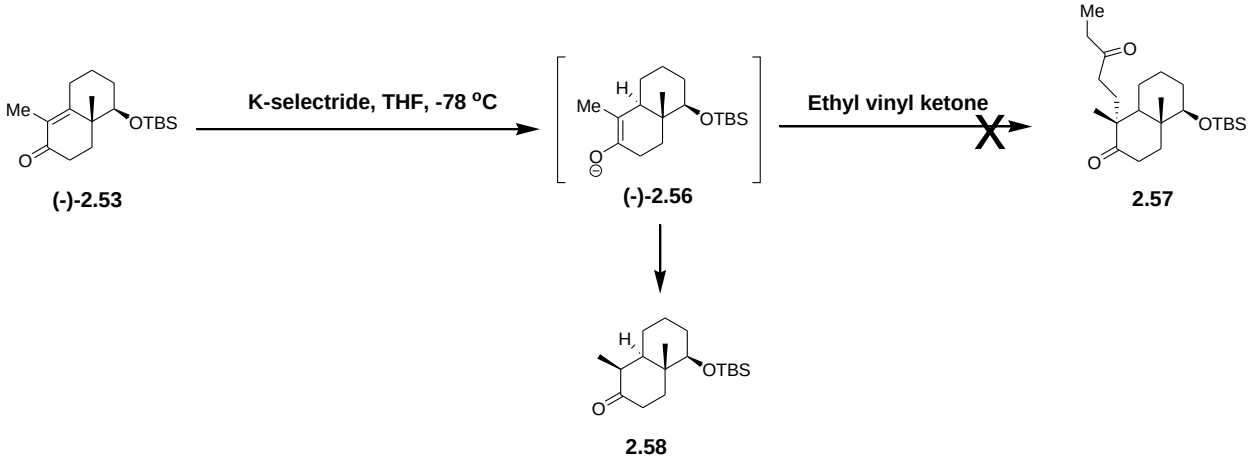
**Scheme 2.15 : Cascade K-selectride reductive-alkylation reaction of enone[18]**




**2.54** **2.55**

Based on Fortunato's strategy,[18] compound **(-)-2.53** was treated with K-selectride to reduce the enone moiety to regio-selectively generate the desired enolate **2.56**, and ethyl vinyl ketone was introduced into the reaction mixture at once. However, at -78 $^{o}$C or elevated temperatures, no Michael addition product **2.57** was formed, but only the reduced ketone **2.58** was detected and isolated (Scheme 2.16).

**Scheme 2.16 : Cascade K-selectride enone reductive-Michael addition reaction of (-)-2.53**

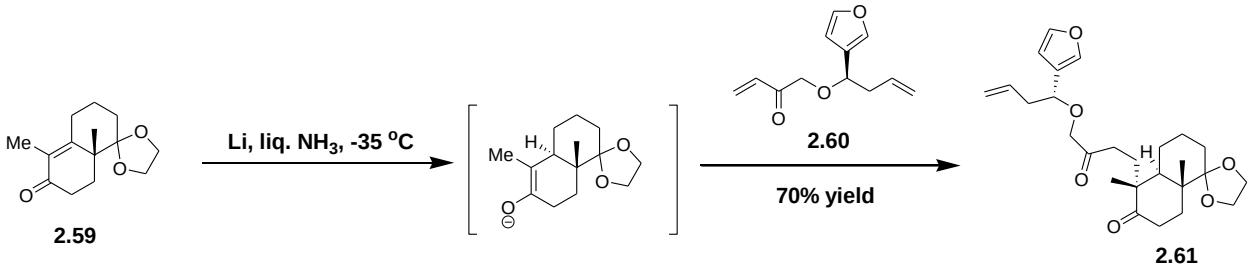



**(-)-2.53** **(-)-2.56** **2.57**

**2.58**

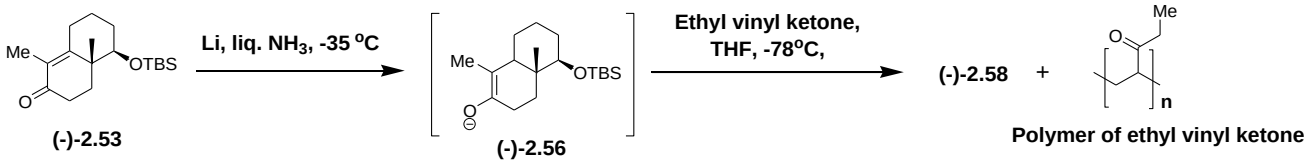
Another domino reductive-Michael addition reaction was reported by Cheung and Snapper with similar bicyclic compound **2.59**. Compound **2.59** firstly was reduced by lithium in liquid ammonia; then, α,β-unsaturated ketone **2.60** was introduced into the corresponded enolate slowly over 30 minutes to give enantio-selective Michael addition product **2.61** (Scheme 2.17). To prevent the polymerization of α,β-unsaturated ester, the reaction was protected from light.

**Scheme 2.17 : Cascade enone reductive-Michael addition reaction of 2.58[19]**



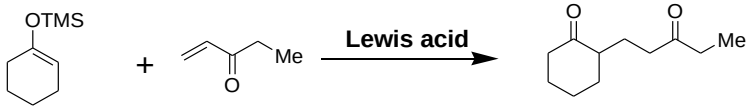

Following the similar strategy, enone **(-)-2.53** was reduced by lithium metal in liquid ammonia at -35°C to give desired enolate **2.56**. After evaporation of ammonia and dilution of the residue with dry THF, ethyl vinyl ketone in diethyl ether was introduced to the resulted enolate **2.56** over 30 minutes with protection from light. Unfortunately, no desired Michael addition product was detected and isolated after the reaction. From the $^1$H NMR of crude mixture, broad signals appeared at 3.0 – 2.0 ppm and 1.5 – 0.8 ppm indicating the formation of polymers of ethyl vinyl ketone.

**Scheme 2.18 : Cascade lithium enone reductive-Michael addition reaction of (-)2.53**



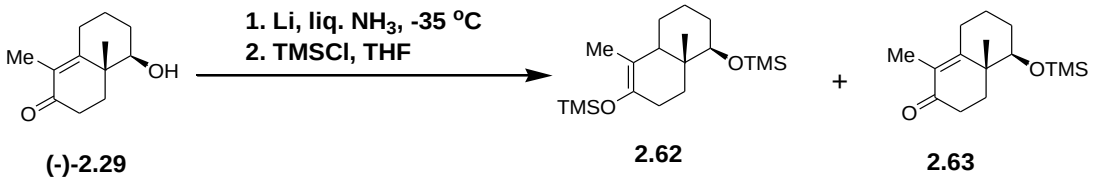

Mukaiyama-type Michael addition reaction was also tried to be applied in the asymmetric synthesis of A-ring. The idea is depicted in the Scheme 2.19.

**Scheme 2.19 : Mukaiyama-type Michael addition**




Silyl enol ether **2.62** was prepared by reducing enone **(-)-2.29** with lithium/ liq. $NH_3$, the enolate was trapped with trimethylsilylchloride (TMSCl) after evaporation of liq. $NH_3$ (Scheme 2.20). This reaction gave a mixture of desired silyl enol ether and a TMS protected compound **2.63**. Due to the instability of enol silyl ether, the mixture was directly used for the next step without purification.

**Scheme 2.20 : Preparation of silyl enol ether 2.62**




**(-)-2.29** **2.62** **2.63**

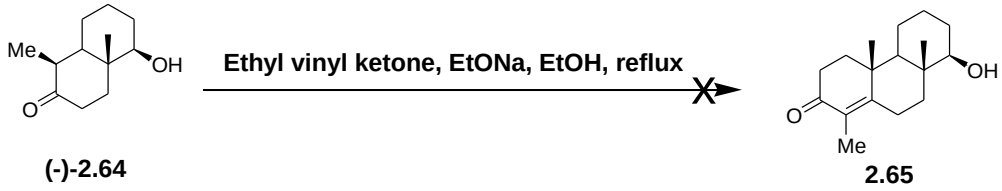
A mixture of **2.62** and **2.63** was mixed with ethyl vinyl ketone and treated with boron trifluoride etherate ($BF_3$·ether). Unfortunately, at -78 $^oC$ or elevated temperatures, no desired Michael addition product was detected. Under reaction conditions, TMS groups were hydrolyzed off to give back enone **(-)-2.29** and ketone **(-)-2.64** (Scheme 2.21).

**Scheme 2.21 : Attempt on Mukaiyama type Michael addition**


**2.62** **2.63** **(-)-2.64**

With compound **(-)-2.64** in hand, traditional Robinson annulation reaction was carried out with ethyl vinyl ketone. With the reflux with sodium ethoxide in ethanol, no desired product was found. Starting material **(-)-2.64** was recovered, and ethyl vinyl ketone's polymers were detected.

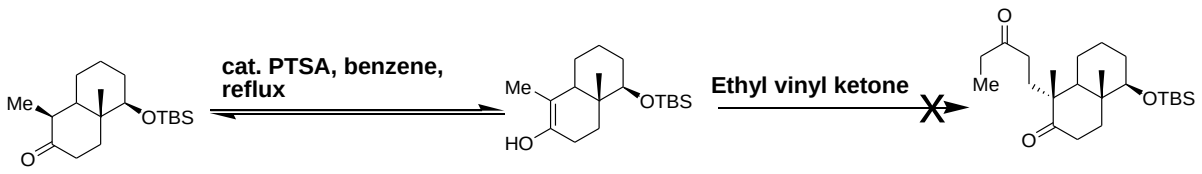
**Scheme 2.22 : Attempt on Robinson annulation of (-)-2.64 with ethyl vinyl ketone**




**(-)-2.64** **2.65**

Acid catalyzed Michael addition was also tested with **(-)-2.58** and ethyl vinyl ketone. It was supposed that under acidic conditions with heating, the ketone would be transferred into its enol form. The enol could attack ethyl vinyl ketone to give a Michael addition product. However, after heat the mixture of **(-)-2.58** and ethyl vinyl ketone with catalytic amount of PTSA for 24 hours, reaction did not give any progress (Scheme 2.23).

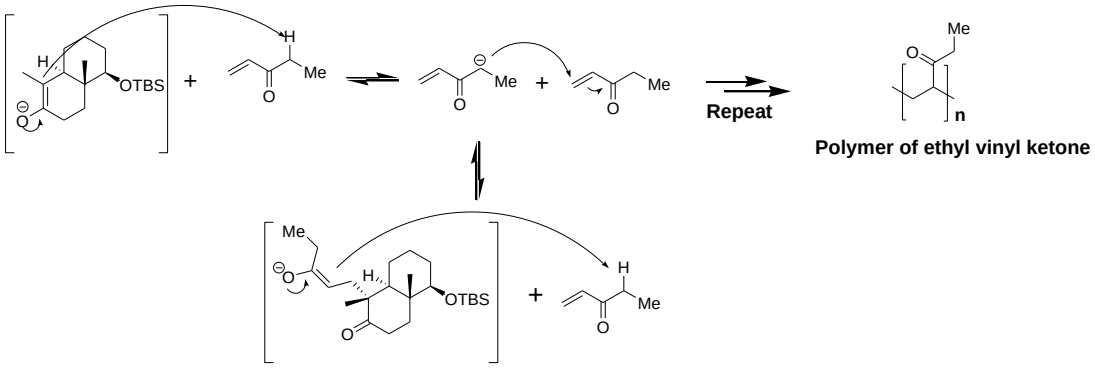
**Scheme 2.23 : Attempt on acid catalyzed Michael addition of (-)-2.58 with ethyl vinyl ketone**




**(-)-2.58** **2.66** **2.57**

After summarizing these reaction outcomes, it becomes clear that the problem of the designed Michael addition is the reactivities of two reactants do not match. When the generated enolate **2.56** is complex with boron (from K-selectirde or $BF_3$.ether), it is unreactive towards Michael addition. When enolate **2.56** stays in its free form (from lithium reduction or generated *in-situ* by EtONa), it is "hard" and acted as base to promote the polymerization of ethyl vinyl ketone. Enol **2.66** was not reactive enough to undergo the Michael addition neither.

**Scheme 2.24 : Self polymerization of ethyl vinyl ketone initiated by enolate 2.56**

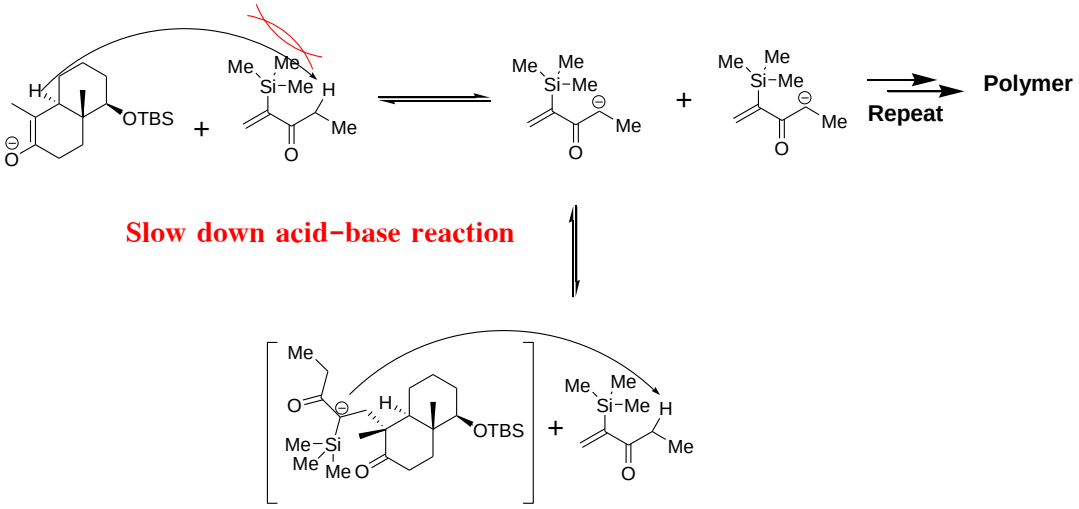



Since attempts on "tuning" the reactivity of Michael donors (enolate **2.56** or enol **2.66**) were all failed, the other solution for this problem was to "tune" the reactivity of Michael acceptor, ethyl vinyl ketone. If the self-polymerization of ethyl vinyl ketone could be slowed down or prevented in the presence of "hot" enolate **2.56**, the desired Michael addition would be preceded smoothly.

To prevent the polymerization of ethyl vinyl ketone, one solution is to use the alternative reagent: α-trimethylsilylvinyl ethyl ketone.[20] Trimethylsilyl group at α position of vinyl ketone blocked this enone's polymerization. The reason is probably the the enolate derived from the Michael addition could be stabilized by overlapping of d-orbital of silicon to prevent the polymerization; also, the strong steric hindrance of this bulky siliyl moiety slows down the deprotonation process of enone by the enolate **2.56**. This silyl group could be readily hydrolyzed

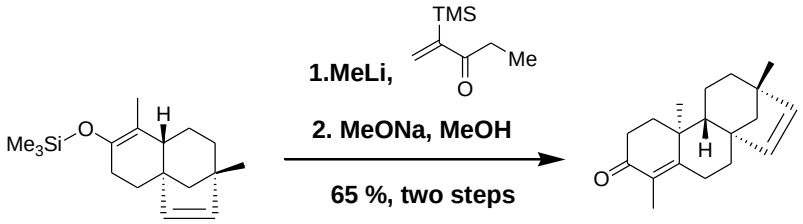
off at base-catalyzed intramolecular aldol condensation step which would give the same Robinson annulation product as ethyl vinyl ketone.

**Scheme 2.25 : TMS group slows down the deprotonation**




One of its applications is the total synthesis of stachenone (Scheme 2.26).[21]

**Scheme 2.26 : Application of α-trimethylsilyl vinyl ethyl ketone in asymmetric ring construction**

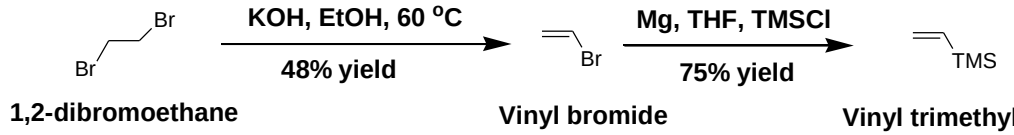



**2.68** **2.69**

The disadvantage of this method is this chemical, α-trimethylsilyl vinyl ethyl ketone, is not commercially available. Hence, it has to be prepared in the laboratory via a six-step synthesis from the commercially available 1,2-dibromoethane.

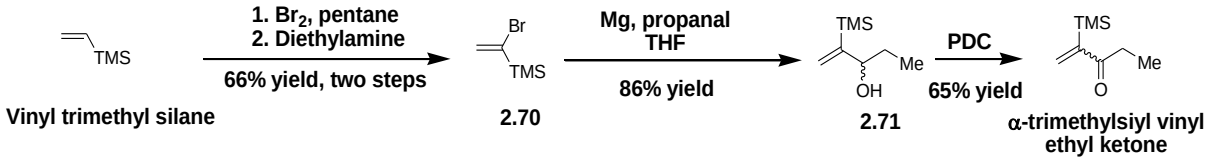
The elimination of 1,2-dibromoethane readily gave vinyl bromide (b.p: 16 $^{o}$C), and the prepared vinyl bromide was introduced to magnesium to generate vinyl magnesium bromide reagent. Vinyl Grignard reagent reacted with TMSCl to give vinyl trimethyl silane which was directly distilled out from the reaction mixture (Scheme 2.27).[22]

**Scheme 2.27 : Synthesis of vinyl trimethyl silane**[22]



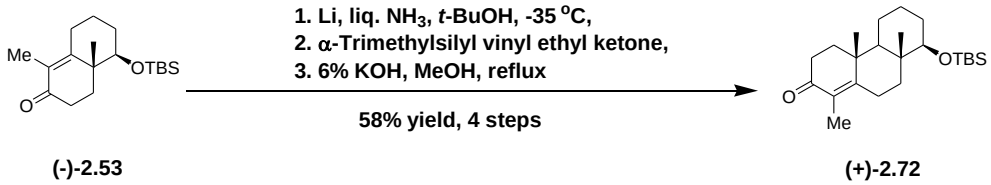

Vinyl trimethyl silane was treated with bromine at -78°C to give an bromine addition product, and this crude product underwent an elimination reaction with diethylamine to give α-trimethylsilyl vinyl bromide (**2.70)**. Bromide **2.70** was used to prepare the corresponding Grignard reagent with magnesium, and the prepared α-trimethylvinyl magnesium bromide was treated with propanal to give allyl alcohol **2.71**. Oxidation of allyl alcohol with pyridinium dichromate (PDC)[23] gave α-trimethylsilyl vinyl ethyl ketone (Scheme 2.28).

**Scheme 2.28 : Synthesis of α-trimethyl vinyl ethyl ketone**




With α-trimethylsilyl vinyl ethyl ketone in hands, the reductive-Michael addition reaction was carried out. Same as before, the bicyclic enone **(-)-2.53** was firstly reduced by lithium to regio-selectively form the enolate **2.56**. After quenching the excess amount of lithium and evaporating off ammonia, enolate **2.56** was dissolved in dry diethyl ether. α-Trimethylsilyl vinyl ethyl ketone was introduced into the mixture at -78°C over 30 minutes with protection from light to finally give the desired stereo-selective Michael addition product. Annulation with KOH as base in MeOH resulted the enantio-pure tricyclic product **(+)-2.72** (Scheme 2.29).

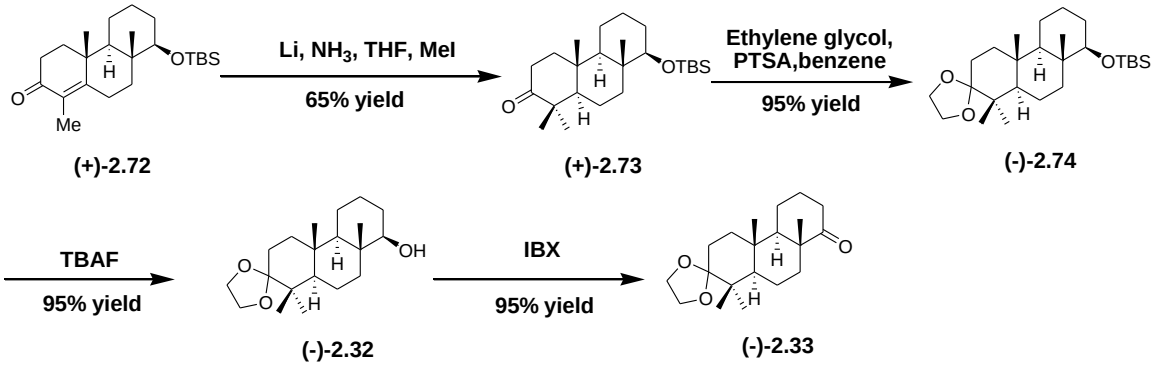
**Scheme 2.29 : Stereoselective synthesis of tricyclic compound (+)-2.72**




Compound **(+)-2.72** underwent reductive-methylation reaction to give tricyclic compound **(+)-2.73**. The ketone **(+)-2.73** was protected by ethylene glycol to form acetal **(-)-2.74**. Deprotection of TBS group in **(-)-2.74** with TBAF generated alcohol **(-)-2.32**. At this stage, the optical rotation of obtained **(-)-2.32** ($[\alpha]_D$ = -45°, c =0.1 in chloroform) was compared with the

reported value of the **(-)-2.32** ($[\alpha]_D$ = -44°, c =0.1 in chloroform, 98%ee, measure by chiral HPLC),[24] and the enantio-purity of the obtained **(-)-2.32** was calculated as 100%ee. Oxidation of alcohol **(-)-2.32** with IBX finally gave acetal ketone **(-)-2.33** (Scheme 2.30).

**Scheme 2.30 : Synthesis of acetal ketone (-)-2.33**



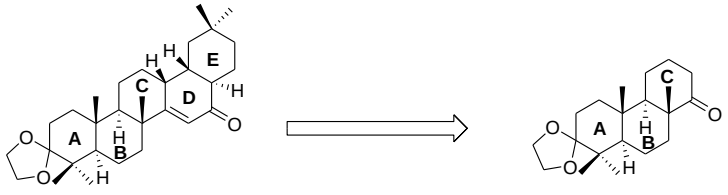

**(+)-2.72** **(+)-2.73** **(-)-2.74** **(-)-2.32** **(-)-2.33**

To sum up, the desired stereo-selective A-ring construction was finally achieved with the reductive-Michael addition-aldol condensation reaction by using α-trimethylsilyl vinyl ethyl ketone as the building block. Functionalization of the resulted tricyclic compound was proceeded smoothly to give the enantio-pure acetal ketone **(-)-2.33** for further exploration on the total synthesis of myriceric acid A.

## 2.5 Synthesis of D, E-rings of myriceric acid A

In this section, the D, E rings construction from A, B, C-ring compound **(-)-2.33** via a tandem aldol-Michael-aldol protocol is introduced and discussed (Figure 2.12).

**Figure 2.12 : Transformation from (-)-2.33 to (+)-2.45**

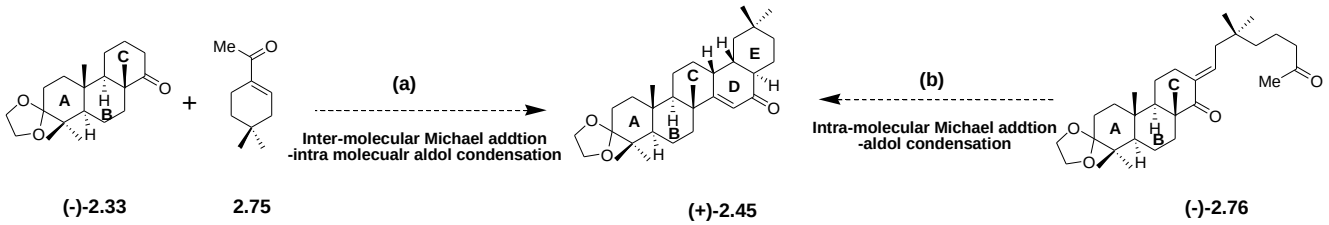



**(+)-2.45** **(-)-2.33**

Since Aguliar[12] already successfully synthesized, functionalized and bio-evaluated the tetracyclic compound **2.38**, my goal is to synthesize pentacyclic compound **(+)-2.45** directly from compound **(-)-2.33**. To achieve this, two possible synthetic approaches could be used: (**a**) D-ring construction via inter-molecular Michael addition-intramolecular aldol condensation by

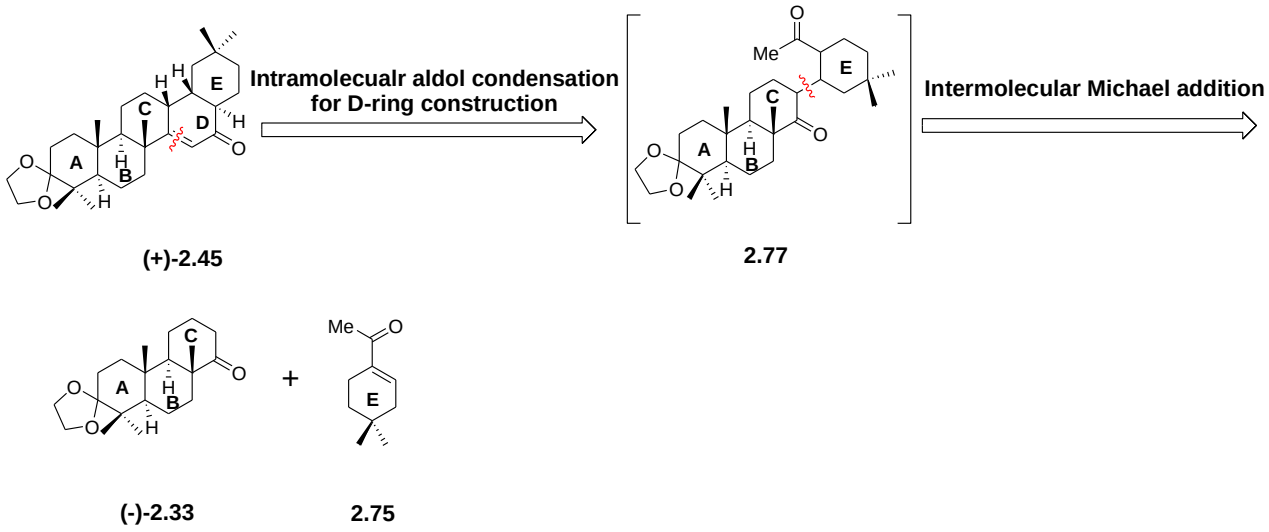
using tricyclic compound **(-)-2.33** (or its derivatives) and monocyclic compound **2.75** which has all the structure features of E-ring; (**b**), D,E-rings construction via intra-molecular Michael addition-aldol condensation process by using compound **(-)-2.76** which is derived from compound **(-)-2.33** (Scheme 2.31).

**Scheme 2.31 : Possible synthetic approaches for synthesis of (+)-2.45**




Approach **(a)** was firstly attempted. The retro-synthetic analysis of **(+)-2.45** via inter-molecular Michael addition approach is depicted in Scheme 2.32. D-ring in **(+)-2.45** could be synthesized via an intramolecular aldol condensation reaction from compound **2.77**. E-ring would be connected with fused A, B, C rings via the intermolecular Michael addition from compound **(-)-2.33** and enone **2.75**.

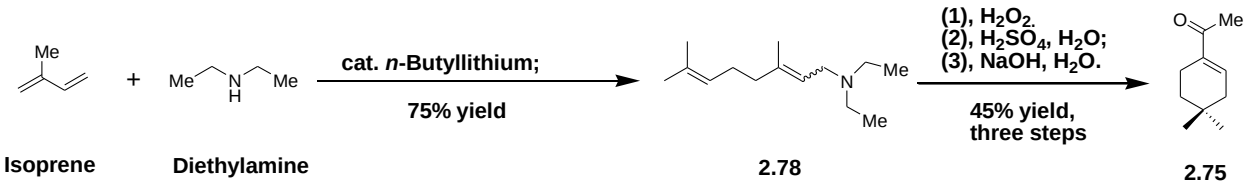
**Scheme 2.32 : Retro-synthetic analysis of (+)-2.45 in approach (a)**




Compound **2.75** was prepared from isoprene and diethylamine via a reported 3-step synthesis.[25, 26] Firstly, isoprene reacted with diethylamine and catalytic amount of *n*-butyllithium to give *N*,*N*,-diethylgeranylamine **2.78**, and the following oxidation of amine was accomplished by hydrogen peroxide to give the corresponding *N*-oxide intermediate, and cyclization reaction

of *N*-oxide was carried out to form the desired monocyclic enone **2.75** in moderate yield (Scheme 2.33).

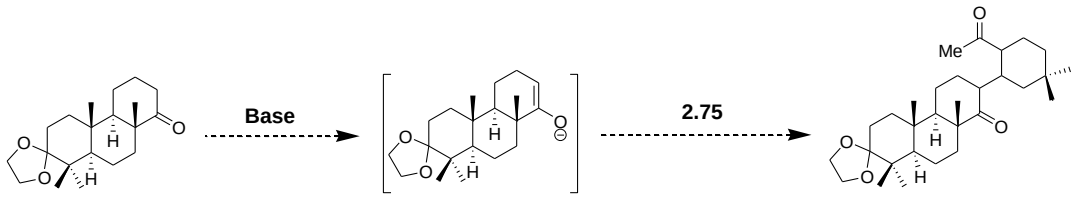
**Scheme 2.33 : Synthesis of compound 2.75**




**Isoprene** **Diethylamine** **2.78** **2.75**

With compound **2.75** in hands, the synthesis of **(+)-2.45** was tried. The basic idea was to use the enolate which derived from **(-)-2.33** as the Michael donor to attack the enone **2.75** (Scheme 2.34).

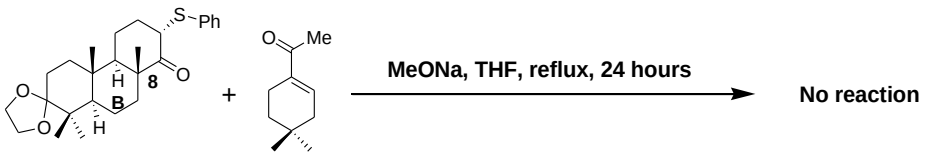
**Scheme 2.34 : Designed Michael Addition of 2.75 with (-)-2.33**




**(-)-2.33** **2.79** **2.77**

Initially, enolate derived from compound **(+)-2.34** was used as the Michael donor. With the phenylsulfide attached, the pKa of α-H of the ketone is lowered to 16; also, this phenylsulfide group is an electron-withdrawing group which could stabilize the formed enolate to enhance the rate of desired Michael addition reaction. However, after refluxing in THF with **2.75** and sodium methoxide for 24 hours, no desired product but only the starting materials were detected (Scheme 2.35). The reason might be the strong steric effects from the B-ring and C8-methyl group. The B-ring blocks the enone approaching from the bottom face of **(+)-2.34**, and the C8-methyl group prevents the enone aligning with the enolate from the top. As the result, the desired Michael addition reaction cannot proceed.

**Scheme 2.35 : Michael addition of (+)-2.34 with 2.75**

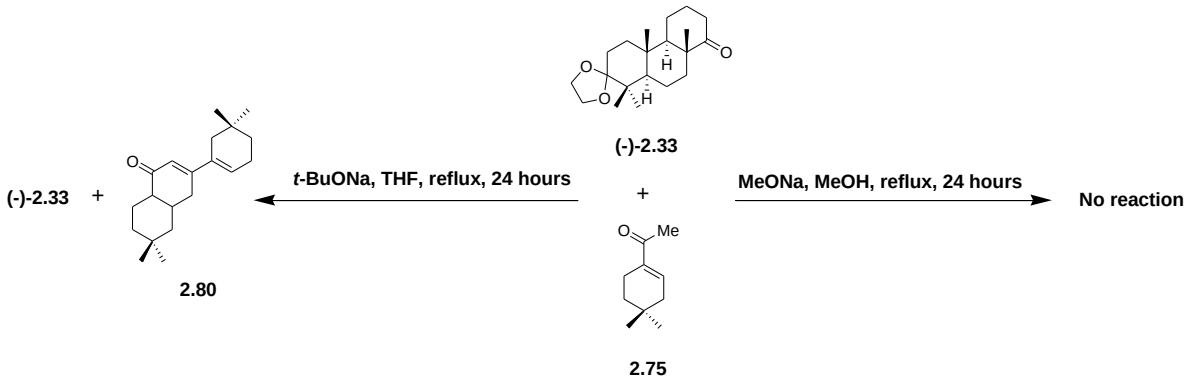



**(+)-2.34** **2.75**

To reduce the steric hindrance, enolate directly derived from ketone **(-)-2.33** was used as Michael donor to attack enone **2.75**. With sodium methoxide as base, no reaction occurred even

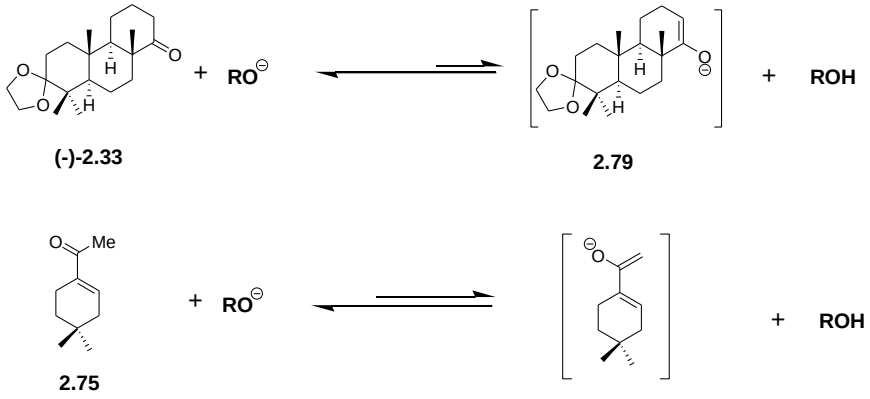
the mixture was heated to reflux or to 120 $^{o}$C (in a sealed tube) in methanol for 24 hours. Then, a stronger base, sodium *t*-butoxide, was employed for this reaction. However, after stirring in refluxed THF for 24 hours, ketone **(-)-2.33** stayed unreacted. Enone **2.75** disappeared, and a new compound was detected by TLC. After isolation, the new compound **2.80** is determined as the self-Robinson annulation product of **2.75** (Scheme 2.36).

**Scheme 2.36 : Michael Addition of 2.75 with (-)-2.33 with MeONa and *t*-BuONa**



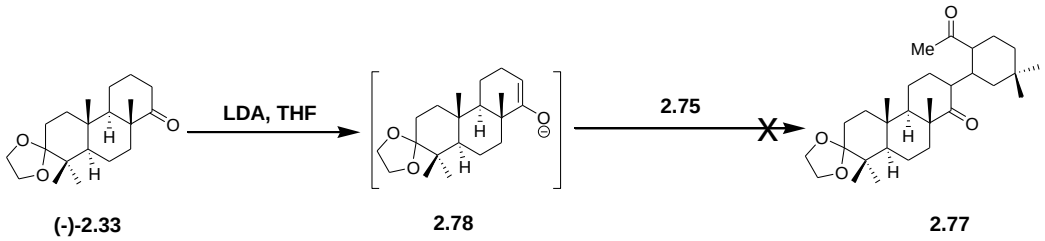

In the attempted reactions, the enolate **2.79** was generated *in-situ*. pKa of α-H of ketone is around 25 and pKa of hydroxyl in alcohol of around 16; so, the enolate **2.79** is highly reactive towards alcohol and easily protonated from the hydroxyl group to give back the ketone (Scheme 2.37). Therefore, the real concentration of enolate is very low, and, considering that enone **2.75** was not that reactive as vinyl ketones, the desired Michael addition would proceed extremely slow. Meanwhile, from the reaction outcome of the *t*-BuONa reaction, it could be tell that the base has a greater chance to deprotonate the α-H of enone to give self-Robinson annulation product. It is understandable. Although both the α-H of enone **2.75** and ketone **(-)-2.33** have similar pKa, the enone **2.75**'s α-H has less steric hindrance than the ketone **(-)-2.33**, which makes the attack by the base much easier.

**Scheme 2.37 : Generation of two enolates with alkoxide**



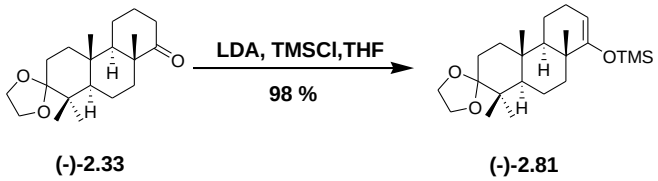

Since the reactions with *in-situ* generated enloates by alkoxides were all unsuccessful, other pathways were to use pure enolate for the Michael addition. The desired enolate could be readily obtained by treating ketone **(-)-2.33** with LDA. To this enolate in THF was added the enone **2.75**. Unfortunately, at -78 $^{o}$C, 25 $^{o}$C and 70 $^{o}$C, no desired Michael addition occurred, and all the starting material were recovered (Scheme 2.38).

**Scheme 2.38 : Michael addition with LDA-generated enolate**




Mukaiyama-type Michael addition[27] was also examined for the synthesis of **2.77**. The advantage of this reaction was that the Lewis acid's chelation with enone could increase its activity as Michael acceptor to promote the Michael addition. The silyl enol ether **(-)-2.81** was readily prepared with ketone **(-)-2.33** in quantitative yield.

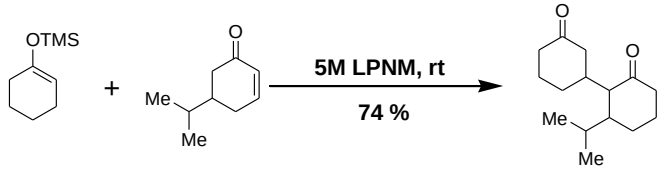
**Scheme 2.39 : Synthesis of (-)-2.81**




Initially, this type of Michael addition was tried with a weak Lewis acid: lithium ion. The 1,4-addition reaction of silyl enol ether to α,β-unsaturated ketone in the medium of lithium perchlorate and nitromethane (LPNM) was reported (Scheme 2.40).[28] The authors stated that

Lewis acidity of lithium ion increases in nitromethane because of its poor coordination with the solvent. With large excessed acidity-increased lithium ion, the Michael addition is catalyzed to give the 1,4-addition product.

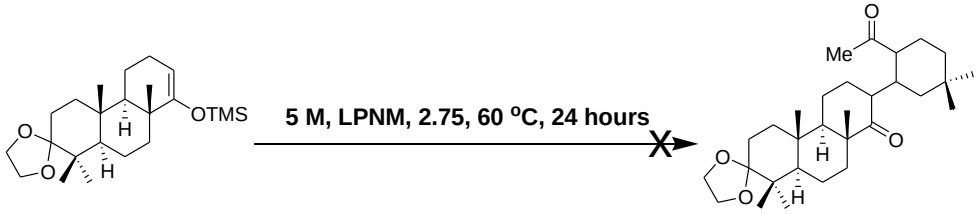
**Scheme 2.40 : Michael addition of silyl enol ether to α,β-unsaturated ketone in LPNM[28]**




**2.82** **2.83** **2.84**

However, the application of this reaction for the synthesis of **2.77** did not give any positive result. After prolong heating, enol silyl ether decomposed to give back the ketone **(-)-2.33**, and **2.75** was also recovered.

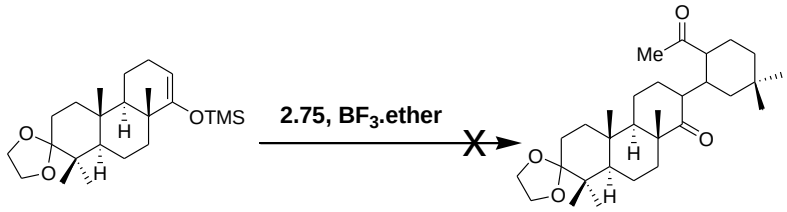
**Scheme 2.41 : Application of LPNM condition to synthesize 2.77**




**(-)-2.81** **2.77**

Stronger Lewis acid, $BF_3$ etherate, was used to try on this reaction as well. However, this reaction also failed and only provided the hydrolyzed product **(-)-2.33** and unreacted **2.75** (Scheme 2.42).

**Scheme 2.42 : Mukaiyama-type Michael addition for synthesis of 2.77**

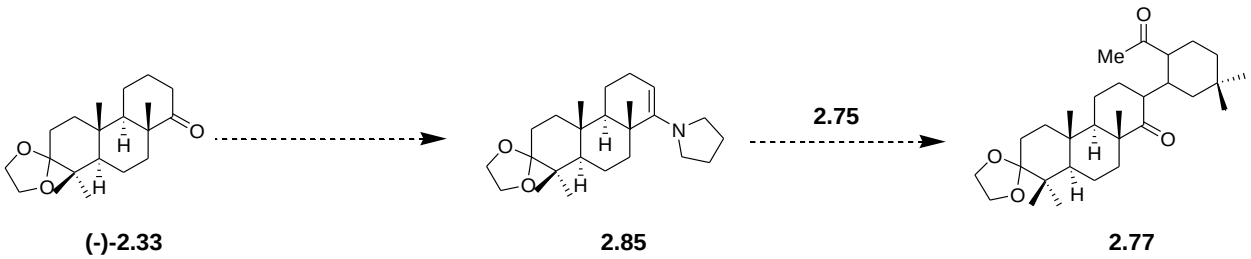



**(-)-2.81** **2.77**

Enamine chemistry[29] was also attempted for synthesis of **2.77** (Scheme 2.43). However, the preparation of enamine **2.85** turned out to be difficult. In the presence of 4 Å molecular sieve

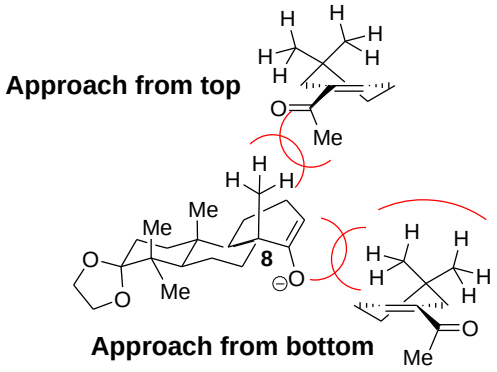
and catalytic amount of PTSA, ketone **(-)-2.33** and pyrrolidine remianed unchange in refluxed toluene for 24 hours.

**Scheme 2.43 : Michael addition for synthesis of 2.77 with enamine 2.85**



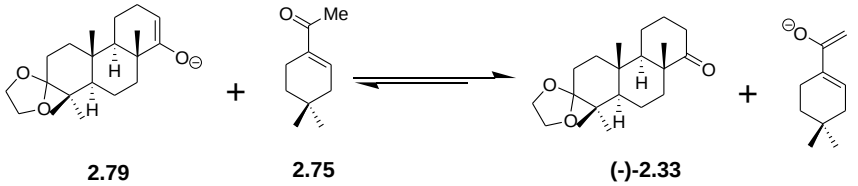

To sum up, all attempts on the intermolecular Michael addition strategies did not give any positive results. The reason might be the strong steric hindrances which were given by the C8-methyl group and B-ring of **(-)-2.33** and gem-dimethyl groups of **2.75**. C8-Methyl group of enolate **2.79** blocks the enone **2.75** approaching from the top side. When enone **2.75** approaches the enolate from its bottom, the B-ring of **(-)-2.33** blocks the two reactants to align in the right position; meanwhile, the gem-dimethyl groups on the enone **2.75** also increase the difficulty for the enolate approach and alignment (Figure 2.13).

**Figure 2.13 : Steric hindrance from 8-methyl group of enolate 2.79 and gem-dimethyl groups of 2.75**




The other possible reason for the failures of intermolecular Michael addition strategies was the competition reaction: acid-base reaction. The enolate would act as the base instead of nucleophile to deprotonate the α-H of enone, which could destruct both the Michael donor and acceptor and slow down the desired Michael addition (Scheme 2.44).

**Scheme 2.44 : Acid base reaction between the enolate and enone**

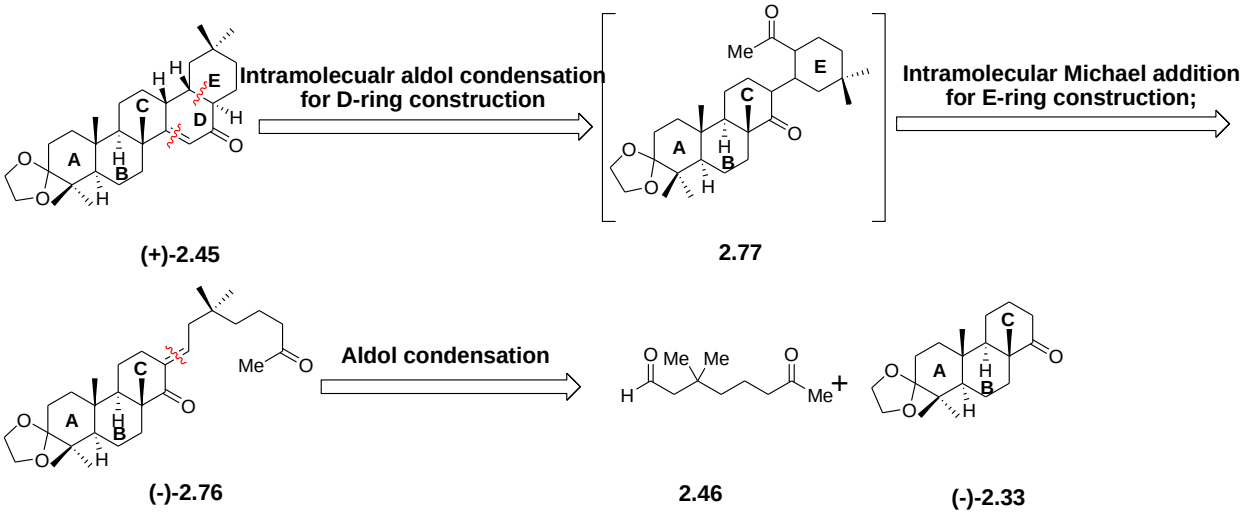


**2.79** **2.75** **(-)-2.33**

One way to overcome the strong steric effect is to go through the intramolecular approach to furnish the construction of pentacyclic structure, which is the above mentioned approach **(b)**.

The retro-synthetic analysis of compound **(+)-2.45** via the approach **(b)** is depicted in Scheme 2.45. Similar as the intermolecular Michael addition approach, D-ring of **(+)-2.45** could be built up via an intramolecular aldol condensation reaction from compound **2.77**; however, the E-ring would be constructed via the intramolecular Michael addition from enone-ketone **(-)-2.76** which would be synthesized from **(-)-2.33** and ketone-aldehyde **2.46** via intermolecular aldol condensation.

**Scheme 2.45 : Retro-synthetic analysis of (+)-2.45 in approach (b)**

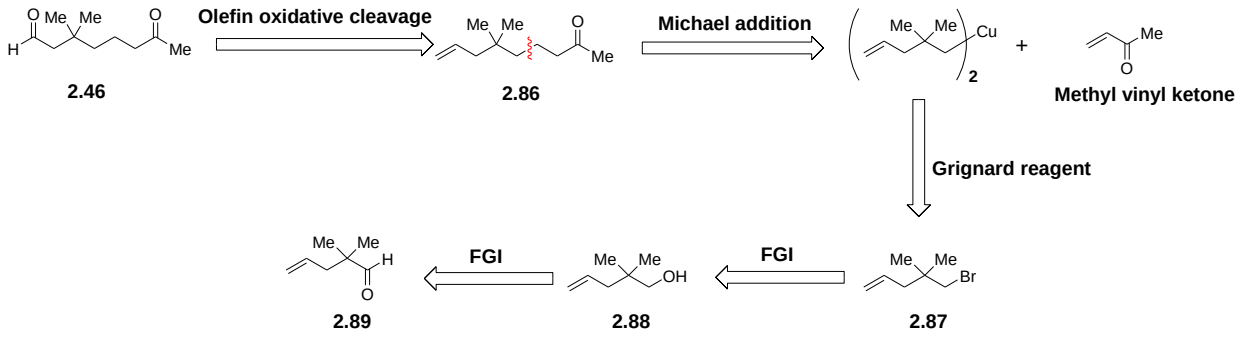



**(+)-2.45** **2.77**

**(-)-2.76** **2.46** **(-)-2.33**

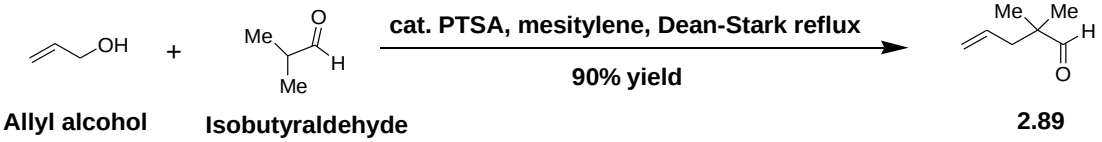
The synthesis of **(+)-2.45** via approach **(b)** started from the preparation of novel ketone aldehyde **2.46**. The retro-synthetic analysis of ketone aldehyde **2.46** is depicted in Scheme 2.46. The aldehyde functionality in **2.46** could be derived from the olefin in compound **2.86** via oxidative cleavage reaction. Olefin ketone **2.86** would be prepared from methyl vinyl ketone with dialkyl cuprous reagent via a 1,4-addition. The dialkyl cuprous reagent would be prepared from the Grignard reagent of bromide **2.87**. Bromide **2.87** could be derived from aldehyde **2.89** via few steps through functional group interconversions.

**Scheme 2.46 : Retro-synthetic analysis of 2.46**



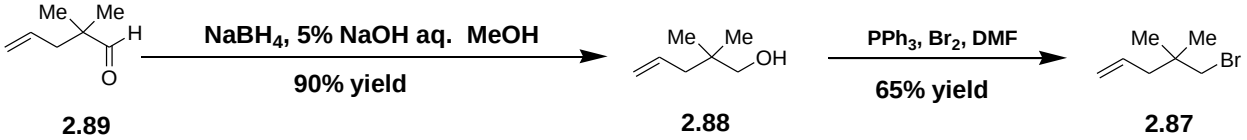

Aldehyde **2.89** was synthesized from a known procedure in excellent yield (Scheme 2.47).[30] This synthesis used allyl alcohol and isobutryaldehyde as the starting materials. The reaction went through a hemiacetal formation-dehydration-Claisen rearrangement sequence to give desired aldehyde **2.89**.

**Scheme 2.47 : Synthesis of 2.89[30]**




The olefin aldehyde **2.89** was readily reduced by sodium borohydride in methanol and 5% aq. sodium hydroxide mixture to give olefin alcohol **2.88** with quantitative yield. Bromination of **2.88** firstly tried with triphenylphosphine and tetrabromomethane. The reaction went smoothly to give desired bromide **2.87**; however, the purification of the product turned out to be difficult. Byproduct bromoform which was formed in the reaction has similar boiling point and polarity as the product and could not be separated. Hence, the alternative bromination method was utilized. Olefin bromide **2.87** was successfully prepared with bromine and triphenylphosphine in DMF and purified by distillation in moderate isolation yield (Scheme 2.48).[31]

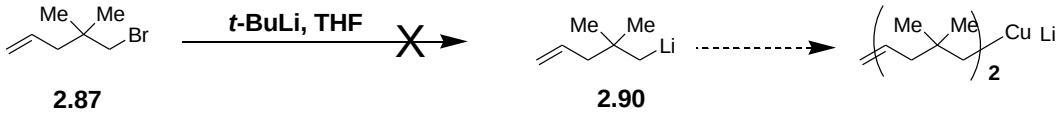
**Scheme 2.48 : Synthesis of 2.87**




With the bromide **2.87** in hands, the next step was to prepare the cuprate reagent. The first attempt was to use *t*-BuLi to generate the organolithium reagent **2.90** for synthesizing cuprate compound.[32] Bromide **2.87** was treated with *t*-BuLi and the reaction was monitored by

$^{1}$H NMR. After prolong time stirring in THF at various temperatures, the bromide still stayed unchanged.

**Scheme 2.49 : Attempt on preparation of lithium reagent from bromide 2.87**

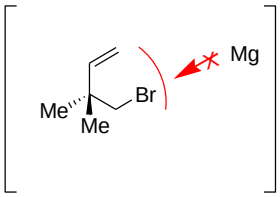



**2.87** **2.90**

Since the cuprate reagent can also be prepared from Grignard reagent, the back-up strategy is to make the corresponding Grignard reagent from bromide **2.87**. However, the ordinary method for the Grignard reagent formation did not work in this case. With iodine or dibromoethane, the reaction was not initiated.

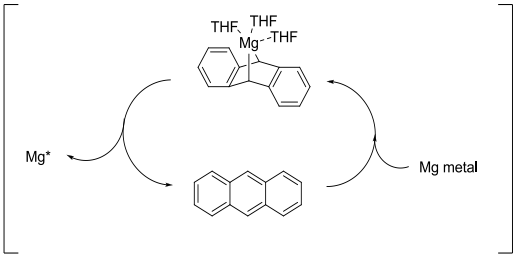
All the failures of the reactions lie on the high stability of bromide **2.87** which may be given by the gem-dimethyl groups. These gem-dimethyl groups in **2.87** shields the bromide against the approach of the metal (Figure 2.14).

**Figure 2.14 : Steric effect from the gem-dimethyl group**



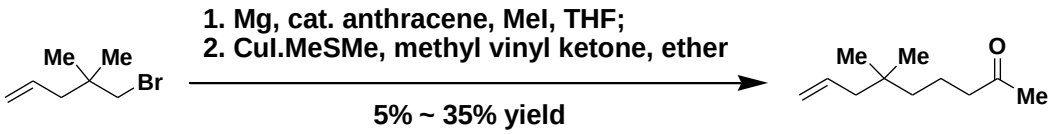

To solve this problem, one of the possible methods was to use the activated magnesium[33] to prepare the Grignard reagent. A procedure was published by Bonnemann, H. *et al*. in 1983 for preparing the activated magnesium.[33] Magnesium was stirred with catalytic amount of anthracene and 0.1 eq. of methyl iodide in THF for 14 hours to form highly active magnesium (Scheme 2.50). The process might start with the formation of methylmagnesium iodide which could clean the surface of the metal. Then, anthracene could form the complex with magnesium and THF. This is an equilibrium process, and the complex could decompose to give free magnesium atom and anthracene. This regenerated magnesium is "solvated" in the solvent (THF) and highly reactive. Therefore, after prolong time stirring, metal turnings are smaller in size than before, and magnesium "mud" appeares at the bottom of the flask.

**Scheme 2.50 : Catalytic cycle for the formation of activated magnesium[33]**




With the activated magnesium, Grignard reagent of bromide **2.87** was prepared successfully. The Grignard reagent was introduced to cuprous iodide dimethylsulfide complex[32] to give the dialkyl cuprate reagent. The 1,4-addition of methyl vinyl ketone was furnished with this organocuprate reagent to give desired product **2.86** (Scheme 2.51).

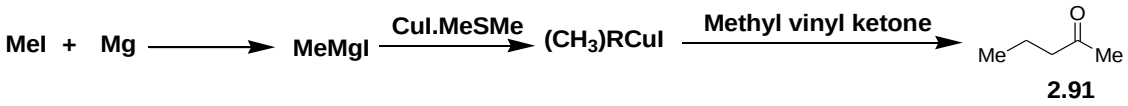
**Scheme 2.51 : Synthesis of 2.86**




**2.87** **2.86**

However, the reaction yields varied from 5% - 35% when reaction scales varied. The reason was explored. For the different qualities of magnesium turnings, it was found that methyl iodide was sometimes needed more than 0.1 eq. to initiate the formation of magnesium*. The generated methyl Grignard reagent remained in the reaction mixture and reacted with cuprous iodide to give dimethyl cuprate which would also undergo a 1,4-addition to methyl vinyl ketone as well (Scheme 2.52).

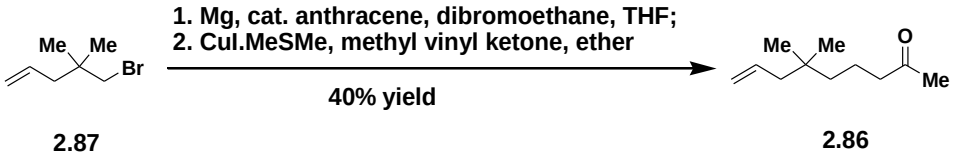
**Scheme 2.52 : Formation of the byproduct 2.91**




**2.91**

Replacement of methyl iodide with dibromoethane solved this problem. Dibromoethane had the same function as methyl iodide and reacted with magnesium gave the ethylene and magnesium bromide which would not affect the subsequent reaction. The reaction yield became repeatable at 40% (Scheme 2.53).

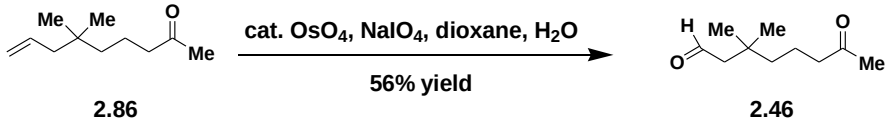
**Scheme 2.53 : Revised procedure for synthesis of 2.86**




**2.87** **2.86**

Transformation from olefin ketone **2.86** to ketone aldehyde **2.46** was initially carried out by using ozone oxidation conditions. However, this reaction did not give any desired product but only decomposed compounds. The alternative condition was the osmium tetraoxide ($OsO_4$) and sodium periodate ($NaIO_4$) olefin oxidative cleavage reaction.[34] $OsO_4$ could oxidize olefin into 1,2-diol, and the diol is cleaved and oxidized by $NaIO_4$ to give desired aldehyde ketone **2.46**.

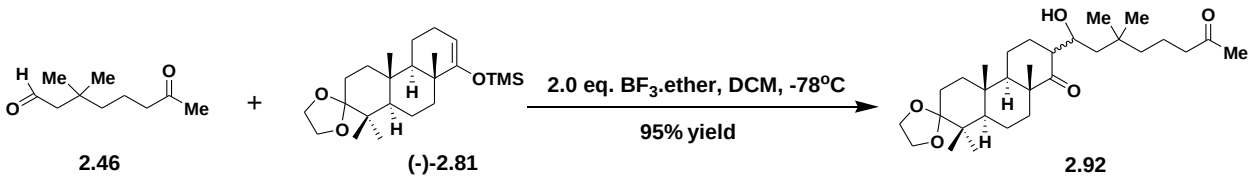
**Scheme 2.54 : Synthesis of 2.46**




**2.86** **2.46**

The synthesis of **(-)-2.76** was continued with both starting materials ready in hands. Mukaiyama aldol reaction[35] was carried out with enol silyl ether **(-)-2.81** and aldehyde ketone **2.46** in DCM with $BF_3$·ether as the Lewis acid, and alcohol **2.92** was obtained as a mixture of diastereomers. Since two carbonyl groups existed in compound **2.46**, 2.0 eq. of $BF_3$.ether was required to finish the reaction; otherwise, the yield of reaction would drop to half (Scheme 2.55).

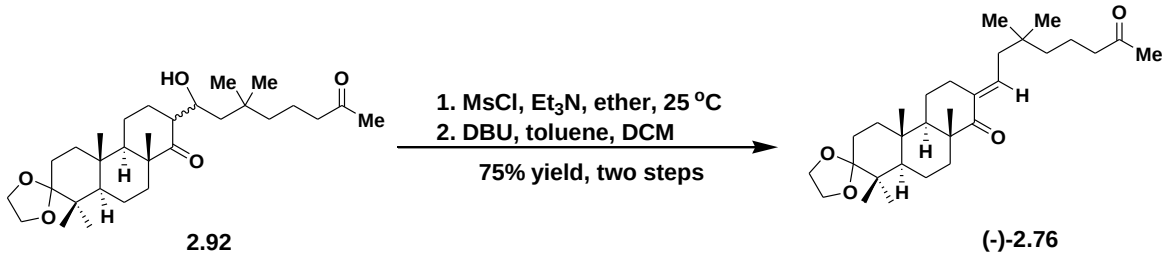
**Scheme 2.55 : Synthesis of 2.92**




**2.46** **(-)-2.81** **2.92**

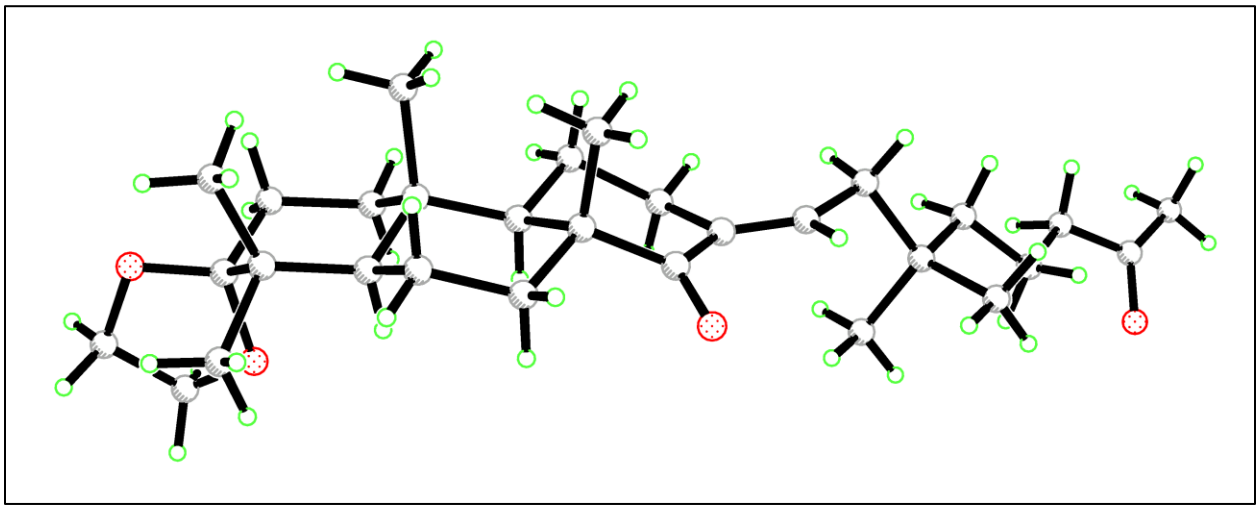
Treatment of **2.92** with methylsulfonyl chloride (MsCl) and triethylamine in diethyl ether gave the corrosponding mesylate. Elimination of the mesylate with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) generated the desired enone ketone **(-)-2.76** in good yield (Scheme 2.56).

**Scheme 2.56 : Synthesis of (-)-2.76**



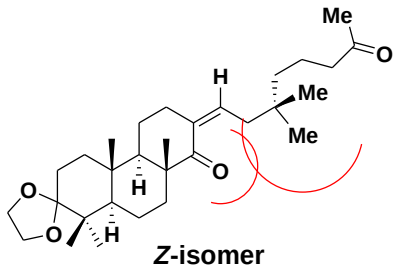

The geometry of the enone in **(-)-2.76** was confirmed by $^{1}$H NMR, NOESY and X-ray analysis to be the E-geometry.

**Figure 2.15 : A single crystal structure of (-)-2.76**



Interestingly, only the *E*-isomer of enone was formed in the elimination reaction. The reason might be the strong steric hindrance between the carbonyl and gem-dimethyl groups in the *Z*-isomer made it difficult to form (Figure 2.16).

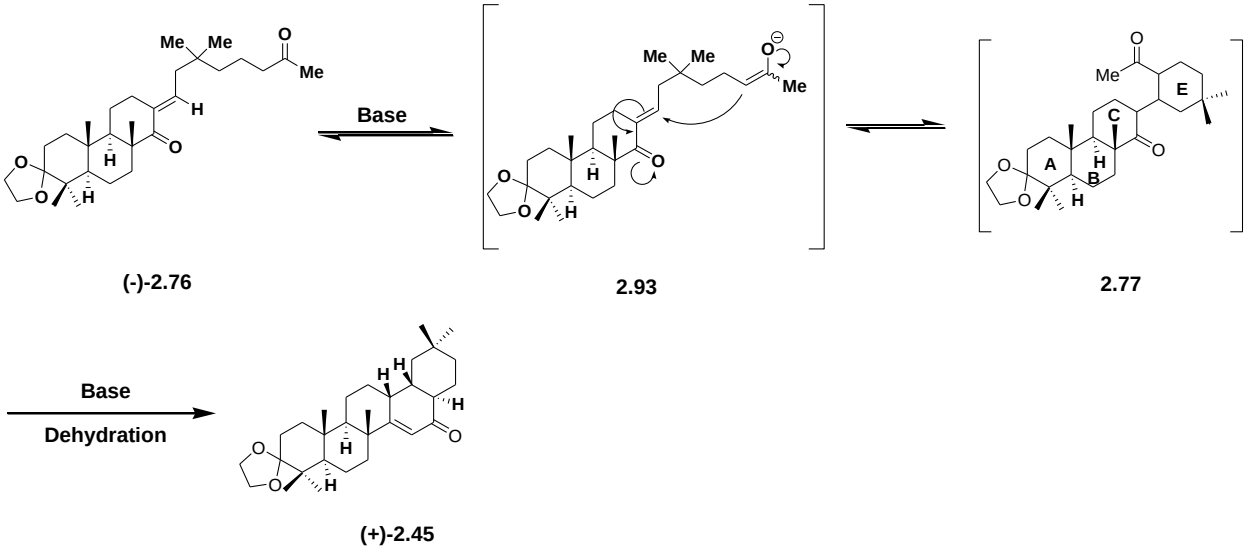
**Figure 2.16 : Steric hindrance between carbonyl and gem-dimethyl in (*Z*)-isomer of 2.76**




Since the enone was successfully prepared, the constructions for D,E-rings were continued. The idea was to use a base to generate the desired enolate **2.93**, and the enolate **2.93** would undergo intramolecular Michael addition to the enone to give **2.77**. In the presence of a

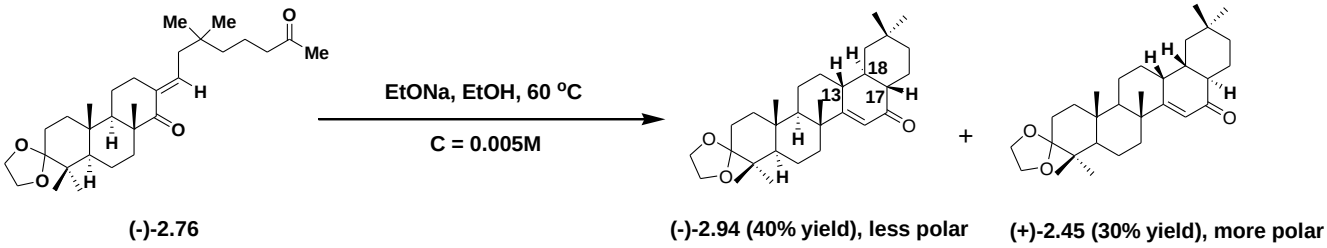
catalytic amount of base, intramolecular aldol condensation of **2.77** proceeded to give pentacyclic compound **(+)-2.45**.

**Scheme 2.57 : Designed annulation for D, E-ring synthesis**




Compound **(-)-2.76** was heated with sodium ethoxide in high-diluted concentration (0.005 M) in ethanol for 14 hours to generate two new compounds with different polarities in TLC. The results of $^{1}H$ NMR and mass spectra indicated that both of them are the annulation products of compound **(-)-2.76** having different stereochemistry at C13, C17 and C18.

**Scheme 2.58 : Annulation reaction of (-)-2.76**



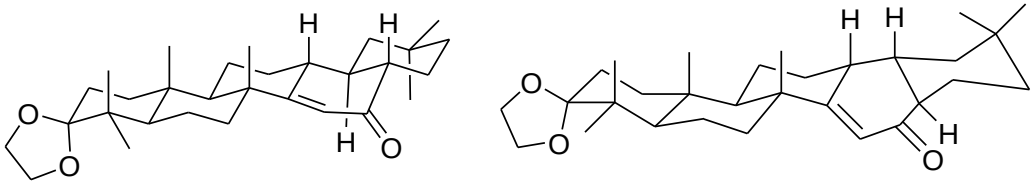

To explain the observation of this reaction and determine the structures of the obtained products were quite challenging.

This domino Michel addition aldol condensation reaction of **(-)-2.76** could generate three new stereo-centers which were at carbon13, 17 and 18 positions; hence, a total number of 8 possible isomers could be formed; but the reaction only gave two of them. The interpretation for this reaction outcome needed to be explored. As mentioned in Scheme 2.9,[12] D-ring could be cyclized only when the C13-H is in axial, and this may work the same in the designed domino

reaction. If this hydrogen was in equatorial and the large substitution stayed in axial, there will be great steric hindrance against the C8-methyl group. Under thermodynamic condition, the C13-H would stay in the axial position to give more stable conformation.[12] For C18-H, it is the least acidic proton among the three, and the conformation of C18-H cannot be changed once E-ring is cyclized. C17-H is the most acidic proton in the final product and could be epimerized easily in ethanol in the presence of sodium ethoxide, and, under thermodynamic conditions, C17-H would stay in the conformation which made the whole system had lowest conformational energy. Therefore, for one possible conformation of C18-H, C17-H would only stay in one conformation which gives the lowest conformational energy of the whole structure. To sum up, under the reaction conditions, C13-H has to stayed in axial to furnish the annulation of D-ring; C18-H in the annulation products could stay in axial or equatorial; the conformation of C17-H relies on the conformation of C18-H. Hence, only two isomers were generated under the reaction conditions.

The next issue was to determine the exact structures of the obtained isomers. Assuming most of the fused six member rings were in chair conformation to maintain the lowest energy of the system, two structures could be constructed and shown in Figure 2.17. One isomer had 13-H(a), 17-H(a) and 18-H(e) conformation, and the other had 13-H(a), 17-H(e) and 18 (a). In myriceric acid A, the 18-H is in axial position; hence, only one isomer [13-H(a), 17-H(e) and 18 (a)] is useful for the continued synthesis of myriceric acid A.

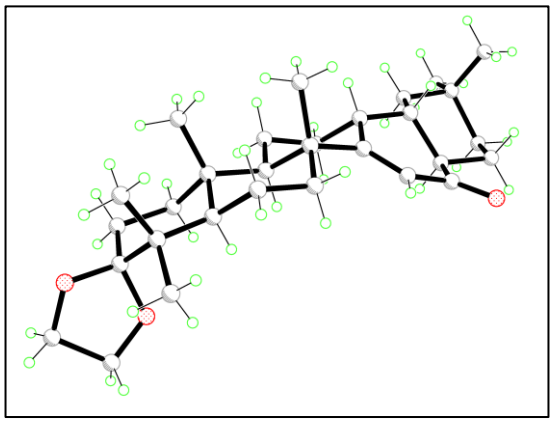
**Figure 2.17 : Possible structures of obtained annulation products**




**Structure 1** **Structure 2**

To assign the structures of each isomer was also difficult. NMR methods, such as $^{1}H$ NMR, COSY, NOESY, do not work on this case because the peak of 18-H is merged with other protons' signals. Luckily, single crystals of the more polar isomer were obtained. A successful X-ray analysis was carried out and gave the crystal structure of the more polar isomer (Figure 2.18).

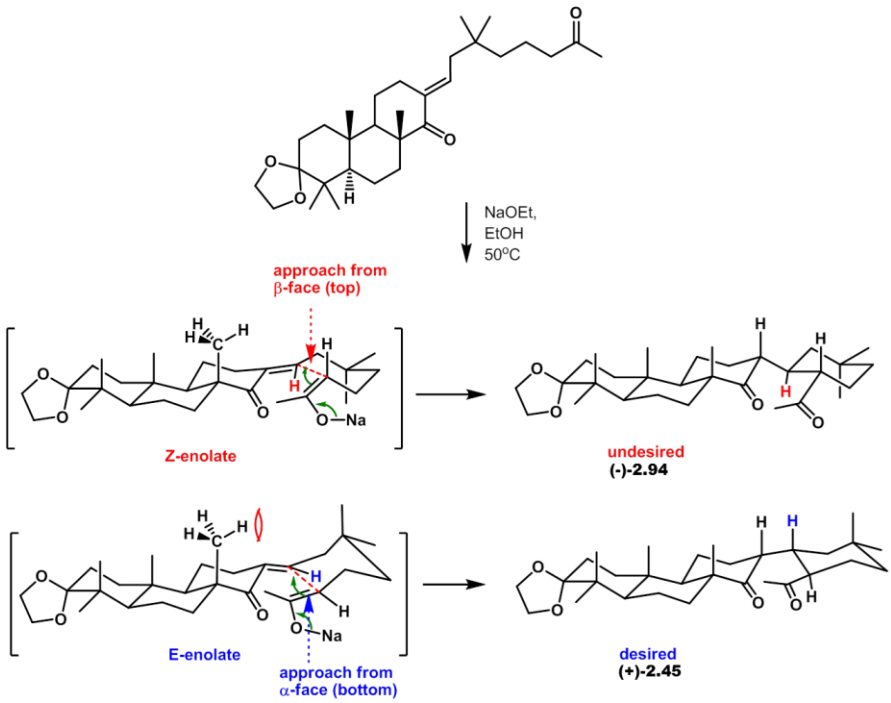
**Figure 2.18 : Crystal structure of more polar (+)-2.45 from X-ray analysis showing it to be the desired isomer**



The structure of **(+)-2.45** which is same as the proposed structure 2 in Figure 2.17 is confirmed as the desired product, and the structure 1 should belong to less polar compound **(-)-2.94**, the undesired isomer.

Since the structures of the obtained products are all assigned, the detailed mechanisms of the formations of these products are investigated to explain the preference of the formation of undesired **(-)-2.94**. When the α-H of side-chain ketone is abstracted, two types of enolates, *Z*- and *E*- enolates, could be formed. *Z*-enolate would prefer to approach the enone from its β-face (top) because of the less steric hindrance to give undesired product **(-)-2.94**; while the *E*-enolate has difficulty in approaching from the β-face because of the steric hindrance between the methyl group of the enolate and C8-methyl group on the C-ring. Therefore, *E*-enolate could only approach the enone from its α-face (bottom side) to give desired pentacyclic product **(+)-2.45**. For the methyl ketone in **(-)-2.76**, the *Z*-enolate was slightly favored to be formed because it has less steric hindrance comparing with *E*-enolate; hence, more undesired annulation product is formed.

**Scheme 2.59 : Detailed mechanisms for the formations of (-)-2.94 and (+)-2.45**




In summary, attempts on the construction of pentacyclic compound **(+)-2.45** via intermolecular Michael addition strategies were not successful. To overcome the problem, ketone aldehyde **2.46** was prepared and used to synthesize the desired compound **(-)-2.76** as the starting material for the intramolecular Michael addition-aldol condensation reaction which finally gave the desired pentacyclic compound. The mechanism of this reaction was investigated as well.

## 2.6 Functionalization of D-ring

In this section, the progress on the functionalization of D-ring in compound **(+)-2.45** to finish the total synthesis of myriceric acid A is introduced and discussed (Scheme 2.60).

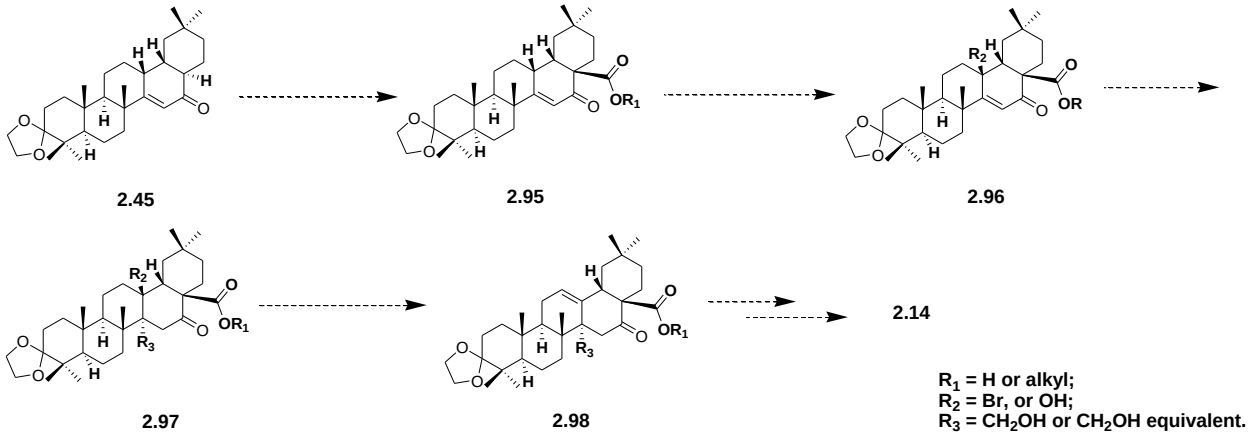
**Scheme 2.60 : Functionalization of D-ring to finish total synthesis of myriceric acid A**

**2.14** **(+)-2.45**

The strategy for the transformation the compound **(+)-2.45** into final target compound **2.14** is rationally designed. Firstly, advantages of using compound **(+)-2.45** to prepare target

molecule **2.14** are fully explored. The enone moiety in compound **(+)-2.45** activates all the necessary position to facilitate the introductions of required functional groups. As the α-H of enone, C17-H is the mostly activated to introduce carboxylic group via enolate (kinetic) chemistry; C13-H is the γ-H of enone which could be functionalized to furnish the formation of olefin double bond by either enolate chemistry or allyl system chemistry; Michael addition on this enone moiety could accomplish the installation of the hydroxyl methylene groups at C14 via few steps. Secondly, the sequence of installations of the functional groups is considered. Since the C17-H is the most acidic proton and could be selectively deprotonated, the installation of carboxylic group should be given the first priority. Functionalization of C13-H requires the existence of enone; so, the second priority should be given to the manipulation of C13-H to alkene. Michael addition of enone could be given the third priority. A few steps of functional group inter-conversion would give the desired compound **2.14**. To sum up, the designed reaction sequence is depicted in Scheme 2.61.

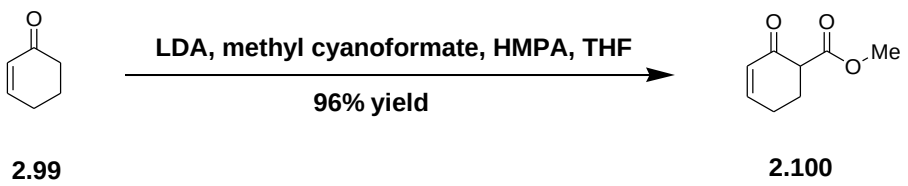
**Scheme 2.61 : Designed reaction sequence for preparing compound 2.14**




Following the proposed strategy, the C17-carboxylic group was firstly introduced.

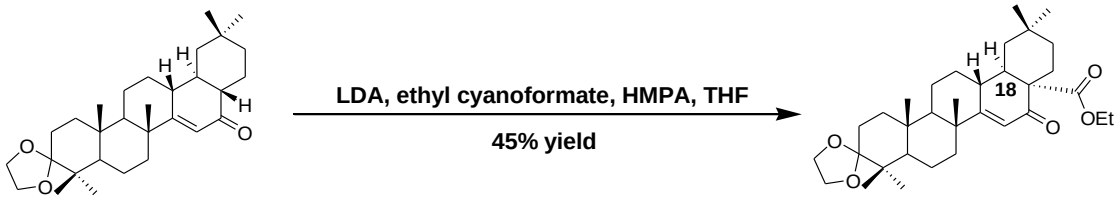
Mander and Sethi reported a method for the regio-selective synthesis of β-ketoester from lithium enolate by using alkyl cyanoformate.[36]

**Scheme 2.62 : Regioselective synthesis of β-ketoester from lithium enolate[36]**



The undesired pentacyclic compound **(-)-2.94** was firstly used for the model study. LDA was used as the base to deprotonated the α-H of the enone in compound **(-)-2.94**, and hexamethylphosphoramide (HMPA) was added to increase the activity of enolate by chelating with lithium. Ethyl cyanoformate was finally introduced to give the compound **(+)-2.101** in moderate yield (Scheme 2.63).

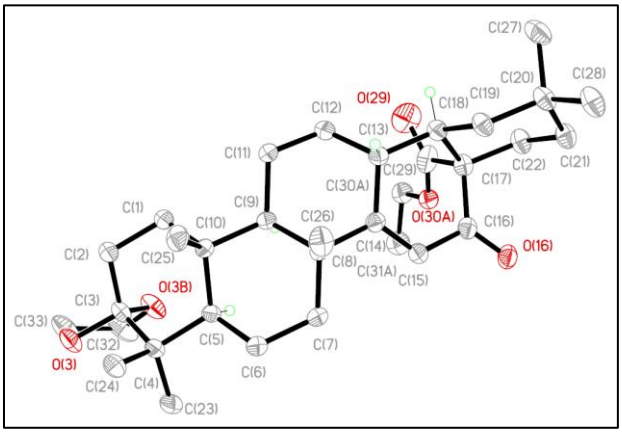
**Scheme 2.63 : Model study of the synthesis of β-ketoester with (-)-2.94**




**(-)-2.94** **(+)-2.101**

The exact structure of compound **(+)-2.101** was confirmed by $^{1}$H NMR, $^{13}$C NMR and X-ray analysis of its single crystal (Figure 2.19).

**Figure 2.19 : Crystal structure of (+)-2.101 from X-ray analysis**



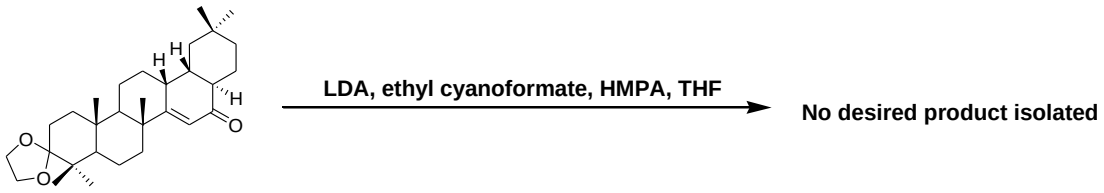

The X-ray analysis result of **(+)-2.101** confirmed our postulation about the structure of compound **(-)-2.94**: the conformation of C13-H is in axial and the conformation of C18-H is in equatorial. The conformation of C17-H in **(-)-2.94** could not be determined since it was no-longer exist in **(+)-2.101**; however, the real conformation of C17-H in **(-)-2.94** is not important because it is destroyed in the deprotonation step eventually.

In compound **(-)-2.101**, the C17-ethyl ester group stays in axial which is the *cis*-conformation of the C18-H. This conformation indicates that the ethyl cyanoformate approaches the enolate from the less hindered side which in this structure is the same side as C18-H. In other words, via this reaction, the conformation of formed ethyl ester depends on the conformation of

C18-H. Therefore, if the C18-H is pointing up, the ester would also pointing up which is the desired conformation of C17-ester group.

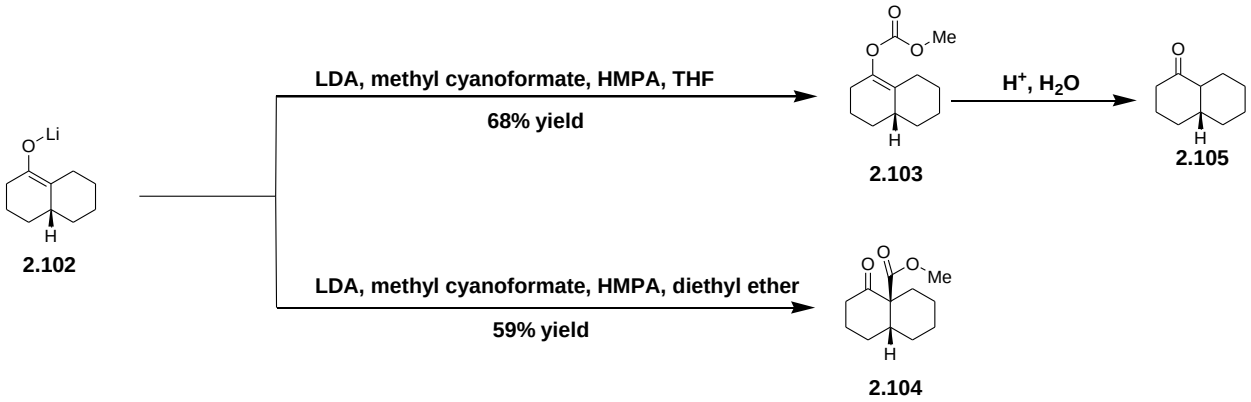
Since this reaction condition worked well in the model study, compound **(+)-2.45** was then treated with LDA, HMPA and ethyl cyanoformate under this condition in THF. However, the reaction outcome was unexpected. Before quenching the reaction with $NH_4Cl$, TLC showed no **(+)-2.45** left but a new less polar spot; however, after the work up, only **(+)-2.45** was detected on the TLC (Scheme 2.64).

**Scheme 2.64 : Synthesis of β-ketoester with (+)-2.45 in THF**




The unsuccessful application of cyanoformate in synthesis of β-ketoester from a steric hindered enolate was also reported by Mander and Sethi in 1990.[37] It was mentioned that O-alkylation is favored to give undesired enol carbonate ester when THF is used as solvent for this type of reaction. This enol carbonate ester is not stable and readily hydrolyzed under acidic condition. The solution for this problem is to use diethyl ether instead of THF as the solvent for the reaction (Scheme 2.65).

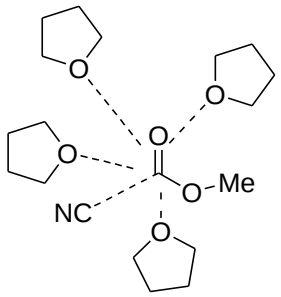
**Scheme 2.65 : Synthesis of β-ketoester with methyl cyanoformate in ether and THF[37]**




The reason might be the reactivity differences of the cyanoformate in different solvents. Comparing with diethyl ether, THF is a better coordinating solvent because of its cyclic structure, and cyanoformate is more "solvated" in THF, which made it a "harder" electrophile (Figure

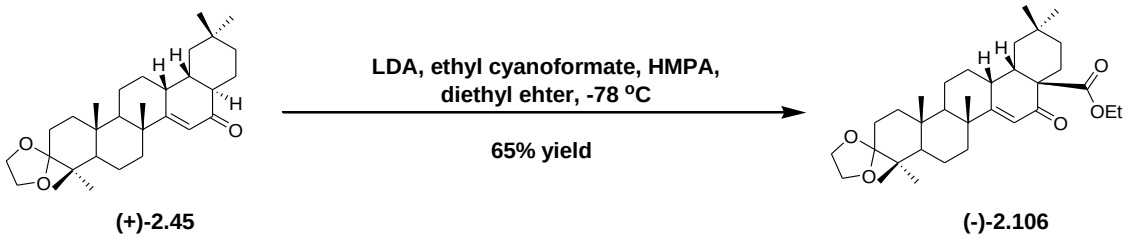
2.20). When enolate orients in a hindered environment, the "hard" electrophile has a better chance to attack the oxygen because it is a "hard" nucleophile and easy to approach as well.

**Figure 2.20 : More "solvated" cyanoformate in THF**




Although the exact reason of the failed synthesis of desired β-ketoester is not confirmed as the formation of enol carbonate, this revised procedure was tried. Compound **(+)-2.45** was then treated with LDA, HMPA and ethyl cyanoformate in diethyl ether. Fortunately, the desired compound **(-)-2.106** was obtained in a good yield (Scheme 2.66).

**Scheme 2.66 : Synthesis of β-ketoester (-)-2.106**




The formation of β-ketoester in **(-)-2.106** was confirmed by $^{1}H$ NMR, $^{13}C$ NMR, and mass spectrums. However, the exact stereochemistry is still not clear. Compound **(-)-2.106** is oil, therefore the single crystal could not be obtained for X-ray analysis. Considering the formate would approach from the less hindered side of the enolate, it is highly possible that the ester in **(-)-2.106** is in *cis* position of C18-H which is the desired conformation.

The functionalization of **(-)-2.106** is carried out; however, because of the time limit, there is still no progress been made.

## 2.7 Conclusion

The total synthesis of myriceric acid A was continued with a revised synthetic strategy. The traditional method for synthesizing the tricyclic compound could not afford enantio-pure

product; therefore, a new method was developed to stereo-selectively generate the tricyclic compound. The new method started with the TBS protected bicyclic compound **(-)-2.53** and α-trimethylsilylvinyl ethyl ketone via a reductive-Michael addition-silyl hydrolyzation-aldol condensation reaction sequence to give the enantio-pure tricyclic compound **(+)-2.72** in a good yield. After protection of carbonyl group, deprotection of TBS group and oxidation of the alcohol, tricyclic intermediate **(-)-2.33** was synthesized.

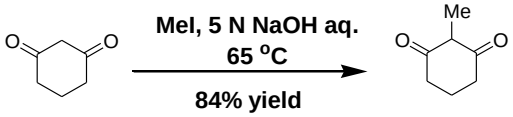
With the enantio-pure tricyclic intermediate ready, the synthesis of pentacyclic intermediate was explored. Initial attempts on the intermolecular Michael addition strategy were not successful because of the steric effect. The intramolecular reaction was designed and used as the alternative method. Ketone aldehyde **2.46** was synthesized over five steps and coupled to the tricyclic compound **(-)-2.81** via Mukaiyama type of aldol condensation reaction. The desired enone-ketone was prepared for the designed intramolecular Michael addition aldol condensation reaction. The desired pentacyclic compound **(+)-2.45** was prepared eventually via the protocol, and the structure was confirmed by X-ray analysis.

Functionalization of the obtained pentacyclic intermediate was started with installation of the 17-carboxylic group. After several attempts, the successful procedure was developed, and the desired pentacyclic carboxyl ester was synthesized in a good yield. Further functionalization of the pentacyclic structure will be pursued.

## 2.7 Experimental Section

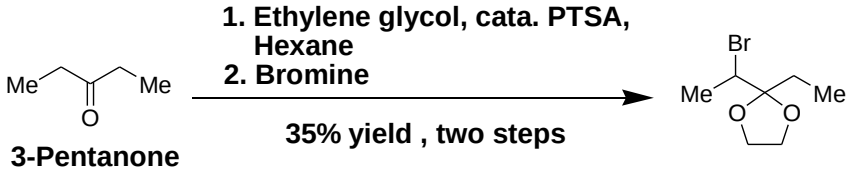
**General procedure:** Melting points were measured on Thomas Hoover capillary melting point apparatus. Nuclear magnetic resonance spectra were obtained at 400 MHz for $^{1}H$ and 100 MHz for $^{13}C$ in deuteriochloroform and reported in ppm, unless otherwise indicated. Solvents and some reagents were dried over $CaH_2$ (DCM, pyridine, $Et_3N$, DMF, diisopropylamine, trimethylsilyl chloride), sodium/benzophenone (THF, ether), magnesium (MeOH, EtOH) and lithium aluminum hydride (toluene, benzene) and distilled under argon. All other reagents were obtained from commercial sources and used without further purification. Reactions were performed under agron unless otherwise indicated.

***2-Methyl-1,3-cyclohexandione.***




1,3-Cyclohexandione (15.0 g, 0.13 mol) was dissolved in 5N NaOH aqueous solution (26 mL, 0.13 mol). The resulted red-brown solution was cooled to 0°C over an ice-water bath. To it at 0°C was added iodomethane (37.0 g, 0.26 mol) slowly. This mixture was heat to 65°C with vigorous stirring for 24 hours and cooled to 25 °C. The white solid was collected by filtration, powderized and washed with 300 mL of hexane and 50 mL of cold water to give white solid as the desired product (13.44 g, 84 % yield) which was sufficiently pure used in the following step. This is a commercial available chemical. The $^1$H NMR is provided herein for reference, and the chemical shifts are identical to that of reported.[13] $^1$H NMR (DMSO-*d*6) δ 10.28 (bs, 1H, enol-OH), 2.28 (m, 4H), 1.81 (m, 2H), 1.53 (s, 3H, -$CH_3$).

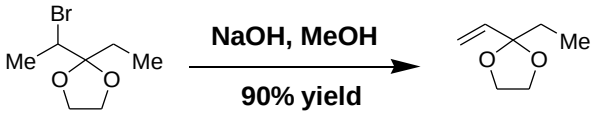
***2-(1-Bromoethyl)-2-ethyl-1,3-dioxolane (2.47).*** [14,15]




**3-Pentanone** **2.47**

3-Pentanone (86.0 g, 1.0 mol), ethylene glycol (70.0 g, 1.1 mol) and PTSA (20 mg, 0.12 mmol) in 100 mL hexane were heated to reflux with Dean-Stark to remove water for 48 hours. To the resulting light brown color solution was added 500 mL of ethylene glycol. This mixture was cooled to 35°C, and bromine (140 g, 0.75 mol) was added dropwisely via a dropping funnel to maintain the reaction temperature below 40 °C. The stirring continued for 15 minutes after the addition of bromine, and the reaction mixture was directly extracted with hexanes (200mL×3). $Na_2CO_3$ (20.0 g) was added to the combined hexane extract, stirred with for 10 minutes, and filtrated off. The hexane was removed over rotavapor, and the product was distilled under vacuum (1~2 torr., b.p.: 49 – 53 °C) to give a colorless liquid 48 g (35% yield). $^1$H NMR δ 4.16 (q, *J* = 6.8 Hz, 1H, BrC-H), 4.09 – 4.03 (m, 4H), 1.99 (m, 1H), 1.79 (m, 1H), 1.68 (d, *J* = 6.8 Hz, 3H), 0.92 (t, *J* = 7.6 Hz, 3H).

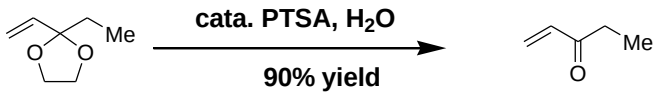
***2-Ethyl-2-vinyl-1,3-dioxolane (2.48).***[15]




**2.47** **2.48**

Compound **2.47** (48.0 g, 0.23 mol) was mixed with sodium hydroxide (32.2 g, 0.8 mol) in 70 mL MeOH under argon. This mixture was heated to reflux for 24 hours. To the cooled reaction mixture was added 150 mL of water and extracted with ether (200 mL×2). The combined organic layer was washed with water (200 mL×2), brine and dired over $MgSO_4$. The ether was removed under vacuum to give 26.1 g of desired product **2.48** (90% yield). $^1$H NMR δ 5.73 (dd, *J* = 17.2, 10.4 Hz, 1H), 5.36 (dd, *J* = 16, 1.6 Hz, 1H), 5.17 (dd, *J* = 10.8, 1.6 Hz, 1H), 3.97 – 3.87 (m, 4H), 1.73 (q, *J* = 7.2 Hz, 2H), 0.93 (t, *J* = 7.2 Hz, 3H).

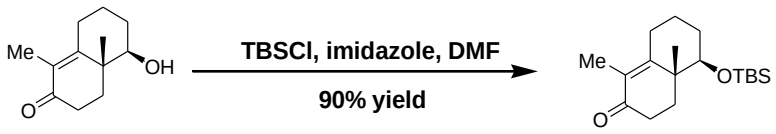
***Ethyl vinyl ketone.***[14]




**2.48** **Ethyl vinyl ketone**

Compound **2.48** (26.1 g, 0.20 mol), PTSA (0.2 g, 0.01 mmol) was stirred in 30 mL water at 25 $^o$C under argon for 10 hours. The organic layer was separated and dried over $Na_2SO_4$ to give 15.2 g of pure ethyl vinyl ketone (90% yield). This is a commercial available chemical. The $^1$H NMR is provided here for reference and is identical to that of the commercial mateiral. $^1$H NMR δ 6.36 (dd, *J* = 16.8, 10.4 Hz, 1H), 6.23 (dd, *J* = 16.8, 1.2 Hz, 1H), 5.82 (dd, *J* = 10.4, 1.2 Hz, 1H), 2.62 (q, *J* = 6.8 Hz, 2H), 1.11 (t, *J* = 6.8 Hz, 3H).

***(-)-(4aR,5R)-5-(tert-butyldimethylsilyloxy)-1,4a-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one [(-)-2.53]. (JL-11-057)***

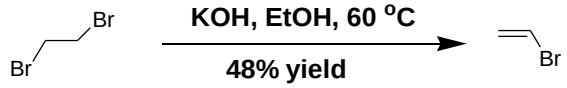



**(-)-2.29** **(-)-2.53**

To **(-)-2.29** (400 mg, 2.06 mmol) and imidazole (272 mg, 4.0 mmol) in 15 mL dry DMF under argon at 25 $^o$C was added TBSCl (467 mg, 3.1 mmol) at once. Then this mixture was stirred overnight. The reaction mixture was diluted with 50 mL aq. $NH_4Cl$ and extracted with

ethyl acetate (50 mL×3). The combined organic layer was washed with water, brine, dried over $MgSO_4$. Ethyl acetate was concentrated off by rota-vapor, the residue was loaded on silica gel column which was eluted firstly with 200 mL hexane and 150 mL the mixture of hexane and ether (5:1) to recover (-)-2.29 (105 mg) and give **(-)-2.53** (430 mg, 90% yield, calculated based on recovered **(-)-2.29**) as colorless oil. **(-)-2.53** became a white solid after stored in the fridge overnight. $[\alpha]_{24}$= -106$^o$, (c = 0.345 g in 100 mL chloroform); $^1$H-NMR: δ 3.35 (dd, *J* = 10.8, 5.6 Hz, 1H), 2.65 (d, *J* = 14.8 Hz, 1H), 2.42 - 2.38 (m, 2H), 2.09 - 2.00 (m, 2H), 1.88-1.81 (m, 1H), 1.77 (s, 3H), 1.71 - 1.62 (m, 3H), 1.36 - 1.24 (m, 1H), 1.14 (s, 3H), 0.90 (s 9H), 0.04 (d, *J* = 7.2 Hz, 6H); $^{13}$C-NMR ($CDCl_3$) δ 199.4, 161.5, 129.9, 79.2, 42.7, 34.2, 33.9, 30.7, 27.3, 26.1 (3 carbons, *t*-Bu), 22.9, 18.3, 16.2, 11.5, -3.7, -4.7.

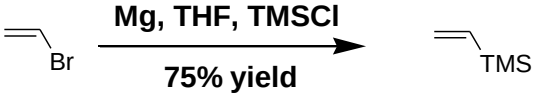
***Vinyl bromide.***




**1,2-dibromoethane** **Vinyl bromide**

KOH (90 g, 1.5 mol), 600 mL Ethanol were added to a three-neck flask which was equipped with distillation apparatus [Long Vigreux column (30 cm), distillation head, long condenser (circulating ice-cold water), distillation adaptor and collection flask which was cooled by dry-ice]. To this mixture was added 1,2-dibromoethane (100 mL, 1.2 mol) over 1 hour via a syringe pump at 40 $^o$C under argon. Vinylbromide was distilled out (b.p. = 16 $^o$C) at 60 $^o$C under argon. The crude product was redistilled over $CaSO_4$ to give dry vinyl bromide 61 g (48% yield). Obtained vinyl bromide should stor at -78$^o$C all the time.

***Vinyl trimethylsilane.***

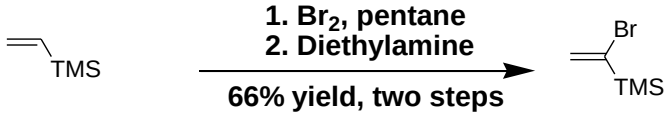



**Vinyl bromide** **Vinyl trimethyl silane**

To a mixture of magnesium (10 g, 0.42 mol, from Strem Chemical Co.) and catalytic amount of iodine in 300 mL THF was slowly added vinyl bromide (30 g, 0.28 mol). Reaction was initiated by adding about 1 mL of vinyl bromide and heated to reflux by heat gun. After the initiation, the rest of bromide was cannulated into the reaction slowly to maintain a gentle reflux

of THF. After the adding of vinyl bromide, the mixture was stirred at 25 $^{o}$C for 20 mins and heated to reflux for 2 hours to result a brown color solution. The mixture was cooled to 25 $^{o}$C, and distilled TMSCl (30 g, 0.28 mol) in 30 mL THF was added slowly. The mixture was stirred for 2 hours at 25 $^{o}$C, and the product was directly distilled out from the reaction mixture as the azeotrope of THF. This clear distillate was washed with water several times to get rid of THF, and the residue was dried over $Na_2SO_4$ to give vinyltrimethylsilane (21 g, 75% yield) as a colorless liquid. This is a commercial available chemical. The $^{1}$H NMR is provided here for reference, and the chemical shifts are identical to that of reported.[22] $^{1}$H-NMR: δ 6.16 (dd, *J* = 20, 16 Hz, 1H), 5.93 (dd, *J* = 16, 4 Hz, 1H), 5.68 (dd, *J* = 20, 4 Hz, 1H), 0.08 (s, 9H).

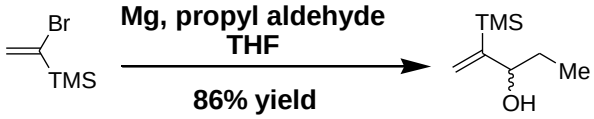
### *α-Trimethylsilyl vinyl bromide (2.70).*[22]




**Vinyl trimethyl silane** **2.70**

To a stirred solution of vinyltrimethylsilane (36 g, 0.36 mol), at -78$^{o}$C, in 50 mL pentane was added bromine (57.6 g, 0.36 mol) dropwisely under argon. The resulted orange color mixture was stirred at -78 $^{o}$C for 1 hour, diluted with water and extracted with ether (150 mL×3). The combined organic layer was washed with aq. $Na_2S_2O_5$ (to remove any excess amount of bromine), aq. $NaHCO_3$, and brine, and dried over $MgSO_4$. The diethyl ether was concentrated by rota-vapor with a cool water bath (<40 $^{o}$C) to give dibromide product. To this dibromide compound was added diethylamine (53 g, 0.72 mol) at 25 $^{o}$C, and this mixture was stirred for 14 hours. The resulted white diethylamine salt was filtrated off. To the clear filtrate was added additional amount of diethylamine (26 g, 0.36 mol). The reaction was kept stirring for 10 hours and monitored by NMR. When no dibromide compound was detected, the diethylamine salt was filtrate off, and the clear solution was diluted with 300 mL ether. This solution was gently washed with 1 N HCl several times until the pH is neutral, water, brine and dried over $MgSO_4$. The ether was distilled out at 1 atm to give crude product. Distillation of this crude product (1 atm, b.p.: 165 $^{o}$C) finally gave pure **2.70** (42 g, 66% yield) as colorless liquid. $^{1}$H-NMR: δ 6.28 (d, *J* = 1.6 Hz, 1H), 6.19 (d, *J* = 1.6Hz, 1H), 0.02 (s, 9H); $^{13}$C-NMR 139.2, 129.6, -2.2 (3 carbons, $Me_3Si$).

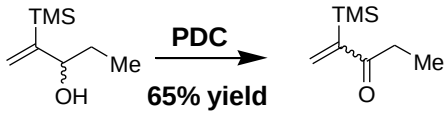
***2-(Trimethylsilyl)pent-1-en-3-ol (2.71).***[22]




**2.70** **2.71**

To a mixture of magnesium (1.4 g, 56 mmol) in 50 mL dry THF was added 0.2 mL of 1,2-dibromoethane, and the mixture was heated to reflux for 3 minutes. Bromide **2.70** (5.0 g, 28 mmol) was added dropwisely. The reaction was initiated by heating with heat gun, and the bromide was slowly added into the mixture it to maintain a gentle reflux. The mixture was stirred at 25 $^{o}$C for 30 minutes, heated to reflux for 1.5 hours and then cooled to -10 $^{o}$C. Distilled propyl aldehyde (2.4 g, 42 mmol) in 10 mL THF was added slowly. Reaction mixture was warmed to 25 $^{o}$C after the addition, stirred for 2 hours and quenched by aq. $NH_4Cl$. The product was extracted out with ether (60 mL×3). Combined organic layer was washed with water, brine, dried over $MgSO_4$. Ether was distilled off at 1 atm, and the crude product was purified on silica gel column by using a mixture of hexane and ether (4:1) as eluent to give **2.71** (3.89 g, 86% yield) as colorless liquid. $^{1}$H-NMR: δ 5.77 (s, 1H), 5.42 (s, 1H), 4.20 (t, *J* = 6.0 Hz, 1H), 1.66 – 1.48 (m, 3H, merged with a broad -OH), 0.91 (t, *J* = 7.2 Hz, 3H), 0.13 (s, 9H); $^{13}$C-NMR 156.3, 124.2, 77.9, 30.2, 10.3, -0.4 (3 carbons, $Me_3Si$).

***α-Trimethylsilyl vinyl ethyl ketone***

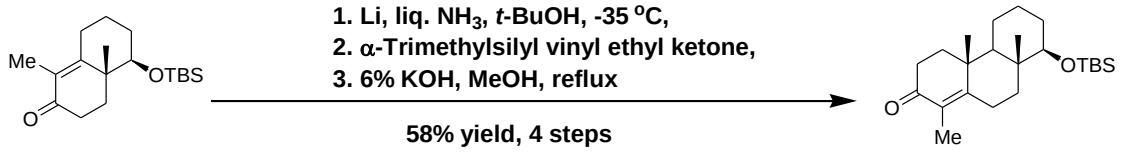



**2.71** **α-trimethylsiyl vinyl ethyl ketone**

To the mixture of PDC (7.7g, 36 mmol) in 50 mL DCM was added 2-(trimethylsilyl) pent-1-en-3-ol (**2.71**) (3.8 g, 24 mmol) in 50 mL of DCM slowly at 0 $^{o}$C. The mixture was warmed up to 25 $^{o}$C and stirred for 14 hours. The resulted brown solid was filtrated off through a short silica gel pad, and the silica gel was washed with 20 mL DCM. The combined DCM was distilled off at 1 atm, and the crude product was purified on silica gel column with a mixture of ether and hexane (1:4) was eluent to give desired product 2.28 g (61 % yield) as yellow liquid. .

$^1$H-NMR: δ 6.45 (d, *J* = 1.6 Hz, 1H), 6.09 (d, *J* = 1.6 Hz, 1H), 2.66 (q, *J* = 7.2 Hz, 2H), 1.08 (t, *J* = 7.2 Hz, 3H), 0.16 (s, 9H); $^{13}$C-NMR 207.2, 154.1, 135.1, 31.8, 8.3, -1.2 (3 carbons, $Me_3Si$).

***(+)-(4aR,8R,8aR)-8-(tert-Butyldimethylsilyloxy)-1,4a,8a-trimethyl-4,4a,4b,5,6,7,8,8a,9,10-decahydrophenanthren-2(3H)-one [(+)-2.72].(JL-12-059)***

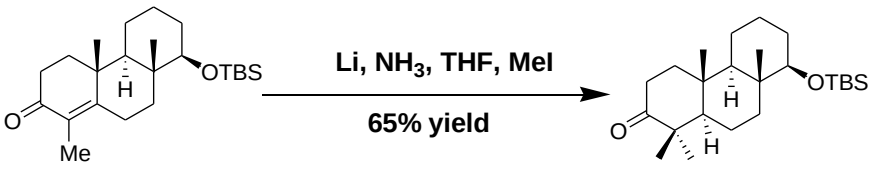



**(-)-2.53** **(+)-2.72**

To liquid $NH_3$ (40 mL) at -78 °C was added lithium (56 mg, 8.1 mmol). After stirring for 30 minutes at this temperature, a solution of (4aR,5R)-5-(*t*-butyldimethylsilyloxy)-1,4a-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one [**(-)-2.53]** (1.0 g, 3.2 mmol) and *t*-butanol (179 mg, 2.56 mmol) in 10 mL dry ether was injected. Then this mixture was refluxed at -35 °C for 2 hours. A few drops of isoprene (freshly distilled over sodium) were injected to quench the excess amount of lithium. Liquid $NH_3$ was evaporated off at room temperature, and the residue was connected to the high vacuum at 40°C for 10 minutes. The resulting white residue was dissolved in 40 mL dry ether again, cooled to -78°C and protected from light by covering with a black cloth. α-Trimethylsilylvinyl ethyl ketone (0.75 g, 4.8 mmol) in 10 mL dry ether was added into this mixture over 30 minutes by syringe pump. The reaction mixture was warmed up to -40 °C and allow the temperature gradually warmed up to -10 °C over 2 hours with stirring. $NH_4Cl$ aq. was added into this mixture, and extracted with ethyl acetate (60 mL×3). The combined organic layer was washed with water, and concentrated off under reduced pressure. The residue was dissolved with 100 mL methanol and 20 mL 6% KOH aq., and this mixture was heated to reflux for 2 hours. Acetic acid was added to neutralize excess amount of base, and the methanol was evaporated under a rotary evaporator. The residue was diluted with aq. $NH_4Cl$, extracted with ethyl acetate (60 mL×3). Combined organic layer was washed with water, brine, dried over $MgSO_4$. The crude product was purified by column chromatography using a mixture of hexane and diethyl ether (3:1) to give desired product 680 mg (58% yield) as colorless oil. $[\alpha]_{27}$= +45.2°, (c = 0.25 in chloroform); $^1$H-NMR: ($CDCl_3$) δ 3.06 (dd, *J* = 11.2, 4.8 Hz, 1H), 2.67 (dt, *J* =11.6, 3.2 Hz, 1H), 2.49 – 2.31 (m, 2H), 2.23 (td, *J* = 12.8, 2.8 Hz, 1H), 2.04 - 1.97 (m, 2H), 1.79 (s,

3H), 1.78 – 1.75 (m, 1H), 1.59 – 1.11 (m, 6H), 1.15 (s, 3H), 1.11 – 1.02 (m, 2H), 1.05 (s, 3H), 0.89 (s, 9H), 0.02 (d, $J$ = 1.6 Hz, 6H); $^{13}$C-NMR ($CDCl_3$) δ 199.2, 164.6, 128.4, 81.1, 55.6, 40.0, 39.4, 38.2, 36.5, 33.5, 31.1, 26.1 (3 carbons, *t*-Bu), 24.6, 24.5, 20.6, 18.6, 18.3, 12.5, 11.3, -3.7, -4.6.

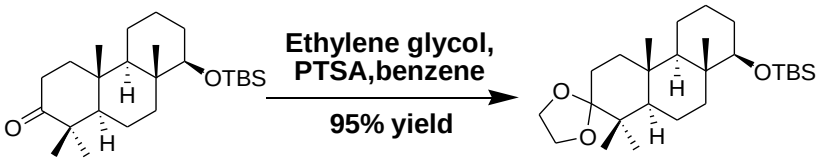
***(+)-(4aR,8R,8aR)-8-(tert-Butyldimethylsilyloxy)-1,1,4a,8a-tetramethyl-decahydrophenanthren-2(1H,3H,4bH)-one [(+)-2.73].(JL-12-087)***




**(+)-2.72** **(+)-2.73**

To liquid $NH_3$ (20 mL) at -78 $^o$C was added lithium (30 mg, 4.3 mmol). After stirring for 30 minutes at this temperature, **(+)-2.72** (400 mg, 1.1 mmol) in 2 mL dry THF was added slowly. Then the mixture was refluxed at -35 $^o$C for 2 hours and cooled to -78 $^o$C degree. Dry THF (35 mL) was injected and the mixture was stirred at -78 $^o$C for 10 minutes. Methyl iodide (1.4 mL, 22 mmol, 20 eq.) was added into the bottom part of the reaction by a long needle. After stirring at -78 $^o$C for 30 minutes, another batch of methyl iodide (1.4 mL, 22 mmol, 20 eq.) was added. This mixture was allowed to warm up to room temperature slowly over 14 hours and diluted with $NH_4Cl$ aq., and extracted with ethyl acetate (40 mL×3). The combined organic layer was washed with water, brine, and dried over $MgSO_4$. The organic layer was concentrated and purified by column chromatography using a mixture of hexane and diethyl ether (10:1) to give desired product 265 mg (65% yield) of **(+)-2.73** as colorless solid. $[\alpha]_{27}$= +8.2$^o$, (c = 0.25 in chloroform); $^1$H-NMR: ($CDCl_3$) δ 3.06 (dd, $J$ = 11.2, 4.8 Hz, 1H), 2.56 – 2.38 (m, 2H), 1.96 - 1.90 (m, 2H), 1.78 - 1.69 (m, 1H), 1.55 - 1.17 (m, 11H), 1.08 (s, 3H), 1.04 (s, 3H), 0.94 (s, 3H), 0.90 (s, 3H), 0.89 (s, 9H), 0.03 (6H); $^{13}$C-NMR ($CDCl_3$) δ 218.2, 81.5, 56.7, 55.4, 47.7, 40.4, 39.6, 39.5, 37.0, 34.4, 31.3, 26.8, 26.1 (3 carbons, *t*-Bu), 24.8, 21.3, 20.7, 19.6, 18.3, 16.4, 13.2, -3.7, -4.5.

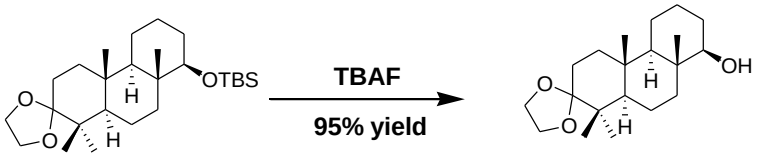
***(-)-(4a'R,8'R,8a'R)-1',1',4a',8a'-8-t-Butyldimethylsilyoxy-tetramethyldodecahydro-1'H-spiro[1,3]dioxolane-2,2'-phenanthren[(-)-2.74].***




**(+)-2.73** **(-)-2.74**

(4a*R*,8*R*,8a*R*)-8-(*tert*-Butyldimethylsilyloxy)-1,1,4a,8a-tetramethyl dodecahydro phenanthren -2 (1H)-one **(+)-2.73** (2.0 g, 5.25 mmol), PTSA (50 mg, 0.3 mmol) and ethylene glycol (3.25 g, 52 mmol) were refluxed in benzene with a Dean-Stark apparatus to remove water for 2 hours. The solution was cooled to room temperature, diluted with aq. $NaHCO_3$, and extracted with ether (50 mL ×3). The combined organic layer was washed with water, brine, and dried over $MgSO_4$. The crude product was purified by column chromatography using a mixture of hexane and ethyl acetate (5:1) to give desired product 2.1 g (95% yield) as a colorless solid. $[\alpha]_{27}$= - 49$^o$, (c = 0.23 in chloroform); $^1$H-NMR: δ 3.97 – 3.87 (m, 4H), 3.05 (dd, *J* = 11.2, 4.8 Hz, 1H), 1.88 – 1.76 (m, 2H), 1.73 – 1.65 (m, 1H), 1.60 (ddd, *J* = 13.2, 7.2, 3.6 Hz, 1H), 1.52 – 1.32 (m, 6H), 1.29 – 1.10 (m, 5H), 1.04 – 0.95 (m, 1H), 0.93 (s, 3H), 0.87 (s, 12 H), 0.86 (s, 3H), 0.84 (s, 3H), 0.00 (s, 6H) ; $^{13}$C-NMR δ 113.6, 81.7, 65.09, 65.07, 57.2, 54.0, 42.4, 40.4, 40.3, 37.3, 37.1, 31.4, 27.1, 26.2 (3 carbons, *t*-Bu), 24.8, 23.1, 20.3, 20.1, 18.4, 18.3, 16.4, 13.6, -3.7, -4.6.

***(-)-(4a'R,8'R,8a'R)-1',1',4a',8a'-Tetramethyldodecahydro-1'H-spiro[[1,3]dioxolane-2,2'-phenanthren] -8'-ol [(-)-2.32].(JL-14-044)***

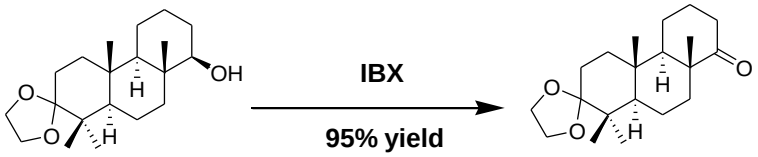



**(-)-2.74** **(-)-2.32**

27 mL of 1.0 M tetrabutylamnium fluoride in THF was diluted with 20 mL dry THF. This solution was pre-dried by 3Å molecular sieves and transferred into *tert*-butyldimethyl((4a'R,8'R,8a'R)-1',1',4a',8a'-tetramethyldodecahydro-1'H-spiro[[1,3] dioxolane -2,2'- phenanthrene]-8'-yloxy)silane [**(-)-2.74**] (2.0 g, 4.6 mmol) in 30 mL dry THF. The resulting

solution was stirred at 60 $^{o}$C under argon for 14 hours, diluted with $NH_4Cl$ aq., and extracted with ethyl acetate (50 mL×3). The combined organic layer was washed with water, brine, dried over $MgSO_4$, and concentrated off under vacuum, and the crude product was purified on silica gel column with a mixture of ether and hexane (1:1) as eluent to give 1.4 g of pure **(+)-2.32** (95% yield) as white solid. $[\alpha]_{25}$= - 45$^{o}$, (c = 0.1 in chloroform; *lit* [24]: $[\alpha]_{25}$= - 44$^{o}$, c = 0.1, 98 %ee); $^{1}$H NMR δ 3.99 – 3.86 (m, 4 H), 3.13 (ddd, *J* = 11.4, 8.4, 4.1 Hz, 1 H), 1.90 – 1.74 (m, 2 H), 1.73 – 1.08 (m, 15 H), 0.93 (s, 3 H), 0.88 (s, 6 H), 0.85 (s, 3 H) ; $^{13}$C-NMR (CDCl3) δ ppm 113.5, 81.4, 65.1, 56.8, 53.8, 42.4, 39.8, 39.4, 37.2, 37.0, 30.4, 27.1, 26.1, 24.8, 23.2, 20.2, 20.1, 18.3, 16.5, 13.3.

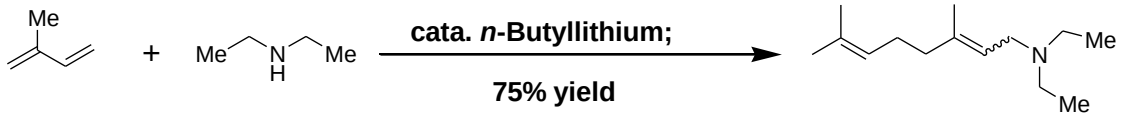
***(-)-(4a'S,8a'R)-1',1',4a',8a'-Tetramethyldecahydro-1'H-spiro[[1,3]dioxolane-2,2'-phenanthren ]-8'(3'H)-one [(-)-2.33].(JL-14-045)***




**(-)-2.32** **(-)-2.33**

To the **(-)-2.32** (240 mg, 0.75 mmol) in 5 mL DMSO was added IBX (208 mg, 0.89 mmol) at 25 $^{o}$C under argon. This solution was stirred for 14 hours. The white participate was filtrated off. The filtrate was diluted with aq. $NaHCO_3$, and extracted with ether (60 mL×3). Combined organic layer was washed with water, brine, and dried over $MgSO_4$ and concentrated under vacuum, and the crude product was purified on silica gel column with a mixture of hexane, DCM, ether (5:3:1) as eluent to give 220 mg of pure **(-)-2.33** (95% yield) as white solid. $[\alpha]_{25}$= - 27$^{o}$, (c = 0.27 in chloroform, 100%ee; *lit.*[24]: $[\alpha]_{25}$= - 26$^{o}$, c = 0.14, 98 %ee); $^{1}$H NMR δ 3.98 – 3.86 (m, 4 H), 2.54 (td, *J* = 14.0, 6.9 Hz, 1 H), 2.18 (dm, 1 H), 2.08 – 2.01 (m, 1 H), 1.82 (td, *J* = 13.9, 4.0 Hz, 1 H), 1.75 – 1.35 (m, 10 H), 1.26 (dd, *J* = 12.3, 2.1 Hz, 1 H), 1.18 (dd, *J* = 11.8, 3.0 Hz, 1 H), 1.14 (s, 3 H), 0.98 (s, 3 H), 0.94 (s, 3 H), 0.84 (s, 3 H); $^{13}$C-NMR δ 215.9, 113.2, 65.1, 65.1, 57.6, 53.2, 49.4, 42.4, 38.3, 37.9, 37.1, 34.7, 27.0, 26.4, 23.1, 20.3, 20.07, 20.04, 18.0, 16.8.

***N, N, -diethylgeranylamine (2.78).***[25]

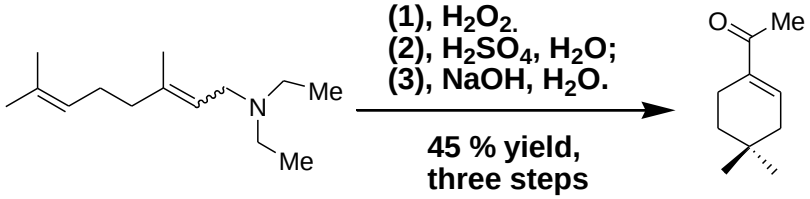



**Isoprene** **Diethylamine** **2.78**

Isoprene was distilled over sodium; and diethylamine was distilled over $CaH_2$ before use.

To a dry sealed tube was added isoprene (20 mL, 0.20 mol) and diethylamine (6 mL, 0.04 mol) at 0 $^oC$ under argon. To this solution was added 1.6 M *n*-BuLi (2.5 mL) to result a light yellow color solution. The tube was capped tightly and heated to 65 $^oC$ 12 hours. The reaction mixture was cooled to 0 $^oC$, and 15 mL of water was added to quench the reaction. The mixture was extracted by ether (20 mL×2), and the combined organic layer was dried over $MgSO_4$. The ether was concentrated under vacuum, and the crude product was purified by vacuum distillation (b.p: 90 – 95 $^oC$, 3 torr.) to give pure amine 5.65 g (75% yield) as colorless oil. $^1H$ NMR δ 5.24 (t, *J* = 6.8 Hz, 1H), 5.09 (s, 1H), 3.04 (dd, *J* = 7.2, 1.2 Hz, 2H), 2.49 (q, *J* = 6.0 Hz, 4H), 2.04 (d, *J* = 3.2 Hz, 4H), 1.71 – 1.60 (m, 9H), 1.01 (*t*, *J* = 6.0 Hz, 6H).

***1-(4,4-dimethylcyclohex-1-enyl)ethanone (2.75).***[26]

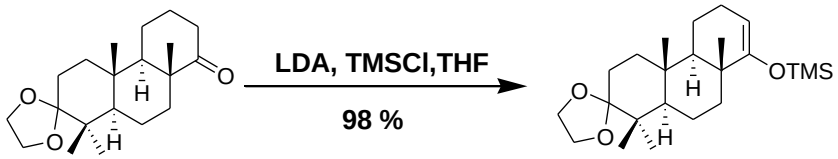



**2.78** **2.75**

A 50 % of hydrogen peroxide aqueous solution was added to compound **2.78** (1.05 g, 5 mmol) in 10 mL methanol at 25 $^oC$. This solution was stirred for 48 hours. Then $PtO_2$ (3 mg) was added to the reaction solution and stirred for 2 hours to destroy the excess amount of hydrogen peroxide. Removal of the methanol to give desired *N*-oxide. The N-oxide residue was diluted with 500 mL $H_2O$. To this diluted solution was added 10 mL of 50 % $H_2SO_4$, and the mixture was heated to 100 $^oC$ for 24 hours and cooled to 0 $^oC$ with ice bath. To the resulted light brown solution was added 10 g of NaOH in 20 mL water. This mixture was heated to 100 $^oC$ for 24 hours and cooled to 25 $^oC$. The excess amount of NaOH was neutralized with 10 % HCl, and the product was extracted with ether (100 mL×3). The combined organic layer washed with water,

brine, dried over $MgSO_4$, and distilled at 1atm to remove ether, and the crude product was purified on silica gel column with a mixture of hexane and ether (1:1) as eluent to give 340 mg of pure **2.75** (45 % yield) as colorless oil with pleasant ordor. $^1$H NMR δ 6.82 (m, 1H), 2.31 (s, 3H, -$CH_3$), 2.26 – 2.24 (m, 2H), 2.05 – 2.03 (m, 2H), 1.41 (t, *J* = 4.8 Hz, 2H), 0.8 (s, 6H).

***(-)-Trimethyl((4a'R,8a'R)-1',1',4a',8a'-tetramethyl-3',4',4a',4b',5',6',8a',9',10',10a'-decahydro-1'H-spiro[[1,3]dioxolane-2,2'-phenanthrene]-8'-yloxy)silane [(-)-2.81].***

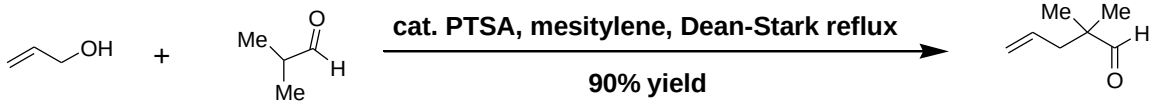



**(-)-2.33** **(-)-2.81**

Trimethylsilyl chloride (TMSCl) was distilled twice over $CaH_2$, and to the distilled TMSCl was added distilled $Et_3N$ (volume ratio: TMSCl : $Et_3N$ = 7 : 1). The mixture was centrifuged for 2 minutes, and the clear supernatant was used for the reaction.

To the solution of diisopropylamine (0.05 mL, 0.35 mmol) in 1.5 mL dry THF was added 1.6 M *n*-BuLi (0.21 mL, 0.33 mmol) at -78 $^o$C under argon. The solution was stirred for 30 minutes and transfered into compound **(-)-2.33** (100 mg, 0.33 mmol) in 2 mL THF at -78 $^o$C under argon. The mixture was warmed up to 25 $^o$C, stirred for 2 hours and cooled to -78 $^o$C. To it was added TMSCl (0.136 mL, 1 mmol), and the mixture stirred at -78 $^o$C for 30 minutes. The reaction was diluted with 5% aqueous $NH_4OH$ solution, extracted with ether (20 mL×3). The combined organic layer washed with water, brine and dried over $Na_2SO_4$. The combined ether was distilled under vacuum, and the crude product was chromatographed on silica gel column with a mixture of hexane, DCM and ether (5:3:1) as eluent to give 110 mg of pure **(-)-2.81** (98 % yield) as white solid. $[\alpha]_{25}$= - 32$^o$, (c = 0.55 in chloroform); $^1$H NMR δ 4.50 – 4.87 (m, 1H), 3.98 – 3.87 (m, 4H), 2.06 – 1.78 (m, 4H), 1.67 – 1.11 (m, 10H), 1.05 (s, 3H), 0.93 (s, 3H), 0.88 (s,3H), 0.83 (s, 3H), 0.15 (s, 9H); $^{13}$C-NMR δ 159.0, 113.6, 100.0, 65.1 (2 carbons, acetal), 55.9, 53.8, 42.5, 39.6, 37.1 (2 carbons, gem-dimethyl), 36.9, 27.1, 24.9, 23.1, 20.9, 20.0, 18.5, 17.9, 16.7, 0.6 (3 carbons. TMS).

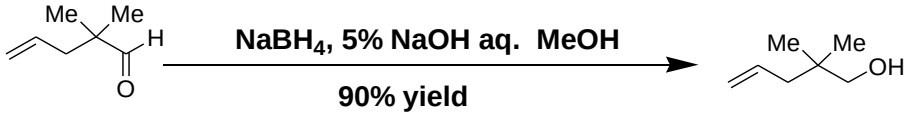
***2,2-Dimethylpent-4-enal (2.89).***




**Allyl alcohol** **Isobutyraldehyde** **2.89**

Allyl alcohol (21.7g, 0.375 mol), isobutyraldehyde (40.5 g, 0.56 mol) and *p*-toluenesulfonic acid(0.125g, 6.5 mmol) in mesitylene (70 mL)was heated at 220 $^{o}$C by heating mental for 48 hours with Dean-Stark apparatus and a long Vigreux column (30 cm). The product was distilled at 1 atm to give 40 g (90 % yield) as colorless liquid. (The product was distilled out as the azeotrope of mesitylene which can be separated at next step); $^{1}$H NMR δ 9.50 (s, 1H), 5.77 – 5.67 (m, 1H), 5.11 – 5.06 (m, 2H), 2.23 (d, *J* = 7.6 Hz, 2H), 1.07 (s, 6H).

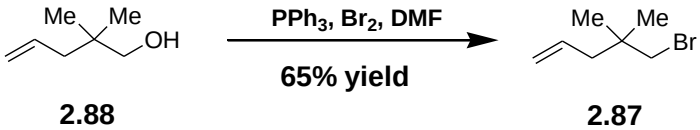
***2,2-Dimethylpent-4-en-1-ol (2.88).***




**2.89** **2.88**

The sodium borohydride (4.8 g, 0.132 mol) in 60 mL 0.2 M NaOH aq. solution was added slowly in to a solution of aldehyde **2.89** (40 g, 0.35 mol) inMeOH (400 mL) over 30 minutes. It was stirred at 25 $^{o}$C for 10 hours. The MeOH was distilled off, and the residue was diluted with $NH_4Cl$ aq., extracted with ether (100 mL×3). The combined organic layer was washed with water, brine, and dried over $MgSO_4$. The ether was removed under reduced pressure, and the residue was purified by column chromatography with pure hexane and the mixture of hexane ether (1:1) to give pure product as colorless oil (38 g, 90% yield); $^{1}$H NMR δ 5.94 – 5.82 (m, 1H), 5.07 – 5.04 (m, 2H), 3.34 (s, 2H), 2.03 (d, *J* = 8.0 Hz, 2H), 0.89 (s, 6H).

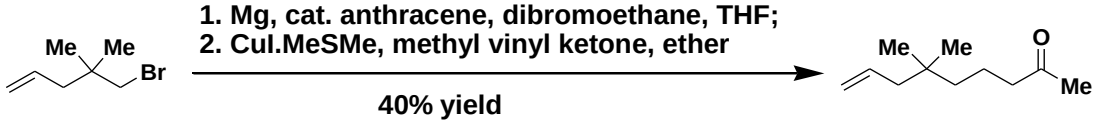
***5-Bromo-4,4-dimethyl-pent-1-ene (2.87).***[31]




**2.88** **2.87**

Bromine (7.7 g, 48.8 mmol) was added to triphenylphsophine (12 g, 45.9mmol) in 30 mL DMF (dried over 3 Å molecular sieve), and the mixture was stirred for 30 minutes. To it, a solution of alcohol **2.88** (5.0 g, 43.8 mmol) in 30 mL DMF was added slowly. The resulting black solution was heated to 130 $^{o}$C for 2 hours, cooled to 25 $^{o}$C and diluted with 70 mL water. The mixture was extracted with pentane (60 mL×10), and the combined organic layer was washed with water, brine, and dried with $MgSO_4$. The pentane was distilled off at 1 atm, and the product was distilled from this residue at 180 $^{o}$C to give a colorless liquid with pleasant odor (4.5 g, 65 % yield).$^{1}$H NMR δ 5.83 – 5.72 (m, 1H), 5.12 – 5.07 (m, 2H), 3.28 (s, 2H), 2.11 (d, *J* = 7.4 Hz, 2H), 1.02 (s, 6H).

***6,6-Dimethylnon-8-en-2-one (2.86).***




**2.87** **2.86**

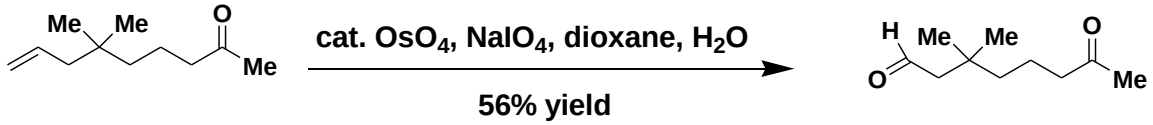
[Activation of magnesium: If the magnesium is not new purchased, it should be activiated by the following procedure: the metal was washed with 1 N HCl several times until a shiny surface appeared, then washed with distilled water several times to remove excess acid; the washed magnesium could be transferred into a Hirsh funnel (without filtering paper) and wash with water, THF and dried under high vacuum for 1 hour with heating to give activiated magnesium]

To a mixture of magnesium (7.0 g, 227 mmol), anthracene (1.0 g, 5.6 mmol) in 100 mL of dry THF under argon was added 1,2-dibromoethane (0.5 mL, 5.7 mmol), and this mixture was heated to reflux with heat gun for 5 minutes. After cooling to 25 $^{o}$C, the mixture stirred for 14 hours to give green-orange color mixture (a green color normally showed up after stirring for 1 hour).

To this green-orange mixture was added bromide **2.87** (8.0 g, 45.5 mmol) to form the Grignard reagent. Firstly, about 1 g of bromide was added into the mixture, the mixture was heated up to reflux with heat gun. The rest of bromide was injected slowly to maintain a gentle reflux of the THF. The mixture was stirred at 25 $^{o}$C for 30 minutes after the addition of the bromide, heated to reflux for 2 hours and cooled to 25 $^{o}$C to give a black color solution.

To a three neck flask equipped with low temperature thermometer were added cuprous iodide dimethyl sulfide complex ($CuI{\cdot}Me_2S$)[31] (5.75 g, 27.8 mmol), 15 mL dimethlsulfide, and 20 mL of dry ether under argon. The mixture was cooled to -40 $^oC$, and the prepared Grignard reagent was cannulated into this mixture slowly to maintain the temperature below -30 $^oC$. The mixture was stirred for 40 minutes to let temperature rise to -20 $^oC$. This mixture was cooled to -40 $^oC$, and methyl vinyl ketone (1.4 g, 26.1 mmol) in 3 mL ether was added. The mixture stirred for 2 hours to allow the temperature raise to 10 $^oC$. To it, 200 mL mixture of $NH_4Cl$ aq. and $NH_4{\cdot}OH$ aq. (4:1) was added into the reaction, and the mixture stirred for 1 minute. The crude product was extracted with ether (50 mL × 4). The combined organic layer was washed with 10 % aqueous $NH_4{\cdot}OH$ two times, water, brine and dried over $MgSO_4$. The ether and THF was distilled out at 1 atm., and the residue was purified by column using a mixture of hexane ether (15:1) as eluent to give pure product as a yellow oil (1.6 g, 40% yield); $^1H$ NMR chromatography with δ 5.84 – 5.73 (m, 1H), 5.01 – 4.94 (m, 2H), 2.38 (t, *J* = 7.6 Hz, 2H), 2.12 (s, 3H), 1.94 (d, *J* = 7.6 Hz, 2H), 1.58 – 1.49 (m, 2H), 1.16 – 1.12 (m, 2H), 0.85 (s, 6H); $^{13}C$ NMR δ 209.4, 135.8, 116.9, 46.5, 44.7, 41.5, 33.3, 30.1, 27.1 (2 carbons, gem-dimethyl), 18.7.

***3,3-Dimethyl-7-oxooctanal (2.46).***



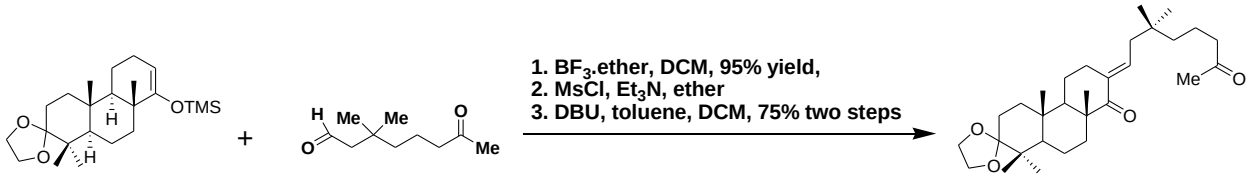

**2.86** **2.46**

**Caution: $OsO_4$ is extremely toxic!**

To compound **2.86** (1.0 g, 6.0 mmol) in 30 mL dioxane and 6 mL $H_2O$ was added $OsO_4$ (12 mg, 0.06 mmol) at 25 $^oC$. The mixture was stirred for 40 minutes to give a dark brown solution. To this solution, sodium perioddate (2.5 g, 12 mmol) was added slowly over 20 minutes. The mixture was stirred at 25 $^oC$ for 4 hours, diluted with water, and extracted with ether (40 mL×4). The combined organic layer washed with water, brine, and dried over $MgSO_4$. Ether and most of the dioxane were distilled off at 1 atm., and the crude product was purified by column chromatography with the mixture of hexane ether (1:1) to give pure product as yellow oil (0.52 g, 56% yield). $^1H$ NMR δ 9.83 (t, *J* = 3.2 Hz, 1H), 2.42 (t, *J* = 6.8 Hz, 2H), 2.27 (d, *J* = 3.2 Hz, 2H),

2.13 (s, 3H), 1.61 – 1.53 (m, 2H), 1.32 – 1.27 (m, 2H), 1.05 (s, 6H); $^{13}$C NMR δ 208.9, 203.8, 54.8, 44.2, 42.2, 33.7, 30.0, 27.6 (2 carbons, gem-dimethyl), 18.5.

***(-)-(4a'S,8a'R,E)-7'-(3,3-dimethyl-7-oxooctylidene)-1',1',4a',8a'-Tetramethyldecahydro-1'H-spiro[[1,3]dioxolane-2,2'-phenanthren]-8'(3'H)-one [(-)-2.76].***



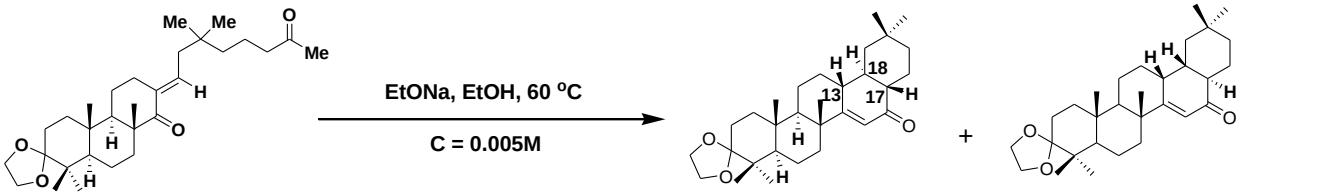

**(-)-2.81** **2.46** **(-)-2.76**

To a solution of compound **(-)-2.81** (0.50 g, 1.1 mmol) and ketone aldehyde **2.46** (0.23 g, 1.3 mmol) in 25 mL distilled DCM at -78 $^{o}$C under argon was added $BF_3$.ether (0.34 mL, 2.7 mmol). This mixture stirred at -78 $^{o}$C for 2 hours and stored in dry-ice for 10 hours. To it (at -78 $^{o}$C) was added 5 mL saturated aqueous $NaHCO_3$ solution to quench the reaction. The mixture was diluted with water, and extracted with ethyl acetate (30 mL×3). The combined organic layer was washed with water, brine, and dried over $MgSO_4$. Ethyl acetate was evaporated off under vacuum, and the residue was column chromatographed on the silica gel column to recover the compound **(-)-2.33** (30 mg, 9% revovery) and get desired aldol product **2.92** [430 mg, 92 % yield, calculated based on the recovery of ketone **(-)-2.33**].

To a solution of compound **2.92** (430 mg, 0.91 mmol) and $Et_3N$ (1.3 mL, 8.1 mmol) in 30 mL distilled ether was added MsCl (342mg, 3 mmol) at 0 $^{o}$C under argon. The mixture was stirred for 14 hours, quenched with 5 % aqueous $NH_4Cl$, and extracted with ethyl acetate (30 mL×3). The combined organic layer was washed with 10 % aqueous $NaHCO_3$, water, brine, dried over $Na_2SO_4$, and concentrated under vacuum. The residue was dissolved in 20 mL of a mixture of DCM and toluene (1:1). To it was added DBU (276 mg, 1.82 mmol) at 25 $^{o}$C. This mixture was stirred for 15 hours, diluted with aqueous $NH_4Cl$, and extracted with ethyl acetate (30 mL×3). The combined organic layer washed with water, brine, and dried over $MgSO_4$. Ethyl acetate was evaporated off under vacuum, the crude product was purified by column chromatography using a mixture of hexane, DCM and ether (5:3:1) as eluent to give pure product as a white solid (0.35 g, 83% yield, two steps). $[\alpha]_{25}$= - 32.5$^{o}$, (c = 0.385 in chloroform); $^{1}$H

NMR δ 6.39 (t, *J* = 9.6 Hz, 1H), 3.99 – 3.85 (m, 4H), 2.77 (d, *J* =15.6, 5.6 Hz, 1H), 2.39 (t, *J* = 7.6 Hz, 2H), 2.13 (s, 3H), 2.12 – 1.62 (m, 9H), 1.58 – 1.16 (m, 10H), 1.05 (s, 3H), 0.95 (s, 3H), 0.93 (s, 3H), 0.89 (s, 6H), 0.85 (s, 3H); $^{13}$C NMR δ 209.4, 208.0, 137.1, 135.2, 113.2 (2 carbons, acetal), 65.12, 65.11, 54.2, 53.1, 47.8, 44.6, 42.4, 41.7, 39.9, 38.0, 36.9, 35.9, 34.4, 30.2, 27.23, 27.19, 27.0, 26.8, 23.1, 20.1, 19.1, 18.7, 18.3, 16.7.

***(+)-(6a'R,8a'R,12a'S,12b'R,14b'R)-4',4',6a',11',11',14b'-Hexamethyl-4', 4a', 5', 6', 6a', 8a', 9', 10', 11',12',12a',12b',13',14',14a',14b'-hexadecahydro-1'H-spiro[[1,3]dioxolane-2,3'-picen]-8'(2'H)-one [(+)-2.45]; (-)-(6a'R,8a'S,12a'R,12b'R,14b'R)-4',4',6a',11',11',14b'-hexamethyl-4',4a',5',6',6a',8a',9',10',11',12',12a',12b',13',14',14a',14b'-hexadecahydro-1'H-spiro [[1,3]dioxolane-2,3'-picen]-8'(2'H)-one [(-)-2.94].***



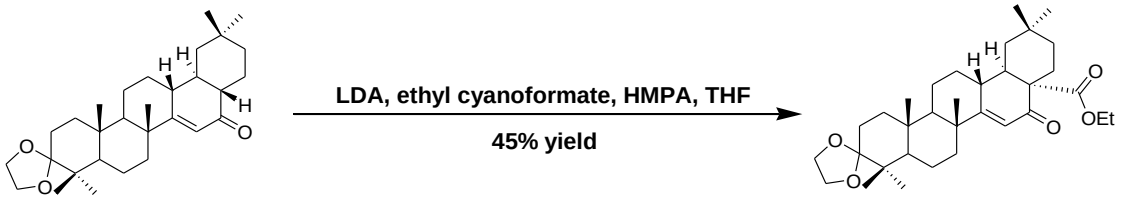

**(-)-2.76** **(-)-2.94 (40% yield), less polar** **(+)-2.45 (30% yield), more polar**

A solution of sodium methoxide was prepared as followed: sodium (11mg, 0.46 mmol) was added into 5 mL distilled ethanol at 25 °C under argon. The mixture was stirred until all the metal dissolved.

To compound **(-)-2.76** (110 mg, 0.23 mmol) in 40 mL distilled ethanol, above sodium ethoxide solution was cannulated. This mixture was stirred at 55 °C under argon for 14 hours. 1 Drop of acetic acid was added into the yellow solution to quench the excess amount of base. Ethanol was evaporated off under vacuum; the residue was diluted with water, and extracted with ethyl acetate (30 mL×3). The combined organic layer washed with water, brine, dried over $MgSO_4$, concentrated under vacuum. The crude product was purified by column chromatography using a mixture of hexane, DCM and ether (7.5:3:1) as eluent to give pure **(-)-2.45** (35 mg, 30 % yield) as white solid and **(-)-2.94** (45 mg, 40 %) as white solid. **(-)-2.94** (Less polar compound, undesired product): $[\alpha]_{25}$= -34.0, (c = 0.15 in chloroform); $^1$H NMR δ 5.81 (d, *J* = 2.0 Hz, 1H), 3.98 – 3.87 (m, 4H), 2.33 – 2.25 (m, 1H), 2.17 – 2.09 (m 1H), 2.02 (ddd, *J* = 15.6, 8.4, 4.4 Hz,

1H), 1.87 – 1.57 (m, 5H), 1.52 – 1.29 (m, 9H), 1.26 – 1.09 (m, 6H), 1.09 (s, 3H), 0.94 (s, 3H), 0.93 (s, 6H), 0.86 (s, 6H); $^{13}$C NMR δ 202.9, 174.7, 119.5, 113.2 (2 carbons, acetal), 65.1, 56.7, 53.3, 48.5, 44.4, 42.3, 41.2, 41.1, 40.5, 38.8, 38.1, 37.9, 37.0, 33.4, 32.8, 30.6, 27.1, 24.8, 23.1, 23.0, 21.5, 20.4, 20.1, 18.7, 16.6; **(+)-2.45** (More polar compound, desired product): $[\alpha]_{25}$= + 222.5$^{o}$, (c = 0.19 in chloroform); $^{1}$H NMR δ 5.75 (s, 1H), 4.02 – 3.84 (m, 4H), 2.37 (ddd, *J* = 13.2, 9.2, 4.4 Hz, 1H), 2.09 – 1.61 (m, 6 H), 1.58 – 1.17 (m, 12 H), 1.14 – 0.98 (m, 4H), 1.13 (s, 3H), 0.94 (s, 9H), 0.87 (s, 3H), 0.84 (s, 3H); $^{13}$C NMR δ 202.7, 176.6, 118.1, 113.1 (2 carbons, acetal), 65.08, 65.02, 59.7, 53.7, 44.0, 43.2, 42.3, 41.9, 39.3, 38.38, 38.35, 37.9, 37.1, 36.7, 33.5, 30.6, 28.0, 27.0, 24.2, 23.1, 22.0, 20.7, 20.1, 18.6, 16.2; the single srystal was grown from a mixture of diethyl ether and hexane (1:1) for X-ray analysis.

***(+)-(6a'R,8a'S,12a'R,12b'R,14b'R)-Ethyl 4',4',6a',11',11',14b'-hexamethyl-8'-oxo-2',4',4a',5',6', 6a', 8',8a',9',10',11',12',12a',12b',13',14',14a',14b'-octadecahydro-1'H-spiro[[1,3]dioxolane-2,3'-picene]-8a'-carboxylate [(+)-2.101].***



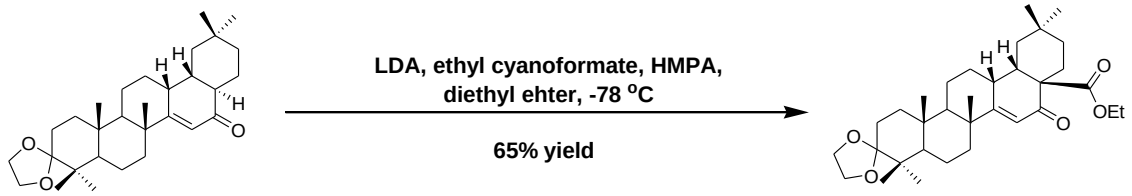

**(-)-2.94** **(+)-2.101**

[LDA was prepared followed the same procedure of **(-)-2.81** and titrated before using. The procedure for the titration is: to the solution of diphenylacetic acid (9.3 mg, 0.043 mmol) in 1 mL dry THF [or ether for **(-)-2.105**]. When a light yellow was shown and last for 10 seconds, the titration was stopped, the volume of LDA solution was recorded and used to calculate the concentration.]

To **(-)-2.94** (173 mg, 0.38 mmol) in 2 mL THF was added freshly made LDA (0.57mmol) in 1 mL THF. The mixture was stirred at -78 $^{o}$C for 1 hour. To it, HMPA (102 mg, 0.57 mmol) was injected, and the mixture was stirred at -78 $^{o}$C for 15 minutes, and ethyl cyanoformate (75 mg, 0.76 mmol) was added. The mixture was stirred at -78 $^{o}$C for 30 minutes, diluted with aq. $NH_4Cl$ solution, and extracted with ethyl acetate (20 mL×3). The combined organic layer was washed with water, brine, dried over $MgSO_4$. Ethyl acetate was evaporated off under vacuum,

and the crude product was purified by column chromatography using a mixture of hexane, DCM and ether (7.5:3:1) as eluent to give 90 mg (45 % yield) of pure **(+)-2.101** as white solid. $[\alpha]_{25}$= + 91.3$^{o}$, (c = 0.425 in chloroform); $^{1}$H NMR δ 5.79 (s, 1H), 4.16 – 4.06 (m, 2H), 3.95 – 3.84 (m, 4H), 2.54 (dd, *J* = 12.8, 4.4 Hz, 1H), 2.34 (ddd, *J* = 13.6, 7.2, 3.2 Hz, 1H), 2.15 (dd, *J* = 13.6, 3.6 Hz, 1H), 1.92 (d, *J* = 12.0 Hz, 1H), 1.80 (td, *J* = 13.6, 3.2 Hz, 2H), 1.71 – 1.57 (m, 5H), 1.51 – 1.28 (m, 6H), 1.24 (t, *J* = 7.6 Hz, 3H), 1.18 – 1.10 (m, 5H), 1.08 (s, 3H), 0.98 (s, 3H). 0.94 (s, 3H), 0.92 (s, 3H), 0.85 (s, 3H), 0.83 (s, 3H); $^{13}$C NMR δ 197.2, 174.6, 172.3, 117.8, 113.2 (2 carbons, acetal), 65.2, 61.4, 58.6, 55.6, 53.6, 43.6, 42.9, 42.4, 41.4, 39.5, 38.3, 38.1, 37.1, 34.96, 34.95, 32.9, 30.6, 27.5, 27.1, 24.6, 23.2, 22.0, 21.3, 20.2, 18.7, 16.4, 14.3; the single srystal was grown from a mixture of diethyl ether and hexane (1:1) for X-ray analysis.

***(-)-(6a'R,8a'R,12a'S,12b'R,14b'R)-ethyl 4',4',6a',11',11',14b'-hexamethyl-8'-oxo-2',4',4a',5',6', 6a', 8', 8a', 9',10',11',12',12a',12b',13',14',14a',14b'-octadecahydro-1'H-spiro[[1,3] dioxolane - 2, 3 '- picene]-8a'-carboxylate [(-)-2.106].***




**(+)-2.45** **(-)-2.106 (assumed structure)**

To **(+)-2.45** (40 mg, 0.088 mmol) in 1 mL distilled diethyl ether was added freshly prepared LDA (0.12mmol) in 1 mL diethyl ether. The mixture was stirred at -78 $^{o}$C for 1 hour. To it, HMPA (24 mg, 0.12 mmol) was added, and the mixture was stirred at -78 $^{o}$C for 15 minutes. Ethyl cyanoformate (18 mg, 0.17 mmol) was added. The mixture was stirred at -78 $^{o}$C for 30 minutes, diluted with aq. $NH_4Cl$ solution, and extracted with ethyl acetate (10 mL ×3). The combined organic layer was washed with water, brine, and dried over $MgSO_4$. Ethyl acetate was evaporated off under vacuum, the crude product was purified by column chromatography with the mixture of hexane, DCM and ether (6:3:1) to give 30 mg (65 % yield) of pure **(-)-2.106** as white solid. $[\alpha]_{25}$= -62.8$^{o}$, (c = 0.20 in chloroform); $^{1}$H NMR δ 5.88 (d, *J* = 2.4 Hz, 1H), 4.16 – 4.05 (m, 2H), 3.96 – 3.86 (m, 4H), 2.89 – 2.82 (m, 1H), 2.59 (dt, *J* = 14.0, 4.4 Hz, 1H), 2.35 (dt, *J* = 13.2, 2.8 Hz, 1H), 1.90 – 1.78 (m, 2H), 1.74 – 1.60 (m, 4H), 1.50 – 1.40 (m, 5H), 1.33 – 1.23

(m, 8H), 1.19 (t, *J* = 7.6 Hz, 3H), 1.05 (s, 3H), 0.93 (s, 6H), 0.91 (s, 3H), 0.85 (s, 6H); $^{13}$C NMR δ 197.1, 173.3, 172.4, 120.4, 113.4 (2 carbons, acetal), 65.2, 61.4, 58.3, 57.0, 53.2, 42.4, 42.3, 38.7, 38.2, 37.9, 37.1, 36.1, 35.6, 34.7, 33.4, 31.0, 30.4, 27.13, 27.05, 24.8, 23.8, 23.0, 20.5, 20.0, 18.6, 16.8, 14.4.

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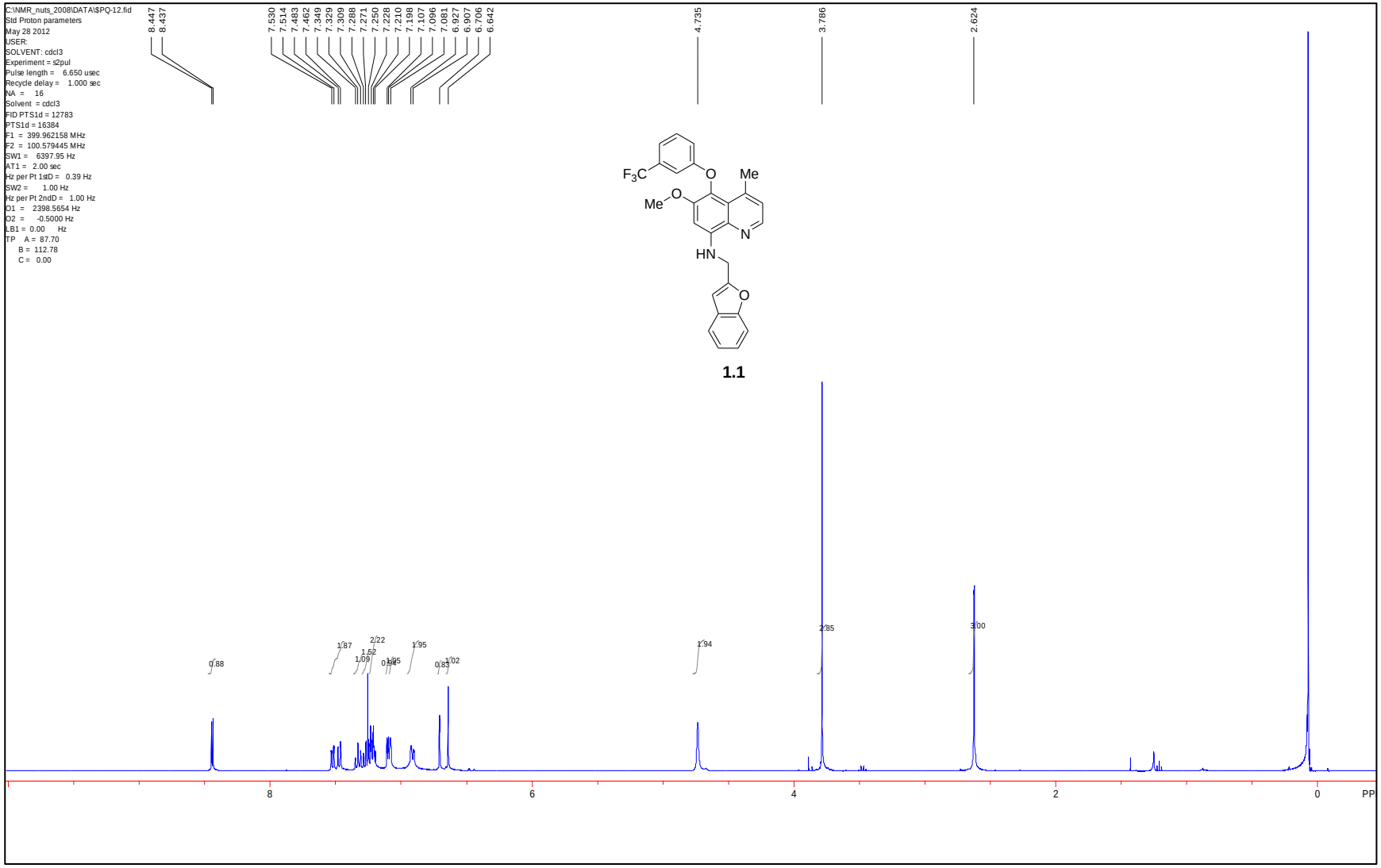
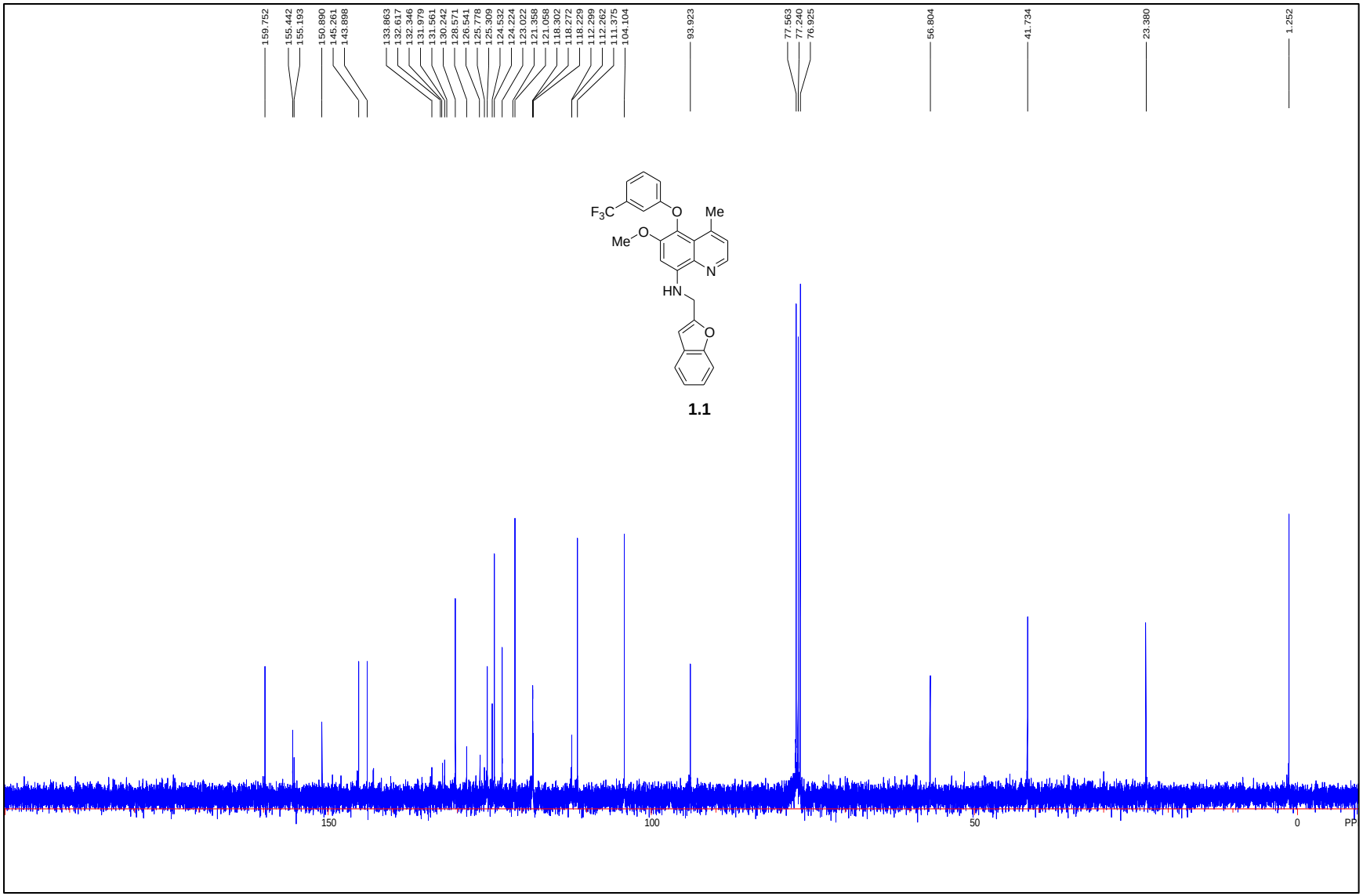
# Appendix A - Chaper 1 $^{1}$H NMR and $^{13}$C NMR

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145.261
143.898
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131.979
131.561
130.242
128.571
126.541
125.778
125.309
124.532
124.224
123.022
121.358
121.058
118.302
118.272
118.229
112.299
112.262
111.375
104.104
93.923
77.563
77.240
76.925
56.804
41.734
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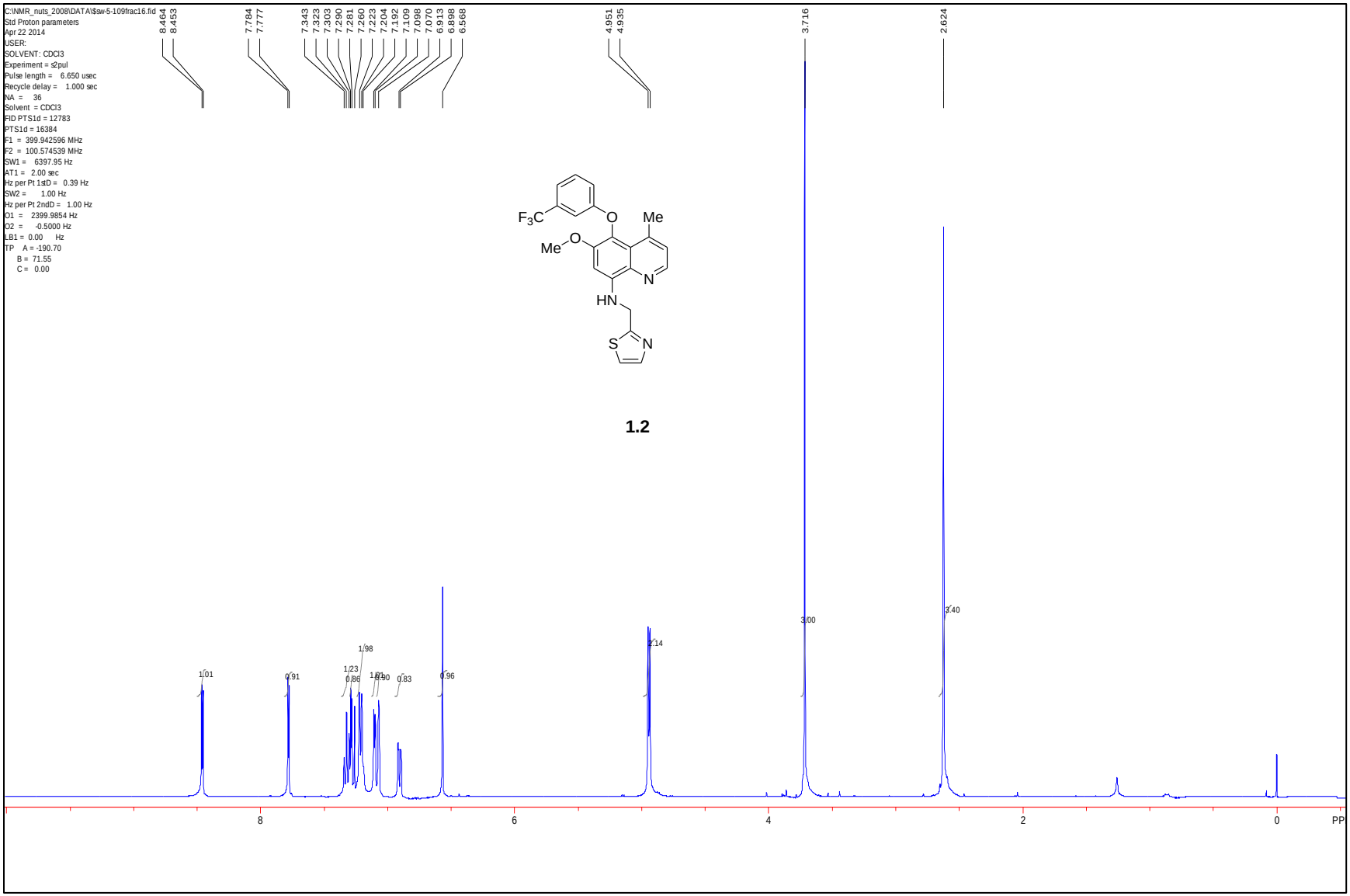
F3C
O
Me
Me
O
N
HN
O
1.1
150
100
50
0
PP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F2 = 100.574539 MHz
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SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
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O2 = -0.5000 Hz
LB1 = 0.00 Hz
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7.343
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7.109
7.098
7.070
6.913
6.898
6.568
4.951
4.935
3.716
2.624
F3C
O
Me
Me
O
N
HN
S
N
1.01
0.91
1.23
0.86
1.98
1.01
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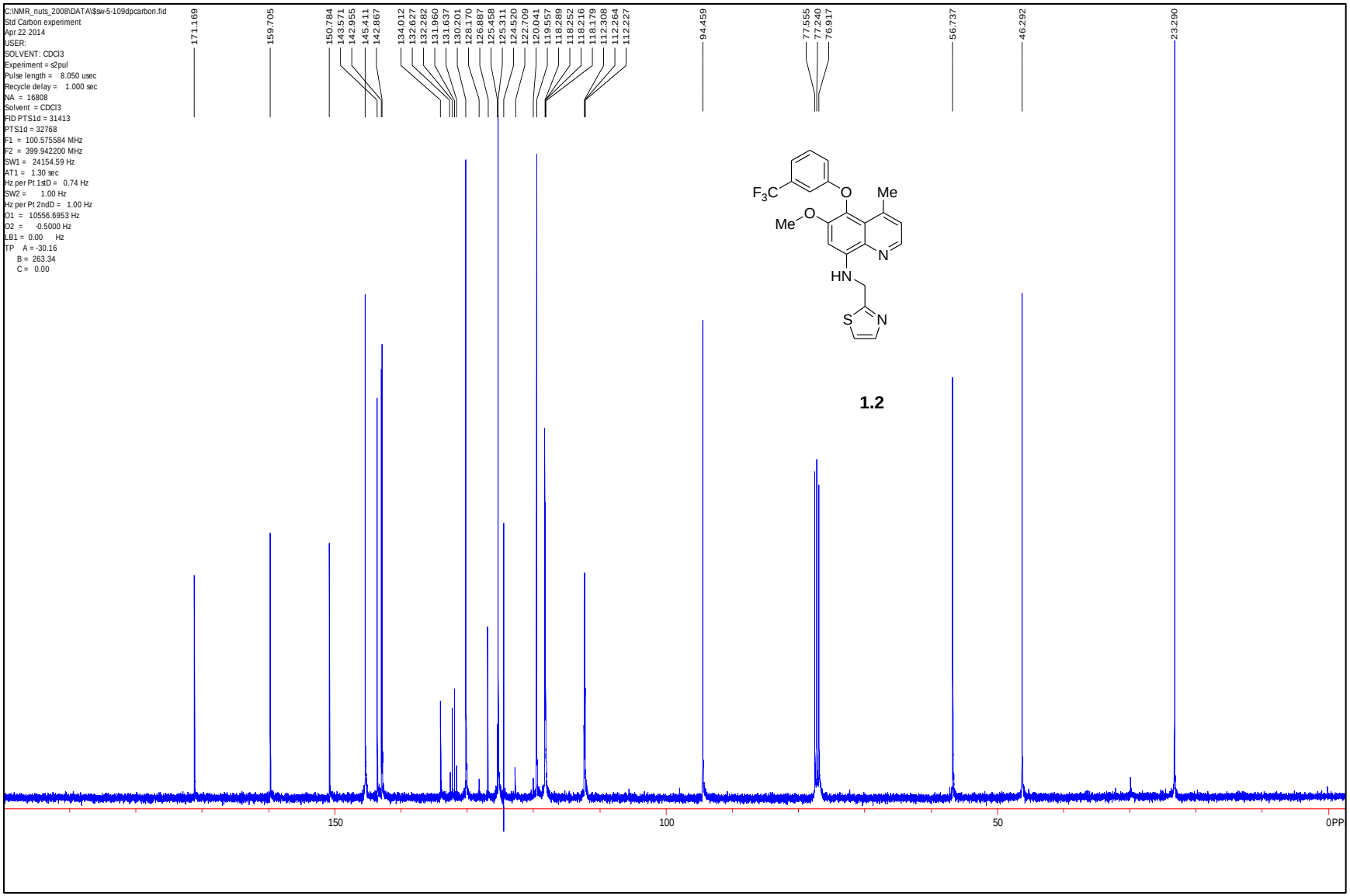
8
6
4
2
0
PPM

**1.2**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SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
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O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -30.16
B = 263.34
C = 0.00
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142.955
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F3C
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HN
S
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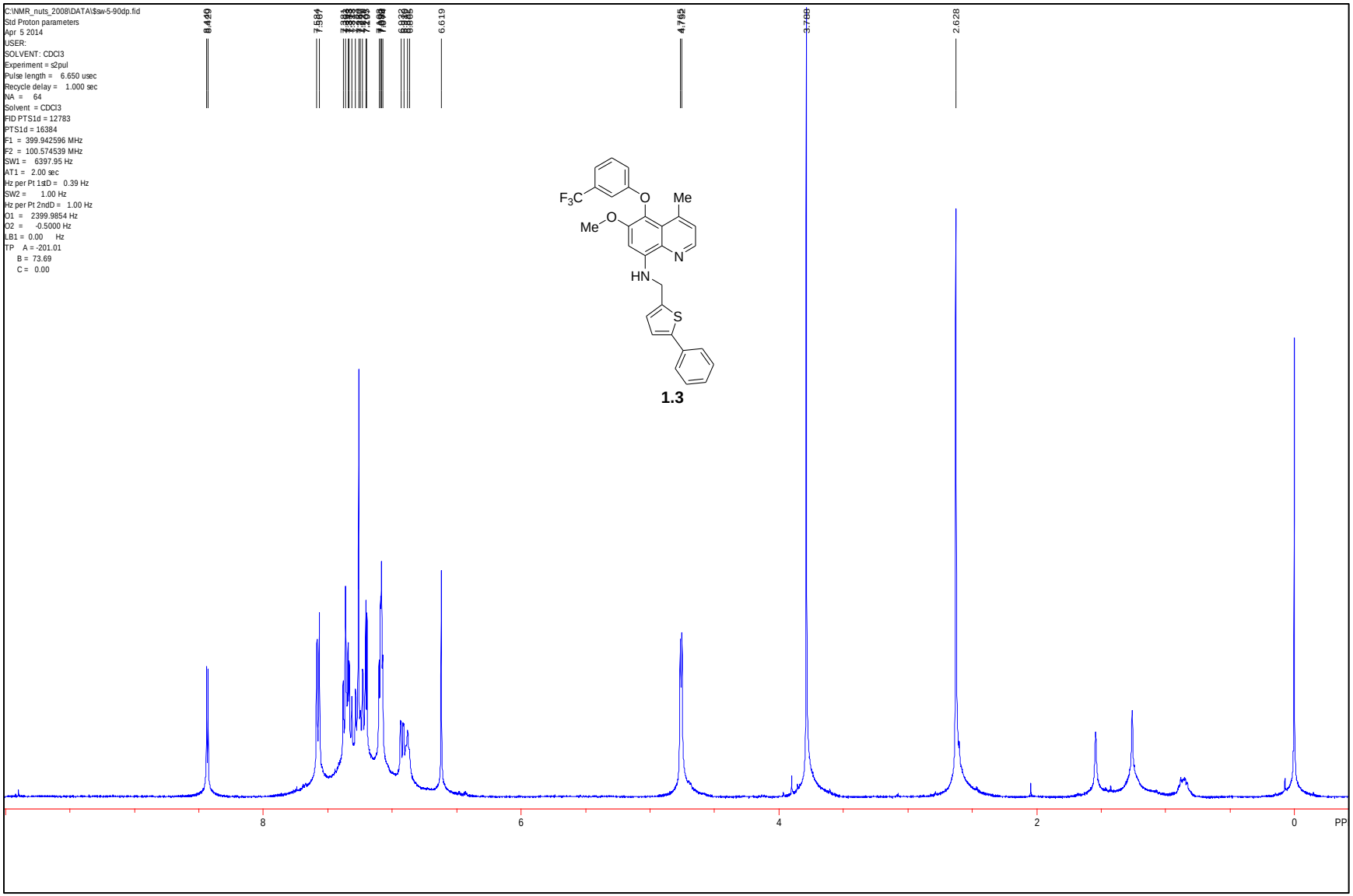
150
100
50
0PP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SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2399.9854 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
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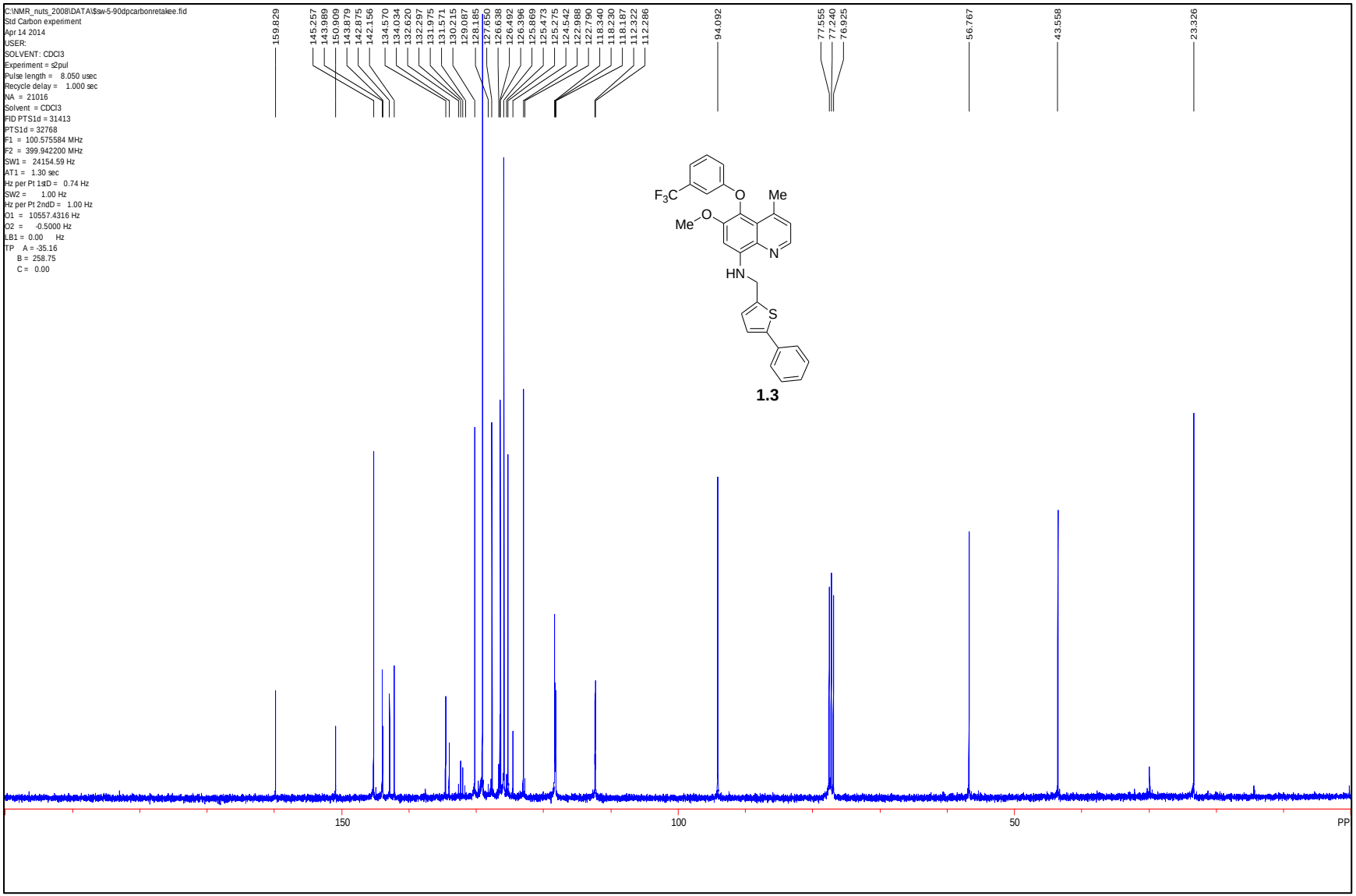
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Hz per Pt 2ndD = 1.00 Hz
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O2 = -0.5000 Hz
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TP A = -35.16
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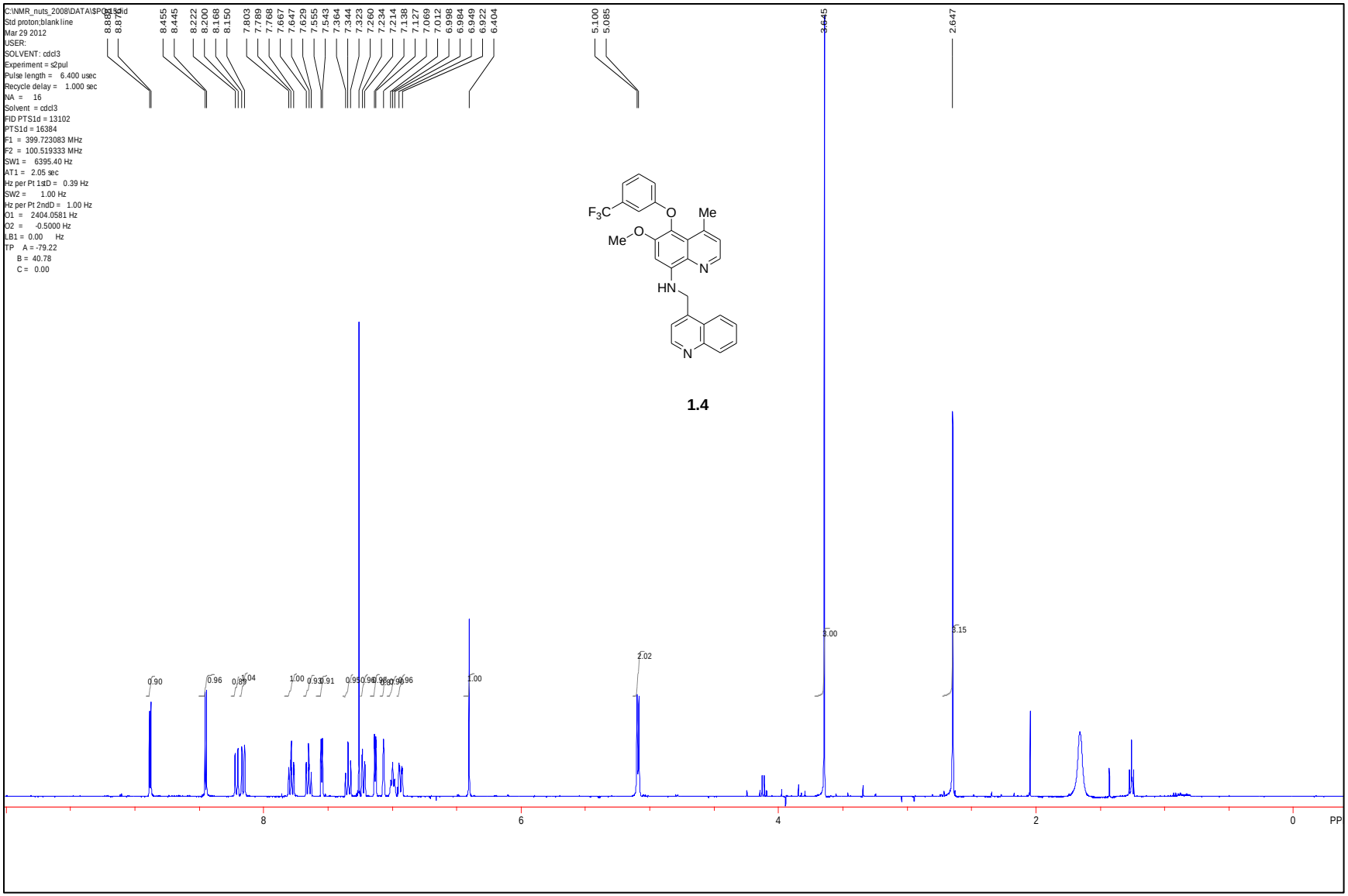
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Me
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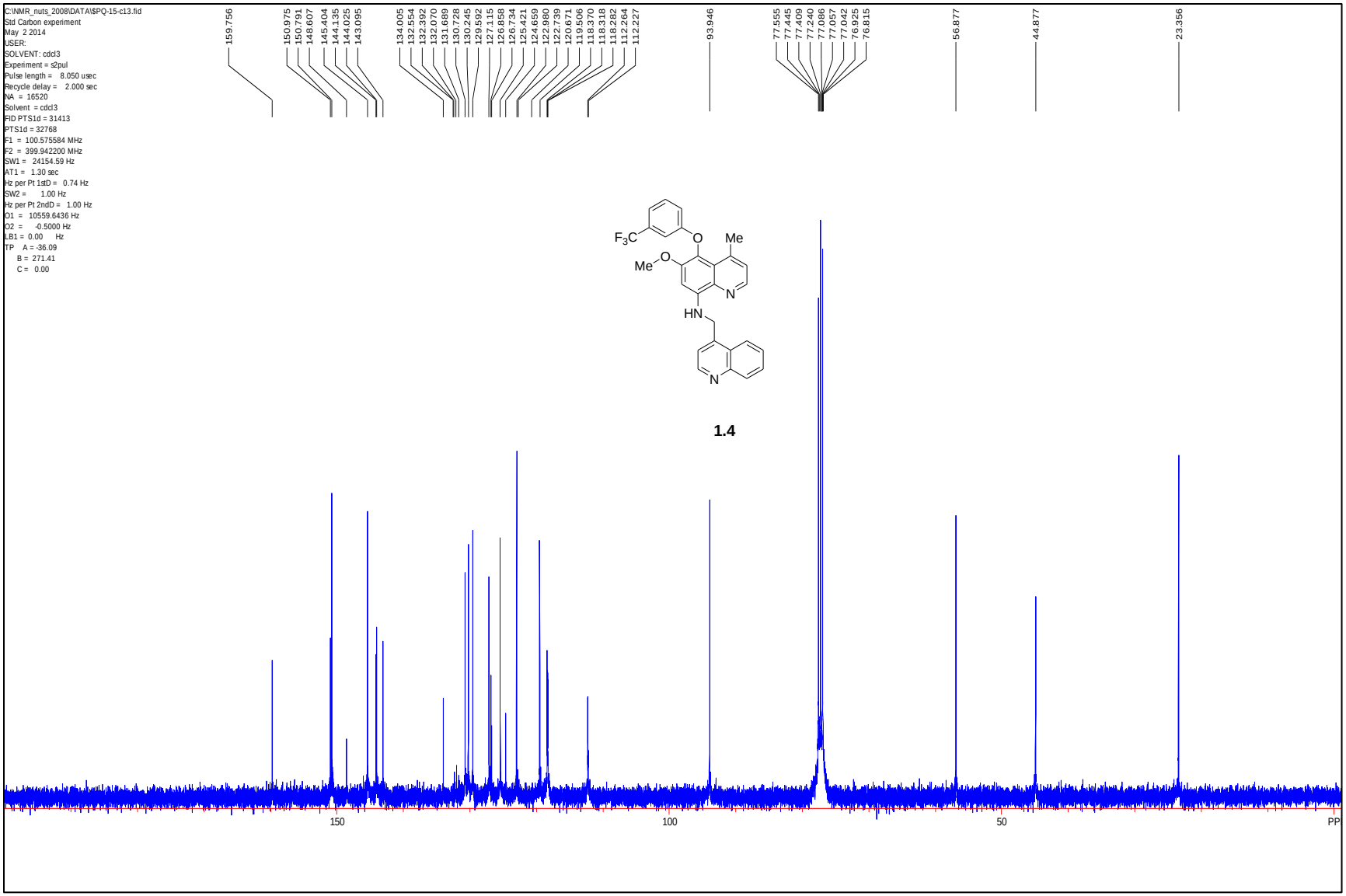
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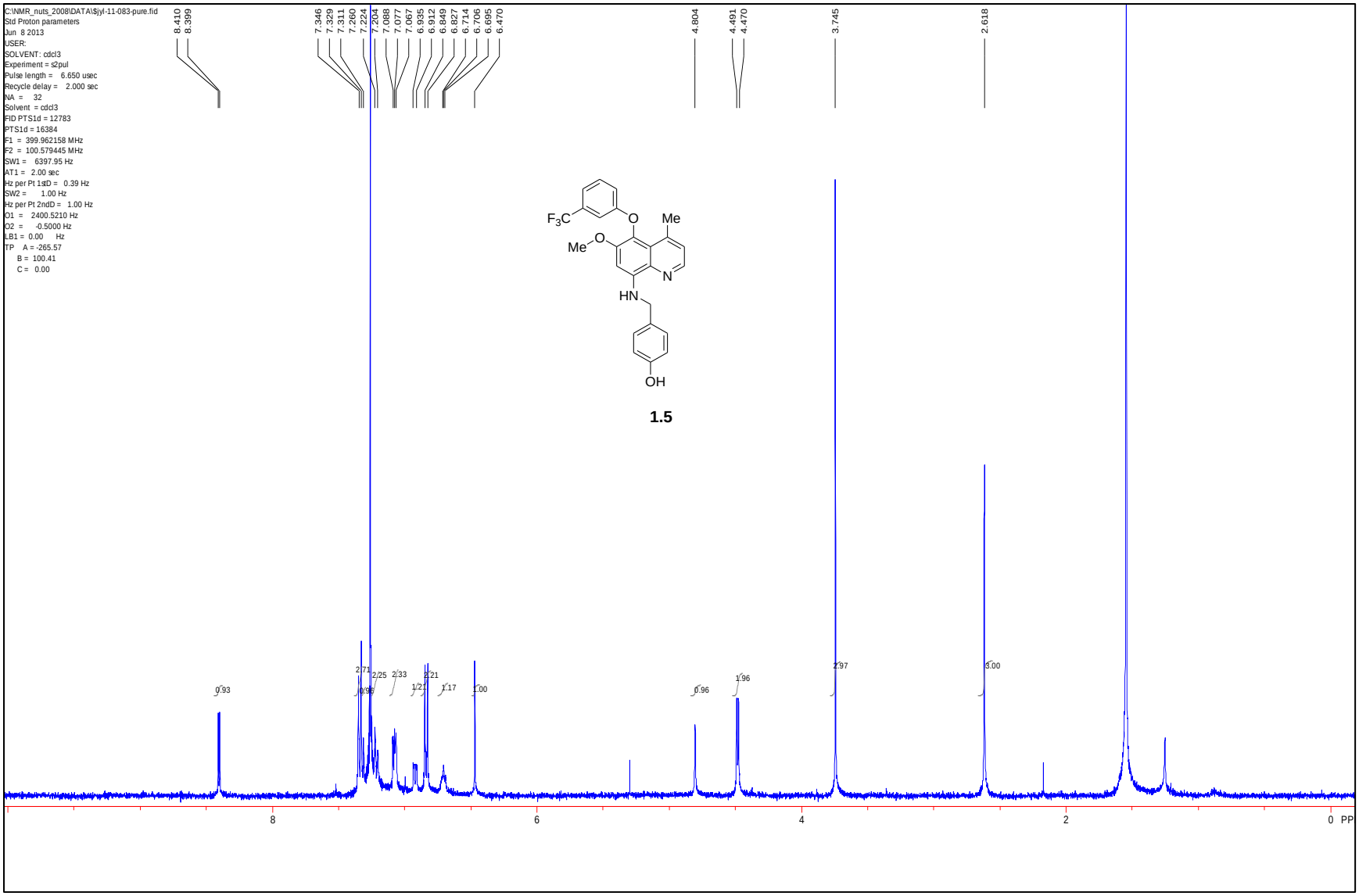
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O2 = -0.5000 Hz
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6
4
2
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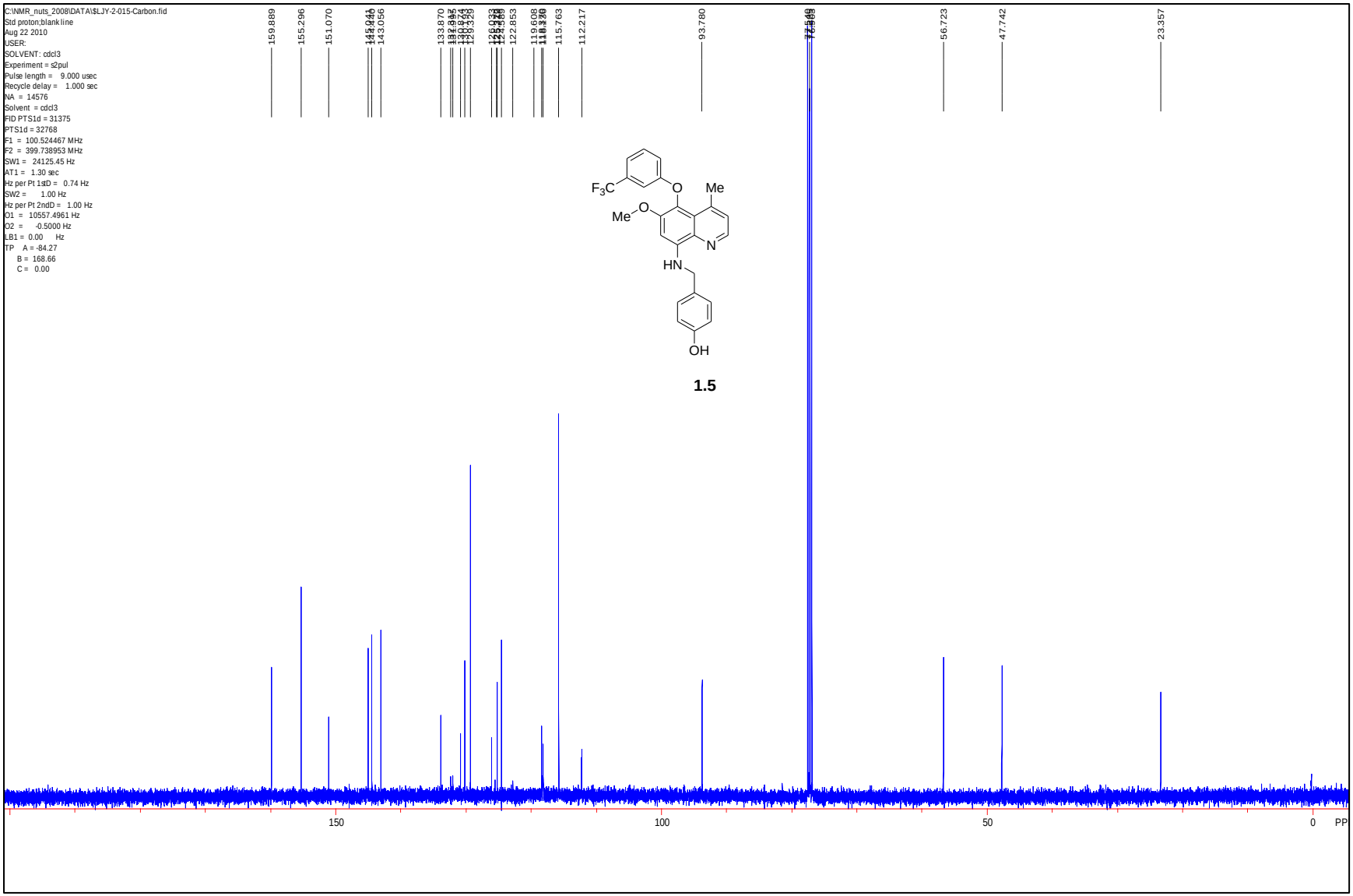
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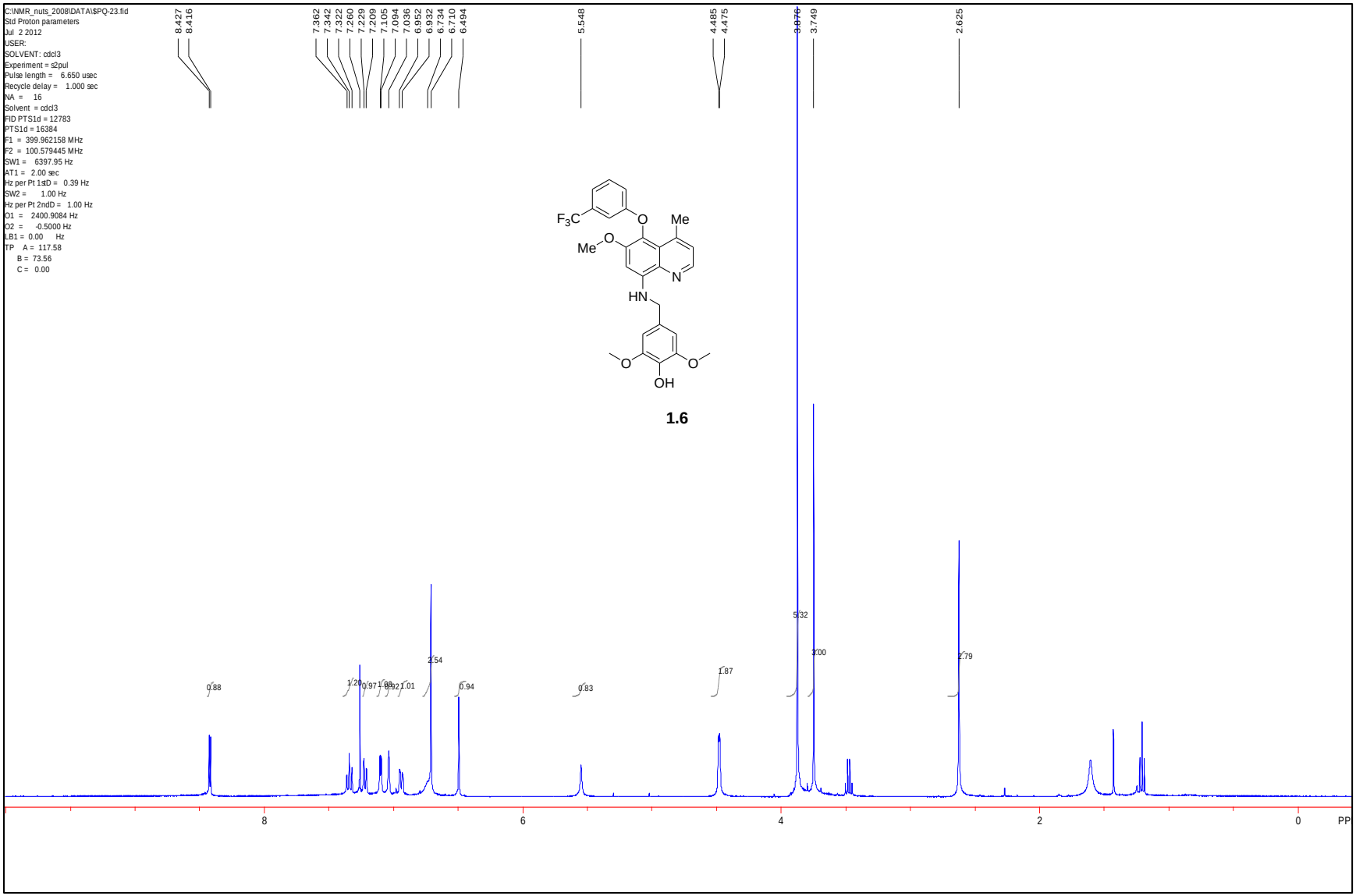
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O2 = -0.5000 Hz
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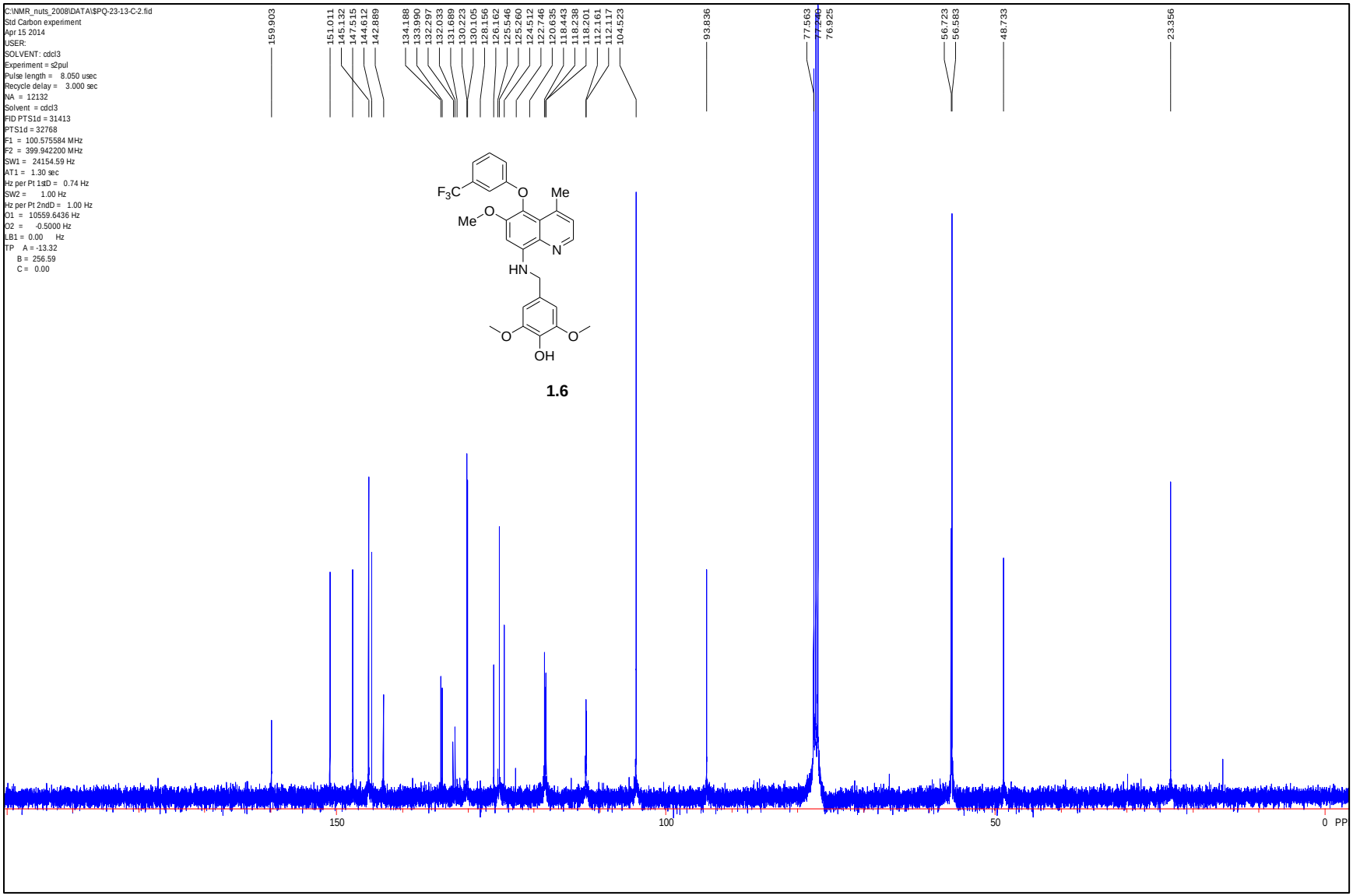
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Hz per Pt 2ndD = 1.00 Hz
O1 = 10559.6436 Hz
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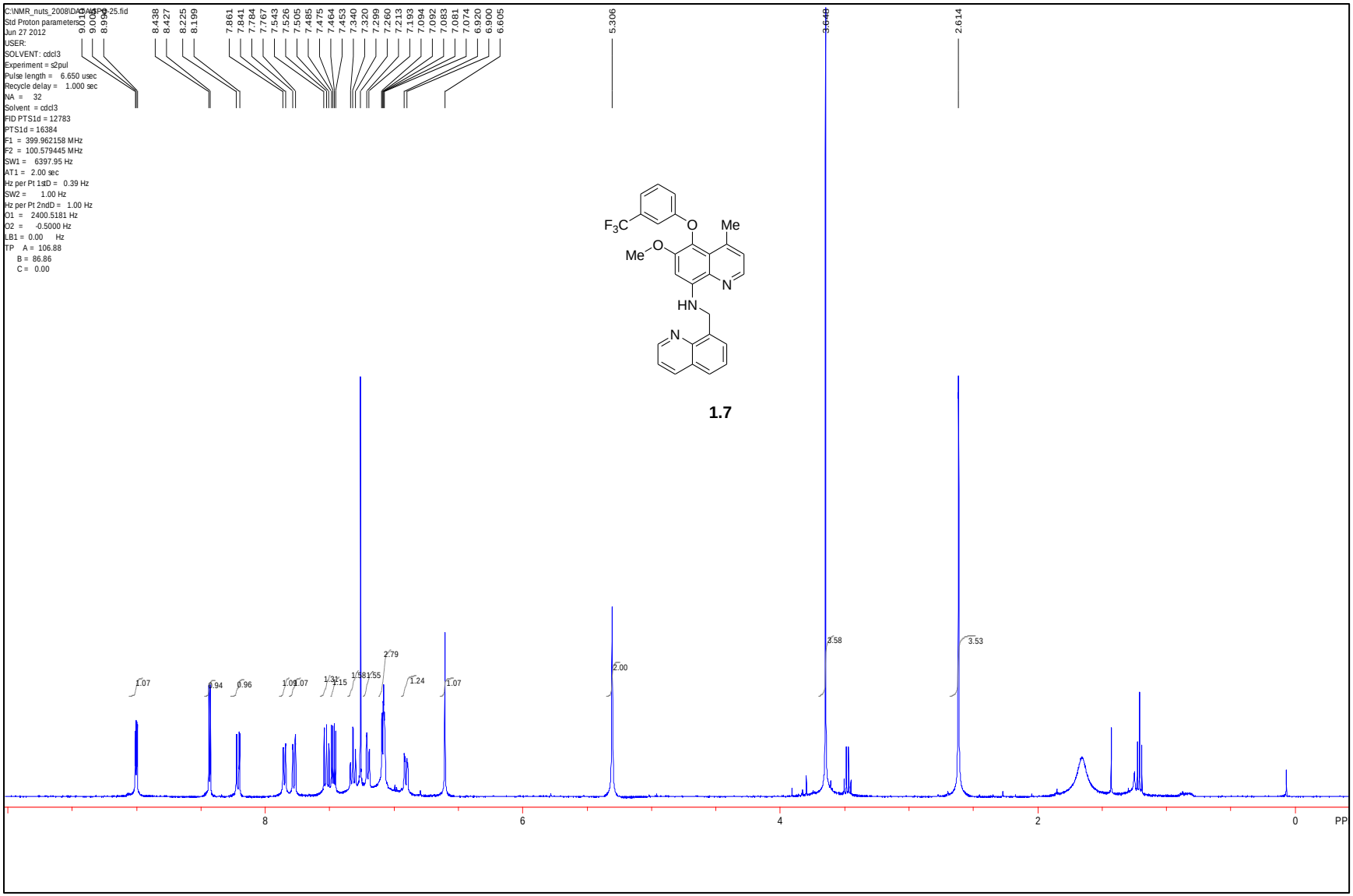
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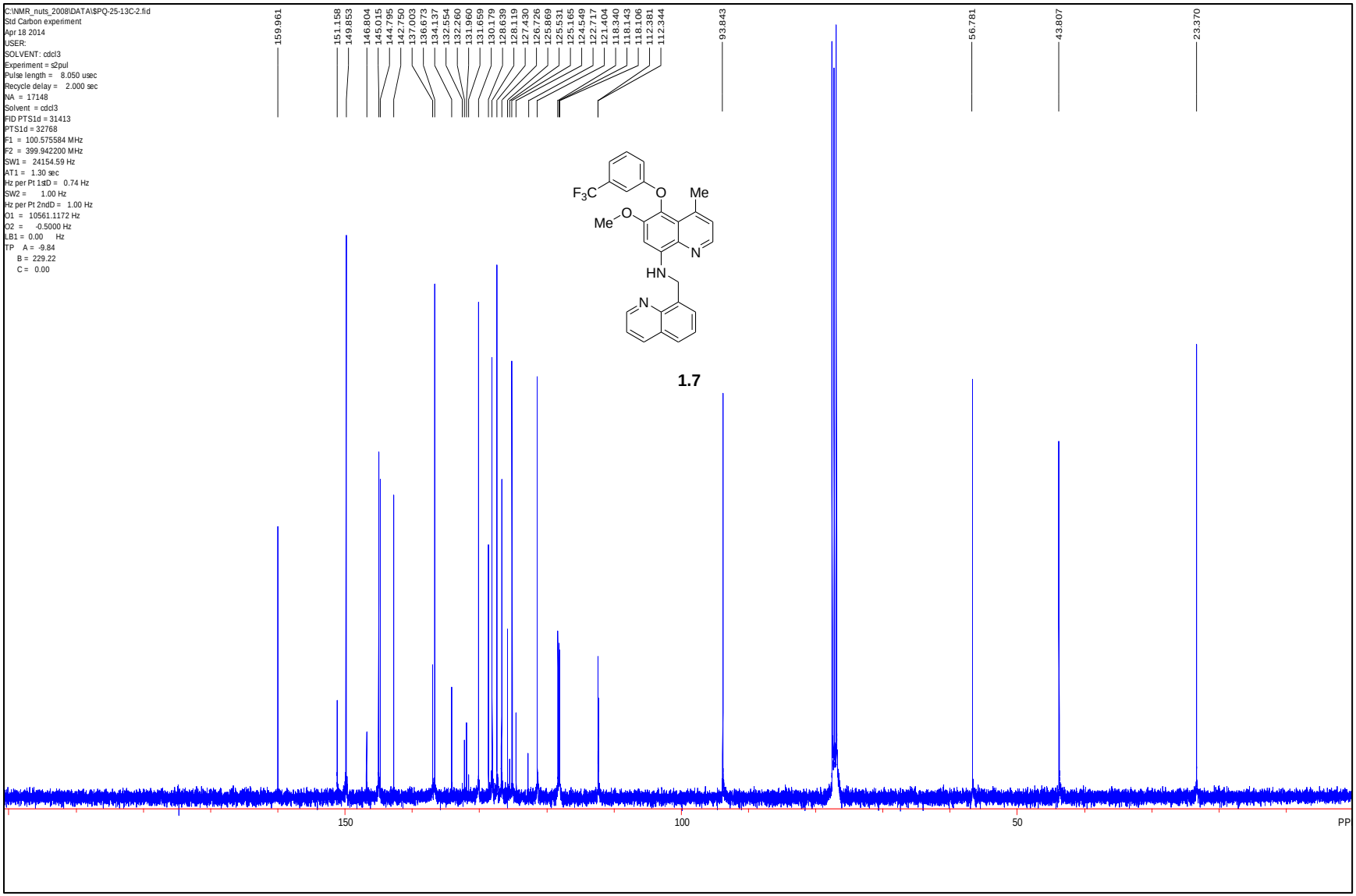
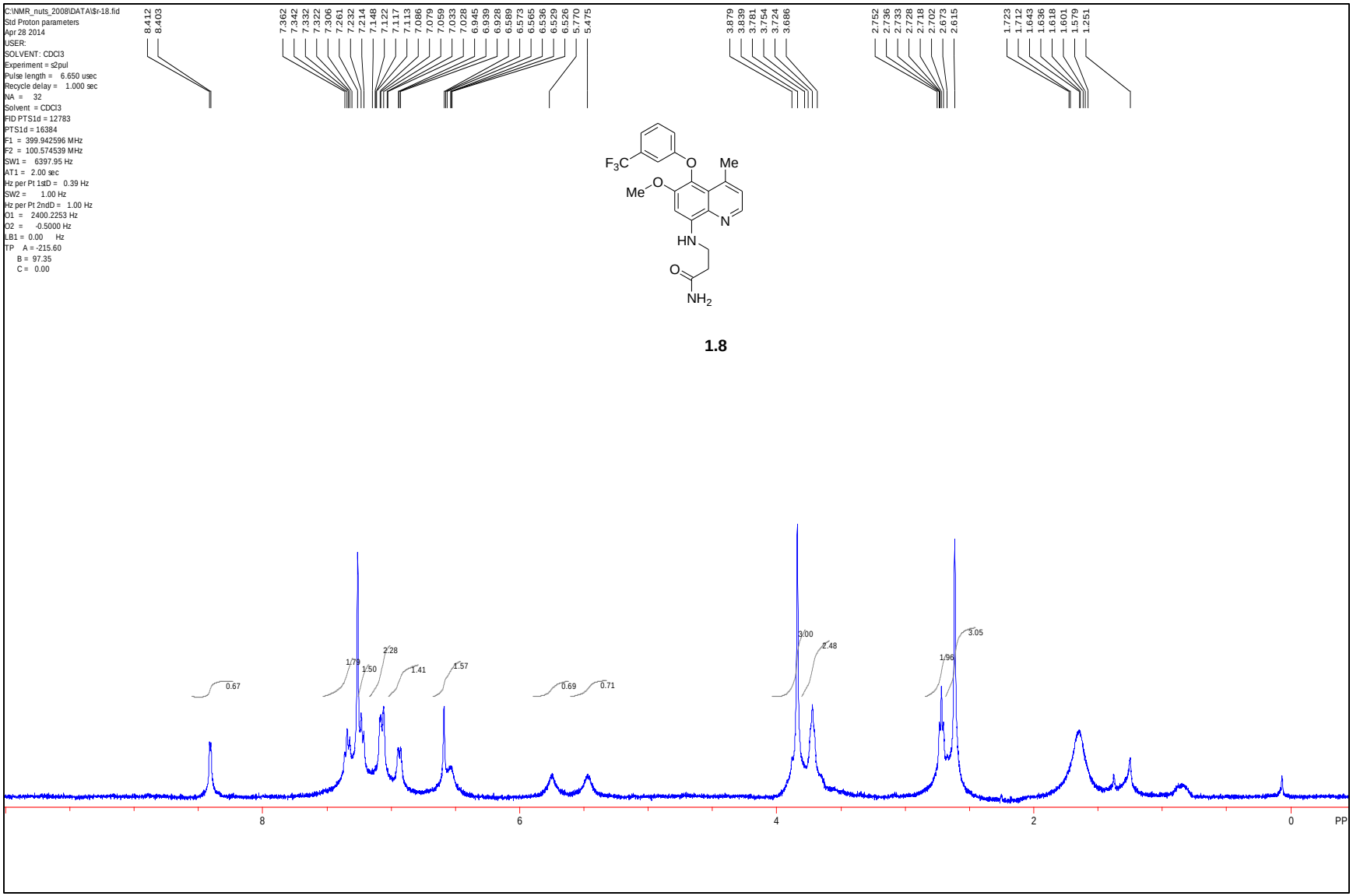
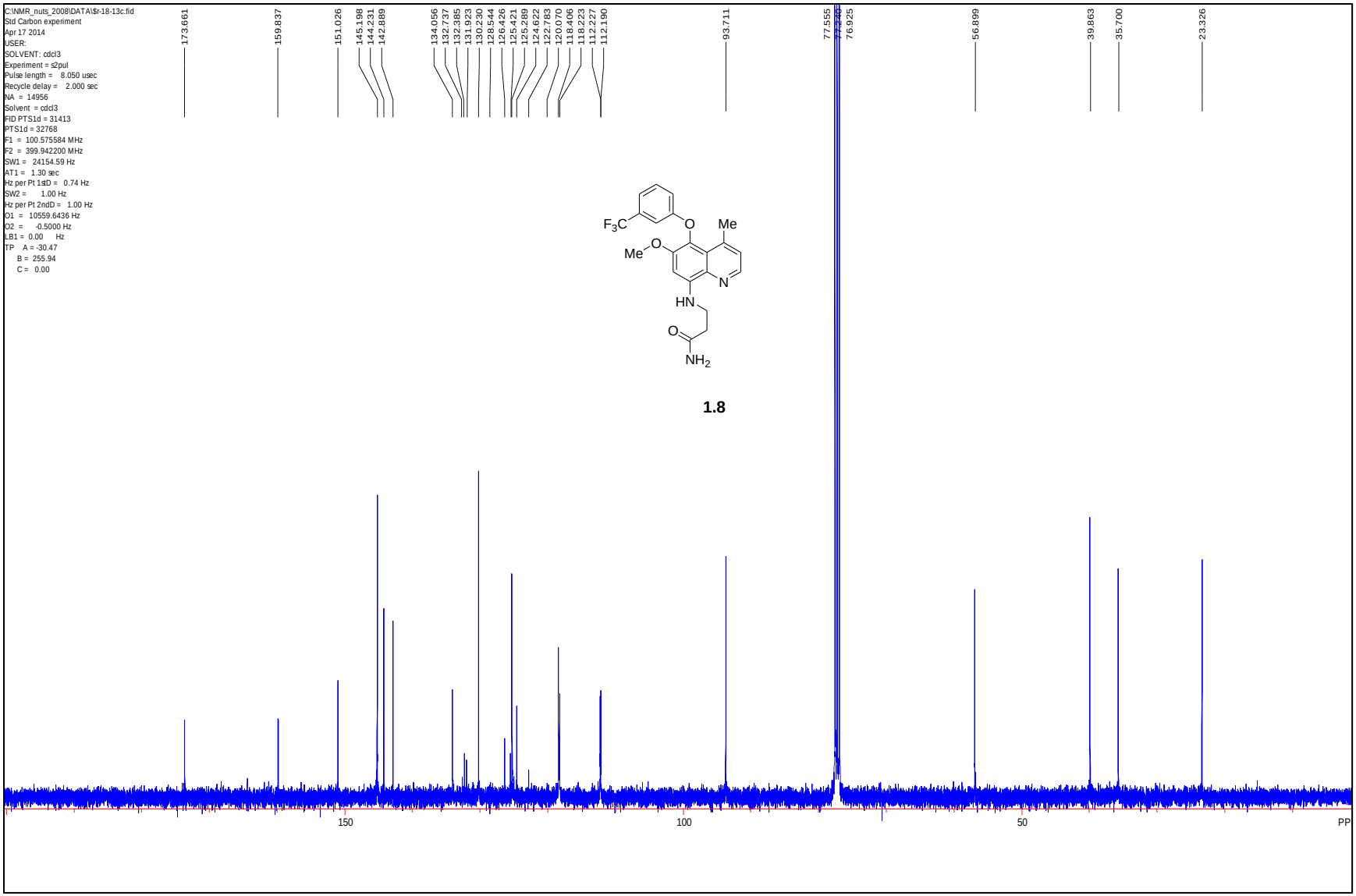
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.962158 MHz
F2 = 100.579445 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2400.5181 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 106.88
B = 86.86
C = 0.00
9.017
9.008
8.994
8.438
8.427
8.225
8.199
7.861
7.841
7.784
7.767
7.543
7.526
7.505
7.485
7.475
7.464
7.453
7.340
7.320
7.299
7.260
7.213
7.193
7.094
7.092
7.083
7.081
7.074
6.920
6.900
6.605
5.306
3.648
2.614
F3C
O
Me
Me
O
N
HN
N
1.07
0.94
0.96
1.09
1.07
1.32
1.15
1.58
1.55
2.79
1.24
1.07
2.00
3.58
3.53
8
6
4
2
0
PPM

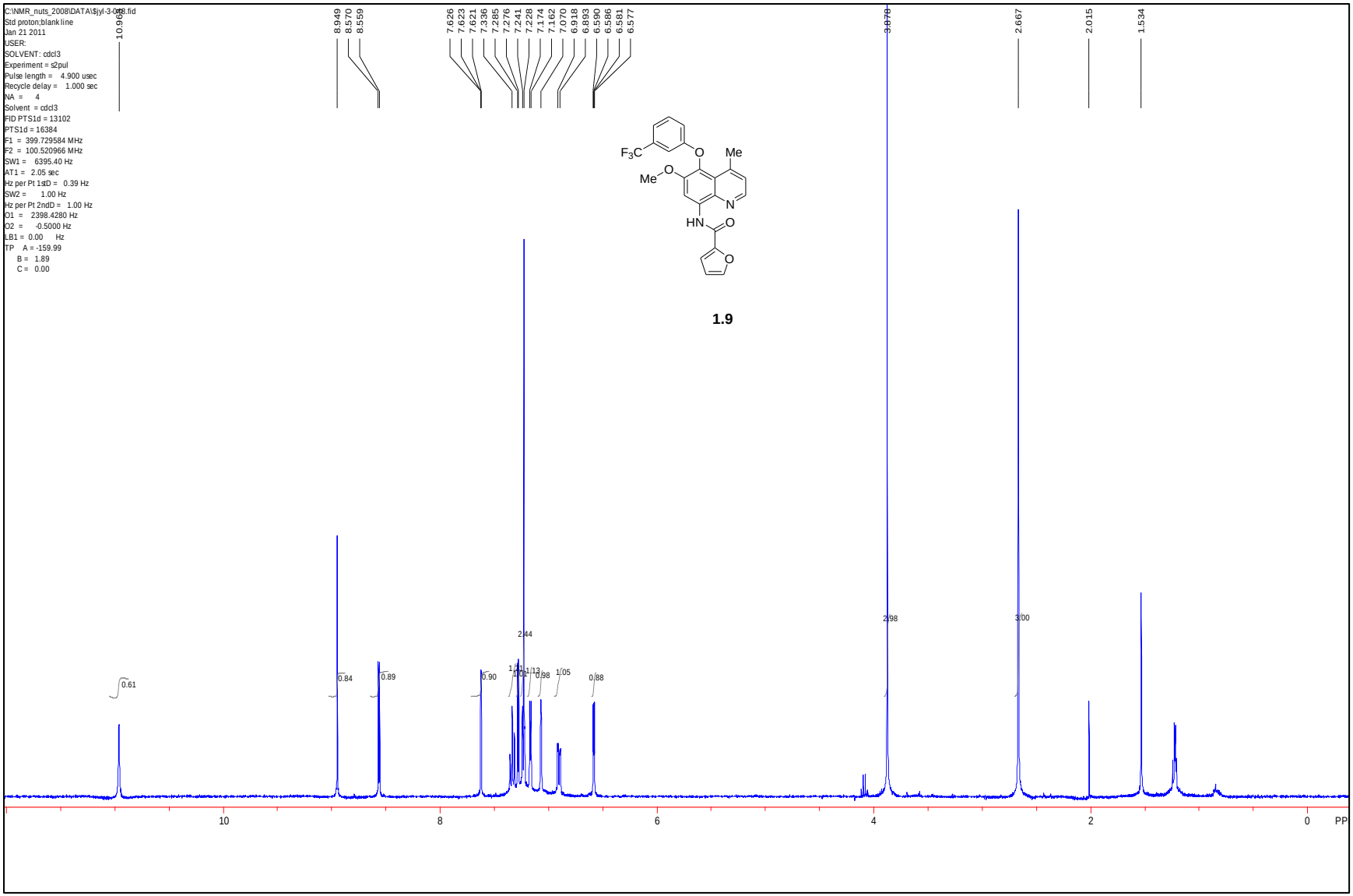
**1.7**

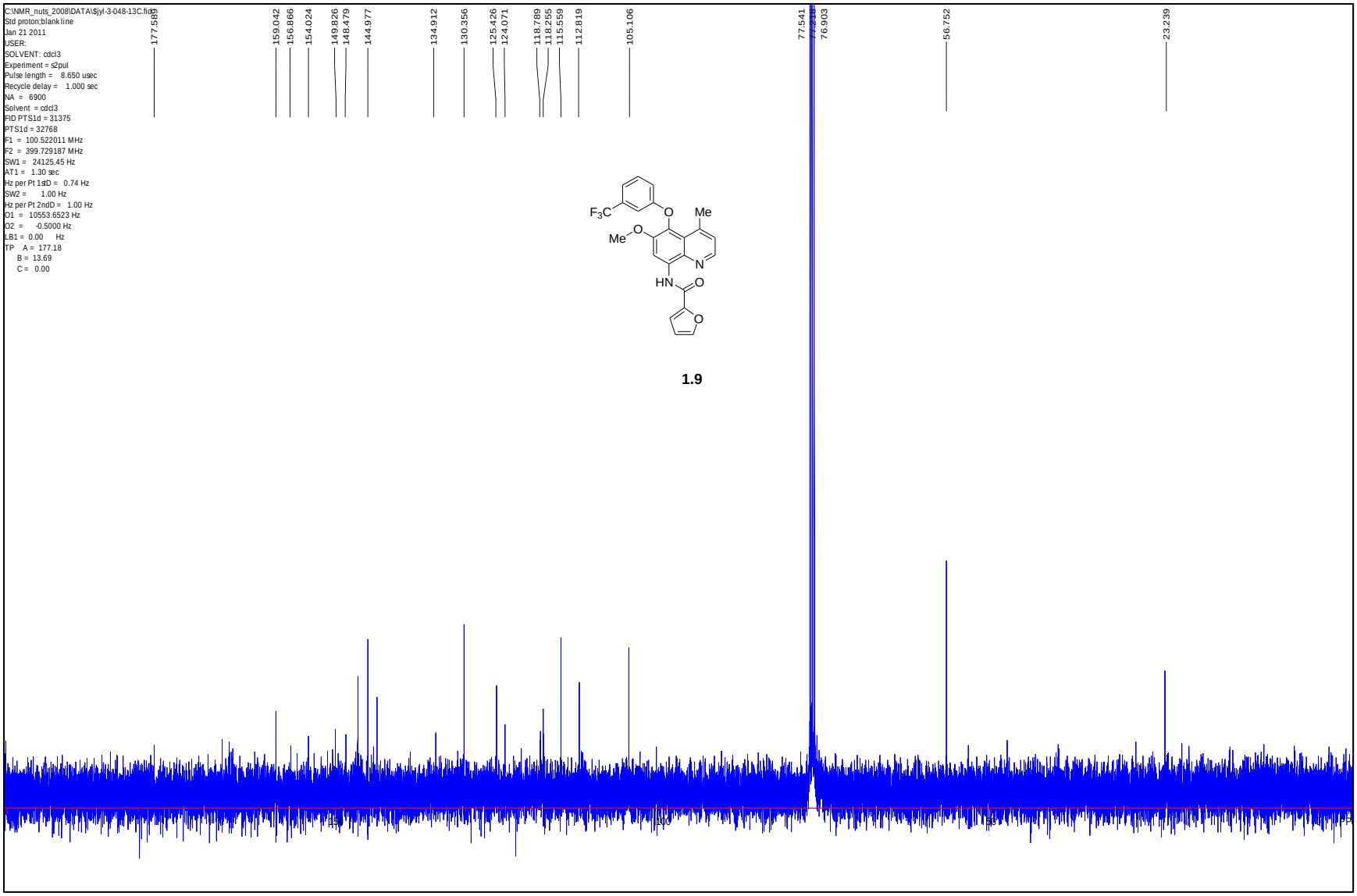

C:\NMR_nuts_2008\DATA\$PQ-25-13C-2.fid
Std Carbon experiment
Apr 18 2014
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 2.000 sec
NA = 17148
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.575584 MHz
F2 = 399.942200 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10561.1172 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -9.84
B = 229.22
C = 0.00
159.961
151.158
149.853
146.804
145.015
144.795
142.750
137.003
136.673
134.137
132.554
132.260
131.960
131.659
130.179
128.639
128.119
127.430
126.726
125.869
125.531
125.165
124.549
122.717
121.404
119.340
119.143
118.106
112.381
112.344
93.843
56.781
43.807
23.370
F3C
O
Me
Me
O
N
HN
N
1.7
150
100
50
PP

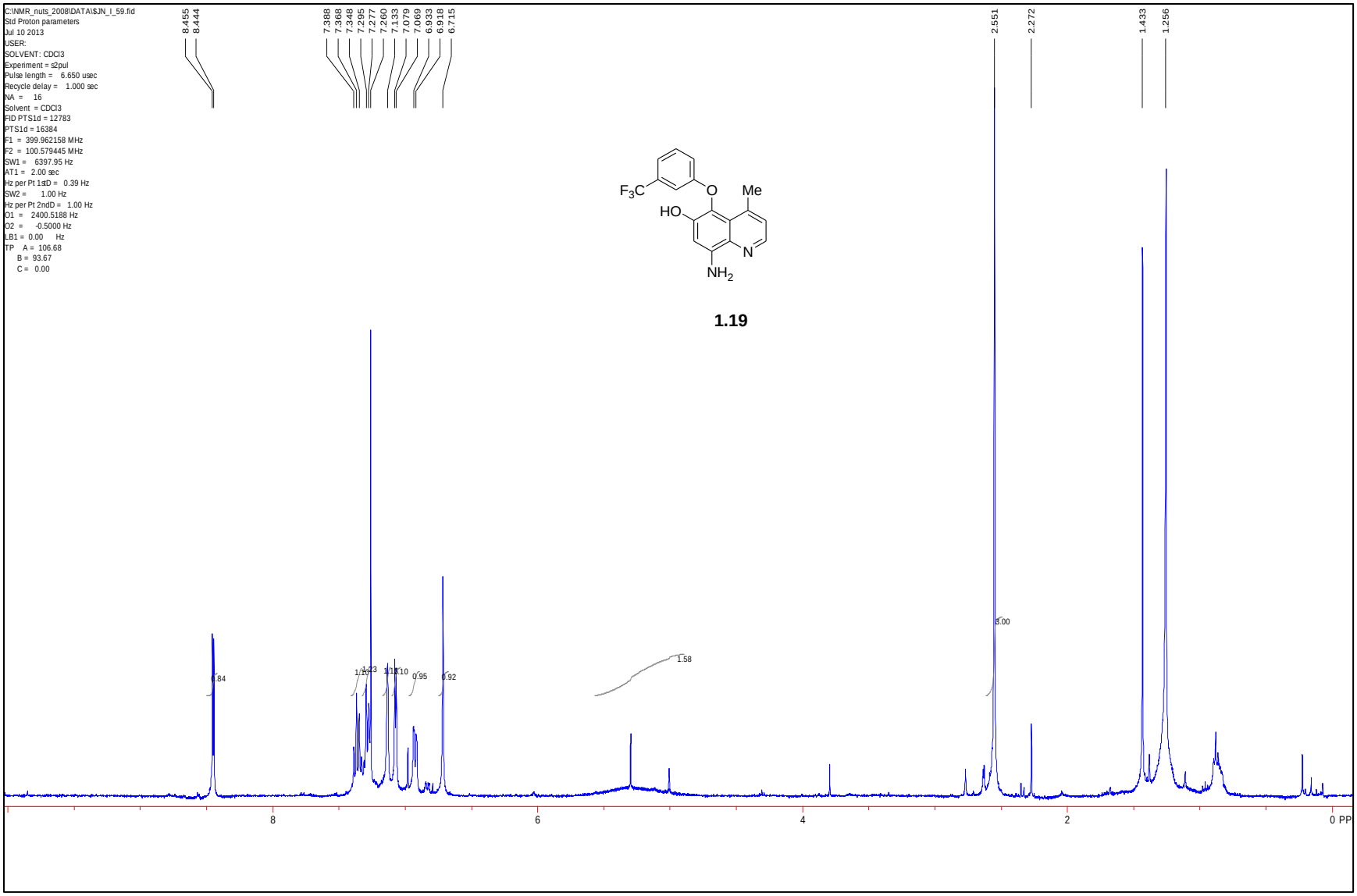

C:\NMR_nuts_2008\DATA\$r-18.fid
Std Proton parameters
Apr 28 2014
USER:
SOLVENT: CDCl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 1.000 sec
NA = 32
Solvent = CDCl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.942596 MHz
F2 = 100.574539 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2400.2253 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -215.60
B = 97.35
C = 0.00
8.412
8.403
7.362
7.342
7.332
7.322
7.306
7.261
7.232
7.214
7.148
7.122
7.117
7.113
7.086
7.079
7.059
7.033
7.028
6.945
6.939
6.928
6.589
6.573
6.565
6.536
6.529
6.526
5.770
5.475
3.879
3.839
3.781
3.754
3.724
3.686
2.752
2.736
2.733
2.728
2.718
2.702
2.673
2.615
1.723
1.712
1.643
1.636
1.618
1.601
1.579
1.251
F3C
O
Me
Me
O
N
HN
O
NH2
0.67
1.79
1.50
2.28
1.41
1.57
0.69
0.71
3.00
2.48
1.96
3.05
8
6
4
2
0
PP

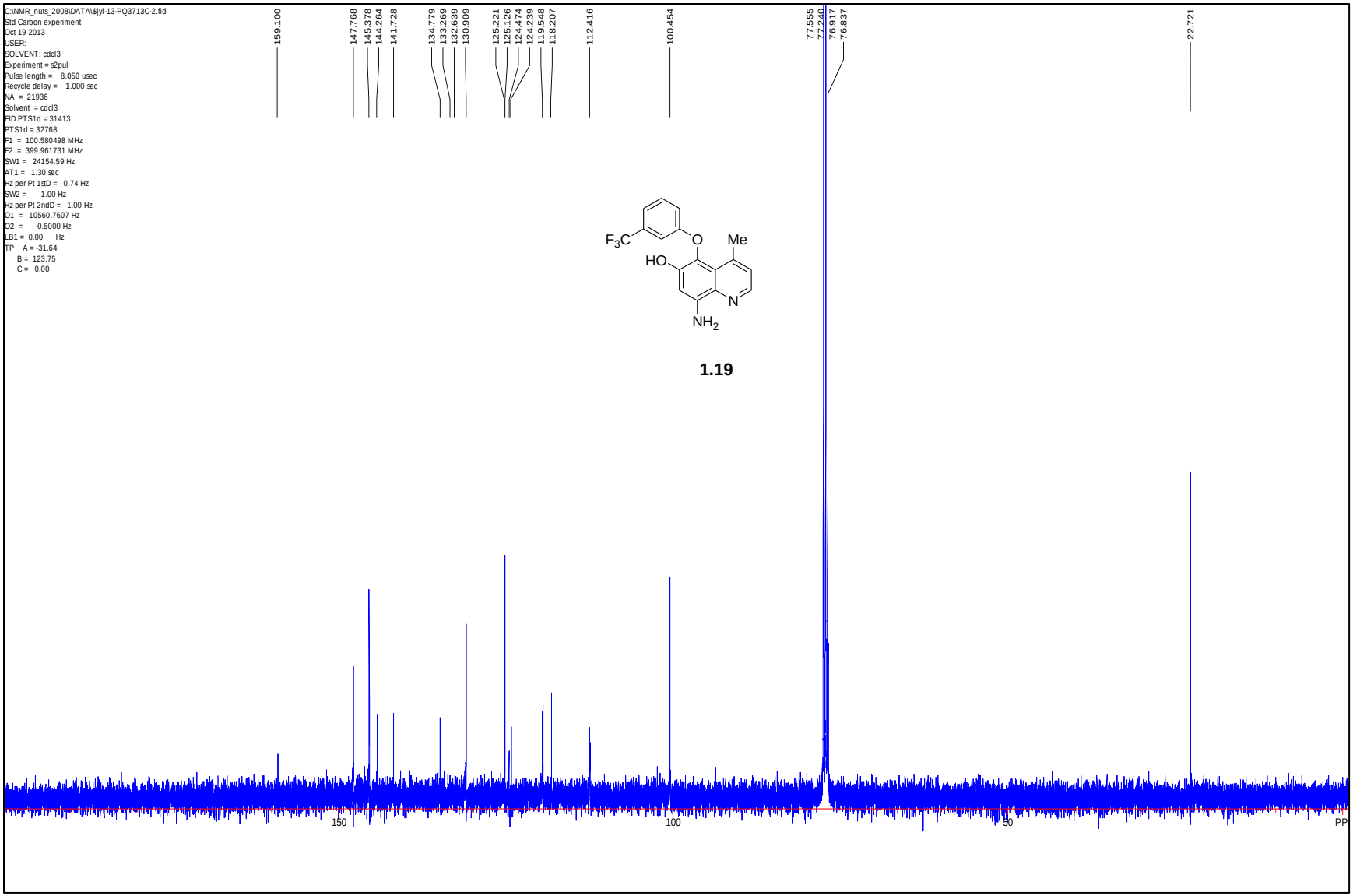
**1.8**

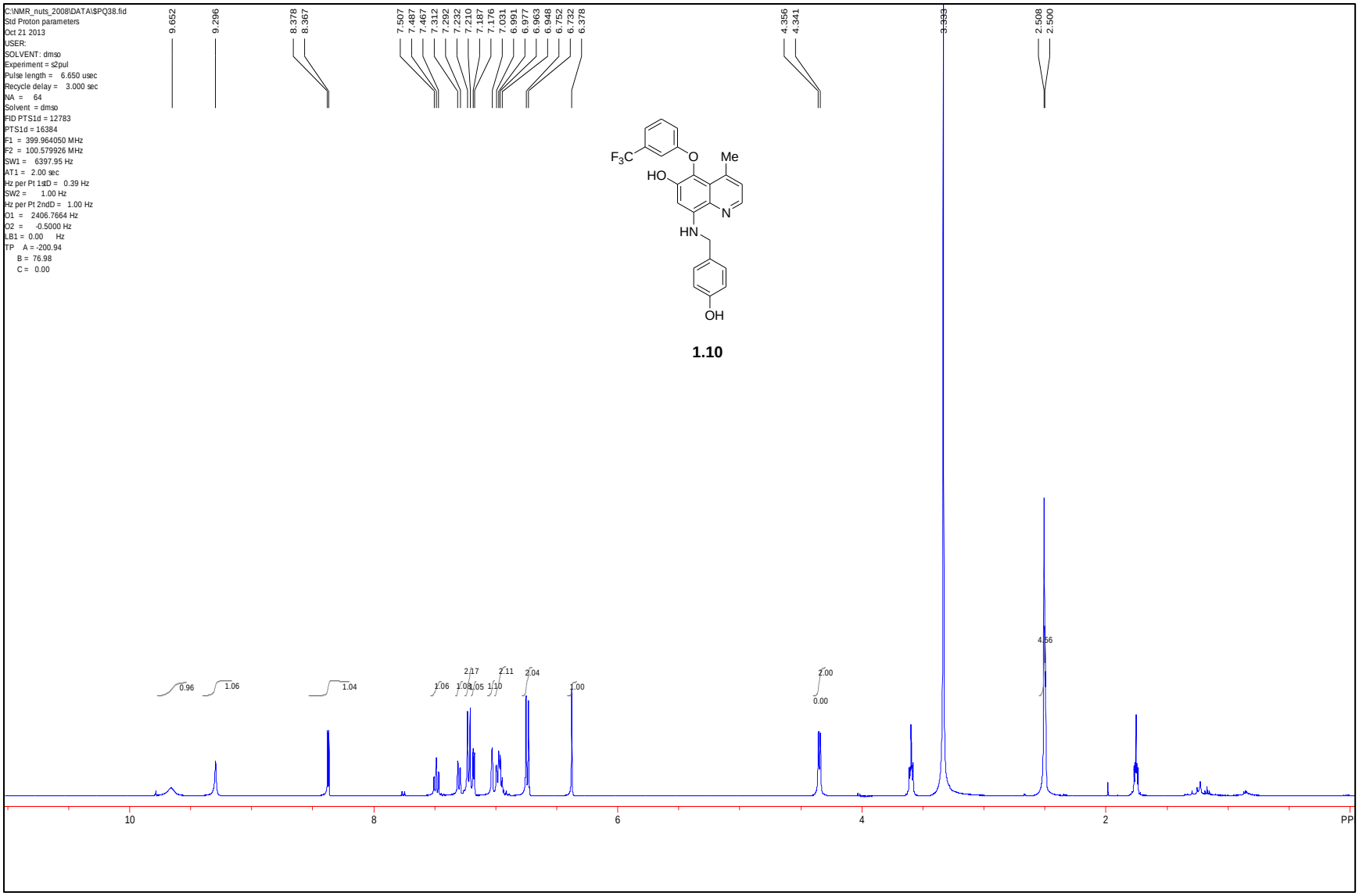

C:\NMR_nuts_2008\DATA\sr-18-13c.fid
Std Carbon experiment
Apr 17 2014
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 2.000 sec
NA = 14956
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.575584 MHz
F2 = 399.942200 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10559.6436 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -30.47
B = 255.94
C = 0.00
173.661
159.837
151.026
145.198
144.231
142.889
134.056
132.737
132.385
131.923
130.230
128.544
126.426
125.421
125.289
124.622
122.783
120.070
118.406
118.223
112.227
112.190
93.711
77.555
77.240
76.925
56.899
39.863
35.700
23.326
F3C
O
Me
Me
O
N
HN
O
NH2
1.8
150
100
50
PP

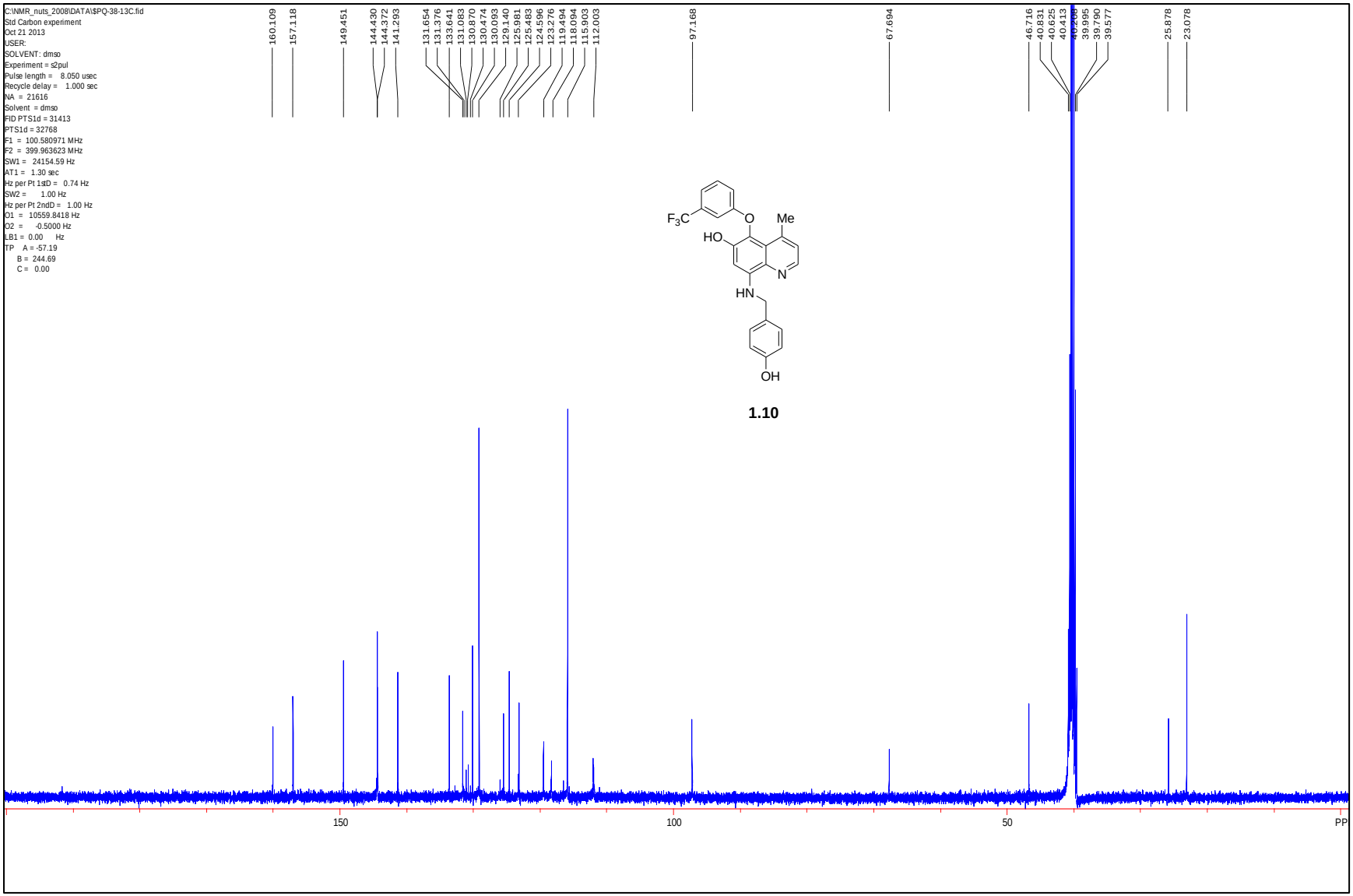

C:\NMR_nuts_2008\DATA\$jyl-3-088.fid
Std proton;blank line
Jan 21 2011
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 4.900 usec
Recycle delay = 1.000 sec
NA = 4
Solvent = cdcl3
FID PTS1d = 13102
PTS1d = 16384
F1 = 399.729584 MHz
F2 = 100.520966 MHz
SW1 = 6395.40 Hz
AT1 = 2.05 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2398.4280 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -159.99
B = 1.89
C = 0.00
10.966
8.949
8.570
8.559
7.626
7.623
7.621
7.336
7.285
7.276
7.241
7.228
7.174
7.162
7.070
6.918
6.893
6.590
6.586
6.581
6.577
3.878
2.667
2.015
1.534
F3C
O
Me
Me
O
N
HN
O
O
1.9
0.61
0.84
0.89
0.90
2.44
1.01
1.02
1.13
0.98
1.05
0.88
2.98
3.00
10
8
6
4
2
0
PPM

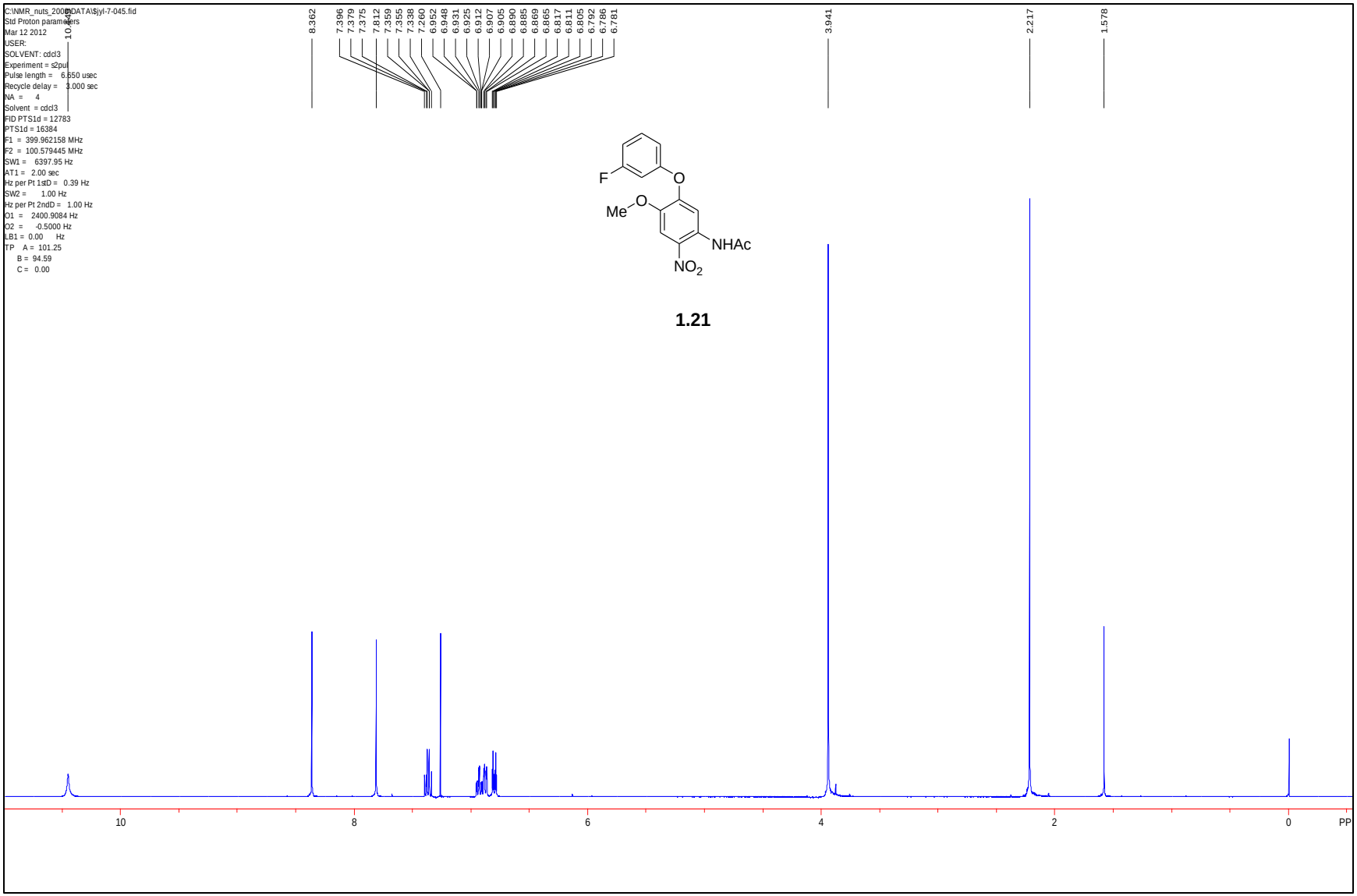

C:\NMR_nuts_2008\DATA\$jyl-3-048-13C.fid
Std proton;blank line
Jan 21 2011
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.650 usec
Recycle delay = 1.000 sec
NA = 6900
Solvent = cdcl3
FID PTS1d = 31375
PTS1d = 32768
F1 = 100.522011 MHz
F2 = 399.729187 MHz
SW1 = 24125.45 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10553.6523 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 177.18
B = 13.69
C = 0.00
177.585
159.042
156.866
154.024
149.826
148.479
144.977
134.912
130.356
125.426
124.071
118.789
118.255
115.559
112.819
105.106
77.541
76.903
56.752
23.239
F3C
O
Me
Me
O
N
HN
O
O
1.9
150
100
50
PPM

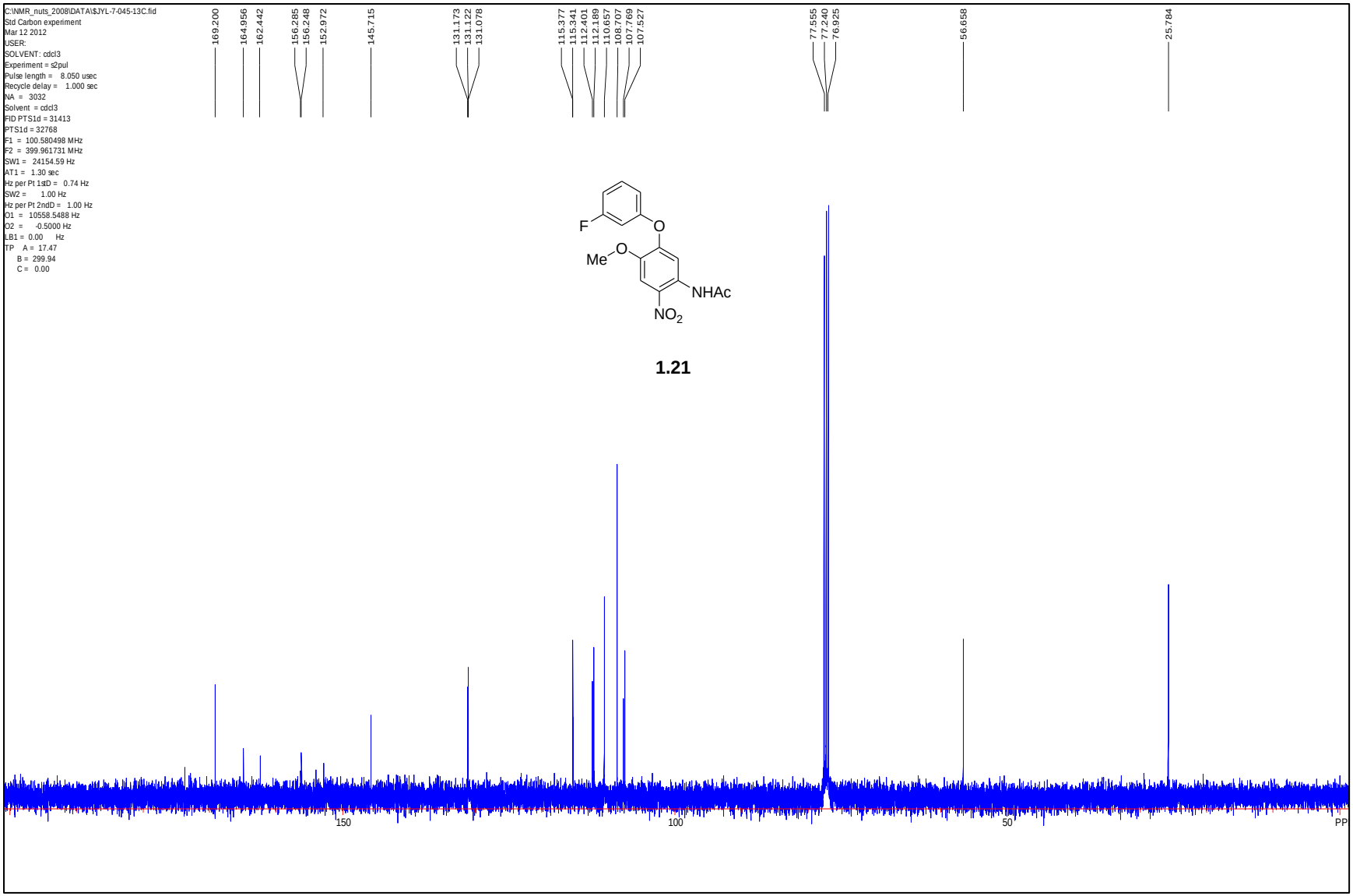

C:\NMR_nuts_2008\DATA\$JN_I_59.fid
Std Proton parameters
Jul 10 2013
USER:
SOLVENT : CDCl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 1.000 sec
NA = 16
Solvent = CDCl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.962158 MHz
F2 = 100.579445 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2400.5188 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 106.68
B = 93.67
C = 0.00
8.455
8.444
7.388
7.368
7.348
7.295
7.277
7.260
7.133
7.079
7.069
6.933
6.918
6.715
2.551
2.272
1.433
1.256
F3C
O
Me
HO
N
NH2
1.19
3.00
1.58
0.84
1.10
1.13
1.10
0.95
0.92
8
6
4
2
0 PP

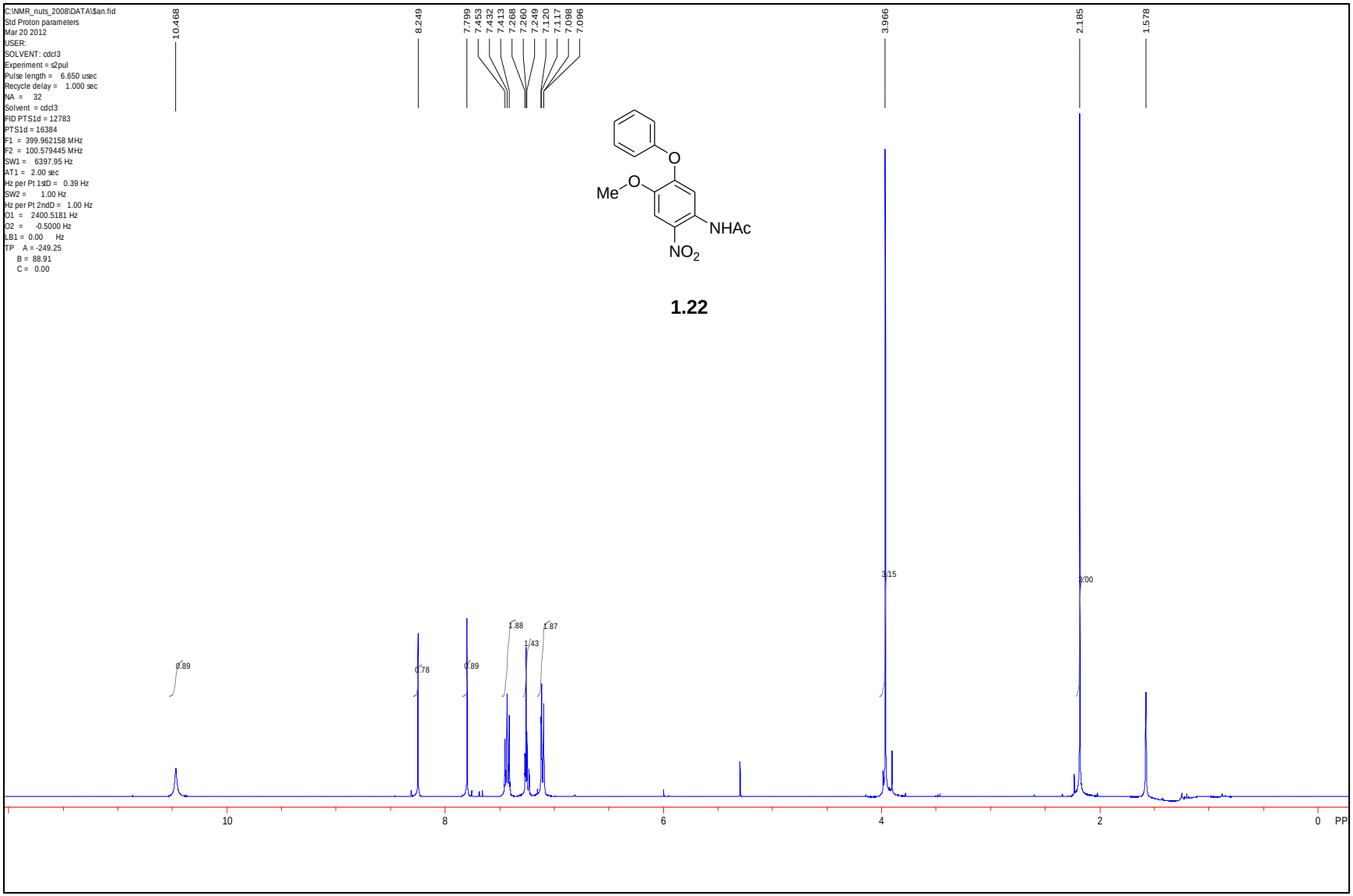

C:\NMR_nuts_2008\DATA\$jyl-13-PQ3713C-2.fid
Std Carbon experiment
Oct 19 2013
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 1.000 sec
NA = 21936
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.580498 MHz
F2 = 399.961731 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10560.7607 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -31.64
B = 123.75
C = 0.00
159.100
147.768
145.378
144.264
141.728
134.779
133.269
132.639
130.909
125.221
125.126
124.474
124.239
119.548
118.207
112.416
100.454
77.555
77.240
76.917
76.837
22.721
F3C
O
Me
HO
N
NH2
1.19
150
100
50
PP

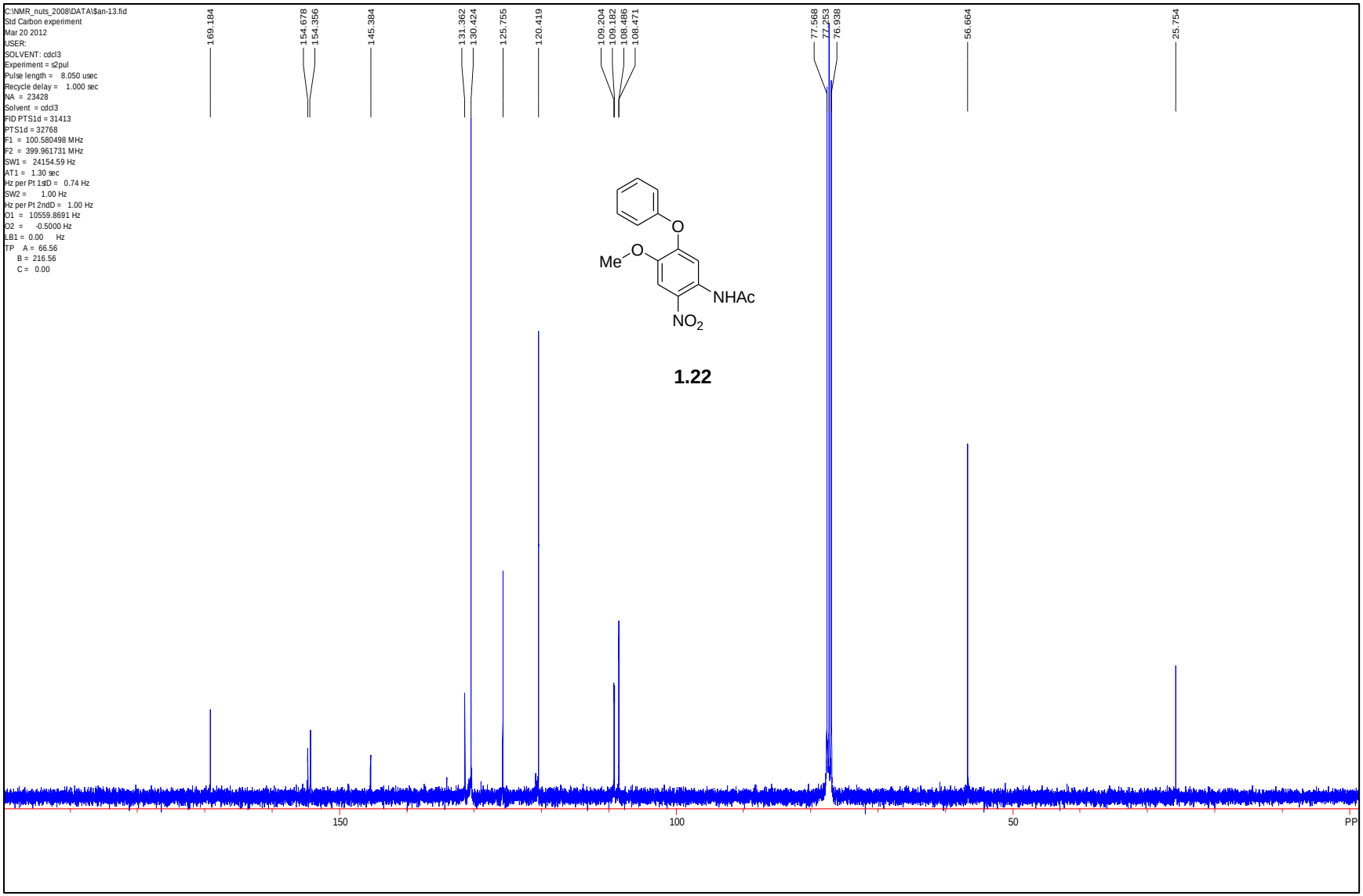

C:\NMR_nuts_2008\DATA\$PQ38.fid
Std Proton parameters
Oct 21 2013
USER:
SOLVENT : dmso
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 3.000 sec
NA = 64
Solvent = dmso
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.964050 MHz
F2 = 100.579926 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2406.7664 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -200.94
B = 76.98
C = 0.00
9.652
9.296
8.378
8.367
7.507
7.487
7.467
7.312
7.292
7.232
7.210
7.187
7.176
7.031
6.991
6.977
6.963
6.948
6.752
6.732
6.378
4.356
4.341
3.393
2.508
2.500
F3C
O
Me
HO
N
HN
OH
1.10
0.96
1.06
1.04
1.06
1.03
1.05
1.10
2.17
2.11
2.04
1.00
2.00
0.00
4.56
10
8
6
4
2
PP

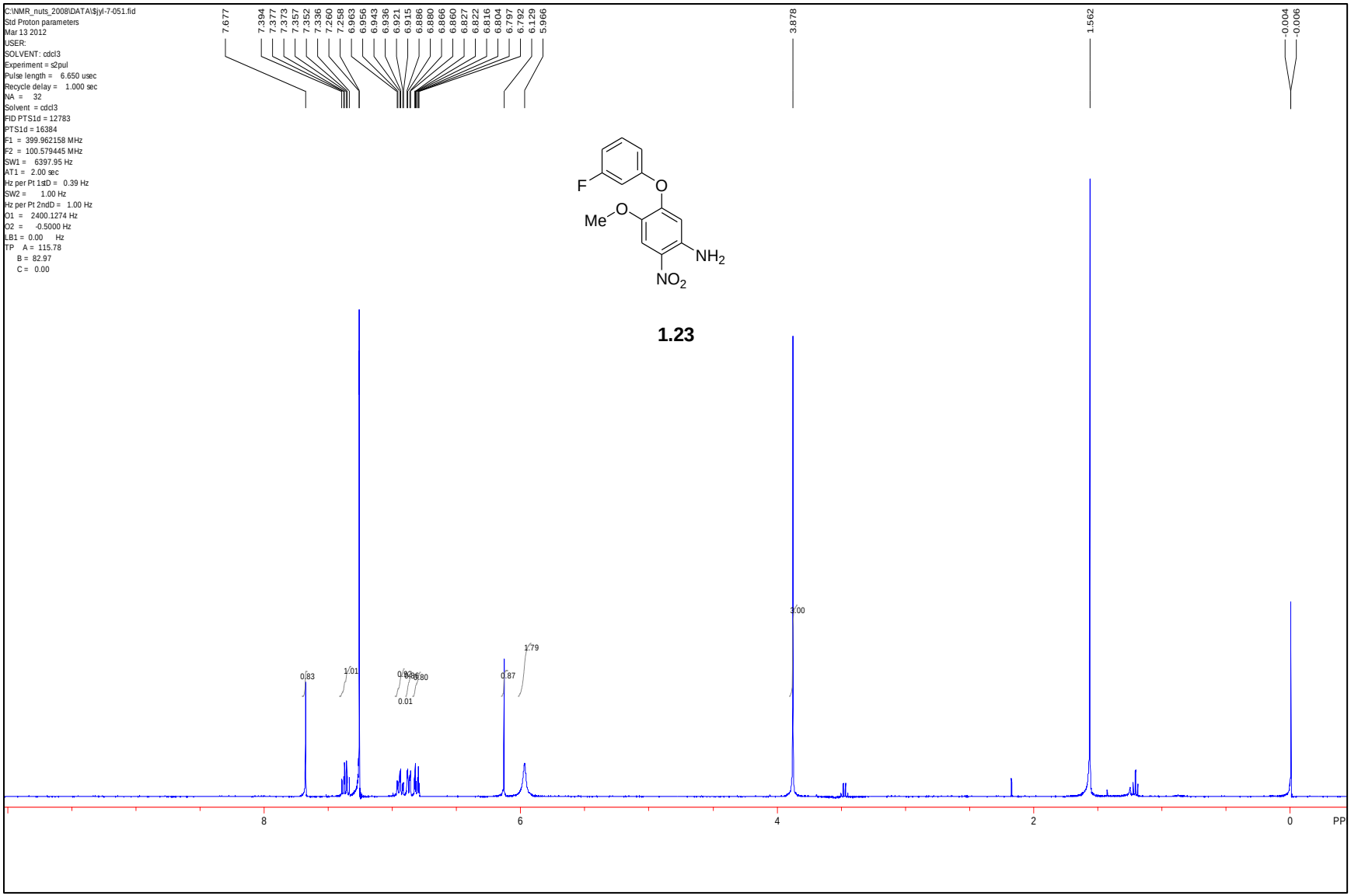

C:\NMR_nuts_2008\DATA\$PQ-38-13C.fid
Std Carbon experiment
Oct 21 2013
USER:
SOLVENT: dmso
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 1.000 sec
NA = 21616
Solvent = dmso
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.580971 MHz
F2 = 399.963623 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10559.8418 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -57.19
B = 244.69
C = 0.00
160.109
157.118
149.451
144.430
144.372
141.293
131.654
131.376
133.641
131.083
130.870
130.474
130.093
129.140
125.981
125.483
124.596
123.276
119.494
118.094
115.903
112.003
97.168
67.694
46.716
40.831
40.625
40.413
39.995
39.790
39.577
25.878
23.078
F3C
O
Me
HO
N
HN
OH
1.10
150
100
50
PP

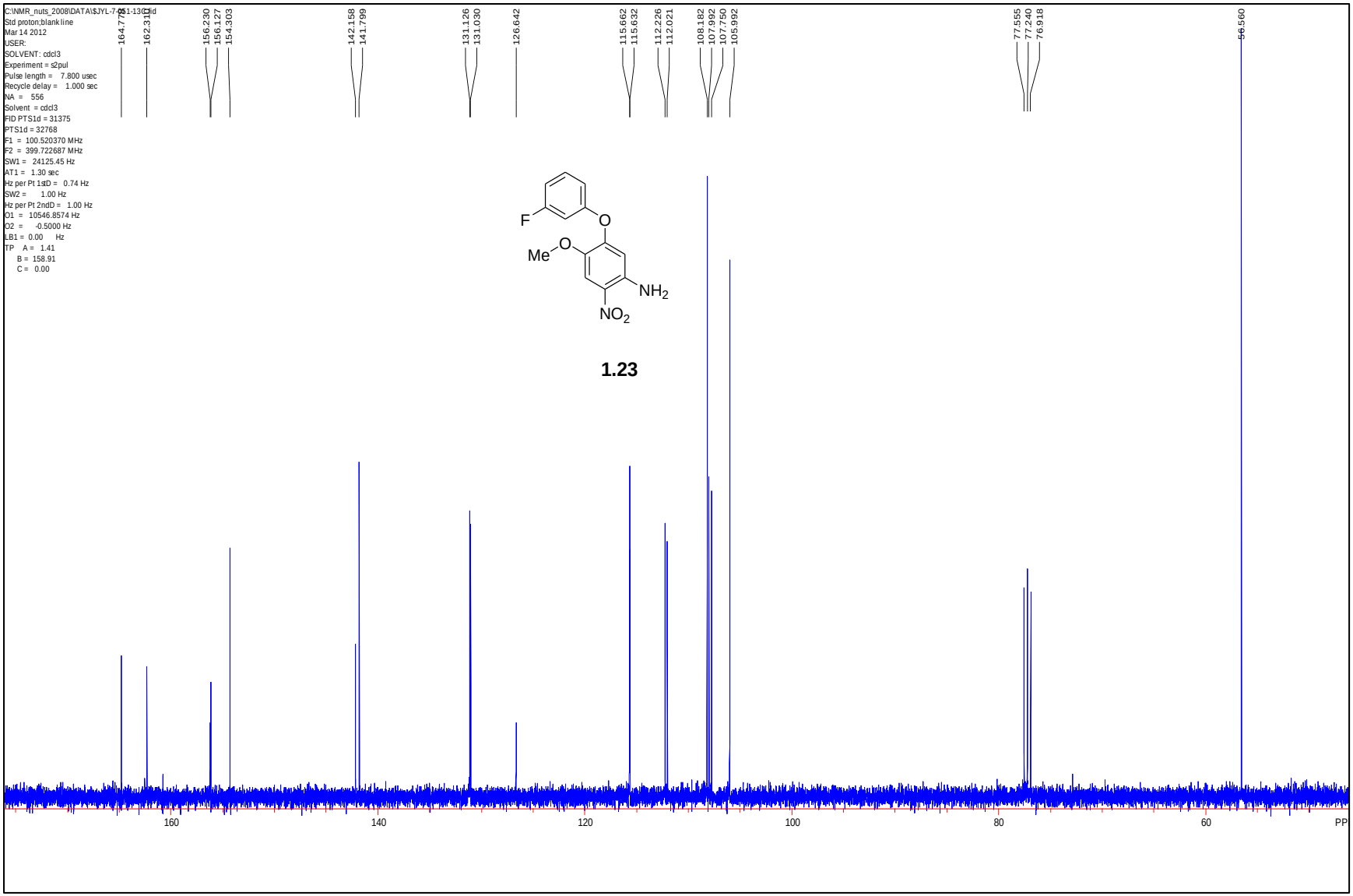

C:\NMR_nuts_2008\DATA\sjyl-7-045.fid
Std Proton parameters
Mar 12 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.850 usec
Recycle delay = 3.000 sec
NA = 4
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.962158 MHz
F2 = 100.579445 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2400.9084 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 101.25
B = 94.59
C = 0.00
10.00
8.362
7.396
7.379
7.375
7.812
7.359
7.355
7.338
7.260
6.952
6.948
6.931
6.925
6.912
6.907
6.905
6.890
6.885
6.869
6.865
6.817
6.811
6.805
6.792
6.786
6.781
3.941
2.217
1.578
F
O
Me
O
NHAc
NO2
1.21
10
8
6
4
2
0
PP

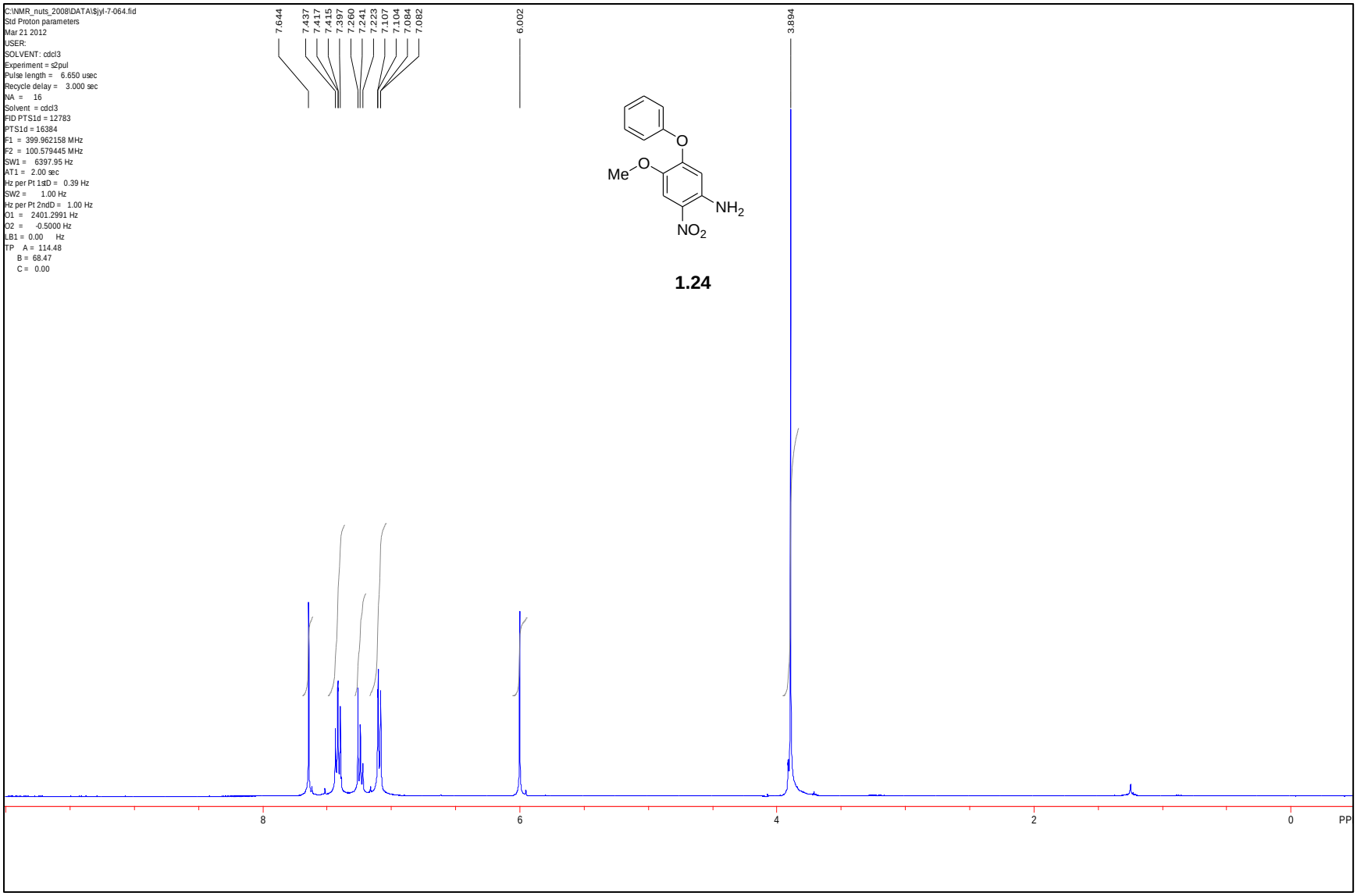

C:\NMR_nuts_2008\DATA\$JYL-7-045-13C.fid
Std Carbon experiment
Mar 12 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 1.000 sec
NA = 3032
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.580498 MHz
F2 = 399.961731 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10558.5488 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 17.47
B = 299.94
C = 0.00
169.200
164.956
162.442
156.285
156.248
152.972
145.715
131.173
131.122
131.078
115.377
115.341
112.401
112.189
110.657
108.707
107.769
107.527
77.555
77.240
76.925
56.658
25.784
F
O
Me
O
NHAc
NO2
1.21
150
100
50
PP

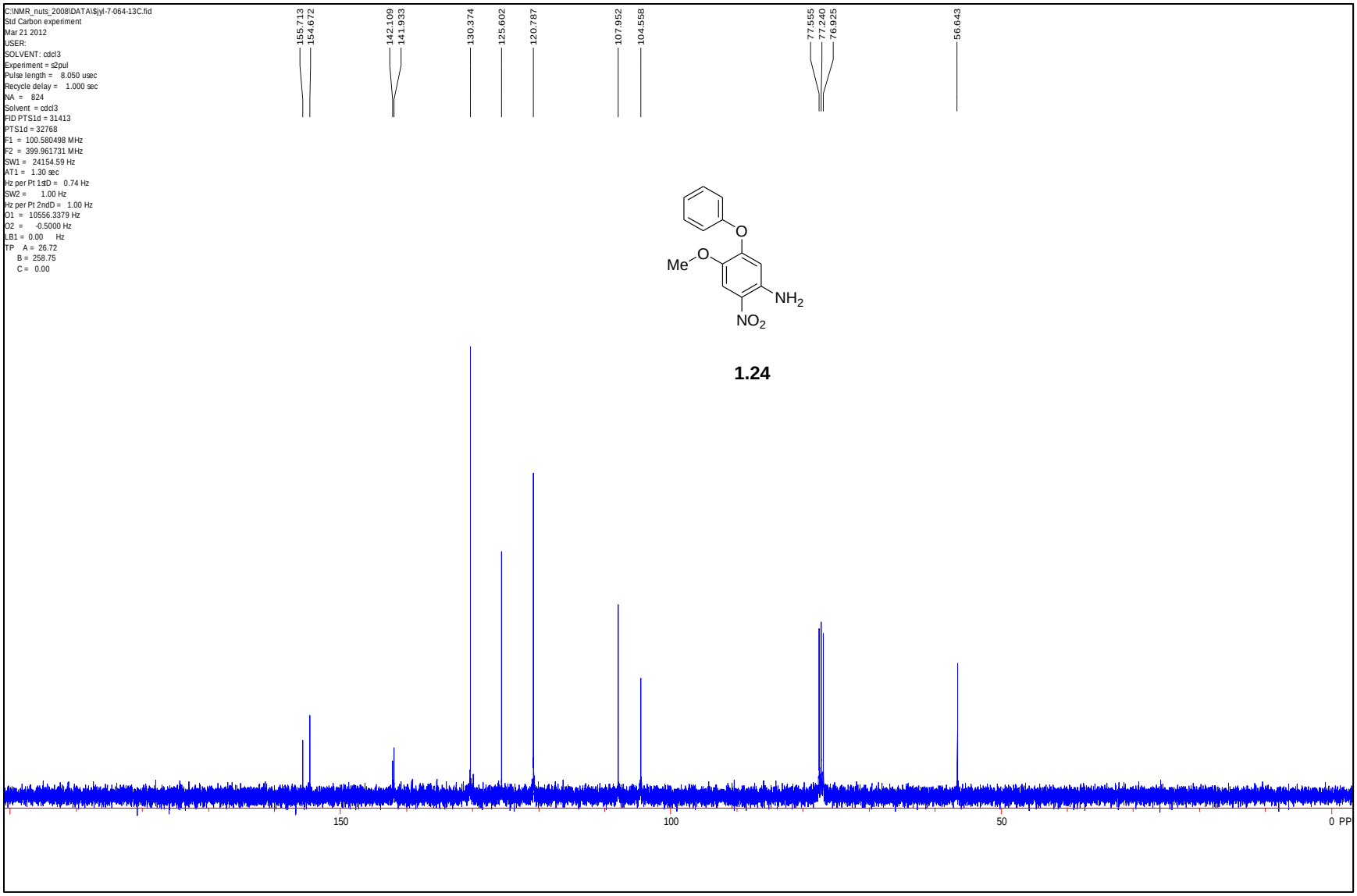

C:\NMR_nuts_2008\DATA\$an.fid
Std Proton parameters
Mar 20 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 1.000 sec
NA = 32
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.962158 MHz
F2 = 100.579445 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2400.5181 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -249.25
B = 88.91
C = 0.00
10.468
8.249
7.799
7.453
7.432
7.413
7.268
7.260
7.249
7.120
7.117
7.098
7.096
3.966
2.185
1.578
Me
O
O
NHAc
NO2
1.22
0.89
0.78
0.89
1.88
1.43
1.87
3.15
3.00
10
8
6
4
2
0
PP

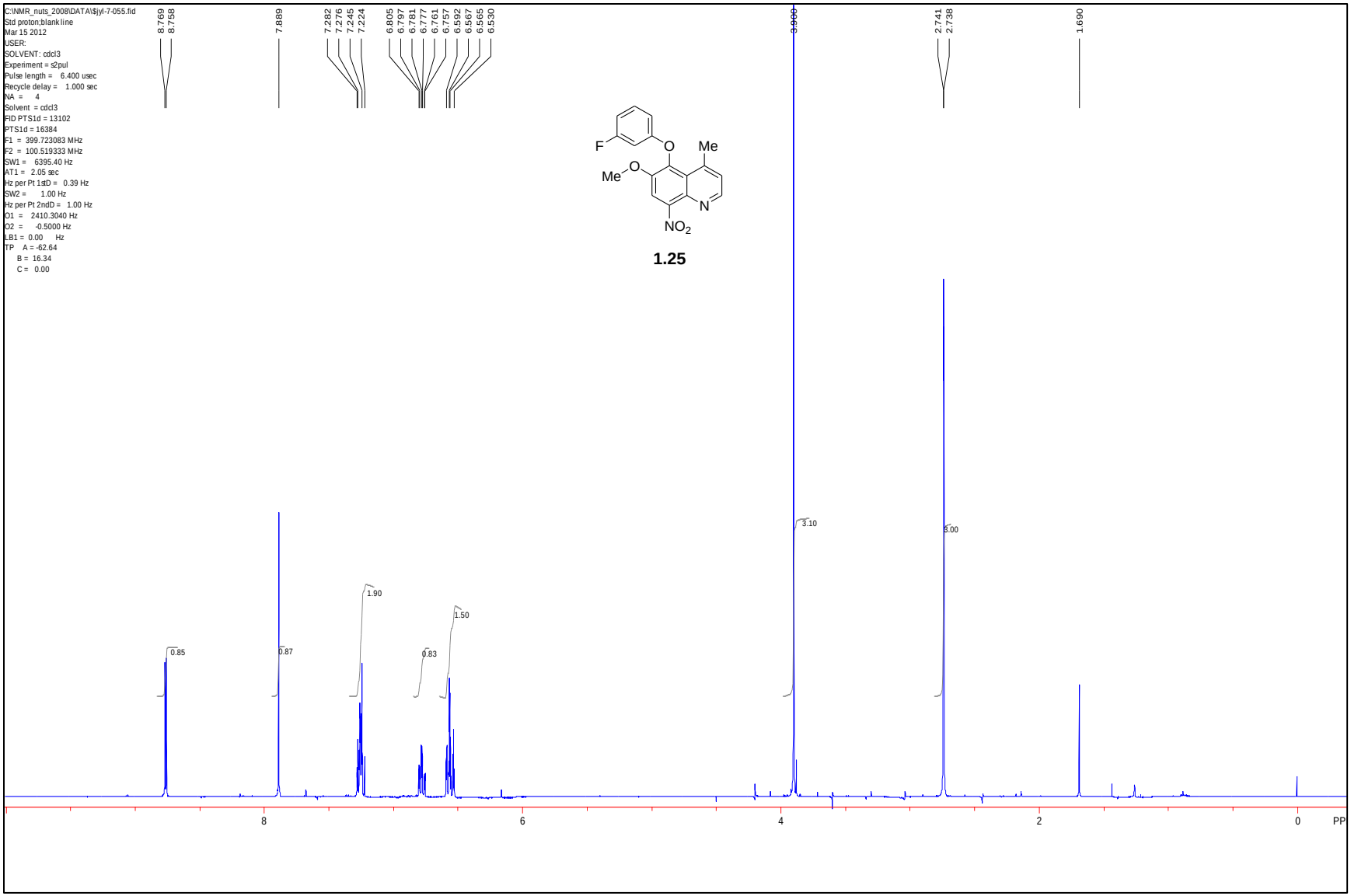

C:\NMR_nuts_2008\DATA\$an-13.fid
Std Carbon experiment
Mar 20 2012
USER:
SOLVENT : cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 1.000 sec
NA = 23428
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.580498 MHz
F2 = 399.961731 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10559.8691 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 66.56
B = 216.56
C = 0.00
169.184
154.678
154.356
145.384
131.362
130.424
125.755
120.419
109.204
109.182
108.486
108.471
77.568
77.253
76.938
56.664
25.754
O
Me
O
NHAc
NO2
1.22
150
100
50
PP

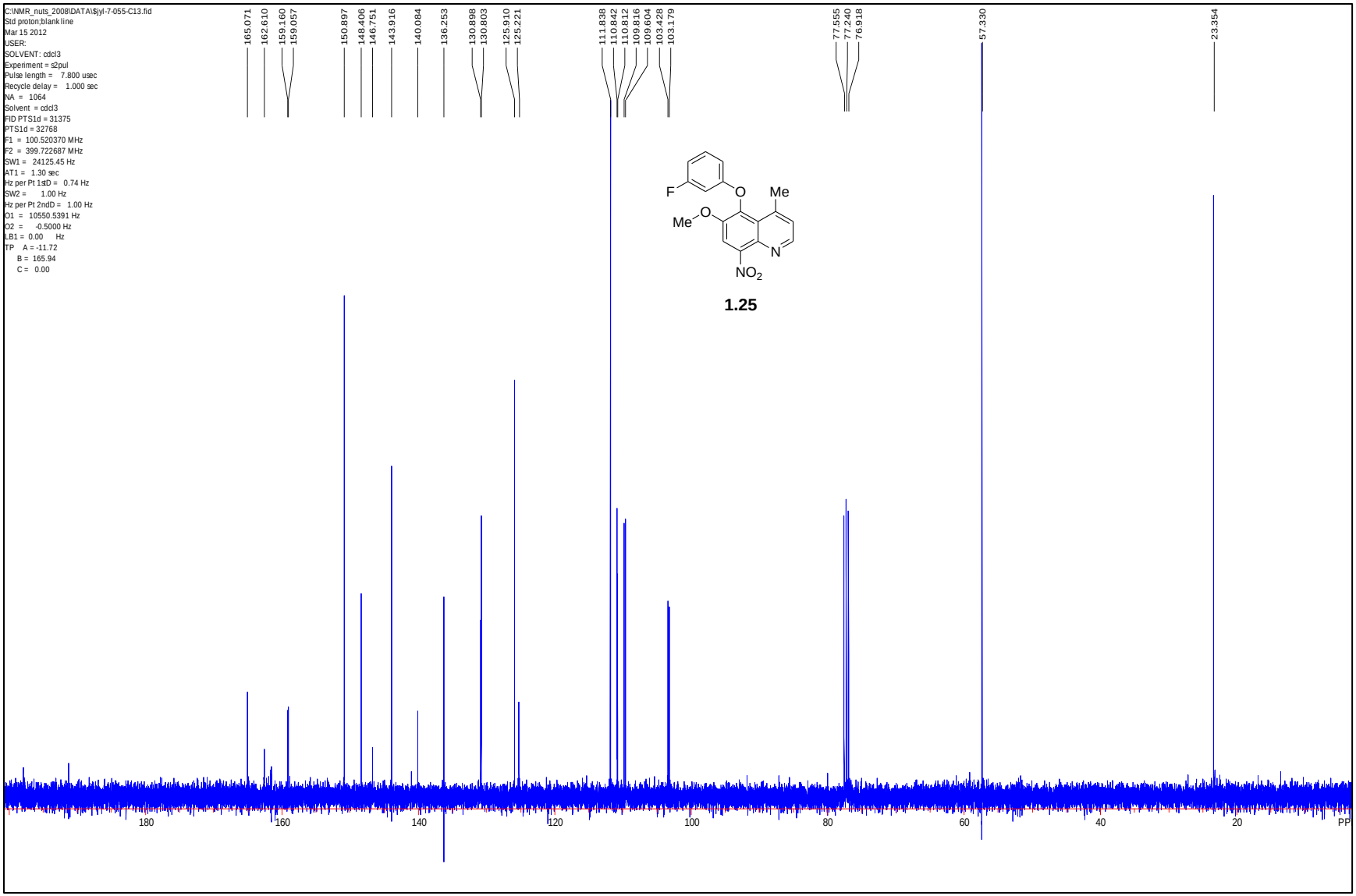

C:\NMR_nuts_2008\DATA\$jyl-7-051.fid
Std Proton parameters
Mar 13 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 1.000 sec
NA = 32
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.962158 MHz
F2 = 100.579445 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2400.1274 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 115.78
B = 82.97
C = 0.00
7.677
7.394
7.377
7.373
7.357
7.352
7.336
7.260
7.258
6.963
6.956
6.943
6.936
6.921
6.915
6.886
6.880
6.866
6.860
6.827
6.822
6.816
6.804
6.797
6.792
6.129
5.966
3.878
1.562
-0.004
-0.006
F
O
Me
O
NH2
NO2
1.23
0.83
1.01
0.01
0.87
1.79
3.00
8
6
4
2
0
PPM

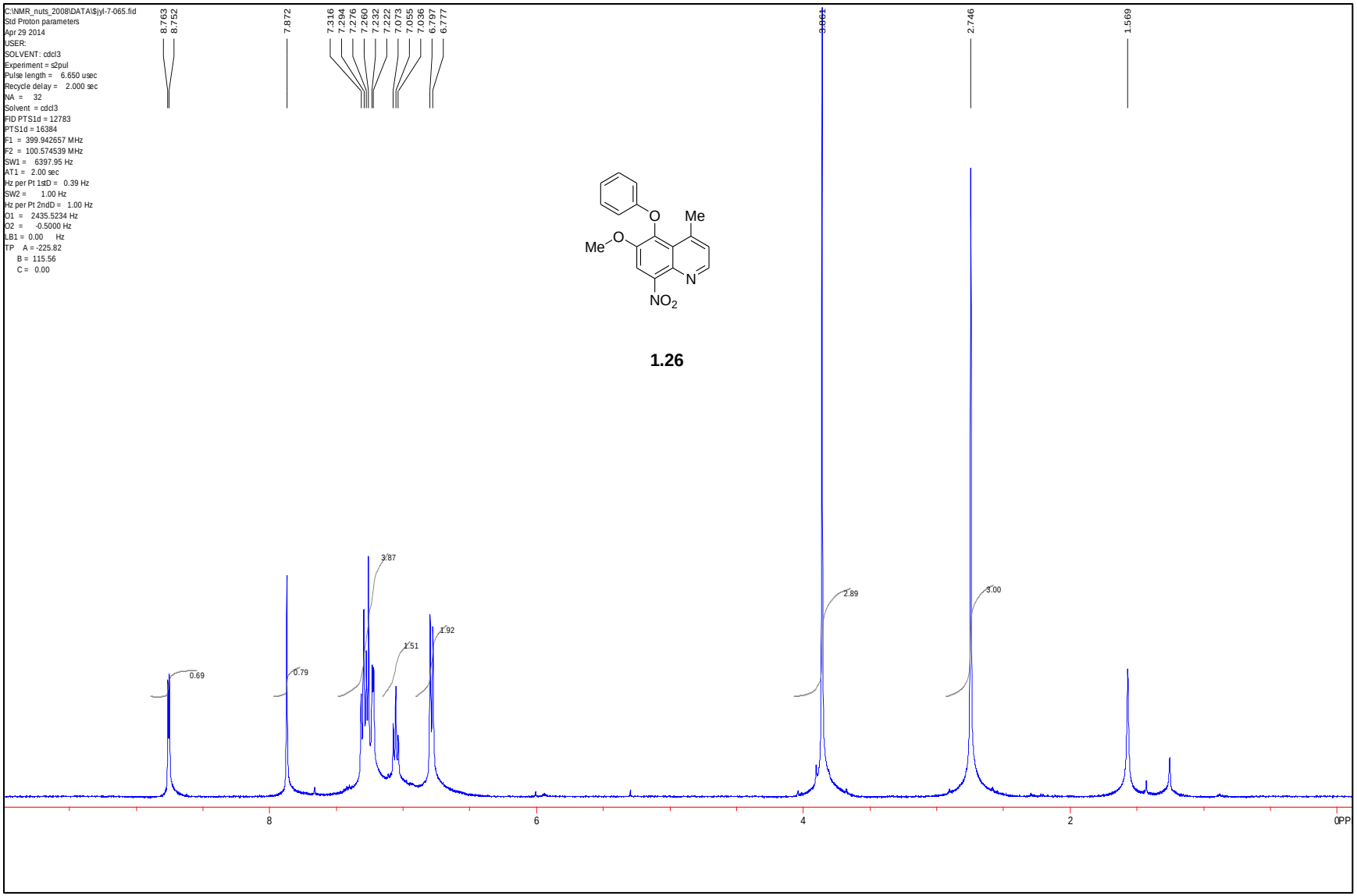

C:\NMR_nuts_2008\DATA\SJYL-7-051-13C.fid
Std proton;blank line
Mar 14 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 7.800 usec
Recycle delay = 1.000 sec
NA = 556
Solvent = cdcl3
FID PTS1d = 31375
PTS1d = 32768
F1 = 100.520370 MHz
F2 = 399.722687 MHz
SW1 = 24125.45 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10546.8574 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 1.41
B = 158.91
C = 0.00
164.778
162.311
156.230
156.127
154.303
142.158
141.799
131.126
131.030
126.642
115.662
115.632
112.226
112.021
108.182
107.992
107.750
105.992
77.555
77.240
76.918
56.560
F
O
Me
O
NH2
NO2
1.23
160
140
120
100
80
60
PP

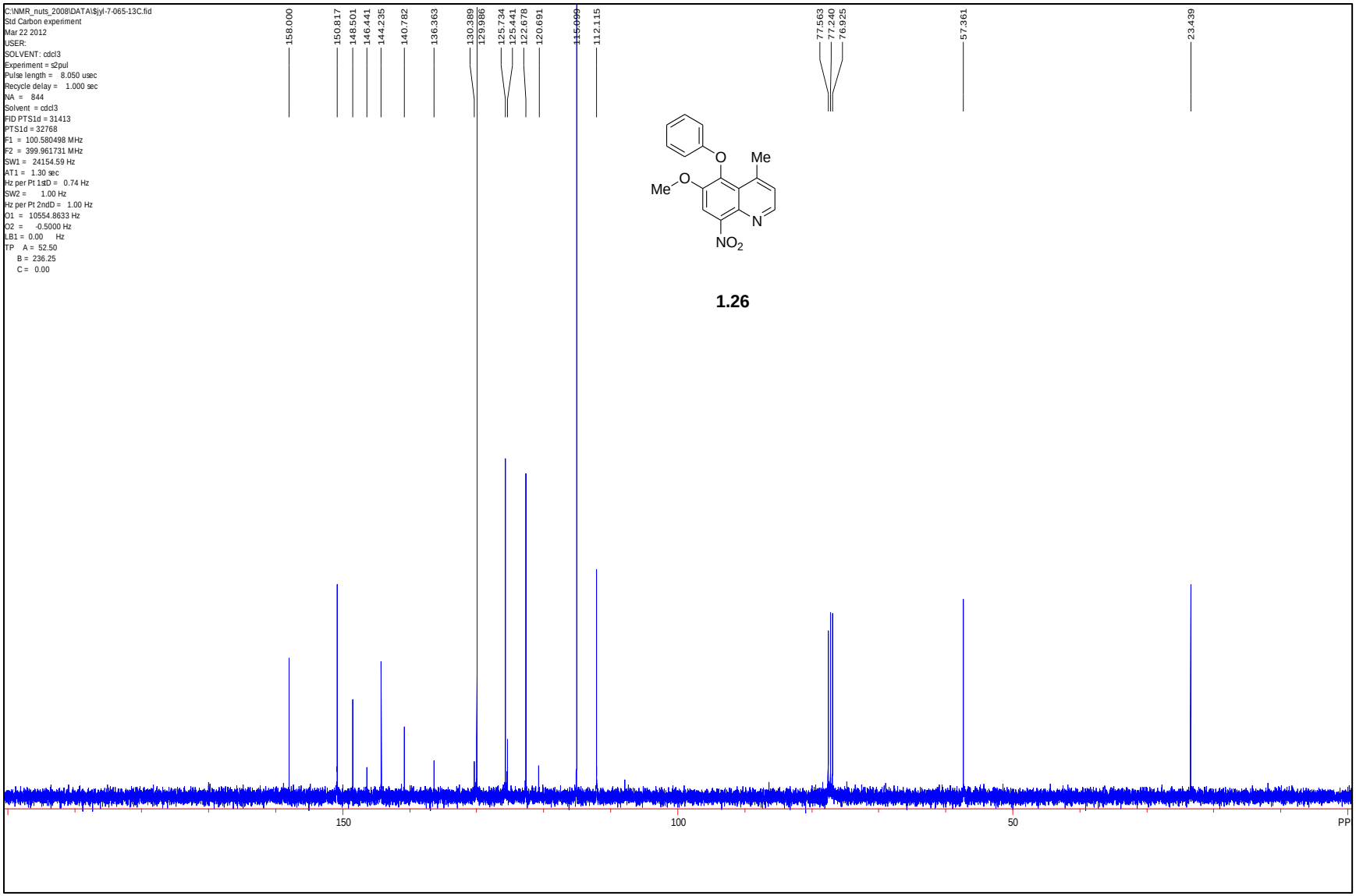

C:\NMR_nuts_2008\DATA\$jyl-7-064.fid
Std Proton parameters
Mar 21 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 3.000 sec
NA = 16
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.962158 MHz
F2 = 100.579445 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2401.2991 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 114.48
B = 68.47
C = 0.00
7.644
7.437
7.417
7.415
7.397
7.260
7.241
7.223
7.107
7.104
7.084
7.082
6.002
3.894
O
Me
O
NH2
NO2
1.24
8
6
4
2
0
PP

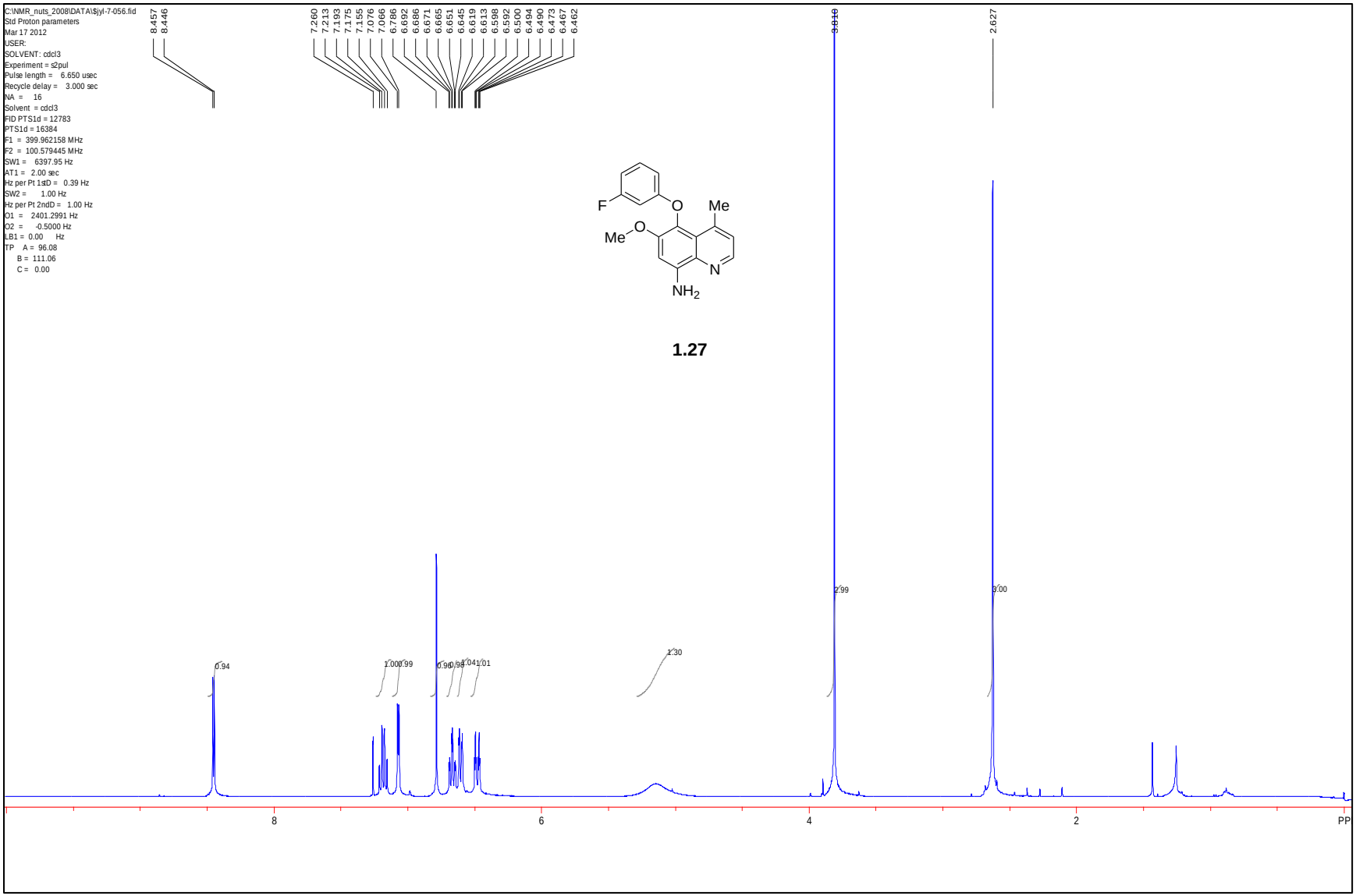

C:\NMR_nuts_2008\DATA\$jyl-7-064-13C.fid
Std Carbon experiment
Mar 21 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 1.000 sec
NA = 824
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.580498 MHz
F2 = 399.961731 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10556.3379 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 26.72
B = 258.75
C = 0.00
155.713
154.672
142.109
141.933
130.374
125.602
120.787
107.952
104.558
77.555
77.240
76.925
56.643
O
Me
O
NH2
NO2
1.24
150
100
50
0 PP

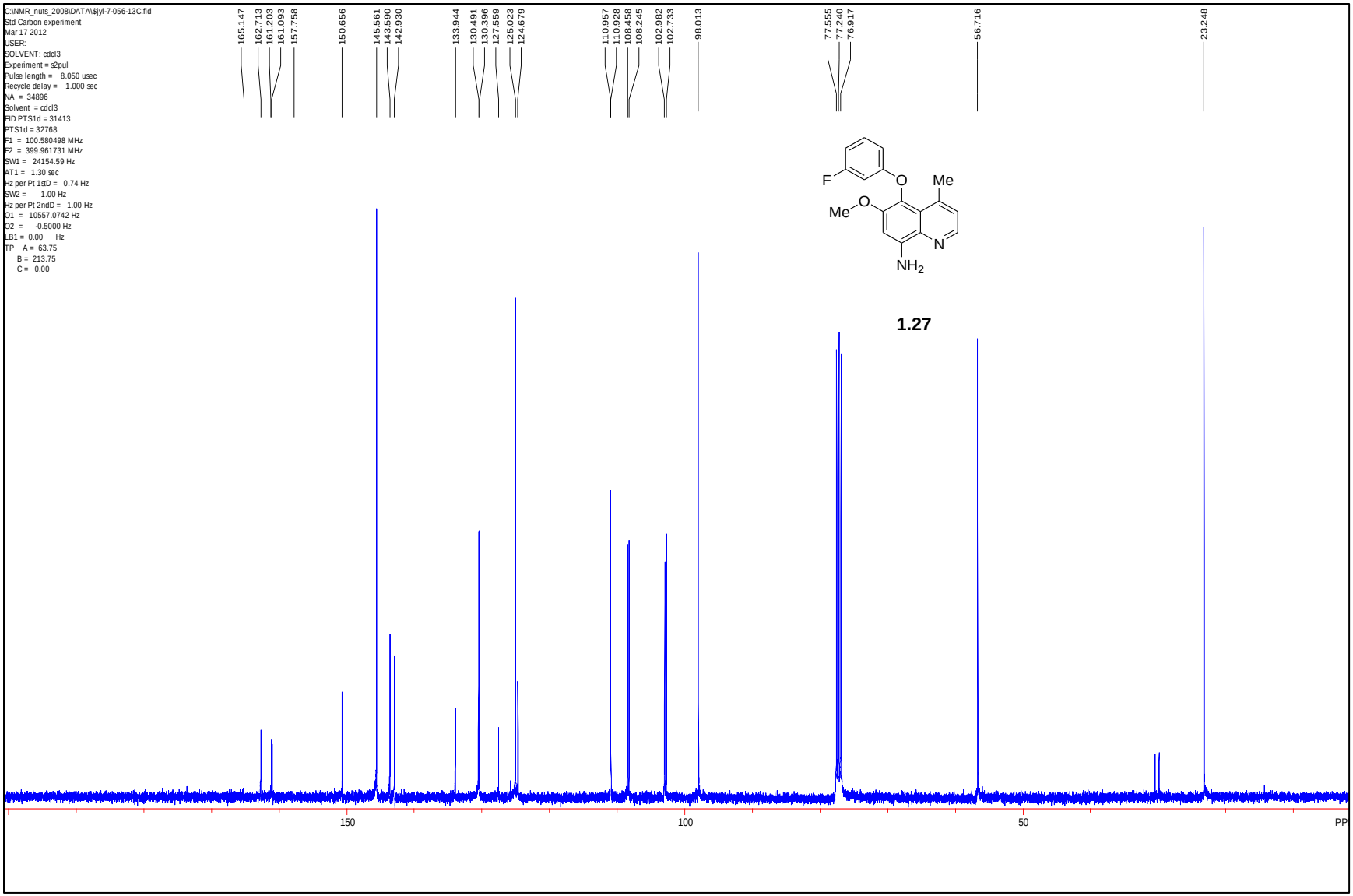

C:\NMR_nuts_2008\DATA\$jyl-7-055.fid
Std proton;blank line
Mar 15 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.400 usec
Recycle delay = 1.000 sec
NA = 4
Solvent = cdcl3
FID PTS1d = 13102
PTS1d = 16384
F1 = 399.723083 MHz
F2 = 100.519333 MHz
SW1 = 6395.40 Hz
AT1 = 2.05 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2410.3040 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -62.64
B = 16.34
C = 0.00
8.769
8.758
7.889
7.282
7.276
7.245
7.224
6.805
6.797
6.781
6.777
6.761
6.757
6.592
6.567
6.565
6.530
3.986
2.741
2.738
1.690
F
O
Me
Me
O
N
NO2
1.25
0.85
0.87
1.90
0.83
1.50
3.10
3.00
8
6
4
2
0
PPM

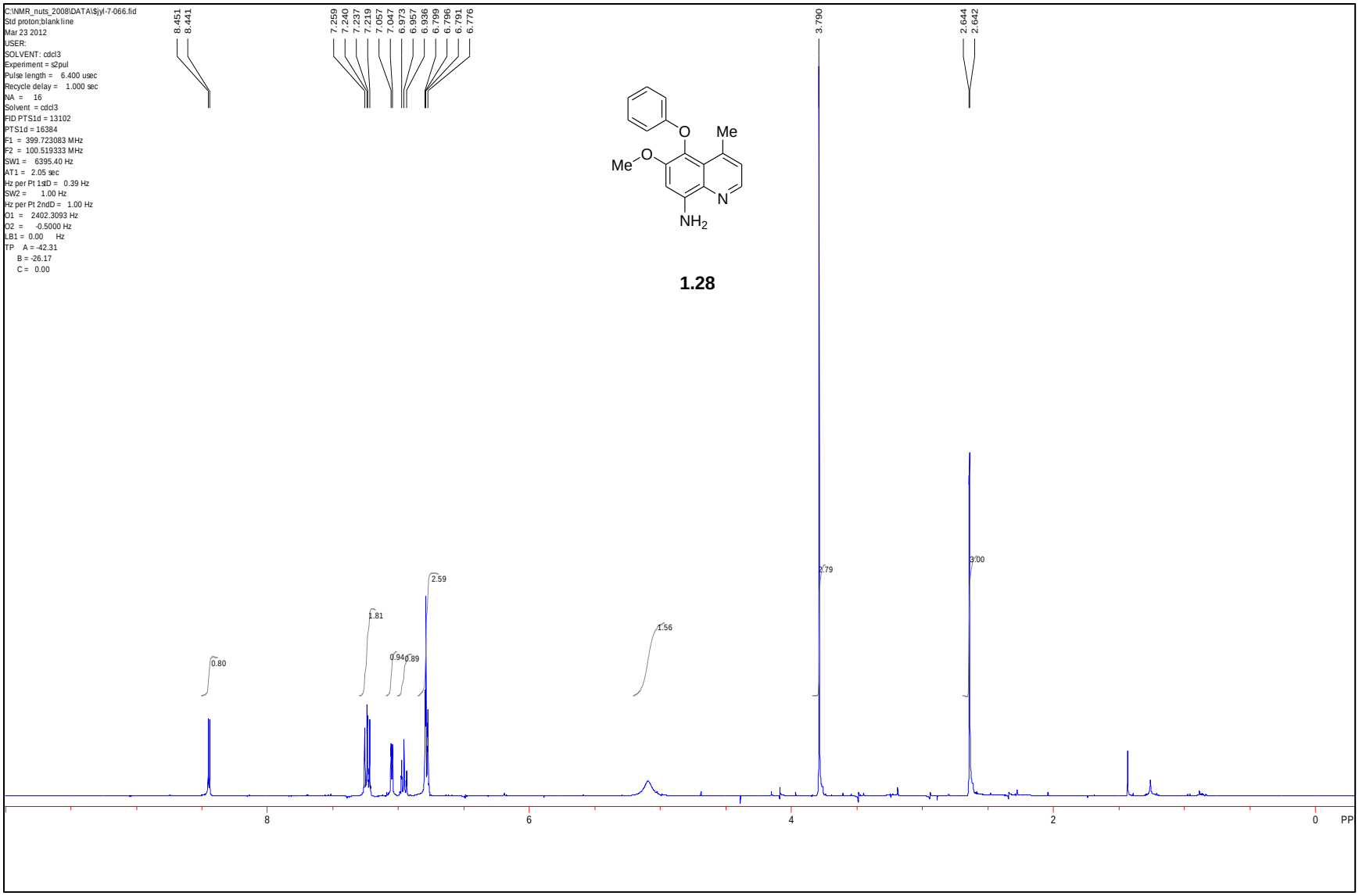

C:\NMR_nuts_2008\DATA\$jyl-7-055-C13.fid
Std proton;blank line
Mar 15 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 7.800 usec
Recycle delay = 1.000 sec
NA = 1064
Solvent = cdcl3
FID PTS1d = 31375
PTS1d = 32768
F1 = 100.520370 MHz
F2 = 399.722687 MHz
SW1 = 24125.45 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10550.5391 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -11.72
B = 165.94
C = 0.00
165.071
162.610
159.160
159.057
150.897
148.406
146.751
143.916
140.084
136.253
130.898
130.803
125.910
125.221
111.838
110.842
110.812
109.816
109.604
103.428
103.179
77.555
77.240
76.918
57.330
23.354
F
O
Me
Me
O
N
NO2
1.25
180
160
140
120
100
80
60
40
20
PP

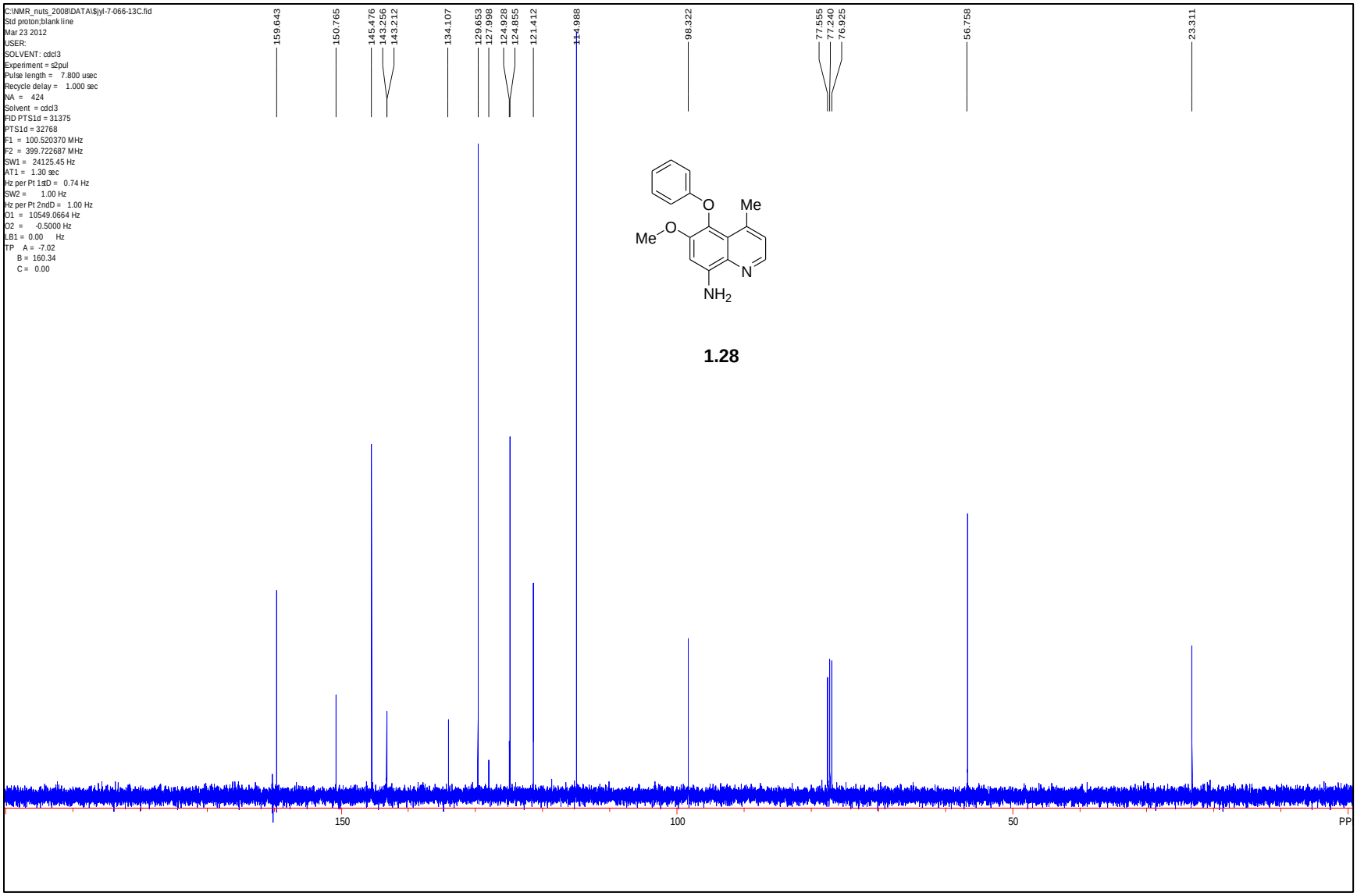

C:\NMR_nuts_2008\DATA\sjyl-7-065.fid
Std Proton parameters
Apr 29 2014
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 2.000 sec
NA = 32
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.942657 MHz
F2 = 100.574539 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2435.5234 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -225.82
B = 115.56
C = 0.00
8.763
8.752
7.872
7.316
7.294
7.276
7.260
7.232
7.222
7.073
7.055
7.036
6.797
6.777
3.861
2.746
1.569
O
Me
Me
O
N
NO2
1.26
0.69
0.79
3.87
1.51
1.92
2.89
3.00
8
6
4
2
0PP

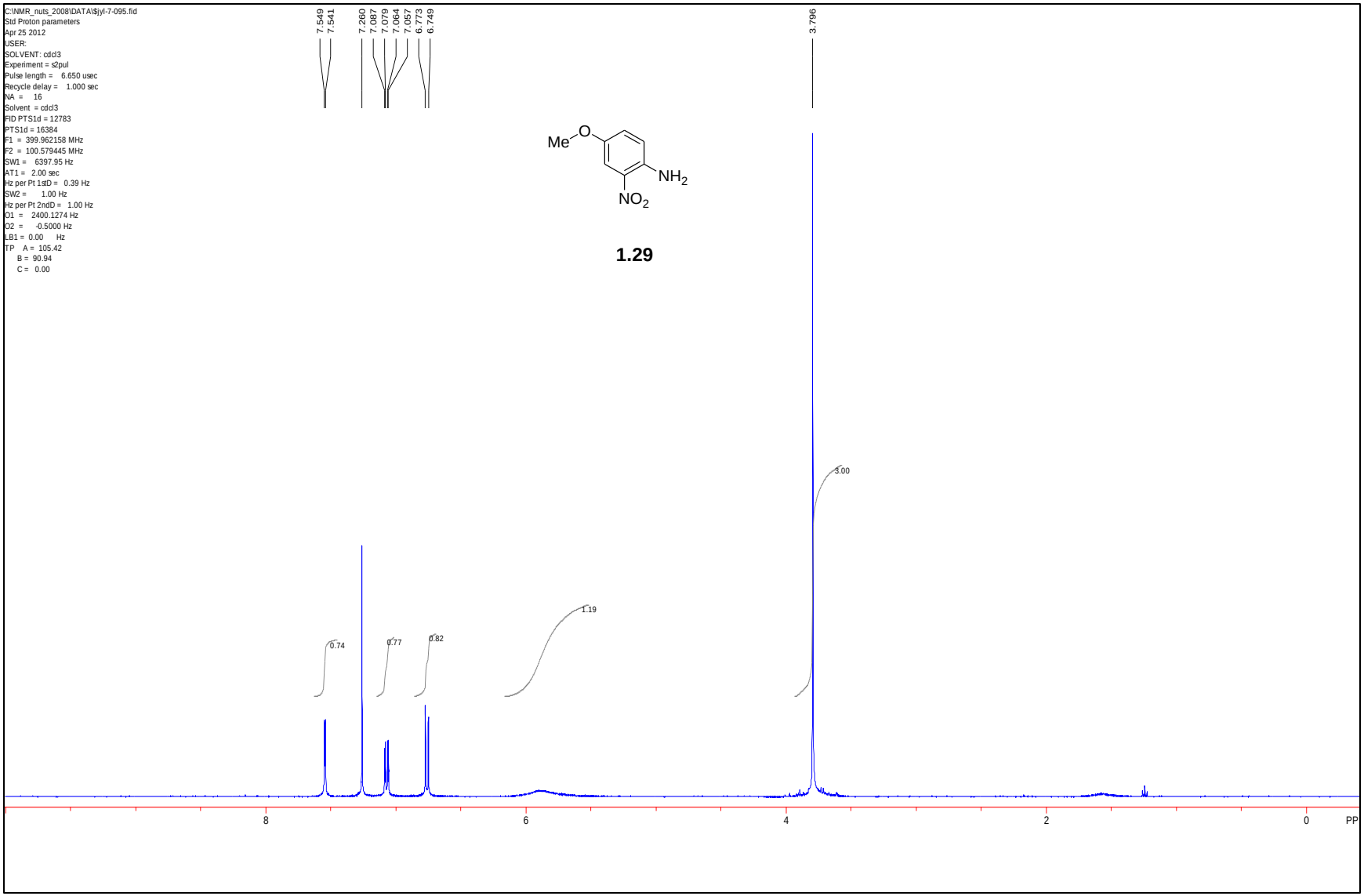

C:\NMR_nuts_2008\DATA\$jyl-7-065-13C.fid
Std Carbon experiment
Mar 22 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 1.000 sec
NA = 844
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.580498 MHz
F2 = 399.961731 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10554.8633 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 52.50
B = 236.25
C = 0.00
158.000
150.817
148.501
146.441
144.235
140.782
136.363
130.389
129.986
125.734
125.441
122.678
120.691
115.099
112.115
77.563
77.240
76.925
57.361
23.439
O
Me
Me
O
N
NO2
1.26
150
100
50
PP

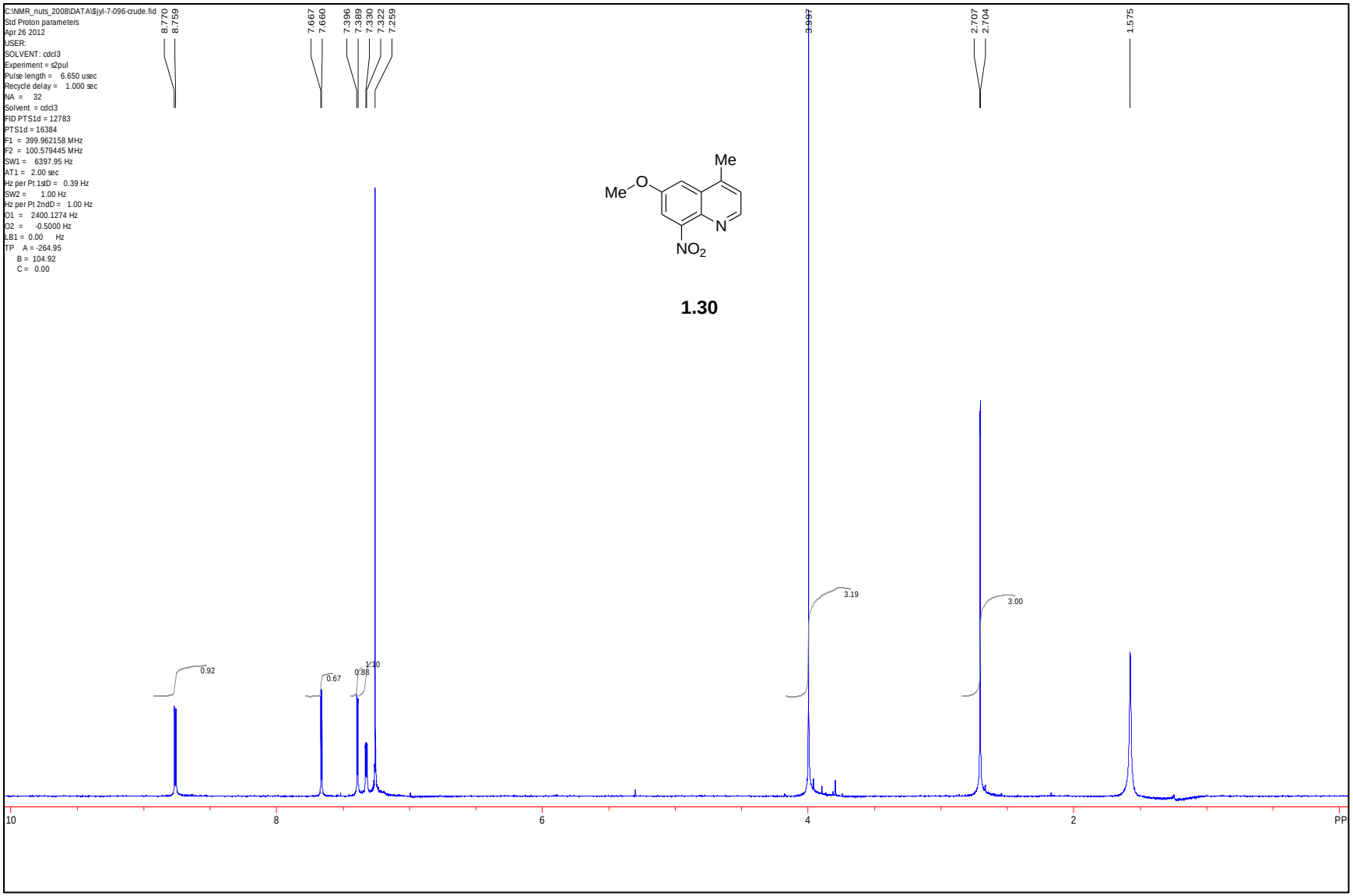

C:\NMR_nuts_2008\DATA\$jyl-7-056.fid
Std Proton parameters
Mar 17 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 3.000 sec
NA = 16
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.962158 MHz
F2 = 100.579445 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2401.2991 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 96.08
B = 111.06
C = 0.00
8.457
8.446
7.260
7.213
7.193
7.175
7.155
7.076
7.066
6.786
6.692
6.686
6.671
6.665
6.651
6.645
6.619
6.613
6.598
6.592
6.500
6.494
6.490
6.473
6.467
6.462
3.810
2.627
F
O
Me
Me
O
N
NH2
1.27
0.94
1.00
0.99
0.96
0.98
1.04
1.01
1.30
2.99
3.00
8
6
4
2
PP

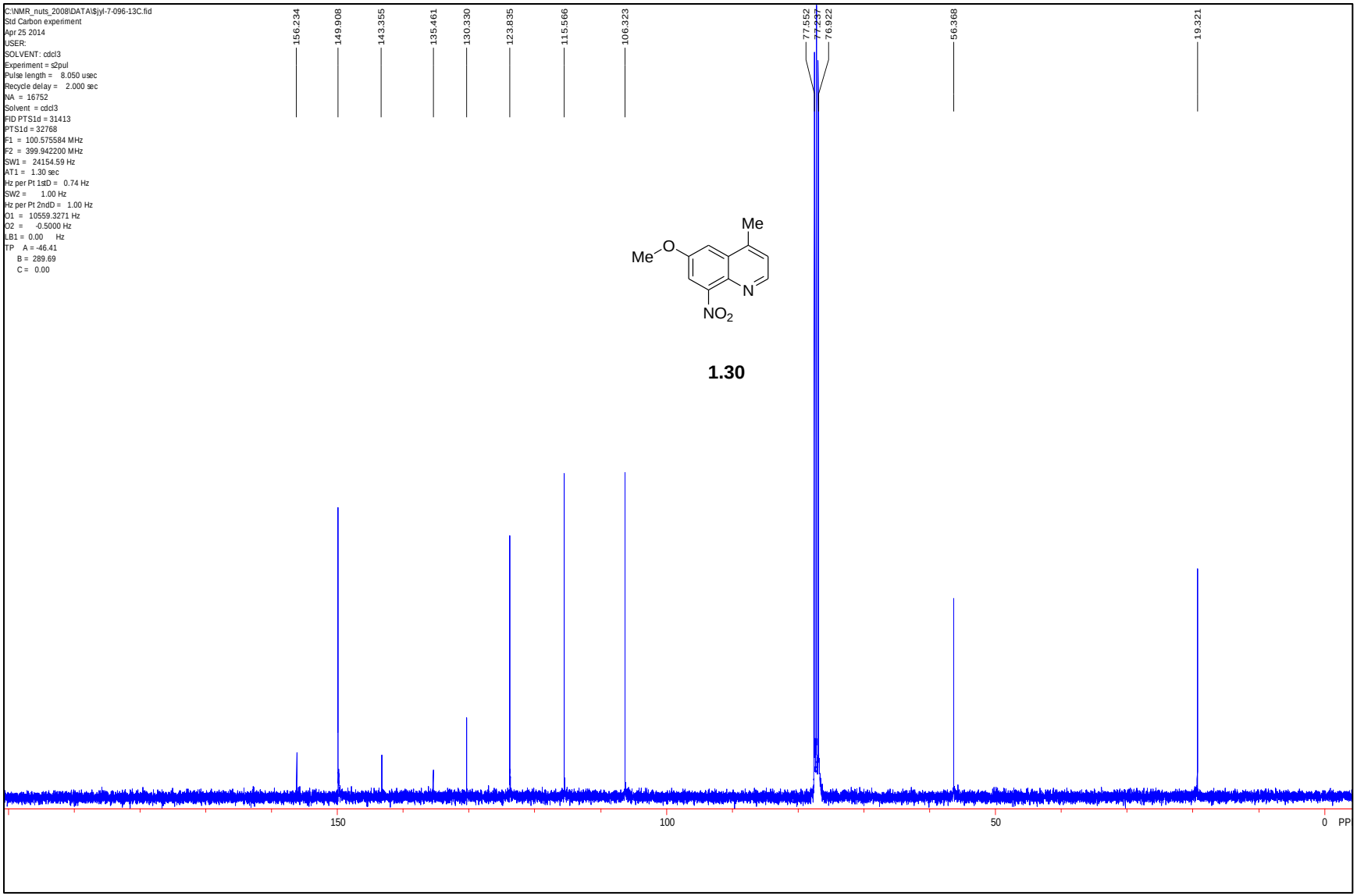

C:\NMR_nuts_2008\DATA\$jyl-7-056-13C.fid
Std Carbon experiment
Mar 17 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 1.000 sec
NA = 34896
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.580498 MHz
F2 = 399.961731 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10557.0742 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 63.75
B = 213.75
C = 0.00
165.147
162.713
161.203
161.093
157.758
150.656
145.561
143.590
142.930
133.944
130.491
130.396
127.559
125.023
124.679
110.957
110.928
108.458
108.245
102.982
102.733
98.013
77.555
77.240
76.917
56.716
23.248
F
O
Me
Me
O
N
NH2
1.27
150
100
50
PP

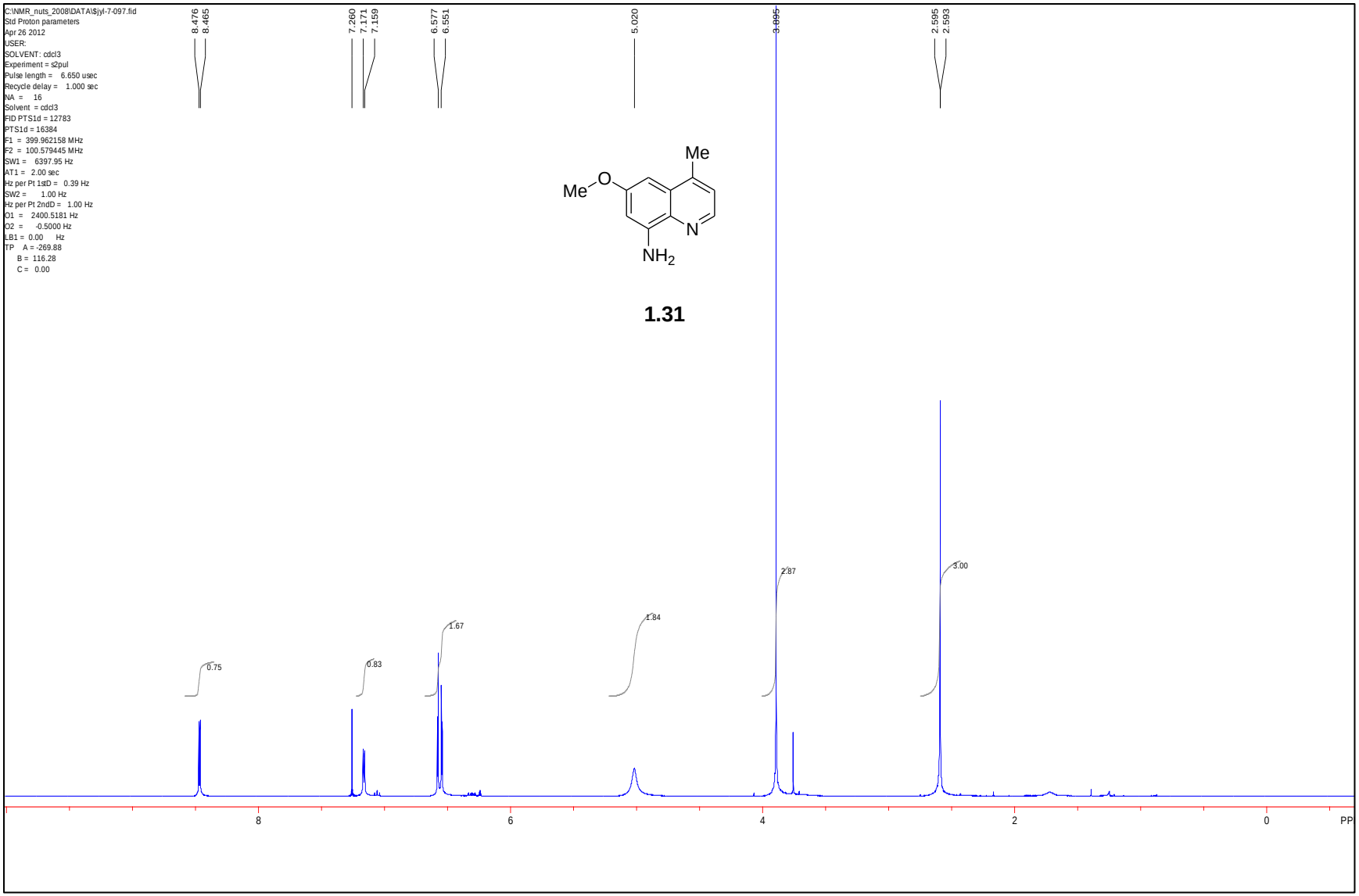

C:\NMR_nuts_2008\DATA\$jyl-7-066.fid
Std proton;blank line
Mar 23 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.400 usec
Recycle delay = 1.000 sec
NA = 16
Solvent = cdcl3
FID PTS1d = 13102
PTS1d = 16384
F1 = 399.723083 MHz
F2 = 100.519333 MHz
SW1 = 6395.40 Hz
AT1 = 2.05 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2402.3093 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -42.31
B = -26.17
C = 0.00
8.451
8.441
7.259
7.240
7.237
7.219
7.057
7.047
6.973
6.957
6.936
6.799
6.796
6.791
6.776
3.790
2.644
2.642
O
Me
Me
O
N
NH2
1.28
0.80
1.81
0.94
0.89
2.59
1.56
2.79
3.00
8
6
4
2
0
PP

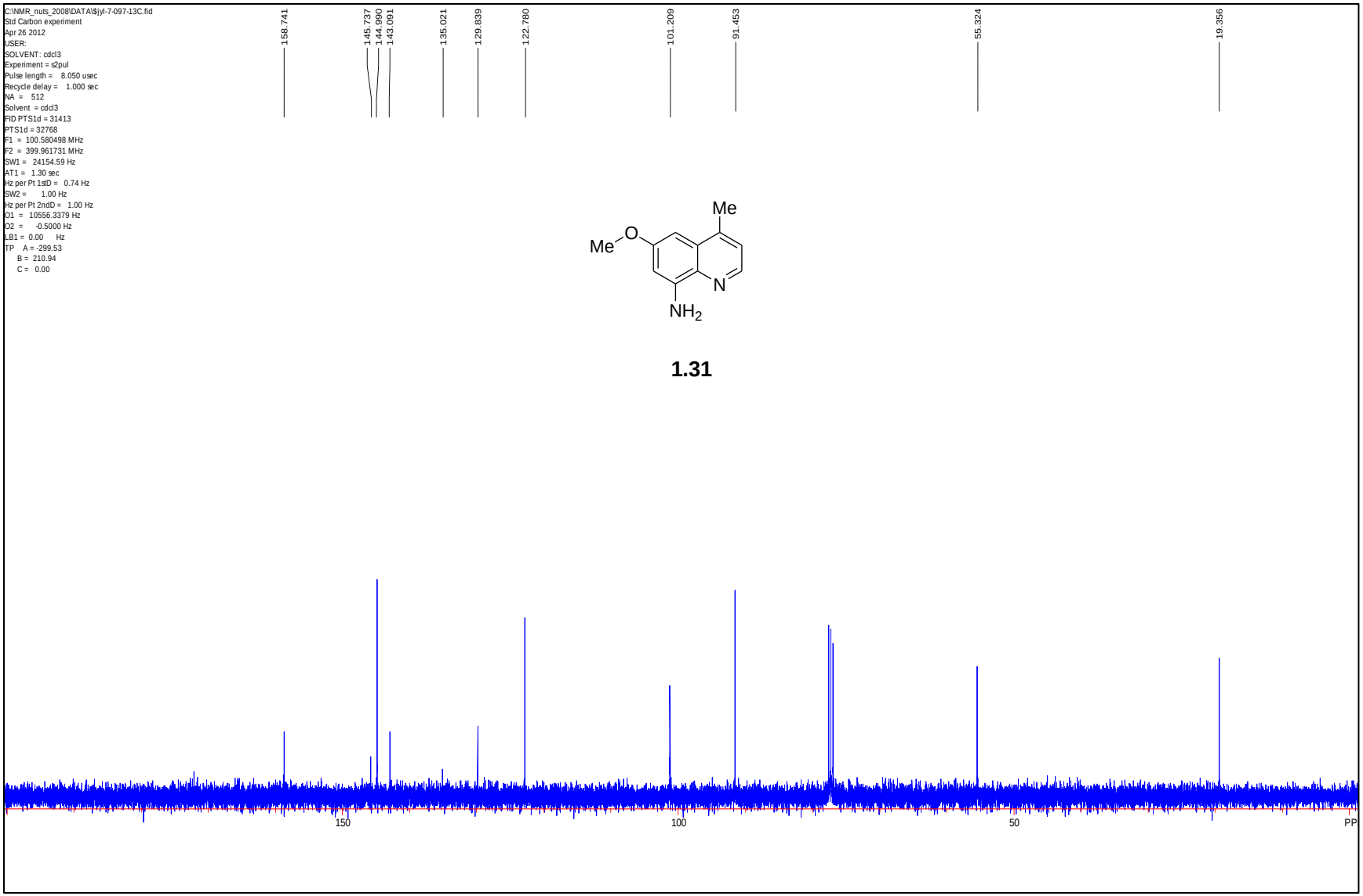

C:\NMR_nuts_2008\DATA\$jyl-7-066-13C.fid
Std proton;blank line
Mar 23 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 7.800 usec
Recycle delay = 1.000 sec
NA = 424
Solvent = cdcl3
FID PTS1d = 31375
PTS1d = 32768
F1 = 100.520370 MHz
F2 = 399.722687 MHz
SW1 = 24125.45 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10549.0664 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -7.02
B = 160.34
C = 0.00
159.643
150.765
145.476
143.256
143.212
134.107
129.653
127.998
124.928
124.855
121.412
114.988
98.322
77.555
77.240
76.925
56.758
23.311
O
Me
Me
O
N
NH2
1.28
150
100
50
PP


C:\NMR_nuts_2008\DATA\$jyl-7-095.fid
Std Proton parameters
Apr 25 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 1.000 sec
NA = 16
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.962158 MHz
F2 = 100.579445 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2400.1274 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 105.42
B = 90.94
C = 0.00
7.549
7.541
7.260
7.087
7.079
7.064
7.057
6.773
6.749
3.796
Me
O
NH2
NO2
1.29
3.00
1.19
0.74
0.77
0.82
8
6
4
2
0
PP

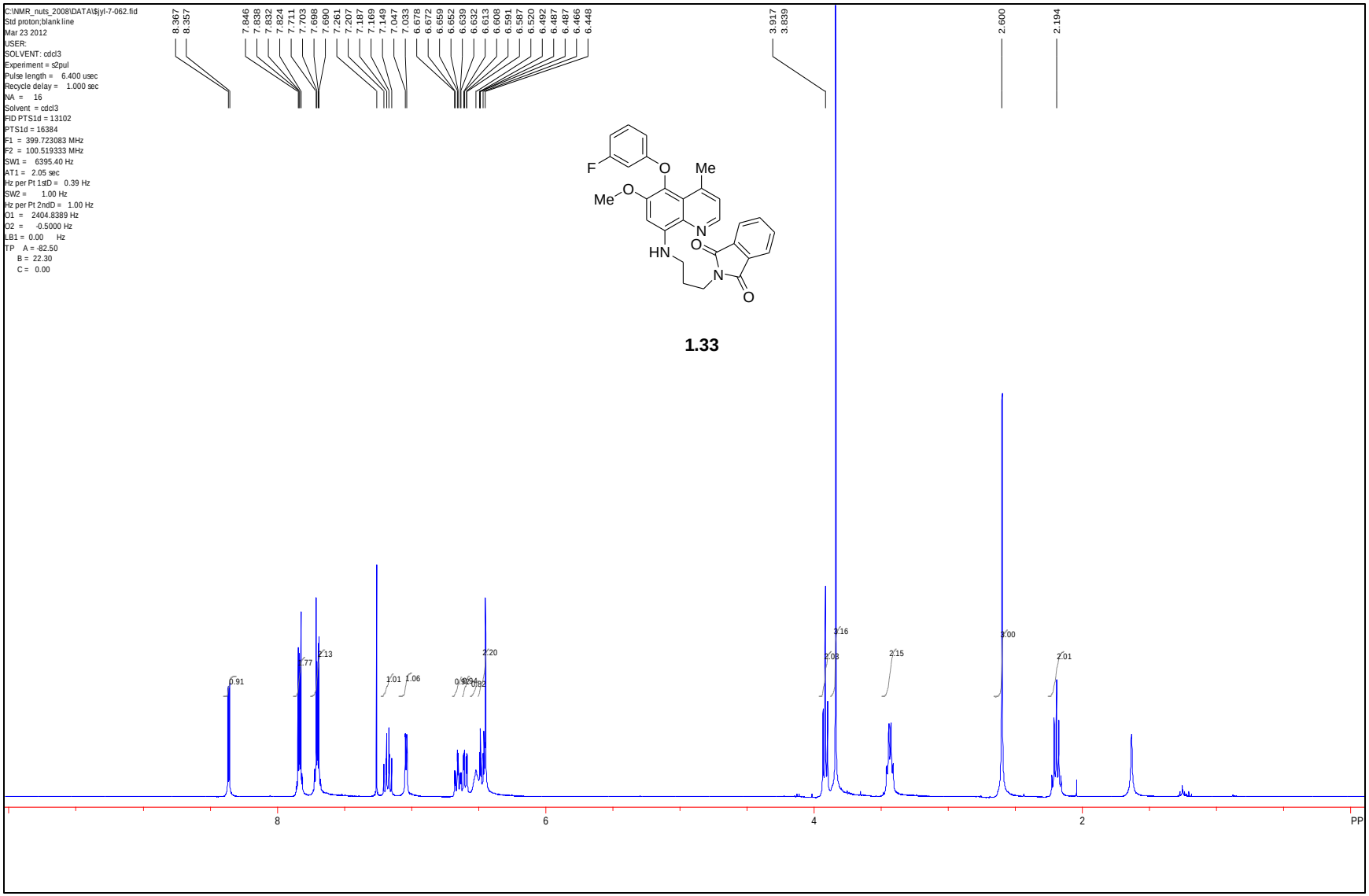

C:\NMR_nuts_2008\DATA\$jyl-7-096-crude.fid
Std Proton parameters
Apr 26 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 1.000 sec
NA = 32
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.962158 MHz
F2 = 100.579445 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2400.1274 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -264.95
B = 104.92
C = 0.00
8.770
8.759
7.667
7.660
7.396
7.389
7.330
7.322
7.259
3.997
2.707
2.704
1.575
Me
Me
O
N
NO2
1.30
0.92
0.67
0.88
1.00
3.19
3.00
10
8
6
4
2
PP


C:\NMR_nuts_2008\DATA\sjyl-7-096-13C.fid
Std Carbon experiment
Apr 25 2014
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 2.000 sec
NA = 16752
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.575584 MHz
F2 = 399.942200 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10559.3271 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -46.41
B = 289.69
C = 0.00
156.234
149.908
143.355
135.461
130.330
123.835
115.566
106.323
77.552
77.237
76.922
56.368
19.321
Me
O
Me
N
NO2
1.30
150
100
50
0
PP

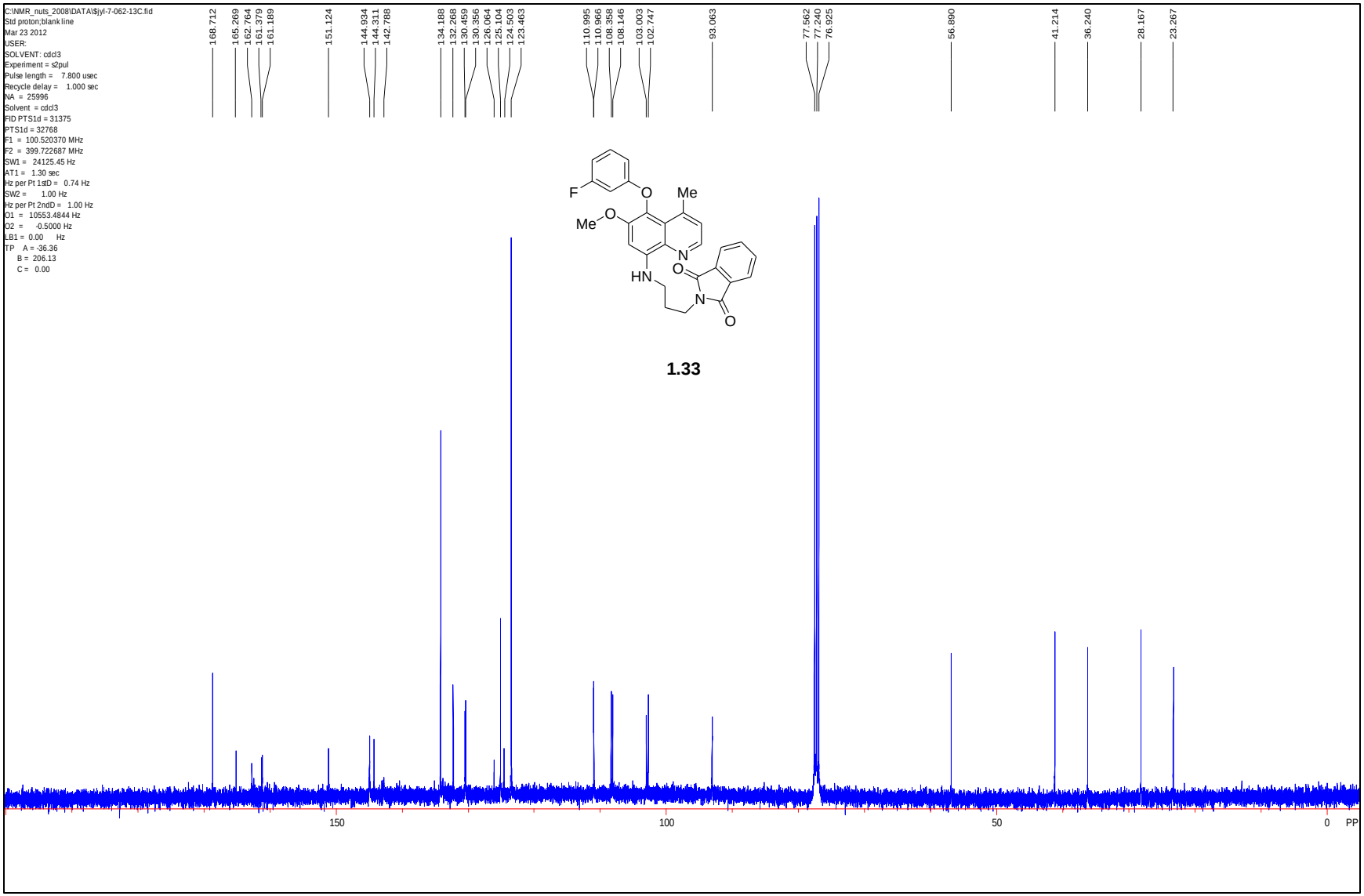

C:\NMR_nuts_2008\DATA\sjyl-7-097.fid
Std Proton parameters
Apr 26 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 1.000 sec
NA = 16
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.962158 MHz
F2 = 100.579445 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2400.5181 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -269.88
B = 116.28
C = 0.00
8.476
8.465
7.260
7.171
7.159
6.577
6.551
5.020
3.895
2.595
2.593
Me
O
Me
N
NH2
1.31
0.75
0.83
1.67
1.84
2.87
3.00
8
6
4
2
0
PP

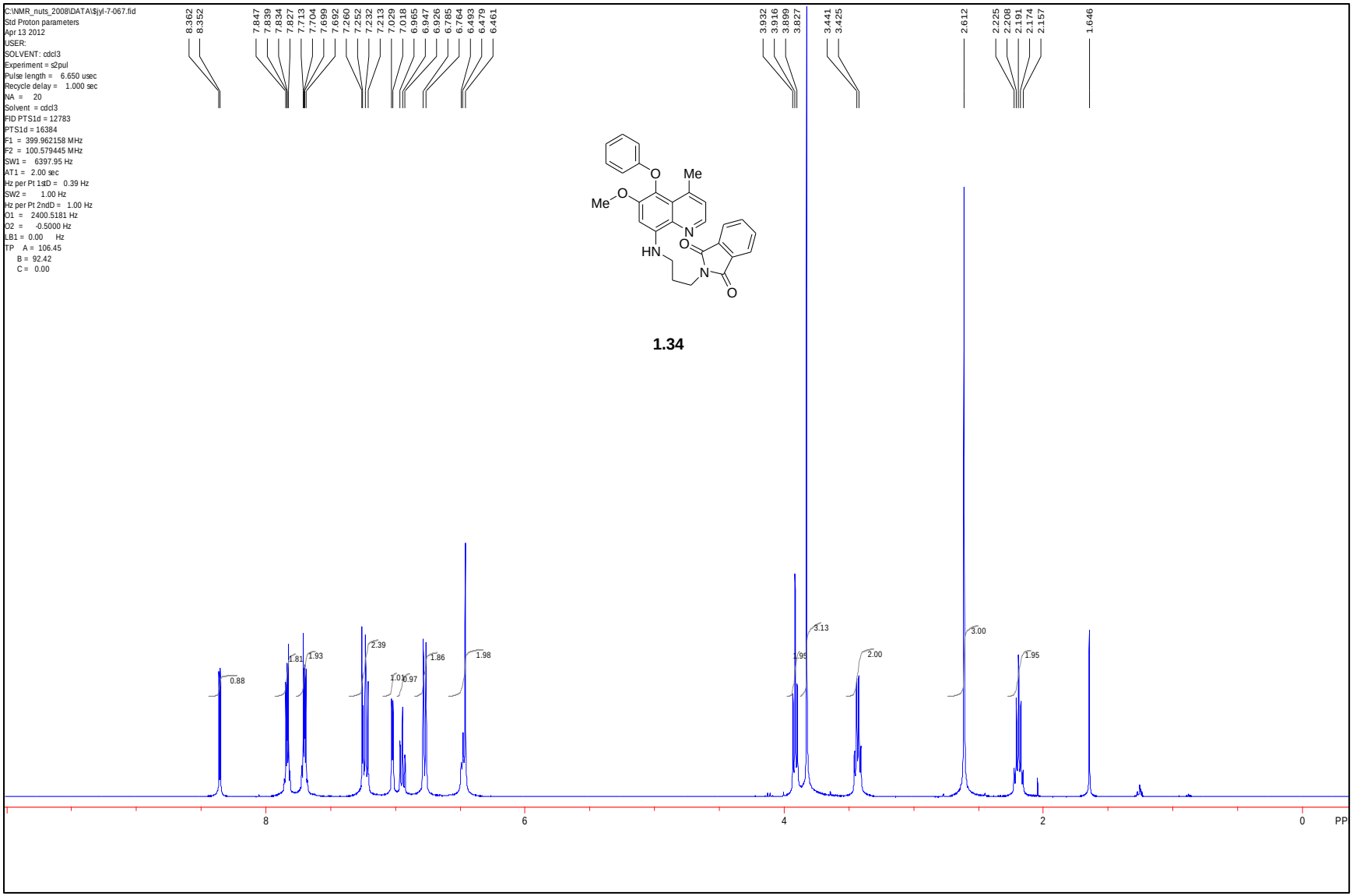

C:\NMR_nuts_2008\DATA\sjyl-7-097-13C.fid
Std Carbon experiment
Apr 26 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 1.000 sec
NA = 512
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.580498 MHz
F2 = 399.961731 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10556.3379 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -299.53
B = 210.94
C = 0.00
158.741
145.737
144.990
143.091
135.021
129.839
122.780
101.209
91.453
55.324
19.356
Me
O
Me
N
NH2
150
100
50
PP

**1.31**

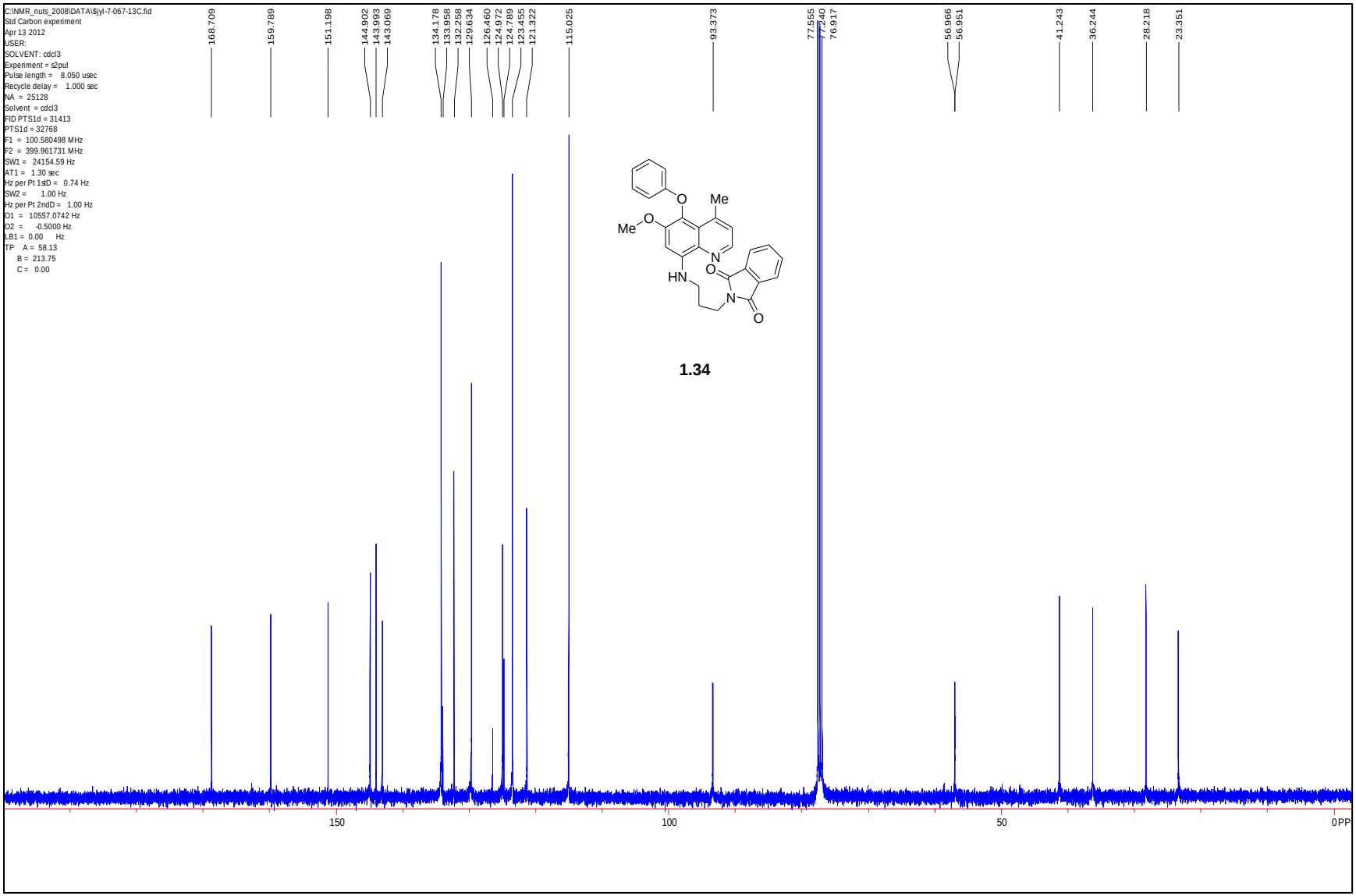

C:\NMR_nuts_2008\DATA\$jyl-7-062.fid
Std proton;blank line
Mar 23 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.400 usec
Recycle delay = 1.000 sec
NA = 16
Solvent = cdcl3
FID PTS1d = 13102
PTS1d = 16384
F1 = 399.723083 MHz
F2 = 100.519333 MHz
SW1 = 6395.40 Hz
AT1 = 2.05 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2404.8389 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -82.50
B = 22.30
C = 0.00
8.367
8.357
7.846
7.838
7.832
7.824
7.711
7.703
7.698
7.690
7.261
7.207
7.187
7.169
7.149
7.047
7.033
6.678
6.672
6.659
6.652
6.639
6.632
6.613
6.608
6.591
6.587
6.520
6.492
6.487
6.487
6.466
6.448
3.917
3.839
2.600
2.194
F
O
Me
Me
O
N
O
HN
N
O
0.91
2.77
2.13
1.01
1.06
2.20
3.16
2.03
2.15
3.00
2.01
8
6
4
2
PP

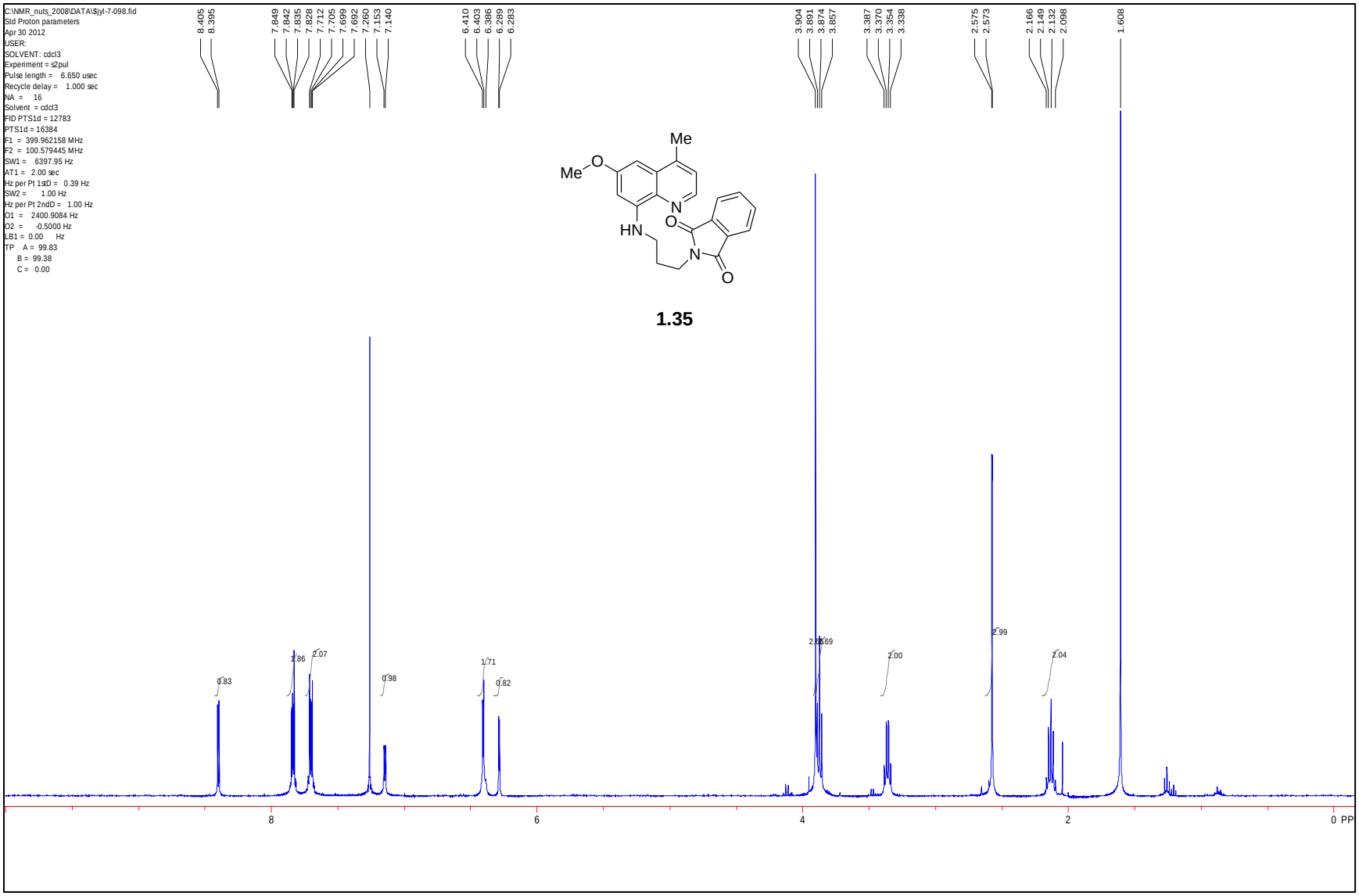
**1.33**

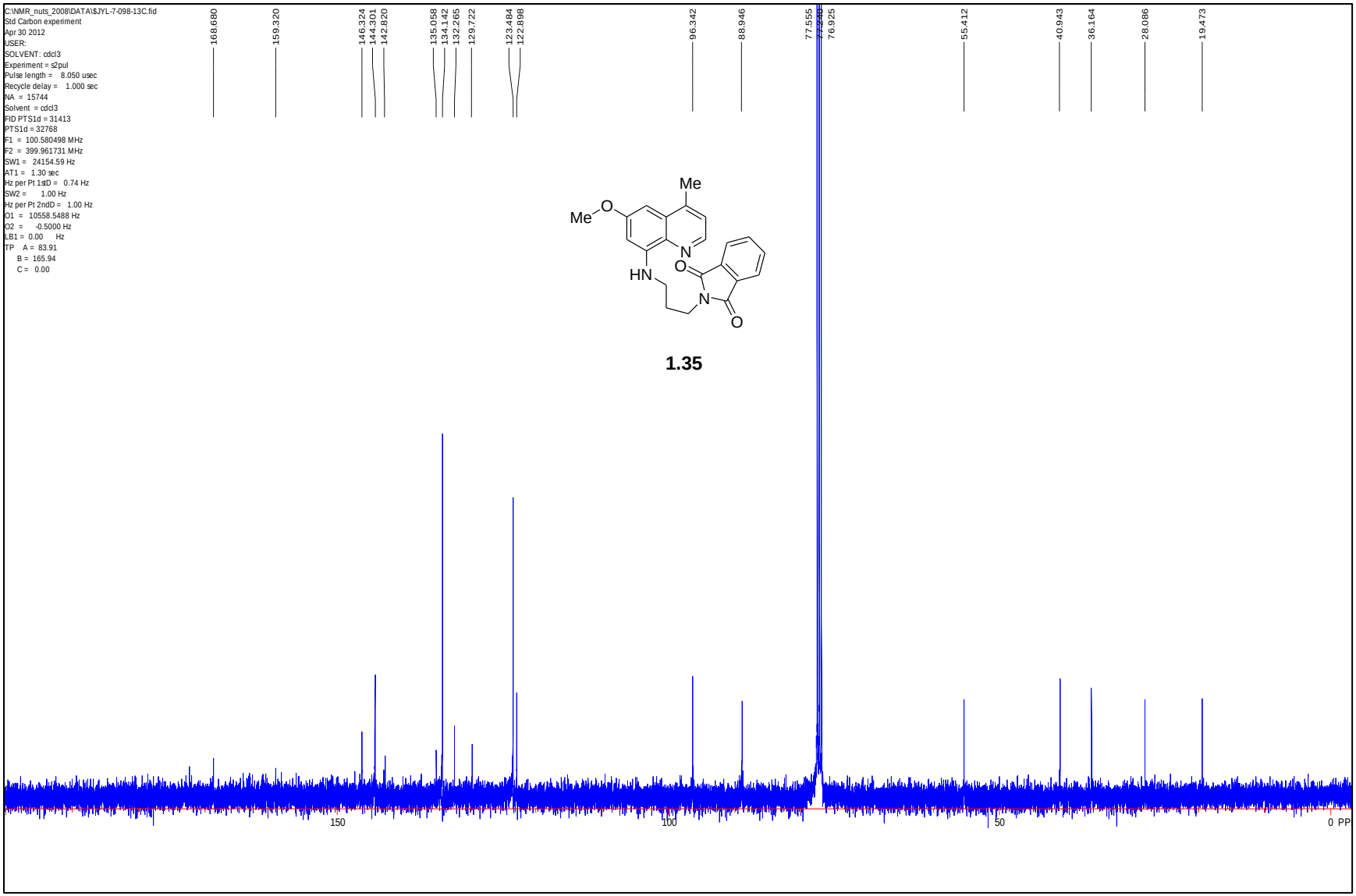

C:\NMR_nuts_2008\DATA\$jyl-7-062-13C.fid
Std proton;blank line
Mar 23 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 7.800 usec
Recycle delay = 1.000 sec
NA = 25996
Solvent = cdcl3
FID PTS1d = 31375
PTS1d = 32768
F1 = 100.520370 MHz
F2 = 399.722687 MHz
SW1 = 24125.45 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10553.4844 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -36.36
B = 206.13
C = 0.00
168.712
165.269
162.764
161.379
161.189
151.124
144.934
144.311
142.788
134.188
132.268
130.459
130.356
126.064
125.104
124.503
123.463
110.995
110.966
108.358
108.146
103.003
102.747
93.063
77.562
77.240
76.925
56.890
41.214
36.240
28.167
23.267
F
O
Me
Me
O
N
O
HN
N
O
1.33
150
100
50
0
PP


C:\NMR_nuts_2008\DATA\$jyl-7-067.fid
Std Proton parameters
Apr 13 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 1.000 sec
NA = 20
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.962158 MHz
F2 = 100.579445 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2400.5181 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 106.45
B = 92.42
C = 0.00
8.362
8.352
7.847
7.839
7.834
7.827
7.713
7.704
7.699
7.692
7.260
7.252
7.232
7.213
7.029
7.018
6.965
6.947
6.926
6.785
6.764
6.493
6.479
6.461
3.932
3.916
3.899
3.827
3.441
3.425
2.612
2.225
2.208
2.191
2.174
2.157
1.646
Me
O
Me
O
N
HN
O
N
O
0.88
1.81
1.93
2.39
1.01
0.97
1.86
1.98
3.13
1.95
2.00
3.00
1.95
8
6
4
2
0
PP

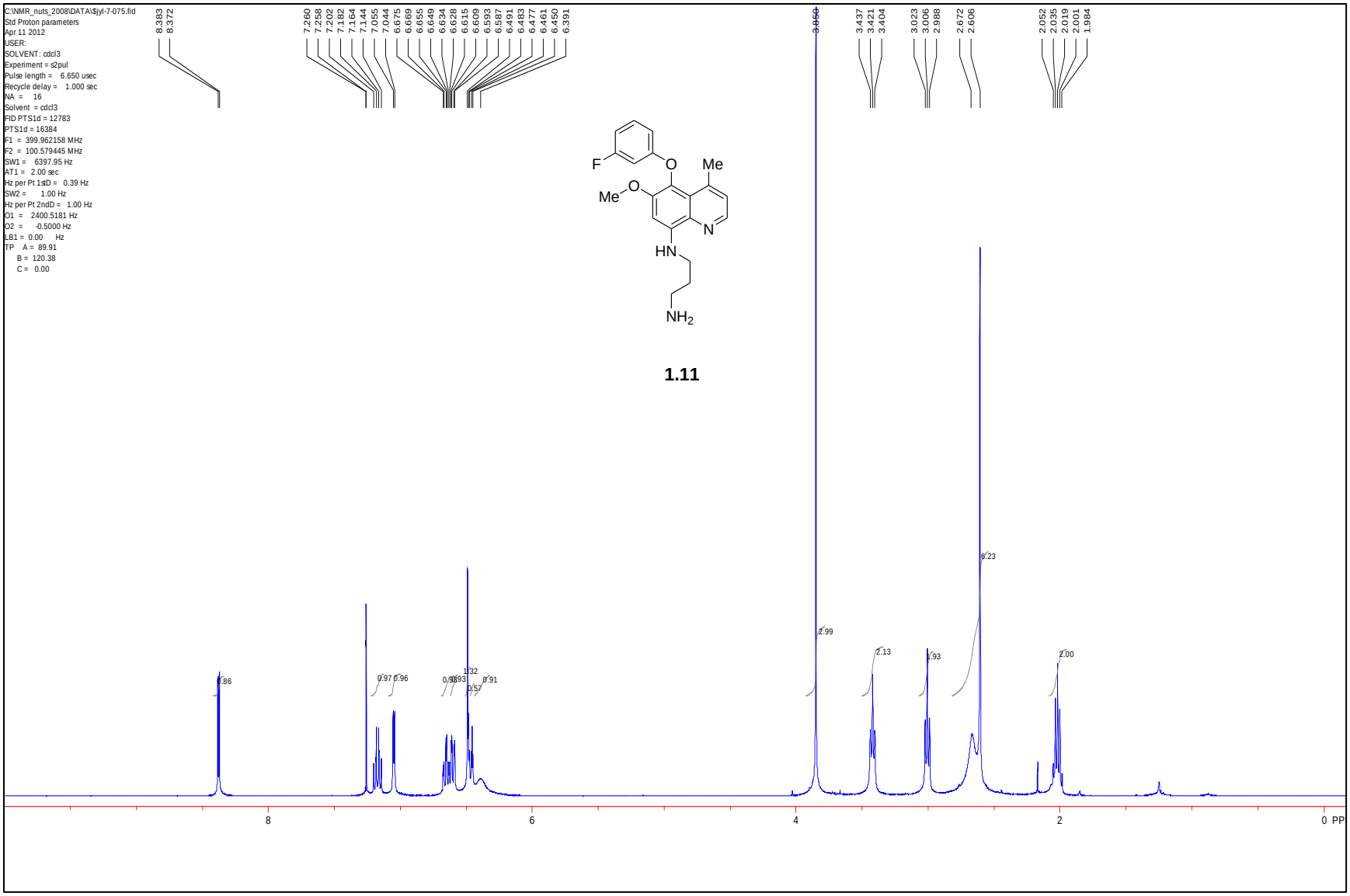
**1.34**

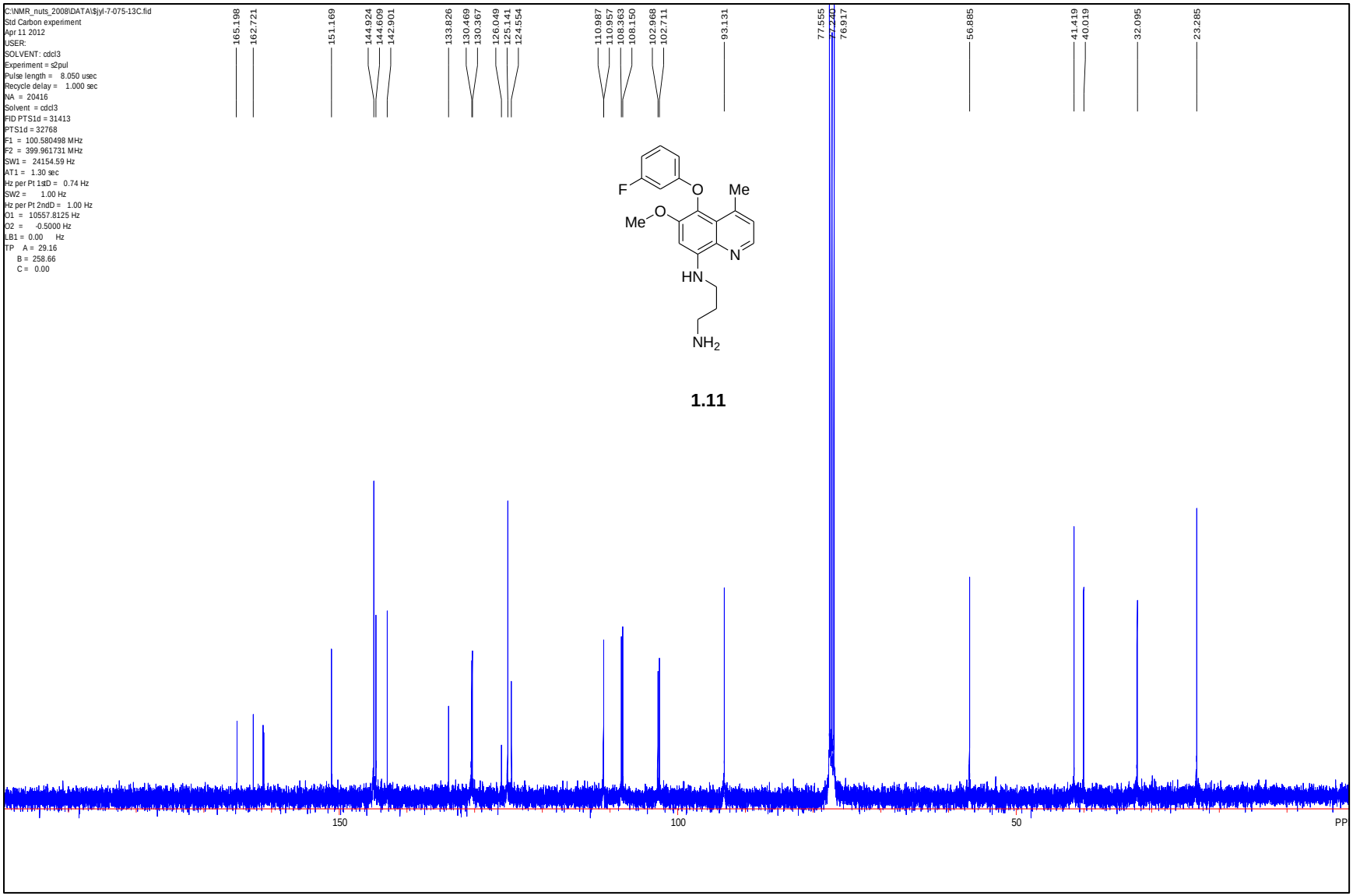

C:\NMR_nuts_2008\DATA\$jyl-7-067-13C.fid
Std Carbon experiment
Apr 13 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 1.000 sec
NA = 25128
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.580498 MHz
F2 = 399.961731 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10557.0742 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 58.13
B = 213.75
C = 0.00
168.709
159.789
151.198
144.902
143.993
143.069
134.178
133.958
132.258
129.634
126.460
124.972
124.789
123.455
121.322
115.025
93.373
77.555
77.240
76.917
56.966
56.951
41.243
36.244
28.218
23.351
Me
O
Me
O
N
HN
N
O
O
1.34
150
100
50
0PPM

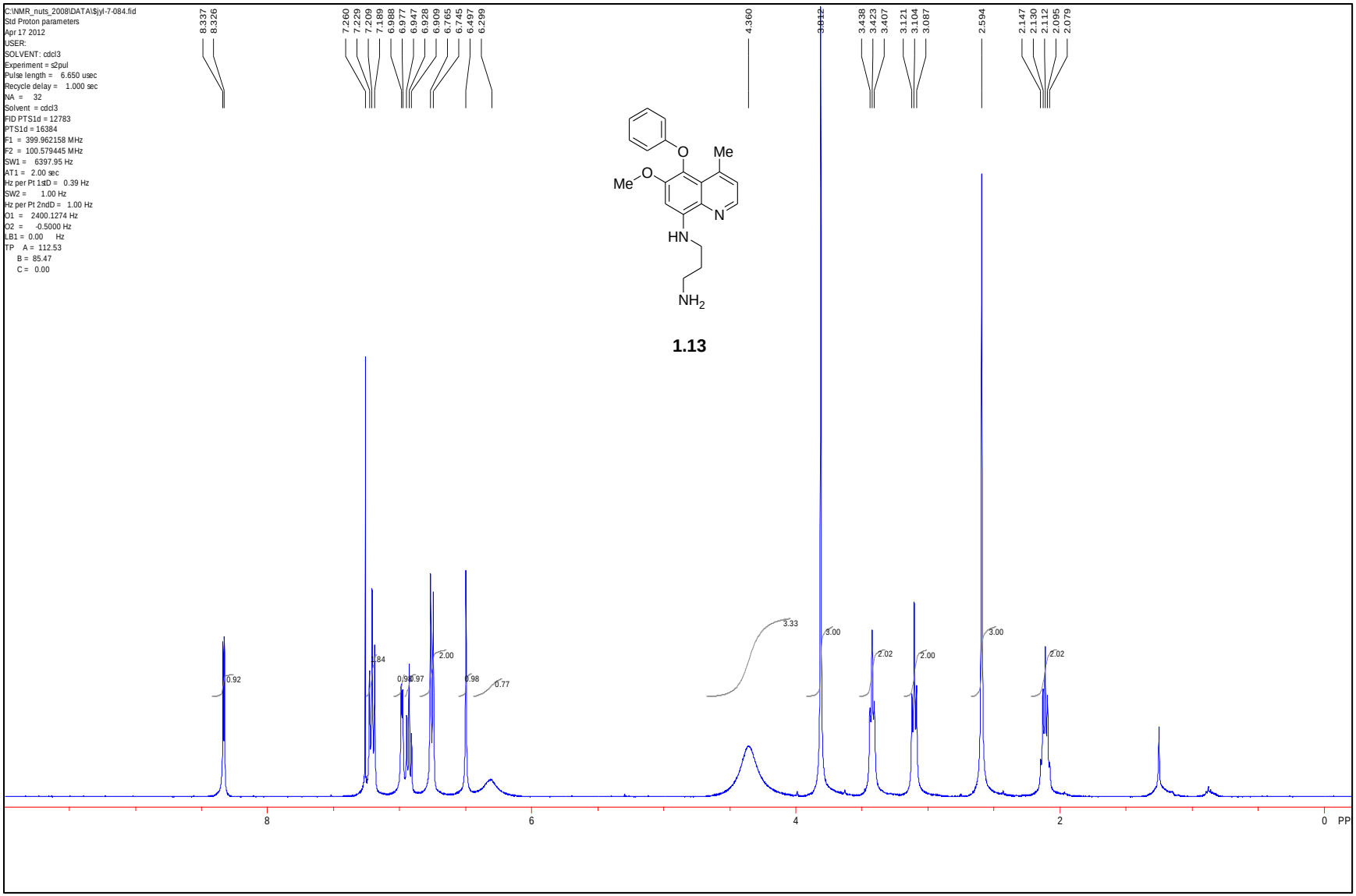

C:\NMR_nuts_2008\DATA\$jyl-7-098.fid
Std Proton parameters
Apr 30 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 1.000 sec
NA = 16
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.962158 MHz
F2 = 100.579445 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2400.9084 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 99.83
B = 99.38
C = 0.00
8.405
8.395
7.849
7.842
7.835
7.828
7.712
7.705
7.699
7.692
7.260
7.153
7.140
6.410
6.403
6.386
6.289
6.283
3.904
3.891
3.874
3.857
3.387
3.370
3.354
3.338
2.575
2.573
2.166
2.149
2.132
2.098
1.608
Me
O
Me
N
O
HN
N
O
1.35
0.83
1.86
2.07
0.98
1.71
0.82
2.00
2.99
2.04
8
6
4
2
0 PP

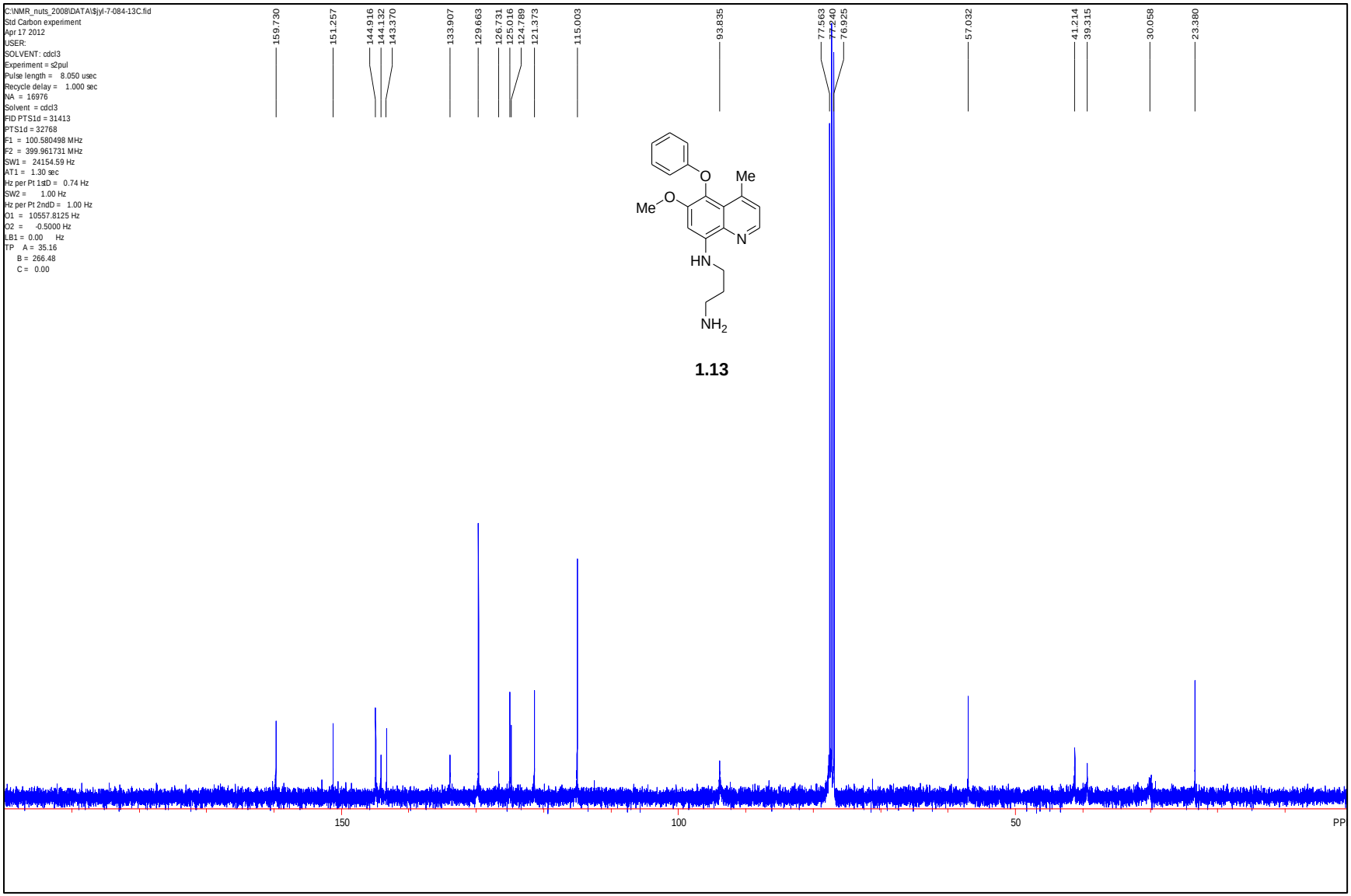

C:\NMR_nuts_2008\DATA\$JYL-7-098-13C.fid
Std Carbon experiment
Apr 30 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 1.000 sec
NA = 15744
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.580498 MHz
F2 = 399.961731 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10558.5488 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 83.91
B = 165.94
C = 0.00
168.680
159.320
146.324
144.301
142.820
135.058
134.142
132.265
129.722
123.484
122.898
96.342
88.946
77.555
77.240
76.925
55.412
40.943
36.164
28.086
19.473
Me
O
Me
N
O
HN
N
O
150
100
50
0 PP

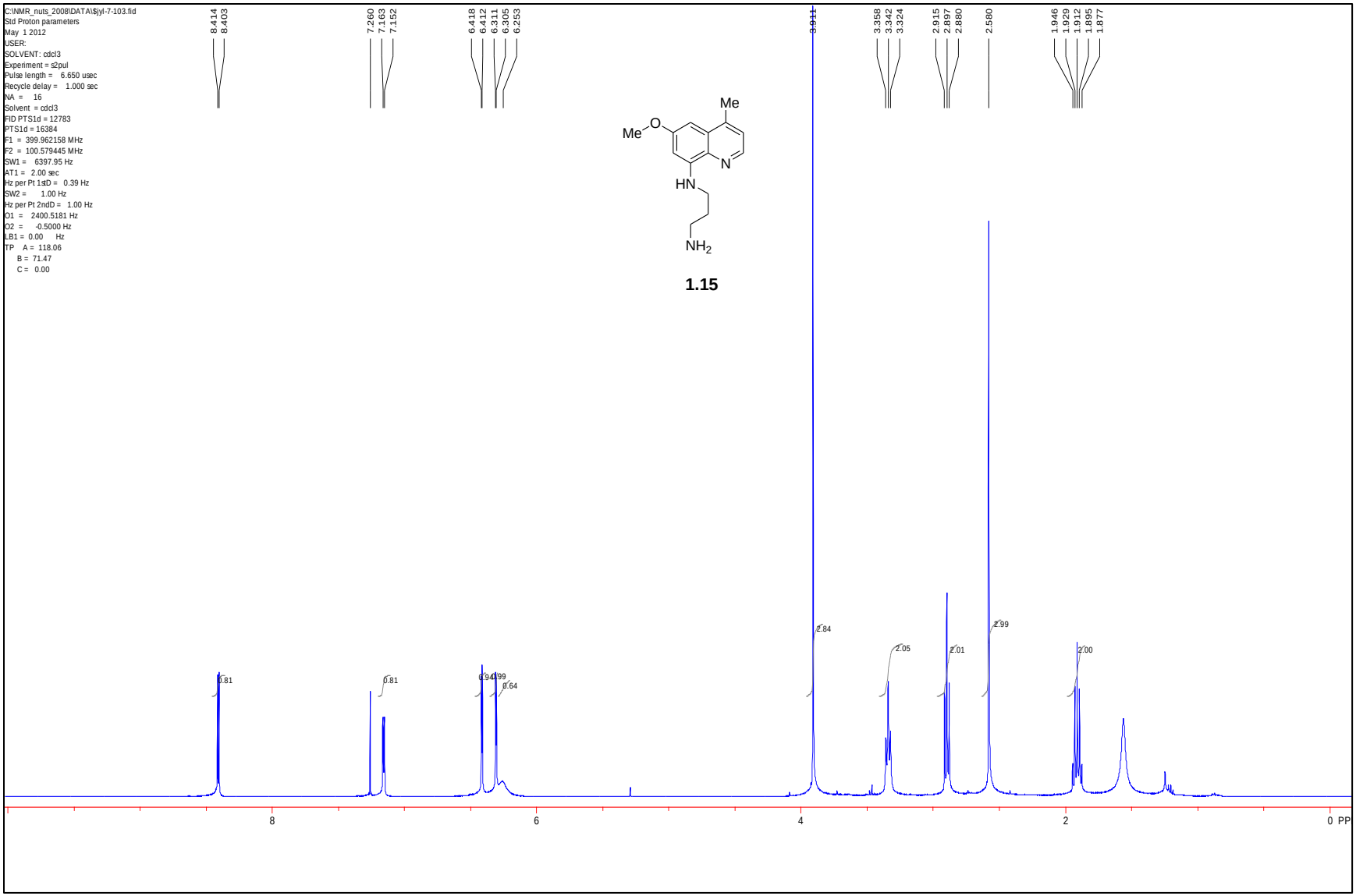
**1.35**

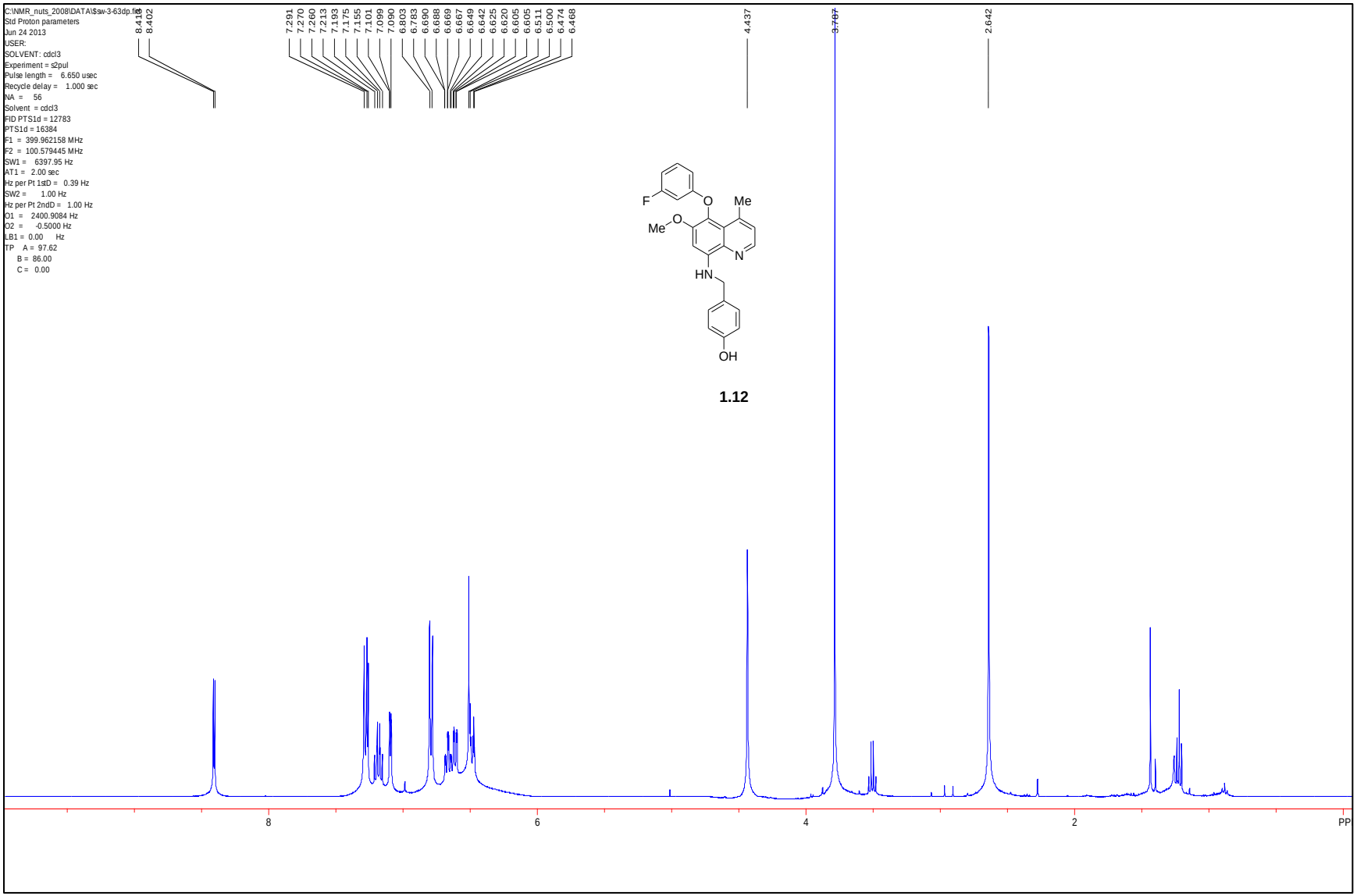

C:\NMR_nuts_2008\DATA\$jyl-7-075.fid
Std Proton parameters
Apr 11 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 1.000 sec
NA = 16
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.962158 MHz
F2 = 100.579445 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2400.5181 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 89.91
B = 120.38
C = 0.00
8.383
8.372
7.260
7.258
7.202
7.182
7.164
7.144
7.055
7.044
6.675
6.669
6.655
6.649
6.634
6.628
6.615
6.609
6.593
6.587
6.491
6.483
6.477
6.461
6.450
6.391
3.850
3.437
3.421
3.404
3.023
3.006
2.988
2.672
2.606
2.052
2.035
2.019
2.001
1.984
F
O
Me
Me
O
N
HN
NH2
1.11
0.86
0.97
0.96
0.91
0.57
2.99
2.13
1.93
6.23
2.00
8
6
4
2
0 PP

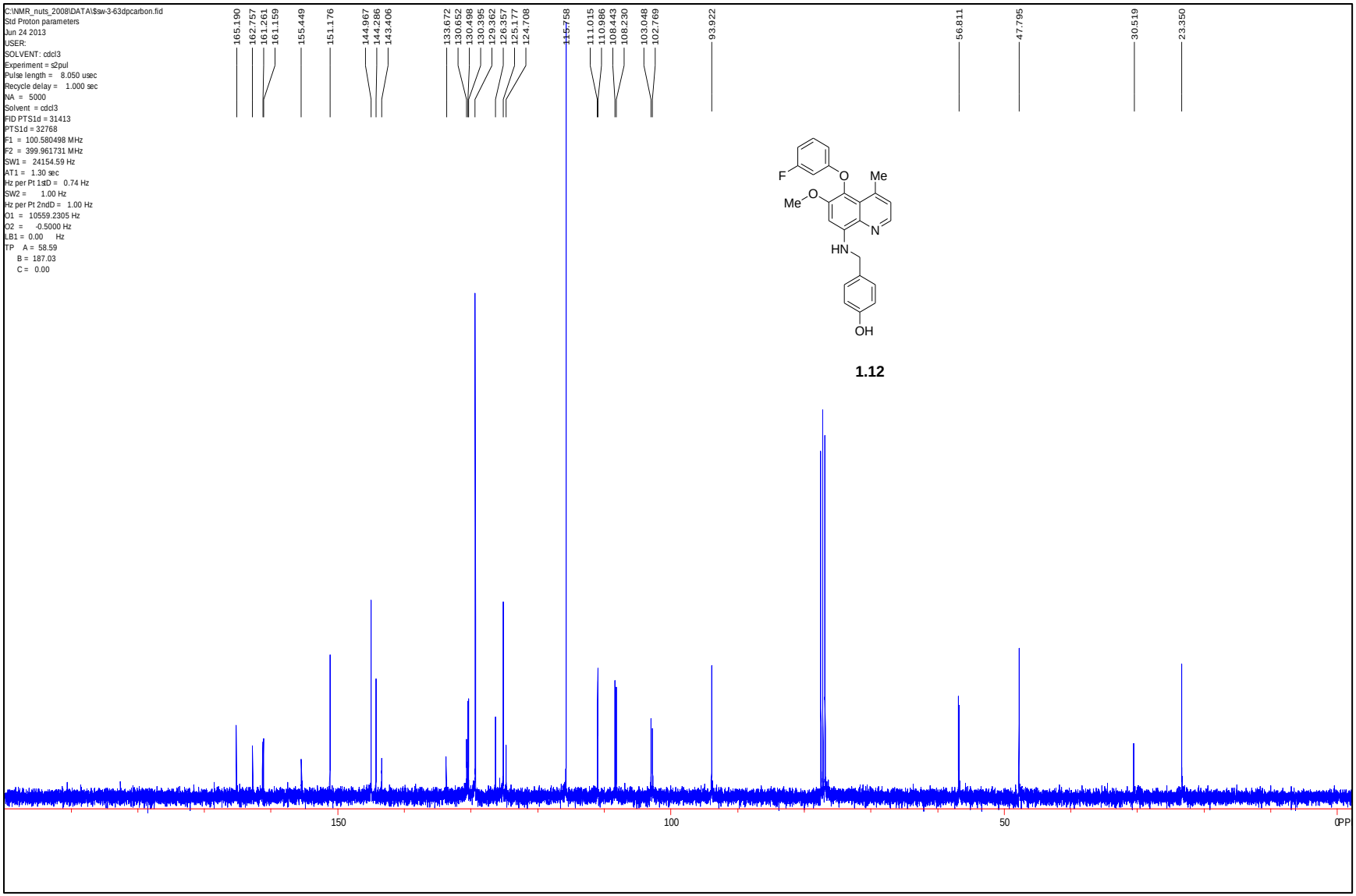

C:\NMR_nuts_2008\DATA\$jyl-7-075-13C.fid
Std Carbon experiment
Apr 11 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 1.000 sec
NA = 20416
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.580498 MHz
F2 = 399.961731 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10557.8125 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 29.16
B = 258.66
C = 0.00
165.198
162.721
151.169
144.924
144.609
142.901
133.826
130.469
130.367
126.049
125.141
124.554
110.987
110.957
108.363
108.150
102.968
102.711
93.131
77.555
77.240
76.917
56.885
41.419
40.019
32.095
23.285
F
O
Me
Me
O
N
HN
NH2
1.11
150
100
50
PP

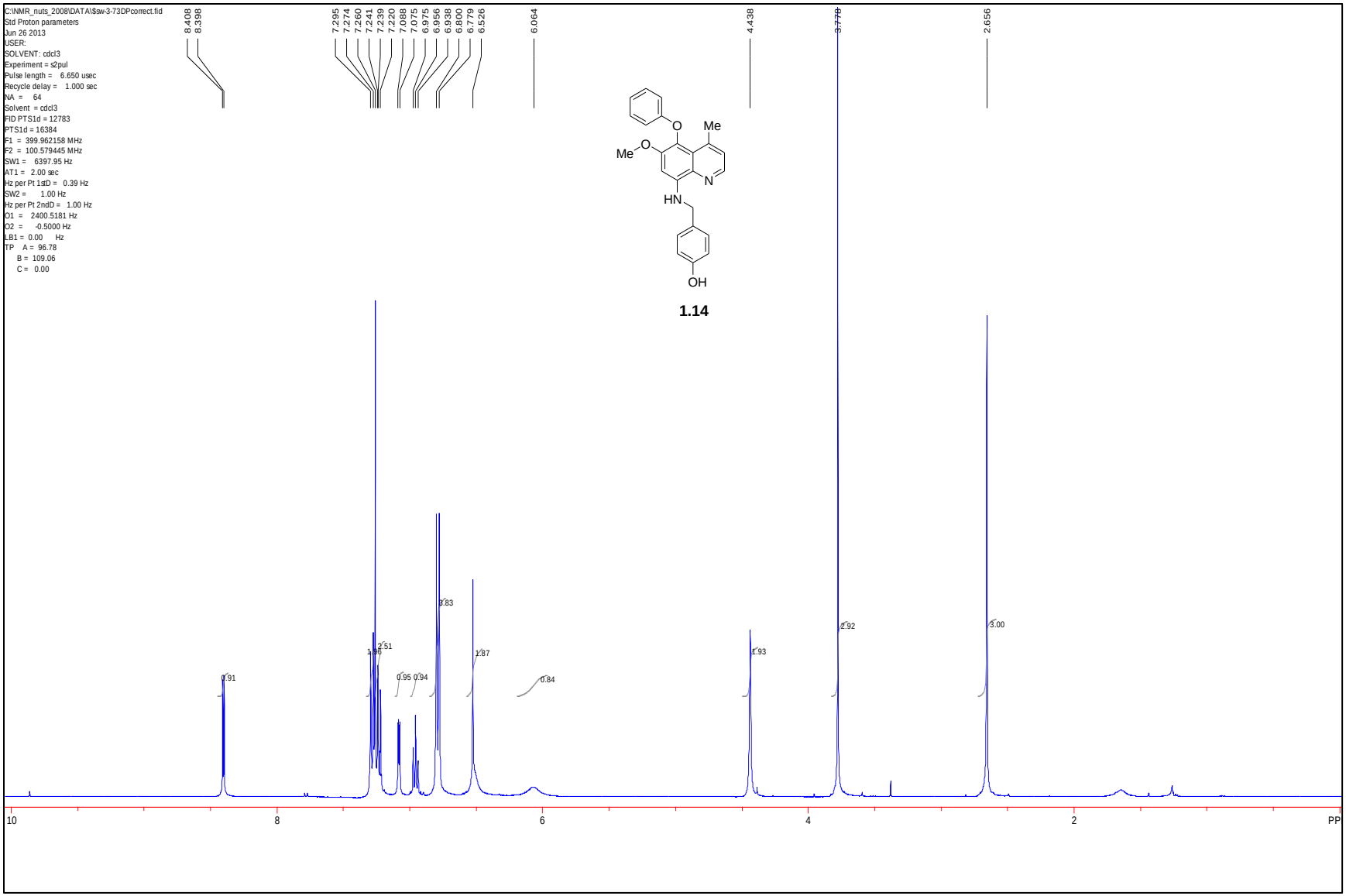

C:\NMR_nuts_2008\DATA\$jyl-7-084.fid
Std Proton parameters
Apr 17 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 1.000 sec
NA = 32
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.962158 MHz
F2 = 100.579445 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2400.1274 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 112.53
B = 85.47
C = 0.00
8.337
8.326
7.260
7.229
7.209
7.189
6.988
6.977
6.947
6.928
6.909
6.765
6.745
6.497
6.299
4.360
3.812
3.438
3.423
3.407
3.121
3.104
3.087
2.594
2.147
2.130
2.112
2.095
2.079
O
Me
Me
O
N
HN
NH2
1.13
0.92
1.84
0.98
0.97
2.00
0.98
0.77
3.33
3.00
2.02
2.00
3.00
2.02
8
6
4
2
0
PP

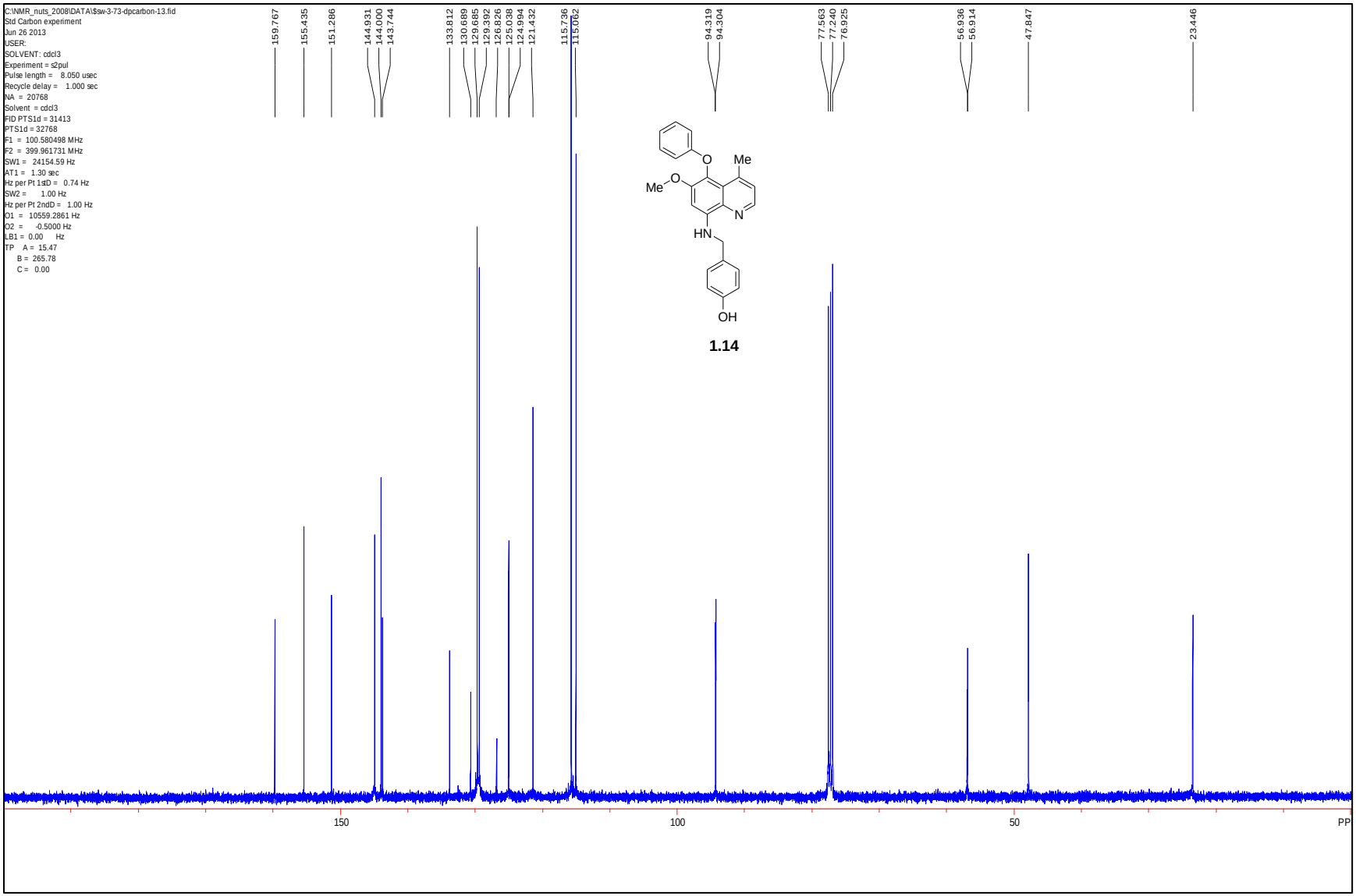

C:\NMR_nuts_2008\DATA\$jyl-7-084-13C.fid
Std Carbon experiment
Apr 17 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 1.000 sec
NA = 16976
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.580498 MHz
F2 = 399.961731 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10557.8125 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 35.16
B = 266.48
C = 0.00
159.730
151.257
144.916
144.132
143.370
133.907
129.663
126.731
125.016
124.789
121.373
115.003
93.835
77.563
77.240
76.925
57.032
41.214
39.315
30.058
23.380
O
Me
Me
O
N
HN
NH2
1.13
150
100
50
PP

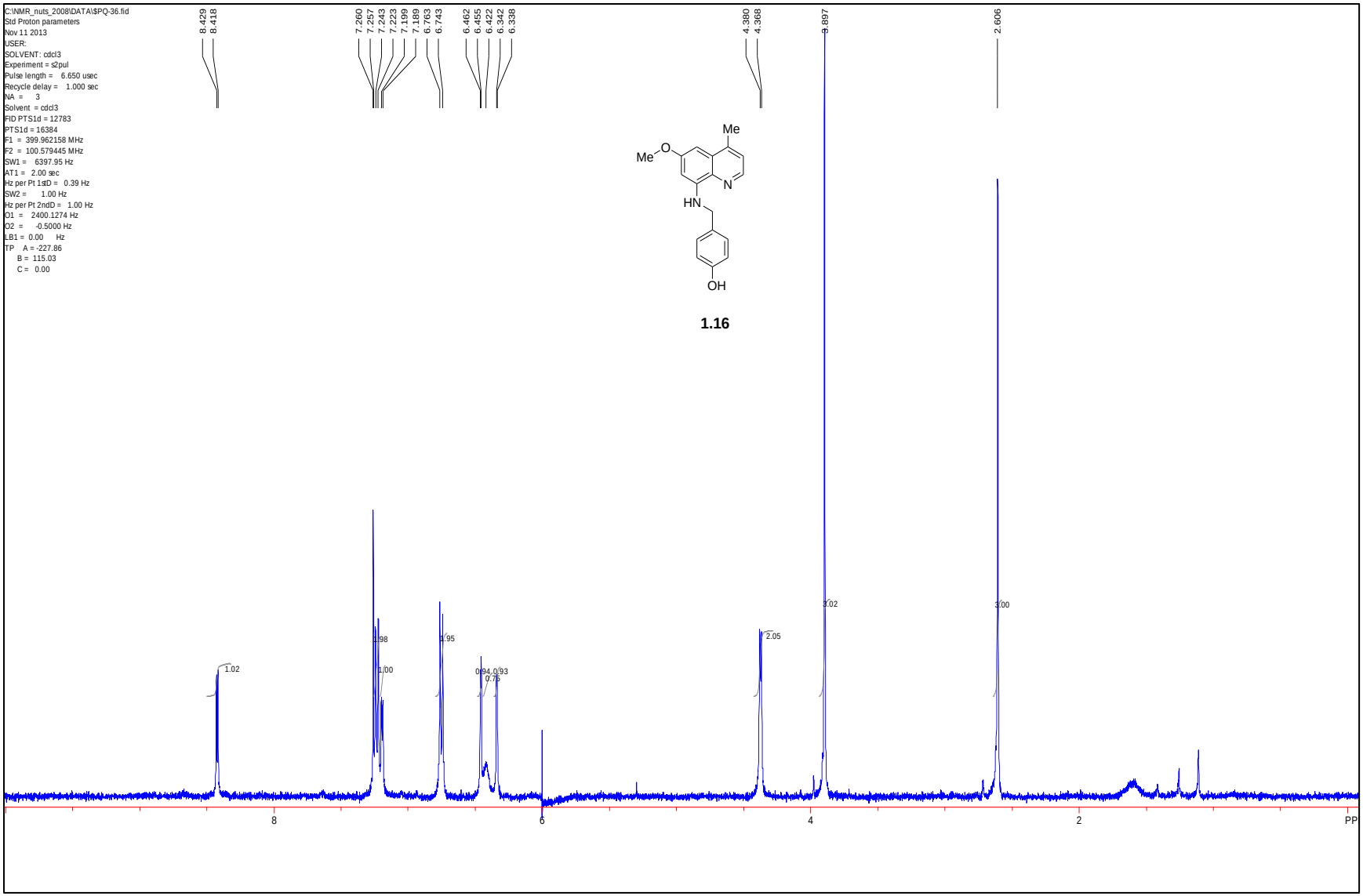

C:\NMR_nuts_2008\DATA\$jyl-7-103.fid
Std Proton parameters
May 1 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 1.000 sec
NA = 16
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.962158 MHz
F2 = 100.579445 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2400.5181 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 118.06
B = 71.47
C = 0.00
8.414
8.403
7.260
7.163
7.152
6.418
6.412
6.311
6.305
6.253
3.911
3.358
3.342
3.324
2.915
2.897
2.880
2.580
1.946
1.929
1.912
1.895
1.877
Me
O
Me
N
HN
NH2
1.15
0.81
0.81
0.94
0.99
0.64
2.84
2.05
2.01
2.99
2.00
8
6
4
2
0 PP


C:\NMR_nuts_2008\DATA\ssw-3-63dp.fid
Std Proton parameters
Jun 24 2013
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 1.000 sec
NA = 56
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.962158 MHz
F2 = 100.579445 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2400.9084 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 97.62
B = 86.00
C = 0.00
8.418
8.402
7.291
7.270
7.260
7.213
7.193
7.175
7.155
7.101
7.099
7.090
6.803
6.783
6.690
6.688
6.669
6.667
6.649
6.642
6.625
6.620
6.605
6.605
6.511
6.500
6.474
6.468
4.437
3.787
2.642
F
O
Me
Me
O
N
HN
OH
1.12
8
6
4
2
PP

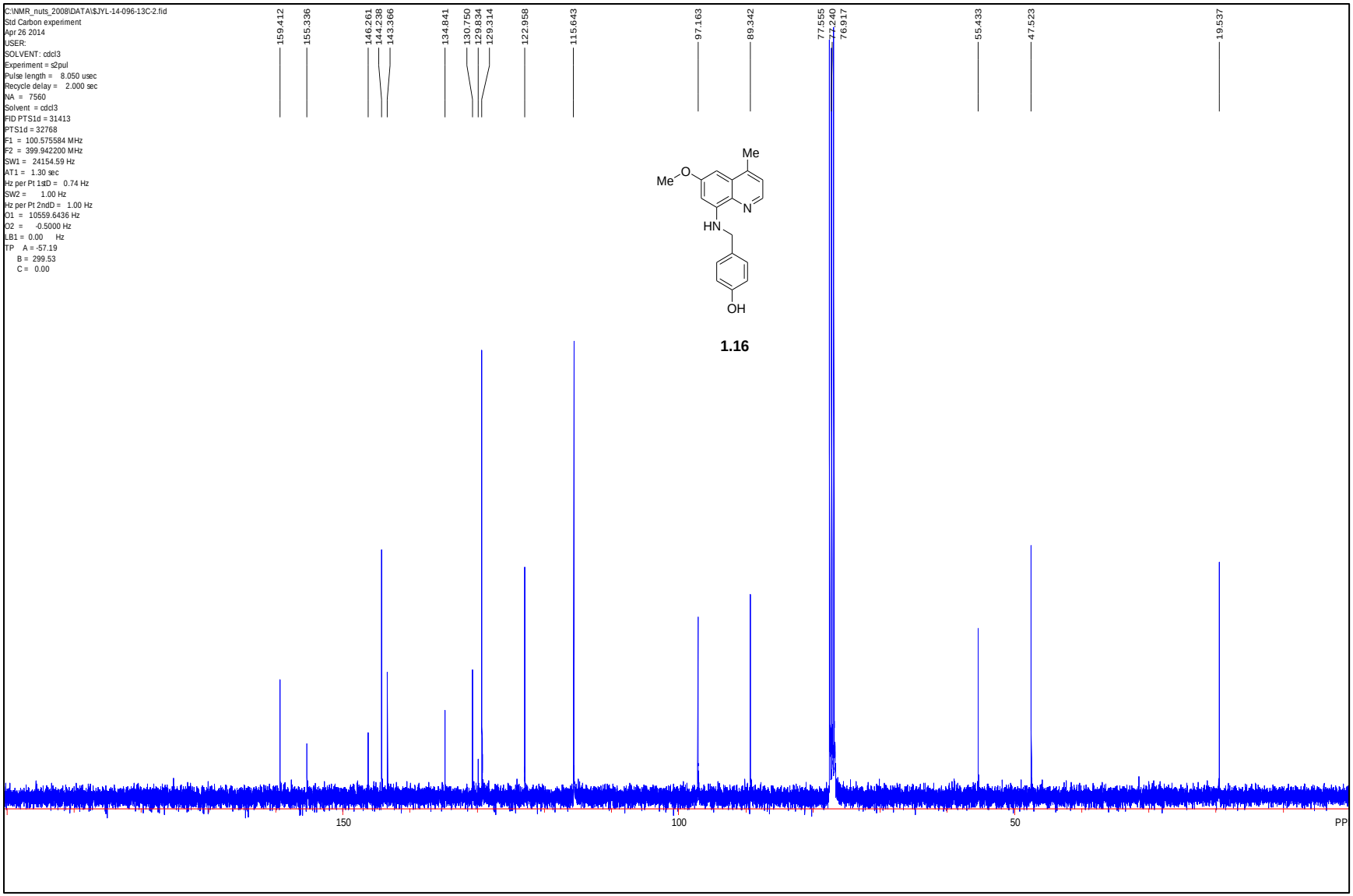

C:\NMR_nuts_2008\DATA\$sw-3-63dpcarbon.fid
Std Proton parameters
Jun 24 2013
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 1.000 sec
NA = 5000
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.580498 MHz
F2 = 399.961731 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10559.2305 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 58.59
B = 187.03
C = 0.00
165.190
162.757
161.261
161.159
155.449
151.176
144.967
144.286
143.406
133.672
130.652
130.498
130.395
129.362
126.357
125.177
124.708
116.758
111.015
110.986
108.443
108.230
103.048
102.769
93.922
56.811
47.795
30.519
23.350
F
O
Me
Me
O
N
HN
OH
1.12
150
100
50
0
PPM


C:\NMR_nuts_2008\DATA\$sw-3-73DPcorrect.fid
Std Proton parameters
Jun 26 2013
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 1.000 sec
NA = 64
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.962158 MHz
F2 = 100.579445 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2400.5181 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 96.78
B = 109.06
C = 0.00
8.408
8.398
7.295
7.274
7.260
7.241
7.239
7.220
7.088
7.075
6.975
6.956
6.938
6.800
6.779
6.526
6.064
4.438
3.776
2.656
O
Me
Me
O
N
HN
OH
1.14
0.91
2.51
1.96
3.83
0.95
0.94
1.87
0.84
1.93
2.92
3.00
10
8
6
4
2
PP

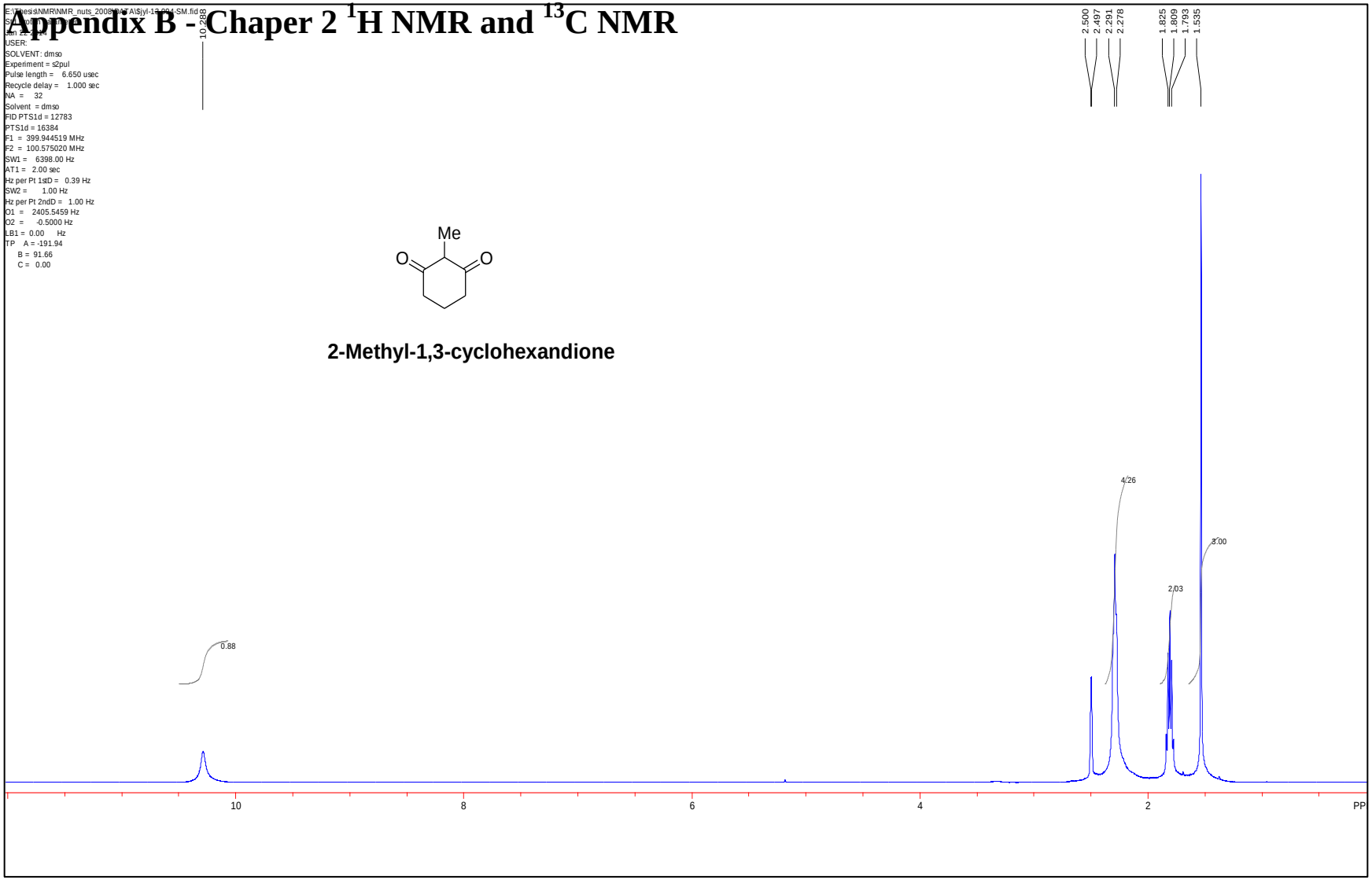

C:\NMR_nuts_2008\DATA\$sw-3-73-dpcarbon-13.fid
Std Carbon experiment
Jun 26 2013
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 1.000 sec
NA = 20768
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.580498 MHz
F2 = 399.961731 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10559.2861 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 15.47
B = 265.78
C = 0.00
159.767
155.435
151.286
144.931
144.000
143.744
133.812
130.689
129.685
129.392
126.826
125.038
124.994
121.432
115.736
115.062
94.319
94.304
77.563
77.240
76.925
56.936
56.914
47.847
23.446
O
Me
Me
O
N
HN
OH
1.14
150
100
50
PP

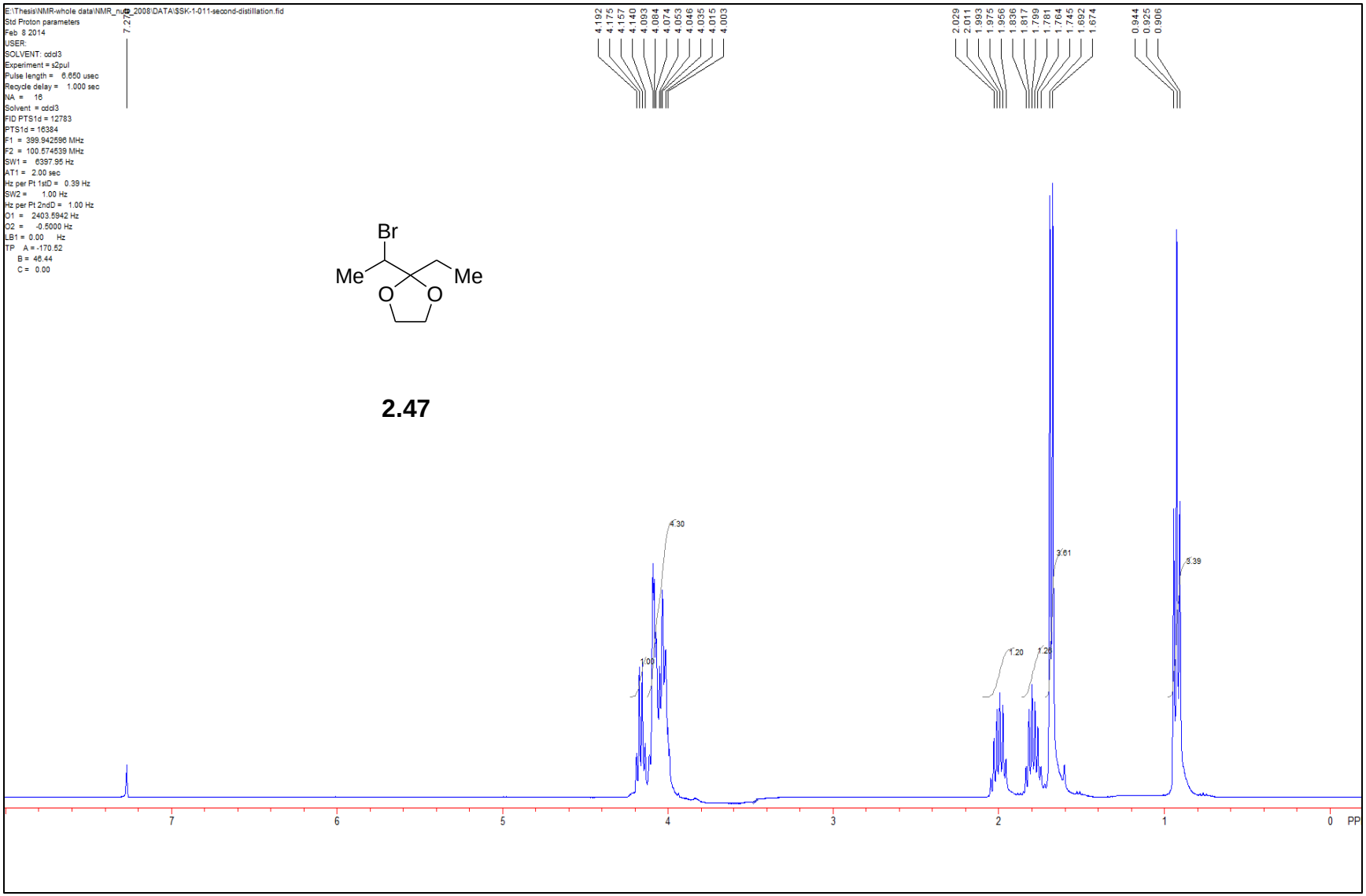

C:\NMR_nuts_2008\DATA\$PQ-36.fid
Std Proton parameters
Nov 11 2013
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 1.000 sec
NA = 3
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.962158 MHz
F2 = 100.579445 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2400.1274 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -227.86
B = 115.03
C = 0.00
8.429
8.418
7.260
7.257
7.243
7.223
7.199
7.189
6.763
6.743
6.462
6.455
6.422
6.342
6.338
4.380
4.368
3.897
2.606
Me
O
Me
N
HN
OH
1.02
1.98
1.00
1.95
0.94
0.93
0.76
2.05
3.02
3.00
8
6
4
2
PP

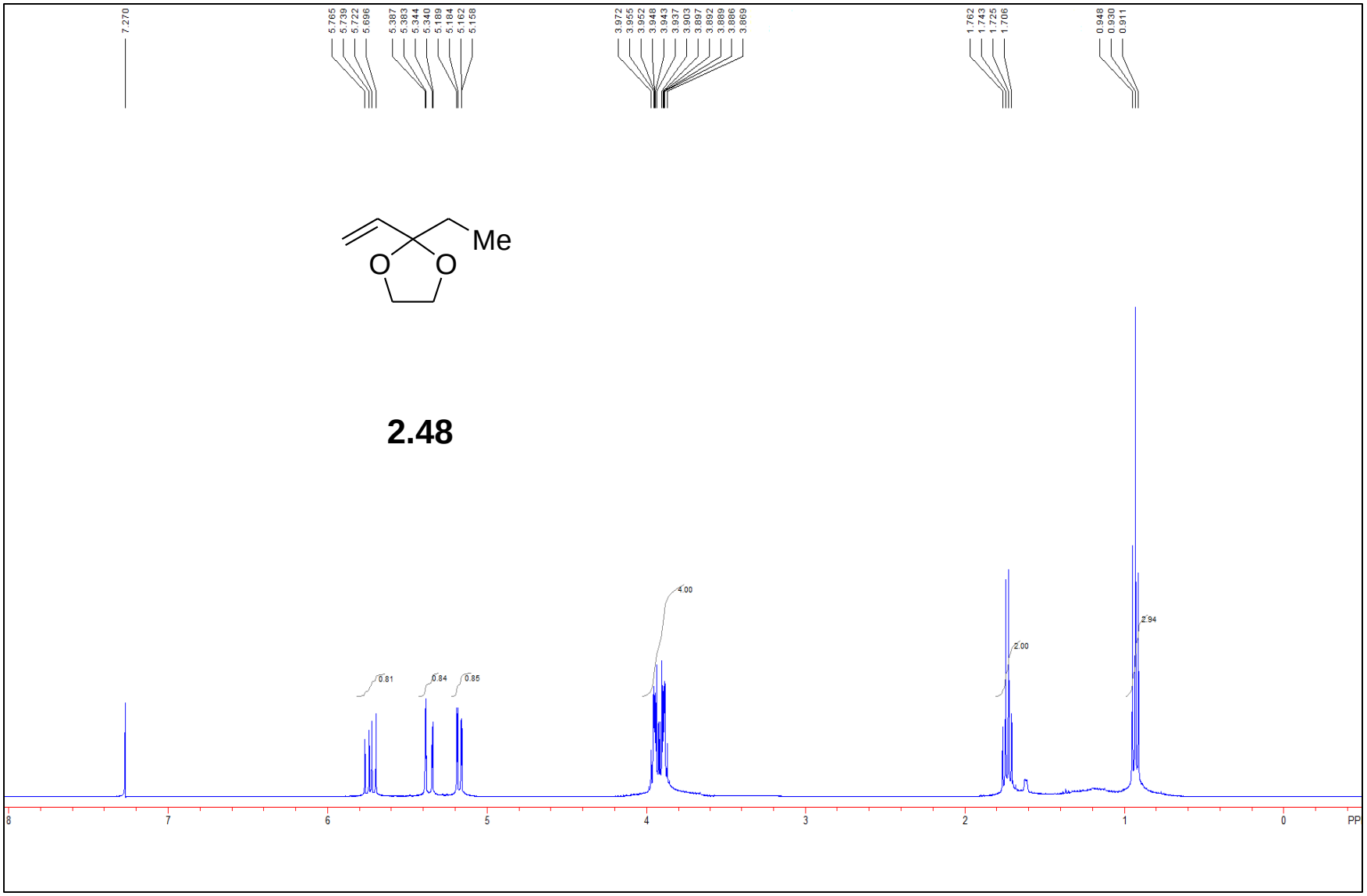
**1.16**

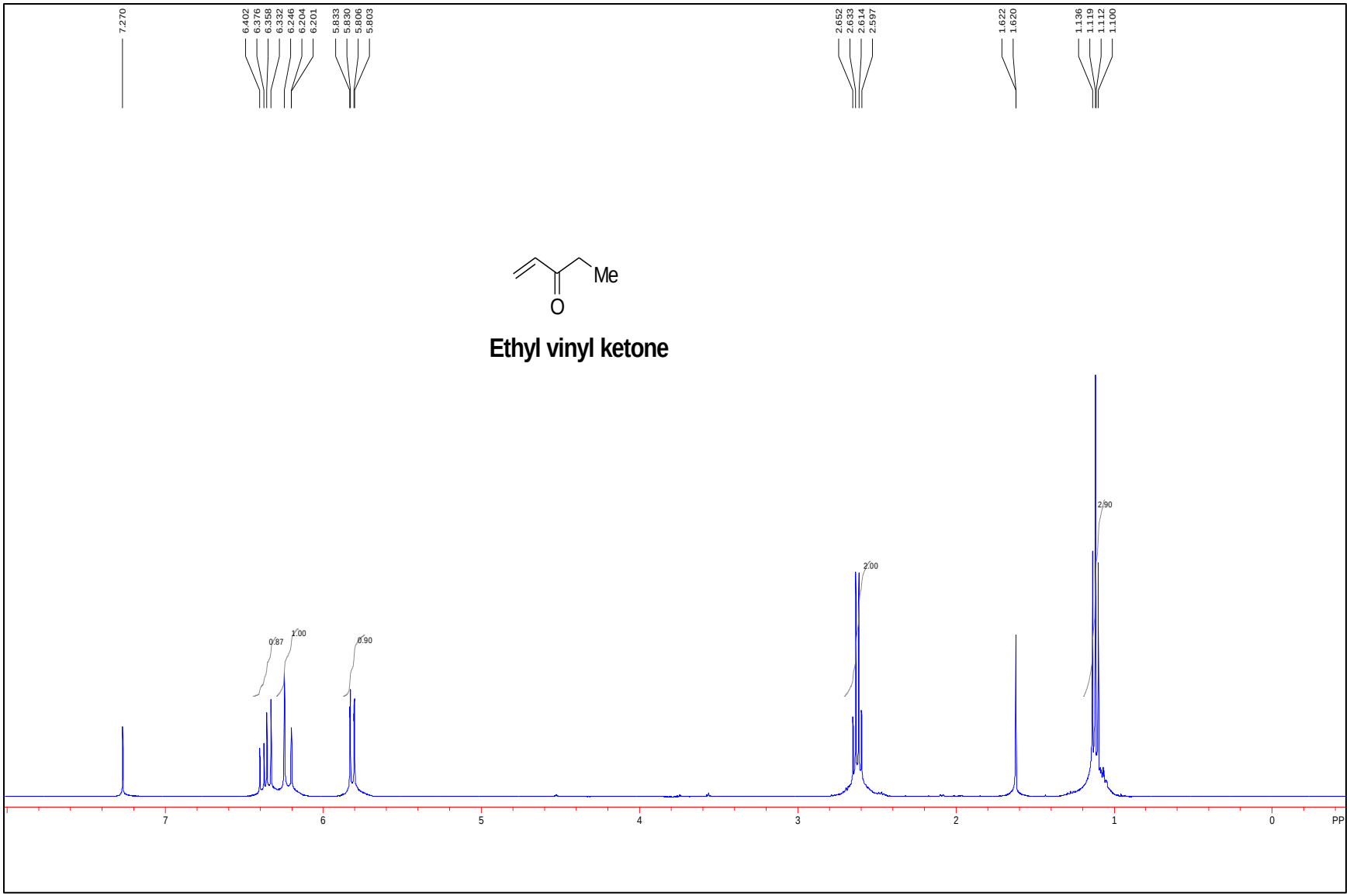

C:\NMR_nuts_2008\DATA\$JYL-14-096-13C-2.fid
Std Carbon experiment
Apr 26 2014
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 2.000 sec
NA = 7560
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.575584 MHz
F2 = 399.942200 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10559.6436 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -57.19
B = 299.53
C = 0.00
159.412
155.336
146.261
144.238
143.366
134.841
130.750
129.834
129.314
122.958
115.643
97.163
89.342
77.555
77.240
76.917
55.433
47.523
19.537
Me
Me
O
N
HN
OH
1.16
150
100
50
PP

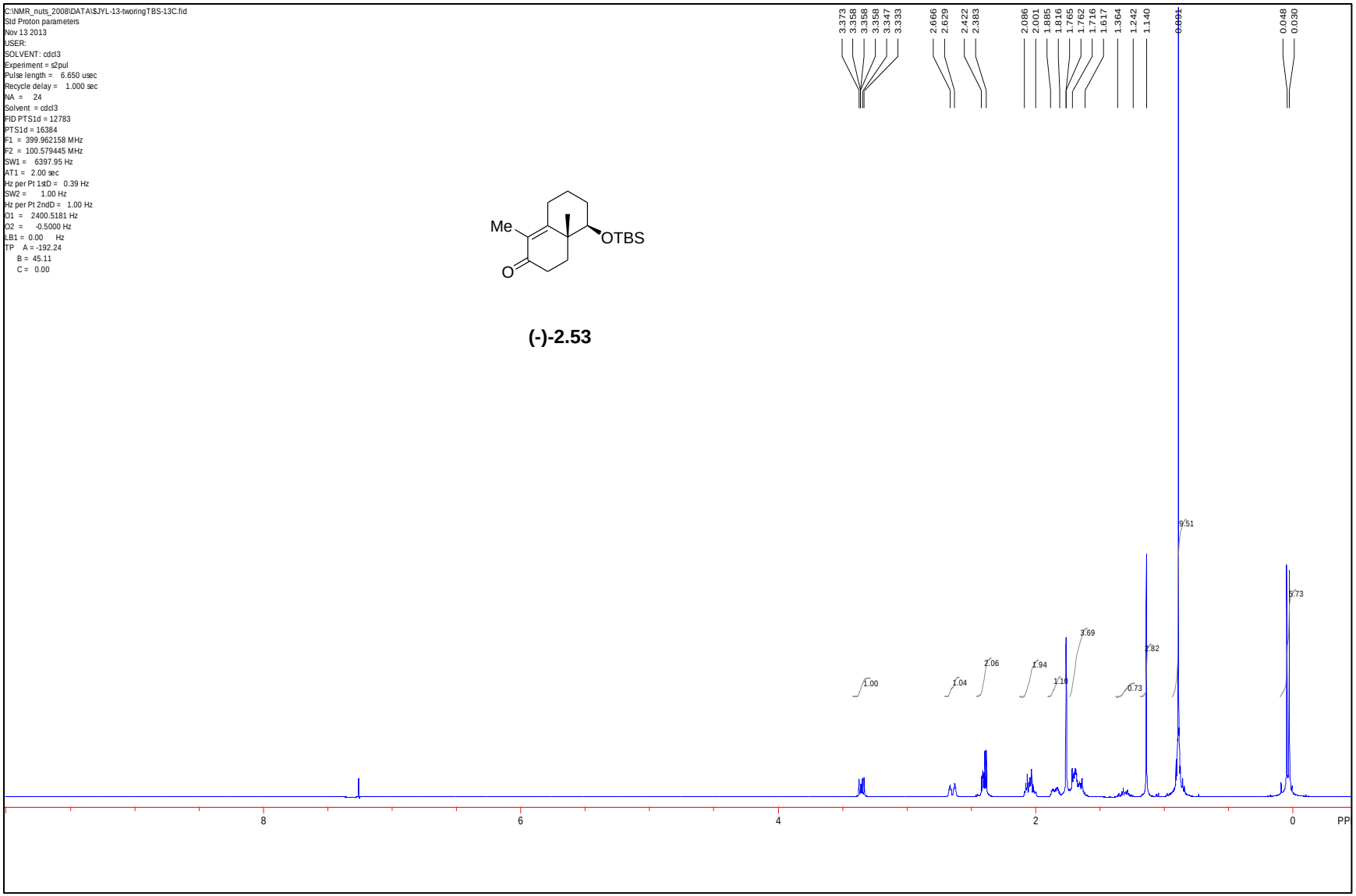
# Appendix B - Chaper 2 $^{1}$H NMR and $^{13}$C NMR

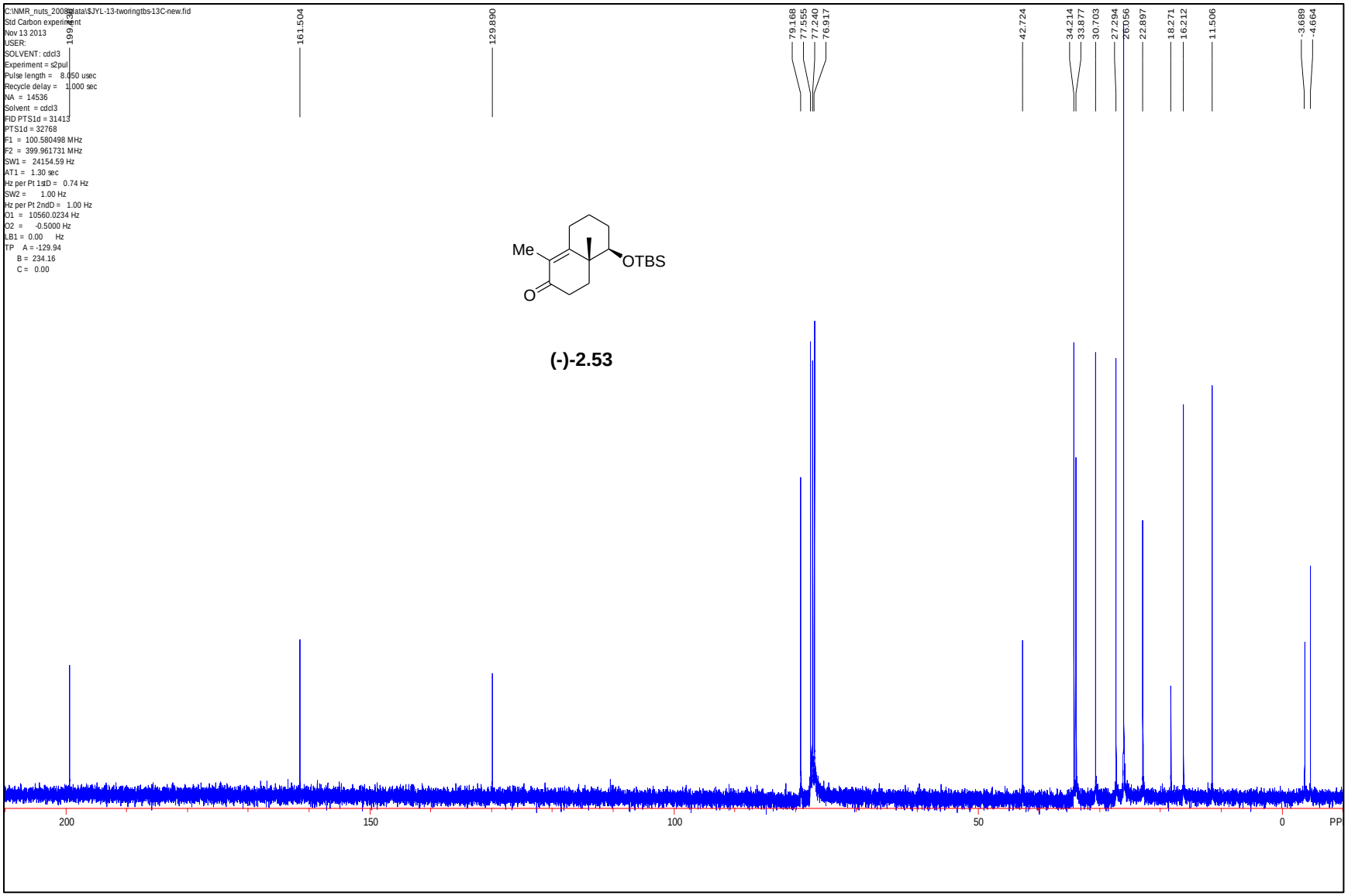


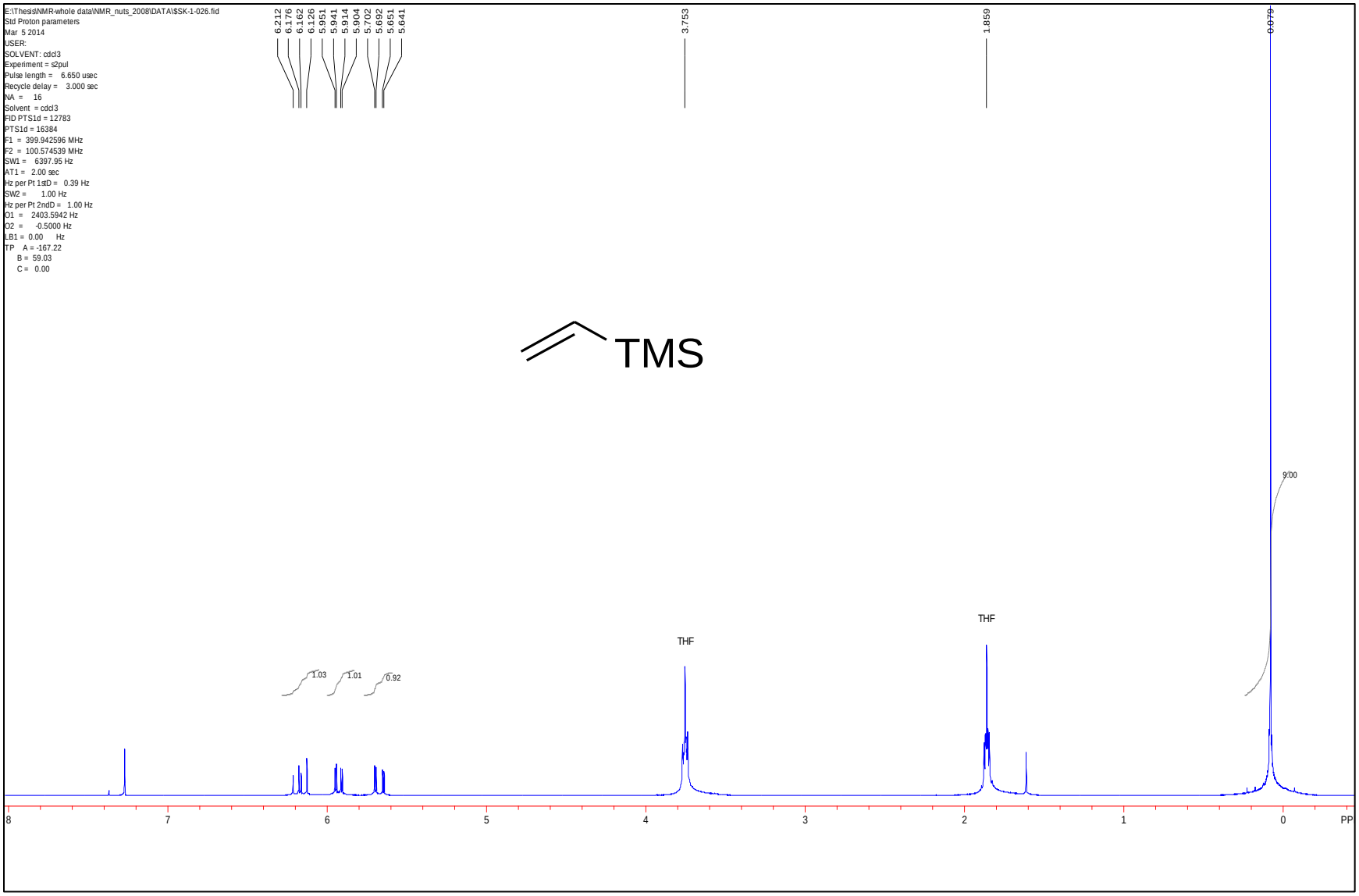

E:\Thesis\NMR-whole data\NMR_nuc_2008\DATA\SSK-1-011-second-distillation.fid
Std Proton parameters
Feb 8 2014
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 1.000 sec
NA = 16
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.942596 MHz
F2 = 100.574539 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2403.5942 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -170.52
B = 46.44
C = 0.00
7.27
4.192
4.175
4.157
4.140
4.093
4.084
4.074
4.053
4.046
4.035
4.015
4.003
2.029
2.011
1.993
1.975
1.956
1.836
1.817
1.799
1.781
1.764
1.745
1.692
1.674
0.944
0.925
0.906
Br
Me
Me
O
O
2.47
4.30
3.61
3.39
1.20
1.26
1.00
7
6
5
4
3
2
1
0
PP

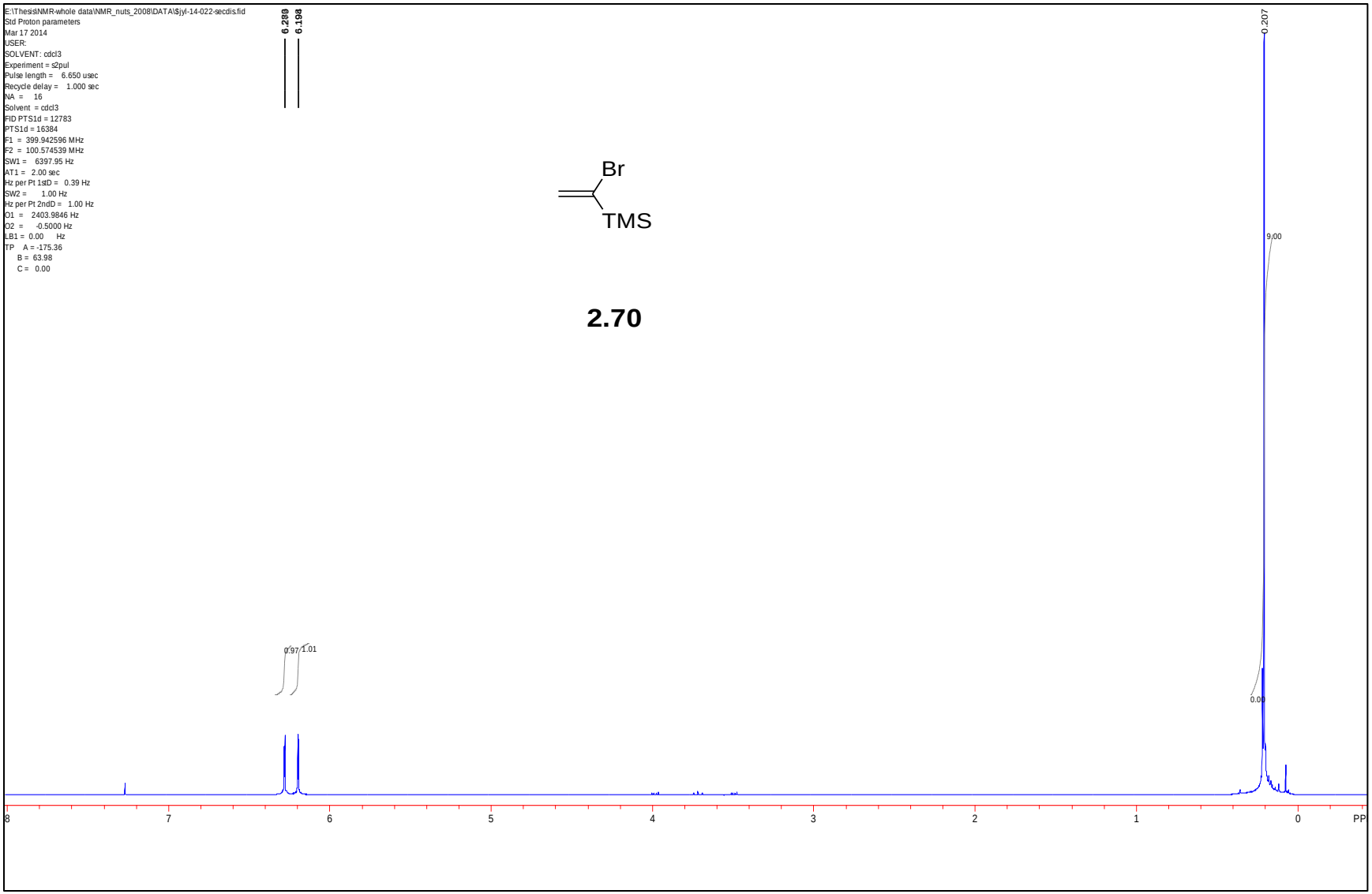

7.270
5.765
5.739
5.722
5.696
5.387
5.383
5.344
5.340
5.189
5.184
5.162
5.158
3.972
3.955
3.952
3.948
3.943
3.937
3.903
3.897
3.892
3.889
3.886
3.869
1.762
1.743
1.725
1.706
0.948
0.930
0.911
Me
O
O
2.48
0.81
0.84
0.85
4.00
2.00
2.94
8
7
6
5
4
3
2
1
0
PP

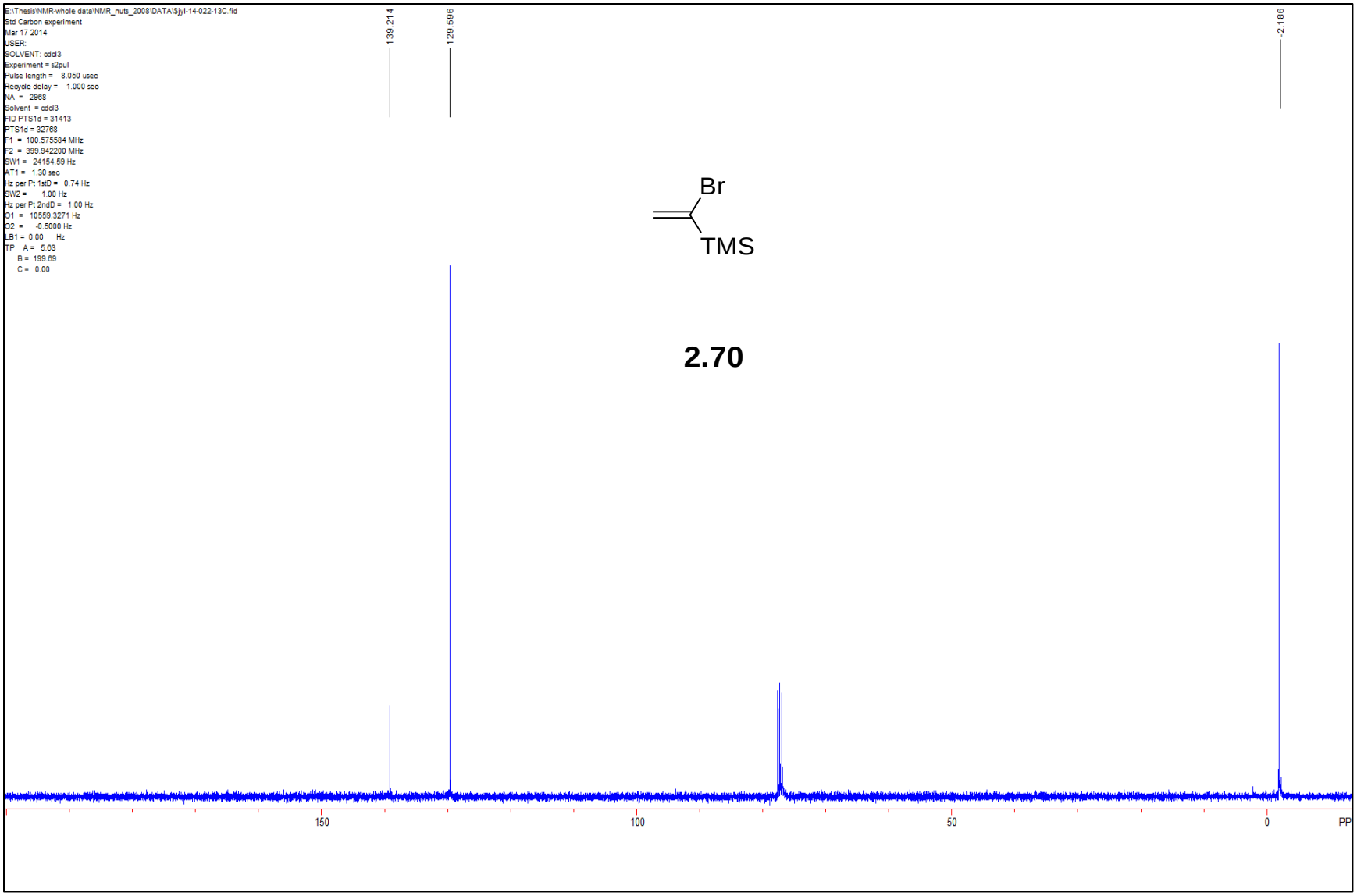

7.270
6.402
6.376
6.358
6.332
6.246
6.204
6.201
5.833
5.830
5.806
5.803
2.652
2.633
2.614
2.597
1.622
1.620
1.136
1.119
1.112
1.100
Me
O
Ethyl vinyl ketone
0.87
1.00
0.90
2.00
2.90
7
6
5
4
3
2
1
0
PP

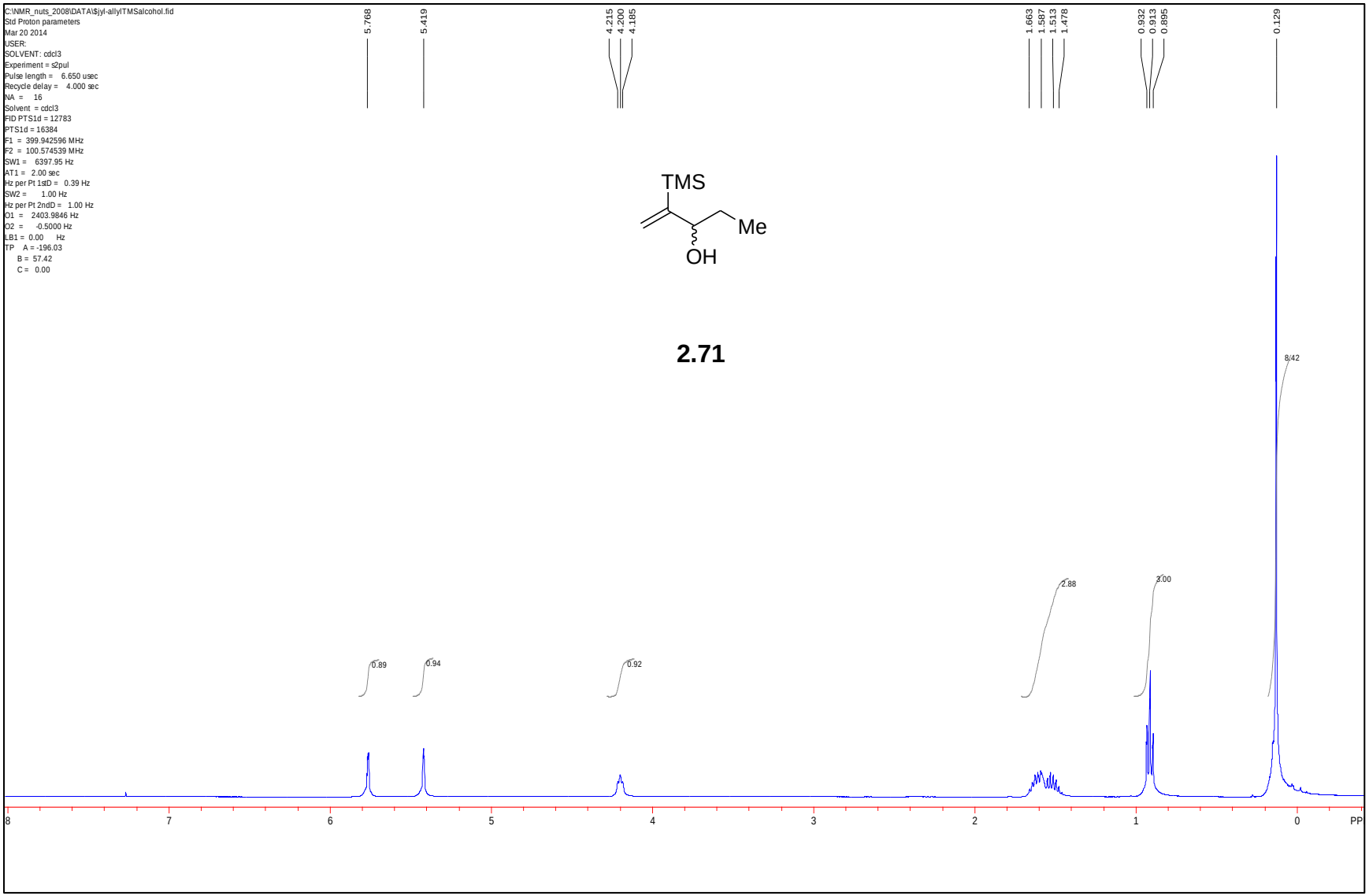

C:\NMR_nuts_2008\DATA\$JYL-13-tworingTBS-13C.fid
Std Proton parameters
Nov 13 2013
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 1.000 sec
NA = 24
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.962158 MHz
F2 = 100.579445 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2400.5181 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -192.24
B = 45.11
C = 0.00
3.373
3.358
3.358
3.358
3.347
3.333
2.666
2.629
2.422
2.383
2.086
2.001
1.885
1.816
1.765
1.762
1.716
1.617
1.364
1.242
1.140
0.891
0.048
0.030
Me
OTBS
O
(-)-2.53
9.51
5.73
3.69
2.82
2.06
1.94
1.10
1.04
1.00
0.73
8
6
4
2
0
PP

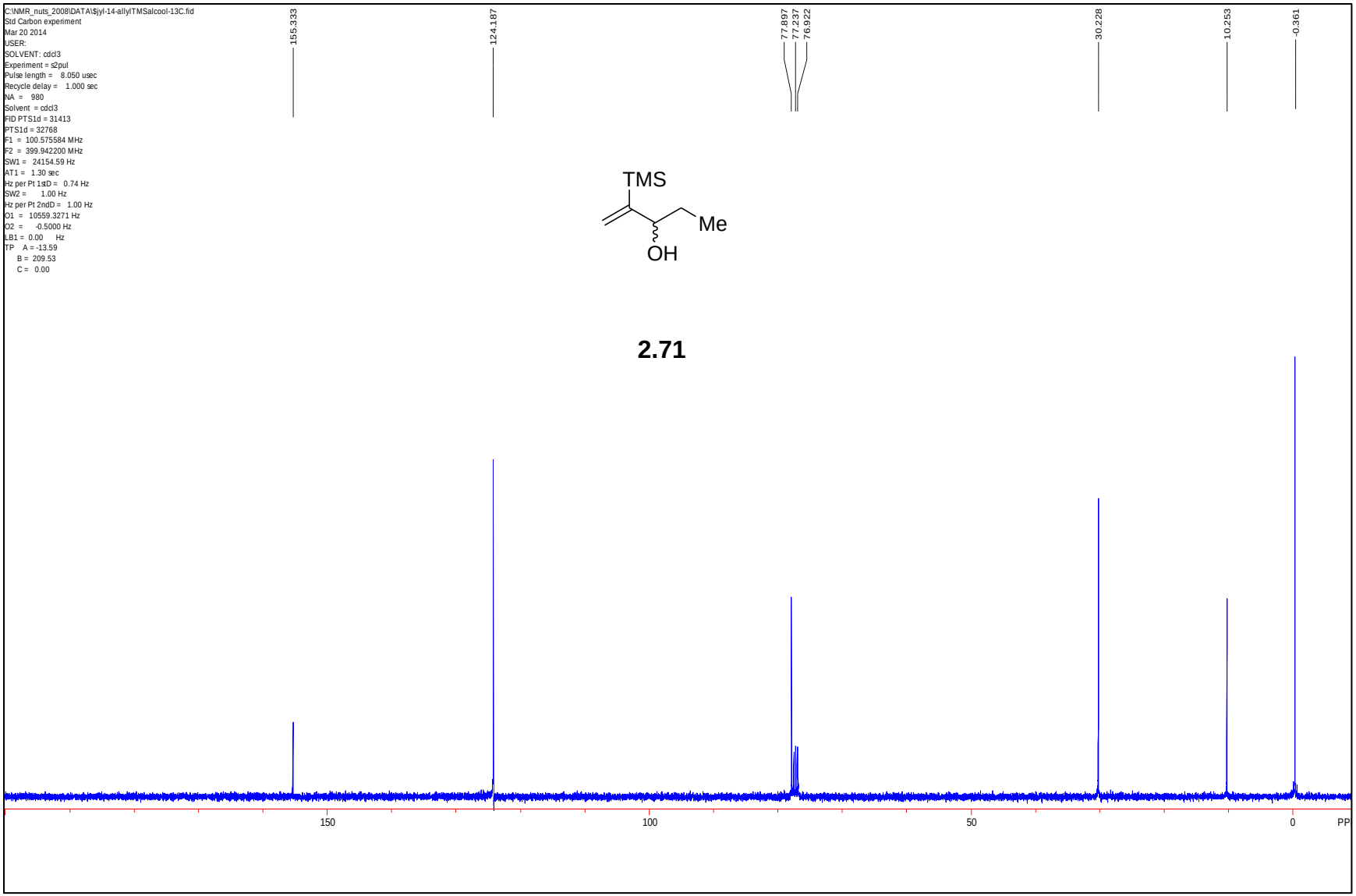

C:\NMR_nuts_2008\data\SJYL-13-tworingtbs-13C-new.fid
Std Carbon experiment
Nov 13 2013
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 1.000 sec
NA = 14536
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.580498 MHz
F2 = 399.961731 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10560.0234 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -129.94
B = 234.16
C = 0.00
197.884
161.504
129.890
79.168
77.555
77.240
76.917
42.724
34.214
33.877
30.703
27.294
26.056
22.897
18.271
16.212
11.506
-3.689
-4.664
Me
OTBS
O
(-)-2.53
200
150
100
50
0
PP

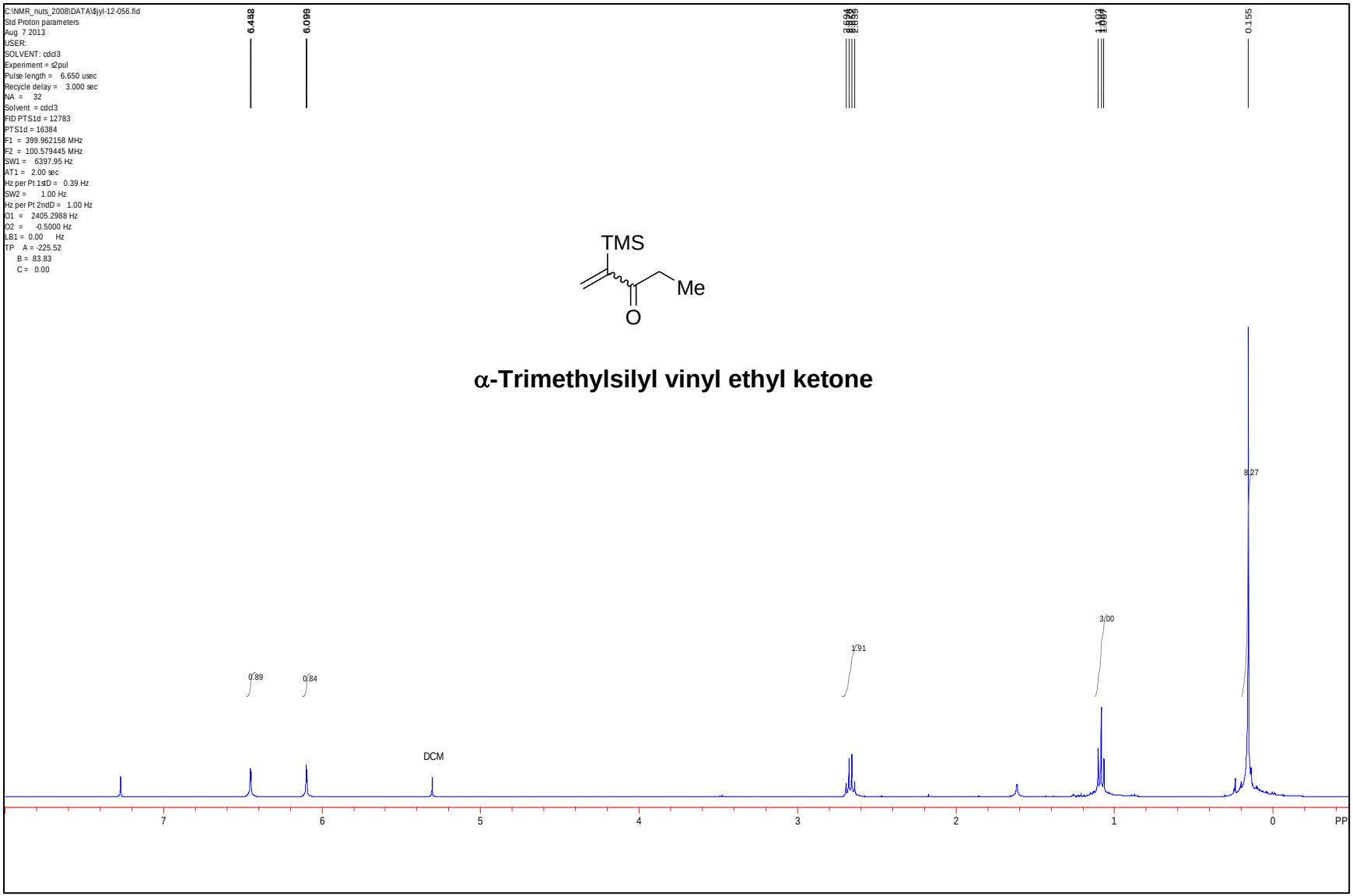

E:\Thesis\NMR-whole data\NMR_nuts_2008\DATA\SSK-1-026.fid
Std Proton parameters
Mar 5 2014
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 3.000 sec
NA = 16
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.942596 MHz
F2 = 100.574539 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2403.5942 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -167.22
B = 59.03
C = 0.00
6.212
6.176
6.162
6.126
5.951
5.941
5.914
5.904
5.702
5.692
5.651
5.641
3.753
1.859
0.079
TMS
9.00
THF
THF
1.03
1.01
0.92
8
7
6
5
4
3
2
1
0
PP

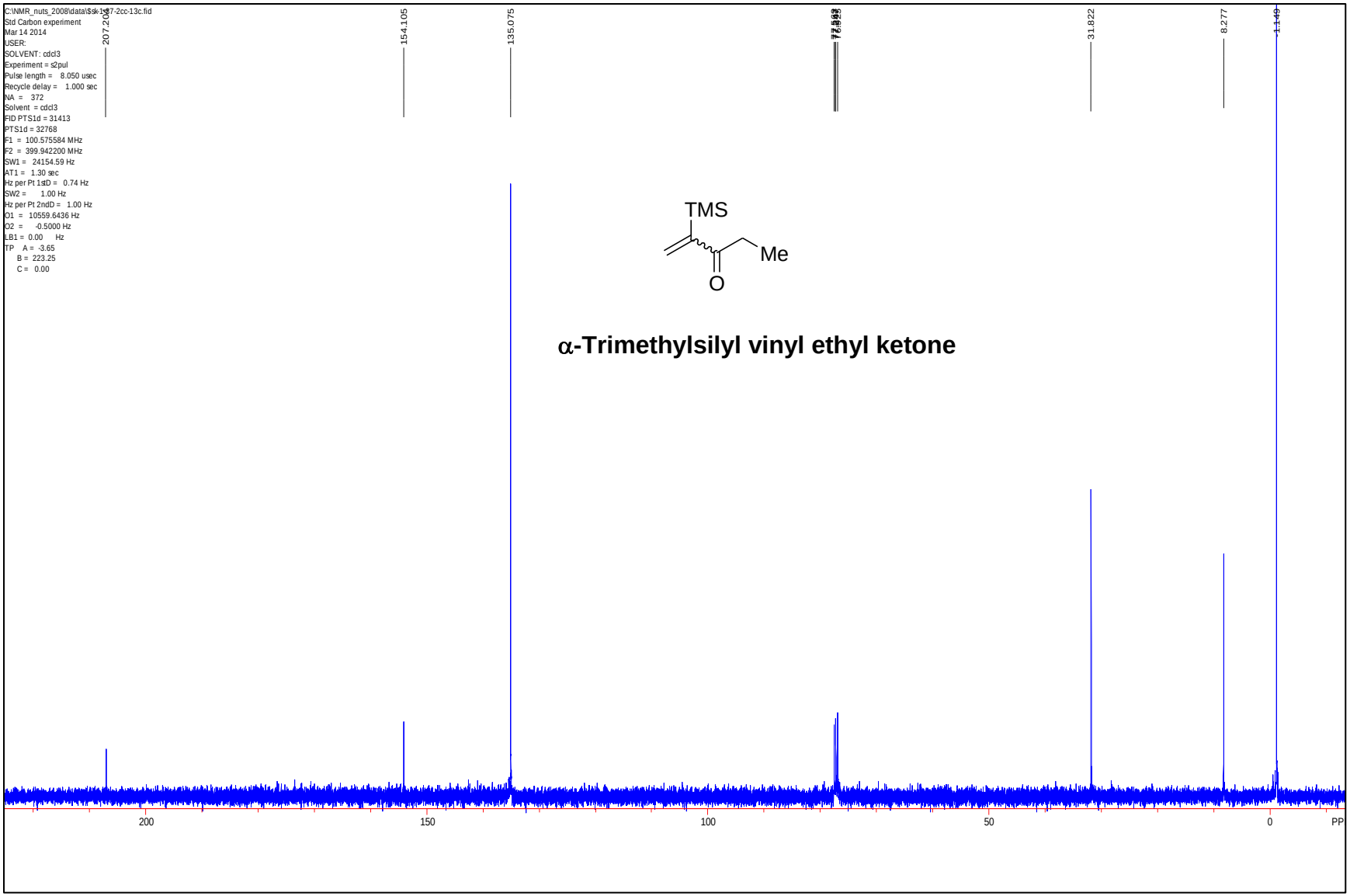

E:\Thesis\NMR-whole data\NMR_nuts_2008\DATA\sjyl-14-022-secdis.fid
Std Proton parameters
Mar 17 2014
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 1.000 sec
NA = 16
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.942596 MHz
F2 = 100.574539 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2403.9846 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -175.36
B = 63.98
C = 0.00
6.289
6.198
0.207
Br
TMS
2.70
9.00
0.97
1.01
0.00
8
7
6
5
4
3
2
1
0
PP

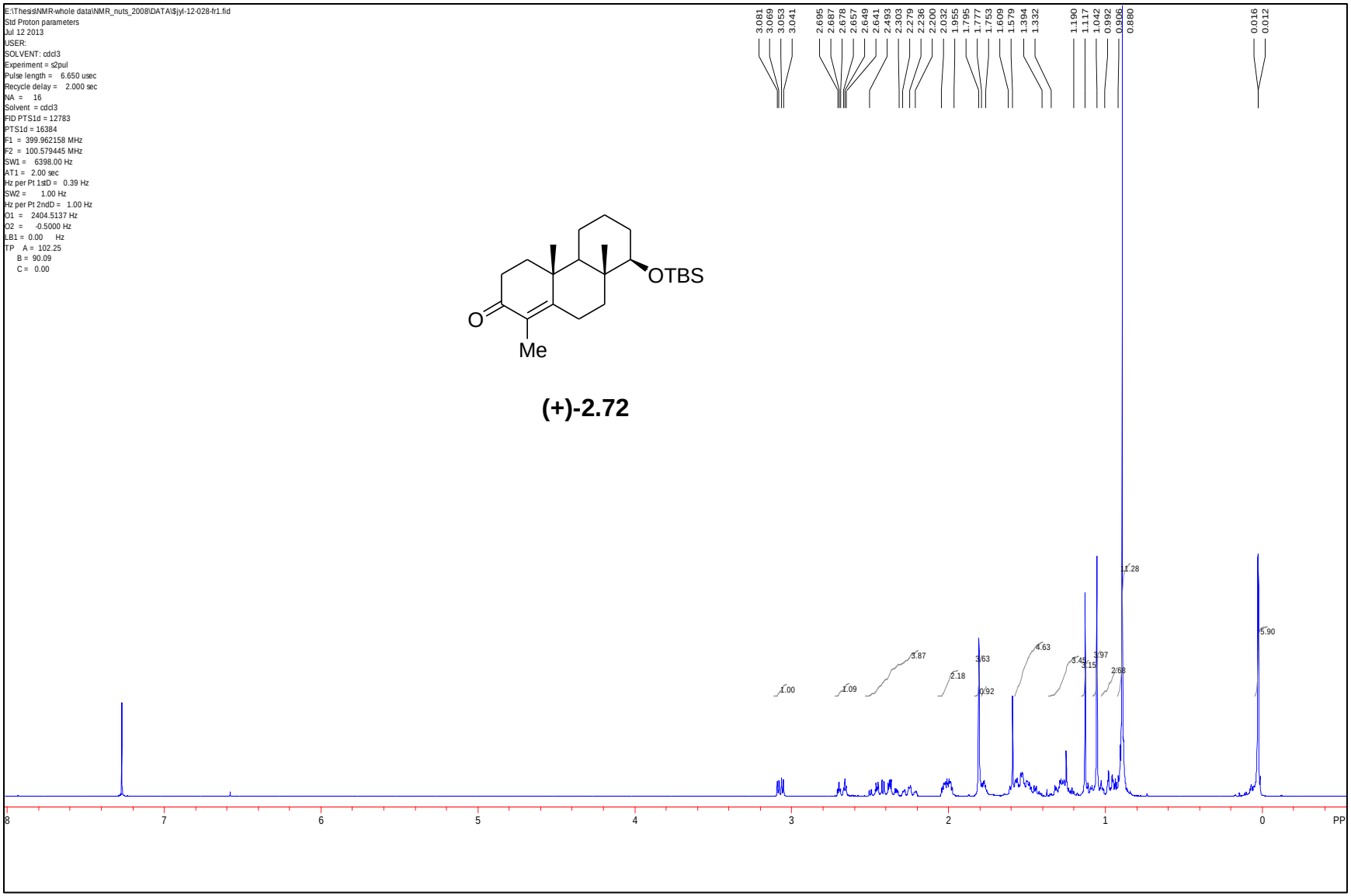

E:\Thesis\NMR-whole data\NMR_nuts_2008\DATA\Sjyl-14-022-13C.fid
Std Carbon experiment
Mar 17 2014
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 1.000 sec
NA = 2968
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.575584 MHz
F2 = 399.942200 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10559.3271 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 5.63
B = 199.69
C = 0.00
139.214
129.596
-2.186
Br
TMS
2.70
150
100
50
0
PP


C:\NMR_nuts_2008\DATA\$jyl-allylTMSalcohol.fid
Std Proton parameters
Mar 20 2014
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 4.000 sec
NA = 16
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.942596 MHz
F2 = 100.574539 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2403.9846 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -196.03
B = 57.42
C = 0.00
5.768
5.419
4.215
4.200
4.185
1.663
1.587
1.513
1.478
0.932
0.913
0.895
0.129
TMS
Me
OH
2.71
0.89
0.94
0.92
2.88
3.00
8.42
8
7
6
5
4
3
2
1
0
PP

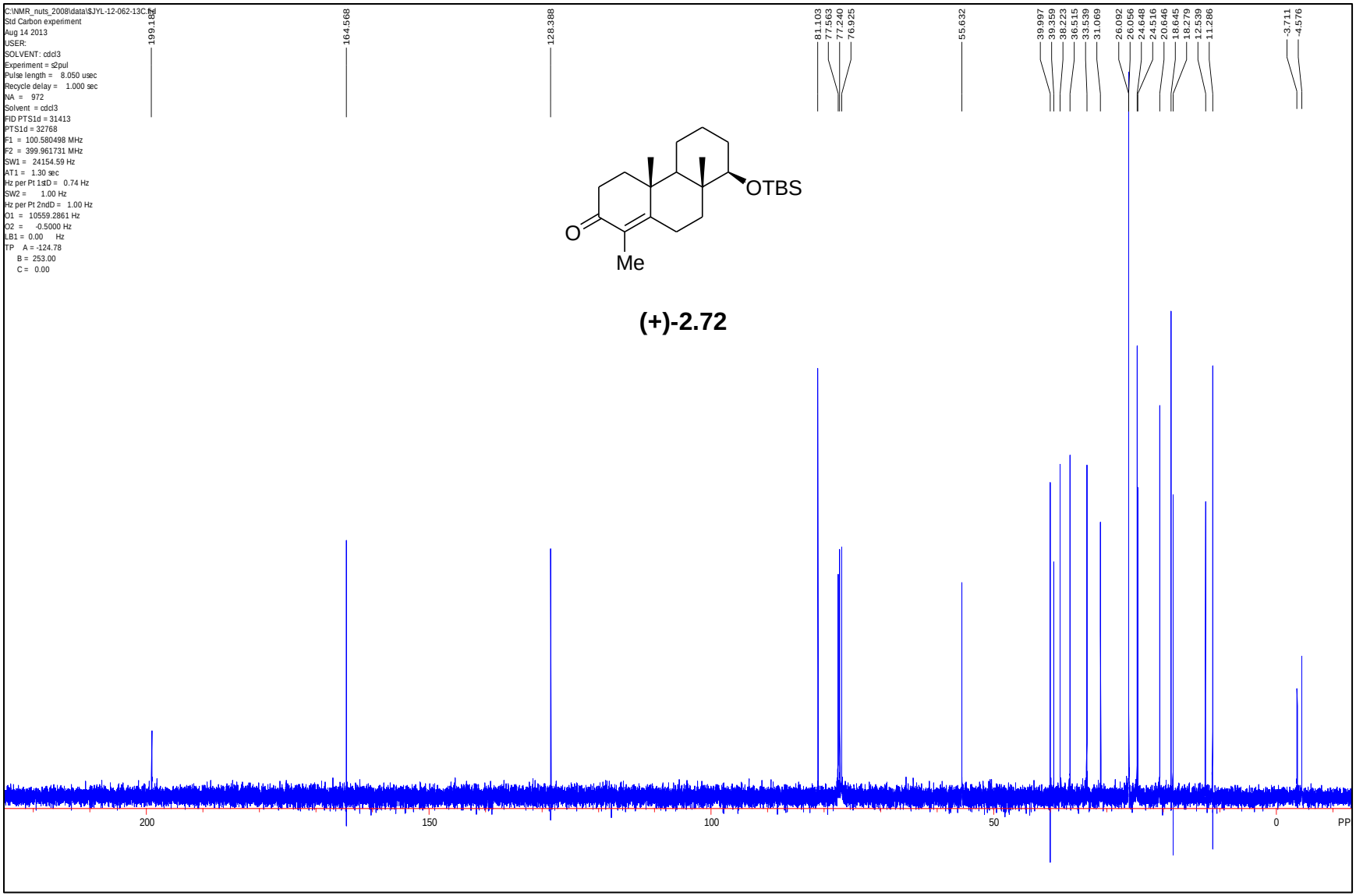

C:\NMR_nuts_2008\DATA\$jyl-14-allylTMSalcool-13C.fid
Std Carbon experiment
Mar 20 2014
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 1.000 sec
NA = 980
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.575584 MHz
F2 = 399.942200 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10559.3271 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -13.59
B = 209.53
C = 0.00
155.333
124.187
77.897
77.237
76.922
30.228
10.253
-0.361
TMS
Me
OH
2.71
150
100
50
0
PP

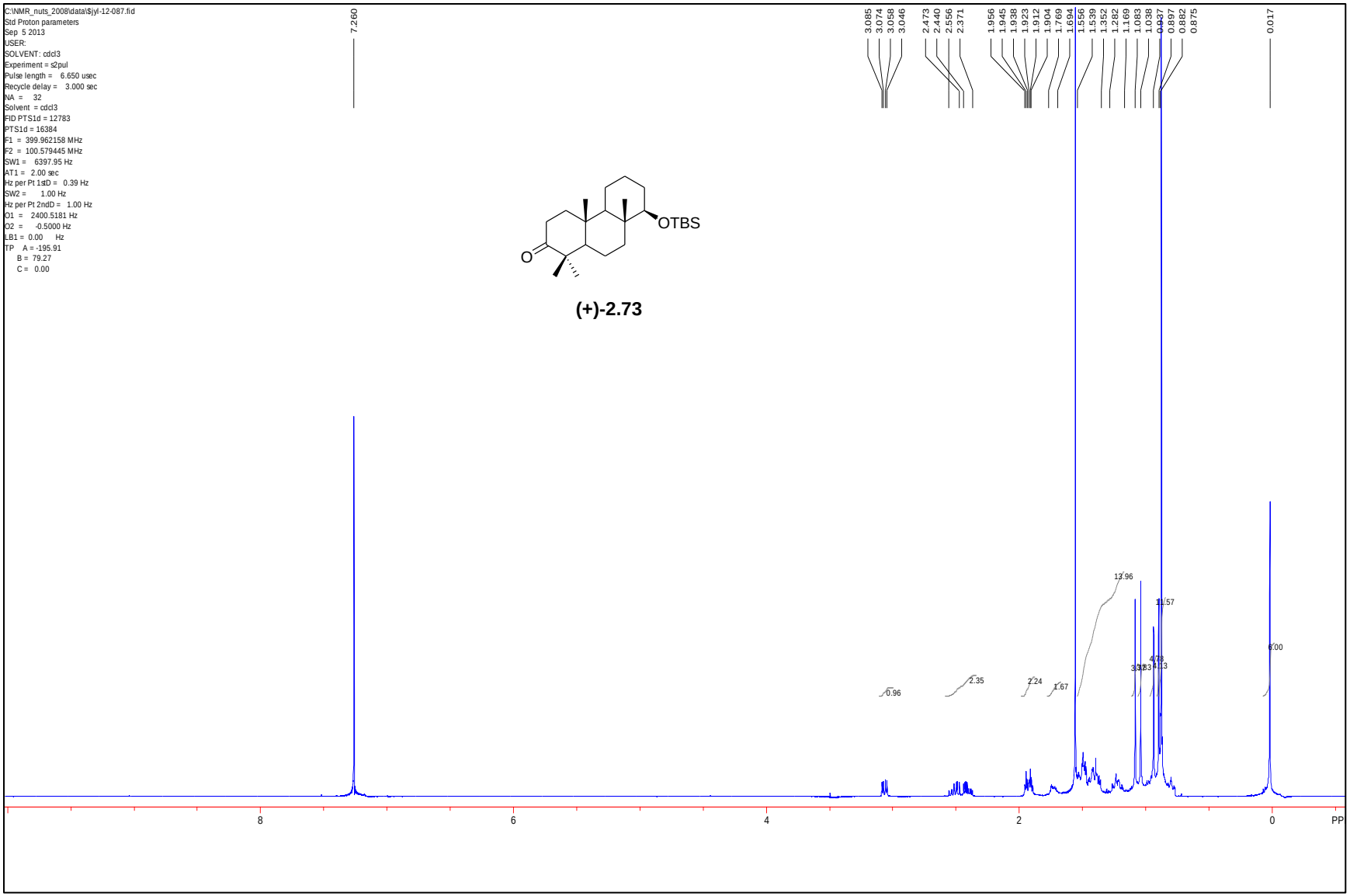

C:\NMR_nuts_2008\DATA\$jyl-12-056.fid
Std Proton parameters
Aug 7 2013
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 3.000 sec
NA = 32
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.962158 MHz
F2 = 100.579445 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2405.2988 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -225.52
B = 83.83
C = 0.00
6.448
6.099
2.826
2.809
1.097
0.155
TMS
Me
O
α-Trimethylsilyl vinyl ethyl ketone
0.89
0.84
DCM
1.91
3.00
8.27
7
6
5
4
3
2
1
0
PPM

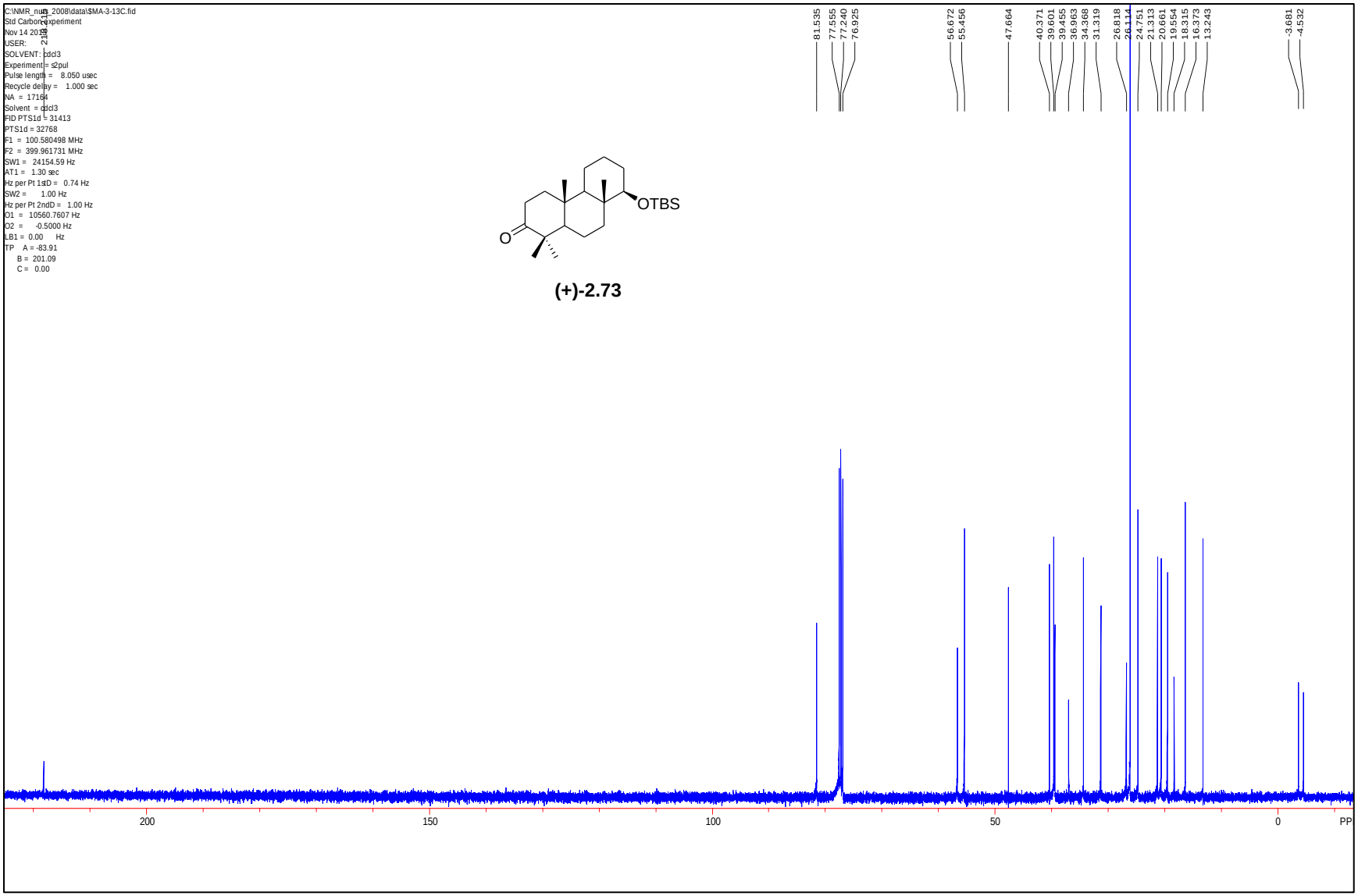

C:\NMR_nuts_2008\data\Sk-197-2cc-13c.fid
Std Carbon experiment
Mar 14 2014
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 1.000 sec
NA = 372
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.575584 MHz
F2 = 399.942200 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10559.6436 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -3.65
B = 223.25
C = 0.00
207.200
154.105
135.075
31.822
8.277
-1.149
TMS
Me
O
α-Trimethylsilyl vinyl ethyl ketone
200
150
100
50
0
PP


E:\Thesis\NMR-whole data\NMR_nuts_2008\DATA\$jyf-12-028-fr1.fid
Std Proton parameters
Jul 12 2013
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 2.000 sec
NA = 16
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.962158 MHz
F2 = 100.579445 MHz
SW1 = 6398.00 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2404.5137 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 102.25
B = 90.09
C = 0.00
3.081
3.069
3.053
3.041
2.695
2.687
2.678
2.657
2.649
2.641
2.493
2.303
2.279
2.236
2.200
2.032
1.955
1.795
1.777
1.753
1.609
1.579
1.394
1.332
1.190
1.117
1.042
0.992
0.906
0.880
0.016
0.012
OTBS
O
Me
11.28
5.90
4.63
3.87
3.63
3.45
3.15
3.97
2.68
2.18
1.00
1.09
0.92
8
7
6
5
4
3
2
1
0
PP

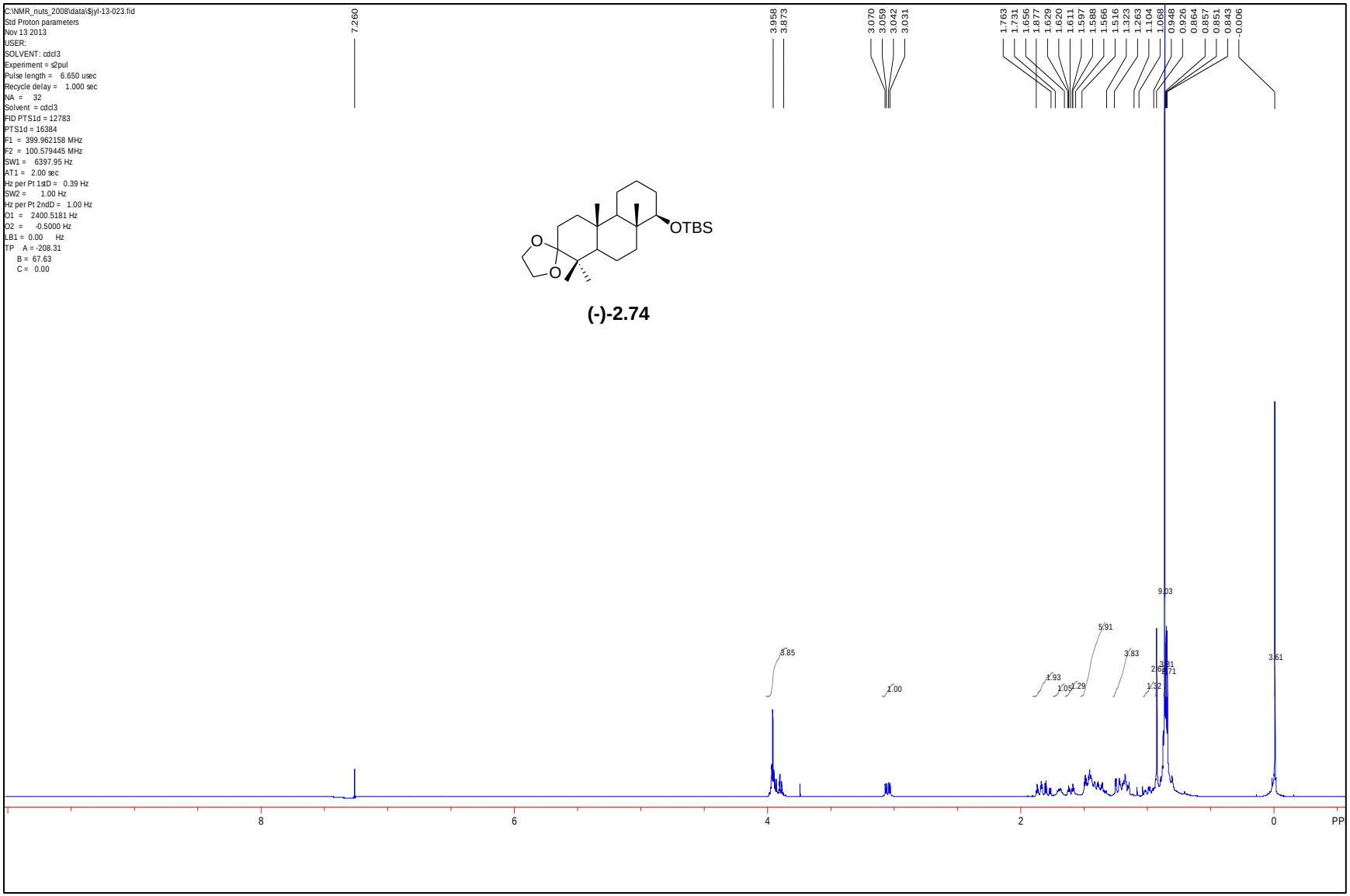
**(+)-2.72**

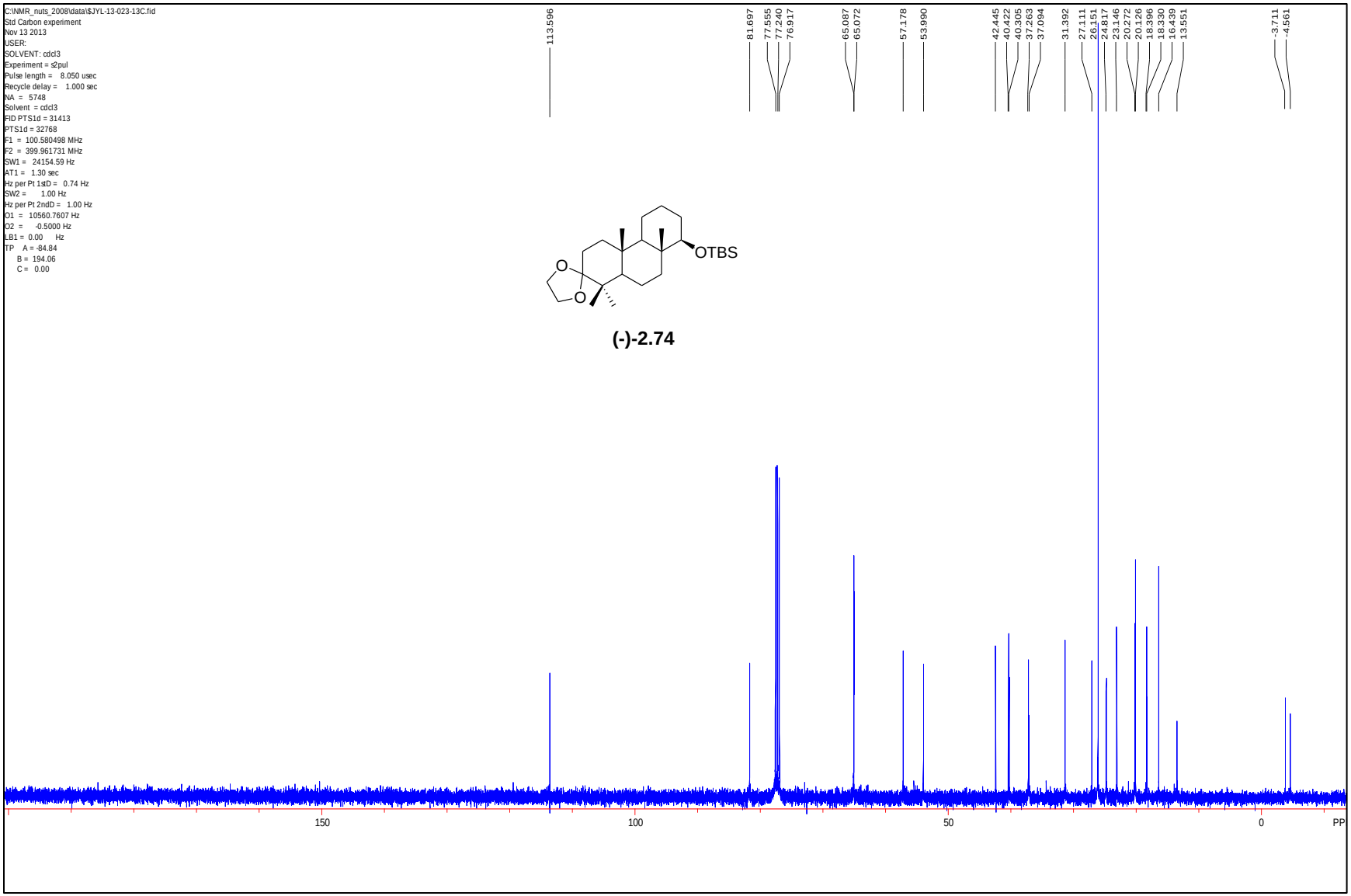

C:\NMR_nuts_2008\data\$JYL-12-062-13C.fid
Std Carbon experiment
Aug 14 2013
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 1.000 sec
NA = 972
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.580498 MHz
F2 = 399.961731 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10559.2861 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -124.78
B = 253.00
C = 0.00
199.182
164.568
128.388
81.103
77.563
77.240
76.925
55.632
39.997
39.359
38.223
35.515
33.539
31.069
26.092
26.056
24.648
24.516
20.646
18.645
18.279
12.539
11.286
-3.711
-4.576
OTBS
O
Me
(+)-2.72
200
150
100
50
0
PP


C:\NMR_nuts_2008\data\$jyl-12-087.fid
Std Proton parameters
Sep 5 2013
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 3.000 sec
NA = 32
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.962158 MHz
F2 = 100.579445 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2400.5181 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -195.91
B = 79.27
C = 0.00
7.260
3.085
3.074
3.058
3.046
2.473
2.440
2.556
2.371
1.956
1.945
1.938
1.923
1.912
1.904
1.769
1.694
1.556
1.539
1.352
1.282
1.169
1.083
1.038
0.897
0.882
0.875
0.017
OTBS
O
(+)-2.73
13.96
11.57
6.00
4.73
4.13
2.35
2.24
1.67
0.96
8
6
4
2
0
PP

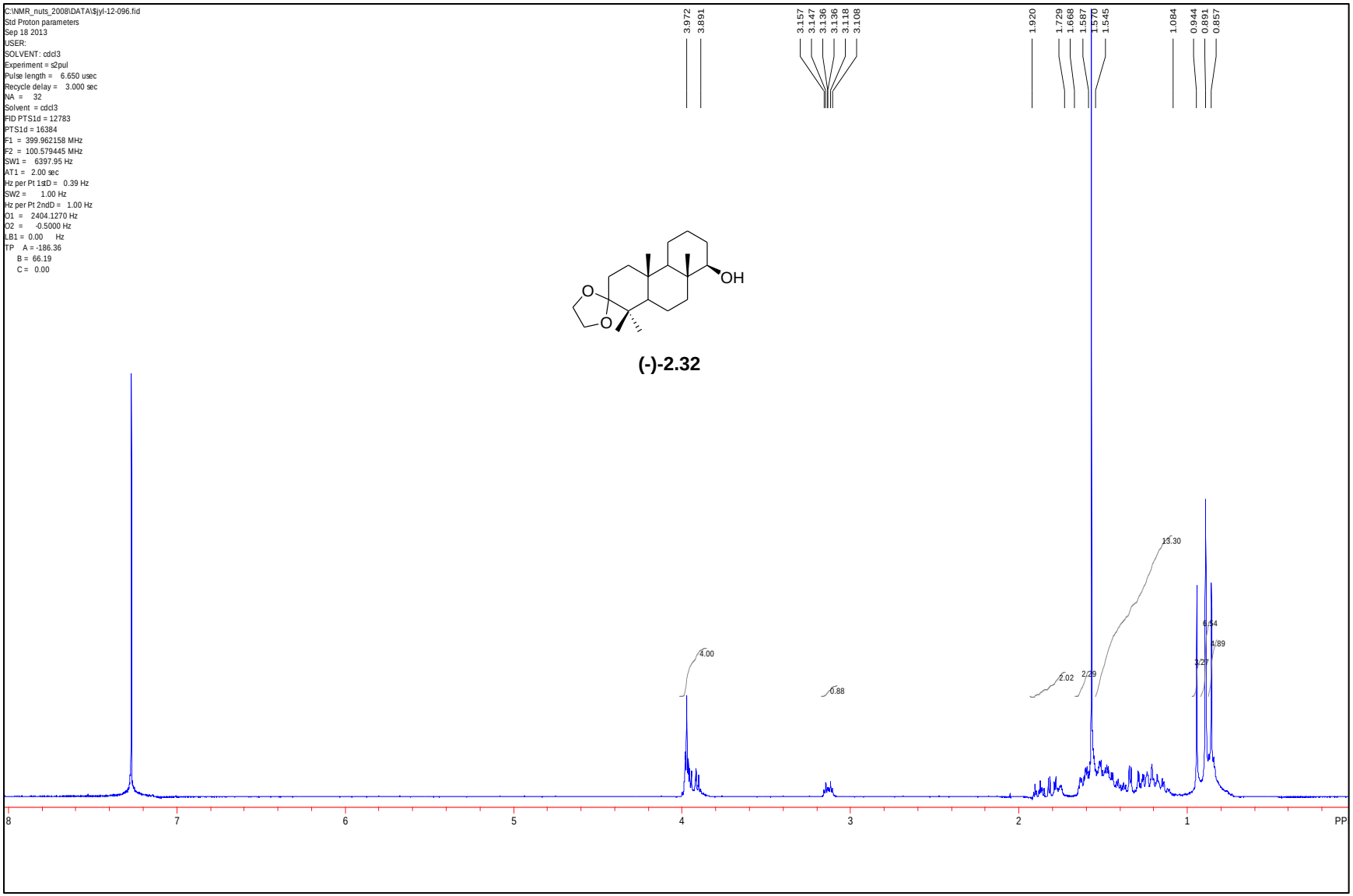

C:\NMR_nuts_2008\data\$MA-3-13C.fid
Std Carbon experiment
Nov 14 2013
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 1.000 sec
NA = 17164
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.580498 MHz
F2 = 399.961731 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10560.7607 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -83.91
B = 201.09
C = 0.00
81.535
77.555
77.240
76.925
56.672
55.456
47.664
40.371
39.601
39.455
36.963
34.368
31.319
26.818
26.114
24.751
21.313
20.661
19.554
18.315
16.373
13.243
-3.681
-4.532
OTBS
O
200
150
100
50
0
PP

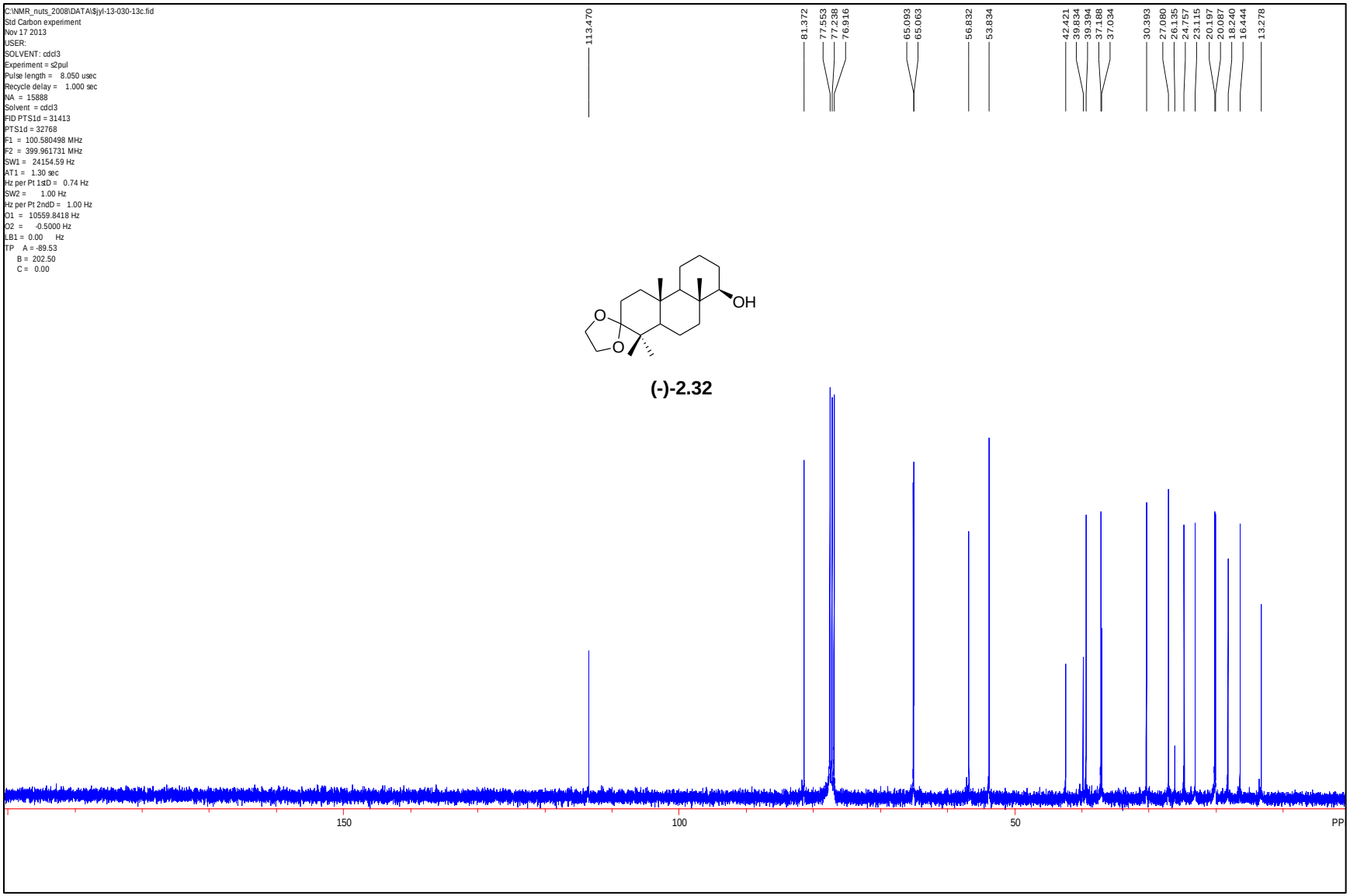
**(+)-2.73**

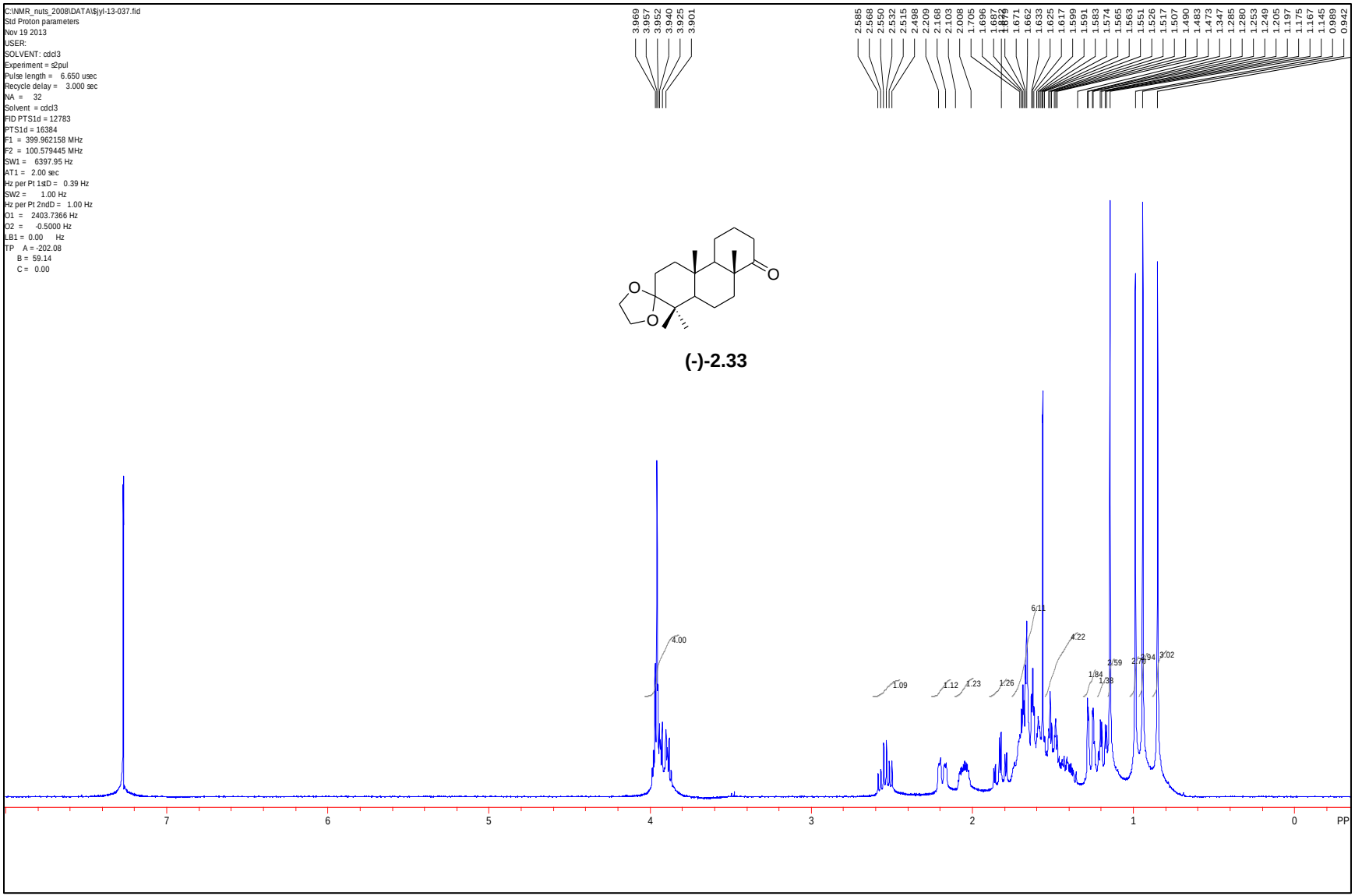

C:\NMR_nuts_2008\data\$jyl-13-023.fid
Std Proton parameters
Nov 13 2013
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 1.000 sec
NA = 32
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.962158 MHz
F2 = 100.579445 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2400.5181 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -208.31
B = 67.63
C = 0.00
7.260
3.958
3.873
3.070
3.059
3.042
3.031
1.763
1.731
1.656
1.877
1.629
1.620
1.611
1.597
1.588
1.566
1.516
1.323
1.263
1.104
1.068
0.948
0.926
0.864
0.857
0.851
0.843
-0.006
OTBS
O
O
(-)-2.74
9.03
5.91
3.85
3.83
3.61
1.93
1.05
1.29
1.00
1.32
8
6
4
2
0
PP

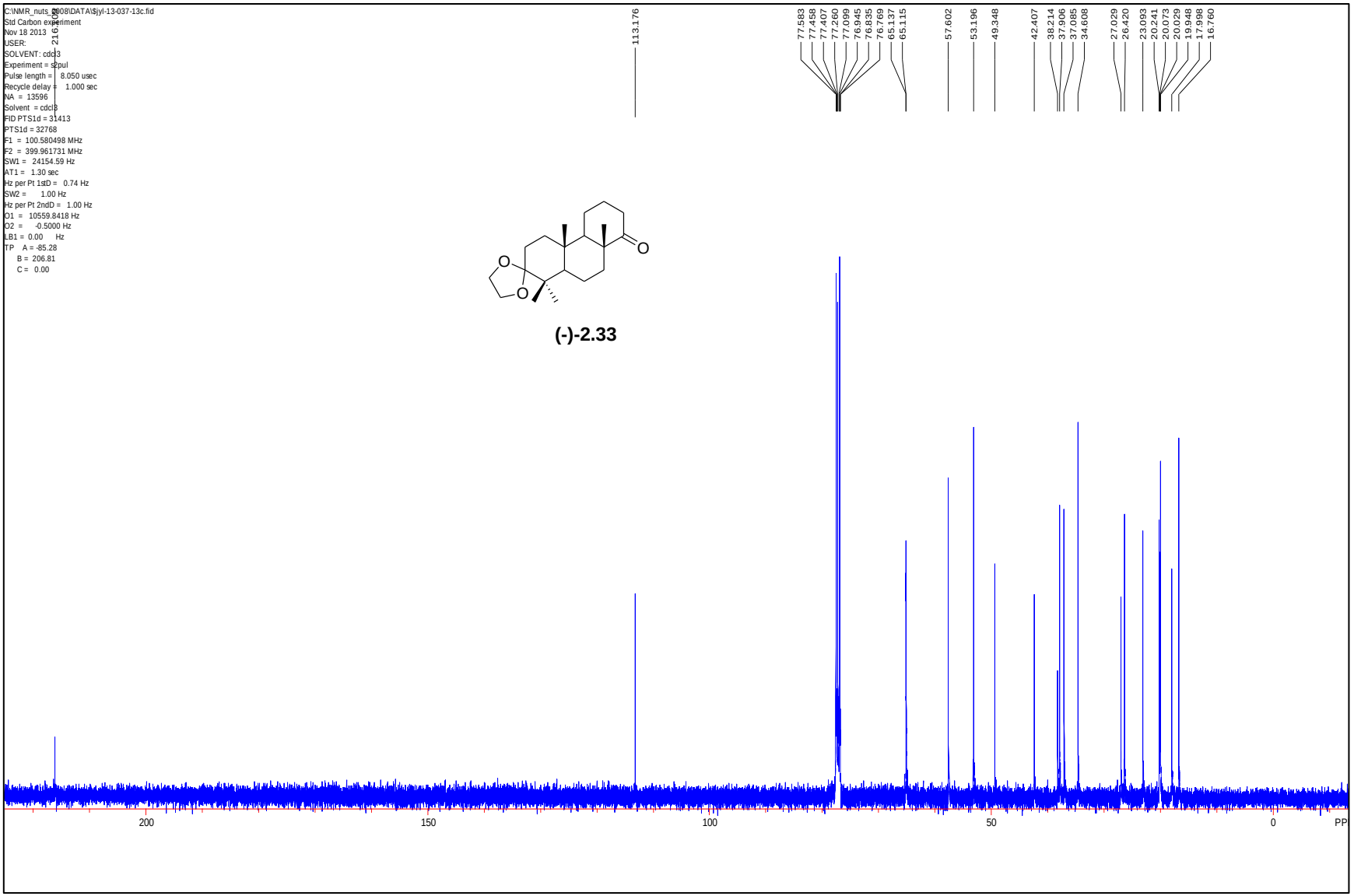

C:\NMR_nuts_2008\data\$JYL-13-023-13C.fid
Std Carbon experiment
Nov 13 2013
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 1.000 sec
NA = 5748
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.580498 MHz
F2 = 399.961731 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10560.7607 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -84.84
B = 194.06
C = 0.00
113.596
81.697
77.555
77.240
76.917
65.087
65.072
57.178
53.990
42.445
40.422
40.305
37.263
37.094
31.392
27.111
26.151
24.817
23.146
20.272
20.126
18.396
18.330
16.439
13.551
-3.711
-4.561
OTBS
O
O
150
100
50
0
PP

**(-)-2.74**

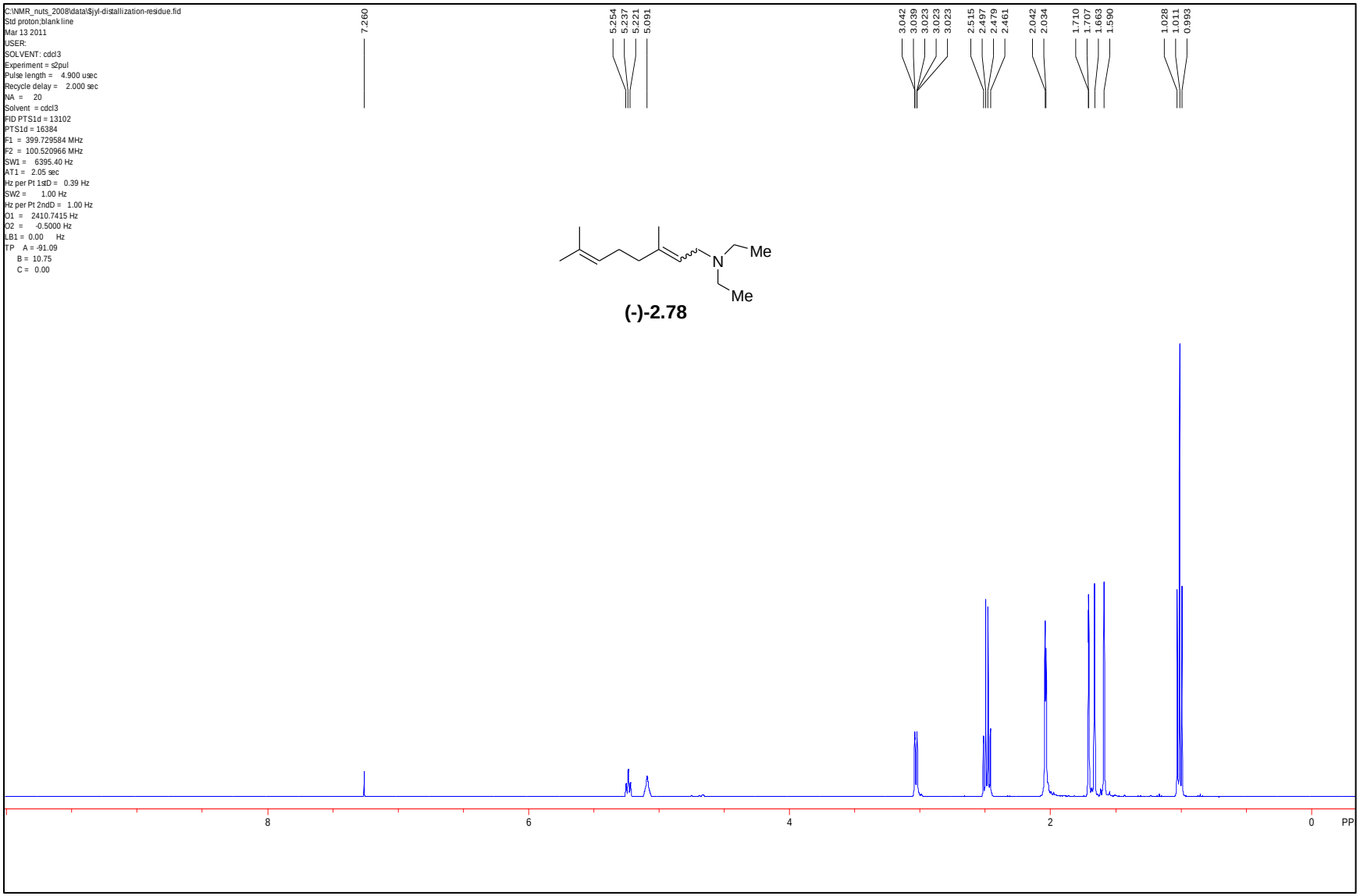

C:\NMR_nuts_2008\DATA\$jyl-12-096.fid
Std Proton parameters
Sep 18 2013
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 3.000 sec
NA = 32
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.962158 MHz
F2 = 100.579445 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2404.1270 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -186.36
B = 66.19
C = 0.00
3.972
3.891
3.157
3.147
3.136
3.136
3.118
3.108
1.920
1.729
1.668
1.587
1.570
1.545
1.084
0.944
0.891
0.857
OH
O
O
(-)-2.32
4.00
0.88
2.02
2.29
13.30
6.54
5.89
3.27
8
7
6
5
4
3
2
1
PP


C:\NMR_nuts_2008\DATA\$jyl-13-030-13c.fid
Std Carbon experiment
Nov 17 2013
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 1.000 sec
NA = 15888
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.580498 MHz
F2 = 399.961731 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10559.8418 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -89.53
B = 202.50
C = 0.00
113.470
81.372
77.553
77.238
76.916
65.093
65.063
56.832
53.834
42.421
39.834
39.394
37.188
37.034
30.393
27.080
26.135
24.757
23.115
20.197
20.087
18.240
16.444
13.278
O
O
OH
(-)-2.32
150
100
50
PP

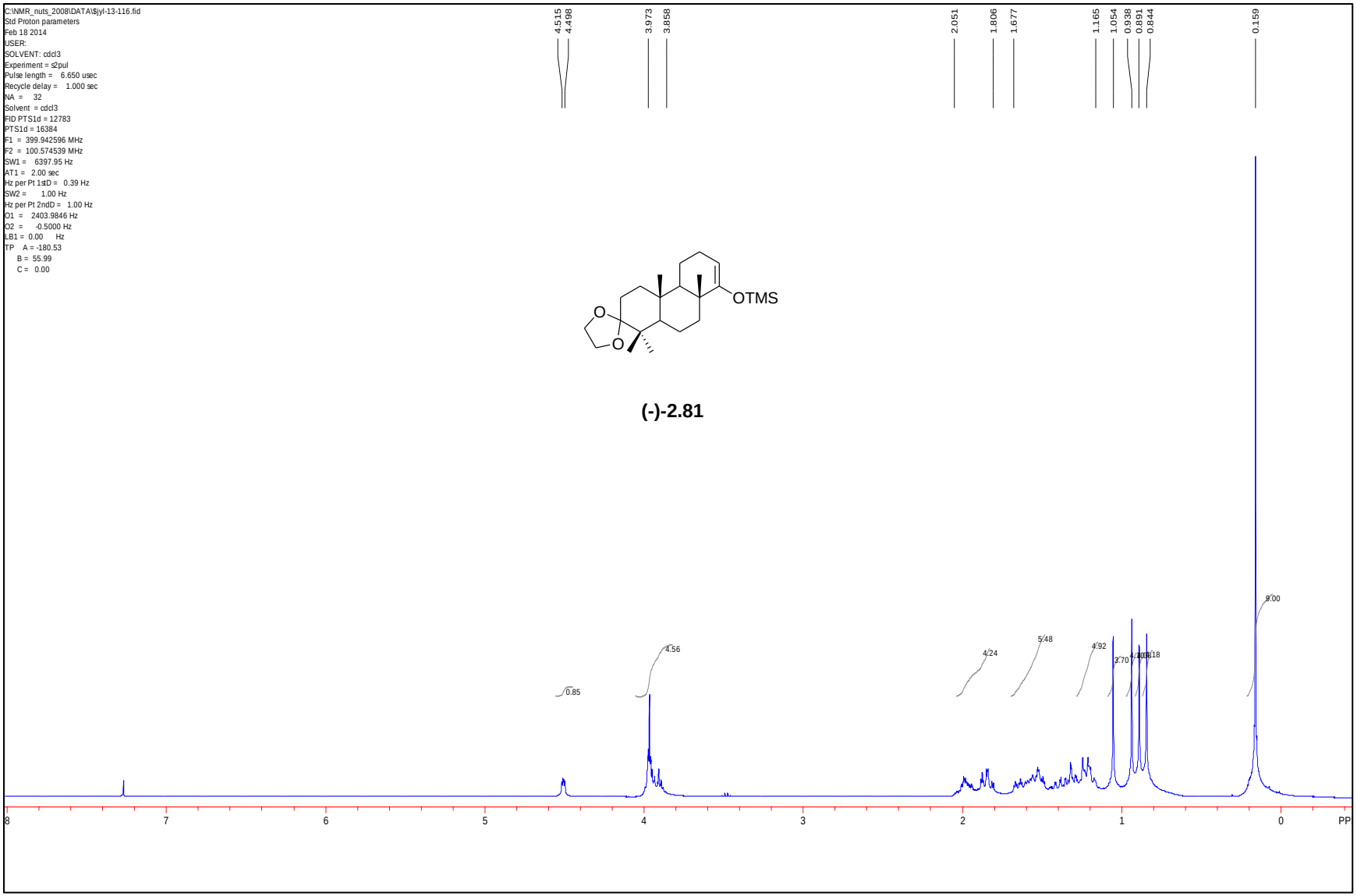

C:\NMR_nuts_2008\DATA\$jyl-13-037.fid
Std Proton parameters
Nov 19 2013
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 3.000 sec
NA = 32
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.962158 MHz
F2 = 100.579445 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2403.7366 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -202.08
B = 59.14
C = 0.00
3.969
3.957
3.952
3.940
3.925
3.901
2.585
2.568
2.550
2.532
2.515
2.498
2.209
2.168
2.103
2.008
1.705
1.696
1.687
1.671
1.662
1.633
1.625
1.617
1.599
1.591
1.583
1.574
1.565
1.563
1.551
1.526
1.517
1.507
1.490
1.483
1.473
1.347
1.285
1.280
1.253
1.249
1.205
1.197
1.175
1.167
1.145
0.989
0.942
O
O
O
(-)-2.33
4.00
1.09
1.12
1.23
1.26
6.11
4.22
1.84
1.38
2.59
2.78
2.94
3.02
7
6
5
4
3
2
1
0
PP

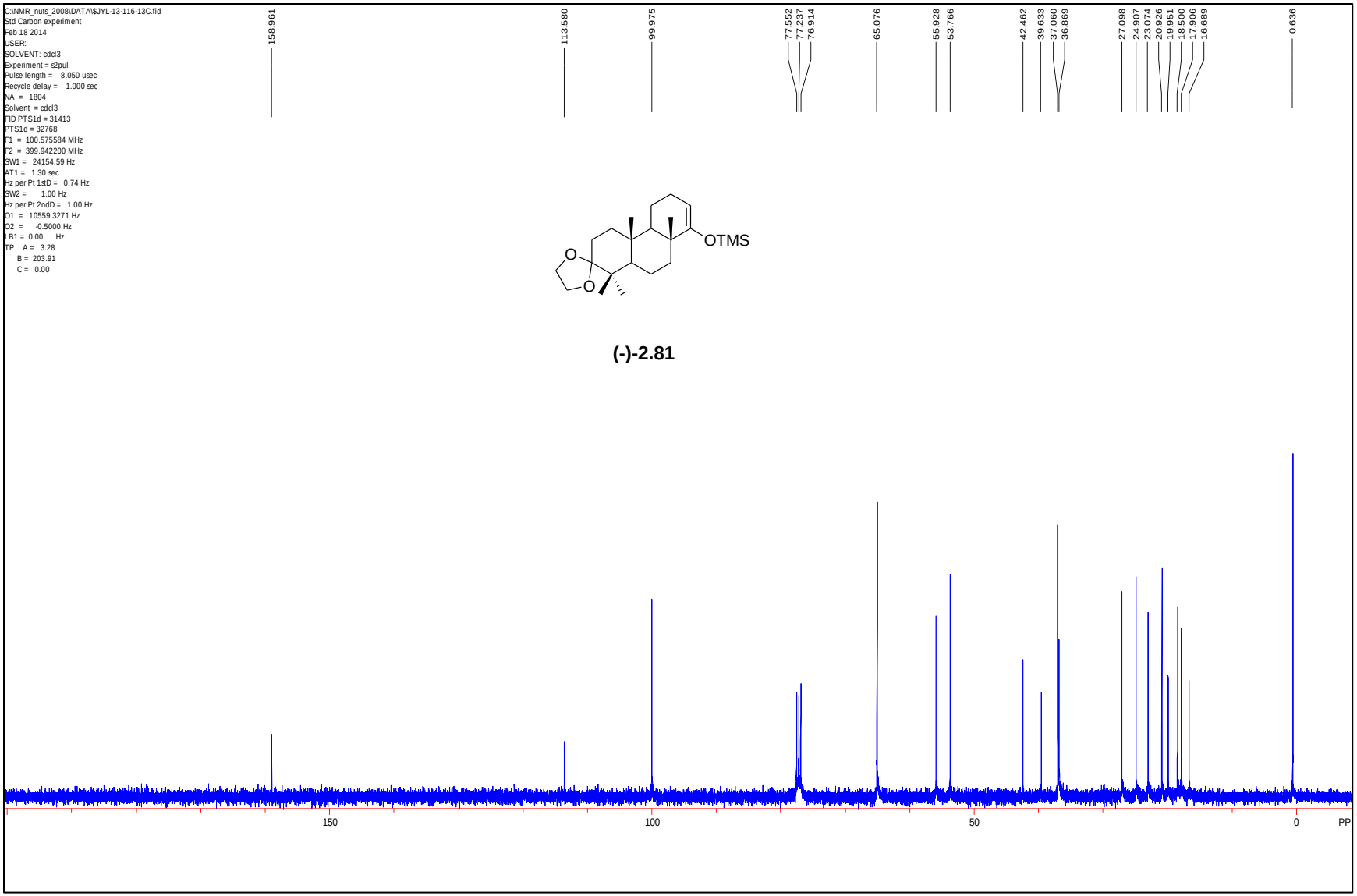

C:\NMR_nuts_2008\DATA\sjyl-13-037-13c.fid
Std Carbon experiment
Nov 18 2013
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 1.000 sec
NA = 13596
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.580498 MHz
F2 = 399.961731 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10559.8418 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -85.28
B = 206.81
C = 0.00
21.00
113.176
77.583
77.458
77.407
77.260
77.099
76.945
76.835
76.769
65.137
65.115
57.602
53.196
49.348
42.407
38.214
37.906
37.085
34.608
27.029
26.420
23.093
20.241
20.073
20.029
19.948
17.998
16.760
O
O
O
200
150
100
50
0
PP

**(-)-2.33**

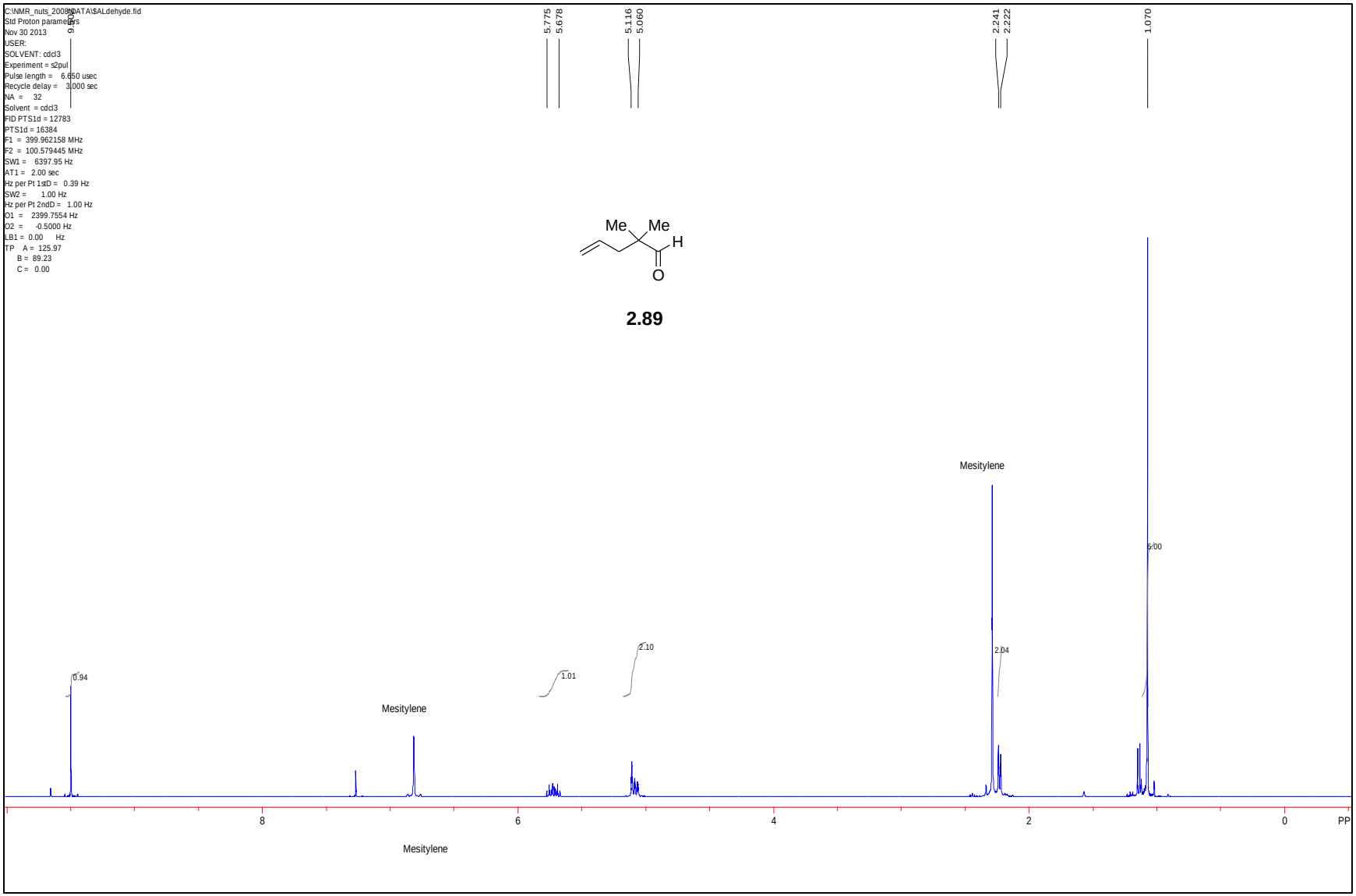

C:\NMR_nuts_2008\data\$jyl-distallization-residue.fid
Std proton;blank line
Mar 13 2011
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 4.900 usec
Recycle delay = 2.000 sec
NA = 20
Solvent = cdcl3
FID PTS1d = 13102
PTS1d = 16384
F1 = 399.729584 MHz
F2 = 100.520966 MHz
SW1 = 6395.40 Hz
AT1 = 2.05 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2410.7415 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -91.09
B = 10.75
C = 0.00
7.260
5.254
5.237
5.221
5.091
3.042
3.039
3.023
3.023
3.023
2.515
2.497
2.479
2.461
2.042
2.034
1.710
1.707
1.663
1.590
1.028
1.011
0.993
N
Me
Me
8
6
4
2
0
PP

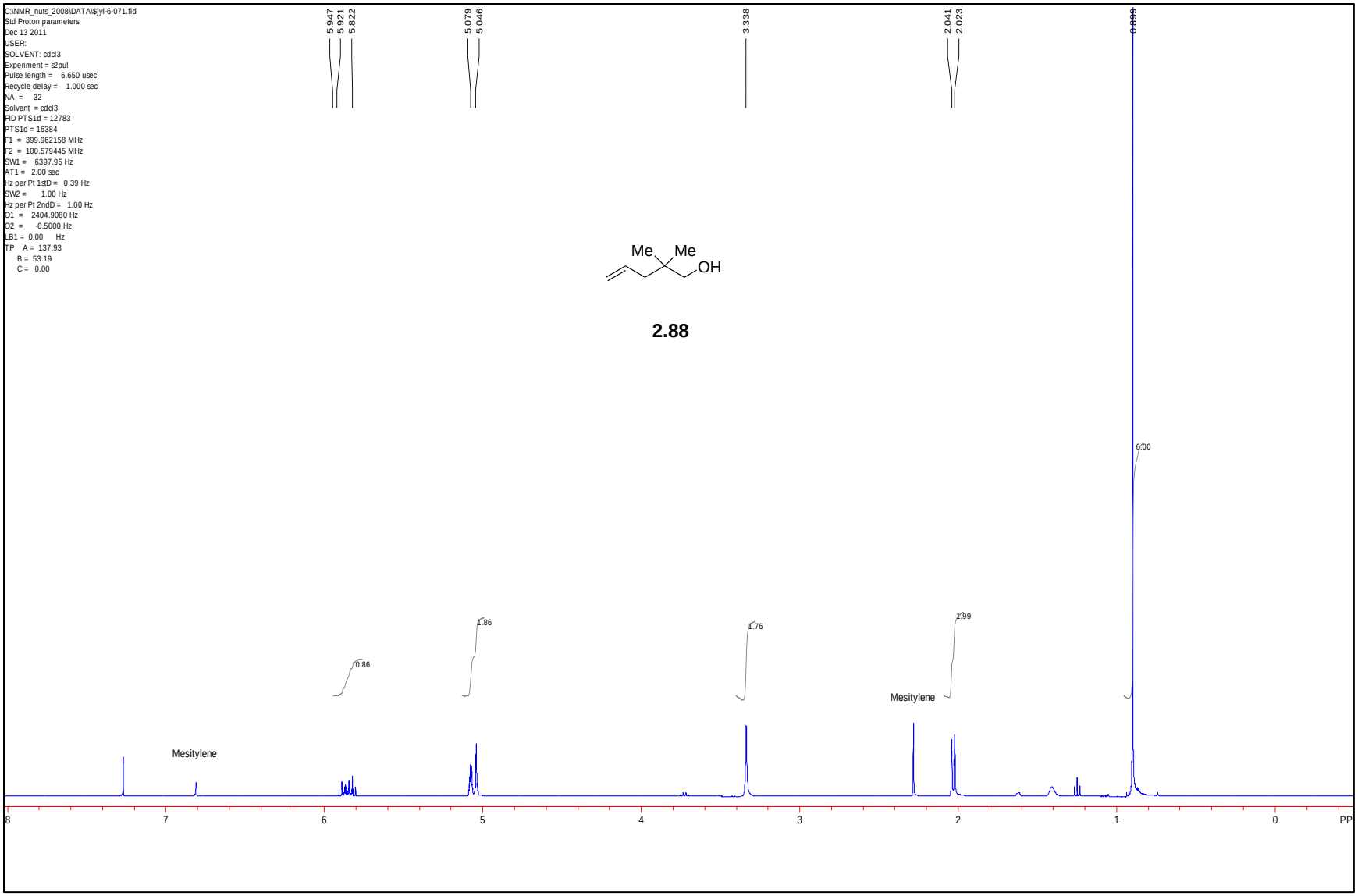
**(-)-2.78**

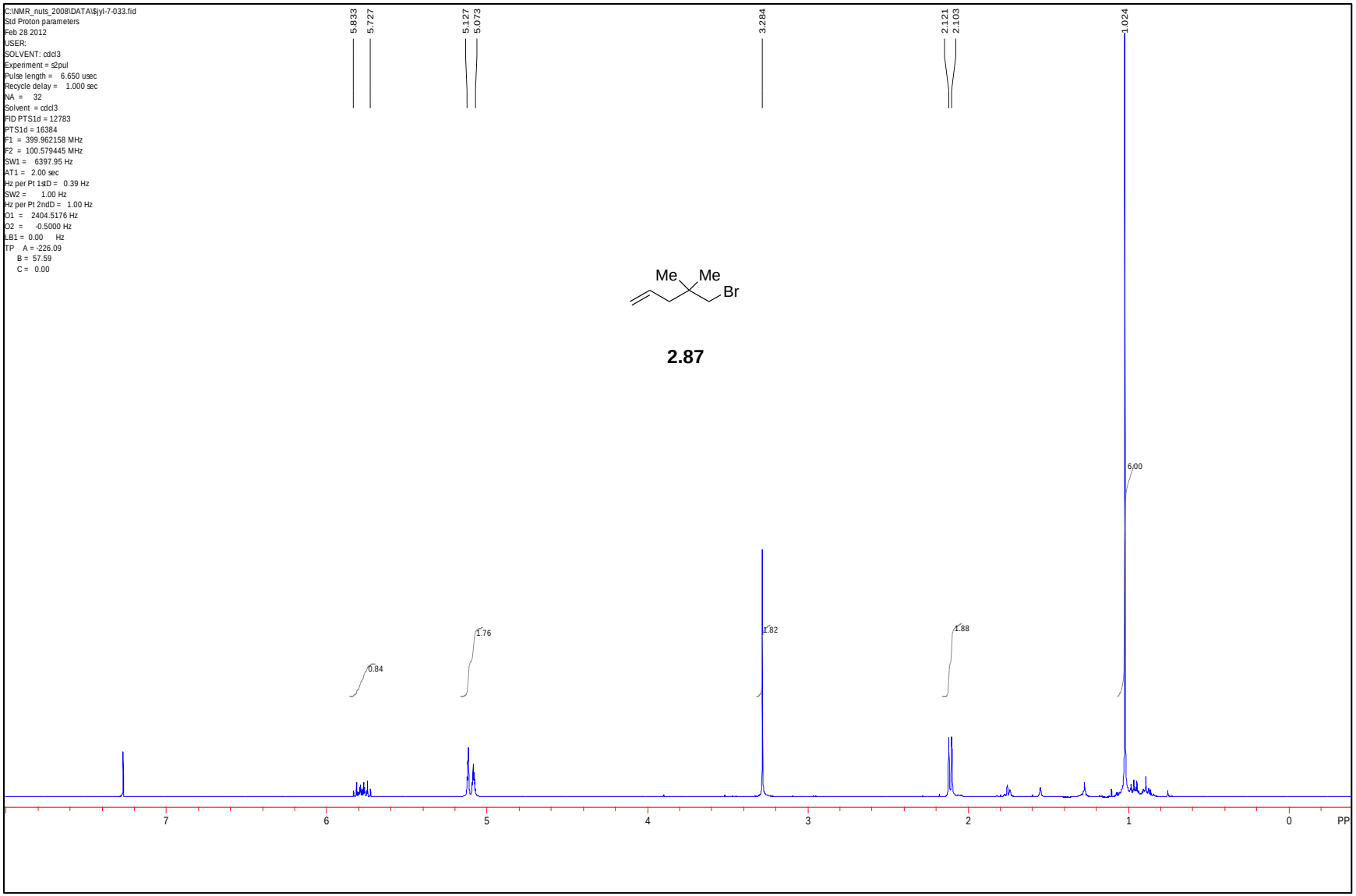

C:\NMR_nuts_2008\DATA\$jyl-13-116.fid
Std Proton parameters
Feb 18 2014
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 1.000 sec
NA = 32
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.942596 MHz
F2 = 100.574539 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2403.9846 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -180.53
B = 55.99
C = 0.00
4.515
4.498
3.973
3.858
2.051
1.806
1.677
1.165
1.054
0.938
0.891
0.844
0.159
OTMS
O
O
(-)-2.81
0.85
4.56
4.24
5.48
4.92
3.70
3.18
9.00
8
7
6
5
4
3
2
1
0
PP

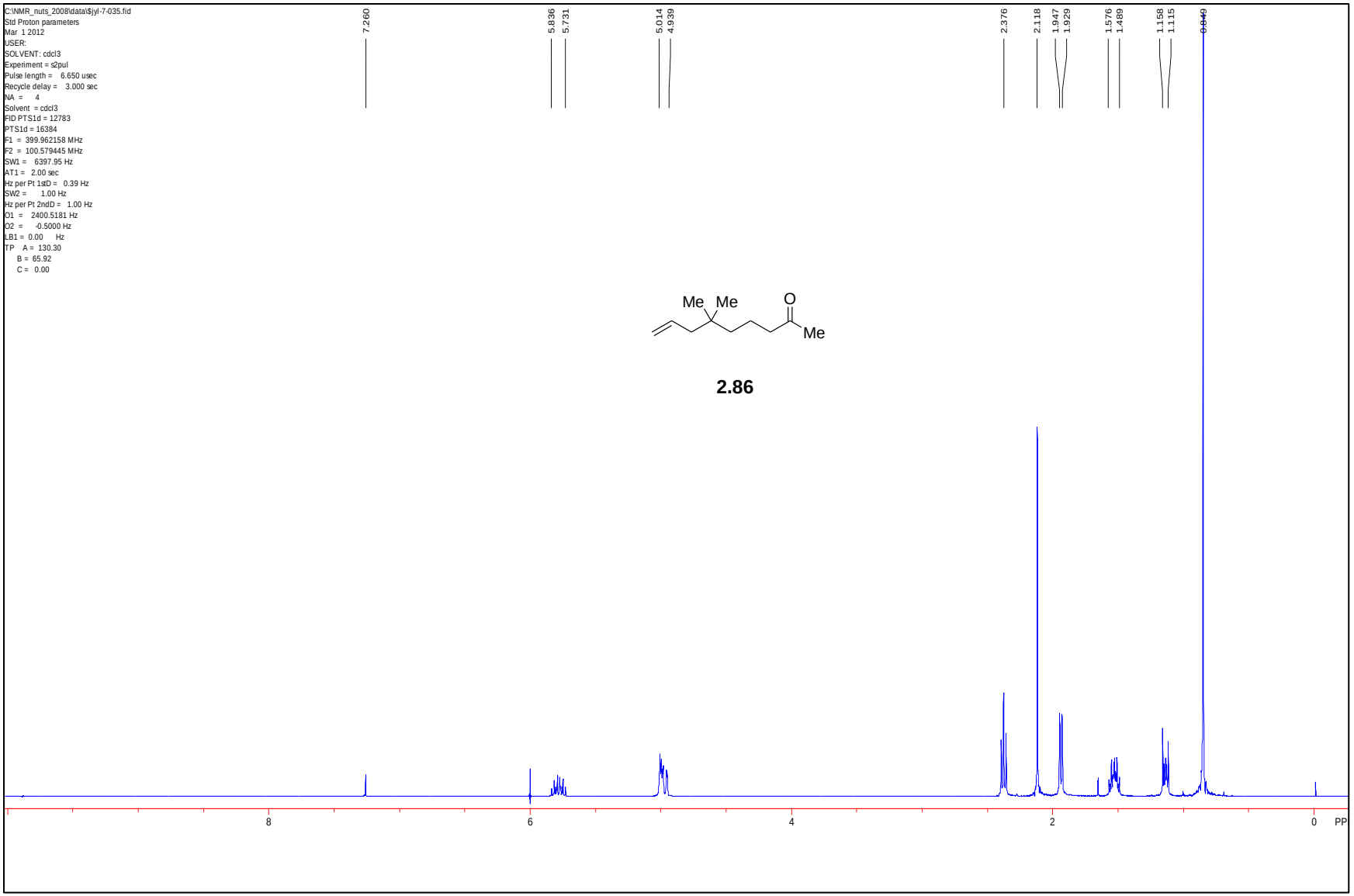

C:\NMR_nuts_2008\DATA\$JYL-13-116-13C.fid
Std Carbon experiment
Feb 18 2014
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 1.000 sec
NA = 1804
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.575584 MHz
F2 = 399.942200 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10559.3271 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 3.28
B = 203.91
C = 0.00
158.961
113.580
99.975
77.552
77.237
76.914
65.076
55.928
53.766
42.462
39.633
37.060
36.869
27.098
24.907
23.074
20.926
19.951
18.500
17.906
16.689
0.636
OTMS
O
O
150
100
50
0
PP

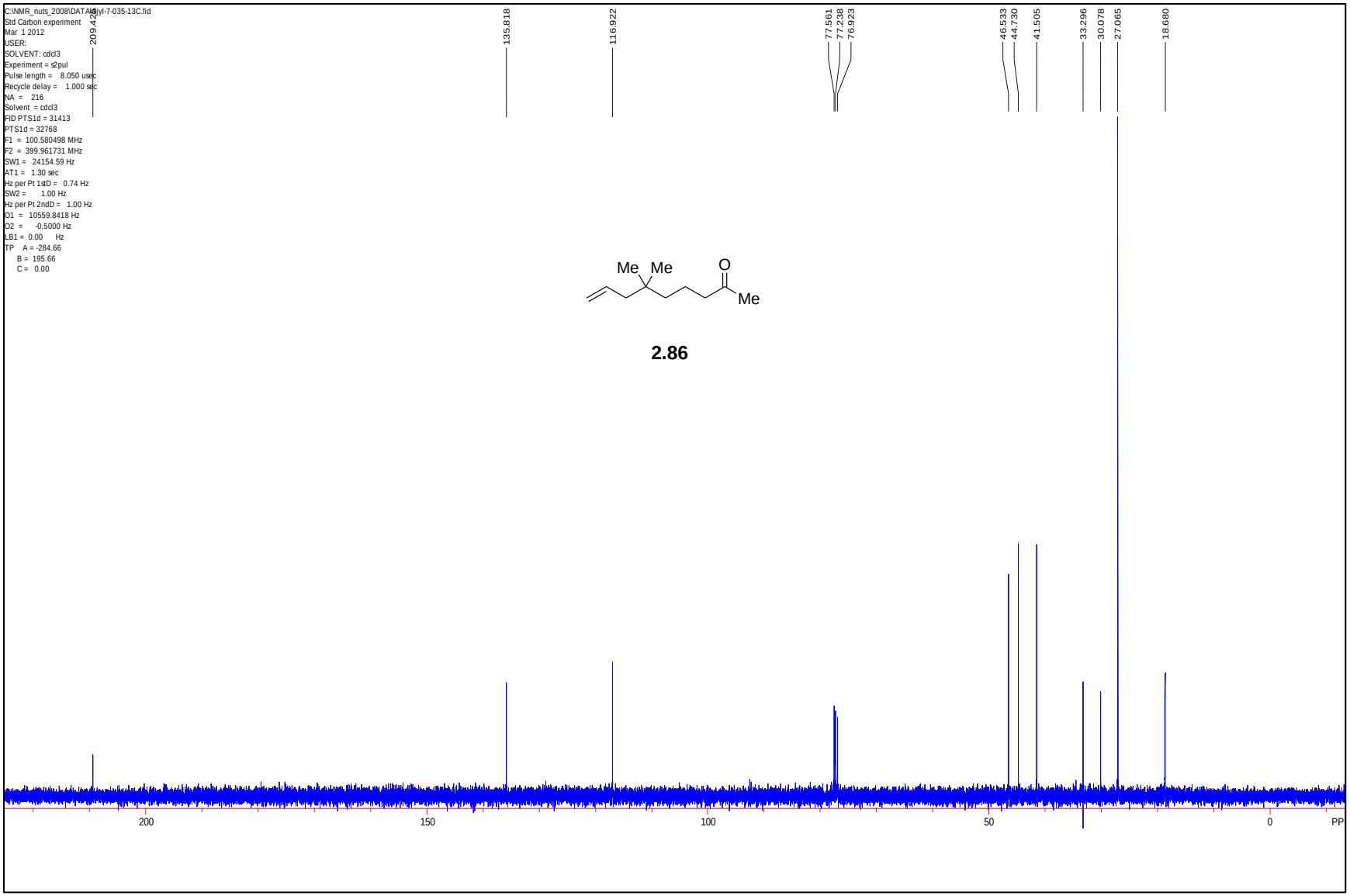
**(-)-2.81**

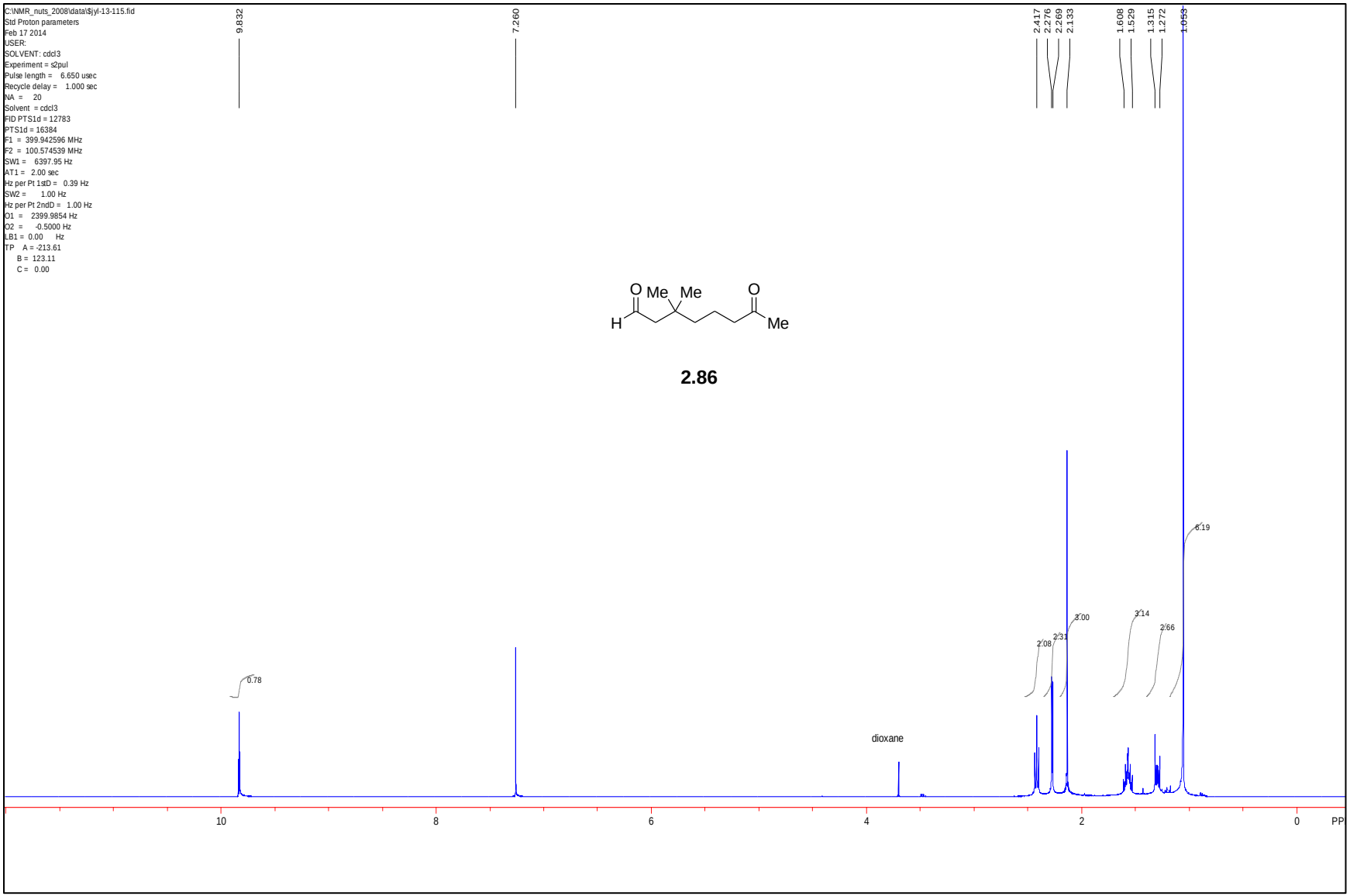

C:\NMR_nuts_2008\DATA\$ALdehyde.fid
Std Proton parameters
Nov 30 2013
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 3.000 sec
NA = 32
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.962158 MHz
F2 = 100.579445 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2399.7554 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 125.97
B = 89.23
C = 0.00
5.775
5.678
5.116
5.060
2.241
2.222
1.070
Me
Me
H
O
2.89
Mesitylene
6.00
2.10
2.04
0.94
1.01
Mesitylene
8
6
4
2
0
PP
Mesitylene

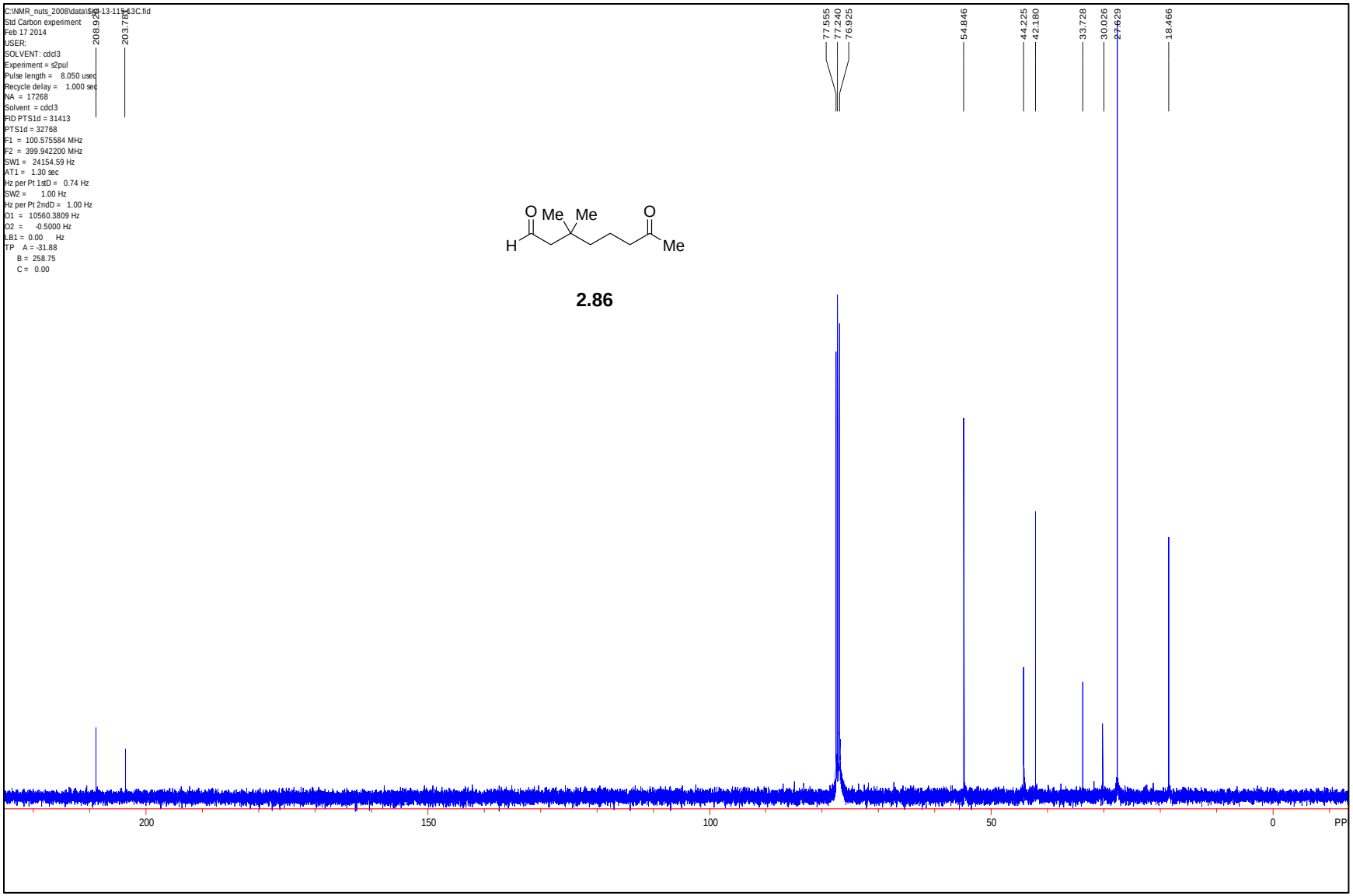

C:\NMR_nuts_2008\DATA\$jyl-6-071.fid
Std Proton parameters
Dec 13 2011
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 1.000 sec
NA = 32
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.962158 MHz
F2 = 100.579445 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2404.9080 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 137.93
B = 53.19
C = 0.00
5.947
5.921
5.822
5.079
5.046
3.338
2.041
2.023
0.899
Me
Me
OH
2.88
6.00
1.86
0.86
1.76
1.99
Mesitylene
Mesitylene
8
7
6
5
4
3
2
1
0
PPM

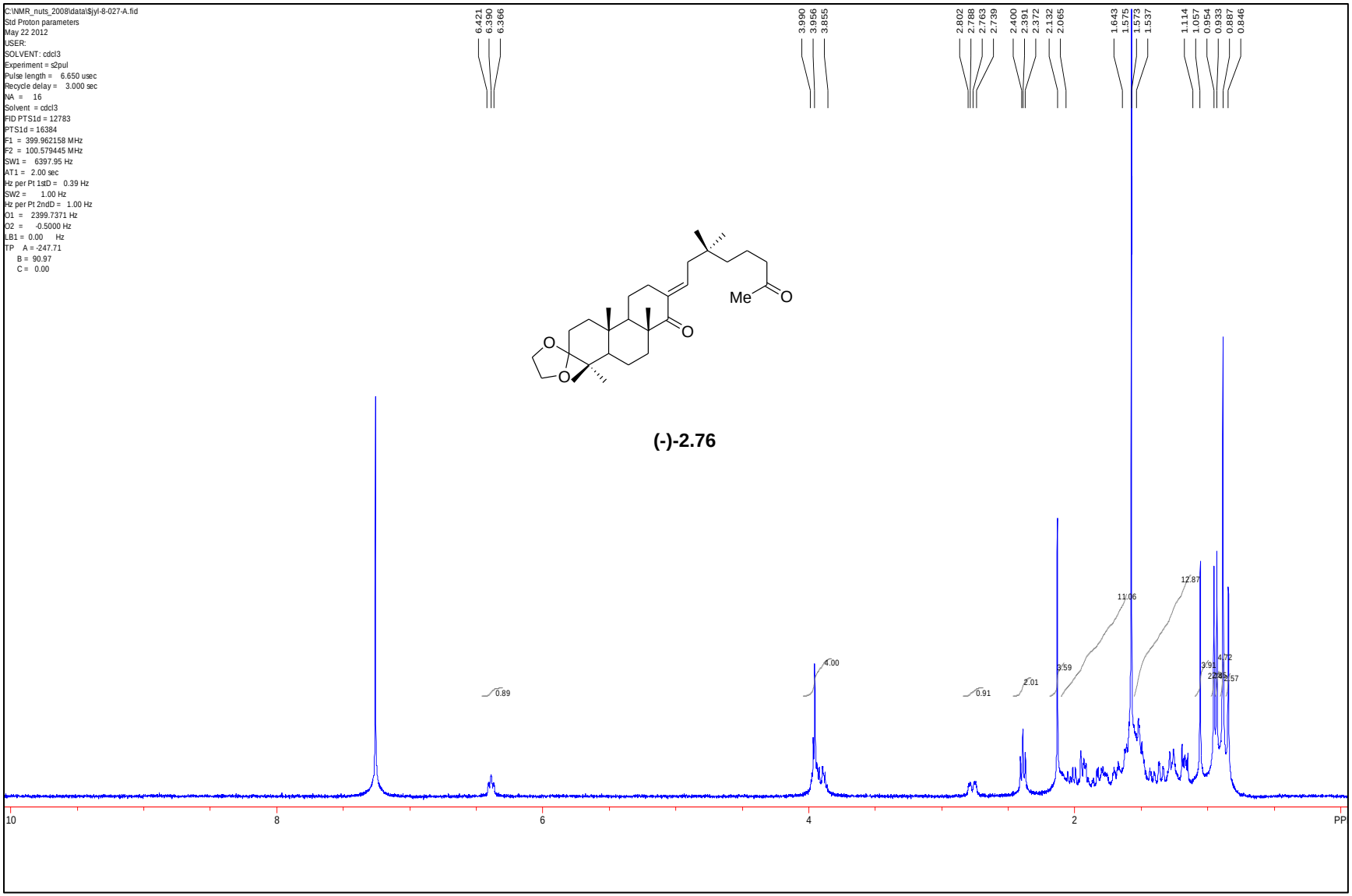

C:\NMR_nuts_2008\DATA\sjyl-7-033.fid
Std Proton parameters
Feb 28 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 1.000 sec
NA = 32
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.962158 MHz
F2 = 100.579445 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2404.5176 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -226.09
B = 57.59
C = 0.00
5.833
5.727
5.127
5.073
3.284
2.121
2.103
1.024
Me
Me
Br
2.87
6.00
1.76
1.82
1.88
0.84
7
6
5
4
3
2
1
0
PP

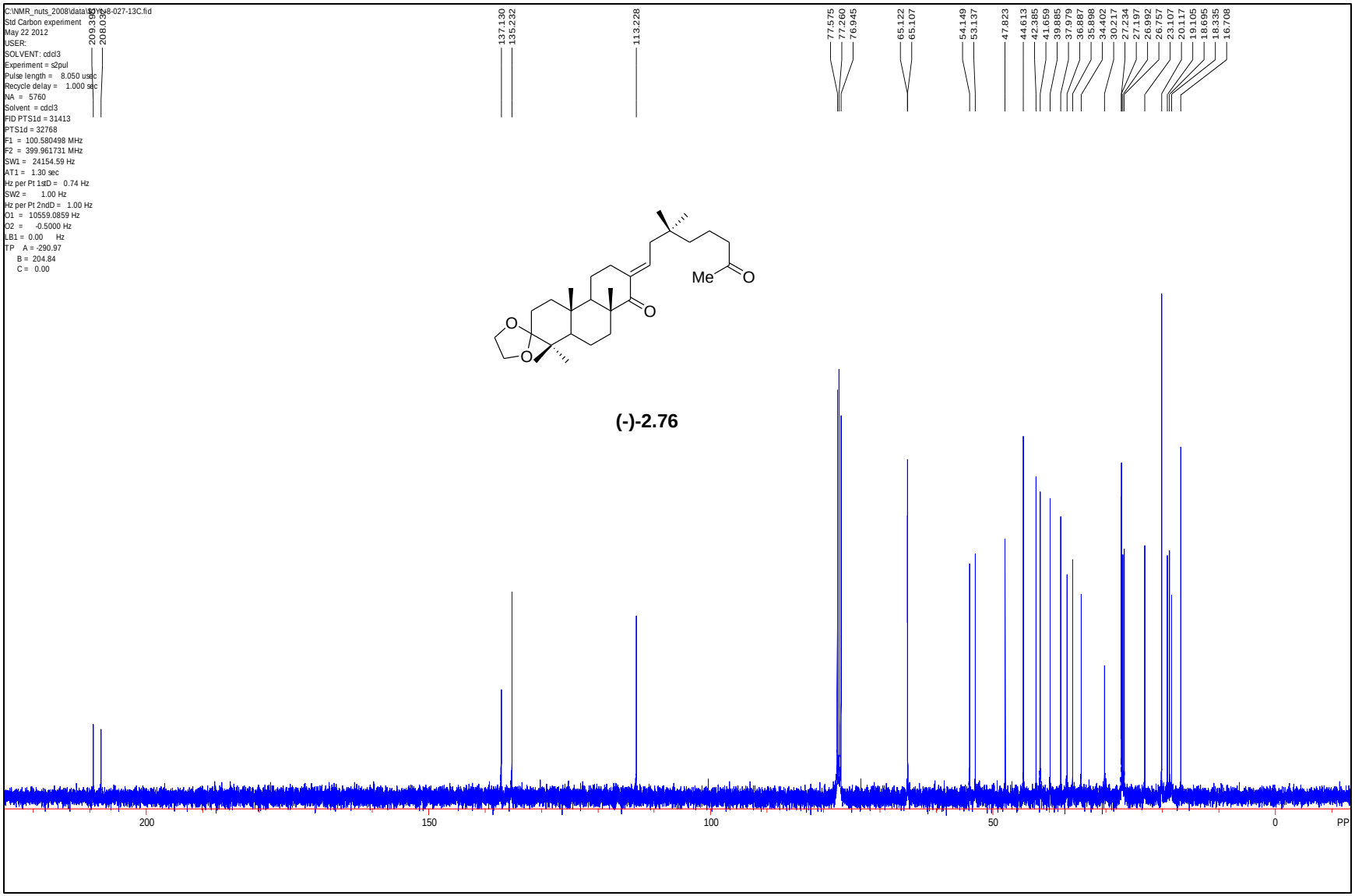

C:\NMR_nuts_2008\data\$jyl-7-035.fid
Std Proton parameters
Mar 1 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 3.000 sec
NA = 4
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.962158 MHz
F2 = 100.579445 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2400.5181 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 130.30
B = 65.92
C = 0.00
7.260
5.836
5.731
5.014
4.939
2.376
2.118
1.947
1.929
1.576
1.489
1.158
1.115
0.849
Me
Me
O
Me
2.86
8
6
4
2
0
PP

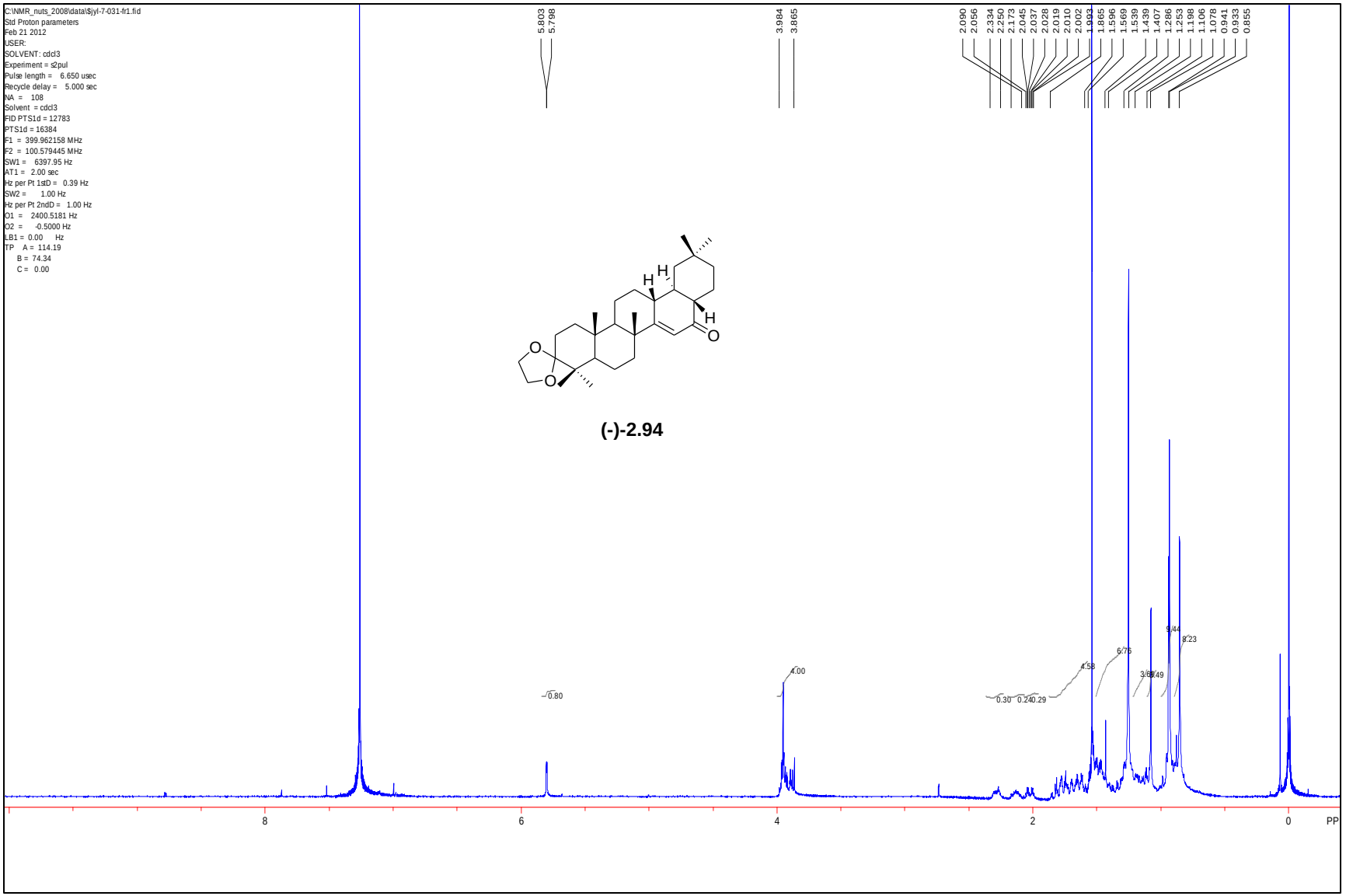

C:\NMR_nuts_2008\DATA\allyl-7-035-13C.fid
Std Carbon experiment
Mar 1 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 1.000 sec
NA = 216
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.580498 MHz
F2 = 399.961731 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10559.8418 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -284.66
B = 195.66
C = 0.00
209.410
135.818
116.922
77.561
77.238
76.923
46.533
44.730
41.505
33.296
30.078
27.065
18.680
Me
Me
O
Me
2.86
200
150
100
50
0
PP

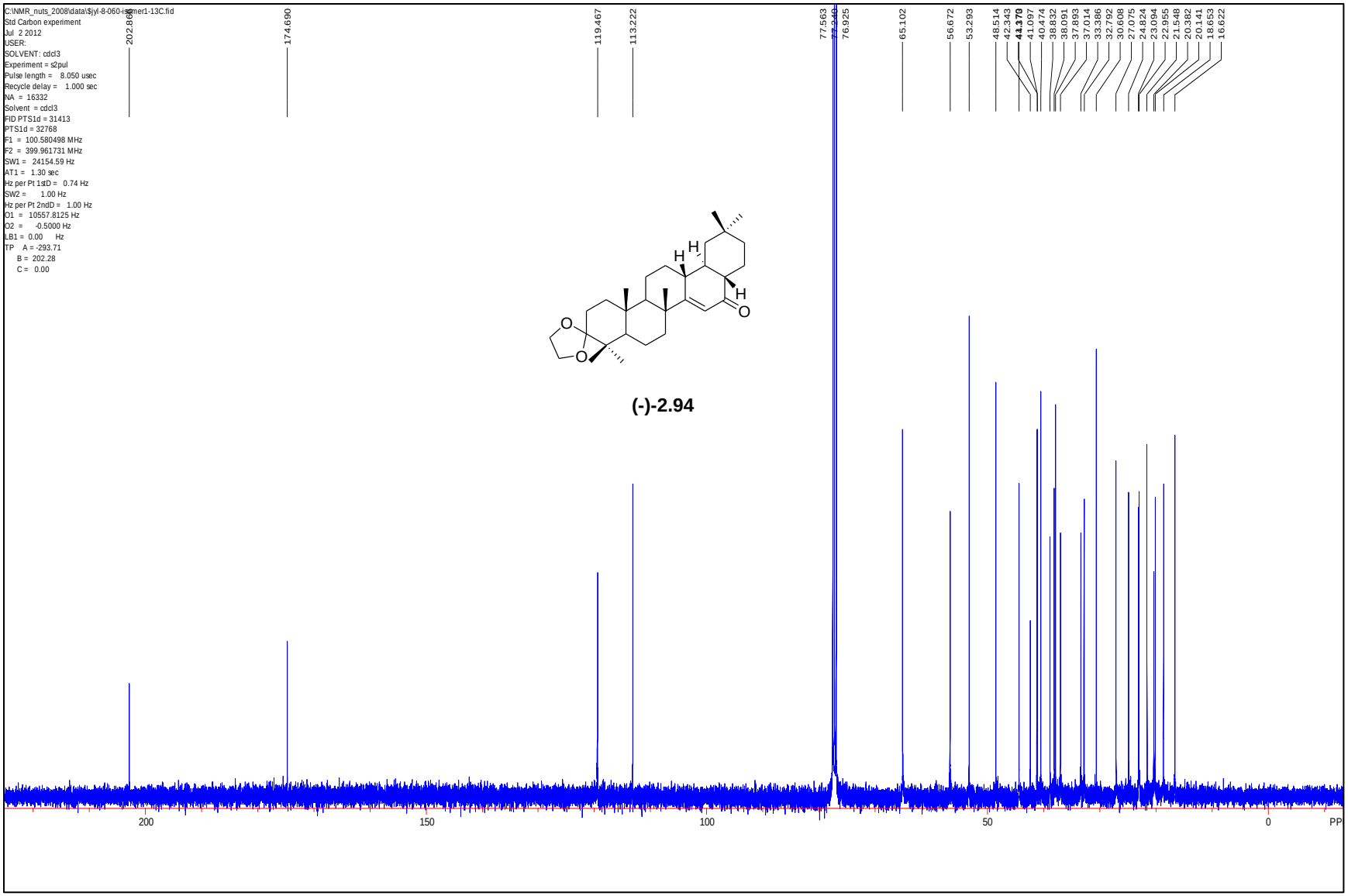

C:\NMR_nuts_2008\data\$jyl-13-115.fid
Std Proton parameters
Feb 17 2014
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 1.000 sec
NA = 20
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.942596 MHz
F2 = 100.574539 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2399.9854 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -213.61
B = 123.11
C = 0.00
9.832
7.260
2.417
2.276
2.269
2.133
1.608
1.529
1.315
1.272
1.053
O Me Me O
H Me
2.86
6.19
3.14
3.00
2.66
2.31
2.08
0.78
dioxane
10
8
6
4
2
0
PP

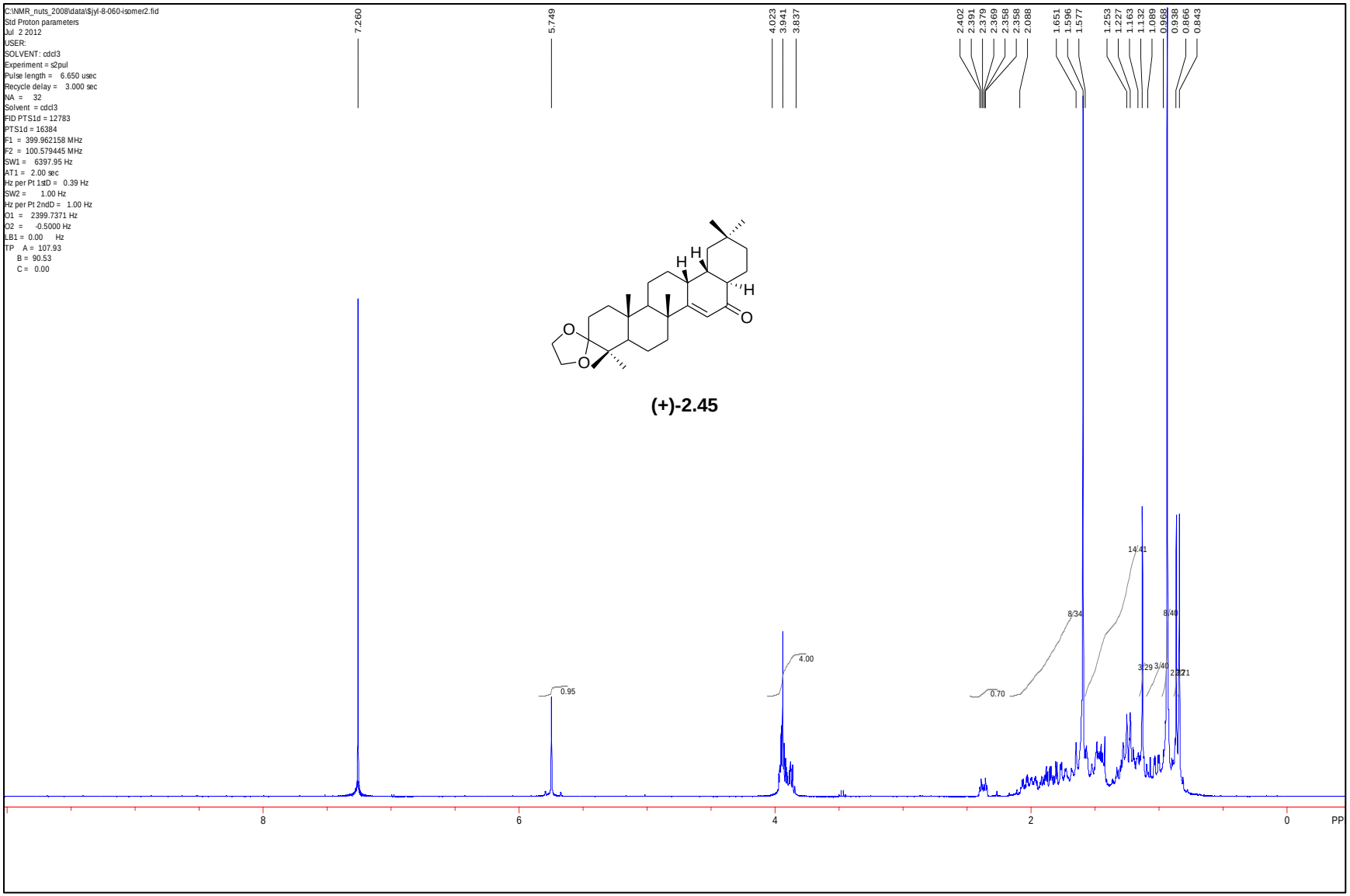

C:\NMR_nuts_2008\data\Sep-13-11-13C.fid
Std Carbon experiment
Feb 17 2014
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 1.000 sec
NA = 17268
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.575584 MHz
F2 = 399.942200 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10560.3809 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -31.88
B = 258.75
C = 0.00
208.922
203.764
77.555
77.240
76.925
54.846
44.225
42.180
33.728
30.026
27.629
18.466
O
Me
Me
O
H
Me
2.86
200
150
100
50
0
PP

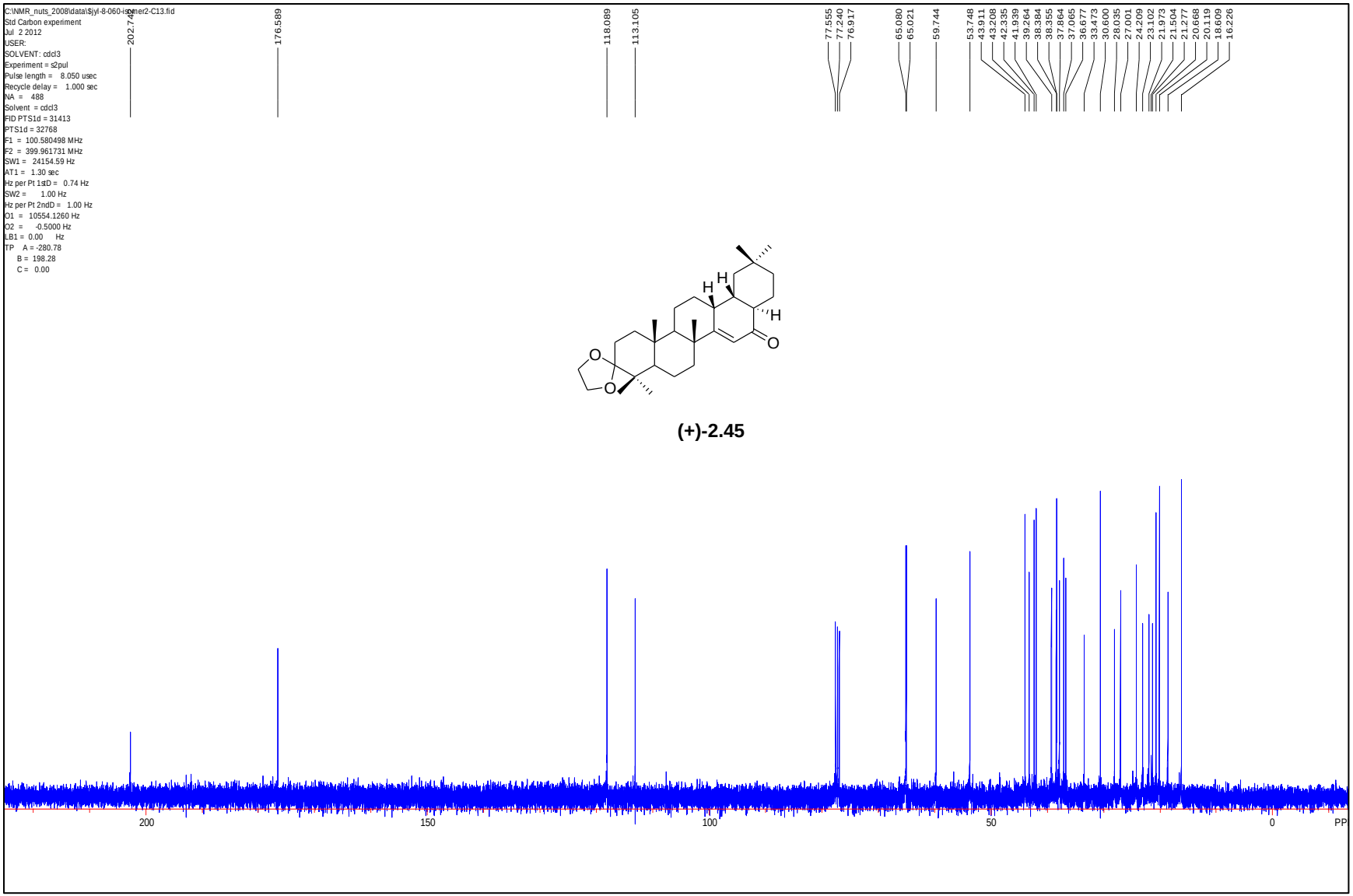

C:\NMR_nuts_2008\data\$jyl-8-027-A.fid
Std Proton parameters
May 22 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 3.000 sec
NA = 16
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.962158 MHz
F2 = 100.579445 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2399.7371 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -247.71
B = 90.97
C = 0.00
6.421
6.390
6.366
3.990
3.956
3.855
2.802
2.788
2.763
2.739
2.400
2.391
2.372
2.132
2.065
1.643
1.575
1.573
1.537
1.114
1.057
0.954
0.933
0.887
0.846
Me
O
O
O
O
(-)-2.76
0.89
4.00
0.91
2.01
3.59
11.06
12.87
3.91
4.72
2.57
10
8
6
4
2
PP

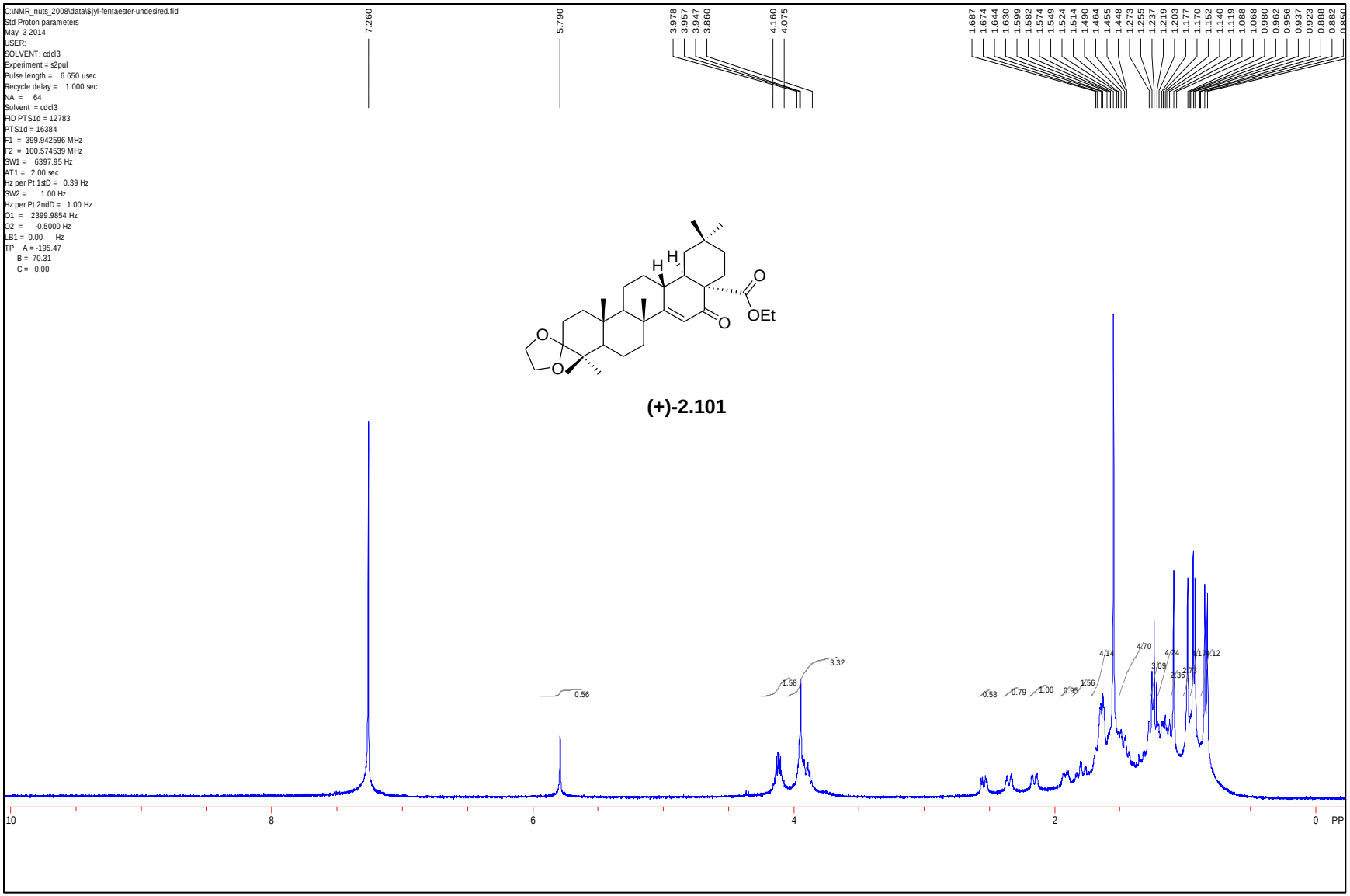

C:\NMR_nuts_2008\data\dyt_jb-027-13C.fid
Std Carbon experiment
May 22 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 1.000 sec
NA = 5760
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.580498 MHz
F2 = 399.961731 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10559.0859 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -290.97
B = 204.84
C = 0.00
209.356
208.078
137.130
135.232
113.228
77.575
77.260
76.945
65.122
65.107
54.149
53.137
47.823
44.613
42.385
41.659
39.885
37.979
36.887
35.898
34.402
30.217
27.234
27.197
26.992
26.757
23.107
20.117
19.105
18.695
18.335
16.708
Me
O
O
O
O
(-)-2.76
200
150
100
50
0
PP

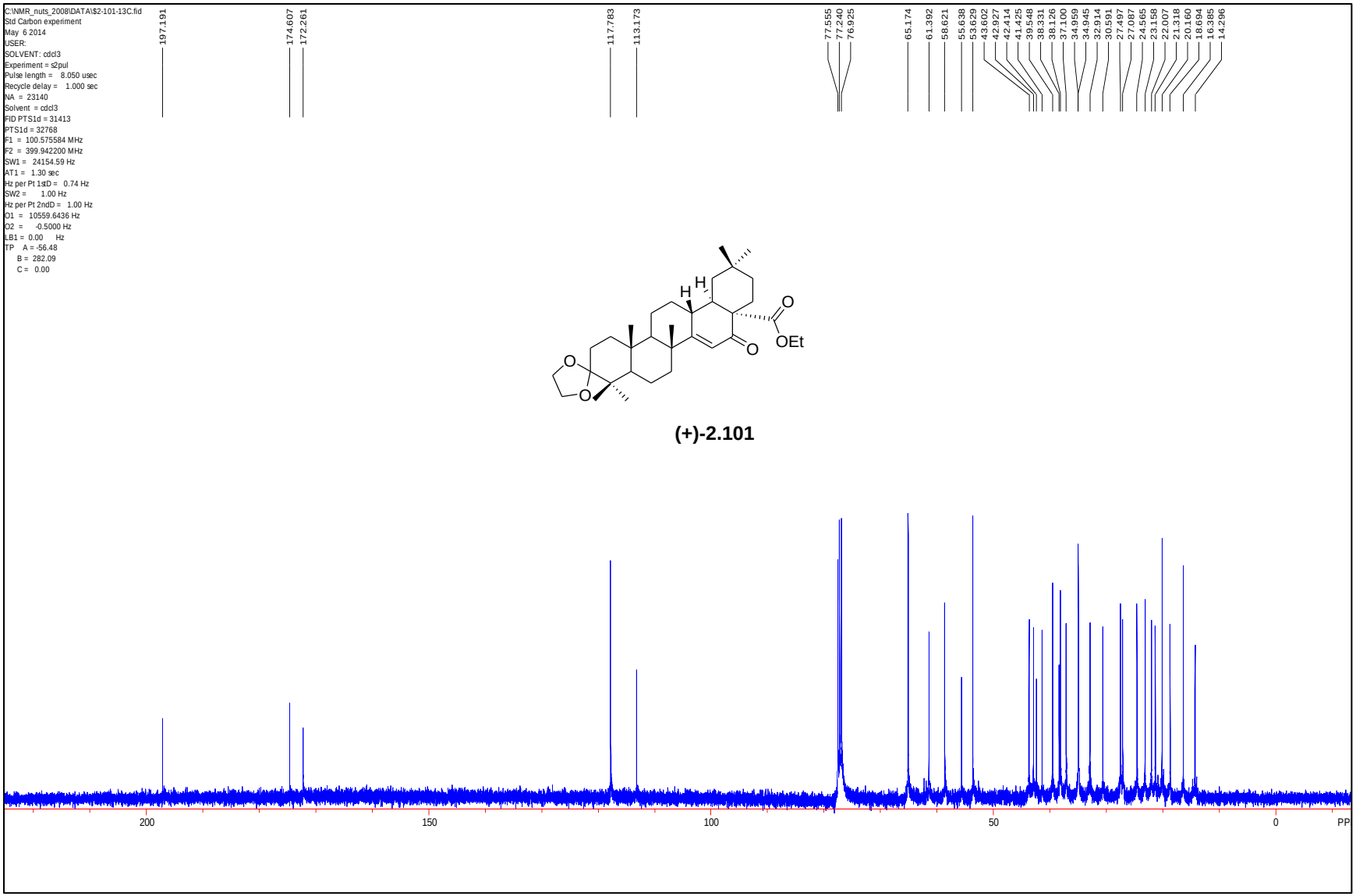

C:\NMR_nuts_2008\data\$jyl-7-031-fr1.fid
Std Proton parameters
Feb 21 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 5.000 sec
NA = 108
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.962158 MHz
F2 = 100.579445 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2400.5181 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 114.19
B = 74.34
C = 0.00
5.803
5.798
3.984
3.865
2.090
2.056
2.334
2.250
2.173
2.045
2.037
2.028
2.019
2.010
2.002
1.993
1.865
1.596
1.569
1.539
1.439
1.407
1.286
1.253
1.198
1.106
1.078
0.941
0.933
0.855
H
H
H
O
O
O
(-)-2.94
0.80
4.00
0.30
0.24
0.29
4.58
6.75
3.08
3.49
9.44
8.23
8
6
4
2
0
PP

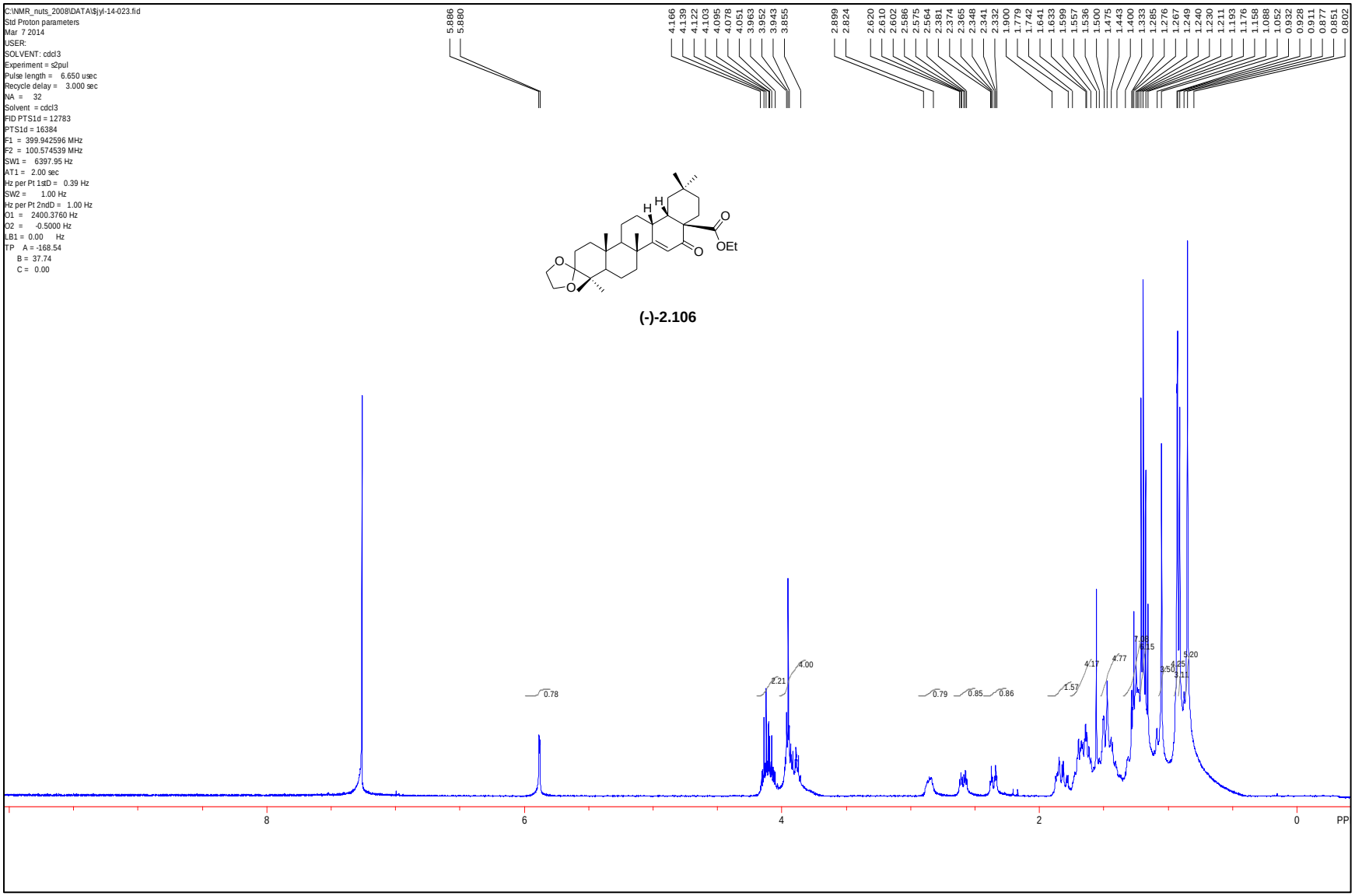

C:\NMR_nuts_2008\data\Sjyl-8-060-ipmer1-13C.fid
Std Carbon experiment
Jul 2 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 1.000 sec
NA = 16332
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.580498 MHz
F2 = 399.961731 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10557.8125 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -293.71
B = 202.28
C = 0.00
202.866
174.690
119.467
113.222
77.563
77.246
76.925
65.102
56.672
53.293
48.514
42.343
41.370
41.097
40.474
38.832
38.091
37.893
37.014
33.386
32.792
30.608
27.075
24.824
23.094
22.955
21.548
20.382
20.141
18.653
16.622
H
H
H
O
O
O
(-)-2.94
200
150
100
50
0
PP


C:\NMR_nuts_2008\data\$jyl-8-060-isomer2.fid
Std Proton parameters
Jul 2 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 3.000 sec
NA = 32
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.962158 MHz
F2 = 100.579445 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2399.7371 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 107.93
B = 90.53
C = 0.00
7.260
5.749
4.023
3.941
3.837
2.402
2.391
2.379
2.369
2.358
2.358
2.088
1.651
1.596
1.577
1.253
1.227
1.163
1.132
1.089
0.968
0.938
0.866
0.843
H
H
H
O
O
O
(+)-2.45
0.95
4.00
0.70
8.34
14.41
8.40
3.29
3.40
2.21
1.71
8
6
4
2
0
PP

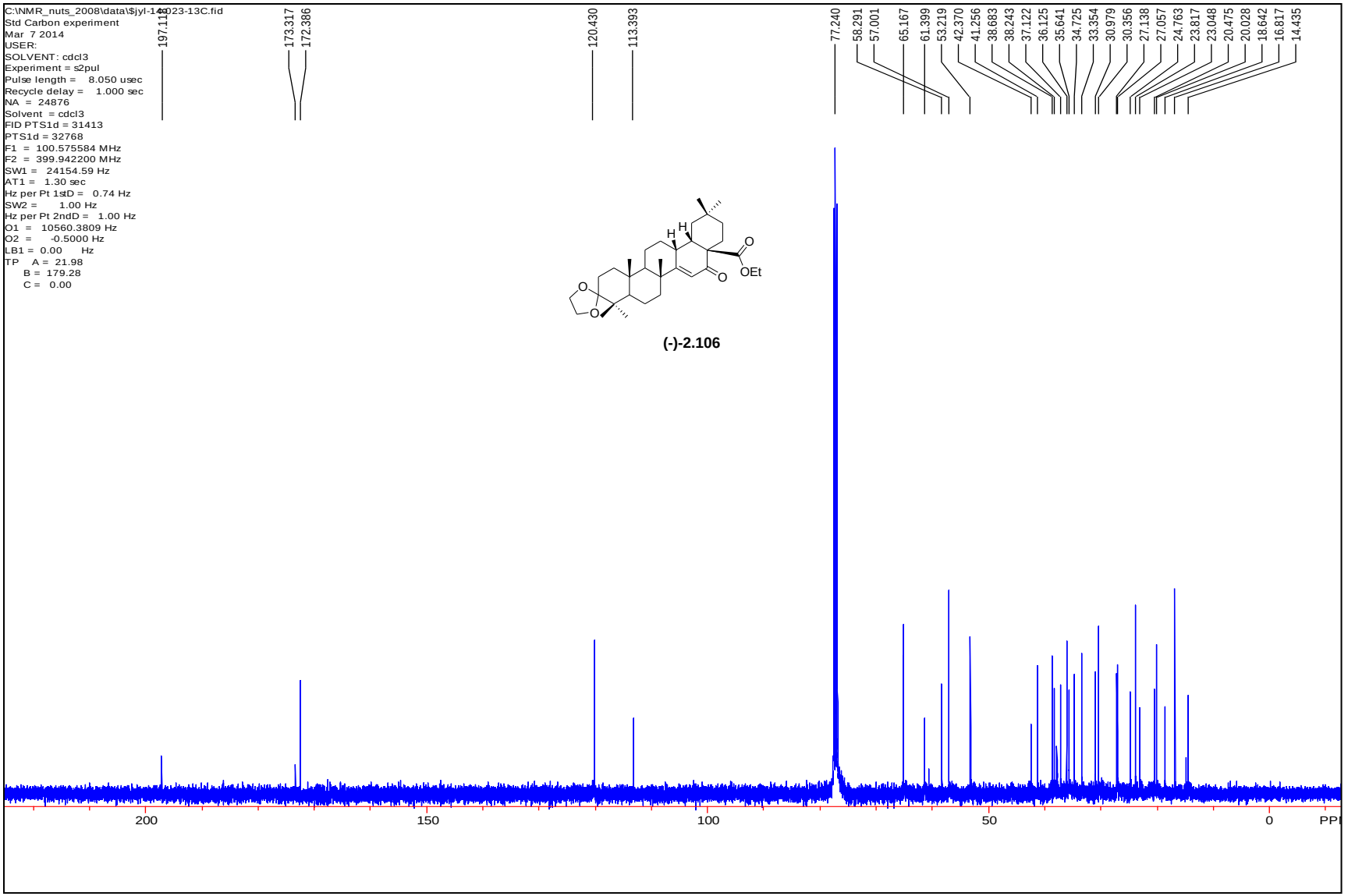

C:\NMR_nuts_2008\data\Sjyl-8-060-isomer2-C13.fid
Std Carbon experiment
Jul 2 2012
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 1.000 sec
NA = 488
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.580498 MHz
F2 = 399.961731 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10554.1260 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -280.78
B = 198.28
C = 0.00
202.744
176.589
118.089
113.105
77.555
77.240
76.917
65.080
65.021
59.744
53.748
43.911
43.208
42.335
41.939
39.264
38.384
38.355
37.864
37.065
36.677
33.473
30.600
28.035
27.001
24.209
23.102
21.973
21.504
21.277
20.668
20.119
18.609
16.226
H
H
H
O
O
O
(+)-2.45
200
150
100
50
0
PP


C:\NMR_nuts_2008\data\$jyl-fentaester-undesired.fid
Std Proton parameters
May 3 2014
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 1.000 sec
NA = 64
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.942596 MHz
F2 = 100.574539 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2399.9854 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -195.47
B = 70.31
C = 0.00
7.260
5.790
3.978
3.957
3.947
3.860
4.160
4.075
1.687
1.674
1.644
1.630
1.599
1.582
1.574
1.549
1.524
1.514
1.490
1.464
1.455
1.448
1.273
1.255
1.237
1.219
1.203
1.177
1.170
1.152
1.140
1.119
1.088
1.068
1.980
0.962
0.956
0.937
0.923
0.888
0.882
0.850
H
H
O
OEt
O
O
O
(+)-2.101
0.56
1.58
3.32
0.58
0.79
1.00
0.95
1.56
4.14
4.70
3.09
4.24
2.36
2.78
4.17
4.12
10
8
6
4
2
0
PP


C:\NMR_nuts_2008\DATA\$2-101-13C.fid
Std Carbon experiment
May 6 2014
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 1.000 sec
NA = 23140
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.575584 MHz
F2 = 399.942200 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10559.6436 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -56.48
B = 282.09
C = 0.00
197.191
174.607
172.261
117.783
113.173
77.555
77.240
76.925
65.174
61.392
58.621
55.638
53.629
43.602
42.927
42.414
41.425
39.548
38.331
38.126
37.100
34.959
34.945
32.914
30.591
27.497
27.087
24.565
23.158
22.007
21.318
20.160
18.694
16.385
14.296
H
H
O
O
OEt
O
O
(+)-2.101
200
150
100
50
0
PP


C:\NMR_nuts_2008\DATA\$jyl-14-023.fid
Std Proton parameters
Mar 7 2014
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 6.650 usec
Recycle delay = 3.000 sec
NA = 32
Solvent = cdcl3
FID PTS1d = 12783
PTS1d = 16384
F1 = 399.942596 MHz
F2 = 100.574539 MHz
SW1 = 6397.95 Hz
AT1 = 2.00 sec
Hz per Pt 1stD = 0.39 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 2400.3760 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = -168.54
B = 37.74
C = 0.00
5.886
5.880
4.166
4.139
4.122
4.103
4.095
4.078
4.051
3.963
3.952
3.943
3.855
2.899
2.824
2.620
2.610
2.602
2.586
2.575
2.564
2.381
2.374
2.365
2.348
2.341
2.332
1.900
1.779
1.742
1.641
1.633
1.599
1.557
1.536
1.500
1.475
1.443
1.400
1.333
1.285
1.276
1.267
1.249
1.240
1.230
1.211
1.193
1.176
1.158
1.088
1.052
0.932
0.928
0.911
0.877
0.851
0.802
H
H
O
OEt
O
O
O
0.78
2.21
4.00
0.79
0.85
0.86
1.57
4.17
4.77
7.08
7.15
3.50
4.05
3.11
5.20
8
6
4
2
0
PP

**(-)-2.106**


C:\NMR_nuts_2008\data\$jyl-14-023-13C.fid
Std Carbon experiment
Mar 7 2014
USER:
SOLVENT: cdcl3
Experiment = s2pul
Pulse length = 8.050 usec
Recycle delay = 1.000 sec
NA = 24876
Solvent = cdcl3
FID PTS1d = 31413
PTS1d = 32768
F1 = 100.575584 MHz
F2 = 399.942200 MHz
SW1 = 24154.59 Hz
AT1 = 1.30 sec
Hz per Pt 1stD = 0.74 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 10560.3809 Hz
O2 = -0.5000 Hz
LB1 = 0.00 Hz
TP A = 21.98
B = 179.28
C = 0.00
197.118
173.317
172.386
120.430
113.393
77.240
58.291
57.001
65.167
61.399
53.219
42.370
41.256
38.683
38.243
37.122
36.125
35.641
34.725
33.354
30.979
30.356
27.138
27.057
24.763
23.817
23.048
20.475
20.028
18.642
16.817
14.435
H
H
O
OEt
O
O
O
(-)-2.106
200
150
100
50
0
PPI